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Asymmetric α-Functionalization of Cyclic Ketones Promoted by Brønsted Base/H-Bond Catalysts

DOCTORAL THESIS

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Summary

Owing to the widespread presence of cyclic ketone fragments in natural products and bioactive compounds (Figure A), asymmetric methods for the generation and control of the reactivity of cyclic ketone enolates or equivalents are in high demand.

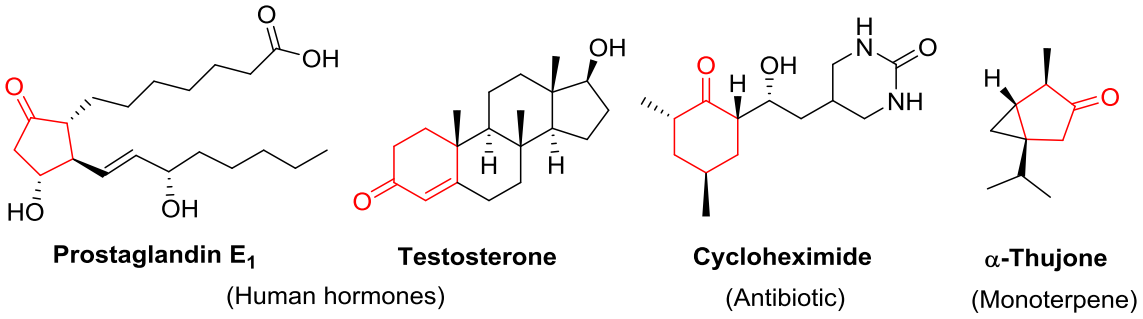


Figure A. Cyclic ketone fragments in natural products and bioactive compounds.

Several methods have been described in order to control the stereochemical outcome of the reaction of an electrophile with an enolate anion or equivalent. However, current catalytic, and particularly organocatalytic, methods for the enantioselective functionalization of (cyclic) ketones are plagued of a number of complications and limitations (Figure B0). These problems are associated mainly to two aspects: i) the lack of threshold reactivity of simple (cyclic) ketones towards base catalyst-promoted proton abstraction (transient generation of enolate) and ii) difficulties in controlling efficiently the α/α' site selectivity in simple (cyclic) non-symmetric ketones. Apart from these two aspects, efficient control of the reaction enantio- and diastereoselectivity is an additional issue that need to be properly addressed, especially when generation of quaternary carbon centers are involved.

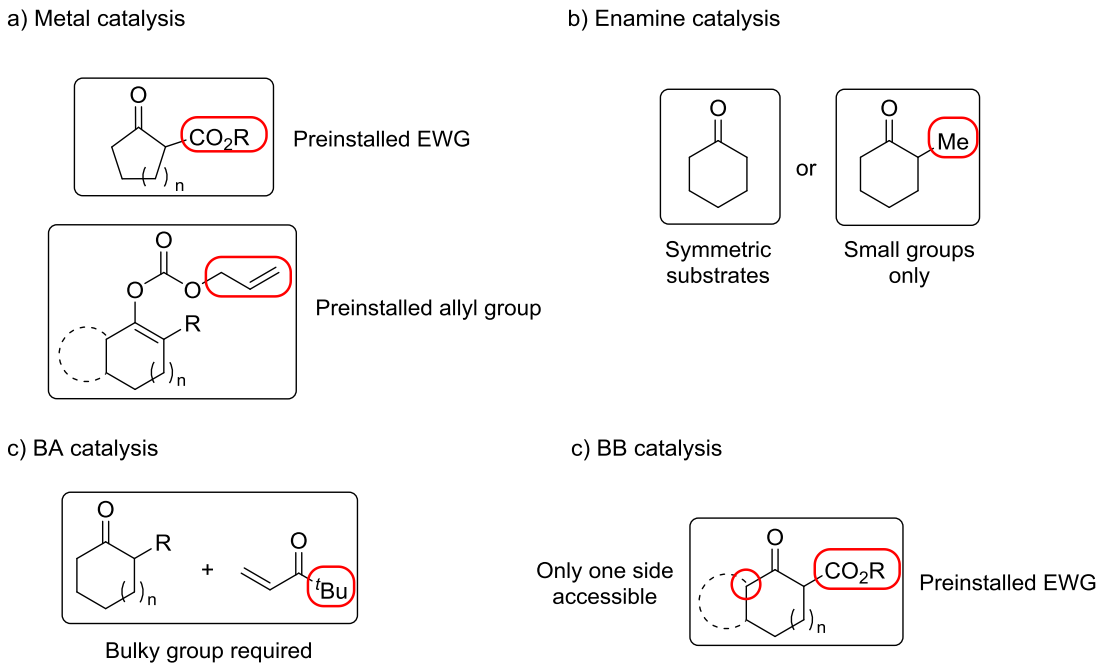
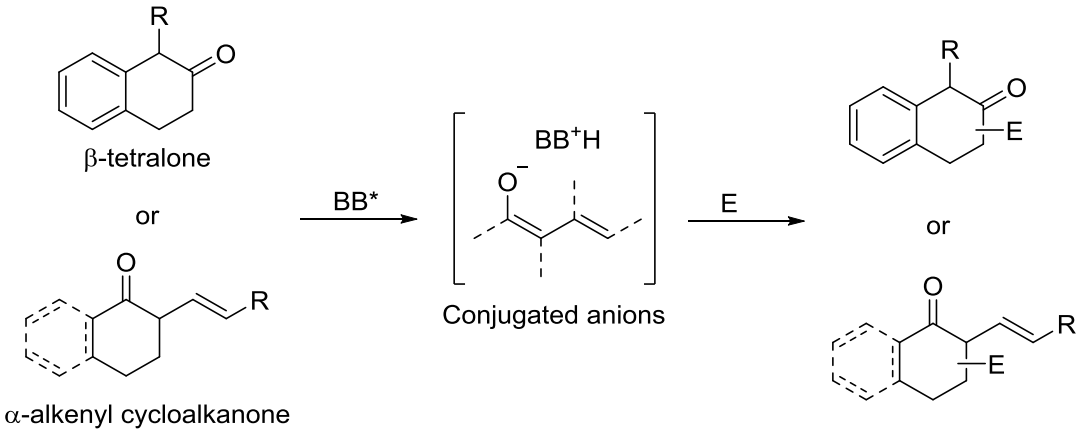


Figure B. Current successful methods and inherent restrictions.

In this context, the aim of this thesis has been the development of new methodologies for regio- and stereoselective α-functionalization of cyclic ketones that would solve some of the above problems and limitations. With this purpose, Brønsted base/H-bonding catalysis has been applied in which proton transfer events are central to the substrate activation and catalysis cycle. For doing so, we envisioned that β-tetralones and α-alkenyl cycloalkanones could be feasible substrates for deprotonation by weakly basic catalysts as they lead to conjugated anions (enolates), thus eventually driving the catalytic process forward (Scheme A).



Scheme A. Favored deprotonation of cyclic ketones due to conjugation.

On the other hand, β-tetralones are important precursors for the synthesis of bioactive compounds with polycyclic structures, including homoerythrina alkaloids, morphan derivatives, glucocorticoid receptors, and stradiols, among others (Figure C).

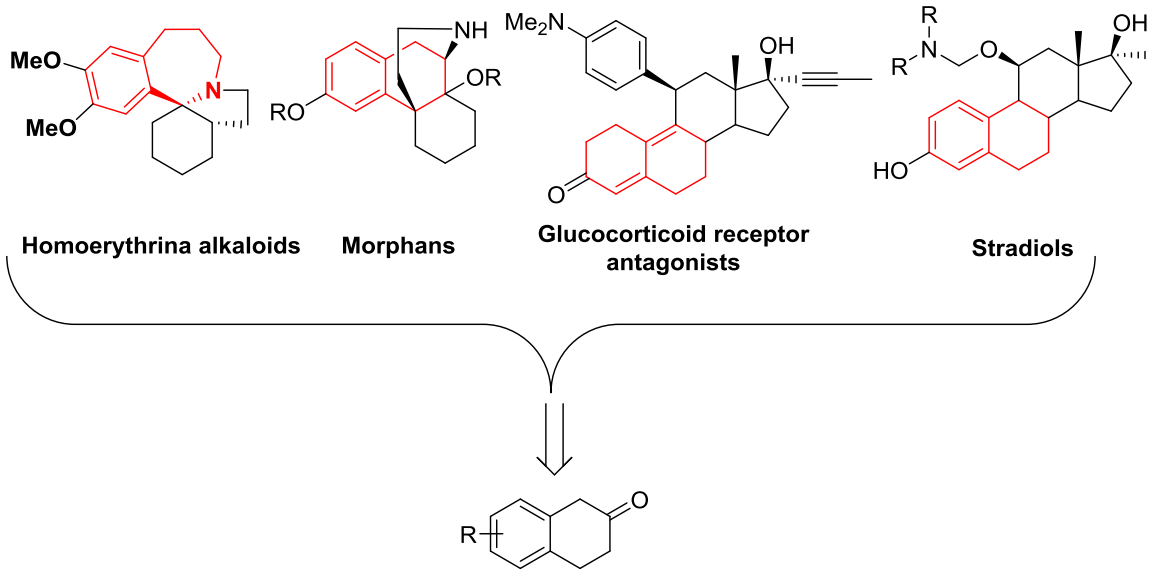
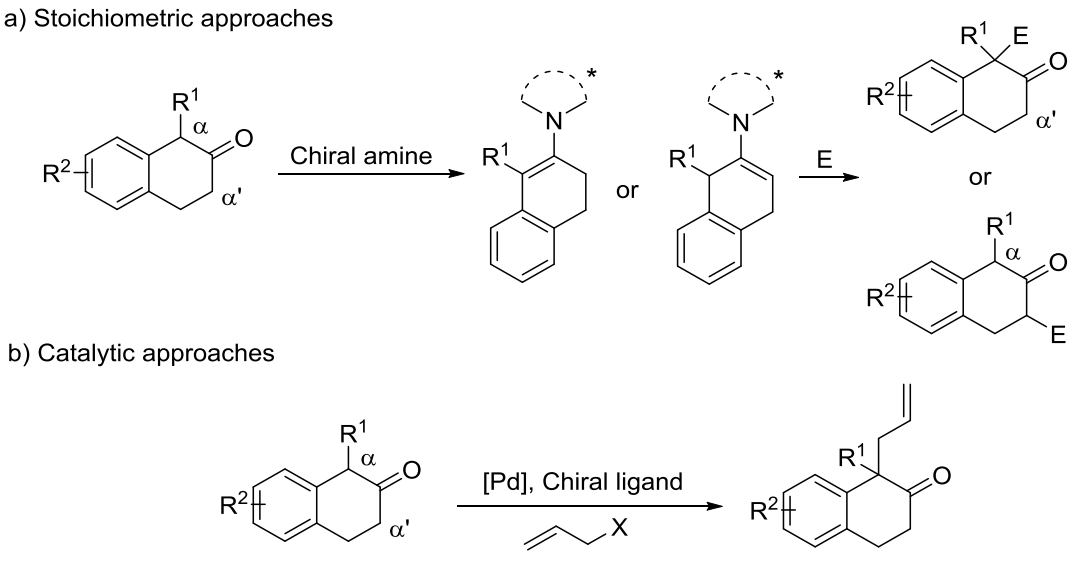


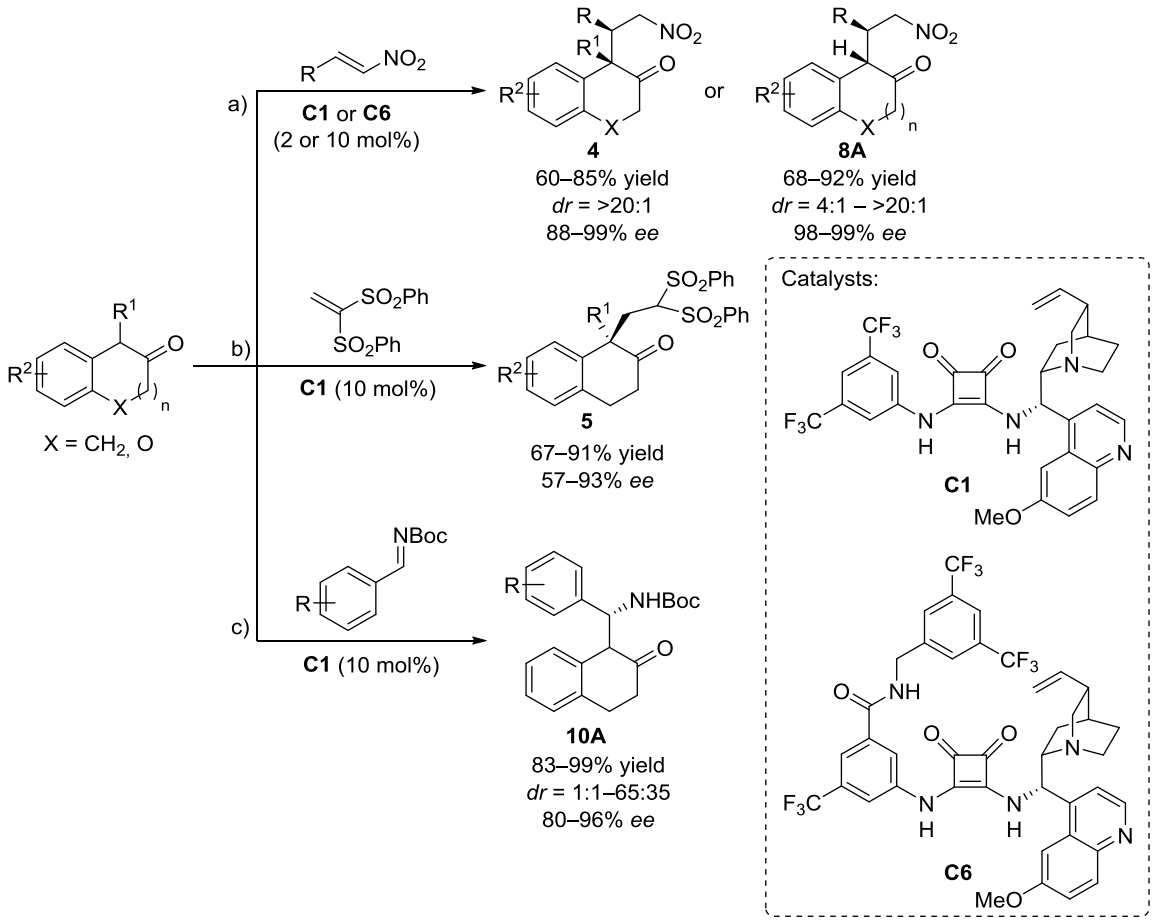
Figure C. Bioactive compounds with polycyclic structures derivable from β-tetralone.

However, this interest did not translate into a variety of approaches for the asymmetric synthesis of α(α')-substituted β-tetralones. Among the few existing approaches, the α/α´-functionalization of β-tetralones have been documented using stoichiometric chiral reagents, mainly involving condensation with a chiral amine and subsequent C-alkylation of the resulting enamine (Scheme Ba), and catalytic methods, mainly based on palladium-catalyzed asymmetric allylation reactions (Scheme Bb).



Scheme B. Main strategies for the asymmetric α- or α´-functionalization of β-tetralones.

In this investigation we have found that α-substituted β-tetralones react with nitroolefins in the presence of 10 mol% of bifunctional Brønsted base/H-bond catalyst **C6** to afford the corresponding α,α-disubstituted adducts **4** in high enantio- and diastereoselectivity (Scheme Ca). Similarly, the reaction with vinyl bis(sulfone) in the presence of catalyst **C1** afforded the enantioenriched products **5** in good yield (Scheme Cb). Interestingly, the reaction of α-unsubstituted β-tetralones with nitroolefins also gave exclusively the α-substituted products **8A** with excellent enantioselectivity and moderate diastereoselectivity (Scheme Ca). The 1,2-addition reaction to *N*-Boc aromatic imines also proceed with essentially perfect regioselectivity and high *ee* values, but with no diastereoselectivity (except in an example, *dr* = 65:35), indicating that there was appreciable racemization under these reaction conditions (Scheme Cc).



Scheme C. BB catalyzed regio- and stereoselective α-alkylation of β-tetralones with different electrophiles.

With regard to α-alkenyl cycloalkanones, besides the problem cited above, the intermediate dienolate may react through either the α or γ nucleophilic carbon, thus demanding stringent reaction control (Figure D).

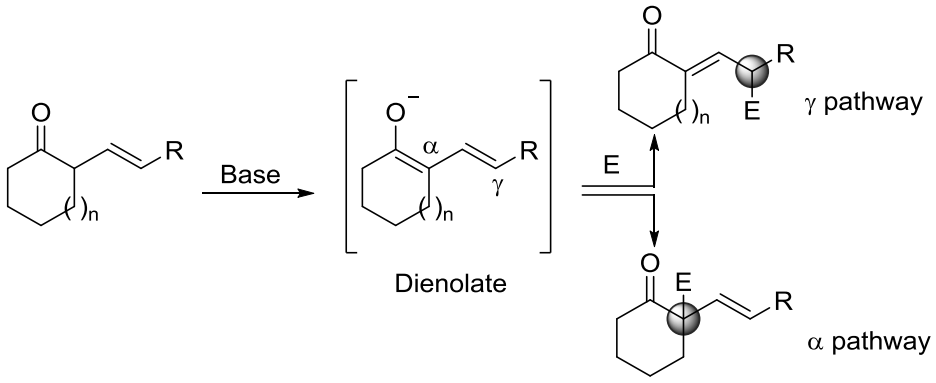
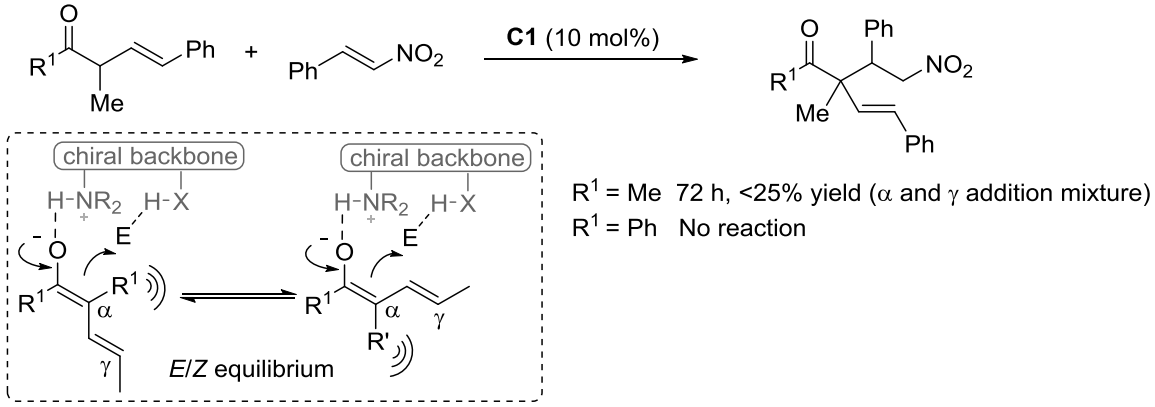


Figure D. Enolization of α-alkenyl cycloalkanones and the emergence of α vs γ reaction selectivity problem.

To date, the majority of catalytic methods involving dienolate or equivalent intermediates deal with α-unsubstituted ketones, and proceed mainly through the γ carbon (vinylogous reactivity). These methods include catalyst-promoted addition reactions of preformed silyl dienol ethers, as well as direct approaches based on metallic catalysis, dienamine activation, and Brønsted acid and base catalysis activation. Exceptions to this mainstream γ-selectivity involve concomitant isomerization of the C=C double bond to yield Morita-Baylis-Hilmann type adducts (no α-stereocenter is formed), require restricted substrate categories or substrates with strong steric bias, or lead to poor enantioselectivity. In addition, none of these α-selective methods has been revealed useful for the enantioselective generation of α-quaternary ketone products.

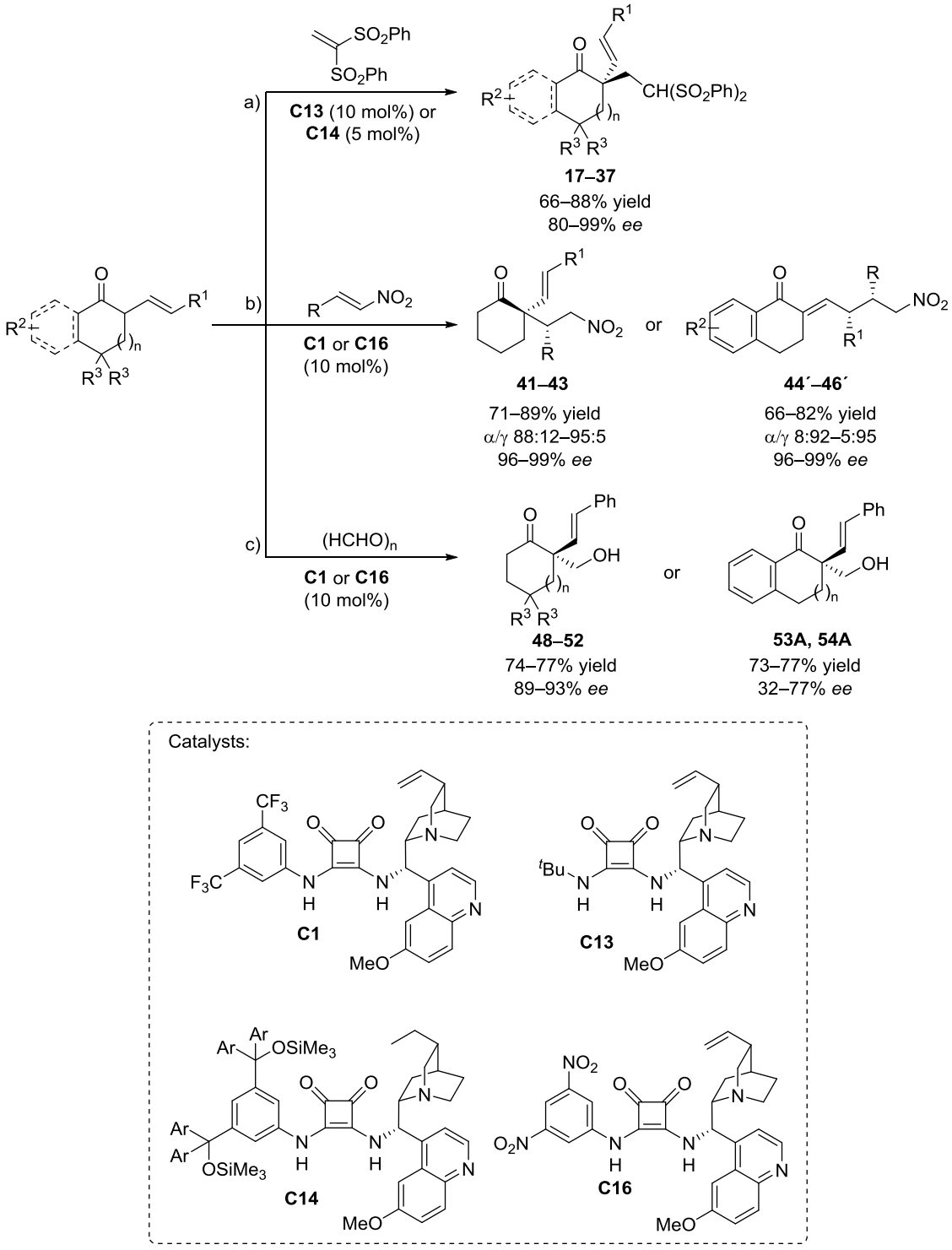
Our initial studies involving acyclic α-branched ketones resulted in the recovery of unreacted enone (R^1 = Ph) or very low conversions (R^1 = Me, <25% conversion) owing to the steric shielding at Cα, confirming the difficulties anticipated (Scheme D).



Scheme D. Impact of α-substitution on the reactivity of transiently formed acyclic ketone dienolates.

Gratifyingly, further studies with cyclic systems enabled the generation of dienolates from α-branched allylic ketones and the following reaction with various carbon electrophiles to occur predominantly at C_α. We have found that the reaction of α-alkenyl cyclohexanones as well as benzo-fused cycloalkanones with vinyl bis(sulfone) provided the corresponding all-carbon quaternary α-addition adducts **17**–**37** in high yield and enantioselectivity (Scheme Ea). When nitroalkenes were used as electrophiles, the α/γ ratios of the isolated products were highly substrate dependent. In the case of α-alkenyl cyclohexanones, the desired adducts **41**–**43** were obtained in good yields, excellent enantioselectivities and generally α/γ ratios between 90:10 and 95:5. On the other hand, the addition of α-alkyliden 1-tetralones gave the γ-addition products **44´**–**46´** almost exclusively (α/γ 5:95) with very high *ee* values suggesting the multivariable α/γ selectivity of dienolate systems (Scheme Eb). The aldol addition to formaldehyde employing catalyst **C16** also proceed with essentially perfect regioselectivity and high enantioselectivity. Surprisingly, the reaction of benzo-fused cycloalkanones with both catalysts **C1** and **C16** provided the corresponding adducts **53A** and **54A** in good yields but low enantioselectivities (Scheme Ec).

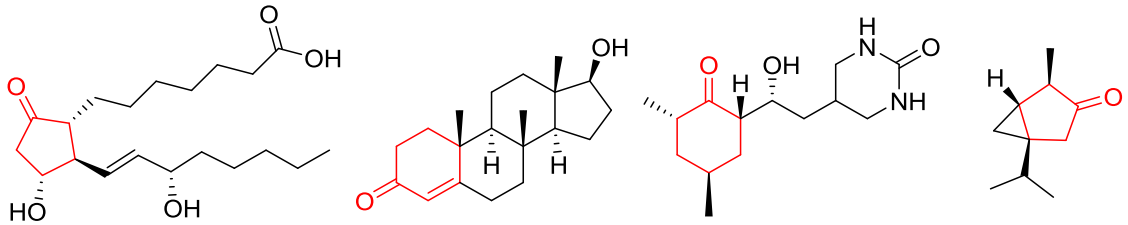
These results show that although the regio-, diastereo- and enantioselective functionalization of α-alkenyl cyclic ketones to produce quaternary carbons is possible under very mild conditions in the presence of a Brønsted base/H-bond catalyst, the degree of selectivity depends on several factors, mainly, on the nature of the cycloalcanone and the electrophilic reagent as well as on the structure of the catalyst.



Scheme E. BB catalyzed C-functionalization of α-branched allylic ketones with various carbon electrophiles.

Resumen

Los métodos asimétricos para la generación y control de la reactividad de enolatos o equivalentes de cetonas cíclicas son de gran interés debido a que estas unidades se hallan en productos naturales y compuestos bioactivos (Figura A).



Prostaglandina E_1 (Hormonas humanas) **Testosterona** **Cycloheximida** (Antibiótico) **α-Tujona** (Monoterpeno)

Figura A. Fragmentos de cetonas cíclicas en productos naturales y compuestos bioactivos.

A pesar de los avances logrados en la funcionalización de cetonas vía enolatos o equivalentes por reacción con el correspondiente electrófilo, la mayoría de métodos asimétricos y catalíticos, y particularmente organocatalíticos, presentan importantes problemas y limitaciones, principalmente: i) la escasa reactividad de las cetonas (cíclicas) simples frente a la abstracción de protón promovida por catalizadores básicos (generación transitoria de enolato) y ii) dificultades en controlar de manera eficiente la selectividad α/α' en cetonas (cíclicas) simples no simétricas. Además de estos dos aspectos, el control eficiente de la enantio- y diastereoselectividad de la reacción es una cuestión adicional que debe abordarse adecuadamente, especialmente en el caso de generación de centros cuaternarios de carbono.

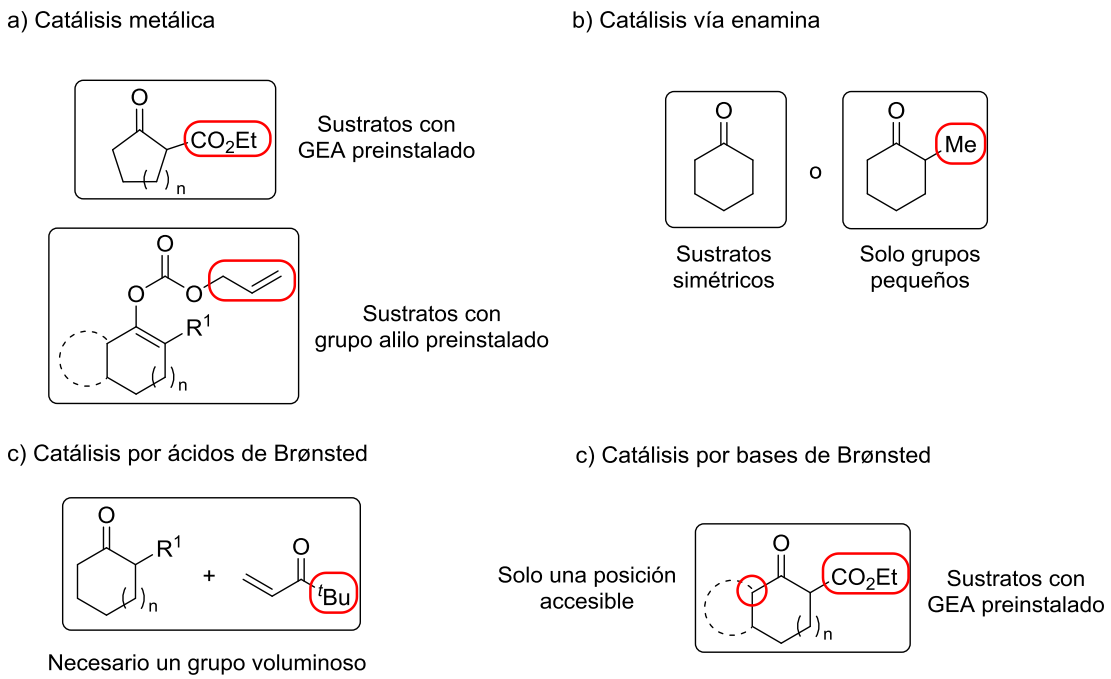
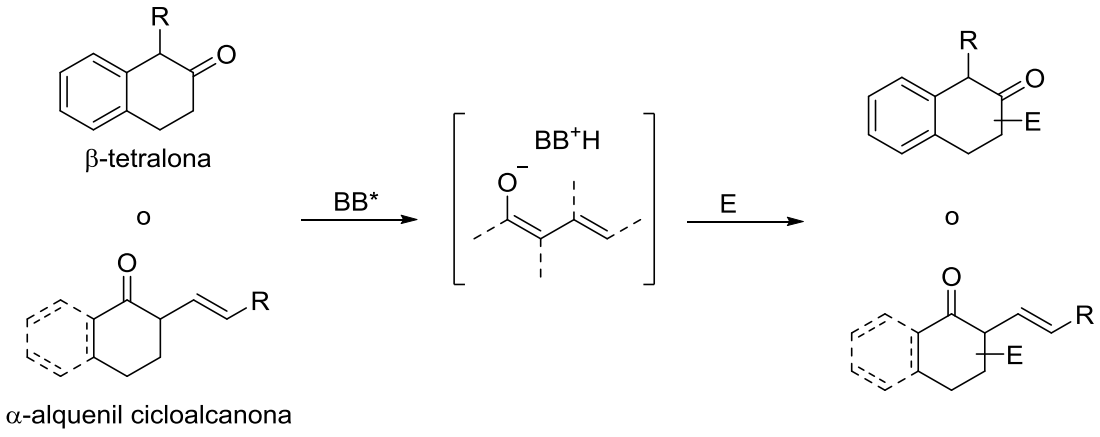


Figura B. Estado del arte en la funcionalización catalítica y asimétrica de cetonas cíclicas.

En este contexto, el objetivo de esta tesis doctoral ha sido el desarrollo de nuevas metodologías para la α-funcionalización regio- y estereoselectiva de cetonas cíclicas que resuelvan algunas de las limitaciones mencionadas arriba. Con este propósito, se han empleado catalizadores con carácter bifuncional base de Brønsted/dador de enlace de H, cuya acción se basa en procesos de transferencia de protón. El estudio se ha basado en la funcionalización de β-tetralonas y α-alquenil cicloalcanonas, ya que dichos sustratos podrían ser desprotonados mediante bases débiles al conducir a enolatos parcialmente estabilizados (anión alílico/bencílico) favoreciendo el proceso catalítico (Esquema A).



Esquema A. Desprotonación favorecida de cetonas cíclicas debido a la conjugación.

La elección de las β-tetralonas como objeto de estudio también obedece a que las mismas son precursoras en la síntesis de compuestos bioactivos con estructuras policíclicas, entre las que se incluyen alcaloides de homoeritrina, derivados de morfano, receptores glucocorticoides y estradioles, entre otros (Figura C).

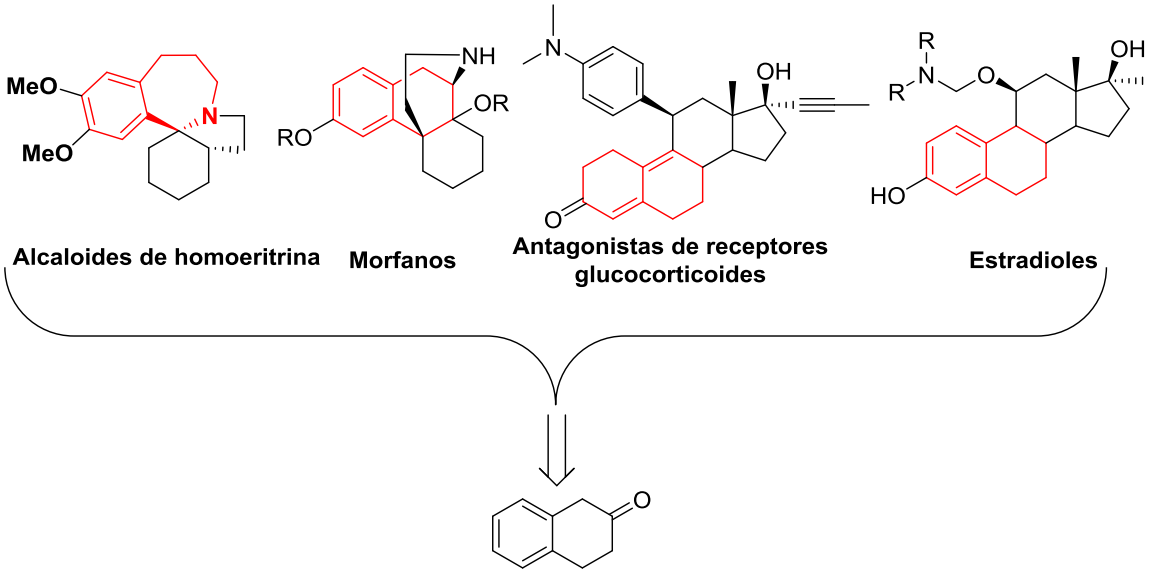
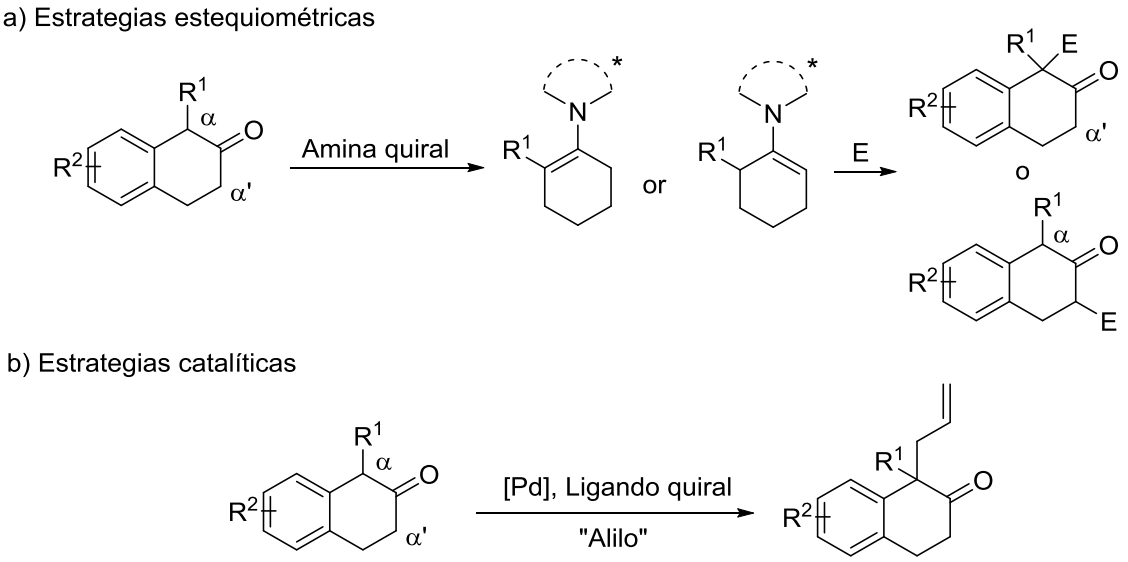


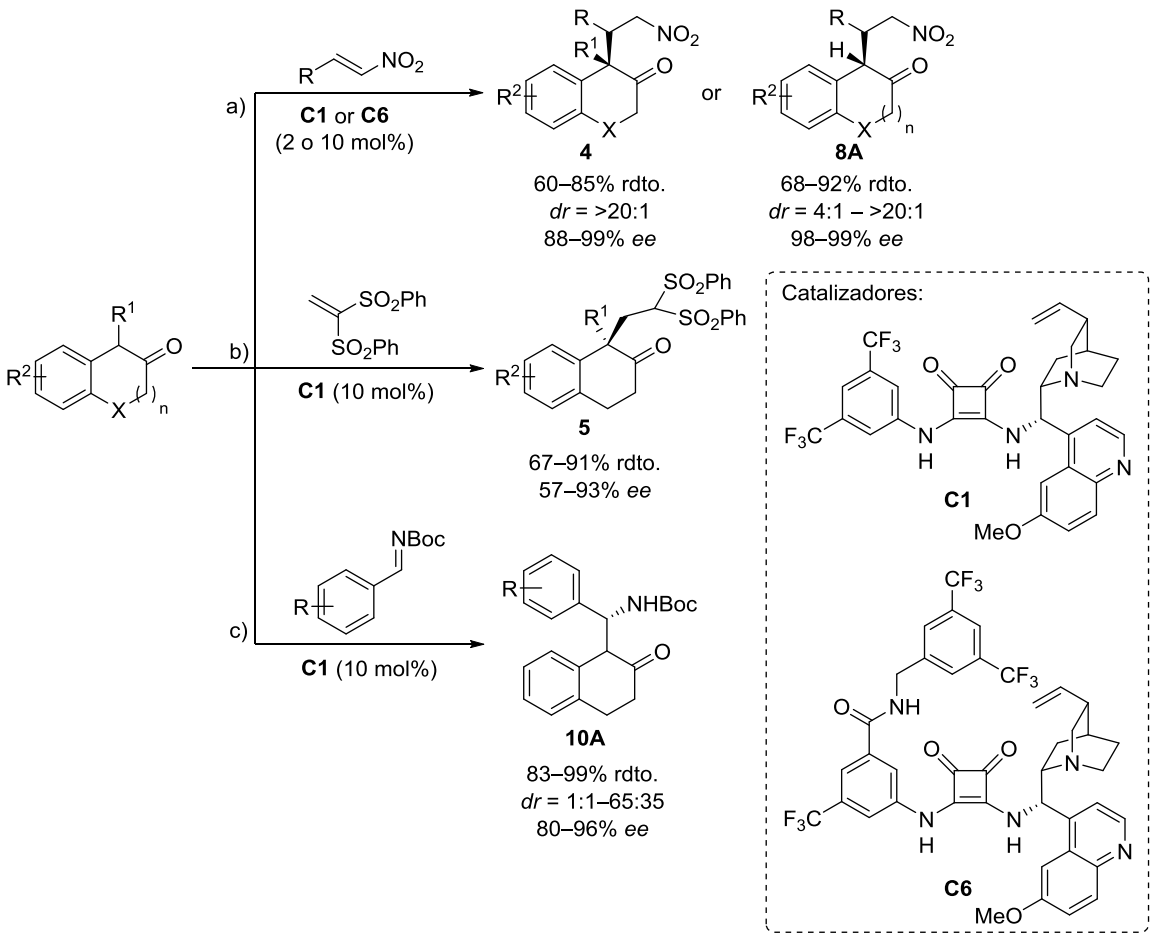
Figura C. Compuestos bioactivos con estructuras policíclicas derivables de la β-tetralona.

A pesar de este potencial interés, hasta la fecha se han descrito pocos procedimientos para la síntesis asimétrica de β-tetralonas α(α')-sustituidas. La α/α´-funcionalización estereoselectiva de β-tetralonas se ha llevado a cabo empleando reactivos quirales en cantidad estequiométrica, principalmente mediante la condensación con una amina quiral y subsiguiente C-alquilación de la enamina resultante (Esquema Ba). En cuanto a los métodos catalíticos, estos se basan principalmente en reacciones de alilación asimétricas catalizadas por paladio (Esquema Bb).



Esquema B. Estrategias principales para la α- o α´-funcionalización asimétrica de β-tetralonas.

En nuestra investigación se ha observado que las β-tetralonas α-sustituidas son capaces de reaccionar con varios aceptores en condiciones suaves por acción de un catalizador bifuncional base de Brønsted/enlace de H adecuado. Así, pueden reaccionar con nitroolefinas en presencia de un 10 mol% del catalizador **C6** para dar lugar a aductos α,α-disustituidos **4** con alta enantio- y diastereoselectividad (Esquema Ca). Similarmente, la reacción con vinil bis(sulfona) en presencia del catalizador **C1** conduce a los productos enantioenriquecidos **5** con buen rendimiento (Esquema Cb). Además, en la reacción de β-tetralonas α-no sustituidas con nitroolefinas se consiguieron exclusivamente los productos α-sustituidos **8A** con excelente enantioselectividad y moderada diastereoselectividad (Esquema 3a). La reacción de adición 1,2 a *N*-Boc iminas también procedió con perfecta regioselectividad y valores altos de *ee*, aunque con nula diastereoselectividad (excepto en un ejemplo, *dr* = 65:35), indicando la existencia de racemización en las condiciones de reacción (Esquema Cc).



Esquema C. α-alquilación regio- y estereoselectiva de β-tetralonas con diferentes electrófilos catalizada por BB.

En el caso de la funcionalización de α-alquenil cicloalcanonas, esta presenta el problema adicional de que el dienolato intermedio que se genera puede reaccionar a través de los carbonos nucleofílicos α y γ, lo que exige un control de la reacción riguroso (Figura D).

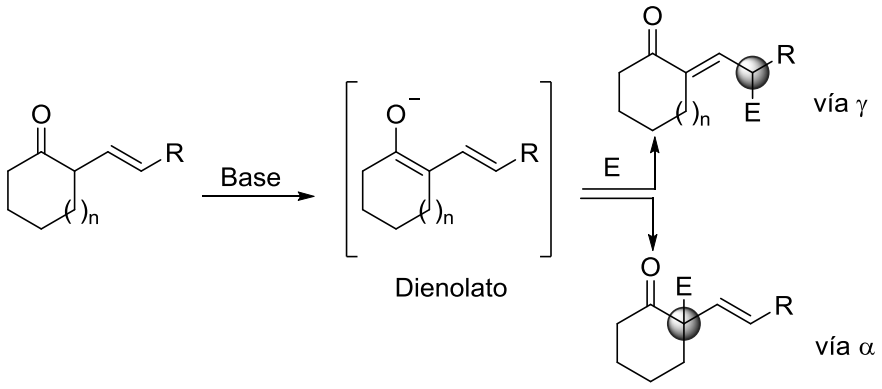
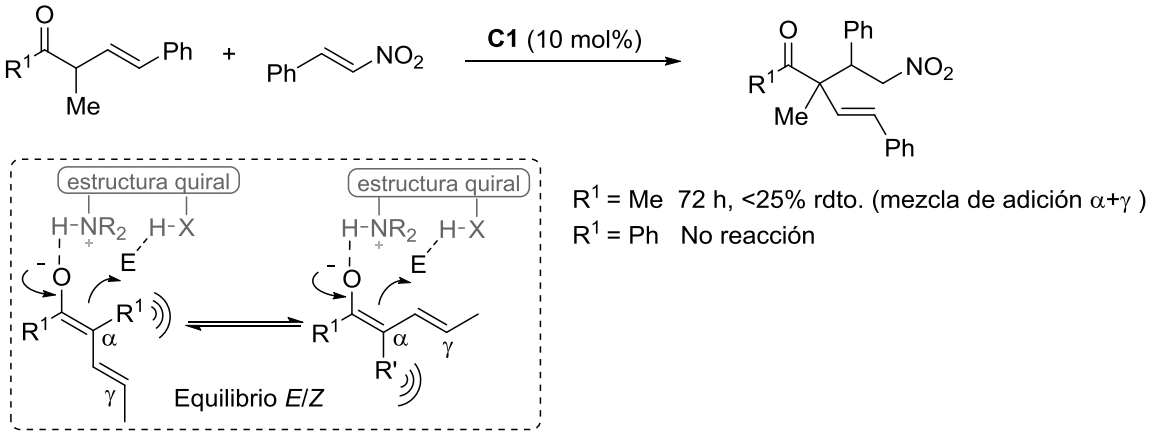


Figura D. Enolización de α-alquenil cicloalcanonas y la aparición del problema de selectividad α vs γ.

Hasta la fecha, la mayoría de los métodos catalíticos de formación de enlaces C–C y C–X con cetonas que implican intermedios de tipo dienolato o equivalentes se limitan al uso de cetonas no sustituidas en α, y reaccionan principalmente a través del carbono γ (reactividad vinílogа). Estos métodos incluyen reacciones catalíticas de adición de dienol éteres de sililo, así como métodos directos basados en catálisis metálica y organocatálisis. Son pocas las excepciones a esta γ-selectividad. Así, se han descrito reacciones catalíticas vía dienol/dienolato/dienamina que transcurren a través del Cα con simultánea isomerización del doble enlace C=C para proporcionar aductos tipo Morita-Baylis-Hilmann (no se forma estereocentro en α), reacciones que requieren tipos de sustratos restringidos o conducen a baja enantioselectividad. Adicionalmente, ninguno de estos métodos α-selectivos ha demostrado ser útil para la generación enantioselectiva de centros cuaternarios en α.

De nuestros estudios iniciales se desprende que las cetonas acíclicas α-sustituidas son muy poco reactivas en estas condiciones, recuperándose la enona de partida (R^1: Ph) o dando lugar a muy bajas conversiones (R^1: Me, <25% conversión), lo que es achacable al impedimento estérico en el Cα (Esquema D).

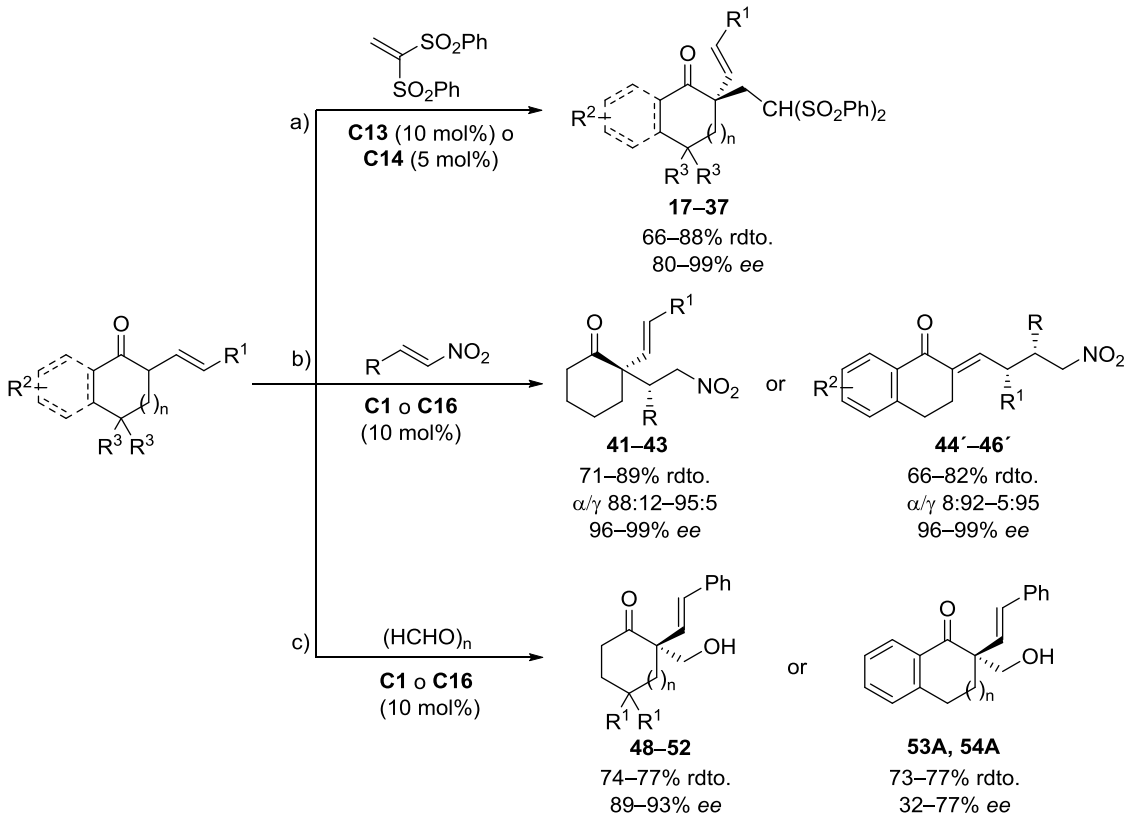


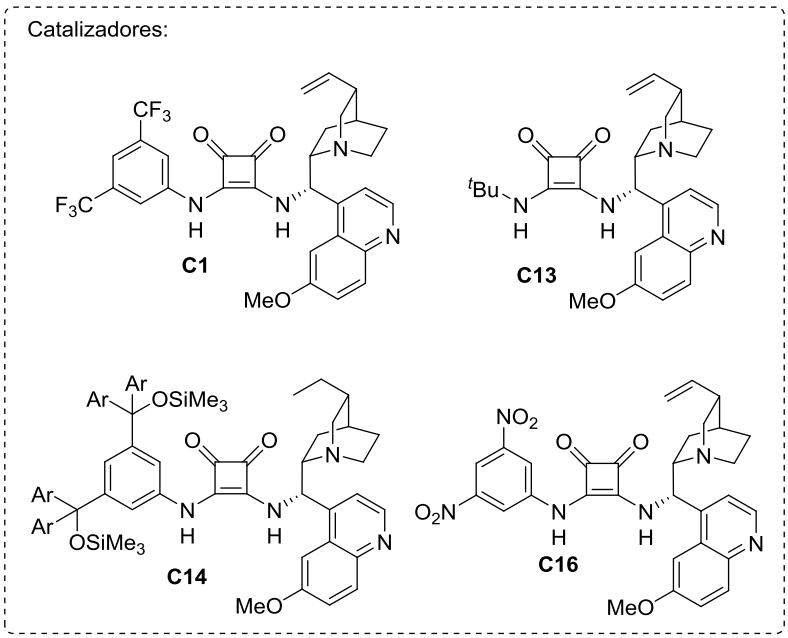
Esquema D. Impacto de la α- sustitución en la reactividad de los dienolatos acíclicos de cetona formados.

Afortunadamente, los estudios posteriores con sistemas cíclicos revelaron que los correspondientes dienolatos generados *in situ* son capaces de reaccionar con varios electrófilos predominantemente en el Cα y de forma estereoselectiva. En concreto se ha podido demostrar que tanto las α-alquenil cicloalcanonas como las α-alquenil 1-tetralonas reaccionan con vinil bis(sulfona) en presencia de diversos catalizadores bifuncionales, como **C13** y **C14**, para obtener los aductos **17**–**37** correspondientes de α-adición cuaternarios con alto rendimiento y enantioselectividad (Esquema Ea). Cuando se emplearon nitroalquenos como electrófilos, la relación de regioisómeros α/γ aislados

fue altamente dependiente del sustrato. En el caso de α-alquenil ciclohexanonas, los aductos **41**–**43** deseados se consiguieron con buen rendimiento, excelente enantioselectividad y generalmente α/γ ratios mayores de 90:10. Por el contrario, la adición de α-alquilidén 1-tetralonas proporcionó los productos de γ-adición **44´**–**46´** casi exclusivamente (α/γ 5:95) con muy buena enantioselectividad, sugiriendo la multivariada α/γ selectividad de los sistemas de dienolato (Esquema Eb). Por otro lado, la adición aldólica a formaldehído empleando el catalizador **C16** también procedió con perfecta regioselectividad y alta enantioselectividad en el caso de cicloalcanos sencillos. Sin embargo, la misma reacción con α-alquenil 1-tetralonas condujo a los aductos **53A** y **54A** con buen rendimiento, pero baja enantioselectividad (Esquema Ec).

Estos resultados muestran que si bien es posible la funcionalización regio-, diastereo- y enantioselectiva de α-alquenil cetonas cíclicas en condiciones muy suaves en presencia de un catalizador de tipo base de Brønsted/enlace de H, para producir carbonos cuaternarios, el sentido y grado de selectividad depende de varios factores, principalmente, de la naturaleza de la cicloalcanona y del reactivo electrófilo así como de la estructura del catalizador.





Esquema E. C-funcionalización de cetonas α-alílicas con varios electrófilos catalizada por BB.

Abbreviations and Acronyms

Standard abbreviations and acronyms have been used as recommended in “Guidelines for authors” (J. Org. Chem., January 2017). Additionally, the following abbreviations and acronyms have been employed:

AAA	Asymmetric allylic alkylation
Alloc	Allyloxycarbonyl group
B	Base
BA	Brønsted acid
BB	Brønsted base
BHT	Butylhydroxytoluene
c	Concentration
Cat	Catalyst
Conv.	Conversion
dba	Dibenzylideneacetone
$(DHQ)_2Pyr$	Hydroquinine 2,5-diphenyl-4,6-pyridineyl ether
DIPEA	Diisopropylethylamine
E	Electrophile
ee	Enantiomeric excess
EWG	Electron withdrawing group
HCLA	Homochiral lithium amide
HFIP	Hexafluoroisopropanol
IPC	Isopropyl phenylcarbamate
KHMDS	Potassium bis(trimethylsilyl)amide
L	Ligand
LA	Lewis acid
M	Metal
m-	*meta*-
MBH	Morita-Baylis-Hillman
MeIm	1-Methylimidazole
MS	Molecular sieves
Np	Naphthyl group
ND	Not determined
NDC	Nicotinium dichromate
NR	No reaction
o-	*ortho*
p-	*para*-
PMP	*para*-Methoxyphenyl group (4-MeO-C6H4-)
rac	Racemic
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine

Ref.	Reference
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
TBDMS	*tert*-Butyldimethylsilyl group (^{t}Bu-$(CH_3)_2$-Si-)
^{t}BuXPhos	2-Di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl
TMS	Trimethyl silyl group
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
y.	yield

INDEX

Chapter 1

Introduction

1. Introduction

1.1. Asymmetric α-Functionalization of Cyclic Ketones

Over the years the production of, and the reactions with, ketone enolates and equivalents have been basic operations in organic chemistry. Since reactions involving ketone enolates lead frequently to the formation of a new stereogenic center, the asymmetric α-functionalization of ketones has been the subject of intense study.[1] A recurrent issue in this field is the control of reaction regioselectivity and stereoselectivity, both diastereo- and enantioselectivity. In this context, owing to the widespread presence of cyclic ketone fragments in natural products and bioactive compounds (Figure 1),[2] asymmetric methods for the generation and control of the reactivity of cyclic ketone enolates or equivalents are in high demand. However, this strategy comes with some complications: the configuration of the newly generated C–C bond should be controlled, as well as the facial approach of the electrophile; site selective enolization is a requirement for non-symmetrical ketones with two sites for deprotonation; in the formation of tertiary stereogenic centers, mild conditions are required in order to prevent racemization of the newly formed stereogenic center while the generation of quaternary stereocenters demands stringent control.[3]

[1] a) M. B. Smith, J. March, *March´s Advanced Organic Chemistry*, Wiley, New York, **2001**. b) C. M. Reeves, B. M. Stoltz, *Asymmetric Synthesis: More Methods and Applications* (Eds.: M. Christmann, N. Br-se), Wiley-VCH, Weinheim, **2012**, 1–10. c) M. Remes, J. Veselý, *Stereoselective Organocatalysis Bond Formation Methodologies and Activation Modes* (Ed.: R. Rios Torres), Wiley, New York, **2013**, 267–312. d) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz*, Acc. Chem. Res*. **2015**, *48*, 740–751. e) U. Kazmaier, *Org. Chem. Front.* **2016**, *3*, 1541–1560.

[2] Plostaglandin E_1: R. T. Schermuly, H. A. Ghofrani, N. Weissmann, *Current Topics in Developmental Biology,* Elsevier, **2005**, *67*, 251–284. Testosterone: R. S. Viger, D. W. Silversides, J. J. Tremblay, *Vitamins & Hormones*, Elsevier, **2005**, *70*, 387–413. Cycloheximide: T. G. Obrig, W. J. Culp, W. L. Mckeehan, B. Hardesty, *J. Biol. Chem.* **1971**, *246*, 174–181. α-Thujone: K. M. Höld, N. S. Sirisoma, T. Ikeda, T. Narahashi, J. E. Casida, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 3826–3831.

[3] A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc*. **2013**, *135*, 7442–7445.

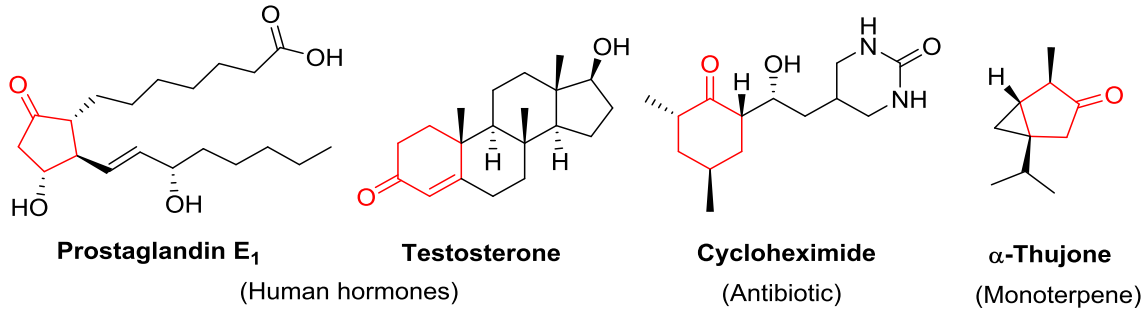


Figure 1. Cyclic ketone fragments in natural products and bioactive compounds.

In order to control the stereochemical outcome of the reaction of an electrophile with an enolate anion or equivalent, three options are possible, namely the use of a chiral auxiliary, a chiral ligand or a chiral catalyst.

Initial advances were made based on the use of covalently bound chiral auxiliaries, which are temporarily anchored to the substrate to control the stereochemical outcome of the reaction, and thus the configuration of the newly formed stereogenic elements generated during the process.

The readily available chiral amines, which upon condensation with ketones form enamine intermediates, are versatile chiral auxiliaries that have been successfully applied in numerous reactions.[4] The first example within this strategy was reported in 1969 by Yamada *et al.*[5] who used L-proline esthers as chiral auxiliary to promote enamine-promoted α-alkylation of cyclohexanone derivatives. Although low yields (<25%) and *ee* values (<60%) were obtained, this work was pioneering and inspired to many other developments in which stoichiometric amounts of a chiral amine induced asymmetric alkylations of cyclohexanones via their enamine intermediates (Figure 2).[6]

[4] a) J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Willey, New York, **1995**. For a general review on chiral auxiliaries, see: b) F. Glorious, Y. Gnass, *Synthesis* **2006**, *12*, 1899–1930. For applications of phenylethylamine as a chiral auxiliary, see: c) E. Juaristi, J. L. León-Romo, A. Reyes, J. Escalante, *Tetrahedron: Asymmetry* **1999**, *10*, 2441.

[5] a) S.-I. Yamada, K. Hiroi, K. Achiwa, *Tetrahedron Lett.* **1969**, *10*, 4233–4236. For more information on the subject see: b) P. W. Hichmott, *Tetrahedron.* **1982**, *38*, 1975–2050.

[6] a) J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **1977**, *42*, 1663–1664. b) S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 1637–1654. c) Y. Ito, M. Sawamura, K. Kominami, T. Saegusa, *Tetrahedron Lett.* **1985**, *26*, 5303–5306. d) M. Pfau, G. Revial, A. Guigant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273–274.

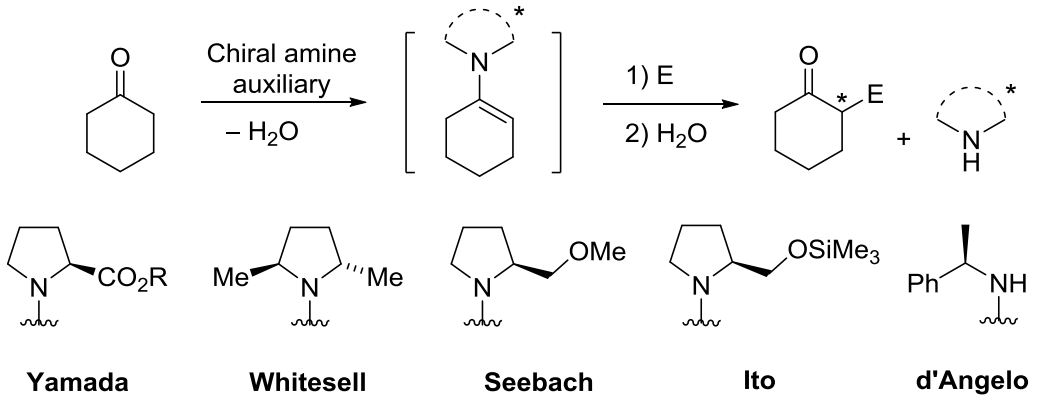


Figure 2. Representative amine auxiliaries for the asymmetric alkylation of cyclohexanone derivatives.

Yamada´s research was highly important not only for the future work in the context of enamine-based asymmetric reactions but also in the area of azaenolate-based ketone alkylation. Koga[7] and Meyers[8] independently reported the use of acyclic amino acid-derived auxiliaries in the asymmetric α-alkylation of ketones via derived imine enolates, with good to very good diastereoselectivity in the case of cyclic ketones but poor selectivity for acyclic ketones (Figure 3).

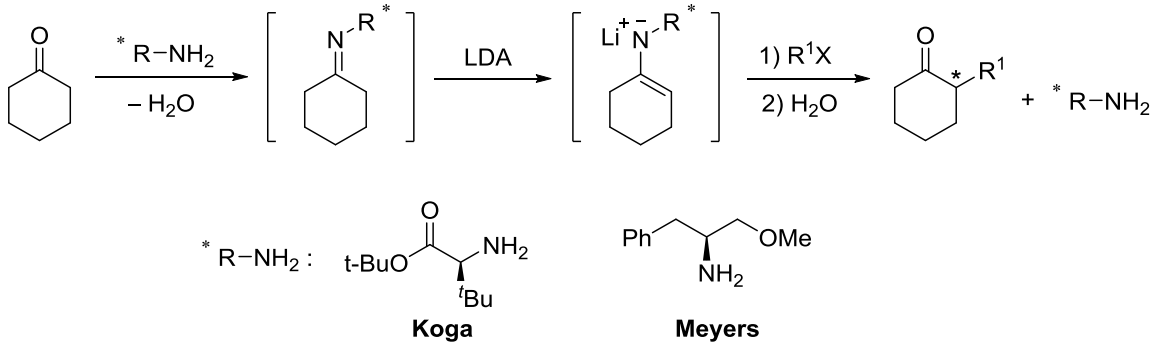


Figure 3. Asymmetric α-alkylation of ketones via lithium enolates of the derived imines.

Hydrazones, which can be easily prepared by condensation of hydrazines with ketones, are another type of good pronucleophiles for deprotonation with strong amide metal bases. In comparison with their corresponding enolates, azaenolates offer notable advantages: Higher stability, greater reactivity towards electrophiles and better

[7] a) S. Hashimoto, K. Koga, *Tetrahedron Lett.* **1978**, *19*, 573–576. b) S. Hashimoto, K. Koga, *Chem. Pharm. Bull.* **1979**, *27*, 2760–2766.

[8] a) A. I. Meyers, D. R. Williams, M. Druelinger, *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033. b) A. I. Meyers, D. R. Williams, *J. Org. Chem.* **1978**, *43*, 3245–3247. c) A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, M. Druelinger, *J. Am. Chem. Soc.* **1981**, *103*, 3081–3087.

regioselectivity.[9] The first widely used approach involved the SAMP/RAMP methodology developed by Enders.[10] His laboratory reported the use of (*S*)- and (*R*)-1-amino-2-methoxypyrrolidine dialkyl hydrazines as chiral auxiliaries for the α-alkylation of ketones (Figure 4).

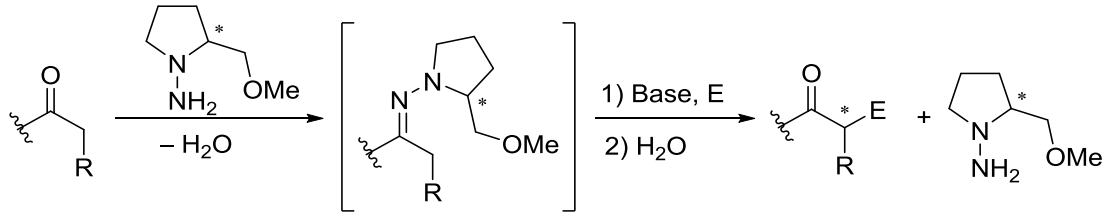


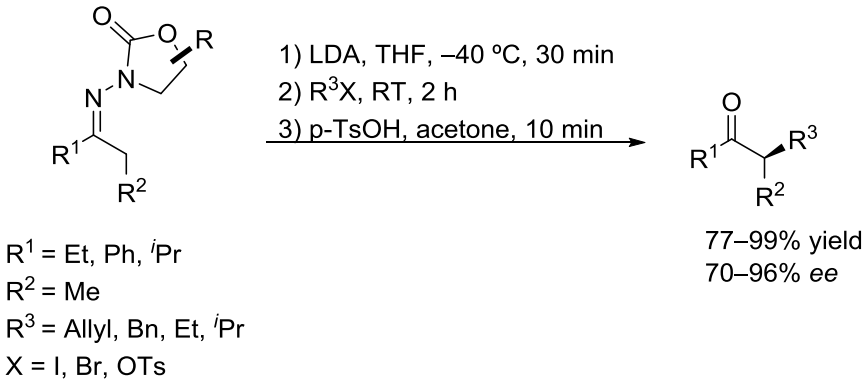
Figure 4. SAMP/RAMP methodology for the α-alkylation of hydrazones.

This methodology has been widely employed in asymmetric synthesis and applied to a number of total syntheses in which cyclic ketones were used as substrates.[11] Unfortunately, its further development has been impeded as a result of certain inherent limitations. For instance, the reactions must be conducted at very low temperatures (−78 °C to −110 °C) because the formation of the azaenolate requires exposure to lithium diisopropylamide (LDA) for long periods (since hydrazones are weakly acidic). Moreover, removal of the costly auxiliary under recommended conditions (ozonolysis or quaternization/hydrolysis) limits functional group compatibility.[10] Finally, the auxiliary itself is liberated in an altered form that hinders recycling.[12]

With a view to addressing this problem, more recently, Coltart has reported the use of chiral *N*-amino cyclic carbamates (Scheme 1).[13] The enhanced acidity of these activated hydrazones enabled a fast deprotonation and avoided the need of low reaction temperatures. Furthermore, it was possible to control the regioselectivity and facilitate the unprecedented α,α-bis-alkylation of ketones.[14] Although this development

[9] R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.*, **2017**, *56*, 9278–9290.
[10] For a review on asymmetric reactions of hydrazones, see: A. Job, C. F. Janeck, W. Bettray, R. Petters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.
[11] For an example of: alkylation: a) M. Schwaebe, R. D. Little *J. Org. Chem*. **1996**, *61*, 3240–324. Aldol reaction: b) Geibel, G. Dissertation, *RWTH Aachen*, **1997**. Michael addition: c) D. Enders, H. J. Scherer, J. Runsink, *Chem. Ber.* **1993**, *126*, 1929–1944.
[12] Other hydrolytic and oxidative methods are available, but have not been widely used. See: D. Enders, L. Wortmann, R. Peters, *Acc. Chem. Res*. **2000**, *33*, 157–169.
[13] a) D. Lim, D. M. Coltart, *Angew. Chem. Int. Ed*. **2008**, *47*, 5207–5210. b) E. H. Krenske, K. N. Houk, D. Lim, S. E. Wengryniuk, D. M. Coltart, *J. Org. Chem*. **2010**, *75*, 8578–8584.
[14] S. E. Wengryniuk, D. Lim, D. M. Coltart, *J. Am. Chem. Soc*. **2011**, *133*, 8714–8720.

was focused on acyclic ketones, in a further work it was proved to be a valid method for the alkylation of cyclohexanone.[15]



Scheme 1. Coltart´s chiral *N*-amino cyclic carbamate hydrazones methodology.

The above methodologies involve the use of chiral auxiliaries and the transfer of chiral information in an intramolecular manner. A different strategy to achieve the asymmetric α-functionalization of cyclic ketones is the use of chiral ligands. These are enantiopure compounds that interact with a metallic center through quelation to generate a chiral reagent, which transfers the information of chirality in an intermolecular manner during the reaction.

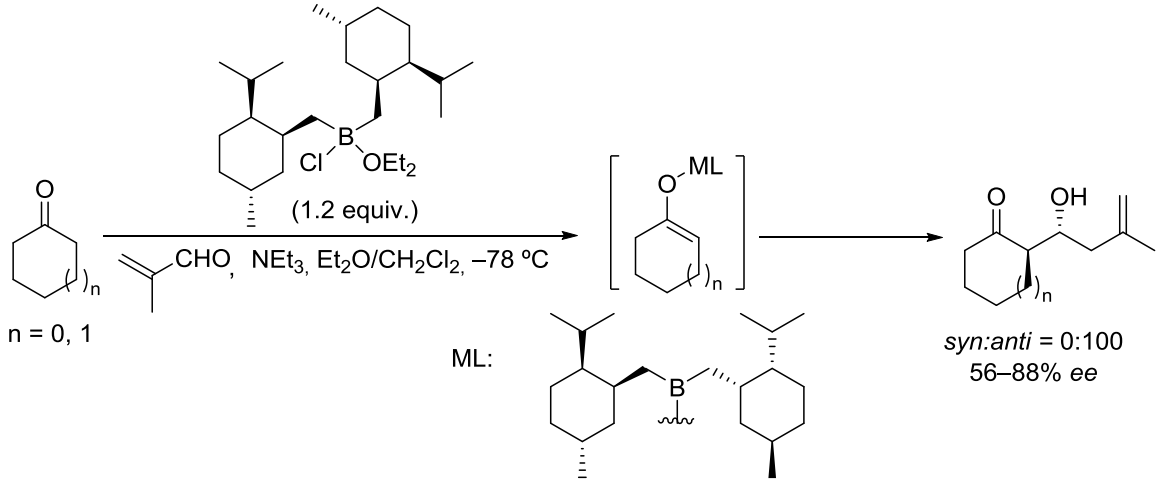
A representative example of this strategy is the stereoselective aldol reaction of ketones using chiral boron ligands that has been pioneered by Paterson and Masamune.[16] The first attempts were performed in the presence of isopinocampheyl (IPC) as the chiral ligand for the reaction of diethylketone with several aldehydes to obtain enantiomerically pure *syn*-aldol products coming from Z-boron enolates.[17] For the development of *anti*-selective asymmetric aldol reaction, Gennari and Paterson designed a menthol derived chiral ligand (Scheme 2) for highly diastereoselective (86:14 to 100:0 *anti*:*syn*) aldol reactions of a range of cyclic and acyclic ketones with good

[15] U. Huynh, S. L. McDonald, D. Lim, Md. N. Uddin, S. E. Wengryniuk, S. Dey, D. M. Coltart, *J. Org. Chem.* **2018**, *83*, 12951–12964.

[16] a) C. J. Cowden, I. Paterson, *Org. React.* Wiley, New York, **1997**, *51* (Chapter 1). b) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357–389. c) D. A. Evans, *Asymmetric Synthesis*, Morrison, J. D. Ed., Academic Press, New York, **1984**, *3*. d) C. H. Heathcock, *Modern Enolate Chemistry: Regio- and Stereoselective Formation of Enolates and the Consequence of Enolate Configuration on Subsequent Reactions*, VCH, Weinheim, **1992**. e) C. Gennari, *Synthesis* **1990**, 629–660. f) A. S. Franklin, I. Paterson, *Contemp. Org. Synth.* **1994**, *1*, 317–338.

[17] I. Paterson, M. A. Lister, C. K. McClure, *Tetrahedron Lett.* **1986**, 4787–4790.

enantiomeric excesses (56–88% *ee*).[18] It should be mentioned that the reaction is stereospecific and since cycloalkanones can only form E enolates, the *anti*-aldol product is obtained exclusively.



Scheme 2. Aldol reaction of cyclic ketones catalyzed by a menthol derived chiral ligand.

Another type of approaches for the α-alkylation of ketones involved the use of homo chiral lithium bases (HCLAs).[19] In pioneering work, Koga[20] and Simpkins[21] independently reported the use of chiral lithium amide bases and substituted cyclohexanones (Scheme 3). In spite of the array of chiral amides reported, the application of this methodology has been limited to desymmetrization of conformationally locked prochiral cyclic ketones.[22]

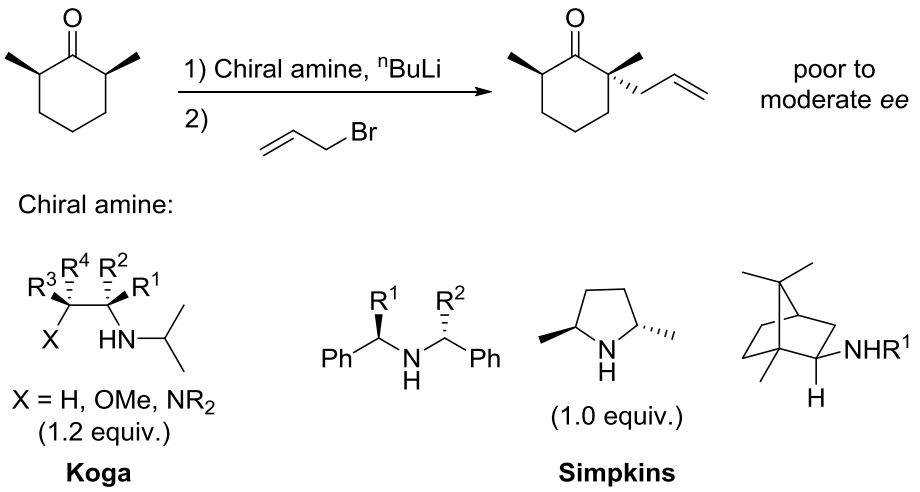
[18] C. Gennari, C. T. Hewkin, F. Molinari, A. Bernardi, A. Comotti, J. M. Goodman, I. Paterson, *J. Org. Chem.* **1992**, *57*, 5173–5177.

[19] a) P. O´Brien, *J. Chem. Soc. Perkin Trans 1* **1998**, 1439–1457; b) J. Eames, *Eur. J. Org. Chem*. **2002**, 393–401.

[20] R. Shirai, M. Tanaka, K. Koga, *J. Am. Chem. Soc.* **1986**, *108*, 543–545.

[21] C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron* **1990**, *46*, 523–544.

[22] For selected examples: a) N. S. Simpkins, *J. Chem. Soc. Chem. Commun.* **1986**, *88*–90. b) E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1984**, *25*, 495–498. c) R. P. C. Cousins, N. S. Simpkins, *Tetrahedron Lett.* **1989**, *30*, 7241–7244. d) D. Sato, H. Kawasaki, I. Shimada, Y. Arata, K. Okamura, T. Date, K. Koga, *J. Am. Chem. Soc.* **1992**, *114*, 761 –763. e) B. J. Bunn, N. S. Simpkins, *J. Org. Chem.* **1993**, *58*, 533–534. f) P. Coggins, S. Gaur, N. S. Simpkins, *Tetrahedron Lett.* **1995**, *36*, 1545–1548. g) B. H. Lipshutz, M. R. Wood, C. W. Lindsley, *Tetrahedron Lett.* **1995**, *36*, 4385–4388. h) M. Toriyama, K. Sugasawa, M. Shindo, N. Tokutake, K. Koga, *Tetrahedron Lett.* **1997**, *38*, 567–570. For a recent review see: i) N. S. Simpkins, M. D. Weller, *Org. React.* **2013**, *79*, 317–635.



Scheme 3. α-allylation of substituted symmetric cyclohexanone using chiral lithium amine bases.

Methods based on chiral auxiliaries and chiral ligands need a stoichiometric amount of the chiral starting material. The use of chiral catalysts has become a major area of study in asymmetric synthesis since it is more convenient from the point of view of atom economy and procedural simplicity.[23] Ideally a substoichiometric amount of a chiral inductor is enough to accomplish the reaction with high chemo-, regio- and stereoselectivity. On the other hand, as compared to chiral auxiliaries, in asymmetric catalysis the auxiliary anchoring and release stages are avoided.

Mukaiyama first described the catalytic enantioselective reaction of silyl enol ethers derived from esters[24] and thioesters[25] employing a tin(II)-chiral diamine complex as the catalyst. Since then, directed methods based on the use of previously generated enolates or enolate equivalents, such as silyl enol ethers, in combination with a chiral Lewis acid (LA) catalyst have been explored profusely.[26] Apart from enoxysilanes derived from esters and thioesters, those derived from ketones have also been found to be useful reagents for the catalytic asymmetric directed aldol reaction based on the

[23] For detailed information on this concept see: B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.
[24] S. Kobayashi, T. Sano, T. Mukaiyama, *Chem. Lett.* **1989**, 1319–1322.
[25] S. Kobayashi, T. Mukaiyama, *Chem. Lett.* **1989**, 297–300.
[26] For reviews on Mukaiyama reaction see: a) E. M. Carreira, *Modern Carbonyl Chemistry*, Wiley-VCH, Winheim, **2000**, 227–248. b) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086–9096. c) S. B. Jennifer Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108. d) J.-I. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118. e) T. Kitanosono, S. Kobayashi, *Chem. Rec.* **2014**, *14*, 130–143. f) W. Gati, H. Yamamoto, *Acc. Chem. Res.* **2016**, *49*, 1757–1768.

activation of silyl enol ethers. The most representative Lewis acids employed in the reactions of cyclic ketone derivatives are shown in Figure 5.[27]

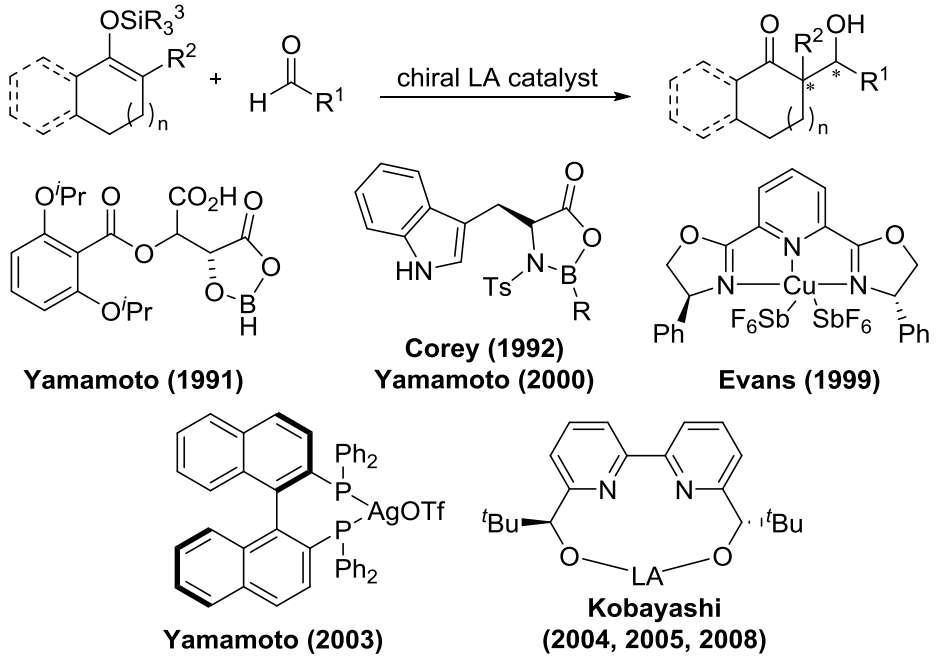


Figure 5. LA-catalyzed Mukaiyama aldol reaction of silyl enol ethers derived from cyclic ketones.

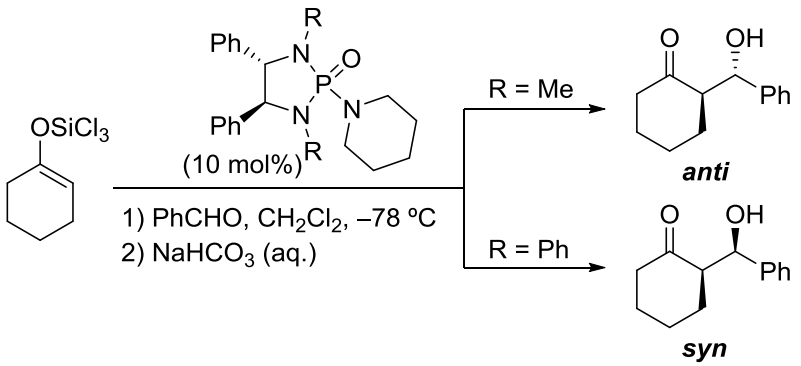
Alternatively, Denmark´s group developed an aldol addition reaction that provides high diastereo- and enantioselectivity from easily prepared[28] (or in situ prepared)[29] trichlorosilyl enolates derived from cyclohexanone in the presence of a chiral phosphoramide Lewis base catalyst (Scheme 4).[30] Remarkably, and contrary to the Lewis acid-catalyzed processes, the diastereoselectivity of the reaction can be controlled by the appropriate choice of the phosphoramide catalyst. Thus, either the *syn*- or the *anti*-diastereomer may be arised through aldolization in a stereospecific manner.

[27] a) K. Furuta, T. Maruyama, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042. b) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, *33*, 6907–6910. c) K. Ishihara, S. Kondo, H. Yamamoto, *J. Org. Chem.* **2000**, *65*, 9125–9128. d) D. A. Evans, C. Kozlowski, J. A. Murry, *J. Am. Chem. Soc.* **1999**, *121*, 669–685. e) N. Ozasa, M. Wadamoto, K. Ishihara, H. Yamamoto, *Synlett* **2003**, *14*, 2219–2221. f) S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237. g) S. Kobayashi, T. Ogino, H. Shimizu, S. Ishikawa, T. Hamada, K. Manabe, *Org. Lett.* **2005**, *7*, 4729–4731. h) M. Kokubo, C. Ogawa, S. Kobayashi, *Angew. Chem. Int. Ed.* **2008**, *47*, 6909–6911.

[28] S. E. Denmark, R. A. Stavenger, S. B. D. Winter, K.-T. Wong, P. A. Barsanti, *J. Org. Chem.* **1998**, *63*, 9517–9523.

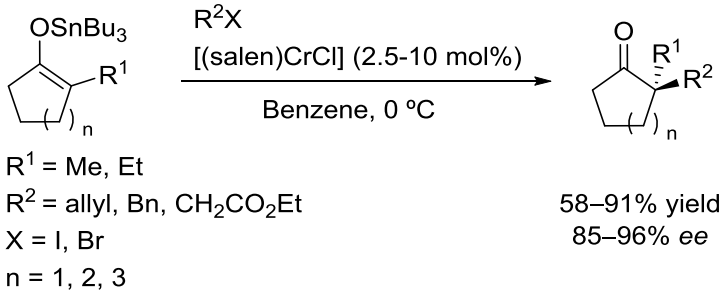
[29] a) S. E. Denmark, R. A. Stavenger, K.-T. Wong, *J. Org. Chem.* **1998**, *63*, 918–919. b) S. E. Denmark, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 9524–9527.

[30] a) S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991. For a review on Lewis base-promoted Mukaiyama reactions see: c) Ref. 26b.



Scheme 4. Lewis base catalyzed Mukaiyama reaction of cyclohexanone-derived trichloro silyl enol ether.

In a Mukaiyama-related approach, for the synthesis of α-alkyl ketones, Jacobsen described Cr/salen complex catalyzed α-alkylation of tributyltin enolates, derived from cyclic and non-cyclic systems (Scheme 5).[31] In comparison with the previous allylations, this method allows the incorporation of alkyl groups other than allyl groups. Indeed, this is one of the exceptions since most of the developments performed for the α-alkylation of ketones were suitable for the incorporation of allyl-based substituents only.[9]



Scheme 5. Enantioselective alkylation of tributyltin cyclic enolates.

The use of chiral Lewis acid and base catalysts with enoxysilanes or derivatives has been very successful for the development of enantioselective aldol reactions. Nevertheless, a common limitation of the classic Mukaiyama aldol and related reactions is the need for the generation of the silyl enolate species in a previous and irreversible synthetic operation with the consumption of, at least, stoichiometric amounts of the silylating reagent and base.[32]

[31] a) A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 62–63; b) A. G. Doyle, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2007**, *46*, 3701–3705.

[32] Truly catalytic methods are under development. For an attempt example, see: S. Kobayashi, H. Kiyohara, M. Yamaguchi, *J. Am. Chem. Soc.* **2011**, *133*, 708–711. For a highlight, see: J. M. García, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2011**, *50*, 8790–8792.

On the other hand, direct methods do not need of a separate prior step, and, thus, are most convenient, especially if a substoichiometric amount of the chiral catalyst is enough to obtain good yield and selectivity.

1.2. Direct Catalytic Asymmetric α-Functionalization of Cyclic Ketones

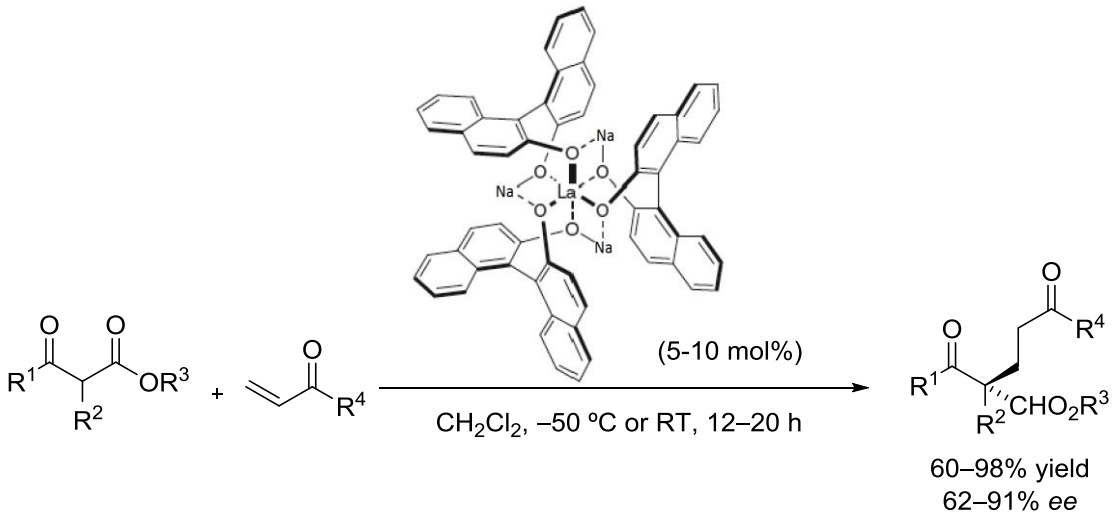
As enzymes do in biological systems, laboratory-designed chiral molecules can promote the formation of chiral product molecules enantioselectively. Thereupon, direct catalytic asymmetric synthesis is the most desirable and the most challenging approach among the types of asymmetric reactions. In this context, several catalysts have been developed capable of promoting the asymmetric α-functionalization of cyclic ketones without the need of a previous preactivation step (direct methods). Herein the main advances of metal catalysis and organocatalysis are described.

1.2.1. Metal catalysis

The concept of bifunctional catalysis, wherein both partners of a bimolecular reaction are simultaneously activated, is very powerful for designing efficient asymmetric catalysts. Compared with conventional (monofunctional) catalysts, bifunctional catalysts generally exhibit enhanced catalytic activity and higher levels of stereodifferentiation under milder reaction conditions.[33] Inspired by the dual activation of enzymes to promote stereoselective reactions, Shibasaki's group developed Lewis acid–Brønsted base bifunctional asymmetric catalysts.[34]

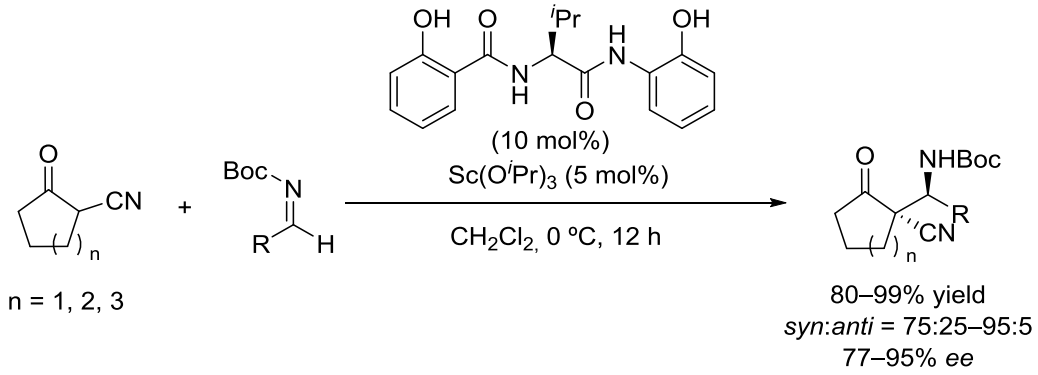
In 1996, Shibasaki and coworkers[35] reported the first asymmetric Michael addition of acyclic and cyclic β-ketoesters in which moderate to good enantioselectivities were obtained (Scheme 6).

[33] M. Shibasaki, M. Kanai, S. Matsunaga, *Acc. Chem. Res.* **2009**, *42*, 1117–1127.
[34] M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1236–1256.
[35] H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 5561–5564.



Scheme 6. Michael addition of β-ketoesters catalyzed by a La-Na BINOL complex.

Since then, the same group has employed similar catalysts for the Mannich and aldol reaction of ketones.[36] In Scheme 7 the Mannich reaction between cyclic α-cyanoketones and *N*-Boc imines catalyzed by a combination of an amide-based ligand and a rare earth metal is shown, in which consecutive all-carbon quaternary and trisubstituted stereocenters are generated in a highly stereoselective manner.[36b] Although good results have been achieved with bifunctional metal complexes, there is room for improvement in terms of substrate scope. Indeed, mostly aryl substituted ketones or activated ketones bearing an electron-withdrawing group at the α-position have been employed.



Scheme 7. Mannich reaction of cyclic α-cyanoketones employing a bifunctional catalyst.

[36] For Mannich reactions, see: a) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307–310. b) A. Nojiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 5630–5631. For aldol reactions, see: a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, Angew. *Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873. b) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467.

On the other hand, in the early 2000s, Tunge,[37] Stoltz[38] and Trost[39] independently reported metal-based methods for the catalytic asymmetric α-allylation of ketones, an enantioselective version of the well-known Tsuji allylation[40] that involves Pd-catalyzed allylic alkylation of ketones with allylic electrophiles. In these developments, the allylations are intramolecular processes from allyl enol carbonates (Scheme 8a)[39c] and allyl β-ketoesters (Scheme 8b).[38b] All these methods require symmetrical ketones, or unsymmetrical precursors possessing only one available side for allylation and in most cases a preinstalled allyl transfer group.[41]

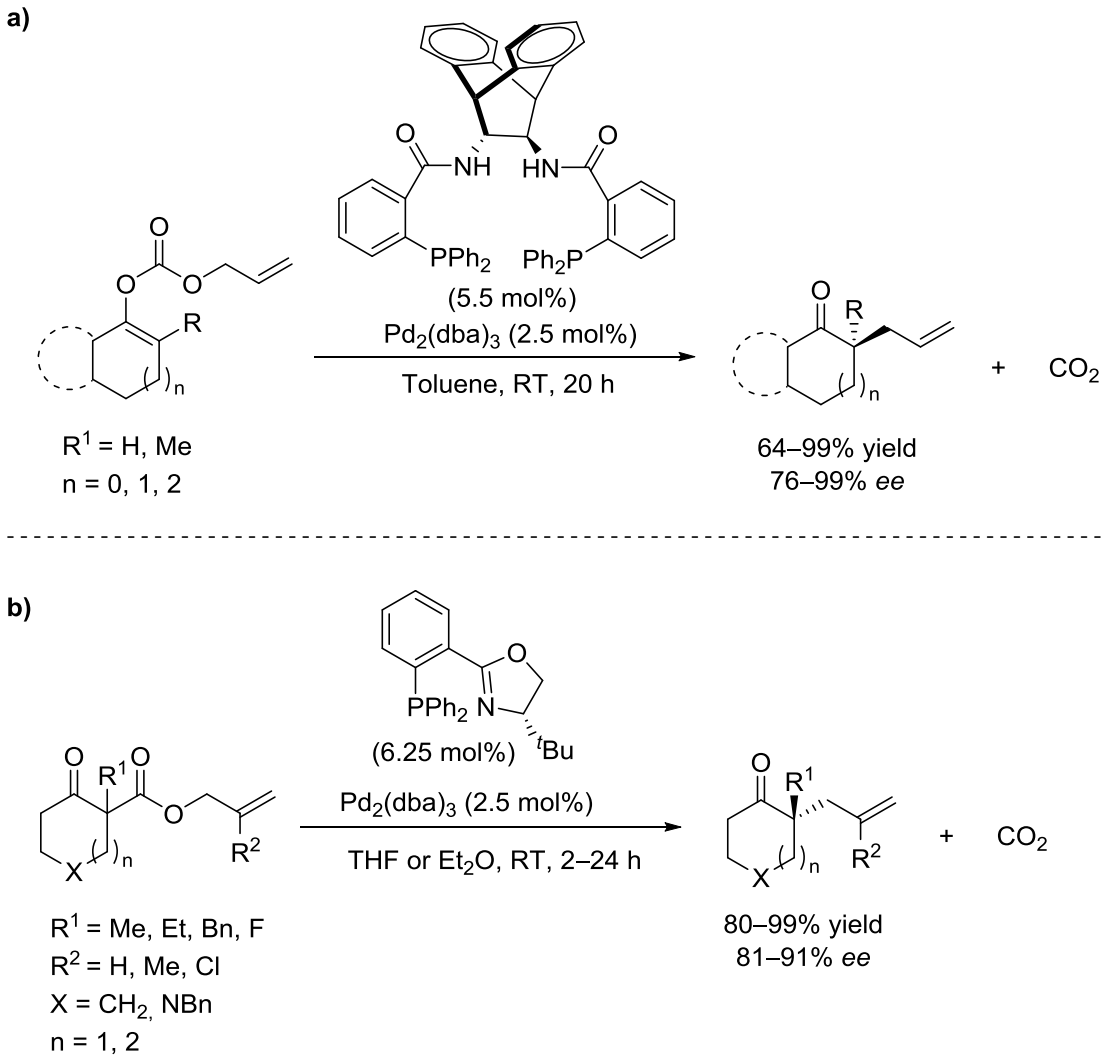
[37] a) E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 2603–2605. b) E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 4113–4115. c) D. K. Rayabarapu, J. A. Tunge, *J. Am. Chem. Soc.* **2005**, *127*, 13510–13511.

[38] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927. c) J. A. Enquist, B. M. Stoltz, *Nature* **2008**, *453*, 1228–1231. d) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323–332.

[39] a) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. b) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181. c) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.

[40] a) I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3199–3202. b) J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 1793–1796. c) J. Tsuji, I. Minami, I. Shimizu, *Chem. Lett.* **1983**, *12*, 1325–1326. For a recent review, see: N. A. Butta, W. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 7929–7967.

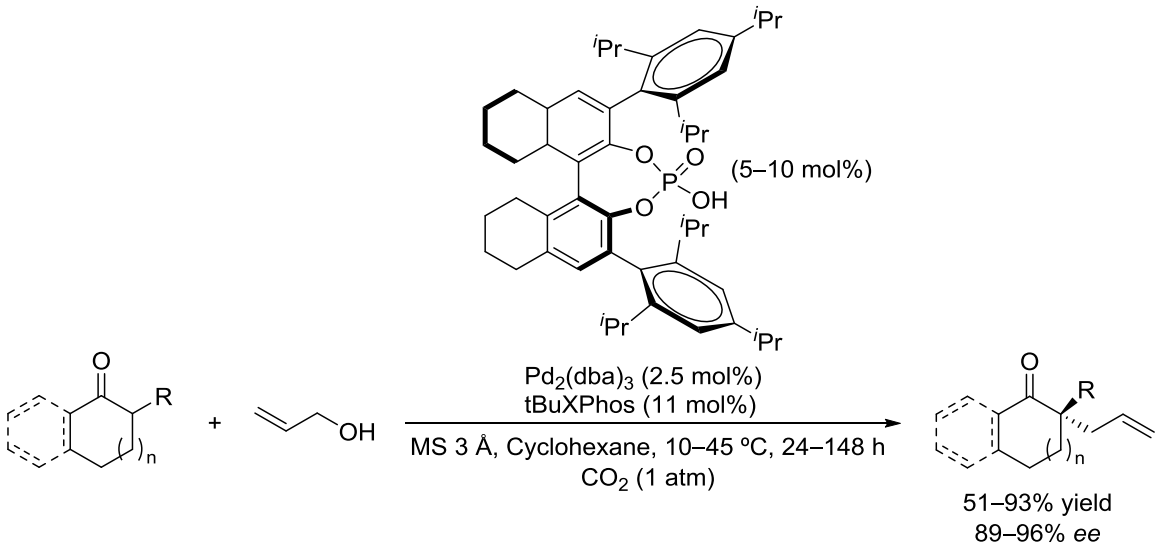
[41] a) M. Braun, F. Laicher, T. Meier, *Angew. Chem. Int. Ed.* **2000**, *39*, 3494–3497; *Angew. Chem.* **2000**, *112*, 3637–3640; b) M. Braun, T. Meier, *Synlett* **2005**, 2968–2972; c) B. M. Trost, J. Xu, M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282–283; d) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11852–11853.



Scheme 8. a) Decarboxilative allylic alkylation of cyclic ketones through allyl enol carbonates. b) Decarboxilative allylation of cyclic β-ketoesters.

Quite recently, List and coworkers developed a direct highly enantioselective and atom-economic Tsuji-Trost allylation of branched cyclic ketones with allylic alcohol employing CO_2 as a formal catalyst.[42] The reaction delivers products bearing quaternary stereocenters with high enantioselectivity and water as the sole by-product (Scheme 9).

[42] G. Pupo, R. Properzi, B. List, *Angew. Chem. Int. Ed*. **2016**, *55*, 6099–6102.



Scheme 9. Tsuji-Trost allylation of branched cyclic ketones employing CO_2 as a formal catalyst.

Metal catalyzed reactions have played an important role in asymmetric catalysis, also in the α-functionalization of ketones. However, they are associated with the limitations of metals having a high cost and toxicity, and the difficult removal of them from the products. In addition, with few exceptions, metal-based catalytic approaches are mainly limited to allylation reactions.

1.2.2. Organocatalysis

For the past few years, organocatalyzed reactions,[43] which utilize substoichiometric amounts of chiral small organic molecules lacking metal elements in their active form, have emerged as a new pillar within asymmetric catalysis. Organic compounds, as compared to metal complexes, tend to be more stable, less expensive, nontoxic, readily available, and environmentally friendly. Besides, organocatalytic reactions are less sensitive to the presence of water or air in comparison to metal-catalyzed reactions.

[43] a) A. Berkessel, H. Groger, *Metal - Free Organic Catalysis in Asymmetric Synthesis*, Wiley - VCH, Weinheim, **2004**. b) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley - VCH, Weinheim, **2007**. c) P. I. Dalko, *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Wiley - VCH, Weinheim, **2013**. For reviews on organocatalysis, see: d) J. Emsley, *Chem. Soc. Rev.*, **1980**, *9*, 91–124. e) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748. f) B. List, *Tetrahedron*, **2002**, *58*, 5573–5590. g) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. h) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724. i) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743. j) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. k) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.

Thus, the reproducibility and operational simplicity of organocatalyzed reactions are usually superior.

Organocatalysts can activate the nucleophile, the electrophile or both reagents (bifunctional catalysis) through strong covalent bonding or weaker non-covalent interactions such as hydrogen bonding or ion pairing. For the α-functionalization of ketones, activation via enamine formation (covalent), Brønsted acid catalysis (non-covalent) and Brønsted base catalysis (non-covalent) have been the most employed mechanisms.

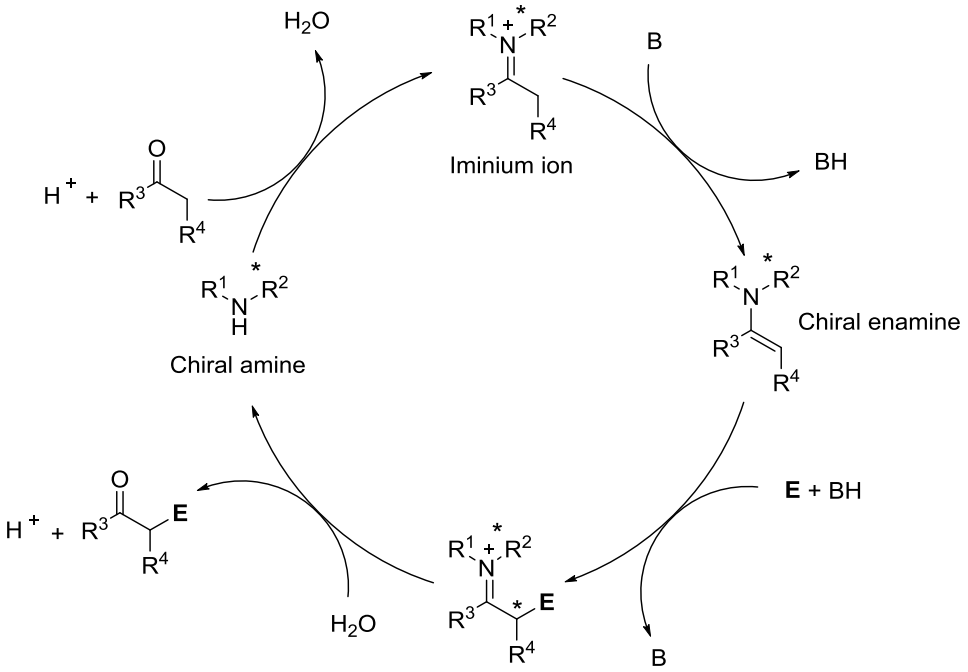
1.2.2.1. *Activation via enamine formation (covalent)*

Enamine-mediated aminocatalysis is based on the reversible generation of enamines from an amine catalyst and an enolizable aldehyde or ketone substrate. To a large degree, this chemistry is reminiscent of the classical methods based on preformed enamine chemistry pioneered by Stork (see pages 6–7).[44]

The catalytic cycle of enamine activation (Scheme 10) consists of: i) formation of the iminium ion between the carbonyl compound and the chiral amine that acts as a catalyst; ii) subsequent deprotonation of the iminic species to generate an enamine; iii) formation of a C-C bond between the enamine and the electrophilic component of the reaction; iv) final hydrolysis of the resulting iminium ion, with the consequent release of the reaction product and recovery of the catalyst.[45]

[44] a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207–222. b) G. Stork, N. A. Saccomano, *Tetrahedron Lett.* **1987**, *28*, 2087–2090. c) Z. Rappoport, *The Chemistry of Enamines*, Wiley, New York, **1994**.

[45] I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New York, **2010**.



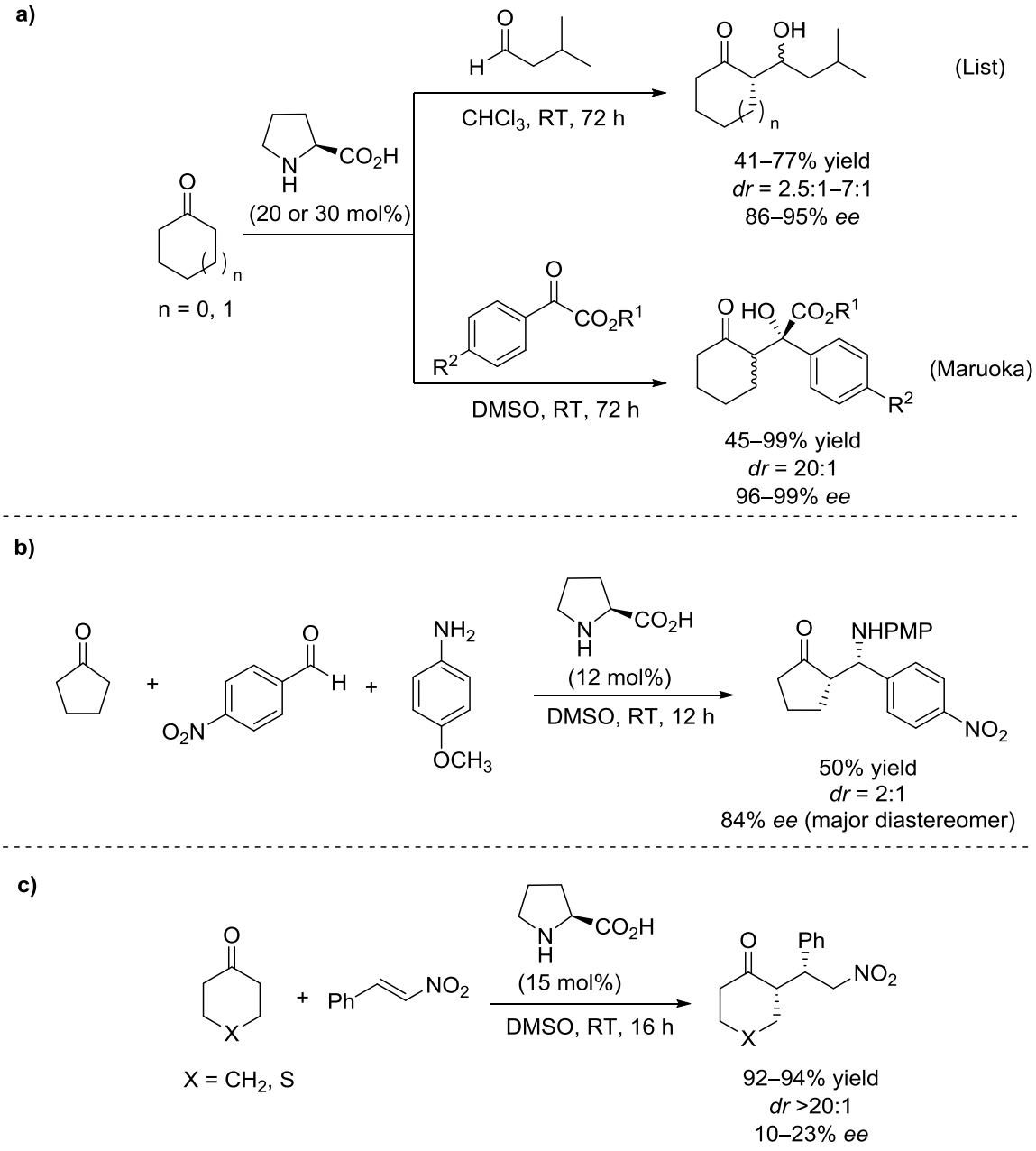
Scheme 10. Catalytic cycle for enamine mediated α-functionalization of aldehydes and ketones.

To date, one of the most profusely employed amine catalysts are proline and the derivatives therefrom. Even though the first application of proline as an asymmetric catalyst was explored in the early seventies,[46] the detailed investigation was carried out by List *et al.* in 2000,[47] when the direct highly enantioselective aldol reactions of ketones and aldehydes using L-proline as a catalyst were described.[47] Since then, recent years have witnessed an explosive growth in the field of asymmetric enamine catalysis, which has unfurled at a breathtaking pace.

List[48] and Maruoka,[49] independently, described the use of cyclic ketones in proline-catalyzed aldolizations with different aldehydes or α-ketoesters, respectively (Scheme 11a). List was also a pioneer in developing efficient proline-catalyzed asymmetric three-component Mannich reactions of different ketones with good yields and enantioselectivities as high as 99% *ee* (Scheme 11b).[50] The same group reported the first enamine-catalytic asymmetric intermolecular Michael reaction.[51] The addition of

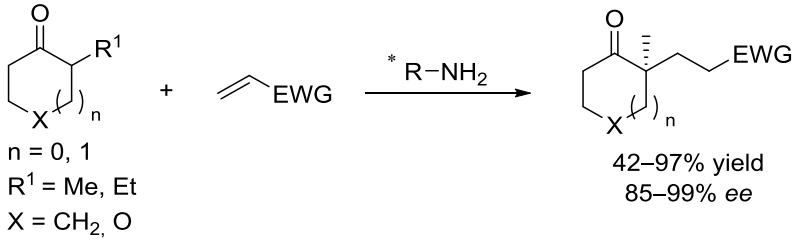
[46] a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, **1971**. b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621. c) S. Terashima, S. Sato, K. Koga, *Tetrahedron Lett.* **1979**, *36*, 3469–3472. d) J. C. Blazejewski, *J. Fluorine Chem.* **1990**, *46*, 515–519.
[47] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[48] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.
[49] O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 5103–5105.
[50] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.
[51] B. List, P. Pojarliev, H. Martin, J. *Org. Lett.* **2001**, *3*, 2423–2425.

unactivated symmetric ketones to nitroolefins was found to proceed in the presence of catalytic amounts of L-proline to furnish the desired γ-nitro ketones in generally high yields and good diastereoselectivities, but only low enantioselectivities (Scheme 11c).



Scheme 11. Proline catalyzed reactions of cyclic ketones: a) Aldol reactions. b) Mannich reaction. c) Michael reaction.

These first examples paved the path for the development of aminocatalysis strategy[52] that resulted in a myriad of proline-catalyzed procedures[53] for the asymmetric reactions of ketones and aldehydes. Besides, new and more efficient catalysts were designed in order to extend the method to a broader scope of substrates.[52a] Even so, this approach is unpractical for ketones bearing at C_α groups larger than methyl or ethyl, owing to steric difficulties for the formation of the enamine intermediate (Scheme 12).[54] Moreover, owing to the hard regiochemical control of the reaction, few examples using unsymmetrical ketones have been reported.



Scheme 12. Primary amine catalyzed Michael addition reactions.

1.2.2.2. *Brønsted acid catalysis (non-covalent)*

Non-covalent catalysis is based on accelerating and controlling the reactions by weak interactions between the substrate and the catalyst.[55] Particularly, Brønsted acid (BA) catalysts[56] may increase the substrate electrophilicity by protonation leading to

[52] For reviews on aminocatalysis see: a) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569. b) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. c) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. d) L. W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807–1821. e) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649. f) B. M. Paz, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2015**, *21*, 1846–1853. g) B. List, *Asymmetric Organocatalysis 1, Lewis base and acid catalysts: Science of Synthesis*, Thieme, Stuttgart, **2012**. h) A. Vega-Peñazola, S. Paria, M. Bonchio, L. Dell´Amico, X. Companyó, *ACS Catal.* **2019**, *9*, 6058–6072.

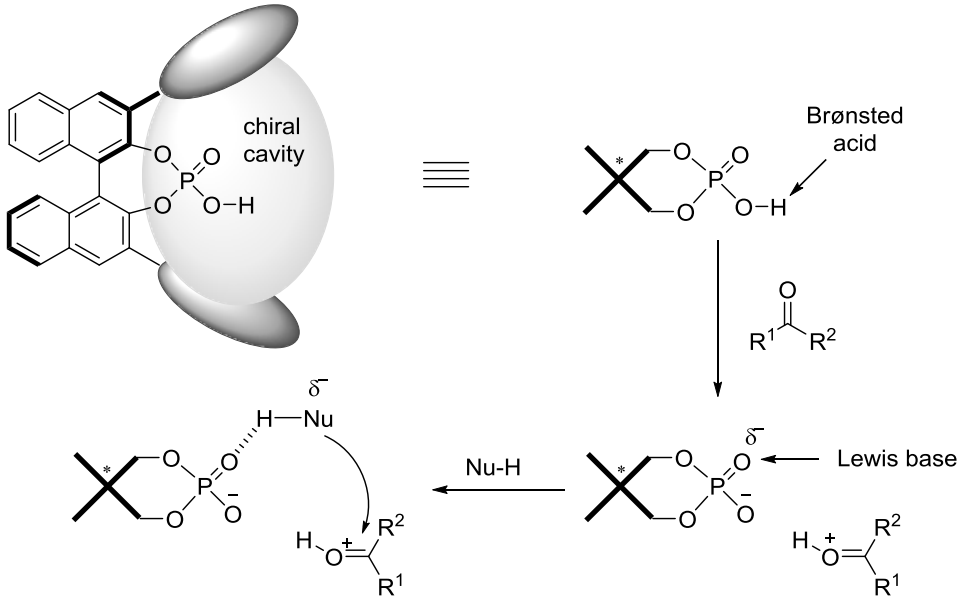
[53] For reviews on proline-catalyzed reactions see: a) S. S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5568. b) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 493–529. c) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 757–797. c) S. K. Panday, *Tetrahedron: Asymmetry* **2011**, *22*, 1817–1847.

[54] a) J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178–3181. b) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, *81*, 3629–3637. c) R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457–4463.

[55] For general reviews on non-covalent catalysis: a) A. Quitavalla, L. Cerisoli, M. Elisa, *Current Organocatalysis*, **2014**, *1*, 107–171. b) R. R. Knowles,; Jacobsen, E. N. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 20678‑20685.

[56] a) K. Maruoka, *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*, Thieme, Stuttgart, **2012**. For reviews on Brønsted acid catalysis see: b) T. Akiyama, J. Itoh, K. Fuchible, *Adv. Synth. Catal.* **2006**, *348*, 999–1010. c) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758. d) M. Terada, *Chem. Commun.* **2008**, 4097–4112. e) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.*

formation of a chiral ion pair. Among them, BINOL-derived phosphoric acids have been mostly employed for the α-functionalization of ketones, partially rationalized by their bifunctional structure (Scheme 13).[56f] In fact, the proton transfer goes together with the increasing Lewis basic character of the catalytic species. This emerging basicity is, in turn, involved in the activation of protic nucleophiles. However, in a strict sense, the phosphoric acid catalysts should be distinguished from most bifunctional organocatalysts, in which rather weak acidic and basic functionalities are introduced individually to the catalyst molecule.[56c]



Scheme 13. General structure and bifunctional reactivity of BINOL-derived phosphoric acid catalysts.

After Terada and coworkers[57] reported the prominent example of asymmetric direct Mannich reaction of acetylacetone with *N*-Boc aldimines catalyzed by chiral phosphoric acid derivatives, Gong *et al.* demonstrated that catalytic amount of a chiral phosphoric acid is sufficient to promote an *anti*-selective direct asymmetric Mannich reaction of cycloalkanones with high diastereo- and enantioselectivity (Scheme 14a).[58] Later, the first asymmetric Brønsted acid catalyzed direct aldol reaction of various ketones with very reactive aldehydes was reported[59] with moderate to excellent diastereo- and

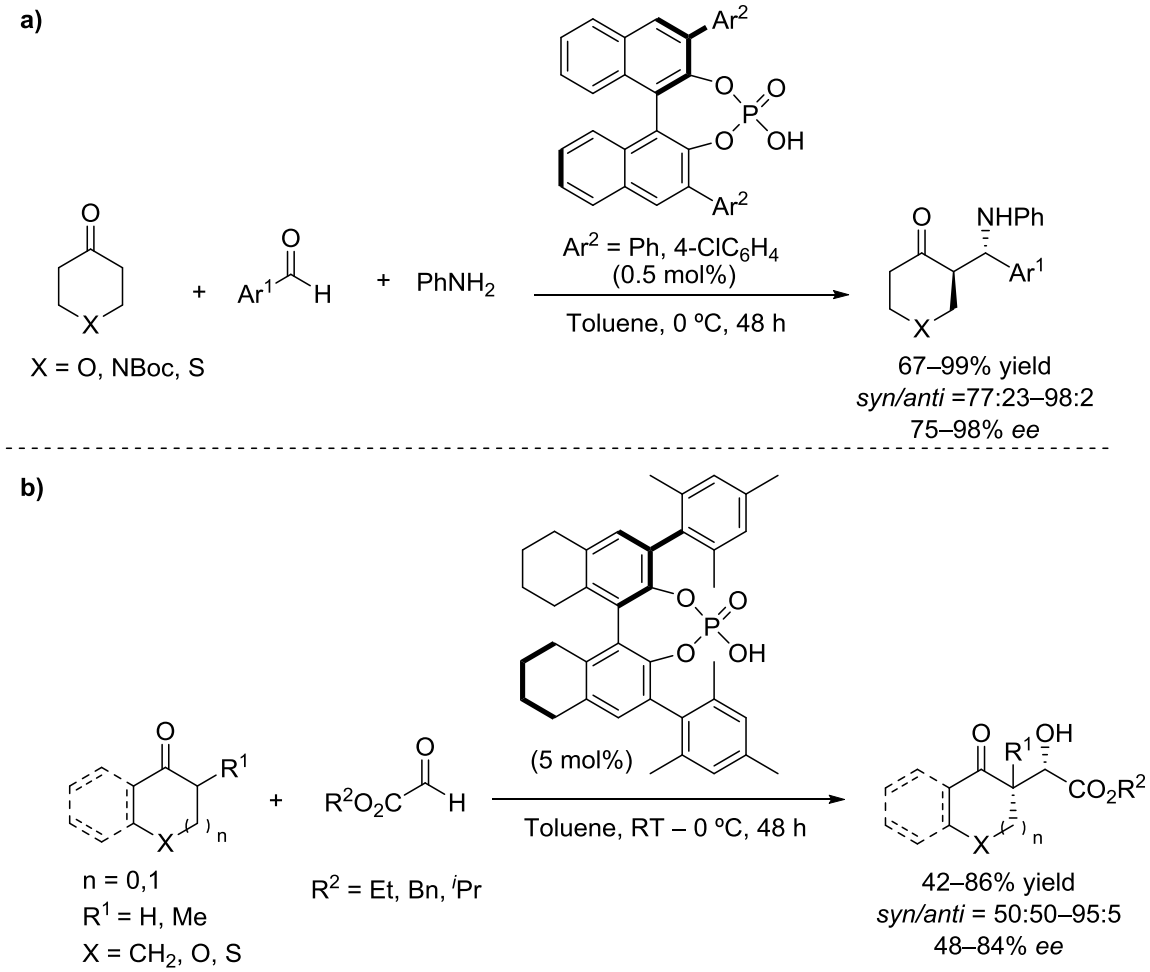
2010, *291*, 395–456. f) M. Terada, *Synthesis* **2010**, 1929–1982. g*)* J. Merad, C. Lalli, G. Bernadat, J. Maury, G. Masson, *Chem. Eur. J.* **2018**, *24*, 3925–3943. h) R. Maji, S. C. Mallojjala, S. E. Wheeler, *Chem. Soc. Rev.* **2018**, *47*, 1142–1158.

