Nire atton-amonei

eman ta zabal zazu

Universidad del País Vasco Euskal Herriko Unibertsitatea

NOVEL STUDIES ON ORGANOCATALYTIC AND STOICHIOMETRIC C-C BOND FORMING REACTIONS

Doctoral Thesis

Maddalen Agirre Goikoetxeaundia

Donostia

2019

Hasteko, eskerrak eman nahi dizkizut Fernando, zure ikerketa taldean jaso eta zientziaz dakidan guztia erakusteagatik, baita ibilbide honetan zehar behar izan ditudan aholkuak eskaintzeagatik ere. Ana, zuri mila esker behar izan dudan guztian laguntzeagatik. Eusko Jaurlaritzari Doktoretza Tesia burutzeko beharrezkoa izan den finantziazio ekonomikoa zor diot. Graci, eskerrik asko por enseñarme a trabajar en el laboratorio, por ayudarme a desarrollar mi criterio científico, por la paciencia, por ayudarme a distancia, y por muchas razones más.

Je voudrais également remercier mes collègues français de m'avoir accueillie en 2015. François, pour votre compréhension et votre aide lorsque j'en ai eu le plus besoin. Bertrand et Aurélie, pour avoir rendu mon quotidien beaucoup plus supportable et m'avoir aidé à tout moment avec les techniques de laboratoire qui m'étaient inconnues jusqu'alors. Je remercie énormément Fabienne et, bien sûr, Sylvain (mon ami français) de m'avoir accompagnée pendant les longs week-ends et de son soutien alors que j'étais loin de chez moi.

Por ayudarme con las incontables dudas en la caracterización de compuestos y en las diversas técnicas de RMN que he necesitado, gracias J.I.

Por hacerme desconectar del mundo de la ciencia, por vuestro apoyo diario y por todas las muestras de cariño, eskerrik asko Celsi y Arancha. Os debo mucho.

Egunero pasiluaz bestalde zuen atea irekitzen nuen bakoitzean irrifarre batekin harrera egiteagatik eta zuekin izan ditudan milaka elkarrizketa eta momentu onengatik, eskerrikasko bizilagunak. Arkaitz, Itzi eta Markos aipamen berezia merezi duzue parrafo honetan, bihotzez eskertzen dizuet dena.

Ez daukat inolako dudarik nire Doktoretza Tesi hau ez litzatekeela den bezalakoa izango nire laborategiko lagunak hor izan ez balira. Asko izan zarete eta zarete, eta denek zuen ekarpena izan duzue nire egunerokotasunean. Esker haundi bat zuentzat. En especial a Tamara ; te debo millones de gracias por tu ayuda y todo el tiempo compartido. A mi amiga mexicana Arlette, por tu alegría y apoyo transatlántico. Dudarik gabe, nire eskerrik beroenak nire mutilentzat: Javi, Aitor, Miquel eta Mikel. Ez dut hitzik sentitzen dudan esker guztia behar bezela adierazteko. Gauza bat argi daukat, ordea, zuei esker irrifarre bat izan dut ahoan egunero, ia momentuero, eta horrek ez du preziorik.

Nire kuadrilari. Gure taldearen parte sentitzeaz harro nago. Zuekin deskonektatzen dut eta zientziaz kanpo mundu izugarria badela ikusi. Uste ez baduzue ere, nere sostengua zarete. Mila momentugatik, bihotz-bihotzez mila esker. Bizitzak zuen ondoan urte asko niretzat gordeta izatearen esperantza daukat. Asko maite zaituztet.

Nire familia osoari.

Anderri eta Markeli, egunero etxera iristean eskaini didazuen harreragatik, zuen laguntzagatik. Amari eta aitari. Nire eredu zarete. Esforzuaren balioa txiki-txikitatik erakusteagatik. Beti, beti laguntzeagatik eta nire ametsak gogor jarraitzea zeinen garrantzitsua den erakusteagatik. Ez dut ia inoiz esaten, baino asko maite zaituztet denoi.

This Thesis Dissertation has been carried out in the Department of Organic Chemistry I of the Chemistry Faculty at the University of the Basque Country, in Donostia-San Sebastián, under the supervision of Prof. Fernando P. Cossío Mora and Dra. Mª de Gracia Retamosa Hernández.

Between September-December 2015; a short-term research stay was done at the Institut de Sciences Chimiques de Rennes, Research unit UMR CNRS 6226, Rennes (France) under the supervision of Dr. François Carreaux.

This Dissertation is divided into two main parts, A and B. Part A comprises organocatalytic studies and is subdivided into three main Chapters. Chapter 1 is an Introduction focused on the concept of chirality and the different approaches for asymmetric synthesis, explaining the use of unnatural amino acid derived organocatalysts in detail. Chapter 2 describes the organocatalytic Michael-Henry-Acetalization strategy towards the synthesis of highly substituted tetrahydropyran scaffolds. To last, Chapter 3 discloses the use of unnatural proline-based organocatalysts for the Diels-Alder reaction between α,β-unsaturated ketones and nitroalkenes. Part B, on the other hand, contains Chapter 4, which gathers the study developed during the short-term stay concerning the unexpected 1,3-dioxo-[3,3]-sigmatropic rearrangement of allylic substituted carbamates. Together with the substrate scope, kinetic, isotope labelling and chirality transfer studies are collected.

The numbering of the tables, figures, schemes and references of this dissertation are independent for each chapter. For an easier understanding, unnatural proline-based first, second and third generation of organocatalysts will use the same numbering along Chapter 2 and 3.

LIST OF PUBLICATIONS

1. *Enantioselective Ring-Opening Polimerization of rac-Lactide Dictated by Densely Substituted Amino Acids.* Sánchez-Sánchez, A.; Rivilla, I.; Agirre, M.; Basterretxea, A.; Etxeberria, A.; Veloso, A.; Sardón, H.; Mecerreyes, D.; Cossío, F. P. *J. Am. Chem. Soc*. **2017**, *139*, 4805-4814.

2. *Organocatalysts Derived from Unnatural α-Amino Acids: Scope and Applications*. Agirre, M.; Arrieta, A.; Arrastia, I.; Cossío, F. P. *Chem. Asian. J*. **2018**. DOI: 10.1002/asia.201801296.

3. *1,3-Dioxa-[3,3]-sigmatropic Oxo-Rearrangement of Substituted Allylic Carbamates: Scope and Mechanistic Studies*. Agirre, M.; Henrion, S.; Rivilla, I.; Miranda, J. I.; Cossío, F. P.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. *J. Org. Chem*. **2018**, *83*, 14861-14881.

4. *Additive and Emergent Catalytic Properties of Dimeric Unnatural Amino Acid Derivatives: Aldol and Conjugate Additions.* Retamosa, M. G.; Ruiz-Olalla, A.; Agirre, M.; de Cózar, A.; Bello, T.; Cossío, F. P. *Manuscript in Preparation*.

5. *Synthesis of Highly Substituted Bicyclic Tetrahydropyrans by Organocatalysed Michael-Henry-Acetalisation Cascade Reactions*. Agirre, M.; Bello, T.; Retamosa, M. G.; Cossío, F. P. *Manuscript in Preparation*.

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PART A: ORGANOCATALYTIC STUDIES

1. Introduction

2. Synthesis of Highly Substituted Bicyclic Tetrahydropyrans by Organocatalysed Michael-Henry-Acetalisation Cascade Reactions

3. Organocatalytic Diels-Alder Reactions Between α,β-Unsaturated Ketones and Nitroalkenes Promoted by Densely Substituted γ-Dipeptides

PART B: STOICHIOMETRIC STUDIES

4. 1,3-Dioxa-[3,3]-Sigmatropic Rearrangement of Substituted Allylic Carbamates: Scope and Mechanistic Studies

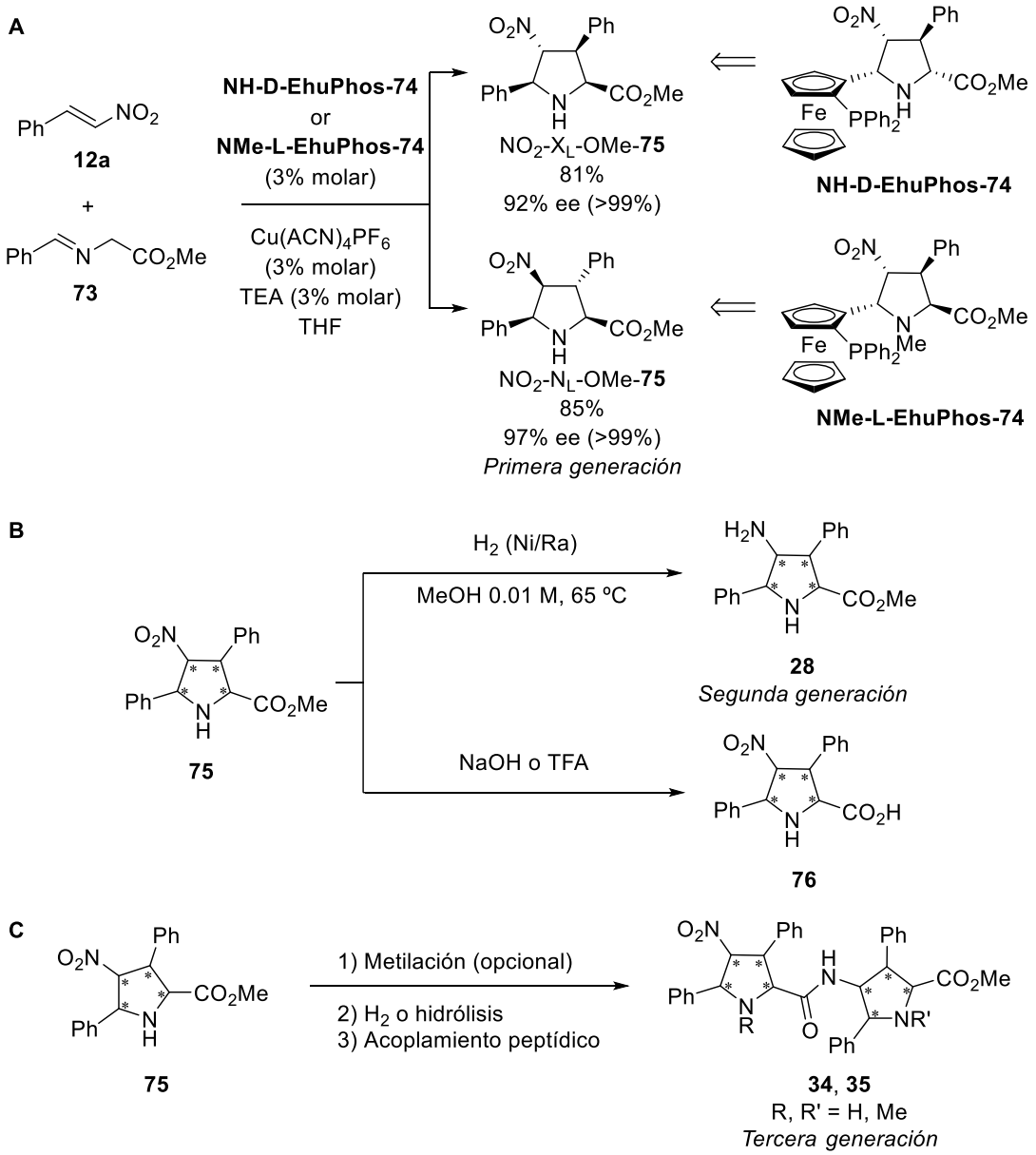
La quiralidad está considerada como la propiedad unificadora de la materia, dado que el universo es inherentemente asimétrico. Es bien conocido que la vida depende de la quiralidad molecular, debido a que los receptores quirales presentes en el cuerpo humano interaccionan únicamente con moléculas de configuración absoluta determinada. Existen numerosos ejemplos de dicha especificidad en la industria farmacéutica. Entre ellos se encuentran la quinina y su enantiómero quinidina, los cuales presentan diferentes actividades farmacológicas. De este modo, mientras que la primera actúa como agente antimalárico, la segunda posee propiedades antiarrítmicas. Comportamientos opuestos como el anteriormente citado han impulsado la demanda de medicamentos que presenten un único enantiómero, promoviendo un rápido desarrollo de la catálisis asimétrica.

La organocatálisis, junto con la catálisis metálica y la biocatálisis, es una de las herramientas más utilizadas para la síntesis de compuestos ópticamente activos. Dicha estrategia acelera las reacciones químicas mediante cantidades subestequiométricas de compuestos orgánicos quirales que no contienen átomos metálicos en su estructura. El empleo de pequeñas moléculas naturales presenta grandes ventajas en comparación a la catálisis organometálica tradicional, tales como: la robustez frente a la humedad y el oxígeno; el respeto al medio ambiente; la disponibilidad a partir de fuentes naturales; y, la facilidad de síntesis. Entre el gran número de organocatalizadores descritos hasta la fecha la *L*-Prolina y sus derivados no naturales merecen especial relevancia. A su vez, cabe destacar los organocatalizadores de tipo peptídico, los cuales muestran propiedades catalíticas diferentes a las observadas en otras moléculas o enzimas. Dichos organocatalizadores han sido ampliamente utilizados en numerosas reacciones orgánicas, especialmente en reacciones de tipo aldólica, Mannich y Michael. El Capítulo 1 de la presente tesis doctoral ofrece una amplia revisión de estos procesos enantioselectivos activados por pequeñas moléculas orgánicas.

A lo largo de los últimos años, en nuestro grupo de investigación se han desarrollado los ligandos híbridos de ferrocenil prolina NH-D-Ehu-Phos-**74** y NMe-L-Ehu-Phos-**74**. Estos ligandos promovieron de manera eficiente la cicloadición (3+2) entre iminoésteres y nitroalquenos para dar lugar a los cicloaductos O_2N-X_L-OMe-**75** y O_2N-N_L-OMe-**75** de primera generación con excelentes excesos enantioméricos (**Esquema 1A**). Debido a la presencia del grupo nitro y éster metílico, estos cicloaductos fueron fácilmente derivatizados para dar lugar a los correspondientes derivados amino H_2N-X_L-OMe-**28** (segunda generación) y ácido O_2N-X_L-OH-**76** (**Esquema 1B**). La posible metilación y el posterior acoplamiento peptídico permitió la obtención de dipéptidos *N*-metilados y no

metilados de distinta configuración, conocidos como organocatalizadores de tercera generación (**Esquema 1B**).

Estos organocatalizadores han sido muy eficientes en reacciones de formación de enlaces carbono-carbono activadas vía enamina. Los cicloaductos nitroderivados de primera generación fueron capaces de catalizar de manera eficiente la reacción aldólica entre cetonas cíclicas y aldehídos aromáticos, dando lugar a los productos correspondientes con buenos rendimientos y excesos enantioméricos (**Figura 1**). A su vez, los organocatalizadores tipo amina de segunda generación promovieron dicha reacción aldólica con resultados similares a sus predecesores O_2N-$X_{L/D}$-OMe-**75**. Además, estos catalizadores de segunda generación permitieron llevar a cabo la reacción de Michael entre centonas cíclicas como la ciclohexenona y nitroalquenos aromáticos de forma eficiente, proporcionando los aductos de Michael con elevados rendimientos y excesos enantioméricos (**Figura 1**). Cabe destacar que los resultados de ambas reacciones manifiestan la importancia de la configuración del catalizador en la inducción quiral. Mientras los catalizadores de configuración *endo*-L dan lugar a los productos con la misma configuración que aquellos obtenidos con la *L*-Prolina, los catalizadores *exo*-L producen los enantiómeros opuestos. Por último, los organocatalizadores de tercera generación **34** y **35** también demostraron su gran capacidad catalítica en las reacciones aldólica y Michael (**Figura 1**). En este caso, se observó que la inducción asimétrica dependía de la configuración de las dos unidades que constituyen el organocatalizador, donde ambos actúan como centros catalíticos independientes. Es preciso destacar que en el proceso de adición Michael catalizada por estos dipéptidos, se observó la formación de un subproducto debido a una reacción multicomponente en la que el aditivo ácido estaba actuando como reactivo. De este modo, el uso de cantidades equimolares del derivado ácido permitieron la obtención de los productos de ciclación en mayores proporciones. Además, posteriores estudios revelaron que el monómero O_2N-X_L-OMe-**75** promovía la formación del producto de ciclación deseado de forma exclusiva con un elevado exceso enantiomérico (**Figura 1**).



Esquema 1. A) Síntesis de las prolinas densamente funcionalizadas O_2N-X_L-OMe-**75** y O_2N-X_D-OMe-**75** mediante la cicloacidión (3+2) promovida por ligandos ferrocenil prolina NH-D-EhuPhos-**74** y NMe-L-EhuPhos-**74**. B) Procesos de hidrogenación catalítica e hidrólisis para dar lugar a los derivados amino y ácido, respectivamente. C) Síntesis de los organocatalizadores de tercera generación **34** y **35**.

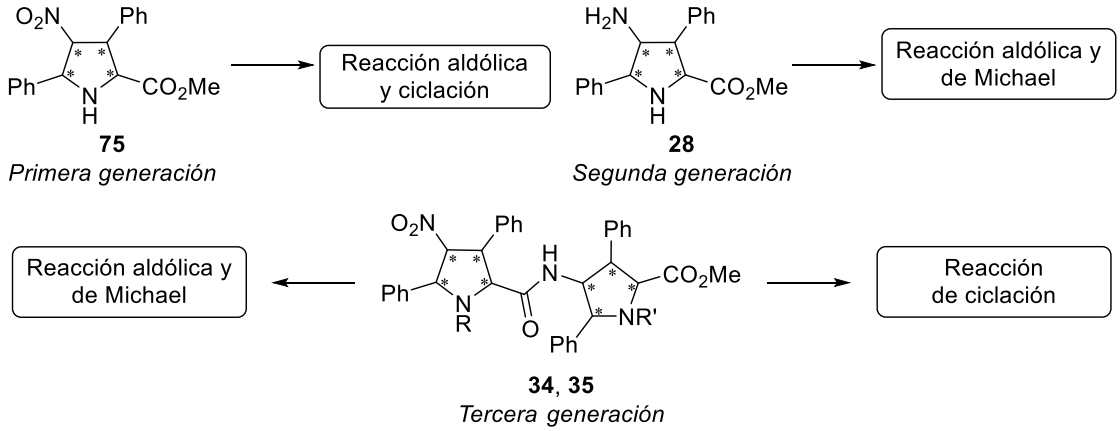


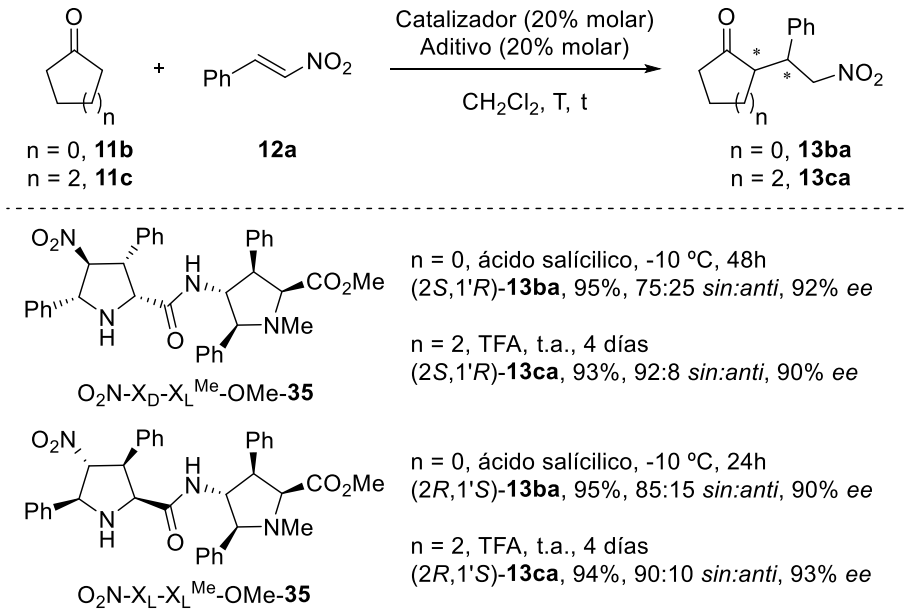
Figura 1. Actividad de los organocatalizadores de primera, segunda y tercera generación en reacciones de formación de enlaces carbono-carbono.

A pesar de los excelentes resultados obtenidos con las aminoprolinas de segunda generación en las reacciones de Michael utilizando la ciclohexanona como nucleófilo, otros derivados cíclicos de menor y mayor tamaño presentaron diastereo- y enantioselectividades moderadas. Por ello, en el segundo Capítulo nos centraremos en el estudio de los catalizadores de tercera generación o dipéptidos tanto en la reacción de adición Michael empleando otras cetonas cíclicas, como en la reacción tándem Michael-Henry-Acetalización. Este último proceso permite la obtención de esqueletos de tetrahidropirano presentes en productos naturales y moléculas con actividad biológica.

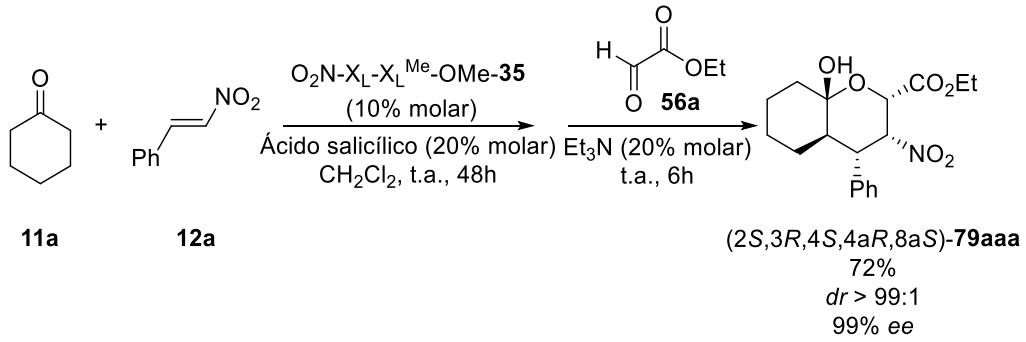
Los estudios de la reacción Michael realizados con la ciclopentanona **11b** y el nitroestireno **12a** subrayaron la emergencia de propiedades predicha de los dipéptidos *N*-metilados. La evaluación de los dipéptidos *N*-metilados en la reacción de Michael con ciclopentanona evidenció que los mejores resultados se obtenían mediante el uso de ácido salicílico como aditivo y -10 °C de temperatura. Bajo estas condiciones, el catalizador O_2N-X_L-X_L^{Me}-OMe-**35** daba lugar al correspondiente cicloaducto (2*S*,1'*R*)-**13ca** con excelente rendimiento y exceso enantiomérico. Por otro lado, el dímero O_2N-X_D-X_L^{Me}-OMe-**35** generó el enantiómero opuesto (2*R*,1'*S*)-**13ca** con similar rendimiento y estereocontrol (**Esquema 2**). En el caso de la cicloheptanona **11c**, la reacción se llevó a cabo a temperatura ambiente debido al largo tiempo de reacción observado. Esta vez, el ácido trifluoroacético (TFA) fue el aditivo de elección, debido a la mayor reactividad y selectividad observada. El empleo de estas condiciones favoreció la formación de los enantiómeros **13ca** con excelentes rendimientos, diastereo- y enantiocontrol (**Esquema 2**).

En cuanto a la reacción en cascada, los primeros análisis se realizaron empleando ciclohexanona **11a**, nitroestireno **12a** y glioxilato de etilo **56a**. La evaluación de las

condiciones de reacción mostró la idoneidad del dímero O_2N-X_L-X_L^{Me}-OMe-**35** para catalizar esta transfomación, generando el compuesto **79aaa** como único diastereoisómero con buen rendimiento y elevado exceso enantiomérico (**Esquema 3**). Asimismo, se determinó que la adición del aldehído **56a** debía hacerse una vez la adición conjugada 1,4 hubiese acabado, ya que la reacción multicomponente no daba lugar al producto de ciclación deseado.



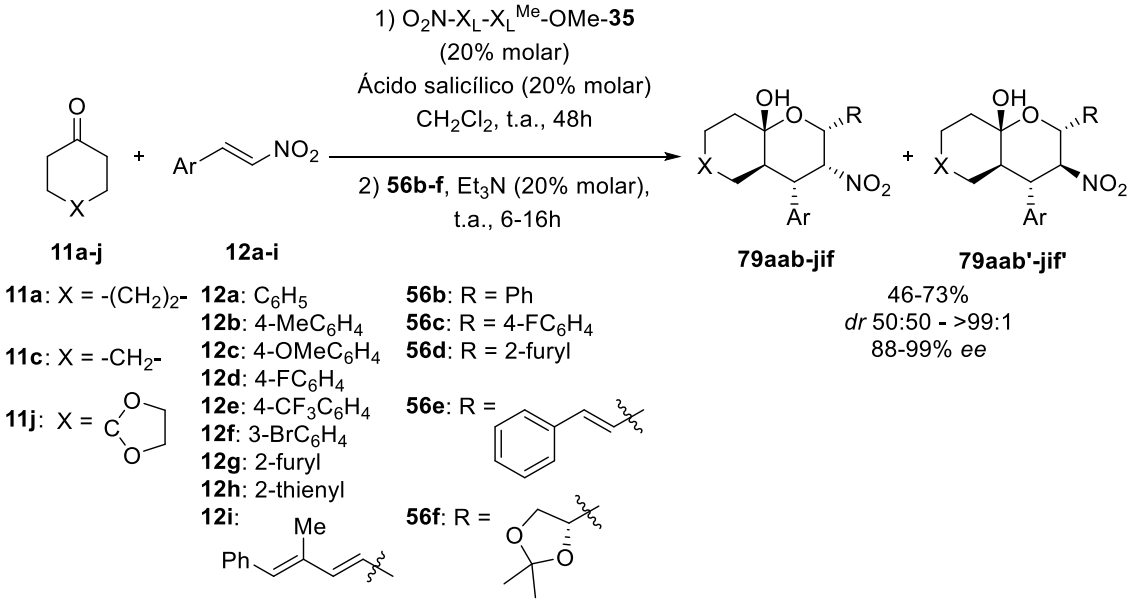
Esquema 2. Reacción de Michael entre ciclopentanona **11b** y cicloheptanona **11c** y nitroestireno **12a** promovida por los organocatalizadores de tercera generación **35**.



Esquema 3. Reacción de Michael/Henry/Acetalización para la formación del esqueleto de tetrahidropirano **79aaa**.

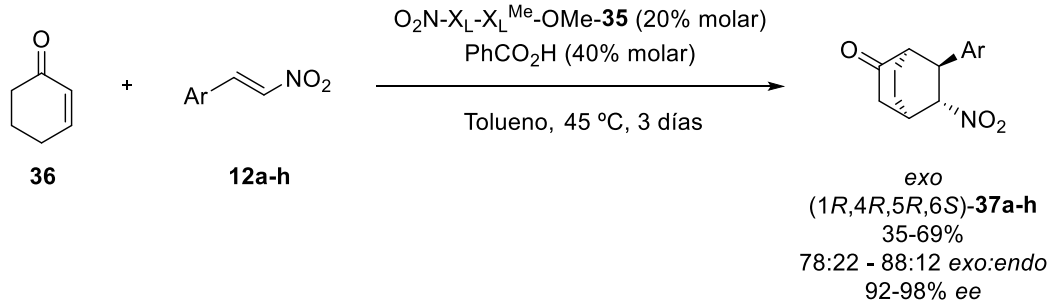
Una vez determinadas las condiciones de reacción se procedió a evaluar el alcance sintético del proceso utilizando para ello diversas cetonas, nitroalquenos y aldehídos (**Esquema 4**). El uso tanto de diferentes cetonas cíclicas como de nitroalquenos tanto alifáticos como aromáticos proporcionó los correspondientes productos de ciclación **79aab**-**jif** con buenos rendimientos y excesos enantioméricos, observándose en todos los casos la formación de un único diastereoisómero. Cuando se modificó el aldehído

electrofílico empleando derivados del benzaldehído la adición de 1 equivalente de trietilamina fue necesaria, ya que las cantidades catalíticas no alcanzaban la conversión total. No obstante, el uso de dichas cantidades estequiométricas conllevaron la epimerización de los correspondientes biciclos formados, obteníendose así dos productos diastereoméricos en diferentes proporciones.



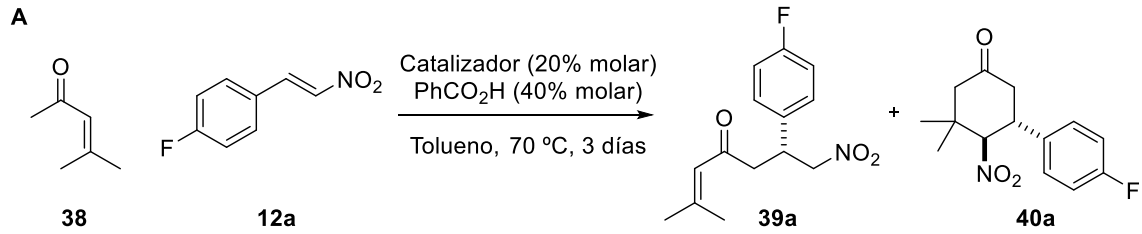
Esquema 4. Reacción de Michael/Henry/Acetalización entre diversas cetonas **11a-j**, nitroalquenos **12a-i** y aldehídos **56b-f**.

Con el objetivo de conocer la versatilidad de estos organocatalizadores basados en prolinas no naturales en otras reacciones de formación de enlaces carbono-carbono, en el Capítulo 3 se aborda la reacción de Diels-Alder organocatalítica entre cetonas α,β-insaturadas y nitroalquenos. En primer lugar, se evaluaron las tres generaciones de organocatalizadores en la reacción entre ciclohex-2-en-1-ona **36** y 4-fluoro-*trans*-nitroestireno **12a**. En este proceso el dímero O_2N-X_L-X_L^{Me}-OMe-**35** con ácido benzoico como aditivo cocatalizador resultó ser el más eficiente dando lugar al cicloaducto *exo*-**37a** con rendimiento moderado, elevado diastereocontrol y excelente exceso enantiomérico. Posteriormente, se decidió evaluar el alcance de la reacción empleando para ello nitroalquenos de diferente densidad electrónica observándose la idoneidad tanto de los sustituyentes electrodadores como de los electroaceptores en dicho proceso. Todos los compuestos fueron sintetizados con rendimientos de moderados a buenos, buen diastereocontrol y altos excesos enantioméricos (**Esquema 5**). Los rendimientos más bajos podrían deberse a la inestabilidad de los productos formados a altas temperaturas.

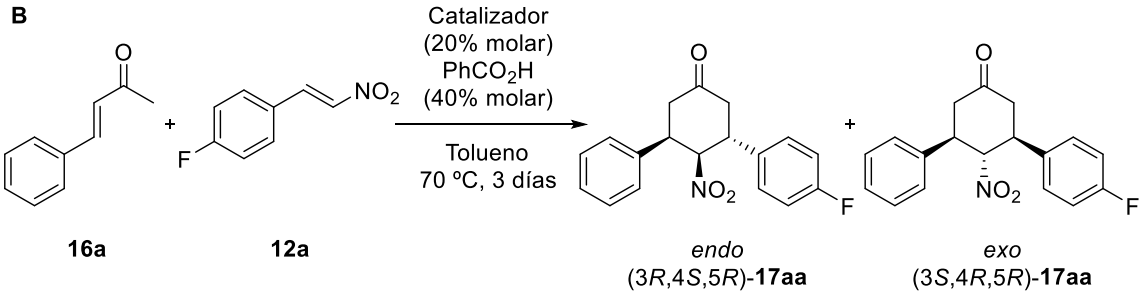


Esquema 5. Reacción de Diels-Alder entre ciclohex-2-en-1-ona **36** y nitroalquenos **12a-h** catalizada por el dímero O_2N-X_L-X_L^{Me}-OMe-**35a**.

El siguiente paso consistió en evaluar la reacción de Diels-Alder haciendo uso de cetonas acíclicas. Cuando se empleó la 4-metilpent-3-en-2-ona **38** se obtuvieron mezclas de los productos Michael y Diels-Alder, siendo imposible promover la aparición exclusiva del cicloaducto **40a** (**Esquema 6A**). Además, los resultados en cuanto a reactividad y estereoselectividad fueron más bajos que los observados anteriormente con la ciclohex-2-en-1-ona. Al igual que en los casos anteriores, el dipéptido *N*-metilado O_2N-X_L-X_L^{Me}-OMe-**35** fue el más eficiente en términos de rendimiento y enantioselectividad, aunque los mejores resultados no superaron valores moderados (**Esquema 6A**). Para poder incrementar las enantioselectividades observadas, el siguiente paso consistió en emplear la cetona **25a** como sustrato. Desafortunadamente, los organocatalizadores generaron mezclas de los diastereoisómeros *endo* y *exo* **26aa** con excesos enantioméricos moderados. El mejor organocatalizador en términos de reactividad fue el dímero O_2N-X_L-X_L-OMe-**35**, mientras que el dímero O_2N-X_D-X_L^{Me}-OMe-**35** mostró los valores más altos de diastereo- y enantiocontrol (**Esquema 6B**).



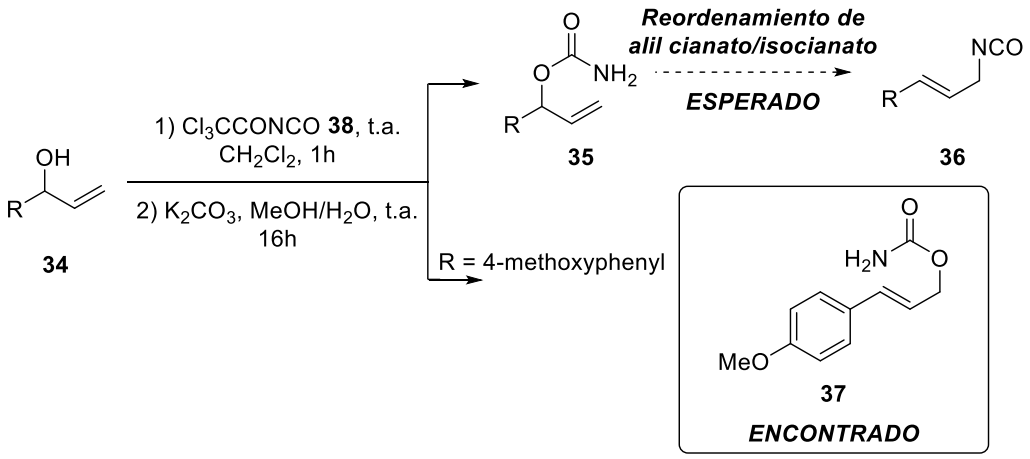
O_2N-X_L-OMe-**75**: Conversión 70%, **39a:40a** 5:95, *ee* (**39a**) n.d., *ee* (**40a**) 40%
H_2N-X_L-OMe-**28**: Conversión 95%, **39a:40a** 45:55, *ee* (**39a**) 50%, *ee* (**40a**) 21%
O_2N-X_L-X_L-OMe-**34**: Conversión >99%, **39a:40a** 34:66, *ee* (**39a**) 61%, *ee* (**40a**) 7%
O_2N-X_D-X_L^{Me}-OMe-**35**: Conversión 85%, **39a:40a** 33:67, *ee* (**39a**) -48%, *ee* (**40a**) -34%
O_2N-X_L-X_L^{Me}-OMe-**35**: Conversión >99%, **39a:40a** 25:75, *ee* (**39a**) 58%, *ee* (**40a**) 26%



O_2N-X_L-OMe-**75**: Conversión 60%, 42:58 *endo:exo*, *ee* (*endo*) 30%, *ee* (*exo*) 37%
H_2N-X_L-OMe-**28**: Conversión 90%, 60:40 *endo:exo*, *ee* (*endo*) 37%, *ee* (*exo*) 5%
O_2N-X_L-X_L-OMe-**34**: Conversión >99%, 68:32 *endo:exo*, *ee* (*endo*) 50%, *ee* (*exo*) 20%
O_2N-X_D-X_L^{Me}-OMe-**35**: Conversión 70%, 90:10 *endo:exo*, *ee* (*endo*) -67%, *ee* (*exo*) -50%
O_2N-X_L-X_L^{Me}-OMe-**35**: Conversión 65%, 83:17 *endo:exo*, *ee* (*endo*) 66%, *ee* (*exo*) 35%

Esquema 6. A) Reacción de Diels-Alder de 4-metilpent-3-en-2-ona **38** y 4-flúor-*trans*-β-nitroestireno **12a** y B) (*E*)-4-fenilbut-3-en-2-ona **25a** y 4-flúor-*trans*-β-nitroestireno **12a** catalizada por derivados de prolina densamente funcionalizados.

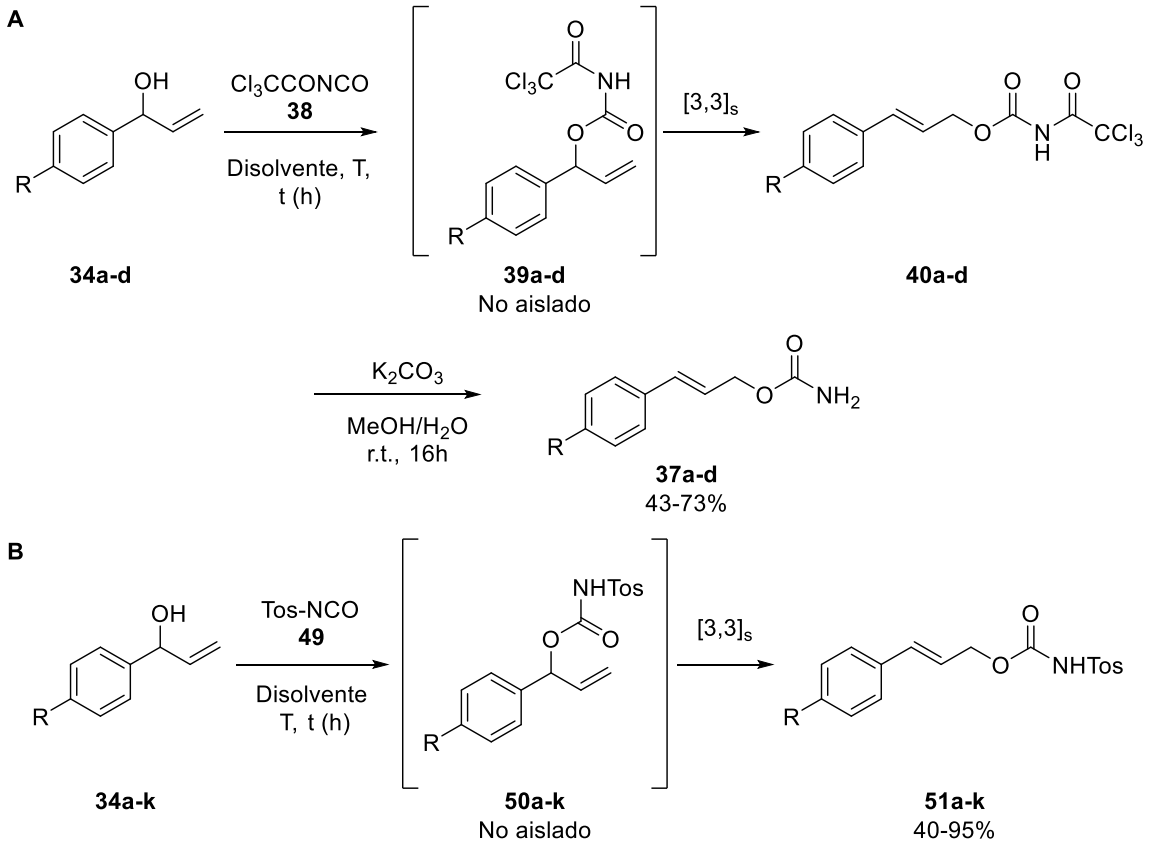
Para finalizar, el último capítulo comprende el trabajo realizado durante la estancia doctoral en el grupo supervisado por François Carreaux en la Université de Rennes 1. El trabajo se centra en estudiar el alcance, las limitaciones y el mecanismo del oxo-reordenamiento sigmatrópico [3,3] nunca antes descrito en literatura. En los resultados preliminares se observó que la reacción entre el alcohol alílico **34a** y el isocianato de tricloroacetilo **38** daba lugar al carbamato lineal de configuración (*E*)- a temperatura ambiente (**Esquema 7**).



Esquema 7. Reordenamiento sigmatrópico [3,3].

Inicialmente, se evaluó la influencia de los sustituyentes del alcohol alílico y el isocianato durante el proceso. En general, se observó que los sustituyentes electroaceptores en el alcohol de partida disminuían la velocidad de reacción y requerían de calentamiento a 90 °C. Los sustituyentes electrodadores, por otro lado, aceleraban la transposición sigmatrópica, dando lugar a los carbamatos lineales a temperatura ambiente y tiempos de reacción cortos. Todo ello ponía de manifiesto el carácter deficiente en electrones del grupo alilo. Igualmente, se determinó que los isocianatos activados eran necesarios para que la reacción tuviera lugar, debido posiblemente al aumento de la acidez del grupo NH del carbamato. A la hora de emplear el isocianato de tricloroacetilo, los productos deseados **37a**-**d** se obtuvieron con buenos rendimientos tras un segundo paso de hidrólisis (**Esquema 8A**). El uso del isocianato de *p*-toluensulfonilo **49** promovió también la síntesis de los carbamatos *N*-tosilados **51a**-**k** con buenos rendimientos y corroboró la teoría de la influencia de la densidad electrónica en la estructura del alilo (**Esquema 8B**). Mismamente, se hizo uso de alcoholes alílicos alquenil sustituidos obteniendo los productos reordenados correspondientes con buenos rendimientos. Merece especial atención el análisis mediante cromatografía líquida en fase quiral que demostró la transferencia de quiralidad 1,3 del alcohol alílico al carbamato final.

Por último, los estudios cinéticos efectuados evidenciaron la mayor reactividad de los sustituyentes electrodadores y permitieron el cálculo de las constantes cinéticas de primer orden para el caso de los alcoholes alílicos OMe, H y Cl sustituidos. Los estudios computacionales DFT, por otro lado, manifestaron el mecanismo asíncrono pero concertado del reordenamiento sigmatrópico mediado por un estado de transición de tipo silla. Además, los puntos silla reflejaron las velocidades y energías de activación relativas obtenidas experimentalmente e ilustraron el carácter polar de los estados de transición.



Esquema 8. Reordenamiento sigmatrópico [3,3] entre A) alcoholes alílicos **34a-d** e isocianato de tricloroacetilo **38** y B) alcoholes alílicos **34a-d** e isocianato de *p*-toluensulfonilo **49**.

ACRONYMS AND ABBREVIATIONS

A	Acid
AcOEt	Ethyl acetate
ACN	Acetonitrile
Ala	Alanine
Asp	Aspartic acid
Ar	Aryl
B	Base
BINAP	(2,2'-bis(diphenylphosphino-1,1'-binaphthyl)
BINOL	1,1'-bi-2-naphtol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
br	Broad
^{t}Bu	*tert*-butyl
cat.	Catalyst
conv.	Conversion
COSY	Correlation Spectroscopy
d	Day(s)
d	Doublet (NMR)
dd	Double doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBSA	*para*-dodecyl benzenesulfonic acid
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DET	diethyl tartrate
de	Diastereomeric excess
DIPEA	*N*,*N*-diisopropylethyl amine
DiPAMP	1,2-bis[(2-Methoxyphenyl)(phenylphosphino)] ethane
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNBSA	2,4-dinitrobenzenesulfonic acid
dr	Diastereomeric ratio
EDG	Electron-donating group
ee	Enantiomeric excess
ent	Enantiomer
eq.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
$Eu(hfc)_3$	Europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate]
EWG	Electron-withdrawing group
FTIR	Fourier Transform Infrared Spectroscopy
Gln	Glutamine

Glu	Glutamic acid
h	Hour(s)
Hex	Hexane
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest Occupied Molecular Orbital
HPLC	High Pressure/Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
INT	Intermediate
J	Coupling constant
Leu	Leucine
LiICA	Lithium *N*-isopropylcyclohexylamide
Ln	Naperian logarithm
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet (NMR)
Me	Methyl
mg	Miligram(s)
mmol	Milimol
MMPP	Magnesium monoperoxyphtalate
min	Minute
mL	Mililitre(s)
m_p	Melting point
MPEG	Poly(ethyleneglycol) methyl ether
MS	Mass Spectrometry
MS	Molecular sieves
n.d.	Not determined
N_D	*endo*-D
N_L	*endo*-L
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidinone
NMR	Muclear Magnetic Resonance
NOESY	Nuclear Overhauser Spectroscopy
Nu	Nucleophile
Ns	Nosyl
P	Product
PCC	Pyridinium chlorochromate
PEG	Polyethylene glycol
PFBA	Pentafluorobenzoic acid
Ph	Phenyl
Phe	Phenylalanine
PNBA	*para*-nitrobenzoic acid
PPG	Polypropylene glycol
Pro	Proline
^{i}Pr	*iso*-propyl
PS	polystyrene
PTM	Post translational modification
PTSA	*para*-toluensulfonic acid

PyBOP	(Benzotriazol-1-yl-oxy)tripyrrolidinophosphonium hexafluorophosphate
R	Arbitrary substituent
RNA	Ribonucleic acid
r. t.	Room temperature
s	Singlet (NMR)
S	Substrate
sc	Supercritic
SOMO	Singly Occupied Molecular Orbital
t	Time
t	Triplet (NMR)
T	Temperature
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBAB	Tetrabutylammonium bromide
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
TFT	α,α,α-trifluorotoluene
Tf	Trifluoromethane sulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tos	*p*-toluenesulfonyl
t_R	Retention time
Ts	Tosyl
TS	Transition State
vs.	Versus
X_D	*exo*-D
X_L	*exo*-L

PART A

Organocatalytic Studies

Chapter 1

Introduction

Abstract: The organocatalytic properties of unnatural α–amino acids are reviewed. Post translational derivatives of natural α–amino acids include 4-hydroxy-*L*-proline and 4-amino-*L*-proline scaffolds, as well as proline homologues. Synthetic unnatural α–amino acid-based organocatalysts whose activity has been reviewed include β–prolines and unnatural pyrrolidine-based derivatives. The organocatalytic properties of unnatural monocyclic, bicyclic and tricyclic proline derivatives are also reviewed. Several families of these organocatalysts permit the efficient and stereoselective synthesis of complex natural products. Most of the reviewed organocatalysts accelerate the reported reactions via HOMO raising (enamine intermediates) or LUMO lowering (iminium intermediates) covalent interactions.

This Chapter has been published as a part of a Focus Review: Agirre, M.; Arrieta, A.; Arrastia, I.; Cossío, F.P. *Chem. Asian J.* **2018**. DOI: 10.1002/asia.201801296

1.1 CHIRALITY

Chirality is believed to be the unifying property of matter: the universe is inherently asymmetric.[1] The concept of chirality was first coined by Lord Kelvin in 1884: "I call any geometrical figure, or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself".[2] The term was derived from the Greek word *cheir* (hand) and was used for describing the left and right handedness of crystal structure resulting from molecular asymmetry.[3]

In a molecular fashion, chirality refers to a molecule that bears a stereogenic element and suffers from an absence of reflection symmetry. The pair of non-superimposable mirror images are called enantiomers. It is well known that life depends on molecular chirality. Chiral receptor sites in the human body interact only with small molecules having the proper absolute configuration.[4]

Many different examples of the relationship between the pharmacological activity and molecular chirality can be found in drug industry. For instance, whilst quinine exhibits antimalarial activity, its enantiomer quinidine has antiarrythmic properties. In addition, the D- enantiomer of L-dopa (used for the treatment of Parkinson's disease) has never been employed because it generates deficiency of white blood cells, and therefore, susceptibility to infections (**Figure 1.1**).[5] Such problems resulted in an increasing demand of single-enantiomer drugs, so the field of asymmetric catalysis boosted rapidly.

[1] Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **2000**, *11*, 2845-2874.
[2] Francotte, E.; Lindner, W. *Chirality in Drug Research*, Wiley-VCH: Weinheim, **2006**.
[3] Chhabra, N.; Aseri, M. L.; Padmanabhan, D. *Int. J. Basic Med. Res.* **2013**, *3*, 16-18.
[4] Noyori, R. *Adv. Synth. Catal*. **2003**, *345*, 15-32.
[5] Cotzias, G. C.; Papavasiliou, P. S.; Gellene, R. *New Engl. J. Med*. **1969**, *280*, 337-345.

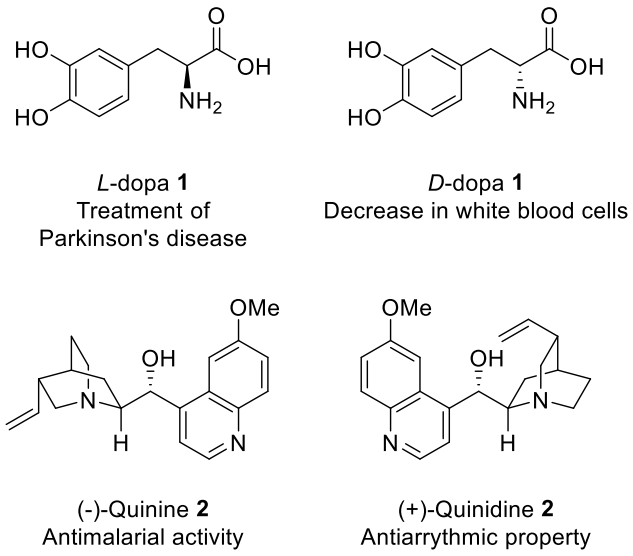


Figure 1.1. Biological activity of each enantiomer entity.

1.2 STRATEGIES FOR THE ELABORATION OF ENANTIOMERICALLY PURE COMPOUNDS (EPC)

There are different synthetic methodologies that lead to enantiomerically pure compounds. Some important features for a convenient EPC synthesis are: 1) the formation of the desired enantiomer with high enantiomeric excess and chemical yield; 2) the ease of pure compounds to be separated from the chiral auxiliary reagent; and 3) the facile recovery of the chiral auxiliary without loss of enantiomeric excess, in case that it is needed.[6]

In general, as gathered in **Figure 1.2** there are three approaches for this purpose: 1) resolution of racemates; 2) the *chiral pool* strategy; and 3) asymmetric synthesis.

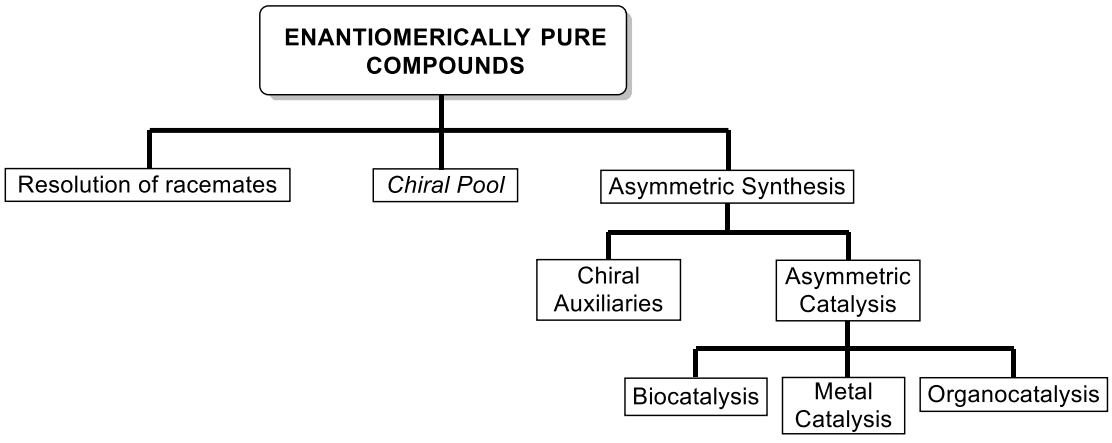


Figure 1.2. Strategies for the obtaining of Enantiomerically Pure Compounds.

[6] Scheffold, R. *Modern Synthetic Methods, Conference Papers of the International Seminar on Modern Synthetic Methods*, Springer-Verlag: Berlin, **1986**.

The *resolution of racemates*[7] is still very used at industrial scale. It consists of a reaction between a racemic substrate and a chiral agent that generates easily separable diastereomeric mixtures by adequate physical or chemical methods such as crystallization and kinetic or chromatographic resolution. One of its main drawbacks is that the products are obtained in a 1:1 ratio of enantiomers; hence, the maximum possible chemical yield of each entity is only 50%. This limitation can be surpassed by dynamic kinetic resolution (DKR) in which an *in situ* interconversion of the less reactive enantiomer into the most reactive one occurs in the reaction medium.[8]

In the *chiral pool*, the chiral source stems from a natural enantiopure compound that will remain included in the structure of the final product without altering the initial stereogenic elements.[9] These chiral elements are integrated by carbohydrates, amino acids, hydroxy acids and terpenes. As a disadvantage, the limited availability of natural resources should be noted.

On the other hand, *asymmetric synthesis* involves stereoselective reactions in which chirality elements are introduced in a prochiral substrate by the use of chiral auxiliaries[10] or chiral catalysts.[11] The corresponding reactions give rise to stereoisomeric products in unequal amounts.

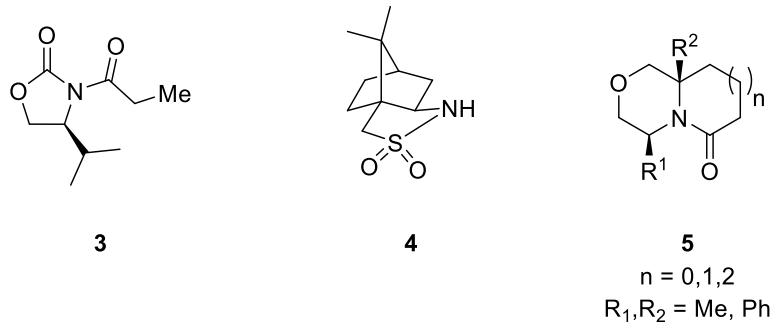
1.2.1 Chiral auxiliaries

The employment of chiral small molecules is based on the temporarily covalent incorporation of a chiral moiety in a prochiral substrate. The process requires high diastereoselectivity in the formation of the new elements, simple separation of the created diastereomeric products and recovery of the chiral auxiliary. The main handicap of this process is that stoichiometric amounts of the chiral auxiliary are necessary. Furthermore, the additional synthetic steps that take place during the whole transformation are also a limitation.

Some of the most robust chiral auxiliaries found in literature are the Evan's oxazolidinones **3**[12] and the Oppolzer's sultames **4**[13]. Additionally, the bicyclic lactams **5**

[7] Anderson, N. G. *Org. Proc. Res. Dev*. **2005**, *9*, 800-813.
[8] Ros, A.; Magritz, A.; Dietrich, H.; Fernández, R.; Álvarez, E.; Lassaletta, J. M. *Org. Lett.* **2006**, *8*, 127-130.
[9] Muñoz-Torrero, D. *Recent Advances in Pharmaceutical Sciences II*, Transworld Research Network: Kerala, **2012**.
[10] Roos, G. *Key Chiral Auxiliary Applications*, Academic Press: New York, **2014**.
[11] McNaught, A. D.; Wilkinson, A. *IUPAC. Compendium of Chemical Terminology 2nd Ed*, Blackwell Scientific Publications: Oxford, **1997**.
[12] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737-1739.
[13] Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett*. **1989**, *30*, 5603-5606.

discovered by Meyers[14] play an important role for the synthesis of alkaloids and nitrogen-containing bioactive compounds (**Figure 1.3**).



3 **4** **5**

n = 0,1,2

R_1,R_2 = Me, Ph

Figure 1.3. Main chiral auxiliaries.

1.2.2 Asymmetric catalysis

With the aim of lowering the stoichiometric amount required by chiral auxiliaries, *asymmetric catalysis* has growth sharply during the last decades. The latter technique transfers chiral information by substoichiometric quantities of a chiral molecule, selectively accelerating the reaction that brings selectively one enantiomer. As Nicolaou reported, "In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used for producing large quantities of an optically active compound from a precursor that may be chiral or achiral".[15] It has become a more direct and atom-economic approach avoiding additional synthetic steps.

For several years, two main efficient methodologies have been considered in the field of asymmetric catalysis: *biocatalysis* and *synthetic metal complexes*. However, since the beginning of the last century a third powerful strategy has emerged in which a purely organic and metal free small molecule is used for catalysing a chemical reaction.[16] Its rebirth has led to the coining of the *asymmetric organocatalysis* term.

In *biocatalysis*[17] an enzyme carries out the acceleration of the chemical process. Thanks to the diversity of the amino acids present in Nature, these processes are highly chemo-, regio-, diastereo-, and enantioselective. Moreover, these reactions operate under environmentally friendly conditions. On the other hand, it constitutes a more limited

[14] Meyers, A. I.; Brengel. G. P. *Chem. Commun*. **1997**, 1-8.
[15] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*, Wiley-VCH: Weinheim, **1996**.
[16] List, B.; Yang, J. W. *Science* **2006**, *313*, 1584-1586.
[17] a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, Wiley-VCH: Weinheim, **2002**. b) Schramm, V. L. *Chem. Rev*. **2006**, *106*, 3029-3030. c) Patel, R. N. *Coord. Chem. Rev*. **2008**, *252*, 659-701.

strategy, mainly owing to the high selectivity that enzymes show, which limits the scope of tolerated substrates.

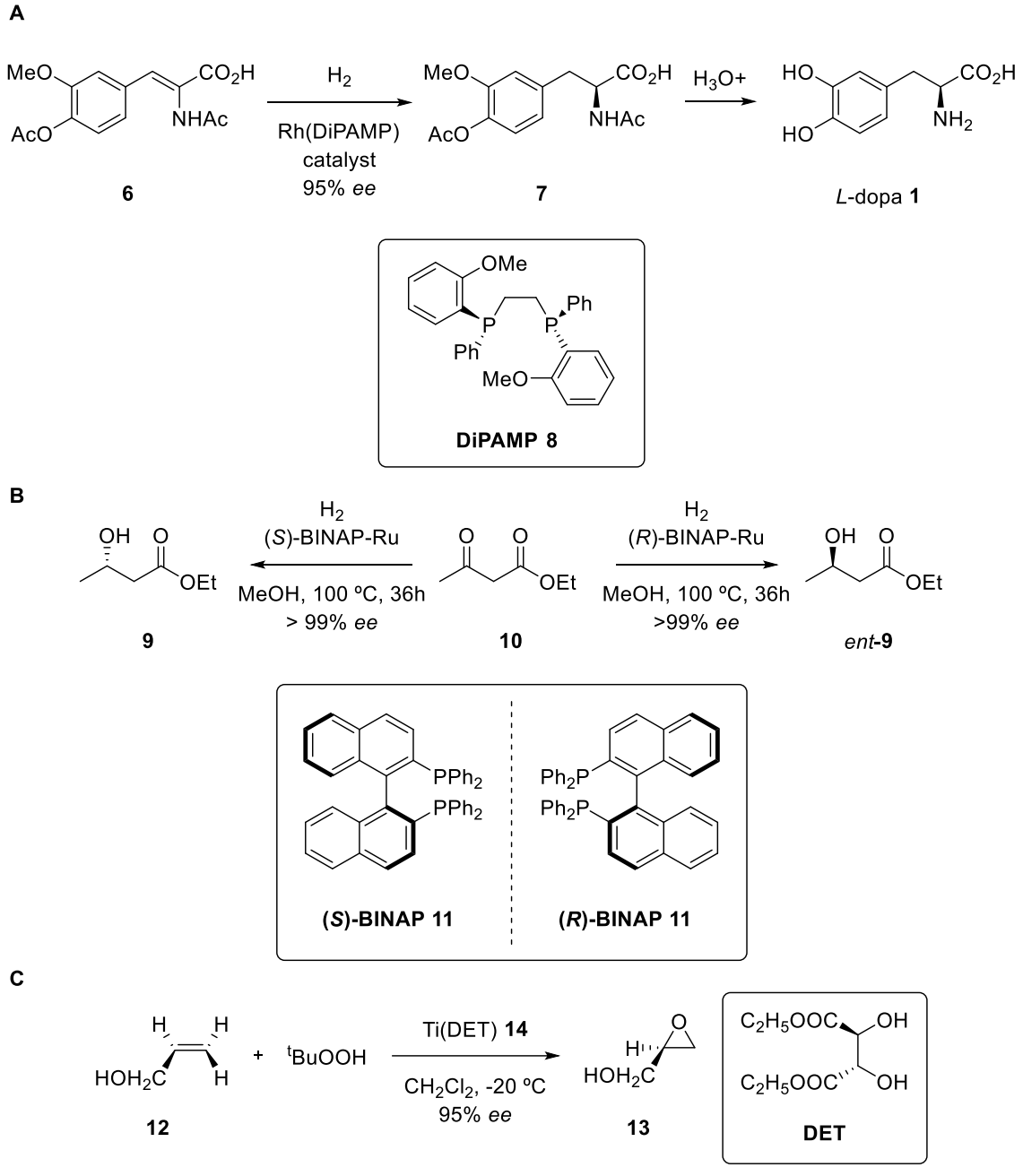
The general principle of *metal catalysis*[2] is the combination of substrates with a small amount of a chiral catalyst containing at least one metallic centre to produce the chiral compound in a stereoselective manner. The mechanism comprises first the coordination of one or both reagents to the metal-ligand complex. Thanks to the proximity of the chiral information around the metallic centre the bond forming step takes place in a stereoselective manner. One last elimination process allows to release the product and the recovery of the catalyst for the next catalytic cycles. The chiral metal-ligand complex must hold suitable three-dimensional structure and functionality so as to generate sufficient reactivity and stereoselectivity.

As an illustrative example of the high value and tremendous impact of these catalytic processes, the Nobel Prize in Chemistry 2011 was jointly awarded to Professors W.S. Knowles, R. Noyori and K.B. Sharpless. Both of the first scientists discovered and worked on asymmetric hydrogenation reactions, whereas the last developed chiral catalysts for asymmetric epoxidation reactions. In 1968 William S. Knowles recognized a catalytic asymmetric hydrogenation reaction of a prochiral olefin **6** in which rhodium and a symmetry bearing C2 phospine ligand (*R*,*R*)-DiPAMP **8** were used as chiral source (**Scheme 1.1A**).[18] The methodology quickly expanded to industry (Monsanto) creating a commercial synthesis of the amino acid *L*-dopa, useful in the treatment of Parkinson's disease. In a similar fashion, Professor R. Noyori proposed a hydrogenation transformation of simple ketone **10** making use of rutenium-BINAP catalyst **11** (**Scheme 1.1B**).[19] These latter enantiomeric catalysts are used for the synthesis of fine chemicals and pharmaceutical products. Besides, K. B. Sharpless expanded the oxidation reaction of the olefinic alcohol **12** to prepare the epoxyalcohol **13** by the use of a titanium-diethyl tartrate complex **14** (**Scheme 1.1C**).[20]

Nowadays the metal catalysis enjoys an elevate grade of development comprising oxidation, reduction, insertion to σ-bonds and π-bond activation reactions, together with reactions catalysed by Lewis acids. Despite its many advantages, organometallic complexes are usually expensive and require strict reaction conditions. Additionally, the toxicity as well as environmental issues and contamination of the final product can make this methodology difficult to apply to the synthesis of commercially available drugs.

[18] Knowles, W. *Adv. Synth. Catal*. **2003**, *345*, 3-13.
[19] Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.
[20] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974-5976.

It is well-known that Nature, our source of inspiration, does not utilize organometallic cofactors for the vast majority of the biocatalytic processes. Thereby, the scientific community has made great efforts for creating metal-free synthetic approaches and the last years have witnessed an impressive growth in catalytic methods based on organic molecules (*organocatalysis*).

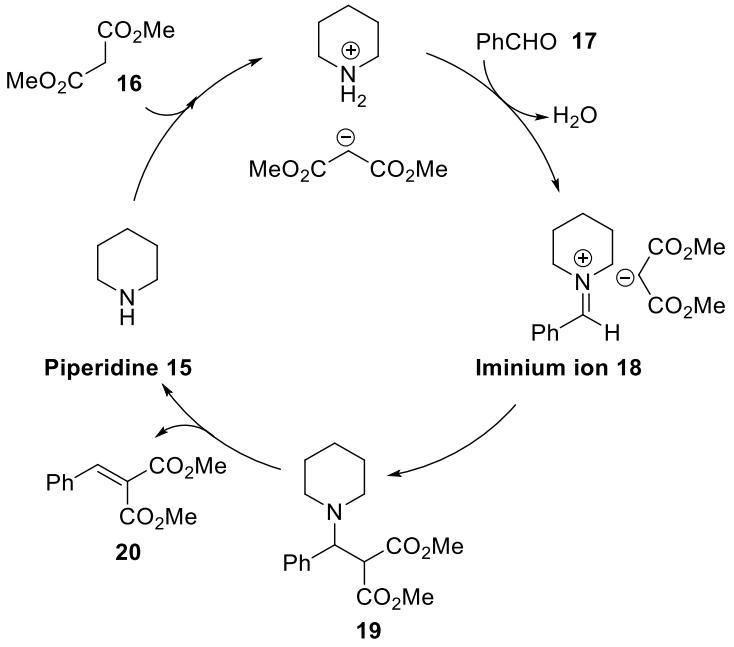


Scheme 1.1. A) Catalytic asymmetric hydrogenation for the synthesis of *L*-dopa by Professor Knowles. B) Catalytic asymmetric hydrogenation process for simple ketones developed by Noyori. C) Sharpless' asymmetric epoxidation of olefinic alcohols.

1.3 ASYMMETRIC ORGANOCATALYSIS

Organocatalysis is defined as the acceleration of chemical reactions employing a substoichiometric quantity of a chiral organic compound which does not contain a metal atom.[21] This strategy shows several advantages compared to conventional organometallic catalysis: organocatalysts are non-toxic, robust and tipically available from commercial sources or easy to synthesise. Of particular interest is their inertness towards moisture and oxygen, so harsh and demanding reaction conditions are not required. They are tolerant to numerous functional groups and there is no necessity of time-consuming protection-deprotection manipulations. Last but not least, these type of catalysts can be easily incorporated onto a support facilitating their recovery and recycling.[22]

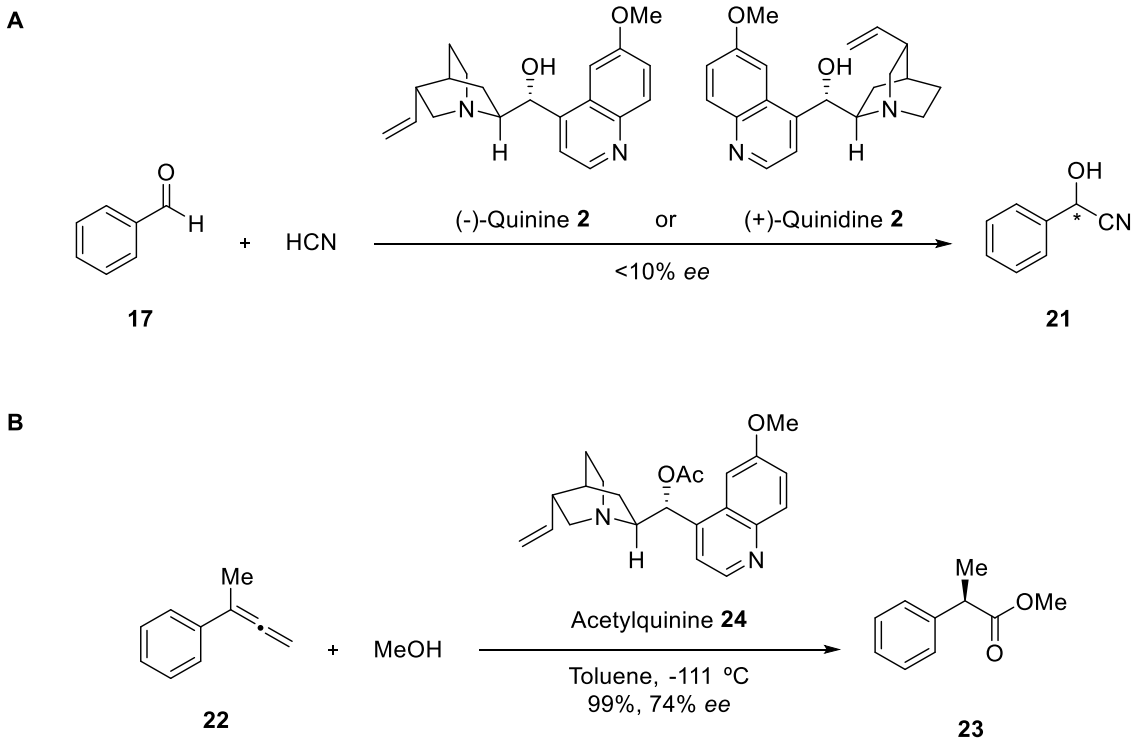
The first attempts in this field were carried out a century ago. In 1896 Emil Knoevenagel found that primary and secondary amines, as well as their salts, catalysed the aldol condensation of β-ketoesters or malonates with aldehydes or ketones (**Scheme 1.2**).[23] The mechanism is believed to go through the iminium ion **18** formed from the condensation of piperidine **15** with benzaldehyde **17**.



Scheme 1.2. Knoevenagel's condensation reaction between dimethyl malonate **16** and benzaldehyde **17** catalysed by piperidine **15**.

[21] Dalko, P. I., Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138-5175.
[22] a) Alemán, J.; Cabrera, S. *Chem. Soc. Rev*. **2013**, *42*, 774-793. b) Pellisier, H. *Tetrahedron* **2007**, *63*, 9267-9331.
[23] Knoevenagel, E. *Ber. Dtsch. Chem. Ges*. **1896**, *29*, 172-174. For a review in Knoevenagel's work, see: List, B. Angew. *Chem., Int. Ed.* **2010**, *49*, 1730-1734.

Some years after Bredig and Fiske reported the asymmetric addition of HCN to benzaldehyde **17** catalysed by quinine or quinidine **2**, but low enantiomeric excess values were observed, below 10% (**Scheme 1.3A**).[24] The first organocatalytic asymmetric reaction achieving high levels of enantioselection was reported by Pracejus in 1960 (**Scheme 1.3B**).[25] This author published the organocatalytic methanolysis of methyl phenyl ketene **22** by means of acetylquinine **24**. These reactions are considered pioneering in the use of *cinchona* alkaloid-based catalysts for organocatalytic transformations.

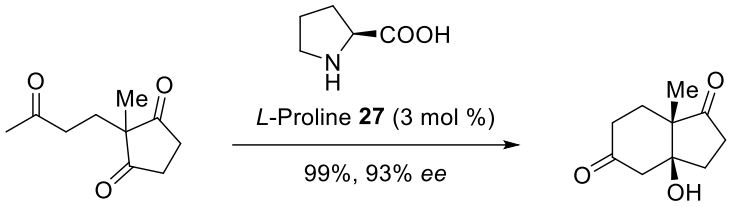


Scheme 1.3. *Cinchona* alkaloid based organocatalytic transformations carried out by A) Bredig and B) Pracejus.

Another remarkable milestone in the field of organocatalysis was the intramolecular enantiogroup-differentiating aldol reaction catalysed by *L*-Proline **27** developed independently by Hajos and Parrish and by Eder, Sauer and Wiechert in the early 1970's (**Scheme 1.4**).[26] This reaction, mimicking type I aldolases and catalytic aldolase antibodies, allows the synthesis of key intermediates for the generation of some natural products. It must be noted that the transformation is based on the Stork enamine reaction

[24] Bredig, G.; Fiske, P. S. *Biochem Z*., **1912**, *46*, 7-23.
[25] Pracejus, H. *Justus Liebigs Ann. Chem*. **1960**, *634*, 9-22.
[26] a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615-1621. b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed*. **1971**, *10*, 496-497.

in which a substoichiometric amount of the secondary amine pyrrolidine could provide a reversible formation of a nucleophilic enamine.[27]

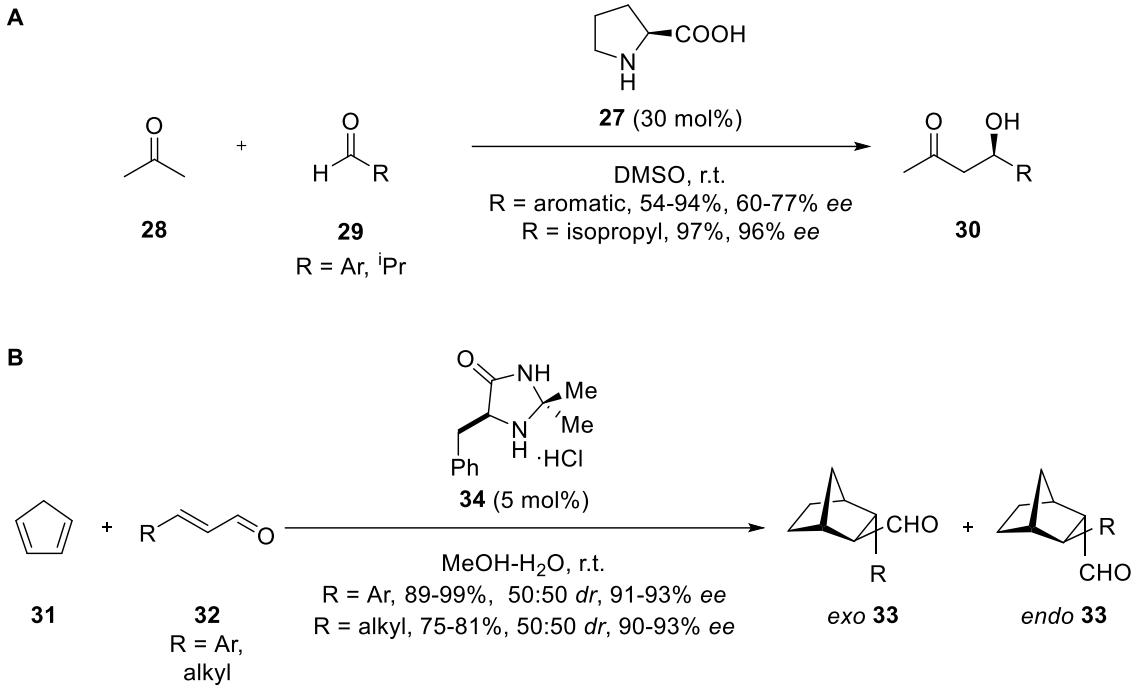


25 **26**

Scheme 1.4. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

Despite these reactions evidenced for the first time that small organic molecules could be of high importance in the area of chemical synthesis, it was not until 2000 that the field of organocatalysis was definitely settled down. Two simultaneous publications, one by Carlos Barbas III, Richard Lerner and Benjamin List on enamine catalysis[28] and the other by MacMillan's group on iminium catalysis, were determining for its launching.[29] Barbas III and co-workers proposed *L*-Proline **27** as an efficient catalyst for the direct intermolecular asymmetric aldol reaction between acetone **28** and a variety of aldehydes (**Scheme 1.5A**). MacMillan, besides, enabled the first highly enantioselective amine catalysed Diels-Alder reaction between cyclopentadiene **31** and diverse aldehydes promoted by imidazolidinone salt **34** (**Scheme 1.5B**).

[27] a) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res*. **2004**, *37*, 580-591. b) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc*. **1954**, *76*, 2029-2030.
[28] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **1998**, *120*, 2395-2396.
[29] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.



Scheme 1.5. A) Intermolecular asymmetric aldol reaction reported by Barbas III. B) Diels-Alder cycloaddition developed by MacMillan.

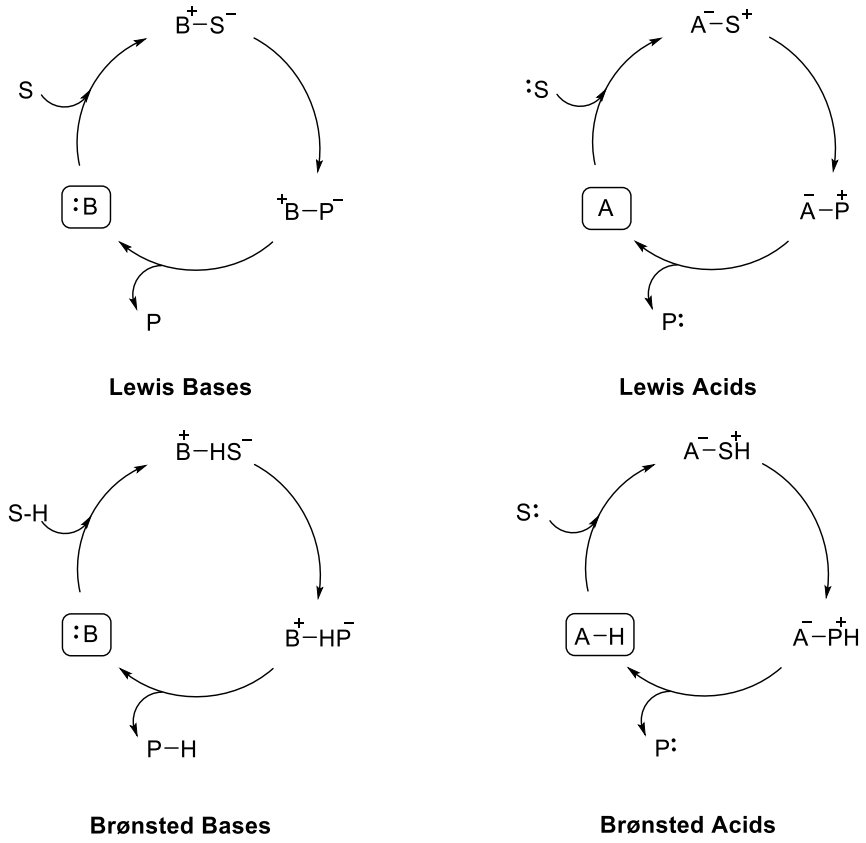
Even though several transformations have been put forward in this field, it is worth noting that very few activation modes have been identified so far. However, this fact should not be taken as a downside, but as a strength, giving evidence of the conceptual simplicity of organocatalysts. The following section focuses more deeply into this area.

1.3.1 Activation methods in organocatalysis

During the development of organocatalysis, several authors have reported different criteria when classifying activation modes. While one classification takes into account the acid/base reactivity of organocatalysts, an alternative and more widely used framework depends on the nature of the reversible interaction between the catalyst and the substrate.

As for the former arrangement, most organocatalysts can be divided into four groups: Lewis acids, Lewis bases, Brønsted acids and Brønsted bases (**Scheme 1.6**).[30]

[30] Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719-724.



Scheme 1.6. Catalytic cycles by organocatalysts acidic/basic nature.

In Lewis base organocatalysis, the acceleration of the transformation is accomplished by the influence of an electron-pair donor over an electron-pair acceptor, providing a transfer in electron density to the acceptor fragment of the new adduct (**Scheme 1.6**).[31] Lewis bases (B) initiate the catalytic cycle via nucleophilic addition or substitution to one of the substrates (S). The resulting complex (B^+S^-) undergoes a reaction and releases the product (P) and the catalyst for further catalytic cycles. Similarly, Lewis acid catalysts work via an electrophilic addition of the Lewis acid organocatalyst (A) to the substrate, generating the intermediate (A^-S^+). The majority of Lewis bases contain donor atoms such as nitrogen, oxygen, phorphorus and sulfur. Among them, aminocatalysts and *N*-heterocyclic carbenes[32] deserve special relevance. Phase transfer catalysts by quaternary ammonium salts,[33] chiral *N*-oxides[34] and Denmark's phosphoramides[35] are included in the family of Lewis acid catalysts.

[31] Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed*. **2008**, *47*, 1560-1638.
[32] Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534-541.
[33] Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2007**, *107*, 5656-5682.
[34] a) Malkov, A.; Kočovský, P. *Eur. J. Org. Chem*. **2007**, 29-36. b) Chen, J.; Takenaka, N. *Chem. Eur. J.* **2009**, *15*, 7268-7276.
[35] Denmark, S. E. *Chimia* **2008**, *62*, 37-40.

On the other hand, Brønsted bases activate the pro-nucleophile by deprotonation, providing a more reactive species (B^+HS^-). Brønsted acids, instead, activate the substrate by protonation or H-bonding interactions. The more reactive adduct A^-PH^+ undergoes a last deprotonation reaction that gives rise to the final product with concomitant recovery of the catalyst (**Scheme 1.6**).[36] According to these cited features, chiral amines[37] or guanidines[38] would belong to the Brønsted base group. BINOL-derived phosphoric acids[39] and phosphamides,[40] instead, are one of the most prominent players of the Brønsted acid category.

Regarding the nature of the bonding between the catalyst and the substrate two generic groups can be distinguished: non-covalent and covalent catalysis.[41] Although Langebeck described these typologies in 1949, the disposition still remains applicable to the contemporary era (**Figure 1.4**).

[36] Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev*. **2009**, *38*, 632-653.
[37] Wu. F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed*. **2006**, *45*, 947-950.
[38] Ye, W.; Jiang, Z.; Zhao, Y.; Goh, S. L. M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal*. **2007**, *349*, 2454-2458.
[39] a) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem*. **2011**, 2209-2222. b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269-279. c) Zamfir, A., Schenker, S., Freund, M., Tsogoeva, S. B. *Org. Biomol. Chem*. **2010**, *8*, 5262-5276.
[40] a) Johnston, J. N. *Angew. Chem., Int. Ed*. **2011**, *50*, 2890-2891. b) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed*. **2011**, *50*, 6706-6720. c) Cheon, C.-H.; Yamamoto, H. *Chem. Commun*. **2011**, *47*, 3043-3056.
[41] Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerfull Tool for the Stereocontrolled Synthesis of Complex Molecules*, The Royal Society of Chemistry (RSC Catalysis): Cambridge, **2010**.

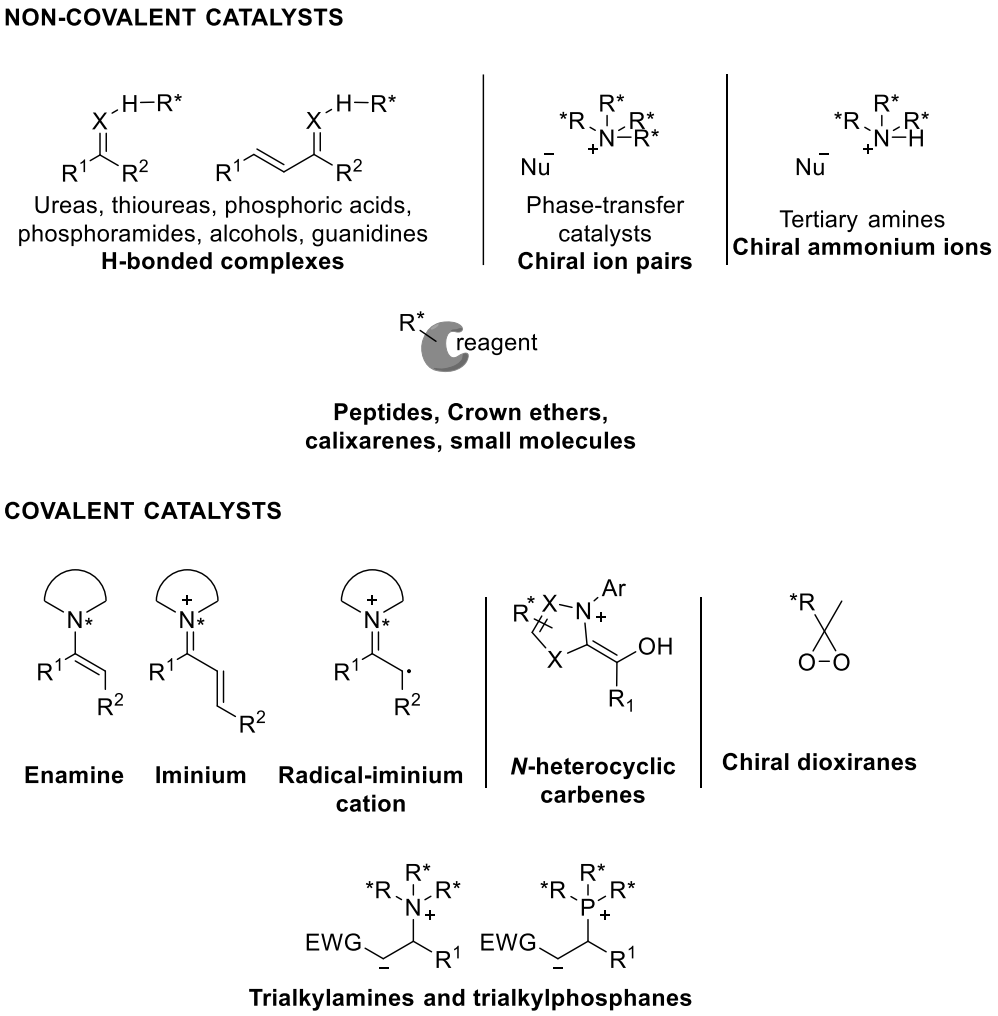


Figure 1.4. Organocatalysts classified by the non-covalent/covalent character of the interactions they form.

The non-covalent catalysis encloses the neutral substrate-catalyst complexation or the acid-base ion pair formation. The most relevant activation mechanism among non-covalent catalysts involves the formation of hydrogen-bond complexes by ureas, thioureas, phosphoric acids and other molecules. Other relevant methodologies are the formation of chiral ion pairs in phase-transfer catalysis and the use of chiral tertiary amines in the activation of a nucleophile by deprotonation in chiral ammonium salts.

The activation modes that entail the strong nature of a covalent bond are the most widely applied types of organocatalysts. This covalent catalytic pathway requires reversible chemical transformations for the attaching and detaching of the catalyst to the substrate/final product in order to allow activation and catalyst turnover. Some significant catalysts are *N*-heterocyclic carbenes, chiral oxiranes[42] used for oxidation reactions, as well as trialkylphosphines and trialkylamines employed in Morita-Baylis-Hillman

[42] Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847-859.

reactions.[43] Special mention deserves the aminocatalysis, where the activation is given by the interaction of the substrate with primary or secondary chiral amines. These amines can act by forming three different species: enamines, iminium ions and SOMO iminium-radicals. The formation of each species depends on the nature of the activated substrate. Enamine activation via HOMO raising enables the formation of α, γ, ε-functionalised carbonyl compounds, whereas iminium-ion activation via LUMO lowering generates β-functionalised compounds by the reaction between α,β-unsaturated carbonyl compounds and nucleophiles. To last, organocatalysts properly activated by photoredox systems generate SOMO radical species. [44]

Aminocatalysts that operate under covalent and non-covalent activation modes comprise a large variety of organocatalysts. Among them, unnatural amino acid-based derivatives provide a significant expansion of the configurational space via *de novo* design of novel catalytic species. Some of the most representative examples will be disclosed next.

1. 4 UNNATURAL AMINO ACID-DERIVED ORGANOCATALYSTS

L-Proline[45] has undoubtedly been the catalyst of choice for organocatalytic transformations due to its versatility and efficiency. However, solubility issues in organic solvents, long reaction times, high catalyst loads and required strong polar solvents led to the development of more reactive catalysts. Hence, along the 21st century, unnatural amino acids have emerged as interesting catalysts for the most important and well-known C-C bond forming transformations. Many of these compounds were already available, as a consequence of their implementation into peptide mimics and isosteres, their utility as versatile chiral intermediates and their interest in agrochemical, pharmaceutical and food industry.[46]

The term *unnatural* includes all except the natural twenty two *L*-α-amino acids that constitute proteins and peptides. Additionally, unnatural amino acids are not biosynthetically incorporated into proteins during translation. They can be found

[43] a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev*. **2009**, *109*, 1-48. b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev*. **2007**, *36*, 1581-1588. c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed*. **2007**, *46*, 4614-4628.
[44] a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, *38*, 2178-2189. b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308.
[45] Liu, J.; Wang, L.; *Synthesis*, **2017**, *49*, 960-972.
[46] Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas III, C. F. *J. Org. Chem*. **2003**, *68*, 9624-9634.

post-translationally in plants and bacteria or chemically synthesised.[47] The most representative families amid post-translational derivatives include 4-hydroxy-*L*-proline and 4-amino-*L*-proline scaffolds. Among synthetic organocatalysts, on the other side, β-prolines and unnatural pyrrolidine-based derivatives should be highlighted. The most representative families of these organocatalysts are detailed next.

1.4.1 Unnatural organocatalysts from Post Translational Modification (PTM) processes

PTM processes represent one useful route to expand the family of non-proteinogenic amino acids. The functional diversity is given by the proteolytic cleavage of regulatory subunits, by degradation of entire proteins or by covalent modifications that occur on the backbone or side chains once DNA has been transcribed into RNA and translated into proteins.[48]

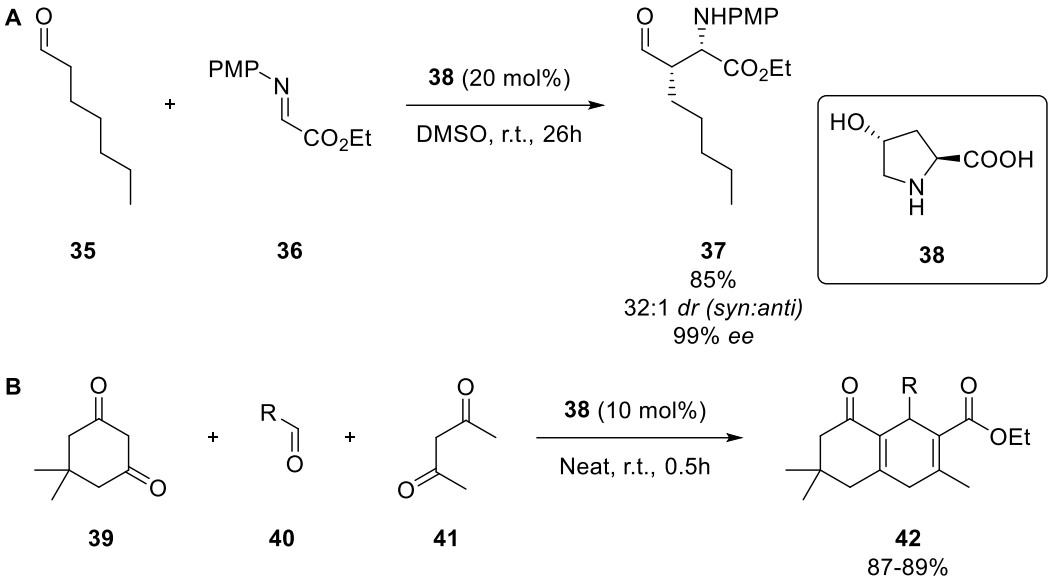
1.4.1.1 *Trans*-4-Hydroxyproline-based organocatalysts

This amino acid is biosynthesised by prolyl 4-hydroxylase[49], a 2-oxoglutarate dioxygenase that catalyses the hydroxylation of proline-containing peptides and proteins such as collagen. (2*S*,4*R*)-4-hydroxyproline derivatives have been widely used in a large variety of organic transformations such as the Mannich reaction,[45,50] the *O*-nitroso aldol/Michael transformation[50a] and the three-component Strecker reaction[51]. Nevertheless, the aldol reaction is undoubtedly the transformation that most benefits from *trans*-4-hydroxyproline derivatives. In order to facilitate the understanding and classification, the following disclosure will present the different catalysts classified according to the substitution pattern of the hydroxyl group: alcohol, ether, silylether, ester and hydroxy anchored polymer derivatives.

Hydroxy derivatives: (2*S*,4*R*)-4-hydroxyproline **38** itself was used by Barbas III in the Mannich reaction between heptanal **35** and α-imino ethyl glioxylate **36** in polar organic solvents to afford *syn* α-amino ester **37** with good yield and high stereoselectivity (**Scheme 1.7A**).[46] This reaction was further studied by Zhao and co-workers. In 2007,

[47] Pollegioni, L.; Servi, S. *Unnatural Amino Acids: Methods and Protocols*, Humana Press: New York, **2011**.
[48] a) Walsh, C. T.; Garneau-Tsodikova, S.; Gatto, G. J. *Angew. Chem., Int. Ed*. **2005**, *44*, 7342-7372. b) Carter, M.; Shieh, J. *Guide to Research Techniques in Neuroscience 2nd Ed*, Academic Press: Oxford, **2015**.
[49] Gorres, K. L.; Raines, R. T. *Critical Rev. Biochem. Mol. Biol*. **2010**, *45*, 106-124.
[50] a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal*. **2004**, *346*, 1435-1439. b) Veverková, E.; Liptáková, L.; Veverka, M.; Šebesta, R. *Tetrahedron: Asymmetry* **2013**, *24*, 548-552.
[51] Wen, Y.; Gao, B.; Fu, Y.; Dong, S.; Liu, X.; Feng, X. *Chem*. *Eur. J*. **2008**, *14*, 6789-6795.

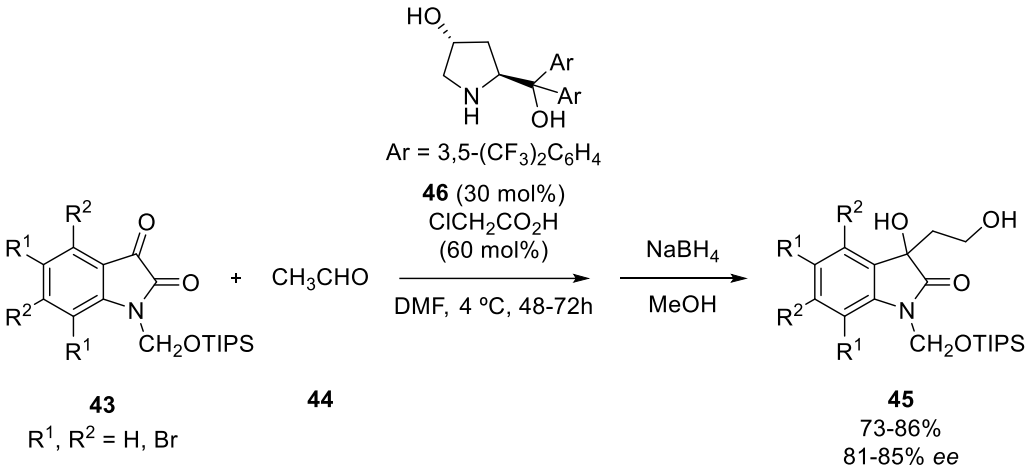
the research group led by Maurya reported the solvent free three-component unsymmetric Hantzsch reaction promoted by catalyst **38**, in which a number of polyhydroquinoline derivatives **42** were synthesised (**Scheme 1.7B**).[52] Unfortunately, the authors did not report the enantioselectivity of the reaction.



Scheme 1.7. (2*S*,4*R*)-4-hydroxyproline catalysed A) Mannich and B) Hantzsch reactions.

To last, in 2009, Hayashi and co-workers described the asymmetric aldol reaction of isatin derivatives **43** and acetaldehyde **44** employing a 4-hydroxydiarylprolinol derivative **46** as organocatalyst. The methodology led to the desired aldol products in good yields and enantioselectivities, enabling the synthesis of useful chiral intermediates for the obtaining of biologically active indole scaffolds (**Scheme 1.8**).[53] Interestingly, the absolute configuration of the final aldol product was reversed when a large substituent was placed in the C5 position of the isatin derivative.

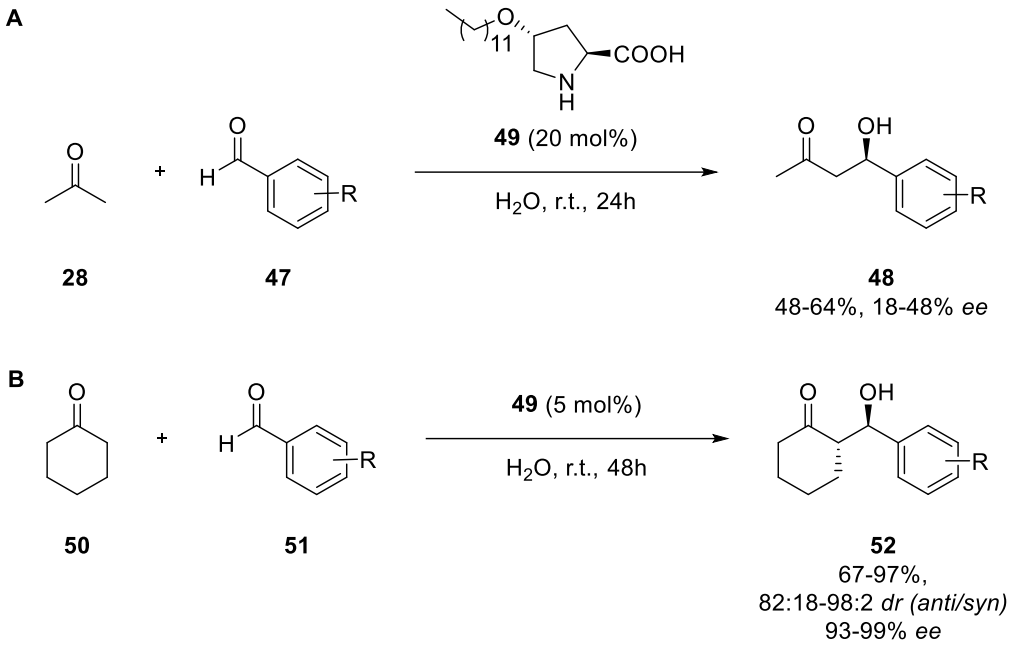
[52] Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1946-1952.
[53] Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett*. **2009**, *11*, 3854-3857.



Scheme 1.8. The asymmetric aldol reaction of acetaldehyde and isatin derivatives developed by Hayashi and co-workers.

Ether derivatives: The use of 4-hydroxyproline ether derivatives has not been widely studied. As far as literature is concerned, two different reports can be found regarding the employment of 4-hydroxyproline based ether catalysts. The description of the first derivative dates back to 2005. Therein, a β-cyclodextrin-immobilized (4*S*)-phenoxy-(*S*)-proline could efficiently promote the aldol reaction between acetone and several substituted benzaldehydes with high yields and moderate to good enantiomeric excesses. The organocatalyst could maintain its activity over four runs, and the product was easily recovered from the catalyst by simple filtration.[54] Independently, Tao and co-workers accomplished another remarkable achievement making use of an amphiphilic proline derived organocatalyst **49** bearing a long alkyl chain on the 4-position. Catalyst **49** promoted the aldol reaction of acetone and various aldehydes in organic solvents and water, furnishing the final *anti*-**48** products in moderate yields and enantioselectivities (**Scheme 1.9A**). Surprisingly, the configuration of the final anti adduct was found to be related to the amount of water. Besides, when cyclic ketones were chosen as aldol donors, high yields and excellent diastereo- and enantioselectivities were observed with 5 mol% of catalyst (**Scheme 1.9B**).[55]

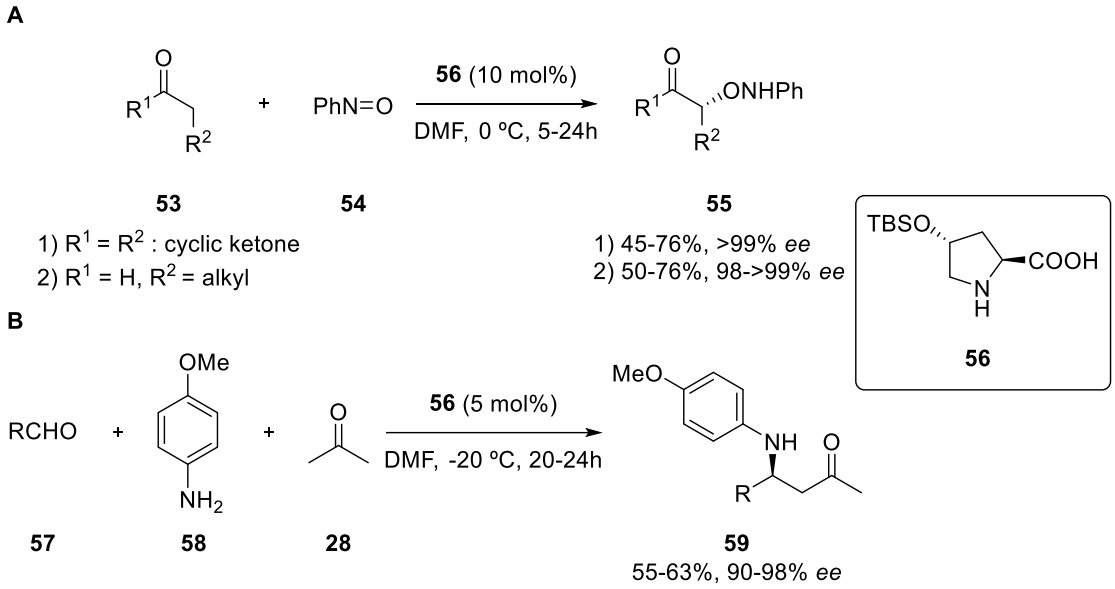
[54] Shen, Z.; Ma, J.; Liu, Y.; Jiao, C.; Li, M.; Zhang, Y. *Chirality* **2005**, *17*, 556-558.
[55] Fu, Y.-Q.; An, Y.-J.; Liu, W.-M.; Li, Z.-C.; Zhang, G.; Tao, J.-C. *Catal. Lett*. **2008**, *124*, 397-404.



Scheme 1.9. 4-hydroxyproline ether **49** promoted aldol reaction of A) acetone and B) cyclohexanone in water.

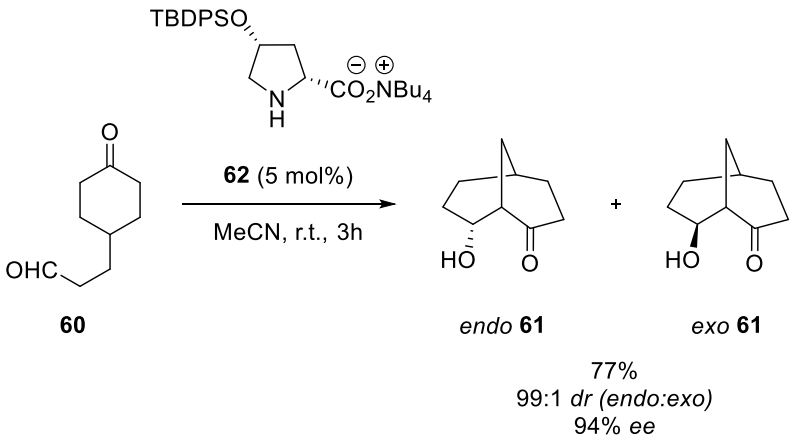
Silylether derivatives: 4-Silyletherprolines constitute another valuable family of organocatalysts for asymmetric transformations. In 2004, the research group led by Hayashi developed a highly active 4-siloxyproline catalyst **56** for diverse asymmetric transformations, aiming to overcome the poor reproducibility of the reactions with *L*-Proline due to its low solubility in organic solvents. The 4-siloxyproline **56** exhibited better reactivity and excellent enantioselectivity in *O*-nitroso aldol/Michael reactions of various aldehydes and ketones, enabling to reduce the catalyst load to 10 mol% (**Scheme 1.10A**).[50a] This catalyst was useful not only for nitroso aldol/Michael processes, but also in Mannich transformations, in which catalyst **56** produced the corresponding adducts in moderate yields and excellent enantioselectivities (**Scheme 1.10B**). A year after, Enders et al. reported a **56** promoted organocatalytic asymmetric three-component Mannich reaction in which the final products were obtained with high yields, diastereo- and enantioselectivities. This Mannich transformation constituted a facile route towards the synthesis of different amino sugars with high diversity.[56]

[56] Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed*. **2005**, *44*, 4079-4083.



Scheme 1.10. Asymmetric A) *O*-nitroso aldol/Michael and B) three-component Mannich reaction reported by Hayashi.

Also in 2005, Iwabuchi and co-workers described an efficient **62** catalysed intramolecular aldolization of σ-symmetric keto-aldehyde **60** (**Scheme 1.11**).[57] The reaction proceeded with high chemo-, diastereo- and enentioselectivities at room temperature giving rise to *endo*-**61** bicyclo systems, potentially useful as chiral building blocks in target oriented synthesis. Unfortunately, the role of TBDPSoxy group and the tetrabutylammonoium salt in the reaction system could not have been elucidated, although the former was considered to be crucial in the enantiodiscrimination.

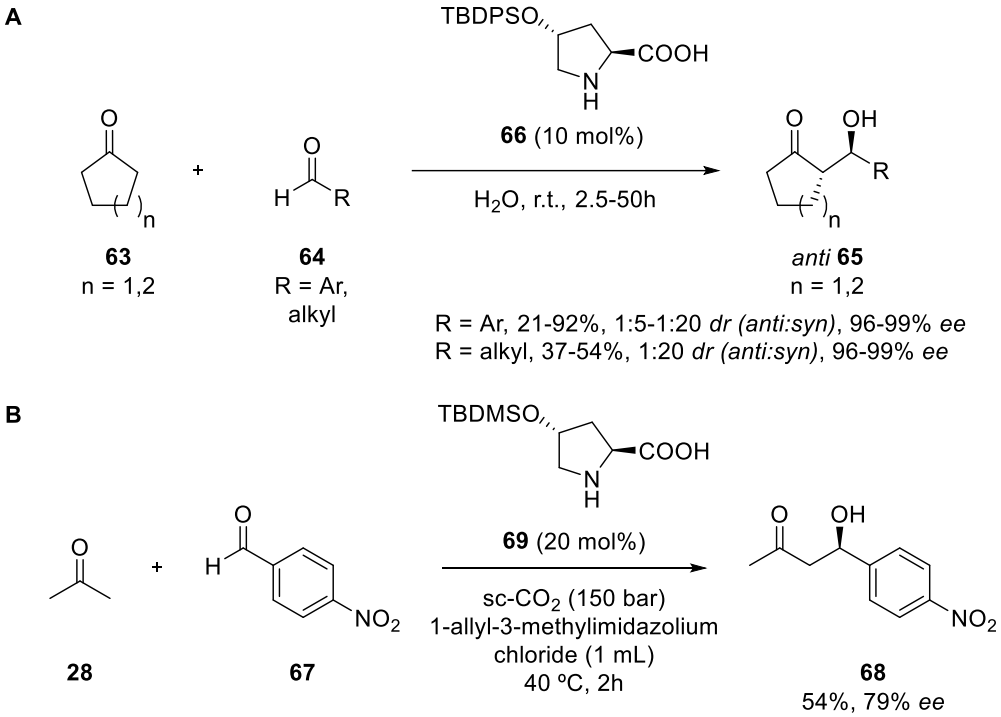


Scheme 1.11. The organocatalytic aldolization of keto-aldehyde **60** reported by Iwabuchi.

Other 4-siloxyprolines were also synthesised and tested for direct asymmetric aldol reactions. In 2006, Hayashi and co-workers developed the first diastereo- and

[57] Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett*. **2005**, *7*, 4185-4188.

enantioselective aldol reaction in the presence of water. The transformation was applicable to a broad variety of nucleophilic ketones and to both electron-rich and electron-defficient aldehydes, with 10 mol% catalyst (**Scheme 1.12A**).[58] Lastly, in 2013, Cassaro et al. described the use of a set of 4-hydroxyproline derivatives as organocatalysts for the aldol reaction between acetone and *p*-nitrobenzaldehyde in supercritical CO_2 and in biphasic systems containing supercritical CO_2 and imidazole derived ionic liquids. Among the tested derivatives, the *tert*-butyldimethylsilyloxy-*L*-Proline **69** performed best under high pressure and temperature in presence of 1-allyl-3-methylimidazolium chloride as ionic liquid yielding the final product in moderate yield and enantioselectivity (**Scheme 1.12B**).[59]

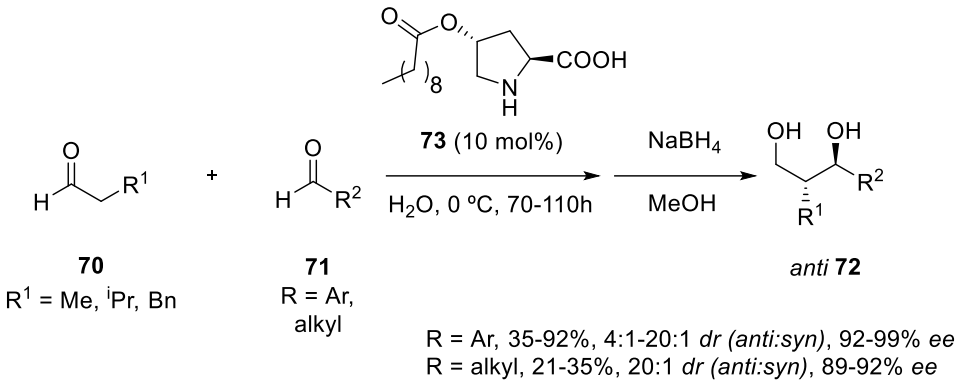


Scheme 1.12. 4-siloxyproline derivatives for the asymmetric aldol reaction between A) cyclic ketones and aryl and alkyl aldehydes and B) acetone and *p*-nitrobenzaldehyde.

Ester derivatives: Many research groups have studied the employment of ester group protected 4-hydroxyproline organocatalysts for asymmetric transformations. In 2006, Hayashi et al. gave an account on a proline-surfactant organocatalyst **73** promoted cross-aldol reaction of two different aldehydes in the presence of water (**Scheme 1.13**).[60] The reaction proceeded smoothly and the long alkyl chain bearing protected derivative

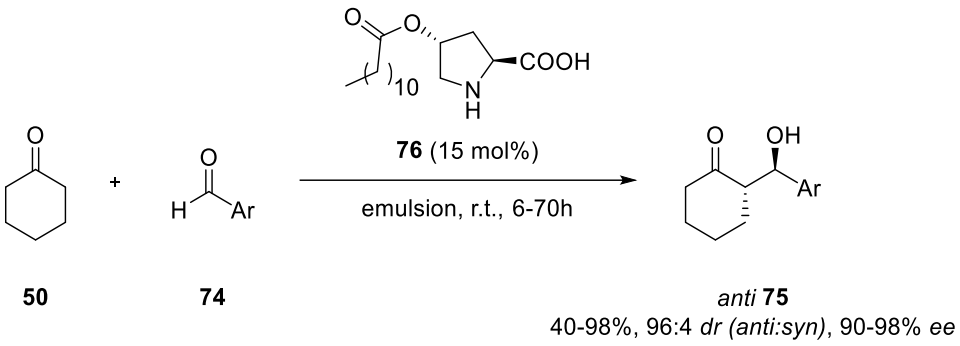
[58] Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 958-961.
[59] Cassaro, R. F.; de Oliveira, L. C.; Gariani, R. A.; do Nascimento, C. A. O.; Bazito, R. C. *Green Process Synth.* **2013**, *2*, 43-50.
[60] Hayashi, Y.; Arakate, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 5527-5529.

furnished the final *anti* **72** aldol products with high diastereo- and enantioselectivity. Curiously, there was no need for neither organic co-solvent nor acidic additive.



Scheme 1.13. The long alkyl-chain containing derivative **73** designed by Hayashi et al. for the cross aldol reaction of two different aldehydes.

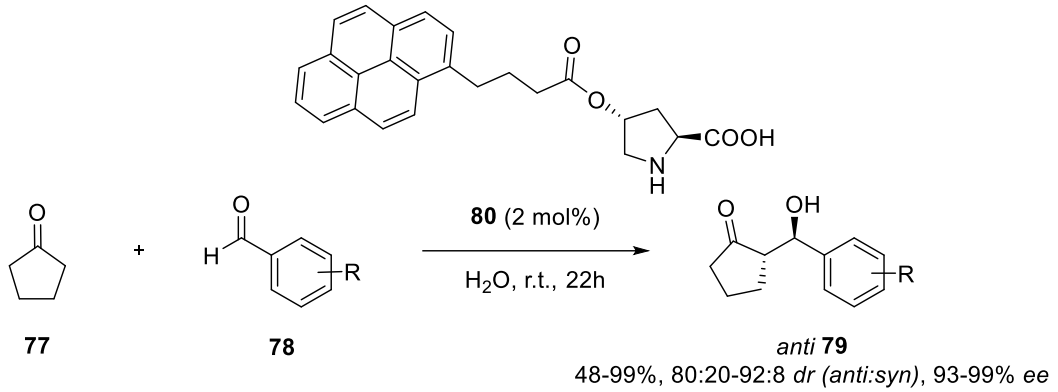
The idea of amphiphilic and surfactant like 4-hydroxyproline-based organocatalysts was further tested by Zhong et al.[61] Together with an extensive substrate scope, they postulated that the balance between hydrophilicity and lipophilicity resulted crucial for the proper distribution of the organocatalyst in the water-oil interface, and hence, for its activity (**Scheme 1.14**).



Scheme 1.14. Direct asymmetric aldol reaction performed by **76** surfactant type catalyst.

Some other research groups evaluated ester group protected 4-hydroxyproline derivatives during 2008. The research group led by Gruttadauria developed a family of hydrophobic catalysts for the asymmetric aldol reaction between various ketones and aldehydes at room temperature, without any additive and with 2 mol% of catalyst.[62] Among the tested substrates, the products obtained from cyclopentanone deserve special remark (**Scheme 1.15**).

[61] Zhong, L.; Gao, Q.; Gao, J.; Xiao, J.; Li, C. *J. Catal*. **2007**, *250*, 360-364.
[62] Giacalone, F.; Gruttadauria, M.; Lo Meo, P.; Riela, S.; Noto, R. *Adv. Synth. Catal*. **2008**, *350*, 2747-2760.

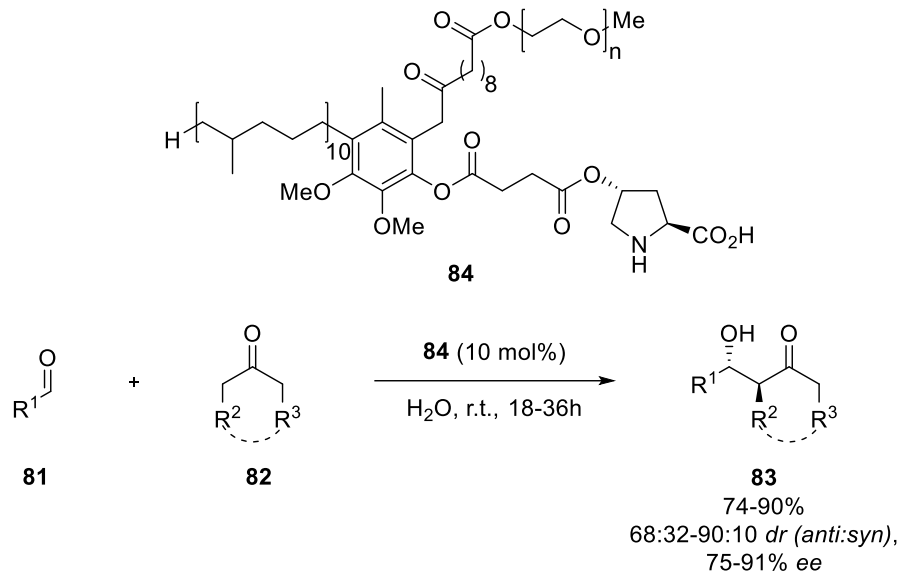


Scheme 1.15. Asymmetric direct aldol reaction between cyclopentanone and aromatic aldehydes catalysed by hydrophobic catalyst **80**.

As the use of ester derivatives began to spread, researchers expressed different opinions concerning the optimal structure of the catalysts. On the one hand, Gruttadauria and co-workers stated that catalysts that do not incorporate more chiral centres than those present in the 4-hydroxyproline scaffold were as efficient as those previously reported for the aldol transformation.[63] On the other hand, Tao produced richly functionalised prolines holding hydrophobic groups for the same catalytic purpose.[64]

In 2012 Lipshutz and Ghorai[65] reported the design and assessment of complex organocatalysts **84** derived from (2*S*,4*R*)-4-hydroxyproline attached to a coenzyme Q_{10}-derived scaffold that, in turn, included a long lipophilic side chain and a MPEG-2000 hydrophilic portion (**Scheme 1.16**). This catalyst promotes efficiently aldol reactions between aromatic aldehydes **81** and cyclic ketones **82**, with high diastereomeric and enantiomeric control. This amphiphilic catalysts self-aggregates in water to form nanoreactors in which the catalytic unit works efficiently at room temperature. Under these conditions, usual extractive work-up is not necessary, and in-flask recycling of catalyst **84** can be performed.

[63] Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Lo Meo, P.; Noto, R. *Eur. J. Org. Chem*. **2010**, 5696-5704.
[64] An. Y.-J.; Zhang, Y.-X.; Wu, Y.; Liu, Z.-M.; Pi, C.; Tao, J.-C. *Tetrahedron: Asymmetry* **2010**, *21*, 688-694.
[65] Lipshutz, B. H.; Ghorai, S. *Org. Lett*. **2012**, *14*, 422-425.

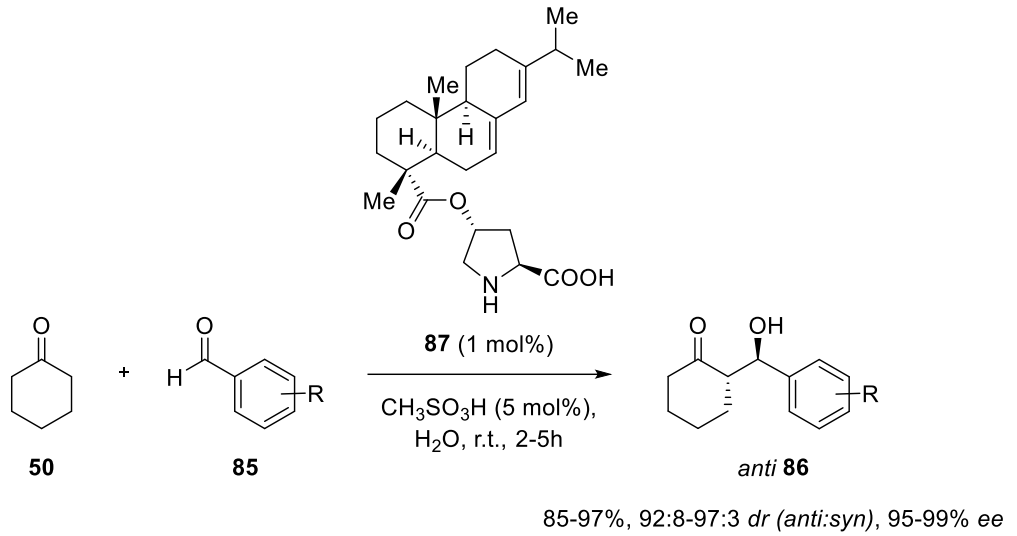


Scheme 1.16. Organocatalyst **84** incorporating hydrophilic and lipophilic units.

In 2013, the scope of organocatalysts that contain a long liphophilic chain was extended successfully to the Mannich transformation between ketones and *N*-protected imines, although the diastereomeric ratio was low and the enantiomeric excess values were moderate.[50b]

In 2014, two different 4-hydroxyproline derivatives were independently studied for the Michael and aldol reaction. Savic and co-workers synthesised a range of derivatives by means of a 1,3-dipolar cycloaddition for the Michael addition of aldehydes and vinyl sulphones but the observed enantioselectivities (52% *ee*) were not of synthetic significance.[66] On the contrary, Bhowmick et al. reported a new catalyst for the aldol reaction bearing abietic acid skeleton in its structure (**Scheme 1.17**). The chemical approach proceeded in presence of a sulfonic acid and it was the first example of the aqueous media mediated reaction with unusually fast reaction rates (all reactions were complete within 6h) even with 1 mol% of catalyts.[67]

[66] Jocanović, P.; Randelović, J.; Ivković, B.; Suteu, C.; Vujošević, Z. T.; Savić, V. *J. Serb. Chem. Soc*. **2014**, *79*, 767-778.
[67] Bhowmick, S.; Kunte, S. S.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2014**, *25*, 1292-1297.



Scheme 1.17. Asymmetric aldol reaction developed by Bhowmick and co-workers.

Also in 2014, Kokotos, Tagmatarchis et al.[68] reported the synthesis and organocatalytic activity of (2*S*,4*R*)-4-hydroxyproline-fullerene hybrids **88** and **89** (**Figure 1.5**). The reaction between acetone and cyclohexanone with 2- and 4-nitrobenzaldehyde furnished the corresponding aldols with up to quantitative yields, but with low to medium enantiomeric excesses.

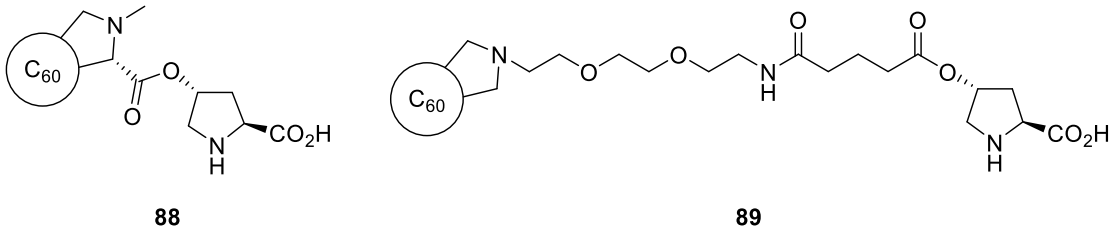


Figure 1.5. Fullerene-proline hybrids with organocatalytic activity in aldol reactions.

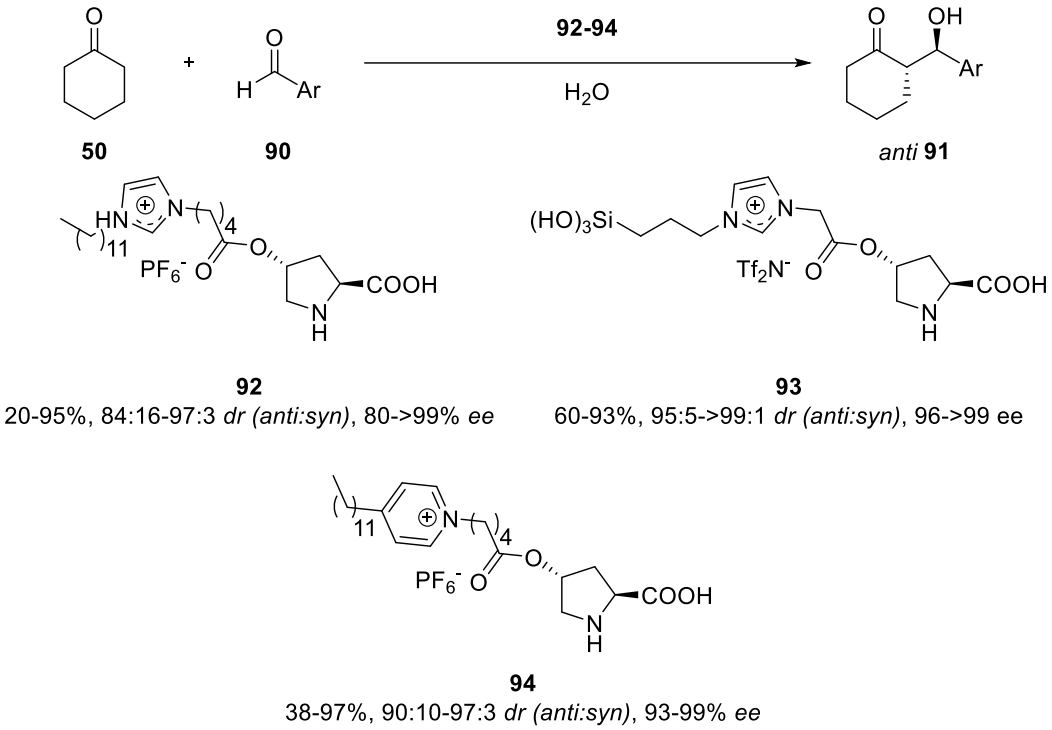
Finally, in 2015 London et al.[69] reported the aldol reaction between acetone and aldehydes catalysed by different esters that incorporate (2*S*,4*R*)-4-hydroxyproline. These authors reported that in the presence of water-PPG425 and NaOAc preferential formation of the (*S*)-aldol was observed with low enantiomeric excesses (ca. 20%), whereas using NH_4Cl the corresponding (*R*)-enantiomer was obtained as major isomers, with ca. 58% *ee*.

Despite the efficient catalytic performance showed by the previously described catalysts, they possessed a weak point in terms of catalyst recovery. With the purpose

[68] Chronopoulos, D. D.; Tsakos, M.; Karousis, N.; Kokotos, C. G.; Tagmatarchis, N. *Mater. Lett*. **2014**, *137*, 343-346.
[69] Gurka, A. A.: Szőri, K.; Szőllősi, G.; Bartók, M.; London, G. *Tetrahedron Lett*. **2015**, *56*, 7201-7205.

of solving this challenge researchers moved to the use of functionalised ionic liquids as reaction media, based on the principle that the solubilities of ionic liquids can be changed to get phase separation from organic and aqueous media by choosing specific anions and cations. In this regard, in 2006, Chen and co-workers employed the first ionic liquid supported proline derivative for the aldol reactions of several aldehydes with acetone.[70] The designed ionic-liquid supported proline showed better catalytic outcomes than *L*-Proline in neat systems (up to 28% *ee* difference). Besides, the catalyst could have been used for four runs with no loss in efficiency. During 2008, the groups of Zlotin and Trombini designed independently chiral amphiphilic 4-hydroxy-α-aminoacids modified by ionic liquids (**Scheme 1.18**). The most efficient derivative **92** developed by Zlotin and co-workers consisted of a chiral imidazolium salt bearing hydrophobic PF_6^- anion in its structure.[71] The catalyst worked as a suspension affording excellent results in the aldol reaction and maintaining its activity over five cycles. Trombini, on the other side, changed the counterion to bis(trifluoromethylsulfonyl)imide (Tf_2N^-).[72] Catalyst **93** operated under biphasic conditions thanks to the best partitioning coefficient exhibited when combining both the hydrophilic cation and the hydrophobic counterion. In terms of catalyst recovery, three entire cycles were conducted without any loss in yield or selectivity. A year after, Zlotin and co-workers reported again another ionic liquid bearing proline derivative to improve catalyst's hydrophobic properties by increasing the C/N ratio of the cationic structure.[73] Shifting the imidazole moiety to pyridine, catalyst **94** retained its activity and selectivity during at least eight reaction cycles.

[70] Miao, W.; Chan, H. *Adv. Synth. Catal*. **2006**, *348*, 1711-1718.
[71] Siyutkin, D. E.; Kucherenko, A. S.; Struchkova, M. I.; Zlotin, S. G. *Tetrahedron Lett.* **2008**, *49*, 1212-1216.
[72] Lombardo, M.; Easwar, S.; De Marco, A.; Pasi, F.; Trombini, C. *Org. Biomol. Chem*. **2008**, *6*, 4224-4229.
[73] Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2009**, *65*, 1366-1372.



Scheme 1.18. Asymmetric aldol reaction between cyclohexanone and aldehydes developed by Zlotin and Trombini.

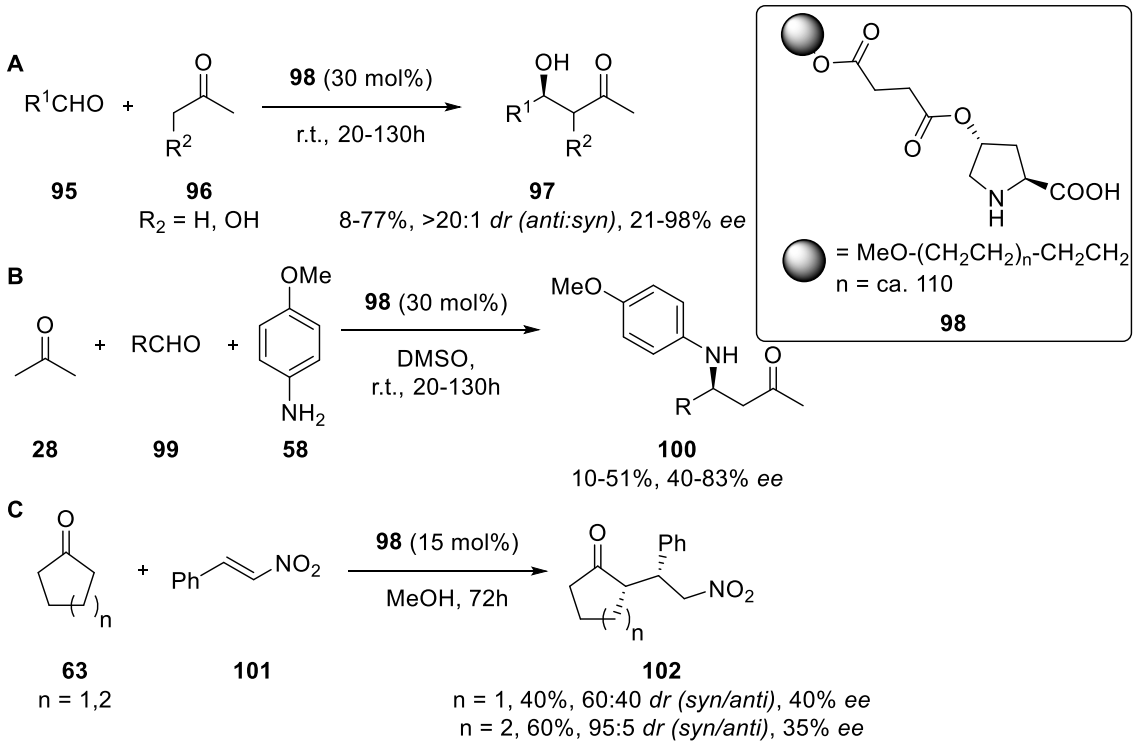
Hydroxy anchored polymer derivatives: Together with the growth of unnatural *L*-Proline derivatives, their immobilization in different supports has gained plenty of attention. At first, it was considered an unpractical methodology, due to the successive synthetic steps required for the whole transformation. However, the ease to recover the supported derivative by physical methods and its reusability without any loss in reactivity and selectivity counterbalanced the downside of the goal. Indeed, immobilization enables the use of different solvents as well as changes in the structure of the support that generate different catalytic activities.[74]

There are three different approaches for the catalyst immobilization, but covalently hold polymers are the most employed ones. Among them, polyethylene glycol (PEG) and polystyrene (PS) deserve special annotation. Immobilization by adsorption in mesophorous silica has also been used, but all transformations gave reduced enantioselectivity.[74]

The first experiments were promoted with polyethylene glycol-supported *trans*-4-hydroxyproline derivatives. PEG immobilized recyclable catalyst **98** has proven great efficiency in enantioselective aldol condensation between acetone or

[74] Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev*. **2008**, *37*, 1666-1688.

hydroxyacetone with several aldehydes,[75] in the Mannich reaction for the synthesis of Wieland-Mieschler ketone,[75b] and in Michael reactions between cyclic and acyclic ketones and *trans*-β-nitrostyrene (**Scheme 1.19**).[76] In the Mannich transformation the reaction outcome was very similar to non-supported proline regarding yield and enantioselectivity. For the Michael reaction, anyhow, it exhibited lower enantiomeric excess values. In all cases, the catalyst was re-used at least three times, despite the observed decreasing yields.



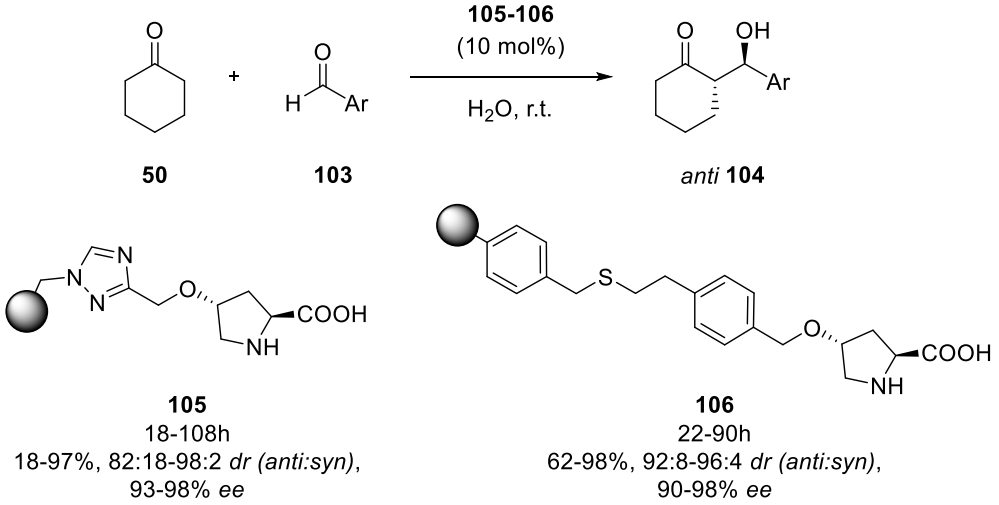
Scheme 1.19. PEG supported 4-hydroxyproline derived catalyst **98** and it's a) aldol B) Mannich and C) Michael transformations.

Shortly after the first implements in PEG anchored organocatalysts, polystyrene was considered as a suitable support for 4-hydroxyproline derivatives, owing to the high hydrophobicity of the polymer chain. This feature, at least initially, would improve the stereocontrol of the asymmetric chemical transformations.

In this event, in 2006 click chemistry was employed for the first time for immobilizing hydroxy-*L*-proline derivatives onto a Merrifield resin.[77] It was demonstrated that organocatalyst **105** promoted direct asymmetric aldol reactions in water with similar performance than their monomeric counterparts (**Scheme 1.20**). The catalyst was

[75] a) Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal*. **2001**, *343*, 171-173. b) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *Adv. Synth. Catal*. **2002**, *344*, 533-542.
[76] Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *J. Mol. Catal. A: Chem*. **2003**, *204-205*, 157-163.
[77] Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653-4655.

recovered by filtration, and its performance did not drop after three uses. Derivative **105** turned out to be efficient not only for aldol transformations, but also for the α-aminoxylation reaction of aldehydes and ketones in organic solvents. The corresponding products were obtained in moderate yields and excellent enantiomeric excesses (97-99%).[78] Subsequent achievements in PS supported field were fulfilled by the research group of Gruttadauria. These authors synthesised mercaptomethyl polymer bound derivative **106** for the water mediated aldol reaction between cyclohexanone and several substituted benzaldehydes (**Scheme 1.20**).[79] The corresponding adducts were obtained in good yields, diastereo- and enantioselectivities, comparable to those obtained with *L*-Proline. As well as the previous supported catalyst, **106** was recovered by filtration and used consecutively four times. The latter resin was also employed in the α-selenylation of aldehydes and the final products were obtained in moderate to good yields and high enantioselectivities.[80] The Baylis-Hillman reaction between methyl or ethyl vinyl ketone and several aldehydes, however, showed no enantioselectivity.[81]

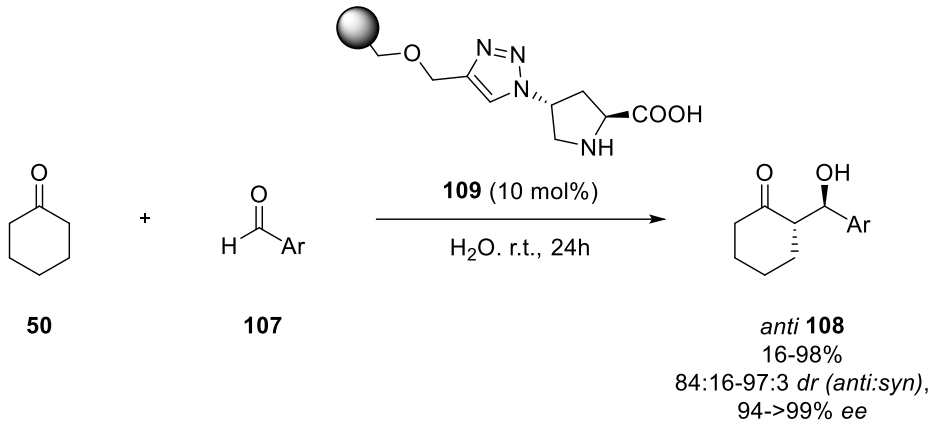


Scheme 1.20. PS supported organocatalysts for the direct asymmetric aldol reaction in water.

In 2008 Pericàs and co-workers synthesised, using the same click chemistry, a triazol bearing resin **109** for the asymmetric reaction between cyclohexanone and aromatic aldehydes in water (**Scheme 1.21**).[82] This organocatalyst afforded the desired aldol adducts in good yields and excellent sterochemical outcome, improving the results

[78] Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2007**, *9*, 1943-1946.
[79] Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Lo Meo, P.; Riela, S.; Noto, R. *Eur. J. Org. Chem*. **2007**, 4688-4698.
[80] Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255-259.
[81] Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; D'Anna, F.; Noto, R. *Catal. Commun*. **2008**, *9*, 1477-1481.
[82] Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2008**, *10*, 337-340.

obtained by the previously studied resins. Furthermore, the resin could have been recycled for at least five times.



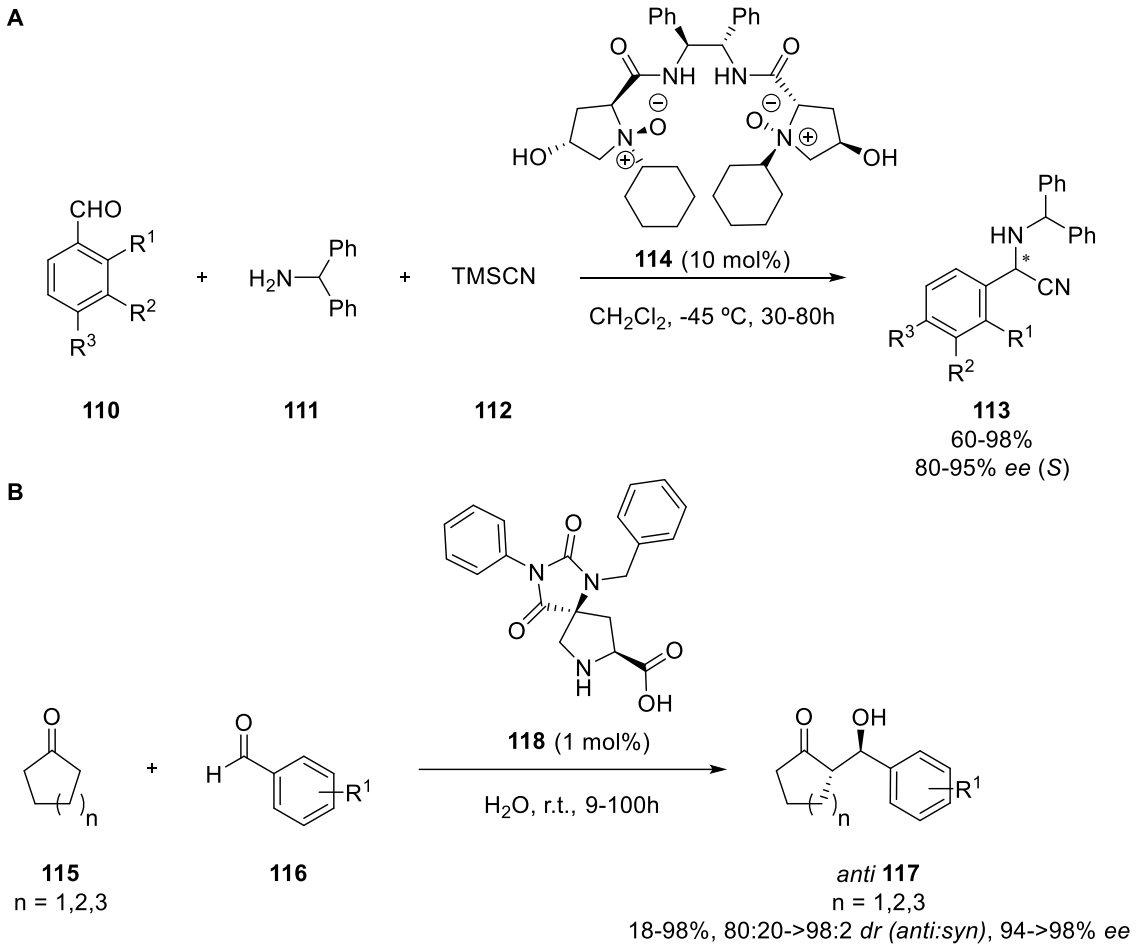
Scheme 1.21. The asymmetric aldol reaction between cyclohexanone and aromatic aldehydes described by Pericàs and co-workers.

Some years passed before acrylic polymers started to grow as suitable resins for organocatalytic purposes. Aiming to overcome the restricted solvent systems valuable for styrenic polymers, synthetic chemists developed acrylic polymers taking advantage of their superabsorbent properties.[83] In 2012 magnetic core-shell nanoparticles were evaluated as organocatalysts for the direct aldol reaction.[84] The observed results were excellent, but benzoic acid was necessary for the interaction of the catalyst with both the aldehydes and the organic shell of the nanoparticles. Surprisingly, the catalyst maintained its activity over ten cycles. It is also noteworthy that nanoparticles represented an environmentally friendly approach thanks to the simple technique for its separation: an external magnet.

Other derivatives: Together with all the previously described organocatalysts, two other *trans*-4-hydroxyproline derivatives can be distinguished. The *N*,*N*'-dioxide derivative **114** was successfully applied by Feng and co-workers to the three-component Strecker Reaction of aldehydes **110** with (1,1-diphenyl)methylamine **111** and TMSCN **112**. The catalyst was found to be efficient for several aromatic and aliphatic aldehydes, yielding the final products with excellent enantioselectivities (**Scheme 1.22A**).[85] Its excellent outcome was accounted for the bifunctional character of the organocatalyst, in which the Lewis base (*N*-oxide) and amide moieties played a crucial role. Schafmeister and co-workers, on the other hand, synthesised a family of proline-based spirocyclic

[83] Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett*. **2009**, *11*, 2968-2971.
[84] Yacob, Z.; Nan, A.; Liebscher, J. *Adv. Synth. Catal*. **2012**, *354*, 3259-3264.
[85] Wen. Y.; Gao, B.; Fu, Y.; Dong, S.; Liu, X.; Feng, X. *Chem. Eur. J.* **2008**, *14*, 6789-6795.

imidazolidinones as organocatalysts for the asymmetric aldol reaction of cyclic ketones and aldehydes in water. Among the tested derivatives, catalyst **118** exhibited the best results affording the *anti* **117** products in good yields and excellent diastereo- and enantioselectivities with 1 mol% of catalyst (**Scheme 1.22B**).[86]



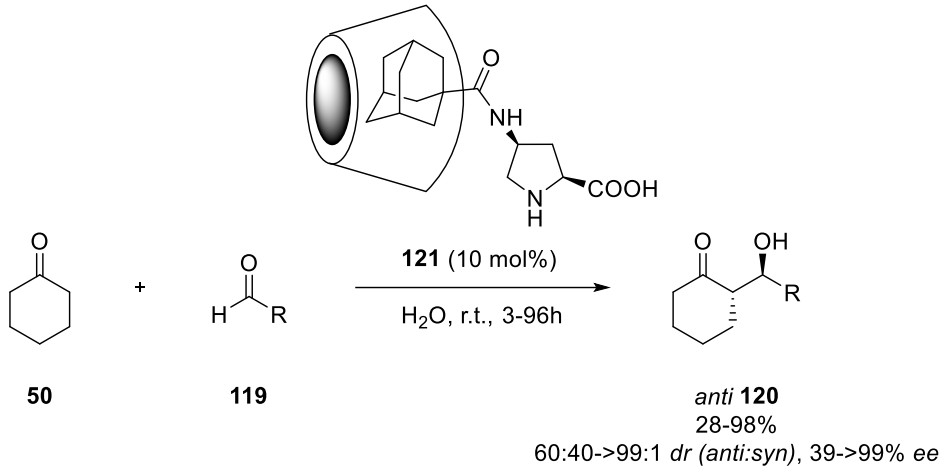
Scheme 1.22. A) The asymmetric Strecker reaction catalysed by **114** *N*,*N*'-dioxide derivative. B) The imidazolidinone **118** catalysed aldol reaction between cyclic ketones and aromatic aldehydes.

1.4.1.2 4-Amino proline-based organocatalysts

In 2007, Liu et al. demonstrated that 4-amino proline derived organocatalysts could efficiently catalyse the asymmetric aldol reaction between cyclohexanone and a set of aromatic and heteroaromatic aldehydes (**Scheme 1.23**).[87] The inclusion complex formed by the β-cyclodextrin bound adamantane amide derivative **121** was completely soluble in water furnishing the corresponding aldol adducts in good yields (except for one case) and excellent diastereo- and enantioselectivities. Interestingly, the catalyst was easily

[86] Zhao, Q.; Lam, Y.-H.; Kheirabadi, M.; Xu, C.; Houk, K. N.; Schafmeister, C. E. *J. Org. Chem*. **2012**, *77*, 4784-4792.
[87] Liu, K.; Häussinger, D.; Woggon, W.-D. *Synlett* **2007**, 2298-2300.

recoverable from the reaction medium by extraction and was recycled four times without any drop in reactivity and enantioselectivity.



Scheme 1.23. The asymmetric aldol reaction in water catalysed by β-cyclodextrin-binding Proline derivative **122**.

Nevertheless, polymer anchored derivatives are the most representative 4-amino proline-based organocatalysts so far. In this event, in 2007, 4-amino proline PEG catalysts (**Figure 1.6**) were prepared to test their catalytic activities towards the Michael reaction between ketones and *trans*-β-nitrostyrene.[88] Catalyst **124** exhibited the best results in terms of yield and enantioselectivity, but they were no better than the ones obtained with derivative **98** (*vide supra*). The recovery of the catalysts was performed by simple physical filtration, and the recycling study showed a dramatic decrease in yield and enantioselectivity after four cycles.

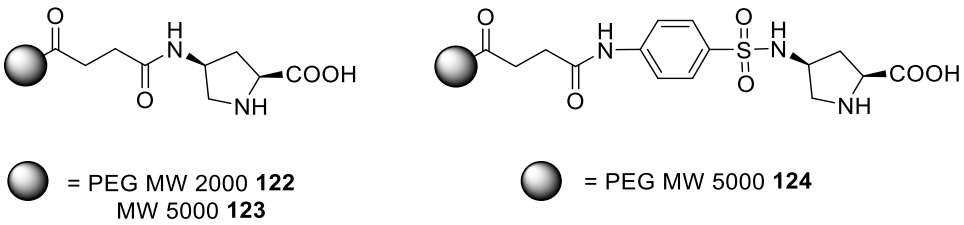
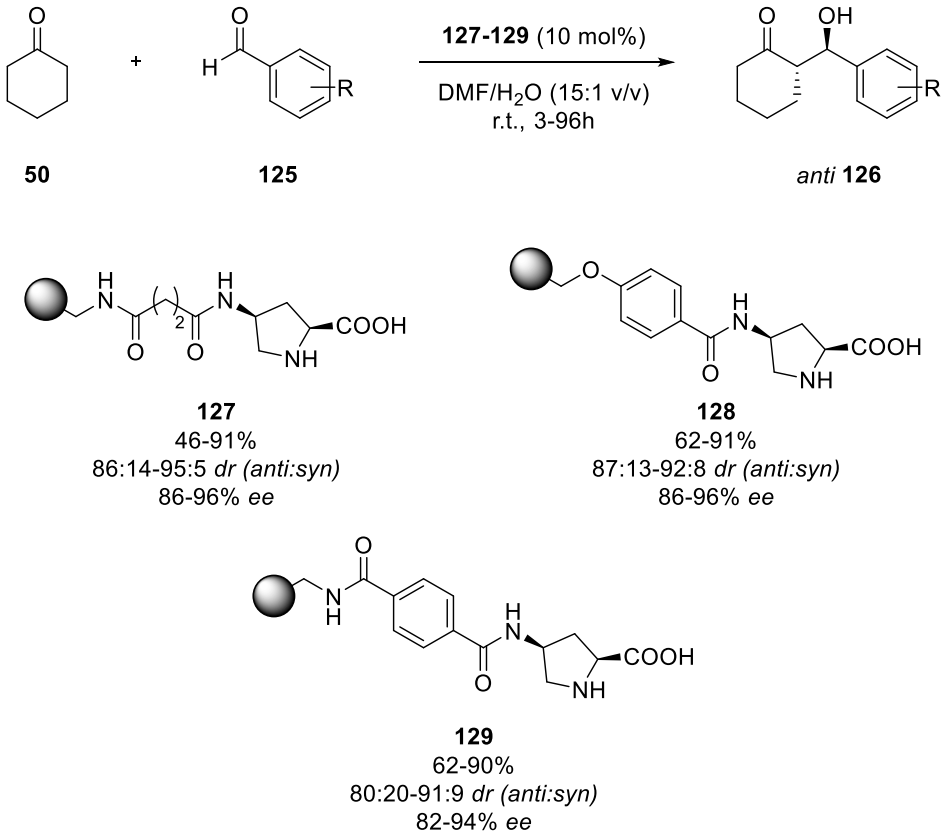


Figure 1.6. 4-aminoproline/PEG type organocatalysts designed by Gu et al.

Also in 2007, Tao and co-workers synthesised a PS supported organocatalyst **127** for the aldol reaction between cyclohexanone and aromatic aldehydes with electron-donating and electron-withdrawing substituents in the presence of water. The amphiphilic and reusable 4-aminoproline supported derivative furnished the final *anti* aldol products with good yields and high stereoselectivities with only 5 mol% of catalyst

[88] Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *J. Mol. Catal. A: Chem*. **2007**, *263*, 186-194.

load (**Scheme 1.24**).[89] A year after, the same research group developed two other polystyrene supported derivatives **128**,**129** to promote the asymmetric aldol reaction in wet DMF and ketone/water mixture (**Scheme 1.24**).[90] The reactions proceeded smoothly reaching good yields and high stereoselectivities. Besides, the catalysts could have been reused for four catalytic cycles.



Scheme 1.24. Polystyrene supported resins developed by Tao.

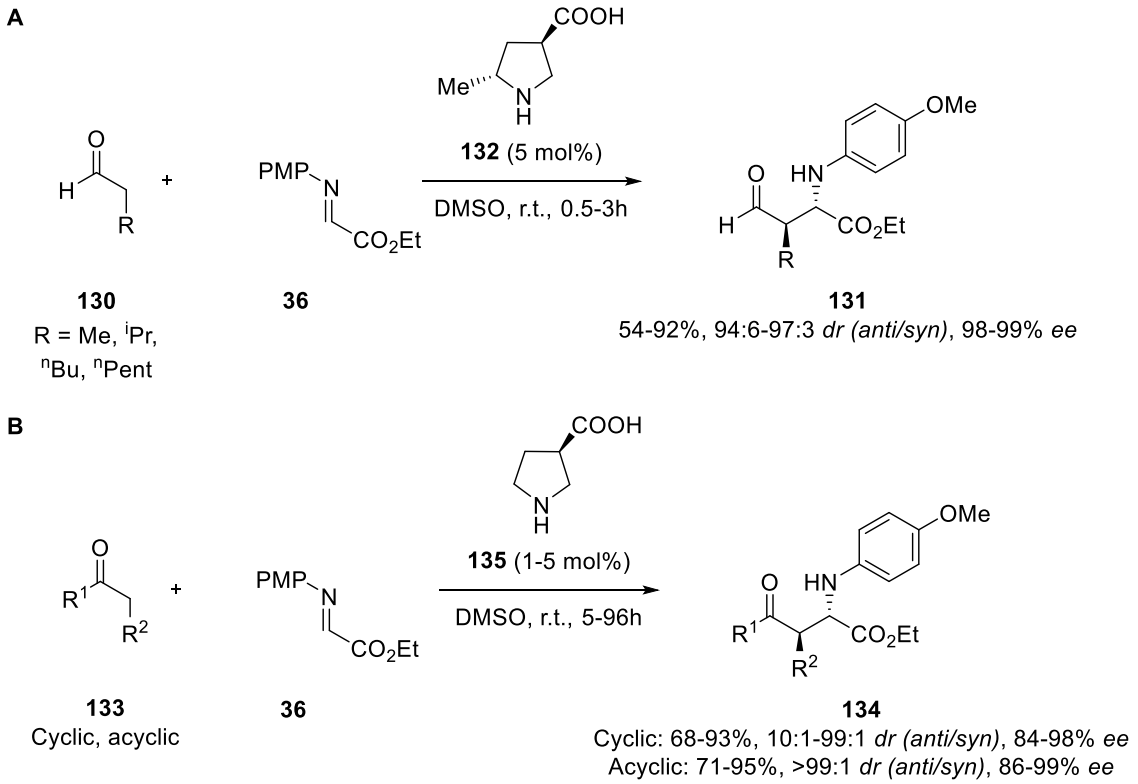
1.4.2 Synthetic unnatural amino acids

The employment of traditional enzymatic PTM synthesis is often ineffective due to the unusual structural features of the substrates. In this regard, chemical synthesis carried out by several stoichiometric or catalytic transformations has increased its development among the scientific universe.[91] Herein, the most illustrative reported synthetic unnatural organocatalysts will be detailed.

[89] Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Liu, W.; Tao, J.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 2649-2656.
[90] Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Tao, J.-C. *Catal. Lett*. **2008**, *120*, 281-287.
[91] Saghyan, A. S.; Langer, P. *Asymmetric Synthesis of Non-Proteinogenic Amino Acids*, Wiley-VCH: Weinheim, **2016**.

1.4.2.1 β-prolines

These unnatural amino acids have been exclusively applied with high efficiency to asymmetric Mannich reactions. As it has been illustrated before, all the previous 4-hydroxy-*L*-Proline derived unnatural organocatalysts formed preferably *syn*-type Mannich products.[92] In contrast, catalyst **132** manifested outstanding efficiency for the *anti*-Mannich reaction between aldehydes and electrophilic imines with excellent diastereomeric ratios and enantioselectivity values (**Scheme 1.25**).[93] However, this transformation was found to be of low efficiency for ketones. Thankfully, parent β-proline **135** was capable of overcoming this weakness, and resulted to be an excellent organocatalyst for both cyclic and acyclic ketones (**Scheme 1.25**). Both studies suggest the key role of the proton transfer from the acid group to the imine nitrogen in the control of *anti/syn* selectivity.



Scheme 1.25. β-Proline derivatives developed for the *anti*-Mannich asymmetric transformation of A) aldehydes and B) ketones.

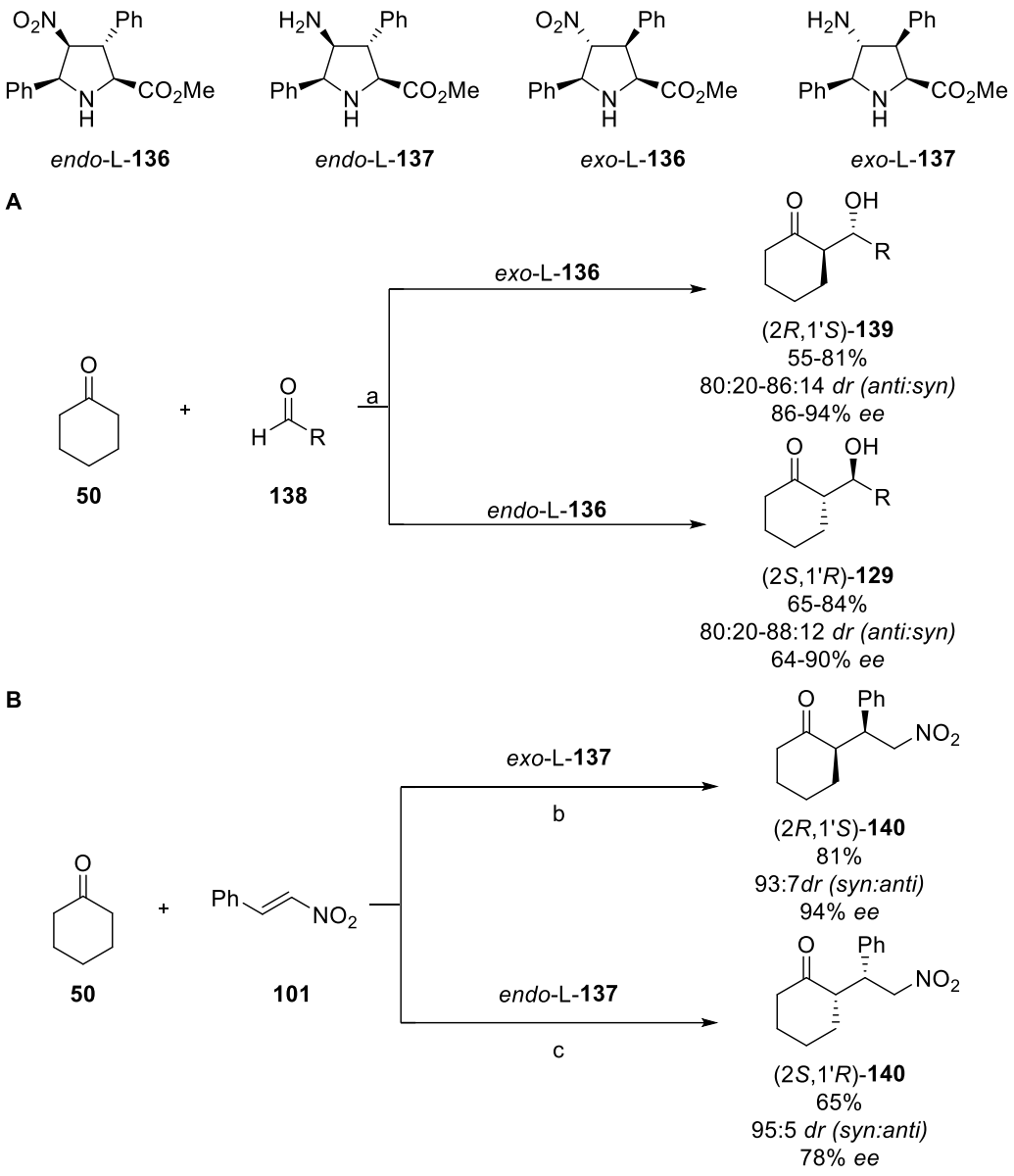
[92] a) Ref 45. b) Girling, P. R.; Kiyoi, T.; Whiting, A. *Org. Biomol. Chem*. **2011**, *9*, 3105-3121.
[93] a) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc*. **2006**, *128*, 1040-1041. b) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc*. **2006**, *128*, 9630-9631.

1.4.2.2 Unnatural pyrrolidine-based derivatives

Throughout the last decade, our research group has focussed its attention on densely substituted nitro and aminoproline catalysed asymmetric reactions, which were synthesised by asymmetric (3+2) cycloaddition reactions and successive hydrogenation processes. The nitro derivatives **136** were found to be efficient catalysts for the asymmetric aldol reactions between cyclic ketones and aldehydes in the presence of TFA (**Scheme 1.26A**).[94] Amongst the tested catalysts, *exo*-L-**136** and *endo*-L-**136** derivatives exhibited the best stereochemical outcomes yielding the desired products in good to high diastereo- and enantioselectivities. Besides, the authors reported that the sterochemical induction was closely related to the configuration of the pyrrolidine ring. In fact, *exo*-L proline esters preferentially promote anti (2*R*,1'*S*) aldols, whereas the *endo*-L organocatalysts furnish the corresponding (2*S*,1'*R*) aldols as major products.

When the applicability of these nitro derivatives was further extended to the Michael reaction, experiments revealed that they were unable to catalyse the asymmetric transformation. Fortunately, the 4-aminoproline **137** derivatives efficiently promoted the Michael reaction between cyclic ketones and nitroalkenes.[95] As well as in the previous case, *endo*-L-**137** derivatives generated the same adduct as Proline (2*S*,1'*R*), whilst *exo*-L-**137** cycloadducts gave rise to the opposite (2*R*,1'*S*) adducts (**Scheme 1.26B**).

[94] a) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F.P. *Chem. Sci*. **2012**, *3*, 1486-1491. b) Retamosa, M. G.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló. L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem*. **2015**, 2503-2516.
[95] Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F.P. *J. Org. Chem*. **2015**, *80*, 5588-5599.



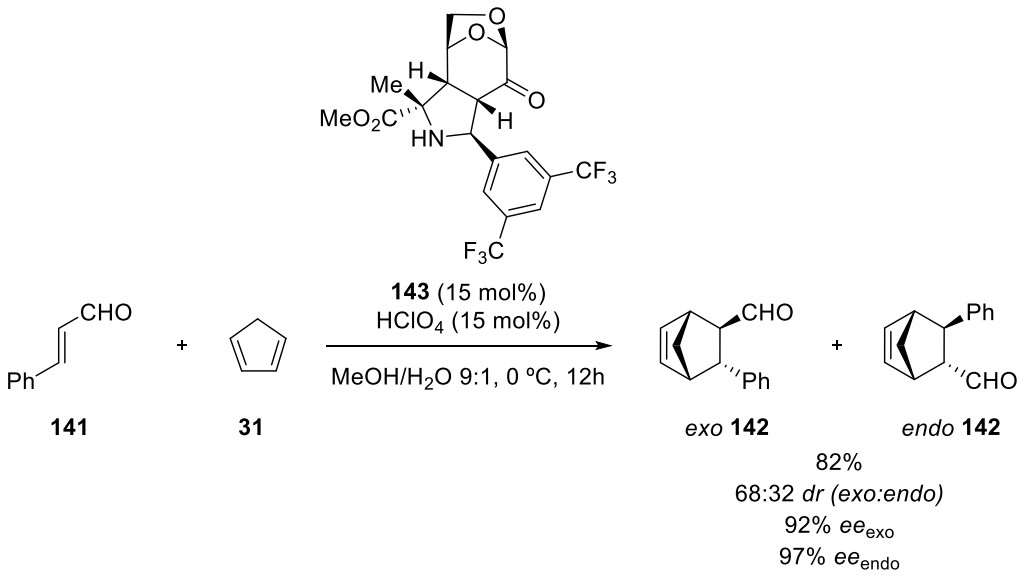
Scheme 1.26. Unnatural nitro- and aminoproline catalysed A) aldol and B) Michael reaction reported by Cossío and co-workers. Reagents and conditions: a) Organocatalyst (30 mol%), TFA (30 mol%), -15 °C, 24h. b) Organocatalyst (30 mol%), PNBA (30 mol%), neat, r.t., 16h. c) Organocatalyst (30 mol%), TFA (30 mol%), neat, r.t., 24h.

In all the previous cases the pyrrolidine moiety was the only source of chirality. However, several authors have also reported the synthesis and use of polycyclic unnatural proline derivatives with fused rings. For instance, Yu, Han and co-workers described the concept of cooperative catalysis between amino acids and modified alkaloids for catalysing Biginelli reactions between cinnamaldehydes, thioureas and β-keto esters.[96] Cai et al., besides, developed a catalytic enantioselective route for [3+2] cycloadditions between acetylenic aldehydes and nitrones under the catalysis of *L*-α,α-bis(3,5-ditrifluoromethylphenyl)prolinol. Although the yield of the reaction was

[96] Yu, H.; Xu, P.; He, H.; Zhu, J.; Lin, H.; Han, S. *Tetrahedron: Asymmetry* **2017**, *28*, 257-265.

excellent, the *ee* values were only moderate.[97] This latter catalyst did not prove to be suitable in Michael reactions. Its structurally rigid tricyclic analogue, anyhow, showed great performance in conjugate addition of aldehydes to nitroalkenes.[98]

The last contribution concerning the employment of synthetic prolines was reported by Sarotti et al., who demonstrated the suitability of levoglucosenone-derived chiral pyrrolidines in the iminium-ion based Diels-Alder reactions between (*E*)-cinnamaldehyde and cyclopentadiene.[99] Amid the tested derivatives, pyrrolidine **143**, in combination with $HClO_4$ as co-catalyst, exhibited the best performance reaching the desired *exo*- and *endo*-**142** Diels-Alder products in moderate diastereomeric ratio and excellent enantiocontrol (**Scheme 1.27**).



Scheme 1.27. Levoglucosenone-derived pyrrolidine catalysed Diels-Alder reaction developed by Sarotti.

1. 5 PEPTIDES IN ENAMINE-BASED ORGANOCATALYTIC REACTIONS

Peptides fulfill a great variety of applications either in Nature or in our daily basis, as they are found in hormones, neurotransmitters, toxins, artificial sweeteners and pharmaceuticals.[100] The tremendous functional and structural diversity they possess is the reason why they accomplish such a wide variety of purposes. Despite the exhibited

[97] Cai, X.; Wang, C.; Sun, J. *Adv. Synth.Catal*. **2012**, *354*, 359-363.
[98] Xiao, J.; Xu, F.-X.; Lu, Y.-P.; Loh, T.-P. *Org. Lett*. **2010**, *12*, 1220-1223.
[99] a) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G.; Echeverría, G. A.; Piro, O. E. *Org. Lett*. **2012**, *14*, 2556-2559. b) Gerosa, G. G.; Spanevello, R. A.; Suárez, A. G.; Sarotti, A. M. *J. Org. Chem*. **2015**, *80*, 7626-7634.
[100] Sewald, N.; Jakubke, H.-D. *Peptides: Chemistry and Biology. 2nd Ed*. Wiley-VCH: Weinheim, **2002**.

well-known features and earlier important examples reported independently by Oku[101] and Julia and Colonna[102] of catalytically active peptides, their utility in asymmetric processes did not come to effect until the 21st century. Only when Miller released their achievements in acylation reactions mediated by rigidified methylimidazole containing peptides[103] did the field receive the necessary impulse for organocatalytic processes.

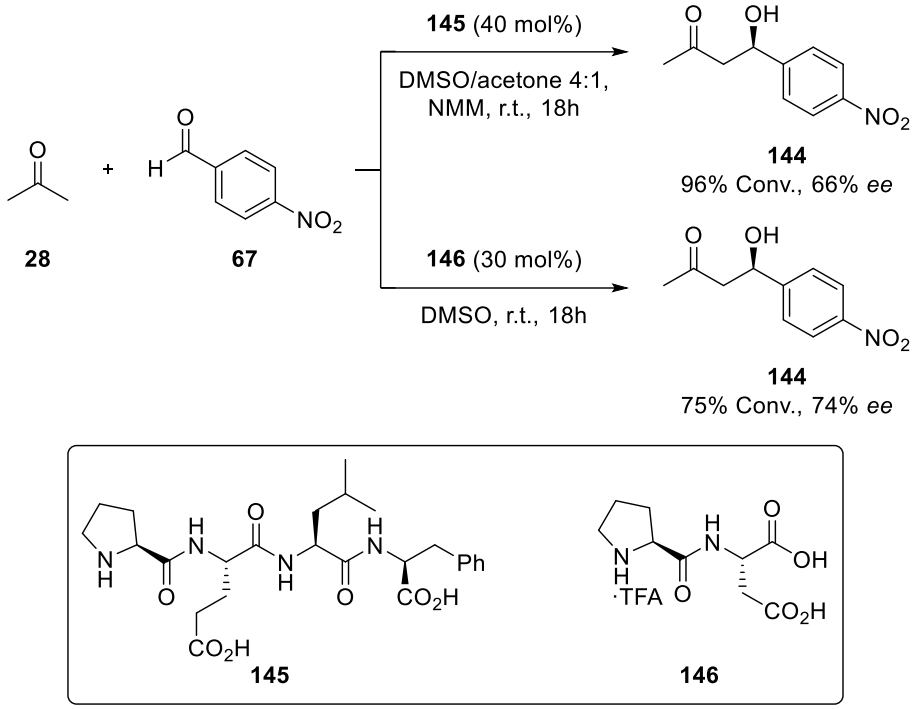
Remarkably, peptidic catalysts exhibit unique characteristics, which, in fact, are difficult to achieve for other small synthetic catalysts or enzymes. Among these properties, high chemoselectivity, versatility towards a large number of substrates, site selectivity over long distances, structural robustness and the ease of modification of catalytic properties deserve special attention. By virtue of the incomparable features showed, over the past decade peptides have become an alternative to enzymes and other small organic synthetic catalysts for different transformations such as C-C bond forming reactions, brominations, oxidations and hydrolytic reactions.[104] The following section will briefly describe the most emblematic natural and non-natural amino acid derived peptides.

1.5.1 Natural amino acid-based peptides

These peptides are widely used as organocatalysts for synthetic asymmetric transformations, among which aldol and Michael approaches play a pivotal role. Some other contributions on Mannich and Diels Alder reactions were also reported, in which the catalytic role was carried out by sulphonamide derived proline catalysts.[105] The very first examples of peptide employment in aldol reactions were the contributions described by the groups of Reymond[106] and List[107] (**Scheme 1.28**). Both publications made use of *N*-terminal proline derived catalysts in the reaction between acetone **28** and *p*-nitrobenzaldehyde **67**. Whereas Reymond designed tetrapeptide Pro-Glu-Leu-Phe **145** as asymmetric inductor, List used a shorter dipeptide Pro-Asp **146**. Both catalysts

[101] a) Oku, J.-I.; Ito, N.; Inoue, S. *Makromol. Chem*. **1979**, *180*, 1089-1091. b) Oku, J.-I. Inoue, S. *Chem. Commun*. **1981**, 229-230.
[102] a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl*. **1980**, *19*, 929-931. b) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1317-1324.
[103] Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc*. **1998**, *120*, 1629-1630.
[104] For an excellent review on peptide catalysed transformations, see: Wennemers, H. *Chem. Commun*. **2011**, *47*, 12036-12041.
[105] a) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed*. **2005**, *44*, 4877-4880. b) Veverková, E.; Štrasserová J.; Šebesta, R.; Toma, Š. *Tetrahedron: Asymmetry* **2010**, *21*, 58-61.
[106] Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2445-2447.
[107] Martin, H. J.; List, B. *Synlett* **2003**, 1901-1902.

incorporated a free carboxyl function so as to compensate the essential role accomplished *L*-Proline's own carboxyl group.



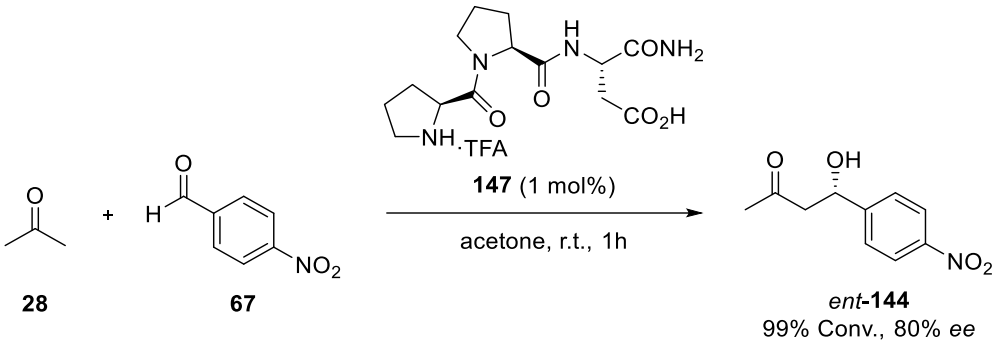
Scheme 1.28. The aldol reaction developed by A) Reymond and B) List by means of peptidic organocatalysts.

These reports led to the implementation of small peptides as modular catalysts for the enantioselective direct aldol reactions. Peptides containing two to four amino acid residues were independently synthesised by the groups of Gong[108] and Wang[109]. The former developed *L*-Proline based amides for the synthesis of chiral 1,4-diols by means of the reaction between hydroxyacetone and several aromatic aldehydes in aqueous media. The latter, on the other side, made use of *L*-Pro-*L*-Val-*S*-amine dipeptide as organocatalyst for the direct asymmetric aldol reaction in brine.

Wennemers and col. achieved another remarkable hit in the field of peptide chemistry by employing a combinatorial method for the generation and testing of a large number of tripeptidic catalysts. The best stereochemical outcome was exhibited by peptide H-Pro-Pro-Asp-NH_2 **147**, even improving the results obtained with *L*-Proline: only 1 mol% catalyst was able to generate the opposite aldol product in 99% yield and 80% *ee* (**Scheme 1.29**).[110] Its optimal activity and the divergent outcome was believed to be

[108] Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.*, **2004**, *6*, 2285-2287.
[109] Hu, X.-M.; Zhang, D.-X.; Zhang, S.-Y.; Wang, P.-A. *RSC Adv*. **2015**, *5*, 39557-39564.
[110] a) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett*. **2005**, *7*, 1101-1103. b) Revell, J. D.; Wennemers, H. *Adv. Synth. Catal*. **2008**, *350*, 1046-1052.

related to the turn-like conformation that the peptide adopted, in which both the secondary amine of Proline and the carboxylic acid of the aspartic acid were in close proximity.



Scheme 1.29. Tripeptide H-Pro-Pro-Asp-NH_2 for the asymmetric aldol reaction between acetone and *p*-nitrobenzaldehyde.

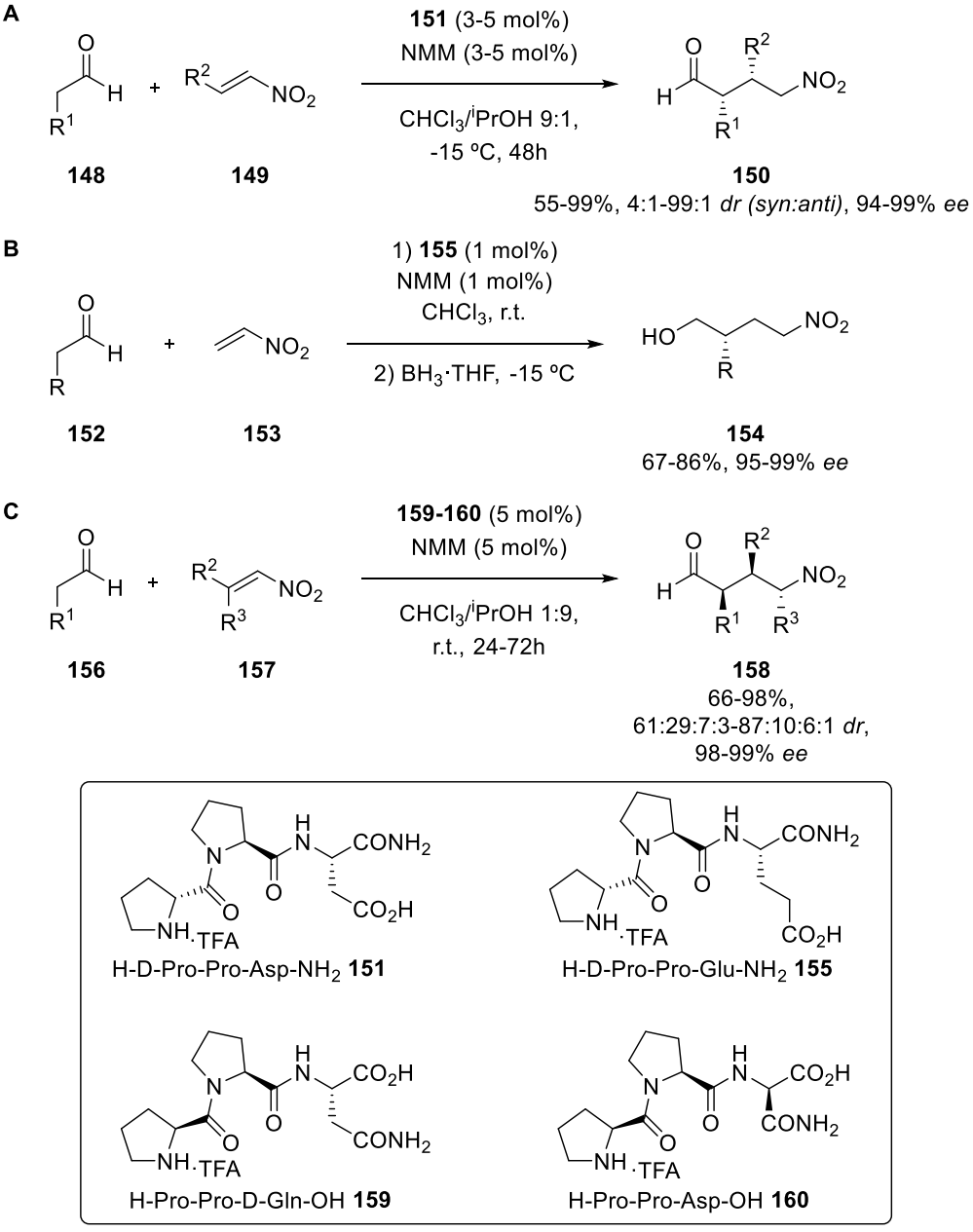
This trend was subsequently followed by several research groups by the design of different prolinamide like organocatalysts for asymmetric aldol reactions, enlarging the scope of the nucleophilic ketones to cyclohexanone. Singh synthesised a series of catalysts in which a *gem*-diphenyl group was incorporated to proline as a second part of the catalyst, thus acting as a hydrophobic part that concentrates the organic phase.[111] The research group led by Guan developed recoverable ftalimido-prolinamide catalysts that could be used several times in large scale without any loss in catalytic activity and stereoselectivity.[112] Consequently, Kokotos and his group configured tripeptide-prolinamide-thioureas bearing diphenylethylenediamine chiral moieties for the same transformation.[113] Muntifunctional “click” prolinamides were also tested for the aldol reaction by Paladhi et al. who brought about C3-symmetric derivatives in which the hydrophobic surface was enlarged.[114]

In 2007, Clarke and co-workers studied novel proline derived organocatalysts generated by the coupling between *L*-Proline and aminonaphtarydine for the 1,4-addition of cyclic ketones to aromatic nitroolefins. Surprisingly, achiral pyridinone additives improved both diastereoselectivity and catalyst turnover. The self-assembled catalytic host-guest system resulted successful for several nitroalkenes, even though the enantioselectivity values ranged from poor to moderate.[115] Two years’ after, Tsogoeva demonstrated the ability of short Pro-Phe-OH like dipeptides to catalyse the Michael reaction of cyclohexanone and nitroolefins. With the aid of catalytic amounts of NaOH,

[111] Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem*. **2009**, *74*, 4289-4297.
[112] Yang, Y.; He, Y.-H.; Guan, Z.; Huang, W.-D. *Adv. Synth. Catal*. **2010**, *352*, 2579-2587.
[113] Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem*. **2012**, *10*, 5613-5619.
[114] Paladhi, S.; Das, J.; Mishra, P. K.; Dash, J. *Adv. Synth. Catal*. **2013**, *355*, 274-280.
[115] Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed*. **2007**, *46*, 930-933.

which improved catalyst solubility in water, several electron-rich and electron-deficient nitrostyrenes were found to be suitable for the chemical transformation, giving rise to the final Michael products in good yields, excellent diastereoselectivities and good *ee* values.[116]

Simultaneously, the research group led by Wennemers broadened the utility of the Pro-Pro-Xaa type tripeptides (where Xaa is an acidic amino acid, *vide supra*) for various 1,4-conjugate addition reactions. These peptides exhibited excellent catalytic properties, accessing the final products with high chemo- and stereoselectivity (**Scheme 1.30**).



Scheme 1.30. H-Pro-Pro-Xaa type tripeptide organocatalysts developed by Wennemers for the Michael reactions of A) β-nitroolefins B) nitroethylene and C) α,β-disubstituted nitroalkenes.

[116] Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem*. **2009**, *7*, 4279-4284.

The pseudo enantiomer **151** of the previously reported organocatalyst **147** was able to smoothly catalyse the reaction between aliphatic aldehydes and β-substituted nitroolefins with 3-5 mol% catalyst load.[117] In comparison to other chiral secondary amines, both aldehyde quantities and substrate scope were further improved. When nitroethylene was employed as a Michael acceptor, homologous peptide **155** afforded the monosubstituted γ-nitroaldehydes in high yields and enantioselectivities.[118] Results showed that the additional methylene group of the glutamic acid residue improved the solubility of the catalyst, and hence, its performance. Last but not least, structure-like catalyst **159** and **160** displayed outstanding activity towards the much less reactive α,β-disubstituted nitroolefins utilizing 5 mol% catalyst load.[119] Bear in mind that in the latter peptides the carboxylic acid moiety is placed in the main chain of the molecule instead of the side chain.

1.5.2 Unnatural amino acid-based amides

Despite the existence of natural amino acid based organocatalysts, unnatural amino acid based derivatives have also been studied for asymmetric substoichiometric chemical transformations. The latter molecules have demonstrated to be suitable not only for C-C bond forming reactions, but also for different cycloadditions, acylations, domino reactions and hydrolytic transformations.[120]

Regarding intermolecular asymmetric aldol reactions, only *trans*-4-hydroxyproline derived prolinamides have been tested. These amides suffered modifications either in the acid moiety or in both hydroxy and carboxylic acid groups. Among the former category, just one example was reported by Fu et al. in which prolinamide phenols enabled the reaction between cyclohexanone and aromatic nitroaldehydes in organic solvents and water.[121] In the field of hydroxy and acid group protected catalysts, however, several reports have been released. In 2007, Cheng demonstrated the catalytic effectivity of the combination of catalyst **163** and the Brønsted acid *p*-dodecyl

[117] Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed*. **2008**, *47*, 1871-1874.
[118] Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc*. **2008**, *130*, 5610-5611.
[119] a) Duschmalé, J.; Wennemers, H. *Chem. Eur. J.* **2012**, *18*, 1111-1120. b) Kastl. R.; Arakawa, Y.; Duschmalé, J.; Wiesner, M.; Wennemers, H. *Chimia*, **2013**, *67*, 279-282.
[120] a) Ref. 104. b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev*. **2007**, *107*, 5759-5812. c) Revell, J. D.; Wennemers, H. *Curr. Opin. Chem. Biol*. **2007**, *11*, 269-278.
[121] Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351-3357.

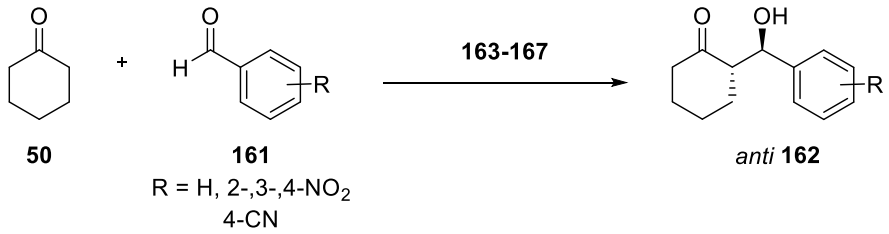
benzenesulfonic acid (DBSA) for the reaction between cyclohexanone and aryl aldehydes in water (**Scheme 1.31**).[122]

Subsequently, Gong studied the same transformation in the presence of 1 mol% of organocatalyst **164**, which was prepared from the commercially available *trans*-4-hydroxyproline and (2*R*,3*R*)-diethyl 2-amino-3-hydroxysuccinate. The products were afforded with excellent *anti*-diastereoselectivities and enantioselectivities (**Scheme 1.31**).[123]

The highly substituted catalyst **165** designed by Zhang et al. yielded the aldol products coming from cyclohexanone and aromatic aldehydes in high diastereoselectivity and *ee* values in presence of large amounts of water (**Scheme 1.31**).[124] Such a high amount was supposed to promote the catalytic activity by means of hydrogen bond interactions that set the catalyst and the reagents closer. Additional hydrophobic interactions between the aldehyde and the ketone would also cause a favourable scenario for the reaction to occur.

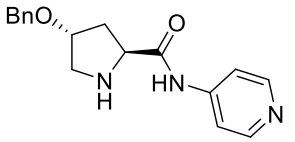
To end with, Chen evaluated bifunctional thiourea-amide organocatalyst **166** bearing one camphor scaffold in water and organic solvents.[125] The corresponding *anti*-aldol products were achieved in high yields and stereoselectivities, and the camphor moiety was believed to play a crucial role in the stereochemical outcome by increasing the hydrophobicity of the catalyst. Also in 2009, Wu developed a series of *N*-prolylsulfonamides to perform the aldol reaction in water. Among the tested derivatives, catalyst **167** should be highlighted, which afforded the final products in excellent diastereo- and enantioselectivities with very good yields with as low as 3 mol% of catalyst **(Scheme 1.31**).[126]

[122] Luo, S.; Xu, H.; Li, J.; Zhang, L.; Mi, X.; Zhenga, X.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 11307-11314.
[123] Zhao, J.-F.; He, L.; Jiang, J.; Tang, Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett*. **2008**, *49*, 3372-3375.
[124] Zhang, S.-P.; Fu, X.-K.; Fu, S. D. *Tetrahedron Lett*. **2009**, *50*, 1173-1176.
[125] a) Tzeng, Z.-H.; Chen, H.-Y.; Huang, C.-T.; Chen, K. *Tetrahedron Lett*. **2008**, *49*, 4134-4137. b) Tzeng, Z-H.; Chen, H.-Y.; Reddy, R. J.; Huang, C.-T.; Chen, K. *Tetrahedron* **2009**, *65*, 2879-2888.
[126] Fu, S.-D.; Fu, X.-K.; Zhang, S.-P.; Zou, X.-C.; Wu, X.-J. *Tetrahedron: Asymmetry* **2009**, *20*, 2390-2396.



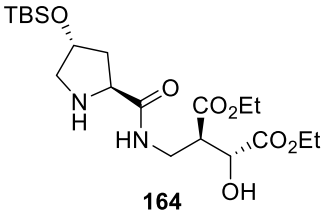
50 **161** *anti* **162**

R = H, 2-,3-,4-NO_2
4-CN



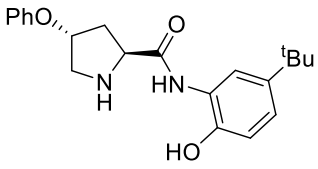
163

Conditions: **163** (10 mol%), DBSA (10 mol%)
H_2O, r.t., 72h
33-95%, 91:9-98:2 *dr (anti:syn)*, 93-99% *ee*



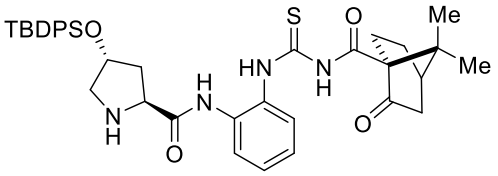
164

Conditions: **164** (1 mol%)
H_2O, r.t., 24h
75-95%, 96:4-99:1 *dr (anti:syn)*, 92-95% *ee*



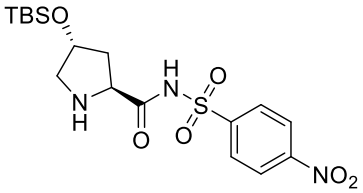
165

Conditions: **165** (2 mol%), TFA (2 mol%)
H_2O, r.t., 72h
72-97%, 92:8-99:1 *dr (anti:syn)*, 84-97% *ee*



166

Conditions: **166** (20 mol%), DBSA (20 mol%)
H_2O, r.t., 24h
75-95%, 96:4-99:1 *dr (anti:syn)*, **-** 92 to -95% *ee*



167

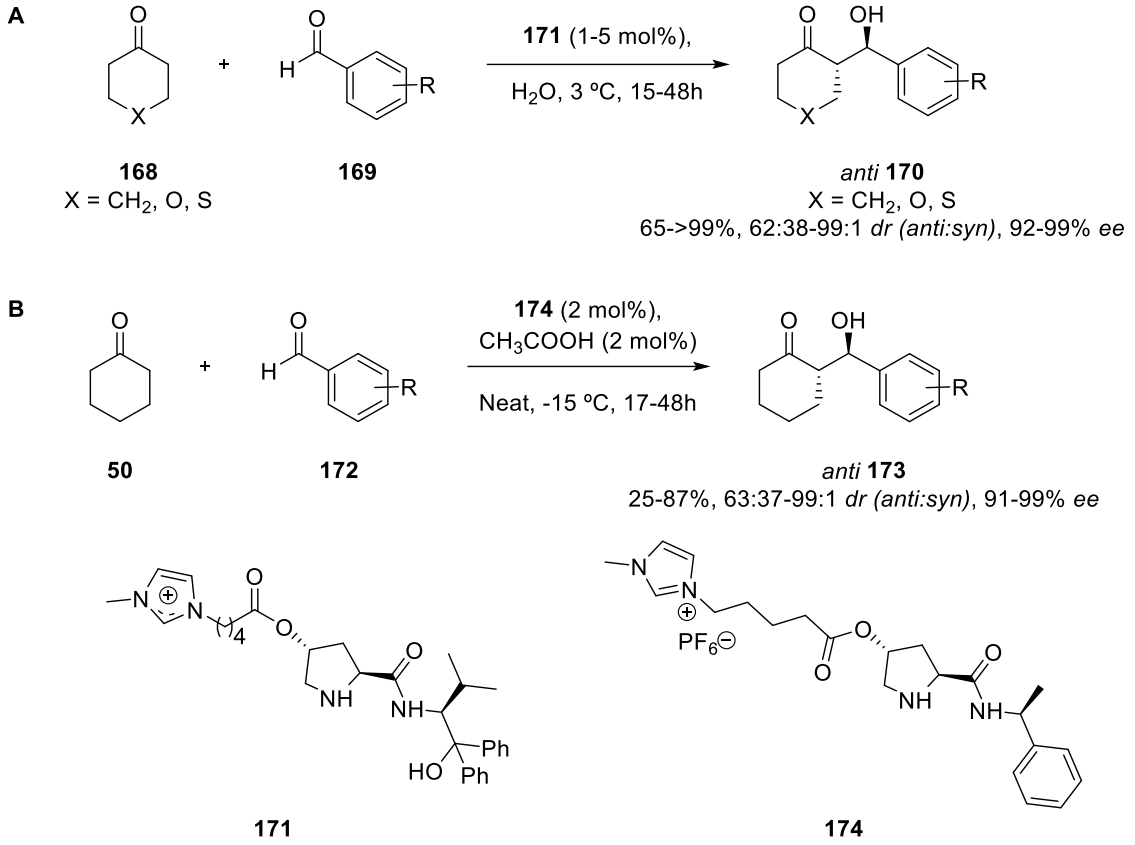
Conditions: **167** (3 mol%)
H_2O, r.t., 12-96h
70->99%, 93:7->99:1 *dr (anti:syn)*, 98-99% *ee*

Scheme 1.31. *trans*-4-hydroxy derived peptidic organocatalysts for intermolecular asymmetric aldol reactions.

Within the last years, Zlotin and Singh have independently developed reusable and efficient ionic liquid attached organocatalysts **171** and **174** for the intermolecular aldol reaction. Derivative **171** showed excellent results in the reaction between cyclic ketones and aromatic aldehydes reaching high yields and excellent regio-, diastereo- and enantioselectivitites (**Scheme 1.32A**).[127] Organocatalyst **174**, in as low as 2 mol% load, enabled the chemical transformation for up to 6 catalytic processes, affording the

[127] Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2010**, *66*, 513-518.

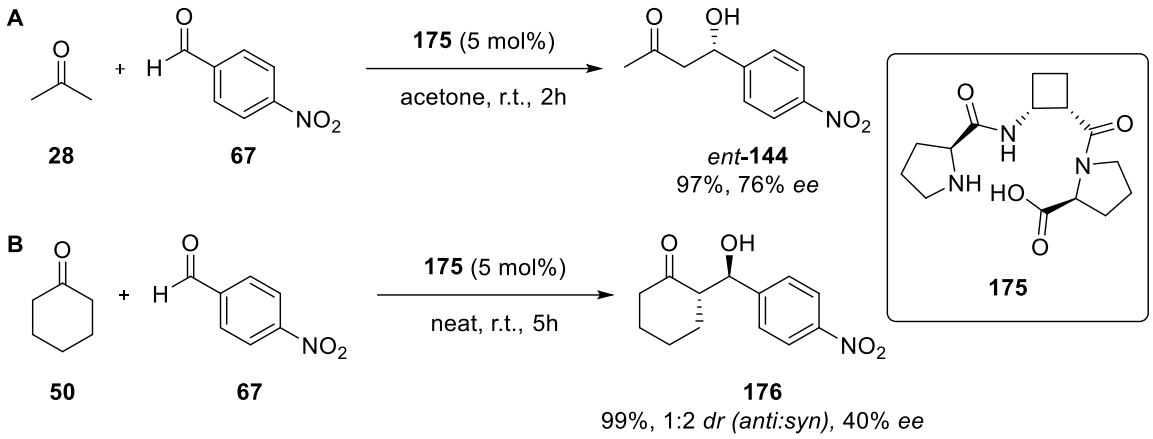
corresponding aldol products in good yields and outstanding diastereo- and enantioselectivities (**Scheme 1.32B**).[128]



Scheme 1.32. Ionic liquid bearing catalyst A) **171** and B) **174** designed by Zlotin and Singh for the direct intermolecular aldol reaction.

To finish, a very recent work carried out by Ortuño on proline containing γ–peptide derivatives should be mentioned.[129] The development of the aldol reaction both with acetone and cyclohexanone gave promising results, although the enantiomeric excess values observed were far below from the other aforementioned catalysts (**Scheme 1.33**). The two Proline residues located at the two ends of the catalysts were supposed to be responsible for the stereochemical outcome of the reaction.

[128] Yadav, G. D.; Singh, S. *RSC Adv*. **2016**, *6*, 100459-100466.
[129] Illa, O.; Porcar-Tost, O.; Robledillo, C.; Elvira, C.; Nolis, P.; Reiser, O.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2018**, *83*, 350-363.

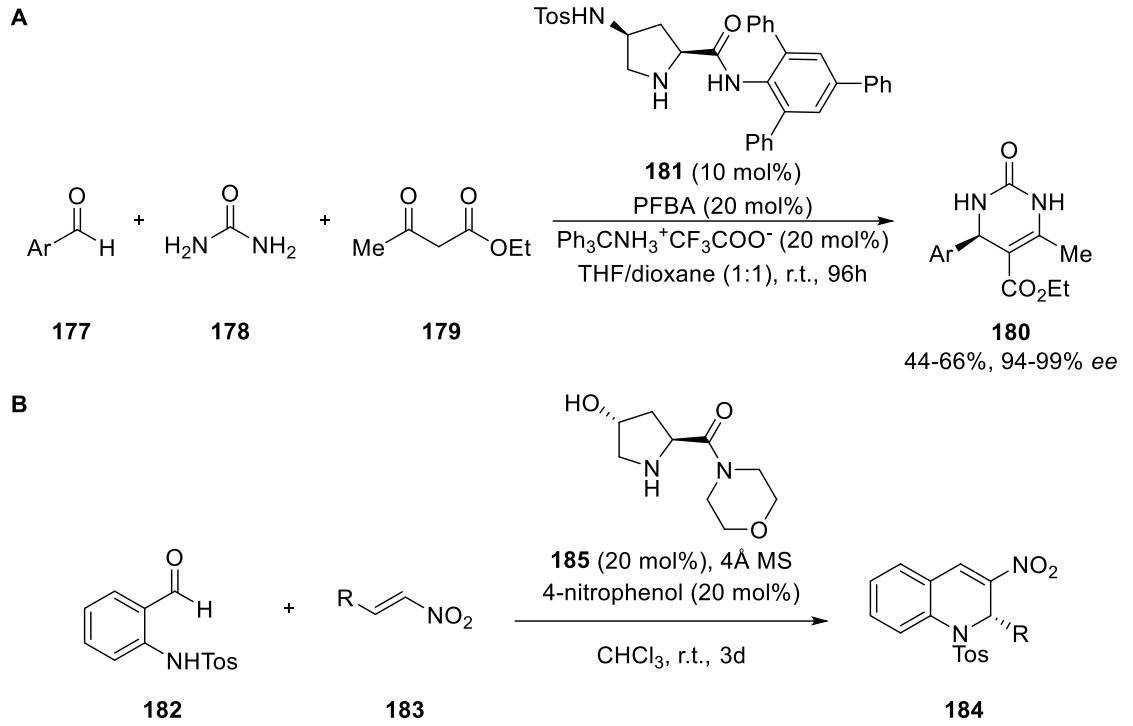


Scheme 1.33. γ-cyclobutane-proline dipeptide developed by Ortuño and its applicability towards intermolecular aldol reaction for A) acetone and B) cyclohexanone.

Peptidic catalysts have also proved to be convenient for several chemical reactions. In recent years, *cis* and *trans*-4-aminoproline as well as *trans*-4-hydroxyproline-based catalysts have been tested in a three-component Biginelli transformation[130] and in a one-pot domino Aza-Michael-Henry reaction,[131] respectively. The former organocatalyst promoted the formation of heterocyclic pyrimidinone products by reaction between urea **178**, ethyl acetoacetate **179** and a number of aromatic and aliphatic aldehydes yielding the corresponding products in good yields and excellent enantioselectivities (**Scheme 1.34A**). The unique features manifested by catalyst **181** allowed the transformation to occur. Indeed, the presence of the hydrogen bond donating sulphonamide group in C4 and the sterically hindered substituent in C2 were believed to play a fundamental role.

On the other side, the asymmetric Aza-Michael-Henry process enabled the synthesis of chiral 3-nitro-1,2-dihydroquinoles **184**, difficult to achieve by means of other chemical transformations. This study demonstrated the versatility of organocatalyst **185** for the domino reaction between protected 2-amino benzaldehydes and *trans*-β-nitroolefins (**Scheme 1.34B**). Along the different tested protecting groups, *tosyl* displayed the best performance in terms of reactivity and stereoselectivity by virtue of the enhanced acidity, ease of deprotonation and subsequent nucleophilicity provided to the NH group.

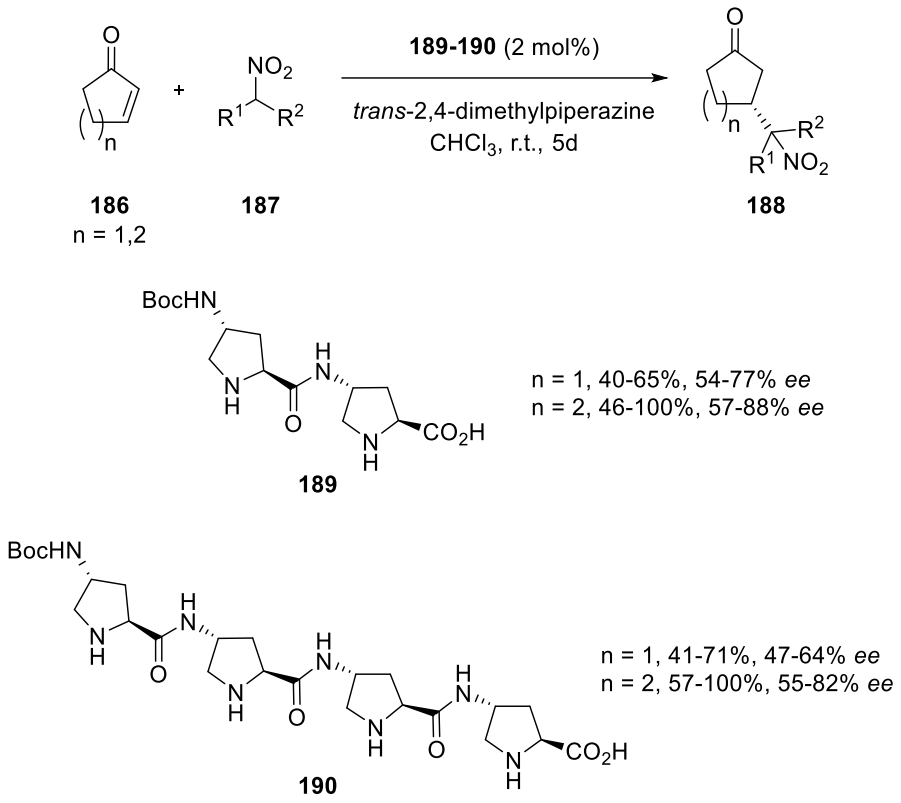
[130] Saha, S.; Moorthy, J. N. *J. Org. Chem*. **2011**, *76*, 396-402.
[131] Luo, H.; Yan, X.; Chen, L.; Li, Y.; Liu, N.; Yin, G. *Eur. J. Org. Chem*. **2016**, 1702-1707.



Scheme 1.34. A) Biginelli reaction catalysed by peptide **181** and B) Domino Aza-Michael-Henry reaction by *trans*-4-hydroxyprolinamide **185**.

To conclude, asymmetric 1-4 addition reactions should also be cited, despite unnatural amino acid-based organocatalysts have scarcely been investigated for such purpose. In 2014, Savic and co-workers designed a variety of substituted proline derivatives for the reaction between aldehydes and vinyl sulphone, but the results obtained were not relevant in terms of reactivity and selectivity (<52% *ee*).[132] Two years later, Tsogoeva reported an interesting conjugate addition reaction between nitroalkanes and cyclic enones catalysed by a family of *trans*-4-aminoproline based peptides with different chain length (**Scheme 1.35**).[133] Both di- and tetrapeptides promoted the reaction smoothly, but, unexpectedly, the sterochemical outcome did not depend on the the number of catalytic centres present in the structure. Actually, the key factors that controlled the reactivity and stereoselectivity were the bulkiness of the substituents in both the nitroalkane and enone reagents.

[132] Jovanovic, P.; Randelovic, J.; Ivkovic, B.; Suteu, C.; Vujosevic, Z. T.; Savic, V. *J. Serb. Chem. Soc*. **2014**, *79*, 767-778.
[133] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron: Asymmetry* **2006**, *17*, 989-992.



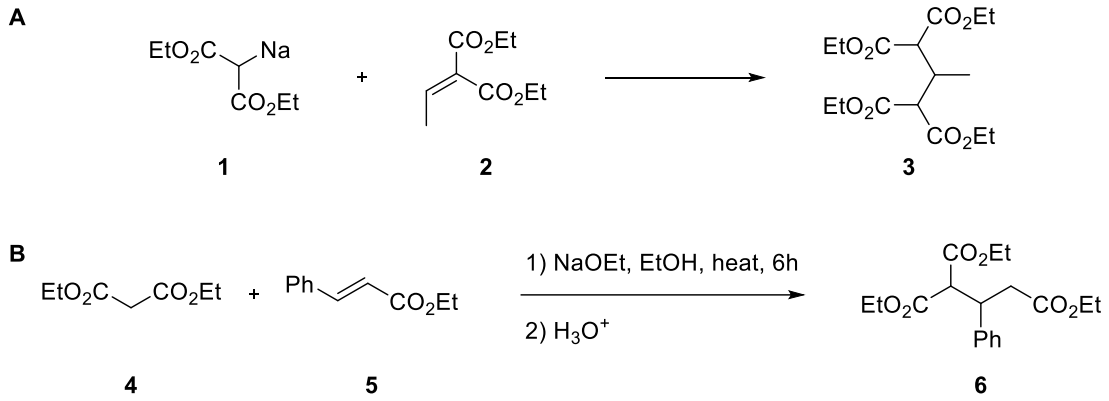
Scheme 1.35. 4-*trans*-aminoproline derived di- and tetrapeptides for the asymmetric Michael reaction between nitroalkenes and cyclic enones.

Chapter 2

Synthesis of Highly Substituted Bicyclic Tetrahydropyrans by Organocatalysed Michael-Henry-Acetalisation Cascade Reactions

2.1 ORGANOCATALYSIS IN ENAMINE ACTIVATED MICHAEL REACTIONS

Michael reactions that involve a conjugate addition of nucleophiles to the β-position of α,β-unsaturated carbonyl compounds are frequently used transformations in the arena of organic synthesis.[1] The very first conjugate addition reaction was conducted by Komnenos in 1883, in which the addition of diethyl sodium malonate **1** to diethyl ethylidenemalonate **2** was described (**Scheme 2.1A**).[2] Nonetheless, the chemistry of conjugate additions did not really begin to be broadly used until the publication of Arthur Michael few years later, when he reported a base-promoted addition of sodium salts of malonates **4** and β-ketoesters to ethyl cinnamate **5** (**Scheme 2.1B**).[3]



Scheme 2.1. First conjugate addition reactions described by A) Komenos and B) Arthur Michael.

From that point on, several nucleophiles have been tested such as β-keto[4] or β-cyano[5] esters, nitroalkanes[6] and organometallic compounds[7]. The variability in the structure of

[1] Perlmutter, A. *Conjugate Addition Reactions in Organic Synthesis,* Pergamon Press, Oxford, **1992**.
[2] Komnenos, T. *Liebigs Ann. Chem*. **1883**, *218*, 145-167.
[3] Michael, A. *J. Prakt. Chem*. **1887**, *35*, 349-356.
[4] a) Elsner, P.; Benardi, L.; Dela Salla, G.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2008**, *130*, 4897-4905. b) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed*. **2006**, *45*, 947-950.
[5] Li, Y.; Wang, C.; Jia, G.; Lu, S.; Li, C. *Tetrahedron* **2013**, *69*, 6585-6590.
[6] a) Rabakalos, C.; Wulff, W.D. *J. Am. Chem. Soc.* **2008**, *130*, 13524-13525. b) Jensen, K. L.; Poulsen, P. H.; Donslund, B. S.; Morana, F.; Jørgensen, K. A. *Org. Lett*. **2012**, *14*, 1516-1519. c) Li, L.; Zhang, S.; Hu, Y.; Li, Y.; Li, C.; Zha, Z.; Wang, Z. *Chem. Eur. J*. **2015**, *21*, 12885-12888.
[7] a) Thaler, T.; Knochel. P. *Angew. Chem., Int. Ed*. **2009**, *48*, 645-648. b) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 794-797.

the Michael acceptors has also been widely studied, making use of the electron-withdrawing nitro[8], nitrile[9], carbonyl[10] or sulphone[11] substituted olefins.

The catalytic asymmetric version of this reaction has become a powerful method for the total synthesis of natural and biologically active compounds.[12] Among the impressive variety of catalysts that have been described in literature over the years, aminocatalysts deserve a special remark. Both primary and secondary amines own the potential to activate the carbonyl substrates by two main routes (**Figure 2.1**).[13] In iminium ion catalysis the reversible condensation of the α,β-unsaturated carbonyl compound with the chiral amine provides an α,β-unsaturated iminium ion with lower energy in its LUMO frontier orbital that reacts with nucleophilic species. On the contrary, in enamine catalysis, the ulterior deprotonation of the iminium ion leads to an enamine nucleophilic intermediate with increased HOMO energy suitable to attack electrophiles. Both catalytic intermediates are considered as opposite and independent entities.[14]

[8] a) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc*. **2008**, *130*, 16464-16465. b) Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem*. **2009**, *74*, 6163-6168. c) Saha, P.; Biswas, A.; Molleti, N.; Singh, V. K.; *J. Org. Chem*. **2015**, *80*, 11115-11122.
[9] a) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J*. **2008**, *14,* 4788-4791. b) Kang, J. Y.; Carter, R. G. *Org. Lett*. **2012**, *14*, 3178-3181. c) Fu, N.; Zhang, L.; Luo, S. *Org. Lett*. **2015**, *17*, 382-385.
[10] Li, B.-J.; Lin, J.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, *4*, 603-606.
[11] a) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc*. **2005**, *127*, 8948-8949. b) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun*. **2007**, 3123-3135.
[12] Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem*. **2002**, 1877-1894.
[13] Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, The Royal Society of Chemistry (RSC Catalysis), Cambridge, **2010**.
[14] Pellisier, H. *Recent Developments in Asymmetric Organocatalysis*, The Royal Society of Chemistry (RSC Catalysis), Cambridge, **2010**.

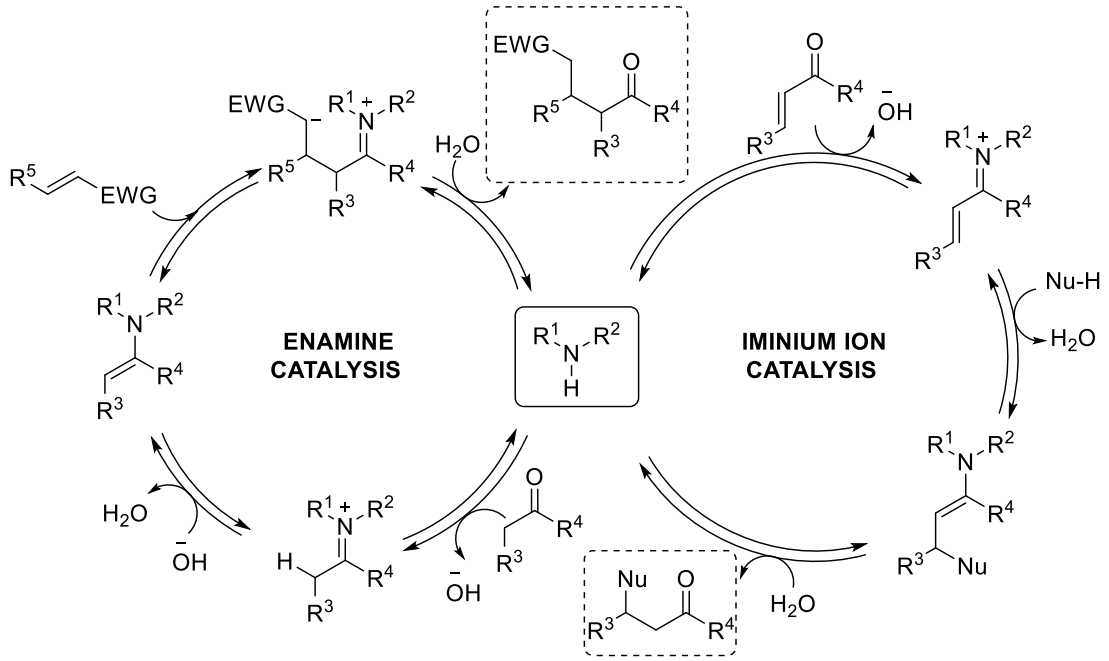


Figure 2.1. Catalytic cycles for the Michael reaction via enamine and imimium ion activation.

There are two main unique features that explain the rapid growth that aminocatalytic Michael reactions have experienced. First, there is no need for prior activation of the carbonyl compound via enolates or silyl enol ether species and, second, time consuming and waste generating additional steps are avoided.[15] However, these methodologies are limited to the utilization of more activated Michael acceptors, due to the lower nucleophilicity of donors capable of forming enamines.

As it is depicted in the catalytic cycle, all the steps are in dynamic equilibrium, so the C-C bond forming step is believed to be crucial for the stereochemical approach of the transformation. Taking into account the effectiveness of *L*-Proline as organocatalyst,[16] the aminocatalysts employed in the Michael reaction are usually pyrrolinide-based heterocycles. One of the most relevant aspects for their high asymmetric induction is the conformational and configurational rigidity of the enamines involved in the transition states. According to steric hindrance issues, the *E*-(*s-trans*) enamine would mainly be formed unless other interactions favour the formation of the *Z*-enamine. Additionally, the catalysts must control the approach of the electrophilic substrate by one of the two possible diastereotopic faces of the generated enamine. This discrimination can be carried out by stereodirecting hydrogen donor substituents in the α-position of the pyrrolidine ring that orientate the approach of the electrophile by hydrogen bonds (**Type**

[15] Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471-5569.
[16] List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett*. **2001**, *3*, 2423-2425.

A catalysts, **Figure 2.2**) or by bulky groups that block one prochiral face of the enamine (**Type B catalysts**, **Figure 2.2**). As a rule, both elements generate final products with opposite configuration.

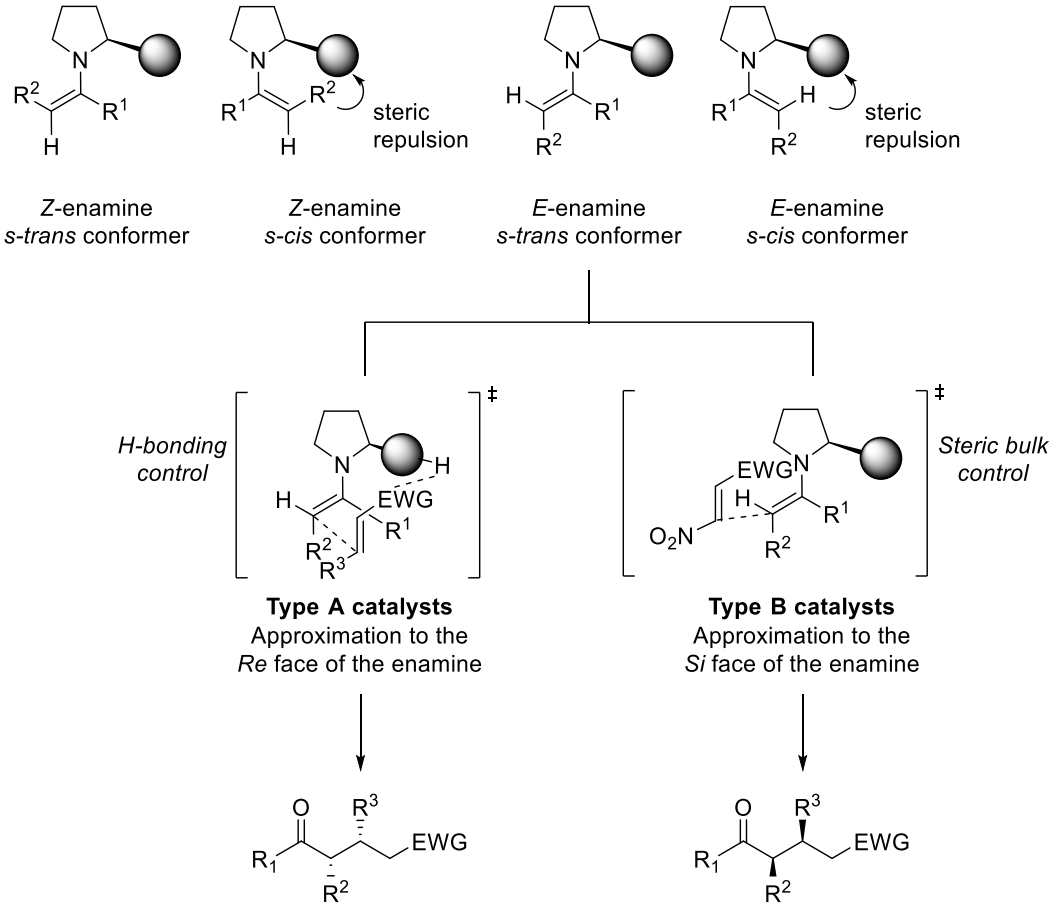


Figure 2.2. Plausible enamine intermediates and approximations in enamine catalysis.

Relevant catalysts that operate by hydrogen bonding control are, for instance, *L*-Proline **7**[16] or tetrazole **8**[17]. Among the group of Type B catalysts, silyl ether **8**[18] and its homologue **10**[19] should be noted (**Figure 2.3**).

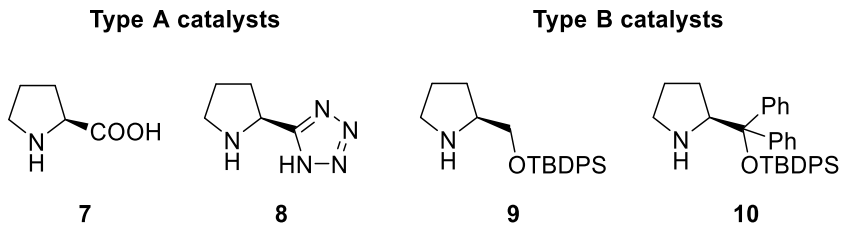


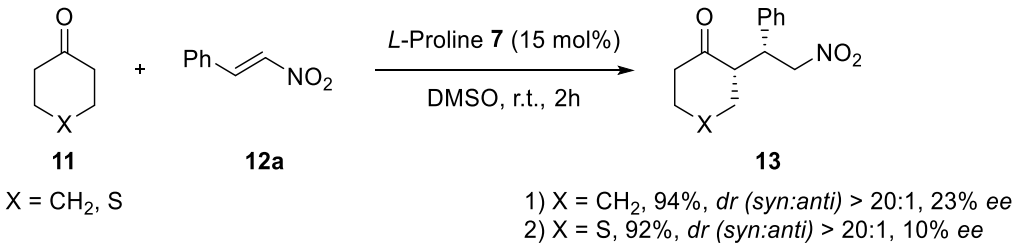
Figure 2.3. Classification of catalysts for the Michael reaction depending on the stereocontrolling elements they possess.

[17] Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun*. **2004**, 1808-1809.
[18] Liu, F.; Wang, S.; Wang, N.; Peng, Y. *Synlett* **2007**, 2415-2419.
[19] Wang, S.-W.; Chen, J.; Chen, G.-H.; Peng, Y.-G. *Synlett* **2009**, 1457-1462.

2.1.1 Michael reaction between cyclic ketones and nitroalkenes

Among the great number of Michael substrates that have been tested over the years, the Michael reaction between cyclic ketones and nitroalkenes is one of the most representative examples ever described.[12] The highest electron-withdrawing potential that nitroalkenes own and the versatility of the final Michael adducts towards further transformations such as the Nef reaction[20], the reduction to an amino group[21] and the nucleophilic displacement[22] make it an attractive transformation.

The first enamine-based catalytic example was reported by List, in which *L*-Proline **7** accomplished the conjugate addition of unmodified ketones to nitroolefins in the presence of DMSO with excellent regio- and diastereoselectivities, albeit with poor enantiomeric excess values (**Scheme 2.2**).[16] However low they may had been, the results illustrated the convenience of enamine catalysis towards this particular reaction.



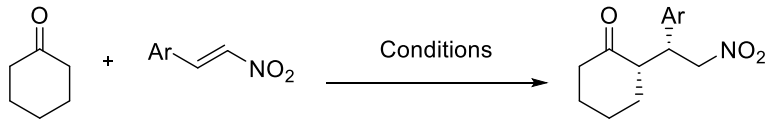
Scheme 2.2. First *L*-Proline catalysed Michael reaction reported by List.

This pioneering reaction encouraged the researchers to develop a plethora of new organocatalysts to perform the amine catalysed conjugate addition reactions. Herein, a brief selection of different organocatalysts for the model Michael reaction between cyclohexanone and trans-β-nitrostyrene will be disclosed.

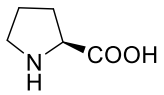
2.1.1.1 Secondary amine catalysts

Since the discovery of List in 2001, secondary-amine catalysts, usually represented by pyrrolidine-based heterocycles, have experienced an impressive development. Some characteristic catalysts are depicted in **Scheme 2.3**.

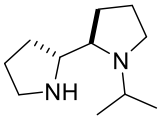
[20] Nef, J. U. *Justus Liebigs Ann. Chem*. **1894**, *280*, 263-291.
[21] a) Laroch, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, New York, **1989**. b) Beck, A. K.; Seebach, D. *Chem. Ber*. **1991**, *124*, 2897-2911. c) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356-1361.
[22] Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434.



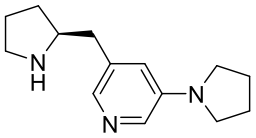
11a **12** (2*S*,1'*R*)-**13**



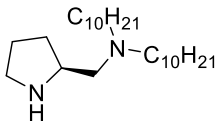
7
(20 mol%)
MeOH, r.t., 2 days
Ar = Ph, 79%, *dr (syn:anti)* 97:3
57% *ee*
Enders, 2002



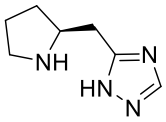
14
(15 mol%)
$CHCl_3$, r.t., 15h
Ar = Ph, 74%, *dr (syn:anti)* 94:6
81% *ee*
Alexakis, 2004



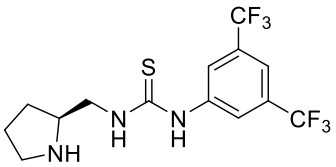
15
(10 mol%)
$CHCl_3$, r.t., 8-48h
98-100%, *dr (syn:anti)* 93:7-98:2
90-96% *ee*
Kotsuki, 2004



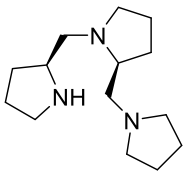
16
(20 mol%)
THF, r.t., 22h
Ar = Ph, 92%, *dr (syn:anti)* 98:2
90% *ee*
Barbas III 2004



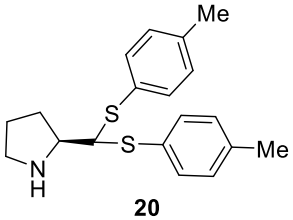
17
(15 mol%)
EtOH/^{i}PrOH (1:1), r.t., 24h
88%, *dr (syn:anti)* > 19:1
91% *ee*
Ley, 2005



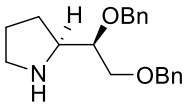
18
(20 mol%)
Neat, 0 ºC, 36-60h
88-95%, *dr (syn:anti)* 94:6-99:1
88-98% *ee*
Tang, 2006



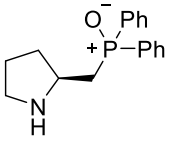
19
(15 mol)
Toluene, 0 ºC, 3-5d
81-99%, *dr (syn:anti)* 96:4-98:2
90-91% *ee*
Gong, 2006



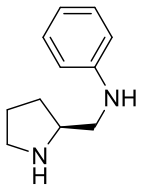
20
(10 mol%)
CH_2Cl_2, r.t., 20-38h
77-90%, *dr (syn:anti)* 99:1
96-99% *ee*
Zhao, 2007



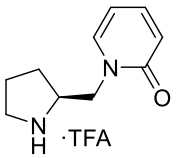
21
(15 mol%)
Toluene, r.t., 12h
77-93%, *dr (syn:anti)* 90:10-97:3
83-91% *ee*
Díez, 2008



22
(15 mol%)
Neat, r.t., 13-26h
92-99%, *dr (syn:anti)* 98:2-99:1
97-99% *ee*
Zhong, 2009



23
(20 mol%)
Toluene, r.t., 48h
77-96%, *dr (syn:anti)* 10:1-12:1
82-89% *ee*
Pansare, 2009



24
(10 mol%)
Neat, r.t., 1.5-4h
70-95%, *dr (syn:anti)* 82:18-97:3
85-97% *ee*
Pramanik, 2017

Scheme 2.3. Reported secondary amine catalysts for the asymmetric Michael addition between cyclohexanone **11a** and different nitroalkenes.

The research group led by Enders modulated the previously described reaction conditions, demonstrating that methanol was the optimal solvent for the reaction.[23] The homogeneity of the resulting mixture was believed to be the main reason behind the improved enantioselectivities observed.