[57] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

[58] Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791.

[59] G. Pousse, F. Le Cavelier, L. Humphreys, J. Rouden, J. Blanchet, *Org. Lett.* **2010**, *12*, 3582–3585.

enantioselectivities using chiral H8-BINOL-derived phosphoric acids (Scheme 14b).[60] The sense of the relative configuration is the opposite as the one in similar proline-catalyzed reactions, favoring the *syn* isomer.



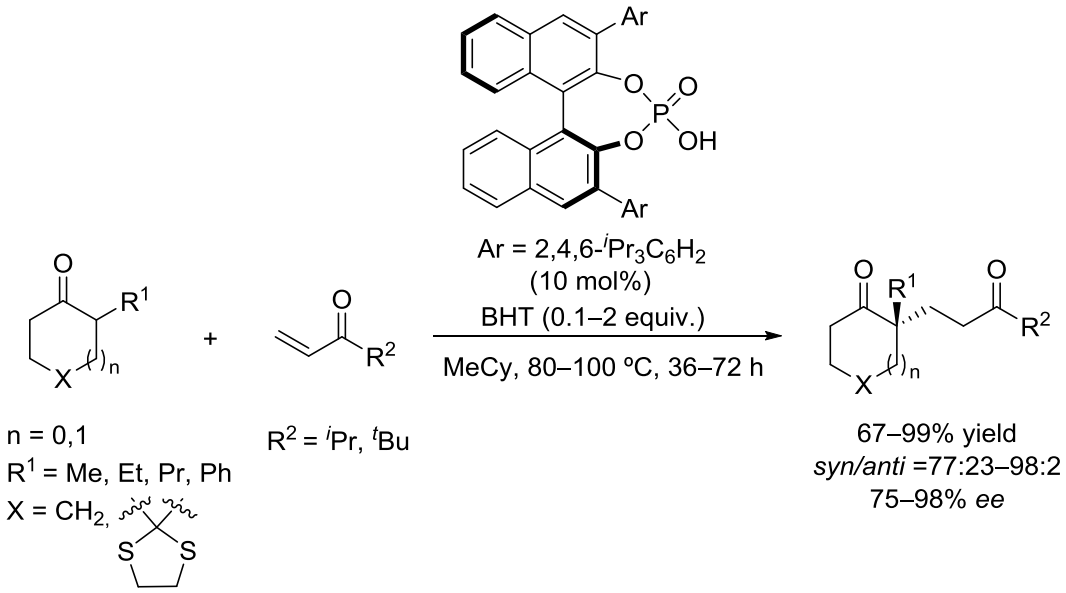
Scheme 14. Phosphoric acid catalyzed reactions of cyclic ketones: a) Mannich reaction. b) Aldol reaction

The Brønsted acid activation strategy has also enabled the α-CH functionalization of α-branched cycloalkanones. Taking into account the difficult formation of the sterically constrained enamine intermediate in enamine catalysis and inspired by the concerted acid–base mechanism found in enzymatic enolization, List *et al.*[61] envisioned a shift from enamine to enol catalysis through a Brønsted acid catalyzed Michael reaction. They reported the asymmetric addition of α-substituted cyclic ketones to alkyl vinyl ketones using (*S*)-TRIP as catalyst (Scheme 15). However, high reaction temperatures were

[60] Only in rare cases were organocatalysts reported to be general *syn*-selective in aldol reactions. a) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075. b) T. Kano, Y. Yamaguchi, Y. Tanaka, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 7606–7608.

[61] I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960–1964.

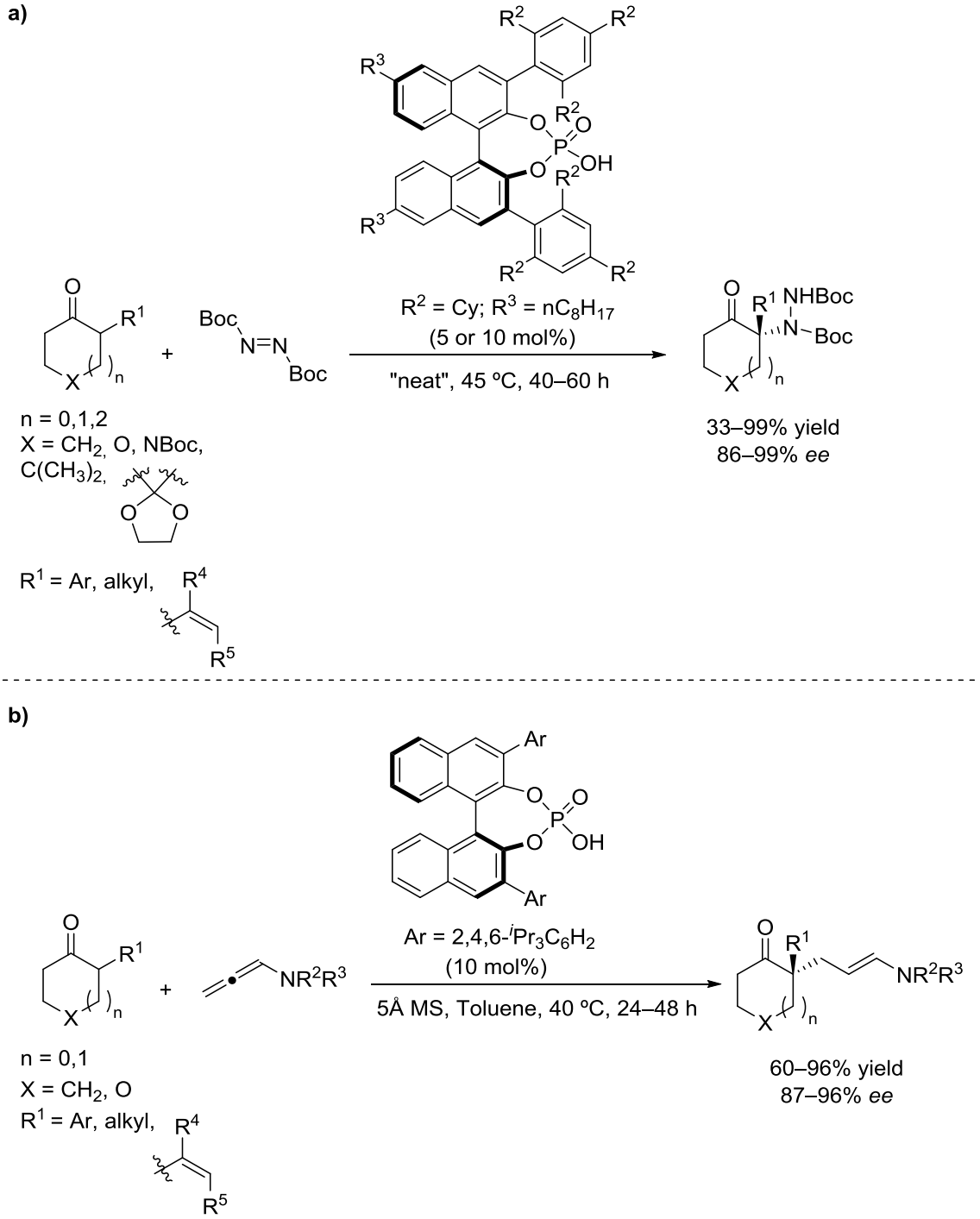
necessary and bulky *tert*-butyl or isopropyl-substituted enones were required in order to achieve high enantioselectivities.



Scheme 15. Michael addition of α-branched cycloalkanones catalyzed by (*S*)-TRIP.

Following their interest in obtaining cyclic ketone units bearing a quaternary α-stereocenter, Toste and coworkers reported the direct asymmetric amination of α-branched cyclic ketones catalyzed by a chiral phosphoric acid to generate *N*-containing tetrasubstituted carbon stereocenters from unactivated cyclic ketones (Scheme 16a).[62] Subsequently, they turned their attention to potential Michael addition of these substrates to conjugated olefins. Despite poor results were obtained with acrolein, methyl acrylate and methyl vinyl ketone as acceptors, the asymmetric addition of unactivated α-branched cyclic ketones to allenamides catalyzed by (*S*)-TRIP was developed with broad substrate scope (Scheme 16b).[63]

[62] X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205–3208.
[63] X. Yang, F. D. Toste, *Chem. Sci.*, **2016**, *7*, 2653–2656.



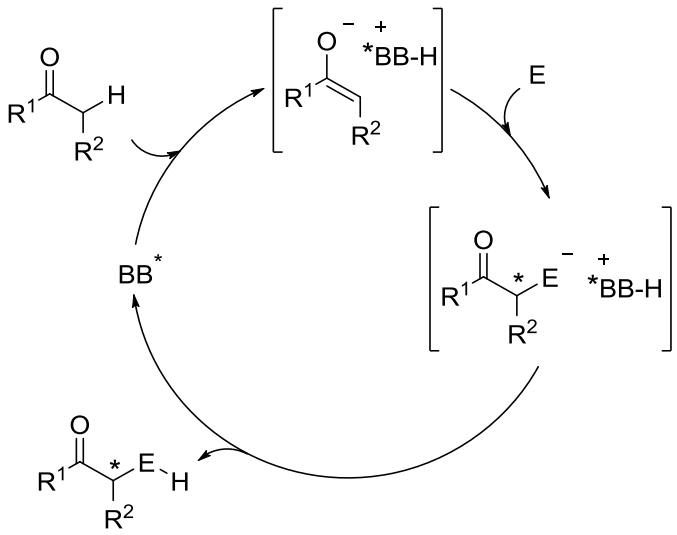
Scheme 16. Phosphoric acid catalyzed reactions of α-branched cyclic ketones developed by Toste: a) Addition to di-*tert*-butyl azodicarboxylate. b) Addition to allenamides.

Although promising results have been achieved following this Brønsted acid catalysis strategy via enolic intermediates, the range of common Michael acceptors compatible with this activation conditions appear to be very limited.[61,63]

1.2.2.3. *Brønsted base catalysis (non-covalent)*

Enantioselective Brønsted base catalyzed reactions have established themselves as powerful tools for the construction of optically pure compounds.[64] A Brønsted base (BB) can be defined as a molecular entity capable of accepting a proton from an acid or the corresponding chemical species. In a broad sense, proton transfer from an acid to a base accounts as one of the most elemental processes in chemistry.

Enolizable carbonyl compounds with relatively small pKa value (10–17 pK_a range)[65] are among the preferable substrates for BB-induced activation, accounting for the vast majority of examples reported. The general catalytic cycle presumed for reactions involving carbonyl compounds is shown in Scheme 17. After α-deprotonation of the carbonylic species by the basic catalyst to form a chiral ionic pair, the resulting enolate reacts with a suitable electrophile in an enantioselective manner to provide a nucleophile-electrophile adduct as the ultimate reaction product. The base might be restored again, allowing to re-enter the activation pathway and render the process catalytic.



Scheme 17. Catalytic cycle of Brønsted base reactions involving carbonyl compounds.

[64] For general reviews on Brønsted base catalysis: a) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632. b) I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley and Sons, New York, **2010**. c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200. d) B. Teng, W. C. Lim, C. H. Tan, *Synlett*, **2017**, *28*, 1272–1277. e) Ref. 56a.

[65] For a webpage of Bordwell pKa Table (acidities in DMSO) of different compounds, see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

The chirality transfer during the new bond forming reaction takes place throughout a non-covalent substrate catalyst ion-pairing complex. Predicting the sense of the stereoinduction exerted from the catalyst is complicated owing to the intrinsic nondirectional nature of interactions in ionic complexes. This may be overcome by combining a site with BB character and another site with hydrogen-bond donor ability (bifunctional catalyst) leading to catalysts that are able to simultaneously activate both nucleophilic and electrophilic components.[66] Consequently, a higher degree of stereochemical order in the transition state is obtained which usually results in better and more predictable asymmetric induction. (Figure 6). Although the concept of bifunctional organocatalysis was anticipated several years ago by Wynberg,[67] it was only in the early 2000s when Takemoto established this idea.[68]

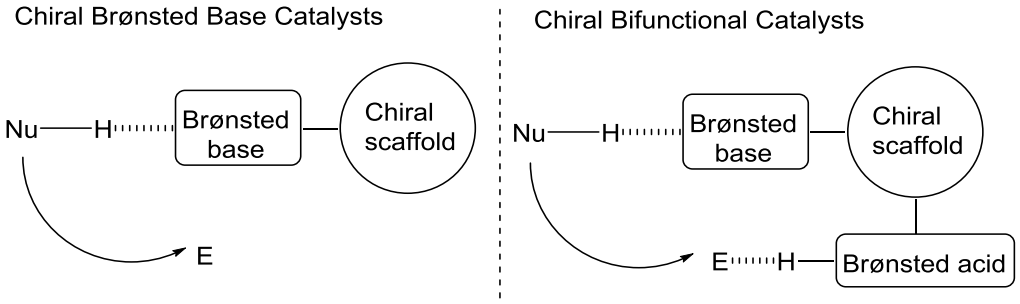


Figure 6. Chiral bifunctional catalyst design.

A variety of nitrogen-containing functionalities has been used for the design of chiral BB catalysts. Among them, tertiary amines, guanidines,[69] amidines, and imidazoles are the most prominent.[70] The selection of the base depends on the availability of the corresponding non-racemic precursors from the chiral pool. In this context, cinchona alkaloids are a straightforward source of enantiopure BB catalyst candidates (Figure 7).

[66] For reviews related to bifunctional organocatalysts, see: a) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504. b) X. Liu, L. Lin, X. Feng, *Chem. Commun.* **2009**, 6145–6158. c) S.-X. Wang, X. Han, F. Zhong, Y. Wang, Y. Lu, *Synlett* **2011**, *19*, 2766–2778. d) L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, *23*, 490–508. e) M. Tsakos, C. G. Kokotos, *Tetrahedron* **2013**, *69*, 10199–10222.

[67] For pioneering work, see: a) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057–4058. b) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244.

[68] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[69] For further information on guanidine-catalyzed reactions see: a) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–725. b) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488–507. c) D. Mailhol, M. M. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 3523–3532.

[70] For a review on organobase-catalyzed reactions, see: T. Ishikawa, *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts* John Wiley and Sons, Chichester, **2009**.

Indeed, the advent of chiral Brønsted base catalysis began with the recognition that the cinchona alkaloids serve as excellent catalysts and privileged structures.[67,71]

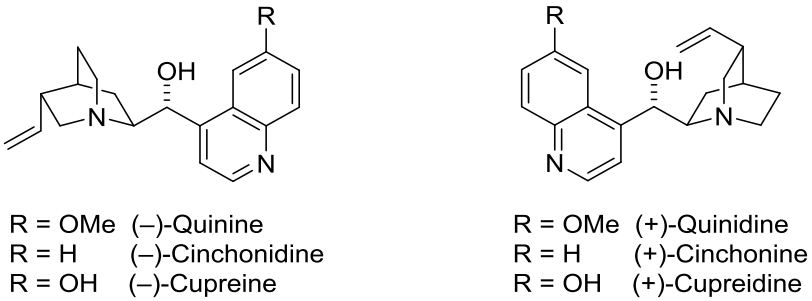
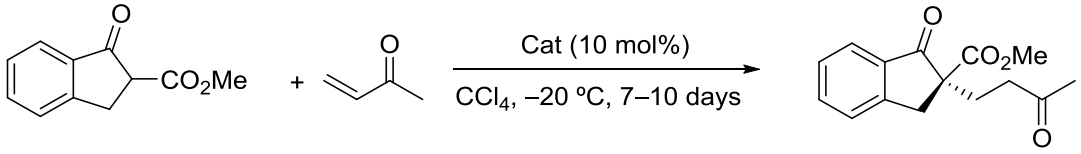


Figure 7. Some cinchona alkaloids and their derivatives.

In that regard, the earliest approaches of bifunctional BB catalyzed α-functionalization of ketones were performed using cinchona-derived catalysts in which C–H groups flanked by one carbonyl and another electron-withdrawing group are the optimal type of substrates. The first catalytic enantioselective conjugate addition was documented in Wynberg's[67a] seminal work on cinchona alkaloid-catalyzed addition of cyclic β-ketoesters to methyl vinyl ketone. After modest initial results, the reaction of 2-carbomethoxyindanone with methyl vinyl ketone was studied in some detail, and led to the Michael addition product in up to 69 and 76% ee, respectively, when natural alkaloids quinidine and quinine were employed (Scheme 18).[67b] The basicity of the quinuclidine nitrogen of cinchona alkaloids combined with the Brønsted acidic C9–OH group, confers a bifunctional catalytic property to cinchona alkaloids.[72]



Cat: quinidine 99% yield, 69% *ee*
Cat: quinine 99% yield, 76% *ee*

Scheme 18. First cinchona alkaloid catalyzed enantioselective conjugate addition.

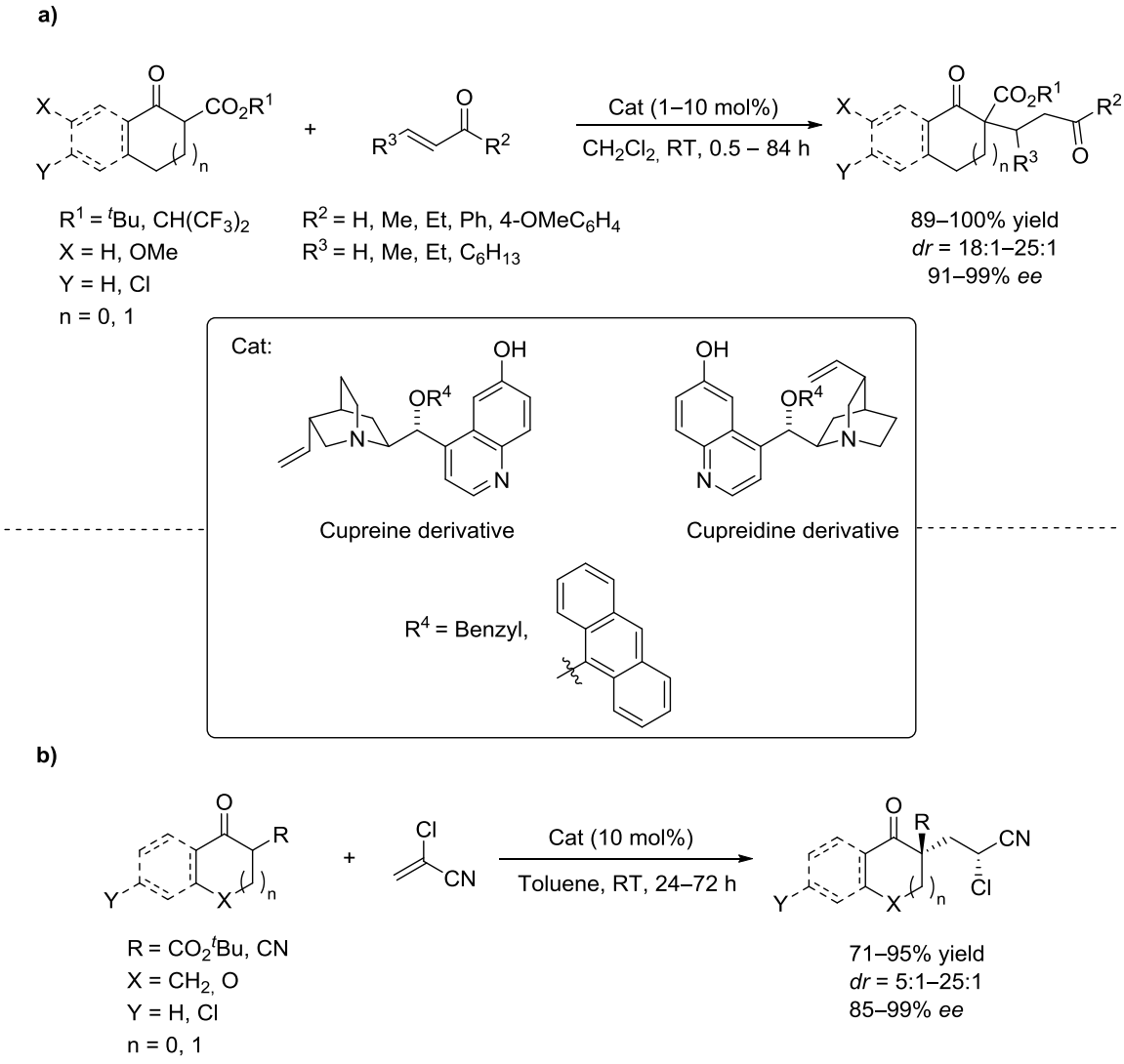
[71] For reviews on cinchona alkaloids in asymmetric organocatalysis see: a) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504. b) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279. c) E. M.O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron*. **2011**, 1725–1762. d) L. A. Bryant, R. Fanelli, A. J. A. Cobb, *Beilstein J. Org. Chem.* **2016**, *12*, 429–443.

[72] For mechanistic studies on bifunctional catalysis promoted by cinchona alkaloids, see: C. S. Cucinotta, M. Kosa, P. Melchiorre, A. Cavalli, F. Gervasio, *Chem. Commun.* **2009**, *15*, 7913–7921.

Some years later, Deng and coworkers investigated the viability of conjugate addition of acyclic and cyclic β-ketoesters employing a variety of Michael acceptors catalyzed by bifunctional cupreine and derived catalysts (Scheme 19a).[73] It was found that the nature of the ester alkyl radical (R^1) of the corresponding β-keto ester could alter dramatically the level of enantioselection. The best options are *tert*-alkyl and (fluorinated) branched-chain alkyl esters. On the other hand, it seems that the presence of phenolic free hydroxy group in the catalysts is a requisite for effective induction.

The utility of these catalysts was also demonstrated by the same group for the conjugate addition of trisubstituted carbon donors to 2-chloroacrylonitrile. α-Cyanoketones and β-ketoesters proceeded well to give products containing 1,3-tertiary-quaternary stereocenters in high yield and stereoselectivity (Scheme 19b).[74]

[73] a) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 947–950. b) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301–4305.
[74] Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930.

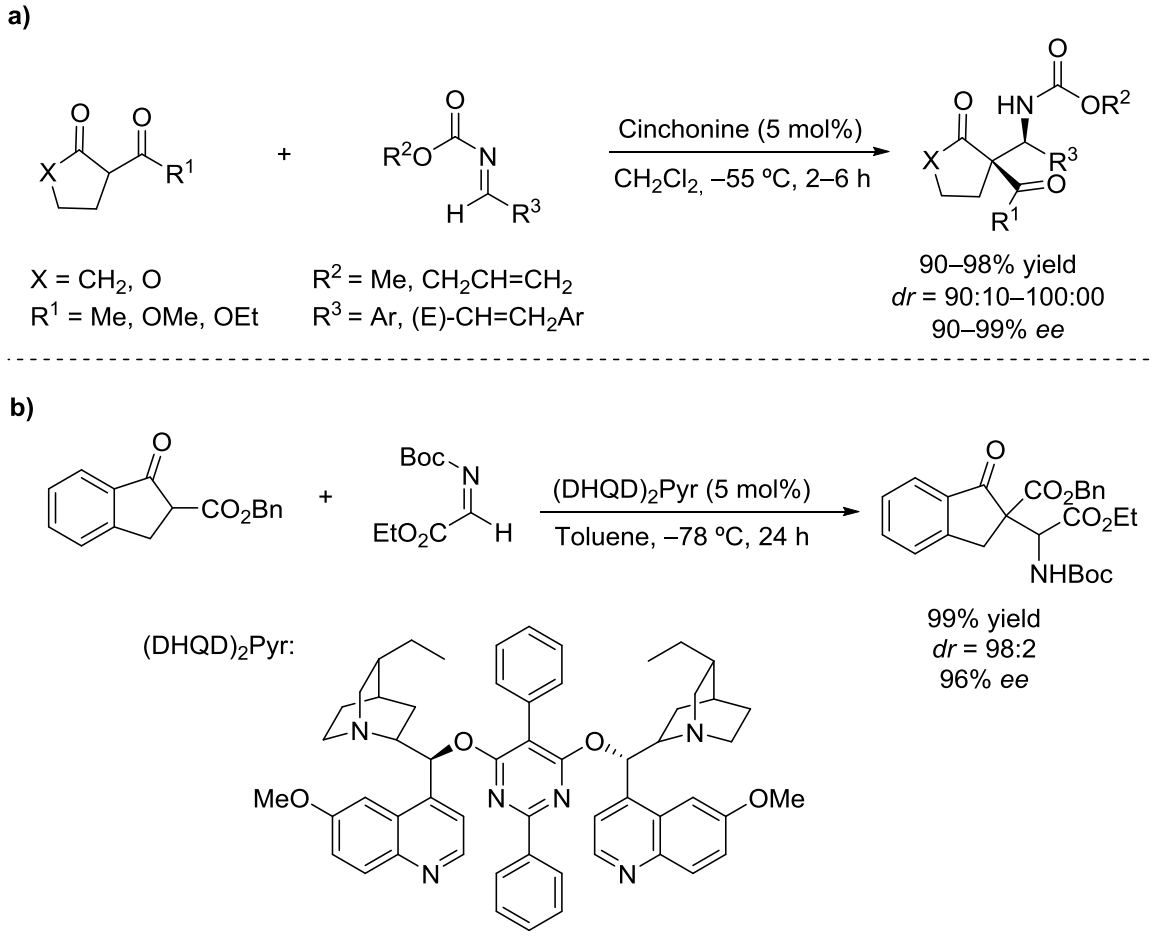


Scheme 19. Conjugate addition of cyclic ketones to different Michael acceptors catalyzed by cupreine and cupreidine derivatives.

Besides Michael additions, various Mannich reactions employing activated ketones have also been carried out. With the aim of investigating the hitherto unexplored addition of 1,3-dicarbonyls to imines and following the cinchonine-catalyzed results obtained previously, Schaus *et al.* reported the use of cyclic 1,3-dicarbonyl donors to access β-aminoesters with α-quaternary stereocenters (Scheme 20a).[75] Independently, Jørgensen described a methodology for the preparation of an α,α-substituted β-keto ester in

[75] a) S. Lou, BM. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257. b) S. Lou, A. Ting, S. E. Schaus, *Org. Lett.* **2006**, *8*, 2003–2006.

excellent yield and stereocontrol using $(DHQD)_2Pyr$, a dimeric quinidine-derived amine, as the catalyst (Scheme 20b).[76]



Scheme 20. Cinchona alkaloid catalyzed Mannich reactions of activated cyclic ketones.

In order to expand the utility of bifunctional BB catalysts, new hydrogen-bond donor capabilities, such as urea, thiourea, squaramide or sulfonamide, as well as readily available chiral amines were incorporated in the design of novel catalysts (Figure 8).

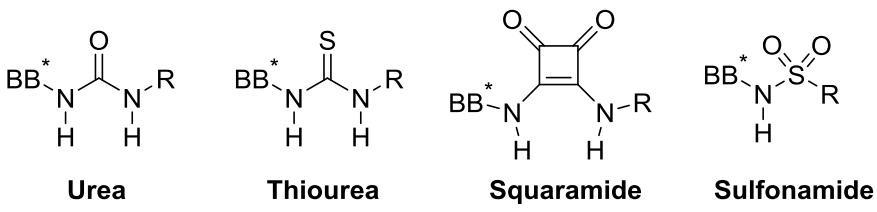
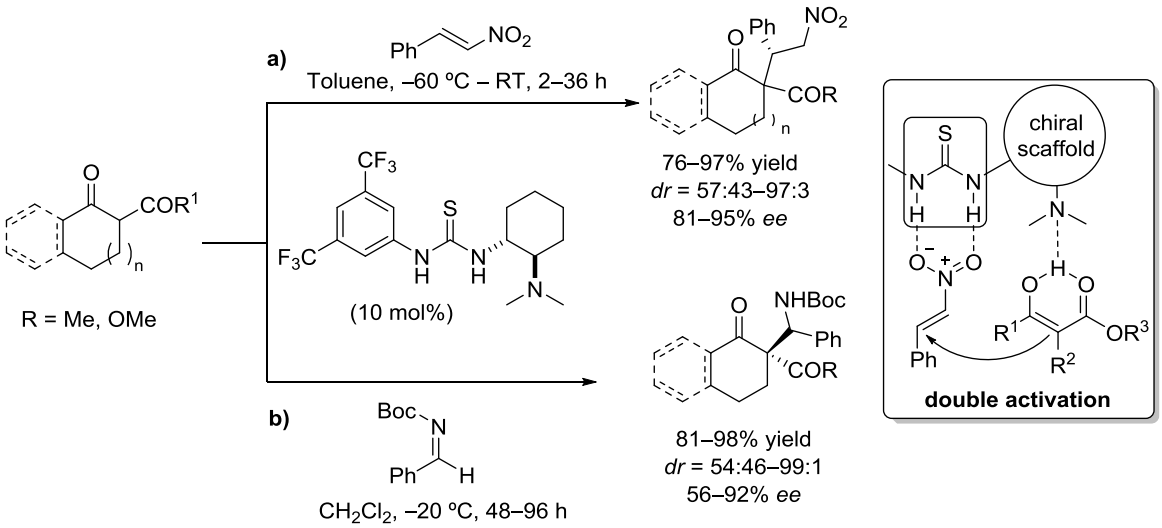


Figure 8. Hydrogen-bond donor groups.

[76] T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 2896–2899.

Takemoto´s group was the first to introduce a chiral bifunctional thiourea bearing the 1,2-diaminocyclohexane group by which highly enantioselective Michael additions of dimethylmalonate to nitroalkenes were promoted.[68] They used the same catalyst for the Michael and Mannich reactions of cyclic β-ketoesters in which ketones bearing quaternary stereocenters were obtained (Scheme 21).[77] It was concluded that the nitroolefin and the nucleophile are simultaneously activated by the thiourea moiety and the amino group, respectively (Takemoto´s activation model, Scheme 21).



Scheme 21. Michael and Mannich reactions of cyclic ketones catalyzed by thiourea-diamine type catalyst.

In view of the precedent set by Takemoto's bifunctional catalyst, the development of thiourea-substituted cinchona alkaloid catalysts was the next logical step, although other amino-thiourea catalysts were also reported. Cinchona alkaloids possess relatively rigid (but not completely locked) structures in which Brønsted basic and hydrogen bond-accepting functionality are located at stereogenic centers in close proximity to one another. Furthermore, the C9 stereocenter is a secondary alcohol, which can readily be transformed into a (thio)urea derivative via the corresponding primary amine.

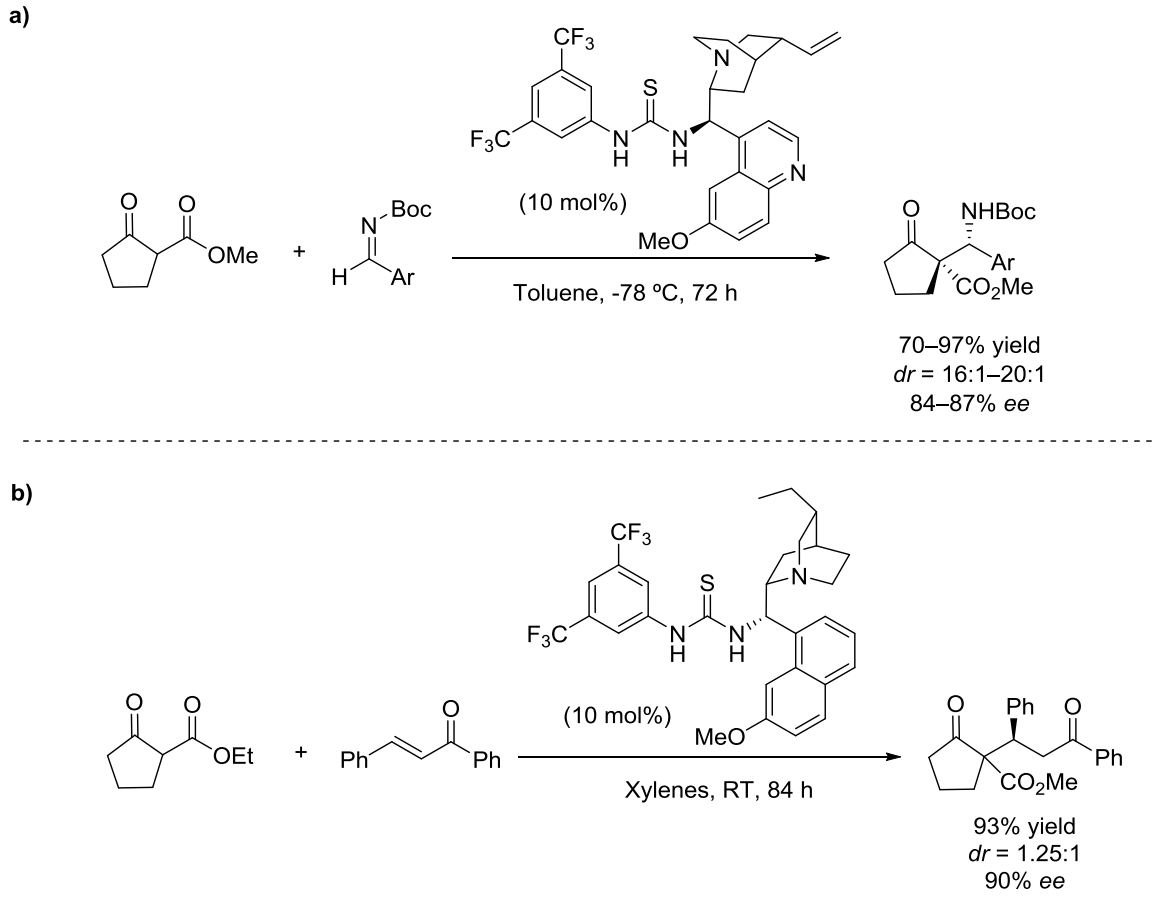
Thus, several research groups began working independently on the design of readily accessible and tunable (from steric-, stereochemical- and electronic standpoints) bifunctional catalyst templates based on cinchona alkaloids.[78] In 2006, Deng,[79] Dixon

[77] a) T. Okino, Y. Hoashi, T. Furakawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125. b) Y. Yamaoka, H. Miyabe, Y. Yasui, Y. Takemoto, *Synthesis* **2007**, 2571–2575.

[78] For a review, see: S. J. Connon, Chem. Commun. 2008, 2499–2510.

[79] J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049, Mannich reaction.

(Scheme 22a)[80] and Wang (Scheme 22b)[81] independently reported first thiourea-cinchona alkaloid catalysts for reactions involving acyclic and cyclic β-ketoesters.



Scheme 22. Mannich and Michael reactions of cyclic β-ketoesters using thiourea-cinchona catalysts.

Two years later, the squaramide group, introduced by Rawal, was identified as another complementary double H-bonding donor.[82] Compared to thiourea, the squaramido functionality differs significantly in some aspects. The most significant difference is the relative distance and spacing between the two N–H groups. In the case of a thiourea, the distance between the two N–H groups attached to the same carbon remains fixed at *ca.* 2.13 Å, whereas in a squaramide this distance is approximately one third (2.73 Å) larger than that in a thiourea (Figure 9).[82,83] In both thioureas and squaramides the lone pair on the nitrogen atom is delocalized, thereby restricting the rotation of the C–N bond. However, only in squaramides can further delocalization occur through the

[80] A. L. Tillman, J. Ye, D. Dixon, *Chem Commun.* **2006**, *42*, 1191–1193, Mannich reaction.
[81] J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653, Michael reaction.
[82] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.
[83] T. Okino, Y. Hoashi, T. Furukawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

cyclobutenedione system. Thus, the N–H acidity of a squaramide is higher as compared to that of a thiourea due to their vinylogous amide nature, providing a polarized nitrogen moiety.[84] Generally, the squaramide moiety forms stronger hydrogen bonds with the substrates bearing nitro, carbonyl, imino, nitrile functionalities, etc.

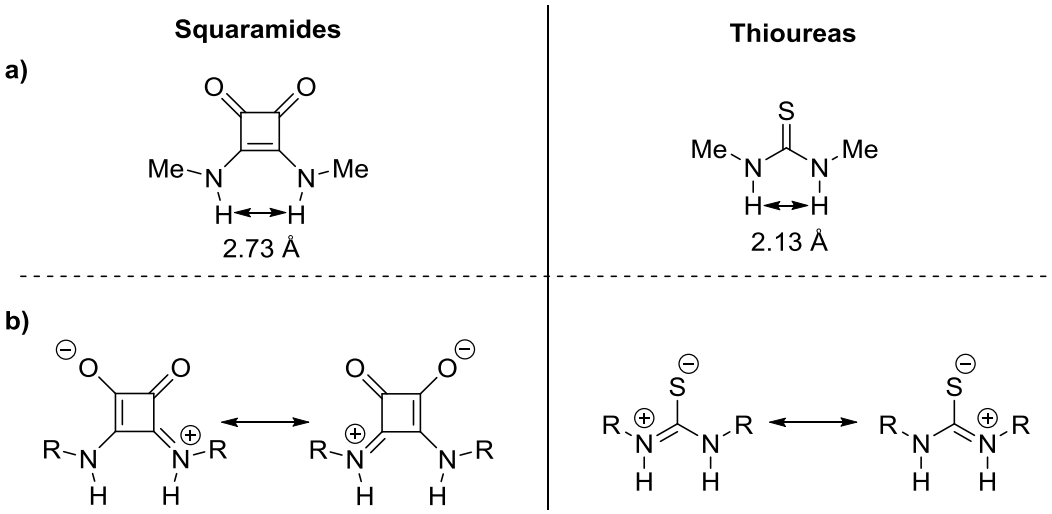


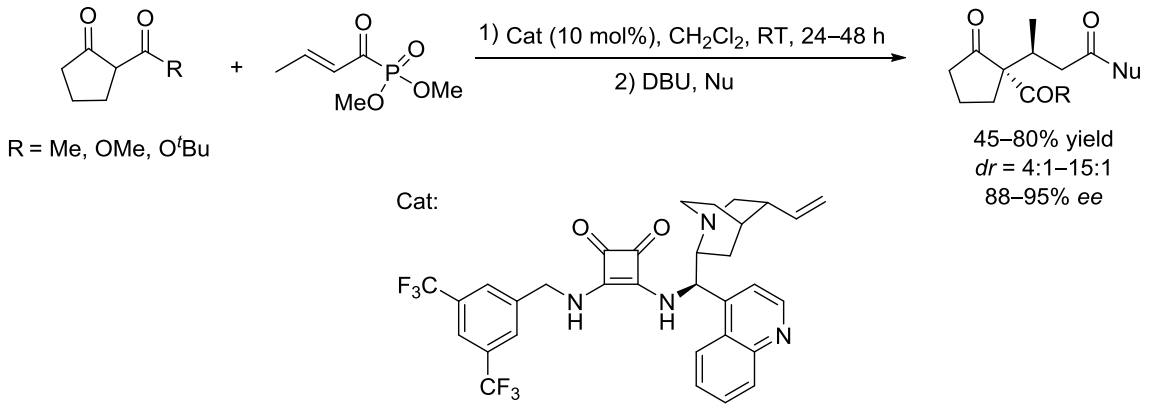
Figure 9. a) H-bond spacing distances in thioureas and squaramides. b) Comparison of zwitterionic forms of thiourea and squaramide skeletons

Since the pioneering report, the chiral amino-squaramides have emerged as bifunctional organocatalysts for promoting several reactions,[85] including the α-functionalization of ketones. For example, Rawal's catalyst derivative based on cinchonine was proved to be efficient for the reaction of cyclic 1,3-dicarbonyls with unsaturated acylphosphonates (Scheme 23), whereas the corresponding cinchona-based thiourea catalyst was not able to provide any significant conversion of the reactant.[86]

[84] X. Ni, X. Li, Z. Wang, J.-P. Cheng, *Org. Lett*. **2014**, *16*, 1786–1789.

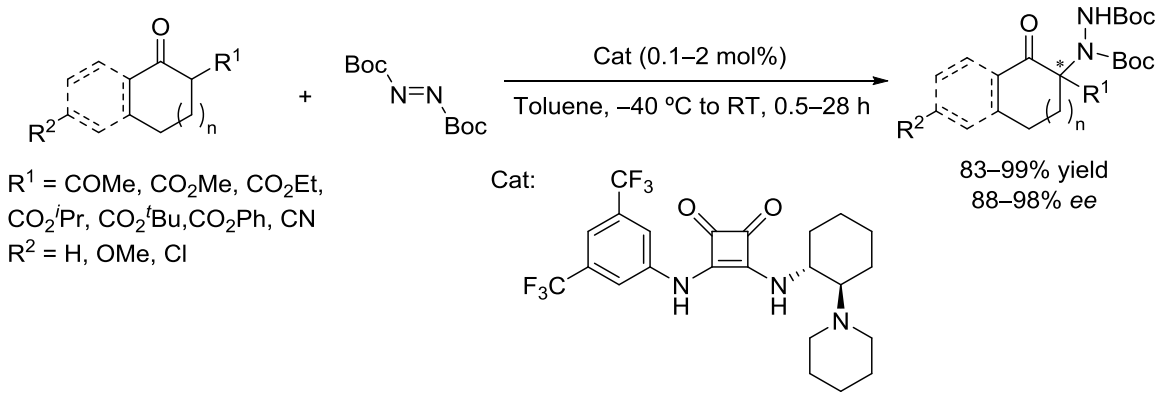
[85] For reviews on squaramide-based catalysts see: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899. b) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330–2346. c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281. d) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–906. e) B.-L. Zhao, J.-H. Li, S.-M. Du, *Chem. Rec.* **2017**, *17*, 994–1018.

[86] H. Jiang, M. W. Paixao, D. Monge, K. A. Jørgensen, *J. Am.Chem. Soc.* **2010**, *132*, 2775–2783.



Scheme 23. Addition of 1,3-dicarbonyls to unsaturated acylphosphonates employing an amino-squaramide type catalyst.

Rawal´s group also developed a new squaramide catalyst, which structurally resembled the analogous bifunctional thioureas prepared by Takemoto *et al.*[68] using the 1,2-diaminocyclohexane scaffold instead of the previously adopted amino-cinchona alkaloid derivatives. The catalyst was applied for the enantioselective α-amination of 1,3-dicarbonyl compounds to attain high yields and excellent enantioselectivities (Scheme 24).[87]

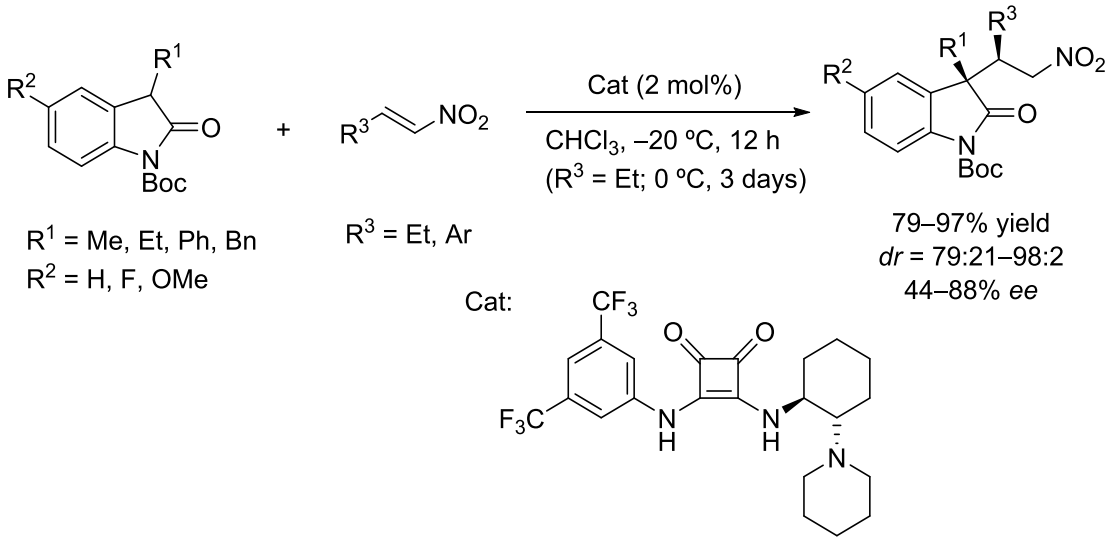


Scheme 24. α-amination of cyclic 1,3-dicarbonyl compounds catalyzed by squaramide-diaminocyclohexane type catalyst.

Wang and coworkers employed the same catalyst to perform the Michael addition of 3-substituted oxindoles with nitroalkenes. This process provides an easy access to 3,3-disubstituted oxindoles bearing adjacent quaternary/tertiary stereocenters in high yields

[87] H. Konishi, T. Y. Lam, J. P. Malerich, V. H. Rawal, *Org. Lett*. **2010**, *12*, 2028–2031.

with good diastereo- and enantioselectivities (Scheme 25).[88] The squaramide type catalysts have also been used successfully for cascade reactions of different oxindoles to obtain spirooxindole derivatives with potential biological and pharmaceutical activities.[85d,89]



Scheme 25. Michael addition of 3-substituted oxindoles with nitroalkenes catalyzed by a squaramide catalyst.

The Michael addition of the challenging 3-substituted oxindoles to afford the corresponding tetrasubstituted carbon stereocenters was also reported by our group.[90] α'-hydroxy enones were used as acceptors in which the hydroxyl group was introduced so as to increase the electrophilicity of the enone as well as facilitate the H-bonding with the Brønsted base catalyst in order to promote the reactions initiated by a proton-transfer event. In the same work, not only α-aryl, but also α-alkyl cyanoacetates, a subclass of substituted cyanoacetates previously documented to be poorly reactive substrates,[91] particularly against alkyl vinyl ketones,[91a] were used in the Brønsted base

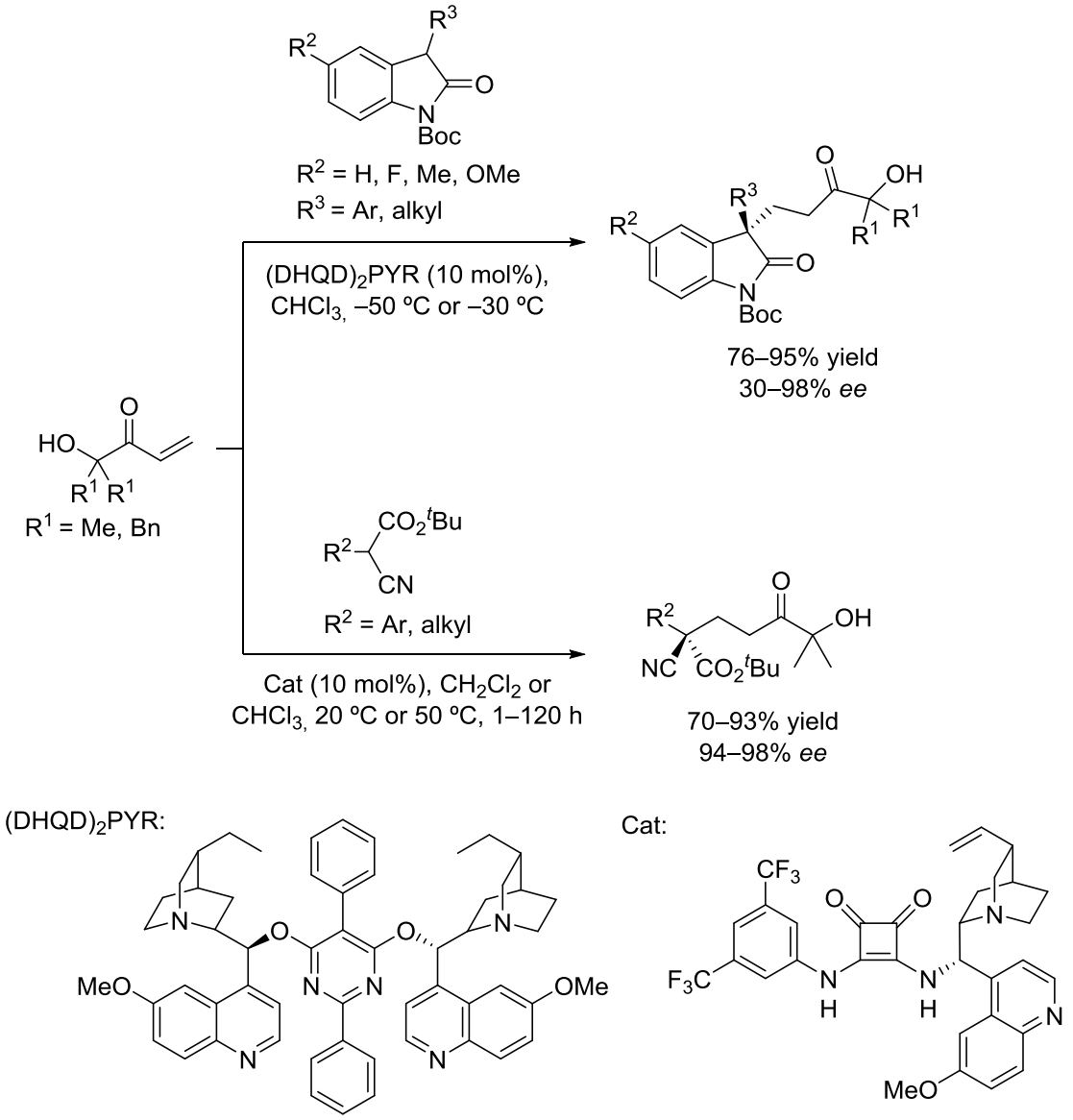
[88] W. Yang, J. Wang, D.-M. Du, *Tetrahedron: Asymmetry* **2012**, *23*, 972–980.

[89] For a review on squaramide-catalyzed domino and cascade reactions see: P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 254–281.

[90] E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.

[91] Asymmetric organocatalytic conjugate additions of α-substituted cyanoacetates. To enones: a) T.-Y. Liu, R. Li, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Chem. Eur. J.* **2007**, *13*, 319−327. b) M. Bell, T. B. Poulsen, A. K. Jørgensen, *J. Org. Chem.* **2007**, *72*, 3053−3056. c) F. Wu, H. Li, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301−4305. To acetylenic carbonyls: d) X. Wang, M. Kitamura, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 1038−1039. To maleimides: e) Y.-H. Liao, X.-L. Liu, Z. J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *Adv. Synth. Catal.* **2011**, *353*, 1720−1728. To vinylsulfones: f) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949. To vinyl selenones: g) F. Marini, S. Sternativo, F. Del

catalyzed reaction with α´-oxy enones. With both challenging prostereogenic C-nucleophiles the corresponding adducts were obtained in high diastereo- and enantioselectivity (Scheme 26).



Scheme 26. Enantioselective Michael addition of 3-oxindoles and α-substituted cyanoacetates to α'-hydroxy enones.

Despite the fact that there are several satisfying procedures for the α-functionalization of cyclic ketones using BB catalysis, most of the methods are still limited to the use of easily enolizable specific nucleophiles bearing an EWG at the α-position like 1,3-

Verne, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2009**, *351*, 1801−1806. To acrylonitriles: h) B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768−769.

diketones, β-ketoesters or α-cyanoketones (Figure 10) or very active electrophiles. Moreover, while most of the reactions are highly enantioselective, the formation of two consecutive new stereogenic centers in a diastereoselective manner remain challenging.

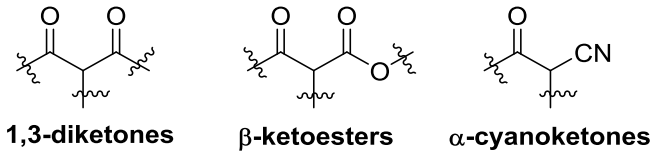


Figure 10. Easily enolizable nucleophiles bearing an EWG at the α-position.

1.3. General Objectives

The overall aim of this research consists of the development of new methodologies for regio- and stereoselective α-functionalization of cyclic ketones that would solve some of the problems of current methodologies. For doing so, Brønsted base/H-bonding catalysis will be applied in which proton transfer events are central to the substrate activation and catalysis cycle.

As it is clear from the examples described in the Introduction, current catalytic, and particularly organocatalytic, methods for the enantioselective functionalization of (cyclic) ketones are plagued of a number of complications and limitations. In Figure 11 some of these problems are highlighted.

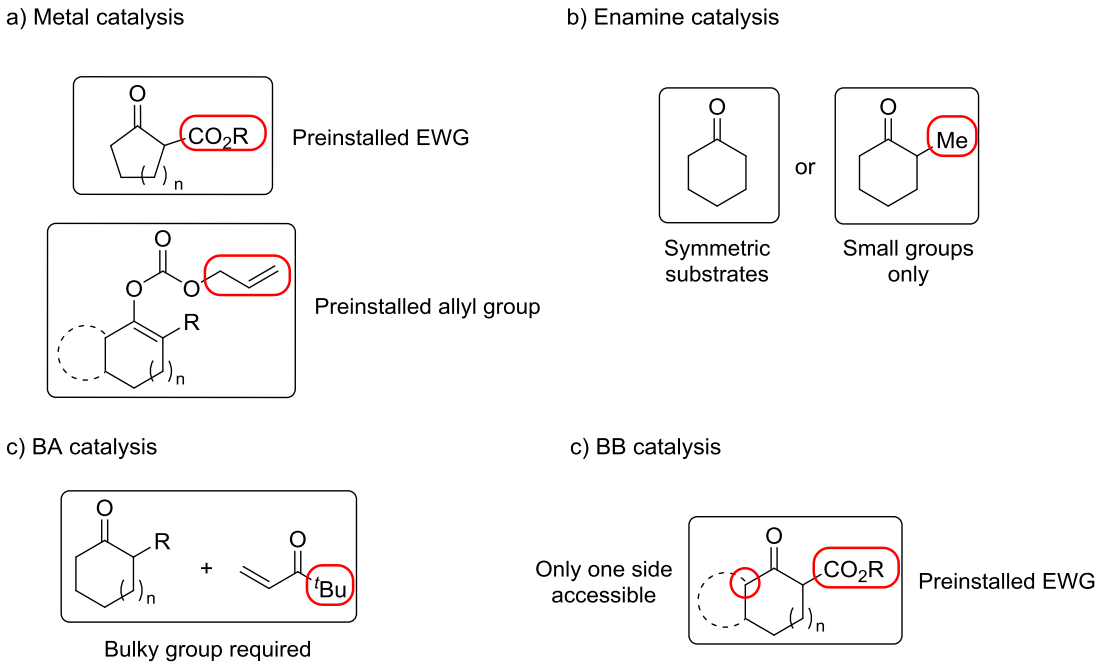


Figure 11. Current successful methods and inherent restrictions.

Briefly, the above complications are associated to two main aspects: i) the lack of threshold reactivity of simple (cyclic) ketones towards base catalyst-promoted proton abstraction (transient generation of enolate) and ii) difficulties in controlling efficiently the α/α' site selectivity in simple (cyclic) ketones.

Apart from these two main aspects, efficient control of the reaction enantio- and diastereoselectivity is an additional issue that need to be properly addressed, especially when generation of quaternary carbon centers are involved. Indeed, despite their widespread presence within natural products and biologically relevant molecules, cyclic ketone units bearing a quaternary α-stereocenter remain challenging synthetic targets.[92]

In order to accomplish the general objective of this thesis, identification of nucleophiles with sufficient reactivity for a Brønsted base/H-bonding catalysis methodology is essential. In this sense, β-tetralones and α-alkenyl cycloalkanones are selected as feasible type of compounds and with a view to addressing the issues mentioned above, in this investigation we have set to study the following aspects:

a) The reactivity profile of transiently generated enolates from β-tetralones for their Brønsted base catalyzed α-functionalization. The following problems shown in Figure 12 should be taken into account:

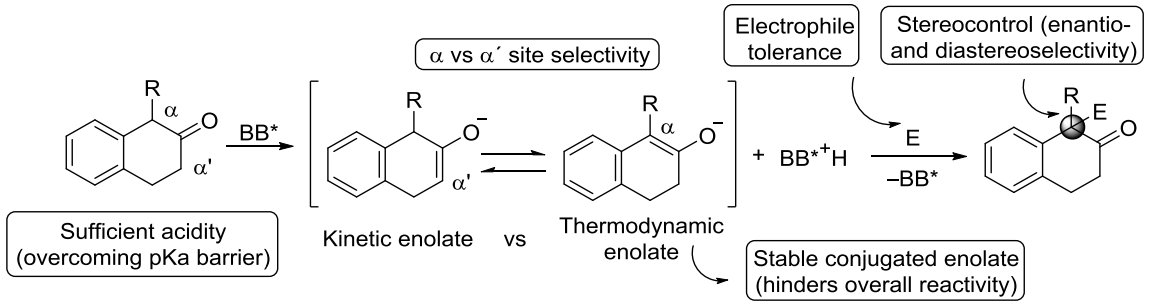


Figure 12. Challenges of the Brønsted base catalyzed α-functionalization of β-tetralones.

b) The reactivity profile of dienolates transiently generated from skipped (cyclic) ketones in order to carry out carbon-carbon bond forming reactions of α-substituted β,γ-unsaturated ketones assisted by bifunctional catalysts. In this case, the Brønsted base

[92] For reviews on the asymmetric construction of quaternary carbon centers, see: a) A. Y. Hong, B. M. Stoltz, Eur. *J. Org. Chem*. **2013**, 2745–2759. b) J. P. Das, I. Marek, *Chem. Commun*. **2011**, *47*, 4593–4623. c) M. Bella, T. Caspery, *Synthesis* **2009**, 1583–1614. d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, Eur. *J. Org. Chem*. **2007**, 5969–1614. e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396. f) J. Christoffers, A. Baro, *Quaternary Stereocenters*, Wiley-VCH, Weinheim, **2005**. g) C. J. Douglas, L. E. Overman, *Proc. Nat. Acad. Sci*. **2004**, *101*, 5363–5367.

should be effective in controlling both α vs γ reactivity as well as the reaction stereoselectivity (Figure 13).

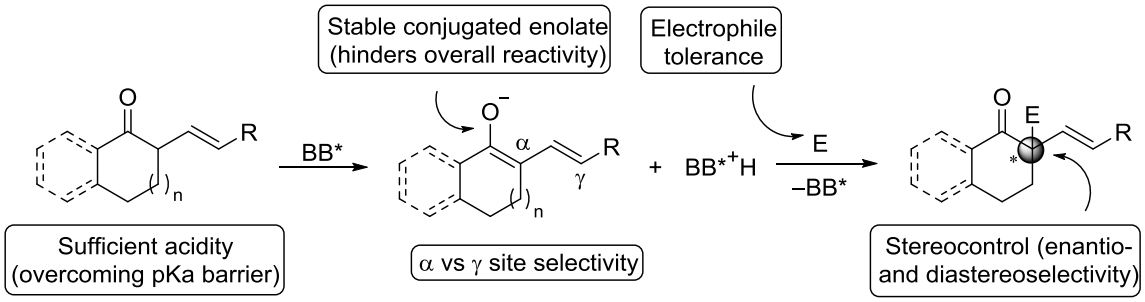


Figure 13. Challenges of the α-functionalization of dienolates catalyzed by Brønsted base catalysts.

Regarding the catalyst, bifunctional Brønsted base/H-bond catalysts should be appropriate as a better enolization power is expected owing to simultaneous double activation of both the nucleophile and the electrophile (Figure 14a). Similar to the soft enolization promoted by metal catalysis in which a Lewis acid and a weak base are used,[93] deprotonation of the nucleophile using a weak base might be plausible in the presence of an H-bond donor group that increases the acidity of the α-carbon. Moreover, the anchoring effect of the bifunctional catalyst would allow a better site- and stereocontrol of the reaction owing to a higher degree of stereochemical order in the transition state (Figure 14b).

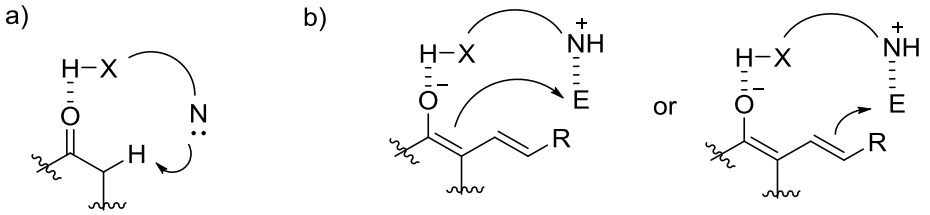


Figure 14. a) Double substrate activation by a bifunctional Brønsted base/H-bond catalyst. b) α and γ attacking trajectories.

[93] For an example, see: D. A. Evans, C.W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706–8707.

Chapter 2

Selective C-functionalization of β-tetralones

2. Selective C-functionalization of β-Tetralones

2.1. Introduction

β-Tetralones have been employed in the synthesis of many bioactive compounds with polycyclic structures, including homoerythrina alkaloids,[94] morphan derivatives,[95] glucocorticoid receptors,[96] and stradiols,[97] among others (0).[98] However, this interest did not translate into a variety of approaches for the asymmetric synthesis of α(α')-substituted β-tetralones.

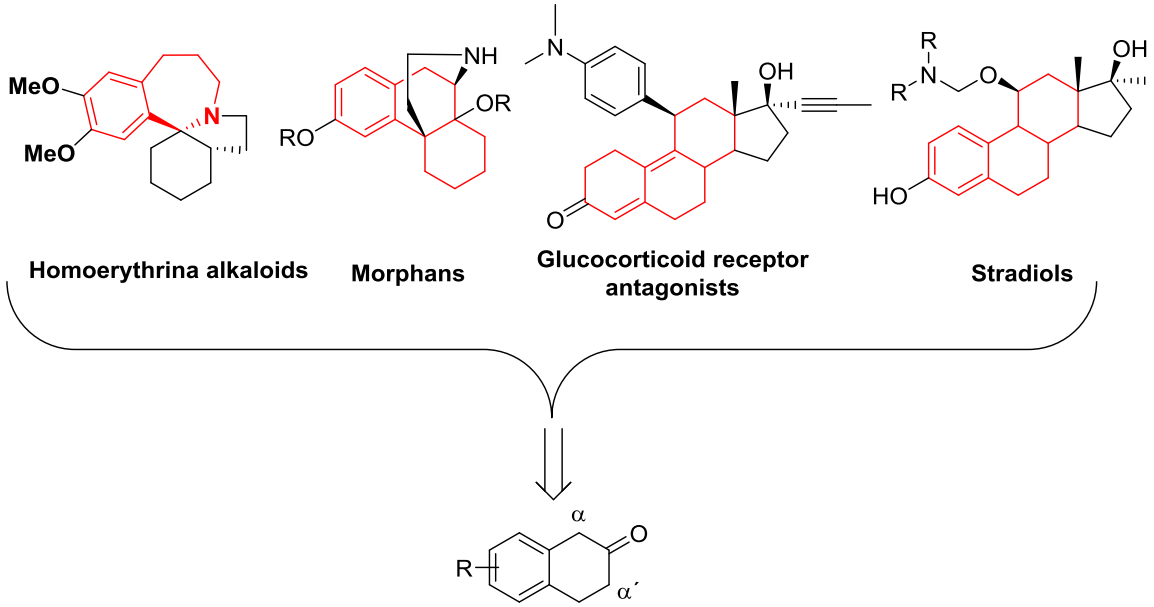


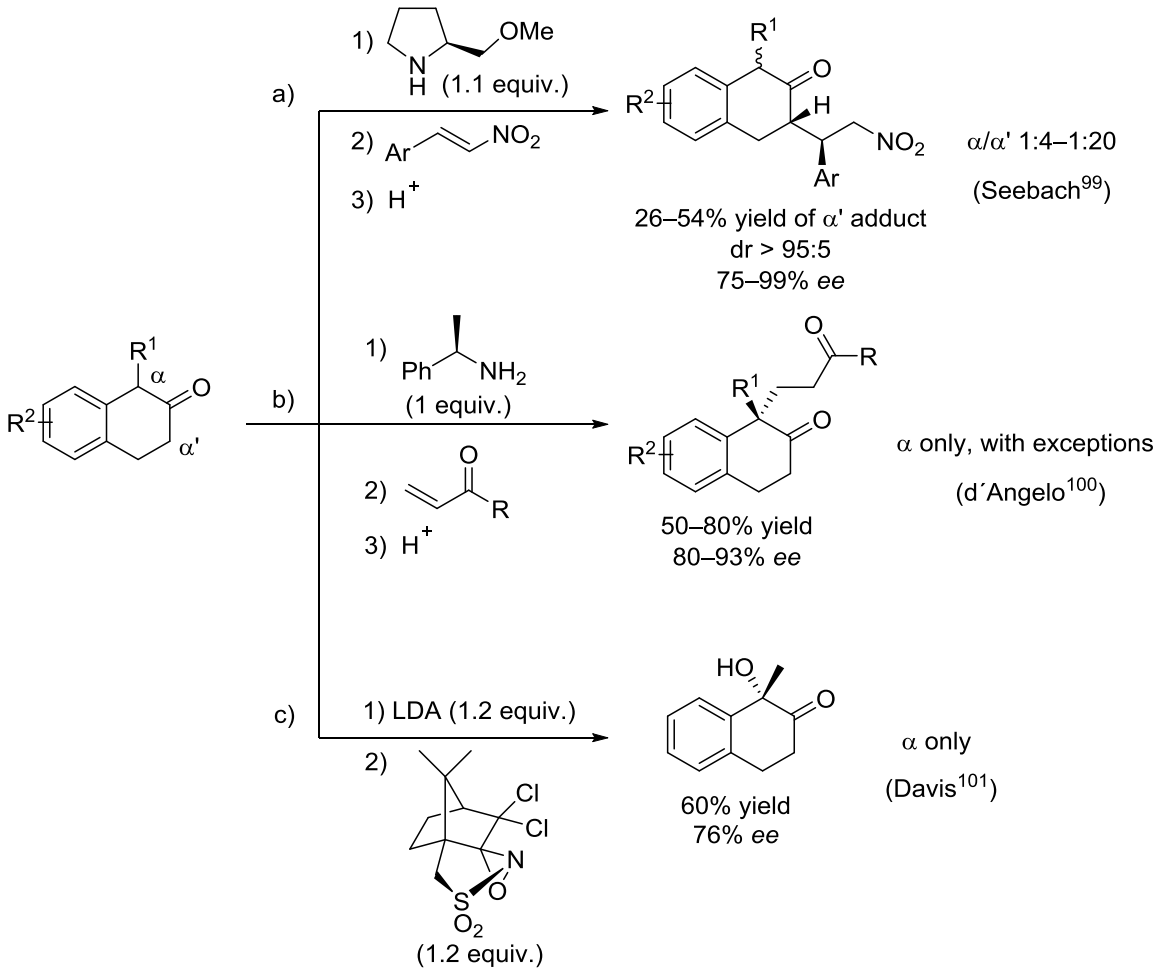
Figure 15. Bioactive compounds with polycyclic structures derivable from β-tetralone.

β-tetralones are nonsymmetric ketones therefore presenting two nonequivalent enolizable sites. Consequently, two regioisomeric enolates (α and α´), or equivalents, can be generated and subsequently functionalized, making regiocontrol one of the key issues in β-tetralone C-functionalization. In this regard, condensation of β-tetralones

[94] Racemic synthesis: a) M. A. Le Dréau, D. Desmaele, F. Dumas, J. d'Angelo, *J. Org. Chem.* **1993**, *58*, 2933–2935.
[95] G. Lim, J. W. Hooper, US Patent 4, 017,497; Apr. 12, **1977**.
[96] B. P. Morgan, A. G. Swick, D. M. Hargrove, J. A. LaFlamme, M. S. Moynihan, R. S. Carrol, K. A. Martin, G. Lee, D. Decosta, J. Bordner, *J. Med. Chem*. **2002**, *45*, 2417–2424.
[97] a) Y. Bouali, F. Nique, J.-G. Teutsch, P. Van de Velde, US Patent 6, 207,657BI, Mar 27, **2001**. b) J. P. Larkin, C. Whrey, P. Boffelli, H. Lagraulet, G. Lamaitre, A. Nedelec, D. Prat, *Org. Proc. Res. Dev.* **2002**, *6*, 20-27.
[98] C. C. Silveira, A. L. Braga, T. S. Kaufman, E. J. Lenardão, *Tetrahedron* **2004**, *60*, 8295-8328.

with a chiral amine and subsequent C-alkylation of the resulting enamine by addition to a Michael acceptor is one of the main strategies for the elaboration of β-tetralones into more complex carbon architectures. Blarer and Seebach[99] reported that the reaction with nitrostyrenes of the enamine derived from (S)-2-methoxymethylpyrrolidine and the respective β-tetralone produced in moderate yields the α'-adduct predominantly (α/α' from 1:4 to 1:20) with generally good diastereo- and enantioselectivity after hydrolysis of the resulting iminium species (Scheme 27a). Alternatively, the groups of Pfau and d´Angelo reported the condensation of β-tetralones with (S)-1-phenylethylamine and subsequent Michael reaction of the resulting enamine to afford the α-substituted adducts preferentially,[100] but with exceptions to this main reactivity trend (Scheme 27b).[100a] A different strategy was used by Davis *et al.*[101] for the α-hydroxylation of α-substituted β-tetralone. They developed a methodology for the reagent controlled asymmetric oxidation of enolates employing chiral N-sulfonyloxaziridines to obtain an α-hydroxy-β-tetralone derivative with moderate yield and enantioselectivity (Scheme 27c).

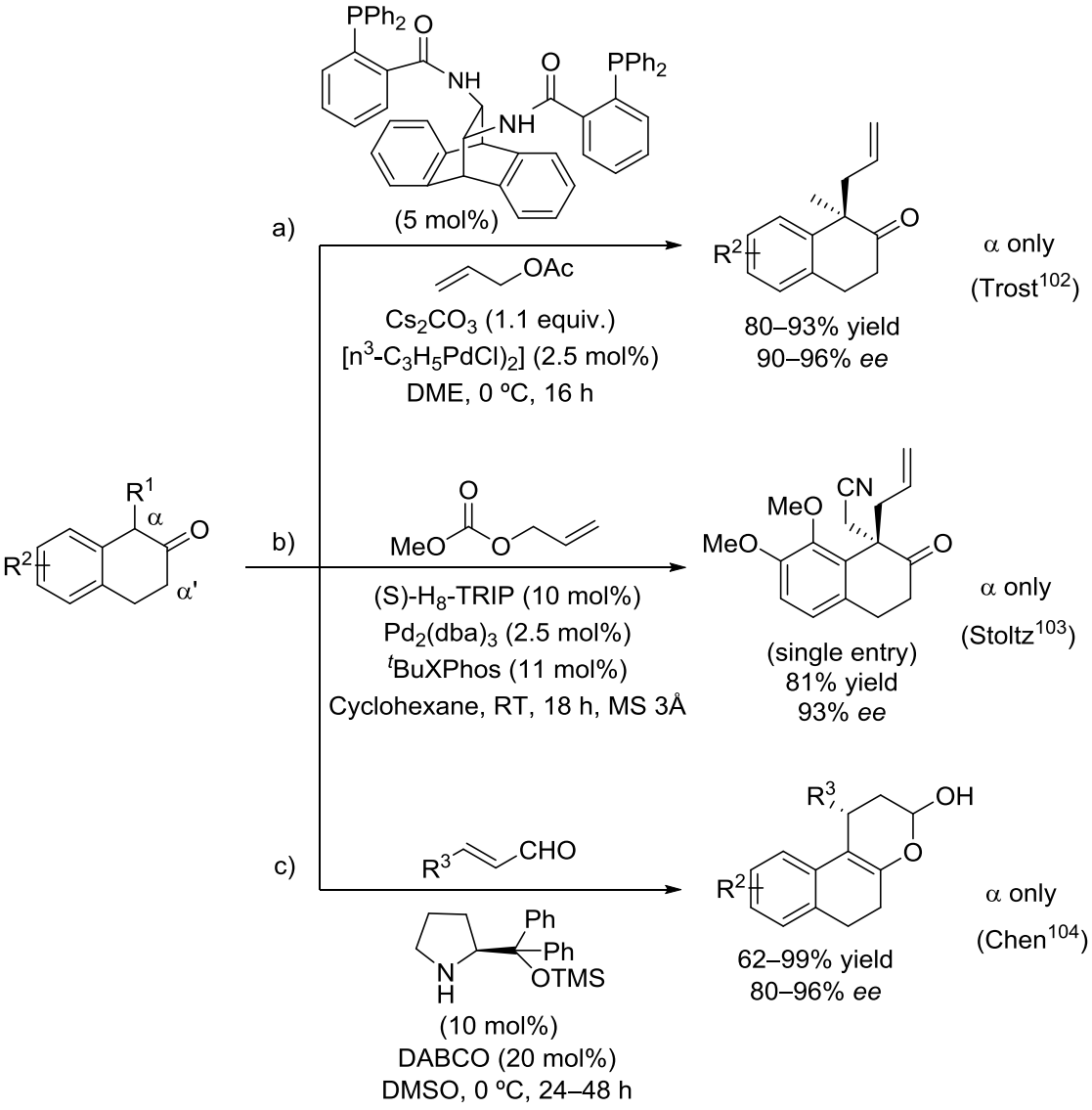
[99] S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, *116*, 3086–3096.
[100] a) T. Volpe, G. Revial, M. Pfau, J. d´Angelo, *Tetrahedron Lett.* **1987**, *28*, 2367–2370. b) J. d´Angelo, G. Revial, T. Volpe, M. Pfau, *Tetrahedron Lett.* **1988**, *29*, 4427–4430.
[101] F. A. Davis, M. C. Weismiller, *J. Org. Chem*. **1990**, *55*, 3715–3717.



Scheme 27. α/α'-functionalization of β-tetralones relying on stoichiometric chiral reagents.

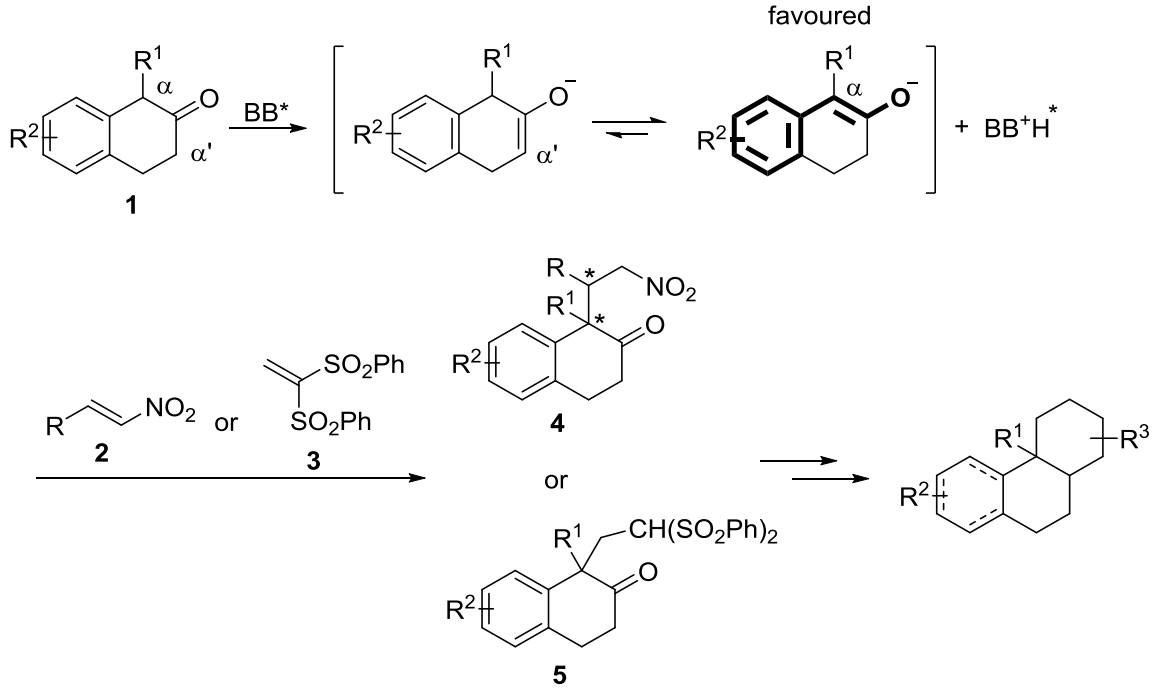
Apart from these approaches based on the use of stoichiometric amount of the chiral inductor, the group of Trost described the intermolecular palladium-catalyzed asymmetric allylic alkylation (AAA) of β-tetralones to produce the α-allylated quaternary products with very good yields and enantioselectivities (Scheme 28a).[102] Very recently, Stoltz and co-workers elaborated another example of palladium-catalyzed AAA with excellent results (Scheme 28b).[103] On the other hand, Chen *et al.* have reported direct reaction of β-tetralones with α,β-unsaturated aldehydes by iminium activation,[104] but stereogenicity at C_α is lost upon spontaneous hemiketal formation (Scheme 28c).

[102] a) B. M. Trost, G. M. Schroeder, J. Kristensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 3492–3495. b) B. M. Trost, W. Tang, *J. Am. Chem. Soc*. **2003**, *125*, 8744–8745.
[103] N. Hartrampf, N. Winter, G. Pupo, B. M. Stoltz, D. Trauner, *J. Am. Chem. Soc.* **2018**, *140*, 8675–8680.
[104] J.-H. Chen, C. Chang, H.-J. Chang, K. Chen, *Org. Biomol. Chem.* **2011**, *9*, 7510–7516.



Scheme 28. Catalytic approaches for the α-functionalization of β-tetralones.

Given the scarcity of direct, catalytic and asymmetric methods for the functionalization of β-tetralones, we decided to explore alternative routes based on a Brønsted base catalysis activation strategy. Our consideration was that the fused aromatic ring in β-tetralones might induce preferential base-promoted enolization at C_{α} rather than $C_{\alpha'}$. In addition, π system conjugation and higher substitution degree may favor threshold concentration of the α-enolate form as to eventually drive the catalytic process forward. On this basis, we set out to study the Brønsted base catalyzed reaction of β-tetralones with Michael acceptors such as nitroalkenes and vinyl sulfone which is expected to deliver synthetically versatile building blocks for the access to increasingly complex molecules (Scheme 29).



Scheme 29. Working hypothesis for the Michael addition of β-tetralones.

Besides the regioselectivity matter, a second significant issue concerns, the effective control of both the absolute and relative stereochemistry during construction of the quaternary carbon stereocenter. The development of new methods for the enantioselective creation of tetrasubstituted stereocenters is among the remaining significant challenges in chemical synthesis. Among the complications are: i) attenuated reactivity due to a severe steric repulsion between the reacting nucleophile and the substrate; ii) reaction reversibility owing to low stability of the resulting products caused by steric repulsion between the substituents, especially when adjacent tertiary-quaternary centers are formed. Specifically, while some success has been achieved in the enantioselective synthesis of α-quaternary carbonyl compounds by Brønsted base catalyzed Michael reactions of α-aryl cyclopentanones,[105] the corresponding α-aryl

[105] For reviews on Brønsted base catalysis, see: a) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632. b) I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley and Sons, New York, **2010**. c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200. d) K. Maruoka, *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*, Thieme, Stuttgart, **2012**. e) B. Teng, W. C. Lim, C. H. Tan, *Synlett*, **2017**, *28*, 1272–1277. For selected reviews on asymmetric organocatalytic conjugate additions, see: b) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselecive Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC Publishing, Cambridge, **2010**. c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716. d) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 –365.

cyclohexanones behaved sluggishly.[106] On the other hand, in the case of functionalization of α-unsubstituted β-tetralones to form tertiary stereogenic centers, product racemization (epimerization) and polyalkylation are additional issues.

2.2. Results and Discussion

2.2.1. Brønsted base catalyzed Michael addition of α-substituted β-tetralones

2.2.1.1. *Nitroolefins as acceptors*

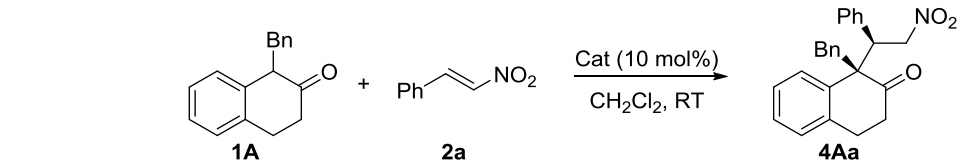
During his PhD thesis, Dr I. Urruzuno[107] studied the model reaction between β-tetralone **1** and nitrostyrene **2** at room temperature for an array of catalysts **C1**–**C5**. As data in Table 1 show, acceptable results were achieved with the new catalyst **C5**[107] bearing a benzylic group instead of an aryl group at the amide nitrogen atom (84% yield, 85% *ee*). However, this catalyst behaved sluggish at subzero temperatures because of limited solubility. At this point, to further optimize the reaction, we decided to extend the catalyst screening and the novel catalyst **C6**[108] was explored. Although the enantioselectivity of the reaction could not be improved at room temperature, lowering the reaction temperature led to a better *ee* value (90% *ee* at −10 °C). In contrast, the *N*-methylated catalyst **C7**[107] provided a moderate 60% *ee*, thus indicating that the amide NH in the former catalyst is important. Therefore, **C6** was chosen as the optimal catalyst for the reaction of α-substituted β-tetralones **1** with nitroalkenes **2**.

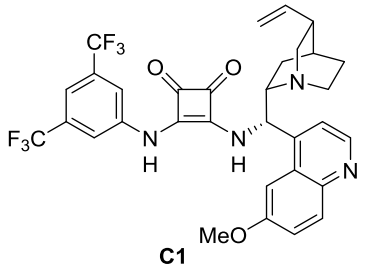
[106] a) X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 6840–6842. b) J. Deutsch, H.-J. Niclas, M. Ramm, *J. Prakt. Chem.* **1995**, *337*, 23–28.

[107] I. Urruzuno, doctoral thesis, *Organocatalytic α-Functionalization of Carbonyl Compounds: Chemo-, Regio- and Stereoselectivity* EHU/UPV, **2018** (https://www.ehu.eus/es/web/gicas/tesiak).

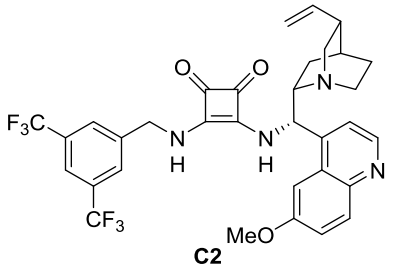
[108] I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063.

Table 1. Catalyst screening for the reaction between **1A** and **2a**.

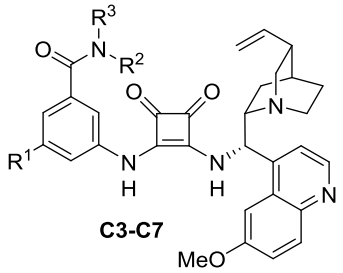




C1
6 h, 87%, 72% *ee*



C2
6 h, 82%,73% *ee*



C3-C7

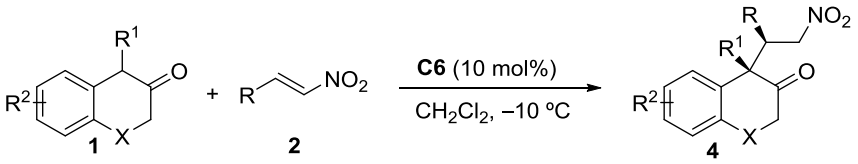
	R^1	R^2	R^3	t (h)	Yield (%)	*ee*
C3	H	H	$(F_3C)_2C_6H_5$	6	87	75
C4	CF_3	H	$(F_3C)_2C_6H_5$	6	85	76
C5	H	H	$CH_2(F_3C)_2C_6H_5$	16	84	85
C6	CF_3	H	$CH_2(F_3C)_2C_6H_5$	16	93	80
C7	H	Me	$CH_2(F_3C)_2C_6H_5$	16	71	60

[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**1A**/**2a** molar ratio = 1:1.2). Yield of isolated product after column chromatography. *dr* = >20:1 in all cases. *ee* determined by chiral HPLC.

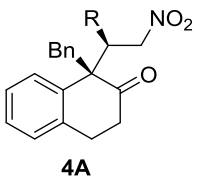
As Table 2 illustrates, the reaction of α-benzyl β-tetralone **1A** with differently β-substituted nitrostyrenes were uniformly good affording the corresponding adducts (**4Aa**–**4Al**) in high selectivity (90–91% *ee*). Nitroalkenes having heteroaromatic (**2j**) or alkynyl β-substituents (**2k**) also led to the corresponding adducts with similarly good yield and enantioselectivity. Remarkably, even the less reactive β-propyl-substituted nitroalkene **2l** afforded the addition adduct **4Al** with equally good yield and *ee* value. In the same manner, good yield and high enantioselectivity was obtained when using β-phenylethyl nitroalkene **2m**. α-Substituted β-tetralones bearing additional functionality (such as propargyl, 2-butenyl and cyanomethyl groups) (**1B**, **1C**, **1D**) were also well tolerated in the reaction leading to good yields and *ee* values of up to 99% *ee* (products **4Ba**, **4Ci** and **4Dg**). The reaction also tolerates the electron donating as well as electron-withdrawing substituents at the aromatic ring of the β-tetralone, which were equally efficient (adducts **4Ec**, **4Fa** and **4Gm**). Interestingly, apart from β-tetralones (a cycloalkanone), aromatic ring-fused cyclic ketone **1H**, with an oxygen heteroatom in the cycle, was also a competent substrate undergoing the conjugate addition with high

stereoselectivity. Importantly, in every case no traces of products from the reaction at the α´-carbon of the cyclic ketone were formed.

Table 2. Scope of the reaction between α-substituted β-tetralones and nitroalkenes.

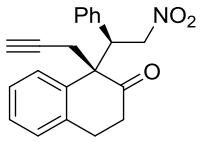


R: (**a**) Ph, (**b**) 4-$MeOC_6H_4$, (**c**) 4-MeC_6H_4, (**e**) 4-BrC_6H_4, (**f**) 3-$MeOC_6H_4$
(**g**) 3-MeC_6H_4, (**i**) 2-ClC_6H_4, (**j**) 2-Furyl, (**k**) PhC≡C, (**l**) $CH_3(CH_2)_2$, (**m**) $Ph(CH_2)_2$

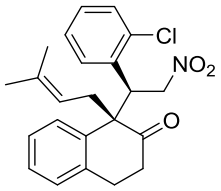


4A

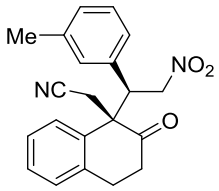
4Aa	R = Ph	82% yield, 90% *ee*
4Ab	R = 4-$MeOC_6H_4$	82% yield, 91% *ee*
4Ae	R = 4-BrC_6H_4	85% yield, 91% *ee*
4Af	R = 3-$MeOC_6H_4$	80% yield, 91% *ee*[b]
4Aj	R = 2-Furyl	60% yield, 92% *ee*[b]
4Ak	R = PhC≡C	70% yield, 88% *ee*[c]
4Al	R = $CH_3(CH_2)_2$	72% yield, 88% *ee*



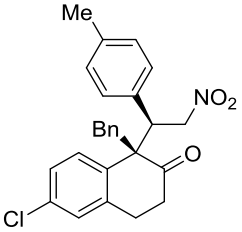
4Ba, 83% yield, 89% *ee*



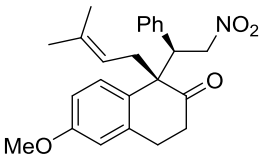
4Ci, 80% yield, 99% *ee*[b]



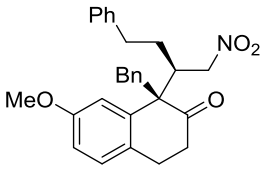
4Dg, 78% yield, 91% *ee*



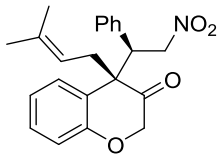
4Ec, 84% yield, 90% *ee*[b],[d]



4Fa, 40% yield, 99% *ee*[e]



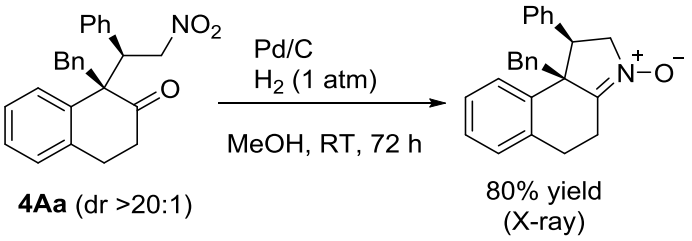
4Gm, 81% yield, 90% *ee*[f]



4Ha, 64% yield, 90% *ee*

[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**1**/**2** molar ratio = 1:1.2). Yield of isolated product after column chromatography. dr = >20:1 in all cases. ee determined by chiral HPLC. [b] Reaction conducted at −20 °C. [c] Obtained as a 1.5:1 mixture diastereomers (94% ee for minor isomer). [d] Using catalyst **C4**. [e] Reaction conducted at RT. [f] Reaction conducted at 0 °C.

The assignment of the absolute configuration for the products was established by assuming a uniform reaction mechanism and by the absolute configuration of the tricyclic compound obtained from **4Aa** (Scheme 30).[107]



Scheme 30. Obtaining of tricyclic compound from **4Aa**.

2.2.1.2. *Vinyl disulfone as acceptor*

At this stage, we decided to extend the method to Michael acceptors other than nitroalkenes and focused on vinyl disulfone as another type of acceptor with great potential in synthesis.[109]

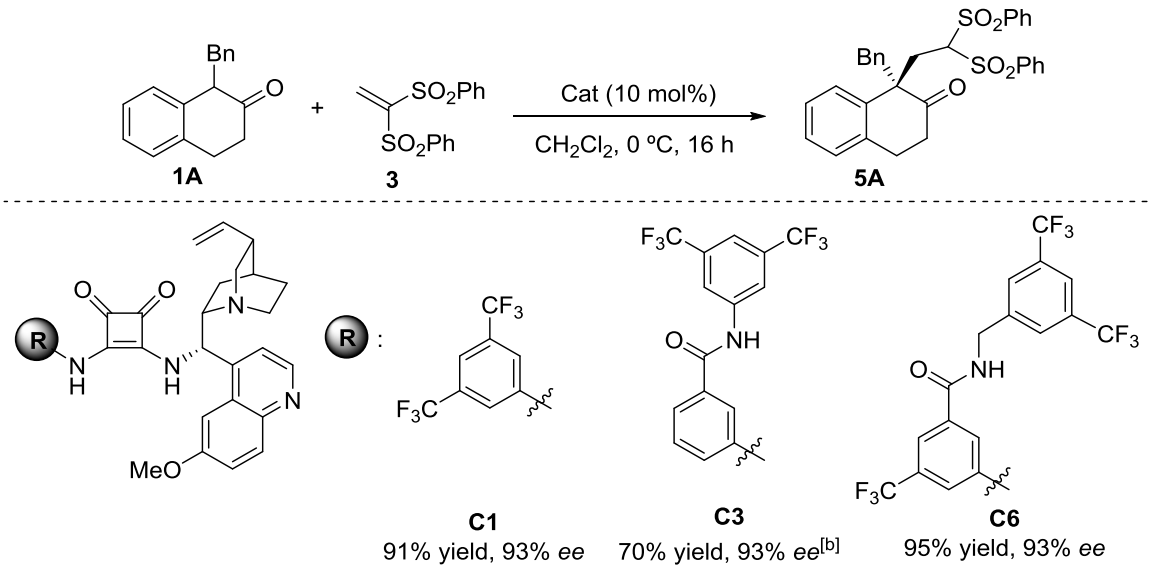
Accordingly, the reaction between **1A** and 1,1-bis(phenylsulfonyl)ethylene (**3**) was studied in the presence of a selection of bifunctional Brønsted base catalysts (**C1**,[110] **C3**[111] and **C6**). As the results in Table 3 show, both **C1** and **C6** gave the desired α-addition product (**5A**) in very good yield and high enantioselectivity. Although **C3** allowed the reaction to proceed in a stereoselective manner, lower conversion (75%) was observed after 48 h, probably as a result of lower solubility of the catalyst.

[109] For reviews on sulfones, see: a) N. S. Simpkins, *Tetrahedron* **1990**, *46*, 6951–6984. b) N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press: Oxford, **1991**. Reviews on sulfones in organocatalysis: c) A.-N.R. Alba, X. Companyó, R. Ríos, *Chem. Soc. Rev.* **2010**, *39*, 2018–2033. d) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 2668–2679.

[110] a) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal*. **2010**, *352*, 2137–2141; b) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450 –5453.

[111] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed*. **2015**, *54*, 6883–6886.

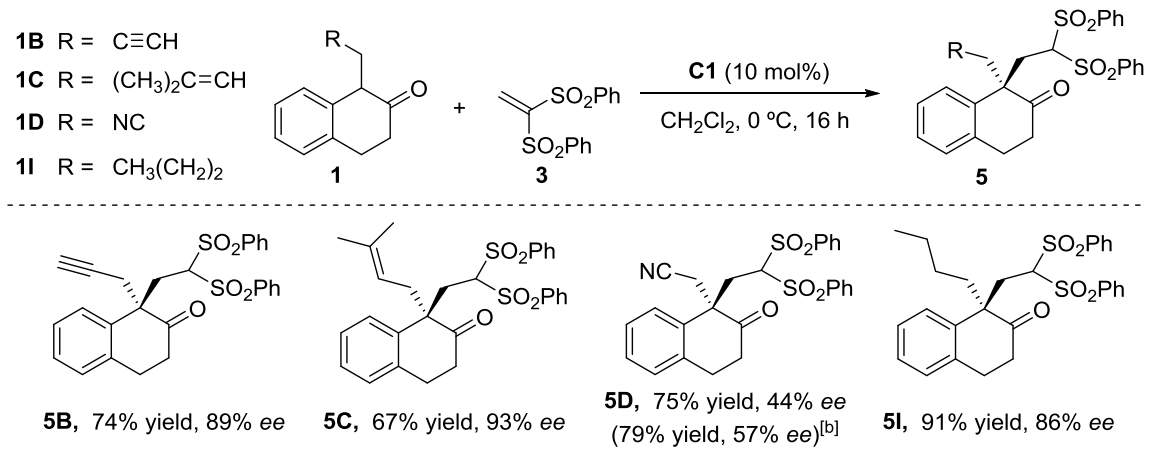
Table 3. Catalyst screening for the reaction between **1A** and **3**.



[a] Reactions conducted on a 0.10 mmol scale in 0.2 mL of CH_2Cl_2 (**1A**/**3** molar ratio = 1:1.5). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC. [b] Reaction conducted in 48 h.

The study of the generality of the method was addressed by carrying out the reaction of β-tetralones **1B**–**1I** using the most conventional catalyst **C1** (Table 4). With the exception of **1D**, it was demonstrated that the stereochemical outcome of the reaction is independent of the α-substituent of the β-tetralone employed since products were obtained with similarly good yield and enantioselectivity. The result for **5D** hardly improved with catalyst **C6** obtaining the product in 57% *ee*.

Table 4. Michael reaction scope between α-substituted β-tetralones and vinyl disulfone **3**.



[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**1**/**3** molar ratio = 1:1.5). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC. [b] Using catalyst **C6**.

Crystallization of compound **5A** allowed the determination of its absolute configuration by single-crystal X-ray analysis (Figure 16) and the R configuration of the rest of adducts was established by assuming a uniform reaction mechanism.

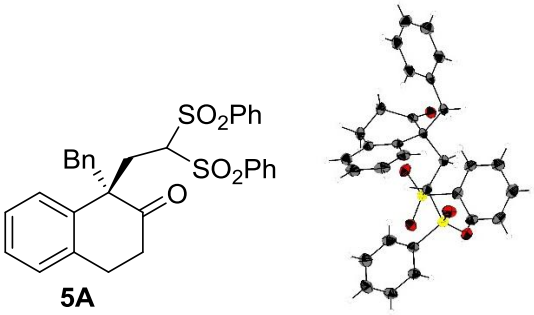


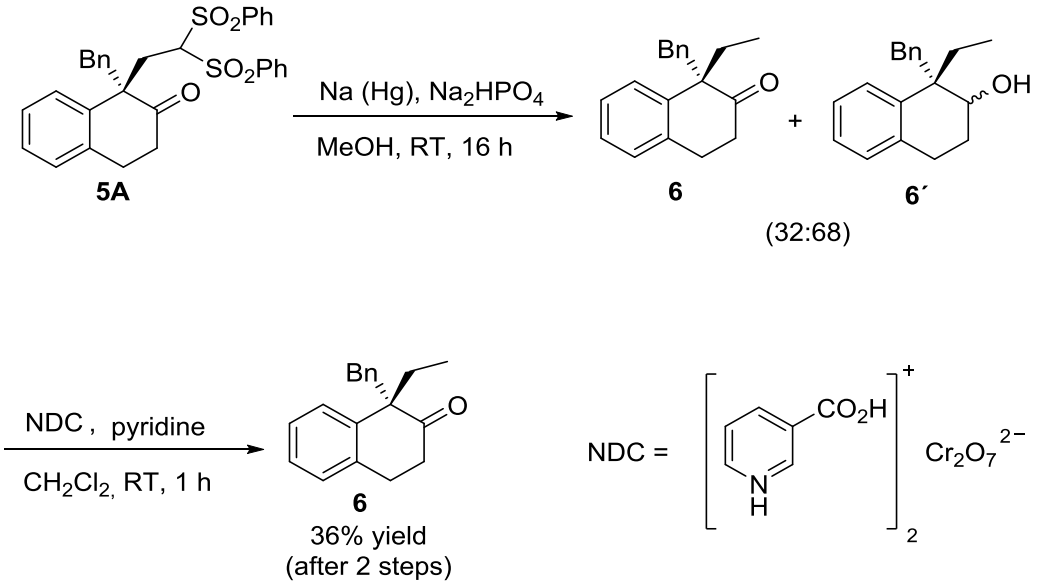
Figure 16. ORTEP diagram of compound **5A**.

With these bis(sulfonylated) adducts at hand, their desulfonylation to yield the corresponding alkyl analogues was explored. The idea was to protect the carbonyl group via ketalization to perform the removal of the sulfonyl group. Since the typical desulfonylation conditions (involving Mg(0) or sodium amalgam) may also reduce the ketone group, first efforts were directed toward the carbonyl group protection. Nevertheless, attempts to protect the carbonyl in the form of a ketal following several procedures described in the literature[112] were in vain leading to the recovery of the starting material, presumably because of the difficult accessibility of the carbonyl group due to steric hindrance of the quaternary stereocenter in the α position of the carbonyl group. Then, we decided to proceed directly to the desulfonylation step.

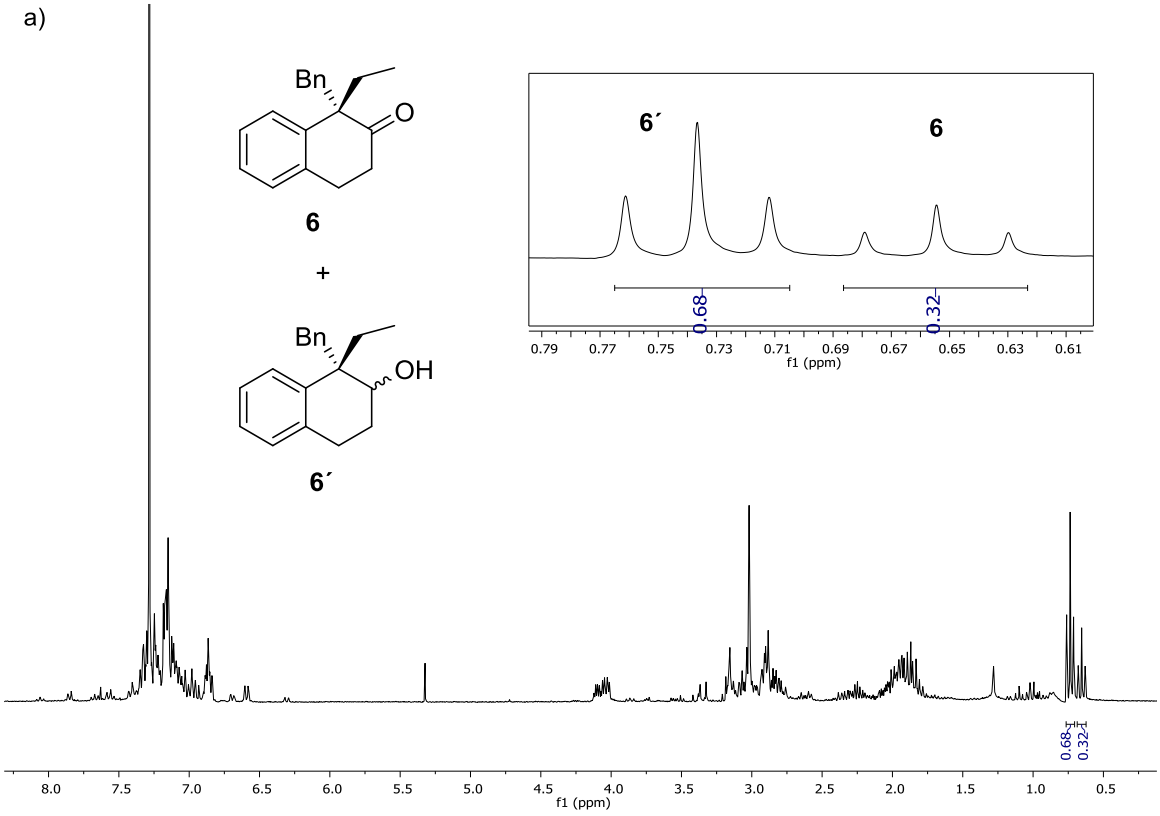
After exploring various reaction conditions using Mg turnings and different ways of activation (by heating at reflux, by adding 1 drop of Me_3SiCl and 1,2-dibromoethane[113] or by washing with 0.5% aqueous HCl[114]), the best results were obtained with the procedure depicted in Scheme 31.[115] The reaction with sodium amalgam provided a mixture of ketone **6** and alcohol **6´** in a 32:68 ratio (Figure 17a).

[112] a) N. M. Leonard, M. C. Oswald, D. A. Freiberg, B. A. Nattier, R. C. Smith, R. S. Mohan, *J. Org. Chem*. **2002**, *67*, 5202. b) J. J.Lee, G. A.Kraus, Tetrahedron Lett. 2013, 54, 2366–2368. c) Z. Bian, C. C. Marvin, S. F. Martin, *J. Am. Chem. Soc*. **2013**, *135*, 10886−10889.
[113] A. Landa, A. Puente, J. I. Santos, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2009**, *15*, 11954–11962.
[114] A. C. Brown, L. A. Carpino, *J. Org. Chem*. **1985**, *50*, 1749−1750.
[115] T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2007**, *46*, 3329–3332.

Treatment of this mixture with NDC (nicotinium dichromate) and pyridine in CH_2Cl_2 as solvent the desired product **6** (Figure 17b) was obtained in moderate isolated yield.[116]



Scheme 31. Desulfonylation of adduct **5A** and reoxidation of the ketone + alcohol mixture to afford **6**.



[116] F. P.Cossio, M.C. Lopez, C. Palomo, *Tetrahedron*, **1987**, *43*, 3963–3974.

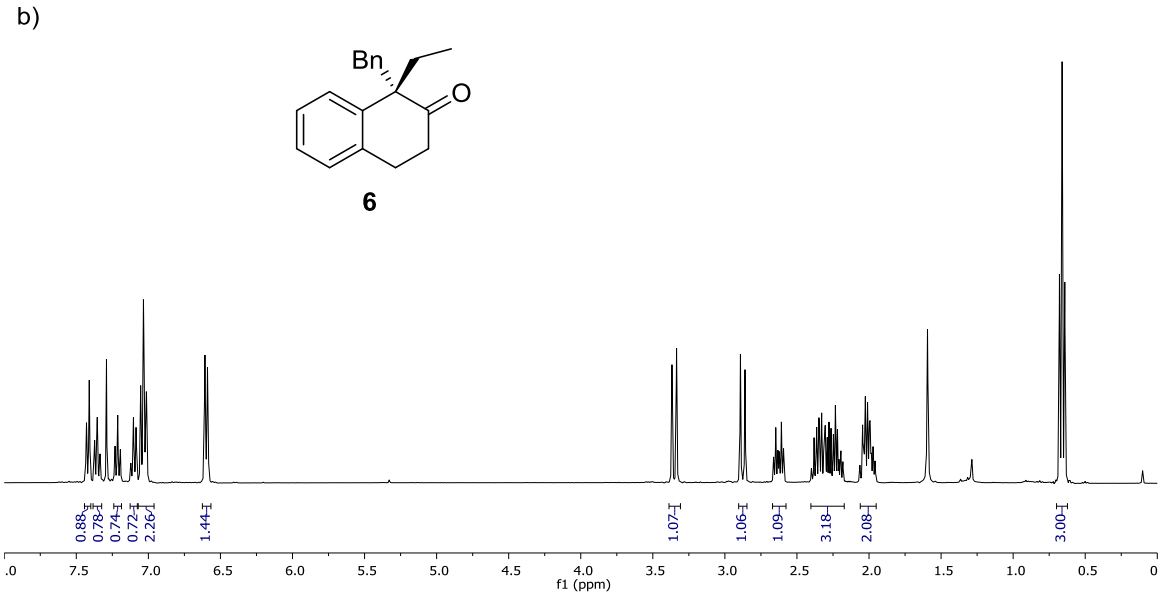
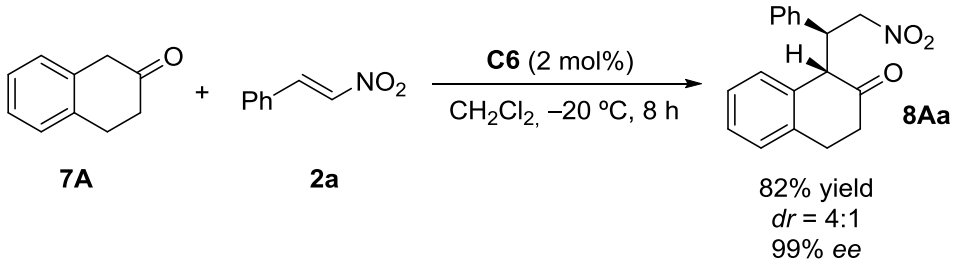


Figure 17. NMR spectra of: a) mixture of **6´** and **6**. b) Pure compound **6**.

2.2.2. α-Alkylation of α-unsubstituted β-tetralones

2.2.2.1. *Michael addition to nitroolefins*

On account of the good results obtained with α-substituted β-tetralones, the behavior of the α-unsubstituted β-tetralones was investigated under similar reaction conditions. In this respect, two main complications were anticipated: i) the effective control of the stereoselectivity of the reaction and ii) the occurrence of two consecutive addition reaction processes. It was delighting to observe that the reaction of the parent β-tetralone **7A** with nitrostyrene **2a** catalyzed by **C6** led to the addition product **8Aa** as a mixture of diastereomers, but each one with essentially complete enantioselectivity (Scheme 32).[117] Moreover, no products from a sequential addition of two equivalents of nitroalkene, either at $C_{\alpha}/C_{\alpha'}$ of the ketone or at C_{α} of the nitro group were detected.

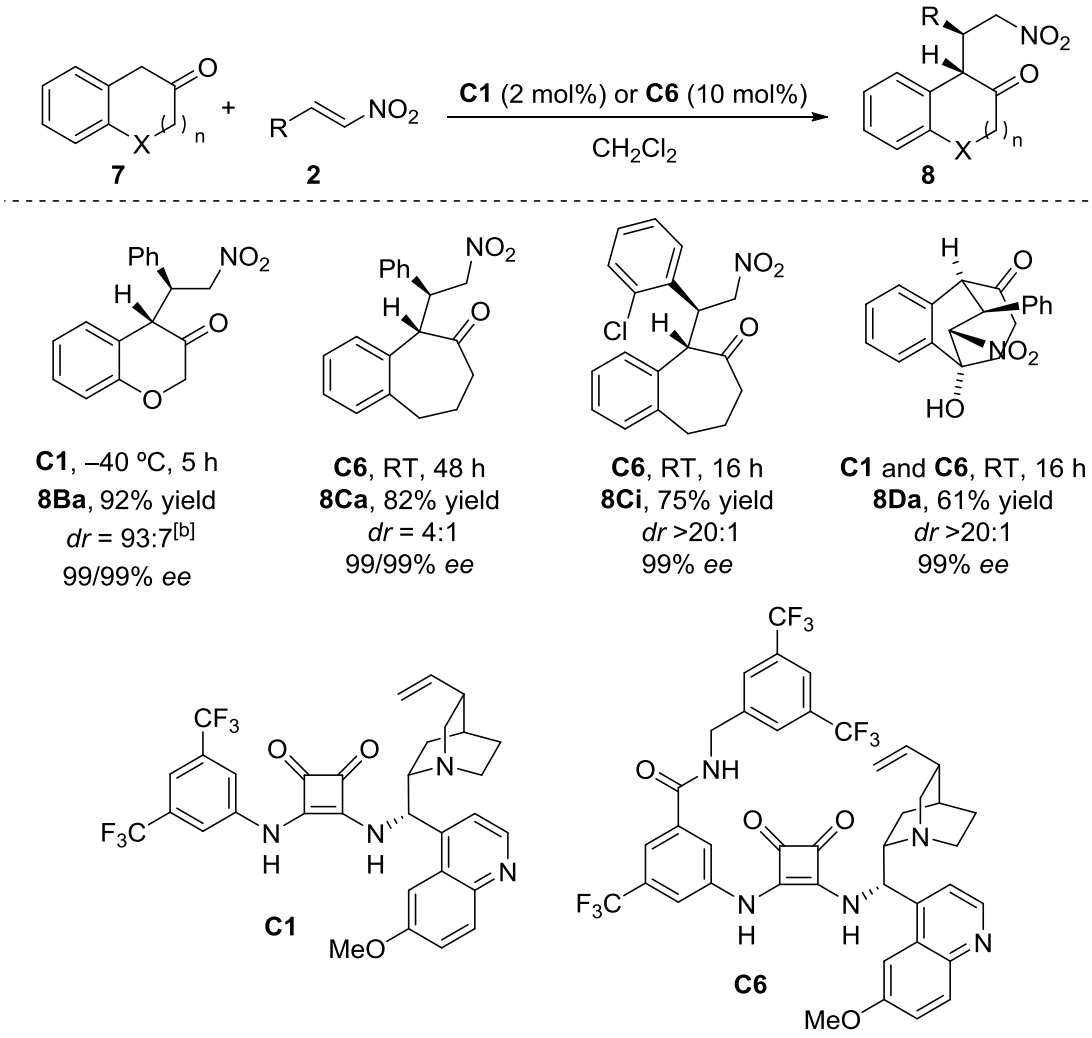


Scheme 32. Michael reaction between β-tetralone **7A** and nitroalkenes **2a**.

[117] For the scope of this reaction with respect the nitroolefin, see: a) Ref. 107. b) Ref. 108.

Extension of this approach to related ketone substrates was next examined using either catalyst **C1** or **C6**. As depicted in Table 5, aromatic ring-fused cycloalkanones with an oxygen heteroatom in the cycle or cycloalkanones of varying ring size were equally competent substrates undergoing the regioselective Michael addition with high enantioselectivity. In particular cases, although the *dr* of the enolizable compound **8Ba** was determined as 93:7, epimerization of the adduct was observed after column chromatography since the product was isolated as an equimolecular mixture of diastereomers. In contrast, in the case of employing a diketone substrate, the adduct **8Da** from a sequential Michael/intramolecular Henry reaction was obtained, as essentially a single diastereomer and very high enantioselectivity.

Table 5. Michael addition of arene-fused cycloalkanones to nitroolefins.



[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (cycloalkanone/**3** molar ratio = 1:1.2). Yield of isolated product after column chromatography. *dr* determined by ^{1}H NMR spectroscopy. *ee* determined by chiral HPLC. [b] Epimerization of the product after column chromatography.

The determination of the absolute configuration of adduct **8Da** was performed by a single-crystal X-ray analysis (Figure 18).

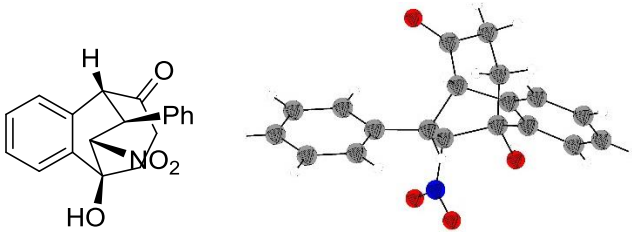


Figure 18. ORTEP diagram of compound **8Da**.

2.2.2.2. *Mannich reaction with N-Boc imines*

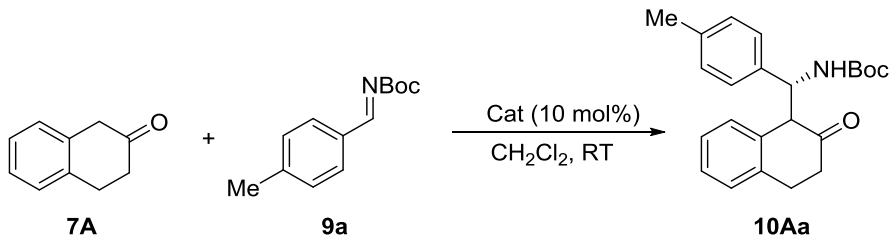
In view of the good results obtained for the Michael reaction of α-unsubstituted β-tetralones, our purpose was to expand the strategy to the asymmetric Mannich reaction using *N*-Boc aldimines as acceptors.

Initially, the reaction between β-tetralone **7A** and *N*-carbamoyl aldimine **9a** to give **10Aa** was taken as a model to find the Brønsted base catalyst for optimum results. With a view to determining the best suited H-bond donor group, we started by comparing catalysts **C1**, **C8**,[118] **C9**[119] and **C10**[120] bearing respectively the squaramide, thiourea, urea, and ureidopeptide moieties. In a first run, reaction with squaramide catalyst **C1** provided the desired adduct in complete regioselectivity and high enantioselectivity, but as an equimolar mixture of diastereomers. Although using the parent thiourea and urea catalysts **C8** and **C9** allowed to obtain the product in complete regioselectivity and good yield, the stereoselectivity of the reaction was very low. On the other hand, when ureidopeptide **C10** was employed, neither diastereoselectivity nor enantioselectivity were improved. In order to achieve higher diastereoselectivity, squaramide type catalysts **C3** and **C6** bearing an amide unit were tested. However, adduct **10Aa** was obtained again as a 1:1 mixture, with moderate *ee* values (68–75% *ee*). In the last attempt, squaramide-dicyclohexyldiamine type catalyst **C11**[121] was proved to be unsuccessful as the reaction between **7A** and **9a** proceed with poor stereoselectivity.