In the following years, several authors designed and tested catalysts bearing hydrogen-bond donating substituents in the α position of the pyrrolidine ring. In 2005, Ley demonstrated that pyrrolidine-tetrazol catalyst **17** was able to improve the performance of *L*-Proline shortening the reaction time and rising the yield, diastereo- and enantioselectivity of the reaction.[24] The replacement of the carboxylic group by its isostere 1,2,4-triazole resulted in better solubility, which was thought to be the main problem of the synthetic transformation. Consecutively, Tang and co-workers tested the suitability of thiourea derivative **18** as catalysts and found that the Michael reaction proceeded smoothly reaching high diastereo- and enantioselectivities.[25] The thiourea motif was considered to enhance the catalytic efficiency by two hydrogen bonding interactions, thus providing a more rigid transition state. Alternatively, Zhong developed the chiral pyrrolidine unit **22** bearing a phosphine oxide moiety to provide a highly stereoselective Michael addition between cyclic ketones and nitroolefins.[26] They evidenced that the strong polar P=O bond was crucial for the excellent stereochemical outcome, allowing water mediated H-bonding interactions with the nitro group. Another remarkable catalyst for the asymmetric conjugate addition transformation was the diamine **23** described by Pansare, by which outstanding results were obtained in terms of stereoselectivity.[27] The observed results were closely related to the H-bond donor ability that the secondary amine of the side chain holds. By last, Pramanik synthesised the pyrrolidine-pyridinone derivative **24** for the Michael transformation under solvent free conditions.[28] The conjugated system exhibited high efficiency even lowering the catalyst load to 10 mol%. Additionally, the reaction times were shortened to at most 4 hours, far below the previously reported examples.

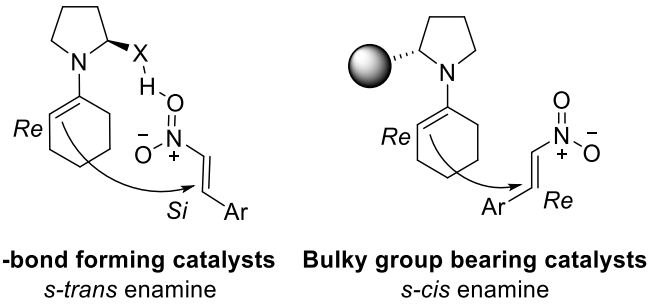
Complementary catalysts that do not include H-donors and hence operate by dint of steric bulk control of one of the two diastereotopic faces have also been studied. In this

[23] Enders, D.; Seki, A. *Synlett*, **2002**, 26-28.
[24] Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611-614.
[25] Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett*. **2006**, *8*, 2901-2904.
[26] Tan, B.; Zeng, X., Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett*. **2009**, *11*, 1927-1930.
[27] Pansare, S. V.; Kirby, R. L. *Tetrahedron* **2009**, *65*, 4557-4561.
[28] Mahato, C. K.; Kundu, M.; Pramanik, A. *Tetrahedron: Asymmetry* **2017**, *28*, 511-515.

regard, catalysts **16**[29], **20**[30] and **21**[31] provided positive results with cyclohexanone yielding the final products in excellent diastereomeric ratios and enantiomeric excesses. Nevertheless, the use of other ketones led to poorer performances. Alternative catalysts are the diamine and triamine catalysts. Whereas Alexakis accounted the first diamine based organocatalyst **14**[32], Kotsuki proved the suitability of the pyrrolidine-pyridine catalyst **15**[33] towards a variety of aromatic olefins. A last representative example is Gong's triamine **19**, which afforded the Michael products of the reaction between cyclohexanone and a range of nitroolefins in high diastereo- and enantioselectivities.[34] It is worth mentioning that all the latter di- and triamines need the incorporation of Brønsted acid additives for the reaction to occur. As the authors suggest, the additive exhibited a vital role by enhancing the rate of the enamine formation step.

Several transition state models have been reported for the aforementioned catalysts concerning the *syn* selectivity and the (2*S*,1'*R*)- stereochemistry of the corresponding Michael adducts. The former is thought to be associated with an acyclic synclinal transition state proposed by Seebach in which there are favourable electrostatic interactions between the nitrogen of the enamine and the nitro group.[35] As for the latter, catalysts are believed to behave in reverse manner. Whereas H-bond forming catalysts favour the formation of the *s-trans* enamine and the attack to the *Si* face of the nitroalkene, catalysts that bear non interacting bulky groups promote the formation of the *s-cis* enamine and the attack to the *Re* face of the Michael acceptor (**Figure 2.4**). In the case of di- and triamines, the key factor has not been yet determined, as both proposals have been described.

[29] a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas III, C. F. *Synthesis* **2004**, *9*, 1509-1521. b) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc*. **2006**, *128*, 4966-4967.
[30] Mandal, T.; Zhao, C.-G. *Tetrahedron Lett.* **2007**, *48*, 5803-5806.
[31] Díez, D.; Antón, A. B.; García, P.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2008**, *19*, 2088-2091.
[32] a) Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611-3614. b) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal*. **2004**, *346*, 1147-1168.
[33] Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc*. **2004**, *126*, 9558-9559.
[34] Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491-493.
[35] Seebach, D.; Goliński, J. *Helv. Chim. Acta* **1981**, *64*, 1413-1423.



H-bond forming catalysts *s-trans* enamine

Bulky group bearing catalysts *s-cis* enamine

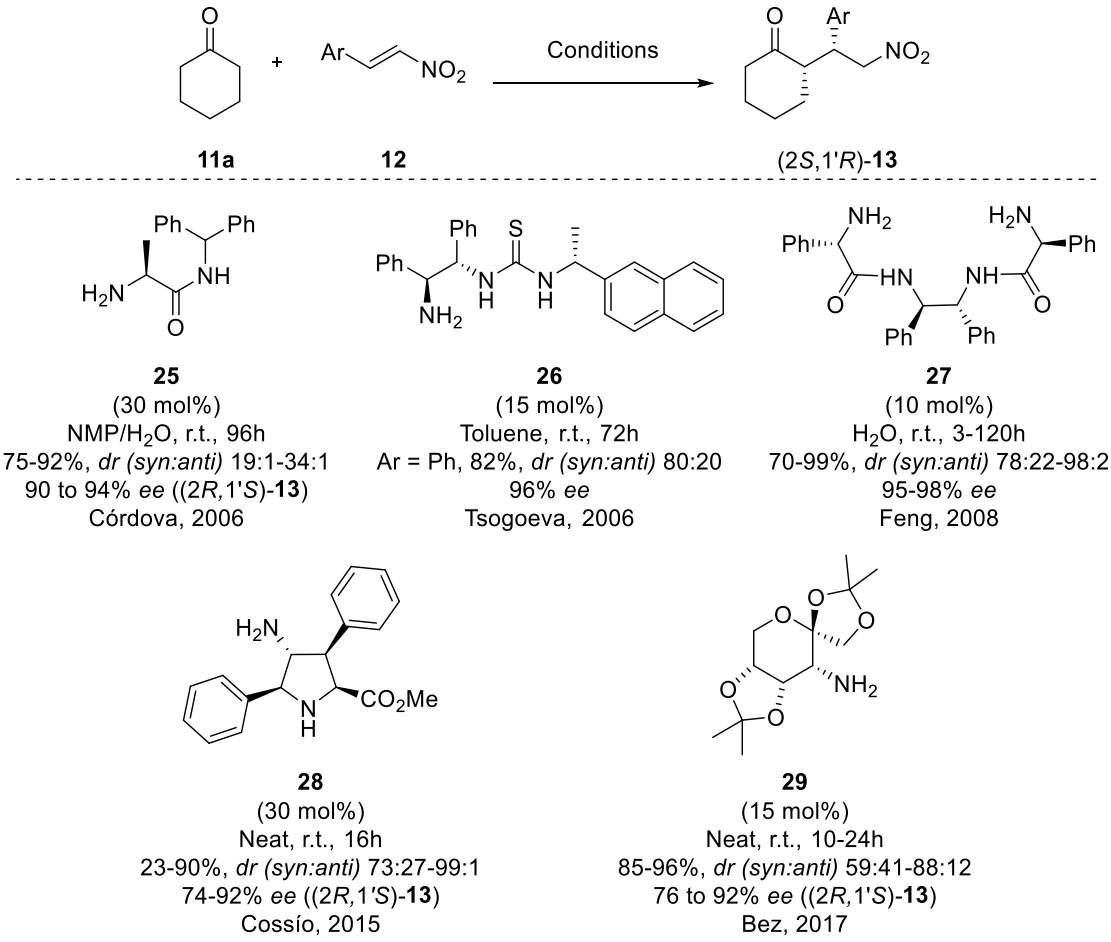
Figure 2.4. Reported transition states to explain the formation of the (2*S*, 1'*R*)- Michael products.

2.1.1.2 Primary amine catalysts

Despite the existence of secondary amine catalysts, it has been demonstrated that they possess a lower catalytic activity when employing cyclic ketones due to the steric congestion in the intermediate enamines. Aiming to overcome this challenge, experts have moved to the use of primary amine catalysts evidencing their convenience for organocatalytic processes (**Scheme 2.4**).

Córdova was the first researcher who stablished the utilization of non-toxic and inexpensive primary amino acid amide **25** catalyst for such reactions. The designed system was able to furnish the final Michael products in high regio-, diastereo- and enantioselectivities in presence of water and a small amount of *N*-methylpyrrolidinone (NMP) as Brønsted acid.[36] The presence of the primary amide was found to play a crucial role regarding stereoselectivity, as a highly organized transition state would be formed by means of hydrogen-bonding interactions between the amido NH and the nitro group.

[36] Xu, Y.; Córdova, A. *Chem. Commun*. **2006**, 460-462.



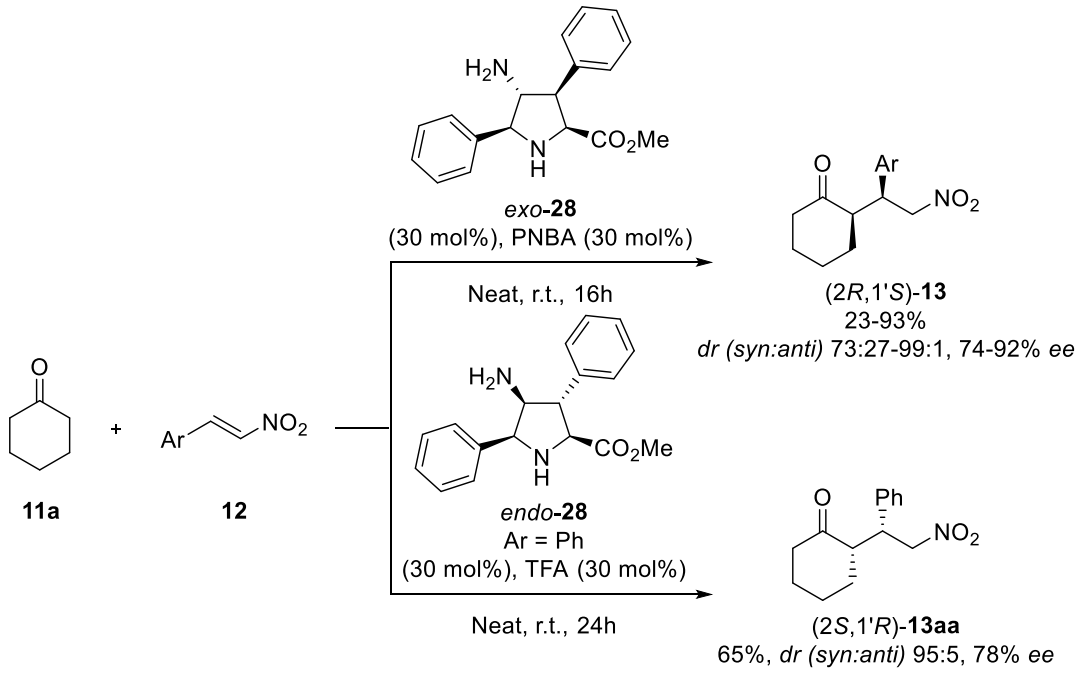
Scheme 2.4. Primary amine catalysts for the Michael addition of cyclohexanone **11a** and aromatic nitrostyrenes.

Within the same year, Tsogoeva reported that bifunctional thiourea-amino catalyst **26** exhibited exceptional performance not only for cyclohexanone, but also for acetone with high degree of enantioselection.[37] Following the same trend, Feng designed the phehylglicine-based diamine **27** for the highly competent Michael addition of cyclohexanone and acetone under mild reaction conditions.[38]

Our research group developed the synthesis of aminopyrrolidine-carboxylate derivative *exo*-**28** for the asymmetric Michael reaction.[39] This catalyst provided the corresponding Michael adducts in presence of *p*-nitrobenzoic acid (PNBA) with good diastereo- and enantioselectivities when employing cyclohexanone as nucleophile, regardless of the nature of the Michael acceptor.

[37] a) Tsogoeva, S. B.; Wei, S. *Chem. Commun*. **2006**, 1451-1453.
[38] Xiong, Y.; Wen, Y.; Wang, F.; Gao, B.; Liu, X.; Huang, X.; Feng, X. *Adv. Synth. Catal*. **2007**, *349*, 2156-2166.
[39] Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F. P. *J. Org. Chem*. **2015**, *80*, 5588-5599.

Despite the demonstrated efficiency of the precursor 4-nitro derivatives towards the aldol reaction of cyclic ketones,[40] they were only able to promote the reaction in combination with TFA, and the observed conversions and enantiomeric excess values were moderate. Changing the additive into benzoic acid resulted in a three-component cyclisation reaction that enabled the efficient synthesis of bicyclic octahydro-*2H*-indol-2-one scaffolds possessing three chiral centres.[41] The suitability of the catalyst relied on the HOMO activation promoted by the enamine moiety likewise the LUMO activation of the Michael acceptor caused by the hydrogen bond between the nitro group and the protonated exocyclic amino group of the pyrrolidine ring. Particularty interesting resulted the association of the *endo*/*exo* configuration of the catalyst with the stereochemical induction. While the *exo*-**28** cycloadduct was responsible for the (2*R*,1'*S*) configuration of the final product, its diastereomeric *endo*-**28** cycloadduct led to opposite enantiomers, being, however, less stereoselective (**Scheme 2.5**).



Scheme 2.5. The asymmetric Michael reaction developed by Cossío and co-workers.

The last example was not long ago accounted by Bez, in which *D*-fructose motif bearing monofunctional primary amine **29** catalysed the enantioselective Michael

[40] a) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci*. **2012**, *3*, 1486-1491. b) Retamosa, M. G.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem*. **2015**, 2503-2516.
[41] Retamosa, M. G.; Ruiz-Olalla, A.; Bello, T.; de Cózar, A.; Cossío, F. P. *Angew. Chem., Int. Ed*. **2018**, *57*, 668-672.

addition of unactivated ketones to nitroolefins.[42] In addition to cyclohexanone, cyclopentanone and acetone were found to be suitable for the reaction, reaching in all cases good yields and diastereoselectivities, as well as good to excellent enantioselectivities.

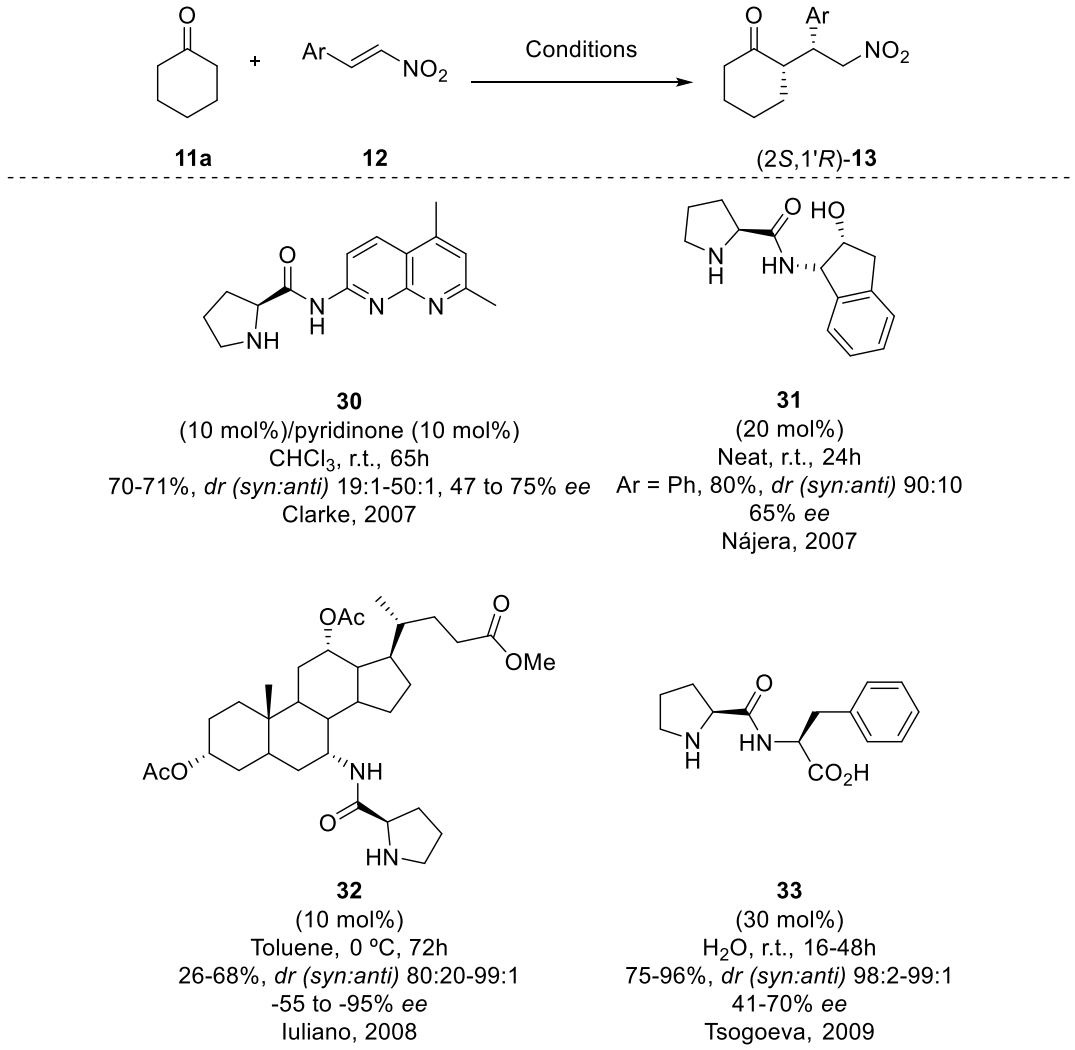
2.1.1.3 Secondary amine based peptidic catalysts

As it has been illustrated in the previous Chapter, peptidic catalysts display exclusive features for the organocatalytic transformations.[43] Aside from the examples that have been already cited, some of the first catalysts for the particular case of cyclic ketones are depicted in **Scheme 2.6**.

In 2007, Clarke and co-workers synthesised proline-naphthyridine catalyst **30** for the asymmetric Michael addition.[44] Surprisingly, the chiral catalyst gave rise to racemic compounds when operating alone, but the addition of achiral pyridinone shifted completely the catalytic activity, reaching moderate to good enantiomeric excess values. The self-assembled organocatalyst would favour the formation of complementary H-bonding interactions that facilitate either the catalytic activity or selectivity.

Consecutively, Nájera achieved the *syn* 1,4-addition products with moderate enantioselectivities in shorter reaction times when employing catalysts **31**. Fortunately, the reaction was widely applied to other nucleophilic acyclic ketones, under which the stereochemical outcome of the reaction raised significantly.[45] Another characteristic catalyst for the asymmetric conjugate addition was the cholic acid derivative **32** synthesised by Iuliano, which enabled the formation of the opposite enantiomer of the final Michael product in excellent diastereomeric ratios and good enantiomeric excesses.[46] The last example consists of the H-Pro-Phe-OH peptide **33** described by Tsogoeva to perform the asymmetric Michael reactions in water. In addition to cyclohexanone, acetone was also tested as nucleophile, but the enantiomeric excess of the final product was almost racemic.[47]

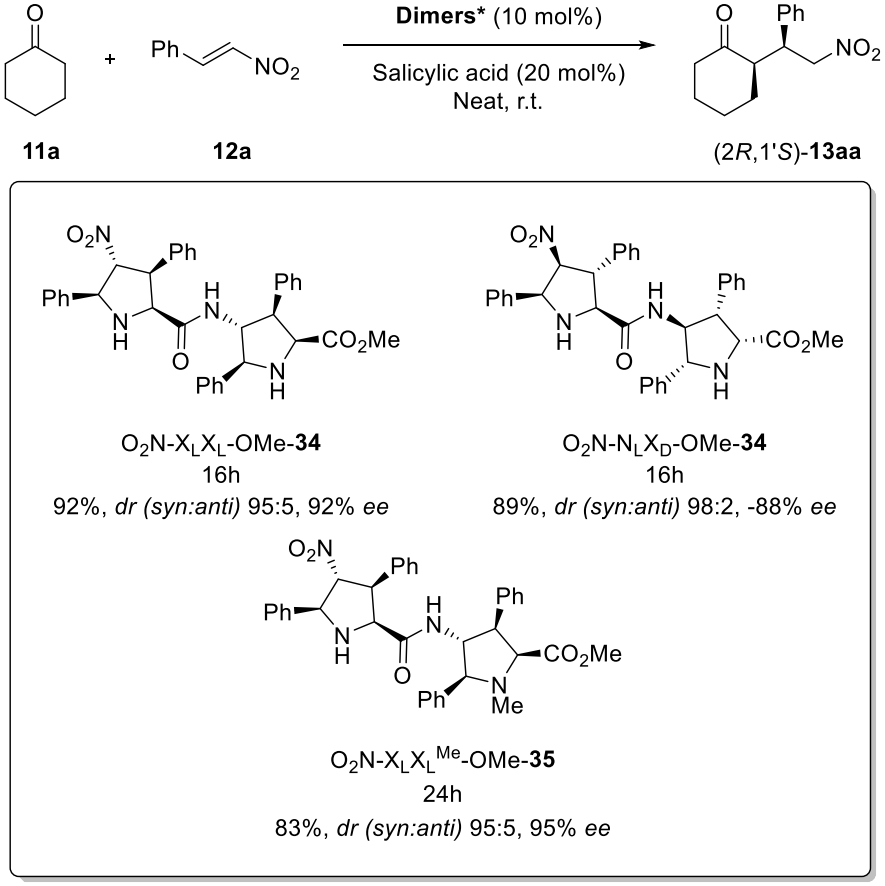
[42] Vanlaldinpuia, K.; Bora, P.; Basumatary, G.; Mohanta, R.; Bez, G. *J. Chem. Sci*. **2017**, *129*, 1603-1610.
[43] Wennemers, H. *Chem. Commun*. **2011**, *47*, 12036-12041.
[44] Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed*. **2007**, *46*, 930-933.
[45] Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nagel Y.; Nájera, C. *Eur. J. Org. Chem*. **2007**, 2328-2343.
[46] Puleo, G. L.; Iuliano, A. *Tetrahedron: Asymmetry* **2008**, *19*, 2045-2050.
[47] Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem*. **2009**, *7*, 4279-4284.



Scheme 2.6. Peptidic catalysts for the asymmetric Michael reaction between cyclohexanone **11a** and nitroalkenes.

In spite of the existence of unnatural amino acid-based peptidic organocatalysts for the asymmetric conjugate addition reactions only a few examples have been detailed concerning nucleophilic cyclic ketones.[48] Aware of this limitation, and bearing in mind the positive results obtained with the former **28** derivatives and their high functionalization (*vide supra*), our research group focused its attention on the synthesis and study of a family of γ-dipeptides as organocatalysts (**Scheme 2.7**).[49]

[48] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron: Asymmetry*, **2006**, *17*, 989-992.
[49] Dr. Andrea Ruiz-Olalla from Universidad del País Vasco/Euskal Herriko Unibertsitatea in her PhD thesis *Novel Studies on Enamine and Acid Organocatalysts in Carbon-Carbon Bond Forming Reactions* disserted in March 2016. Her dissertation text is available free of charge via the Internet at http://addi.ehu.es/handle/10810/20926.



Scheme 2.7. The γ-dipeptide organocatalysts for the asymmetric Michael reaction developed by our research group.

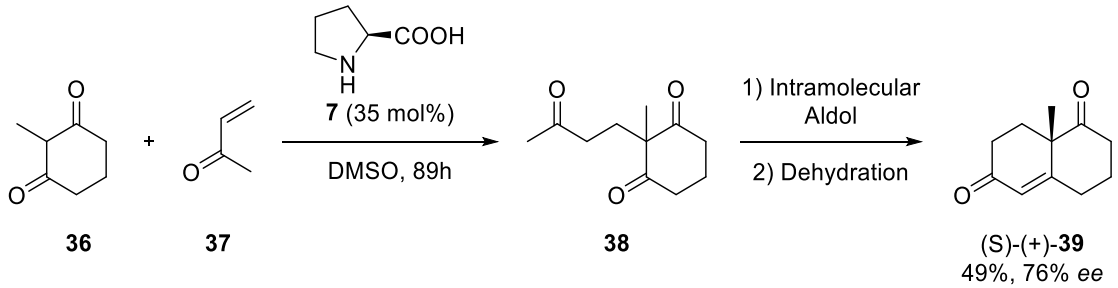
Among all the tested dimeric species, catalyst O_2N-X_L-X_L-OMe-**34**, O_2N-N_L-X_D-OMe-**34** and O_2N-X_L-X_L^{Me}-OMe-**35** showed the best performance towards Michael reactions, reaching excellent results in terms of yield, diastereo- and enantioselectivity in the presence of salicylic acid (**Scheme 2.7**). Along the extensive research work that was carried out, matching and mismatching effects were observed, taking into account the Proline-like or *anti*-Proline-like behaviour each monomeric unit shows. Briefly described, X_L and N_D monomers generated *anti*-Proline (2*R*,1'*S*)- Michael products whereas X_D and N_L monomers led to Proline-like (2*S*,1'*R*)- adducts. In addition, O_2N-X_L-X_L-OMe-**34** and O_2N-X_L-X_L^{Me}-OMe-**35** catalysts also provided good results when 1,1-bis(phenylsulphonyl)ethane was used as Michael acceptor.

2.2 ORGANOCATALYTIC ENANTIOSELECTIVE DOMINO MICHAEL-HENRY-ACETALISATION REACTIONS

One of the most appealing characteristics of the Michael reaction is that the conjugate addition product can suffer further inter- or intramolecular reactions that generate more

complex molecules by domino or cascade processes.[50] These reactions were defined by Tietze as methodologies in which two or more chemical bonds are formed under the same reaction conditions based on the functional groups produced in the previous step.[51] Such features make them rather short and atom-economical transformations avoiding protection/deprotection steps and intermediates' isolation. Moreover, they are one of the most frequently used transformations for the synthesis of structurally complex bioactive molecules and natural products.

The first report based on organocatalytic asymmetric domino transformation was accomplished by the research group led by Barbas III, in which pyrrolidine type secondary amines that bear a carboxylic functionality were able to catalyze the Robinson annulation of 2-methyl-1,3-cyclohexadione **36** to methylvinyl ketone **37** in good yields and enantioselectivities (**Scheme 2.8**).[52]



Scheme 2.8. The first organocatalytic asymmetric domino reaction reported by Barbas III.

Since then, the development of asymmetric one-pot transformations has witnessed an exponential growth.[53] Among the vast small organic molecules that researchers have utilized for the cited processes, benzotetramisole derivatives[54], Brønsted acid catalysts[55],

[50] Sukhorukov, A. Y.; Sukhanova, A. A.; Zlotin, S. G. *Tetrahedron* **2016**, *72*, 6191-6281.
[51] Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[52] Bui, T.; Barbas III, C. F. *Tetrahedron Lett*. **2000**, *41*, 6951-6954.
[53] For excellent reviews regarding organocatalytic asymmetric cascade transformations, see: a) Enders, D.; Grondal, C.; Hüttl, M. R. *Angew. Chem., Int. Ed*. **2007**, *46*, 1570-1581. b) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492-8509. c) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res*. **2015**, *48*, 1832-1844. d) Chanda, T.; Zhao, J. C.-G. *Adv. Synth. Catal*. **2018**, *360*, 2-79.
[54] a) Ahlemeyer, N. A.; Birman, V. B. *Org. Lett*. **2016**, *18*, 3454-3457. b) Izquierdo, J.; Pericás, M. A. *ACS Catal.* **2016**, *6*, 348-356.
[55] For selected examples, see: a) Shi, F.; Zhang, H.-H.; Sun, X.-X.; Liang, J.; Fan, T.; Tu, S.-J. *Chem. Eur. J.* **2015**, *21*, 3465-3471. b) Dai, W.; Lu, H.; Li, X.; Shi, F.; Tu, S.-J. *Chem. Eur. J*. **2014**, *20*, 11382-11389. c) Yang, B.-M.; Cai, P.-J.; Tu, Y.-Q.; Yu, Z.-X.; Chen, Z.-M.; Wang, S.-H.; Wang, S.-H.; Zhang, F.-M. *J. Am. Chem. Soc.* **2015**, *137*, 8344-8347.

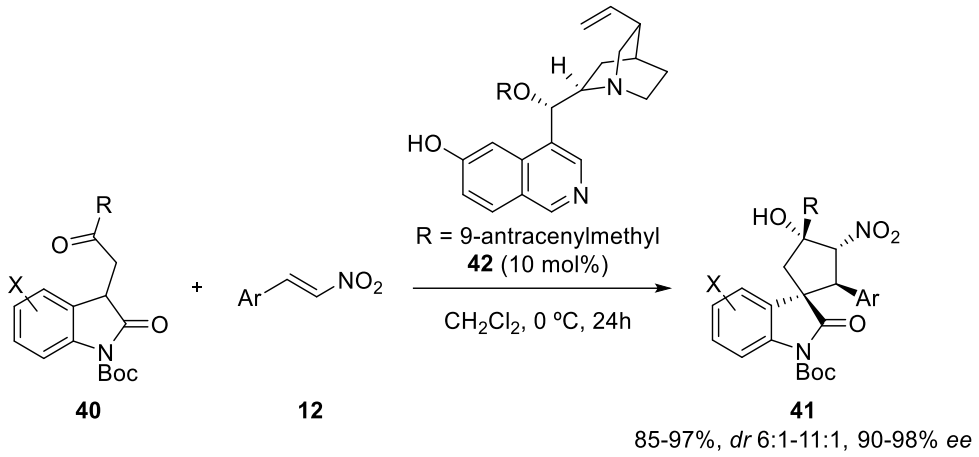
N,*N*'-dioxides[56], *N*-heterocyclic carbenes[57], *cinchona* alkaloids[58] and other multifunctional thiourea[59] and squaramide[60] catalysts and primary[61] or secondary[62] amines can be mentioned.

Taking into consideration the versatile reactivity and ease of transformation into other functional groups that nitro- group bearing substrates hold,[20-22] the intermolecular Michael-Henry sequence has shown particular interest. In fact, in comparison with multistep synthesis, these tandem processes are the most direct methods for the construction of structures with multiple stereogenic centres.[58c] During the last decade, a great deal of highly efficient asymmetric domino Michael-Henry reactions have been described. Herein, some of the most characteristic examples will be highlighted.

Cinchona alkaloids have exhibited great performance in promoting organocatalytic Michael-Henry cascade reactions. In this regard, Albertshofer et al. described the antracenyl-quinine derivative **42** catalysed synthesis of highly substituted spirocyclopentaneoxindoles with four contiguous stereogenic centres.[63] The reaction resulted applicable to a range of nitrostyrenes and oxindole derivatives, reaching in all cases excellent yields, diastereo- and enantioselectivities (**Scheme 2.9**). Consequently,

[56] a) Feng, J.; Fu, X.; Chen, Z.; Lin, L.; Liu, X.; Feng, X. *Org. Lett*. **2013**, *15*, 2640-2643. b) Feng, J.; Lin, L.; Yu, K.; Liu, X.; Feng, X. *Adv. Synth. Catal*. **2015**, *357*, 1305-1310.
[57] For an excellent review, check: Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Synthesis* **2017**, *49*, 451-471.
[58] For selected examples, see: a) Connon, S. J. *Chem. Commun*. **2008**, 2499-2510. b) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc*. **2008**, *130*, 14416-14417. c) Jaiswal, P. K.; Biswas, S.; Singh, S.; Pathak, B.; Mobin, S. M.; Samanta, S. *RSC Adv*. **2013**, *3*, 10644-10649. d) Huang, J.-R.; Sohail, M.; Taniguchi, R.; Monde, K.; Tanaka, F. *Angew. Chem., Int. Ed*. **2017**, *56*, 5853-5857. e) Capobianco, A.; Di Mola, A.; Intintoli, V.; Massa, A.; Capaccio, V.; Roiser, L.; Waser, M.; Palombi, L. *RSC Adv*. **2016**, *6*, 31861-31870.
[59] For selected examples, see: a) Tiso, S.; Palombi, L.; Vignes, C.; Di Mola, A.; Massa, A. *RSC Adv*. **2013**, *3*, 19380-19387. b) Kang, K.-T.; Kim, S.-G. *Synthesis* **2014**, *46*, 3365-3373. c) Dou, X.; Han, X.; Lu, Y. *Chem. Eur. J.* **2012**, *18*, 85-89. d) Mei, R.-Q.; Xu, X.-Y.; Peng, L.; Wang, F.; Tian, F.; Wang, L.-X. *Org. Biomol. Chem*. **2013**, *11*, 1286-1289.
[60] For selected examples, see: a) Yang, W.; He, H.-X.; Gao, Y.; Du, D.-M. *Adv. Synth. Catal*. **2013**, *355*, 3670-3678. b) Blümel, M.; Chauhan, P.; Hahn, R.; Raabe, G.; Enders, D. *Org. Lett*. **2014**, *16*, 6012-6015. c) Chauhan, P.; Urbanietz, G.; Raabe, G.; Enders, D. *Chem. Commun*. **2014**, *50*, 6853-6855. d) Chauhan, P.; Mahajan, S.; Raabe, G.; Enders, D. *Chem. Commun*. **2015**, *51*, 2270-2272.
[61] For selected examples, see: a) Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Eur. J. Org. Chem.* **2012**, 1318-1327. b) Li, J.-H.; Du, D.-M. *Org. Biomol. Chem*. **2015**, *13*, 9600-9609. c) Sun, X.; Fei, J.; Zou, C.; Lu, M.; Ye, J. *RSC. Adv*. **2016**, *6*, 106676-106679.
[62] a) Shen, J.; Liu, D.; An, Q.; Liu, Y.; Zhang, W. *Adv. Synth. Catal*. **2012**, *354*, 3311-3325. b) Zeng, X.; Ni, Q.; Raabe, G.; Enders, D. *Angew. Chem., Int. Ed*. **2013**, *52*, 2977-2980. c) Poulsen, P. H.; Feu, K. S.; Paz. B. M.; Jensen, F.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2015**, *54*, 8203-8207. d) Zhang, J.; Ajitha, M. J.; He, L.; Liu, K.; Dai, B.; Huang, K.-W. *Adv. Synth. Catal*. **2015**, *357*, 967-973. e) Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D. K. B.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2016**, *138*, 6412-6415.
[63] Albertshofer, K.; Tan, B.; Barbas III, C. F. *Org. Lett*. **2012**, *14*, 1834-1837.

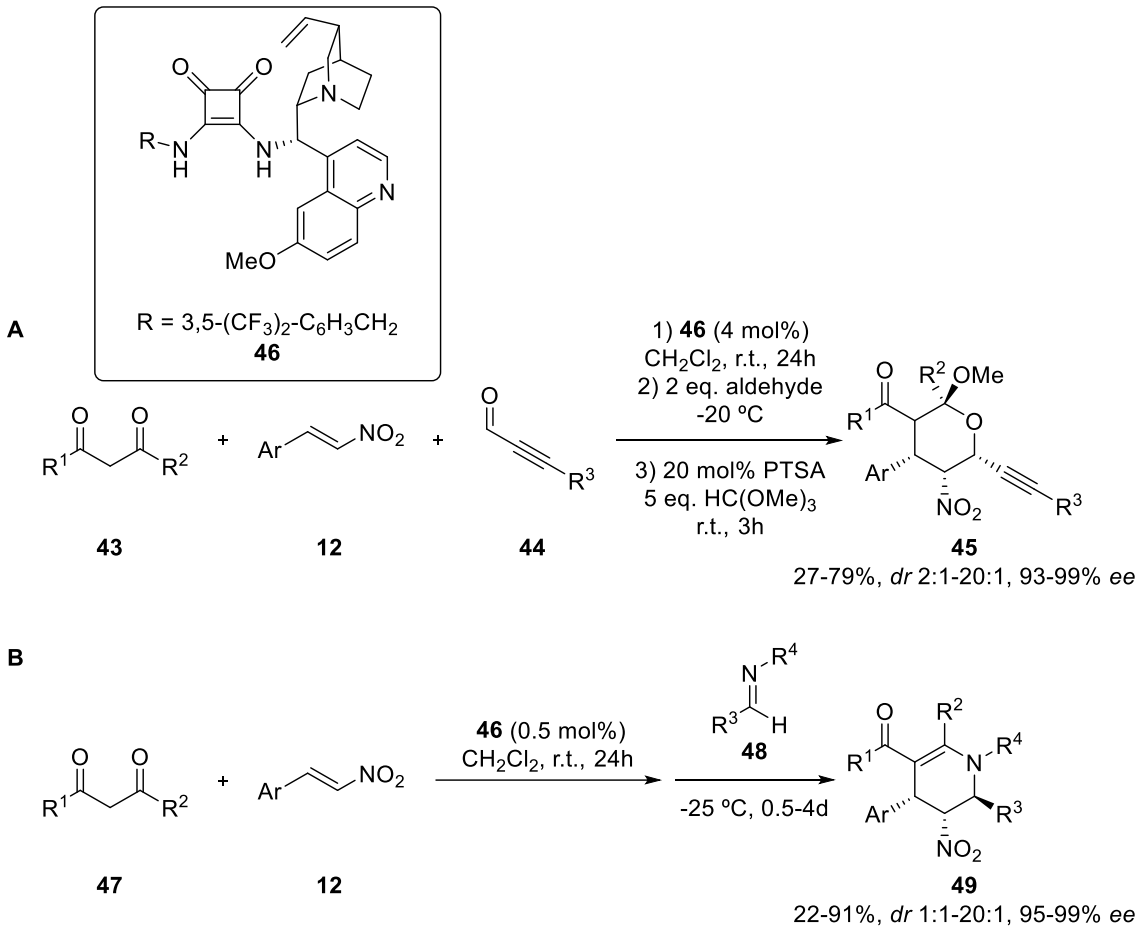
benzyl protected cinchonidine was employed by the research group led by Samanta for the one-pot stereoselective synthesis of tetrahydrocarbazol derivatives with good to excellent yields, high diasteromeric ratios and excellent enantiomeric excess values.[58c]



Scheme 2.9. Organocatalytic Michael-Henry cascade reaction between various oxindoles and nitroolefins reported by Albertshofer et al.

The bifunctional squaramide derivatives of quinine have also been widely used for one-pot synthetic routes. Enders and co-workers have described the most representative catalyst **46** and tested its applicability towards the generation of highly functionalized tetrahydropyrans[64] and tetrahydropyridines[60c]. In all cases, the stereochemical outcome of the reaction was excellent with very low catalyst load, although the chemical yields ranged from moderate to good (**Scheme 2.10**). Shortly after, the same catalyst was found to be suitable for indolin-3-one substrates.[65]

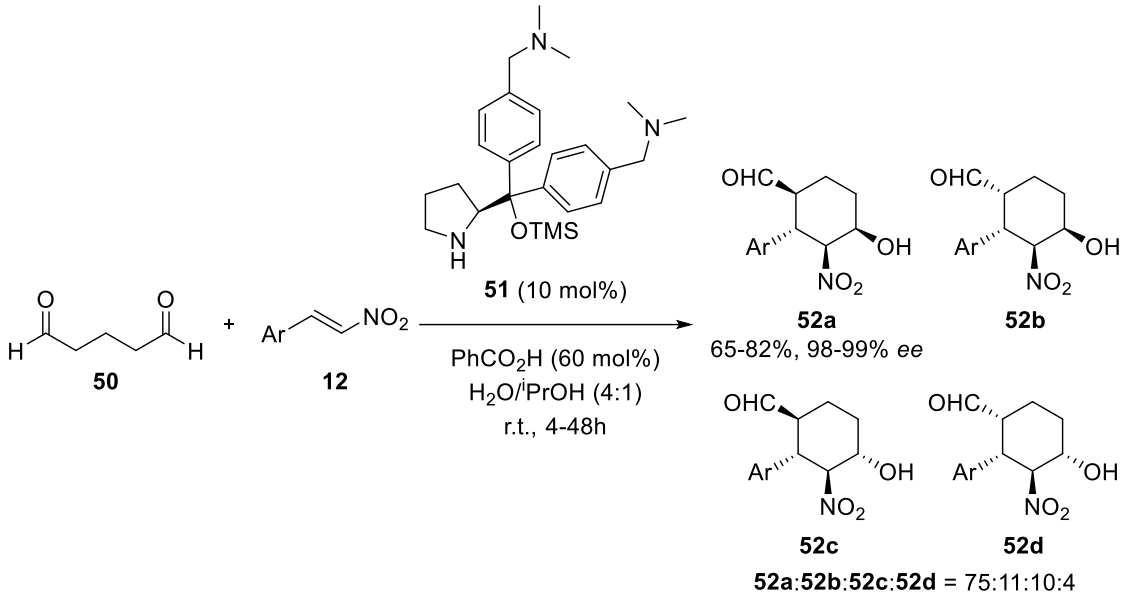
[64] Hahn, R.; Raabe, G.; Enders, D. *Org. Lett*. **2014**, *16*, 3636-3639.
[65] Mahajan, S.; Chauhan, P.; Loh, C. C. J.; Uzungelis, S.; Raabe, G.; Enders, D. *Synthesis* **2015**, *47*, 1024-1031.



Scheme 2.10. Bifunctional squaramide catalyst **46** for the domino Michael-Henry-cyclisation reactions for the synthesis of A) tetrahydropyrans and B) tetrahydropyridines designed by Enders.

Finally, proline type catalysts should be mentioned as well. In 2011, Headley unveiled the use of the recyclable catalyst **51** for the synthesis of highly substituted cyclohexane rings in aqueous media (**Scheme 2.11**).[66] The most important advantage of the catalyst was the formation of an ammonium ionic liquid in the reaction environment, which made it soluble in water in the presence of the acidic additive. Recyclability experiments showed that the catalyst can be reused at least four times with no loss in diastereo- and enantioselectivity but a slight drop in yield.

[66] Chintala, P.; Ghosh, S. K.; Long, E.; Headley, A. D.; Ni, B. *Adv. Synth. Catal*. **2011**, *353*, 2905-2909.



Scheme 2.11. The proline-based catalytic system described by Headley.

Within the same context, Hong and co-workers described the use of Jørgensen-Hayashi catalyst for the tandem Michael-Henry-cyclisation reaction between succinaldehyde and nitroolefins. The final cyclopentanecarbaldehydes contained four contiguous stereogenic centres and were obtained in good yields and excellent enantioselectivities.[67] The same derivative was further applied to glutaraldehyde surrogates that gave access to 3-oxabicyclo[3.3.1]nonan-2-ones in an enantioselective manner.[68]

Interestingly, proline-based catalysts have shown paramount activities concerning the synthesis of tetrahydropyran skeletons, which constitute a core structure of a wide array of bioactive natural products. The next section gives a deeper account on the topic.

2.2.1 Synthetic routes towards Tetrahydropyran skeletons

Tetrahydropyrans (THPs) are six-membered oxygenated heterocycles that incorporate up to five stereogenic centres and possess high diversity of functionalities. They are found not only in natural products and biologically active molecules, but also in carbohydrates that take part in a large number of metabolic processes, both in plants and animals. Some examples are gathered in **Figure 2.5**.[69]

[67] Hong, B.-C.; Chen, P.-Y.; Kotame, P.; Lu, P.-Y.; Lee, G.-H.; Liao, J.-H. *Chem. Commun*. **2012**, *48*, 7790-7792.
[68] Hong, B.-C.; Lan, D.-J.; Dange, N. S.; Lee, G.-H.; Liao, J.-H. *Eur. J. Org. Chem*. **2013**, 2472-2478.
[69] For a recent review, check: Vetica, F.; Chauhan, P.; Dochain, S.; Enders, D. *Chem. Soc. Rev*. **2017**, *46*, 1661-1674.

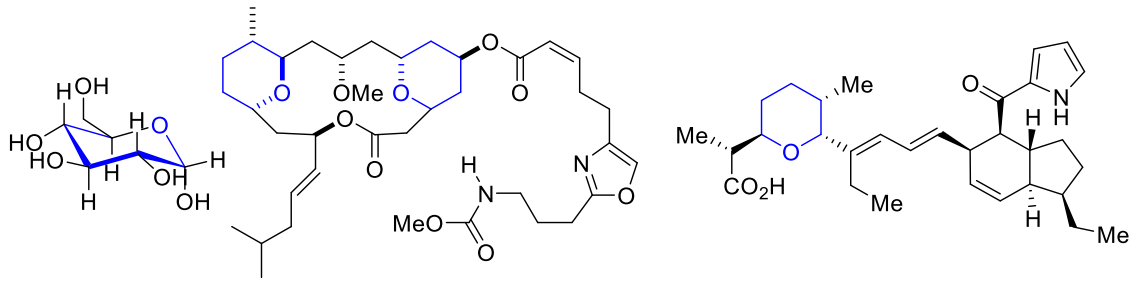
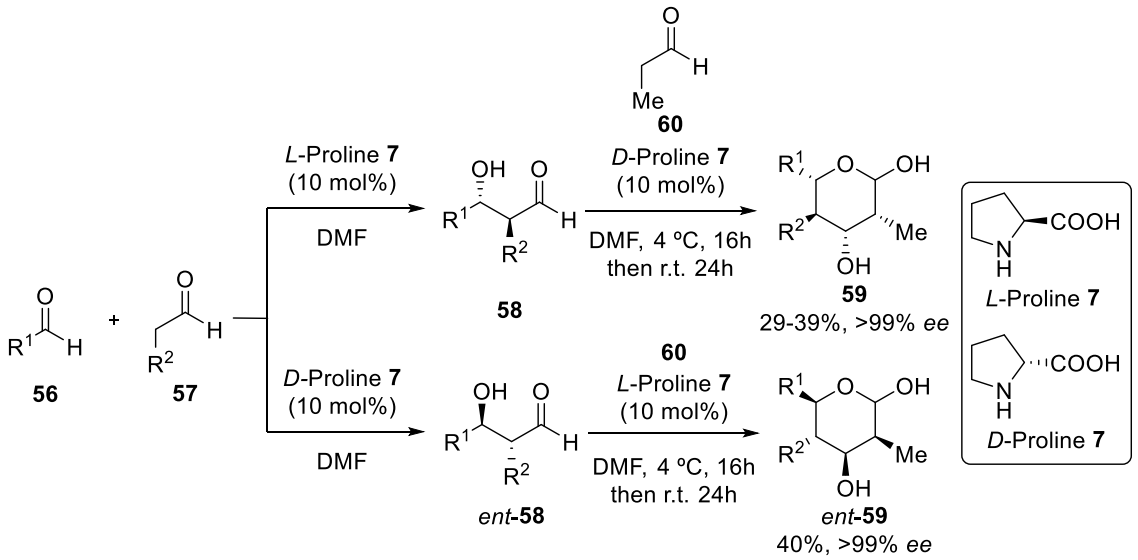


Figure 2.5. Natural products and bioactive compounds containing THP core (in blue).

Several methods have been developed for the construction of such molecular scaffolds among which asymmetric organocatalysis deserves special attention. Although a few examples exist as for organocatalysts that operate through H-bonding interactions[70] and primary amines[71], secondary amines are by far the most common catalysts. In this arena, the first organocatalytic synthesis of THP moieties was accomplished by Córdova in 2005. The iterative aldol reaction between three carbonyl compounds gave access to the corresponding hexoses in excellent chemo-, diastereo- and enantioselectivities.[72] Unfortunately, the initial one-pot strategy resulted unsuccessful in terms of yield, so the aldol intermediate **58** needed to be isolated performing a two-step synthesis. In this way, it was possible to reach enantiomeric hexoses, depending on the chirality of the catalysts employed (**Scheme 2.12**).

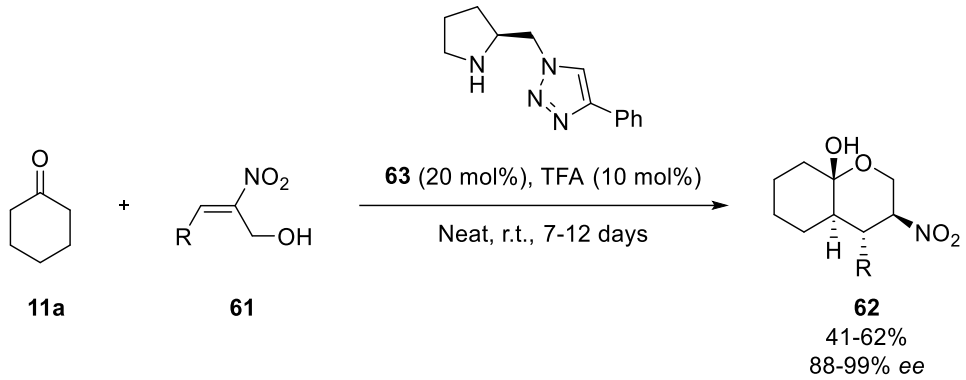
[70] a) Asano, K.; Matsubara, S. *J. Am. Chem. Soc*. **2001**, *133*, 16711-16713. b) Fukata, Y.; Miyaji, R.; Okamura, T.; Asano, K.; Matsubara, S. *Synthesis* **2013**, 1627-1634. c) Ref. 64.
[71] a) Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas III, C. F. *Proc. Natl. Acad. Sci. U. S. A*. **2010**, *107*, 20672-20677. b) Cui, H.-L.; Tanaka, F. *Chem. Eur. J*. **2013**, *19*, 6213-6216.
[72] Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343-1345.



Scheme 2.12. The first organocatalytic iterative aldol approach to THP skeleton.

This work inspired other research groups to work on organocatalytic approaches for the construction of tetrahydropyran skeletons.[73] The majority of them have been performed by means of Michael/acetalyzation sequences between α,β-unsaturated aldehydes and nitroalcohols where the sterochemical outcome is induced by diphenylprolinol silyl ether catalysts.[74] The group of Bonne and Rodriguez, on the other side, made use of the same type of catalyst to perform a two-step enantioselective synthesis of 2,3,4-trisubstituted tetrahydropyrans via chemoselective *C-N* cleavage of bicycle[3.2.1]octanes synthesised from 1,2-ketoamides and enals.[75] It is noteworthy that there is one only example that makes use of cyclohexanone as nucleophile being a triazole based proline the catalyst under which the reaction operates (**Scheme 2.13**).[76]

[73] a) Following Morita-Bailys-Hillman route: Han, B.; Xie, X.; Huang, W.; Li, X.; Yang, L.; Peng, C. *Adv. Synth*. *Catal*. **2014**, *356*, 3676-3682. b) By oxa-Diels-Alder sequence: Lu, L.-Q.; Xing, X.-N.; Wang, X.-F.; Ming, Z.-H.; Wang, H.-M.; Xiao, W.-J. *Tetrahedron Lett*. **2008**, *49*, 1631-1635. c) By [2+2] cyloaddition-hemiacetalisation route: Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem., Int. Ed*. **2012**, *51*, 4104-4107.
[74] a) Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett*. **2009**, *11*, 4056-4059. b) Wei, M.-H.; Zhou, Y.-R.; Gu, L.-H.; Luo, F.; Zhang, F.-L. *Tetrahedron Lett*. **2013**, *54*, 2546-2548.
[75] D'Elia, C. S.; Goudedranche, S.; Constantieux, T.; Bella, M.; Bonne, D.; Rodriguez, J. *Adv. Synth. Catal.* **2017**, *359*, 3638-3641.
[76] Chandrasekhar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Rao, K. V.; Jagadesh, B. *Chem. Commun*. **2009**, 4985-4987.

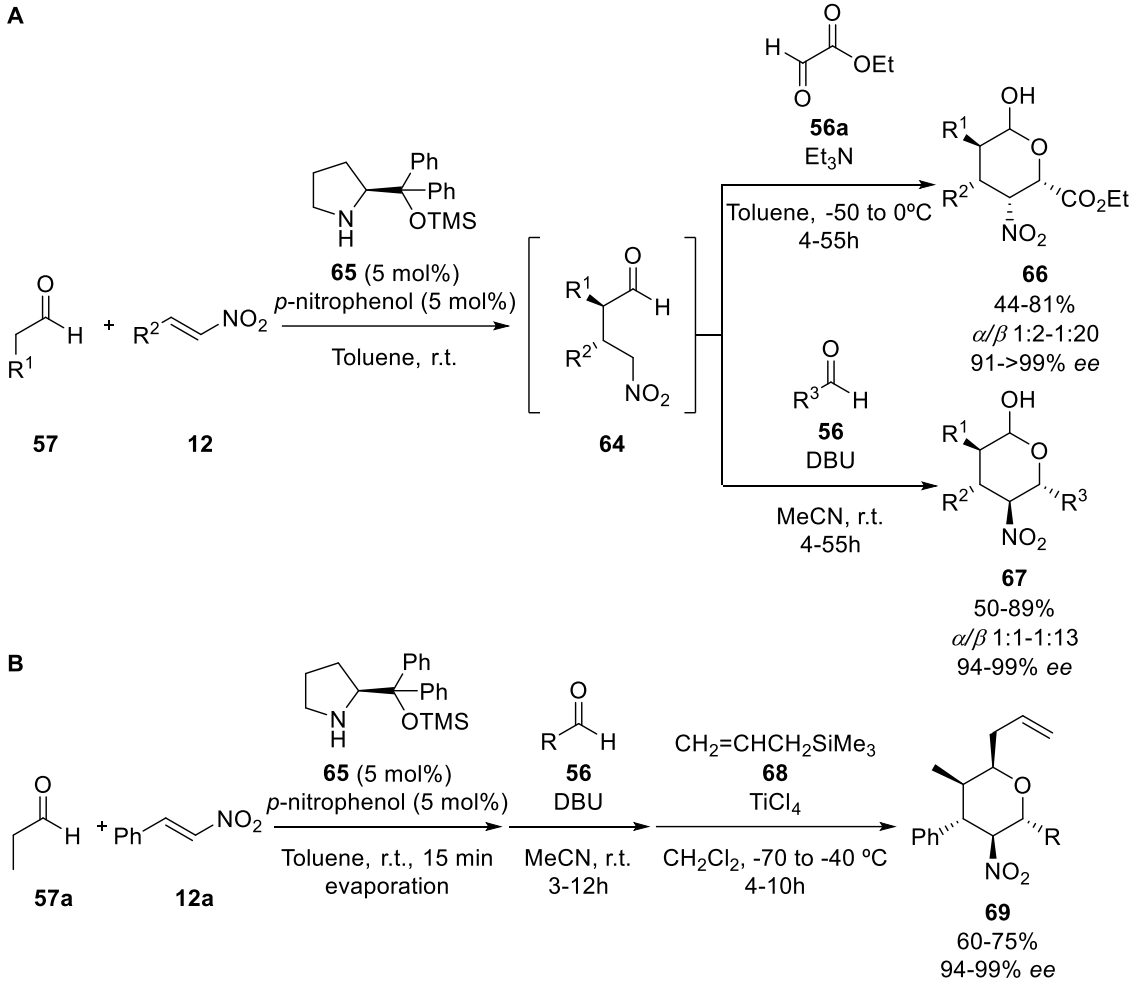


Scheme 2.13. Michael-acetalisation reaction between cyclohexanone and 2,3-disubstituted nitroolefins described by Chandrasekar.

2.2.1.1 Michael-Henry-cyclisation reaction for the synthesis of highly functionalized tetrahydropyrans

The use of three-component Michael-Henry-Acetalisation reactions has scarcely been investigated. It was not until 2011 that the field started to generate interest, thanks to the pioneering research accomplished by Hayashi and co-workers. Therein, the diphenylprolinol silyl ether mediated reaction between aldehydes and nitroalkenes afforded a family of THP derivatives with excellent diastereo- and enantioselectivities.[77] During the extensive study of the optimal base additive for the final Henry-acetalisation step these authors discovered the possibility to selectively generate the kinetic **66** or thermodynamic **67** products by employing Et_3N or DBU, respectively. Besides, DBU was able to promote the isomerization from **66** to **67** without any loss in the observed *ee* values (**Scheme 2.14A**). As a counterpart, mention that all the tetrahydropyranols were synthesised as a mixture of α and β anomers. With the aim to overcome this limitation, they further treated the generated tetrahydropyranols with allylating reagents obtaining, in all cases, highly substituted tetrahydropyrans **69** with excellent enantioselectivities (**Scheme 2.14B**).

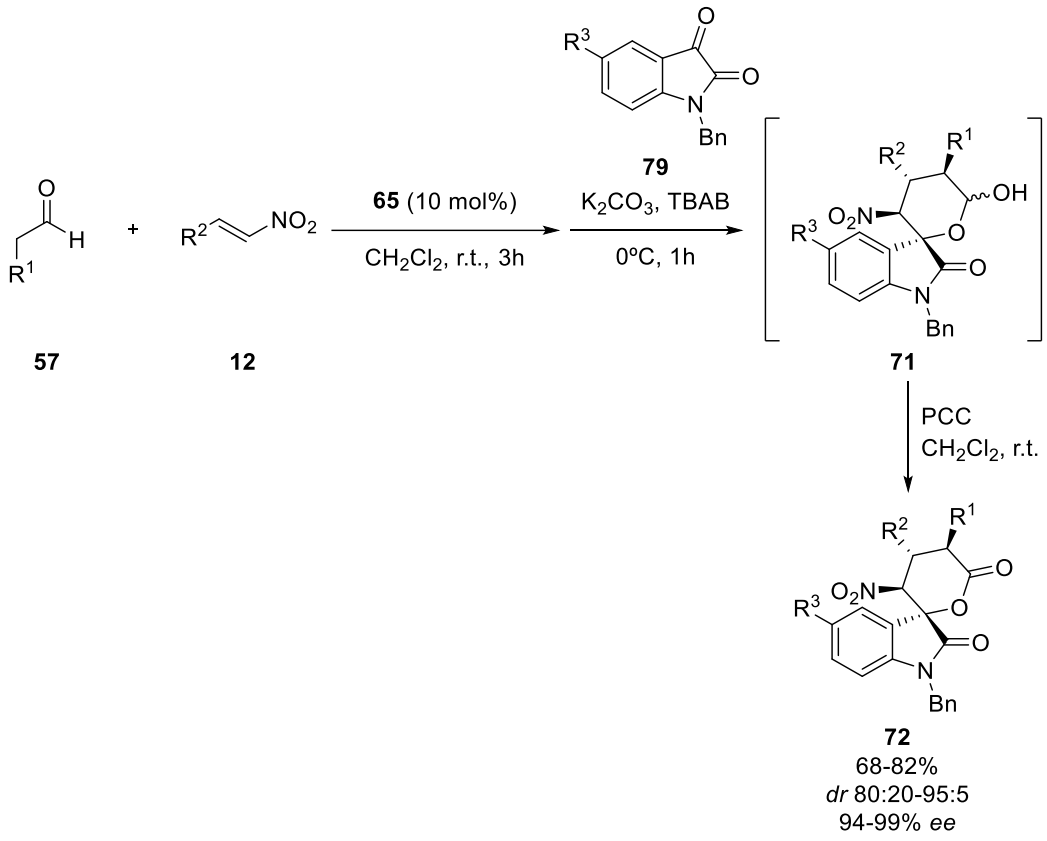
[77] Ishikawa, H.; Sawano, S.; Yasui, Y.; Shibata, Y.; Hayashi, Y. *Angew. Chem., Int. Ed*. **2011**, *50*, 3774-3779.



Scheme 2.14. A) The three-component Michael-Henry-Acetalisation process towards tetrahydropyranol cores developed by Hayashi. B) The successive allylation step for the synthesis of tetrahydropyran skeletons with five contiguous stereogenic centres.

In a similar fashion, more complex THP-based structures have been achieved. Indeed, Huang, Peng and Han reported the synthesis of spirooxindole pyran scaffolds making use of aldehydes, nitroalkenes and benzyl-*N*-protected isatins as starting materials employing again the diphenyl silyl prolinol catalyst **65**.[78] Once the one-pot cascade process ended, an *in situ* oxidation of the hemiacetal with PCC gave access to lactones **72** in moderate to good yields and high stereoselectivities (**Scheme 2.15**). Changes in three of the reaction components led to the formation of a library of oxaspiroindoles with good yields and excellent stereoselectivities.

[78] Xie, X.; Peng, C.; He, G.; Leng, H.-J.; Wang, B.; Huang, W.; Han, B. *Chem. Commun*. **2012**, *48*, 10487-10489.



Scheme 2.15. Synthesis of spirooxindole pyran scaffolds reported by Huang and Peng.

2.3 OBJECTIVES

According to the previous results published by our research group, densely substituted unnatural proline-based primary amines and γ-dipeptides exhibit novel emergent catalytic properties for the Michael reaction between cyclic ketones and β-nitrostyrenes. In particular, *exo*-**28** amine and O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** dipeptides were found to be the best catalysts in terms of activity and selectivity. However, the diastereomeric ratios and enantiomeric excesses observed with the primary amine derivative were moderate when cyclopentanone and cycloheptanone were used as nucleophilic ketones. Therefore, one of the main goals of the following chapter focuses on the study of the suitability of the best dimeric catalyst **35** towards the above mentioned conjugate addition reaction employing different ketones as nucleophiles.

The one-pot organocatalytic Michael-Henry-acetalisation cascade transformation deserves equal attention, taking into consideration the previously reported excellent findings. Nonetheless, and despite the profound research concerning aldehyde donors, no examples are found for nucleophilic ketones. Encouraged by our outcomes in the

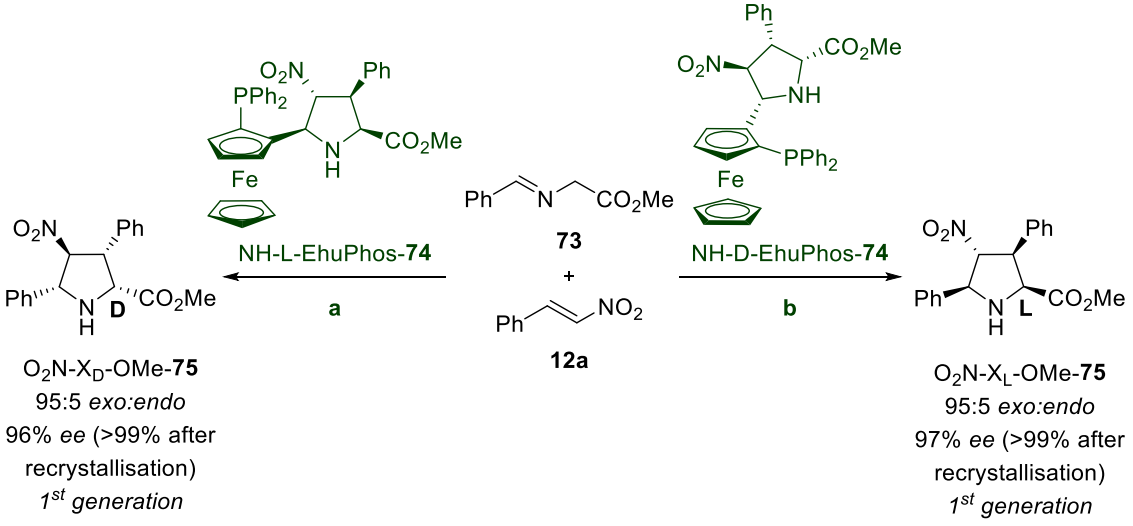
1,4-addition reaction, the second main objective that is pursued in this Chapter is the discussion of the catalytic activity of our best derivatives in the Michael-Henry-acetalisation reaction. The versatility of the catalyst will also be tested by employing different starting materials.

2.4 SYNTHESIS OF DENSELY SUBSTITUTED ORGANOCATALYTIC DERIVATIVES

In order to synthesise the target amino and dipeptide derivatives several chemical transformations were required. After the copper (I) assisted (3+2) cycloaddition reactions, subsequent hydrolysis, hydrogenation, optional methylation and amide coupling reactions have been carried out.

2.4.1. 1st and 2nd generation catalysts

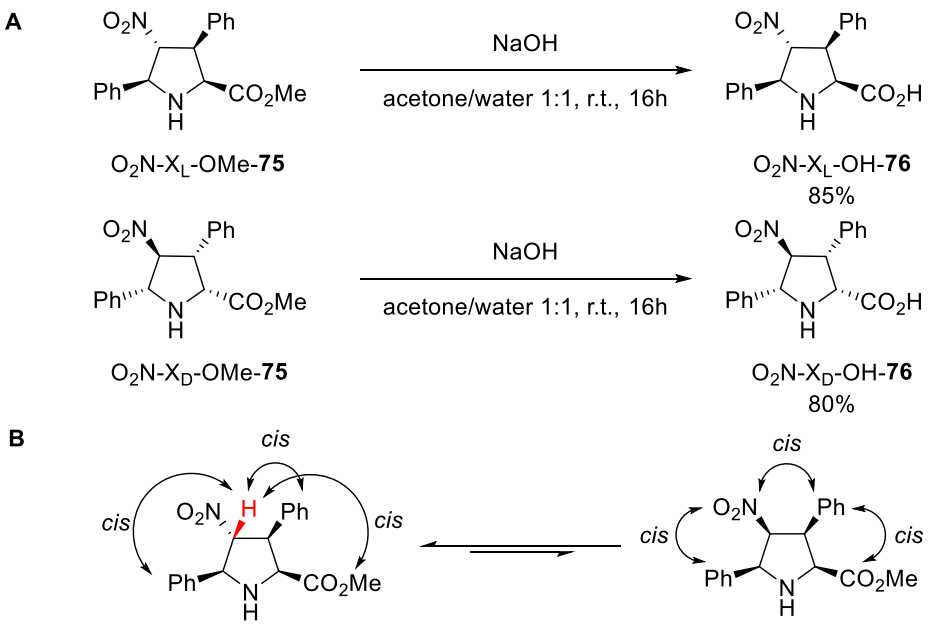
Previous studies in our research group evidenced the exceptional catalytic activity of the hybrid ferrocenyl pyrrolidine ligands in the copper (I) assisted (3+2) cycloaddition reaction between azometine ylides and π-defficient alkenes (**Scheme 2.16**).[40] Therein, whereas NH-D-EhuPhos-**74** provided O_2N-X_L-OMe-**75** derivatives in high yields and enantioselectivities, its enantiomer NH-L-EhuPhos-**74** promoted O_2N-X_D-OMe-**75** pyrrolidines with the same stereoselection.



Scheme 2.16. Synthesis of first generation of organocatalysts O_2N-X_D-OMe-**75** and O_2N-X_L-OMe-**75**. The *L*- and *D*- configuration of the proline derivatives are highlighted. Reagents and conditions: a) NH-L-EhuPhos-**73** (3 mol%), $Cu(CH_3CN)_4PF_6$ (3 mol%), Et_3N (5 mol%), THF, -20 °C, 16h. b) NH-D-EhuPhos-**73** (3 mol%), $Cu(CH_3CN)_4PF_6$ (3 mol%), Et_3N (5 mol%), THF, -20 °C, 16h.

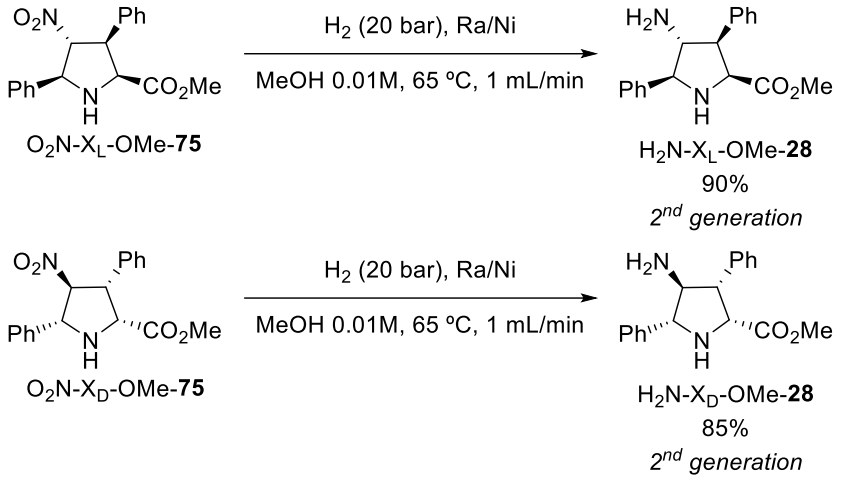
Subsequent simple basic hydrolysis by means of NaOH in acetone/water gave the corresponding acid O_2N-$X_{L/D}$-OH-**76** derivatives in high yields (**Scheme 2.17A**). Such

conditions did not entail any risk of epimerization, owing to the configuration of the *exo*-cycloadduct. The possible epimerization would abstract the more acidic C4 proton of the pyrrolidine ring, the one that is adjacent to the nitro functional group. However, this proton is in *cis* disposition in comparison with all the other substituents, and the higher steric hindrance makes more difficult for a base to approach (**Scheme 2.17B**, left). Besides, the stability of the generated epimer should also be considered. Indeed, the epimerization of the *exo* pyrrolidine increases the number of *cis* orientation of vicinal substituents, leading to the most thermodynamically disfavoured product (**Scheme 2.17B**, right).



Scheme 2.17. A) Hydrolisis step for the synthesis of acid O_2N-$X_{L/D}$-OH-**76** derivatives; B) Possible epimerization equilibriums. Left: disposition of the C4 proton (in red) with respect to the other substituents of the pyrrolidine ring. Right: structure of the final product after epimerization. To an easier understanding, *exo*-L configuration was chosen as a model.

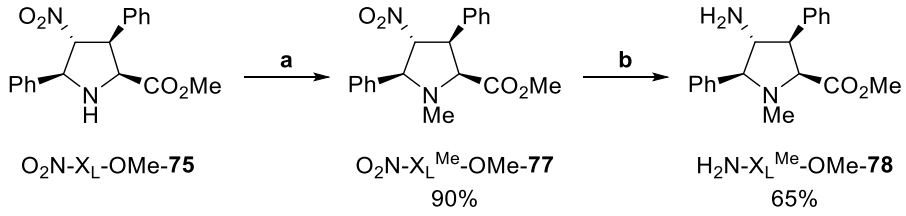
Together with the hydrolysis step, Raney-Ni catalysed continuous flow hydrogenation at 65 °C produced the second generation H_2N-X_L-OMe-**28** and H_2N-X_D-OMe-**28** catalysts in 90 % and 85% yield, respectively (**Scheme 2.18**).



Scheme 2.18. Hydrogenation reaction for the synthesis of 2nd generation H_2N-$X_{L/D}$-OMe-**28** derivatives.

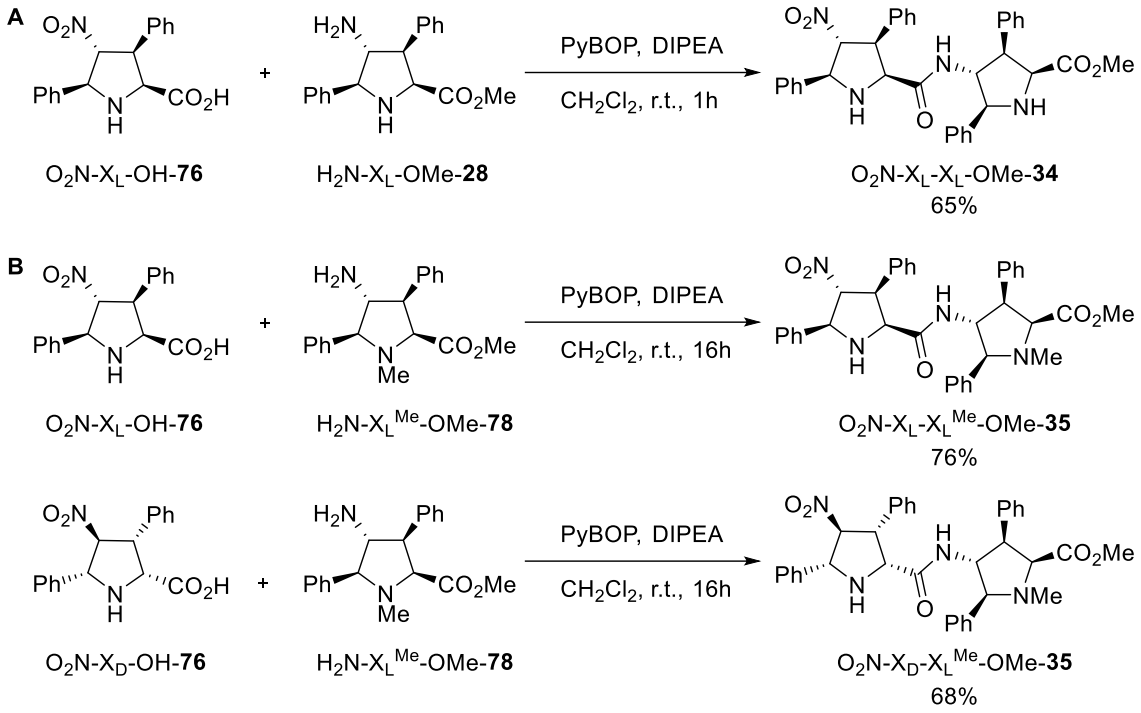
2.4.2. 3rd generation catalysts

The last step consisted of a coupling reaction between monomeric amines and acid derivatives. However, in the case of peptides in which one of the two secondary amine units is blocked, the synthetic route requires an additional methylation process before the hydrogenation step. For that purpose O_2N-X_L-OMe-**74** pyrrolidine was subjected to a reductive amination reaction in the presence of formaldehyde and formic acid. The subsequent hydrogenation provided smoothly the amino methyl ester moiety H_2N-X_L^{Me}-OMe-**77** in moderate yields (**Scheme 2.19**).



Scheme 2.19. Synthesis of O_2N-X_L^{Me}-OMe-**77**and H_2N-X_L^{Me}-OMe-**78**. Yields refer to each step. Conditions: a) H_2CO/HCO_2H, 100 °C, 2h; b) H_2 (20 bar), Ra/Ni, MeOH [0.01M], 65 °C, 1 mL/min.

Precedent screening studies to find the optimal conditions for amide-bond forming reactions showed that PyBOP was the best coupling agent for this type of dimeric species.[49] Thus, the coupling procedures were fulfilled at room temperature in presence of PyBOP and DIPEA. Dipeptide O_2N-X_L-X_L-OMe-**34** was achieved in a good yield of 65% within 1h (**Scheme 2.20A**). Methylated dipeptides O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** instead, demanded longer reaction times achieving the target catalysts in good yields (**Scheme 2.20B**).

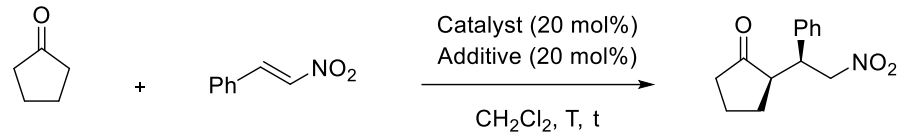


Scheme 2.20. Synthesis of A) O_2N-X_L-X_L-OMe-**34** and B) *N*-methylated O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** dipeptides using PyBOP as coupling agent.

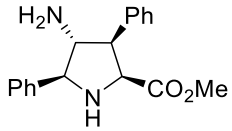
2.5 MICHAEL ADDITION OF CYCLOPENTANONE AND CYCLOHEPTANONE TO *TRANS*-β-NITROSTYRENE.

As we have previously indicated, unnatural nitroprolines like **75** cannot catalyse Michael addition reactions between ketones and nitroalkenes, whereas the corresponding 4-amino analogues **28** (**Schemes 2.4** and **2.5**) are suitable catalysts for this reaction.[39] However, when the reaction was tested with cyclopentanone **11b** and cycloheptanone **11c**, both the diastereoselectivities and the enantioselectivities of these reactions were lower than those observed for cyclohexanone **11a** (see **Scheme 2.5**, **Table 2.1**, entries 1,2 and **Table 2.2**, entries 1,2).

Table 2.1. H_2N-X_L-OMe-**28** promoted organocatalytic Michael reaction between cyclopentanone **11b** and *trans*-β-nitrostyrene **12a** .[a]

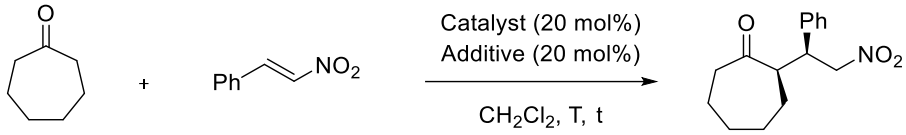


11b **12a** (2*R*,1'*S*)-**13ba**

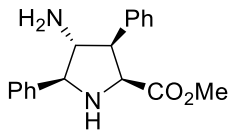
Entry	Catalyst	Additive	T (°C)	time (h)	*syn/anti*[b]	Yield (%)[c]	*ee* (%)[d]
1		PNBA[e]	r.t.	16	47:53	88	64
2	H_2N-X_L-OMe-**28**	TFA[f]	r.t.	16	50:50	75	72

a) Data taken from ref. 39. b) *syn/anti* ratio was measured by ^{1}H-NMR analysis of crude reaction mixtures. c) Yields refer to the isolated pure Michael adducts. d) Enantiomeric excesses measured by HPLC correspond to the major *syn* diastereomer (2*R*,1*'S*)-**13ba**. e) PNBA: *p*-nitrobenzoic acid. f) TFA: trifluoroacetic acid.

Table 2.2. H_2N-X_L-OMe-**28** promoted organocatalytic Michael reaction between cycloheptanone **11c** and *trans*-β-nitrostyrene **12a** .[a]



11c **12a** (2*R*,1'*S*)-**13ca**

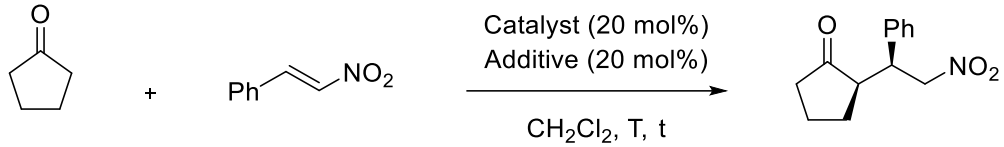
Entry	Catalyst	Additive	T (°C)	time (h)	*syn/anti*[b]	Yield (%)[c]	*ee* (%)[d]
1		PNBA[e]	r.t.	16	78:22	20	71
2	H_2N-X_L-OMe-**28**	TFA[f]	r.t.	16	93:7	84	80

a) Data taken from ref. 39. b) *syn/anti* ratio was measured by ^{1}H-NMR analysis of crude reaction mixtures. c) Yields refer to the isolated pure Michael adducts. d) Enantiomeric excesses measured by HPLC correspond to the major *syn* diastereomer (2*R*,1*'S*)-**13ca**. e) PNBA: *p*-nitrobenzoic acid. f) TFA: trifluoroacetic acid.

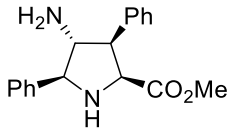
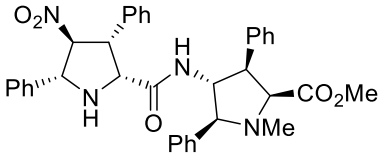
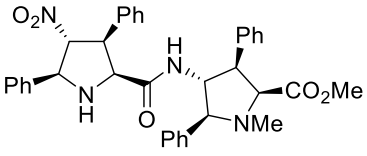
With the aim to improve the results obtained with 4-aminoproline derivatives and encouraged by the upgrade of the γ-*N*-methylated dipeptides in the case of cyclohexanone (see **Scheme 2.7**), we carried out the O_2N-X_L-X_L^{Me}-OMe-**35** and O_2N-X_D-X_L^{Me}-OMe-**35** dipeptide mediated asymmetric Michael reaction of cyclopentanone and cycloheptanone. In addition, the influence of the reaction temperature and the acidic derivative was also evaluated. Initially, cyclopentanone was

the ketone of choice in the Michael process with both methylated dimers. The obtained results are gathered in **Table 2.3**.

Table 2.3. Organocatalytic Michael reaction between cyclopentanone **11b** and *trans*-β-nitrostyrene **12a**.[a]



11b **12a** (2*R*,1'*S*)-**13ba**

Entry	Catalyst	Additive	T (°C)	time (h)	*syn/anti*[b]	Yield (%)[c]	*ee* (%)[d]
1		PNBA[e]	r.t.	16	47:53	88	64
2	H_2N-X_L-OMe-**28**	TFA[f]	r.t.	72	50:50	75	72
3		SA[g]	r.t.	24	70:30	94	-89
4		TFA	r.t.	72	60:40	nd[h]	nd
5		SA	0	24	70:30	95	-90
6		SA	-10	48	75:25	95	-92
7	O_2N-X_D-X_L^{Me}-OMe-**35**	SA	-20	96	80:20	93	-91
8		SA	r.t.	16	75:25	94	85
9		TFA	r.t.	48	60:40	nd	nd
10	O_2N-X_L-X_L^{Me}-OMe-**35**	SA	-10	24	85:15	95	90

a) The reaction was conducted using **11b** (0.10 mmol) and **12a** (0.11 mmol) in the presence of 20 mol % catalyst and 20 mol % additive until total consumption of starting ketone **11b** (Conv. > 99%). b) *syn/anti* ratio was measured by ^{1}H-NMR analysis of crude reaction mixtures. c) Yields refer to the isolated pure Michael adducts. d) Enantiomeric excesses measured by HPLC correspond to the major *syn* diastereomer (2*R*,1'*S*)-**13ba**. Negative values indicate that the opposite (2*S*,1'*R*)-**13ba** enantiomer is formed. e) PNBA: *p*-nitrobenzoic acid. f) TFA: trifluoroacetic acid. g) SA: salicylic acid. h) nd: not determined.

When the reaction was performed at room temperature with O_2N-X_D-X_L^{Me}-OMe-**35** catalyst and salycilic acid the final *syn*-(2*S*,1'*R*)-**13ba** Michael adduct was achieved within 24h in high yields, moderate diastereoselectivities and excellent enantiomeric excess values (**Table 2.3**, entry 3). The observed absolute configuration is (2*S*,1'*R*)- due to the blockage in the second *exo*-L pyrrolidine ring, being the first *exo*-D monomeric unit the responsible for the catalytic outcome. So as to test if the final result could be extra improved, the more acidic TFA was employed. Nevertheless, the model reaction lasted

three days until completion and the *syn/anti* ratio dropped to almost racemic values (**Table 2.3**, entry 4).

Once salicylic acid was chosen as the optimal additive, screening of different reaction temperatures was performed. When the temperature was lowered to 0 °C there were no meaningful changes in any of the values of interest (**Table 2.3**, entry 5 vs entry 3). Further lowering to -10 °C and -20 °C increased the reaction time to 48h and 96h respectively, but both diastereo- and enantioselectivities showed slight enhancements (**Table 2.3**, entries 6 and 7). The best temperature/time compromise was achieved at -10 °C. Under the best reaction conditions, the desired Michael adducts were obtained in reasonable reaction times with good *syn/anti* ratios and excellent enantiomeric excess values (**Table 2.3**, entry 6).

When the model reaction was carried out by means of the diastereomeric O_2N-X_L-X_L^{Me}-OMe-**35** dipeptide instead, *anti*-Proline like (2*R*,1'*S*)-**13ba** adduct was achieved. Salicylic acid exhibited a good 75:25 *syn/anti* ratio and 85% *ee* values when the reaction was accomplished at room temperature (**Table 2.3**, entry 8). Changing the acidic additive into TFA deteriorated the diastereoselectivity of the chemical process, similar to the previous case (**Table 2.3**, entry 9). Finally, the lowering of the temperature to -10 °C led to the best outcomes in terms of *syn*/*anti* ratio and enantiomeric excess (**Table 2.3**, entry 10).

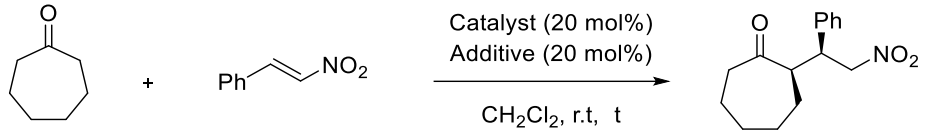
Those results clearly demonstrate that O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** dimeric species exhibit superior catalytic performances than their 2nd generation analogues (*vide supra*). Both species enlarge the family of efficient organocatalysts for the attainment of Michael adducts. Concerning literature, the former catalyst ameliorates the results obtained with other derivatives[79] and almost equals the best outcomes found to date by sulfinyl pyrrolidine derivatives.[80] Interestingly, the latter dipeptide improves the catalytic outcomes described so far.[81]

Consequently, the scope of the asymmetric Michael reaction was broadened to cycloheptanone (**Table 2.4**). The reaction was first performed at room temperature, and both O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** catalysts gave the corresponding Michael adduct with good diastereo- and enantioselectivities in presence of salicylic acid

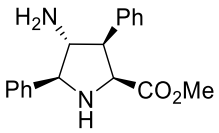
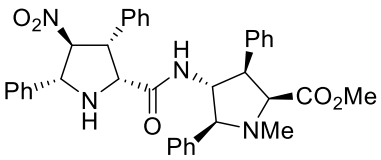
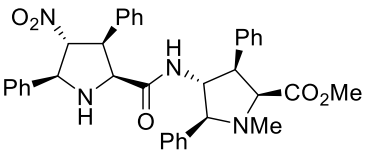
[79] For the latest representative examples, see: a) Azad, C. S.; Khan, I. A.; Narula, A. K. *Org. Biomol. Chem*. **2016**, *14*, 11454-11461. b) Wang, Z.-Y.; Ban, S.-R.; Yang, M. C.; Li, Q.-S. *Chirality* **2016**, *28*, 721-727.
[80] Singh, K. M.; Singh, P.; Kaur, A.; Singh, P.; Sharma, S. K.; Khullar, S.; Mandal, S. K. *Synthesis* **2013**, *45*, 1406-1413.
[81] a) Ref 32a. b) Xu, Y.; Zou, W.; Sundén, H.; Ibrahem, I.; Córdova, A. *Adv. Synth. Catal*. **2006**, *348*, 418-424. c) Wang, Y.; Li, D.; Lin, J.; Wei, K. *RSC Adv*. **2015**, *5*, 5863-5874.

(**Table 2.4**, entries 3 and 5). Nonetheless, the lower nucleophilicity of cycloheptanone made it impossible to reach full conversion, even with long reaction times. Pursuing better catalyst activity, stronger TFA was alternatively utilized. In the case of O_2N-X_D-X_L^{Me}-OMe-**35**, changes in the additive enabled the total consumption of the starting materials (conv. >99%) and the final product was attained with excellent *syn/anti* ratio and *ee* values (**Table 2.4**, entry 4). The same behaviour was observed when O_2N-X_L-X_L^{Me}-OMe-**35** was employed as catalysts and desired *syn*-(2*R*, 1'*S*)-**13ca** products exhibited great results in terms of diastereo- and enantioselectivity (**Table 2.4**, entry 6). Due to the required long reaction times, further screening of temperature was not conducted.

Table 2.4. Organocatalytic Michael reaction between cycloheptanone **11c** and *trans*-β-nitrostyrene 1**2a**.[a]



11c **12a** (2*R*,1'*S*)-**13ca**

Entry	Catalyst	Additive	Conv. (%)[b]	time (h)	*syn/anti*[c]	Yield (%)[d]	*ee* (%)[e]
1		PNBA[f]	r.t.	16	78:22	20	71
2	H_2N-X_L-OMe-**28**	TFA[g]	r.t.	16	93:7	84	80
3		SA[h]	90	5	82:18	70	-71
4	O_2N-X_D-X_L^{Me}-OMe-**35**	TFA	>99	4	92:8	93	-90
5		SA	90	5	73:27	75	73
6	O_2N-X_L-X_L^{Me}-OMe-**35**	TFA	>99	4	90:10	94	93

a) The reaction was conducted at room temperature using **11c** (0.10 mmol) and **12a** (0.11 mmol) in the presence of 20 mol % catalyst and 20 mol % additive until total consumption of starting material. b) Conversions were measured by ^{1}H-NMR analysis of the crude reaction mixtures. c) *syn/anti* ratio was measured by ^{1}H-NMR analysis of crude reaction mixtures. d) Yields refer to the isolated pure Michael adducts. e) Enantiomeric excesses measured by HPLC correspond to the major *syn* diastereomer (*2R,1'S*)-**13ca**. Negative values indicate that the opposite (2*S,1'R*)-**13ca** enantiomer is formed. f) PNBA: *p*-nitrobenzoic acid. g) TFA: trifluoroacetic acid. h) SA: salicylic acid.

These results complement the aforementioned emergent organocatalytic properties of γ-dipeptides **35**. It is worth noting that few examples have been described in literature that comprehend the use of cycloheptanone as nucleophilic ketone. What is more, in all cases the designed catalysts led to the (2*S*,1'*R*)-**13ca** enantiomer[82], and there is only one example that surpasses the results obtained with our derivatives.[83] Overall, it can be concluded that O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** are suitable catalysts for the diastereo- and enantioselective Michael reaction between cyclic ketones **11b,c** and *trans*-β-nitrostyrene **12a**.

These results can be rationalised according to the general model outlined in **Figure 2.6**. In γ-dipeptides O_2N-X_D-X_L^{Me}-OMe-**35**, O_2N-X_L-X_L^{Me}-OMe-**35**, the *N*-methylated pyrrolidine ring is available for protonation, whereas the *N*-unsubstituted prolyl moiety can form the enamine intermediate **INT1**. Coordination of the electrophilic nitrostyrene **12a** to the protonated *N*-methyl amino group (see **INT2** in **Figure 2.6B**) results in LUMO activation of the electrophile thus facilitating the C-C bond forming step leading to the iminium-nitronate intermediate **INT3**. Hydrolysis of this latter intermediate leads to the Michael adduct **13** with concomitant release of the organocatalyst (**Figure 2.6B**).

[82] For selected examples, check: a) Betancort, J. M.; Saktivel, K.; Thayumanavan, R.; Barbas III, C. F. *Tetrahedron Lett*. **2001**, *42*, 4441-4444. b) Vega-Peñolaza, A.; Sánchez-Antonio, O.; Ávila-Ortiz, C. G.; Escudero-Casao, M.; Juaristi, E. *Asian J. Org*. *Chem*. **2014**, *3*, 487-496.
[83] Xu, D.-Z.; Shi, S.; Wang, Y.; *Eur. J. Org. Chem*. **2009**, 4848-4853.

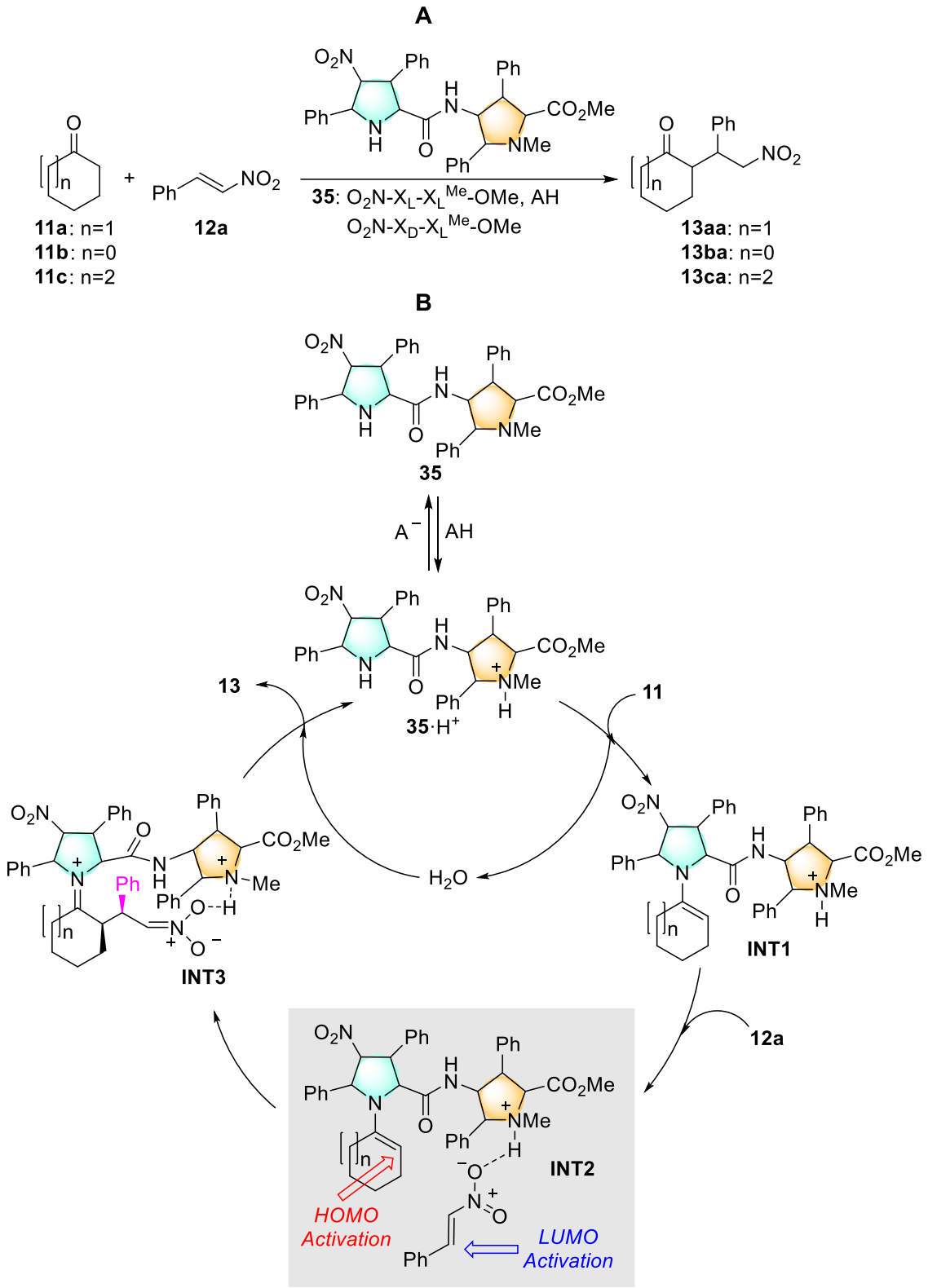


Figure 2.6. A) General Michael addition between ketones **11a-c** and nitrostyrene **12a** catalysed by γ-dipeptides **35** to yield γ-nitroketones **13aa-ca**. AH stands for a carboxylic acid. B) Simplified catalytic cycle involving dual HOMO-LUMO activation by means of enamine and protonated pyrrolidine moieties, respectively.

The origins of the diastereo- and enantiocontrol associated with the C-C bond forming step can be attributed to the geometric restrains imposed by the organocatalyst that,

aside the limited conformational freedom about the amide bond, incorporates eight chiral centres. For instance, in **Figure 2.7** the geometry of the zwitterionic **INT3a** resulting from the reaction between cyclopentanone **11b** and nitrostyrene **12a** is shown.

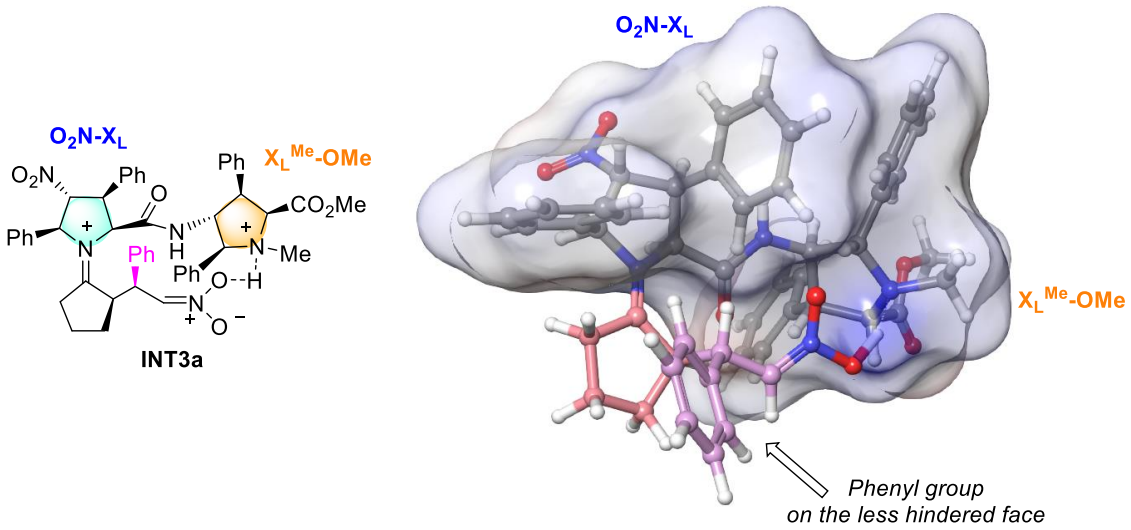


Figure 2.7. Optimized structure (RHF/PM6 level of theory) of zwitterionic intermediate **INT3a** associated with the reaction between cyclopentanone **11b** and nitroalkene **12a**. The surface (probe radius: 1.8 Å) determined by organocatalyst O_2N-X_L-X_L^{Me}-OMe-**35** is shown in grey.

Inspection of the surface generated by the O_2N-X_L-X_L^{Me}-OMe-**35** catalyst reveals a very hindered side deformed by the large organocatalyst that blocks one prochiral side of the enamine and nitroalkene moieties thus promoting the formation of the (2*S*,1'*R*)-Michael adduct. Similar effects should operate in catalytic cycles associated with ketones **11c** (cycloheptanone) and **11a** (cyclohexanone).

2.6 ORGANOCATALYTIC MICHAEL-HENRY-ACETALISATION APPROACH TOWARDS THE SYNTHESIS OF TETRAHYDROPYRAN SKELETONS

2.6.1 Reaction conditions screening

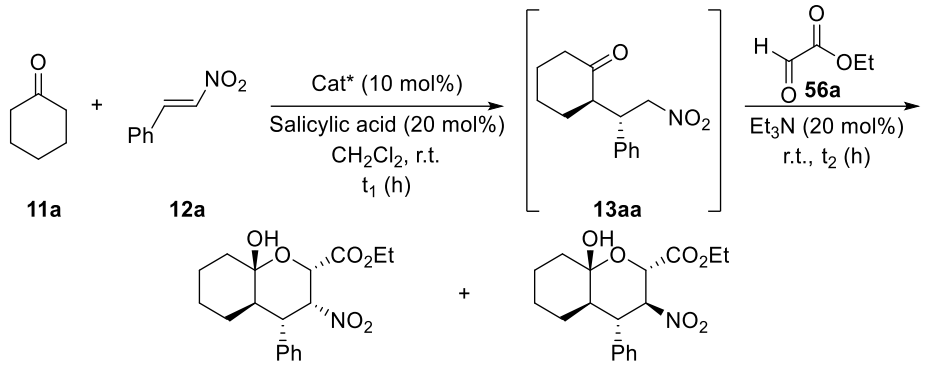
The hypothesis of the possible generation of THP scaffolds by the reaction of the Michael adduct with an aldehyde was the starting point of the approach. The testing of the conditions under which the reaction operated was first carried out taking into account the optimal conditions for the Michael reaction between cyclohexanone and *trans*-β-nitrostyrene (10 mol% catalyst, 20 mol% salicylic acid). Additionally, ethyl glyoxylate was chosen as the model electrophilic aldehyde for the subsequent Henry reaction because of the synthetic importance of the generated 6-carboxy tetrahydropyran derivative as a building block.

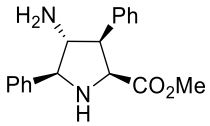
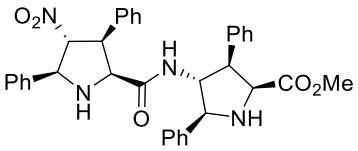
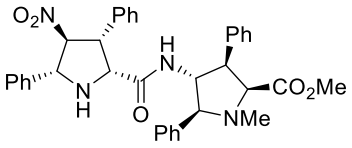
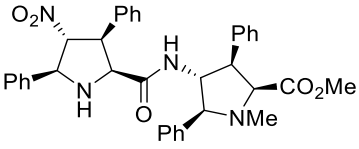
At the outset two parallel experiments were performed. In one of them, the three of the starting reagents were mixed together initially. On the contrary, the analogous essay implied the generation of the Michael product prior to the addition of the required reagents for the second Henry-acetalisation transformation. The former experiment led to traces of the desired product owing to the competitive aldol reaction between cyclohexanone and ethyl glyoxalate. The latter, instead, resulted in the effective formation of the tetrahydropyran skeleton. Bear in mind that the last alternative is still a one-pot transformation, because there is no purification of the intermediate species.

Additional investigations were developed in order to comprehend the role of the catalyst during the transformation. As control experiments, several analogous reactions were studied, in which the γ-nitroketone intermediates were purified before the addition of ethyl glyoxylate and triethylamine. HPLC analyses of these experiments showed no enantiomeric excess differences between both the purified and non-purified cases. Hence, the stereochemical outcome of the second step is directly addressed to the determining conjugate addition pace, becoming a substrate-controlled transformation.

Thus, the γ-nitroketone **13aa** generated from the Michael addition of cyclohexanone **11a** to *trans*-β-nitrostyrene **12a** was treated with ethyl glyoxylate in the presence of triethylamine to produce the tetrahydropyran derivative. All the results are gathered in **Table 2.5**. The catalyst was the first evaluated parameter. The O_2N-$X_{L/D}$-OMe-**75** monomeric species were not of interest, due to their inability to catalyze the required Michael step. The amino H_2N-X_L-OMe-**28** catalyst demanded long reaction times for the second cyclisation step (10 days, **Table 2.5**, entry 1). In view of the poor results, dimeric species were tested next. The reaction promoted by dipeptide O_2N-X_L-X_L-OMe-**34** showed reasonable reaction times for the 1,4-conjugate addition. Besides, the Henry-cyclisation step was completed within 6h, and the final product was obtained in good yields, good diastereomeric **79aaa:79aaa'** ratio and excellent enantiomeric excess (**Table 2.5**, entry 3). Compound **79aaa** is the kinetic product obtained, whereas compound **79aaa'** is the thermodynamically favoured product. By the employment of catalyst O_2N-X_D-X_L^{Me}-OMe-**35**, the Michael addition required longer reaction times and despite the good diasteromeric ratios, the yield and *ee* values dropped significantly (**Table 2.5**, entry 5). Finally, excellent results were achieved when the congener O_2N-X_L-X_L^{Me}-OMe-**35** was utilized. As it can be seen, it promoted the generation of the **79aaa** product in high yields, good **79aaa:79aaa'** ratio and excellent enantioselectivities (**Table 2.5**, entry 6).

Table 2.5. Evaluation of reaction conditions for the Michael-Henry-Acetalisation sequence.[a,b]



Entry	Catalyst	t_1 (h)	t_2 (h)	*dr*[c]	79aaa Yield (%)[d]	79aaa *ee* (%)[e]	79aaa' Yield (%)[d]	79aaa' *ee* (%)[e]
1		48	240	nd[f]	nd	nd	nd	nd
2[g]	H_2N-X_L-OMe-**28**	48	216	nd	nd	nd	nd	nd
3		48	6	85:15	73	93	nd	nd
4[h]	O_2N-X_L-X_L-OMe-**34**	16	6	75:25	70	91	23	60
5		144	6	84:16	69	-63	nd	nd
	O_2N-X_D-X_L^{Me}-OMe-**35**							
6		24	6	80:20	47	99	9	82
7[h]		24	6	>99:1	72	99	nd	nd
8[h,i]		24	168	nd	nd	nd	nd	nd
9[h,j]	O_2N-X_L-X_L^{Me}-OMe-**35**	24	48	50:50	27	96	26	90
10[h,k]		24	48	nd	30	65	nd	nd

a) The 1st step was conducted using ketone **11a** (0.10 mmol), *trans*-β-nitrostyrene **12a** (0.11 mmol) in the presence of 10 mol % catalyst and 20 mol % salicylic acid. The 2nd step was conducted using aldehyde **56a** (0.20 mmol) and 20 mol % Et_3N. b) Reactions were monitored by ^{1}H-NMR and were stirred at room temperature until total consumption of starting materials (Conv. >99%). c) *dr* refers to **79aaa**:**79aaa'** ratios and were measured by ^{1}H-NMR of crude reaction mixtures. d) Yields refer to isolated products. e) Enantiomeric excesses measured by HPLC correspond to the major enantiomer (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aaa**, (2*S*,3*S*,4*S*,4a*R*,8a*S*)-**79aaa'**. f) nd: not determined. g) 30 mol % catalyst, 30 mol % *p*-nitrobenzoic acid. h) 20 mol % catalyst. i) 40 mol % DIPEA. j) 40 mol% DBU. k) 40 mol% DABCO.

Once the organocatalysts have been studied and in order to improve the results, the catalyst load was increased for all but O_2N-X_D-X_L^{Me}-OMe-**34** organocatalysts. In the case of the amino derivative, no differences were observed and the second step still lasted too long (**Table 2.5**, entry 2). With dimer O_2N-X_L-X_L-OMe-**35** the conjugate addition step was accelerated, but a loss in diastereoselectivity was observed. In this case, the major diastereomer was obtained in good yield and high enantioselectivities, whereas the minor **79aaa'** product showed moderate enantiocontrol (**Table 2.5**, entry 4). To last, O_2N-X_L-X_L^{Me}-OMe-**35** γ-dipeptide exhibited paramount performance towards the whole transformation, as the final **79aaa** scaffold was achieved as a sole product in good yield and superb enantiomeric excess values (**Table 2.5**, entry 7).

Final experiments comprised the study of the effect of the base in the reaction. However, none of the tested basic additives was able to improve the results obtained with Et_3N (**Table 2.5**, entry 7). Treatment with DIPEA end DABCO entailed long cyclisation times (**Table 2.5**, entries 8 and 10, respectively) and the use of DBU resulted in an equilibrium of both diastereomeric species (**Table 2.5**, entry 9).

All these results suggest the use of O_2N-X_L-X_L^{Me}-OMe-**35** dipeptide in 20 mol% load as the catalytic source for the asymmetric Michael-Henry-Acetalyzation reaction. The second cyclisation step requires the use of triethylamine for the diastereo- and enantioselective approach to THP cores.

The structure and stereochemistry of both **79aaa** and **79aaa'** were confirmed by X-Ray diffraction analysis. To facilitate the understanding of the bicyclic structure, the atoms are numbered counter clockwise being C1 the hemiacetal carbon. The absolute configuration of **79aaa** was assigned for all asymmetric carbons C1, C6, C7, C8, C9 as *S*, *R*, *S*, *R*, *S*, respectively (to check the ORTEP diagram, see **Figure 2.8**). The corresponding assignation of **79aaa'** was *S*, *R*, *S*, *S*, *S* (**Figure 2.9**).

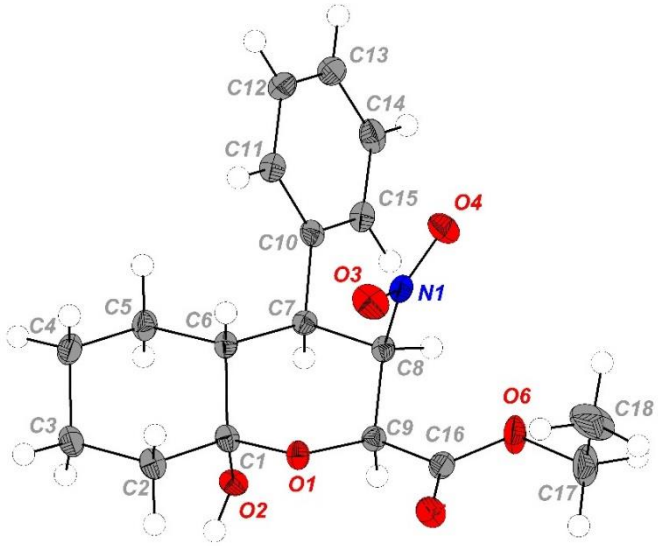


Figure 2.8. ORTEP diagram with thermal ellipsoids in 50% probability for (2*S*, 3*R,* 4*S*, 4a*R*, 8a*S*)-**79aaa**.

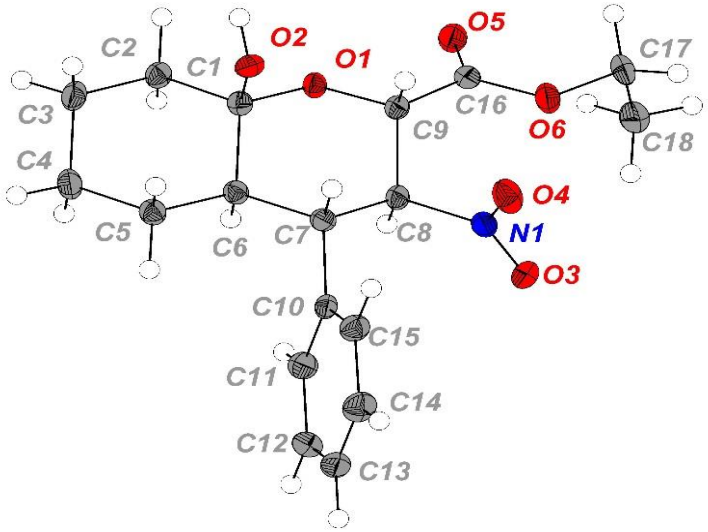
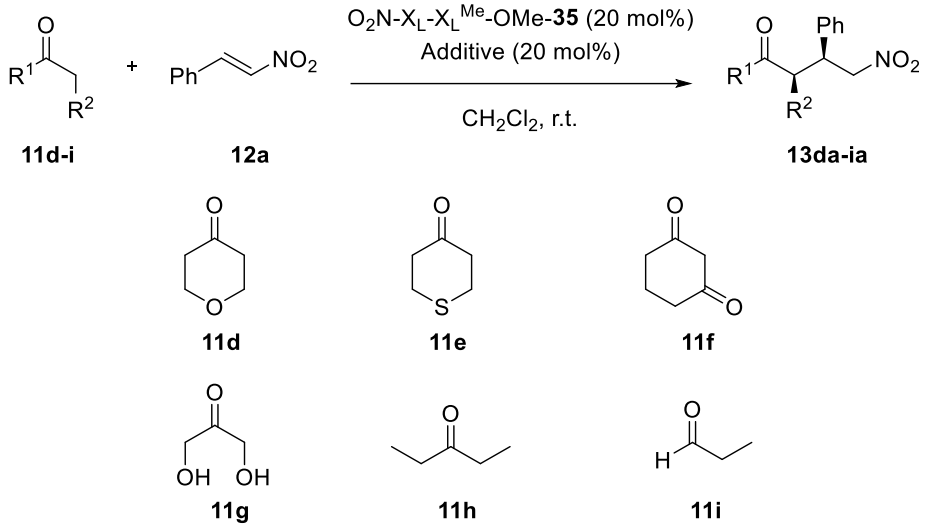


Figure 2.9. ORTEP diagram with thermal ellipsoids in 50% probability for (2*S*, 3*S*, 4*S*, 4a*R*, 8a*S*)-**79aaa'**.

2.6.2 Exploring the scope of the nucleophilic species for the asymmetric transformation

Having determined the best reaction conditions, the general nature of this process was investigated. In addition to cyclohexanone, other linear and cyclic derivatives were tested. Unfortunately, the reaction presented some restrictions regarding the nature of the nucleophiles. For instance, when tetrahydro-*4H*-pyran-4-one **11d**, tetrahydro-*4H*-thiopyran-4-one **11e**, cyclohexane-1,3-dione **11f**, 1,3-dihydroxyacetone **11g** and pentan-3-one **11h** were selected as starting materials, no formation of the

limiting Michael step was observed with salicylic acid. This fact could be reasoned by the equimolar ratios of the starting materials and the possible competitive formation of the cyclisation product that consumes the benzoic acid derived additive and avoids the excision of the catalyst after the formation of the intermediate enamine.[49] Changing the acidic additive into TFA did not still show any formation of the Michael adduct. Besides, the more reactive propionaldehyde **11i** showed total consumption of starting materials but competitive aldol and Michael reactions were observed. To last, when cyclopentanone **11b** was employed as the nucleophilic species, the final tetrahydropyran derivative could not have been isolated due to instability issues. All the negative results are gathered in **Scheme 2.21**.



Scheme 2.21. Unsuitable nucleophiles for the asymmetric Michael-Henry-Acetalisation reaction.

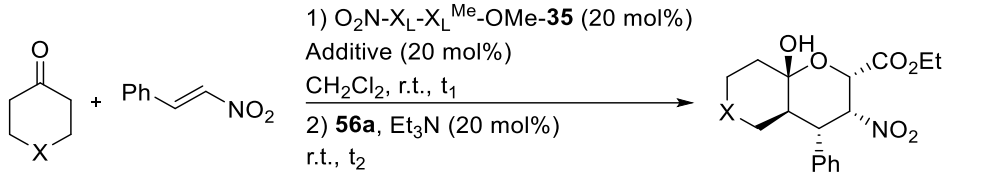
Luckily, our attempts turned successful when cycloheptanone **11c** and 1,4-cyclohexanedione monoethylene acetal **11j** were chosen as starting materials (**Table 2.6**). However, small changes were necessary for the proper synthesis of the corresponding derivatives.

Derivative **79caa** demanded equimolar amounts of Et_3N for the total consumption of the γ-nitroketone intermediate. Longer reaction times related to catalytic equivalents resulted in a severe decrease in yield. It should be mentioned that the final product was achieved in moderate yield and excellent enantioselectivites, but in a 92:8 mixture of non-separable diastereomers (**Table 2.6**, entry 1). Such proportion could be explained by the cyclisation of both the *syn*- and *anti*- Michael adducts.

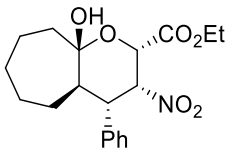
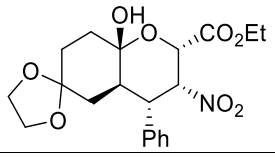
In the case of the synthesis of **79jaa**, the Michael step required 7 days to reach full conversion. In order to shorten the reaction time, the temperature was raised to 45 °C,

but sluggish mixtures were observed. The following Henry-acetalisation step, on the contrary, was completed in 1 hour. Hence, catalyst O_2N-X_L-X_L^{Me}-OMe-**35** provided the desired **79jaa** product as a single diastereomer in 62% yield and 89% of enantiomeric excess (**Table 2.6**, entry 2).

Table 2.6. The general reaction of ketone, *trans*-β-nitrostyrene and ethyl glyoxylate in the one-pot synthesis of tetrahydropyrans.[a,b]



11c,j **12a** (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79caa-jaa**

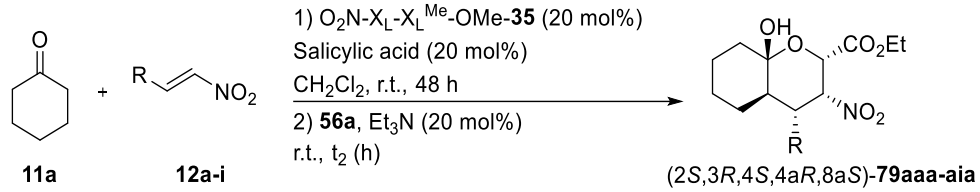
Entry	X	Additive	t_1 (days)	t_2 (h)	Product	Structure	Yield (%)[c]	*ee* (%)[d]
1[e]	-$(CH_2)_2$-	TFA[f]	4	16	**79caa**		53 (92:8)[g]	90
2		SA[h]	7	1	**79jaa**		62	88

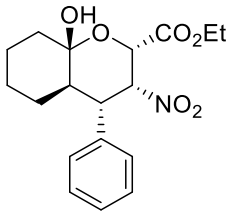
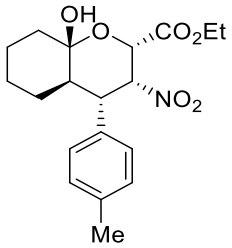
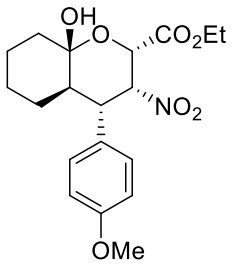
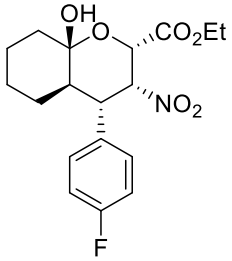
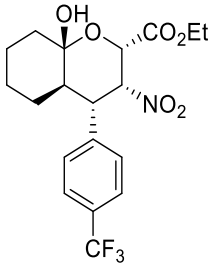
a) The 1st step was conducted using ketones **11c,j** (0.10 mmol), *trans*-β-nitrostyrene **12a** (0.11 mmol) in the presence of 10 mol % catalyst and 20 mol % additive. The 2nd step was conducted using aldehyde **56a** (0.20 mmol) and 20 mol % Et_3N. b) Reactions were monitored by ^{1}H-NMR and were stirred at room temperature until total consumption of starting materials (Conv. >99%). c) Yields refer to isolated products. d) Enantiomeric excesses measured by HPLC correspond to the major enantiomer (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79baa-jaa**. e) 1 equivalent of Et_3N was added. f) TFA: trifluoroacetic acid g) Diastereomeric ratio related to the cyclisation of *syn*- and *anti*-Michael adducts. h) SA: salicylic acid.

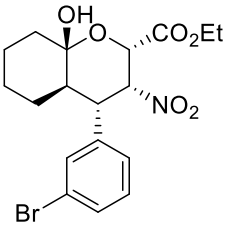
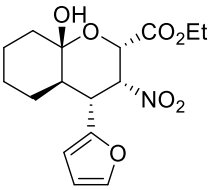
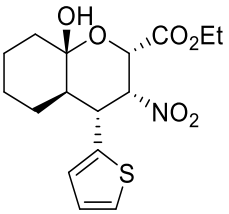
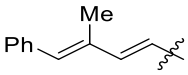
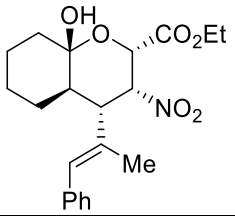
2.6.2 Nitroalkene scope

With the aim to test the suitability of other components, several nitroalkenes were evaluated. The reaction proceeded smoothly with aliphatic conjugated nitroolefins, along with aromatic and heteroaromatic substituted nitroalkenes (**Table 2.7**).

Table 2.7. Nitroalkene scope catalysed by O_2N-X_L-X_L^{Me}-OMe-**35**.[a,b]



Entry	R	t_2 (h)	Product	Structure	Yield (%)[c]	*ee* (%)[d]
1	Ph	6	**79aaa**		72	>99
2	4-MeC_6H_4	6	**79aba**		47	95
3[e]	4-$OMeC_6H_4$	6	**79aca**		65	96
4	4-FC_6H_4	6	**79ada**		62	>99
5[f]	4-$CF_3C_6H_4$	4	**79aea**		60	98

6	3-BrC_6H_4	9	**79afa**		54	99
7[g]	2-furyl	1	**79aga**		73	95
8[g]	2-thienyl	0.5	**79aha**		46	95
9[g,h]		2	**79aia**		55	99

a) The 1st step was conducted using ketone **11a** (0.10 mmol) and the corresponding *trans*-β-nitrostyrene **12a-i** (0.11 mmol) in the presence of 10 mol % O_2N-X_L-X_L^{Me}-OMe-**35** and 20 mol % salicylic acid, at room temperature and 48h. The 2nd step was conducted using aldehyde **56a** (0.20 mmol) and 20 mol % Et_3N and monitored by ^{1}H-NMR until total consumption of starting materials (Conv. >99%). b) All **79aaa-aia:79aaa-aia'** ratios were >99:1. c) Yields refer to isolated products. d) Enantiomeric excesses measured by HPLC correspond to the major enantiomer (2*S*,3*R*,4*S*,4*aR*,8*aS*)-**79aaa-aia**. e) The Michael reaction required 3 days to reach full conversion. f) Performed in toluene. g) The second step was performed at 0 °C. h) The Michael reaction required 6 days to reach full conversion.

The one-pot reaction was found to proceed uneventfully, achieving quantitative conversions and excellent enantioselectivities in all cases. It is important to mention that the stereochemistry at the C8 position was completely controlled, reaching the final **79aaa-aia** products as sole diastereomers. Aromatic nitroalkenes that bear electron-withdrawing and electron-donating groups at the *para* position led to the corresponding tetrahydropyran derivatives in moderate to good yields and excellent enantioselectivities (**Table 2.7**, entries 2 to 5). In the case of *trans*-4-methoxy-β-nitrostyrene, the lower electrophilicity of the nitroalkene resulted in longer reaction times for the determining Michael step. However, no significant effect was observed in terms of final yield and enantiocontrol (**Table 2.7**, entry 3). It should also be mentioned that *trans*-4-trifluoromethyl-β-nitrostyrene required the use of toluene as solvent since the solubility issues when employing the model conditions resulted in low conversions (**Table 2.7**, entry 5). Not only *para*- substituted nitroolefins but also *meta*-

substituted nitroalkenes were successfully employed in the asymmetric transformation. The desired product **79afa** was furnished with total enantiocontrol in a moderate yield of 54% in 9 hours reaction time (**Table 2.7**, entry 6).

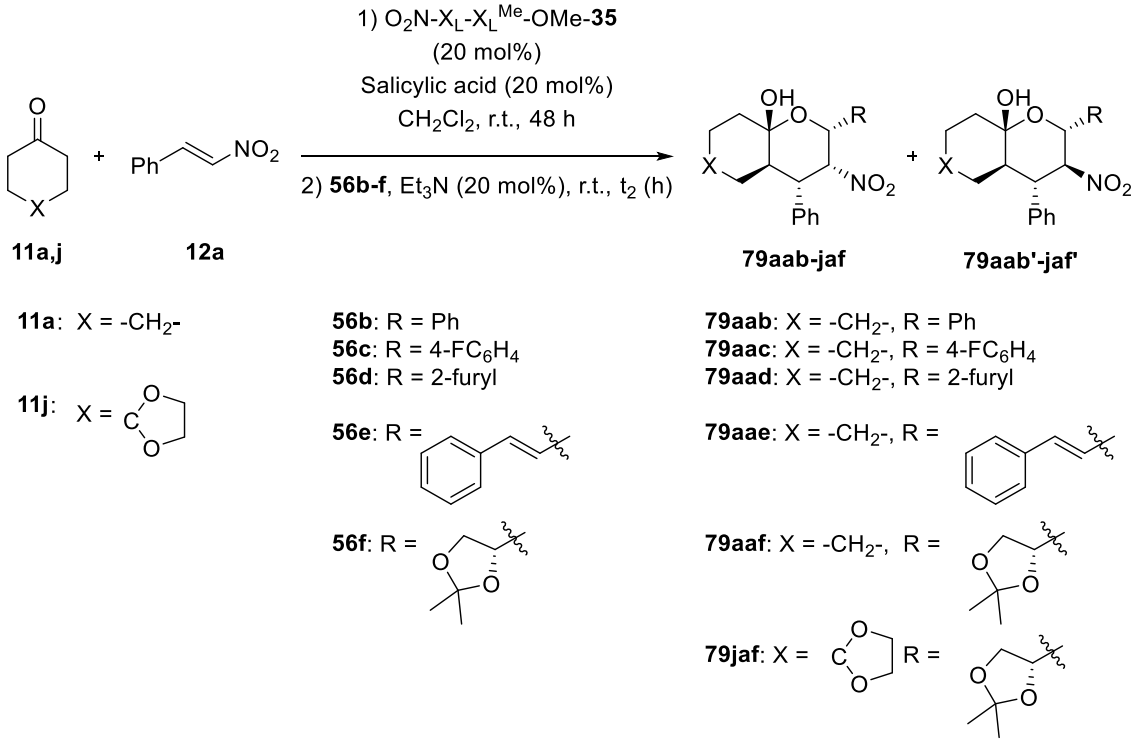
When more reactive heteroaromatic motifs were introduced, the temperature of the second step was reduced to 0 °C (**Table 2.7**, entries 7 and 8). Otherwise, competitive formation of the corresponding epimerization product was observed in almost 50:50 ratio. The new reaction conditions led to the corresponding **79aga, 79aha** products in very short reaction times with excellent enantioselectivities, albeit the moderate yield observed for the thienyl derivative. Finally, the aliphatic conjugated nitroalkene **12i** was also found convenient for the transformation. The same tendency to epimerization was observed with this derivative. Hence, the second cyclisation step was conducted at 0 °C and the final product was achieved within 2h in moderate yield and excellent enantioselectivity (**Table 2.7**, entry 9). The structure of the last **79aia** product was confirmed with the aid of bidimensional COSY experiments (see experimental section for details).

All these results highlight the paramount sterochemical outcome of the synthetic route towards highly substituted tetrahydropyrans regardless of the nature of the chosen nitroalkene.

2.6.3 Scope of electrophilic aldehydes

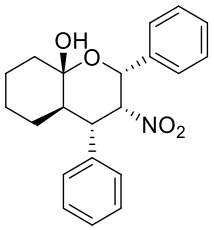
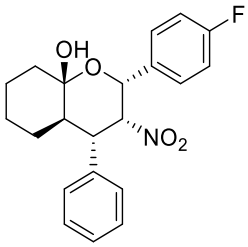
To last, the family of tetrahydropyran scaffolds was enlarged by testing other electrophilic aldehydes for the synthetic process (**Scheme 2.22**). All of the studied cases were less activated in comparison to the model ethyl glyoxylate. Thus, in some cases, changes in the equivalents of both the aldehyde and triethylamine were demanded for the reaction to occur. All the results are gathered in **Table 2.8**.

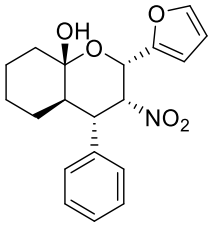
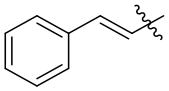
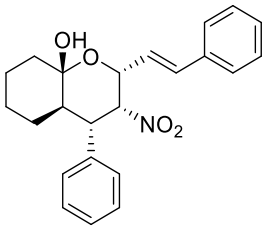
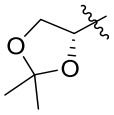
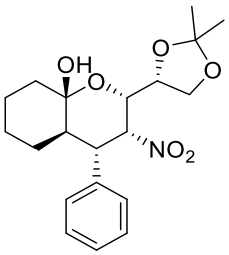
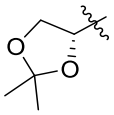
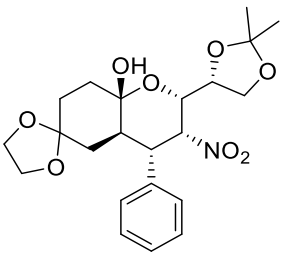
In general, the reaction was applicable to a broad scope of aldehydes and the corresponding tetrahydropyrans were achieved in good overall yields and excellent enantioselectivities. Nevertheless, the diasteroselectivity of the process fluctuated from low to excellent values depending on the nature of the electrophilic aldehyde.



Scheme 2.22. The one-pot Michael-Henry-Acetalisation reaction between ketones **11a,j**, *trans*-β-nitrostyrene **12a** and electrophilic aldehydes **56b-f** catalysed by O_2N-X_L-X_L^{Me}-OMe-**35**.

Table 2.8. 11a,j+12a+56b-f → (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aab-jaf** reaction scope catalysed by O_2N-X_L-X_L^{Me}-OMe-**35**.[a]

Entry	X	R	t_2 (h)	Structure	*dr*[b]	Yield (%)[c]	*ee* (%)[d] main	*ee* (%)[d] minor
1[e]	-(CH_2)-	Ph	48	 **79aab**	50:50	65	>99	96
2[e]	-(CH_2)-	4-FC_6H_4	16	 **79aac**	65:35	81	>99	95

3[e]	-(CH_2)-	2-furyl	16		50:50	65	98	98
				79aad				
4	-(CH_2)-		96		90:10	58[f]	>99	nd[g]
				79aae				
5	-(CH_2)-		3		>99:1	64	>99[h]	nd
				79aaf				
6			3		>99:1	52	>99[h]	nd
				79jaf				

a) The 1st step was conducted using ketone **11a,j** (0.10 mmol) and *trans*-β-nitrostyrene **12a** (0.11 mmol) in the presence of 10 mol % O_2N-X_L-X_L^{Me}-OMe-**35** and 20 mol % salicylic acid, at room temperature and 48h. The 2nd step was conducted using aldehyde **56b-f** (0.20 mmol) and 20 mol % Et_3N and monitored by ^{1}H-NMR until total consumption of starting materials (Conv. >99%). b) *dr* refers to the **79aab-jaf:79aab'-jaf'** ratio. c) Yields refer to the sum of both diastereomers. d) Enantiomeric excesses measured by HPLC are related to the corresponding (2*S*,3*R*,4*S*,4*aR*,8*aS*)-**79aab-jaf**, (2*S*,3*S*,4*S*,4*aR*,8*aS*)-**79aab':jaf'**enantiomers. e) 1 equivalent of Et_3N was added. f) Yield refers to the major **79cae** diastereoisomer. g) nd: not determined. h) *ee* refers to *de* (diastereomeric excess) measured by ^{1}H-NMR.

When aromatic benzaldehyde **56b** and 4-fluorobenzaldehyde **56c** were employed, 1 equivalent of triethylamine was necessary for the reaction to reach complete conversion. Such equimolar amounts of the basic additive entailed the formation of the corresponding epimers. Hence, the asymmetric version with aldehyde **56b** led to the formation of **79aab** and **79aab'** derivatives in 50:50 diastereomeric ratio, good overall yield and excellent enantiomeric excesses for the two of the diastereomers (**Table 2.8**,

entry 1). The more electrophilic aldehyde **56c** required shorter reaction times for the reaction to occur. As a consequence, better diastereomeric ratios were observed in favour of the kinetic **79aac** product (65:35). Overall, both diastereomers were afforded in excellent enantiomeric excess values (**Table 2.8**, entry 2).

We also performed DFT calculations (B3LYP-D3(PCM)/6-31G(d) level of theory[84,85,86,87,88]) on the formation of cycloadducts **79** via Michael-Henry cascade reactions. Formation of adduct **79aaa** formed from cyclohexanone **11a**, trans-β-nitrostyrene **12a** and ethyl glyoxylate **56a** in the presence of trimethylamine and salicylic acid was chosen as model system. The reaction profile obtained for this specific transformation is gathered in **Figure 2.10**.

[84] B3LYP functional: a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.
[85] D3 dispersion empirical correction: Grimme, S.; Antony, J.; Enrlich, S.; Krieg, S. J. Chem. Phys. **2010**, *132*, 154104.
[86] 6-31G(d) basis set: Hehre, W. J.; Random, L.; Schleyer, P. V. Pople, J. A. *Ab Initio Molecular Orbital Theory*, Wiley: New York, **1986**.
[87] PCM method: a) Cammi, R.; Mennucci, B.; Tomasi, J. *J. Phys. Chem. A* **2000**, *104*, 5631-5637. b) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev*. **2005**, *105*, 2999-3094.
[88] Gaussian 09 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision E.01, Gaussian, Inc., Wallingford CT, **2013**. NBO program, as implemented in Gaussian 09: Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc*. **1980**, *102*, 7211-7218. b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys*. **1985**, *83*, 735-746. c) Reed, A. E.; Weinhold, F. *J. Chem. Phys* **1985**, *83*, 1736-1740. d) Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 899-926.

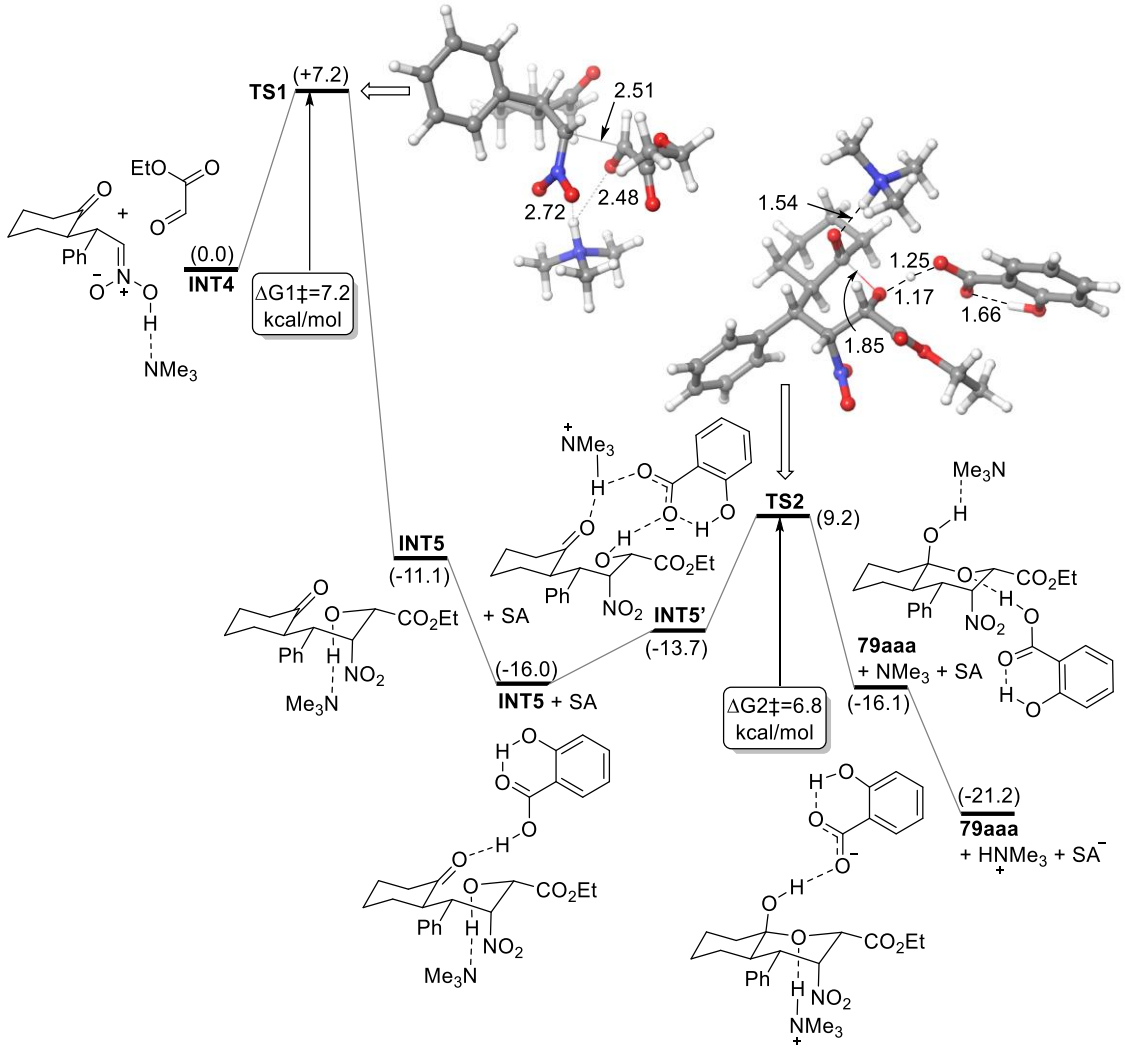
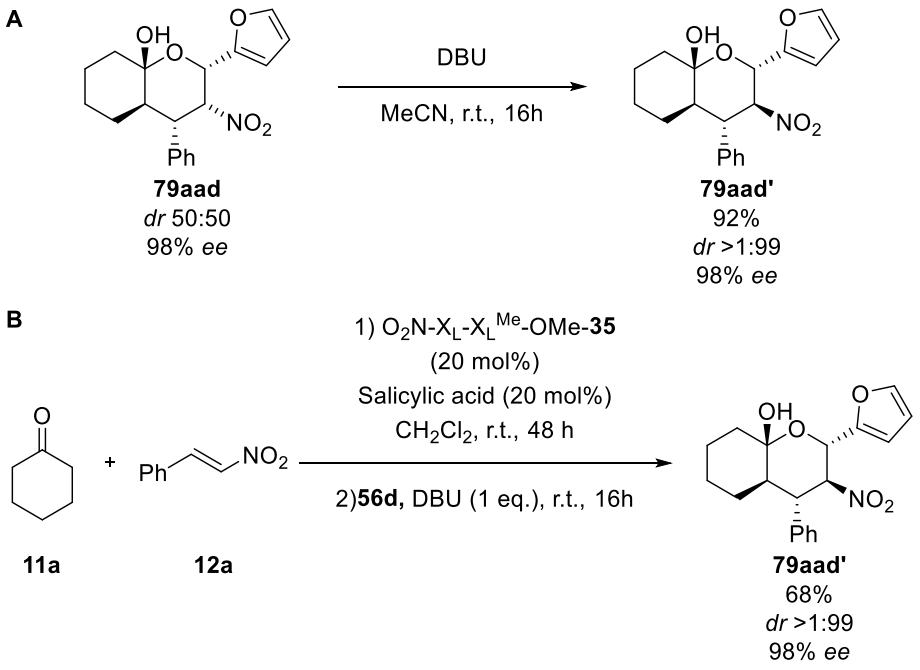


Figure 2.10. Reaction profile (B3LYP-D3(PCM)/6-31G(d) level of theory) associated with formation of bicyclic hemiacetal **79aaa** via nitronate intermediate **INT3** derived from **13aa**. Trimethylamine has been used as a computational model of Et_3N. SA stands for salicylic acid. Calculations were performed in dichloromethane solution. Numbers in parentheses are relative Gibbs energies (298 K) with respect to **INT3** and are given in kcal/mol. Bond distances are given in Å.

Once Michael intermediate **13aa** is formed (**Table 2.5**) nitronate **INT4** is formed as a consequence of the interaction between this latter intermediate and trimethylamine, which is a suitable computational model of triethylamine. Nucleophilic addition of **INT4** on the aldehyde group of **56a** results in the formation of adduct **INT5** with a calculated activation energy of ca. 7 kcal/mol. All our attempts of connecting this latter alcohol adduct with hemiacetal **79aaa** met with no success. Instead, our calculations showed that participation of one equivalent of salicylic acid (SA) results in the activation of nucleophilicity of the alcohol group of **INT5**, together with a slight enhancement of the electrophilicity of the ketone group. As a consequence, **79aaa** is formed from **INT5'** via **TS2**, with an activation energy similar to that found for the previous step via **TS1** (**Figure 2.10**). Reorganization of the acid and base additives leads to hemiacetal **79aaa** with a considerably exergonic thermodynamic balance from nitronate **INT4**. It is

noteworthy that the C-O bond forming step takes place via an equatorial nucleophilic attack on the cyclohexanone moiety, which determines the (4*aR*,8*aS*) configuration of the *trans*-octahydro-2H-chromene moiety of **79aaa**, in which all the substituents occupy equatorial positions, with the only exception of the nitro group.

Heteroaromatic aldehydes such as furfural were also applicable to the transformation, and the process underwent smoothly giving rise to derivative **79aad** with 1 equivalent of triethylamine. The final products were obtained as a 50:50 mixture of diastereomers, in good overall yield and excellent enantioselectivities (**Table 2.8**, entry 3). Since problems arose in the purification of the final products, isomerization of **79aad** into **79aad'** was investigated. Treatment with DBU (1 equivalent) at room temperature for 16 hours led to **79aad'** quantitatively with no loss of enantioselection (**Scheme 2.23A**). Hence, in the one-pot process for the straight synthesis of epimer **79aad'** the second step was conducted using 1 equivalent of DBU and the desired product was obtained in a good 68% yield with excellent diastereo- and enantiocontrol (**Scheme 2.23B**).



Scheme 2.23. A) Isomerization reaction for the formation of **79aad'** derivative. b) One-pot synthesis of compound **79aad'** with 1 equivalent of DBU.

This isomerization is compatible with the change of configuration of the carbon atom contiguous to the nitro group, which passes from an axial position in **79aad** (see **Figure 2.11**) to a thermodynamically favoured equatorial geometry in **79aad'**. This process is mediated by a suitable base such as DBU via nitronate **INTaad** shown in **Figure 2.11**. In effect, DFT calculations on these three local minima (B3LYP-D3(PCM)/6-31G* level of theory[84-88]) showed that all-equatorial isomer **79aad'**

is ca. 4 kcal/mol more stable than **79aad**, the nitronate intermediate **INTaad** laying only ca. 2 kcal/mol above **79aad**. These results indicate that in the presence of DBU and a polar solvent such as acetonitrile the equilibrium is completely shifted towards the all-equatorial isomer, in nice agreement with our experimental finding.

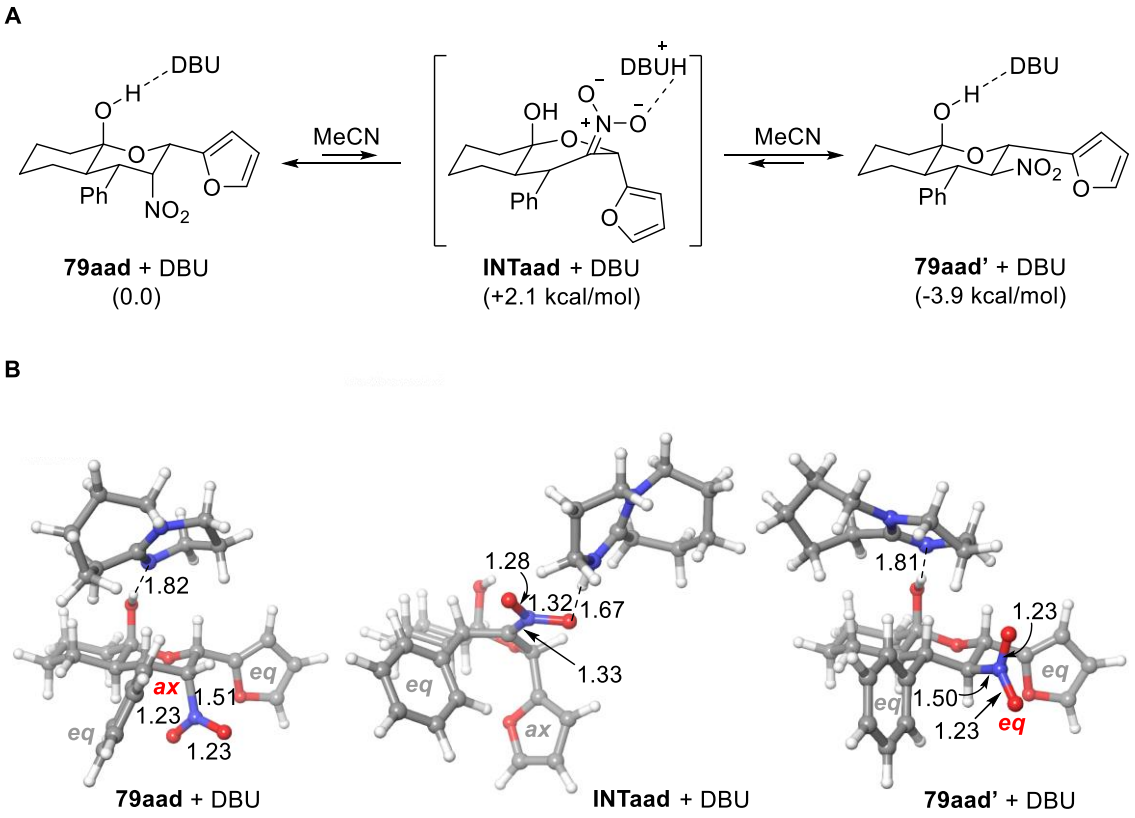


Figure 2.11. A) Reaction profile (B3LYP-D3(PCM)/6-31G(d) level of theory) associated with isomerization of bicyclic hemiacetal **79aad** to yield compound **79aad'** mediated by DBU nitronate **INTaad** in acetonitrile solution. Numbers in parentheses are relative Gibbs energies (298 K), in kcal/mol. B) Structures of local minima **79aad**,**79aad'** and **INTaad** bound to DBU. The axial (ax) and equatorial (eq) positions of the different substituents are highlighted. Bond distances are given in Å.

When cinnamaldehyde **56e** was employed as electrophilic aldehyde, model reaction conditions led to the corresponding tetrahydropyran **79aae** in 96h with moderate yield but total stereocontrol (**Table 2.8**, entry 4). The last trials were carried out by means of chiral **56f** aldehyde. We hypothesised that the asymmetric carbon of the aldehyde would act as a chiral auxiliary leading to the formation of a single diastereomer. Indeed, the final product was achieved within 3 hours in good yield and excellent diastereo- and enantioselectivity (**Table 2.8**, entry 5). This result encouraged us to synthesise more complex structures that could led to sugar-like structures after some derivatizations. For so, the nucleophilic ketone was replaced by 1,4-cyclohexanedione monoethylene acetal **11j** obtaining the desired **79jaf** derivative in moderate yields and complete stereocontrol (**Table 2.8**, entry 6).

All in all, dipeptide O_2N-X_L-X_L^{Me}-OMe-**35** is an efficient catalyst to promote the one-pot Michael-Henry-Acetalisation reaction with several aldehydes, reaching the desired compounds in good yields and enantiocontrol. Taking into consideration the general nature of our system, it can be stated that our results complement the excellent outcome reported by Hayashi in which aldehydes were used as nucleophilic species.[77] In addition, it also expands the family of cycloalkane-fused tetrahydropyran skeletons previously reported by the research group led by Chandrasekhar.[76]

2.7 CONCLUSIONS

From the experimental and computational studies reported and discussed along this chapter, the following conclusions can be drawn:

1. *N*-methylated hybrid O_2N-X_D-X_L^{Me}-OMe-**35** and O_2N-X_L-X_L^{Me}-OMe-**35** dipeptides were synthesised in good yields starting from densely substituted unnatural proline O_2N-$X_{L/D}$-OMe-**75** derivatives.
2. Both dimeric organocatalysts were able to promote the enamine-based asymmetric Michael reaction of cyclopentanone and cycloheptanone with excellent diastereo- and enantioselectivities. The obtained results confirm the emergence of properties that dipeptide derivatives present in comparison with their first and second generation catalysts.
3. The paramount catalytic activity exhibited by the unnatural proline based second and third generation of catalysts entailed the testing of their suitability in the three-component Michael-Henry-Acetalisation reaction. Therein, dipeptide O_2N-X_L-X_L^{Me}-OMe-**35** along with salicylic acid and triethylamne demonstrated its effectiveness for the one-pot asymmetric transformation.
4. The general nature of the reaction has been extensively demonstrated. The robustness of the catalyst enabled its implementation to several nucleophilic ketones, nitroalkenes and electrophilic aldehydes. All the tetrahydropyran derivatives were obtained in good yields and excellent enantioselectivities. In the particular case of aldehydes, the use of higher amount of trimethylamine had a significative influence in the diastereomeric ratio.
5. The gathered data constitute the first study concerning the three-component one-pot Michael-Henry-Acetalisation reaction of nucleophilic ketones for the synthesis of tetrahydropyran cores.

2.8 EXPERIMENTAL SECTION

General remarks

Unless otherwise noted, reagents and substrates were purchased from comercial suppliers. Ligands NH-L-EhuPhos-**74** and NH-D-EhuPhos-**74** were prepared following our previously described procedure.[40]

TLC was performed on 0.25mm silica gel 60 F254 aluminum plates and visualized with UV lamps or potassium permanganate stain. Flash column chromatography was carried out on columns of silica gel 60 (particle size 23-40 μm).

For hydrogenation reactions a Raney-Nickel cartridge equipped continuous flow reactor was employed. Hydrogen gas was in situ generated by electrolysis of water.

Optical rotations were measured at 589 nm (Sodium line) in a digital polarimeter with a thermally jacketed 5 cm cell at approximately 20 °C. Concentrations are given in g/100 mL.

Infrared spectra were recorded on an Alpha-Bruker FT-IR spectrometer with a single reflection ATR module. Wavenumbers are given in cm^{-1}.

High Resolution Mass Spectra (HRMS) analyses were carried out by SGIker services (Central Service of Alava and Bizkaia, University of the Basque Country) and performed on a LC/QTOF, Agilent mass spectrometer using electrospray ionization (ESI) mode.

NMR spectra were recorded at 400 or 500 MHz for ^{1}H NMR, 101 or 126 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR using $CDCl_3$, acetone-*d6* and methanol-*d4* as solvents and TMS as internal standard. The data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad signal, coupling constant(s) (*J*) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H decoupling.

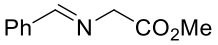
Enantioselectivities were measured by HPLC using chiral stationary phases. In these experiments the racemic mixtures were analysed in order to establish the enantiomeric parameters of each enantiomer.

For X-Ray diffraction analyses Agilent Technologies Super-Nova diffractometer was employed, equipped with monochromated Cu kα radiation (λ = 1.54184 Å) and Atlas CCD detector. Measurements were accomplished at 100 K with the aid of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) utilizing the Crysalis

software package.[89] The structure was solved by Superflip[90] and refined by full-matrix least-squares with SHELXL-97[91]. Final geometrical calculations were carried out on Mercury[92] and PLATON[93] as integrated in WinGX[94].

Synthesis of imine 73

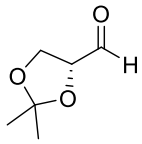
Glycine methyl ester hydrochloride (376.6 mg, 3.0 mmol, 1 eq.), triethylamine (420 µL, 3.0 mmol, 1 eq.) and $MgSO_4$ were dissolved in 5 mL of dry CH_2Cl_2. The suspension was stirred at room temperature for one hour and 2.3 mmol (0.8 eq.) of benzaldehyde **56b** were added. The resulting mixture was allowed to stir for 16 hours, filtered, washed three times with H_2O, dried on Na_2SO_4 and evaporated under reduced pressure. The resulting imine was employed in the following steps without further purification.



Methyl (E)-2-(benzylideneamino)acetate (**73**). Yield: 84 % (446 mg, 2.51 mmol). Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, CH), 7.82 – 7.76 (m, 2H, ArH), 7.50 – 7.38 (m, 3H, ArH), 4.42 (s, 2H, CH_2), 3.78 (s, 3H, CO_2CH_3).

Synthesis of aldehyde 56f

To solution of *D*-mannitol-1,2:5,6-bis-acetonide (1 g , 4.30 mmol, 1 eq.) in CH_2Cl_2 (10 mL) $NaIO_4$ (1.80 g, 8.60 mmol, 2 eq.) and saturated $NaHCO_3$ (0.45 mL) were added and the mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was filtered and washed three times with CH_2Cl_2, dried on Na_2SO_4, filtered and evaporated under reduced pressure.



(*R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde* (**56f**).[95] Yield: 75 % (419 mg, 3.22 mmol). Pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.9 Hz, 1H, CHO), 4.39 (ddd, *J* = 7.0, 4.7, 1.9 Hz, 1H, CH), 4.19 – 4.12 (m, 1H, CH_2), 4.10 (d, *J* = 4.0 Hz, 1H, CH_2), 1.49 (s, 3H, CH_3), 1.42 (s, 3H, CH_3).

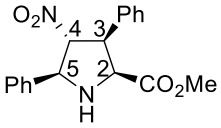
General Procedure for the Synthesis of *exo*-cycloadducts 75

For *exo*-L cycloadduct: A solution of NH-D-EhuPhos-**74** (9 mg, 0.015 mmol, 0.03 eq.) and $Cu(CH_3CN)_4PF_6$ (5 mg, 0.014 mmol, 0.03 eq.) in 1.0 mL of dry THF was stirred

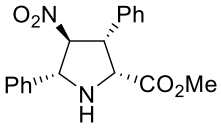
[89] CrysAlisPro, Agilent Technologies, Version 1.171.37.31.
[90] Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786-790.
[91] a) Sheldrick, G. M. *Acta Cryst*. **2008**, A64, 112-122. b) Sheldrick, G. M. *Acta Cryst*. **2015**, C71, 3-8.
[92] Macrae, C. F. *J. Appl. Cryst*. **2008**, *41*, 466-470.
[93] a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Utretch University, The Nederlands **2010**. b) Spek, A. L. *J. Appl. Cryst*. **2003**, *36*, 7-13.
[94] Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838.
[95] Leyes, A. E.; Poulter, C. D. *Org. Lett*. **1999**, *1*, 1067-1070.

at -20 °C for 15 minutes. Then, a solution of imine **73** (80 mg, 0.45 mmol, 1 eq.) in 1.0 mL of solvent, triethylamine (3 µL, 0.023 mmol, 0.05 eq.) and *trans*-β-nitrostyrene **12a** (75 mg, 0.50 mmol, 1.1 eq.) in 1.0 mL of solvent were successively added. The course of the reaction was monitored by TLC and, once the starting material was consumed, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:2 EtOAc:Hexane). For *exo*-D cycloadduct, NH-L-EhuPhos-**74** ligand was employed. The enantiomeric excesses were determined by comparison of the HPLC chromatogram recorded for the racemic mixture with that corresponding to the enantiomerically enriched cycloadducts.

Nomenclature: Carbon atoms in densely substituted pyrrolidine rings are numbered as in pyrrolidine, the nitrogen atom numbered 1, and proceeding towards the ester group.[96]



Methyl (2S,3S,4R,5S)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (O_2N-X_L-OMe-**75**).[97] Yield: 85% (125 mg, 0.38 mmol), white solid. 97% *ee* after column chromatography and >99% *ee* after recrystallization in EtOAc/hexane mixture. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.0 Hz, 2H, ArH), 7.46 – 7.36 (m, 3H, ArH), 7.35 – 7.19 (m, 5H, ArH), 5.22 (t, *J* = 8.1 Hz, 1H, C^4H), 4.77 (d, *J*=8.2, 1H, C^5H), 4.51 (d, *J* = 7.9 Hz, 1H, C^2H), 4.39 (t, *J* = 8.5 Hz, 1H, C^3H), 3.29 (s, 3H, CO_2CH_3), 2.74 (bs, 1H, NH). **HPLC** (Chiralcel IB, Hexane:^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 254 nm), t_R (major) = 6.92 min, t_R (minor) = 12.49 min; *ee* = 97%.



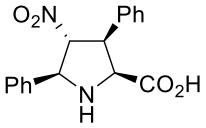
Methyl (2R,3R,4S,5R)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (O_2N-X_D-OMe-**75**).[39] Yield: 84% (123 mg, 0.37 mmol), white solid. 96% *ee* after column chromatography and 99% ee after recrystallization in EtOAc/hexane. Analytical and spectroscopic data were coincident with the previously reported material. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.0 Hz, 2H, ArH), 7.46 – 7.36 (m, 3H, ArH), 7.35 – 7.19 (m, 5H, ArH), 5.22 (t, *J* = 8.1 Hz, 1H, C^4H), 4.77 (d, *J*=8.2, 1H, C^5H), 4.51 (d, *J* = 7.9 Hz, 1H, C^2H), 4.39 (t, *J* = 8.5 Hz, 1H, C^3H), 3.29 (s, 3H, CO_2CH_3), 2.74 (bs, 1H, NH). HPLC (Chiralcel IB, Hexane:^{i}PrOH =

[96] Nomenclature and Symbolism for Amino Acids and Peptides. *Eur. J. Biochem*. **1984**, *138*, 9-37.
[97] Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed*. **2006**, *45*, 1979-1983.

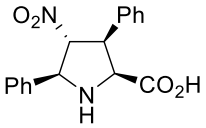
80:20, flow rate 1 mL/min, λ = 254 nm), t_R (minor) = 6.92 min, t_R (major) = 12.49 min; *ee* = 96%.

General Procedure for hydrolysis

To a solution of O_2N-$X_{L/D}$-OMe-**75** (326 mg, 1.0 mmol, 1 eq.) in acetone (3 mL) stirred at room temperature, a solution of sodium hydroxide (88 mg, 2.20 mmol, 2.2 eq.) in water (3 mL) was added. The reaction mixture was stirred for 16 hour. Then, the solution was cooled to 0 °C and acidified with 2N HCl to pH ≈ 2. A solid precipitated from the solution. This solid was filtered, washed with water and dried under reduced pressure to afford the desired product.



(2S,3S,4R,5S)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylic acid (O_2N-X_L-OH-**76**).[40b] Yield: 85% (265 mg, 0.85 mmol), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.51 (d, *J* = 7.4 Hz, 4H, ArH), 7.41 (t, *J* = 7.5 Hz, 2H, ArH), 7.38 – 7.28 (m, 4H, ArH), 5.57 (dd, *J* = 6.8, 4.3 Hz, 1H, C^4H), 5.20 (d, *J* = 6.7 Hz, 1H, C^5H), 4.30 – 4.24 (m, *J* =9.1 Hz, 1H, C^2H), 4.19 (d, *J* = 7.7 Hz, 1H, C^3H), 2.78 (bs, 1H, NH).

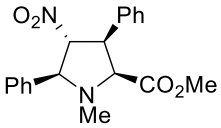


(2R,3R,4S,5R)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylic acid (O_2N-X_L-OH-**76**).[40b] Yield: 80% (250 mg, 0.80 mmol), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.51 (d, *J* = 7.4 Hz, 4H, ArH), 7.41 (t, *J* = 7.5 Hz, 2H, ArH), 7.38 – 7.28 (m, 4H, ArH), 5.57 (dd, *J* = 6.8, 4.3 Hz, 1H, C^4H), 5.20 (d, *J* = 6.7 Hz, 1H, C^5H), 4.30 – 4.24 (m, *J* =9.1 Hz, 1H, C^2H), 4.19 (d, *J* = 7.7 Hz, 1H, C^3H), 2.78 (bs, 1H, NH).

General Procedure for the methylation of O_2N-X_L-OMe-75.[98]

Pyrrolidine O_2N-X_L-OMe-**75** (500 mg, 1.53 mmol) was dissolved in 10 mL of 88% aqueous formic acid. 10 mL of 35% aqueous formaldehyde were added and the reaction mixture was heated at 100 °C for two hours. After cooling to room temperature, the acidic solution was basified with saturated K_2CO_3 solution from which a precipitate appeared. Then, the solution was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (1:5 EtOAc:Hexane).

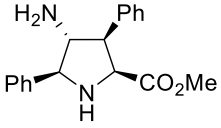
[98] Denmark, S. E.; Matsuhashi, H. *J. Org. Chem*. **2002**, *67*, 3479-3486.



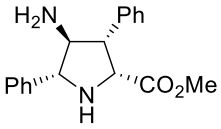
Methyl (2S,3S,4R,5S)-1-methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (O_2N-X_L^{Me}-OMe-**77**).[39] Yield: 90% (470 mg, 1.38 mmol), dark yellow solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H, ArH), 7.45 – 7.24 (m, 8H, ArH), 5.05 – 4.96 (m, 1H, C^4H), 4.24 (dd, *J* = 9.3, 5.9 Hz, 1H, C^3H), 3.97 (d, *J* = 8.0 Hz, 1H, C^5H), 3.92 (d, *J* = 9.3 Hz, 1H, C^2H), 3.27 (s, 3H, CO_2CH_3), 2.33 (s, 3H, NCH_3).

General Procedure for the Synthesis of Amino Derivatives

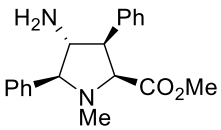
A solution of the corresponding cycloadduct (1.0 mmol) in 100 mL of methanol was pumped at 1 mL/min through the H-Cube® Hydrogenation Reactor using a Raney/Nickel CatCart® catalyst. The pressure of the system was set to 20 bars and the temperature to 65 °C. Once the reaction mixture had passed through the reactor, the solvent was reduced to dryness. The crude mixture was filtered through a plug of silica eluting with ethyl acetate affording the pure product.



Methyl (2S,3R,4R,5S)-4-amino-3,5-diphenylpyrrolidine-2-carboxylate (H_2N-X_L-OMe-**28**).[39] The expected product was obtained from O_2N-X_L-OMe-**75**. Yield: 90% (266 mg, 0.90 mmol), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 2H, ArH), 7.40 (t, *J* = 7.2 Hz, 2H, ArH), 7.34 – 7.29 (m, 3H, ArH), 7.24 (d, *J* = 7.0 Hz, 3H, ArH), 4.26 (d, *J* = 9.7 Hz, 1H, C^5H), 3.92 (d, *J* = 8.7 Hz, 1H, C^2H), 3.60 (t, *J* = 9.5 Hz, 1H, C^3H), 3.49 (t, *J* = 9.9 Hz, 1H, C^4H), 3.22 (s, 3H, CO_2CH_3).



Methyl (2R,3S,4S,5R)-4-amino-3,5-diphenylpyrrolidine-2-carboxylate (H_2N-X_D-OMe-**28**).[39] The expected product was obtained from O_2N-X_D-OMe-**75**. Yield: 85% (252 mg, 0.85 mmol), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 2H, ArH), 7.40 (t, *J* = 7.2 Hz, 2H, ArH), 7.34 – 7.29 (m, 3H, ArH), 7.24 (d, *J* = 7.0 Hz, 3H, ArH), 4.26 (d, *J* = 9.7 Hz, 1H, C^5H), 3.92 (d, *J* = 8.7 Hz, 1H, C^2H), 3.60 (t, *J* = 9.5 Hz, 1H, C^3H), 3.49 (t, *J* = 9.9 Hz, 1H, C^4H), 3.22 (s, 3H, CO_2CH_3).

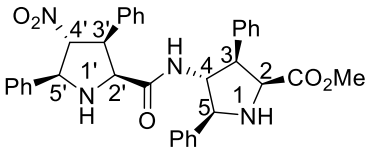


Methyl (2S,3R,4R,5S)-4-amino-1-methyl-3,5-diphenylpyrrolidine-2-carboxylate (H_2N-X_L^{Me}-OMe-**78**).[39] The expected product was obtained from O_2N-X_L^{Me}-OMe-**77**. Yield: 65% (202 mg, 0.65 mmol), bright yellow solid. Analytical and spectroscopic data were in good agreement with those

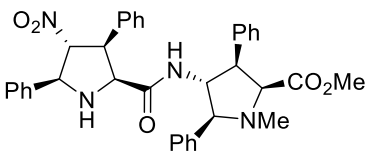
reported in literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 2H, ArH), 7.38 (t, *J* = 7.5 Hz, 2H, ArH), 7.35-7.16 (m, 6H, ArH), 3.70 (d, *J* = 10.4 Hz, 1H, C^5H), 3.50 (t, *J* = 8.4 Hz, 1H, C^3H), 3.38-3.26 (m, 1H, C^4H), 3.19 (s, 3H, CO_2CH_3), 3.15 (d, *J* = 8.3 Hz, 1H, C^2H), 2.23 (s, 3H, NCH_3), 1.33 (s, 2H, NH_2).

General Procedure for coupling reactions

To a stirred solution of the corresponding amine (0.80 mmol) in CH_2Cl_2 (10 mL), acid O_2N-X_L-OH-**76** (1.0 mmol, 1.25 eq.), PyBOP (520 mg, 1.0 mmol, 1.25 eq.) and diisopropyl ethyl amine (250 µL, 1.44 mmol, 1.8 eq.) were added. The resulting mixture was allowed to stir at room temperature until completion. Then, the reaction mixture was diluted with CH_2Cl_2, washed three times with a 1M HCl solution, twice with saturated aqueous $NaHCO_3$, once with brine and dried over Na_2SO_4. After evaporation to dryness, the crude mixture was purified by flash column chromatography on silica gel (1:2 EtOAc:Hexane).

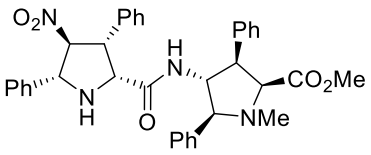


Methyl (2S,3R,4R,5S)-4-((2S,3S,4R,5S)-4-nitro-3,5-diphenylpyrrolidine-2-carboxamido)-3,5-diphenylpyrrolidine-2-carboxylate (O_2N-X_L-X_L-OMe-**34**). The title product was obtained from H_2N-X_L-OMe-**28**. Yield: 65% (307 mg, 0.52 mmol), white solid. **m_p** = 136-137 °C. $[\alpha]_D^{25}$ = +129.9 (*c* 0.43, acetone). **FTIR** (neat, cm^{-1}) 1732, 1671, 1546, 696. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.33 (m, 10H, ArH), 7.30 – 7.17 (m, 5H, ArH), 7.11 (t, *J* = 7.4 Hz, 1H, ArH), 7.00 (t, *J* = 7.7 Hz, 2H, ArH), 6.93 (d, *J* = 8.8 Hz, 1H, CONH), 6.77 (d, *J* = 7.3 Hz, 2H, ArH), 4.93 (t, *J* = 8.6 Hz, 1H, $C^{4'}H$), 4.79 (d, *J* = 8.4 Hz, 1H, $C^{5'}H$), 4.59 (q, *J* = 9.0 Hz, 1H, C^4H), 4.33 – 4.17 (m, 3H, $C^{2'}H$, $C^{3'}H$, C^2H), 4.15 – 4.07 (m, 1H, C^5H), 3.52 (t, *J* = 9.1 Hz, 1H, C^3H), 3.20 (s, 3H, CO_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1, 169.3, 137.2, 134.5, 129.4, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.2 (2 signals), 127.7, 127.5, 126.7, 94.4, 67.08, 66.1, 64.2, 63.7, 60.2, 54.3, 53.5, 51.7. **HRMS** (ESI) for $C_{35}H_{35}N_4O_5$: calculated $[M+H]^+$: 591.2607, found: 591.2617.



Methyl (2S,3R,4R,5S)-1-methyl-4-((2S,3S,4R,5S)-4-nitro-3,5-diphenylpyrrolidine-2-carboxamido)-3,5-diphenylpyrrolidine-2-carboxylate (O_2N-X_L-X_L^{Me}-OMe-**35**). The title product was obtained from H_2N-X_L^{Me}-OMe-**78**. Yield: 76% (368 mg, 0.61 mmol), white solid. **m_p** = 201-204 °C. $[\alpha]_D^{25}$ = +125.3 (*c* 0.50, acetone). **FTIR** (neat, cm^{-1}) 1745, 1672, 1551. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (m, 10H, ArH), 7.33 – 7.16 (m, 6H, ArH), 7.10 (t, *J* = 7.4 Hz, 2H, ArH), 6.90 (d, *J* = 7.4 Hz, 2H, ArH), 6.83 (d, *J* = 7.8 Hz, 1H, CONH), 4.98 (d, *J* = 4.9 Hz, 1H, $C^{4'}H$), 4.81 (d, *J* = 7.8

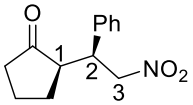
Hz, 1H, $C^{5'}H$), 4.29 (s, 2H, $C^{2'}H$ and $C^{3'}H$), 4.11 (q, *J* = 7.8 Hz, 1H, C^4H), 3.68 (d, *J* = 9.5 Hz, 1H, C^2H), 3.43 (d, *J* = 8.6 Hz, 1H, C^5H), 3.31 (t, *J* = 8.2 Hz, 1H, C^3H), 3.19 (s, 3H, CO_2CH_3), 2.58 (m, 1H, NH), 2.22 (s, 3H, NCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.25, 169.5, 139.7, 139.6, 137.9, 135.0, 129.3, 129.3, 129.0, 128.9, 128.9, 128.5, 128.3 (2 signals), 128.2, 128.0, 127.2, 126.8, 94.8, 74.8, 72.1, 66.3, 64.3, 64.2, 53.4, 51.8, 51.3, 39.9. **HRMS** (ESI) for $C_{36}H_{37}N_4O_5$: calculated $[M+H]^+$: 605.2764, found: 605.2778.



Methyl (2S,3R,4R,5S)-1-methyl-4-((2R,3R,4S,5R)-4-nitro-3,5-diphenylpyrrolidine-2-carboxamido)-3,5-diphenylpyrrolidine-2-carboxylate (O_2N-X_D-X_L^{Me}-OMe-**35**). The title product was obtained from H_2N-X_L^{Me}-OMe-**78**. Yield: 68% (329 mg, 0.54 mmol), white solid. **m_p** = 99-100 °C. $[\alpha]_D^{25}$ = -19.0 (*c* 0.51, acetone). **FTIR** (neat, cm^{-1}) 1748, 1669, 1547. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.11 (m, 20H, ArH), 6.70 (d, *J* = 7.2 Hz, 1H, CONH), 5.17 – 4.99 (m, 1H, $C^{4'}H$), 4.82 (d, *J* = 7.4 Hz, 1H, $C^{5'}H$), 4.28 (m, 2H, $C^{2'}H$ and $C^{3'}H$), 4.04 (dd, *J* = 13.7, 7.2 Hz, 1H, C^4H), 3.54 (d, *J* = 9.2 Hz, 1H, C^2H), 3.23 (s, 3H, CO_2CH_3), 3.16 (d, *J* = 8.1 Hz, 1H, C^5H), 2.90 (dd, *J* = 8.7, 6.1 Hz, 1H, C^3H), 2.62 (bs, 1H, NH), 2.23 (s, 3H, NCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8, 169.0, 140.3, 139.2, 138.0, 136.2, 129.4, 129.2, 128.9, 128.9, 128.7, 128.7, 128.4, 128.4, 128.1, 127.9, 127.1, 126.8, 95.7, 76.4, 72.3, 66.5, 64.9, 64.4, 53.0, 52.2, 51.3, 39.8. **HRMS** (ESI) for $C_{36}H_{37}N_4O_5$: calculated $[M+H]^+$: 605.2764, found: 605.2773.

General Procedure for the Asymmetric Michael Reaction

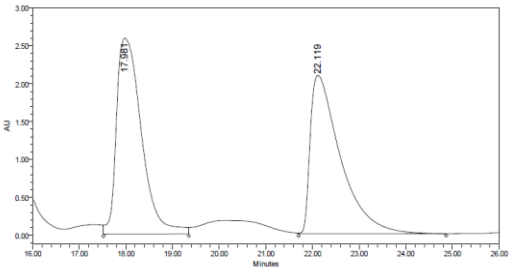
A reaction mixture of dimeric catalyst (12.10 mg, 0.02 mmol, 0.2 eq.), salicylic acid (2.76 mg, 0.02 mmol, 0.2 eq.), ketone **11b,c** (0.10 mmol, 1 eq.) and *trans*-β-nitrostyrene **12a** (14.90 mg, 0.11 mmol, 1.1 eq.) was stirred at -10 °C until total consumption of the nitroalkene. Afterwards, the crude mixture was evaporated under reduced pressure and purified by flash column chromatography on silica gel (1:2 EtOAc:Hexane). For the racemic compounds, the reactions were carried out using pyrrolidine (8 µL, 0.10 mmol, 1 eq.).

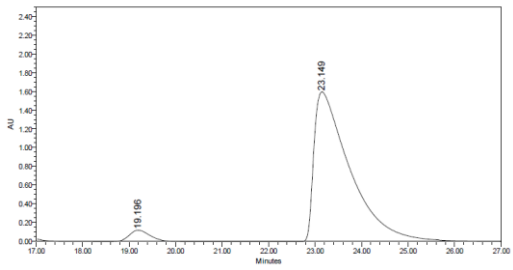


(R)-2-((S)-2-nitro-1-phenylethyl)cyclopentan-1-one (**13ba**).[99] The title product was obtained from cyclopentanone **11b**. Yield: 95% (22 mg, 0.095 mmol), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35

[99] Vishnumaya, Singh, V. K. *Org. Lett*. **2007**, *9*, 1117-1119.

– 7.24 (m, 3H, ArH), 7.20 – 7.15 (m, 2H, ArH), 5.35 (d, *J* = 5.6 Hz, 1H, C^3H), 4.71 (dd, *J* = 12.8, 10.0 Hz, 1H, C^3H), 3.69 (td, *J* = 9.5, 5.5 Hz, 1H, C^2H), 2.45 – 2.27 (m, 2H, CH_2), 2.12 (ddd, *J* = 19.0, 10.6, 8.7 Hz, 1H, C^1H), 1.97 – 1.78 (m, 2H, CH_2), 1.74 – 1.66 (m, 1H, CH_2), 1.54 – 1.39 (m, 1H, CH_2). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 17.98 min, t_R (major) = 22.12 min; *ee* = 90%.





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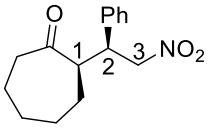
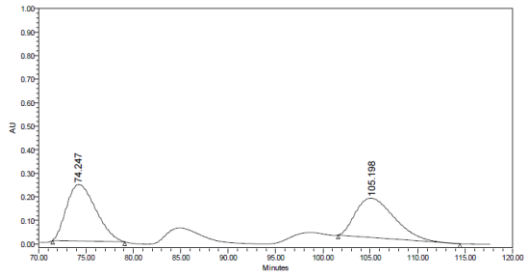
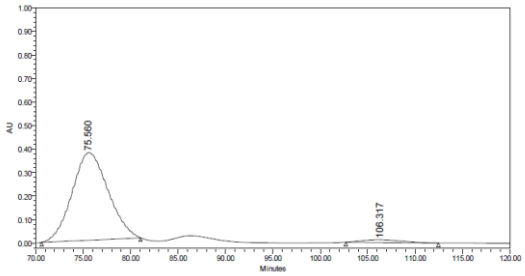


(R)-2-((S)-2-nitro-1-phenylethyl)cycloheptan-1-one (**13ca**). The title product was obtained from cycloheptanone **11c**. Yield 94% (25 mg, 0.094 mmol), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature.[100] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 14.8, 7.8, 6.2 Hz, 3H, ArH), 7.20 – 7.16 (m, 2H, ArH), 4.67 – 4.63 (m, 2H, C^3H), 3.68 (ddd, *J* = 10.2, 8.3, 5.1 Hz, 1H, C^2H), 3.00 (td, *J* = 10.3, 3.4 Hz, 1H, C^1H), 2.57 – 2.47 (m, 2H, CH_2), 1.99 – 1.82 (m, 2H, CH_2), 1.80 – 1.52 (m, 3H, CH_2), 1.29 – 1.12 (m, 3H, CH_2). **HPLC** (Daicel Chiralpak AD-H, Hexane:^{i}PrOH = 99:1, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 74.25 min, t_R (minor) = 105.20 min; *ee* = 93%.

[100] Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *Journal of Molecular Catalysis A: Chemical* **2007**, *263*, 186-194.





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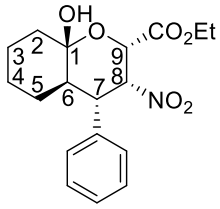
	RT	Height	Area	% Area
1	75.560	372306	98576963	96.58
2	106.317	12229	3491361	3.42

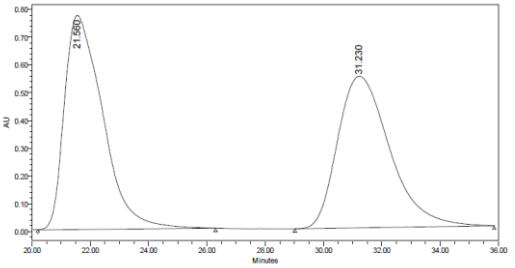
General Procedure for the One-pot Michael-Henry-Acetalisation Reaction

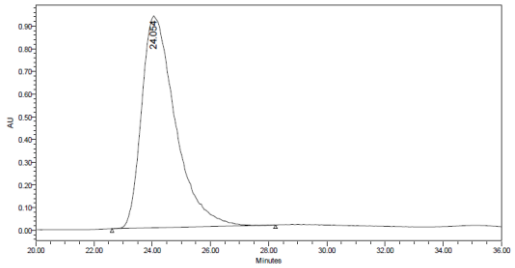
A reaction mixture of O_2N-X_L-X_L^{Me}-OMe-**35** (12.10 mg, 0.02 mmol, 0.2 eq.), acid derivative (0.02 mmol, 0.2 eq.), ketone **11a-j** (0.1 mmol, 1.0 eq.) and nitroolefins **12a-i** (0.11 mmol, 1.1 eq.) was stirred at room temperature until total consumption of the nitroalkene. Then, the corresponding aldehyde (0.20 mmol, 0.2 eq.) and triethylamine (3 µL, 0.02 mmol, 0.2 eq.) were successively added and the resulting reaction mixture was allowed to stir at the indicated temperature until total consumption of the intermediate γ-nitroketone. Afterwards, the crude mixture was evaporated under reduced pressure and purified by flash column chromatography on silica gel (check each compound for conditions). For the racemic compounds, the reactions were carried out using pyrrolidine (8 µL, 0.10 mmol, 1 eq.).



Ethyl (2S,3R,4S,4aR,8aS)-8a-hydroxy-3-nitro-4-phenyloctahydro-2H-chromene-2-carboxylate (**79aaa**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 72% (27 mg, 0.072 mmol), white solid. $\mathbf{m_p}$ = 169-171 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +52.63 (*c* 0.95, chloroform). **FTIR** (neat, cm^{-1}) 3507, 1756, 1545, 1313. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.4 Hz, 3H, ArH), 7.13 (d, *J* = 7.3 Hz, 2H, ArH), 5.14 (d, *J* = 3.0 Hz, 1H, C^9H), 5.12 (d, *J* = 4.4 Hz, 1H, C^8H), 4.33 – 4.13 (m, 2H, CH_2CH_3), 3.52 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.61 (td, *J* = 12.2, 3.3 Hz, 1H, C^6H), 2.09 – 1.97 (m, 2H, CH_2, OH), 1.95 (s, 1H, CH_2), 1.78 (d, *J* = 13.7 Hz, 1H, CH_2), 1.74 – 1.60 (m, 2H, CH_2), 1.39 (d, *J* = 14.4 Hz, 1H, CH_2), 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.18 – 0.98 (m, 1H, CH_2), 0.92 – 0.79 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7 (C=O), 136.2(ArC),

129.1 (ArC), 128.3 (ArC), 128.2 (ArC), 98.1 (C^1), 86.9 (C^8), 69.3(C^9), 62.3 (CH_2CH_3), 44.1 (C^7), 38.9 (C^6), 38.5 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 14.1 (CH_2CH_3). **HRMS** (ESI) for $C_{18}H_{24}NO_6$: calculated $[M+H]^+$: 350.1603, found 350.1605. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 21.56 min, t_R (minor) = 31.23 min; *ee* = 99%.





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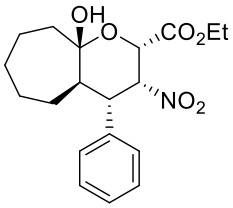
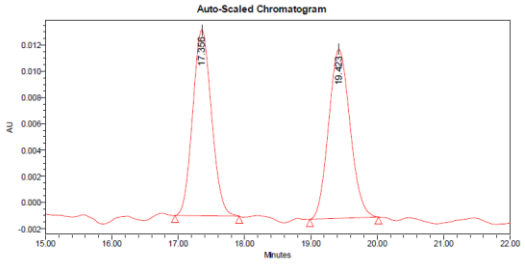
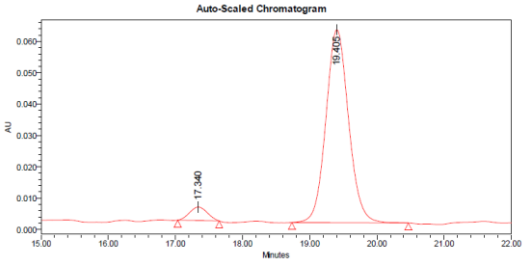


Ethyl (2S,3R,4S,4aR,9aS)-9a-hydroxy-3-nitro-4-phenyldecahydrocyclohepta[b]pyran-2-carboxylate (**79caa**). The title product was obtained from cycloheptanone **11c**, *trans*-β-nitrostyrene **12a** and ethyl glyoxylate **56a** employing TFA as additive. Purified on 1:1 Diethyl ether:Hexane mixture. Yield: 53% (19 mg, 0.053 mmol), colorless oil. $[\alpha]_D^{25}$ = +42.64 (*c* 0.25, chloroform). **FTIR** (neat, cm^{-1}) 3404, 2982, 1740, 1552, 1370. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.1, 6.5 Hz, 2H, ArH), 7.34 – 7.25 (m, 3H, ArH), 5.25 (dd, *J* = 11.1, 2.3 Hz, 1H, C^9H), 4.35 – 4.16 (m, 2H, CH_2CH_3), 4.16 – 4.08 (m, 1H, C^8H), 3.94 – 3.86 (m, 1H, C^7H), 3.24 – 3.14 (m, 1H, OH), 2.85 (ddd, *J* = 11.6, 8.1, 3.8 Hz, 1H, C^6H), 2.38 – 2.21 (m, 1H, CH_2), 1.88 – 1.73 (m, 3H, CH_2), 1.66 (d, *J* = 53.8 Hz, 3H, CH_2), 1.43 (s, 1H, CH_2), 1.28 (d, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.25 (d, *J* = 4.0 Hz, 1H, CH_2), 1.22 – 1.06 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8, 136.5, 129.2, 129.1, 128.1, 90.1, 69.8, 62.8, 55.2, 46.8, 42.8, 29.5, 28.3, 28.1, 24.8, 14.0. **HRMS** (ESI) for $C_{19}H_{26}NO_6$: calculated $[M+H]^+$: 364.1760, found 364.1761. **HPLC** (Chiralcel IC, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 214 nm), t_R (minor) = 17.35 min, t_R (major) = 19.42 min, *ee* = 90%.





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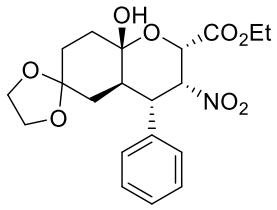
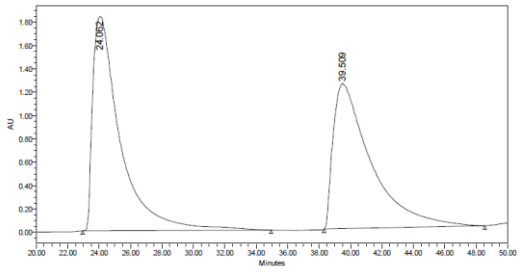
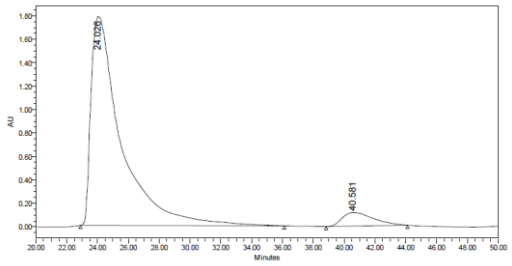


Ethyl (2S,3R,4S,4aR,8aS)-8a-hydroxy-3-nitro-4-phenylhexahyhdro-2H,5H-spiro[chromene-6,2'-[1,3]dioxolane]-2-carboxylate (**79jaa**). The title product was obtained from 1,4-cyclohexanedione monoethylene acetal **11j**, *trans*-β-nitrostyrene **12a** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield: 62% (25 mg, 0.062 mmol), colorless oil. $[\alpha]_D^{25}$ = +13.31 (*c* 0.7, chloroform). **FTIR** (neat, cm^{-1}) 3445, 2963, 1734, 1550, 1370. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 3H, ArH), 7.18 – 7.12 (m, 2H, ArH), 5.13 (d, *J* = 3.1 Hz, 1H, C^9H), 5.10 (dd, *J* = 4.8, 3.2 Hz, 1H, C^8H), 4.28 (dd, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 4.26 – 4.07 (m, 1H, CH_2CH_3), 3.98 – 3.92 (m, 1H, CH_2O), 3.86 (ddd, *J* = 12.5, 6.9, 5.5 Hz, 2H, CH_2O), 3.82 – 3.74 (m, 1H, CH_2O), 3.53 (dd, *J* = 12.7, 4.8 Hz, 1H, C^7H), 3.00 (ddd, *J* = 12.7, 9.9, 6.5 Hz, 1H, CH_2), 2.35 (td, *J* = 15.1, 4.8 Hz, 1H, C^6H), 2.21 (s, 1H, OH), 2.01 – 1.87 (m, 2H, CH_2), 1.86 – 1.75 (m, 1H, CH_2), 1.45 (dd, *J* = 8.7, 1.8 Hz, 2H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 136.0, 129.5, 128.6, 108.6, 97.7, 86.5, 69.9, 64.9, 64.7, 62.7, 43.9, 36.2, 35.9, 35.1, 32.3. **HRMS** (ESI) for $C_{20}H_{24}NO_7$ $[M+H-H_2O]^+$: calculated 390.1546, found 390.1541. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 24.06 min, t_R (minor) = 39.51 min, *ee* = 88%.





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2	39.509	1242793	207365753	48.07

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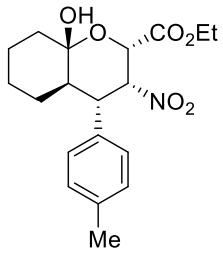
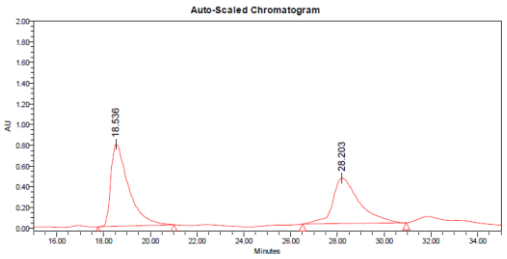
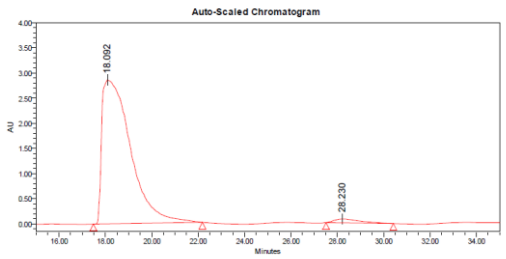


Ethyl (2S,3R,4S,4aR,8aS)-8a-hydroxy-3-nitro-4-(p-tolyl)octahydro-2H-chromene-2-carboxylate (**79aba**). The title product was obtained from cyclohexanone **11a**, *trans*-4-methyl-β-nitrostyrene **12b** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 47% (17 mg, 0.047 mmol), white solid. $\mathbf{m_p}$ = 174-177 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +57.69 (*c* 0.5, chloroform). **FTIR** (neat, cm^{-1}) 3475, 1750, 1549, 1372. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 2H, ArH), 7.01 (d, *J* = 7.6 Hz, 2H, ArH), 5.13 (d, *J* = 3.0 Hz, 1H, C^9H), 5.09 (s, 1H, C^8H), 4.27 (dd, *J* = 10.8, 7.0 Hz, 1H, CH_2CH_3), 4.17 (dd, *J* = 11.0, 6.9 Hz, 1H, CH_2CH_3), 3.48 (dd, *J* = 12.5, 4.9 Hz, 1H, C^7H), 2.57 (td, *J* = 12.5, 3.4 Hz, 1H, C^6H), 2.32 (s, 3H, CH_3), 2.16 (s, 1H, OH), 2.00 (td, *J* = 13.7, 4.3 Hz, 1H, CH_2), 1.93 (d, *J* = 14.1 Hz, 1H, CH_2), 1.77 (d, *J* = 13.7 Hz, 1H, CH_2), 1.71 – 1.53 (m, 2H, CH_2), 1.44 – 1.26 (m, 2H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.09 (qd, *J* = 12.8, 3.4 Hz, 1H, CH_2).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 137.8, 133.1, 129.8, 128.1, 98.2, 87.1, 69.4, 62.3, 43.7, 39.0, 38.6, 26.2, 25.6, 23.1, 21.2, 14.1. **HRMS** (ESI) for $C_{19}H_{26}NO_6$ $[M+H]^+$: calculated 364.1951, found 364.1948. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 18.53 min, t_R (minor) = 28.20 min, *ee* = 95%.





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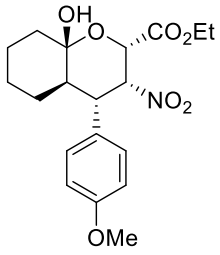
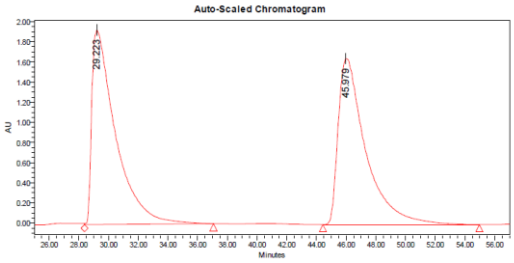
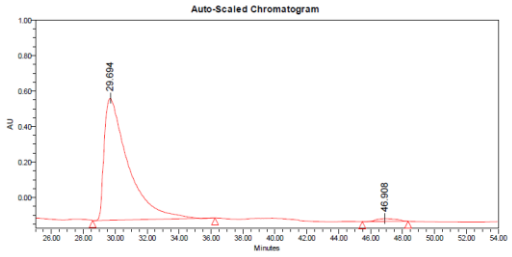


Ethyl (2S,3R,4S,4aR,8aS)-8a-hydroxy-4-(4-methoxyphenyl)-3-nitrooctahydro-2H-chromene-2-carboxylate (**79aca**). The title product was obtained from cyclohexanone **11a**, *trans*-4-methoxy-β-nitrostyrene **12c** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 65% (25 mg, 0.065 mmol), pale brown solid. $\mathbf{m_p}$ = 166-168 °C. $[\alpha]_D^{25}$ = +57.84 (*c* 0.75, chloroform). **FTIR** (neat, cm^{-1}) 3460, 2939, 1754, 1548, 1514, 1249. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 – 6.98 (m, 2H, ArH), 6.85 (d, *J* = 8.6 Hz, 2H, ArH), 5.12 (d, *J* = 3.2 Hz, 1H, C^9H), 5.08 (dd, *J* = 4.9, 3.2 Hz, 1H, C^8H), 4.32 – 4.22 (m, 1H, CH_2CH_3), 4.22 – 4.13 (m, 1H, CH_2CH_3), 3.78 (s, 3H, OCH_3), 3.46 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.55 (td, *J* = 12.4, 3.2 Hz, 1H, C^6H), 2.22 (bs, 1H, OH), 2.04 – 1.87 (m, 2H, CH_2), 1.83 – 1.73 (m, 1H, CH_2), 1.63 (dddd, *J* = 26.2, 17.5, 9.5, 6.1 Hz, 2H, CH_2), 1.42 – 1.35 (m, 1H, CH_2), 1.31 (dt, *J* = 12.9, 4.0 Hz, 1H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.08 (qd, *J* = 12.6, 3.4 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 159.3, 129.3, 128.2, 114.5, 98.1, 87.2, 69.3, 62.3, 55.3, 43.28, 39.2, 38.5, 26.2, 25.7, 23.1, 14.1. **HRMS** (ESI) for $C_{19}H_{25}NO_7Na$ $[M+Na]^+$: calculated 402.1521, found 402.1514. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 29.22 min, t_R (minor) = 45.97 min, *ee* = 96%.





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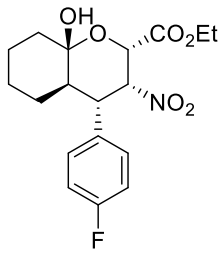
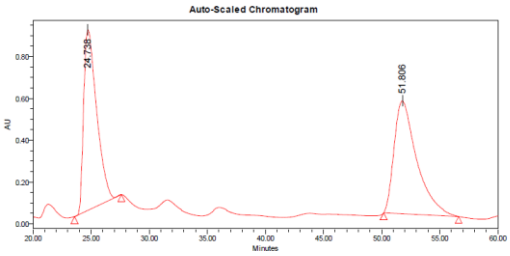
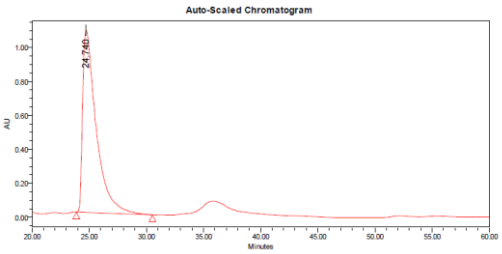
2	46.908	16266	1427149	1.95



Ethyl (2S,3R,4S,4aR,8aS)-4-(4-fluorophenyl)-8a-hydroxy-3-nitrooctahydro-2H-chromene-2-carboxylate (**79ada**). The title product was obtained from cyclohexanone **11a**, *trans*-4-fluoro-β-nitrostyrene **12d** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 62% (23 mg, 0.062 mmol), white solid. $\mathbf{m_p}$ = 179-181 °C. $[\alpha]_D^{25}$ = +57.03 (*c* 0.42, chloroform). **FTIR** (neat, cm^{-1}) 3483, 2937, 1747, 1548, 1225. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 2H, ArH), 7.02 (t, *J* = 8.6 Hz, 2H, ArH), 5.13 (d, *J* = 3.1 Hz, 1H, C^9H), 5.08 (dd, *J* = 4.8, 3.2 Hz, 1H, C^8H), 4.27 (dq, *J* = 10.7, 7.1 Hz, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.51 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.55 (tdd, *J* = 12.5, 3.3, 1.5 Hz, 1H, C^6H), 2.12 (s, 1H, OH), 1.97 (dddd, *J* = 17.8, 14.3, 9.4, 3.3 Hz, 2H, CH_2), 1.77 (ddt, *J* = 11.1, 4.5, 2.2 Hz, 1H, CH_2), 1.72 – 1.65 (m, 1H, CH_2), 1.59 (d, *J* = 6.7 Hz, 1H, CH_2), 1.33 (ddd, *J* = 15.4, 13.1, 4.1 Hz, 2H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.09 (qd, *J* = 14.1, 13.3, 4.2 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.6, 162.5 (d, $^1J_{C\text{-}F}$ = 246.9 Hz), 131.9 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.9, 116.1 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 98.1, 86.9, 69.3, 62.4, 43.4, 39.2, 38.5, 26.2, 25.6, 23.1, 14.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.91. **HRMS** (ESI) for $C_{18}H_{22}FNO_6K$ $[M+K]^+$: calculated 406.1062, found 406.1058. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 24.74 min, t_R (minor) = 51.81 min, *ee* = 99%.





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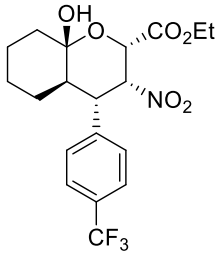
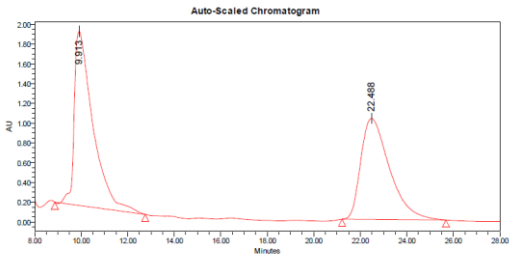
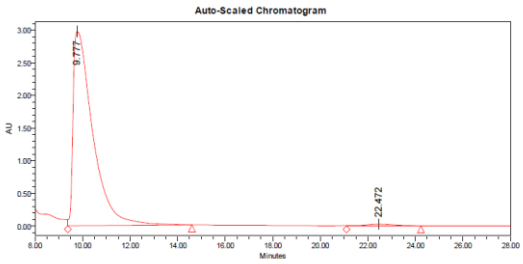


Ethyl (2S,3R,4S,4aR,8aS)-8a-hydroxy-3-nitro-4-(4-(trifluoromethyl)phenyl)octahydro-2H-chromene-2-carboxylate (**79aea**). The title product was obtained from cyclohexanone **11a**, *trans*-4-trifluoromethyl-β-nitrostyrene **12e** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 60% (25 mg, 0,060 mmol), white solid. $\mathbf{m_p}$ = 167-169 °C. $[\alpha]_D^{25}$ = +27.00 (*c* 0.80, chloroform). **FTIR** (neat, cm^{-1}) 3474, 2938, 1751, 1551, 1325. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H, ArH), 7.31 – 7.21 (m, 2H, ArH), 5.15 (d, *J* = 3.1 Hz, 1H, C^9H), 5.11 (dd, *J* = 4.8, 3.2 Hz, 1H, C^8H), 4.28 (dq, *J* = 10.8, 7.2 Hz, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.60 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.61 (td, *J* = 12.4, 3.1 Hz, 1H, C^6H), 2.18 (s, 1H, OH), 2.06 – 1.90 (m, 2H, CH_2), 1.83 – 1.73 (m, 1H, CH_2), 1.66 (ddt, *J* = 31.0, 13.1, 4.2 Hz, 2H, CH_2), 1.32 (dt, *J* = 14.2, 3.0 Hz, 2H, CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.11 (qd, *J* = 13.3, 2.8 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5, 140.4, 130.5 (d, $^2J_{C-F}$ = 32.7 Hz), 128.8, 126.1 (q, $^3J_{C-F}$ = 3.7 Hz), 124.04 (d, $^1J_{C-F}$ = 272.2 Hz), 97.98, 86.50, 69.27, 62.46, 43.92, 38.99, 38.44, 26.17, 25.54, 23.04, 14.06. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.69. **HRMS** (ESI) for $C_{19}H_{22}F_3NO_6Na$ $[M+Na]^+$: calculated 440.1297, found 440.1287. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 9.91 min, t_R (minor) = 22.49 min, *ee* = 98%.





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2	22.488	1023519	87536948	47.12

	RT	Height	Area	% Area
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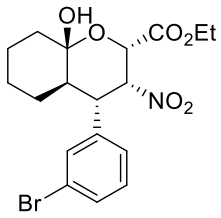
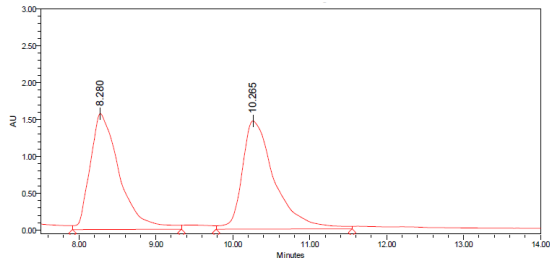
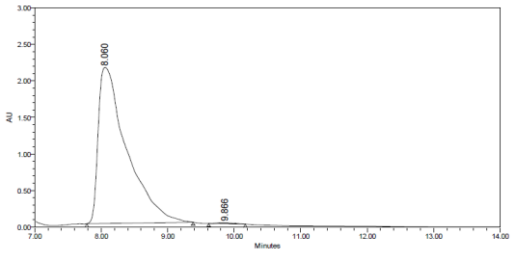
2	22.472	23819	1910951	1.11



Ethyl (2S,3R,4S,4aR,8aS)-4-(3-bromophenyl)8a-hydroxy-3-nitrooctahydro-2H-chromene-2-carboxylate (**79afa**). The title product was obtained from cyclohexanone **11a**, *trans*-3-bromo-β-nitrostyrene **12f** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 54% (23 mg, 0.054 mmol), yellow oil. $[\alpha]_D^{25}$ = +41.57 (*c* 0.75, chloroform). **FTIR** (neat, cm^{-1}) 3469, 2938, 1750, 1549, 1339. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 8.2, 1.2 Hz, 1H, ArH), 7.31 (d, *J* = 1.9 Hz, 1H, ArH), 7.20 (t, *J* = 7.9 Hz, 1H, ArH), 7.04 (d, *J* = 7.8 Hz, 1H, ArH), 5.12 (d, *J* = 3.1 Hz, 1H, C^9H), 5.09 (dd, *J* = 4.7, 3.2 Hz, 1H, C^8H), 4.28 (dq, *J* = 11.0, 7.1 Hz, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.49 (dd, *J* = 12.4, 4.7 Hz, 1H, C^7H), 2.55 (td, *J* = 12.4, 3.1 Hz, 1H, C^6H), 2.05 – 1.86 (m, 2H, CH_2), 1.78 – 1.67 (m, 4H, CH_2, OH), 1.41 – 1.27 (m, 2H, CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.12 (td, *J* = 12.5, 3.4 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5, 138.6, 131.4, 130.7, 123.1, 98.0, 86.6, 69.3, 62.4, 43.8, 38.9, 38.5, 26.2, 25.6, 23.1, 14.1. **HRMS** (ESI) for $C_{18}H_{22}BrNO_6Na$ $[M+Na]^+$: calculated 452.0505, found 452.0494. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 8.28 min, t_R (minor) = 10.27 min, *ee* = 99%.





	RT	Height	Area	% Area
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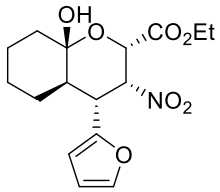
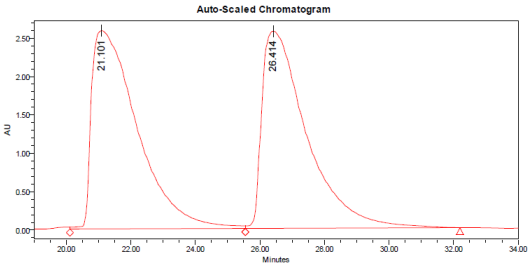
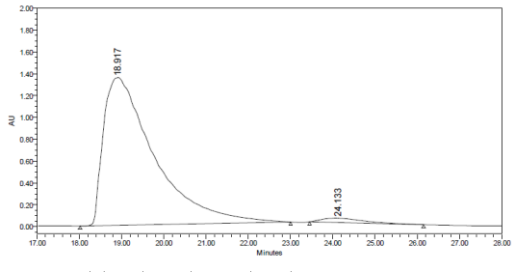
2	10.265	1464174	42949216	50.68

	RT	Height	Area	% Area
1	8.063	2140905	63722679	99.53
2	9.864	16484	302834	0.47



Ethyl (2S,3R,4R,4aR,8aS)-4-(furan-2-yl)-8a-hydroxy-3-nitrooctahydro-2H-chromene-2-carboxylate (**79aga**). The title product was obtained at 0 °C from cyclohexanone **11a**, *trans*-2-(2-nitrovinyl)furan **12g** and ethyl glyoxylate **56a** employing salicylic acid as additive . Purified on 1:2 EtOAc:Hexane mixture. Yield 73% (25 mg, 0.073 mmol), white solid. $\mathbf{m_p}$ = 173-175 °C. $[\alpha]_D^{25}$ = +89.49 (*c* 0.85, chloroform). **FTIR** (neat, cm^{-1}) 3480, 2938, 1754, 1552, 1209. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 1.8, 0.8 Hz, 1H, ArH), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H, ArH), 6.17 (d, *J* = 3.2 Hz, 1H, ArH), 5.19 (dd, *J* = 4.8, 3.1 Hz, 1H, C^8H), 5.05 (d, *J* = 3.1 Hz, 1H, C^9H), 4.31 – 4.23 (m, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.7, 7.1 Hz, 1H, CH_2CH_3), 3.66 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.48 (td, *J* = 12.4, 3.4 Hz, 1H, C^6H), 2.24 (s, 1H, OH), 1.92 (t, *J* = 4.1 Hz, 2H, CH_2), 1.74 (dddd, *J* = 23.5, 12.9, 5.3, 2.9 Hz, 2H, CH_2), 1.66 – 1.53 (m, 1H, CH_2), 1.44 – 1.37 (m, 1H, CH_2), 1.35 – 1.27 (m, 1H, CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.22 – 1.11 (m, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.6, 150.3, 142.6, 110.5, 108.5, 97.8, 84.8, 68.9, 62.3, 39.2, 38.3, 26.3, 25.5, 23.0, 14.1. **HRMS** (ESI) for $C_{16}H_{20}NO_6$ $[M+H-H_2O]^+$: calculated 322.1287, found 322.1282. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 21.10 min, t_R (minor) = 26.41 min, *ee* = 95%.





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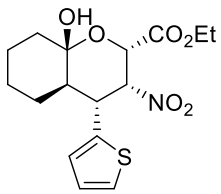
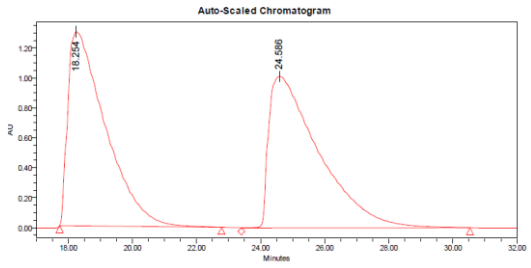
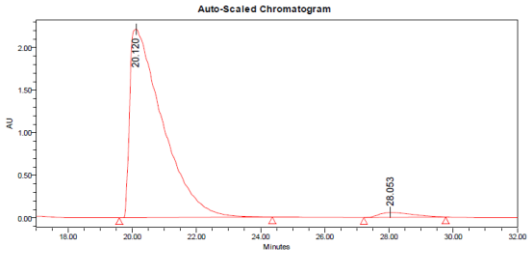
2	26.414	2566784	247343884	49.23

	RT	Height	Area	% Area
1	18.917	1353275	113436994	97.63
2	24.133	39861	2751261	2.37



Ethyl (2S,3R,4R,4aR,8aS)-8a-hydroxy-3-nitro-4-(thiophen-2-yl)octahydro-2H-chromene-2-carboxylate (**79aha**). The title product was obtained at 0 °C from cyclohexanone **11a**, *trans*-2-(2-nitrovinyl)thiophene **12h** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 46% (16 mg, 0.046 mmol), white solid. $\mathbf{m_p}$ = 144-146 °C. $[\alpha]_D^{25}$ = +57.84 (*c* 0.75, chloroform). **FTIR** (neat, cm^{-1}) 3484, 2939, 1749, 1550, 856. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.1, 1.1 Hz, 1H, ArH), 6.96 (dd, *J* = 5.2, 3.5 Hz, 1H, ArH), 6.84 (d, *J* = 3.5 Hz, 1H, ArH), 5.15 (m, 2H, C^9H, C^8H), 4.32 – 4.24 (m, 1H, CH_2CH_3), 4.19 (dt, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.78 (dd, *J* = 12.3, 4.5 Hz, 1H, C^7H), 2.60 (td, *J* = 12.3, 3.4 Hz, 1H, C^6H), 2.15 (s, 1H, OH), 2.04 – 1.94 (m, 1H, CH_2), 1.90 (dt, *J* = 14.0, 3.0 Hz, 1H, CH_2), 1.81 – 1.59 (m, 3H, CH_2), 1.55 – 1.45 (m, 1H, CH_2), 1.32 (dt, *J* = 13.0, 3.9 Hz, 1H, CH_2), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.15 (td, *J* = 12.8, 3.5 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 138.6, 127.5, 126.0, 125.0, 98.1, 87.0, 69.3, 62.4, 40.9, 39.61, 38.4, 26.3, 25.6, 23.1, 14.1. **HRMS** (ESI) for $C_{16}H_{21}NO_6SNa$ $[M+Na]^+$: calculated 378.0979, found 378.0978. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 97:3, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 18.25 min, t_R (minor) = 25.59 min, *ee* = 95%.





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1	18.254	1296216	105677092	49.08
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	RT	Height	Area	% Area
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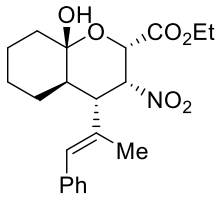
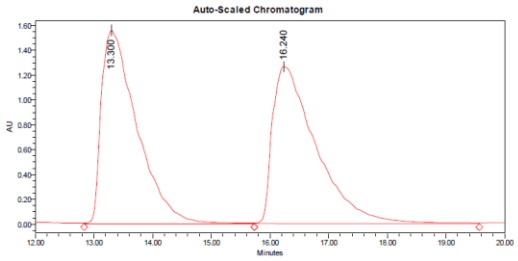
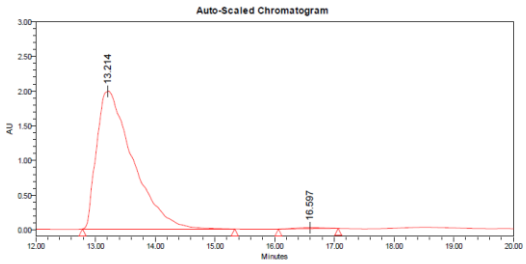


Ethyl (2S,3R,4S,4aR,8aS)-8a-hydroxy-3-nitro-4-((E)-1-phenylprop-1-en-2-yl)octahydro-2H-chromene-2-carboxylate (**79aia**). The title product was obtained at 0 °C from cyclohexanone **11a**, ((1*E*,3*E*)-2-methyl-4-nitrobuta-1,3-dien-1-yl)benzene **12i** and ethyl glyoxylate **56a** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 55% (21 mg, 0.055 mmol), white solid. $\mathbf{m_p}$ = 157-159 °C. $[\alpha]_D^{25}$ = +54.56 (*c* 0.60, chloroform). **FTIR** (neat, cm^{-1}) 3467, 2938, 1740, 1552, 1372. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.7, 6.7 Hz, 2H, ArH), 7.26 (dd, *J* = 7.9, 6.3 Hz, 3H, ArH), 6.35 (s, 1H, C*H*=C), 5.22 (dd, *J* = 4.9, 3.2 Hz, 1H, C^8H), 5.08 (d, *J* = 3.2 Hz, 1H, C^9H), 4.40 – 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H, C$H_2$$CH_3$), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H, C$H_2$$CH_3$), 3.02 (dd, *J* = 12.3, 4.9 Hz, 1H, C^7H), 2.37 (td, *J* = 12.2, 2.9 Hz, 1H, C^6H), 2.18 (s, 1H, OH), 2.06 – 1.92 (m, 2H, CH_2), 1.88 (d, *J* = 1.3 Hz, 3H, CH_3C=CH), 1.85 – 1.76 (m, 3H, CH_2), 1.73 – 1.60 (m, 1H, CH_2), 1.38 (dq, *J* = 12.8, 5.3, 4.5 Hz, 1H, CH_2), 1.30 (d, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.24 (dd, *J* = 13.0, 9.7 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.8, 137.3, 132.8, 129.6, 129.1, 128.2, 126.9, 97.9, 84.8, 69.2, 62.4, 46.6, 38.6, 38.4, 26.1, 25.7, 23.1, 14.1. **HRMS** (ESI) for $C_{21}H_{28}NO_6$ $[M+H]^+$: calculated 390.1922, found 390.1924. **HPLC** (Chiralcel IB, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 13.30 min, t_R (minor) = 16.24 min, *ee* = 99%.





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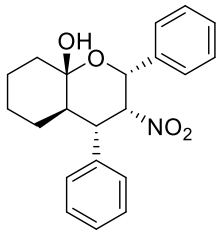
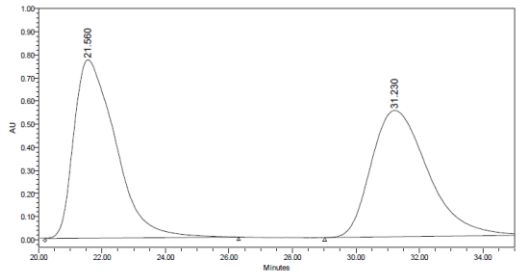
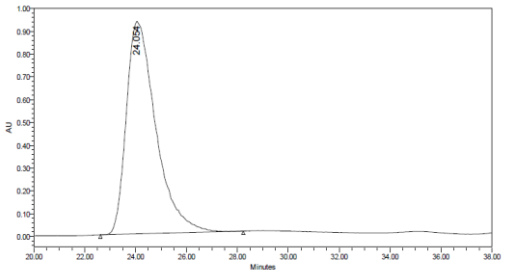
1	13.300	1555120	65385927	49.88
2	16.240	1264166	65691329	50.12

	RT	Height	Area	% Area
1	13.214	1984612	83765571	99.40
2	16.597	15026	503719	0.60



(2R,3R,4S,4aR,8aS)-3-nitro-2,4-diphenyloctahydro-8aH-chromen-8a-ol (**79aab**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and benzaldehyde **56b** employing salicylic acid as additive and 1 equivalent of triethylamine. Purified on 1:3 EtOAc:Hexane mixture. Global yield 65%. Isolated yield 30% (11 mg, 0.030 mmol), white solid. $\mathbf{m_p}$ = 195-197 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +26.45 (*c* 0.40, chloroform). **FTIR** (neat, cm^{-1}) 3511, 2922, 1548, 1335. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H, ArH), 7.35 – 7.28 (m, 4H, ArH), 7.27 – 7.24 (m, 2H, ArH), 7.17 (dd, *J* = 7.0, 1.7 Hz, 2H, ArH), 5.66 (d, *J* = 3.1 Hz, 1H, C^9H), 4.95 (dd, *J* = 4.6, 3.2 Hz, 1H, C^8H), 3.59 (dd, *J* = 12.5, 4.5 Hz, 1H, C^7H), 2.97 (ddt, *J* = 14.7, 11.4, 1.6 Hz, 1H, C^6H), 2.07 (td, *J* = 13.7, 4.5 Hz, 1H, CH_2), 1.92 (bs, 1H, OH), 1.87 (ddt, *J* = 13.7, 4.0, 2.1 Hz, 1H, CH_2), 1.84 – 1.76 (m, 1H, CH_2), 1.76 – 1.64 (m, 1H, CH_2), 1.48 – 1.35 (m, 2H, CH_2), 1.26 (m, 1H, CH_2), 1.19 (td, *J* = 12.6, 3.1 Hz, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.9, 136.7, 129.2, 128.7, 128.5, 127.9, 126.0, 97.9, 91.9, 71.1, 44.4, 38.9, 38.7, 26.1, 25.9, 23.2. **HRMS** (ESI) for $C_{21}H_{22}NO_3$ $[M+H-H_2O]^+$: calculated 336.1592, found 336.1589. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 21.56 min, t_R (minor) = 31.23 min, *ee* = >99%.





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	RT	Height	Area	% Area
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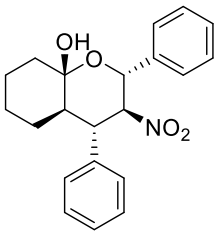
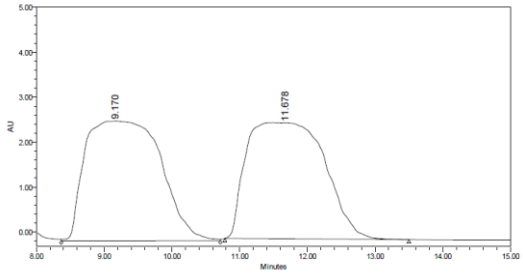
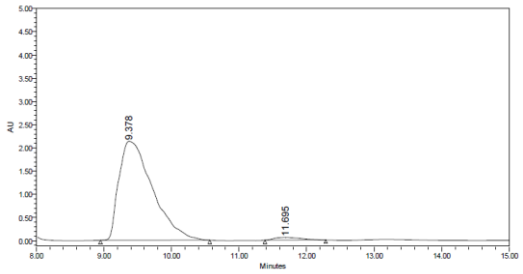


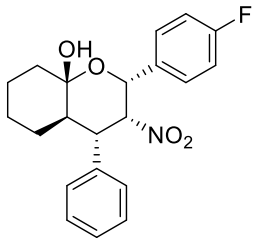
(2R,3S,4S,4aR,8aS)-3-nitro-2,4-diphenyloctahydro-8aH-chromen-8a-ol (**79aab'**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and benzaldehyde **56b** employing salicylic acid as additive and 1 equivalent of triethylamine. Purified on 1:3 EtOAc:Hexane mixture. Global yield 65%. Isolated yield 35% (12 mg, 0.035 mmol), white solid. $\mathbf{m_p}$ = 223-225 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +31.48 (*c* 0.25, chloroform). **FTIR** (neat, cm^{-1}) 3552, 2928, 1544, 1123. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 10H), 5.55 (d, *J* = 10.0 Hz, 1H, C^9H), 4.77 (t, *J* = 10.6 Hz, 1H, C^8H), 3.72 (t, *J* = 11.6 Hz, 1H, C^7H), 2.17 (s, 1H, OH)2.05 (s, 1H, CH_2), 1.88 (d, *J* = 11.8 Hz, 1H, C^6H), 1.84 – 1.74 (m, 2H, CH_2), 1.69 (d, *J* = 15.3 Hz, 2H, CH_2), 1.38 – 1.22 (m, 1H, CH_2), 1.19 (d, *J* = 5.4 Hz, 2H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.9, 136.7, 129.2, 128.7, 128.5, 127.9, 126.0, 97.9, 91.9, 71.1, 44.4, 38.9, 38.7, 26.1, 25.9, 23.2. **HRMS** (ESI) for $C_{21}H_{22}NO_3$ $[M+H-H_2O]^+$: calculated 336.1592, found 336.1591. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 9.17 min, t_R (minor) = 11.68 min, *ee* = 96%.



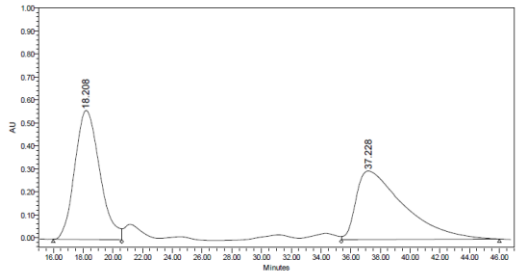


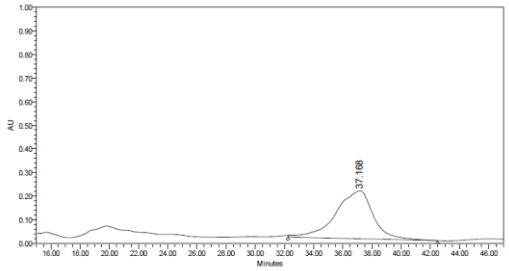
	RT	Height	Area	% Area
1	9.170	2662130	207821990	49.94
2	11.678	2582615	208361441	50.06

	RT	Height	Area	% Area
1	9.378	2131827	73579930	97.92
2	11.695	56958	1565685	2.08



(2R,3R,4S,4aR,8aS)-2-(4-fluorophenyl)-3-nitro-4-phenyloctahydro-8aH-chromen-8a-ol (**79aac**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and 4-fluorobenzaldehyde **56c** employing salicylic acid as additive and 1 equivalent of triethylamine. Purified on 1:3 EtOAc:Hexane mixture. Global yield 81%. Isolated yield 54% (20 mg, 0.054 mmol), white solid. $\mathbf{m_p}$ = 198-200 °C. $[\alpha]_D^{25}$ = +12.05 (*c* 0.60, chloroform). **FTIR** (neat, cm^{-1}) 3510, 2950, 1551, 1118. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H, ArH), 7.21 – 7.11 (m, 2H, ArH), 7.01 (t, *J* = 8.7 Hz, 2H, ArH), 5.64 (d, *J* = 3.2 Hz, 1H, C^9H), 4.91 (t, *J* = 3.9 Hz, 1H, C^8H), 3.57 (dd, *J* = 12.5, 4.5 Hz, 1H, C^7H), 3.04 – 2.89 (m, 1H, C^6H), 2.05 (td, *J* = 13.6, 4.4 Hz, 1H, CH_2), 1.89 (d, *J* = 1.5 Hz, 1H, CH_2), 1.88 – 1.77 (m, 1H, CH_2), 1.77 – 1.60 (m, 2H, CH_2), 1.41 (td, *J* = 13.4, 12.5, 3.8 Hz, 2H, CH_2), 1.28 – 1.10 (m, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C\text{-}F}$ = 246.8 Hz), 136.7, 132.5 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.2, 128.0, 127.8 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 97.9, 92.0, 70.5, 44.4, 38.9, 38.6, 26.1, 25.8, 23.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.56. **HMRS** (ESI) for $C_{21}H_{21}FNO_3$ $[M+H-H_2O]^+$: calculated 354.1499, found 354.1495. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 18.21 min, t_R (major) = 37.22 min, *ee* = >99%.





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2	37.228	298237	66684317	50.48

	RT	Height	Area	% Area
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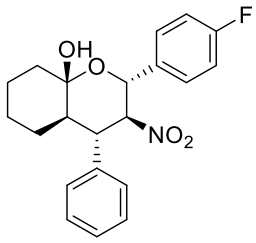
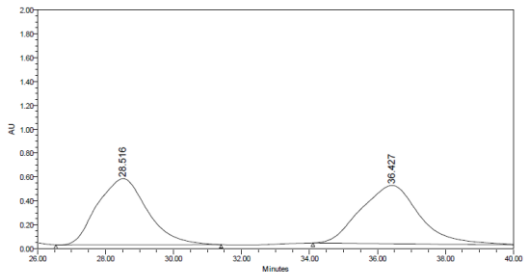
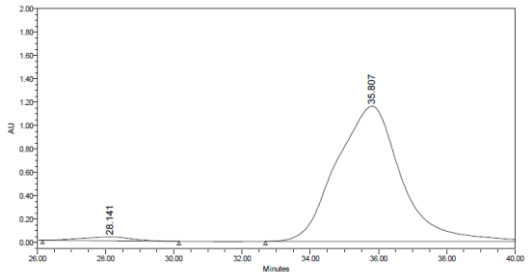
2	37.168	203128	36380394	100.0



(2R,3S,4S,4aR,8aS)-2-(4-fluorophenyl)-3-nitro-4-phenyloctahydro-8aH-chromen-8a-ol (**79aac'**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and 4-fluorobenzaldehyde **56c** employing salicylic acid as additive and 1 equivalent of triethylamine. Purified on 1:3 EtOAc:Hexane mixture. Global yield 81%. Isolate yield 27% (10 mg, 0.027 mmol), white solid. $\mathbf{m_p}$ = 206-209 °C. $[\alpha]_D^{25}$ = +61.88 (*c* 0.60, chloroform). **FTIR** (neat, cm^{-1}) 3484, 2936, 1547, 1115. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.5, 5.3 Hz, 2H, ArH), 7.31 – 7.16 (m, 5H, ArH), 7.04 (t, *J* = 8.6 Hz, 2H, ArH), 5.54 (d, *J* = 9.9 Hz, 1H, C^9H), 4.72 (t, *J* = 10.6 Hz, 1H, C^8H), 3.71 (t, *J* = 11.6 Hz, 1H, C^7H), 2.10 (s, 1H, OH), 1.88 (td, *J* = 11.8, 3.3 Hz, 1H, C^6H), 1.77 – 1.55 (m, 4H, CH_2), 1.29 – 1.11 (m, 4H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{C\text{-}F}$ = 247.9 Hz), 136.8, 132.7 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.1 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 128.1, 115.9 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 97.5, 95.1, 73.2, 47.1, 46.9, 38.8, 26.2, 25.7, 23.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.35. **HRMS** (ESI) for $C_{21}H_{23}FNO_4$ [M+H]+: calculated 372.1721, found 372.1720. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 28.52 min, t_R (major) = 36.43 min, *ee* = 95%.