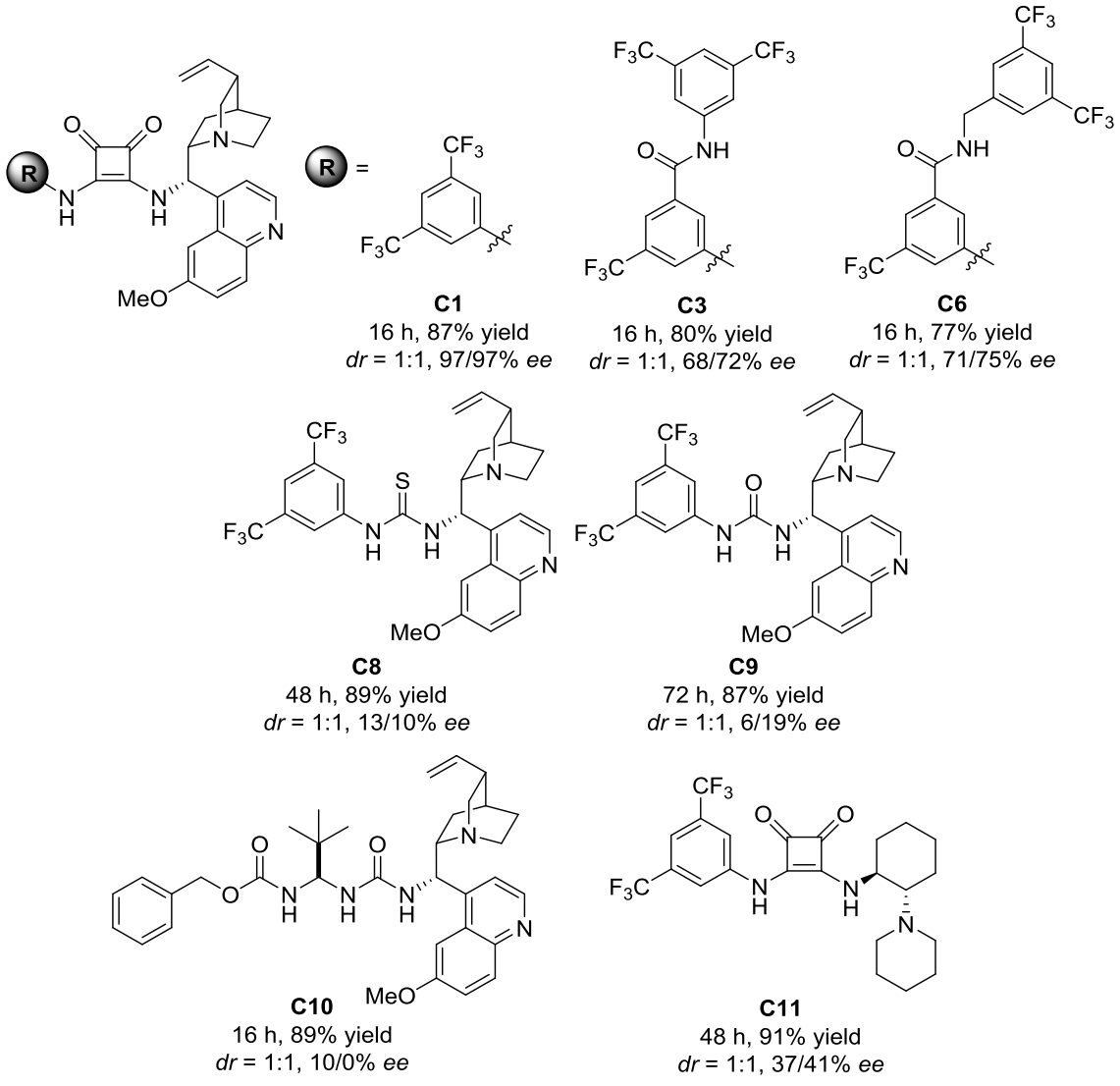
[118] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967–1969.
[119] K. Greenaway, P. Dambruoso, A. Ferrali, A. J. Hazelwood, F. Sladojevich, D. J. Dixon, *Synthesis* **2011**, *12*, 1880–1886.
[120] S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.
[121] W. Yang, D.-M Du, *Adv. Synth. Catal*. **2011**, *353*, 1241–1246.

These results show that very likely the initially obtained α-monosubstituted β-tetralones are prone toward epimerization under basic conditions at room temperature.

Table 6. Catalyst screening for the reaction between **1A** and **9a**.



7A **9a** **10Aa**



C1
16 h, 87% yield
dr = 1:1, 97/97% *ee*

C3
16 h, 80% yield
dr = 1:1, 68/72% *ee*

C6
16 h, 77% yield
dr = 1:1, 71/75% *ee*

C8
48 h, 89% yield
dr = 1:1, 13/10% *ee*

C9
72 h, 87% yield
dr = 1:1, 6/19% *ee*

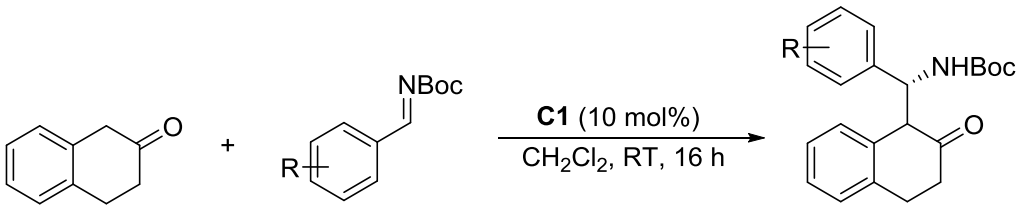
C10
16 h, 89% yield
dr = 1:1, 10/0% *ee*

C11
48 h, 91% yield
dr = 1:1, 37/41% *ee*

[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**7A**/**9a** molar ratio = 1:2). Yield of isolated product after column chromatography. *dr* determined by ^1H NMR spectroscopy. *ee* determined by chiral HPLC.

A selection of *N*-Boc imines was evaluated in order to establish the generality of this asymmetric route to α-substituted β-tetralones. As data in Table 7 illustrate, catalyst **C1** promoted the addition reaction of **7A** withing 16 hours at room temperature to afford the corresponding enantioenriched adducts in high yield. Once again, the products were obtained as a mixture of diastereomers, except in the case of **10Af** (*dr* = 65:35). In general, enantiomeric excesses were excellent for aryl *N*-Boc imines with electron-donating and electron-withdrawing groups.

Table 7. Mannich reaction scope between β-tetralone **7A** and *N*-Boc imines **9**.



7A **9** **10A**

Entry	Product	R	Yield (%)	*dr*	*ee* (%)
1	**10Ab**	Ph	91	1:1	91/99
2	**10Ac**	4-$MeOC_6H_4$	94	1:1	97/93
3	**10Ad**	4-ClC_6H_4	89	1:1	96/95
4	**10Ae**	4-FC_6H_4	90	1:1	93/99
5	**10Af**	2-MeC_6H_4	93	65:35	83/88
6	**10Ag**	3-ClC_6H_4	90	1:1	99/95

[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**7A**/**9** molar ratio = 1:2). Yield of isolated product after chromatography. *dr* determined by ^1H NMR spectroscopy. *ee* determined by chiral HPLC.

The absolute configurations of both diastereomers of compound **10Ad** were determined by X-ray crystallographic analysis (Figure 19) and the configuration of remaining adducts was assigned by analogy and by assuming a uniform mechanism.

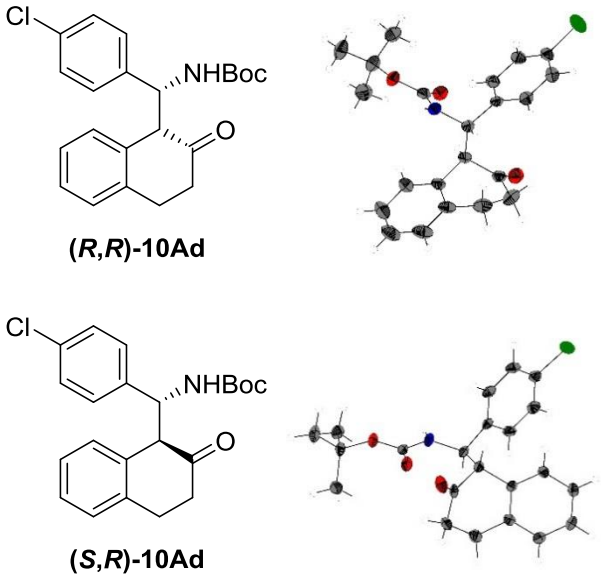
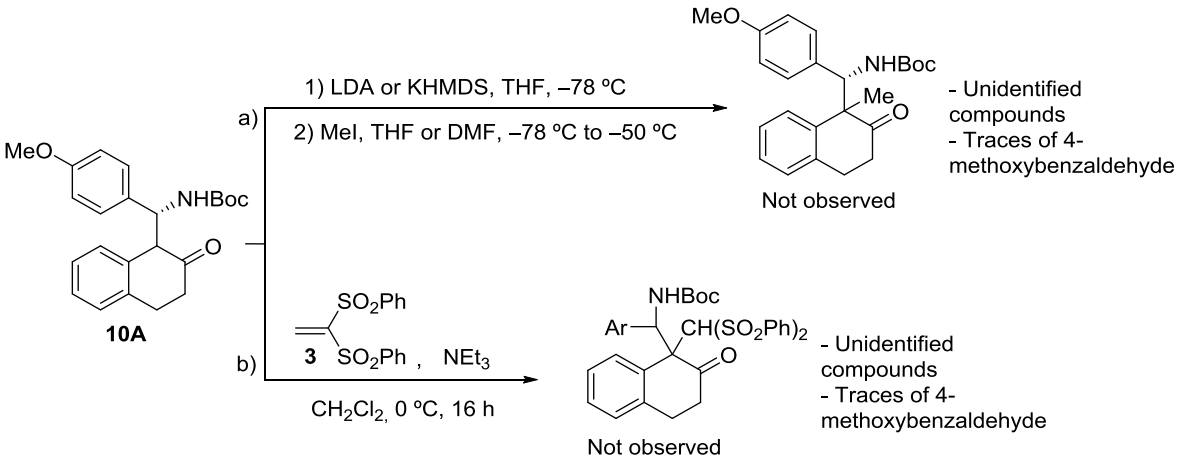


Figure 19. ORTEP diagrams of both diastereomers of **10Ad**.

On the other hand, attempts to alkylate the α-position of these β-tetralone adducts were unfruitful. For example, methylation of **10Ac** under the conditions shown in Scheme 33a led to a messy crude with the presence of 4-methoxybenzaldehyde. Moreover, Michael reaction of adduct **10Ac** with vinyl disulfone **3** was carried out using triethylamine as a base (Scheme 33b). Unfortunately, the expected addition adduct was not observed, instead other products which were not characterized were formed. These results bring up that adducts **10A** are prone to retro-Mannich processes under basic conditions and thus, further investigation of their elaboration to proof their synthetic value is pending.



Scheme 33. Unfructuous transformations of **10Ac**.

Chapter 3

Selective Addition Reactions Involving α-Branched Ketone Dienolates

3. Selective Addition Reactions Involving α-Branched Ketone Dienolates

3.1. Introduction

Cyclic ketone units bearing a quaternary α-stereocenter are common in a wide variety of natural products and biologically relevant molecules. For example, such structural units are found in alkaloids, terpenes and other type of compounds (Figure 20).

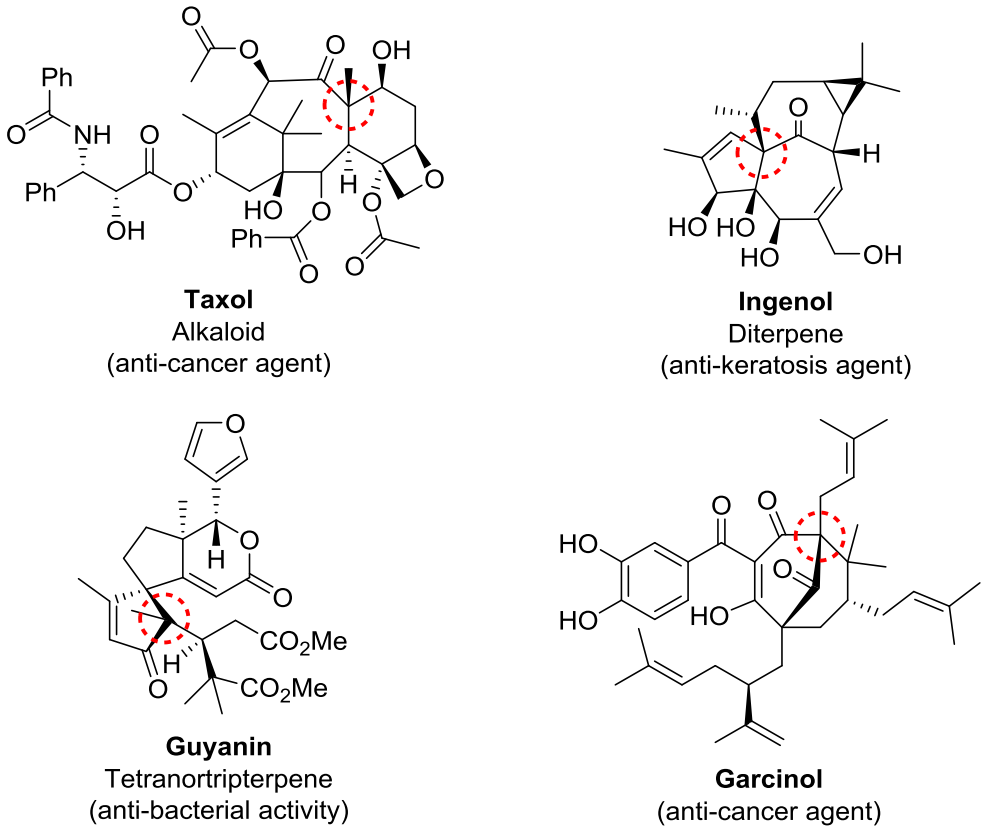


Figure 20. Cyclic ketone units with a quaternary α-stereocenter in natural products and bioactive compounds.

At the same time, the synthesis of these units in an enantioselective manner using catalytic direct approaches from readily accessible starting materials continues to be a considerable challenge.[122] A straightforward route would rely on the α-CH functionalization of the parent α-branched cycloalkanone (Figure 21).

[122] For reviews on the asymmetric construction of quaternary carbon centers, see: a) A. Y. Hong, B. M. Stoltz, Eur. *J. Org. Chem*. **2013**, 2745–2759. b) J. P. Das, I. Marek, *Chem. Commun*. **2011**, *47*, 4593–4623. c)

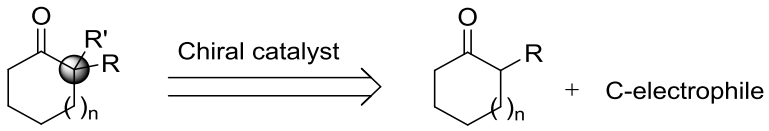
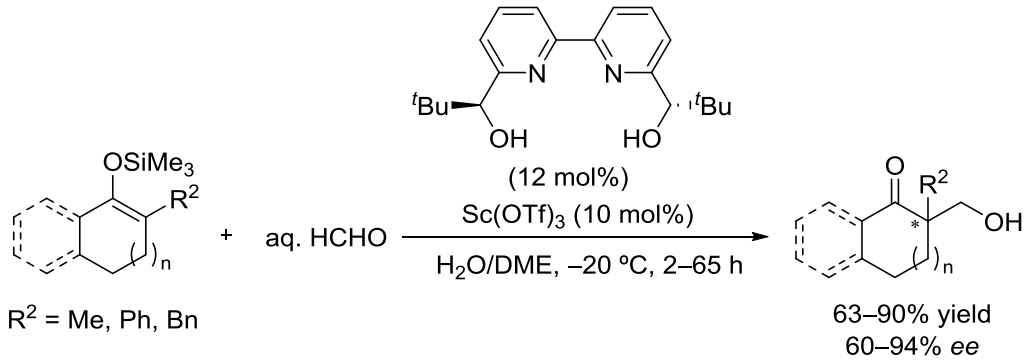


Figure 21. Catalytic direct approach for the α-functionalization of α-branched cycloalkanones.

However, this approach has to face a number of issues, among them the use of non-symmetrical unactivated ketones with two sites for deprotonation remains a highly demanding task.[123]

Most of the current catalytic asymmetric α-functionalization procedures of carbonylic compounds are limited to the use of either chiral auxiliaries or preformed enolates and equivalents. Just as an illustrative example, the catalytic asymmetric α-functionalization of silyl enolates with a chiral scandium complex is shown in Scheme 34.[124]



Scheme 34. Hydroxymethylation of silyl enolates using a chiral scandium complex.

On the other hand, metal (mainly Pd, Ir)[125] and phase transfer catalysis[126] are useful approaches for the asymmetric allylic/benzylic α-alkylations of α-substituted (mainly

M. Bella, T. Caspery, *Synthesis* **2009**, 1583–1614. d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, Eur. *J. Org. Chem*. **2007**, 5969–1614. e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396. f) J. Christoffers, A. Baro, *Quaternary Stereocenters*, Wiley-VCH, Weinheim, **2005**. g) C. J. Douglas, L. E. Overman, *Proc. Nat. Acad. Sci*. **2004**, *101*, 5363–5367.

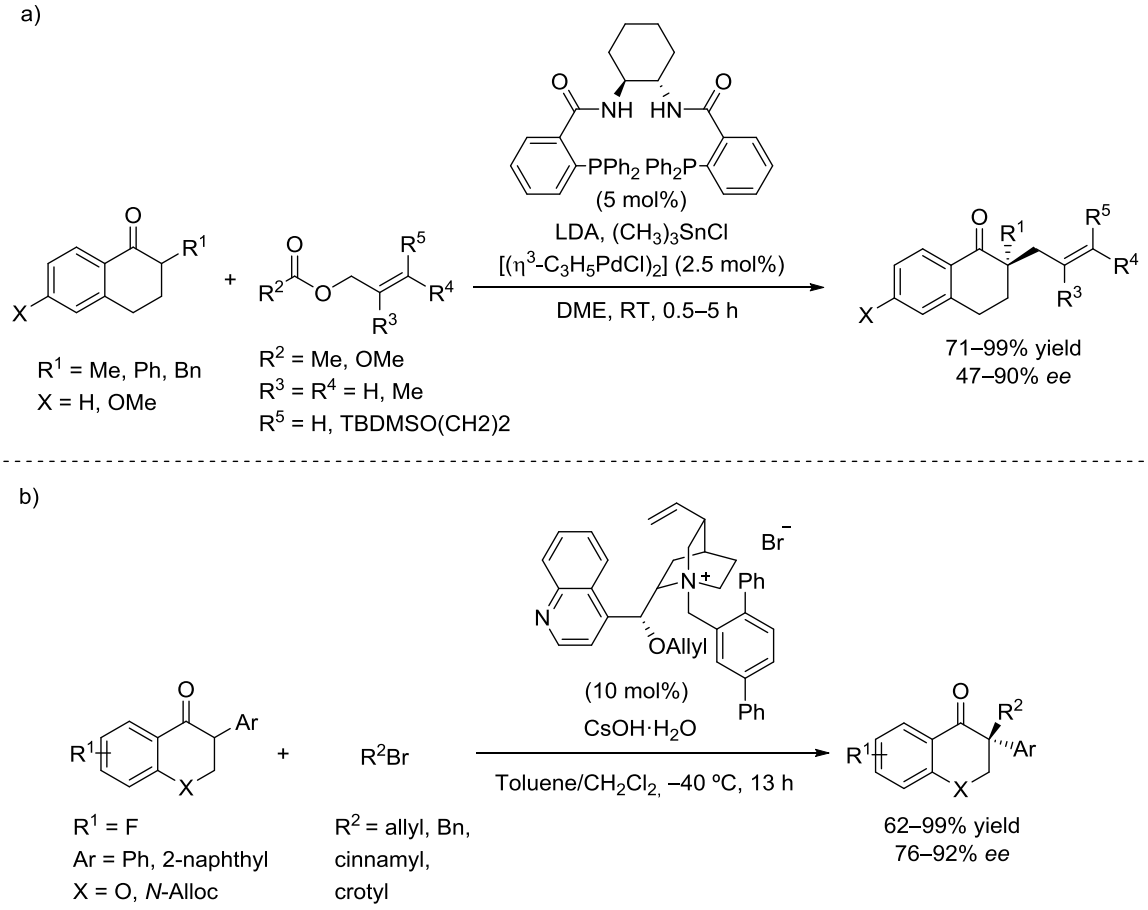
[123] R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.*, **2017**, *56*, 9278–9290.

[124] S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237.

[125] For reviews on transition metal catalyzed allylations, see: a) B. M. Trost, C. Lee, *Catalytic Asymmetric Synthesis*, 2nd ed. Wiley- VCH, New York, **2000**, 593–649. b) A. Pfaltz, M. Lautens, *Comprehensive Asymmetric Catalysis*, Springer, New York, **1999**, *2*, 833–884. c) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476–1491. d) B. M. Trost, *Tetrahedron* **2015**, *71*, 5708–5733.

[126] a) A. E. Nibbs, A.-L. Baize, R. M. Herter, K. A. Scheidt, *Org. Lett.* **2009**, *11*, 4010–4013. b) T. Kano, Y. Hayashi, K. Maruoka, *J. Am. Chem. Soc.* **2013**, *135*, 7134–7137. c) B. Teng, W. Chen, S. Dong, C. W. Kee, D. A. Gandamana, L. Zong C.-H. Tan *J. Am. Chem. Soc.* **2016**, *138*, 9935– 9940.

benzo-fused or $C_{\alpha'}$-protected) cyclic ketones, but rather inefficient for other type of alkylating processes. Palladium catalyzed asymmetric alkylation of α-tetralones (Scheme 35a)[127] or alkylation of substituted isoflavones catalyzed by a cinchonidinium bromide phase-transfer catalyst (Scheme 35b)[128] are significant examples of such strategies. In the latter case, cinnamyl and crotyl groups were also used as alkylating agents.



Scheme 35. a) Pd-catalyzed asymmetric alkylation of 1-tetralones. b) Asymmetric phase-transfer-catalyzed alkylation of isoflavones.

As already discussed in Chapter 1 (pages 19–26), a few organocatalytic methods based on enamine and Brønsted acid activation strategies have enabled to further advance the field by using Michael acceptors as the alkylating reagent, but important restrictions apply. More specifically, formation of the requisite enamine from cyclic ketones bearing α-substituents larger than methyl or ethyl is not viable because steric hindrance (Figure

[127] B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc*. **1999**, *121*, 6759–6760.
[128] A. E. Nibbs, A.-L. Baize, R. M. Herter, K. A. Scheidt, *Org. Lett.* **2009**, *11*, 4010–4013.

22a),[129] while the extension of the Brønsted acid catalysis approach to reactions involving π-deficient olefins as electrophiles seems troublesome based on the poor results documented with acrolein, methyl acrylate,[130] or sterically undemanding enones (Figure 22b).[131] In addition, α-branched cycloalkanones other than cyclopentanones and cyclohexanones remain elusive substrates.

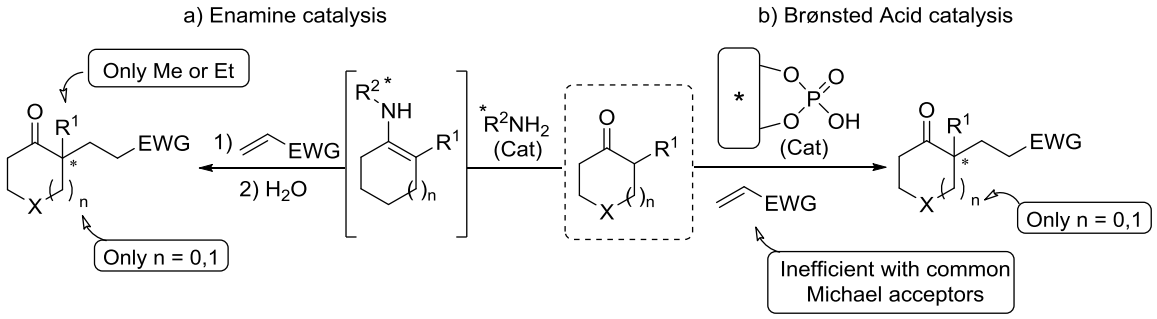


Figure 22. α-Functionalization of α-branched cycloalkanones via enamine and Brønsted acid catalysis.

Alternatively, bifunctional Brønsted base/H-bond catalysis has been also applied to promote Michael reactions of α-branched cyclic ketones. However, the overwhelming majority of examples deal with activated ketone donors bearing at C_α an additional functionality such as COR, CO_2R, NO_2 or CN (Figure 23).[132]

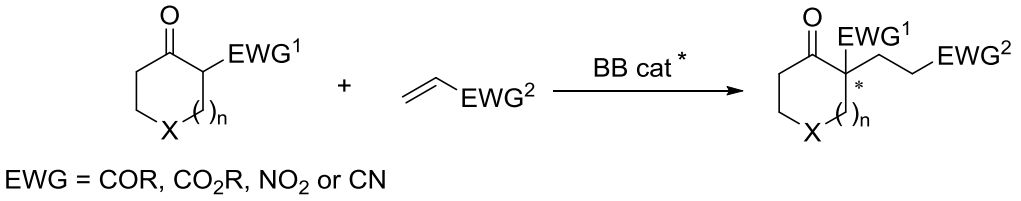


Figure 23. Common ketone donors in Brønsted base catalysis.

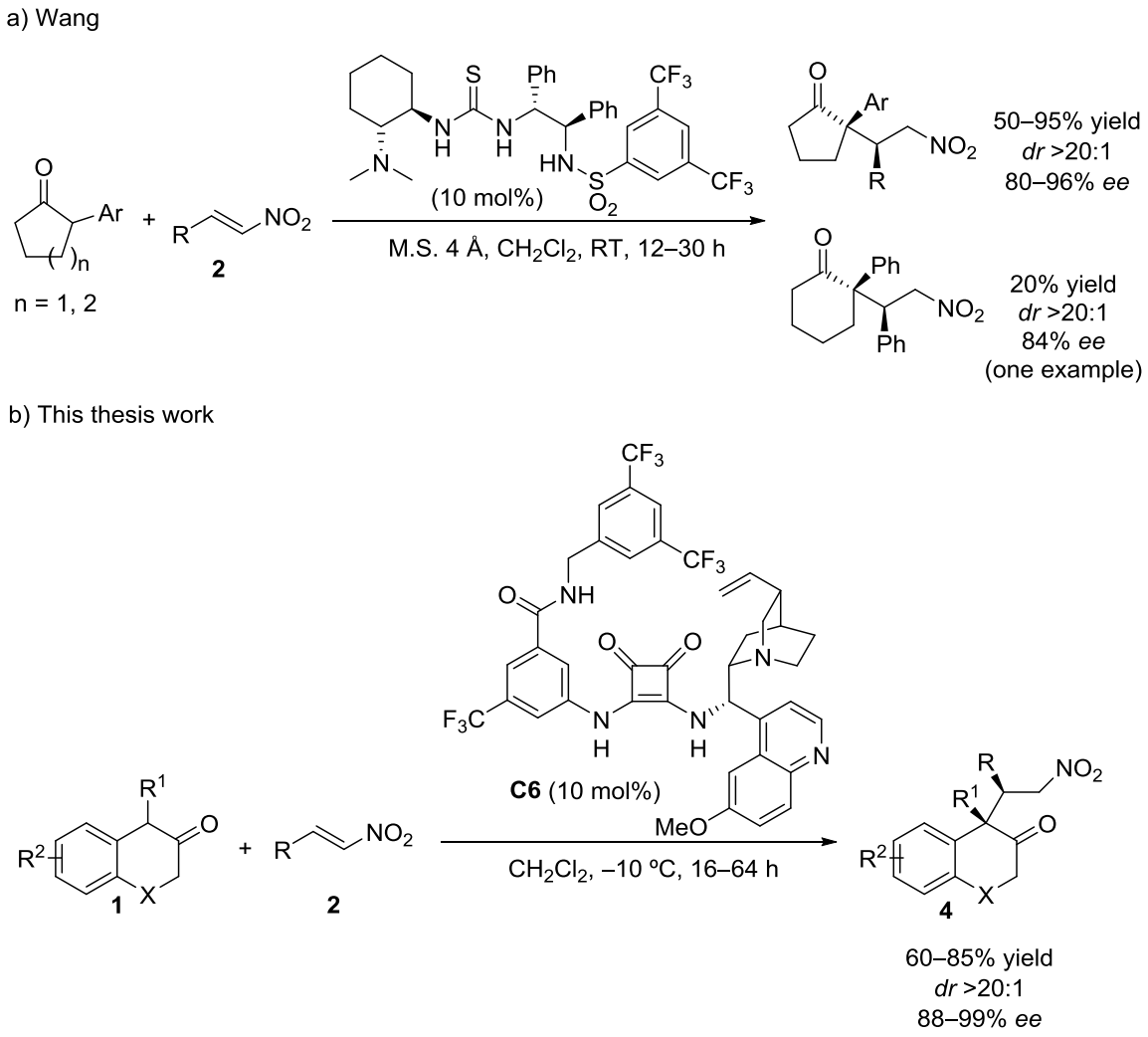
[129] a) J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178–3181. b) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, *81*, 3629–3637. c) R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457–4463.

[130] X. Yang, F. D. Toste, *Chem. Sci.*, **2016**, *7*, 2653–2656.

[131] I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960–1964.

[132] For general reviews on Brønsted base catalysis: a) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632. b) I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley and Sons, New York, **2010**. c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200. d) K. Maruoka, *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*, Thieme, Stuttgart, **2012**. e) B. Teng, W. C. Lim, C. H. Tan, *Synlett*, **2017**, *28*, 1272–1277.

Two exceptions have been described: the highly enantioselective addition of α-aryl cyclopentanones to nitroolefins by Wang (Scheme 36a)[133] and as described in Chapter 2, the BB-catalyzed addition of β-tetralones by us (Scheme 36b).[134] Nonetheless, while Wang´s approach is unsuccessful for cycloalkanones with seven or more carbon atoms, our method uses to β-tetralones as specific substrates, with α-tetralones showing to be unreactive materials under same conditions.



Scheme 36. Michael reaction of α-branched cycloalkanones catalyzed by a Brønsted base/H-bond catalyst.

With the aim to broaden our method to other cyclic ketones, including α-tetralones, we hypothesized that cycloalkanones with an α-alkenyl group may be effective owing to: i)

[133] X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem Commun.* **2010**, *46*, 6840–6842.
[134] I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063.

increased α-CH acidity as the resulting enolate would be stabilized through charge delocalization and ii) availability of a strategically positioned C=C double bond in adducts for ulterior chemical exploitation. Nevertheless, ketone dienolates and their equivalents pose some unique challenges since dienolates may react through either the α or the γ nucleophilic carbon thus demanding stringent reaction control (0).

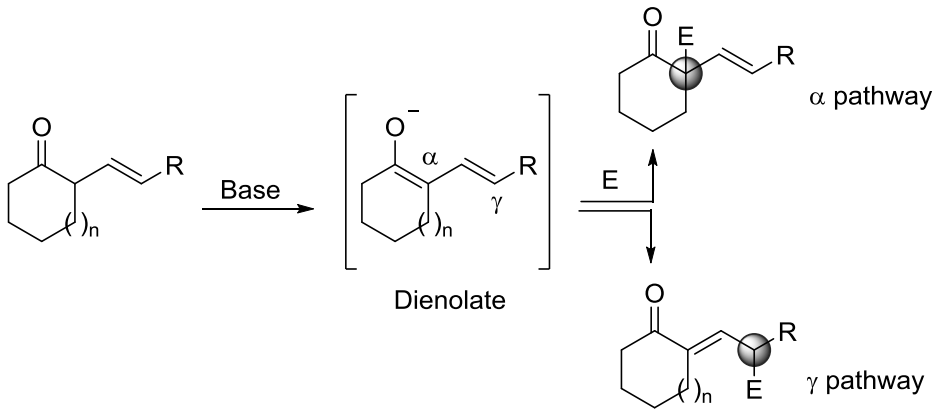
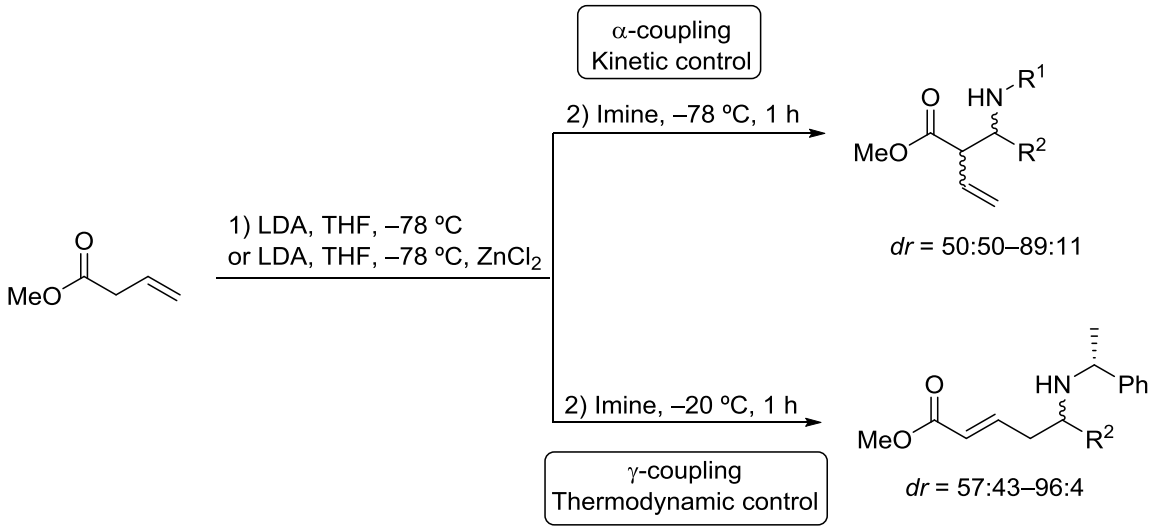


Figure 24. Enolization of α-alkenyl cycloalkanones and the emergence of α vs. γ reaction selectivity problem.

Few previous studies in the literature show that the α/γ selectivity problem in reactions systems involving metal dienolates is multivariable. The formation of α- and γ-addition products has been interpreted in terms of the effect of polarity of the substituents and the solvent, as well as the effect of temperature and steric hindrance.[135] These studies about aldol reactions using lithium and zinc dienolates suggested that the α-coupled product was the kinetic product of the reaction, while raising the temperature, the thermodynamically more stable γ-coupled products were formed. For instance, van Koten and coworkers analyzed the dualistic reactivity of lithium and zinc dienolates with imines.[135b,136] It was observed that depending on the metal counterion, temperature and the substituents, the C–C coupling occurs either at the α or the γ position preferentially, giving β-amino esters and α,β-unsaturated esters, respectively (Scheme 37).

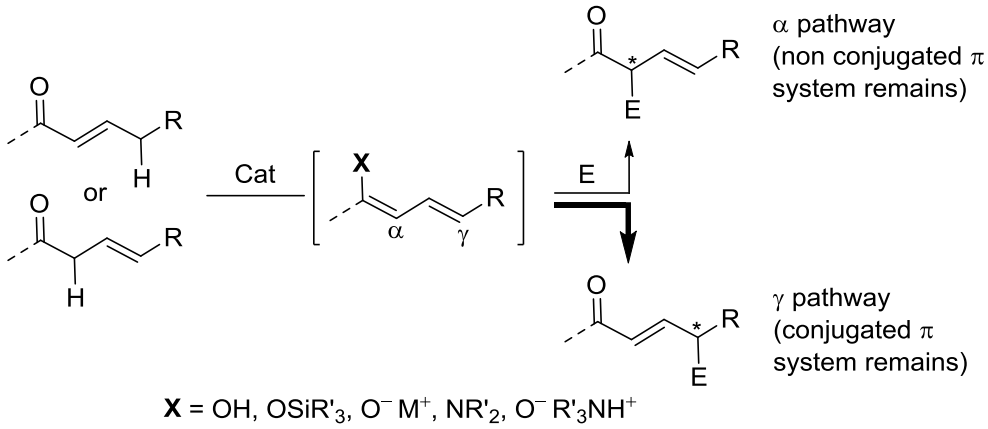
[135] a) R. Gompper, H. U. Wagner, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 321–333. b) H. L. van Maanen, H. Kleijn, J. T. B. H. Jastrzebski, M. T. Lakin, A. L. Spek, G. van Koten, *J. Org. Chem.* **1994**, *59*, 7839–7848. c) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813–814.

[136] For examples involving lithium dienolates, see: a) I. Casinos, R. Mestres, *J. Chem. Soc.*, *Perkin Trans. 1*, **1978**, 1651–1655. b) R. W. Dugger, C. H. Heathcock, *J. Org. Chem.* **1980**, *45*, 1181–1184. c) P. R. Johnson, J. D. White, *J. Org. Chem.* **1984**, *49*, 4424–4429.



Scheme 37. Dualistic reactivity of lithium and zinc dienolates with imines.

To date, the majority of catalytic methods involving dienolate or equivalent intermediates deal with α-unsubstituted systems and proceed mainly through the γ carbon (vinylogous reactivity, Scheme 38).[137] These methods include catalyst-promoted addition reactions of preformed silyl dienol ethers (X: $OSiR'_3$) as well as direct approaches based on metallic catalysis (X: O^-M^+), dienamine activation (X: NR'_2), and Brønsted acid and base catalysis activations. The prevalence of the γ-attack vs. the α-pathway might be due to the fact that in the former case there is no disruption of the π-conjugation along the reaction coordinate.



Scheme 38. Divergent reaction pathways of dienolates and equivalents.

[137] a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076–3154. b) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531–3543. c) Y. Yin, Z. Jiang, *ChemCatChem* **2017**, *9*, 4306–4318.

Among this mainstream γ-reaction pathway, methods employing silyl dienol ethers (X: $OSiR'_3$)[138] to yield the corresponding γ-addition products have been reported. The vinylogous Mukaiyama aldol reaction, which uses silyloxydienes as the nucleophiles, has been extensively investigated. Although the vast majority of these studies employ metal-based catalysts,[138a] organocatalysis has attracted considerable interest for the vinylogous aldol reaction.[138b] In contrast, the Mukaiyama-Michael reaction has been less explored.[138e] The most representative substrates employed in the reactions with preformed silyl dienol ethers are shown in Figure 25.

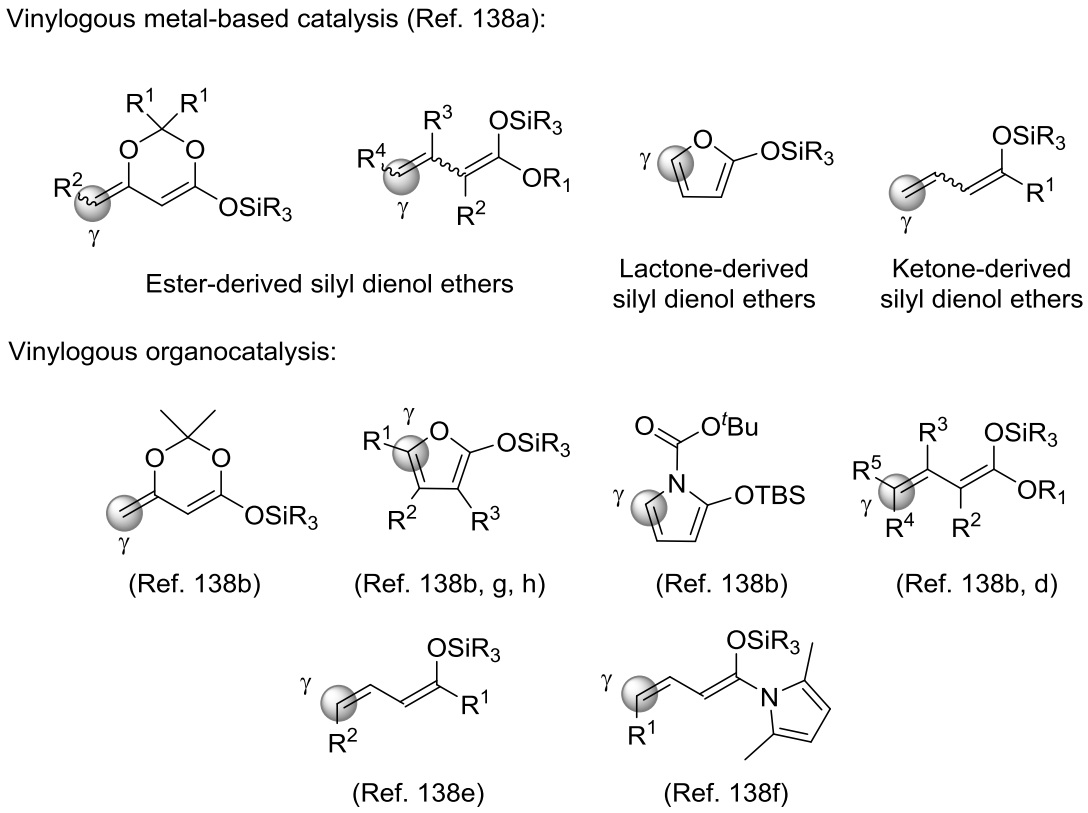


Figure 25. Most representative substrates employed in vinylogous reactions using silyl dienol ethers.

On the other hand, efforts have focused on the development of efficient methods to perform direct addition of unmodified carbonyl compounds to different electrophiles that proceed through dienolate or equivalent intermediates. In this context, approaches

[138] Reviews: a) S. E. Denmark, J. R. Heemstra, G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698. b) S. V. Pansare, E. K. Paul, *Chem. Eur. J*. **2011**, *17*, 8770–8779. Selected examples; for aldol reaction, see: c) S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800–7801. d) L. Ratjen, P. García-García, F. Lay, M. E. Beck, B. List, *Angew. Chem. Int. Ed*. **2011**, *50*, 754–758. For Michael reaction, see: e) V. Gupta, S. Sudhir, T. Mandal, C. Schneider, *Angew. Chem., Int. Ed.* **2012**, *51*, 12609–12612. f) S. Basu, V. Gupta, J. Nickel, C. Schneider, *Org. Lett*. **2014**, *16*, 274–277. g) A. P. Jadhav, V. U. B. Rao, P. Singh, R. G. Gonnadeb, R. P. Singh, *Chem. Commun.* **2015**, *51*, 13941—13944. h) Y. Wang, Z. Li, L. Lv, Z. Xie, *Org. Lett.* **2016**, *18*, 792−795.

based on metallic catalysis, in which reactions proceed through a transiently generated metal enolate intermediate (X: O^-M^+)[139] to obtain γ-functionalized products, have been described, including Michael, Mannich, aldol and allylation reactions. Examples involving metal-catalyzed γ-addition of vinylogous systems include both cyclic and acyclic substrates as depicted in Figure 26.

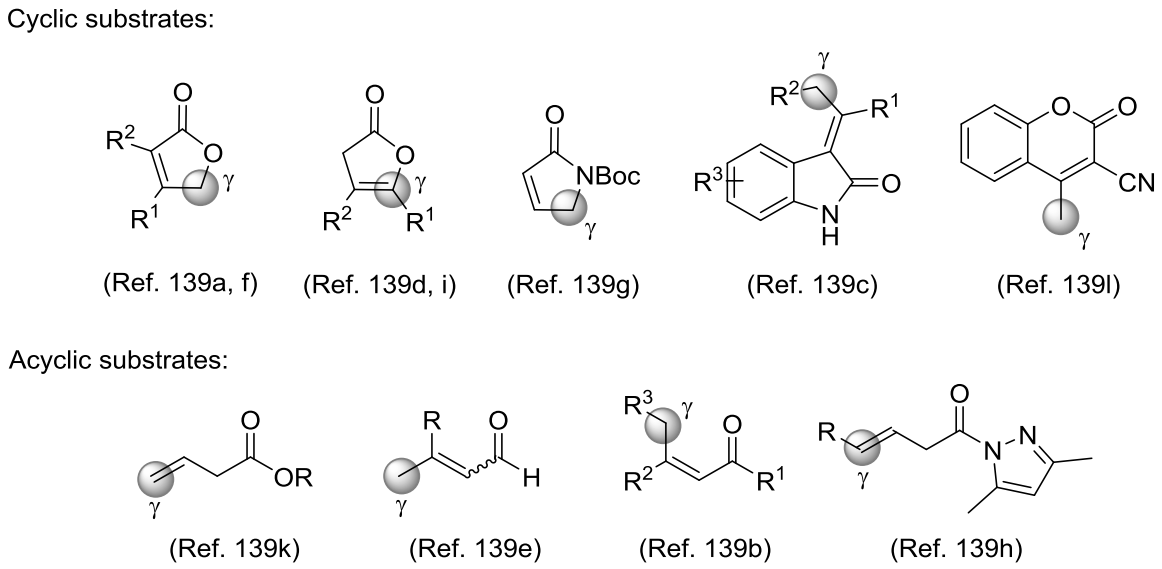


Figure 26. Examples of various substrates used in direct metal-catalyzed vinylogous addition reactions.

Direct methods to trigger the γ-functionalization of unsaturated carbonyl compounds via organocatalytic activation have also been developed to some extent. Among them, dienamine mediated activation (X: NR'_2)[140] has emerged as a powerful tool to develop

[139] Selected examples; for Michael reaction, see: a) B. M. Trost, J. Hitce, *J. Am. Chem. Soc.* **2009**, *131*, 4572–4573. b) D. Yang, L. Wang, F. Han, D. Zhao, B. Zhang, R. Wang, *Angew. Chem. Int. Ed*. **2013**, *52*, 6739–6742. c) X. Xiao, H. Mei, Q. Chen, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Commun.* **2015**, *51*, 580—583. d) J. Ji, L. Lin, Q. Tang, T. Kang, X. Liu, X. Feng, *ACS Catal.* **2017**, *7*, 3763−3767. e) X.-Y. Chen, Q. Liu, P. Chauhan, S. Li, A. Peuronen, K. Rissanen, E. Jafari, D. Enders, *Angew. Chem. Int. Ed.* **2017**, *56*, 6241–6245. For Mannich reaction, see: f) L. Yin, H. Takada, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed*. **2013**, *52*, 7310–7313. g) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc*. **2010**, *132*, 3666–3667. h) H.-J. Zhang, C.-Y. Shi, F. Zhong L. Yin, *J. Am. Chem. Soc.* **2017**, *139*, 2196–2199. i) B. M. Trost, E. Gnanamani, J. S. Tracy, C. A. Kalnmals, *J. Am. Chem. Soc.* **2017**, *139*, 18198−18201. j) F. Zhong, W.-J. Yue, H.-J. Zhang, C.-Y. Zhang, L. Yin, *J. Am. Chem. Soc.* **2018**, *140*, 15170−15175. For aldol reaction, see: k) H.-J. Zhang, L. Yin, *J. Am. Chem. Soc.* **2018**, *140*, 12270−12279. For allylation reaction, see: l) C.-Y. Shi, J.-Z. Xiao, L. Yin, *Chem. Commun.* **2018**, *54*, 11957−11960.

[140] Reviews: a) I. D. Jurberg, I. Chatterjee, R. Tannerta, P. Melchiorre, *Chem. Commun*. **2013**, *49*, 4869–4883. b) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812–6832. Selected examples; for Michael reaction, see: c) G. Bencivenni, P. Galzeranoa, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642–20647 (correction *PNAS* **2013**, *110*, 4852–4853). d) Q. Guo, A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett*. **2016**, *18*, 2628–2631. e) G.-Y. Ran, M. Gong, J.-F. Yue, X.-X. Yang, S.-L. Zhou, W. Du, Y.-C. Chen, *Org. Lett.* **2017**, *19*, 1874−1877. For [4+2] cycloaddition, see: f) M.-L. Shi, G. Zhan, S.-L.

vinylogous processes leading to γ-functionalized building blocks. Some representative substrates that have been used for γ-functionalization are depicted in Figure 27.

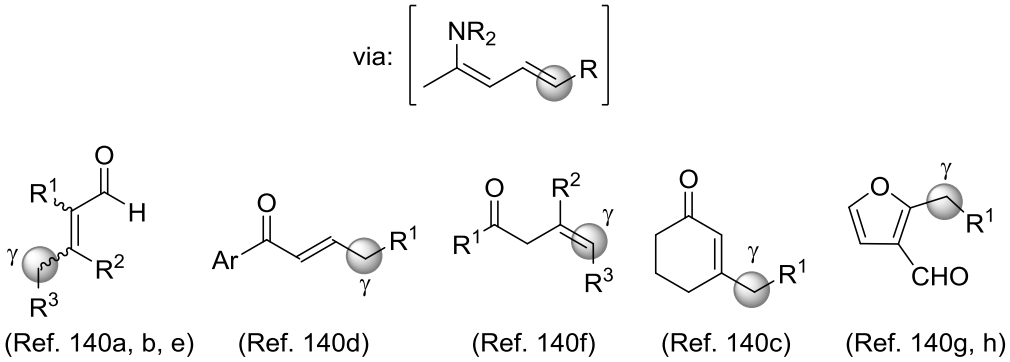


Figure 27. Representative substrate examples employed in γ-addition reactions by dienamine activation.

As a complement to these approaches, catalytically generated dienols and dienolates (Brønsted acid[141] or Brønsted base[142] catalysis, respectively), from unsaturated ketones, have been found to react with a suitable acceptor to afford the corresponding γ-addition adduct. With respect to Brønsted acid activation strategy, few examples have been reported as collected in Figure 28. It should be noted that in these instances, parallel activation of the acceptor component via iminium ion has been shown necessary in most cases.

Zhou, W. Du, Y.-C. Chen, *Org. Lett*. **2016**, *18*, 6480–6483. g) C.-Q. Duan, X.-L. He, W. Du, Y.-C. Chen, *Org. Chem. Front.* **2018**, *5*, 2057–2060. h) J. Bojanowsky, A. Skrzynska, A. Albrecht, *Asian J. Org. Chem*. **2019**, *8*, 844–848.

[141] Selected examples: a) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem. Int. Ed*. **2014**, *53*, 14128–14131. b) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479. c) Z.-L. Jia, Y. Wang, C.-G. Zhao, X.-H. Zhang, P.-F. Xu, *Org. Lett.* **2017**, *19*, 2130−2133.

[142] Selected examples; allyl ketones: a) B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem. Int. Ed*. **2013**, *52*, 6666–6670. b) B. Ray, S. Mukherjee, *J. Org. Chem*. **2018**, *83*, 10871–10880. c) M.-Y. Han, W.-Y. Luan, P.-L. Mai, P. Li, L. Wang, *J. Org. Chem.* **2018**, *83*, 1518–1524. d) X. Li, X. Kong, S. Yang, M. Meng, X. Zhan, M. Zeng, X. Fang, *Org. Lett.* **2019**, *21*, 1979−1983. Allyl pyrazoleamides: e) T.-Z. Li, Y. Jiang, Y.-Q. Guan, F. Sha, X.-Y. Wu, *Chem. Commun*. **2014**, 50, 10790–10792. 1,1-Dicyanoalkylidenes: f) T. B. Poulsen, M. Bell, K. A. Jørgensen, *Org. Biomol. Chem.* **2006**, *4*, 63–70. 3-Alkylidene oxindoles: g) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi, G. Casiraghi, *Angew. Chem. Int. Ed*. **2012**, *51*, 6200–6204. h) K. Kumar, M. K. Jaiswal, R. P. Singh, *Adv. Synth. Catal.* **2017**, *359*, 4136–4140. Allyl thioesters: i) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed*. **2012**, *51*, 2382–2386. α-Aryl α,β-enals: j) J.-K. Xie, Y. Wang, J.-B. Lin, X.-R. Ren, P.-F. Xu, *Chem. Eur. J.* **2017**, *23*, 6752–6756. Butenolides: k) S. K. Deepake, A. B. Lanjewar, T. Thatikonda, R. G. Gonnade, U. Das, *ChemistrySelect* **2018**, *3*, 8189–8192. l) S. Rout, H. Joshi, V. K. Singh, *Org. Lett.* **2018**, *20*, 2199−2203. m) V. Gupta, R. P. Singh, *New J. Chem.* **2019**, *43*, 9771–9775. n) W. Lin, X. Lin, Y. Cheng, X. Chang, S. Zhou, P. Li, W. Li, *Org. Chem. Front.* **2019**, *6*, 2452–2456. 2-allyl azaarenes: ñ) X. Bai, G. Zeng, T. Shao, Z. Jiang, *Angew. Chem. Int. Ed.* **2017**, *56*, 3684–3688.

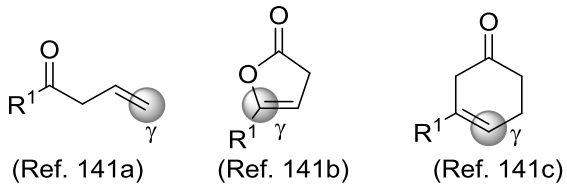


Figure 28. Examples of substrates employed in Brønsted acid catalyzed γ-functionalization.

On the other hand, Brønsted base catalysts have demonstrated to be able to promote the asymmetric γ-functionalization of unsaturated carbonyl and related compounds via *in situ* generation of the corresponding dienolate systems (Figure 29).

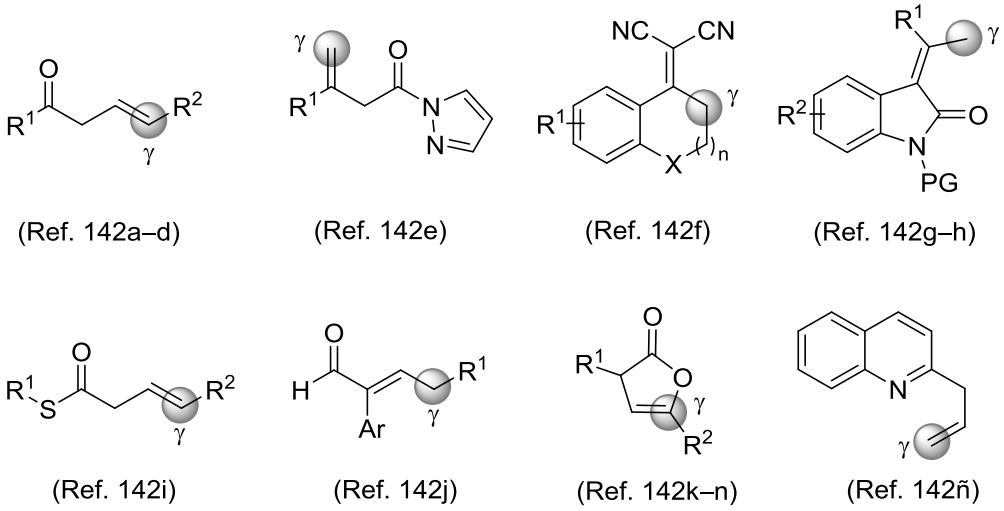
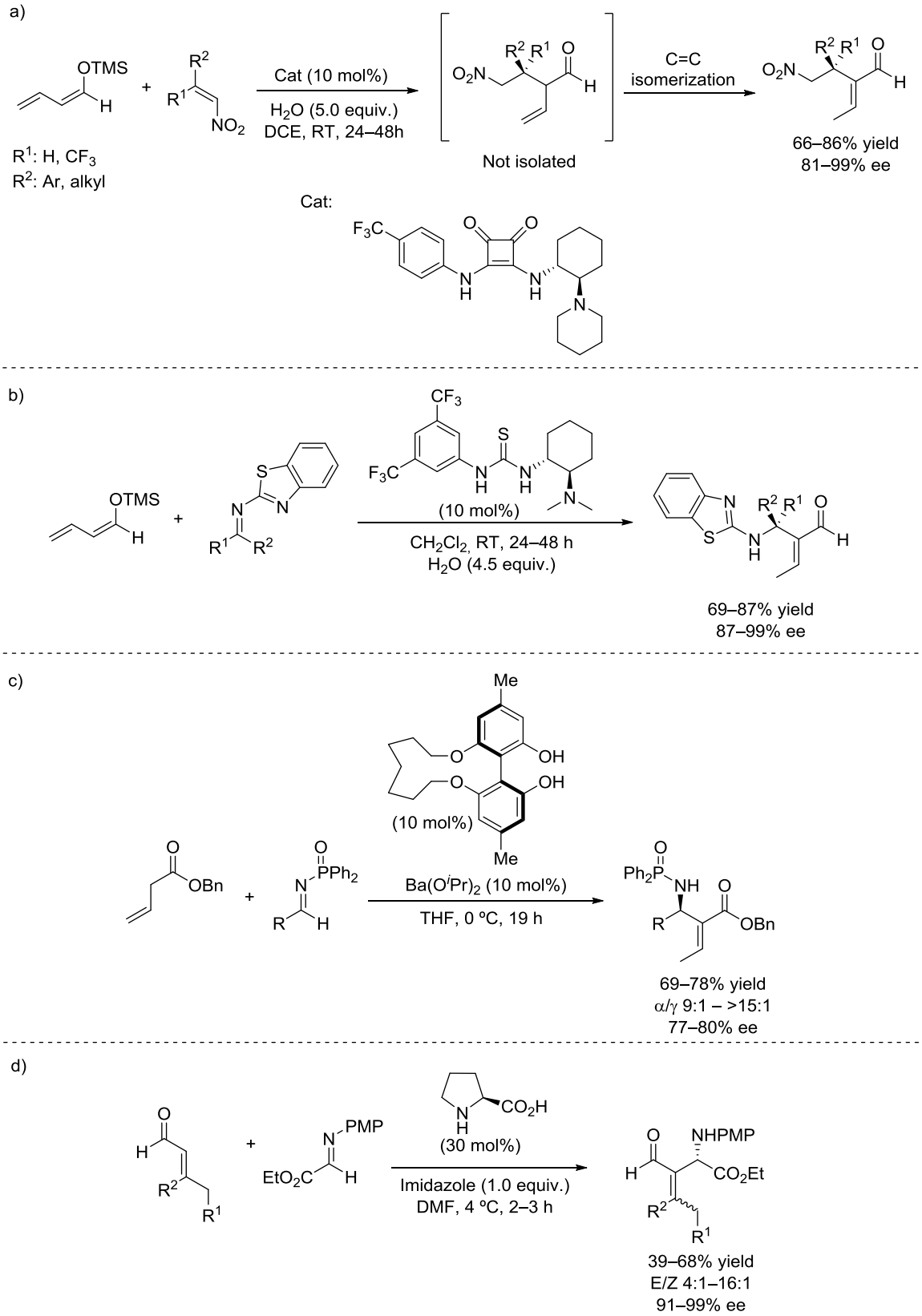


Figure 29. Various substrates used in γ-addition reactions catalyzed by Brønsted bases.

There are a few exceptions to this mainstream γ-selectivity pathway, that is, methods that proceed through α-carbon, but each has important restrictions. Alemán *et al.* reported the α-addition of preformed aldehyde-derived silyl enol ethers to nitroalkenes (Scheme 39a)[143a] and to imines (Scheme 39b)[143b] in the presence of tertiary amine catalysts. Although α-addition of the intermediate dienol occurs, stereogenicity at C_α is lost upon concomitant isomerization of the C=C double bond to yield Morita-Baylis-Hilmann (MBH) or Rauhut Currier (RC) adducts. Similar examples of α-addition leading to MBH type adducts were reported earlier by Shibasaki (Scheme 39c)[143c] and Barbas III (Scheme 39d) using other activation approaches.[143d]

[143] a) M. Frias, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, *J. Am. Chem. Soc.* **2017**, *139*, 672–679. b) M. Frias, A. C. Carrasco, A. Fraile, J. Alemán, *Chem. Eur. J.* **2018**, *24*, 3117–3121. c) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387–3390. d) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas, III, *Angew. Chem. Int. Ed*. **2007**, *46*, 1878–1880.

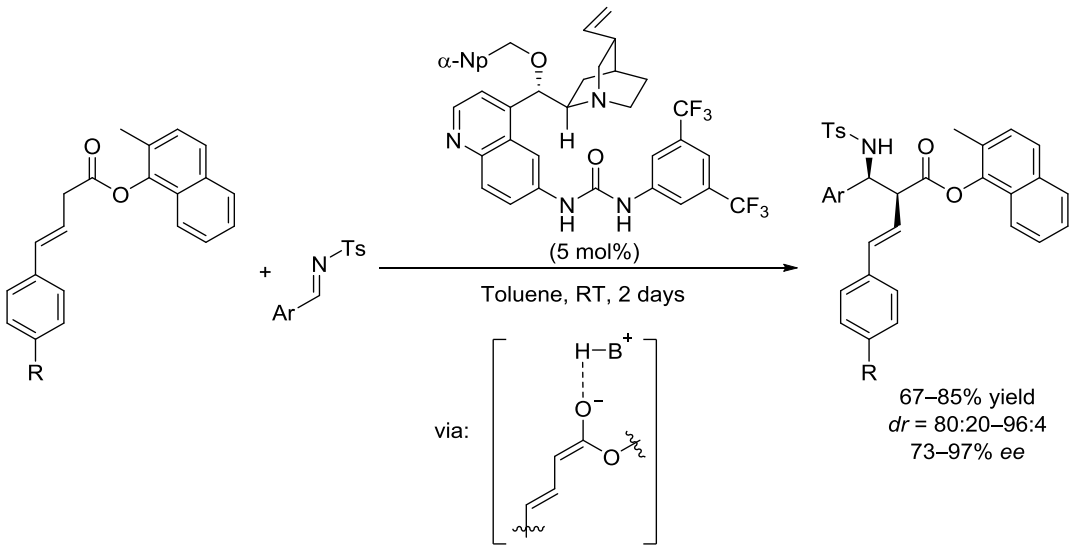


Scheme 39. α-addition examples of dienolates or equivalents leading to MBH-type adducts.

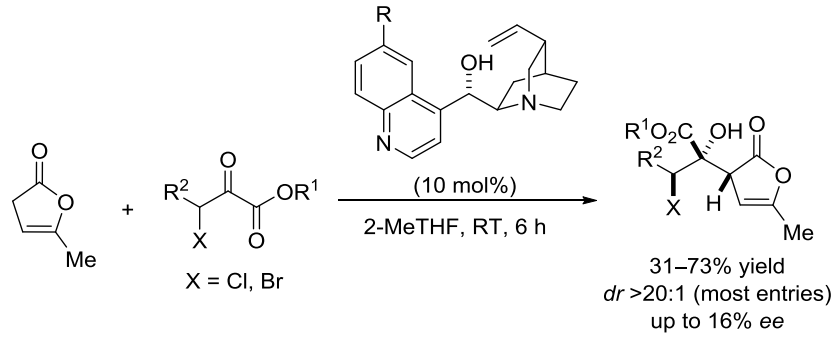
On the other hand, during the development of this thesis work, a few Brønsted base catalyzed α-site functionalization of transiently generated dienolates have been reported, but these examples were restricted to specific substrates, such as the α-styryl acetates (Scheme 40a),[144a] α-angelica lactones (Scheme 40b)[144b] or deconjugated butenolides (Scheme 40c and d).[144c,d] In the first case, the 2-methyl-1-naphthyl ester group was required since other aromatic groups provided worse reactivity or stereoselectivity. In the case of α-angelica lactone, quinidine led to a racemic product and the maximum enantioselectivity observed for the title reaction with any catalyst was 16% *ee*. Better enantioselectivities were obtained by Zhou and Lan in the regioselective α-addition of deconjugated butenolides, including, α-angelica lactone, in which the naphthol moiety in the acceptor was necessary in order to achieve good diastereoselectivity values (Scheme 40c). More recently, Xiao and coworkers reported a palladium-catalyzed asymmetric [4+2] cycloaddition by the α-addition of decongujated butenolides to vinyl carbamates with very good *ee* values (Scheme 40d).

[144] For reactions with α-styryl acetates: a) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2016**, *18*, 2648–2651; with α-angelica lactone: b) J. A. Griswold, M. A. Horwitz, L. V. Leiva, J. S. Johnson, *J. Org. Chem.* **2017**, *82*, 2276–2280; with deconjugated butenolides: c) B. Wu, Z. Yu, X. Gao, Y. Lan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 4006–4010. d) Y.-N. Wang, Q. Xiong, L.-Q. Lu, Q.-L. Zhang, Y. Wang, Y. Lan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2019**, *58*, 11013–11017.

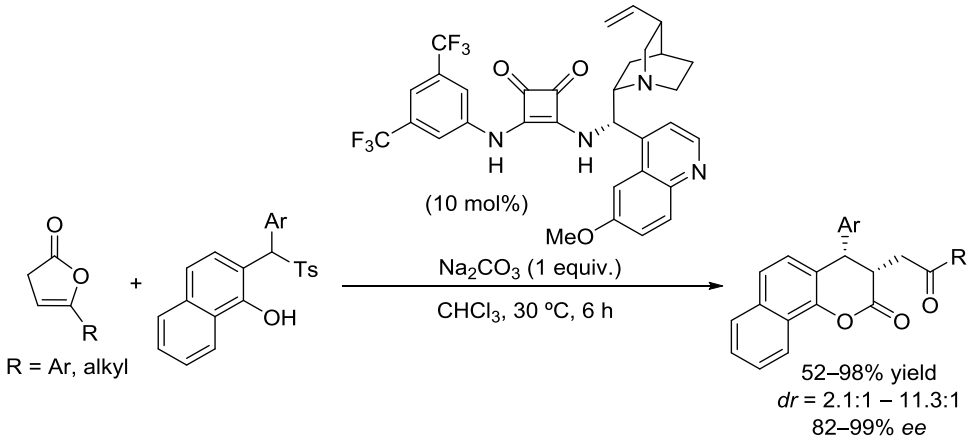
a)


α-Np
CF3
Ts
NH
Ar
(5 mol%)
Toluene, RT, 2 days
via:
67–85% yield
dr = 80:20–96:4
73–97% ee

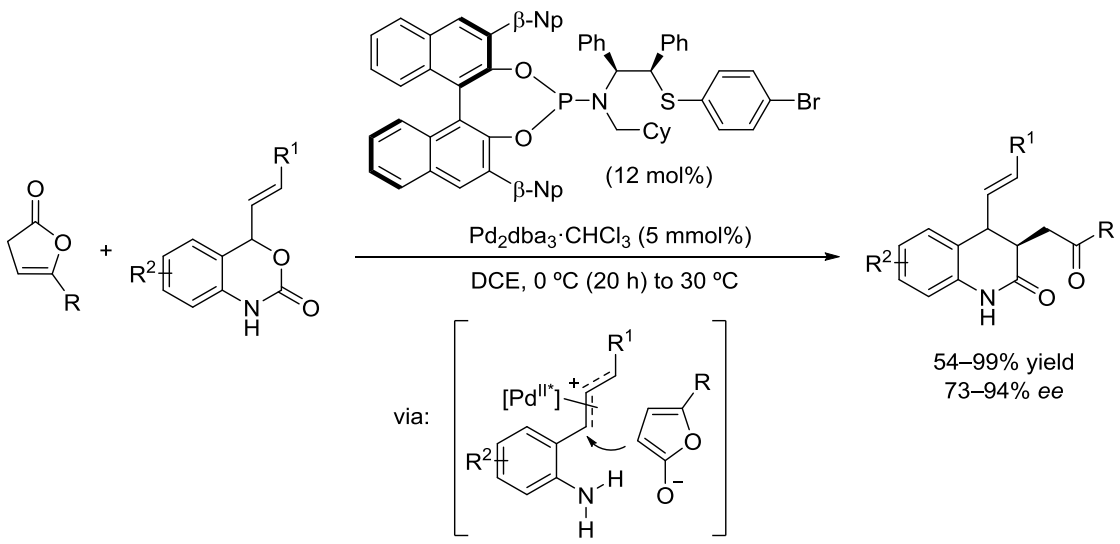
b)


OH
(10 mol%)
2-MeTHF, RT, 6 h
X = Cl, Br
31–73% yield
dr >20:1 (most entries)
up to 16% ee
via:

c)


CF3
F3C
(10 mol%)
MeO
Na2CO3 (1 equiv.)
CHCl3, 30 °C, 6 h
R = Ar, alkyl
52–98% yield
dr = 2.1:1 – 11.3:1
82–99% ee

d)

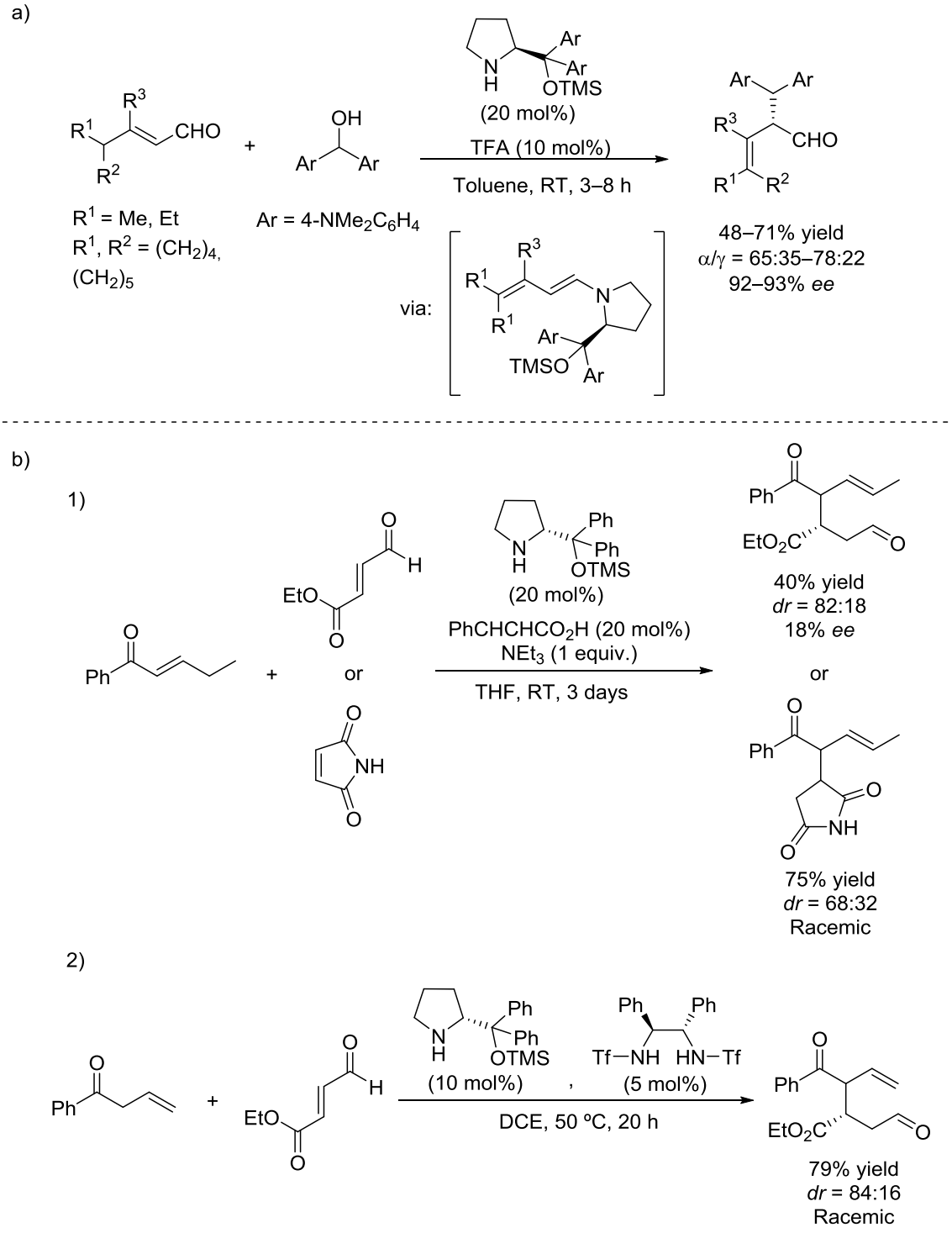


Scheme 40. α-addition reactions of a) α-styryl acetates, b) α-angelica lactones, c) and d) deconjugated butenolides.

Apart from the examples mentioned above, γ,γ-disubstituted enals have been found to react through the α-carbon atom of the dienamine intermediate because the disubstituted γ-carbon atom is sterically shielded (Scheme 41a).[145a] α-Substituted products were also obtained in the addition of linear enones to different electrophiles promoted by iminium activation, but these reactions featured poor enantioselectivity or provided racemic products (Scheme 41b).[146]

[145] a) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett*. **2011**, *13*, 70–73. For more examples, see: b) E. Marqués- López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, *Org. Lett.* **2009**, *11*, 4116-4119. c) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660–4663. d) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian. J.* **2011**, *6*, 2255–2259. e) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.- C. Chen, *Angew. Chem. Int. Ed*. **2009**, *48*, 5474–5477. For a review, see: f) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812–6832.

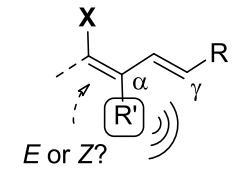
[146] Reference 140d includes three examples of (essentially racemic) direct α-functionalization of α,β-unsaturated ketones.



Scheme 41. α-selective examples of a) γ,γ-disubstituted enals, b) linear enones.

In addition, it is remarkable that none of these α-selective methods have been revealed useful for enantioselective generation of α-quaternary ketone (or related carbonyl) products, a process that would necessarily involve as intermediates α-substituted dienolates or equivalents (Figure 30). Such a realization would not only require a

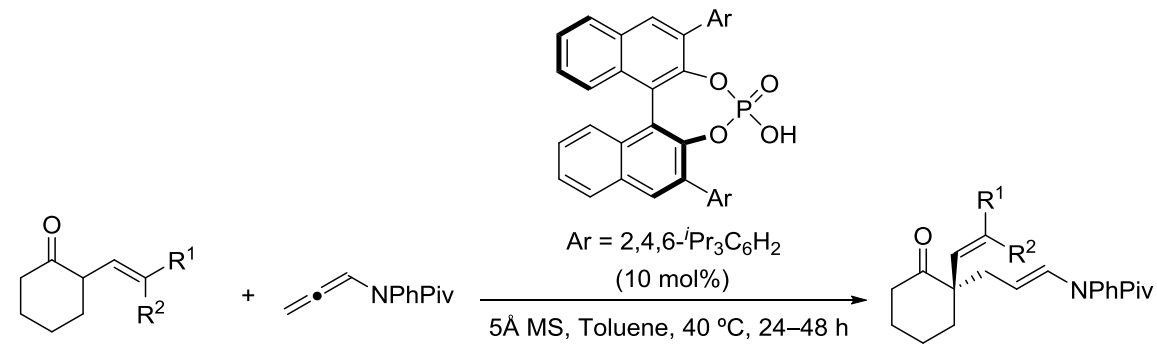
stringent control over the *E/Z* geometry of the evolved enolate and the face selectivity, but should also retain sufficient α-reactivity despite the steric congestion at Cα.



X = OH, $OSiR'_3$, $O^- M^+$, NR'_2, $O^- R'_3NH^+$

Figure 30. Challenging issues to control reactions involving α-branched dienolates.

As depicted in Chapter 1 (pages 25–26), this problem has recently been addressed by Toste via Brønsted acid catalysis and, as far as we know, no other solutions have been reported. However, as already discussed (pages 71–72), while the Brønsted acid activation approach is well suited for α-aminations,[147] apparently it shows limitations with common carbon electrophiles such as conjugated olefins, with allenamides being a notable exception (Scheme 42).[130]



Scheme 42. α-functionalization of α-alkenyl cycloalkanones with allenamides.

Overall, the development of direct site- and stereoselective C–C bond formation of α-branched β,γ-unsaturated ketones under proton transfer conditions must face the following problems: i) the relatively high pK_a value of simple unactive ketone substrates

[147] X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205–3208.

(pK_a > 18)[144a,148,] and ii) the steric hindrance at the carbonyl C_α. Both aspects difficult enolate generation by a bifunctional Brønsted base (pK_a values of conjugated acids ≈ 9–14)[148] and compromise nucleophilicity (reactivity) and regio- and stereoselectivity.

In order to overcome these difficulties, α-alkenyl ketones were selected as plausible substrates for development assuming that the α-vinyl appendage would not only provide versatility to the resulting adducts for further proliferation or simple reduction to the parent "alkyl" series, but also assist enolization via charge delocalization. According to this hypothesis, a Brønsted base would be able to promote the reaction in which α vs. α´ and α vs. γ site selectivity, as well as the enantio- and diastereoselectivity during the generation of the quaternary stereocenter could be controlled (Figure 31).

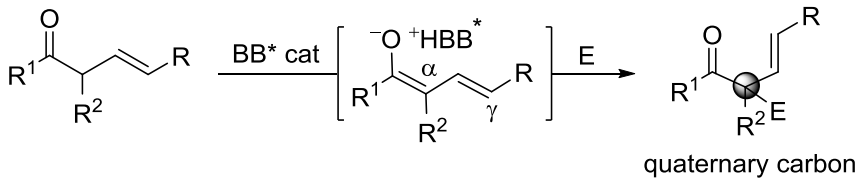


Figure 31. Enolization of α-alkenyl ketones and addition of the resulting intermediate dienolate to an electrophile (E).

3.2. Results and Discussion

3.2.1. Background and initial difficulties

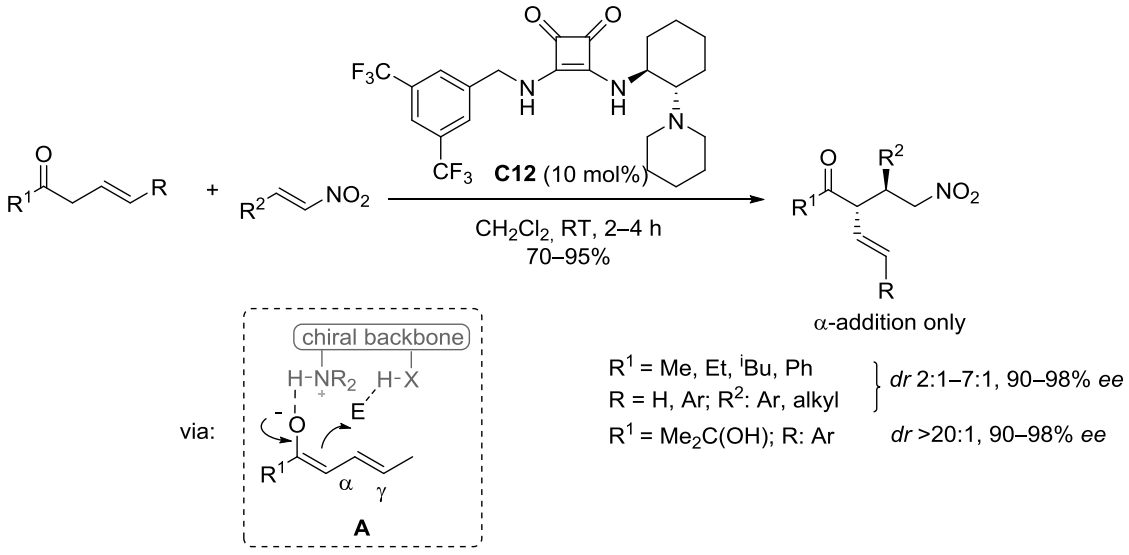
Quite recently, our laboratory found that chiral Brønsted base/H-bonding catalysts are able to promote the smooth, enantioselective addition of β,γ-unsaturated ketones to nitroolefins, yielding the α-addition adducts as exclusive products (Scheme 43a).[149] This process involves *in situ* generation of the corresponding ketone dienolate and its subsequent regio- and stereoselective addition to the acceptor olefin, with the bifunctional catalyst acting as an anchor which embraces both the nucleophile and the electrophile in the correct orientation, as in the simplified stereomodel **A**. While extrapolation of model **A** to α-branched ketone dienolates is conceivable, two apparent problems to overcome in this model **B** (Scheme 43b) are the steric shielding at C_α and

[148] For a webpage of Bordwell pKa Table (acidities in DMSO) of different compounds, see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

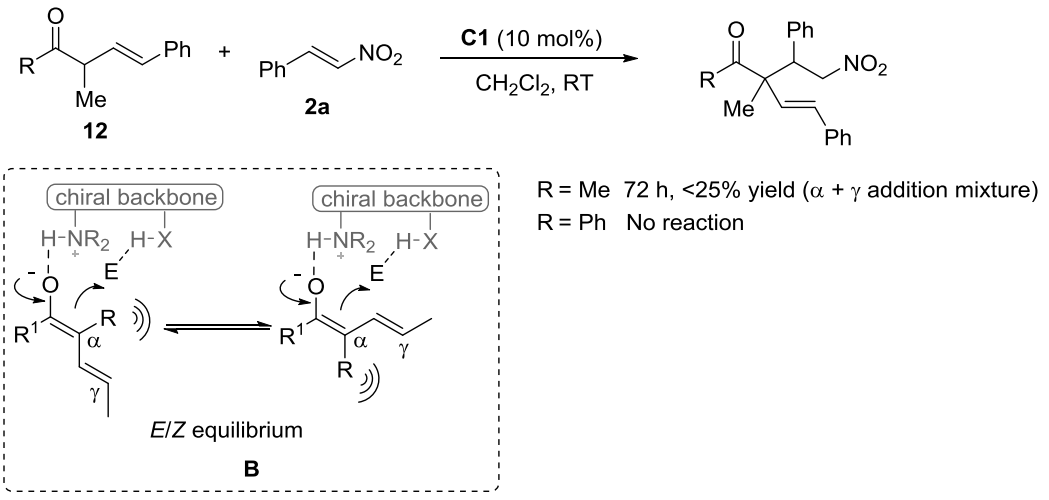
[149] I. Iriarte, O. Olaizola, S. Vera, I. Ganboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864.

the enolate *E*/*Z* configurational uncertainty. With regard to the former aspect, complications may be foreseen during both the enolate generation and the subsequent approaching of the electrophilic reagent. Initial attempts to perform the reaction between nitrostyrene **2a** and α-branched ketones **12** using bifunctional catalyst **C1** confirmed the anticipated pitfalls, resulting in the recovery of unreacted enone (R^1: Ph) or very low conversions (R^1: Me, <25% conversion after 72 h) (Scheme 43b). Moreover, the product was obtained as a mixture of α/γ isomers.

a) Previous work (Reference 149):



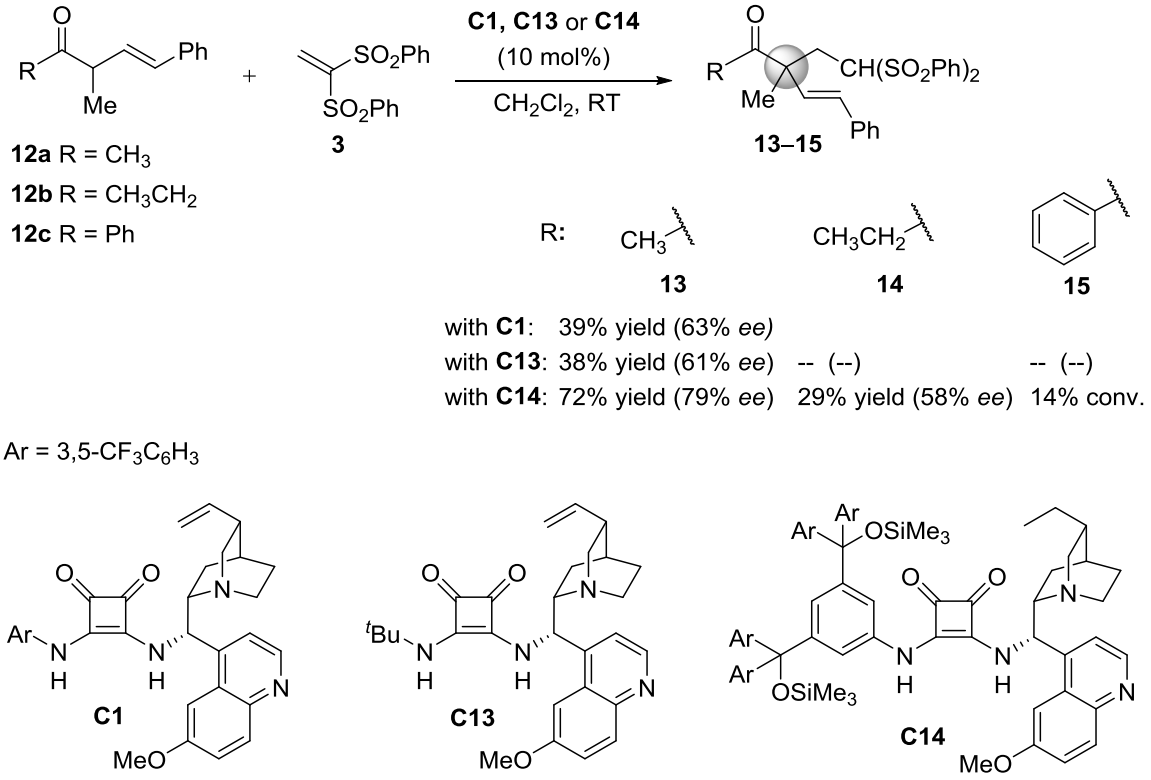
b) This thesis:



Scheme 43. Impact of α-substitution on the reactivity of transiently formed acyclic ketone dienolates.

We reasoned that highly reactive and sterically less demanding Michael acceptors such as 1,1-bis(phenylsulfonyl)ethylene **3** might counterbalance the low reactivity of these

ketones. To our delight, as the results in Scheme 44 show, α-branched ketones **12** reacted with **3** in the presence of **C1**, **C13**[150] or **C14**[151] to afford adducts **13–15** from reaction at the α-site exclusively, although in variable yields and enantioselectivity. For example, the reaction between methyl ketone **12a** and **3** in the presence of **C16** reached 82% conversion (Figure 32a) after 16 h at room temperature, and product **13** was obtained with 79% *ee* (Scheme 44). Catalysts **C1** and **C13** were less efficient leading to **13** in yields of 39% and 38% and 63/61% *ee*, respectively. The reaction with the ethylketone **12b** also proceeded giving product **14** but at much more paucity (35% conversion, Figure 32b) and with poor enantioselectivity, while the reaction of phenylketone **12c** to give **15** was sluggish.



Scheme 44. Impact of ketone side-chain R on the reactivity of derived dienolates (data correspond to isolated yields).

[150] F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed*. **2014**, *53*, 2628–2632.
[151] I. Urruzuno, O. Mugica, G. Zanella, S. Vera, E. Gomez-Bengoa, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2019**, 25, 9701–9709.

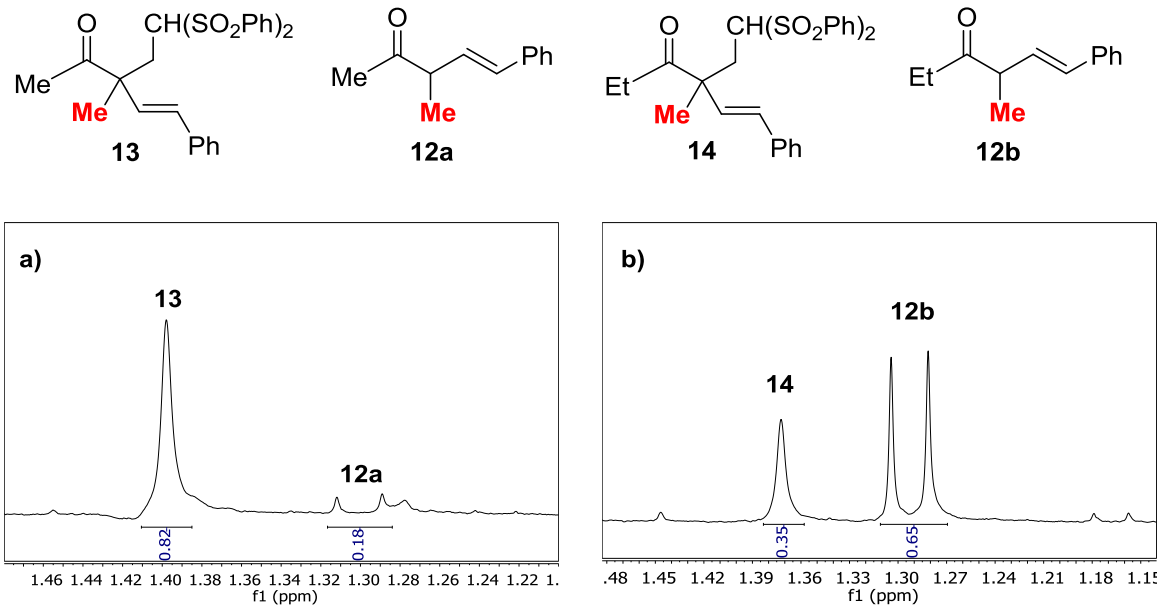


Figure 32. ^{1}H NMR spectra insets of an aliquot of the reaction of a) **12a** to obtain **13**, b) **12b** to obtain **14**.

These results, whilst promising, highlighted the two main problems of catalytically generated trisubstituted carbon nucleophiles: their attenuated reactivity and the difficulties in controlling enantioface selectivity. Moreover, the significant variations on the reaction outcome when shifting from methyl to ethyl or phenyl ketone side-chain seem to indicate that slight structural changes on the substrate ketone might have huge impact on reactivity and selectivity. The above observations also corroborate the multivariable origin of the Cα/Cγ selectivity in reactions involving dienolate systems.[152]

3.2.2. Michael addition of *in situ* generated cyclic dienolates to vinyl disulfone

To surmount the intrinsic difficulties mentioned above, cyclic ketones were adopted in which the double bond is tethered at the Cα-position of the carbonyl function. The corresponding dienolates might fit better based on: i) the higher nucleophilicity of cyclic systems as compared with the more flexible, open-chain counterparts;[153] ii) a more rigidified transition state and, thus, more efficient chirality transfer; iii) the problem of enolate geometry (*E*/*Z* uncertainty) gets cancelled.

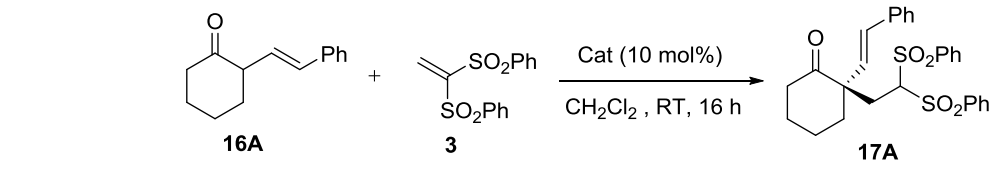
[152] a) R. Gompper, H. U. Wagner, *Angew. Chem. Int. Ed. Engl*. **1976**, *15*, 321–333. b) H. L. van Maanen, H. Kleijn, J. T. B. H. Jastrzebski, M. T. Lakin, A. L. Spek, G. van Koten, *J. Org. Chem*. **1994**, *59*, 7839–7848. c) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc*. **1998**, *120*, 813–814.
[153] Nucleophilicity enhancement of cyclic vs. acyclic carbanions: E. P. Kündig, A. F. Cunningham Jr., *Tetrahedron* **1988**, *44*, 6855–6860.

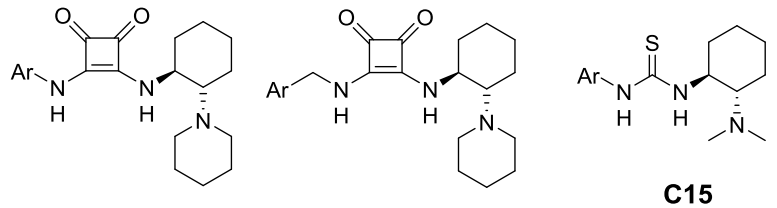
3.2.2.1. *Catalyst screening*

On this basis, the reaction between α-styryl cyclohexanone **16A** and bis(phenylsulfonyl)ethylene **3** was studied in the presence of an assortment of chiral bifunctional catalysts (Table 8). By using Takemoto's catalyst **C15**[154] in CH_2Cl_2 as solvent at room temperature, product **17A** was formed in a poor 26% isolated yield. Further screening showed that both the nature of the H-bond donor site and the structure of the tertiary amine in the catalyst were critical in terms of reactivity as well as stereoselectivity. Thus, the reaction did not proceed at all with squaramides **C11** and **C12**.[155] Catalyst **C6** containing an additional amide group suitable to engage in hydrogen bonding, provided the addition adduct in good yield but not with optimal enantioselectivity. We thought that these suboptimal results may be attributable to the moderate ability of the sulfone group for hydrogen bonding[156] and the tendency of squaramides for self-aggregation.[157] We then focused on bulky squaramide **C13** in order to try to prevent this self-aggregation problem. To our delight, catalyst **C13** promoted the reaction between **16A** and **3** to afford **17A** in 87% isolated yield and 98% *ee*. Interestingly, it was found that **C14**, a catalyst developed in our laboratory,[151,158] was equally selective giving **17A** as the only detected product. Accordingly, the scope of the reaction was explored with either catalyst **C13** and **C14**.

[154] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[155] H. Konishi, T. Y. Lam, J. P. Malerich, V. H. Rawal, *Org. Lett*. **2010**, *12*, 2028–2031.
[156] R. S. Drago, B. Wayland, R. L. Carlson, *J. Am. Chem. Soc.* **1963**, *85*, 3125–3128.
[157] For selected reviews on squaramide catalysts, see a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899. b) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330–2346. c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281. d) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–906. e) B.-L. Zhao, J.-H. Li, S.-M. Du, *Chem. Rec.* **2017**, *17*, 994–1018.
[158] I. Urruzuno, doctoral thesis, *Organocatalytic α-Functionalization of Carbonyl Compounds: Chemo-, Regio- and Stereoselectivity* EHU/UPV, **2018** (https://www.ehu.eus/es/web/gicas/tesiak).

Table 8. Catalyst screening for the reaction of cyclohexanone **16A** with vinyl sulfone **3**.

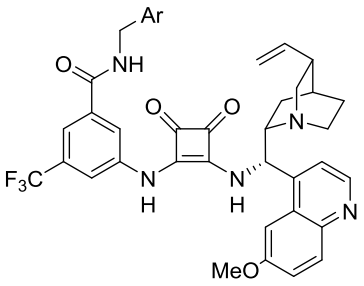




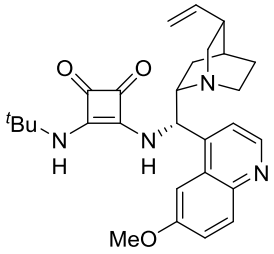
C11
NR

C12
NR

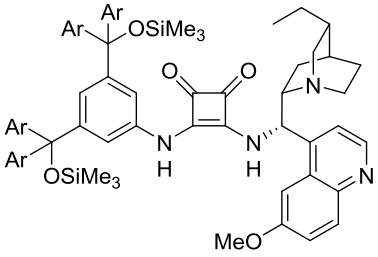
C15
26% yield
ND



C6
81% yield
72% *ee*



C13
87% yield
98% *ee*



C14[b]
89% yield
98% *ee*

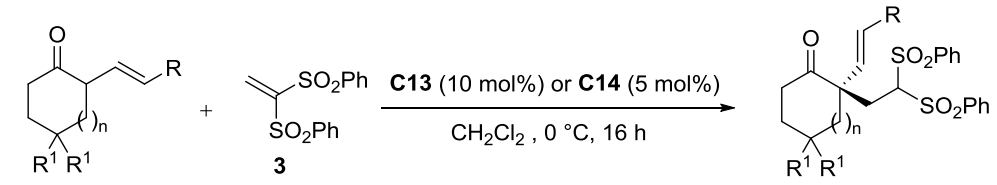
[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**16A**/**3** molar ratio = 1:2). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC. No product from γ-addition was detected by ^1H NMR (Cα/C γ >95:5). [b] Reaction run at 0 °C. Ar = 3,5-$CF_3C_6H_3$.

3.2.2.2. *Reaction scope*

As Table 9 shows, 4-substituted cyclohexanones **18B** and **20A** provided the corresponding addition products **19B** and **21A** in good yield and high enantioselectivity. Most important, the method turned out to be equally effective with cycloalkanones of varying ring size. For instance, the **C14**-catalyzed reaction of α-branched cycloheptanones **22A** and **22D** afforded adducts **23A** and **23D** in yields of 86% and 79%, and selectivities of 96% *ee* and 93% *ee*, respectively. Likewise, reaction with branched cyclooctanone **24A** afforded product **25A** in high yield, although diminished (88% *ee*) enantioselectivity. In this latter case, shifting the solvent from CH_2Cl_2 to toluene caused the increase of enantioselectivity to 94% *ee*. Under these conditions, **24B** led to **25B** in 88% yield and essentially single enantiomer. The method also tolerates alkenyl

cyclopentanones like **26A** and **26E** which produced **27A** and **27E** with acceptable *ee*'s. Cyclohexanone **16F** was an exception, leading to the corresponding adduct **17F** in good yield, but limited 65% *ee*. Eventually, the enantioselectivity could be increased to 80% *ee* by carrying out the reaction at –20 °C. In general, similar results were obtained with both catalysts **C13**/**C14** albeit the latter led to better chemical yields for cycloalkanones bearing the *p*-methoxyphenylvinyl moiety (products **17B**, **19B** and **25B**). It is worth mentioning that all the products remain stable at room temperature for long periods on the bench without any especial precautions.

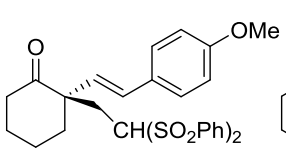
Table 9. Scope of the reaction of α-alkenyl cycloalkanones with **3** catalyzed by **C13**/**C14**.



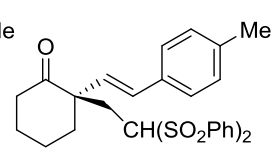
16 R^1 = H n=1
18 R^1 = Me n=1
20 R^1,R^1 = $O(CH_2)_2O$ n=1
22 R^1 = H n=2
24 R^1 = H n=3
26 R^1 = H n=0

A R = Ph
B R = 4-$MeOC_6H_4$
C R = 4-MeC_6H_4
D R = 4-ClC_6H_4
E R = 3-MeC_6H_4
F R = H

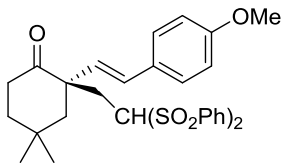
17 R^1 = H n=1
19 R^1 = Me n=1
21 R^1,R^1 = $O(CH_2)_2O$ n=1
23 R^1 = H n=2
25 R^1 =H n=3
27 R^1 =H n=0



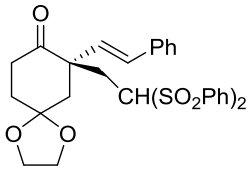
17B
C13, 59% y., 57% *ee*
C14, 66% y., 95% *ee*



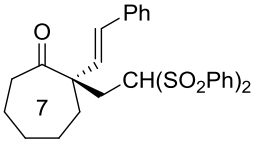
17C
C13, 77% y., 92% *ee*
C14, 84% y., 94% *ee*



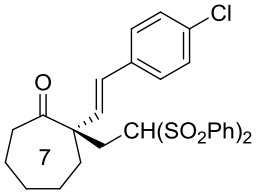
19B
C13, 14% conv., *ee ND*
C14, 70% y., 92% *ee*[e]



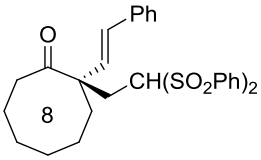
21A
C13, 78% y., 92% *ee*



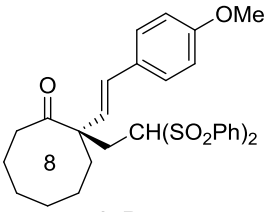
23A
C13, 72% y., 91% *ee*[c]
C14, 86% y., 96% *ee*[e]



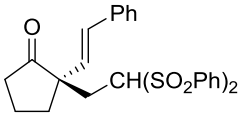
23D
C14, 79% y., 93% *ee*



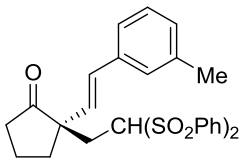
25A
C13, 73% y., 98% *ee*[b],[c]
C14, 83% y., 94% *ee*[b],[e]



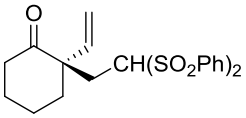
25B
C13, 47% conv., *ee* ND
C14, 88% y., 99% *ee*[b],[d]



27A
C13, 82% y., 95% *ee*[b]
C14, 85% y., 80% *ee*[b],[e]



27E
C13, 82% y., 82% *ee*[b]
C14, 79% y., 91% *ee*[b]



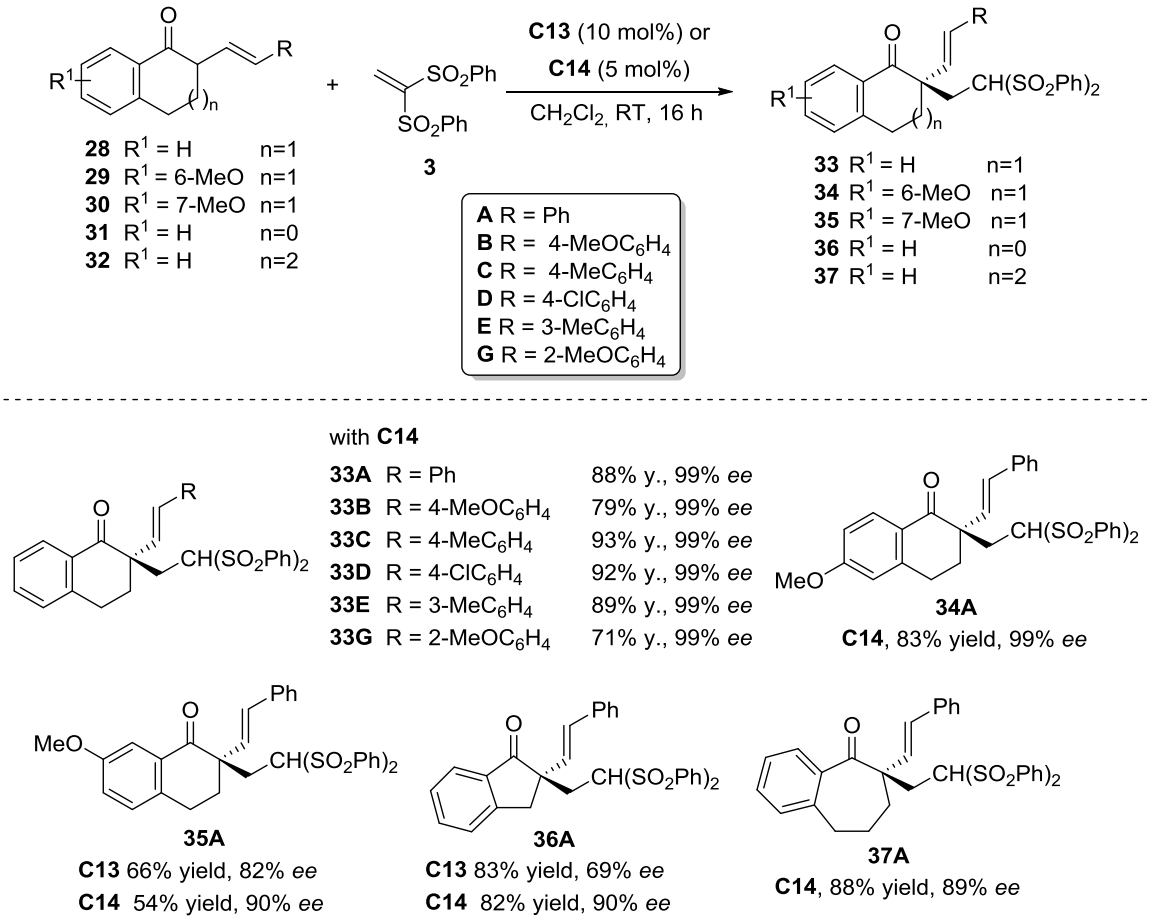
17F
C14(–20 ºC), 82% y., 80% *ee*[b],[d]

[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (ketone/**3** molar ratio = 1:2). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC. [b] Reaction carried out in toluene at RT. [c] With 3 equivalents of **3** and 48 h reaction. [d] 10 mol% of catalyst loading. ND = not determined. NR = no reaction. [e] Experiments performed by Dr. I. Urruzuno.

The corresponding alkenyl-substituted α-tetralones and related benzo-fused cycloalkanones **28–32** were also excellent substrates for this catalytic reaction, affording the α-quaternary cycloalkanones **33–37** in good yields and remarkably high

enantioselectivities using catalyst **C14** (Table 10). Excellent results were obtained regardless the electron-donor (**28B**, **28C**, **28E**, **28G**) or electron-acceptor (**28D**) character of the aryl groups in the ketone donor, leading to the respective adducts (**33A**–**33G**) in high yield. The method turned out to be equally stereoselective for substrates bearing fused aromatic rings with a methoxy group at various positions (adducts **34A** and **35A**), although adduct **35A** was achieved in moderate yield. Once again, the method demonstrated generality with regard to the ketone ring size and equally tolerated 5, 6 or 7-membered cycloalkanones (adducts **33A**, **36A** and **37A**). When catalyst **C13** was tested, worse enantioselectivity was obtained. It is important to note that in none of the above reactions was formation of γ-addition product observed.

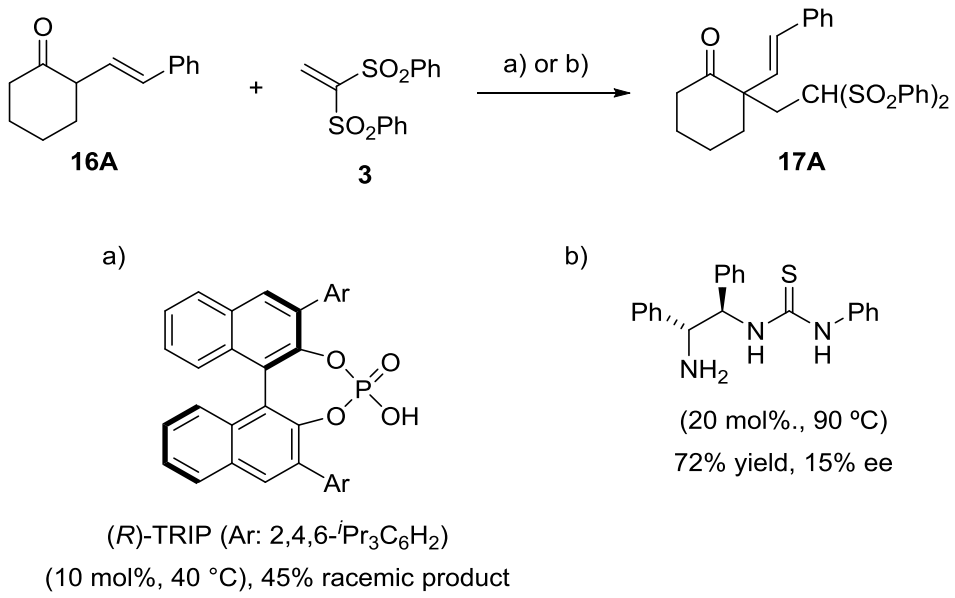
Table 10. Extension to benzo-fused cycloalkanones.



[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (ketone/**3** molar ratio = 1:1.5). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC.

Control experiments showed that for the above reactions the alternative Brønsted acid and enamine activation approaches were clearly inferior. For example (Scheme 45), in the presence of 10 mol% (*R*)-TRIP in toluene at room temperature no reaction occurred

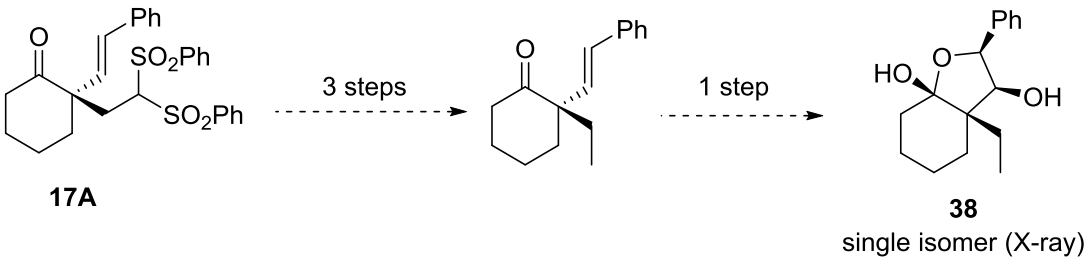
between **16A** and **3**, while the same reaction at 40 °C proceeded to give product **17A** in 45% yield, but essentially racemic. Likewise, while the addition of unsubstituted ketones to vinyl bis(sulfone) **3** had been reported to proceed selectively via enamine intermediacy,[159] attempts to react **16A** with **3** in the presence of chiral primary amines at room temperature were unfruitful. At 90 °C product **17A** was formed (72% yield) albeit in very low (15% *ee*) selectivity, indicating that the amine catalyst is probably acting as a base rather than via enamine formation. This latter observation suggests that the enamine pathway is marginal with sterically congested ketones such as **16A**, in line with previous observations by Carter[129a,b] and Kotsuki[129c] who have shown that amine catalysis is still unpractical for branched ketones with α- substituents larger than methyl or ethyl.



Scheme 45. Control experiments in the formation of adduct **17A** involving Brønsted acid and enamine based activation approaches.

These adducts are of interest in that they may be readily transformed, as demonstrated by Dr. I. Urruzuno[158] into several cyclic ketones or derivatives therefrom with a quaternary stereogenic center that otherwhise are difficult to construct (Scheme 46). These elaborations allowed to get a crystal structure of intermediate **38** which served to determine the configuration of adducts.[160]

[159] Q. Zhu, L. Cheng, Y. Lu, *Chem. Commun*. **2008**, 6315–6317.
[160] For more details, see Ref. 151.



Scheme 46. Chemical elaboration of the bis(sulfonyl) adducts.

3.2.2.3. *Theoretical studies*

With a view to explaining the results noted above, we considered that the reaction of α-branched allylic ketones with vinyl bis(sulfone) **3** deserved a more thorough research in terms of cyclic vs. acyclic systems, α/γ-site selectivity as well as stereoselectivity. For that purpose, we asked our colleague Dr. Enrique Gómez-Bengoa to carry out the theoretical studies. First, Dr. Gómez-Bengoa and his PhD student Giovanna Zanella determined the charge distribution and Fukui nucleophilicity index (f^-)[161] at the α carbon of linear (**I**) and cyclic (**II**) dienolates (Figure 33). Computed data[162] showed that the differences in negative charge at that specific carbon is negligible in the two enolates considered. Similarly, the Fukui indexes of these enolates showed to be essentially identical (–0.34 and –0.35, respectively). Accordingly, it appears that purely intrinsic electronic properties might not be informative in dictating these reactivity trends, and the role of the bifunctional catalyst as well as structural factors (steric hindrance, enolate rigidity) or α-CH acidity should also be considered.

For a more comprehensive analysis, they computed the energies for the reaction of each enolate system with bis(sulfone) **3** in the presence of a model achiral squaramide-tertiary amine catalyst ($TS_{(I–II)}$). As data in Figure 33 show, the computed activation energy for the reaction of cyclic dienolate **II** (20.8 kcal/mol) is affordable at room temperature. In contrast, the activation barrier for the reaction involving acyclic species **I** is ca. 24.6 kcal/mol, which correlate with a much more sluggish reactivity, in good agreement with our preliminary experimental studies. Calculated data for this model reaction involving **II** also support the preference of the α-addition pathway vs. the γ-addition pathway, the latter showing a barrier about 6 kcal/mol higher. They also

[161] The Fukui functions were calculated from the NBO charge distribution: a) W. Yang, W. J. Mortier, *J. Am. Chem. Soc.* **1986**, *108*, 5708–5711. b) P. W. Ayers, W. Yang, L. J. Bartolotti, *The Fukui Function in Chemical Reactivity Theory: A Density Functional View,* Taylor & Francis, Boca Raton, FL, **2009**, 255–267.
[162] DFT calculations were carried out with the Gaussian16 set of programs and the M06-2X functional. For computational details, see the Supplementary Information of Ref. 151.

found the preference of the α- vs. the γ- addition pathway for the catalysed reaction involving acyclic enolate **I** (24.6 vs. 27.4 kcal/mol). These data were revealing given the scarcity of mechanistic information dealing with latent dienolate systems.[163]

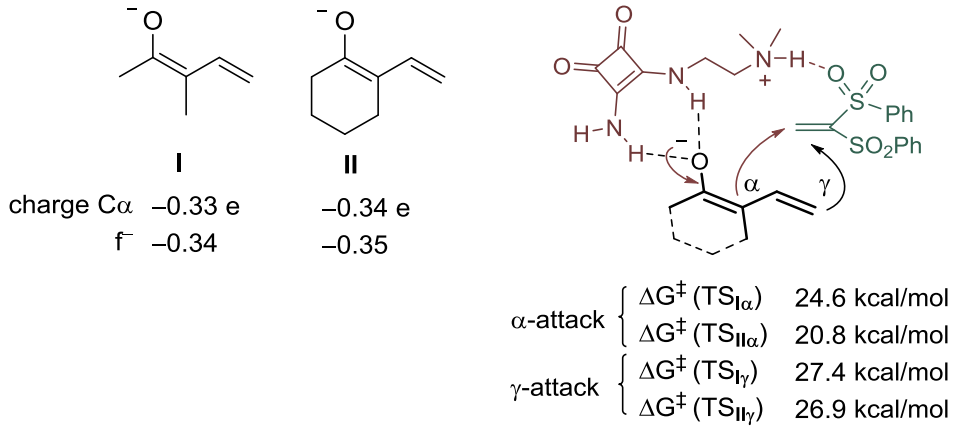


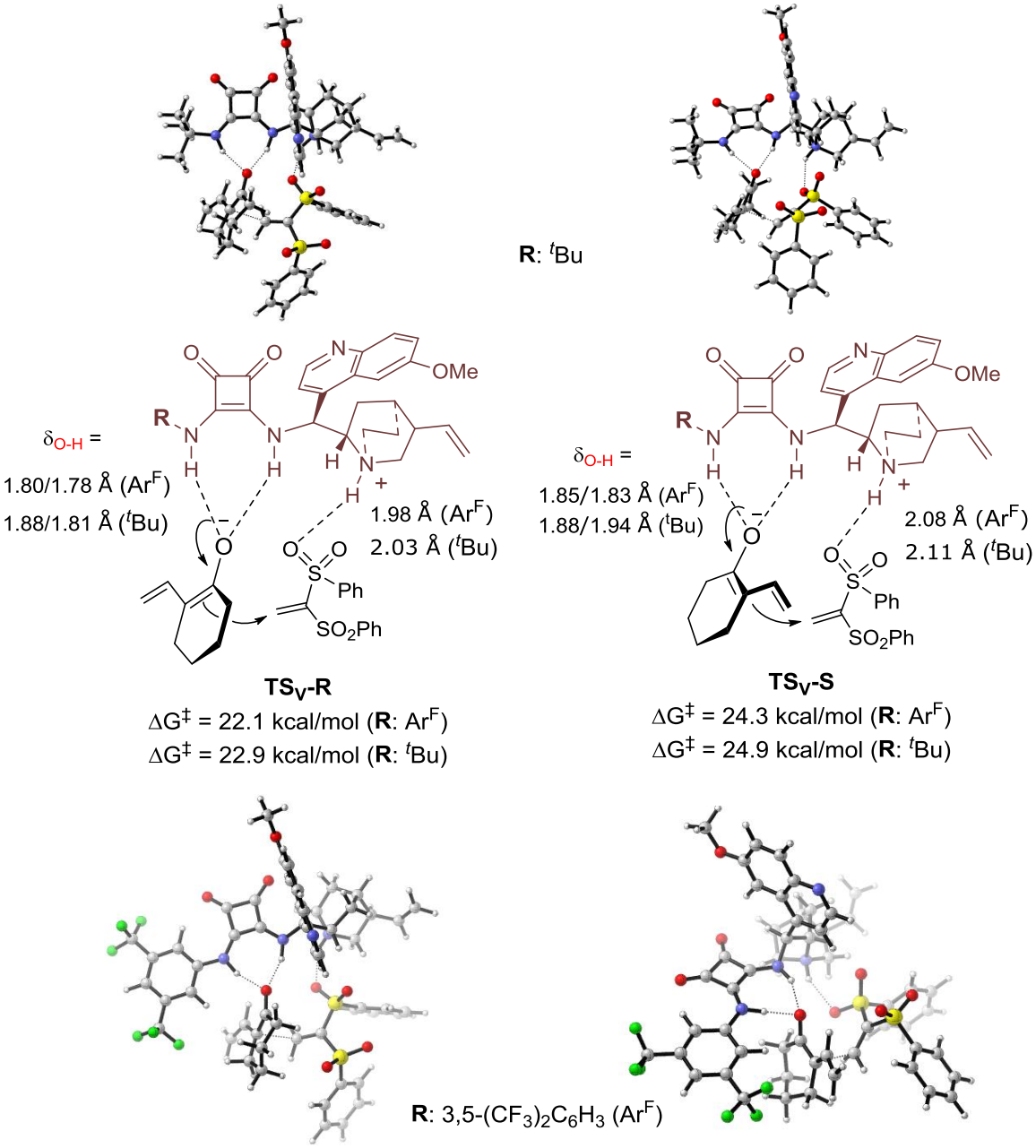
Figure 33. Reactivity parameters of two representative ketone dienolates.

Next, in order to shed light on the most favorable arrangement of the substrates and the catalyst during the transition state and find out the origin of stereoselectivity, DFT calculations for the model reaction between the vinyl cyclohexanone enolate **II**, vinyl bis(sulfone) **3** and either catalyst **C1** (R=Ar^F: 3,5-$(CF_3)_2C_6H_3$) or **C13** (R: ^{t}Bu) were also performed.[162] As could be anticipated for this type of bifunctional Brønsted base/H-bonding catalysis, the located TS structures each showed well defined H-bond networks that strongly bias the spatial arrangement of reactants, determining the stereochemical outcome of the reaction. Calculations at the M06/def2tzvpp (IEFPCM, solvent = dichloromethane)//B3LYP/6-31g(d,p) level of theory for the reaction above identified two Pápai-type[164] TS exclusively, namely **TS-R**, leading to the *R*-configured product, and **TS-S**, leading to the *S* enantiomer, for each catalyst (Scheme 47). In spite of serious efforts, they could not found the alternative Takemoto-type activation mode[165] with the sulfone oxygens hydrogen-bonded to the squaramide NH groups, probably due to the low H-bond acceptor character and high steric hindrance of the sulfone group.

[163] For a theoretical justification of the preferred γ-addition pathway (vinylogous reactivity) of certain alkylidene 2-oxindoles against nitroolefins, see: C. Curti, L. Battistini, A. Sartori, G. Rassu, G. Pelosi, M. Lombardo, F. Zanardi, *Adv. Synth. Catal*. **2018**, *360*, 711–721.

[164] a) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J*. **2014**, *20*, 5631–5639. b) C. Trujillo, I. Rozas, A. Botte, S. J. Connon, *Chem. Commun*. **2017**, *53*, 8874–8877.

[165] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672 –12673. b) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.



Scheme 47. TS structures and selected parameters for the model reaction between α-branched dienolate **II** and bis(phenylsulfonyl)ethane **3**

In agreement with the experimental observations, transition state **TS-R** presents the lowest activation energy (22.1 kcal/mol for catalyst **C1**) in comparison to 24.3 kcal/mol predicted for **TS-S** (slightly higher values of 22.9 and 24.9 kcal/mol, respectively, for catalyst **C13**). They measured the strongest H-bonds (shortest XH···Y bond) for the interaction between oxyanion **II** and the two squaramide NH moieties (1.80 and 1.78 Å for catalyst **C1**) in **TS-R**, in comparison to the values found for **TS-S** (1.85 and 1.83 Å). Similarly, the weak interaction between one oxygen of the bis(sulfone) group and the

protonated amine group in **C1** is less notorious in **TS-S** vs. **TS-R** (2.08 and 1.98 Å bond distances, respectively). This same trend in H-bonds strength was calculated for TS involving catalyst **C13**, although the slightly longer δ(O···H) values between dienolate oxygen and squaramide NH groups (1.88/1.81 Å vs. 1.80/1.78 Å) in this latter case appear to indicate a worse accommodation of the large ^{t}Bu group. Summarizing, with this study, it seems that an optimally congested microenvironment is formed around protonated catalyst **C1** for best fitting of both reactants through an efficient H-bond network.

Overall, these theoretical studies reinforced the multivariability of α/γ selectivity of dienolate systems. Although the majority of the methods proceed mainly through the γ carbon and this reactivity has been justified in some cases theoretically by DFT calculations,[163,166] we show here both experimental evidences and theoretical explanations of α-selective reactivity.[167] Hence, it is concluded that the reaction pathway of dienolate systems depends on the role of the catalyst as well as on the character of the reactants, both of the nucleophile and the electrophile.

3.2.3. Additions to nitroolefins

Given the observations noted above, the suitability of carbon electrophiles other than the vinyl bis(sulfone) **3** was next explored. Initial attempts with some α-substituted Michael acceptors like α- phenyl vinylsulfones and chalcones proved unsuccessful. However, it was delighting to observe that β-substituted nitroolefins were competent reaction partners, affording the corresponding adducts with two contiguous stereocenters.

3.2.3.1. *Catalyst screening*

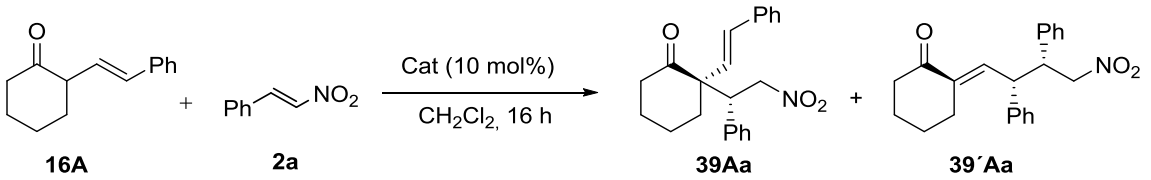
At first, the reaction between α-alkenyl cyclohexanone **16A** and nitrostyrene **2a** was taken as a model in order to find the optimal conditions. As the most representative experiments summarised in Table 11 show, all catalysts afforded a mixture of α- and γ-addition products in variable ratios, but with perfect diastereoselectivity. The α/γ selectivity as well as the enantioselectivity of each regioisomer happened to be highly

[166] B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6666–6670.

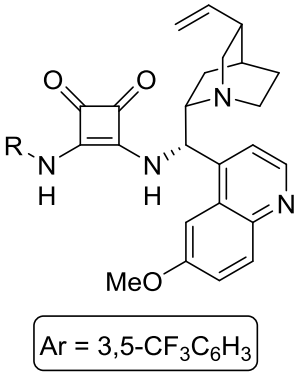
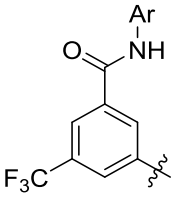
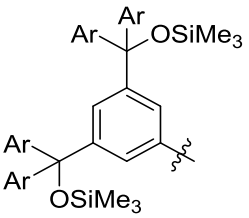
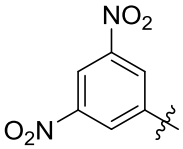
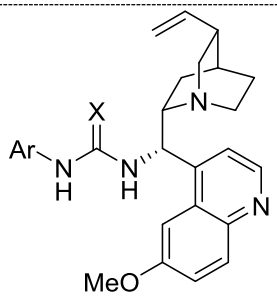
[167] Alemán *et al.* have also studied the α-selectivity trend of BB-catalyzed reaction of silyl dienol ethers with nitroolefins. See ref. 143a for details.

catalyst-dependent. Catalyst **C1** bearing the squaramide H-bonding structure exhibited superior regio- and enantiocontrol (α/γ 75:25, 95%/90% *ee*) when compared to catalysts with other functionalities such as urea (**C8**) and thiourea (**C9**) which afforded a mixture of products **39Aa** and **39´Aa** in ratios around 60:40 and in moderate *ee* (49–74% *ee*). The α/γ selectivity was further improved with **C1** to 92:8, with essentially perfect enantiocontrol (99% *ee*) for the major isomer, by carrying out the reaction at 0 °C. These results contrast with the poor behaviour of the parent open chain α-branched allyl ketones which under same conditions resulted to be unreactive. When catalyst **C4** bearing an additional amide group was employed, a slightly better α/γ selectivity was employed, but lower enantioselectivity (90% *ee*) and in longer reaction time (72 h). We found that the reaction in the presence of newly developed catalyst **C16**[151] afforded predominantly the desired α-addition product **39Aa** in a 95:5 ratio and perfect enantioselectivity at 0 °C, although 48 h reaction needed for completion. Most intriguing, with bulky catalysts **C13** and **C14** the reaction regioselectivity was switched in favor of the γ-adduct leading to α/γ ratios of 41:59 and 33:67, respectively.

Table 11. Catalyst screening for the reaction of **16A** with **2a**.



16A **2a** **39Aa** **39´Aa**

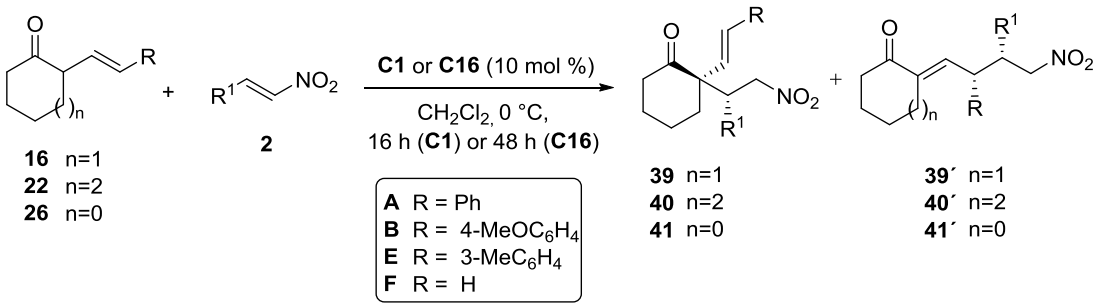
Cat			T (°C)	Yield (%)	α/β	*ee* (%)
	R:	**C1**	RT	83	75:25	95/90
	Ar	**C1**	0 °C	76[c]	92:8	99/--
		**C4**	0 °C	82[c],[e]	95:5	90/--
		**C13**	RT	85	41:59	94/97
		**C14**	RT	85	33:67	52/93
		**C16**	RT	80	85:15	98/94
		C16	0 °C	78[c],[d]	95:5	99/--
	X = S	**C8**	RT	88	60:40	54/73
	X = O	**C9**	RT	82	62:38	49/74

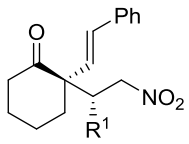
[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**16A**/**2a** molar ratio = 1:2). Yield of isolated products α and γ after column chromatography. α/γ ratio determined by ^{1}H NMR spectroscopy. *dr* = >20:1 in all cases. *ee* determined by chiral HPLC. [b] The double bond of the quinuclidine ring is hydrogenated. [c] Isolated yield of product α. [d] Reaction run for 48 h. [e] Reaction run for 72 h.

3.2.3.2. *Reaction scope*

With both **C1** and **C16** selected as the best catalysts, various α-alkenyl cycloalkanones and nitroalkenes were examined and the results are shown in Table 12. The reaction of **16A** with nitrostyrenes **2b**–**h** afforded the desired products **39Ab**–**h** in good yields, α/γ ratio of about 90:10 and 95:5 with **C1** and **C16**, respectively, and excellent enantioselectivity for the major isomer, regardless the electron-donor (4-$MeOC_6H_4$, 4-MeC_6H_4) or electron-acceptor (4-ClC_6H_4, 3-ClC_6H_4) character of the aryl groups. Similar effectiveness was achieved in the reactions involving cyclohexanones **16B**, **16E** and **16F**, which upon reaction with the respective nitroolefin led to adducts **39Ba**, **39Ed** and **39Fh**, being the formation of the latter one slower. The 7- and 5-membered cycloalkanones **22A** and **26A** led, again, to the respective addition products (**40Ah** and **41Ab**) in excellent enantioselectivities (*ee´*s higher than 95%) and good α/γ ratio for **41Ab**. In both cases, the reaction reached almost complete conversion (92% for **41Ab**, Figure 34). Surprisingly, the α/γ selectivity obtained with substrate **22A** dramatically decreased to 58:42. A comparison of both catalysts **C1**/**C16** indicates that the latter led to slightly better α/γ selectivities, although longer reaction times were needed and lower chemical yields for the reactions of cycloalkanones bearing electron-donor aryl groups (products **39Ba** and **39Ed**). It should be noted that in all cases α and γ regioisomers were easily separated by flash column chromatography.

Table 12. Scope of the reaction of α-alkenyl cycloalkanones with nitroolefins catalyzed by **C1**/**C16**.



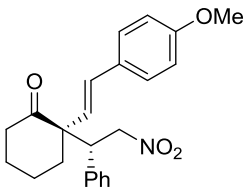


39Ab R^1= 4-$MeOC_6H_4$ — **C1**, 74%, α/γ 90:10, 96%/-- *ee*

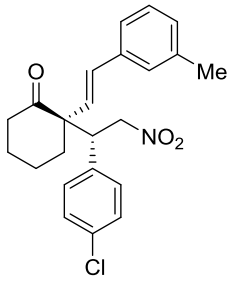
39Ac R^1= 4-MeC_6H_4 — **C1**, 75%, α/γ 90:10, 98%/-- *ee*; **C16**, 81%, α/γ 95:5, 98%/-- *ee*

39Ad R^1= 4-ClC_6H_4 — **C1**, 73%, α/γ 90:10, 98%/-- *ee*; **C16**, 78%, α/γ 95:5, 99%/-- *ee*

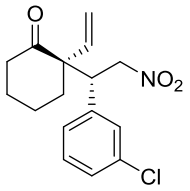
39Ah R^1= 3-ClC_6H_4 — **C1**, 73%, α/γ 88:12, 98%/-- *ee*



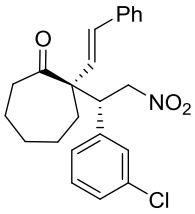
39Ba
C1, 76%, α/γ 87:13, 98%/-- *ee*
C16, 44%, α/γ 91:9, 99%/-- *ee*



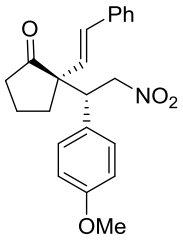
39Ed
C1, 71%, α/γ 80:20, 99%/-- *ee*[b]
C16, 46%, α/γ 92:8, 99%/-- *ee*



39Fh
C16, 70%, α/γ 95:5, 99%/-- *ee*[c]



40Ah
C1, 72%, α/γ 58:42, 98%/-- *ee*[b]



41Ab
C1, 76%, α/γ 92:8, 97%/-- *ee*

[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (ketone/**2** molar ratio = 1:2). Yield of major product after column chromatography. α/γ ratio determined by ^{1}H NMR spectroscopy. *dr* = >20:1 in all cases. *ee* determined by chiral HPLC. [b] Isolated yield of product α and γ. [c] Reaction run for 72 h.

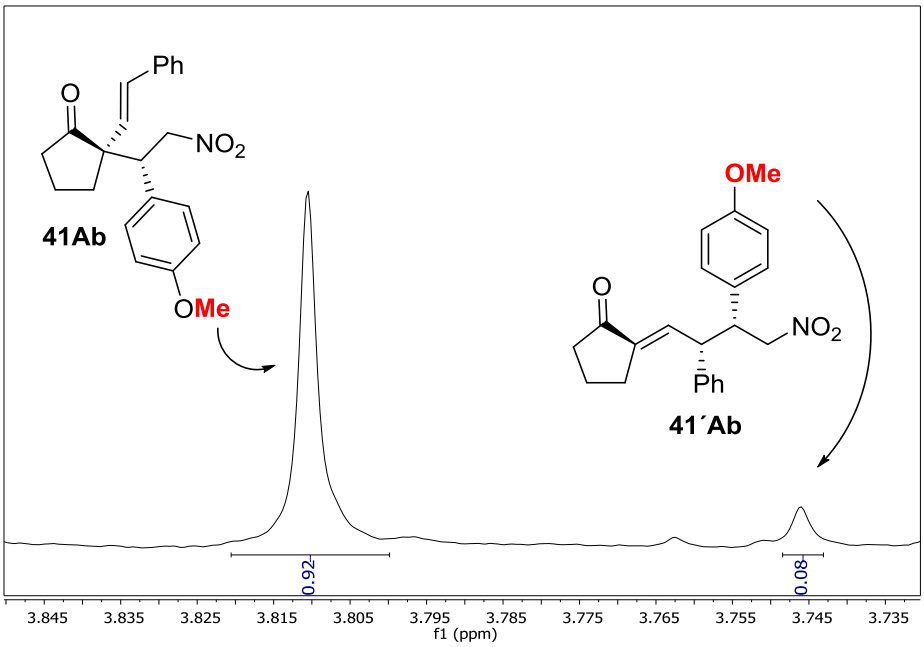


Figure 34. ^{1}H NMR spectrum inset of an aliquot of the reaction of **26A** with **2b**.

Crystallization of adduct **39Aa** from EtOH, allowed to obtain a crystalline sample of this compound suitable for X-ray structure analysis and determination of its absolute configuration (Figure 35). Configuration of the remaining adducts was assigned by analogy and by assuming a uniform reaction mechanism. Homochirality of adducts was also supported by the uniformly negative optical rotation values.

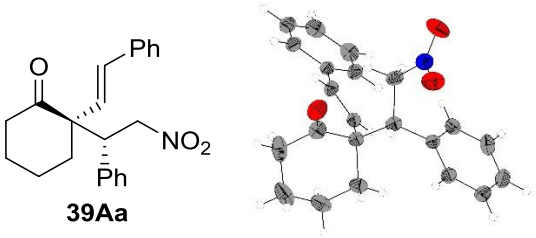
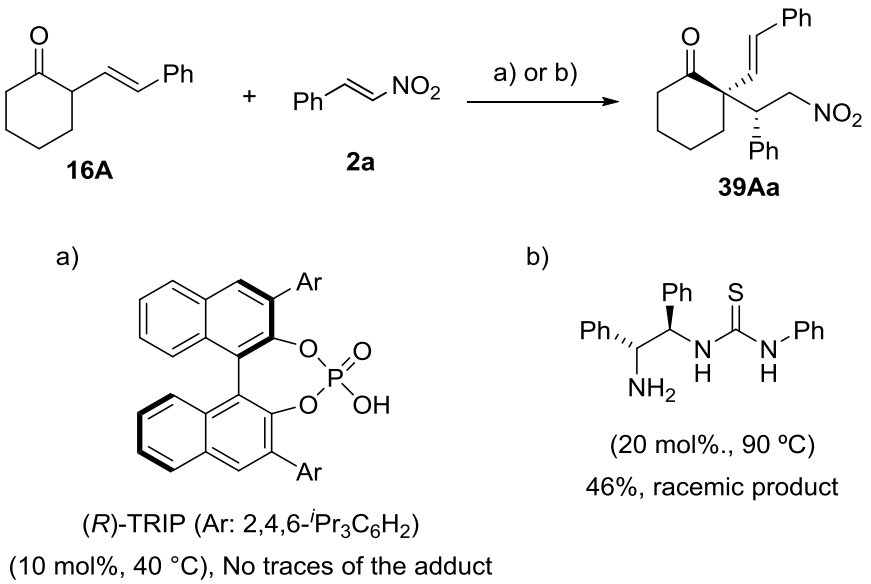


Figure 35. ORTEP diagram of compound **39Aa**.

Comparison of the efficiency of BB/H-bonding catalysis versus Brønsted acid and enamine catalysis for this transformation was, once again, informative. Control experiment with **16A** and **2a** in the presence of TRIP, a chiral phosphoric acid catalyst, showed no reaction progress at all, even upon heating at 40 °C. Similarly, no reaction was observed in the presence of the primary amine/thiourea catalyst shown in Scheme 48. In this latter case, upon heating the mixture at 90 °C for 16 h, 46% of isolated yield was obtained, but of essentially racemic product.

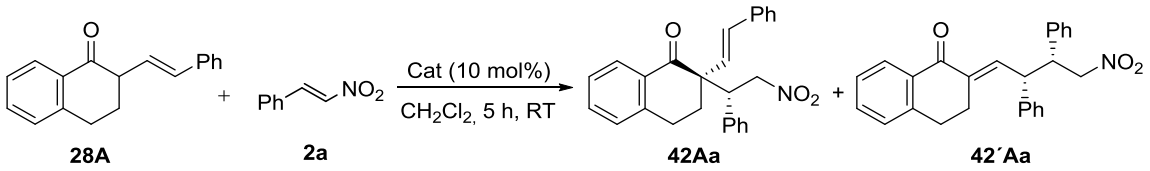


Scheme 48. Control experiments in the formation of adduct **39Aa** involving Brønsted acid and enamine based activation approaches.

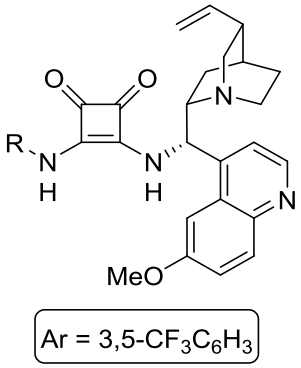
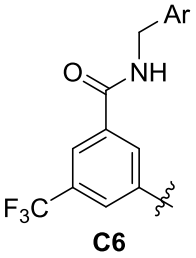
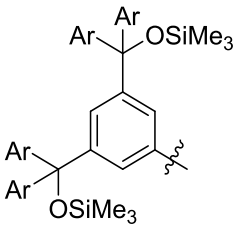
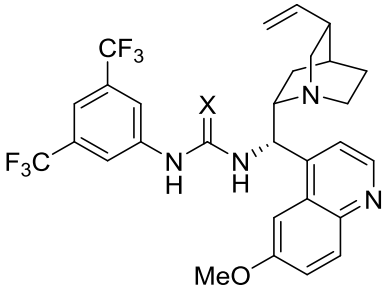
3.2.3.3. *Extension to benzo-fused cycloalkanones*

Paralelling the study with vinyl bis(sulfone), the scope of the catalytic reaction with nitroolefins was further extended to benzo-fused cycloalkanones. Initially, the reaction between **28A** and nitrostyrene **2a** was studied in the presence of a selection of bifunctional Brønsted base catalysts at room temperature. Surprisingly, when using benzo-fused α-alkenyl cyclohexanones, the γ-addition adduct was obtained predominantly with excellent enantioselectivity regardless the catalyst employed. For instance, catalysts with the squaramide moiety (**C1**, **C2**, **C6**, **C13** and **C14**) as well as thiourea (**C8**) and urea (**C9**) catalysts afforded γ adduct **42´Aa** in high *ee* value. However, the α/γ selectivity was variable depending on the catalyst employed. Catalysts bearing the squaramide moiety exhibited a superior α/γ ratio when compared to catalysts with other functionalities such as thiourea (**C8**) and urea (**C9**). Among them, catalyst **C1** as well as the bulky **C14** gave the best results in terms of yield, regio- and stereoselectivity (80% yield, α/γ 5:95, 99% *ee*).

Table 13. Catalyst screening for the reaction of **28A** with **2a**.



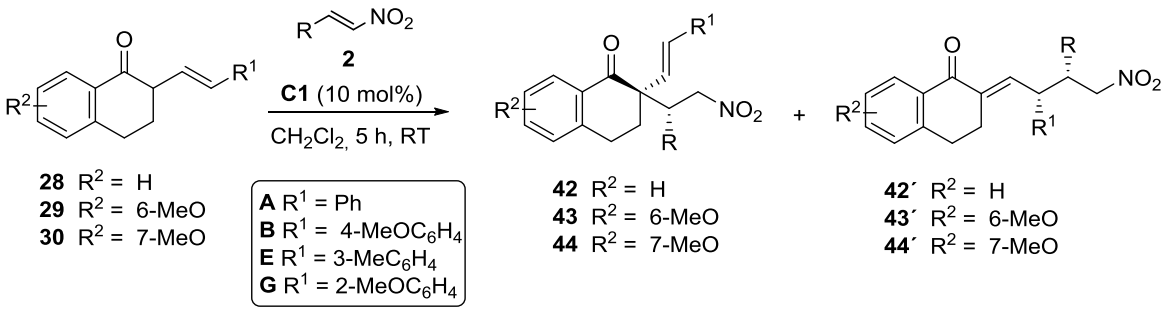
28A **2a** **42Aa** **42´Aa**

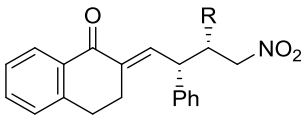
Cat		Yield (%)	α/β	*ee* (%)
 Ar = 3,5-$CF_3C_6H_3$	R:  **C1**	80	5:95	99
	 **C2**	75	18:82	97
	 **C6**	72	15:85	90
	 **C13**	69	15:85	97
	 **C14**	80	5:95	99
	**C8,** X = S	67	25:75	97
	C9, X = O	68	25:75	96

[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**28A**/**2a** molar ratio = 1:1.2). Yield of isolated γ product after column chromatography. α/γ ratio determined by ^{1}H NMR spectroscopy. *dr* = >20:1 in all cases. *ee* of major isomer determined by chiral HPLC.

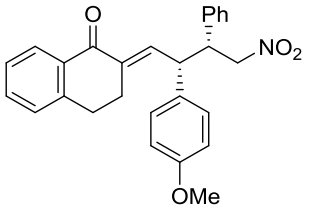
The scope of the reaction with various α-alkyliden 1-tetralones **28**–**30** and differently β-substituted nitroalkenes (**2b**–**n**) was studied. In every case, the γ-addition products **44´**–**46´** were obtained almost exclusively (Table 14). Remarkably, the respective α,β-unsaturated ketones were isolated as single diastereomers and in very high enantioselectivity. For instance, the reactions of **28A** with nitroolefins **2b**–**n** provided adducts **42´Ab–n** in good yield and 96% or higher *ee*. The reaction also worked well with the more challenging aliphatic nitroolefins **2l** and **2n** affording adducts **42´Al** and **42´An** with essentially perfect regio- and stereoselectivity. Equally good results were obtained with substrates bearing fused aromatic rings with substituents at various positions (adducts **43´Aa** and **44´Aa**) or different aryl groups at the olefinic moiety (adducts **42´Ba**, **42´Ea**, **42´Ga** and **42´Ge**). The products were isolated as stable white foams.

Table 14. Scope of the reaction of benzo-fused cycloalkanones with nitroolefins catalyzed by **C1**.

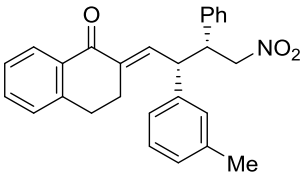




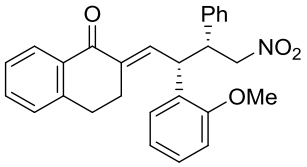
42´Ab	R = 4-$MeOC_6H_4$	76%, α/γ 5:95, 99% *ee*
42´Ac	R = 4-MeC_6H_4	81%, α/γ 5:95, 97% *ee*
42´Ad	R = 4-ClC_6H_4	77%, α/γ 5:95, 98% *ee*
42´Ah	R = 3-ClC_6H_4	79%, α/γ 5:95, 96% *ee*
42´Al	R = $CH_3(CH_2)_2$	69%, α/γ 5:95, 99% *ee*
42´An	R = C_6H_{11}	66%, α/γ 5:95, 98% *ee*



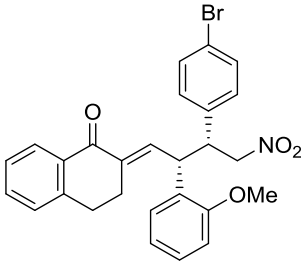
42´Ba
80%, α/γ 8:92, 98% *ee*



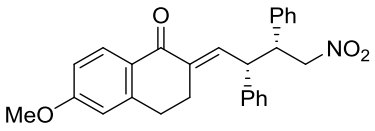
42´Ea
77%, α/γ >5:95, 97% *ee*



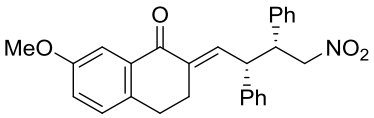
42´Ga
82%, α/γ >5:95, 99% *ee*



42´Ge (X-ray)
81%, α/γ 5:95, 98% *ee*



43´Aa
79%, α/γ 7:93, 99% *ee*



44´Aa
78%, α/γ 8:92, 97% *ee*

[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**28-30**/**2** molar ratio = 1:1.2). Yield of isolated γ product after column chromatography. α/γ ratio determined by ^1H NMR spectroscopy. *dr* = >20:1 in all cases. *ee* of major isomer determined by chiral HPLC.

The absolute configuration of γ adduct **42´Ge** was determined by single-crystal X-ray analysis (Figure 36) and for the remaining adducts it was established by assuming a uniform reaction mechanism. All adducts **42**–**44** exhibited positive optical rotations, which further support the assumption of homochirality of these series of adducts.

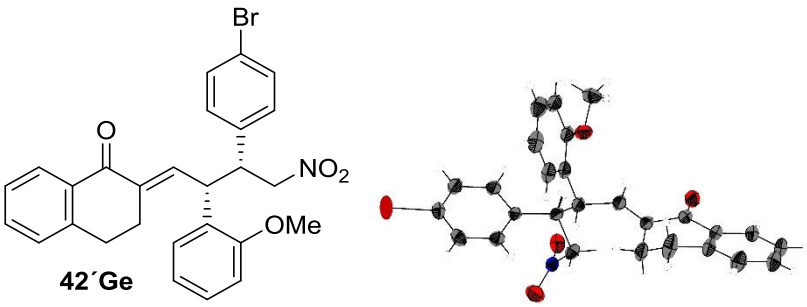


Figure 36. ORTEP diagram of compound **42´Ge**.

Based on the most widely accepted mode of concurrent activation of nucleophilic and electrophilic reactants in this type of bifunctional catalysis,[164] general stereomodel in Figure 37 would account for the main α-pathway reactivity pattern observed in reactions of transiently generated cyclic ketone dienolates with nitroolefins.

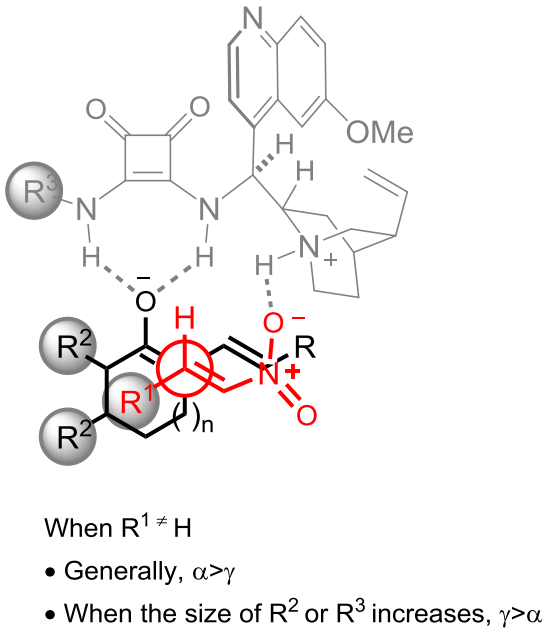


Figure 37. Proposed bifunctional activation model for the reaction of cyclic dienolates with nitroolefins.

This model may also be used to discuss the switch from the exclusive formation of α adduct to the formation of an increasing amount of γ product based on an increase of nonbonding interactions between R^3 and/or R^2 groups and the R^1 substituent of the nitroolefin owing to growth in size of such groups. While this model does not explain the γ-reactivity pathway observed for some donor/acceptor combinations, it may serve to discuss the factors that would destabilize it, and so, disfavor the α-reaction pathway. Thus, it has been observed experimentally that when moving to bulky catalysts such as **C13** and **C14** (see Table 11), increased nonbonding interactions may operate in the α-

reaction pathway owing to the size of R^3 group attached to the catalyst squaramide, presumably shifting the electrophile towards the γ position, hence explaining the observed preference of these catalysts for the γ-reaction pathway in the addition of α-alkenyl cycloalkanone **16A** to nitrostyrene **2a**. When benzo-fused α-alkenyl cycloalkanones ($R^2 \neq H$) are used in the reaction with nitroolefins, the steric hindrance of R^2 groups may increase blocking the α-position and making the γ-addition more accessible, regardless the catalyst employed, hence explaining the γ-selectivity of this particular type of substrates. It is worth mentioning that in the reaction of benzofused cycloalkanones with vinyl bis(sulfone) **3** the α product was obtained exclusively. This might be due to the small size of R^1 substituent minimizing nonbonding interactions with R^2 and R^3 groups, which may favor the γ-reaction pathway.

3.2.4. Aldol addition to formaldehyde

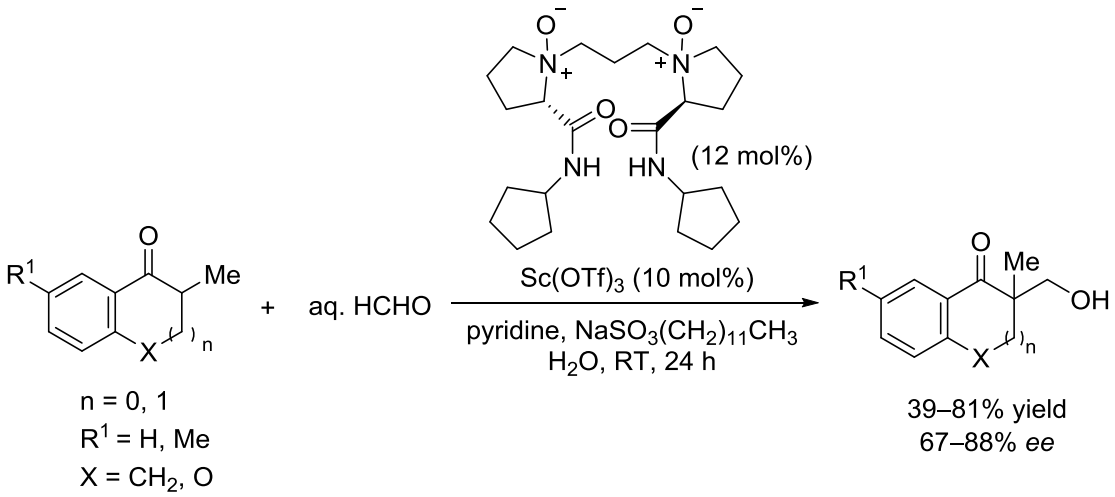
At this stage, the suitability of *in situ* generated dienolates to react with C-electrophile reagents other than Michael acceptors (e. g. vinyl sulfones, nitroolefins) was briefly explored. Thus, the utility of this catalytic activation was explored in the α-hydroxymethylation reaction as well in which formaldehyde would be the electrophilic reagent. The asymmetric hydroxymethylation of carbonyl compounds at their α-position employing formaldehyde as the C1 unit has been shown to be a useful method for the construction of chiral building blocks and some progress has been made in this area.[168] Nevertheless, the use of formaldehyde in direct asymmetric aldol reactions is relatively limited, presumably due to the special chemical properties of the electrophile, such as i) high reactivity and ii) the source of purely monomeric formaldehyde (traditionally exists as aqueous formaldehyde solution, i.e. formalin).[169a]

Some efforts have been focused on developing selective methodologies for the asymmetric aldol reactions using formaldehyde to install the hydroxymethyl group. Readily available aqueous formaldehyde has been successfully applied in a chiral-ligand scandium-catalyzed process, either with preformed enolates or directly from carbonyl compounds in organic or pure water as media.[168] An illustrative example of a direct version of the hydroxymethylation reaction of a variety of ketones using a scandium/chiral *N*-oxide ligand complex with *ee* values in the range of 67–88% is shown

[168] For a review on asymmetric aldol reactions with formaldehyde, see: S. Meninno, A. Lattanzi, *Chem. Rec.* **2016**, *16*, 2016–2030.

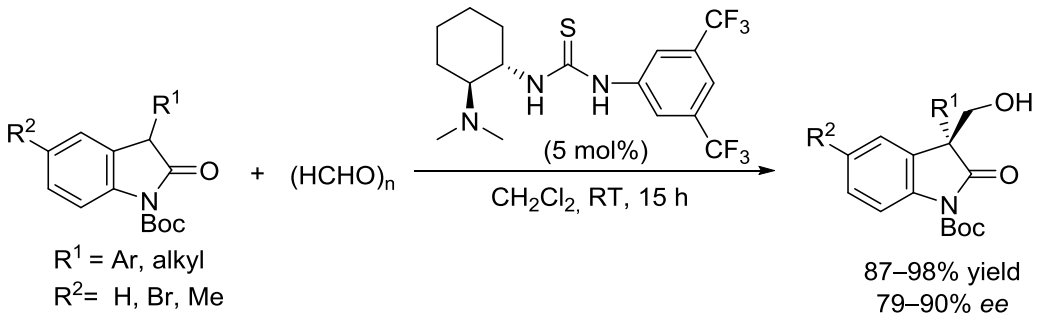
[169] a) X.-L Liu, Y.-H. Liao, Z.-J. Wu, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem*. **2010**, *75*, 4872–4875. b) S. De, M. K. Das, S. Bhunia, A. Bisai, *Org. Lett*. **2015**, *17*, 5922–5925.

in Scheme 49a.[170] Other systems, based on chiral bismuth[171] and zinc[172] Lewis acids, have been added to accomplish this goal with similar efficiency.



Scheme 49. Hydroxymethylation of cyclic ketones using a scandium/ chiral *N*-oxide ligand complex.

In the realm of organocatalysis, some examples have been developed using commercially available paraformaldehyde and a bifunctional amino thiourea catalyst.[169] Enantiomerically enriched 3,3-disubstituted 2-oxindoles were obtained in high yield and *ee* values in the range of 79–90% in the instance depicted in Scheme 50b.[169a] Paraformaldehyde was thought to serve as a C1 electrophile instead of formaldehyde because its polymeric structure allows the gradual release of monomeric formaldehyde under suitable reaction conditions. This slow release is favorable for keeping a low concentration of formaldehyde monomer in the reaction system so as to control its high reactivity.



Scheme 50. Hydroxymethylation of 2-oxindoles using a bifunctional amino thiourea catalyst.

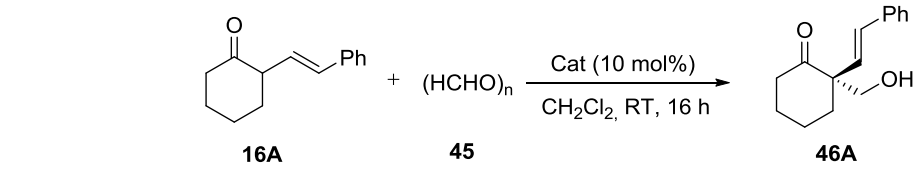
[170] S. Kobayashi, M. Kokubo, K. Kawasumi, T. Nagano, *Chem. Asian J.* **2010**, *5*, 490–492.
[171] S. Kobayashi, T. Ogino, H. Shimizu, S. Ishikawa, T. Hamada, K. Manabe, *Org. Lett.* **2005**, *7*, 4729–4731.
[172] a) M. Pasternak, J. Paradowska, M. Rogozinska, J. Mlynarski, *Tetrahedron Lett*. **2010**, *51*, 4088–4090. b) J. Paradowska, M. Pasternak, B. Gut, B. Gryzło, J. Mlynarski, *J. Org. Chem*. **2012**, *77*, 173–187.

Despite significant improvements have been achieved to perform this reaction catalytically, the substrate scope (with *ee* values tipically <90% in the formation of quaternary stereocenters) and synthetic applications for constructing more complex scaffolds are still limited.

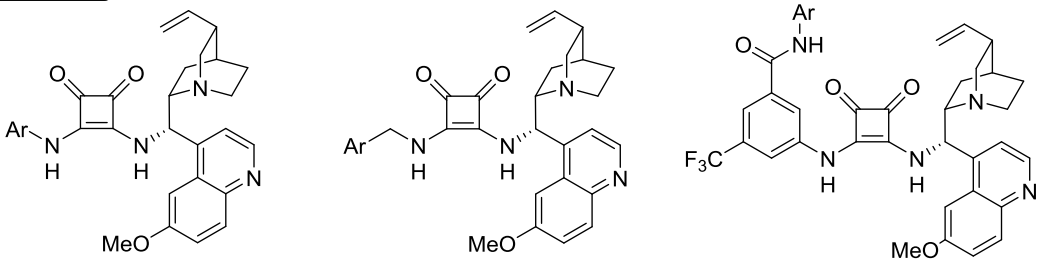
3.2.4.1. *Catalyst screening*

We started by screening a selection of Brønsted base catalysts bearing squaramide moiety for the reaction of cycloalkanone **16A** and paraformaldehyde (**45**). As shown in Table 15, all the catalysts afforded the α-adduct exclusively in moderate to good yields (59–87%) with the exception of catalyst **C2**, in which conversion of only 18% was achieved. In terms of enantioselectivity, catalysts **C1** and **C4** gave an acceptable 73% ee, while with bulky catalyst **C14** an enantiomeric excess of just 59% was obtained. Attempts to improve these results by changing the solvent to toluene, acetonitrile or tetrahydrofuran, resulted in lower *ee* values in the reaction with both catalysts **C1** and **C14**. We found again that in the presence of newly developed catalyst **C16** the product was isolated in good yield and enantioselectivity (89% *ee*) after 16-hour reaction. In order to improve the enantiocontrol of the reaction, the modified catalysts **C17** and **C18**, with the nitro group at *para*- and *ortho*- positions respectively, were prepared and examined. However, when *para*-substituted catalyst **C17** was employed the enantioselectivity worsened, whereas with *ortho*-substituted catalyst **C18** the reaction did not even work.

Table 15. Catalyst screening for the reaction of cycloalkanone **16A** with **45**.



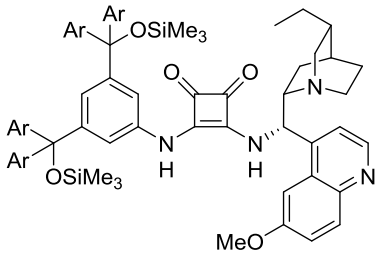
Ar = 3,5-$CF_3C_6H_3$



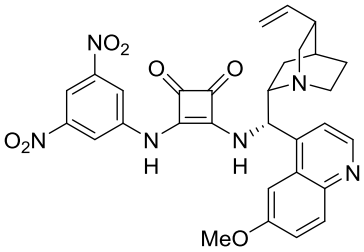
C1
63% yield, 73% *ee*

C2
18% conv, --% *ee*

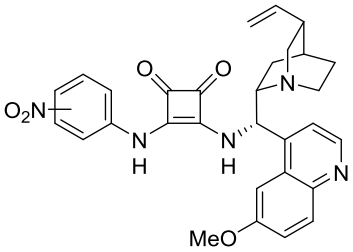
C4
59% yield, 73% *ee*



C14
74% yield, 59% *ee*



C16
79% yield, 89% *ee*



C17, 4-NO_2 87% yield, 70% *ee*
C18, 2-NO_2 NR

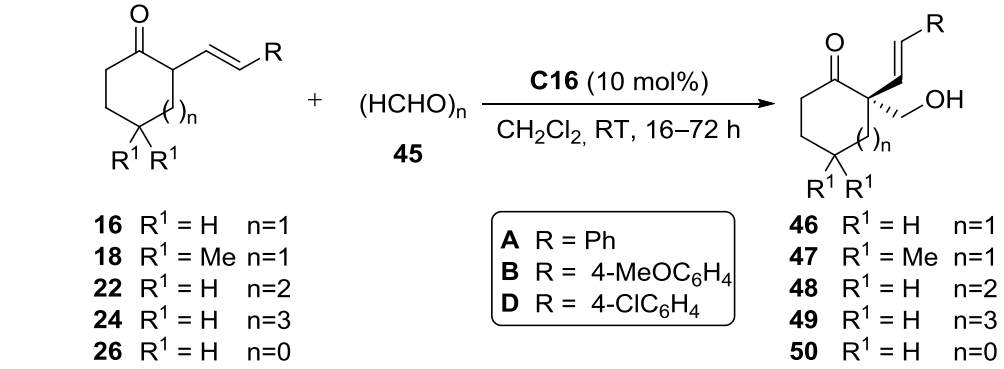
[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**16A**/**45** molar ratio = 1:10). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC.

3.2.4.2. *Reaction scope*

Then, the scope of suitable alkenyl cycloalkanone substrates was explored briefly with **C16** selected as the best catalyst (Table 16). It was observed that adducts **46**–**50** were formed in *ee´*s in the range of 89–93% *ee* irrespective of the cycloalkanone ring size achieving successful results for cyclohexanones (**46B**, **46D**, **47B**) as well as 5-, 7- and 8-membered cyclic ketones. Good yields and high enantioselectivities were obtained regardless the nature of the substituents at the aromatic ring of the cycloalkanone as the results leading to adducts **46B** and **47B** show. Furthermore, the method turned out to be equally effective with 4-substituted cycloalkanone **18B** which provided the corresponding product **47B** in good yield and enantioselectivity. In prospect, these results suggest that application of this Brønsted base/H-bonding strategy might be

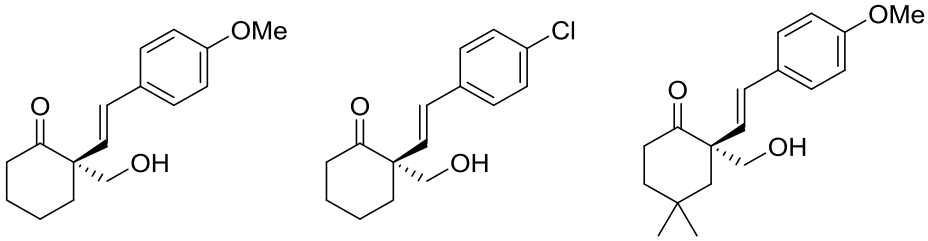
suitable to additional carbon electrophiles considerably broadening the pool of α,α-disubstituted cycloalkanones available until now.

Table 16. Scope of the reaction of α-alkenyl cycloalkanones with paraformaldehyde catalyzed by **C16**.



16 R^1 = H n=1
18 R^1 = Me n=1
22 R^1 = H n=2
24 R^1 = H n=3
26 R^1 = H n=0

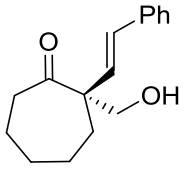
46 R^1 = H n=1
47 R^1 = Me n=1
48 R^1 = H n=2
49 R^1 = H n=3
50 R^1 = H n=0



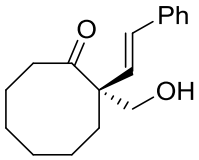
46B 48 h, 77% yield, 91% *ee*

46D 16 h, 75% yield, 89% *ee*

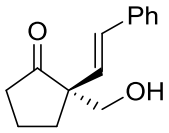
47B 48 h, 77% yield, 91% *ee*



48A 72 h, 77% yield, 91% *ee*



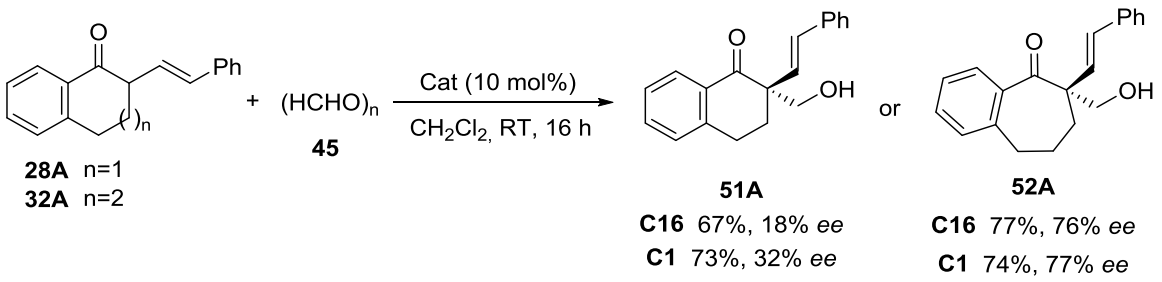
49A 72 h, 77% yield, 90% *ee*



50A 16 h, 74% yield, 93% *ee*

[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (ketone/**45** molar ratio = 1:10). Yield of isolated product after column chromatography. *ee* determined by chiral HPLC.

The suitability of this method for the α-hydroxymethylation of benzo-fused cycloalkanones was also investigated (Scheme 51). Surprisingly, the reaction of α-tetralone derivative **28A** with paraformaldehyde catalyzed by **C16** provided adduct **51A** in good yield but low enantioselectivity (18% *ee*), while changing the catalyst to **C1** lead to a little improvement (32% *ee*). The behavior of a 7-membered cycloalkanone was tested under the same reaction conditions leading to better results and adduct **52A** was obtained in 77% *ee* (with catalyst **C1**).



Scheme 51. Hydroxymethylation reaction of benzofused cycloalkanones **28A** and **32A**.

The absolute configuration of compound **46B** was determined by X-ray crystallographic analysis (Figure 38) and the configuration of remaining adducts was assigned by analogy and by assuming a uniform mechanism which was supported by the positive sign of the optical rotation values of all adducts **46**–**52**.

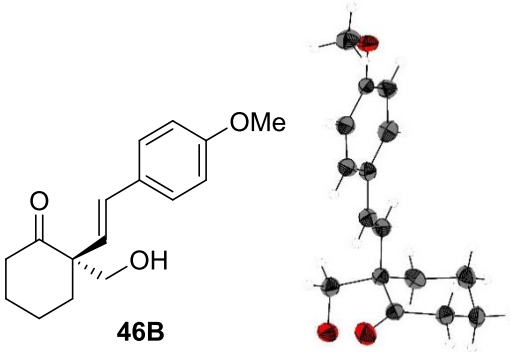


Figure 38. ORTEP diagram of compound **46B**.

It should be noted that the facial selectivity of the *in situ* generated dienolate against vinyl disulfone and nitroolefins is opposite to that against formaldehyde (note the opposite configuration at C_α of adduct **46B** when compared to **17A** and **39Aa**, Figure 39). The origin of this enantioreversal remains unknown yet, although it might be related to the large difference in size and π-extension between both types of electrophiles, i.e. Michael acceptors vs. formaldehyde.

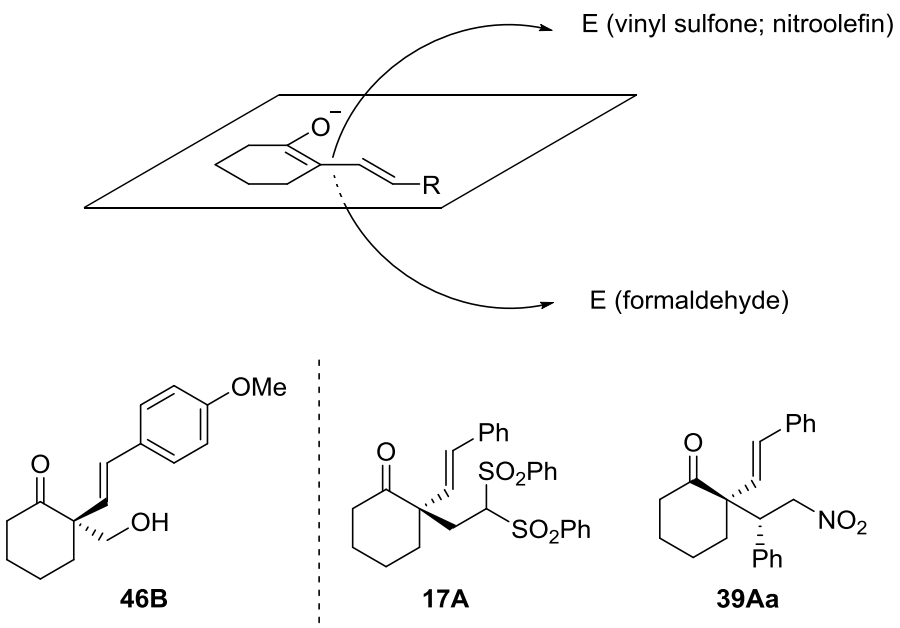


Figure 39. Divergent facial selectivity of transient dienolates against different electrophiles.

Chapter 4

Conclusions

4. Conclusions

New methodologies for the direct catalytic regio- and stereoselective α-functionalization of cyclic ketones have been developed.

Thus, β-tetralones and α-alkenyl cycloalkanones have been proved to be feasible ketone substrates for the Brønsted base-catalyzed asymmetric α-functionalizations enabling a route to enantioenriched all-carbon quaternary α-addition adducts.

In the case of β-tetralones functionalization, the first examples of catalytic regio- and stereoselective α-alkylation of both α-unsubstituted and α-substituted β-tetralones with Michael acceptors as well as *N*-Boc imines have been reported, leading to the formation of either a tri- or tetrasubstituted stereogenic carbon atom. Importantly, the reactions proceed with efficient α/α' site selectivity and enantioselectivity, with other aromatic ring-fused cycloalkanones being equally tolerated.

On the other hand, it has been demonstrated that bifunctional Brønsted base/H-bonding catalysis activation is able to generate dienolates from α-branched allylic ketones (α-alkenyl cycloalkanones) and induce their reaction with various carbon electrophiles to occur predominantly at C_α. Under these catalytic conditions, the reaction of α-branched cyclic ketone dienolates with vinyl bis(sulfone), nitroolefins or formaldehyde afforded the corresponding all-carbon quaternary α-addition adducts in a regio- and stereoselective manner. Remarkably, the approach could be extended to benzo-fused cycloalkanones, but the addition of such nucleophiles to nitroolefins diverts providing the corresponding γ-adducts predominantly. This observation corroborates that the α/γ selectivity of dienolate systems is multivariable.

Chapter 5

Experimental Section

5. Experimental Section

5.1. Materials and Techniques

5.1.1. Reagents and solvents

Reagents were purchased from common commercial suppliers such as Aldrich, Across, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc., stored as specified by the manufacturer and used without previous purification unless otherwise stated.

Triethylamine, DBU and DIPEA were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at –30 °C under nitrogen.

Anhydrous solvents were dried following established procedures.[173] Dichloromethane was dried over CaH_2, diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder 150 mesh, pore size 58 Å, basic Sigma Aldrich) columns.

5.1.2. General experimental

All non-aqueous reactions were performed under inert atmosphere using oven-dried glassware and were magnetically stirred. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Heat requiring reactions were performed using a hotplate with a sand bath and condenser. Reactions requiring low temperatures were performed using cooling bath circulators *Huber* T100E and acetone or isopropanol baths.

Organic layers washed with aqueous phases were dried over $MgSO_4$ or Na_2SO_4 and filtered through cotton.

Organic solvents were evaporated under reduced pressure using rotavapors Büchi R-100, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller. For the complete removal of solvents vacuum pump Telstar Top-3 (P ≈ 0.5 mmHg) was employed.

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[173] W. L. F. Armanego, D. D. Perrin, *Purification of laboratory Chemicals,* 3rd Edition Butterworth Heinemann, Oxford, **1988**.

5.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Biolock lamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1g) in 100 ml of water (limited lifetime), followed by heating.

Purification by column chromatography was performed on ROCC 60 silica gel 40-63 µm as stationary phase and a suitable mixture of solvents (typically hexane: ethyl acetate, pentane: diethyl ether or dichloromethane: methanol) as eluent.

5.1.4. Optical rotation

Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg.cm^2.g^{-1}; concentrations (*c*) are quoted in g/100 mL; $_D$ refers to the D-line of sodium (589 nm); temperatures (T) are given in degree Celsius (°C).

5.1.5. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected.

5.1.6. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for $_1$H, 75 MHz for $_{13}$C) spectrometer, Bruker 400 spectrometer (400 MHz for $_1$H, 100 MHz for $_{13}$C) Varian 400 MR (400 MHz for $_1$H, 100 MHz for $_{13}$C) or Bruker AV-500 spectrometer (500 MHz for $_1$H, 125 MHz for $_{13}$C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, $_1$H (δ = 7.26) and $_{13}$C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (HZ).

MestrReNova Mnova 11.0 program was used to process and edit the registered spectra.

5.1.7. Mass spectra

Ms spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model) on a UPLC-DAD-QTOF, Ultra High Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU).

5.1.8. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film.

5.1.9. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters-600E (equipped with 2996 and 2998 photodiode array UV detector) employing Daicel columns (4.6 x 250 mm, 5 μm particle size).

5.1.10. X-Ray diffraction analysis

The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using difractometers for monocrystals.

5.2. Preparation of Catalysts

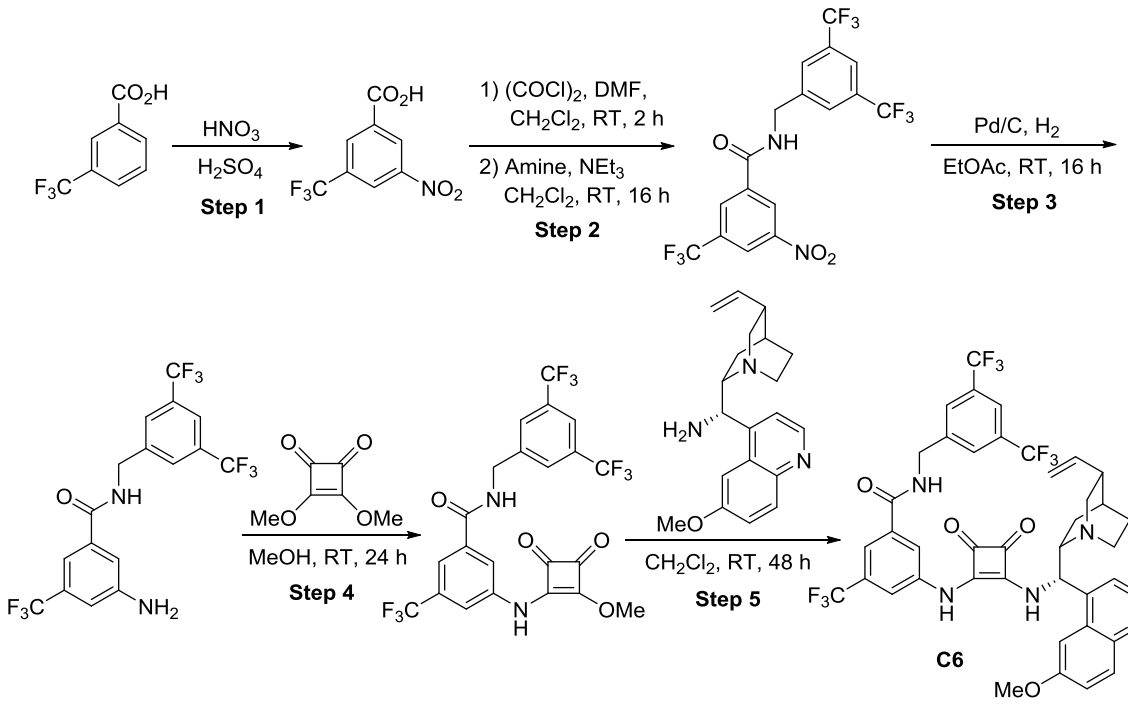
9-amino-(9-deoxy)epiquinine[174] and catalysts **C1**,[175] **C2**,[176] **C3**,[177] **C4**,[177] **C5**,[177] **C7**,[177] **C8**,[178] **C9**,[179] **C10**,[180] **C11**,[181] **C12**[182], **C13**,[183] **C14**,[177] **C15**,[184] and **C19**[185] were prepared following

[174] M. S. Manna, S. Mukherjee, *Chem. Eur. J.* **2012**, *18*, 15277–15282.
[175] W. Yang, D.-M. Du, *Org. Lett*. **2010**, *12*, 5450–5453.
[176] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416−14417.
[177] a) I. Urruzuno, Doctoral Thesis, *Organocatalytic α-Functionalization of Carbonyl Compounds: Chemo-, Regio- and Stereoselectivity* EHU/UPV, **2018**. b) a) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063. c) I. Urruzuno, O. Mugica, G. Zanella, S. Vera, E. Gomez-Bengoa, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2019**, 25, 9701−9709.
[178] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967–1969.
[179] K. Greenaway, P. Dambruoso, A. Ferrali, A. J. Hazelwood, F. Sladojevich, D. J. Dixon, *Synthesis* **2011**, *12*, 1880–1886.

the procedures described in the literature. Catalysts **C6** and **C16**-**C18** were prepared starting from (*S,S*)-9-deoxy-9-epiaminoquinine and the corresponding squaric amide-ester.

5.2.1. Preparation of catalyst C6[186]

Catalyst **C6** was prepared following the same procedure as for catalysts **C3**, **C4**, **C5** and **C7**:



Step 1: To a solution of 3-trifluoromethylbenzoic acid (2 g, 10 mmol) in concentrated sulfuric acid (10 mL) was added nitric acid (2 mL) at 0 °C over 15 min. The mixture was stirred at 35 °C for 3 h, and slowly poured onto ice. The precipitate was filtrated with water (100 mL), and dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water, and dried, and the solvent was evaporated under reduced pressure

[180] S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.
[181] Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.
[182] H. Konishi, T. Y. Lam, J. P. Malerich, V. H. Rawal, *Org. Lett*. **2010**, *12*, 2028–2031.
[183] F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed*. **2014**, *53*, 2628–2632.
[184] T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 2896–2899.
[185] Procedure adapted from: a) R. C. Pratt, B. G. Lohmeijer, D. A. Long, P. N. Lundberg, A. P. Dove, H. B. Li, C. G. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules*, **2006**, *39*, 7863–7871. b) S. M. Opalka, J. L. Steinbacher, B. A. Lambiris, D. T. McQuade. *J. Org. Chem.* **2011**, *76*, 6503–6571.
[186] The data for this compound is also described in Ref. 177a.

to give 3-nitro-5-(trifluoromethyl) benzoic acid. Yield: 91% (2.14 g, 9.12 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.74 (s, 1H), 8.69 (s, 1H).

Step 2: Oxalyl chloride (0.47 mL, 5.5 mmol, 1.1 equiv.) was added to a suspension of 3-nitro-5-(trifluoromethyl)benzoic acid (1.16 g, 5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) at 0 ^oC under nitrogen atmosphere. DMF (1 drop) was then added and the mixture was allowed to stir at room temperature for 2 h, observing the complete dissolution of the solid. The resulting crude was concentrated under reduced pressure and slowly added to a solution of (3,5-bis(trifluoromethyl)phenyl)methanamine (1.22 g, 5 mmol, 1 equiv.) and triethylamine (2.1 mL, 15 mmol, 3 equiv.) in CH_2Cl_2 (15 mL) at 0 ^oC under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and EtOAc (30 mL) was added. The organic phase was washed with aqueous HCl (1M) (2 x 30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The obtained amide was pure enough to be used in the next step without further purification. Quantitative yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.69 (s, 1H), 8.60 (s, 1H), 8.00 (s, 2H), 7.89 (s, 1H), 4.77 (s, 2H).

Step 3: To a solution of the previous benzamide (2.30 g, 5 mmol) in EtOAc (15 mL) under inert atmosphere, Pd/C was added (230 mg, Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. After that the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product. Quantitative yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.32–7.27 (m, 2H), 7.02 (s, 1H), 6.64 (s, 1H), 4.75 (d, *J*= 6.1 Hz, 2H), 4.04 (bs, 2H).

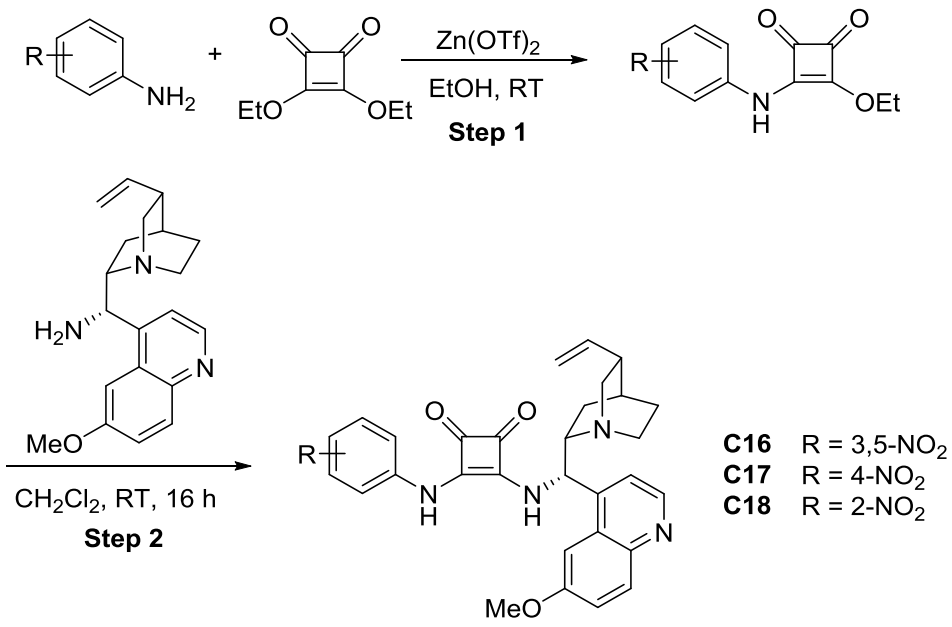
Step 4:[187] To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (355 mg, 2.5 mmol, 1 equiv.) in MeOH (5 mL) was added the amine obtained in the previous step (354 mg, 2.5 mmol, 1 equiv.) at room temperature. The mixture was stirred at room temperature for 24 h. The white precipitate was filtered and washed with Et_2O. The resulting white solid was dried in vacuo to give the desired product as a white solid. Yield: 86% (1.16 g, 2.2 mmol). **^{1}H NMR** (300 MHz, Acetone-d_6) δ δ 9.89 (s, 1H), 8.72 (s, 1H), 8.26 (s, 1H), 8.09 (s, 3H), 7.95 (s, 2H), 4.86 (d, *J*= 5.9 Hz, 2H), 4.47 (s, 3H).).

[187] Adapted from: Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao, V. H. Rawal, *Chem. Commun*. **2010**, *46*, 3004-3006.

Step 5: To a suspension of squaric ester monoamide prepared above (270 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2.5 mL) was added (*R,R*)-9-deoxy-9-epiaminoquinine (162 mg, 0.55 mmol, 1.1 equiv.) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 days. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) to obtain a yellow solid. Decomposition at 218 °C. Yield: 84% (349 mg, 0.42 mmol). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.38 (t, *J*= 5.9 Hz, 1H), 8.80 (d, *J*= 4.5 Hz, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 8.02 (s, 2H), 8.01–7.94 (m, 2H), 7.92 (t, *J*= 1.8 Hz, 1H), 7.84 (s, 1H), 7.75 (d, *J*= 2.7 Hz, 1H), 7.66 (d, *J*= 4.6 Hz, 1H), 7.44 (dd, *J*= 9.2, 2.5 Hz, 1H), 5.97 (ddd, *J*= 17.6, 10.2, 7.7 Hz, 2H), 5.15–4.89 (m, 2H), 4.66 (d, *J*= 5.8 Hz, 2H), 3.95 (s, 3H), 3.33–3.08 (m, 3H), 2.81–2.55 (m, 2H), 2.34–2.18 (m, 1H), 1.69–1.40 (m, 4H), 0.77–0.59 (m, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 184.6, 180.0, 168.4, 164.8, 163.1, 157.9, 147.8, 144.3, 143.1, 142.8, 142.1, 140.1, 136.0, 131.5 (q), 130.5 (q), 130.2, 128.3, 128.3, 127.4, 125.5, 125.2, 121.9, 121.6, 120.9, 120.8, 120.8, 120.7, 117.3, 117.3, 117.1, 114.4, 101.5, 58.9, 55.7, 42.2, 27.3, 26.0. **MS** (ESI, m/z): calculated for $C_{41}H_{35}N_5O_4F_9$ ($M+H^+$), 832.2545; found, 832.2559.

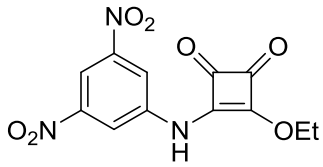
5.2.2. Preparation of catalysts C16–C18

Catalysts **C16**–**C18** were prepared according to the following procedure:



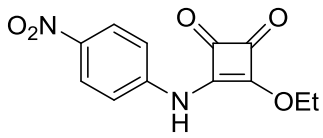
Step 1:[188] To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (0.09mL, 0.6 mmol, 1.2 equiv.) and zinc trifluoromethanesulfonate (18 mg, 0.05 mmol, 10 mol%) in ethanol (1.5 mL) at room temperature was added the corresponding aniline (0.5 mmol, 1.0 equiv). The mixture was allowed to stir at room temperature until complete conversion of the starting material was observed by TLC analysis. A yellow precipitate was formed, which was filtered and washed with ethanol to obtain the desired product.

3-((3,5-Dinitrophenyl)amino)-4-ethoxycyclobut-3-ene-1,2-dione



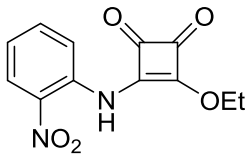
The title compound was obtained starting from 3,5-dinitroaniline (91 mg, 0.5 mmol, 1 equiv.). Yellow solid. Yield: 66% (96 mg, 0.330 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.80 (t, J = 1.9 Hz, 1H), 8.62 (d, J = 1.9 Hz, 2H), 5.02 (q, J = 7.1 Hz, 2H), 3.76 (dd, J = 12.5, 5.4 Hz, 1H), 1.30 – 1.24 (m, 3H).

3-Ethoxy-4-((4-nitrophenyl)amino)cyclobut-3-ene-1,2-dione



The title compound was obtained starting from 4-nitroaniline (69 mg, 0.5 mmol, 1 equiv.). Yellow solid. Yield: 69% (90 mg, 0.345 mmol). The NMR spectra match the data found in the literature.[188] **^{1}H NMR** (300 MHz, DMSO-d6) δ 11.22 (s, 1H), 8.25 (d, J = 9.2 Hz, 2H), 7.61 (d, J = 9.2 Hz, 2H), 4.83 – 4.80 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H).

3-Ethoxy-4-((2-nitrophenyl)amino)cyclobut-3-ene-1,2-dione



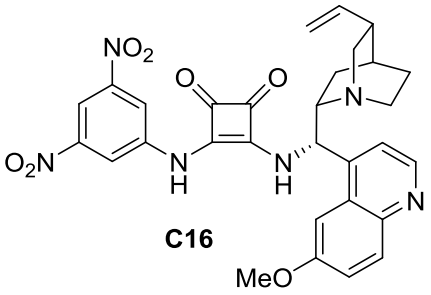
The title compound was obtained starting from 2-nitroaniline (69 mg, 0.5 mmol, 1 equiv.). Yellow solid. Yield: 19% (25 mg, 0.095 mmol). The NMR spectra match the data found in the literature.[189] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.24 (ddd, J = 23.7, 8.5, 1.4 Hz, 2H), 7.74 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.24 (ddd, J = 8.5, 7.2, 1.2 Hz, 1H), 4.93 (q, J = 7.1 Hz, 2H), 1.58 (t, J = 7.1 Hz, 3H).

Step 2: To a solution of the squaric ester monoamide prepared above (0.2 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) was added 9-amino-(9-deoxy)epiquinine (78 mg, 0.24 mmol, 1.2 equiv.) and the reaction mixture was stirred for 16 h at room temperature. The solvent

[188] A. Rostami, A. Colin, X. Yu Li, M. G. Chudzinski, A. J. Lough, M. S. Taylor, *J. Org. Chem.* **2010**, *75*, 3983–3992.
[189] C. Jin, M. Zhang, C. Deng, Y. Guan, J. Gong, D. Zhu, Y. Pan, J. Jiang, L. Wang, *Tetrahedron Letters*, **2013**, *54*, 796–801.

was evaporated, and the crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH) affording the pure catalyst.

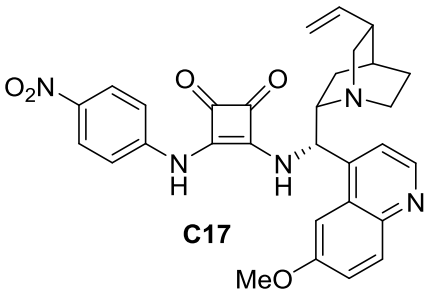
3-((3,5-Dinitrophenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C16)



C16

The title compound was obtained starting from 3-ethoxy-4-((3,5-dinitrophenyl)amino)cyclobut-3-ene-1,2-dione (59 mg, 0.20 mmol, 1 equiv.) and (*S,S*)-9-deoxy-9-epiaminoquinine (78 mg, 0.24 mmol, 1.2 equiv.). Brown solid. M.p. = decomposed before melting. Yield: 91% (106 mg, 0.182 mmol). $[\alpha]_D^{23}$ = –25.3° (*c* = 0.25, DMSO). **^{1}H NMR** (500 MHz, DMSO-d6, 80 °C) δ 8.80 (d, J = 4.5 Hz, 1H), 8.55 (d, J = 2.0 Hz, 2H), 8.36 (d, J = 1.9 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 2.7 Hz, 1H), 7.62 (d, J = 4.6 Hz, 1H), 7.44 (dd, J = 9.2, 2.6 Hz, 1H), 6.04 (d, J = 10.8 Hz, 1H), 5.95 (ddd, J = 17.5, 10.4, 7.3 Hz, 1H), 5.11 – 5.00 (m, 2H), 3.98 (s, 3H), 3.54 (s, 1H), 3.39 – 3.23 (m, 3H), 2.85 – 2.75 (m, 2H), 2.36 (s, 1H), 1.67 – 1.47 (m, 4H), 0.78 (dd, J = 13.6, 7.3 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d6, 80 °C) δ 184.7, 180.2, 168.8, 162.3, 157.6, 148.5, 147.3, 144.1, 142.4, 141.4, 131.2, 127.0, 121.3, 119.5, 117.4, 114.0, 110.3, 101.6, 59.0, 55.4, 55.2, 40.1, 39.0, 38.5, 26.8, 26.7, 25.4. **MS** (ESI, m/z): calculated for $C_{30}H_{29}N_6O_7$ ($M + H^+$), 585.2098; found, 585.2100.

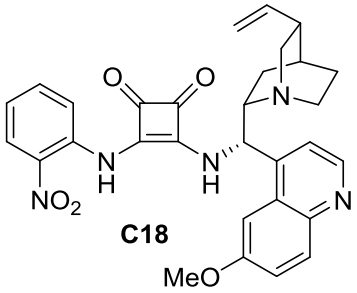
3-(((*S*)-(6-Methoxyquinolin-4-yl)((1S,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((4-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (C17)



C17

The title compound was obtained starting from 3-ethoxy-4-((4-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (52 mg, 0.20 mmol, 1 equiv.) and (*S,S*)-9-deoxy-9-epiaminoquinine (78 mg, 0.24 mmol, 1.2 equiv.). Orange solid. M.p. = 180–185 °C. Yield: 68% (73 mg, 0.136 mmol). $[\alpha]_D^{23}$ = –113.5° (*c* = 0.25, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.74 – 8.69 (m, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.85 – 7.73 (m, 3H), 7.61 – 7.58 (m, 1H), 7.42 (dd, J = 9.1, 2.2 Hz, 1H), 7.07 – 7.02 (m, 2H), 6.29 (s, 1H), 5.89 – 5.78 (m, 1H), 5.02 (t, J = 13.1 Hz, 2H), 3.97 (s, 3H), 3.79 – 3.71 (m, 1H), 3.54 – 3.44 (m, 1H), 3.22 – 3.13 (m, 1H), 2.89 – 2.76 (m, 2H), 2.38 – 2.30 (m, 1H), 1.78 – 1.57 (m, 4H), 1.26 (d, J = 7.1 Hz, 1H), 0.91 – 0.84 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 184.0, 181.0, 170.1, 162.2, 158.8, 147.6, 144.8, 143.8, 143.0, 142.5, 140.6, 131.8, 127.8, 125.1, 122.3, 119.2, 118.2, 115.3, 101.4, 60.2, 55.9, 55.6, 54.0, 41.0, 39.1, 29.7, 27.3, 25.9. **MS** (ESI, m/z): calculated for $C_{30}H_{30}N_5O_5$ ($M + H^+$), 540.2247; found, 540.2249.

3-(((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((2-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (C18)



C18

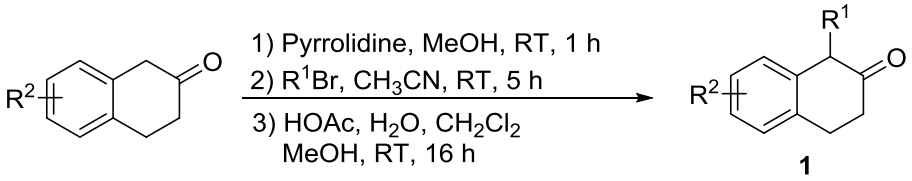
The title compound was obtained starting from 3-ethoxy-4-((2-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (52 mg, 0.20 mmol, 1 equiv.) and (*S,S*)-9-deoxy-9-epiaminoquinine (78 mg, 0.24 mmol, 1.2 equiv.). Brown solid. M.p. = 198–202 °C. Yield: 72% (78 mg, 0.144 mmol). $[\alpha]_D^{23}$ = –126.3° (*c* = 0.25, MeOH). **^{1}H NMR** (300 MHz, MeOD-d4) δ 8.75 (d, J = 4.7 Hz, 1H), 8.13 (dd, J = 8.4, 1.5 Hz, 1H), 7.97 (d, J = 9.3 Hz, 1H), 7.89 (d, J = 2.7 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.50 – 7.44 (m, 1H), 7.18 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 6.36 (d, J = 11.0 Hz, 1H), 5.97 (ddd, J = 17.4, 10.3, 7.4 Hz, 1H), 5.14 – 5.03 (m, 2H), 4.03 (s, 3H), 3.63 – 3.47 (m, 3H), 3.40 – 3.33 (m, 1H), 2.90 – 2.77 (m, 2H), 2.48 – 2.39 (m, 1H), 1.74 – 1.60 (m, 4H), 0.74 (dd, J = 13.1, 7.4 Hz, 1H). **^{13}C NMR** (75 MHz, MeOD-d4) δ 187.7, 182.1, 171.7, 164.3, 160.5, 148.4, 145.5, 145.3, 142.5, 138.5, 136.3, 135.3, 131.7, 129.5, 126.8, 124.5, 124.3, 120.6, 115.2, 102.1, 61.1, 57.0, 56.7, 54.9, 41.8, 40.6, 28.8, 28.4, 27.3. **MS** (ESI, m/z): calculated for $C_{30}H_{30}N_5O_5$ ($M + H^+$), 540.2247; found, 540.2249.

5.3. Experimental Section of Chapter 2

5.3.1. General procedure for the synthesis of *rac*-1-substituted β-tetralones 1

β-tetralones **1B-G** have not been previously reported. They were prepared according to the procedure described in the literature.[190] The data for these compounds were also described in Ref. 177a.

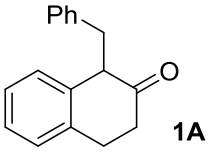
[190] M. A. Youngman, N. M. Willard, S. L. Dax, J. J. McNally, *Synth. Commun.* **2003**, *33*, 2215–2227.



1A	$R^1 = CH_2Ph$	$R^2 = H$
1B	$R^1 = CH_2C{\equiv}CH$	$R^2 = H$
1C	$R^1 = CH_2CHC(CH_3)_2$	$R^2 = H$
1D	$R^1 = CH_2CN$	$R^2 = H$
1E	$R^1 = CH_2Ph$	$R^2 = 6\text{-Cl}$
1F	$R^1 = CH_2CHC(CH_3)_2$	$R^2 = 6\text{-OMe}$
1G	$R^1 = CH_2Ph$	$R^2 = 7\text{-OMe}$

Pyrrolidine (0.46 mL, 6 mL, 1.2 equiv.) was added to a solution of the corresponding β-tetralone (5 mmol, 1 equiv.) in MeOH under argon and the resulting mixture was stirred for 1 h at room temperature, observing the precipitation of the enamine. The solvent was evaporated and 1,2-dichloroethane (10 mL) was added and evaporated to eliminate the excess pyrrolidine. The residue was dissolved in acetonitrile (10 mL) and the corresponding alkyl bromide (6 mmol, 1.2 equiv.) was added. The resulting solution was stirred at room temperature for 5 h and the solvent was eliminated under reduced pressure. The obtained crude was dissolved in a mixture of dichloromethane (7 mL), water (7 mL), methanol (15 mL) and acetic acid (1 mL) and the mixture was stirred at room temperature overnight. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The corresponding products were purified by flash column chromatography (hexane/EtOAc 90:10).

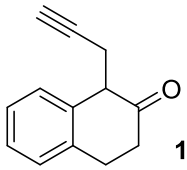
1-Benzyltetralone (1A)



1A

The adduct was obtained following the general procedure. Yellow oil. Yield: 68% (803 mg, 3.4 mmol). Spectroscopic data were coincident with the previously reported.[190] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22–7.08 (m, 6H), 6.99–6.86 (m, 3H), 3.74 (t, *J*= 6.4 Hz, 1H), 3.23 (d, *J*= 2.8 Hz, 1H), 3.21 (d, *J*= 1.9 Hz, 1H), 2.90–2.75 (m, 1H), 2.69–2.39 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 138.1, 136.9, 136.4, 129.4, 128.5, 128.1, 127.6, 126.8, 126.6, 126.4, 55.0, 39.0, 38.3, 27.2.

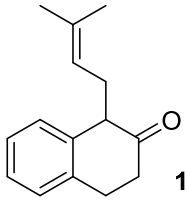
1-(Prop-2-yn-1-yl)-tetralone (1B)



1B

The adduct was obtained following the general procedure. Yellow oil. Yield: 70% (645 mg, 3.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 4H), 3.64 (m, 1H), 3.16–3.06 (m, 2H), 3.01–2.78 (m, 3H), 2.73–2.50 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.9, 137.3, 135.3, 127.8, 127.2, 127.2, 127.1, 81.7, 70.4, 51.5, 37.8, 27.9, 19.4. **MS** (ESI, m/z): calculated for $C_{13}H_{13}O$ ($M + H^+$), 185.0966; found, 185.0958.

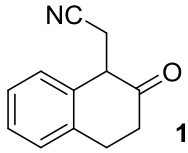
1-(3-Methylbut-2-en-1-yl)-tetralone (1C)



1C

The adduct was obtained following the general procedure. Yellow oil. Yield: 82% (879 mg, 4.1 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24–7.11 (m, 4H), 5.06 (m, 1H), 3.43 (t, *J*= 6.8 Hz, 1H), 3.15 (m, 1H), 3.01 (m, 1H), 2.59 (m, 4H), 1.65 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.5, 137.2, 136.6, 134.3, 128.3, 127.8, 126.8, 126.7, 120.5, 53.8, 37.9, 30.8, 27.9, 25.8, 17.7. **MS** (ESI, m/z): calculated for $C_{15}H_{19}O$ ($M + H^+$), 215.1436; found, 215.1433.

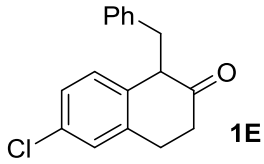
2-(2-Oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (1D)



1D

The adduct was obtained following the general procedure. Yellow oil. Yield: 43% (394 mg, 2.1 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 4H), 3.85–3.80 (m, 1H), 3.15–2.98 (m, 4H), 2.80–2.70 (m, 1H), 2.53 (ddd, *J*= 17.6, 8.7, 6.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 207.7, 137.3, 133.1, 128.2, 128.0, 127.7, 125.8, 118.3, 48.9, 37.2, 27.9, 16.9. **MS** (ESI, m/z): calculated for $C_{13}H_{13}O$ ($M + H^+$), 185.0966; found, 185.0958.

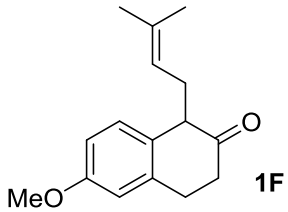
1-Benzyl-6-chlorotetralone (1E)



1E

The adduct was obtained following the general procedure. Yellow oil. Yield: 56% (758 mg, 2.8 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20–7.15 (m, 3H), 7.15–7.10 (m, 2H), 6.87 (dd, *J*= 6.4, 3.1 Hz, 2H), 6.82 (d, *J*= 7.9 Hz, 1H), 3.70 (t, *J*= 6.4 Hz, 1H), 3.22–3.16 (m, 2H), 2.83–2.74 (m, 1H), 2.62–2.54 (m, 1H), 2.53–2.40 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.4, 138.6, 137.7, 134.9, 132.5, 130.0, 129.3, 128.2, 127.7, 126.7, 126.6, 54.5, 39.2, 37.9, 27.0. **MS** (ESI, m/z): calculated for $C_{17}H_{19}OCl$ ($M + H^+$), 271.0890; found, 271.0895.

6-Methoxy-1-(3-methylbut-2-en-1-yl)-tetralone (1F)

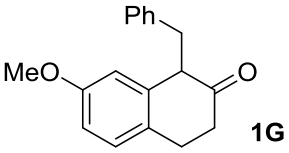


1F

The adduct was obtained following the general procedure. Yellow oil. Yield: 46% (561 mg, 2.3 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.86–6.65 (m, 3H), 5.04 (t, *J*= 7.3 Hz, 1H), 3.79 (s, 3H),

3.36 (t, *J*= 6.6 Hz, 1H), 3.17–3.02 (m, 1H), 3.02–2.87 (m, 1H), 2.67–2.40 (m, 4H), 1.63 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.5, 158.2, 137.7, 134.0, 129.1, 120.5, 113.1, 112.1, 55.2, 52.9, 37.7, 30.8, 28.0, 25.6, 17.6. **MS** (ESI, m/z): calculated for $C_{15}H_{19}O_2$ (M + H^+), 231.1385; found, 231.1372. .

1-Benzyl-7-methoxytetralone (1G)

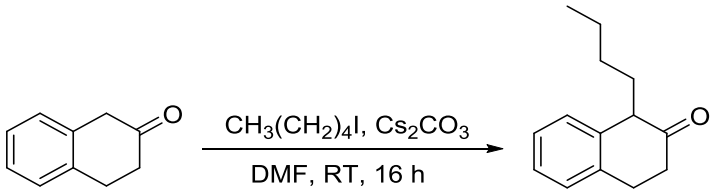


1G

The adduct was obtained following the general procedure. Yellow oil. Yield: 60% (799 mg, 3.0 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25–7.10 (m, 3H), 7.05 (d, *J*= 8.3 Hz, 1H), 6.92 (dd, *J*= 6.6, 2.9 Hz, 2H), 6.73 (dd, *J*= 8.3, 2.6 Hz, 1H), 6.40 (d, *J*= 2.6 Hz, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 3.29–3.08 (m, 2H), 2.87–2.73 (m, 1H), 2.69–2.35 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 158.2, 138.1, 137.5, 129.4, 128.8, 128.6, 128.1, 126.4, 113.6, 112.7, 55.2, 39.1, 38.5, 26.4. **MS** (ESI, m/z): calculated for $C_{18}H_{19}O_2$ (M + H^+), 167.1385; found, 167.1392.

5.3.2. Preparation of 1-butyltetralone 1I

The title compound **1I** was synthesized according to the following procedure described in the literature:[191]



1I

A solution of 2-tetralone (1.32 mL, 10 mmol, 1.5 equiv.) in dry DMF (3 mL mL) was added dropwise to a degassed suspension of dried cesium carbonate (5.7 g, 17.5 mmol, 2.65 equiv.) in DMF (5 mL). 1-Iodobutane (0.75 mL, 6.6 mmol, 1 equiv.) was then added and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was poured into aqueous HCl 1M and extracted with ethyl acetate (3 X 20 mL). The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The oily residue was purified by flash column chromatography (hexane/EtOAc 98:2). Yellow oil. Yield: 71% (948 mg, 4.7 mmol). Spectroscopic data were coincident with the previously reported.[192] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 – 7.11 (m, 4H), 3.39 (t, J = 6.9 Hz, 1H), 3.18 (ddd, J = 15.6, 9.8, 5.8 Hz, 1H), 2.99 (ddd, J = 15.7, 6.3, 5.2 Hz, 1H), 2.66 (dt,

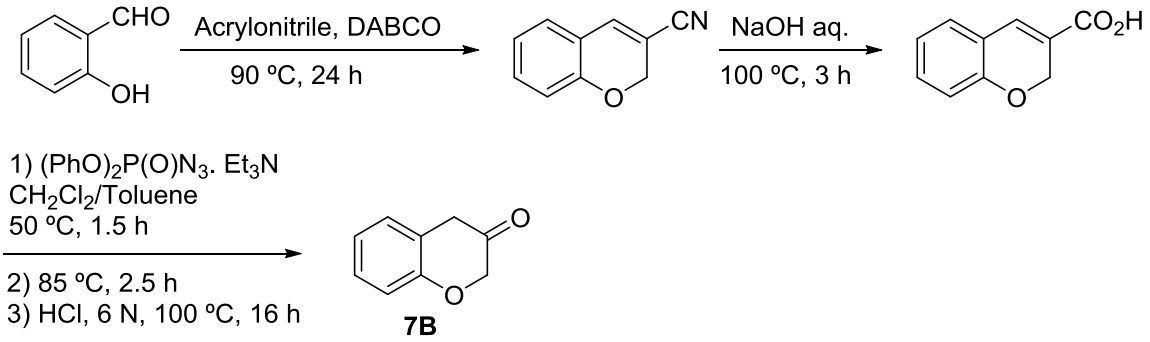
[191] a) M. A. Le Dréau, D. Desmaele, F. Dumas, J. d'Angelo, *J. Org. Chem.* **1993**, *58*, 2933–2935.
[192] L. Li, P. Cai, Q. Guo, S. Xue, *J. Org. Chem.* **2008**, *73*, 3516–3522.

J = 17.3, 5.5 Hz, 1H), 2.51 (ddd, J = 17.3, 9.8, 6.4 Hz, 1H), 1.88 – 1.80 (m, 2H), 1.31 – 1.27 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H).

5.3.3. Preparation of chroman-3-ones 1H and 7B

Chroman-3-one (7B)

The title compound was prepared according to the following synthetic sequence described in the literature:[193]



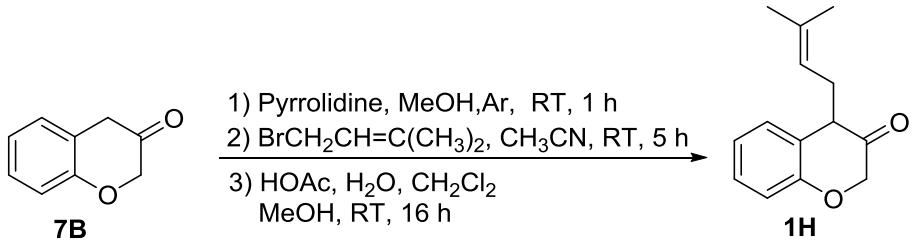
Step 1: 2-Hydroxybenzaldehyde (1.05 mL, 10 mmol, 1 equiv.), acrylonitrile (3.28 mL, 50 mmol, 5 equiv.) and DABCO (247 mg, 2.2 mmol, 0.22 equiv.) were stirred for 24 h at 90 °C. The course of the reaction was followed by TLC on silica (hexane/CH_2Cl_2 70:30). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 (30 mL) and successively washed with a saturated solution of $NaHCO_3$ and brine. The organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The corresponding products were purified by flash column chromatography on silica gel (hexane/EtOAc 80:20).

Step 2: An aqueous solution of NaOH (10%, 23 mL) was added to the 2H-chromenecarbonitrile (1.29 g, 8.2 mmol, 1 equiv.). The reaction mixture was heated to 100 °C for 3 h. The course of the reaction was followed by TLC on silica (hexane/CH_2Cl_2 1:1). The reaction mixture was cooled to room temperature and an aqueous solution of HCl (3 N) was carefully added dropwise until pH 3 was reached. The product precipitated as a pale yellow solid. The product was filtered, recrystallized from MeOH and dried overnight over $CaCl_2$ in a dessicator.

[193] D. Pressnitz, C. S. Fuchs, J. H. Sattler, T. Knaus, P. Macheroux, F. G. Mutti, W. Kroutil. *ACS Catal.* **2013**, *3*, 555–559.

Step 3: The reaction was performed under argon atmosphere. 2*H*-Chromenecarboxylic acid (881 mg, 5 mmol, 1 equiv.) was suspended in CH_2Cl_2 (11.5 mL). After addition of Et_3N (0.9 mL, 6.5 mmol, 1.3 equiv.), a homogeneous solution was obtained. Then, a solution of $(PhO)_2P(O)N_3$ (1.19 mL, 5.5 mmol, 1.1 equiv.) in toluene (5 mL) was added dropwise to the reaction mixture over a period of 15 minutes. Afterwards, the solution was heated to 50 °C for 1.5 h. Another aliquot of toluene (11.5 mL) was added and the solution was heated to 85 °C and maintained at that temperature for 2.5 h. The quantitative formation of the isocyanate intermediate was followed by TLC on silica (hexane/CH_2Cl_2 20:80). Finally, the reaction mixture was cooled down and an aqueous solution of HCl (6 N, 50 mL) was added. The biphasic system was heated under reflux for 16 h. The course of the reaction was controlled by TLC on silica gel (hexane/CH_2Cl_2 20:80). Then, the layers were separated; the organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The corresponding product was purified by column purification on silica gel (hexane/EtOAc 90:10). Yellow oil. Yield (after 3 steps): 25% (370 mg, 2.5 mmol). Spectroscopic data were coincident with the previously reported.[193] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28–7.21 (m, 1H), 7.14–7.02 (m, 3H), 4.40 (s, 2H), 3.61 (s, 2H).

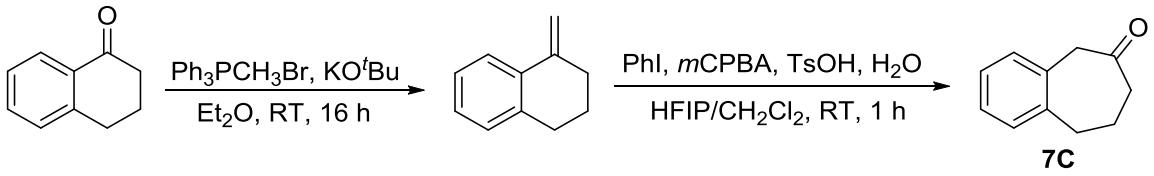
4-(2-Methylprop-1-en-1-yl)chroman-3-one (1H)



The same procedure employed for the synthesis of *rac* 1-substituted β-tetralones (Section 5.3.1., page 134) was used starting from chroman-3-one **7B** (740 mg, 5 mmol). Yellow oil. Yield: 38% (411 mg, 1.9 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28–7.19 (m, 1H), 7.14–6.97 (m, 3H), 5.13–5.06 (m, 1H), 4.51 (d, *J*= 17.7 Hz, 1H), 4.36 (d, *J*= 17.7 Hz, 1H), 3.46 (t, *J*= 6.9 Hz, 1H), 2.58 (t, *J*= 7.1 Hz, 2H), 1.66 (s, 3H), 1.44 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.3, 154.2, 134.8, 128.5, 128.1, 125.2, 122.8, 119.2, 117.3, 72.4, 50.6, 30.0, 25.4, 17.3. **MS** (ESI, m/z): calculated for $C_{13}H_{14}O_2Na$ (M + Na^+), 239.1048; found, 203.1330.

5.3.4. Preparation of 5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one (7C)

Known cycloalkanone **7C** was prepared according to the following synthetic sequence:



7C

Step 1:[194] Under argon atmosphere, potassium *tert*-butoxide (1.35 g, 12 mmol, 1.2 equiv.) was added to mixture of methyltriphenylphosphonium bromide (4.29 g, 12 mmol, 1.2 equiv.) in anhydrous Et_2O. The resulting mixture was stirred at room temperature for 1 h and a solution of α-tetralone (1.3 mL, 10 mmol, 1 equiv.) in Et_2O (5 mL) was slowly added. The resulting mixture was allowed to stir overnight, passed through a pad of celite and washed with Et_2O. The solvent was eliminated under reduced pressure and the crude was diluted with hexane before passing it again trough a pad of celite. The alkene was purified by flash column chromatography (hexane/EtOAc 99:1).

Step 2:[195] Iodobenzene (1.3 mL, 11.5 mmol, 1.15 equiv.), *meta*-chloroperbenzoic acid (70%) (2.6 g, 11.5 mmol, 1.15 equiv.) and *para*-toluenesulfonic acid monohydrate (2.2 g, g, 11.5 mmol, 1.15 equiv.) were stirred together in hexafluoroisopropanol/CH_2Cl_2 (1:6) (50 mL) for 30 min before the previously obtained alkene was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with $NaHCO_3$, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The desired ketone was purified by flash column chromatography (hexane/EtOAc 92:8). Yellow oil. Yield after two steps: 90% (1.44 g, 9.0 mmol). The spectroscopic data were identical to those reported in the literature.[196] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24–7.12 (m, 4H), 3.73 (s, 2H), 3.10–2.80 (m, 2H), 2.57 (t, *J*= 6.9 Hz, 2H), 2.00 (dt, *J*= 13.2, 6.6 Hz, 2H).

[194] D. H. T. Phan, K. G. M. Kou, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16354−16355.
[195] A. Ahmad, P. Scarassati, N. Jalalian, B. Olofsson, L. F. Silva Jr., *Tetrahedron Lett.* **2013**, *54*, 5818−5820.
[196] L. Li, P. Cai, Q. Guo, S. Xue, *J. Org. Chem.* **2008**, *73*, 3516–3522.

5.3.5. Preparation of 6,7-dihydro-5*H*-benzo[7]annulene-5,8(9*H*)-dione (7D)

Known diketone **7D** was synthesized according to the following procedure described in the literature:[197]

In an oven dried round-bottom flask was taken anhydrous CsF (0.61 mL, 2.5 mmol, 1.25 equiv.) and to this was added a solution of 1,3-cyclopentanedione (196 mg, 2 mmol, 1 equiv.) in anhydrous acetonitrile (20 mL), followed by aryne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.61 mL, 2.5 mmol, 1.25 equiv.) in anhydrous acetonitrile (20 mL) and the reaction mixture was heated at 75 °C for 2 h. The progress of the reaction was monitored by TLC, after completion of the reaction, cooled to room temperature, diluted with H_2O (50 mL) and extracted with ethyl acetate (3x100 mL). The combined organic extract was washed with brine (100 mL) and dried over Na_2SO_4, volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 85:15). Yellow oil. Yield: 33% (115 mg, 0.66 mol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99–7.82 (m, 1H), 7.51–7.37 (m, 2H), 7.26–7.18 (m, 1H), 4.01 (s, 2H), 3.10–3.06 (m, 2H), 2.70–2.65 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.8, 200.3, 133.8, 130.8, 130.2, 130.0, 128.2, 121.2, 50.4, 39.2, 35.4. **MS** (ESI, m/z): calculated for $C_{11}H_{11}O_2$ ($M + H^+$), 175.0759; found, 175.0754.

5.3.6. Preparation of electrophiles 2, 3 and 9

Nitroalkenes **2a-f, 2h** and **2i** were purchased from commercial suppliers. Nitroalkenes **2g**, **2j**, **2k**, **2l**, **2m** and **2n** were prepared according to the methods reported.[198]

1,1-bis(phenylsulfonyl)ethylene **3**[199] and *N*-Boc imines **9**[200] were synthesized following the procedures described in the literature.

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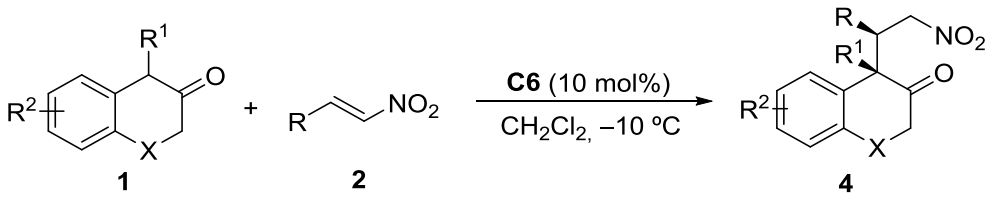
[197] R. Samineni, P. Srihari, G. Mehta, *Org. Lett*. **2016**, *18*, 2832−2835.

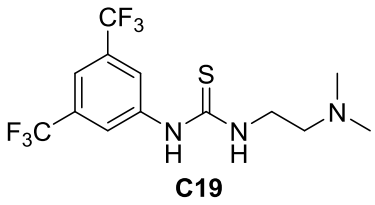
[198] For aromatic nitroalkenes **2g** and **2j** see: a) J. Bourguignon, G. Le Nard, G. Queguiner, *Can. J. Chem.* **1985**, *63*, 2354−2361. For nitroalkene **2k,** see: b) U. Kaya, P. Chauhan, D. Hack, K. Deckers, R. Puttreddy, K. Rissanen, D. Enders, *Chem. Commun.* **2016**, *52*, 1669−1672. For aliphatic nitroalkenes **2l** and **2m**, see: c) B. M. Trost, C. Muller, *J. Am. Chem. Soc.* **2008**, *130*, 2438−2439. For nitroalkenes **2n**, see: d) D. Lucet, S. Sabelle, O. Kostelitz, T. Le Gall, C. Mioskowski, *Eur. J. Org. Chem.* **1999**, 2583−22591.

5.3.7. General procedure for the conjugate addition of α-substituted β-tetralones to nitroalkenes 2

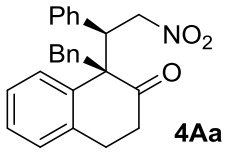


Catalyst **C6** (10 mol%) was added to a solution of the corresponding β-tetralone **1** (0.3 mmol, 1 equiv.) and nitroalkene **2** (0.36 mmol, 1,2 equiv.) in CH_2Cl_2 (0.6 mL) at −10 °C (unless otherwise stated). The resulting solution was stirred at −10 °C until the reaction was completed (commonly 16 h). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 90:10), affording the corresponding Michael adduct as essentially pure compound.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing NEt_3. Racemic adducts **4Ak**, **4Al**, and **4Gm** were prepared employing achiral catalyst **C19**.



(*S*)-1-Benzyl-1-((*R*)-2-nitro-1-phenylethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Aa)[186]



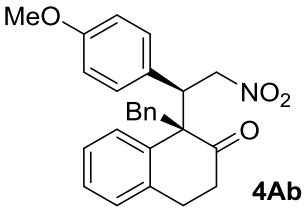
4Aa

General procedure was applied by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.). Foam. Yield: 82 % (95 mg, 0.261 mmol). $[\alpha]_D^{23}$= –105.7º (*c*= 2,00, 92% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, *J*= 7.3 Hz, 1H), 7.54–7.42 (m, 1H), 7.36–7.24 (m, 1H), 7.20–7.09 (m, 1H), 7.08–7.00 (m, 5H), 6.93 (d, *J*= 7.5 Hz, 1H), 6.84–6.74 (m, 2H), 6.53 (d, *J*= 7.3 Hz, 2H), 5.10 (dd, *J*= 12.4, 4.2 Hz, 1H), 4.85 (t, *J*= 12.0 Hz, 1H), 4.63 (dd, *J*= 11.7, 4.2 Hz, 1H), 3.60 (d, *J*= 12.5 Hz, 1H), 3.35 (d, *J*= 12.6 Hz, 1H), 2.16–2.04 (m, 2H), 1.28–1.12 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.0, 139.9, 135.6, 135.2, 134.9, 130.3, 129.5, 128.7, 128.0, 128.0, 127.8, 127.7, 127.6, 126.7, 126.4, 76.5, 60.4, 52.1, 43.3, 40.3, 26.1. **MS** (ESI, m/z): calculated for

[199] A. Quintard, A. Alexakis, *Chem. Commun*. **2011**, *47*, 7212−7214.
[200] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965.

$C_{25}H_{23}NO_3Na$ (M + H^+), 408.1576; found, 408.1587. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times: 11.8 min (minor), 14.7 min (major)).

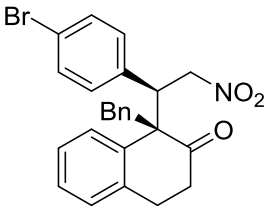
(*S*)-1-Benzyl-1-((*R*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Ab)[186]



4Ab

General procedure was applied by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and *p*-methoxynitrostyrene **2b** (65 mg, 0.36 mmol, 1.2 equiv.). Foam. Yield: 79% (98 mg, 0.24 mmol). **[α]$_D^{23}$**= –114.7º (*c*= 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J*= 7.5 Hz, 1H), 7.47 (t, *J*= 7.6 Hz, 1H), 7.30 (t, *J*= 7.4 Hz, 1H), 7.09–7.00 (m, 3H), 6.95 (d, *J*= 7.6 Hz, 1H), 6.82–6.76 (m, 2H), 6.58 (d, *J*= 9.0 Hz, 2H), 6.43 (d, *J*= 8.0 Hz, 2H), 5.06 (dd, *J*= 12.1, 4.1 Hz, 1H), 4.78 (t, *J*= 12.0 Hz, 1H), 4.57 (dd, *J*= 11.9, 4.2 Hz, 1H), 3.70 (s, 3H), 3.57 (d, *J*= 12.5 Hz, 1H), 3.33 (d, *J*= 12.6 Hz, 1H), 2.22–2.01 (m, 2H), 1.42–1.07 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 159.1, 139.9, 135.7, 135.0, 130.6, 130.3, 128.7, 128.0, 127.7, 127.6, 127.0, 126.6, 126.4, 113.3, 76.8, 60.4, 55.1, 51.5, 43.3, 40.3, 26.2. **MS** (ESI, m/z): calculated for $C_{26}H_{25}NO_4Na$ (M + Na^+), 438.1681; found, 438.1687. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 21.4 min (major), 29.3 min (minor)).

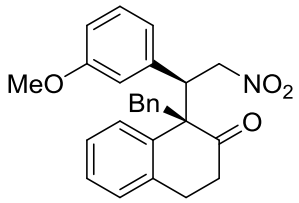
(*S*)-1-Benzyl-1-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Ae)[186]



4Ae

General procedure was applied by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and *p*-bromonitrostyrene **2e** (82 mg, 0.36 mmol, 1.2 equiv.). Foam. Yield: 85% (118 mg, 0.26 mmol). **[α]$_D^{23}$**= –138.9º (*c*= 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J*= 7.5 Hz, 1H), 7.48 (t, *J*= 7.2 Hz, 1H), 7.32 (t, *J*= 7.9 Hz, 1H), 7.19 (d, *J*= 8.7 Hz, 2H), 7.12–7.00 (m, 3H), 6.97 (d, *J*= 7.5 Hz, 1H), 6.77 (d, *J*= 9.3 Hz, 2H), 6.40 (d, *J*= 8.0 Hz, 2H), 5.08 (dd, *J*= 12.3, 4.0 Hz, 1H), 4.79 (t, *J*= 12.2 Hz, 1H), 4.60 (dd, *J*= 12.0, 4.0 Hz, 1H), 3.58 (d, *J*= 12.5 Hz, 1H), 3.30 (d, *J*= 12.5 Hz, 1H), 2.25–2.13 (m, 1H), 2.13–2.02 (m, 1H), 1.39–1.11 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.9, 139.7, 135.3, 134.7, 134.3, 131.1, 130.2, 128.9, 128.1, 127.8, 127.6, 126.8, 126.6, 122.1, 76.4, 60.1, 51.5, 43.5, 40.2, 26.3. **MS** (ESI, m/z): calculated for $C_{25}H_{22}NO_3BrNa$ (M + Na^+), 486.0681; found, 486.0682. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 12.5 min (major), 19.4 min (minor)).

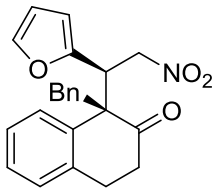
(*S*)-1-Benzyl-1-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Af)[186]



4Af

General procedure was applied by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and *m*-methoxynitrostyrene **2f** (66 mg, 0.36 mmol, 1.2 equiv.), and carrying out the reaction at –20 °C for 48 h. Foam. Yield: 80% (100 mg, 0.258 mmol). $[\alpha]_D^{23}$= –78.5° (*c*= 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, *J*= 7.7 Hz, 1H), 7.48 (t, *J*= 7.5 Hz, 1H), 7.30 (t, *J*= 7.5 Hz, 1H), 7.09–7.00 (m, 3H), 7.00–6.92 (m, 2H), 6.79 (d, *J*= 7.0 Hz, 2H), 6.68 (d, *J*= 8.3 Hz, 1H), 6.18 (d, *J*= 7.4 Hz, 1H), 5.98 (s, 1H), 5.10 (dd, *J*= 12.4, 4.2 Hz, 1H), 4.83 (t, *J*= 12.0 Hz, 1H), 4.61 (dd, *J*= 11.6, 4.2 Hz, 1H), 3.59 (d, *J*= 12.5 Hz, 1H), 3.53 (s, 3H), 3.34 (d, *J*= 12.5 Hz, 1H), 2.26–2.00 (m, 2H), 1.37–1.09 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.0, 158.91 , 140.0, 136.7, 135.6, 135.1, 130.3, 129.0, 128.8, 128.0, 127.7, 127.6, 126.7, 126.4, 122.2, 114.2, 76.5, 60.4, 54.9, 52.0, 43.3, 40.3, 26.2. **MS** (ESI, m/z): calculated for $C_{26}H_{26}NO_4$ (M + H^+), 416.1862; found, 416.1870. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 11.0 min (minor), 15.4 min (major)).

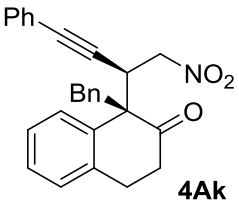
(*S*)-1-Benzyl-1-((*R*)-1-(furan-2-yl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Aj)[186]



4Aj

General procedure was applied by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and 2-(2-nitrovinyl)furan **2j** (50 mg, 0.36 mmol, 1.2 equiv.), and carrying out the reaction at –20 °C for 48 h. Foam. Yield: 60% (68 mg, 0.216 mmol). $[\alpha]_D^{23}$= –9.0° (*c*= 2.00, 90% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 (d, *J*= 7.8 Hz, 1H), 7.41 (t, *J*= 7.6 Hz, 1H), 7.26 (t, *J*= 7.4 Hz, 1H), 7.20 (s, 1H), 7.03 (d, *J*= 24.3 Hz, 4H), 6.71 (dd, *J*= 7.8, 1.6 Hz, 2H), 6.23 (dd, *J*= 3.3, 1.8 Hz, 1H), 6.01–5.93 (m, 1H), 4.89–4.74 (m, 2H), 4.65 (dd, *J*= 10.0, 5.3 Hz, 1H), 3.48–3.31 (m, 2H), 2.27 (ddt, *J*= 16.4, 10.8, 5.2 Hz, 2H), 2.11–1.96 (m, 1H), 1.66–1.52 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.5, 149.7, 142.3, 138.6, 135.6, 135.6, 130.3, 130.1, 128.6, 128.0, 127.5, 127.4, 126.7, 110.6, 109.7, 74.8, 59.3, 46.4, 43.5, 40.5, 26.7. **MS** (ESI, m/z): calculated for $C_{23}H_{22}NO_4$ (M + H^+), 376.1549; found, 376.1555. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 17.0 min (major), 24.4 min (minor)).

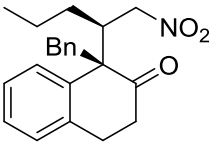
(S)-1-Benzyl-1-((R)-1-nitro-4-phenylbut-3-yn-2-yl)-3,4-dihydronaphthalen-2(1H)-one (4Ak)



4Ak

The adduct was obtained as a 60:40 mixture of diastereomers following the general procedure by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and (4-nitrobut-3-en-1-yn-1-yl)benzene **2k** (62 mg, 0.36 mmol, 1.2 equiv.). Foam. Yield: 70% (86 mg, 0.21 mmol).**[α]$_D^{23}$**= –38.0º (*c*= 1,00, 88% *ee*, *dr* = 60:40, CH_2Cl_2). (Major diastereomer) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (dd, *J*= 8.0, 1.4 Hz, 1H), 7.41 (dd, *J*= 7.3, 1.5 Hz, 1H), 7.38–7.27 (m, 6H), 7.15–7.02 (m, 4H), 6.75–6.70 (m, 2H), 4.53 (d, *J*= 1.5 Hz, 1H), 4.50 (d, *J*= 4.7 Hz, 1H), 4.37 (dd, *J*= 8.9, 5.6 Hz, 1H), 3.62 (d, *J*= 12.8 Hz, 1H), 3.35 (d, *J*= 12.8 Hz, 1H), 3.02–2.89 (m, 1H), 2.54–2.36 (m, 2H), 1.96–1.84 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.6, 138.6, 135.8, 135.5, 131.9, 130.5, 130.2, 129.0, 128.6, 128.4, 128.2, 128.0, 127.4, 127.2, 127.0, 123.3, 122.6, 86.8, 84.9, 58.3, 44.1, 40.8, 40.3, 27.8. (Minor diastereomer) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10–8.06 (m, 1H), 7.44–7.27 (m, 6H), 7.23–7.19 (m, 1H), 7.14–7.02 (m, 4H), 6.74–6.68 (m, 2H), 4.60 (dd, *J*= 10.6, 4.1 Hz, 1H), 4.38 (dd, *J*= 12.4, 4.0 Hz, 1H), 4.21 (dd, *J*= 12.4, 10.6 Hz, 1H), 3.54 (d, *J*= 12.8 Hz, 1H), 3.39 (d, *J*= 12.8 Hz, 1H), 2.80–2.67 (m, 1H), 2.55–2.34 (m, 2H), 1.93–1.81 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.4, 137.3, 136.3, 135.6, 131.8, 130.2, 128.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.3, 127.1, 126.4, 122.4, 87.6, 85.5, 57.9, 46.3, 40.4, 40.1, 34.2, 27.9. **MS** (ESI, m/z): calculated for $C_{27}H_{24}NO_3$ ($M + H^+$), 410.1756; found, 410.1754. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times of major diastereomer: 13.6 min (major), 14.9 min (minor). Retention times of minor diastereomer: 10.2 min (minor), 17.1 min (major)).

(*S*)-1-Benzyl-1-((*R*)-1-nitropentan-2-yl)-3,4-dihydronaphthalen-2(1*H*)-one (4Al)[186]

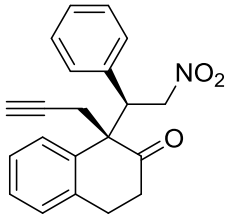


4Al

General procedure was applied by using 1-benzyl-β-tetralone (70 mg, 0.3 mmol, 1 equiv.) and 1-nitropent-1-ene **2l** (42 mg, 0.36 mmol, 1.2 equiv.), and carrying out the reaction at room temperature for 48 h. Colourless oil. Yield: 72% (77 mg, 0.22 mmol). **[α]$_D^{23}$**= +53.7º (*c*= 2.00, 88% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J*= 7.3 Hz, 1H), 7.39 (t, *J*= 8.3 Hz, 1H), 7.28–7.21 (m, 1H), 7.19–7.13 (m, 1H), 7.09–6.98 (m, 3H), 6.62 (d, *J*= 7.7 Hz, 2H), 4.57 (dd, *J*= 13.0, 4.1 Hz, 1H), 4.19 (dd, *J*= 13.0, 8.3 Hz, 1H), 3.48 (d, *J*= 12.6 Hz, 1H), 3.31 (dq, *J*= 8.1, 4.1 Hz, 1H), 3.13 (d, *J*= 12.6 Hz, 1H), 2.87–2.72 (m, 1H), 2.40–2.23 (m, 2H), 1.88–1.64 (m, 2H), 1.34–1.10 (m, 3H), 0.87 (t, *J*= 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.1, 137.6, 136.9, 135.7, 129.8, 129.0, 128.3, 127.4, 127.0, 126.9, 126.6, 126.1, 76.2, 58.8, 54.5, 45.9, 43.8, 40.1, 32.2, 27.1, 20.9, 13.7. **MS** (ESI, m/z): calculated

for $C_{22}H_{26}NO_3$ (M + H^+), 352.1913; found, 352.1928. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 98:2; flux= 1 mL/min; retention times: 9.4 min (minor), 12.1 min (major)).

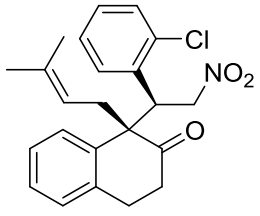
(*S*)-1-((*R*)-2-Nitro-1-phenylethyl)-1-(prop-2-yn-1-yl)-3,4-dihydronaphthalen-2(1H)-one (4Ba)



4Ba

General procedure was applied by using 1-(prop-2-yn-1-yl)-β-tetralone (56 mg, 0.3 mmol, 1 equiv.) and nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.). Foam. Yield: 83% (84 mg, 0.25 mmol). **$[\alpha]_D^{23}$**= –85.1° (*c*= 1,00, 89% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, CDCl3) δ 7.39–7.28 (m, 2H), 7.23–7.05 (m, 5H), 6.53 (dd, *J*= 8.3, 1.3 Hz, 2H), 4.85 (dd, *J*= 12.8, 4.8 Hz, 1H), 4.69 (dd, *J*= 12.8, 10.9 Hz, 1H), 4.34–4.28 (m, 1H), 3.14–2.92 (m, 2H), 2.59–2.35 (m, 4H), 1.60–1.48 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.6, 139.5, 134.7, 134.5, 129.6, 128.8, 128.4, 128.0, 127.2, 126.9, 79.5, 76.0, 71.7, 58.2, 50.5, 40.2, 26.5. **MS** (ESI, m/z): calculated for $C_{21}H_{20}NO_3$ (M + H^+), 334.1443; found, 334.1447. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times: 14.4 min (minor), 20.7 min (major)).

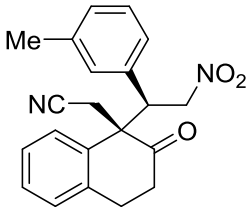
(*S*)-1-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-1-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-2(1*H*)-one (4Ci)[186]



4Ci

General procedure was applied by using 1-(3-methylbut-2-en-1-yl)-β-tetralone (64 mg, 0.3 mmol, 1 equiv.) and *o*-chloronitrostyrene **2i** (66 mg, 0.36 mmol, 1.2 equiv.), and carrying out the reaction at –20 °C for 48 h. Foam. Yield: 80% (95 mg, 0.240 mmol). **$[\alpha]_D^{23}$**= –59.7° (*c*= 2.00, 99% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H), 7.23–7.09 (m, 3H), 6.90 (d, *J*= 7.5 Hz, 1H), 4.99 (dd, *J*= 11.3, 4.0 Hz, 1H), 4.91–4.70 (m, 2H), 4.58 (t, *J*= 7.1 Hz, 1H), 2.94–2.73 (m, 3H), 2.70–2.53 (m, 2H), 2.49–2.33 (m, 1H), 1.51 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.8, 138.4, 137.0, 136.2, 135.4, 133.5, 130.0, 129.5, 129.0, 128.4, 127.4, 127.0, 126.3, 117.8, 76.6, 57.5, 46.1, 40.5, 34.8, 27.7, 25.7, 18.0. **MS** (ESI, m/z): calculated for $C_{23}H_{25}NO_3Cl$ (M + H^+), 398.1523; found, 398.1536. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 19.1 min (major), 25.8 min (minor)).

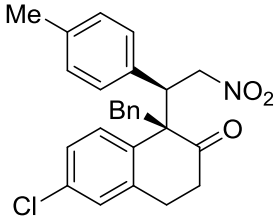
2-((*S*)-1-((*R*)-2-Nitro-1-(m-tolyl)ethyl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (4Dg)[186]



4Dg

General procedure was applied by using 1-cyanomethyl-β-tetralone (56 mg, 0.3 mmol, 1 equiv.) and *m*-methylnitrostyrene **2g** (58 mg, 0.36 mmol, 1.2 equiv.). Foam. Yield: 78% (82 mg, 0.23 mmol). $[\alpha]_D^{23}$= –31.5° (*c*= 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 2H), 7.23–7.17 (m, 1H), 7.10–6.97 (m, 3H), 6.49–6.37 (m, 1H), 6.30 (s, 1H), 4.80–4.60 (m, 2H), 4.18 (dd, *J*= 9.1, 6.1 Hz, 1H), 3.19 (d, *J*= 16.0 Hz, 1H), 2.94 (d, *J*= 16.0 Hz, 1H), 2.85–2.73 (m, 1H), 2.72–2.56 (m, 2H), 2.16 (s, 3H), 2.22–2.08 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.9, 138.3, 138.2, 133.2, 130.1, 129.4, 129.1, 128.6, 128.4, 127.3, 126.8, 126.2, 116.4, 75.4, 56.6, 50.0, 38.9, 26.7, 24.2, 21.2. **MS** (ESI, m/z): calculated for $C_{18}H_{18}NO_3$ (M + H^+), 371.1372; found, 371.1372. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 13.4 min (minor), 15.4 min (major)).