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2	36.427	1062962	226837738	50.08

	RT	Height	Area	% Area
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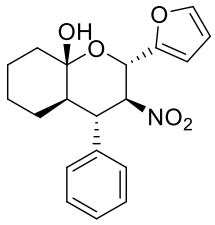
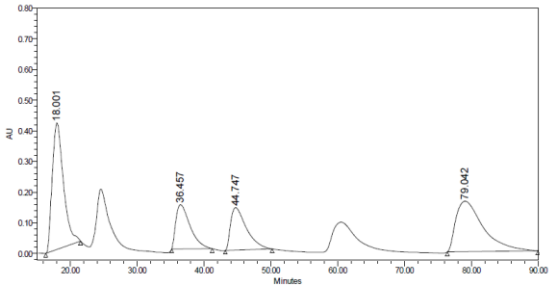
2	35.807	1155871	152946036	97.90

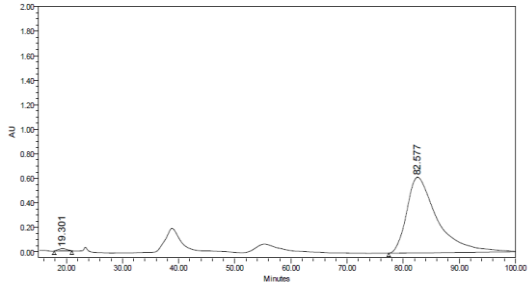


(2S,3S,4S,4aR,8aS)-2-(furan-2-yl)-3-nitro-4-phenyloctahydro-8aH-chromen-8a-ol (**79aad'**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and furfural **56d** employing salicylic acid as additive. When 1 equivalent of Et_3N was used an inseparable 50:50 mixture of **79aad:79aad'** isomers was obtained. Global yield 65% (22 mg, 0.65 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (s, 2H, ArH), 7.52 – 7.00 (m, 10H, ArH), 6.61 (s, 1H, ArH), 6.41 (d, *J* = 3.3 Hz, 1H, ArH), 6.35 (d, *J* = 3.3 Hz, 1H, ArH), 6.32 (t, *J* = 2.5 Hz, 1H, ArH), 5.71 (d, *J* = 3.0 Hz, 1H, **79aad**), 5.65 (d, *J* = 10.3 Hz, 1H, **79aad**'), 5.11 (t, *J* = 10.8 Hz, 1H, **79aad**'), 4.98 (t, *J* = 3.8 Hz, 1H, **79aad**), 3.66 (t, *J* = 11.7 Hz, 1H, **79aad**'), 3.52 (dd, *J* = 12.5, 4.4 Hz, 1H, **79aad**), 2.98 – 2.87 (m, 1H, **79aad**), 2.08 – 1.96 (m, 1H, **79aad**'), 1.93 – 1.81 (m, 2H, **79aad** and **79aad**'), 1.77 (m, 2H, **79aad** and **79aad**'), 1.66 (m, 4H, **79aad** and **79aad**'), 1.39 (m, 2H, **79aad** and **79aad**'), 1.15 (m, 8H, **79aad** and **79aad**'). With 1 eq. of DBU complete conversion to **79aad'** was observed. Purified on 1:2 EtOAc:Hexane mixture. Yield 68% (23 mg, 0.068 mmol), white solid. $\mathbf{m_p}$ = 252-254 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +5.66 (*c* 0.60, chloroform). **FTIR** (neat, cm^{-1}) 3539, 2935, 1546, 1124. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.7 Hz, 1H, ArH), 7.26 (s, 5H, ArH), 6.41 (d, *J* = 3.3 Hz, 1H, ArH), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H, ArH), 5.65 (d, *J* = 10.2 Hz, 1H, C^9H), 5.11 (dd, *J* = 11.4, 10.2 Hz, 1H, C^8H), 3.66 (t, *J* = 11.6 Hz, 1H, C^7H), 2.15 (s, 1H, OH), 1.89 (tdd, *J* = 12.0, 3.7, 1.4 Hz, 1H, C^6H), 1.83 – 1.75 (m, 2H, CH_2), 1.75 – 1.67 (m, 1H, CH_2), 1.67 – 1.60 (m, 1H, CH_2), 1.32 – 1.11 (m, 4H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.2, 143.9, 136.9, 128.1, 110.5, 110.4, 97.6, 91.3, 67.1, 46.8, 46.7, 38.6, 26.2, 25.6, 23.0. **HPLC** (Chiralcel IA,

Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (**79aad'** minor) = 18.00 min, t_R (**79aad** major) = 36.46 min, t_R (**79aad** minor) = 44.74 min, t_R (**79aad'** major) = 79.02 min. *ee* **79aad** = 98%. *ee* **79aad'** = 98%.

79aad





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2	36.456	224401	36263819	15.58
3	44.743	202476	35966472	15.45
4	79.042	267732	78351878	33.66

	RT	Height	Area	% Area
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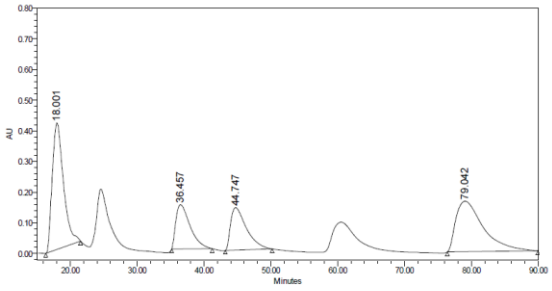
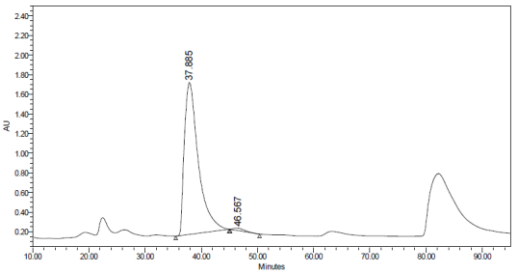
3				
4	82.577	617310	232611786	99.14

79aad'





	RT	Height	Area	% Area
1	18.000	692107	82178228	35.51
2	36.456	224401	36263819	15.58
3	44.743	202476	35966472	15.45
4	79.042	267732	78351878	33.66

	RT	Height	Area	% Area
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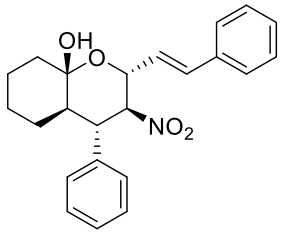
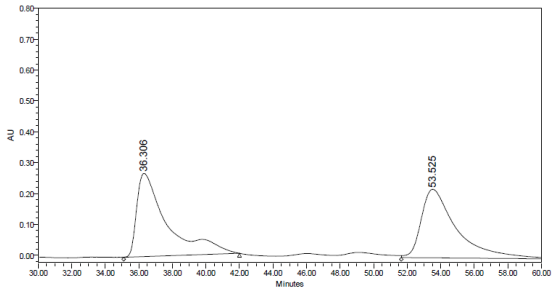
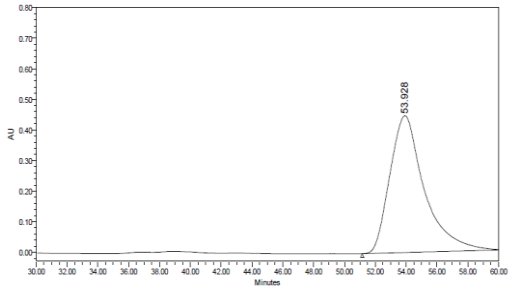
2	37.885	1548286	267427094	99.19
3	46.633	19736	2173050	0.81
4				



(2R,3R,4S,4aR,8aS)-3-nitro-4-phenyl-2-((E)-styryl)octahydro-8aH-chromen-8a-ol (**79aae**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and cinnamaldehyde **56e** employing salicylic acid as additive. Purified on 1:4 EtOAc:Hexane mixture. Global yield 58% (22 mg, 0.058 mmol), white solid. $\mathbf{m_p}$ = 198-200 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +58.20 (*c* 0.10, chloroform). **FTIR** (neat, cm^{-1}) 3499, 2922, 1713, 1546. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.74 (d, *J* = 3.2 Hz, 1H, CH=C*H*Ph), 7.33 – 7.22 (m, 8H, ArH), 7.22 – 7.14 (m, 2H, ArH), 4.93 (t, *J* = 4.5 Hz, 1H, C^8H), 4.10 (dd, *J* = 12.6, 4.5 Hz, 1H, C^9H), 3.98 (dd, *J* = 12.7, 3.3 Hz, 1H, C*H*=CHPh), 3.46 (dd, *J* = 12.2, 4.5 Hz, 1H, C^7H), 2.65 (td, *J* = 12.2, 3.3 Hz, 1H, C^6H), 2.39 (s, 1H, OH), 1.89 (d, *J* = 13.6 Hz, 1H, CH_2), 1.76 (td, *J* = 13.5, 4.3 Hz, 1H, CH_2), 1.68 (d, *J* = 13.0 Hz, 2H, CH_2), 1.39 – 1.23 (m, 3H, CH_2), 1.21 – 1.10 (m, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.9, 137.5, 136.0, 129.4, 129.2, 128.5, 128.2, 127.9, 94.9, 73.1, 54.9, 46.8, 42.9, 40.3, 37.5, 25.6, 25.1, 21.2. **HRMS** (ESI) for $C_{23}H_{26}NO_4$ $[M+H]^+$: calculated 380.1840, found 380.1827. **HPLC** (Chiralcel IA, Hexane:^{i}PrOH = 95:5, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 36.31 min, t_R (major) = 53.53 min, *ee* = >99%.





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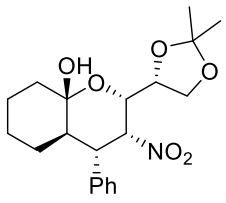
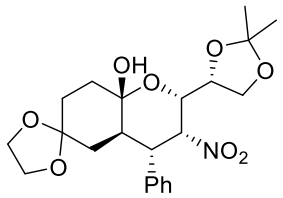
2	53.928	447019	159851852	100.0



(2S,3R,4S,4aR,8aS)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-nitro-4-phenyloctahydro-8aH-chromen-8a-ol (**79aaf**). The title product was obtained from cyclohexanone **11a**, *trans*-β-nitrostyrene **12a** and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **56f** employing salicylic acid as additive. Purified on 1:3 EtOAc:Hexane mixture. Yield 64% (24 mg,

0.064 mmol), colorless oil. $[\alpha]_D^{25}$ = +34.32 (*c* 0.53, chloroform). **FTIR** (neat, cm^{-1}) 3434, 2986, 1545. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 13.3, 7.0 Hz, 3H, ArH), 7.17 – 7.09 (m, 2H, ArH), 4.94 (dd, *J* = 4.7, 2.8 Hz, 1H, C^8H), 4.29 (dd, *J* = 8.9, 2.8 Hz, 1H, C^9H), 4.13 – 4.05 (m, 1H, CHO), 4.00 – 3.92 (m, 2H, CH_2O), 3.40 (dd, *J* = 12.4, 4.8 Hz, 1H, C^7H), 2.73 (d, *J* = 3.2 Hz, 1H, C^6H), 2.27 (s, 1H, OH), 1.89 – 1.78 (m, 1H, CH_2), 1.78 – 1.52 (m, 4H, CH_2), 1.44 (s, 3H, CH_3), 1.37 (dd, *J* = 12.1, 6.5 Hz, 2H, CH_2), 1.29 (s, 3H, CH_3), 1.22 – 0.97 (m, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.8, 129.1, 127.9, 110.2, 97.5, 87.5, 74.2, 70.6, 67.5, 43.9, 39.1, 38.8, 27.1, 26.2, 25.8, 25.1, 23.2. **HRMS** (ESI) for $C_{20}H_{26}NO_5$ $[M+H-H_2O]^+$: calculated 360.1801, found 360.1802.



(2S,3R,4S,4aR,8aS)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-nitro-4-phenylhexahydro-2H,8aH-spiro[chromene-6,2'-[1,3]dioxolan]-8a-ol (**79jaf**). The title product was obtained from 1,4-cyclohexanedione monoethylene acetal **11j**, *trans*-β-nitrostyrene **12a** and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **56f** employing salicylic acid as additive. Purified on 1:2 EtOAc:Hexane mixture. Yield 52 % (23 mg, 0.052 mmol), colorless oil. $[\alpha]_D^{25}$ = +22.62 (*c* 0.33, chloroform). **FTIR** (neat, cm^{-1}) 3393, 2960, 1546. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H, ArH), 7.30 – 7.26 (m, 1H, ArH), 7.15 (dd, *J* = 7.1, 1.7 Hz, 2H, ArH), 4.93 (dd, *J* = 4.7, 2.8 Hz, 1H, C^8H), 4.29 (dd, *J* = 8.8, 2.8 Hz, 1H, C^9H), 4.09 (td, *J* = 7.3, 2.6 Hz, 1H, CHO), 3.99 – 3.97 (m, 1H, CH_2O), 3.96 – 3.94 (m, 1H, CH_2O), 3.91 – 3.83 (m, 2H, CH_2O), 3.83 – 3.77 (m, 1H, CH_2O), 3.42 (dd, *J* = 12.7, 4.6 Hz, 1H, C^7H), 3.16 – 3.08 (m, 1H, CH_2O), 2.18 (td, *J* = 13.7, 4.4 Hz, 1H, C^6H), 2.13 – 2.10 (bs, 1H, OH), 1.94 (td, *J* = 13.4, 4.5 Hz, 1H, CH_2), 1.82 – 1.71 (m, 2H, CH_2), 1.45 (d, *J* = 8.7 Hz, 2H, CH_2), 1.43 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.25 (s, 1H, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.3, 129.2, 128.1, 110.3, 108.5, 96.7, 86.1, 74.2, 70.9, 67.5, 64.6, 64.4, 43.5, 36.1, 35.6, 34.7, 32.2, 27.1, 25.1. **HRMS** (ESI) for $C_{22}H_{28}NO_7$ $[M+H-H_2O]^+$: calculated 418.1859, found 418.1857.

Computational details

All stationary points on the potential surface were fully optimised with the hybrid density functional B3LYP[84] and the 6-31G(d)[86] basis set. Harmonic analyses were performed at this level of theory to verify the nature of the corresponding stationary points (minima or transition states), as well as to provide the thermodynamic contributions to the enthalpy and free energy for T = 298 K. Moreover, intrinsic reaction coordinate[101] calculations

[101] a) Ishida, K.; Morokuma, K.; Kormornicki, A. *J. Chem. Phys*. **1977**, *66*, 2153-2156. b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys*. **1989**, *90*, 2154-2161. c) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990,** *94*, 5523-5527.

were performed to ensure that the transition states connect the reactants and products belonging to the reaction coordinate under study. Solvent effects were considered by means of PCM method.[87] The solvent introduced in the calculations was dichloromethane. For the computational study of the general Michael addition between cyclopentanone **11b** and nitroalkene **12a** catalysed by organocatalyts O_2N-X_L-X_L^{Me}-OMe-**35**, the two layer integrated molecular orbital and molecular procedure (ONIOM[102]) has been used. The quantum mechanis (QM) region was treated using the Hartree-Fock method with 6-31G(d) basis set, whereas the semiempirical PM6[103] methodology was used for the low layer. Hydrogen link atoms were applied to treat the boundaries.

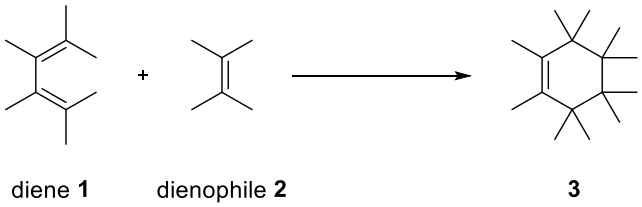
[102] a) Maseras, F.; Morokuma, K. *J. Comput. Chem.* **1995**, *16*, 1170–1179; b) Dapprich, S.; Komarómi, I.; Byun, K. S.; Morokuma, M.; Frisch, M. *J. Mol. Struct. (Theochem)* **1999**, *462*, 1-21; c) Vreven, T.; Morokuma, K.; Farkas, Ö.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **2003**, *24*, 760-769; d) Chung, L. W.; Sameera, W. M. C.; Ramozzi, R.; Page, A. J.; Hatanaka, M.; Petrova, G. P.; Harris, T. V.; Li, X.; Ke, Z.; Liu, F.; Li; H.; Ding, L; Morokuma, K. *Chem. Rev.* **2015**, *115*, 5678-5696.
[103] Stewart, J. J. P. *J. Comput. Chem*. **1989**, *10*, 209-220.

Chapter 3

Organocatalytic Diels-Alder Reactions Between α,β-Unsaturated Ketones and Nitroalkenes Promoted by Densely Substituted γ-Dipeptides

3.1 THE DIELS-ALDER REACTION. GENERAL CONSIDERATIONS

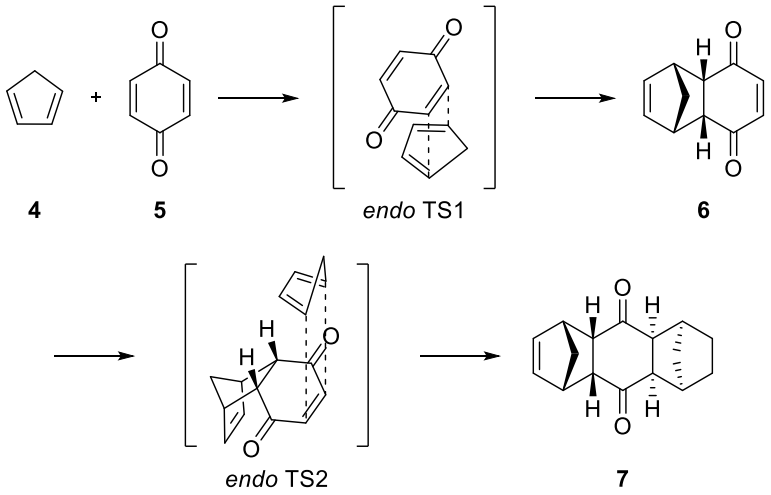
The Diels-Alder cycloaddition is one of the most commonly used synthetic transformations for the construction of six-membered rings in a regio- and stereocontrolled manner.[1] This process allows the possible simultaneous generation of up to four stereogenic centres in one synthetic step. In addition, the possibility of obtaining carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds makes it a rather versatile approach for the design of simple and complex natural compounds.[2] In the classic Diels-Alder cycloaddition, the reaction takes place between a conjugated diene (the 4π component) and a dienophile (the 2π component) to generate a cyclohexene ring (**Scheme 3.1**). As a consequence of this transformation, two new single bonds are formed at the expense of two double bonds, a σ/π-bond balance that provides a significant driving force for the (4+2) cyclisation process.



Scheme 3.1. The general Diels-Alder reaction between a diene and a dienophile to yield cyclohexene rings. The possible substituents at the different positions are not indicated.

The transformation was first discovered in 1928 when Otto Diels and his student Kurt Alder identified products **6** and **7** that arose from the reaction between cyclopentadiene **4** and quinone **5** (**Scheme 3.2**).[3] This milestone in the area of organic chemistry was awarded with the Nobel Prize in 1950 and, since then, a myriad of publications has been reported concerning synthetic, mechanistic and theoretical aspects.[4]

[1] Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction. Selected Practical Methods*, John Wiley & Sons: West Sussex, **2002**.
[2] a) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH: Weinheim, **2001**. b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed*. **2002**, *41*, 1668-1698. c) Ran, H.; Huang, G. *Curr. Org. Synth*. **2016**, *13*, 847-860.
[3] Diels, O.; Alder, J. *Justus Liebigs Ann. Chem*. **1928**, *460*, 98-122.
[4] Franzen, J. in *Kirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons: New Jersey, **2016**.



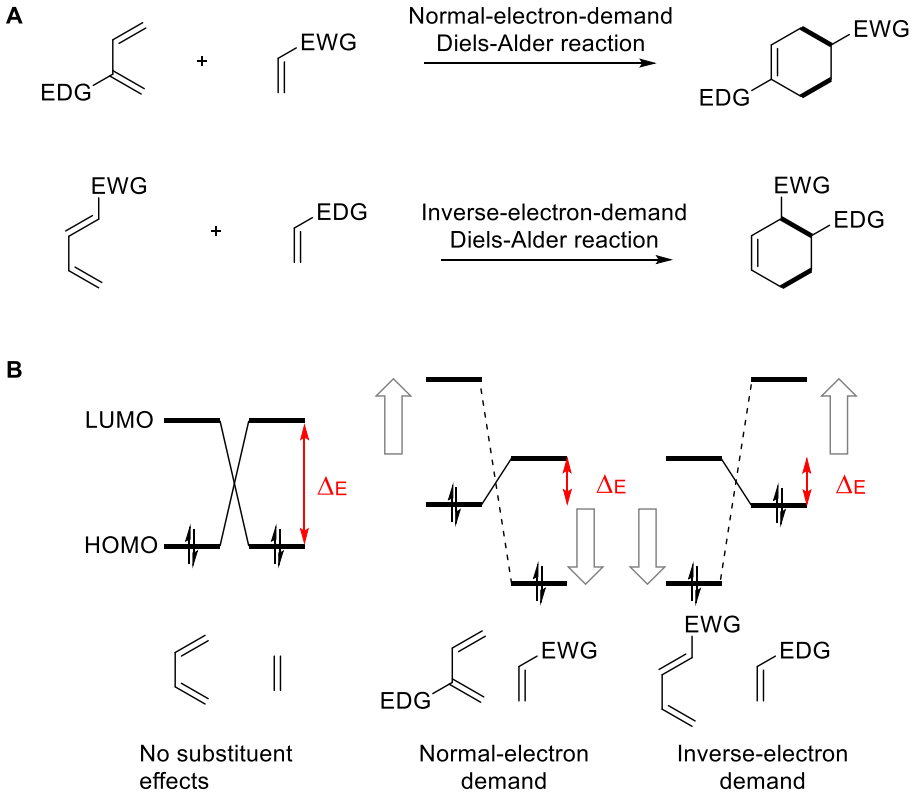
Scheme 3.2. The first Diels-Alder reaction reported in 1928.

3.1.1 Mechanistic aspects

Taking into consideration the electronic features of the reactants, the Diels-Alder reaction can be classified as a normal or inverse-electron demand process.[5] In general, in the former transformation, electron-rich dienes react with electron-deficient dienophiles, whilst in the latter, electron-deficient dienes are more reactive towards electron-rich dienophiles (**Scheme 3.3A**).[6] In a normal Diels-Alder reaction, the main molecular orbital interaction is between the HOMO of the diene and the LUMO of the dienophile. In inverse-electron-demand Diels-Alder reactions, the course of the reaction is mainly associated with the dienophile-HOMO/diene-LUMO overlap (**Scheme 3.3B**). Since the reaction rate depends on the HOMO-LUMO gap, all the factors that lower this energy separation increase the reaction rate. In this regard, several publications have been reported focusing upon the external conditions of the reactions, such as the use of

[5] Klier, L.; Tur, F.; Poulsen P. H.; Jørgensen, K. A. *Chem. Soc. Rev*. **2017**, *46*, 1080-1102.
[6] Spino, C.; Rezaei, H.; Dory, Y. L. *J. Org. Chem*. **2004**, *69*, 757-764.

Lewis acids[7], high pressure and temperature[8], ultrasound[9], microwave irradiation[10] and the use of water or polar solvents[11].



Scheme 3.3. A) Classification of the Diels-Alder reaction concerning the electronic properties of the reactants. B) The HOMO-LUMO energy barriers for non-substituted, Normal-electron-demand and Inverse-electron-demand Diels-Alder reactions.

In order to understand the origins of the reactivity of the Diels-Alder reaction, several theories and models have been reported. At the beginning of 1965, Woodward and Hoffmann described the principle of conservation of orbital symmetry, which predicts that reactions occur in a way to maintain maximum bondings throughout the course of the

[7] a) For some examples, see: Yates, P.; Eaton, P. E. *J. Am. Chem. Soc*. **1960**, *82*, 4436-4437. b) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc*. **1969**, *91*, 5675-5677. c) Inukai, T.; Kojima, T. *J. Org. Chem*. **1967**, *32*, 869-871.
[8] For some examples, check: Li, T.-T.; Wu, Y.-L. *J. Am. Chem. Soc*. **1981**, *103*, 7007-7009. b) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc*. **1980**, *102*, 6893-6894. c) Ballerini, E.; Minuti, L.; Piermatti, O. *J. Org. Chem*. **2010**, *75*, 4251-4260. d) Araujo, N.; Gil, M. V.; Roman, E.; Serrano, J. A. *Tetrahedron* **2010**, *66*, 2664-2674.
[9] Raj, C. P.; Dhas, N. A.; Cherkinski, M.; Gedanken, A.; Braverman, S. *Tetrahedron Lett*. **1998**, *39*, 5413-5416.
[10] a) Liu, X.; Wan, Q.; Zhao, Z.; Liu, J.; Zhang, Z.; Deng, F.; Liu, M.; Wen, Y.; Zhang, X. *Mat. Chem. Phys*. **2017**, *197*, 256-265. b) Zheng, S.; Chowdhury, A.; Ojima, I.; Honda, T. *Tetrahedron* **2013**, *69*, 2052-2055. c) Dejmek, M.; Hřebabecký, H.; Šála, M.; Dračínský, M.; Nencka, R. *Synthesis* **2011**, *24*, 4077-4083.
[11] For recent examples, check: a) Ayerbe, M.; Cossío, F.P. *Tetrahedron Lett*. **1995**, *36*, 4447-4450. b) Asaad, N.; Jetta den Otter, M.; Engberts, J. B. F. N. *Org. Biomol. Chem*. **2004**, *2*, 1404-1412. c) Chen, I.-H.; Young, J.-N.; Yu, S. J. *Tetrahedron* **2004**, *60*, 11903-11909. d) Bhowmick, K. C.; Bihani, M.; Zhao, J. C.-G. *Mini-reviews in Organic Chemistry* **2018**, *15*, 3-19.

reactions.[12] In 1967, Fukui reported an alternative approach that was focussed on the interaction of frontier molecular orbitals (FMOs).[13] This method suggests that "thermal reactions are allowed only when all overlaps between the HOMO of one reactant and the LUMO of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe".[14] One last approximation for the concept of orbital symmetry was described by Zimmerman, who extended the symmetry rules into the context of the Hückel and Möbius aromaticity.[15]

This (4+2) process is considered pericyclic when both the bond-breaking and bond-forming processes are concerted in a single six-membered transition state. Nonetheless, a concerted mechanism does not necessarily mean that it is synchronous.[16] In fact, a Diels-Alder reaction can as well be asynchronous, in which the two bonds are formed to different extent in the transition state.[17] Most Diels-Alder reactions, specially the thermal ones, are described by a concerted mechanism.[18] On the contrary, when conjugated cations, anions and radicals are involved the two bonds can be formed in a stepwise manner.[19] In the case of concerted reactions, the process is allowed by the Woodward-Hoffman rules for thermal cycloadditions and the Diels-Alder reaction is classified as a [π4s+π2s] cycloaddition where 4 and 2 indicate the number of π electrons involved and s indicates that the reaction takes place suprafacially on both components.[12] Therein, the interaction between the HOMO of the diene and LUMO of the dienophile is commonly the most relevant interaction in the aromatic transition state.[20]

[12] Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*, Verlag Chemie: Weinheim, **1970**.
[13] Smith, M. B.; March, J. *March's Advanced Organic Chemistry. Reactions, Mechanisms and Structure, 6th Ed.*, Wiley-Interscience: New Jersey, **2007**.
[14] a) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn*. **1967**, *40*, 2018-2025. b) For a monograph on Frontier Orbitals, see: Fleming, I. *Pericyclic Reactions*, Oxford University Press: Oxford, **1999**.
[15] Zimmerman, H. E.; Marchand, A. P.; Lehr, R. E. *Pericyclic Reactions, Vol. 2*, Academic Press: New York, **1977**.
[16] Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc*. **1986**, *108*, 5771-5779.
[17] Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem*. **1986**, *51*, 2642-2649.
[18] a) Fukui, K. *Acc. Chem. Res*. **1971**, *4*, 57-64. b) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B.; Wolber, J. *J. Org. Chem*. **1989**, *54*, 2931-2935. c) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem*. **1989**, *54*, 1129-1134.
[19] a) Gorman, D. B.; Gassman, P. G. *J. Org. Chem*. **1995**, *60*, 977-985. b) de Pascual-Teresa, B.; Houk, K. N. *Tetrahedron Lett*. **1996**, *37*, 1759-1762.
[20] Schleyer, P. v.; Wu, J. I.; Cossío, F. P.; Fernández, I. *Chem. Soc. Rev*. **2014**, *43*, 4909-4921.

3.1.2 Regio- and stereoselectivities

The use of non-symmetric dienes and dienophiles results in the possible formation of different regioisomers. The regioselectivity of the reaction depends on the individual nature of the substituents of both the diene and the dienophile and on the reaction conditions.[21] In concordance with frontier orbital theory, the regiochemistry is governed by the magnitude of the atomic orbital coefficients in the FMOs of the reaction partners. Furthermore, when the diene holds two different substituents, one of them directs the addition. In general, in normal-electron-demand reactions, substituents at C-1 on the diene direct the addition towards the *ortho* product, whereas substituents at C-2 promote preferentially the *para* adduct (**Figure 3.1**).

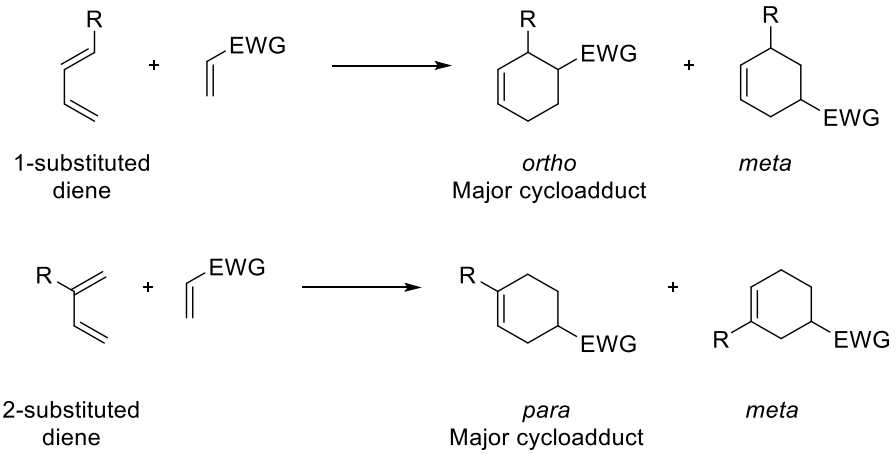
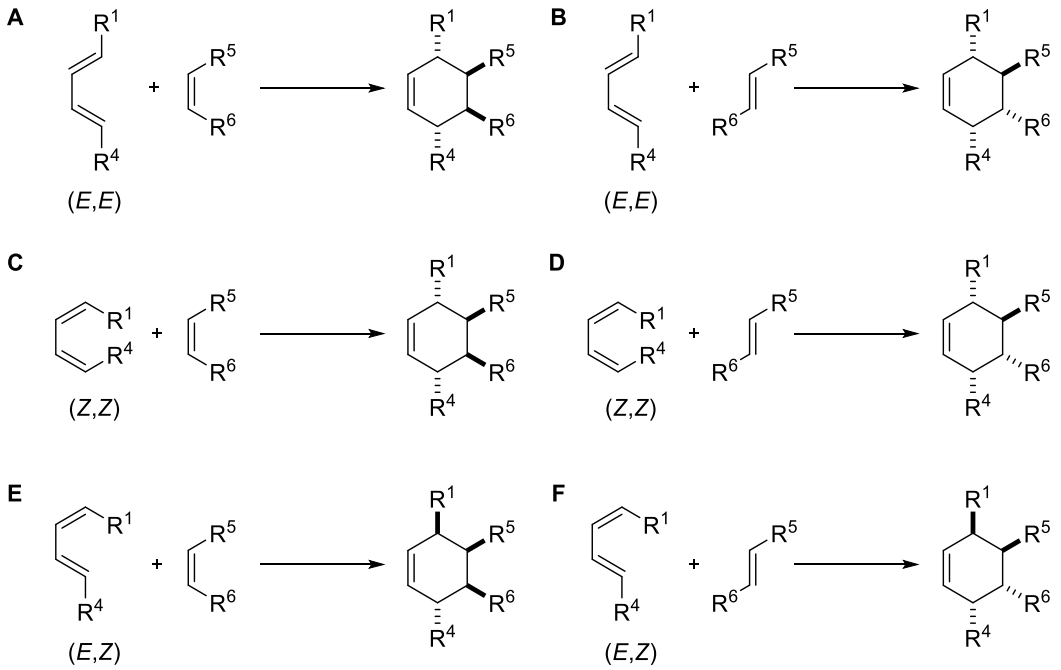


Figure 3.1. The *ortho-para* rule for Diels-Alder reactions.

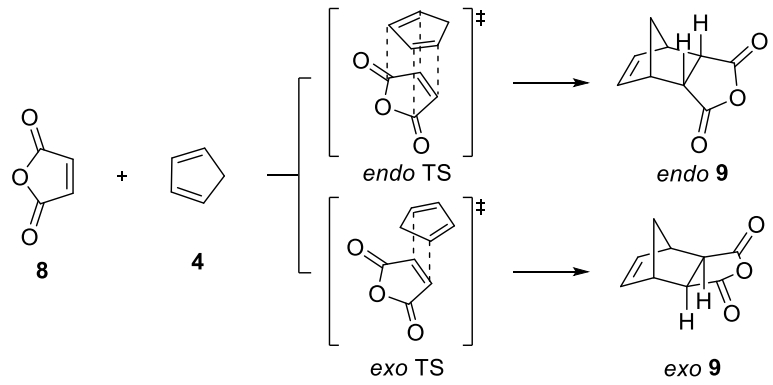
Concerning stereochemistry, several factors need to be taken into consideration.[22] In agreement with the supra-supra topology, the diene must hold a cisoid (*s-cis*) conformation. Besides, the addition of both the diene and the dienophile is *syn* and stereospecific. As a consequence, the disposition of the substituents of both components will be retained in the final adducts. Hence, (*E*,*E*)- and (Z,Z)-dienes promote the formation of adducts that bear R^1 and R^4 substituents in *cis* disposition, and (*E*,*Z*)-dienes give rise to the *trans* disposition of R^1 and R^4.[23] Comparatively, (*Z*)-dienophiles yield adducts that hold a *cis* disposition in R^5 and R^6 substituents, whereas (*E*)-dienophiles provide adducts with *trans* R^5/R^6 relationship (**Scheme 3.4**).

[21] Oppolzer, W. in *Comprehensive Organic Synthesis, Vol. 5.* Pergamon Press: Oxford, **1991**.
[22] a) Smith, M. B. *Organic Synthesis*, *2nd Ed*., McGraw-Hill: New York, **2001**. b) Woodward, R. B.; Hoffman, R. *Angew. Chem., Int. Ed.* **1969**, *81*, 781-853.
[23] Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem*. **2002**, *67*, 6823-6826.



Scheme 3.4. Stereochemistry rules depending on the disposition of the substituents of both the diene and dienophile. The *endo*/*exo* approximation has not been taken into account. B) (*E*,*E*)-diene and (*E*)-dienophile. C) (*Z*,*Z*)-diene and (*Z*)-dienophile. D) (*Z*,*Z*)-diene and (*E*)-dienophile. E) (*E*,*Z*)-diene and (*E*)-dienophile. F) (*E*,*Z*)-diene and (*Z*)-dienophile.

Finally, it is worth mentioning that the relative configuration of the adduct is fixed by two possible suprafacial approaches, *endo* and *exo*. In the endo transition state the bulkier side of the dienophile is oriented towards the π-system, while in the *exo* is oriented away from it (**Scheme 3.5**). In the majority of the reactions, the *endo* addition predominates (Alder's rule) [24], but in many cases mixtures of *endo* and *exo* products are found. Such *endo* preference has been accounted for secondary orbital interactions described by Woodward and Hoffman[25] and confirmed by more detailed calculations[26].



Scheme 3.5. The *endo* and *exo* transition states and adducts.

[24] Alder, K.; Stein, G. *Justus Liebigs Ann. Chem*. **1934**, *514*, 1-33.
[25] Hoffman, R.; Woodward, R. B. *J. Am. Chem. Soc*. **1965**, *87*, 4388-4389.
[26] Arrieta, A.; Lecea, B.; Cossío, F.P. *J. Org. Chem*. **2001**, *66*, 6178-6180.

During the last years, not only diastereo- but also enantioselective versions of the (4+2) cycloaddition have been widely investigated, so as to promote the preferential formation of one of the two possible enantiomers of the *endo* or *exo* diastereomers in the chemical transformation.[27] The following section will focus more deeply into this topic.

3.2 ENAMINE-MEDIATED ASYMMETRIC DIELS-ALDER REACTIONS

The asymmetric version of the Diels-Alder cycloaddition enables a facile route towards the synthesis of chiral cyclic and polycyclic compounds, relevant in the total synthesis of bioactive compounds.[28] Among the reported methodologies, three main approaches can be distinguished: the employment of 1) chiral auxiliaries; 2) metal complexes; and 3) organocatalysts.

Chiral auxiliaries can be bound either to the diene[29] or the dienophile[30], even though the majority of the examples found in literature are attached to the latter species. Nevertheless, due to the required stoichometric amounts and the additional synthetic steps, researchers focused their attention in the use of catalytic reactions. Traditionally, catalytic approaches resulted mainly from the activity of Lewis acids, from which cationic oxazaborolidines and different copper (II) bis(oxazolines), arylalanine amide complexes and DNA complexes deserve a special remark.[31] It was not until 1989 that the use of organocatalysts was extended to Diels-Alder reactions[32], and a vast number of small organic molecules have been reported ever since, such as sulfonyl hydrazines[33],

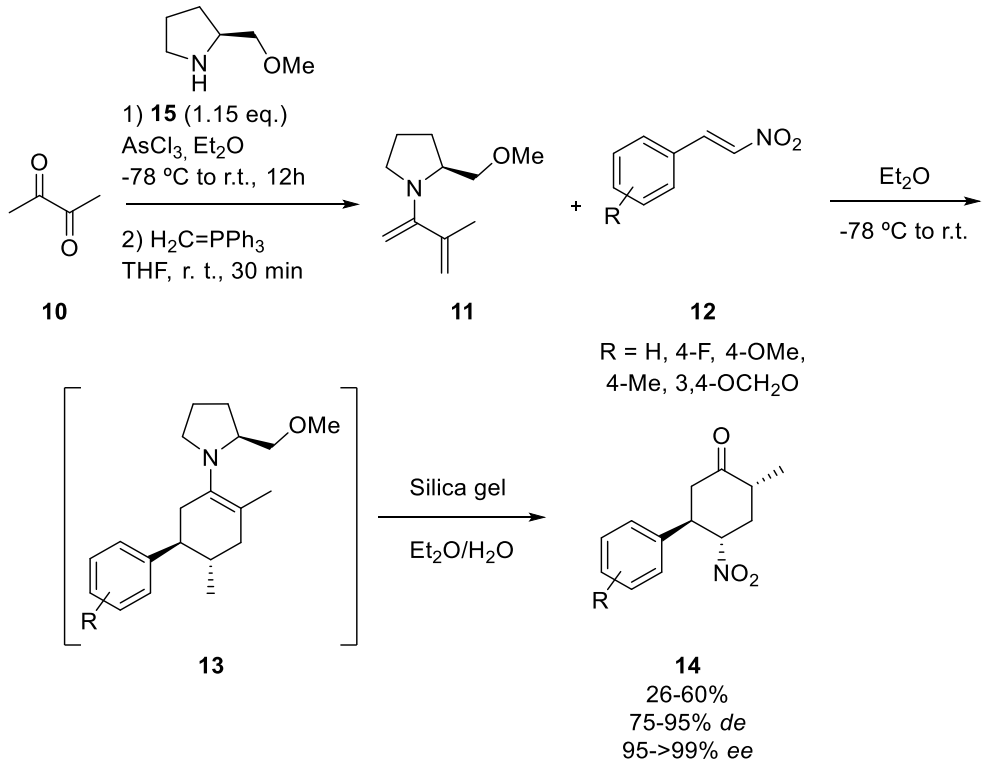
[27] Miller, M. P. in *Advances in Chemistry Research*, *Volume 18*, Nova Science Publishers: New York, **2013**.
[28] Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667.
[29] For some examples, see: a) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc*. **1980**, *102*, 7595-7596. b) Kita, Y.; Maeda, H.; Takahashi, F.; Fukui, S. *J. Chem. Soc., Perkin Trans*. 1, **1993**, 2639-2649. c) Miller, J. P. ; Stoodley, R. J. *J. Saudi Chem. Soc.* **2001**, 10.1016/j.jscs.2011.02.019. d) Tadano, K.; Totani, K. *Glycoscience. Epimerisation, Isomerisation and Rearrangement Reactions of Carbohydrates*, Springer: Berlin, **2008**. e) Jones, A. L.; Liu, X.; Snyder, J. K. *Tetrahedron Lett*. **2010**, *51*, 1091-1094. f) Miller, J. P. Stoodley, R. J. *J. Saudi. Chem. Soc*. **2011**, *15*, 275-281.
[30] a) Caygill, G. B.; Larsen, D. S.; Brooker, S. *J. Org. Chem*. **2001**, *66*, 7427-7431. b) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron* **2009**, *65*, 3502-3508. c) Hirama, M.; Kato, Y.; Seki, C.; Nakano, H.; Takeshita, M.; Oshikiri, N.; Iyoda, M.; Matsuyama, H. *Tetrahedron* **2010**, *66*, 7618-7624. d) Seki, C.; Hirama, M.; Hutabarat, N. D. M. R.; Takada, J.; Suttibut, C.; Takahashi, H.; Takaguchi, T.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Yasui, M.; Okuyama, Y.; Takeshita, M.; Matsuyama, M. *Tetrahedron* **2012**, 68, 1774-1781.
[31] For excellent compilations in metal catalysis, see: a) Ref 27. b) Ishikara, K.; Sakakura, A. *Comprehensive Organic Synthesis II, Volume 5*, Elsevier: Oxford, **2014**. c) Chen, X.; Lu, Z. *Org. Biomol. Chem*. **2017**, *15*, 2280-2306. d) Beletskaya, I. P.; Nájera, C.; Yus, Y. *Chem. Rev*. **2018**, *118*, 5080-5200.
[32] Riant, O.; Kagan. H. B. *Tetrahedron Lett*. **1989**, *30*, 7403-7406.
[33] a) He, H.; Pei, B.-J.; Chou, H.-H.; Tian, T.; Chan, W.-H.; Lee, A. W. M. *Org. Lett*. **2008**, *10*, 2421-2424. b) Langlois, Y.; Petit, A.; Rémy, P.; Scherrmann, M.-C. Kouklovsky, C. *Tetrahedron Lett*. **2008**, *49*, 5576-5579.

cinchona alkaloids[34], imidazolidinones[35], bisoxazolines[36], and proline derivatives[37]. They all were found to be particularly applicable to α,β-unsaturated aldehydes and ketones through the generation of iminium ion and dienamine intermediate species formed by the reversible reaction of the amine catalyst with the carbonyl compound.[38]

3.2.1 Dienamine-mediated Diels-Alder reactions

The use of transient-enamine strategy for the activation of (4+2) cycloadditions was first described by Enders and co-workers in 1992. These authors developed a new route towards the synthesis of 4-nitrocyclohexenes **14**, in which the stereochemical outcome was exerted by equimolar amounts of (*S*)-2-(methoxymethyl)pyrrolidine **15**. Therein, the desired cycloadducts were obtained in moderate yields, high diastereoselectivities and excellent enantioselectivities (**Scheme 3.6**).[39] It is worth nothing that a prior synthesis and isolation of 2-amino-1,3-butadiene **11** was essential for the (4+2) annulation to occur.

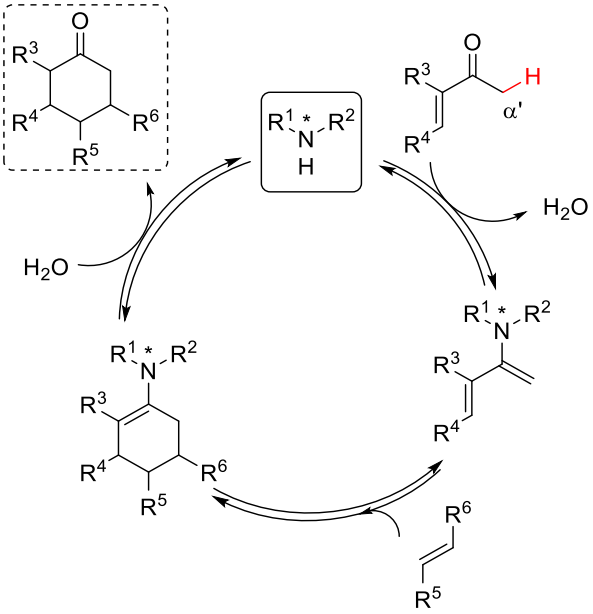
[34] a) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 9236-9239. b) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc*. **2008**, *130*, 2422-2423. c) Bella, M.; Schietroma, D. M. S.; Cusella, P. P.; Gasperi, T. Visca, V. *Chem. Commun*. **2009**, 597-599. d) Shen, J.; Tan, C.-H. *Org. Biomol. Chem*. **2008**, *6*, 4096-4098.
[35] a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243-4244. b) Mitsudome, T.; Nose, K.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Tetrahedron Lett*. **2008**, *49*, 5464-5466.
[36] Akalay, D.; Dürner, G.; Göbel, M. W. *Eur. J. Org. Chem.* **2008**, 2365-2368.
[37] For an excellent review, see: Pellisier, H. *Recent Developments in Asymmetric Organocatalysis*, RSC Catalysis: Cambridge, **2010**.
[38] a) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1-26. b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748-9770. c) Arrastia, I.; Arrieta, A.; Cossío, F.P. *Lett. Org. Chem.* **2018**, *15*, 394-403.
[39] Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242-1244.



Scheme 3.6. The first dienamine mediated Diels-Alder reaction reported by Enders and co-workers.

The first iminium-ion mediated catalytic version of the (4+2) cycloaddition reaction dates back to 2000 (see Chapter 1, page 10).[35a] This reported reaction was activated by LUMO lowering of the α,β-unsaturated carbonyl compound, which acted as the dienophile. However, a second activation mode is possible, in which the dienamine mediated Diels-Alder reaction operates by HOMO raising of the unsaturated carbonyl moiety. In accordance with the catalytic cycle, the reversible condensation of the enolizable α,β-unsaturated ketone with the organocatalyst generates the transient dienamine. This latter species reacts with the dienophile to yield the cyclic enamine via a concerted or stepwise mechanism. A final hydrolysis of the enamine enables the recovery of the catalyst and the release of the desired cycloadduct. The only requisite for the application of this strategy is the need for an enolizable proton at the α' position of the starting unsaturated ketone (**Scheme 3.7**).[40]

[40] Arrastia, I.; Arrieta, A.; Cossío, F. P. *Lett. Org. Chem*. **2018**, *15*, 394-403.



Scheme 3.7. The catalytic cycle for the Diels-Alder reaction via dienamine species. The proton in red indicates that the carbonyl compound should be enolizable.

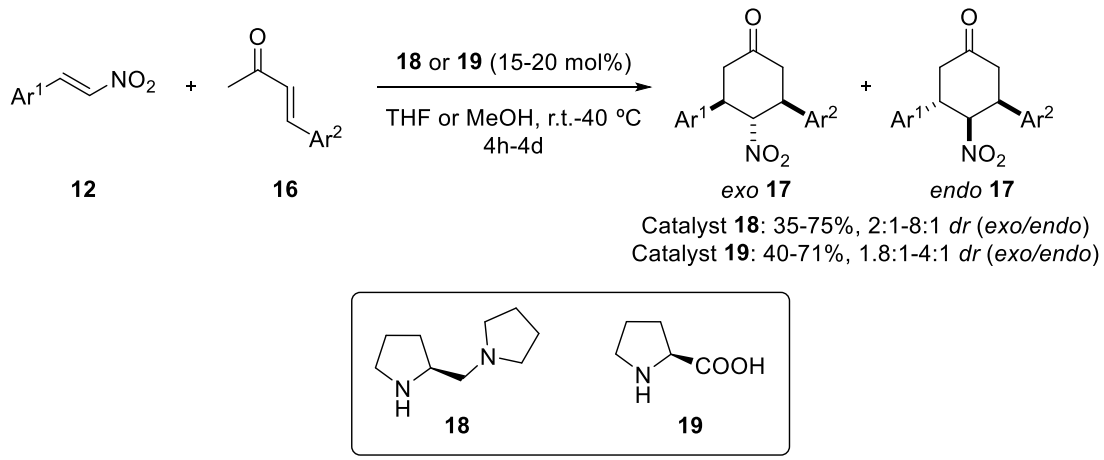
This methodology has been successfully implemented for a wide variety of dienophiles. According to the literature, α,β-unsaturated ketones[41], *in situ* generated acceptors[42], maleimides[43], indolin-2-ones[44] and malonitriles[45] are usually employed. Nitroalkenes have also been successfully implemented in (4+2) annulation reactions. In this context, the Diels-Alder reaction between α,β-unsaturated ketones and nitroalkenes is a particularly useful and versatile process since it permits the synthesis of

[41] a) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Tetrahedron Lett*. **2002**, *43*, 6743-6746. b) Huang, H.; Wu, W.; Zhu, K.; Hu, J.; Ye, J. *Chem. Eur. J*. **2013**, *19*, 3838-3841.
[42] a) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Synlett* **2003**, 1910-1914. b) Ramachary, D. B.; Chowdary, N. S.; Barbas III, C. F. *Angew. Chem., Int. Ed*. **2003**, *42*, 4233-4237. c) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas III, C. F. *J. Org. Chem*. **2004**, *69*, 5838-5849. d) Ramachary, D. B.; Barbas III, C. F. *Chem. Eur. J*. **2004**, *10*, 5323-5331. e) Ramachary, D. B.; Reddy, Y. V.; Prakash, B. V. *Org. Biomol. Chem*. **2008**, *6*, 719-726. f) Jiang, B.; Hao, W.-J.; Zhang, J.-P.; Tu, S.-J.; Shi, F. *Org. Biomol. Chem*. **2009**, *7*, 2195-2201. g) Pizzirani, D.; Roberti, M.; Grimaudo, S.; Cristina, A. D.; Pipitone, R. M.; Tolomeo, M.; Recanatini, M. *J. Med. Chem*. **2009**, *52*, 6936-6940. h) Shi, J.; Liu, Y.; Wang, M.; Lin, L.; Liu, X.; Feng, X. *Tetrahedron* **2011**, *67*, 1781-1787. i) Ramachary, D. B.; Krishna, P. M. *Asian J. Org. Chem*. **2016**, *5*, 729-734.
[43] a) Tanaka, F.; Thayumanavan, R.; Barbas III, C. F. *J. Am. Chem. Soc*. **2003**, *125*, 8523-8528. b) Wu, L.-Y.; Bencivenni, M.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed*. **2009**, *48*, 7196-7199. c) Wu, X.; Li, M.-L.; Chen, D.-F.; Chen, S. S. *J. Org. Chem.* **2014**, *79*, 4743-4750. d) Eudier, F.; Righi, P.; Mazzanti, A.; Ciogli, A.; Bencivenni, G. *Org. Lett*. **2015**, *17*, 1728-1731.
[44] a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed*. **2009**, *48*, 7200-7203. b) Lan, Y.-B.; Zhao, H.; Liu, Z.-M.; Liu, G.-G.; Tao, J.-C.; Wang, X.-W. *Org. Lett*. **2011**, *13*, 4866-4869. c) Ramachary, D. B.; Reddy, P. S.; Shruthi, K. S.; Madhavachari, R.; Reddy, P. V. G. *Eur. J. Org. Chem*. **2016**, 5220-5226.
[45] Feng, X.; Zhaou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *J. Am. Chem. Soc*. **2012**, *134*, 19942-19947.

cycloadducts that can be further converted into other functional groups. Some of the most representative examples will be commented next.

3.2.1.1 Organocatalytic Diels-Alder reaction of α,β-unsaturated ketones to nitroalkenes

The first study of secondary amine catalysed Diels-Alder reaction was reported by the group of Barbas III, who demonstrated that the dienamine moiety can be generated *in situ* in the reaction medium, without any previous synthetic and isolation steps.[46] The reaction between different α,β-unsaturated ketones and aromatic nitroolefins, catalysed by either (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **18** or *L*-Proline **29**, furnished the corresponding cyclohexanone derivatives in moderate yields and low stereocontrol (**Scheme 3.8**).

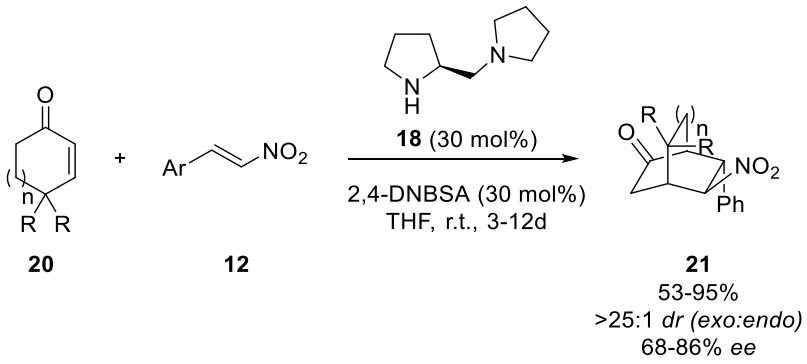


Scheme 3.8. The first secondary amine catalysed Diels-Alder reaction described by Barbas III.

Shortly after, Córdova tested several proline-based catalysts for the synthesis of bicyclic products that hold four contiguous stereogenic centres.[47] Among the tested derivatives, the previously described diamine **18** was able to promote the corresponding *exo* cycloadducts in high yields with excellent diastereoselectivities and good to high enantioselectivities. The nature of the reaction was broadly applied to diverse cyclic ketones and nitroalkenes, and the use of catalytic amounts of 2,4-dinitrobenzenesulfonic acid (DNBSA) resulted to be crucial for rate enhancement (**Scheme 3.9**). Besides, the absolute configuration of the final product was believed to be related to a stepwise

[46] Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F. *Tetrahedron Lett*., **2002**, *43*, 3817-3820.
[47] Sundén, H.; Rios, R.; Xu, Y.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal*. **2007**, *349*, 2549-2555.

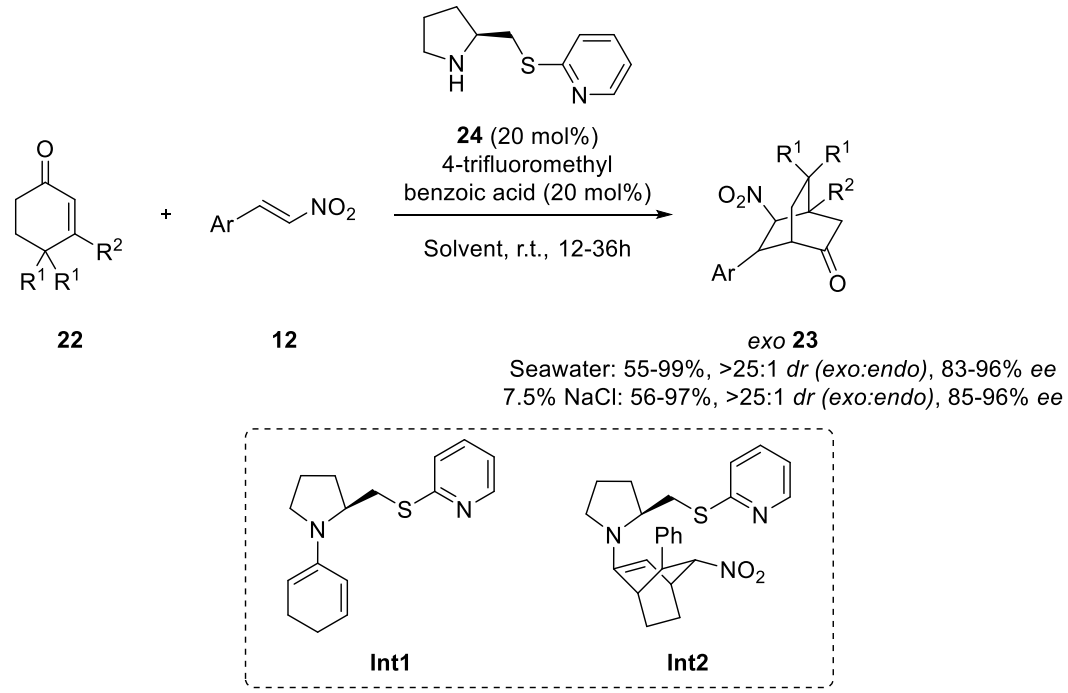
Michael-cyclisation transformation, in which the first addition of the nitroolefin to the diene determined the absolute configuration of the final cycloadduct.



Scheme 3.9. The direct enantioselective synthesis towards bicyclic products developed by Córdova and co-workers.

The next breakthrough in this area was accomplished by Xu et al., who developed a highly efficient asymmetric organocatalytic Diels-Alder reaction of cyclic ketones and nitroolefins in seawater and 7.5% aqueous salt solutions.[48] Among the tested catalysts, derivative **24** exhibited the best performance in terms of conversion and enantioselectivity, in the presence of 4-trifluoromethylbenzoic acid. The asymmetric process was suitable for aromatic and heteroaromatic nitroolefins bearing different substitution patterns and in all cases the *exo* **23** cycloadducts were obtained as major diastereomers (**Scheme 3.10**). Interestingly, the existence of dienamine **Int1** and enamine **Int2** intermediates was confirmed by ESI-MS experiments but no Michael adduct was observed during the chemical transformation. Hence, the cyclisation was considered to evolve through a one-step concerted pathway, opposite to the previous double-Michael sequential cases.

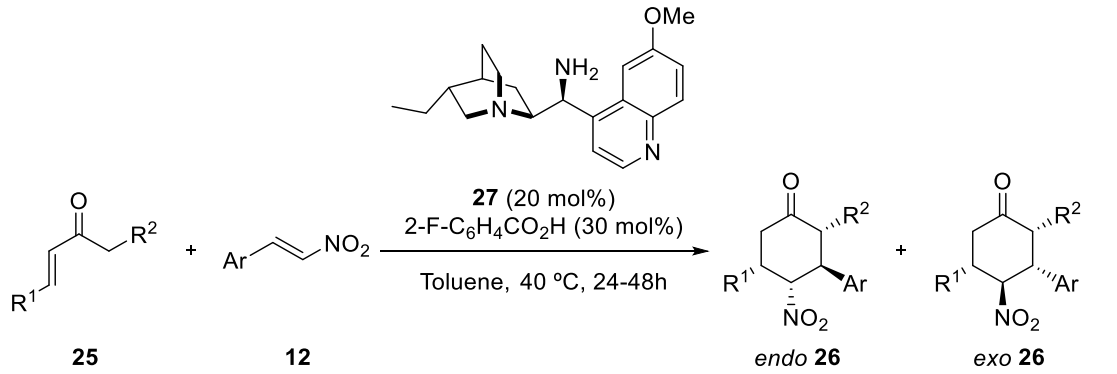
[48] Xu, D.-Q.; Xia, A,-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem., Int. Ed*. **2009**, *48*, 3821-3824.



Scheme 3.10. The Diels-Alder reaction of cyclohex-2-en-1-ones **22** to nitroolefins in aqueous salt solutions.

Within the same year, the research group led by Melchiorre demonstrated that primary amine catalysts were also capable of yielding complex cyclohexanone motifs with three or four stereogenic centres.[44a] These authors made use of cinchona-derived primary amine **27** to activate acyclic α,β-unsaturated ketones. Therefore, the reaction between the activated species and nitroalkenes furnished a set of *endo* **26** cycloadducts in good yields and excellent stereochemical outcomes (**Scheme 3.11**). The unexpectedly high *endo:exo* ratios were accounted for the nature of the carboxylic acid used as co-catalyst. In addition, the proposed sequential double-Michael addition was verified by the isolation and NMR characterization of some intermediate Michael adducts. Following the same trend, Stowe and Janda reported another Diels-Alder reaction promoted by nornicotine type catalysts. Nonetheless, neither yield nor enantiomeric excess values were satisfactory, probably due to aqueous instability of the transient enamine species.[49]

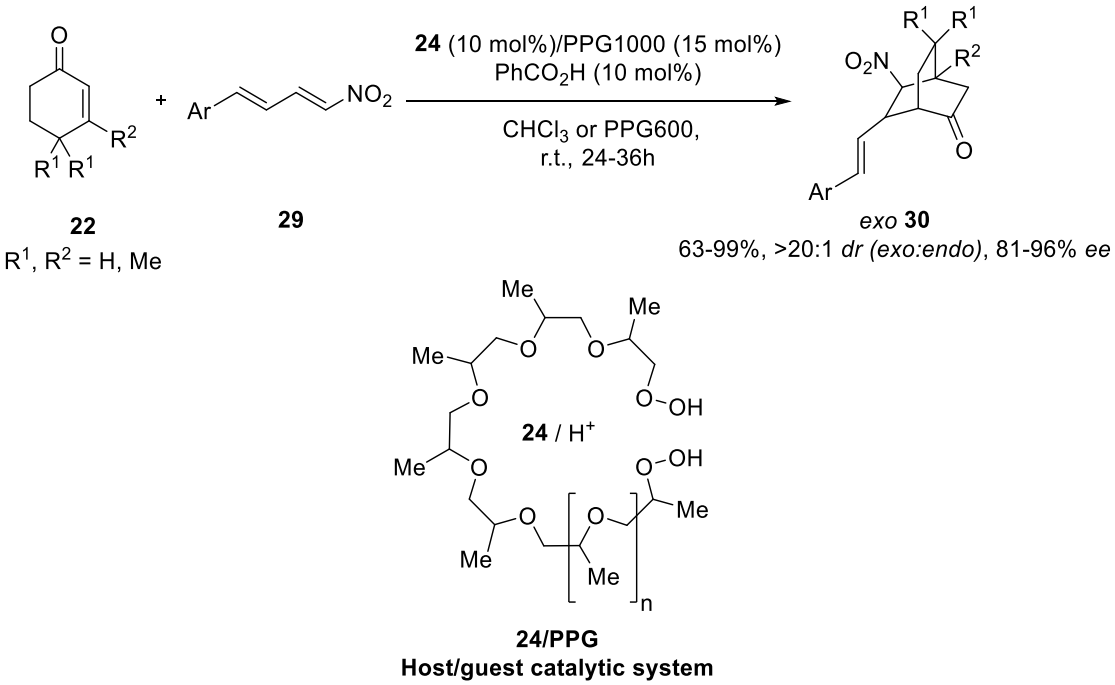
[49] Stowe, G. N.; Janda, K. D. *Tetrahedron Lett*. **2011**, *52*, 2085-2087.



Scheme 3.11. Primary amine catalysed Diels-Alder reaction between enones and nitroalkenes reported by Melchiorre.

In 2012, Xu and co-workers described an alternative route to perform asymmetric Diels-Alder reactions of cyclohex-2-en-1-ones **22** to nitrodienes **29**. Therein, the catalytic activity was accomplished by a host-guest supramolecular system, generated by the combination of the chiral amine **24** and poly(ethylene glycol)s (PEG) or poly(propylene glycol)s (PPG).[50] The transformation exhibited excellent asymmetric activity for a range of enones and nitrodienes in presence of PPG1000 and 10 mol% of $PhCO_2H$, regardless of the electronic properties and the position of the substituents on the aromatic ring of the nitrodiene (**Scheme 3.12**). NMR spectroscopy, circular dichroism and ESI-MS experiments corroborated the existence of this supramolecular system, in which the polymer chains strengthened the association between the chiral amine and the acid additive.

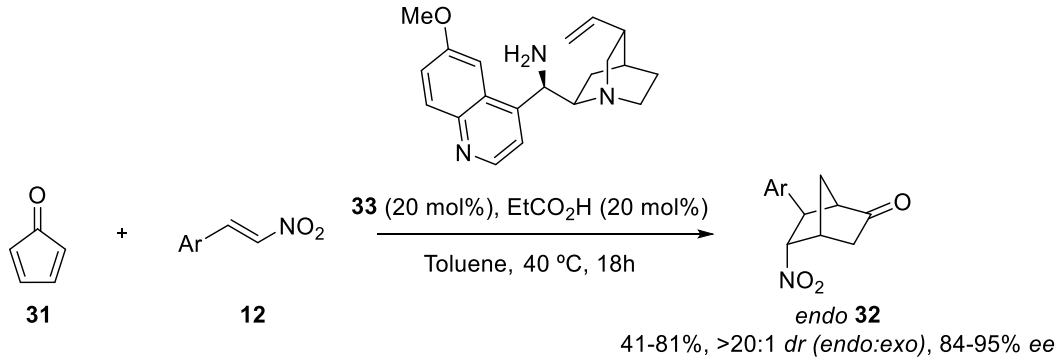
[50] Xia, A.-B.; Xu, D.-Q.; Wu, C.; Zhao, L.; Xu, Z.-Y. *Chem. Eur. J*. **2012**, *18*, 1055-1059.



Scheme 3.12. The supramolecular catalytic assembly designed by Xu for the Diels-Alder reaction between cyclic enones and nitrodienes.

To finish, a recent work carried out by Jørgensen must be cited. The primary amine **33** catalysed Diels-Alder reaction between cyclopentenone and a number of dienophiles gave access to norcamphor scaffolds in good to high yields and high enantioselectivities (**Scheme 3.13**).[51] The reaction was performed in the presence of weak acids, being both electron-donating and electron-withdrawing substituents well tolerated, together with heteroaromatic nitroolefins. Interestingly, the reaction was further applied to several dienophiles, such as chalcones and malononitriles, providing an efficient access to a new family of norcamphor coumpounds. From a mechanistic point of view, the authors suggested an asynchronous concerted cycloaddition, although a stepwise mechanism was not totally excluded.

[51] Mose, R.; Jensen, M. E.; Preegel, G.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2015**, *54*, 13630-13634.



Scheme 3.13. Primary amine **33** catalysed Diels-Alder reaction developed by Jørgensen and co-workers.

3.3 OBJECTIVES

All the previously described organocatalytic Diels-Alder approaches are based on either primary or secondary amines. Nevertheless, no contributions are found regarding the use of unnatural amino acid containing structures so far. In addition, considering the excellent results obtained by our three generation catalysts in aldol[52], Michael[53], cyclisation[54] and Michael-Henry-Acetalization reactions, one of the goals of the present Chapter will consist of studying their suitability towards the Diels-Alder reaction. Moreover, different dienes and dienophiles will be tested in order to assess the scope of this reaction.

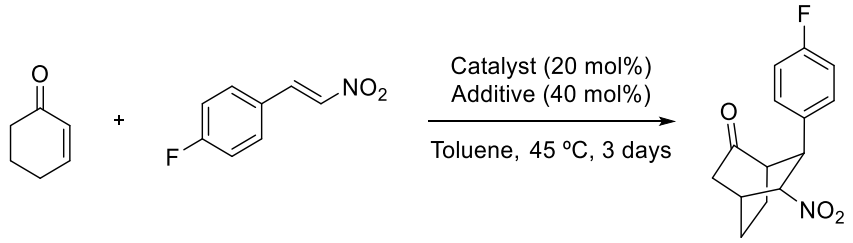
3.4 ORGANOCATALYTIC DIELS-ALDER REACTION OF CYCLOHEX-2-EN-1-ONE WITH NITROALKENES

3.4.1 Optimisation studies

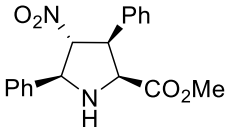
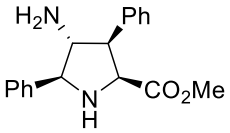
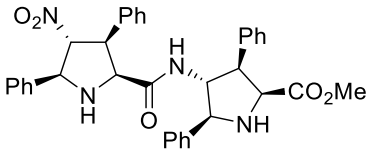
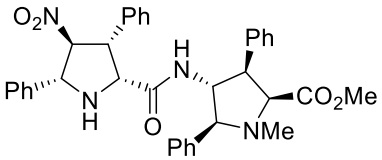
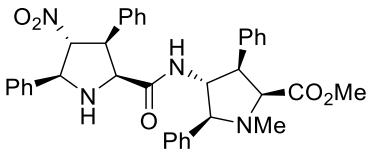
According to the reactivity rules of the (4+2) cyclisation reaction, cyclic dienes are usually more reactive than their acyclic analogues, based on the preorganised cisoid (*s-cis*) geometry they hold. In addition, EWG-containing nitroalkenes favour the reaction to occur, lowering the HOMO-LUMO energy difference in the transition state. Within this context, the effect of monomeric and γ-dimeric organocatalysts on the Diels-Alder reaction between cyclohex-2-en-1-one **36** and (*E*)-nitrostyrene **12a** was studied first. The results obtained are gathered in **Table 3.1**.

[52] a) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci*. **2012**, *3*, 1486-1491. b) Retamosa, M. G.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem*. **2015**, 2503-2516.
[53] Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F. P. *J. Org. Chem*. **2015**, *80*, 5588-5599.
[54] Retamosa, M. G.; Ruiz-Olalla, A.; Bello, T.; de Cózar, A.; Cossío, F. P. *Angew. Chem., Int. Ed*. **2018**, *57*, 668-672.

Table 3.1. The Diels-Alder reaction between cyclohex-2-en-1-one **36** and 4-fluoro-*trans*-β-nitrostyrene **12a** catalysed by densely substituted pyrrolidines.[a]



36 **12a** *exo* (1*R*,4*R*,5*R*,6*S*)-**37a**

Entry	Catalyst	Additive	Conversion (%)[b]	*exo*/*endo*[c]	Yield (%)[d]	*ee* (%)[e]
1	 O_2N-X_L-OMe-**75**	$PhCO_2H$	87	80:20	39	97
2	 H_2N-X_L-OMe-**28**	$PhCO_2H$	95	82:18	41	86
3	 O_2N-X_L-X_L-OMe-**34**	$PhCO_2H$	97	70:30	43	90
4	 O_2N-X_D-X_L^{Me}-OMe-**35**	$PhCO_2H$	>99	85:15	52	-96
5		$PhCO_2H$	>99	88:12	60	97
6		PNBA[f]	>99[g]	90:10	46	95
7	 O_2N-X_L-X_L^{Me}-OMe-**35**	SA[h]	-[i]	nd[j]	nd	nd
8		TFA[k]	-[i]	nd	nd	nd
9		*p*CF_3CO_2H	>99	90:10	45	93
10[l]		$PhCO_2H$	60	nd	nd	nd
11[m]		$PhCO_2H$	>99	86:14	50	95

12[n]	$PhCO_2H$	>99[o]	70:30	27	93
13[p]	$PhCO_2H$	>99	87:13	50	95

a) The reaction was conducted using ketone **36** (0.10 mmol) and 4-fluoro-*trans*-β-nitrostyrene **12a** (0.10 mmol) in the presence of 20 mol% catalyst and 40 mol% additive at 45 °C. b) The reactions were monitored by ^{1}H-NMR analysis of the reaction mixtures. c) The *exo*/*endo* ratio was measured by ^{1}H-NMR analysis of the crude reaction mixtures. d) Yields refer to the sum of both diastereomers. e) Enantiomeric excesses measured by HPLC correspond to the major *exo* enantiomer (1*R*,4*R*,5*R*,6*S*)-**37a**. Negative values indicate that the opposite enantiomer is formed. f) PNBA: *p*-nitrobenzoic acid. g) Conversion after 4 days (within 3 days, only 60% conversion was reached. h) SA: salicylic acid i) No formation of the desired Diels-Alder cycloadduct was observed. j) nd: not determined. k) TFA: trifluoroacetic acid. l) 10 mol% catalyst, 20 mol% $PhCO_2H$. m) 70 °C. n) Biotage μW, 90 °C, 100 W, 5h. o) After 90 minutes, 50% conversion was observed. Within 3h, 75% of conversion was reached. p) 2 eq. of ketone **36** were used.

The first generation nitro O_2N-X_L-OMe-**75** catalyst exhibited a moderate conversion of 87% towards the final product yielding the *exo* **37a** diasteromer in a promising diastereomeric ratio and enantiomeric excess (**Table 3.1**, entry 1). Changing the catalyst to the second generation amino derivative H_2N-X_L-OMe-**28** showed a slightly superior conversion, but, unfortunately, the final product was still furnished in low yield and lower enantiomeric excess (**Table 3.1**, entry 2).

Aiming to overcome these poor conversion and yield values, γ-dipeptidic derivatives were tested next. The use of O_2N-X_L-X_L-OMe-**34** organocatalyst did not improve significantly the previous results. Thus, despite the high enantiomeric excess achieved, the *exo/endo* ratio decreased to 70:30 and the yield did not significantly improve (**Table 3.1**, entry 3). *N*-methylated derivative O_2N-X_D-X_L^{Me}-OMe-**35** and its diastereomer O_2N-X_L-X_L^{Me}-OMe-**35**, however, were able to enhance the reaction rate and full conversions were observed in both cases (**Table 3.1**, entries 4 and 5). Catalyst O_2N-X_D-X_L^{Me}-OMe-**35** led to the formation of the *ent*-**37a** product in moderate yield, good diastereomeric ratio and excellent enantiomeric excess (**Table 3.1**, entry 4). The yield was further improved by the employment of O_2N-X_L-X_L^{Me}-OMe-**35** dipeptide, and *exo*-**37a** cycloadduct was achieved in moderate yield, good *exo/endo* ratio and excellent enantiocontrol (**Table 3.1**, entry 5). At this point, it should be mentioned that our O_2N-X_L-X_L^{Me}-OMe-**35** catalyst and the proline derived organocatalyst reported by Xu and co-workers[48] (*vide supra*) promote the formation of opposite *exo*-**37a** enantiomers.

The following step consisted of testing different acidic additives, so as to evaluate their influence in both the reactivity and stereoselectivity. When *p*-nitrobenzoic acid was employed as the additive of choice, the final product was isolated in a lower yield, despite the comparable *exo/endo* ratio and enantiomeric excess values (**Table 3.1**, entry 6). The stronger salicylic acid and TFA did not promote any formation of the cyclisation product (**Table 3.1**, entries 7 and 8) and *p*-CF_3COOH exhibited a slight decrease in yield and enantiocontrol (**Table 3.1**, entry 9).

Other reaction parameters were also evaluated. Reducing the amount of the catalyst and the additive by half did not allow the reaction to reach full conversion (**Table 3.1**, entry 10). When the temperature was raised to 70 °C lower yield and enantiomeric excess values were observed (**Table 3.1**, entry 11). Besides, microwave irradiation led to sluggish crude reaction mixtures and a low isolated yield (**Table 3.1**, entry 12). Finally, increasing the amount of the starting ketone up to two equivalents did not improve the yield (**Table 3.1**, entry 13).

All the collected experimental data suggested the use of γ-dipeptide O_2N-X_L-X_L^{Me}-OMe-**35** and benzoic acid in 20 and 40 mol% load, respectively. Besides, the reaction should be carried out at 45 °C by conventional heating, making use of an equimolar ketone:nitroalkene ratio.

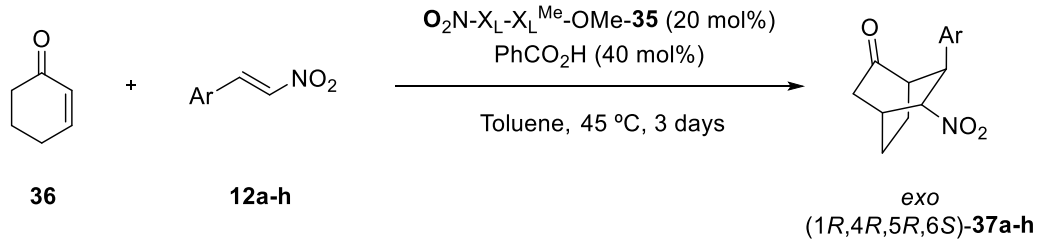
3.4.2 Scope

In order to explore the versatility of our catalysts in other Diels-Alder reactions, a number of aromatic and heteroaromatic nitroalkenes were tested. Both electron-donating and electron-withdrawing substituents were studied. The results of this series of experiments are shown in **Table 3.2**.

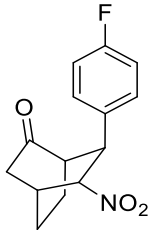
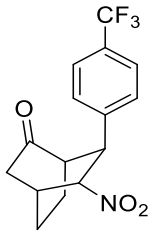
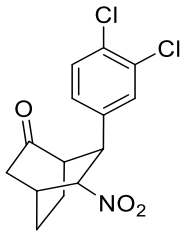
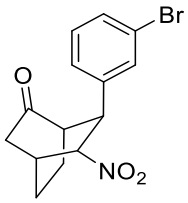
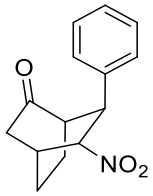
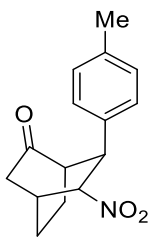
In general, the Diels-Alder reaction proceeded smoothly and the final *exo* **37a-h** cycloadducts were furnished in moderate yields, good *exo*/*endo* ratios and excellent enantiomeric excess values. In addition, we observed that either the electronic properties of the aromatic ring or their substitution pattern had little effect on the diastereo- and enantiocontrol of the process. However, the yields did show dependence on the electron-donating or electron-withdrawing character of the aromatic ring. The more activating electron-withdrawing substituents exhibited superior yields (**Table 3.2**, entries 1 and 2). On the contrary, electron-donating substituents led to lower yields (**Table 3.2**, entries 6 and 7). In fact, 4-methoxy-*trans*-β-nitrostyrene **12g** bearing the strongest deactivating substituent was not able to achieve full conversion after 3 days of reaction time (**Table 3.2**, entry 7).

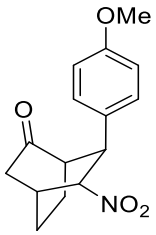
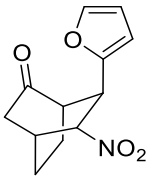
Along with the previous examples, other structural motifs were also applicable to the reaction. In this regard, 3,4-dichloro-*trans*-β-nitrostyrene **12c** gave access to the corresponding Diels-Alder cycloadduct **37c** in 54% yield, good diastereomeric ratio and high *ee* (**Table 3.2**, entry 3). Heterocyclic 2-furyl substituted nitroalkene **12h** underwent the Diels-Alder reaction in moderate yields, good *exo*/*endo* ratio and excellent enantiocontrol (**Table 3.2**, entry 8). Finally, 3-bromo-*trans*-β-nitrostyrene **12d** furnished the corresponding cycloadduct **37d** in a poor yield of 35% (**Table 3.2**, entry 4).

Table 3.2. O_2N-X_L-X_L^{Me}-OMe-**35** promoted Diels-Alder reaction of cyclohex-2-en-1-one **36** to nitroolefins **12a-h**.[a,b]



36 **12a-h** *exo* (1*R*,4*R*,5*R*,6*S*)-**37a-h**

Entry	Ar	Product	Structure	*exo*/*endo*[c]	Yield (%)[d]	*ee* (%)[e]
1	4-F	**37a**		85:15	65	97
2	4-CF_3	**37b**		84:16	69	96
3	3,4-Cl	**37c**		78:22	54	98
4	3-Br	**37d**		85:15	35	96
5	Ph	**37e**		86:14	61	95
6	4-Me	**37f**		85:15	51	96

7	4-OMe	**37g**		80:20	47[f]	96
8	2-furyl	**37h**		81:19	47	92

a) The reaction was conducted at 45 °C using cyclohex-2-en-1-one **36** (0.10 mmol) and the corresponding nitroalkene **12a-h** (0.10 mmol) in presence of 20 mol% O_2N-X_L-X_L^{Me}-OMe-**35** and 40 mol% $PhCO_2H$. b) Reactions were monitored by ^{1}H-NMR until total consumption of starting materials (Conv. > 99%). c) The *exo*/*endo* ratio was measured by ^{1}H-NMR of the crude reaction mixtures. d) Yield refers to the sum of both diastereomers. e) Enantiomeric excesses measured by HPLC correspond to the major *exo* (1*R*,4*R*,5*R*,6*S*)-**37a-h** enantiomer. f) 95% conversion was reached.

These results indicate that our O_2N-X_L-X_L^{Me}-OMe-**35** catalyst is able to promote the Diels-Alder reaction between cyclohexanone and substituted (*E*)-nitrostyrenes uneventfully, reaching moderate to good yields, good diastereoselectivities and excellent enantiomeric excesses in all cases.

3.5 ORGANOCATALYTIC DIELS-ALDER REACTION BETWEEN ACYCLIC α,β-UNSATURATED KETONES AND NITROALKENES

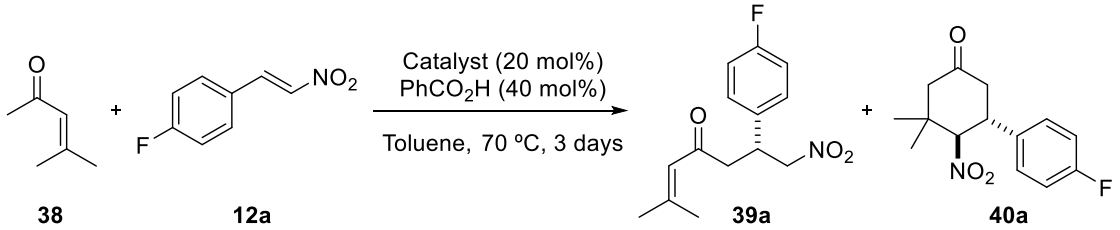
With the aim to evaluate the applicability of our organocatalysts to Diels-Alder reactions involving acyclic dienes derived from α,β-unsaturated ketones, the next step was conducted employing 4-methylpent-3-en-2-one **38** and the three generations of organocatalysts based on densely substituted unnatural prolines. *L*-Proline **19** was used as the reference catalyst (**Table 3.3**).

According to the previous results, the best catalytic performance was achieved by 20 mol% of catalyst and 40 mol% of $PhCO_2H$. In order to favour the formation of the Diels-Alder product, the reactions between the cited components were first carried out at 70 °C. Under these conditions, *L*-Proline was able to achieve full conversion. Nevertheless, it showed a 1:1 ratio between the Michael and Diels-Alder products, and both turned out to be racemic (**Table 3.3**, entry 1). In contrast, the three generations of unnatural proline-based catalysts could promote better enantioselectivities to some extent, highlighting the importance of the substituents on these catalysts (**Table 3.3**, entries 2 to 6).

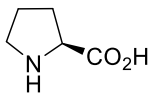
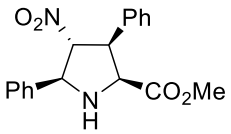
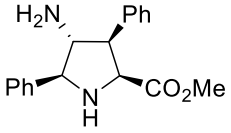
The nitroproline O_2N-X_L-OMe-**75** could almost exclusively furnish the (4+2) cyclisation **40a** product. However, the conversion and the enantiomeric excess of the final product were low (**Table 3.3**, entry 2). The use of second generation H_2N-X_L-OMe-**28** derivative

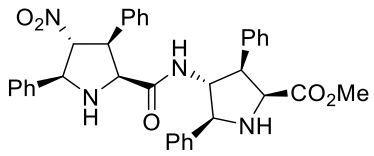
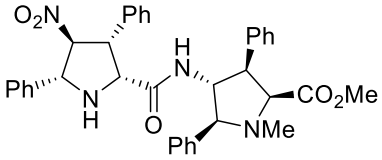
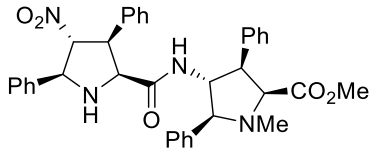
decreased the Michael:Diels-Alder proportion, providing **39a** and **40a** products in almost 1:1 ratio and moderate yields. The Michael product exhibited a moderate enantiomeric excess of 50%, whereas the *ee* of the Diels-Alder product was low (**Table 3.3**, entry 3). Dipeptide O_2N-X_L-X_L-OMe-**35** could also reach full conversion and slightly favour the formation of **40a** affording the desired products in good yields. Unfortunately, the enantiomeric excess of both products decreased (**Table 3.3**, entry 4). When *N*-methylated O_2N-X_D-X_L^{Me}-OMe-**35** dipeptide was employed, the reaction did not reach full conversion and the Michael:Diels-Alder ratio was comparable to the one obtained with non *N*-methylated dimer **35**. The enantiomeric excesses improved for both products, but did not surpass moderate values (**Table 3.3**, entry 5). Dipeptide O_2N-X_L-X_L^{Me}-OMe-**35** enabled the reaction to reach full conversion and also favoured the formation of the Diels-Alder product **40a**. Despite these improved results, the enantiomeric excess of the Michael **39a** and Diels-Alder **40a** products did not still show chemical significance (**Table 3.3**, entry 6).

Table 3.3. The Diels-Alder reaction between 4-methylpent-3-en-2-one **38** and 4-fluoro-*trans*-β-nitrostyrene **12a**.[a]



38 **12a** **39a** **40a**

Entry	Catalyst	Conversion (%)[b]	39a:40a[c]	Yield (%)[d]		*ee* (%)[e]	
				39a	40a	39a	40a
1	 *L*-Proline **19**	>99	43:57	22	38	3	0
2	 O_2N-X_L-OMe-**75**	70	5:95	nd[f]	48	nd	40
3	 H_2N-X_L-OMe-**28**	95	45:55	24	32	50	21

4	 O_2N-X_L-X_L-OMe-**34**	>99	34:66	12	61	40	7
5	 O_2N-X_D-X_L^{Me}-OMe-**35**	85	33:67	21	48	-60	-34
6	 O_2N-X_L-X_L^{Me}-OMe-**35**	>99	25:75	12	58	56	26
7[g]		40	20:80	nd	nd	nd	nd
8[h]		30[i]	30:70	nd	nd	nd	nd
9[j]		45[i]	>99:1	nd	nd	nd	nd
10[k]		50	50:50	21	32	56	46

a) The reaction was conducted at 70 °C using 4-methylpent-3-en-2-one **38** (0.10 mmol) and 4-fluoro-*trans*-β-nitrostyrene **12a** (0.10 mmol) in presence of 20 mol% catalyst and 40 mol% $PhCO_2H$. b) Conversions were measured by ^{1}H-NMR of the crude reaction mixtures. c) The **39a**:**40a** ratio was measured by ^{1}H-NMR of the crude reaction mixtures. d) Yield refers to isolated products. e) Enantiomeric excesses measured by HPLC correspond to the major **39a** or **40a** enantiomer. Negative values indicate that the opposite enantiomer was generated. f) nd: not determined. g) Biotage μW, 90 °C, 100 W, 5h. h) Salicylic acid was used as additive. i) Conversion after 6 days. j) Reaction performed at r. t. k) Reaction performed at 45 °C.

With the aim to improve the last results obtained by dipeptide O_2N-X_L-X_L^{Me}-OMe-**35**, we next studied other reaction parameters. Although several trials were performed, none of them resulted to be satisfactory. The use of microwave irradiation as well as the employment of salicylic acid led to poor conversions (**Table 3.3**, entries 7 and 8, respectively). Lowering the temperature down to 45°C and room temperature favoured the formation of the Michael adduct, but did not allow the reaction to get full conversion (**Table 3.3**, entries 9 and 10).

In summary, the results obtained with 4-methylpent-3-en-2-one **38** are not as good as those previously reported with cyclohex-2-en-1-one **36**, both in terms of reactivity and stereoselectivity.

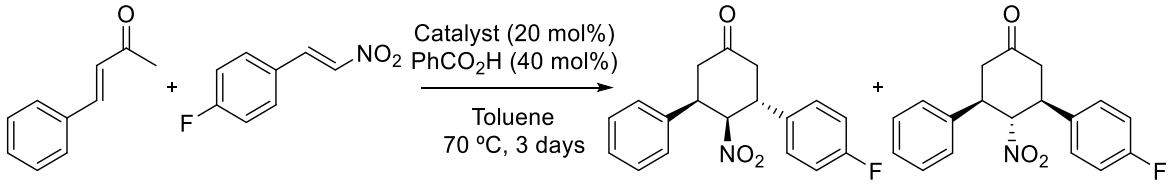
In order to determine the absolute configuration of the unknown products **39a** and **40a** we next moved to analyse the reactivity of (*E*)-4-phenylbut-3-en-2-one **16a**, as the final Diels-Alder adducts have been previously described by Melchiorre and co-workers.[44a] Its employment would also add steric hindrance to the diene and thus possibly enhance the enantioselectivity of the Diels-Alder reaction leading to complex cyclohexanone scaffolds with three contiguous stereogenic centres. Thus, the reaction between **16a** and

4-fluoro-*trans*-β-nitrostyrene **12a** was tested at 70 °C under our previously presented catalysts (**Table 3.4**).

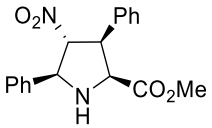
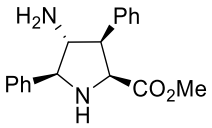
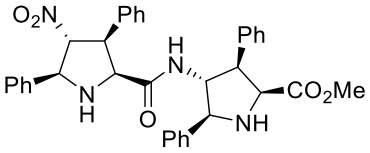
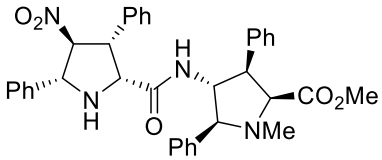
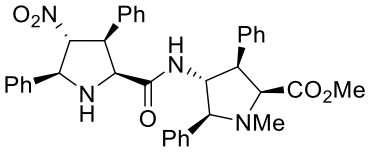
The first generation O_2N-X_L-OMe-**75** led to 60% conversion and poor enantiomeric excess. This monomeric organocatalyts afforded almost equal amounts of both *endo* and *exo* **17aa** diastereomers, although the formation of the latter was slightly favoured (**Table 3.4**, entry 1). The amino derivative H_2N-X_L-OMe-**28** was able to increase the reaction rate reaching almost full conversion. It is worth mentioning that opposite to the nitro congener, this secondary amine catalyst slightly favoured the formation of the *endo* **17aa** cycloadduct. However, neither the diastereo- nor the enantiocontrol of the reaction showed any significant improvement with respect to **75** (**Table 3.4**, entry 2).

The use of O_2N-X_L-X_L-OMe-**35** γ-dipeptide enabled the process to get full conversion. In this case, *endo* preference was also observed, and the diastereomeric ratio increased to a moderate 70:30 ratio. The enantiocontrol also improved, but still exhibited a low 20% *ee* for *exo* **17aa** cycloadduct and a moderate 50% *ee* for *endo* **17aa** (**Table 3.4**, entry 3). Finally, when *N*-methylated dimers were the catalysts of choice, the reactions could only reach approximately 70% conversion (**Table 3.4**, entries 4 and 5). The stereochemical outcome improved considerably, reaching good *endo*:*exo* ratios in both cases. The same trend was observed for the enantiomeric excess values. Nevertheless, the most suitable catalyst O_2N-X_D-X_L^{Me}-OMe-**35** did not exceed a moderate 67% *ee* for the *endo* and 50% *ee* for the *exo* cycloadducts (**Table 3.4**, entry 4). It should be mentioned that no formation of the Michael product was observed in any of these reactions.

Table 3.4. Optimisation conditions for the Diels-Alder reaction of (*E*)-4-phenylbut-3-en-2-one **16a** to 4-fluoro-*trans*-β-nitrostyrene **12a**.[a]



16a **12a** *endo* (3*R*,4*S*,5*R*)-**17aa** *exo* (3*S*,4*R*,5*R*)-**17aa**

Entry	Catalyst	Conversion (%)[b]	*endo*/*exo*[c]	Yield (%)[d]	*ee* (%)[e]	
					endo **17aa**	*exo* **17aa**
1	 O_2N-X_L-OMe-**75**	60	42:58	30	30	37
2	 H_2N-X_L-OMe-**28**	90	60:40	34	37	5
3	 O_2N-X_L-X_L-OMe-**34**	>99	68:32	54	50	20
4	 O_2N-X_D-X_L^{Me}-OMe-**35**	70	90:10	39	-67	-50
5	 O_2N-X_L-X_L^{Me}-OMe-**35**	65	83:17	34	66	35

a) The reaction was conducted at 70 °C using (*E*)-4-phenylbut-3-en-2-one **16a** (0.10 mmol) and 4-fluoro-*trans*-β-nitrostyrene **12a** (0.10 mmol) in presence of 20 mol% catalyst and 40 mol% $PhCO_2H$. b) Conversions were measured by ^{1}H-NMR of the crude reaction mixtures. c) The *endo*/*exo* ratio was measured by ^{1}H-NMR of the crude reaction mixtures. d) Yield refers to the sum of both diastereomers. e) Enantiomeric excesses measured by HPLC correspond to the major *endo* **17aa** or *exo* **17aa** enantiomer. Negative values indicate that the opposite enantiomer was generated.

The stereochemisty of the *exo* **17aa** cycloadduct was unambiguously determined by X-Ray diffraction analysis. The absolute configuration for all C3, C4 and C5 asymmetric carbons was *S*, *R*, *R*, respectively, as it is shown in **Figure 3.2**.

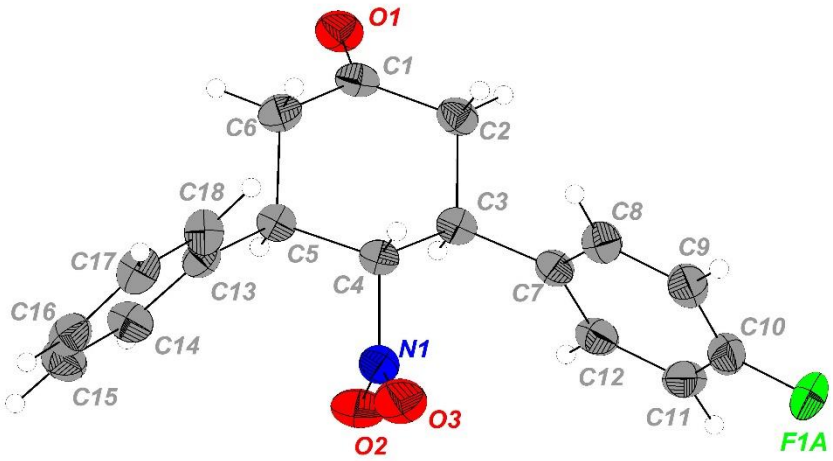


Figure 3.2. ORTEP diagram with thermal ellipsoids in 50% probability of the *exo* (3*S*,4*R*,5*R*)-**17aa** cycloadduct.

3.6 PRELIMINARY COMPUTATIONAL STUDIES

A preliminary computational study performed in our laboratory has permitted to identify the chief geometric and energetic features of the catalytic cycle associated with these enamine-mediated Diels-Alder (EMDA) reactions. These calculations were performed at the M06-2X/6-31G(d)//B3LYP/6-31G(d) level of theory.[55,56,57,58] We chose

[55] M06-2X functional: Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
[56] B3LYP functional: a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.
[57] 6-31G(d) basis set: Hehre, W. J.; Random, L.; Schleyer, P. V. Pople, J. A. *Ab Initio Molecular Orbital Theory*, Wiley: New York, **1986**.
[58] Gaussian 09 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision E.01, Gaussian, Inc., Wallingford CT, **2013**.

the reaction between methyl vinylketone **R1a** and ethylene **R2a** in the presence of pyrrolidine **Ca** as a suitable parent reaction in order to determine the main features of the reaction in the absence of substituents. The relative Gibbs energies, calculated at 298 K of the most relevant species involved in the catalytic cycle of this model reaction are gathered in **Figure 3.3**.

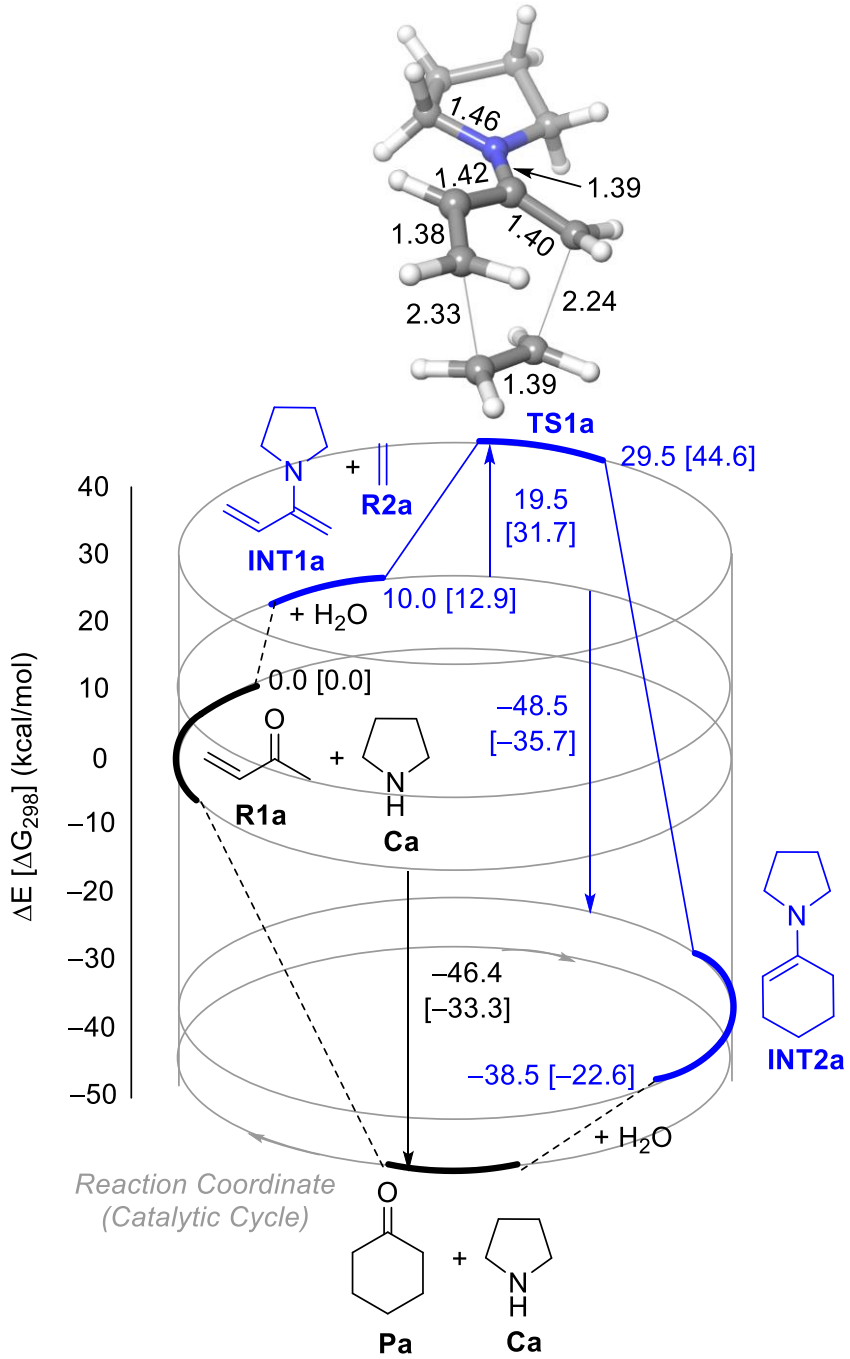


Figure 3.3. Relative energies and relative free energies (in square brackets, at 298 K), in kcal/mol, of the most relevant stationary points associated with the reaction between methyl vinylketone **R1a** and ethylene **R2a** catalysed by pyrrolidine **Ca**. All calculations were performed at the M06-2X/6-31-G(d)//B3LYP/6-31G(d) level of theory. Bond distances of transition structure **TS1a** are given in Å.

According to our calculations, formation of enamine **INT1a** is endothermic, with a relative free energy of ca. 13 kcal/mol with respect to the reactants. According to other calcutions performed with other enamine catalysed processes, it is most likely that this pre-EMDA step has a noticeable activation energy, and is therefore one of the steps responsible for the long reaction times to complete the catalytic cycle.[59]

The Diels-Alder reaction between dienamine **INT1a** and ethylene **R2a** yields enamine **INT2a** with a calculated activation energy of ca. 20 kcal/mol that results in ca. 32 kcal/mol in terms of Gibbs activation energy, because of the negative activation entropy of this bimolecular step. The calculated geometric features of this saddle point show a quite synchronous structure, with the C-C bonds being formed in the short range of 2.2-2.3 Å. It is expected that more polarised dienophiles such as nitroalkenes result in more asynchronous transition structures and lower activation energies. This EMDA process is, however, exergonic with a ΔG_{rxn} value of ca. -23 kcal/mol. From this enamine intermediate **INT2a** the reaction product cyclohexanone **Pa** and the concomitant release of the catalyst **Ca** via hydrolisis of **INT2a** complets the catalytic cycle with a total Gibbs reaction energy of -33.3 kcal/mol with respect to methyl vinyl ketone **R1a** and pyrrolidine **Ca**. This ensures the thermodinamic feasibility of the catalytic reaction, although both the formation and hydrolisis of the enamine intermediates **INT1a** and **INT2a** are the ultimate responsibles for the long reaction times and relatively high catalytic loads (*vide supra*).

3.7 CONCLUSIONS

From the experimental and computational studies reported and discussed along this Chapter, the following conclusions can be drawn:

1. The three generations of unnatural proline based organocatalysts have demonstrated to catalyse the dienamine mediated Diels-Alder reaction of cyclohex-2-en-1-one. Among the tested derivatives, *N*-methylated O_2N-X_L-X_L^{Me}-OMe-**35** γ-dipeptide showed the best performance, yielding the *exo* cycloadduct with good diastereomeric ratio and high enantiomeric excess.
2. The unnatural proline based organocatalysts that bear *exo*-L monomeric units led to opposite enantiomers to those previously reported by Xu and co-workers, in which the catalytic activity was exerted by a Proline derived secondary amine with *L* configuration. Dipeptide O_2N-X_D-X_L^{Me}-OMe-**35** in which the catalytic activity is

[59] a) Ashley, M. A.; Hirschi, J. S.; Izzo, J. A.; Vetticatt, M. J. *J. Am. Chem. Soc*. **2016**, *138*, 1756-1759. b) Renzi, P.; Hioe, J.; Gschwind, R. M. *Acc. Chem. Res*. **2017**, *50*, 2936-2948. c) Haindl, M. H.; Hioe, J.; Gschwind, R. M. *J. Am. Chem. Soc*. **2015**, *137*, 12835-12842.

fulfilled by the first *exo*-D monomeric unit enables the same enantiomer to the reported.

3. Several aromatic and heteroaromatic nitroolefins were studied so as to assess the versatility of O_2N-X_L-X_L^{Me}-OMe-**35** dipeptide. The Diels-Alder reaction proceeded uneventfully furnishing the corresponding *exo* cycloadducts in moderate yields, good diastereocontrol and excellent enantiomeric excesses. Aromatic nitroalkenes with *para*- substitution exhibited higher yields than the *meta*-counterpart.
4. The employment of acyclic enones led to poorer results, and no general trend could have been established concerning the different behaviours of the catalysts. The use of 4-methylpent-3-en-2-one gave rise to mixtures of Michael and Diels-Alder products with low to moderate enantiomeric excesses. When (*E*)-4-phenylbut-3-en-2-one was the ketone of choice the nitro O_2N-X_L-OMe-**75** catalyst showed a preferential formation of the *exo* cycloadduct with low *ee*-s. On the contrary, second and third generation of catalysts favoured the generation of *endo* cycloadducts. The best stereochemical outcome was exerted by O_2N-X_L-X_L^{Me}-OMe-**35** dipeptide, but the reaction could not reach full conversion.

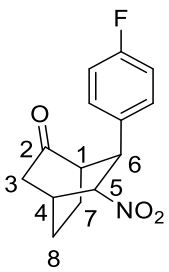
3.8 EXPERIMENTAL SECTION

General remarks

See Chapter 2 section 2.8

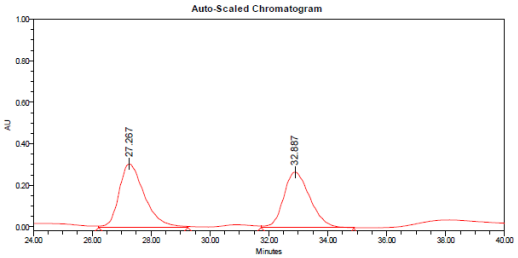
General Procedure for the Diels-Alder reaction

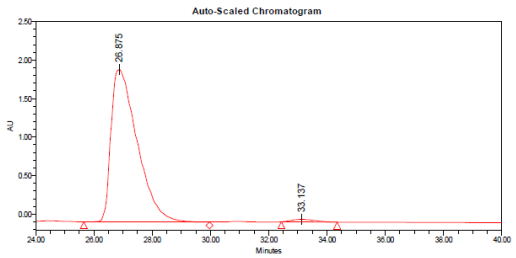
A reaction mixture of the required catalyst (0.02 mmol, 0.2 eq.), $PhCO_2H$ (0.04 mmol, 0.4 eq.), α,β-unsaturated ketone **36, 38, 25a** (0.10 mmol, 1.0 eq.) and nitroolefins **12a-h** (0.11 mmol, 1.1 eq.) in toluene was stirred at 45 °C or 70 °C. The progress of the reactions were monitored by ^{1}H-NMR spectroscopy. After total consumption of the nitroalkene, the crude mixture was evaporated under reduced pressure and purified by flash column chromatography on silica gel (check each compound for conditions). The synthesis of racemic compounds was carried out by *D*/*L*-Proline (0.04 mmol, 0.4 eq.).



(1R,4R,5R,6S)-6-(4-fluorophenyl)-5-nitrobicyclo[2.2.2]octan-2-one (*exo* **37a**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and 4-fluoro-*trans*-β-nitrostyrene **12a** employing catalyst O_2N-X_L-X_L^{Me}-OMe**-35**. Purified on 1:1 Et_2O:Hexane mixture. Global yield 65% (0.065 mmol, 17 mg), white solid. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR**

(400 MHz, CDCl3) δ 7.11 – 7.04 (m, 2H, ArH), 7.04 – 6.96 (m, 2H, ArH), 4.73 (dt, *J* = 6.7, 2.0 Hz, 1H, C^5H), 4.13 (dt, *J* = 6.0, 3.2 Hz, 1H, C^6H), 2.97 (q, *J* = 2.9 Hz, 1H, C^4H), 2.66 (q, *J* = 2.7 Hz, 1H, C^1H), 2.53 – 2.46 (m, 2H, C^3H), 2.27 – 2.18 (m, 1H, C^7H), 2.01 – 1.87 (m, 2H, C^8H, C^7H), 1.79 – 1.66 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 27.27 min, t_R (minor) = 32.89 min; *ee* = 97%.





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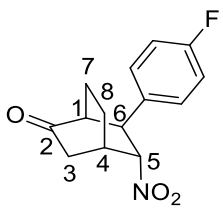
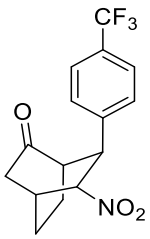
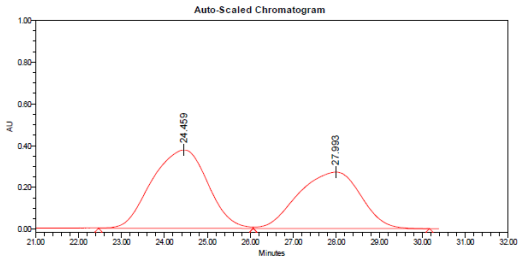
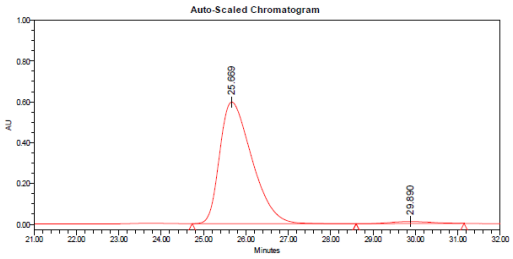


(1S,4S,5R,6S)-6-(4-fluorophenyl)-5-nitrobicyclo[2.2.2]octan-2-one (*endo* **37a**). The title product was obtained from cyclohex-2-en-1-one **36** and 4-fluoro-*trans*-β-nitrostyrene **12a** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:1 Et_2O:Hexane mixture. Global yield 65% (0.065 mmol, 17 mg), yellow oil. The relative configuration has been assumed considering the same configuration for the 6-(4-fluorophenyl) substituent. **FTIR** (neat, cm^{-1}) 2954, 2922, 1728, 1549, 1376. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.6, 5.3 Hz, 2H, ArH), 7.09 (t, *J* = 8.6 Hz, 2H, ArH), 5.03 (dt, *J* = 6.8, 1.9 Hz, 1H, C^5H), 4.07 (d, *J* = 6.8 Hz, 1H, C^6H), 3.02 (m, 1H, C^4H), 2.63 (dt, *J* = 19.5, 2.6 Hz, 1H, C^3H), 2.50 (d, *J* = 2.7 Hz, 1H, C^1H), 2.30 (ddd, *J* = 19.4, 3.0, 1.4 Hz, 1H, C^3H), 2.03 – 1.82 (m, 3H, C^8H, C^7H), 1.79 – 1.67 (m, 1H, C^7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.41 (C=O), 163.61 (ArC), 133.57 (ArC), 129.12 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, ArC), 116.35 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, ArC), 88.11 (C^5), 48.91 (C^1), 42.04 (C^6), 38.66 (C^3), 34.80 (C^4), 24.10 (C^7), 16.86 (C^8). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.23. **HRMS** (ESI) for $C_{14}H_{15}FNO_3$: calculated $[M+H]^+$: 264.1036, found 264.1033.



(1R,4R,5R,6S)-5-nitro-6-(4-(trifluoromethyl)phenyl)bicycle[2.2.2]octan-2-one (*exo* **37b**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and 4-trifluoromethyl-*trans*-β-nitrostyrene **12b** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:3 EtOAc:Hexane mixture. Global yield 69% (0.069 mmol, 22 mg), pale yellow solid. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H, ArH), 7.25 (d, *J* = 9.0 Hz, 2H, ArH), 4.75 (dt, *J* = 6.8, 1.9 Hz, 1H, C^5H), 4.22 (dd, *J* = 6.7, 1.9 Hz, 1H, C^6H), 3.01 (q, *J* = 2.9 Hz, 1H, C^4H), 2.74 – 2.67 (m, 1H, C^1H), 2.61 – 2.43 (m, 2H, C^3H), 2.24 (ddt, *J* = 15.4, 12.0, 3.8 Hz, 1H, C^7H), 1.96 (m, 2H, C^8H, C^7H), 1.82 – 1.68 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 24.46 min, t_R (minor) = 27.99 min; *ee* = 96%.





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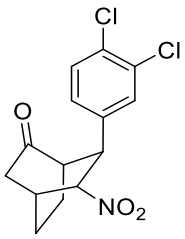
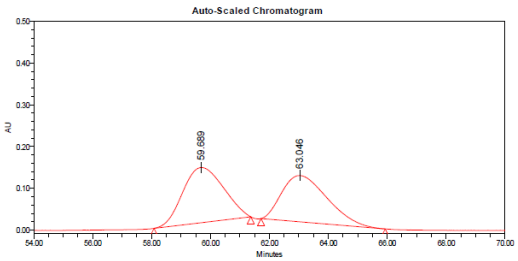
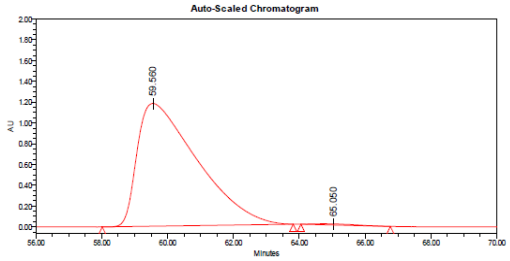


(1R,4R,5R,6S)-6-(3,4-dichlorophenyl)-5-nitrobicyclo[2.2.2]octan-2-one (*exo* **41c**). The title product was obtained from cyclohex-2-en-1-one **36** and 3,4-dichloro-*trans*-β-nitrostyrene **12c** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:3 EtOAc:Hexane mixture. Global yield 54% (0.054 mmol, 17 mg), white solid. $\mathbf{m_p}$ = 97-99 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +14.34 (*c* 0.25, chloroform). **FTIR** (neat, cm^{-1}) 2952, 2922, 1726, 1547, 1372. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.3 Hz, 1H, ArH), 7.27 – 7.21 (m, 1H, ArH), 6.94 (d, *J* = 8.3, 1H, ArH), 4.70 (dt, *J* = 6.8, 2.0 Hz, 1H, C^5H), 4.11 (dd, *J* = 6.7, 2.0 Hz, 1H, C^6H), 3.00 (m, 1H, C^4H), 2.65 (m, 1H, C^1H), 2.54 – 2.45 (m, 2H, C^3H), 2.20 (ddt, *J* = 15.5, 12.1, 4.0 Hz, 1H, C^7H), 1.94 (m, 2H, C^8H, C^7H), 1.80 – 1.67 (m, 1H, C^8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.21 (C=O), 141.22(ArC), 133.50 (ArC), 132.26 (ArC), 131.32 (ArC), 129.32 (ArC), 126.23 (ArC), 90.76 (C^5), 47.38 (C^1), 44.29 (C^2), 42.36 (C^3), 34.34 (C^4), 23.32 (C^7),

18.25 (C^8). **HRMS** (ESI) for $C_{14}H_{14}Cl_2NO_3$: calculated $[M+H]^+$: 314.0350, found 314.0352. **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 97:3, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 59.56 min, t_R (minor) = 63.05 min; *ee* = 98%.





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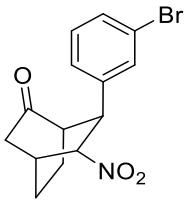
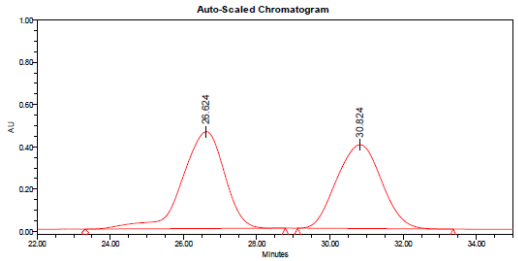
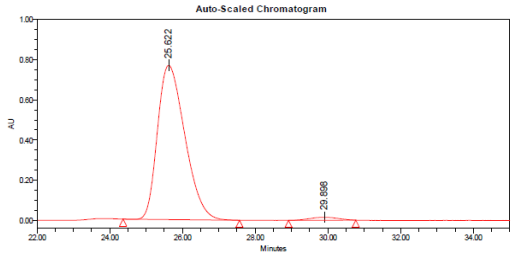


(1R,4R,5R,6S)-6-(3-bromophenyl)-5-nitrobicyclo[2.2.2]octan-2-one (*exo* **37d**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and 3-bromo-*trans*-β-nitrostyrene **12d** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:3 EtOAc:Hexane mixture. Global yield 35% (0.035 mmol, 11 mg), yellow oil. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 1H, ArH), 7.19 (t, *J* = 7.9 Hz, 2H, ArH), 7.05 – 7.00 (m, 1H, ArH), 4.76 (dt, *J* = 6.7, 2.2 Hz, 1H, C^5H), 4.12 (dd, *J* = 6.9, 1.9 Hz, 1H, C^6H), 3.00 – 2.94 (m, 1H, C^4H), 2.67 (q, *J* = 2.7 Hz, 1H, C^1H), 2.54 – 2.47 (m, 2H, C^3H), 2.20 (ddd, *J* = 12.0, 9.8, 5.7 Hz, 1H, C^7H), 1.99 – 1.86 (m, 2H, C^8H, C^7H, C^8H), 1.79 – 1.64 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 26.62 min, t_R (minor) = 29.89 min; *ee* = 96%.





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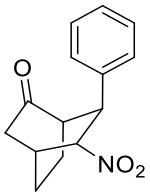
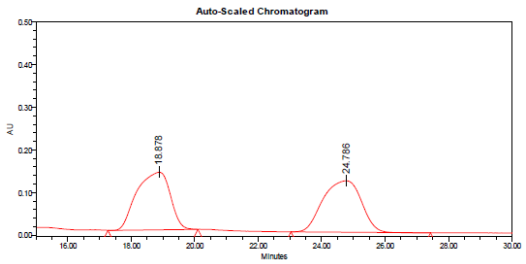
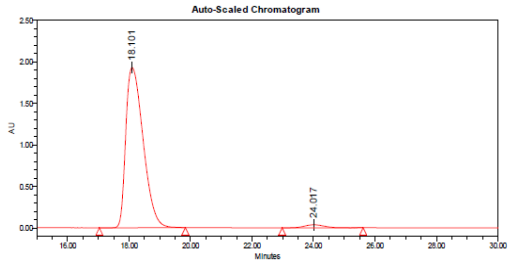


(1R,4R,5R,6S)-5-nitro-6-phenylbicyclo[2.2.2]octan-2-one (*exo* **37e**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and *trans*-β-nitrostyrene **12e** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:3 EtOAc:Hexane mixture. Global yield 61% (0.061 mmol, 15 mg), white solid. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.2, 6.4 Hz, 2H, ArH), 7.27 (d, *J* = 4.9 Hz, 1H, ArH), 7.10 (dd, *J* = 7.2, 1.8 Hz, 2H, ArH), 4.82 (dt, *J* = 6.8, 2.0 Hz, 1H, C^5H), 4.17 – 4.14 (m, 1H, C^6H), 2.97 (q, *J* = 2.9 Hz, 1H, C^4H), 2.69 (q, *J* = 2.7 Hz, 1H, C^1H), 2.50 (t, *J* = 2.9 Hz, 2H, C^3H), 2.28 – 2.16 (m, 1H, C^7H), 1.94 (m, 2H, C^8H, C^7H), 1.78 – 1.65 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 18.88 min, t_R (minor) = 24.78 min; *ee* = 95%.





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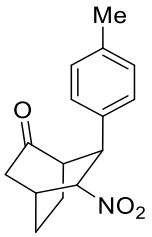
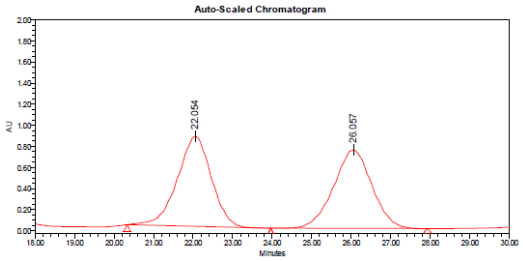
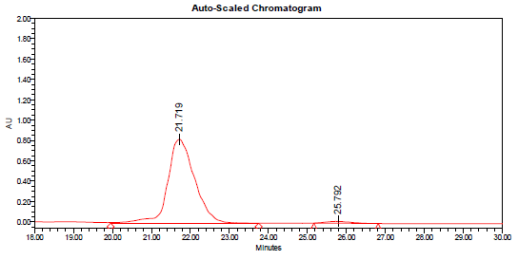


(1R,4R,5R,6S)-5-nitro-6-(p-tolyl)bicyclo[2.2.2]octan-2-one (*exo* **37f**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and 4-methyl-*trans*-β-nitrostyrene **12f** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:2 EtOAc:Hexane mixture. Global yield 51% (0.051 mmol, 13 mg), pale brown solid. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.9 Hz, 2H, ArH), 6.98 (d, *J* = 8.0 Hz, 2H, ArH), 4.80 (ddd, *J* = 6.6, 2.6, 1.6 Hz, 1H, C^5H), 4.10 (dd, *J* = 6.6, 2.0 Hz, 1H, C^6H), 2.96 (q, *J* = 2.9 Hz, 1H, C^4H), 2.66 (q, *J* = 2.7 Hz, 1H, C^1H), 2.49 (t, *J* = 2.6 Hz, 2H, C^3H), 2.26 – 2.15 (m, 1H, C^7H), 1.94 (m, 2H, C^8H, C^7H), 1.75 – 1.65 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 22.05 min, t_R (minor) = 26.06 min; *ee* = 96%.





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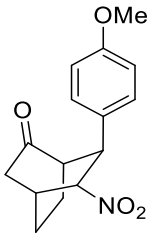
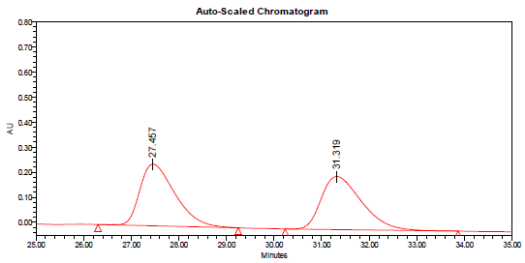
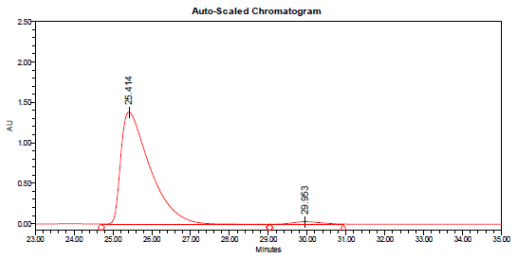


(1R,4R,5R,6S)-6-(4-methoxyphenyl)-5-nitrobicyclo[2.2.2]octan-2-one (*exo* **37g**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and 4-methoxy-*trans*-β-nitrostyrene **12g** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:3 EtOAc:Hexane mixture. Global yield 47% (0.047 mmol, 13 mg), yellow solid. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.5 Hz, 2H, ArH), 6.85 – 6.78 (m, 2H, ArH), 4.77 (dt, *J* = 6.8, 2.0 Hz, 1H, C^5H), 4.08 (dd, *J* = 6.6, 2.1 Hz, 1H, C^6H), 3.77 (s, 3H, OCH_3), 2.95 (m, 1H, C^4H), 2.65 (d, *J* = 2.7 Hz, 1H, C^1H), 2.48 (q, *J* = 2.9, 2.5 Hz, 2H, C^3H), 2.25 – 2.15 (m, 1H, C^7H), 1.93 (m, 2H, C^8H, C^7H), 1.69 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 27.46 min, t_R (minor) = 31.32 min; *ee* = 96%.





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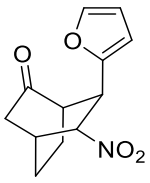
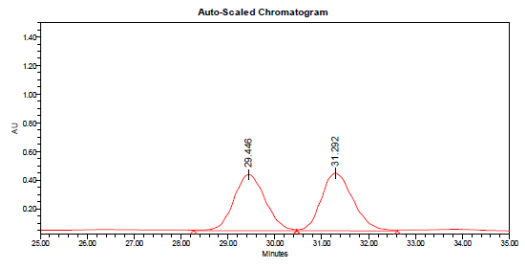
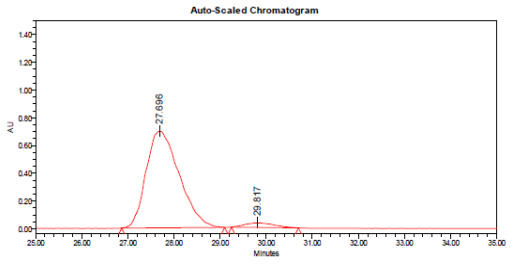


(1R,4R,5R,6R)-6-(furan-2-yl)-5-nitrobicyclo[2.2.2]octan-2-one (*exo* **37h**).[48] The title product was obtained from cyclohex-2-en-1-one **36** and 2-(2-nitrovinyl)furan **12h** employing catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:3 EtOAc:Hexane mixture. Global yield 47% (0.047 mmol, 13 mg), white solid. Analytic and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.8 Hz, 1H, ArH), 6.27 (dd, *J* = 3.3, 1.9 Hz, 1H, ArH), 6.12 (d, *J* = 3.3 Hz, 1H, ArH), 4.93 (ddd, *J* = 5.0, 3.1, 1.6 Hz, 1H, C^5H), 4.27 (dd, *J* = 5.3, 2.5 Hz, 1H, C^6H), 2.98 (m, 1H, C^4H), 2.70 (m, 1H, C^1H), 2.46 (m, 2H, C^3H), 2.15 (m, 1H, C^7H), 1.98 – 1.87 (m, 1H, C^8H), 1.85 – 1.77 (m, 1H, C^7H), 1.71 – 1.59 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 208 nm), t_R (major) = 29.44 min, t_R (minor) = 31.92 min; *ee* = 92%.





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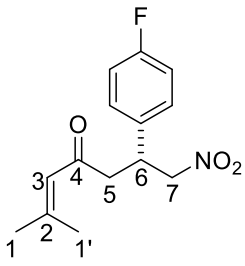
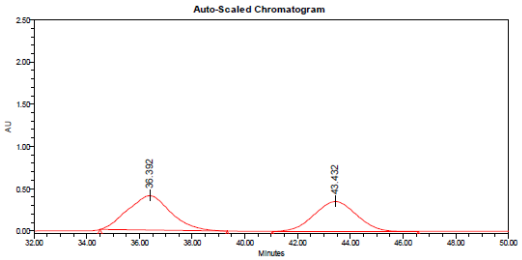
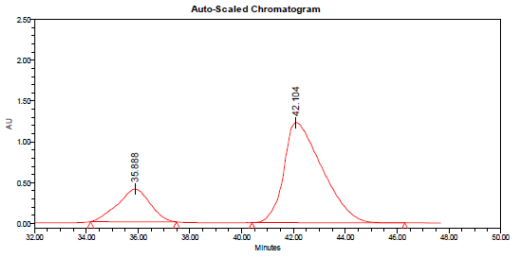


(R)-6-(4-fluorophenyl)-2-methyl-7-nitrohept-2-en-4-one (**39a**). The title product was obtained from 4-methylpent-3-en-2-one **38** and 4-fluoro-*trans*-β-nitrostyrene **12a**, in a 25:75 **39a**:**40a** ratio with catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. The relative configuration has been determined considering the absolute configuration of **26aa**. Purified on 1:2 EtOAc:Hexane mixture. Yield 12% (0.012 mmol, 4 mg), yellow oil. $[\alpha]_D^{25}$ = -16.27 (*c* 0.15, chloroform). **FTIR** (neat, cm^{-1}) 2919, 2850, 1684, 1551, 1377. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H, ArH), 7.00 (t, *J* = 8.6 Hz, 2H, ArH), 6.04 – 5.98 (m, 1H, C^3H), 4.72 (dd, *J* = 12.4, 6.3 Hz, 1H, C^7H), 4.56 (dd, *J* = 12.4, 8.4 Hz, 1H, C^7H), 4.04 (dd, *J* = 8.1, 6.5 Hz, 1H, C^6H), 2.84 (d, *J* = 7.1 Hz, 2H, C^5H), 2.11 (d, *J* = 1.1 Hz, 3H, CH_3^1), 1.88 (d, *J* = 1.3 Hz, 3H, $CH_3^{1'}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.79 (C=O), 162.30 (d, $^1J_{C\text{-}F}$ = 246.7 Hz, ArC), 157.75 (C^2), 135.15 (ArC), 129.21 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, ArC), 123.30 (ArC), 116.03 (d, $^2J_{C\text{-}F}$ = 21.5 Hz, ArC), 79.83 (C^7), 46.82 (C^5), 38.83 (C^6), 27.91 (CH_3^1), 21.11 ($CH_3^{1'}$). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.50. **HRMS** (ESI) for $C_{14}H_{16}FNO_3$: calculated $[M+H]^+$: 266.1192, found 266.1180. **HPLC** (Daicel Chiralcel OJ-H, Hexane:^{i}PrOH = 90:10, flow rate 1 mL/min, λ = 214 nm), t_R (minor) = 36.39 min, t_R (major) = 43.43 min; *ee* = 56%.





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2	43.432	353504	39263108	46.00

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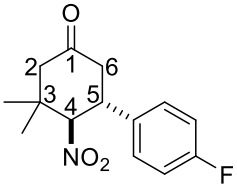
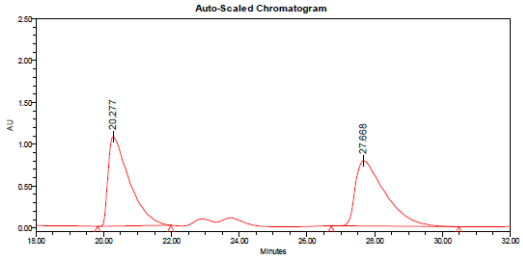
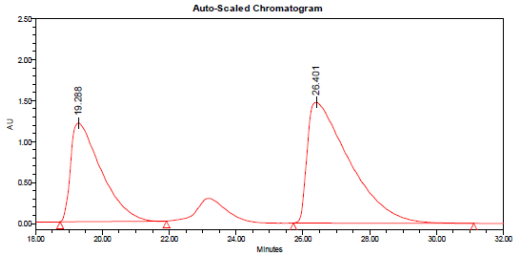


(4R,5R)-5-(4-fluorophenyl)-3,3-dimethyl-4-nitrocyclohexan-1-one (**40a**). The title product was obtained from 4-methylpent-3-en-2-one **38** and 4-fluoro-*trans*-β-nitrostyrene **12a**, in a 25:75 **39a**:**40a** ratio with catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. The relative configuration has been determined considering the absolute configuration of **26aa**. Purified on 1:2 EtOAc:Hexane mixture. Yield 58% (0.058 mmol, 15 mg), yellow oil. $[\alpha]_D^{25}$ = -23.82

(*c* 0.17, chloroform). **FTIR** (neat, cm^{-1}) 3054, 2969, 1721, 1551, 1378. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H, ArH), 7.03 (t, *J* = 8.5 Hz, 2H, ArH), 4.98 (d, *J* = 12.0 Hz, 1H, C^5H), 3.77 (td, *J* = 12.5, 5.4 Hz, 1H, C^4H), 2.67 (ddd, *J* = 15.1, 5.7, 2.3 Hz, 1H, C^6H), 2.55 (d, *J* = 14.6 Hz, 2H, C^6H, C^2H), 2.38 (dd, *J* = 14.2, 2.3 Hz, 1H, C^2H), 1.23 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.98 (C=O), 162.50 (d, $^{1}J_{C\text{-}F}$ = 247.7 Hz, ArC), 134.02 (ArC), 128.99 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, ArC), 116.33 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, ArC), 97.19 (C^4H), 53.99 (C^2), 47.00 (C^6), 42.66 (C^5), 38.55 (C^3), 28.88 (CH_3), 21.11 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.59. **HRMS** (ESI) for $C_{14}H_{16}FNO_3$: calculated $[M+H]^+$: 266.1192, found 266.1189. **HPLC** (Daicel Chiralcel OJ-H, Hexane:^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 214 nm), t_R (minor) = 20.28 min, t_R (major) = 27.69 min; *ee* = 26%.





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2	27.688	778829	47589034	50.56

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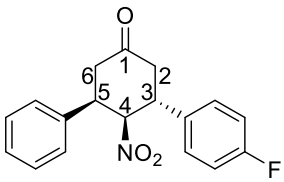
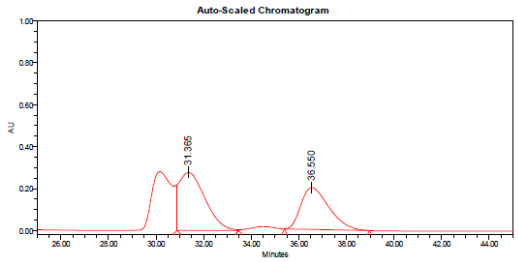
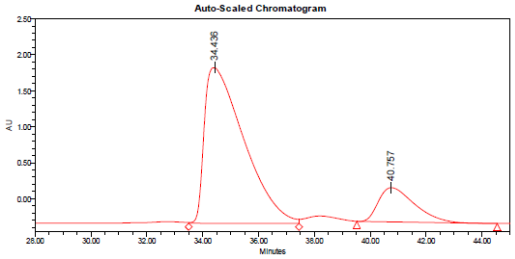
2	26.401	1474496	129174876	62.87



(3R,4S,5R)-3-(4-fluorophenyl)-4-nitro-5-phenylcyclohexan-1-one (*endo* **17aa**). The title product was obtained from (*E*)-4-phenylbut-3-en-2-one **16a** and 4-fluoro-*trans*-β-nitrostyrene **12a** in a 83:17 ***endo/exo*** ratio with catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:1 Et_2O:Hexane mixture. Global yield 34% (0.034 mmol, 11 mg), yellow oil. $[\alpha]_D^{25}$ = +15.97 (*c* 0.30, chloroform). **FTIR** (neat, cm^{-1}) 3054, 2987, 1715, 1551, 1263. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 3H, ArH), 7.27 – 7.16 (m, 3H, ArH), 7.06 (m, 3H, ArH), 5.25 (dd, *J* = 7.5, 4.9 Hz, 1H, C^4H), 3.91 (td, *J* = 8.3, 6.1 Hz, 1H, C^3H), 3.80 (dt, *J* = 8.9, 5.3 Hz, 1H, C^5H), 3.30 (ddd, *J* = 16.0, 8.7, 1.3 Hz, 1H, C^6H), 3.04 (ddd, *J* = 16.3, 5.9, 1.3 Hz, 1H, C^2H), 2.86 (dd, *J* = 16.1, 5.7 Hz, 1H, C^2H), 2.79 (dd, *J* = 16.3, 8.8 Hz, 1H, C^6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.34 (C=O), 162.39 (d, $^{1}J_{C\text{-}F}$ = 247.8 Hz, ArC), 136.77 (ArC), 135.21 (ArC), 129.16 (ArC), 129.03 (ArC), 128.61 (ArC), 127.74 (ArC), 116.44 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz, ArC), 91.62 (C^4), 43.70

(C^6), 42.44 (C^3), 42.12 (C^2), 41.84 (C^5). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -113.64. **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 214 nm), t_R (major) = 31.37 min, t_R (minor) = 36.55 min; *ee* = 66%.





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2	36.550	198730	16289840	43.98

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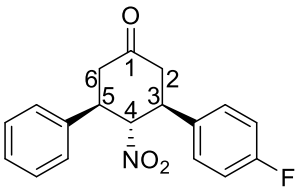
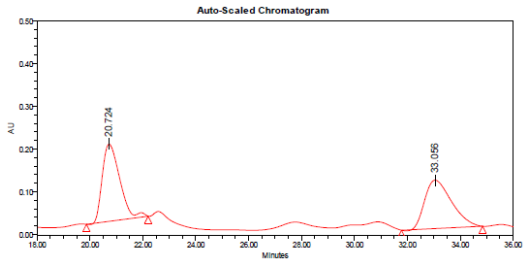
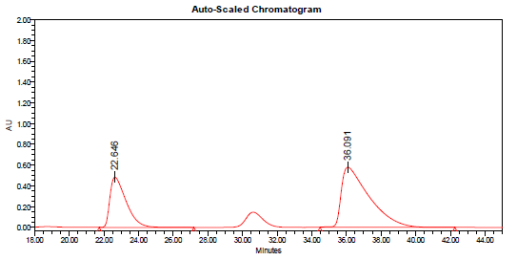


(3S,4R,5R)-3-(4-fluorophenyl)-4-nitro-5-phenylcyclohexan-1-one (*exo* **17aa**). The title product was obtained from (*E*)-4-phenylbut-3-en-2-one **16a** and 4-fluoro-*trans*-β-nitrostyrene **12a** in a 83:17 ***endo/exo*** ratio with catalyst O_2N-X_L-X_L^{Me}-OMe-**35**. Purified on 1:1 Et_2O:Hexane mixture. Global yield 34% (0.034 mmol, 11 mg), yellow oil. $[\alpha]_D^{25}$ = +15.97 (*c* 0.35, chloroform). **FTIR** (neat, cm^{-1}) 3021, 2965, 1720, 1552, 1235. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (m, 3H, ArH), 7.28 – 7.19 (m, 4H, ArH), 7.04 (t, *J* = 8.6 Hz, 2H, ArH), 5.17 (t, *J* = 11.2 Hz, 1H, C^4H), 3.69 (m, 2H, C^3H, C^5H), 2.89 – 2.73 (m, 4H, C^2H, C^6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.16 (C=O), 162.69 (d, $^1J_{C\text{-}F}$ = 247.9 Hz, ArC), 137.36 (ArC), 133.28 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 129.46 (ArC), 128.86 (ArC), 128.77 (ArC), 128.74 (ArC), 127.09 (ArC), 116.45 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, ArC), 94.67 (C^4), 47.65 (C^3), 47.03 (C^5), 46.43 (C^6), 46.38 (C^2). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -113.04. **HPLC** (Daicel Chiralcel OD-H, Hexane:^{i}PrOH = 80:20, flow rate 1 mL/min, λ = 214 nm), t_R (minor) = 20.72 min, t_R (major) = 33.06 min; *ee* = 35%.





	RT	Height	Area	% Area
1	20.724	180924	8293293	50.80
2	33.056	113422	8031357	49.20

	RT	Height	Area	% Area
1	22.646	482299	31309587	32.82
2	36.091	576223	64087010	67.18

Computational details

All stationary points on the potential surface were fully optimised with the hybrid density functional B3LYP[56] and the 6-31G(d)[57] basis set. Harmonic analyses were performed at this level of theory to verify the nature of the corresponding stationary points (minima or transition states), as well as to provide the thermodynamic contributions to the enthalpy and free energy for T = 298 K. Moreover, intrinsic reaction coordinate[60] calculations were performed to ensure that the transition states connect the reactants and products belonging to the reaction coordinate under study. The final energies were obtained by performing single-point M06-2X[55] calculations with the 6-31G(d) basis set at the optimised B3LYP geometries.

[60] a) Ishida, K.; Morokuma, K.; Kormornicki, A. *J. Chem. Phys*. **1977**, *66*, 2153-2156. b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys*. **1989**, *90*, 2154-2161. c) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990,** *94*, 5523-5527.

PART B

Stoichiometric Studies

Chapter 4

1,3-Dioxa-[3,3]-Sigmatropic Rearrangement of Substituted Allyl Carbamates: Scope and Mechanistic Studies

Abstract: An unexpected 1,3-dioxa-[3,3]-sigmatropic rearrangement during the treatment of aryl- and alkenyl-substituted allyl alcohols with activated isocyanates is reported. The reorganization of bonds is highly dependent on the electron density of the aromatic ring and the nature of the isocyanate used. This metal-free tandem reaction from branched allyl alcohols initiated by a carbamoylation reaction and followed by a sigmatropic rearrangement thus offers a new access to (*E*)-cinnamyl and conjugated (*E*,*E*)-diene carbamates such as *N*-acyl and *N*-sulfonyl derivatives. A computational study was conducted in order to rationalise this phenomenon as well as a kinetic analysis of the rearrangement progress.

Part of this Chapter has been published as: Agirre, M.; Henrion, S.; Rivilla, I.; Miranda, J. I.; Cossío, F. P.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. *J. Org. Chem*. **2018**, *83*, 14861-14881.

4.1 SIGMATROPIC REARRANGEMENTS. INTRODUCTION

Sigmatropic shifts comprise a relevant type of concerted pericyclic reactions governed by orbital symmetry. They are defined as a migration of an atom or a group of atoms from one atom to another in the same molecule.[1] Woodward and Hoffmann considered sigmatropic rearrangements of order [*i*,*j*] to be "the migration of a σ bond, flanked by one or more π electron systems, to a new position whose termini are *i*-1 and *j*-1 atoms removed from the original bonded loci, in an uncatalysed, intramolecular process."[2] The total number of σ and π bonds remains unchanged being the latter reorganized in the process. Besides, the order [*i*,*j*] establishes the number of atoms in the migrating fragment and the π system. Figuratively, the numbers indicate how many atoms the σ bond traverses on each side of the cyclic array to form the new bond (**Figure 4.1**).[3]

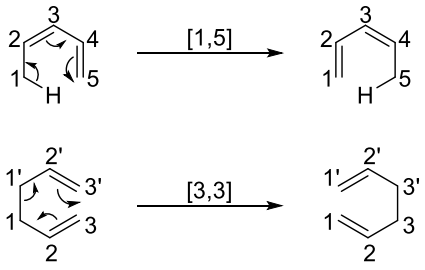


Figure 4.1. [1,5]- and [3,3]-sigmatropic rearrangements of hydrogen and allyl groups.

Due to the concerted nature of these processes, sigmatropic rearrangements can take place regio- and stereoselectively. However, some sigmatropic reactions are not concerted and proceed via radical or ionic intermediates.[4] According to Woodward and Hoffman, there are two topologically distinct processes for a concerted sigmatropic migration to occur, which determine the facility and the stereochemistry of each reaction.[5] In the *suprafacial* process, the transferred group remains associated with the same face of the π system. In the *antarafacial* process the migrating group moves to the opposite face of the π system during the migration (**Figure 4.2**).[6]

[1] Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH: Weinheim, **2005**.
[2] Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res*. **1968**, *1*, 17-22.
[3] Smith, M. B.; March, J. *March's Advanced Organic Chemistry. Reactions, Mechanisms and Structure, 5th Ed*. Wiley & Sons, New York, **2001**.
[4] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: London, **1976**.
[5] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, 5th Ed. Part A: Structure and Mechanisms,* Springer: New York, **2007**.
[6] Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511-2513.

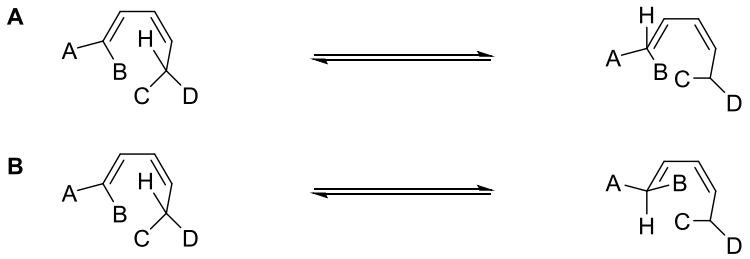


Figure 4.2. A) suprafacial and B) antarafacial approaches for a [1,5] hydrogen rearrangement described by Woodward and Hoffmann.

An alternative analysis results from the Hückel or Möbius classification of the atomic orbitals in which the electrons involved in the process are counted to determine if the transition state is aromatic or antiaromatic.[7] Another important aspect should also be taken into account when the migrating group is an alkyl substituent that possesses an available π orbital. Therein, the migrating group can retain its original configuration or undergo inversion. The stereochemical features in that particular case are aswell determined by the number of electrons involved and follow the symmetry selection rules defined by Woodward and Hoffmann (**Table 4.1** and **Figure 4.3**).[8]

Table 4.1. Woodward-Hoffman rules for sigmatropic reactions.

	Allowed mode			
Number of electrons	**Retention or Hydrogen migration**		**Inversion**	
	Thermal	Photochemical	Thermal	Photochemical
4n	antarafacial	suprafacial	suprafacial	antarafacial
4n+2	suprafacial	antarafacial	antarafacial	suprafacial

[7]a) Schleyer, P. v.; Wu, J. I.: Cossío, F. P.; Fernández, I. *Chem. Soc. Rev*. **2014**, *43*, 4909-4921. b) Zimmerman, H. E.; Marchand, A. P.; Lehr, R. E. *Pericyclic Reactions, Vol. 2*, Academic Press: New York, **1977**. c) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 761-776.
[8] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Verlag Chemie: Weinheim, **1970**.

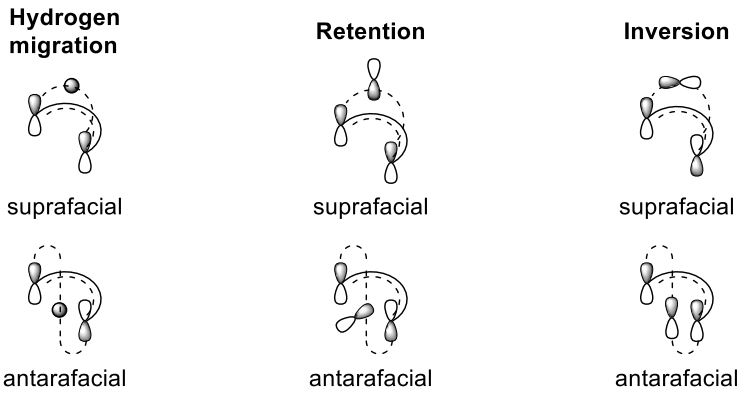


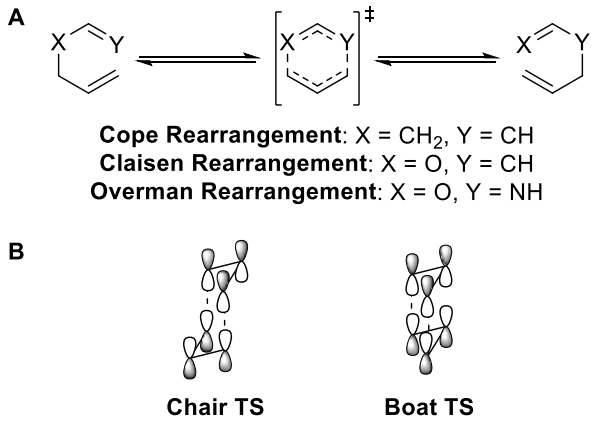
Figure 4.3. Supra- and antarafacial topologies associated with [1,j]-sigmatropic shifts involving hydrogen migration, retention and inversion of configuration of the migrating group.

4.1.1 [3,3]-Sigmatropic rearrangements

Among the existent sigmatropic shifts, the [3,3]-sigmatropic rearrangement constitutes a general and useful procedure for the chemical synthesis of 1,5-dienes or γ,δ-unsaturated carbonyl and related compounds. In fact, recent years have witnessed an impressive growth in the applicability of [3,3]-sigmatropic rearrangements for the generation of complex natural products and modern drugs.[9] There are several different [3,3]-sigmatropic rearrangement variants. Whereas the Cope and the Claisen reactions are prevalent for the obtaining of new carbon-carbon bonds, the Overman rearrangement should be highlighted for carbon-heteroatom bond forming reactions (**Scheme 4.1A**).[10]

One of the main features of these procedures is the formation of six-membered and highly ordered transition states (considered to be two interacting allyl or heteroaryl fragments) where repulsive interactions are minimised. In general, this cyclic transition state adopts a chair-like conformation, although a boat-like conformation is also possible (**Scheme 4.1B**).[5]

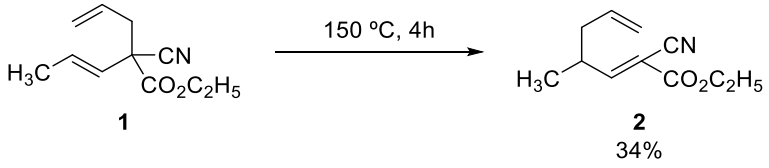
[9] Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev*. **2009**, *38*, 3133-3148.
[10] Wang, Z. *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons: Hoboken, **2010**.



Scheme 4.1. A) General [3,3] sigmatropic shifts. B) Chair-like and boat-like supra-supra structures for the transition states.

4.1.1.1 Cope rearrangements

The thermal all-carbon Cope rearrangement of 1,5-hexadienes was discovered by Arthur Cope in 1940.[11] Therein, ester **1** completely rearranged to the isomeric product **2** when heated to 150 °C. During the process the allyl group shifts from a more electron-attracting carbon to one which is less electron-attracting and conjugated with the cyano and the carbonyl groups (**Scheme 4.2**).

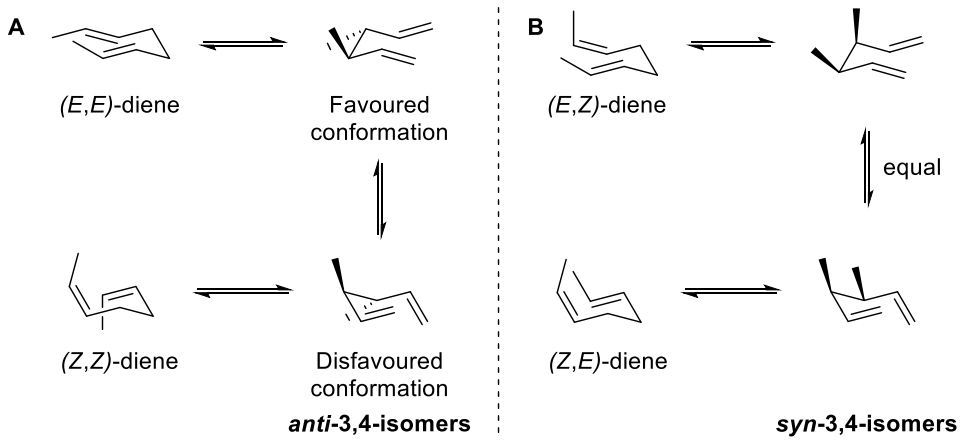


1 **2**
34%

Scheme 4.2. The thermal [3,3]-rearrangement of 1,5 hexadiene **1** discovered by Cope.

The Cope rearrangement is both stereospecific and stereoselective. In this regard, the *(Z)*- or *(E)*- configuration at either double bond is maintained in the transition state governing the relationship of the single bond generated in the final product.[12] When a chair-like TS is favoured, *(E*,*E)*- and *(Z*,*Z)*- dienes give rise to *anti*-3,4-diastereomers. On the contrary, *(E*,*Z)*- and *(Z*,*E)*- isomers lead to *syn*-3,4-products (**Scheme 4.3**). In addition, the reaction is also stereoselective in regard to the newly formed double bond, being the *(E)*- arrangement normally favoured. When enantiomerically pure starting materials are used, stereospecificity establishes that the chiral information is maintained throughout the course of the reaction.[13]

[11] Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc*. **1940**, *62*, 441-444.
[12] Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67-74.
[13] Hill, R. K.; Gilman, N. W. *Chem. Commun*. **1967**, 619-620.



Scheme 4.3. Stereochemical rules for the Cope Rearrengements. A) (*E*,*E*)- and (*Z*,*Z*)- dienes. B) (*E*,*Z*)- and (*Z*,*E*)- dienes.

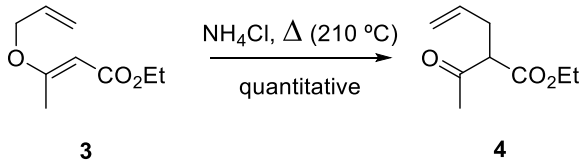
Due to the fact that there is no change in the number or type of bonds in the chemical process, Cope rearrangements are reversible reactions. This reversibility presents a challenge for synthetic and practical purposes and additional requirements must be taken into consideration in order to reassure the unique sense of the process. The strain-release strategy[14], ion stabilization (oxy-Cope)[15], introduction of aromaticity[16] and inclusion in domino processes[17] have found to be reliable methodologies to provide a significant thermodynamic driving force towards the desired final product. The first two strategies are commonly used for asymmetric versions in which complex natural products are synthesised.[18] The former takes advantage of cyclopropanation/Cope[19] and cyclobutanation/Cope[20] rearrangement duets and allows the reaction to occur with complete conversion at much lower temperatures. The latter, on the other hand, makes

[14] a) Brown, J. M.; Bolding, B. T.; Stofko, J. F. Jr. *Chem. Commun*. **1973**, 319-320. b) Schneider, M. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 707-708. c) Schneider, M. P.; Rau, A. *J. Am. Chem. Soc*. **1979**, *101*, 4426-4427.
[15] For some examples, check: a) Berson, J. A.; Jones, M. Jr. *J. Am. Chem. Soc*. **1964**, *86*, 5019-5020. b) Berson, J. A.; Walsh, E. J. Jr. *J. Am. Chem. Soc*. **1968**, *90*, 4730-4732. c) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765-4766.
[16] For selected examples, see: a) Miller, B. *J. Am. Chem. Soc*. **1965**, *87*, 5115-5120. b) Kawasaki, T.; Nonaka, Y.; Watanabe, K.; Ogawa, A.; Higuchi, K.; Terashima, R.; Masuda, K.; Sakamoto, M. *J. Org. Chem*. **2001**, *66*, 1200-1204. c) Bramley, R. K.; Grigg, R. *J. Chem. Soc. D*. **1969**, 99b-100.
[17] a) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc*. **1995**, *117*, 5776-5788. b) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971-14020.
[18] a) Nubbemeyer, U. *Synthesis* **2003**, 961-1008. b) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2014**, *53*, 2556-2591.
[19] For recent selected examples, check: a) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc*. **2006**, *128*, 2609-2614. b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed*. **2007**, *46*, 3410-3449. c) Hashmi, A. S. K. *Angew. Chem., Int. Ed*. **2008**, *47*, 6754-6756. d) Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329-8332. e) Felix, R. J.; Weber, D.; Gutierrez, O.; Tantillo, D. J.; Gagné, M. R. *Nat. Chem*. **2012**, *4*, 405-409.
[20] a) Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. K. *J. Am. Chem. Soc*. **1989**, *111*, 5312-5320. b) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc*. **2000**, *122*, 8071-8072.

the reaction irreversible by the keto-enol tautomerization of the C-3 hydroxy substituent of the diene system.[21]

4.1.1.2 Claisen rearrangements

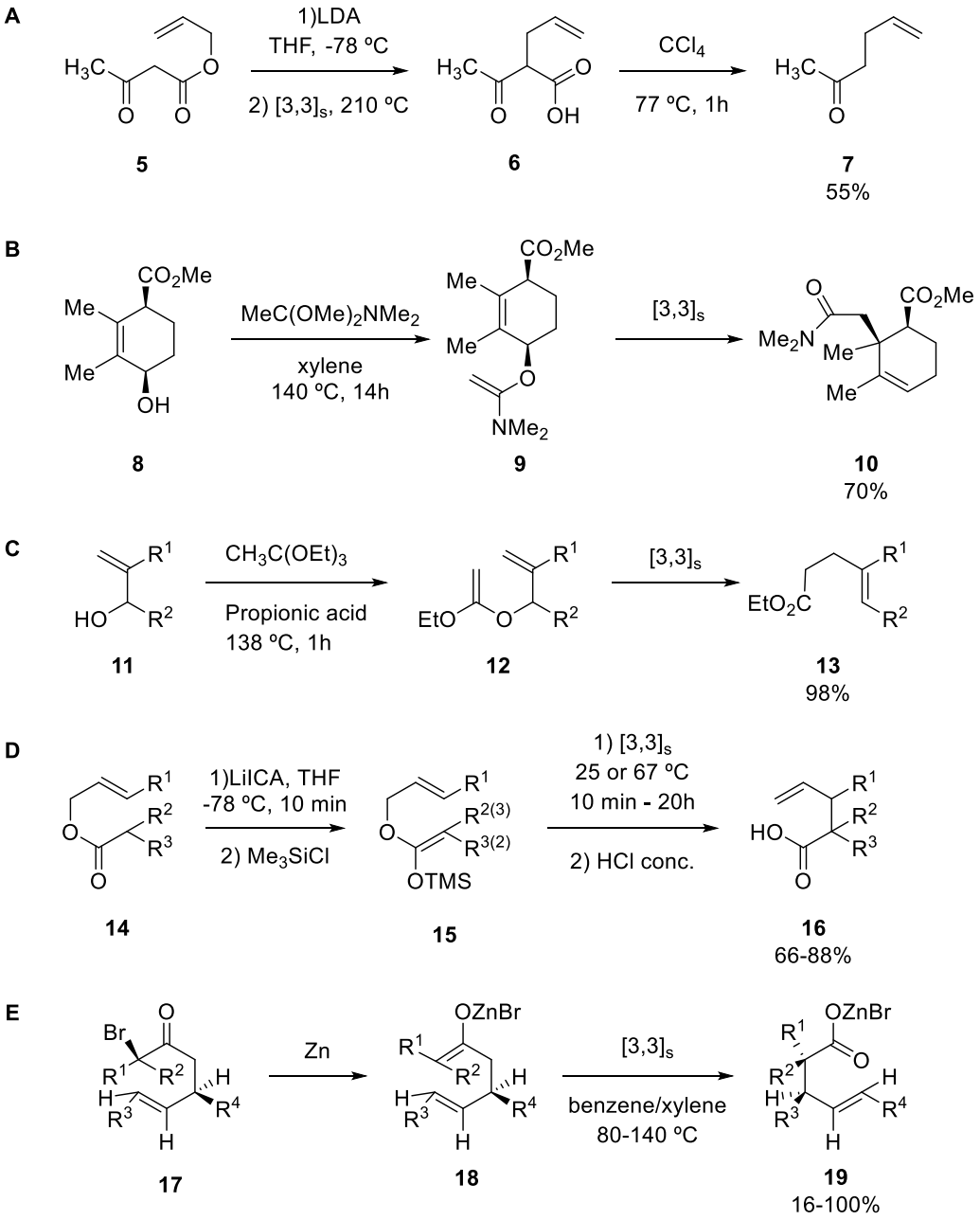
The Claisen rearrangement is a thermal [3,3]-sigmatropic shift of allyl vinyl ethers that allows the preparation of unsaturated carbonyl compounds. It can also be defined as the heteroatom variant of the Cope rearrangement. This reaction was first described by Ludwig Claisen in 1912 as "the thermal isomerization of an allyl vinyl ether -or of its nitrogen or sulphur containing analogue derivatives- to afford a bifunctionalised molecule in a [π2s + σ2s + π2s] process". [22] This first publication reported the transformation of the *O*-allylated ethyl acetoacetate **3** into its *C*-allyl isomer **4** after distillation in the presence of NH_4Cl (**Scheme 4.4**). Since its discovery, the Claisen rearrangement is the most synthetically useful and widely studied [3,3]-sigmatropic rearrangement mainly due to the ease of generation of the allyl vinyl system and the smooth and irreversible formation of the final product.[18a] Even though the Claisen rearrangement is not strictly irreversible, the reaction equilibria usually tend to the formation of carbonyl-type products.[18b]



Scheme 4.4. The [3,3]-sigmatropic rearrangement of allyl vinyl ether **3** first reported by Claisen.

The stereochemical nature of this reaction is closely related to the features previously described for the Cope rearrangement. The major product has preferentially an (*E*)-configuration in the newly formed double bond because of the placing of the larger substituent in the pseudoecuatorial position in the transition state.[23] Additionally, the presence of the heteroatom makes it a rather interesting synthetic transformation providing a much broader array of reactions in comparison with the all-carbon variant. Several research groups have made great efforts to generalise the reaction to a wide variety of substrates and a considerable number of versions have been reported to date (**Scheme 4.5**).[24]

[21] For recent selected examples, see: a) Arns, S.; Barriault, L. *Chem. Commun*. **2007**, 2211-2221. b) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc*. **2007**, *129*, 3520-3521. c) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418-419.
[22] Claisen, L. *Chem. Ber*. **1912**, *45*, 3157-3166.
[23] a) Burgstahler, A. W. *J. Am. Chem. Soc*. **1960**, *82*, 4681-4685. b) Perrin, C. L.; Faulkner, D. J. *Tetrahedron Lett.* **1969**, *10*, 2783-2786.
[24] For an excellent review, check: Martín Castro, A. M. *Chem. Rev*. **2004**, *104*, 2939-3002.



Scheme 4.5. Variants of the Claisen Rearrangement: A) Carroll Rearrangement. B) Eschenmoser Rearrangement. C) Johnson Rearrangement. D) Ireland-Claisen Rearrangement. E) Reformatsky-Claisen Rearrangement.

The first reaction described was the Carroll Rearrangement. Reported in 1940, this thermal rearrangement of allyl β-ketoesters **5** gave access to γ,δ-unsaturated ketones **7** (**Scheme 4.5A**).[25] Due to the required harsh conditions under which the reaction operates, it has not been widely developed by the scientific community. The next Eschenmoser variant described in 1964 consisted of a [3,3]-rearrangement of

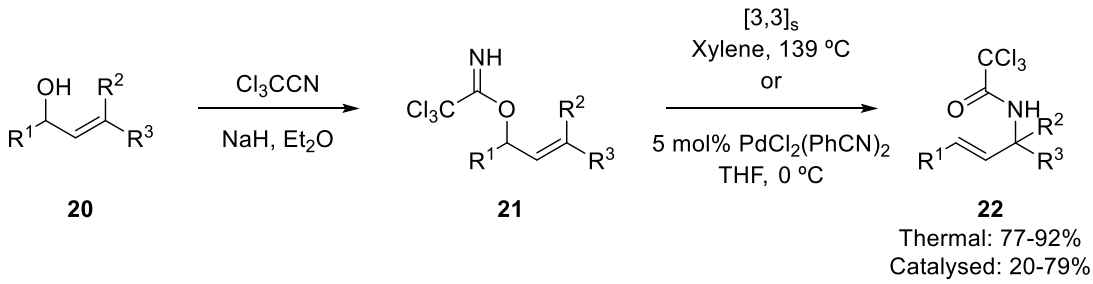
[25] a) Carroll, M. F. *J. Chem. Soc*. **1940**, 704-706. b) Carrol, M. F. *J. Chem. Soc*. *Chem. Commun*. **1941**, 507-511.

N,*O*-ketene acetals **9** that yielded γ,δ-unsaturated amides **10** (**Scheme 4.5B**).[26] Such transformation enables the generation of carbon-carbon bonds at the β-position to a nitrogen atom, being of great applicability in alkaloid synthesis. The Johnson rearrangement, first reported in 1970, was developed as a [3,3]-shift of ketene acetal **12** that led to γ,δ-unsaturated esters **13** (**Scheme 4.5C**).[27] Two years after, the Ireland-Claisen variant was reported, in which allyl trimethylsilyl ketene acetals **15** furnished γ,δ-unsaturated carboxylic acids **16** (**Scheme 4.5D**).[28] As compared to other rearrangements the reaction proceeded under mild neutral or basic conditions. Finally, the Reformatsky-Claisen rearrangement, described in 1973, involves the rearrangement of zinc enolates **18** to generate the corresponding γ,δ-unsaturated zinc carboxylates **19** (**Scheme 4.5E**).[29] The proven synthetic potential of the process has made this reaction widely applicable to the generation of natural products.[30]

4.1.1.3 Overman rearrangements

The Overman rearrangement is a useful carbon-nitrogen bond forming reaction that permits the chemical synthesis of allyl amide derivatives from allyl alcohols.[31] Albeit the carbon-carbon bond forming [3,3]-sigmatropic shifts exist since the beginning of the 20th century, the development of the heteroatom variant did not occur until the early 1970's. This rearrangement was initially described as the thermal or Hg(II) or Pd(II) promoted rearrangement of allyl trichloroacetimidates **21** to afford the corresponding trichloroacetamidates **22** (**Scheme 4.6**).[32] This reaction is generally carried out in dry and non-nucleophilic solvents to minimise the hydrolysis of the intermediate trichloroacetimidate species.[10] This reaction is especially useful for the synthesis of sterically hindered allyl amines that are otherwise troublesome to synthesise.

[26] a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425-2429. b) Wick, A. E.; Felix, D.; Gschwend-Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030-1042.
[27] Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
[28] a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc*. **1972**, *94*, 5897-5898. b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1976**, *98*, 2868-2877.
[29] Baldwin, J. E.; Walker, J. A. *J. Chem. Soc., Chem. Commun*. **1973**, 116-117.
[30] a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847-1882. b) Ito, H.; Taguchi, T. *Chem. Soc. Rev*. **1999**, *28*, 43-50. c) Rodrigues, T. C. A. F.; Silva, W. A.; Machado, A. H. L. *Curr. Org. Synth*. **2015**, *12*, 795-805.
[31] Fernandes, R. A.; Kattanguru, P.; Gholap, S. P.; Chaudhari, D. A. *Org. Biomol. Chem*. **2017**, *15*, 2672-2710.
[32] a) Overman, L. E. *J. Am. Chem. Soc*. **1974**, *96*, 597-599. b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579-586. c) Overman, L. E. *J. Am. Chem. Soc*. **1976**, *98*, 2901-2910. d) Overman, L. E. *Acc. Chem. Res*. **1980**, *13*, 218-224.

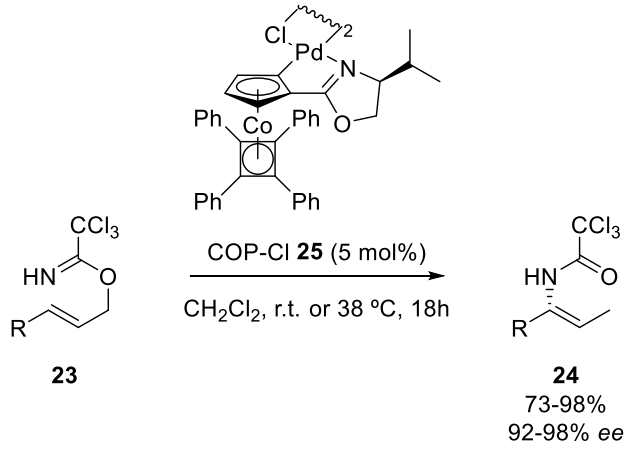


20 **21** **22**

Thermal: 77-92%
Catalysed: 20-79%

Scheme 4.6. The Overman Rearrangement of trichloroacetimidates to trichloroacetamidates reported in 1974.

The enantioselective version of the Overman rearrangement was first reported in 2004 by the same research group. Therein, the Pd(II) COP-Cl complex **25** catalysed the rearrangement of prochiral allyl alcohols furnishing enantioenriched allyl amines in good yields (**Scheme 4.7**).[33] The development of the chiral version enabled the implementation of mild and selective procedures to introduce the allyl amine functionality into many natural products.[34]



23 **24**

73-98%
92-98% *ee*

Scheme 4.7. The enantioselective COP-Cl complex **25** catalysed Overman rearrangement.

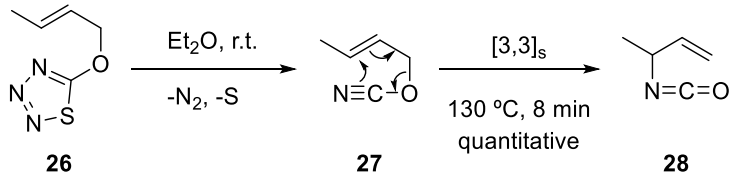
4.1.1.4 Allyl Cyanate/Isocyanate rearrangements

Initially reported by Holm and co-workers in 1970, the allyl cyanate/isocyanate rearrangement is considered as an attractive alternative method to the Overman rearrangement, due to the required milder reaction conditions. In his work Holm described an unexpected rearrangement that gave access to allyl isocyanate **28** by a cascade retro-[3+2]/[3,3] reaction of allyl thiatriazole **26** at room temperature

[33] a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412-12413. b) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett*. **2003**, *5*, 1809-1812. c) Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem*. **2004,** 69, 8101-8104.

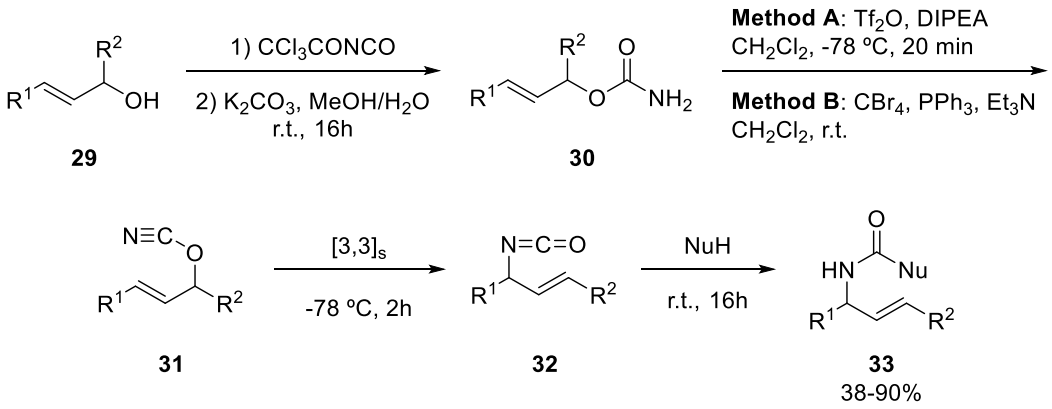
[34] a) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117-2142. b) Arnold. J. S.; Zhang, Q.; Nguyen, H. M. *Eur. J. Org. Chem*. **2014**, 4925-4948. c) Cannon, J. S.; Overman, L. E. *Acc. Chem. Res*. **2016**, *49*, 2220-2231.

(**Scheme 4.8**).[35] One of the main limitations of this methodology was the preparation and instability of the intermediate allyl cyanate species **27**.



Scheme 4.8. The unexpected allyl cyanate/isocyanate rearrangement reported by Holm.

This challenge was overcome twenty years later by the group of Ichikawa, who reported an efficient synthesis of the required allylcyanates by dehydration of the corresponding allyl carbamates **30**. Two different strategies were described for the dehydration step: Method A made use of trifluoromethanesulfonic anhydride (Tf_2O) and diisopropylethylamine. In Method B, on the other hand, carbon tetrabromide and triphenylphosphine were used for such purposes. The following [3,3]-sigmatropic rearrangement underwent smoothly at -78 °C and the corresponding isocyanates were trapped by diverse nucleophiles giving rise to a wide variety of derivatives **33** (**Scheme 4.9**).[36]



Scheme 4.9. The allyl cyanate/isocayanate version reported by Ichikawa.

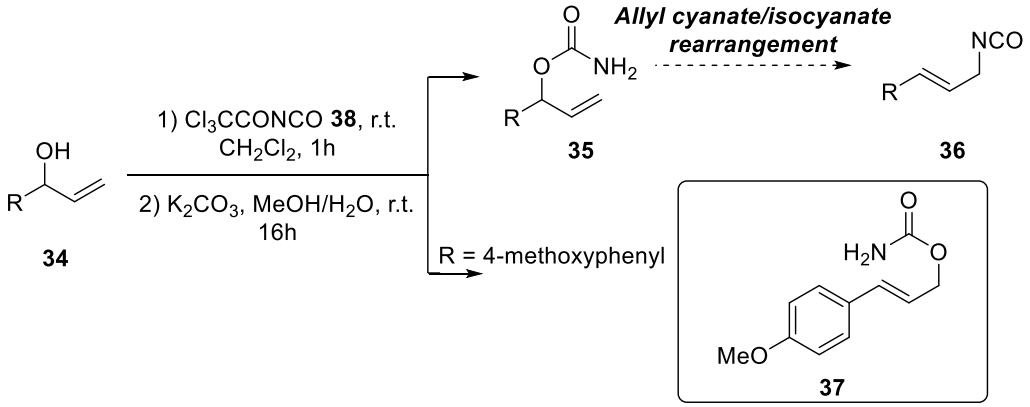
Shortly after, the same authors stated that the reaction proceeded through a six-membered transition state affording exclusively the *E*-configuration at the newly formed double bond. Besides, the chirality transfer experiment carried out by chiral allyl cyanates demonstrated that the rearrangement occurred with no racemisation or epimerisation.[37]

[35] Christophersen, C.; Holm, A. *Acta. Chem. Scand*. **1970**, *24*, 1512-1526.
[36] a) Ichikawa, Y. *Synlett* **1991**, 238-240. b) Ichikawa, Y.; Yamazaki, M.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429-2432. c) Ichikawa, Y.; Osada, M.; Ohtani, I. I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449-1456.
[37] Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791-2796.

In the last decade, this dehydration/sigmatropic rearrangement sequence has been successfully applied for the synthesis of a handful of original compounds.[38] Among the described derivatives, quaternary chiral carbon bearing amino acids and *N*-heterocycles[39], fluorinated thioureas[40], α-aminoboronates[41], α-amino allylsilanes[42] and seven-membered-ring carbamates[43] should be highlighted.

4.2 OBJECTIVES

Previous studies carried out by the group of François Carreaux on the allyl cyanate/isocyanate rearrangement with 1-(4-methoxyphenyl)prop-2-en-1-ol **34** and trichloroacetyl isocyanate **38** exhibited the unexpected formation of primary (*E*)-carbamate **37** with a well-defined stereochemistry (**Scheme 4.10**).



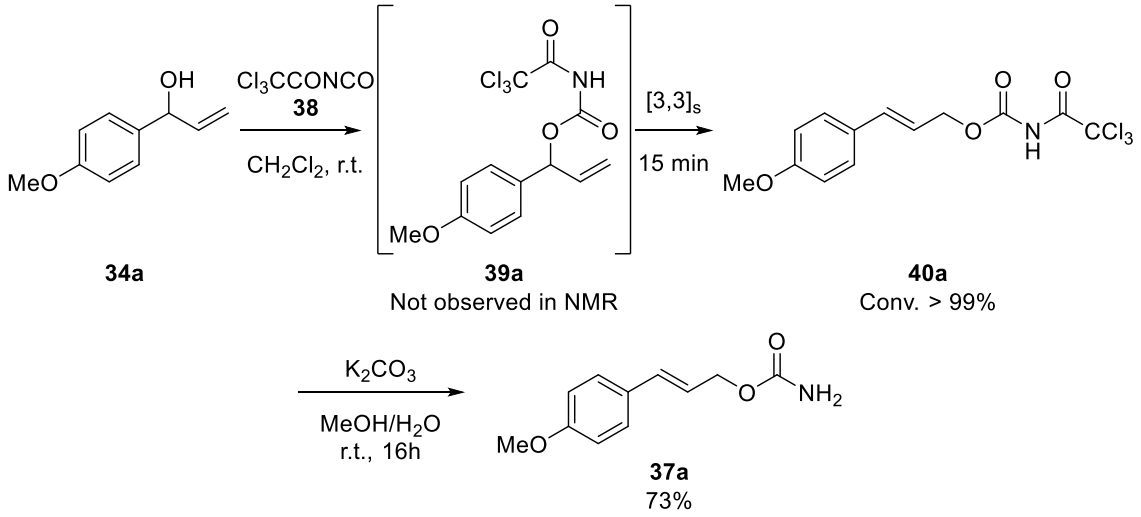
Scheme 4.10. The unexpected formation of carbamate **37** instead of **35** when of 1-(4-methoxyphenyl)prop-2-en-1-ol **34** was subjected to the dehydration/rearrangement sequence.

Taking into consideration the importance of carbamates as synthetic intermediates and drugs, the main objective pursued in this Chapter will be study of the suitability of diverse aryl and alkenyl substituted allyl alcohols as well as isocyanates in this formal [1,3] or [3,3]-sigmatropic oxo-rearrangement. In addition, experimental and computational studies will be performed in order to rationalise the mechanistic pathway of this unexpected behaviour.

[38] Nocquet, P.-A.; Henrion, S.; Macé, A.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. *Eur. J. Org. Chem*. **2017**, 1295-1307.
[39] Roy, S.; Spino, C. *Org. Lett*. **2006**, *8*, 939-942.
[40] Ramb, D. C.; Kost, L.; Haufe, G. *Chimia* **2014**, *68*, 436-441.
[41] Touchet, S.; Macé, A.; Roisnel. T.; Carreaux, F.; Bouillon, A.; Carboni, B. *Org. Lett*. **2013**, *15*, 2712-2715.
[42] Henrion, S.; Carboni, B.; Cossío, F. P.; Roisnel, T.; Villalgordo, J. M.; Carreaux, F. *J. Org. Chem*. **2016**, *81*, 4633-4644.
[43] Macé, A.; Touchet, S.; Andres, P.; Cossío, F.; Dorcet, V.; Carreaux, F.; Carboni, B. *Angew. Chem., Int. Ed*. **2016**, *55*, 1025-1029.

4.3 THE DISCOVERY OF THE UNPRECEDENTED METAL FREE 1,3-DIOXA-[3,3]-SIGMATROPIC REARRANGEMENT

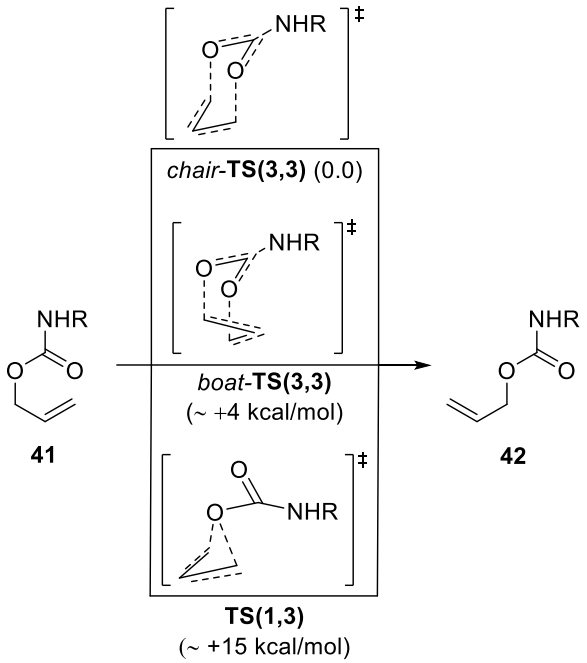
According to the preliminary results, when allyl alcohol **34a** was treated with trichloroacetyl isocyanate, a direct and fast formation (15 minutes) of the rearranged product **40a** was observed (**Scheme 4.11**). Attempts to isolate and characterise the intermediate species **39a** resulted unsuccessful, highlighting the fast and irreversible nature of the [3,3]-sigmatropic rearrangement. This final rearranged acetyl carbamate **40a** was further treated under basic conditions affording the linear carbamoyl derivative **37a** in good yield (**Scheme 4.11**).[44]



Scheme 4.11 The unprecedented 1,3-dioxa-[3,3]-sigmatropic rearrangement with allyl alcohol **34a** and trichloroacetyl isocyanate **38**.

Although the **39a** → **40a** transformation can be envisaged as a [1,3] or [3,3] rearrangement, previous computational studies[45] showed that the [1,3] transition structure lies ca. 15 kcal/mol above either the chair and boat transition structures associated with the [3,3] process (**Scheme 4.12**). Therefore, in the subsequent discussion only the [3,3] route will be considered.

[44] The synthesis of product **37a** was earlier reported in: Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745-11750.
[45] Cossío, F. P. *Unpublished results*.



Scheme 4.12. Computed relative energies of transition structures (TS) associated with [1,3] and [3,3] sigmatropic shifts.

In order to analyse the factors that could govern the sigmatropic rearrangement, the next step consisted of the study of the influence of the substituents of both components in the chemical process.

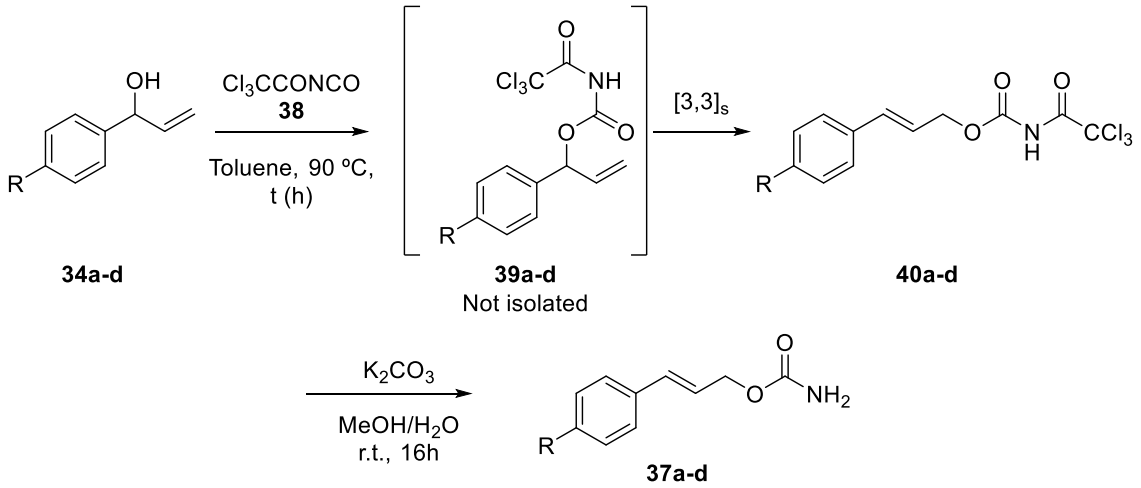
4.3.1 1,3-dioxa-[3,3]-sigmatropic rearrangement using trichloroacetyl isocyanate

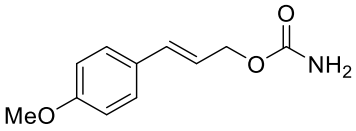
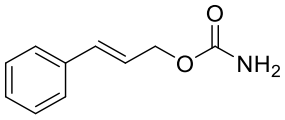
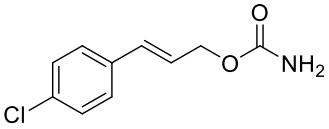
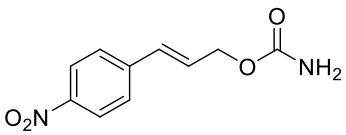
The first experiments were carried out employing different secondary allyl alcohols that bear both electron-withdrawing and electron-donating groups at *para* position (**Table 4.2**). As it can be seen in the gathered results, the reaction rate is highly dependent on the electron density of the allyl moiety. In general, electron-donating substituents in the aromatic ring enhance the rate of the sigmatropic rearrangement, whereas the rate decreases with electron-withdrawing substituents. For instance, when electron-donating *p*-methoxy substituted allyl alcohol **34a** was used, the reaction proceeded smoothly at room temperature and the final product was obtained in good yield (**Table 4.2**, entry 1). However, allyl alcohols that hold electron-withdrawing substituents required higher reaction temperatures to reach completion (**Table 4.2**, entries 2-4). In fact, non-substituted aromatic allyl alcohol **34b** required 6h of reaction time to reach full conversion at 90 °C (**Table 4.2**, entry 2). The *p*-chloro substituted allyl alcohol **34c** demanded longer reaction times, reaching full conversion after 20h (**Table 4.2**, entry 3). Lastly, with the strongest electron-withdrawing *p*-nitro substituent, only 50% conversion was observed after 5 days (**Table 4.2**, entry 4). These results suggest an electron-deficient character of the allyl moiety during the sigmatropic

process. As a general rule, the more electron-rich the allyl moiety is, the faster the sigmatropic rearrangement ocurs. The last basic hydrolysis proceeded uneventfully in all cases, and the final carbamates **37a-d** were achieved in moderate to good yields as single (*E*)-stereoisomers.

At this point, it should be noted that, in the cases in which the reaction lasted longer, intermediates **39b-d** were identified during the NMR analyses, strongly supporting the initial hypothesis of the 1,3-dioxa[3,3]-sigmatropic rearrangement.

Table 4.2. 1,3-dioxa-[3,3]-sigmatropic rearrangement of aromatic allyl alcohols **34a-d** and trichloroacetyl isocyanate **38**.[a,b]



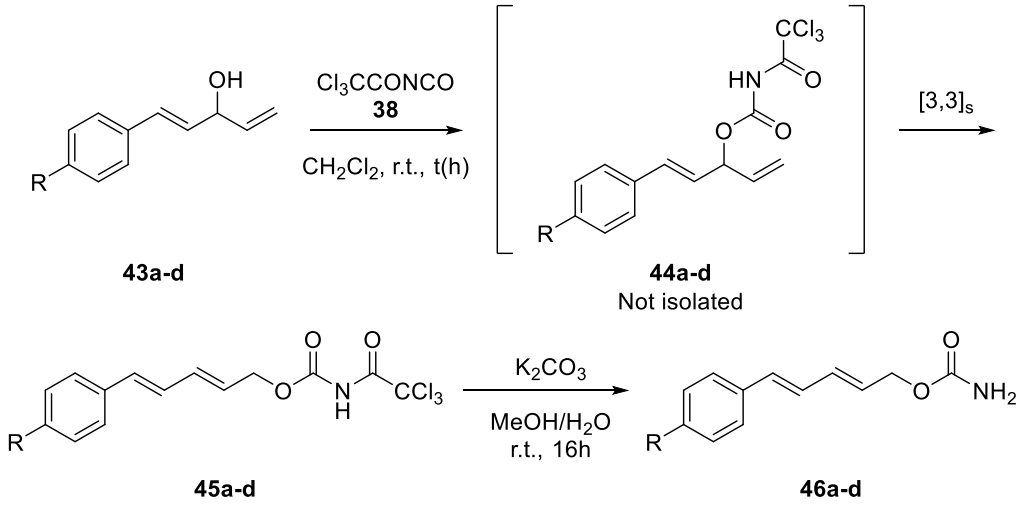
Entry	R	t (h)	Product	Structure	Yield (%)[c]
1[d]	4-OMe	0.25	**37a**		73
2	H	16	**37b**		92
3	4-Cl	20	**37c**		50
4	4-NO_2	120[e]	**37d**		43

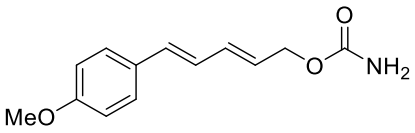
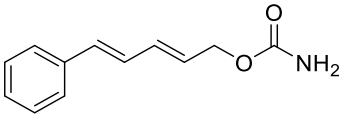
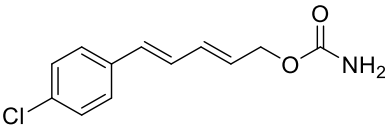
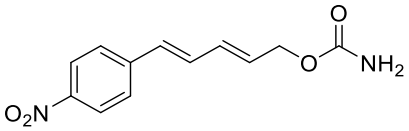
a) The reaction was conducted employing allyl alcohol **34a-d** (0.3 mmol) and trichloroacetyl isocyanate **38** (0.36 mmol) in toluene (0.2 M) at the indicated temperature. b) The reaction was monitored by ^{1}H NMR until total consumption of starting alcohol employing the corresponding deuterated solvent. c) Yield refers to isolated products. d) The reaction was conducted in CH_2Cl_2 at room temperature. e) 50% of conversion was observed.

Taking into consideration the relevance of dienyl carbamates in the synthesis of natural products[46], we next evaluated the suitability of alkenyl substituted allyl alcohols in the dehydration/rearrangement/hydrolysis sequence (**Table 4.3**). The results obtained with the alkenyl substituted starting alcohols followed the same trend as the previous ones, highlighting the importance of the electronic properties of the allyl moiety in the sigmatropic rearrangement. Nevertheless, higher reaction rates were observed in the case of alkenyl substituted allyl alcohols and all the reactions proceeded smoothly at room temperature. For instance, when alcohol **43a** with a methoxy electron-donating substituent was employed, the sigmatropic rearrangement lasted 2 hours and the final carbamate **46a** was isolated in a poor yield of 24%, due to the loss of product during the purification on silica gel (**Table 4.3**, entry 1). The non-substituted and *p*-Cl substituted allyl alcohols **43b**,**c** required 4h to reach full conversion, and the desired carbamates were obtained in good yields after the hydrolysis step (**Table 4.3**, entries 2 and 3). Unfortunately, alcohol **43d** did not lead to the formation of the final rearranged product **46d**, probably due to the instability of the corresponding reaction intermediates at high temperatures (**Table 4.3**, entry 4). The higher reactivity of alcohols **43a**-**c** might be partially explained by the generation of a more stable conjugated diene.

[46] For some recent applications of dienyl carbamates, check: a) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett*. **2007**, *9*, 1725-1728. b) Unsworth, W. P.; Lamont, S. G.; Robertson, J. *Tetrahedron* **2014**, *70*, 7388-7394. c) Guasch, J.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Chem. Commun.* **2014**, *50*, 7344-7347. d) Guasch, J.; Giménez-Nueno, I.; Funes-Ardoiz, I.; Bernús, M.; Matheu, M. I.; Maseras, F.; Castillón, S.; Díaz, Y. *Chem. Eur. J.* **2018**, *24*, 4635-4642.

Table 4.3. 1,3-dioxa-[3,3]-sigmatropic rearrangement of alkenyl substituted allyl alcohols **43a-d** and trichloroacetyl isocyanate **38**.[a,b]

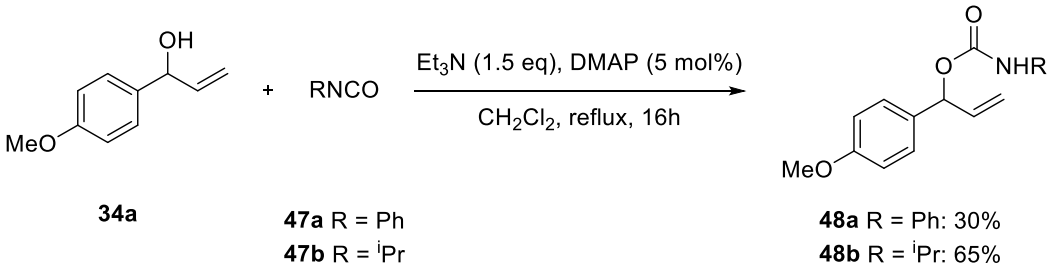


Entry	R	t (h)	Product	Structure	Yield (%)[c]
1	4-OMe	2	**46a**		24 (65)[d]
2	H	4	**46b**		65
3	4-Cl	4	**46c**		75
4[e]	4-NO_2	178[f]	**46d**		nd[g]

a) The reaction was conducted employing alkenyl substituted allyl alcohol **43a-d** (0.3 mmol) and trichloroacetyl isocyanate (0.36 mmol) in CH_2Cl_2 (0.2 M) at room temperature. b) The reaction was monitored by ^{1}H-NMR until total consumption of starting alcohol employing the corresponding deuterated solvent. c) Yield refers to isolated products. d) The yield in parentheses was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal reference. e) The reaction was conducted in toluene-*d8* at 90 °C. f) No formation of the desired product was observed. g) Not determined.

In order to determine the influence of the nature of the isocyanate in the rearrangement, the next experiments were carried out making use of non-activated isocyanates (**Scheme 4.13**). Interestingly, treatment of 1-(4-methoxyphenyl)prop-2-en-1-ol **34a** with phenyl and isopropyl isocyanates did not afford any traces of rearranged linear carbamates. During the NMR analysis only branched carbamates **48a**,**b** were observed, and in the particular case of phenyl isocyanate, the conversion towards the branched carbamate was not complete. When

isopropyl isocyanate was employed, full conversion was observed and the corresponding branched carbamate **48b** was isolated in a moderate yield (**Scheme 4.13**).[47] These results highlight the key role of activated isocyanates for the sigmatropic shift to occur, that make the NH group of the carbamate more acidic.



Scheme 4.13. Results obtained with non-activated phenyl and isopropyl isocyanates **46a,b**.

4.3.2 1,3-dioxa-[3,3]-sigmatropic rearrangement using *p*-toluenesulfonyl isocyanate

With the aim to evaluate the applicability of other activated isocyanates, *p*-toluenesulfonyl isocyanate was tested next (**Table 4.4**). These experiments would also support the hypothesis on the dependence of the sigmatropic rearrangement on the acidity of the carbamate NH.

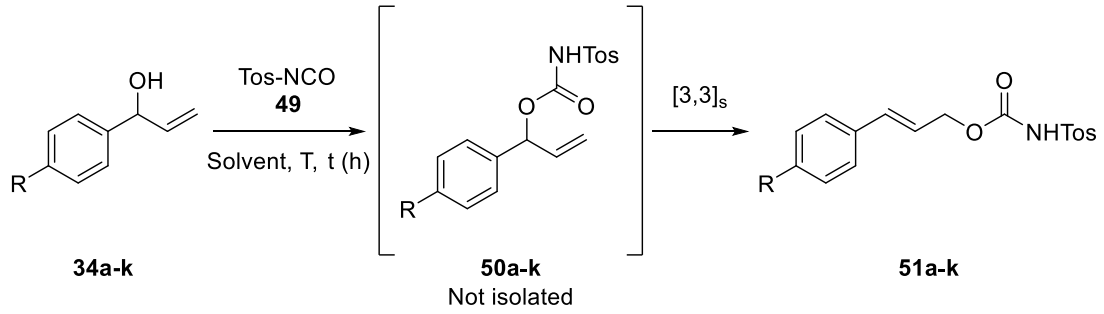
When electron-donating substituents were present in the allyl alcohols **34a** and **34f**, the [3,3]-sigmatropic rearrangement proceeded smoothly in 15 minutes and the corresponding linear **51a** and **51f** (*E*)-carbamates were obtained in high yields. With **34b**-**d** allyl alcohols heating to 90 °C was required for the reaction to reach full conversion and the desired rearranged carbamates were furnished in good yields. Among them, weakly deactivating substituted alcohols **34b** and **34e** required shorter reaction times. Nonetheless, the strongest deactivating *p*-NO_2 substituted allyl alcohol could only reach 70% conversion after 4 days and the corresponding **51d** carbamate was obtained in moderate yield.

Other substitution patterns were also found to be applicable to the dehydration/sigmatropic rearrangement sequence. The *o*-methoxy substituted allyl alcohol **34g** afforded the rearranged carbamate at room temperature after 16h of reaction in good yield. The 3,4-disubstituted allyl alcohols **34i**,**j** also furnished the corresponding linear carbamates in good yields and short reaction times. In these particular cases the positioning of electron-donating substituents in *meta* position resulted in slightly superior reaction times in comparison to the mono-substituted **34a** counterpart. Finally, the

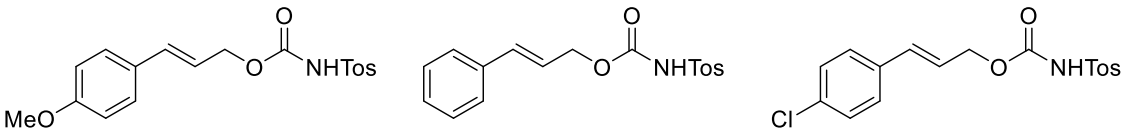
[47] To avoid a slight formation of the rearranged carbamate during the purification, prior deactivation of silica gel with triethylamine was needed.

employment of allyl alcohols with fused rings **34h**,**k** led to the desired carbamates in high yields at room temperature.

Table 4.4. 1,3-dioxa-[3,3]-sigmatropic rearrangement of allyl alcohols **34a-k** with *p*-toluenesulfonyl isocyanate **49**.[a,b,c]



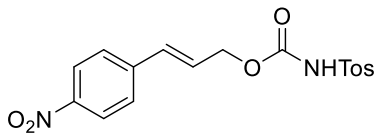
34a-k | **50a-k** Not isolated | **51a-k**



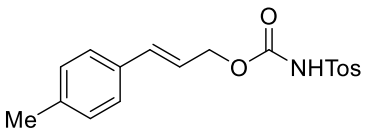
51a, CH_2Cl_2, r.t.
15 min, 90%

51b, Toluene, 90 ºC
6h, 95%

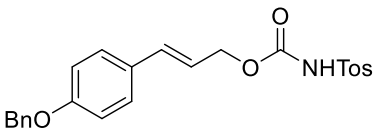
51c, Toluene, 90 ºC
20h, 70%



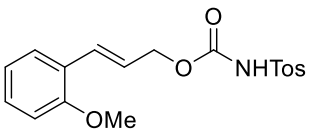
51d, Toluene, 90 ºC
4 days, 40%[d]



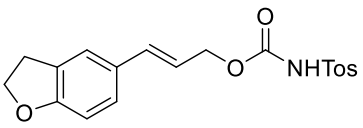
51e, Toluene, 90 ºC
6h, 70%



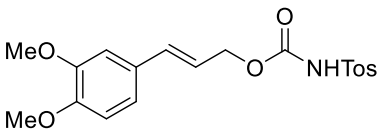
51f, CH_2Cl_2, r.t.
15 min, 74%



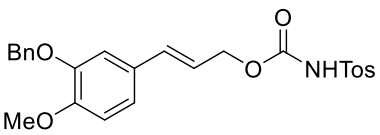
51g, CH_2Cl_2, r.t.
16h, 85%



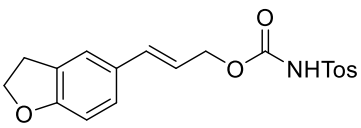
51h, CH_2Cl_2, r.t.
1h, 36% (85%)[e]



51i, CH_2Cl_2, r.t.
45 min, 32% (80%)[e]



51j, CH_2Cl_2, r.t.
45 min, 54%



51k, CH_2Cl_2, r.t.
3h, 84%

a) The reaction was conducted employing **34a-k** allyl alcohol (0.3 mmol) and *p*-toluenesulfonyl isocyanate (0.36 mmol) (in the indicated solvent and temperature. b) The reaction was monitored by ^{1}H-NMR until total consumption of starting alcohol employing the corresponding deuterated solvent. c) Yield refers to isolated products. d) 70% of conversion was observed after 4 days. e) Yields in parentheses were determined by ^{1}H-NMR employing 1,3,5-trimethoxybenzene as internal reference.

In general, the [3,3]-sigmatropic rearrangement was suitable for a wide variety of allyl alcohols with different electronic properties. They all enabled the exclusive formation of (*E*)-carbamates in good to high yields. Compounds **51h** and **51i** required the use of

1,3,5-trimethoxybenzene as internal reference to determine the yield of the chemical process due to the low isolated yields observed. The structure of compound **51e** was confirmed by X-Ray diffraction analysis, in which the (*E*)-configuration of the internal double bond was unambiguously determined (**Figure 4.4**).

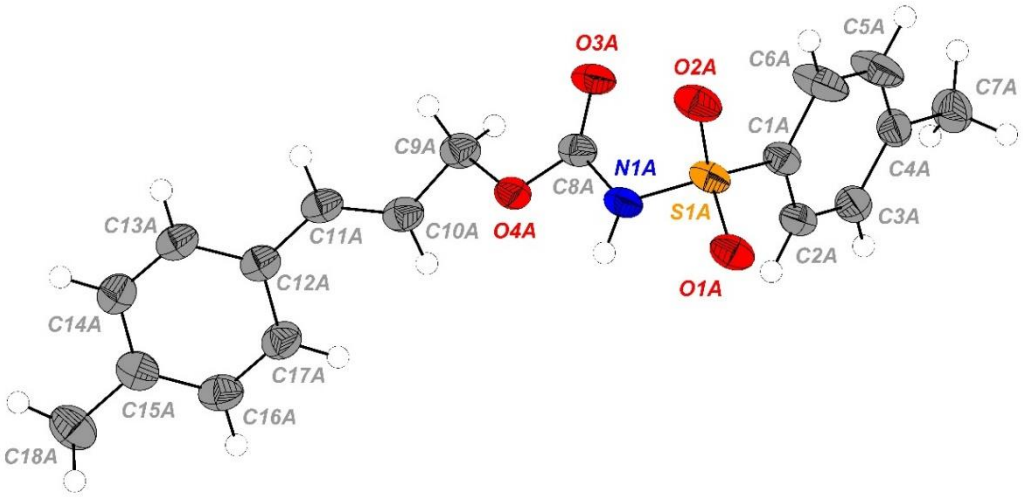
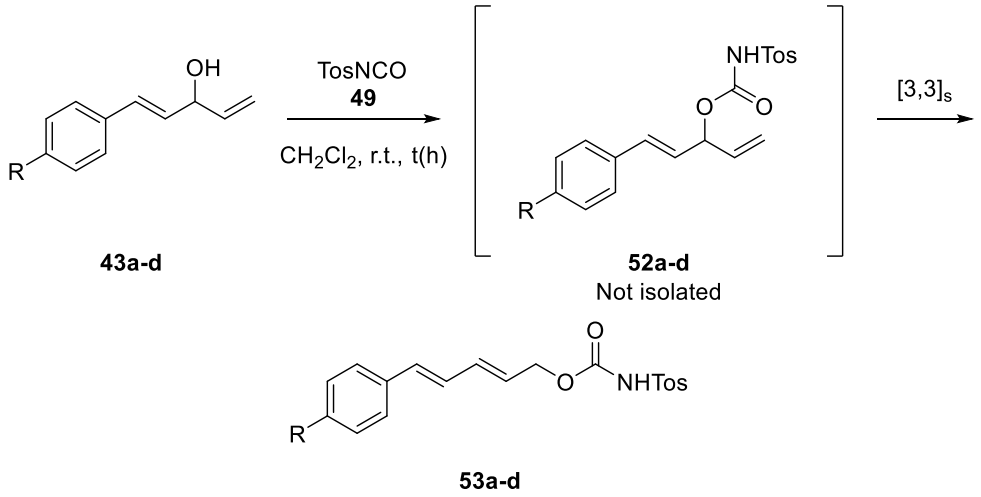


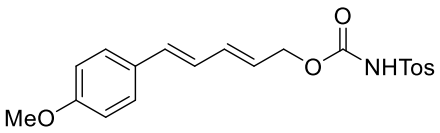
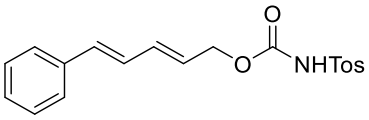
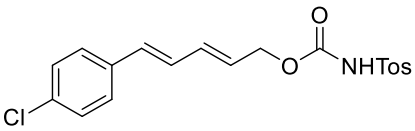
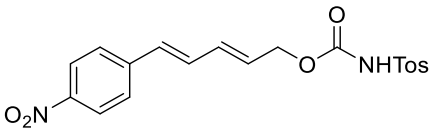
Figure 4.4. ORTEP diagram with thermal ellipsoids in 50% probability of compound **51e**.

The use of *p*-toluenesulfonyl isocyanate **49** was likewise applied to alkenyl-substituted allyl alcohols **43a**-**d** (**Table 4.5**). The results gathered in this Table show a similar behaviour with respect to the one observed with trichloroacetyl isocyanate. Electron-donating group-containing allyl alcohol **43a** exhibited longer reaction rates and the final rearranged (*E*,*E*)-carbamate was obtained within 30 minutes at room temperature in poor isolated yield. The use of 1,3,5-trimethoxybenzene as internal reference revealed the high yield towards the desired **53a** carbamate, thus indicating that the low isolated yield is due to its low stability during the purification (**Table 4.5**, entry 1). Besides, non-substituted and *p*-Cl substituted allyl alcohols required 4h to reach full conversion and carbamates **53b,c** were obtained in good yields (**Table 4.5**, entries 2 and 3). Lastly, derivative **43d** required 90 °C and 5 days to reach 50% conversion, affording the corresponding linear conjugated carbamate in 36 % yield (**Table 4.5**, entry 4).

Table 4.5. Carbamoylation/rearrangement sequence for alkenyl-substituted allyl alcohols **43a-d** employing *p*-toluenesulfonyl isocyanate **49**.[a,b]



43a-d **52a-d** Not isolated **53a-d**

Entry	R	t (h)	Product	Structure	Yield (%)[c]
1	4-OMe	0.5	**53a**		25(85)[d]
2	H	4	**53b**		75
3	4-Cl	4	**53c**		68
4[e]	4-NO_2	120[f]	**53d**		36

a) The reaction was conducted employing alkenyl substituted allyl alcohol **43a-d** (0.3 mmol) and trichloroacetyl isocyanate **49** (0.36 mmol) in CH_2Cl_2 (0.2 M) at room temperature. b) The reaction was monitored by ^{1}H-NMR until total consumption of starting alcohol employing the corresponding deuterated solvent. c) Yield refers to isolated products. d) The yield in parentheses was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal reference. e) The reaction was conducted in toluene-*d8* at 90 °C. f) 50% of conversion was observed after 5 days.

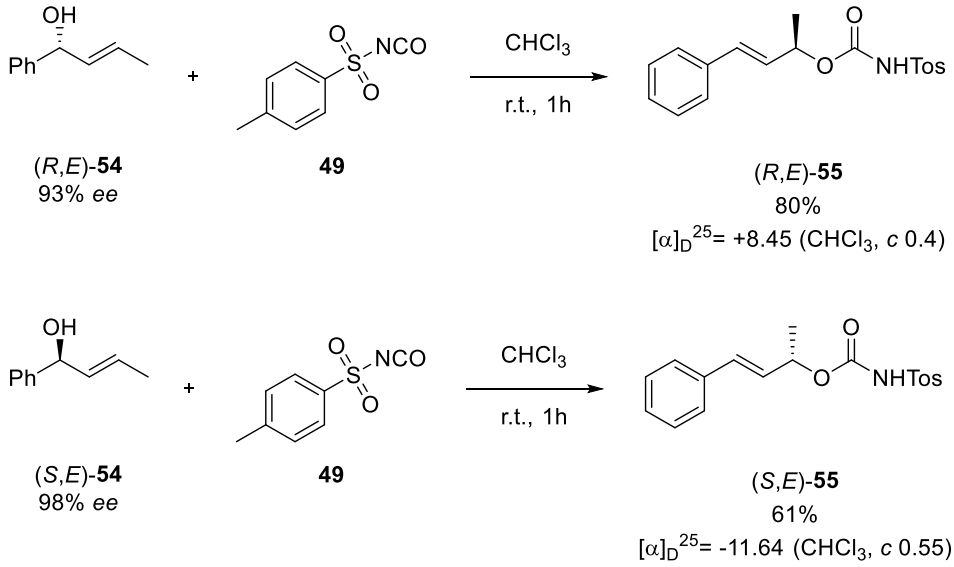
4.4 MECHANISTIC STUDIES

4.4.1 Analysis of the concertedness of the reaction

According to the Woodward and Hoffmann rules, the thermally allowed [3,3]-sigmatropic rearrangements proceed regioselectively and stereospecifically. With the aim to assess the chirality transfer of these processes and discard stepwise mechanisms involving cleavage of the reactants to generate carboxylate/allyl cations,

ionic pairs or radicals, the behaviour of racemic (*E*)-1-phenylbut-2-en-1-ol **54** and its (*R,E*)- and (*S*,*E*)- enantiomers was analysed by NMR and HPLC studies. This latter starting alcohol was separated from the racemic mixture by chiral preparative HPLC.

First, *p*-toluenesulfonyl isocyanate **49** was chosen as starting material. The rearrangement proceeded uneventfully with both (*R*,*E*)- and (*S*,*E*)-**54** alcohols at room temperature, yielding the corresponding (*R*,*E*)- and (*S*,*E*)-**55** carbamates in 1h and good yields (**Scheme 4.14**). Optical rotation measurements showed that both compounds were chiral, but, unfortunately, when HPLC experiments were carried out to determine the enantiomeric excess of the final product instability issues arose, making the quantification impossible.

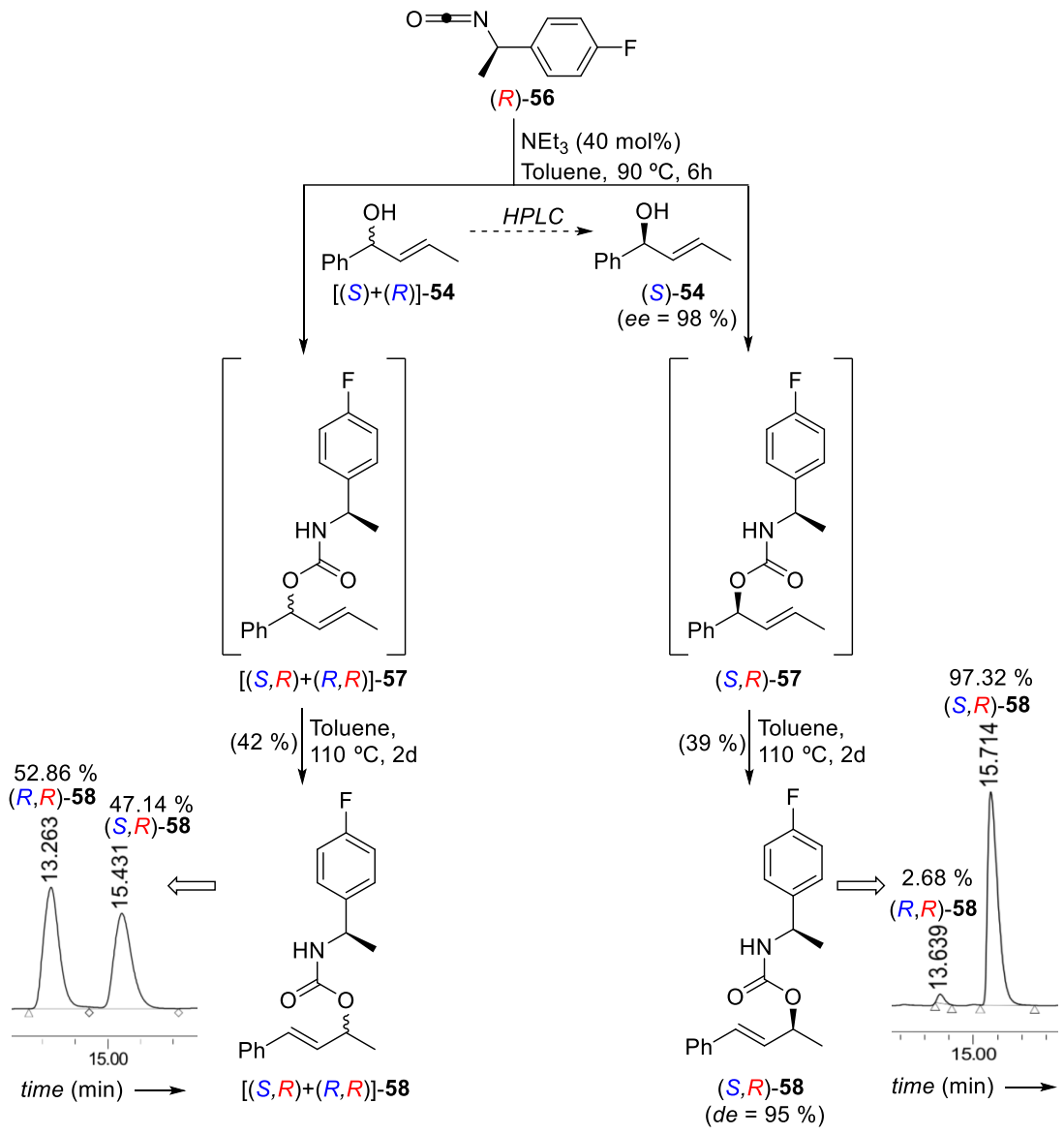


Scheme 4.14. Obtained results for the chirality transfer reactions employing chiral alcohol **54** and *p*-toluenesulfonyl isocyanate.

We next employed $Eu(hfc)_3$ shift reagent and analysed the resulting NMR mixtures. Nevertheless, its use also led to ambiguous results from which determination of the enantiomeric excess was not possible. The crude reaction mixtures did not allow the separation of NMR signals before saturation.

In view of the non-conclusive results obtained with *p*-toluenesulfonyl isocyanate we hypothesised that the use of a chiral isocyanate might facilitate our study. In this regard, racemic allyl alcohol **54** was treated with (*R*)-[1-(4-fluorophenyl)ethyl]isocyanate **56** in the presence of triethylamine (**Scheme 4.15**). After the generation of the starting carbamate **57**, the rearrangement step was conducted at 110 °C and the final carbamate was obtained in 50% of conversion. Longer reaction times resulted in loss of product due to the instability of the intermediate carbamate at high reaction temperatures. This time, ^{1}H, ^{13}C and ^{19}F NMR experiments did not show any separable set of signals for the

mixture of diastereomers, so HPLC analyses were carried out. Therein, the HPLC profile of the diastereomeric (*S*,*R*)+(*R*,*R*)-**58** mixture of carbamates showed two well-defined peaks in 52:48 ratio (**Scheme 4.15**).



Scheme 4.15. Evaluation of the chirality transfer in the reaction between allyl alcohol **54** and (*R*)-**56** isocyanate. HPLC chromatograms of racemic and chiral **56** compounds are also shown.

When chiral allyl alcohol (*S*)-**54** was employed (98% *ee* after HPLC separation), formation of (*S*,*R*)-**58** carbamate was observed in 39% yield. The HPLC analysis revealed that this final product was obtained in 95% diastereomeric excess, demonstrating that the chiral information is retained during the chemical process. With this last result we assume that the chiral transfer was also complete with *p*-toluenesulfonyl isocyanate, although no evidence could have been given.

4.4.2 Determination of first order kinetic constants

Once the general features of the electronic properties of the reactants were investigated, we carried out kinetic studies in order to quantify the impact of these effects on the reactivity of the reaction. Conversion of the starting alcohols **34b**,**c** (R = H, Cl respectively) into the rearranged products **51b**,**c** was monitored by ^{1}H-NMR experiments in deuterated toluene at 90 °C. In the case of alcohol **34a** (R = OMe) those experimental conditions were not suitable to obtain a reliable kinetic constant, due to the fast nature of the reaction. However, the first-order reaction rate could be measured at room temperature in 15 minutes of reaction. Similar experiments with alcohol **34d** (R = NO_2) were not possible because of the previously observed long reaction time.

Figure 4.5 shows the evolution in time of the selected reaction between 1-(4-chlorophenyl)prop-2-en-1-ol **34c** and *p*-toluenesulfonyl isocyanate **49** in deuterated toluene at 90 °C. Previous experiments showed that the first dehydration step in which the intermediate carbamate is formed is immediate. Besides, this **50c** intermediate carbamate evolved towards the rearranged carbamate **51c** with no detectable intermediate species.

The kinetic constants associated with the reaction **50a**-**c** → **51a**-**c** were measured under first-order conditions in which the observed reaction rates depend on the concentration of **50a**-**c** according to equation 1:

$$rate = -\frac{d[\mathbf{50}\boldsymbol{a}\text{-}\boldsymbol{c}]}{dt} \approx k_{obs}[\mathbf{50}\boldsymbol{a}\text{-}\boldsymbol{c}] \qquad (1)$$

The integrated first order equation should depend linearly on the logarithms of the intermediate carbamate concentration, as indicated in equation 2:

$$\ln[\mathbf{50}\boldsymbol{a}\text{-}\boldsymbol{c}]_t - \ln[\mathbf{50}\boldsymbol{a}\text{-}\boldsymbol{c}]_0 = -k_{obs}t \qquad (2)$$

The calculated experimental measurements in **Table 4.6** were averaged for three sets of signals related to **Hb'**, **Hc'** and **Hd'** protons of compound **50a**-**c** (check Annex III for details). Overall, the results obtained are in total agreement with the reactivity reported in **Table 4.4**. The kinetic constant of alcohol **34c** is slightly lower than its analogous alcohol **34b**, giving evidence of the higher reaction time required for the reaction to reach full conversion (**Table 4.6**, entry 3 vs 2). The rate constant for alcohol **34a**, on the other hand, was one order of magnitude faster than those measured for the remaining cases. The collected data show that allyl alcohols possessing electron-withdrawing groups exhibit lower reactivity, whereas electron-donating substituents accelerate the sigmatropic rearrangement. This latter conclusion is in good agreement with the electron-deficient character of the allyl moiety at the corresponding transition state.

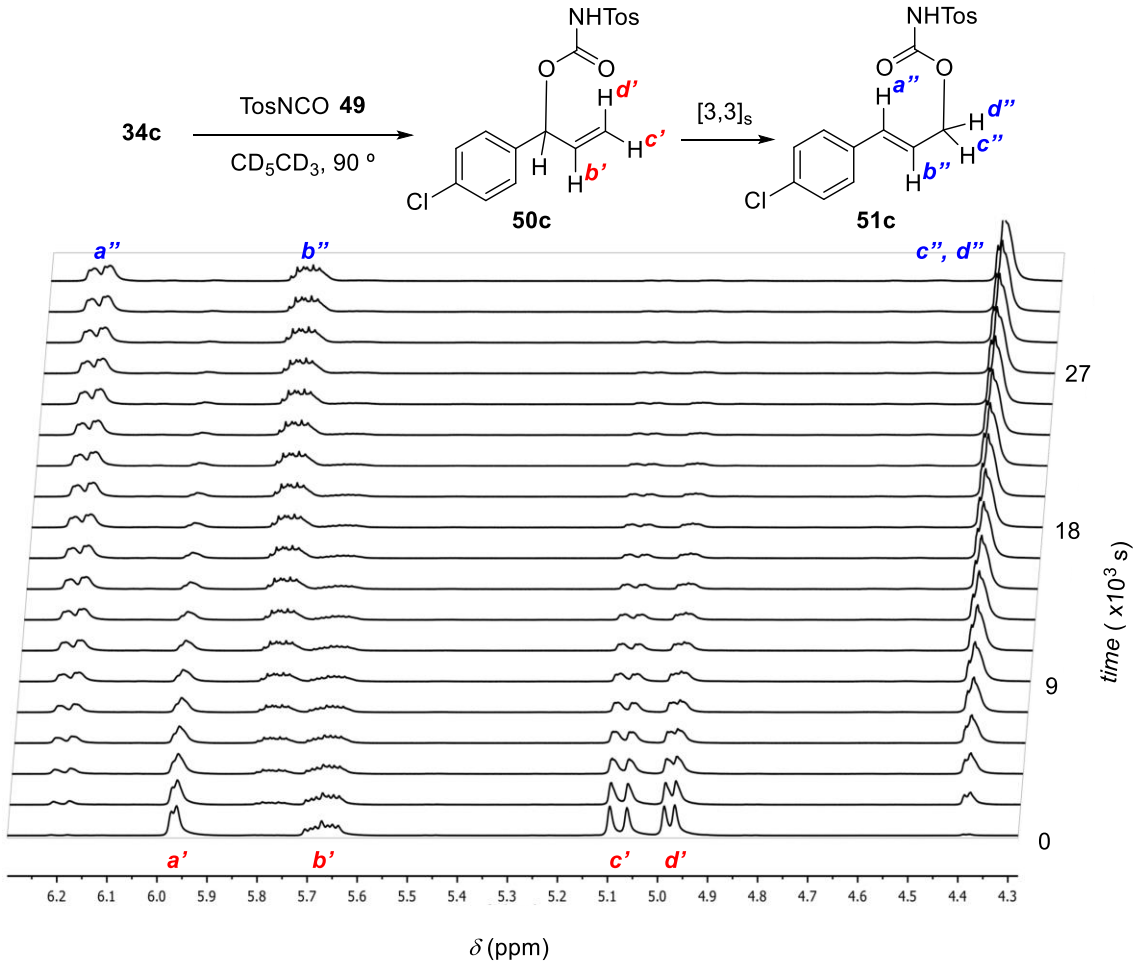


Figure 4.5. ^{1}H-NMR plots (500 MHz) corresponding to the reaction of 1-(4-chlorophenyl)prop-2-en-1-ol **34c** with *p*-toluenesulfonyl isocyanate at 90 °C to yield rearranged carbamate **51c** via intermediate **50c**. The successive spectra, recorded at different reaction times, show the evolution of the allyl hydrogens of both carbamates.

Table 4.6. Measured kinetic constants (k_{obs}) for the 1,3-dioxa-[3,3]-sigmatropic rearrangement of alcohols **34a-c**.[a,b,c]

Entry	Allyl alcohol	k_{obs} $(x10^{-4}s^{-1})$
1[d]	**34a**	16.3 (±0.50)
2	**34b**	1.62 (±0.06)
3	**34c**	1.08 (±0.04)

a) First-order constants calculated by means of eq. 2. b) All reactions were monitored by ^{1}H-NMR at 90 °C in 500 MHz. c) Errors were calculated from the standard deviations of the kinetic constants.[48] d) Monitored at room temperature.

[48] Harris, D.C. *Experimental Error in Quantitative Chemical Analysis*, 8th Ed. W.H. Freeman: New York, **2010**, pp 51-67.

4.4.3 Isotope labelling experiments

Along with kinetic measurements, isotope labelling ^{17}O-NMR experiments were also conducted, in order to verify the concerted pericyclic mechanism of the 1,3-dioxa-[3,3]-sigmatropic rearrangement and to discard the alternative [1,3] mechanism (**Scheme 4.12**). These experiments were performed by the employment of a mixture of 11.1% $H_2{}^{17}O$, 29.7% $H_2{}^{18}O$ and 59.2% $H_2{}^{16}O$. Conversion of (trichloromethyl)benzene **59** into labelled benzoic acid [*O_2]**60** by microwave irradiation[49] allowed two synthetic routes (**Figure 4.6A**). The first[50] led to diester **61**, which permitted the calibration of the performance of ^{17}O-NMR to distinguish between differently hybridised oxygen atoms (**Figure 4.6B**). Therein, two well separated signals can be distinguished (340 and 136 ppm), which were assigned to the sp^2 and sp^3 hybrydised ^{17}O nuclei, respectively. This separation would permit to differentiate between the starting and final resonances associated with the [$^{17}O_1$]**50b** → [$^{17}O_1$]**51b** transformation via a [3,3] topology.

The second synthetic route consisted of the conversion of labelled benzoic acid [*O_2]**60** into alcohol [*O_1]**34b**, following a reduction, oxidation and addition sequence (**Figure 4.6A**). Reaction of [*O_1]**34b** with tosyl isocyanate led immediately the labelled carbamate [*O_1]**50b**. Its ^{17}O-NMR spectrum showed a broad signal at 150 ppm, superimposed to the signal related to the sulfone moiety in natural abundance (check Annex III for details). Heating [$^{17}O_1$]**50b** at 90 °C enabled to observe a new ^{17}O signal at 264 ppm (**Figure 4.7**), which was interpreted to correspond to the sp^2-hybrydized ^{17}O nucleus of [$^{17}O_1$]**51b**. Furthermore, the increase of the [$^{17}O_1$]**51b** was coincident with the decrease of the broad signal of [$^{17}O_1$]**50b**, being the broad signals of the sulfone groups of both tosyl carbamates of similar chemical shift and intensity. These results led to the conclusion that the conversion of carbamates **50** into **51** occurs via a concerted pericyclic 1,3-dioxa-[3,3]-sigmatropic rearrangement.

[49] a) Retamosa, M. G.; Ruiz-Olalla, A.; Bello, T.; de Cózar, A.; Cossío, F. P. *Angew. Chem., Int. Ed.* **2018**, *57*, 668-672. b) Haiss, P.; Zeller, K.-P. *Angew. Chem., Int. Ed*. **2003**, *42*, 303-305.
[50] Chen, J.; Shao, Y.; Ma, L.; Ma, M.; Wan, X. *Org. Biomol. Chem*. **2016**, *14*, 10723-10732.

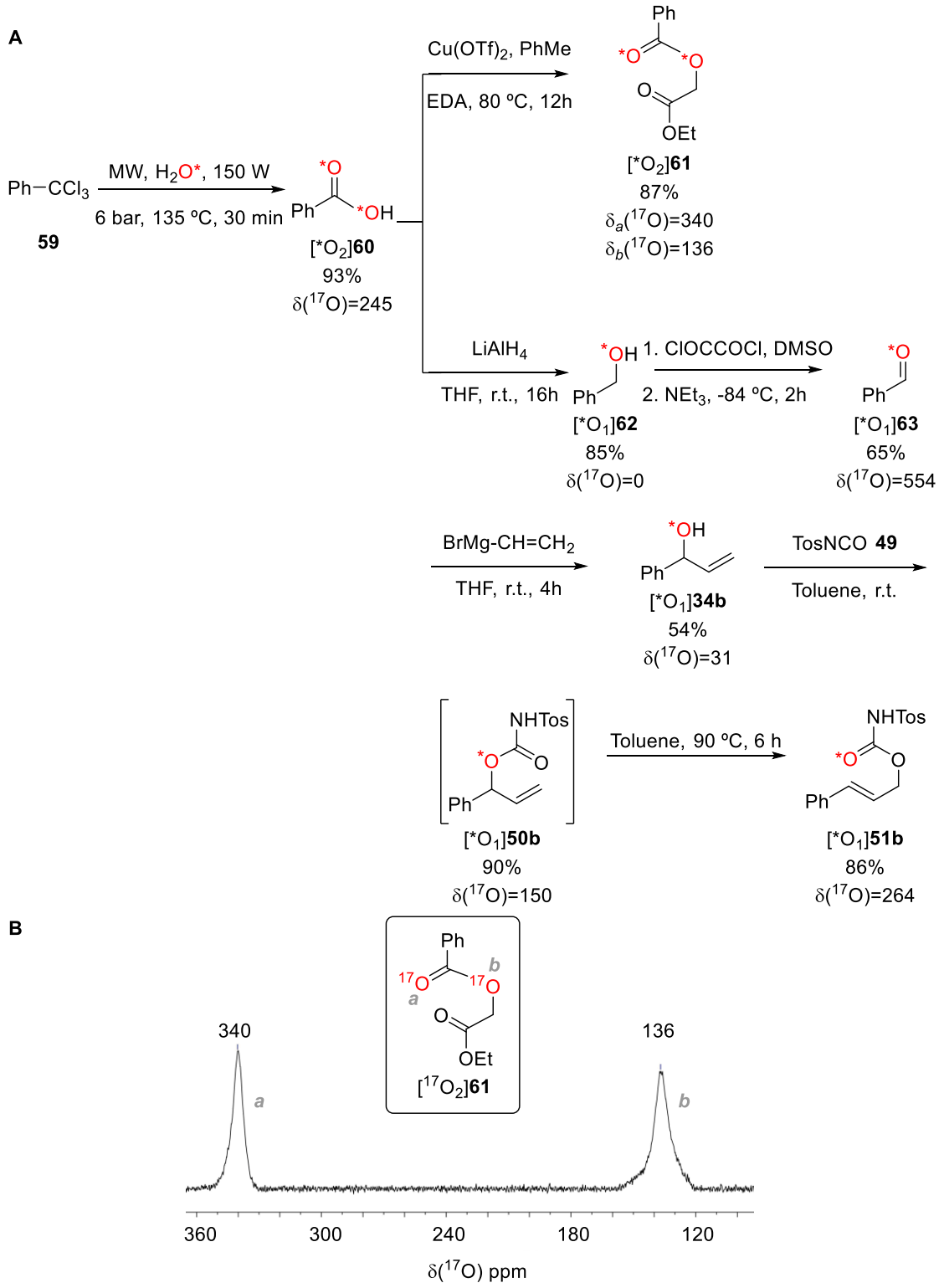


Figure 4.6. A) Synthesis of labelled allyl tosylcarbamates [*O$_1$]**50b** and [*O$_1$]**51b**, and diester [*O$_2$]**61**. The δ (^{17}O) chemical shifts of the [^{17}O]-labelled compounds are given in ppm. B) ^{17}O-NMR spectrum of diester [^{17}O$_2$]**61**, in which the sp^2 and sp^3-hybrydized oxygen atoms can be distinguished.

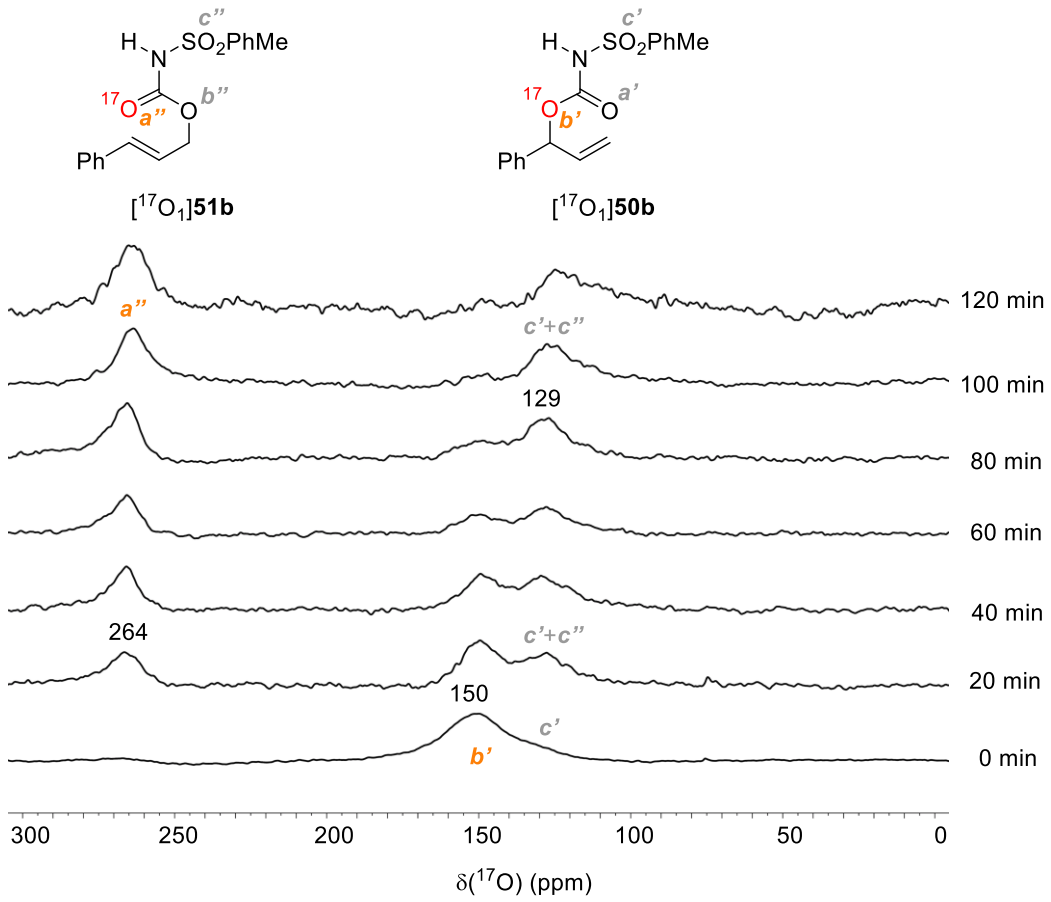


Figure 4.6. ^{17}O-NMR spectra of the [$^{17}O_1$]**50b** → [$^{17}O_1$]**51b** transformation recorded in deuterated toluene at different reaction times. The signals of the sulfone oxygen atoms (c' and c", natural abundances) are also indicated.

4.4.4 Computational studies

Since the ^{1}H-NMR experiments showed that the formation of 1-arylallyl tosylcarbamates **50b**,**c** was not kinetically relevant, DFT calculations were performed over **50b**,**c** → **51b**,**c** transformation at B3LYP-D3(PCM)/6-311++G(d,p) level of

theory.[51,52,53,54,55,56] Toluene was introduced as solvent, the Gibbs energies were calculated at 90 °C (363.15 K) and the [3,3] mechanism was assumed.

[51] B3LYP functional: a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.
[52] D3 dispersion empirical correction: Grimme, S.; Antony, J.; Enrlich, S.; Krieg, S. J. Chem. Phys. 2010, 132, 154104.
[53] 6-311++G(d,p) basis set: a) Wiberg, K. *J. Comp. Chem*. **2004**, *25*, 1342-1349. b) Hehre, W. J.; Random, L.; Schleyer, P. V. Pople, J. A. *Ab Initio Molecular Orbital Theory*, Wiley: New York, **1986**.
[54] PCM method: a) Cammi, R.; Mennucci, B.; Tomasi, J. *J. Phys. Chem. A* **2000**, *104*, 5631-5637. b) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev*. **2005**, *105*, 2999-3094.
[55] Gaussian 09 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision E.01, Gaussian, Inc., Wallingford CT, **2013**. NBO program, as implemented in Gaussian 09: Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc*. **1980**, *102*, 7211-7218. b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys*. **1985**, *83*, 735-746. c) Reed, A. E.; Weinhold, F. *J. Chem. Phys* **1985**, *83*, 1736-1740. d) Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 899-926.
[56] NBO program, as implemented in Gaussian 09: Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc*. **1980**, *102*, 7211-7218. b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys*. **1985**, *83*, 735-746. c) Reed, A. E.; Weinhold, F. *J. Chem. Phys* **1985**, *83*, 1736-1740. d) Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 899-926.

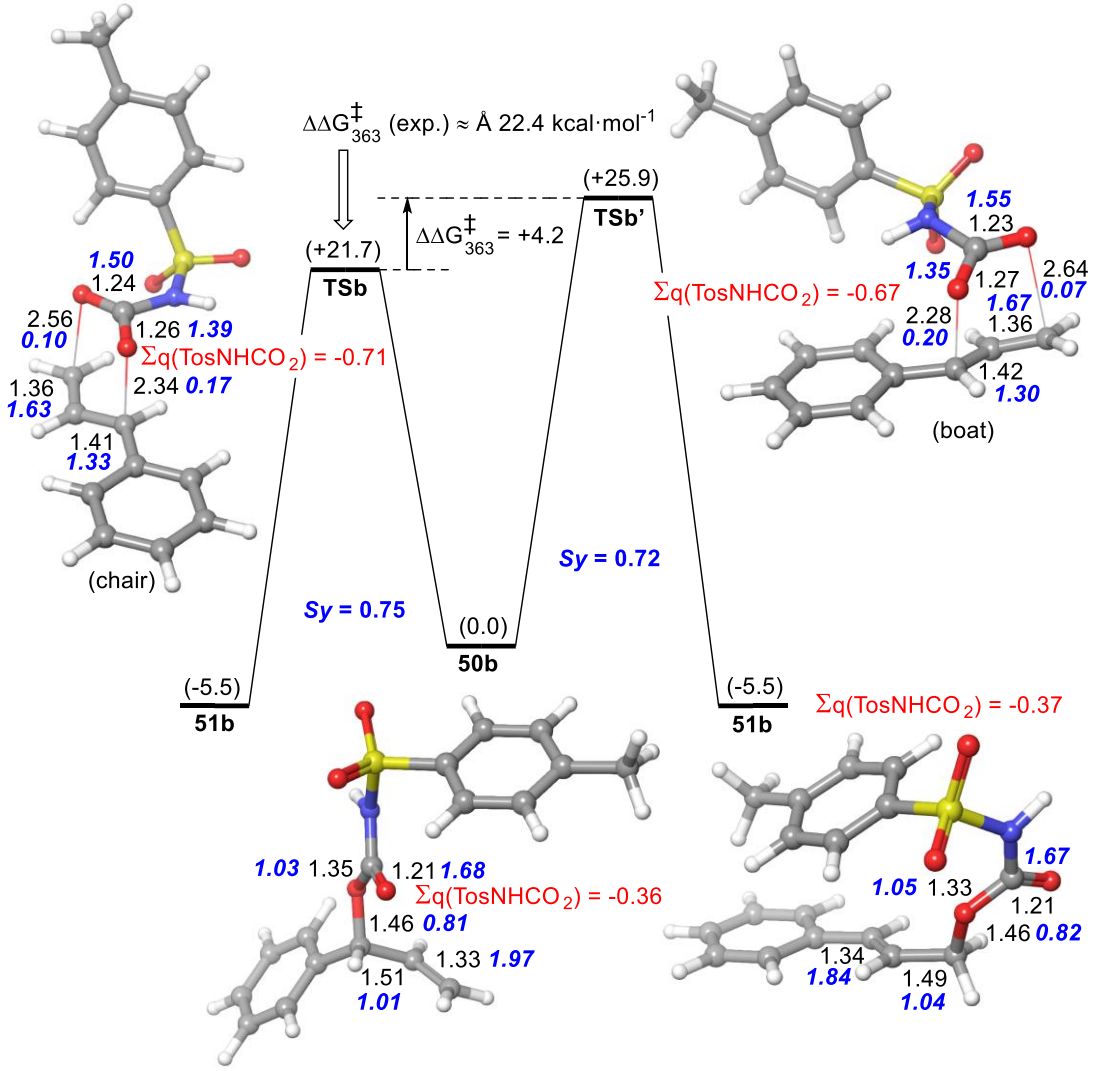


Figure 4.8. Reaction profile of the thermal rearrangement of 1-phenylallyltosylcarbamate **50b** to yield cinnamyl tosylcarbamate **51b**. All stationary points were calculated at the B3LYP-D3(PCM,solvent=toluene)/6-311++G(d,p) level of theory. Numbers in parentheses are the relative free energies, in kcal/mol, calculated at 363.15 K with respect to **50b**. The experimental Gibbs activation energy, estimated at the same temperature, is also provided. Bond distances are given in Å. Σq(CO_2) values, displayed in red, correspond to the natural charges of the carboxy moieties and are given in a. u. Numbers in blue correspond to the respective bond orders. The *Sy* parameter stands for the synchronicity of each elementary process via **TSb** and **TSb'**. For a perfectly synchronous transformation, *Sy*=1 (see text).

The reaction coordinate associated with the [3,3]-sigmatropic rearrangement of 1-phenylallyl tosylcarbamate **50b** to yield cinnamyl tosylcarbamate **51b** was analysed first (check **Figure 4.8**). Two transition structures **TSb** and **TSb'** were found, which respectively correspond to chair-like and boat-like geometries. The former saddle point was found to be ca. 4 kcal/mol less energetic than its boat congener, indicating that the only kinetically relevant reaction coordinate is **50b** → **TSb** → **51b**. The theoretical activation energy was calculated to be 21.7 kcal/mol. From the ^{1}H-NMR data (*vide supra*) the experimental Gibbs activation energy at 363 K was estimated from the Eyring equation (3) associated with k_{obs}:

$$k_{obs} = \kappa \frac{k_B \cdot 363.15}{h} exp\left[-\frac{\Delta G^{\ddagger}_{363}(exp)}{R \cdot 363.15}\right] \qquad (3)$$

Assuming $\kappa \approx 1$, the estimated activation energy was calculated to be 22.4 kcal/mol which is in excellent agreement with the computational value. Additionally, using the bond orders associated with the suprafacial [3,3]-sigmatropic shift, the earliness of the reaction path was computed via **TSb** as the average of the degree of advancement δB_{AV} of both saddle points, according to the following expression:

$$\delta B_{AV} = \frac{1}{6}\sum_{i=1}^{6} \delta B_i = \frac{1}{6}\sum_{i=1}^{6} \frac{B_i^{TS} - B_i^R}{B_i^P - B_i^R} \qquad (4)$$

where B_i is the bond order of the *i*-th bond involved in the pericyclic reaction at the reactant (*R*) **50b**, transtition state (TS) **TSb** and product (*P*) **51b**. For the **50b** → **TSb** → **51b** transformation it was found that δB_{AV} = 0.42. Since for an exactly midway transition structure δB_{AV} = 0.50, this result indicates an slightly early saddle point, with ΔG_{rxn}=-5.5 kcal/mol. The synchronicity *Sy* of the reaction was also calculated as

$$Sy = 1 - \frac{1}{10}\sum_{i=1}^{6} \frac{|\delta B_i - \delta B_{AV}|}{\delta B_{AV}} \qquad (5)$$

According to expression (5), for a perfectly synchronous [3,3]-sigmatropic shift, $\delta B_i = \delta B_{AV}$ for any i=1,2, … ,6 and therefore $|\delta B_i - \delta B_{AV}| = 0$ and *Sy*=1. In our case, a value of *Sy*=0.75 was found for the **50b** → **51b** mediated by **TSb**, which suggested a noticeable asynchronicity. When the same reaction is mediated by **TSb'**, the reaction was computed to be slightly more asynchronous (**Figure 4.8**). These results are in line with the geometries obtained for both saddle points, with two C···O distances associated with the bonds being broken and formed (**Figure 4.8**). This partially asynchronous but still concerted character of the reaction mechanism agrees with the preservation of the chiral information contained in the starting enantiopure allyl alcohol (**Scheme 4.15**). Finally, the charge analysis of the carboxylate moiety along the reaction coordinate showed that this charge was ca. 0.3 electrons higher in the transition structure than in the reactant and product (**Figure 4.8**). This result indicates relatively polar transition structures, with an associated positive charge delocalized in the allyl moiety. Thus, electron-withdrawing groups present in the starting allyl alcohol should destabilize this partial cationic character, leading to higher activation energies. Likewise, electron-donating substituents should accelerate the sigmatropic rearrangement, in good agreement with the experimental results (see **Tables 4.2**-**4.5**).

The above described DFT study was also conducted with intermediate tosylcarbamate **50c** which furnished *p*-chlorocynnamyl tosylcarbamate **51c** (**Figure 4.9**). In this case, the computed reaction profile was similar to that found for **51b** case. As

expected, the activation energy computed for the **50c** → **TSc** → **51c** reaction was calculated to be $\Delta G^{\ddagger}_{363}$ = 22.6 kcal/mol, a slightly higher value than the one found for the parent **50b** → **51b** transformation. However, the agreement between this latter computational value and the experimental estimate (22.7 kcal/mol) was lower than that found for the parent reaction, but still acceptable in qualitative terms, since it correctly reproduces the lower reaction rate of *p*-Cl substituted allyl alcohol in comparison to the non-substituted counterpart.

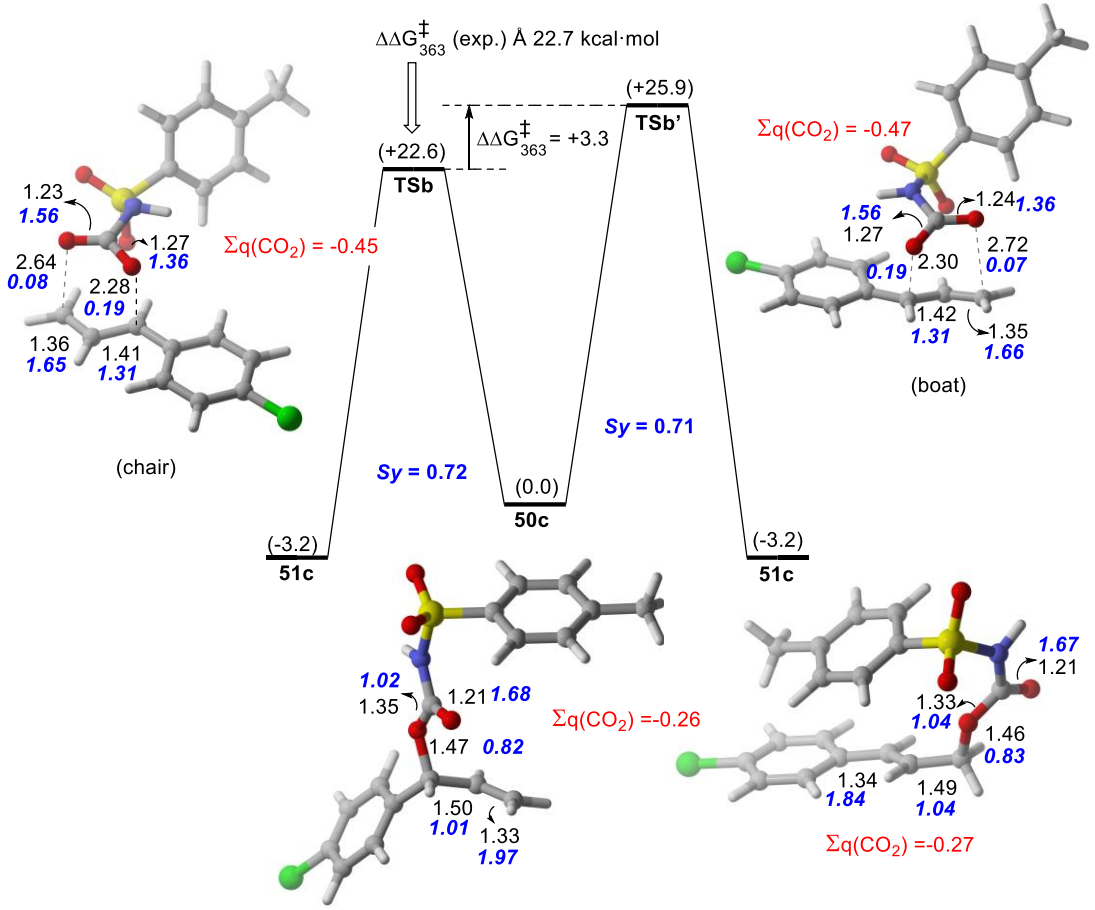


Figure 4.9. Reaction profile of the thermal rearrangement of 1-(4-chlorophenyl)allyltosylcarbamate **50c** to yield cinnamyl tosylcarbamate **51c**. All stationary points were calculated at the B3LYP-D3(PCM,solvent=toluene)/6-311++G(d,p) level of theory. Numbers in parentheses are the relative free energies, in kcal/mol, calculated at 363.15 K with respect to **50c**. The experimental Gibbs activation energy, estimated at the same temperature, is also provided. Bond distances are given in Å. Σq(CO_2) values, displayed in red, correspond to the natural charges of the carboxy moieties and are given in a. u. Numbers in blue correspond to the respective bond orders. The *Sy* parameter stands for the synchronicity of each elementary process via **TSb** and **TSb'**. For a perfectly synchronous transformation, *Sy*=1 (see text).

4.5 CONCLUSIONS

From the experimental and computational studies reported and discussed along this Chapter, the following conclusions can be drawn:

1. The unprecedented addition/[3,3]-sigmatropic oxo-rearrangement has been described, from which (*E*)-linear carbamates were synthesised. The mild reaction conditions under which the reaction operates make it a useful methodology for the generation of synthetically relevant carbamates.
2. The general nature of this tandem transformation was extended to a number of aryl and alkenyl substituted allyl alcohols and isocyanates. The electronic properties of the allyl moiety as well as the nature of the isocyanate resulted crucial for the reaction to occur. In general, electron-donating groups in the aromatic ring of the starting alcohols accelerate the process, whereas electron-withdrawing substituents decrease the reaction rate. As for isocyanates, activated derivatives are required.
3. HPLC studies corroborated the complete transfer of chiral information and the concerted character of the [3,3]-sigmatropic shift. This evidence supports the symmetry allowed concerted supra-supra mechanism in which a total transfer of the chiral information contained in the starting alcohol is achieved.
4. The ^{1}H-NMR studies carried out showed the very fast conversion of allyl alcohols **34b**,**c** into the intermediate tosylcarbamates **50b**,**c**. The kinetic studies over **50b**,**c** → **51b**,**c** process enabled the calculation of the k_{obs} values under first-order kinetic conditions. The corresponding calculated first-order reaction rates showed a relative MeO>H>Cl>>NO_2 reactivity, in good agreement with the previously reported experimental studies.
5. Isotope labelling experiments showed the interconversion of alcohol [$^{17}O_1$]**50b** into its regioisomer [$^{17}O_1$]**51b** giving evidence of the concerted pericyclic nature of the dioxa-[3,3]-sigmatropic rearrangement.
6. DFT computational studies showed an asynchronous but concerted suprafacial process mediated by chair-like transition structures, in agreement with the observed stereoselectivities during chirality transfer studies. Besides, the obtained saddle points reflected correctly the relative reaction rates and activation energies. The polar character of the transition structures was also illustrated. Therein, whilst the carboxy moiety bears a significant negative charge, an associated positive charge is delocalized in the allyl moiety.

4.6 EXPERIMENTAL SECTION

General remarks

Tetrahydrofuran (THF) was distilled over sodium/benzophenone and dichloromethane (CH_2Cl_2) was distilled over P_2O_5. All other commercially available

chemicals were used without further purification. 1-(phenyl)prop-2-en-1-ol is a commercially available compound. The [$^{17}O_1$] labelled H_2O (11.1% $H_2{}^{17}O$, 29.7% $H_2{}^{18}O$ and 59.2% $H_2{}^{16}O$) was purchased from Cortecnet.

TLC was performed on 0.25mm silica gel 60 F254 aluminum plates and visualized with UV lamps or potassium permanganate stain. Flash column chromatography was carried out on columns of silica gel 60 (particle size 23-40 μm). Compound **56** was purified using neutral aluminium oxide.

Optical rotations were measured at 589 nm (Sodium line) in a digital polarimeter with a thermally jacketed 5 cm cell at approximately 20 °C. Concentrations are given in g/100 mL.

Infrared spectra were recorded on an Alpha-Bruker FT-IR spectrometer with a single reflection ATR module. Wavenumbers are given in cm^{-1}.

High Resolution Mass Spectra (HRMS) analyses were recorded on a Micro-Tof-Q II or on a Q-Tof2 using positive ion electrospray.

NMR spectra were recorded at 400 or 500 MHz for ^1H NMR, 101 or 126 MHz for ^{13}C NMR, 376 MHz for ^{19}F NMR and 68 MHz for ^{17}O NMR using $CDCl_3$, acetone-*d6*, methanol-*d4* and toluene-*d8* as solvents and TMS as internal standard. The data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad signal, coupling constant(s) (*J*) in Hz, integration. ^{13}C NMR spectra were recorded with ^1H decoupling. Melting points were measured without correction on a digital melting point apparatus.

High Performance Liquid Chromatography (HPLC) analyses were performed using a Daicel ChiralPak IB column.

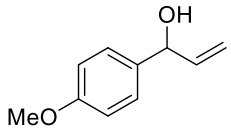
For X-Ray diffraction analyses Agilent Technologies Super-Nova diffractometer was employed, equipped with monochromated Cu kα radiation (λ = 1.54184 Å) and Atlas CCD detector. Measurements were accomplished at 100 K with the aid of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) utilizing the Crysalis software package.[57] The structure was solved by Superflip[58] and refined by full-matrix

[57] CrysAlisPro, Agilent Technologies, Version 1.171.37.31.
[58] Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786-790.

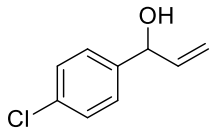
least-squares with SHELXL-97[59]. Final geometrical calculations were carried out on Mercury[60] and PLATON[61] as integrated in WinGX[62].

General Procedure for the synthesis of allyl alcohols

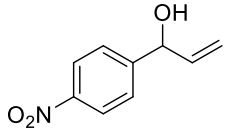
To a solution of the corresponding aldehyde (1.50 mmol, 1 eq.) in THF (10 mL) at 0 °C a solution of vinyl or phenylmagnesium bromide (1.80 mmol, 1.2 eq.) in THF was slowly added. The reaction mixture was stirred at room temperature for 16h and quenched with a saturated NH_4Cl (10 mL) solution. The aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (check each compound for conditions).



1-(4-methoxyphenyl)prop-2-en-1-ol (**34a**).[63] The title product was obtained from 4-methoxybenzaldehyde and vinyl magnesium bromide. Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.25). Yield 81% (1.22 mmol, 200 mg), yellow oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.05 (ddd, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.22 – 5.12 (m, 3H), 3.81 (s, 3H), 1.89-1.86 (br s, 1H).



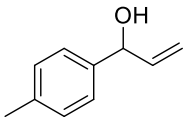
1-(4-chlorophenyl)prop-2-en-1-ol (**34c**).[44] The title product was obtained from 4-chlorobenzaldehyde and vinyl magnesium bromide. Purified on a 15:85 EtOAc:Hexane mixture (R_f 0.30). Yield 74% (1.10 mmol, 187 mg), pale yellow oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.31 (m, 4H), 6.01 (ddd, *J* = 17.0, 10.1, 6.1 Hz, 1H), 5.34 (dt, *J* = 17.0, 1.2 Hz, 1H), 5.25-5.15 (m, 2H), 1.95 (d, *J* = 3.7 Hz, 1H).



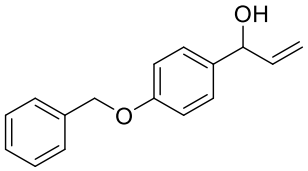
1-(4-nitrophenyl)prop-2-en-1-ol (**34d**).[64] The title product was obtained from 4-nitrobenzaldehyde and vinyl magnesium bromide. Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.20). Yield 30% (0.45 mmol, 81 mg), orange oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz,

[59] a) Sheldrick, G. M. *Acta Cryst*. **2008**, A64, 112-122. b) Sheldrick, G. M. *Acta Cryst*. **2015**, C71, 3-8.
[60] Macrae, C. F. *J. Appl. Cryst*. **2008**, *41*, 466-470.
[61] a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Utretch University, The Nederlands, **2010**. b) Spek, A. L. *J. Appl. Cryst*. **2003**, *36*, 7-13.
[62] Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838.
[63] Deng, Z.; Wei, J.; Liao, L.; Huang, H.; Zhao, X. *Org. Lett*. **2015**, *17*, 1834-1837.
[64] Slagbrand, T.; Lundberg, H.; Adolfsson, H. *Chem. Eur. J.* **2014**, *20*, 16102-16106.

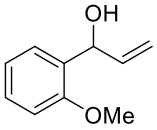
2H), 7.52 (d, *J* = 8.7 Hz, 2H), 5.96 (ddd, *J* = 17.1, 10.2, 6.4 Hz, 1H), 5.36 (ddd, *J* = 17.1, 1.2, 1.2 Hz, 1H), 5.28 (d, *J* = 6.4 Hz, 1H), 5.23 (ddd, *J* = 10.3, 1.1, 1.1 Hz, 1H), 2.67-2.65 (br s, 1H).



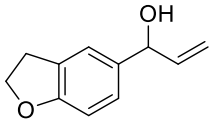
1-(p-tolyl)prop-2-en-1-ol (**34e**).[65] The title product was obtained from 4-methylbenzaldehyde and vinyl magnesium bromide. Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.32). Yield 98% (1.47 mmol, 218 mg), yellow oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.05 (ddd, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.21-5.17 (m, 2H), 2.35 (s, 3H), 1.93 (d, *J* = 5.98 Hz, 1H).



1-(4-(benzyloxy)phenyl)prop-2-en-1-ol (**34f**).[66] The title product was obtained from 4-benzyloxybenzaldehyde and vinyl magnesium bromide. Purified on a 25:75 EtOAc:Hexane mixture (R_f 0.30). Yield 79% (1.19 mmol, 284 mg), colorless oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 5H), 7.35 – 7.22 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.05 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.21 – 5.15 (m, 2H), 5.07 (s, 3H), 1.86 (d, *J* = 3.4 Hz, 1H).



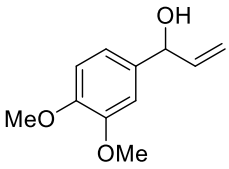
1-(2-methoxyphenyl)prop-2-en-1-ol (**34g**).[67] The title product was obtained from 2-methoxybenzaldehyde and vinyl magnesium bromide. Purified on a 15:85 EtOAc:Hexane mixture (R_f 0.44). Yield 70% (1.05 mmol, 172 mg), colorless oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.01 – 6.94 (m, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.14 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.41 (d, *J* = 5.6 Hz, 1H), 5.31 (dd, *J* = 17.2, 4.4 Hz, 1H), 5.17 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.87 (s, 3H), 2.77 (dd, *J* = 4.5, 3.8 Hz, 1H).



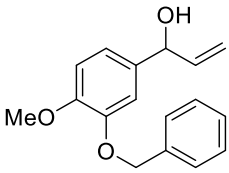
1-(2,3-dihydrobenzofuran-5-yl)prop-2-en-1-ol (**34h**).[68] The title product was obtained from 2,3-dihydrobenzofuran-5-carboxaldehyde and vinyl magnesium bromide. Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.33). Yield 98% (1.47 mmol, 259 mg), colorless oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, J = 13.8 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.81 (d,

[65] Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863-8874.
[66] Njiojob, C. N.; Rhinehart, J. L.; Bozell, J. J.; Long, B. K. *J. Org. Chem*. **2015**, *80*, 1771-1780.
[67] Morril, C.; Grubbs, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 2842-2843.
[68] Lin, H.; Liu, Y.; Wu, Z.-L. *Chem. Commun*. **2011**, *47*, 2610-2612.

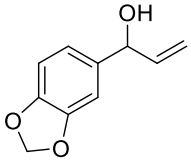
J = 8.2 Hz, 1H), 6.10 (ddd, *J* = 16.7, 10.3, 5.8 Hz, 1H), 5.34 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.24 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H), 5.19 (d, *J* = 5.8 Hz, 1H), 4.63 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H), 1.89 (br s, 1H).



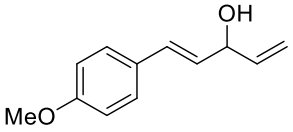
1-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**34i**).[69] The title product was obtained from 3,4-dimethoxybenzaldehyde and vinyl magnesium bromide. Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.27). Yield 40% (0.60 mmol, 117 mg), pale yellow oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94-6.89 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.09 – 5.98 (ddd, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 5.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 1.93 (br s, 1H).



1-(3-(benzyloxy)-4-methoxyphenyl)prop-2-en-1-ol (**34j**). Prepared from 3-benzyloxy-4-methoxybenzaldehyde and vinylmagnesium bromide. Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.21). Yield 80% (1.20 mmol, 324 mg), pale yellow oil. **FTIR (neat, cm^{-1})** 3488, 3054, 2935, 1511, 1263, 1157, 730, 698. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 6.94 – 6.90 (m, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.99 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.17 (m, 1H), 5.14 (s, 2H), 5.10 (m, 1H), 3.87 (s, 3H), 1.87 (d, J = 3.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1, 148.1, 140.3, 136.9, 135.3, 128.4, 127.7, 127.4, 119.2, 114.6, 112.3, 111.6, 74.6, 70.9, 55.9. **HRMS** (ESI) for $C_{17}H_{19}O_3$ $[M+H]^+$: calculated 271.1256, found 271.1256.



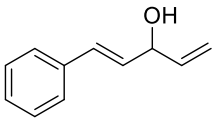
1-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (**34k**).[70] The title product was obtained from piperonal and vinylmagnesium bromide. Purified on a 10:90 EtOAc:Hexane mixture (R_f 0.17). Yield 76% (1.12 mmol, 203 mg), colorless oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 1.6 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.02 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.95 (s, 2H), 5.34 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.19 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H), 5.13 (m, 1H), 1.88 (d, *J* = 3.6 Hz, 1H).



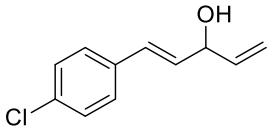
(E)-1-(4-methoxyphenyl)penta-1,4-dien-3-ol (**43a**). The title product was obtained from (*E*)-3-(4-methoxyphenyl)-2-propenal and vinylmagnesium bromide. Purified on a 25:75

[69] Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Org. Chem*. **2004**, *69*, 122-129.
[70] Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2012**, *51*, 3470-3473.

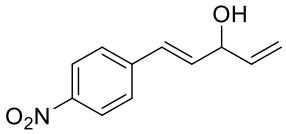
EtOAc:Hexane mixture (R_f 0.24). Yield 85% (1.28 mmol, 242 mg), yellow oil. **FTIR (neat, cm^{-1})** 3422, 3052, 1510, 1174, 1031. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.33 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.19 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 4.80-4.78 (m, 1H), 3.81 (s, 3H), 1.76 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 139.6, 130.6, 129.5, 128.3, 127.9, 115.3, 114.1, 74.1, 55.4. **HRMS** (ESI) for $C_{12}H_{13}O$ $[M+H-H_2O]^+$: calculated 173.0960, found 173.0933.



(E)-1-phenylpenta-1,4-dien-3-ol (**43b**).[71] The title product was obtained from (*E*)-3-phenyl-2-propenal and vinyl magnesium bromide. Purified on a 15:85 EtOAc:Hexane mixture (R_f 0.23). Yield 85% (1.28 mmol, 204 mg), pale yellow oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 7.30 – 7.20 (m, 2H), 6.62 (d, *J* = 16.1 Hz, 1H), 6.23 (dd, *J* = 16.1, 6.4 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.34 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.20 (ddd, *J* = 10.4, 1.3, 1.3 Hz, 1H), 4.89 – 4.76 (m, 1H), 1.75 (m, 1H).



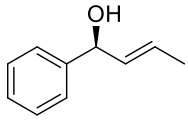
(E)-1-(4-chlorophenyl)penta-1,4-dien-3-ol (**43c**). The title product was obtained from (*E*)-3-(4-chlorophenyl)-2-propenal and vinyl magnesium bromide. Purified on a 25:75 EtOAc:Hexane mixture (R_f 0.35). Yield 73% (1.10 mmol, 213 mg), pale yellow oil. **FTIR (neat, cm^{-1})** 3271, 3086, 2982, 1638, 1581, 1488, 1085, 1008, 967, 805. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 4H), 6.57 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.21 (dd, *J* = 16.0, 6.3 Hz, 1H), 5.96 (ddd, *J* = 17.4, 10.3, 6.0 Hz, 1H), 5.34 (ddd, *J* = 17.4, 1.3, 1.3 Hz, 1H), 5.21 (ddd, *J* = 10.4, 1.3, 1.3 Hz, 1H), 4.83-4.79 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.1, 135.1, 133.3, 131.1, 129.4, 128.7, 127.7, 115.5, 73.5. **HRMS** (ESI) for $C_{11}H_{10}Cl$ $[M+H-H_2O]^+$: calculated 177.0467, found 177.0469.



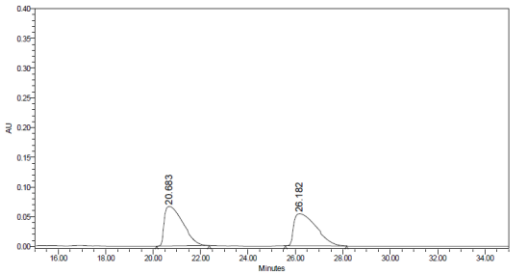
(E)-1-(4-nitrophenyl)penta-1,4-dien-3-ol (**43d**).[72] The title product was obtained from (*E*)-3-(4-nitrophenyl)-2-propenal and vinyl magnesium bromide. Purified on a 25:75 EtOAc:Hexane mixture (R_f 0.24). Yield 40% (0.60 mmol, 123 mg), orange oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 – 8.16 (m, 2H), 7.56 – 7.47 (m, 2H), 6.71 (d, *J* = 16.9 Hz, 1H), 6.42 (dd, *J* = 16.9, 5.8 Hz, 1H), 5.97 (ddd, *J* = 17.1, 10.3, 6.1 Hz, 1H), 5.38 (ddd, *J* =

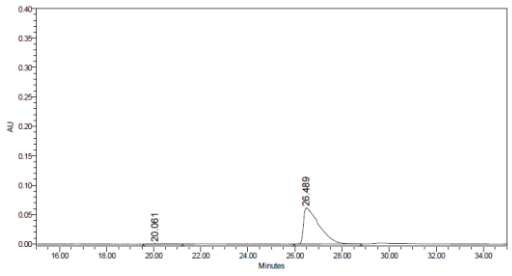
[71] Lindstedt, E.; Ghosh, R.; Olofsson, E. *Org. Lett*. **2013**, *15*, 6070-6073.
[72] Han, S. B.; Krische, M. J. *Org. Lett*. **2006**, *8*, 5657-5660.

17.1, 1.2, 1.2 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.2, 1.2 Hz, 1H), 4.93 – 4.82 (m, 1H), 1.83 (d, *J* = 4.2 Hz, 1H).



(S,E)-phenylbut-2-en-1-ol (**54**).[73] The title product was obtained from (*E*)-crotonaldehyde and phenylmagnesium bromide. Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.25). Yield 85% (1.28 mmol, 190 mg), yellow oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.32 (m, 4H), 7.31 - 7.27 (m, 1H), 5.84 - 5.63 (m, 2H), 5.16 (d, *J* = 6.4 Hz, 1H), 1.72 (d, *J* = 5.9 Hz, 3H), 1.61 (d, *J* = 3.4 Hz, 1H). **HPLC** (Daicel Chiralpak IB Hexane:^{i}PrOH = 99:1, flow rate = 1 mL/min, λ = 220 nm), t_R (minor) =20.68 min, t_R (major) =26.18 min (*ee* 98%, $[\alpha]_D^{25}$ = +24.6 (*c* 0.65, chloroform)).





	RT	Height	Area	% Area
1	20.683	66612	3620094	50.50
2	26.182	54062	3548264	49.50

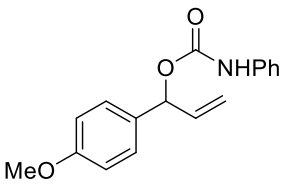
	RT	Height	Area	% Area
1	20.061	643	32048	1.19
2	26.489	61082	2787453	98.86

General Procedure for the synthesis of allyl carbamates

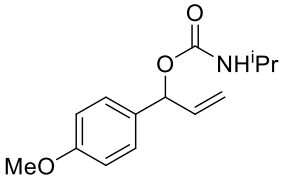
Using phenyl and isopropyl isocyanate

To a solution of allyl alcohol **34a** (0.7 mmol) in anhidrous CH_2Cl_2 (0.35 M) the corresponding isocyanate (1.05 mmol, 1.5 eq), Et_3N (1.05 mmol, 1.5 eq) and DMAP (0.04 mmol, 5 mol%) were successively added. The reaction was stirred at reflux for 16 hours. Dichloromethane was evaporated under reduced pressure and the crude product was purified by silica gel chromatography (check each compound for conditions).

[73] Srinivas, H. D.; Zhou, Q.; Watson, M. P. *Org. Lett*. **2014**, *16*, 3596-3599.



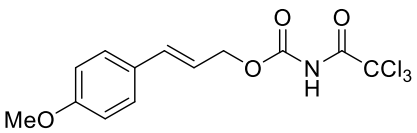
1-(4-Methoxyphenyl)allyl phenylcarbamate (**48a**). The title product was obtained from phenyl isocyanate. Purified on a 20:80 EtOAc:Cyclohexane mixture (R_f 0.28). Yield 30% (0.21 mmol, 59 mg), colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 6H), 7.11 – 7.05 (m, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.87-6.83 (br s, 1H), 6.28 (d, *J* = 5.7 Hz, 1H), 6.10 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.42 – 5.26 (m, 2H), 3.83 (s, 3H). **^{13}C NMR** (101 MHz, Acetone-*d6*) δ 160.5, 153.5, 140.1, 138.1, 132.4, 129.6, 129.4, 123.4, 119.1, 116.2, 114.6, 76.7, 55.5. **HRMS** (ESI) for $C_{17}H_{17}NO_3Na$ $[M+Na]^+$: calculated 306.1101, found 306.1099.



1-(4-Methoxyphenyl)allyl isopropylcarbamate (**48b**). The title product was obtained from isopropyl isocyanate. Purified on a 10:90 EtOAc:Cyclohexane mixture (R_f 0.18). Yield 65% (0.45 mmol, 113 mg), yellow solid. **m_p** = 120 - 123 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.13 (d, *J* = 5.7 Hz, 1H), 6.01 (ddd, *J* = 17.1, 10.4, 5.6 Hz, 1H), 5.34 - 5.11 (m, 2H), 4.60-4.55 (br s, 1H), 3.88 - 3.80 (m, 1H), 3.80 (s, 3H), 1.14 (dd, *J* = 8.7, 6.4 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.5, 154.9, 137.1, 131.7, 128.7, 116.1, 114.0, 113.6, 76.0, 55.3, 23.1. **HRMS** (ESI) for $C_{14}H_{19}NO_3Na$ $[M+Na]^+$: calculated 272.1257, found 272.1254.

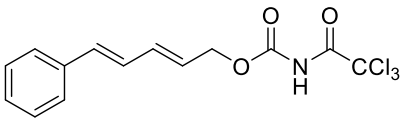
Using trichloroacetyl isocyanate

A solution of the corresponding allyl alcohol **34a**-**d, 43a**-**d** (0.30 mmol, 1 eq.) in anhydrous toluene or CH_2Cl_2 (0.2 M) under argon atmosphere was cooled down to 0 °C and trichloroacetyl isocyanate (0.36 mmol, 1.2 eq.) was slowly added. The reaction mixture was stirred until total consumption of the starting alcohol. The solvent was evaporated under reduced pressure and the resulting intermediate was dissolved in methanol (0.15 M). A solution of K_2CO_3 (1.2 mmol, 4 eq.) in water (0.6 M) was added, the resulting mixture was stirred at room temperature for 16h and MeOH was evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (4 x 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (check each compound for conditions). In some cases the intermediates could have been identified.

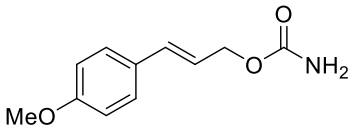


(E)-3-(4-methoxyphenyl)allyl (2,2,2-trichloroacetyl)carbamate (**40a**). The title product was obtained from allyl alcohol **34a** (r.t., 15 min.). Yield 98% (0.29 mmol, 103 mg), colorless oil. The intermediate was used in the

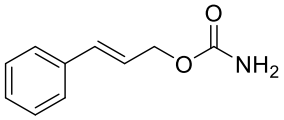
next step without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.50-8.46 (br s, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.7, 6.9 Hz, 1H), 4.88 (dd, *J* = 6.9, 1.2 Hz, 2H), 3.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.9, 157.9, 149.8, 136.2, 128.1, 118.9, 114.1, 91.8, 68.3, 55.3.



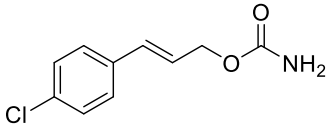
(2E,4E)-5-phenylpenta-2,4-dien-1-yl (2,2,2-trichloroacetyl)carbamate (**45b**). The title product was obtained from allyl alcohol **43b** (r.t., 4h). Yield 98% (1.28 mmol, 102 mg), white solid. The intermediate was used in the next step without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.50-8.45 (br s, 1H), 7.42 – 7.36 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.21 (m, 1H), 6.76 (dd, *J* = 15.6, 10.2 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.53 (ddd, *J* = 15.1, 1.1, 1.1 Hz, 1H), 5.88 (dt, *J* = 15.1, 6.9 Hz, 1H), 4.83 (dd, *J* = 6.9, 1.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.8, 149.7, 136.7, 135.1, 128.7, 128.2, 127.2, 126.7, 124.7, 91.8, 67.7.



(E)-3-(4-methoxyphenyl)allyl carbamate (**37a**). The title compound was obtained from intermediate **39a**. Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.31). Yield 73% (0.22 mmol, 45 mg), white solid. **m_p** = 131-134 °C. **FTIR (neat, cm^{-1})** 3423, 3263, 3204, 3009, 1682, 1244, 1028. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.17 (dt, *J* = 15.9, 6.3 Hz, 1H), 5.90-5.84 (br s, 2H), 4.57 (dd, *J* = 6.3, 1.5 Hz, 2H), 3.75 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 161.0, 159.8, 134.1, 130.5, 128.8, 122.7, 115.0, 66.4, 55.7. **HRMS** (ESI) for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$: calculated 230.0793, found 230.0786.



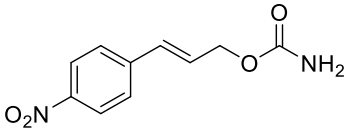
(E)-(phenyl)allyl carbamate (**37b**). The title compound was obtained from 1-(phenyl)prop-2-en-1-ol (90 °C, 16h). Purified on a 30/70 EtOAc:Hexane mixture (R_f 0.28). Yield 92% (0.28 mmol, 49 mg), white solid. **m_p** = 116-119 °C. **FTIR (neat, cm^{-1})** 3409, 3263, 3052, 3028, 1681, 1408, 501. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.9, 6.3 Hz, 1H), 5.01-4.92 (br s, 2H), 4.70 (dd, *J* = 6.3, 1.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9 , 136.4 , 133.9 , 128.7 , 128.1 , 126.7 , 123.7 , 65.8. **HRMS** (ESI) for $C_{10}H_{11}NO_2Na$ $[M+Na]^+$: calculated 200.0687, found 200.0686.



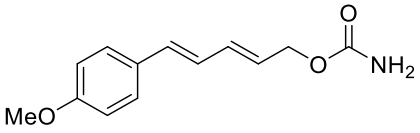
(E)-3-(4-chlorophenyl)allyl carbamate (**37c**).[74] The title product was obtained from allyl alcohol **34c** (90 °C, 20h).

[74] Deng, Q.-H.; Wang, J.-C.; Xu, Z.-J.; Zhou, C.-Y.; Che, C.-M. *Synthesis* **2011**, *18*, 2959-2967.

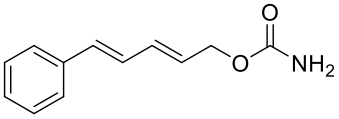
Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.27). Yield 50% (0.15 mmol, 32 mg), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 4H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.26 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.78-4.74 (br s, 2H), 4.72 (dd, *J* = 6.3, 1.4 Hz, 2H).



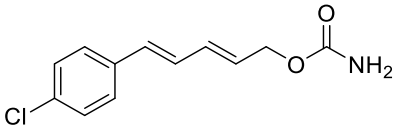
(E)-3-(4-nitrophenyl)allyl carbamate (**37d**).[19] The title product was obtained from allyl alcohol **34d** (90 °C, 120 h). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.10). Yield 43% (0.13 mmol, 28 mg), yellow solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.46 (dt, *J* = 16.0, 5.8 Hz, 1H), 4.78 (dd, *J* = 5.8, 1.5 Hz, 2H), 4.73-4.66 (br s, 2H).



(2E,4E)-5-(4-methoxyphenyl)penta-2,4-dien-1-yl carbamate (**46a**). The title product was obtained from allyl alcohol **43a** (r.t., 2h). Purified on a 35:65 EtOAc:Hexane mixture (R_f 0.29). Yield 25% (0.07 mmol, 17 mg), pale yellow solid. **m_p** = 150-153 °C. **FTIR (neat, cm^{-1})** 3436, 3269, 3014, 1685, 1508, 522. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.65 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.43 (dd, *J* = 15.2, 10.2 Hz, 1H), 5.83 (dt, *J* = 15.1, 6.6 Hz, 1H), 4.71-4.67 (br s, 2H), 4.64 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6, 156.8, 134.9, 133.5, 129.9, 127.9, 126.2, 125.9, 114.36, 65.7, 55.5. **HRMS** (ESI) for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$: calculated 256.0950; found 256.0956.



(2E,4E)-5-phenylpenta-2,4-dien-1-yl carbamate (**46b**).[46c] The title compound was obtained from intermediate **43b**. Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.27). Yield 65% (0.20 mmol, 40 mg), yellow solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.37 – 7.29 (m, 2H), 7.29 – 7.22 (m, 1H), 6.78 (dd, *J* = 15.8, 10.4 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.46 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.89 (dt, *J* = 15.3, 6.4 Hz, 1H), 4.77-4.68 (br s, 2H), 4.66 (dd, *J* = 6.6, 1.5 Hz, 2H).

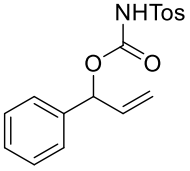


(2E,4E)-5-(4-chlorophenyl)penta-2,4-dien-1-yl carbamate (**46c**). The title product was obtained from allyl alcohol **43c** (r.t., 4h). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.27). Yield 75% (0.23 mmol, 53 mg), yellow solid. **m_p** = 167-170 °C. **FTIR (neat, cm^{-1})** 3410, 3286, 3028, 1699, 1486, 827, 508. **^{1}H NMR** (400

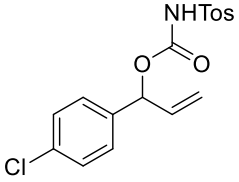
MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 4H), 6.74 (dd, *J* = 15.8, 10.4 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.44 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.90 (dt, *J* = 15.2, 6.4 Hz, 1H), 4.66 (dd, *J* = 6.4, 1.5 Hz, 2H), 4.63-4.58 (br s, 2H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 159.7, 137.3, 134.4, 134.2, 132.9, 130.0, 129.9, 129.8, 128.9, 65.8. **HRMS** (ESI) for $C_{12}H_{12}ClNO_2Na$ $[M+Na]^+$: calculated 260.0454; found 260.0461.

Using *p*-toluenesulfonyl isocyanate

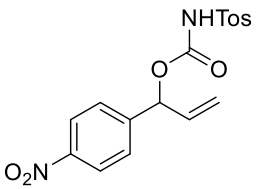
To a solution of allyl alcohol **34a-k** or **43a-d** (0.30 mmol, 1 eq.) in anhydrous toluene or CH_2Cl_2 (0.2 M) under argon atmosphere, *p*-toluenesulfonyl isocyanate (0.36 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred until total consumption of the starting alcohol. The solvent was evaporated under reduced pressure and the product was purified by flash column chromatography (check each compound for conditions). In some cases the intermediates could have been identified.



1-phenylallyl tosylcarbamate (**50b**).[75] The title product was obtained from 1-(phenyl)prop-2-en-1-ol (r.t., 5 min). Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.31). Yield 92% (0.28 mmol, 91 mg), colorless oil. Analytical and spectroscopic data were in good agreement with those reported in the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.55-7.53 (br s, 1H), 7.34 – 7.26 (m, 5H), 7.21 (dd, *J* = 6.8, 3.0 Hz, 2H), 6.11 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.92 (ddd, *J* = 16.7, 10.5, 5.9 Hz, 1H), 5.27-5.23 (m, 2H), 2.43 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 145.2, 137.5, 135.1, 129.7, 128.7, 128.5, 127.3, 118.2, 79.4, 21.8.



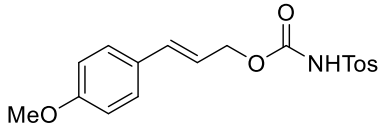
1-(4-chlorophenylallyl) tosylcarbamate (**50c**). The title product was obtained from allyl alcohol **34c** (r.t., 5 min). Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.30). Yield 85% (0.26 mmol, 93 mg), colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.70-7.67 (br s, 1H), 7.33 – 7.23 (m, 4H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.07 (d, *J* = 5.9 Hz, 1H), 5.87 (ddd, *J* = 16.7, 10.8, 5.9 Hz, 1H), 5.27-5.23 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 145.3, 136.1, 135.6, 134.6, 129.8, 128.9, 128.7, 128.5, 118.6, 78.5, 21.8. **HRMS** (ESI) for $C_{17}H_{16}ClNO_4SNa$ $[M+Na]^+$: calculated 388.0381; found: 388.0380.



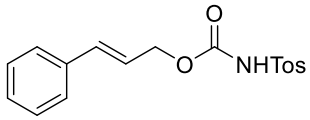
1-(4-nitrophenylallyl) tosylcarbamate (**50d**). The title product was obtained from allyl alcohol **34d** (r.t., 5 min). Purified on a 40:60 EtOAc:Hexane mixture (R_f 0.31). Yield 90% (0.27 mmol, 101 mg),

[75] Xing, D.; Yang, D. *Org. Lett*. **2010**, *12*, 1068-1071.

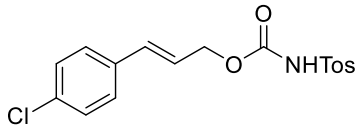
yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.16 (d, *J* = 6.1 Hz, 1H), 5.85 (ddd, *J* = 16.8, 10.5, 6.1 Hz, 1H), 5.33 – 5.24 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.5, 147.9, 145.5, 144.7, 135.5, 133.9, 129.8, 128.4, 127.8, 123.9, 119.7, 77.9, 21.8. **HRMS** (ESI) for $C_{17}H_{20}N_3O_6S$ $[M+NH_4]^+$: calculated 394.1073; found: 394.1068.



(E)-3-(4-methoxyphenyl)allyl tosylcarbamate (**51a**). The title product was obtained from allyl alcohol **34a** (r.t., 15 min). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.23). Yield 90% (0.27 mmol, 98 mg), colorless oil. NMR spectra in $CDCl_3$ at 298K revealed the presence of two conformers (rotamers) in a 55/45 ratio. **FTIR (neat, cm^{-1})** 3590, 3356, 3259, 2959, 1744, 1510, 1300, 1245. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 1.1H), 7.81 (d, *J* = 8.6 Hz, 0.9H), 7.37 – 7.28 (m, 4H), 6.85 (d, *J* = 4.7 Hz, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.01 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.77-4.75 (br s, 1H), 4.69 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.81 (s, 3H), 2.43 (s, 1.65H), 2.42 (s, 1.35H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 150.6, 145.1, 143.6, 139.2, 135.6, 135.3, 129.8, 129.7, 128.6, 128.5, 128.1, 126.5, 119.4, 114.2, 67.8, 55.4, 21.8, 21.6. **HRMS** (ESI) for $C_{18}H_{23}N_2O_5S$ $[M+NH_4]^+$: calculated 379.1328, found 379.1324.



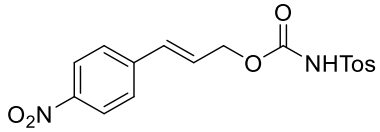
(E)-3-phenylallyl tosylcarbamate (**51b**).[76] The title product was obtained from intermediate **50b** (90 °C, 6h). Purified on a 40:60 EtOAc:Hexane mixture (R_f 0.39). Yield 95% (0.28 mmol, 94 mg), white solid. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 75/25 ratio. **m_p** = 73-76 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 1.5H), 7.82 (m, 0.5H), 7.37 – 7.25 (m, 7H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.72 (dd, *J* = 6.6, 1.3 Hz, 2H), 2.43 (s, 0.75H), 2.42 (s, 2.25H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.7, 145.1, 143.5, 139.2, 135.8, 135.5, 135.2, 129.7, 129.6, 128.7, 128.4, 128.3, 126.7, 126.4, 121.7, 67.3, 21.7, 21.5. **HRMS** (ESI) for $C_{17}H_{21}N_2O_4S$ $[M+NH_4]^+$: calculated 349.1227, found 349.1222.



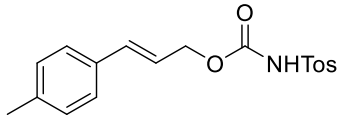
(E)-3-(4-chlorophenyl)allyl tosylcarbamate (**51c**). The title product was obtained from intermediate **50c** (90 °C, 20h). Purified on a 35:65 EtOAc:Hexane mixture (R_f 0.26). Yield 70% (0.21 mmol, 77 mg), white solid. Analytical and spectroscopic data were in good agreement with those reported in the literature. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 60/40 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1.2H), 7.82 (d, *J* = 8.1 Hz, 0.8H), 7.37 – 7.22 (m, 6H), 6.53 (d, *J* =

[76] Chow, S. Y.; Stevens, M. Y.; Odell, L. R. *J. Org. Chem*. **2016**, *81*, 2681-2691.

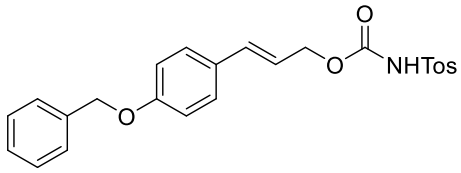
15.9 Hz, 1H), 6.12 (dt, *J* = 16.0, 6.6 Hz, 1H), 4.83-4.81 (br s, 1H), 4.71 (dd, *J* = 6.6, 1.3 Hz, 2H), 2.43 (s, 1.8H), 2.42 (s, 1.2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.6, 145.2, 143.7, 139.2, 134.4, 134.1, 133.9, 129.8, 129.7, 129.6, 128.9, 128.5, 128.3, 127.9, 126.5, 122.5, 67.1, 21.8.



(E)-3-(4-nitrophenyl)allyl tosylcarbamate (**51d**). The title product was obtained from intermediate **50d** (90 °C, 4 days, 70% conversion). Purified on a 20:80 EtOAc:Hexane mixture (R_f 0.15). Yield 40% (0.12 mmol, 45 mg), yellow oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 99/1 ratio. **FTIR (neat, cm^{-1})** 3534, 3237, 1748, 1520, 1345. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.77 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.43 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.4, 142.3, 135.5, 132.41, 129.8, 128.6, 127.4, 126.8, 124.2, 66.6, 21.9. **HRMS** (ESI) for $C_{17}H_{20}N_3O_6S$ $[M+NH_4]^+$: calculated 394.1067, found: 394.1067.

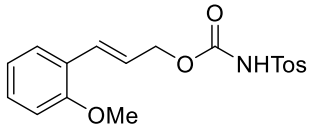


(E)-3-(4-methylphenyl)allyl tosylcarbamate (**51e**). The title product was obtained from allyl alcohol **34e** (90 °C, 6h). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.26). Yield 70% (0.21 mmol, 72 mg), white solid. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 65/35 ratio. **m_p** = 82-85 °C. **FTIR (neat, cm^{-1})** 3354, 2948, 1754, 1436, 1344. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1.3 H), 7.82 (d, *J* = 8.1 Hz, 0.7H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.73-4.69 (br s, 1H), 4.71 (dd, *J* = 6.7, 1.2 Hz, 2H), 2.43 (s, 1.05H), 2.42 (s, 1.95H), 2.34 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.7, 145.1, 143.6, 139.2, 138.4, 135.4, 133.1, 129.8, 129.7, 129.4, 128.4, 126.7, 126.5, 120.7, 67.6, 21.7, 21.6, 21.3. **HRMS** (ESI) for $C_{18}H_{23}N_2O_4S$ $[M+NH_4]^+$: calculated 363.1379, found 363.1378.

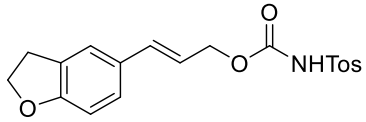


(E)-3-(4-benzyloxy)phenyl)allyl tosylcarbamate (**51f**). The title product was obtained from allyl alcohol **34f** (r.t., 15 min). Purified on a 35:65 EtOAc:Hexane mixture (R_f 0.38). Yield 74% (0.22 mmol, 97 mg), white solid. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 65/35 ratio. **m_p** = 106-109. **FTIR (neat, cm^{-1})** 3356, 1739, 1512, 1153. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.88 (d, *J* = 8.42 Hz, 1.3H), 7.86 – 7.78 (d, *J* = 8.15 Hz , 0.7H), 7.50 – 7.25 (m, 9H), 6.97 – 6.86 (d, *J* = 8.42 Hz , 2H), 6.53 (d, *J*

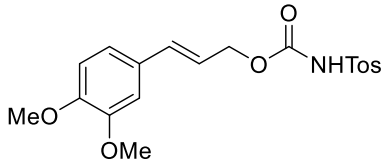
= 15.8 Hz, 1H), 6.01 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.07 (s, 2H), 4.76-4.73 (br s, 1H), 4.69 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.43 (s, 1.05H), 2.42 (s, 1.95H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.1, 150.6, 145.2, 143.6, 139.2, 136.8, 135.6, 135.2, 129.8, 129.7, 128.9, 128.7, 128.5, 128.2, 128.1, 127.6, 126.5, 119.6, 115.1, 70.1, 67.7, 21.76, 21.62. **HRMS** (ESI) for $C_{24}H_{27}N_2O_5S$ $[M+NH_4]^+$: calculated 455.1641, found 455.1647.



(E)-3-(2-methoxyphenyl)allyl tosylcarbamate (**51g**). The title product was obtained from allyl alcohol **34g** (r.t., 16h). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.24). Yield 85% (0.26 mmol, 92 mg), yellow oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 65/35 ratio. **FTIR (neat, cm^{-1})** 3257, 3067, 1744, 1152. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 1.3H), 7.81 (d, *J* = 8.1 Hz, 0.7H), 7.34-7.22 (m, 4H), 6.94 – 6.84 (m, 2H), 6.16 (dt, *J* = 16.0, 6.6 Hz, 1H), 5.25-5.20 (br s, 1H), 4.70 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 1.05H), 2.39 (s, 1.95H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.0, 150.6, 145.1, 143.5, 139.3, 135.6, 130.6, 129.8, 129.7, 129.5, 128.5, 127.3, 126.5, 124.9, 122.3, 120.7, 111.0, 68.0, 55.5, 21.7, 21.6. **HRMS** (ESI) for $C_{18}H_{23}N_2O_5S$ $[M+NH_4]^+$: calculated 379.1328, found 379.1325.

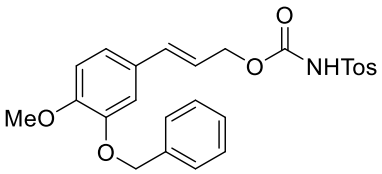


(E)-3-(2,3-dihydrobenzofuran-5-yl)allyl tosylcarbamate (**51h**). The title product was obtained from allyl alcohol **34h** (r.t., 1h). Purified on a 40:60 EtOAc:Hexane mixture (R_f 0.30). Yield 36% (0.11 mmol, 40 mg), colorless oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 99/1 ratio. **FTIR (neat, cm^{-1})** 3374, 3280, 1746, 1599, 1161. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 2H), 7.31 (m, 2H), 7.22 – 7.19 (m, 1H), 7.07 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 15.7 Hz, 1H), 5.98 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.68 (dd, *J* = 6.8, 1.2 Hz, 2H), 4.58 (t, *J* = 8.7 Hz, 2H), 3.19 (t, *J* = 8.7 Hz, 2H), 2.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6, 150.5, 145.2, 135.9, 135.6, 129.7, 128.6, 127.5, 123.2, 118.7, 109.5, 71.7, 67.9, 29.6, 21.8. **HRMS** (ESI) for $C_{19}H_{19}NO_5SNa$ $[M+Na]^+$: calculated 396.0875, found 396.0876.

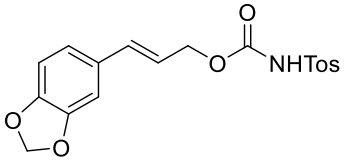


(E)-3-(3,4-dimethoxyphenyl)allyl tosylcarbamate (**51i**). The title product was obtained from allyl alcohol **34i** (r.t., 45 min.). Purified on a 40:60 EtOAc:Hexane mixture (R_f 0.20). Yield 32% (0.10 mmol, 38 mg), colorless oil. NMR spectra in $CDCl_3$ at 298K revealed the presence of two conformers (rotamers) in a 99/1 ratio. **FTIR (neat, cm^{-1})** 3254, 3057, 1746, 1513, 1158, 1089. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.90 – 6.84 (m, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 15.8

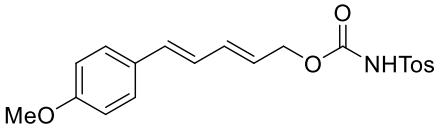
Hz, 1H), 6.02 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.69 (dd, *J* = 6.7, 0.9 Hz, 2H), 3.86 (s, 6H), 2.39 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.6, 149.5, 149.1, 145.1, 135.6, 135.5, 129.7, 128.9, 128.57, 120.3, 119.7, 111.1, 108.9, 67.6, 56.0, 55.9, 21.7. **HRMS** (ESI) for $C_{19}H_{25}N_2O_6S$ $[M+NH_4]^+$: calculated 409.1433, found 409.1431.



(E)-3-(3-(benzyloxy)-4-methoxyphenyl)allyl tosylcarbamate (**51j**). The title product was obtained from allyl alcohol **34j** (r.t., 45 min). Purified on a 40:60 EtOAc:Hexane mixture (R_f 0.33). Yield 54% (0.16 mmol, 76 mg), yellow oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 90/10 ratio. **FTIR (neat, cm^{-1})** 3063, 1744, 1510, 1257, 1155. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (d, *J* = 8.3 Hz, 1.8H), 7.80 (d, *J* = 8.3 Hz, 0.2H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.40 – 7.30 (m, 5H), 6.95 – 6.83 (m, 3H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.95 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.13 (s, 2H), 4.67 (dd, *J* = 6.7, 1.3 Hz, 2H), 3.88 (s, 3H), 2.42 (s, 0.3H), 2.40 (s, 2.7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 150.3, 148.4, 145.2, 137.1, 135.6, 129.7, 128.9, 128.7, 128.6, 128.1, 127.5, 120.8, 119.6, 112.2, 111.8, 71.3, 67.7, 56.2, 21.8. **HRMS** (ESI) for $C_{25}H_{29}N_2O_6S$ $[M+NH_4]^+$: calculated 485.1746, found 485.1745.

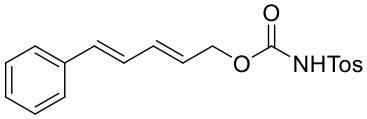


(E)-3-(benzo[d][1,3]dioxol-5-yl)allyl tosylcarbamate (**51k**). The title product was obtained from allyl alcohol **34k** (r.t., 3h). Purified on a 35:65 EtOAc:Hexane mixture (R_f 0.27). Yield 84% (0.25 mmol, 95 mg), white solid. NMR spectra in $CDCl_3$ at 298K revealed the presence of two conformers (rotamers) in a 90/10 ratio. **m_p** = 89-91 °C. **FTIR (neat, cm^{-1})** 3355, 1737, 1492, 1250, 1156. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 1.6H), 7.81 (d, *J* = 8.1 Hz, 0.4H), 7.33 – 7.29 (m, 2H), 6.84 (s, 1H), 6.75 (d, *J* = 2.2 Hz, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.04 – 5.88 (m, 3H), 5.05-5.00 (br s, 1H), 4.68 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6 , 148.2 , 147.9 , 145.2 , 135.6, 135.3, 130.3, 129.7, 128.5, 126.5, 121.8, 119.9, 108.4, 105.9, 101.3, 67.5, 21.7, 21.6. **HRMS** (ESI) for $C_{18}H_{17}NO_6SNa$ $[M+Na]^+$: calculated 398.0670, found 398.0672.

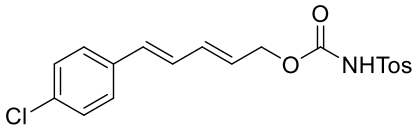


(2E,4E)-5-(4-methoxyphenyl)penta-2,4-dien-1-yl tosylcarbamate (**53a**). The title product was obtained from allyl alcohol **43a** (r.t., 30 min.). Purified on a 35:65 EtOAc:Hexane mixture (R_f 0.24). Yield 25% (0.08 mmol, 29 mg), yellow oil. NMR spectra in $CDCl_3$ at 298K revealed the presence of two conformers (rotamers) in a 75/25 ratio. **FTIR (neat, cm^{-1})** 3268, 2957, 1735, 1510, 1160. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1.5H), 7.82 (d, *J* = 8.2 Hz, 0.5H), 7.36 – 7.30 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.63 – 6.52 (m, 2H), 6.36 (dd, *J* = 15.1, 9.8 Hz, 1H), 5.70

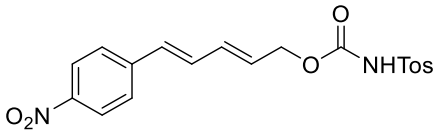
(dt, *J* = 14.5, 6.9 Hz, 1H), 4.75-4.74 (br s, 1H), 4.63 (d, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 2.25H), 2.41 (s, 0.75H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 150.4, 145.2, 136.4, 134.4, 129.8, 128.6, 127.9, 126.6, 124.0, 114.3, 67.4, 55.5, 21.8, 21.7. **HRMS** (ESI) for $C_{20}H_{21}NO_5SNa$ $[M+Na]^+$: calculated 410.1038, found 410.1026.



(2E,4E)-5-phenylpenta-2,4-dien-1-yl tosylcarbamate (**53b**). The title product was obtained from allyl alcohol **43b** (r.t., 4h). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.29). Yield 75% (0.23 mmol, 80 mg), yellow oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 63/37 ratio. **FTIR (neat, cm^{-1})** 3272, 3054, 1751, 1597. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 1.3H), 7.84 – 7.80 (m, 0.7H), 7.41 – 7.36 (m, 2H), 7.36 – 7.29 (m, 4H), 7.27 – 7.24 (m, 1H), 6.71 (dd, *J* = 15.7, 10.3 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H), 6.37 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.75 (dt, *J* = 14.1, 6.7 Hz, 1H), 5.02-4.93 (br s, 1H), 4.64 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 1. 9H), 2.42 (s, 1.1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.6, 145.2, 143.6, 139.2, 136.8, 135.6, 134.5, 129.8, 128.7, 128.4, 128.1, 127.4, 126.6, 126.5, 125.4, 67.1, 21.7, 21.6. **HRMS** (ESI) for $C_{19}H_{19}NO_4SNa$ $[M+Na]^+$: calculated 380.0933, found 380.0924.



(2E,4E)-5-(4-chlorophenyl)penta-2,4-dien-1-yl tosylcarbamate (**53c**). The title product was obtained from allyl alcohol **43c** (r.t., 4h). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.22). Yield 68% (0.20 mmol, 80 mg), pale yellow oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 75/25 ratio. **FTIR (neat, cm^{-1})** 3272, 3055, 1749, 1595, 1344. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 1.5H), 7.85 – 7.76 (m, 0.5H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.22 (m, 4H), 6.64 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.33 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.75 (dt, *J* = 15.2, 6.5 Hz, 1H), 4.62 (d, *J* = 6.5 Hz, 2H), 2.40 (s, 2.25H), 2.39 (s, 0.75H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.5, 145.2, 143.7, 139.2, 135.5, 135.2, 133.7, 133.1, 129.8, 129.7, 128.9, 128.5, 127.9, 127.8, 126.5, 125.9, 67.0, 21.8, 21.6. **HRMS** (ESI) for $C_{19}H_{18}ClNO_4SNa$ $[M+Na]^+$: calculated 414.0540, found 414.0542.



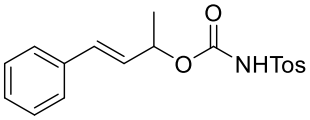
(2E,4E)-5-(4-nitrophenyl)penta-2,4-dien-1-yl tosylcarbamate (**53d**). The title product was obtained from allyl alcohol **43d** (90 °C, 5 days). Purified on a 40:60 EtOAc:Hexane mixture (R_f 0.26). Yield 36% (0.11 mmol, 44 mg), orange oil. NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 99/1 ratio. **FTIR (neat, cm^{-1})** 3524, 3237, 1749, 1514, 1340, 1158. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.85 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.60 (d, *J* = 15.7

Hz, 1H), 6.41 (dd, *J* = 15.3, 10.6 Hz, 1H), 5.90 (dt, *J* = 15.3, 5.9 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 2H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3, 147.1, 145.4, 143.3, 135.5, 134.3, 131.9, 129.8, 128.7, 128.5, 127.1, 124.2, 66.6, 21.8. **HRMS** (ESI) for $C_{19}H_{18}N_2O_6SNa$ $[M+Na]^+$: calculated 425.0779, found 425.0785.

Chirality transfer studies

Using *p*-toluenesulfonyl isocyanate

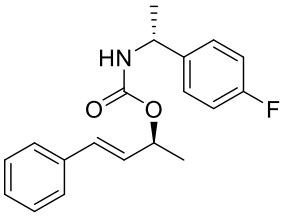
To a solution of (*S*,*E*)- or (*R*,*E*)-phenylbut-2-en-1-ol **54** (50 mg, 0.33 mmol, 1 eq.) in CH_2Cl_2 (0.2 M) under inert atmosphere *p*-toluenesulfonyl isocyanate (62 µL, 0.41 mmol, 1.2 eq.) was added and the mixture was stirred at room temperature for 1h. The solvent was evaporated under reduced pressure and the product was purified by flash column chromatography.



(E)-4-phenylbut-3-en-2-yl tosylcarbamate (**55**). Purified on a 30:70 EtOAc:Hexane mixture (R_f 0.31). From (*R*,*E*)-**54** (93% *ee*) yield 80% (0.26 mmol, 90 mg), colorless oil. $[\alpha]_D^{25}$ = +8.45 (*c* 0.40, chloroform). From (*S*,*E*)-**52** (98% *ee*) yield 61% (0.20 mmol, 69 mg), colorless oil. $[\alpha]_D^{25}$ = -11.64 (*c* 0.55, chloroform). NMR spectra in $CDCl_3$ at 298 K revealed the presence of two conformers (rotamers) in a 90/10 ratio. **FTIR (neat, cm^{-1})** 3355, 3259, 1748, 1596, 1299, 1151. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 1.8H), 7.78 (d, *J* = 8.3 Hz, 0.2H), 7.26 (t, *J* = 4.7 Hz, 6.3H), 7.22 (t, *J* = 4.3 Hz, 0.7H), 6.47 (dd, *J* = 16.0, 1.1 Hz, 1H), 6.00 (dd, *J* = 15.9, 6.9 Hz, 1H), 5.36 (td, *J* = 6.6, 1.1 Hz, 1H), 2.37 (s, 0.3H), 2.36 (s, 2.7H), 1.33 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.2, 145.0, 135.9, 135.7, 132.5, 129.6, 128.6, 128.4, 128.2, 127.3, 126.7, 74.6, 21.7, 20.3.

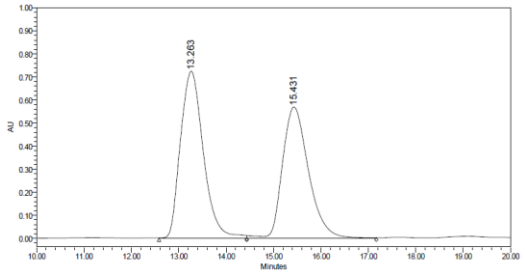
Using (*R*)-(+)-(4-fluorophenyl)ethyl isocyanate

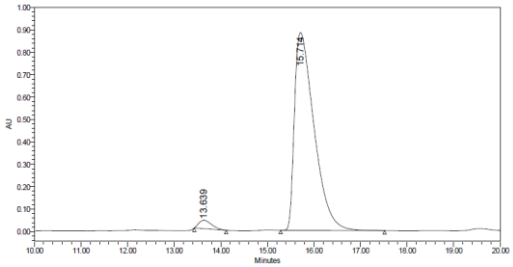
To a solution of (*S*,*E*)-phenylbut-2-en-1-ol **54** (22 mg, 0.15 mmol, 1 eq.) in toluene (0.2 M) under argon atmosphere (*R*)-(+)-(4-fluorophenyl)ethyl isocyanate (26 µL, 0.18 mmol, 1.2 eq.) and triethylamine (8 µL, 0.06 mmol, 0.4 eq.) were added and the mixture was stirred at 90 °C for 6h. The initial reaction mixture was concentrated under reduced pressure, diluted with Et_2O (2 mL) and washed with saturated NaCl (3 x 2 mL). The resulting crude mixture was diluted in toluene (0.2 M) and stirred at 110 °C for 48h. The final mixture was purified by flash column chromatography on neutral aluminium oxide.



(S,E)-4-phenylbut-3-en-2-yl ((R)-1-(4-fluorophenyl)ethyl)carbamate (**58**). Purified on a 17:83 EtOAc:Hexane mixture (R_f 0.64). Yield 39% (0.06 mmol, 19 mg), colorless oil. $[\alpha]_D^{25}$ = -15.91 (*c* 0.35, chloroform). **FTIR (neat,**

cm^{-1}) 3343, 2979, 1680, 1529, 1508. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 7H), 7.00 (dd, *J* = 8.6, 8.6 Hz, 2H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.41 (dd, *J* = 6.5, 6.5 Hz, 1H), 4.92-4.90 (br s, 1H), 4.86 – 4.78 (m, 1H), 1.47 (m, 3H), 1.43 – 1.36 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.08 (d, $^{1}J_{C\text{-}F}$ = 244.9 Hz), 155.21, 136.56, 131.24, 129.38, 128.68, 127.97, 127.68 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 126.68, 115.53 (d, $^{2}J_{C\text{-}F}$ = 21.1 Hz), 71.66, 50.15, 22.68, 20.75. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.58. **HRMS** (ESI) for $C_{19}H_{20}FNO_2Na$ $[M+Na]^+$: calculated 336.1631, found 336.1361. **HPLC** (Daicel ChiralPak IB Hexane:^{i}PrOH = 97:3, flow rate 1 mL/min, λ 210 nm), t_R (minor) 13.26 min, t_R (major) 15.43 min; 95% *ee*.





	RT	Height	Area	% Area
1	13.263	722894	24178704	52.86
2	15.431	567782	21562041	47.14

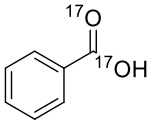
	RT	Height	Area	% Area
1	13.639	37547	709445	2.68
2	15.714	883664	25796538	97.32

Determination of first order kinetic constants

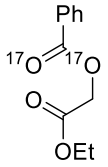
To a solution of the corresponding allyl alcohol **34a**-**c** (0.3 mmol, 1 eq.) in toluene-*d8* (0.2 M) under argon atmosphere, *p*-toluenesulfonyl isocyanate (0.36 mmol, 1.2 eq.) was added dropwise. This mixture was transferred to a NMR tube. The sample was stabilized at 363 K. The kinetic studies were performed by monitoring the three ^{1}H-NMR signals of the immediately formed initial carbamate **50a**-**c**. NMR measurements were carried out at 500.13 MHz with a Bruker Avance 500 NMR spectrometer, equipped with a BBO probe incorporating *z*-gradients. FID files were obtained with a spectral window of 16 ppm and transformed with 65536 points. All spectra were recorded by accumulating 16 acquisitions, with recycling delays of 1s. Measurements were performed directly on the reaction mixtures in the NMR tubes every 5 minutes. When alcohol **34a** was employed, the measurements were performed every minute. Relative concentrations of **50a**-**c** at different times were quantified by integration and statistical treatment of the three sets of

^{1}H signals. Kinetic constants reported in **Table 4.6** were obtained from equation 2. See Annex III for the first-order linear plots, standard deviation and error calculations.

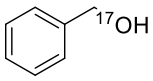
Preparation of [^{17}O] labelled compounds



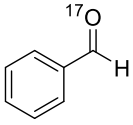
Benzoic acid (**[$^{17}O_2$]60**).[48] (Trichloromethyl)benzene (1.75 mmol) and 0.59 mL of $H_2{}^{17}O$ were placed in a microwave vessel and sealed. The resulting mixture was irradiated with microwaves at 150 W, 130 °C and 6 bar for 30 minutes. Once the mixture was cooled down to room temperature, the solid formed was filtered and washed with hexane. The desired pure compound was obtained as a white solid (200 mg) in 93% yield. **^{1}H NMR** (400 MHz, Acetone-d_6): δ 8.07 – 8.02 (m, 2H), 7.66 – 7.60 (m, 1H), 7.51 (dd, *J* = 8.4, 7.1 Hz, 2H). **^{17}O NMR** (68 MHz, Acetone-d_6): δ 245.



2-ethoxy-2-oxoethyl benzoate (**[$^{17}O_2$]61**).[49] To a solution of **[$^{17}O_2$]60** (1.62 mmol) and Cu(OTf)$_2$ (5.9 mg) in toluene (10 mL) ethyl diazoacetate was added dropwise (3.24 mmol) and the resulting mixture was warmed up to 80 ºC and stirred for 12h. After completion, the reaction mixture was filtered and toluene was evaporated in vacuo. The final product was used without further purification. **^{1}H NMR** (500 MHz, Acetone-d_6): δ 8.09 (d, *J* = 7.7 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 (q, *J* = 8.0 Hz, 2H), 4.91 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.27 (tq, *J* = 7.2, 3.6, 2.6 Hz, 3H). **^{17}O NMR** (68 MHz, Acetone-d_6): δ 340, 136.



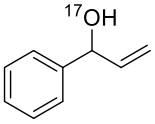
Phenylmethanol (**[$^{17}O_1$]62**). Compound **[$^{17}O_2$]60** (1.60 mmol) was dissolved in THF (20 mL). A solution of $LiAlH_4$ in THF (1.48 mL, 2.5 M) was slowly added to the resulting mixture at 0 °C and the reaction was allowed to stir at room temperature until total consumption of starting material. After completion, a solution of NaOH 1N (10 mL) was used to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were dried over MgSO4, filtered and concentrated *in vacuo*. The final product was purified by flash column chromatography on silica gel using a hexane/ethyl acetate mixture (60/40, R_f 0.59) as eluent, and isolated as a pale yellow oil (149 mg) in 85% yield**. ^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 4.5 Hz, 4H), 7.32 – 7.28 (m, 1H), 4.70 (d, *J* = 2.3 Hz, 2H), 1.67 (s, 1H). **^{17}O NMR** (68 MHz, Acetone-d_6): δ 0.



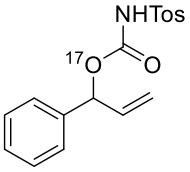
Benzaldehyde (**[$^{17}O_1$]63**).[77] A solution of oxalyl chloride (2.33 mmol) in CH_2Cl_2 (3 mL) was cooled to -84 °C and dimethyl sulfoxide (4.65 mmol)

[77] Neuvonen, A. J.; Földes, T.; Madarász, Á.; Pápai, I.; Pihko, P. M. *ACS Catal*. **2017**, *7*, 3284-3294.

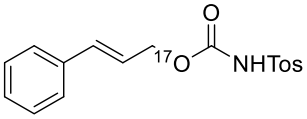
was added slowly. The resulting mixture was stirred for additional 15 minutes. **[$^{17}O_1$]62** (1.37 mmol) was added to the reaction and the mixture was allowed to stir for 15 minutes. Triethylamine (6.85 mmol) was slowly added and the resulting white suspension was stirred at the indicated temperature for 2h. After completion, the reaction was warmed up to 0 °C, quenched with HCl 3 mL) and extracted with CH_2Cl_2 (3x 5 mL). The organic layer was washed with $NaHCO_3$ sat. (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 0 ºC. The desired compound was isolated as a colorless oil (95 mg) in 65% yield and used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.95 – 7.88 (m, 2H), 7.72 – 7.63 (m, 1H), 7.57 (dd, *J* = 8.2, 6.9 Hz, 2H). **^{17}O NMR** (68 MHz, $CDCl_3$): δ 554.



1-phenylprop-2-en-1-ol (**[$^{17}O_1$]34b**).[78] To a solution of **[$^{17}O_1$]63** (0.89 mmol) in THF (6 mL) was slowly added at 0° C a solution of vinylmagnesium bromide in THF (1.07 mmol, 1 M). The reaction mixture was stirred at room temperature for 4 hours after which a saturated NH_4Cl solution (3 mL) was added. The aqueous layer was extracted with Et_2O (4 x 6 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using a hexane/ethyl acetate mixture (70:30, R_f 0.60) to afford the desired product as a yellow oil (64 mg) in 54% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 4H), 7.29 (td, *J* = 5.7, 2.5 Hz, 1H), 6.06 (ddd, *J* = 16.7, 10.3, 6.0 Hz, 1H), 5.35 (dd, *J* = 16.7, 1.6 Hz, 1H), 5.24 – 5.18 (m, 2H). **^{17}O NMR** (68 MHz, $CDCl_3$): δ 31.



1-phenylallyl tosylcarbamate (**[$^{17}O_1$]50b**). To a solution of 1-phenylprop-2-en-1-ol **[$^{17}O_1$]34b** (0.073 mmol) in toluene (0.2 M) under argon atmosphere, *p*-toluenesulfonylisocyanate (0.088 mmol) was added dropwise and the mixture was stirred at room temperature for 5 minutes. The resulting mixture was concentrated *in vacuo* and purified using a hexane/ethyl acetate mixture (80/20, R_f 0.31) as eluent. The product was isolated as a colorless oil (21 mg) in 90% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.55–7.53 (br s, 1H), 7.34–7.26 (m, 5H), 7.21 (dd, *J* = 6.8, 3.0 Hz, 2H), 6.11 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.92 (ddd, *J* = 16.7, 10.5, 5.9 Hz, 1H), 5.27–5.23 (m, 2H), 2.43 (s, 3H). **^{17}O NMR** (68 MHz, $CDCl_3$): δ 150, 129.



(E)-3-(phenyl)allyl tosylcarbamate (**[$^{17}O_1$]51b**). Prepared from **[$^{17}O_1$]34b** (90 °C, 4 h) and purified using a hexane/ethyl acetate mixture (60/40, R_f 0.39) as eluent. The

[78] Hanessian, S.; Focken, T.; Oza, R. *Tetrahedron* **2011**, *67*, 9870-9884.

product was isolated as a white solid (21 mg) in 86% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97–7.90 (m, 1.5H), 7.82 (m, 0.5H), 7.37–7.25 (m, 7H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.72 (dd, *J* = 6.6, 1.3 Hz, 2H), 2.43 (s, 0.75H), 2.42 (s, 2.25H). **^{17}O NMR** (68 MHz, $CDCl_3$) δ 264, 125. **HRMS** (ESI) for **[$^{17}O_1$]14b***:* calculated $C_{17}H_{17}NO_4SNa$ $[M+Na]^+$ 354.0763; found: 354.0763 (59%); calculated $C_{17}H_{17}NO_3{}^{17}OSNa$ $[(M+1)+Na]^+$ 355.0805; found: 355.0799 (11%); calculated $C_{17}H_{17}NO_3{}^{18}OSNa$ $[(M+2)+Na]^+$ 356.0806; found: 356.0799 (30%).

Procedure for NMR monitoring of the [$^{17}O_1$]50b → [$^{17}O_1$]51b transformation

To a solution of 1-phenylprop-2-en-1-ol **[$^{17}O_1$]34b** (0.373 mmol) in toluene (0.2 M) under argon atmosphere, *p*-toluenesulfonylisocyanate (0.447 mmol) was added dropwise. The reaction was heated to 90 °C, and 200 µL were taken from the reaction medium every 20 minutes. The solvent was removed and the resulting colorless oil was dissolved in $CDCl_3$ to perform ^{17}O NMR experiments at room temperature.

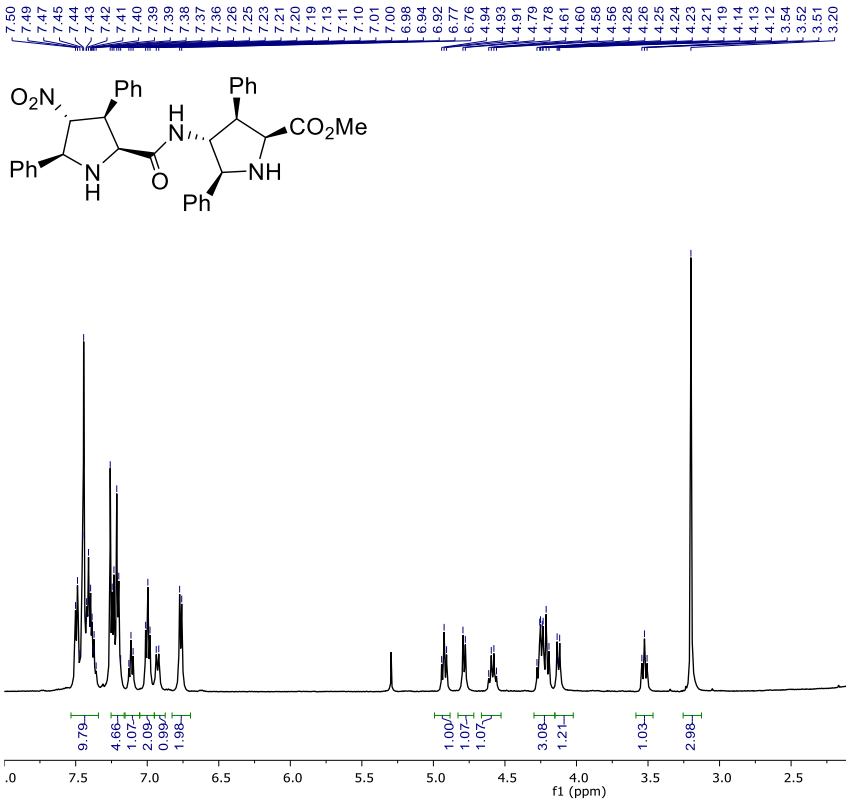
Computational details

All the calculations reported in this work were carried out with the GAUSSIAN 09 suite of programs[55] and using the hybrid DFT functional B3LYP[51] with the D3 dispersion empirical correction[52] and the 6-311++G(d,p) basis set.[53] All the stationary points were characterized by harmonic analysis. Reactants and products showed positive definite Hessians. Transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation under study. Free energies at 363.15 K were calculated by including the corresponding thermal corrections to Gibbs free energies (TCGE). Solvent effects were considered by means of PCM method.[54] The solvent introduced in the calculations was toluene. Natural bonding analysis calculations were performed using the NBO program[56] as implemented in Gaussian 09.

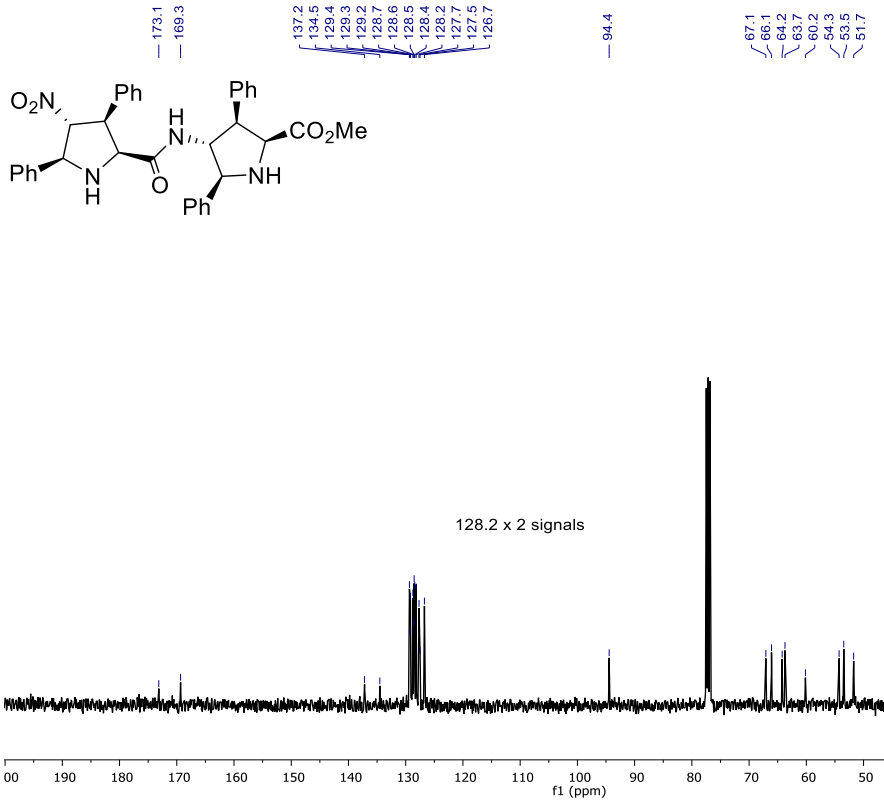
Annexes

Annex I. NMR spectra selection for Chapter 2

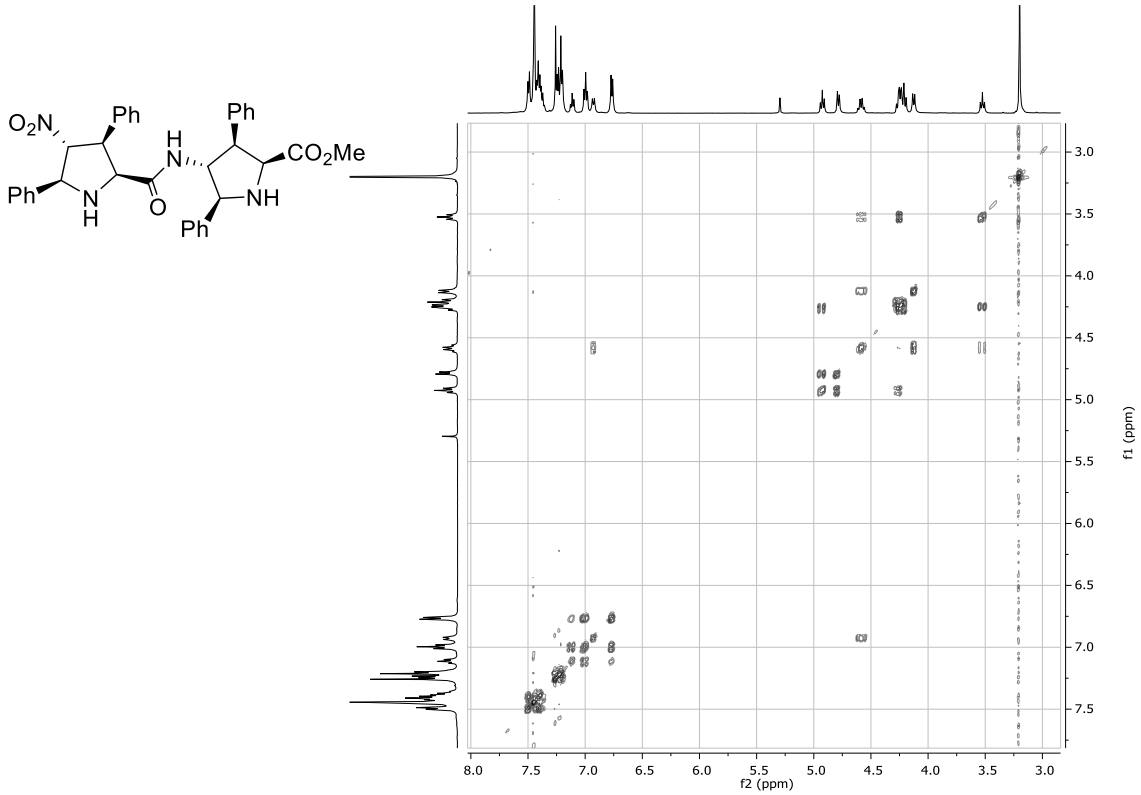
Compound O_2N-X_L-X_L-OMe-**34.** ^{1}**H NMR (**$CDCl_3$**)**



^{13}**C NMR (**$CDCl_3$**)**

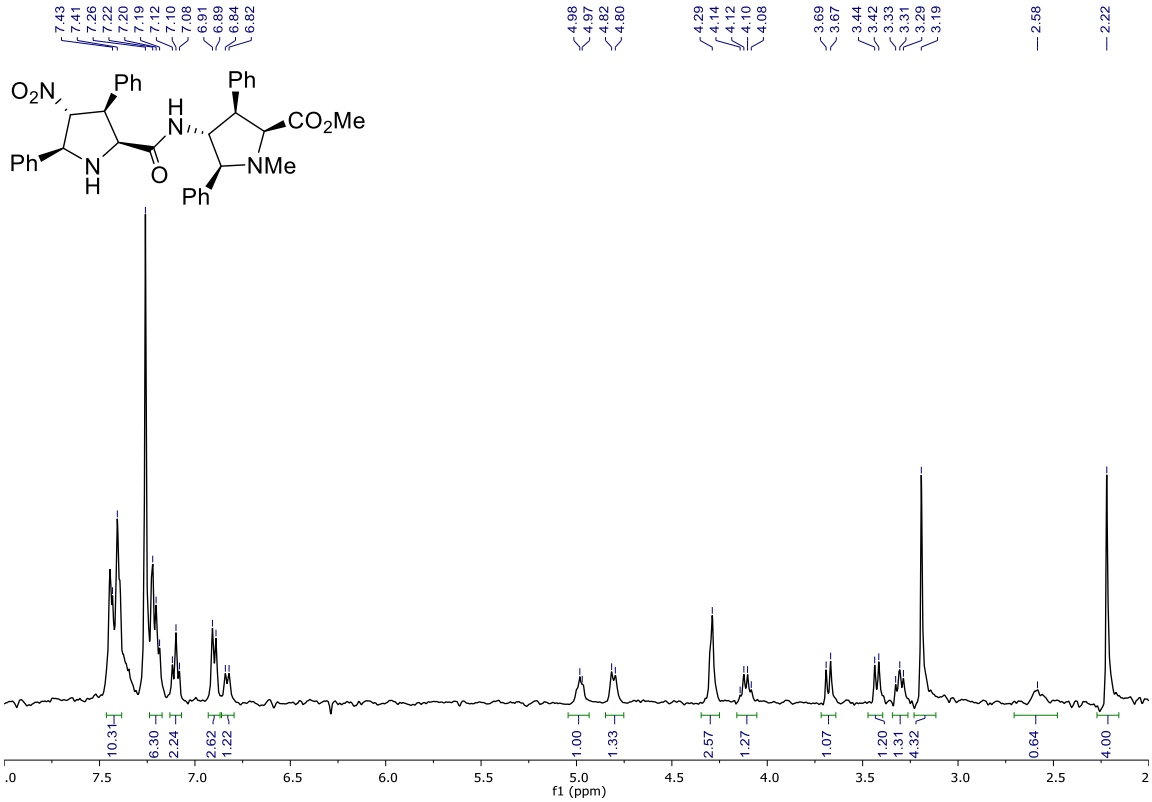


COSY ($CDCl_3$)

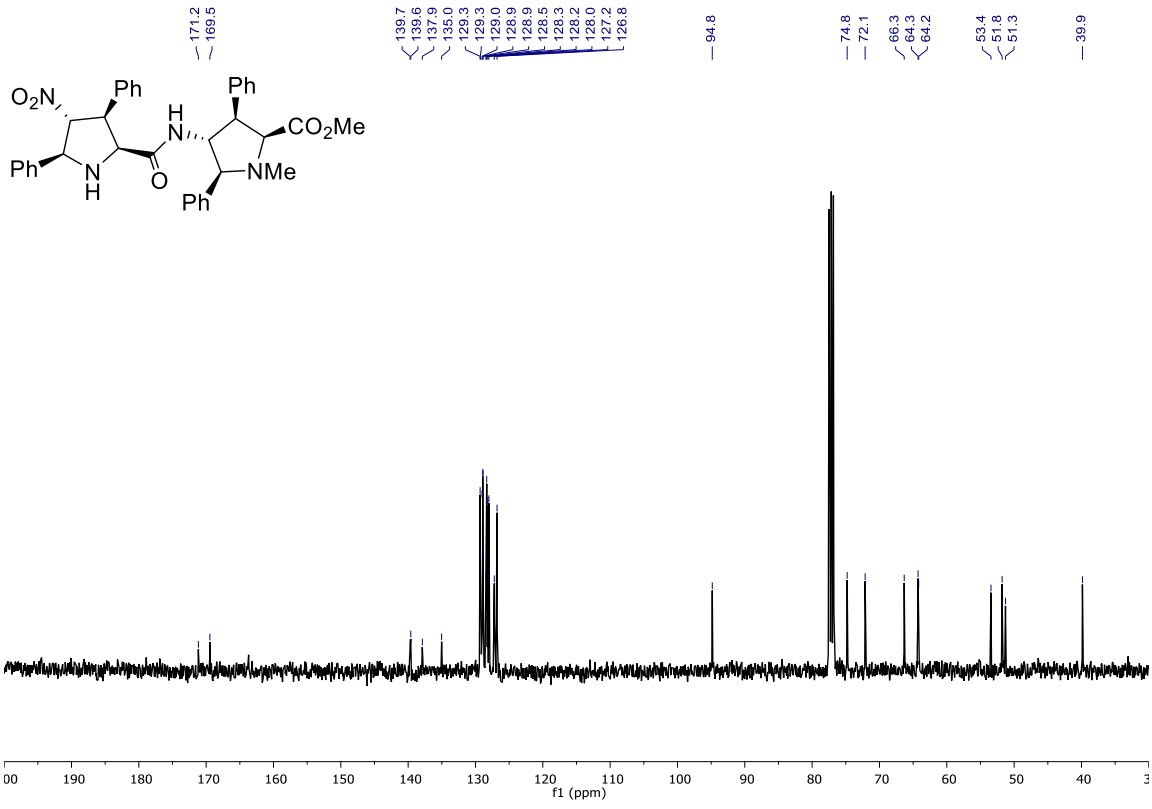


Compound O_2N-X_L-X_L^{Me}-OMe-**35**

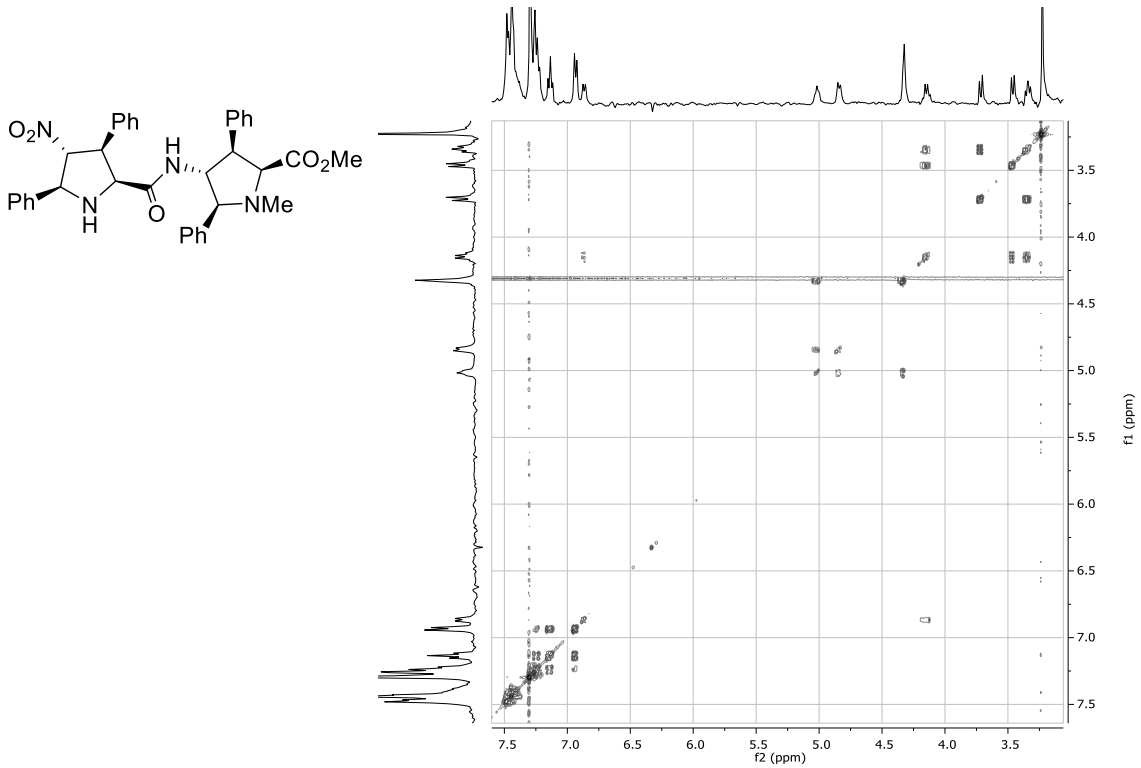
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

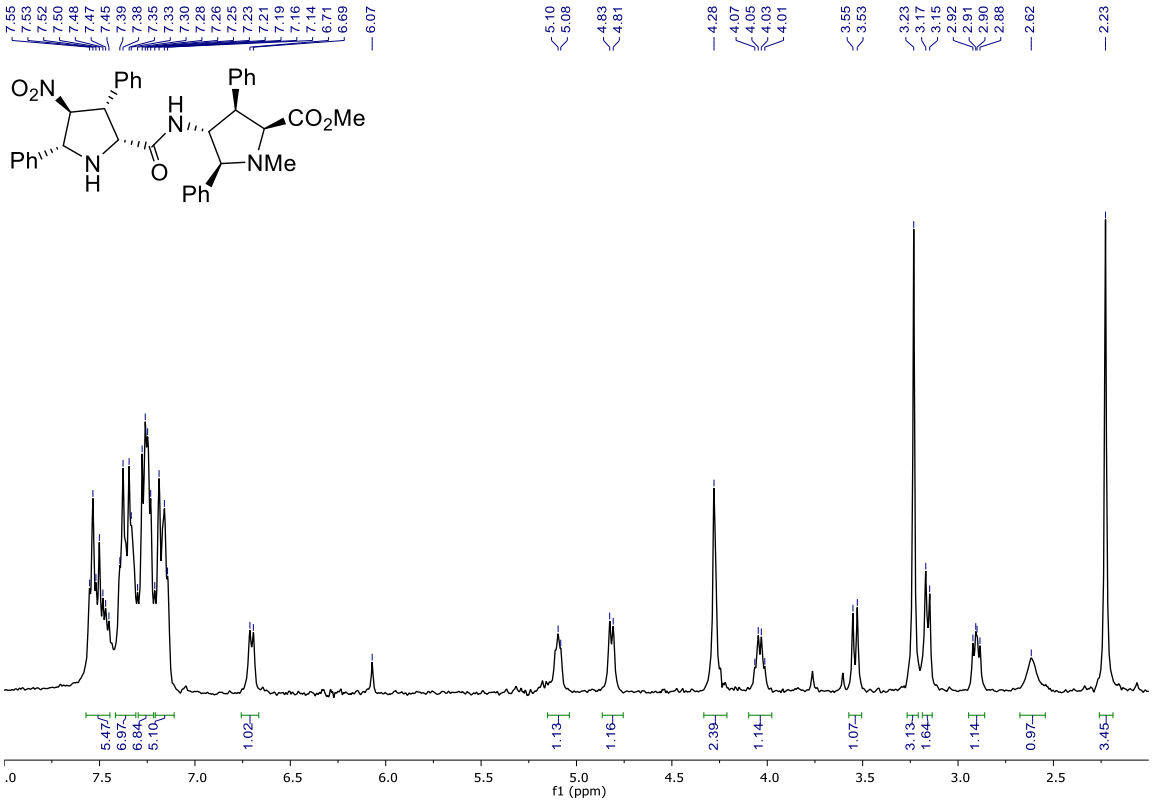


COSY ($CDCl_3$)

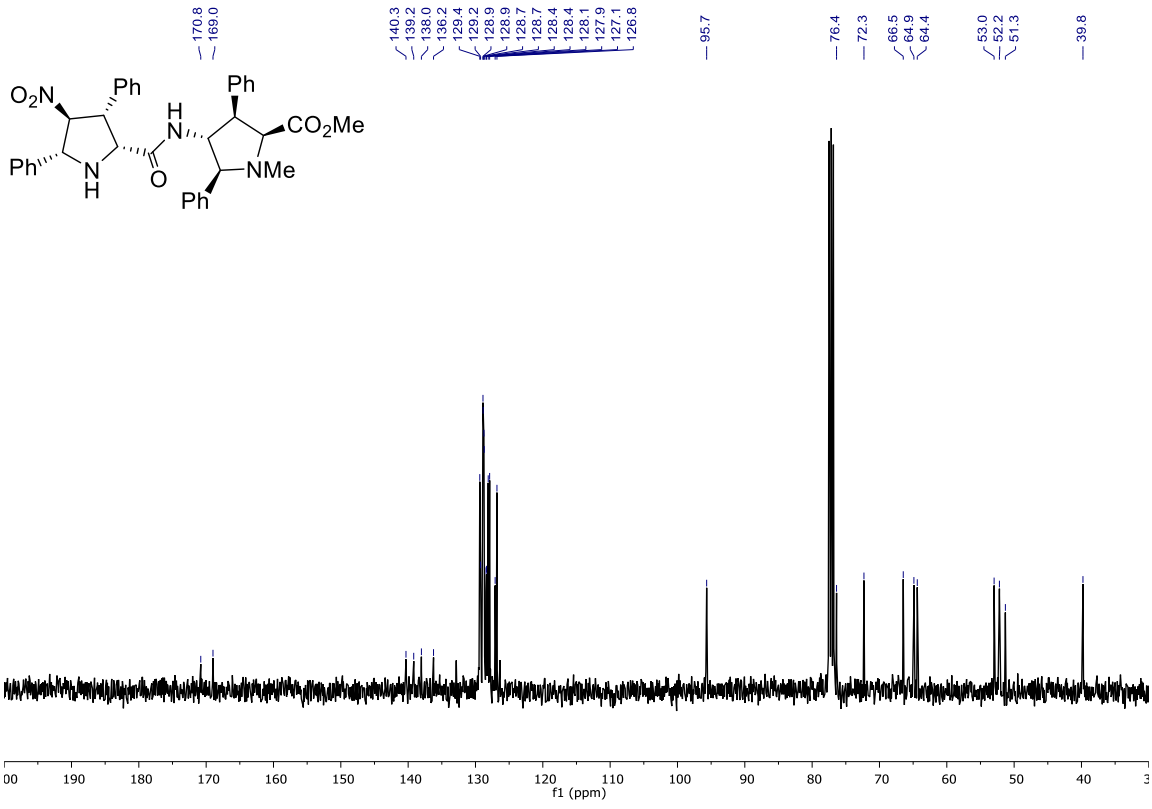

O2N
Ph
H
N
CO2Me
Ph
N
H
O
Ph
NMe
Ph
f1 (ppm)
f2 (ppm)
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

Compound O_2N-$X_DX_L^{Me}$-OMe-**35**

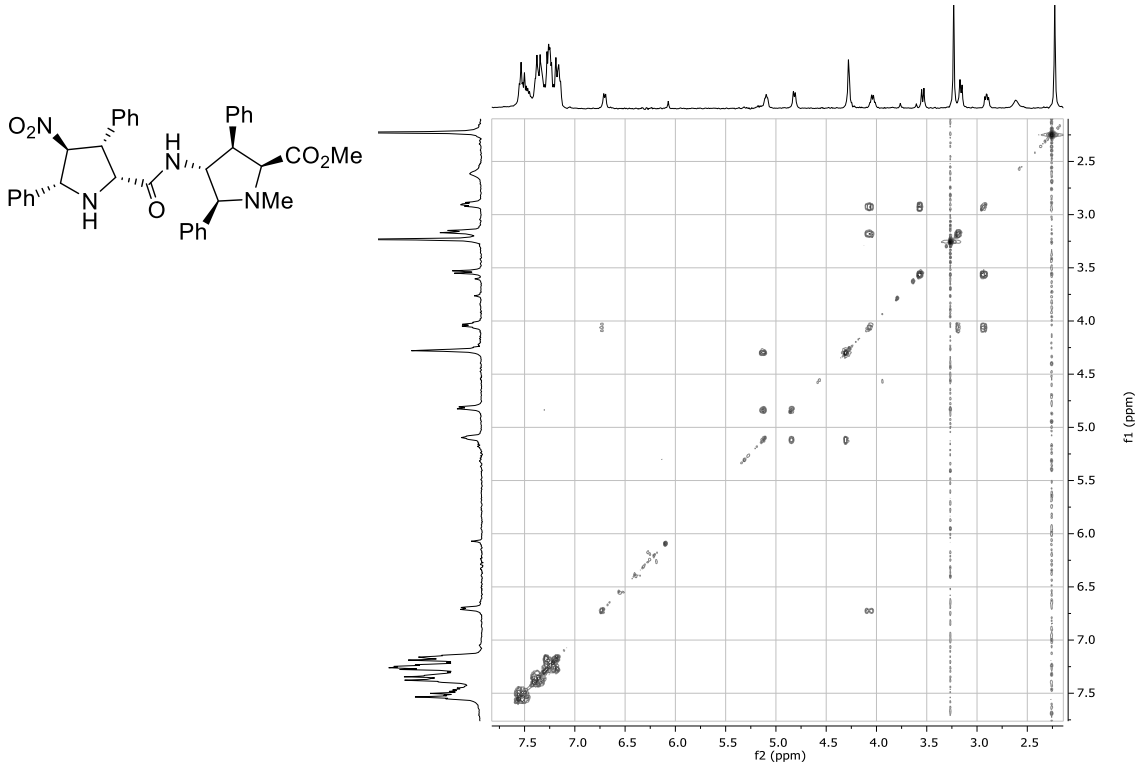
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

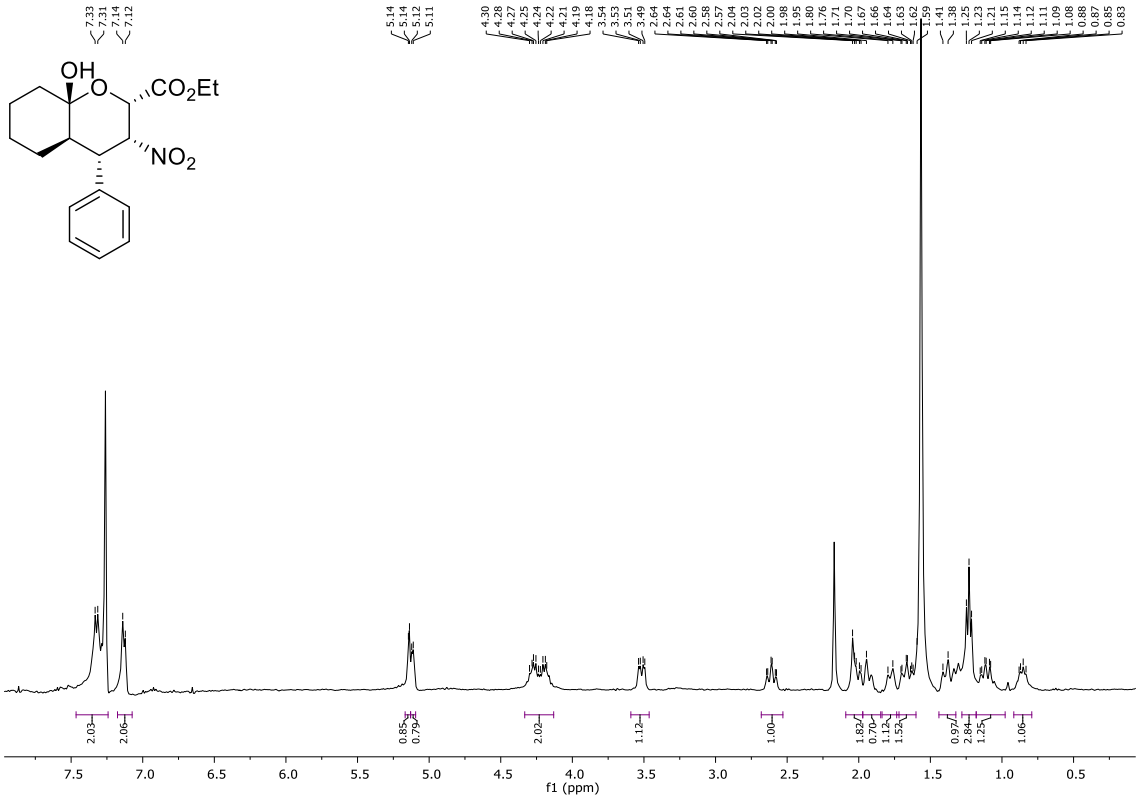


COSY ($CDCl_3$)

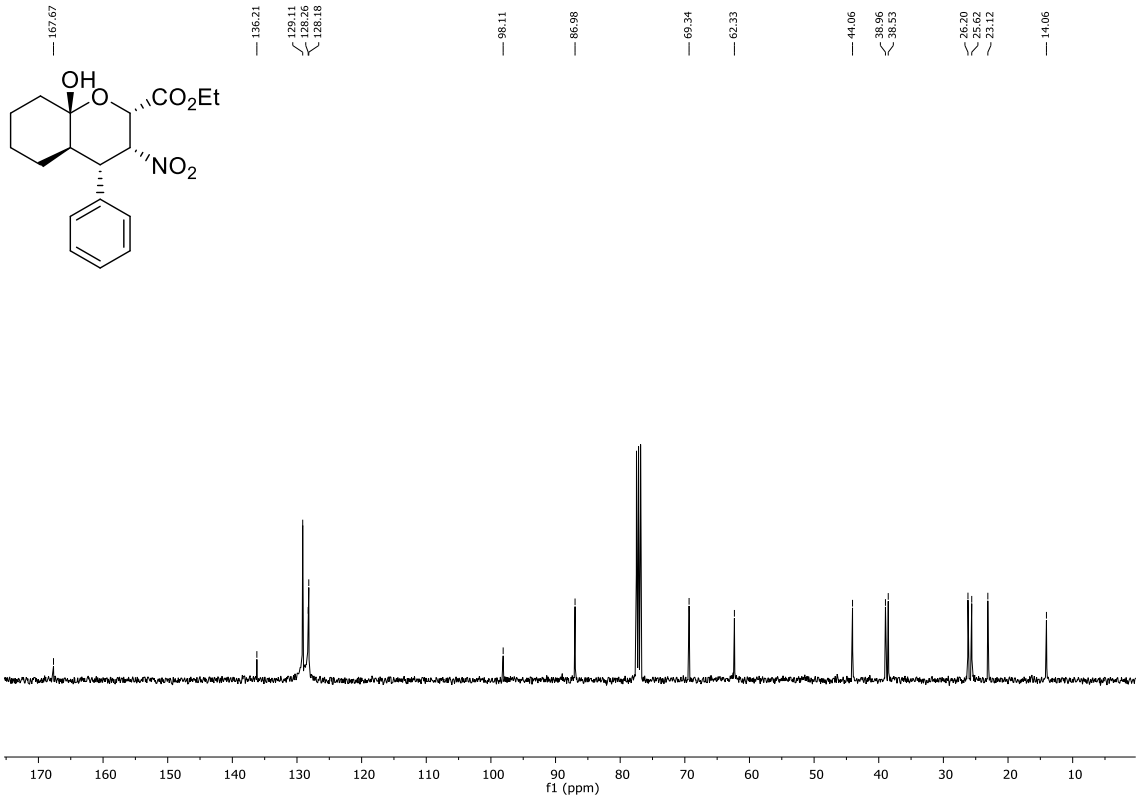

O2N
Ph
Ph
N
H
H
N
O
Ph
Ph
CO2Me
NMe
f1 (ppm)
f2 (ppm)
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aaa**

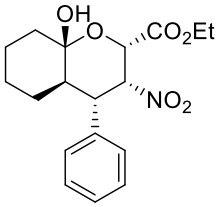
^{1}H NMR ($CDCl_3$)

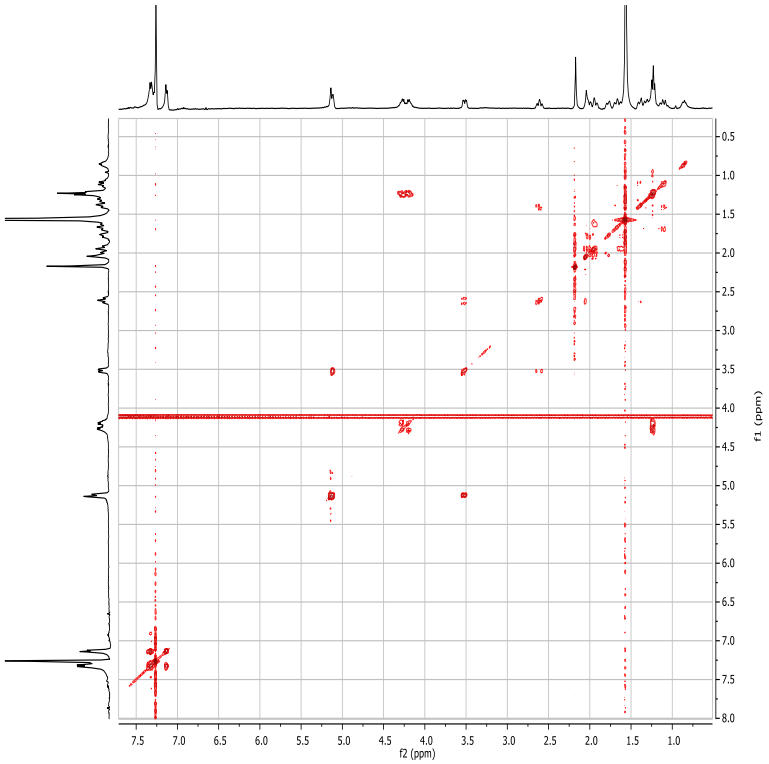


^{13}C NMR ($CDCl_3$)

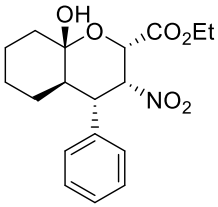


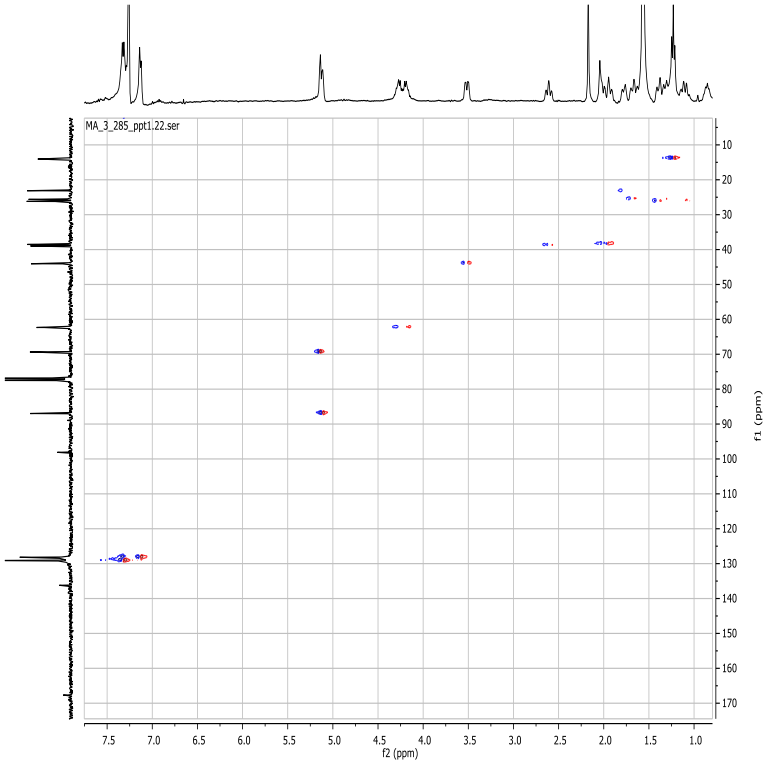
COSY ($CDCl_3$)





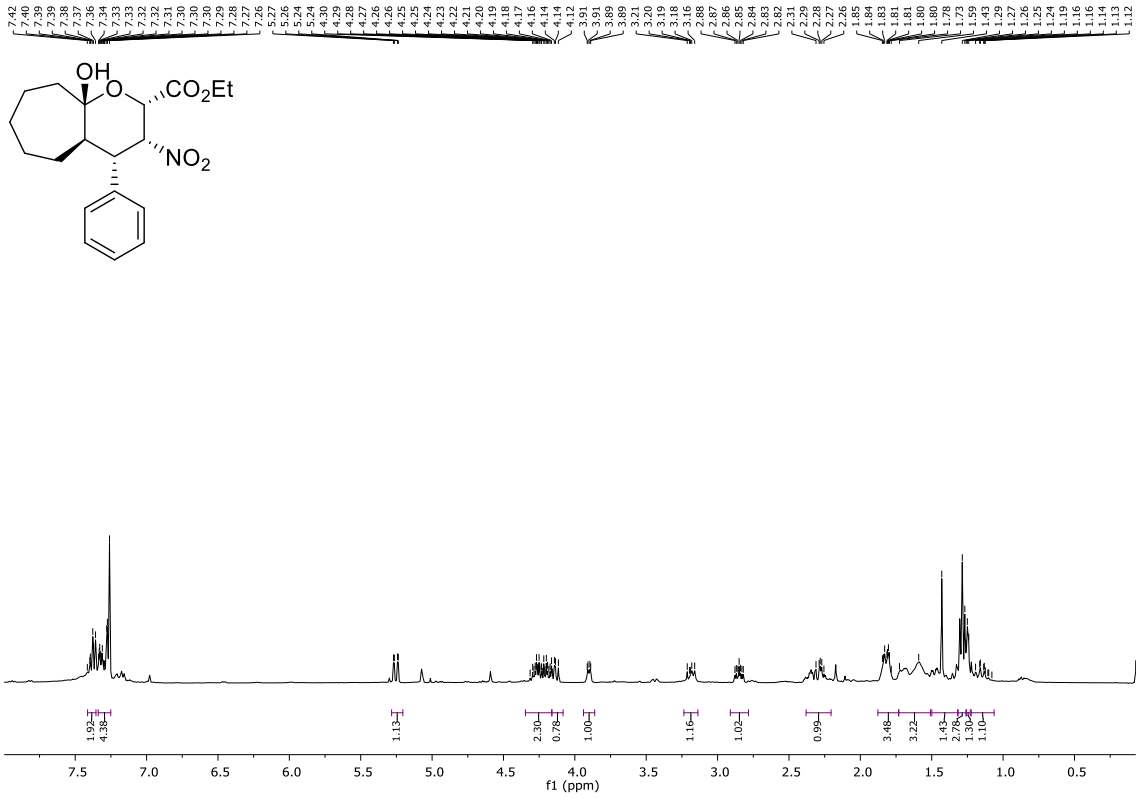
HSQC ($CDCl_3$)



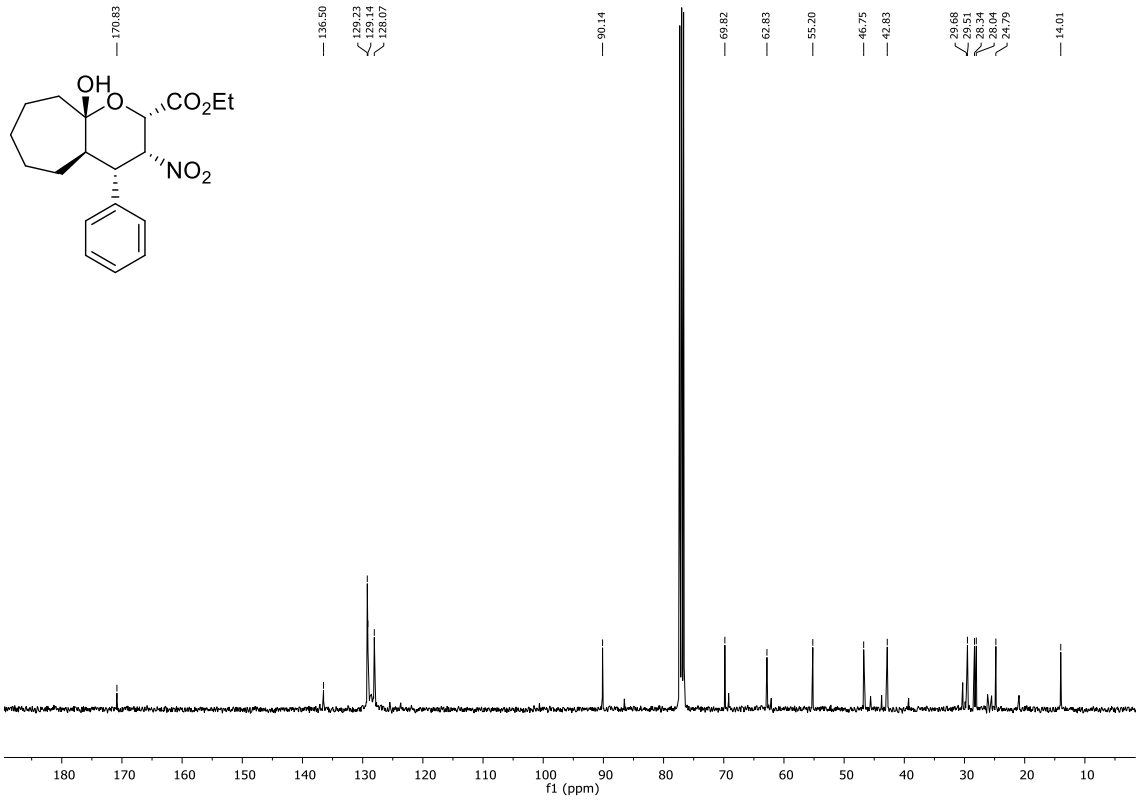


Compound (2*S*,3*R*,4*S*,4a*R*,9a*S*)-**79caa**

^{1}H NMR ($CDCl_3$)

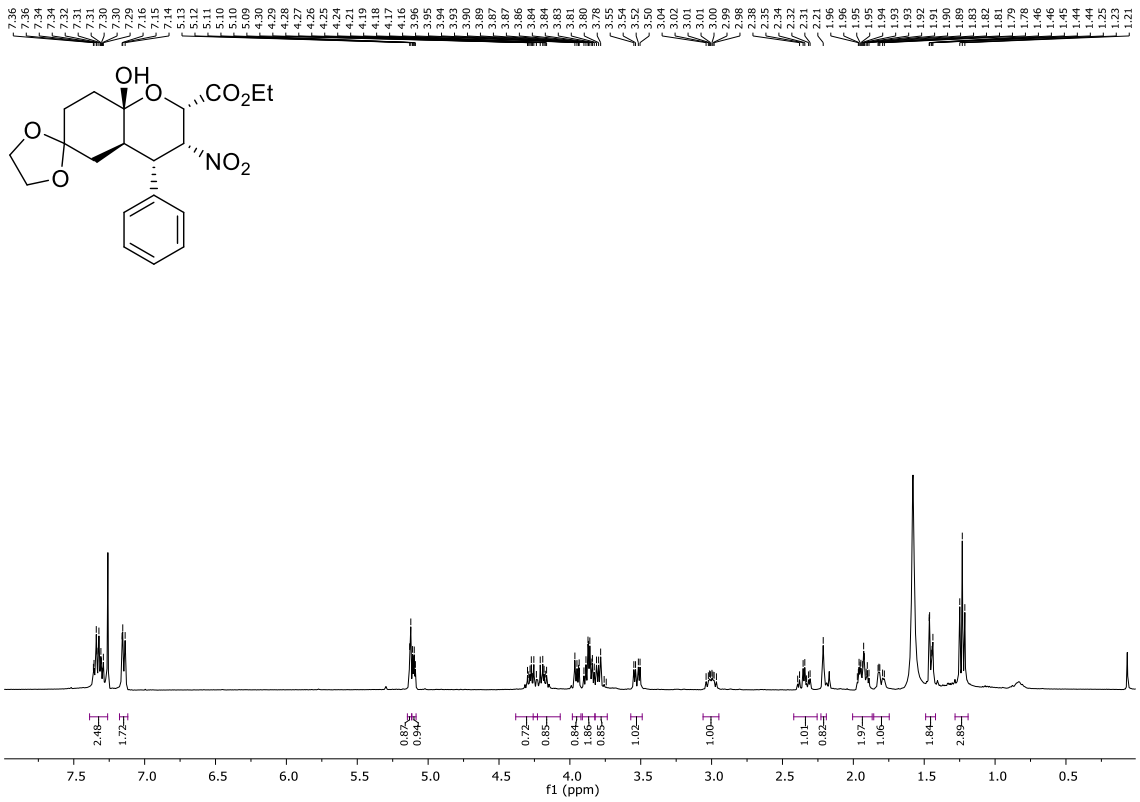


^{13}C NMR ($CDCl_3$)

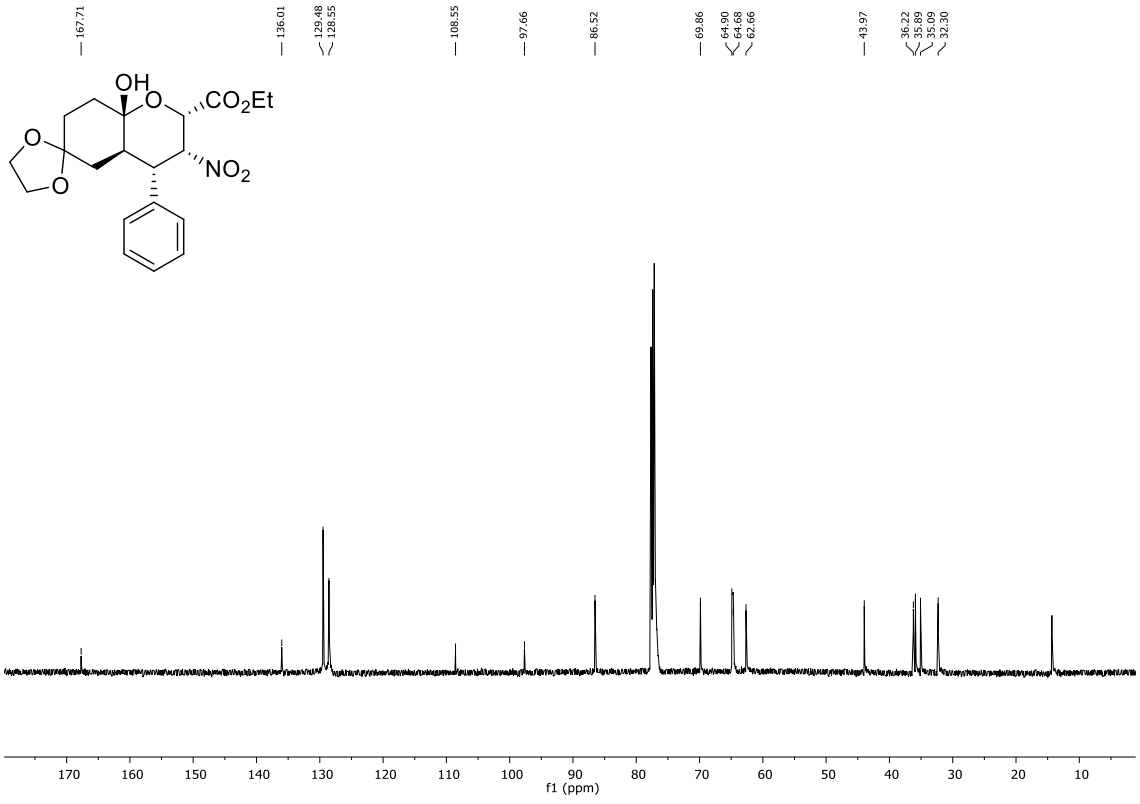


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79jaa**

^{1}H NMR ($CDCl_3$)

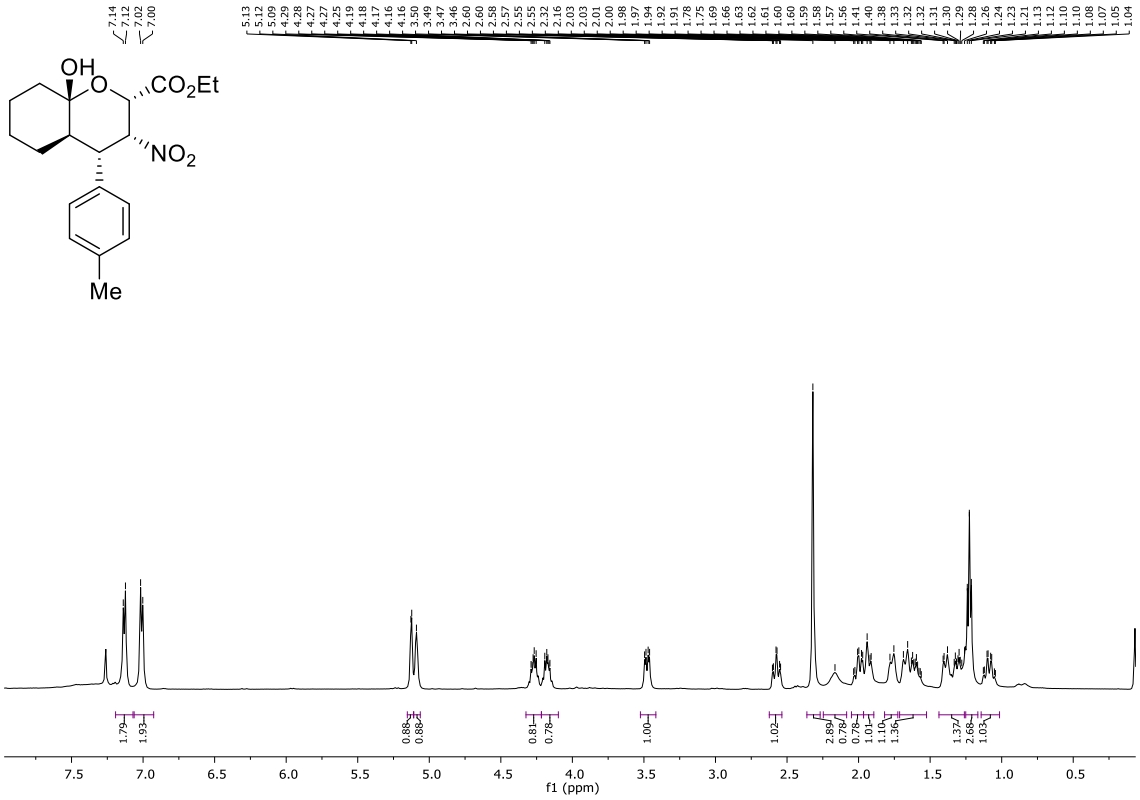


^{13}C NMR ($CDCl_3$)

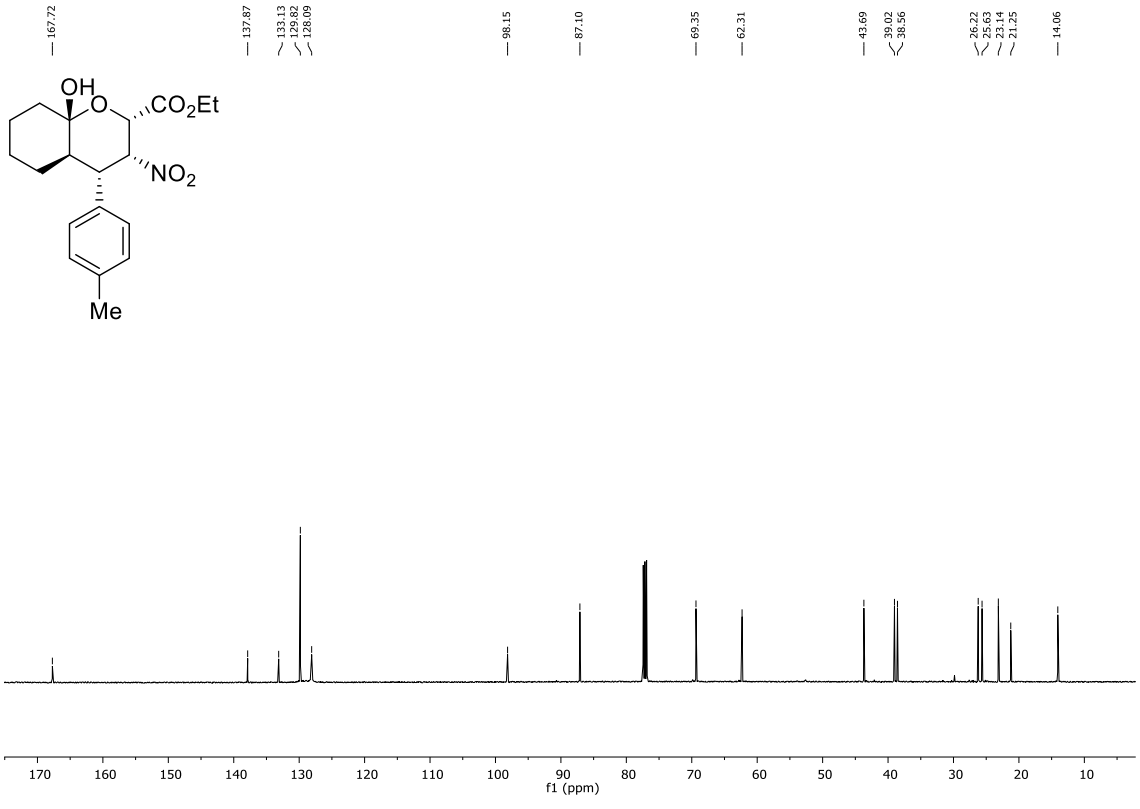


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aba**

^{1}H NMR ($CDCl_3$)

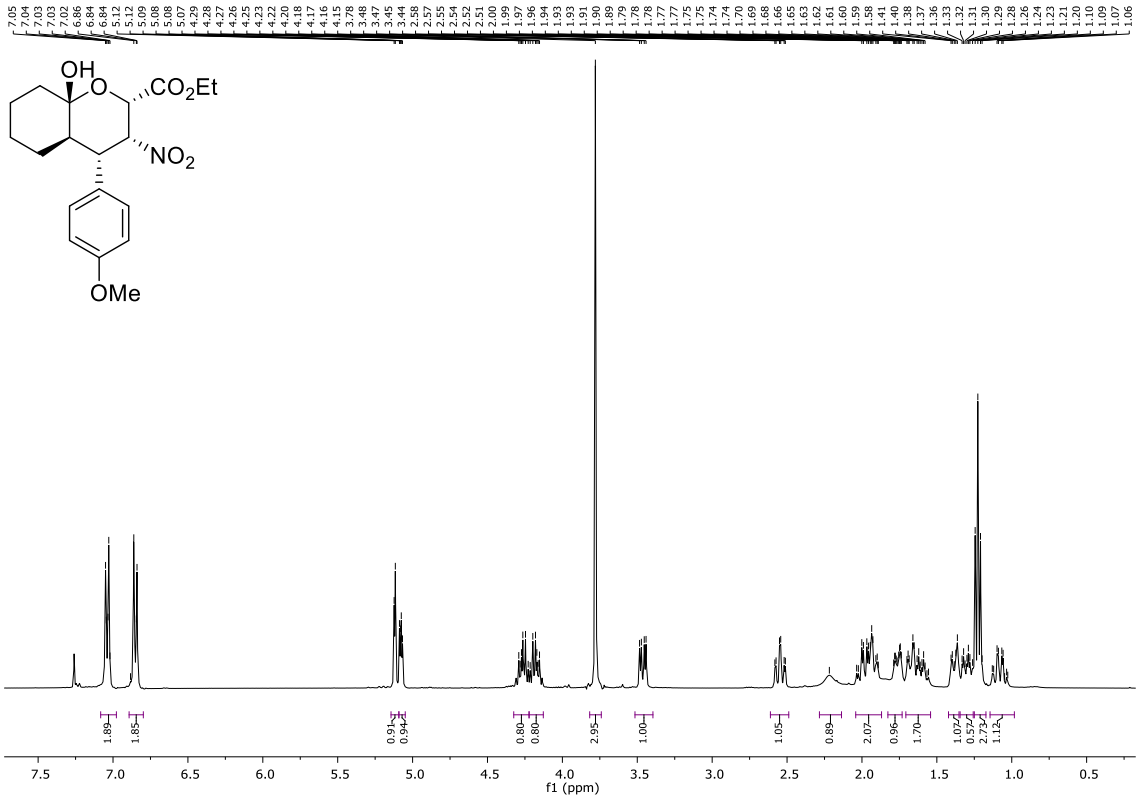


^{13}C NMR ($CDCl_3$)

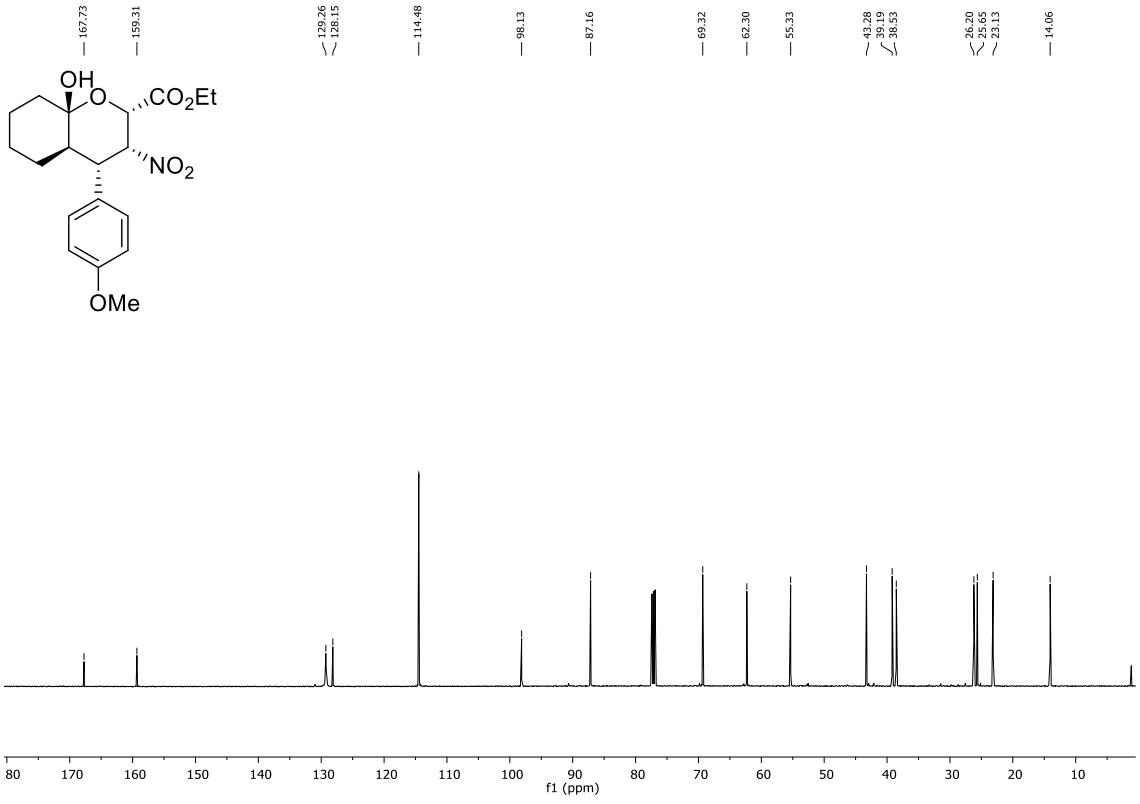


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aca**

^{1}H NMR ($CDCl_3$)

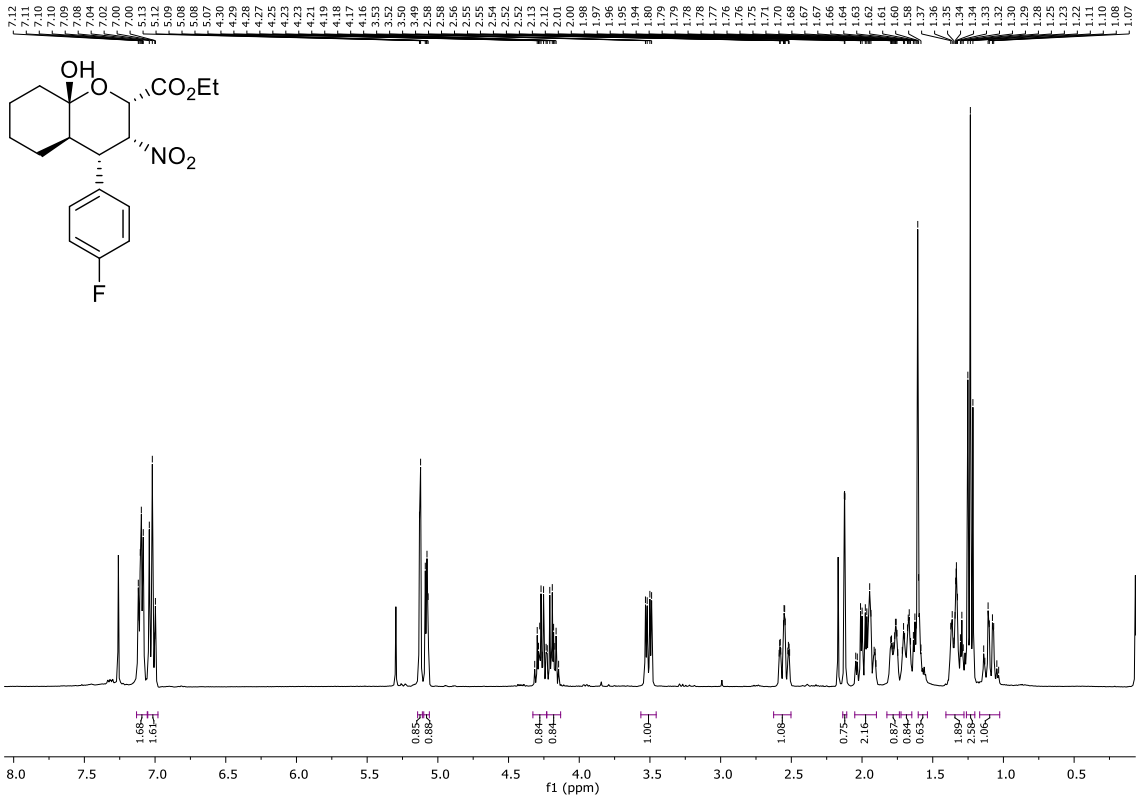


^{13}C NMR ($CDCl_3$)

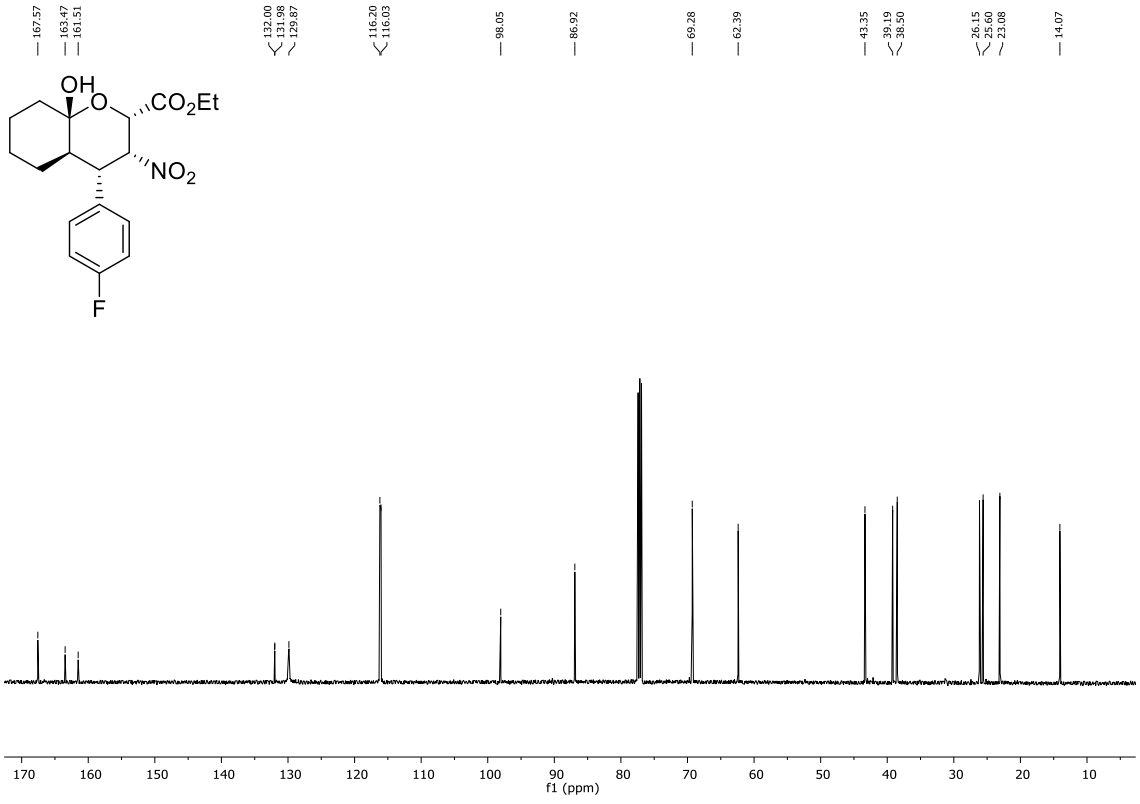


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79ada**

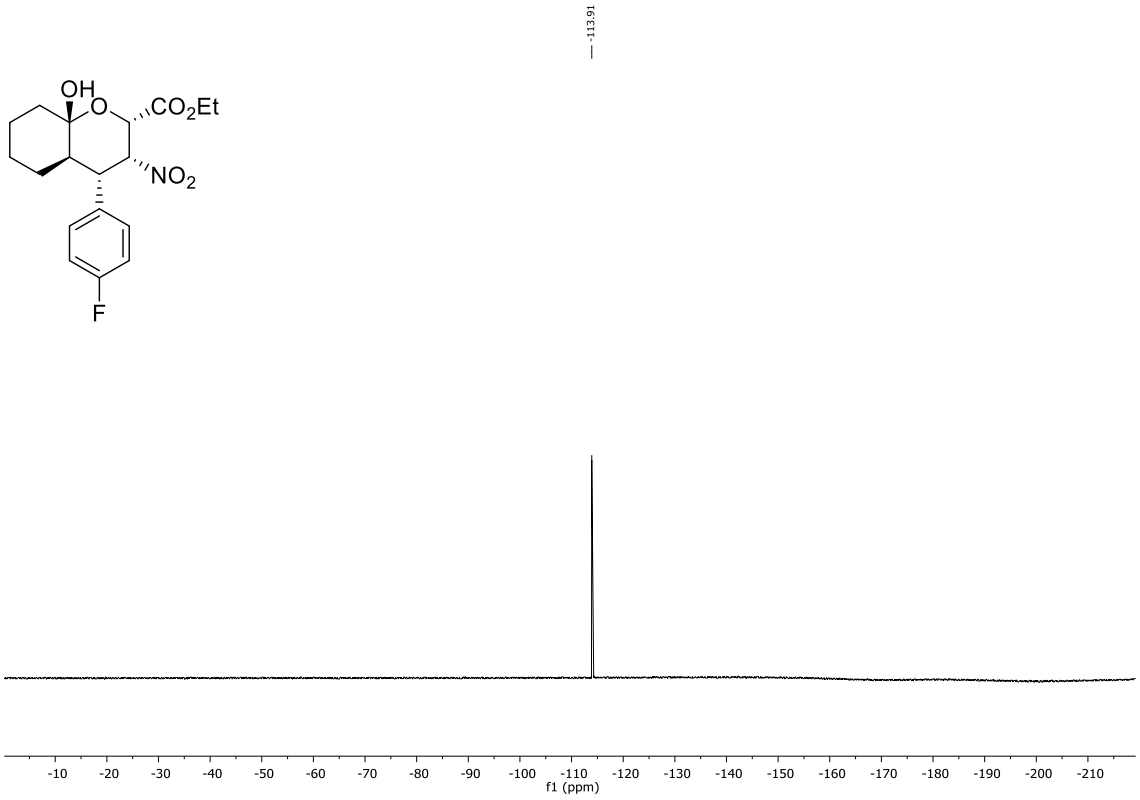
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

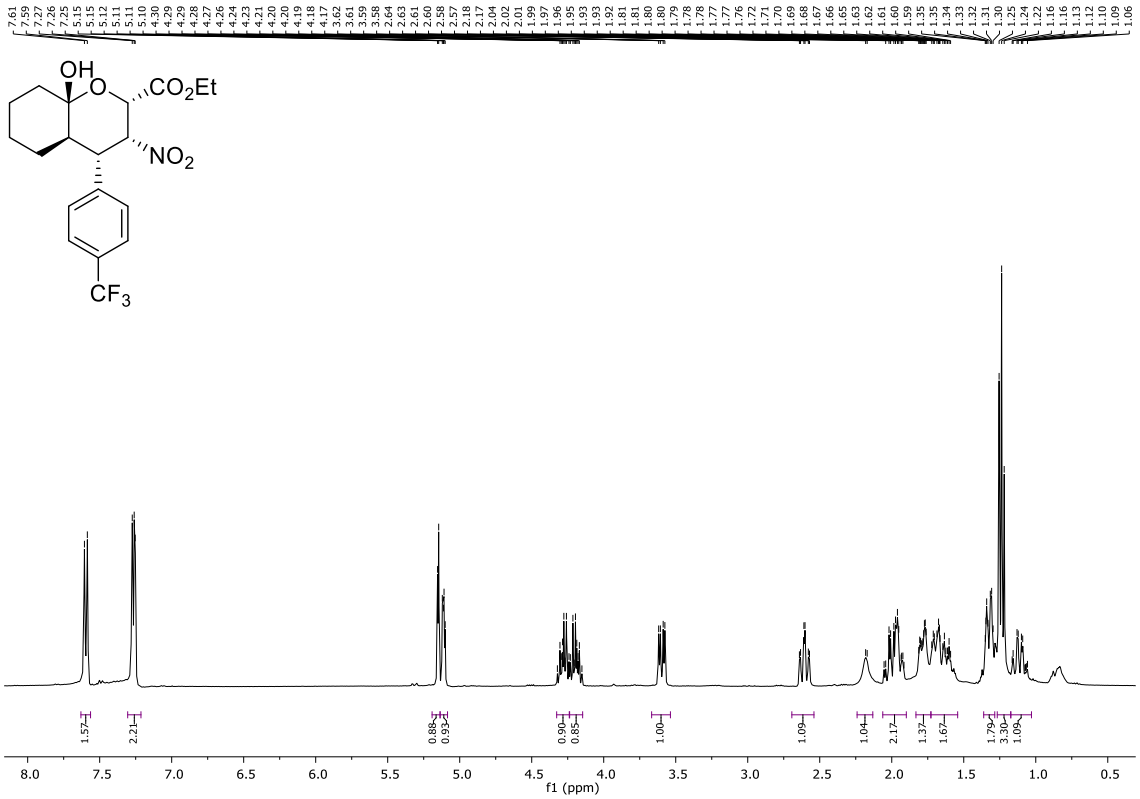


^{19}F NMR ($CDCl_3$)

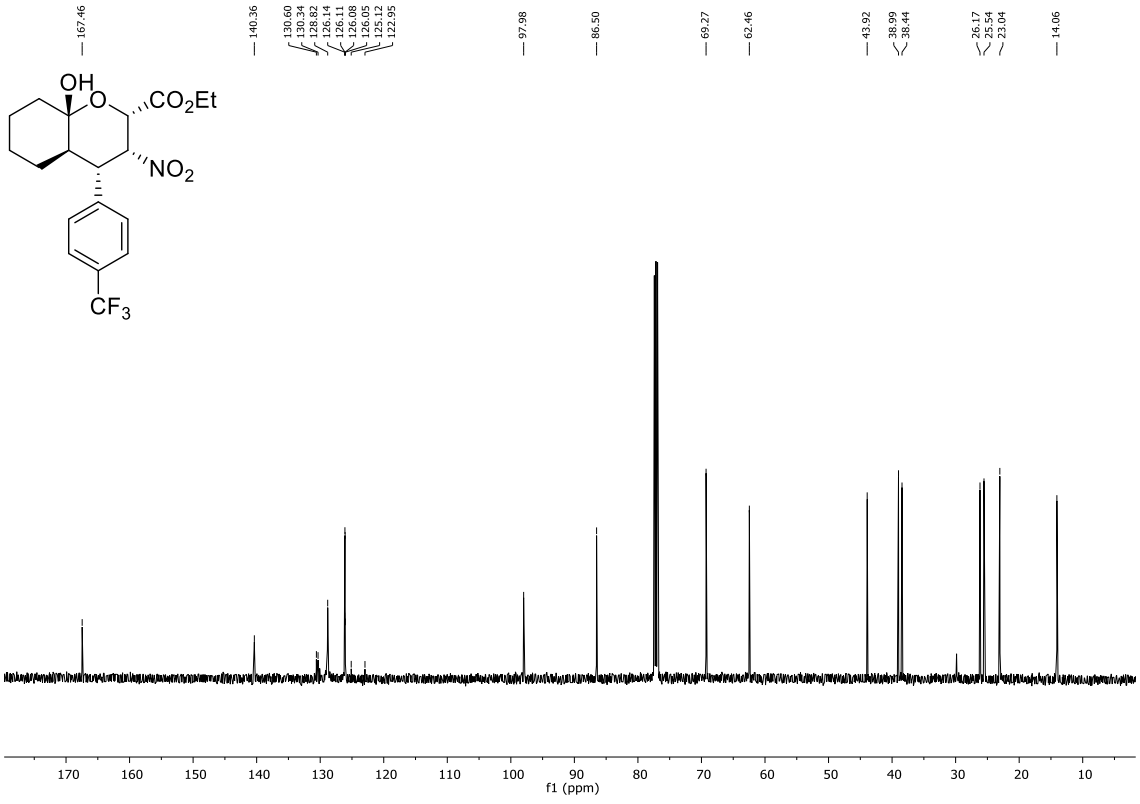


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aea**

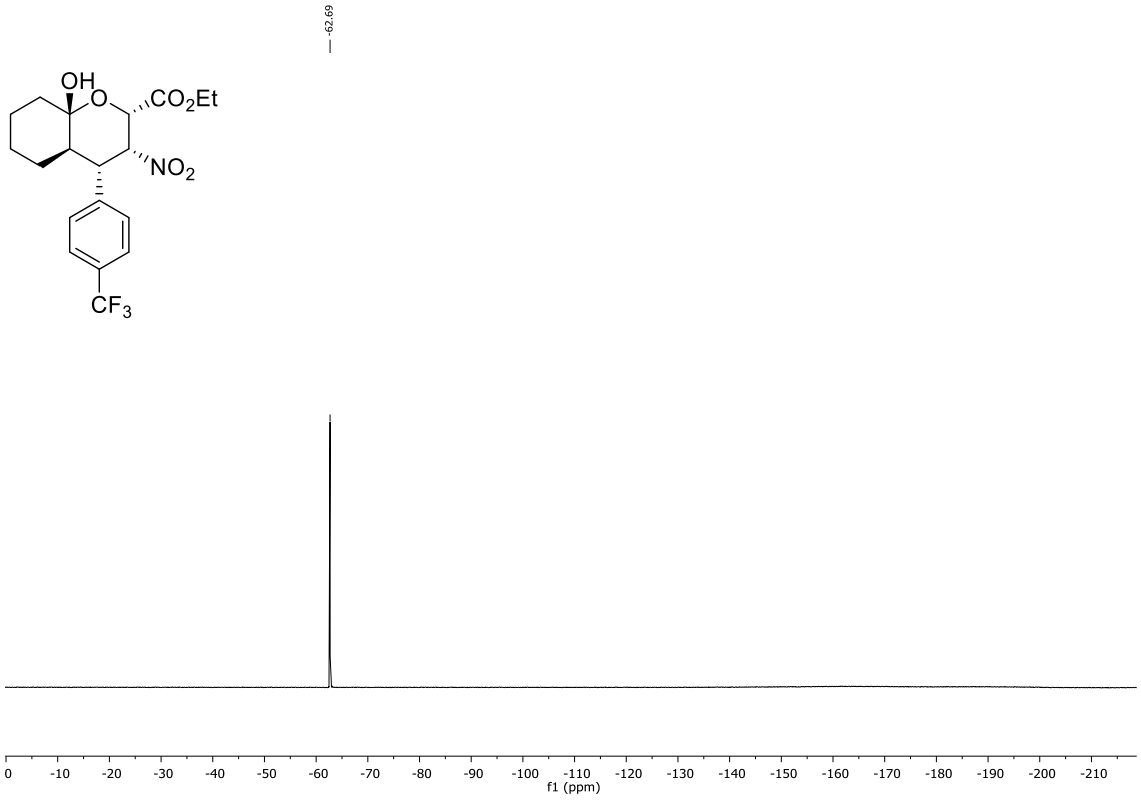
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

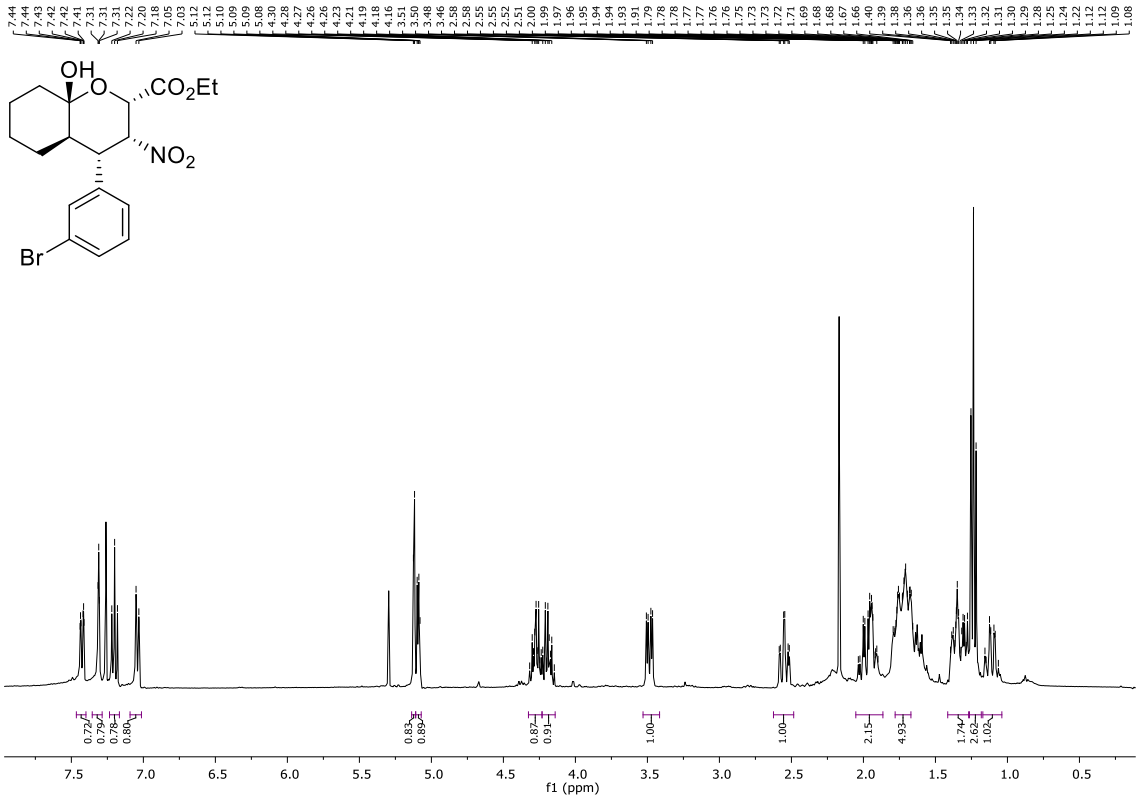


^{19}F NMR ($CDCl_3$)

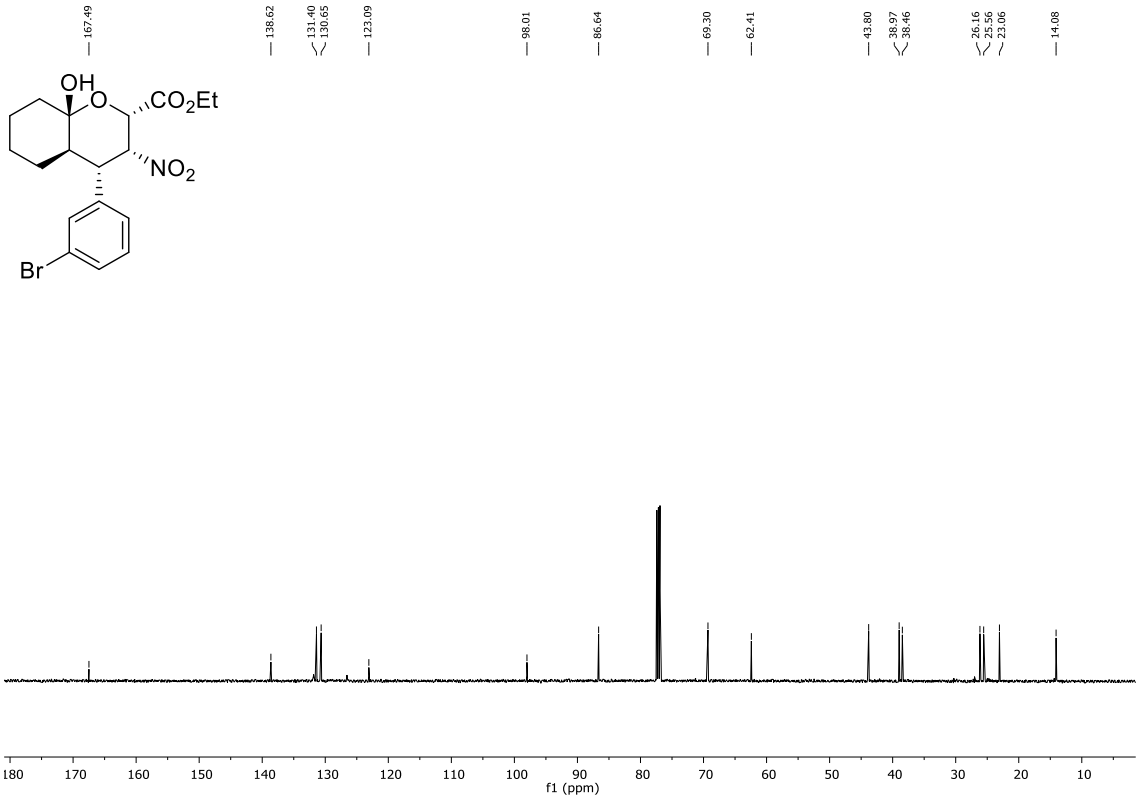


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79afa**

^{1}H NMR ($CDCl_3$)

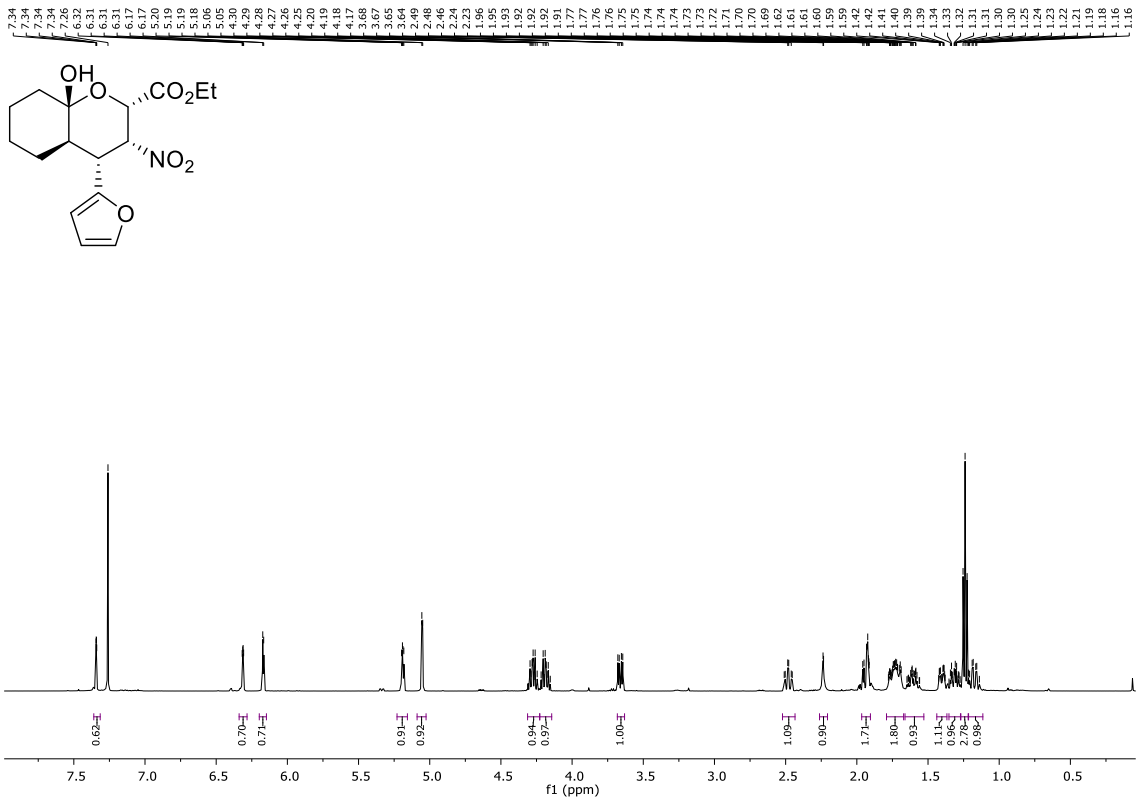


^{13}C NMR ($CDCl_3$)

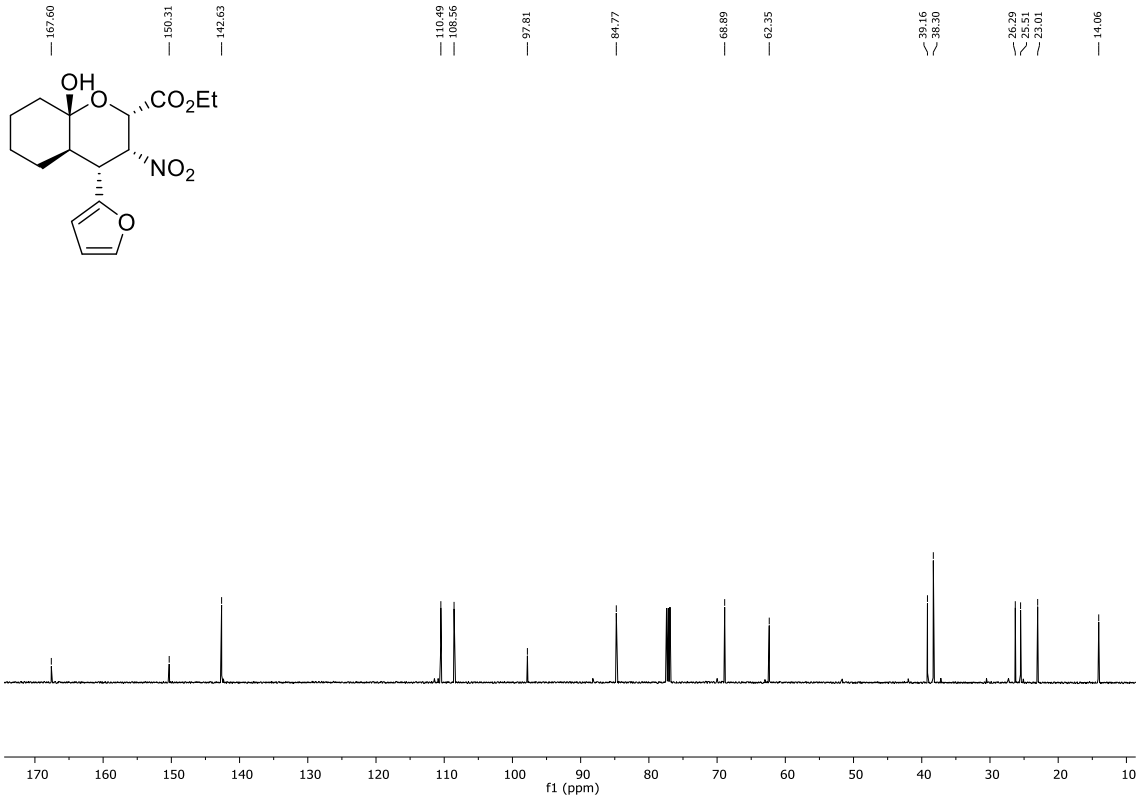


Compound (2*S*,3*R*,4*R*,4a*R*,8a*S*)-**79aga**

^{1}H NMR ($CDCl_3$)

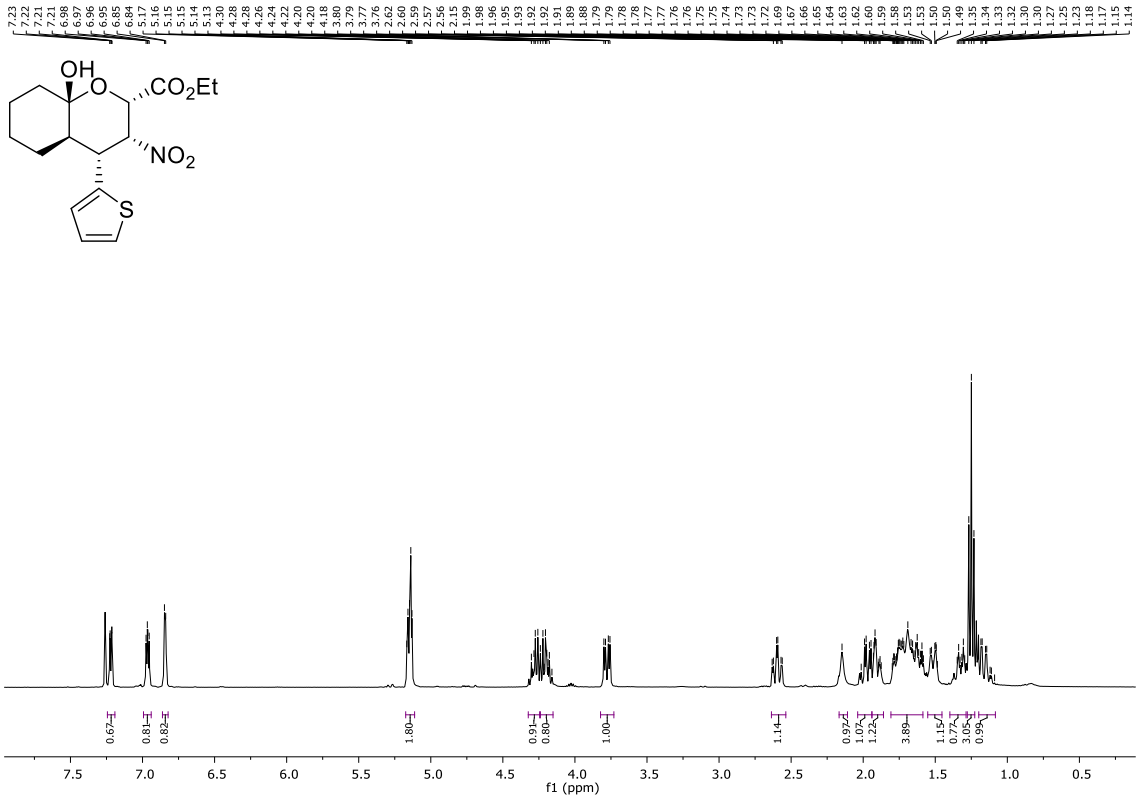


^{13}C NMR ($CDCl_3$)

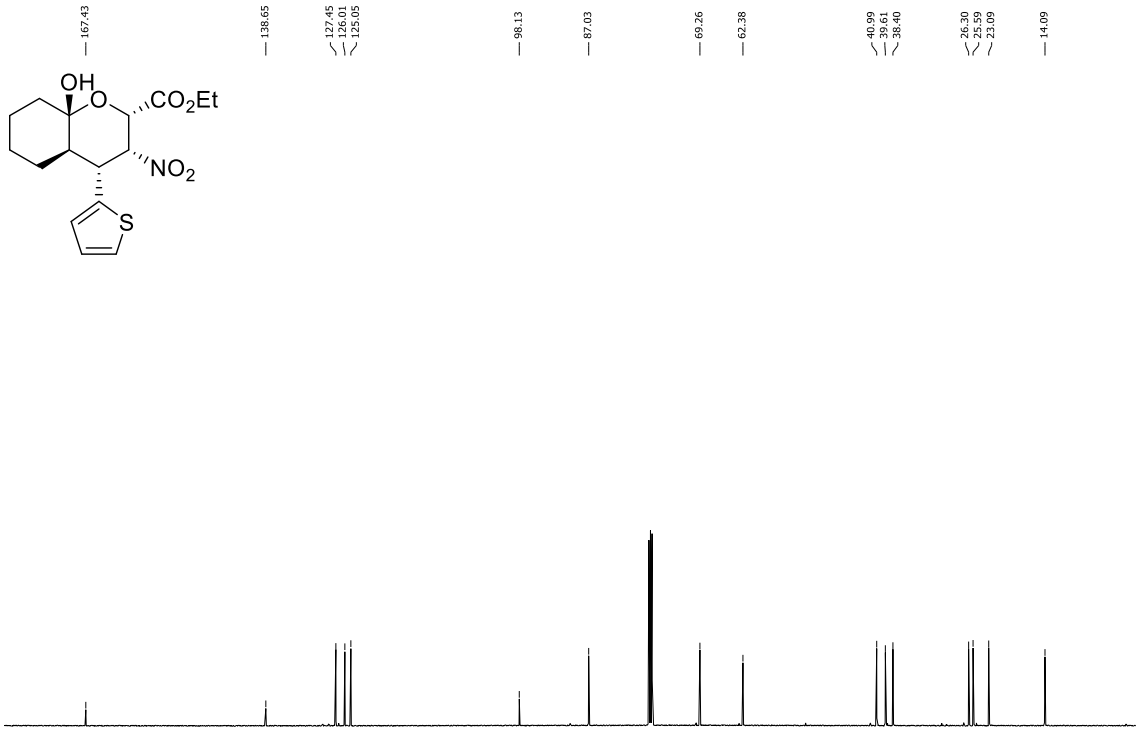


Compound (2*S*,3*R*,4*R*,4a*R*,8a*S*)-**79aha**

^{1}H NMR ($CDCl_3$)

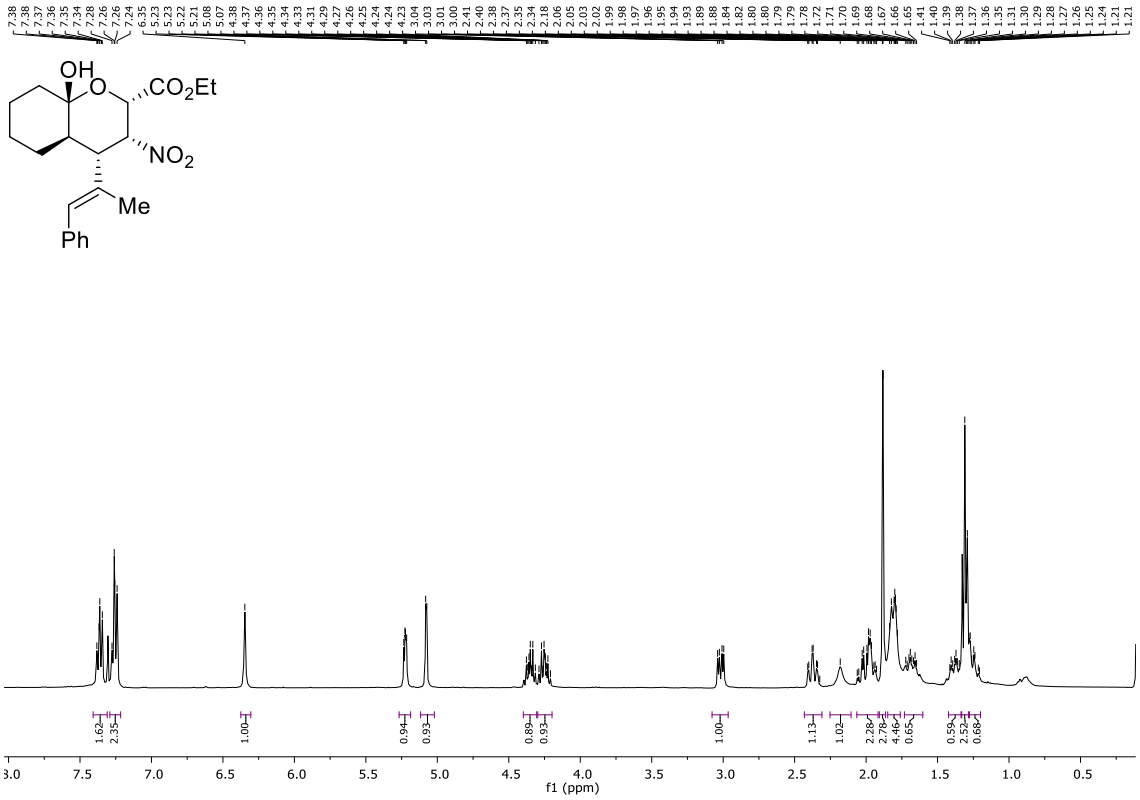


^{13}C NMR ($CDCl_3$)

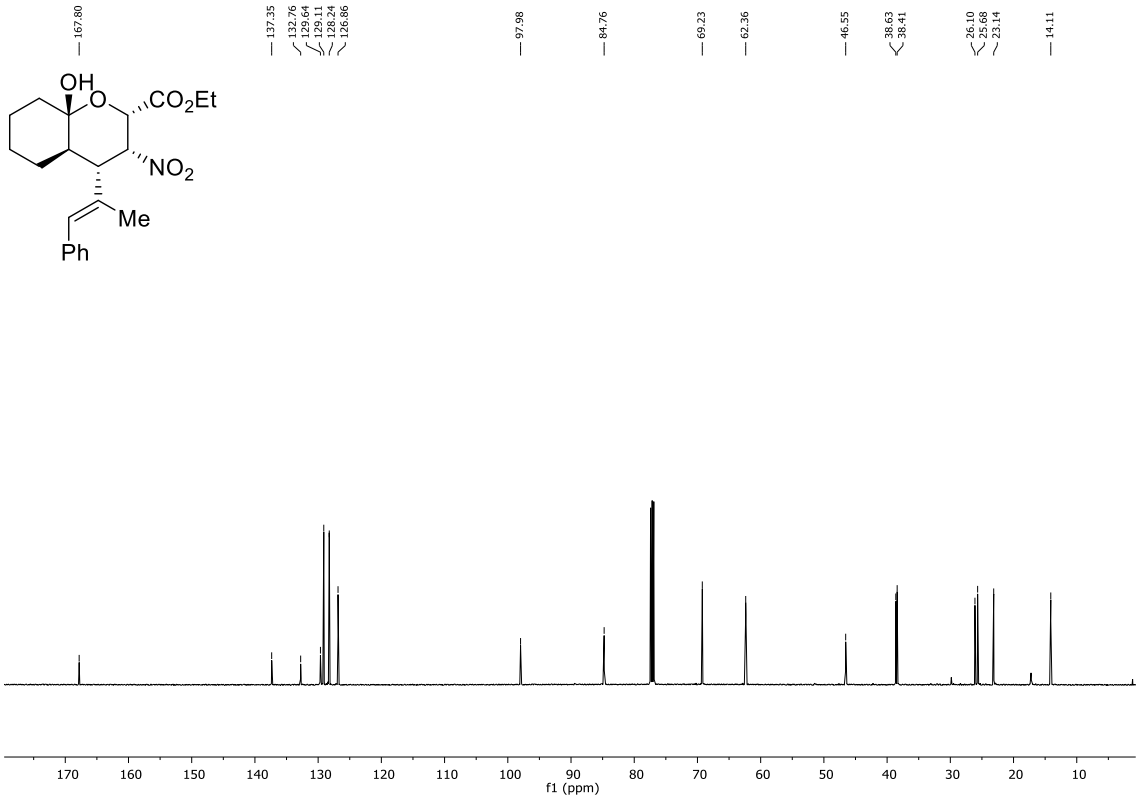


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aia**

^{1}H NMR ($CDCl_3$)

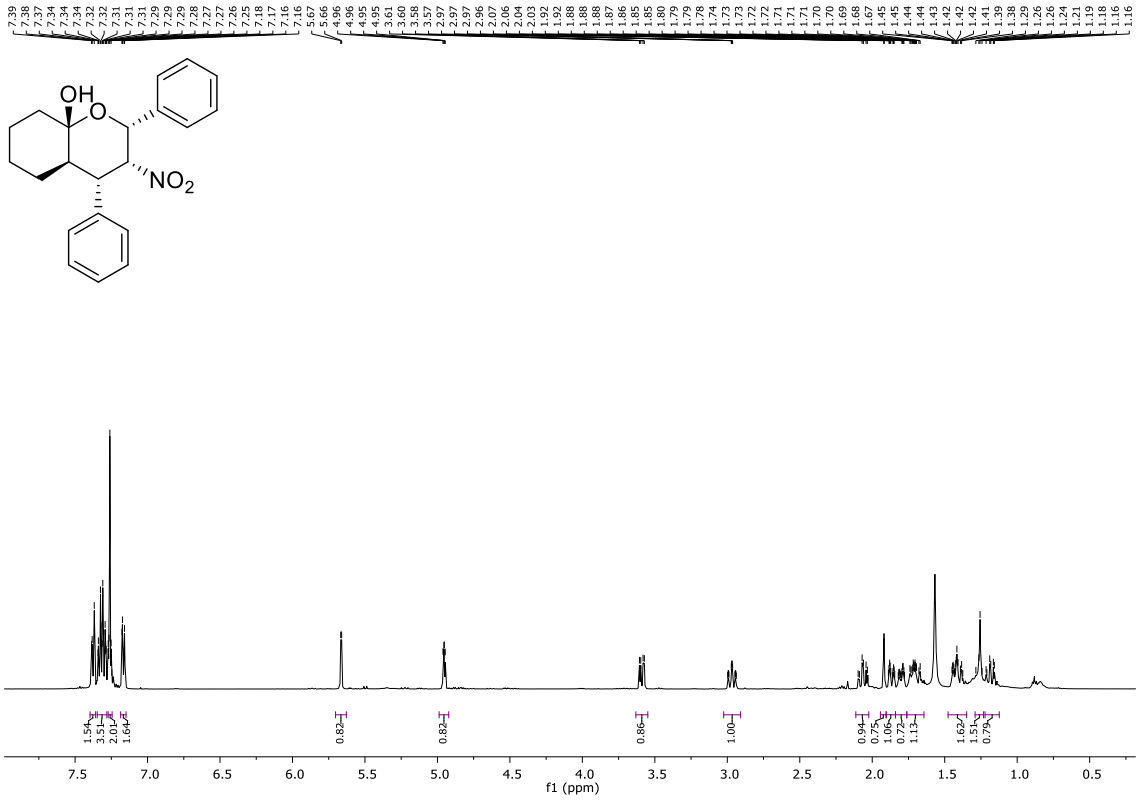


^{13}C NMR ($CDCl_3$)

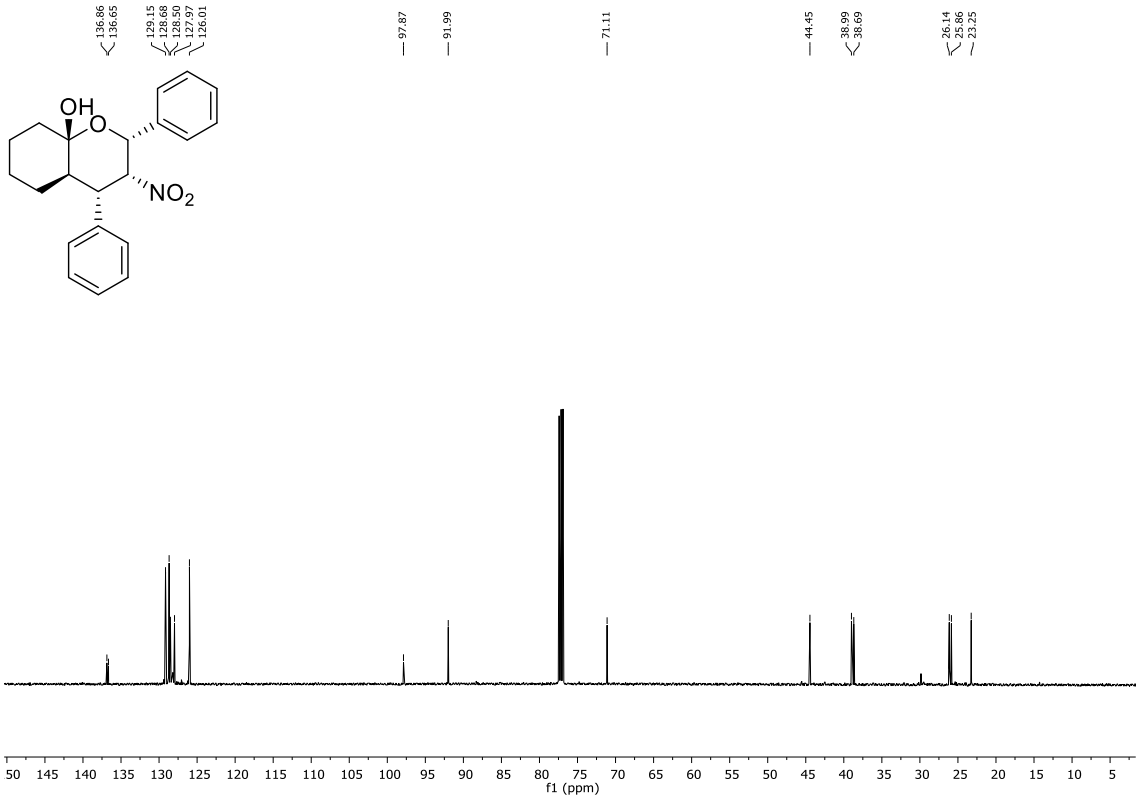


Compound (2*R*,3*R*,4*S*,4a*R*,8a*S*)-**79aab**

^{1}H NMR ($CDCl_3$)

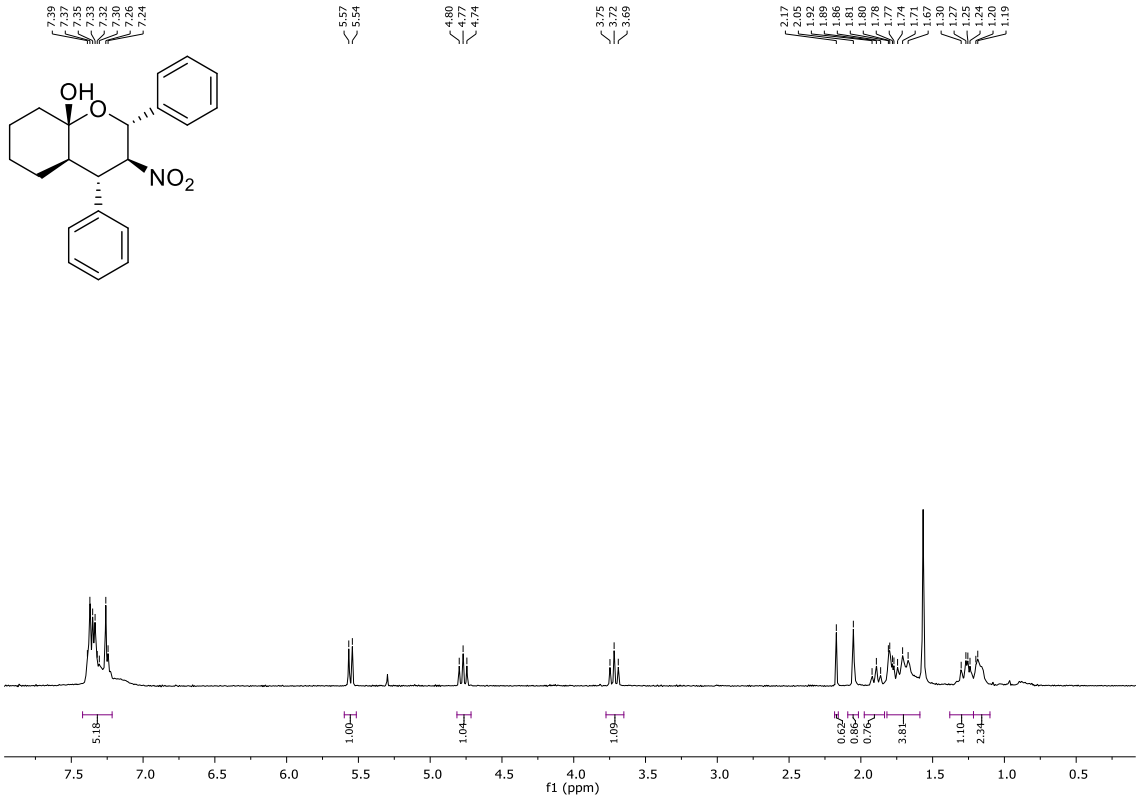


^{13}C NMR ($CDCl_3$)

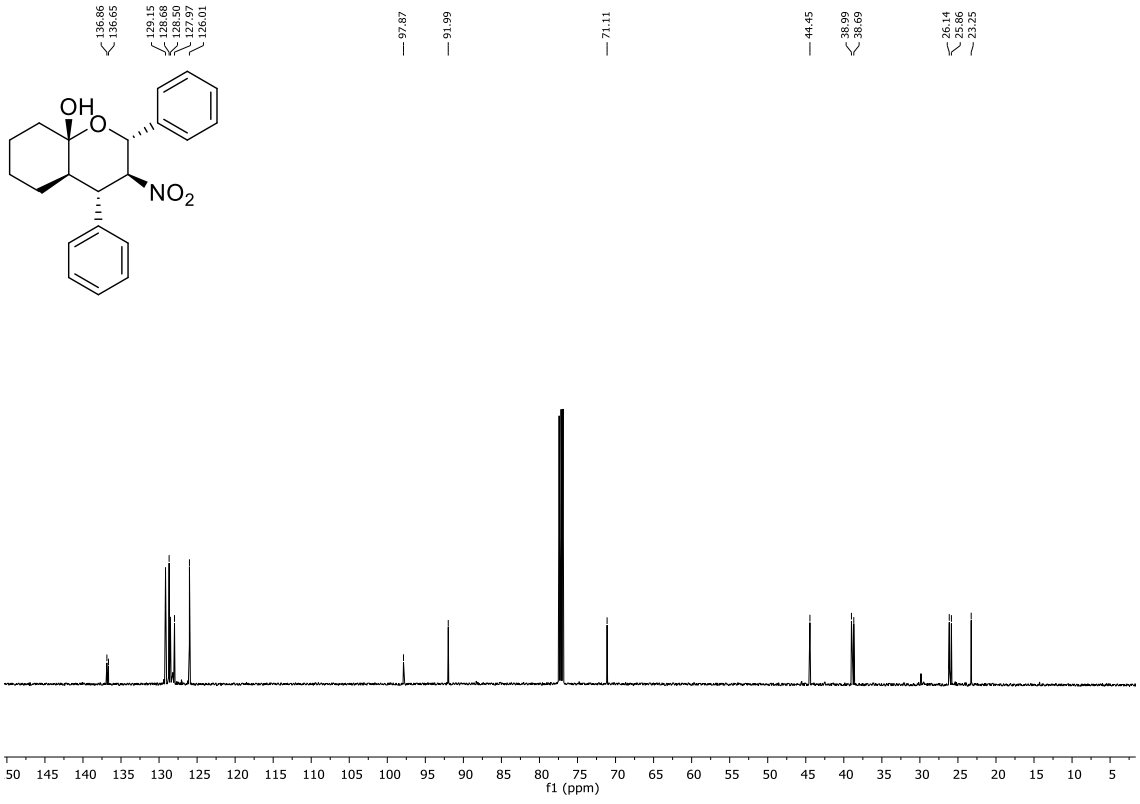


Compound (2*R*,3*S*,4*S*,4a*R*,8a*S*)-**79aab'**

^{1}H NMR ($CDCl_3$)

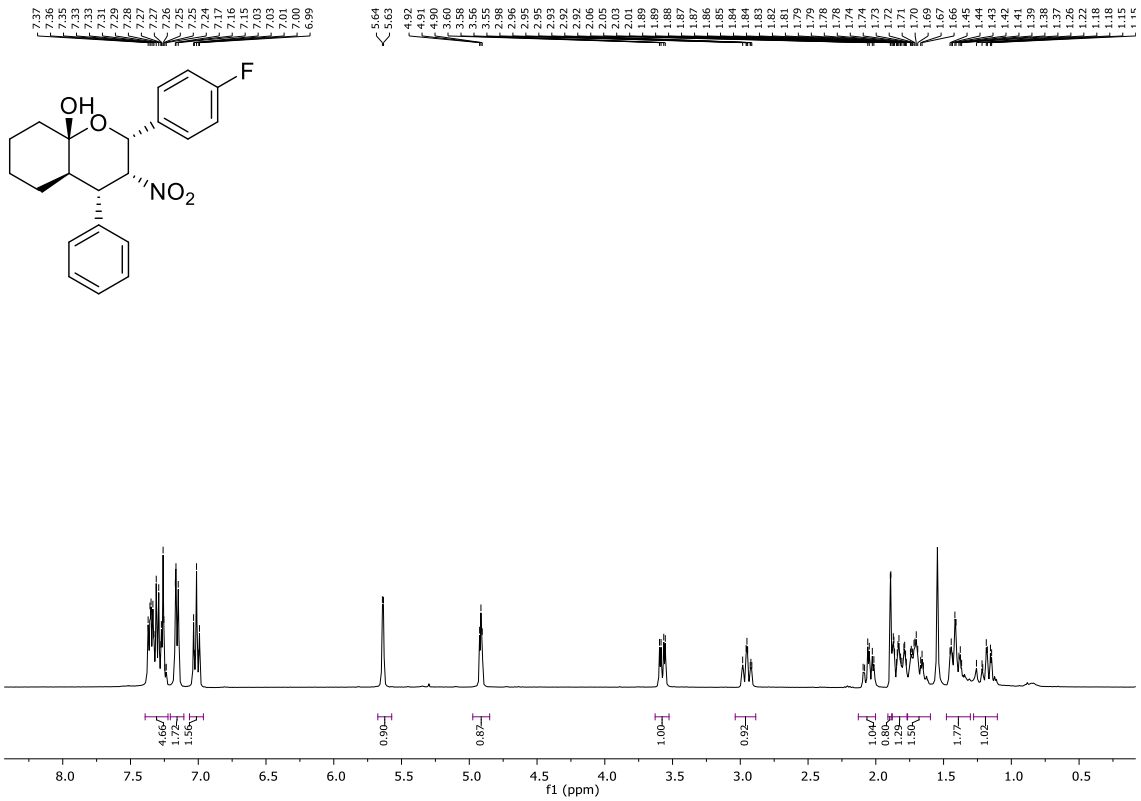


^{13}C NMR ($CDCl_3$)

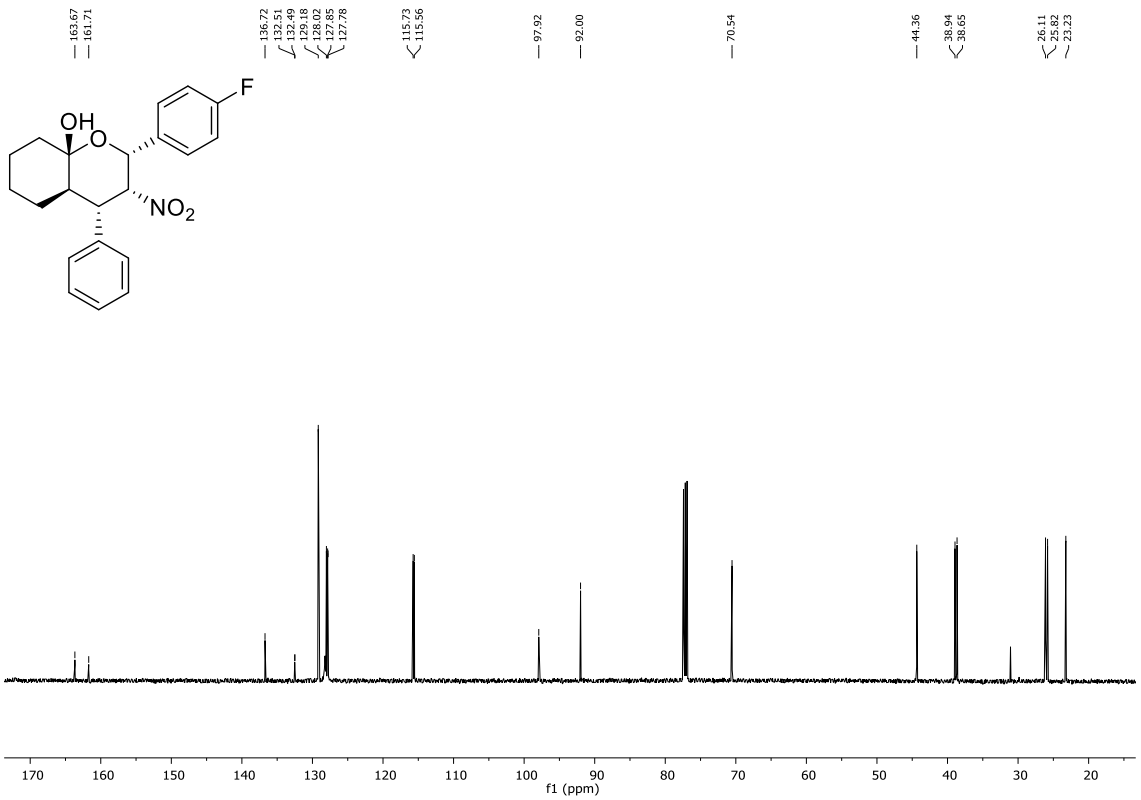


Compound (2*R*,3*R*,4*S*,4a*R*,8a*S*)-**79aac**

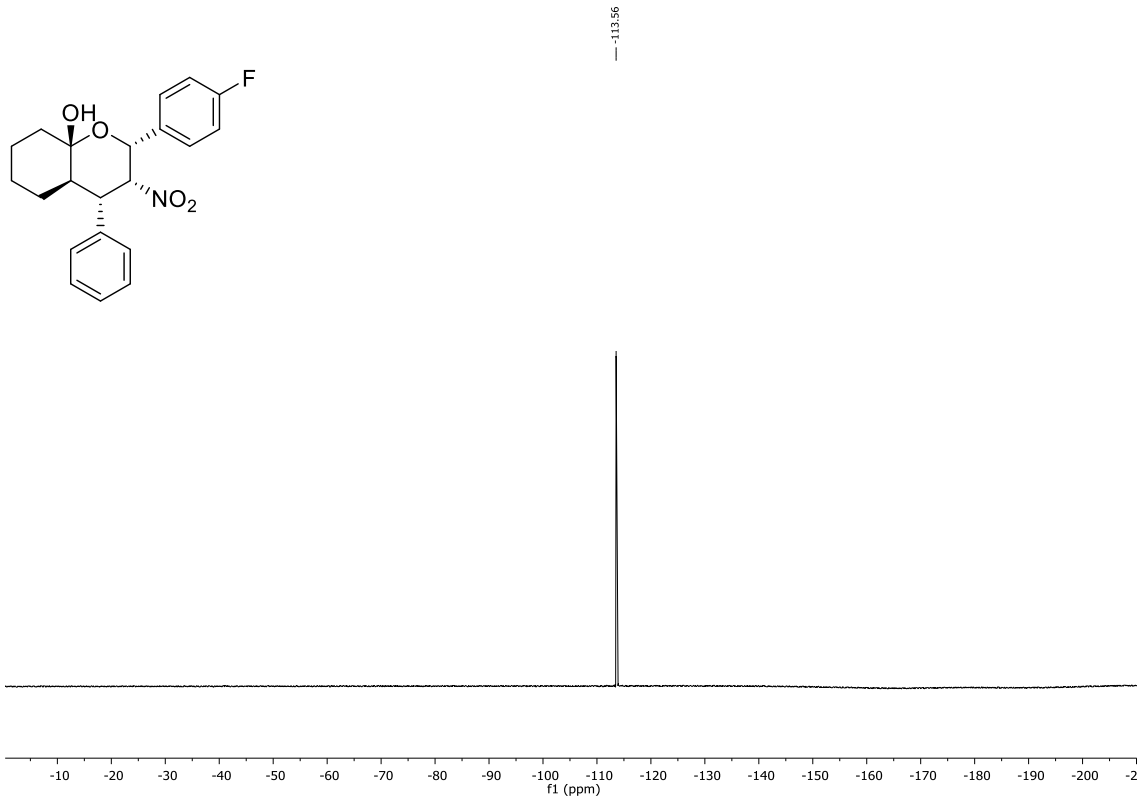
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

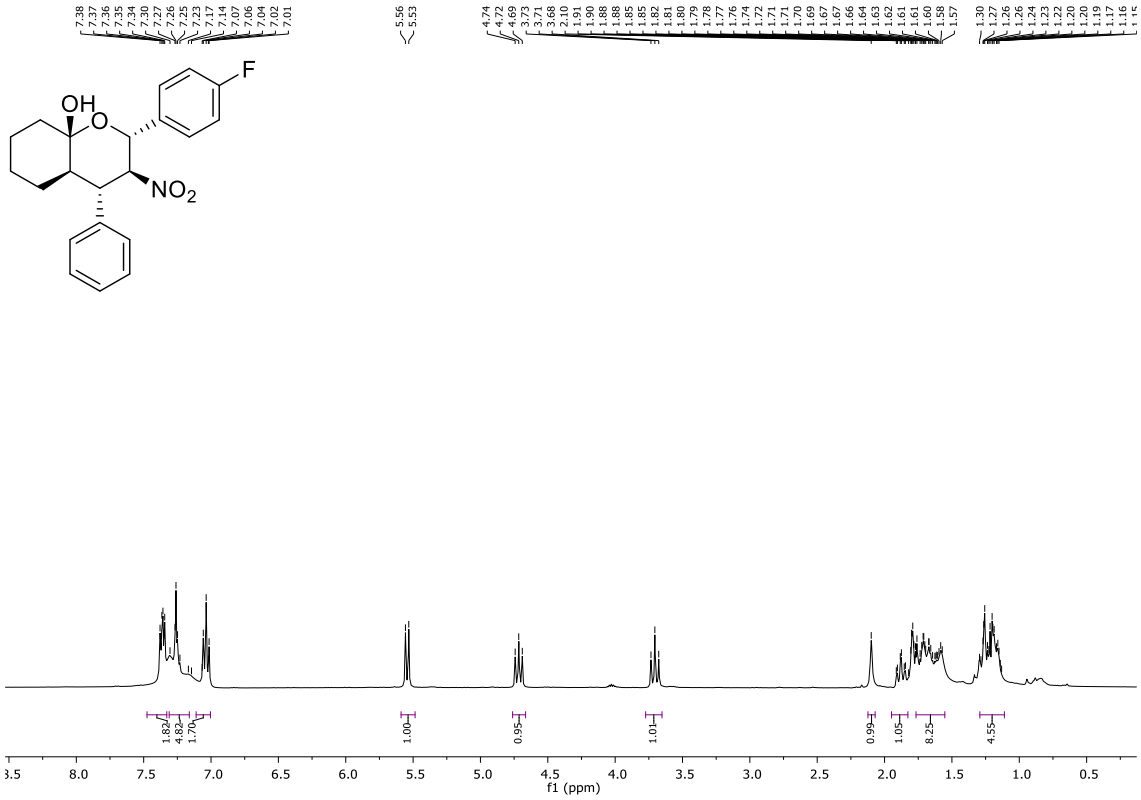


^{19}F NMR ($CDCl_3$)

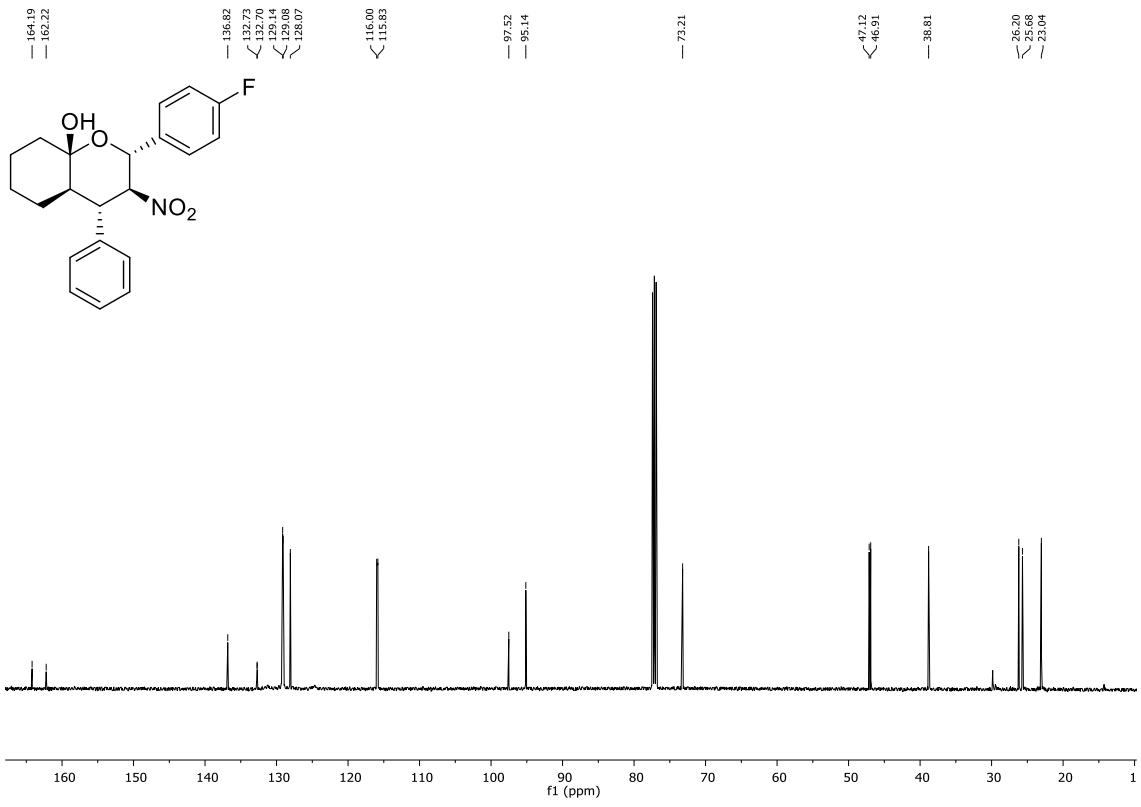


Compound (2*R*,3*S*,4*S*,4a*R*,8a*S*)-**79aac'**

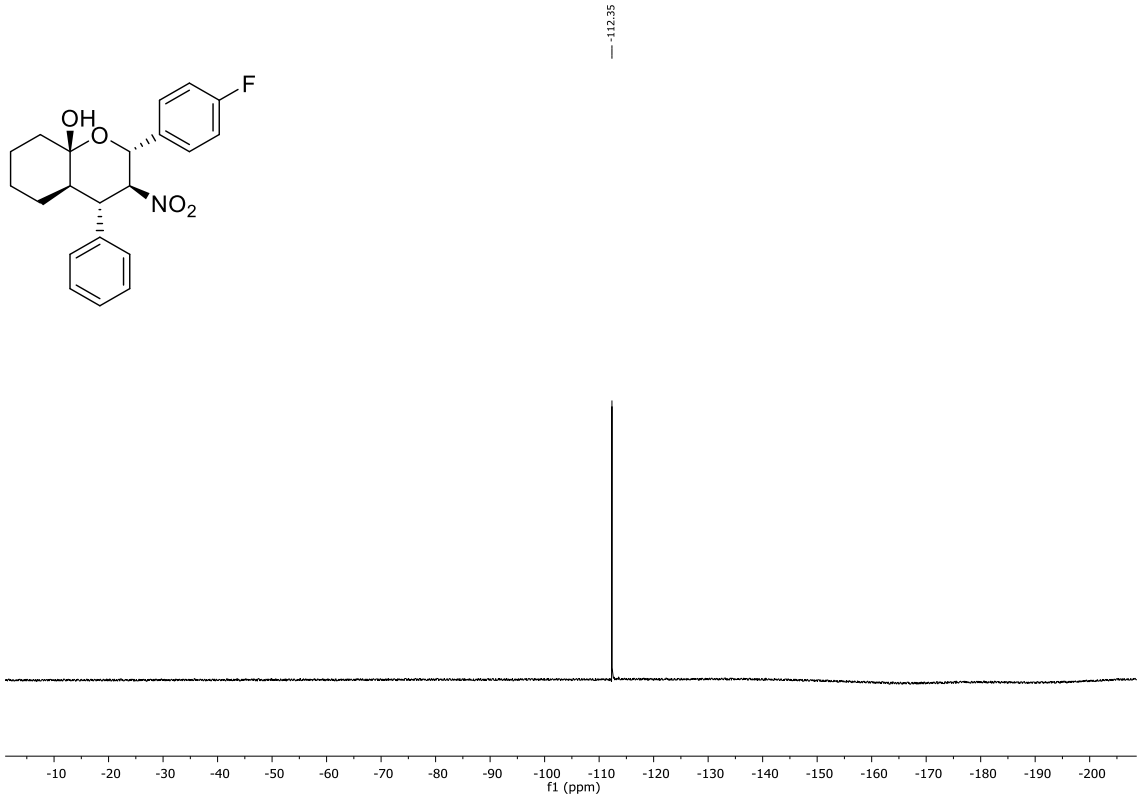
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

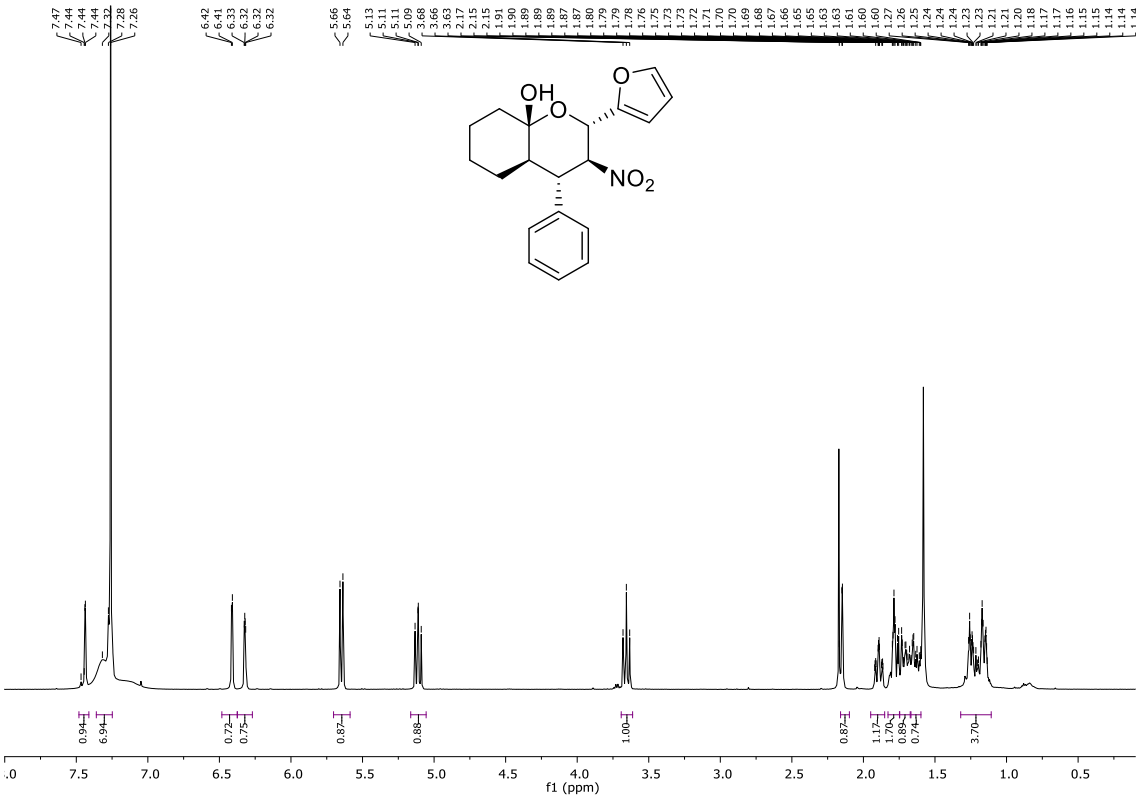


^{19}F NMR ($CDCl_3$)