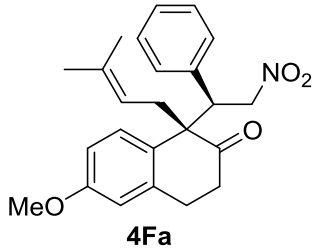
(*S*)-1-Benzyl-6-chloro-1-((*R*)-2-nitro-1-(p-tolyl)ethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Ec)[186]



4Ec

General procedure was applied by using 1-benzyl-6-chloroβ-tetralone (81 mg, 0.3 mmol, 1 equiv.) and *p*-methylnitrostyrene **2c** (58 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C4**, and carrying out the reaction at –20 °C. Foam. Yield: 84% (109 mg, 0.252 mmol). $[\alpha]_D^{23}$= – 162° (*c*= 2.00, 90% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 (d, *J*= 8.5 Hz, 1H), 7.45 (dd, *J*= 8.5, 2.2 Hz, 1H), 7.20–6.99 (m, 3H), 6.96 (d, *J*= 2.1 Hz, 1H), 6.89 (d, *J*= 7.9 Hz, 2H), 6.77 (dd, *J*= 7.3, 2.2 Hz, 2H), 6.44 (d, *J*= 7.8 Hz, 2H), 5.04 (dd, *J*= 12.2, 4.3 Hz, 1H), 4.77 (t, *J*= 11.9 Hz, 1H), 4.56 (dd, *J*= 11.7, 4.3 Hz, 1H), 3.50 (d, *J*= 12.7 Hz, 1H), 3.35 (d, *J*= 12.7 Hz, 1H), 2.23 (s, 3H), 2.14–2.01 (m, 2H), 1.30–1.10 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.9, 142.4, 138.4, 136.0, 134.4, 134.0, 132.4, 130.9, 129.9, 129.8, 129.5, 129.2, 128.7, 127.4, 127.2, 77.0, 60.9, 52.3, 43.8, 40.5, 26.6, 21.6. **MS** (ESI, m/z): calculated for $C_{26}H_{24}NO_3ClNa$ (M + Na^+), 456.1342; found, 456.1346. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 12.8 min (minor), 17.9 min (major)).

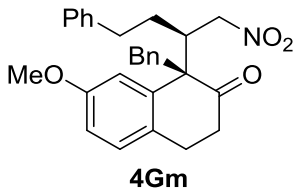
(*S*)-6-Methoxy-1-(3-methylbut-2-en-1-yl)-1-((*R*)-2-nitro-1-phenylethyl)-3,4-dihydronaphthalen-2(1*H*)-one (4Fa)[186]



4Fa

General procedure was applied by using 6-methoxy-1-cyanomethyl-β-tetralone (72 mg, 0.3 mmol, 1 equiv.) and nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.), and carrying out the reaction at room temperature for 48 h. Foam. Yield: 40% (47 mg, 0.120 mmol). $[\alpha]_D^{23}$= –81.9° (*c*= 2.00, 98% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (dd, *J*= 8.0, 4.2 Hz, 2H), 7.09 (t, *J*= 7.5 Hz, 2H), 6.93 (dd, *J*= 8.6, 2.6 Hz, 1H), 6.64–6.48 (m, 3H), 5.02 (dd, *J*= 12.6, 4.5 Hz, 1H), 4.81–4.66 (m, 2H), 4.40 (dd, *J*= 11.4, 4.6 Hz, 1H), 3.89 (s, 3H), 3.00 (dd, *J*= 13.7, 9.2 Hz, 1H), 2.77 (dd, *J*= 13.5, 4.9 Hz, 1H), 2.47–2.30 (m, 2H), 2.18–2.02 (m, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 1.36–1.16 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.8, 158.6, 141.2, 135.5, 129.5, 128.3, 128.0, 127.8, 127.1, 117.9, 113.5, 112.3, 76.4, 58.2, 55.3, 51.4, 40.4, 35.7, 26.5, 25.8, 18.0. **MS** (ESI, m/z): calculated for $C_{24}H_{28}NO_4$ (M + H^+), 394.2023; found, 394.2018. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 98:2; flux= 1 mL/min; retention times: 12.7 min (minor), 18.3 min (major)).

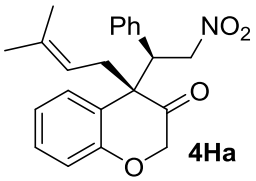
(*S*)-1-Benzyl-7-methoxy-1-((*R*)-1-nitro-4-phenylbutan-2-yl)-3,4-dihydronaphthalen-2(1*H*)-one (4Gm)[186]



4Gm

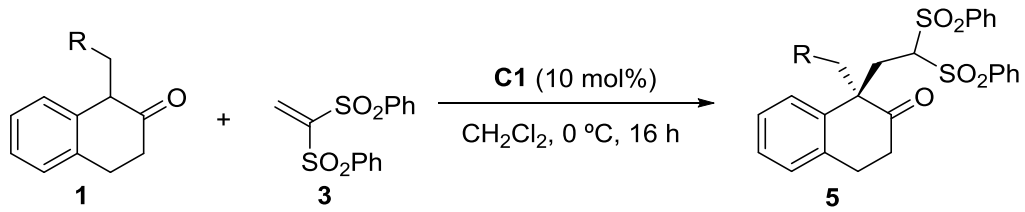
General procedure was applied by using 1-benzyl-7-methoxy-β-tetralone (80 mg, 0.3 mmol, 1 equiv.) and (4-nitrobut-3-en-1-yl)benzene **2m** (64 mg, 0.36 mmol, 1.2 equiv.), and carrying out the reaction at 0 °C for 64 h. Foam. Yield: 81% (108 mg, 0.243 mmol). $[\alpha]_D^{23}$= +45.6° (*c*= 2.00, 89% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.23–7.10 (m, 3H), 7.10–6.98 (m, 4H), 6.94 (d, *J*= 8.4 Hz, 1H), 6.80 (dd, *J*= 8.4, 2.5 Hz, 1H), 6.63 (d, *J*= 6.7 Hz, 2H), 4.59 (dd, *J*= 12.8, 4.0 Hz, 1H), 4.28 (dd, *J*= 12.8, 8.5 Hz, 1H), 3.88 (s, 3H), 3.42 (d, *J*= 11.7 Hz, 1H), 3.34–3.23 (m, 1H), 2.95 (d, *J*= 12.7 Hz, 1H), 2.74–2.45 (m, 3H), 2.39–2.08 (m, 3H), 1.95–1.78 (m, 1H), 1.67–1.50 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.3, 158.5, 141.0, 138.5, 135.9, 131.5, 130.2, 129.6, 128.5, 128.4, 127.9, 126.6, 126.2, 113.0, 112.9, 78.1, 59.0, 55.4, 45.8, 44.0, 40.8, 34.4, 32.2, 26.7. **MS** (ESI, m/z): calculated for $C_{28}H_{30}NO_4$ (M + H^+), 444.2175; found, 444.2176. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 11.4 min (major), 18.7 min (minor)).

(S)-4-(3-Methylbut-2-en-1-yl)-4-((R)-2-nitro-1-phenylethyl)chroman-3-one (4Ha)



General procedure was applied by using 4-(3-methylbut-2-en-1-yl)chroman-3-one (64 mg, 0.3 mmol, 1 equiv.) and nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.). Colourless oil. Yield: 64% (70 mg, 0.20 mmol). $[\alpha]_D^{23}$= –30.2º (*c*= 1.00, 90% *ee*, *dr* >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.25 (m, 1H), 7.19 (d, *J*= 7.3 Hz, 1H), 7.15–7.08 (m, 2H), 7.03 (td, *J*= 7.5, 1.3 Hz, 1H), 6.95 (d, *J*= 8.0 Hz, 2H), 6.65 (d, *J*= 7.1 Hz, 2H), 4.92–4.73 (m, 2H), 4.69–4.63 (m, 1H), 4.24 (d, *J*= 17.2 Hz, 1H), 4.15 (dd, *J*= 10.7, 4.8 Hz, 1H), 4.00 (d, *J*= 17.2 Hz, 1H), 3.02 (dd, *J*= 14.2, 8.0 Hz, 1H), 2.72 (dd, *J*= 14.2, 5.6 Hz, 1H), 1.61 (s, 3H), 1.52 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.6, 155.8, 136.0, 134.5, 129.2, 128.3, 128.2, 123.4, 122.9, 118.4, 117.7, 76.0, 73.2, 56.8, 50.7, 31.5, 25.9, 18.3. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_4$ ($M + H^+$), 388.1525; found, 388.1524. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times: 12.4 min (major), 22.2 min (minor)).

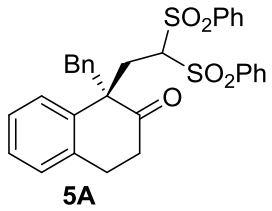
5.3.8. General procedure for the conjugate addition of α-substituted β-tetralones to 1,1-bis(phenylsulfonyl)ethylene 3



Catalyst **C1** (10 mol%) was added to a solution of the corresponding β-tetralone **1** (0.3 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene **3** (139 mg, 0.45 mmol, 1,5 equiv.) in CH_2Cl_2 (0.6 mL) at 0 °C. The resulting solution was stirred at the specified temperature for 16 h. Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc), affording the corresponding Michael adduct as essentially pure compound.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing NEt_3 as a catalyst.

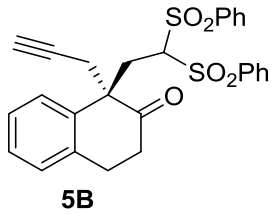
(*R*)-1-Benzyl-1-(2,2-bis(phenylsulfonyl)ethyl)-3,4-dihydronaphthalen-2(1*H*)-one (5A)



5A

General procedure was applied by using 1-benzyl-β-tetralone (24 mg, 0.1 mmol, 1 equiv.). White foam. Yield: 95% (52 mg, 0.095 mmol). **$[\alpha]_D^{23}$**= +16.2° (*c*= 1.00, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 – 8.02 (m, 2H), 7.79 – 7.75 (m, 2H), 7.72 – 7.50 (m, 6H), 7.42 – 7.39 (m, 2H), 7.33 – 7.28 (m, 1H), 7.11 – 6.98 (m, 4H), 6.60 – 6.56 (m, 2H), 4.70 (dd, J = 6.7, 2.8 Hz, 1H), 3.25 (d, J = 12.7 Hz, 1H), 3.15 (dd, J = 16.4, 6.8 Hz, 1H), 3.04 – 2.86 (m, 3H), 2.70 – 2.59 (m, 1H), 2.31 – 2.16 (m, 1H), 1.79 – 1.68 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.5, 138.6, 138.4, 137.3, 136.2, 136.0, 134.9, 134.4, 131.1, 130.3, 129.4, 129.1, 129.0, 129.0, 128.0, 127.9, 127.5, 127.2, 126.9, 80.2, 55.3, 49.0, 39.7, 33.1, 27.4. **MS** (ESI, m/z): calculated for $C_{31}H_{29}O_5S_2$ (M + H^+), 545.1460; found, 545.1456. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane:isopropanol, 90/10; flux= 1 mL/min; retention times: 26.8 min (major), 36.0 (minor)).

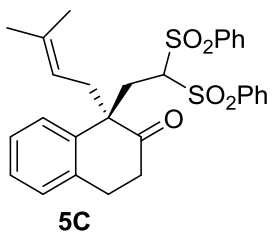
(*R*)-1-(2,2-Bis(phenylsulfonyl)ethyl)-1-(prop-2-yn-1-yl)-3,4-dihydronaphthalen-2(1*H*)-one (5B)



5B

General procedure was applied by using 1-(prop-2-yn-1-yl)-3,4-dihydronaphthalen-2(1*H*)-one (18 mg, 0.1 mmol, 1 equiv.). White foam. Yield: 75% (37 mg, 0.075 mmol). **$[\alpha]_D^{23}$**= +40.5° (*c*= 0.50, 96% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 2H), 7.80 – 7.75 (m, 2H), 7.64 (dd, J = 8.7, 7.4 Hz, 2H), 7.56 – 7.49 (m, 4H), 7.34 – 7.28 (m, 4H), 4.84 (t, J = 4.3 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.07 – 2.95 (m, 3H), 2.76 – 2.59 (m, 4H), 1.77 (t, J = 2.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.1, 138.2, 137.6, 137.4, 136.2, 134.8, 134.2, 130.5, 129.2, 129.0, 128.8, 127.6, 127.4, 126.7, 79.9, 78.8, 70.8, 53.0, 39.6, 33.0, 28.3, 27.4. **MS** (ESI, m/z): calculated for $C_{27}H_{25}O_5S_2$ (M + H^+), 493.1143; found, 493.1143. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 15.1 min (major), 22.4 (minor)).

(*R*)-1-(2,2-Bis(phenylsulfonyl)ethyl)-1-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-2(1*H*)-one (5C)

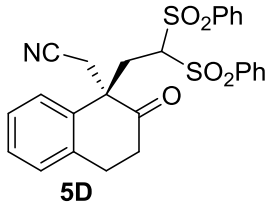


5C

General procedure was applied by using 1-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-2(1*H*)-one (21 mg, 0.1 mmol, 1 equiv.). White foam. Yield: 67% (35 mg, 0.067 mmol). **$[\alpha]_D^{23}$**= +15.05° (*c*= 0.50, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 2H), 7.81 – 7.76 (m, 2H), 7.70 – 7.62 (m, 2H), 7.61 – 7.54 (m, 4H),

7.30 – 7.26 (m, 4H), 4.74 (dd, J = 5.6, 3.6 Hz, 1H), 4.63 – 4.57 (m, 1H), 3.39 – 3.25 (m, 1H), 2.97 – 2.78 (m, 5H), 2.52 – 2.40 (m, 1H), 2.26 (dd, J = 14.2, 6.0 Hz, 1H), 1.51 (s, 3H), 1.44 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.9, 140.3, 138.6, 138.1, 137.7, 136.4, 135.3, 134.7, 134.2, 130.7, 129.3, 128.9, 128.8, 127.2, 127.0, 118.4, 79.6, 53.4, 39.7, 39.5, 33.2, 27.6, 25.7, 17.9. **MS** (ESI, m/z): calculated for $C_{29}H_{31}O_5S_2$ (M + H^+), 523.1613; found, 523.1613. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 20.6 min (major), 27.9 (minor)).

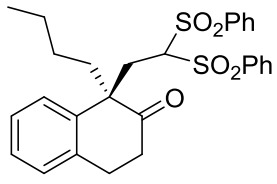
(*R*)-2-(1-(2,2-Bis(phenylsulfonyl)ethyl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (5D)



5D

General procedure was applied by using 2-(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (18 mg, 0.1 mmol, 1 equiv.). White foam. Yield: 75% (37 mg, 0.075 mmol). **$[\alpha]_D^{23}$**= −3.8° (*c*= 1.00, 57% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.81 – 7.76 (m, 2H), 7.74 – 7.66 (m, 2H), 7.60 – 7.54 (m, 4H), 7.44 – 7.35 (m, 4H), 4.88 (t, J = 4.1 Hz, 1H), 3.45 – 3.38 (m, 1H), 3.31 (d, J = 16.6 Hz, 1H), 3.17 – 3.11 (m, 2H), 2.92 – 2.82 (m, 2H), 2.76 – 2.66 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.1, 137.7, 137.1, 136.0, 135.9, 135.0, 134.5, 130.3, 129.4, 129.2, 128.5, 127.9, 126.0, 116.7, 78.1, 51.8, 38.6, 32.9, 27.4, 25.6. **MS** (ESI, m/z): calculated for $C_{26}H_{24}NO_5S_2$ (M + H^+), 494.1096; found, 494.1104. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 40.6 min (major), 45.8 (minor)).

(*R*)-1-(2,2-Bis(phenylsulfonyl)ethyl)-1-butyl-3,4-dihydronaphthalen-2(1*H*)-one (5I)

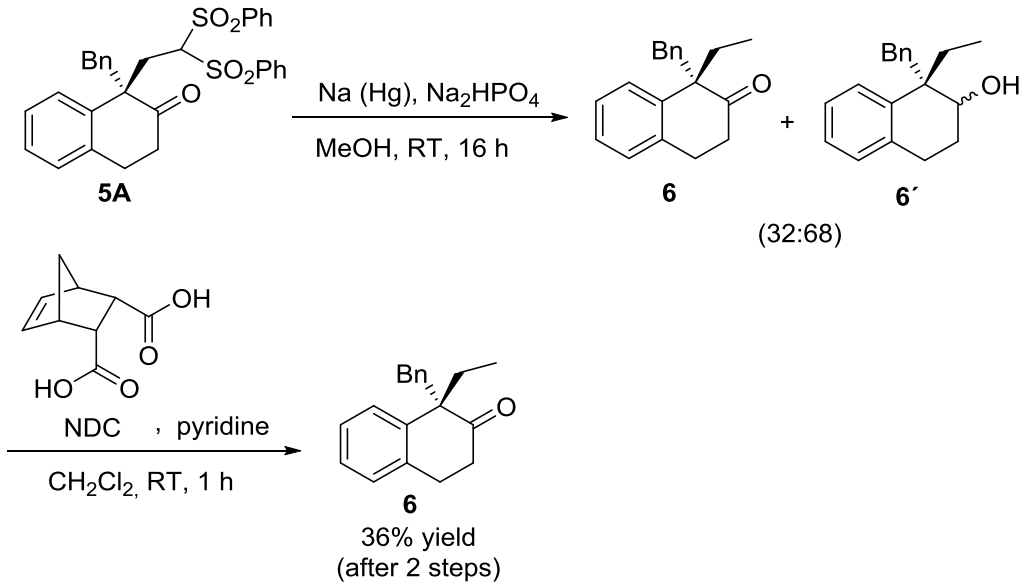


5I

General procedure was applied by using 1-butyl-3,4-dihydronaphthalen-2(1*H*)-one (20 mg, 0.1 mmol, 1 equiv.). White foam. Yield: 91% (46 mg, 0.091 mmol). **$[\alpha]_D^{23}$**= +32.18° (*c*= 0.50, 86% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.4, 1.3 Hz, 2H), 7.87 (dd, J = 8.4, 1.3 Hz, 2H), 7.75 – 7.68 (m, 2H), 7.63 – 7.56 (m, 4H), 7.33 – 7.25 (m, 4H), 4.91 (t, J = 4.3 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.05 – 2.96 (m, 2H), 2.73 (dd, J = 8.9, 4.4 Hz, 2H), 2.56 – 2.48 (m, 1H), 2.00 – 1.92 (m, 1H), 1.53 – 1.45 (m, 1H), 1.18 – 1.10 (m, 2H), 0.91 – 0.77 (m, 5H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.8, 138.8, 138.6, 137.5, 136.6, 134.7, 134.1, 130.5, 129.3, 129.0, 128.9, 128.7, 127.3, 127.0, 126.5, 79.1, 53.1, 40.0, 38.7, 34.5, 27.6, 26.9, 22.9, 13.7. **MS** (ESI, m/z): calculated for $C_{28}H_{31}O_5S_2$ (M + H^+), 511.1613; found, 511.1613. The enantiomeric purity was

determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 9.7 min (major), 13.2 (minor)).

5.3.9. Desulfonylation of adduct 5A



Step 1:[201] Adduct **5A** was dissolved in MeOH (25 mL) and treated with 5% Na(Hg) (1.21 g) and Na_2HPO_4 (213 mg, 1.5 mmol, 3 equiv.). The resulting suspension was stirred for 5 h at room temperature before it was poured into CH_2Cl_2 (10 mL), filtered and washed with water (2 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product (**6**/**6´** 32:68) was used in the next step without further purification.

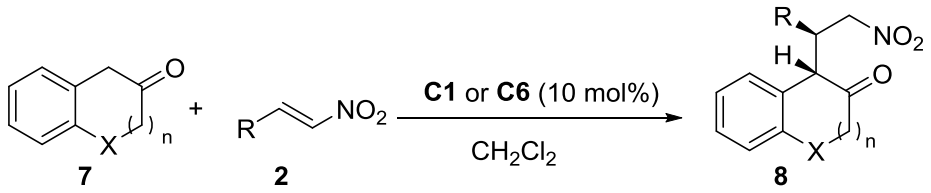
Step 2:[202] To a suspension of previously prepared NDC[202] (580 mg, 1.25 mmol, 2.5 equiv.) in CH_2Cl_2 (4 ml), pyridine (0.81 ml, 10 mmol, 20 equiv.) and the mixture of the ketone **6** and alcohol **6´** were added and the resulting mixture was stirred at room temperature for 2 h. Then, the reaction mixture was filtered off through a pad of silica gel and washed with water (5 ml), 6N HCl (5 ml) and a saturated solution of $NaHCO_3$ (5 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc 98:2). White solid. M.p. = 94–97 ^oC. Yield after two steps: 36% (47 mg, 0.18 mmol). $\mathbf{[\alpha]}_D^{23}$ = +20.3^o (*c* = 1.00, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (dd, J = 7.9, 1.3 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.21 (td, J = 7.4, 1.4 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.06 – 7.02 (m, 3H), 6.62 – 6.58 (m, 2H),

[201] T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2007**, *46*, 3329–3332.
[202] F. P.Cossio, M.C. Lopez, C. Palomo, *Tetrahedron*, **1987**, *43*, 3963–3974.

3.35 (d, J = 12.7 Hz, 1H), 2.88 (d, J = 12.7 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.37 – 2.23 (m, 3H), 2.06 – 1.99 (m, 2H), 0.66 (t, J = 7.4 Hz, 3H). **^{13}C NMR** δ 215.2, 138.7, 138.2, 137.1, 130.0, 127.7, 127.6, 126.9, 126.7, 126.3, 126.2, 58.2, 49.1, 40.9, 33.5, 26.9, 9.5.

MS (ESI, m/z): calculated for $C_{19}H_{21}O$ ($M + H^+$), 265.1592; found, 265.1588.

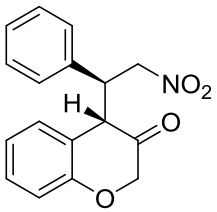
5.3.10. General procedure for the catalytic conjugate addition of α-unsubstituted arene-fused cycloalkanones to nitroalkenes 2



The selected catalyst (10 mol%) was added over a solution of the corresponding cycloalkanone **7** (0.3 mmol, 1 equiv.) and nitroalkene **2** (0.36 mmol, 1,2 equiv.) in CH_2Cl_2 (0.6 mL) at the specified temperature. The resulting solution was stirred at the specified temperature until the reaction was completed (monitored by TLC hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc), affording the corresponding Michael adduct as essentially pure compound.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing NEt_3 as a catalyst. Racemic adduct **8Da** was prepared using achiral catalyst **C19**.

(*S*)-4-((*S*)-2-Nitro-1-phenylethyl)chroman-3-one (8Ba)

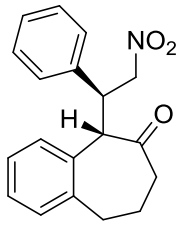


8Ba

The general procedure was applied starting from chroman-3-one **7B** (44 mg, 0.3 mmol, 1 equiv.), nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C1** (4 mg, 0.006 mmol, 2 mol%), and carrying out the reaction at –40 °C. The product was a beige solid obtained as 1:1 mixture of diastereomers (*dr*= 53:47; 99% *ee* for both isomers). Combined yield: 92 % (82 mg, 0.28 mmol). M. p. of the mixture = 97–99 °C. (Major diastereomer) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.18 (m, 5H), 6.83 (m, 3H), 6.61 (dd, *J*= 7.6, 1.6 Hz, 1H), 4.96–4.75 (m, 2H), 4.54–4.22 (m, 2H), 4.14–4.04 (m, 1H), 3.68 (d, *J*= 8.4 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.9, 155.1, 135.7, 130.2, 129.6, 128.9, 128.5, 128.1, 123.3, 122.2, 118.2, 77.2, 73.1, 55.1, 45.9. (Minor diastereomer) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.18 (m, 5H), 6.99–6.93 (m, 3H), 6.61 (dd, *J*= 7.6, 1.6 Hz,

1H), 4.96–4.75 (m, 2H), 4.26 (m, 2H), 4.14–4.04 (m, 1H), 3.81 (d, *J*= 6.6 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 207.5, 154.8, 135.2, 129.9, 129.8, 129.1, 128.7, 128.0, 123.8, 122.7, 118.4, 77.2, 73.1, 53.7, 47.8. **MS** (ESI, m/z): calculated for $C_{17}H_{15}NO_4Na$ (M + Na^+), 320.0899; found, 320.0900**.** The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times of major diastereomer: 20.7 min (major), 30.0 min (minor). Retention times of minor diastereomer: 10.6 min (minor), 12.9 min (major)).

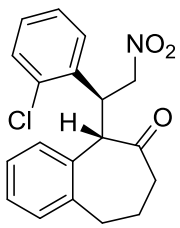
(*S*)-5-((*S*)-2-Nitro-1-phenylethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (8Ca)[186]



8Ca

The general procedure was applied starting from 5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one **7C** (48 mg, 0.3 mmol, 1 equiv.), nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C6** (25 mg, 0.03 mmol, 10 mol%), and carrying out the reaction at room temperature for 48 h. Foam. 4:1 mixture of diastereomers (99% *ee* for both isomers). Combined yield: 82 % (76 mg, 0.25 mmol). (Major diastereomer) (*S*,*S*) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4H), 7.23–7.09 (m, 4H), 6.89–6.82 (m, 1H), 4.86 (dd, *J*= 12.8, 5.0 Hz, 1H), 4.70 (dd, *J*= 12.9, 9.5 Hz, 1H), 4.39 (td, *J*= 9.3, 4.9 Hz, 1H), 4.28 (d, *J*= 9.3 Hz, 1H), 2.81 (dt, *J*= 14.6, 5.0 Hz, 1H), 2.69–2.56 (m, 1H), 2.50–2.39 (m, 2H), 1.97–1.85 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.0, 141.0, 137.0, 133.7, 130.4, 129.1, 128.8, 128.4, 128.3, 128.0, 127.6, 78.8, 61.1, 44.4, 43.2, 32.9, 28.2. (Minor diastereomer) (*R*,*S*) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4H), 7.23–7.09 (m, 4H), 7.06–6.99 (m, 1H), 4.88–4.80 (m, 1H), 4.76–4.64 (m, 1H), 4.45–4.34 (m, 1H), 4.15 (d, *J*= 5.7 Hz, 1H), 2.88–2.76 (m, 1H), 2.69–2.56 (m, 1H), 2.50–2.39 (m, 2H), 1.97–1.85 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.4, 141.0, 136.2, 133.2, 129.9, 129.8, 128.7, 128.3, 128.2, 127.7, 126.9, 78.5, 58.9, 42.3, 41.0, 31.4, 27.8. **MS** (ESI, m/z): calculated for $C_{19}H_{19}NO_3Na$ (M + Na^+), 332.1263; found, 332.1265. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times of major diastereomer: 14.3 min (major), 23.2 min (minor). Retention times of minor diastereomer: 10.6 min (major), 10.8 min (minor)).

(*S*)-5-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (8Ci)[186]

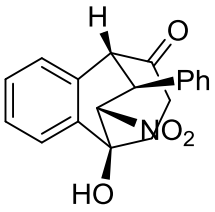


8Ci

The general procedure was applied starting from 5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one **7C** (48 mg, 0.3 mmol, 1 equiv.), *o*-chloronitrostyrene **2i** (66 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C6** (25 mg, 0.03 mmol, 10 mol%), and carrying out the reaction at room temperature for 16 h. Foam. Single diastereomer. Yield: 75 % (77 mg,

0.23 mmol). **$[\alpha]_D^{23}$**= –23.1º (*c*= 2.00, 99% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (d, *J*= 7.9 Hz, 1H), 7.18–7.11 (m, 1H), 7.11–6.94 (m, 5H), 6.81 (d, *J*= 7.6 Hz, 1H), 5.00–4.76 (m, 4H), 3.25 (ddd, *J*= 13.7, 10.4, 2.8 Hz, 1H), 3.06–2.87 (m, 2H), 2.68 (ddd, *J*= 12.3, 5.2, 3.4 Hz, 1H), 2.33–2.18 (m, 1H), 1.95–1.77 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.1, 141.5, 134.3, 134.1, 132.8, 130.2, 129.5, 128.9, 128.6, 127.6, 127.3, 127.2, 77.5, 54.7, 45.4, 38.7, 33.4, 28.7. **MS** (ESI, m/z): calculated for $C_{19}H_{18}ClNO_3Na$ (M + Na^+), 366.0873; found, 366.0869. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 7.2 min (major), 8.4 min (minor)).

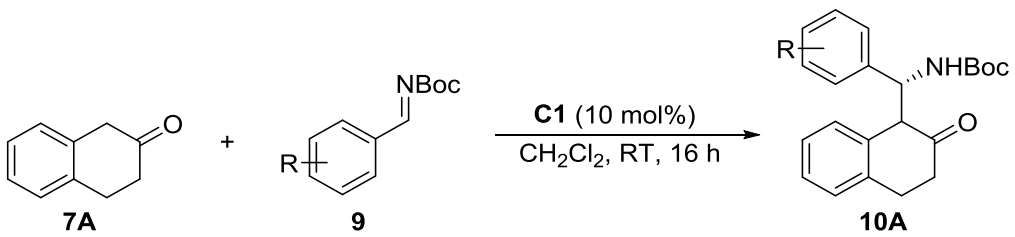
(5*S*,9*R*,10*S*,11*R*)-5-Hydroxy-11-nitro-10-phenyl-5,6,7,9-tetrahydro-8*H*-5,9-ethanobenzo[7]annulen-8-one (8Da)



8Da

The general procedure was applied starting from diketone **7D** (52 mg, 0.3 mmol, 1 equiv.), nitrostyrene **2a** (54 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C6** (25 mg, 0.03 mmol, 10 mol%), and carrying out the reaction at room temperature for 24 h. White solid. Single diastereomer. Yield: 61 % (59 mg, 0.18 mmol). Decomposition at 194 ºC. **$[\alpha]_D^{23}$**= –69.5º (*c*= 1.00, 98% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (dd, *J*= 7.7, 1.4 Hz, 1H), 7.49 (td, *J*= 7.5, 1.5 Hz, 1H), 7.41–7.33 (m, 5H), 7.24 (m, 2H), 5.67 (d, *J*= 6.7 Hz, 1H), 4.11 (d, *J*= 4.7 Hz, 1H), 4.01 (dd, *J*= 6.6, 4.8 Hz, 1H), 2.82 (s, 1H), 2.40–2.33 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.1, 137.9, 137.8, 133.2, 129.5, 129.1, 128.3, 127.3, 127.2, 123.3, 97.5, 74.0, 59.6, 47.9, 39.5, 37.3. **MS** calculated for $C_{19}H_{17}NO_4Na$ (M + Na^+), 346.1055; found, 346.1050. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 15.8 min (major), 21.4 min (minor)).

5.3.11. General procedure for the Mannich reaction of β-tetralone 7A with *N*-Boc imines 9



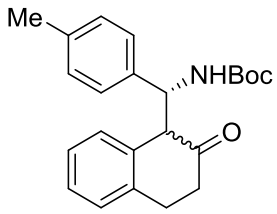
7A **9** **10A**

Catalyst **C1** (9 mg, 10 mol%) was added to a solution of β-tetralone **7A** (22 mg, 0.15 mmol, 1 equiv.) and the corresponding *N*-Boc imine **9** (0.30 mmol, 2 equiv.) in CH_2Cl_2

(0.6 mL) at room temperature. The resulting solution was stirred until the reaction was completed (monitored by TLC hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography (hexane/CH_2Cl_2 60:40), affording the corresponding adduct as essentially pure compound.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing achiral catalyst **C19**.

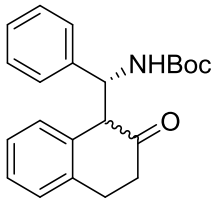
tert-Butyl((1*R*)-(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)(p-tolyl)methyl)carbamate (10Aa)



10Aa

The adduct was obtained as a 50:50 mixture of diastereomers following the general procedure by using 4-methylbenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9a** (66 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 87% (48 mg, 0.130 mmol). Both diastereomers were separated by flash column chromatography. (Diastereomer 1) (*R*,*R*) $[\alpha]_D^{23}$= –165.2º (*c*= 1.00, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 3H), 6.99 (dd, J = 30.4, 7.6 Hz, 3H), 6.59 (dd, J = 25.4, 8.3 Hz, 2H), 5.04 (dd, J = 8.9, 4.3 Hz, 1H), 3.90 (d, J = 4.3 Hz, 1H), 2.49 (dt, J = 12.8, 4.4 Hz, 1H), 2.37 – 2.32 (m, 3H), 2.28 (s, 3H), 1.46 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.9, 154.8, 137.4, 137.2, 135.7, 134.6, 129.6, 128.7, 127.7, 127.3, 127.0, 126.6, 79.5, 59.8, 56.9, 39.9, 28.3, 26.3, 21.0. **MS** (ESI, m/z): calculated for $C_{23}H_{27}NO_3Na$ (M + Na^+), 388.1889; found, 388.1898. (Diastereomer 2) (*S*,*R*) $[\alpha]_D^{23}$= +16.2º (*c*= 1.00, 97% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 3H), 7.02 (m, 3H), 6.81 (m, 1H), 6.64 (m, 1H), 5.32 (d, J = 8.7 Hz, 1H), 5.17 (t, J = 8.2 Hz, 1H), 3.79 (d, J = 7.7 Hz, 1H), 3.03 – 2.66 (m, 2H), 2.47 – 2.26 (m, 5H), 1.46 (s, 9H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.0, 155.0, 137.7, 137.4, 136.2, 133.6, 129.4, 129.0, 127.8, 127.2, 126.9, 126.4, 79.9, 61.1, 56.1, 37.7, 28.3, 27.0, 21.1. **MS** (ESI, m/z): calculated for $C_{23}H_{27}NO_3Na$ (M + Na^+), 388.1889; found, 388.1894. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times of diastereomer 1: 14.3 min (major), 55.3 (minor). Retention times of diastereomer 2: 22.0 min (major), 31.0 (minor)).

tert-Butyl((1*R*)-(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)(phenyl)methyl)carbamate (10Ab)

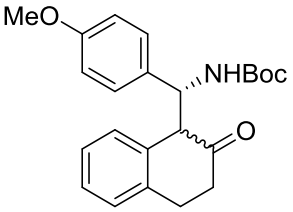


10Ab

The adduct was obtained as a 50:50 mixture of diastereomers following the general procedure by using benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9b** (62 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 91% (48 mg, 0.136 mmol). Both diastereomers were separated

by flash column chromatography. (Diastereomer 1) (*R*,*R*) **$[\alpha]_D^{23}$**= –106.5º (*c*= 1.00, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.07 (m, 6H), 7.01 (d, J = 7.5 Hz, 1H), 6.66 (dd, J = 38.9, 8.2 Hz, 2H), 5.06 (dd, J = 8.9, 4.3 Hz, 1H), 3.90 (d, J = 4.3 Hz, 1H), 2.44 (dd, J = 15.4, 4.7 Hz, 1H), 2.39 – 2.28 (m, 2H), 1.62 – 1.53 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.8, 154.8, 138.7, 137.4, 134.5, 129.6, 128.0, 127.7, 127.5, 127.4, 127.1, 126.8, 79.6, 60.1, 56.8, 39.9, 28.4, 26.1. **MS** (ESI, m/z): calculated for $C_{22}H_{25}NO_3Na$ (M + Na^+), 374.1732; found, 374.1740. (Diastereomer 2) (*S*,*R*) **$[\alpha]_D^{23}$**= –1. 60º (*c*= 1.00, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 5H), 7.03 (m, 1H), 6.94 – 6.89 (m, 2H), 6.60 (d, J = 7.8 Hz, 1H), 5.35 (d, J = 8.7 Hz, 1H), 5.18 (t, J = 8.3 Hz, 1H), 3.77 (d, J = 7.8 Hz, 1H), 2.99 – 2.82 (m, 2H), 2.69 (d, J = 18.6 Hz, 1H), 2.47 – 2.35 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.9, 155.0, 139.3, 137.6, 133.5, 129.3, 128.4, 127.8, 127.7, 127.3, 127.1, 126.4, 80.0, 61.1, 56.2, 37.7, 28.3, 26.9. **MS** (ESI, m/z): calculated for $C_{22}H_{25}NO_3Na$ (M + Na^+), 374.1732; found, 374.1738. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AS-H, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times of diastereomer 1: 6.4 min (minor), 23.5 (major). Retention times of diastereomer 2: 16.0 min (major), 57.3 (minor)).

tert-Butyl((1*R*)-(4-methoxyphenyl)(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)carbamate (10Ac)

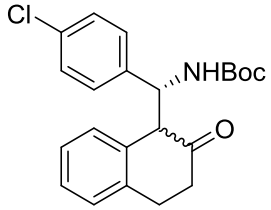


10Ac

The adduct was obtained as a 50:50 mixture of diastereomers following the general procedure by using 4-methoxybenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9c** (71 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 94% (54 mg, 0.141 mmol). Both diastereomers were separated by flash column chromatography. (Diastereomer 1) (*R*,*R*) **$[\alpha]_D^{23}$**= –133.8º (*c*= 0.50, 97% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 13.7, 7.4 Hz, 1H), 7.21 (td, J = 7.3, 1.8 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.64 (s, 5H), 4.99 (dd, J = 9.1, 4.1 Hz, 1H), 3.87 (d, J = 4.2 Hz, 1H), 3.73 (s, 3H), 2.53 – 2.43 (m, 1H), 2.35 – 2.29 (m, 2H), 1.67 (m, 1H), 1.44 – 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.0, 159.0, 154.8, 137.4, 134.6, 130.8, 129.6, 128.2, 127.8, 127.3, 127.1, 113.4, 79.5, 59.6, 56.8, 55.2, 40.0, 28.4, 28.2, 26.3. **MS** (ESI, m/z): calculated for $C_{23}H_{27}NO_4Na$ (M + Na^+), 404.1839; found, 404.1838. (Diastereomer 2) (*S*,*R*) **$[\alpha]_D^{23}$**= +48.2º (*c*= 0.25, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 (d, J = 6.8 Hz, 2H), 7.04 (m, 1H), 6.81 (d, J = 8.3 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 9.3 Hz, 1H), 5.26 (m, 1H), 5.19 – 5.08 (m, 1H), 3.76 (s, 3H), 3.74 (d, J = 3.8 Hz, 1H), 2.87 (m, 2H), 2.68 (d, J = 18.2 Hz, 1H), 2.46 – 2.32 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.1, 159.1, 155.0, 137.7, 131.4, 129.5, 128.2, 127.8, 127.3, 126.4, 113.7, 113.4, 79.9, 61.1, 55.9, 55.2, 37.8, 28.3, 26.9. **MS** (ESI, m/z): calculated for $C_{23}H_{27}NO_4Na$ (M + Na^+),

404.1837; found, 404.1838. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times of diastereomer 1: 21.5 min (major), 109.3 (minor). Retention times of diastereomer 2: 37.2 min (major), 52.1 (minor)).

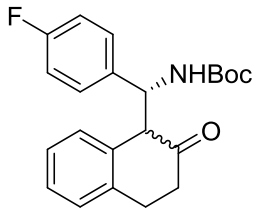
tert-Butyl((1*R*)-(4-chlorophenyl)(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)carbamate (10Ad)



10Ad

The adduct was obtained as a 50:50 mixture of diastereomers following the general procedure by using 4-chlorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9d** (72 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 89% (51 mg, 0.133 mmol). Both diastereomers were separated by flash column chromatography. (Diastereomer 1) (*R*,*R*) $[\alpha]_D^{23}$= –141.2º (*c*= 1.00, 96% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.24 – 7.17 (m, 1H), 7.11 – 7.04 (m, 3H), 6.68 – 6.63 (m, 2H), 5.07 – 5.02 (m, 1H), 3.89 (d, J = 4.2 Hz, 1H), 2.52 (dt, J = 15.6, 4.8 Hz, 1H), 2.34 (dd, J = 8.9, 4.8 Hz, 2H), 1.72 – 1.60 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.6, 154.8, 137.5, 137.3, 134.2, 133.4, 129.5, 128.2, 128.0, 127.6, 127.3, 79.8, 59.5, 56.3, 40.0, 28.4, 26.3. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3ClNa$ (M + Na^+), 408.1342; found, 408.1349. (Diastereomer 2) (*S*,*R*) $[\alpha]_D^{23}$= +45.1º (*c*= 1.00, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 4H), 7.07 (m, 1H), 6.86 (d, J = 8.1 Hz, 2H), 6.65 (m, 1H), 5.41 (d, J = 8.6 Hz, 1H), 5.17 (t, J = 8.2 Hz, 1H), 3.72 (d, J = 7.7 Hz, 1H), 3.01 – 2.81 (m, 2H), 2.67 (dt, J = 18.3, 4.7 Hz, 1H), 2.48 – 2.35 (m, 1H), 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.7, 154.9, 138.2, 137.5, 133.5, 129.1, 128.5, 128.4, 128.2, 127.9, 127.5, 126.7, 80.1, 60.7, 55.2, 37.6, 28.3, 27.0. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3ClNa$ (M + Na^+), 408.1342; found, 408.1347. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times of diastereomer 1: 9.7 min (major), 23.1 (minor). Retention times of diastereomer 2: 12.9 min (major), 16.0 (minor)).

tert-Butyl((1*R*)-(4-fluorophenyl)(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)carbamate (10Ae)

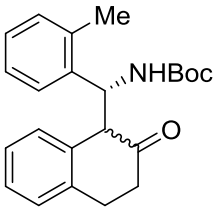


10Ae

The adduct was obtained as a 50:50 mixture of diastereomers following the general procedure by using 4-fluorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9e** (67 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 90% (50 mg, 0.135 mmol). Both diastereomers were separated by flash column chromatography. (Diastereomer 1) (*R*,*R*) $[\alpha]_D^{23}$= –118.8º (*c*= 0.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$)

δ 7.36 – 7.23 (m, 3H), 7.02 (d, J = 7.5 Hz, 1H), 6.80 (t, J = 8.5 Hz, 2H), 6.68 (dd, J = 8.5, 5.5 Hz, 2H), 5.03 (dd, J = 8.8, 4.2 Hz, 1H), 3.89 (d, J = 4.2 Hz, 1H), 2.56 – 2.47 (m, 1H), 2.34 (dd, J = 9.0, 4.8 Hz, 2H), 1.68 – 1.58 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.8, 163.8, 160.6, 154.8, 137.3, 134.5 (d, J = 21.9 Hz), 129.6, 128.3 (d, J = 7.9 Hz), 127.9, 127.5, 127.2, 114.9 (d, J = 21.3 Hz), 79.7, 59.5, 56.4, 40.0, 28.4, 26.2. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3FNa$ (M + Na^+), 392.1638; found, 392.1640. (Diastereomer 2) (*S*,*R*) **$[\alpha]_D^{23}$**= –27.1° (*c*= 0.25, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (m, 2H), 7.09 – 7.02 (m, 1H), 6.89 (d, J = 7.1 Hz, 4H), 6.64 (m, 1H), 5.40 – 5.32 (m, 1H), 5.17 (t, J = 8.2 Hz, 1H), 3.72 (dd, J = 7.7, 2.0 Hz, 1H), 2.88 (m, 2H), 2.68 (d, J = 18.5 Hz, 1H), 2.49 – 2.37 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.8, 163.8, 160.5, 155.0, 137.5, 135.3, 129.3, 128.7, 128.6, 127.9, 127.5, 126.6, 115.2 (d, J = 21.4 Hz), 80.1, 60.9, 55.4, 37.7, 28.3, 28.2, 27.0. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3FNa$ (M + Na^+), 392.1638; found, 392.1644. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AS-H, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times of diastereomer 1: 14.2 min (major), 48.4 (minor). Retention times of diastereomer 2: 6.5 min (minor), 37.7 (major)).

tert-Butyl((1*R*)-(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)(o-tolyl)methyl)carbamate (10Af)

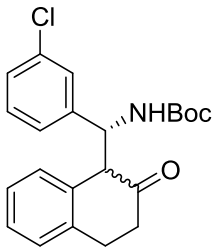


10Af

The adduct was obtained as a 65:35 mixture of diastereomers following the general procedure by using 2-methylbenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9f** (66 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 93% (51 mg, 0.139 mmol). Both diastereomers were separated by flash column chromatography. (Diastereomer 1) (*R*,*R*) **$[\alpha]_D^{23}$**= –191.4° (*c*= 0.25, 88% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22 (m, 3H), 7.12 – 7.05 (m, 4H), 6.96 (m, 1H), 6.23 (d, J = 8.6 Hz, 1H), 5.36 (dd, J = 8.9, 4.3 Hz, 1H), 3.87 (d, J = 4.1 Hz, 1H), 2.48 – 2.30 (m, 3H), 1.77 (m, 1H), 1.66 (s, 3H), 1.41 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.2, 154.7, 137.8, 137.4, 136.4, 133.9, 130.5, 128.0, 127.5, 127.5, 126.9, 126.2, 125.9, 110.0, 79.6, 57.6, 55.3, 39.6, 28.4, 25.9, 18.6. **MS** (ESI, m/z): calculated for $C_{23}H_{27}NO_3Na$ (M + Na^+), 388.1889; found, 388.1896. (Diastereomer 2) (*S*,*R*) **$[\alpha]_D^{23}$**= +20.3° (*c*= 0.50, 83% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 5H), 6.97 – 6.88 (m, 2H), 6.30 (d, J = 7.6 Hz, 1H), 5.41 (m, 2H), 3.61 (m, 2H), 2.95 (dddd, J = 35.1, 18.7, 6.5, 2.6 Hz, 2H), 2.49 – 2.44 (m, 1H), 1.75 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.0, 155.2, 138.2, 137.5, 136.3, 133.4, 130.5, 130.1, 129.3, 127.6, 127.4, 126.4, 126.2, 125.8, 79.9, 62.6, 51.1, 37.2, 28.3, 27.2, 18.8. **MS** (ESI, m/z): calculated for $C_{23}H_{27}NO_3Na$ (M + Na^+), 388.1889; found, 388.1892. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol,

95:5; flux= 1 mL/min; retention times of diastereomer 1:. 16.0 min (major), 21.3 (minor). Retention times of diastereomer 2: 8.3 min (major), 9.5 (minor)).

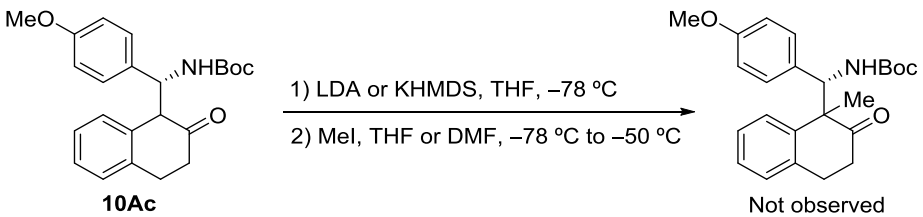
tert-Butyl((1_R_)-(3-chlorophenyl)(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)carbamate (10Ag)



10Ag

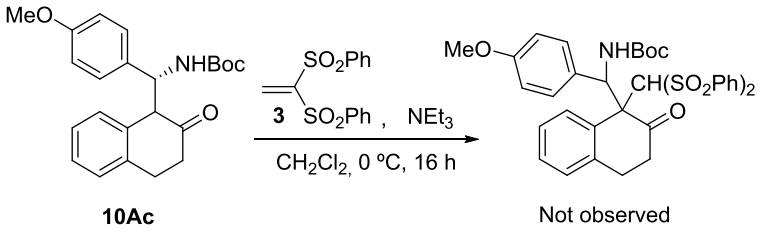
The adduct was obtained as a 50:50 mixture of diastereomers following the general procedure by using 3-chlorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **9g** (72 mg, 0.30 mmol, 2 equiv.). White foam. Yield: 90% (52 mg, 0.135 mmol). Submission of the mixture to flash column chromatography afforded diastereomer 1 as a single isomer and another fraction with a mixture of both isomers. (Diastereomer 1) (*R*,*R*) $[\alpha]_D^{23}$= –127.5º (*c*= 0.25, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 2H), 7.28 – 7.25 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.8 Hz, 2H), 6.63 (m, 2H), 5.04 (dd, J = 8.8, 4.3 Hz, 1H), 3.90 (d, J = 4.3 Hz, 1H), 2.54 (dt, J = 15.8, 4.6 Hz, 1H), 2.40 – 2.35 (m, 2H), 1.74 – 1.67 (m, 1H), 1.45 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.4, 154.8, 141.0, 137.3, 134.1, 134.0, 129.5, 129.3, 127.9, 127.7, 127.7, 127.3, 127.0, 124.9, 79.9, 59.5, 56.3, 39.9, 28.4, 26.3. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3ClNa$ (M + Na^+), 408.1342; found, 408.1349. (Diastereomer 2) (*S*,*R*): (99% *ee*). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 4H), 7.05 (d, J = 7.7 Hz, 3H), 6.97 – 6.81 (m, 1H), 5.42 (m, 1H), 5.18 (t, J = 8.3 Hz, 1H), 3.73 (d, J = 7.6 Hz, 1H), 2.96 (d, J = 23.4 Hz, 1H), 2.67 (d, J = 18.4 Hz, 1H), 2.42 – 2.35 (m, 2H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.6, 150.8, 141.0, 137.5, 134.0, 129.6, 129.0, 127.8, 127.7, 127.6, 127.2, 126.7, 125.3, 60.6, 55.2, 37.5, 29.7, 28.3, 27.1. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AS-H, solvent gradient: hexane/isopropanol, 90:10; flux= 1 mL/min for 15 min; hexane/isopropanol, 80:20; flux= 1 mL/min for 20 min; hexane/isopropanol, 70:30; flux= 1 mL/min for 3 min; hexane/isopropanol, 60:40; flux= 1 mL/min for 3 min; hexane/isopropanol, 50:50; flux= 1 mL/min; retention times of diastereomer 1: 15.8 min (major), 59.2 (minor). Retention times of diastereomer 2: 5.7 min (major), 23.6 min (minor)).

5.3.12. Attempts of chemical elaborations of compound 10A



10Ac Not observed

A solution of **10A** (38 mg, 0.1 mmol, 1 equiv.) in dry THF (0.2 mL) was added dropwise over a solution of KHMDS (0.5 M in toluene, 0.5 mL, 0.25 mmol, 2.5 equiv.) or LDA (0.04 mL, 0.3 mmol, 3 equiv.) in THF () at −78 °C and the mixture was stirred at the same temperature (for 4 h in the case of KHMDS and for 1 h in the case of LDA). MeI (16 μL, 0.25 mmol, 2.5 equiv.) (in 0.5 mL of DMF in the case of LDA) was added and the mixture was allowed to reach −50 °C and stirred at this temperature for 3 h. The reaction was quenched with 3 mL of saturated aqueous NH_4Cl and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was submitted to a silica gel flash column chromatography. Unidentified compounds were isolated.



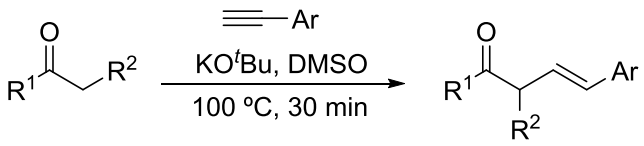
Triethylamine (16 μL, 0.25 mmol, 0.3 equiv.) was added over a solution of **10Ac** (38 mg, 0.1 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene **3** (62 mg, 0.2 mmol, 2 equiv.) in CH_2Cl_2 (0.3 mL) at 0 °C. The resulting solution was stirred at the same temperature for 16 h. The reaction mixture was directly submitted to a flash column chromatography.

5.4. Experimental Section of Chapter 3

5.4.1. Preparation of α-branched ketones

All α-branched ketones were prepared following the general procedures described bellow.

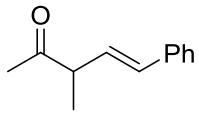
General procedure[203]



[203] B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova, I. A. Ushakov, *J. Org. Chem*. **2012**, *77*, 6880−6886.

A solution of the corresponding ketone (8 mmol, 1 equiv.), aromatic alkyne (8 mmol, 1 equiv.) and potassium tert-butoxide (900 mg, 8 mmol, 1 equiv.) in DMSO (20 mL) was stirred at 100 °C for 30 min in a sealed tube under argon. The reaction mixture was then cooled to room temperature, water (20 mL) was added and the mixture was neutralized with a saturated solution of NH_4Cl. The resulting biphasic mixture was extracted with Et_2O (4 x 20 mL), the combined organic extract was washed with water (2 x 20 mL) and dried over $MgSO_4$. Volatiles were removed under reduced pressure and the resulting crude compound was purified by silica gel flash column chromatography (hexane/CH_2Cl_2 1:1).

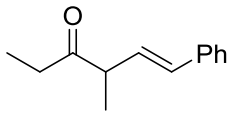
(*E*)-3-Methyl-5-phenylpent-4-en-2-one (12a)



12a

The general procedure was applied starting from butanone (0.72 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 43% (599 mg, 3.4 mmol). The NMR spectrum matched that reported in the literature.[204] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.17 (m, 5H), 6.53 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 15.9, 8.5 Hz, 1H), 3.36 (p, J = 7.0 Hz, 1H), 2.20 (s, 3H), 1.28 (d, J = 6.9 Hz, 3H).

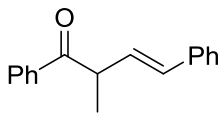
(*E*)-4-Methyl-6-phenylhex-5-en-3-one (12b)



12b

The general procedure was applied starting from propan-3-one (0.85 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 48% (723 mg, 3.8 mmol). The NMR spectrum matched that reported in the literature.[205] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 5H), 6.50 (d, J = 15.8 Hz, 1H), 6.17 (dd, J = 15.9, 8.6 Hz, 1H), 3.38 (dt, J = 14.4, 6.6 Hz, 1H), 2.68 – 2.43 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H), 1.05 (t, J = 7.3 Hz, 3H).

(*E*)-2-Methyl-1,4-diphenylbut-3-en-1-one (12c)



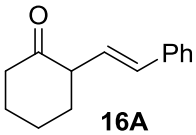
12c

The general procedure was applied starting from propiophenone (1.08 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 57% (1.08 g, 4.6 mmol). The NMR spectrum matched that reported in the literature.[203] **^{1}H NMR** (300

[204] L. Chapado, P. J. Linares-Palomino, C. Badia, S. Salido, M. Nogueras, A. Sanchez, J. Altarejos, *Molecules*, **2009**, 14, 2780–2800.
[205] C. Li, Y. Zhang, Q. Sun, T. Gu, H. Peng, W. Tang, *J. Am. Chem. Soc*. **2016**, *138*, 10774–10777.

MHz, $CDCl_3$) δ 8.03 (d, J = 7.1 Hz, 2H), 7.60 – 7.44 (m, 3H), 7.38 – 7.19 (m, 5H), 6.53 (d, J = 16.0 Hz, 1H), 6.37 (dd, J = 16.0, 8.0 Hz, 1H), 4.33 (p, J = 7.1 Hz, 1H), 1.43 (d, J = 6.8 Hz, 3H).

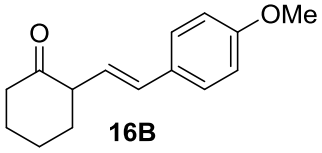
(*E*)-2-(2-Styryl)cyclohexanone (16A)



16A

The general procedure was applied starting from cyclohexanone (0.83 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow solid. Yield: 50% (803 mg, 4.0 mmol). The NMR spectrum matched that reported in the literature.[206] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (d, J = 7.4 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.52 – 6.31 (m, 2H), 3.26 – 3.15 (m, 1H), 2.55 – 2.44 (m, 1H), 2.44 – 2.32 (m, 1H), 2.25 – 2.13 (m, 1H), 2.13 – 2.01 (m, 1H), 1.99 – 1.86 (m, 1H), 1.85 – 1.68 (m, 3H).

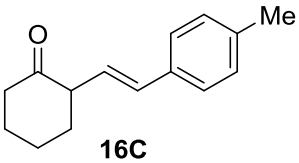
(*E*)-2-(4-Methoxystyr-2-yl)cyclohexanone (16B)



16B

The general procedure was applied starting from cyclohexanone (0.83 mL, 8 mmol, 1 equiv.) and 4-ethynylanisole (1.04 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 28% (520 mg, 2.2 mmol). The NMR spectrum matched that reported in the literature.[206] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.35 – 6.29 (m, 2H), 3.80 (s, 3H), 3.23 – 3.10 (m, 1H), 2.52 – 2.45 (m, 1H), 2.39 – 2.31 (m, 1H), 2.21 – 2.12 (m, 1H), 2.05 (dd, J = 2.6, 1.6 Hz, 1H), 1.93 (s, 1H), 1.80 – 1.70 (m, 3H).

(E)-2-(4-Methylstyr-2-yl)cyclohexanone (16C)

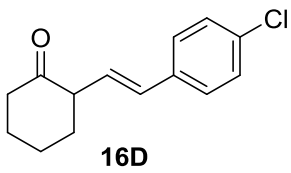


16C

The general procedure was applied starting from cyclohexanone (0.83 mL, 8 mmol, 1 equiv.) and 4-ethynyltoluene (1.01 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 33% (570 mg, 2.7 mmol). The NMR spectrum matched that reported in the literature.[206] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 2H), 7.16 – 6.98 (m, 2H), 6.37 (m, 2H), 3.21 – 3.17 (m, 1H), 2.51 – 2.45 (m, 1H), 2.40 – 2.35 (m, 1H), 2.33 (s, 3H), 2.20 – 2.16 (m, 1H), 2.09 – 2.05 (m, 1H), 1.95 – 1.89 (m, 1H), 1.80 – 1.75 (m, 3H).

[206] L.-L. Zhu, X.-X. Li, W. Zhou, X. Li, Z. Chen, *J. Org. Chem*. **2011**, *76*, 8814–8823.

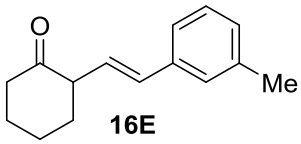
(*E*)-2-(4-Chlorostyr-2-yl)cyclohexanone (16D)



16D

The general procedure was applied starting from cyclohexanone (0.83 mL, 8 mmol, 1 equiv.) and 1-chloro-4-ethynylbenzene (1.10 g, 8 mmol, 1 equiv.) as a yellow solid. Yield: 25% (474 mg, 2.0 mmol). M.p. = 48–51 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 4H), 6.61 – 6.23 (m, 2H), 3.29 – 3.15 (m, 1H), 2.54 – 2.47 (m, 1H), 2.43 – 2.37 (m, 1H), 2.22 – 2.18 (m, 1H), 2.12 – 2.09 (m, 1H), 2.01 – 1.95 (m, 1H), 1.81 – 1.74 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.9, 135.6, 132.9, 130.1, 128.6, 128.3, 127.5, 53.9, 41.8, 34.4, 27.6, 24.5. **MS** (ESI, m/z): calculated for $C_{14}H_{16}OCl$ (M + H^+), 235.0890; found, 235.0898.).

(*E*)-2-(3-Methylstyr-2-yl)cyclohexanone (16E)

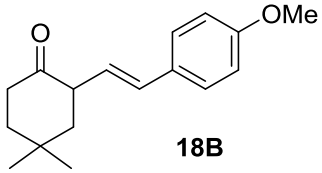


16E

The general procedure was applied starting from cyclohexanone (0.83 mL, 8 mmol, 1 equiv.) and 3-ethynyltoluene (1.03 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 28% (485 mg, 2.3 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 3H), 7.12 – 7.05 (m, 1H), 6.55 – 6.34 (m, 2H), 3.27 – 3.18 (m, 1H), 2.58 – 2.47 (m, 1H), 2.48 – 2.37 (m, 1H), 2.39 (s, 3H), 2.26 – 2.18 (m, 1H), 2.14 – 2.05 (m, 1H), 2.03 – 1.93 (m, 1H), 1.85 – 1.76 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.9, 137.8, 137.0, 131.3, 128.2, 128.0, 127.2, 126.8, 123.4, 53.8, 41.6, 34.3, 27.5, 24.3, 21.2. **MS** (ESI, m/z): calculated for $C_{15}H_{19}O$ (M + H^+), 215.1436; found, 215.1438.

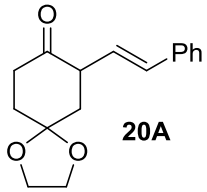
(*E*)-2-(4-Methoxystyr-2-yl)-4,4-dimethylcyclohexanone (18B)[186]



18B

The general procedure was applied starting from 4,4-dimethylcyclohexanone (1.01g mL, 8 mmol, 1 equiv.) and 4-ethynylanisole (1.04 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 27% (485 mg, 1.9 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.40 – 6.21 (m, 2H), 3.82 (s, 3H), 3.37 – 3.24 (m, 1H), 2.64 – 2.46 (m, 1H), 2.41 – 2.30 (m, 1H), 1.95 – 1.64 (m, 4H), 1.29 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.9, 159.0, 130.6, 130.0, 127.4, 125.4, 113.6, 55.3, 49.7, 47.2, 38.2, 31.4, 30.8, 24.6. **MS** (ESI, m/z): calculated for $C_{17}H_{23}O_2$ (M + H^+), 259.1698; found, 259.1711.

(*E*)-7-(2-Styryl)-1,4-dioxaspiro[4.5]decan-8-one (20A)

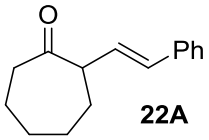


20A

The general procedure was applied starting from 1,4-cyclohexanedione monoethylene acetal (1.25 g, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as an orange oil. Yield:

68% (1.41 g, 5.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 1H), 6.43 – 6.37 (m, 2H), 4.07 – 3.96 (m, 4H), 3.52 (dtd, J = 12.3, 6.1, 0.9 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.51 – 2.41 (m, 1H), 2.24 – 2.19 (m, 1H), 2.09 – 2.05 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.5, 136.9, 131.5, 128.4, 127.4, 126.4, 126.3, 64.8, 64.6, 64.3, 49.9, 40.8, 38.0, 34.4. **MS** (ESI, m/z): calculated for $C_{16}H_{19}O_3$ ($M + H^+$), 259.1334; found, 259.1336.

(*E*)-2-(2-Styryl)cycloheptanone (22A)[186]

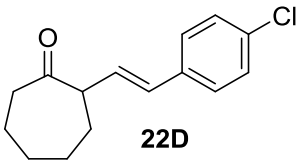


22A

The general procedure was applied starting from cycloheptanone (0.94 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 67% (1.15 g, 5.4 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H), 7.39 – 7.24 (m, 2H), 7.25 – 7.18 (m, 1H), 6.43 (d, J = 16.1 Hz, 1H), 6.32 (dd, J = 16.0, 7.2 Hz, 1H), 3.35 (ddd, J = 11.0, 7.2, 4.0 Hz, 1H), 2.66 – 2.45 (m, 2H), 2.06 – 1.82 (m, 4H), 1.77 – 1.57 (m, 2H), 1.54 – 1.38 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.7, 137.0, 130.8, 128.5, 128.4, 127.3, 126.2, 56.2, 42.4, 31.5, 29.7, 27.9, 24.8. **MS** (ESI, m/z): calculated for $C_{15}H_{19}O$ ($M + H^+$), 215.1436; found, 215.1432.

(*E*)-2-(4-Chlorostyr-2-yl)cycloheptanone (22D)

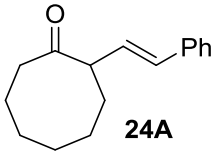


22D

The general procedure was applied starting from cycloheptanone (0.94 mL, 8 mmol, 1 equiv.) and 1-chloro-4-ethynylbenzene (1.09 g, 8 mmol, 1 equiv.) as a yellow solid. Yield: 24% (478 mg, 1.9 mmol). M.p. = 52–54 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 4H), 6.41 – 6.30 (m, 2H), 3.37 – 3.30 (m, 1H), 2.58 – 2.53 (m, 2H), 1.98 – 1.88 (m, 4H), 1.71 – 1.61 (m, 2H), 1.47 – 1.42 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.6, 135.6, 132.9, 129.6, 129.3, 128.6, 127.4, 56.1, 42.5, 31.6, 29.6, 28.0, 24.7. **MS** (ESI, m/z): calculated for $C_{15}H_{18}OCl$ ($M + H^+$), 249.1046; found, 249.1047.

(*E*)-2-(2-Styryl)cyclooctanone (24A)[186]

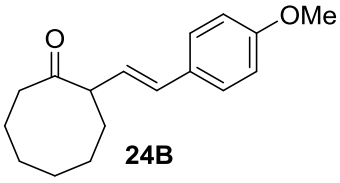


24A

The general procedure was applied starting from cyclooctanone (1.01g mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 74% (1.35 mg, 5.9 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) 7.39 – 7.18 (m, 5H), 6.45 (d, J = 16.0 Hz, 1H), 6.27 (dd, J = 16.0, 7.7 Hz, 1H), 3.39 (ddd, J = 11.2, 7.7, 3.7 Hz, 1H), 2.60 – 2.23 (m, 2H), 2.11 – 1.79 (m, 4H), 1.79 – 1.63 (m, 2H), 1.60 – 1.37 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 216.7, 136.9, 130.9, 128.4, 128.3, 127.3, 126.1, 55.0, 40.7, 32.4, 26.9, 26.1, 25.8, 24.5. **MS** (ESI, m/z): calculated for $C_{16}H_{21}O$ ($M + H^+$), 229.1592; found, 229.1604.

(*E*)-2-(4-Methoxystyr-2-yl)cyclooctanone (24B)

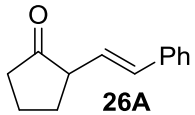


24B

The general procedure was applied starting from cyclooctanone (1.05 mL, 8 mmol, 1 equiv.) and 4-ethynylanisole (1.04 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 24% (1.20 g, 4.6 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.38 (d, J = 15.9 Hz, 1H), 6.11 (dd, J = 15.9, 7.8 Hz, 1H), 3.77 (s, 3H), 3.38 – 3.32 (m, 1H), 2.51 – 2.46 (m, 1H), 2.39 – 2.35 (m, 1H), 2.02 – 1.91 (m, 4H), 1.70 – 1.65 (m, 2H), 1.52 – 1.39 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.0, 159.0, 130.4, 129.7, 127.3, 126.1, 113.8, 55.1, 40.6, 32.4, 26.8, 26.3, 25.9, 24.6. **MS** (ESI, m/z): calculated for $C_{17}H_{23}O_2$ ($M + H^+$), 259.1698; found, 259.1704.

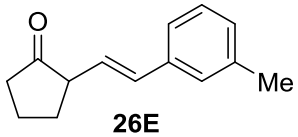
(*E*)-2-(2-Styryl)cyclopentanone (26A)



26A

The general procedure was applied starting from cyclopentanone (0.71 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 62% (1.28 g, 6.9 mmol). The NMR spectrum matched that reported in the literature.[6] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 6.92 (m, 5H), 6.47 (d, J = 16.1 Hz, 1H), 6.24 (dd, J = 16.1, 6.2 Hz, 1H), 3.02 – 2.87 (m, 1H), 2.45 – 2.02 (m, 4H), 1.97 – 1.80 (m, 2H).

(*E*)-2-(3-Methylstyr-2-yl)cyclopentanone (26E)

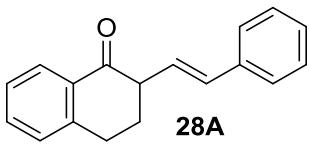


26E

The general procedure was applied starting from cyclopentanone (0.70 mL, 8 mmol, 1 equiv.) and 3-ethynyltoluene (1.03 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 58% (929 mg, 4.6 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 3H), 7.05 – 7.00 (m, 1H), 6.45 (dd, J = 16.1, 1.5 Hz, 1H), 6.23 (dd, J = 16.1, 6.1 Hz, 1H), 2.98 – 2.94 (m, 1H), 2.38 – 2.32 (m, 5H), 2.26 – 2.20 (m, 1H), 2.13 – 2.09 (m, 1H), 1.95 – 1.89 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.1, 138.0, 136.9, 132.0, 128.3, 128.2, 126.8, 125.8, 123.4, 52.5, 37.8, 29.7, 21.3, 20.8. **MS** (ESI, m/z): calculated for $C_{14}H_{17}O$ ($M + H^+$), 201.1279; found, 201.1288.

(*E*)-2-(2-Styryl)-3,4-dihydronaphthalen-1(2*H*)-one (28A)



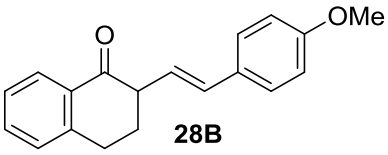
28A

The general procedure was applied starting from α-tetralone (1.1 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 47% (938 mg, 3.8 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.8, 1.3 Hz, 1H), 7.55 – 7.43 (m, 1H), 7.46 – 7.36 (m, 2H), 7.37 – 7.21 (m, 5H), 6.58 – 6.50 (m, 2H), 3.48 – 3.38 (m, 1H), 3.15 – 3.03 (m, 2H), 2.46 – 2.33 (m, 1H), 2.27 – 2.15 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.0, 143.8, 137.0,

133.47, 133.1, 131.9, 128.7, 128.4, 127.6, 127.4, 127.1, 126.7, 126.3, 50.8, 29.4, 28.1. **MS** (ESI, m/z): calculated for $C_{18}H_{17}O$ (M + H^+), 249.1279; found, 249.1283.

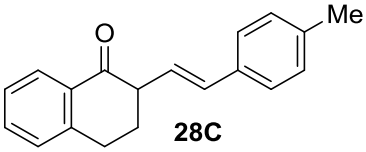
(*E*)-2-(4-Methoxystyry-2-l)-3,4-dihydronaphthalen-1(2*H*)-one (28B)



28B

The general procedure was applied starting from α-tetralone (1.1 mL, 8 mmol, 1 equiv.) and 4-ethynylanisole (1.04 mL, 8 mmol, 1 equiv.) as a yellow solid. Yield: 61% (1.36 g, 4.9 mmol). M.p. = 83–85 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (ddd, J = 7.9, 1.4, 0.6 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.38 – 7.29 (m, 3H), 7.31 – 7.21 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.54 – 6.30 (m, 2H), 3.80 (s, 3H), 3.45 – 3.33 (m, 1H), 3.13 – 3.02 (m, 2H), 2.42 – 2.33 (m, 1H), 2.26 – 2.10 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.4, 159.2, 144.0, 133.5, 132.5, 131.5, 130.1, 128.8, 127.8, 127.6, 126.8, 124.9, 114.0, 55.4, 50.9, 29.6, 28.2. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O_2$ (M + H^+), 279.1385; found, 279.1391.

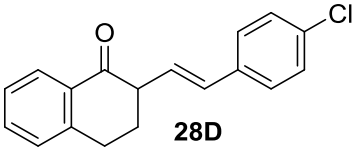
(*E*)-2-(4-Methylstyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (28C)



28C

The general procedure was applied starting from α-tetralone (1.1 mL, 8 mmol, 1 equiv.) and 4-ethynyltoluene (1.01 mL, 8 mmol, 1 equiv.) as a yellow solid. Yield: 60% (1.27 g, 4.8 mmol). M.p. = 82–84 °C. **^{1}H NMR** (300 MHz, $CDCl_3$ δ 8.09 (dd, J = 7.9, 1.4 Hz, 1H), 7.49 (td, J = 7.5, 1.5 Hz, 1H), 7.38 – 7.23 (m, 4H), 7.17 – 7.07 (m, 2H), 6.53 – 6.45 (m, 2H), 3.47 – 3.33 (m, 1H), 3.15 – 3.03 (m, 2H), 2.44 – 2.36 (m, 1H), 2.34 (s, 3H), 2.26 – 2.14 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.3, 144.0, 137.3, 134.4, 133.5, 132.5, 132.0, 129.3, 128.8, 127.8, 126.8, 126.3, 126.1, 50.9, 29.5, 28.2, 21.3. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O$ (M + H^+), 263.1436; found, 263.1439.

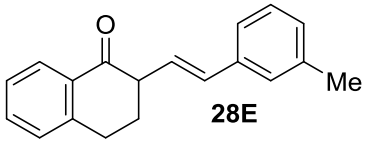
(*E*)-2-(4-Chlorostyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (28D)



28D

The general procedure was applied starting from α-tetralone (1.1 mL, 8 mmol, 1 equiv.) and 1-chloro-4-ethynylbenzene (1.09 g, 8 mmol, 1 equiv.) as a yellow solid. Yield: 28% (632 mg, 2.2 mmol). M.p. = 87–89 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.8, 1.5 Hz, 1H), 7.49 (td, J = 7.5, 1.5 Hz, 1H), 7.39 – 7.27 (m, 3H), 7.32 – 7.21 (m, 3H), 6.55 – 6.45 (m, 2H), 3.45 – 3.33 (m, 1H), 3.14 – 3.03 (m, 2H), 2.43 – 2.32 (m, 1H), 2.23 – 2.15 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.0, 144.0, 135.7, 133.6, 133.1, 132.4, 130.9, 128.9, 128.7, 128.0, 127.8, 127.6, 126.88, 50.9, 29.4, 28.3. **MS** (ESI, m/z): calculated for $C_{18}H_{16}OCl$ (M + H^+), 283.0890; found, 283.0893.

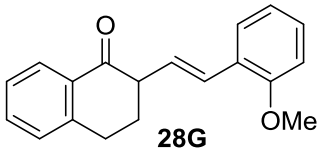
(*E*)-2-(3-Methylstyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (28E)



28E

The general procedure was applied starting from α-tetralone (1.1 mL, 8 mmol, 1 equiv.) and 3-ethynyltoluene (1.0 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 79% (1.36 g, 6.3 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 (d, J = 7.8 Hz, 1H), 7.56 – 7.42 (m, 1H), 7.40 – 7.17 (m, 5H), 7.10 – 6.97 (m, 1H), 6.62 – 6.47 (m, 2H), 3.42 (dt, J = 9.8, 4.8 Hz, 1H), 3.08 (q, J = 4.9, 4.4 Hz, 2H), 2.46 – 2.29 (m, 4H), 2.27 – 2.12 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.9, 143.8, 137.8, 136.9, 133.3, 131.9, 128.6, 128.2, 128.1, 127.5, 126.8, 126.8, 126.6, 123.4, 50.7, 29.2, 28.0, 21.3. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O$ ($M + H^+$), 263.1436; found, 263.1437.

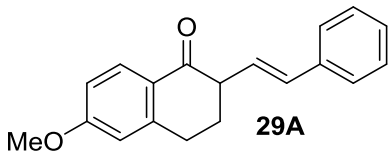
(*E*)-2-(2-Methoxystyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (28G)



28G

The general procedure was applied starting from α-tetralone (1.1 mL, 8 mmol, 1 equiv.) and 2-ethynylanisole (1.03 mL, 8 mmol, 1 equiv.) as a brown oil. Yield: 58% (1.29 g, 4.6 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 (dd, J = 7.9, 1.0 Hz, 1H), 7.52 (ddd, J = 12.4, 7.5, 1.6 Hz, 2H), 7.39 – 7.22 (m, 3H), 6.99 – 6.84 (m, 3H), 6.59 (dd, J = 16.3, 6.7 Hz, 1H), 3.86 (s, 3H), 3.49 – 3.44 (m, 1H), 3.14 – 3.07 (m, 2H), 2.47 – 2.40 (m, 1H), 2.30 – 2.23 (m, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.1, 156.4, 143.9, 133.2, 132.3, 128.6, 128.4, 127.5, 127.5, 126.6, 126.6, 126.1, 120.5, 110.7, 55.3, 51.2, 29.4, 28.2. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O_2$ ($M + H^+$), 279.1385; found, 279.1387.

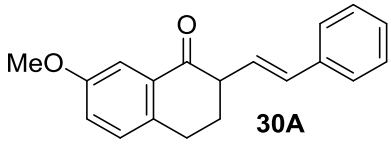
(*E*)-6-Methoxy-2-(2-styryl)-3,4-dihydronaphthalen-1(2*H*)-one (29A)



29A

The general procedure was applied starting from 6-methoxy-1-tetralone (1.41 g, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow solid. Yield: 48% (1.05 g, 3.8 mmol). M.p. = 72–74 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.8 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.31 (t, J = 1.2 Hz, 2H), 7.26 – 7.22 (m, 1H), 6.86 (dd, J = 8.8, 2.5 Hz, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.57 – 6.52 (m, 2H), 3.86 (s, 3H), 3.42 – 3.34 (m, 1H), 3.06 – 3.03 (m, 2H), 2.40 – 2.34 (m, 1H), 2.25 – 2.14 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.9, 163.7, 146.5, 139.8, 137.2, 131.9, 130.2, 128.5, 127.5, 127.4, 126.4, 113.3, 112.6, 55.5, 50.6, 29.5, 28.6. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O_2$ ($M + H^+$), 279.1385; found, 279.1389.

(*E*)-7-Methoxy-2-(2-styryl)-3,4-dihydronaphthalen-1(2*H*)-one (30A)

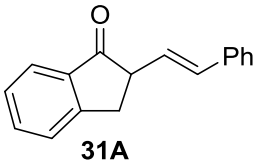


30A

The general procedure was applied starting from 7-methoxy-1-tetralone (1.41 g, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow

solid. Yield: 44% (980 mg, 3.5 mmol). M.p. = 59-62 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, J = 2.8 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.38 – 7.26 (m, 2H), 7.26 – 7.17 (m, 2H), 7.09 (dd, J = 8.4, 2.8 Hz, 1H), 6.54 (d, J = 2.6 Hz, 2H), 3.85 (s, 3H), 3.43 – 3.40 (m, 1H), 3.04 – 3.01 (m, 2H), 2.42 – 2.34 (m, 1H), 2.23 – 2.13 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.0, 158.4, 137.1, 136.5, 133.0, 131.9, 129.9, 128.4, 127.4, 127.1, 126.3, 121.8, 109.5, 55.5, 50.6, 29.6, 27.3. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O_2$ (M + H^+), 279.1385; found, 279.1389.

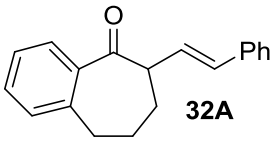
(*E*)-2-(2-Styryl)-2,3-dihydro-1*H*-inden-1-one (31A)



31A

The general procedure was applied starting from 1-indanone (0.96 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow solid. Yield: 39% (724 mg, 3.1 mmol). M.p. = 75–77 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.53 – 7.48 (m, 1H), 7.41 – 7.36 (m, 3H), 7.28 – 7.23 (m, 3H), 6.68 – 6.61 (m, 1H), 6.30 (dd, J = 15.9, 6.9 Hz, 1H), 3.60 – 3.50 (m, 2H), 3.20 – 3.10 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.6, 153.2, 136.9, 136.2, 135.0, 132.7, 128.5, 127.6, 127.5, 126.6, 126.5, 126.3, 124.4, 50.9, 33.2. **MS** (ESI, m/z): calculated for $C_{17}H_{15}O$ (M + H^+), 235.1123; found, 235.1131.

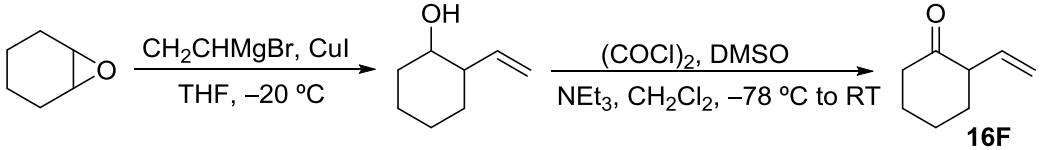
(*E*)-6-(2-Styryl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (32A)



32A

The general procedure was applied starting from 1-benzosuberone (1.20 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 28% (588 mg, 2.2 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 1H), 7.42 – 7.39 (m, 3H), 7.32 – 7.24 (m, 4H), 7.11 – 7.08 (m, 1H), 6.61 (dd, J = 16.0, 7.9 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.11 – 3.03 (m, 1H), 2.12 – 1.95 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.6, 141.8, 139.6, 137.1, 131.4, 130.9, 129.8, 128.5, 128.4, 128.1, 127.3, 126.4, 126.3, 53.5, 33.5, 31.2, 25.2. **MS** (ESI, m/z): calculated for $C_{19}H_{19}O$ (M + H^+), 263.1436; found, 263.1443.

Synthesis of 2-vinylcyclohexanone (16F)[207]



16F

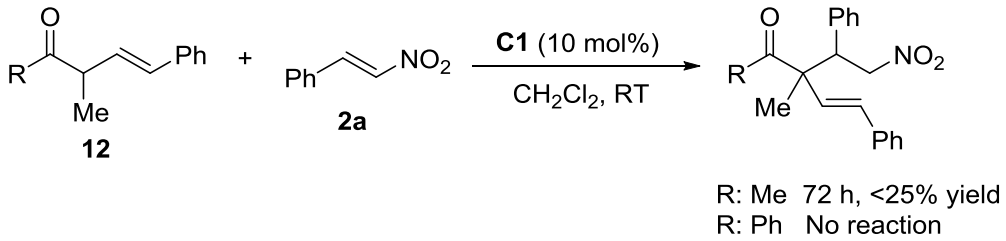
[207] X. Yang, F. D. Toste, *J. Am. Chem. Soc*. **2015**, *137*, 3205–3208.

Step 1: To a solution of CuI (380 mg, 2 mmol, 0.1 equiv.) in THF (20 mL) 1M vinyl magnesium bromide solution (26 mL, 26 mmol, 1.3 equiv.) was added at −78 °C. The mixture was stirred for 30 min before adding cyclohexene oxide (2.0 mL, 20 mmol, 1 equiv.) and stirring for 2 h at −20 °C. The reaction was quenched adding an aqueous saturated solution of NH_4Cl (50 mL) and the mixture was extracted with ether (3 x 50 mL). The combined organic extract was washed with brine (50 mL) and dried over $MgSO_4$, volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 80:20).

Step 2: DMSO (1.1 mL, 15 mmol, 3 equiv.) was added to a solution of $(COCl)_2$ (0.64 mL, 7.5 mmol, 1.5 equiv.) in dichloromethane (15 mL) at −78 °C. After stirring for 30 min a solution of the alcohol obtained above (5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was slowly added. After stirring for 2 h at the same temperature, NEt_3 (4.2 mL, 30 mmol, 6 equiv.) was added and the mixture was slowly warmed to room temperature. The reaction was stirred for 1 h and the reaction was quenched adding an aqueous saturated solution of NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extract was washed with brine (50 mL) and dried over $MgSO_4$, volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/CH_2Cl_2 65:25) to obtain the desired product as a colourless liquid. Yield after two steps: 15% (372 mg, 1.0 mmol). The NMR spectrum matched that reported in the literature.[208] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.08 – 5.97 (m, 1H), 5.18 – 4.97 (m, 2H), 3.04 – 3.00 (m, 1H), 2.43 – 2.31 (m, 2H), 2.12 – 2.01 (m, 2H), 1.91 – 1.89 (m, 1H), 1.74 – 1.67 (m, 3H).

5.4.2. General procedure for the catalytic addition of open-chain α-alkenyl ketones 12

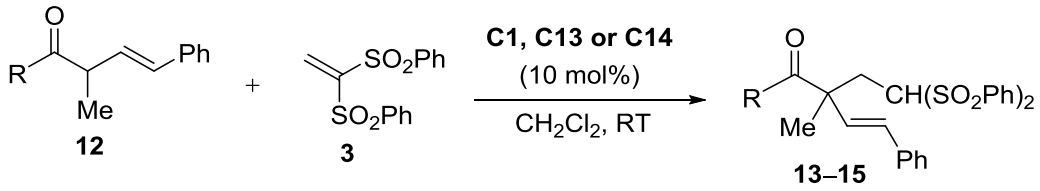
To nitrostyrene 2a



[208] K. Sunggak, L. Sangphil, *Tetrahedron Lett.* **1991**, *32*, 6575–6578.

Catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.) was added to a solution of the corresponding ketone **12** (0.15 mmol, 1 equiv.) and nitrostyrene **2a** (33 mg, 0.23 mmol, 1.5 equiv.) in CH_2Cl_2 (0.3 mL) at room temperature. The resulting solution was stirred for 16 h in the case of phenyl ketone **12c** and no reaction at all was observed. In the case of methyl ketone **12a** even after 72 h of reaction the conversion remained low (25% of isolated product).

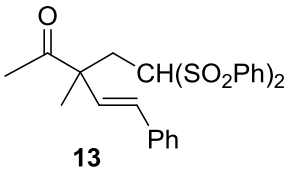
To 1,1-bis(phenylsulfonyl)ethylene 3



The selected catalyst (0.015 mmol, 0.1 equiv.) was added to a solution of the corresponding ketone **12** (0.15 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene **3** (69 mg, 0.23 mmol, 1.5 equiv.) in CH_2Cl_2 at room temperature. The resulting solution was stirred overnight (16 h). Then the mixture was directly submitted to a flash column chromatography.

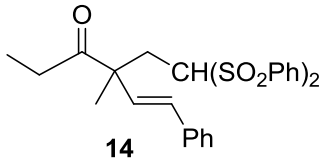
Data of the reactions performed using catalyst **C14** (23 mg):

(*E*)-3-(2,2-Bis(Phenylsulfonyl)ethyl)-3-methyl-5-phenylpent-4-en-2-one (13)



The general procedure was applied starting from ketone **12a** (26 mg, 0.15 mmol, 1 equiv.). Colourless oil. Yield: 71% (46 mg, 0.106 mmol). $[\alpha]_D^{23}$= –59.6° (*c*= 0.25, 79% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 (dt, J = 8.6, 1.6 Hz, 2H), 7.76 – 7.66 (m, 3H), 7.59 – 7.52 (m, 3H), 7.51 – 7.43 (m, 2H), 7.42 – 7.29 (m, 5H), 6.66 – 6.52 (m, 1H), 6.45 – 6.34 (m, 1H), 4.50 (td, J = 4.2, 1.6 Hz, 1H), 2.90 (ddd, J = 16.5, 4.3, 1.6 Hz, 1H), 2.50 (ddd, J = 16.5, 4.1, 1.7 Hz, 1H), 2.22 (s, 3H), 1.38 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.4, 138.2, 137.1, 136.2, 134.6, 134.2, 131.8, 130.9, 130.3, 129.5, 129.0, 128.9, 128.8, 128.3, 126.7, 80.6, 53.5, 30.8, 26.7, 19.9. **MS** (ESI, m/z): calculated for $C_{26}H_{27}O_5S_2$ ($M + H^+$), 483.1300; found, 483.1306. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 74.1 min (minor), 95.5 min (major)).

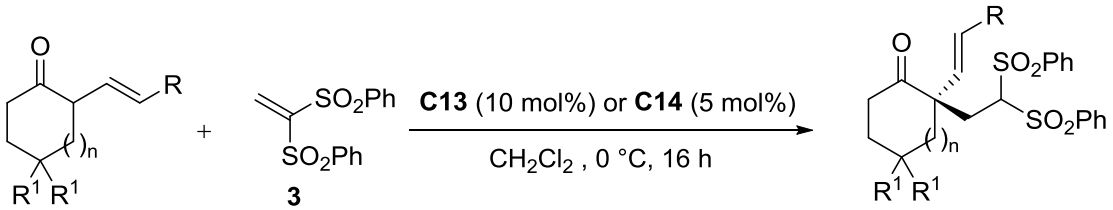
(*E*)-4-(2,2-Bis(Phenylsulfonyl)ethyl)-4-methyl-6-phenylhex-5-en-3-one (14)



14

The general procedure was applied starting from ketone **12b** (28 mg, 0.15 mmol, 1 equiv.). Colourless oil. Yield: 29% (22 mg, 0.043 mmol). $[\alpha]_D^{23}$= –74.6º (*c*= 0.25, 58% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 5.8, 3.5 Hz, 2H), 7.76 – 7.65 (m, 3H), 7.55 (dd, J = 8.1, 5.7 Hz, 3H), 7.50 – 7.27 (m, 7H), 6.56 (d, J = 16.3 Hz, 1H), 6.42 (d, J = 16.2 Hz, 1H), 4.56 (t, J = 4.0 Hz, 1H), 2.83 (dd, J = 16.5, 4.1 Hz, 1H), 2.62 – 2.55 (m, 3H), 1.35 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.3, 138.2, 137.3, 136.3, 134.6, 134.2, 131.5, 131.3, 130.3, 129.6, 129.0, 128.9, 128.8, 128.2, 126.7, 80.4, 53.0, 32.4, 31.2, 20.1, 8.0. **MS** (ESI, m/z): calculated for $C_{27}H_{29}O_5S_2$ ($M + H^+$), 497.1456; found, 497.1456. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 60:40; flux= 1 mL/min; retention times: 41.4 min (minor), 63.6 min (major)).

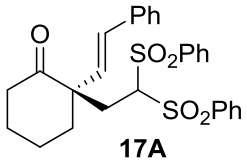
5.4.3. General procedure for the catalytic addition of α-alkenyl cycloalkanones to 1,1-bis(phenylsulfonyl)ethylene 3



16–26 **3** **17–27**

Catalyst **C13** (10 mol%) or **C14** (5 mol%) was added to a solution of the corresponding cyclic α-alkenyl ketone (0.15 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene **3** (69 mg, 0.23 mmol, 1.5 equiv.) in CH_2Cl_2 (0.3 mL) at 0 °C. The resulting solution was stirred until the reaction was completed (typically 16 h) as monitored by TLC (hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography, affording the corresponding adducts as essentially pure compounds.

(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)cyclohexanone (17A)[186]

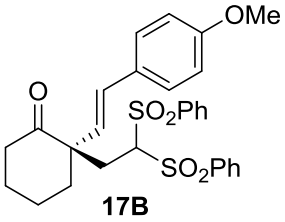


17A

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White solid. M.p. = 92 °C. Yield: 89% (68 mg, 0.133 mmol). $[\alpha]_D^{23}$= –95.8º (*c*= 1.00, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 – 7.85 (m, 2H), 7.71 – 7.61 (m, 3H), 7.57 – 7.45 (m, 3H), 7.45 – 7.25 (m, 7H), 6.42 (d, J = 16.6 Hz, 1H), 6.12 (d, J = 16.6 Hz, 1H), 4.56 (t, J = 4.3 Hz, 1H), 3.18 (dd, J =

16.6, 4.0 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.49 – 2.37 (m, 2H), 2.26 (dd, J = 16.6, 4.6 Hz, 1H), 2.06 – 1.69 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.0, 138.3, 137.3, 136.1, 134.5, 134.1, 132.6, 130.3, 130.2, 129.5, 128.9, 128.8, 128.3, 126.6, 80.8, 54.4, 39.7, 36.1, 31.1, 27.0, 21.3. **MS** (ESI, m/z): calculated for $C_{28}H_{32}N_2O_5S_2$ (M + NH_4^+), 526.6855; found, 526.1727. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 17.6 min (minor), 18.9 min (major)).

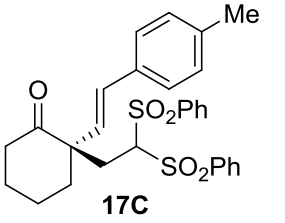
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-methoxystyr-2-yl)cyclohexanone (17B)



17B

The general procedure was applied starting from ketone **16B** (34 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 78% (63 mg, 0.117 mmol). **$[\alpha]_D^{23}$**= –78.2º (*c*= 1.00, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7.93 (d, J = 8.0 Hz, 2H), 7.72 – 7.64 (m, 3H), 7.56 – 7.49 (m, 3H), 7.39 – 7.29 (m, 4H), 6.95 – 6.87 (m, 2H), 6.36 (d, J = 16.7 Hz, 1H), 5.96 (d, J = 16.6 Hz, 1H), 4.55 (t, J = 4.2 Hz, 1H), 3.84 (s, 3H), 3.17 (dd, J = 16.6, 3.9 Hz, 1H), 2.61 – 2.53 (m, 1H), 2.41 (td, J = 11.1, 10.1, 6.1 Hz, 2H), 2.23 (dd, J = 16.7, 4.5 Hz, 1H), 1.99 (m, 1H), 1.85 – 1.74 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.7, 138.4, 137.3, 134.5, 134.0, 132.0, 130.3, 129.7, 129.5, 128.9, 128.8, 127.9, 127.8, 114.2, 80.9, 55.4, 54.4, 39.7, 36.1, 31.2, 27.0, 21.4, 21.2. **MS** (ESI, m/z): calculated for $C_{29}H_{31}O_6S_2$ (M + H^+), 539.1562; found, 539.1566. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 50:50; flux= 1 mL/min; retention times: 61.4 min (major), 70.1 min (minor)).

(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-methylstyryl)cyclohexanone (17C)

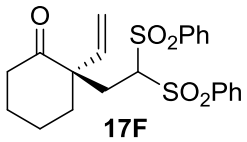


17C

The general procedure was applied starting from ketone **16C** (32 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 84% (66 mg, 0.126 mmol). **$[\alpha]_D^{23}$**= –92.9º (*c*= 1.00, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$). δ 7.93 (dt, J = 7.3, 1.3 Hz, 2H), 7.73 – 7.60 (m, 3H), 7.54 – 7.49 (m, 3H), 7.36 – 7.28 (m, 4H), 7.18 (d, J = 7.8 Hz, 2H), 6.38 (d, J = 16.6 Hz, 1H), 6.05 (d, J = 16.6 Hz, 1H), 4.56 (t, J = 4.2 Hz, 1H), 3.17 (dd, J = 16.6, 3.9 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.47 – 2.42 (m, 2H), 2.37 (s, 3H), 2.25 (dd, J = 16.6, 4.6 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.86 – 1.78 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.0, 138.3, 138.2, 137.3, 134.5, 134.0, 133.4, 132.5, 130.3, 129.5, 129.5, 129.0, 128.9, 128.8, 126.5, 80.9, 39.7, 36.1, 31.1, 29.7, 27.0, 21.4. **MS** (ESI, m/z): calculated for $C_{29}H_{30}O_5S_2Na$ (M + Na^+), 545.1432; found, 545.1437. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC,

hexane/isopropanol, 50:50; flux= 1 mL/min; retention times: 47.9 min (major), 56.4 min (minor)).

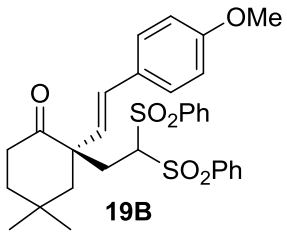
(*R*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-vinylcyclohexanone (17F)



17F

The general procedure was applied starting from ketone **16F** (19 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.) in toluene at −20 °C. Colourless oil. Yield: 82% (53 mg, 0.123 mmol). $[\alpha]_D^{23}$= +34.6º (*c*= 1.00, 80% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 4H), 7.69 – 7.66 (m, 2H), 7.59 – 7.55 (m, 4H), 5.59 – 5.45 (m, 1H), 5.21 (dd, J = 10.7, 0.8 Hz, 1H), 5.05 (dd, J = 17.8, 0.8 Hz, 1H), 4.54 (dd, J = 4.7, 3.9 Hz, 1H), 2.97 (dd, J = 16.7, 3.9 Hz, 1H), 2.49 – 2.41 (m, 2H), 2.32 – 2.25 (m, 2H), 1.97 – 1.89 (m, 1H), 1.81 – 1.73 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.1, 138.6, 138.3, 137.9, 134.5, 134.3, 130.1, 129.8, 128.9, 118.1, 80.7, 54.3, 39.5, 35.5, 31.1, 26.6, 21.1. **MS** (ESI, m/z): calculated for $C_{22}H_{25}O_5S_2$ (M + H^+), 433.1143; found, 433.1154. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 22.8 min (major), 26.9 min (minor)).

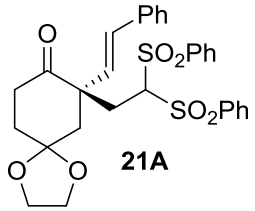
(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)cyclohexanone (19B)[186]



19B

The general procedure was applied starting from ketone **19B** (39 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White solid. M.p. = 107 °C. Yield: 70% (59 mg, 0.105 mmol). $[\alpha]_D^{23}$= +10.8º (*c*= 1.00, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.72 (m, 4H), 7.66 – 7.51 (m, 2H), 7.49 – 7.22 (m, 6H), 6.89 (d, J = 8.8 Hz, 2H), 6.13 (d, J = 16.7 Hz, 1H), 5.98 (d, J = 16.7 Hz, 1H), 4.89 – 4.80 (m, 1H), 3.83 (s, 3H), 2.98 (d, J = 20.0 Hz, 1H), 2.74 – 2.54 (m, 1H), 2.42 – 2.32 (m, 1H), 2.32 – 2.21 (m, 1H), 2.13 (d, J = 14.2 Hz, 1H), 1.75 (d, J = 14.2 Hz, 1H), 1.68 (dd, J = 9.1, 4.6 Hz, 2H), 1.16 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.0, 159.6, 138.3, 134.1, 134.1, 130.8, 130.3, 129.7, 129.7, 129.1, 128.8, 128.8, 127.7, 114.2, 80.9, 55.3, 52.5, 51.0, 38.3, 36.3, 33.0, 32.1, 30.9, 27.3. **MS** (ESI, m/z): calculated for $C_{31}H_{35}O_6S_2$ (M + H^+), 567.1875; found, 567.1882. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 16.7 min (minor), 23.2 min (major)).

(*R,E*)-7-(2,2-Bis(Phenylsulfonyl)ethyl)-7-(2-styryl)-1,4-dioxaspiro[4.5]decan-8-one (21A)

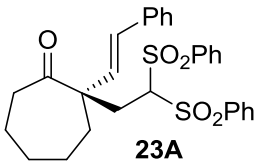


21A

The general procedure was applied starting from ketone **20A** (30 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (6 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 78% (66 mg, 0.117 mmol). $[\alpha]_D^{23}$= +2.4º

(*c*= 0.50, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 4H), 7.59 – 7.53 (m, 2H), 7.41 – 7.34 (m, 9H), 6.40 (d, J = 4.1 Hz, 2H), 4.75 (t, J = 4.3 Hz, 1H), 4.10 – 4.00 (m, 4H), 3.35 (dd, J = 16.6, 4.3 Hz, 1H), 2.77 – 2.67 (m, 2H), 2.49 – 2.43 (m, 2H), 2.28 – 2.19 (m, 1H), 2.07 (t, J = 6.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.8, 138.3, 137.5, 136.5, 134.3, 134.1, 131.7, 130.6, 129.9, 129.6, 128.8, 128.6, 128.0, 126.7, 107.2, 80.5, 64.6, 51.9, 44.1, 36.5, 33.4, 32.2. **MS** (ESI, m/z): calculated for $C_{30}H_{31}O_7S_2$ (M + H^+), 567.1511; found, 567.1511. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 21.2 min (major), 33.0 min (minor)).

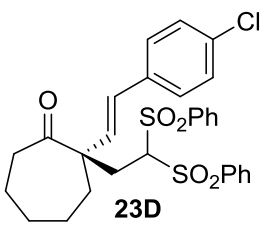
(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)cycloheptanone (23A)[186]



23A

The general procedure was applied starting from ketone **22A** (32 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 86% (67 mg, 0.129 mmol). **$[\alpha]_D^{23}$**= –123.0° (*c*= 1.00, 96% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.55 (q, J = 7.3 Hz, 2H), 7.51 – 7.16 (m, 9H), 6.51 (d, J = 16.5 Hz, 1H), 6.14 (d, J = 16.5 Hz, 1H), 4.63 (t, J = 4.0 Hz, 1H), 3.12 (dd, J = 16.6, 4.5 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.61 – 2.50 (m, 1H), 2.30 (dd, J = 16.5, 3.5 Hz, 1H), 2.20 – 1.99 (m, 2H), 1.68 (dp, J = 31.2, 11.0, 9.1 Hz, 5H), 1.52 – 1.38 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.9, 138.5, 137.1, 136.5, 134.5, 134.0, 132.4, 130.5, 130.1, 129.5, 128.9, 128.8, 128.7, 128.0, 126.7, 80.5, 57.0, 41.1, 32.6, 30.2, 29.9, 26.5, 24.4. **MS** (ESI, m/z): calculated for $C_{29}H_{31}O_5S_2$ (M + H^+), 523.1613; found, 523.1620. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 50:50; flux= 1 mL/min; retention times: 33.4 min (minor), 49.5 min (major)).

(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-chlorostyr-2-yl)cycloheptanone (23D)

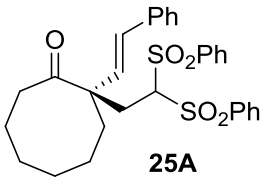


23D

The general procedure was applied starting from ketone **23D** (37 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 79% (66 mg, 0.118 mmol). **$[\alpha]_D^{23}$**= –51.2° (*c*= 0.50, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H), 7.74 (dd, J = 8.5, 1.3 Hz, 2H), 7.57 (d, J = 7.5 Hz, 2H), 7.46 – 7.30 (m, 8H), 6.47 (d, J = 16.4 Hz, 1H), 6.15 (d, J = 16.4 Hz, 1H), 4.64 (dd, J = 4.5, 3.4 Hz, 1H), 3.07 (dd, J = 16.6, 4.5 Hz, 1H), 2.65 – 2.61 (m, 2H), 2.31 (dd, J = 16.6, 3.4 Hz, 1H), 2.11 – 2.04 (m, 2H), 1.74 – 1.66 (m, 5H), 1.57 – 1.46 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.0, 138.4, 137.0, 135.1, 134.5, 134.1, 133.7, 131.4, 131.0, 130.1, 129.5, 128.9, 128.9, 128.8, 127.9, 80.3, 56.9, 41.3, 33.0, 30.3, 30.2, 26.5, 24.5. **MS** (ESI, m/z): calculated for $C_{29}H_{30}O_5S_2Cl$ (M + H^+), 557.1213; found, 557.1213. The enantiomeric

purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 33.0 min (minor), 50.5 min (major)).

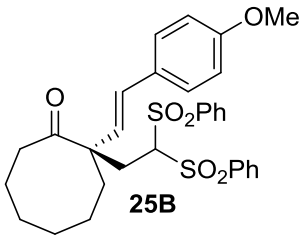
(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)cyclooctanone (25A)[186]



25A

The general procedure was applied starting from ketone **24A** (34 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.) in toluene at room temperature. White foam. Yield: 83% (67 mg, 0.124 mmol). $[\alpha]_D^{23}$= –87.6º (*c*= 1.00, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.3 Hz, 2H), 7.69 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.49 – 7.41 (m, 4H), 7.41 – 7.26 (m, 5H), 6.63 (d, J = 16.6 Hz, 1H), 6.23 (d, J = 16.6 Hz, 1H), 3.19 (dd, J = 16.7, 4.2 Hz, 1H), 2.85 – 2.68 (m, 1H), 2.46D – 2.26 (m, 4H), 2.25 – 2.14 (m, 1H), 1.87 – 1.62 (m, 5H), 1.58 – 1.38 (m, 2H), 1.25 – 1.07 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.9, 138.4, 137.3, 136.4, 134.4, 134.0, 132.8, 130.1, 129.8, 129.5, 128.8, 128.8, 128.2, 126.7, 81.3, 56.6, 38.0, 30.0, 29.4, 26.7, 26.2, 24.7, 24.2. **MS** (ESI, m/z): calculated for $C_{30}H_{33}O_5S_2$ (M + H^+), 137.1769; found, 137.1766. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 30:70; flux= 0.5 mL/min; retention times: 20.6 min (minor), 26.5 min (major)).

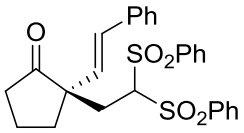
(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-methoxystyr-2-yl)cyclooctanone (25B)



25B

The general procedure was applied starting from ketone **24B** (39 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (24 mg, 0.015 mmol, 0.1 equiv.) in toluene at room temperature. White foam. Yield: 88% (75 mg, 0.132 mmol). $[\alpha]_D^{23}$= –41.4º (*c*= 1.00, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.72 – 7.68 (m, 2H), 7.65 – 7.60 (m, 1H), 7.56 – 7.52 (m, 1H), 7.50 – 7.46 (m, 2H), 7.40 – 7.31 (m, 4H), 6.91 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 16.5 Hz, 1H), 6.07 (d, J = 16.5 Hz, 1H), 4.55 (t, J = 4.1 Hz, 1H), 3.83 (s, 3H), 3.19 (dd, J = 16.7, 4.2 Hz, 1H), 2.77 (ddd, J = 12.0, 10.2, 4.3 Hz, 1H), 2.38 – 2.29 (m, 3H), 2.20 – 2.15 (m, 1H), 1.80 – 1.70 (m, 6H), 1.45 – 1.40 (m, 1H), 1.15 (d, J = 4.9 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.0, 159.7, 138.4, 137.4, 134.4, 134.0, 132.2, 130.2, 129.5, 129.2, 128.8, 128.8, 128.0, 127.5, 114.2, 81.4, 56.6, 55.4, 37.9, 29.8, 29.4, 26.4, 26.3, 24.7, 24.2. **MS** (ESI, m/z): calculated for $C_{31}H_{35}O_6S_2$ (M + H^+), 567.1875; found, 567.1888. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 60:40; flux= 1 mL/min; retention times: 24.7 min (minor), 33.9 min (major)).

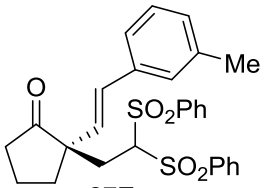
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)cyclopentanone (27A)[186]



27A

The general procedure was applied starting from ketone **26A** (28 mg, 0.15 mmol, 1 equiv.) using catalyst **C13** (6 mg, 0.015 mmol, 0.1 equiv.) in toluene at room temperature. White solid. M.p. = 154–156 °C. Yield: 85% (62 mg, 0.128 mmol). $[\alpha]_D^{23}$= –45.0° (*c*= 0.75, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 4H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.45 – 7.37 (m, 4H), 7.35 – 7.25 (m, 5H), 6.37 (d, J = 16.3 Hz, 1H), 5.93 (d, J = 16.3 Hz, 1H), 4.89 (t, J = 4.2 Hz, 1H), 2.91 (dd, J = 16.4, 4.3 Hz, 1H), 2.49 – 2.25 (m, 4H), 2.23 – 1.87 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.0, 140.3, 138.3, 137.2, 136.2, 134.9, 134.5, 134.2, 131.5, 129.9, 129.5, 128.9, 128.6, 128.0, 126.7, 79.5, 53.7, 37.9, 35.1, 31.4, 18.7. **MS** (ESI, m/z): calculated for $C_{27}H_{27}O_5S_2Na$ (M + Na^+), 495.1300; found, 495.1299. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 12.6 min (major), 14.2 min (minor)).

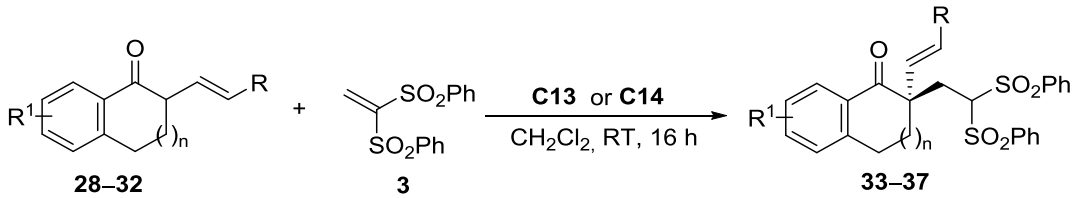
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(3-methylstyr-2-yl)cyclopentanone (27E)



27E

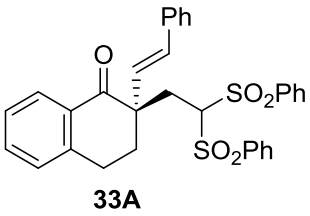
The general procedure was applied starting from ketone **26E** (30 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.) in toluene at room temperature. White solid. M.p. = 170–172 °C. Yield: 79% (60 mg, 0.118 mmol). $[\alpha]_D^{23}$= –37.6° (*c*= 0.50, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 4H), 7.61 – 7.57 (m, 1H), 7.52 – 7.48 (m, 1H), 7.43 – 7.38 (m, 4H), 7.22 – 7.18 (m, 1H), 7.09 (d, J = 7.5 Hz, 3H), 6.34 (d, J = 16.3 Hz, 1H), 5.87 (d, J = 16.3 Hz, 1H), 4.88 (t, J = 4.2 Hz, 1H), 2.91 (dd, J = 16.4, 4.3 Hz, 1H), 2.42 – 2.27 (m, 7H), 2.21 – 1.98 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.1, 138.4, 138.1, 137.3, 136.2, 134.5, 134.2, 131.7, 129.9, 129.6, 128.9, 128.8, 128.6, 128.5, 127.3, 123.9, 79.6, 53.8, 37.8, 35.2, 31.5, 21.4, 18.7. **MS** (ESI, m/z): calculated for $C_{22}H_{25}O_5S_2$ (M + H^+), 509.1456; found, 509.1463. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 85:15; flux= 1 mL/min; retention times: 28.1 min (minor), 25.6 min (major)).

5.4.4. General procedure for the catalytic addition of benzo-fused cycloalkanones to 1,1-bis(phenylsulfonyl)ethylene 3



Catalyst **C13** (10 mol%) or **C14** (5 mol%) was added to a solution of the corresponding cyclic α-alkenyl ketone (0.15 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene **3** (69 mg, 0.23 mmol, 1.5 equiv.) in CH_2Cl_2 (0.3 mL) at room temperature. The resulting solution was stirred for 16 h. Then the mixture was directly submitted to a flash column chromatography, affording the corresponding adducts essentially pure.

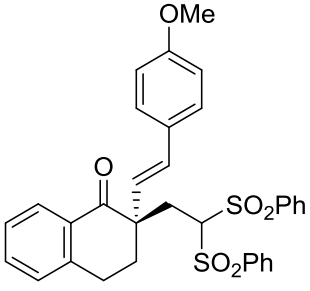
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)-3,4-dihydronaphthalen-1(2*H*)-one (33A)



33A

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 88% (73 mg, 0.132 mmol). **$[\alpha]_D^{23}$**= –41.0º (*c*= 0.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.9 Hz, 1H), 7.88 (dd, J = 8.4, 1.4 Hz, 2H), 7.80 (dd, J = 8.5, 1.4 Hz, 2H), 7.58 – 7.54 (m, 2H), 7.38 – 7.25 (m, 12H), 6.38 – 6.22 (m, 2H), 5.03 (dd, J = 4.7, 3.6 Hz, 1H), 3.19 (dd, J = 16.5, 3.7 Hz, 2H), 3.06 – 3.02 (m, 1H), 2.54 – 2.46 (m, 2H), 2.34 – 2.28 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.0, 143.2, 138.3, 137.8, 136.3, 134.4, 134.1, 133.7, 132.0, 131.8, 130.0, 129.7, 129.5, 128.9, 128.6, 128.5, 128.2, 128.1, 126.8, 126.7, 80.6, 50.5, 33.2, 31.6, 25.6. **MS** (ESI, m/z): calculated for $C_{32}H_{29}O_5S_2$ (M + H^+), 557.1456; found, 557.1462. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 25.2 min (major), 28.7 min (minor)).

(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-methoxystyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (33B)

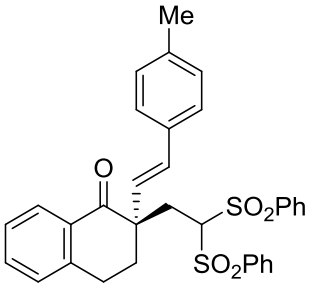


33B

The general procedure was applied starting from ketone **28B** (42 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 79% (69 mg, 0.118 mmol). **$[\alpha]_D^{23}$**= –37.2º (*c*= 0.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 1H), 7.91 – 7.87 (m, 2H), 7.82 –

7.78 (m, 2H), 7.59 – 7.55 (m, 3H), 7.45 – 7.37 (m, 5H), 7.31 – 7.26 (m, 2H), 7.22 – 7.19 (m, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.33 – 6.07 (m, 2H), 5.02 (dd, J = 4.7, 3.6 Hz, 1H), 3.80 (s, 3H), 3.19 (dd, J = 16.5, 3.6 Hz, 1H), 3.04 – 2.97 (m, 2H), 2.50 – 2.43 (m, 2H), 2.31 – 2.26 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.1, 159.6, 143.2, 138.4, 137.8, 135.0, 134.3, 134.0, 133.6, 131.8, 131.4, 130.0, 129.7, 129.7, 129.2, 128.8, 128.5, 128.2, 127.9, 127.0, 126.7, 114.0, 80.6, 55.3, 50.4, 33.1, 31.7, 25.5. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_6S_2$ (M + H^+), 587.1562; found, 587.1551. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 42.8 min (major), 53.1 min (minor)).

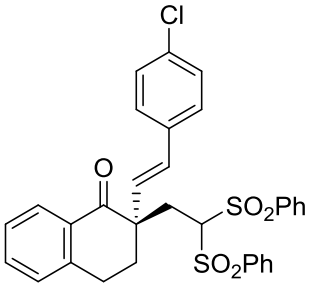
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-methylstyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (33C)



33C

The general procedure was applied starting from ketone **28C** (39 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 93% (80 mg, 0.139 mmol). **$[\alpha]_D^{23}$**= –23.7° (*c*= 1.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.9, 1.4 Hz, 1H), 7.90 – 7.86 (m, 2H), 7.82 – 7.78 (m, 2H), 7.58 – 7.55 (m, 2H), 7.45 – 7.37 (m, 6H), 7.27 – 7.22 (m, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.25 (q, J = 16.5 Hz, 2H), 5.06 – 5.01 (m, 1H), 3.22 – 3.14 (m, 1H), 3.08 – 3.00 (m, 2H), 2.53 – 2.44 (m, 2H), 2.33 (s, 3H), 2.30 – 2.24 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.0, 143.2, 138.3, 137.9, 137.8, 134.3, 134.1, 133.6, 133.5, 131.8, 131.8, 130.0, 129.7, 129.3, 128.8, 128.5, 128.2, 128.2, 126.7, 126.6, 80.6, 50.4, 33.2, 31.6, 25.5, 21.2. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_5S_2$ (M + H^+), 571.1613; found, 571.1612. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 28.6 min (major), 32.6 min (minor)).

(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(4-chlorostyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (33D)

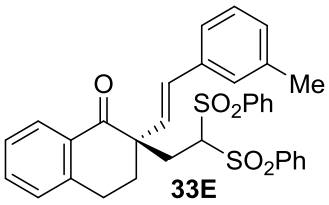


33D

The general procedure was applied starting from ketone **28D** (42 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White solid. M.p. = 160-163 °C. Yield: 92% (82 mg, 0.138 mmol). **$[\alpha]_D^{23}$**= –19.2° (*c*= 0.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 – 7.99 (m, 1H), 7.88 – 7.85 (m, 2H), 7.82 – 7.78 (m, 2H), 7.60 – 7.54 (m, 2H), 7.46 – 7.39 (m, 5H), 7.34 – 7.30 (m, 1H), 7.28 (s, 4H), 7.24 – 7.20 (m, 1H), 6.30 (s, 2H), 5.06 (dd, J = 4.5, 3.7 Hz, 1H), 3.15 (dd, J = 16.5, 3.8 Hz, 1H), 3.03 (t, J = 4.9

Hz, 2H), 2.55 – 2.41 (m, 2H), 2.34 – 2.26 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.9, 143.1, 138.2, 137.7, 134.9, 134.4, 134.1, 133.8, 133.7, 131.7, 130.6, 130.5, 130.0, 129.6, 128.9, 128.9, 128.7, 128.5, 128.2, 127.9, 126.9, 80.3, 50.3, 33.2, 31.6, 25.5. **MS** (ESI, m/z): calculated for $C_{32}H_{28}O_5S_2Cl$ (M + H^+), 591.1067; found, 591.1064. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 41.0 min (minor), 52.4 min (major)).

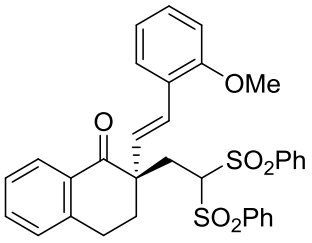
(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(3-methylstyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (33E)



33E

The general procedure was applied starting from ketone **28E** (39 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 89% (74 mg, 0.134 mmol). **$[\alpha]_D^{23}$**= –25.1° (*c*= 0.65, 99%*ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.62 – 7.52 (m, 2H), 7.51 – 7.27 (m, 6H), 7.24 – 7.05 (m, 5H), 6.31 (d, J = 16.6 Hz, 1H), 6.21 (d, J = 16.6 Hz, 1H), 5.02 (t, J = 4.2 Hz, 1H), 3.19 (dd, J = 16.5, 3.7 Hz, 1H), 3.16 – 2.93 (m, 2H), 2.48 (dd, J = 16.6, 4.7 Hz, 2H), 2.33 (s, 3H), 2.33 – 2.22 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.0, 143.2, 138.4, 138.2, 137.9, 136.2, 134.3, 134.1, 133.7, 132.2, 131.8, 130.0, 129.7, 129.1, 128.8, 128.5, 128.9, 127.4, 126.8, 123.9, 80.6, 50.5, 33.2, 31.6, 25.5, 21.4. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_5S_2$ (M + H^+), 571.1613; found, 571.1610. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 17.4 (major), 19.3 min (minor)).