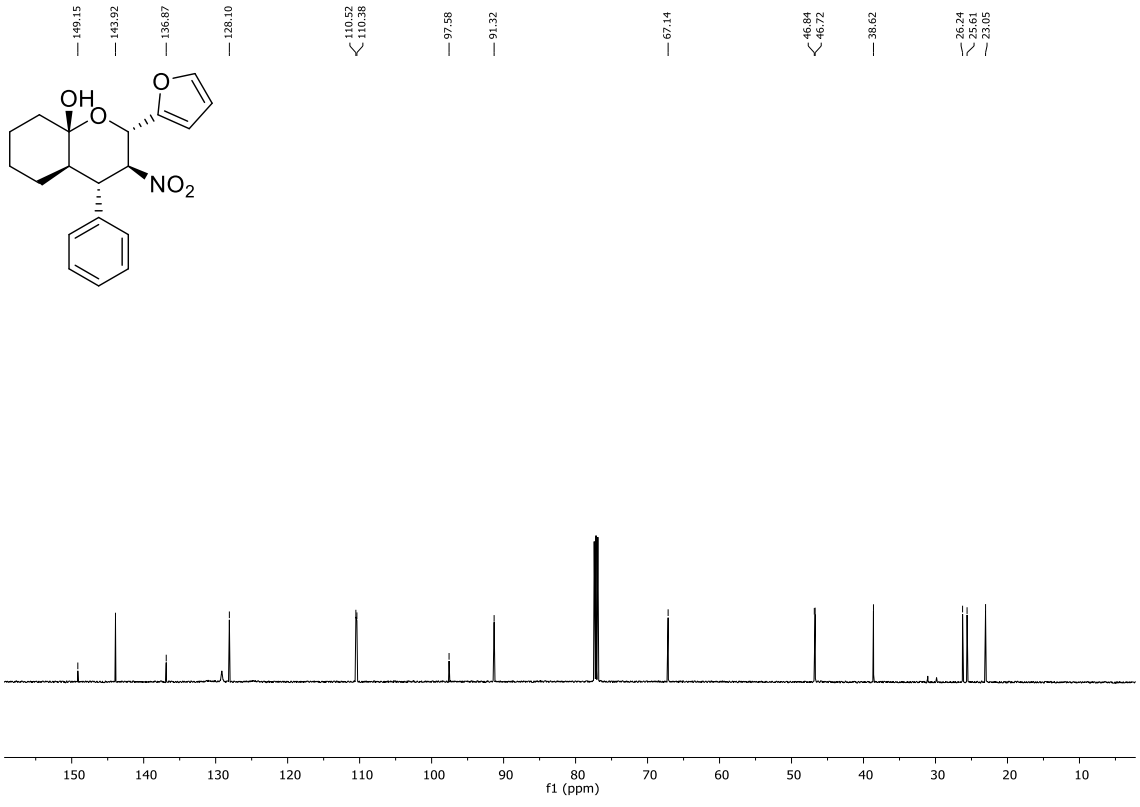


Compound (2*S*,3*S*,4*S*,4a*R*,8a*S*)-**79aad'**

^{1}H NMR ($CDCl_3$)

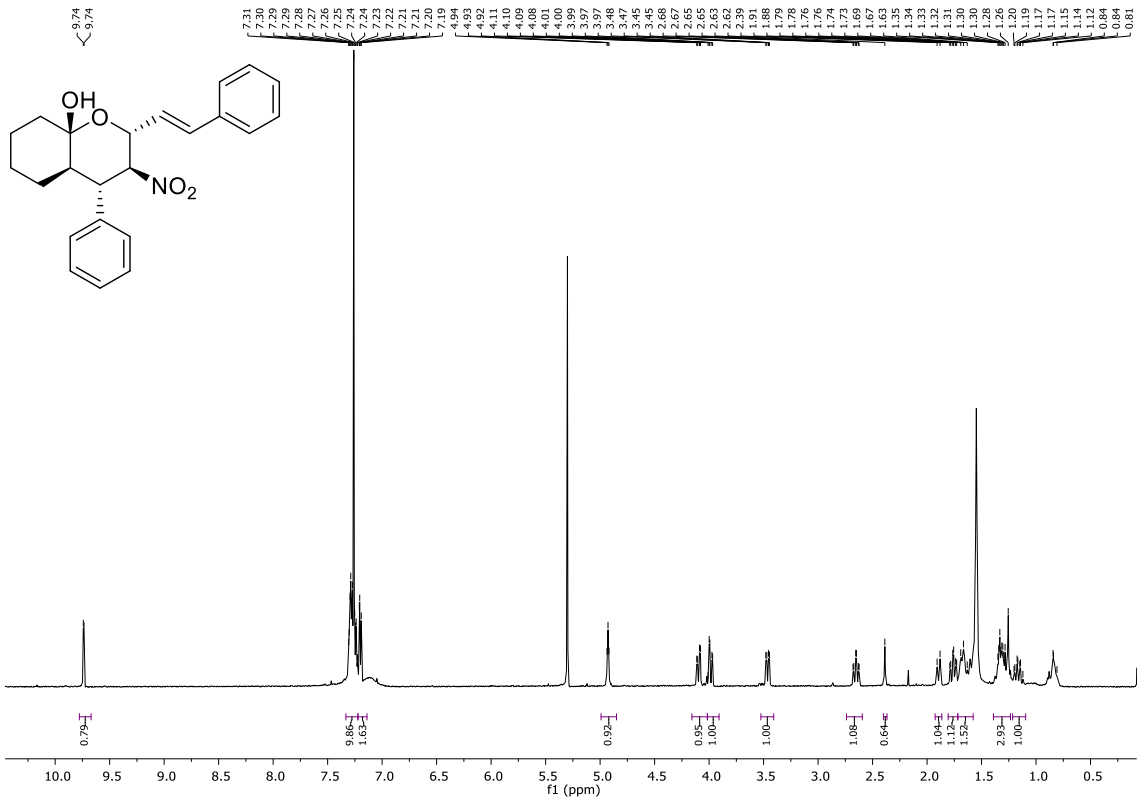


^{13}C NMR ($CDCl_3$)

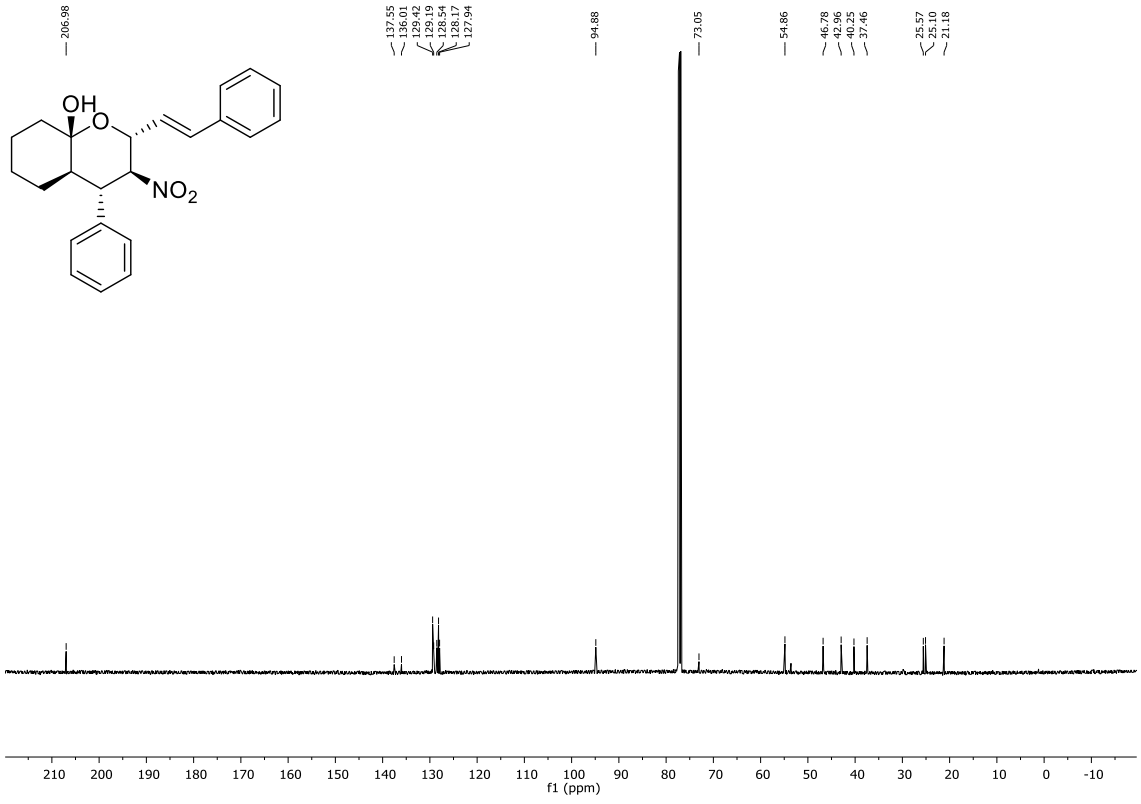


Compound (2*R*,3*R*,4*S*,4a*R*,8a*S*)-**79aae**

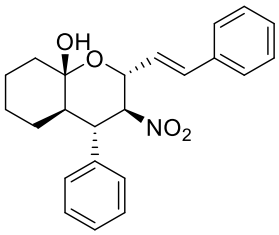
^{1}H NMR ($CDCl_3$)

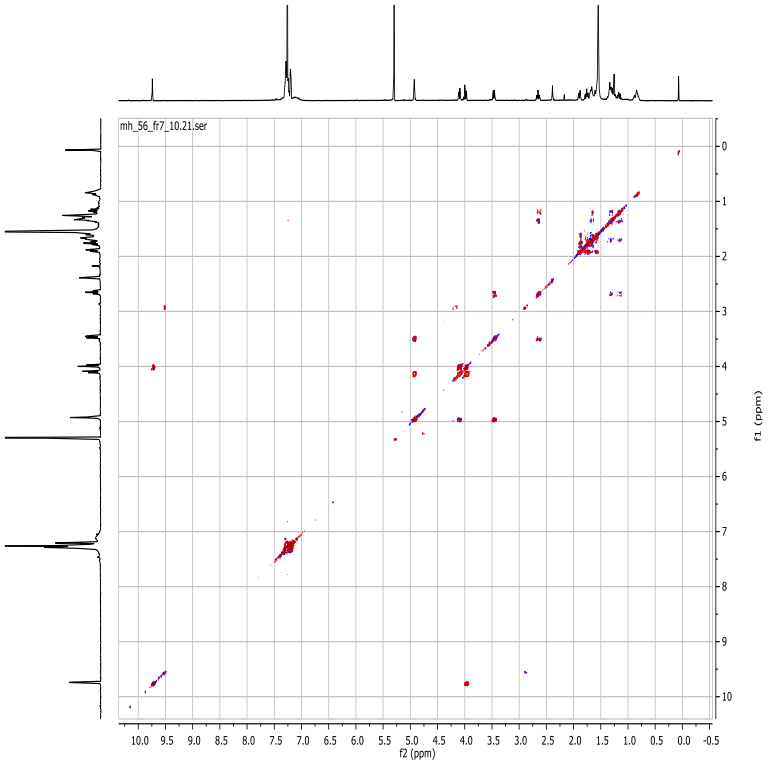


^{13}C NMR ($CDCl_3$)



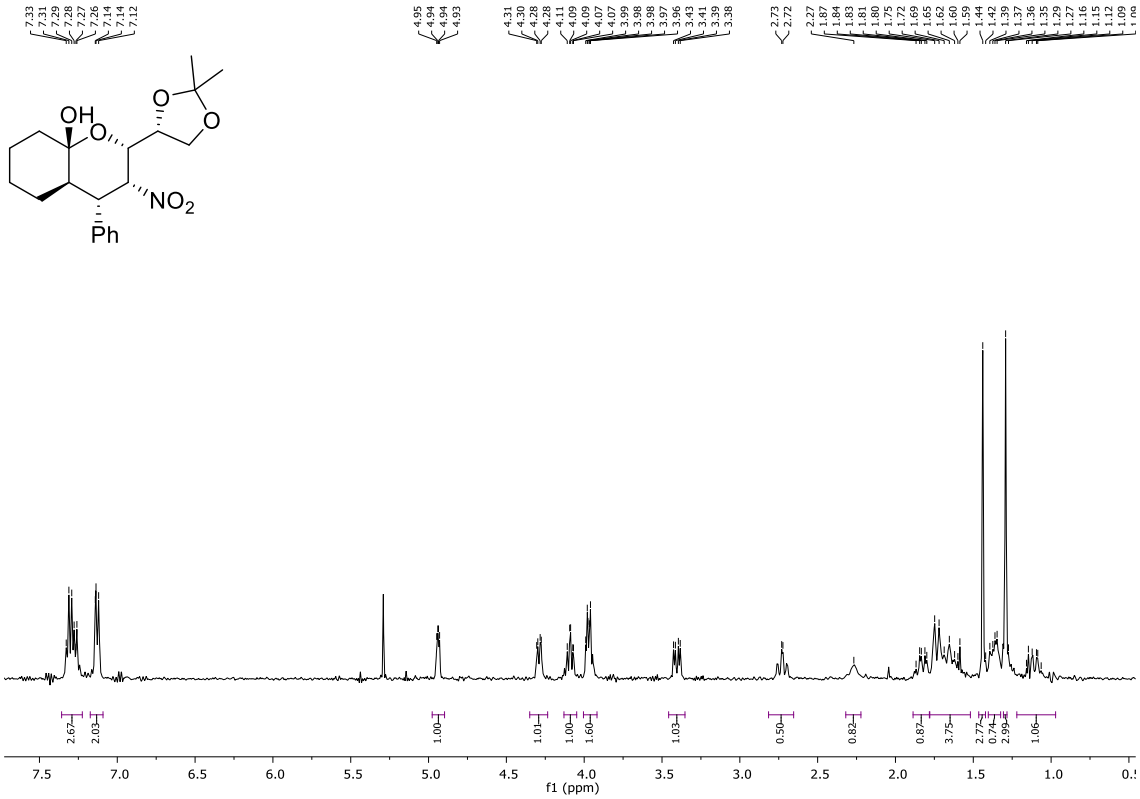
COSY ($CDCl_3$)



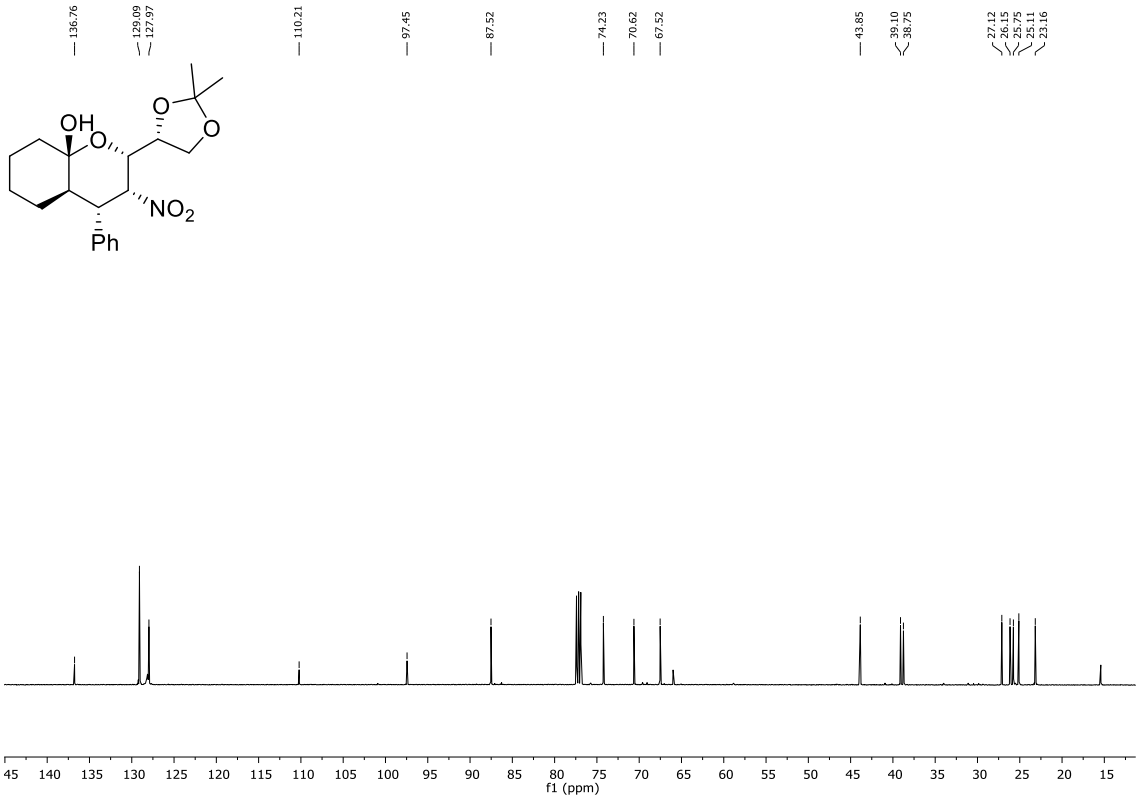


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79aaf**

^{1}H NMR ($CDCl_3$)

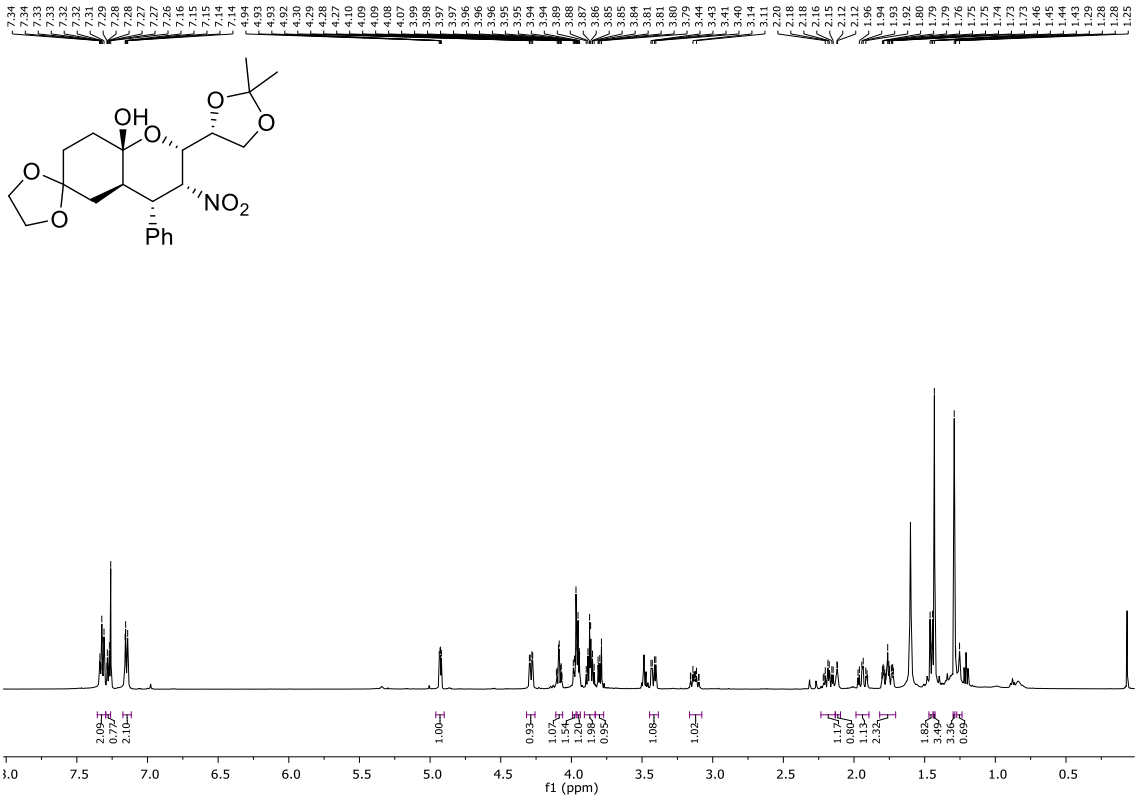


^{13}C NMR ($CDCl_3$)

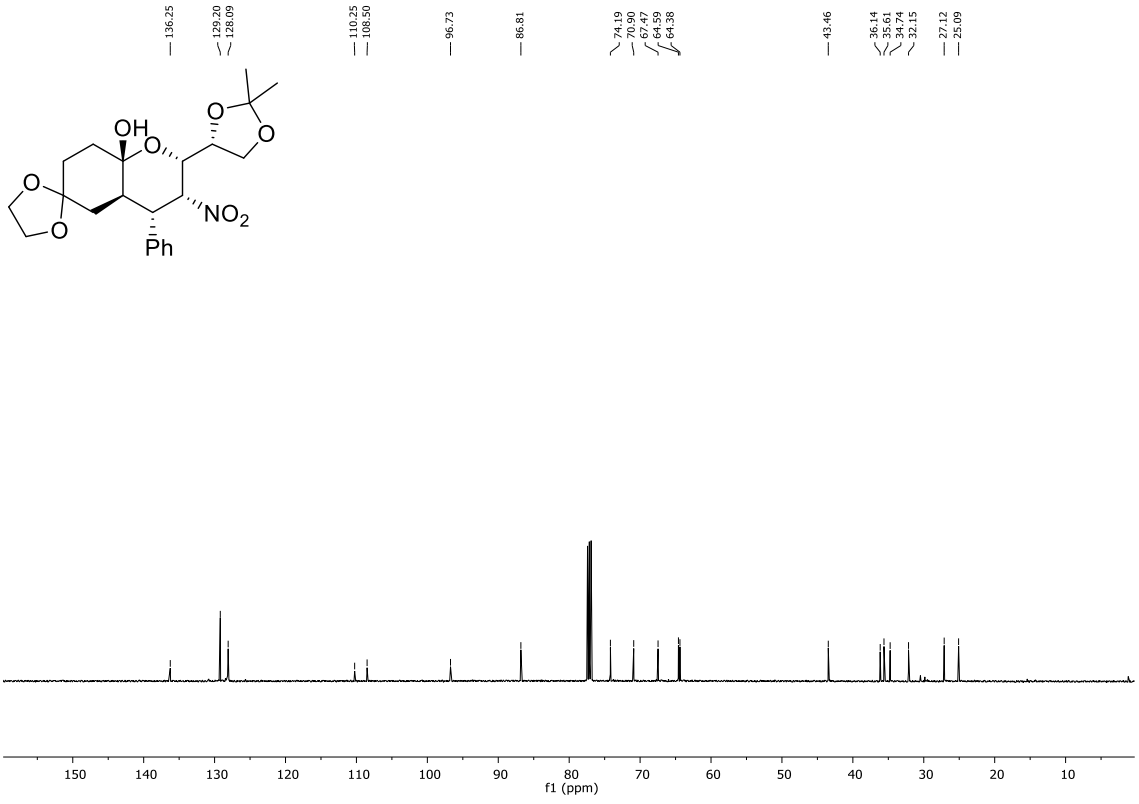


Compound (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**79jaf**

^{1}H NMR ($CDCl_3$)

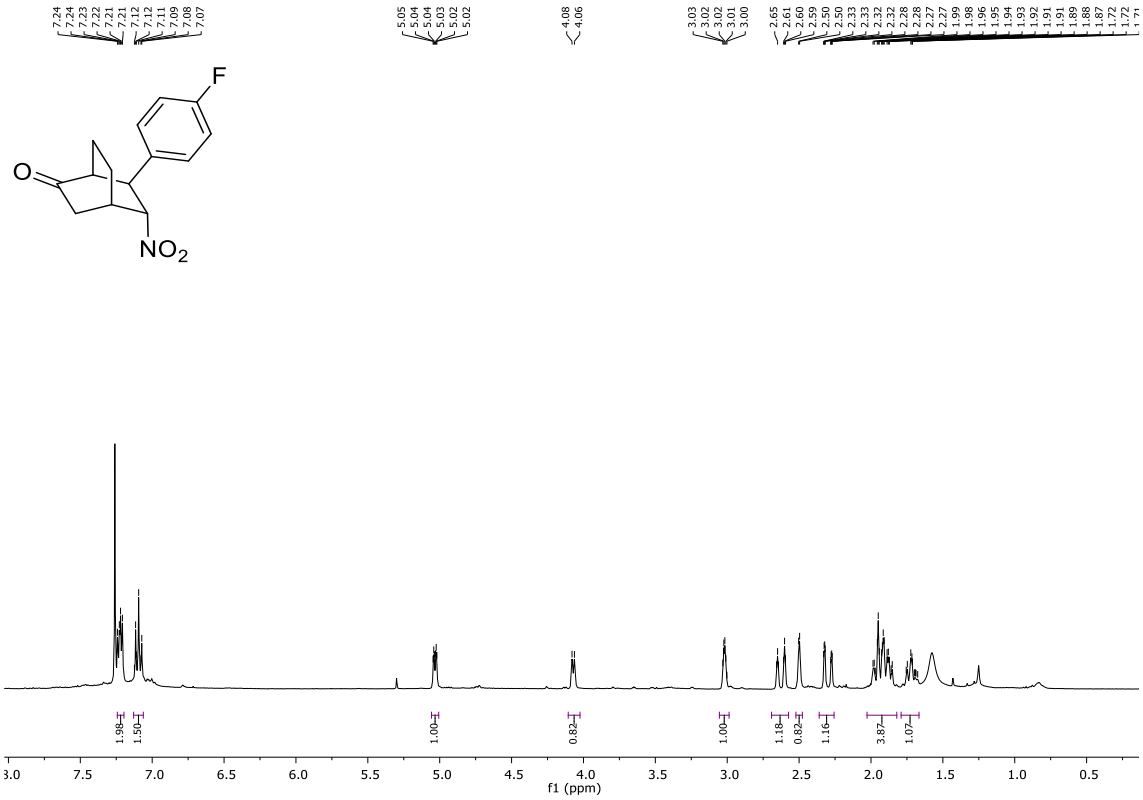


^{13}C NMR ($CDCl_3$)

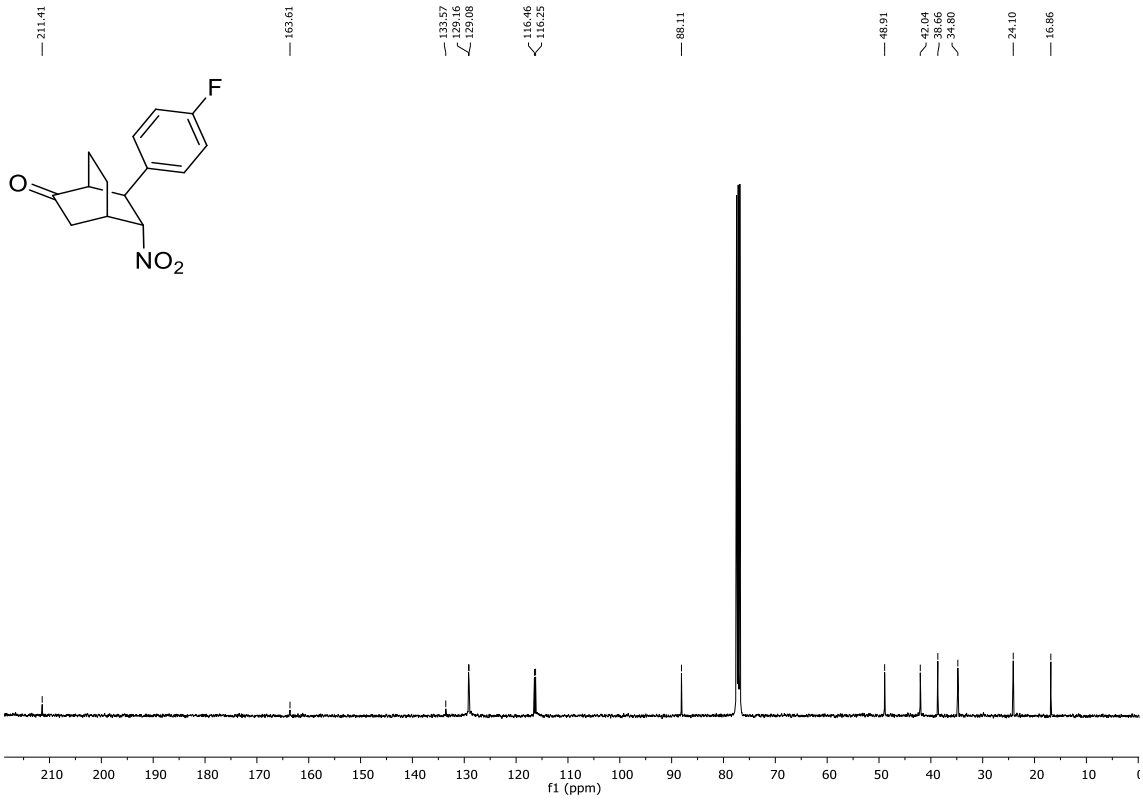


Annex II. NMR spectra selection for Chapter 3

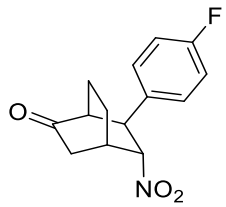
Compound *(1S,4S,5R,6S)- endo* **37a. ^{1}H NMR ($CDCl_3$)**



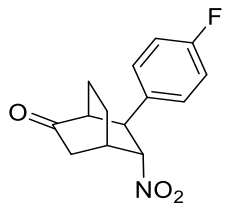
^{13}C NMR ($CDCl_3$)

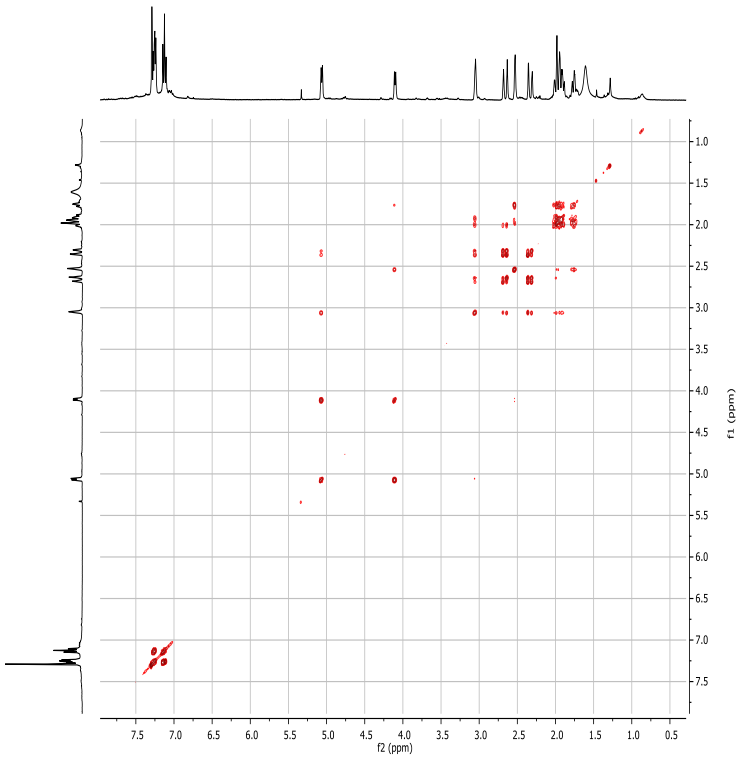


^{19}F NMR ($CDCl_3$)

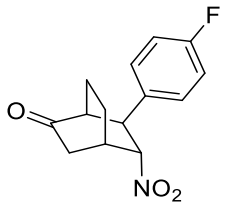


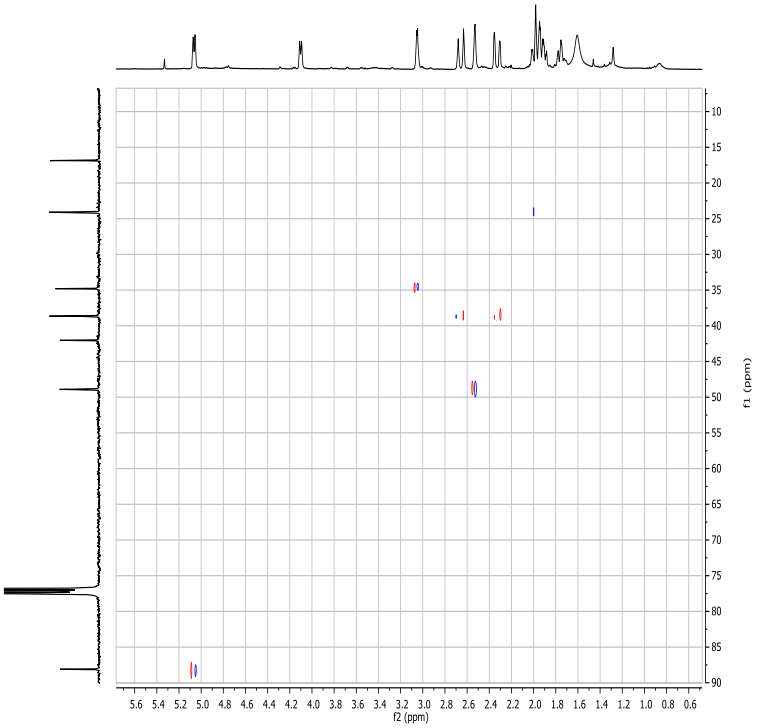
COSY ($CDCl_3$)





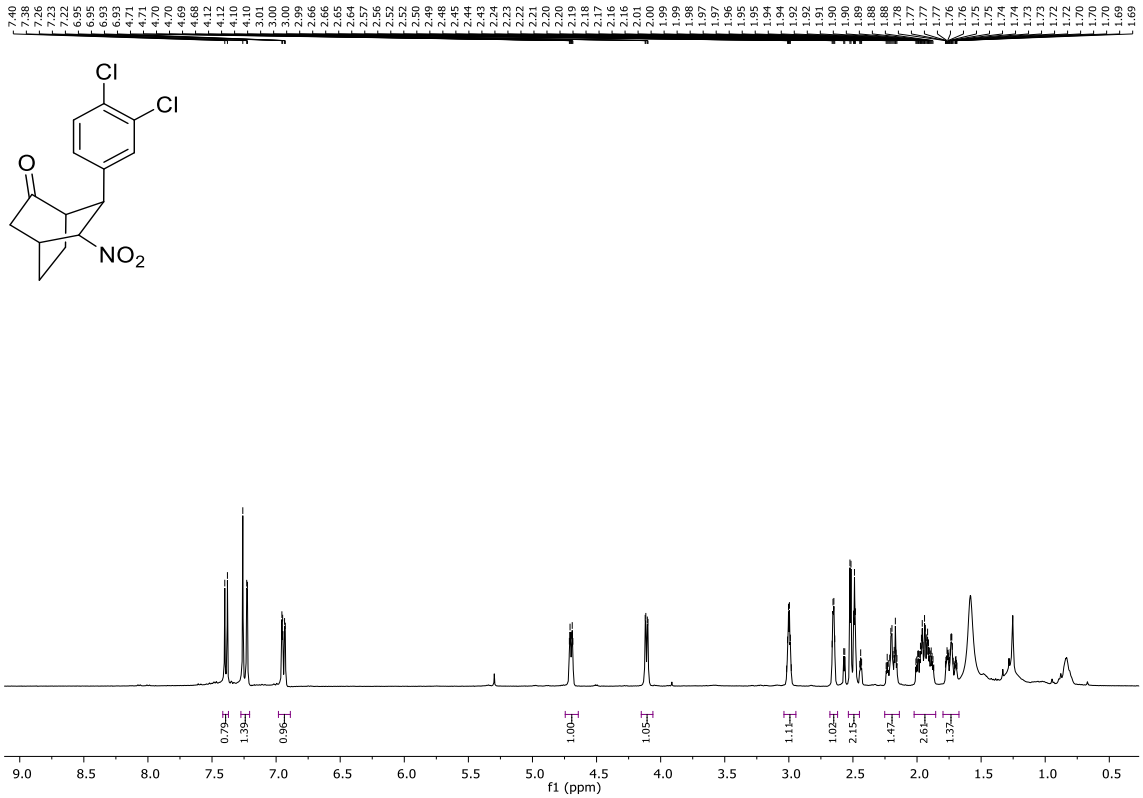
HSQC ($CDCl_3$)



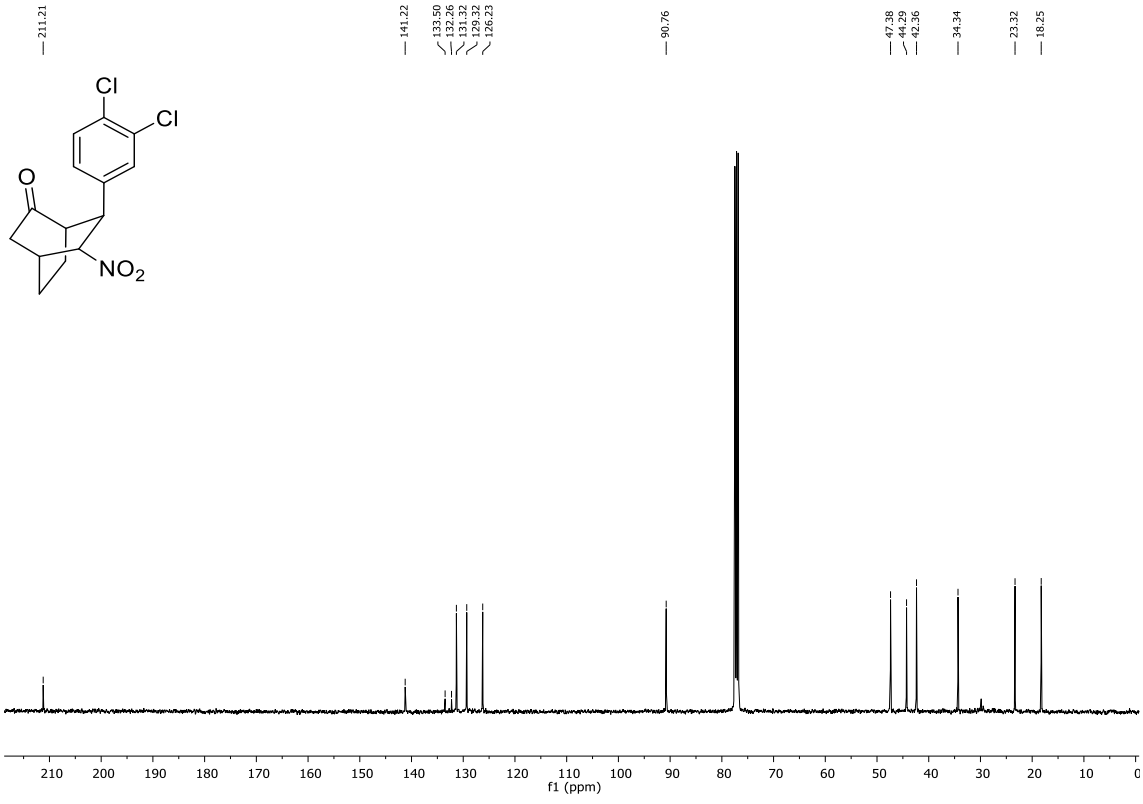


Compound *(1R,4R,5R,6S)- exo* **37c**

^{1}H NMR ($CDCl_3$)

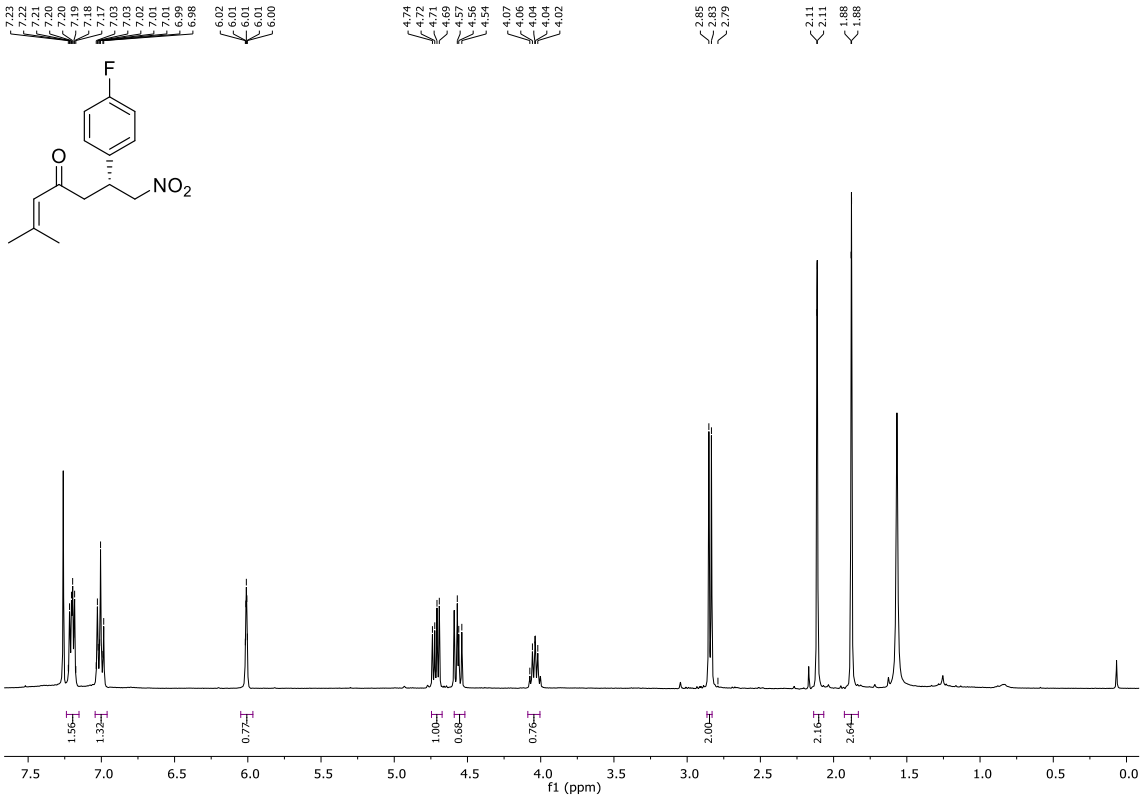


^{13}C NMR ($CDCl_3$)

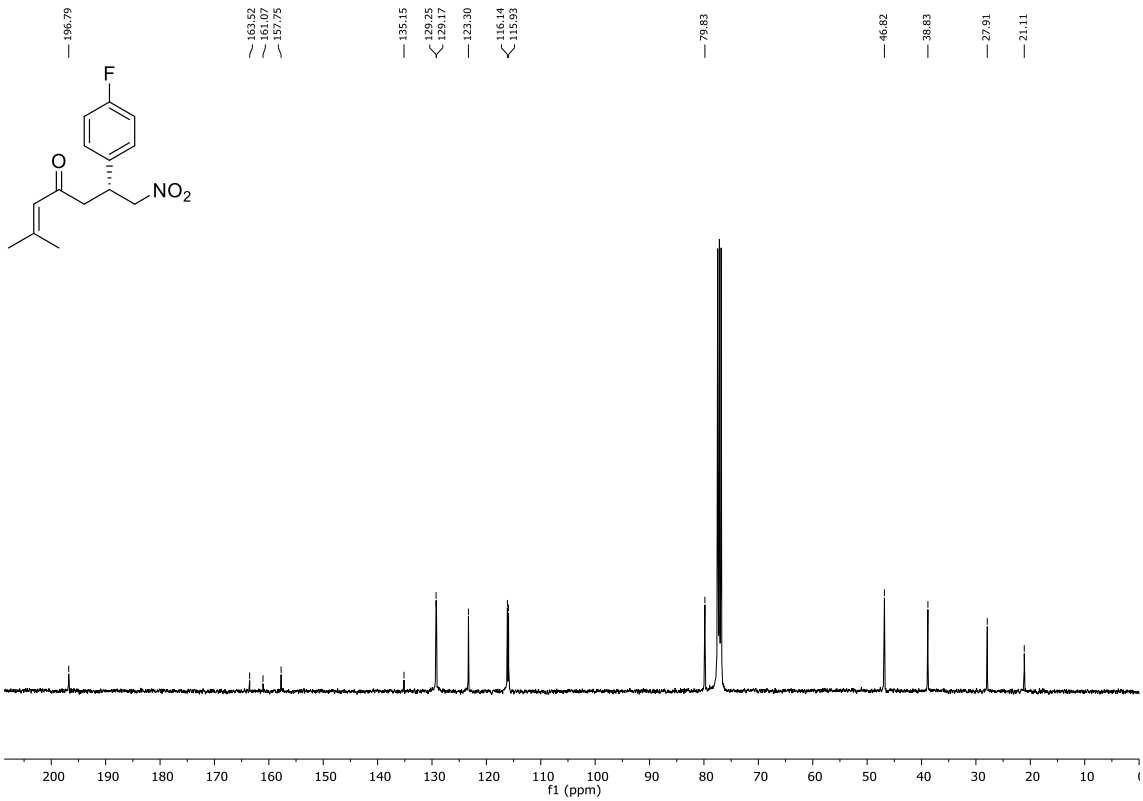


Compound (*R*)- **39a**

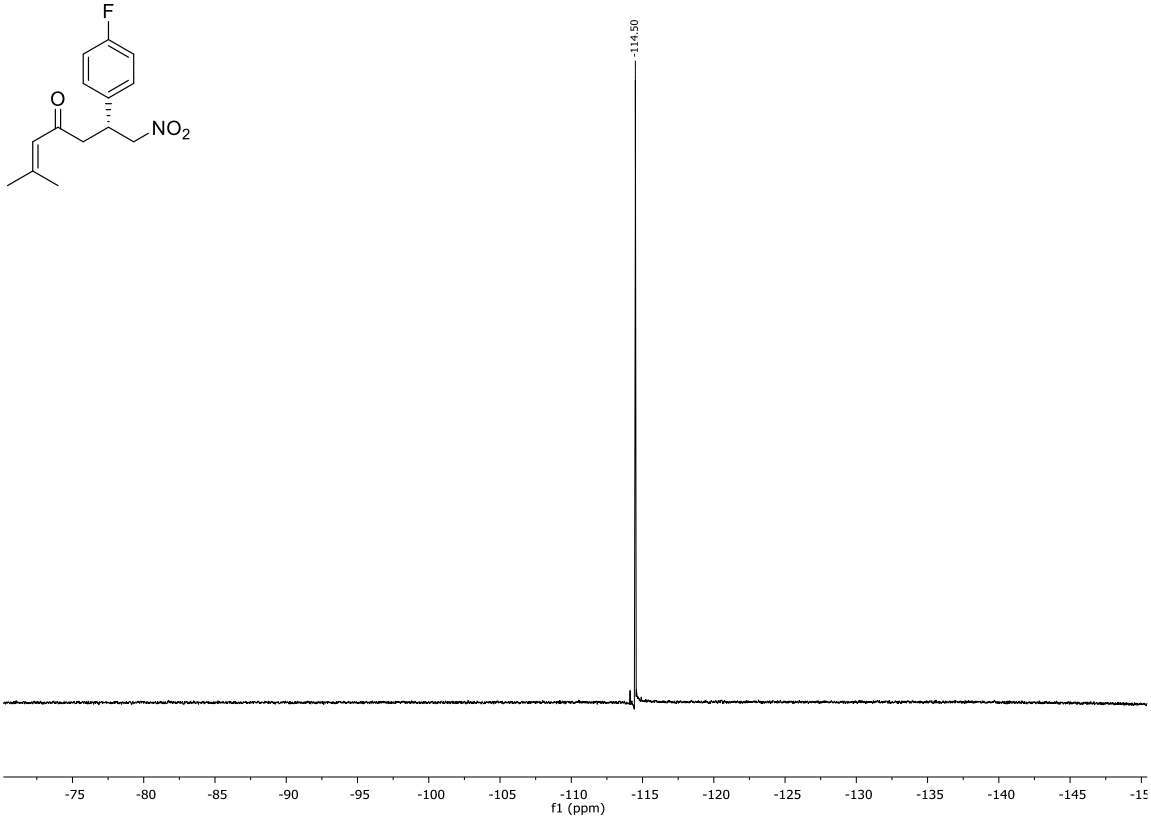
^{1}H NMR ($CDCl_3$)



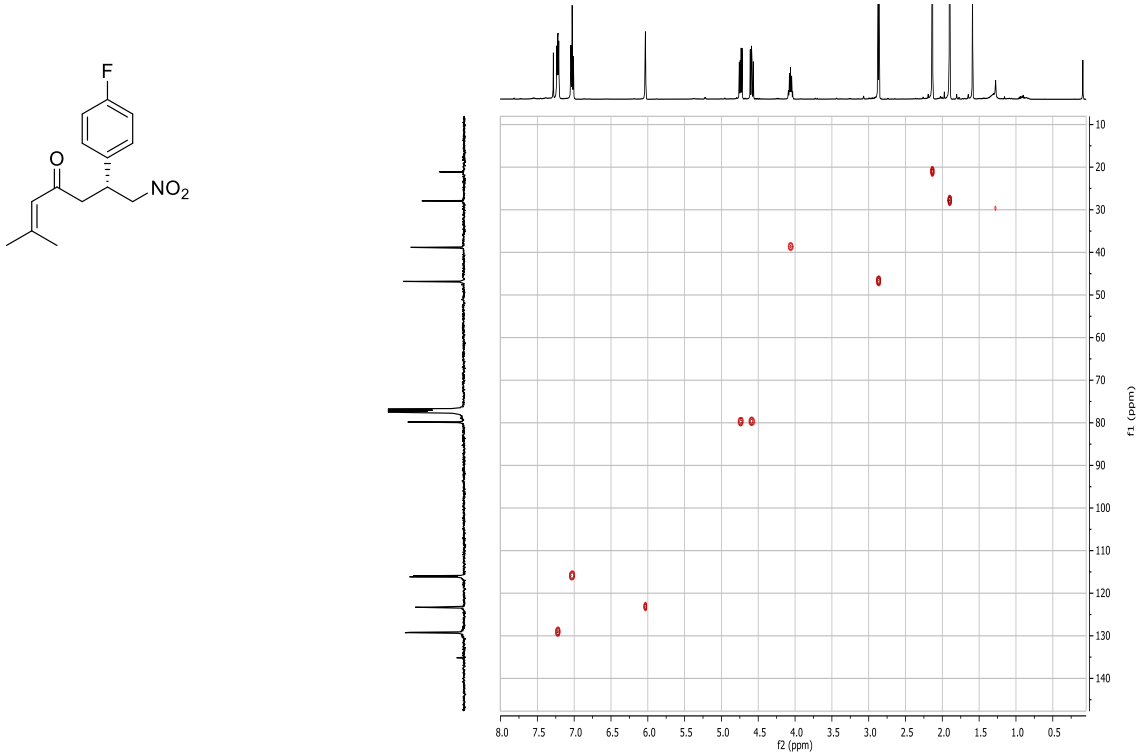
^{13}C NMR ($CDCl_3$)



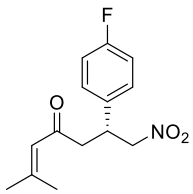
^{19}F NMR ($CDCl_3$)

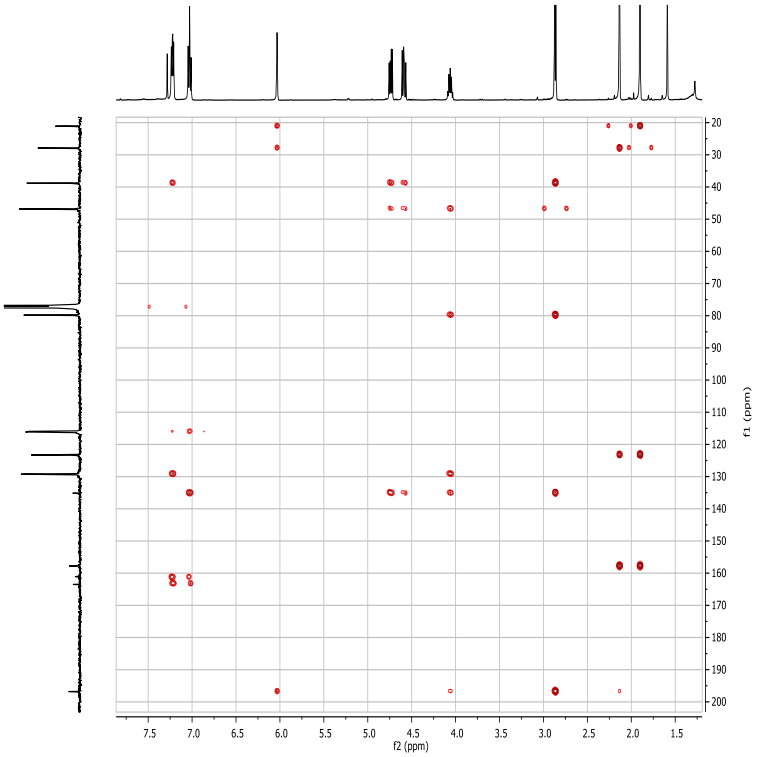


HSQC ($CDCl_3$)



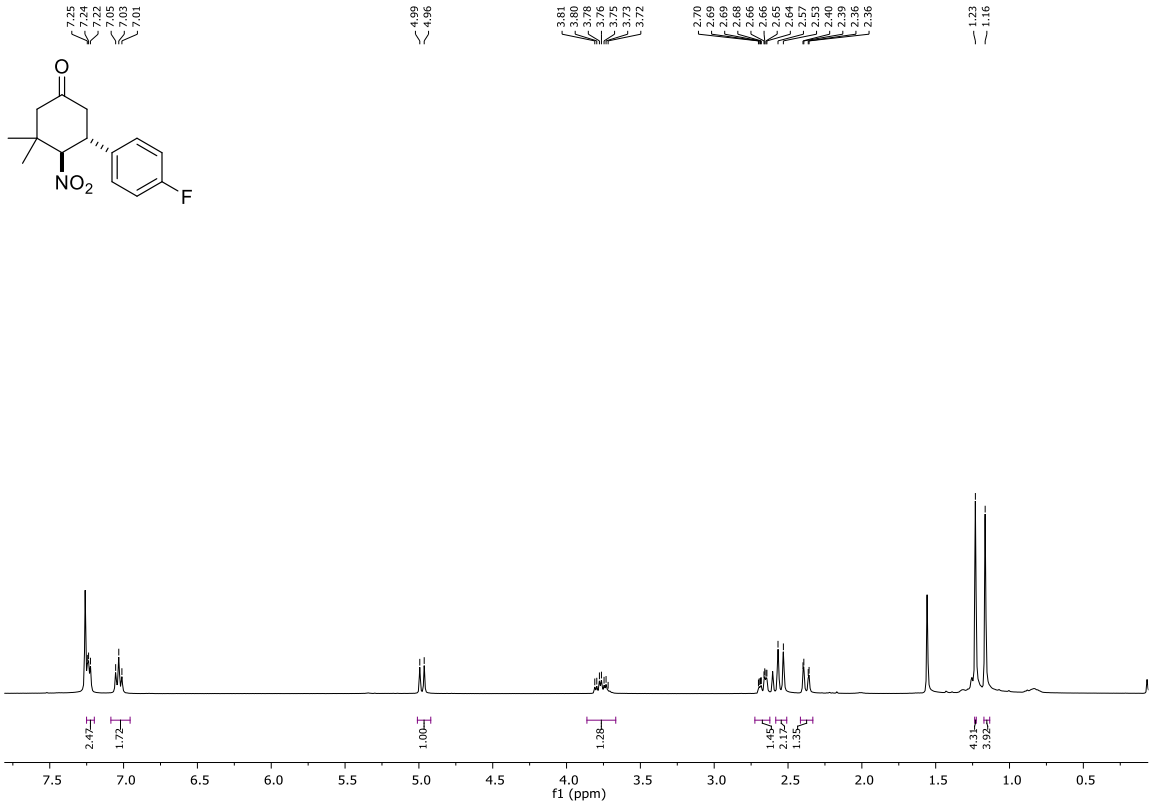
HMBC ($CDCl_3$)



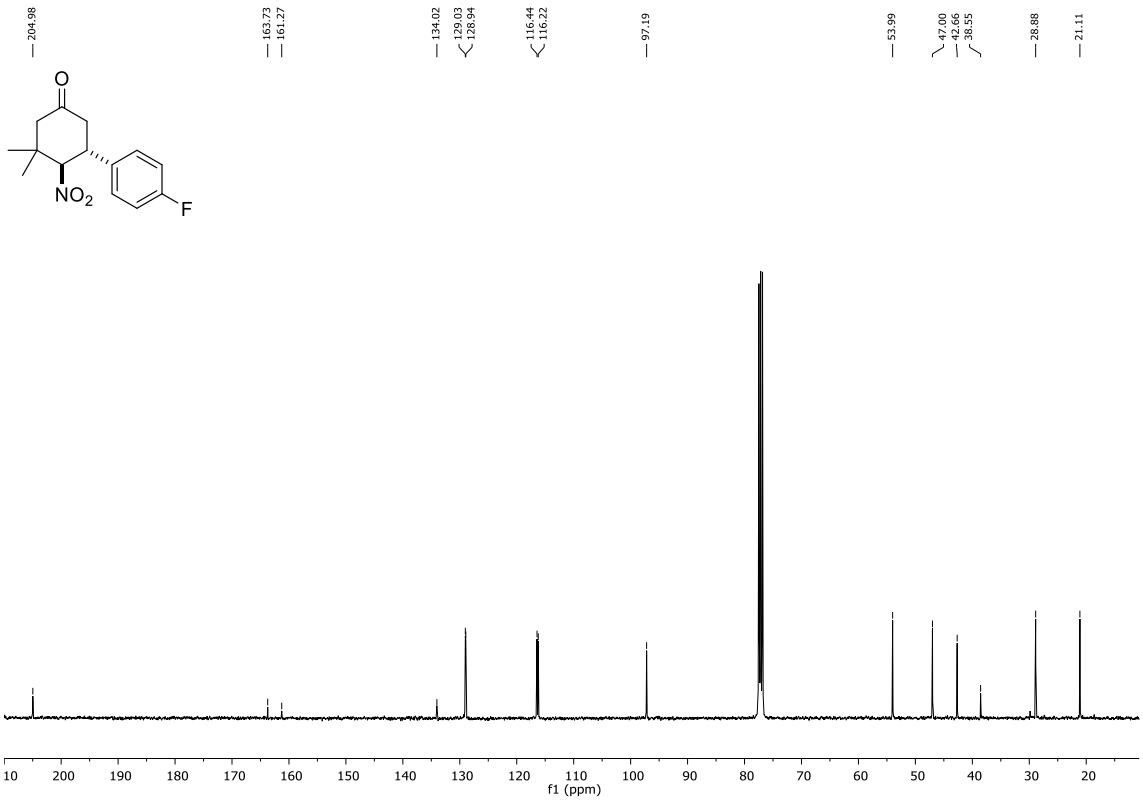


Compound (4*R*,5*R*)- **40a**

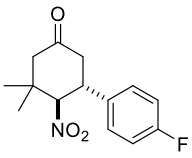
^{1}H NMR ($CDCl_3$)

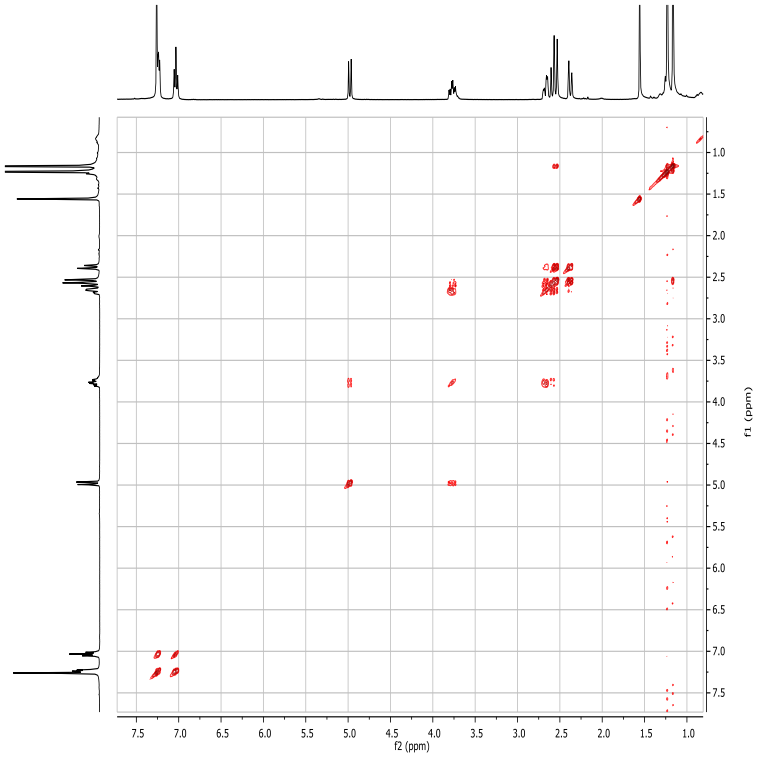


^{13}C NMR ($CDCl_3$)

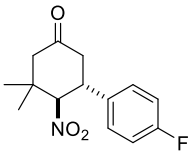


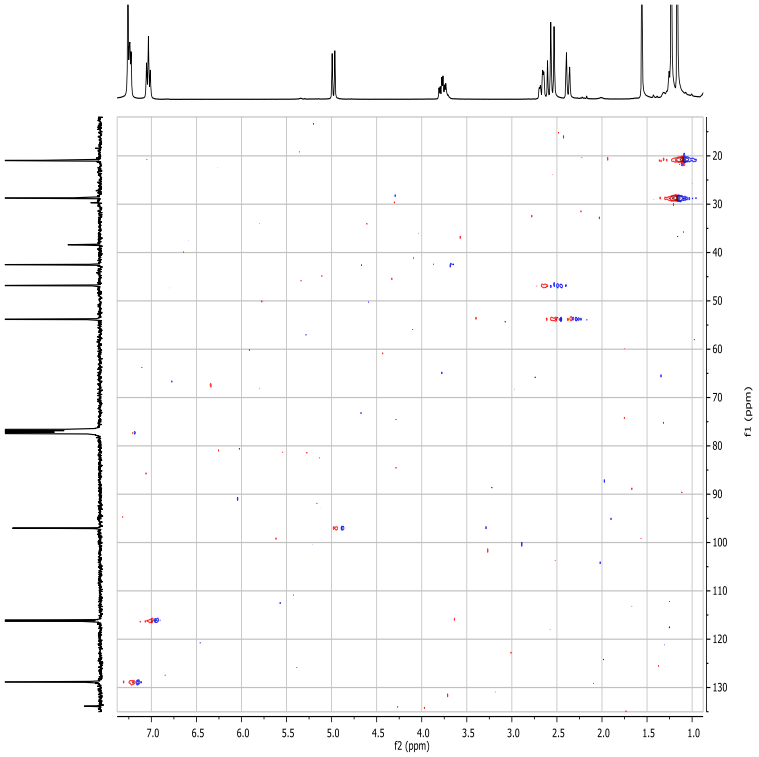
COSY ($CDCl_3$)





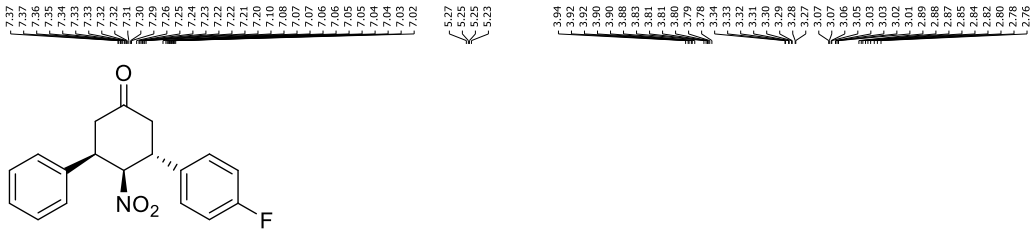
HSQC ($CDCl_3$)

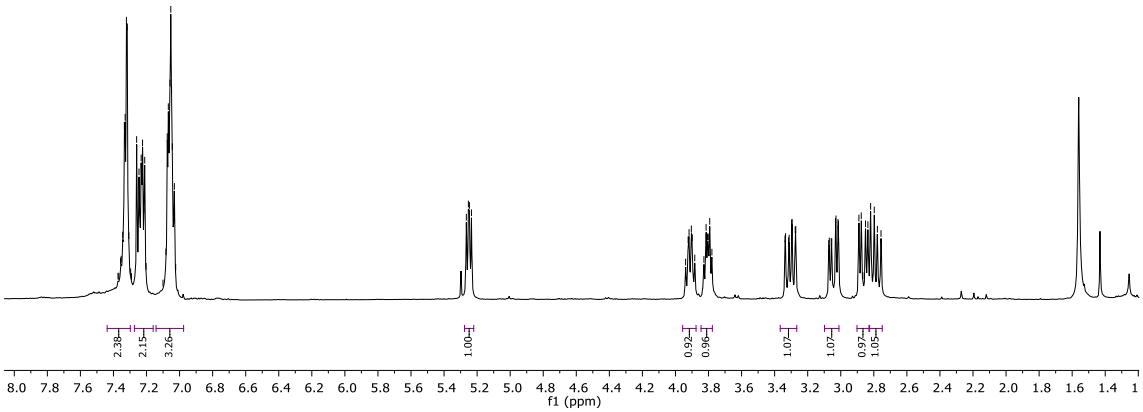




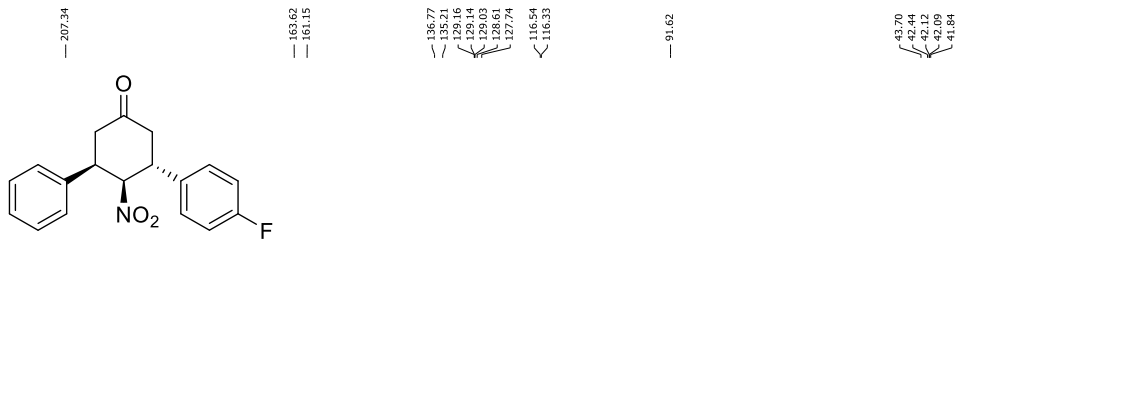
Compound *(3R,4S,5R)- endo* **17aa**

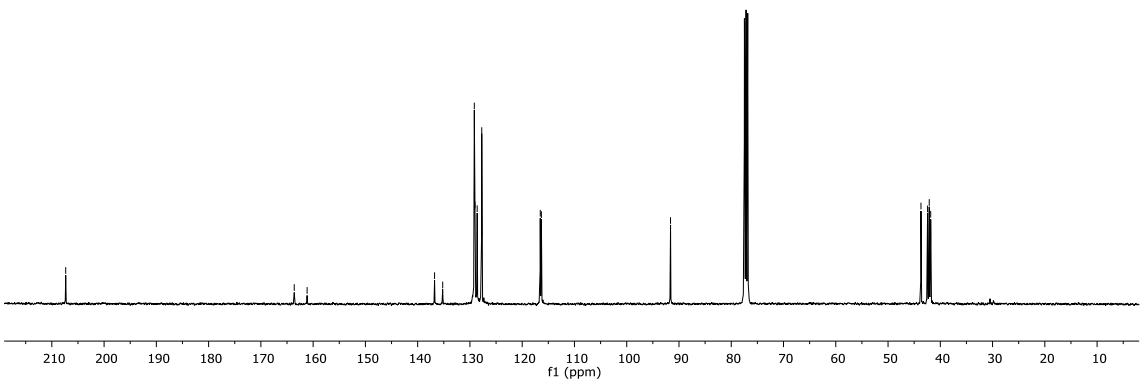
^{1}H NMR (CDCl3)



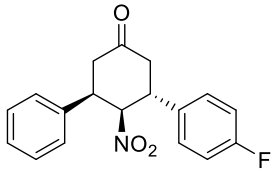


^{13}C NMR ($CDCl_3$)

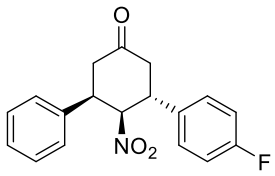


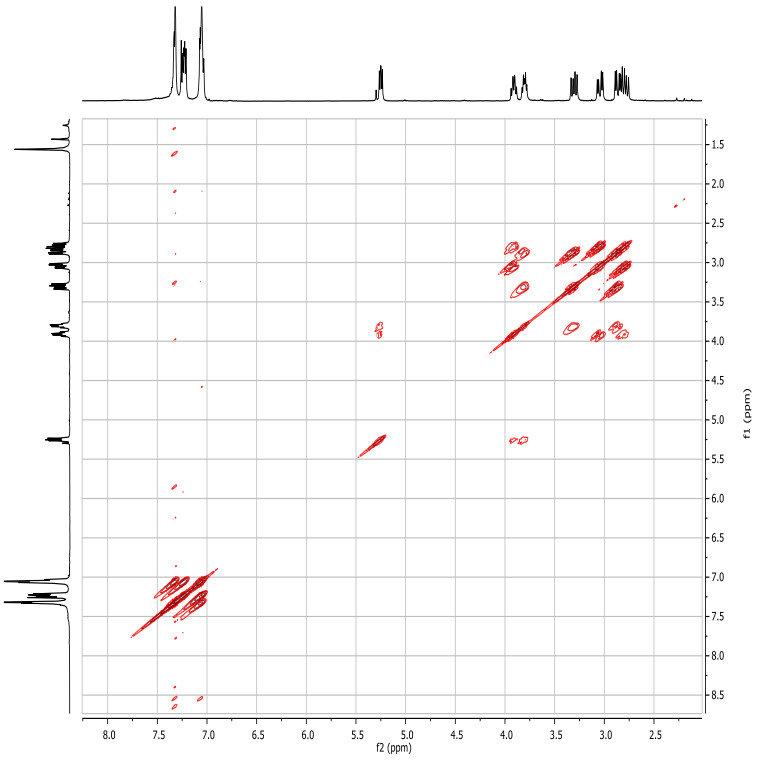


^{19}F NMR ($CDCl_3$)

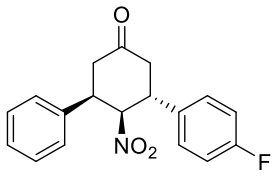


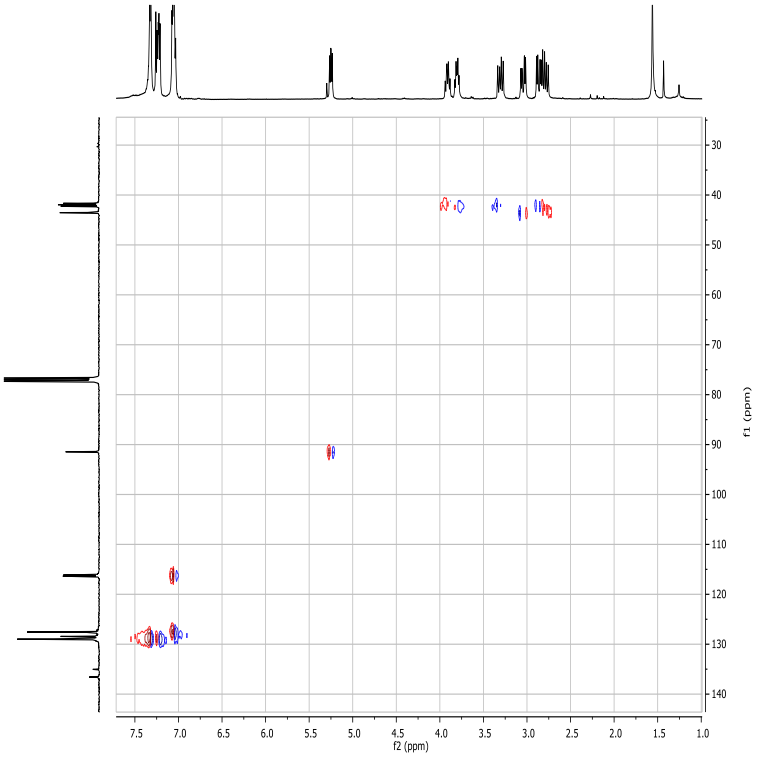
COSY ($CDCl_3$)





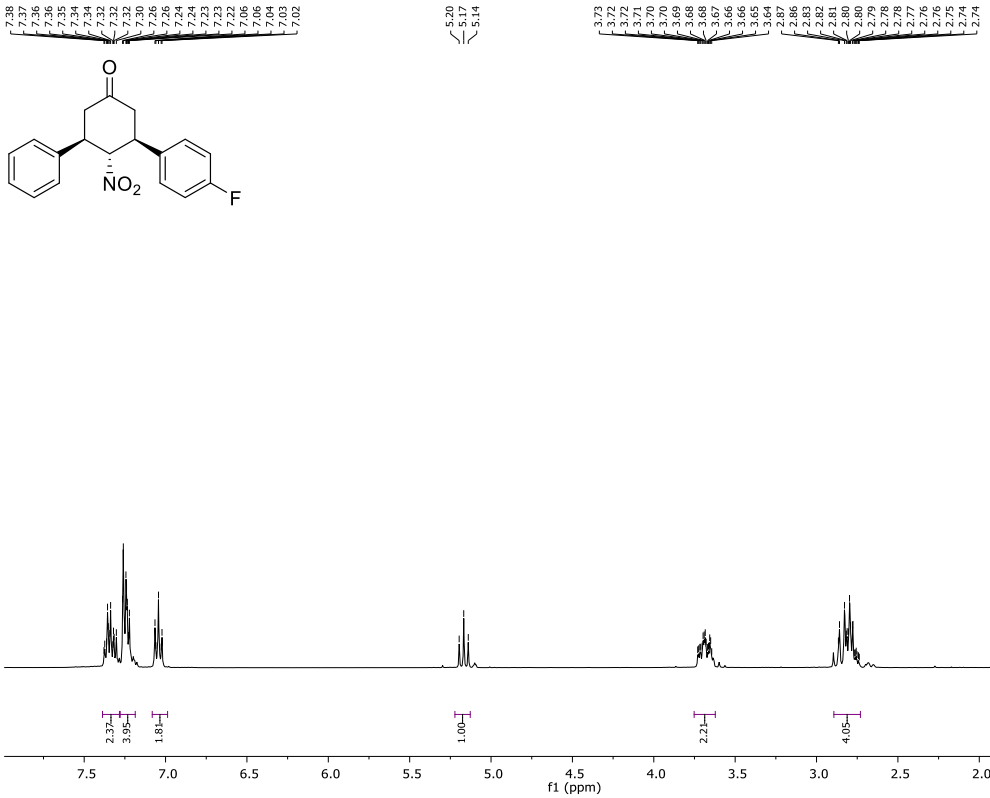
HSQC ($CDCl_3$)



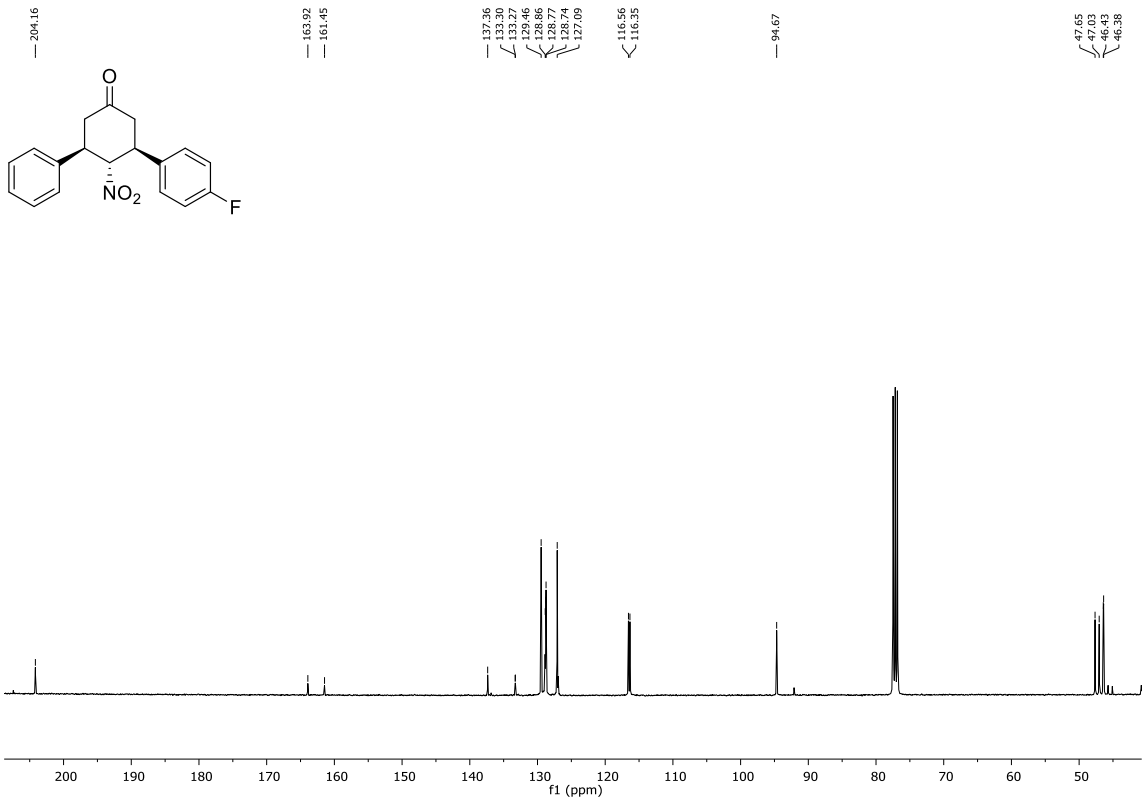


Compound *(3R,4S,5S)- exo* **17aa**

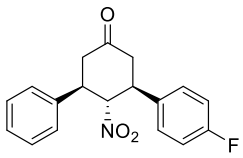
^{1}H NMR (CDCl3)



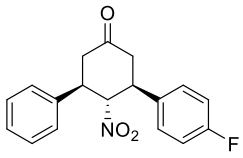
^{13}C NMR (CDCl3)

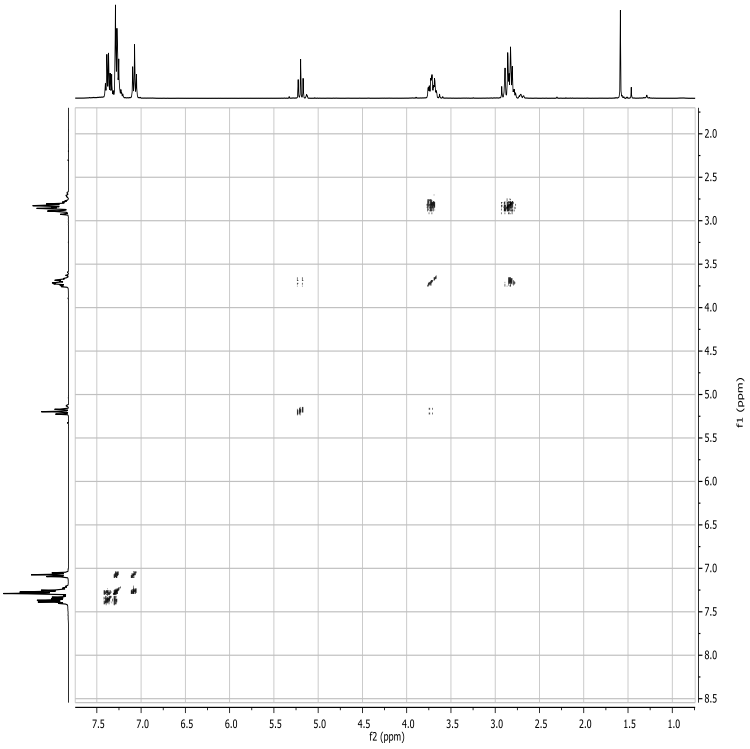


^{19}F NMR ($CDCl_3$)

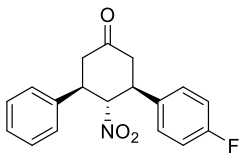


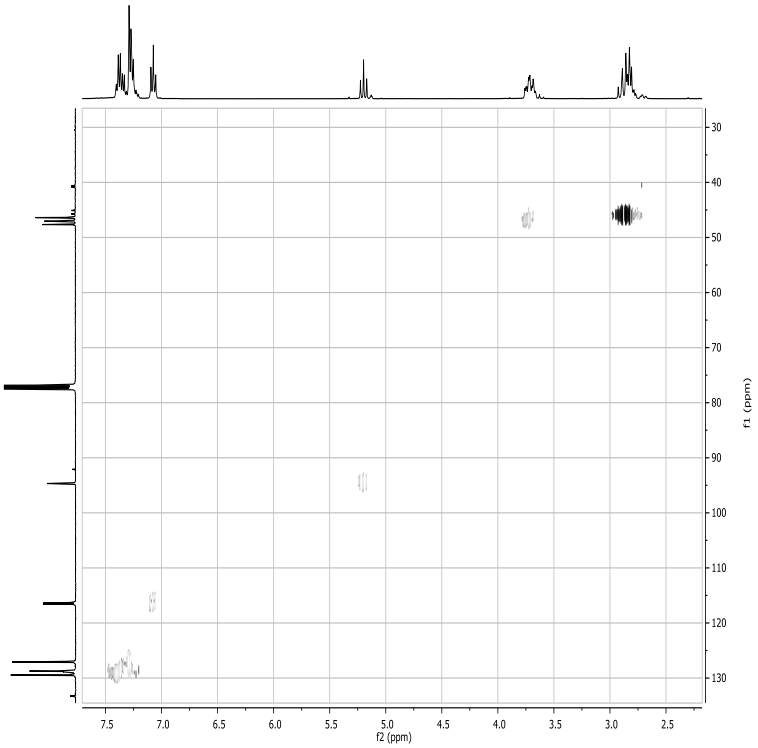
COSY ($CDCl_3$)





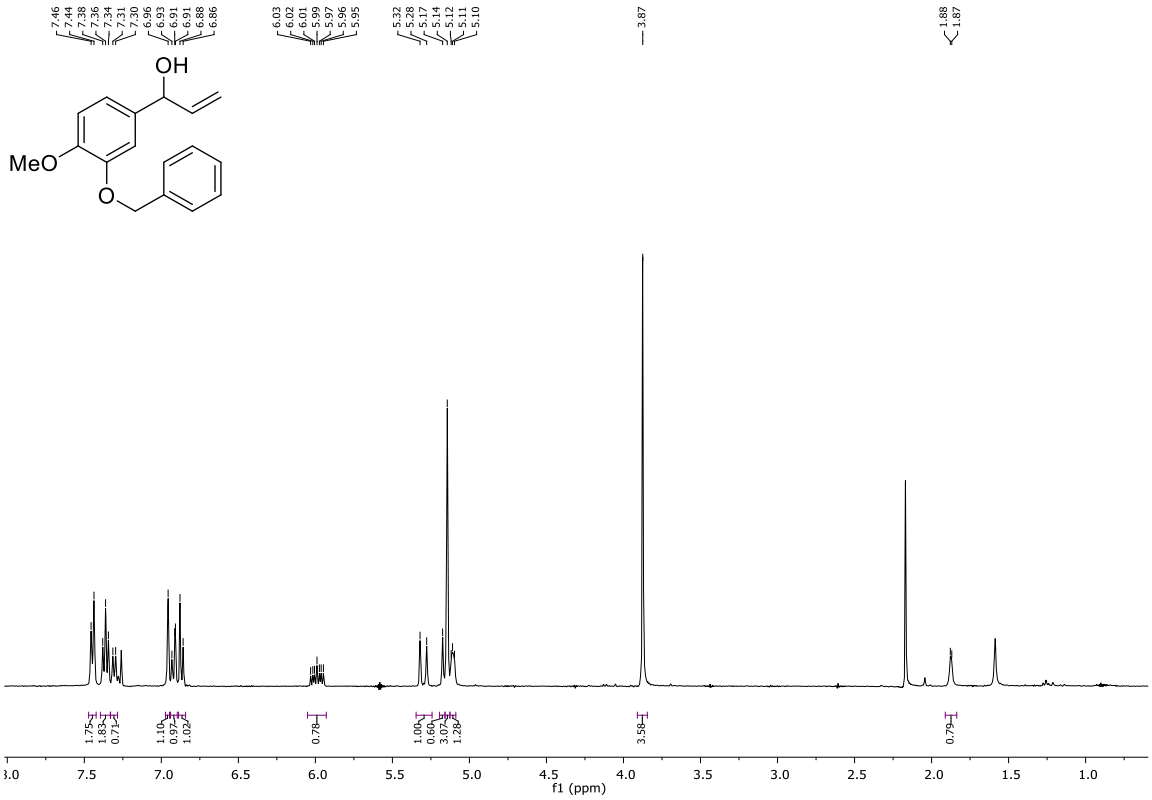
HSQC ($CDCl_3$)



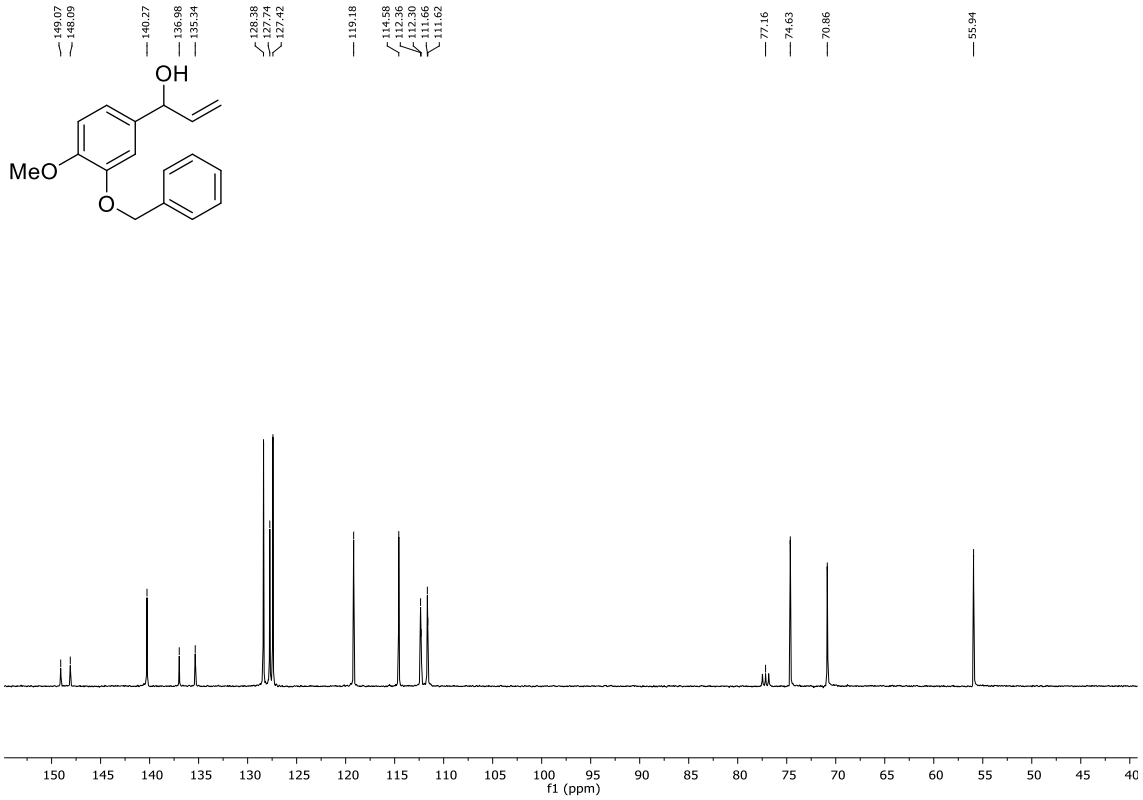


Annex III. NMR spectra selection for Chapter 4

Compound **34j**. **^{1}H NMR ($CDCl_3$)**

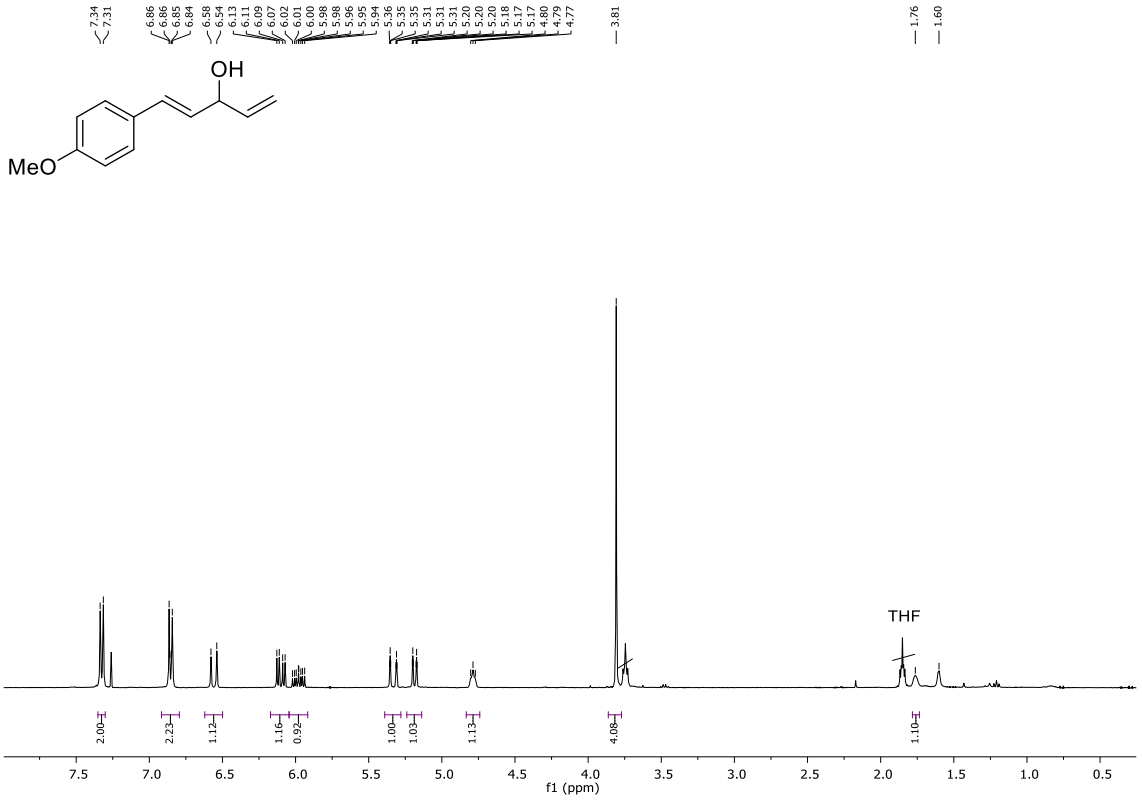


^{13}C NMR ($CDCl_3$)

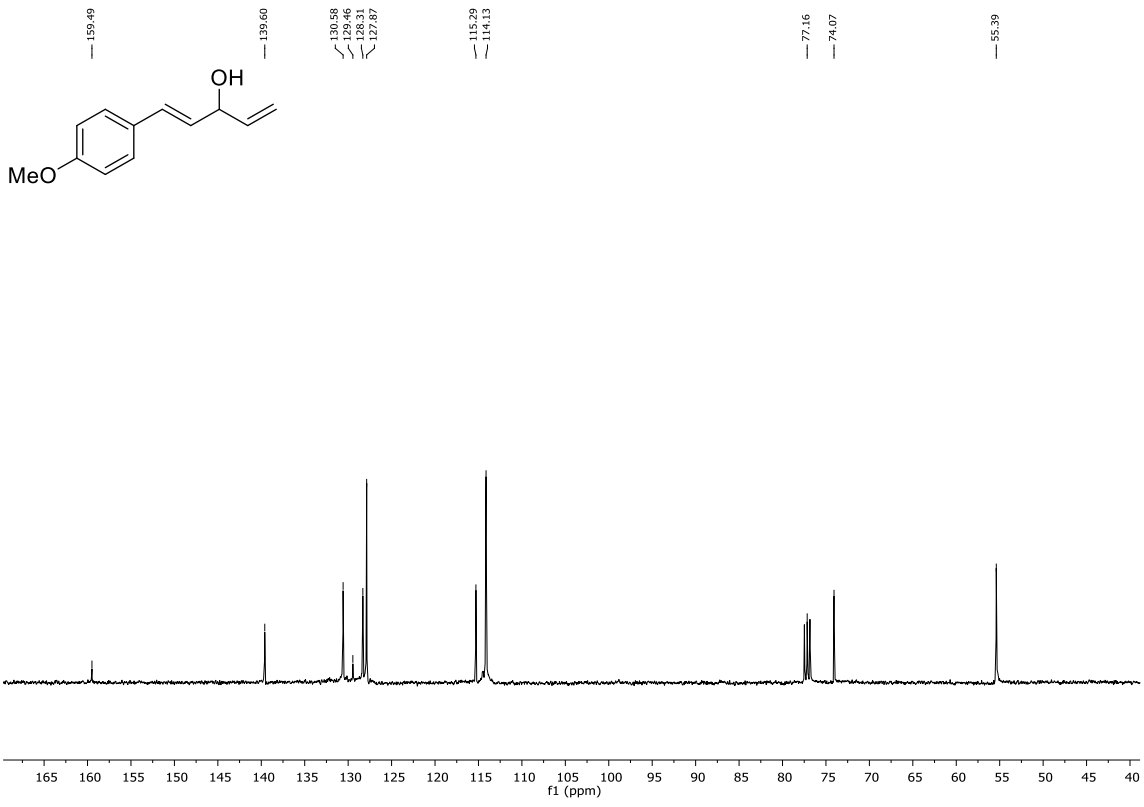


Compound **43a**

^{1}H NMR ($CDCl_3$)

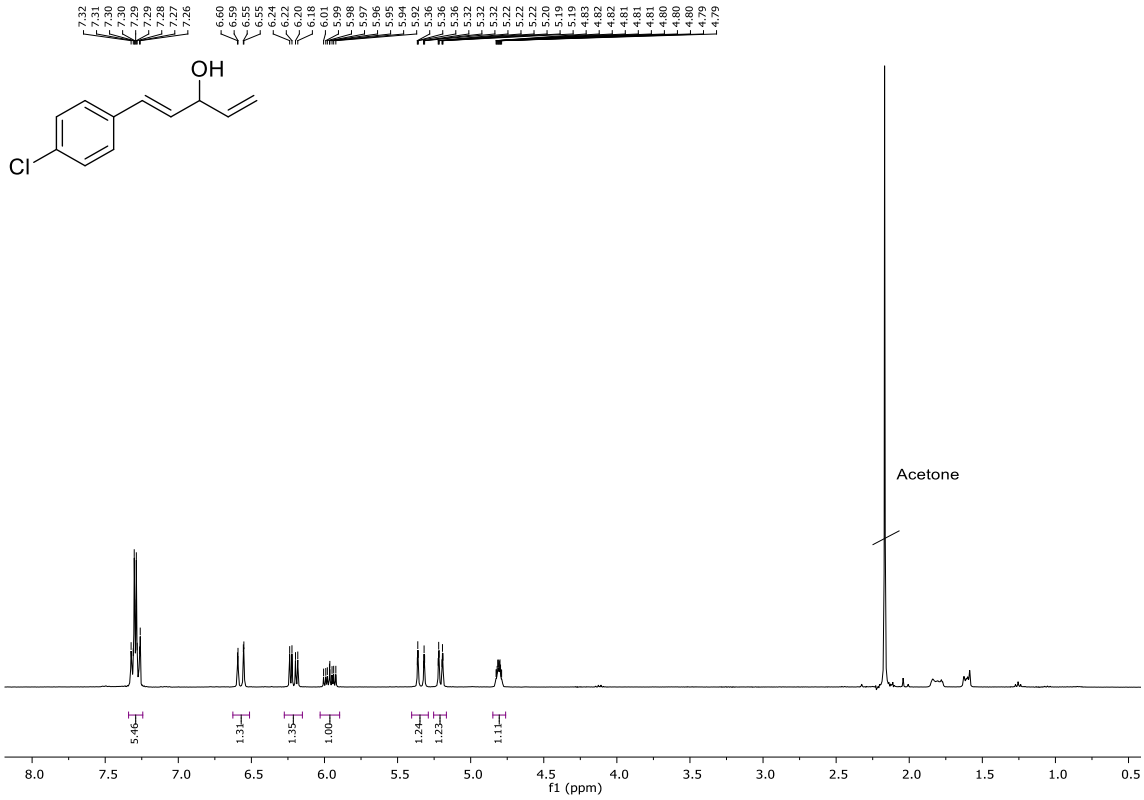


^{13}C NMR ($CDCl_3$)

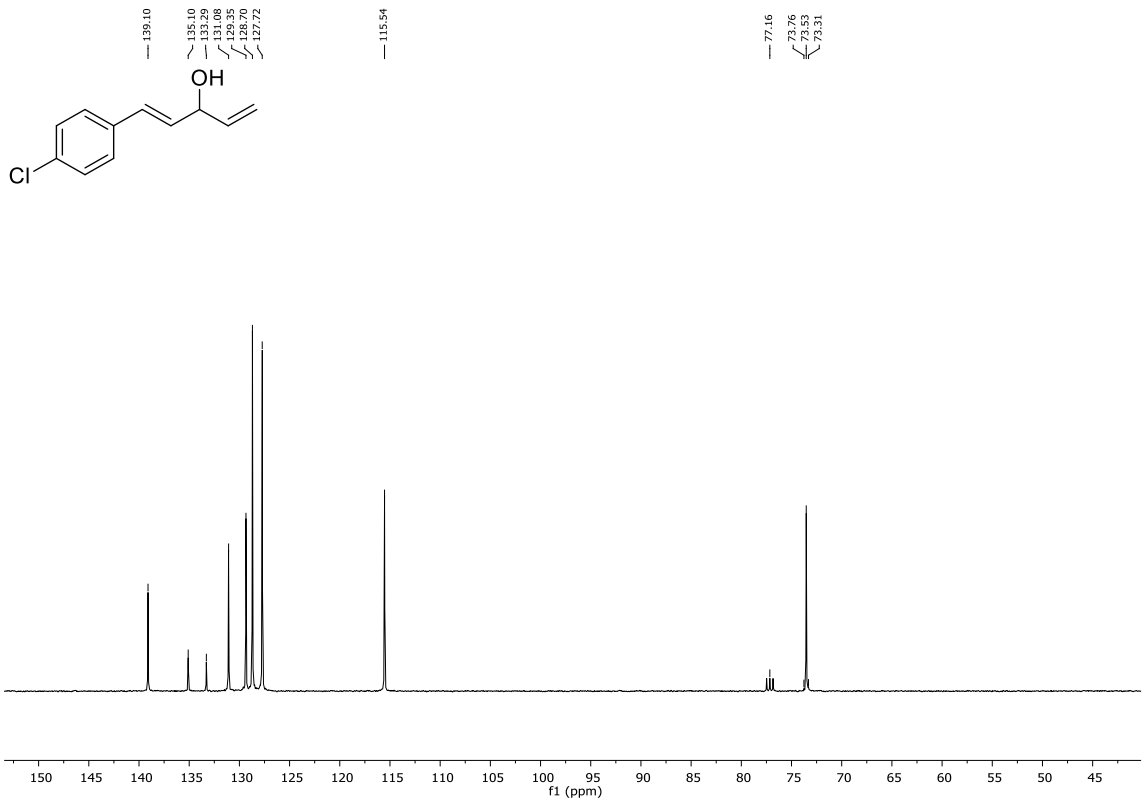


Compound **43c**

^{1}H NMR ($CDCl_3$)

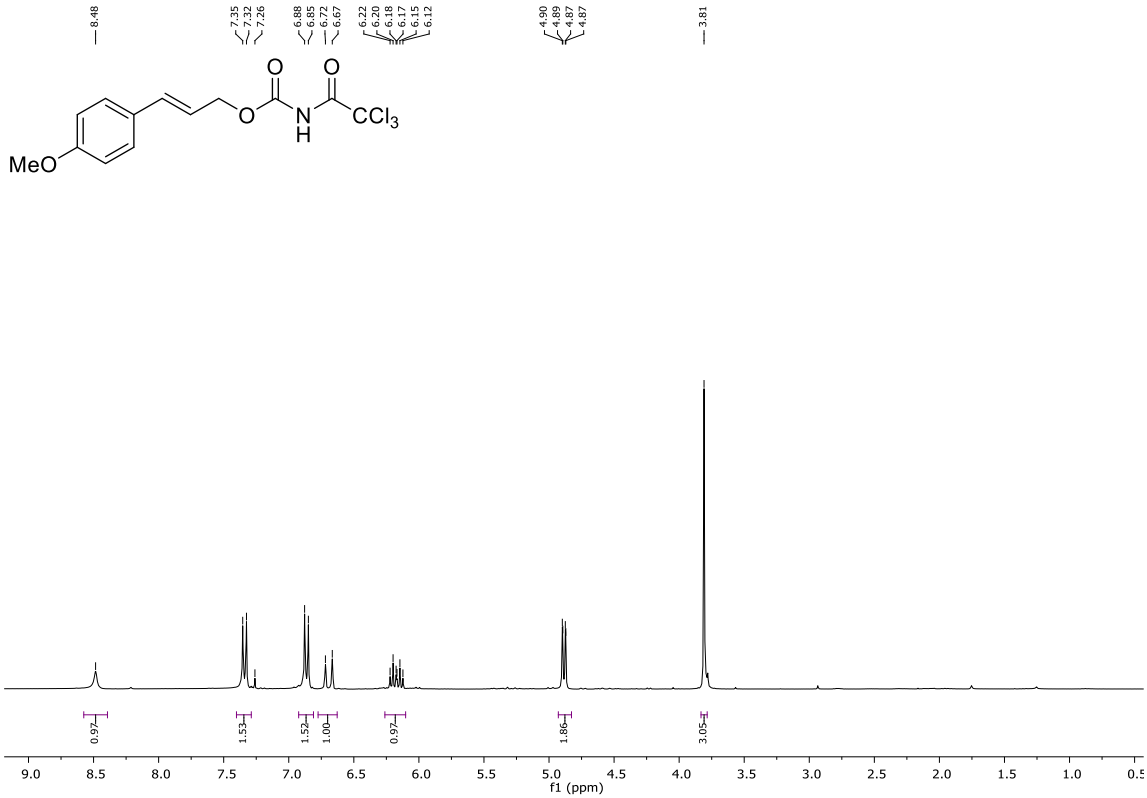


^{13}C NMR ($CDCl_3$)

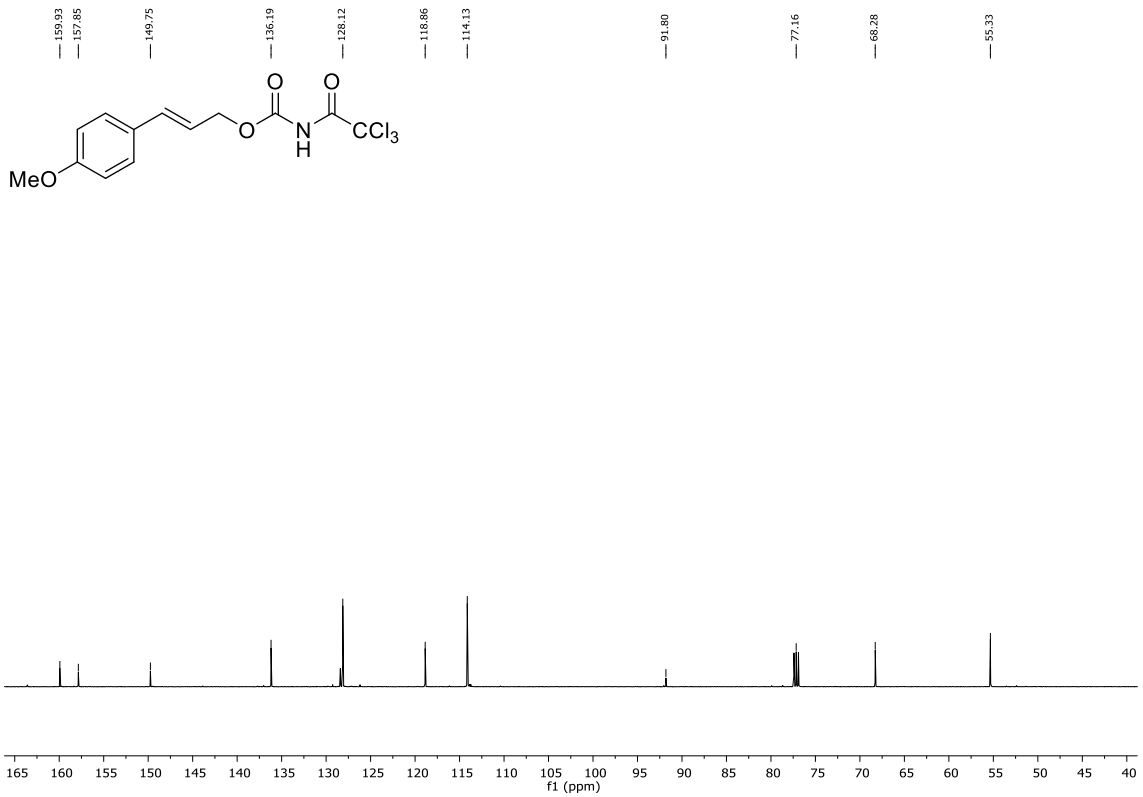


Compound **40a**

^{1}H NMR ($CDCl_3$)

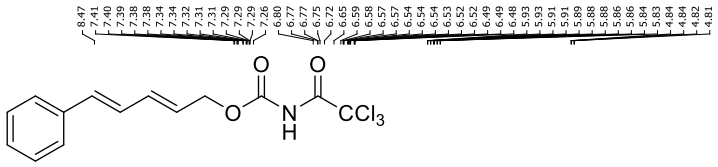


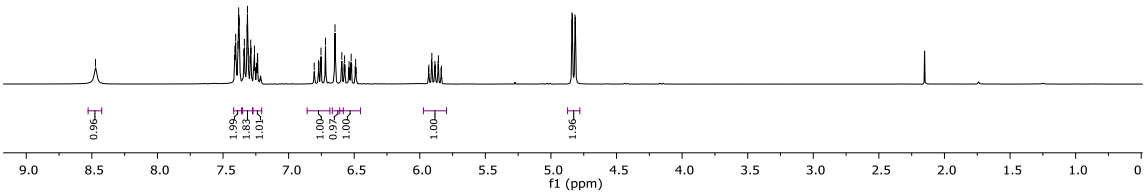
^{13}C NMR ($CDCl_3$)



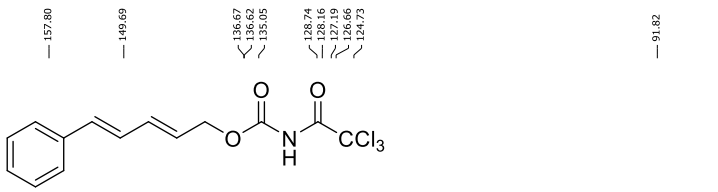
Compound **45b**

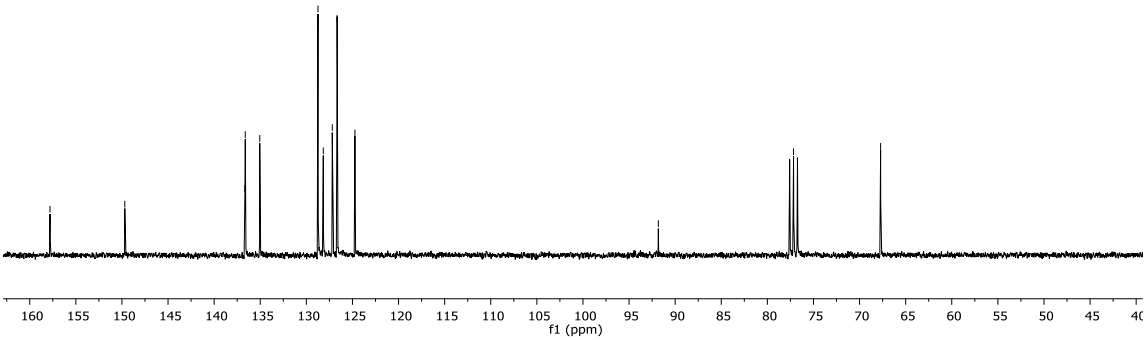
^{1}H NMR ($CDCl_3$)





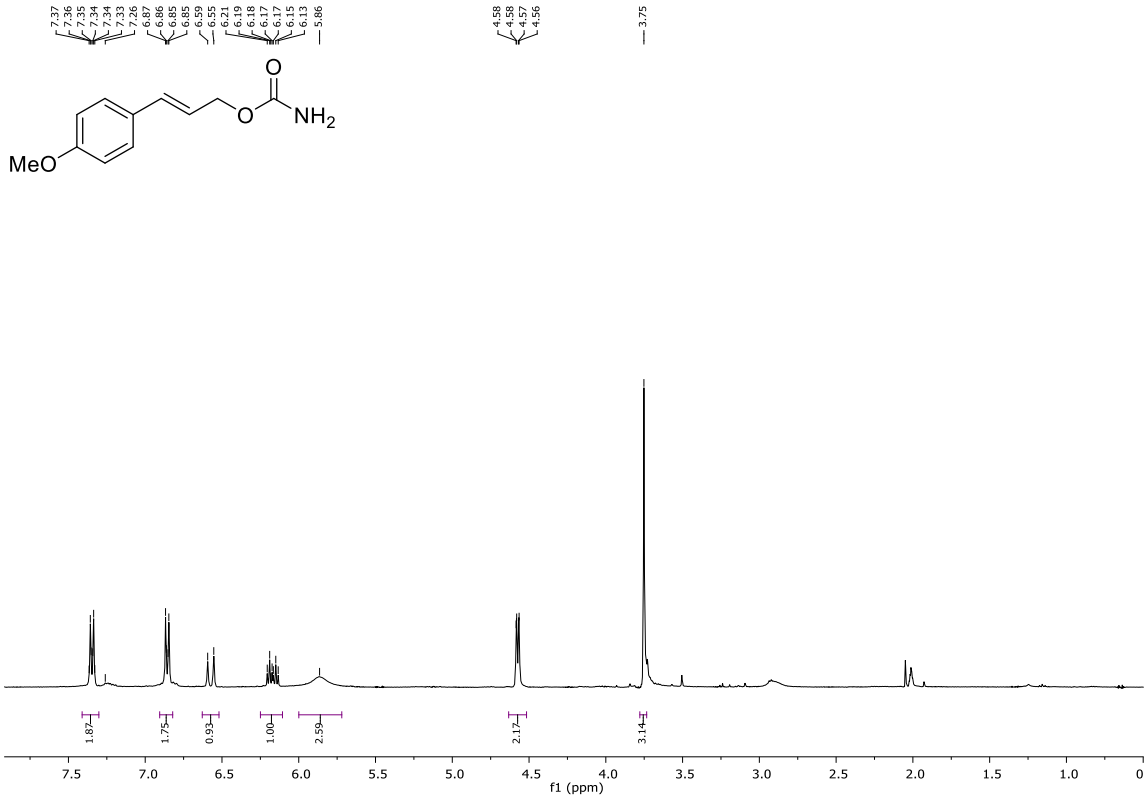
^{13}C NMR ($CDCl_3$)



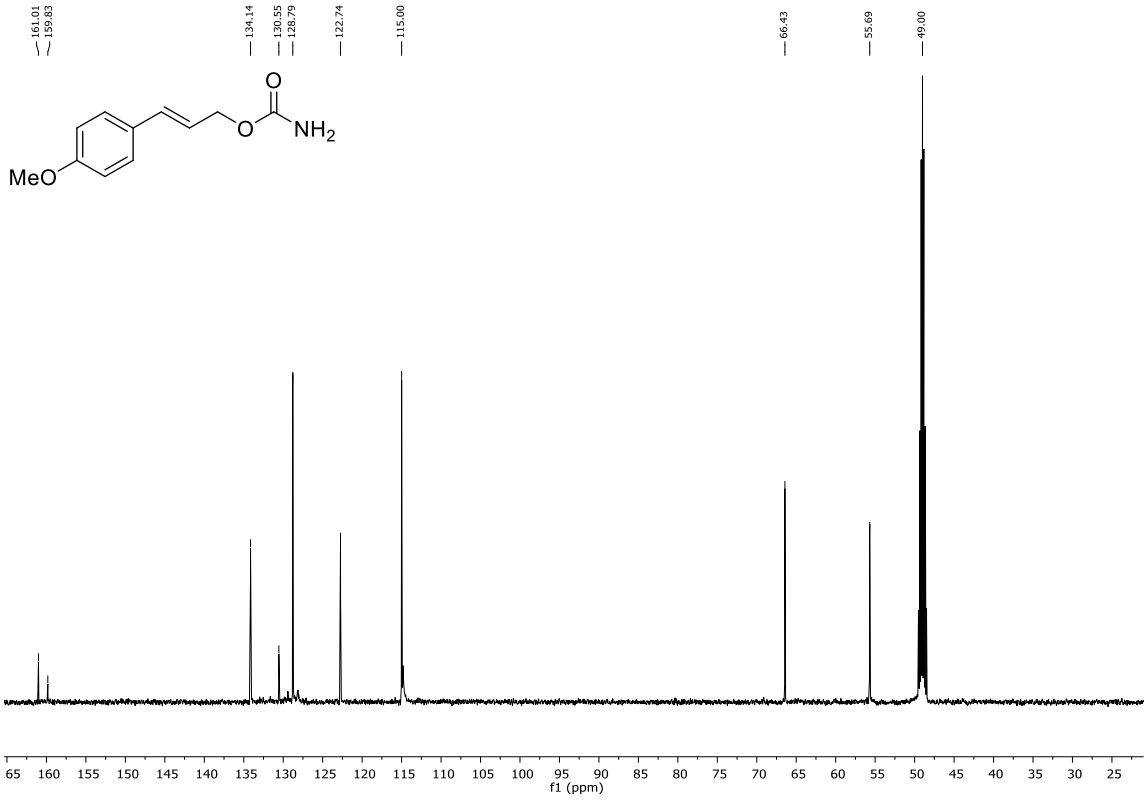


Compound **37a**

^{1}H NMR (Acetone-*d*6)

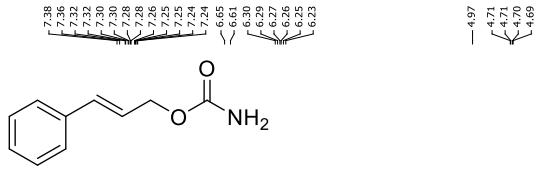


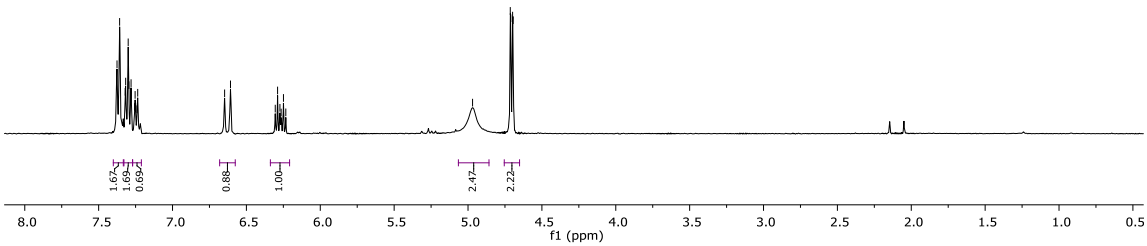
^{13}C NMR (Methanol-*d*4)



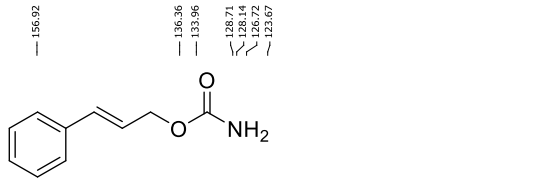
Compound **37b**

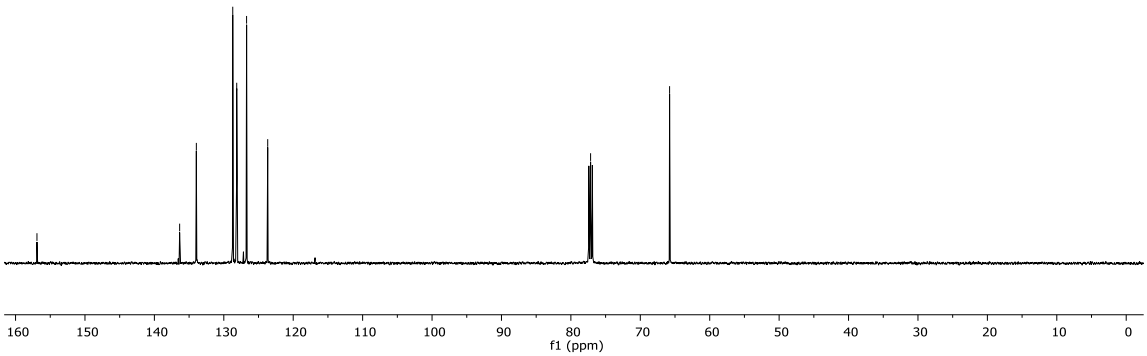
^{1}H NMR ($CDCl_3$)





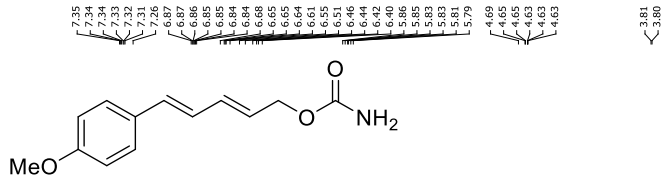
^{13}C NMR (CDCl3)

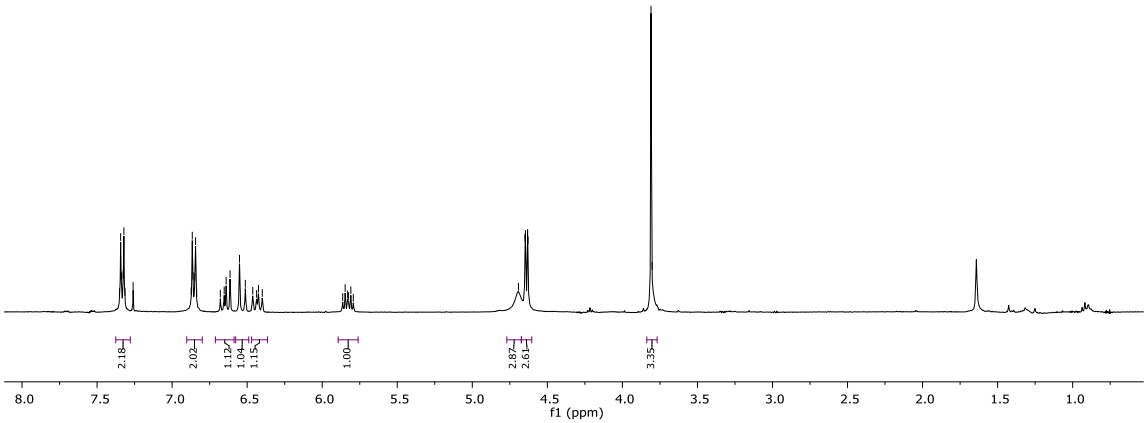




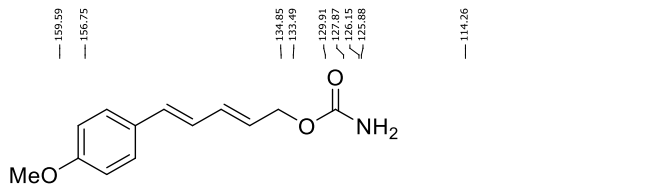
Compound **46a**

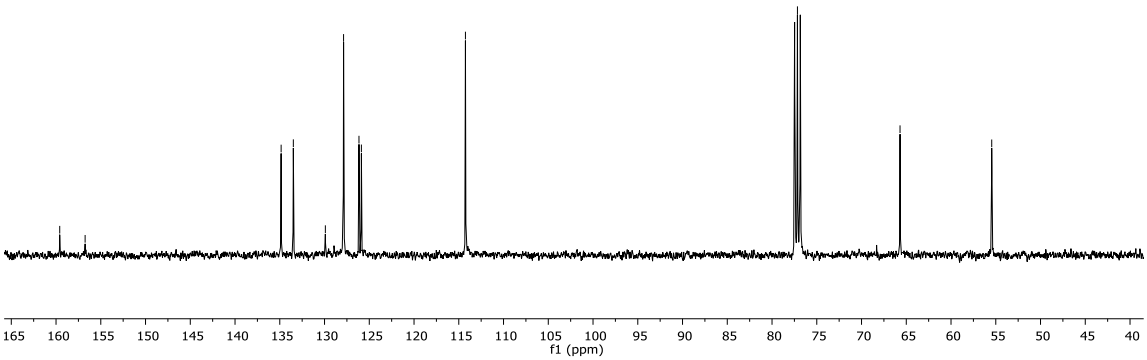
^{1}H NMR ($CDCl_3$)





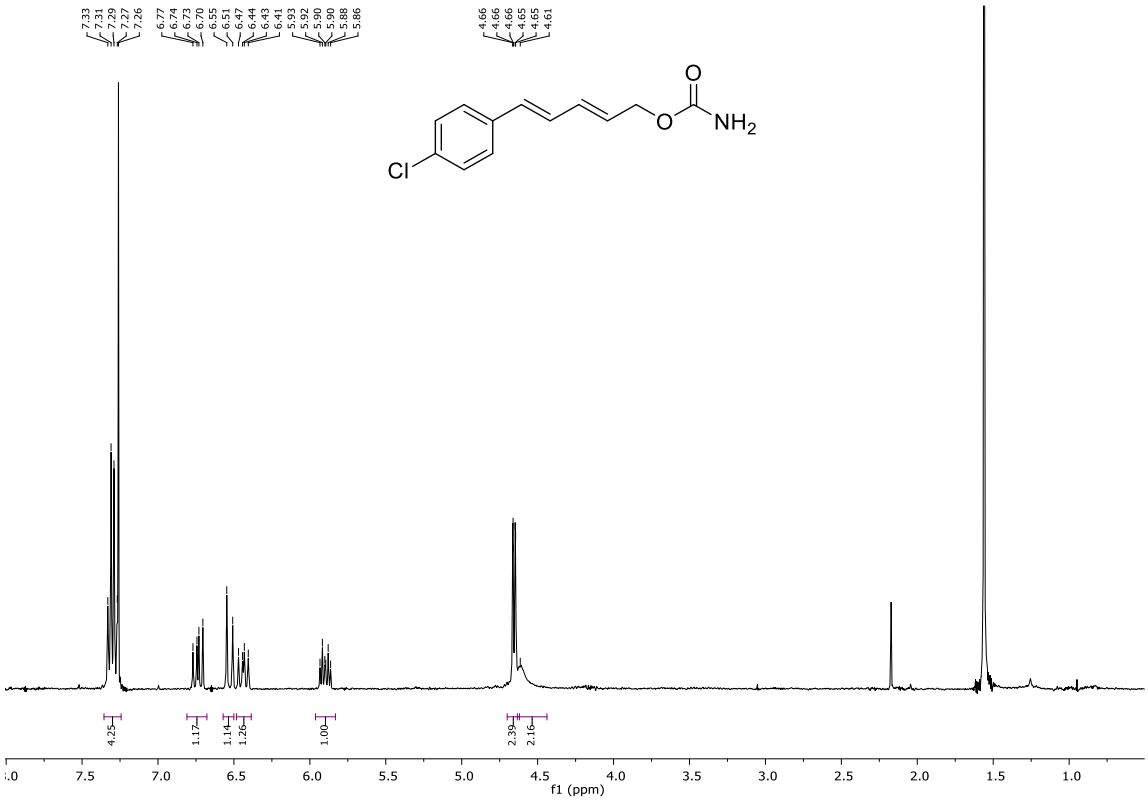
^{13}C NMR ($CDCl_3$)



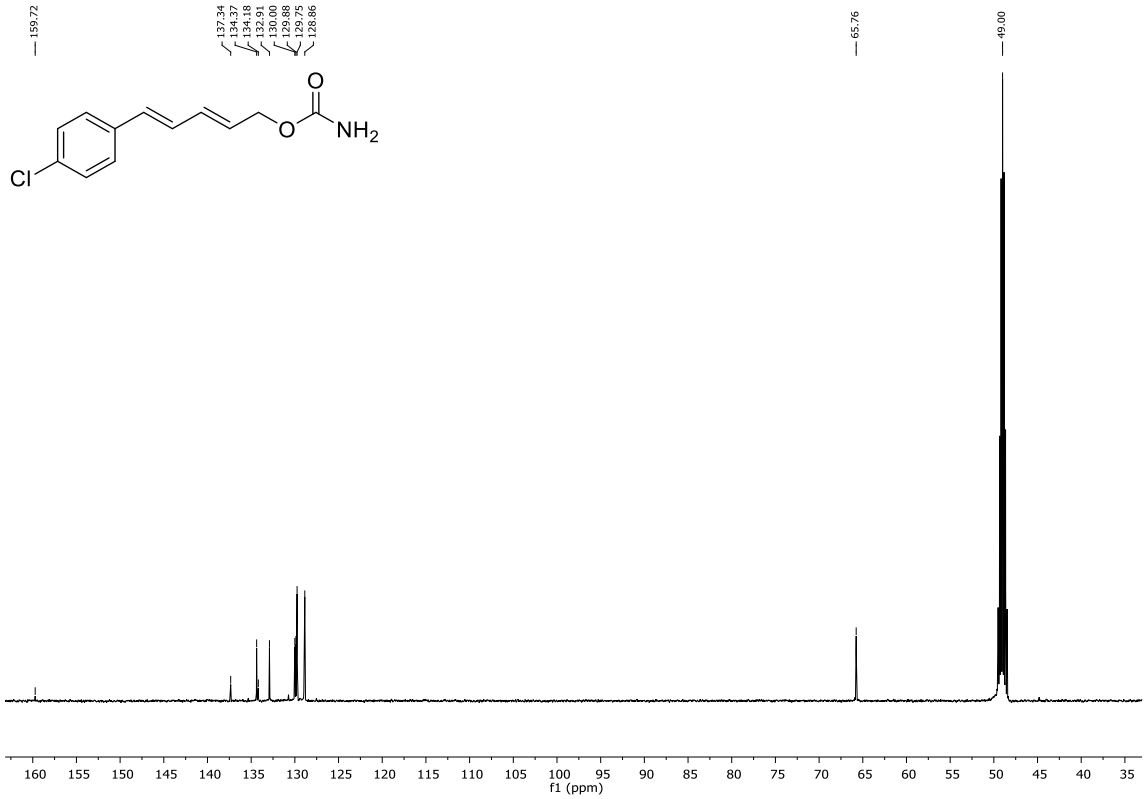


Compound **46c**

^{1}H NMR ($CDCl_3$)

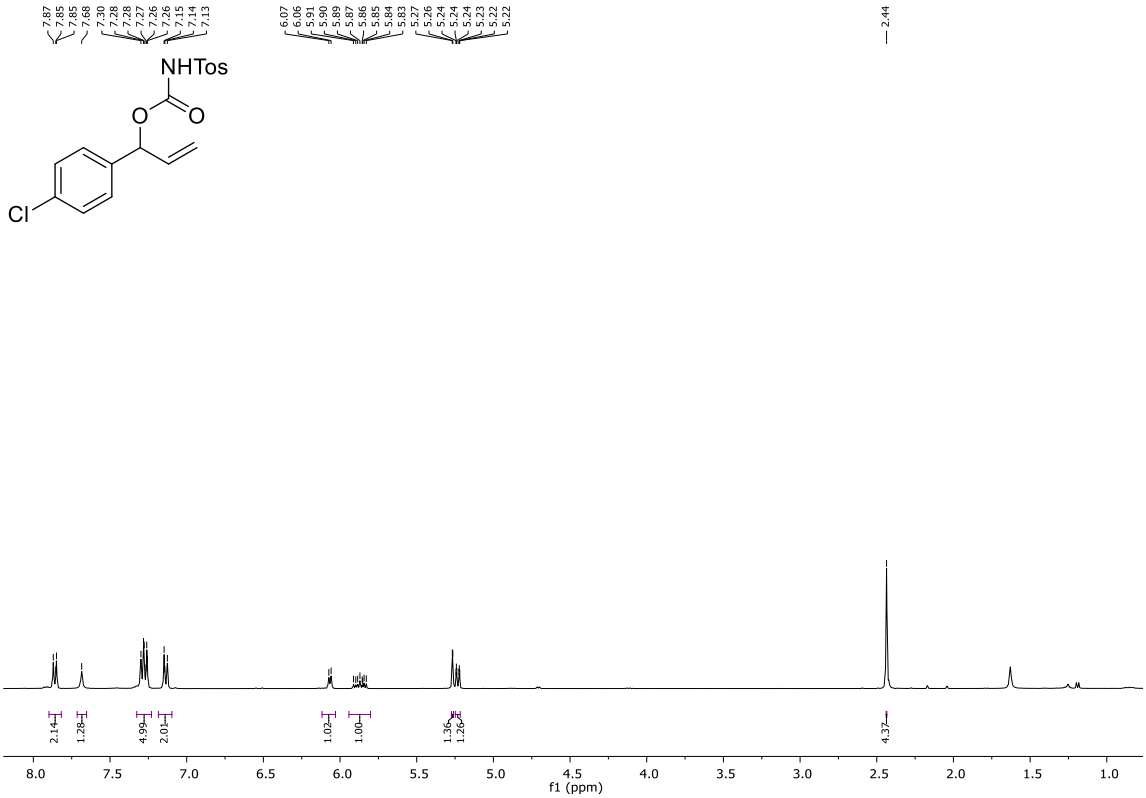


^{13}C NMR (Methanol-*d*4)

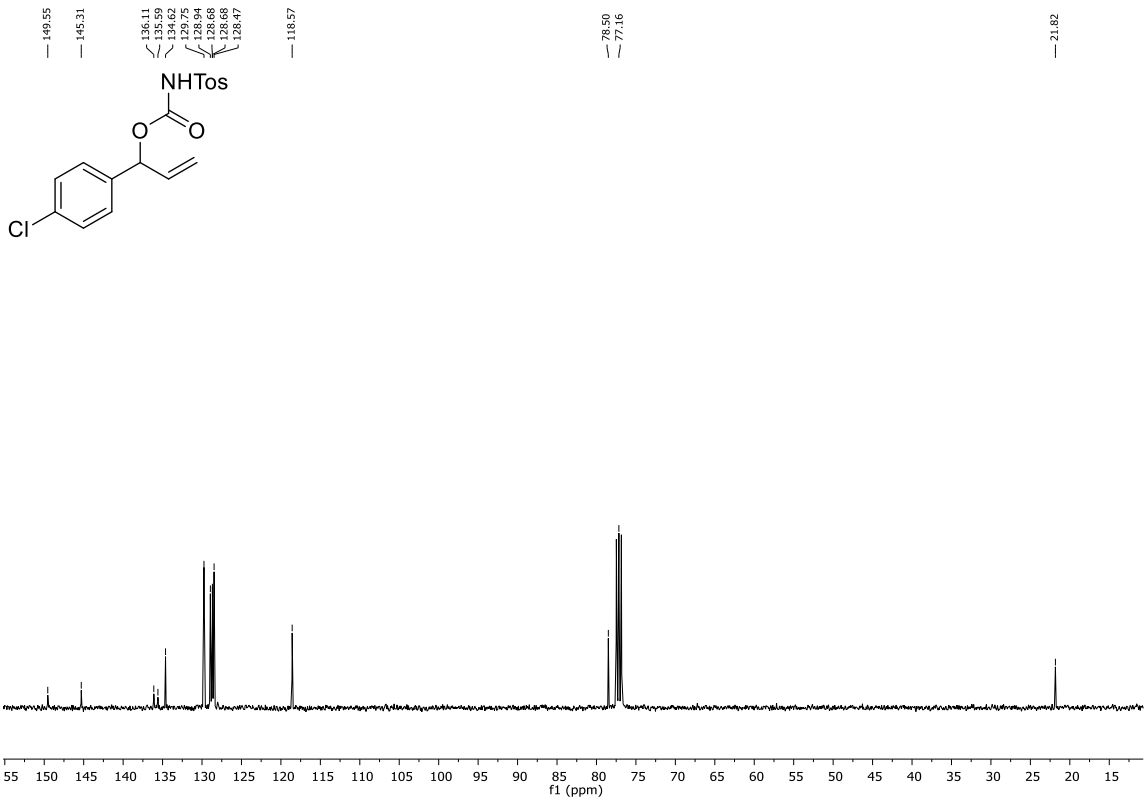


Compound **50c**

^{1}H NMR ($CDCl_3$)

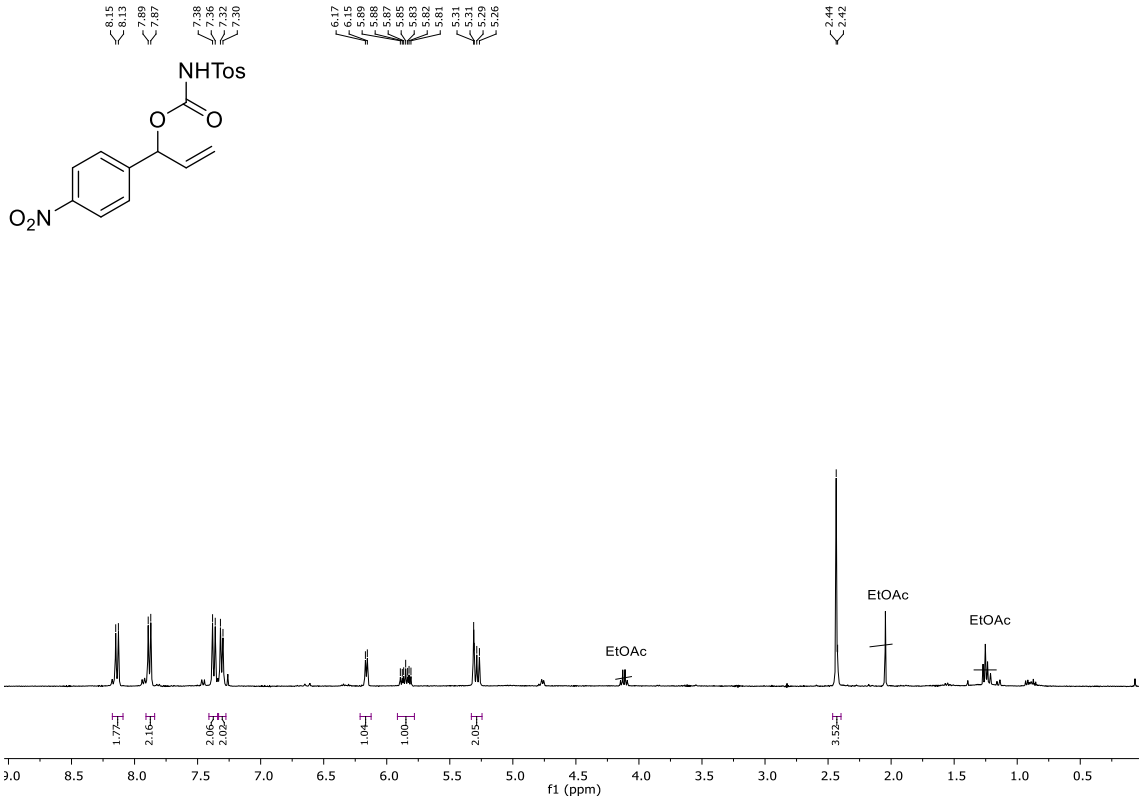


^{13}C NMR ($CDCl_3$)

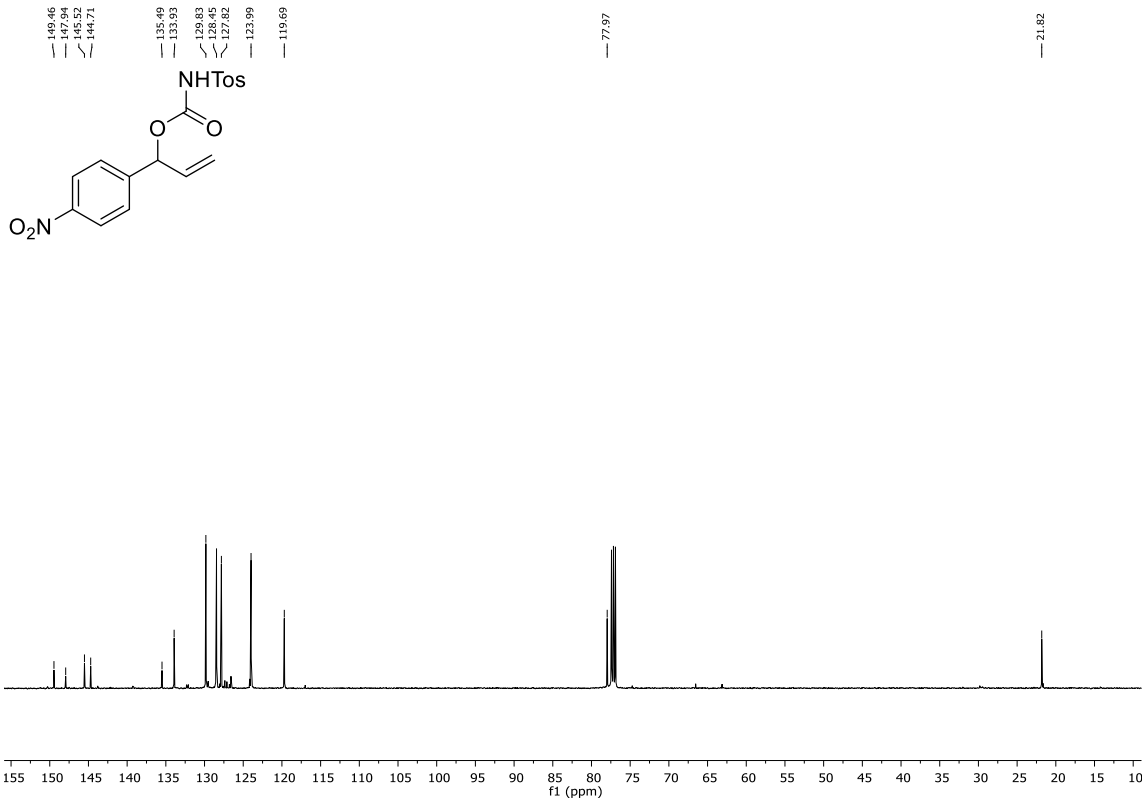


Compound **50d**

^{1}H NMR ($CDCl_3$)

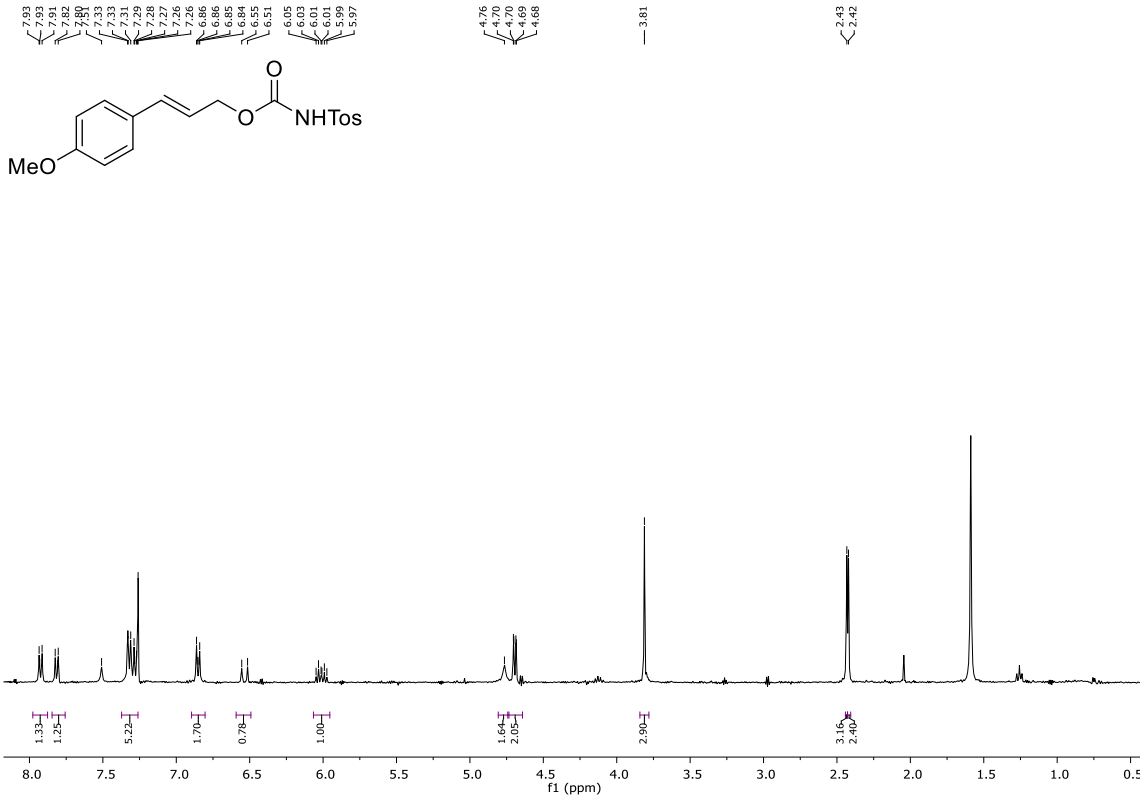


^{13}C NMR ($CDCl_3$)

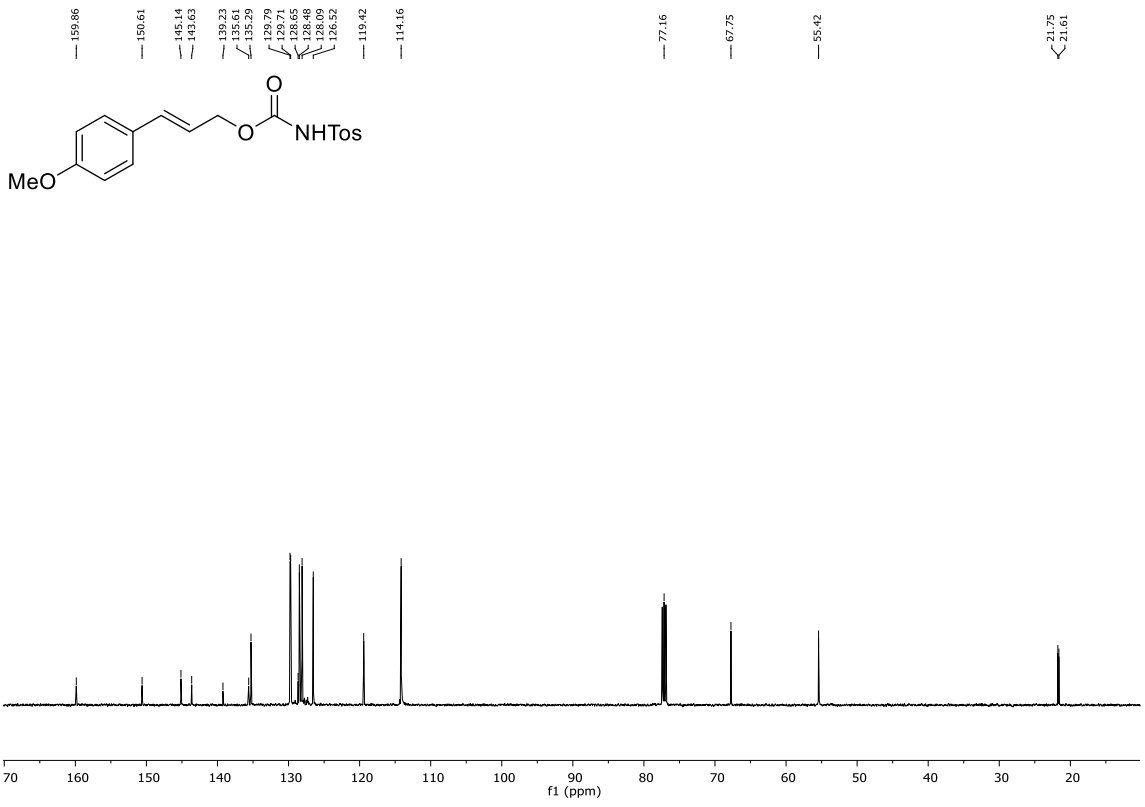


Compound **51a**

^{1}H NMR ($CDCl_3$)

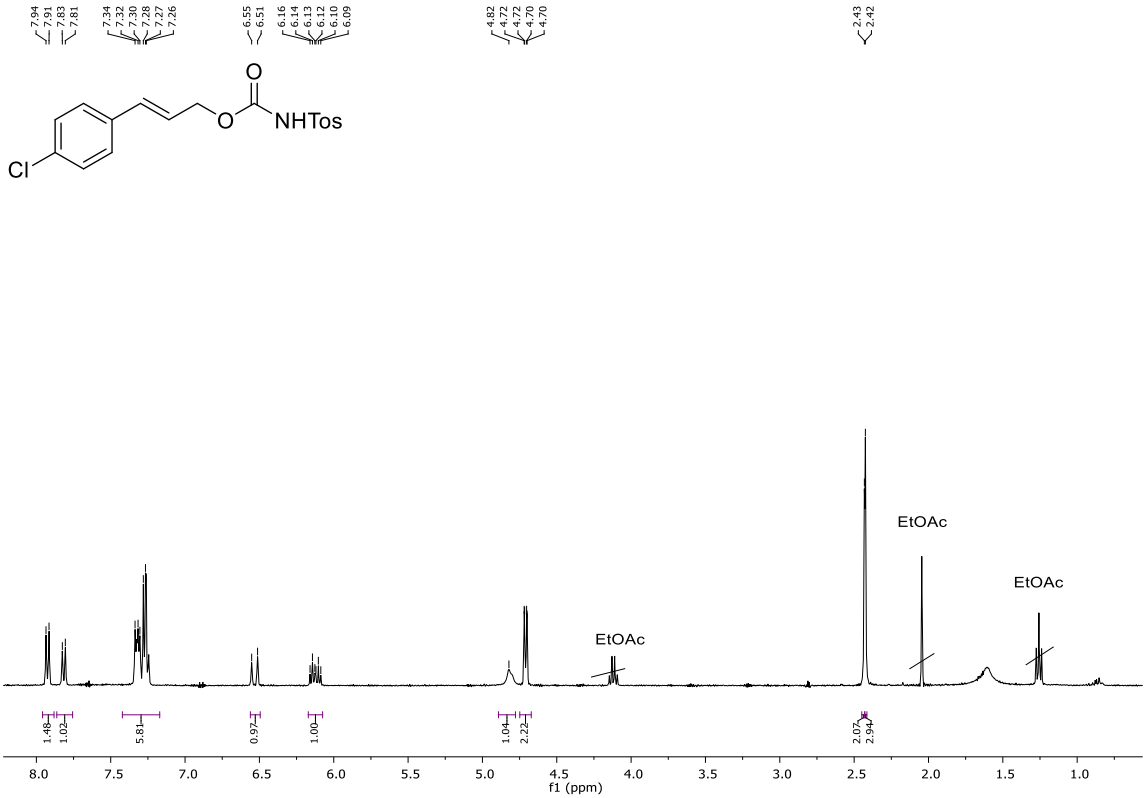


^{13}C NMR ($CDCl_3$)

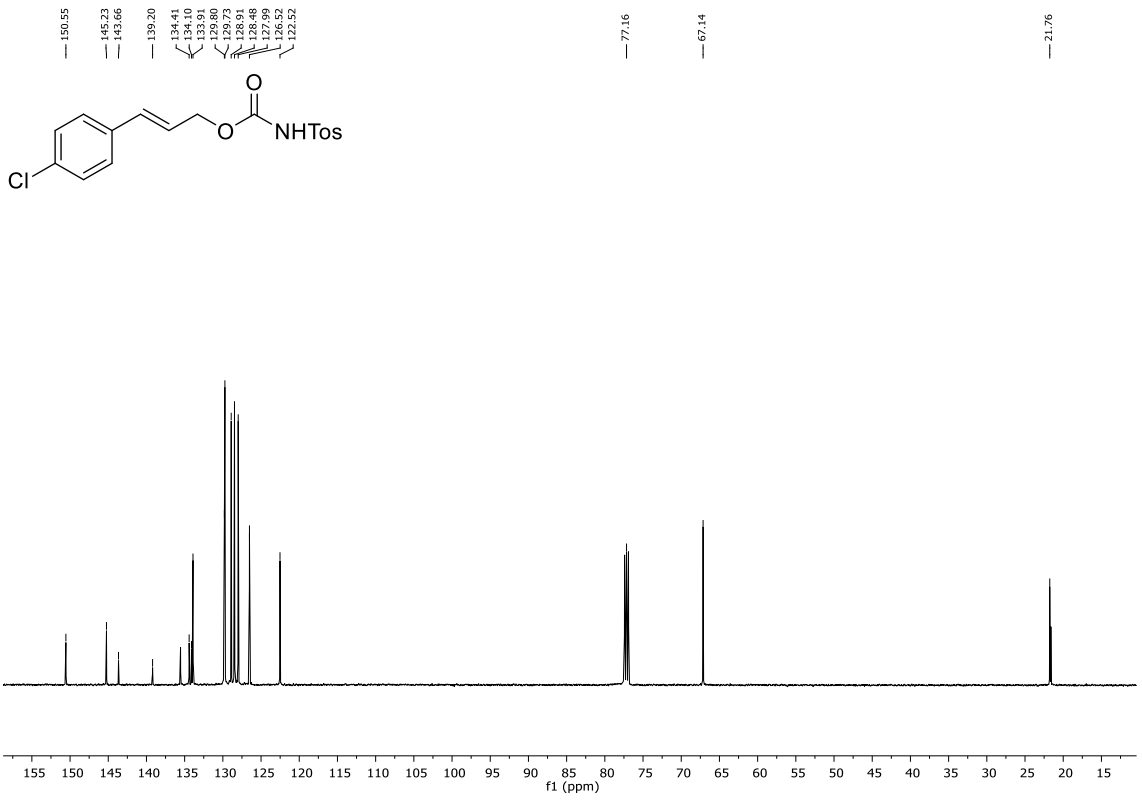


Compound **51c**

^{1}H NMR ($CDCl_3$)

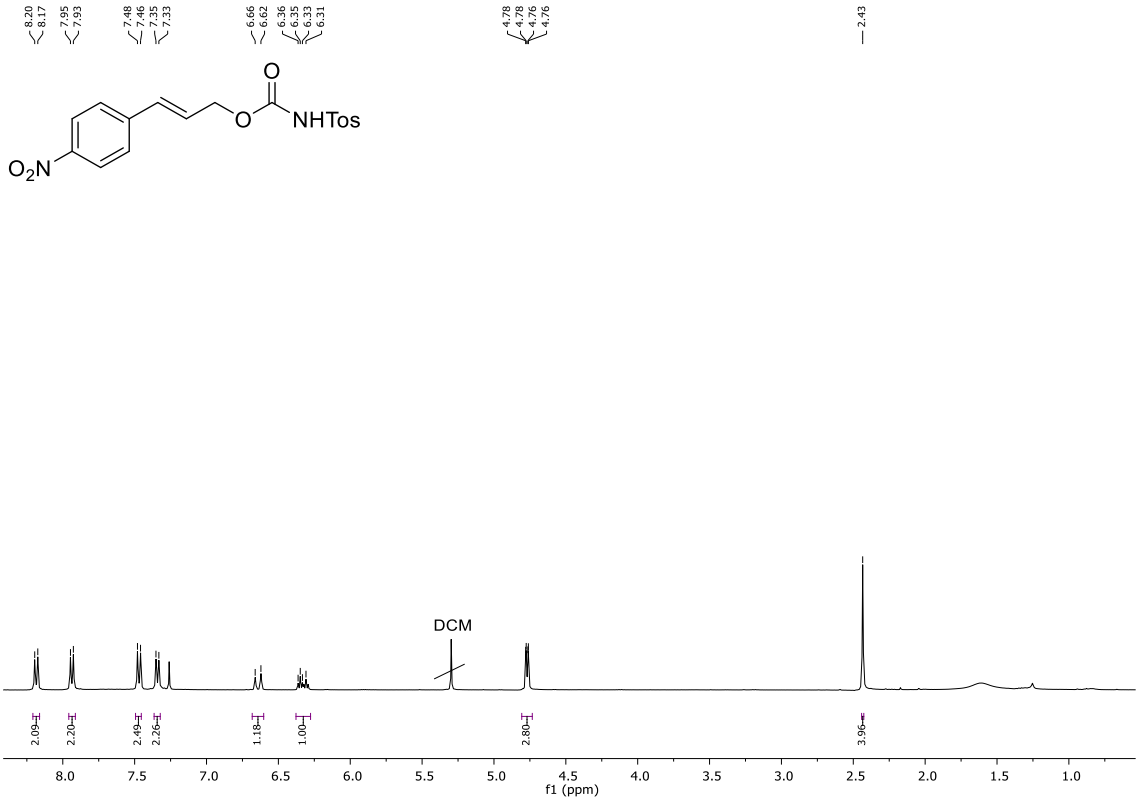


^{13}C NMR ($CDCl_3$)

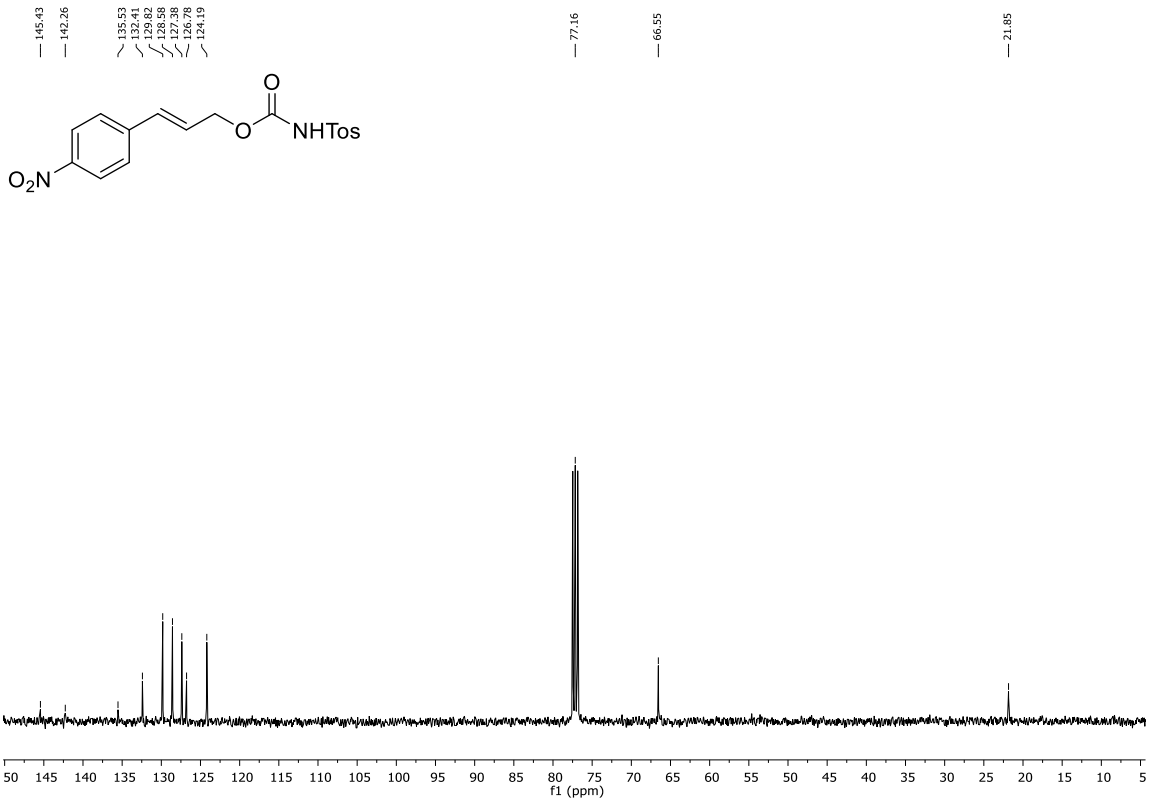


Compound **51d**

^{1}H NMR ($CDCl_3$)

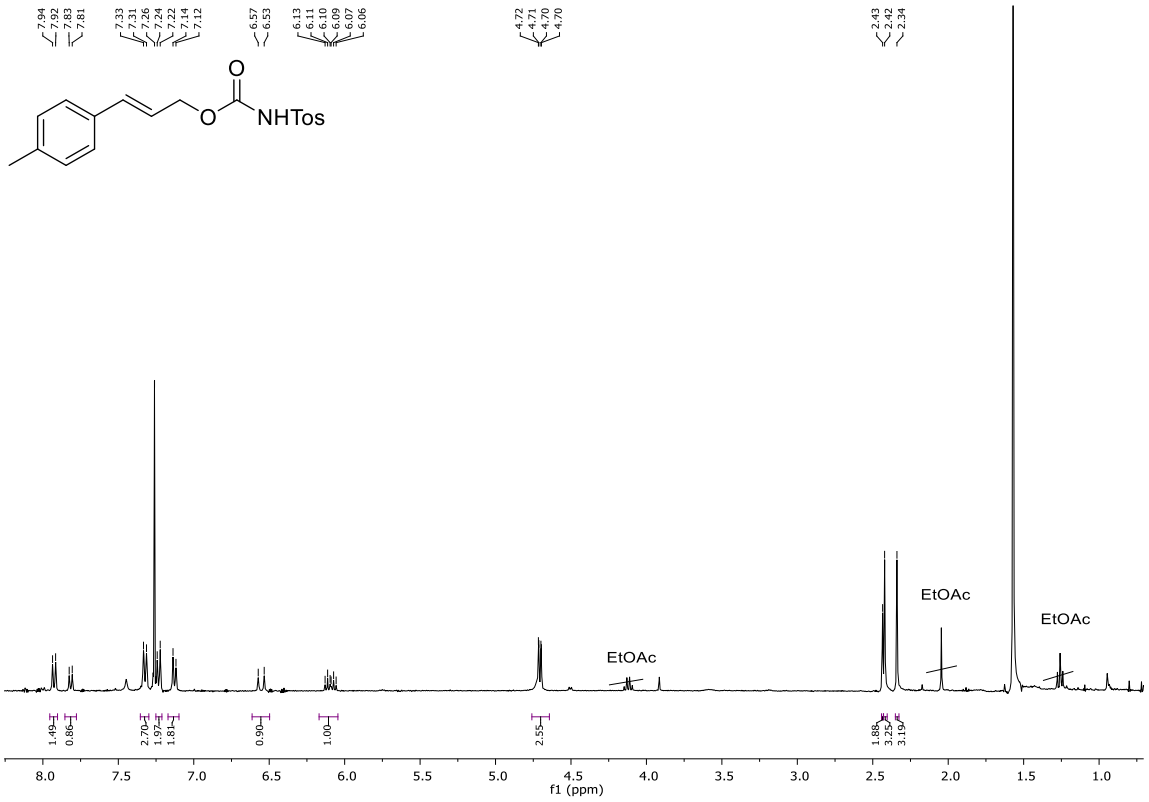


^{13}C NMR ($CDCl_3$)

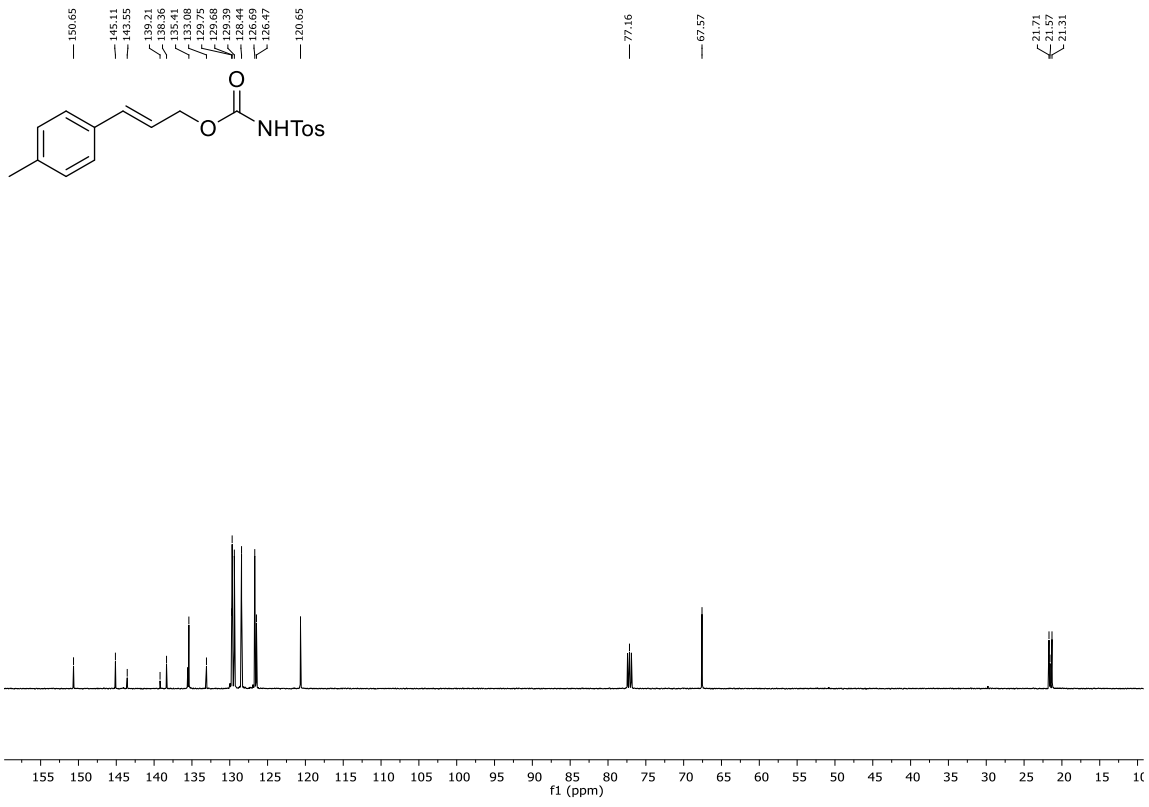


Compound **51e**

^{1}H NMR ($CDCl_3$)

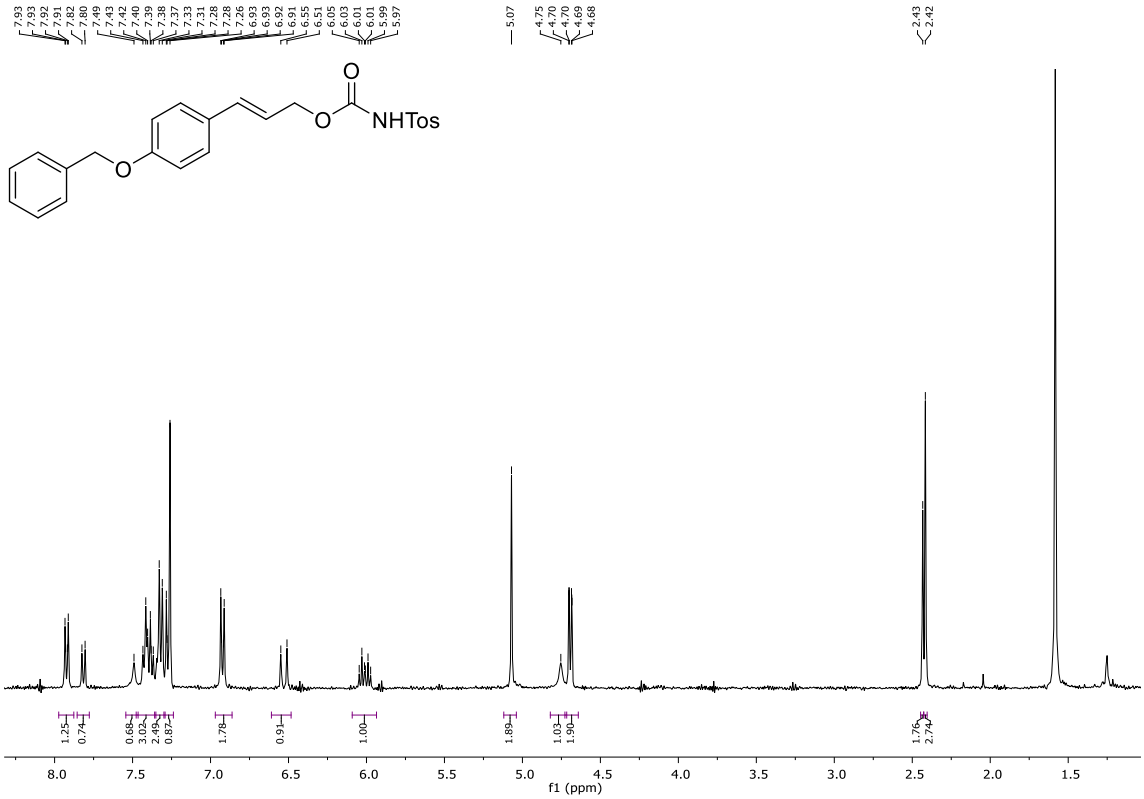


^{13}C NMR ($CDCl_3$)

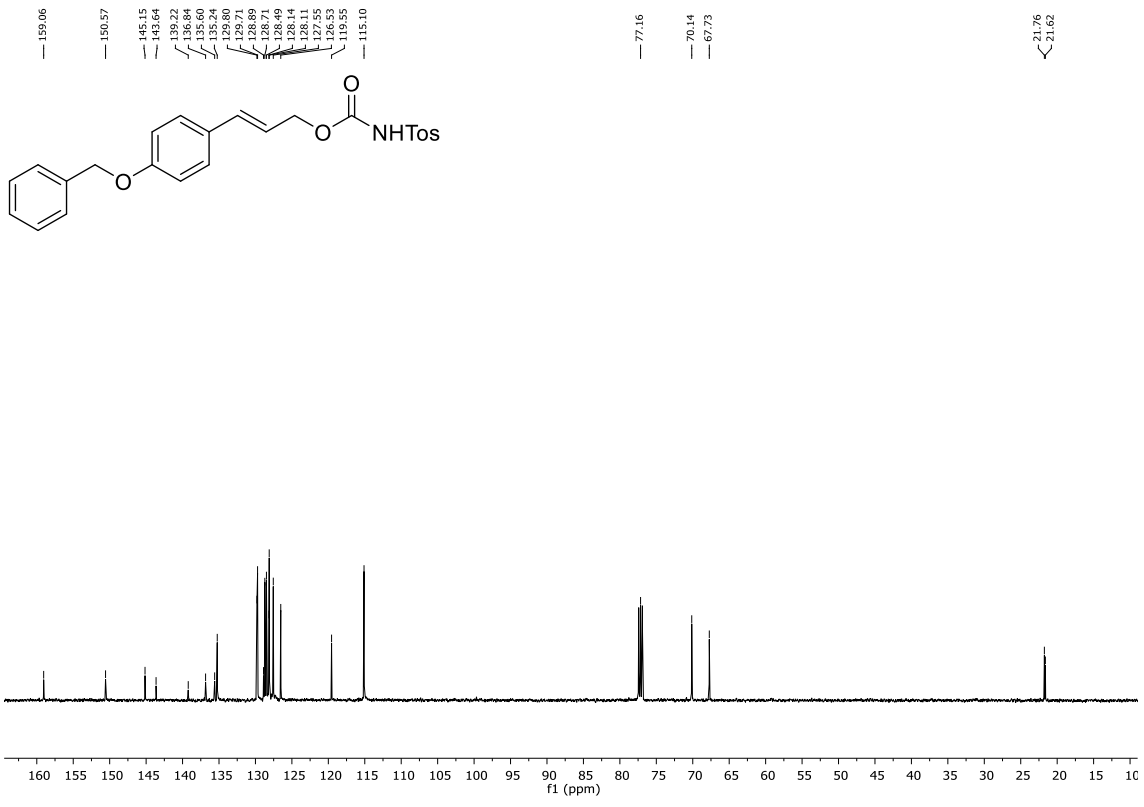


Compound **51f**

^{1}H NMR ($CDCl_3$)

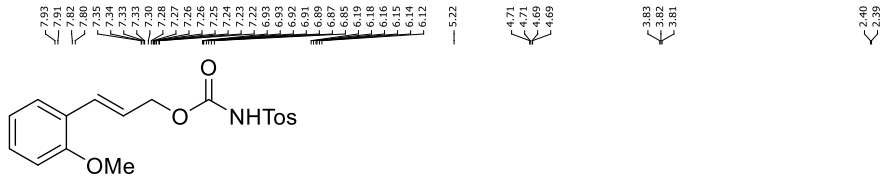


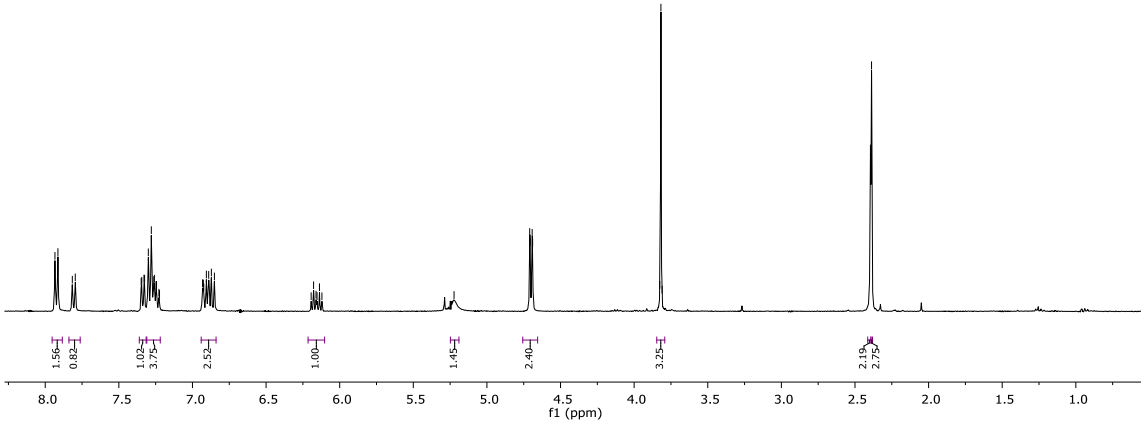
^{13}C NMR ($CDCl_3$)



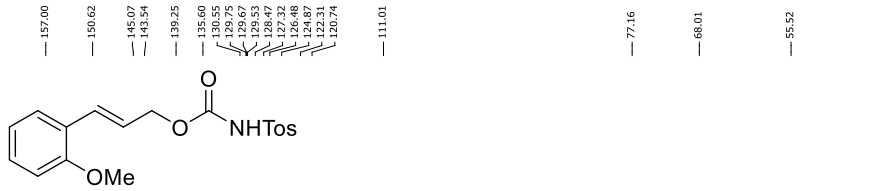
Compound **51g**

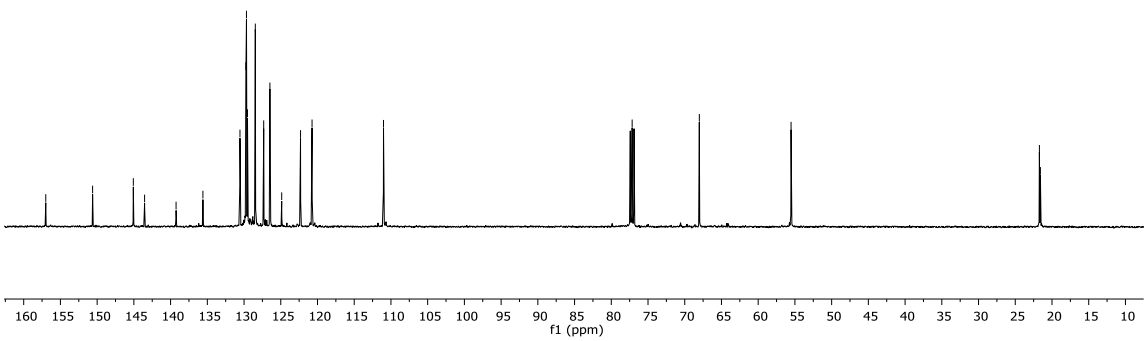
^{1}H NMR ($CDCl_3$)





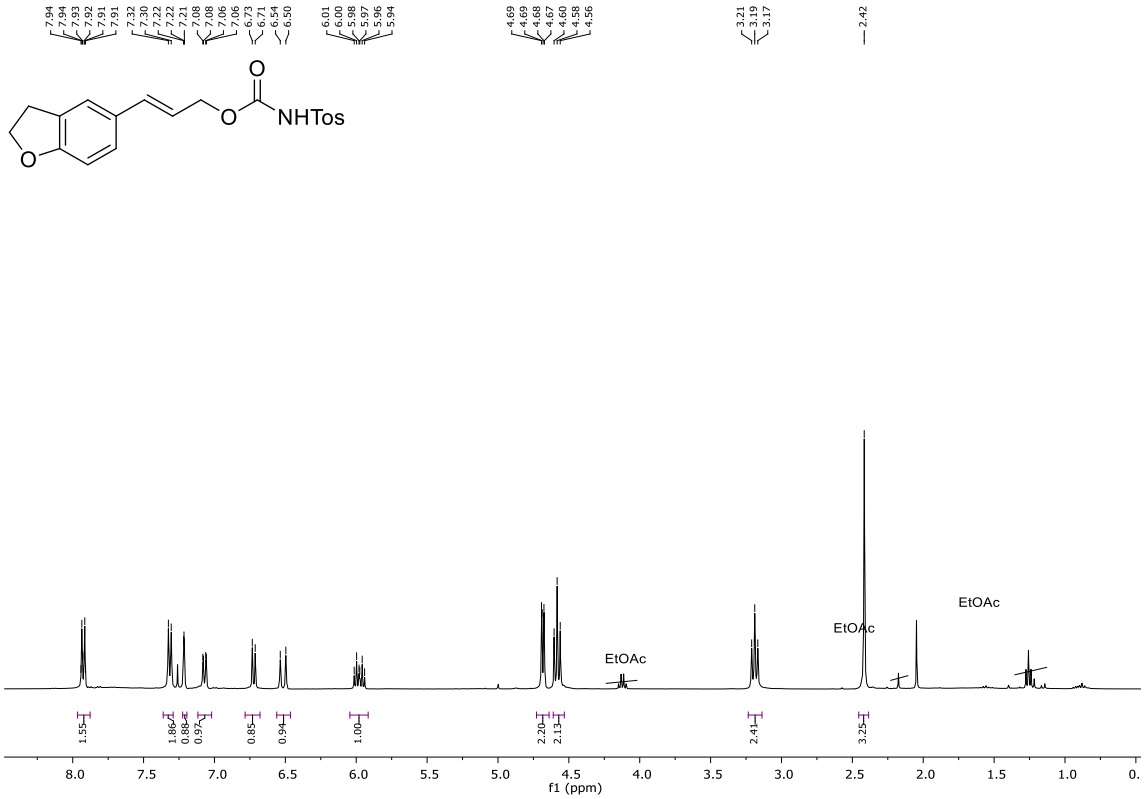
^{13}C NMR ($CDCl_3$)



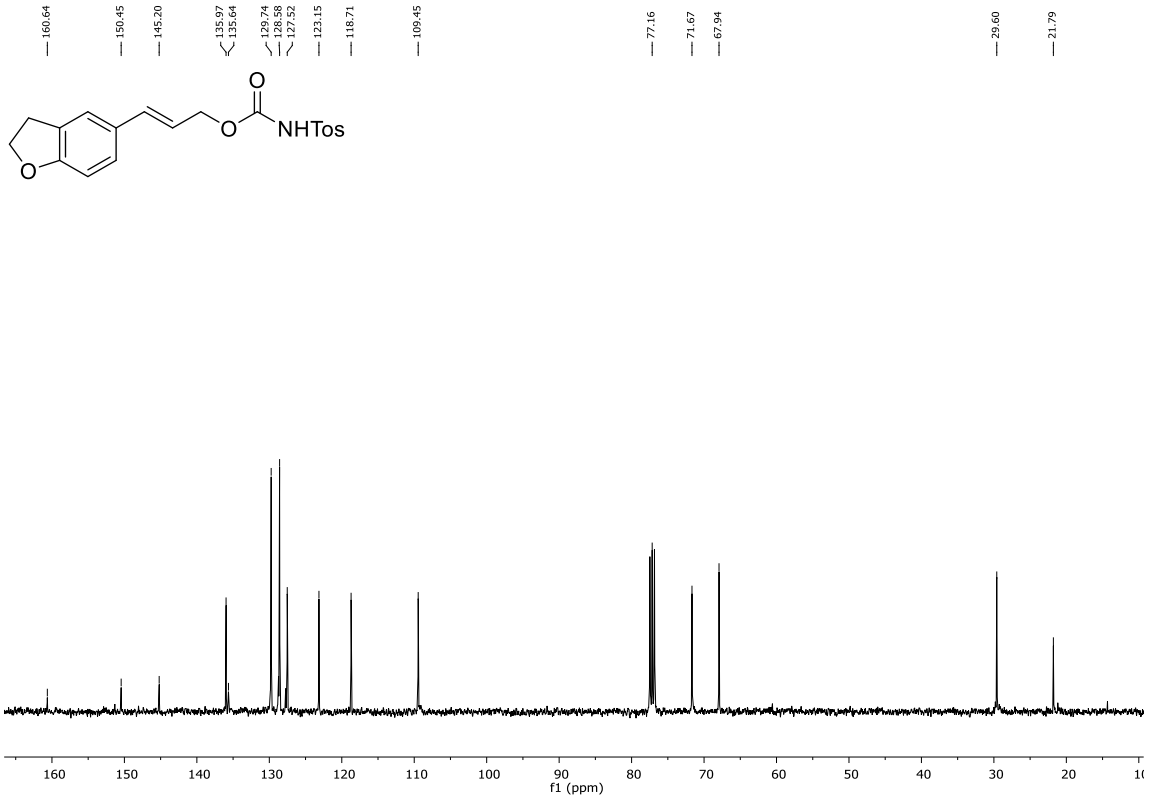


Compound **51h**

^{1}H NMR ($CDCl_3$)

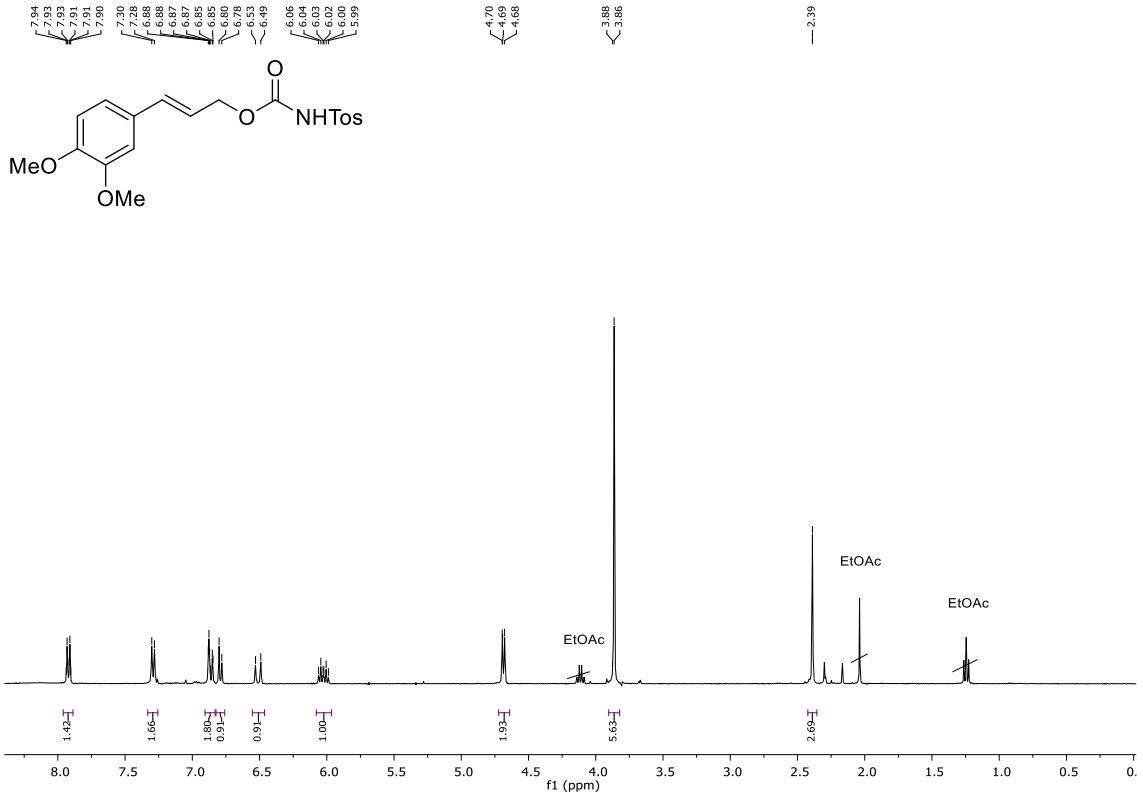


^{13}C NMR ($CDCl_3$)

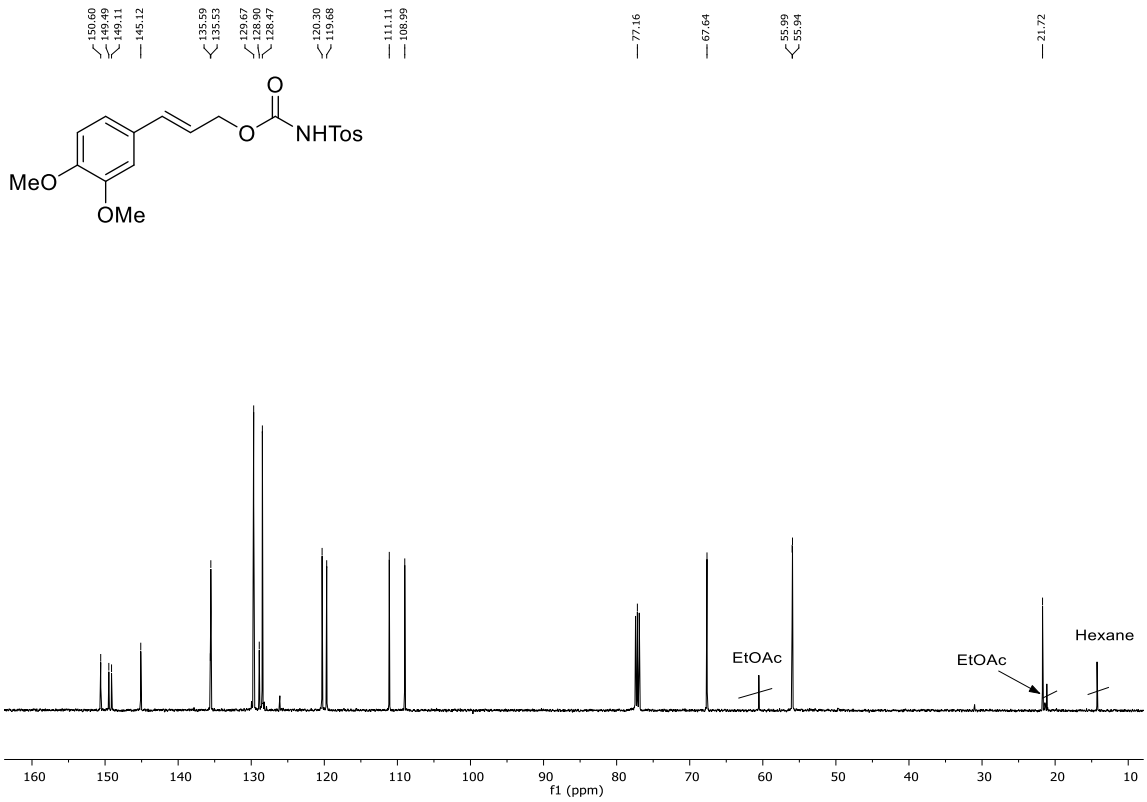


Compound **51i**

^{1}H NMR ($CDCl_3$)

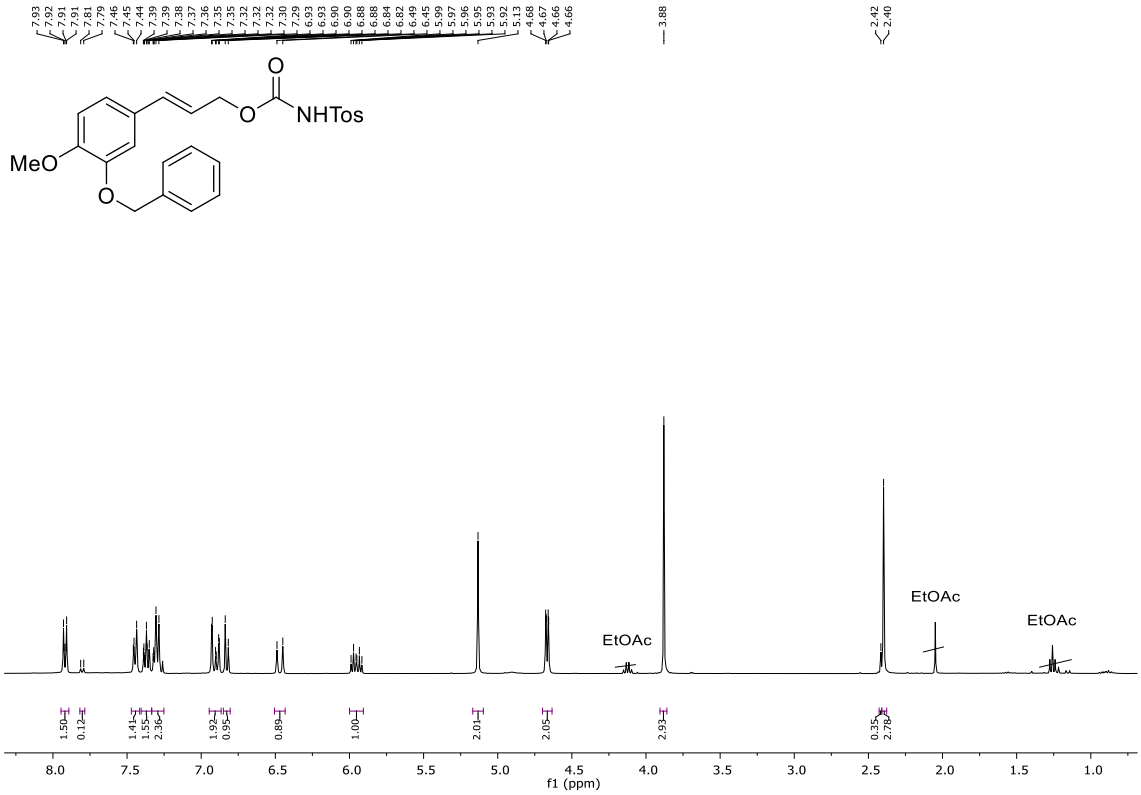


^{13}C NMR ($CDCl_3$)

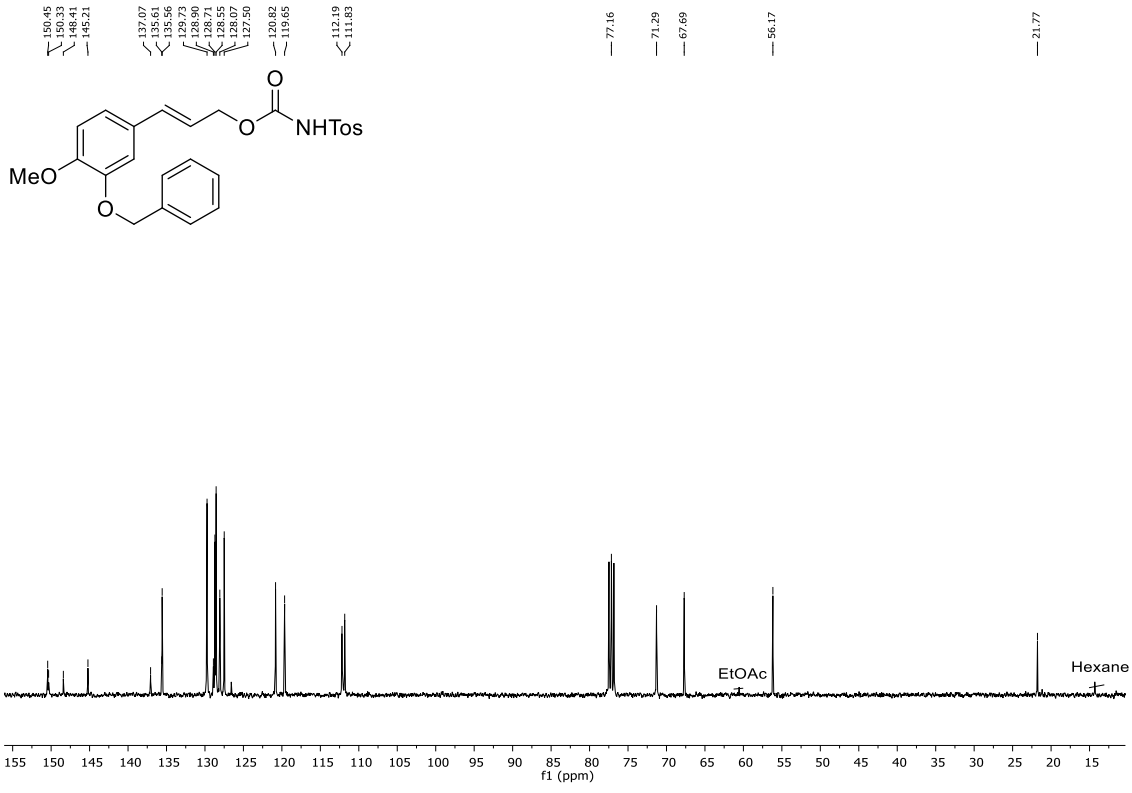


Compound **51j**

^{1}H NMR ($CDCl_3$)

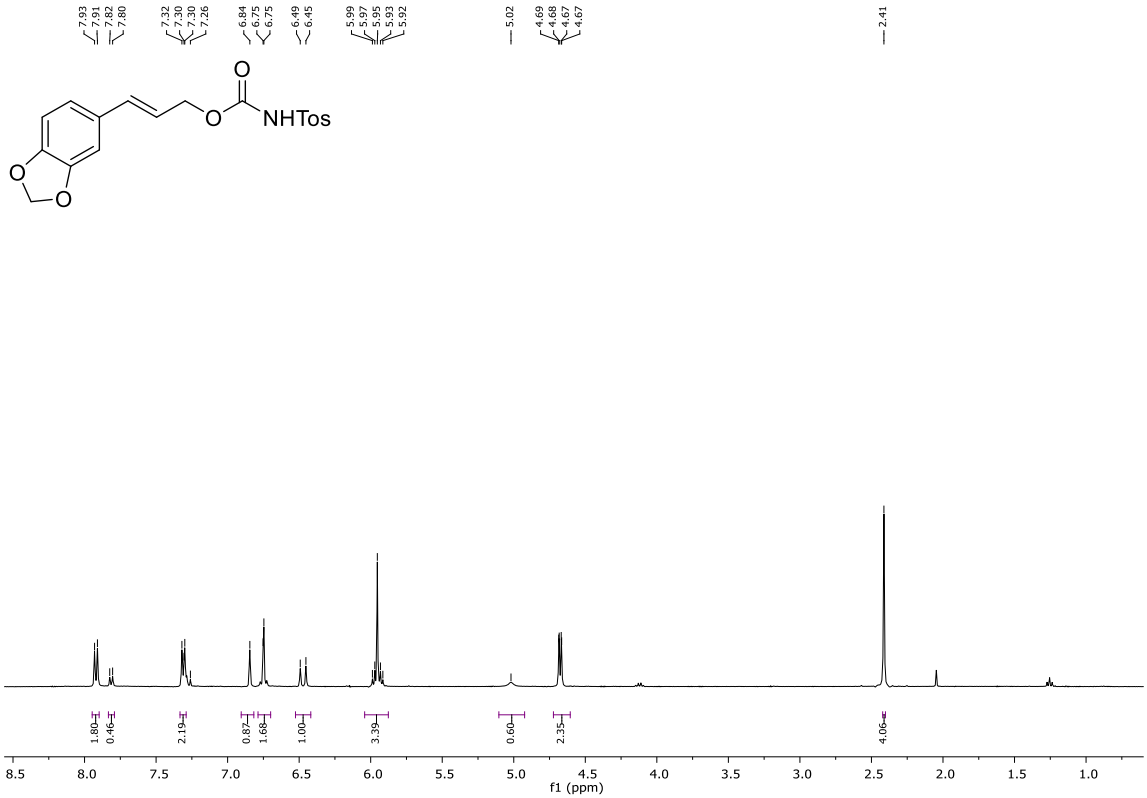


^{13}C NMR ($CDCl_3$)

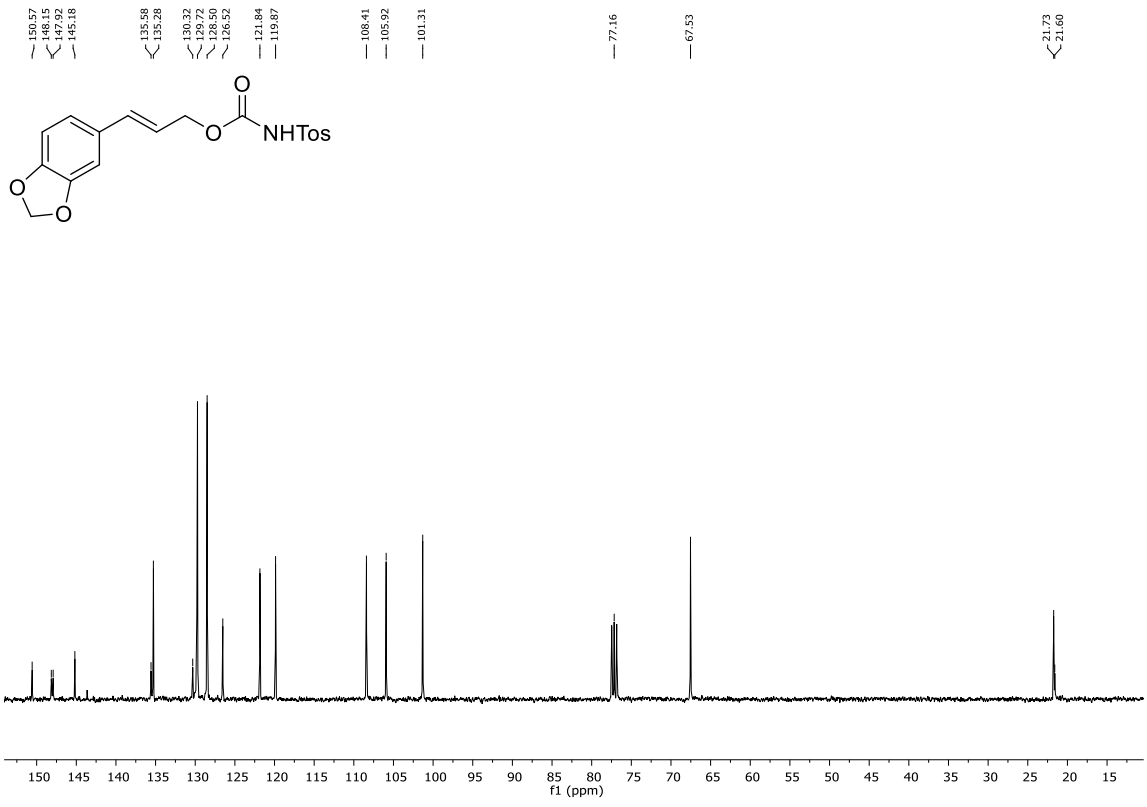


Compound **51k**

^{1}H NMR ($CDCl_3$)

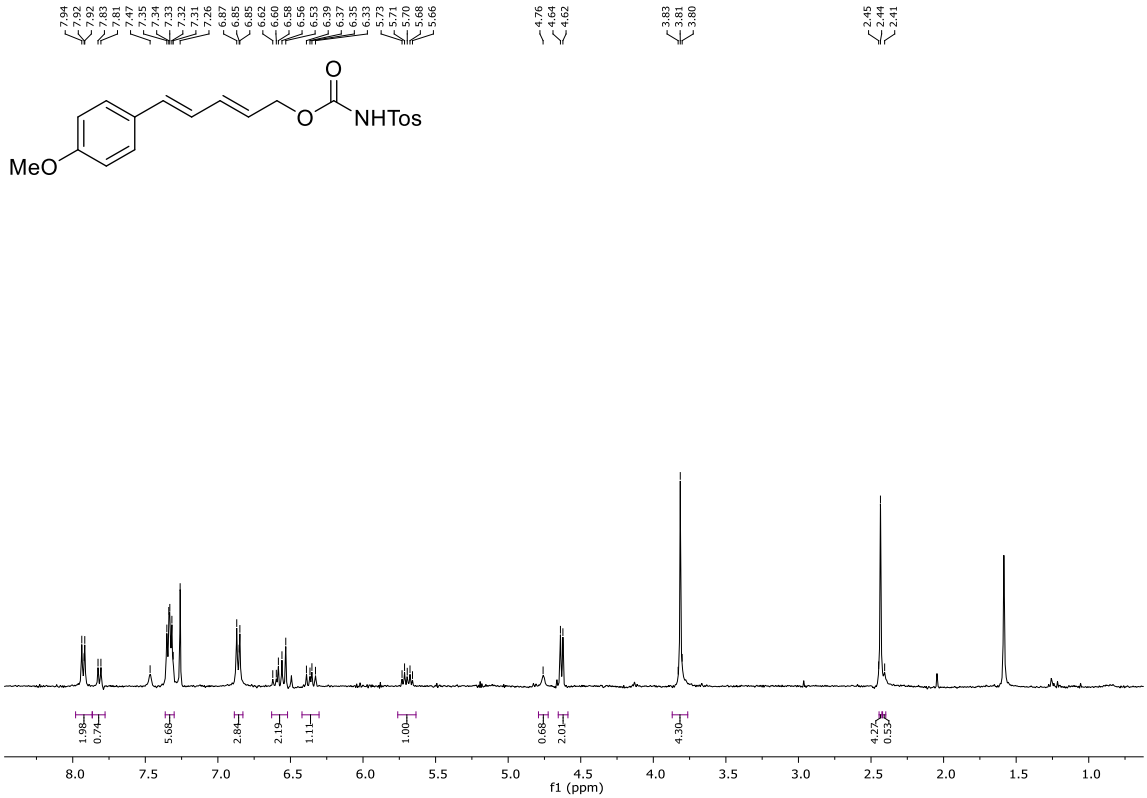


^{13}C NMR ($CDCl_3$)

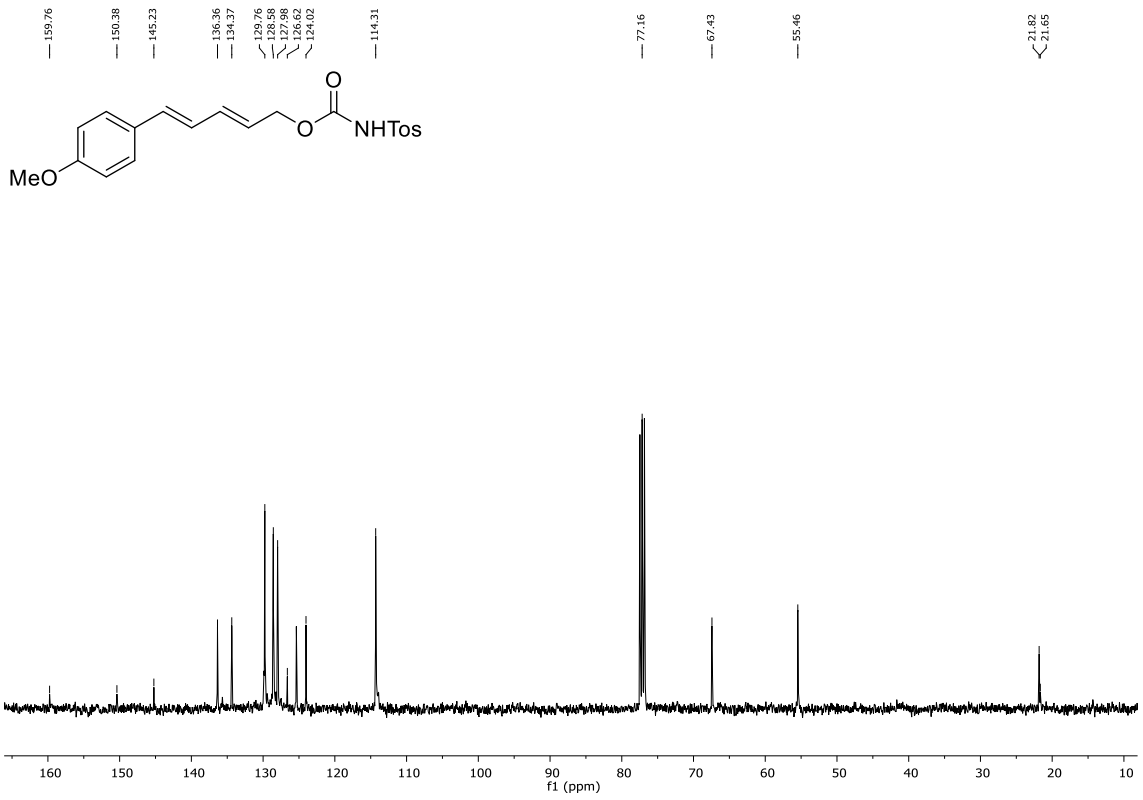


Compound **53a**

^{1}H NMR ($CDCl_3$)

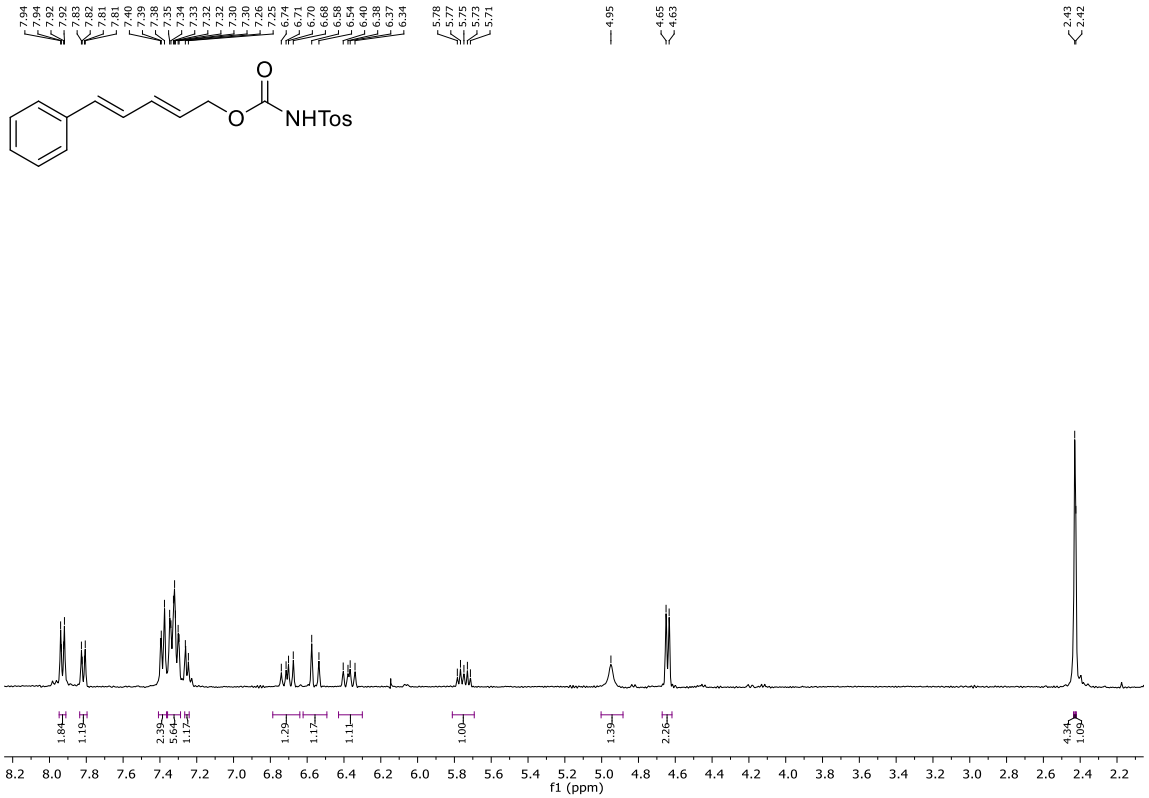


^{13}C NMR ($CDCl_3$)

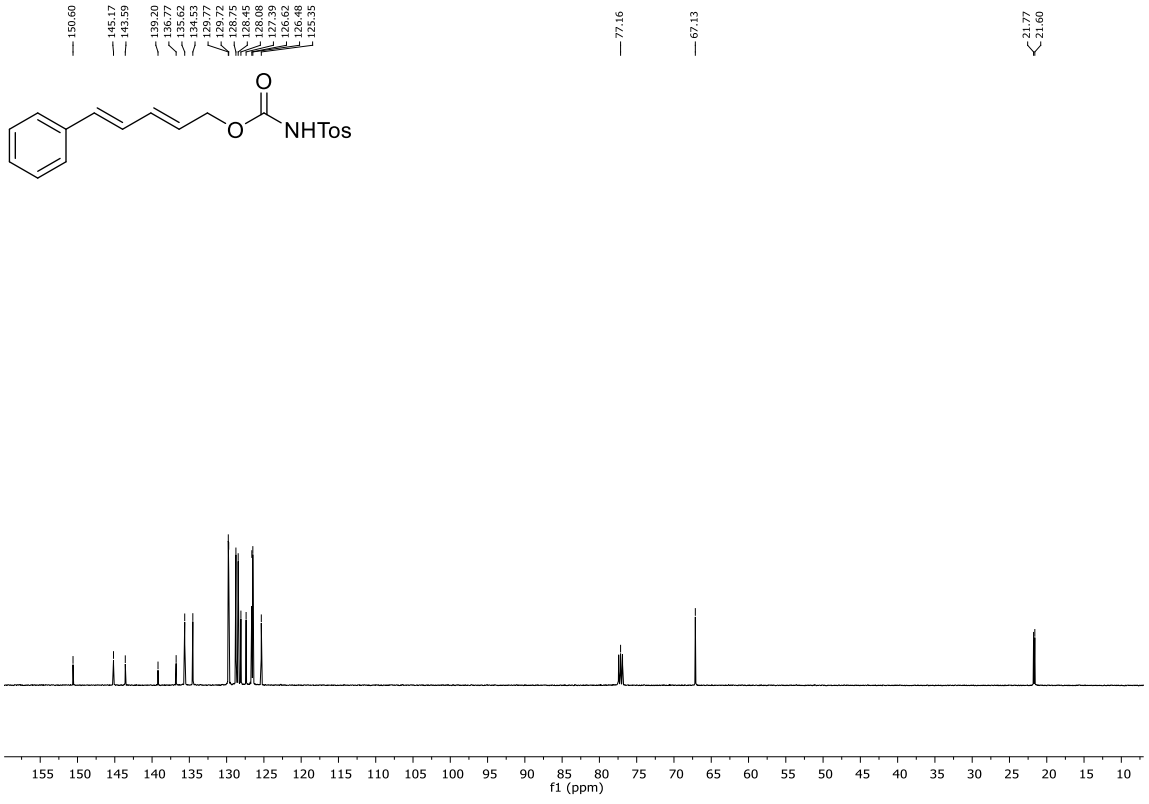


Compound **53b**

^{1}H NMR ($CDCl_3$)

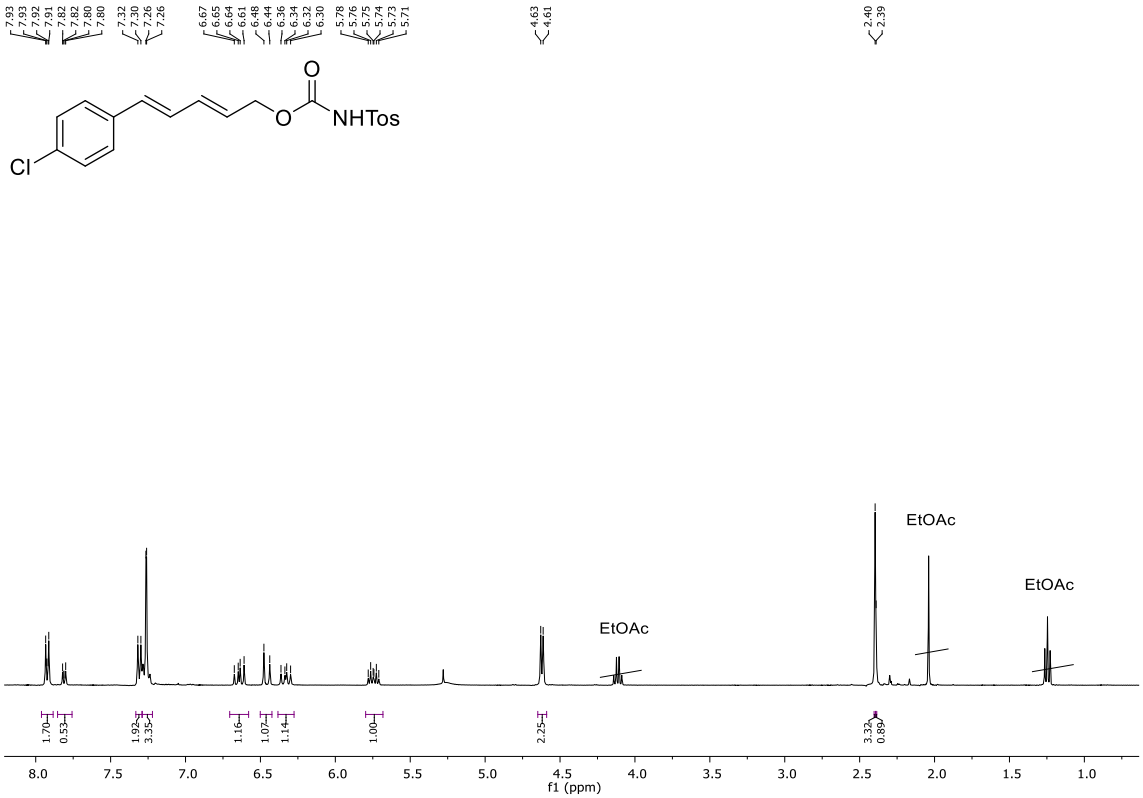


^{13}C NMR ($CDCl_3$)

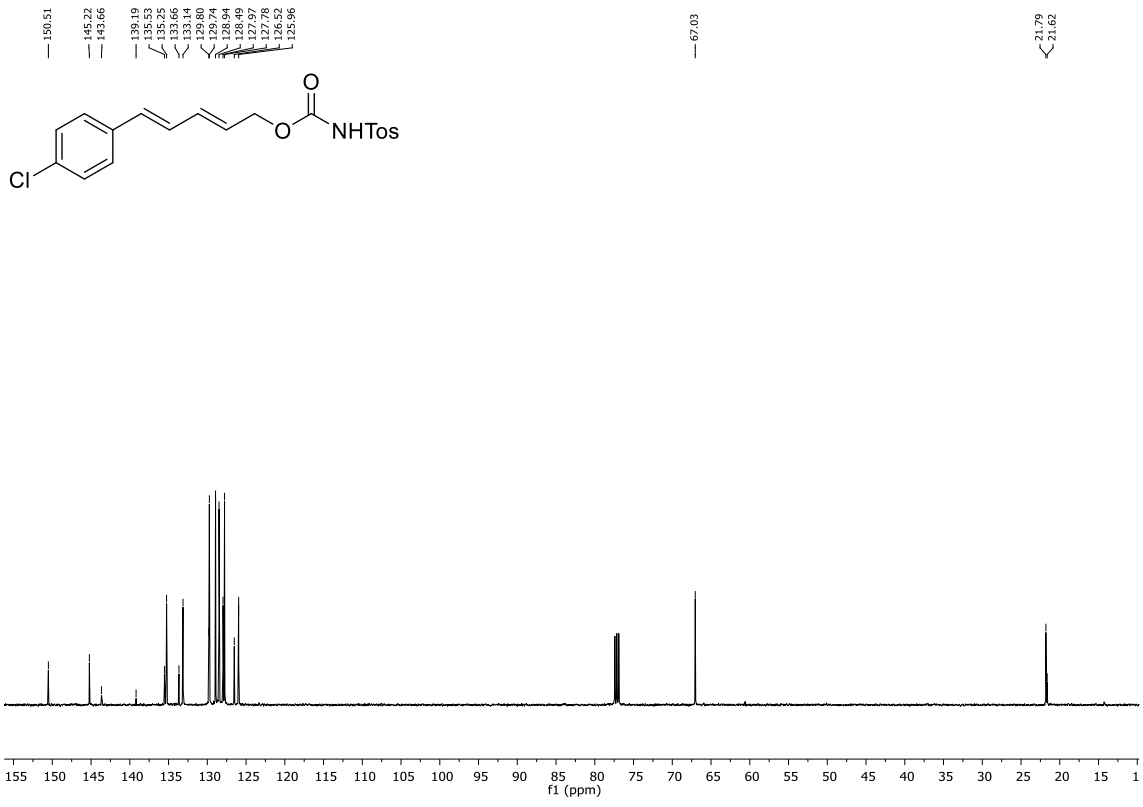


Compound **53c**

^{1}H NMR ($CDCl_3$)

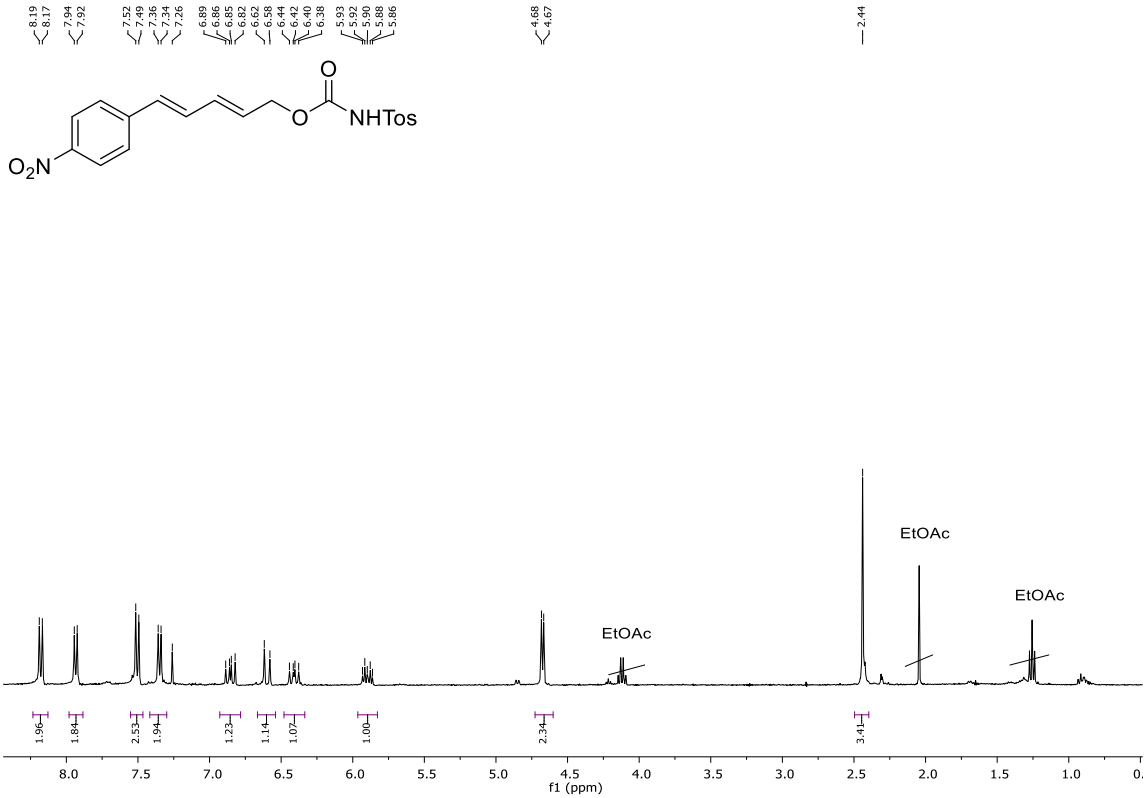


^{13}C NMR ($CDCl_3$)

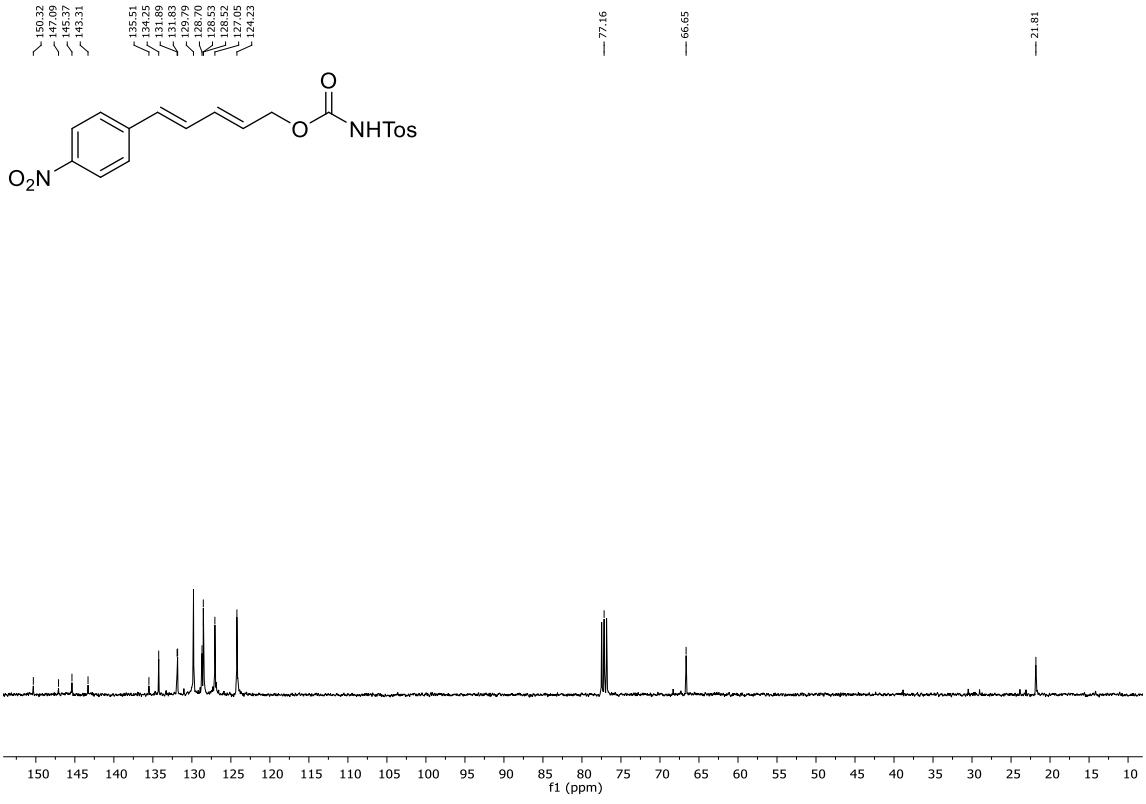


Compound **53d**

^{1}H NMR ($CDCl_3$)

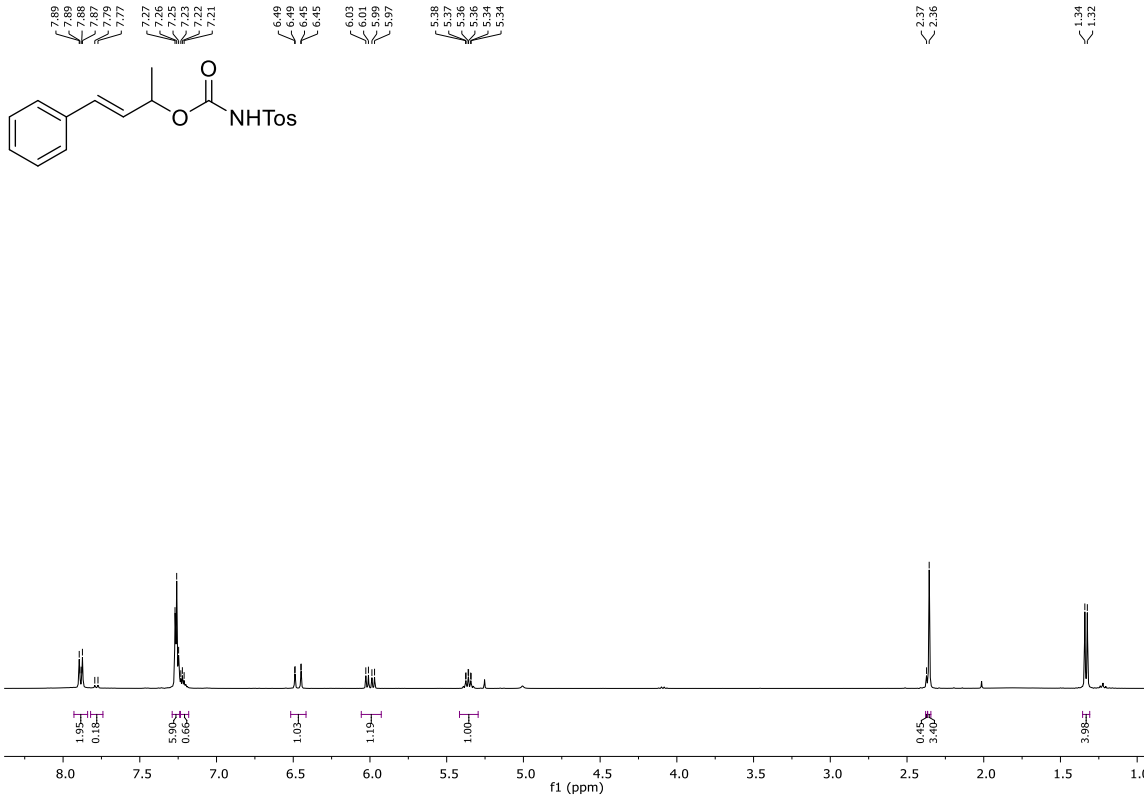


^{13}C NMR ($CDCl_3$)

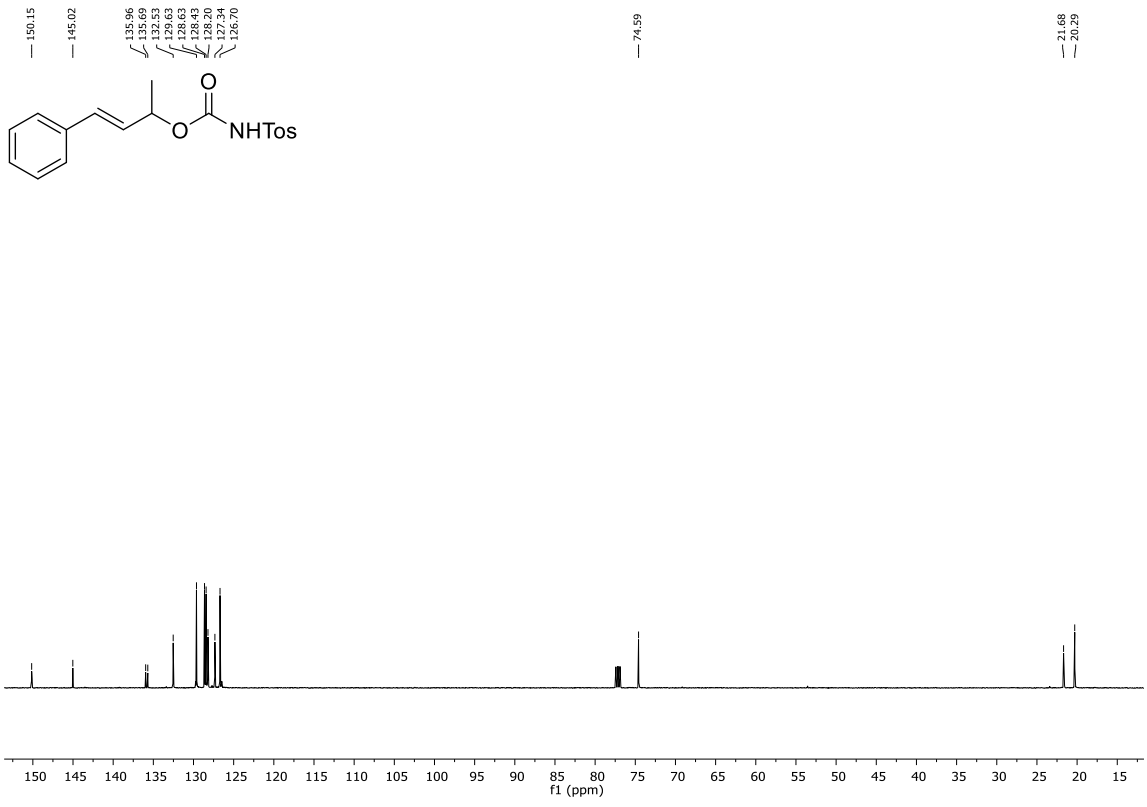


Compound **55**

^{1}H NMR ($CDCl_3$)

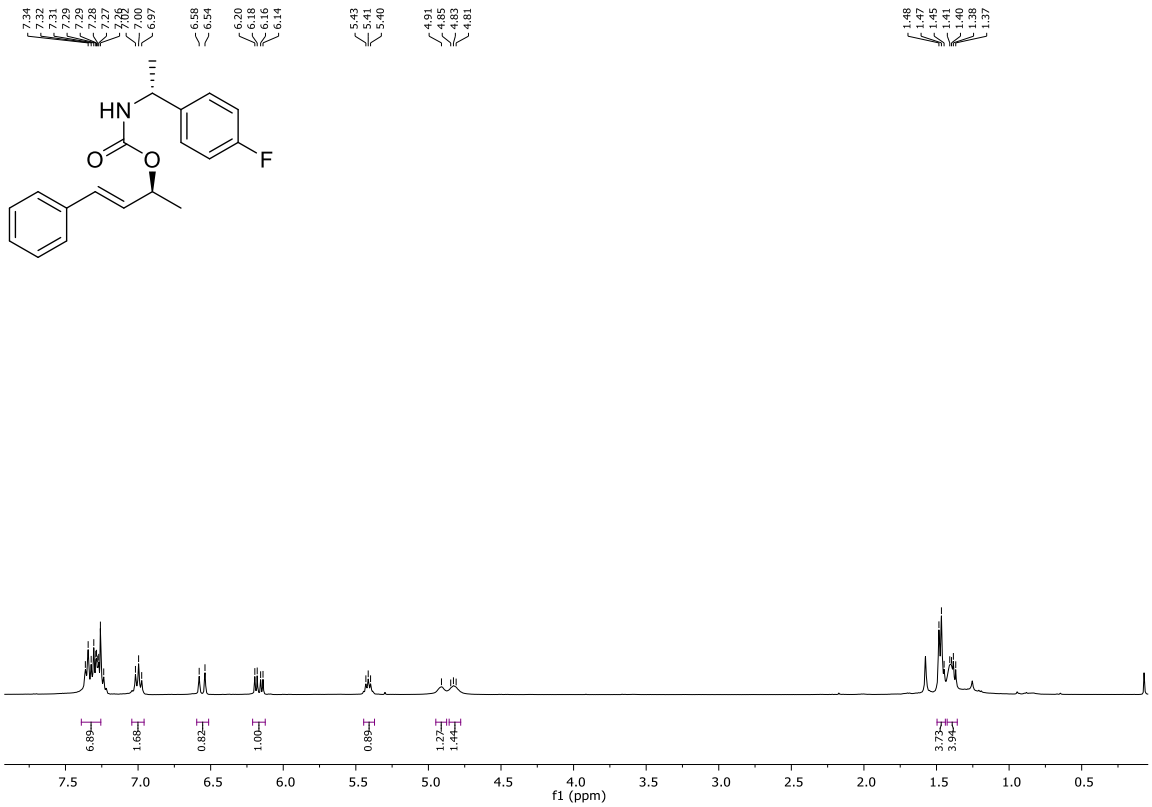


^{13}C NMR ($CDCl_3$)

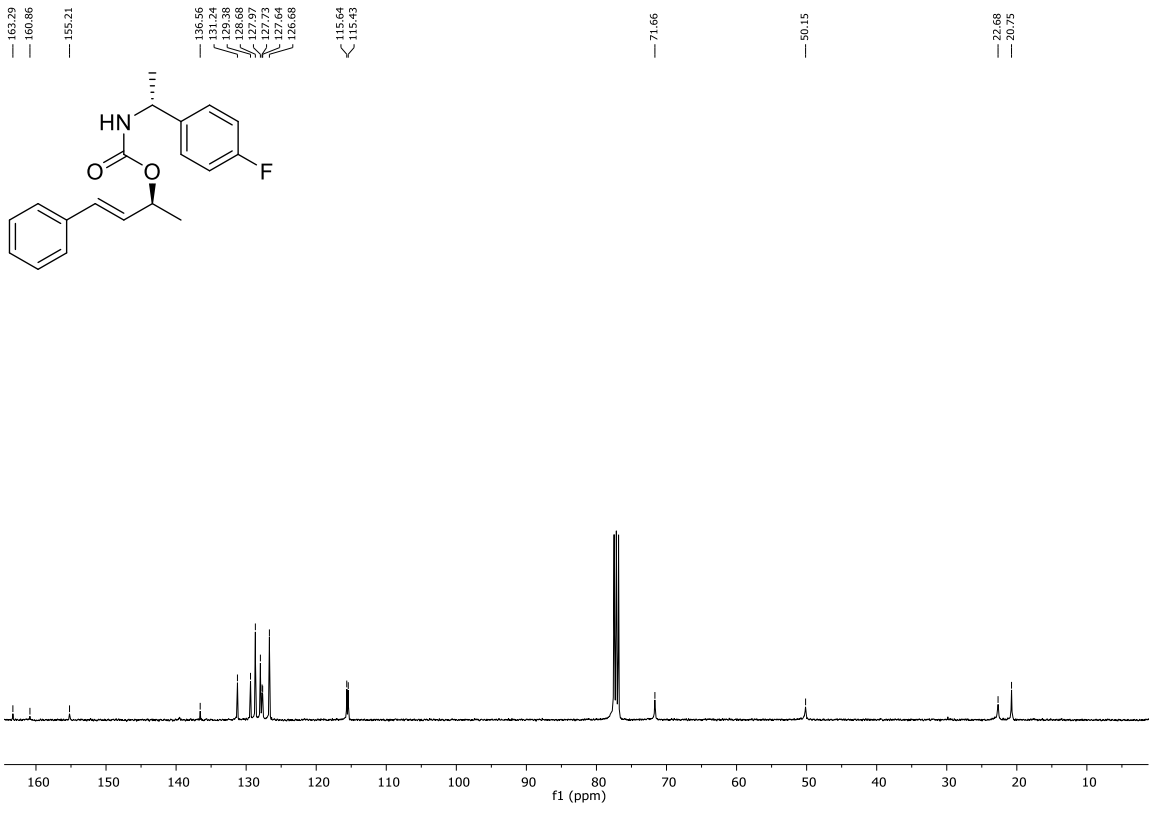


Compound **58**

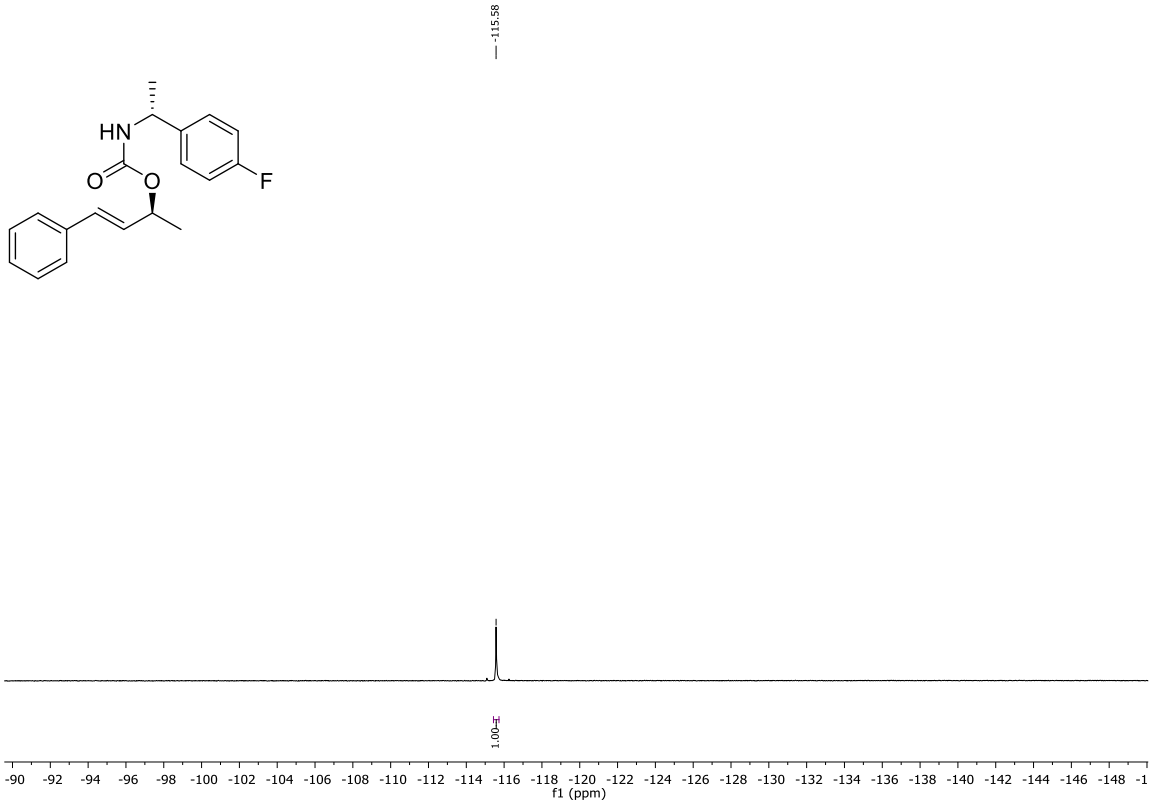
^{1}H NMR ($CDCl_3$)



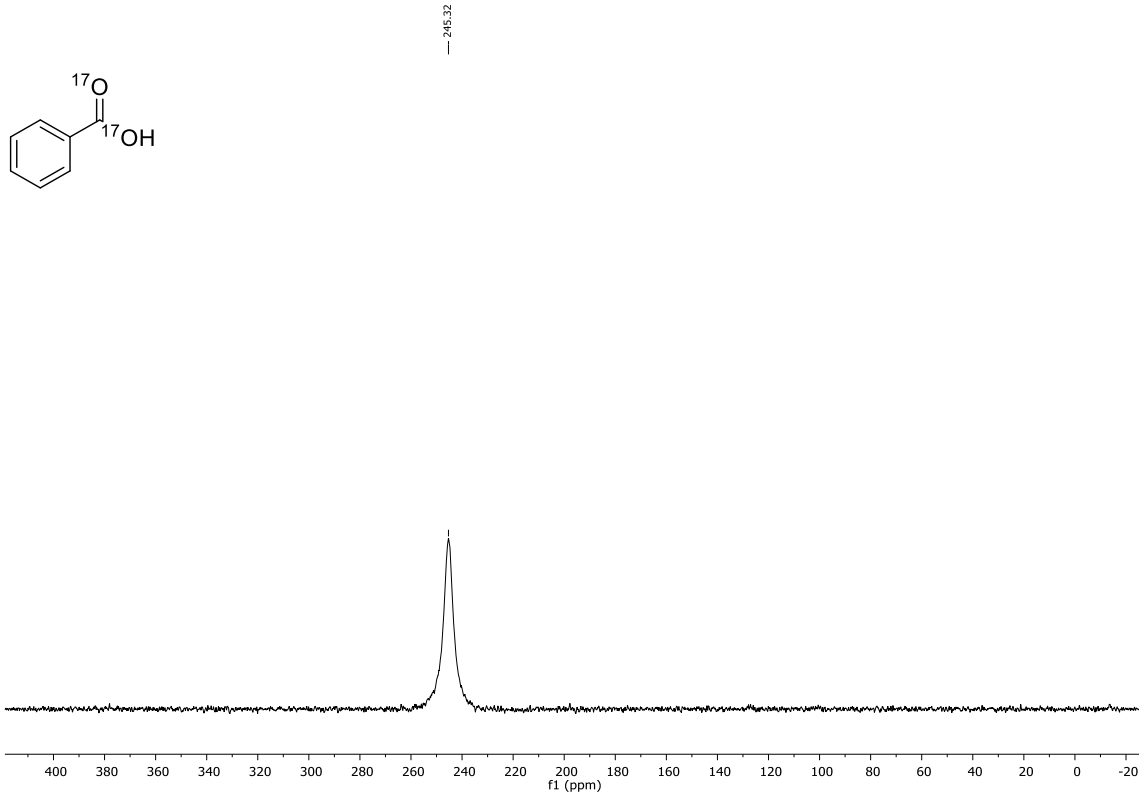
^{13}C NMR ($CDCl_3$)



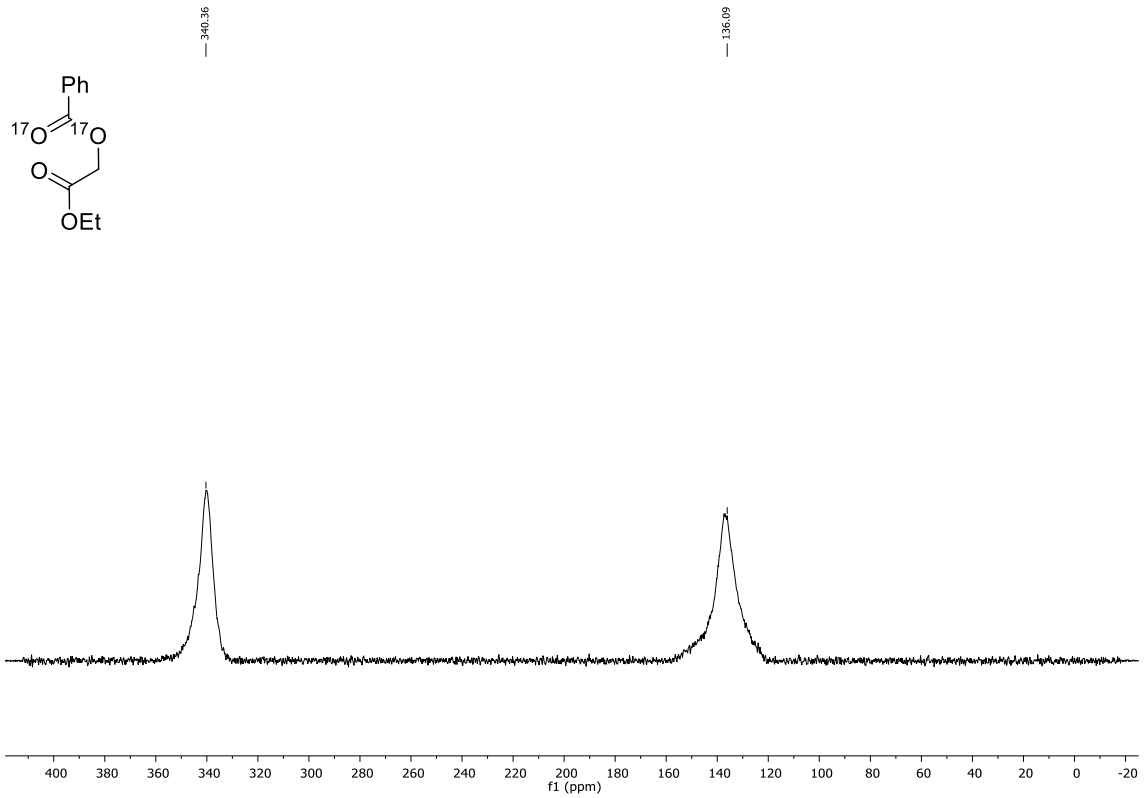
^{19}F NMR ($CDCl_3$)



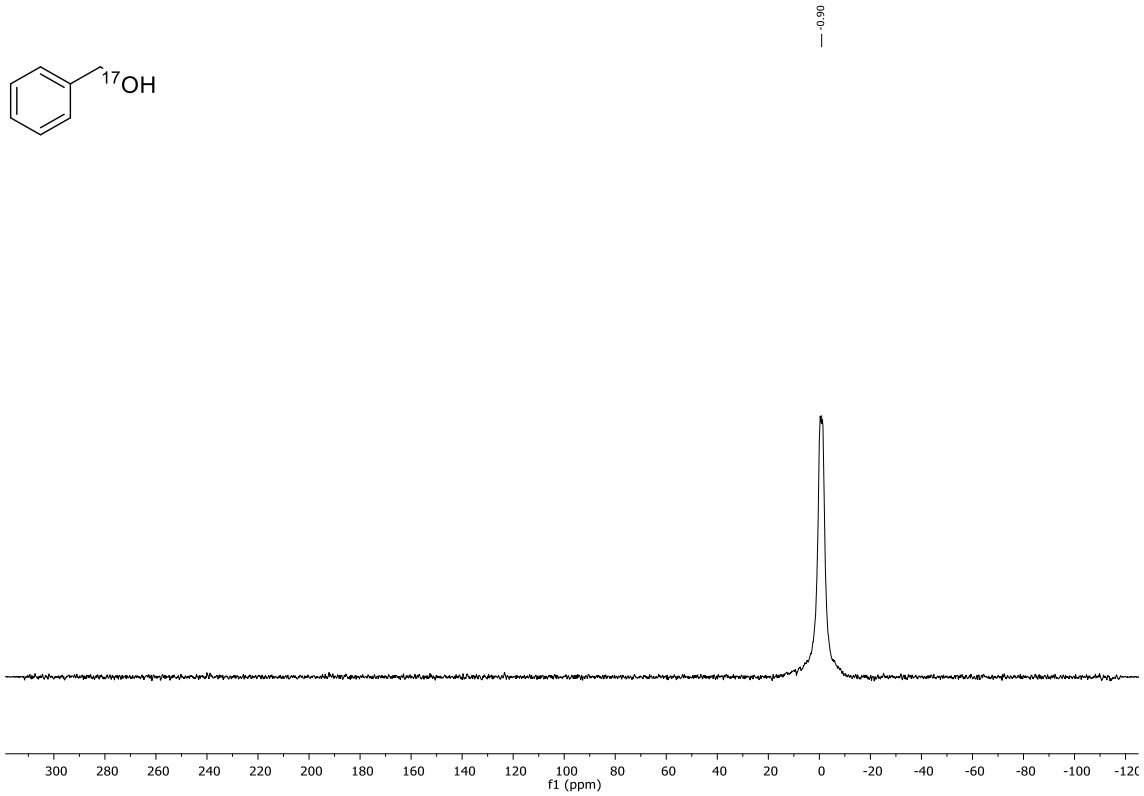
Compound **[$^{17}O_2$]60. ^{17}O NMR (Acetone-*d*6)**



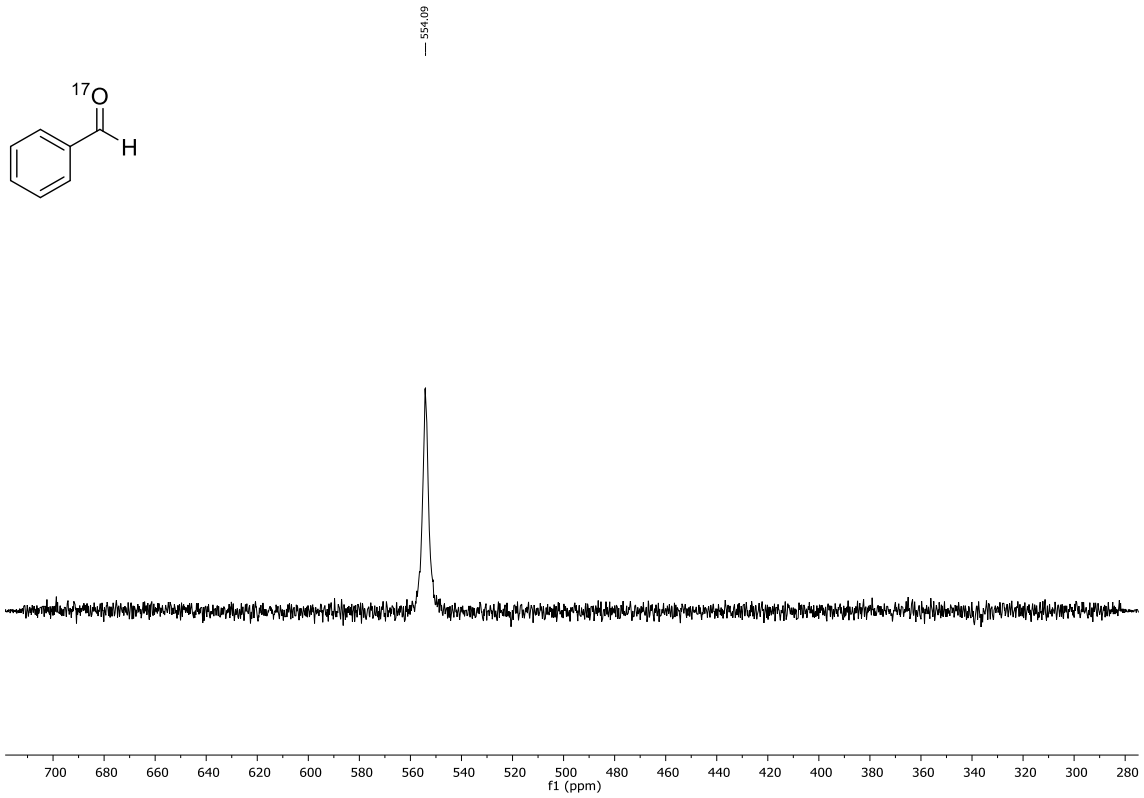
Compound **[$^{17}O_2$]61**. **^{17}O NMR (Acetone-*d*6)**



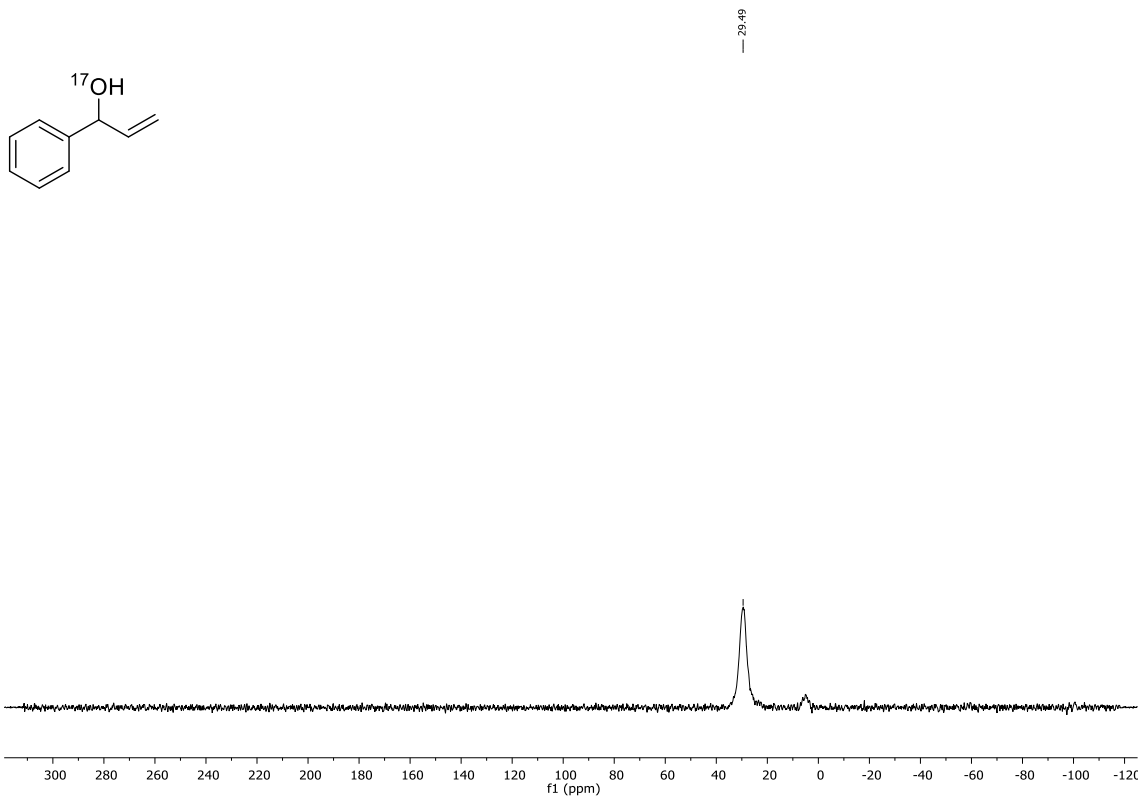
Compound **[$^{17}O_1$]62. ^{17}O NMR ($CDCl_3$)**



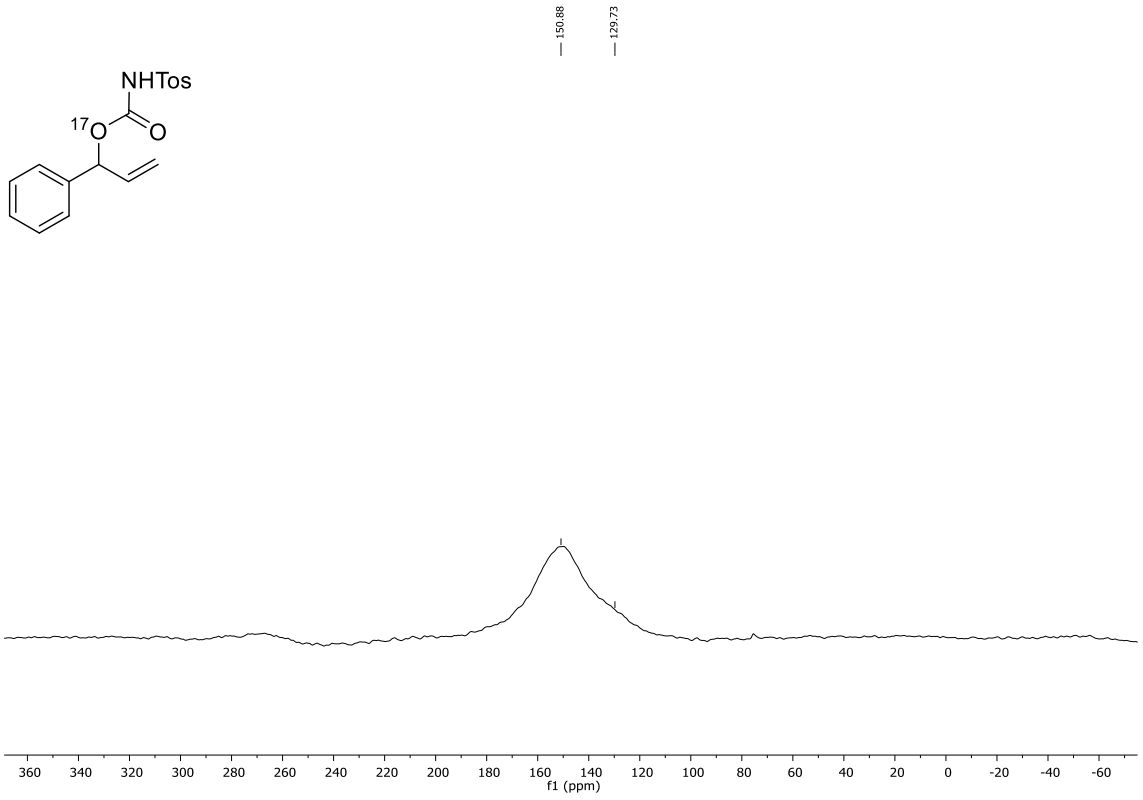
Compound **[$^{17}O_1$]63. ^{17}O NMR ($CDCl_3$)**



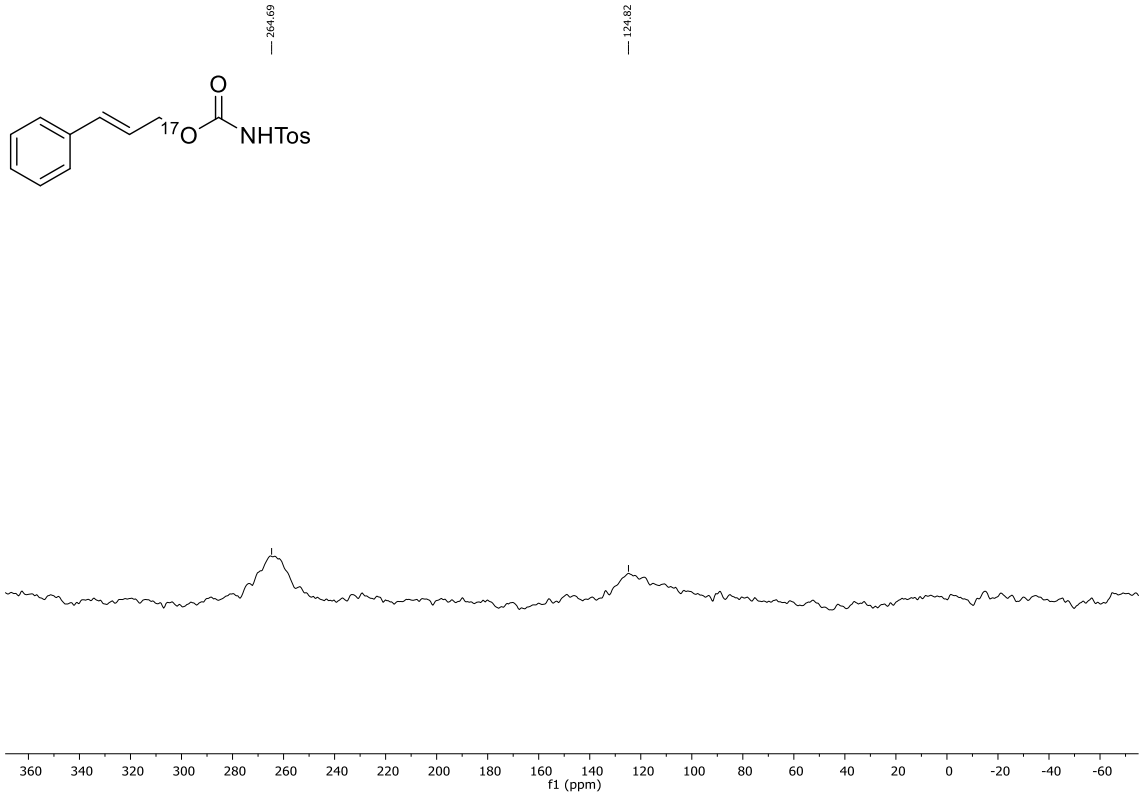
Compound **[$^{17}O_1$]34b. ^{17}O NMR ($CDCl_3$)**



Compound **[$^{17}O_1$]50b. ^{17}O NMR ($CDCl_3$)**

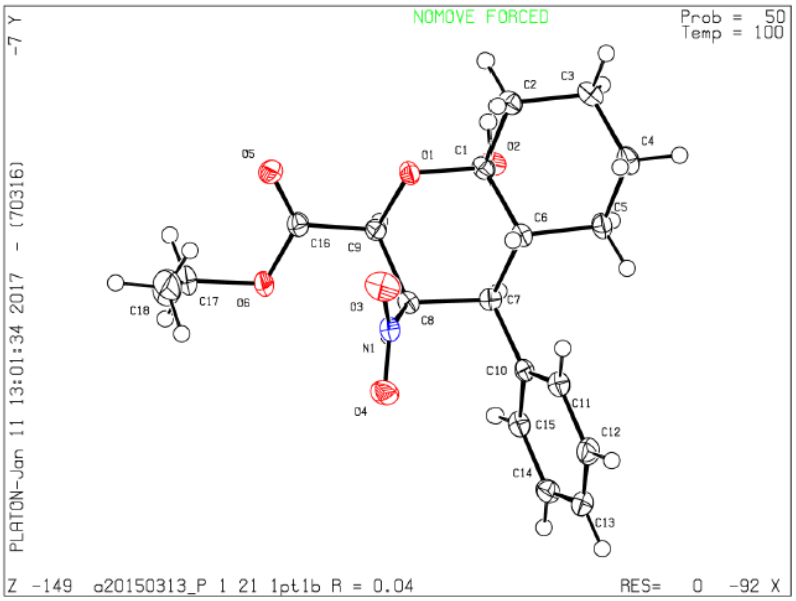


Compound **[$^{17}O_1$]51b. ^{17}O NMR ($CDCl_3$)**



Annex IV. X-Ray structures for Chapters 2, 3 and 4

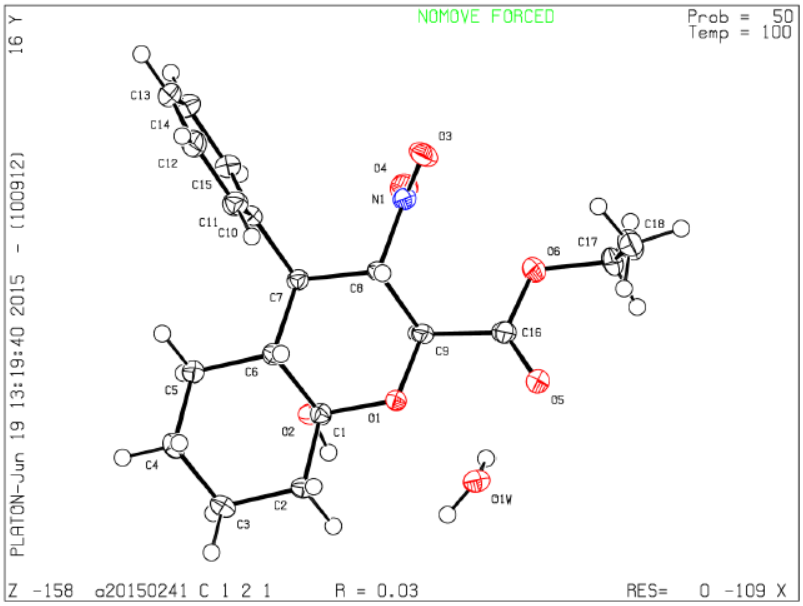
Compound **79aaa**



Crystal Data		Data Collection and Refinement	
Formula	C18 H23 N1 O6	Difractometer	Agilent SuperNova Cu
Formula Weight	349.37	Detector	CCD (Atlas)
Crystal System	monoclinic	Temperature (K)	100.01(10)
Space group	P 2_1 (No.4)	λ (CuKα) (Å)	1.54184
a (Å)	12.2192(6)	Monochromator	Óptica multicapa
b (Å)	5.5685(2)	Collimator (mm)	0.2
c (Å)	12.6363(6)	Scan mode	Rotación ω
α (°)	90	Scan width (°)	1.0
β (°)	90.969(4)	Time per frame (s) (Total, h)	2;8 (14)
γ (°)	90	Interval of θ (°)	3.62, 68.90
V (Å^3)	859.68(7)	(hkl) minimum	(-12 -6 -14)
Z (Z')	2(1)	(hkl) maximum	(14 6 15)
D_x (g·cm^{-3})	1.350	Reflections measures	10201
μ (CuKα) (mm^{-1})	0.844	Reflections independent (R_{int})	5436(0.075)
F (000)	372	Reflections observed [I>2σ(I)]	5245
Morphology	prism	Absorption correction	Multi-scan
Colour	colourless	Solution	OLEX2
Size (mm)	0.14x0.35x0.68	Refinement	SHELXL97(14/7)
		Number of parameters	229
		Number of restrictions	1
		Δ/σ maximum	0.000
		Δ/σ medium	0.000
		Δρ maximum (eÅ^{-3})	0.167
		Δρ minimum (eÅ^{-3})	-0.184
Friedel coverage	**97%**	S (GOF)	1.040
Flack *x*	**-0.23(18)**	Secondary extinction coefficient [b]	0
Hooft *y*	**0.29(4)**	R(F) (I>2σ, all)	0.0438, 0.0452
P2(wrong)	**<10^{-183}**	$R_w(F^2)$ [a] (I>2σ ,all)	0.1217, 0.1231

[a] Esquema de pesado: $1/[\sigma^2(F_o^2)+(0.0950P)^2+0.0957P]$ donde $P=[Max(F_o^2,0)+2F_c^2]/3$.
[b] Expresión de extinción secundaria tipo SHELXL: $F_c^* = kF_c[1+0.001F_c^2\lambda^3/sen(2\theta)]^{-0.25}$

Compound **79aaa'**



Crystal Data		Data Collection and Refinement	
Formula	$C_{18}H_{24}NO_{6.50}$ $C_{18}H_{23}NO_6$, 0.5(H_2O)	Difractometer	Agilent SuperNova Cu
Formula Weight	358.38	Detector	CCD (Atlas)
Crystal System	monoclinic	Temperature (K)	99.99(10)
Space group	C2 (No.5)	λ (CuKα) (Å)	1.54184
a (Å)	24.8420(5)	Monochromator	Optica multicapa
b (Å)	5.36209(11)	Collimator (mm)	0.2
c (Å)	13.5597(2)	Scan mode	Rotación ω
α (°)	90	Scan width (°)	1.0
β (°)	93.6312(16)	Time per frame (s) (Total, h)	2;8 (6)
γ (°)	90	Interval of θ (°)	3.27, 72.37
V (Å^3)	1802.59(6)	(hkl) minimum	(–30 –6 –17)
Z	4	(hkl) maximum	(30 6 17)
D_x (g·cm^{-3})	1.3219	Reflections measures	17859
μ (CuKα) (mm^{-1})	0.839	Reflections independent (R_{int})	3539(0.039)
F (000)	764	Reflections observed [I>2σ(I)]	3443
Morphology	needle	Absorption correction	Multi-scan
Colour	colourless	Solution	OLEX2
Size (mm)	0.07x0.08x0.45	Refinement	SHELXL97(14/7)
		Number of parameters	237
		Number of restrictions	1
		Δ/σ maximum	0.000
		Δ/σ medium	0.000
		Δρ maximum (eÅ^{-3})	0.170
		Δρ minimum (eÅ^{-3})	-0.200
Friedel coverage	**98%**	S (GOF)	1.043
Flack *x*	**-0.04(8)**	Secondary extinction coefficient [b]	0
Hooft *y*	**-0.01(6)**	R(F) (I>2σ$_I$, all)	0.0275, 0.0284
P2(wrong)	**<10^{-67}**	$R_w(F^2)$[a] (I>2σ$_I$,all)	0.0685, 0.0692

[a] Esquema de pesado: $1/[\sigma^2(F_o^2)+(0.0327P)^2+0.7962P]$ donde $P=[Max(F_o^2,0)+2F_c^2]/3$.
[b] Expresión de extinción secundaria tipo SHELXL: $F_c^* = kF_c[1+0.001F_c^2\lambda^3/sen(2\theta)]^{-0.4}$

Compound *exo* **17aa**

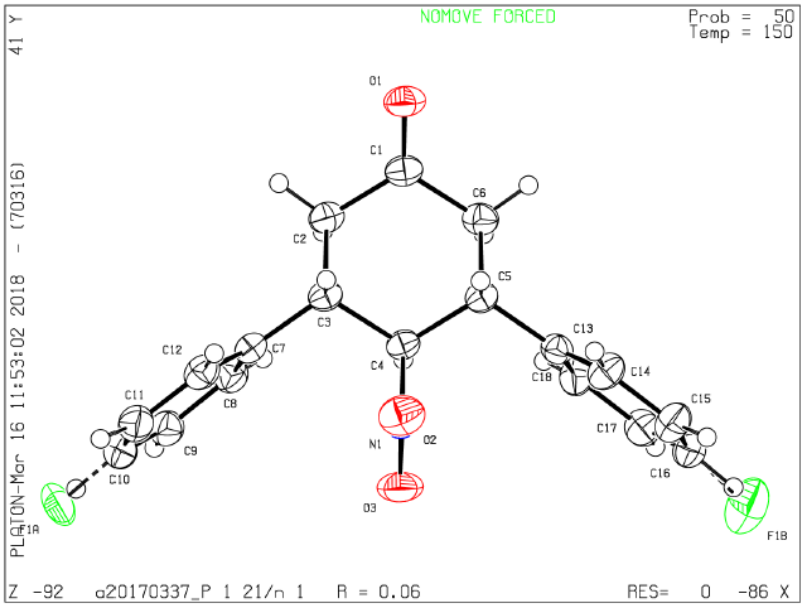
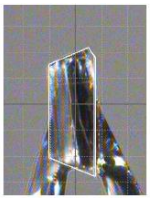


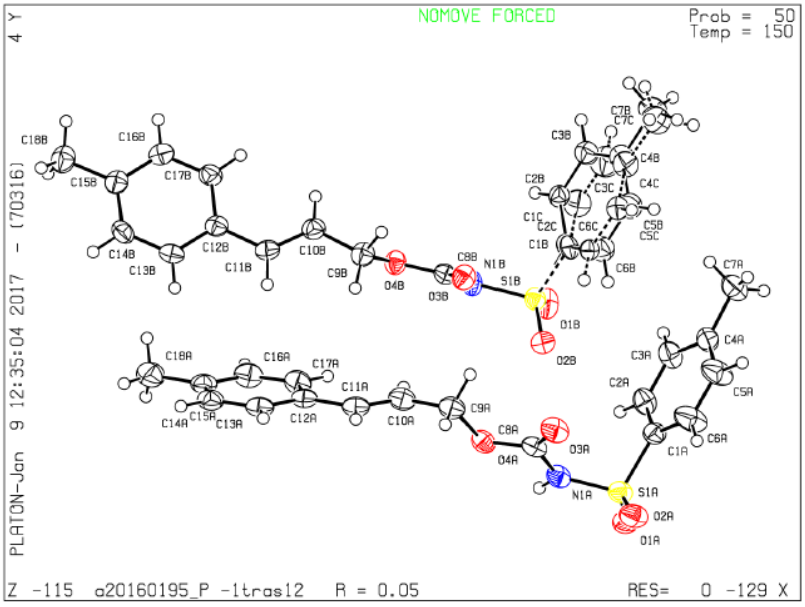
Table 1 Crystal data and structure refinement for a20170377_DA88FR23.

Identification code	a20170337_DA88fr23
Empirical formula	$C_{18}H_{16}FNO_3$
Formula weight	313.32
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.59500(10)
b/Å	13.7464(3)
c/Å	19.8100(3)
α/°	90
β/°	90.540(2)
γ/°	90
Volume/Å^3	1523.54(5)
Z	4
ρ_{calc}g/cm^3	1.366
μ/mm^{-1}	0.845
F(000)	656.0
Crystal size/mm^3	0.494 × 0.222 × 0.083
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.828 to 139.998
Index ranges	-5 ≤ h ≤ 6, -16 ≤ k ≤ 16, -24 ≤ l ≤ 24
Reflections collected	16792
Independent reflections	2891 [R_{int} = 0.0469, R_{sigma} = 0.0273]
Data/restraints/parameters	2891/2/217
Goodness-of-fit on F^2	1.191
R(F) (I>2σ(I), all)	0.0568, 0.0609
$R_w(F^2)^{[a]}$ (I>2σ(I), all)	0.1295, 0.1306
Largest diff. peak/hole / e Å^{-3}	0.33/-0.49



[a] Esquema de pesado: $1/[\sigma^2(F_o^2)+(0.0452P)^2+0.5260P]$ donde $P = [Max(F_o^2,0)+2F_c^2]/3$.
[b] Expresión de extinción secundaria tipo SHELXL: $F_c' = kF_c[1+0.001F_c^2\lambda^3/\sin(2\theta)]^{-0.5}$

Compound **51e** (***CCDC 1824810)***



Crystal Data	
Formula	C18 H19 N1 O4 S1
Formula Weight	345.4
Crystal System	triclinic
Space group	P -1 (No.2)
a (Å)	10.6301(4)
b (Å)	12.3190(3)
c (Å)	13.3645(5)
α (°)	95.356(2)
β (°)	92.661(3)
γ (°)	96.203(2)
V (Å^3)	1729.43(9)
Z (Z')	4(2)
D_x (g·cm^{-3})	1.327
μ (CuKα) (mm^{-1})	1.847
F (000)	728
Morphology	plate
Colour	colourless
Size (mm)	0.35x0.11x0.05

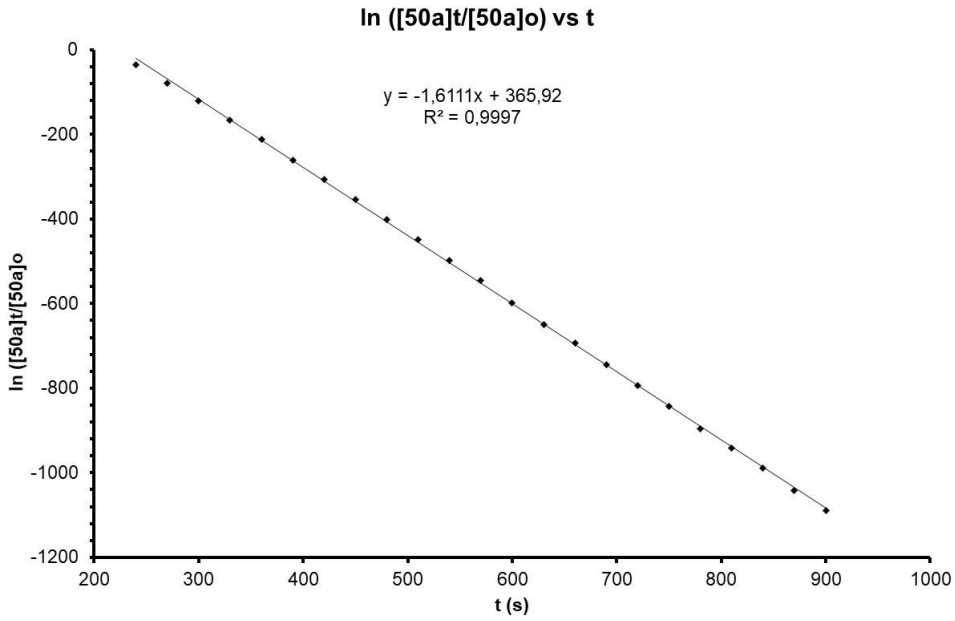
Data Collection and Refinement	
Difractometer	Agilent SuperNova Cu
Detector	CCD (Atlas)
Temperature (K)	150.01(10)
λ (CuKα) (Å)	1.54184
Monochromator	Óptica multicapa
Collimator (mm)	0.2
Scan mode	Rotación ω
Scan width (°)	1.0
Time per frame (s) (Total, h)	2;8 (14)
Interval of θ (°)	3.33, 68.98
(hkl) minimum	(-12 -12 -16)
(hkl) maximum	(12 14 16)
Reflections measures	13169
Reflections independent (R_{int})	6412(0.0440)
Reflections observed [I>2σ(I)]	5186
Absorption correction	Analytical
Solution	OLEX2
Refinement	SHELXL97(14/7)
Number of parameters	478
Number of restrictions	78
Δ/σ maximum	0.000
Δ/σ medium	0.000
Δρ maximum (eÅ^{-3})	0.474
Δρ minimum (eÅ^{-3})	-0.406
S (GOF)	1.047
Secondary extinction coefficient [b]	0
R(F) (I>2σ$_I$, all)	0.0525, 0.0651
$R_w(F^2)$[a] (I>2σ$_I$,all)	0.1359, 0.1467

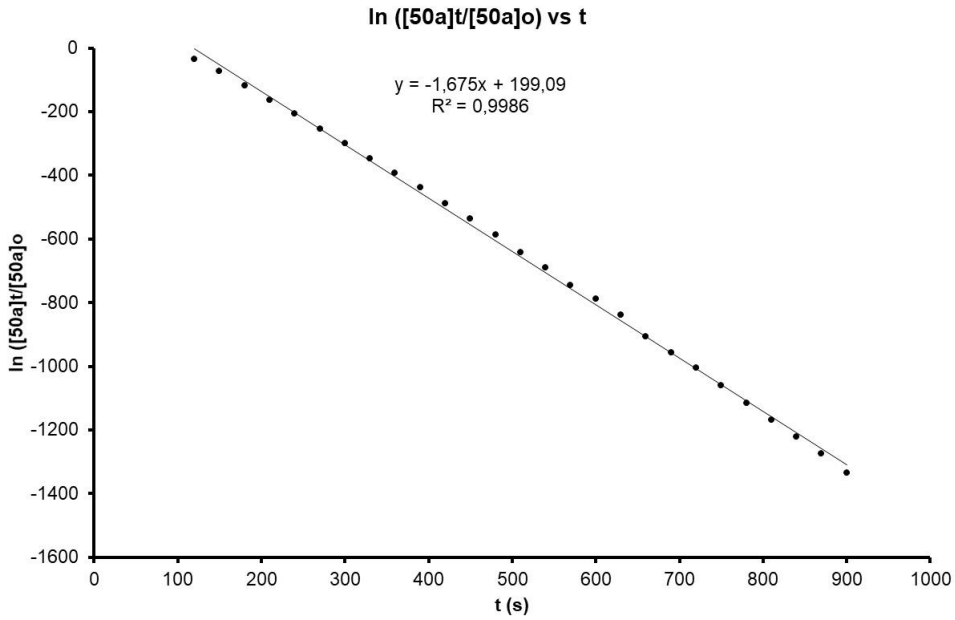
[a] Esquema de pesado: $1/[\sigma^2(F_o^2)+(0.0771P)^2+0.3670P]$ donde $P = [Max(F_o^2,0)+2F_c^2]/3$.
[b] Expresión de extinción secundaria tipo SHELXL: $F_c^* = kF_c[1+0.001F_c^2\lambda^3/sen(2\theta)]^{-1/4}$

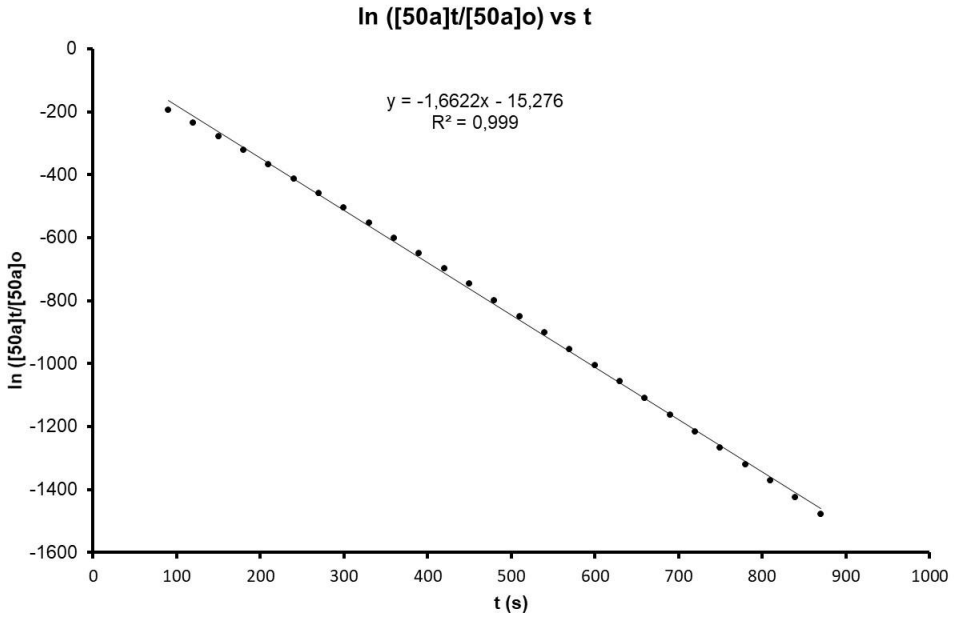
Annex V. Pseudo-first order linear plots, standard deviations and error calculation for Chapter 4

Pseudo-first order linear plots

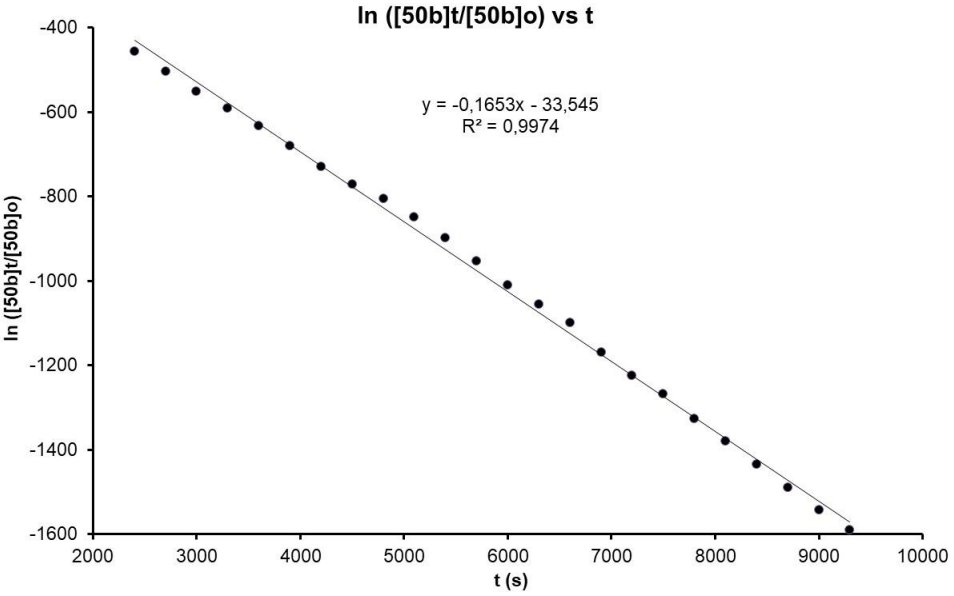
Compound **51a**

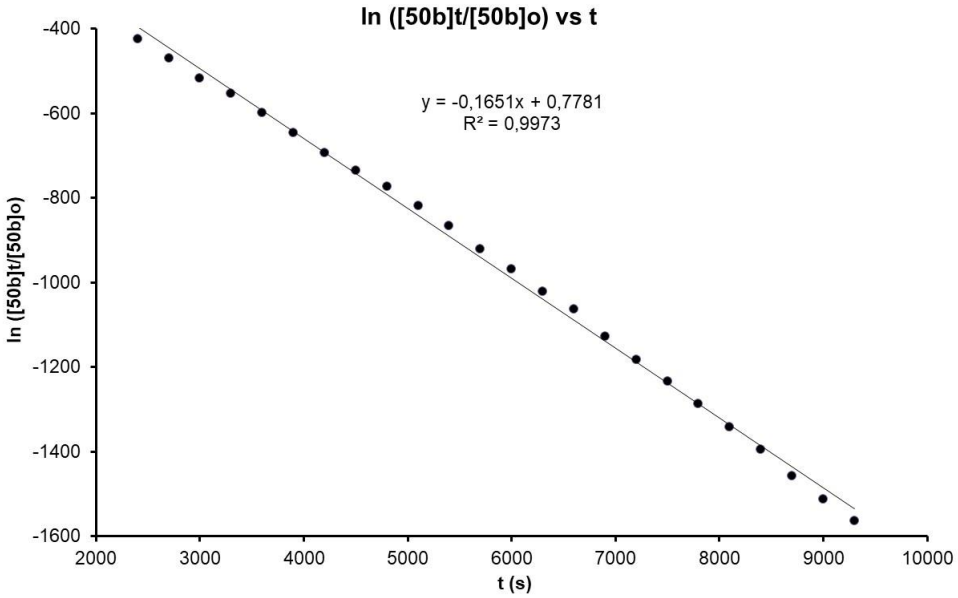


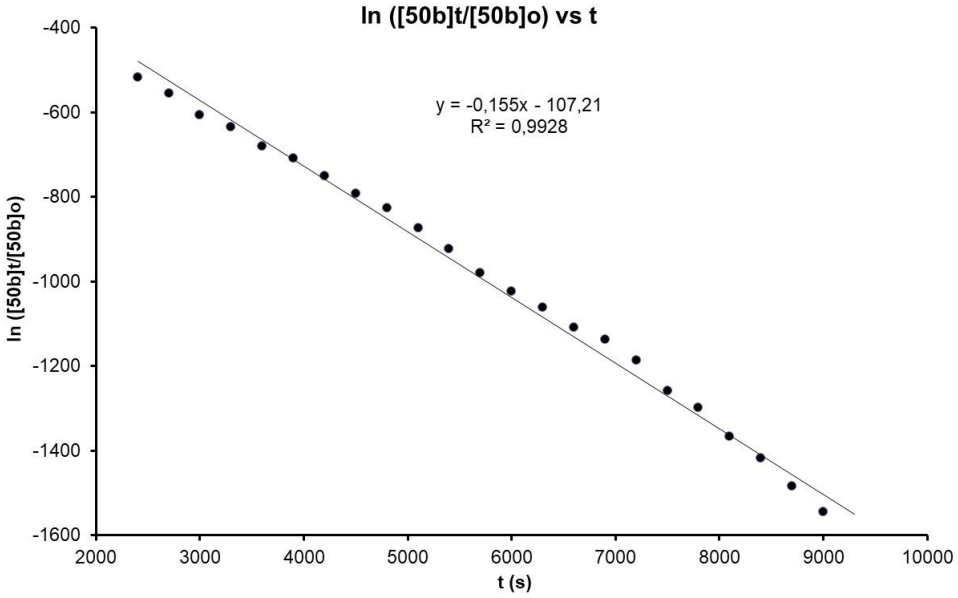




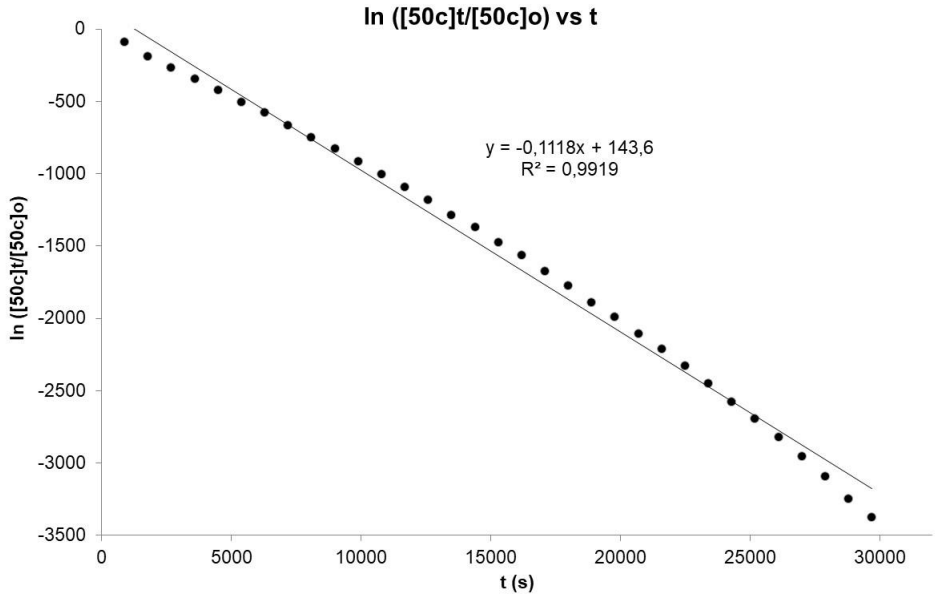
Compound **51b**

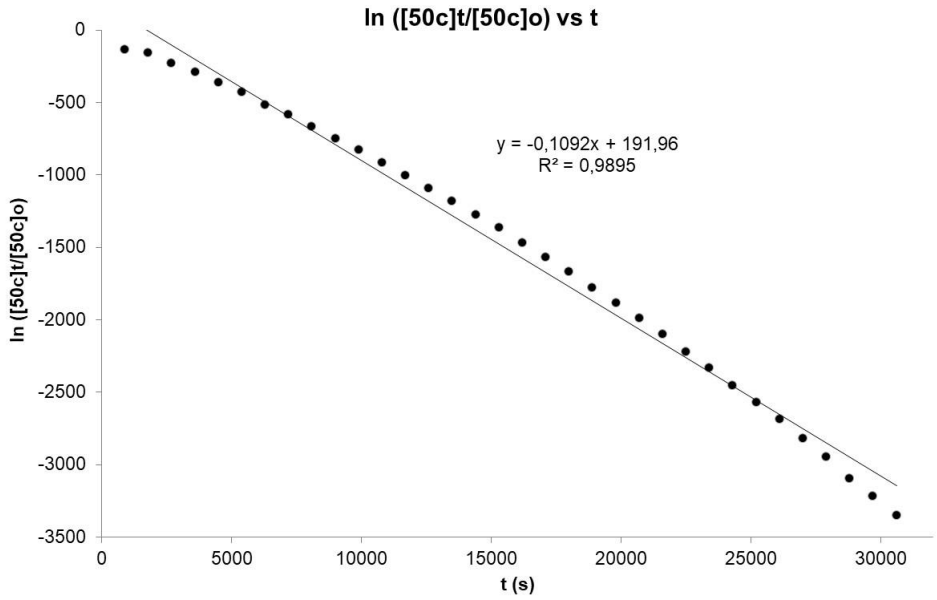


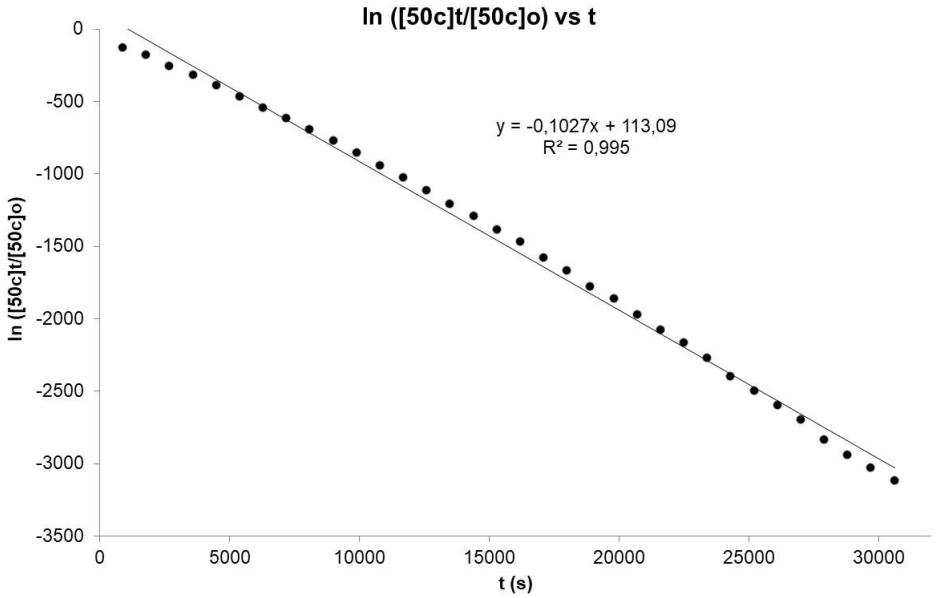

ln ([50b]t/[50b]o) vs t
y = -0,1651x + 0,7781
R² = 0,9973
ln ([50b]t/[50b]o)
t (s)
-400
-600
-800
-1000
-1200
-1400
-1600
2000
3000
4000
5000
6000
7000
8000
9000
10000


ln ([50b]t/[50b]o) vs t
y = -0,155x - 107,21
R² = 0,9928
ln ([50b]t/[50b]o)
t (s)
-400
-600
-800
-1000
-1200
-1400
-1600
2000
3000
4000
5000
6000
7000
8000
9000
10000

Compound **51c**







Standard deviations and error calculations. Errors for k_{obs} were calculated employing the standard deviation (*s*) in equation 1:[1]

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2} \qquad (1)$$

where

X stands for the different kobs values calculated by ^{1}H NMR.

$\bar{X}$ is the average k_{obs}.

n is the number of values (k_{obs}) in the final calculations.

[1] a) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem*. **2002**, *67*, 3479-3486. b) Kudryavtsev, K. V.; Tsentalovich, M. Y.; Yegorov, A. S.; Kolychev, E. L. *J. Het. Chem*. **2006**, *43*, 1461-1466.

^{17}O NMR Spectra at natural abundance

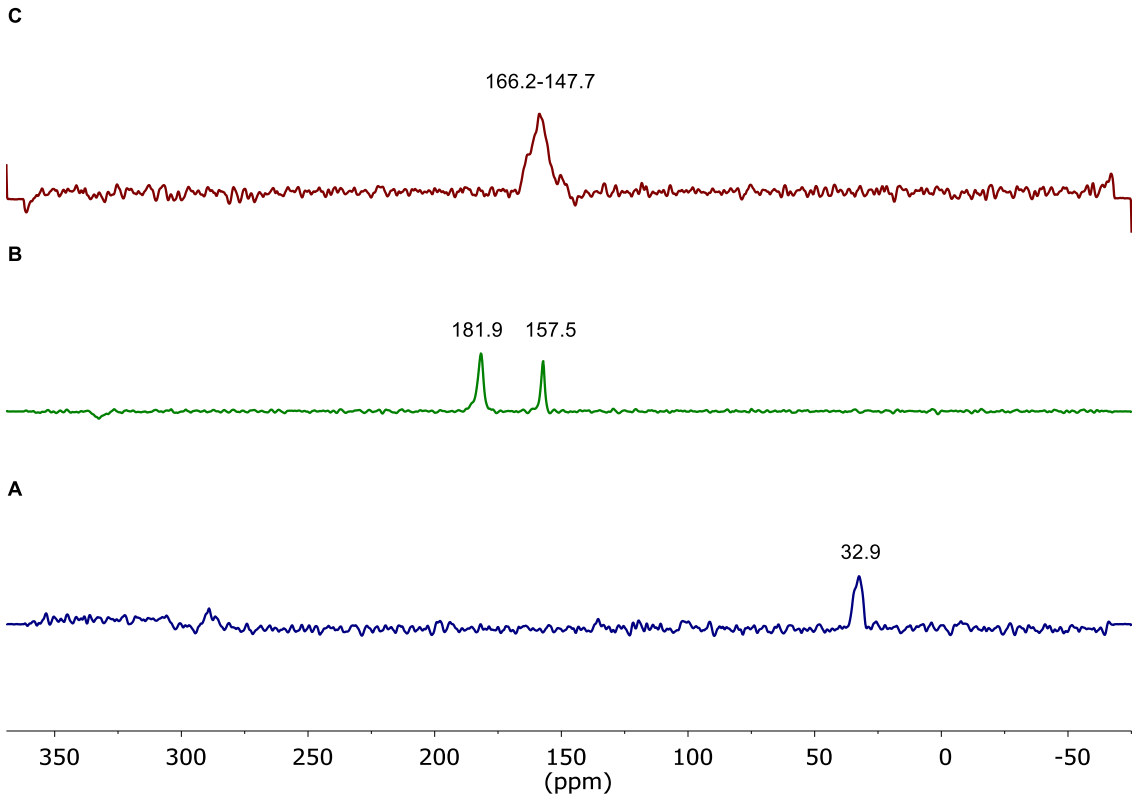


Figure 1. ^{17}O NMR spectra recorded at natural abundance in $CDCl_3$ on Brucker Avance Neo 500 MHz spectrometer equipped with BBOF probe with gradient in Z-axis (^{17}O frequency 67.79 MHz). The δ (^{17}O) chemical shifts of the non-labelled compounds are given in ppm. A) Compound **34b**. B) *p*-toluenesulfonyl isocyanate. C) Reaction of **34b** with *p*-toluenesulfonyl isocyanate at r.t. to yield carbamate intermediate **50b**.

Nire atton-amonei

eman ta zabal zazu
Universidad del País Vasco
Euskal Herriko Unibertsitatea

KARBONO-KARBONO LOTURA BERRIEN FORMAZIO ERREAKZIO ORGANOKATALITIKO ETA ESTEKIOMETRIKOEI BURUZKO IKERKETAK

Doktoretza Tesia

Maddalen Agirre Goikoetxeaundia

Donostia

2019

Hasteko, eskerrak eman nahi dizkizut Fernando, zure ikerketa taldean jaso eta zientziaz dakidan guztia erakusteagatik, baita ibilbide honetan zehar behar izan ditudan aholkuak eskaintzeagatik ere. Ana, zuri mila esker behar izan dudan guztian laguntzeagatik. Eusko Jaurlaritzari Doktoretza Tesia burutzeko beharrezkoa izan den finantziazio ekonomikoa zor diot. Graci, eskerrik asko por enseñarme a trabajar en el laboratorio, por ayudarme a desarrollar mi criterio científico, por la paciencia, por ayudarme a distancia, y por muchas razones más.

Je voudrais également remercier mes collègues français de m'avoir accueillie en 2015. François, pour votre compréhension et votre aide lorsque j'en ai eu le plus besoin. Bertrand et Aurélie, pour avoir rendu mon quotidien beaucoup plus supportable et m'avoir aidé à tout moment avec les techniques de laboratoire qui m'étaient inconnues jusqu'alors. Je remercie énormément Fabienne et, bien sûr, Sylvain (mon ami français) de m'avoir accompagnée pendant les longs week-ends et de son soutien alors que j'étais loin de chez moi.

Por ayudarme con las incontables dudas en la caracterización de compuestos y en las diversas técnicas de RMN que he necesitado, gracias J.I.

Por hacerme desconectar del mundo de la ciencia, por vuestro apoyo diario y por todas las muestras de cariño, eskerrik asko Celsi y Arancha. Os debo mucho.

Egunero pasiluaz bestalde zuen atea irekitzen nuen bakoitzean irrifarre batekin harrera egiteagatik eta zuekin izan ditudan milaka elkarrizketa eta momentu onengatik, eskerrikasko bizilagunak. Arkaitz, Itzi eta Markos aipamen berezia merezi duzue parrafo honetan, bihotzez eskertzen dizuet dena.

Ez daukat inolako dudarik nire Doktoretza Tesi hau ez litzatekeela den bezalakoa izango nire laborategiko lagunak hor izan ez balira. Asko izan zarete eta zarete, eta denek zuen ekarpena izan duzue nire egunerokotasunean. Esker haundi bat zuentzat. En especial a Tamara ; te debo millones de gracias por tu ayuda y todo el tiempo compartido. A mi amiga mexicana Arlette, por tu alegría y apoyo transatlántico. Dudarik gabe, nire eskerrik beroenak nire mutilentzat: Javi, Aitor, Miquel eta Mikel. Ez dut hitzik sentitzen dudan esker guztia behar bezela adierazteko. Gauza bat argi daukat, ordea, zuei esker irrifarre bat izan dut ahoan egunero, ia momentuero, eta horrek ez du preziorik.

Nire kuadrilari. Gure taldearen parte sentitzeaz harro nago. Zuekin deskonektatzen dut eta zientziaz kanpo mundu izugarria badela ikusi. Uste ez baduzue ere, nere sostengua zarete. Mila momentugatik, bihotz-bihotzez mila esker. Bizitzak zuen ondoan urte asko niretzat gordeta izatearen esperantza daukat. Asko maite zaituztet.

Nire familia osoari.

Anderri eta Markeli, egunero etxera iristean eskaini didazuen harreragatik, zuen laguntzagatik. Amari eta aitari. Nire eredu zarete. Esforzuaren balioa txiki-txikitatik erakusteagatik. Beti, beti laguntzeagatik eta nire ametsak gogor jarraitzea zeinen garrantzitsua den erakusteagatik. Ez dut ia inoiz esaten, baino asko maite zaituztet denoi.

Doktoretza Tesi hau Kimika Fakultateko Kimika Organikoa I Sailan burutu da, Donostian, Fernando P. Cossío Mora Katedraduna eta Mª de Gracia Retamosa Hernández Doktorearen gidaritzapean.

2015eko Iraila eta Abendu artean ikerketa egonaldi laburra burutu zen Rennesen (Frantzia) Institut de Sciences Chimiques de Rennes ikerketa zentroan (UMR CNRS 6226 Ikerketa Unitatea), François Carreaux Doktorearen gidaritzapean.

Doktoretza Tesi hau bi atal nagusitan banatzen da, A eta B. A Atalak azterketa organokatalitikoak biltzen ditu, eta hiru Kapitulu nagusitan zatituta dago. 1. Kapituluak kiralitate kontzeptua eta sintesi asimetrikoko hurbilketak garatzen ditu, aminoazido ez-naturaletatik eratorritako organokatalizatzaileen xehetasunak izendatuz. 2. Kapituluak Michael-Henry-Azetalizazio erreakzioa aztertzen du funtzionalizazio altuko tetrahidropirano eraztunen sintesirako. 3. Kapituluak, azkenik, prolina ez-naturaletatik eratorritako organokatalizatzaileak zetona α,β-asegabeen eta nitroalkenoen arteko Diels-Alder erreakzioan aplikatzen ditu. B Atalak, bestalde, 4. Kapitulua biltzen du, eta ikerketa egonaldian landutako [3,3]-berrantolaketa sigmatropikoko emaitzak elkartzen ditu. Substratuen egokitasunaz gain, ikerketa zinetiko zein isotopikoak azaltzen ditu, baita kiralitate transferentzia azterketak ere.

Taula, irudi, eskema eta erreferentzien zenbaketa independientea da Kapitulu bakoitzarentzat. Prolina ez-naturaletan oinarritutako lehen, bigarren eta hirugarren generazioko organokatalizatzaileek zenbaki berdinak izango dituzte 2 eta 3 Kapituluetan, ulermen errazagorako.

ARGITALPEN ZERRENDA

1. *Enantioselective Ring-Opening Polimerization of rac-Lactide Dictated by Densely Substituted Amino Acids.* Sánchez-Sánchez, A.; Rivilla, I.; Agirre, M.; Basterretxea, A.; Etxeberria, A.; Veloso, A.; Sardón, H.; Mecerreyes, D.; Cossío, F. P. *J. Am. Chem. Soc*. **2017**, *139*, 4805-4814.

2. *Organocatalysts Derived from Unnatural α-Amino Acids: Scope and Applications*. Agirre, M.; Arrieta, A.; Arrastia, I.; Cossío, F. P. *Chem. Asian. J*. **2018**. DOI: 10.1002/asia.201801296.

3. *1,3-Dioxa-[3,3]-sigmatropic Oxo-Rearrangement of Substituted Allylic Carbamates: Scope and Mechanistic Studies*. Agirre, M.; Henrion, S.; Rivilla, I.; Miranda, J. I.; Cossío, F. P.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. *J. Org. Chem*. **2018**, *83*, 14861-14881.

4. *Additive and Emergent Catalytic Properties of Dimeric Unnatural Amino Acid Derivatives: Aldol and Conjugate Additions.* Retamosa, M. G.; Ruiz-Olalla, A.; Agirre, M.; de Cózar, A.; Bello, T.; Cossío, F. P. *Manuscript in Preparation*.

5. *Synthesis of Highly Substituted Bicyclic Tetrahydropyrans by Organocatalysed Michael-Henry-Acetalisation Cascade Reactions*. Agirre, M.; Bello, T.; Retamosa, M. G.; Cossío, F. P. *Manuscript in Preparation*.

KARBONO-KARBONO LOTURA BERRIEN FORMAZIO ERREAKZIO ORGANOKATALITIKO ETA ESTEKIOMETRIKOEI BURUZKO IKERKETAK

A ATALA: AZTERKETA ORGANOKATALITIKOAK

1. Sarrera

2. Michael-Henry-Azetalizazio Kaskada Erreakzio Organokatalitiko Bidezko Ordezkapen Altuko Tetrahidropirano Biziklikoen Sintesia

3. Funtzionalizazio Altuko g-Dipeptidoek Katalizatutako Zetona α,β-Asegabeen eta Nitroalkenoen arteko Diels-Alder Erreakzio Organokatalitikoak

AKRONIMO ETA LABURDURAK

A	Azidoa
AcOEt	Etil azetatoa
ACN	Azetonitriloa
Ala	Alanina
Asp	Azido Aspartikoa
Ar	Ariloa
B	Basea
BINAP	(2,2'-bis(difenilfosfino-1,1'-binaftilo)
BINOL	1,1'-bi-2-naftola
Bn	Benziloa
Boc	*tert*-butoxikarboniloa
br	Broad (seinale zabala)
^{n}Bu	Butiloa
^{t}Bu	*tert*-butiloa
cat.	Katalizatzailea
COSY	Correlation Spectroscopy
d	Eguna(k)
d	Dobletea (NMR)
dd	Doble dobletea (NMR)
DABCO	1,4-diazabiziklo[2.2.2]oktanoa
DBSA	Azido *para*-dodezil benzenosulfonikoa
DBU	1,8-diazabiziklo(5.4.0)undek-7-enoa
DET	Dietil tartratoa
de	Soberakin diastereomerikoa
DIPEA	*N*,*N*-diisopropiletil amina
DiPAMP	1,2-bis[(2-metoxifenil)(fenilfosfino)] etanoa
DMAP	4-dimetilaminopiridina
DMF	*N*,*N*-dimetil formamida

DMSO	Dimetil sulfoxidoa
DNA	Azido deoxiribonukleikoa
DNBSA	Azido 2,4-dinotrobenzenosulfonikoa
dr	Erlazio diastereomerikoa
EDG	Talde elektroi emailea
ee	Soberakin enantiomerikoa
ent	Enantiomeroa
eq.	Baliokidea(k)
ESI	Elektroesprai ionizazioa
Et	Etiloa
$Eu(hfc)_3$	Europio(III) tris[3-(heptafluoropropilhidroximetileno)-*d*-kanforatoa]
EWG	Talde elektroi erakarlea
FTIR	Espektroskopia infragorria
Gln	Glutamina
Glu	Azido glutamikoa
g.t.	Giro tenperatura
h	Ordua(k)
Hex	Hexanoa
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest Occupied Molecular Orbital
HPLC	Presio Handiko Isurkinen Kromatografia
HRMS	Erresoluzio Handiko Masa Espektrometria
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertzio
INT	Artekaria
J	Akoplamendu konstantea
konb.	Konbertsioa
Leu	Leuzina
LiICA	Litio *N*-isopropilziklohexilamida

Ln	Logaritmo nepertarra
LUMO	Lowest Unoccupied Molecular Orbital
m	Multipletea (RMN)
Me	Metiloa
mg	Miligramo
mmol	Milimol
MMPP	Magnesio monoperoxiftalatoa
min	Minutu
mL	Mililitro
MPEG	Poli(etilenglikol) metil eterra
MS	Masa espektrometria
MS	Bahe molekularra
N_D	*Endo*-D
N_L	*Endo*-L
NMM	*N*-metilmorfolina
NMP	*N*-metil-2-pirrolidinona
NMR	Erresonantzia Magnetiko Nuklearra
NOESY	Nuclear Overhauser Spectroscopy
Nu	Nukleozalea
Ns	Nosiloa
P	Produktua
PCC	Piridina klorokromatoa
PEG	Polietilen glikola
^{n}Pent	Pentiloa
PFBA	Azido pentafluorobenzoikoa
Ph	Feniloa
Phe	Fenilalanina
PNBA	Azido *para*-nitrobenzoikoa
PPG	Polipropilen glikola
Pro	Prolina
^{i}Pr	*iso*-propila
PS	Poliestirenoa

PTM	Aldaketa post traslazionala
PTSA	Azido *para*-toluensulfonikoa
PyBOP	(benzotriazol-1-il-oxi)tripirrolidinofosfonio hexafluorofosfatoa
R	Hautazko ordezkaria
RNA	Azido erribonukleikoa
R.T..	Erretentzio denbora
s	Singletea (NMR)
S	Substratua
sc	Superkritikoa
SOMO	Singly Occupied Molecular Orbital
t	Denbora
t	Tripletea (NMR)
T	Tenperatura
TBDMS	*tert*-butildimetilsilila
TBDPS	*tert*-butildifenilsilila
TBAB	Tetrabutilamonio bromuroa
TFA	Azido trifluoroazetikoa
Tf_2O	Anhidrido trifluorometanosulfonikoa
TFT	α,α,α-trifluorotoluenoa
Tf	Trifluorometano sulfoniloa
THF	Tetrahidrofuranoa
THP	Tetrahidropiranoa
TIPS	Triisopropilsilila
TLC	Geruza meheko kromatografia
TMS	Trimetilsilila
Tos	*p*-toluenosulfoniloa
t_R	Erretentzio denbora
Ts	Tosiloa
TS	Trantsizio egoera
u_p	Urtze puntua
vs.	Versus

X_D	*Exo*-D
X_L	*Exo*-L
zg	Zehaztugabea

A ATALA

Azterketa Organokatalitikoak

1. Kapitulua

Sarrera

Abstract: The organocatalytic properties of unnatural α–amino acids are reviewed. Post translational derivatives of natural α–amino acids include 4-hydroxy-*L*-proline and 4-amino-*L*-proline scaffolds, as well as proline homologues. Synthetic unnatural α–amino acid-based organocatalysts whose activity has been reviewed include β–prolines and unnatural pyrrolidine-based derivatives. The organocatalytic properties of unnatural monocyclic, bicyclic and tricyclic proline derivatives are also reviewed. Several families of these organocatalysts permit the efficient and stereoselective synthesis of complex natural products. Most of the reviewed organocatalysts accelerate the reported reactions via HOMO raising (enamine intermediates) or LUMO lowering (iminium intermediates) covalent interactions.

Kapitulu hau review baten atal nagusi bezala argitaratu da: Agirre, M.; Arrieta, A.; Arrastia, I.; Cossío, F.P. *Chem. Asian J.* **2018**. DOI: 10.1002/asia.201801296

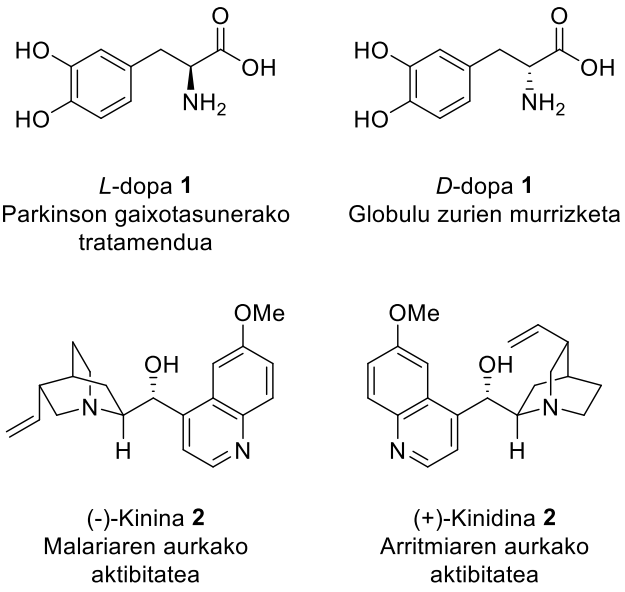
1.1 KIRALITATEA

Kiralitatea materiaren propietate bateratzaile bezala kontsidera daiteke: unibertsoa, berezko eran, asimetrikoa da.[1] Kiralitate moduan ezagutzen den ezaugarri geometrikoa Lord Kelvinek deskribatu zuen 1884. urtean: “edozein figura geometriko edo puntu sortari kiral deitzen diot, edota kiralitatea daukala esan, bere ispilu irudiak, idealki eginda, harekin berarekin bat egiten ez badu”.[2] Kiralitate kontzeptua *cheir* (eskua) hitz grekotik eratorri da eta asimetria molekularrak eragindako egitura kristalinoaren ezker edo eskuintartasuna deskribatzeko erabiltzen da.[3]

Maila molekularrean, kiralitateak elementu estereogenikoren bat eta erreflexio simetriarik ez duen edozein molekulari egiten dio erreferentzia. Testuinguru honetan, gainezartezinak diren ispilu irudi pareari enantiomero esaten zaie. Ongi ezaguna da ere bizitzak kiralitate molekularrarekiko duen menpekotasuna. Izan ere, gorputzeko errezeptore kiralek konfigurazio absolutu zehatza duten molekula txikiekin besterik ez dute elkarrekintza egiten.[4]

Molekularen kiralitateak eta aktibitate farmakologikoak duten erlazioa aditzera eramaten duten adibide dexente aurki daitezke industria farmazeutikoan (**1.1 Irudia**). Esaterako, kininak malariaren aurkako aktibitatea erakusten duen bitartean, bere kinidina enantiomeroak arritmiaren aurkako propietateak ditu. Bestalde, *L*-doparen (Parkinsonaren tratamenduan erabilia) *D*- enantiomeroa ez da inoiz medikuntza arloan erabili, globulu zurien urritasuna eta infekzioekiko suszeptibilitatea sortzen baititu.[5] Honelako arazoak direla medio, enantiomero-bakarreko sendagaien eskariak bultzada handia jasan du, katalisi asimetriko moduan ezagutzen den alorraren garapena sustatuz.

[1] Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **2000**, *11*, 2845-2874.
[2] Francotte, E.; Lindner, W. *Chirality in Drug Research*, Wiley-VCH: Weinheim, **2006**.
[3] Chhabra, N.; Aseri, M. L.; Padmanabhan, D. *Int. J. Basic Med. Res*. **2013**, *3*, 16-18.
[4] Noyori, R. *Adv. Synth. Catal*. **2003**, *345*, 15-32.
[5] Cotzias, G. C.; Papavasiliou, P. S.; Gellene, R. *New. Engl. J. Med*. **1969**, *280*, 337-345.



L-dopa **1**
Parkinson gaixotasunerako tratamendua

D-dopa **1**
Globulu zurien murrizketa

(-)-Kinina **2**
Malariaren aurkako aktibitatea

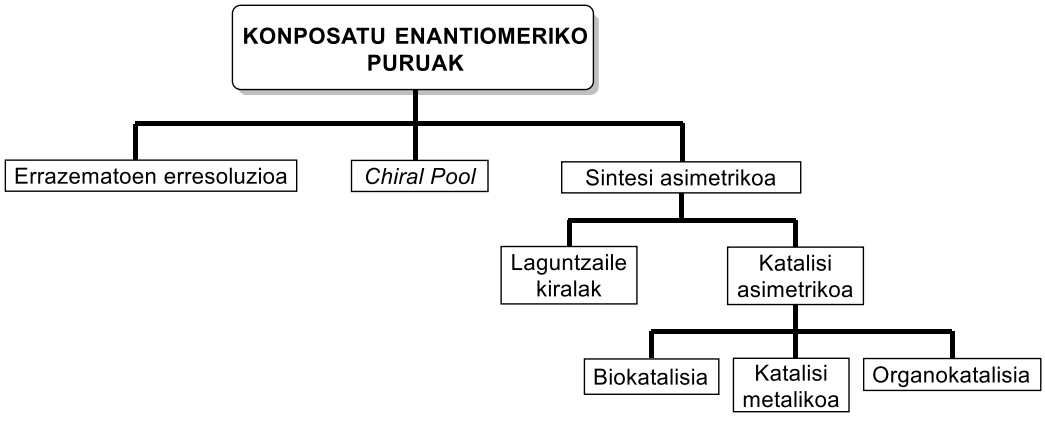
(+)-Kinidina **2**
Arritmiaren aurkako aktibitatea

1.1 Irudia. Enantiomero bakoitzaren aktibitate biologikoa.

1.2 KONPOSATU ENANTIOMERIKO PURUEN LANKETARAKO ESTRATEGIAK

Enantiomero bakarreko konposatuak sortzeko metodologia sintetiko ugari daude. Metodologia hauek egokitzat hartzeko, ondorengo ezaugarriak bete behar dituzte: 1) enantiomeroaren eraketa etekin kimiko zein soberakin enantiomeriko altuarekin lortzea; 2) konposatu purua languntzaile kiraletik erraz bereizi ahal izatea; eta 3) beharrezkoa denean, laguntzaile kirala soberakin enantiomeriko galerarik gabe berreskuratzea.[6]

Hiru hurbilketa orokor daude konposatu enantiomeriko puruak lortzeko: a) errazematoen erresoluzioa; 2) *Chiral Pool* estrategia; eta 3) sintesi asimetrikoa (**1.2 Irudia**).



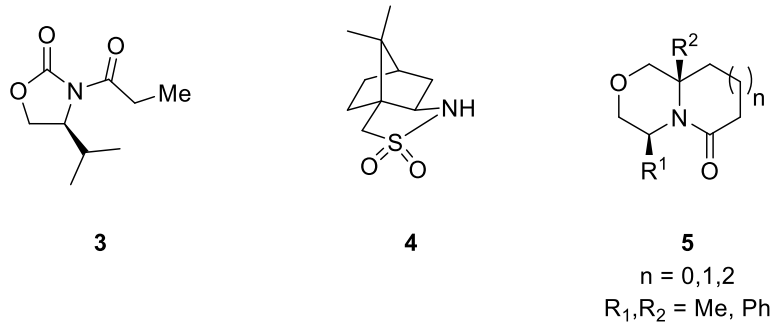
1.2 Irudia. Konposatu enantiomeriko puruak lortzeko estrategiak.

[6] Scheffold, R. *Modern Synthetic Methods, Conference Papers of the International Seminar on Modern Synthetic Methods*, Springer-Verlag: Berlin, **1986**.

Errazematoen erresoluzioa[7] oso teknika erabilia da gaur egun industrian, eta bertan, substratu errazemikoek eta laguntzaile kiralek diastereomero nahasteak sortzen dituzte, teknika fisiko zein kimiko egokien bidez bana daitezkeenak. *Chiral Pool* teknikan, bestalde, kiralitate iturria naturako karbohidrato, aminoazido, hidroxiazido edota terperno enantiopuruetatik dator. Hauek, amaierako produktuaren egituraren barne izango dira gainera, elementu estereogenikoetan inolako aldaketarik jasan gabe.[8] Azkenik, *sintesi asimetrikoak* elementu kiralak laguntzaile[9] edota katalizatzaile[10] kiralen bidez substratu prokiralean sartzen ditueneko metodologiak elkartzen ditu.

1.2.1 Laguntzaile kiralak

Laguntzaile kiralek substratu prokiralaren eta entitate kiralaren behin-behineko lotura kobalentea dute oinarri. Elementu kiral berrien formazioa diastereoselektibitate handiarekin gauzatu behar da, eta diastereoisomero hauen banaketa erraza zein laguntzaile kiralaren birziklapena ezinbestekoak dira. Hala ere, laguntzaile kiralaren kantitate estekiometrikoak nahitaezkoak direnez, transformazioak pausu sintetiko gehiagoren premia du. Literaturan aurki daitezkeen laguntzaile kiral esanguratsuenak Evansen oxazolidinona **3**[11], Oppolzerren sultama **4**[12] eta Meyerren laktama biziklikoa **5**[13] dira (**1.3 Irudia**).



1.3 Irudia. Laguntzaile kiral esanguratsuak.

1.2.2 Katalisi asimetrikoa

Katalisi asimetrikoak bilakaera azkarra jasan du azken hamarkadetan, laguntzaile kiralek beharrezko dituzten kantitate estekiometrikoak gutxitu asmoz. Teknika honek

[7] Anderson, N. G. *Org. Proc. Res. Dev*. **2005**, *9*, 800-813.
[8] Muñoz-Torrero, D. *Recent Advances in Pharmaceutical Sciences II*, Transworld Research Network: Kerala, **2012**.
[9] Roos, G. *Key Chiral Auxiliary Applications*, Academic Press: New York, **2014**.
[10] McNaught, A. D.; Wilkinson, A. *IUPAC: Compendium of Chemical Terminology 2nd Ed*, Blackwell Scientific Publications: Oxford, **1997**.
[11] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737-1739.
[12] Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett*. **1989**, *30*, 5603-5606.
[13] Meyers, A. I.; Brengel, G. P. *Chem. Commun*. **1997**, 1-8.

molekula kiral baten kantitate subestekiometrikoak erabiltzen ditu informazio kirala lekuz aldatzeko, enantiomero bakarra sortzen duen erreakzioa selektiboki azkartuz. Nicolaouk jakinarazi bezala, “erreakzio katalitiko asimetriko batean enantiomerikoki purua den katalizatzaile kantitate txiki batek (enzima zein trantsizio metalez osaturiko konplexu disolbagarri sintetikoa) kirala edo akirala izan daitekeen molekula aintzindari batetatik optikoki aktiboa den konposatu baten kantitate handiak sortzen ditu”.[14] Orokorrean, katalisi asimetrikoa gehiegizko pausu sintetikoak saihesten dituen metodologia zuzena bihurtu da.

Katalisi asimetrikoaren eremuan bi metodologia eraginkor nagusi hartu dira kontuan azken urteotan: *biokatalisia*[15] eta *konplexu metaliko sintetikoen erabilera*[2]. Lehenean entzimek edo entzimetan oinarritutako konposatuek azkartzen dute erreakzio kimikoa. Bigarrenak, ordea, gutxienez zentro metaliko bat duen katalizatzaile kiralaren kantitate txiki baten eta substratuaren arteko konbinazioa du oinarri, konposatu kirala modu estereoselektiboan lortuz. Abantaila asko izan arren, konplexu organometalikoak garestiak izan ohi dira eta erreakzio baldintza zehatz eta zorrotzak behar dituzte emaitza egokiak lortzeko. Bestalde, metalen toxikotasunak ingurumena kutsa dezake eta metala amaierako produktutik kentzeak zailtasun ugari sor ditzake. Jakina da ere naturak ez duela kofaktore metalikorik erabiltzen burutzen dituen prozesu biokatalitiko gehienetan. Beraz, komunitate zientifikoak esfortzu ugari egin du metalik gabeko prozedura sintetikoen bilakaera bultzatzen. Honela, molekula organiko txikietan oinarritutako metodologia katalitikoek (*organokatalisia*) eboluzio izugarria lekukotu dute.[16]

1.3 ORGANOKATALISI ASIMETRIKOA

Organokatalisia bere baitan atomo metalikorik ez duen molekula organiko kiralen kantitate subestekiometrikoen erabilpenean oinarritzen da.[17] Teknika honek abantaila ugari ditu katalisi organometalikoarekin alderatuz, toxikotasun eza eta sintesirako erraztasuna, esaterako. Bereziki interesgarria suertatzen da ere katalizatzaileen oxigeno eta hezetasunarekiko egonkortasuna, erreakzioak baldintza leunetan burutzeko aukera emanez. Gainera, funtzio talde ugari erabili daitezke eta ez dago protekzio-desprotekzio

[14] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods,* Wiley-VCH: Weinheim, **1996**.
[15] a) Drauz, K.; Waldmann, H. Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook, Wiley-VCH: Weinheim, 2002. b) Schramm, V. L. Chem. Rev. 2006, 106, 3029-3030. c) Patel, R. N. Coord. Chem
[16] List, B.; Yang, J. W. *Science* **2006**, *313*, 1584-1586.
[17] Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138-5175.

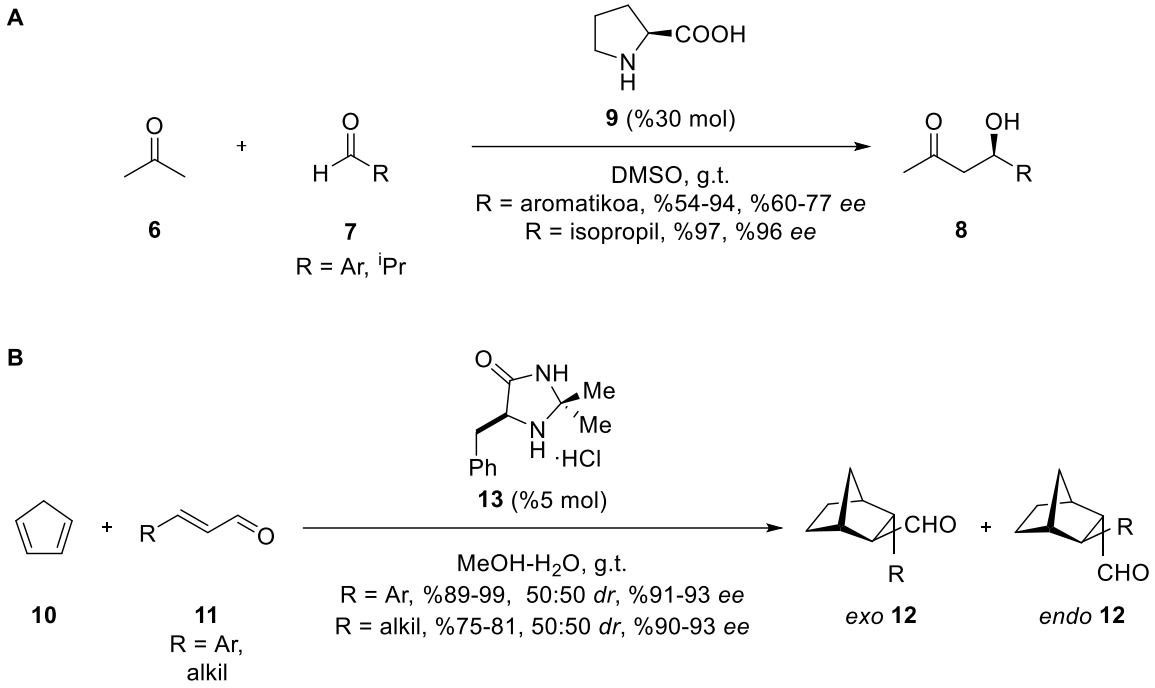
manipulazio beharrik. Euskarri desberdinetarako txertaketa ere aise egin daiteke, beraien berreskuratze zein birziklapena erraztuz.[18]

Arlo honetako lehen ikerketa Emil Knoevenagelek burutu zuen 1896. urtean.[19] Urte batzuk beranduago, Bredig eta Fiske kimikariek kinina edo kinidinak katalizatutako azido zianidrikoaren bentzaldehidoarekiko adizioa deskribatu zuten.[20] Hajos eta Parrishek eta Eder, Sauer eta Wichertek independienteki deskribaturiko *L*-Prolinak katalizatutako erreakzio aldoliko intramolekularra ere gertakari esanguratsua izan zen organokatalisiaren eremuan[21].

Erreakzio hauek guztiek molekula organiko txikiek sintesi kimikoan garrantzia izugarria izan lezaketela erakutsi arren, organokatalisia ez zen guztiz xedatu 21. menderarte. 2000. urtean, Carlos Barbas III, Richard Lerner eta Benjamin List zientzialariek *L*-Prolina **9**, azetona eta aldehidoen arteko erreakzio aldolikorako katalizatzaile eraginkorra zela postulatu zuten (**1.1A Eskema**).[22] MacMillanek ere amina motako **13** katalizatzailea erabiliz ziklopentadieno eta aldehidoen arteko Diels-Alder

[18] a) Alemán, J.; Cabrera, S. *Chem. Soc. Rev*. **2013**, *42*, 774-793. b) Pellisier, H. *Tetrahedron* **2007,** *63*, 9267-9331.
[19] a) Knoevenagel, E. *Ber. Dtsch, Chem. Ges*. **1896**, *29*, 172-174. b) List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 1730-1734.
[20] Bredig, G.; Fiske, P. S. *Biochem Z*., **1912**, *46*, 7-23.
[21] a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615-1621. b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed*. **1971**, *10*, 496-497.
[22] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **1998**, *120*, 2395-2396.

erreakzioa deskribatu zuen (**1.1B Eskema**).[23] Aldibereko bi argitalpen hauek erabakior suertatu ziren organokatalisiaren garapenean.



1.1 Eskema. A) Barbas III-k deskribatutako erreakzio aldoliko intermolekularra. B) MacMillanen taldeak garatutako Diels-Alder zikloadizioa.

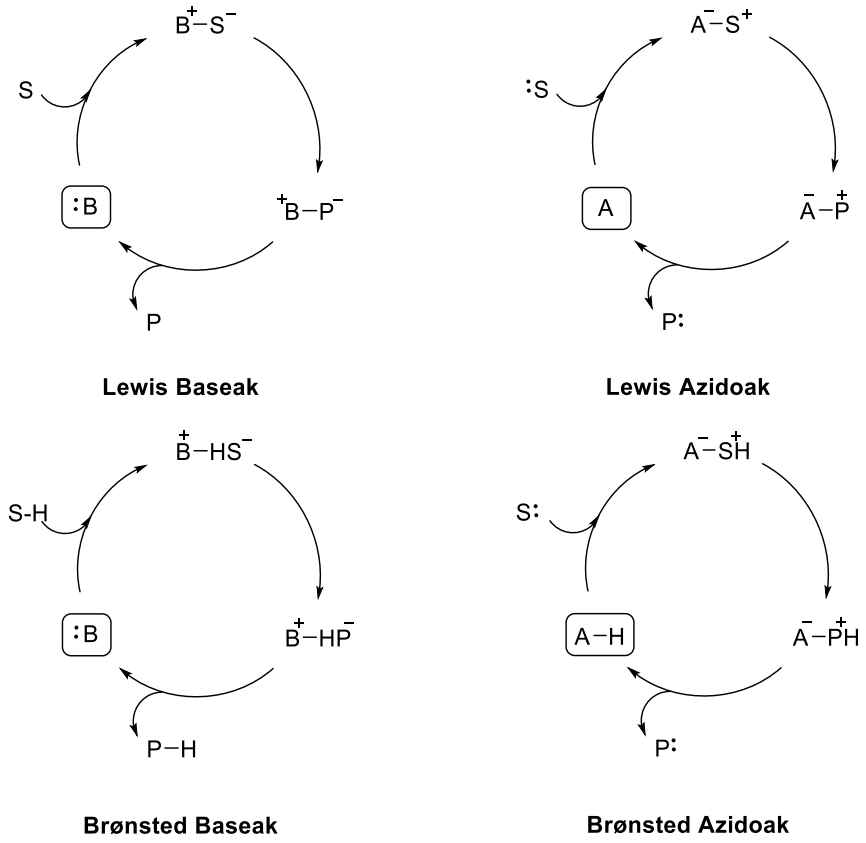
Transformazio organokatalitikoen inguruko lan anitz argitaratu diren arren, organokatalizatzaileek lan egiteko dituzten aktibazio mota gutxi identifikatu dira gaur egun arte. Jarraian, aktibazio motak zehaztuko dira.

1.3.1 Aktibazio motak organokatalisian

Autore desberdinek irizpide ezberdinak deskribatu dituzte aktibazio motak sailkatzeko. Ordenazio mota batek organokatalizatzaileen azido/base erreaktibotasuna kontutan hartzen duen bitartean, erabilera zabalagoa duen hurrenkera alternatiboak katalizatzailearen eta substratuaren arteko elkarrekintza itzulezina du oinarri.

Lehen antolamenduaren arabera, organokatalizatzaileak lau talde nagusitan sailka daitezke: Lewis azidoak, Lewis baseak, Brønsted azidoak eta Brønsted baseak (**1.2 Eskema**).[24]

[23] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243-4244.
[24] Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719-724.



1.2 Eskema. Organokatalizatzaileen azidotasun/basikotasunaren araberako ziklo katalitikoak.

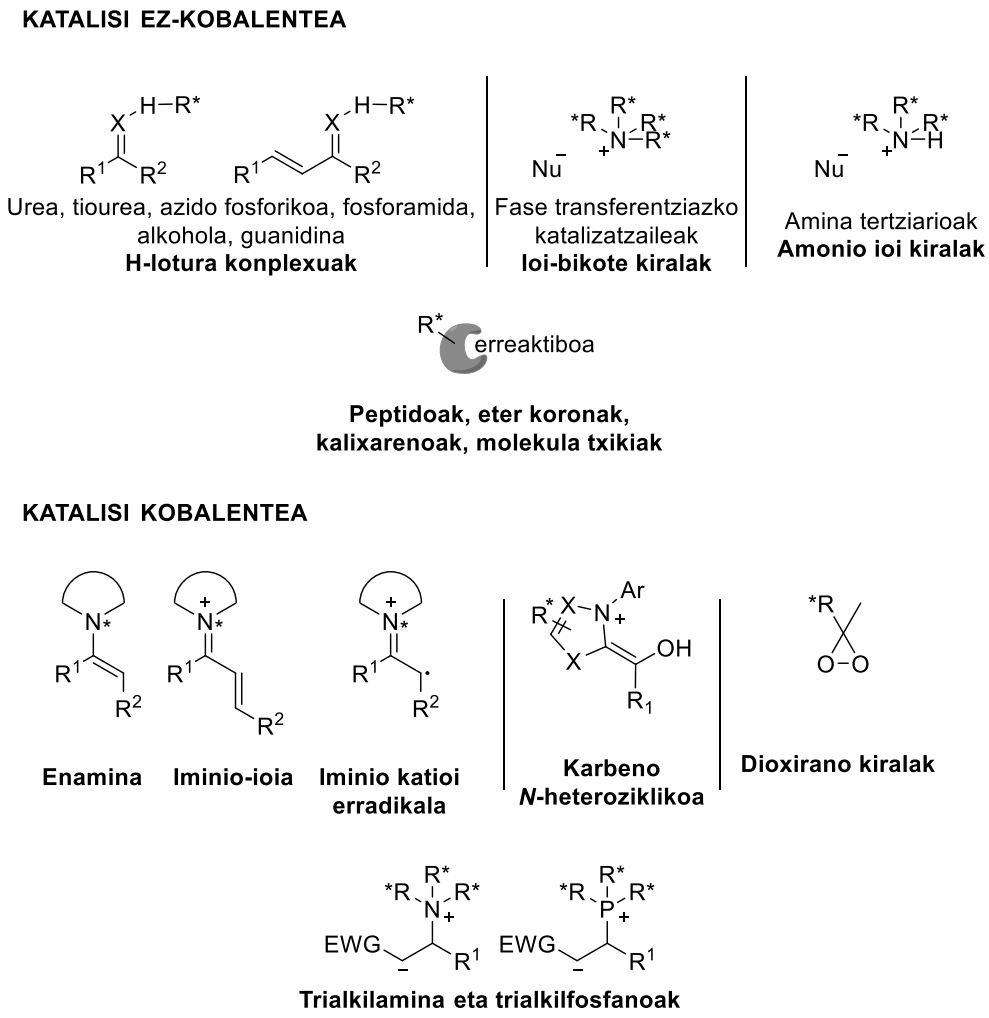
Lewis baseen bidezko organokatalisian, erreakzioaren azkartzea elektroi-pare emaile den molekulak elektroi-pare hartzaileagan duen eraginak erdiesten du, sortutako aduktu berrian elektroi-hartzailearekiko elektroi transferentzia bultzatuz (**1.2 Eskema**).[25] Lewis baseak (B) ziklo katalitikoari hasiera ematen dio substratuetako batekiko ordezkapen edo adizio nukleofilikoa gauzatuz. Honen bidez sortutako konplexuak (B^+S^-) erreakzioa jasaten du, amaierako produktua (P) eta ondorengo ziklo katalitikoetan berrerabiliko den katalizatzailea askatuz. Antzera jokatzen dute Lewis azidoek (A), substratuarekiko adizio elektrozalea bultzatzen baitute A^-S^+ artekaria sortuz. Lewis base gehienek nitrogeno, oxigeno, fosforo eta azufre moduko atomo emaileak dituzte beraien egituran. Hauen artean, aminokatalizatzaileak eta karbeno *N*-heteroziklikoak[26] aparteko gailentasuna dute. Amonio gatz kuaternarioek sortutako fase transferentziazko katalizatzaileak[27], *N*-oxido kiralak[28] eta Denmark motako fosforamidak[29], bestalde, Lewis azidoen barne mailakatzen dira.

[25] Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed*. **2008**, *47*, 1560-1638.
[26] Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534-541.
[27] Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2007**, *107*, 5656-5682.
[28] a) Malkov, A.; Kočovský, P. *Eur. J. Org. Chem*. **2007**, 29-36. b) Chen. J.; Takenaka, N. *Chem. Eur. J.* **2009**, *15*, 7268-7276.
[29] Denmark, S. E. *Chimia* **2008**, *62*, 37-40.

Brønsted baseek, bestalde, pronukleozalea desprotonazio bidez aktibatzen dute, are eta erreaktiboagoa den B^+HS^- espeziea sortuz. Brønsted azidoek aldiz, protonazio edo hidrogeno loturen bidezko aktibazioa burutzen dute eta A^-PH^+ aduktuak azken desprotonazio erreakzioa jasaten du amaierako produktua eta katalizatzailea askatuz.[30] Propietate hauek kontutan izanik, amina kiralak[31] eta guanidinak[32] Brønsted base bezala sailkatu daitezke. BINOL erako azido fosforikoak[33] eta fosfamidak[34] berriz, Brønsted azidoen kategoriako eratorri garrantzitsuenak dira.

Katalizatzailearen eta substratuaren arteko lotura mota erreferentziatzat hartuta bi multzo orokor bana daitezke: katalisi kobalentea eta ez-kobalentea.[35] Sailkapen hau 1949. urtean burutu zen arren, gaur egun ere antolaera berberaren erabilera egiten da (**1.4 Irudia**).

[30] Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev*. **2009**, *38*, 632-653.
[31] Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed*. **2006**, *45*, 947-950.
[32] Ye, W.; Jiang, Z.; Zhao, Y.; Goh, S. L. M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal*. **2007**, *349*, 2454-2458.
[33] a) Schrenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem*. **2011**, 2209-2222. b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev*. **2006**, *35*, 269-279. c) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem*. **2010**, *8*, 5262-5276.
[34] a) Johnston, J. N. *Angew. Chem., Int. Ed*. **2011**, *50*, 2890-2891. b) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed*. **2011**, *50*, 6706-6720. c) Cheon, C.-H.; Yamamoto, H. *Chem. Commun*. **2011**, *47*, 3043-3056.
[35] Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, The Royal Society of Chemistry (RSC Catalysis): Cambridge, **2010**.



1.4. Irudia. Organokatalizatzaile eta substratuaren arteko lotura kobalente/ez-kobalente ezaugarriak kontuan hartuta egindako sailkapena.

Katalisi ez-kobalenteak substratu-katalizatzaile arteko konplexazio neutroa edo azido-base ioi-pare formazioa biltzen ditu. Aktibazio mekanismo esanguratsuena urea, tiourea, azido fosforiko eta antzerako molekulek sortutako hidrogeno-lotura bidezko konplexuen formazioa da. Metodologia garrantzitsuak dira ere fase-transferentziazko katalizatzaileetan gertatzen den ioi-bikote kiralen eraketa eta amonio gatz kiraletako amina tertziarioek eragindako nukleozalearen desprotonazio bidezko aktibazioa.

Organokatalizatzaile erabilienak lotura kobalenteak burutzen dituztenak dira. Katalisi kobalente honetan katalizatzailearen eta erreaktibo/produktuaren arteko lotura eta askatzea itzulgarria izatea beharrezkoa da. Karbeno *N*-heterozikliokoak, oxidazio erreakzioetan erabilitako oxirano kiralak[36] eta Morita-Baylis-Hillman erreakzioetan aplikatutako trialkilfosfinak eta trialkilaminak molekula adierazkorrak dira.[37]

[36] Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847-859.
[37] a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev*. **2009**, *109*, 1-48. b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev*. **2007**, *36*, 1581-1588. c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed*. **2007**, *46*, 4614-4628.

Aminokatalisiak ere aparteko aipamena merezi du, non aktibazioa erreaktibo eta amina primario edo sekundarioen arteko elkarrekintza bidez gertatzen den. Amina hauek hiru espezie desberdin sor ditzakete: enaminak, iminio-ioiak eta SOMO iminio-erradikalak. Espezie bakoitzaren sormena aktibatzen duten substratoaren araberakoa da. HOMO orbitalaren energiaren igoera bidezko aktibazioak $\alpha,\gamma,\varepsilon$-funtzionalizatutako konposatu karbonilikoen formazioa bultatzen du, eta LUMO orbitalaren energiaren jaitsiera bultzatzen duen iminio-ioi bidezko aktibazioak konposatu β-funtzionalizatuak gauzatzen ditu. Azkenik, erredox sistema bitartez aktibatutako organokatalizatzaileek SOMO espezie erradikalen formazioa bultatzen dute.[38]

Lotura kobalente zein ez-kobalenteen bidez lan egiten duten aminokatalizatzaileek hainbat organokatalizatzaile biltzen dituzte. Haien artean, aminoazido ez naturaletan oinarritutako deribatuek, katalizatzaile berrien *de novo* diseinuaren bidez espazio konfigurazionalaren zabaltze garrantzitsua eragin dute. Ondorengo ataletan kasu esanguratsuenak garatzen dira.

1.4 AMINOAZIDO EZ-NATURALETAN OINARRITUTAKO ORGANOKATALIZATZAILEAK

L-Prolina[39] da transformazio organokatalitikoetan gehien erabili den organokatalizatzailea, duen aldakortasun eta eraginkortasuna dela medio. Dena den, disolbatzaile organikoetako disolbagarritasun baxuak, erreakzio denbora luzeak, katalizatzaile kantitate handiak eta disolbatzaile polarren erabilpenak bere enplegua murriztu du. Hau dela eta, 21. mendean C-C lotura berrien formazio erreakzio garrantzitsuenetan aminoazido ez-naturalen erabilera interesgarri suertatu da. Konposatu hauek gehienak eskura errazak izan ohi dira, isostere eta peptidomimetikoen egitura askotan presente daudelako, eta janari industria, industria farmazeutiko zein agrokimikoan interesgarri direlako.[40]

Ez-natural kontzeptuak proteina edo peptidoen egituren parte ez diren aminoazido guztiak barne hartzen ditu. Gainera, ez dira proteinetan biosintetikoki txertatzen translazio prozesuan. Orokorrean, kimikoki sintetizatu edo bakteria eta landareetan post-translazionalki aurki daitezke.[41] Mota honetako organokatalizatzaile familia esanguratsuenak zehazten dira jarraian.

[38] a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, *38*, 2178-2189. b) MacMillan, D. W. C. *Nature* **2008***, 455*, 304-308.
[39] Liu, J.; Wang, L. *Synthesis* **2017**, *49*, 960-972.
[40] Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas III, C. F. *J. Org. Chem*. **2003**, *68*, 9624-9634.
[41] Pollegioni, L.; Servi, S. *Unnatural Amino Acids: Methods and Protocols*, Humana Press: New York, **2011**.

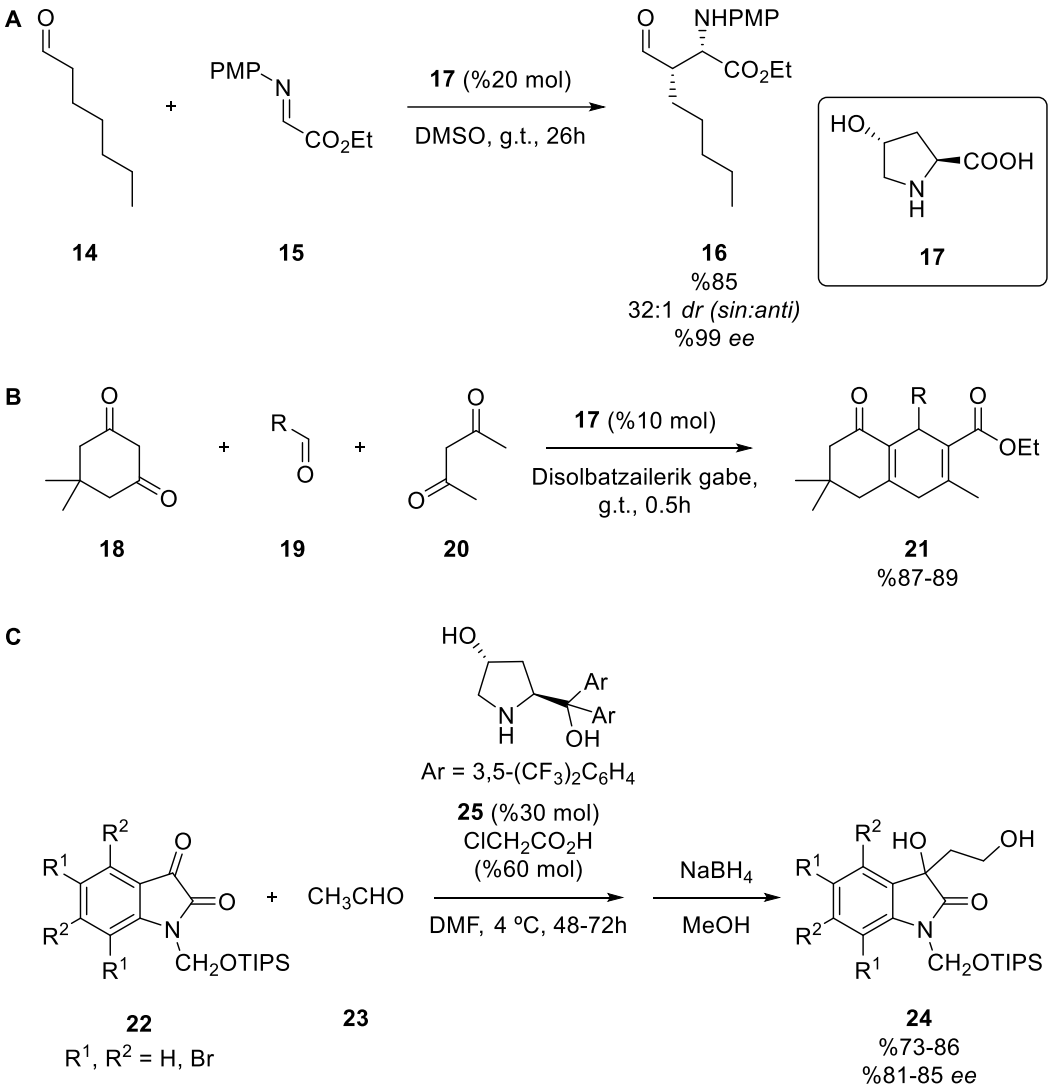
1.4.1 Aldaera Post-Translazional bidez lortutako organokatalizatzaile ez-naturalak

Modifikazio post-translazionala amino azido ez-proteinogenikoen familia zabaltzeko erabiltzen den metodologia garrantzitsuena da. Subunitate erregulatzaileen zatitze proteolitiko edo proteina osoen degradazioaz baliatzen da egitura aniztasuna lortzeko, baita proteinetako hezurdura edo albo kateetan gerta daitezkeen aldaketa kobalenteetan ere.[42]

1.4.1.1 *Trans*-4-Hidroxiprolinan oinarritutako organokatalizatzaileak

Hidroxi deribatuak: (2*S*,4*R*)-4-hidroxiprolina **17** Barbas III-ren lan taldeak heptanalaren eta α-imino etil glioxilatoaren arteko Mannich erreakzioan erabili zuen lehenengoz, amaierako *sin* **16** produktuak etekin eta estereoselektibitate altuan lortuz (**1.3A Eskema**).[40] 2007an, Maurya eta lankideek hiru-osagaiko Hantzsch erreakzioa deskribatu zuten organokatalizatzaile berbera enplegatuz (**1.3B Eskema**).[43] Azkenik, 2009. urtean Hayashik **25** molekulak katalizatutako isatina deribatuen eta azetaldehidoaren arteko erreakzio aldoliko asimetrikoa argitaratu zuen, indol erako molekula aktiboak lortzea ahalbidetuz (**1.3C Eskema**).[44]

[42] a) Walsh, C. T.; Garneu-Tsodikova, S.; Gatto, G. J. *Angew. Chem., Int. Ed*. **2005**, *44*, 7342-7372. b) Carter, M.; Shieh, J. *Guide to Research Techniques in Neuroscience 2nd Ed*, Academic Press: Oxford, **2015**.
[43] Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1946-1952.
[44] Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett*. **2009**, *11*, 3854-3857.



1.3 Eskema. A) Barbas III-k deskribatutako Mannich erreakzioa. B) Hiru-osagaiko Hantzsch erreakzioa. C) **25** hidroxi deribatuak katalizatutako erreakzio aldoliko asimetrikoa.

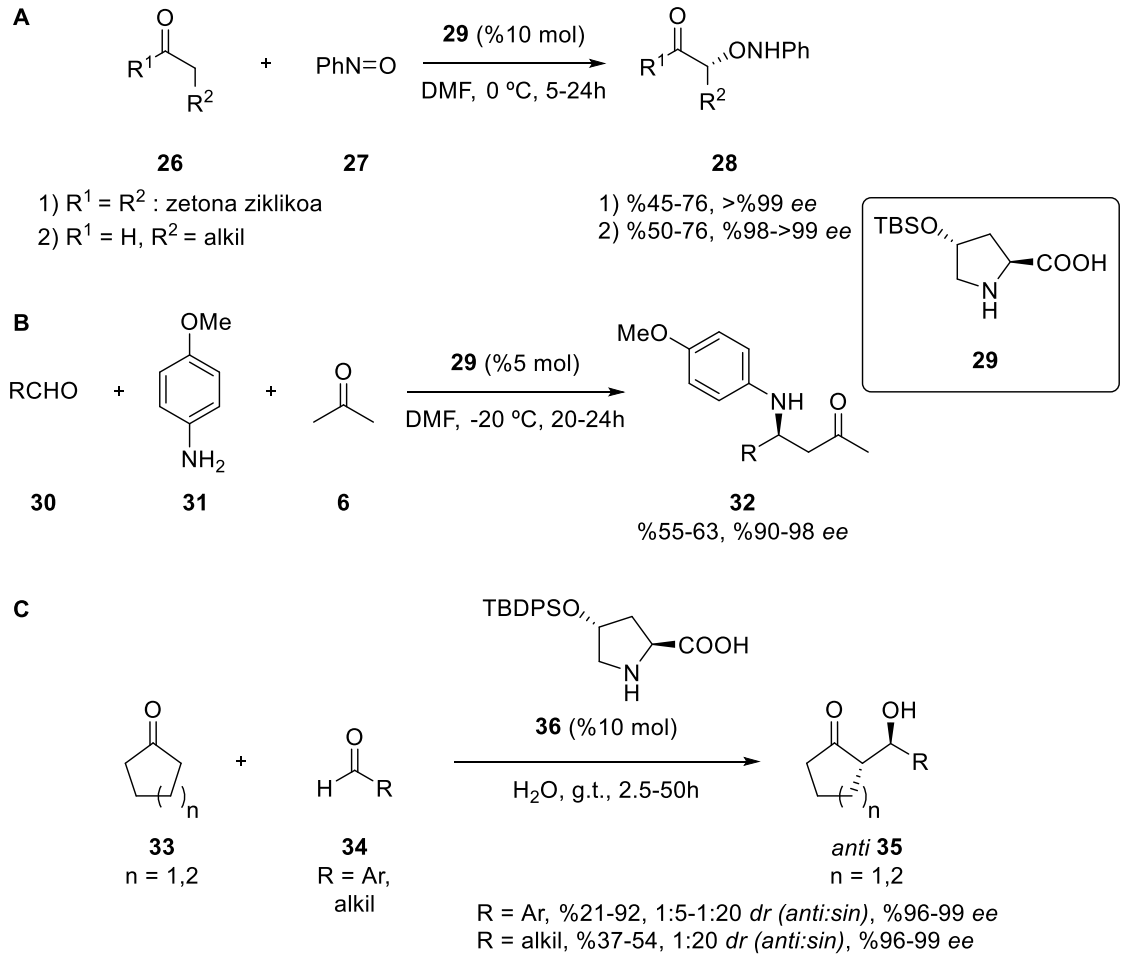
Eter deribatuak: literaturari dagokionez, eter deribatuetan oinarritutako bi lan bakarrik aurki daitezke. Lehenak, β-ziklodextrinari atxikitako katalizatzaileak erabiltzen ditu azetona eta bentzaldehido desberdinen arteko erreakzio aldolikoa gauzatzeko.[45] Bigarrenak, aldiz, albo kate luzeko organokatalizatzaile anfifilikoak deskribatzen ditu azetona eta aldehidoen arteko erreakzio aldolikorako.[46]

Silileter deribatuak: 4-silileterprolinak transformazio asimetrikoetan oso erabiliak izan dira. 2004. urtean Hayashiren ikerkuntza taldeak **29** 4-siloxiprolina garatu zuen hainbat erreakzio asimetrikorako, *L*-Prolinaren erreproduzibilitate baxua hobetu asmoz. Honela, **29** katalizatzaileak erreaktibitate eta enantioselektibitate altuak lortu zituen aldehido eta zetonen arteko *O*-nitroso aldol/Michael erreakzioetan, karga katalitikoa %10 mol-ra

[45] Shen, Z.; Ma, J.; Liu, Y.; Jiao, C.; Li, M.; Zhang, Y. *Chirality* **2005**, *17*, 556-558.
[46] Fu, Y.-Q.; An, Y.-J.; Liu, W.-M.; Li, Z.-C.; Zhang, G.; Tao, J.-C. *Catal. Lett*. **2008**, *124*, 397-404.

jaitsiz (**1.4A Eskema**).[47] Katalizatzaile berbera Mannich erreakzioetan ere aplikagarri suertatu zen, amaierako aduktuak etekin moderatu eta enantioselektibitate altuetan lortuz (**1.4B Eskema**). Urte bat beranduago, Enders eta kolaboratzaileek **30** organokatalizatzailearen erabilpena uztartu zuten dibertsitate altuko amino azukre desberdinak lortzeko.[48] Iwabuchiren ikerketa taldeak, bestalde, amonio kuaternario gatzak sortu zituzten α-zetoaldehido simetrikoen aldolizazio intermolekularrerako.[49] 2006. urtean, Hayashik lehen ur inguruneko erreakzio aldoliko diastereo- eta enantioselektiboa deskribatu zuen. Erreakzioa zetona nukleofiliko ugarirentzat aplikagarri suertatu zen, baita aldehido elektroi aberats zein elektroi defizienterentzat ere (**1.4C Eskema**).[50] Azkenik, 2013an, Cassaroren ikerketa taldeak 4-siloxiprolina desberdinak sintetizatu zituen CO_2 superkritikoko atmosferan gauzatutako azetona eta *p*-nitrobenzaldehidoaren arteko erreakzio aldolikorako.[51]

[47] Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal*. **2004,** *346,* 1435-1439.
[48] Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Ind. Ed*. **2005**, *44*, 4079-4083.
[49] Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett*. **2005**, *7*, 4185-4188.
[50] Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958-961.
[51] Cassaro, R. F.; de Oliveira, L. C.; Gariani, R. A.; do Nascimento, C. A. O.; Bazito, R. C. *Green Process Synth.* **2013**, *2*, 43-50.



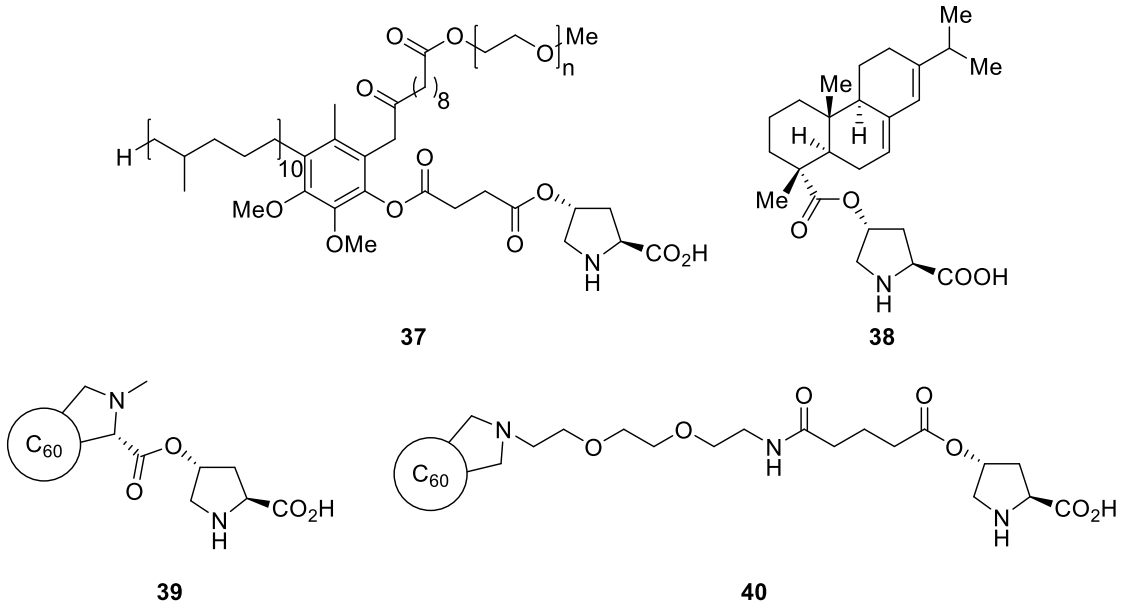
1.4 Eskema. Hayashik landutako A) *O*-nitrosoaldol/Michael, B) hiru-osagaiko Mannich eta C) erreakzio aldoliko asimetrikoak.

Ester deribatuak: ester talde bidez babesturiko 4-hidroxiprolina deribatuak ikerketa talde ugarik aztertu dituzte. Surfaktante moduan jokatzen duten organokatalizatzaile anfifilikoen erabilera Hayashi[52] eta Zhongen[53] taldeek sustatu zuten lehenengoz. Guttadauriaren taldeak ere organokatalizatzaile hidrofobiko familia sintetizatu zuen zetona eta aldehidoen arteko erreakzio aldoliko asimetrikoa gauzatzeko.[54]

Esterren erabilpena zabaldu ahala, ikerlariek katalizatzailearen egitura optimoaren inguruko irizpide desberdinak aditzera eraman zituzten. Gruttadauria eta kolaboratzaileek funtzionalizazio baxuko organokatalizatzaileak landu bitartean[55], Taok funtzionalizazio altuko prolinak sintetizatu zituen helburu katalitiko berberetarako[56].

[52] Hayashi, Y. Arakate, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 5527-5529.
[53] Zhong, L.; Gao, Q.; Gao, J.; Xiao, J.; Li, C. *J. Catal*. **2007**, *250*, 360-364.
[54] Giacalone, F.; Gruttadauria, M.; Lo Meo, P.; Riela, S.; Noto, R. *Adv. Synth. Catal*. **2008**, *350*, 2747-2760.
[55] Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Lo Meo, P.; Noto, R. *Eur. J. Org. Chem*. **2010**, 5696-5704.
[56] An, Y.-J.; Zhang, Y.-X.; Wu, Y.; Liu, Z.-M.; Pi, C.; Tao, J.-C. *Tetrahedron: Asymmetry* **2010**, *21*, 688-694.

Funtzionalizazio desberdinetako katalizatzaileez gain, kate lipofiliko luzedun organokatalizatzaileak ere erabili dira erreakzio aldolikoak sustatzeko. Testuinguru honetan, Lipshutz eta Goraik sortutako **37** Q_{10}-koentzima deribatua[57], Bhowmickek argitaratutako **38** azido abietiko deribatua[58] eta Kokotos eta Tagmatarchisek sintetizatutako **39**,**40** fullereno hibridoak[59] aurki ditzakegu (**1.5 Irudia**). Kate lipofiliko luzeko katalizatzaileak Mannich[60] eta Michael[61] erreakzioetan ere aplikagarri izan dira.

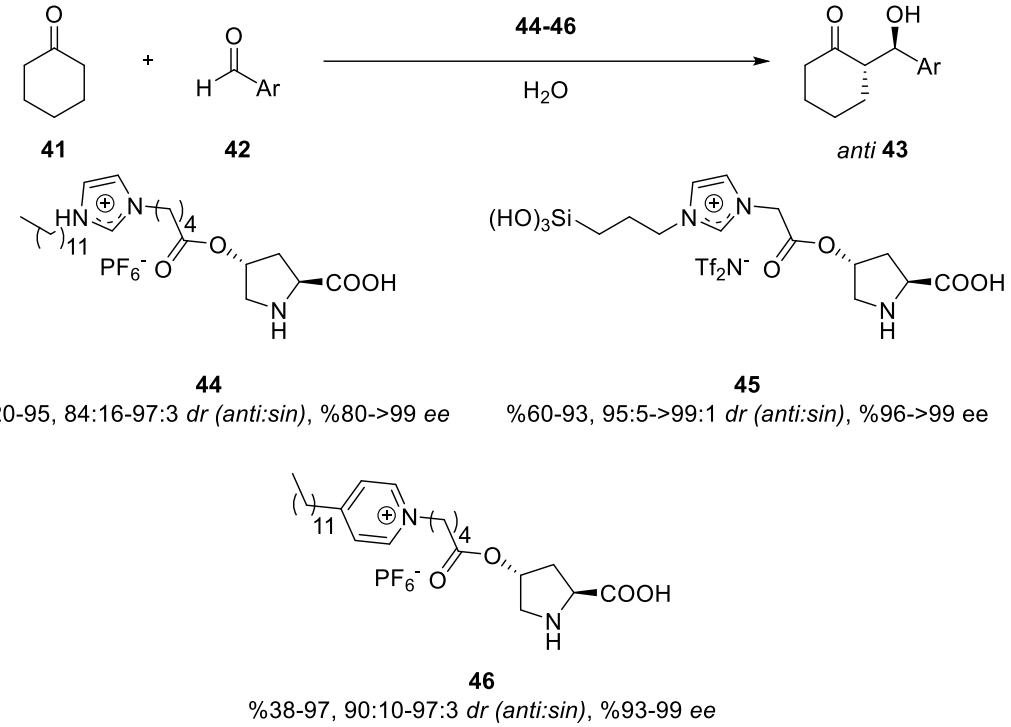


1.5 Irudia. Kate lipofiliko luzedun organokatalizatzaileak.

Organokatalizatzaile hauek ahalmen katalitiko altua erakutsi arren, erreakzio inguruneko berreskurapen baxuak bestelako katalizatzaileen erabilera bultzatu zuen. Hori horrela, likido ioniko bidez modifikatutako deribatuak garatu ziren, katioi eta anioi espezifikoen hautaketak likido ionikoen solubilitatea aldatzen baitu, ingurune akuoso eta organikoaren arteko fase banaketa erraztuz. Lehen likido ioniko erako organokatalizatzailea Chen eta kolaboratzaileek sintetizatu zuten, aldehido eta azetonaren arteko erreakzio aldolikoan aplikatuz.[62] 2008. urtean, Zlotin eta Trombinik ere deribatu anfifiliko gehiago sintetizatu zituzten (**1.5 Eskema**). Zlotinek sortutako **44** deribatu eraginkorrenak PF_6^- anioi hidrofobikodun imidazolio gatz kirala du egituratzat.[63]

[57] Lipshutz, B. H.; Ghorai, S. *Org. Lett*. **2012**, *14*, 422-425.
[58] Bhowmick, S.; Kunte, S. S.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2014**, *25*, 1292-1297.
[59] Chronopoulos, D. D.; Tsakos, M.; Karousis, N.; Kokotos, C. G.; Tagmatarchis, N. *Mater. Lett*. **2014,** *137*, 343-346.
[60] Veverková, E.; Liptáková, L.; Veverka, M.; Šebesta, R. *Tetrahedron: Asymmetry* **2013**, *24*, 548-552.
[61] Jocanović, P.; Randelović, J.; Ivković, B.; Suteu, C.; Vujošević, Z. T.; Savić, V. *J. Serb. Chem. Soc*. **2014**, *79*, 767-778.
[62] Miao, W.; Chan, H. *Adv. Synth. Catal*. **2006**, *348*, 1711-1718.
[63] Siyutkin, D. E.; Kucherenko, A. S.; Stuchkova, M. I.; Zlotin, S. G. *Tetrahedron Lett*. **2008**, *49,* 1212-1216.

Katalizatzaileak oso emaitza onak erakutsi zituen erreakzio aldolikoan, aktibitatea bost ziklo katalitikotan mantenduz. Trombinik, bestalde, kontraioia bis(trifluorometilsulfonil)imida (Tf_2N^-) taldeagatik aldatu zuen, **45** katalizatzaileak baldintza bifasikoetan lan egitea ahalbidetuz.[64] Urtebete beranduago, Zlotinen taldeak **6** prolina deribatua sintetizatu zuen katalizatzailearen C/N ratioa handituz eta katalizatzailearen propietate hidrofobikoak hobetuz. Honela, **46** katalizatzaileak bere aktibitate eta selektibitatea zortzi ziklotan mantendu zuen.[65]



1.5 Eskema. Zlotin eta Trombinik deskribatutako ziklohexanona eta aldehido aromatikoen arteko erreakzio aldoliko asimetrikoa.

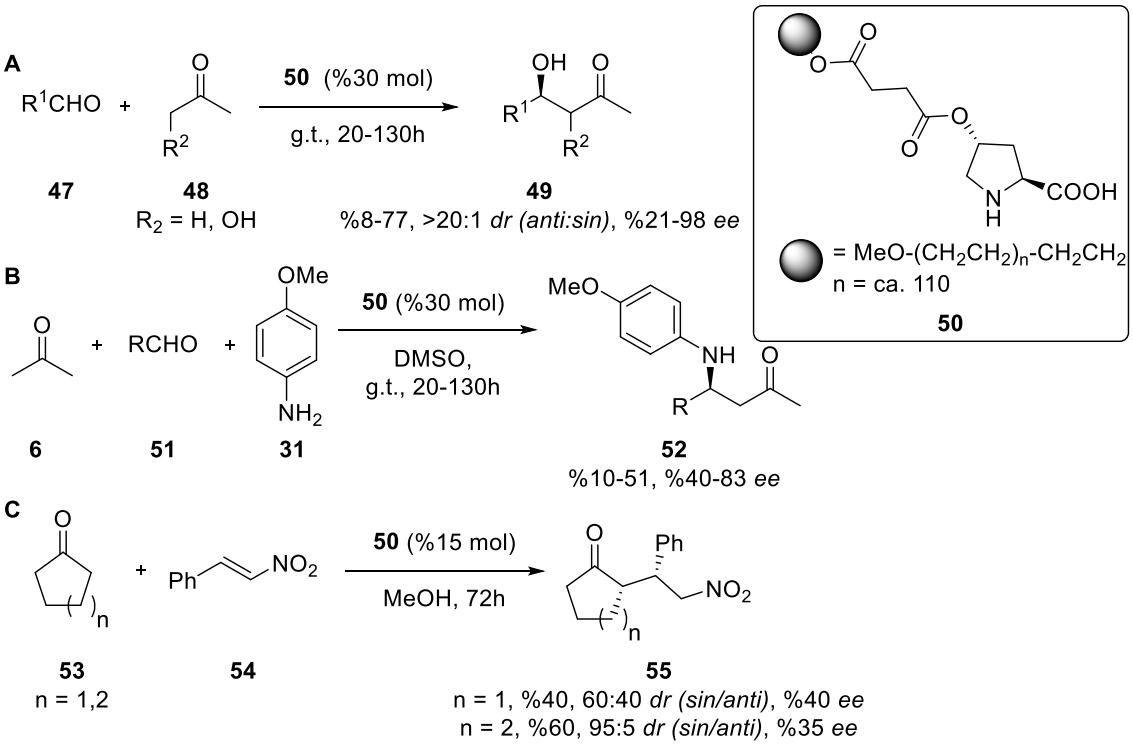
Polimeroetara atxikitako hidroxi deribatuak: prolinaren deribatu ez-naturalen garapenarekin batera, hauen euskarrirako inmobilizazioak arreta handia jasan du. Hasieran praktikotasun gutxiko metodologia kontsideratu arren, atxikitako deribatuaren berreskurapen errazak eta berrerabilpen altuak hauen erabilera sustatu du. Hain zuzen, inmobilizazioak disolbatzaile desberdinen enplegua eta euskarrien egituran aldaketak posible bihurtzen ditu.[66]

Hiru metodologia ezberdin ezagutzen dira katalizatzailea inmobilizatzeko, baina kobalenteki lotutako polimeroak dira usantza altuena dutenak. Hauen artean, polietilen glikolak (PEG) eta poliestirenoak (PS) aipamen berezia merezi dute. Silikako adsortzioa

[64] Lombardo, M.; Easwar, S.; De Marco, A.; Pasi, F.; Trombini, C. *Org. Biomol. Chem*. **2008**, *6*, 4224-4229.
[65] Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2009**, *65*, 1366-1372.
[66] Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev*. **2008**, *37*, 1666-1688.

ere eskukatu izan da, baina transformazio guztietan enantioselektibitate maila baxuagoak erakutsi dituzte.[56]

Mota honetako lehen esperimentuak PEG-ak inmobilizatutako **50** katalizatzaile bidez burutu ziren. Honek, emaitza oso onak erakutsi zituen azetona eta hidroxiazetonaren eta aldehidoen arteko kondentsazio aldoliko enantioselektiboan[67], Wieland-Mieschler zetonaren sintesirako Mannich erreakzioan[67b] eta zetona eta *trans*-β-nitroestirenoaren arteko Michael erreakzioan (**1.6 Eskema**).[68]



1.6 Eskema. PEG-ari atxikitako **50** 4-hidroxiprolina deribatua eta bere A) aldol B) Mannich eta C) Michael erreakzioak.

PEG-aren erabilpenean oinarritutako ikerketen ondoren poliestirenoa ere 4-hidroxiprolinatik eratorritako katalizatzaileen euskarri egoki izan litekeela kontsideratu zen, polimero katearen hidrofobia altua dela eta. Honela, 2006. urtean hidroxi-*L*-prolina Merrifield resinan inmobilizatzea lortu zen, eta mota honetako katalizatzaileak ur inguruneko erreakzio aldolikoetan[69] zein aldehido eta zetonen arteko α-aminoxilazio erreakzioan[70] erabili. Gruttadauriaren ikerketa taldeak ere merkaptometil deribatuak sortu zituen ziklohexanona eta bentzaldehido desberdinen arteko erreakzio

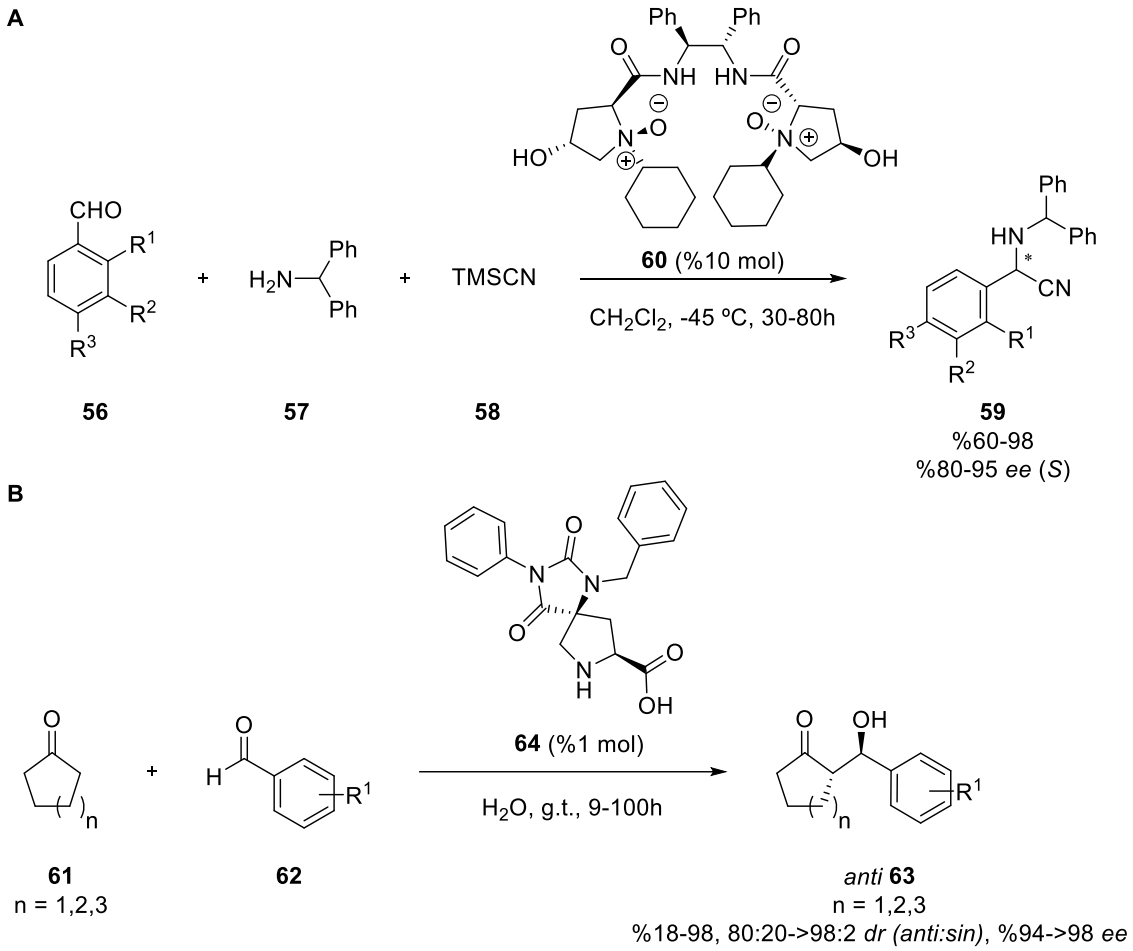
[67] a) Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal*. **2001**, *343*, 171-173. b) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *Adv. Synth. Catal*. **2002**, *344*, 533-542.
[68] Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *J. Mol. Catal. A: Chem*. **2003**, *204-205*, 157-163.
[69] Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2006**, *8*, 4653-4655.
[70] Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2007**, *9*, 1943-1946.

aldolikorako.[71] 2008. urtean, azkenez, Pericàs eta kolaboratzaileek triazol erako organokatalizatzailea sintetizatu zuten transformazio kimiko berdinerako, aldol aduktuak etekin eta selektibitate altuarekin lortuz.[72]

Polimero akrilikoak funtzio organokatalitikoetara aplikatzeko urte dexente itxaron behar izan zen. Polimero estirenikoek onartzen zituzten disolbatzaile sistema mugatuak gainditu asmoz, kimikari sintetikoek polimero akrilikoak sortu zituzten, hauen propietate superabsorbenteak ustiatuz.[73] Era berean, nanopartikula magnetikoen enplegua ere aztertu zen, eta azken hauek abantaila esanguratsu bat agerrarazi zuten beste deribatuen aurrean: kanpoko iman baten bidezko banaketa fisiko erraza.[74]

Bestelako deribatuak: deskribatutako deribatu guztiez gain, beste *trans*-4-hidroxiprolinatik eratorritako bi katalizatzaile marratu daitezke. **60** *N*,*N*'-dioxidoa **56** aldehido, (1,1-difenil)metilamina **57** eta TMSCN **58** arteko hiru-osagaiko Strecker erreakzioan aplikatu zen, amaierako produktuak enantioselektibitate altuekin lortuz (**1.7A Eskema**).[75] Schafmeister eta kolaboratzaileek, aitzitik, prolinan oinarritutako imidazolidinona espiroziklikoak sintetizatu zituzten zetona zikliko eta aldehidoen arteko erreakzio aldoliko asimetrikorako. Deskribatutako deribatuen artean emaitza altuenak **64** katalizatzaileak lortu zituen, *anti* **63** produktuak etekin on eta diastereo- zein enantioselektibitate altuarekin sortuz (**1.7B Eskema**).[76]

[71] Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Lo Meo, P.; Riela, S.; Noto, R. *Eur. J. Org. Chem*. **2007**, 4688-4698.
[72] Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2008**, *10*, 337-340.
[73] Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett*. **2009**, *11*, 2968-2971.
[74] Yacob, Z.; Nan, A.; Liebscher, J. *Adv. Synth. Catal*. **2012**, *354*, 3259-3264.
[75] Wen, Y.; Gao, B.; Fu, Y.; Dong, S.; Liu, X.; Feng, X. *Chem. Eur. J.* **2008**, *14*, 6789-6795.
[76] Zhao, Q.; Lam, Y.-H.; Kheirabadi, M.; Xu, C.; Houk, K. N.; Schafmeister, C. E. J. Org. Chem. 2012, 77, 4784-4792.



1.7 Eskema. A) **60** *N*,*N*'-dioxido deribatuak katalizatutako Strecker erreakzioa. B) **64** imidazolidinonak katalizatutako zetona zikliko eta aldehido aromatikoen arteko erreakzio aldolikoa.

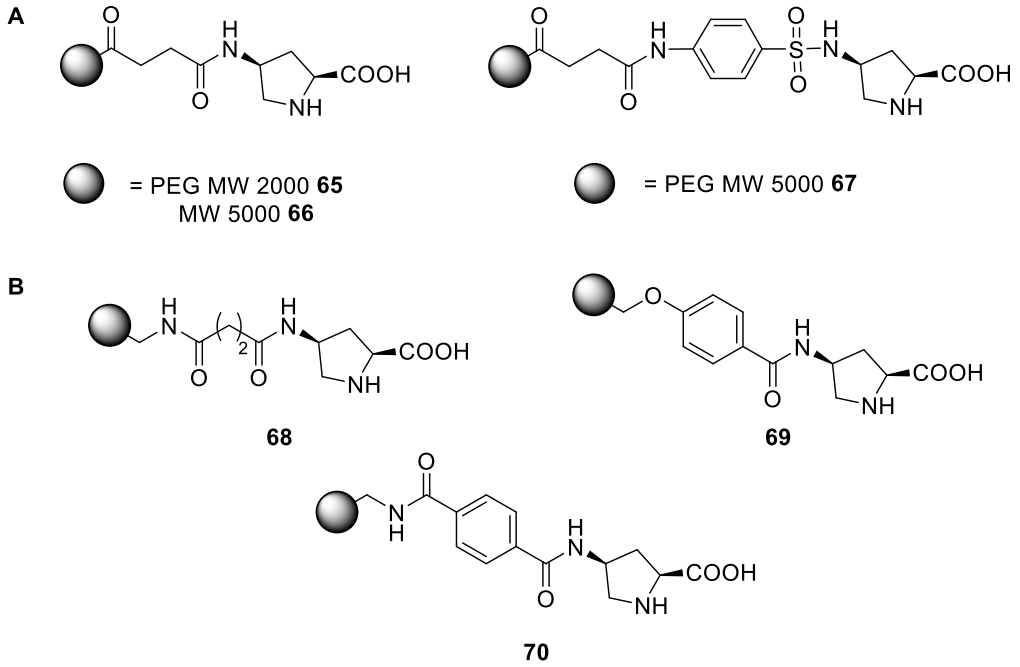
1.4.1.2 4-amino prolinan oinarritutako organokatalizatzaileak

2007. urtean, Liu eta kolaboratzaileek 4-amino prolinatik eratorritako organokatalizatzaileek ziklohexanona eta aldehido aromatiko zein heteroaromatikoen arteko erreakzio aldoliko asimetrikoa katalizatu zezaketela baieztatu zuten. Hala ere, 4-amino prolinan erratutako organokatalizatzaile esanguratsuenak polimeroei atxikitako deribatuak dira. Zentzu honetan, 4-amino prolina PEG katalizatzaileak prestatu ziren lehenik zetona eta *trans*-β-nitroestirenoaren arteko Michael erreakzioa gauzatzeko.[77] Aztertutako eratorrien artean, **67** katalizatzaileak etekin eta enantioselektibitate altuenak erakutsi zituen (**1.6A Irudia**). Katalizatzailearen berreskurapena filtrazio fisiko bidez burutu zen, baina birziklapen esperimentuek jaitsiera nabaria azaleratu zuten lau ziklo katalitikoren ondoren.

2007an ere Tao eta kolaboratzaileek poliestirenoari atxikitako **68** organokatalizatzailea sintetizatu zuten ziklohexanona eta aldehido aromatikoen arteko

[77] Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *J. Mol. Catal. A: Chem*. **2007**, *263*, 186-194.

ur inguruneko erreakzio aldolikorako.[78] Urte baten buruan, ikerketa talde berdinak beste bi **69**,**70** deribatu sortu zituen, erreakzio aldolikoa DMF edo zetona/ur nahastean gauzatzeko (**1.6B Irudia**).[79]



1.6 Irudia. A) Zetona eta *trans*-β-nitroestirenoaren arteko Michael erreakzioa katalizatzeko sintetitzatutako 4-amino prolina PEG katalizatzaileak. B) Erreakzio aldolikorako poliestirenoari atxikitako organokatalizatzaileak.

1.4.2. Aminoazido ez-natural sintetikoak

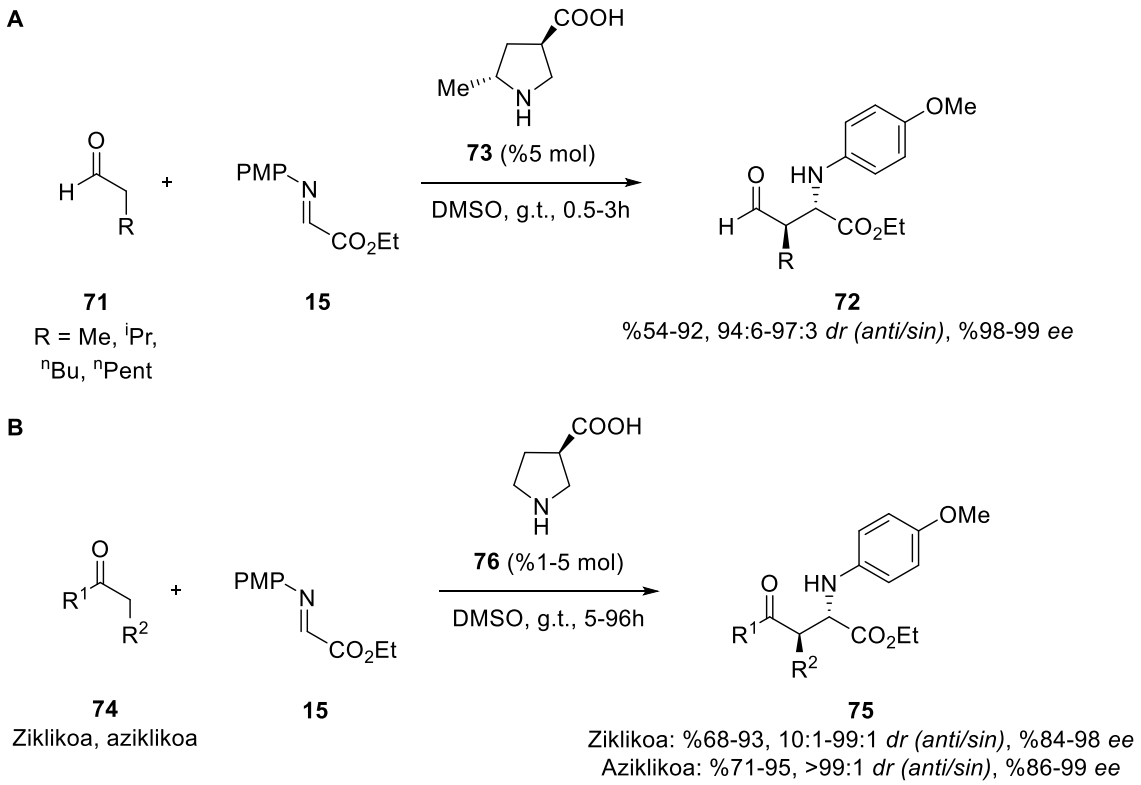
Aldaera post translazional erako metodologia sintetikoek eraginkortasun baxua erakutsi ohi dute, substratuen ezaugarri estruktural zehatzak direla medio. Honela, eraldaketa katalitiko zein estekiometrikoetan oinarritutako sintesi kimikoek garapen handia jasan dute.[80] Ondoren, organokatalizatzaile sintetiko ez-natural aipagarrienak zehaztuko dira.

1.4.2.1 β-prolinak

Amino azido ez-natural hauek Mannich erreakzioetan besterik ez dira aplikatu. Aitzitik aipaturiko organokatalizatzaileek *sin*-erako Mannich produktuen sorrera bultzatzen zuten.[81] **73** katalizatzaileak ordea, aldehido eta imina elektrozaleen arteko *anti*-Mannich

[78] Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Tao, J.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 2649-2656.
[79] Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Tao, J.-C. *Catal. Lett*. **2008**, *120*, 281-287.
[80] Saghyan, A. S.; Langer, P. *Asymmetric Synthesis of Non-Proteinogenic Amino Acids*, Wiley-VCH: Weinheim, **2016**.
[81] Girling, P. R.; Kiyoi, T.; Whiting, A. *Org. Biomol. Chem*. **2001**, *9*, 3105-3121.

erreakzioetan aktibitate katalitiko altua adierazi zuen (**1.8A Eskema**).[82] Zoritxarrez, prozedura honek efizientzia baxua zuen zetona nukleofilikoen kasuan, baina **76** β-prolinak ahultasun hau gainditu ahal izan zuen, zetona zikliko zein aziklikoentzat paregabeko katalizatzaile suertatuz (**1.8B Eskema**).



1.8 Eskema. A) aldehido eta B) zetonen arteko *anti*-Mannich erreakzioetarako deskribatutako β-Prolinak.

1.4.2.2 Pirrolidina ez-naturaletan oinarritutako deribatuak

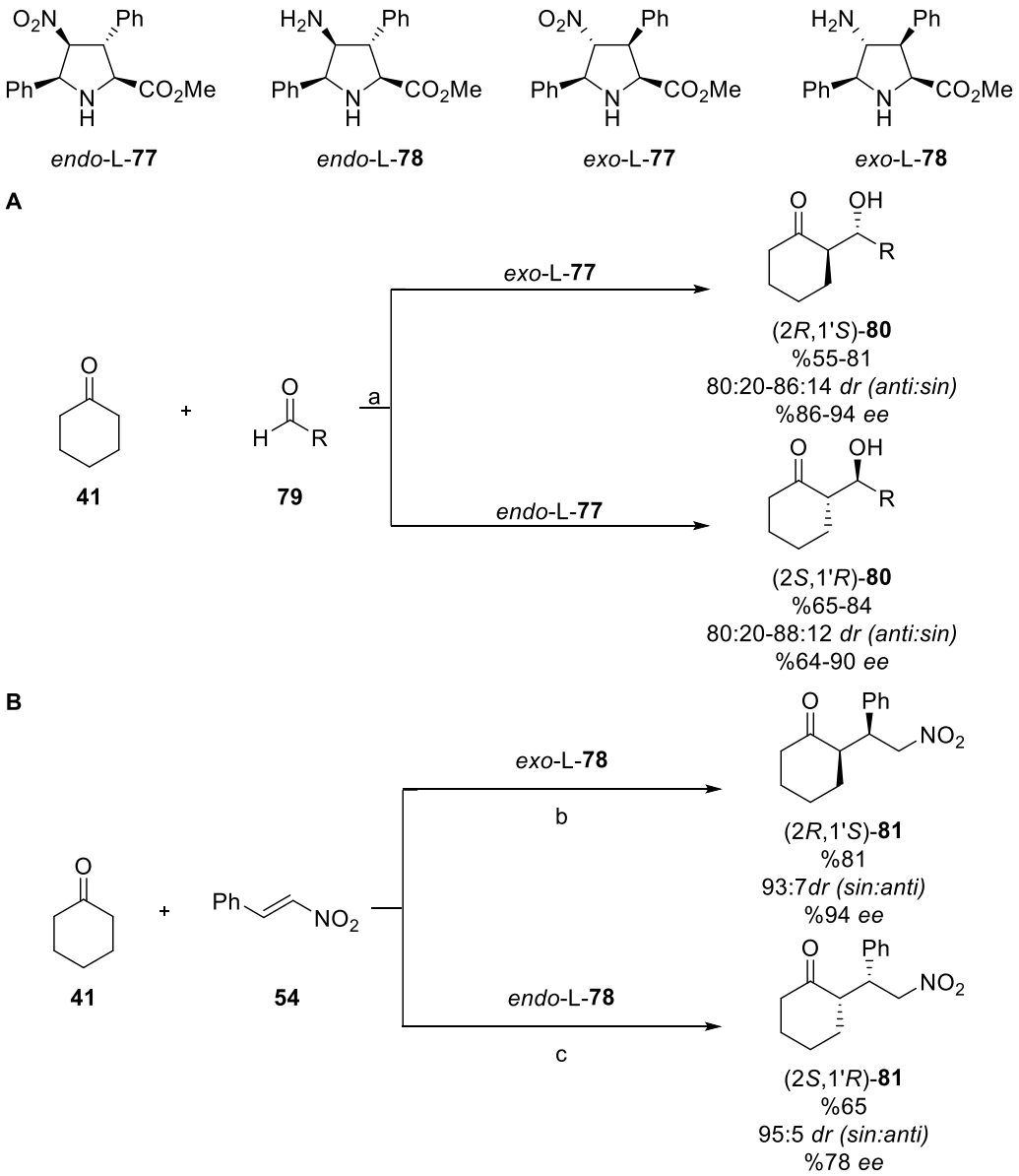
Gure ikerketa taldeak funtzionalizazio altuko nitro eta aminoprolinek katalizatutako erreakzio asimetrikoen inguruan egin du lan azken hamarkadan. Katalizatzaile hauek (3+2) zikloadizio eta ondorengo hidrogenazio prozesuen bidez sintetizatu ziren. **77** nitro deribatuek zetona zikliko eta aldehidoen arteko erreakzio asimetrikoak gauzatzeko gaitasun handia erakutsi zuten, azido trifluoroazetikoa (TFA) aditibo moduan erabiliz (**1.9A Eskema**).[83] Azterturiko organokatalizatzaileen artean emaitza esterokimiko altuenak *exo*-L-**77** eta *endo*-L-**77** deribatuek ezagutarazi zituzten, amaierako produktuak diastereo- eta enantioselektibitate altuarekin sortuz. Gainera, indukzio estereokimikoa pirrolidina eraztunaren egiturarekin estuki erlazionatuta zegoela frogatu zen. Hala nola,

[82] a) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041. b) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc*. **2006**, *128*, 9630-9631.

[83] a) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci*. **2012**, *3*, 1486-1491. b) Retamosa, M. G.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem.* **2015**, 2503-2516.

exo-L esterrek (2*R*,1'*S*) aldolen formazioa bultzatzen zuten bitartean, *endo*-L organokatalizatzaileekin (2*S*,1'*R*) aldolak ziren erreakzio produktu nagusi.

Nitro deribatuak Michael erreakzioetan aplikatzea ezinezko izan zen ordea. Zorionez, 4-amino prolina **78** deribatuek zetona zikliko eta nitroalkenoen arteko Michael erreakzioa efizientzia altuarekin katalizatzea lortu zuten.[84] Aurreko kasuan bezalaxe, endo-L-**78** katalizatzaileek Prolina erako (2*S*,1'*R*) produktuak sortzen zituzten; exo-L-**78** deribatuek, berriz, (2*R*,1'*S*) aduktuak bultzatuz (**1.9B Eskema**).



1.9. Eskema. Cossío eta kolaboratzaileek deskribaturiko nitro eta aminoprolina ez-naturalek katalizatutako A) aldol eta B) Michael erreakzioak. Erreaktibo eta baldintzak: a) Organokatalizatzailea (%30 mol), TFA (%30 mol), -15 °C, 24h. b) Organokatalizatzailea (%30 mol), PNBA (%30 mol), disolbatzailerik gabe, g.t., 16h. c) Organokatalizatzailea (%30 mol), TFA (%30 mol), disolbatzailerik gabe, r.t., 24h.

[84] Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F. P. *J. Org. Chem*. **2015**, *80*, 5588-5599.

Kasu guzti hauetan pirrolidina eraztuna zen kiralitate iturri bakarra. Hala ere, autore gehiagok katalizatzailearen egituran eraztun fusionatuak dituzten prolina ez-naturalen enplegua azaldu zuten. Testuinguru honetan aurki daitezke Yu, Han eta kolaboratzaileek deskribaturiko Biginelli erreakzioa[85], Caik ezagutaraziko (3+2) zikloadizio enantioselektiboa[86], Xiaoren taldeak azalduriko Michael erreakzioa[87], eta Sarottik garatutako iminio-ioi bidezko Diels-Alder erreakzioa[88].

1.5 PEPTIDOAK ENAMINA BIDEZKO ERREAKZIO ORGANOKATALITIKOETAN

Peptidoek funtzio anitz betetzen dituzte naturan zein eguneroko bizitzan, hormona, neurotransmisore, toxina, gozagarri artifizial eta sendagaien parte baitira.[89] Hauen egitura eta funtzio dibertsitatea da jomuga zabal honen arrazoi nagusia. Esan behar da ere katalizatzaile peptidikoek aparteko ezaugarriak dituztela, bestelako katalizatzaile sintetiko eta entzimek lortu ezin dituztenak. Kimioselektibitate altua, substratu familia desberdinen erabilpena, distantzia luzeetarako selektibitatea, egonkortasun estrukturala eta aldakortasuna adibide esanguratsu dira.[90]

1.5.1 Aminoazido naturaletatik eratorritako peptidoak

Peptido hauek oso erabiliak dira transformazio sintetiko asimetrikoetan, aldol eta Michael erreakzioak hauen artean gailenduz. Mannich eta Diels-Alder erako erreakzioak ere aztertu izan dira, non katalisia sulfonamida deribatuen bidez burutzen den.[91]

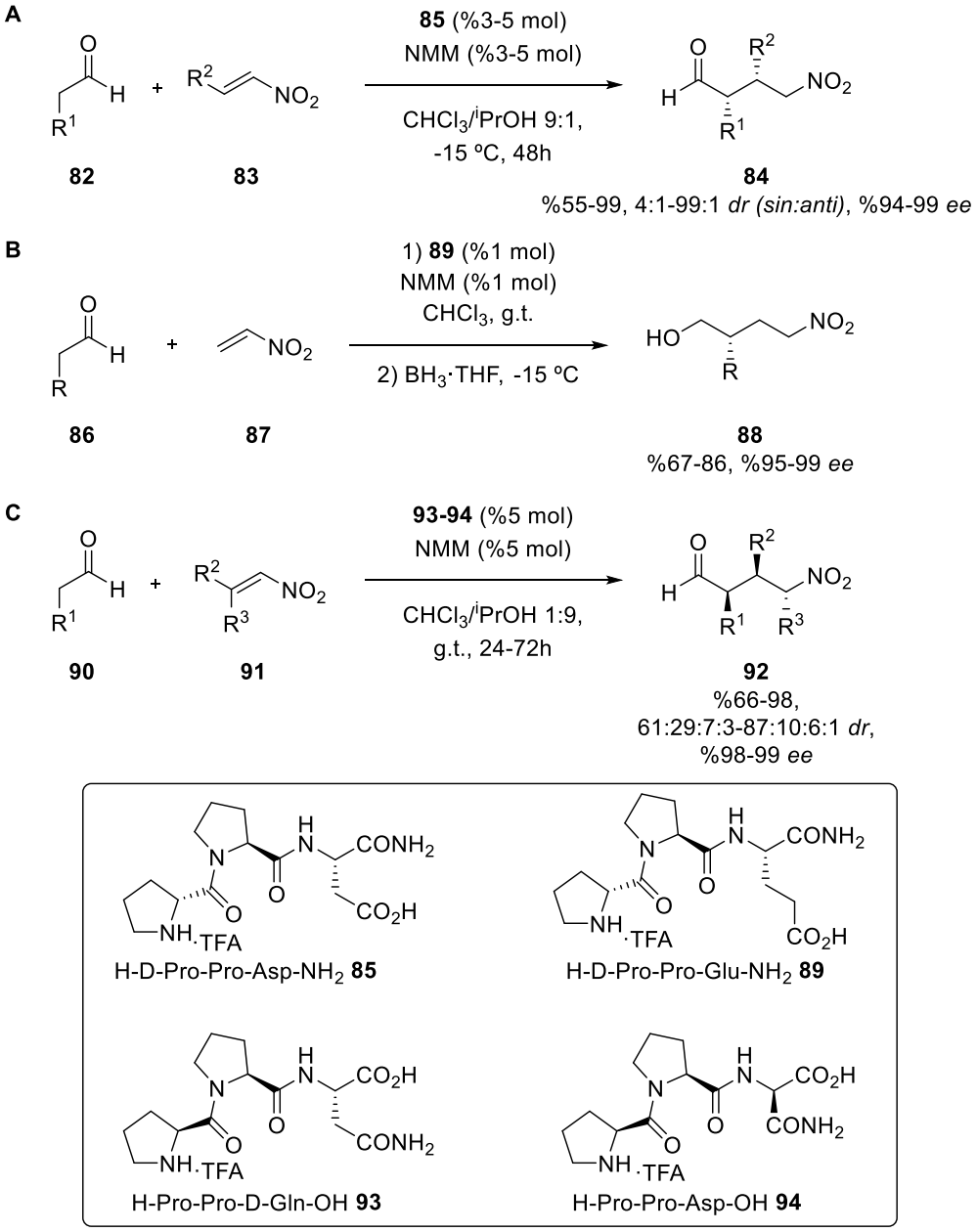
List[92] eta Reymonden[93] ikerketa taldeak izan ziren peptidoak erreakzio aldolikoetan aplikatzen lehenak. Aurrekari hauek peptidoak erreakzio aldoliko enantioselektiboetan inplementatzea bultzatu zuten. Gong[94] eta Wangen[95] kolaboratzaileek bi eta lau amino azido bitarteko peptidoak sintetizatu zituzten, eta Wennemers eta lankideek kimika

[85] Yu, H.; Xu. P.; He, H.; Zhu, J.; Lin, H.; Han, S. *Tetrahedron: Asymmetry* **2017**, *28*, 257-265.
[86] Cai, X.; Wang, C.; Sun, J. *Adv. Synth. Catal*. **2012**, *354*, 359-363.
[87] Xiao, J.; Xu, F.-X.; Lu, Y.-P.; Loh, T.-P. *Org. Lett*. **2010**, *12*, 1220-1223.
[88] a) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G.; Echeverría, G. A.; Piro, O. E. *Org. Lett*. **2012**, *14*, 2556-2559. b) Gerosa, G. G.; Spanevello, R. A.; Suárez, A. G.; Sarotti, A. M. *J. Org. Chem*. **2015**, *80*, 7626-7634.
[89] Sewald, N.; Jakubke, H.-D. *Peptides: Chemistry and Biology*. *2nd Ed*. Wiley-VCH:Weinheim, **2002**.
[90] Wennemers, H. *Chem. Commun*. **2011**, *47*, 12036-12041.
[91] a) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed*. **2005**, *44*, 4877-4880. b) Veverková, E.; Štrasserová, J.; Šebesta, R.; Toma, Š. *Tetrahedron: Asymmetry* **2010**, *21*, 58-61.
[92] Martin, H. J.; List, B. *Synlett* **2003**, 1901-1902.
[93] Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2445-2447.
[94] Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett*. **2004**, *6*, 2285-2287.
[95] Hu, X.-M.; Zhang, D.-X.; Zhang, S.-Y.; Wang, P.-A. *RSC Adv*. **2015**, *5*, 39557-39564.

konbinatorio bidez sortutako katalizatzaile tripeptidikoak aztertu zituzten[96]. Singhek, bestalde, prolina eta *gem*-difenilo taldeez osatutako katalizatzaile familia garatu zuen[97]. Kokotos eta bere taldeak tripeptido-prolinamida-tiourea erako katalizatzaileak deskribatu zituzten helburu katalitiko bera jarraituz[98], eta Paladhi eta kolaboratzaileek C3 simetriadun prolinamiden erabilpena ikertu zuten[99].

Michael erreakzioari dagokionez, Clarke eta kolaboratzaileek *L*-Prolina eta aminonaftaridinaren akoplamentu bidez sortutako katalizatzaileen erabilera deskribatu zuten lehenengoz 2007. urtean.[100] Bi urteren buruan, Tsogoevak Pro-Phe-OH motako dipeptidoek ziklohexanona eta nitroolefinen arteko Michael erreakzioa kataliza zezaketela frogatu zuten.[101] Wennemersek, azkenik, Pro-Pro-Xaa erako tripeptidoen (non Xaa aminoazido azidikoa den) erabilera sustatu zuen 1,4-adizio konjugatu desberdinetarako (**1.10 Eskema**).

[96] a) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101-1103. b) Revell, J. D.; Wennemers, H. *Adv. Synth. Catal*. **2008**, *350*, 1046-1052.
[97] Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem*. **2009**, *74*, 4289-4297.
[98] Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem*. **2012**, *10*, 5613-5619.
[99] Paladhi, S.; Das, J.; Mishra, P. K.; Dash, J. *Adv. Synth. Catal*. 2013, *355*, 274-280.
[100] Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed*. **2007**, *46*, 930-933.
[101] Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem*. **2009**, *7*, 4379-4284.



1.10 Eskema. H-Pro-Pro-Xaa erako katalizatzaile tripeptidikoak A) β-nitroolefina, B) nitroetilenoa eta C) α,β-diordezkatutako nitroalkenoen Michael erreakzioetarako.

1.5.2 Amino azido ez-naturaletatik eratorritako peptidoak

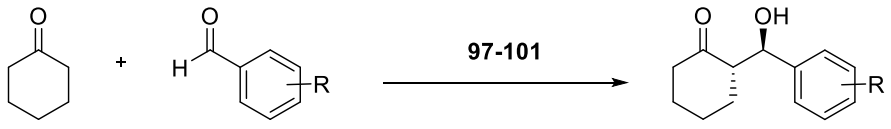
Aminoazido naturaletan erroturiko organokatalizatzaileez gain, aminoazido ez-naturaletan oinarriturikoak ere erreakzio subestekiometriko asimetriko askotan eskukatu izan dira. Aipatzekoak dira, hots, zikloadizio, azilazio, domino erreakzio eta transformazio hidrolitikoak.[102]

Erreakzio aldoliko asimetriko intermolekularraren kasuan, *trans*-4-hidroxiprolinatik eratorritako prolinamidak besterik ez dira ebaluatu. Honelako amidek azido taldean

[102] a) 90. erreferentzia. b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. Chem. Rev. 2007, 107, 5759-5812. c) Revell, J. D.; Wennemers, H. *Curr. Opin. Chem. Biol*. 2007, *11*, 269-278.

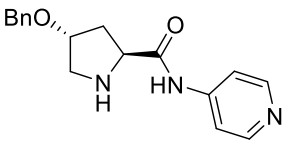
jasan izan dituzte aldaketak, baita azido eta karboxi taldeetan bietan ere. Lehen kategorian Fu eta kolaboratzaileek deskribaturiko prolinamida fenolak besterik ez dira aurkitzen literaturan, ziklohexanona eta nitroaldehido aromatikoen arteko erreakzioa sustatzen dutenak.[103] Hidroxi zein azido taldeetan babesturiko katalizatzaileen artean lan ugari aurki daitezke, ordea (**1.11 Eskema**). 2007an, Cheng eta kolaboratzaileek **97** katalizatzaileak eta azido *p*-dodezilbenzenosulfonikoak burututako ziklohexanona eta aril aldehidoen ur inguruneko erreakzio aldolikoaren sustapena argitaratu zuten.[104] Gongek **98** organokatalizatzailea erabili zuen helburu katalitiko berdinerako, amaierako produktuak diastereo- eta enantioselektibitate altuarekin sortuz.[105] Zhangek diseinaturiko **99** katalizatzaileak ur kantitate handitan burutu zituen erreakzioak, diastereoselektibitate eta *ee* balio altuak lortuz.[106] Chenek tiourea-amida **100** organokatalizatzaile bifuntzionala erabili zuen ur zein disolbatzaile organiko inguruneko erreakziorako, amaierako produkutak etekin eta estereoselektibitate altuarekin lortuz.[107] Wuk, azkenekoz, **101** *N*-prolilsulfonamidak amaierako produktuak etekin, diastereoselektibitate eta enantioselektibitate handiarekin sortzea lortu zuen, %3 mol-ko katalizatzaile karga baxua enplegatuz.[108]

[103] Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006,** *17,* 3351-3357.
[104] Luo, S.; Xu, H.; Li, J.; Zhang, L.; Mi, X.; Zhenga, X.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 11307-11314.
[105] Zhao, J.-F.; He, L.; Jiang, J.; Tang, Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett*. **2008**, *49*, 3372-3375.
[106] Zhang, S.-P.; Fu, X.-K.; Fu, S. D. *Tetrahedron Lett*. **2009**, *50*, 1173-1176.
[107] a) Tzeng, Z.-H.; Chen, H.-Y.; Huang, C.-T.; Chen, K. *Tetrahedron Lett*. **2008**, *49*, 4134-4137. b) Tzeng, Z.-H.; Chen, H.-Y.; Reddy, R. J.; Huang, C.-T.; Chen, K. *Tetrahedron* **2009**, *65*, 2879-2888.
[108] Fu, S.-D.; Fu, X.-K.; Zhang, S.-P.; Zou, X.-C.; Wu, X.-J. *Tetrahedron: Asymmetry* **2009**, *20*, 2390-2396.



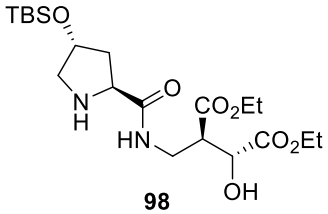
41 **95** *anti* **96**

R = H, 2-,3-,4-NO_2
4-CN



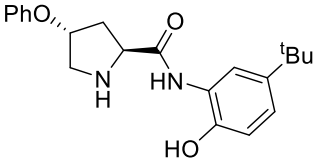
97

Baldintzak: **97** (%10 mol), DBSA (%10 mol)
H_2O, g.t., 72h
%33-95, 91:9-98:2 *dr (anti:sin)*, %93-99 *ee*



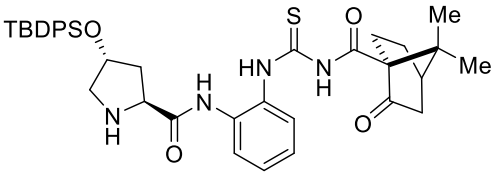
98

Baldintzak: **98** (%1 mol)
H_2O, g.t., 24h
%75-95, 96:4-99:1 *dr (anti:sin)*, %92-95 *ee*



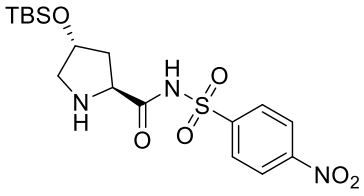
99

Baldintzak: **99** (%2 mol), TFA (%2 mol)
H_2O, g.t., 72h
%72-97, 92:8-99:1 *dr (anti:sin)*, %84-97 *ee*



100

Baldintzak: **100** (%20 mol), DBSA (%20 mol)
H_2O, g.t., 24h
%75-95, 96:4-99:1 *dr (anti:sin)*, % -92tik -95ra *ee*



101

Baldintzak: **101** (%3 mol)
H_2O, g.t., 12-96h
%70->99, 93:7->99:1 *dr (anti:sin)*, %98-99 *ee*

1.11. Eskema. Erreakzio aldoliko asimetriko intermolekularrerako sortutako *trans*-4-hidroxiprolina peptidoak.

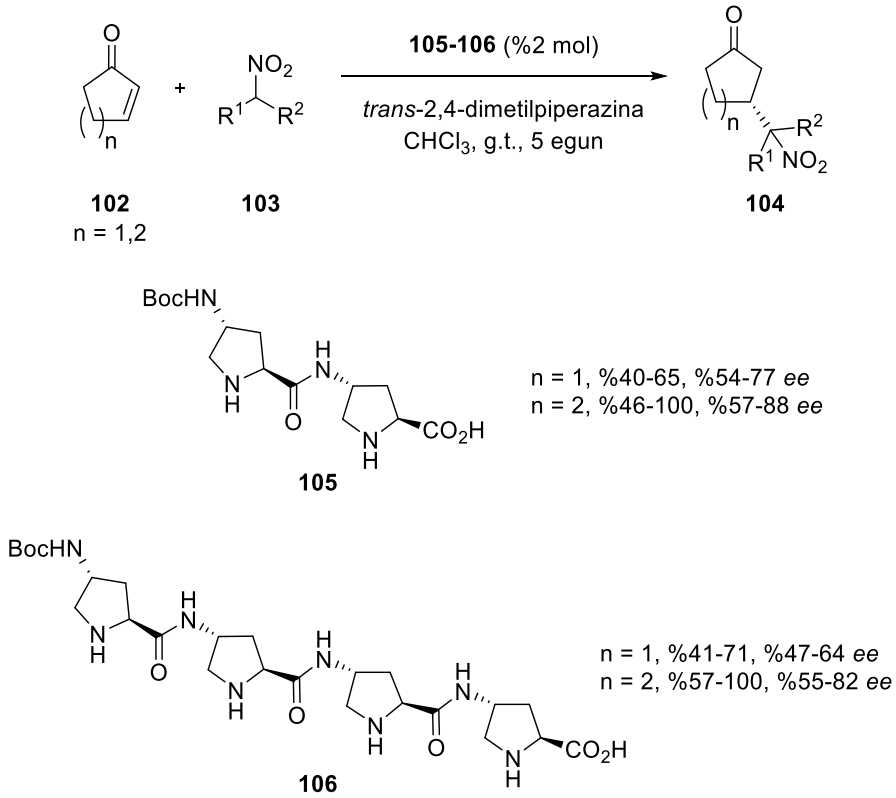
Azken urteotan likido ionikoetara atxikitako organokatalizatzaileez gain[109], ziklobutano-prolina egituradun γ-peptidoak ere erabili dira erreakzio aldolikoetan[110].

Era berean, katalizatzaile peptidikoak bestelako erreakzio asimetrikoetan aplikatu dira. *Cis* eta *trans*-4-amino prolina zein *trans*-4-hidroxiprolinan oinarritutako

[109] a) Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2010**, *66*, 513-518. b) Yadav, G. D.; Singh, S. *RSC Adv*. **2016**, *6*, 100459-100466.
[110] Illa, O.; Porcar-Tost, O.; Robledillo, C.; Elvira, C.; Nolis, P.; Reiser, O.; Branchadell, V.; Ortuño, R. J. *J. Org. Chem*. **2018**, *83*, 350-363.

katalizatzaileak hiru-osagaiko Biginelli erreakzioan[111] eta one-pot Aza-Michael-Henry erreakzioan[112] aztertu dira, hurrenez-hurren.

Amaitzeko, 1,4 adizio erreakzio asimetrioek ere merezi dute aipamenik, nahiz amino azido ez-naturaletatik eratorritako organokatalizatzaileak ez diren oso aplikagarri suertatu kasu hauetan. 2014an, Savic eta kolaboratzaileek ordezkapen desberdineko prolina ugari diseinatu zituzten aldehido eta binil sulfona arteko Michael erreakziorako. Haatik, lortutako emaitzek ez zuten interes berezirik sustatu ikerlarien artean, erreaktibitate eta selektibitate baxua erakutsi baitzuten (*ee* <%52).[113] Bi urteren buruan, Tsogoeva eta lankideek nitroalkano eta enona ziklikoen arteko adizio konjugatu interesgarria publikatu zuten, *trans*-4-amino prolina deribatuak katalitzatzailetzat hartuz (**1.12 Eskema**).[114] Bai di- bai tetrapeptidoek erreakzioa katalizatzeko gaitasuna adierazi zuten, baina harrigarriki, emaitza estereokimikoak ez zuen katalizatzailearen egiturako zentro katalitikoen kantitatearen menpekotasunik.



1.12. Eskema. Nitroalkano eta enona ziklikoen arteko Michael erreakzioa katalizatzeko sortutako 4-*trans*-amino prolinatik eratorritako di- eta tetrapeptidoak.

[111] Saha, S.; Moorthy, J. N. *J. Org. Chem*. **2011**, *76*, 396-402.
[112] Luo, H.; Yan, X.; Chen, L.; Li, Y.; Liu, N.; Yin, G. *Eur. J. Org. Chem*. **2016**, 1702-1707.
[113] Jovanovic, P.; Randelovic, J.; Ivcovic, B.; Suteu, C.; Vujosevic, Z. T.; Savic, V. *J. Serb. Chem. Soc*. **2014**, *79*, 767-778.
[114] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron: Asymmetry* **2006**, *17*, 989-992.

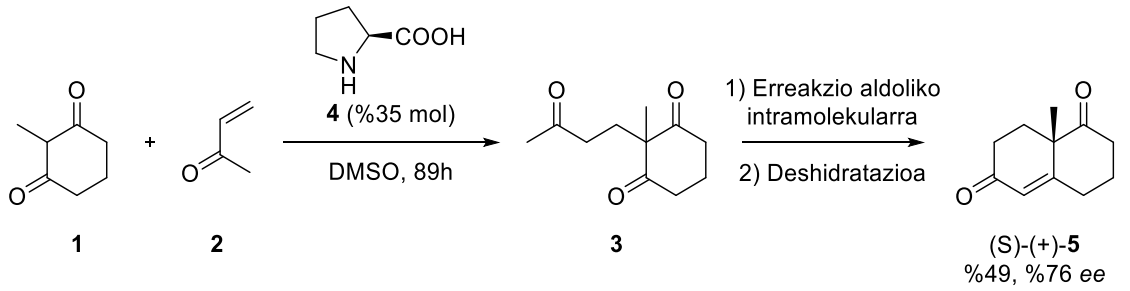
2. Kapitulua

Michael-Henry-Azetalizazio Kaskada Erreakzio Organokatalitiko Bidezko Ordezkapen Altuko Tetrahidropirano Biziklikoen Sintesia

2.1 MICHAEL-HENRY-AZETALIZAZIO ERREAKZIO ORGANOKATALITIKO ENANTIOSELEKTIBOAK

Michael erreakzioen ezaugarri erakargarrienen artean amaierako produktuak jasan ditzakeen erreakzio inter- edota intramolekularrak aurki daitezke, zeinak domino edo kaskada prozesuen bidez egitura konplexuak lortzea ahalbidetzen duten.[1] Tietzeren aburuz, metodologia hauetan bi lotura kimiko edo gehiago sortu daitezke erreakzio baldintza berberetan.[2]

Domino prozesu asimetriko organokatalitikoetan errotutako lehen lana Barbas III-ren ikerketa taldeak publikatu zuen, non pirrolidina erako amina sekundarioek 2-metil-1,3-ziklohexadiona **1** eta metilbinil zetona **2**-aren arteko Robinsonen anulazioa katalizatzen zuten, etekin eta enantioselektibitate maila altuak lortuz (**2.1 Eskema**).[3]



2.1 Eskema. Barbas III-k argitaratutako lehen domino erreakzio organokatalitikoa.

Aurkikuntza honen ostean, *one-pot* transformazio asimetrikoek bilakaera itzela jasan dute.[4] Ikerlariek erabili izan dituzten molekula txiki organikoen artean, benzotetramisol deribatuek[5], Brønsted azido erako katalizatzaileek[6], *N*,*N*'-dioxidoek[7], karbeno

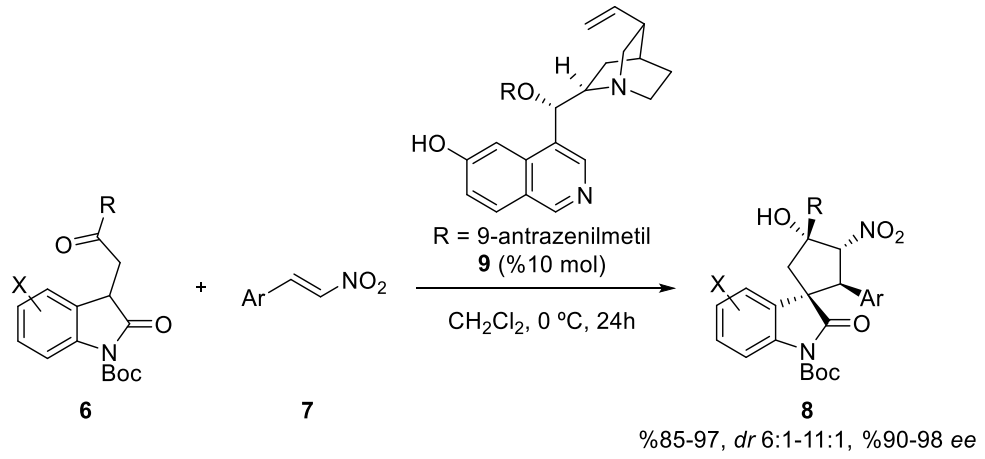
[1] Sukhorukov, A. Y.; Sukhanova, A. A.; Zlotin, S. G. *Tetrahedron* **2016**, *72*, 6191-6281.
[2] Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[3] Bui, T.; Barbas III, C. F. *Tetrahedron Lett*. **2000**, *41*, 6951-6954.
[4] a) Enders, D.; Grondal, C.; Hüttl, M. R. *Angew. Chem., Int. Ed*. **2007**, *46*, 1570-1581. b) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2011**, *50*, 8492-8509. c) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res*. **2015**, *48*, 1832-1844. d) Chanda, T.; Zhao, J. C.-G. *Adv. Synth. Catal*. **2018**, *360*, 2-79.
[5] a) Ahlemeyer, N. A.; Birman, V. B. *Org. Lett*. **2016**, *18*, 3454-3457. b) Izquierdo, J.; Pericás, M. A. *ACS Catal.* **2016**, *6*, 348-356.
[6] a) Shi, F.; Zhang, H.-H.; Sun, X.-X.; Liang, J.; Fan, T.; Tu, S.-J. *Chem. Eur. J.* **2015**, *21*, 3465-3471. b) Dai, W.; Lu, H.; Li, X.; Shi, F.; Tu, S.-J. *Chem. Eur. J*. **2014**, *20*, 11382-11389. c) Yang, B.-M.; Cai, P.-J.; Tu, Y.-Q.; Yu, Z.-X.; Chen, Z.-M.; Wang, S.-H.; Wang, S.-H.; Zhang, F.-M. *J. Am. Chem. Soc.* **2015**, *137*, 8344-8347.
[7] a) Feng, J.; Fu, X.; Chen, Z.; Lin, L.; Liu, X.; Feng, X. *Org. Lett*. **2013**, *15*, 2640-2643. b) Feng, J.; Lin, L.; Yu, K.; Liu, X.; Feng, X. *Adv. Synth. Catal*. **2015**, *357*, 1305-1310.

N-heteroziklikoek[8], *cinchona* alkaloideek[9], tiourea[10] eta eskuaramida[11] multifuntzionalek eta amina primario[12] eta sekundarioek[13] aipamen berezia merezi dute.

Nitro motako talde funtzionalen erreaktibitate anitzak eta eraldaketa errazak kontuan izanik, Michael-Henry sekuentziak paregabeko interesa sustatu du.[14] Izan ere, pausu anitzeko sintesiarekin alderatuz, tandem prozesu hauek zentro estereogeniko askoko molekulen konstrukziorako metodologia zuzenena bihurtu dira.[9c] Hots, azken urteotan Michael-Henry domino erreakzio asimetriko franko argitaratu dira.

Cinchona alkaloideek, esaterako, Michael-Henry kaskada erreakzioak emaitza itzelekin katalizatu dituzte. Testuinguru honetan, Albertshoferren lan taldeak antrazenil-kinina **9** deribatuak katalizaturiko lau zentro estereogenikodun spiroziklopentanooxindolen sintesia deskribatu zuen lehenik.[15] Erreakzioa nitroestireno zein oxindol askorentzat aplikagarri izan zen, etekin, diastereo- eta enantioselektibitate altuak erdietsiz (**2.2 Eskema**). Jarraiki, Samantaren ikerketa taldeak bentzil taldeaz babesturiko zinkonidinen erabilpena bultzatu zuen tetrahidrokarbazolen sintesi estereoselektiborako, etekin onak, ratio diastereomeriko altuak eta soberakin enantiomeriko itzelak lortuz.[9c]

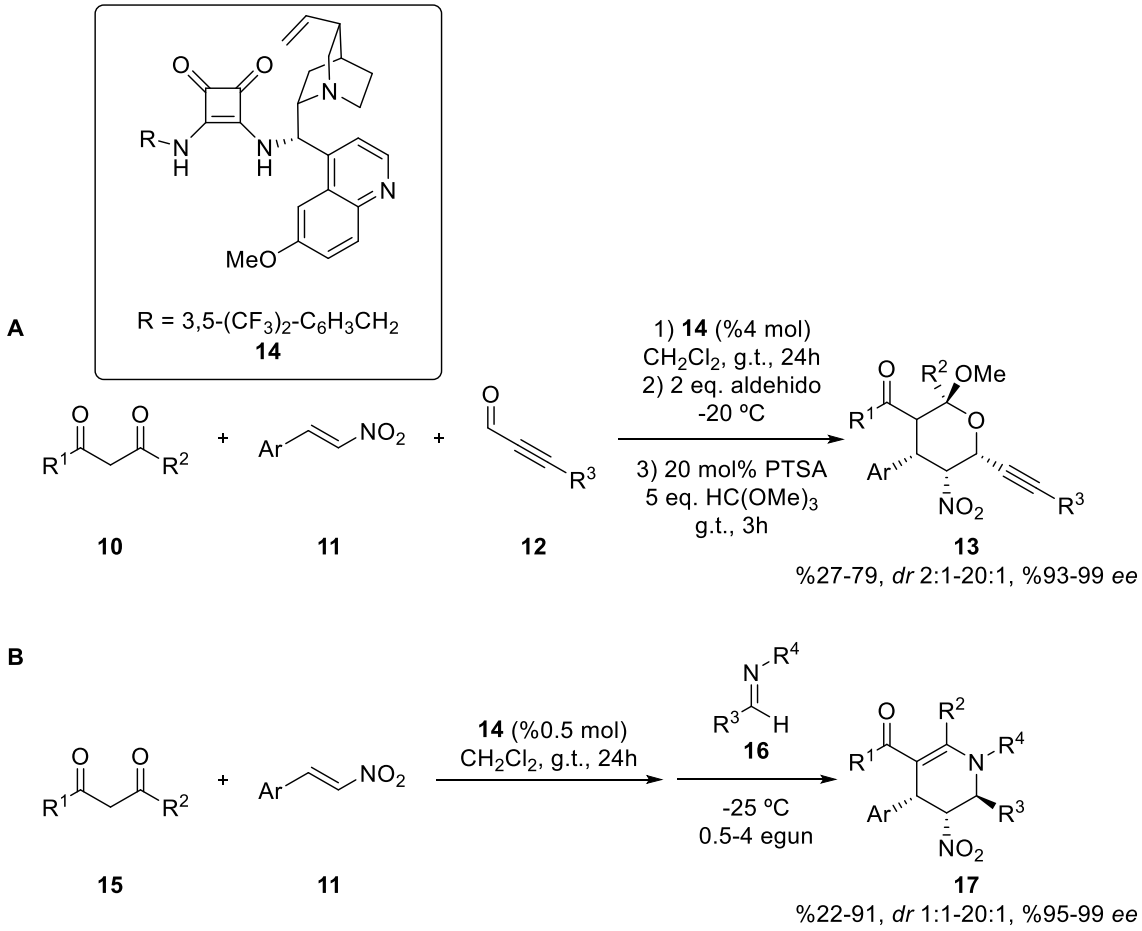
[8] Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Synthesis* **2017**, *49*, 451-471.
[9] a) Connon, S. J. *Chem. Commun*. **2008**, 2499-2510. b) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc*. **2008**, *130*, 14416-14417. c) Jaiswal, P. K.; Biswas, S.; Singh, S.; Pathak, B.; Mobin, S. M.; Samanta, S. *RSC Adv*. **2013**, *3*, 10644-10649. d) Huang, J.-R.; Sohail, M.; Taniguchi, R.; Monde, K.; Tanaka, F. *Angew. Chem., Int. Ed*. **2017**, *56*, 5853-5857. e) Capobianco, A.; Di Mola, A.; Intintoli, V.; Massa, A.; Capaccio, V.; Roiser, L.; Waser, M.; Palombi, L. *RSC Adv*. **2016**, *6*, 31861-31870.
[10] a) Tiso, S.; Palombi, L.; Vignes, C.; Di Mola, A.; Massa, A. *RSC Adv*. **2013**, *3*, 19380-19387. b) Kang, K.-T.; Kim, S.-G. *Synthesis* **2014**, *46*, 3365-3373. c) Dou, X.; Han, X.; Lu, Y. *Chem. Eur. J.* **2012**, *18*, 85-89. d) Mei, R.-Q.; Xu, X.-Y.; Peng, L.; Wang, F.; Tian, F.; Wang, L.-X. *Org. Biomol. Chem*. **2013**, *11*, 1286-1289.
[11] a) Yang, W.; He, H.-X.; Gao, Y.; Du, D.-M. *Adv. Synth. Catal*. **2013**, *355*, 3670-3678. b) Blümel, M.; Chauhan, P.; Hahn, R.; Raabe, G.; Enders, D. *Org. Lett*. **2014**, *16*, 6012-6015. c) Chauhan, P.; Urbanietz, G.; Raabe, G.; Enders, D. *Chem. Commun*. **2014**, *50*, 6853-6855. d) Chauhan, P.; Mahajan, S.; Raabe, G.; Enders, D. *Chem. Commun*. **2015**, *51*, 2270-2272.
[12] a) Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Eur. J. Org. Chem.* **2012**, 1318-1327. b) Li, J.-H.; Du, D.-M. *Org. Biomol. Chem*. **2015**, *13*, 9600-9609. c) Sun, X.; Fei, J.; Zou, C.; Lu, M.; Ye, J. *RSC. Adv*. **2016**, *6*, 106676-106679.
[13] a) Shen, J.; Liu, D.; An, Q.; Liu, Y.; Zhang, W. *Adv. Synth. Catal*. **2012**, *354*, 3311-3325. b) Zeng, X.; Ni, Q.; Raabe, G.; Enders, D. *Angew. Chem., Int. Ed*. **2013**, *52*, 2977-2980. c) Poulsen, P. H.; Feu, K. S.; Paz. B. M.; Jensen, F.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2015**, *54*, 8203-8207. d) Zhang, J.; Ajitha, M. J.; He, L.; Liu, K.; Dai, B.; Huang, K.-W. *Adv. Synth. Catal*. **2015**, *357*, 967-973. e) Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D. K. B.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2016**, *138*, 6412-6415.
[14] a) Nef, J. U. *Justus Liebigs Ann. Chem*. **1894**, *280*, 263-291. b) Laroch, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, New York, **1989**. c) Beck, A. K.; Seebach, D. *Chem. Ber*. **1991**, *124*, 2897-2911. d) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434. e) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356-1361.
[15] Albertshofer, K.; Tan, B.; Barbas III, C. F. *Org. Lett*. **2012**, *14*, 1834-1837.



2.2 Eskema. Albertshoferrek deskribaturiko oxindol eta nitroolefinen arteko Michael-Henry kaskada erreakzio organokatalitikoa.

Kininatik eratorritako eskuaramida bifuntzionalen erabilpena ere sarri ikertu izan da. Enders eta kolaboratzaileek **14** katalizatzaile esanguratsuena garatu eta ebaluatu zuten tetrahidropirano[16] eta tetrahidropiridina[11c] egitura funtzionalizatuen bilakaera aurrera eramateko. Emaitza estereokimiko altuak lortu ziren kasu guztietan, katalizatzaile karga oso baxuekin lan eginez. Amaierako produktuak etekin moderatuetan lortu ziren, ordea (**2.3 Eskema**). Denbora gutxira, katalizatzaile berberak indolin-3-ona substratuentzat ere baliagarri izatea frogatu zuen.[17]

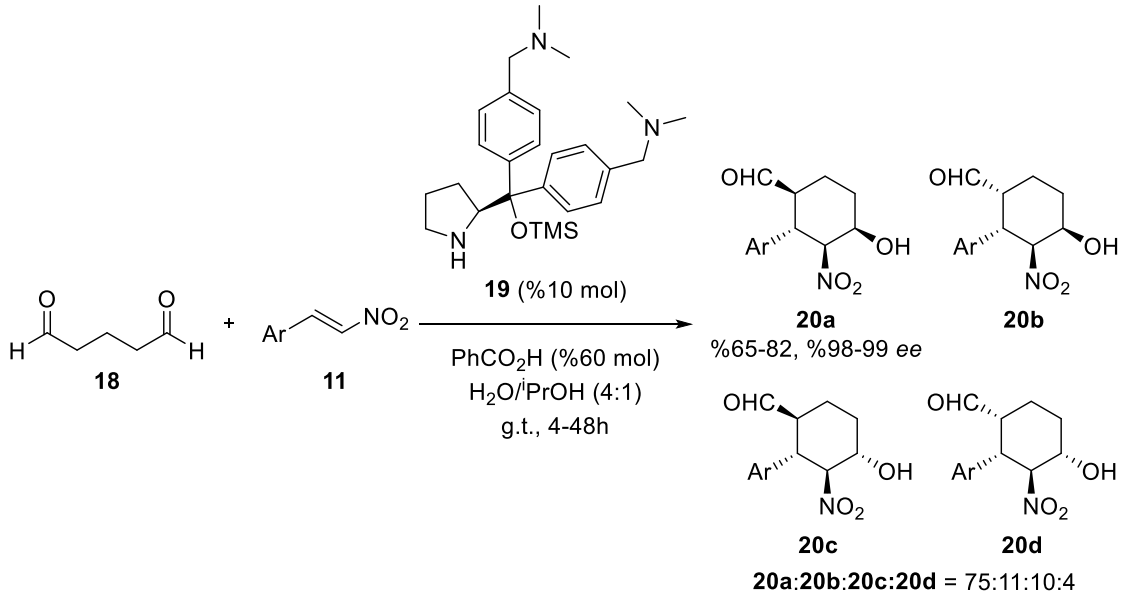
[16] Hahn, R.; Raabe, G.; Enders, D. *Org. Lett*. **2014**, *16*, 3636-3639.
[17] Mahajan, S.; Chauhan, P.; Loh, C. C. J.; Uzungelis, S.; Raabe, G.; Enders, D. *Synthesis* **2015**, *47*, 1024-1031.



2.3 Eskema. Endersek sortutako 14 eskuaramida katalizatzaile bifuntzionala eta bere A) tetrahidropirano eta B) tetrahidropiridinen sintesia.

Prolina erako katalizatzaileak aipatu behar dira, halaber. 2011an, Headleyk **19** katalizatzaile birziklagarriaren erabilera erazagutu zuen ur ingurunean burututako ziklohexano eraztunen sintesirako (**2.4 Eskema**).[18] Katalizatzaile honek amonio motako likido ionikoa sortzen zuen erreakzio ingurunean, eta beraz, uretan disolbagarri bihurtzen zen aditibo azidoen presentzian. Gainera, birziklapen ikerketek katalizatzailea lau ziklo katalitiko kontsekutibotan erabilgarri zela erakutsi zuten, diastereo- eta enantioselektibitatean inolako galerarik pairatu gabe.

[18] Chintala, P.; Ghosh, S. K. ; Long, E.; Headley, A. D.; Ni, B. *Adv. Synth. Catal*. **2011**, *353*, 2905-2909.



2.4 Eskema. Headleyk ezagutarazitako prolina egituran oinarritutako sistema katalitikoa.

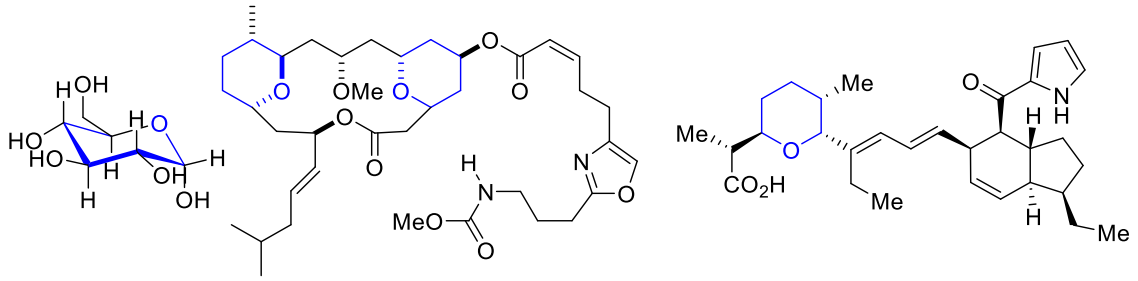
Ildo honetan, Hong eta kolaboratzaileek Jørgensen-Hayashi katalizatzailea enplegatu zuten sukzinaldehido eta nitroolefinen arteko Michael-Henry-ziklaziorako.[19] Amaierako ziklopentanokarbaldehidoek ondoko lau zentro estereogeniko zituzten egituran, eta etekin eta enantioselektibitate altuak azaleratu zituzten. Jørgensen-Hayashi deribatua glutaraldehido ordezkatzaileetan ere aplikatu zen, 3-oxabiziklo[3.3.1]nona-2-onak enantioselektiboki sortuz.[20]

Interes berezia du prolina erako katalizatzaileek tetrahidropirano eskeletoen formazioan izandako jokaerak. Jarraian, gai hau sakonki aurkeztuko da.

2.1.1 Tetrahidropirano eskeletoak lortzeko sintesi bideak

Tetrahidropiranoa (THP) sei osagaiko heterozoiklo oxigenatua da. Ezaugarri esanguratsuenen artean, alde batetik, bost zentro estereogeniko adina izateko aukera eta bestetik, daukaten funtzionalitate aniztasuna aipatu behar dira.[21] **2.1 Irudia**k THP egitura bere baitan duten molekula esanguratsuak biltzen ditu.

[19] Hong, B.-C.; Chen, P.-Y.; Kotame, P.; Lu, P.-Y.; Lee, G.-H.; Liao, J.-H. *Chem. Commun*. **2012**, *48*, 7790-7792.
[20] Hong, B.-C.; Lan, D.-J.; Dange, N. S.; Lee, G.-H.; Liao, J.-H. *Eur. J. Org. Chem*. **2013**, 2472-2478.
[21] Vetica, F.; Chauhan, P.; Dochain, S.; Enders, D. *Chem. Soc. Rev*. **2017**, *46*, 1661-1674.



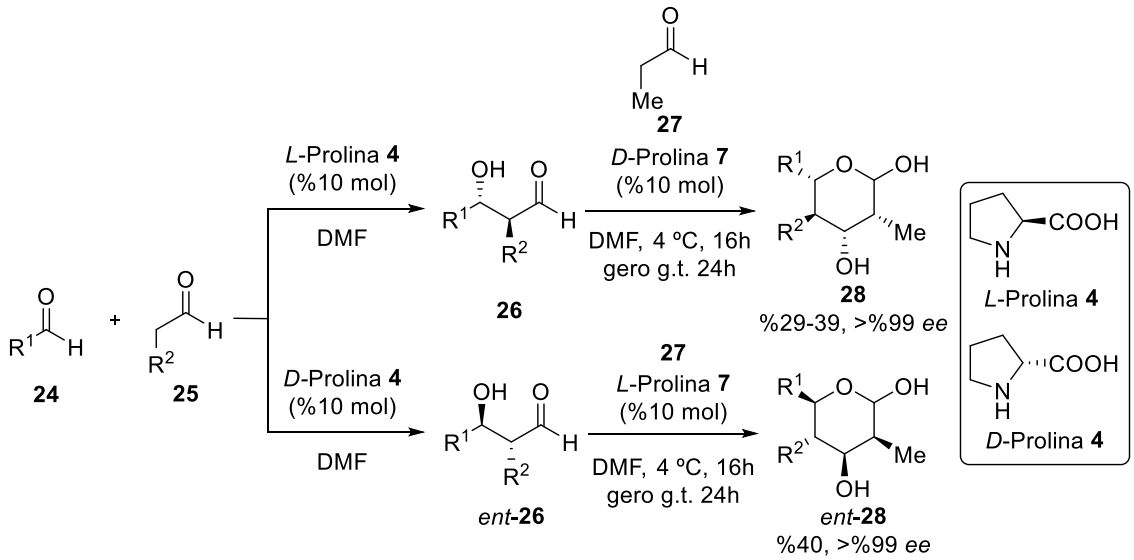
2.1 Irudia. THP egitura (urdinez) barne duten produktu natural eta konposatu bioaktiboak.

Egitura molekular hauek eratzeko metodologia aunitz garatu dira, haien artean organokatalisi asimetrikoa bereziki interesgarri gertatuz. Hidrogeno lotura bidez lan egiten duten molekulak[22] eta amina primarioak[23] organokatalizatzaile gisa erabili izan diren arren, amina sekundarioak dira, dudarik gabe, katalizatzaile ohikoenak. Lehen tetrahidropiranoen sintesi organokatalitikoa Córdovaren taldeak gauzatu zuen 2005. urtean. Hiru konposatu karbonilikoen jarraikako erreakzio aldolikoak dagozkien hexosak kimio-, diastereo- eta enantioselektibitate itzelekin erdietsi zituen.[24] Zoritxarrez, hasiera batean ebaluatutako *one-pot* estrategiak ez zuen arrakastarik izan, eta **26** aldol artekaria isolatzea beharrezko egokitu zen bi-pausuko sintesia burutuz. Honek, katalizatzailearen kiralitatearen araberako hexosa enantiomerikoen lorpena ahalbideratu zuen (**2.5 Eskema**).

[22] a) Asano, K.; Matsubara, S. *J. Am. Chem. Soc*. **2001**, *133*, 16711-16713. b) Fukata, Y.; Miyaji, R.; Okamura, T.; Asano, K.; Matsubara, S. *Synthesis* **2013**, 1627-1634. c) 16. Erreferentzia.

[23] a) Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas III, C. F. *Proc. Natl. Acad. Sci. U. S. A*. **2010**, *107*, 20672-20677. b) Cui, H.-L.; Tanaka, F. *Chem. Eur. J*. **2013**, *19*, 6213-6216.

[24] Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343-1345.



2.5 Eskema. THP eskeletoak lortzeko lehen bide sintetikoa.

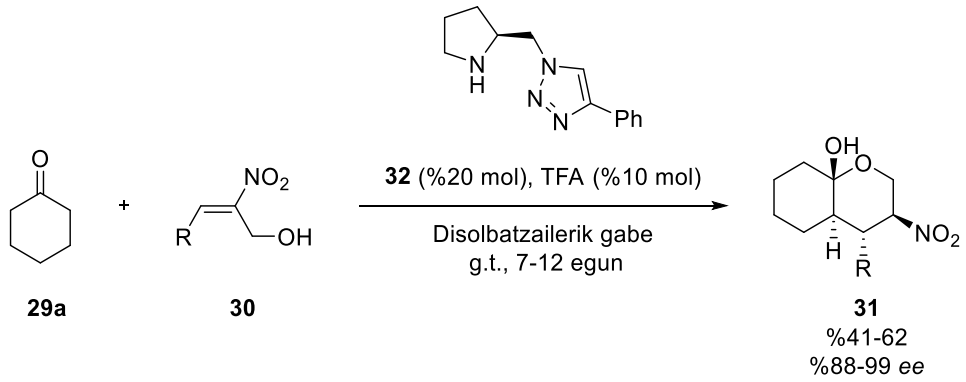
Córdovaren lan honek ikerketa talde gehiagok tetrahidropirano eskeletoen sintesian lan egitea bulkatu zuen.[25] Gehienek aldehido α,β-asegabeen eta nitroalkoholen arteko Michael/azetalizazio erreakzioak erabiltzen zituzten, non indukzio estereokimikoa difenilprolinol silil eter motako katalizatzeileen mendeko zen.[26] Rodriguez eta Bonneren taldeak bestalde, silil eter katalizatzaileen enplegua aztertu zuen 2,3,4-triordezkatutako tetrahidropiranoen sintesirako, biziklo[3.2.1]oktanoen C-N loturaren apurketa kimioselektiboaz baliatuz.[27] Aitatu behar da ziklohexanona nukleozale moduan erabiltzen duen adibide bat badela literaturan (**2.6 Eskema**).[28]

[25] a) Morita-Bailys-Hillman sintesi bidea jarraituz: Han, B.; Xie, X.; Huang, W.; Li, X.; Yang, L.; Peng, C. *Adv. Synth*. *Catal*. **2014**, *356*, 3676-3682. b) Oxa-Diels-Alder sekuentzia jarraituz: Lu, L.-Q.; Xing, X.-N.; Wang, X.-F.; Ming, Z.-H.; Wang, H.-M.; Xiao, W.-J. *Tetrahedron Lett*. **2008**, *49*, 1631-1635. c) [2+2] zikloadizio-hemiazetalizazio bidea jarraituz: Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem., Int. Ed*. **2012**, *51*, 4104-4107.

[26] a) Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett*. **2009**, *11*, 4056-4059. b) Wei, M.-H.; Zhou, Y.-R.; Gu, L.-H.; Luo, F.; Zhang, F.-L. *Tetrahedron Lett*. **2013**, *54*, 2546-2548.

[27] D'Elia, C. S.; Goudedranche, S.; Constantieux, T.; Bella, M.; Bonne, D.; Rodriguez, J. *Adv. Synth. Catal.* **2017**, *359*, 3638-3641.

[28] Chandrasekar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Rao, K. V.; Jagadesh, B. *Chem. Commun.* **2009**, 4985-4987.

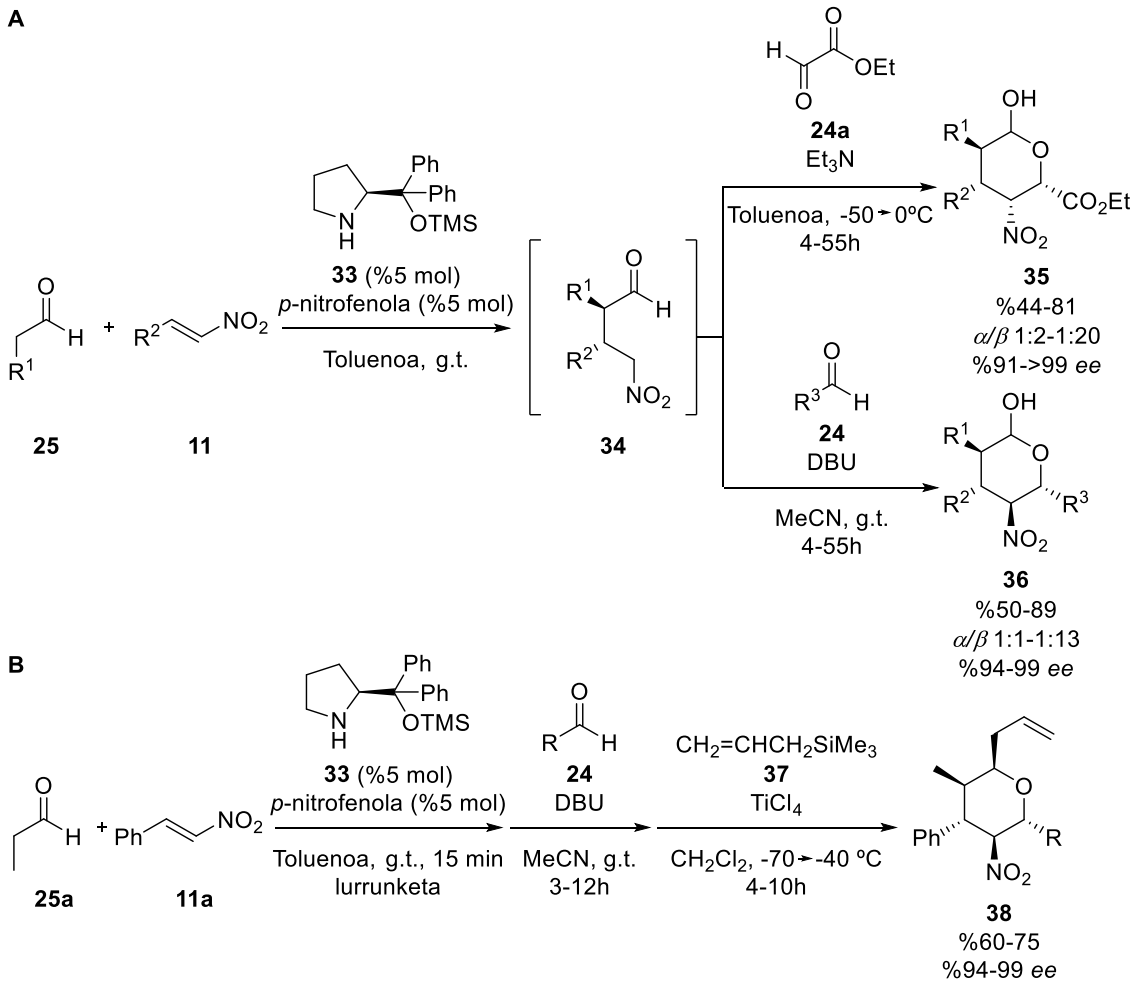


2.6. Eskema. Ziklohexanona eta 2,3-diordezkatutako nitroolefinen arteko Michael-azetalizazio erreakzioa.

2.1.1.1 Michael-Henry-Azetalizazio bidezko tetrahidropiranoen sintesia

Hiru-osagaiko Michael-Henry-azetalizazio erreakzioak ez dira oso ikertuak izan literaturan. 2011. urterarte itxarotea beharrezko izan zen arlo honek interesa sortzeko. Eremu honetan argitaratutako lehen lanak Hayashi eta kolaboratzaileek burututako aldehido eta nitroalkenoen arteko tandem prozesua deskribatu zuen, non THP eskeletoak diastereo- eta enantioselektibitate altuarekin lortu ziren, difenilprolinol silil eter **33** katalizatzailearen usadio bidez.[29] Sintesiko azken Henry-azetalizazio urratsa aurrera eramateko base egokienaren azterketa burutzean **35** produktu zinetikoa edo **36** termodinamikoa selektiboki lor zitekeela atzeman zuten. Hau da, trietilaminak produktu zinetikoaren formazioa bultzatzen zuen artean, DBUak produktu termodinamikoa sortzen zuen produktu nagusitzat. Azken base honen erabilerak **35** produktu zinetikoaren **36** produkturako isomerizazioa gauzatu zezakeela ere deskribatu zuten, enantiomero soberakin baloreetan galerarik izan gabe (**2.7A Eskema**). Lan honek, hala ere, desabantaila badu: tetrahidropiranol eraztun guztiak α eta β anomeroen nahaste bezala lortzen ziren. Muga hau gainditu asmoz, sortutako tetrahidropiranolak erreaktibo alilatzaileekin erreakzionarazi zituzten, **38** tetrahidropirano ordezkatuak enantioselektibitate altuetan sortuz (**2.7B Eskema**).