(*R,E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-methoxystyr-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (33G)

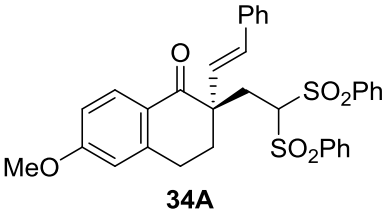


33G

The general procedure was applied starting from ketone **28G** (42 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 71% (62 mg, 0.106 mmol). **$[\alpha]_D^{23}$**= –45.0° (*c*= 0.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.9, 1.4 Hz, 1H), 7.95 (dd, J = 8.4, 1.3 Hz, 2H), 7.78 (dd, J = 8.4, 1.3 Hz, 2H), 7.61 – 7.57 (m, 2H), 7.49 – 7.45 (m, 4H), 7.34 – 7.31 (m, 4H), 7.24 – 7.19 (m, 1H), 6.91 – 6.84 (m, 2H), 6.74 (d, J = 16.7 Hz, 1H), 6.01 (d, J = 16.7 Hz, 1H), 4.96 (dd, J = 4.6, 3.6 Hz, 1H), 3.81 (s, 3H), 3.24 (dd, J = 16.5, 3.7 Hz, 1H), 3.04 – 2.98 (m, 2H), 2.57 – 2.51 (m, 1H), 2.44 (dd, J = 16.5, 4.6 Hz, 1H), 2.33 – 2.28 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.1, 156.5, 143.4, 138.3,

137.9, 135.0, 134.3, 134.0, 133.6, 131.8, 130.1, 129.6, 129.3, 129.2, 129.1, 128.8, 128.8, 128.5, 128.2, 127.0, 126.7, 126.7, 120.7, 110.6, 80.4, 55.4, 50.9, 32.3, 31.4, 25.4. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_6S_2$ ($M + H^+$), 587.1562; found, 587.1567. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 28.6 min (major), 43.6 min (minor)).

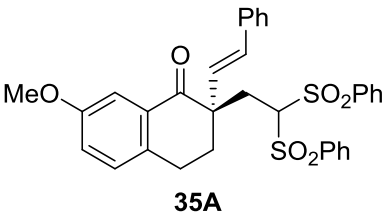
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-6-methoxy-2-(2-styryl)-3,4-dihydronaphthalen-1(2*H*)-one (34A)



34A

The general procedure was applied starting from ketone **29A** (42 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 83% (73 mg, 0.124 mmol). $[\alpha]_D^{23}$= –18.5° (*c*= 1.50, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.82 – 7.77 (m, 2H), 7.58 – 7.53 (m, 3H), 7.41 – 7.33 (m, 8H), 7.28 – 7.23 (m, 2H), 6.38 – 6.22 (m, 2H), 5.07 (dd, J = 4.6, 3.6 Hz, 1H), 3.84 (s, 3H), 3.18 (dd, J = 16.4, 3.7 Hz, 1H), 3.03 – 2.98 (m, 2H), 2.51 – 2.41 (m, 2H), 2.30 – 2.25 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.6, 163.8, 145.8, 138.4, 137.9, 136.4, 135.0, 134.3, 134.0, 131.6, 130.7, 130.0, 129.9, 129.6, 129.2, 128.8, 128.6, 128.0, 126.7, 113.6, 112.1, 80.6, 55.4, 50.1, 33.2, 31.6, 25.9. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_6S_2$ ($M + H^+$), 587.1562; found, 587.1564. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 30.4 min (major), 37.3 min (minor)).

(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-7-methoxy-2-(2-styryl)-3,4-dihydronaphthalen-1(2*H*)-one (35A)

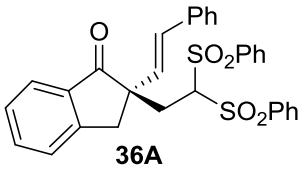


35A

The general procedure was applied starting from ketone **30A** (42 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 66% (58 mg, 0.099 mmol). $[\alpha]_D^{23}$= –50.1° (*c*= 1.00, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 – 7.95 (m, 1H), 7.91 – 7.87 (m, 2H), 7.82 – 7.79 (m, 2H), 7.59 – 7.53 (m, 3H), 7.49 (d, J = 2.7 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.34 (ddd, J = 8.6, 6.4, 0.8 Hz, 4H), 7.29 – 7.26 (m, 1H), 7.13 – 7.06 (m, 2H), 6.38 – 6.22 (m, 2H), 5.01 (dd, J = 4.7, 3.6 Hz, 1H), 3.84 (s, 3H), 3.18 (dd, J = 16.5, 3.6 Hz, 1H), 3.00 – 2.95 (m, 2H), 2.52 – 2.44 (m, 2H), 2.30 – 2.25 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 139.0, 138.3, 137.8, 136.3, 135.8, 134.4, 134.1, 131.9, 130.0, 129.8, 129.7, 129.5, 129.1, 129.0, 128.9, 128.6, 128.1, 126.7, 122.1, 110.1, 80.6, 55.5, 50.4,

33.3, 31.6, 24.7. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_6S_2$ (M + H^+), 587.1562; found, 587.1570. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 25.2 min (major), 30.4 min (minor)).

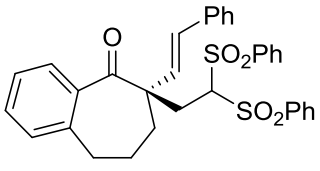
(*R*,*E*)-2-(2,2-Bis(Phenylsulfonyl)ethyl)-2-(2-styryl)-2,3-dihydro-1*H*-inden-1-one (36A)



36A

The general procedure was applied starting from ketone **31A** (35 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 82% (67 mg, 0.123 mmol). **$[\alpha]_D^{23}$**= +5.7° (*c*= 1.00, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 4H), 7.76 (d, J = 7.7 Hz, 1H), 7.61 – 7.51 (m, 4H), 7.43 – 7.38 (m, 5H), 7.33 – 7.29 (m, 5H), 6.47 (d, J = 16.3 Hz, 1H), 6.29 (d, J = 16.3 Hz, 1H), 5.05 (dd, J = 4.6, 3.6 Hz, 1H), 3.52 (d, J = 2.3 Hz, 2H), 3.04 (dd, J = 16.2, 3.7 Hz, 1H), 2.62 (dd, J = 16.3, 4.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.0, 151.5, 138.2, 137.5, 136.2, 135.5, 134.8, 134.5, 134.2, 131.3, 129.9, 129.5, 129.5, 129.0, 128.9, 128.6, 128.0, 127.9, 126.7, 126.4, 124.9, 80.1, 54.5, 39.2, 32.4. **MS** (ESI, m/z): calculated for $C_{31}H_{27}O_5S_2$ (M + H^+), 543.1300; found, 543.1307. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, solvent gradient: hexane/isopropanol, 80:20; flux= 1 mL/min for 63 min; hexane/isopropanol, 70:30; flux= 1 mL/min; retention times: 110.6 min (major), 132.2 min (minor)).

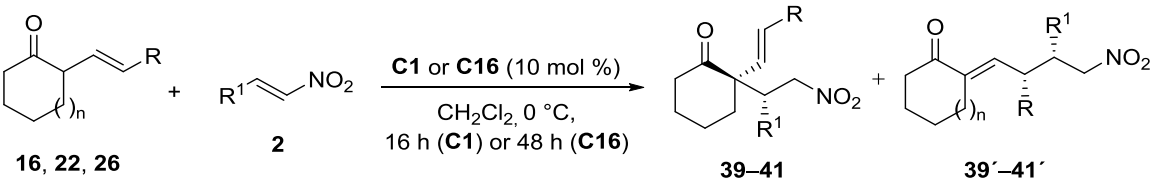
(*R*,*E*)-6-(2,2-Bis(phenylsulfonyl)ethyl)-6-(2-styryl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (37A)



37A

The general procedure was applied starting from ketone **32A** (39 mg, 0.15 mmol, 1 equiv.) using catalyst **C14** (12 mg, 0.0075 mmol, 0.05 equiv.). White foam. Yield: 89% (76 mg, 0.133 mmol). **$[\alpha]_D^{23}$**= –48.4° (*c*= 0.50, 89% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.4, 1.3 Hz, 2H), 7.76 (dd, J = 8.4, 1.3 Hz, 2H), 7.66 – 7.60 (m, 1H), 7.56 – 7.52 (m, 1H), 7.51 – 7.32 (m, 12H), 7.18 – 7.12 (m, 1H), 6.54 (d, J = 16.4 Hz, 1H), 6.18 (d, J = 16.4 Hz, 1H), 5.48 (t, J = 3.9 Hz, 1H), 3.05 (dd, J = 16.5, 4.1 Hz, 1H), 2.85 – 2.76 (m, 2H), 2.51 (dd, J = 16.5, 3.8 Hz, 1H), 2.01 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.3, 140.3, 138.6, 137.6, 137.3, 136.6, 134.2, 134.0, 132.0, 131.7, 129.8, 129.7, 129.6, 128.9, 128.8, 128.6, 128.2, 128.1, 127.9, 126.8, 126.7, 79.5, 53.2, 32.9, 32.1, 30.5, 22.4. **MS** (ESI, m/z): calculated for $C_{33}H_{31}O_5S_2$ (M + H^+), 571.1613; found, 571.1612. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 32.9 min (major), 41.6 min (minor)).

5.4.5. General procedure for the catalytic addition of α-alkenyl cycloalkanones to nitroolefins 2

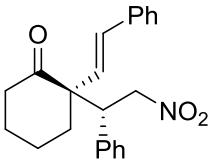


16, **22**, **26** + **2** → **39–41** + **39´–41´**

The corresponding catalyst (0.015 mmol, 0.1 equiv.) was added to a solution of the corresponding α-alkenyl ketone (0.15 mmol, 1 equiv.) and nitroalkene **2** (0.30 mmol, 2 equiv.) in CH_2Cl_2 (0.3 mL) at 0 °C. The resulting solution was stirred until the reaction was completed as monitored by TLC (hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 95:5) to afford each regioisomer separately and as a single diastereomer.

Some reactions were also performed using catalyst **C16** and γ adduct was obtained as the major isomer. Data for such adducts is also described below.

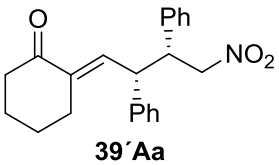
(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)-2-((*E*)-(2-styryl))cyclohexanone (39Aa)



39Aa

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), nitrostyrene **2a** (45 mg, 0.30 mmol, 2 equiv.) and catalyst **C16** (9 mg, 0.015 mmol, 0.1 equiv.). Colourless oil. Yield: 78% (41 mg, 0.117 mmol). $[\alpha]_D^{24}$= –123.4º (*c*= 1.00, 99% *ee*, α/γ 95:5, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 8H), 7.18 (dd, J = 7.4, 2.0 Hz, 2H), 6.18 (d, J = 4.0 Hz, 2H), 5.23 (dd, J = 13.0, 3.8 Hz, 1H), 4.64 (dd, J = 12.9, 11.4 Hz, 1H), 4.03 (dd, J = 11.3, 3.8 Hz, 1H), 2.88 – 2.73 (m, 1H), 2.45 – 2.21 (m, 2H), 2.08 – 1.91 (m, 1H), 1.76 – 1.57 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.6, 136.4, 135.8, 134.7, 129.5, 129.2, 128.9, 128.6, 128.4, 127.8, 126.3, 77.8, 56.5, 49.1, 39.7, 38.9, 28.1, 21.6. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3$ ($M + H^+$), 350.1756; found, 350.1761. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 24.3 min (minor), 27.8 min (major)).

(*E*)-2-((2*R*,3*R*)-4-Nitro-2,3-diphenylbutylidene)cyclohexanone (39´Aa)

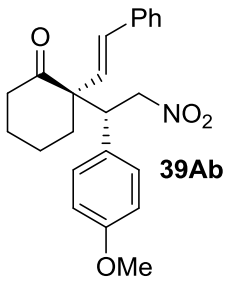


39´Aa

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), nitrostyrene **2a** (45 mg, 0.30 mmol, 2 equiv.) and catalyst **C14** (23 mg, 0.015 mmol, 0.1 equiv.). White

foam. Yield: 60% (31 mg, 0.091 mmol). **$[\alpha]_D^{27}$**= +21.6º (*c*= 1.00, 93% *ee*, α/γ 33:67, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 – 7.11 (m, 6H), 7.06 – 6.98 (m, 4H), 6.89 (d, J = 10.2 Hz, 1H), 4.77 – 4.63 (m, 2H), 3.99 – 3.79 (m, 2H), 2.55 – 2.26 (m, 4H), 1.90 – 1.77 (m, 2H), 1.77 – 1.63 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.4, 139.1, 137.7, 136.8, 136.6, 128.6, 128.5, 128.1, 128.1, 127.6, 127.1, 78.1, 49.5, 47.2, 40.1, 27.0, 23.3, 23.0. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_3$ (M + H^+), 350.1756; found, 350.1761. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 8.6 min (minor), 11.1 min (major)).

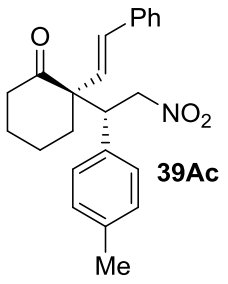
(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-2-((*E*)-styryl)cyclohexanone (39Ab)



39Ab

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), *p*-methoxynitrostyrene **2b** (56 mg, 0.30 mmol, 2 equiv.) and catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 74% (42 mg, 0.111 mmol). **$[\alpha]_D^{24}$**= –63.2º (*c*= 0.50, 96% *ee*, α/γ 90:10, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 7.09 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 6.27 – 6.07 (m, 2H), 5.20 (dd, J = 12.8, 3.8 Hz, 1H), 4.59 (dd, J = 12.8, 11.5 Hz, 1H), 3.98 (dd, J = 11.5, 3.7 Hz, 1H), 3.79 (s, 3H), 2.87 – 2.71 (m, 1H), 2.43 – 2.31 (m, 1H), 1.98 (td, J = 8.7, 7.4, 4.3 Hz, 1H), 1.73 – 1.58 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.7, 159.1, 135.8, 134.6, 130.4, 129.2, 128.9, 128.5, 128.1, 126.3, 113.8, 77.9, 56.7, 55.2, 48.4, 39.7, 38.7, 28.1, 21.6. **MS** (ESI, m/z): calculated for $C_{23}H_{26}NO_4$ (M + H^+), 380.1862; found, 380.1862. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 35.3 min (minor), 51.1 min (major)).

(*S*)-2-((*R*)-2-Nitro-1-(p-tolyl)ethyl)-2-((*E*)-(2-styryl))cyclohexanone (39Ac)

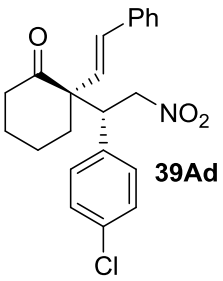


39Ac

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), *p*-methylnitrostyrene **2c** (49 mg, 0.30 mmol, 2 equiv.) and catalyst **C16** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 81% (44 mg, 0.121 mmol). **$[\alpha]_D^{24}$**= –144.8º (*c*= 1.00, 98% *ee*, α/γ 95:5, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 4H), 7.40 – 7.30 (m, 1H), 7.08 (q, J = 8.1 Hz, 4H), 6.18 (d, J = 3.1 Hz, 2H), 5.22 (dd, J = 12.8, 3.8 Hz, 1H), 4.62 (dd, J = 12.8, 11.4 Hz, 1H), 4.00 (dd, J = 11.4, 3.8 Hz, 1H), 2.87 – 2.76 (m, 1H), 2.41 – 2.34 (m, 1H), 2.32 (s, 3H), 2.02 – 1.96 (m, 1H), 1.72 – 1.61 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.7, 137.5, 135.8, 134.6, 133.20, 129.3, 129.1, 128.90, 128.5, 126.2, 77.9, 56.5, 48.7, 39.7, 38.8, 28.1, 21.6, 21.0. **MS** (ESI, m/z): calculated for $C_{23}H_{26}NO_3$ (M + H^+), 364.1913; found, 364.1909. The enantiomeric purity was

determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 24.6 min (minor), 33.1 min (major)).

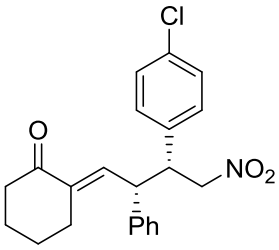
(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-((*E*)-(2-styryl))cyclohexanone (39Ad)



39Ad

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), *p*-chloronitrostyrene **2d** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C16** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 78% (45 mg, 0.117 mmol). $[\alpha]_D^{24}$= –53.6º (*c*= 0.50, 99% *ee*, α/γ 95:5, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 5H), 7.30 – 7.25 (m, 2H), 7.14 – 7.09 (m, 2H), 6.26 – 6.04 (m, 2H), 5.22 (dd, J = 13.1, 3.8 Hz, 1H), 4.59 (dd, J = 13.0, 11.5 Hz, 1H), 4.02 (dd, J = 11.5, 3.8 Hz, 1H), 2.84 – 2.73 (m, 1H), 2.43 – 2.31 (m, 1H), 2.03 – 1.98 (m, 1H), 1.70 – 1.61 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.3, 135.6, 135.1, 134.9, 133.8, 130.7, 129.0, 128.7, 128.6, 128.5, 126.3, 77.5, 56.4, 48.6, 39.6, 38.7, 28.1, 21.5. **MS** (ESI, m/z): calculated for $C_{22}H_{23}NO_3Cl$ (M + H^+), 384.1366; found, 384.1371. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 21.2 min (minor), 25.8 min (major)).

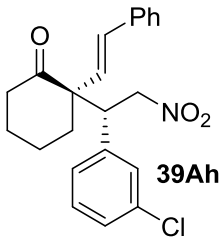
(*E*)-2-((2*R*,3*R*)-3-(4-Chlorophenyl)-4-nitro-2-phenylbutylidene)cyclohexanone (39´Ad)



39´Ad

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), *p*-chloronitrostyrene **2d** (55 mg, 0.30 mmol, 2 equiv.)and catalyst **C14** (23 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 69 % (40 mg, 0.103 mmol). $[\alpha]_D^{24}$= +33.6º (*c*= 0.50, 86% *ee*, α/γ 29:71, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 – 7.13 (m, 5H), 7.02 – 6.99 (m, 2H), 6.96 – 6.92 (m, 2H), 6.85 (dt, J = 10.3, 2.2 Hz, 1H), 4.74 – 4.56 (m, 2H), 3.92 – 3.88 (m, 1H), 3.81 (q, J = 10.0 Hz, 1H), 2.51 – 2.41 (m, 4H), 1.85 – 1.80 (m, 2H), 1.76 – 1.68 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.3, 138.8, 137.9, 136.3, 135.4, 133.5, 129.5, 128.8, 128.7, 128.1, 127.3, 78.0, 49.0, 47.1, 40.2, 27.1, 23.3, 23.0. **MS** (ESI, m/z): calculated for $C_{22}H_{23}NO_3Cl$ (M + H^+), 384.1366; found, 384.1373. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 10.9 min (minor), 14.5 min (major)).

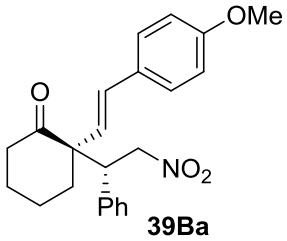
(*S*)-2-((*R*)-1-(3-Chlorophenyl)-2-nitroethyl)-2-((*E*)-styryl)cyclohexanone (39Ah)



39Ah

The general procedure was applied starting from ketone **16A** (30 mg, 0.15 mmol, 1 equiv.), *m*-chloronitrostyrene **2h** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 73% (42 mg, 0.110 mmol). $[\alpha]_D^{27}$= –77.3º (*c*= 0.50, 98% *ee*, α/γ 88:12, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 5H), 7.27 – 7.19 (m, 3H), 7.09 – 7.06 (m, 1H), 6.27 – 6.04 (m, 2H), 5.22 (dd, J = 13.2, 3.7 Hz, 1H), 4.59 (dd, J = 13.2, 11.3 Hz, 1H), 4.01 (dd, J = 11.3, 3.7 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.43 – 2.33 (m, 1H), 2.01 (tt, J = 6.7, 3.2 Hz, 1H), 1.72 – 1.58 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 138.7, 135.6, 135.2, 134.3, 129.7, 129.0, 128.7, 128.5, 128.1, 127.5, 126.3, 77.5, 56.4, 48.9, 39.6, 38.8, 28.1, 21.5. **MS** (ESI, m/z): calculated for $C_{22}H_{23}NO_3Cl$ (M + H^+), 384.1366; found, 384.1371. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 18.3 min (minor), 23.2 min (major)).

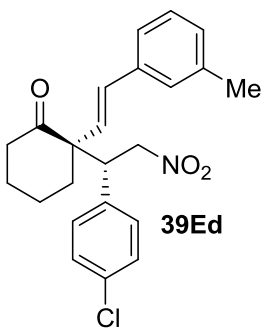
(*S*)-2-((*E*)-4-Methoxystyryl)-2-((*R*)-2-nitro-1-phenylethyl)cyclohexanone (39Ba)



39Ba

The general procedure was applied starting from ketone **16B** (34 mg, 0.15 mmol, 1 equiv.), nitrostyrene **2a** (45 mg, 0.30 mmol, 2 equiv.) and catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 76% (45 mg, 0.114 mmol). $[\alpha]_D^{24}$= –75.1º (*c*= 0.50, 98% *ee*, α/γ 87:13, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 7.19 – 7.15 (m, 2H), 6.95 – 6.91 (m, 2H), 6.18 – 5.94 (m, 2H), 5.23 (dd, J = 13.0, 3.8 Hz, 1H), 4.63 (dd, J = 13.0, 11.3 Hz, 1H), 4.01 (dd, J = 11.3, 3.8 Hz, 1H), 3.85 (s, 3H), 2.88 – 2.74 (m, 1H), 2.40 – 2.33 (m, 1H), 2.02 – 1.96 (m, 1H), 1.68 – 1.55 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.8, 159.9, 136.6, 134.1, 129.5, 128.6, 128.4, 127.7, 127.5, 126.7, 114.3, 77.9, 56.5, 55.4, 49.2, 39.6, 39.0, 28.2, 21.6. **MS** (ESI, m/z): calculated for $C_{23}H_{26}NO_4$ (M + H^+), 380.1862; found, 380.1862. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 40.8 min (minor), 45.8 min (major)).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-((*E*)-3-methylstyryl)cyclohexanone (39Eb)

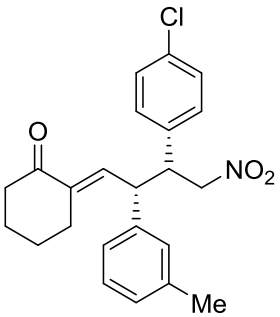


39Ed

The general procedure was applied starting from ketone **16E** (32 mg, 0.15 mmol, 1 equiv.), *p*-chloronitrostyrene **2d** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 71% (42 mg, 0.106 mmol). $[\alpha]_D^{24}$= –162.7º (*c*= 1.00, 99% *ee*, α/γ 80:20, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 3H), 7.25 – 7.14 (m, 3H), 7.18 – 7.07 (m, 2H), 6.25 –

6.00 (m, 2H), 5.22 (dd, J = 13.0, 3.8 Hz, 1H), 4.59 (dd, J = 13.0, 11.5 Hz, 1H), 4.02 (dd, J = 11.5, 3.8 Hz, 1H), 2.87 – 2.72 (m, 1H), 2.40 (s, 3H), 2.36 – 2.33 (m, 1H), 2.02 – 1.97 (m, 1H), 1.69 – 1.60 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.3, 138.7, 135.5, 135.2, 135.0, 133.8, 130.7, 129.5, 128.9, 128.6, 128.2, 127.0, 123.4, 77.6, 56.4, 48.6, 39.6, 38.7, 28.1, 21.5, 21.4. **MS** (ESI, m/z): calculated for $C_{23}H_{25}NO_3Cl$ (M + H^+), 398.1523; found, 398.1519. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 18.6 min (minor), 23.2 min (major)).

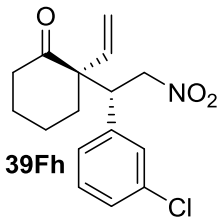
(*E*)-2-((2*R*,3*R*)-3-(4-Chlorophenyl)-4-nitro-2-(m-tolyl)butylidene)cyclohexanone (39´Ed)



39´Ed

The general procedure was applied starting from ketone **16E** (32 mg, 0.15 mmol, 1 equiv.), *p*-chloronitrostyrene **2d** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C14** (23 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 69% (41 mg, 0.103 mmol). **$[\alpha]_D^{24}$**= +5.8º (*c*= 1.00, 94% *ee*, α/γ 31:69, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 – 7.14 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.86 – 6.77 (m, 3H), 4.70 – 4.60 (m, 2H), 3.91 – 3.86 (m, 1H), 3.80 – 3.75 (m, 1H), 2.49 – 2.43 (m, 4H), 2.24 (s, 3H), 1.84 – 1.72 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.4, 138.6, 138.4, 137.7, 136.4, 135.5, 133.5, 129.5, 128.9, 128.7, 128.6, 128.1, 125.2, 78.0, 48.9, 47.0, 40.2, 27.1, 23.3, 23.0, 21.4. **MS** (ESI, m/z): calculated for $C_{23}H_{25}NO_3Cl$ (M + H^+), 398.1523; found, 398.1528.The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 8.7 min (minor), 10.9 min (major)).

(*S*)-2-((*R*)-1-(3-Chlorophenyl)-2-nitroethyl)-2-vinylcyclohexanone (39Fh)

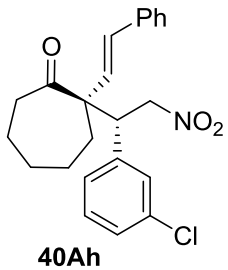


39Fh

The general procedure was applied starting from ketone **16F** (19 mg, 0.15 mmol, 1 equiv.), *m*-chloronitrostyrene **2h** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C16** (9 mg, 0.015 mmol, 0.1 equiv.). Colourless oil. Yield: 70% (32 mg, 0.105 mmol). **$[\alpha]_D^{24}$**= –53.2º (*c*= 0.50, 99% *ee*, α/γ 95:5, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 7.17 (s, 1H), 7.09 – 7.05 (m, 1H), 5.80 (dd, J = 18.0, 10.8 Hz, 1H), 5.56 (d, J = 10.9 Hz, 1H), 5.12 (dd, J = 13.3, 3.7 Hz, 1H), 4.99 (d, J = 18.0 Hz, 1H), 4.57 (dd, J = 13.2, 11.3 Hz, 1H), 3.93 (dd, J = 11.4, 3.6 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.39 – 2.28 (m, 1H), 2.04 – 1.98 (m, 1H), 1.68 – 1.48 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 138.7, 134.3, 129.6, 129.5, 128.1, 127.6, 121.0, 77.7, 56.9, 48.0, 39.4, 38.4, 28.0, 21.4. **MS** (ESI, m/z): calculated for $C_{16}H_{19}NO_3Cl$ (M + H^+), 308.1053; found, 308.1050.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times: 8.9 min (major), 10.5 min (minor)).

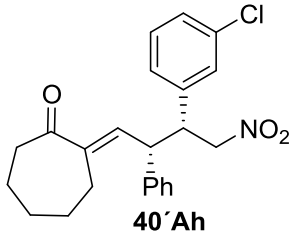
(*S*)-2-((*R*)-1-(3-Chlorophenyl)-2-nitroethyl)-2-((*E*)-styryl)cycloheptanone (40Ah)



40Ah

The general procedure was applied starting from ketone **22A** (32 mg, 0.15 mmol, 1 equiv.), *m*-chloronitrostyrene **2h** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 72% (43 mg, 0.108 mmol). $[\alpha]_D^{24}$= –26.3º (*c*= 0.50, 98% *ee*, α/γ 58:42, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 3H), 7.37 – 7.28 (m, 2H), 7.31 – 7.23 (m, 2H), 7.23 – 7.16 (m, 1H), 7.06 (dt, J = 6.9, 1.8 Hz, 1H), 6.37 – 6.15 (m, 2H), 5.09 (dd, J = 13.4, 3.8 Hz, 1H), 4.64 (dd, J = 13.4, 11.3 Hz, 1H), 3.91 (dd, J = 11.3, 3.9 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.52 – 2.42 (m, 1H), 1.73 – 1.54 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.7, 138.4, 136.0, 134.5, 133.1, 129.8, 129.5, 128.9, 128.4, 128.3, 127.4, 127.0, 126.5, 77.3, 58.7, 48.6, 41.2, 32.3, 29.8, 26.5, 23.8. **MS** (ESI, m/z): calculated for $C_{23}H_{25}NO_3Cl$ ($M + H^+$), 398.1523; found, 398.1522. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 13.2 min (minor), 18.0 min (major)).

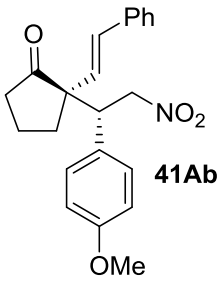
(*E*)-2-((2*R*,3*R*)-3-(3-Chlorophenyl)-4-nitro-2-phenylbutylidene)cycloheptanone (40´Ah)



40´Ah

The general procedure was applied starting from ketone **22A** (32 mg, 0.15 mmol, 1 equiv.), *m*-chloronitrostyrene **2h** (55 mg, 0.30 mmol, 2 equiv.) and catalyst **C14** (23 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 60% (36 mg, 0.09 mmol). $[\alpha]_D^{24}$= +15.8º (*c*= 0.25, 96% *ee*, α/γ 23:77, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 – 7.00 (m, 8H), 6.92 – 6.79 (m, 2H), 4.75 – 4.57 (m, 2H), 3.94 – 3.82 (m, 2H), 2.60 (dd, J = 4.8, 2.2 Hz, 1H), 2.45 (t, J = 5.6 Hz, 2H), 1.73 – 1.63 (m, 3H), 1.55 – 1.48 (m, 2H), 1.26 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.7, 142.3, 139.2, 139.1, 135.9, 134.4, 129.8, 128.8, 128.1, 127.9, 127.3, 126.6, 77.8, 49.2, 47.5, 43.1, 31.0, 29.2, 27.5, 25.1. **MS** (ESI, m/z): calculated for $C_{23}H_{25}NO_3Cl$ ($M + H^+$), 398.1523; found, 398.1528. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 8.9 min (minor), 11.2 min (major)).

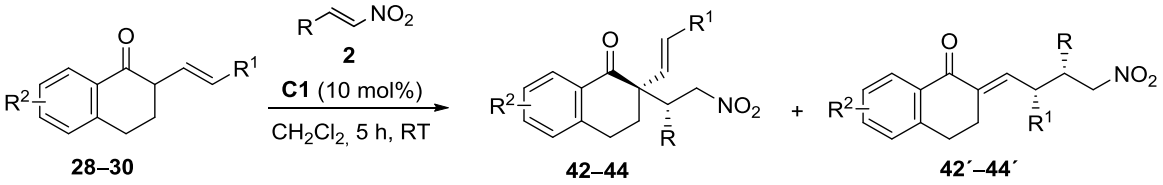
(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-2-((*E*)-styryl)cyclopentanone (41Ab)



41Ab

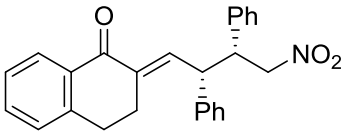
The general procedure was applied starting from ketone **26A** (32 mg, 0.15 mmol, 1 equiv.), *p*-methoxynitrostyrene **2b** (56 mg, 0.30 mmol, 2 equiv.) and catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.). White foam. Yield: 76% (42 mg, 0.114 mmol). $[\alpha]_D^{24}$= –61.1º (*c*= 1.00, 97% *ee*, α/γ 92:8, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 5H), 7.14 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.45 (d, J = 16.4 Hz, 1H), 6.06 (d, J = 16.4 Hz, 1H), 5.28 (dd, J = 13.2, 4.2 Hz, 1H), 4.72 (dd, J = 13.2, 11.8 Hz, 1H), 3.86 (dd, J = 11.8, 4.2 Hz, 1H), 3.78 (s, 3H), 2.38 – 2.30 (m, 1H), 2.15 – 2.05 (m, 1H), 1.98 – 1.95 (m, 1H), 1.90 – 1.82 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.2, 159.2, 135.9, 133.8, 130.1, 128.8, 128.4, 127.6, 126.5, 126.5, 113.9, 76.3, 57.0, 55.2, 47.6, 37.7, 33.0, 18.4. **MS** (ESI, m/z): calculated for $C_{22}H_{24}NO_4$ (M + H^+), 366.1705; found, 366.1709. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 6.8 min (major), 8.2 min (minor)).

5.4.6. General procedure for the catalytic addition of benzo-fused cycloalkanones to nitroolefins 2



Catalyst **C1** (9 mg, 10 mol %) was added to a solution of the corresponding benzo-fused cycloalkanone (0.15 mmol, 1 equiv.) and nitroalkene (0.18 mmol, 1.2 equiv.) in CH_2Cl_2 (0.3 mL) at room temperature. The resulting solution was stirred for 5 h. Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 95:5), affording the major regioisomer as essentially pure compound and as a single diastereomer.

(*E*)-2-((2*R*,3*R*)-4-Nitro-2,3-diphenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Aa)

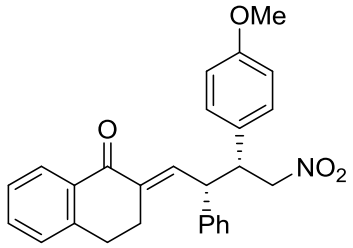


42´Aa

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2a** (27 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 80% (48 mg, 0.120 mmol). $[\alpha]_D^{23}$= +21.6º (*c*= 1.30, 97% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.5 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz,

1H), 7.34 (td, J = 7.6, 1.3 Hz, 1H), 7.24 – 7.15 (m, 8H), 7.12 – 7.03 (m, 4H), 4.77 – 4.73 (m, 2H), 4.08 – 4.01 (m, 2H), 2.90 – 2.85 (m, 2H), 2.81 – 2.76 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.8, 143.4, 139.4, 137.1, 136.9, 136.8, 133.4, 133.1, 128.7, 128.6, 128.3, 128.3, 128.2, 128.2, 127.7, 127.2, 127.1, 78.0, 49.6, 47.6, 28.6, 26.0. **MS** (ESI, m/z): calculated for $C_{26}H_{24}NO_3$ ($M + H^+$), 398.1756; found, 398.1758. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 9.1 min (minor), 12.4 min (major)).

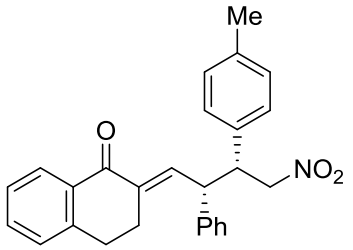
(*E*)-2-((2*R*,3*R*)-3-(4-methoxyphenyl)-4-nitro-2-phenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ab)



42´Ab

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2b** (32 mg, 0.18 mmol, 1.2 equiv.). White foam. White foam. Yield: 81% (49 mg, 0.114 mmol). **$[\alpha]_D^{23}$**= +24.3^o (*c*= 2.00, 98% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 – 8.07 (m, 1H), 7.47 (td, J = 7.4, 1.5 Hz, 1H), 7.37 – 7.29 (m, 1H), 7.22 – 7.16 (m, 5H), 7.12 – 7.06 (m, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 4.76 – 4.66 (m, 2H), 4.05 – 3.96 (m, 2H), 3.71 (s, 3H), 2.93 – 2.86 (m, 2H), 2.83 – 2.75 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.8, 158.8, 143.3, 139.5, 137.4, 136.6, 133.4, 133.1, 129.2, 128.7, 128.2, 128.2, 128.2, 127.1, 127.0, 113.9, 78.3, 55.1, 48.8, 47.6, 28.6, 26.0. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_4$ ($M + H^+$), 428.1862; found, 428.1862. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 11.3 min (minor), 15.0 min (major)).

(*E*)-2-((2*R*,3*R*)-4-nitro-2-phenyl-3-(p-tolyl)butylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ac)

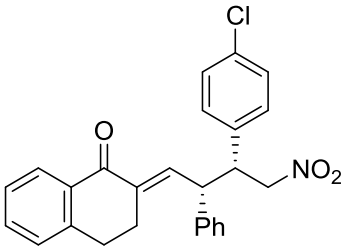


42´Ac

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2c** (29 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 81% (50 mg, 0.121 mmol). **$[\alpha]_D^{23}$**= +19.6^o (*c*= 0.50, 97% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.8, 1.5 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.34 (td, J = 7.6, 1.3 Hz, 1H), 7.25 – 7.07 (m, 7H), 7.03 – 6.91 (m, 4H), 4.74 – 4.69 (m, 2H), 4.09 – 3.96 (m, 2H), 2.91 – 2.85 (m, 2H), 2.82 – 2.75 (m, 2H), 2.24 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 187.6, 144.1, 140.2, 138.1, 138.0, 137.3, 134.4, 134.1, 133.8, 129.9, 129.4, 128.9, 128.9, 128.7, 127.8, 127.8, 78.9, 49.8, 48.2, 29.3, 26.7, 21.7. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_3$

(M + H^+), 412.1913; found, 412.1911.The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 8.8 min (minor), 11.3 min (major)).

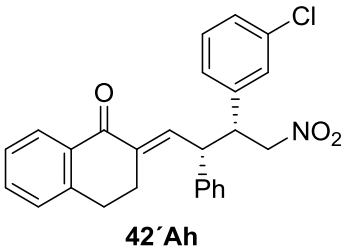
(*E*)-2-((2*R*,3*R*)-3-(4-chlorophenyl)-4-nitro-2-phenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ad)



42´Ad

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2d** (33 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 81% (50 mg, 0.115 mmol). **$[\alpha]_D^{23}$**= +20.5º (*c*= 1.20, 98% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.8, 1.5 Hz, 1H), 7.48 (td, J = 7.4, 1.5 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.22 – 7.14 (m, 7H), 7.09 – 7.05 (m, 2H), 6.99 (d, J = 8.5 Hz, 2H), 4.77 – 4.68 (m, 2H), 4.03 – 3.96 (m, 2H), 2.96 – 2.85 (m, 2H), 2.82 – 2.79 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.7, 143.3, 139.1, 136.9, 136.8, 135.4, 133.6, 133.5, 133.0, 129.5, 128.8, 128.3, 128.0, 127.3, 127.1, 78.0, 49.0, 47.4, 28.6, 26.1. **MS** (ESI, m/z): calculated for $C_{26}H_{23}NO_3Cl$ (M + H^+), 432.1366; found, 432.1366. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 10.1 min (minor), 14.5 min (major)).

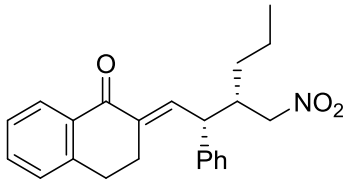
(*E*)-2-((2*R*,3*R*)-3-(3-chlorophenyl)-4-nitro-2-phenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ah)



42´Ah

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2h** (33 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 79% (51 mg, 0.118 mmol). **$[\alpha]_D^{23}$**= +24.7º (*c*= 1.35, 96% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.4 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.34 (td, J = 7.6, 1.3 Hz, 1H), 7.22 – 7.08 (m, 10H), 6.97 – 6.92 (m, 1H), 4.77 – 4.69 (m, 2H), 4.02 – 3.97 (m, 2H), 2.93 – 2.86 (m, 2H), 2.82 – 2.79 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.7, 143.3, 139.1, 139.0, 137.0, 136.6, 134.4, 133.5, 133.0, 129.8, 128.8, 128.3, 128.1, 128.0, 128.0, 127.4, 127.1, 126.5, 77.8, 49.2, 47.4, 28.6, 26.1. **MS** (ESI, m/z): calculated for $C_{26}H_{23}NO_3Cl$ (M + H^+), 432.1366; found, 432.1370. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 8.9 min (minor), 12.1 min (major)).

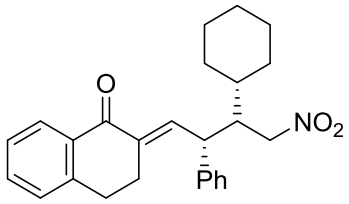
(*E*)-2-((2*R*,3*S*)-3-(nitromethyl)-2-phenylhexylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Al)



42´Al

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2l** (21 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 69% (38 mg, 0.103 mmol). **$[\alpha]_D^{23}$**= +10.4º (*c*= 0.80, 99% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 1H), 7.46 (td, J = 7.4, 1.5 Hz, 1H), 7.32 – 7.23 (m, 7H), 7.08 (dd, J = 10.5, 1.3 Hz, 1H), 4.46 (d, J = 5.7 Hz, 2H), 3.86 (dd, J = 10.5, 8.4 Hz, 1H), 2.95 – 2.86 (m, 3H), 2.71 – 2.66 (m, 2H), 1.42 – 1.38 (m, 2H), 1.30 – 1.23 (m, 2H), 0.83 (t, J = 6.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 187.1, 143.6, 140.2, 137.9, 136.8, 133.3, 129.0, 128.6, 128.3, 128.2, 128.0, 127.2, 127.0, 76.6, 45.3, 42.6, 31.0, 28.7, 26.0, 19.6, 13.9. **MS** (ESI, m/z): calculated for $C_{23}H_{26}NO_3$ (M + H^+), 364.1913; found, 364.1915. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times: 22.0 min (minor), 43.1 min (major)).

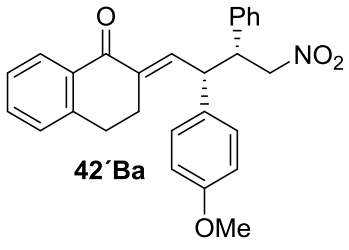
(*E*)-2-((2*R*,3*R*)-3-cyclohexyl-4-nitro-2-phenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´An)



42´An

The general procedure was applied starting from ketone **28A** (37 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2n** (28 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 66% (40 mg, 0.099 mmol). **$[\alpha]_D^{23}$**= +3.15º (*c*= 0.80, 98% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.8, 1.5 Hz, 1H), 7.44 – 7.35 (m, 5H), 7.28 – 7.25 (m, 3H), 7.15 (d, J = 7.6 Hz, 1H), 4.76 (t, J = 7.8 Hz, 1H), 3.22 (td, J = 9.3, 7.8 Hz, 1H), 2.87 – 2.78 (m, 2H), 2.75 – 2.65 (m, 2H), 2.03 – 1.95 (m, 1H), 1.82 – 1.52 (m, 7H), 1.21 – 1.06 (m, 3H), 0.92 – 0.86 (m, 1H), 0.71 – 0.60 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.4, 143.6, 142.7, 133.6, 131.9, 128.7, 128.6, 127.6, 127.5, 127.1, 126.8, 83.7, 55.3, 51.1, 47.2, 44.1, 42.8, 30.1, 29.8, 28.5, 26.8, 26.1, 25.6. **MS** (ESI, m/z): calculated for $C_{26}H_{30}NO_3$ (M + H^+), 404.2226; found, 404.2224. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 7.7 min (minor), 15.3 min (major)).

(*E*)-2-((2*R*,3*R*)-2-(4-methoxyphenyl)-4-nitro-3-phenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ba)

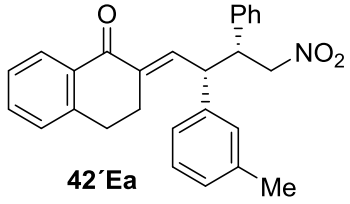


42´Ba

The general procedure was applied starting from ketone **28B** (42 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2a** (27 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 80% (52 mg,

0.121 mmol). **$[\alpha]_D^{23}$**= +39.0º (*c*= 1.15, 98% *ee*, α/γ 8:92, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.21 – 7.18 (m, 5H), 7.07 – 6.98 (m, 4H), 6.73 (d, J = 8.7 Hz, 2H), 4.75 – 4.70 (m, 2H), 4.03 – 3.97 (m, 2H), 3.72 (s, 3H), 2.89 – 2.84 (m, 2H), 2.79 – 2.73 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.9, 158.5, 143.4, 137.4, 136.9, 136.3, 133.4, 133.1, 131.3, 129.1, 128.5, 128.2, 127.6, 127.0, 114.1, 78.0, 55.1, 49.6, 46.6, 28.6, 26.0. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_4$ ($M + H^+$), 428.1862; found, 428.1859. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 12.2 min (minor), 18.4 min (major)).

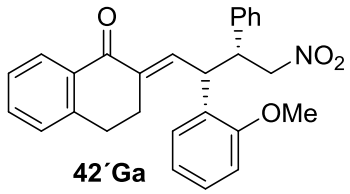
(*E*)-2-((2*R*,3*R*)-4-nitro-3-phenyl-2-(m-tolyl)butylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ea)



42´Ea

The general procedure was applied starting from ketone **28E** (39 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2a** (27 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 77% (48 mg, 0.115 mmol). **$[\alpha]_D^{23}$**= +50.1º (*c*= 0.50, 97% *ee*, α/γ >5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.5 Hz, 1H), 7.47 (td, J = 7.4, 1.5 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.23 – 7.17 (m, 5H), 7.10 – 7.06 (m, 2H), 6.99 – 6.87 (m, 3H), 4.75 (d, J = 7.1 Hz, 2H), 4.01 (td, J = 5.4, 4.8, 1.6 Hz, 2H), 2.87 (dd, J = 8.4, 5.5 Hz, 2H), 2.76 (ddd, J = 7.1, 4.1, 1.4 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.9, 143.4, 139.2, 138.3, 137.1, 136.9, 136.6, 133.4, 133.1, 128.8, 128.5, 128.2, 128.2, 128.0, 127.7, 127.1, 125.2, 77.8, 49.5, 47.5, 28.6, 26.0, 21.4. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_3$ ($M + H^+$), 412.1913; found, 412.1909. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 7.8 min (minor), 9.8 min (major)).

(*E*)-2-((2*R*,3*R*)-2-(2-methoxyphenyl)-4-nitro-3-phenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ga)

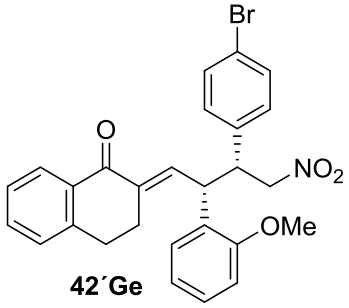


42´Ga

The general procedure was applied starting from ketone **28G** (42 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2a** (27 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 82% (53 mg, 0.123 mmol). **$[\alpha]_D^{23}$**= +44.8º (*c*= 0.85, 99% *ee*, α/γ >5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 – 8.07 (m, 1H), 7.46 (td, J = 7.4, 1.5 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.18 – 7.09 (m, 9H), 6.82 – 6.74 (m, 2H), 4.73 (d, J = 7.4 Hz, 2H), 4.60 – 4.53 (m, 1H), 4.21 – 4.11 (m, 1H), 3.81 (s, 3H), 2.85 (dd, J = 6.2, 4.1 Hz, 2H), 2.78 (dt, J = 6.0, 1.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 187.1, 156.6, 143.5, 137.4, 137.3, 136.8, 133.3, 128.3, 128.2, 128.1, 128.1, 127.7, 127.4, 127.0, 120.7, 110.7, 78.2, 55.4, 47.8,

40.6, 28.7, 26.1. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_4$ (M + H^+), 428.1862; found, 428.1872. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA - IA, hexane/isopropanol, 95:5; flux= 1 mL/min; retention times: 51.9 min (minor), 75.4 min (major)).

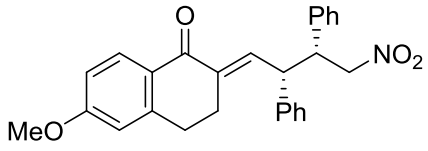
(*E*)-2-((2*R*,3*R*)-3-(4-bromophenyl)-2-(2-methoxyphenyl)-4-nitrobutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (42´Ge)



42´Ge

The general procedure was applied starting from ketone **28G** (42 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2e** (41 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 77% (58 mg, 0.115 mmol). **$[\alpha]_D^{23}$**= +26.0º (*c*= 0.50, 98% *ee*, α/γ 5:95, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.8, 1.5 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.35 – 7.31 (m, 3H), 7.26 – 7.11 (m, 4H), 7.01 (d, J = 8.4 Hz, 2H), 6.86 – 6.75 (m, 2H), 4.76 – 4.67 (m, 2H), 4.55 (dd, J = 10.5, 9.1 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.82 (s, 3H), 2.93 – 2.88 (m, 2H), 2.85 – 2.79 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 187.0, 156.4, 143.5, 137.0, 136.5, 133.3, 133.1, 131.4, 131.3, 129.8, 128.9, 128.3, 128.2, 128.2, 127.3, 127.0, 121.4, 120.8, 110.8, 78.1, 55.3, 47.5, 40.3, 28.7, 26.1. **MS** (ESI, m/z): calculated for $C_{27}H_{25}NO_4Br$ (M + H^+), 506.0967; found, 506.0967. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 24.5 min (minor), 36.2 min (major)).

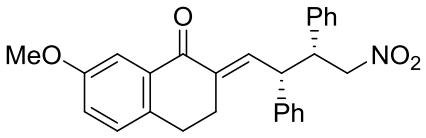
(*E*)-6-methoxy-2-((2*R*,3*R*)-4-nitro-2,3-diphenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (43´Aa)



43´Aa

The general procedure was applied starting from ketone **29A** (42 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2a** (27 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 79% (51 mg, 0.118 mmol). **$[\alpha]_D^{23}$**= +37.2º (*c*= 0.85, 99% *ee*, α/γ 7:93, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8 Hz, 1H), 7.20 – 7.03 (m, 11H), 6.85 (dd, J = 8.8, 2.5 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H), 4.78 – 4.73 (m, 2H), 4.05 – 4.00 (m, 2H), 3.84 (s, 3H), 2.85 – 2.80 (m, 2H), 2.79 – 2.74 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 185.6, 163.6, 145.8, 139.5, 136.9, 136.8, 136.3, 130.7, 128.6, 128.5, 128.1, 128.1, 127.6, 127.1, 126.6, 113.4, 112.3, 78.0, 55.4, 49.6, 47.5, 29.0, 26.1. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_4$ (M + H^+), 428.1862; found, 428.1864. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 19.8 min (minor), 32.9 min (major)).

(*E*)-7-methoxy-2-((2*R*,3*R*)-4-nitro-2,3-diphenylbutylidene)-3,4-dihydronaphthalen-1(2*H*)-one (44´Aa)

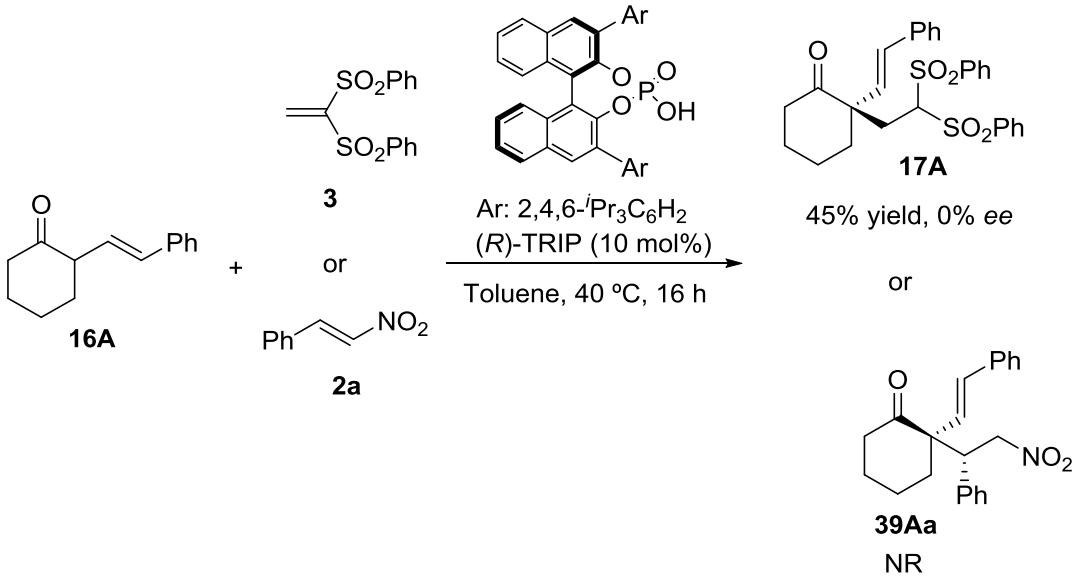


44´Aa

The general procedure was applied starting from ketone **30A** (42 mg, 0.15 mmol, 1 equiv.) and nitrostyrene **2a** (27 mg, 0.18 mmol, 1.2 equiv.). White foam. Yield: 78% (50 mg, 0.117 mmol). $[\alpha]_D^{23}$= +10.7º (*c*= 1.40, 98% *ee*, α/γ 8:92, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, J = 2.8 Hz, 1H), 7.22 – 7.15 (m, 7H), 7.12 – 7.04 (m, 6H), 4.77 – 4.73 (m, 2H), 4.09 – 4.00 (m, 2H), 3.84 (s, 3H), 2.83 – 2.76 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.7, 158.6, 139.4, 137.2, 136.9, 136.7, 136.1, 133.9, 129.5, 128.7, 128.5, 128.2, 128.1, 127.7, 127.1, 121.6, 110.3, 78.0, 55.5, 49.5, 47.6, 27.8, 26.2. **MS** (ESI, m/z): calculated for $C_{27}H_{26}NO_4$ (M + H^+), 428.1862; found, 428.1856. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 80:20; flux= 1 mL/min; retention times: 11.8 min (minor), 20.1 min (major)).

5.4.7. Control experiments based on alternative catalytic approaches

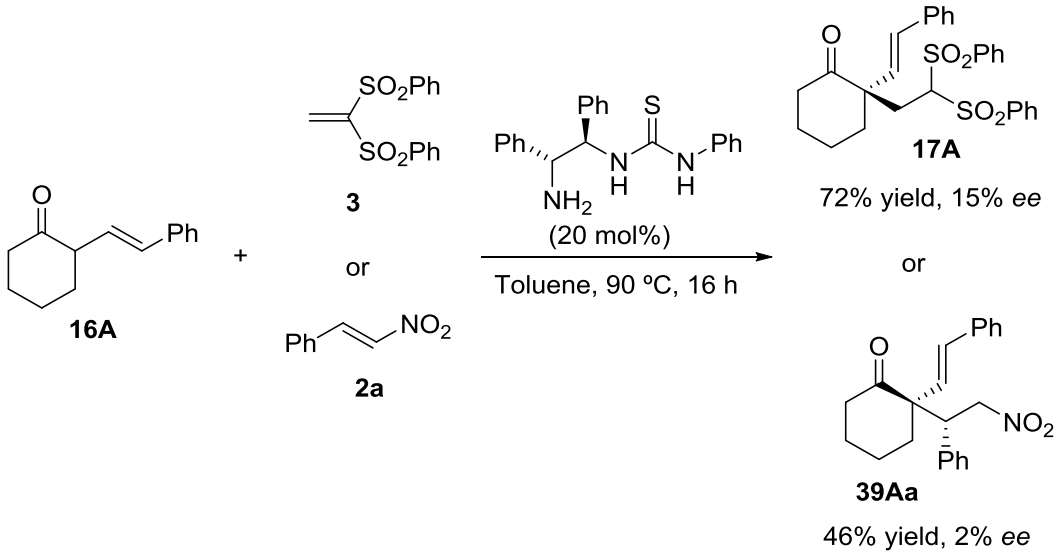
5.4.7.1. *Using Brønsted acid catalysis*



The chiral phosphoric acid (*R*)-TRIP (15 mg, 0.015 mmol, 0.1 equiv.) was added to a solution of 2-(2-styryl)cyclohexanone **16A** (30 mg, 0.15 mmol, 1 equiv.) and **3** or **2a** (0.30 mmol, 2 equiv.) in toluene and the mixture was heated at 40 °C for 16 h. The resulting solution was directly submitted to a flash column chromatography affording 45% of

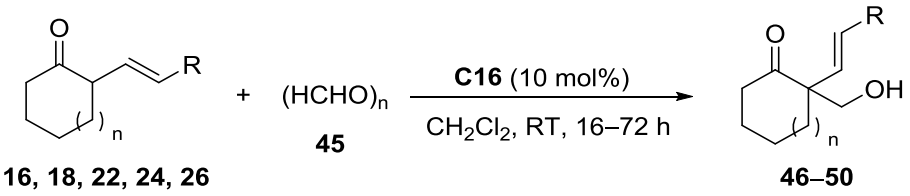
essentially racemic adduct **17A** in the former case. In the latter case no even traces of adduct **41Aa** were detected and only unreacted starting material was isolated.

5.4.7.2. *Using primary amine catalysts*



The primary amine-thiourea catalyst (10 mg, 0.03 mmol, 0.2 equiv.) was added to a solution of 2-(2-styryl)cyclohexanone **16A** (30 mg, 0.15 mmol, 1 equiv.) and **3** or **2a** (0.30 mmol, 2 equiv.) in toluene and the mixture was heated at 90 °C for 16 h. The resulting solution was directly submitted to a flash column chromatography affording, in the former case, 72% of product **17A** of 15% enantioselectivity. In the latter case, a 46% of essentially racemic product **41Aa** was isolated.

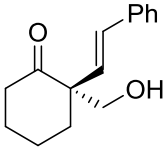
5.4.8. General procedure for the catalytic addition of α-alkenyl cycloalkanones to formaldehyde 45



Catalyst **C16** (9 mg, 0.015 mmol, 0.1 equiv.) was added to a solution of the corresponding α-alkenyl cycloalkanone (0.10 mmol, 1 equiv.) and paraformaldehyde (30 mg, 1 mmol, 10 equiv.) in CH_2Cl_2 (0.2 mL) at room temperature. The resulting solution was stirred until the reaction was completed as monitored by TLC (hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography

(hexane/EtOAc 90:10), affording the corresponding adducts as essentially pure compounds.

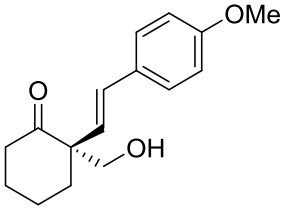
(*R*,*E*)-2-(Hydroxymethyl)-2-(2-styryl)cyclohexanone (46A)



46A

The general procedure was applied starting from ketone **16A** (20 mg, 0.10 mmol, 1 equiv.) after 16 h. White foam. Yield: 79% (18 mg, 0.079 mmol). **$[\alpha]_D^{23}$**= +20.7º (*c*= 0.50, 89% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 6.36 (d, J = 16.6 Hz, 1H), 6.14 (d, J = 16.6 Hz, 1H), 3.83 (d, J = 11.4 Hz, 1H), 3.44 (d, J = 11.5 Hz, 1H), 2.64 (td, J = 13.8, 6.0 Hz, 1H), 2.49 (bs, 1H), 2.38 – 2.28 (m, 1H), 2.04 (m, 3H), 1.84 (m, 2H), 1.70 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.9, 136.4, 133.2, 129.8, 128.6, 128.0, 126.3, 67.9, 57.3, 40.0, 34.6, 27.5, 21.5. **MS** (ESI, m/z): calculated for $C_{15}H_{19}O_2$ (M + H^+), 231.1385; found, 231.1389. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 14.5 min (major), 21.0 min (minor)).

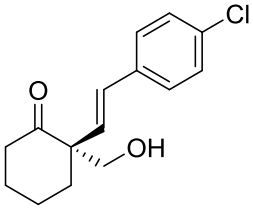
(*R*,*E*)-2-(Hydroxymethyl)-2-(4-methoxystyr-2-yl)cyclohexanone (46B)



46B

The general procedure was applied starting from ketone **16B** (23 mg, 0.10 mmol, 1 equiv.) after 48 h. White foam. Yield: 77% (20 mg, 0.077 mmol). **$[\alpha]_D^{23}$**= +29.3º (*c*= 0.50, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 6.88 – 6.83 (m, 2H), 6.29 (d, J = 16.6 Hz, 1H), 5.98 (d, J = 16.6 Hz, 1H), 3.81 (m, 4H), 3.41 (dd, J = 11.6, 5.3 Hz, 1H), 2.72 – 2.57 (m, 1H), 2.45 (bs, 1H), 2.30 (dddd, J = 14.1, 4.3, 2.8, 1.5 Hz, 1H), 2.11 – 2.01 (m, 3H), 1.93 – 1.84 (m, 2H), 1.74 – 1.64 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.2, 159.5, 132.6, 129.2, 127.4, 114.0, 68.0, 57.2, 55.3, 39.9, 34.6, 27.5, 21.5. **MS** (ESI, m/z): calculated for $C_{16}H_{20}O_3Na$ (M + Na^+), 283.1310; found, 283.1315. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ID, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 35.2 min (minor), 43.7 min (major)).

(*R*,*E*)-2-(4-Chlorostyryl)-2-(hydroxymethyl)cyclohexan-1-one (46D)

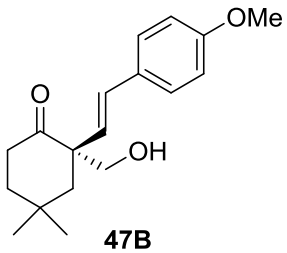


46D

The general procedure was applied starting from ketone **16D** (23 mg, 0.10 mmol, 1 equiv.) after 16 h. White foam. Yield: 75% (20 mg, 0.075 mmol). **$[\alpha]_D^{23}$**= +50.7º (*c*= 0.50, 89% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 (bs, 4H), 6.33 (d, J = 16.6 Hz, 1H), 6.14 (d, J = 16.6 Hz, 1H), 3.82 (d, J = 11.5 Hz, 1H), 3.49 (d, J = 11.5 Hz, 1H), 2.63 (ddd, J = 14.1, 13.2, 6.3 Hz, 1H), 2.56 – 2.51 (bs, 1H), 2.35 (dddd, J = 14.2, 4.1, 2.8, 1.3 Hz, 1H), 2.08 – 2.03 (m, 3H), 1.88 – 1.83 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.8,

134.9, 133.6, 132.0, 130.5, 128.8, 127.5, 67.9, 57.2, 40.0, 34.6, 27.4, 21.5. **MS** (ESI, m/z): calculated for $C_{15}H_{17}O_2Na$ (M + Na^+), 287.0815; found, 287.0819. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 14.8 min (major), 19.8 min (minor)).

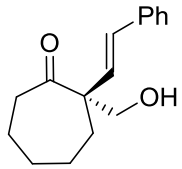
(*R*,*E*)-2-(Hydroxymethyl)-2-(4-methoxystyryl)-4,4-dimethylcyclohexan-1-one (47B)



47B

The general procedure was applied starting from ketone **18B** (26 mg, 0.10 mmol, 1 equiv.) after 48 h. White foam. Yield: 62% (20 mg, 0.062 mmol). **$[\alpha]_D^{23}$**= +44.3º (*c*= 0.25, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 2H), 6.93 – 6.81 (m, 2H), 6.17 – 5.87 (m, 2H), 3.80 (s, 3H), 3.70 (d, J = 11.5 Hz, 1H), 3.30 (d, J = 11.5 Hz, 1H), 2.80 (ddd, J = 14.8, 13.0, 6.4 Hz, 1H), 2.45 (bs, J = 11.8 Hz, 1H), 2.23 (dt, J = 14.8, 3.9 Hz, 1H), 2.09 (d, J = 14.1 Hz, 1H), 1.82 – 1.66 (m, 4H), 1.24 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.8, 159.4, 129.3, 127.4, 114.1, 110.0, 68.3, 56.3, 55.3, 47.3, 39.5, 36.4, 32.3, 30.8, 26.8. **MS** (ESI, m/z): calculated for $C_{18}H_{24}O_3Na$ (M + Na^+), 311.1623; found, 311.1633. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 19.2 min (major), 33.4 min (minor)).

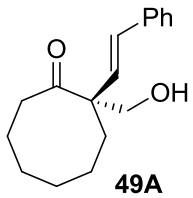
(*R*,*E*)-2-(Hydroxymethyl)-2-styrylcycloheptan-1-one (48A)



48A

The general procedure was applied starting from ketone **22A** (21 mg, 0.10 mmol, 1 equiv.) after 72 h. White foam. Yield: 70% (17 mg, 0.070 mmol). **$[\alpha]_D^{23}$**= +83.6º (*c*= 0.25, 84% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 6.43 (d, J = 16.6 Hz, 1H), 6.23 (d, J = 16.6 Hz, 1H), 3.83 (dd, J = 11.3, 5.0 Hz, 1H), 3.65 (dd, J = 11.3, 8.1 Hz, 1H), 2.77 – 2.68 (m, 1H), 2.59 (dd, J = 8.3, 5.4 Hz, 1H), 2.44 (ddd, J = 12.2, 7.9, 2.2 Hz, 1H), 2.01 – 1.79 (m, 5H), 1.60 – 1.49 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 216.4, 136.6, 131.8, 129.6, 128.6, 127.9, 126.3, 68.6, 58.5, 41.9, 32.6, 30.5, 26.0, 24.8. **MS** (ESI, m/z): calculated for $C_{16}H_{20}O_2Na$ (M + Na^+), 267.1361; found, 267.1369. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ID, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 14.5 min (minor), 17.0 min (major)).

(*R*,*E*)-2-(Hydroxymethyl)-2-(2-styryl)cyclooctanone (49A)

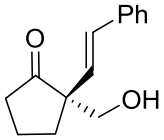


49A

The general procedure was applied starting from ketone **24A** (23 mg, 0.10 mmol, 1 equiv.) after 72 h. White foam. Yield: 77% (20 mg, 0.077 mmol). **$[\alpha]_D^{23}$**= +125.4º (*c*= 0. 50, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.24 (m, 5H), 6.52 (d, J = 16.6 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 4.08 (dd, J = 11.5, 3.3 Hz, 1H), 3.67 (dd, J = 11.5, 7.5 Hz, 1H),

2.78 (td, J = 11.8, 3.7 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.29 – 2.16 (m, 1H), 1.98 – 1.65 (m, 8H), 1.45 – 1.34 (m, 1H), 1.19 – 1.12 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.1, 136.6, 132.3, 129.1, 128.6, 127.9, 126.4, 66.2, 57.5, 38.3, 30.1, 30.0, 25.8, 24.7, 24.4. **MS** (ESI, m/z): calculated for $C_{17}H_{22}O_2Na$ (M + Na^+), 281.1518; found, 281.1524. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ID, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 19.6 min (minor), 22.1 min (major)).

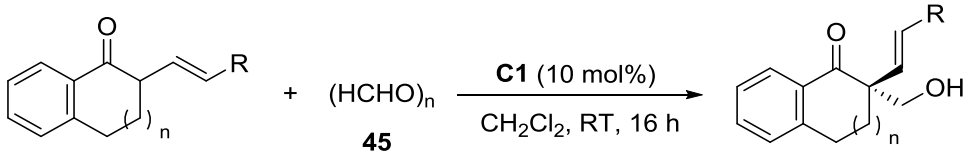
(*R*,*E*)-2-(Hydroxymethyl)-2-(2-styryl)cyclopentanone (50A)



50A

The general procedure was applied starting from ketone **26A** (19 mg, 0.10 mmol, 1 equiv.) after 16 h. White foam. Yield: 74% (16 mg, 0.074 mmol). **$[\alpha]_D^{23}$**= +25.4° (*c*= 0. 50, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 6.49 (d, J = 16.4 Hz, 1H), 6.10 (d, J = 16.4 Hz, 1H), 3.81 (dd, J = 11.1, 5.9 Hz, 1H), 3.60 (dd, J = 11.2, 2.9 Hz, 1H), 2.41 – 2.37 (m, 1H), 2.29 – 2.19 (m, 3H), 2.05 – 1.92 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.0, 136.4, 132.1, 128.6, 127.9, 127.7, 126.4, 66.1, 57.8, 38.1, 31.2, 18.9. **MS** (ESI, m/z): calculated for $C_{14}H_{16}O_2Na$ (M + Na^+), 239.1048; found, 239.1057. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 96.8 min (major), 3.2 min (minor)).

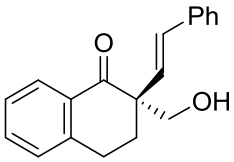
5.4.9. General procedure for the catalytic addition of benzo-fused cycloalkanones to formaldehyde 45



28A, 32A **51A, 52A**

Catalyst **C1** (9 mg, 0.015 mmol, 0.1 equiv.) was added to a solution of the corresponding benzo-fused cycloalkanone (0.10 mmol, 1 equiv.) and paraformaldehyde (30 mg, 1 mmol, 10 equiv.) in CH_2Cl_2 (0.2 mL) at room temperature. The resulting solution was stirred until the reaction was completed (16 h) as monitored by TLC (hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 90:10), affording the corresponding adducts as essentially pure compounds.

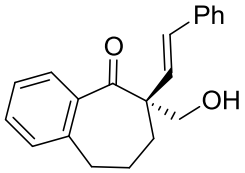
(*R*,*E*)-2-(Hydroxymethyl)-2-styryl-3,4-dihydronaphthalen-1(2*H*)-one (51A)



51A

The general procedure was applied starting from ketone **28A** (25 mg, 0.10 mmol, 1 equiv.). White foam. Yield: 73% (20 mg, 0.073 mmol). **$[\alpha]_D^{23}$**= +24.6º (*c*= 0. 50, 32% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (dd, J = 7.9, 1.5 Hz, 1H), 7.48 (td, J = 7.4, 1.5 Hz, 1H), 7.38 – 7.19 (m, 7H), 6.47 – 6.12 (m, 2H), 3.99 (dd, J = 11.3, 5.5 Hz, 1H), 3.81 – 3.69 (m, 1H), 3.26 – 3.19 (m, 1H), 2.93 (dt, J = 17.0, 3.7 Hz, 1H), 2.63 (s, 1H), 2.52 – 2.37 (m, 1H), 2.19 – 2.06 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.0, 143.8, 136.4, 133.8, 133.1, 132.1, 128.8, 128.5, 127.9, 127.7, 127.3, 126.7, 126.3, 68.3, 53.8, 30.6, 25.6. **MS** (ESI, m/z): calculated for $C_{19}H_{18}O_2Na$ ($M + Na^+$), 301.1205; found, 301.1207. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 14.7 min (minor), 22.5 min (major)).

(*R*,*E*)-6-(Hydroxymethyl)-6-styryl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (52A)

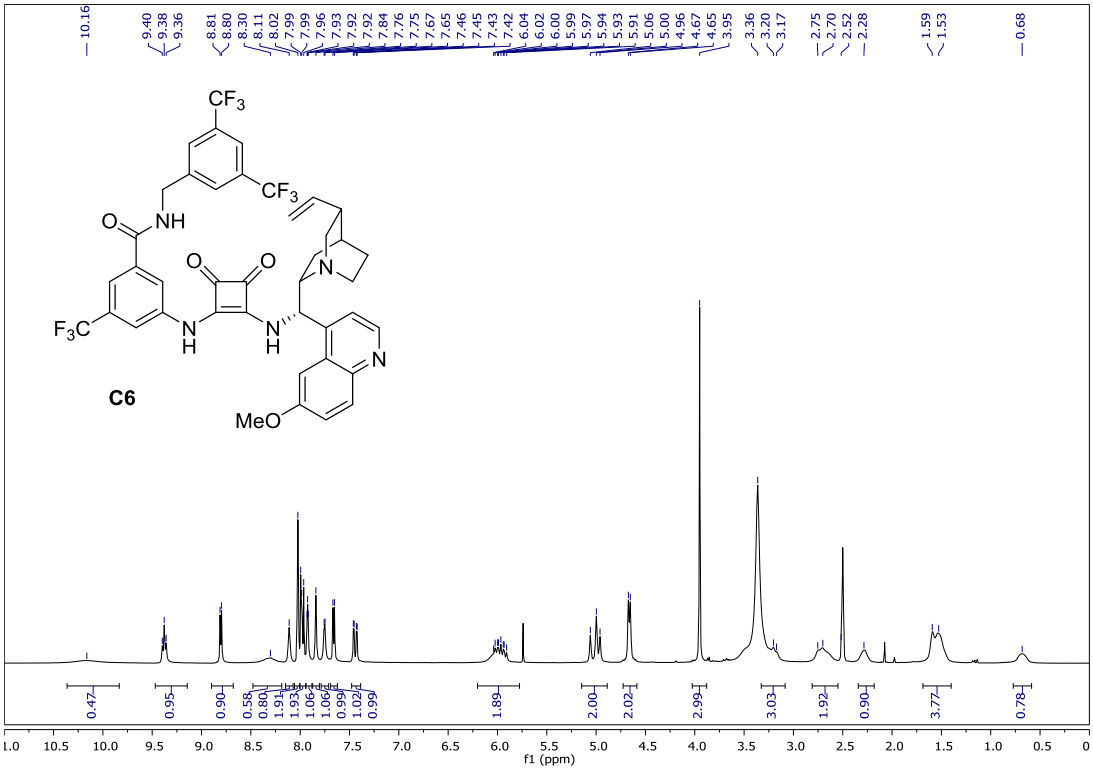


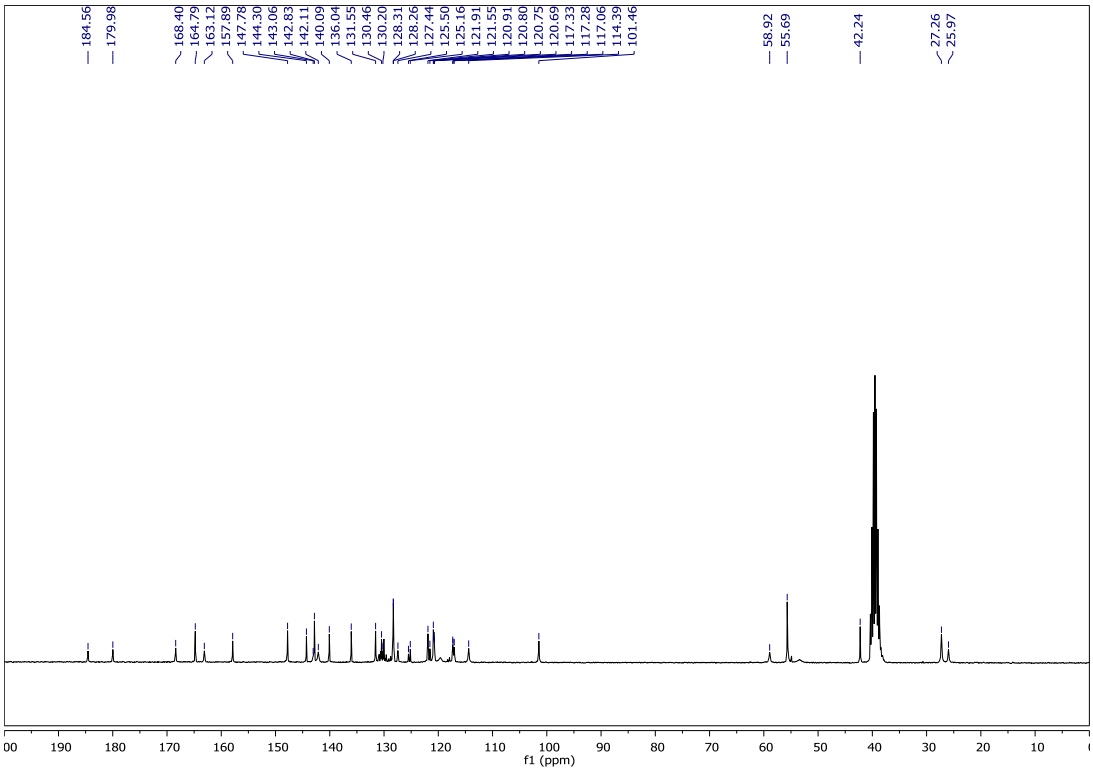
52A

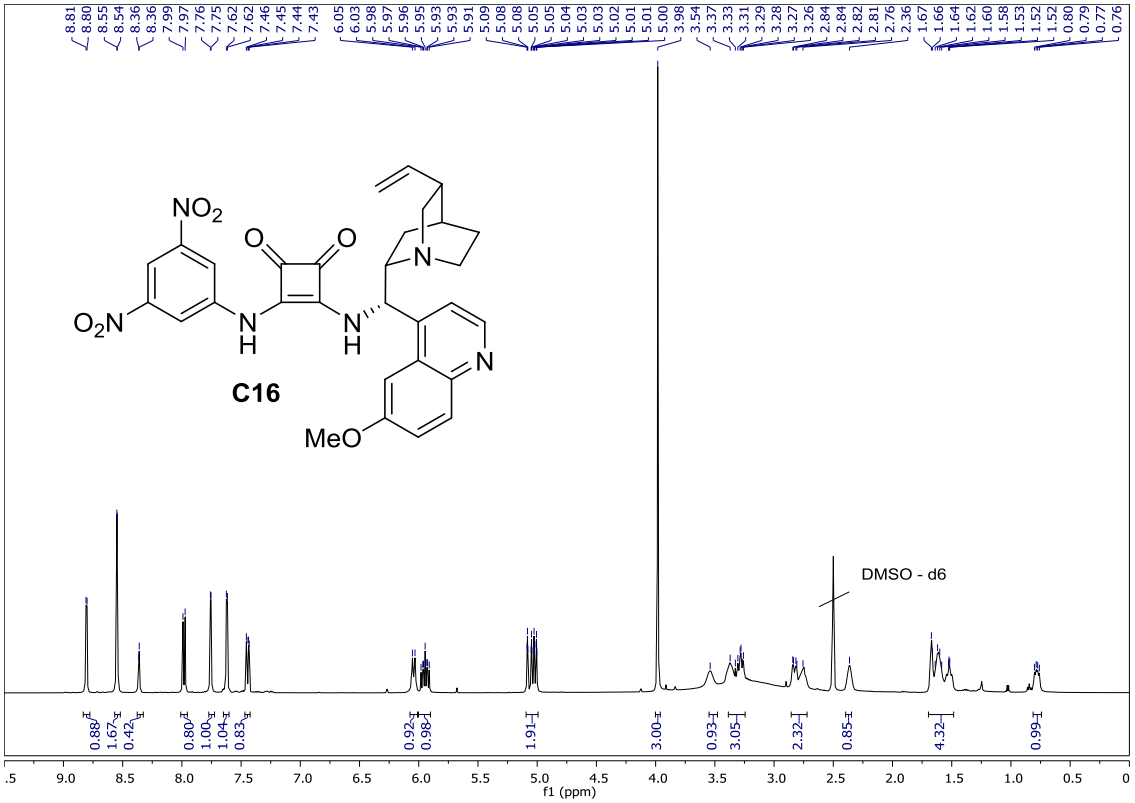
The general procedure was applied starting from ketone **32A** (26 mg, 0.10 mmol, 1 equiv.). White foam. Yield: 74% (22 mg, 0.073 mmol). **$[\alpha]_D^{23}$**= +31.4º (*c*= 0. 25, 77% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 – 7.19 (m, 9H), 6.50 (d, J = 16.5 Hz, 1H), 6.29 (d, J = 16.5 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H), 3.69 (d, J = 10.7 Hz, 1H), 2.93 – 2.74 (m, 2H), 2.58 – 2.43 (m, 1H), 2.16 – 1.98 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.6, 140.1, 138.6, 136.7, 132.4, 131.8, 128.9, 128.6, 128.2, 127.8, 127.7, 126.7, 126.3, 70.1, 57.4, 32.5, 30.1, 22.8. **MS** (ESI, m/z): calculated for $C_{20}H_{20}O_2Na$ ($M + Na^+$), 315.1361; found, 315.1367. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux= 1 mL/min; retention times: 12.4 min (major), 17.2 min (minor)).

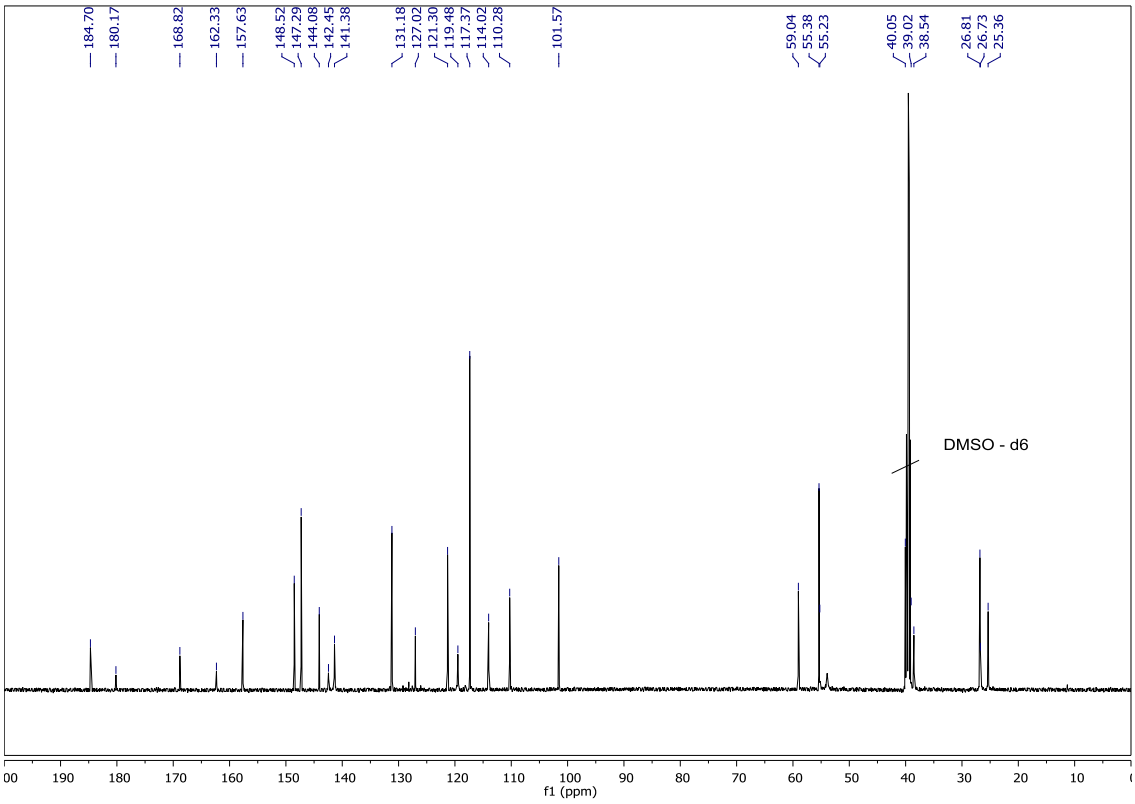
5.5. NMR Spectra of Representative Compounds

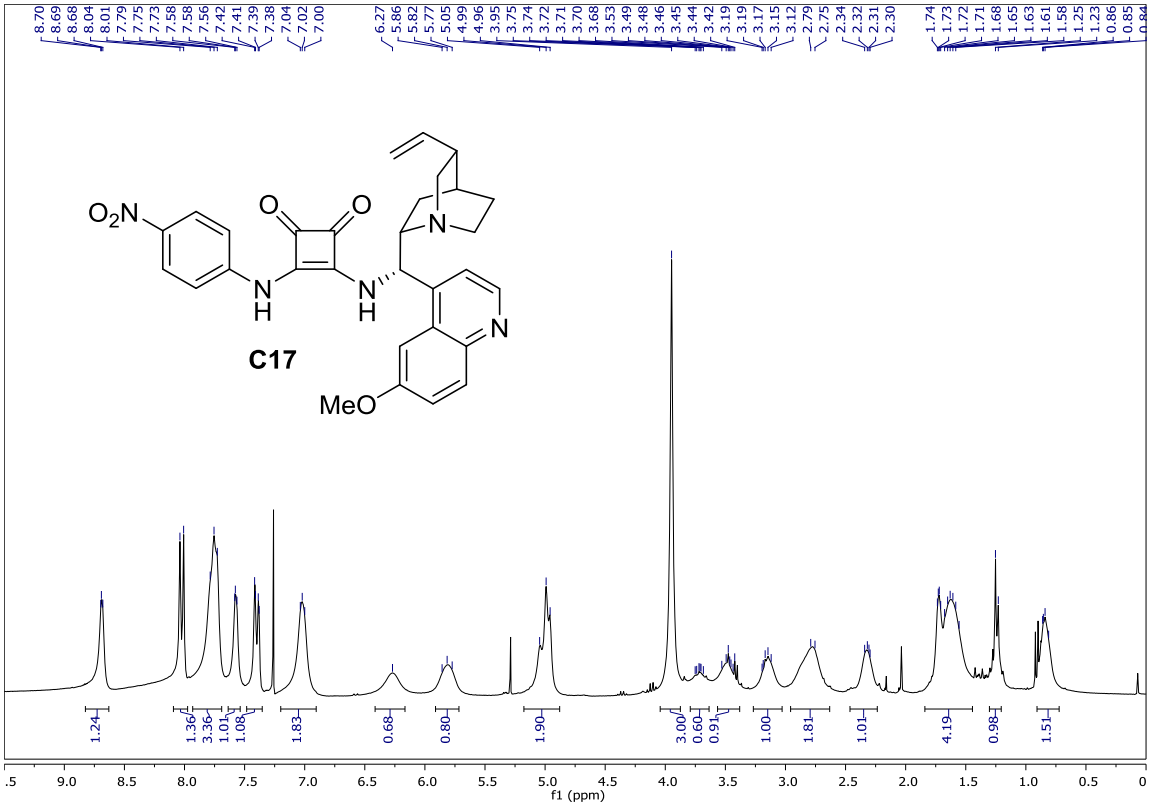
5.5.1. Catalysts

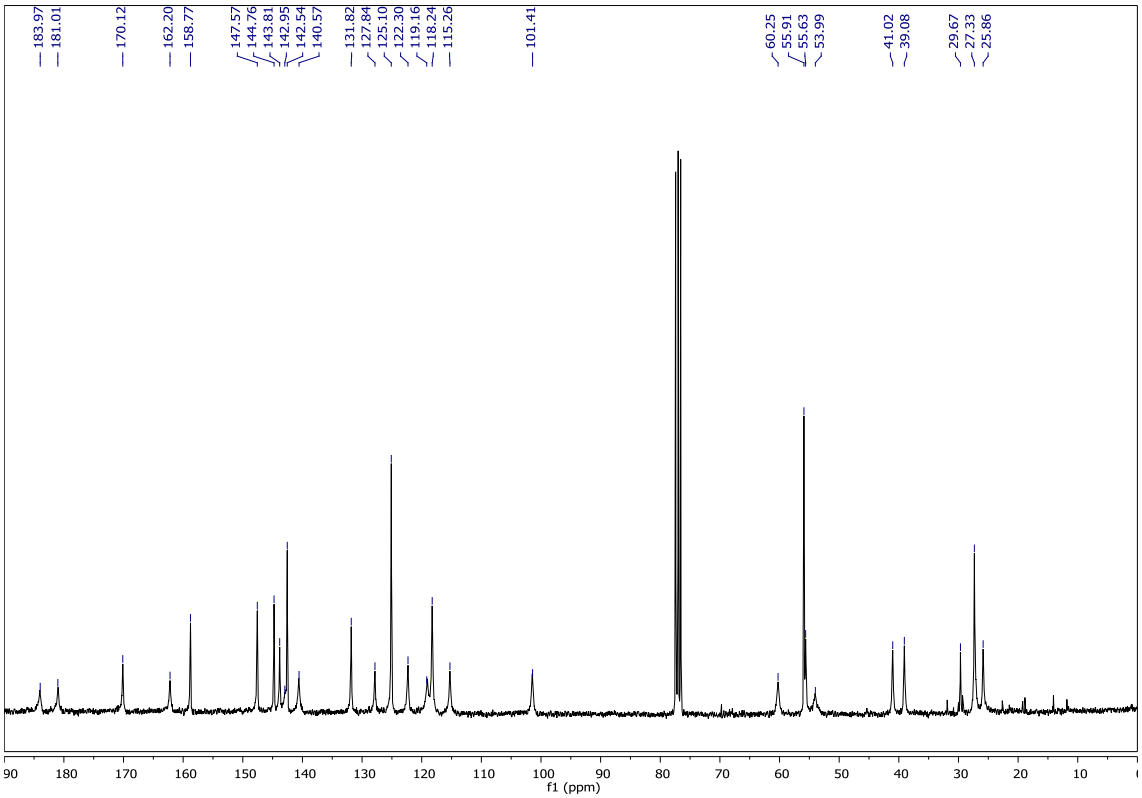


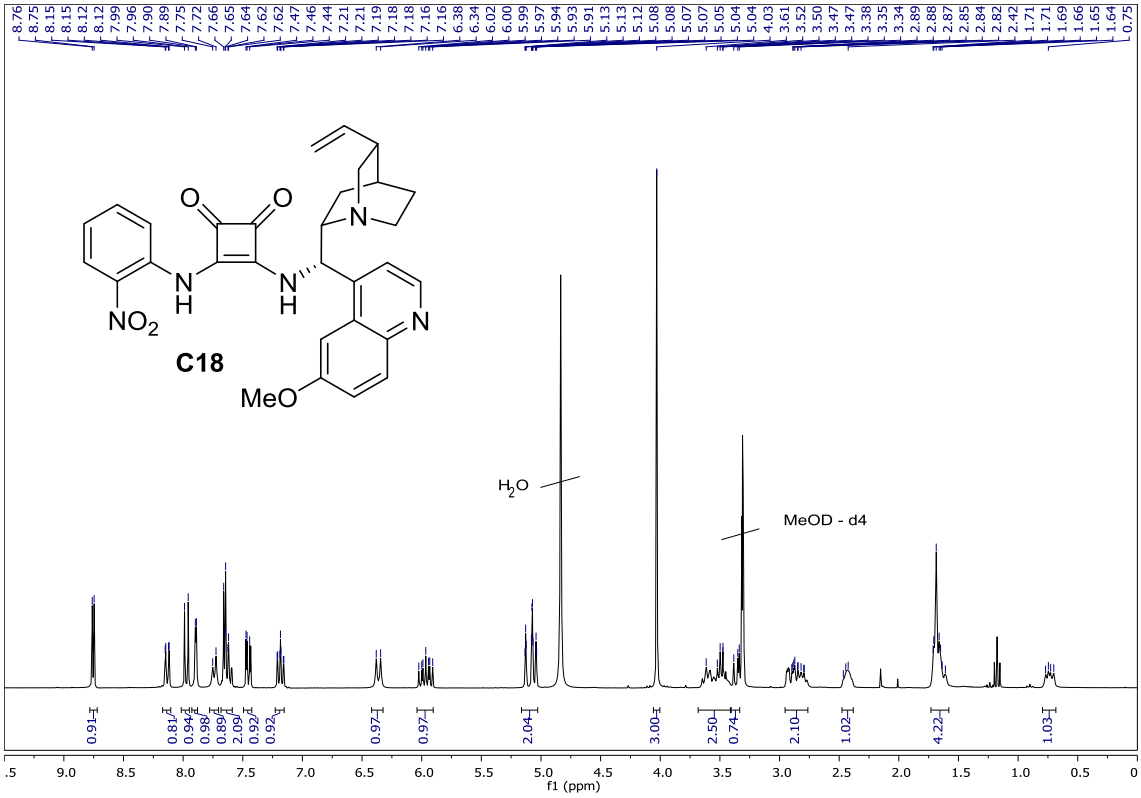


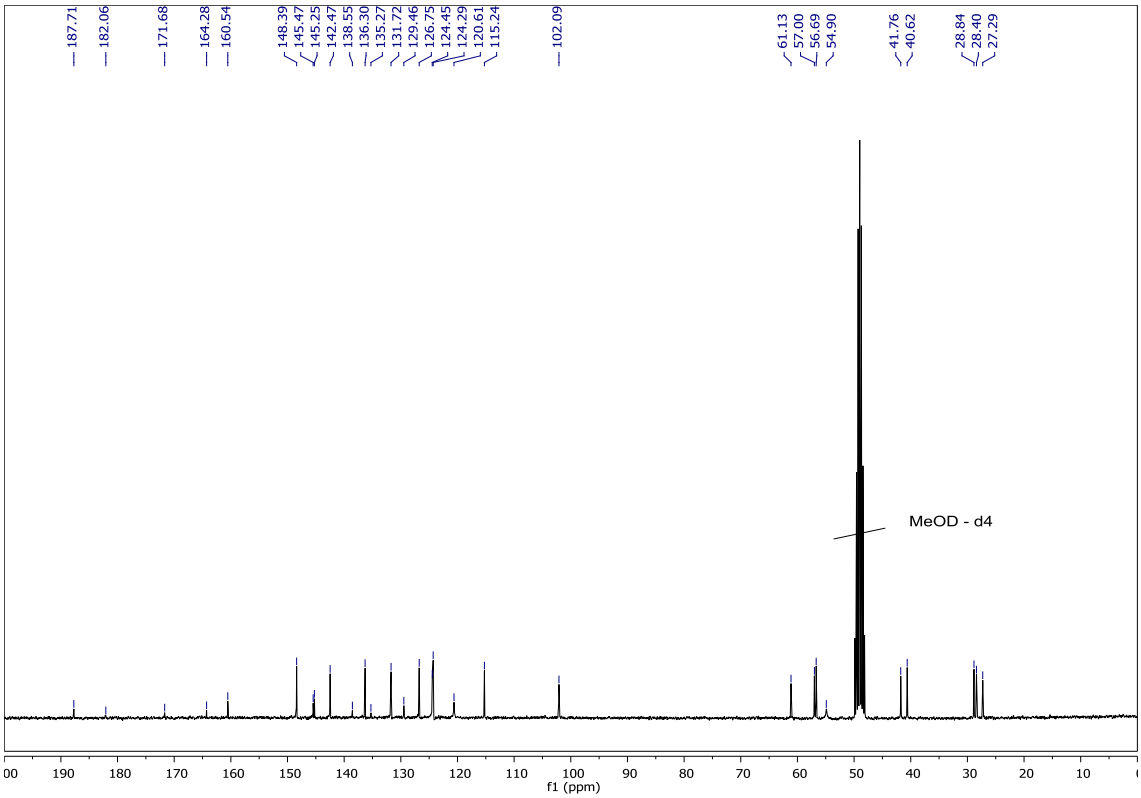

C16
DMSO - d6
f1 (ppm)


DMSO - d6
f1 (ppm)

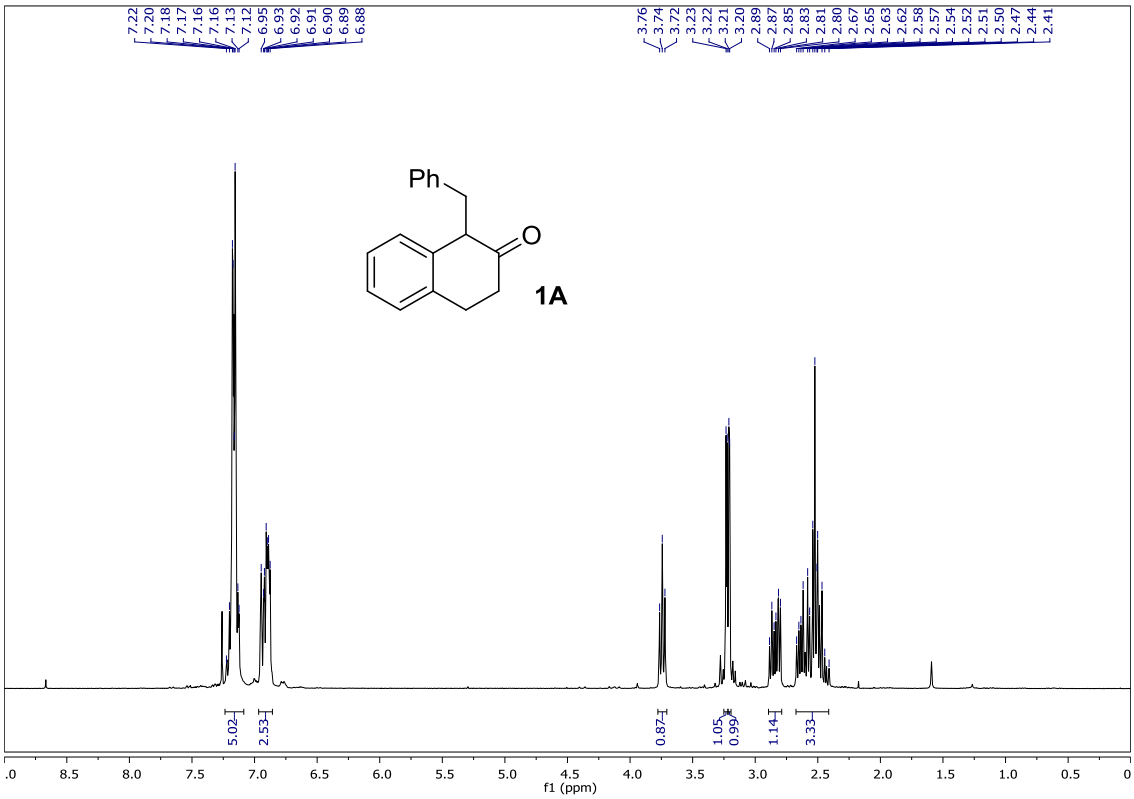

C17
f1 (ppm)

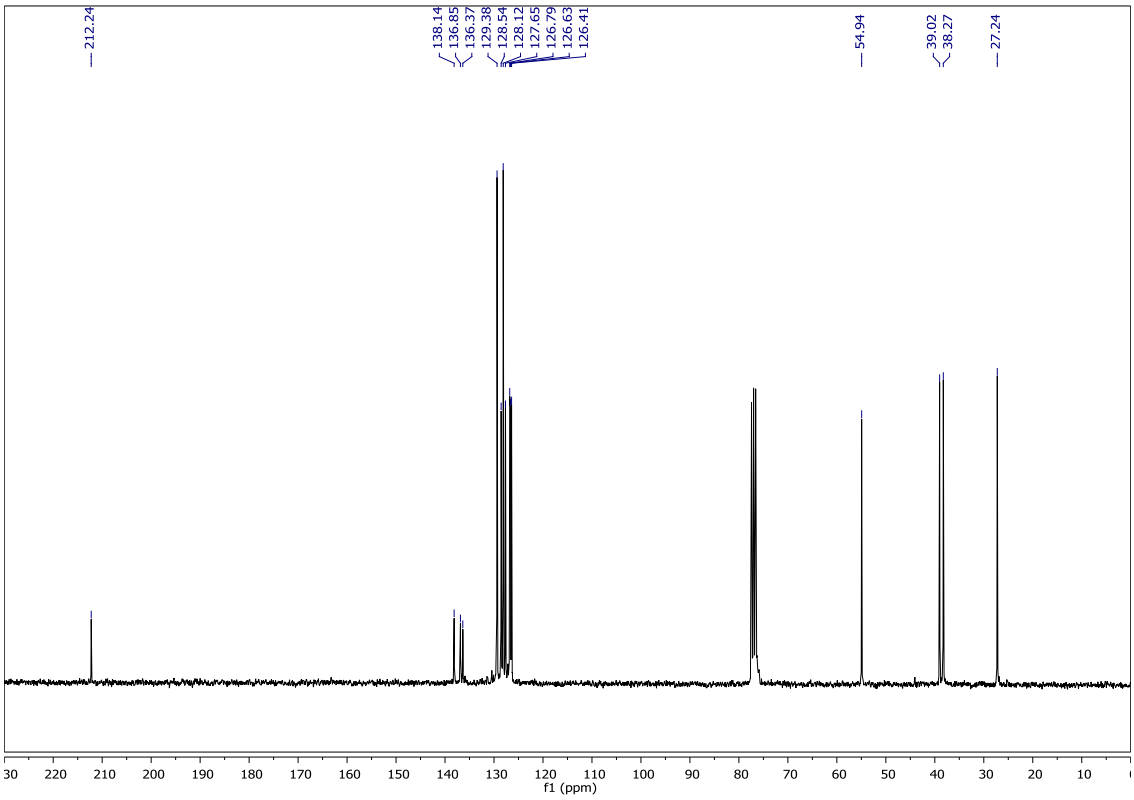

f1 (ppm)

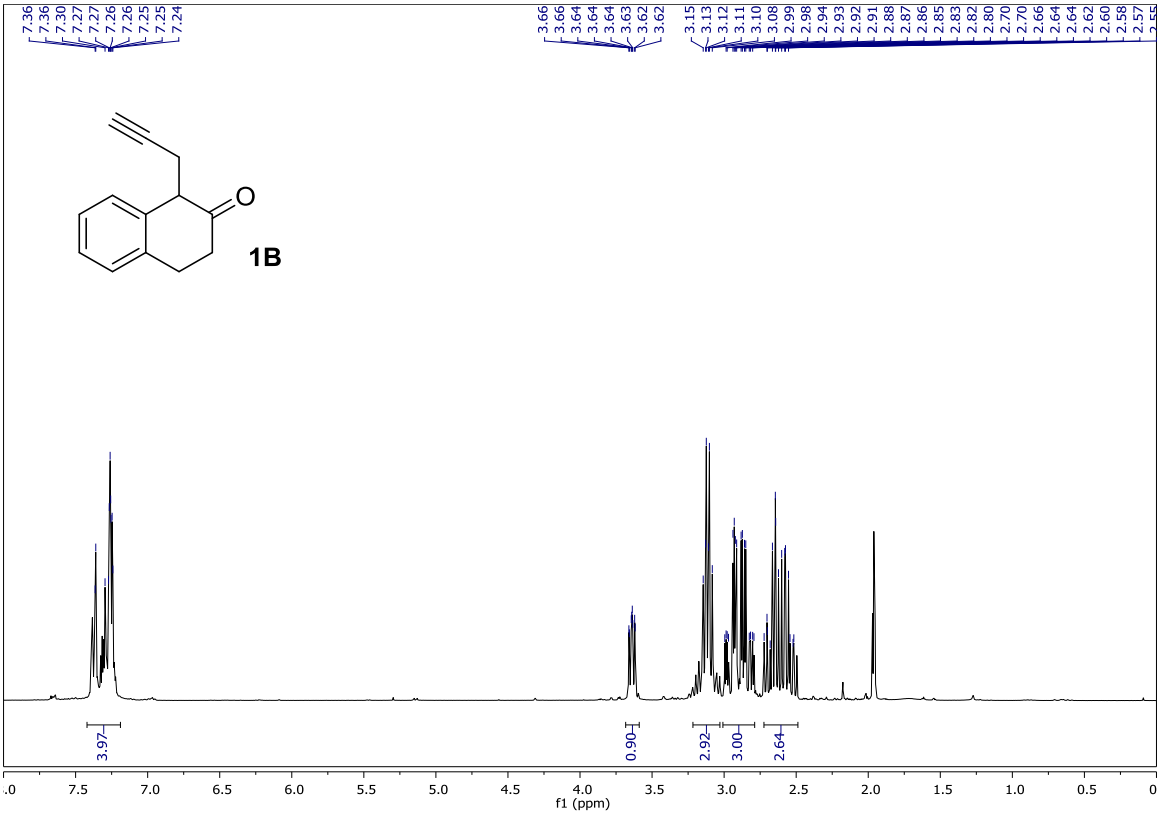

C18
H2O
MeOD - d4
f1 (ppm)


MeOD - d4
f1 (ppm)

5.5.2. NMR spectra for Chapter 2



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7.30
7.27
7.27
7.26
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7.25
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3.66
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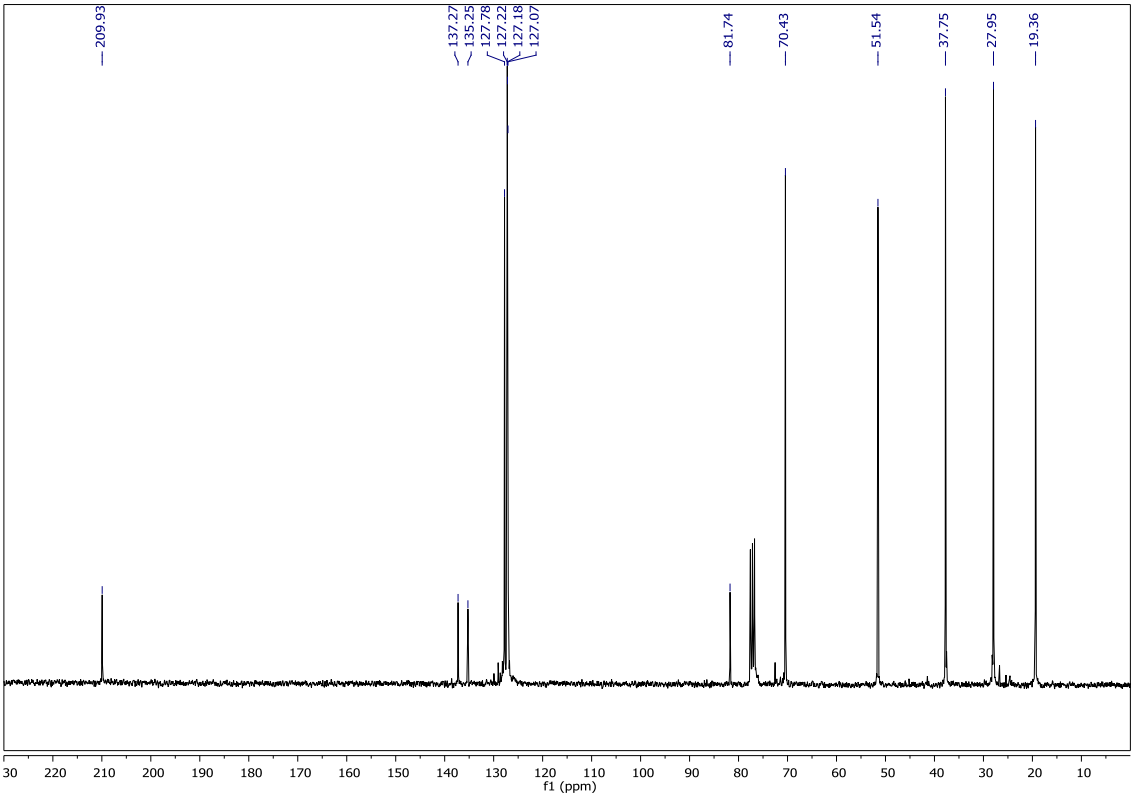
3.64
3.64
3.64
3.63
3.62
3.62
3.15
3.13
3.12
3.11
3.10
3.08
2.99
2.98
2.94
2.93
2.92
2.91
2.88
2.87
2.86
2.85
2.83
2.82
2.80
2.70
2.70
2.66
2.64
2.64
2.62
2.60
2.58
2.57
O
1B
3.97
0.90
2.92
3.00
2.64
f1 (ppm)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137.27
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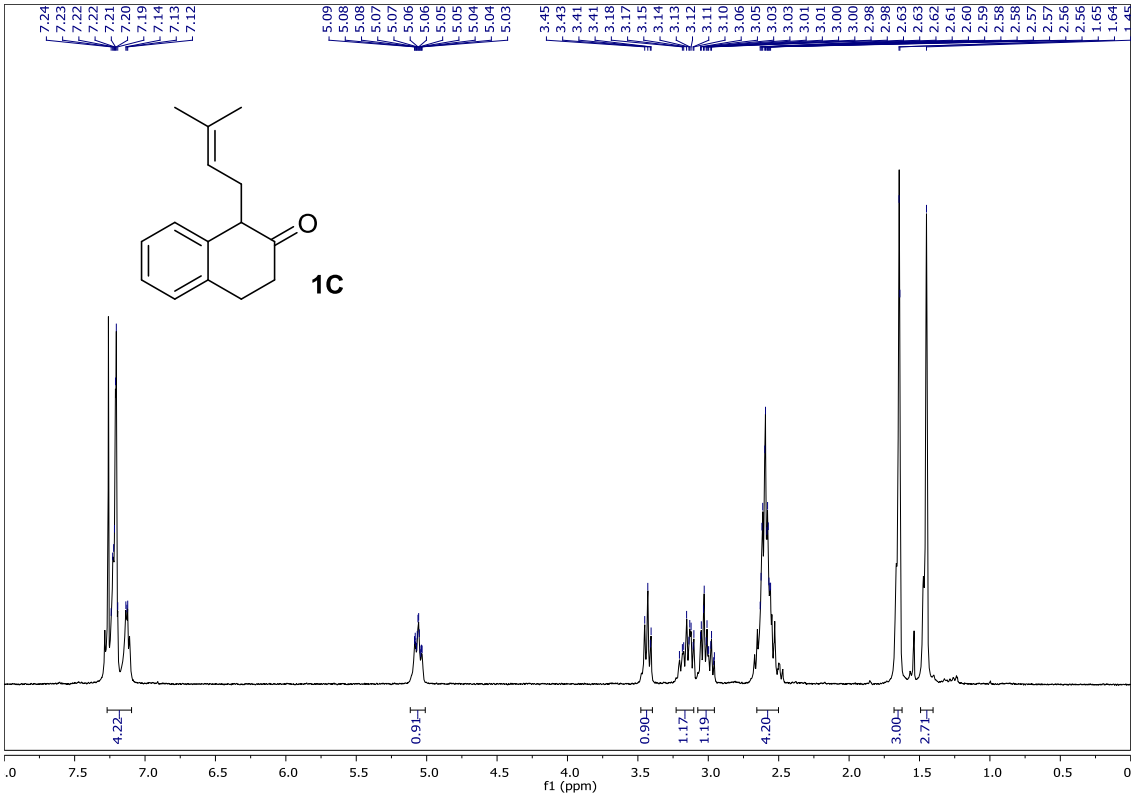
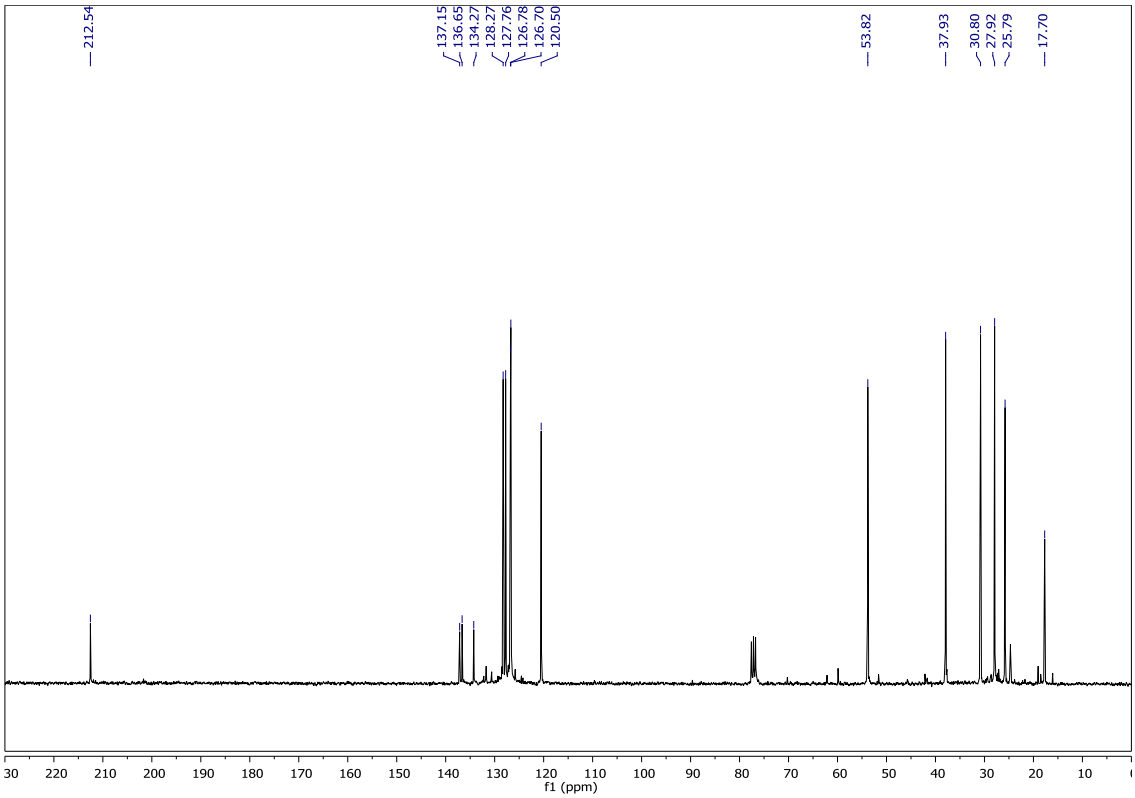
127.22
127.18
127.07
81.74
70.43
51.54
37.75
27.95
19.36
f1 (ppm)


7.24 7.23 7.22 7.22 7.21 7.20 7.19 7.14 7.13 7.12
5.09 5.08 5.08 5.07 5.07 5.06 5.06 5.05 5.05 5.04 5.04 5.03
3.45 3.43 3.41 3.41 3.18 3.17 3.15 3.14 3.13 3.12 3.11 3.10 3.06 3.05 3.03 3.03 3.01 3.01 3.00 3.00 2.98 2.98 2.63 2.63 2.62 2.61 2.60 2.59 2.58 2.58 2.57 2.57 2.56 2.56 1.65 1.64
O
1C
4.22
0.91
0.90
1.17
1.19
4.20
3.00
2.71
.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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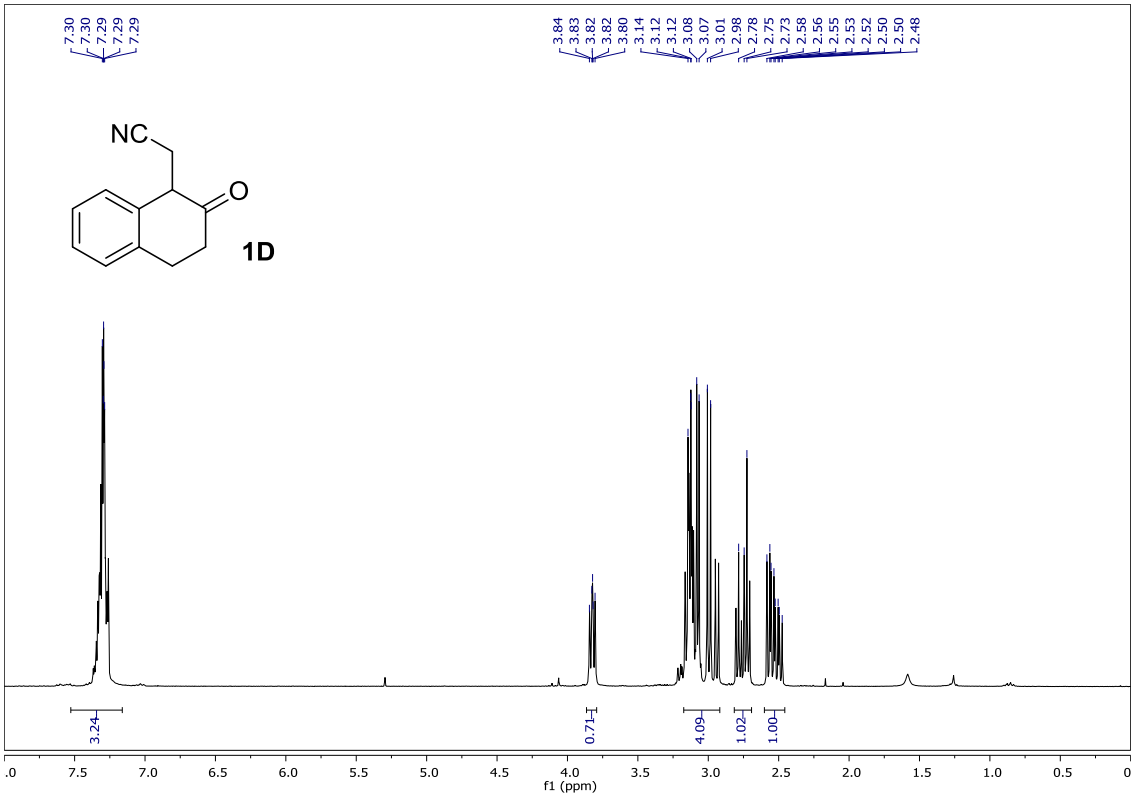
137.15
136.65
134.27
128.27
127.76
126.78
126.70
120.50
53.82
37.93
30.80
27.92
25.79
17.70
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


7.30
7.30
7.29
7.29
7.29
3.84
3.83
3.82
3.82
3.80
3.14
3.12
3.12
3.08
3.07
3.01
2.98
2.78
2.75
2.73
2.58
2.56
2.55
2.53
2.52
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2.48
NC
O
1D
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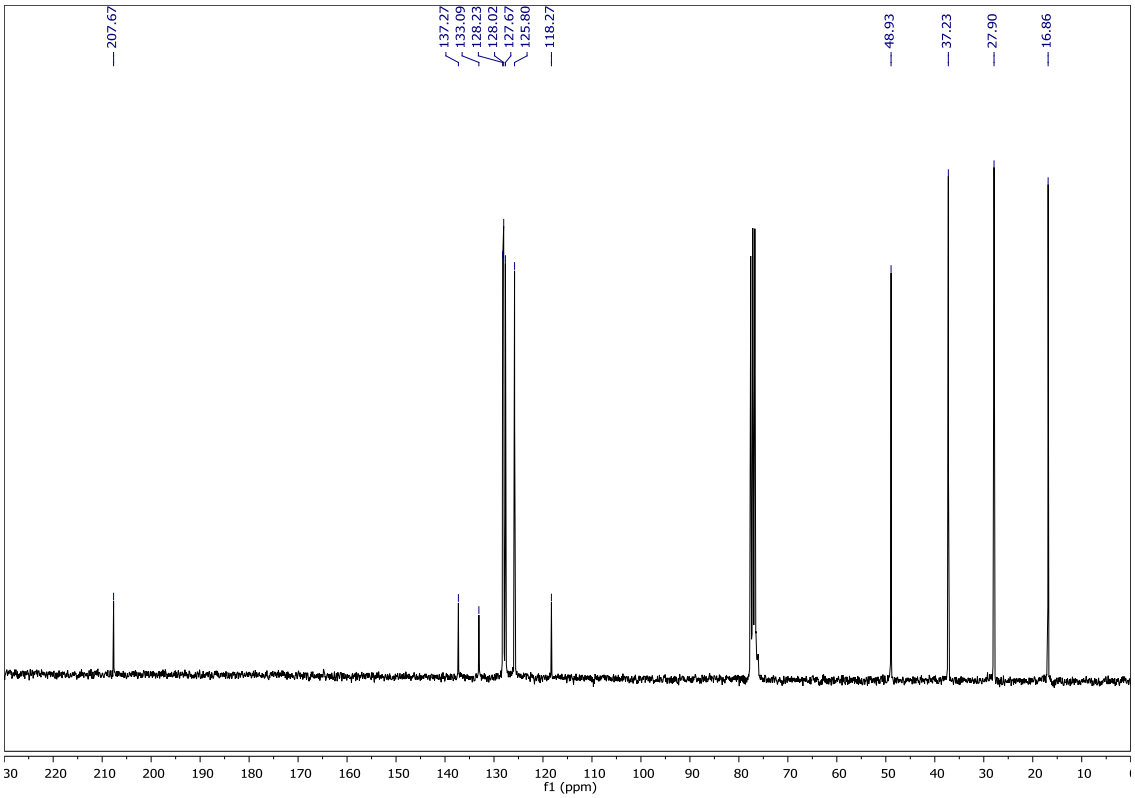
0.71
4.09
1.02
1.00
f1 (ppm)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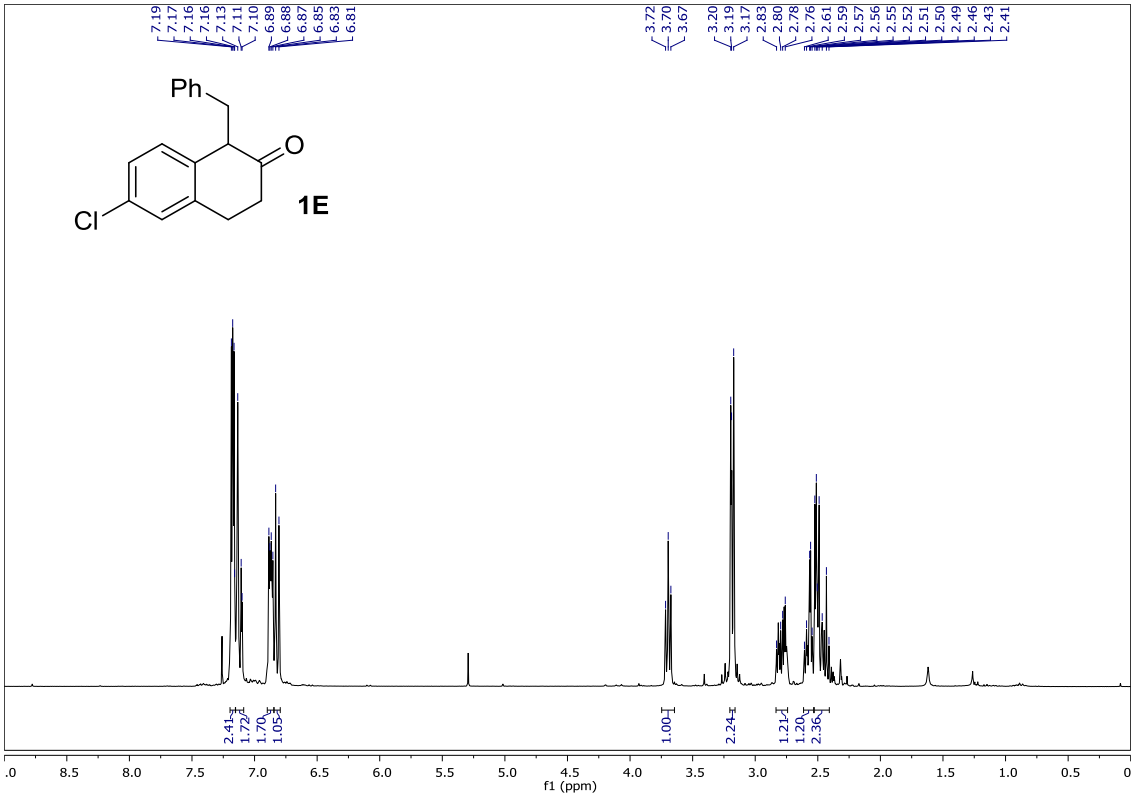
127.67
125.80
118.27
48.93
37.23
27.90
16.86
f1 (ppm)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6.87
6.85
6.83
6.81
3.72
3.70
3.67
3.20
3.19
3.17
2.83
2.80
2.78
2.76
2.61
2.59
2.57
2.56
2.55
2.52
2.51
2.50
2.49
2.46
2.43
2.41
Ph
O
Cl
1E
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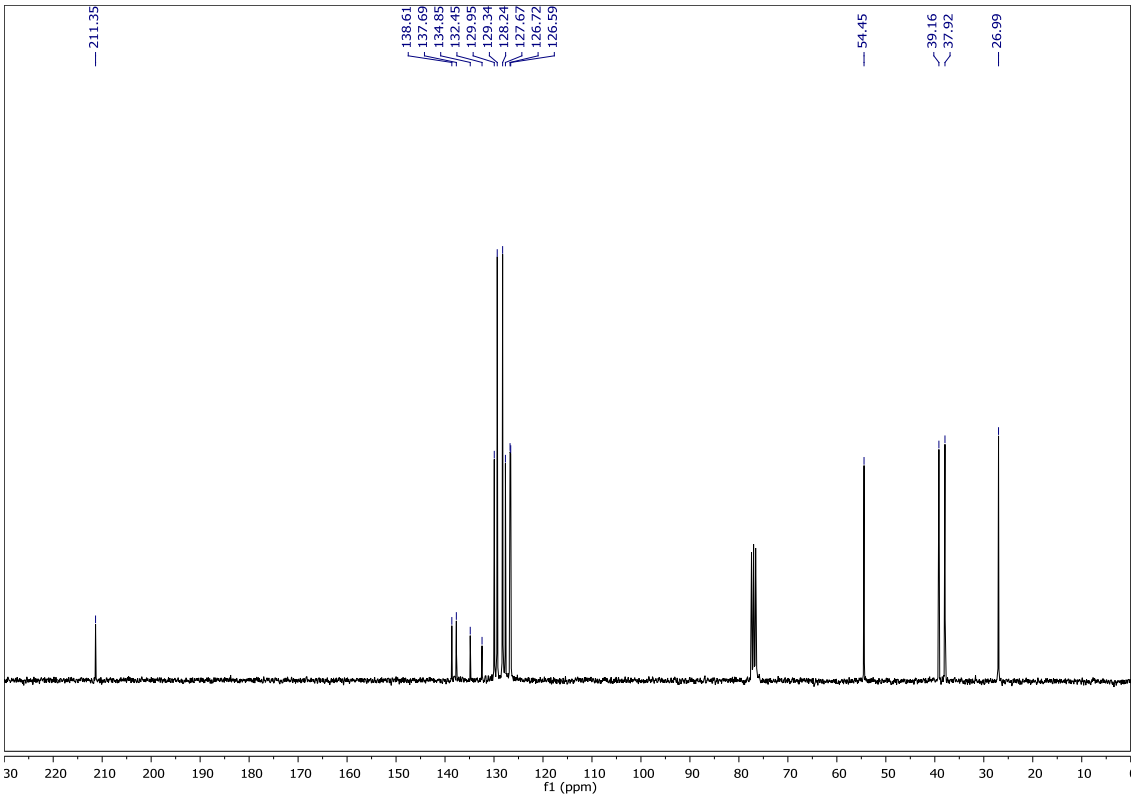
1.72
1.70
1.05
1.00
2.24
1.21
1.20
2.36
f1 (ppm)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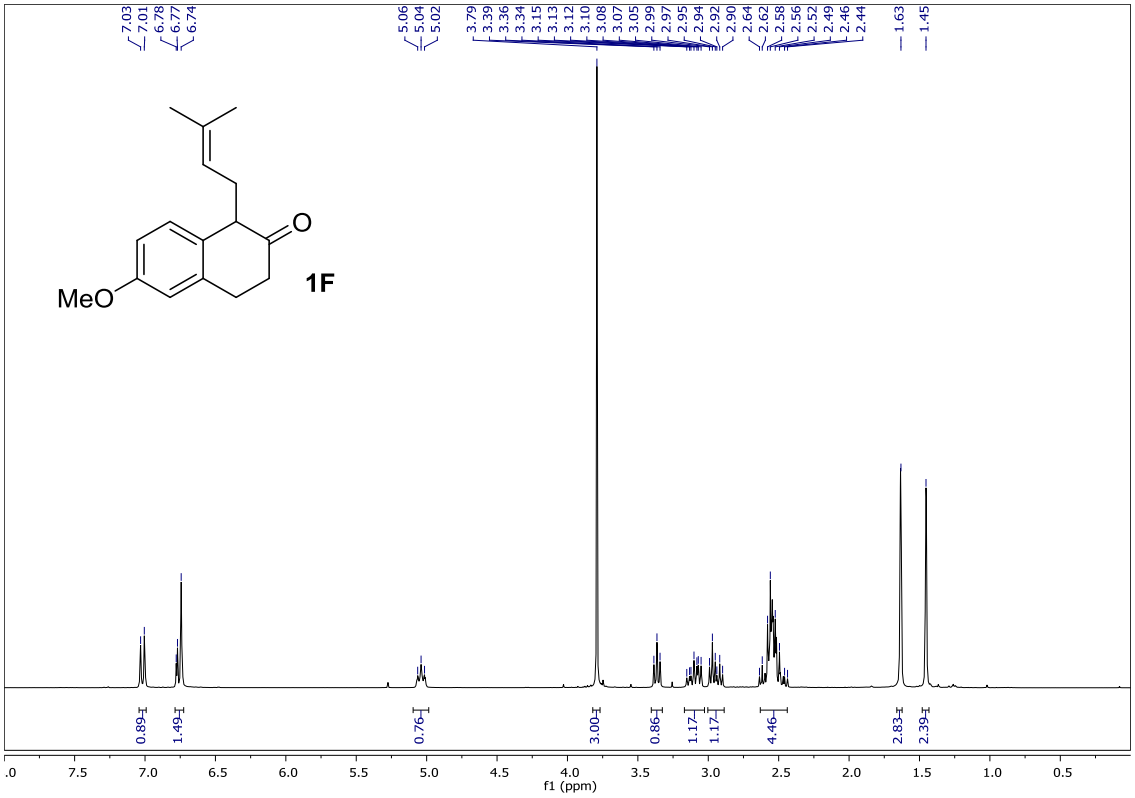
126.72
126.59
54.45
39.16
37.92
26.99
f1 (ppm)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6.78
6.77
6.74
5.06
5.04
5.02
3.79
3.39
3.36
3.34
3.15
3.13
3.12
3.10
3.08
3.07
3.05
2.99
2.97
2.95
2.94
2.92
2.90
2.64
2.62
2.58
2.56
2.52
2.49
2.46
2.44
1.63
1.45
O
MeO
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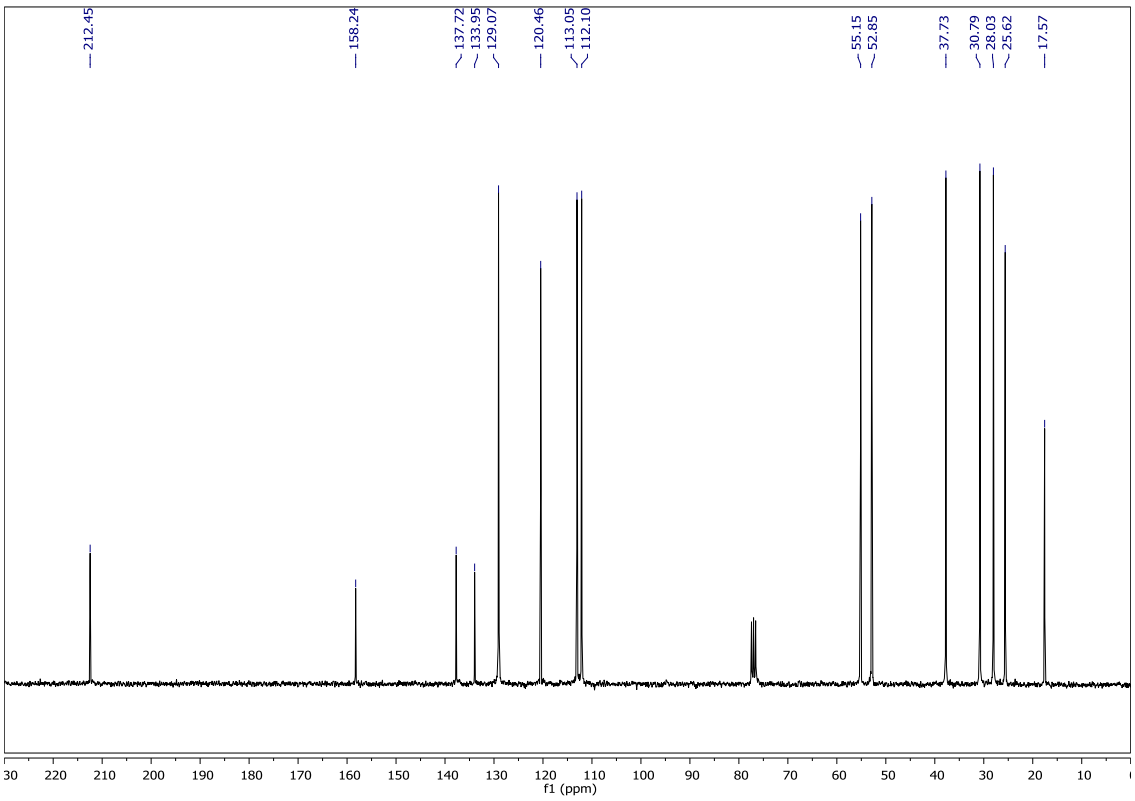
0.86
1.17
1.17
4.46
2.83
2.39
f1 (ppm)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37.73
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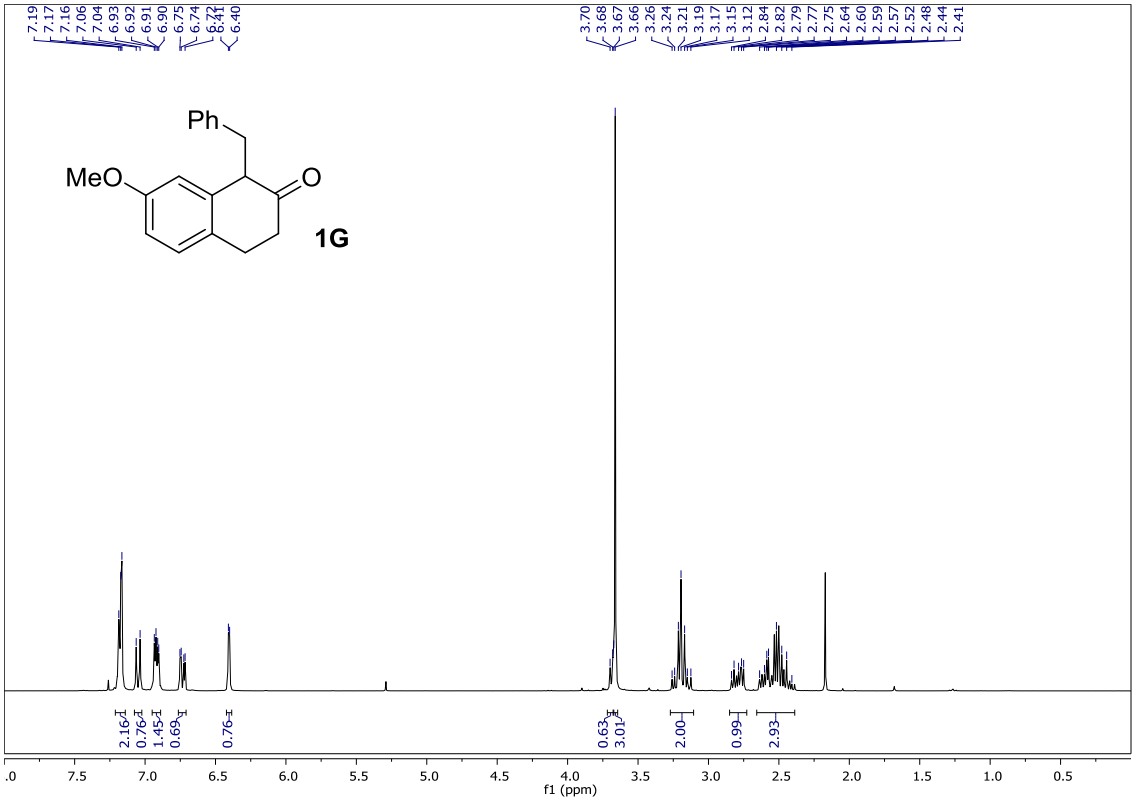
28.03
25.62
17.57
f1 (ppm)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6.74
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6.40
3.70
3.68
3.67
3.66
3.26
3.24
3.21
3.19
3.17
3.15
3.12
2.84
2.82
2.79
2.77
2.75
2.64
2.60
2.59
2.57
2.52
2.48
2.44
2.41
Ph
MeO
O
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0.63
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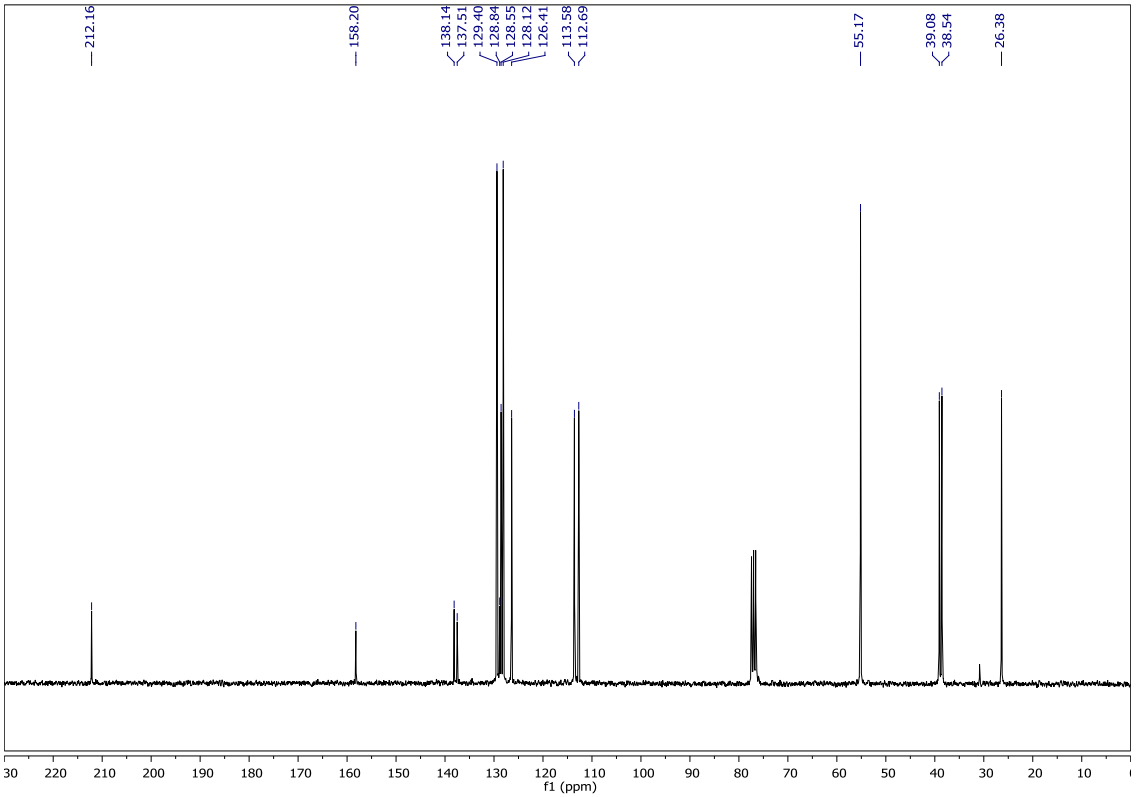
2.93
f1 (ppm)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112.69
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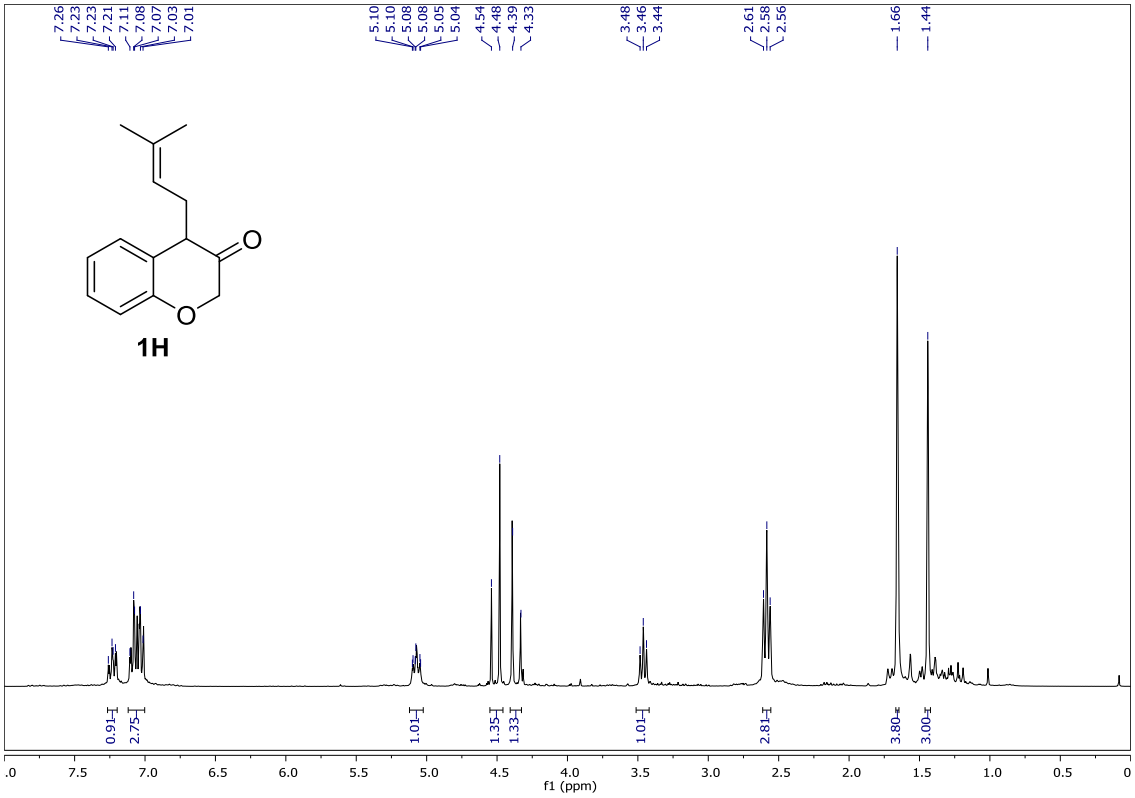
39.08
38.54
26.38
f1 (ppm)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5.08
5.05
5.04
4.54
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4.39
4.33
3.48
3.46
3.44
2.61
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2.56
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1.44
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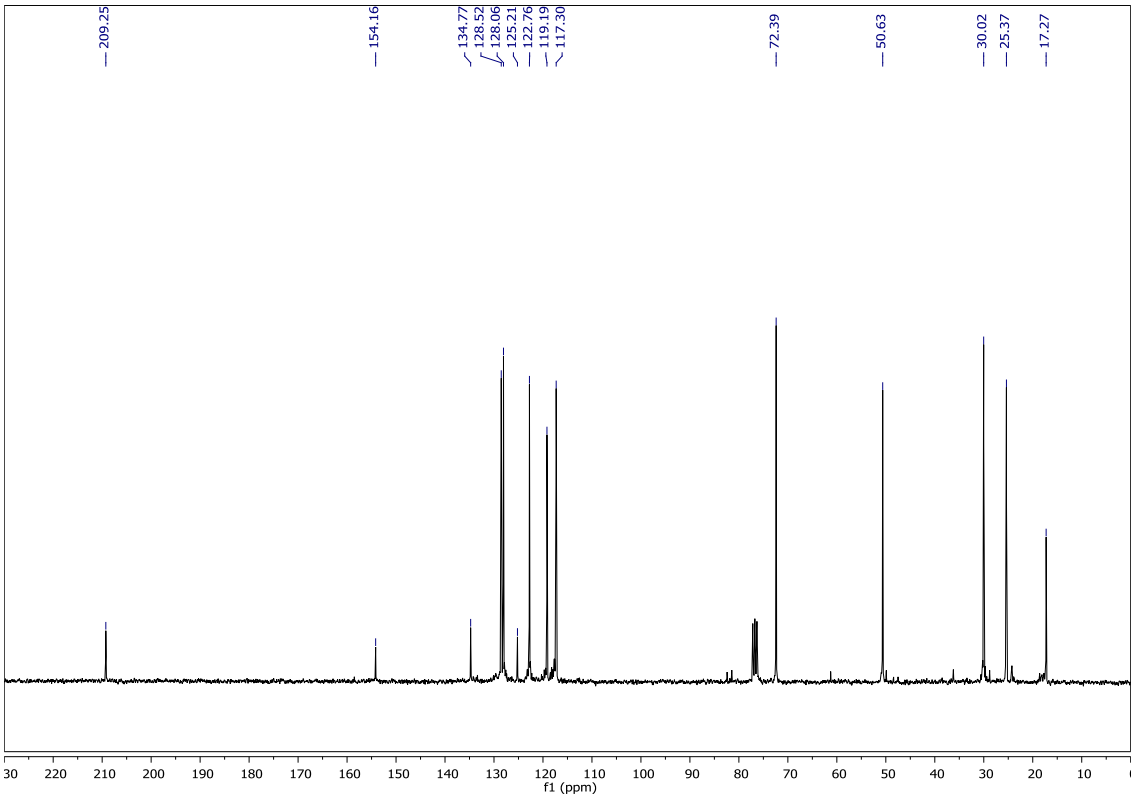
f1 (ppm)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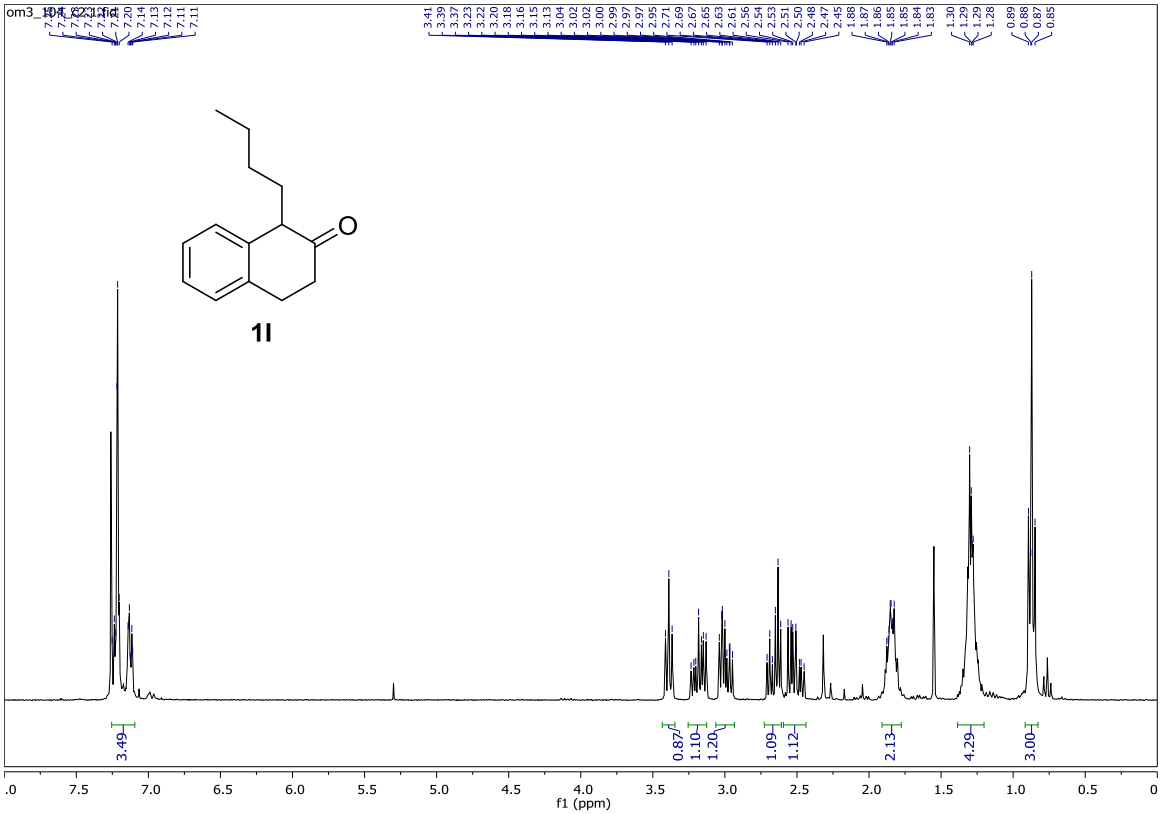
17.27
f1 (ppm)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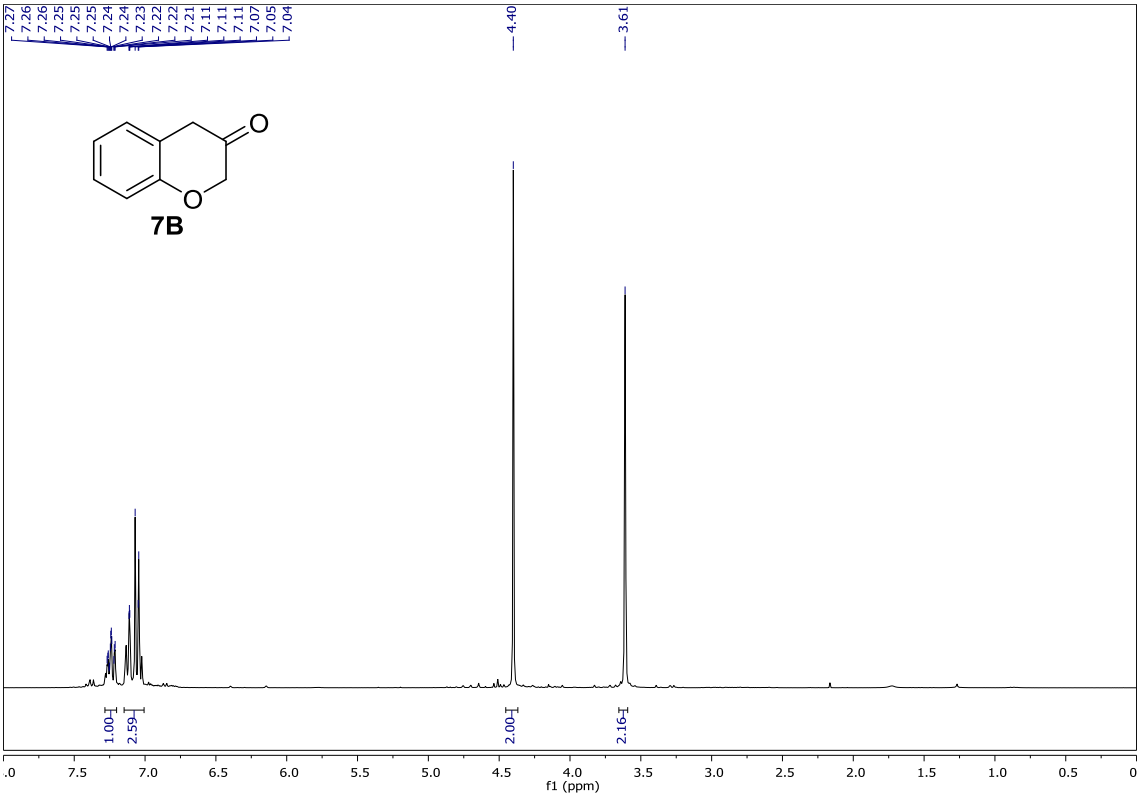
3.00
f1 (ppm)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7.11
7.11
7.07
7.05
7.04
4.40
3.61
O
O
7B
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6.5
6.0
5.5
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1.5
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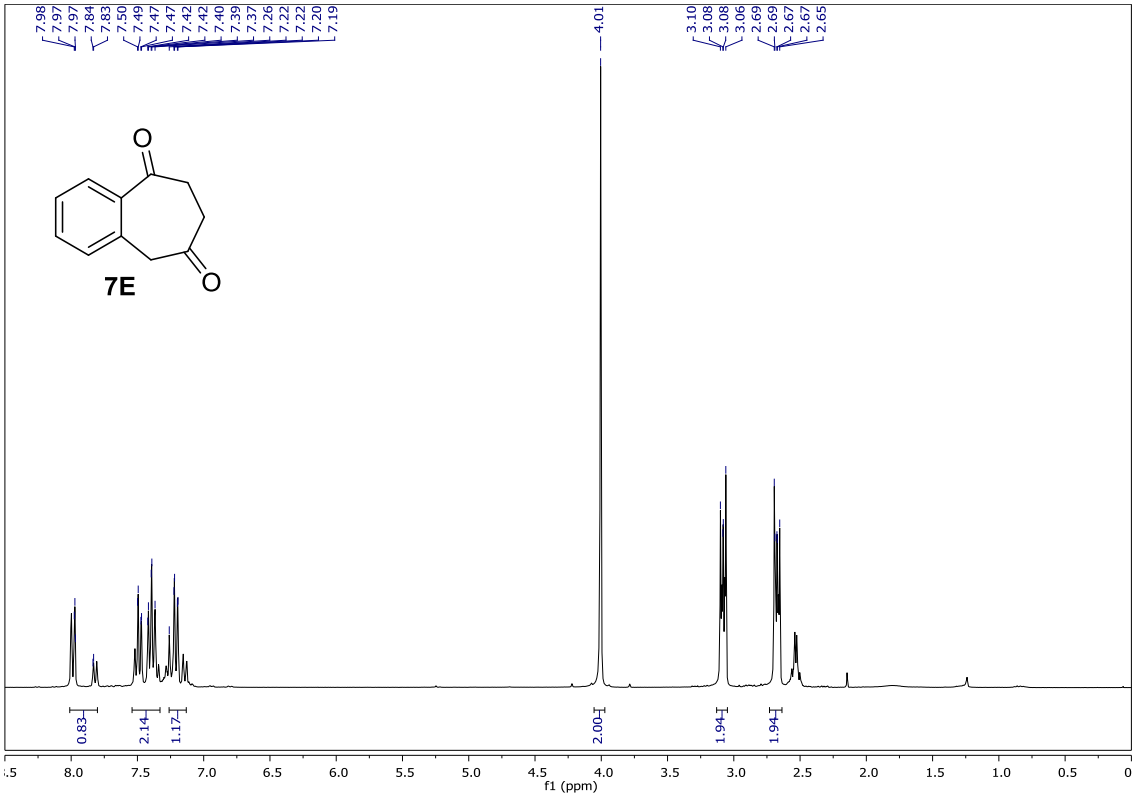
f1 (ppm)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7.37
7.26
7.22
7.22
7.20
7.19
4.01
3.10
3.08
3.08
3.06
2.69
2.69
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O
O
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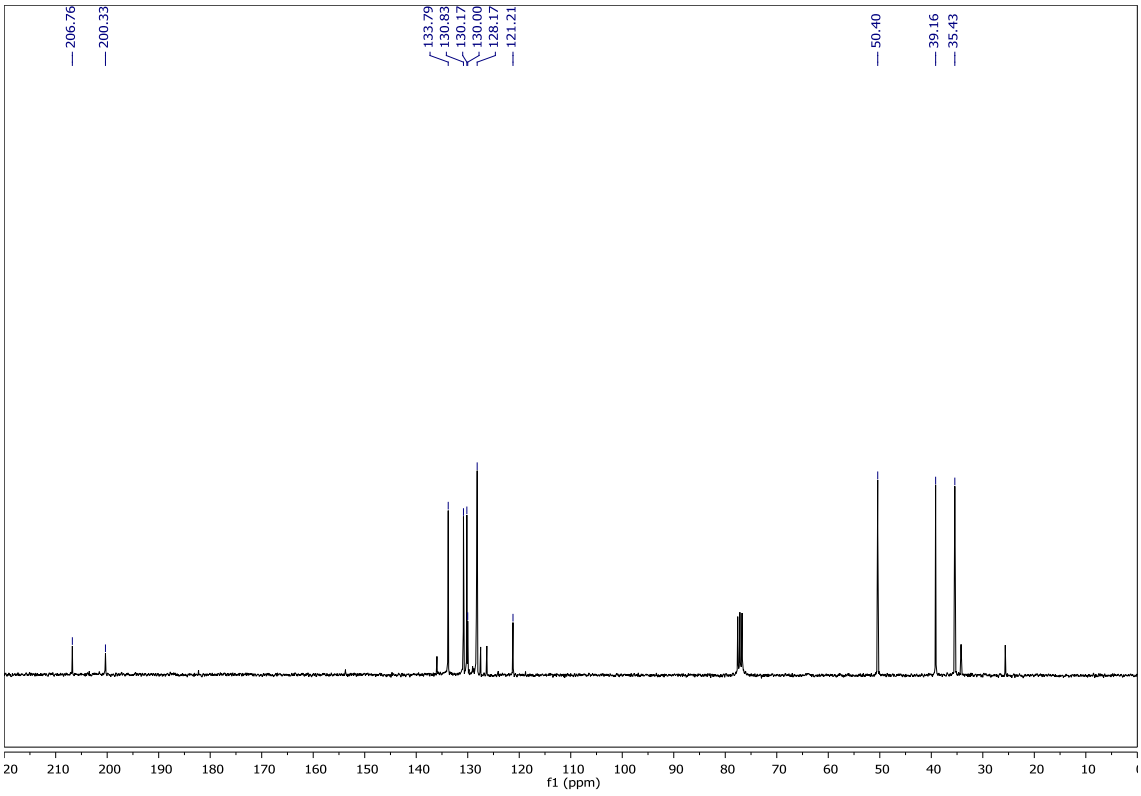
f1 (ppm)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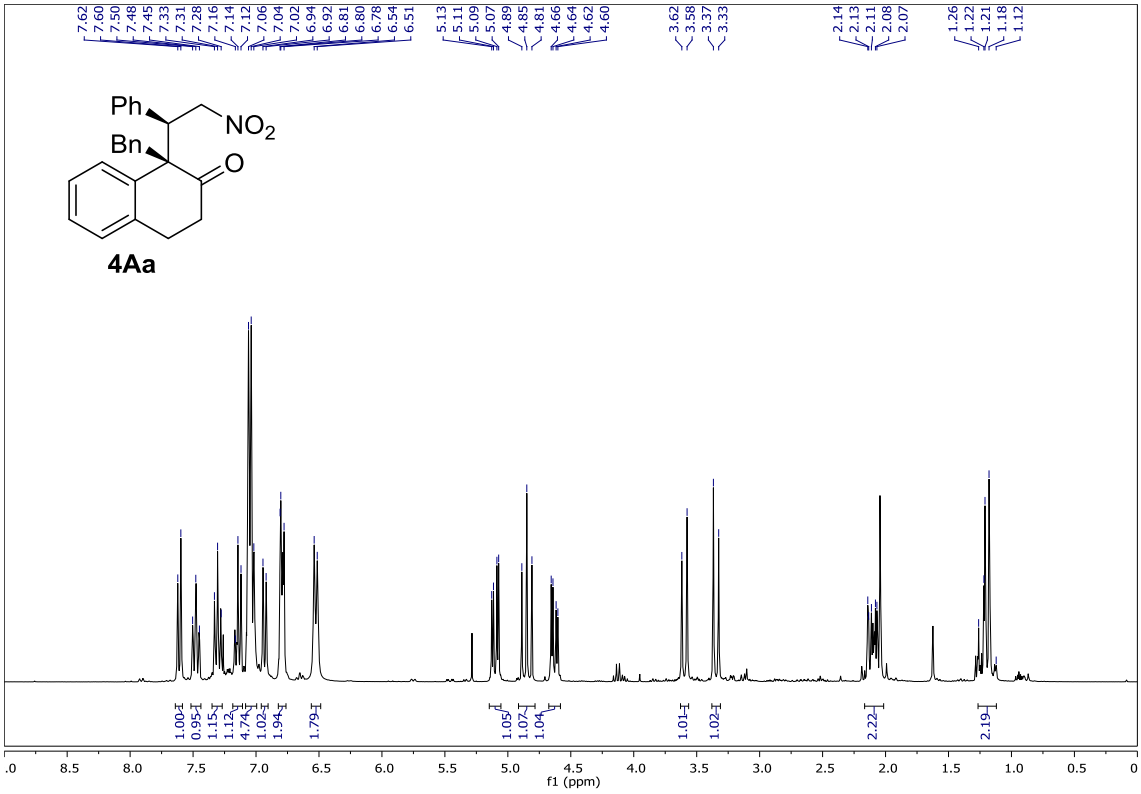
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7.02
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6.92
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6.78
6.54
6.51
5.13
5.11
5.09
5.07
4.89
4.85
4.81
4.66
4.64
4.62
4.60
3.62
3.58
3.37
3.33
2.14
2.13
2.11
2.08
2.07
1.26
1.22
1.21
1.18
1.12
Ph
Bn
NO2
O
4Aa
1.00
0.95
1.15
1.12
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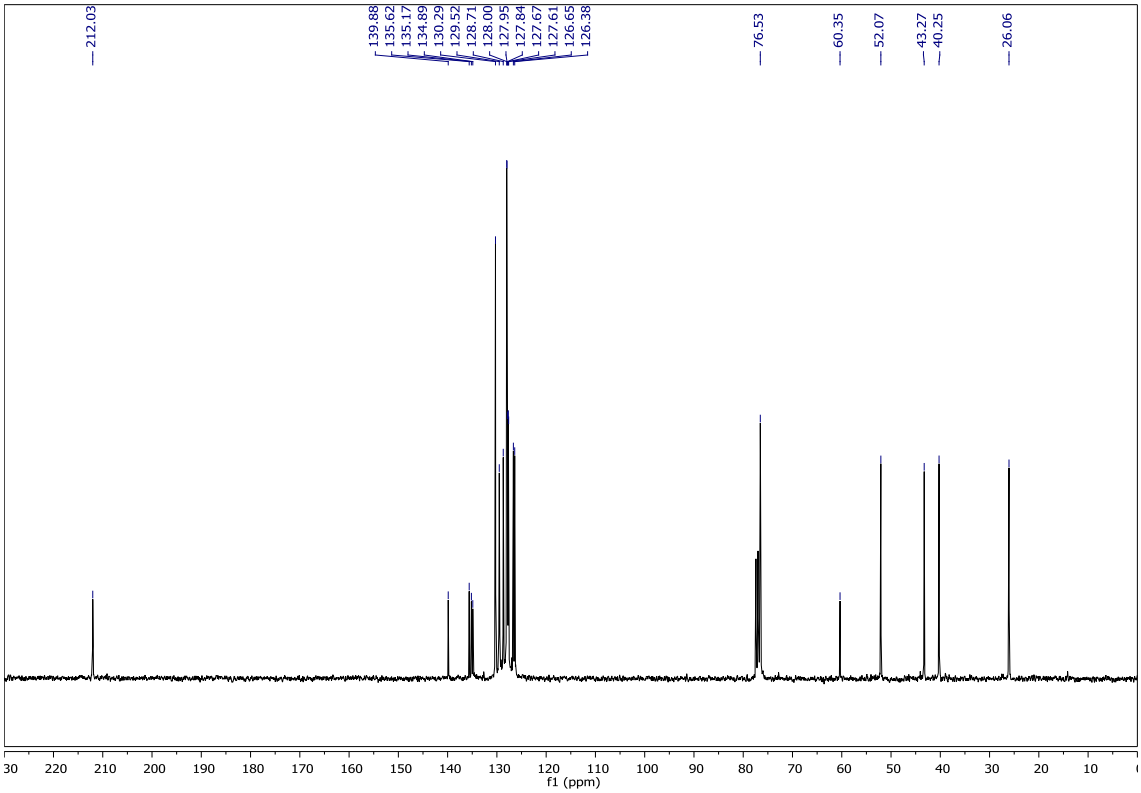
1.79
1.05
1.07
1.04
1.01
1.02
2.22
2.19
f1 (ppm)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128.00
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127.67
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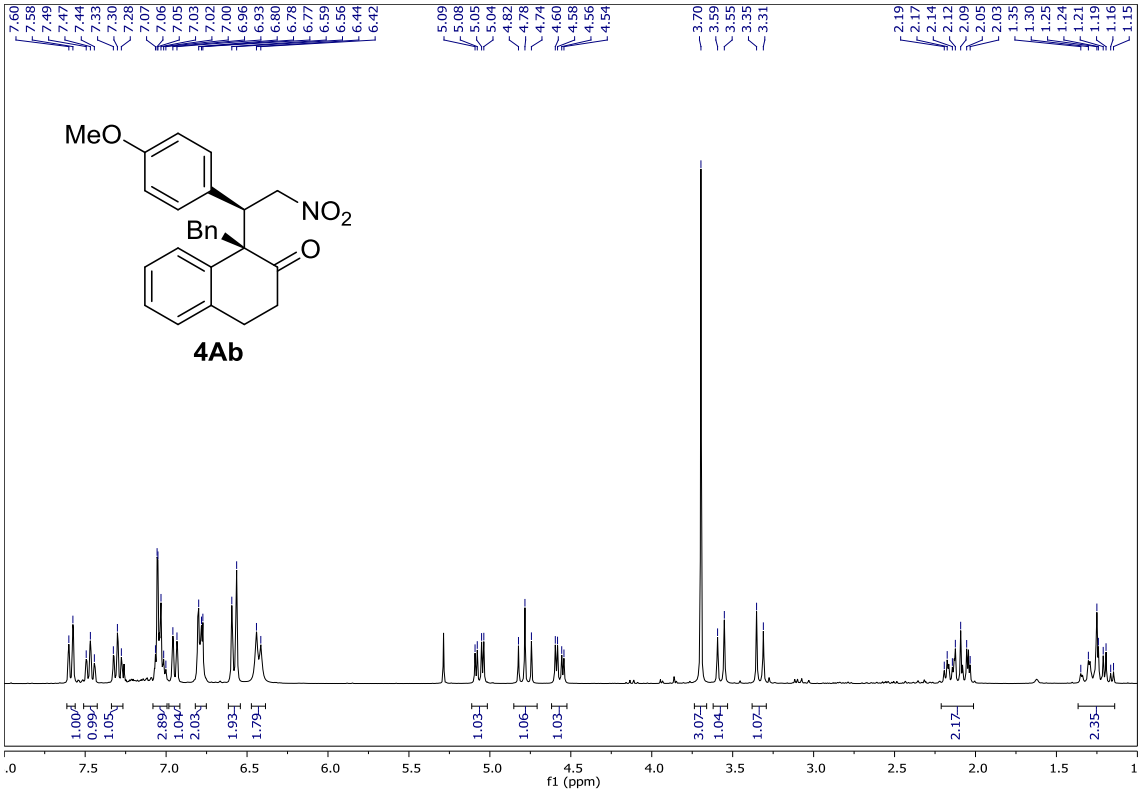
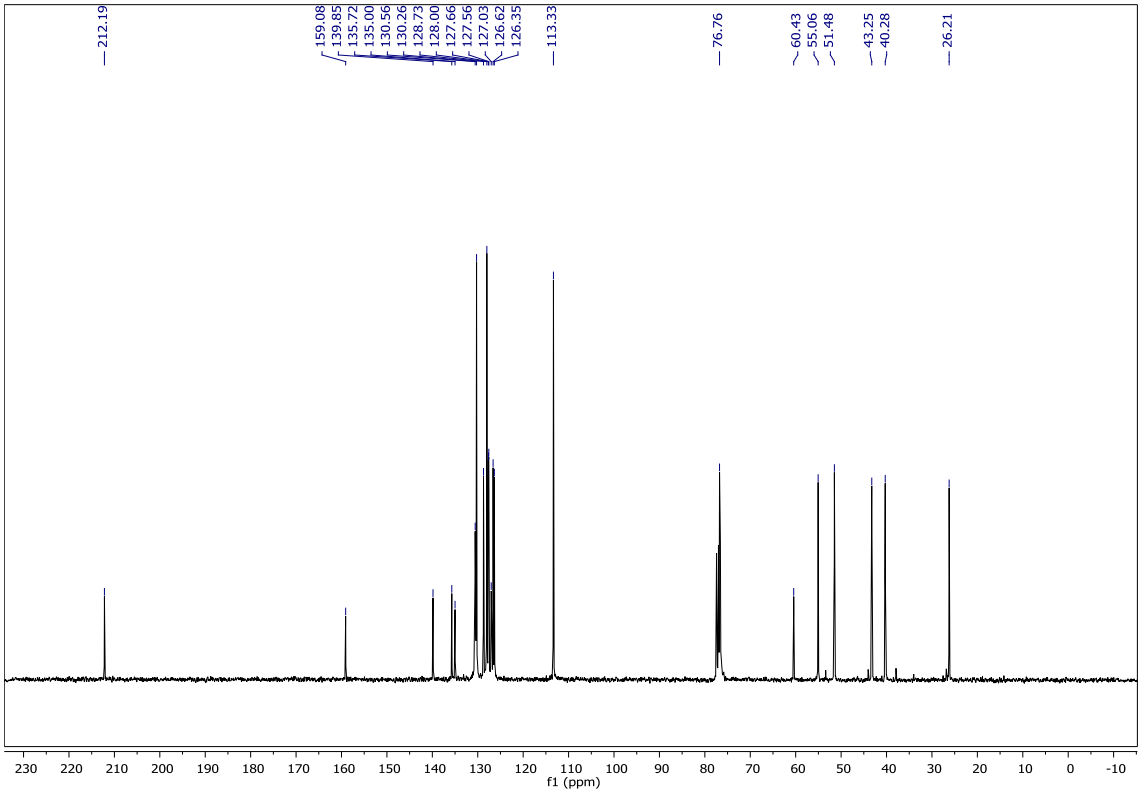
126.65
126.38
76.53
60.35
52.07
43.27
40.25
26.06
f1 (ppm)


MeO
NO2
Bn
O
4Ab
f1 (ppm)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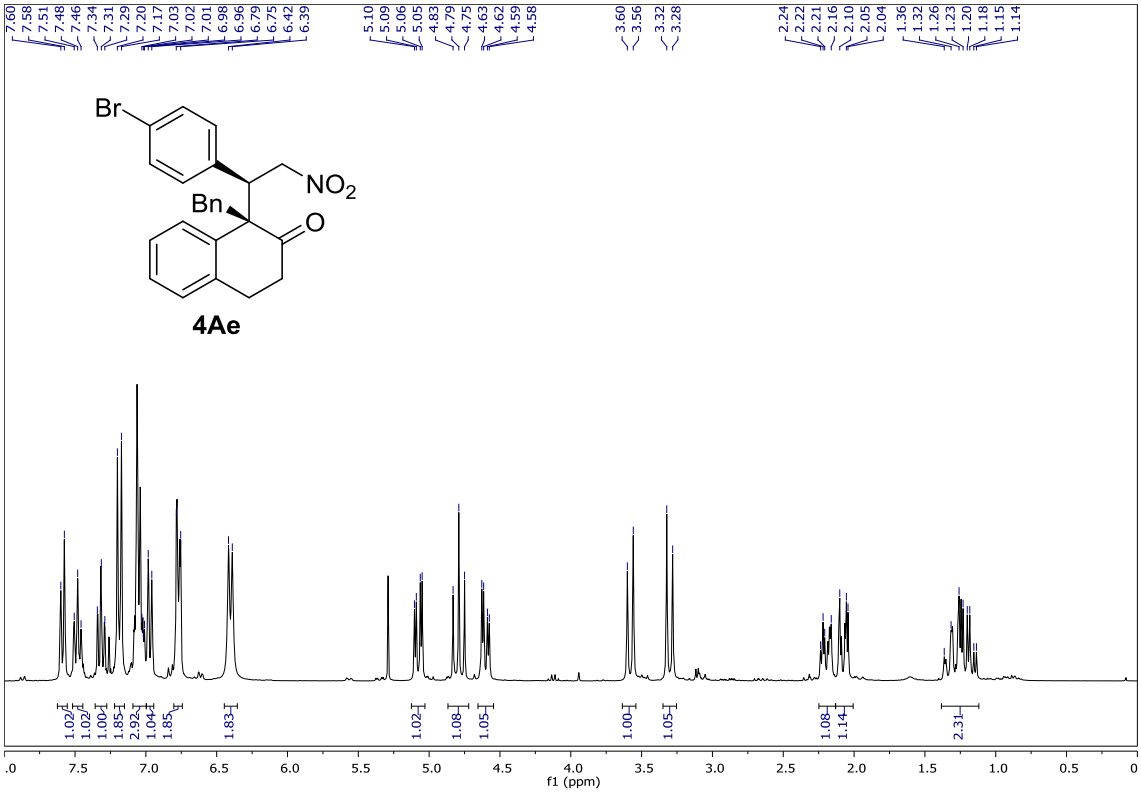
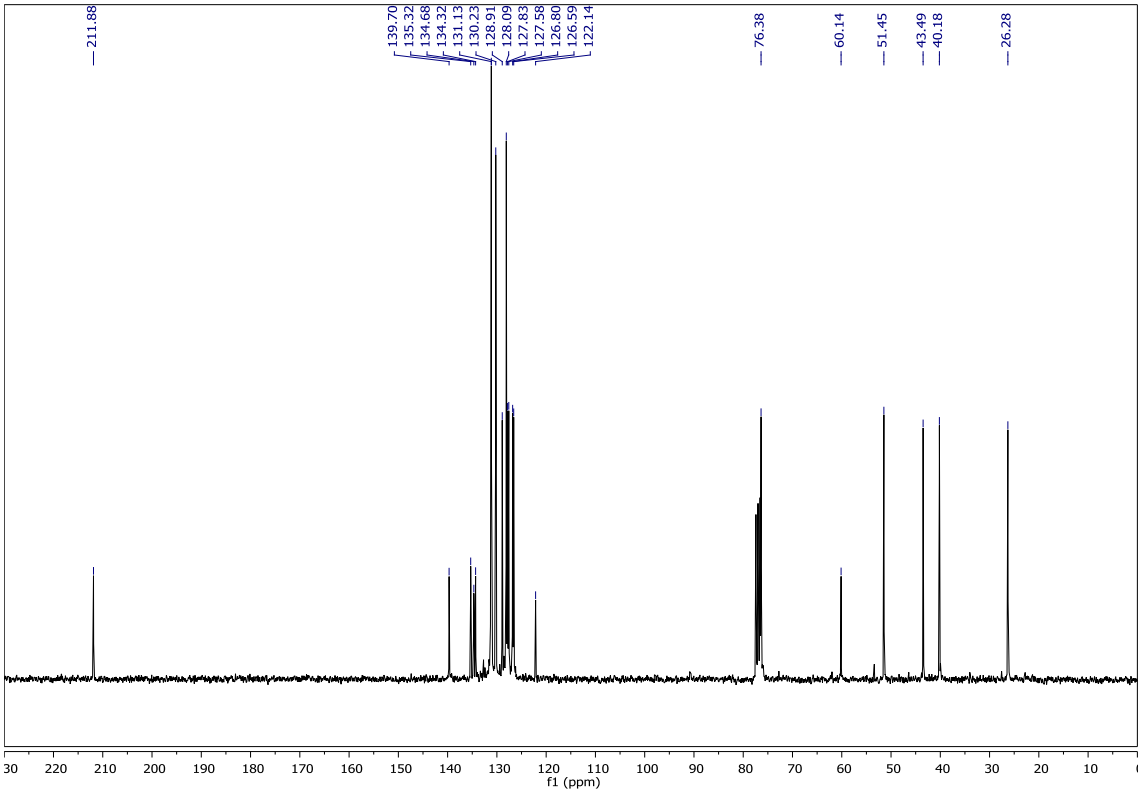

Br
NO2
Bn
O
4Ae
f1 (ppm)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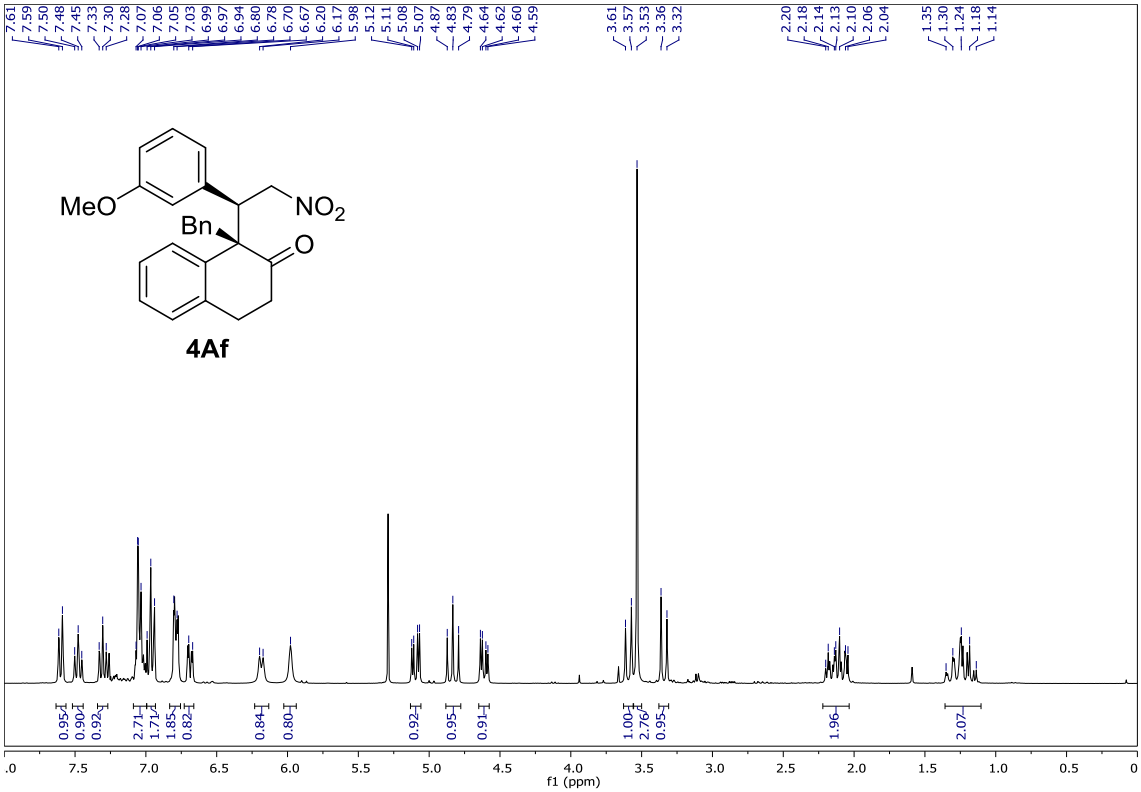
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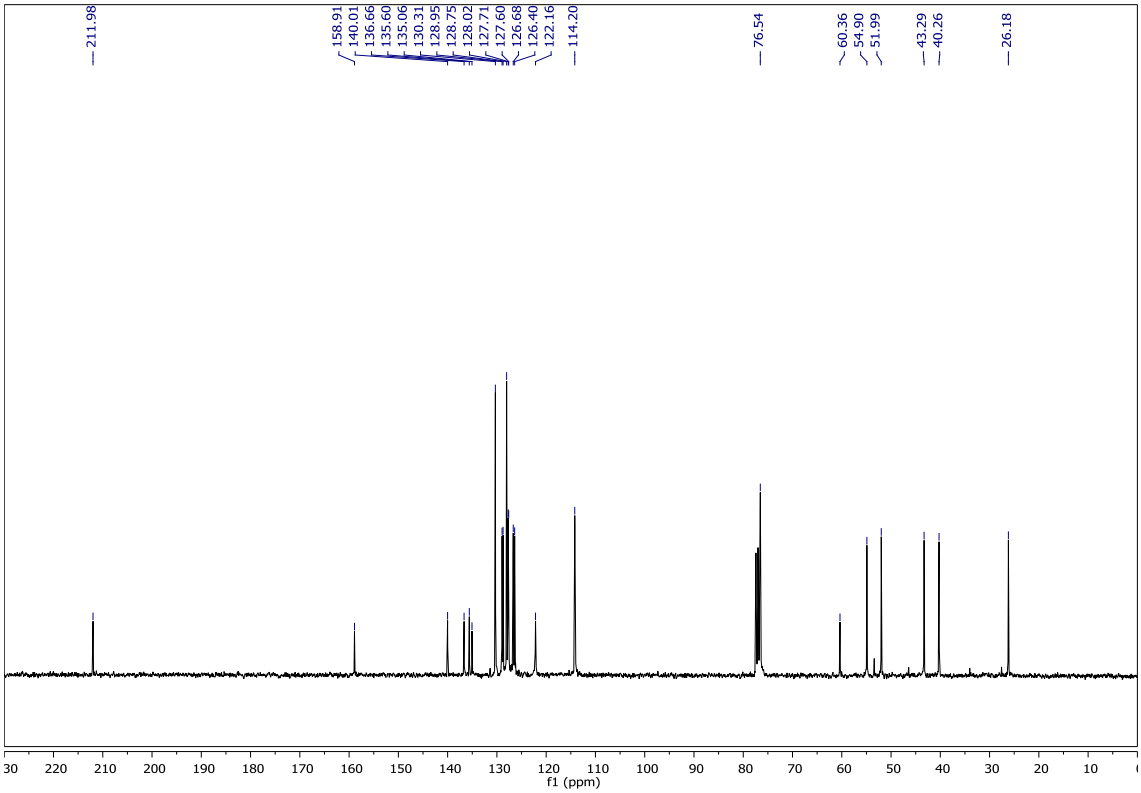
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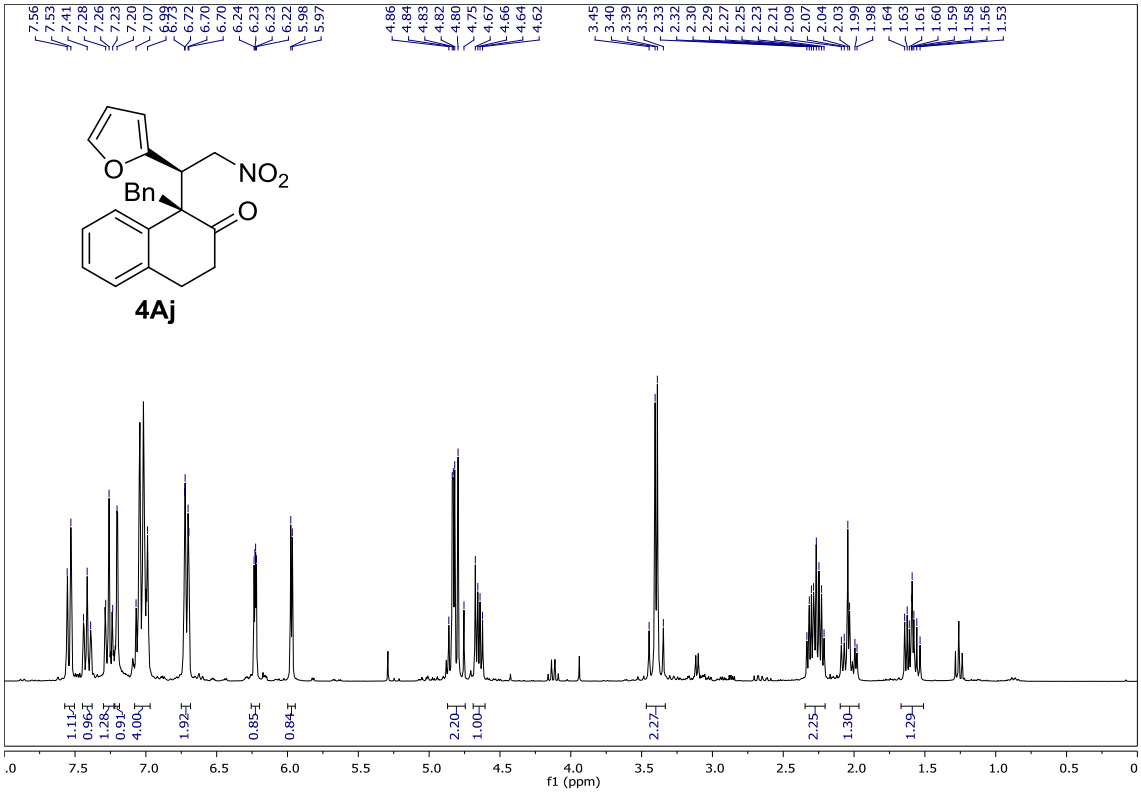
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4.86 4.84 4.83 4.82 4.80 4.75 4.67 4.66 4.64 4.62
3.45 3.40 3.39 3.35 2.33 2.32 2.30 2.29 2.27 2.25 2.23 2.21 2.09 2.07 2.04 2.03 1.99 1.98 1.64 1.63 1.61 1.60 1.59 1.58 1.56 1.53
O
Bn
NO2
O
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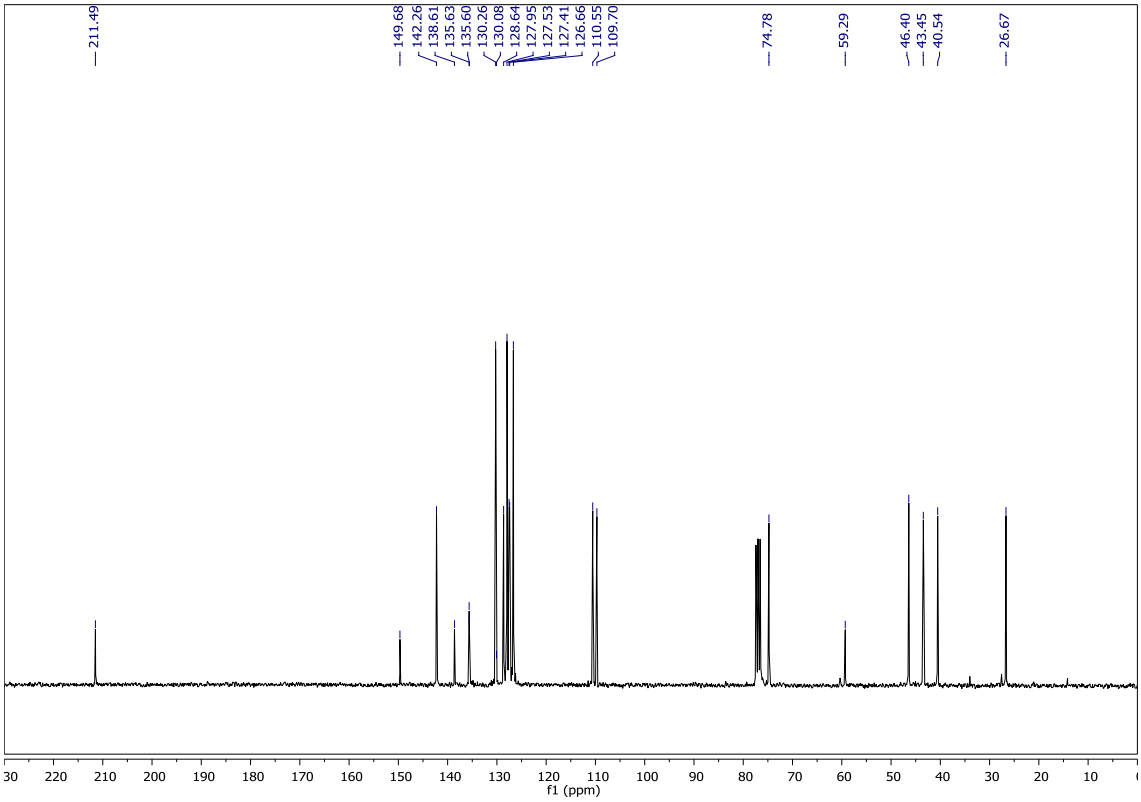
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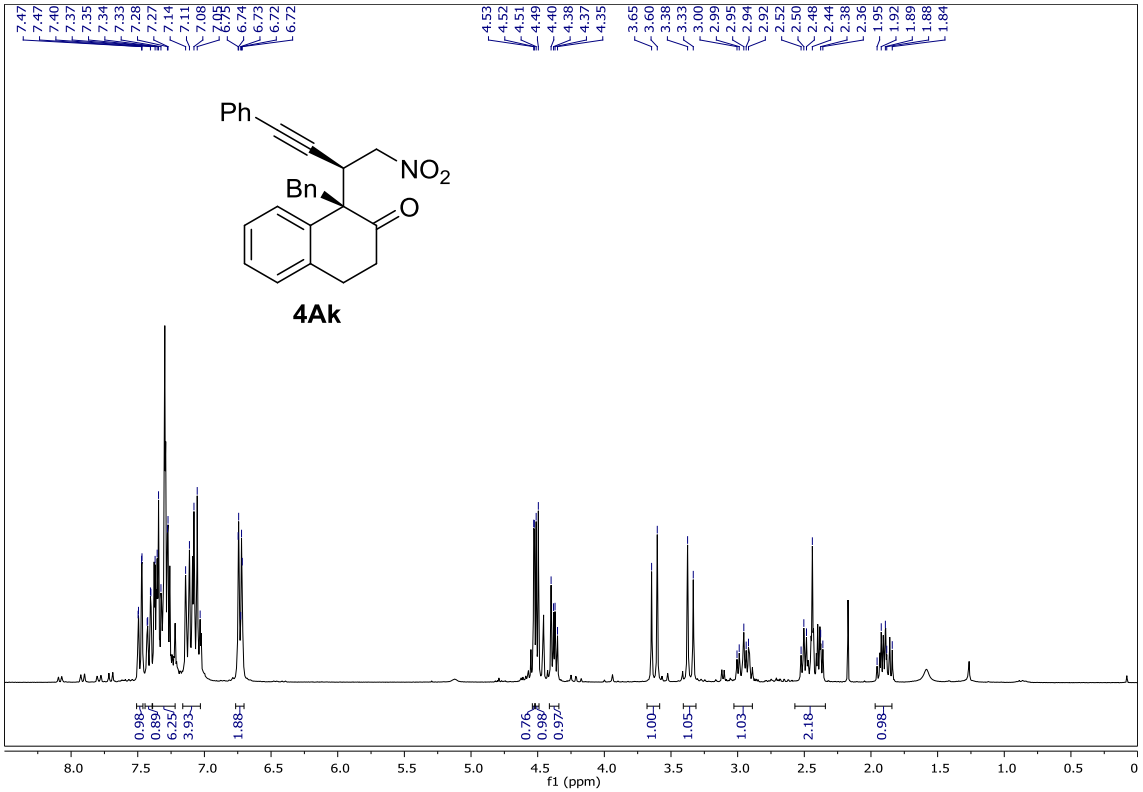
149.68 142.26 138.61 135.63 135.60 130.26 130.08 128.64 127.95 127.53 127.41 126.66 110.55 109.70
74.78
59.29
46.40 43.45 40.54
26.67
f1 (ppm)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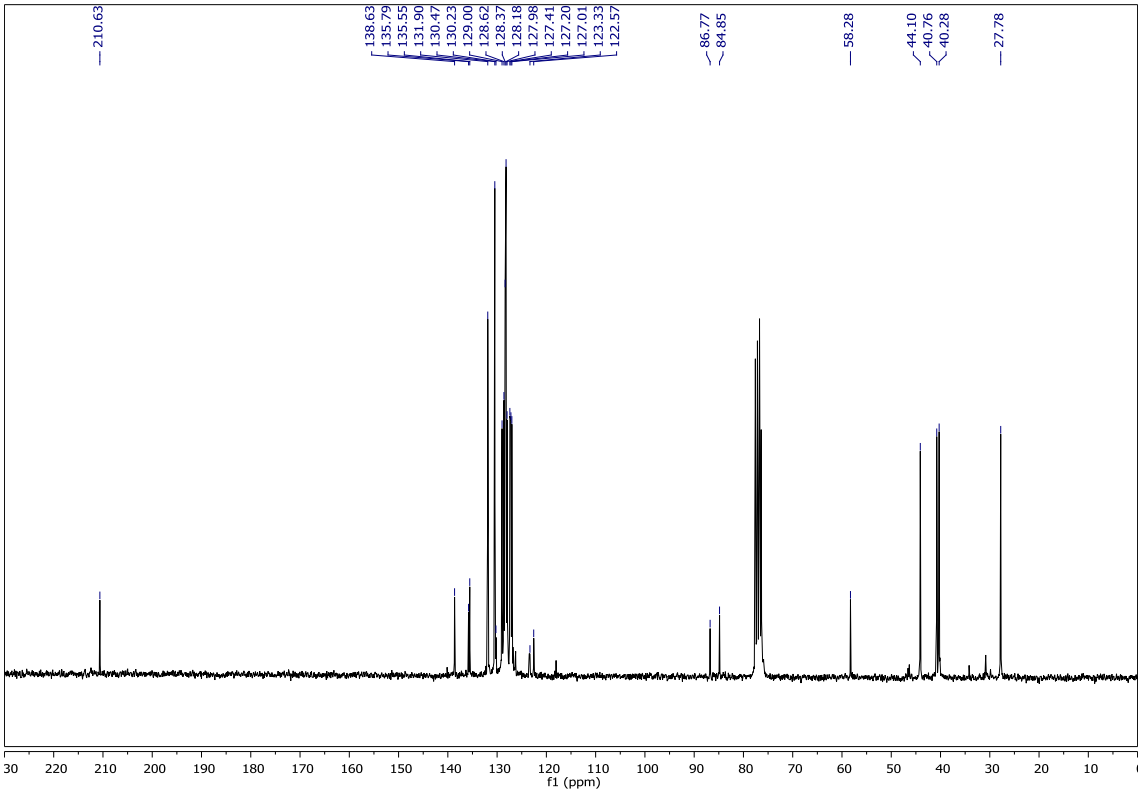
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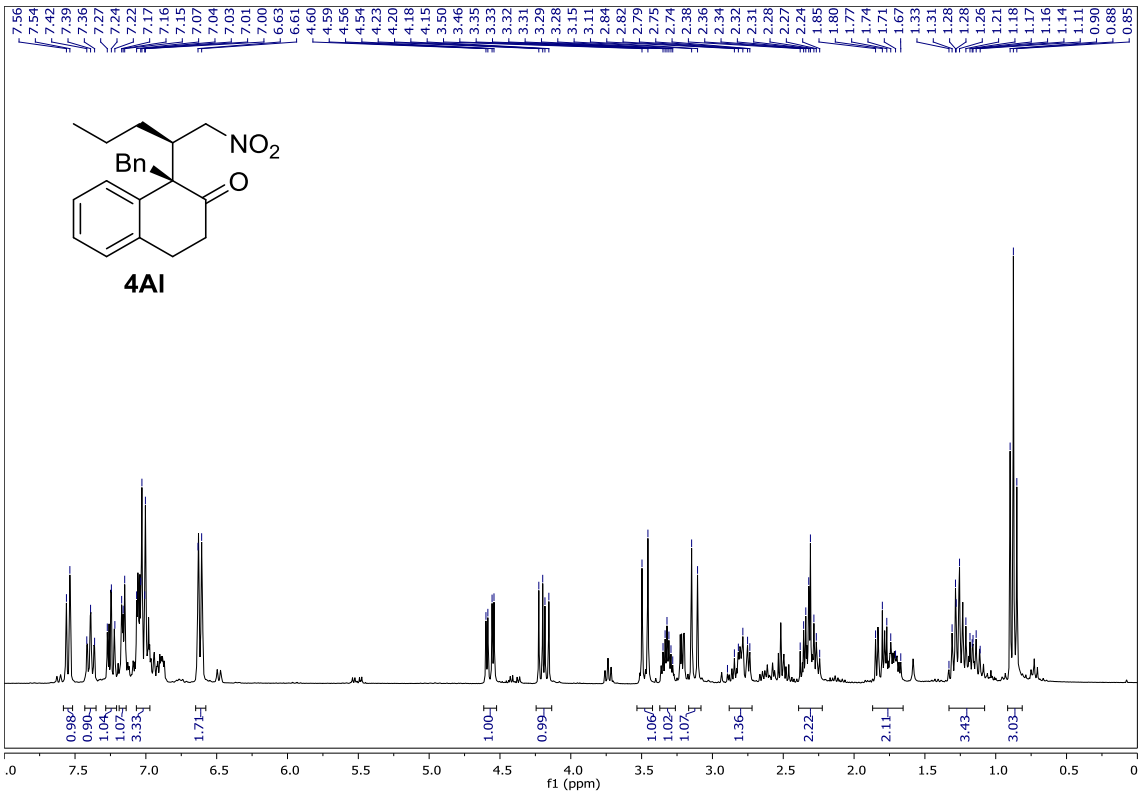
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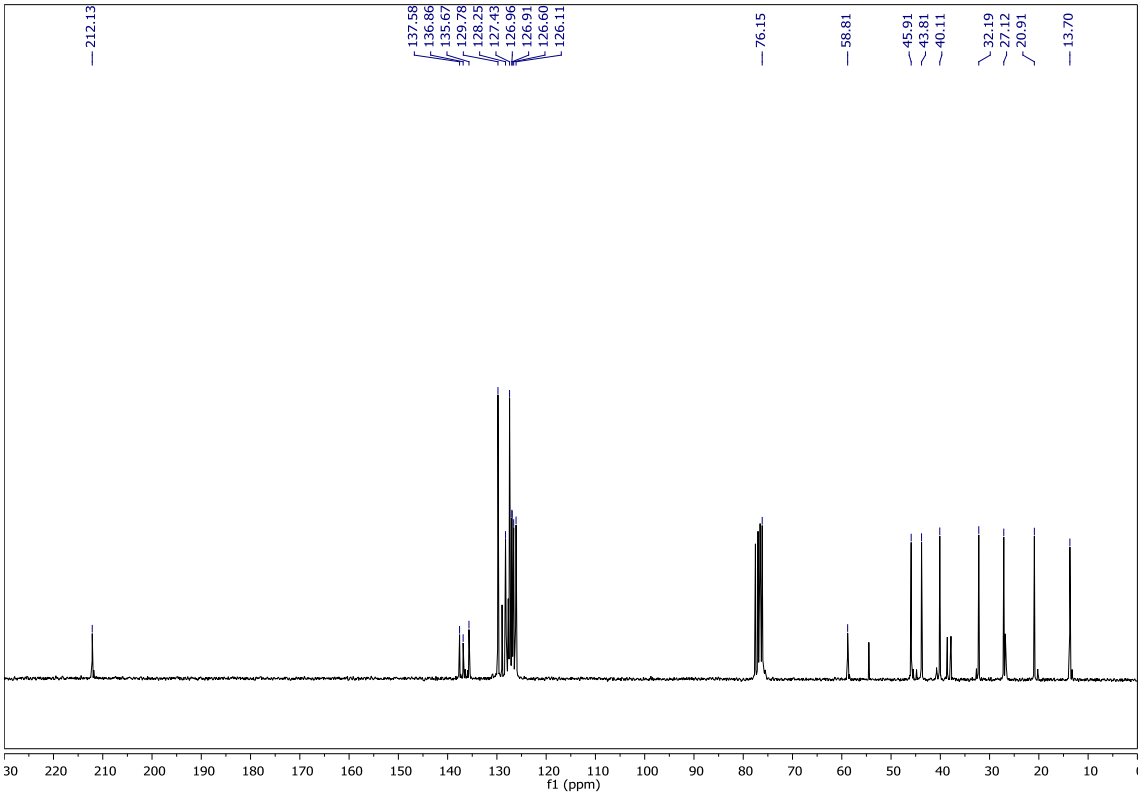
NO2
Bn
O
4AI
0.98 0.90 1.04 1.07 3.33 1.71 1.00 0.99 1.06 1.02 1.07 1.36 2.22 2.11 3.43 3.03
f1 (ppm)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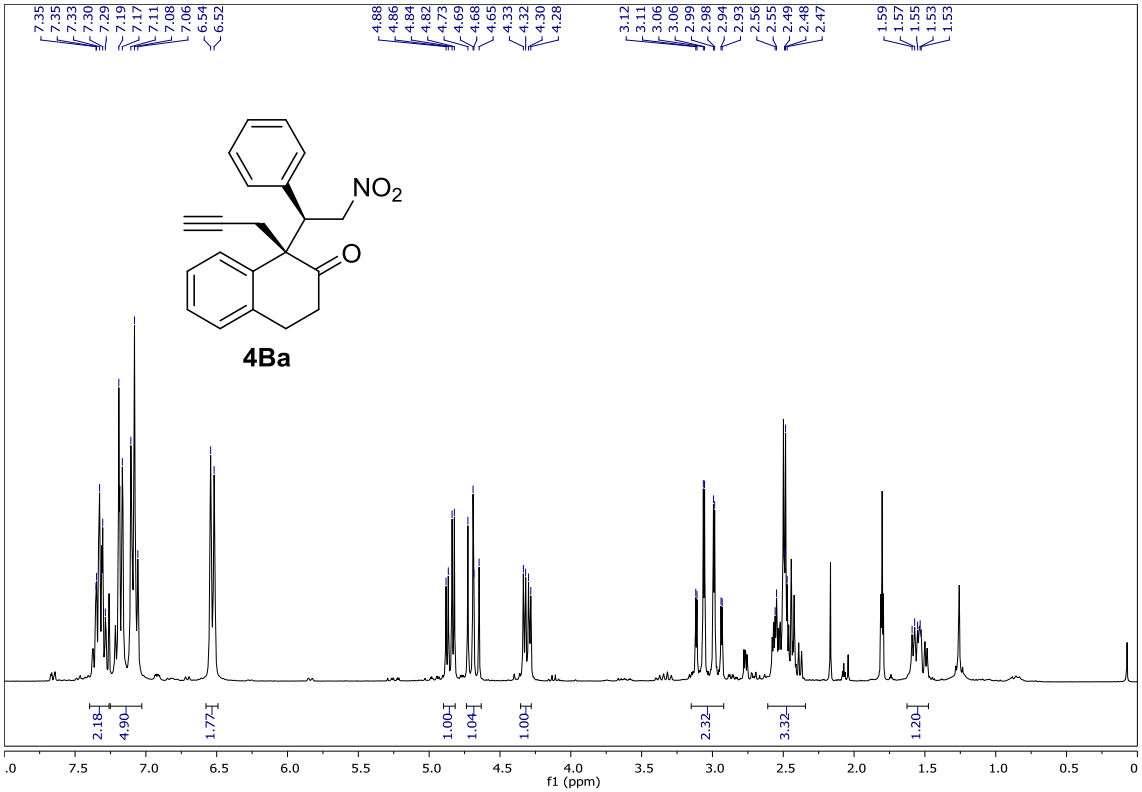
137.58 136.86 135.67 129.78 128.25 127.43 126.96 126.91 126.60 126.11
76.15
58.81
45.91 43.81 40.11
32.19 27.12 20.91
13.70
f1 (ppm)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7.11
7.08
7.06
6.54
6.52
4.88
4.86
4.84
4.82
4.73
4.69
4.68
4.65
4.33
4.32
4.30
4.28
3.12
3.11
3.06
3.06
2.99
2.98
2.94
2.93
2.56
2.55
2.49
2.48
2.47
1.59
1.57
1.55
1.53
1.53
NO2
O
4Ba
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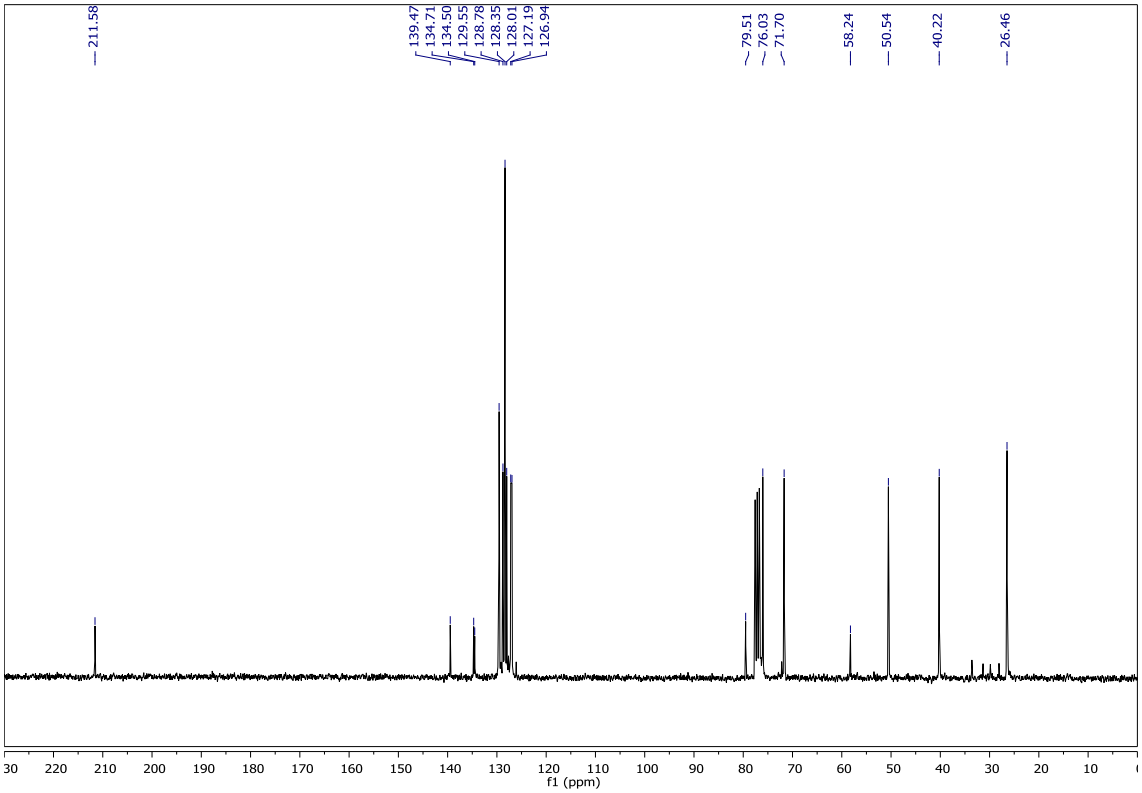
4.90
1.77
1.00
1.04
1.00
2.32
3.32
1.20
f1 (ppm)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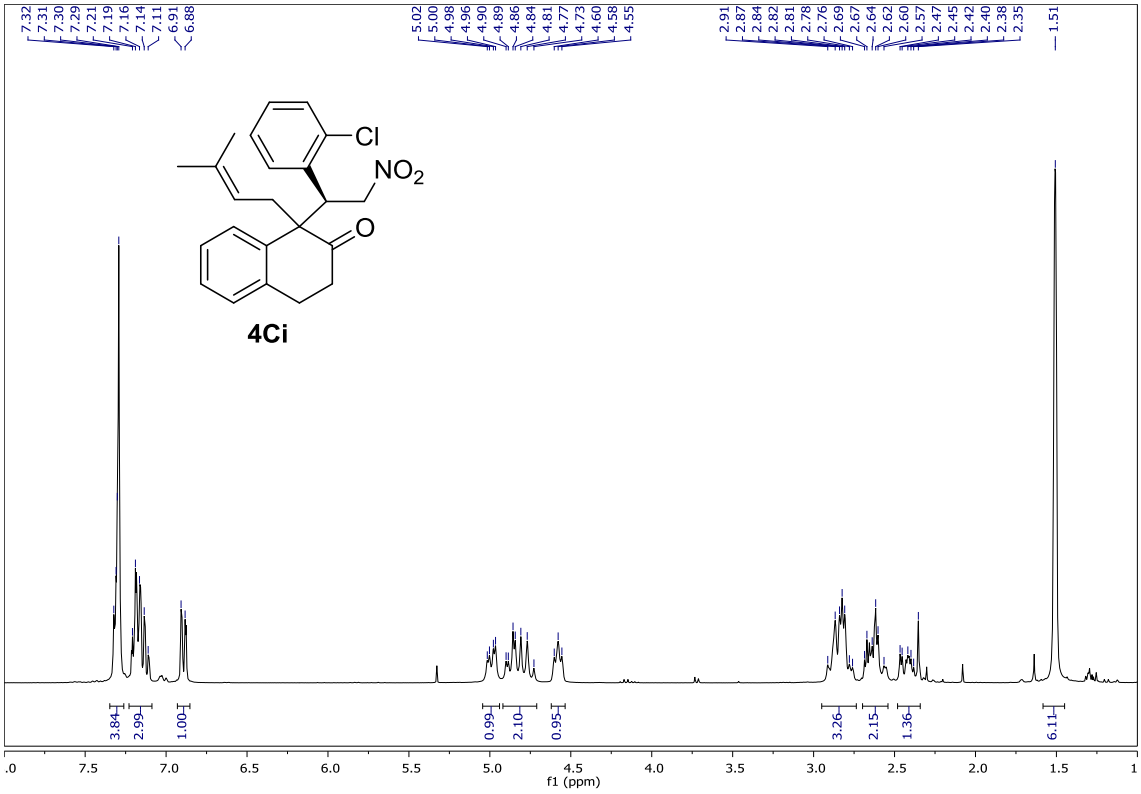
71.70
58.24
50.54
40.22
26.46
f1 (ppm)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7.19
7.16
7.14
7.11
6.91
6.88
5.02
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4.96
4.90
4.89
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4.55
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2.84
2.82
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2.64
2.62
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2.47
2.45
2.42
2.40
2.38
2.35
1.51
Cl
NO2
O
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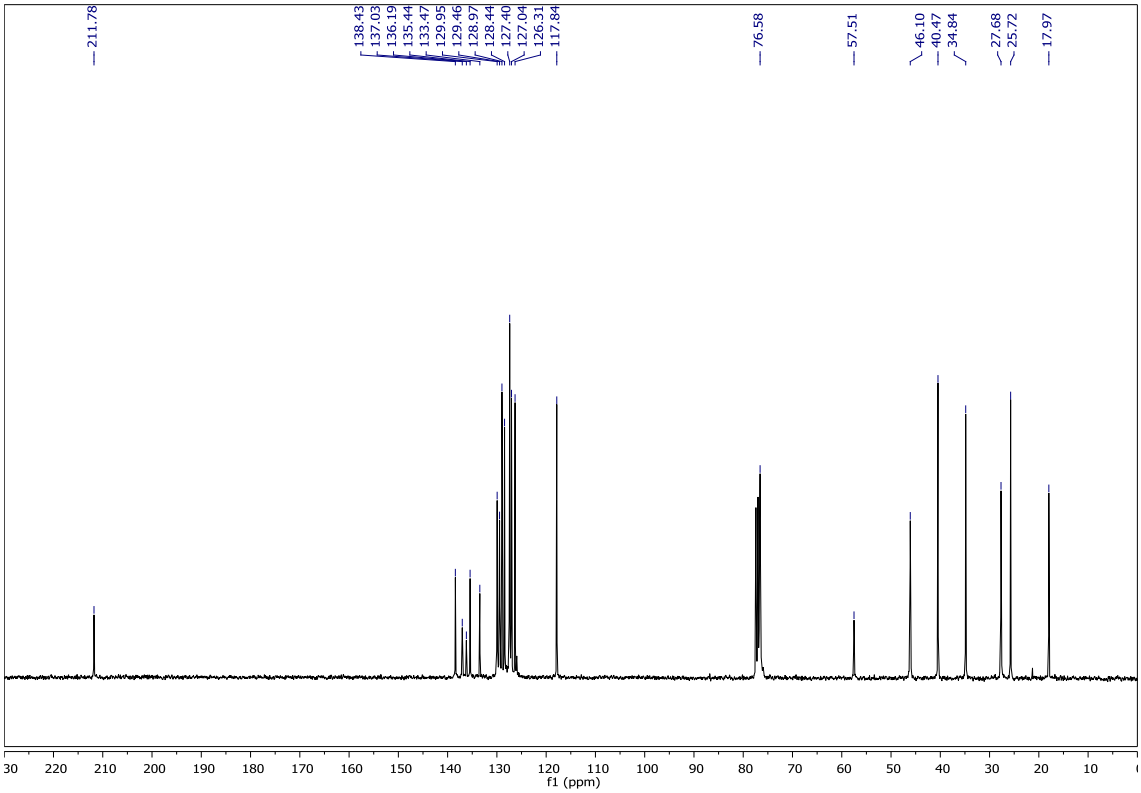
1.00
0.99
2.10
0.95
3.26
2.15
1.36
6.11
f1 (ppm)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128.44
127.40
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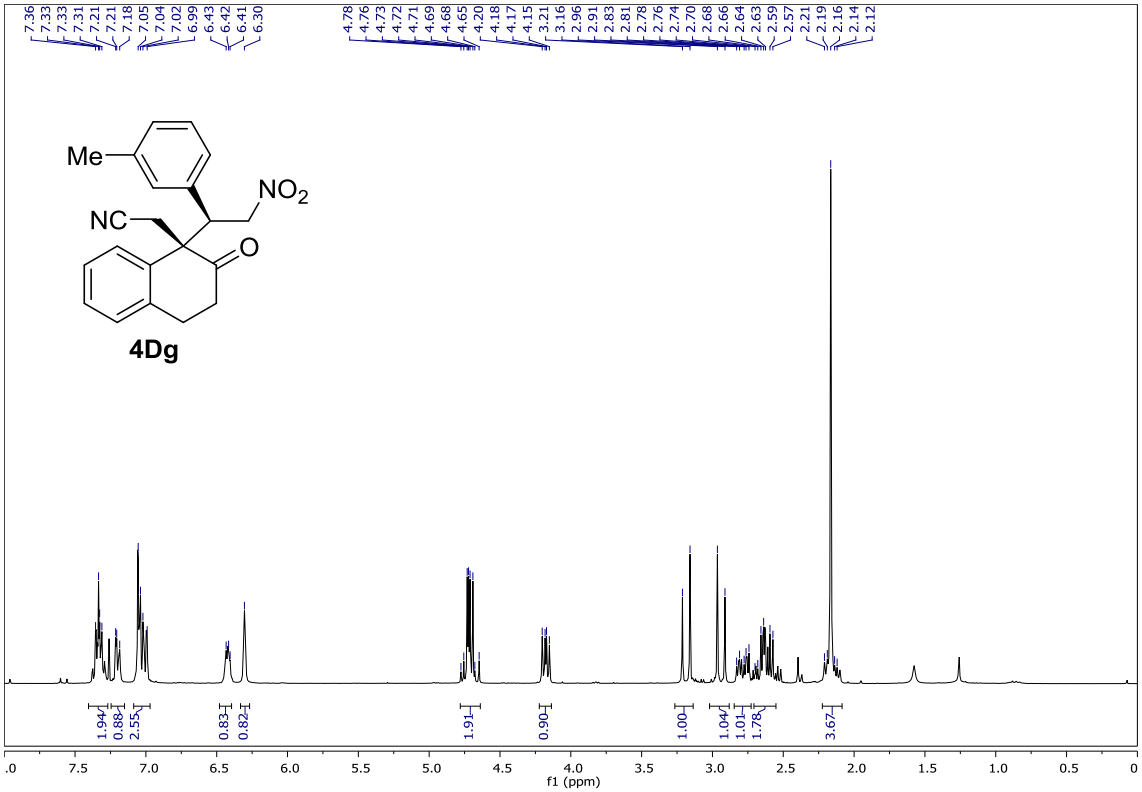
46.10
40.47
34.84
27.68
25.72
17.97
f1 (ppm)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NC
O
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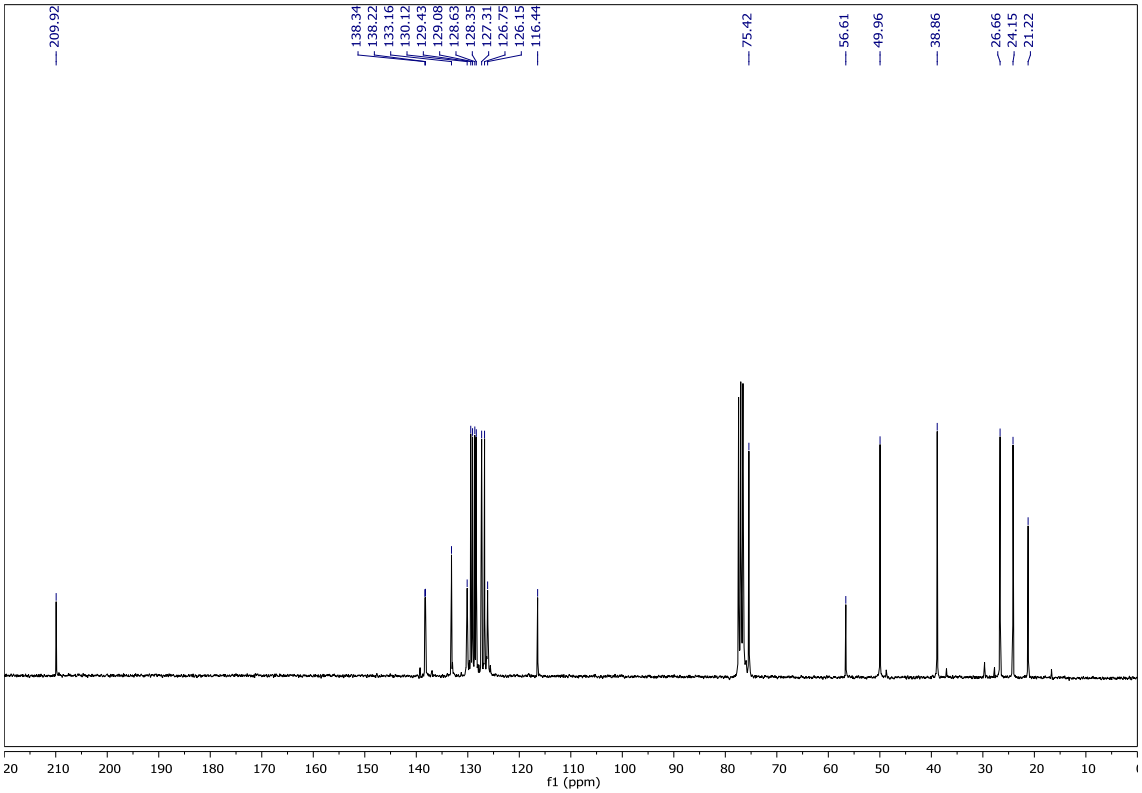
f1 (ppm)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129.43
129.08
128.63
128.35
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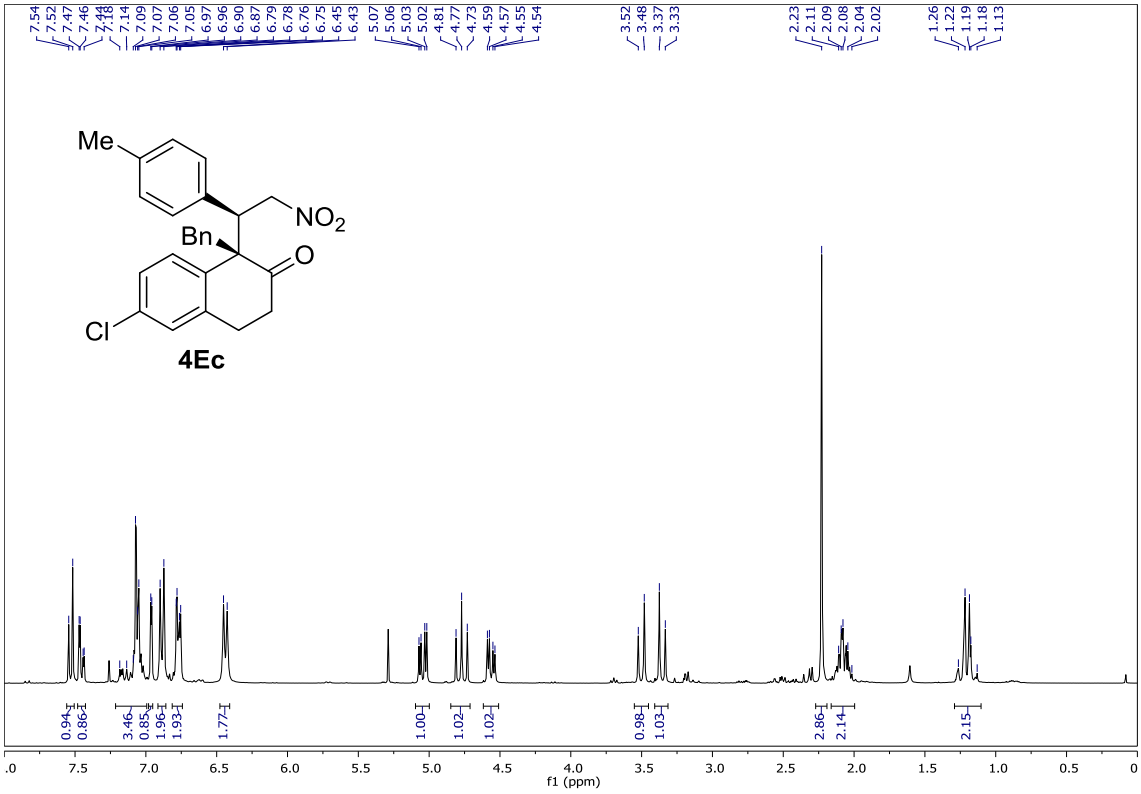
38.86
26.66
24.15
21.22
f1 (ppm)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O
Cl
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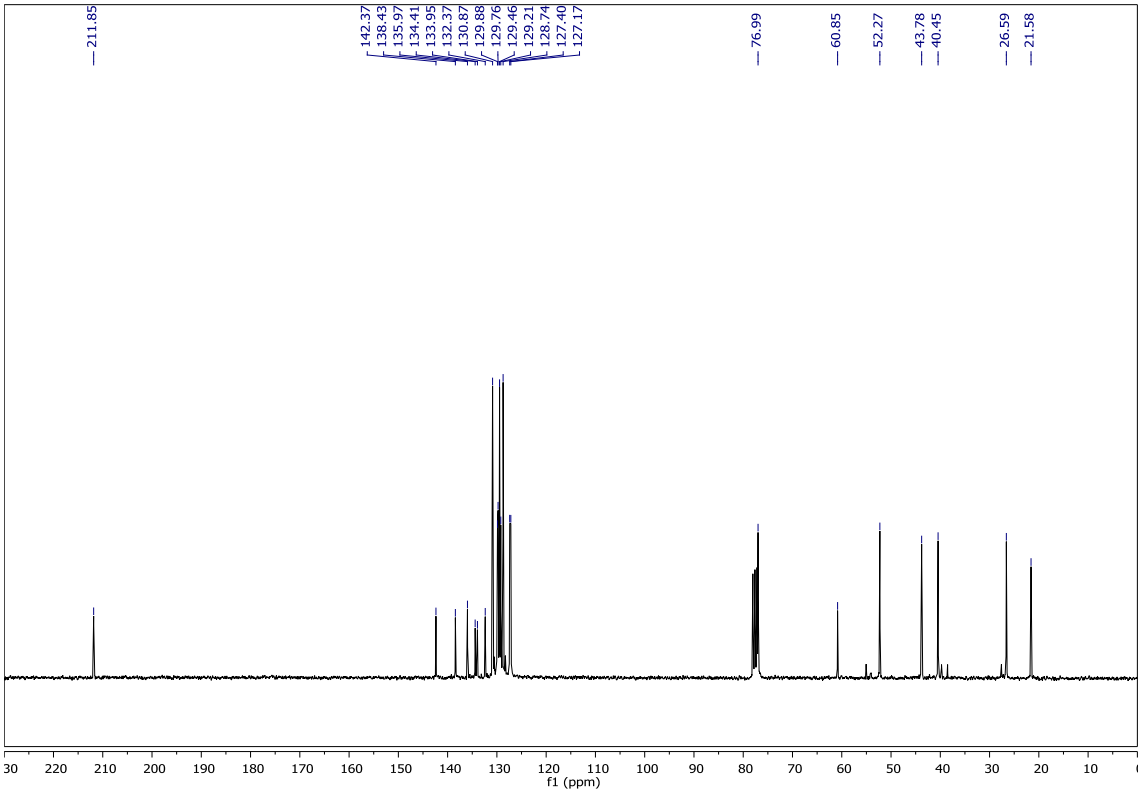
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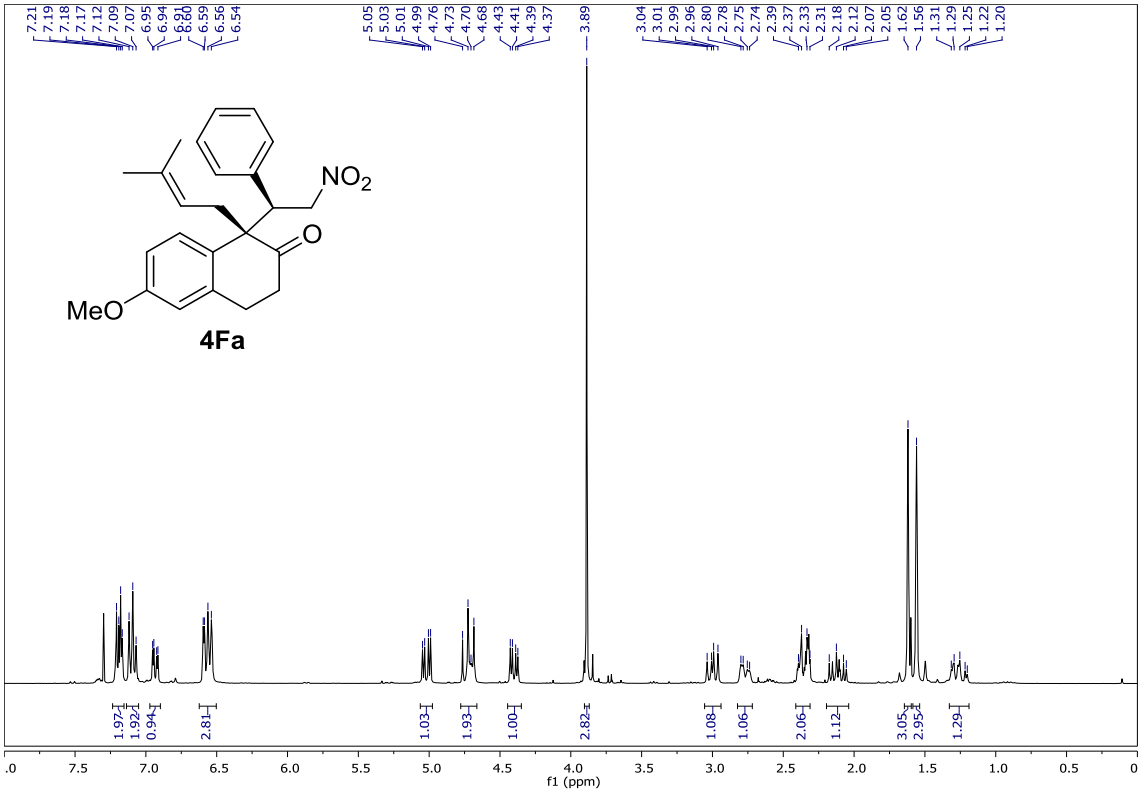
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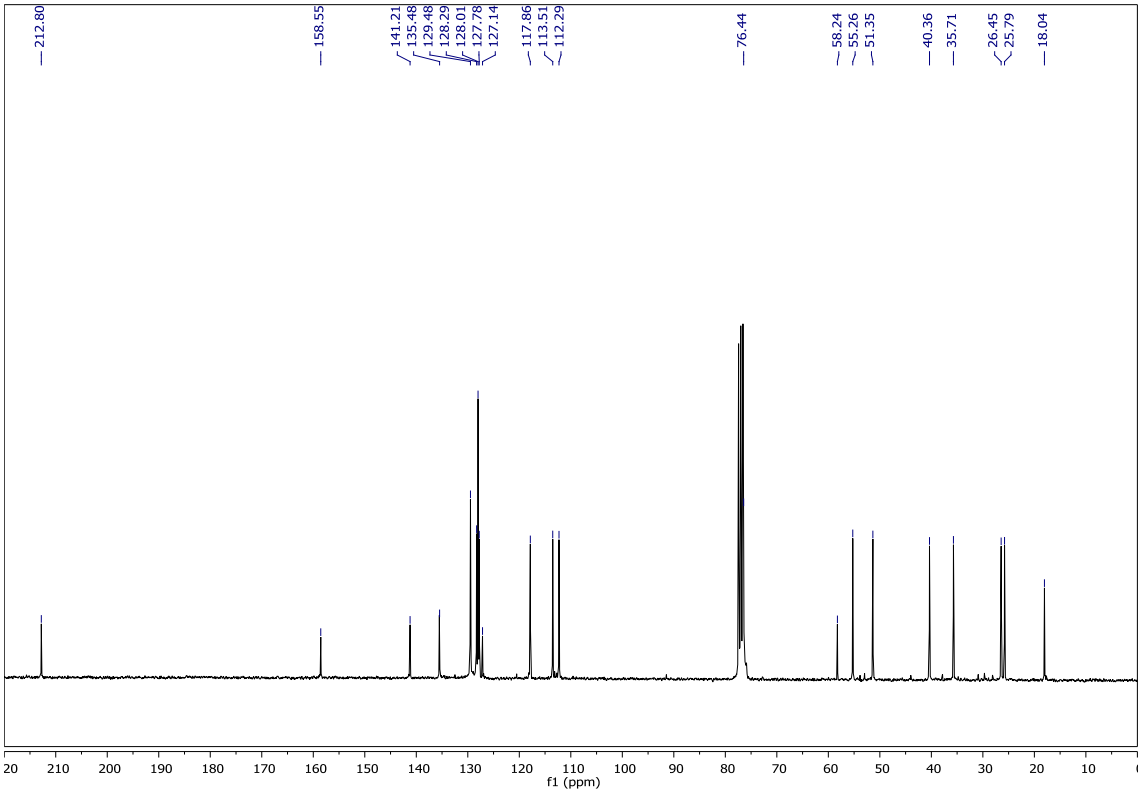
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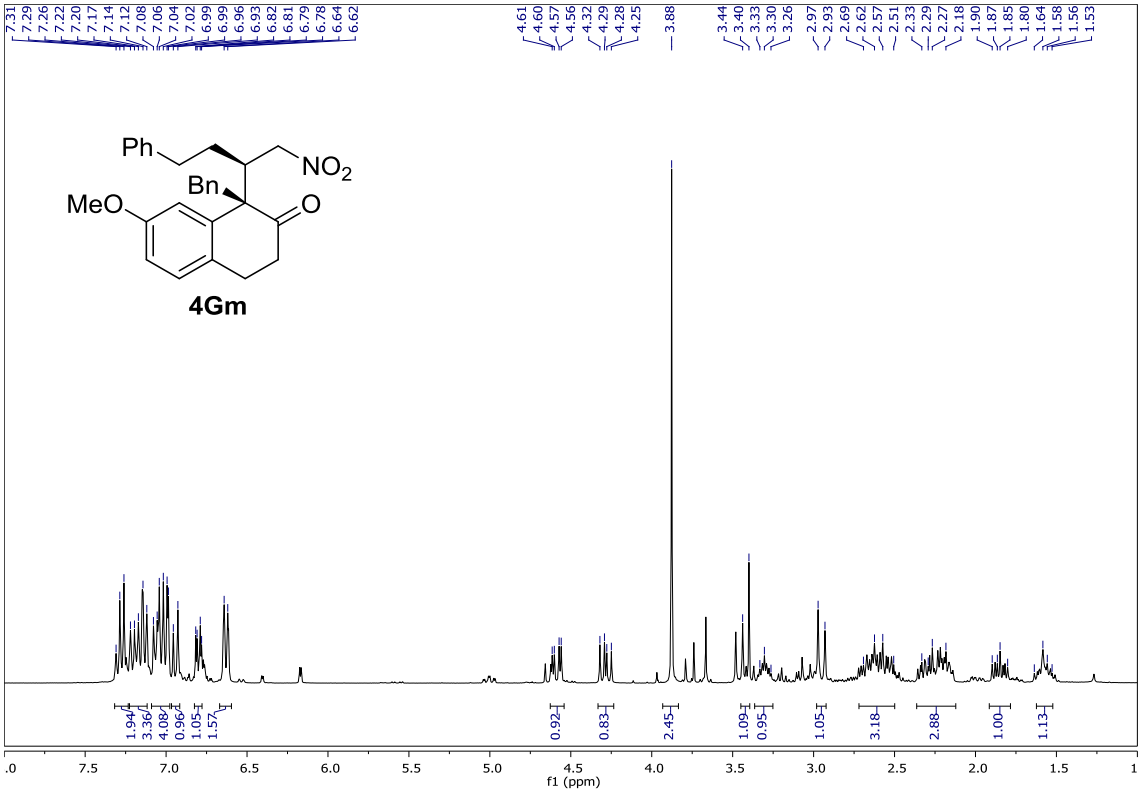
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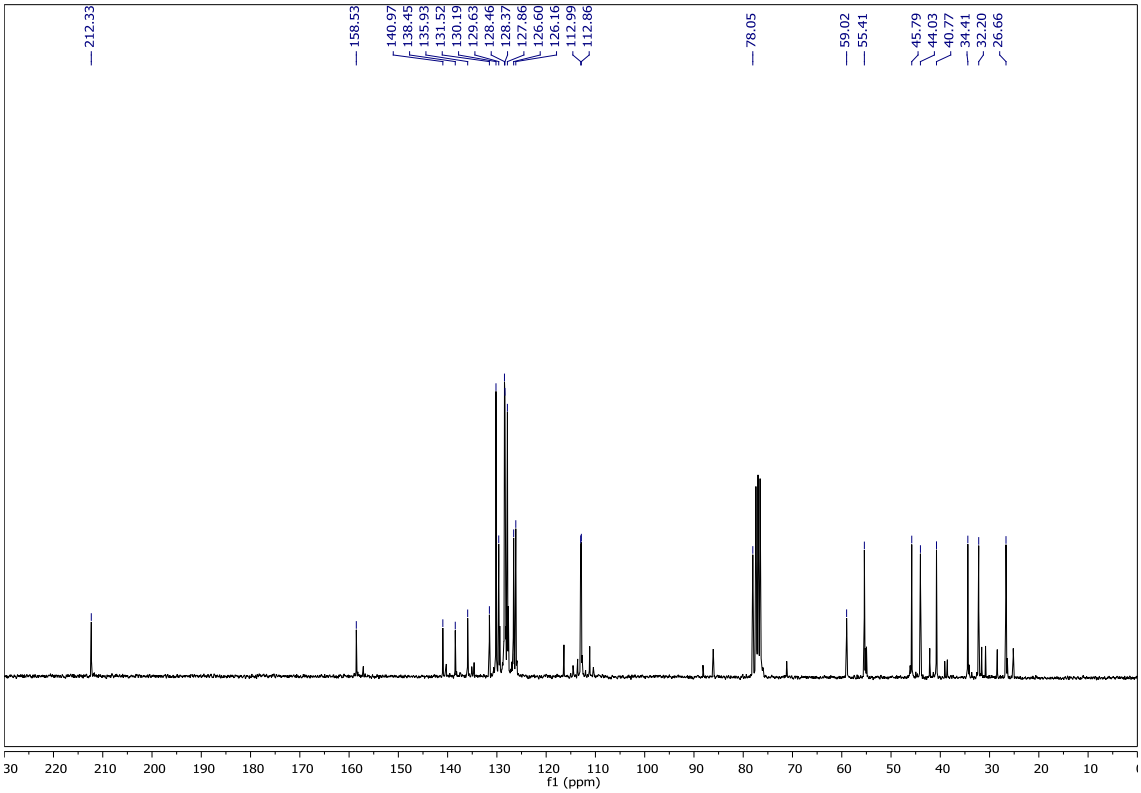
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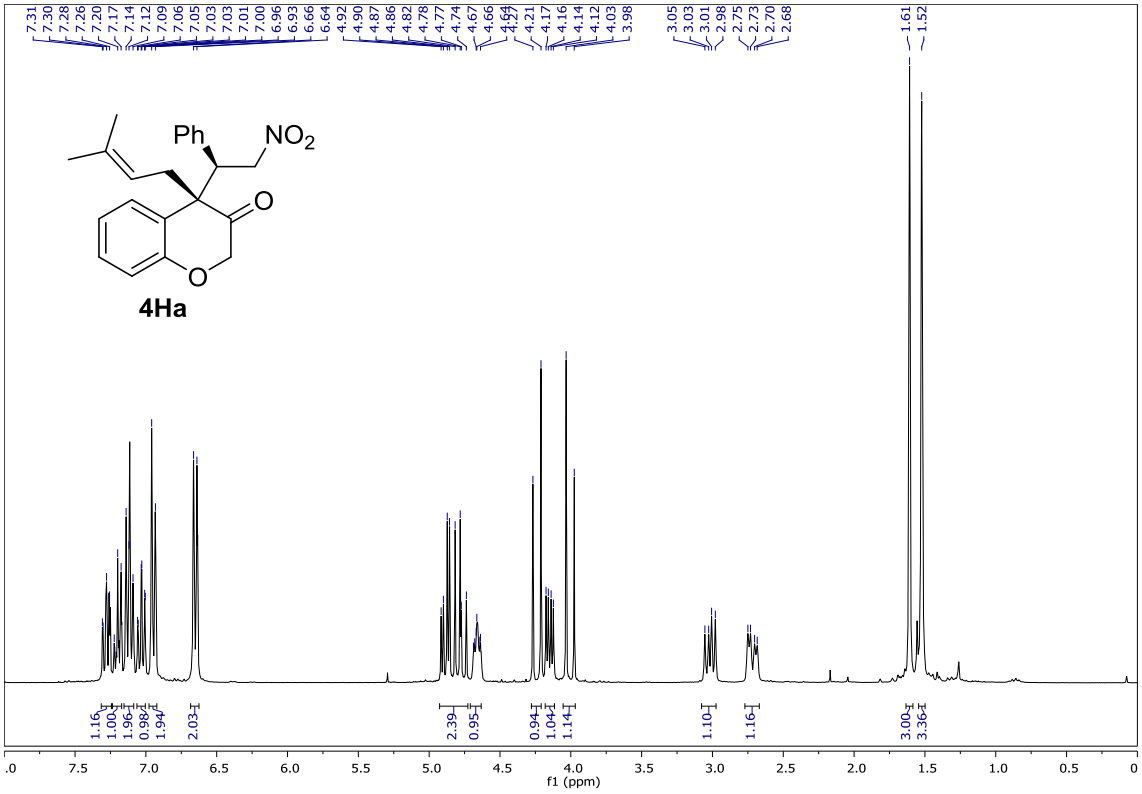
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O
O
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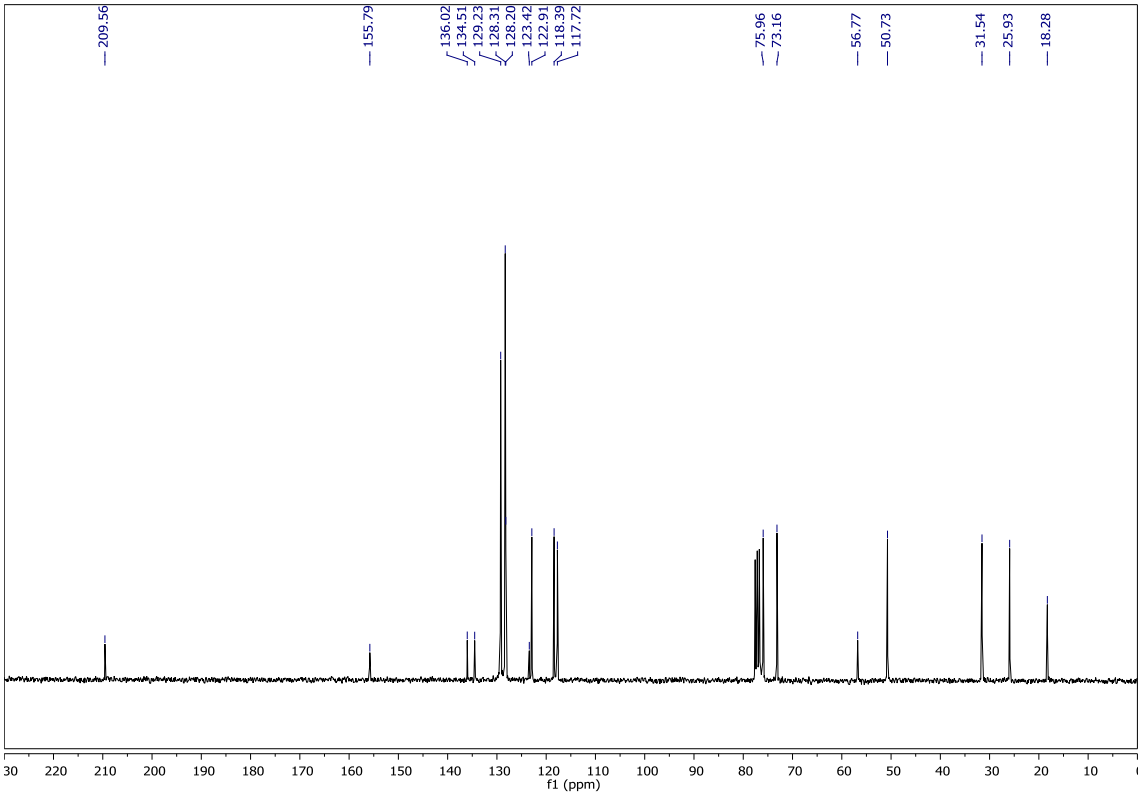
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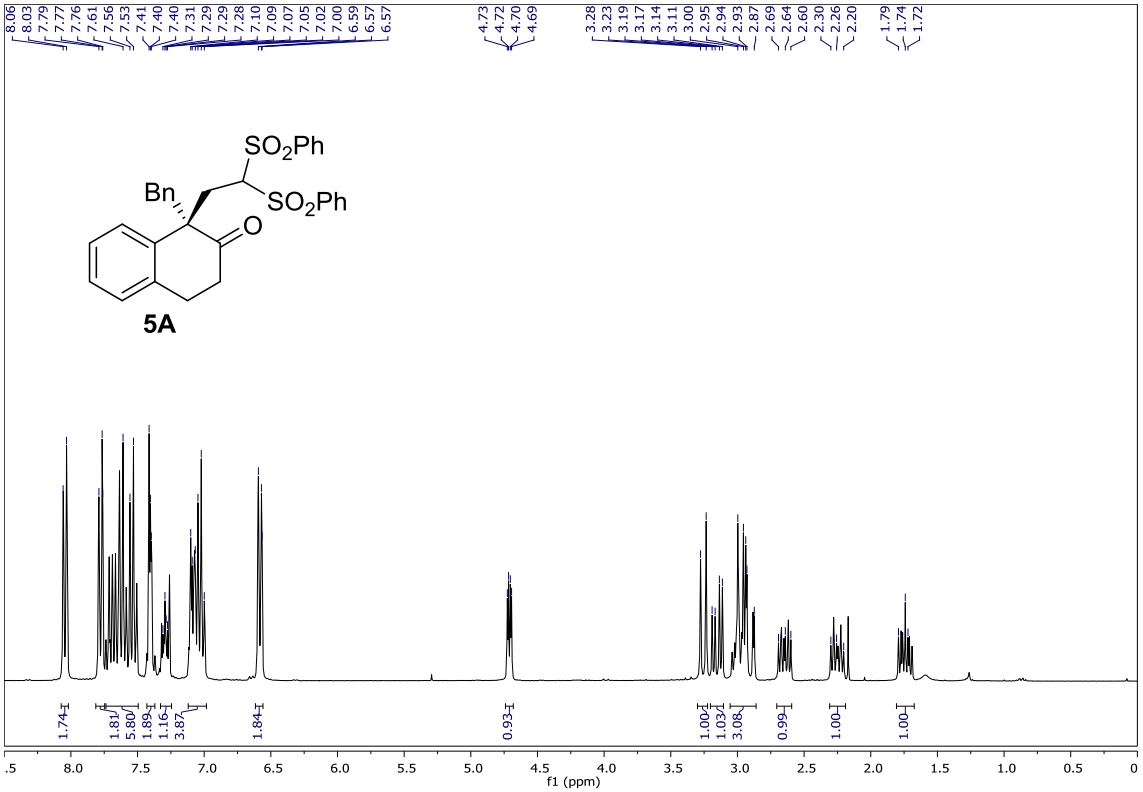
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7.29
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7.10
7.09
7.07
7.05
7.02
7.00
6.59
6.57
6.57
4.73
4.72
4.70
4.69
3.28
3.23
3.19
3.17
3.14
3.11
3.00
2.95
2.94
2.93
2.87
2.69
2.64
2.60
2.30
2.26
2.20
1.79
1.74
1.72
SO2Ph
Bn
SO2Ph
O
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1.81
5.80
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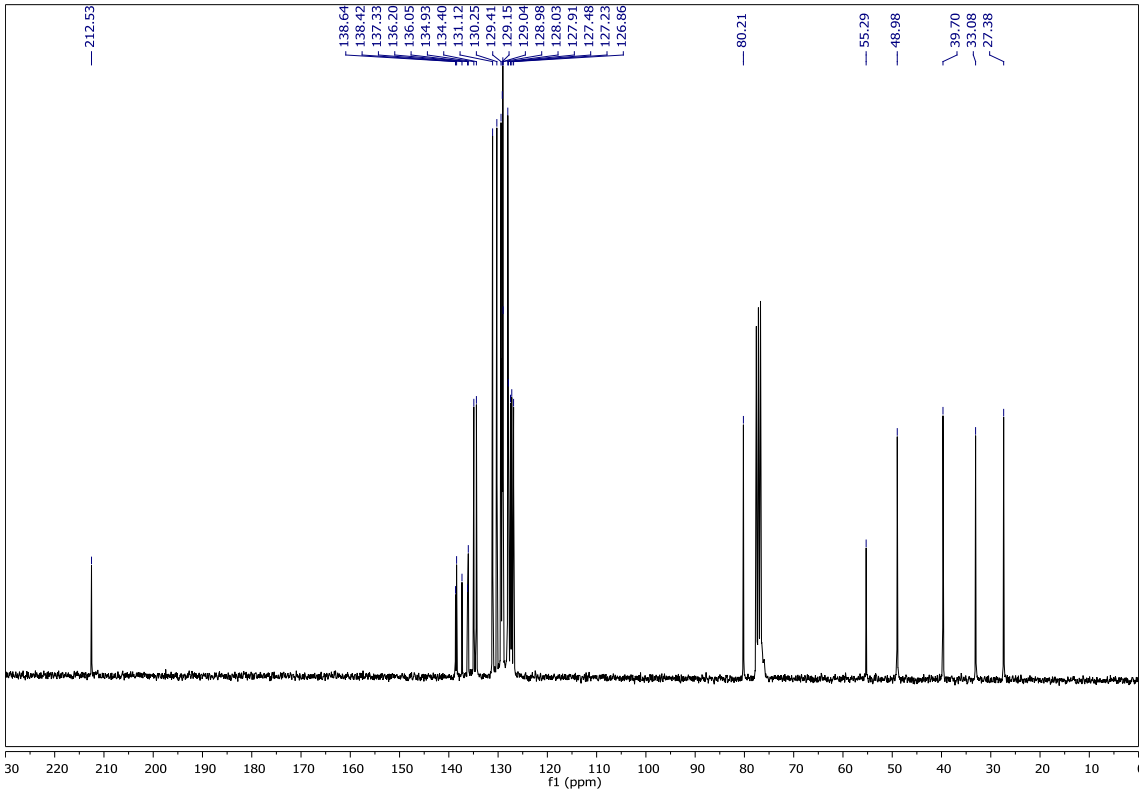
1.00
f1 (ppm)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48.98
39.70
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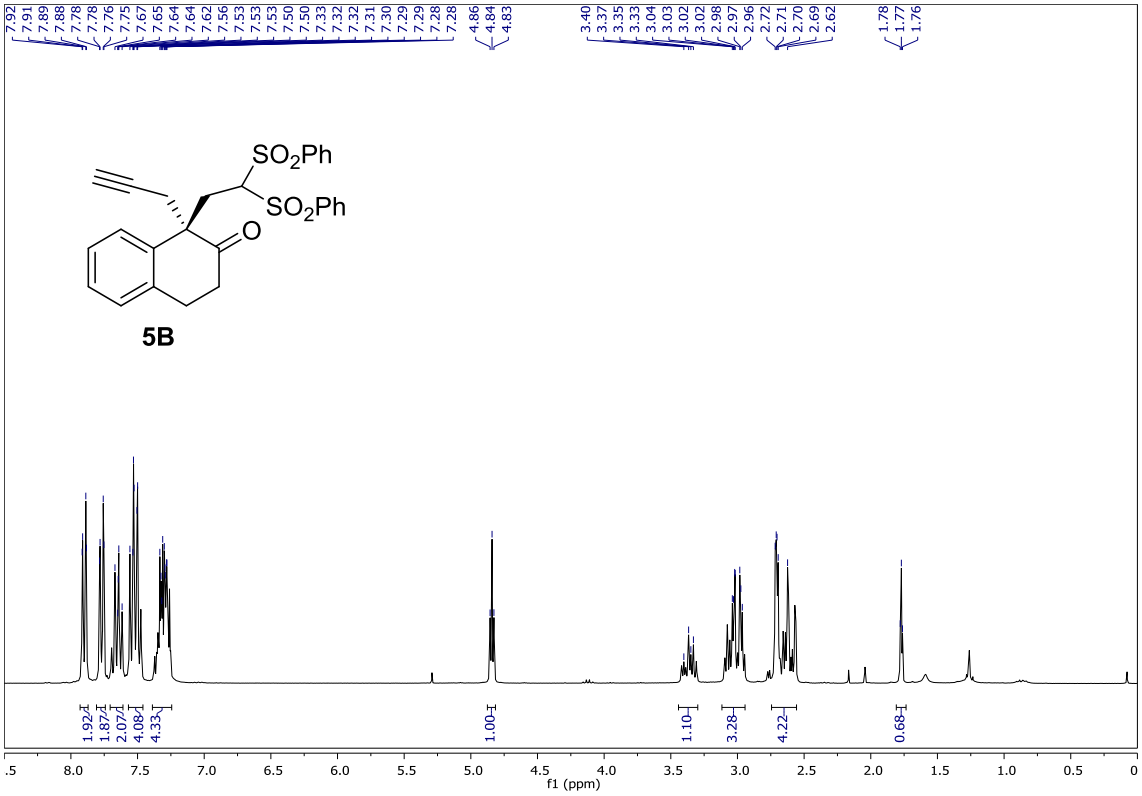
27.38
f1 (ppm)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2.97
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2.70
2.69
2.62
1.78
1.77
1.76
SO2Ph
SO2Ph
O
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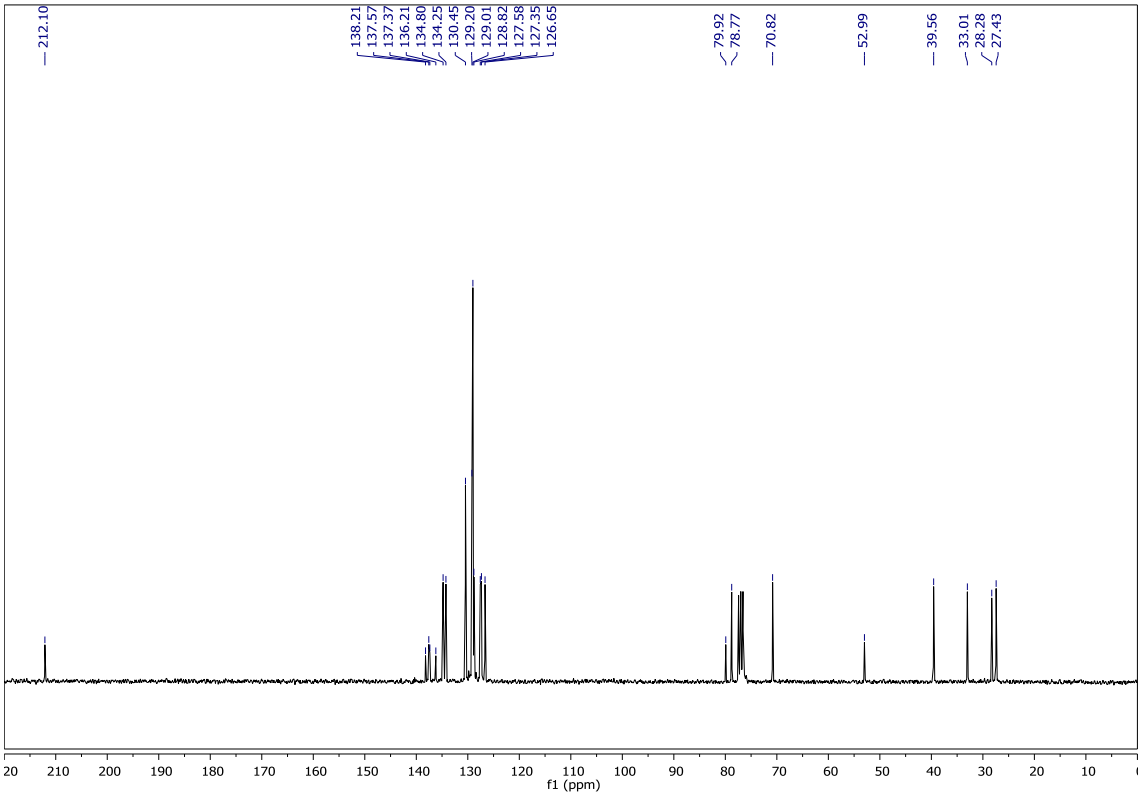
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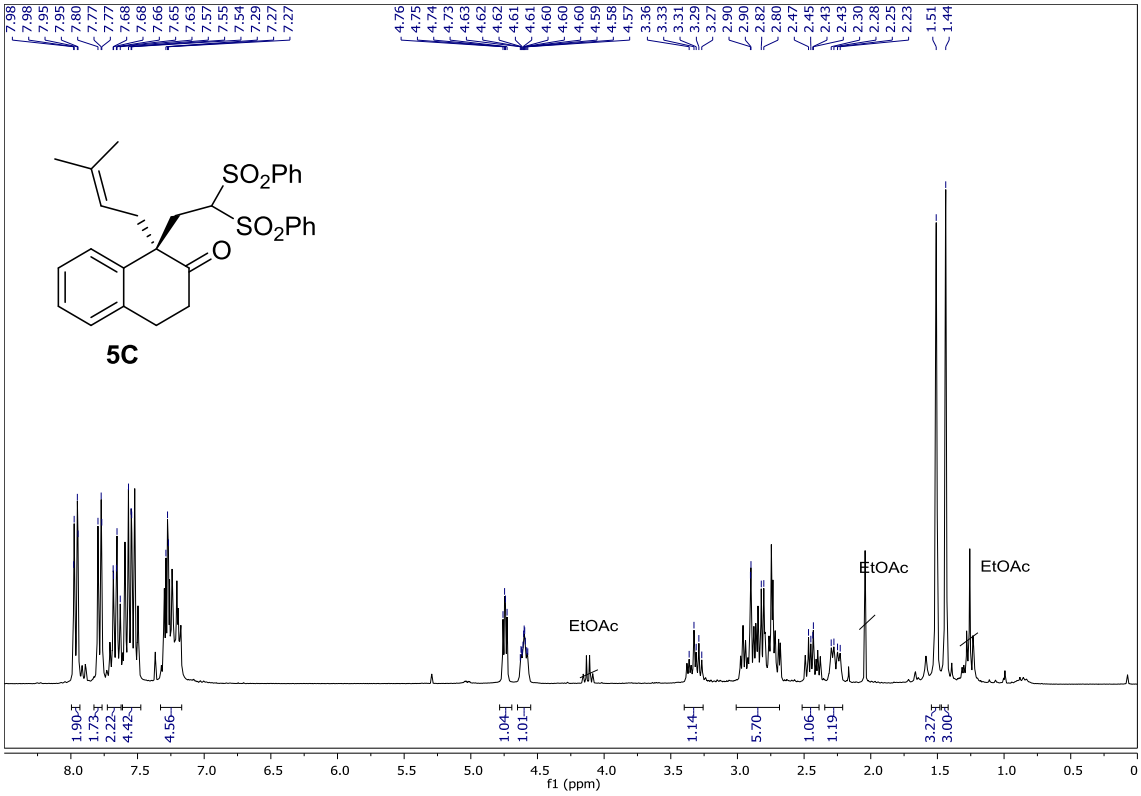
33.01
28.28
27.43
f1 (ppm)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SO2Ph
O
5C
EtOAc
EtOAc
EtOAc
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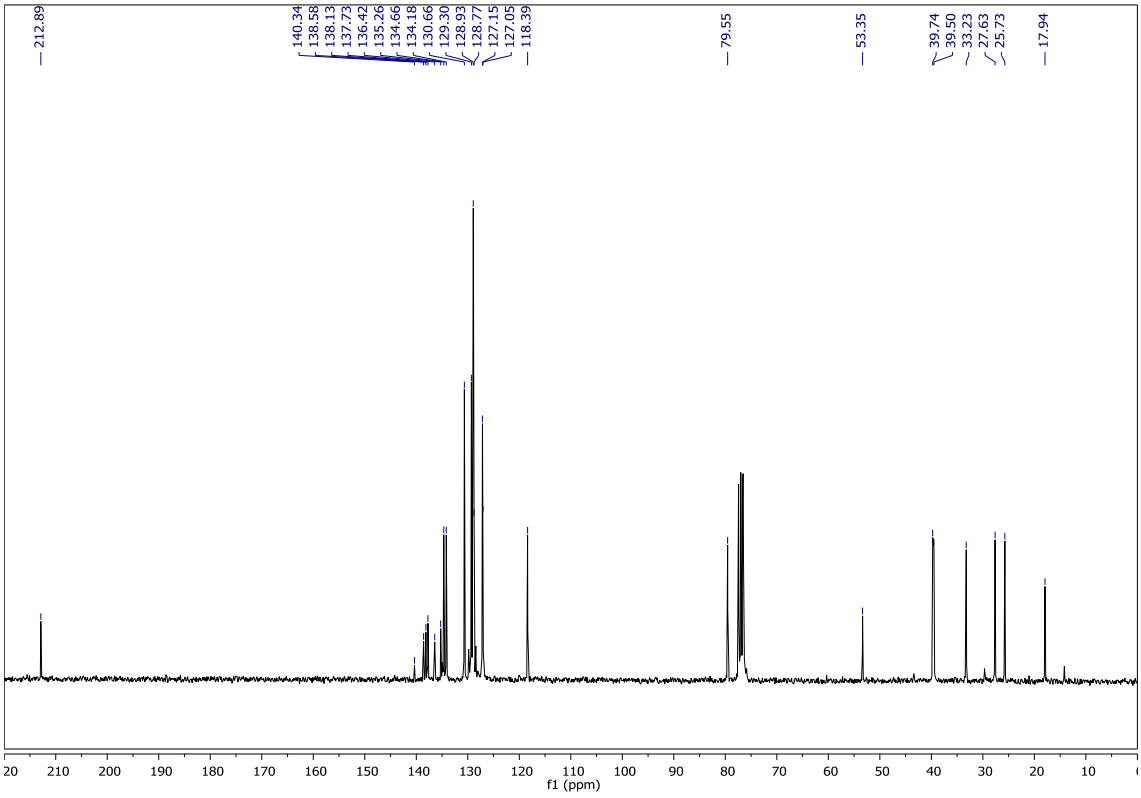
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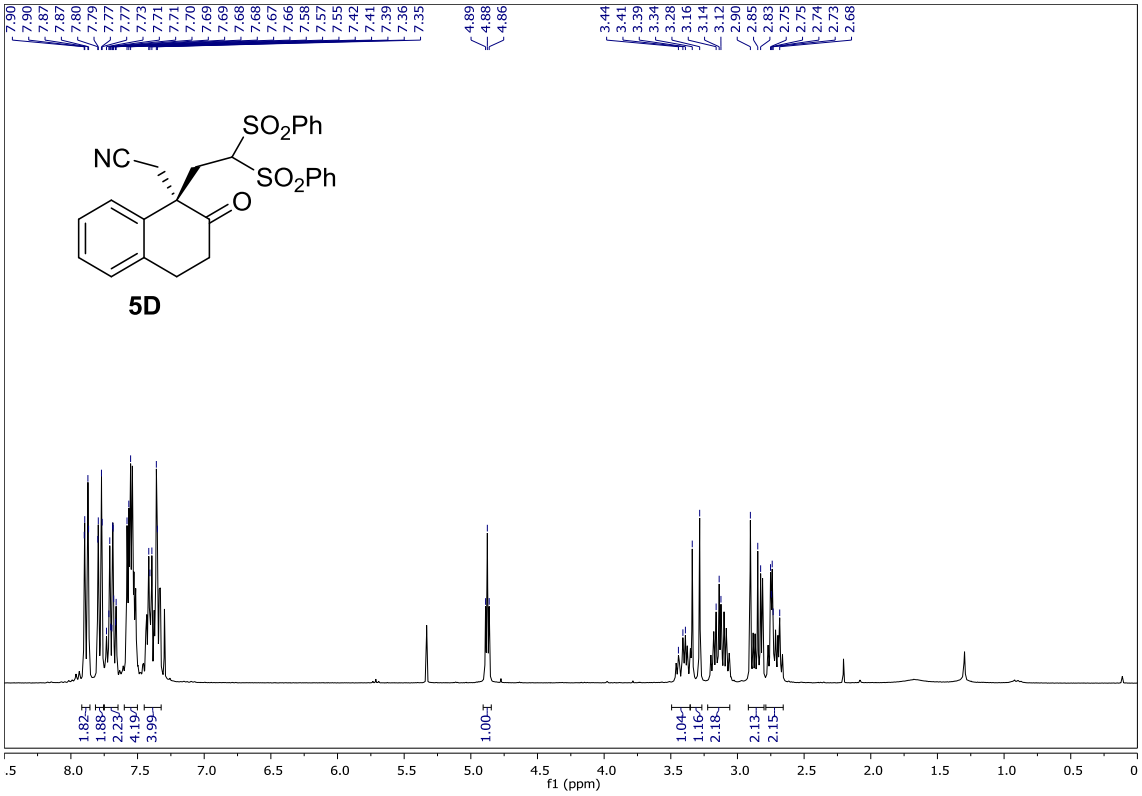
33.23
27.63
25.73
17.94
f1 (ppm)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SO2Ph
O
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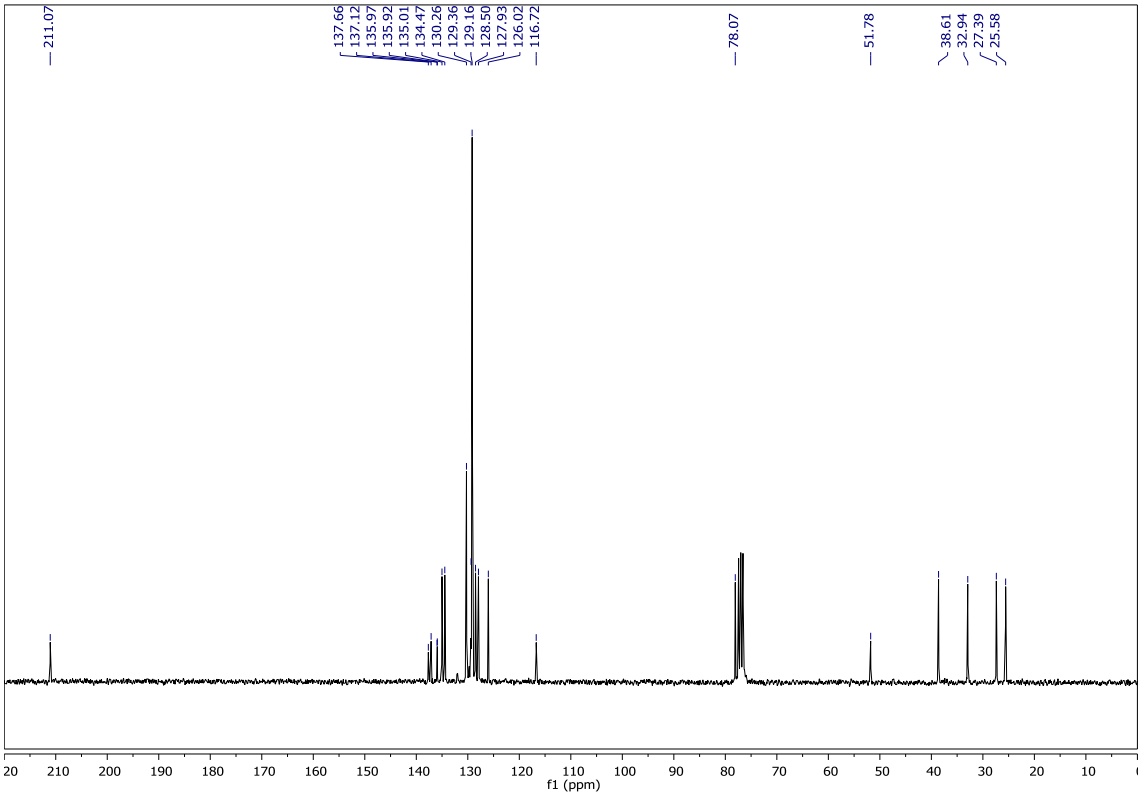
f1 (ppm)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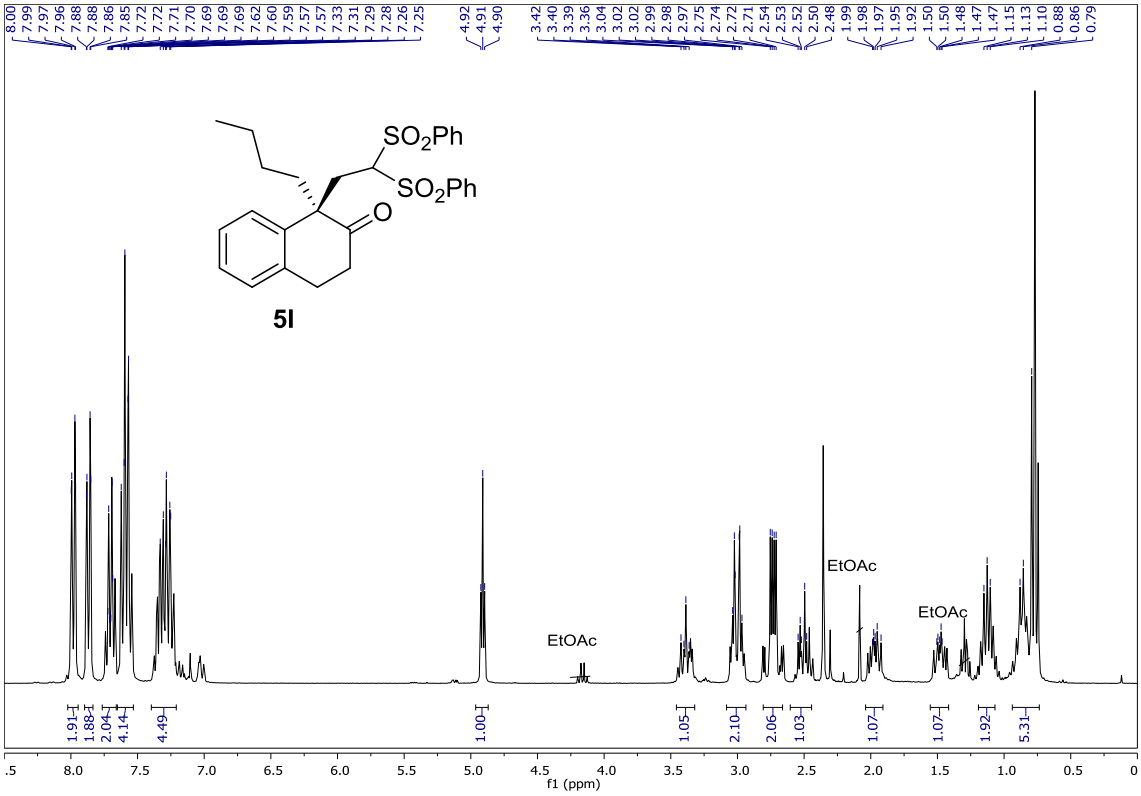
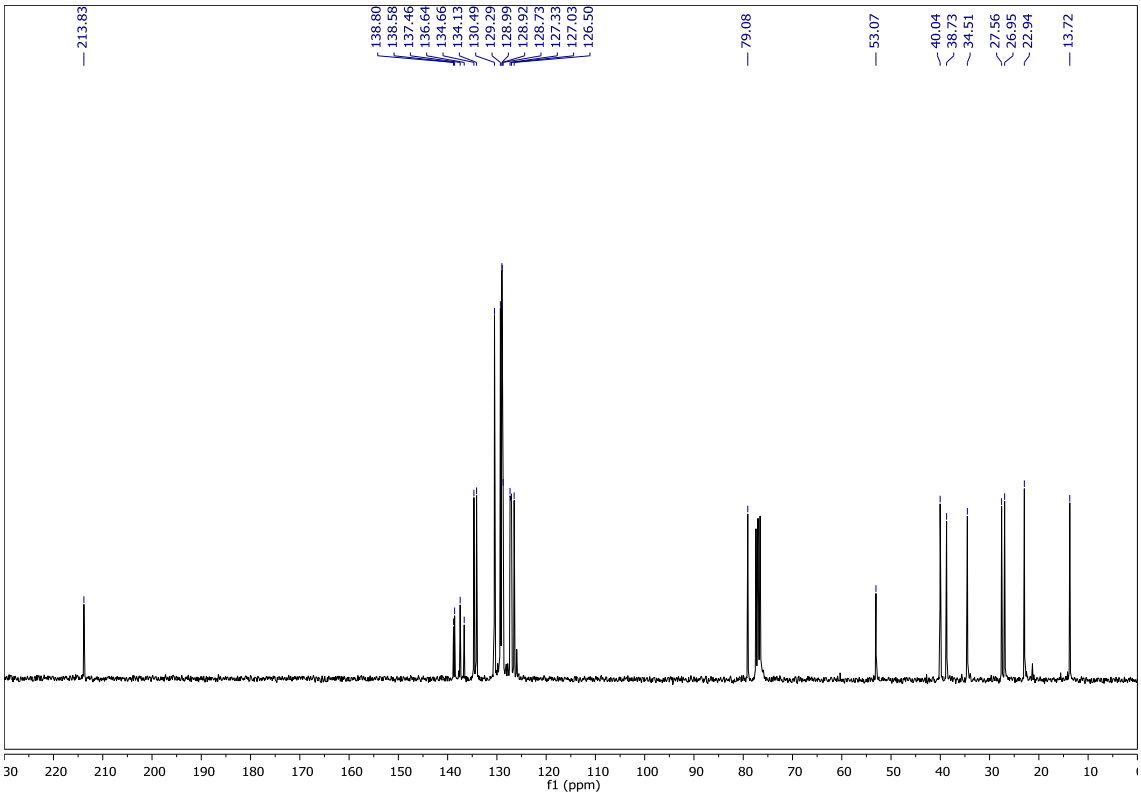
51.78
38.61
32.94
27.39
25.58
f1 (ppm)