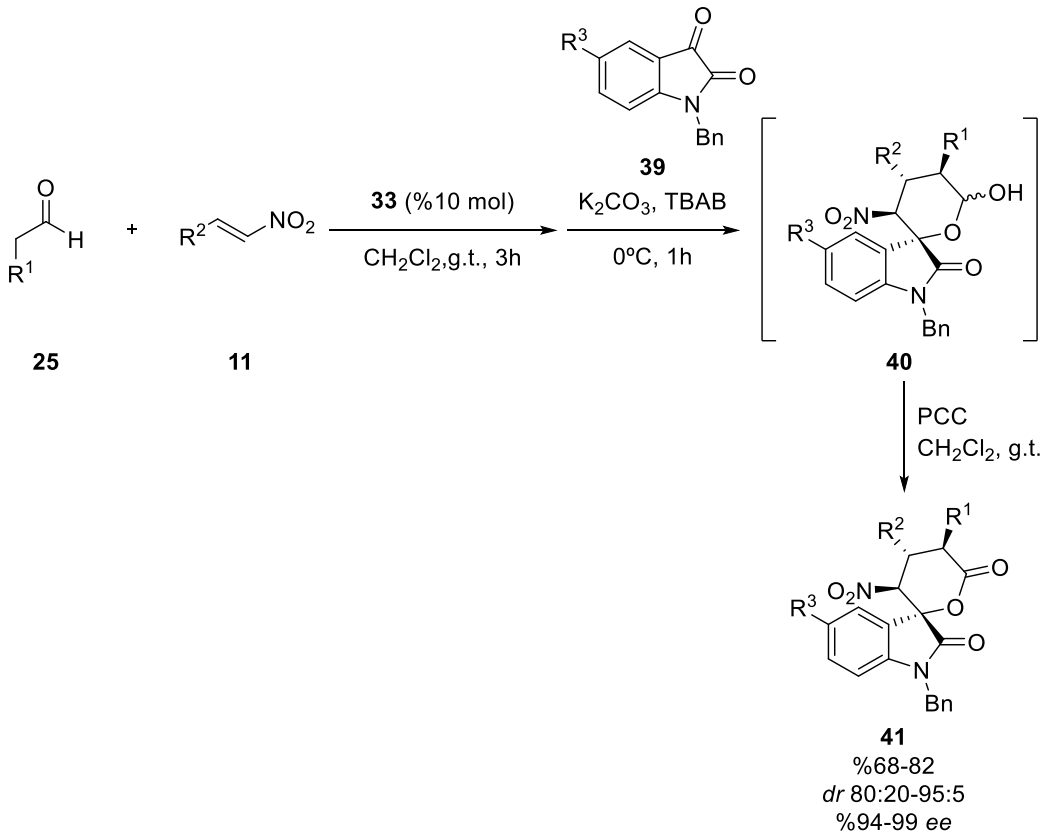
[29] Ishikawa, H.; Sawano, S.; Yasui, Y.; Shibata, Y.; Hayashi, Y. *Angew. Chem., Int. Ed*. **2011**, *50*, 3774-3779.



2.7 Eskema. Hayashik landutako A) hiru-osagaiko Michael-Henry-Azetalizatio bidea tetrahidropiranol egiturak sortzeko. B) Tetrahidropiranoletatik tetrahidropiranoak lortzeko alilazio prozesua.

THP eraztunetan oinarritutako egitura konplexuagoak ere sintetizatu izan dira, antzeko metodologiak jarraituz. Huang, Peng eta Hanek adibidez, espirooxiindol pirano estrukturen sintesia publikatu zuten aldehido, nitroalkeno eta isatina *N*-babestuak hasierako erreaktibo moduan erabiliz.[30] *One-pot* domino prozesua amaitu ondoren, hemiazetalaren PCC bidezko oxidazioa burutu zuten, **41** laktonak etekin on eta estereoselektibitate altuarekin lortuz (**2.8 Eskema**). Hiru osagaietako egitura aldaketek oxaspiroindol familia zabalaren formazioa ere ahalbidetu zuten.

[30] Xie, X.; Peng, C.; He, G.; Leng, H.-J.; Wang, B.; Huang, W.; Han, B. *Chem. Commun*. **2012**, *48*, 10487-10489.



2.8 Eskema. Huang eta Pengek garatutako spirooxindol pirano egituren sintesia.

2.2 HELBURUAK

Gure ikerketa taldeak publikatutako aurreko emaitzen aburuz, funtzionalizazio altuko pirrolidina ez-naturaletan oinarritutako amina primario[31] zein γ-dipeptidoek[32] propietate katalitiko berriak dituzte zetona zikliko eta β-nitroestirenoen arteko Michael erreakzioetan. Hala ere, amina primarioen erabilerak emaitza baxuak erakutsi zituen ziklopentanona eta zikloheptanona zetona nukleozale moduan enplegatzean. Honenbestez, katalizatzaile dimerikoak zetona desberdinen Michael erreakzioan aplikatzea da Kapitulu honen jomuga nagusi.

Michael-Henry-azetalizazio *one-pot* domino prozesuak ere interes berbera merezi du, aintzinean aipatutako kasuak kontuan hartuz. Aitzitik, aldehidoen erabilerak ikerketa sakona izan duen bitartean, zetona nukleozaleak aztertu gabe dira oraindik. Gure 1,4 adizio erreakzioetan ikuskatutako emaitza oparoak kontutan izanez, Kapitulu honen bigarren xedea katalizatzaile dimeriko onenak Michael-Henry-azetalizazio erreakzioetan

[31] Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F. P. *J. Org. Chem*. **2015**, *80*, 5588-5599.
[32] Andrea Ruiz-Olalla Doktoreak, bere Doktoretza Tesian: *Novel Studies on Enamine and Acid Organocatalysts in Carbon-Carbon Bond Forming Reactions*, Universidad del País Vasco/Euskal Herriko Unibertsitatea. 2016ko martxoa. http://addi.ehu.es/handle/10810/20926.

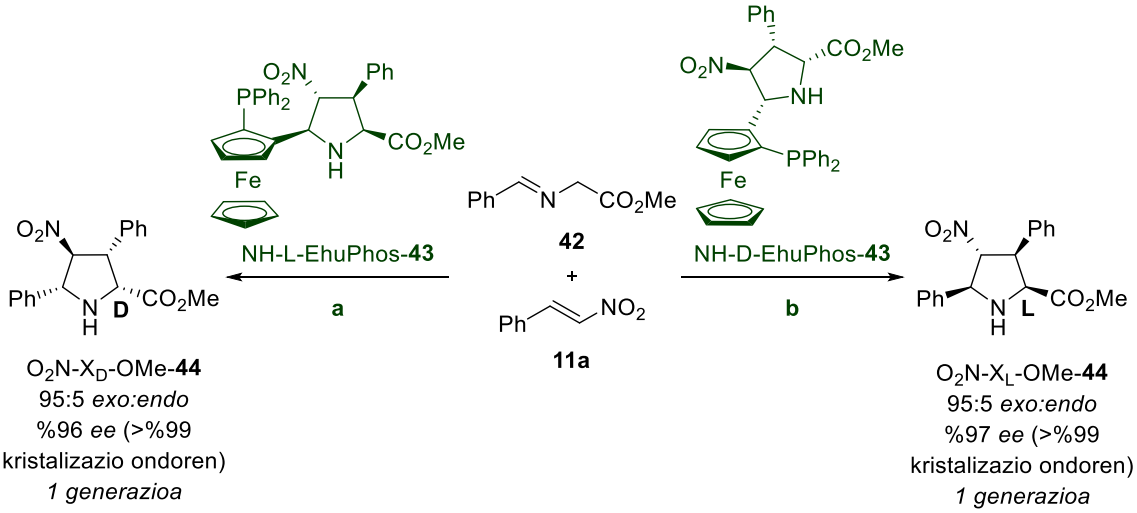
aplikatzea da. Katalizatzaileen aldakortasuna ere aztertuko da, hasierako erreaktibo desberdinak ebaluatuz.

2.3 FUNTZIONALIZAZIO ALTUKO PIRROLIDINA EZ-NATURALEN SINTESIA

Jomugako amino eta dipeptido deribatuak sintetizatzeko pausu sintetiko ugari burutu behar dira. Honela, kobre (I) bidezko (3+2) zikloadizio erreakzioaren ondoren, hidrolisi, hidrogenazio, hautazko metilazio eta akoplamendu peptidiko erreakzioak aurrera eraman ziren.

2.3.1 Lehen eta bigarren generazioko katalizatzaileak

Gure ikerketa taldean gauzaturiko aurretiko esperimentuetan ikusi moduan, ferrozenilo-pirrolidina ligando hibridoek azometino iluroen eta elektroietan urriak diren alkenoen arteko (3+2) zikloadizio erreakzioa katalizatzeko gaitasun handia zuten (**2.9 Eskema**).[33] Bertan, NH-D-EhuPhos-**43** ligandoak O_2N-X_L-OMe-**44** konfigurazioko pirrolidinak etekin eta enantioselektibotasun altuarekin sortzen zituen bitartean, bere enantiomero den NH-L-EhuPhos-**43** ligandoak O_2N-X_D-OMe-**44** erako pirrolidinak sustatzen zituen, estereoselektibitate maila berberarekin.

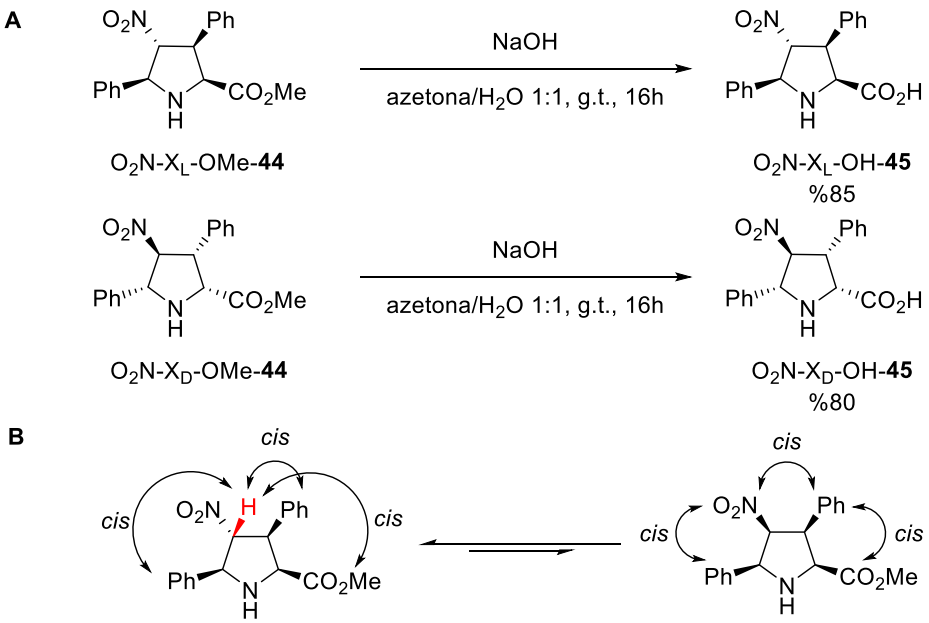


2.9 Eskema. Lehen generazioko O_2N-X_D-OMe-**44** eta O_2N-X_L-OMe-**44** organokatalizatzaileen sintesia. Pirrolidinaren *L* eta *D* konfigurazioa nabarmendu da. Erreaktibo eta baldintzak; a) NH-L-EhuPhos-**43** (3 mol%), $Cu(CH_3CN)_4PF_6$ (3 mol%), Et_3N (5 mol%), THF, -20 °C, 16h. b) NH-D-EhuPhos-**73** (3 mol%), $Cu(CH_3CN)_4PF_6$ (3 mol%), Et_3N (5 mol%), THF, -20 °C, 16h.

Jarraiko NaOH bidezko azetona/ur inguruneko hidrolisi basikoak ondorengo O_2N-$X_{L/D}$-OMe-**45** deribatuak etekin altuetan sortu zituen (**2.10A Eskema**). Baldintza

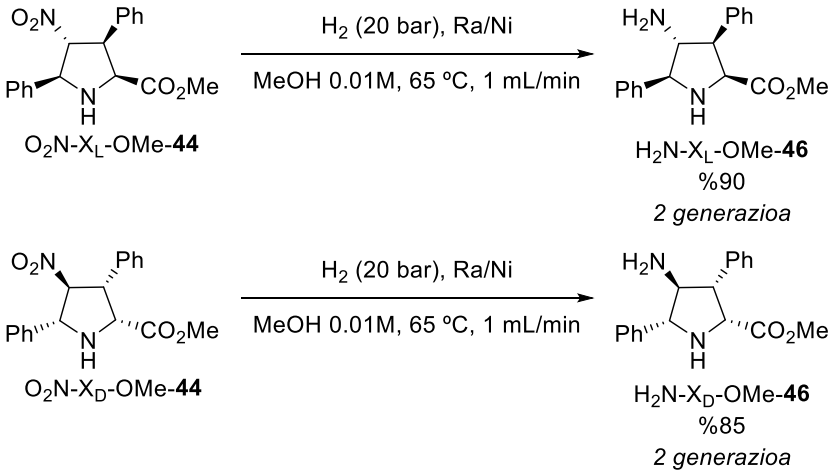
[33] a) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci*. **2012**, *3*, 1486-1491. b) Retamosa, M. G.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem*. **2015**, 2503-2516.

hauek ez zuten epimerizazio arriskurik suposatzen, *exo*- zikloaduktuen konfigurazioa dela eta. Epimerizazio posibleak C4 posizioko protoi azidoena kenduko luke (nitro funtzio taldearen ondokoa), baina protoi hau gainerako talde guztiekiko *cis* disposizioan aurkitzen da, basearen hurbilketa zailduz (**2.10B Eskema**, ezkerra). Sortutako epimeroaren egonkortasuna ere aztertu behar da. Izan ere, *exo*- pirrolidinen epimerizazioak alboz-alboko ordezkatzaileen arteko *cis* orientazioen kantitatea handitzen du, termodinamikoki ezegonkorragoa den produktua sortuz (**2.10B Eskema**, eskuina).



2.10 Eskema. A) O_2N-$X_{L/D}$-OH-**45** deribatu azidoen sintesia. B) Epimerizazio oreka posibleak. Ezkerra: C4 protoi azidoenaren (gorria) disposizioa, gainerako ordezkatzaileekin alderatuz. Eskuina: epimerizazioaren ondorengo produktuaren egitura. *exo*-L konfigurazioa hartu da eredutzat, ulermena errazteko.

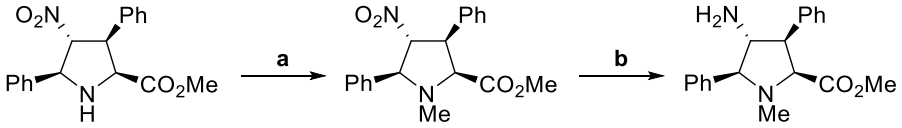
Hidrolisiarekin batera, Raney-Nikel-ak katalizatutako fluxu jarraiko hidrogenazioak bigarren generazioko H_2N-X_L-OMe-**46** eta H_2N-X_D-OMe-**46** katalizatzaileak sortu zituen, %90 eta %85-eko etekinarekin, hurrenez-hurren (**2.11 Eskema**).



2.11 Eskema. Bigarren generazioko H_2N-$X_{L/D}$-OMe-**46** katalizatzaileen hidrogenazio bidezko sintesia.

2.3.2. Hirugarren generazioko katalizatzaileak

Dipeptido hauen sintesirako azken pausuak amina eta azido deribatuen arteko akoplamendu erreakzioa biltzen du. Hala ere, bi amina unitate katalitikotik bat blokeatu nahi den dipeptidoen kasuan, bide sintetikoak metilazio prozesu gehigarri baten beharra du, hidrogenazio pausuaren aurretik. Helburu hau kontuan izanik, O_2N-X_L-OMe-**44** pirrolidina formaldehido eta azido formikoaren presentziako aminazio erreduktibo urratsera azpiratu zen. Segidako hidrogenazio erreakzioak H_2N-X_L^{Me}-OMe-**48** amino metil esterra etekin moderatuetan sortu zuen (**2.12 Eskema**).



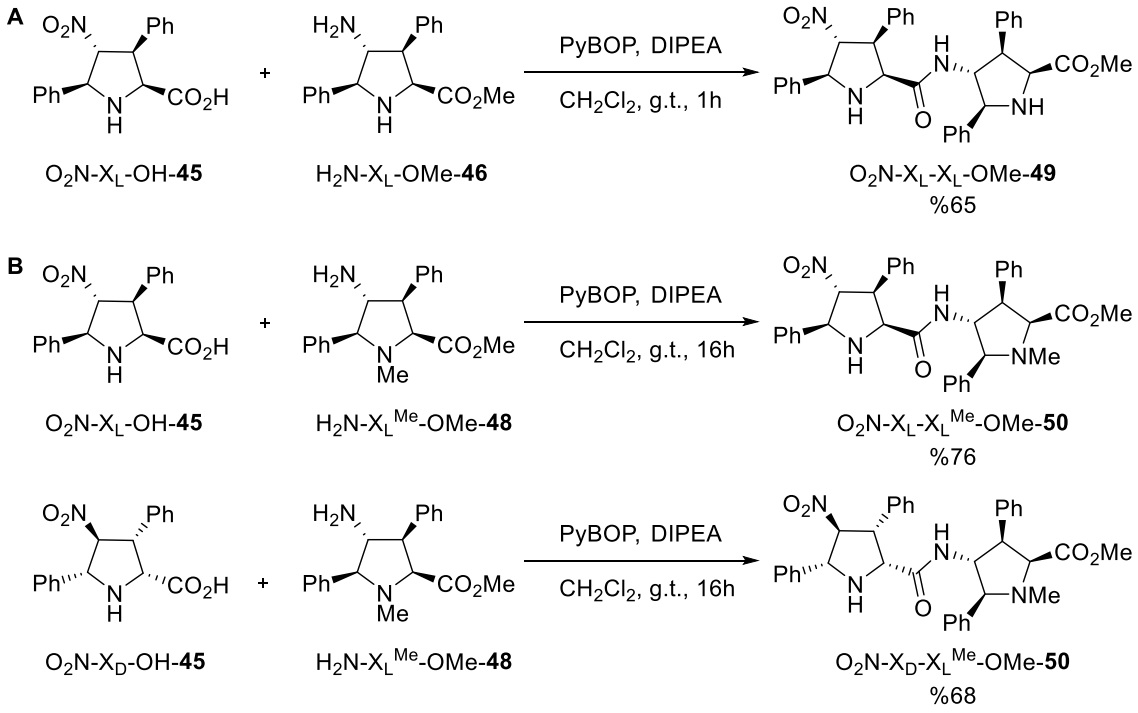
O_2N-X_L-OMe-**44**

O_2N-X_L^{Me}-OMe-**47**
%90

H_2N-X_L^{Me}-OMe-**48**
%65

2.12 Eskema. O_2N-X_L^{Me}-OMe-**47** eta H_2N-X_L^{Me}-OMe-**48** pirrolidinen sintesia. Etekinak dagokion pausuari egiten dio erreferentzia. Baldintzak: a) H_2CO/HCO_2H, 100 °C, 2h; b) H_2 (20 bar), Ra/Ni, MeOH [0.01M], 65 °C, 1 mL/min.

Amiden formazio erreakzioetarako burututako aurretiko ikerketek gure sistema dimerikoen kasurako PyBOP akoplamentu agentearen optimotasuna frogatu zuten.[31] Honela, akoplamendu erreakzioak PyBOP eta DIPEAren presentzian gauzatu ziren, giro tenperaturan. O_2N-X_L-X_L-OMe-**49** dipeptidoa %65-eko etekinean lortu zen, ordu baten buruan (**2.13A Eskema**). O_2N-X_L-X_L^{Me}-OMe-**50** eta O_2N-X_D-X_L^{Me}-OMe-**50** dipeptido metilatuek, bestalde, erreakzio denbora luzeagoak behar izan zituzten (**2.13B Eskema**).

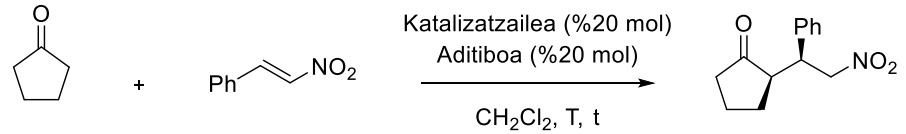


2.13 Eskema. A) O_2N-X_L-X_L-OMe-**49** eta B) O_2N-$X_{L/D}$-X_L^{Me}-OMe-**50** dipeptidoen PyBOP bidezko sintesia.

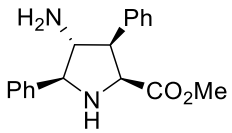
2.4 ZIKLOPENTANONA EDO ZIKLOHEPTANONA ETA *TRANS*-β-NITROESTIRENOAREN ARTEKO MICHAEL ERREAKZIOA

Taldean buruturiko aurretiazko ikerketek frogatu bezala, lehen generazioko **44** deribatuek ezinezko zuten zetona eta nitroalkenoen arteko Michael erreakzioa katalizatzea. Bigarren generazioko **45** deribatu analogoak, berriz, transformazio honetarako katalizatzaile egokiak ziren, baina ziklopentanona **29b** eta zikloheptanona **29c** nukleozale moduan erabiltzerako garaian, ziklohexanona **29a** baino diastereo- eta enantioselektibitate baxuagoak lortu ziren (**2.1 Taula** eta **2.2 Taula**).

2.1 Taula. H_2N-X_L-OMe-**45** katalizatzaileak gauzatutako ziklopentanona **29b** eta *trans*-β-nitroestirenoa **11a** arteko Michael erreakzio organokatalitikoa.[a,b]

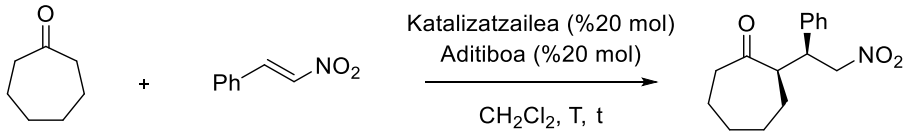


29b **11a** (2*R*,1'*S*)-**51ba**

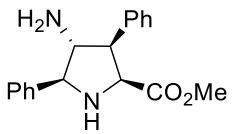
Sarrera	Katalizatzailea	Aditiboa	T (°C)	Denbora (h)	*sin/anti*[b]	Etekina (%)[c]	*ee* (%)[d]
1	 H_2N-X_L-OMe-**45**	PNBA[e]	g.t.	16	47:53	88	64
2		TFA[f]	g.t.	16	50:50	75	72

a) 30. erreferentziako datuak. b) *sin/anti* erlazioa erreakzio nahastearen ^{1}H-RMN esperimentu bidez kalkulatu zen. c) Etekinak isolatutako Michael aduktu puruari egiten dio erreferentzia. d) HPLC bidez neurtutako enantiomero soberakinak *sin* (2*R*,1*'S*)-**51ba** diastereomero nagusiari egiten dio erreferentzia. e) PNBA: Azido *p*-nitrobenzoikoa. f) TFA: Azido trifluoroazetikoa.

2.2 Taula. H_2N-X_L-OMe-**45** katalizatzaileak gauzatutako zikloheptanona **29c** eta *trans*-β-nitroestirenoa **11a** arteko Michael erreakzio organokatalitikoa.[a,b]



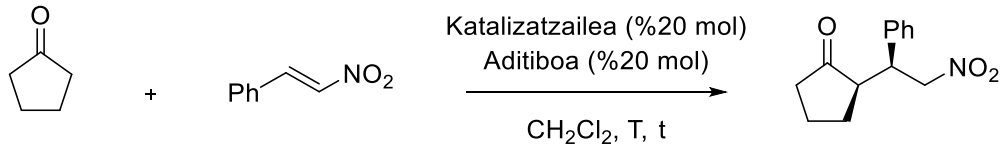
29c **11a** (2*R*,1'*S*)-**51ca**

Sarrera	Katalizatzailea	Aditiboa	T (°C)	Denbora (h)	*sin/anti*[b]	Etekina (%)[c]	*ee* (%)[d]
1	 H_2N-X_L-OMe-**45**	PNBA[e]	r.t.	16	78:22	20	71
2		TFA[f]	r.t.	16	93:7	84	80

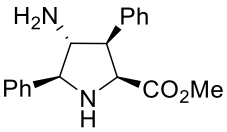
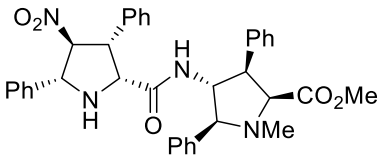
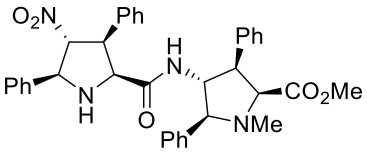
a) 30. erreferentziako datuak. b) *sin/anti* erlazioa erreakzio nahastearen ^{1}H-RMN esperimentu bidez kalkulatu zen. c) Etekinak isolatutako Michael aduktu puruari egiten dio erreferentzia. d) HPLC bidez neurtutako enantiomero soberakinak *sin* (2*R*,1*'S*)-**51ca** diastereomero nagusiari egiten dio erreferentzia. e) PNBA: Azido *p*-nitrobenzoikoa. f) TFA: Azido trifluoroazetikoa.

4-aminoprolina bidez lortutako emaitzak hobetu asmoz, eta dimero γ-*N*-metilatuen emaitza altuak ikusita, O_2N-X_D-X_L^{Me}-OMe-**50** eta O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoek katalizatutako ziklopentanona eta zikloheptanonaren Michael erreakzio asimetrikoak gauzatu ziren lehenik. Erreakzio tenperatura eta aditibo azidoaren influentzia ere analizatu zen. **2.3 Taula**k ziklopentanonaren kasuko Michael erreakzioaren emaitzak biltzen ditu.

2.3 Taula. Ziklopentanona **29b** eta *trans*-β-nitroestirenoa **11a**-ren arteko Michael erreakzio organokatalitikoa.[a]



29b **11a** (2*R*,1'*S*)-**51ba**

Sarrera	Katalizatzailea	Aditiboa	T (°C)	t (h)	*sin/anti*[b]	Etekina (%)[c]	*ee* (%)[d]
1		PNBA[e]	g.t.	16	47:53	88	64
2	H_2N-X_L-OMe-**46**	TFA[f]	g.t.	72	50:50	75	72
3		SA[g]	g.t.	24	70:30	94	-89
4		TFA	g.t.	72	60:40	zg[h]	zg
5		SA	0	24	70:30	95	-90
6		SA	-10	48	75:25	95	-92
7	O_2N-X_D-X_L^{Me}-OMe-**50**	SA	-20	96	80:20	93	-91
8		SA	g.t.	16	75:25	94	85
9		TFA	g.t.	48	60:40	zg	zg
10	O_2N-X_L-X_L^{Me}-OMe-**50**	SA	-10	24	85:15	95	90

a) Erreakzioa **29b** (0.10 mmol) eta **11a** (0.11 mmol) erabiliz gauzatu zen, %20 mol katalizatzaile eta %20 mol aditibo erabiliz **29b** zetona amaitu arte (Konb. > %99). b) *sin/anti* erlazioa erreakzio nahastearen ^{1}H-RMN esperimentu bidez kalkulatu zen. c) Etekinak isolatutako Michael aduktu puruari egiten dio erreferentzia. d) HPLC bidez neurtutako enantiomero soberakinak *sin* (2*R*,1*'S*)-**51ba** diastereomero nagusiari egiten dio erreferentzia. Balio negatiboek (2*S*,1*'R*)-**51ba** enantiomeroa sortzen zela adierazten du. e) PNBA: Azido *p*-nitrobenzoikoa f) TFA: Azido trifluoroazetikoa. g) SA: Azido salizilikoa h) zg: zehaztugabea.

Erreakzioa giro tenperaturan burutu zenean O_2N-X_D-X_L^{Me}-OMe-**50** katalizatzailea eta azido salizilikoa enplegatuz, amaierako *sin* (2*S*,1'*R*)-**51ba** produktua 24 orduren buruan lortu zen, etekin altu, diastereoselektibitate moderatu eta enantiomero soberakin balio paregabeekin (**2.3 Taula**, 3. sarrera). Produktuaren konfigurazio absolutua (2*S*,1'*R*)-izatearen arrazoia katalizatzaileko bigarren *exo*-L eraztunaren blokeoa da, lehenengo exo-D unitate monomerikoa indukzio estereokimikoaren erantzule bakarra izanez. Lorturiko emaitza are hobea izan asmoz, azidotasun handiagoko TFA erabili zen aditibo gisa. Zoritxarrez, erreakzioak hiru egun behar izan zituen konbertsio osoa lortzeko, eta *sin/anti* erlazioak balore errazemikoak erakutsi zituen (**2.3 Taula**, 4. sarrera).

Behin azido salizilikoa aditibo moduan hautetsita, erreakzio tenperatura desberdinak aztertu ziren. Tenperatura 0 °C-tara jaistean, ez zen aldaketa esanguratsurik nabaritu intereseko balioetan (**2.3. Taula**, 5. sarrera vs 3. sarrera). Tenperatura -10 ºC eta -20 ºC-ra gutxitzeak erreakzio denbora 48 eta 96 ordura luzatu zuen, diastereo- eta enantioselektibitate balioak apur bat hobetuz (**2.3 Taula**, 6 eta 7 sarrerak). Honela, tenperatura/denbora konpromezu onena -10 ºC-tan lortzen zela ikusi zen. Baldintza hauek jarraiki, desirako Michael aduktuak erreakzio denbora onargarritan sortzen ziren, *sin/anti* erlazio onak eta enantiomero soberakin itzelak atzituz (**2.3 Taula**, 6. sarrera).

Erreakzio hau O_2N-X_L-X_L^{Me}-OMe-**50** dipeptido diastereomerikoarekin katalizatzean, aldiz, *anti*-Prolina erako (2*R*,1'*S*)-**51ba** aduktua lortu zen. Azido salizilikoak 75:25 *sin/anti* erlazioa erakutsi zuen, eta %85-ko enantiomero soberakina, erreakzioa giro tenperaturan burutzean (**2.3 Taula**, 8. sarrera). Aditibo azidoa TFA-ra aldatzean, diastereoselektibitatean jaitsiera nabaria hatzeman zen, aurreko kasuan bezalaxe (**2.3 Taula**, 9. sarrera). Azkenik, tenperatura -10 ºC-ra jaisteak erlazio diastereomeriko eta *ee* balio onenak lortu zituen (**2.3 Taula**, 10. sarrera).

Emaitza hauek O_2N-X_D-X_L^{Me}-OMe-**50** eta O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaileek beraien aurrekariek baino emaitza hobeak lortzen zituztela argitzen dute. Bi espezieek Michael aduktuak erdiesteko organokatalizatzaileen familia zabaltzen dute honela. Literaturari dagokionez, lehen katalizatzaileak bestelako deribatu bidez lortutako emaitzak hobetzen ditu[34], eta sulfinil pirrolidina erako katalizatzaileek lorturiko emaitza hoberenak ia berdindu.[35] Bereziki interesgarri da ere O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoak egun arte deskribaturiko emaitzarik onenak jadesten dituela.[36]

Jarraian, zikloheptanona **29c** Michael erreakziora aplikatu zen (**2.4 Taula**). Hasteko, erreakzioa giro tenperaturan gauzatu zen, eta **50** dimeroek dagozkien Michael aduktuak diastereo eta enantioselektibitate altuekin sortu zituzten azido salizilikoa aditibo moduan erabiliz (**2.4 Taula**, 3 eta 5 sarrerak). Hala eta guztiz ere, zikloheptanonaren nukleozaletasun baxuagoak ezinezko bihurtu zuen erreakzioen konbertsio totala. Katalizatzaile aktibitate hobea aurkitu nahian, TFA aditibo azidoagoa usatu zen. O_2N-X_D-X_L^{Me}-OMe-**50** dimeroaren kasuan, hasierako zetonaren desagerpen osoa hatzeman zen, amaierako produktua diastereo eta *ee* balore itzelekin lortuz (**2.4 Taula**,

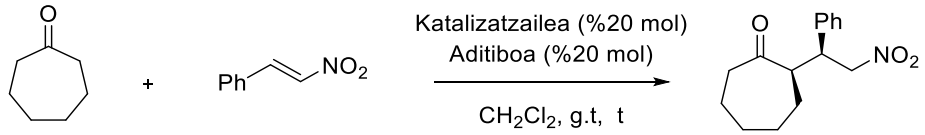
[34] Azken adibide esanguratsuenen kasurako, ikusi: a) Azad, C. S.; Khan, I. A.; Narula, A. K. *Org. Biomol. Chem*. **2016**, *14*, 11454-11461. b) Wang, Z.-Y.; Ban, S.-R.; Yang, M. C.; Li, Q.-S. *Chirality* **2016**, *28*, 721-727.

[35] Singh, K. M.; Singh, P.; Kaur, A.; Singh, P.; Sharma, S. K.; Khullar, S.; Mandal, S. K. *Synthesis* **2013**, *45*, 1406-1413.

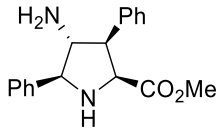
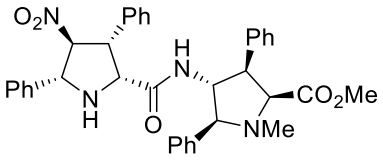
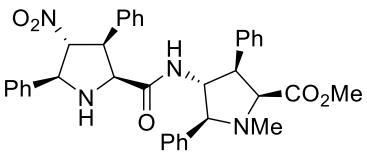
[36] a) Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611-3614. b) Xu, Y.; Zou, W.; Sundén, H.; Ibrahem, I.; Córdova, A. *Adv. Synth. Catal*. **2006**, *348*, 418-424. c) Wang, Y.; Li, D.; Lin, J.; Wei, K. *RSC Adv*. **2015**, *5*, 5863-5874.

4. sarrera). O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaileak ere joera berdina erakutsi zuen, desioko *sin* (2*R*,1'*S*)-**51ca** produktuak diastereo- zein enantioselektibitate altuekin erdietsiz (**2.4 Taula**, 6. sarrera). Beharrezko erreakzio denbora luzeak ikusirik, tenperaturaren azterketa sakonagoa ez burutzea erabaki zen.

2.4 Taula. Zikloheptanona **29c** eta *trans*-β-nitroestirenoa **11a**-ren arteko Michael erreakzio organokatalitikoa.[a]



29c **11a** (2*R*,1'*S*)-**51ca**

Sarrera	Katalizatzailea	Aditiboa	Konb (%)[b]	t (h)	*sin/anti*[c]	Etekin (%)[d]	*ee* (%)[e]
1	 H_2N-X_L-OMe-**45**	PNBA[f]	r.t.	16	78:22	20	71
2		TFA[g]	r.t.	16	93:7	84	80
3	 O_2N-X_D-X_L^{Me}-OMe-**50**	SA[h]	90	5	82:18	70	-71
4		TFA	>99	4	92:8	93	-90
5	 O_2N-X_L-X_L^{Me}-OMe-**50**	SA	90	5	73:27	75	73
6		TFA	>99	4	90:10	94	93

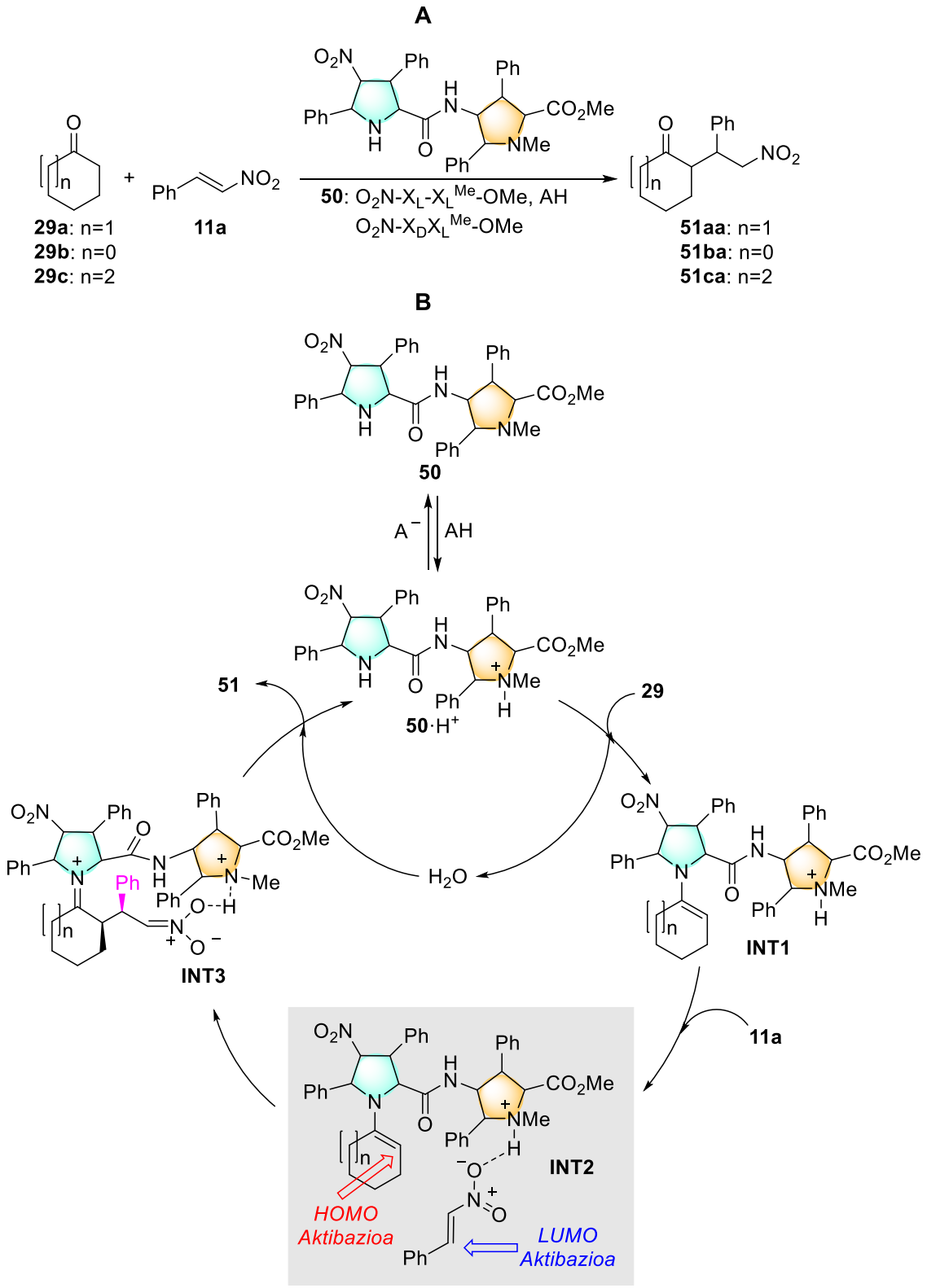
a) Erreakzioa **29c** (0.10 mmol) eta **11a** (0.11 mmol) erabiliz gauzatu zen, giro tenperaturan, %20 mol katalizatzaile eta %20 mol aditibo erabiliz **29c** zetona amaitu arte (Konb. > %99). b) Konbertsioak erreakzio nahastearen ^{1}H-RMN esperimentuen analisi bidez neurtu ziren. c) *sin/anti* erlazioa erreakzio nahastearen ^{1}H-RMN esperimentu bidez kalkulatu zen. d) Etekinak isolatutako Michael aduktu puruari egiten dio erreferentzia. e) HPLC bidez neurtutako enantiomero soberakinak *sin* (2*R*,1'*S*)-**51ca** diastereomero nagusiari egiten dio erreferentzia. Balio negatiboek (2*S*,1'*R*)-**51ba** enantiomeroa sortzen zela adierazten du. f) PNBA: Azido *p*-nitrobenzoikoa. g) TFA: Azido trifluoroazetikoa. h) SA: Azido salizilikoa.

Zikloheptanonarekin lortutako emaitzek **50** γ-dipeptidoen propietate katalitiko berriak osatzen dituzte. Esan behar da ere, zikloheptanonaren enplegua egiten duten kasu gutxi aurki daitezkela literaturan, eta, hauetan, (2*S*,1'*R*)-**51ca** enantiomeroaren formazioa kausatzen dela.[37] Hitz batez, gure O_2N-X_D-X_L^{Me}-OMe-**50** eta O_2N-X_L-X_L^{Me}-OMe-**50**

[37] Adibide esanguratsuenak ezagutzeko, ikusi: a) Betancort, J. M.; Saktivel, K.; Thayumanavan, R.; Barbas III, C. F. *Tetrahedron Lett*. **2001**, *42*, 4441-4444. b) Vega-Peñolaza, A.; Sánchez-Antonio, O.; Ávila-Ortiz, C. G.; Escudero-Casao, M.; Juaristi, E. *Asian J. Org*. *Chem*. **2014**, *3*, 487-496. c) Xu, D.-Z.; Shi, S.; Wang, Y.; *Eur. J. Org. Chem*. **2009**, 4848-4853.

dipeptidoak zetona zikliko eta *trans*-β-nitroestirenoaren arteko Michael erreakzio diastero- eta enantioselektiborako katalizatzaile aproposak direla ondoriozta daiteke.

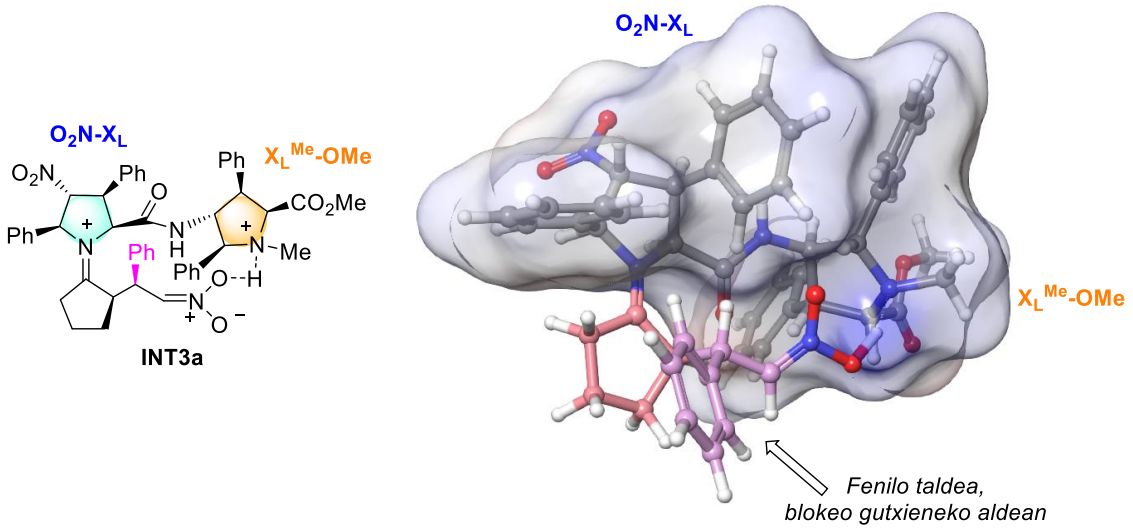
Emaitza hauek **2.2 Irudia**n laburtzen den modelo orokorraren bidez arrazoitu daitezke. O_2N-X_D-X_L^{Me}-OMe-**50** eta O_2N-X_L-X_L^{Me}-OMe-**50** γ-dipeptidoetan pirrolidina *N*-metilatua protonaziorako libre da, eta ordezkatu gabeko *N*-prolinak **INT1** enamina artekaria sortzen du. **11a** nitroestireno elektrozalearen *N*-metil amino taldearekiko koordinazioak (**2.2B irudi**ko **INT2** artekaria begiratu) konposatu elektrozalearen LUMO aktibazioa bulkatzen du, C-C lotura berriaren formazioa erraztuz eta **INT3** iminio-nitronatoa eratuz. Azken artekari honen hidrolisiak **51** Michael aduktura gidatzen du, organokatalizatzailea askatuz (**2.2B Irudia**).



2.2 Irudia. A) **50** γ-dipeptidoek katalizatutako **29a-c** zetonen eta **11a** nitroestirenoaren arteko Michael adizio erreakzio orokorra. AH akronimoak azido karboxilikoa errepresentatzen du. B) HOMO-LUMO aktibazioa kontuan hartzen duen ziklo katalitiko sinplifikatua.

C-C loturaren formazio urratsarekin erlazionaturiko diastereo- eta enantiokontrolaren jatorria organokatalizatzaileak inposatutako blokeo geometrikoekin estuki lotua dago. Organokatalizatzaileak, amida lotura inguruko askatasun konformazional mugatuaz

gain, zortzi zentro kiral ere baditu. **2.3 Irudia**k ziklopentanona **29c** eta nitroestirenoa **11a**-ren arteko erreakziotik datorren **INT3a** zwitterioiaren geometria irudikatzen du. O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaileak eratutako ingurunea ikuskatuz, organokatalizatzaileak enaminaren zein nitroalkenoaren albo prokiraletako bat blokeatzen duela ikus daiteke, (2*S*,1'*R*)-Michael aduktua erdietsiz. **29c** (zikloheptanona) eta **29a** (ziklohexanona) zetonetan ere efektu berdinek parte hartzen dutela suposatu daiteke.



2.3 Irudia. **INT3a** artekari zwitterionikoaren egitura optimizatua (RHF/PM6 teoria maila). O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaileak mugatutako azalera (erradioa 1.8 Å) grisez marratzen da.

2.5 TETRAHIDROPIRANO ESKELETOEN SINTESIRAKO MICHAEL-HENRY-AZETALIZAZIO ERREAKZIO ORGANOKATALITIKOA

2.5.1 Erreakzio baldintzen hautaketa

Michael aduktuak aldehidoekin izan dezakeen erreakzio posiblea da THP eraztunen sintesirako abiapuntu nagusia. Erreakzioa gertatzeko beharrezko diren baldintzen azterketa erdiesteko ziklohexanona eta *trans*-β-nitroestirenoaren arteko Michael erreakzioko baldintza optimoak kontutan hartu ziren (%10 mol katalizatzaile, %20 mol azido saliziliko). Etil glioxilatoa izan zen aukerako aldehido elektrozalea, sortutako 6-karboxi tetrahidropirano eraztunaren garrantzia sintetikoa kontsideratuz.

Bi esperimentu paralelo gauzatu ziren hasteko. Batean, hiru erreaktiboak elkarrekin nahasten ziren erreakzio hasieratik. Bestean, ordea, Michael produktuaren generazioa bigarren Henry-azetalizazio urratsa gertatzeko beharrezkoa zen aldehidoaren gehikuntzaren aurretik burutzen zen. Lehen esperimentuak desioko produktuaren trazak besterik ez zituen sortu, ziklohexanona eta etil glioxilatoaren arteko erreakzio aldoliko konpetitiboa zela eta. Bigarrenak, bestalde, tetrahidropirano eraztunaren formazioa ahalbidetu zuen. Puntu honetan aipatzekoa da bigarren aukera hau ere *one-pot* prozesu

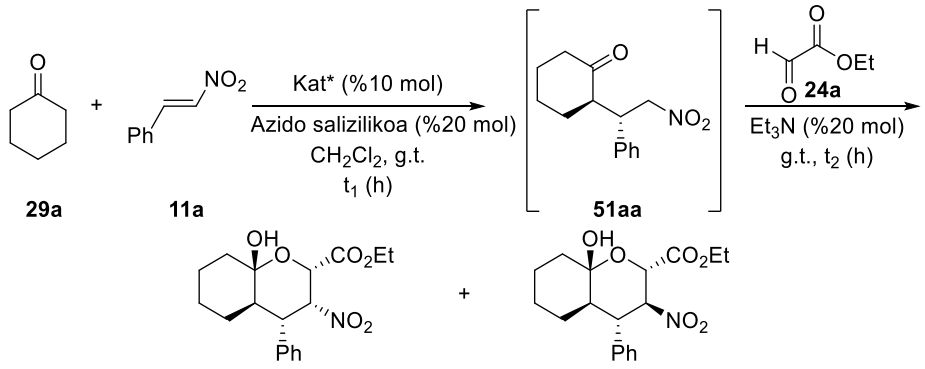
bezala kontsidera daitekeela, ez baita Michael artekariaren inolako purifikazio prozesurik burutzen.

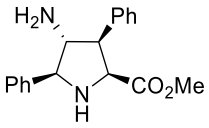
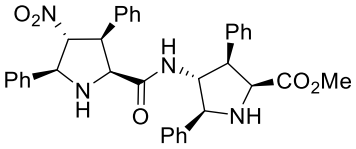
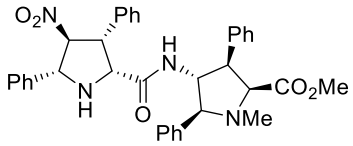
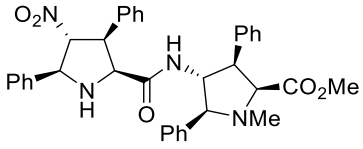
Katalizatzailearen funtzioa ulertu asmoz azterketa gehiago ere aurrera eraman ziren. Kontrol esperimentu moduan, antzerako erreakzio ugari zertu ziren, non γ-nitrozetona artekariak etil glioxilato eta trietilaminaren adizio aurretik purifikatzen ziren. Esperimentu hauen HPLC analisiek ez zuten inolako desberdintasunik erakutsi purifikatutako eta purifikatu gabeko laginen artean. Hots, bigarren urratseko emaitza estereokimikoak adizio konjugatuaren erabateko menpekotasuna du.

Hori honela, ziklohexanona **29a** eta *trans*-β-nitroestirenoa **11a**-ren arteko erreakziotik sortutako **51aa** γ-nitrozetona etil glioxilatoarekin erreakzionarazi zen, trietilaminaren presentzian (**2.5 Taula**). Katalizatzailea izan zen ebaluatutako lehenengo parametroa. O_2N-$X_{L/D}$-OMe-**44** espezie monomerikoak ez ziren aztertu, ez baitute Michael erreakzioa katalizatzeko gaitasunik. H_2N-X_L-OMe-**45** amino deribatuak erreakzio denbora luzeak behar izan zituen bigarren ziklazio urratsa gauzatzeko (10 egun, **2.5 Taula**, 1. sarrera). O_2N-X_L-X_L-OMe-**49** dimeroak bulkatutako erreakzioak denbora onargarriak manifestatu zituen 1,4 adiziorako. Henry-ziklazio etapa 6 ordutan amaitu zen, eta amaierako produktua etekin, **52aaa:52aaa'** erlazio diastereomeriko eta enantiomero soberakin itzelekin lortu zen (**2.5 Taula**, 3. Sarrera). Aipatzeko da **52aaa** konposatua produktu zinetikoa dela, eta **52aaa'**, berriz, produktu termodinamikoa. O_2N-X_D-X_L^{Me}-OMe-**50** katalizatzailea erabiltzean, Michael urratsak erreakzio denbora luzeagoak erakutsi zituen, eta erlazio diastereomerikoak onak izan arren, etekin eta ee baloreek jaitsiera nabarmena pairatu zuten (**2.5 Taula**, 5. sarrera). Azkenik, bere kide den O_2N-X_L-X_L^{Me}-OMe-**50** organokatalizatzaileak **52aaa** produktuaren formazioa etekin altu, erlazio diastereomeriko on eta enantioselektibitate itzelekin burutu zuen (**2.5 Taula**, 6. sarrera).

Organokatalizatzailea ebaluatu ondoren, organokatalizatzaileen karga katalitikoa igo zen, emaitzak hobetu asmoz. Amino deribatuaren kasuan, ez zen aldaketa esanguratsurik nabaritu, eta bigarren urratsak denbora luzeegiak manifestatu zituen (**2.5 Taula**, 2. sarrera). O_2N-X_L-X_L-OMe-**49** dimeroak Michael erreakzioa azkartzea lortu zuen, diastereoselektibitatea kaltetuz. Kasu honetan, diastereomero nagusiak etekin eta enantioselektibitate altuak erakutsi zituen; **52aaa'** diastereoisomeroak, aldiz, enantiokontrol moderatua azalduz (**2.5 Taula**, 4. sarrera). Azkenik, O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaileak paregabeko emaitzak azaleratu zituen, **52aaa** zikloa erreakzioko produktu bakarra izanik (**2.5 Taula**, 7. sarrera).

2.5 Taula. Michael-Henry-Azetalizazio erreakziorako baldintzen ebaluaketa.[a,b]



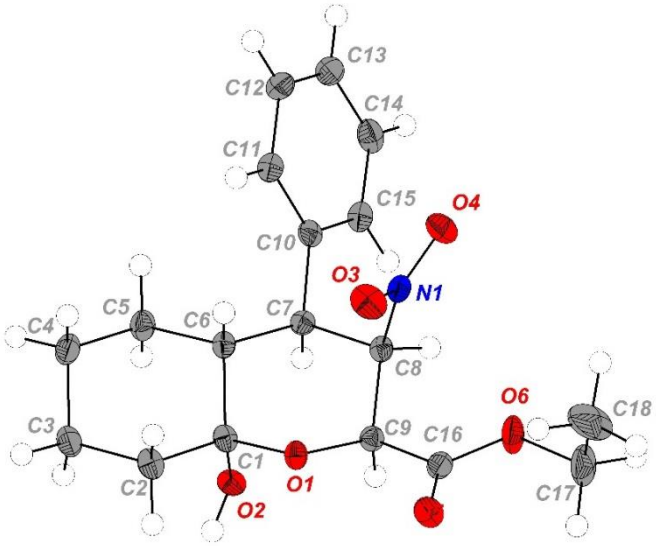
Sarrera	Katalizatzailea	t_1 (h)	t_2 (h)	*dr*[c]	Etekina (%)[d]		*ee* (%)[e]	
					52 aaa	**52 aaa'**	**52 aaa**	**52 aaa'**
1		48	240	zg[f]	zg	zg	zg	zg
2[g]	H_2N-X_L-OMe-**45**	48	216	zg	zg	zg	zg	zg
3		48	6	85:15	73	zg	93	zg
4[h]	O_2N-X_L-X_L-OMe-**49**	16	6	75:25	70	23	91	60
5		144	6	84:16	69	zg	-63	zg
	O_2N-X_D-X_L^{Me}-OMe-**50**							
6		24	6	80:20	47	9	99	82
7[h]		24	6	>99:1	72	zg	99	zg
8[h,i]		24	168	zg	zg	zg	zg	zg
9[h,j]	O_2N-X_L-X_L^{Me}-OMe-**50**	24	48	50:50	27	26	96	90
10[h,k]		24	48	zg	30	zg	65	zg

a) Lehen urratsa **29a** (0.10 mmol), eta *trans*-β-nitroestirenoa **11a** (0.11 mmol) erabiliz burutu zen, %10 mol katalizatzaile eta %20 mol azido saliziliko erabiliz. Bigarren urratsa **24a** (0.20 mmol) eta 20 mol% Et_3N erabiliz burutu zen. b) Erreakzioak ^{1}H-RMN bidez jarraitu ziren giro tenperturan, hasierako erreaktiboak erabat amaitu arte c) *dr*-ak ^{1}H-RMN bidez neurtutako **52aaa**:**52aaa'** erlazioari egiten dio erreferentzia. d) Etekinak produktu puruei egiten die erreferentzia e) HPLC bidez neurtutako *ee* balioek (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**52aaa**, (2*S*,3*S*,4*S*,4a*R*,8a*S*)-**52aaa'** enantiomerioei egiten die erreferentzia. f) zg: zehaztugabea. g) %30 mol katalizatzaile, %30 mol Azido *p*-nitrobenzoiko. h) %20 mol katalizatzaile. i) %40 mol DIPEA. j) %40 mol DBU. k) %40 mol DABCO.

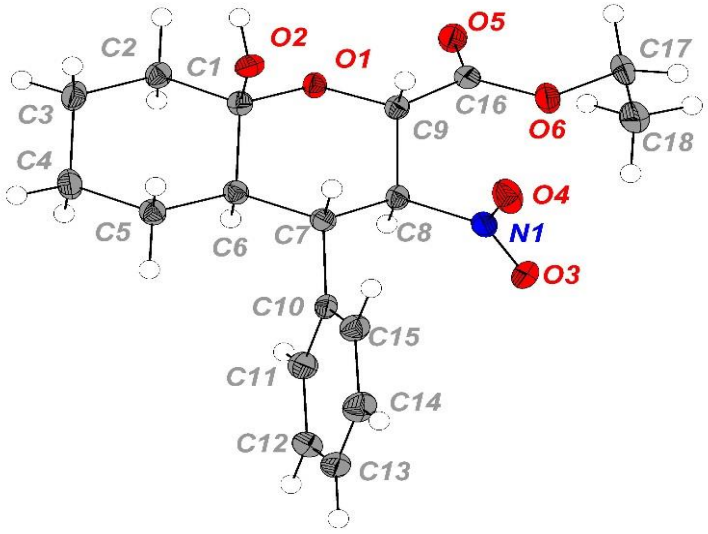
Akaberako saiakuntzek basearen efektua aztertu zuten. Ebaluatutako aditibo basikoek, ordea, ez zuten trietilaminak lortutako emaitzik ondu (**2.5 Taula**, 7. sarrera). DIPEA eta DABCO erabiltzean, ziklazio denbora luzeak hatzeman ziren (**2.5 Taula**, 8 eta 10 sarrerak, hurrenez-hurren) eta DBUaren erabilerak espezie diastereomerikoen oreka bultzatu zuen (**2.5 Taula**, 9. sarrera).

Emaitza hauek guztiek O_2N-X_L-X_L^{Me}-OMe-**50** dimeroaren usantza iradoki zuten, 20 mol%-ko karga katalitikoan. Bigarren ziklazio urratsak trietilaminaren beharra azaleratu zuen THP eraztunen formazio diastereo- eta enantioselektiborako.

52aaa eta **52aaa'** produktuen egitura eta estereokimika X-izpien difrakzio analisi bidez berretsi zen. Egitura biziklikoaren ulermena errazteko, atomoak erlojuaren norantzaren aurka zenbatu dira, C1 karbono hemiazetalikoa izanik. **52aaa**-ren konfigurazio asimetrikoa C1, C6, C7, C8 eta C9 karbono asimetrikoentzat *S*, *R*, *S*, *R*, *S* bezala esleitu zen (**2.4 Irudia**). **52aaa'**-ri dagokion esleipena *S*, *R*, *S*, *S*, *S*, izan zen (**2.5 Irudia**).



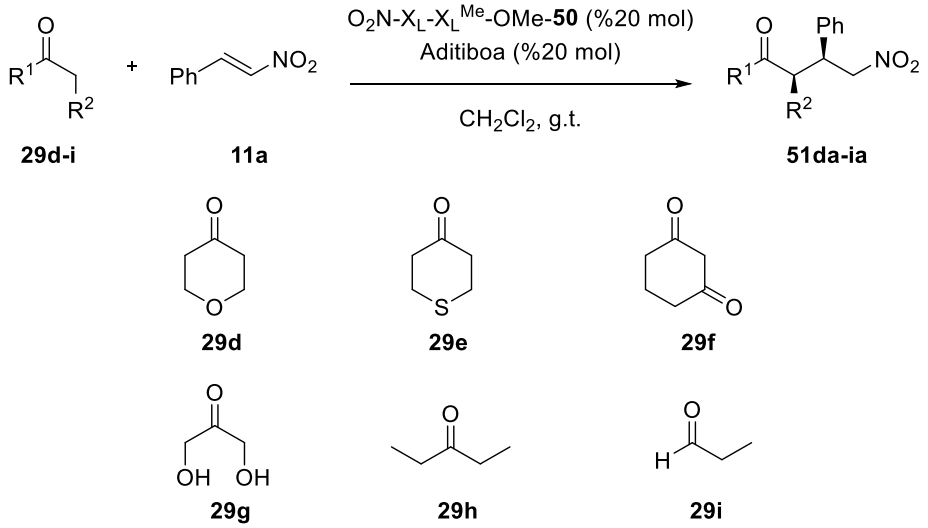
2.4 Irudia. 52aaa eraztunaren ORTEP diagrama, %50-eko probabilitateko elipsoide termikoekin.



2.5 Irudia. 52aaa' eraztunaren ORTEP diagrama, %50-eko probabilitateko elipsoide termikoekin.

2.5.2 Espezie nukleozaleen azterketa

Erreakzio baldintza optimoak zehaztu ondoren, prozesu kimikoaren orokortasuna aztertu zen. Ziklohexanonaz gain, bestelako eratorri lineal eta ziklikoak ere baloratu ziren. Zoritxarrez, transformazio kimikoak muga dexente erakutsi zituen nukleozaleen egiturari dagokionez. Esaterako, tetrahidro-*4H*-piran-4-ona **29d**, tetrahidro-*4H*-tiopiran-4-ona **29e**, ziklohexano-1,3-diona **29f**, 1,3-dihidroxiazetona **29g** eta pentan-3-ona **29h** hasierako erreaktibo moduan hautatzean, ez zen inolako Michael aduktuaren formaziorik gertatu azido salizilikoa aditibo moduan erabiliz. Jazoera hau sortu litekeen ziklazio produktuaren konpetizioaren bidez azal liteke[31], baita erreaktiboen arteko 1:1 erlazioaz ere. Aditibo azidoa TFA bidez aldatzeak ere ez zuen Michael aduktuaren sorrerarik gauzatu. Horrez gain, erreaktibotasun altuagokoa den propionaldehido **29i-k** konbertsio totala jasan zuen, baina Michael erreakzioaren eta erreakzio aldolikoaren arteko konpetentziak bi produktuen sorrera bultzatu zuen. Azkenekoz, ziklopentanona espezie nukleozale moduan erabiltzean, amaierako tetrahidropirano egituraren isolamentua ezinezko izan zen, produktuaren ezegonkortasuna zela medio. Emaitza negatibo guztiak **2.14 Eskema**n biltzen dira.



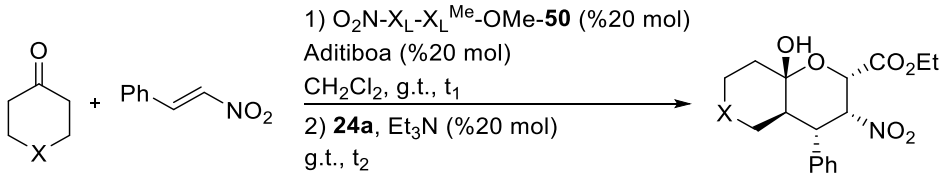
2.14 Eskema. Michael-Henry-Azetalizazio erreakziorako nukleozale desegokiak.

Gure saiakerak egoki bihurtu ziren zikloheptanona **29c** eta 1,4-zikohexanodiona monoetilen azetala **29j** hasierako erreaktibo moduan enplegatzean (**2.6 Taula**). Hauek, hala ere, erreakzio baldintzetan aldaketak egitea beharrezko izan zuten.

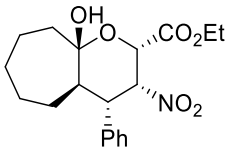
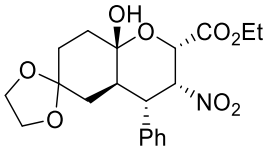
52caa deribatuak trietilamina kantitate ekimolekularrak behar izan zituen γ-nitrozetona artekaria guztiz kontsumitzeko. Kantitate katalitikoak erabiltzerako garaian, erreakzio denbora luzeak hatzeman ziren, etekinak jatsiera nabaria pairatuz. Aipatzekoa da ere amaierako produktua 92:8-ko diastereomero nahaste banaezin bezala sortu zela, etekin moderatuan eta itzelezko enantiomero soberakin balioekin (**2.6 Taula**, 1. sarrera). Proportzio hau *sin*- eta *anti*-Michael aduktuen ziklazioaren bidez argitu daiteke.

52jaa deribatuen kasuan, hasierako Michael erreakzioak 7 egun behar izan zituen erabateko konbertsioa lortzeko. Erreakzio denbora laburtu asmoz, tenperatura 45 ºC-ra igo zen, baina erreakzio nahaste narratsak lortu ziren honela. Ondorengo Henry-azetalizazio urratsak, bestalde, ordu bat besterik ez zuen behar izan amaitzeko. Hortaz, O_2N-X_L-X_L^{Me}-OMe-**50** organokatalizatzaileak **52jaa** produktuaren formakuntza eraginkorra burutu zuen, amaierako produktua diastereomero bakar moduan sortuz, %62-ko etekina eta %89-ko enantiomero soberakinarekin (**2.6 Taula**, 2. sarrera).

2.6 Taula. Zetona zikliko eta nitroestirenoaren arteko Michael-Henry-Azetalizazio erreakzioa.



29c,j **11a** (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**52caa-jaa**

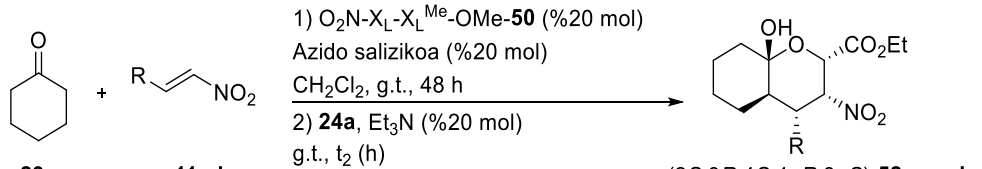
Sarrera	X	Aditiboa	t_1 (egun)	t_2 (h)	Prod.	Egitura	Etekin (%)[c]	*ee* (%)[d]
1[e]	-$(CH_2)_2$-	TFA[f]	4	16	**52caa**		53 (92:8)[g]	90
2		SA[h]	7	1	**52jaa**		62	88

a) Lehen urratsa **29c,j** (0.10 mmol), eta *trans*-β-nitroestirenoa **11a** (0.11 mmol) erabiliz burutu zen, % 10 mol katalizatzaile eta %20 mol aditibo erabiliz. Bigarren pausua **24a** aldehidoa erabiliz burutu zen (0.20 mmol) eta %20 mol Et_3N. b) Erreakzioak ^{1}H-RMN bidez jarraitu ziren eta giro tenperaturan nahastu hasierako erreaktiboak amaitu arte (Konb. >%99). c) Etekinak produktu puruei egiten die erreferentzia. d) HPLC bidez neurtutako enantiomero soberakinak (2*S*,3*R*,4*S*,4*aR*,8*aS*)-**52baa-jaa** enantiomero nagusiei egiten die erreferentzia. e) Et_3N baliokide bat gehitu zen. f) TFA: azido trifluoroazetikoa g) *sin* eta *anti* Michael produktuen ziklazioari esleituriko erlazio diastereomerikoa. h) SA: azido salizilikoa

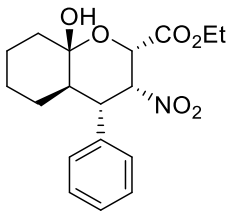
2.5.3 Nitroalkenoen azterketa

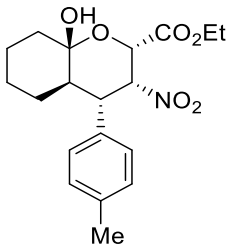
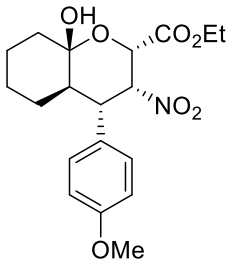
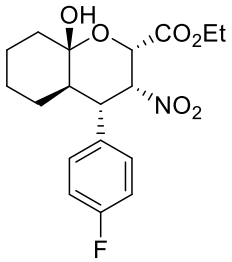
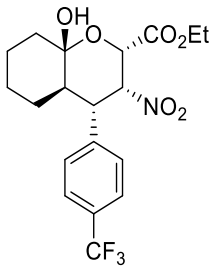
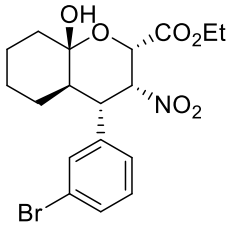
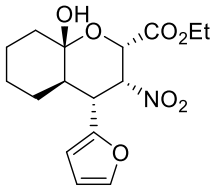
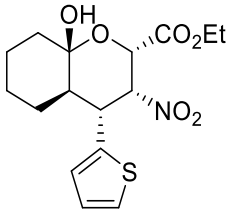
Nitroalkeno desberdinen ebaluazioa gauzatu zen jarraiki, erreakzioko beste osagaien eraginkortasuna ezagutu asmoz. Orokorrean, erreakzioa nitroolefina konjugatu alifatiko zein nitroolefina aromatiko eta heteroaromatikoei aplikagarri suertatu zitzaien (**2.7 Taula**).

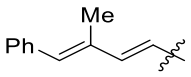
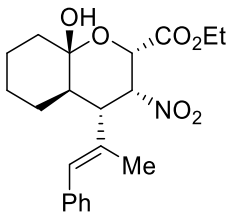
2.7 Taula. O_2N-X_L-X_L^{Me}-OMe-**50** bidez katalizatutako nitroalkenoen azterketa.



29a **11a-i** (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**52aaa-aia**

Sarrera	R	t_2 (h)	Produktua	Egitura	Etekina (%)[c]	*ee* (%)[d]
1	Ph	6	**52aaa**		72	>99

2	4-MeC_6H_4	6	**52aba**		47	95
3[e]	4-$OMeC_6H_4$	6	**52aca**		65	96
4	4-FC_6H_4	6	**52ada**		62	>99
5[f]	4-$CF_3C_6H_4$	4	**52aea**		60	98
6	3-BrC_6H_4	9	**52afa**		54	99
7[g]	2-furil	1	**52aga**		73	95
8[g]	2-tienil	0.5	**52aha**		46	95

9[g,h]		2	**52aia**		55	99

a) Lehen urratsa **29a** (0.10 mmol), eta dagokion nitroalkenoa **11a-i** (0.11 mmol) erabiliz burutu zen, 10 mol% katalizatzaile eta 20 mol% aditibo erabiliz, giro tenperaturan, 48 orduz. Bigarren pausua **24a** aldehidoa erabiliz burutu zen (0.20 mmol) eta 20 mol% Et_3N. Erreakzioak ^{1}H-RMN bidez jarraitu ziren hasierako erreaktiboak amaitu arte (Konb. >99%). b) **52aaa-aia**:**52aaa'-aia'** erlazio guztiak >99:1 izan ziren. c) Etekinak produktu puruei egiten die erreferentzia. d) HPLC bidez neurtutako enantiomero soberakinak (2*S*,3*R*,4*S*,4*aR*,8*aS*)-**52aaa-aia** enantiomero nagusiei egiten die erreferentzia. e) Michael erreakzioak 3 egun behar izan zituen konbertsio osoa izateko. f) Toluenoan burutua. g) Bigarren urratsa 0 ºC-tan burutu zen. h) Michael erreakzioak 6 egun behar izan zituen konbertsio osoa lortzeko.

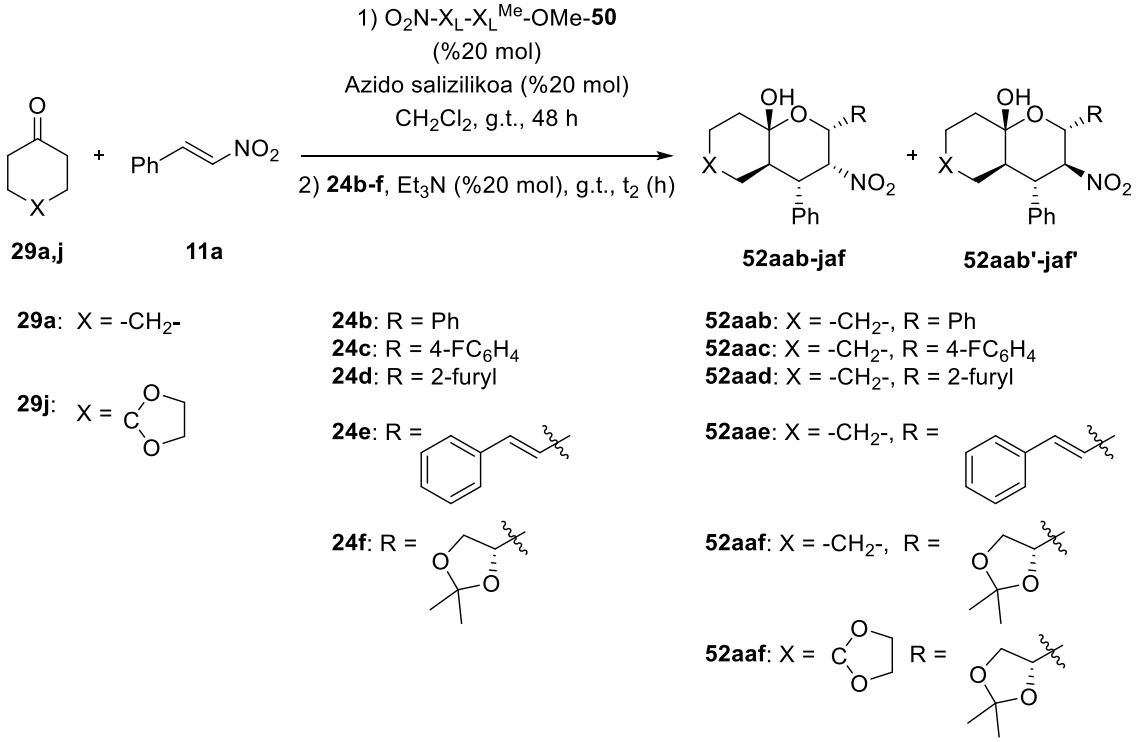
One-pot erreakzioa arazorik gabe gauzatu zen kasu guztietan, konbertsio kuantitatiboak eta enantioselektibitate altuak lortuz. Aipamen berezia merezi du C8 posizioko estereokimika guztiz kontrolatzea lortu zela esateak, amaierako **52aaa-aia** produktuak diastereoisomero bakar moduan erdietsiz. *Para* posizioan talde elektroi erakarleak dituzten nitroalkeno aromatikoek zein talde elektroi emaledunak dituztenek tetrahidropirano deribatuak etekin moderatu edo onekin sortu zituzten, baita enantioselektibitate itzelekin ere (**2.7-Taula**, 2-5 sarrerak). *Trans*-4-metoxi-β-nitroestirenoaren kasuan, nitroalkenoaren elektrofilia baxuagoak Michael urratsak erreakzio denbora luzeagoak behar izatea eragin zuen. Hala ere, amaierako produktuak ez zuen etekin eta enantiokontrolean jaitsierarik suposatu (**2.7 Taula**, 3. sarrera). Esan behar da ere *trans*-4-trifluorometil-β-nitroestirenoak toluenoa disolbatzaile gisa erabiltzea bultzatu zuela, bestelako baldintzetako disolbagarritasun urriak konbertsio baxuak eragin baitzituen (**2.7 Taula**, 5. sarrera). *Meta*- posizioan ordezkaturiko nitroalkenoak ere aplikagarri suertatu ziren hiru-osagaiko transformazio asimetrikoan. **52afa** produktua enantiokontrol osoarekin eta etekin moderatuekin sortu zen, 9 ordutan (**2.7 Taula**, 6. sarrera).

Egitura heteroaromatiko erreaktiboagoen usadioa egitean, bigarren urratseko tenperatura 0 ºC-ra jaitsi zen (**2.7 Taula**, 7 eta 8 sarrerak). Bestela, epimerizazio produktuaren sorrera konpetitiboa gauzatzen zen, ia 50:50 erlazioan. Erreakzio baldintza berriek **52aga**, **52aha** produktuak erreakzio denbora oso laburretan sortu zituzten, enantioselektibitate altuekin. Azkenik, **12i** nitroalkeno konjugatuaren erabilera ere positiboa izan zen, nahiz honek ere tenperatura 0 ºC-tara jaistea behar izan. Hots, desioko THP eraztuna 2 orduren baitan sortu zen, etekin moderatu eta enantioselektibitate maila altuekin (**2.7 Taula**, 9. sarrera). **52aia** produktu honen egitura COSY esperimentu bidimentsionalen laguntzaz esleitu zen (begiratu atal esperimentala).

Emaitza hauek guztiek funtzionalizazio maila altuko tetrahidropirano eraztunen sintesiko emaitza estereokimiko goienak azpimarratzen dituzte, hautako nitroalkenoaren egiturako aldaketak eragin berezirik izan gabe.

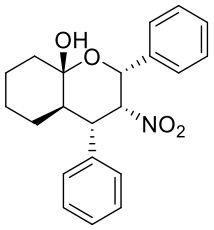
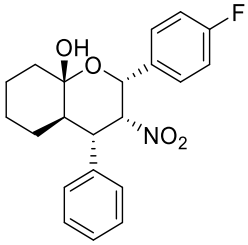
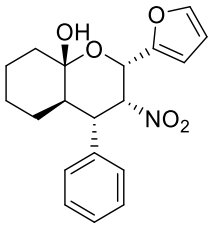
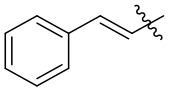
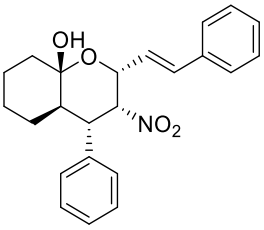
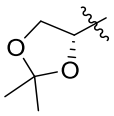
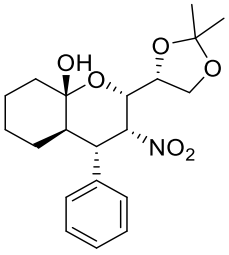
2.5.4 Aldehido elektrofilikoen hautaketa

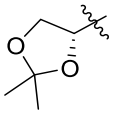
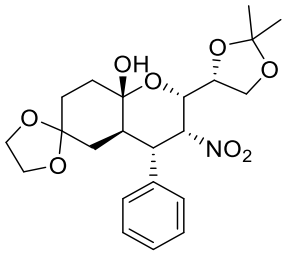
Amaitzeko, tetrahidropirano eraztunen familia zabaltzeko bestelako aldehido elektrofilikoak ebaluatu ziren (**2.15 Eskema**). Azterturiko kasu guztiek etil glioxilatoa baino aktibazio baxuagoa dute. Beraz, kasu batzuetan aldehido zein trietilamina baliokideetan aldaketak burutzea ezinbestekoa suertatu zen erreakzioa akaberara eramateko. Emaitza guztiak **2.8 Taula**n laburtzen dira.



2.15 Eskema. 29a,j zetona, **11a** *trans*-β-nitroestirenoa eta **24b-f** aldehido elektrozaleen arteko Michael-Henry-azetalizazio erreakzioa.

2.8 Taula. O_2N-X_L-X_L^{Me}-OMe-**50** dimeroak organokatalizatutako **29a,j**+**11a**+**24b-f** → (2S,3R,4S,4aR,8aS)-**52aab-jaf** erreakzioa.[a]

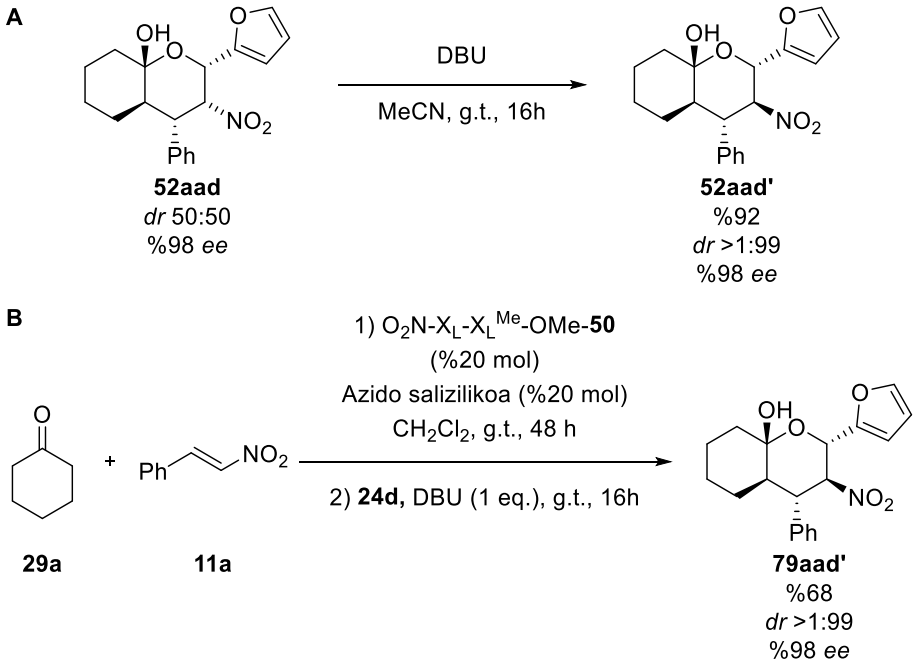
Sarrera	X	R	t_2 (h)	Egitura	*dr*[b]	Etekina (%)[c]	*ee* (%)[d]	
							52	**52'**
1[e]	-(CH_2)-	Ph	48	 **52aab**	50:50	65	>99	96
2[e]	-(CH_2)-	4-FC_6H_4	16	 **52aac**	65:35	81	>99	95
3[e]	-(CH_2)-	2-furil	16	 **52aad**	50:50	65	98	98
4	-(CH_2)-		96	 **52aae**	90:10	58[f]	>99	zg[g]
5	-(CH_2)-		3	 **52aaf**	>99:1	64	>99[h]	zg

6			3		>99:1	52	>99[h]	zg
				52jaf				

a) Lehen urratsa **29a,j** (0.10 mmol), eta **11a** *trans*-β-nitroestirenoa (0.11 mmol) erabiliz burutu zen, %10 mol katalizatzaile eta %20 mol aditibo erabiliz, giro tenperaturan, 48 orduz. Bigarren pausua **24b-f** aldehidoa erabiliz burutu zen (0.20 mmol) eta %20 mol Et_3N. Erreakzioak ^{1}H-RMN bidez jarraitu ziren hasierako erreaktiboak amaitu arte (Konb. >%99). b) *dr*-ak **52aab-jaf:52aab'-jaf'** erlazioari egiten dio erreferentzia c) Etekinak bi diastereomeroen gehiketari egiten dio erreferentzia. d) HPLC bidez neurtutako enantiomero soberakinak (2*S*,3*R*,4*S*,4*aR*,8*aS*)-**52aab-jaf,** (2*S*,3*S*,4*S*,4*aR*,8*aS*)-**52aab':jaf'** enantiomeroei egiten die erreferentzia. e) Et_3N baliokide bat gehitu zen f) Etekinak **52cae** diastereoisomeroari egiten dio erreferentzia. g) zg: zehaztugabea h) *ee*-k *de*-ri (soberakin diastereomerikoa) egiten dio erreferentzia.

24b bentzaldehidoa eta **24c** 4-fluorobentzaldehidoa erabiltzean, trietilamina baliokide bat beharrezko suertatu zen. Kantitate ekimolar hauek dagokien epimeroen formazioa ondorioztatu zuten. Beraz, **24b** aldehidoaren bertsio asimetrikoak **52aab** eta **52aab'** produktuen formazioa 50:50 erlazio diastereomerikoarekin gauzatu zuen, etekin altu eta bi diastereoisomeroen *ee* balore altuekin (**2.8 Taula**, 1. sarrera). **24c** aldehido elektrozaleagoak erreakzio denbora laburragoak erakutsi zituen erabateko konbertsioa lortzeko. Hots, **52aac** produktuaren aldeko formazioa erlazio diastereomeriko hobearekin gauzatu zen (65:35). Bi diastereoisomeroek enantiomero soberakin balore altuak erakutsi zituzten (**2.8 Taula**, 2. sarrera).

Furfural aldehido heteroaromatikoak ere trietilamina baliokide baten beharra izan zuen. Honela, amaierako bi diastereoisomeroak 50:50 erlazioan lortu ziren, etekin orokor onarekin eta enantioselektibitate itzelekin (**2.8 Taula**, 3. sarrera). Amaierako produktuen purifikazioan arazoak sortu ziren, ordea, **52aad**-tik **52aad'**-rako isomerizazio erreakzioa aztertzea bultzatuz. DBU basearen baliokide baten usadioak **52aad'** produktua erdietsi zuen enantioselekzio galerarik gabe (**2.16A Eskema**). Hau dela eta, **52aad'** epimeroaren sintesi zuzena bigarren urratsean DBU baliokide bat erabiliz burutu zen, desirako produktua %68ko etekin eta diastereo- zein enantiokontrol altuarekin lortuz (**2.16B Eskema**).



2.16 Eskema. A) **52aad'** sortzeko isomerizazio erreakzioa B) **52aad'** konposatuaren *one-pot* sintesia.

24e zinamaldehidoa erabiltzean, erreakzio baldintza estandarrek **52aae** tetrahidropirano eraztuna etekin moderatu eta estereokontrol osoarekin sortu zuten (**2.8 Taula**, 4. sarrera). Azken saiakuntzak **24f** aldehido kiralarekin gauzatu ziren. Honen egiturako karbono asimetrikoak laguntzaile kiral moduan joka zezakeela suposatu genuen, diastereomero bakarraren formazioa eraginez. Honela, amaierako produktua diastereoselektibitate altuarekin lortu zen, etekin eta enantioselektibitate itzelekin (**2.8 Taula**, 5. sarrera). Paregabeko emaitza honek egitura konplexuagoak sintetizatzera bultzatu gintuen, azukre-motako molekulak sortu asmoz. Honela, 1,4-ziklohexanodiona monoetileno azetala **11j** nukleozale moduan usatu zen, desioko **52jaf** deribatua etekin moderatu eta estereokontrol osoarekin sortuz (**2.8 Taula**, 6. sarrera).

Hitz batez: O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoa *one-pot* Michael-Henry-azetalizazio erreakzioa katalizatzeko gaitasun handikoa da aldehido askorentzat, desioko konposatuak etekin eta enantiokontrol onekin sortuz. Gure sistemaren izaera orokorra kontutan izanda, Hayashik publikatutako emaitzen osagarri dela esan daiteke.[29] Gainera, Chandrasekarren taldeak sintetizatutako zikloalkano-fusionatuko tetrahidropirano eskeletoen familia zabaltzen dutela ere aipatzekoa da.[28]

2.6 ONDORIOAK

Kapitulu honetan azaldu eta eztabaidatutako azterketen ondoren, hurrengo ondorioak laburtu daitezke:

1. O_2N-X_D-X_L^{Me}-OMe-**50** eta O_2N-X_L-X_L^{Me}-OMe-**50** dipeptido *N*-metilatu hibridoak etekin onekin sintetizatu ziren, O_2N-$X_{L/D}$-OMe-**44** funtzionalizazio altuko prolina ez-naturaletatik hasita.
2. Organokatalizatzaile dimeriko hauek ziklopentanona eta zikloheptanonaren enamina-bidezko Michael erreakzio asimetrikoak diastereo- eta enantioselektibitate itzelekin gauzatzeko gaitasuna hatzeman zuten. Lortutako emaitzek dipeptido hauen propietate berriak marratu zituzten.
3. Funtzionalizazio altuko prolina ez-naturaletatik eratorritako bigarren zein hirugarren generazioko katalizatzaileek Michael-Henry-azetalizazio erreakzioa burutzeko duten egokitasuna nabarmendu zen. Hauen artean, O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoak, azido saliziliko eta trietilaminarekin batera, sistema katalitiko eraginkorra osatzen zuen.
4. Prozesu kimikoaren izaera orokorra guztiz frogatua geratu zen. Katalizatzailearen egonkortasunak zetona nukleofiliko, nitroalkeno zein aldehido elektrofiliko ugariren erabilera onartu zuen. Tetrahidropirano deribatu guztiak etekin on eta enantiomero soberakin altuekin lortu ziren. Aldehidoen kasu partikularrerako, beharrezko trietilaminakantitate estekiometrikoek erlazio diastereomerikoan eragin nabaria izan zuten.
5. Elkartutako datu guztiek tetrahidropirano funtzionalizatuak lortzeko zetona nukleofilikoen erabilera egiten duen lehen hiru-osagaiko *one-pot* Michael-Henry-azetalizazio erreakzioa osatzen dute.

2.7 ATAL ESPERIMENTALA

Ohar orokorrak

Besterik esan ezean, erreaktibo eta substratu guztiak hornitzaile komertzialetatik lortu ziren. NH-L-EhuPhos-**43** eta NH-D-EhuPhos-**43** ligandoak gure prozedura jarraituz sintetizatu ziren.[33a]

Geruza meheko kromatografia (TLC) aluminio oinarridun 0.25mm-ko silika gel 60 F254 plakak erabiliz burutu zen, ultramore argiarekin behatu eta potasio permanganatoz errebelatuz. Zutabe kromatografikoak silika gel60-ko zutabeetan egin ziren (partikula tamaina: 23-40 μm).

Hidrogenazio erreakziotearako fluxu jarraiko Raney-Nikelezko kartutxodun erreaktorea erabili zen. Hidrogeno gasa momentuan sortzen zen uraren elektrolisitik.

Errotazio optikoak 589nm-ra neurtu ziren, 5 cm-ko zeldan eta 20 ºC inguruan. Kontzentrazioak g/100 mL moduan espresatzen dira.

Infragorri espektroak erreflexio bakarreko ATR moduludun Alpha-Bruker FT-IR espektrometroan burutu ziren. Uhin luzerak cm^{-1} moduan ematen dira.

Erresoluzio altuko masa espektroak (HRMS) SGIker zerbitzuak (Araba, Bizkaiko kanpuseko Zerbitzu Zentrala, Euskal Herriko Unibertsitatea) burutu zituen, LC/QTOF bidez, elektrospray ionizazioa erabiltzen duen Agilent masa espektrometroan.

RMN espektroak 400 edo 500 MHz-tan erregistratu ziren ^{1}H nukleoarentzat, 101 edo 126 MHz-tan ^{13}C nukleoarentzat eta 376 MHz-tan ^{19}F nukleoarentzat, $CDCl_3$, azetona-*d6* edo metanol-*d4* disolbatzailetzat erabiliz eta trimetilsilanoa erreferentziatzat hartuz. Datuak honela adierazten dira: s = singletea, d = dobletea, t = tripletea, q = kuadrupletea, m = multipletea edo erresolbatu gabea, bs = seinale zabala, akoplamendu konstantea (*J*) Hz-tan, integrazioa. ^{13}C RMN espektroak ^{1}H nukleoa desaklopatuz burutu ziren.

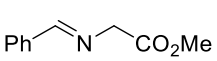
Enantiomero soberakinak HPLC bidez neurtu ziren, fase geldikor kiralak enplegatuz. Enantiomero bakoitzaren parametro enantiomerikoak zehazteko nahaste errazemikoak aztertu ziren lehenik.

X-izpien difrakzio analisirako Agilent Technologies Super-Nova difraktometroa erabili zen, Cu kα erradiazio monokromatikoaz (λ = 1.54184 Å) eta CCD detektoreaz ekipatua. Neurketak 100 K-tan burutu ziren, Oxford Cryostream 700 PLUS tenperatura aparatuaz lagunduz. Datuak Crysalis softwerra bidez prozesatu ziren (zelda unitatearen determinazioa, absortzio analitikoaren korrekzioa, intentsitate integrazioa eta Lorentz eta polarizazio efektuen korrekzioa).[38] Egitura Superflip[39] bidez ebatzi zen, eta SHELXL-97[40] bidez errefinatu. Amaierako kalkulo geometrikoak Mercury[41] eta PLATON[42]-en burutu ziren, WinGX[43]-en integratuta ageri den moduan.

42 iminaren sintesia

Glizina metil ester hidrokloruroa (376.6 mg, 3.0 mmol, 1 eq.), trietilamina (420 µL, 3.0 mmol, 1 eq.) eta $MgSO_4$ CH_2Cl_2 lehorretan (5 mL) disolbatu ziren. Suspentsioa giro tenperaturan nahastu zen ordubetez, eta 2.3 mmol (0.8 eq.) benzaldehido gehitu ziren. Sortutako nahastea 16 orduz erreakzionarazi zen, filtratu, H_2O-z garbitu, Na_2SO_4-az lehortu eta presio erreduzituan lurrundu. Lorturiko imina ondorengo pausuetan erabili zen, inolako purifikaziorik gabe.

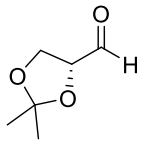
[38] CrysAlisPro, Agilent Technologies, Version 1.171.37.31.
[39] Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786-790.
[40] a) Sheldrick, G. M. *Acta Cryst*. **2008**, A64, 112-122. b) Sheldrick, G. M. *Acta Cryst*. **2015**, C71, 3-8.
[41] Macrae, C. F. *J. Appl. Cryst*. **2008**, *41*, 466-470.
[42] a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Utretch University, The Nederlands **2010**. b) Spek, A. L. *J. Appl. Cryst*. **2003**, *36*, 7-13.
[43] Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838.



Metil (E)-2-(benzilidenamino)azetatoa (**43**). Etekina: %84 (446 mg, 2.51 mmol). Olio koloregabea. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, CH), 7.82 – 7.76 (m, 2H, ArH), 7.50 – 7.38 (m, 3H, ArH), 4.42 (s, 2H, CH_2), 3.78 (s, 3H, CO_2CH_3).

24f aldehidoaren sintesia

D-manitol-1,2:5,6-bis-azetonido (1g, 4.30 mmol, 1 eq.) CH_2Cl_2 disoluzioari (10 mL) $NaIO_4$ (1.80g, 8.60 mmol, 2 eq.) eta $NaHCO_3$ disoluzio saturatua (0.45 mL) gehitu zitzaizkion eta nahastea giro tenperaturan nahastu zen 2 orduz. Erreakzio nahastea filtratu eta CH_2Cl_2 bidez garbitu zen. Fase organikoa Na_2SO_4 bidez lehortu zen, filtratu eta presio erreduzituan lurrundu.

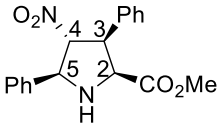


(*R)-2,2-dimetil-1,3-dioxolano-4-karbaldehidoa* (**24f**).[44] Etekina: %75 (419 mg, 3.22 mmol). Olio hori argia. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.9 Hz, 1H, CHO), 4.39 (ddd, *J* = 7.0, 4.7, 1.9 Hz, 1H, CH), 4.19 – 4.12 (m, 1H, CH_2), 4.10 (d, *J* = 4.0 Hz, 1H, CH_2), 1.49 (s, 3H, CH_3), 1.42 (s, 3H, CH_3).

Exo-44 zikloaduktuen sintesirako prozedura orokorra

Exo-L zikloaduktoarentzat: NH-D-EhuPhos-**43** (9 mg, 0.015 mmol, 0.03 eq.) eta $Cu(CH_3CN)_4PF_6$ (5 mg, 0.014 mmol, 0.03 eq.) THF (1mL) disoluzioa -20 ºC-tan nahastu zen 15 minutuz. Gero, **42** imina (80 mg, 0.45 mmol, 1 eq.) 1 mL disoluzio, trietilamina (3 µL, 0.023 mmol, 0.05 eq.) eta *trans*-β-nitroestirenoa **11a** (75 mg, 0.50 mmol, 1,1 eq.) 1 mL disoluzio banan-bana gehitu ziren. Erreakzioa TLC bidez jarraitu zen, eta behin hasierako erreaktiboak amaituta, nahastea zelita bidez filtratu zen eta disoluzioa presio erreduzituan lurrundu. Gero, amaierako nahastea silika gelezko zutabe kromatografiko bidez purifikatu zen (1:2 EtOAc:Hexano). *Exo*-D zikloaduktorako NH-L-EhuPhos-**43** ligandoa erabili zen. Soberakin enantiomerikoak nahaste errazemikoen kromatogramekin konparatuz determinatu ziren.

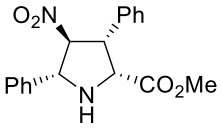
Nomenklatura: Funtzionalizazio altuko pirrolidina eraztunetako karbono atomoak pirrolidinan bezala zenbatzen dira, nitrogeno atomoa 1 izanik eta ester taldearen ordezkapenaz jarraituz.[45]



Metil (2S,3S,4R,5S)-4-nitro-3,5-difenilpirrolidina-2-karboxilatoa (O_2N-X_L-OMe-**44**).[46] Etekina: %85 (125 mg, 0.38 mmol), solido zuria. %97 *ee* zutabearen ondoren eta >%99 *ee* EtOAc/hexano bidezko

[44] Leyes, A. E.; Poulter, C. D. *Org. Lett*. **1999**, *1*, 1067-1070.
[45] Amino Azido eta Peptidoen Nomenklatura eta Sinbolismoa. *Eur. J. Biochem*. **1984**, *138*, 9-37.
[46] Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed*. **2006**, *45*, 1979-1983.

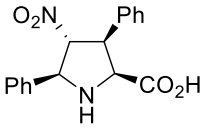
errekristalizazio ondoren. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.0 Hz, 2H, ArH), 7.46 – 7.36 (m, 3H, ArH), 7.35 – 7.19 (m, 5H, ArH), 5.22 (t, *J* = 8.1 Hz, 1H, C^4H), 4.77 (d, *J*=8.2, 1H, C^5H), 4.51 (d, *J* = 7.9 Hz, 1H, C^2H), 4.39 (t, *J* = 8.5 Hz, 1H, C^3H), 3.29 (s, 3H, CO_2CH_3), 2.74 (bs, 1H, NH). **HPLC** (Chiralcel IB, Hexano:^{i}PrOH = 80:20, fluxua 1 mL/min, λ = 254 nm), t_R (nagusia) = 6.92 min, t_R (gutxiengoa) = 12.49 min; *ee* = %97.



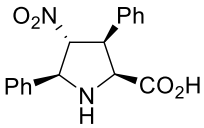
Metil (2R,3R,4S,5R)-4-nitro-3,5-difenilpirrolidina-2-karboxilatoa (O_2N-X_D-OMe-**44**).[33a] Etekina: %84 (123 mg, 0.37 mmol), solido zuria. %96 *ee* zutabearen ondoren eta >%99 *ee* EtOAc/hexano bidezko errekristalizazio ondoren. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.0 Hz, 2H, ArH), 7.46 – 7.36 (m, 3H, ArH), 7.35 – 7.19 (m, 5H, ArH), 5.22 (t, *J* = 8.1 Hz, 1H, C^4H), 4.77 (d, *J*=8.2, 1H, C^5H), 4.51 (d, *J* = 7.9 Hz, 1H, C^2H), 4.39 (t, *J* = 8.5 Hz, 1H, C^3H), 3.29 (s, 3H, CO_2CH_3), 2.74 (bs, 1H, NH). HPLC (Chiralcel IB, Hexano:^{i}PrOH = 80:20, fluxua 1 mL/min, λ = 254 nm), t_R (gutxiengoa) = 6.92 min, t_R (nagusia) = 12.49 min; *ee* = %96.

Hidrolisi prozedura orokorra

O_2N-$X_{L/D}$-OMe-**44**-ko (326 mg, 1.0 mmol, 1 eq.) azetona disoluzioa (3 mL) giro tenperaturan nahastu zen, eta NaOH-zko (88 mg, 2.20 mmol, 2.2 eq.) 3mL ur disoluzio gehitu. Erreakzioa 16 orduz nahastu zen. Ondoren, nahastea 0 ºC-ra hoztu zen eta pH = 2 ingurura azidifikatu HCl 2N bidez. Sortutako hauspeakina filtratu, uraz garbitu eta presiopean lehortu zen.



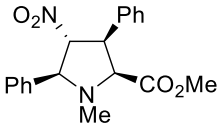
Azido (2S,3S,4R,5S)-4-nitro-3,5-difenilpyrrolidina-2-karboxilikoa (O_2N-X_L-OH-**45**).[31] Etekina: %85 (265 mg, 0.85 mmol), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (500 MHz, azetona-d_6) δ 7.51 (d, *J* = 7.4 Hz, 4H, ArH), 7.41 (t, *J* = 7.5 Hz, 2H, ArH), 7.38 – 7.28 (m, 4H, ArH), 5.57 (dd, *J* = 6.8, 4.3 Hz, 1H, C^4H), 5.20 (d, *J* = 6.7 Hz, 1H, C^5H), 4.30 – 4.24 (m, *J* =9.1 Hz, 1H, C^2H), 4.19 (d, *J* = 7.7 Hz, 1H, C^3H), 2.78 (bs, 1H, NH).



Azido (2R,3R,4S,5R)-4-nitro-3,5-difenilpirrolidina-2-karboxilikoa (O_2N-X_L-OH-**45**).[31] Etekina: %80 (250 mg, 0.80 mmol), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (500 MHz, azetona-d_6) δ 7.51 (d, *J* = 7.4 Hz, 4H, ArH), 7.41 (t, *J* = 7.5 Hz, 2H, ArH), 7.38 – 7.28 (m, 4H, ArH), 5.57 (dd, *J* = 6.8, 4.3 Hz, 1H, C^4H), 5.20 (d, *J* = 6.7 Hz, 1H, C^5H), 4.30 – 4.24 (m, *J* =9.1 Hz, 1H, C^2H), 4.19 (d, *J* = 7.7 Hz, 1H, C^3H), 2.78 (bs, 1H, NH).

O_2N-X_L-OMe-44 pirrolidinen metilaziorako prozedura orokorra

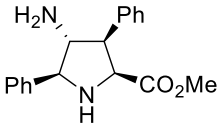
O_2N-X_L-OMe-**44** pirrolidina (500 mg, 1.53 mmol) 10 mL %88 azido formiko akuosotan disolbatu ziren. 10 mL %35 formaldehido akuoso gehitu zitzaizkion eta erreakzioa 100 ºC-ra berotu bi orduz. Erreakzio tenperatura giro tenperaturara jaistean K_2CO_3 bidez basifikatu zen hauspeakin bat agertu arte. Disoluzioa H_2O-z diluitu zen, eta CH_2Cl_2 bidez erauzi. Fase organikoak Na_2SO_4-an lehortu ziren, filtratu eta presio erreduzituan kontzentratu. Nahastea silika gelezko zutabe kromatografiko bidez purifikatu zen (1:5 EtOAc:hexanoa).



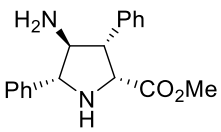
Metil (2S,3S,4R,5S)-1-metil-4-nitro-3,5-difenilpirrolidina-2-karboxilatoa (O_2N-X_L^{Me}-OMe-**47**).[31] Etekina: %90 (470 mg, 1.38 mmol), solido hori iluna. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H, ArH), 7.45 – 7.24 (m, 8H, ArH), 5.05 – 4.96 (m, 1H, C^4H), 4.24 (dd, *J* = 9.3, 5.9 Hz, 1H, C^3H), 3.97 (d, *J* = 8.0 Hz, 1H, C^5H), 3.92 (d, *J* = 9.3 Hz, 1H, C^2H), 3.27 (s, 3H, CO_2CH_3), 2.33 (s, 3H, NCH_3).

Amino deribatuen sintesirako prozedura orokorra

Dagokion zikloaduktoaren (1.0 mmol) 100 mL-ko metanoleko disoluzioa H-Cube hidrogenazio erreaktorean ponpatu zen 1 mL/minutuko fluxuarekin, Raney-Nikel katalizatzailea erabiliz. Sistemako presioa 20 bar-tan finkatu zen, eta tenperatura 65 ºC-tan. Behin nahastea erreaktoretik pasata, disolbatzailea lurrundu zen, eta erreakzio nahastea silika geletik filtratu zen etil azetatoa erabiliz.

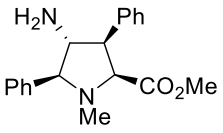


Metil (2S,3R,4R,5S)-4-amino-3,5-difenilpirrolidina-2-karboxilatoa (H_2N-X_L-OMe-**46**).[31] Produktua O_2N-X_L-OMe-**45**-tik sortu zen. Etekina: %90 (266 mg, 0.90 mmol), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 2H, ArH), 7.40 (t, *J* = 7.2 Hz, 2H, ArH), 7.34 – 7.29 (m, 3H, ArH), 7.24 (d, *J* = 7.0 Hz, 3H, ArH), 4.26 (d, *J* = 9.7 Hz, 1H, C^5H), 3.92 (d, *J* = 8.7 Hz, 1H, C^2H), 3.60 (t, *J* = 9.5 Hz, 1H, C^3H), 3.49 (t, *J* = 9.9 Hz, 1H, C^4H), 3.22 (s, 3H, CO_2CH_3).



Metil (2R,3S,4S,5R)-4-amino-3,5-difenilpirrolidina-2-karboxilatoa (H_2N-X_D-OMe-**46**).[31] Produktua O_2N-X_D-OMe-**45**-tik sortu zen. Etekina: %85 (252 mg, 0.85 mmol), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 2H, ArH), 7.40 (t, *J* = 7.2 Hz, 2H, ArH), 7.34 – 7.29 (m, 3H, ArH),

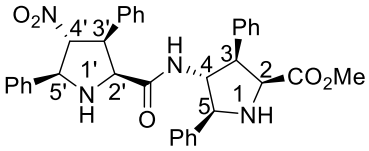
7.24 (d, *J* = 7.0 Hz, 3H, ArH), 4.26 (d, *J* = 9.7 Hz, 1H, C^5H), 3.92 (d, *J* = 8.7 Hz, 1H, C^2H), 3.60 (t, *J* = 9.5 Hz, 1H, C^3H), 3.49 (t, *J* = 9.9 Hz, 1H, C^4H), 3.22 (s, 3H, CO_2CH_3).



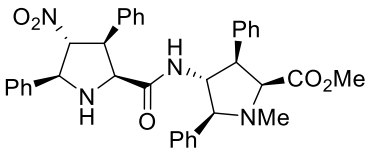
Metil (2S,3R,4R,5S)-4-amino-1-metil-3,5-difenilpirrolidina-2-karboxilatoa (H_2N-X_L^{Me}-OMe-**48**).[31] Produktua O_2N-X_L^{Me}-OMe-**47**-tik sortu zen. Etekina: %65 (202 mg, 0.65 mmol), solido hori argia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz.[1]**H RMN** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 2H, ArH), 7.38 (t, *J* = 7.5 Hz, 2H, ArH), 7.35-7.16 (m, 6H, ArH), 3.70 (d, *J* = 10.4 Hz, 1H, C^5H), 3.50 (t, *J* = 8.4 Hz, 1H, C^3H), 3.38-3.26 (m, 1H, C^4H), 3.19 (s, 3H, CO_2CH_3), 3.15 (d, *J* = 8.3 Hz, 1H, C^2H), 2.23 (s, 3H, NCH_3), 1.33 (s, 2H, NH_2).

Akoplamendu erreakzioetarako prozedura orokorra

Dagokion aminaren (0.80 mmol, 1 eq.) CH_2Cl_2 10 mL disoluziori O_2N-X_L-OH-**45** (1.0 mmol, 1.25 eq.), PyBOP (520 mg, 1.0 mmol, 1.25 eq.) eta DIPEA (250 µL, 1.44 mmol, 1.8 eq.) gehitu zitzaizkion. Sortutako nahastea giro tenperaturan nahastu zen hasierako erreaktiboak desagertu arte. Erreakzio nahastea CH_2Cl_2-tan diluitu zen, HCl 1M disoluzioaz (3x10 mL), $NaHCO_3$ saturatuaz (2x10 mL) eta NaCl saturatuaz (1x10 mL) garbitu, eta Na_2SO_4-an lehortu. Lurrundu ondoren, nahastea zutabe kromatografikoan purifikatu zen (1:2 EtOAc:Hexano).

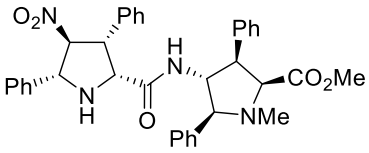


Metil (2S,3R,4R,5S)-4-((2S,3S,4R,5S)-4-nitro-3,5-difenilpirrolidina-2-karboxamido)-3,5-difenilpirrolidina-2-karboxilatoa (O_2N-X_L-X_L-OMe-**49**). Produkuta H_2N-X_L-OMe-**46**-tik sortu zen. Etekina: %65 (307 mg, 0.52 mmol), solido zuria. $\mathbf{u_p}$ = 136-137 °C. $[\alpha]_D^{25}$ = +129.9 (*c* 0.43, azetona). **FTIR** (neat, cm^{-1}) 1732, 1671, 1546, 696. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.56 – 7.33 (m, 10H, ArH), 7.30 – 7.17 (m, 5H, ArH), 7.11 (t, *J* = 7.4 Hz, 1H, ArH), 7.00 (t, *J* = 7.7 Hz, 2H, ArH), 6.93 (d, *J* = 8.8 Hz, 1H, CONH), 6.77 (d, *J* = 7.3 Hz, 2H, ArH), 4.93 (t, *J* = 8.6 Hz, 1H, $C^{4'}H$), 4.79 (d, *J* = 8.4 Hz, 1H, $C^{5'}H$), 4.59 (q, *J* = 9.0 Hz, 1H, C^4H), 4.33 – 4.17 (m, 3H, $C^{2'}H$, $C^{3'}H$, C^2H), 4.15 – 4.07 (m, 1H, C^5H), 3.52 (t, *J* = 9.1 Hz, 1H, C^3H), 3.20 (s, 3H, CO_2CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 173.1, 169.3, 137.2, 134.5, 129.4, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.2 (2 seinale), 127.7, 127.5, 126.7, 94.4, 67.08, 66.1, 64.2, 63.7, 60.2, 54.3, 53.5, 51.7. **HRMS** (ESI) $C_{35}H_{35}N_4O_5$: kalkulatua $[M+H]^+$: 591.2607, aurkitua: 591.2617.



Metil (2S,3R,4R,5S)-1-metil-4-((2S,3S,4R,5S)-4-nitro-3,5-difenilpirrolidina-2-karboxamido)-3,5-difenilpirrolidina-2-karboxilatoa (O_2N-X_L-X_L^{Me}-OMe-**50**). Produktua H_2N-X_L^{Me}-OMe-**48-**tik sortu zen. Etekina: %76 (368 mg, 0.61 mmol), solido

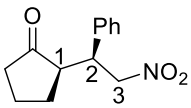
zuria. **u_p** = 201-204 °C. $[\alpha]_D^{25}$ = +125.3 (*c* 0.50, azetona). **FTIR** (neat, cm^{-1}) 1745, 1672, 1551. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.42 (m, 10H, ArH), 7.33 – 7.16 (m, 6H, ArH), 7.10 (t, *J* = 7.4 Hz, 2H, ArH), 6.90 (d, *J* = 7.4 Hz, 2H, ArH), 6.83 (d, *J* = 7.8 Hz, 1H, CONH), 4.98 (d, *J* = 4.9 Hz, 1H, $C^{4'}$H), 4.81 (d, *J* = 7.8 Hz, 1H, $C^{5'}$H), 4.29 (s, 2H, $C^{2'}$H and $C^{3'}$H), 4.11 (q, *J* = 7.8 Hz, 1H, C^4H), 3.68 (d, *J* = 9.5 Hz, 1H, C^2H), 3.43 (d, *J* = 8.6 Hz, 1H, C^5H), 3.31 (t, *J* = 8.2 Hz, 1H, C^3H), 3.19 (s, 3H, CO_2CH_3), 2.58 (m, 1H, NH), 2.22 (s, 3H, NCH_3). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 171.25, 169.5, 139.7, 139.6, 137.9, 135.0, 129.3, 129.3, 129.0, 128.9, 128.9, 128.5, 128.3 (2 seinale), 128.2, 128.0, 127.2, 126.8, 94.8, 74.8, 72.1, 66.3, 64.3, 64.2, 53.4, 51.8, 51.3, 39.9. **HRMS** (ESI) $C_{36}H_{37}N_4O_5$: kalkulatua $[M+H]^+$: 605.2764, aurkitua: 605.2778.



Metil (2S,3R,4R,5S)-1-metil-4-((2R,3R,4S,5R)-4-nitro-3,5-difenilpirrolidina-2-karboxamido)-3,5-difenilpirrolidina-2-karboxilatoa (O_2N-X_D-X_L^{Me}-OMe-**50**). Produktua H_2N-X_L^{Me}-OMe-**48**-tik sortu zen. Etekina: %68 (329 mg, 0.54 mmol), solido zuria. **u_p** = 99-100 °C. $[\alpha]_D^{25}$ = -19.0 (*c* 0.51, azetona). **FTIR** (neat, cm^{-1}) 1748, 1669, 1547. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.59 – 7.11 (m, 20H, ArH), 6.70 (d, *J* = 7.2 Hz, 1H, CONH), 5.17 – 4.99 (m, 1H, $C^{4'}$H), 4.82 (d, *J* = 7.4 Hz, 1H, $C^{5'}$H), 4.28 (m, 2H, $C^{2'}$H and $C^{3'}$H), 4.04 (dd, *J* = 13.7, 7.2 Hz, 1H, C^4H), 3.54 (d, *J* = 9.2 Hz, 1H, C^2H), 3.23 (s, 3H, CO_2CH_3), 3.16 (d, *J* = 8.1 Hz, 1H, C^5H), 2.90 (dd, *J* = 8.7, 6.1 Hz, 1H, C^3H), 2.62 (bs, 1H, NH), 2.23 (s, 3H, NCH_3). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 170.8, 169.0, 140.3, 139.2, 138.0, 136.2, 129.4, 129.2, 128.9, 128.9, 128.7, 128.7, 128.4, 128.4, 128.1, 127.9, 127.1, 126.8, 95.7, 76.4, 72.3, 66.5, 64.9, 64.4, 53.0, 52.2, 51.3, 39.8. **HRMS** (ESI) $C_{36}H_{37}N_4O_5$: kalkulatua $[M+H]^+$: 605.2764, aurkitua: 605.2773.

Michael erreakzio asimetrikorako prozedura orokorra

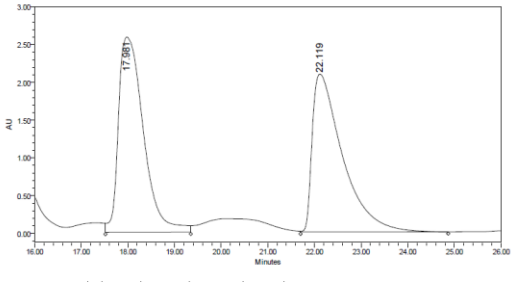
Katalizatzaile dimeriko (12.10 mg, 0.02 mmol, 0.2 eq.), azido saliziliko (2.76 mg, 0.02 mmol, 0.2 eq.), **29b,c** zetona (0.10 mmol, 1 eq.) eta **11a** *trans*-β-nitroestirenoaren (14.90 mg, 0.11 mmol, 1.1 eq.) erreakzio nahastea -10 ºC-tan nahastu zen nitroalkenoaren erabateko desagerpena arte. Erreakzio nahastea presio erreduzituan lurrundu zen eta zutabe kromatografiko bidez purifikatu (1:2 EtOAc:Hexano). Konposatu errazemikoak pirrolidina (8 µL, 0.10 mmol, 1 eq.) erabiliz sintetizatu ziren.

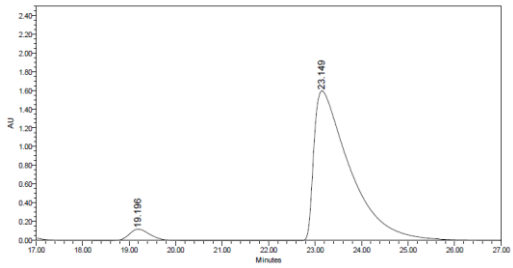


(R)-2-((S)-2-nitro-1-feniletil)ziklopentan-1-ona (**51ba**).[47] Produktua ziklopentanona **29b**-tik sortu zen. Etekina: %95 (22 mg, 0.095 mmol), solido zuria. Datu analitiko eta espektroskopikoak literaturako

[47] Vishnumaya, Singh, V. K. *Org. Lett*. **2007**, *9*, 1117-1119.

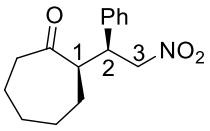
publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 3H, ArH), 7.20 – 7.15 (m, 2H, ArH), 5.35 (d, *J* = 5.6 Hz, 1H, C^3H), 4.71 (dd, *J* = 12.8, 10.0 Hz, 1H, C^3H), 3.69 (td, *J* = 9.5, 5.5 Hz, 1H, C^2H), 2.45 – 2.27 (m, 2H, CH_2), 2.12 (ddd, *J* = 19.0, 10.6, 8.7 Hz, 1H, C^1H), 1.97 – 1.78 (m, 2H, CH_2), 1.74 – 1.66 (m, 1H, CH_2), 1.54 – 1.39 (m, 1H, CH_2). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 210 nm), t_R (gutxiengoa) = 17.98 min, t_R (nagusia) = 22.12 min; *ee* = %90.





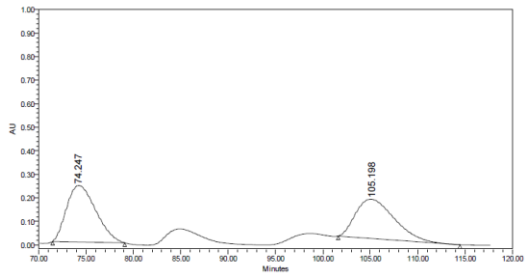
	RT	Altuera	Azalera	% Azal.
1	17.981	2585598	96504734	50.58
2	22.119	2092659	94307764	49.42

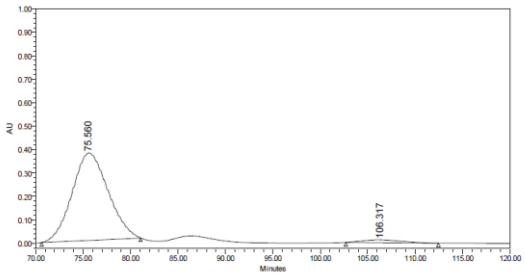
	RT	Altuera	Azalera	% Azal.
1	19.196	121177	3717563	4.13
2	23.149	1600476	86208468	95.87



(R)-2-((S)-2-nitro-1-feniletil)zikloheptan-1-ona (**51ca**).[48] Produktua zikloheptanona **29c**-tik sortu zen. Etekina %94 (25 mg, 0.094 mmol), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 14.8, 7.8, 6.2 Hz, 3H, ArH), 7.20 – 7.16 (m, 2H, ArH), 4.67 – 4.63 (m, 2H, C^3H), 3.68 (ddd, *J* = 10.2, 8.3, 5.1 Hz, 1H, C^2H), 3.00 (td, *J* = 10.3, 3.4 Hz, 1H, C^1H), 2.57 – 2.47 (m, 2H, CH_2), 1.99 – 1.82 (m, 2H, CH_2), 1.80 – 1.52 (m, 3H, CH_2), 1.29 – 1.12 (m, 3H, CH_2). **HPLC** (Daicel Chiralpak AD-H, Hexano:^{i}PrOH = 99:1, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 74.25 min, t_R (gutxiengoa) = 105.20 min; *ee* = %93.

[48] Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *Journal of Molecular Catalysis A: Chemical* **2007**, *263*, 186-194.



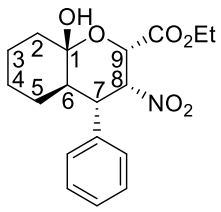


	RT	Altuera	Azalera	% Azal.
1	74.247	240065	51426808	52.07
2	105.198	166817	47346104	47.93

	RT	Altuera	Azalera	% Azal.
1	75.560	372306	98576963	96.58
2	106.317	12229	3491361	3.42

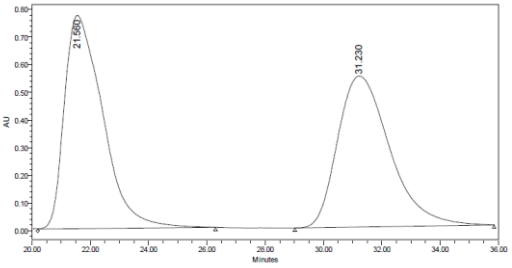
Michael-Henry-Azetalizazio erreakziorako prozedura orokorra

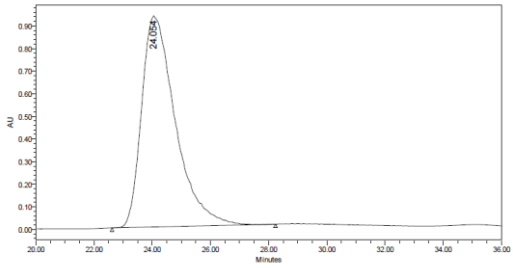
O_2N-X_L-X_L^{Me}-OMe-**50** (12.10 mg, 0.02 mmol, 0.2 eq.), deribatu azido (0.02 mmol, 0.2 eq.), **29a-j** zetona (0.1 mmol, 1.0 eq.) eta **11a-i** nitroalkeno (0.11 mmol, 1.1 eq.)-ko erreakzio nahastea giro tenperaturan nahastu zen nitroalkenoa guztiz desagertu arte. Ondoren, dagokion aldehidoa (0.20 mmol, 0,2 eq.) eta trietilamina (3 µL, 0.02 mmol, 0.2 eq.) gehitu ziren eta erreakzioa zehaztutako tenperaturan nahastu zen γ-nitrozetona artekaria desagertu arte. Erreakzio nahastea lurrundu zen eta zutabe kromatografiko bidez purifikatu (baldintzak ezagutzeko konposatu bakoitza ikuskatu). Konposatu errazemikoak pirrolidina bidez sintetizatu ziren (8 µL, 0.10 mmol, 1 eq.).



Etil (2S,3R,4S,4aR,8aS)-8a-hidroxi-3-nitro-4-feniloktahidro-2H-kromeno-2-karboxilatoa (**52aaa**). Ziklohexanona **29a**, *trans*-β-nitrostirenoa **11a** eta etil glioxilatoa **24a**-tik sortua, azido salizilikoa aditibo bezala erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %72 (27 mg, 0.072 mmol), solido zuria. $\mathbf{u_p}$ = 169-171 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +52.63 (*c* 0.95, kloroformoa). **FTIR** (neat, cm^{-1}) 3507, 1756, 1545, 1313. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.4 Hz, 3H, ArH), 7.13 (d, *J* = 7.3 Hz, 2H, ArH), 5.14 (d, *J* = 3.0 Hz, 1H, C^9H), 5.12 (d, *J* = 4.4 Hz, 1H, C^8H), 4.33 – 4.13 (m, 2H, CH_2CH_3), 3.52 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.61 (td, *J* = 12.2, 3.3 Hz, 1H, C^6H), 2.09 – 1.97 (m, 2H, CH_2, OH), 1.95 (s, 1H, CH_2), 1.78 (d, *J* = 13.7 Hz, 1H, CH_2), 1.74 – 1.60 (m, 2H, CH_2), 1.39 (d, *J* = 14.4 Hz, 1H, CH_2), 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.18 – 0.98 (m, 1H, CH_2), 0.92 – 0.79 (m, 1H, CH_2). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 167.7 (C=O), 136.2(ArC), 129.1 (ArC), 128.3 (ArC), 128.2 (ArC), 98.1 (C^1), 86.9 (C^8), 69.3(C^9), 62.3 (CH_2CH_3), 44.1 (C^7), 38.9 (C^6), 38.5 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 14.1 (CH_2CH_3). **HRMS** (ESI) $C_{18}H_{24}NO_6$:

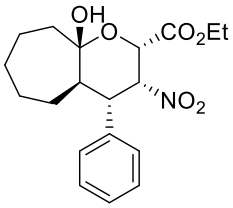
kalkulatua $[M+H]^+$: 350.1603, aurkitua 350.1605. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 21.56 min, t_R (gutxiengoa) = 31.23 min; *ee* = %99.



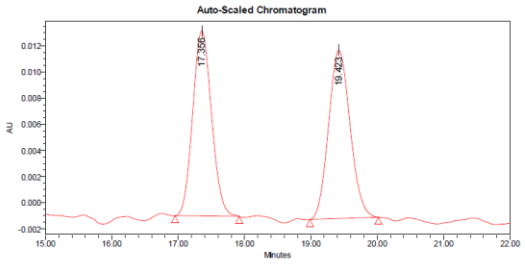


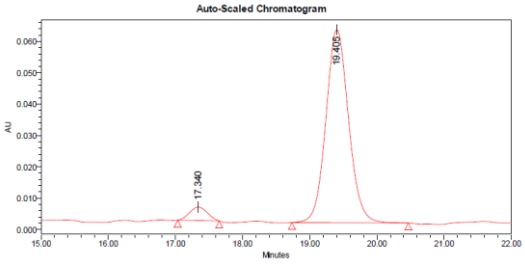
	RT	Altuera	Azalera	% Azal.
1	21.560	772486	70549380	50.95
2	31.230	546319	67923484	49.05

	RT	Altuera	Azalera	% Azal.
1	24.054	932234	74986663	100.0
2				



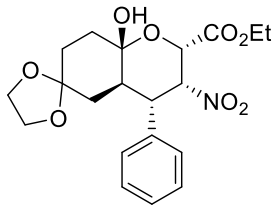
Etil (2S,3R,4S,4aR,9aS)-9a-hidroxi-3-nitro-4-fenildekahidroziklohepta[b]piran-2-karboxilatoa (**52caa**). Zikloheptanona **29c**, *trans*-β-nitrostirenoa **11a** eta etil glioxilatoa **24a**-tik sortua, TFA aditibo moduan erabiliz. 1:1 Dietil eterra:Hexano nahasteaz purifikatua. Etekina: %53 (19 mg, 0.053 mmol), olio koloregabea. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +42.64 (*c* 0.25, kloroformoa). **FTIR** (neat, cm^{-1}) 3404, 2982, 1740, 1552, 1370. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.1, 6.5 Hz, 2H, ArH), 7.34 – 7.25 (m, 3H, ArH), 5.25 (dd, *J* = 11.1, 2.3 Hz, 1H, C^9H), 4.35 – 4.16 (m, 2H, CH_2CH_3), 4.16 – 4.08 (m, 1H, C^8H), 3.94 – 3.86 (m, 1H, C^7H), 3.24 – 3.14 (m, 1H, OH), 2.85 (ddd, *J* = 11.6, 8.1, 3.8 Hz, 1H, C^6H), 2.38 – 2.21 (m, 1H, CH_2), 1.88 – 1.73 (m, 3H, CH_2), 1.66 (d, *J* = 53.8 Hz, 3H, CH_2), 1.43 (s, 1H, CH_2), 1.28 (d, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.25 (d, *J* = 4.0 Hz, 1H, CH_2), 1.22 – 1.06 (m, 1H, CH_2). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 170.8, 136.5, 129.2, 129.1, 128.1, 90.1, 69.8, 62.8, 55.2, 46.8, 42.8, 29.5, 28.3, 28.1, 24.8, 14.0. **HRMS** (ESI) $C_{19}H_{26}NO_6$: kalkulatua $[M+H]^+$: 364.1760, aurkitua 364.1761. **HPLC** (Chiralcel IC, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 214 nm), t_R (gutxiengoa) = 17.35 min, t_R (nagusia) = 19.42 min, *ee* = %90.



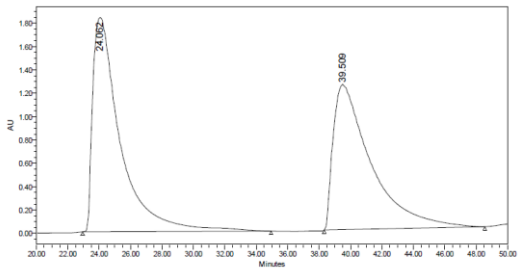


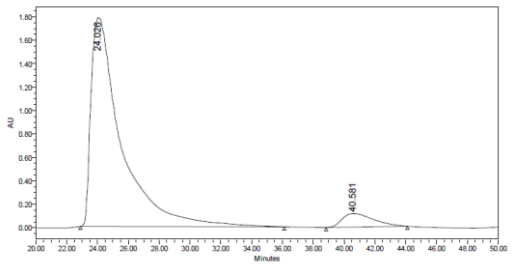
	RT	Altuera	Azalera	% Azal.
1	17.356	14190	279399	49.08
2	31.230	12896	289826	50.92

	RT	Altuera	Azalera	% Azal.
1	17.340	4299	78850	5.18
2	17.405	61608	1443594	94.82



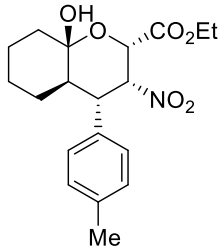
Etil (2S,3R,4S,4aR,8aS)-8a-hidroxi-3-nitro-4-fenilhexahidro-2H,5H-espiro[kromeno-6,2'-[1,3]dioxolano]-2-karboxilatoa (**52jaa**). 1,4-ziklohexanodiona monoetileno azetal **29j**, *trans*-β-nitroestireno **11a** eta etil glioxilato **24a**-tik sortua, azido salizilikoa aditibo bezala erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %62 (25 mg, 0.062 mmol), olio koloregabea. $[\alpha]_D^{25}$ = +13.31 (*c* 0.7, kloroformoa). **FTIR** (neat, cm^{-1}) 3445, 2963, 1734, 1550, 1370. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 3H, ArH), 7.18 – 7.12 (m, 2H, ArH), 5.13 (d, *J* = 3.1 Hz, 1H, C^9H), 5.10 (dd, *J* = 4.8, 3.2 Hz, 1H, C^8H), 4.28 (dd, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 4.26 – 4.07 (m, 1H, CH_2CH_3), 3.98 – 3.92 (m, 1H, CH_2O), 3.86 (ddd, *J* = 12.5, 6.9, 5.5 Hz, 2H, CH_2O), 3.82 – 3.74 (m, 1H, CH_2O), 3.53 (dd, *J* = 12.7, 4.8 Hz, 1H, C^7H), 3.00 (ddd, *J* = 12.7, 9.9, 6.5 Hz, 1H, CH_2), 2.35 (td, *J* = 15.1, 4.8 Hz, 1H, C^6H), 2.21 (s, 1H, OH), 2.01 – 1.87 (m, 2H, CH_2), 1.86 – 1.75 (m, 1H, CH_2), 1.45 (dd, *J* = 8.7, 1.8 Hz, 2H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.7, 136.0, 129.5, 128.6, 108.6, 97.7, 86.5, 69.9, 64.9, 64.7, 62.7, 43.9, 36.2, 35.9, 35.1, 32.3. **HRMS** (ESI) $C_{20}H_{24}NO_7$ $[M+H-H_2O]^+$: kalkulatua 390.1546, aurkitua 390.1541. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 24.06 min, t_R (gutxiengoa) = 39.51 min, *ee* = %88.



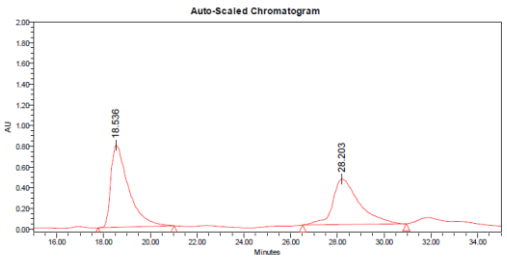


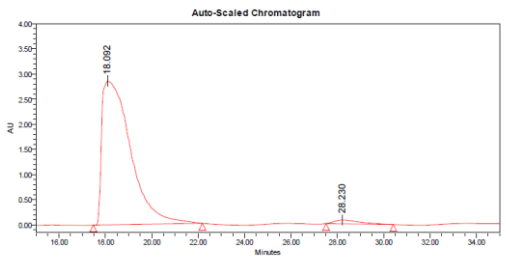
	RT	Altuera	Azalera	% Azal.
1	24.062	1834217	224008004	51.93
2	39.509	1242793	207365753	48.07

	RT	Altuera	Azalera	% Azal.
1	24.026	1781292	242669095	93.70
2	40.581	116739	16322493	6.30



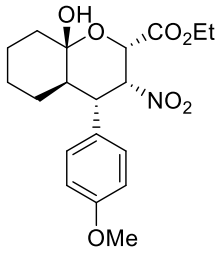
Etil (2S,3R,4S,4aR,8aS)-8a-hidroxi-3-nitro-4-(p-tolil)oktahidro-2H-kromeno-2-karboxilatoa (**52aba**). Ziklohexanona **29a**, *trans*-4-metil-β-nitroestirenoa **11b** eta etil glioxilato **24a**-tik sortua, azido salizilikoa aditibo moduan erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %47 (17 mg, 0.047 mmol), solido zuria. $\mathbf{u_p}$ = 174-177 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +57.69 (*c* 0.5, kloroformoa). **FTIR** (neat, cm^{-1}) 3475, 1750, 1549, 1372. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 2H, ArH), 7.01 (d, *J* = 7.6 Hz, 2H, ArH), 5.13 (d, *J* = 3.0 Hz, 1H, C^9H), 5.09 (s, 1H, C^8H), 4.27 (dd, *J* = 10.8, 7.0 Hz, 1H, CH_2CH_3), 4.17 (dd, *J* = 11.0, 6.9 Hz, 1H, CH_2CH_3), 3.48 (dd, *J* = 12.5, 4.9 Hz, 1H, C^7H), 2.57 (td, *J* = 12.5, 3.4 Hz, 1H, C^6H), 2.32 (s, 3H, CH_3), 2.16 (s, 1H, OH), 2.00 (td, *J* = 13.7, 4.3 Hz, 1H, CH_2), 1.93 (d, *J* = 14.1 Hz, 1H, CH_2), 1.77 (d, *J* = 13.7 Hz, 1H, CH_2), 1.71 – 1.53 (m, 2H, CH_2), 1.44 – 1.26 (m, 2H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.09 (qd, *J* = 12.8, 3.4 Hz, 1H, CH_2).**^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.7, 137.8, 133.1, 129.8, 128.1, 98.2, 87.1, 69.4, 62.3, 43.7, 39.0, 38.6, 26.2, 25.6, 23.1, 21.2, 14.1. **HRMS** (ESI) $C_{19}H_{26}NO_6$ $[M+H]^+$: kalkulatua 364.1951, aurkitua 364.1948. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 18.53 min, t_R (gutxiengoa) = 28.20 min, *ee* = %95.



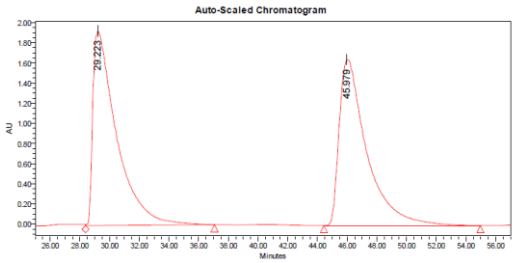


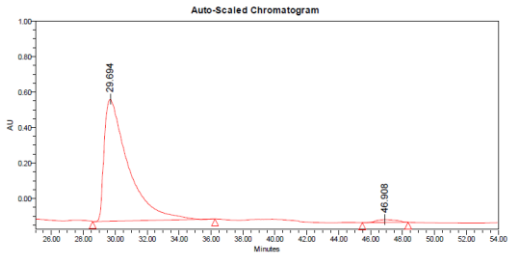
	RT	Altuera	Azalera	% Azal.
1	18.536	791336	41797044	54.69
2	28.203	439680	34632155	45.31

	RT	Altuera	Azalera	% Azal.
1	18.092	2861341	24594501	97.63
2	28.230	77664	5977755	2.37



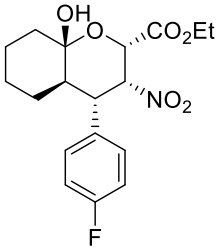
Etil (2S,3R,4S,4aR,8aS)-8a-hidroxi-4-(4-metoxifenil)-3-nitrooktahidro-2H-kromeno-2-karboxilatoa (**52aca**). Ziklohexanona **29a**, *trans*-4-metoxi-β-nitroestirenoa **11c** eta etil glioxilatoa **24a**-tik sortua, azido salizilikoa aditibo bezala erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %65 (25 mg, 0.065 mmol), solido marroi argia. $\mathbf{u_p}$ = 166-168 °C. $[\alpha]_D^{25}$ = +57.84 (*c* 0.75, kloroformoa). **FTIR** (neat, cm^{-1}) 3460, 2939, 1754, 1548, 1514, 1249. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.08 – 6.98 (m, 2H, ArH), 6.85 (d, *J* = 8.6 Hz, 2H, ArH), 5.12 (d, *J* = 3.2 Hz, 1H, C^9H), 5.08 (dd, *J* = 4.9, 3.2 Hz, 1H, C^8H), 4.32 – 4.22 (m, 1H, CH_2CH_3), 4.22 – 4.13 (m, 1H, CH_2CH_3), 3.78 (s, 3H, OCH_3), 3.46 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.55 (td, *J* = 12.4, 3.2 Hz, 1H, C^6H), 2.22 (bs, 1H, OH), 2.04 – 1.87 (m, 2H, CH_2), 1.83 – 1.73 (m, 1H, CH_2), 1.63 (dddd, *J* = 26.2, 17.5, 9.5, 6.1 Hz, 2H, CH_2), 1.42 – 1.35 (m, 1H, CH_2), 1.31 (dt, *J* = 12.9, 4.0 Hz, 1H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.08 (qd, *J* = 12.6, 3.4 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.7, 159.3, 129.3, 128.2, 114.5, 98.1, 87.2, 69.3, 62.3, 55.3, 43.28, 39.2, 38.5, 26.2, 25.7, 23.1, 14.1. **HRMS** (ESI) $C_{19}H_{25}NO_7Na$ $[M+Na]^+$: kalkulatua 402.1521, aurkitua 402.1514. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 29.22 min, t_R (gutxiengoa) = 45.97 min, *ee* = %96.



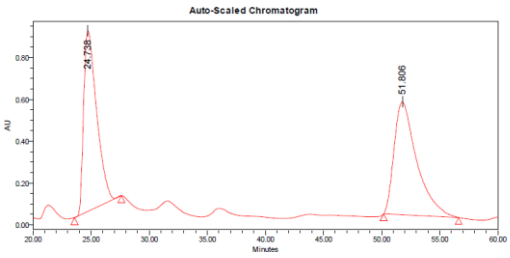


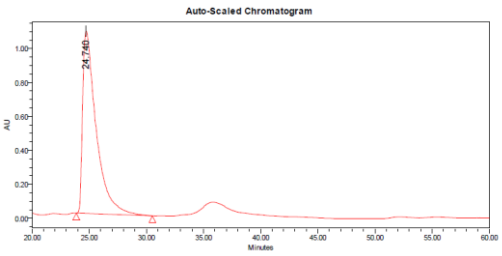
	RT	Altuera	Azalera	% Azal.
1	29.223	1932825	214068574	50.19
2	45.979	1652558	212420464	49.81

	RT	Altuera	Azalera	% Azal.
1	29.694	688406	71643586	98.05
2	46.908	16266	1427149	1.95



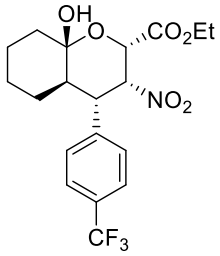
Etil (2S,3R,4S,4aR,8aS)-4-(4-fluorofenil)-8a-hidroxi-3-nitrooktahidro-2H-kromeno-2-karboxilatoa (**52ada**). Ziklohexanona **29a**, *trans*-4-fluoro-β-nitroestirenoa **11d** eta etil glioxilato **24a**-tik sortua, azido salizilikoa aditibo moduan erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %62 (23 mg, 0.062 mmol), solido zuria. $\mathbf{u_p}$ = 179-181 °C. $[\alpha]_D^{25}$ = +57.03 (*c* 0.42, kloroformoa). **FTIR** (neat, cm^{-1}) 3483, 2937, 1747, 1548, 1225. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 2H, ArH), 7.02 (t, *J* = 8.6 Hz, 2H, ArH), 5.13 (d, *J* = 3.1 Hz, 1H, C^{9}H), 5.08 (dd, *J* = 4.8, 3.2 Hz, 1H, C^{8}H), 4.27 (dq, *J* = 10.7, 7.1 Hz, 1H, C*H*$_2$CH$_3$), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H, C*H*$_2$CH$_3$), 3.51 (dd, *J* = 12.5, 4.8 Hz, 1H, C^{7}H), 2.55 (tdd, *J* = 12.5, 3.3, 1.5 Hz, 1H, C^{6}H), 2.12 (s, 1H, OH), 1.97 (dddd, *J* = 17.8, 14.3, 9.4, 3.3 Hz, 2H, CH_2), 1.77 (ddt, *J* = 11.1, 4.5, 2.2 Hz, 1H, CH_2), 1.72 – 1.65 (m, 1H, CH_2), 1.59 (d, *J* = 6.7 Hz, 1H, CH_2), 1.33 (ddd, *J* = 15.4, 13.1, 4.1 Hz, 2H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.09 (qd, *J* = 14.1, 13.3, 4.2 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.6, 162.5 (d, $^1J_{C\text{-}F}$ = 246.9 Hz), 131.9 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.9, 116.1 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 98.1, 86.9, 69.3, 62.4, 43.4, 39.2, 38.5, 26.2, 25.6, 23.1, 14.1. **^{19}F RMN** (376 MHz, $CDCl_3$) δ -113.91. **HRMS** (ESI) $C_{18}H_{22}FNO_6K$ $[M+K]^+$: kalkulatua 406.1062, aurkitua 406.1058. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 24.74 min, t_R (gutxiengoa) = 51.81 min, *ee* = %99.



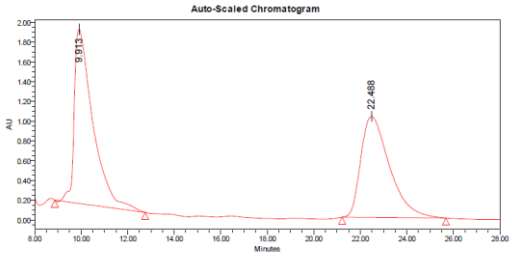


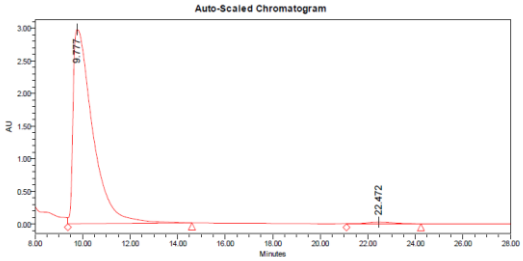
	RT	Altuera	Azalera	% Azal.
1	24.738	863261	66962000	47.46
2	51.806	540955	73245314	52.24

	RT	Altuera	Azalera	% Azal.
1	24.740	1075388	38657722	100.0
2				



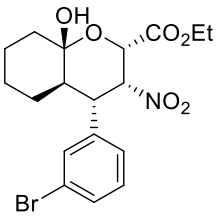
Etil (2S,3R,4S,4aR,8aS)-8a-hidroxi-3-nitro-4-(4-(trifluorometil)fenil)oktahidro-2H-kromeno-2-karboxilatoa (**52aea**). Ziklohexanona **29a**, *trans*-4-trifluorometil-β-nitroestirenoa **11e** eta etil glioxilatoa **24a**-tik sortua, azido salizilikoa aditibo bezala erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina %60 (25 mg, 0,060 mmol), solido zuria. $\mathbf{u_p}$ = 167-169 °C. $[\alpha]_D^{25}$ = +27.00 (*c* 0.80, kloroformoa). **FTIR** (neat, cm^{-1}) 3474, 2938, 1751, 1551, 1325. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H, ArH), 7.31 – 7.21 (m, 2H, ArH), 5.15 (d, *J* = 3.1 Hz, 1H, C^9H), 5.11 (dd, *J* = 4.8, 3.2 Hz, 1H, C^8H), 4.28 (dq, *J* = 10.8, 7.2 Hz, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.60 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.61 (td, *J* = 12.4, 3.1 Hz, 1H, C^6H), 2.18 (s, 1H, OH), 2.06 – 1.90 (m, 2H, CH_2), 1.83 – 1.73 (m, 1H, CH_2), 1.66 (ddt, *J* = 31.0, 13.1, 4.2 Hz, 2H, CH_2), 1.32 (dt, *J* = 14.2, 3.0 Hz, 2H, CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.11 (qd, *J* = 13.3, 2.8 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.5, 140.4, 130.5 (d, $^2J_{C\text{-}F}$ = 32.7 Hz), 128.8, 126.1 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.04 (d, $^1J_{C\text{-}F}$ = 272.2 Hz), 97.98, 86.50, 69.27, 62.46, 43.92, 38.99, 38.44, 26.17, 25.54, 23.04, 14.06. **^{19}F RMN** (376 MHz, $CDCl_3$) δ -62.69. **HRMS** (ESI) for $C_{19}H_{22}F_3NO_6Na$ $[M+Na]^+$: kalkulatua 440.1297, aurkitua 440.1287. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 9.91 min, t_R (gutxiengoa) = 22.49 min, *ee* = %98.



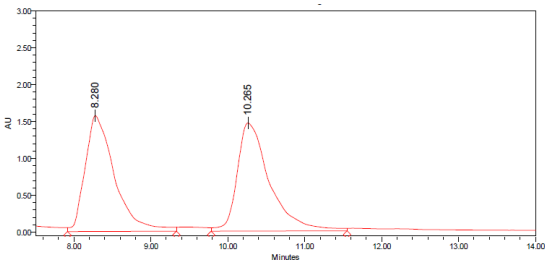


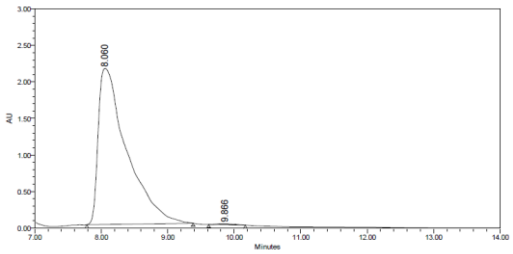
	RT	Altuera	Azalera	% Azal.
1	9.913	1763203	98242087	52.88
2	22.488	1023519	87536948	47.12

	RT	Altuera	Azalera	% Azal.
1	9.777	2971511	170166051	98.89
2	22.472	23819	1910951	1.11



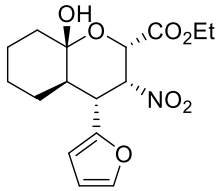
Etil (2S,3R,4S,4aR,8aS)-4-(3-bromofenil)8a-hidroxi-3-nitrooktahidro-2H-kromeno-2-karboxilatoa (**52afa**). Ziklohexanona **29a**, *trans*-3-bromo-β-nitroestirenoa **11f** eta etil glioxilatoa **24a**-tik sortua, azido salizilikoa azido bezala erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %54 (23 mg, 0.054 mmol), olio horia. $[\alpha]_D^{25}$ = +41.57 (*c* 0.75, kloroformoa). **FTIR** (neat, cm^{-1}) 3469, 2938, 1750, 1549, 1339. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 8.2, 1.2 Hz, 1H, ArH), 7.31 (d, *J* = 1.9 Hz, 1H, ArH), 7.20 (t, *J* = 7.9 Hz, 1H, ArH), 7.04 (d, *J* = 7.8 Hz, 1H, ArH), 5.12 (d, *J* = 3.1 Hz, 1H, C^9H), 5.09 (dd, *J* = 4.7, 3.2 Hz, 1H, C^8H), 4.28 (dq, *J* = 11.0, 7.1 Hz, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.49 (dd, *J* = 12.4, 4.7 Hz, 1H, C^7H), 2.55 (td, *J* = 12.4, 3.1 Hz, 1H, C^6H), 2.05 – 1.86 (m, 2H, CH_2), 1.78 – 1.67 (m, 4H, CH_2, OH), 1.41 – 1.27 (m, 2H, CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.12 (td, *J* = 12.5, 3.4 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.5, 138.6, 131.4, 130.7, 123.1, 98.0, 86.6, 69.3, 62.4, 43.8, 38.9, 38.5, 26.2, 25.6, 23.1, 14.1. **HRMS** (ESI) $C_{18}H_{22}BrNO_6Na$ $[M+Na]^+$: kalkulatua 452.0505, aurkitua 452.0494. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 8.28 min, t_R (gutxiengoa) = 10.27 min, *ee* = %99.



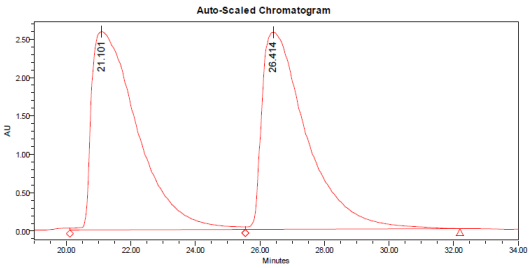


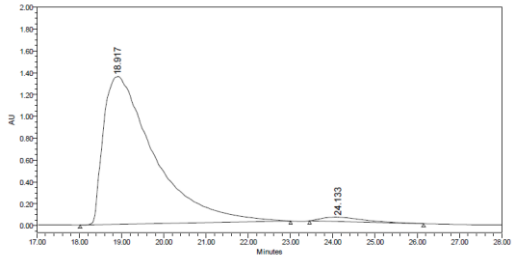
	RT	Altuera	Azalera	% Azal.
1	8.280	1569463	41788944	49.32
2	10.265	1464174	42949216	50.68

	RT	Altuera	Azalera	% Azal.
1	8.063	2140905	63722679	99.53
2	9.864	16484	302834	0.47



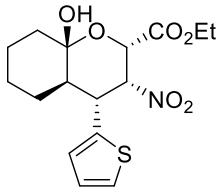
Etil (2S,3R,4R,4aR,8aS)-4-(furan-2-il)-8a-hidroxi-3-nitrooktahidro-2H-kromeoe-2-karboxilatoa (**52aga**). 0 ºCtan ziklohexanona **29a**, *trans*-2-(2-nitrovinil)furan **11g** eta etil glioxilato **24a**-tik lortua, azido salizilikoa aditibo moduan erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %73 (25 mg, 0.073 mmol), solido zuria. $\mathbf{u_p}$ = 173-175°C. $[\alpha]_D^{25}$ = +89.49 (*c* 0.85, kloroformoa). **FTIR** (neat, cm^{-1}) 3480, 2938, 1754, 1552, 1209. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 1.8, 0.8 Hz, 1H, ArH), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H, ArH), 6.17 (d, *J* = 3.2 Hz, 1H, ArH), 5.19 (dd, *J* = 4.8, 3.1 Hz, 1H, C^8H), 5.05 (d, *J* = 3.1 Hz, 1H, C^9H), 4.31 – 4.23 (m, 1H, CH_2CH_3), 4.19 (dq, *J* = 10.7, 7.1 Hz, 1H, CH_2CH_3), 3.66 (dd, *J* = 12.5, 4.8 Hz, 1H, C^7H), 2.48 (td, *J* = 12.4, 3.4 Hz, 1H, C^6H), 2.24 (s, 1H, OH), 1.92 (t, *J* = 4.1 Hz, 2H, CH_2), 1.74 (dddd, *J* = 23.5, 12.9, 5.3, 2.9 Hz, 2H, CH_2), 1.66 – 1.53 (m, 1H, CH_2), 1.44 – 1.37 (m, 1H, CH_2), 1.35 – 1.27 (m, 1H, CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.22 – 1.11 (m, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.6, 150.3, 142.6, 110.5, 108.5, 97.8, 84.8, 68.9, 62.3, 39.2, 38.3, 26.3, 25.5, 23.0, 14.1. **HRMS** (ESI) $C_{16}H_{20}NO_6$ $[M+H-H_2O]^+$: kalkulatua 322.1287, aurkitua 322.1282. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 21.10 min, t_R (gutxiengoa) = 26.41 min, *ee* = %95.



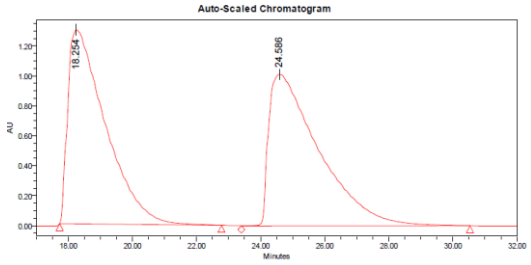


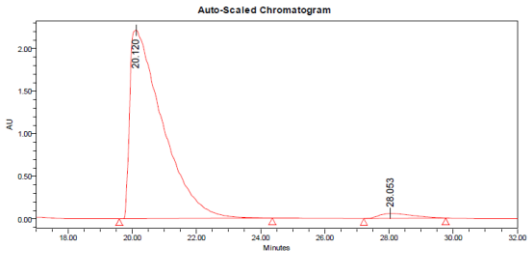
	RT	Altuera	Azalera	% Azal.
1	21.101	2583249	255048833	50.77
2	26.414	2566784	247343884	49.23

	RT	Altuera	Azalera	% Azal.
1	18.917	1353275	113436994	97.63
2	24.133	39861	2751261	2.37



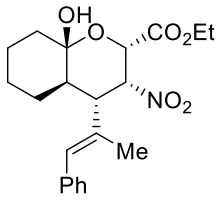
Etil (2S,3R,4R,4aR,8aS)-8a-hidroxi-3-nitro-4-(tiofen-2-il)oktahidro-2H-kromeno-2-karboxilatoa (**52aha**). 0 °C-tan ziklohexanona **29a**, *trans*-2-(2-nitrovinil)tiofeno **11h** eta etil glioxilato **24a**-tik sortua, azido salizilikoa aditibo moduan erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %46 (16 mg, 0.046 mmol), solido zuria. $\mathbf{u_p}$ = 144-146 °C. $[\alpha]_D^{25}$ = +57.84 (*c* 0.75, kloroformoa). **FTIR** (neat, cm^{-1}) 3484, 2939, 1749, 1550, 856. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.1, 1.1 Hz, 1H, ArH), 6.96 (dd, *J* = 5.2, 3.5 Hz, 1H, ArH), 6.84 (d, *J* = 3.5 Hz, 1H, ArH), 5.15 (m, 2H, C^9H, C^8H), 4.32 – 4.24 (m, 1H, CH_2CH_3), 4.19 (dt, *J* = 10.8, 7.1 Hz, 1H, CH_2CH_3), 3.78 (dd, *J* = 12.3, 4.5 Hz, 1H, C^7H), 2.60 (td, *J* = 12.3, 3.4 Hz, 1H, C^6H), 2.15 (s, 1H, OH), 2.04 – 1.94 (m, 1H, CH_2), 1.90 (dt, *J* = 14.0, 3.0 Hz, 1H, CH_2), 1.81 – 1.59 (m, 3H, CH_2), 1.55 – 1.45 (m, 1H, CH_2), 1.32 (dt, *J* = 13.0, 3.9 Hz, 1H, CH_2), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.15 (td, *J* = 12.8, 3.5 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.4, 138.6, 127.5, 126.0, 125.0, 98.1, 87.0, 69.3, 62.4, 40.9, 39.61, 38.4, 26.3, 25.6, 23.1, 14.1. **HRMS** (ESI) $fC_{16}H_{21}NO_6SNa$ $[M+Na]^+$: kalkulatua 378.0979, aurkitua 378.0978. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 97:3, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 18.25 min, t_R (gutxiengoa) = 25.59 min, *ee* = %95.



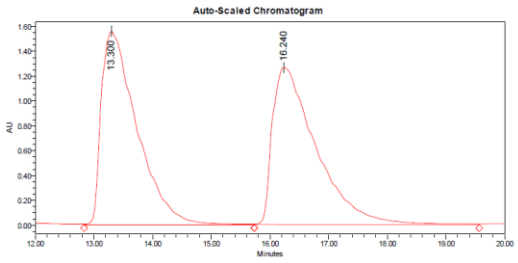


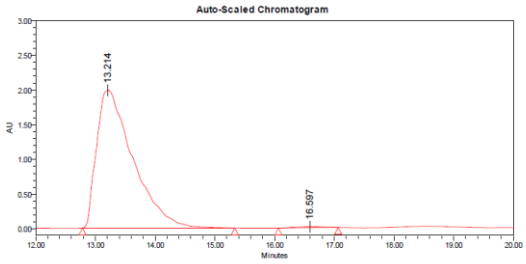
	RT	Altuera	Azalera	% Azal.
1	18.254	1296216	105677092	49.08
2	24.586	1011380	109649986	50.92

	RT	Altuera	Azalera	% Azal.
1	20.127	2645688	189249045	97.82
2	28.053	65015	4210109	2.18



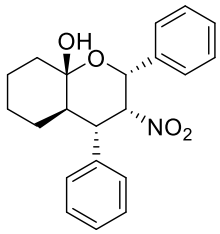
Etil (2S,3R,4S,4aR,8aS)-8a-hidroxi-3-nitro-4-((E)-1-fenilprop-1-en-2-il)oktahidro-2H-kromeno-2-karboxilatoa (**52aia**). 0 °C-tan ziklohexanona **29a**, ((1*E*,3*E*)-2-metil-4-nitrobuta-1,3-dien-1-il)benzeno **11i** eta etil glioxilato **24a**-tik sortua azido salizilikoa aditibo moduan erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %55 (21 mg, 0.055 mmol), solido zuria. $\mathbf{u_p}$ = 157-159 °C. $[\alpha]_D^{25}$ = +54.56 (*c* 0.60, kloroformoa). **FTIR** (neat, cm^{-1}) 3467, 2938, 1740, 1552, 1372. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.7, 6.7 Hz, 2H, ArH), 7.26 (dd, *J* = 7.9, 6.3 Hz, 3H, ArH), 6.35 (s, 1H, C*H*=C), 5.22 (dd, *J* = 4.9, 3.2 Hz, 1H, C^{8}H), 5.08 (d, *J* = 3.2 Hz, 1H, C^{9}H), 4.40 – 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H, C*H*$_2$CH$_3$), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H, C*H*$_2$CH$_3$), 3.02 (dd, *J* = 12.3, 4.9 Hz, 1H, C^{7}H), 2.37 (td, *J* = 12.2, 2.9 Hz, 1H, C^{6}H), 2.18 (s, 1H, OH), 2.06 – 1.92 (m, 2H, CH_2), 1.88 (d, *J* = 1.3 Hz, 3H, C*H*$_3$C=CH), 1.85 – 1.76 (m, 3H, CH_2), 1.73 – 1.60 (m, 1H, CH_2), 1.38 (dq, *J* = 12.8, 5.3, 4.5 Hz, 1H, CH_2), 1.30 (d, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.24 (dd, *J* = 13.0, 9.7 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 167.8, 137.3, 132.8, 129.6, 129.1, 128.2, 126.9, 97.9, 84.8, 69.2, 62.4, 46.6, 38.6, 38.4, 26.1, 25.7, 23.1, 14.1. **HRMS** (ESI) $C_{21}H_{28}NO_6$ $[M+H]^+$: kalkulatua 390.1922, aurkitua 390.1924. **HPLC** (Chiralcel IB, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 13.30 min, t_R (gutxiengoa) = 16.24 min, *ee* = %99.



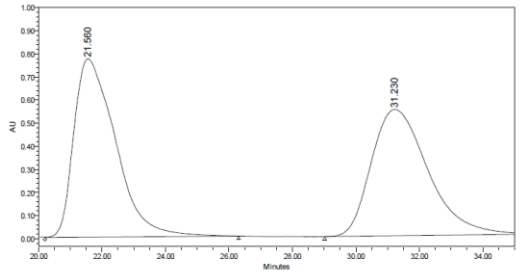


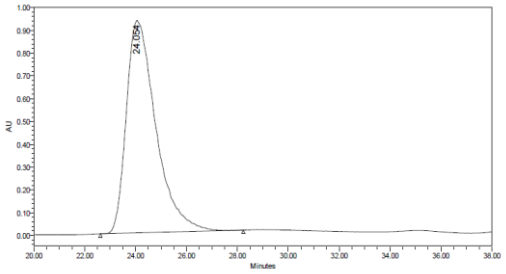
	RT	Altuera	Azalera	% Azal.
1	13.300	1555120	65385927	49.88
2	16.240	1264166	65691329	50.12

	RT	Altuera	Azalera	% Azal.
1	13.214	1984612	83765571	99.40
2	16.597	15026	503719	0.60



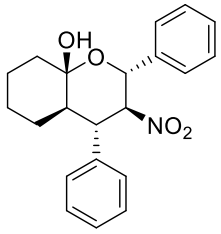
(2R,3R,4S,4aR,8aS)-3-nitro-2,4-difeniloktahidro-8aH-kromen-8a-ola (**52aab**). Ziklohexanona **29a**, *trans*-β-nitroestirenoa **11a** eta benzaldehidoa **24b**-tik sortua, azido salizilikoa eta 1 eq. trietilamina erabilita. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %65. Isolatutako etekina %30 (11 mg, 0.030 mmol), solido zuria. $\mathbf{u_p}$ = 195-197 °C. $[\alpha]_D^{25}$ = +26.45 (*c* 0.40, kloroformoa). **FTIR** (neat, cm^{-1}) 3511, 2922, 1548, 1335. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H, ArH), 7.35 – 7.28 (m, 4H, ArH), 7.27 – 7.24 (m, 2H, ArH), 7.17 (dd, *J* = 7.0, 1.7 Hz, 2H, ArH), 5.66 (d, *J* = 3.1 Hz, 1H, C^9H), 4.95 (dd, *J* = 4.6, 3.2 Hz, 1H, C^8H), 3.59 (dd, *J* = 12.5, 4.5 Hz, 1H, C^7H), 2.97 (ddt, *J* = 14.7, 11.4, 1.6 Hz, 1H, C^6H), 2.07 (td, *J* = 13.7, 4.5 Hz, 1H, CH_2), 1.92 (bs, 1H, OH), 1.87 (ddt, *J* = 13.7, 4.0, 2.1 Hz, 1H, CH_2), 1.84 – 1.76 (m, 1H, CH_2), 1.76 – 1.64 (m, 1H, CH_2), 1.48 – 1.35 (m, 2H, CH_2), 1.26 (m, 1H, CH_2), 1.19 (td, *J* = 12.6, 3.1 Hz, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 136.9, 136.7, 129.2, 128.7, 128.5, 127.9, 126.0, 97.9, 91.9, 71.1, 44.4, 38.9, 38.7, 26.1, 25.9, 23.2. **HRMS** (ESI) $C_{21}H_{22}NO_3$ $[M+H-H_2O]^+$: kalkulatua 336.1592, aurkitua 336.1589. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 21.56 min, t_R (gutxiengoa) = 31.23 min, *ee* = >%99.



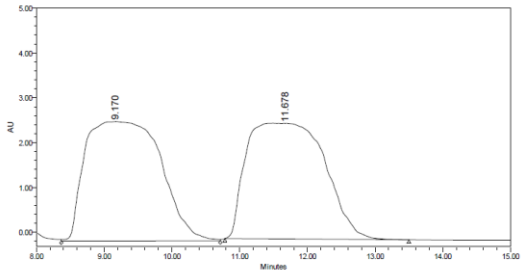


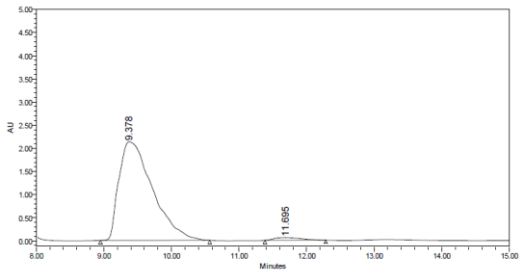
	RT	Altuera	Azalera	% Azal.
1	21.560	772486	70549380	50.95
2	31.230	546319	67923484	49.05

	RT	Altuera	Azalera	% Azal.
1	24.054	932234	74986663	100.0
2				



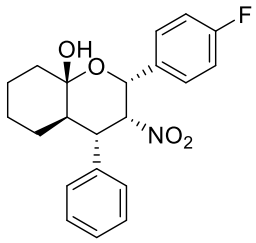
(2R,3S,4S,4aR,8aS)-3-nitro-2,4-difeniloktahidro-8aH-kromen-8a-ola (**52aab'**). Ziklohexanona **29a**, *trans*-β-nitroestirenoa **11a** eta benzaldehidoa **24b**-tik sortua, azido salizilikoa eta 1 eq. trietilamina erabilita. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %65. Isolatutako etekina %35 (12 mg, 0.035 mmol), solido zuria. $\mathbf{u_p}$ = 223-225 °C. $[\alpha]_D^{25}$ = +31.48 (*c* 0.25, kloroformoa). **FTIR** (neat, cm^{-1}) 3552, 2928, 1544, 1123. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 10H), 5.55 (d, *J* = 10.0 Hz, 1H, C^9H), 4.77 (t, *J* = 10.6 Hz, 1H, C^8H), 3.72 (t, *J* = 11.6 Hz, 1H, C^7H), 2.17 (s, 1H, OH)2.05 (s, 1H, CH_2), 1.88 (d, *J* = 11.8 Hz, 1H, C^6H), 1.84 – 1.74 (m, 2H, CH_2), 1.69 (d, *J* = 15.3 Hz, 2H, CH_2), 1.38 – 1.22 (m, 1H, CH_2), 1.19 (d, *J* = 5.4 Hz, 2H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 136.9, 136.7, 129.2, 128.7, 128.5, 127.9, 126.0, 97.9, 91.9, 71.1, 44.4, 38.9, 38.7, 26.1, 25.9, 23.2. **HRMS** (ESI) $C_{21}H_{22}NO_3$ $[M+H-H_2O]^+$: kalkulatua 336.1592, aurkitua 336.1591. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (nagusia) = 9.17 min, t_R (gutxiengoa) = 11.68 min, *ee* = %96.



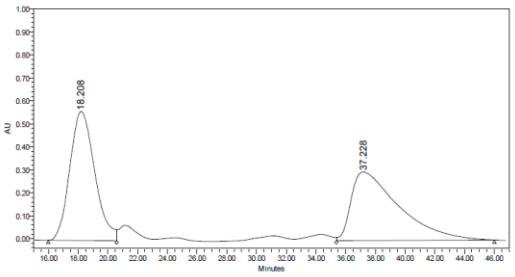


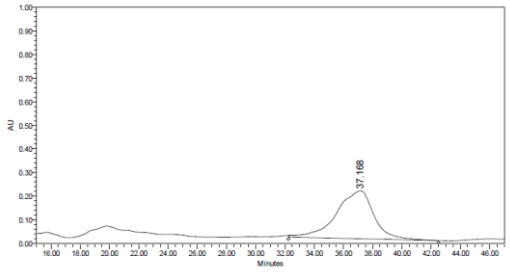
	RT	Altuera	Azalera	% Azal.
1	9.170	2662130	207821990	49.94
2	11.678	2582615	208361441	50.06

	RT	Altuera	Azalera	% Azal.
1	9.378	2131827	73579930	97.92
2	11.695	56958	1565685	2.08



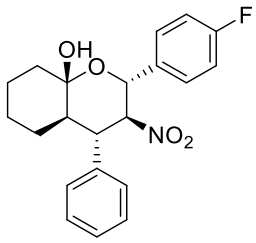
(2R,3R,4S,4aR,8aS)-2-(4-fluorofenil)-3-nitro-4-feniloktahidro-8aH-kromen-8a-ola (**52aac**). Ziklohexanona **29a**, *trans*-β-nitroestirenoa **11a** eta 4-fluorobenzaldehidoa **24c**-tik sortua, azido salizilikoa eta 1 eq. trietilamina erabilita. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %81. Isolatutako etekina %54 (20 mg, 0.054 mmol), solido zuria. $\mathbf{u_p}$ = 198-200 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +12.05 (*c* 0.60, kloroformoa). **FTIR** (neat, cm^{-1}) 3510, 2950, 1551, 1118. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H, ArH), 7.21 – 7.11 (m, 2H, ArH), 7.01 (t, *J* = 8.7 Hz, 2H, ArH), 5.64 (d, *J* = 3.2 Hz, 1H, C^9H), 4.91 (t, *J* = 3.9 Hz, 1H, C^8H), 3.57 (dd, *J* = 12.5, 4.5 Hz, 1H, C^7H), 3.04 – 2.89 (m, 1H, C^6H), 2.05 (td, *J* = 13.6, 4.4 Hz, 1H, CH_2), 1.89 (d, *J* = 1.5 Hz, 1H, CH_2), 1.88 – 1.77 (m, 1H, CH_2), 1.77 – 1.60 (m, 2H, CH_2), 1.41 (td, *J* = 13.4, 12.5, 3.8 Hz, 2H, CH_2), 1.28 – 1.10 (m, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C\text{-}F}$ = 246.8 Hz), 136.7, 132.5 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.2, 128.0, 127.8 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 97.9, 92.0, 70.5, 44.4, 38.9, 38.6, 26.1, 25.8, 23.2. **^{19}F RMN** (376 MHz, $CDCl_3$) δ -113.56. **HMRS** (ESI) $C_{21}H_{21}FNO_3$ $[M+H\text{-}H_2O]^+$: kalkulatua 354.1499, aurkitua 354.1495. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (gutxiengoa) = 18.21 min, t_R (nagusia) = 37.22 min, *ee* = >%99.



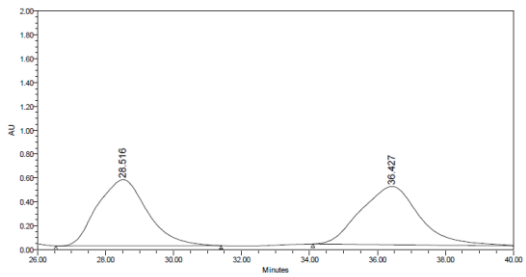


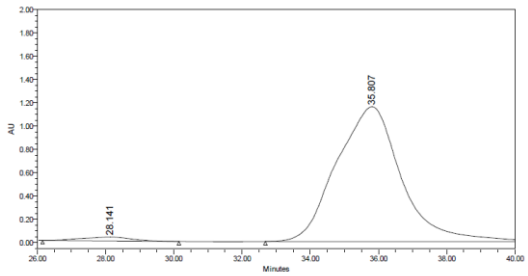
	RT	Altuera	Azalera	% Azal.
1	18.208	561795	65417617	49.52
2	37.228	298237	66684317	50.48

	RT	Altuera	Azalera	% Azal.
1				
2	37.168	203128	36380394	100.0



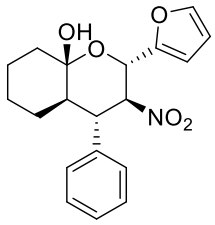
(2R,3S,4S,4aR,8aS)-2-(4-fluorofenil)-3-nitro-4-feniloktahidro-8aH-kromen-8a-ola (**52aac'**). Ziklohexanona **29a**, *trans*-β-nitroestirenoa **11a** eta 4-fluorobenzaldehidoa **24c**-tik sortua, azido salizilikoa eta 1 eq. trietilamina erabilita. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %81. Isolatutako etekina %27 (10 mg, 0.027 mmol), solido zuria. $\mathbf{u_p}$ = 206-209 °C. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +61.88 (*c* 0.60, kloroformoa). **FTIR** (neat, cm^{-1}) 3484, 2936, 1547, 1115. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.5, 5.3 Hz, 2H, ArH), 7.31 – 7.16 (m, 5H, ArH), 7.04 (t, *J* = 8.6 Hz, 2H, ArH), 5.54 (d, *J* = 9.9 Hz, 1H, C^9H), 4.72 (t, *J* = 10.6 Hz, 1H, C^8H), 3.71 (t, *J* = 11.6 Hz, 1H, C^7H), 2.10 (s, 1H, OH), 1.88 (td, *J* = 11.8, 3.3 Hz, 1H, C^6H), 1.77 – 1.55 (m, 4H, CH_2), 1.29 – 1.11 (m, 4H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{C\text{-}F}$ = 247.9 Hz), 136.8, 132.7 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.1 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 128.1, 115.9 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 97.5, 95.1, 73.2, 47.1, 46.9, 38.8, 26.2, 25.7, 23.0. **^{19}F RMN** (376 MHz, $CDCl_3$) δ -112.35. **HRMS** (ESI) $C_{21}H_{23}FNO_4$ [M+H]+: kalkulatua 372.1721, aurkitua 372.1720. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (gutxiengoa) = 28.52 min, t_R (nagusia) = 36.43 min, *ee* = %95.





	RT	Altuera	Azalera	% Azal.
1	28.516	2034883	226075356	49.92
2	36.427	1062962	226837738	50.08

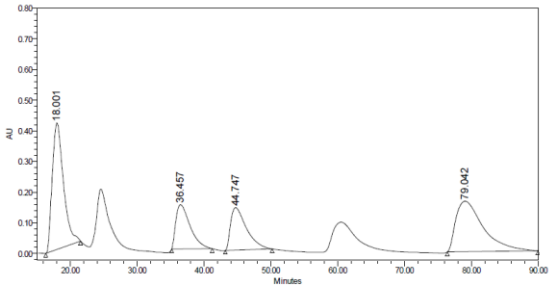
	RT	Altuera	Azalera	% Azal.
1	28.141	32644	3278255	2.10
2	35.807	1155871	152946036	97.90

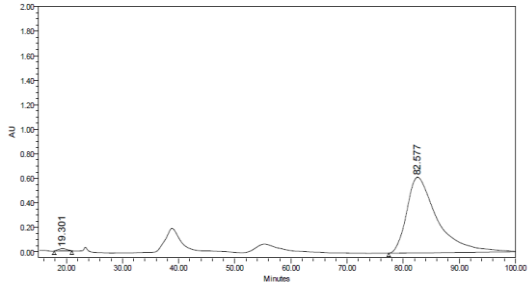


(2S,3S,4S,4aR,8aS)-2-(furan-2-il)-3-nitro-4-feniloktahidro-8aH-kromen-8a-ola (**52aad'**). Ziklohexanona **29a**, *trans*-β-nitroestireno **11a** eta furfural **24d**-tik sortua, azido salizilikoa aditibo moduan erabiliz. Et_3N 1 eq. usatzean **52aad:52aad'** 50:50 nahaste banaezina lortu zen. Etekin globala: %65 (22 mg, 0.65 mmol). **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.70 (s, 2H, ArH), 7.52 – 7.00 (m, 10H, ArH), 6.61 (s, 1H, ArH), 6.41 (d, *J* = 3.3 Hz, 1H, ArH), 6.35 (d, *J* = 3.3 Hz, 1H, ArH), 6.32 (t, *J* = 2.5 Hz, 1H, ArH), 5.71 (d, *J* = 3.0 Hz, 1H, **52aad**), 5.65 (d, *J* = 10.3 Hz, 1H, **52aad**'), 5.11 (t, *J* = 10.8 Hz, 1H, **52aad**'), 4.98 (t, *J* = 3.8 Hz, 1H, **52aad**), 3.66 (t, *J* = 11.7 Hz, 1H, **52aad**'), 3.52 (dd, *J* = 12.5, 4.4 Hz, 1H, **52aad**), 2.98 – 2.87 (m, 1H, **52aad**), 2.08 – 1.96 (m, 1H, **52aad**'), 1.93 – 1.81 (m, 2H, **52aad** and **52aad**'), 1.77 (m, 2H, **52aad** and **52aad**'), 1.66 (m, 4H, **52aad** and **52aad**'), 1.39 (m, 2H, **52aad** and **52aad**'), 1.15 (m, 8H, **52aad** and **52aad**'). DBU 1 eq.-k **52aad'**-rako konbertsio totala erakutsi zuen. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina: %68 (23 mg, 0.068 mmol), solido zuria. $\mathbf{u_p}$ = 252-254 °C. $[\alpha]_D^{25}$ = +5.66 (*c* 0.60, kloroformoa). **FTIR** (neat, cm^{-1}) 3539, 2935, 1546, 1124. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.7 Hz, 1H, ArH), 7.26 (s, 5H, ArH), 6.41 (d, *J* = 3.3 Hz, 1H, ArH), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H, ArH), 5.65 (d, *J* = 10.2 Hz, 1H, C^9H), 5.11 (dd, *J* = 11.4, 10.2 Hz, 1H, C^8H), 3.66 (t, *J* = 11.6 Hz, 1H, C^7H), 2.15 (s, 1H, OH), 1.89 (tdd, *J* = 12.0, 3.7, 1.4 Hz, 1H, C^6H), 1.83 – 1.75 (m, 2H, CH_2), 1.75 – 1.67 (m, 1H, CH_2), 1.67 – 1.60 (m, 1H, CH_2), 1.32 – 1.11 (m, 4H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 149.2, 143.9, 136.9, 128.1, 110.5, 110.4, 97.6, 91.3, 67.1, 46.8, 46.7, 38.6, 26.2, 25.6, 23.0. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (**52aad'** gutxiengoa) = 18.00 min,

t_R (**52aad** nagusia) = 36.46 min, t_R (**52aad** gutxiengoa) = 44.74 min, t_R (**52aad'** nagusia) = 79.02 min. *ee* **52aad** = %98. *ee* **52aad'** = %98.

52aad

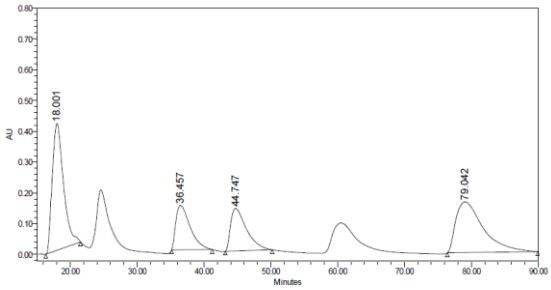


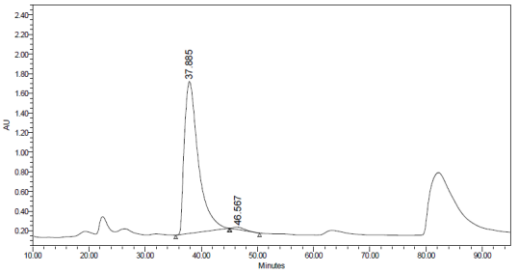


	RT	Altuera	Azalera	% Azal.
1	18.000	692107	82178228	35.51
2	36.456	224401	36263819	15.58
3	44.743	202476	35966472	15.45
4	79.042	267732	78351878	33.66

	RT	Altuera	Azalera	% Azal.
1	19.301	19103	2017127	0.86
2				
3				
4	82.577	617310	232611786	99.14

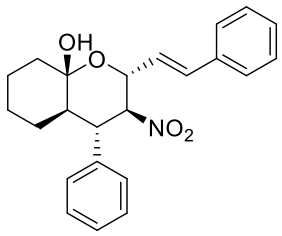
52aad'



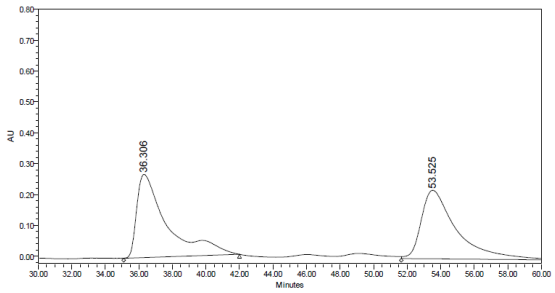


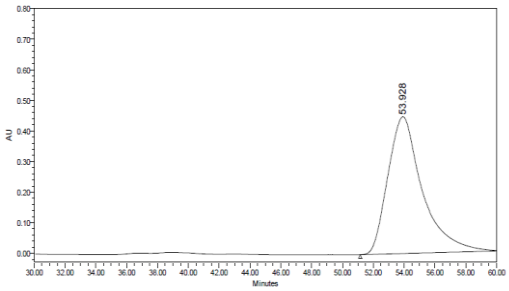
	RT	Altuera	Azalera	% Azal.
1	18.000	692107	82178228	35.51
2	36.456	224401	36263819	15.58
3	44.743	202476	35966472	15.45
4	79.042	267732	78351878	33.66

	RT	Altuera	Azalera	% Azal.
1				
2	37.885	1548286	267427094	99.19
3	46.633	19736	2173050	0.81
4				



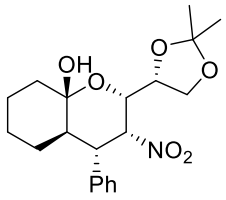
(2R,3R,4S,4aR,8aS)-3-nitro-4-fenill-2-((E)-estiril)oktahidro-8aH-kromen-8a-ola (**52aae**). Ziklohexanona **29a**, *trans*-β-nitroestireno **11a** eta zinamaldehido **24e**- tik sortua, azido salizilikoa aditibo moduan erabiliz. 1:4 EtOAc:Hexano nahasteaz purifikatua. Etekina: %58 (22 mg, 0.058 mmol), solido zuria. $\mathbf{u_p}$ = 198-200 °C. $[\alpha]_D^{25}$ = +58.20 (*c* 0.10, kloroformoa). **FTIR** (neat, cm^{-1}) 3499, 2922, 1713, 1546. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 9.74 (d, *J* = 3.2 Hz, 1H, CH=C*H*Ph), 7.33 – 7.22 (m, 8H, ArH), 7.22 – 7.14 (m, 2H, ArH), 4.93 (t, *J* = 4.5 Hz, 1H, C^8H), 4.10 (dd, *J* = 12.6, 4.5 Hz, 1H, C^9H), 3.98 (dd, *J* = 12.7, 3.3 Hz, 1H, C*H*=CHPh), 3.46 (dd, *J* = 12.2, 4.5 Hz, 1H, C^7H), 2.65 (td, *J* = 12.2, 3.3 Hz, 1H, C^6H), 2.39 (s, 1H, OH), 1.89 (d, *J* = 13.6 Hz, 1H, CH_2), 1.76 (td, *J* = 13.5, 4.3 Hz, 1H, CH_2), 1.68 (d, *J* = 13.0 Hz, 2H, CH_2), 1.39 – 1.23 (m, 3H, CH_2), 1.21 – 1.10 (m, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 206.9, 137.5, 136.0, 129.4, 129.2, 128.5, 128.2, 127.9, 94.9, 73.1, 54.9, 46.8, 42.9, 40.3, 37.5, 25.6, 25.1, 21.2. **HRMS** (ESI) $C_{23}H_{26}NO_4$ $[M+H]^+$: kalkulatua 380.1840, aurkitua 380.1827. **HPLC** (Chiralcel IA, Hexano:^{i}PrOH = 95:5, fluxua 1 mL/min, λ = 210 nm), t_R (gutxiengoa) = 36.31 min, t_R (nagusia) = 53.53 min, *ee* = >%99.





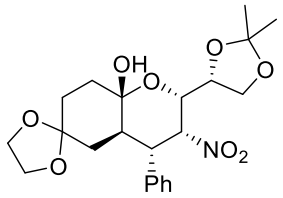
	RT	Altuera	Azalera	% Azal.
1	36.314	122720	33828331	50.96
2	53.522	99835	32558850	49.04

	RT	Altuera	Azalera	% Azal.
1				
2	53.928	447019	159851852	100.0



(2S,3R,4S,4aR,8aS)-2-((R)-2,2-dimetil-1,3-dioxolan-4-il)-3-nitro-4-feniloktahidro-8aH-kromen-8a-ola (**52aaf**). Ziklohexanona **29a**, *trans*-β-nitroestireno **11a** eta (*R*)-2,2-dimetil-1,3-dioxolano-4-karbaldehido **24f**-tik sortua, azido salizilikoa aditibo moduan erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekina %64 (24 mg, 0.064 mmol), olio koloregabea. $[\alpha]_D^{25}$ = +34.32 (*c* 0.53, kloroformoa). **FTIR** (neat, cm^{-1}) 3434, 2986, 1545.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 13.3, 7.0 Hz, 3H, ArH), 7.17 – 7.09 (m, 2H, ArH), 4.94 (dd, *J* = 4.7, 2.8 Hz, 1H, C^8H), 4.29 (dd, *J* = 8.9, 2.8 Hz, 1H, C^9H), 4.13 – 4.05 (m, 1H, CHO), 4.00 – 3.92 (m, 2H, CH_2O), 3.40 (dd, *J* = 12.4, 4.8 Hz, 1H, C^7H), 2.73 (d, *J* = 3.2 Hz, 1H, C^6H), 2.27 (s, 1H, OH), 1.89 – 1.78 (m, 1H, CH_2), 1.78 – 1.52 (m, 4H, CH_2), 1.44 (s, 3H, CH_3), 1.37 (dd, *J* = 12.1, 6.5 Hz, 2H, CH_2), 1.29 (s, 3H, CH_3), 1.22 – 0.97 (m, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 136.8, 129.1, 127.9, 110.2, 97.5, 87.5, 74.2, 70.6, 67.5, 43.9, 39.1, 38.8, 27.1, 26.2, 25.8, 25.1, 23.2. **HRMS** (ESI) $C_{20}H_{26}NO_5$ $[M+H-H_2O]^+$: kalkulatua 360.1801, aurkitua 360.1802.



(2S,3R,4S,4aR,8aS)-2-((R)-2,2-dimetil-1,3-dioxolan-4-il)-3-nitro-4-fenilhexahidro-2H,8aH-espiro[kromeno-6,2'-[1,3]dioxolan]-8a-ola (**52jaf**). 1,4-ziklohexanodiona monoetileno azetala **29j**, *trans*-β-nitroestireno **11a** eta (*R*)-2,2-dimetil-1,3-dioxolano-4-karbaldehido **24f-**tik sortua, azido salizilikoa aditibo moduan erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina %52 (23 mg, 0.052 mmol), olio koloregabea. $[\alpha]_D^{25}$ = +22.62 (*c* 0.33, kloroformoa). **FTIR** (neat, cm^{-1}) 3393, 2960, 1546. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H, ArH), 7.30 – 7.26 (m, 1H, ArH), 7.15 (dd, *J* = 7.1, 1.7 Hz, 2H, ArH), 4.93 (dd, *J* = 4.7, 2.8 Hz, 1H, C^8H), 4.29 (dd, *J* = 8.8, 2.8 Hz, 1H, C^9H), 4.09 (td, *J* = 7.3, 2.6 Hz, 1H, CHO), 3.99 – 3.97 (m, 1H, CH_2O), 3.96 – 3.94 (m, 1H, CH_2O), 3.91 – 3.83 (m, 2H, CH_2O), 3.83 – 3.77 (m, 1H, CH_2O), 3.42 (dd, *J* = 12.7, 4.6 Hz, 1H, C^7H), 3.16 – 3.08 (m, 1H, CH_2O), 2.18 (td, *J* = 13.7, 4.4 Hz, 1H, C^6H), 2.13 – 2.10 (bs, 1H, OH), 1.94 (td, *J* = 13.4, 4.5 Hz, 1H, CH_2), 1.82 – 1.71 (m, 2H, CH_2), 1.45 (d, *J* = 8.7 Hz, 2H, CH_2), 1.43 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.25 (s, 1H, CH_2). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 136.3, 129.2, 128.1, 110.3, 108.5, 96.7, 86.1, 74.2, 70.9, 67.5, 64.6, 64.4, 43.5, 36.1, 35.6, 34.7, 32.2, 27.1, 25.1. **HRMS** (ESI) $C_{22}H_{28}NO_7$ $[M+H-H_2O]^+$: kalkulatua 418.1859, aurkitua 418.1857.

3. Kapitulua

Funtzionalizazio altuko γ-Dipeptidoek Katalizatutako Zetona α,β-asegabeen eta Nitroalkenoen Arteko Diels-Alder Erreakzio Organokatalitikoak

3.1 ENAMINA BIDEZKO DIELS-ALDER ERREAKZIO ASIMETRIKOAK

Diels-Alder zikloadizioaren bertsio asimetrikoak konposatu kiral zikliko eta poliziklikoen sintesi erraza ahalbidetzen du, aktibitate biologikoa duten molekulen sintesi totalean funtsezko eginkizuna izanik.[1] Publikatutako lanen artean, hiru hurbilketa nagusi bereiz daitezke: 1) laguntzaile kiralak; 2) konplexu metalikoak; eta 3) organokalizatzaileen enplegua egiten dutenak.

Laguntzaile kiralak dieno[2] edo dienozalera[3] lotu daitezke, nahiz literaturako adibideek azken kasuari egiten dieten erreferentzia gehienbat. Hala ere, galdatutako kantitate estekiometrikoek eta sintesi urrats adizionalek ikerlarien interesa erreakzio katalitikoetara bideratu zuten. Sintesi bide katalitikoek Lewis azidoen usadio egiten zuten tradizionalki. Hauen artean oxazoborolidina kationikoak eta kobre (II) bis(oxazolina), arilalanina amida eta DNA konplexuak aipu berezia merezi dute.[4] Hala ere, organokatalizatzaileak Diels-Alder erreakzioetara aplikatzeko 1989. urtera arte itxarotea beharrezko izan zen.[5] Molekula organiko txiki asko argitaratu dira orduz gero; hala nola, sulfonil hidrazinak[6], *cinchona* alkaloideak[7], imidazolidinonak[8], bisoxazolinak[9] eta prolina deribatuak[10]. Hauek guztiak partikularki baliozko izan dira aldehido eta zetona α,β-

[1] Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667.
[2] a) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc*. **1980**, *102*, 7595-7596. b) Kita, Y.; Maeda, H.; Takahashi, F.; Fukui, S. *J. Chem. Soc., Perkin Trans*. 1, **1993**, 2639-2649. c) Miller, J. P. ; Stoodley, R. J. *J. Saudi Chem. Soc.* **2001**, 10.1016/j.jscs.2011.02.019. d) Tadano, K.; Totani, K. *Glycoscience. Epimerisation, Isomerisation and Rearrangement Reactions of Carbohydrates*, Springer: Berlin, **2008**. e) Jones, A. L.; Liu, X.; Snyder, J. K. *Tetrahedron Lett*. **2010**, *51*, 1091-1094. f) Miller, J. P. Stoodley, R. J. *J. Saudi. Chem. Soc*. **2011**, *15*, 275-281.
[3] a) Caygill, G. B.; Larsen, D. S.; Brooker, S. *J. Org. Chem*. **2001**, *66*, 7427-7431. b) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron* **2009**, *65*, 3502-3508. c) Hirama, M.; Kato, Y.; Seki, C.; Nakano, H.; Takeshita, M.; Oshikiri, N.; Iyoda, M.; Matsuyama, H. *Tetrahedron* **2010**, *66*, 7618-7624. d) Seki, C.; Hirama, M.; Hutabarat, N. D. M. R.; Takada, J.; Suttibut, C.; Takahashi, H.; Takaguchi, T.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Yasui, M.; Okuyama, Y.; Takeshita, M.; Matsuyama, M. *Tetrahedron* **2012**, 68, 1774-1781.
[4] Katalisi metralikoaren inguruko lan aipagarriak, hemen: a) Ref 27. b) Ishikara, K.; Sakakura, A. *Comprehensive Organic Synthesis II, Volume 5*, Elsevier: Oxford, **2014**. c) Chen, X.; Lu, Z. *Org. Biomol. Chem*. **2017**, *15*, 2280-2306. d) Beletskaya, I. P.; Nájera, C.; Yus, Y. *Chem. Rev*. **2018**, *118*, 5080-5200.
[5] Riant, O.; Kagan. H. B. *Tetrahedron Lett*. **1989**, *30*, 7403-7406.
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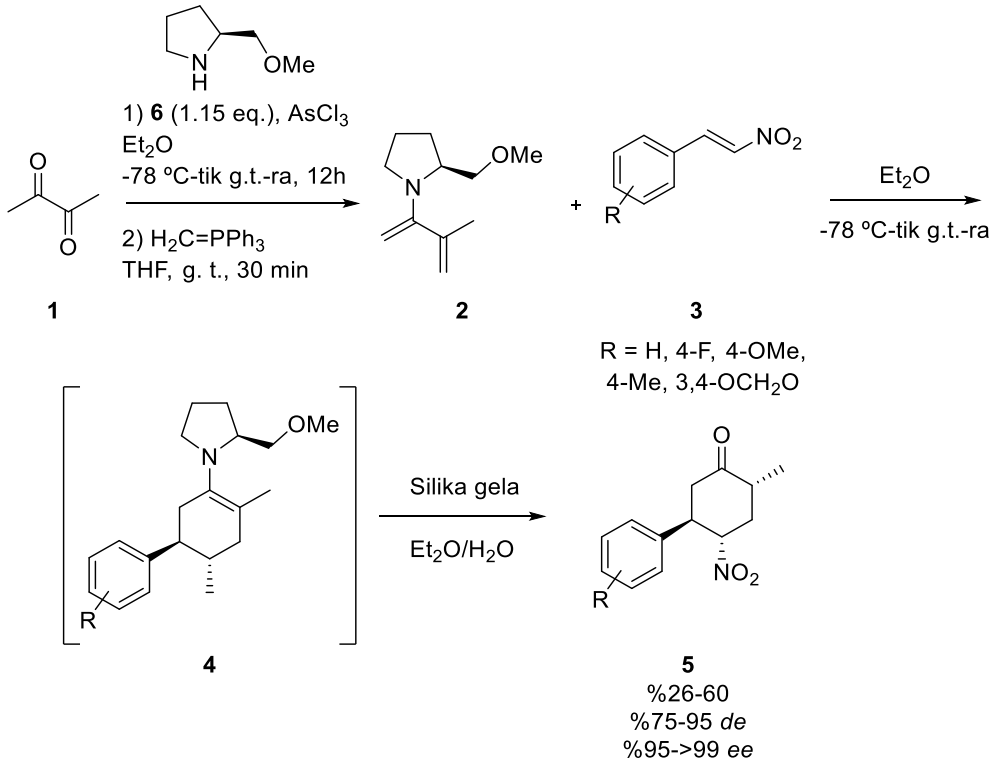
[7] a) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 9236-9239. b) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc*. **2008**, *130*, 2422-2423. c) Bella, M.; Schietroma, D. M. S.; Cusella, P. P.; Gasperi, T. Visca, V. *Chem. Commun*. **2009**, 597-599. d) Shen, J.; Tan, C.-H. *Org. Biomol. Chem*. **2008**, *6*, 4096-4098.
[8] a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243-4244. b) Mitsudome, T.; Nose, K.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Tetrahedron Lett*. **2008**, *49*, 5464-5466.
[9] Akalay, D.; Dürner, G.; Göbel, M. W. *Eur. J. Org. Chem.* **2008**, 2365-2368.
[10] Pellisier, H. *Recent Developments in Asymmetric Organocatalysis*, RSC Catalysis: Cambridge, **2010**.

asegabeaentzako. Kasu partikular honetan, katalizatzaileak eta konposatu karbonilikoak dienamina eta iminio-ioi erako artekariak sortzen dituzte.[11]

3.1.1 Dienamina-bidezko Diels-Alder erreakzioak

Dienamina trantsitorioen erabilera egiten duen lehen (4+2) zikloadizio estrategia 1992. urtean azaldu zuen Endersen ikerketa taldeak.[12] Autore hauek **5** 4-nitroziklohexenoen sintesirako bide berria garatu zuten, non emaitza estereokimikoa (*S*)-2-(metoximetil)pirrolidina **6**-ren kantitate ekimolarrek gauzatzen zuten. Bertako zikloaduktuak etekin moderatu, diastereoselektibitate altu eta enantioselektibitate itzelekin sortu ziren (**3.1 Eskema**). Aipatzekoa da 2-amino-1,3-butadienoa **2**-ren aurretiko sintesi eta isolamendua beharrezko suertatu zela (4+2) anulazio erreakzioa gertatzeko.

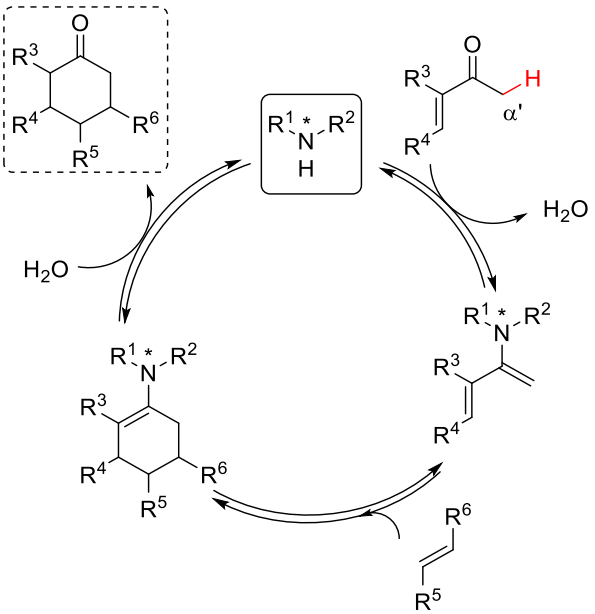


3.1 Eskema. Enders eta kolaboratzaileek argitaratutako lehen dienamina bidezko Diels-Alder erreakzioa.

Lehen iminio-ioi bidezko (4+2) zikloadizio katalitikoa 2000. urtean gauzatu zen.[8a] Erreakzio hau dienofilo eran jokatzen zuen α,β-konposatu karbonilikoaren LUMO jaitsieraz aktibatua zegoen. Bigarren aktibazio modu posible bat ere badago, ordea. Dienamina espezieen sorreraren bidez aktibatutako Diels-Alder erreakzioek konposatu karboniliko asegabearen HOMO orbitalaren igoera erdiesten dute. Ziklo katalitikoan

[11] a) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1-26. b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748-9770. c) Arrastia, I.; Arrieta, A.; Cossío, F.P. *Lett. Org. Chem.* **2018**, *15*, 394-403.
[12] Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242-1244.

zetona α,β-asegabearen eta organokatalizatzailearen kondentsazio itzulgarriak dienamina trantsitorioa sortzen du. Espezie honek dienozalearekin erreakzionatzen du gero, eta urratsezko mekanismo edo mekanismo kontzertatu bidez enamina ziklikoa eman. Enaminaren azken hidrolisi urratsak katalizatzailearen berreskurapena eta desioko zikloaduktoaren askapena ahalbidetzen du. Estrategia hau aplikatzeko derrigorrezkoa da zetona asegabeak α' posizioan protoi enolizagarria izatea (**3.2 Eskema**).[13]



3.2 Eskema. Dienamina bidezko Diels-Alder erreakzioaren ziklo katalitikoa. Gorriz marratutako protoiak konposatu karbonilikoak enolizagarria izan behar duela adierazten du.

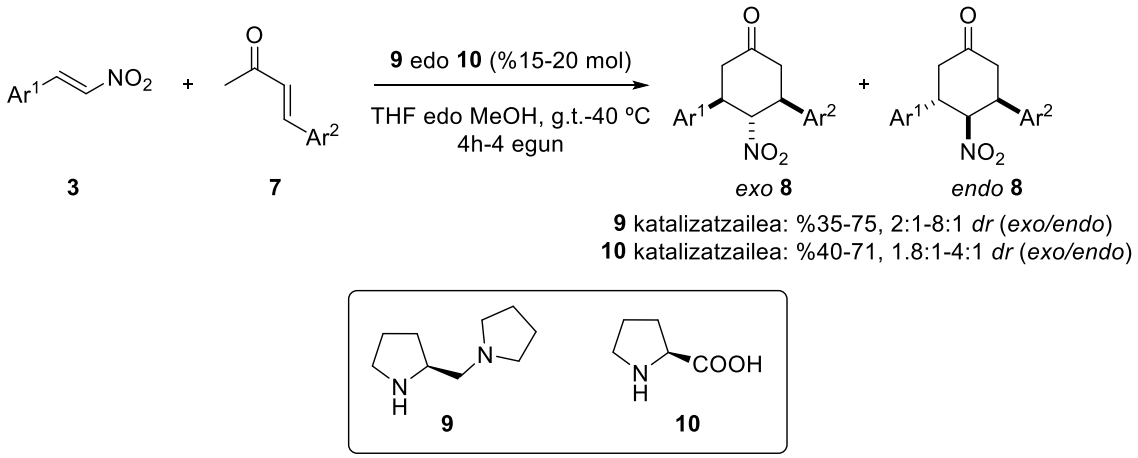
Metodologia hau dienozale askorekin arrakastatsu suertatu da. Literaturan ageri den moduan, zetona α,β-asegabeak[14], *in situ* sortutako hartzaileak[15], maleimidak[16], indolin-

[13] Arrastia, I.; Arrieta, A.; Cossío, F. P. *Lett. Org. Chem*. **2018**, *15*, 394-403.
[14] a) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Tetrahedron Lett*. **2002**, *43*, 6743-6746. b) Huang, H.; Wu, W.; Zhu, K.; Hu, J.; Ye, J. *Chem. Eur. J*. **2013**, *19*, 3838-3841.
[15] a) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Synlett* **2003**, 1910-1914. b) Ramachary, D. B.; Chowdary, N. S.; Barbas III, C. F. *Angew. Chem., Int. Ed*. **2003**, *42*, 4233-4237. c) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas III, C. F. *J. Org. Chem*. **2004**, *69*, 5838-5849. d) Ramachary, D. B.; Barbas III, C. F. *Chem. Eur. J*. **2004**, *10*, 5323-5331. e) Ramachary, D. B.; Reddy, Y. V.; Prakash, B. V. *Org. Biomol. Chem*. **2008**, *6*, 719-726. f) Jiang, B.; Hao, W.-J.; Zhang, J.-P.; Tu, S.-J.; Shi, F. *Org. Biomol. Chem*. **2009**, *7*, 2195-2201. g) Pizzirani, D.; Roberti, M.; Grimaudo, S.; Cristina, A. D.; Pipitone, R. M.; Tolomeo, M.; Recanatini, M. *J. Med. Chem*. **2009**, *52*, 6936-6940. h) Shi, J.; Liu, Y.; Wang, M.; Lin, L.; Liu, X.; Feng, X. *Tetrahedron* **2011**, *67*, 1781-1787. i) Ramachary, D. B.; Krishna, P. M. *Asian J. Org. Chem*. **2016**, *5*, 729-734.
[16] a) Tanaka, F.; Thayumanavan, R.; Barbas III, C. F. *J. Am. Chem. Soc*. **2003**, *125*, 8523-8528. b) Wu, L.-Y.; Bencivenni, M.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed*. **2009**, *48*, 7196-7199. c) Wu, X.; Li, M.-L.; Chen, D.-F.; Chen, S. S. *J. Org. Chem.* **2014**, *79*, 4743-4750. d) Eudier, F.; Righi, P.; Mazzanti, A.; Ciogli, A.; Bencivenni, G. *Org. Lett*. **2015**, *17*, 1728-1731.

2-onak[17] eta malonitriloak[18] sarri enplegatzen dira. Nitroalkenoak ere arrakasta handiarekin inplementatu dira (4+2) anulazio erreakzioetan. Alor honetan, zetona α,β-asegabeen eta nitroalkenoen arteko Diels-Alder erreakzioak erabilgarritasun zein aldakortasun handiko prozesuak dira, bestelako talde funtzionaletan bihur daitezkeen zikloaduktuak sortzen baitituzte. Jarraian adibide esanguratsuenak garatuko dira.

3.1.1.1 Zetona α,β-asegabeen eta nitroalkenoen arteko Diels-Alder erreakzio organokatalitikoak

Amina sekundarioek katalizatutako Diels-Alder erreakzioen lehen azterketa Barbas III-ren ikerketa taldeak publikatu zuen, dienamina espeziea erreakzio ingurunean *in situ* sortzea posible zela frogatuz.[19] Zetona α,β-asegabe desberdinen eta nitroolefina aromatikoen arteko erreakzioak dagozkien ziklohexanona eraztunak etekin moderatu eta estereokontrol baxuarekin erdietsi zituen, (*S*)-1-(2-pirrolidinilmetil)pirrolidina **9** edo *L*-Prolina **10** katalitzatzaile gisa enplegatuz (**3.3 Eskema**).



3.3 Eskema. Barbas III eta kolaboratzaileek deskribaturiko amina sekundarioek katalizatutako lehen Diels-Alder erreakzioa.

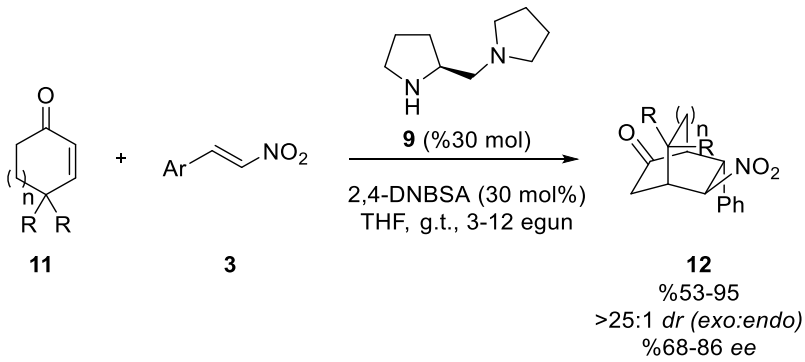
Córdovak ere lau zentro estereogenikoko produktu biziklikoen sintesirako prolinan oinarritutako katalizatzaile familia ebaluatu zuen. Aztertutako deribatuen artean, aurretik deskribaturiko **9** diaminak dagozkien *exo* zikloaduktuak etekin altu, diastereoselektibitate

[17] a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed*. **2009**, *48*, 7200-7203. b) Lan, Y.-B.; Zhao, H.; Liu, Z.-M.; Liu, G.-G.; Tao, J.-C.; Wang, X.-W. *Org. Lett*. **2011**, *13*, 4866-4869. c) Ramachary, D. B.; Reddy, P. S.; Shruthi, K. S.; Madhavachari, R.; Reddy, P. V. G. *Eur. J. Org. Chem*. **2016**, 5220-5226.

[18] Feng, X.; Zhaou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *J. Am. Chem. Soc*. **2012**, *134*, 19942-19947.

[19] Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F. *Tetrahedron Lett*., **2002**, *43*, 3817-3820.

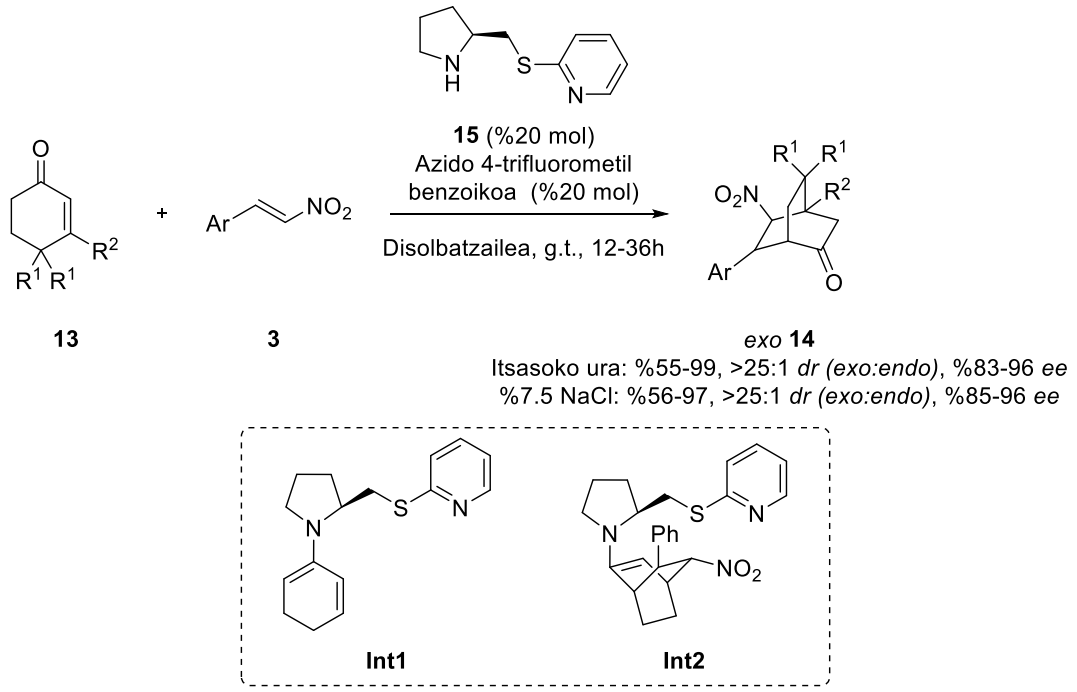
itzel eta enantioselektibitate altuekin sortu zituen.[20] Azido 2,4-dinitrobenzenosulfonikoaren (DNBSA) kantitate katalitikoak ezinbestekoak izan ziren abiadura azkartu eta konbertsio osoak lortzeko (**3.4 Eskema**). Amaierako produktuaren konfigurazio absolutua Michael-ziklizazio erako transformazioaren ondorio zela proposatu zuten, nitroolefinaren dienoarekiko lehenengo adizioak konfigurazioa determinatuz.



3.4 Eskema. Córdova eta lankideek aurkitutako Diels-Alder erreakzio enantioselektiboa.

Arlo honetako hurrengo erreakzio esanguratsua Xu eta lankideek landu zuten. Bertan, zetona ziklikoen eta nitroolefinen arteko itsas ur inguruneko edo %7.5-eko ur disoluzio gatzaduneko Diels-Alder erreakzio asimetriko organokatalitikoa deskribatu zen.[21] Aztertutako katalizatzaileen artean, **15** deribatuak konbertsio eta enantioselektibitate altuenak erakutsi zituen, azido 4-trifluorometilbentzoikoa aditibo moduan enplegatuz. Prozesu asimetrikoa ordezkapen desberdineko nitroolefina aromatiko eta heteroaromatikoentzat aproposa izan zen, kasu guztietan *exo* **14** zikloaduktuak produktu nagusi izanez (**3.5 Eskema**). **Int1** eta **Int2** enaminen presentzia ESI-MS esperimentuei esker berretsi zen, eta ez zen inolako Michael adukturik ikusi transformazio kimikoan zehar. Hots, aurretiko Michael-prozesu sekuentzialetan ez bezala, ziklizazioak mekanismo kontzertatua jarraitzen zuela kontsideratu zen.

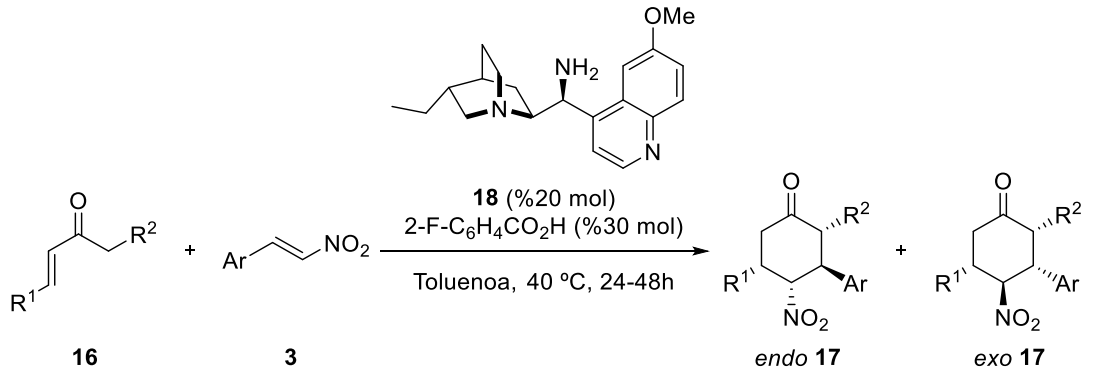
[20] Sundén, H.; Rios, R.; Xu, Y.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal*. **2007**, *349*, 2549-2555.
[21] Xu, D.-Q.; Xia, A,-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem., Int. Ed*. **2009**, *48*, 3821-3824.



3.5 Eskema. Ziklohex-2-en-1-ona eta nitroolefinen arteko gatz disoluzioetako Diels-Alder erreakzioa.

Urte berean, Melchiorreren ikerketa taldeak amina primario erako katalizatzaileek hiru edo lau zentro estereogenikoko ziklohexanona egitura konplexuak erdiesteko gaitasuna bazutela ere frogatu zuen.[17a] Bertan, *cinchona*n oinarritutako **18** amina primarioak zetona α,β-asegabeak aktibatzen zituen, eta nitroalkenoekin erreakzionatuz *endo* **17** zikloaduktuak etekin on eta estereokimika itzelekin sortu (**3.6 Eskema**). *Endo*:*exo* erlazio altuak ko-katalizatzaile gisa erabilitako azido karboxilikoarekin erlazionatuta zeudela postulatu zen. Gainera, proposatutako Michael adizio bikoitza Michael artekarien isolamendu eta RMN karakterizazio bidez baieztatu zen. Lan modu berbera jarraituz, Stowe eta Jandak nornikotina katalizatzaileek burututako Diels-Alder erreakzioa publikatu zuten. Lortutako etekin eta enantiomero soberakin baloreak ez ziren onak izan ordea, enamina trantsitorioen ur inguruneko ezegonkortasuna medio.[22]

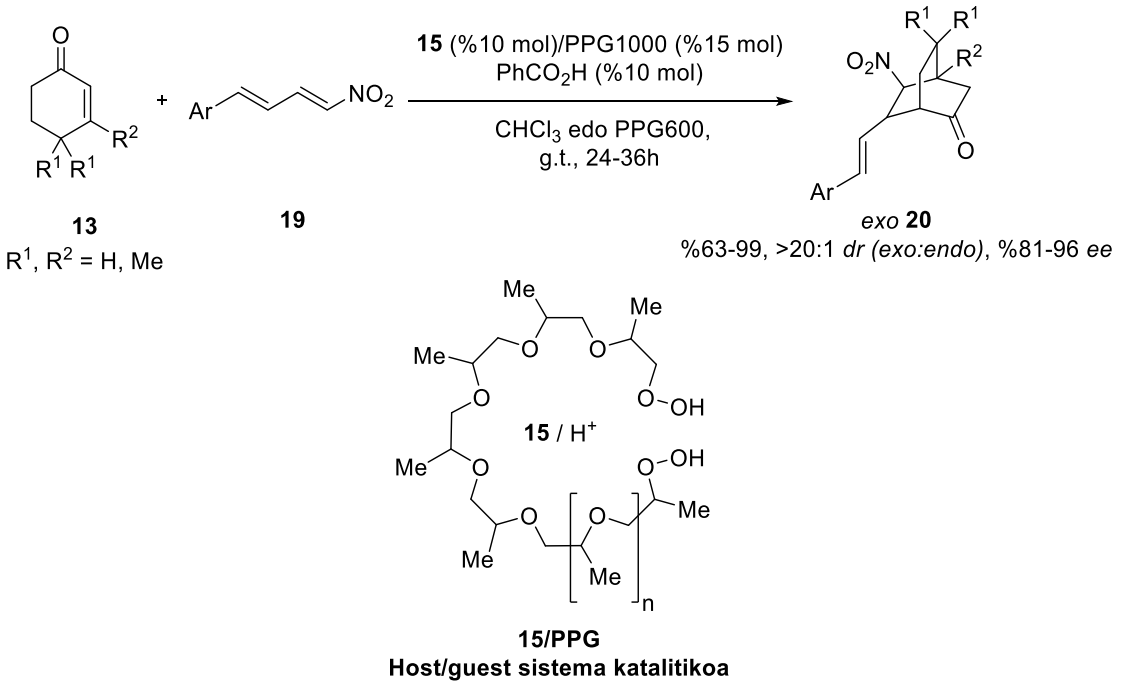
[22] Stowe, G. N.; Janda, K. D. *Tetrahedron Lett*. **2011**, *52*, 2085-2087.



3.6 Eskema. Melchiorrek garatutako enona eta nitroalkenoen arteko Diels-Alder erreakzioa.

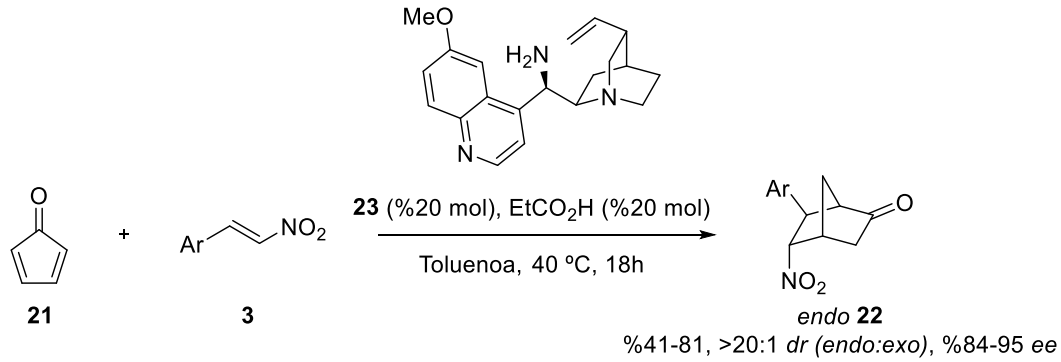
2012 urtean, Xu eta kolaboratzaileek ziklohex-2-en-1-ona **12** eta nitrodieno **19** arteko Diels-Alder erreakzioa katalizatzeko bide alternatiboa deskribatu zuten. Bertan, **15** amina kirala eta polietilenglikol (PEG) edota polipropilenglikol (PPG) arteko konbinazioz sortutako *host-guest* erako sistema supramolekularrak gauzatzen zuen aktibitate katalitikoa.[23] Prozesu kimikoak paregabeko aktibitate asimetrikoa erakutsi zuen enona eta nitrodieno ugarirentzat, nitrodienoko ordezkatzaileen posizioak zein propietate elektronikoek eraginik izan gabe (**3.7 Eskema**). RMN espektroskopiak, dikroismo zirkularrak eta ESI-MS esperimentuek sistema supramolekularraren existentzia baieztatu zuten, non polimero kateek amina kiralaren eta aditibo azidoaren asoziazioa indartzen zuen.

[23] Xia, A.-B.; Xu, D.-Q.; Wu, C.; Zhao, L.; Xu, Z.-Y. *Chem. Eur. J*. **2012**, *18*, 1055-1059.



3.7 Eskema. Enona eta nitrodieno arteko Diels-Alder erreakziorako Xuk diseinatutako sistema katalitiko supramolekularra.

Amaitzeko, Jørgensenen ikerketa taldeak publikatutako lan berria aipatu beharra dago. Deskribaturiko **23** amina primarioak katalizatutako ziklopentenona eta dienozaleen arteko Diels-Alder erreakzioak norkanfor egiturak etekin eta enantioselektibitate altuekin erdietsi zituen (**3.8 Eskema**).[24] Erreakzioa azido ahulen presentzian burutu zen, talde elektroi emaile eta elektroi erakarleak dituzten nitroolefina aromatiko zein heteroaromatikoak aplikagarri izanez. Malononitrilo eta txalkonentzat ere egoki suertatu zen prozesu kimikoa, norkanfor erako konposatu familia zabala sintetizatzeko bide eraginkorra bihurtuz. Autoreek erreakzioa zikloadizio kontzertatu asinkronoa zela postulatu zuten, urratsezko mekanismoa guztiz alboratu gabe, ordea.



3.8 Eskema. Jørgensenek publikatutako **23** amina primarioak katalizatutako Diels-Alder erreakzioa.

[24] Mose, R.; Jensen, M. E.; Preegel, G.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2015**, *54*, 13630-13634.

3.2 HELBURUAK

Deskribaturiko Diels-Alder erreakzio organokatalitikoak amina primario zein sekundarioen usadioan errotzen dira. Gainera, ez dago aminoazido ez-naturaletan oinarritutako katalizatzaileen erabilpena egiten duen prozesuen deskribapenik. Gure organokatalizatzaileen hiru generazioek aldol[25], Michael[26], ziklazio[27] eta Michael-Henry-azetalizazio erreakzioetan erakutsitako emaitza onak kontuan hartuta, Kapitulu honen xede nagusia katalizatzaile γ-dipeptidikoen Diels-Alder erreakziorako egokitasuna aztertzea da. Dieno eta dienozale desberdinen erabilera ere ebaluatuko da, erreakzioaren ahalmena ikertu asmoz.

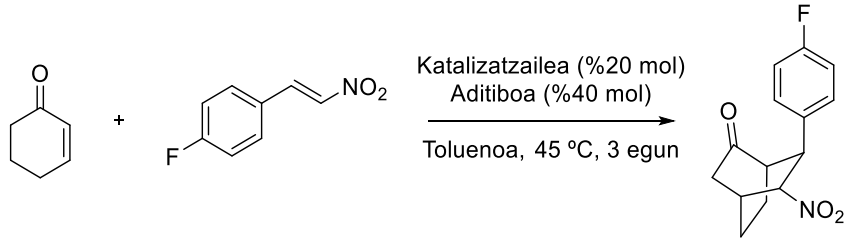
3.3 ZIKLOHEX-2-EN-1-ONA ETA NITROALKENOEN ARTEKO DIELS-ALDER ERREAKZIO ORGANOKATALITIKOA

3.3.1 Erreakzio baldintzen optimizazioa

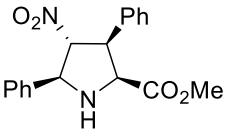
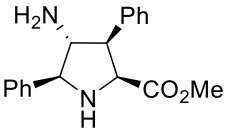
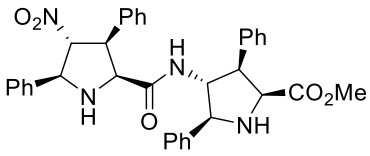
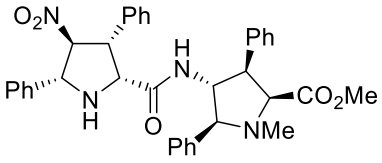
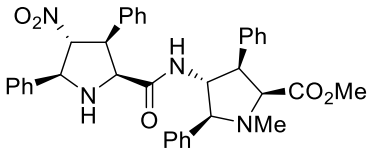
(4+2) zikloadizioen erreaktibitate arauak kontuan hartuta, dieno ziklikoak aziklikoak baino erreaktiboagoak izan ohi dira, duten aurrez antolatutako konformazio cisoidea (*s-cis*) dela eta. Gainera, talde elektroi erakarleak dituzten nitroalkenoek erreakzioa errazten dute, trantsizio egoerako HOMO-LUMO energia diferentzia gutxitzen baitute. Testuinguru honetan, ziklohex-2-en-1-ona **13a** eta (*E*)-nitroestirenoa **3a**-ren arteko Diels-Alder erreakzioa aztertu da lehenik, organokatalizatzaile monomeriko eta γ-dimerikoen eragina ebaluatuz (**3.1 Taula**).

[25] a) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci*. **2012**, *3*, 1486-1491. b) Retamosa, M. G.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem*. **2015**, 2503-2516.
[26] Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F. P. *J. Org. Chem*. **2015**, *80*, 5588-5599.
[27] Retamosa, M. G.; Ruiz-Olalla, A.; Bello, T.; de Cózar, A.; Cossío, F. P. *Angew. Chem., Int. Ed*. **2018**, *57*, 668-672.

3.1 Taula. Ziklohex-2-en-1-ona **13a** eta 4-fluoro-*trans*-β-nitroestirenoa **3a**-ren arteko Diels-Alder erreakzio organokatalitikoa.[a]



13a **3a** *exo* (1*R*,4*R*,5*R*,6*S*)-**14aa**

Sarrera	Katalizatzailea	Aditiboa	Konb. (%)[b]	*exo*/*endo*[c]	Etekina (%)[d]	*ee* (%)[e]
1	 O_2N-X_L-OMe-**44**	$PhCO_2H$	87	80:20	39	97
2	 H_2N-X_L-OMe-**46**	$PhCO_2H$	95	82:18	41	86
3	 O_2N-X_L-X_L-OMe-**49**	$PhCO_2H$	97	70:30	43	90
4	 O_2N-X_D-X_L^{Me}-OMe-**50**	$PhCO_2H$	>99	85:15	52	-96
5		$PhCO_2H$	>99	88:12	60	97
6		PNBA[f]	>99[g]	90:10	46	95
7	 O_2N-X_L-X_L^{Me}-OMe-**50**	SA[h]	-[i]	zg[j]	zg	zg
8		TFA[k]	-[i]	zg	zg	zg
9		pCF_3CO_2H	>99	90:10	45	93
10[l]		$PhCO_2H$	60	zg	zg	zg
11[m]		$PhCO_2H$	>99	86:14	50	95

12[n]	$PhCO_2H$	>99[o]	70:30	27	93
13[p]	$PhCO_2H$	>99	87:13	50	95

a) Erreakzioa **13a** zetona (0.10 mmol) eta 4-fluoro-*trans*-β-nitroestirenoa **3a** (0.10 mmol) erabiliz gauzatu zen, 20 mol% katalizatzaile eta 40 mol% aditiborekin 45 ºC-tan. b) Erreakzioak ^{1}H-RMN bidez jarraitu ziren. c) *endo*/*exo* erlazioa erreakzio nahastearen ^{1}H-RMN analisi bidez determinatu zen. d) Etekinak bi diastereomeroen gehiketari egiten dio erreferentzia. e) HPLC bidez neurturiko enantiomero soberakinak *exo* (1*R*,4*R*,5*R*,6*S*)-**14aa** nagusiari egiten dio erreferentzia. Balore negatiboek kontrako enantiomeroa sortzen dela adierazten dute. f) PNBA: Azido *p*-nitrobenzoikoa. g) 4 egun igarota ikusitako konbertsioa (3 egunen ondoren %60-ko konbertsioa besterik ez zen ikusi) h) SA: Azido salizilikoa i) Ez zen Diels-Alder zikloadukturik sortu. j) zg: zehaztugabea. k) TFA: Azido trifluoroazetikoa. l) 10 mol% katalizatzaile, 20 mol% PhCO2H. m) 70 ºC. n) Biotage μW, 90 °C, 100 W, 5h. o) 90 minutu ostean, %50-ko konbertsioa behatu zen. 3 orduren buruan, %75-ekoa. p) 2 eq. zetona erabili ziren.

Lehen generazioko O_2N-X_L-OMe-**44** katalizatzaileak %87-ko konbertsio moderatua erakutsi zuen *exo* **14aa** zikloa erlazio diastereomeriko eta soberakin enantiomeriko onekin sortuz (**3.1 Taula**, 1. sarrera). Katalizatzailea bigarren generazioko H_2N-X_L-OMe-**46** amina deribatura aldatzean, konbertsio apur bat altuagoak lortu ziren, baina, etekin eta soberakin enantiomerikoak moderatuak ziren oraindik (**3.1 Taula**, 2. sarrera).

Konbertsio eta etekin balore hauek hobetu asmoz, γ-dipeptidoen erabilpena aztertu zen ondoren. O_2N-X_L-X_L-OMe-**49** organokatalizatzaileak ez zituen aurretiko emaitzak hobetu. Nahiz soberakin enantiomeriko altuak lortu, *exo*/*endo* ratioa 70:30-ra jaitsi zen (**3.1 Taula**, 3. sarrera). O_2N-X_D-X_L^{Me}-OMe-**50** dimero *N*-metilatuak eta bere diastereomero den O_2N-X_L-X_L^{Me}-OMe-**50**-ak erreakzio denbora azkartu ahal izan zuten eta konbertsio osoak lortuz bi kasuetan (**3.1 Taula**, 4 eta 5 sarrerak). O_2N-X_D-X_L^{Me}-OMe-**50** katalizatzaileak *ent*-**14aa**-ren sorrera bultzatu zuen etekin moderatu, erlazio diastereomeriko on eta enantiomero soberakin itzelekin (**3.1 Taula**, 4 sarrera). Etekin are eta altuagoa lortu zen O_2N-X_L-X_L^{Me}-OMe-**50** organokatalizatzailearekin, *exo*-**14aa** zikloaduktua etekin moderatu, exo/*endo* erlazio on eta enantiokontrol itzelarekin sortuz (**3.1 Taula**, 5. sarrera). Puntu honetan gure organokatalizatzaileek Xu eta kolaboratzaileek publikatutako *exo*-**14aa** zikloen enantiomeroak sortzen dituztela aipatu beharra dago.

Jarraian, aditibo azido desberdinen erabilera ikertu zen, honek erreaktibitate zein estereoselektibitatean izan zezakeen portaera ebaluatzeko. Azido *p*-nitrobenzoikoaren uso egitean, amaierako produktua etekin baxuagoetan sortu zen, nahiz erlazio diastereomeriko eta enantiokontrolean balore antzekoak ikusi (**3.1 Taula**, 6. sarrera). Azido saliziliko eta TFA-k (azidotasun altuagodunak) ez zuten inolako Diels-Alder zikloaduktuaren formaziorik bultzatu (**3.1 Taula**, 7 eta 8 sarrerak) eta *p*-CF_3COOH-aren erabilerak etekin eta enantiokontrolean jaitsiera txikia erakutsi zuten (**3.1 Taula**, 9. sarrera).

Beste erreakzio parametro batzuk aztertzerako garaian, katalizatzaile eta aditiboaren kantitatea erdira jaisteak konbertsioa gutxitu zutela ikusi zen (**3.1 Taula**, 10. sarrera). Tenperatura 70 ºC-ra igotzeak etekin eta *ee* balio baxuagoak erakutsi zituen (**3.1 Taula**, 11. sarrera). Mikrouhin erradiazioak erreakzio nahaste narratsak eta etekin baxuak eman zituen (**3.1 Taula**, 12. sarrera). Azkenik, zetonaren 2 baliokideren erabilpenak ez zuen etekina hobetzerik lortu (**3.1 Taula**, 13. sarrera).

Datu esperimentalek, beraz, erreakzioa 45 ºC-tan burutu behar zela iradoki zuten,O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoa eta azido bentzoikoa %20 eta %40-ko karga katalitikoan erabiliz.

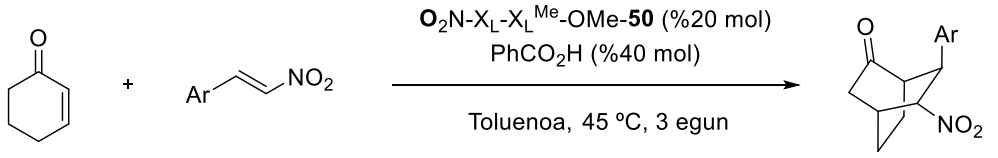
3.3.2 Substratu desberdinen azterketa

Gure katalizatzailearen Diels-Alder erreakzioetako egokitasuna ikertu asmoz, talde elektroi emaile zein elektroi erakarlez ordezkaturiko nitroalkeno aromatiko eta heteroaromatiko desberdinak aztertu ziren. Esperimentu hauen emaitzak **3.2 Taula**n laburtzen dira.

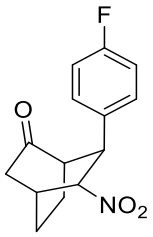
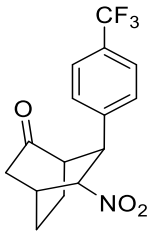
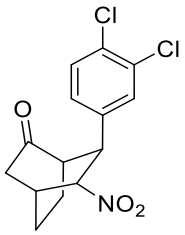
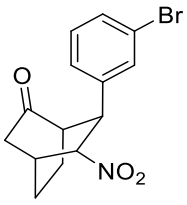
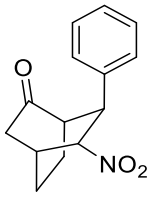
Orokorrean, Diels-Alder erreakzioak arazorik gabe jardun zuen kasu guztietan, amaierako *exo* **14aa-ah** zikloaduktuak etekin moderatu, *exo*/*endo* erlazio on eta enantiomero soberakin balio ezin hobeekin sortuz. Eraztun aromatikoaren propietate elektronikoek eta beraien ordezkapen ereduak diastereo- eta enantioselektibitatean eragin gutxi zuela ere hauteman zen. Etekinak, eraztun aromatikoren izaera elektroi emaile edo elektroi erakarlearekiko menpekotasuna zutela ikusi zen ordea. Elektroi erakarle taldeak dituzten nitroalkeno aktibatuek etekin altuagoak erakutsi zituzten (**3.2 Taula**, 1 eta 2 sarrerak). Talde elektroi emaileak dituztenek, bestalde, amaierako produktuak etekin baxuagoetan erdietsi zituzten (**3.2 Taula**, 6 eta 7 sarrerak). Izan ere, 4-metoxi-*trans*-β-nitroestirenoa **3g**-k 4 egun behar izan zituen konbertsio osora heltzeko.

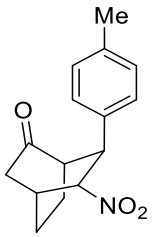
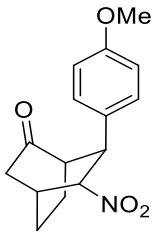
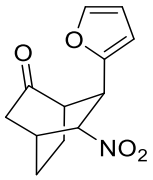
Aurreko adibideekin batera, bestelako egiturak ere aplikagarri suertatu ziren. Zentzu honetan 3,4-dikloro-*trans*-β-nitroestirenoa **3c**-k aurki genezake, dagokion Diels-Alder zikloaduktua %54-ko etekinarekin erdietsi zuena, ratio diastereomeriko on eta *ee* balio altuekin (**3.2 Taula**, 3. sarrera). **3h** nitroalkeno heteroziklikoak ere etekin moderatu, erlazio diastereomeriko on eta enantiomero soberakin itzelekin sortu zuen Diels-Alder zikloaduktua (**3.2 Taula**, 8. sarrera). Azkenik, 3-bromo-*trans*-β-nitroestirenoa **3d**-k %35-eko etekin baxua erakutsi zuen Diels-Alder zikloadizio prozesuan (**3.2 Taula**, 4. sarrera).

3.2 Taula. Ziklohex-2-en-1-ona eta nitroalkenoen arteko Diels-Alder erreakzio organokatalitikoa.[a,b]



13a **3a-h** *exo* (1*R*,4*R*,5*R*,6*S*)-**14aa-ah**

Sarrera	Ar	Produktua	Egitura	*exo*/*endo*[c]	Etekina (%)[d]	*ee* (%)[e]
1	4-F	**14aa**		85:15	65	97
2	4-CF_3	**14ab**		84:16	69	96
3	3,4-Cl	**14ac**		78:22	54	98
4	3-Br	**14ad**		85:15	35	96
5	Ph	**14ae**		86:14	61	95

6	4-Me	**14af**		85:15	51	96
7	4-OMe	**14ag**		80:20	47[f]	96
8	2-furil	**14ah**		81:19	47	92

a) Erreakzioa ziklohex-2-en-1-ona **13a** (0.10 mmol) eta dagokion nitroalkenoa **3a-h** (0.10 mmol) erabiliz gauzatu zen, 45 ºC-tan, 20 mol% O_2N-X_L-X_L^{Me}-OMe-**50** eta 40 mol% $PhCO_2H$-ren laguntzaz. b) Erreakzioak ^{1}H-RMN bidez jarraitu ziren hasierako erreaktiboen desagerpena arte (Konb. > %99). c) *exo*/*endo* erlazioa erreakzio nahasteen ^{1}H-RMN analisi bidez gauzatu zen. d) Etekinak bi diastereomeroen gehiketari egiten dio erreferentzia. e) HPLC bidez neurtutako soberakin enantiomerikoak *exo* (1*R*,4*R*,5*R*,6*S*)-**14aa-ah** enantiomeroari egiten dio erreferentzia. f) %95-eko konbertsioa lortu zen.

Emaitza hauek gure O_2N-X_L-X_L^{Me}-OMe-**50** γ-dipeptidoa ziklohexanona eta ordezkapen desberdineko nitroalkenoen Diels-Alder erreakzioa katalizatzeko gai dela frogatu zuen, etekin moderatuak eta estereokontrol itzelak lortuz kasu guztietan.

3.4 ZETONA AZIKLIKO α,β-ASEGABE ETA NITROESTIRENOEN ARTEKO DIELS-ALDER ERREAKZIO ORGANOKATALITIKOA

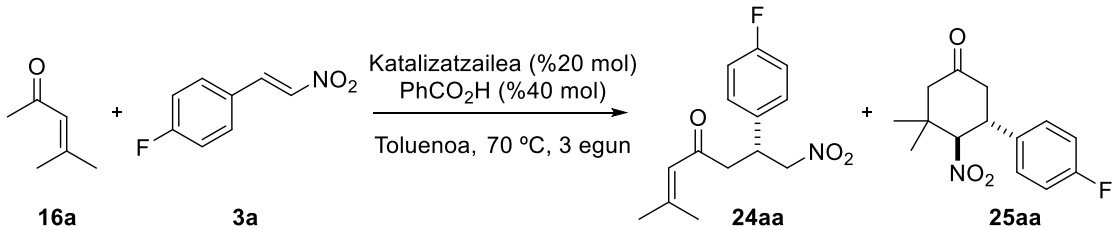
Gure organokatalizatzaileek zetona aziklikoekin duten aplikagarritasuna ikertzeko, jarraiko esperimentuak 4-metilpent-3-en-2-ona **7a** eta funtzionalizazio altuko prolina ez-naturalen hiru generazioak erabiliz gauzatu ziren. *L*-Prolina **10** erreferentziazko katalizatzaile gisa enplegatu zen (**3.3 Taula**).

Diels-Alder produktuaren formazioa bultzatu asmoz, erreakzioak 70 ºC-tan burutu ziren lehenik. Baldintza hauetan, *L*-Prolinak konbertsio osoak lortu zituen. Hala ere, Michael eta Diels-Alder prodktuak 1:1 erlaziotan lortu ziren, biak errazemikoak izanik (**3.3 Taula**, 1. sarrera). Prolina ez-naturaletan oinarritutako hiru organokatalizatzaile generazioek enantioselektibitate pixkat hobeak sorrarazi zituzten, katalizatzaile hauetako ordezkatzaileen garrantzia marratuz (**3.3 Taula**, 2-6 sarrerak).

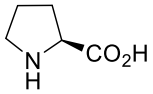
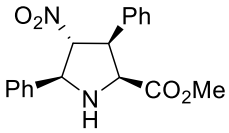
O_2N-X_L-OMe-**44** nitroprolinak **25aa** ziklizazio produktuaren formazio ia esklusiboa erdietsi zuen, baina amaierako produktuaren konbertsio eta soberakin enantiomeriko

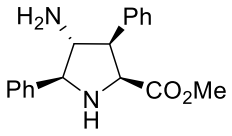
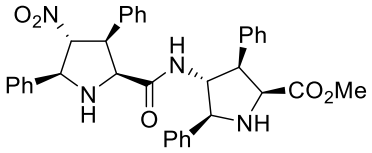
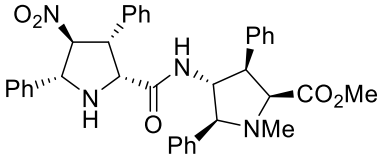
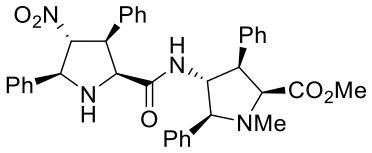
balioak baxuak izan ziren kasu honetan (**3.3 Taula**, 2. sarrera). Bigarren generazioko H_2N-XL-OMe-**46** deribatuaren enpleguak Michael:Diels-Alder proportzioa jaitsi zuen, **24aa** eta **25aa** produktuak ia 1:1 erlazioan erdietsiz, etekin moderatuekin. Michael produktuak %50-ko enantiomero soberakina erakutsi zuen; Diels-Alder produktuaren *ee* balioa baxua izanik (**3.3 Taula**, 3. sarrera). O_2N-X_L-X_L-OMe-**49** dipeptidoak ere konbertsio osoa lortu zuen, Diels-Alder produktuarekiko formazioaren alde eginez. Zoritxarrez, bai Michael bai Diels-Alder produktuen enantiomero soberakinek balore baxuagoak izan zituzten (**3.3 Taula**, 4. sarrera). O_2N-X_D--X_L^{Me}-OMe-**50** dipeptido *N*-metilatuaren kasuan, erreakzioak ez zuen konbertsio totala lortu eta Michael:Diels-Alder produktuen arteko erlazioa dipeptido ez metilatuaren usadioaz lortutakoaren parekoa izan zen. Bi produktuen *ee* baloreak hobetzea lortu zen arren, hauek ez zituzten balore moderatuak gainditu (**3.3 Taula**, 5. sarrera). O_2N-X_L--X_L^{Me}-OMe-**50** dipeptidoak, azkenekoz, erreakzioak konbertsio totala lortzea ahalbidetu zuen, eta Diels-Alder **25aa** produktuaren formazioa faboratu (**3.3 Taula**, 6, sarrera). Hala eta guztiz, katalizatzaile peptidikoek emaitza hobeak erakutsi arren, Michael **24aa** eta Diels-Alder **25aa** produktuen enantiomero soberakinek ez zuten garrantzia kimikorik erakutsi.

3.3 Taula. 4-metilpent-3-en-2-ona **7a** eta 4-fluoro-*trans*-β-nitroestirenoa **3a**-ren arteko Diels-Alder erreakzioa.[a]



16a **3a** **24aa** **25aa**

Sarrera	Katalizatzailea	Konbertsioa (%)[b]	24aa:25aa[c]	Etekina (%)[d]		*ee* (%)[e]	
				24aa	**25aa**	**24aa**	**25aa**
1	 *L*-Prolina **10**	>99	43:57	22	38	3	0
2	 O_2N-X_L-OMe-**44**	70	5:95	zg[f]	48	zg	40

3	 H_2N-X_L-OMe-**46**	95	45:55	24	32	50	21
4	 O_2N-X_L-X_L-OMe-**49**	>99	34:66	12	61	40	7
5	 O_2N-X_D-X_L^{Me}-OMe-**50**	85	33:67	21	48	-60	-34
6	 O_2N-X_L-X_L^{Me}-OMe-**50**	>99	25:75	12	58	56	26
7[g]		40	20:80	zg	zg	zg	zg
8[h]		30[i]	30:70	zg	zg	zg	zg
9[j]		45[i]	>99:1	zg	zg	zg	zg
10[k]		50	50:50	21	32	56	46

a) Erreakzioa 70 ºC-tan burutu zen. 4-metilpent-3-en-2-ona **16a** (0.10 mmol) eta 4-fluoro-*trans*-β-nitroestirenoa **3a** (0.10 mmol) erabiliz, %20 mol katalizatzaile eta %40 mol $PhCO_2H$-ren laguntzaz. b) Konbersioak erreakzio nahasteen ^{1}H-RMN bidez neurtu ziren. c) **24aa**:**25aa** erlazioa erreakzio nahasteen ^{1}H-RMN bidez neurtu ziren. d) Etekinak produktu isolatu puruei egiten die erreferentzia. e) HPLC bidez neurtutako enantiomero soberakinak **24aa** edo **25aa** enantiomero nagusiari egiten dio erreferentzia. Balore negatiboek kontrako enantiomeroa sortzen dela adierazten dute. f) zg: zehaztugabea g) Biotage µW, 90 °C, 100 W, 5h.h) Azido salizilikoa erabili zen aditibotzat. i) 6 egun osteko konbertsioa. j) Giro tenperaturan burutua. k) 45 ºC-tan burutua.

O_2N-X_L-X_L^{Me}-OMe-**50** dipeptido bidez lortutako azken emaitzak hobetu asmoz, erreakzio parametro desberdinen ikerketa burutu zen. Saiakera ugari egin arren, inorrek ez zuen emaitza positiborik erakutsi. Mikrouhin erradiazioak eta azido salizilikoaren erabilerak konbertsio baxuak eman zituen (**3.3 Taula**, 7 eta 8 sarrerak, hurrenez hurren). Tenperatura 45 ºC eta giro tenperaturara jaisteak Michael aduktuaren formazioa bultzatu zuen, baina konbertsio osoak lortu gabe (**3.3 Taula**, 9 eta 10 sarrerak).

Laburtuz, 4-metilpent-3-en-2-ona **16a**-ak erakutsitako emaitzak ez ziren ziklohex-2-en-1-ona **13a**-ren bidez lortutakoak bezain onak izan, ez erreaktibitate ez estereoselektibitate terminoetan.

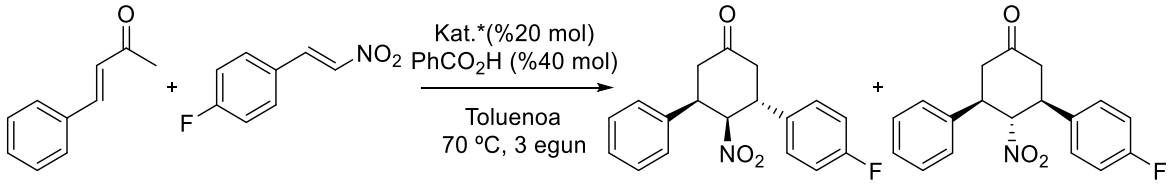
24aa eta **25aa** produktu ezezagunen konfigurazio absolutua determinatzeko (*E*)-4-fenilbut-3-en-2-ona **16b**-ren erreaktibitatea ikuskatu zen, amaierako Diels-Alder aduktuak Melchiorre eta lankideek aurrez deskribatu baitzituzten.[17a] Zetona honen erabilerak dienoari eragozpen esterikoa ere handituko dio, hiru zentro estereogenikodun

ziklohexanona egitura konplexuen sintesirako Diels-Alder erreakzioaren enantioselektibitatea igotzea posible bihurtuz. Beraz, **16b** eta 4-fluoro-*trans*-β-nitroestirenoa **3a**-ren erreakzioa 70 ºC-tan gauzatu zen, prolina ez-naturaletan oinarritutako hiru generazioak katalizatzaile gisa erabiliz (**3.4 Taula**).

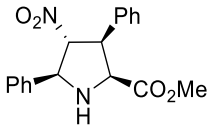
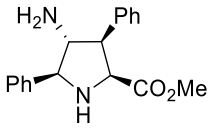
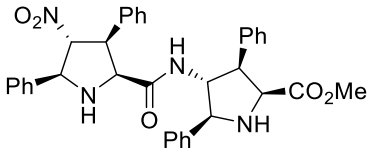
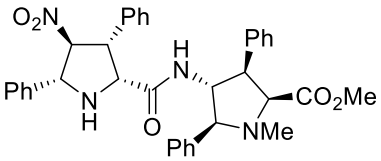
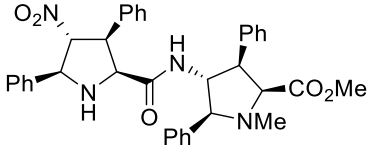
Lehen generazioko O_2N-X_L-OMe-**44** organokatalizatzaileak %60-ko konbertsioa eta enantiomero soberakin baxuak erakutsi zituen. Deribatu monomeriko honek *endo*-1**7ba** eta *exo*-**17ba** diastereomeroen kantitate ia berdinak sortu zituen, azkenaren formazioa apur bat faboratua egon arren (**3.4 Taula**, 1. sarrera). H_2N-X_L-OMe-**46** amino deribatuak erreakzio abiadura azkartu zuen, ia konbertsio totala lortuz. Nitro kideak ez bezala, amino katalizatzaileak *endo*-**17ba** zikloaduktuaren formazioaren alde egin zuen. Zoritxarrez, erreakzioko diastereo- eta enantioselektibitateek ez zuten inolako hobekuntzarik demostratu **44** deribatuarekin alderatuz (**3.4 Taula**, 2. sarrera).

O_2N-X_L-X_L-OMe-**49** dipeptidoaren erabilerak, bestalde, konbertsio totalak erdietsi zituen. Kasu honetan ere *endo* zikloaduktuaren alderako formazioa gauzatu zen, erlazio diastereomerikoa 70:30 balioetara iritsiz. Enantiokontrolak hobera egin arren, *exo*-**17ba** zikloaduktuak %20-ko *ee*-a erakutsi zuen, eta *endo*-ak %50-koa (**3.4 Taula**, 3. sarrera). Azkenik, dimero N-metilatuak katalizatzaile gisa erabiltzean, erreakzioak %70 inguruko konbertsiora heldu ziren soilik (**3.4 Taula**, 4 eta 5 sarrerak). Emaitza estereokimikoak nabarmenki hobetu ziren, bi kasutan *endo:exo* ratio onak lortuz. Soberakin enantiomerikoetan ere joera berdina ikuskatu zen. Alabaina, O_2N-X_D-X_L^{Me}-OMe-**50** katalizatzaile egokienak ez zuen *endo* zikloaduktuaren %67-ko *ee* balioa hobetu, ez *exo* zikloaduktuaren %50-eko balio moderatua pasa ere (**3.4 Taula**, 4. sarrera). Esan beharra dago ez zela inolako Michael artekarien formaziorik behatu erreakzio guzti hauetan.

3.4 Taula. (*E*)-4-fenilbut-3-en-2-ona **16b** eta 4-fluoro-*trans*-β-nitroestirenoa **3a**-ren arteko Diels-Alder erreakzio organokatalitikoa.[a,b]

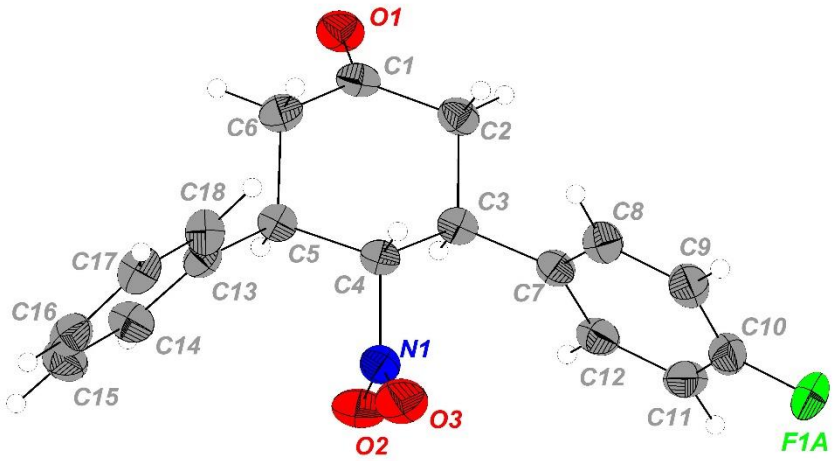


16b **3a** *endo* (3*R*,4*S*,5*R*)-**17ba** *exo* (3*S*,4*R*,5*R*)-**17ba**

Sarrera	Katalizatzailea	Konbertsioa (%)[b]	*endo*/*exo*[c]	Etekina (%)[d]	*ee* (%)[e]	
					endo **17ba**	*exo* **17ba**
1	 O_2N-X_L-OMe-**44**	60	42:58	30	30	37
2	 H_2N-X_L-OMe-**46**	90	60:40	34	37	5
3	 O_2N-X_L-X_L-OMe-**49**	>99	68:32	54	50	20
4	 O_2N-X_D-X_L^{Me}-OMe-**50**	70	90:10	39	-67	-50
5	 O_2N-X_L-X_L^{Me}-OMe-**50**	65	83:17	34	66	35

a) Erreakzioa 70 ºC-tan gauzatu zen (*E*)-4-fenilbut-3-en-1-ona **16b** (0.10 mmol) eta 4-fluoro-trans-β-nitroestirenoa **3a** (0.10 mmol) erabiliz, 20 mo% katalizatzaile eta 40 mol% $PhCO_2H$ erabiliz. b) Konbertsioak erreakzio nahastearen ^{1}H-RMN analisi bidez aztertu ziren. c) *Endo*/*exo* ratioak erreakzio nahastearen ^{1}H-RMN analisi bidez aztertu ziren. d) Etekinak bi diastereoisomeroen gehiketari egiten dio erreferentzia. e) HPLC bidez neurtutako soberakin enantiomerikoak *endo* **17ba** edo *exo* **17ba** enantiomero nagusiari egiten dio erreferentzia. Balio negatiboek kontrako enantiomeroa sortzen dela adierazten dute.

Exo-**17ba** zikloaduktuaren estereokimika X-izpien difrakzio bidez baieztatu zen. C3, C4 eta C5 karbono asimetrikoen konfigurazio absolutua *S*, *R*, *R* da, hurrenez-hurren (**3.1 Irudia**).



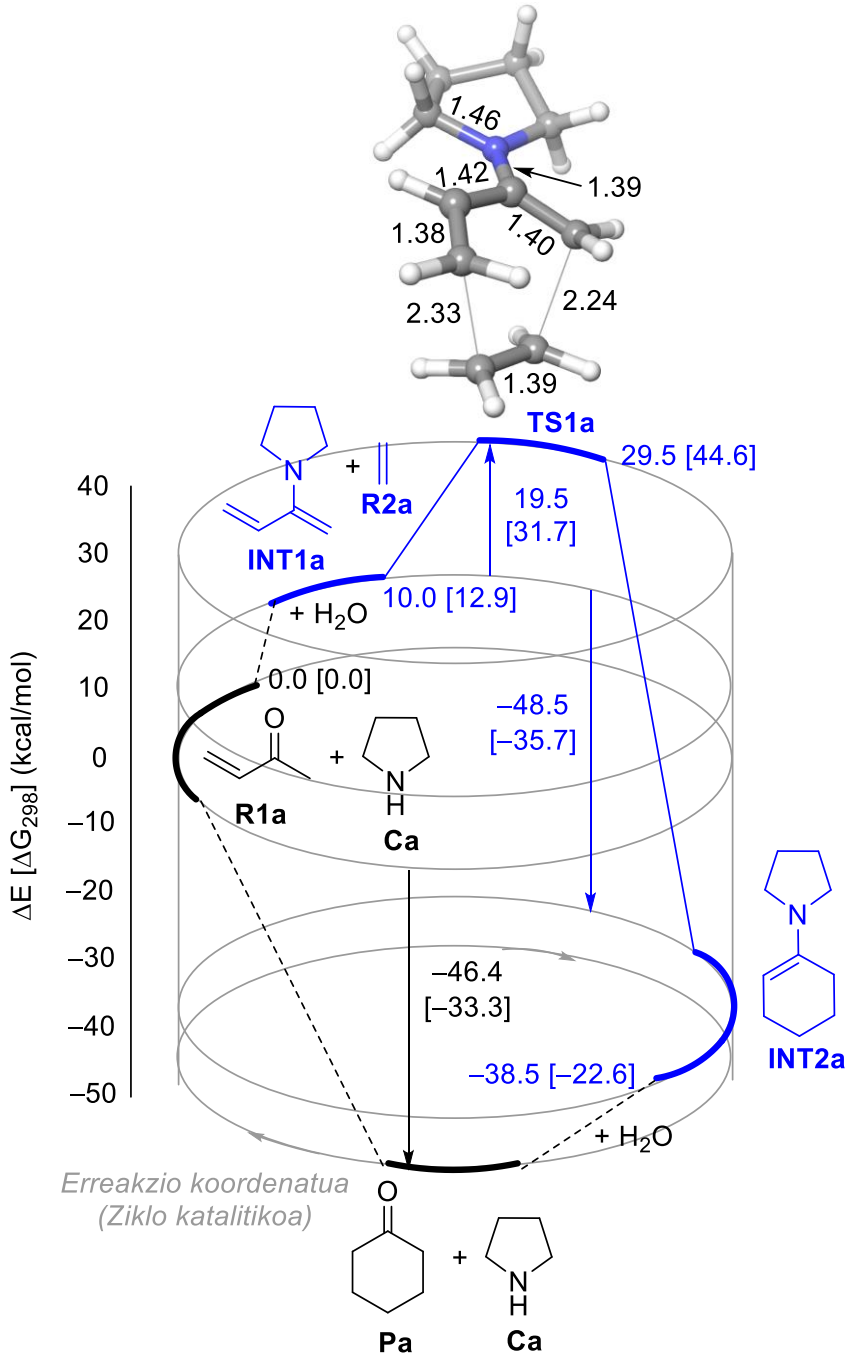
3.1Irudia. *Exo* (3*S*,4*R*,5*R*)-**17ba**-ren ORTEP diagrama, %50-eko probabilitateko elipsoide temailekin.

3.5 ATARIKO AZTERKETA KONPUTAZIONALAK

Gure ikerketa taldean buruturiko azterketa konputazionalek enamina-bidezko Diels-Alder (EMDA) erreakzio hauetako ziklo katalitikoaren ezaugarri geometriko eta energetikoen identifikazioa ahalbidetu zuten. Kalkulu hauek M06-2X/6-31G(d)//B3LYP/6-31G(d)[28,29,30,31] teoria mailan gauzatu ziren. Metil binilzetona **R1a** eta etileno **R2a**-ren pirrolidina **Ca** bidez katalizaturiko prozesua hartu zen eredutzat, ordezkatzailerik gabeko erreakzioaren propietate nagusiak zehaztu

[28] M06-2X funtzionala: Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
[29] B3LYP funtzionala: a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.
[30] 6-31G(d) basea: Hehre, W. J.; Random, L.; Schleyer, P. V. Pople, J. A. *Ab Initio Molecular Orbital Theory*, Wiley: New York, **1986**.
[31] Gaussian 09 programa: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision E.01, Gaussian, Inc., Wallingford CT, **2013**.

asmoz. Ziklo katalitikoan parte hartzen duten espezie esanguratsuenen Gibbs energiak (298 K) **3.2 Irudia**n elkartzen dira.



3.2 Irudia. **Ca** pirrolidinak katalizatutako binil zetona **R1a** eta etileno **R2a**-ren arteko erreakzioko energia erlatibo eta barne energia erlatiboak (kako artean, 298 K-tan), kcal/mol-tan. Kalkuluak M06-2X/6-31G(d)//B3LYP/6-31G(d) teoria mailan burutu ziren. **TS1a** trantsizio egituraren lotura distantziak Å-tan emanten dira.

Kalkuluen arabera, **INT1a** enaminaren formazioa endotermikoa zen, erreaktiboekiko 13 kcal/mol inguruko energia libre erlatiboa izanik. Enamina bidez katalizatutako beste

kalkuluak kontsultatuz, EMDA-ren aurreko pausuak aktibazio energia altua izan dezake, ziklo katalitikoa osatzeko behar diren denbora luzeen eragile izanez.[32]

INT1a dienamina eta etileno **R2a**-ren arteko Diels-Alder erreakzioak **INT2a** enamina erdiesten zuen, 20 kcal/mol inguruko aktibazio energiarekin. Prozesu bimolekularraren entropia negatiboa zela eta, energia honek 32 kcal/mol-ko Gibbs energia izatea bultzatzen zuen. Trantsizio egoeraren ezaugarri geometriko kalkulatuek egitura nahiko sinkronoa islatu zuten, C-C loturak 2.2-2.3 Å artean sortuz. EMDA prozesu hau exergonikoa zen, ordea, -23 kcal/mol-eko $\Delta G_{erreak.}$ balorearekin. **INT2a** enamina artekariak ziklohexanona **Pa** eta **Ca** katalizatzailearen askapena erdietsi zuen hidrolisi urratsaren ondoren, -33.3 kcal/mol-eko Gibbs erreakzio energia totalarekin. Honek erreakzio katalitikoaren bideragarritasun termodinamikoa bermatu zuen, **INT1a** eta **INT2a** enamina artekarien formazio eta hidrolisiak erreakzio denbora luze eta katalizatzaile karga altuekin erlazio zuzena izan arren (*vide supra*).

3.6 ONDORIOAK

Kapitulu honetan azaldu eta eztabaidatutako azterketen ondoren, hurrengo ondorioak laburtu daitezke:

1. Prolina ez-naturaletan oinarritutako hiru katalizatzaile generazioek ziklohex-2-en-1-onaren dienamina bidezko Diels-Alder erreakzioa katalizatzea frogatu zuten. Ebaluatutako deribatuen artean, O_2N-X_L-X_L^{Me}-OMe-**50** dipeptido *N*-metilatuak emaitza onenak erakutsi zituen, *exo* zikloaduktuak erlazio diastereomeriko on eta enantiomero soberakin altuekin sortuz.
2. *Exo*-L unitate monomerikodun prolina ez-naturaletan oinarritutako katalizatzaileek Xu eta kolaboratzaileek lortutako enantiomeroen aurkakoak erdietsi zituzten. O_2N-X_D-X_L^{Me}-OMe-**50**-ren kasuan, non aktibitate katalitikoa lehen *exo*-D monomeroak gauzatzen duen, publikatutakoaren enantiomero berdina sortu zen.
3. O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoaren ahalmena ikertzeko nitroolefina aromatiko eta heteroaromatiko desberdinen usadio egin zen. Diels-Alder erreakzioak aparteko arazorik gabe gauzatu ziren, *exo* zikloaduktoak etekin moderatu, diastereokontrol on eta enantiomero soberakin itzelekin lortuz. Orokorrean, *para*-posizioan ordezkaturiko nitroalkenoek *meta*- ordezkaturikoek baino etekin handiagoak izan zituzten.

[32] a) Ashley, M. A.; Hirschi, J. S.; Izzo, J. A.; Vetticatt, M. J. *J. Am. Chem. Soc*. **2016**, *138*, 1756-1759. b) Renzi, P.; Hioe, J.; Gschwind, R. M. *Acc. Chem. Res*. **2017**, *50*, 2936-2948. c) Haindl, M. H.; Hioe, J.; Gschwind, R. M. *J. Am. Chem. Soc*. **2015**, *137*, 12835-12842.

4. Zetona aziklikoen erabilerak emaitza kaxkarragoak erakutsi zituen, katalizatzaileen portaeraren inguruko joera orokor bat ondorioztatzea ezinezko eginez. 4-metilpent-3-en-2-ona erabiltzean enantiomero soberakin balore baxu edo moderatudun Michael eta Diels-Alder produktuen nahasteak lortu ziren. (*E*)-4-fenilbut-3-en-2-ona zetona gisa hartzean, O_2N-X_L-OMe-**44** katalitzatzaileak *exo* zikloaduktuarekiko formazioa faboratu zuen, *ee* balore baxuekin. Bestalde, bigarren eta hirugarren generazioko katalizatzaileek *endo* zikloaduktuen formazioa faboratu zuten. Emaitza estereokimiko onenak O_2N-X_L-X_L^{Me}-OMe-**50** dipeptidoaren usadioaz lortu ziren, baina erreakzioak ezin izan zuen konbertsio totala heldu.

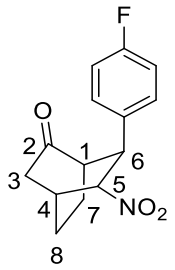
3.7 ATAL ESPERIMENTALA

Ohar orokorrak

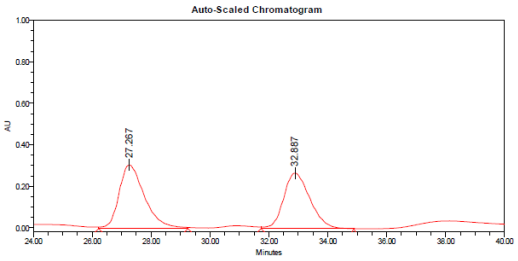
2. Kapitulua, 2.8 atala begiratu

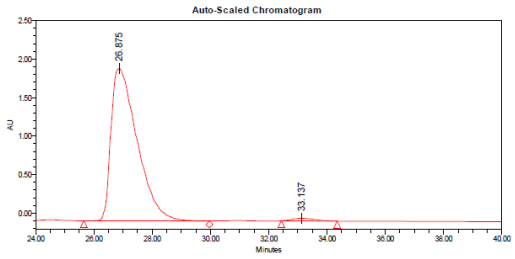
Diels-Alder erreakziorako prozedura orokorra

Dagokion katalizatzaile (0.02 mmol, 0.2 eq.), $PhCO_2H$ (0.04 mmol, 0.4 eq.), **13a**, **16a,b** zetona α,β-asegabea (0.10 mmol, 1.0 eq.) eta **3a-h** nitroolefinen (0.11 mmol, 1.1 eq.) tolueno nahastea 45 edo 70 ºC-tan nahastu zen. Erreakzioa 1H-RMN bidez jarraitu zen. Nitroalkenoa erabat desagertu ondoren, disolbatzailea presio erreduzituan lurrundu zen eta erreakzio nahastea silika gelezko zutabe kromatografiko bidez purifikatu (baldintzak konposatu bakoitzaren kasurako begiratu). Konposatu errazemikoen sintesia *D*/*L*-Prolina bidez burutu zen (0.04 mmol, 0.4 eq.)



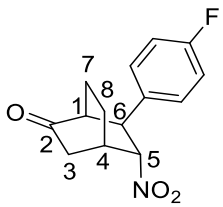
(1R,4R,5R,6S)-6-(4-fluorofenil)-5-nitrobiziklo[2.2.2]oktan-2-ona (*exo* **14aa**).[21] Ziklohex-2-en-1-ona **13a** eta 4-fluoro-*trans*-β-nitroestireno **3a**-tik sortua, O_2N-X_L-X_L^{Me}-OMe**-50** katalizatzaile gisa erabiliz. 1:1 Et_2O:Hexano nahasteaz purifikatua. Etekin globala: %65 (0.065 mmol, 17 mg), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, CDCl3) δ 7.11 – 7.04 (m, 2H, ArH), 7.04 – 6.96 (m, 2H, ArH), 4.73 (dt, *J* = 6.7, 2.0 Hz, 1H, C^5H), 4.13 (dt, *J* = 6.0, 3.2 Hz, 1H, C^6H), 2.97 (q, *J* = 2.9 Hz, 1H, C^4H), 2.66 (q, *J* = 2.7 Hz, 1H, C^1H), 2.53 – 2.46 (m, 2H, C^3H), 2.27 – 2.18 (m, 1H, C^7H), 2.01 – 1.87 (m, 2H, C^8H, C^7H), 1.79 – 1.66 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 27.27 min, t_R (gutxiengoa) = 32.89 min; *ee* = %97.



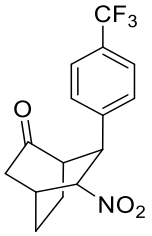


	RT	Altuera	Azalera	% Azal.
1	27.267	306776	18488030	52.79
2	32.887	266861	16536630	47.21

	RT	Altuera	Azalera	% Azal.
1	26.875	1977940	122981062	98.51
2	33.137	34568	1862527	1.49

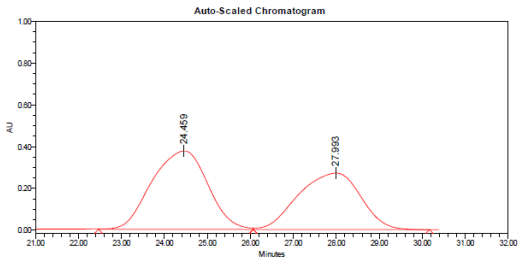


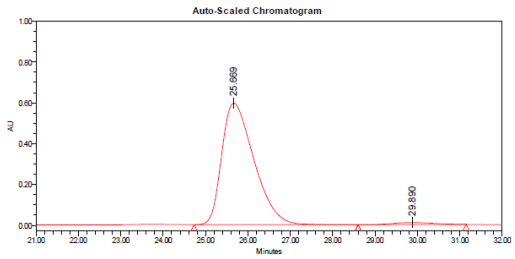
(1S,4S,5R,6S)-6-(4-fluorofenil)-5-nitrobiziklo[2.2.2]oktan-2-ona (*endo* **14aa**). Ziklohex-2-en-1-ona **13a** eta 4-fluoro-*trans*-β-nitroestireno **3a**-tik sortua, O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:1 Et_2O:Hexano nahasteaz purifikatua. Etekin globala: %65 (0.065 mmol, 17 mg), olio horia. Konfigurazio erlatiboa 6-(4-fluorofenil) ordezkatzaileak konfigurazio berbera izango duela suposatuz determinatu da. **FTIR** (neat, cm^{-1}) 2954, 2922, 1728, 1549, 1376. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.6, 5.3 Hz, 2H, ArH), 7.09 (t, *J* = 8.6 Hz, 2H, ArH), 5.03 (dt, *J* = 6.8, 1.9 Hz, 1H, C^5H), 4.07 (d, *J* = 6.8 Hz, 1H, C^6H), 3.02 (m, 1H, C^4H), 2.63 (dt, *J* = 19.5, 2.6 Hz, 1H, C^3H), 2.50 (d, *J* = 2.7 Hz, 1H, C^1H), 2.30 (ddd, *J* = 19.4, 3.0, 1.4 Hz, 1H, C^3H), 2.03 – 1.82 (m, 3H, C^8H, C^7H), 1.79 – 1.67 (m, 1H, C^7H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 211.41 (C=O), 163.61 (ArC), 133.57 (ArC), 129.12 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, ArC), 116.35 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, ArC), 88.11 (C^5), 48.91 (C^1), 42.04 (C^6), 38.66 (C^3), 34.80 (C^4), 24.10 (C^7), 16.86 (C^8). **^{19}F RMN** (376 MHz, $CDCl_3$) δ -114.23. **HRMS** (ESI) $C_{14}H_{15}FNO_3$: kalkulatua $[M+H]^+$: 264.1036, aurkitua 264.1033.



(1R,4R,5R,6S)-5-nitro-6-(4-(trifluorometil)fenil)biziklo[2.2.2]oktan-2-ona (*exo* **14ab**).[21] Ziklohex-2-en-1-ona **13a** eta 4-trifluorometil-*trans*-β-nitroestireno **3b**-tik sortua, O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %69 (0.069 mmol, 22 mg), solido hori argia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H, ArH), 7.25 (d, *J* = 9.0 Hz, 2H, ArH), 4.75 (dt, *J* = 6.8, 1.9 Hz, 1H, C^5H), 4.22 (dd, *J* = 6.7, 1.9 Hz, 1H, C^6H), 3.01 (q, *J* = 2.9 Hz, 1H, C^4H), 2.74 – 2.67 (m,

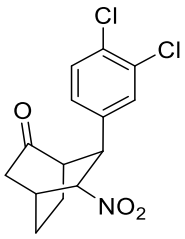
1H, C[1]H), 2.61 – 2.43 (m, 2H, C[3]H), 2.24 (ddt, *J* = 15.4, 12.0, 3.8 Hz, 1H, C[7]H), 1.96 (m, 2H, C[8]H, C[7]H), 1.82 – 1.68 (m, 1H, C[8]H). **HPLC** (Daicel Chiralcel OD-H, Hexano:[i]PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 24.46 min, t_R (gutxiengoa) = 27.99 min; *ee* = %96.



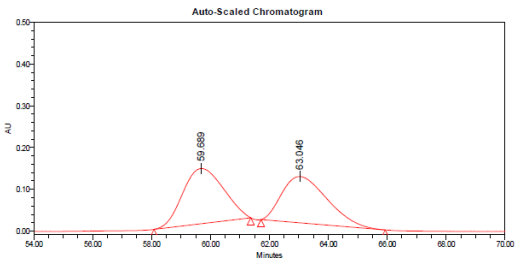


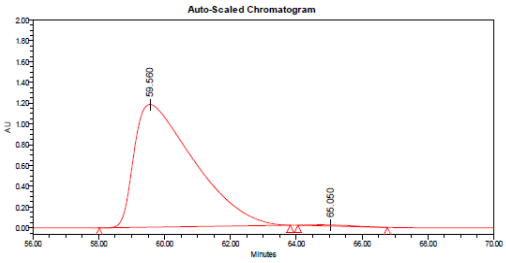
	RT	Altuera	Azalera	% Azal.
1	24.459	375823	33979448	55.53
2	27.993	270442	27209238	44.47

	RT	Altuera	Azalera	% Azal.
1	25.669	595616	31414153	97.89
2	29.890	10260	675897	2.11



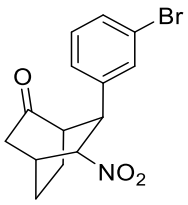
(1R,4R,5R,6S)-6-(3,4-diklorofenil)-5-nitrobiziklo[2.2.2]oktan-2-ona (*exo* **14ac**). Ziklohex-2-en-1-ona **13a** eta 3,4-dikloro-*trans*-β-nitroestireno **3c**-tik sortua, O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %54 (0.054 mmol, 17 mg), solido zuria. $\mathbf{u_p}$ = 97-99 °C. $[\alpha]_D^{25}$ = +14.34 (*c* 0.25, chloroform). **FTIR** (neat, cm^{-1}) 2952, 2922, 1726, 1547, 1372. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.3 Hz, 1H, ArH), 7.27 – 7.21 (m, 1H, ArH), 6.94 (d, *J* = 8.3, 1H, ArH), 4.70 (dt, *J* = 6.8, 2.0 Hz, 1H, C[5]H), 4.11 (dd, *J* = 6.7, 2.0 Hz, 1H, C[6]H), 3.00 (m, 1H, C[4]H), 2.65 (m, 1H, C[1]H), 2.54 – 2.45 (m, 2H, C[3]H), 2.20 (ddt, *J* = 15.5, 12.1, 4.0 Hz, 1H, C[7]H), 1.94 (m, 2H, C[8]H, C[7]H), 1.80 – 1.67 (m, 1H, C[8]H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 211.21 (C=O), 141.22(ArC), 133.50 (ArC), 132.26 (ArC), 131.32 (ArC), 129.32 (ArC), 126.23 (ArC), 90.76 (C[5]), 47.38 (C[1]), 44.29 (C[2]), 42.36 (C[3]), 34.34 (C[4]), 23.32 (C[7]), 18.25 (C[8]). **HRMS** (ESI) $C_{14}H_{14}Cl_2NO_3$: kalkulatua $[M+H]^+$: 314.0350, aurkitua 314.0352. **HPLC** (Daicel Chiralcel OD-H, Hexano:[i]PrOH = 97:3, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 59.56 min, t_R (gutxiengoa) = 63.05 min; *ee* = %98.



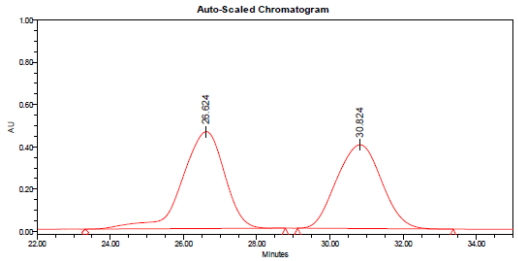


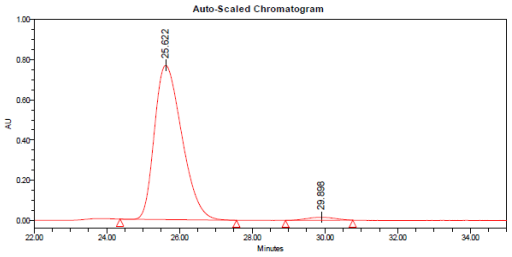
	RT	Altuera	Azalera	% Azal.
1	59.689	132215	12675573	51.61
2	63.046	110840	11884641	48.39

	RT	Altuera	Azalera	% Azal.
1	59.560	1181930	149171309	99.39
2	65.050	11071	921878	0.61



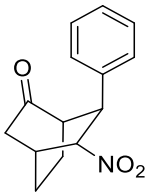
(1R,4R,5R,6S)-6-(3-bromofenil)-5-nitrobiziklo[2.2.2]oktan-2-ona (*exo* **14ad**).[21] Ziklohex-2-en-1-ona **13a** eta 3-bromo-*trans*-β-nitroestireno **3d**-tik sortua, O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %35 (0.035 mmol, 11 mg), olio horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 1H, ArH), 7.19 (t, *J* = 7.9 Hz, 2H, ArH), 7.05 – 7.00 (m, 1H, ArH), 4.76 (dt, *J* = 6.7, 2.2 Hz, 1H, C^5H), 4.12 (dd, *J* = 6.9, 1.9 Hz, 1H, C^6H), 3.00 – 2.94 (m, 1H, C^4H), 2.67 (q, *J* = 2.7 Hz, 1H, C^1H), 2.54 – 2.47 (m, 2H, C^3H), 2.20 (ddd, *J* = 12.0, 9.8, 5.7 Hz, 1H, C^7H), 1.99 – 1.86 (m, 2H, C^8H, C^7H, C^8H), 1.79 – 1.64 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 26.62 min, t_R (gutxiengoa) = 29.89 min; *ee* = %96.



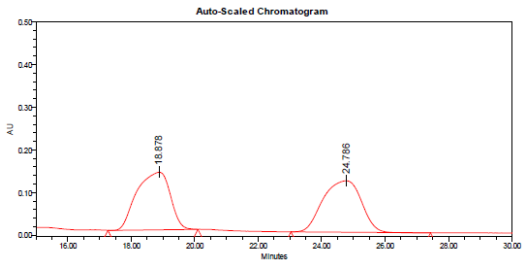


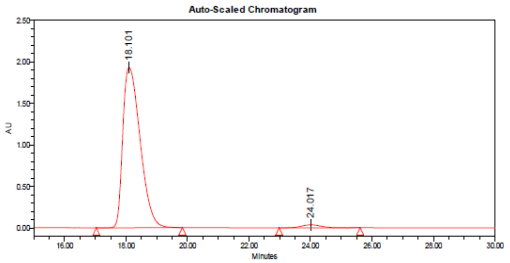
	RT	Altuera	Azalera	% Azal.
1	26.624	458222	36838878	52.12
2	30.824	396517	33846539	47.88

	RT	Altuera	Azalera	% Azal.
1	25.622	766310	40073467	98.00
2	29.898	15133	816303	2.00



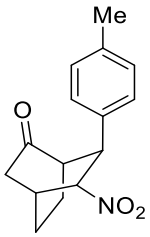
(1R,4R,5R,6S)-5-nitro-6-fenilbiziklo[2.2.2]oktan-2-ona (*exo* **14ae**).[21] Ziklohex-2-en-1-ona **13a** eta *trans*-β-nitroestireno **3e**-tik sortua, O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala: %61 (0.061 mmol, 15 mg), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.2, 6.4 Hz, 2H, ArH), 7.27 (d, *J* = 4.9 Hz, 1H, ArH), 7.10 (dd, *J* = 7.2, 1.8 Hz, 2H, ArH), 4.82 (dt, *J* = 6.8, 2.0 Hz, 1H, C^5H), 4.17 – 4.14 (m, 1H, C^6H), 2.97 (q, *J* = 2.9 Hz, 1H, C^4H), 2.69 (q, *J* = 2.7 Hz, 1H, C^1H), 2.50 (t, *J* = 2.9 Hz, 2H, C^3H), 2.28 – 2.16 (m, 1H, C^7H), 1.94 (m, 2H, C^8H, C^7H), 1.78 – 1.65 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 18.88 min, t_R (gutxiengoa) = 24.78 min; *ee* = %95.



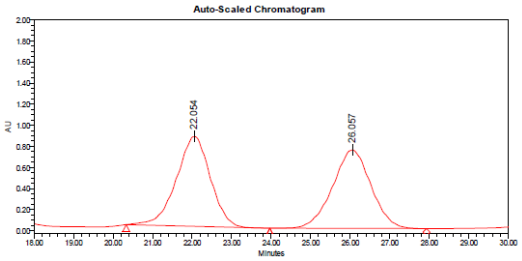


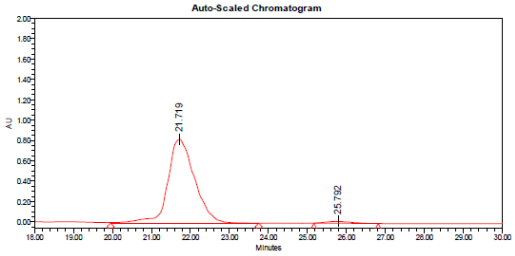
	RT	Altuera	Azalera	% Azal.
1	18.878	134853	9873186	49.37
2	24.786	120519	10126261	50.63

	RT	Altuera	Azalera	% Azal.
1	18.101	1928524	75291805	97.86
2	24.017	37080	1649011	2.14



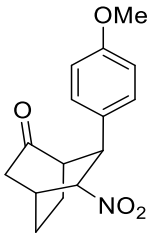
(1R,4R,5R,6S)-5-nitro-6-(p-tolil)biziklo[2.2.2]oktan-2-ona (*exo* **14af**).[21] Ziklohex-2-en-1-ona **13a** eta 4-metil-*trans*-β-nitroestireno **3e**-tik sortua O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekin globala %51 (0.051 mmol, 13 mg), solido marroi argia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.9 Hz, 2H, ArH), 6.98 (d, *J* = 8.0 Hz, 2H, ArH), 4.80 (ddd, *J* = 6.6, 2.6, 1.6 Hz, 1H, C^5H), 4.10 (dd, *J* = 6.6, 2.0 Hz, 1H, C^6H), 2.96 (q, *J* = 2.9 Hz, 1H, C^4H), 2.66 (q, *J* = 2.7 Hz, 1H, C^1H), 2.49 (t, *J* = 2.6 Hz, 2H, C^3H), 2.26 – 2.15 (m, 1H, C^7H), 1.94 (m, 2H, C^8H, C^7H), 1.75 – 1.65 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 22.05 min, t_R (gutxiengoa) = 26.06 min; *ee* = %96.



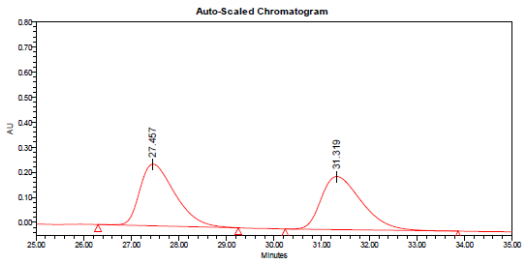


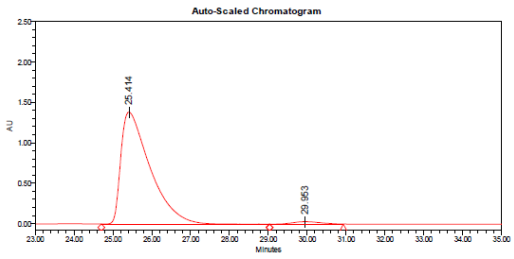
	RT	Altuera	Azalera	% Azal.
1	22.054	851369	50932534	50.38
2	26.057	742378	50160382	49.62

	RT	Altuera	Azalera	% Azal.
1	27.719	826251	35981800	98.02
2	25.792	17882	800543	1.98



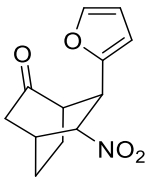
(1R,4R,5R,6S)-6-(4-metoxifenil)-5-nitrobiziklo[2.2.2]oktan-2-ona (*exo* **14ag**).[21] Ziklohex-2-en-1-ona **13a** eta 4-metoxi-*trans*-β-nitroestireno **3e**-tik sortua O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala %47 (0.047 mmol, 13 mg), solido horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.5 Hz, 2H, ArH), 6.85 – 6.78 (m, 2H, ArH), 4.77 (dt, *J* = 6.8, 2.0 Hz, 1H, C^5H), 4.08 (dd, *J* = 6.6, 2.1 Hz, 1H, C^6H), 3.77 (s, 3H, OCH_3), 2.95 (m, 1H, C^4H), 2.65 (d, *J* = 2.7 Hz, 1H, C^1H), 2.48 (q, *J* = 2.9, 2.5 Hz, 2H, C^3H), 2.25 – 2.15 (m, 1H, C^7H), 1.93 (m, 2H, C^8H, C^7H), 1.69 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 27.46 min, t_R (gutxiengoa) = 31.32 min; *ee* = %96.



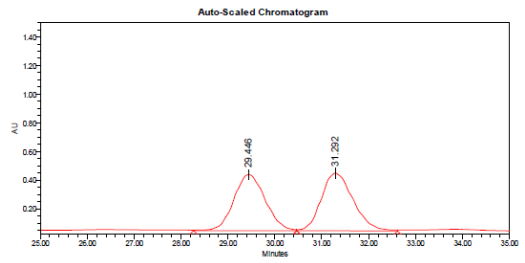


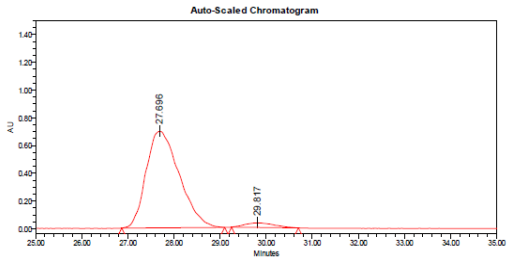
	RT	Altuera	Azalera	% Azal.
1	27.457	246156	12614583	50.27
2	31.319	211837	12477653	49.73

	RT	Altuera	Azalera	% Azal.
1	25.414	1384193	72089543	98.08
2	29.953	29197	1411362	1.92



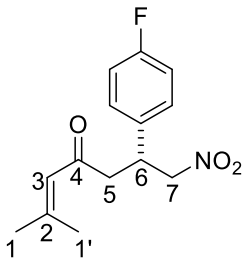
(1R,4R,5R,6R)-6-(furan-2-il)-5-nitrobiziklo[2.2.2]oktan-2-ona (*exo* **14ah**).[21] Ziklohex-2-en-1-ona **13a** eta 2-(2-nitrobinil)-*trans*-β-nitroestireno **3h**-tik sortua O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:3 EtOAc:Hexano nahasteaz purifikatua. Etekin globala %47 (0.047 mmol, 13 mg), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.8 Hz, 1H, ArH), 6.27 (dd, *J* = 3.3, 1.9 Hz, 1H, ArH), 6.12 (d, *J* = 3.3 Hz, 1H, ArH), 4.93 (ddd, *J* = 5.0, 3.1, 1.6 Hz, 1H, C^5H), 4.27 (dd, *J* = 5.3, 2.5 Hz, 1H, C^6H), 2.98 (m, 1H, C^4H), 2.70 (m, 1H, C^1H), 2.46 (m, 2H, C^3H), 2.15 (m, 1H, C^7H), 1.98 – 1.87 (m, 1H, C^8H), 1.85 – 1.77 (m, 1H, C^7H), 1.71 – 1.59 (m, 1H, C^8H). **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 208 nm), t_R (nagusia) = 29.44 min, t_R (gutxiengoa) = 31.92 min; *ee* = %92.



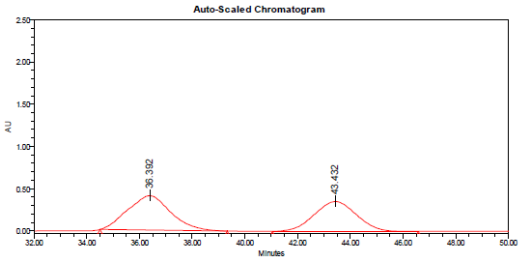


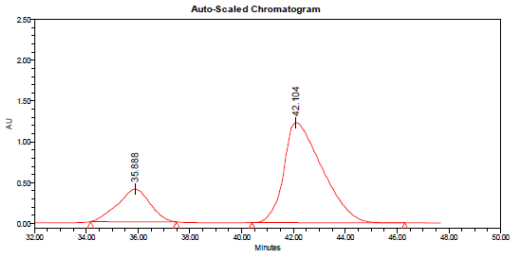
	RT	Altuera	Azalera	% Azal.
1	29.446	390077	18182703	48.96
2	31.292	402436	18956219	51.04

	RT	Altuera	Azalera	% Azal.
1	27.696	697090	34869229	96.02
2	29.817	32565	1444197	3.98



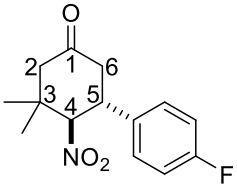
(R)-6-(4-fluorofenil)-2-metil-7-nitrohept-2-en-4-ona (**24aa**). 4-metilpent-3-en-2-ona **16a** eta 4-fluoro-*trans*-β-nitroestireno **3a**-tik sortua, 25:75 **24aa:25aa** erlazioan O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. Konfigurazio erlatiboa *exo*-**17ba**-ren konfigurazio absolutua kontuan hartuta determinatu da. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina %12 (0.012 mmol, 4 mg), olio horia. $[\alpha]_D^{25}$ = -16.27 (*c* 0.15, kloroformoa). **FTIR** (neat, cm^{-1}) 2919, 2850, 1684, 1551, 1377. **^{1}H RMN** (500 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H, ArH), 7.00 (t, *J* = 8.6 Hz, 2H, ArH), 6.04 – 5.98 (m, 1H, C^3H), 4.72 (dd, *J* = 12.4, 6.3 Hz, 1H, C^7H), 4.56 (dd, *J* = 12.4, 8.4 Hz, 1H, C^7H), 4.04 (dd, *J* = 8.1, 6.5 Hz, 1H, C^6H), 2.84 (d, *J* = 7.1 Hz, 2H, C^5H), 2.11 (d, *J* = 1.1 Hz, 3H, CH_3^1), 1.88 (d, *J* = 1.3 Hz, 3H, $CH_3^{1'}$). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 196.79 (C=O), 162.30 (d, $^1J_{C\text{-}F}$ = 246.7 Hz, ArC), 157.75 (C^2), 135.15 (ArC), 129.21 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, ArC), 123.30 (ArC), 116.03 (d, $^2J_{C\text{-}F}$ = 21.5 Hz, ArC), 79.83 (C^7), 46.82 (C^5), 38.83 (C^6), 27.91 (CH_3^1), 21.11 ($CH_3^{1'}$). **^{19}F RMN** (376 MHz, $CDCl_3$) δ -114.50. **HRMS** (ESI) $C_{14}H_{16}FNO_3$: kalkulatua $[M+H]^+$: 266.1192, aurkitua 266.1180. **HPLC** (Daicel Chiralcel OJ-H, Hexano:^{i}PrOH = 90:10, fluxua 1 mL/min, λ = 214 nm), t_R (gutxiengoa) = 36.39 min, t_R (nagusia) = 43.43 min; *ee* = %56.





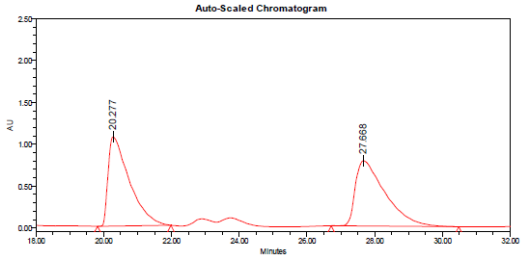
	RT	Altuera	Azalera	% Azal.
1	36.392	406723	46092564	54.00
2	43.432	353504	39263108	46.00

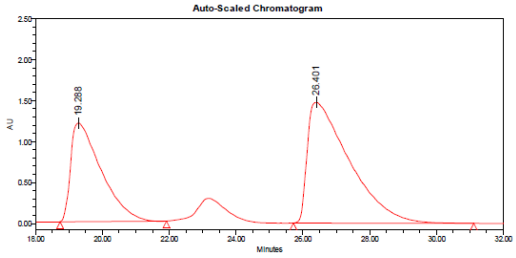
	RT	Altuera	Azalera	% Azal.
1	35.888	399679	34853246	21.68
2	42.104	1224821	125894204	78.32



(4R,5R)-5-(4-fluorofenil)-3,3-dimetil-4-nitroziklohexan-1-ona (**25aa**). 4-metilpent-3-en-2-ona **16a** eta 4-fluoro-*trans*-β-nitroestirenoa **3a**-tik sortua, 25:75 **25aa:26aa** erlazioan O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. Konfigurazio erlatiboa *exo*-**17ba**-ren konfigurazio absolutua kontuan hartuta determinatu da. 1:2 EtOAc:Hexano nahasteaz purifikatua. Etekina %58 (0.058 mmol, 15 mg), olio horia.

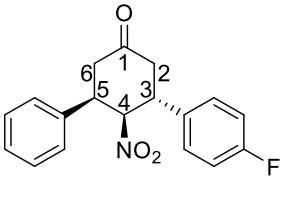
$[\alpha]_D^{25}$ = -23.82 (*c* 0.17, kloroformoa). **FTIR** (neat, cm^{-1}) 3054, 2969, 1721, 1551, 1378. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H, ArH), 7.03 (t, *J* = 8.5 Hz, 2H, ArH), 4.98 (d, *J* = 12.0 Hz, 1H, C^5H), 3.77 (td, *J* = 12.5, 5.4 Hz, 1H, C^4H), 2.67 (ddd, *J* = 15.1, 5.7, 2.3 Hz, 1H, C^6H), 2.55 (d, *J* = 14.6 Hz, 2H, C^6H, C^2H), 2.38 (dd, *J* = 14.2, 2.3 Hz, 1H, C^2H), 1.23 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 204.98 (C=O), 162.50 (d, $^1J_{C\text{-}F}$ = 247.7 Hz, ArC), 134.02 (ArC), 128.99 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, ArC), 116.33 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, ArC), 97.19 (C^4H), 53.99 (C^2), 47.00 (C^6), 42.66 (C^5), 38.55 (C^3), 28.88 (CH_3), 21.11 (CH_3). **^{19}F RMN** (376 MHz, $CDCl_3$) δ -113.59. **HRMS** (ESI) $C_{14}H_{16}FNO_3$: kalkulatua $[M+H]^+$: 266.1192, aurkitua 266.1189. **HPLC** (Daicel Chiralcel OJ-H, Hexano:^{i}PrOH = 80:20, fluxua 1 mL/min, λ = 214 nm), t_R (gutxiengoa) = 20.28 min, t_R (nagusia) = 27.69 min; *ee* = %26.





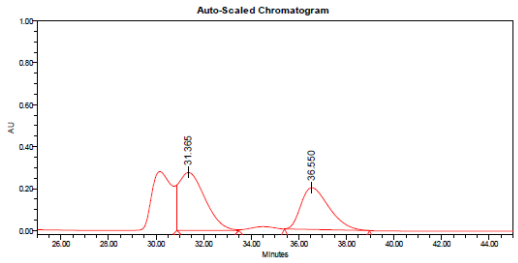
	RT	Altuera	Azalera	% Azal.
1	20.277	1069723	46539641	49.44
2	27.688	778829	47589034	50.56

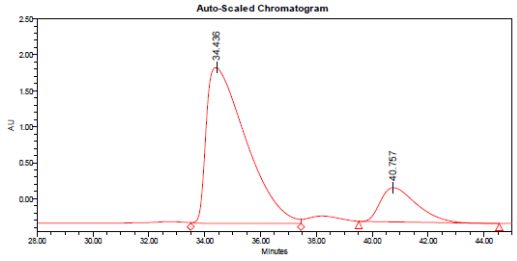
	RT	Altuera	Azalera	% Azal.
1	19.288	1204525	76292498	37.13
2	26.401	1474496	129174876	62.87



(3R,4S,5R)-3-(4-fluorofenil)-4-nitro-5-fenilziklohexan-1-ona (*endo* **17ba**). (*E*)-4-fenilbut-3-en-2-one **16b** eta 4-fluoro-*trans*-β-nitroestireno **3a**-tik sortua, 83:17 ***endo/exo*** erlazioan O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:1 Et_2O:Hexano nahasteaz purifikatua. Etekin globala %34 (0.034 mmol, 11 mg), olio horia. $[\alpha]_D^{25}$ = +15.97 (*c* 0.30, kloroformoa). **FTIR** (neat, cm^{-1}) 3054, 2987, 1715, 1551, 1263. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 3H, ArH), 7.27 – 7.16 (m, 3H, ArH), 7.06 (m, 3H, ArH), 5.25 (dd, *J* = 7.5, 4.9 Hz, 1H, C^4H), 3.91 (td, *J* = 8.3, 6.1 Hz, 1H, C^3H), 3.80 (dt, *J* = 8.9, 5.3 Hz, 1H, C^5H), 3.30 (ddd, *J* = 16.0, 8.7, 1.3 Hz, 1H, C^6H), 3.04 (ddd, *J* = 16.3, 5.9, 1.3 Hz, 1H, C^2H), 2.86 (dd, *J* = 16.1, 5.7 Hz, 1H, C^2H), 2.79 (dd, *J* = 16.3, 8.8 Hz, 1H, C^6H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 207.34 (C=O), 162.39 (d, $^1J_{C\text{-}F}$ = 247.8 Hz, ArC), 136.77 (ArC), 135.21 (ArC), 129.16 (ArC), 129.03 (ArC), 128.61 (ArC), 127.74

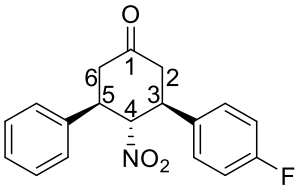
(ArC), 116.44 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz, ArC), 91.62 (C^4), 43.70 (C^6), 42.44 (C^3), 42.12 (C^2), 41.84 (C^5). **^{19}F RMN** (471 MHz, $CDCl_3$) δ -113.64. **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 80:20, fluxua 1 mL/min, λ = 214 nm), t_R (nagusia) = 31.37 min, t_R (gutxiengoa) = 36.55 min; *ee* = %66.



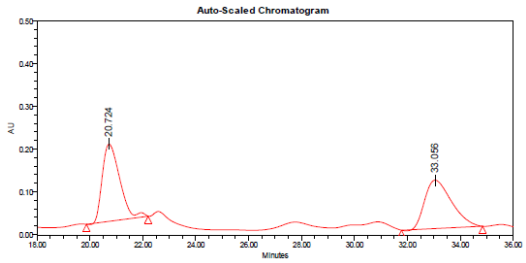


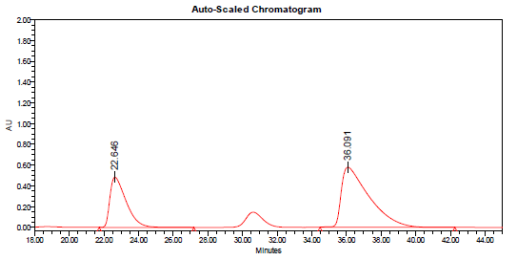
	RT	Altuera	Azalera	% Azal.
1	31.365	275976	20751888	56.02
2	36.550	198730	16289840	43.98

	RT	Altuera	Azalera	% Azal.
1	34.436	2164562	213252378	83.30
2	40.757	476014	42743019	16.70



(3S,4R,5R)-3-(4-fluorofenil)-4-nitro-5-fenilziklohexan-1-ona (*exo* **17ba**). (*E*)-4-fenilbut-3-en-2-one **16b** eta 4-fluoro-*trans*-β-nitroestireno **3a**-tik sortua, 83:17 ***endo/exo*** erlazioan O_2N-X_L-X_L^{Me}-OMe-**50** katalizatzaile gisa erabiliz. 1:1 Et_2O:Hexano nahasteaz purifikatua. Etekin globala %34 (0.034 mmol, 11 mg), olio horia. $[\alpha]_D^{25}$ = +15.97 (*c* 0.35, kloroformoa). **FTIR** (neat, cm^{-1}) 3021, 2965, 1720, 1552, 1235. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.34 (m, 3H, ArH), 7.28 – 7.19 (m, 4H, ArH), 7.04 (t, *J* = 8.6 Hz, 2H, ArH), 5.17 (t, *J* = 11.2 Hz, 1H, C^4H), 3.69 (m, 2H, C^3H, C^5H), 2.89 – 2.73 (m, 4H, C^2H, C^6H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 204.16 (C=O), 162.69 (d, $^{1}J_{C\text{-}F}$ = 247.9 Hz, ArC), 137.36 (ArC), 133.28 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 129.46 (ArC), 128.86 (ArC), 128.77 (ArC), 128.74 (ArC), 127.09 (ArC), 116.45 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, ArC), 94.67 (C^4), 47.65 (C^3), 47.03 (C^5), 46.43 (C^6), 46.38 (C^2). **^{19}F RMN** (471 MHz, $CDCl_3$) δ -113.04. **HPLC** (Daicel Chiralcel OD-H, Hexano:^{i}PrOH = 80:20, fluxua 1 mL/min, λ = 214 nm), t_R (gutxiengoa) = 20.72 min, t_R (nagusia) = 33.06 min; *ee* = %35.





	RT	Altuera	Azalera	% Azal.
1	20.724	180924	8293293	50.80
2	33.056	113422	8031357	49.20

	RT	Altuera	Azalera	% Azal.
1	22.646	482299	31309587	32.82
2	36.091	576223	64087010	67.18

Xehetasun konputazionalak

Potentzial gainazaleko puntu geldikor guztiak B3LYP dentsitate funtzional hibrido eta 6-31G(d) basearekin optimizatu ziren. Analisi harmonikoak teoria maila berberean gauzatu ziren puntu geldikorren izaera baieztatzeko (trantsizio egoera edo minimoa), baita 298 K-ko entalpia eta energia askeko ekarpen termodinamikoak emateko ere. Erreakzio koordenatuen kalkulu intrintsekoak burutu ziren gainera, trantsizio egoerak erreakzio koordenatuko erreaktibo eta produktuekin konektatzen zutela ziurtatzeko. Amaierako energiak lortzeko, B3LYP metodoan optimizatutako geometriei kalkulu puntualak burutu zitzaizkien M06-2X funtzional eta 6-31G(d) basearekin

B ATALA

Ikerketa Estekiometrikoak

4. Kapitulua

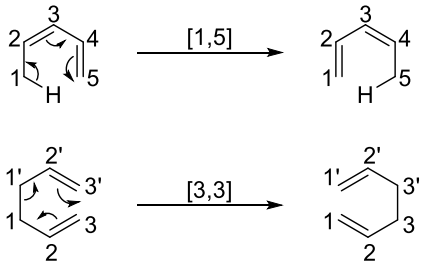
Karbamato Alilikoen 1,3-Dioxa-[3,3]-Berrantolaketa Sigmatropikoa: Erreakzio Ahalmena eta Azterketa Mekanistikoak

Abstract: An unexpected 1,3-dioxa-[3,3]-sigmatropic rearrangement during the treatment of aryl- and alkenyl-substituted allyl alcohols with activated isocyanates is reported. The reorganization of bonds is highly dependent on the electron density of the aromatic ring and the nature of the isocyanate used. This metal-free tandem reaction from branched allyl alcohols initiated by a carbamoylation reaction and followed by a sigmatropic rearrangement thus offers a new access to (*E*)-cinnamyl and conjugated (*E*,*E*)-diene carbamates such as *N*-acyl and *N*-sulfonyl derivatives. A computational study was conducted in order to rationalise this phenomenon as well as a kinetic analysis of the rearrangement progress.

Kapitulu hau artikulo bezala argitaratu da: Agirre, M.; Henrion, S.; Rivilla, I.; Miranda, J. I.; Cossío, F. P.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. *J. Org. Chem*. **2018**, *83*, 14861-14881.

4.1 BERRANTOLAKETA SIGMATROPIKOAK. SARRERA

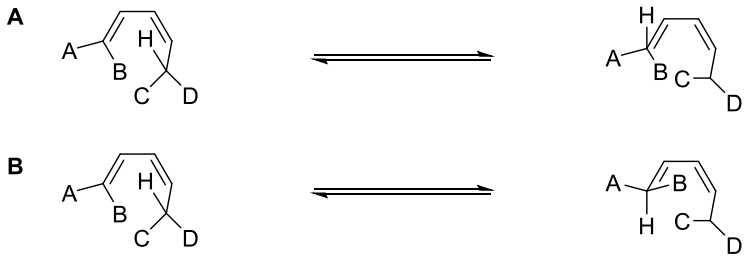
Berrantolaketa sigmatropikoak orbital simetriaz arauturiko erreakzio periziklikoak dira. Bertan, molekula bateko atomo batek edo atomo sorta batek molekula berdineko beste atomo batera migratzen du.[1] σ eta π loturen kantitateak ez du aldaketarik jasaten, azkenak prozesuan zehar berriro antolatuz. Gainera, [*i*,*j*] ordenak π sisteman eta migratzen duen atalean dauden atomo kantitatea zehazten du. Irudizko adieran, ordenak σ loturak lotura berria sortzeko zeharkatzen dituen atomoak zenbatzen ditu (**4.1 Irudia**).[2]



4.1 Irudia. Hidrogenoaren eta alil taldearen [3,3]-berrantolaketa sigmatropikoak.

Prozesu hauen izaera kontzertatua kontuan hartuta, berrantolaketa sigmatropikoak regio- eta estereoselektiboki jazotzen dira. Hala ere, badaude artekari ioniko edo erradikalen bidez gertatzen diren erreakzioak ere.[3] Woordward eta Hoffmanen ikerketen aburuz, erreakzioaren estereokimika eta erraztasuna zehazten duten bi topologia desberdin daude berrantolaketa sigmatropikoetan.[4] Prozesu suprafazialean, transferitzen den taldea π sistemaren aurpegi berari lotua geratzen da. Prozesu antarafazialean berriz, talde migratzailea π sistemaren aurkako aurpegira mugitzen da (**4.2 Irudia**).[5]

[1] a) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH: Weinheim, **2005**. b) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res*. **1968**, *1*, 17-22.
[2] Smith, M. B.; March, J. *March's Advanced Organic Chemistry. Reactions, Mechanisms and Structure, 5th Ed*. Wiley & Sons, New York, **2001**.
[3] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: London, **1976**.
[4] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, 5th Ed. Part A: Structure and Mechanisms,* Springer: New York, **2007**.
[5] Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511-2513.



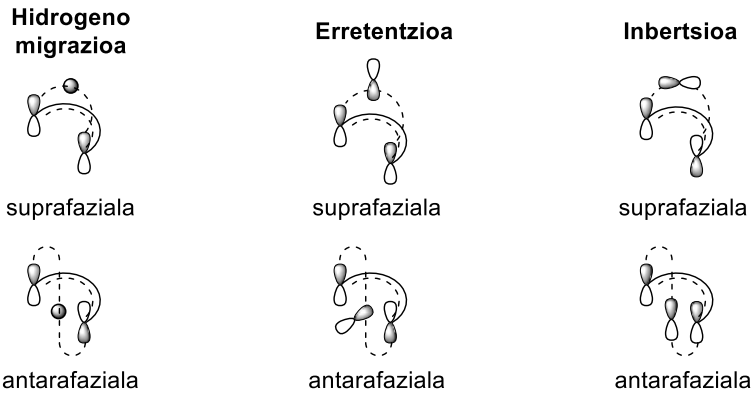
4.2 Irudia. Woodward eta Hoffmann-ek deskribaturiko [1,5] hidrogeno berrantolaketa A) suprafazial eta B) antarafaziala.

Hurrenkera alternatiboak ere badaude berrantolaketa hauek deskribatzeko. Hückel eta Möbiusek burututako orbital atomikoen sailkapenak prozesuan parte hartzen duten elektroiak kontuan hartzen ditu trantsizio egoera aromatikoa edo antiaromatikoa den zehazteko.[6] Migratzen duen taldea π orbitala eskuragai duen alilo taldea bada, beste aldaera bat ere kontuan hartu behar da: honek, hasierako konfigurazioa mantendu dezake, edo inbertsioa jasan. Kasu partikular honetako ezaugarri estereokimikoek, era berean, Woodward eta Hoffmanek deskribaturiko simetria arauak jarraitzen dituzte (**4.1 Taula** eta **4.3 Irudia**).[7]

4.1 Taula. Berrantolaketa sigmatropikoetarako Woodward-Hoffman arauak.

	Modu onartuak			
Elektroi kantitatea	**Erretentzioa edo hidrogeno migrazioa**		**Inbertsioa**	
	Termikoa	Fotokimikoa	Termikoa	Fotokimikoa
4n	antarafaziala	suprafaziala	suprafaziala	antarafaziala
4n+2	suprafaziala	antarafaziala	antarafaziala	suprafaziala

[6] a) Schleyer, P. v.; Wu, J. I.: Cossío, F. P.; Fernández, I. *Chem. Soc. Rev*. **2014**, *43*, 4909-4921. b) Zimmerman, H. E.; Marchand, A. P.; Lehr, R. E. *Pericyclic Reactions, Vol. 2*, Academic Press: New York, **1977**. c) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 761-776.
[7] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Verlag Chemie: Weinheim, **1970**.



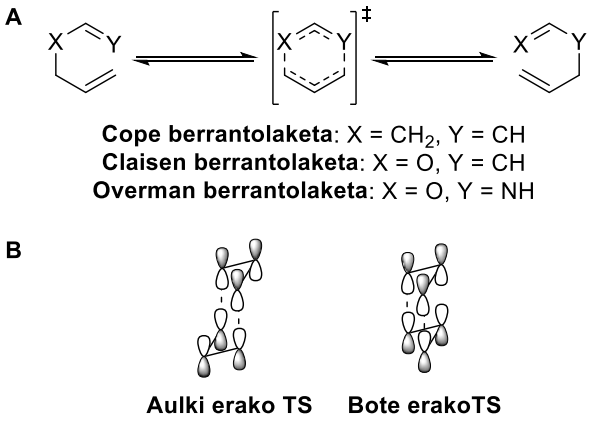
4.1 Irudia. Hidrogeno [1,j]-berrantolaketa sigmatropikoekin erlazionaturiko topologia supra- eta antarafazialak

4.1.1 [3,3]-berrantolaketa sigmatropikoak

Berrantolaketa sigmatropikoen artean, [3,3]-erreakzio sigmatropikoak 1,5-dieno eta konposatu γ,δ-asegabe edo antzekoen sintesirako prozedura erabilgarri dira. Azken urteotan, [3,3]-berrantolaketa sigmatropikoek aplikagarritasun izugarria izan dute produktu natural konplexu zein sendagaien sintesian. [3,3]-berrantolaketa sigmatropiko asko ezagutzen dira.[8] Hauen artean, karbono-karbono lotura berrien sorrerarako Cope eta Claisen erreakzioak gailentzen dira. Karbono-heteroatomo loturen sintesirako Overman berrantolaketa goraipatu behar da, bestalde (**4.1A Eskema**).[9]

Prozedura hauen ezaugarri nagusiena sei-osagaiko eta ordenamendu altuko trantsizio egoeren formazioa da, non aldarapen interakzioak minimizatzen diren. Orokorrean, trantsizio egoera ziklikoak aulki-erako konformazioa hartzen du, baina bote-erako konformazioa hartzea ere posible da (**4.1B Eskema**).[4]

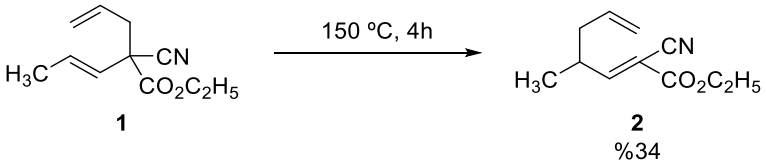
[8] Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev*. **2009**, *38*, 3133-3148.
[9] Wang, Z. *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons: Hoboken, **2010**.



4.1 Eskema. A) [3,3] berrantolaketa orokorrak. B) Trantsizio egoeren aulki eta bote erako supra-supra egiturak.

4.1.1.1 Cope eta Claisen berrantolaketak

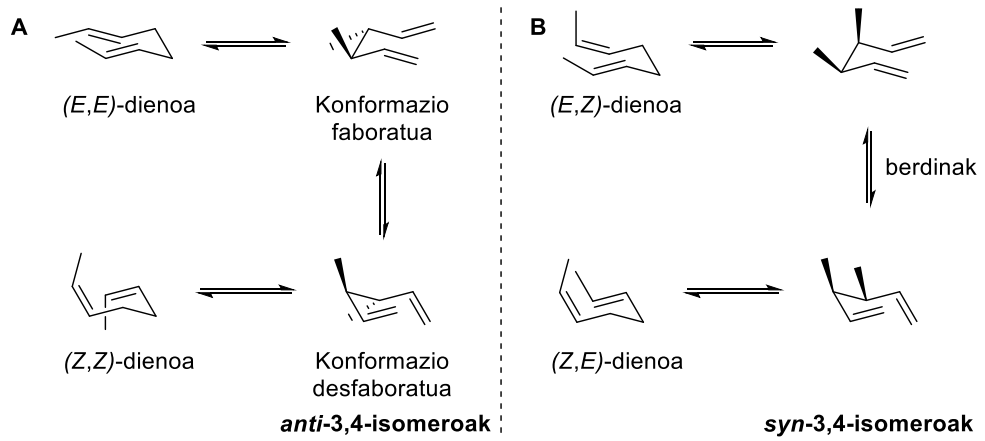
1,5-hexadienoen Cope berrantolaketa termikoa Arthur Cope-k deskribatu zuen 1940an.[10] Bertan, **1** esterrak bere isomeroa den **2** produktua erdiesten zuen, 150 ºC-tan berotzean (**4.2 Eskema**).



4.2 Eskema. Copek deskribatutako **1** 1,5-hexadienoaren [3,3]-berrantolaketa sigmatropikoa.

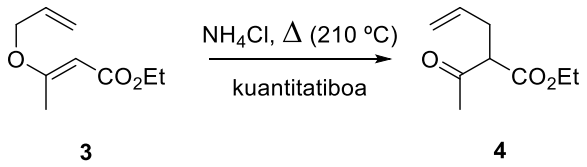
Cope berrantolaketa estereoespezifikoa eta estereoselektiboa da. Honenbestez, trantsizio egoeran bi lotura bikoitzen (*Z*)- edo (*E*)- konfigurazioa mantendu egiten da.[11] Aulki-erako trantsizio egoera faboratzen denean, (*E*,*E*)- eta (*Z*,*Z*)- dienoek *anti*-3,4-diastereoisomeroak sortzen dituzte. (*E*,*Z*)- eta (Z,*E*) dienoek, ordea, *sin*-3,4-produktuen sorrera bultzatzen dute (**4.3 Eskema**). Erreakzioa estereoselektiboa da ere sortzen den lotura berriarekiko, (*E*)- antolamendua nagusituz. Hasierako erreaktiboak enantiomero bakarrekoak diren kasurako, estereoespezifikotasunak informazio kirala mantentzen dela agintzen du.[12]

[10] Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc*. **1940**, *62*, 441-444.
[11] Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67-74.
[12] Hill, R. K.; Gilman, N. W. *Chem. Commun*. **1967**, 619-620.



4.3 Eskema. Cope berrantolaketen arau estereokimikoak. A) (*E*,*E*)- eta (*Z*,*Z*)- dienoak. B) (*E*,*Z*)- eta (*Z*,*E*)-dienoak.

Claisen berrantolaketa, bestalde, alil binil eterren [3,3]-berrantolaketa sigmatropiko termikoa da. 1912an Ludwig Claisenek aurkitu zuen, **3** etil azetoazetato *O*-alilatua NH_4Cl-ren presentzian destilatzerako garaian *C*-alilo isomero **4**-an berrantolatzen zela ikustean (**4.4 Eskema**).[13] Hau, [3,3]-berrantolaketen artean metodologia erabili eta ikertuena da, alil binil sistemen sorrera erraza eta amaierako produktuaren formazio itzulezina direla medio.[14] Izatez, Claisen berrantolaketa ez da hertsiki itzulezina, baina erreakzio orekek karbonilo-erako produktuen formaziora jo ohi dute.[15]



4.4 Eskema. Claisenek argitaratutako **3** alil binil eterraren [3,3]-berrantolaketa sigmatropikoa.

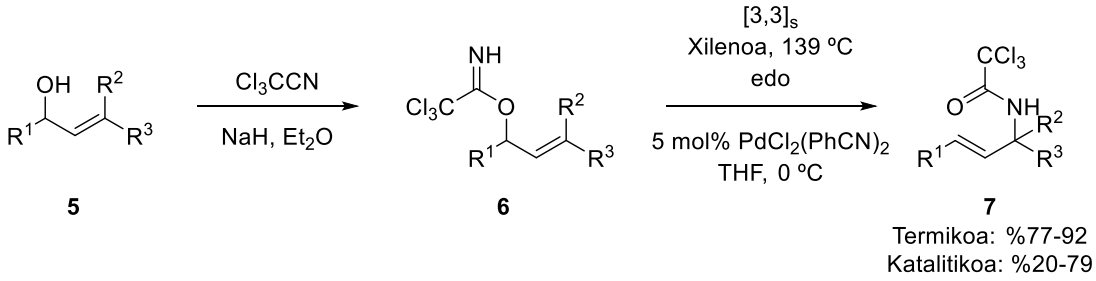
Erreakzio honen izaera estereokimikoa Cope berrantolaketarentzat deskribaturiko ezaugarriekin estuki erlazionaturik dago. Gainera, heteroatomoaren presentziak Claisen berrantolaketa metodologia interesgarriagoa bihurtzen du analogo den Cope erreakzioarekin alderatuz, transformazio kimiko gehiagorako sarbide baita. Erreakzioa substratu gehiagotara zabaltzeko saiakuntzek berrantolaketa bertsio desberdinen

[13] Claisen, L. *Chem. Ber*. **1912**, *45*, 3157-3166.
[14] Nubbemeyer, U. *Synthesis* **2003**, 961-1008.
[15] Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2014**, *53*, 2556-2591.

garapena bultzatu du.[16] Hauen artean, Carrol[17], Eschenmoser[18], Johnson[19], Ireland-Claisen[20] eta Reformatsky-Claisen[21] berrantolaketak aurki daitezke.

4.1.1.2 Overman berrantolaketa

Overman berrantolaketa karbono-nitrogeno loturak sortzeko bide sintetiko erabilgarria da, alkohol alilikoetatik alil amida deribatuak sintetizatzea ahalbidetzen duelarik.[22] Erreakzio hau Hg(II) edo Pd(II) bidez gauzatutako trikloroazetimidato **5**-en berrantolaketa termiko bezala deskribatu zen (**4.5 Eskema**).[23] Normalean, disolbatzaile lehor eta ez-nukleozaleekin egiten da lan, trikloroazetimidato artekarien hidrolisia ekiditeko.[9] Erreakzioa eragozpen esteriko handia duten alil amidak sintetizatzeko bereziki erabilgarria da, beste metodologia sintetiko bidezko sorrerak arazo ugari izan ohi baitituzte.



4.5 Eskema. Trikloroazetimidatetik trikloroazetamidetarako Overman berrantolaketa.

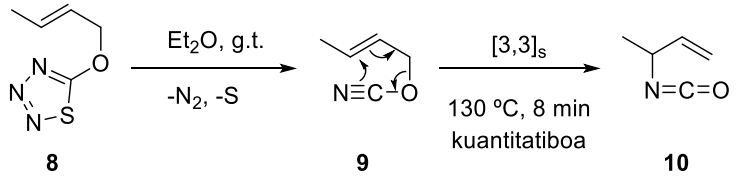
Erreakzio honen bertsio enantioselektiboa 2004an deskribatu zen lehenengoz.[24] Bertsio honen garapenak alil amina funtzionalizazioa produktu naturaletan sartzea

Review zabala ikuskatzeko: Martín Castro, A. M. *Chem. Rev*. **2004**, *104*, 2939-3002.
[17] a) Carroll, M. F. *J. Chem. Soc*. **1940**, 704-706. b) Carrol, M. F. *J. Chem. Soc*. *Chem. Commun*. **1941**, 507-511.
[18] a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425-2429. b) Wick, A. E.; Felix, D.; Gschwend-Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030-1042.
[19] Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
[20] a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc*. **1972**, *94*, 5897-5898. b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1976**, *98*, 2868-2877.
[21] Baldwin, J. E.; Walker, J. A. *J. Chem. Soc., Chem. Commun*. **1973**, 116-117.
[22] Fernandes, R. A.; Kattanguru, P.; Gholap, S. P.; Chaudhari, D. A. *Org. Biomol. Chem*. **2017**, *15*, 2672-2710.
[23] a) Overman, L. E. *J. Am. Chem. Soc*. **1974**, *96*, 597-599. b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579-586. c) Overman, L. E. *J. Am. Chem. Soc*. **1976**, *98*, 2901-2910. d) Overman, L. E. *Acc. Chem. Res*. **1980**, *13*, 218-224.
[24] a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412-12413. b) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett*. **2003**, *5*, 1809-1812. c) Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem*. **2004,** 69, 8101-8104.

ahalbidetzen duen prozedura sintetiko leun eta selektiboen inplementazioa bultzatu zuen.[25]

4.1.1.3 Alil zianato/isozianato berrantolaketa

Berrantolaketa hau Overman berrantolaketaren ordezko metodologia kontsidera daiteke, erreakzio baldintza leunagoak galdatzen baititu. 1970. urtean deskubritu zen, non alil tiatriazol **8**-ak **10** alil isozianatoa erdiesten zuen giro tenperaturan, retro-[3+2]/[3,3] erako berrantolaketa jarraituz (**4.6 Eskema**).[26] Metodologia honen muga esanguratsuena **9** alil zianato artekariaren sorrera eta ezegonkortasuna ziren.

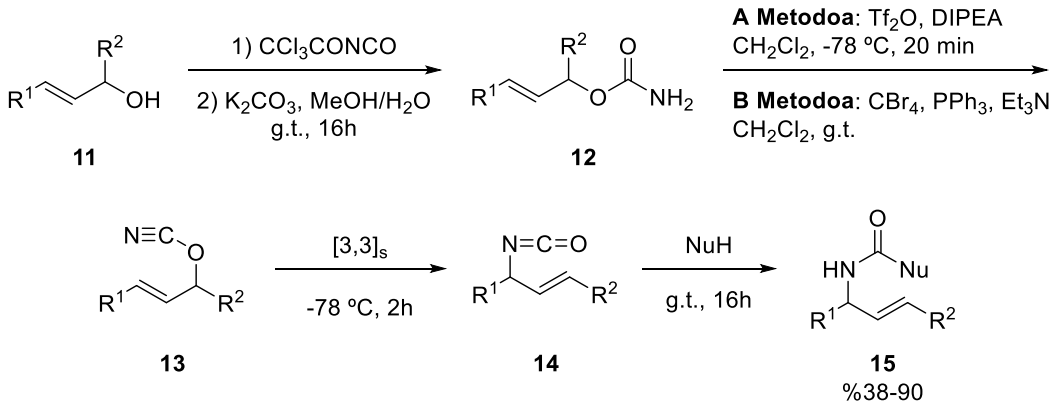


4.6 Eskema. Holmek deskribaturiko alil zianato/isozianato berrantolaketa.

Ichikawaren ikerketa taldeak deshidratazio/berrantolaketa sigmatropiko sekuentzia aplikatu zuen muga hau gainditzeko (**4.7 Eskema**).[27] Autore hauek erreakzioak sei-osagaiko trantsizio egoera bidez gauzatzen zirela ere frogatu zuten, *E*-konfigurazioko produktuen formazio esklusiboa jazoz. Gainera, alil zianato kiralekin egindako kiralitate transferentzia esperimentuek berrantolaketa inolako errazemizazio edo epimerizaziorik gabe gertatzen zela baieztatu zuten.[28] Azken hamarkadan, deshidratazio/berrantolaketa sekuentzia hau konposatu askoren sintesian aplikatu da.[29]

[25] a) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117-2142. b) Arnold. J. S.; Zhang, Q.; Nguyen, H. M. *Eur. J. Org. Chem*. **2014**, 4925-4948. c) Cannon, J. S.; Overman, L. E. *Acc. Chem. Res*. **2016**, *49*, 2220-2231.
[26] Christophersen, C.; Holm, A. *Acta. Chem. Scand*. **1970**, *24*, 1512-1526.
[27] a) Ichikawa, Y. *Synlett* **1991**, 238-240. b) Ichikawa, Y.; Yamazaki, M.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429-2432. c) Ichikawa, Y.; Osada, M.; Ohtani, I. I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449-1456.
[28] Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791-2796.

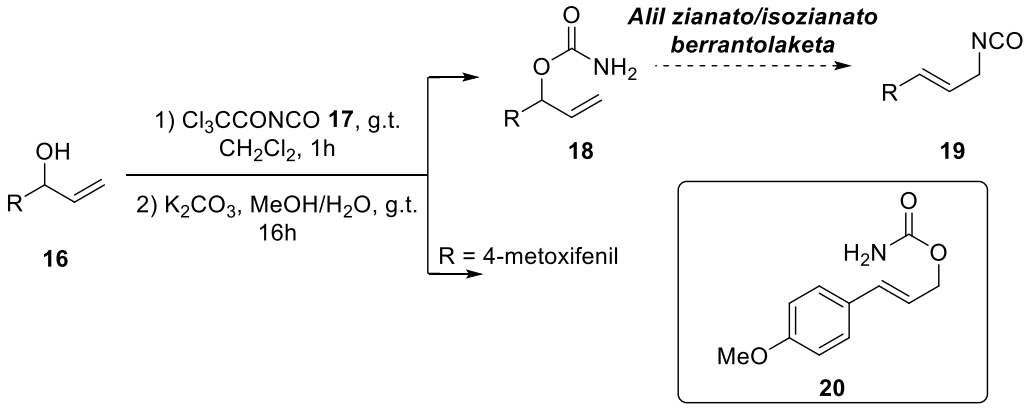
[29] a) Nocquet, P.-A.; Henrion, S.; Macé, A.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. *Eur. J. Org. Chem*. **2017**, 1295-1307. b) Roy, S.; Spino, C. *Org. Lett*. **2006**, *8*, 939-942. c) Ramb, D. C.; Kost, L.; Haufe, G. *Chimia* **2014**, *68*, 436-441. d) Touchet, S.; Macé, A.; Roisnel. T.; Carreaux, F.; Bouillon, A.; Carboni, B. *Org. Lett*. **2013**, *15*, 2712-2715. e) Henrion, S.; Carboni, B.; Cossío, F. P.; Roisnel, T.; Villalgordo, J. M.; Carreaux, F. *J. Org. Chem*. **2016**, *81*, 4633-4644. f) Macé, A.; Touchet, S.; Andres, P.; Cossío, F.; Dorcet, V.; Carreaux, F.; Carboni, B. *Angew. Chem., Int. Ed*. **2016**, *55*, 1025-1029.



4.7 Eskema. Ichikawak publikatutako alil zianato/isozianato bertsioa.

4.2 HELBURUAK

François Carreux-ren ikerketa taldean buruturiko 1-(4-metoxifenil)prop-2-en-1-ol **16**-ren eta **17** trikloroazetil isozianatoaren arteko alil zianato/isozianato berrantolaketako aurretiko ikerketek **20** (*E*)-karbamatoaren ustekabeko sorrera erakutsi zuten (**4.8 Eskema**).



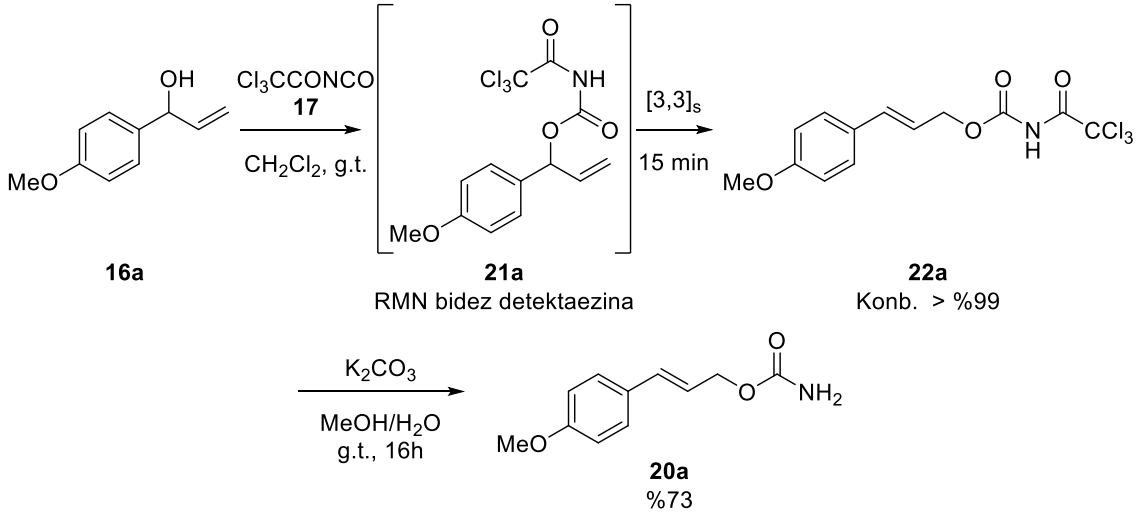
4.8 Eskema. 18 karbamatoaren ordezko **20** produktuaren ustekabeko sorrera.

Karbamatoak artekari sintetiko garrantzitsuak dira. Honenbestez, Kapitulu honetako xede nagusia prozesu honetan aril eta alkenil alkohol zein isozianato aktibatuen egokitasuna aztertzea izango da. Bestalde, ezusteko portaera honen mekanismoaren arrazionalizaziorako azterketa konputazional eta esperimentalak burutuko dira.

4.3 METALIK GABEKO 1,3-DIOXA-[3,3]-BERRANTOLAKETA SIGMATROPIKOAREN AURKIKUNTZA

Esan bezala, **16a** alkohol alilikoa **17** trikloroazetil isozianatoarekin tratatzean, berrantolatutako **20a** produktuaren sorrera azkar eta zuzena gertatzen zela ikusi zen (**4.9 Eskema**). **21a** artekaria isolatu eta karakterizatzeko saiakerak arrakastarik gabeak

izan ziren, [3,3]-berrantolaketa sigmatropikoaren izaera azkar eta itzulezina marratuz. Amaierako **22a** karbamato berrantolatua baldintza basikoetan tratatu zen gero, **20a** karbamoil deribatua etekin onekin lortuz (**4.9 Eskema**).[30]



4.9 Eskema. 16a alil alkohola **17** trikloroazetil isozianatoarekin tratatzean jazotako 1,3-dioxa-[3,3]-berrantolaketa sigmatropikoa.

Berrantolaketa sigmatropikoa arautzen duten faktoreak analizatu asmoz, hurrengo urratsean bi erreaktiboetan dauden ordezkatzaileek prozesu kimikoan zuten eragina aztertu zen.

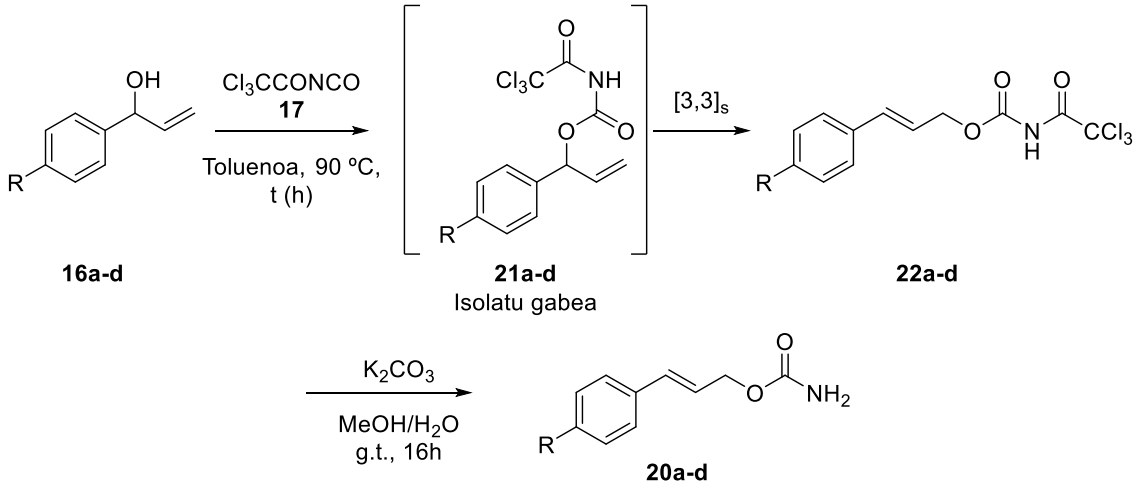
4.3.1 Trikloroazetil isozianatoa erabiliz emandako 1,3-dioxa-[3,3]-berrantolaketa sigmatropikoa

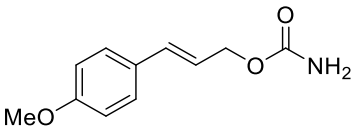
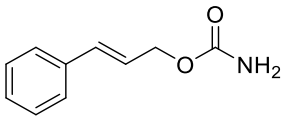
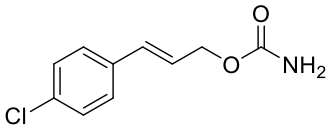
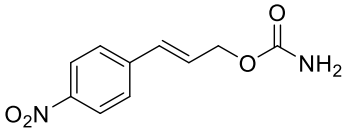
Lehenengo esperimentuak *para* posizioan talde elektroi emaile zein elektroi hartzaileak dituzten alil alkohol sekundarioen usadio eginez burutu ziren (**4.2 Taula**). Emaitzetan ikusi daitekeen moduan, erreakzio abiadurak alil zatiaren elektroi dentsitatearen menpekotasun altua zuen. Orokorrean, ordezkatzaile elektroi emaileek berrantolaketaren abiadura azkartzen zuten. Elektroi hartzaileek aldiz, azkartasuna jaisten zuten. *p*-Metoxi talde elektroiaren emaile kasurako, erreakzioa giro tenperaturan gauzatu zen 15 minututan, amaierako produktua etekin altuan lortuz (**4.2 Taula**, 1. sarrera). Hala ere, elektroi hartzaile taldeak zituzten substratuek erreakzio tenperatura altuen erabilera beharrezko izan zuten konbertsio osora heltzeko (**4.2 Taula**, 2-4 sarrerak). Izan ere, **16b** alkoholak 6h behar izan zituen 90 ºC-tan (**4.2 Taula**, 2. sarrera). *p*-kloro taldeaz ordezkaturiko **16c** alkoholak erreakzio denbora luzeagoak

[30] **20a** produktuaren sintesia aurretik argitaratua izan da: Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745-11750.

behar izan zituen, 20h-en buruan konbertsio totalera iritsiz (**4.2 Taula**, 3. sarrera). Azkenik, *p*-nitro talde desaktibatzaileena duen **16d** alkoholak %50-ko konbertsioa besterik ez zuen erakutsi 5 egun ondoren (**4.2 Taula**, 4. sarrera). Arau orokor moduan esan daiteke alil zatiaren elektroi dentsitatea handitu ahala berrantolaketa sigmatropikoa azkartzen zela. Azken hidrolisi basiko urratsa arazorik gabe jazo zen kasu guztietan, **20a-d** (*E*)-karbamatoak etekin moderatu eta onen artean lortuz.

4.2 Taula. 16a-d eta trikloroazetil isozianatoa **17** arteko 1,3-dioxa-[3,3]-berrantolaketa sigmatropikoa.[a,b]

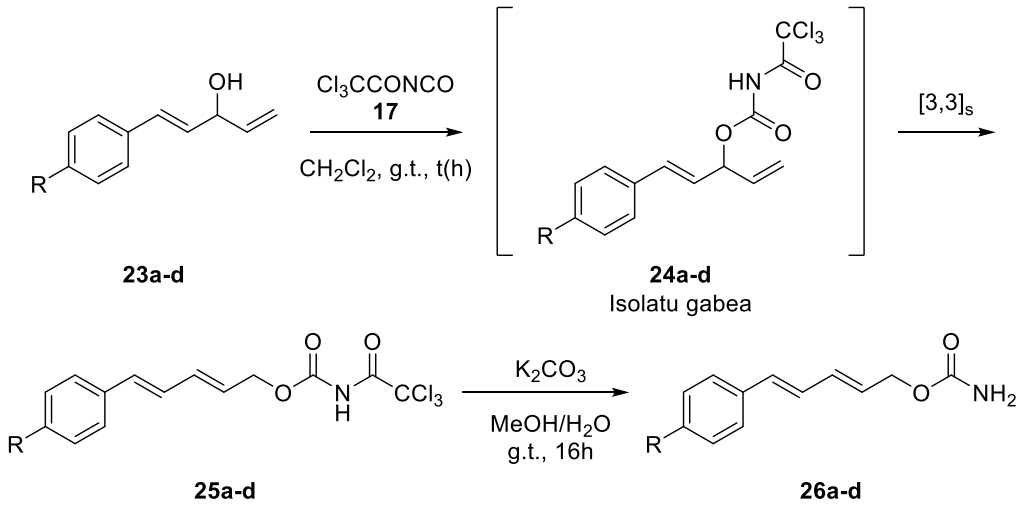


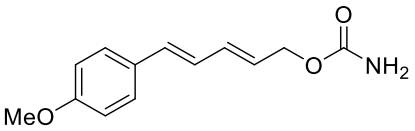
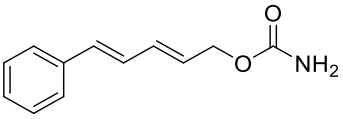
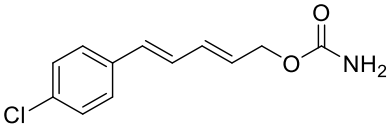
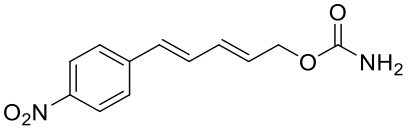
Sarrera	R	t (h)	Produktua	Egitura	Etekina (%)[c]
1[d]	4-OMe	0.25	**20a**		73
2	H	16	**20b**		92
3	4-Cl	20	**20c**		50
4	4-NO_2	120[e]	**20d**		43

a) Erreakzioa **16a-d** alkohol alilikoa (0.3 mmol) eta trikloroazetil isozianatoa **17** (0.36 mmol) erabiliz gauzatu zen, toluenoan (0.2M), kasuan kasuko tenperaturan. b) Erreakzioa ^{1}H-RMN analisi bidez jarraitu zen hasierako alkohola guztiz amaitu arte. c) Etekinak produktu isolatuei egiten die erreferentzia. d) Erreakzioa CH_2Cl_2-tan burutu zen, giro tenperaturan. e) %50-ko konbertsioa.

Dienil karbamatoek produktu naturalen sintesian duten gailentasuna kontuan izanda,[31] alkenil ordezkaturiko alkohol alilikoen egokitasuna aztertu zen jarraian (**4.3 Taula**).

4.3 Taula. Alkenil ordezkaturiko alkohol alilikoen eta trikloroazetil isozianatoaren arteko 1,3-dioxa-[3,3]-berrantolaketa sigmatropikoa.[a,b]



Sarrera	R	t (h)	Produktua	Egitura	Etekina (%)[c]
1	4-OMe	2	**26a**		24 (65)[d]
2	H	4	**26b**		65
3	4-Cl	4	**26c**		75
4[e]	4-NO_2	178[f]	**26d**		zg[g]

a) Erreakzioa **23a-d** (0.3 mmol) alkenil ordezkaturiko alkohol alilikoak eta trikloroazetil isozianatoa (0.36 mmol) erabiliz burutu ziren, CH_2Cl_2-an (0.2 M), giro tenperaturan. b) Erreakzioa ^{1}H-RMN analisi bidez jarraitu zen, hasierako alkohola guztiz amaitu arte. c) Etekinak produktu isolatuei egiten die erreferentzia. d) Kako arteko etekina ^{1}H-RMH bidez determinatu zen, 1,3,5-trimetoxibenzenoa barne erreferentziatzat erabiliz. e) Erreakzioa tolueno deuteratuan burutu zen, 90 ºC-tan. f) Ez zen desioko produkturik sortu. g) zg: zehaztu gabea.

[31] Dienil karbamatoen aplikazioak ezagutzeko, ikusi: a) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett*. **2007**, *9*, 1725-1728. b) Unsworth, W. P.; Lamont, S. G.; Robertson, J. *Tetrahedron* **2014**, *70*, 7388-7394. c) Guasch, J.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Chem. Commun.* **2014**, *50*, 7344-7347. d) Guasch, J.; Giménez-Nueno, I.; Funes-Ardoiz, I.; Bernús, M.; Matheu, M. I.; Maseras, F.; Castillón, S.; Díaz, Y. *Chem. Eur. J.* **2018**, *24*, 4635-4642.

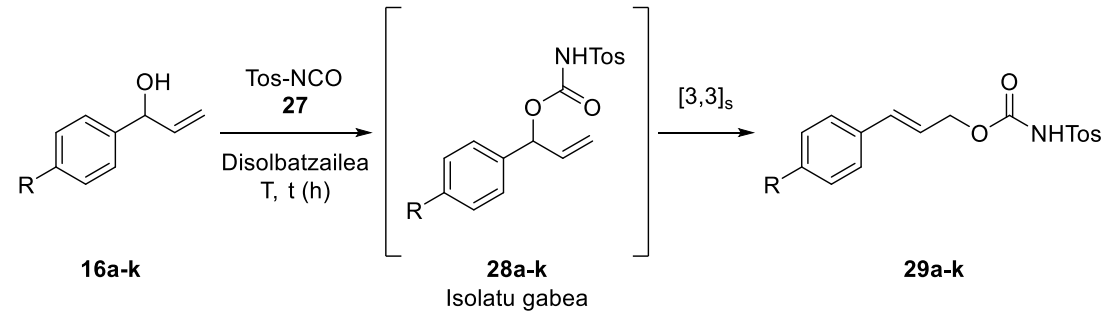
Kasu honetako emaitzak alkohol alilikoekin lortutakoekin bat datoz, tendentzia berdina jarraituz. Aipatzekoa da, hala ere, alkenil ordezkaturiko alkohol alilikoek erreakzio denbora laburragoak erakutsi zituztela eta hauek guztiak giro tenperaturan eman zirela. **23a** alkoholaren kasuan, adibidez, berrantolaketa sigmatropikoak 2 ordu iraun zuen, **26a** amaierako produktua %24-ko etekin baxuan lortuz, silika gel bidezko purifikazioko ezegonkortasuna zela eta (**4.3 Taula**, 1. sarrera). Ordezkatu gabeko eta *p*-Cl taldeaz ordezkaturiko **23b,c** alkoholek 4h behar izan zituzten konbertsio totala lortzeko, hidrolisia eta gero produktuak etekin onetan lortuz (**4.3 Taula**, 2 eta 3 sarrerak). Zoritxarrez, **23d** alkoholak ez zuen desioko produkturik hornitu, artekariaren tenperatura altuko ezegonkortasuna zela medio (**4.3 Taula**, 4. sarrera). **23a-c** alkoholen erreaktibitate altuagoa dieno konjugatu egonkorragoaren formazioak azal lezake partzialki.

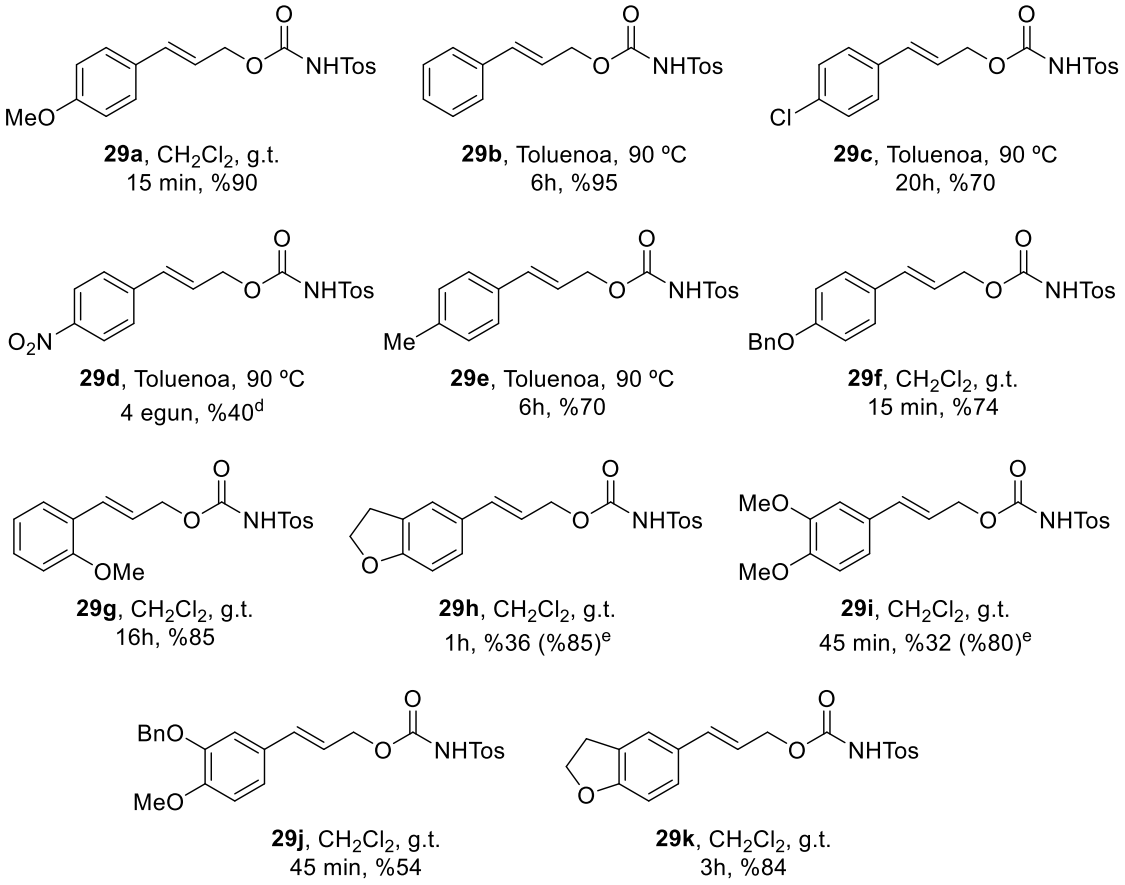
4.3.2 *p*-Toluensulfonilo isozianatoa erabiliz emandako 1,3-dioxa-[3,3]-berrantolaketa sigmatropikoa

Bestelako isozianato aktibatuen aplikagarritasuna ebaluatzeko *p*-toluensulfonil isozianatoaren erabilpena ikertu zen ondoren (**4.4 Taula**). Ordezkatzaile elektroi emaileen kasuan (**16a** eta **16f**), berrantolaketa sigmatropikoa 15 minututan gauzatu zen, **29a** eta **29f** (*E*)-karbamato linealak etekin altuetan sortuz. **16b-d** alkoholen kasuan, tenperatura 90 ºC-tara igotzea beharrezko suertatu zen. Hauen artean, desaktibatzaile ahulak dituzten **16b** eta **16e** alkoholek erreakzio denbora laburragoak behar izan zituzten erreakzioa amaitzeko. *p*-NO_2 taldeaz ordezkaturiko alkohola %70-ko konbertsiora besterik ez zen heldu 4 egunen buruan, **29d** karbamatoa etekin moderatuetan sortuz.

Ordezkapen patroi gehiago ere aplikagarri izan ziren deshidratazio/berrantolaketa sigmatropikoan. *o*-metoxi taldeaz ordezkatutako **16g** alkoholak 16h behar izan zituen desioko produktua etekin onetan erdiesteko. 3,4-diordezkatutako **16i**,**j** alkoholek ere erreakzio denbora laburretan eta etekin onetan sortu zituzten dagozkien karbamatoak. Kasu partikular hauetan, *meta* posizioko talde elektroi emaileen presentziak erreakzio denborak apur bat altuagoak izatea eragin zuen. Azkenekoz, eraztun fusionatuak dituzten **16h,k** alkoholek berrantolatutako produktuak giro tenperaturan eta etekin altuetan erdietsi zituzten.

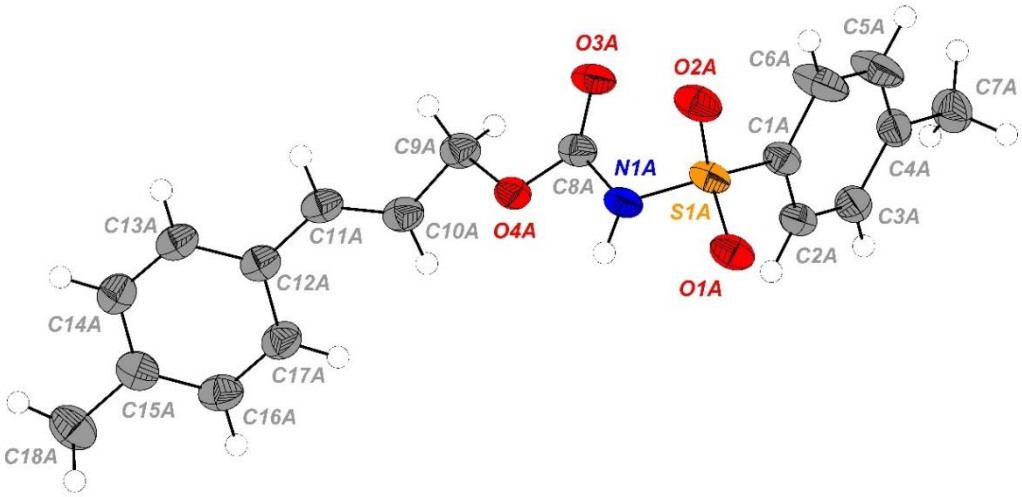
4.4 Taula. 16a-k alkohol alilikoen eta *p*-toluensulfonil isozianatoaren 1,3-dioxa-[3,3]-berrantolaketa sigmatropikoa.[a,b]





a) Erreakzioa **16a-k** (0.3 mmol) alkohol alilikoak eta *p*-toluensulfonil isozianatoa (0.36 mmol) erabiliz burutu ziren, adierazitako disolbatzaile eta tenperaturan. b) Erreakzioa ^{1}H-RMN analisi bidez jarraitu zen, hasierako alkohola guztiz desagertu arte. c) Etekinak produktu isolatuei egiten die erreferentzia. d) 4 egun ondoren, %70-ko konbertsioa ikusi zen. e) Kako arteko etekinak ^{1}H-RMN bidez kalkulatu ziren, 1,3,5-trimetoxibenzenoa barne erreferentziatzat erabiliz.

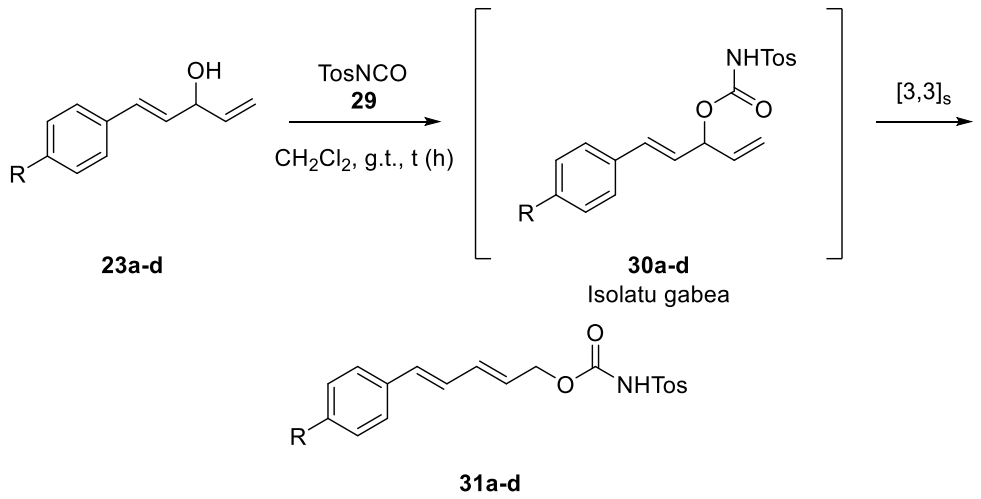
Orohar, [3,3]-berrantolaketa sigmatropikoa propietate elektroniko desberdinak dituzten alil alkohol ugariri egokitu zitzaien. Hauek guztiek (*E*)-karbamato linealen formazio esklusiboa ahalbidetu zuten. **29h** eta **29i** konposatuek 1,3,5-trimetoxibenzenoa barne erreferentzia gisa erabiltzea behar izan zuten prozesuaren etekin kimiko zehatza ezagutzeko. **29e** konposatuaren egitura X-izpien difrakzio analisi bidez determinatu zen, barneko lotura bikoitzaren (*E*)-konfigurazioa baieztatuz (**4.2 Irudia**).

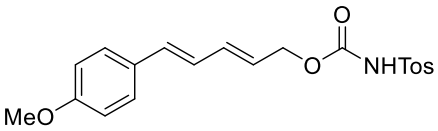
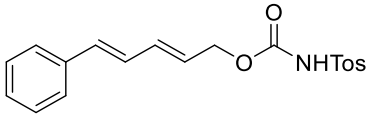
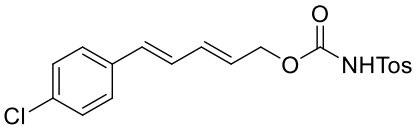
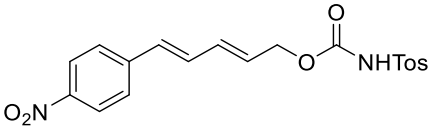


4.2 Irudia. 29e konposatuaren ORTEP diagrama, %50-ko probabilitateko elipsoide termikoekin.

p-Toluensulfonil isozianatoa alkenil ordezkaturiko alkohol alilikoekin ere aplikatu zen (**4.5 Taula**). Taulan bildutako emaitzek trikloroazetil isozianatoarekin lortutako emaitzen portaera antzekoa irudikatzen dute. Elektroi emaile taldea duen **23a** alkoholak erreakzio abiadura azkarragoak erakutsi zituen, amaierako (*E*,*E*)-karbamato berrantolatua giro tenperaturan eta 30 minututan sortuz. 1,3,5-trimetoxibenzenoaren erabilpenak **31a** karbamatoarekiko etekin teoriko altua nabarmendu zuen, isolatutako etekin baxua produktuaren purifikazio urratseko ezegonkortasunaren ondorio zela agerian utziz (**4.5 Taula**, 1. sarrera). Ordezkapenik gabeko eta *p*-Cl ordezkaturiko alkohol alilikoak, bestalde, 4 ordutan heldu ziren konbertsio osora, **31b,c** karbamatoak etekin onetan erdietsiz (**4.5 Taula**, 2 eta 3 sarrerak). Azkenik, **23d** deribatuak 90 ºC eta 5 egun behar izan zituen %50-ko konbertsioa lortzeko, dagokion karbamato konjugatua %36-ko etekinean erdietsiz (**4.5 Taula**, 4. sarrera).

4.5 Taula. Alkenil ordezkaturiko alkoholen karbamoilazio/berrantolaketa sekuentzia.[a,b]



Sarrera	R	t (h)	Produktua	Egitura	Etekina (%)[c]
1	4-OMe	0.5	**31a**		25(85)[d]
2	H	4	**31b**		75
3	4-Cl	4	**31c**		68
4[e]	4-NO_2	120[f]	**31d**		36

a) Erreakzioa **23a-d** (0.3 mmol) alkenil ordezkaturiko alkohol alilikoak eta *p*-toluensulfonil isozianatoa (0.36 mmol) erabiliz burutu ziren, CH_2Cl_2-an (0.2 M), giro tenperaturan. b) Erreakzioa ^{1}H-RMN analisi bidez jarraitu zen, hasierako alkohola guztiz amaitu arte. c) Etekinak produktu isolatuei egiten die erreferentzia. d) Kako arteko etekina ^{1}H-RMH bidez determinatu zen, 1,3,5-trimetoxibenzenoa barne erreferentziatzat erabiliz. e) Erreakzioa tolueno deuteratuan burutu zen, 90 ºC-tan. f) %50-ko konbertsioa, 5 egun ondoren.

4.4 AZTERKETA MEKANISTIKOAK

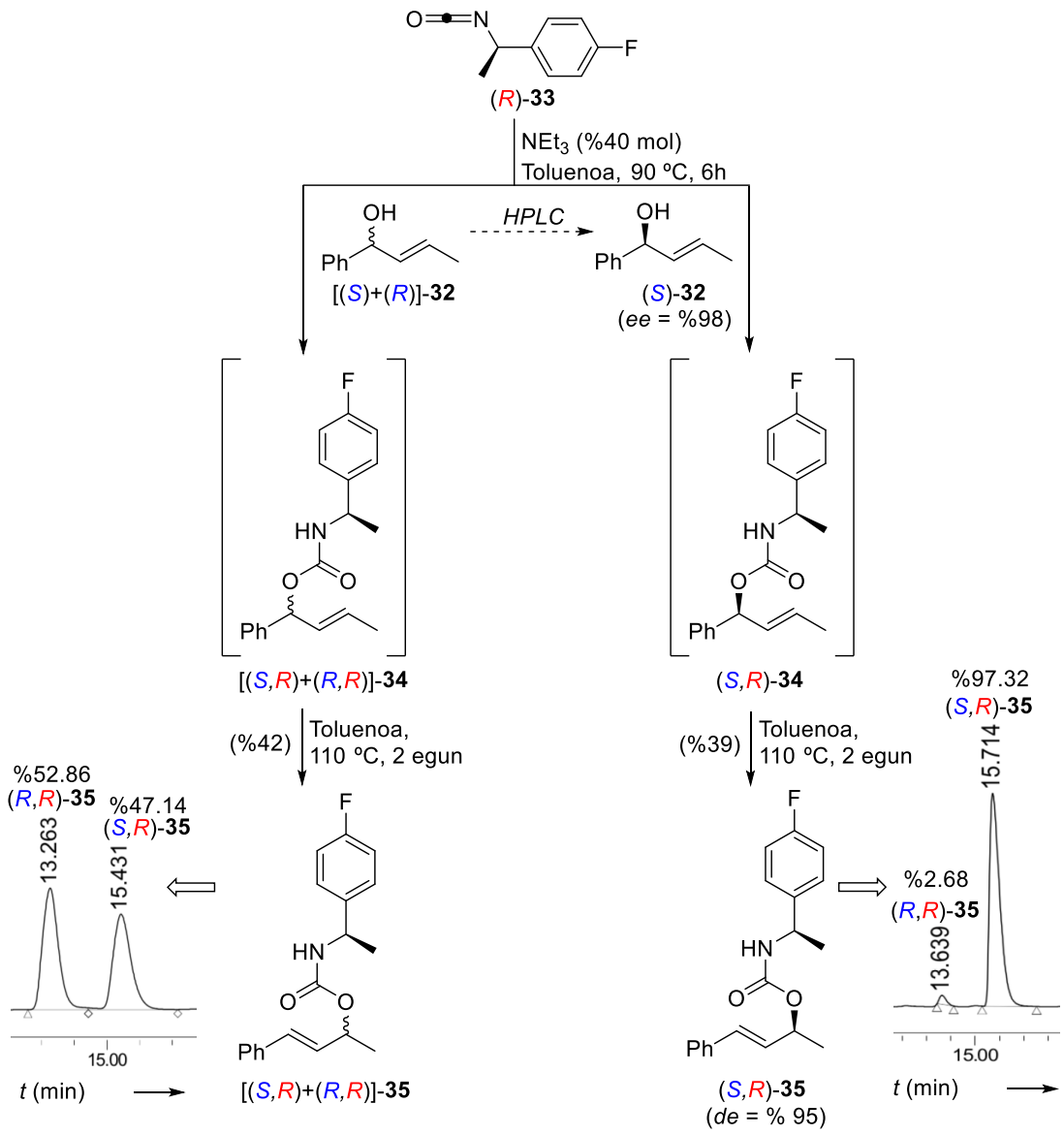
4.4.1 Erreakzioaren izaera kontzertatua aztertzeko analisiak

Woodward eta Hoffmanen legeen arabera, termikoki onartutako [3,3]-berrantolaketa sigmatropikoak erregioselektiboki eta estereoespezifikoki gauzatzen dira. Honela, aztergai ziren prozesuen kiralitate transferentzia ebaluatu eta urratsezko mekanismoak baztertzeko (*E*)-1-fenilbut-2-en-1-ol **32** eta bere (*R*,*E*)- eta (*S*,*E*)- enantiomeroen

portaera RMN eta HPLC bidez ikertu zen. Azken alkohol kiral hau nahaste errazemikoari egindako HPLC preparatibo bidez banatu zen.

p-toluenosulfonil isozianatoaren usadio egitean, HPLC bidezko determinazioa ezinezko izan zen sorturiko produktuen ezegonkortasuna zela medio. $Eu(hfc)_3$ erreaktiboaren erabilera ere ez zen baliagarri izan, saturaziora iritsi aurretik RMN-ko seinaleak bereizezinak baitziren.

Emaitza negatibo guzti hauek ikusirik, isozianato kiralek ikerketa erraztu zezaketela postulatu zen. Honela, **32** alkohol errazemikoa (*R*)-[1-(4-fluorofenil)etil]isozianato **33**-rekin tratatu zen, trietilaminaren presentzian (**4.10 Eskema**). Hasierako karbamatoa sortu ostean, berrantolaketa urratsa 110 ºC-tan gauzatu zen, amaierako karbamatoa %50-ko konbertsioan lortuz. Erreakzio denbora luzeagoek produktuaren deskonposaketa eragiten zuten. ^{1}H, ^{13}C eta ^{19}F esperimentuek seinale banagarriak erakusten ez zituztenez, HPLC analisiak erabilgarri izan zitezkeela suposatu zen. (*S*,*R*)+(*R*,*R*)-**35** karbamatoen nahastearen HPLC profilak bi piko desberdin irudikatu zituen, 52:48 proportzioan (**4.10 Eskema**). (*S*)-**32** alkohol aliliko kirala erabiltzean (%98 *ee*, HPLC banaketa ondoren), (*S*,*R*)-**35** karbamatoaren sorrera behatu zen. HPLC analisiek produktu berrantolatu honek %95-ko soberakin diastereomerikoa zuela erakutsi zuen, prozesuan zehar informazio kirala mantentzen zela frogatuz. Emaitza honekin gainerako kasuetan ere kiralitate transferentzia totala gertatzen dela suposatu zen.



4.10 Eskema. **32** alkohol alilikoaren eta (*R*)-**33** isozianatoaren arteko erreakzioaren kiralitate transferentziaren ebaluazioa. **35** karbamato errazemiko eta kiralen kromatogramak ere adierazten dira.

4.4.2 Lehen ordenako konstante zinetikoen determinazioa

Erreaktiboen propietate elektronikoen ezaugarri orokorrak ezagutu ondoren, ikerketa zinetikoak burutu ziren efektu hauek erreaktibitatean duten eragina kuantifikatzeko. Honetarako, **16b,c** alkoholen **29b,c** (R = H, Cl, hurrenez-hurren) produktuetarako berrantolaketak 90 ºC eta tolueno deuteraturan monitorizatu ziren ^{1}H-RMN esperimentu bidez. **16a** alkoholaren kasuan (R = OMe) esperimentua giro tenperaturan burutu zen, 15 minutuz. **16d** alkoholaren analisia ezinezko izan zen, erreakzio denbora luzeak medio.

4.3 Irudiak 1-(4-klorofenil)prop-2-en-1-ol **16c** alkoholaren eta *p*-toluensulfonil isozianatoaren arteko 90 ºC-ko erreakzioaren denborarekiko eboluzioa irudikatzen du.

Aurrez burututako esperimentuek karbamatoaren formaziorako deshidratazio erreakzioa berehalakoa zela erakutsi zuten, baita **28c** → **29c** pausua espezie artekari detektagarririk gabe gauzatzen zela ere.

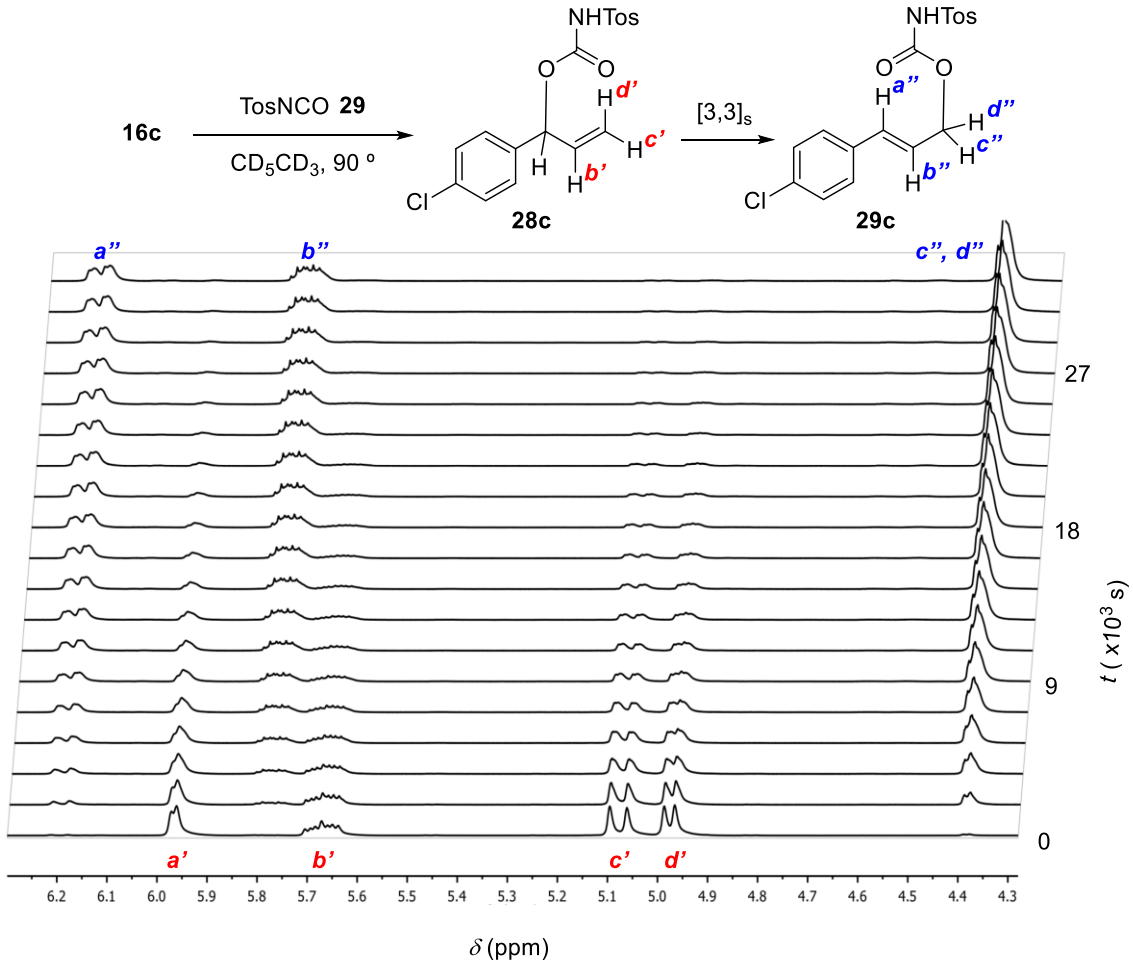
Hots, **28a-c** → **29a-c** erreakzioarekin erlazionaturiko konstante zinetikoak lehen-ordenako baldintzapean neurtu ziren, non erreakzio abiadurek **28a-c** espezieen kontzentrazioarekiko menpekotasuna duten (1 ekuazioa).

$$abiadura = -\frac{d[\mathbf{28}\boldsymbol{a}\text{-}\boldsymbol{c}]}{dt} \approx k_{obs}[\mathbf{28}\boldsymbol{a}\text{-}\boldsymbol{c}] \qquad (1)$$

Lehen-ordenako ekuazio integratuak karbamato artekariaren kontzentrazioaren logaritmoarekiko zuzenki proportzionalak dira, 2. ekuazioan adierazi moduan:

$$\ln[\mathbf{28}\boldsymbol{a}\text{-}\boldsymbol{c}]_t - \ln[\mathbf{28}\boldsymbol{a}\text{-}\boldsymbol{c}]_0 = -k_{obs}t \qquad (2)$$

4.6 Taulako datu esperimentalak **28a-c** konposatuen **Hb**', **Hc**' eta **Hd**' protoiei dagozkien seinaleen batazbestekoa eginez kalkulatu ziren. Orohar, lortutako emaitzak **4.4 Taula**n adierazitako erreaktibitatearekin guztiz kointziditzen dute. **16c** alkoholaren konstante zinetikoa bere kide den **16b** alkoholarena baino apur bat baxuagoa da, erreakzioa denbora luzeagoak baieztatuz (**4.6 Taula**, 2 eta 3 sarrerak). **16a** alkoholaren erreakzio abiadura beste kasuetan baino magnitude orden bat azkarragoa zen. Lortutako datuek talde elektroi hartzaileak dituzten alkohol alilikoen erreaktibitate baxuagoa berretsi zuten, baita ordezkatzaile elektroi emaileen erreaktibitate azkarragoa ere.



4.3 Irudia. 1-(4-klorofenil)prop-2-en-1-ol **16c** eta *p*-toluensulfonil isozianatoaren arteko erreakzioari dagozkion ^{1}H-RMN espektroak (500 MHz). Espektro hauek guztiak erreakzio denbora desberdinetan erregistratu ziren eta bi karbamatoen hidrogeno alilikoen eboluzioa irudikatzen dute.

4.6 Taula. 16a-c alkoholentzat neurtutako konstante zinetikoak[a,b,c]

Sarrera	Alkohol alilikoa	k_{obs} $(x10^{-4}s^{-1})$
1[d]	**16a**	16.3 (±0.50)
2	**16b**	1.62 (±0.06)
3	**16c**	1.08 (±0.04)

a) 2. ekuazioa jarraituz kalkulatutako lehen-ordenako konstanteak. b) Erreakzioak 500 MHz-tan burututako ^{1}H-RMN espektroskopia bidez monitorizatu ziren, 90 ºC-tan. c) Erroreak konstante zinetikoen desbiazio estandarretatik kalkulatu ziren.[32] d) Giro tenperaturan neurtua.

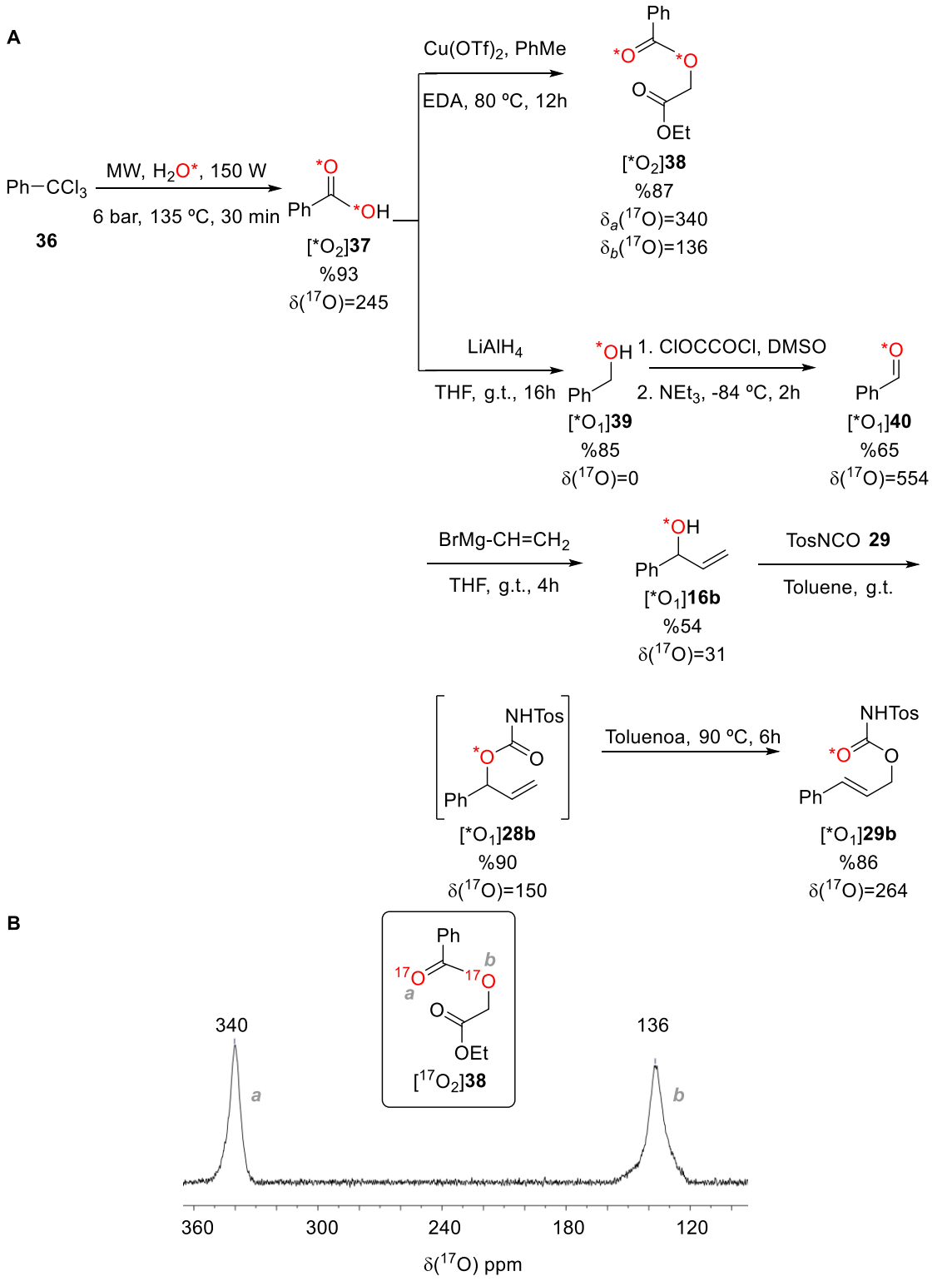
[32] Harris, D.C. *Experimental Error in Quantitative Chemical Analysis*, 8th Ed. W.H. Freeman: New York, **2010**, pp 51-67.

4.4.3 Markaketa isotopikoak

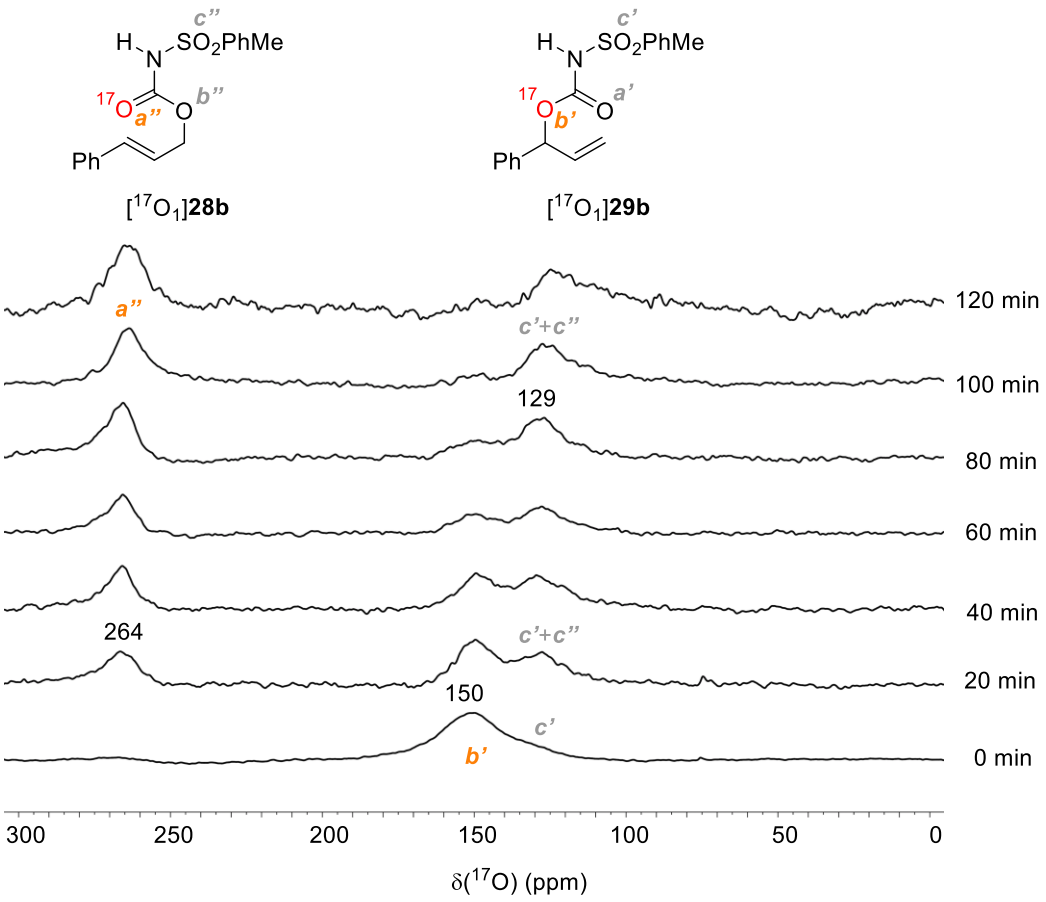
Neurketa zinetikoekin bat, ^{17}O isotopoz markatutako konposatuen ^{17}O-RMN esperimentuak gauzatu ziren, 1,3-dioxa-[3,3]-berrantolaketa isotopikoaren mekanismo kontzertatu periziklikoa baieztatu asmoz (**4.11 Eskema**). Azterketa hauek aurrera eramateko %11.1 $H_2{}^{17}O$, %29.7 $H_2{}^{18}O$ eta %59.2% $H_2{}^{16}O$ nahastea erabili zen. (Triklorometil)bentzenoa **36**-ren mikrouhin erradiazio bidezko[33] [$^*O_2$]**37** azido benzoiko markaturako konbertsioak bi bide sintetiko ahalbidetu zituen (**4.4A Irudia**). Lehenak[34] **38** diesterra sortu zuen eta hibridazio desberdineko oxigeno atomoen ^{17}O-RMN seinaleak kalibratzea posible egin (**4.4B Irudia**). Bertan, sp^2 eta sp^3 hibridazioko ^{17}O nukleoei dagozkien bi seinale desberdin ageri ziren (340 eta 136 ppm, hurrenez-hurren). Banaketa honek [$^{17}O_1$]**28b** → [$^{17}O_1$]**29b** transformazioarekin erlazionaturiko erresonantziak desberdintzea ahalbidetu zuen.

Bigarren bide sintetikoak [$^*O_2$]**37** azidoa [$^*O_1$]**16b** alkoholean bihurtzea ahalbidetu zuen, erredukzio, oxidazio eta adizio sekuentzia jarraituz (**4.4A Irudia**). [$^*O_1$]**16b**-ak tosil isozianatoarekin erreakzionatzean [$^*O_1$]**28b** karbamatoa sortu zen. Bere ^{17}O-RMN espektroak 150 ppm-tan seinale zabala erakutsi zuen, sulfona atalak ugaritasun naturalean erakusten duen seinalearekin gainezarrita. [$^{17}O_1$]**28b** 90 ºC-tara berotzeak 264 ppm-tan seinale berria agertzea bideratu zuen, [$^{17}O_1$]**29b** espeziearen sp^2 hibridazioko ^{17}O nukleoarekin erlazionatu zena (**4.5 Irudia**). Horrez gain, [$^{17}O_1$]**29b** seinalearen handitzeak [$^*O_1$]**28b** seinalearen jaitsierarekin bat egin zuen, bi karbamatoen sulfona taldeen seinaleen intentsitate eta desplazamentuak antzekoak izanik. Emaitza hauek **28** → **29** konbertsio guztiek 1,3-dioxa-[3,3]-berrantolaketa sigmatropiko perizikliko kontzertatu bidez jazotzen zirela frogatu zuten.

[33] a) Retamosa, M. G.; Ruiz-Olalla, A.; Bello, T.; de Cózar, A.; Cossío, F. P. *Angew. Chem., Int. Ed.* **2018**, *57*, 668-672. b) Haiss, P.; Zeller, K.-P. *Angew. Chem., Int. Ed*. **2003**, *42*, 303-305.
[34] Chen, J.; Shao, Y.; Ma, L.; Ma, M.; Wan, X. *Org. Biomol. Chem*. **2016**, *14*, 10723-10732.



4.4 Irudia. A) [*O$_1$]**28b**, [*O$_1$]**29b** eta [*O$_2$]**38** konposatuen sintesia. δ (^{17}O) desplazamentu kimikoak ppm-tan ematen dira. B) [*O$_2$]**38** diesterraren ^{17}O-RMN espektroa, sp^2 eta sp^3 hibridazioko oxigeno atomoak bereizten direlarik.



4.5 Irudia. [$^{17}O_1$]**28b** → [$^{17}O_1$]**29b** transformazioari dagokion ^{17}O-RMN espektroen bilketa, denbora desberdinetan. Sulfonaren oxigeno seinaleak (c' eta c'', ugaritasun naturala) ere indikatzen dira.

4.5 ONDORIOAK

Kapitulu honetan azaldu eta eztabaidatutako azterketen ondoren, hurrengo ondorioak laburtu daitezke:

1. Karbamato (*E*)-linealen sintesia ahalbidetzen duen aurrekaririk gabeko adizio/[3,3]-berrantolaketa sigmatropikoa deskribatu zen. Erreakzio baldintza leunek metodologia sintetiko hau karbamato esanguratsuen lorpenerako sintesi bide baliagarri bilakatzen dute.
2. Transformazio honen izaera orokorra aril zein alkenil taldeez ordezkaturiko alkohol alilikoei aplikatu zitzaien, baita isozianatoei ere. Alil atalaren propietate elektronikoak eta isozianatoaren izaerak funtsezko garrantzia izan zuten erreakzioaren bilakaeran. Orohar, talde elektroi emaileek erreakzioa azkartzen zuten; talde elektroi hartzaileek, berriz, erreakzio abiadura gutxitu. Isozianatoei dagokionez, aktibazio maila altuko deribatuak beharrezko suertatu ziren.
3. HPLC analisiek [3,3]-berrantolaketa sigmatropikoaren izaera kontzertatua eta informazio kiralaren transferentzia totala baieztatu zuten. Gertakari honek

simetriaz onarturiko supra-supra mekanismoa indartu zuen, non hasierako alkoholareko informazio kirala amaierako produktuan guztiz mantentzea lortu zen.

4. Gauzaturiko ^{1}H-RMN esperimentuek **16b,c** alkohol alilikoen **28b,c** karbamatoetarako konbertsio azkarra frogatu zuten. **28b,c** → **29b,c** prozesuen jarraipenak k_{obs} balioak kalkulatzea posible bihurtu zuen, lehen ordenako baldintza zinetikoetan. Kalkulaturiko erreakzio abiadurek MeO>H>Cl>>NO_2 erreaktibotasun erlatiboa erakutsi zuten, datu esperimentalekin bat eginez.
5. Markaketa isotopikoak [$^{17}O_1$]**28b**-ren [$^{17}O_1$]**29**-rako interkonbertsioa jarraitzea ahalbidetu zuen, dioxa-[3,3]-berrantolaketa sigmatropikoaren izaera perizikliklo kontzertatua baieztatuz.

4.6 ATAL ESPERIMENTALA

Ohar orokorrak

Tetrahidrofuranoa (THF) sodio/benzofenona bidez destilatu zen, eta diklorometanoa (CH_2Cl_2) P_2O_5 erabiliz. Gainerako erreaktibo komertzialak purifikazio gehiagorik gabe erabili ziren. 1-(fenil)prop-2-en-1-ol-a baliabide komertzialetatik eskura daiteke. [17O1] markaturiko H_2O (%11.1 $H_2{}^{17}O$, %29.7 $H_2{}^{18}O$ eta %59.2 $H_2{}^{16}O$) Cortecnet-etik erosi zen.

Geruza meheko kromatografia (TLC) aluminio oinarridun 0.25mm-ko silika gel 60 F254 plakak erabiliz burutu zen, ultramore argiarekin behatu eta potasio permanganatoz errebelatuz. Zutabe kromatografikoak silika gel 60-ko zutabeetan egin ziren (partikula tamaina: 23-40 µm).

Errotazio optikoak 589nm-ra neurtu ziren, 5 cm-ko zeldan eta 20 ºC inguruan. Kontzentrazioak g/100 mL moduan espresatzen dira.

Infragorri espektroak erreflexio bakarreko ATR moduludun Alpha-Bruker FT-IR espektrometroan burutu ziren. Uhin luzerak cm^{-1} moduan ematen dira.

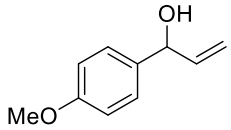
RMN espektroak 400 edo 500 MHz-tan erregistratu ziren ^{1}H nukleoarentzat, 101 edo 126 MHz-tan ^{13}C nukleoarentzat, 376 MHz-tan ^{19}F nukleoarentzat eta 68MHz-tan ^{17}O nukleoarentzat, $CDCl_3$, azetona-*d6* edo metanol-*d4* disolbatzailetzat erabiliz eta trimetilsilanoa erreferentziatzat hartuz. Datuak honela adierazten dira: s = singletea, d = dobletea, t = tripletea, q = kuadrupletea, m = multipletea edo erresolbatu gabea, bs = seinale zabala, akoplamendu konstantea (*J*) Hz-tan, integrazioa. ^{13}C RMN espektroak ^{1}H nukleoa desaklopatuz burutu ziren.

HPLC analisiak Daicel ChiralPak IB zutabea erabiliz gauzatu ziren.

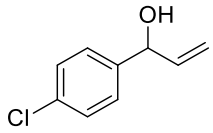
X-izpien difrakzio analisirako Agilent Technologies Super-Nova difraktometroa erabili zen, Cu kα erradiazio monokromatikoaz (λ = 1.54184 Å) eta CCD detektoreaz ekipatua. Neurketak 100 K-tan burutu ziren, Oxford Cryostream 700 PLUS tenperatura aparatuaz lagunduz. Datuak Crysalis softwerra bidez prozesatu ziren (zelda unitatearen determinazioa, absortzio analitikoaren korrekzioa, intentsitate integrazioa eta Lorentz eta polarizazio efektuen korrekzioa).[35] Egitura Superflip[36] bidez ebatzi zen, eta SHELXL-97[37] bidez errefinatu. Amaierako kalkulo geometrikoak Mercury[38] eta PLATON[39]-en burutu ziren, WinGX[40]-en integratuta ageri den moduan.

Alkol alilikoen sintesirako prozedura orokorra

Dagokion aldehidoaren (1.50 mmol, 1 eq.) THF disoluzioari (10 mL) binil edo fanilmagnesio bromuroa (1.80 mmol, 1.2 eq.) gehitu zitzaion 0 ºC-tan, tantaz-tanta. Erreakzio nahastea giro tenperaturan nahastu zen 16 orduz, eta NH_4Cl disoluzio saturatua gehituz geratu (10 mL). Fase akuosoa Et_2O-z erauzi zen (4x10 mL). Konbinatutako fase organikoak Na_2SO_4 bidez lehortu ziren, filtratu eta presio erreduzituan kontzentratu. Erreakzio nahastea silika gelezko zutabe kromatografikoz purifikatu zen (konposatu bakoitzaren baldintzak, ondoren).

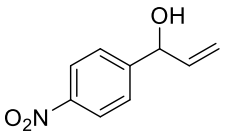


1-(4-metoxifenil)prop-2-en-1-ola (**16a**).[41] 4-metoxibentzaldehido eta binil magnesio bromurotik sortua. 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.25). Etekina %81 (1.22 mmol, 200 mg), olio horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.05 (ddd, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.22 – 5.12 (m, 3H), 3.81 (s, 3H), 1.89-1.86 (br s, 1H).

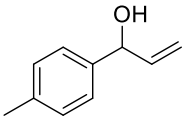


1-(4-klorofenil)prop-2-en-1-ola (**16c**).[44] 4-klorobentzaldehido eta binil magnesio bromurotik sortua. 15:85 EtOAc:Hexano nahasteaz purifikatua (R_f 0.30). Etekina %74 (1.10 mmol, 187 mg), olio hori argia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (300 MHz, $CDCl_3$) δ 7.33-7.31 (m, 4H), 6.01 (ddd, *J* = 17.0, 10.1, 6.1 Hz, 1H), 5.34 (dt, *J* = 17.0, 1.2 Hz, 1H), 5.25-5.15 (m, 2H), 1.95 (d, *J* = 3.7 Hz, 1H).

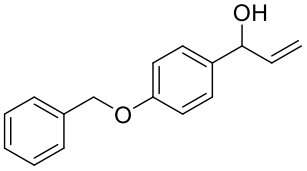
[35] CrysAlisPro, Agilent Technologies, Version 1.171.37.31.
[36] Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786-790.
[37] a) Sheldrick, G. M. *Acta Cryst*. **2008**, A64, 112-122. b) Sheldrick, G. M. *Acta Cryst*. **2015**, C71, 3-8.
[38] Macrae, C. F. *J. Appl. Cryst*. **2008**, *41*, 466-470.
[39] a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Utretch University, The Nederlands **2010**. b) Spek, A. L. *J. Appl. Cryst*. **2003**, *36*, 7-13.
[40] Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838.
[41] Deng, Z.; Wei, J.; Liao, L.; Huang, H.; Zhao, X. *Org. Lett*. **2015**, *17*, 1834-1837.



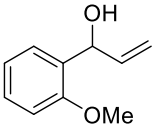
1-(4-nitrofenil)prop-2-en-1-ola (**16d**).[42] 4-nitrobentzaldehido eta binil magnesio bromurotik sortua. 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.20). Etekina %30 (0.45 mmol, 81 mg), olio laranja. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 5.96 (ddd, *J* = 17.1, 10.2, 6.4 Hz, 1H), 5.36 (ddd, *J* = 17.1, 1.2, 1.2 Hz, 1H), 5.28 (d, *J* = 6.4 Hz, 1H), 5.23 (ddd, *J* = 10.3, 1.1, 1.1 Hz, 1H), 2.67-2.65 (br s, 1H).



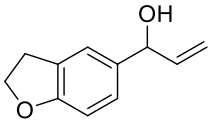
1-(p-tolil)prop-2-en-1-ola (**16e**).[43] 4-metilbentzaldehido eta binil magnesio bromurotik sortua. 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.32). Etekina %98 (1.47 mmol, 218 mg), olio horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.05 (ddd, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.21-5.17 (m, 2H), 2.35 (s, 3H), 1.93 (d, *J* = 5.98 Hz, 1H).



1-(4-(benziloxi)fenil)prop-2-en-1-ola (**16f**).[44] 4-benziloxibentzaldehido eta binil magnesio bromurotik sortua. 25:75 EtOAc:Hexano nahasteaz purifikatua (R_f 0.30). Etekina %79 (1.19 mmol, 284 mg), olio koloregabea. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 5H), 7.35 – 7.22 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.05 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.21 – 5.15 (m, 2H), 5.07 (s, 3H), 1.86 (d, *J* = 3.4 Hz, 1H).



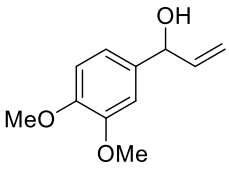
1-(2-metoxifenil)prop-2-en-1-ola (**16g**).[45] 2-metoxibentzaldehido eta binil magnesio bromurotik sortua. 15:85 EtOAc:Hexano nahasteaz purifikatua (R_f 0.44). Etekina %70 (1.05 mmol, 172 mg), olio koloregabea. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.01 – 6.94 (m, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.14 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.41 (d, *J* = 5.6 Hz, 1H), 5.31 (dd, *J* = 17.2, 4.4 Hz, 1H), 5.17 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.87 (s, 3H), 2.77 (dd, *J* = 4.5, 3.8 Hz, 1H).



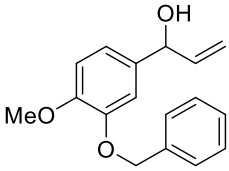
1-(2,3-dihidrobenzofuran-5-il)prop-2-en-1-ola (**16h**).[46] 2,3-dihidrobenzofurano-5-karboxaldehido eta binil magnesio bromurotik

[42] Slagbrand, T.; Lundberg, H.; Adolfsson, H. *Chem. Eur. J.* **2014**, *20*, 16102-16106.
[43] Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863-8874.
[44] Njiojob, C. N.; Rhinehart, J. L.; Bozell, J. J.; Long, B. K. *J. Org. Chem*. **2015**, *80*, 1771-1780.
[45] Morril, C.; Grubbs, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 2842-2843.
[46] Lin, H.; Liu, Y.; Wu, Z.-L. *Chem. Commun*. **2011**, *47*, 2610-2612.

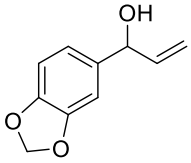
sortua. 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.33). Etekina %98 (1.47 mmol, 259 mg), olio koloregabea. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.30 (d, J = 13.8 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.10 (ddd, *J* = 16.7, 10.3, 5.8 Hz, 1H), 5.34 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.24 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H), 5.19 (d, *J* = 5.8 Hz, 1H), 4.63 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H), 1.89 (br s, 1H).



1-(3,4-dimetoxifenil)prop-2-en-1-ola (**16i**).[47] 3,4-dimetoxibentzaldehido eta binil magnesio bromurotik sortua. 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.27). Etekina %40 (0.60 mmol, 117 mg), olio hori argia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 6.94-6.89 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.09 – 5.98 (ddd, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 5.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 1.93 (br s, 1H).

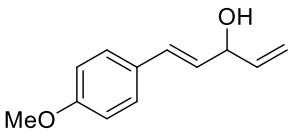


1-(3-(benziloxi)-4-metoxifenil)prop-2-en-1-ola (**16j**). 3-benziloxi-4-metoxibentzaldehido eta binil magnesio bromurotik sortua. 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.21). Etekina %80 (1.20 mmol, 324 mg), olio hori argia. **FTIR (neat, cm^{-1})** 3488, 3054, 2935, 1511, 1263, 1157, 730, 698. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 6.94 – 6.90 (m, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.99 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.17 (m, 1H), 5.14 (s, 2H), 5.10 (m, 1H), 3.87 (s, 3H), 1.87 (d, J = 3.8 Hz, 1H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 149.1, 148.1, 140.3, 136.9, 135.3, 128.4, 127.7, 127.4, 119.2, 114.6, 112.3, 111.6, 74.6, 70.9, 55.9. **HRMS** (ESI) $C_{17}H_{19}O_3$ $[M+H]^+$: kalkulatua 271.1256, aurkitua 271.1256.

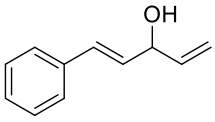


1-(benzo[d][1,3]dioxol-5-il)prop-2-en-1-ola (**16k**).[48] Piperonal eta binil magnesio bromurotik sortua. 10:90 EtOAc:Hexano nahasteaz purifikatua (R_f 0.17). Etekina %76 (1.12 mmol, 203 mg), olio koloregabea. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 1.6 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.02 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.95 (s, 2H), 5.34 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.19 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H), 5.13 (m, 1H), 1.88 (d, *J* = 3.6 Hz, 1H).

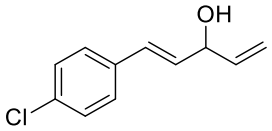
[47] Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Org. Chem*. **2004**, *69*, 122-129.
[48] Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2012**, *51*, 3470-3473.



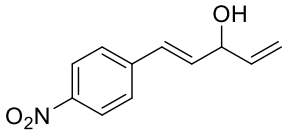
(E)-1-(4-metoxifenil)penta-1,4-dien-3-ola (**23a**). (*E*)-3-(4-metoxifenil)-2-propenal eta binil magnesio bromurotik sortua. 25:75 EtOAc:Hexano nahasteaz purifikatua (R_f 0.24). Etekina %85 (1.28 mmol, 242 mg), olio horia. **FTIR (neat, cm^{-1})** 3422, 3052, 1510, 1174, 1031. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.33 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.19 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 4.80-4.78 (m, 1H), 3.81 (s, 3H), 1.76 (br s, 1H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 159.5, 139.6, 130.6, 129.5, 128.3, 127.9, 115.3, 114.1, 74.1, 55.4. **HRMS** (ESI) $C_{12}H_{13}O$ $[M+H-H_2O]^+$: kalkulatua 173.0960, aurkitua 173.0933.



(E)-1-fenilpenta-1,4-dien-3-ola (**23b**).[49] (*E*)-3-fenil-2-propenal eta binil magnesio bromurotik sortua. 15:85 EtOAc:Hexano nahasteaz purifikatua (R_f 0.23). Etekina %85 (1.28 mmol, 204 mg), olio hori argia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (300 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 7.30 – 7.20 (m, 2H), 6.62 (d, *J* = 16.1 Hz, 1H), 6.23 (dd, *J* = 16.1, 6.4 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.34 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.20 (ddd, *J* = 10.4, 1.3, 1.3 Hz, 1H), 4.89 – 4.76 (m, 1H), 1.75 (m, 1H).



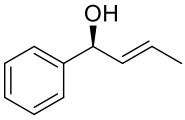
(E)-1-(4-klorofenil)penta-1,4-dien-3-ola (**23c**). (*E*)-3-(4-klorofenil)-2-propenal eta binil magnesio bromurotik sortua. 25:75 EtOAc:Hexano nahasteaz purifikatua (R_f 0.35). Etekina %73 (1.10 mmol, 213 mg), olio hori argia. **FTIR (neat, cm^{-1})** 3271, 3086, 2982, 1638, 1581, 1488, 1085, 1008, 967, 805. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 4H), 6.57 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.21 (dd, *J* = 16.0, 6.3 Hz, 1H), 5.96 (ddd, *J* = 17.4, 10.3, 6.0 Hz, 1H), 5.34 (ddd, *J* = 17.4, 1.3, 1.3 Hz, 1H), 5.21 (ddd, *J* = 10.4, 1.3, 1.3 Hz, 1H), 4.83-4.79 (m, 1H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 139.1, 135.1, 133.3, 131.1, 129.4, 128.7, 127.7, 115.5, 73.5. **HRMS** (ESI) $C_{11}H_{10}Cl$ $[M+H-H_2O]^+$: kalkulatua 177.0467, aurkitua 177.0469.



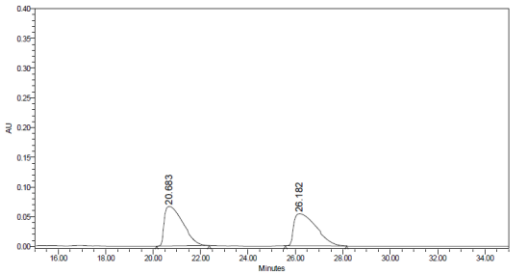
(E)-1-(4-nitrofenil)penta-1,4-dien-3-ola (**43d**).[50] (*E*)-3-(4-nitrofenil)-2-propenal eta binil magnesio bromurotik sortua. 25:75 EtOAc:Hexano nahasteaz purifikatua (R_f 0.24). Etekina %40 (0.60 mmol, 123 mg), olio laranja. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.21 – 8.16 (m, 2H), 7.56 – 7.47

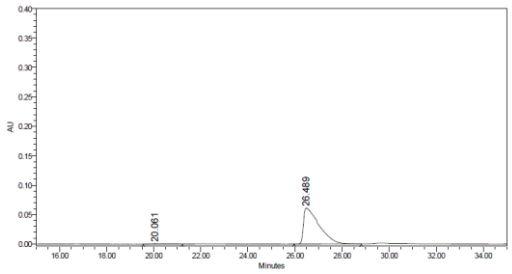
[49] Lindstedt, E.; Ghosh, R.; Olofsson, E. *Org. Lett*. **2013**, *15*, 6070-6073.
[50] Han, S. B.; Krische, M. J. *Org. Lett*. **2006**, *8*, 5657-5660.

(m, 2H), 6.71 (d, *J* = 16.9 Hz, 1H), 6.42 (dd, *J* = 16.9, 5.8 Hz, 1H), 5.97 (ddd, *J* = 17.1, 10.3, 6.1 Hz, 1H), 5.38 (ddd, *J* = 17.1, 1.2, 1.2 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.2, 1.2 Hz, 1H), 4.93 – 4.82 (m, 1H), 1.83 (d, *J* = 4.2 Hz, 1H).



(S,E)-fenilbut-2-en-1-ola (**54**).[51] (*E*)-krotonaldehido eta fenilmagnesio bromurotik sortua. 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.25). Etekina %85 (1.28 mmol, 190 mg), olio horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.40 - 7.32 (m, 4H), 7.31 - 7.27 (m, 1H), 5.84 - 5.63 (m, 2H), 5.16 (d, *J* = 6.4 Hz, 1H), 1.72 (d, *J* = 5.9 Hz, 3H), 1.61 (d, *J* = 3.4 Hz, 1H). **HPLC** (Daicel Chiralpak IB Hexano:^{i}PrOH = 99:1, fluxua = 1 mL/min, λ = 220 nm), t_R (gutxiengoa) =20.68 min, t_R (nagusia) =26.18 min (*ee* %98, $[\alpha]_D^{25}$ = +24.6 (*c* 0.65, kloroformoa)).





	RT	Altuera	Azalera	% Azal.
1	20.683	66612	3620094	50.50
2	26.182	54062	3548264	49.50

	RT	Altuera	Azalera	% Azal.
1	20.061	643	32048	1.19
2	26.489	61082	2787453	98.86

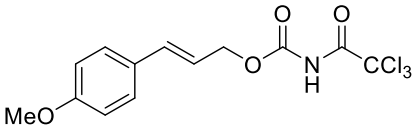
Karbamato alilikoen sintesirako prozedura orokorra

Trikloroazetil isozianatoa erabiliz

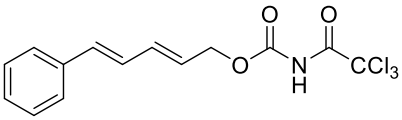
Dagokion alkohol aliliko **16a-d**, **23a-d** (0.30 mmol, 1 eq.) tolueno edo CH_2Cl_2 disoluzioa 0 ºC-tan jarri zen, argoi atmosferapean, eta trikloroazetil isozianatoa (0.36 mmol. 1,2 eq.) poliki gehitu. Erreakzio nahastea hasierako alkohola desagertu arte nahastu zen. Disolbatzailea presio erreduzituan lurrundu zen, eta sortutako artekaria metanoletan disolbatu (0.15 M). K_2CO_3 (1.2 mmol, 4 eq.) ur disoluzioa (0.6 M) gehitu zitzaion, 16 orduz giro tenperaturan nahastu eta MeOH presio erreduzituan lurrundu. Ur fasea CH_2Cl_2-z erauzi zen (4 x 1 Ml) eta fase organikoak Na_2SO_4an lehortu, filtratu eta

[51] Srinivas, H. D.; Zhou, Q.; Watson, M. P. *Org. Lett*. **2014**, *16*, 3596-3599.

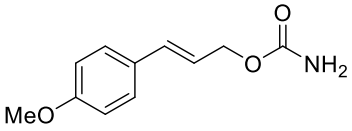
presio erreduzituan lurrundu ziren. Erreakzio nahastea silika gelezko zutabe kromatografikoz purifikatu zen. Kasu batzuetan artekariak identifikatu ziren.



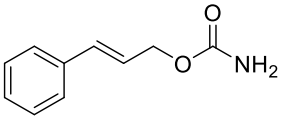
(E)-3-(4-metoxifenil)alil (2,2,2-trikloroazetil)karbamatoa (**19a**). **16a** alkoholetik sortua (g.t., 15 min.). Etekina %98 (0.29 mmol, 103 mg), olio koloregabea. Artekaria ondorengo urratsean erabili zen, purifikaziorik gabe. **^{1}H RMN** (300 MHz, $CDCl_3$) δ 8.50-8.46 (br s, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.7, 6.9 Hz, 1H), 4.88 (dd, *J* = 6.9, 1.2 Hz, 2H), 3.81 (s, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$) δ 159.9, 157.9, 149.8, 136.2, 128.1, 118.9, 114.1, 91.8, 68.3, 55.3.



(2E,4E)-5-fenilpenta-2,4-dien-1-il (2,2,2-trikloroazetil)karbamatoa (**25b**). **23b** alcohol alilikotik sortua (g.t., 4h). Etekina %98 (1.28 mmol, 102 mg), solido zuria. Artekaria ondorengo urratsean erabili zen, purifikaziorik gabe. **^{1}H RMN** (300 MHz, $CDCl_3$) δ 8.50-8.45 (br s, 1H), 7.42 – 7.36 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.21 (m, 1H), 6.76 (dd, *J* = 15.6, 10.2 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.53 (ddd, *J* = 15.1, 1.1, 1.1 Hz, 1H), 5.88 (dt, *J* = 15.1, 6.9 Hz, 1H), 4.83 (dd, *J* = 6.9, 1.1 Hz, 2H). **^{13}C RMN** (75 MHz, $CDCl_3$) δ 157.8, 149.7, 136.7, 135.1, 128.7, 128.2, 127.2, 126.7, 124.7, 91.8, 67.7.

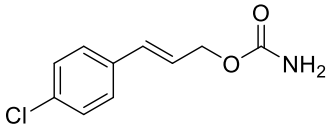


(E)-3-(4-metoxifenil)alil karbamatoa (**20a**). **19a** artekaritik sortua. 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.31). Etekina %73 (0.22 mmol, 45 mg), solido zuria. **u_p** = 131-134 °C. **FTIR (neat, cm^{-1})** 3423, 3263, 3204, 3009, 1682, 1244, 1028. **^{1}H RMN** (400 MHz, Acetone-d_6) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.17 (dt, *J* = 15.9, 6.3 Hz, 1H), 5.90-5.84 (br s, 2H), 4.57 (dd, *J* = 6.3, 1.5 Hz, 2H), 3.75 (s, 3H). **^{13}C RMN** (126 MHz, Metanol-d_4) δ 161.0, 159.8, 134.1, 130.5, 128.8, 122.7, 115.0, 66.4, 55.7. **HRMS** (ESI) $C_{11}H_{13}NO_3Na$ $[M+Na]^+$: kalkulatua 230.0793, aurkitua 230.0786.

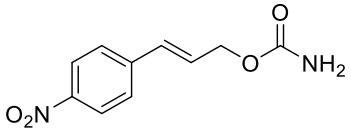


(E)-(fenil)alil karbamatoa (**20b**). 1-(fenil)prop-2-en-1-ol-etik sortua (90 °C, 16h). 30/70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.28). Etekina %92 (0.28 mmol, 49 mg), solido zuria. **u_p** = 116-119 °C. **FTIR (neat, cm^{-1})** 3409, 3263, 3052, 3028, 1681, 1408, 501. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.9, 6.3 Hz, 1H), 5.01-4.92 (br s, 2H), 4.70 (dd, *J* = 6.3, 1.4 Hz, 2H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 156.9 , 136.4 , 133.9 , 128.7 , 128.1 ,

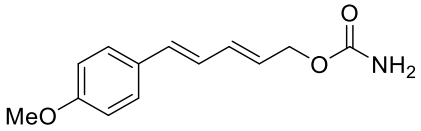
126.7 , 123.7 , 65.8. **HRMS** (ESI) $C_{10}H_{11}NO_2Na$ $[M+Na]^+$: kalkulatua 200.0687, aurkitua 200.0686.



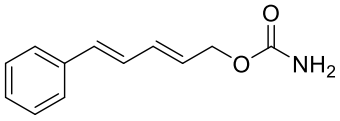
(E)-3-(4-klorofenil)alil karbamatoa (**20c**).[52] **16c** alkoholetik sortua (90 °C, 20h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.27). Etekina %50 (0.15 mmol, 32 mg), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 4H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.26 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.78-4.74 (br s, 2H), 4.72 (dd, *J* = 6.3, 1.4 Hz, 2H).



(E)-3-(4-nitrofenil)alil karbamatoa (**20d**).[19] **16d** alkoholetik sortua (90 °C, 120 h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.10). Etekina %43 (0.13 mmol, 28 mg), solido horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.46 (dt, *J* = 16.0, 5.8 Hz, 1H), 4.78 (dd, *J* = 5.8, 1.5 Hz, 2H), 4.73-4.66 (br s, 2H).

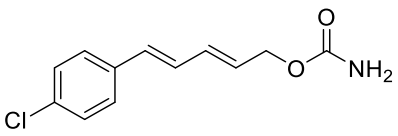


(2E,4E)-5-(4-metoxifenil)penta-2,4-dien-1-il karbamatoa (**26a**). **23a** alkoholetik sortua (g.t., 2h). 35:65 EtOAc:Hexano nahasteaz purifikatua (R_f 0.29). Etekina %25 (0.07 mmol, 17 mg), solido hori argia. **u_p** = 150-153 °C. **FTIR (neat, cm^{-1})** 3436, 3269, 3014, 1685, 1508, 522. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.65 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.43 (dd, *J* = 15.2, 10.2 Hz, 1H), 5.83 (dt, *J* = 15.1, 6.6 Hz, 1H), 4.71-4.67 (br s, 2H), 4.64 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.81 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 159.6, 156.8, 134.9, 133.5, 129.9, 127.9, 126.2, 125.9, 114.36, 65.7, 55.5. **HRMS** (ESI) $C_{13}H_{15}NO_3Na$ $[M+Na]^+$: kalkulatua 256.0950; aurkitua 256.0956.



(2E,4E)-5-fenilpenta-2,4-dien-1-il karbamatoa (**26b**).[46c] **25b** artekaritik sortua. 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.27). Etekina %65 (0.20 mmol, 40 mg), solido horia. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.37 – 7.29 (m, 2H), 7.29 – 7.22 (m, 1H), 6.78 (dd, *J* = 15.8, 10.4 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.46 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.89 (dt, *J* = 15.3, 6.4 Hz, 1H), 4.77-4.68 (br s, 2H), 4.66 (dd, *J* = 6.6, 1.5 Hz, 2H).

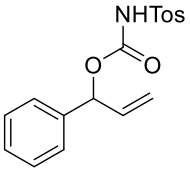
[52] Deng, Q.-H.; Wang, J.-C.; Xu, Z.-J.; Zhou, C.-Y.; Che, C.-M. *Synthesis* **2011**, *18*, 2959-2967.



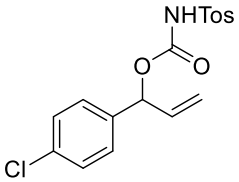
(2E,4E)-5-(4-klorofenil)penta-2,4-dien-1-il karbamatoa (**26c**). **23c** alkoholetik sortua (g.t., 4h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.27). Etekina %75 (0.23 mmol, 53 mg), solido horia. **u_p** = 167-170 °C. **FTIR (neat, cm^{-1})** 3410, 3286, 3028, 1699, 1486, 827, 508. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 4H), 6.74 (dd, *J* = 15.8, 10.4 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.44 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.90 (dt, *J* = 15.2, 6.4 Hz, 1H), 4.66 (dd, *J* = 6.4, 1.5 Hz, 2H), 4.63-4.58 (br s, 2H). **^{13}C RMN** (126 MHz, Metanol-d_4) δ 159.7, 137.3, 134.4, 134.2, 132.9, 130.0, 129.9, 129.8, 128.9, 65.8. **HRMS** (ESI) $C_{12}H_{12}ClNO_2Na$ [M+Na]$^+$: kalkulatua 260.0454; aurkitua 260.0461.

***p*-toluensulfonil isozianatoa erabiliz**

Dagokion alkohol aliliko **16a-k**, **23a-d** (0.30 mmol, 1 eq.) tolueno edo CH_2Cl_2 disoluzioa 0 ºC-tan jarri zen, argoi atmosferapean, eta *p*-toluensulfonil isozianatoa (0.36 mmol. 1,2 eq.) poliki gehitu. Erreakzio nahastea hasierako alkohola desagertu arte nahastu zen. Disolbatzailea presio erreduzituan lurrundu zen eta erreakzio nahastea silika gelezko zutabe kromatografikoz purifikatu zen.

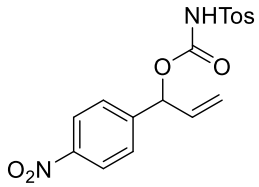


1-fenilalil tosilkarbamatoa (**28b**).[53] 1-(fenil)prop-2-en-1-ol-etik sortua (g.t., 5 min). 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.31). Etekina %92 (0.28 mmol, 91 mg), olio koloregabea. Datu analitiko eta espektroskopikoak literaturako publikazioarekin bat datoz. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.55-7.53 (br s, 1H), 7.34 – 7.26 (m, 5H), 7.21 (dd, *J* = 6.8, 3.0 Hz, 2H), 6.11 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.92 (ddd, *J* = 16.7, 10.5, 5.9 Hz, 1H), 5.27-5.23 (m, 2H), 2.43 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 149.6, 145.2, 137.5, 135.1, 129.7, 128.7, 128.5, 127.3, 118.2, 79.4, 21.8.

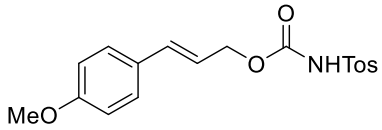


1-(4-klorofenilalil) tosilkarbamatoa (**28c**). **16c** alcoholetik sortua (g.t., 5 min). 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.30). Etekina %85 (0.26 mmol, 93 mg), olio koloregabea. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.70-7.67 (br s, 1H), 7.33 – 7.23 (m, 4H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.07 (d, *J* = 5.9 Hz, 1H), 5.87 (ddd, *J* = 16.7, 10.8, 5.9 Hz, 1H), 5.27-5.23 (m, 2H), 2.44 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 149.6, 145.3, 136.1, 135.6, 134.6, 129.8, 128.9, 128.7, 128.5, 118.6, 78.5, 21.8. **HRMS** (ESI) $C_{17}H_{16}ClNO_4SNa$ [M+Na]$^+$: kalkulatua 388.0381; aurkitua: 388.0380.

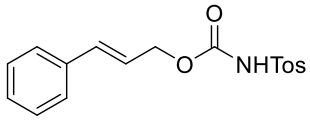
[53] Xing, D.; Yang, D. *Org. Lett*. **2010**, *12*, 1068-1071.



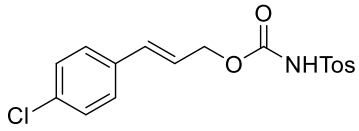
1-(4-nitrofenilalil) tosilkarbamatoa (**28d**). **16d** alkoholetik sortua (g.t., 5 min). 40:60 EtOAc:Hexano nahasteaz purifikatua (R_f 0.31). Etekina %90 (0.27 mmol, 101 mg), olio horia. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.16 (d, *J* = 6.1 Hz, 1H), 5.85 (ddd, *J* = 16.8, 10.5, 6.1 Hz, 1H), 5.33 – 5.24 (m, 2H), 2.44 (s, 3H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 149.5, 147.9, 145.5, 144.7, 135.5, 133.9, 129.8, 128.4, 127.8, 123.9, 119.7, 77.9, 21.8. **HRMS** (ESI) $C_{17}H_{20}N_3O_6S$ $[M+NH_4]^+$: kalkulatua 394.1073; aurkitua: 394.1068.



(E)-3-(4-metoxifenil)alil tosilkarbamatoa (**29a**). **16a** alkoholetik sortua (g.t., 15 min). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.23). Etekina %90 (0.27 mmol, 98 mg), olio koloregabea. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 55/45 erlazioan. **FTIR (neat, cm^{-1})** 3590, 3356, 3259, 2959, 1744, 1510, 1300, 1245. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 1.1H), 7.81 (d, *J* = 8.6 Hz, 0.9H), 7.37 – 7.28 (m, 4H), 6.85 (d, *J* = 4.7 Hz, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.01 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.77-4.75 (br s, 1H), 4.69 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.81 (s, 3H), 2.43 (s, 1.65H), 2.42 (s, 1.35H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 159.9, 150.6, 145.1, 143.6, 139.2, 135.6, 135.3, 129.8, 129.7, 128.6, 128.5, 128.1, 126.5, 119.4, 114.2, 67.8, 55.4, 21.8, 21.6. **HRMS** (ESI) $C_{18}H_{23}N_2O_5S$ $[M+NH_4]^+$: kalkulatua 379.1328, aurkitua 379.1324.



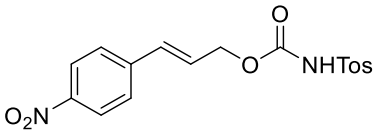
(E)-3-fenilalil tosilkarbamatoa (**29b**).[54] **28b** artekaritik sortua (90 °C, 6h). 40:60 EtOAc:Hexano nahasteaz purifikatua (R_f 0.39). Etekina %95 (0.28 mmol, 94 mg), solido zuria. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 75/25 erlazioan. **u_p** = 73-76 °C. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 1.5H), 7.82 (m, 0.5H), 7.37 – 7.25 (m, 7H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.72 (dd, *J* = 6.6, 1.3 Hz, 2H), 2.43 (s, 0.75H), 2.42 (s, 2.25H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 150.7, 145.1, 143.5, 139.2, 135.8, 135.5, 135.2, 129.7, 129.6, 128.7, 128.4, 128.3, 126.7, 126.4, 121.7, 67.3, 21.7, 21.5. **HRMS** (ESI) $C_{17}H_{21}N_2O_4S$ $[M+NH_4]^+$: kalkulatua 349.1227, aurkitua 349.1222.



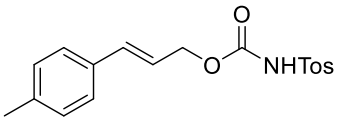
(E)-3-(4-klorofenil)alil tosilkarbamatoa (**29c**). **28c** artekaritik sortua (90 °C, 20h). 35:65 EtOAc:Hexano nahasteaz purifikatua (R_f 0.26). Etekina %70 (0.21 mmol, 77 mg), solido zuria. Datu analitiko eta espektroskopikoak literaturako publikazioarekin

[54] Chow, S. Y.; Stevens, M. Y.; Odell, L. R. *J. Org. Chem*. **2016**, *81*, 2681-2691.

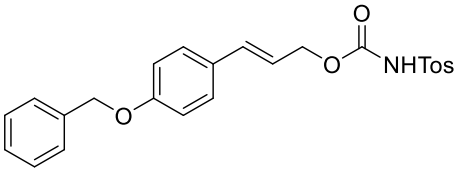
bat datoz. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 60/40 erlazioan. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1.2H), 7.82 (d, *J* = 8.1 Hz, 0.8H), 7.37 – 7.22 (m, 6H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 16.0, 6.6 Hz, 1H), 4.83-4.81 (br s, 1H), 4.71 (dd, *J* = 6.6, 1.3 Hz, 2H), 2.43 (s, 1.8H), 2.42 (s, 1.2H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 150.6, 145.2, 143.7, 139.2, 134.4, 134.1, 133.9, 129.8, 129.7, 129.6, 128.9, 128.5, 128.3, 127.9, 126.5, 122.5, 67.1, 21.8.



(E)-3-(4-nitrofenil)alil tosilkarbamatoa (**29d**). **28d** artekaritik sortua (90 °C, 4 egun, %70 konbertsioa). 20:80 EtOAc:Hexano nahasteaz purifikatua (R_f 0.15). Etekina %40 (0.12 mmol, 45 mg), olio horia. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 99/1 erlazioan. **FTIR (neat, cm^{-1})** 3534, 3237, 1748, 1520, 1345. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.77 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.43 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 145.4, 142.3, 135.5, 132.41, 129.8, 128.6, 127.4, 126.8, 124.2, 66.6, 21.9. **HRMS** (ESI) $C_{17}H_{20}N_3O_6S$ $[M+NH_4]^+$: kalkulatua 394.1067, aurkitua: 394.1067.

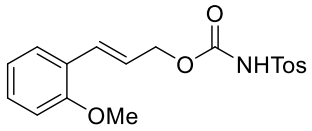


(E)-3-(4-metilfenil)alil tosilkarbamatoa (**29e**). **16e** alkoholetik sortua (90 °C, 6h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.26). Etekina %70 (0.21 mmol, 72 mg), solido zuria. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 65/35 erlazioan. **u_p** = 82-85 °C. **FTIR (neat, cm^{-1})** 3354, 2948, 1754, 1436, 1344. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1.3 H), 7.82 (d, *J* = 8.1 Hz, 0.7H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.73-4.69 (br s, 1H), 4.71 (dd, *J* = 6.7, 1.2 Hz, 2H), 2.43 (s, 1.05H), 2.42 (s, 1.95H), 2.34 (s, 3H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 150.7, 145.1, 143.6, 139.2, 138.4, 135.4, 133.1, 129.8, 129.7, 129.4, 128.4, 126.7, 126.5, 120.7, 67.6, 21.7, 21.6, 21.3. **HRMS** (ESI) $C_{18}H_{23}N_2O_4S$ $[M+NH_4]^+$: kalkulatua 363.1379, aurkitua 363.1378.

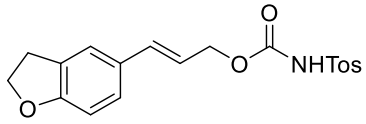


(E)-3-(4-benziloxi)fenil)alil tosilkarbamatoa (**29f**). **16f** alkoholetik sortua (g.t., 15 min). 35:65 EtOAc:Hexano nahasteaz purifikatua (R_f 0.38). Etekina %74 (0.22 mmol, 97 mg), solido zuria. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 65/35 erlazioan. **u_p** = 106-109. **FTIR (neat, cm^{-1})** 3356, 1739, 1512, 1153.

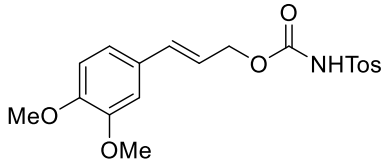
^{1}H RMN (400 MHz, $CDCl_3$) δ 7.97 – 7.88 (d, *J* = 8.42 Hz, 1.3H), 7.86 – 7.78 (d, *J* = 8.15 Hz , 0.7H), 7.50 – 7.25 (m, 9H), 6.97 – 6.86 (d, *J* = 8.42 Hz , 2H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.01 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.07 (s, 2H), 4.76-4.73 (br s, 1H), 4.69 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.43 (s, 1.05H), 2.42 (s, 1.95H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 159.1, 150.6, 145.2, 143.6, 139.2, 136.8, 135.6, 135.2, 129.8, 129.7, 128.9, 128.7, 128.5, 128.2, 128.1, 127.6, 126.5, 119.6, 115.1, 70.1, 67.7, 21.76, 21.62. **HRMS** (ESI) $C_{24}H_{27}N_2O_5S$ $[M+NH_4]^+$: kalkulatua 455.1641, aurkitua 455.1647.



(E)-3-(2-metoxifenil)alil tosilkarbamatoa (**29g**). **16g** alkoholetik sortua (g.t., 16h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.24). Etekina %85 (0.26 mmol, 92 mg), olio horia. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 65/35 erlazioan. **FTIR (neat, cm^{-1})** 3257, 3067, 1744, 1152. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 1.3H), 7.81 (d, *J* = 8.1 Hz, 0.7H), 7.34-7.22 (m, 4H), 6.94 – 6.84 (m, 2H), 6.16 (dt, *J* = 16.0, 6.6 Hz, 1H), 5.25-5.20 (br s, 1H), 4.70 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 1.05H), 2.39 (s, 1.95H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 157.0, 150.6, 145.1, 143.5, 139.3, 135.6, 130.6, 129.8, 129.7, 129.5, 128.5, 127.3, 126.5, 124.9, 122.3, 120.7, 111.0, 68.0, 55.5, 21.7, 21.6. **HRMS** (ESI) $C_{18}H_{23}N_2O_5S$ $[M+NH_4]^+$: kalkulatua 379.1328, aurkitua 379.1325.

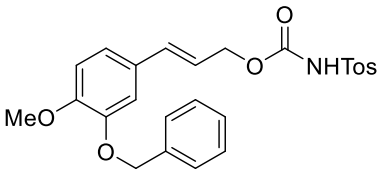


(E)-3-(2,3-dihidrobenzofuran-5-il)alil tosilkarbamatoa (**29h**). **16h** alkoholetik sortua (g.t., 1h). 40:60 EtOAc:Hexano nahasteaz purifikatua (R_f 0.30). Etekina %36 (0.11 mmol, 40 mg), olio koloregabea. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 99/1 erlazioan. **FTIR (neat, cm^{-1})** 3374, 3280, 1746, 1599, 1161. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 2H), 7.31 (m, 2H), 7.22 – 7.19 (m, 1H), 7.07 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 15.7 Hz, 1H), 5.98 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.68 (dd, *J* = 6.8, 1.2 Hz, 2H), 4.58 (t, *J* = 8.7 Hz, 2H), 3.19 (t, *J* = 8.7 Hz, 2H), 2.42 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 160.6, 150.5, 145.2, 135.9, 135.6, 129.7, 128.6, 127.5, 123.2, 118.7, 109.5, 71.7, 67.9, 29.6, 21.8. **HRMS** (ESI) $C_{19}H_{19}NO_5SNa$ $[M+Na]^+$: kalkulatua 396.0875, aurkitua 396.0876.

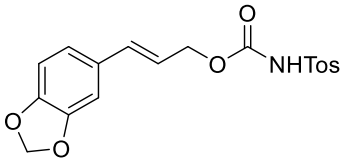


(E)-3-(3,4-dimetoxifenil)alil tosilkarbamatoa (**29i**). **16i** alkoholetik sortua (g.t., 45 min.). 40:60 EtOAc:Hexano nahasteaz purifikatua (R_f 0.20). Etekina %32 (0.10 mmol, 38 mg), olio koloregabea. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 99/1 erlazioan. **FTIR (neat, cm^{-1})**

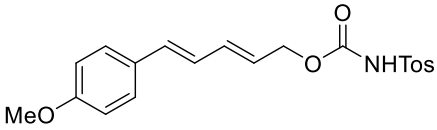
3254, 3057, 1746, 1513, 1158, 1089. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.90 – 6.84 (m, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.02 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.69 (dd, *J* = 6.7, 0.9 Hz, 2H), 3.86 (s, 6H), 2.39 (s, 3H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 150.6, 149.5, 149.1, 145.1, 135.6, 135.5, 129.7, 128.9, 128.57, 120.3, 119.7, 111.1, 108.9, 67.6, 56.0, 55.9, 21.7. **HRMS** (ESI) $C_{19}H_{25}N_2O_6S$ $[M+NH_4]^+$: kalkulatua 409.1433, aurkitua 409.1431.



(E)-3-(3-(benziloxi)-4-metoxifenil)alil tosilkarbamatoa (**29j**). **16j** alkoholetik sortua (g.t., 45 min). Purified on a 40:60 EtOAc:Hexano nahasteaz purifikatua (R_f 0.33). Etekina %54 (0.16 mmol, 76 mg), olio horia. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 90/10 erlazioan. **FTIR (neat, cm^{-1})** 3063, 1744, 1510, 1257, 1155. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (d, *J* = 8.3 Hz, 1.8H), 7.80 (d, *J* = 8.3 Hz, 0.2H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.40 – 7.30 (m, 5H), 6.95 – 6.83 (m, 3H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.95 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.13 (s, 2H), 4.67 (dd, *J* = 6.7, 1.3 Hz, 2H), 3.88 (s, 3H), 2.42 (s, 0.3H), 2.40 (s, 2.7H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 150.4, 150.3, 148.4, 145.2, 137.1, 135.6, 129.7, 128.9, 128.7, 128.6, 128.1, 127.5, 120.8, 119.6, 112.2, 111.8, 71.3, 67.7, 56.2, 21.8. **HRMS** (ESI) $C_{25}H_{29}N_2O_6S$ $[M+NH_4]^+$: kalkulatua 485.1746, aurkitua 485.1745.

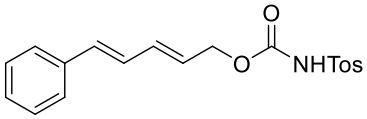


(E)-3-(benzo[d][1,3]dioxol-5-il)alil tosilkarbamatoa (**29k**). **16k** alkoholetik sortua (g.t., 3h). 35:65 EtOAc:Hexano nahasteaz purifikatua (R_f 0.27). Etekina %84 (0.25 mmol, 95 mg), solido zuria. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 90/10 erlazioan. **u_p** = 89-91 °C. **FTIR (neat, cm^{-1})** 3355, 1737, 1492, 1250, 1156. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 1.6H), 7.81 (d, *J* = 8.1 Hz, 0.4H), 7.33 – 7.29 (m, 2H), 6.84 (s, 1H), 6.75 (d, *J* = 2.2 Hz, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.04 – 5.88 (m, 3H), 5.05-5.00 (br s, 1H), 4.68 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.41 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 150.6 , 148.2 , 147.9 , 145.2 , 135.6, 135.3, 130.3, 129.7, 128.5, 126.5, 121.8, 119.9, 108.4, 105.9, 101.3, 67.5, 21.7, 21.6. **HRMS** (ESI) $C_{18}H_{17}NO_6SNa$ $[M+Na]^+$: kalkulatua 398.0670, aurkitua 398.0672.

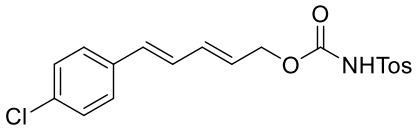


(2E,4E)-5-(4-metoxifenil)penta-2,4-dien-1-il tosilkarbamatoa (**31a**). **23a** alkoholetik sortua (g.t., 30 min.). 35:65 EtOAc:Hexano nahasteaz purifikatua (R_f 0.24). Etekina %25 (0.08 mmol, 29 mg), olio horia. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 75/25 erlazioan. **FTIR (neat, cm^{-1})** 3268, 2957, 1735, 1510, 1160. **^{1}H RMN** (400 MHz, $CDCl_3$)

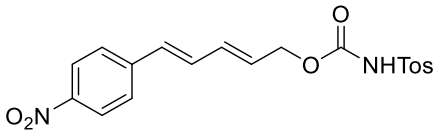
δ 7.93 (d, *J* = 8.2 Hz, 1.5H), 7.82 (d, *J* = 8.2 Hz, 0.5H), 7.36 – 7.30 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.63 – 6.52 (m, 2H), 6.36 (dd, *J* = 15.1, 9.8 Hz, 1H), 5.70 (dt, *J* = 14.5, 6.9 Hz, 1H), 4.75-4.74 (br s, 1H), 4.63 (d, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 2.25H), 2.41 (s, 0.75H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 159.8, 150.4, 145.2, 136.4, 134.4, 129.8, 128.6, 127.9, 126.6, 124.0, 114.3, 67.4, 55.5, 21.8, 21.7. **HRMS** (ESI) $C_{20}H_{21}NO_5SNa$ $[M+Na]^+$: kalkulatua 410.1038, aurkitua 410.1026.



(2E,4E)-5-fenilpenta-2,4-dien-1-il tosilkarbamatoa (**31b**). **23b** alkoholetik sortua (g.t., 4h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.29). Etekina %75 (0.23 mmol, 80 mg), olio horia. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 63/37 erlazioan. **FTIR (neat, cm^{-1})** 3272, 3054, 1751, 1597. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 1.3H), 7.84 – 7.80 (m, 0.7H), 7.41 – 7.36 (m, 2H), 7.36 – 7.29 (m, 4H), 7.27 – 7.24 (m, 1H), 6.71 (dd, *J* = 15.7, 10.3 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H), 6.37 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.75 (dt, *J* = 14.1, 6.7 Hz, 1H), 5.02-4.93 (br s, 1H), 4.64 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 1. 9H), 2.42 (s, 1.1H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 150.6, 145.2, 143.6, 139.2, 136.8, 135.6, 134.5, 129.8, 128.7, 128.4, 128.1, 127.4, 126.6, 126.5, 125.4, 67.1, 21.7, 21.6. **HRMS** (ESI) $C_{19}H_{19}NO_4SNa$ $[M+Na]^+$: kalkulatua 380.0933, aurkitua 380.0924.



(2E,4E)-5-(4-klorofenil)penta-2,4-dien-1-il tosilkarbamatoa (**31c**). **23c** alkoholetik sortua (g.t., 4h). 30:70 EtOAc:Hexano nahasteaz purifikatua (R_f 0.22). Etekina %68 (0.20 mmol, 80 mg), olio hori argia. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 75/25 erlazioan. **FTIR (neat, cm^{-1})** 3272, 3055, 1749, 1595, 1344. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 1.5H), 7.85 – 7.76 (m, 0.5H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.22 (m, 4H), 6.64 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.33 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.75 (dt, *J* = 15.2, 6.5 Hz, 1H), 4.62 (d, *J* = 6.5 Hz, 2H), 2.40 (s, 2.25H), 2.39 (s, 0.75H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 150.5, 145.2, 143.7, 139.2, 135.5, 135.2, 133.7, 133.1, 129.8, 129.7, 128.9, 128.5, 127.9, 127.8, 126.5, 125.9, 67.0, 21.8, 21.6. **HRMS** (ESI) $C_{19}H_{18}ClNO_4SNa$ $[M+Na]^+$: kalkulatua 414.0540, aurkitua 414.0542.

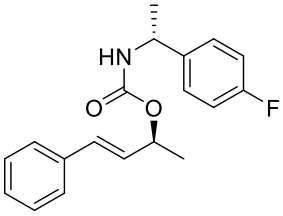


(2E,4E)-5-(4-nitrofenil)penta-2,4-dien-1-il tosilkarbamatoa (**31d**). **23d** alkoholetik sortua (90 °C, 5 egun). 40:60 EtOAc:Hexano nahasteaz purifikatua (R_f 0.26). Etekina %36 (0.11 mmol, 44 mg), olio laranja. RMN espektroak 298K-tan eta $CDCl_3$-an bi konformeroen presentzia (errotameroak) erakusten du 99/1 erlazioan. **FTIR (neat, cm^{-1})** 3524, 3237, 1749, 1514, 1340, 1158. **^{1}H RMN** (400 MHz,

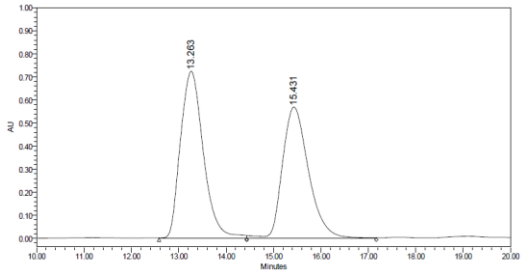
$CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.85 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.41 (dd, *J* = 15.3, 10.6 Hz, 1H), 5.90 (dt, *J* = 15.3, 5.9 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 2H), 2.44 (s, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 150.3, 147.1, 145.4, 143.3, 135.5, 134.3, 131.9, 129.8, 128.7, 128.5, 127.1, 124.2, 66.6, 21.8. **HRMS** (ESI) $C_{19}H_{18}N_2O_6SNa$ $[M+Na]^+$: kalkulatua 425.0779, aurkitua 425.0785.

Kiralitate transferentzia azterketak

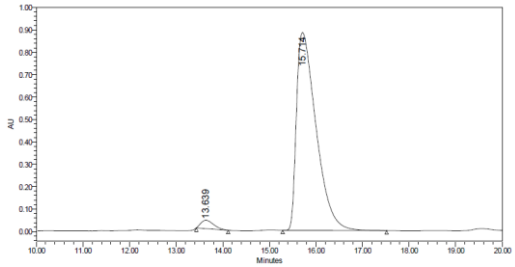
(*S*,*E*)-fenilbut-2-en-1-ol **32** (22 mg, 0.15 mmol, 1 eq.) tolueno (0.2 M) disoluzioari (*R*)-(+)-(4-fluorofenil)etil isozianatoa (26 µL, 0.18 mmol, 1.2 eq.) eta trietilamina (8 µL, 0.06 mmol, 0.4 eq.) gehitu zitzaizkion, eta erreakzioa 6 orduz nahastu zen 90 ºC-tan. Hasierako nahaste hau presio erreduzituan kontzentratu zen, Et_2O-tan diluitu (2 mL) eta NaCl saturatuarekin garbitu (3 x 2 mL). Sorturiko nahastea toluenotan diluitu zen (0.2 M) eta 110 ºC-tan nahastu 48 orduz. Azken nahastea aluminio oxidozko zutabe kromatografiko bidez purifikatu zen.



(S,E)-4-fenilbut-3-en-2-il ((R)-1-(4-fluorofenil)etil)karbamatoa (**35**). 17:83 EtOAc:Hexano nahasteaz purifikatua (R_f 0.64). Etekina %39 (0.06 mmol, 19 mg), olio koloregabea. $[\alpha]_D^{25}$ = -15.91 (*c* 0.35, kloroformoa). **FTIR (neat, cm^{-1})** 3343, 2979, 1680, 1529, 1508. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 7H), 7.00 (dd, *J* = 8.6, 8.6 Hz, 2H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.41 (dd, *J* = 6.5, 6.5 Hz, 1H), 4.92-4.90 (br s, 1H), 4.86 – 4.78 (m, 1H), 1.47 (m, 3H), 1.43 – 1.36 (m, 3H). **^{13}C RMN** (101 MHz, $CDCl_3$) δ 162.08 (d, $^1J_{C\text{-}F}$ = 244.9 Hz), 155.21, 136.56, 131.24, 129.38, 128.68, 127.97, 127.68 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 126.68, 115.53 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 71.66, 50.15, 22.68, 20.75. **^{19}F RMN** (376 MHz, $CDCl_3$) δ -115.58. **HRMS** (ESI) $C_{19}H_{20}FNO_2Na$ $[M+Na]^+$: kalkulatua 336.1631, aurkitua 336.1361. **HPLC** (Daicel ChiralPak IB Hexano:^{i}PrOH = 97:3, fluxua 1 mL/min, λ 210 nm), t_R (gutxiengoa) 13.26 min, t_R (nagusia) 15.43 min; %95 *ee*.



	RT	Altuera	Azalera	% Azal.
1	13.263	722894	24178704	52.86
2	15.431	567782	21562041	47.14

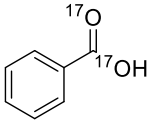


	RT	Altuera	Azalera	% Azal.
1	13.639	37547	709445	2.68
2	15.714	883664	25796538	97.32

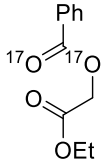
Lehen ordenako konstante zinetikoen kalkulua

Dagokion alkohol alilikoaren **16b,c** (0.3 mmol, 1 eq.) tolueno-*d8* disoluzioari (0.2 M), atmosfera inertean, *p*-toluensulfonil isozianatoa (0.36 mmol, 1.2 eq.) gehitu zitzaion tantaz-tanta. Nahaste hau RMN tubo batera pasatu zen eta lagina 363 K-tan egonkortu. Azterketa zinetikoak **29a-c** karbamatoaren hiru ^{1}H-RMN seinale analizatuz gauzatu ziren. RMN neurketak 500.13 MHz-tan burutu ziren, Bruker Avance 500 NMR espektrometroan, BBO probetan, z-gradienteekin. FID fitxeroak 16ppm-ko lehioekin prozesatu ziren, 65536 puntuz transformatuta. Espektro guztiak 16 adkisizio metatuz lortu ziren, segundu bateko delay-arekin. Neurketak erreakzio nahastean gauzatu ziren, 5 minuturo. **16a** alkoholaren kasuan, neurketak minuturo egin ziren.

[^{17}O] isotopoz markatutako laginen prestaketa

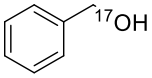


Azido benzoikoa (**[$^{17}O_2$]37**).[48] (Triklorometil)benzenoa (1.75 mmol) eta 0.59 mL of $H_2{}^{17}O$ mikrouhin ontzian jarri ziren, eta itxi. Nahastea mikrouhin bidez irradiatu zen (150 W, 130 °C 6 bar, 30 minutu). Erreakzioa hoztu ondoren, sortutako solido zuria filtratu zen eta hexanoz garbitu. Konpostau purua solido zuri bezala lortu zen. Etekina: %93 (200 mg). **^{1}H RMN** (400 MHz, Azetona-*d6*): δ 8.07 – 8.02 (m, 2H), 7.66 – 7.60 (m, 1H), 7.51 (dd, *J* = 8.4, 7.1 Hz, 2H). **^{17}O RMN** (68 MHz, Azetona-*d6*): δ 245.

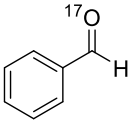


2-etoxi-2-oxoetil benzoatoa (**[$^{17}O_2$]38**).[49] **[$^{17}O_2$]37** (1.62 mmol) eta $Cu(OTf)_2$ (5.9 mg) tolueno disoluzioari (10 mL) etil diazoazetatoa gehitu zitzaion tantaka (3.24 mmol) eta nahastea 80 ºC-tan berotu zen 12 orduz. Erreakzio nahastea silikan filtratu zen eta toluenoa lurrundu. Amaierako

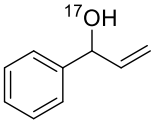
produktua purifikazio adizionalik gabe erabili zen. **^{1}H RMN** (500 MHz, Azetona-d_6): δ 8.09 (d, *J* = 7.7 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 (q, *J* = 8.0 Hz, 2H), 4.91 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.27 (tq, *J* = 7.2, 3.6, 2.6 Hz, 3H). **^{17}O RMN** (68 MHz, Azetona-d_6): δ 340, 136.



Fenilmetanola (**[^{17}O$_1$]39**). **[^{17}O$_2$]37** (1.60 mmol) THF-tan disolbatu zen (20 mL). $LiAlH_4$-ko THF disoluzioa (1.48 mL, 2.5 M) 0 ºC-tan poliki gehitu zen eta erreakzioa giro tenperaturan nahastu hasierako azidoa amaitu arte. NaOH 1N (10 mL) disoluzioa gehitu zen erreakzioa geratzeko, eta ur fasea CH_2Cl_2 bidez erauzi (3 x 10 mL). Fase organikoak $MgSO_4$ bidez lehortu ziren, filtratu eta presio erreduzituan lurrundu. Amaierako produktua silika gelezko zutabe kromatografiko bidez purifikatu zen (60/40, R_f 0.59). Etekina %85 (149 mg), olio koloregabea**. ^{1}H RMN** (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 4.5 Hz, 4H), 7.32 – 7.28 (m, 1H), 4.70 (d, *J* = 2.3 Hz, 2H), 1.67 (s, 1H). **^{17}O RMN** (68 MHz, Azetona-d_6): δ 0.

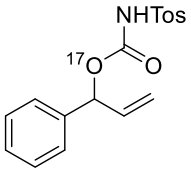


Bentzaldehidoa (**[^{17}O$_1$]40**).[55] Oxalil klorurozko (2.33 mmol) CH_2Cl_2 (3 mL) disoluzioa -84 ºC-tara hoztu zen eta dimetil sulfoxidoa poliki gehitu (4.65 mmol) . Sortutako nahastea 15 minutu gehiagoz nahastu zen. **[^{17}O$_1$]37** (1.37 mmol) gehitu zitzaion eta beste 15 minutuz nahastu. Azkenik, trietilamina (6.85 mmol) gehitu zen eta nahastea -84 ºC-tan 2 ordu gehiagoz nahastu. Erreakzioa 0 ºC-tara iristean, HCl-z gehituz geratu (3 mL) eta CH_2Cl_2 (3x 5 mL) erauzi. Fase organikoa $NaHCO_3$ sat. (2 x 5 mL) bidez garbitu zen eta konbinaturiko fase organikoak MgSO4 bidez lehortu, filtratu eta 0 ºC-tan presio erreduzituaz lurrundu. Etekina %65 (95 mg), olio koloregabea. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.95 – 7.88 (m, 2H), 7.72 – 7.63 (m, 1H), 7.57 (dd, *J* = 8.2, 6.9 Hz, 2H). **^{17}O RMN** (68 MHz, $CDCl_3$): δ 554.

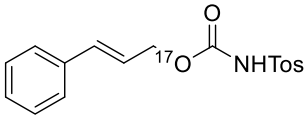


1-fenilprop-2-en-1-ol (**[^{17}O$_1$]16b**).[56] **[^{17}O$_1$]40** (0.89 mmol) THFtan disolbatu zen (6 mL) eta binilmagnesio bromuroa (1.07 mmol, 1 M) poliki gehitu. Errreakzio nahastea giro tenperaturan nahastu zen 4 orduz eta NH_4Cl disoluzio saturatua (3 mL) gehitu. Fase akuosoa Et_2O-z erauzi zen(4 x 6 mL). Fase organikoa $MgSO_4$-an lehortu zen, filtratu eta presio erreduzituan lurrundu. Amaierako produktua silika gelezko zutabe kromatografikoan purifikatu zen (70:30, R_f 0.60). Etekina %54 (64 mg), olio horia. **^{1}H RMN** (400 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 4H), 7.29 (td, *J* = 5.7, 2.5 Hz, 1H), 6.06 (ddd, *J* = 16.7, 10.3, 6.0 Hz, 1H), 5.35 (dd, *J* = 16.7, 1.6 Hz, 1H), 5.24 – 5.18 (m, 2H). **^{17}O RMN** (68 MHz, $CDCl_3$): δ 31.

[55] Neuvonen, A. J.; Földes, T.; Madarász, Á.; Pápai, I.; Pihko, P. M. *ACS Catal*. **2017**, *7*, 3284-3294.
[56] Hanessian, S.; Focken, T.; Oza, R. *Tetrahedron* **2011**, *67*, 9870-9884.



1-fenilalil tosilkarbamatoa (**[$^{17}O_1$]28b**). 1-fenilprop-2-en-1-ol **[$^{17}O_1$]34b** (0.073 mmol) tolueno (0.2 M) disoluzioari *p*-toluenosulfonil isozianatoa (0.088 mmol) gehitu zitzaion atmosfera inertean tantaka, eta 5 minutuz nahastu. Disolbatzailea presio erreduzituan lurrundu zen eta erreakzio nahastea 80/20 nahasteaz purifikatu (R_f 0.31). Etekina %90 (21 mg), olio koloregabea. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.55–7.53 (br s, 1H), 7.34–7.26 (m, 5H), 7.21 (dd, *J* = 6.8, 3.0 Hz, 2H), 6.11 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.92 (ddd, *J* = 16.7, 10.5, 5.9 Hz, 1H), 5.27–5.23 (m, 2H), 2.43 (s, 3H). **^{17}O RMN** (68 MHz, $CDCl_3$): δ 150, 129.



(E)-3-(fenil)alil tosilkarbamatoa (**[$^{17}O_1$]29b**). **[$^{17}O_1$]28b**-tik sortua (90 °C, 4 h) 60/40 nahasteaz purifikatua (R_f 0.39) Etekina %86 (21 mg), solido zuria. **^{1}H RMN** (400 MHz, $CDCl_3$) δ 7.97–7.90 (m, 1.5H), 7.82 (m, 0.5H), 7.37–7.25 (m, 7H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.72 (dd, *J* = 6.6, 1.3 Hz, 2H), 2.43 (s, 0.75H), 2.42 (s, 2.25H). **^{17}O RMN** (68 MHz, $CDCl_3$) δ 264, 125. **HRMS** (ESI) **[$^{17}O_1$]14b***:* kalkulatua $C_{17}H_{17}NO_4SNa$ $[M+Na]^+$ 354.0763; aurkitua: 354.0763 (59%); kalkulatua $C_{17}H_{17}NO_3{}^{17}OSNa$ $[(M+1)+Na]^+$ 355.0805; aurkitua: 355.0799 (11%); kalkulatua $C_{17}H_{17}NO_3{}^{18}OSNa$ $[(M+2)+Na]^+$ 356.0806; aurkitua: 356.0799 (30%).

[$^{17}O_1$]28b → [$^{17}O_1$]29b transformazioa RMN-z monitorizatzeko prozedura

1-fenilprop-2-en-1-ol **[$^{17}O_1$]16b** (0.373 mmol) tolueno (0.2 M) disoluzioa atmosfera inertean jarri zen, eta *p*-toluensulfonil isozianatoa (0.447 mmol, 1.2 eq.) tantaka gehitu. Erreakzioa 90 ºC-tara berotu zen, eta 20 minuturo 200 µL hartu. Toluenoa lurrundu zen aldiro, eta sorturiko olio koloregabea $CDCl_3$-tan disolbatu zen giro tenperaturako ^{17}O RMN esperimentuak burutzeko.