SO2Ph
SO2Ph
O
5l
EtOAc
EtOAc
EtOAc
f1 (ppm)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134.13
130.49
129.29
128.99
128.92
128.73
127.33
127.03
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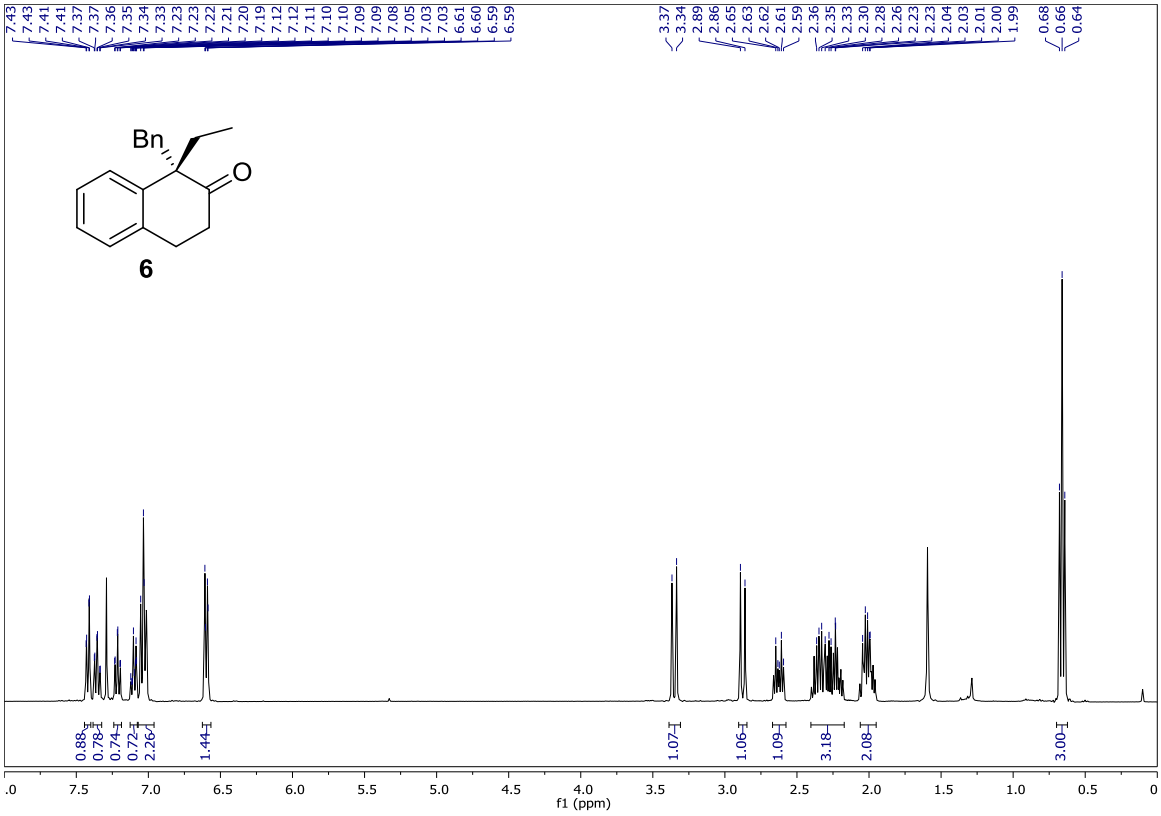
40.04
38.73
34.51
27.56
26.95
22.94
13.72
f1 (ppm)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7.21
7.20
7.19
7.12
7.12
7.11
7.10
7.10
7.09
7.09
7.08
7.05
7.03
7.03
6.61
6.60
6.59
6.59
3.37
3.34
2.89
2.86
2.65
2.63
2.62
2.61
2.59
2.36
2.35
2.33
2.30
2.28
2.26
2.23
2.23
2.04
2.03
2.01
2.00
1.99
0.68
0.66
0.64
Bn
O
6
0.88
0.78
0.74
0.72
2.26
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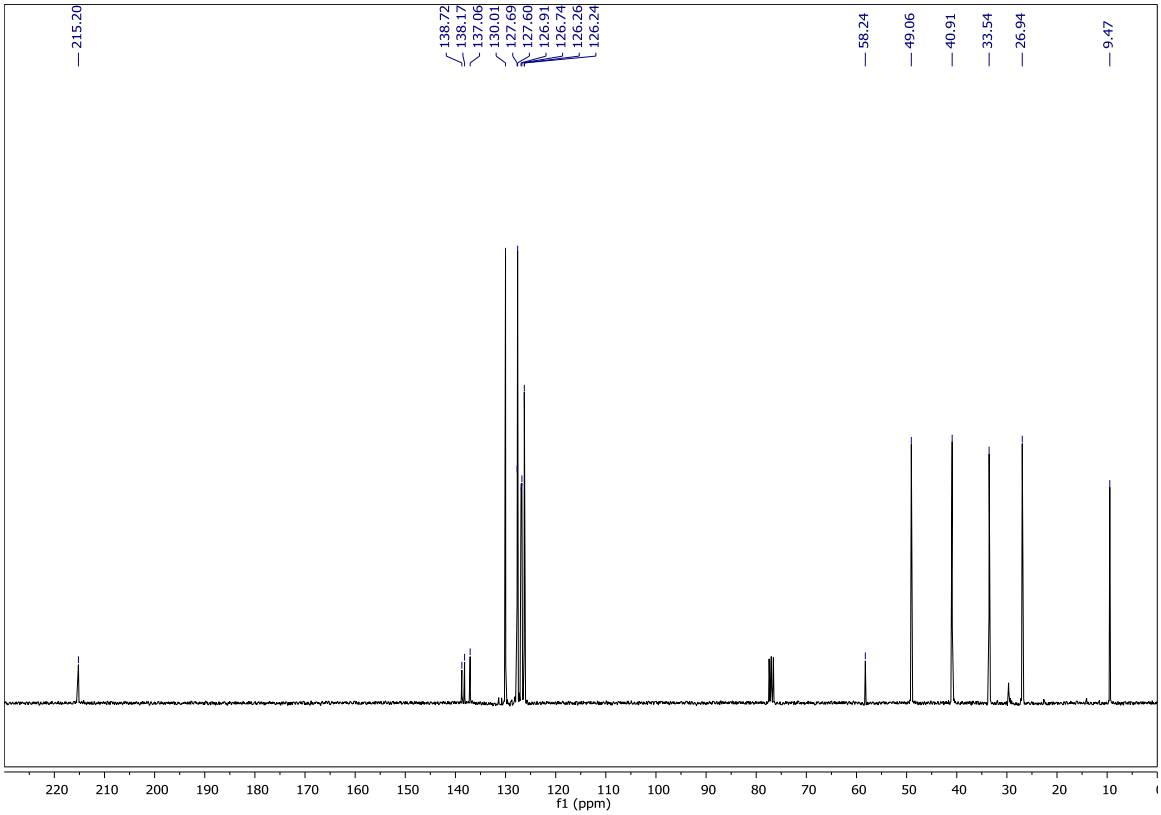
1.07
1.06
1.09
3.18
2.08
3.00
f1 (ppm)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138.72
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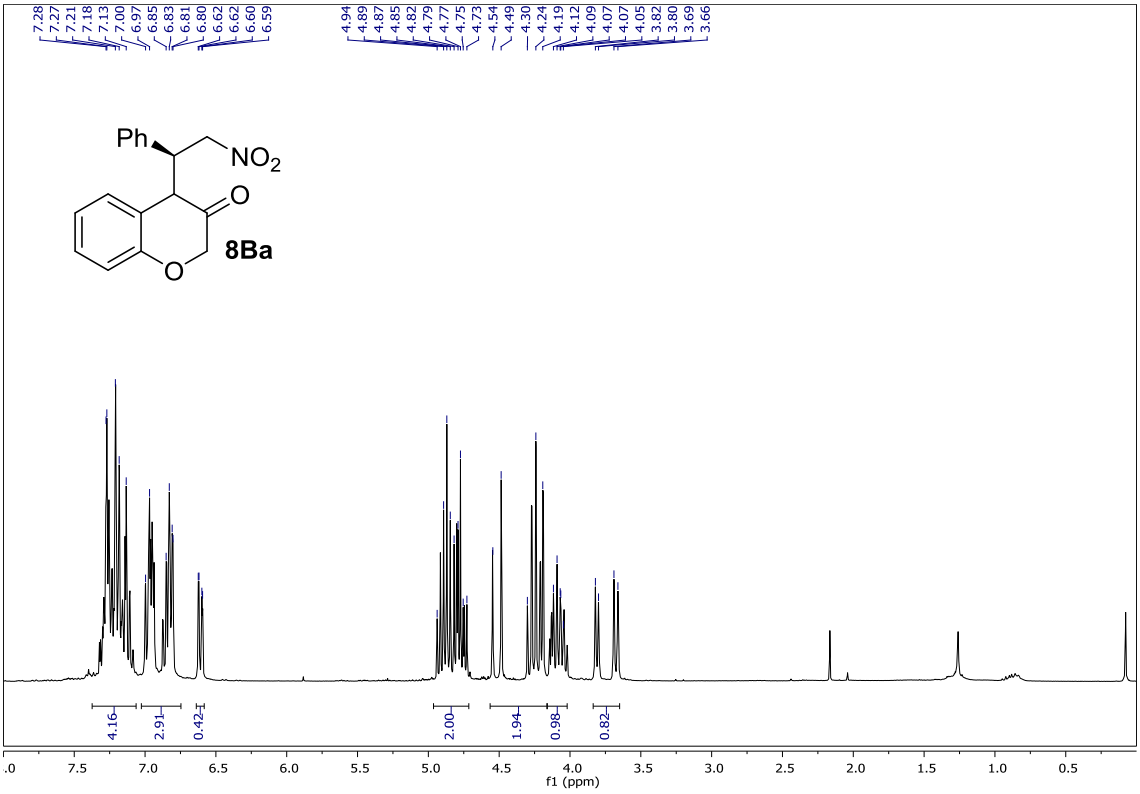
127.69
127.60
126.91
126.74
126.26
126.24
58.24
49.06
40.91
33.54
26.94
9.47
f1 (ppm)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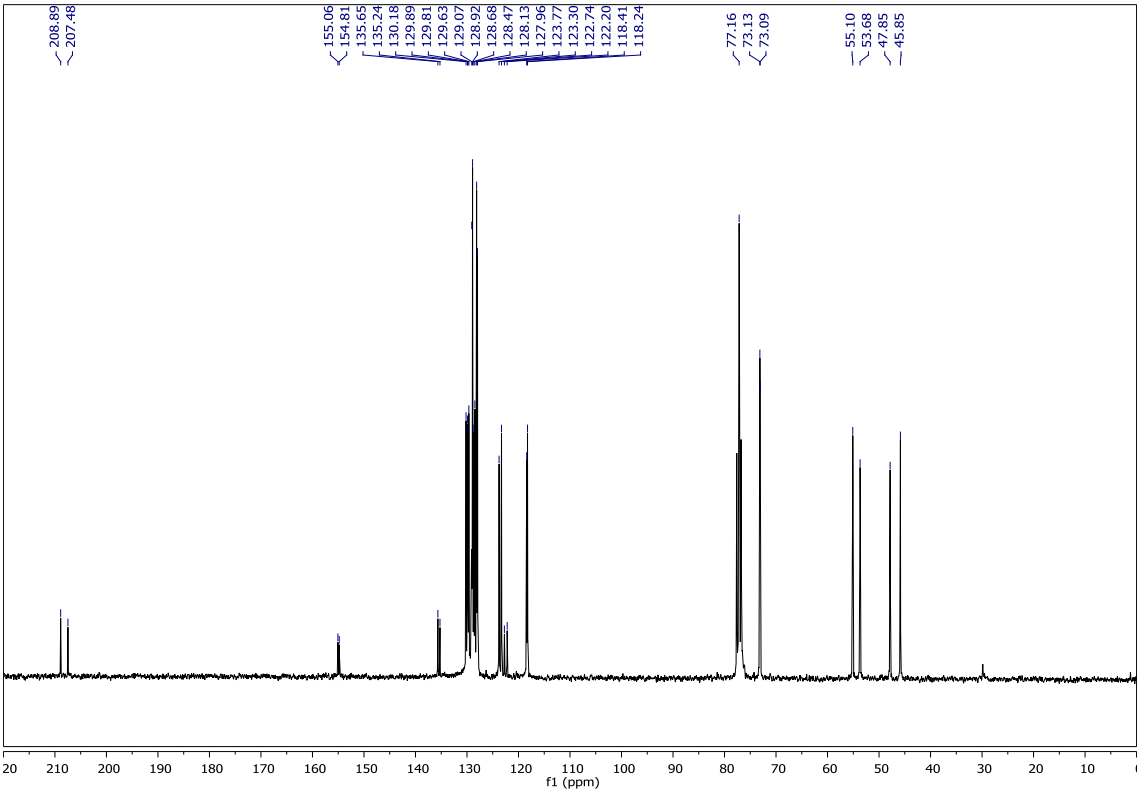
6.62
6.60
6.59
4.94
4.89
4.87
4.85
4.82
4.79
4.77
4.75
4.73
4.54
4.49
4.30
4.24
4.19
4.12
4.09
4.07
4.07
4.05
3.82
3.80
3.69
3.66
Ph
NO2
O
O
8Ba
4.16
2.91
0.42
2.00
1.94
0.98
0.82
f1 (ppm)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130.18
129.89
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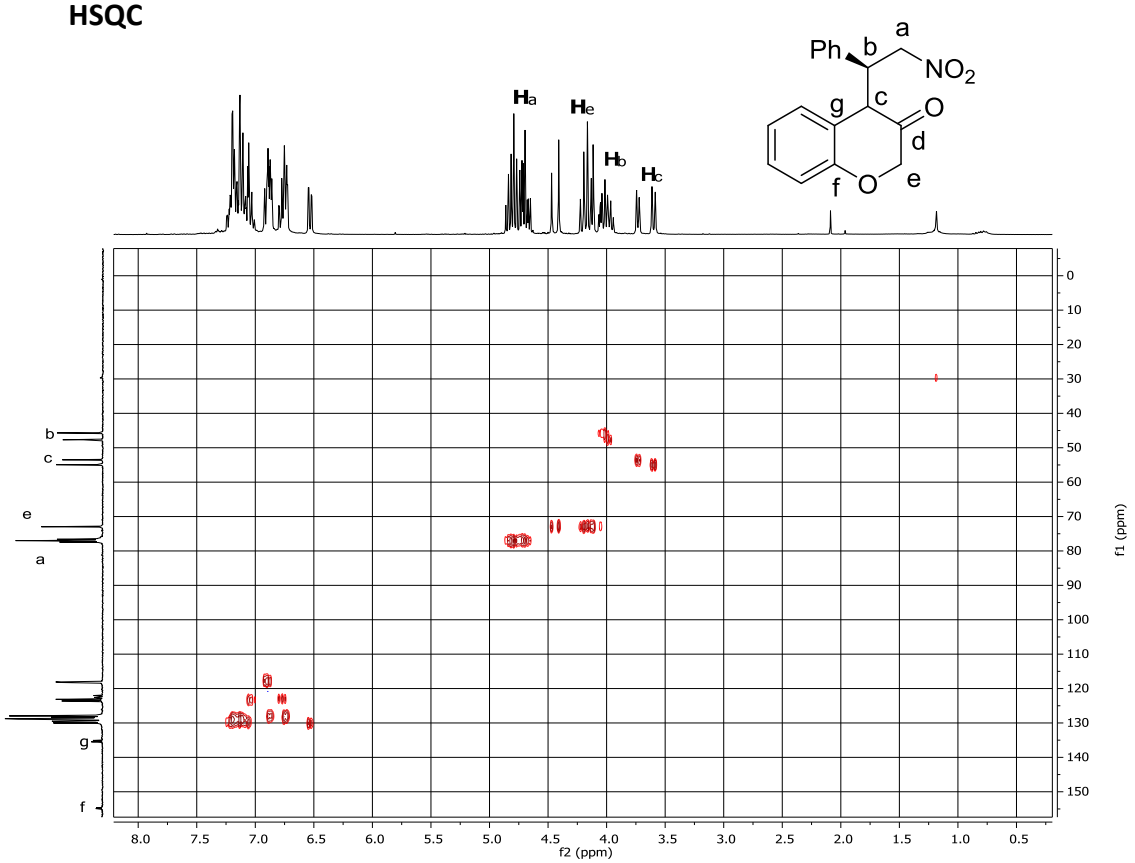
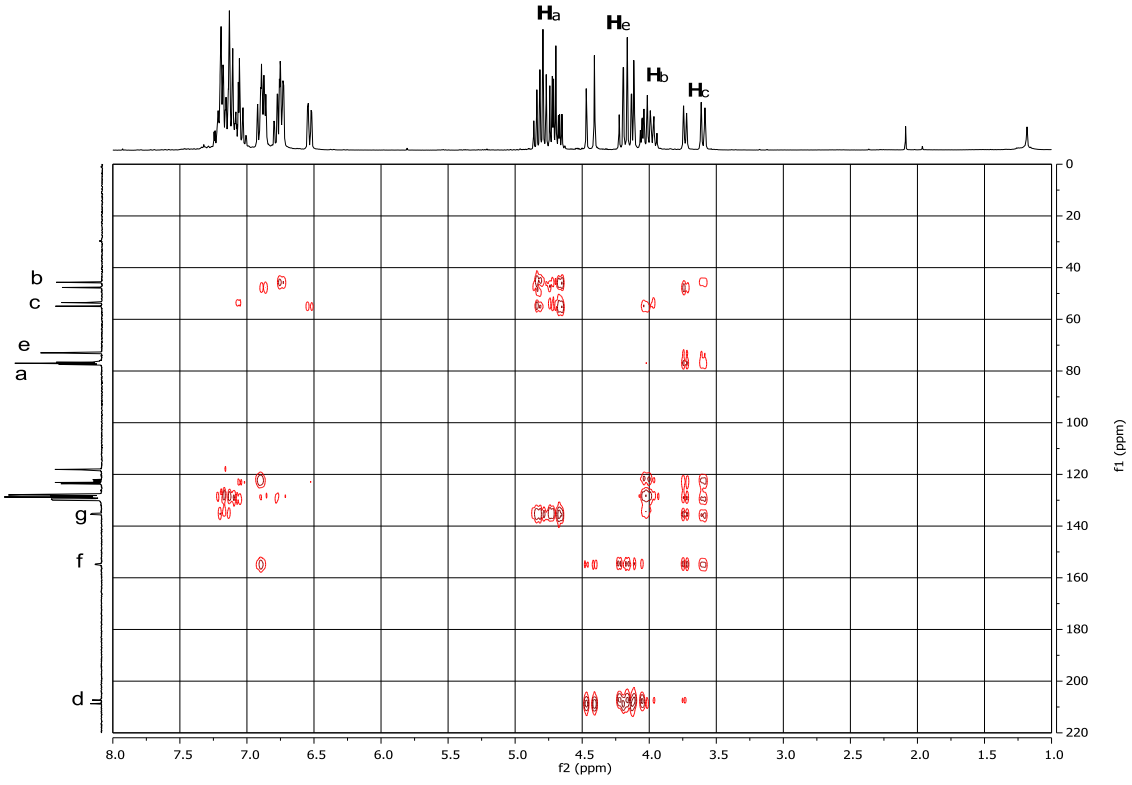
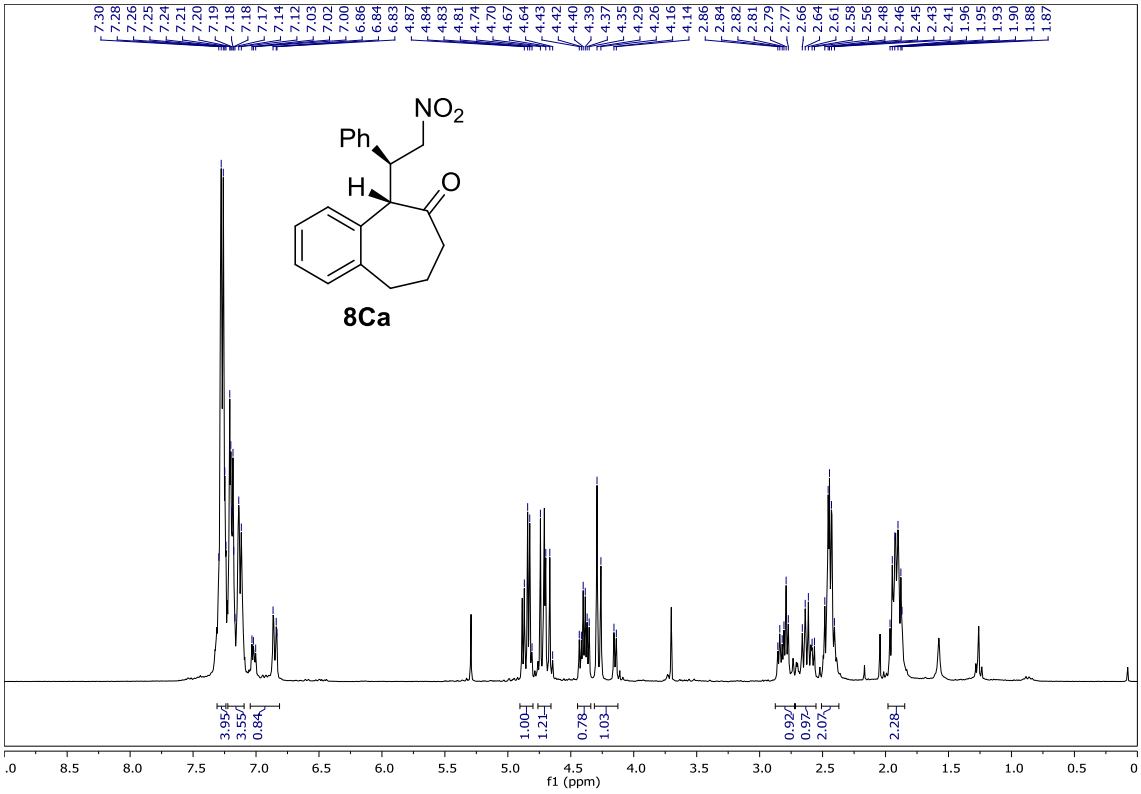
129.07
128.92
128.68
128.47
128.13
127.96
123.77
123.30
122.74
122.20
118.41
118.24
77.16
73.13
73.09
55.10
53.68
47.85
45.85
f1 (ppm)

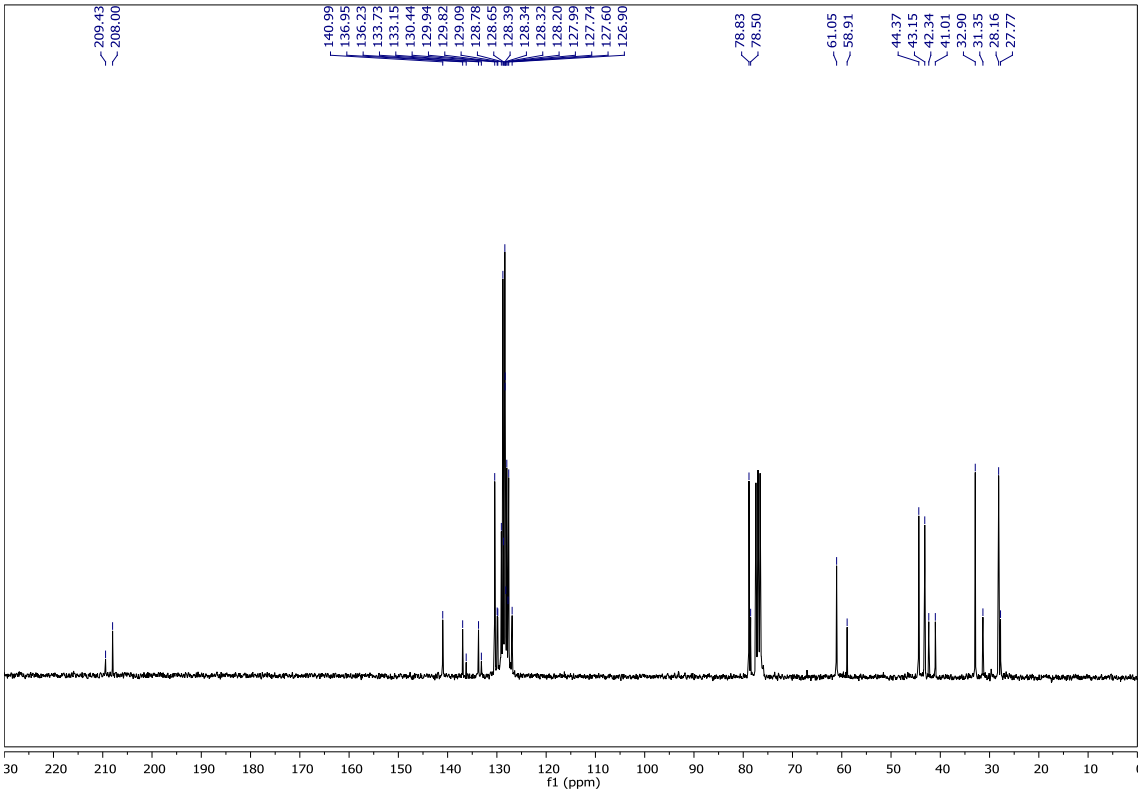
HSQC

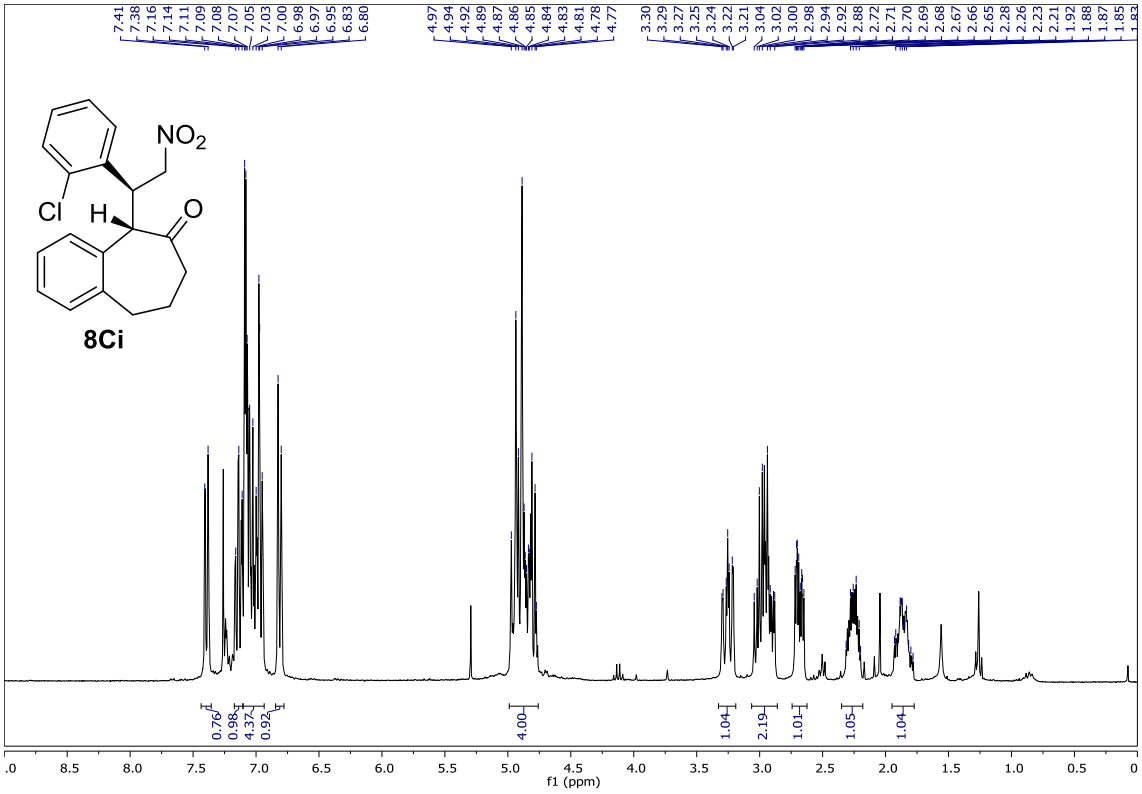

Ha
He
Hb
Hc
Ph
a
b
NO2
c
g
O
d
f
O
e
b
c
e
a
g
f
f2 (ppm)
f1 (ppm)

HMBC


Ha
He
Hb
Hc
b
c
e
a
g
f
d
f2 (ppm)
f1 (ppm)


NO2
Ph
H
O
8Ca
f1 (ppm)


f1 (ppm)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7.14
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7.09
7.08
7.07
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7.03
7.00
6.98
6.97
6.95
6.83
6.80
4.97
4.94
4.92
4.89
4.87
4.86
4.85
4.84
4.83
4.81
4.78
4.77
3.30
3.29
3.27
3.25
3.24
3.22
3.21
3.04
3.02
3.00
2.98
2.94
2.92
2.88
2.72
2.71
2.70
2.69
2.68
2.67
2.66
2.65
2.28
2.26
2.23
2.21
1.92
1.88
1.87
1.85
NO2
Cl
H
O
8Ci
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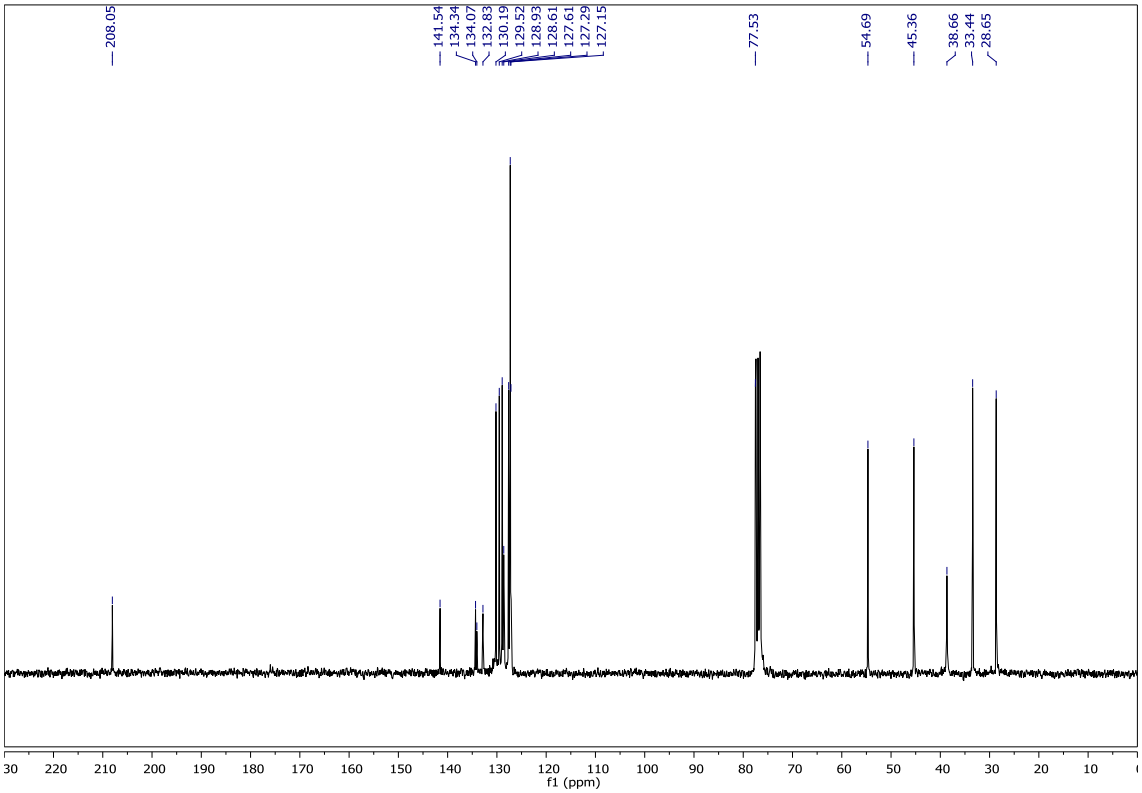
0.92
4.00
1.04
2.19
1.01
1.05
1.04
f1 (ppm)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141.54
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134.07
132.83
130.19
129.52
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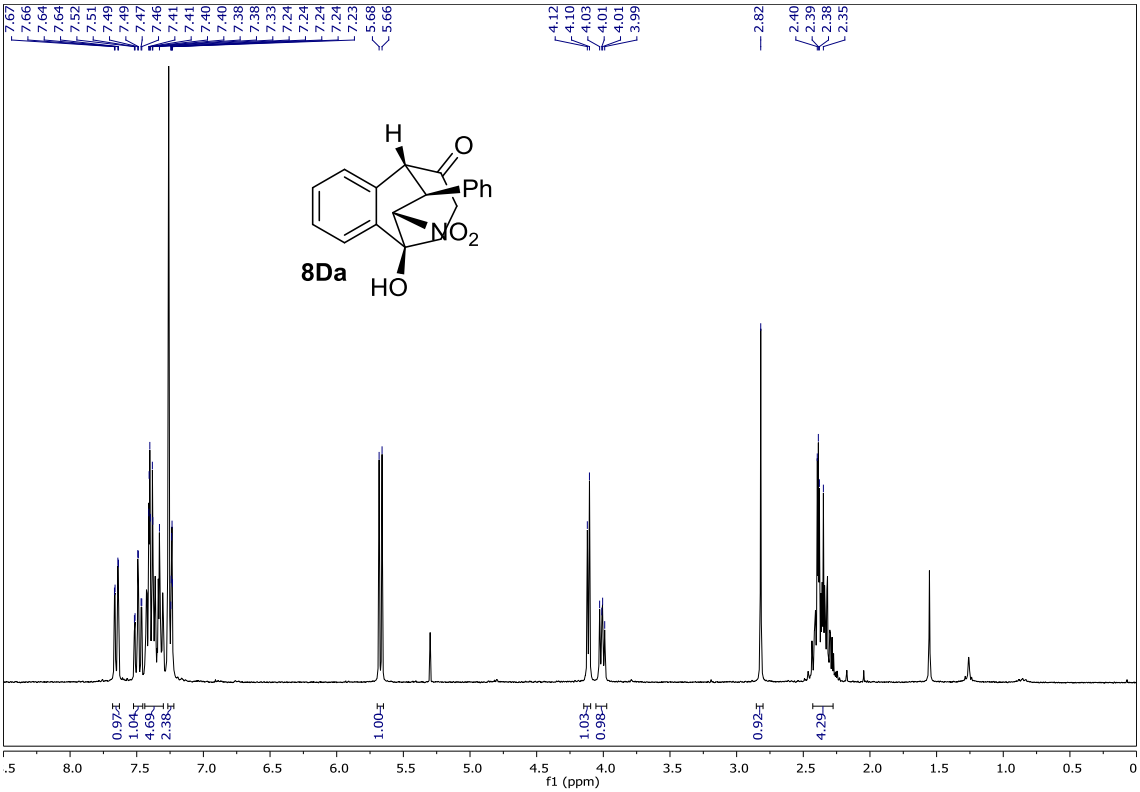
127.29
127.15
77.53
54.69
45.36
38.66
33.44
28.65
f1 (ppm)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7.64
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7.51
7.49
7.49
7.47
7.46
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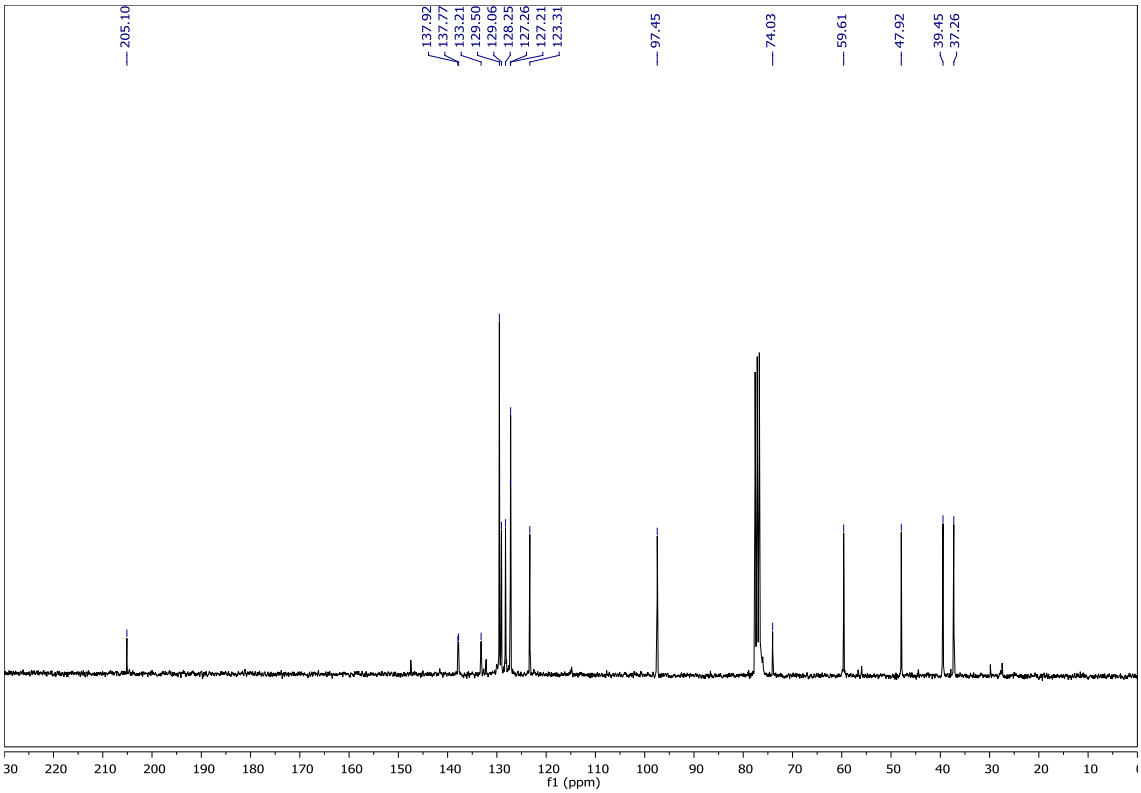
7.41
7.40
7.40
7.38
7.38
7.33
7.24
7.24
7.24
7.23
5.68
5.66
4.12
4.10
4.03
4.01
4.01
3.99
2.82
2.40
2.39
2.38
2.35
H
O
Ph
NO2
HO
8Da
0.97
1.04
4.69
2.38
1.00
1.03
0.98
0.92
4.29
f1 (ppm)


205.10
137.92
137.77
133.21
129.50
129.06
128.25
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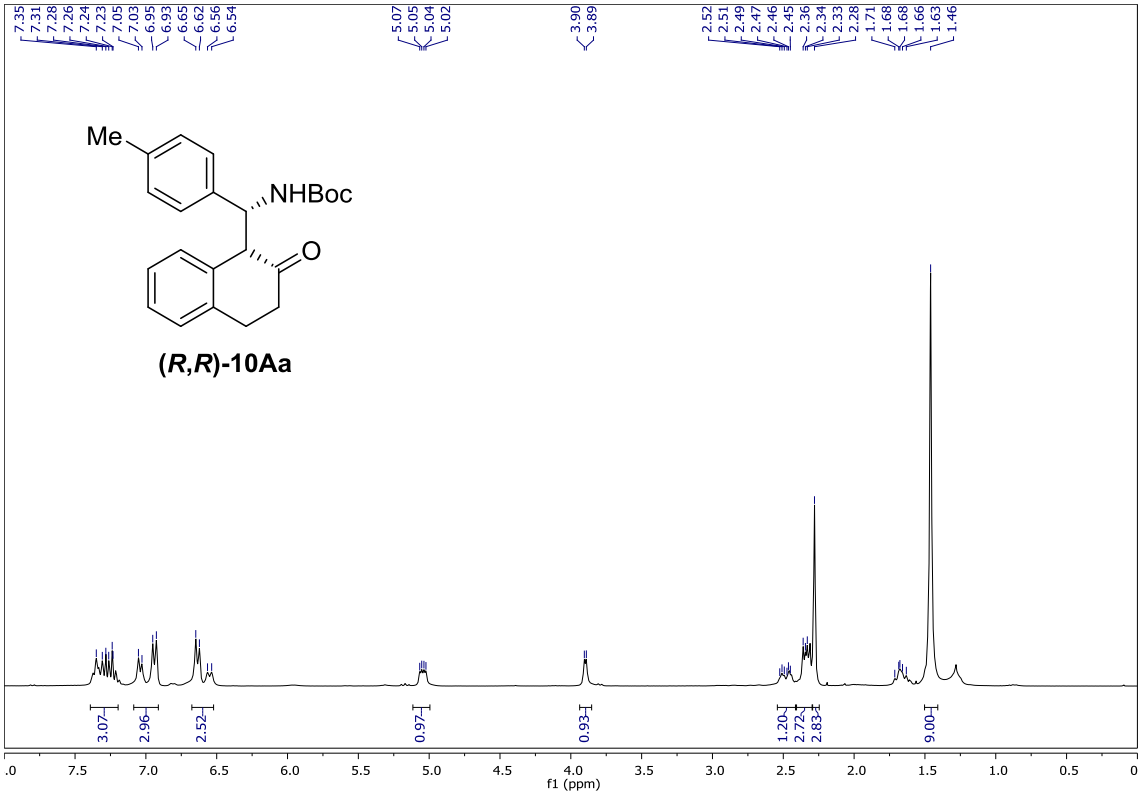
127.21
123.31
97.45
74.03
59.61
47.92
39.45
37.26
f1 (ppm)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7.31
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7.24
7.23
7.05
7.03
6.95
6.93
6.65
6.62
6.56
6.54
5.07
5.05
5.04
5.02
3.90
3.89
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2.51
2.49
2.47
2.46
2.45
2.36
2.34
2.33
2.28
1.71
1.68
1.68
1.66
1.63
1.46
Me
NHBoc
O
(R,R)-10Aa
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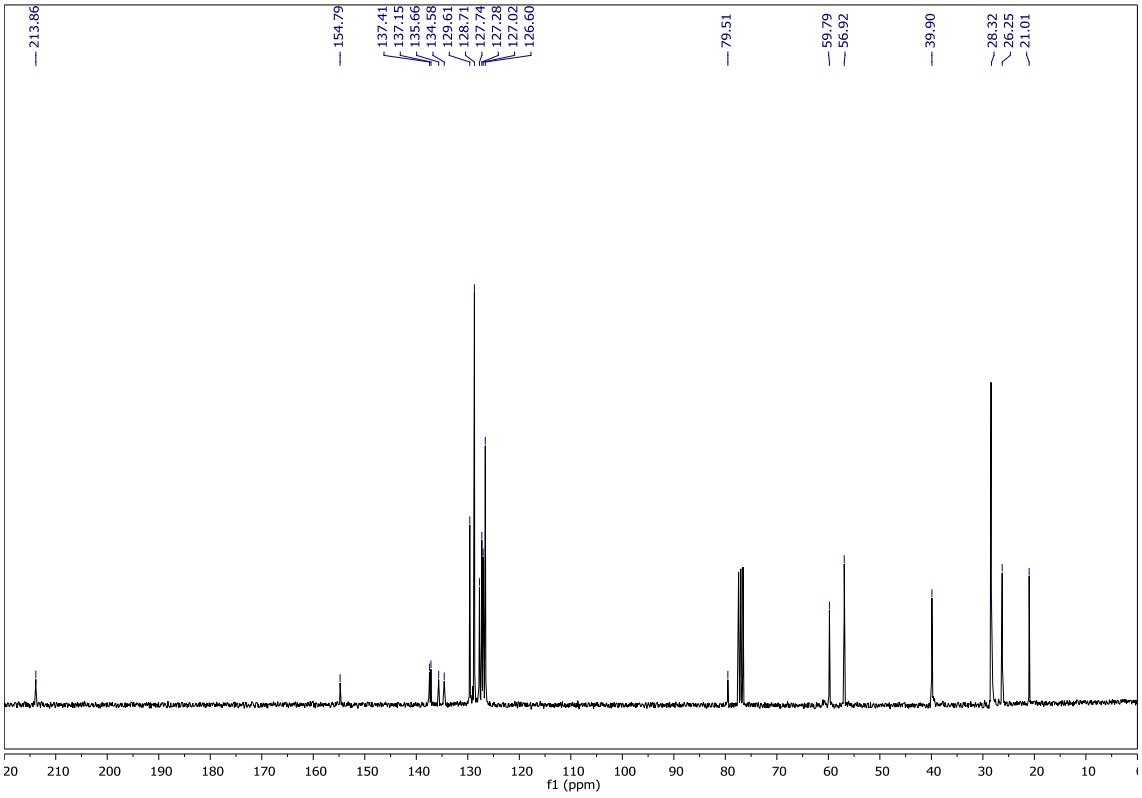
2.96
2.52
0.97
0.93
1.20
2.72
2.83
9.00
f1 (ppm)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134.58
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128.71
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126.60
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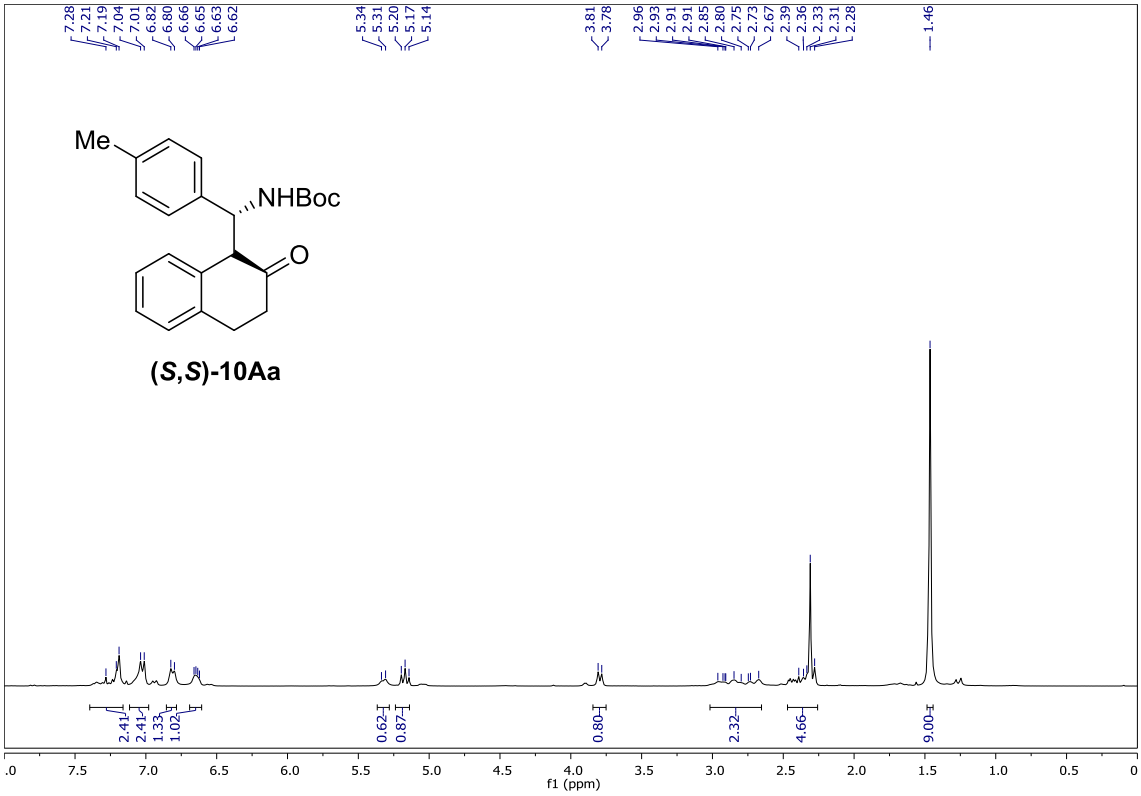
39.90
28.32
26.25
21.01
f1 (ppm)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7.01
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6.80
6.66
6.65
6.63
6.62
5.34
5.31
5.20
5.17
5.14
3.81
3.78
2.96
2.93
2.91
2.91
2.85
2.80
2.75
2.73
2.67
2.39
2.36
2.33
2.31
2.28
1.46
Me
NHBoc
O
(S,S)-10Aa
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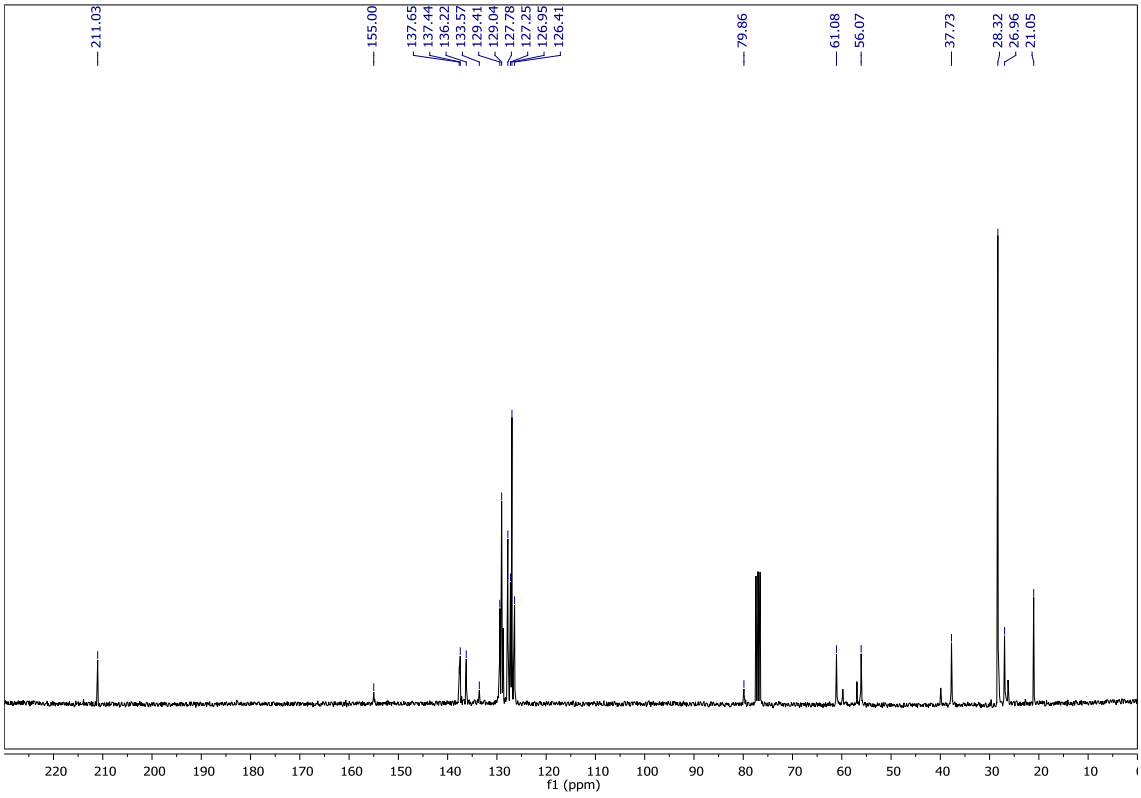
2.41
1.33
1.02
0.62
0.87
0.80
2.32
4.66
9.00
f1 (ppm)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129.04
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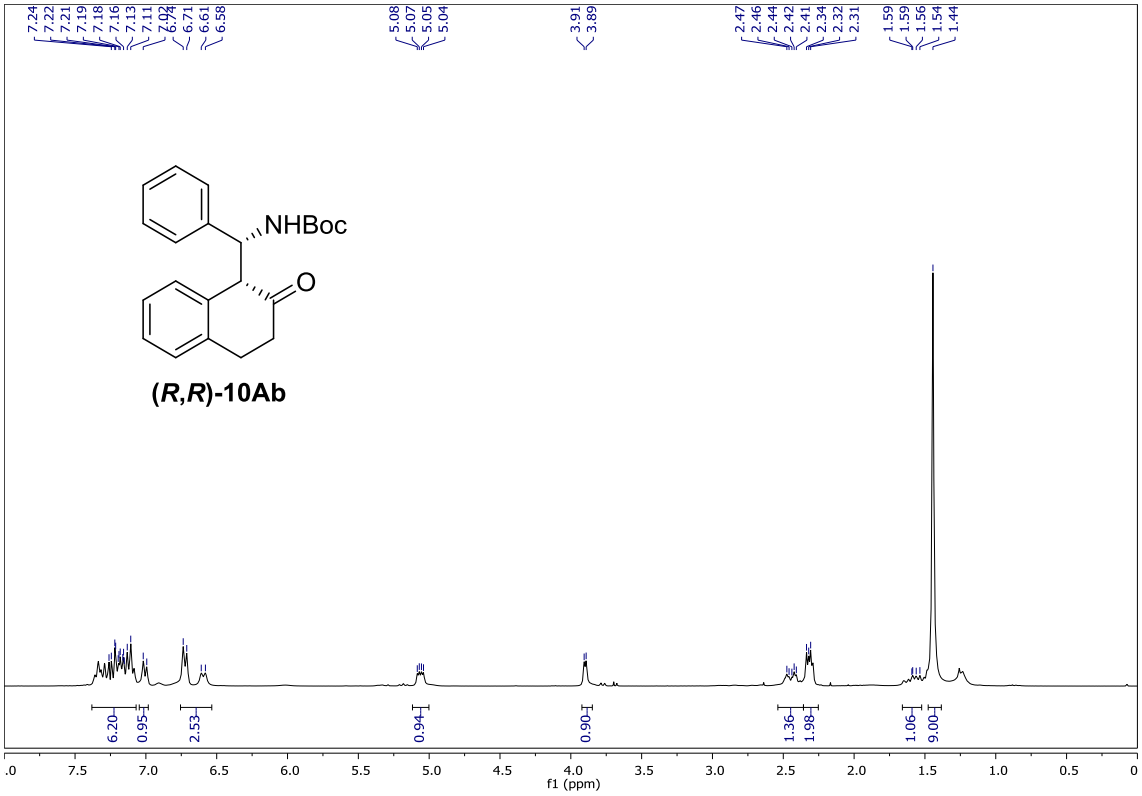
126.41
79.86
61.08
56.07
37.73
28.32
26.96
21.05
f1 (ppm)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5.08
5.07
5.05
5.04
3.91
3.89
2.47
2.46
2.44
2.42
2.41
2.34
2.32
2.31
1.59
1.59
1.56
1.54
1.44
NHBoc
O
(R,R)-10Ab
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0.95
2.53
0.94
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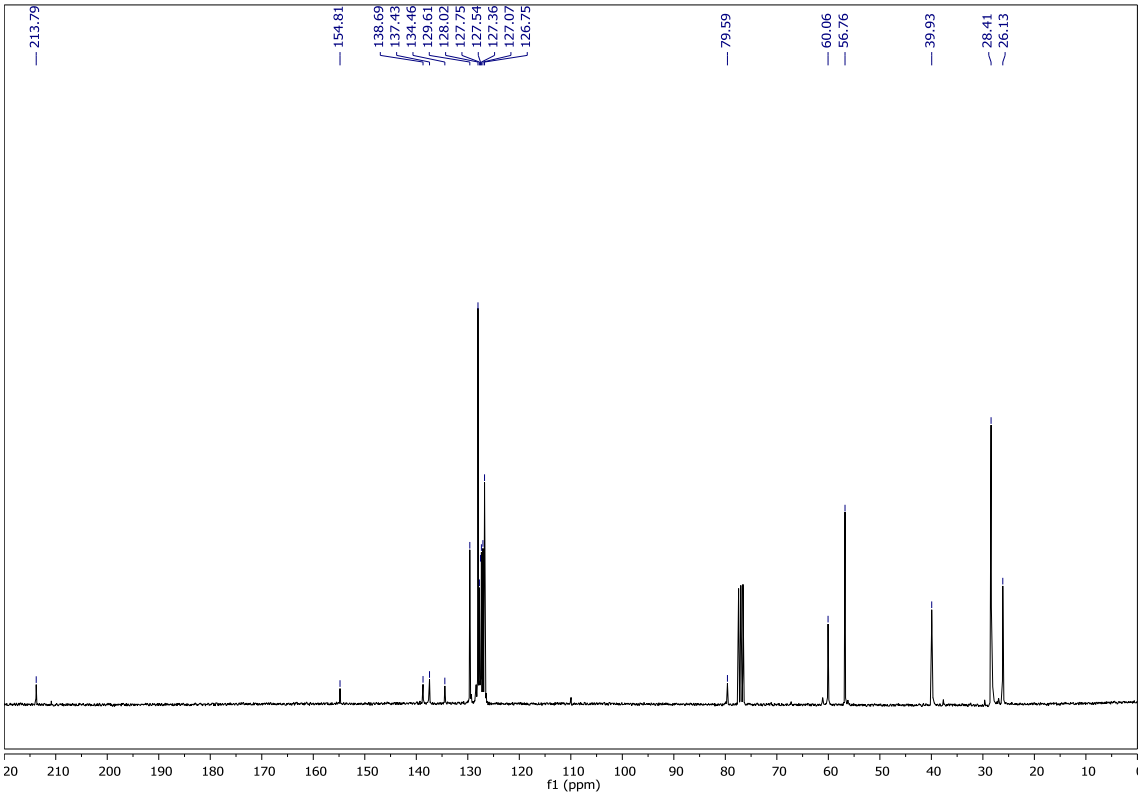
1.36
1.98
1.06
9.00
f1 (ppm)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128.02
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127.54
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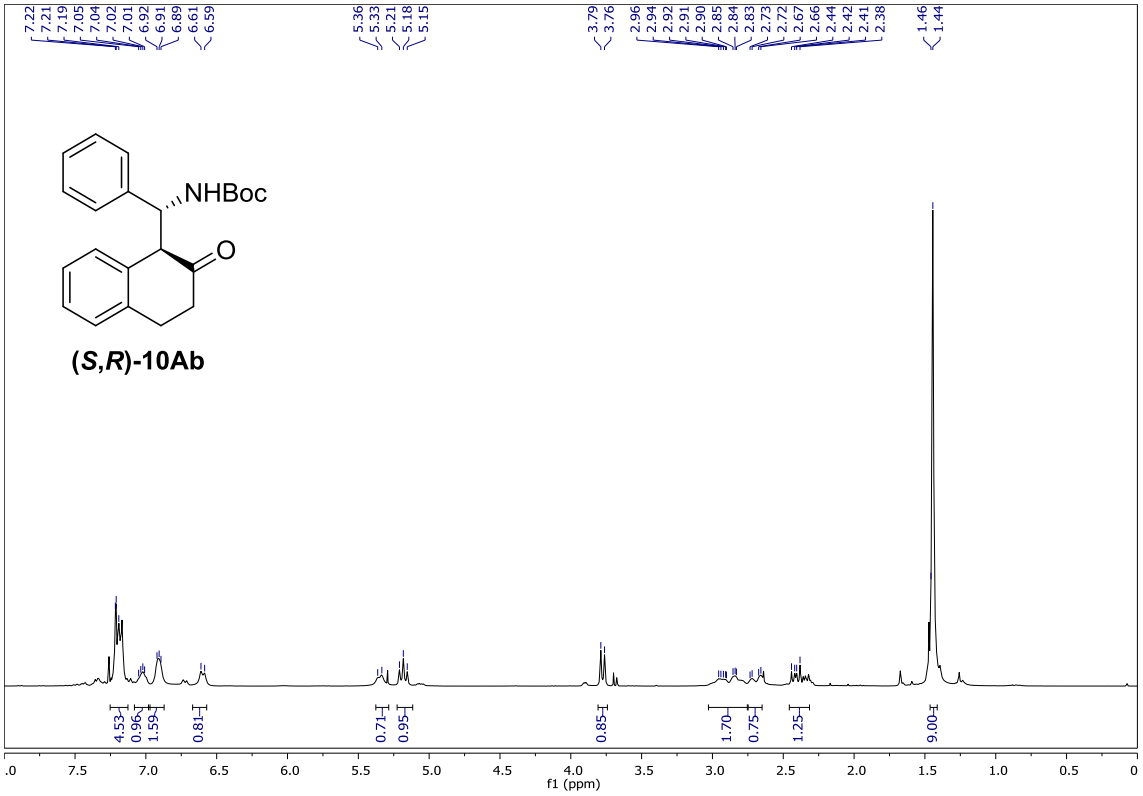
127.07
126.75
79.59
60.06
56.76
39.93
28.41
26.13
f1 (ppm)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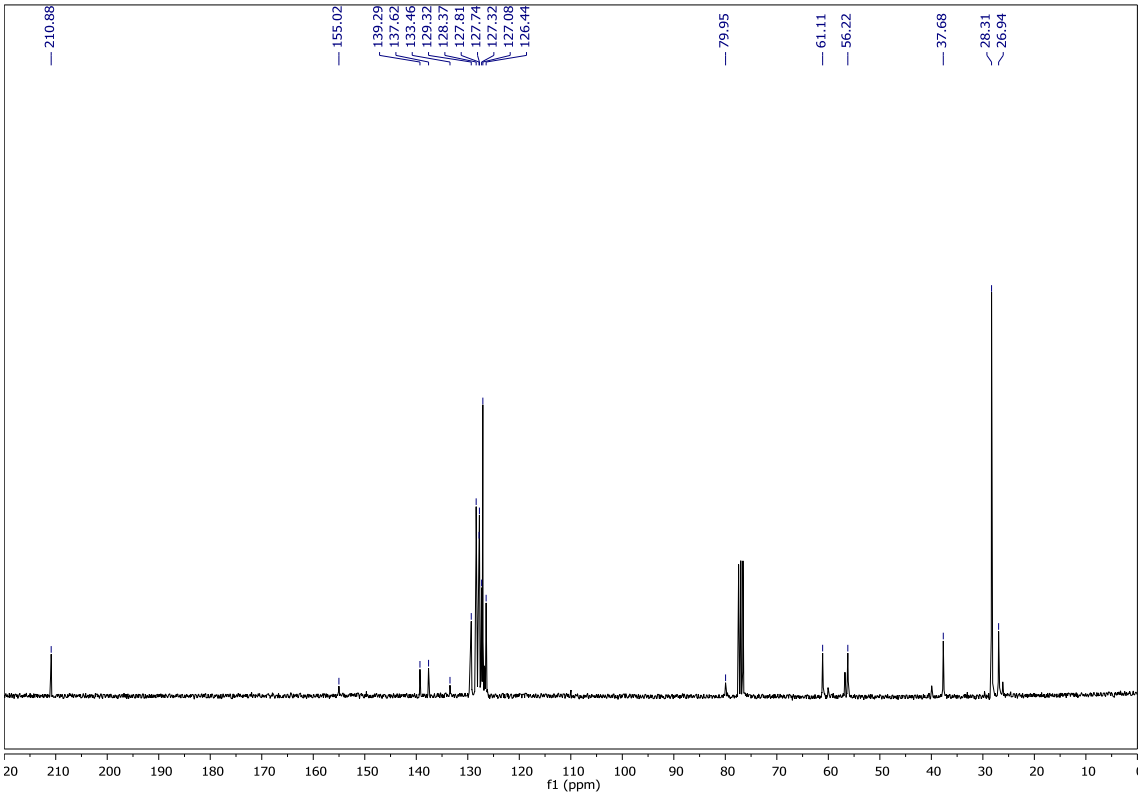
7.02
7.01
6.92
6.91
6.89
6.61
6.59
5.36
5.33
5.21
5.18
5.15
3.79
3.76
2.96
2.94
2.92
2.91
2.90
2.85
2.84
2.83
2.73
2.72
2.67
2.66
2.44
2.42
2.41
2.38
1.46
1.44
NHBoc
O
(S,R)-10Ab
4.53
0.96
1.59
0.81
0.71
0.95
0.85
1.70
0.75
1.25
9.00
f1 (ppm)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127.08
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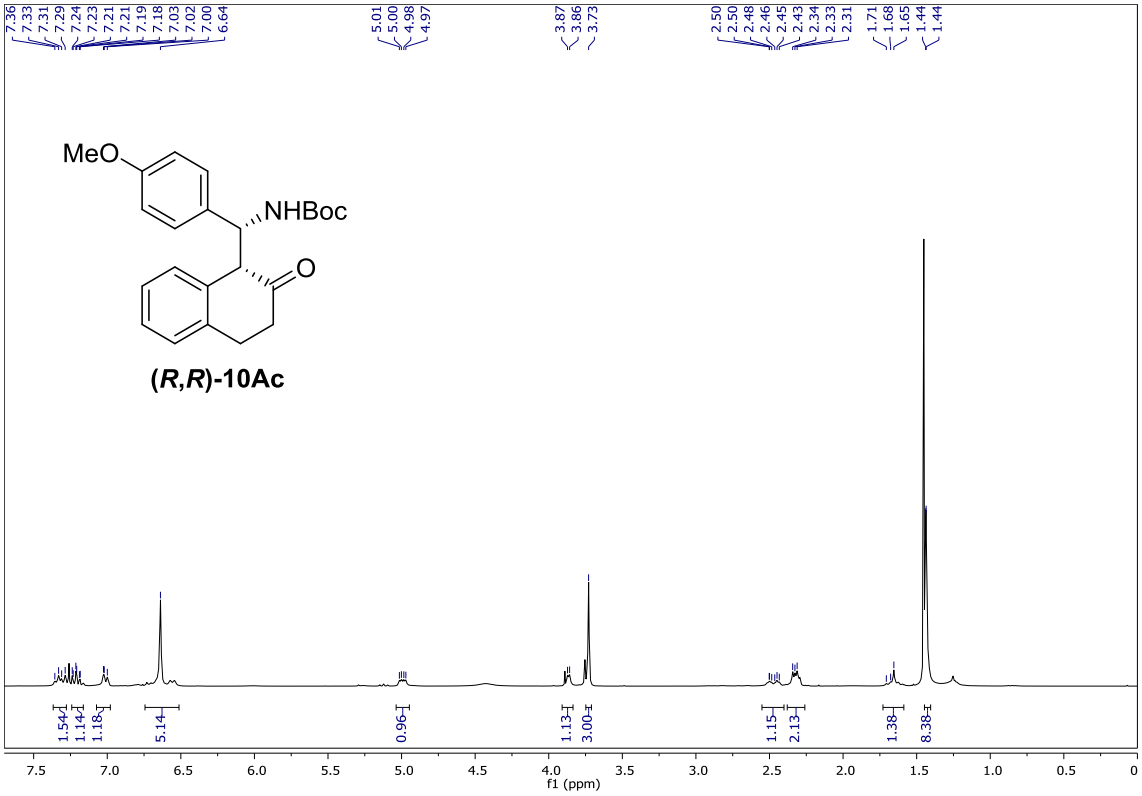
56.22
37.68
28.31
26.94
f1 (ppm)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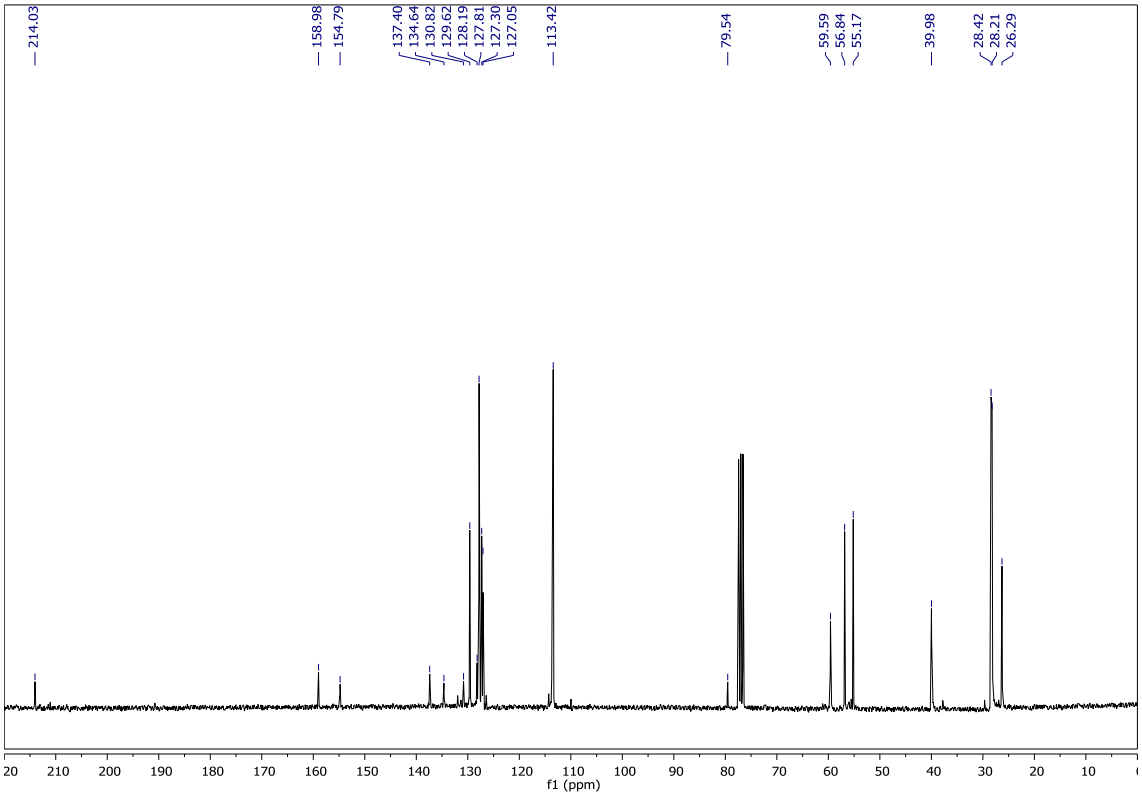
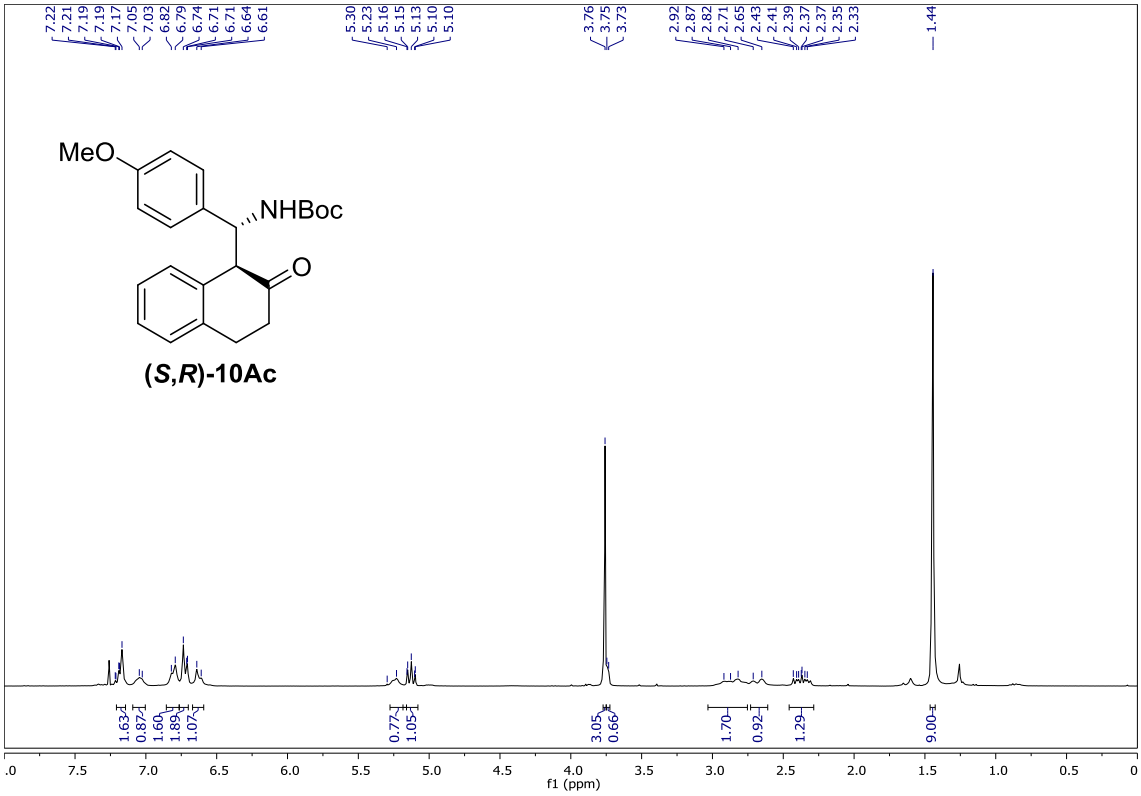
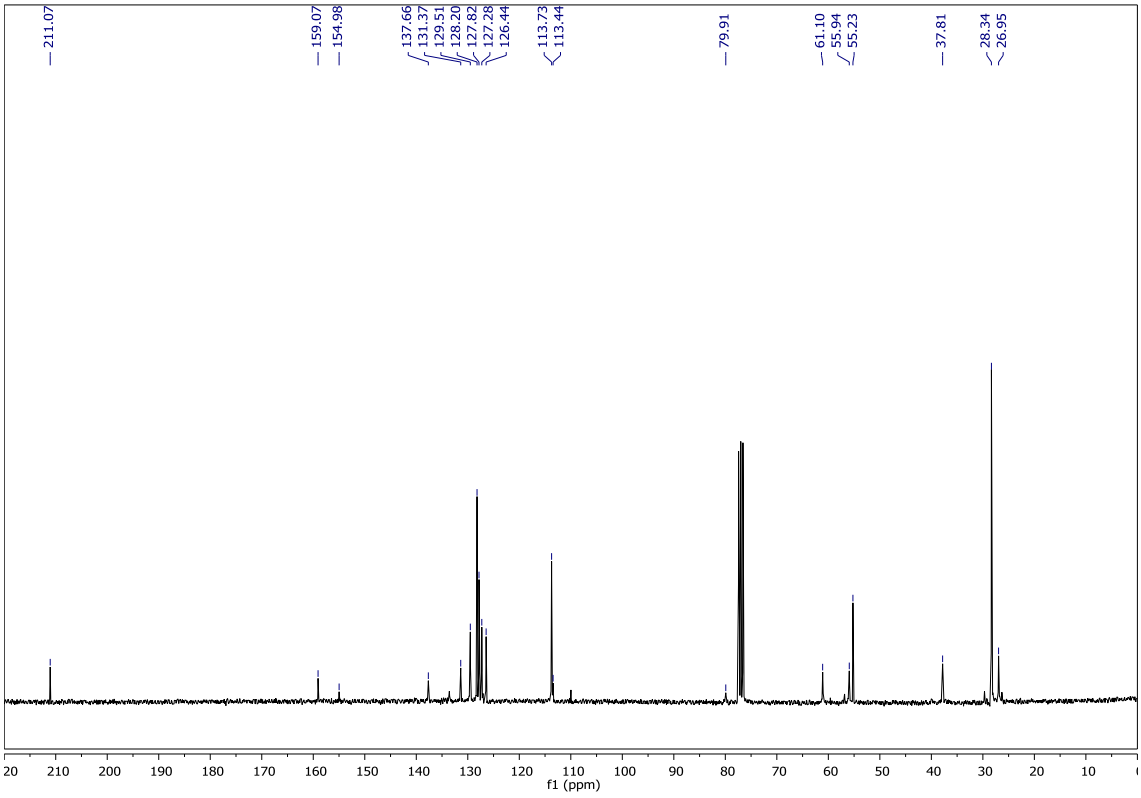
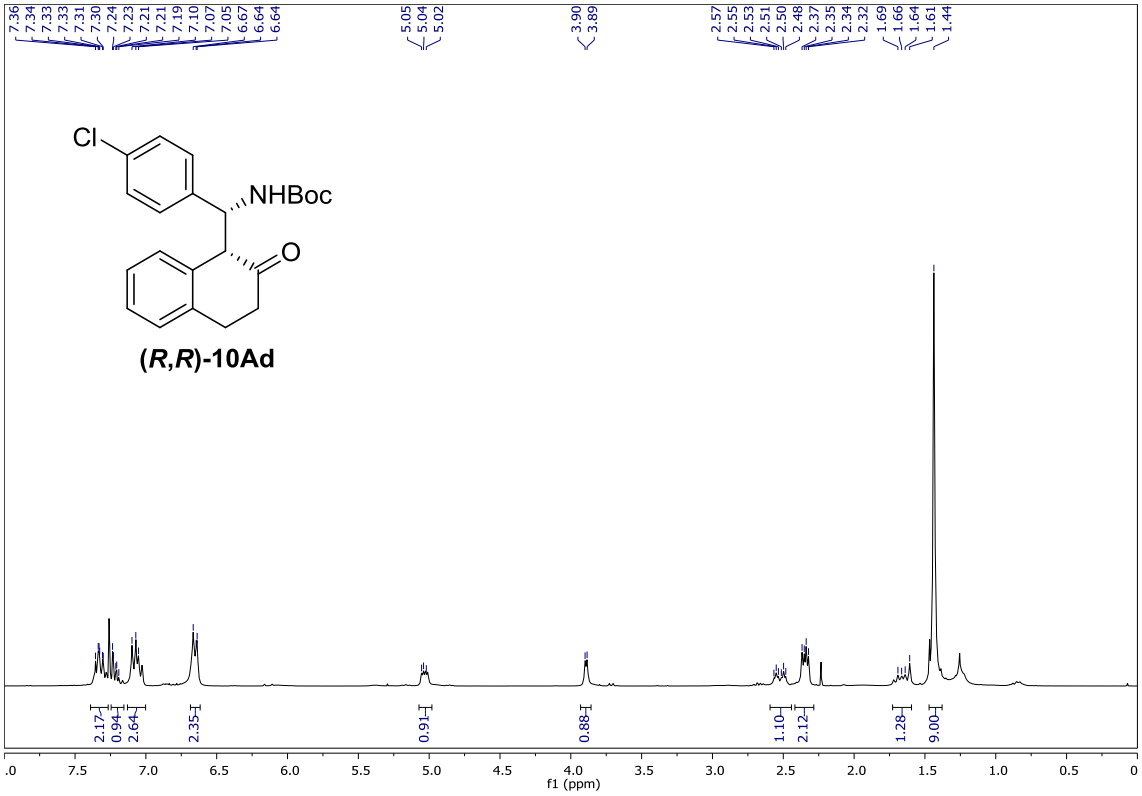
NHBoc
O
(R,R)-10Ac
f1 (ppm)


f1 (ppm)


MeO
NHBoc
O
(S,R)-10Ac
f1 (ppm)


f1 (ppm)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7.23
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7.19
7.10
7.07
7.05
6.67
6.64
6.64
5.05
5.04
5.02
3.90
3.89
2.57
2.55
2.53
2.51
2.50
2.48
2.37
2.35
2.34
2.32
1.69
1.66
1.64
1.61
1.44
Cl
NHBoc
O
(R,R)-10Ad
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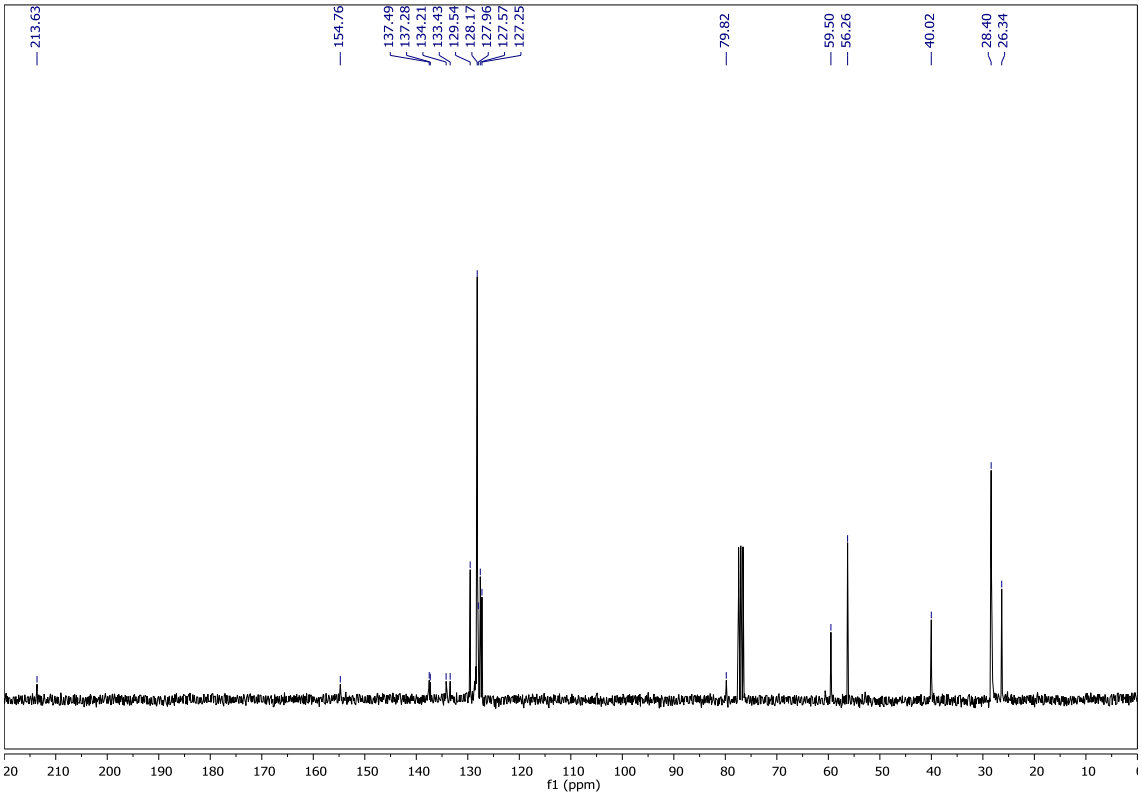
2.64
2.35
0.91
0.88
1.10
2.12
1.28
9.00
f1 (ppm)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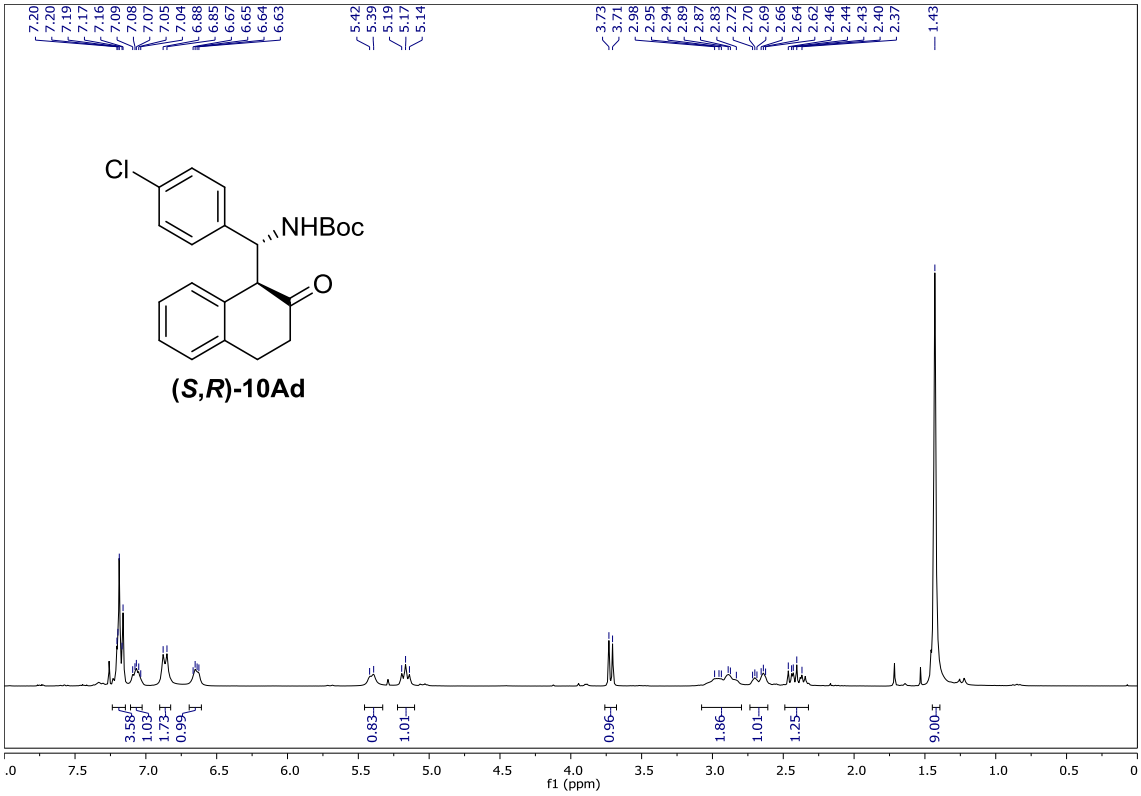
127.25
79.82
59.50
56.26
40.02
28.40
26.34
f1 (ppm)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2.69
2.66
2.64
2.62
2.46
2.44
2.43
2.40
2.37
1.43
Cl
NHBoc
O
(S,R)-10Ad
3.58
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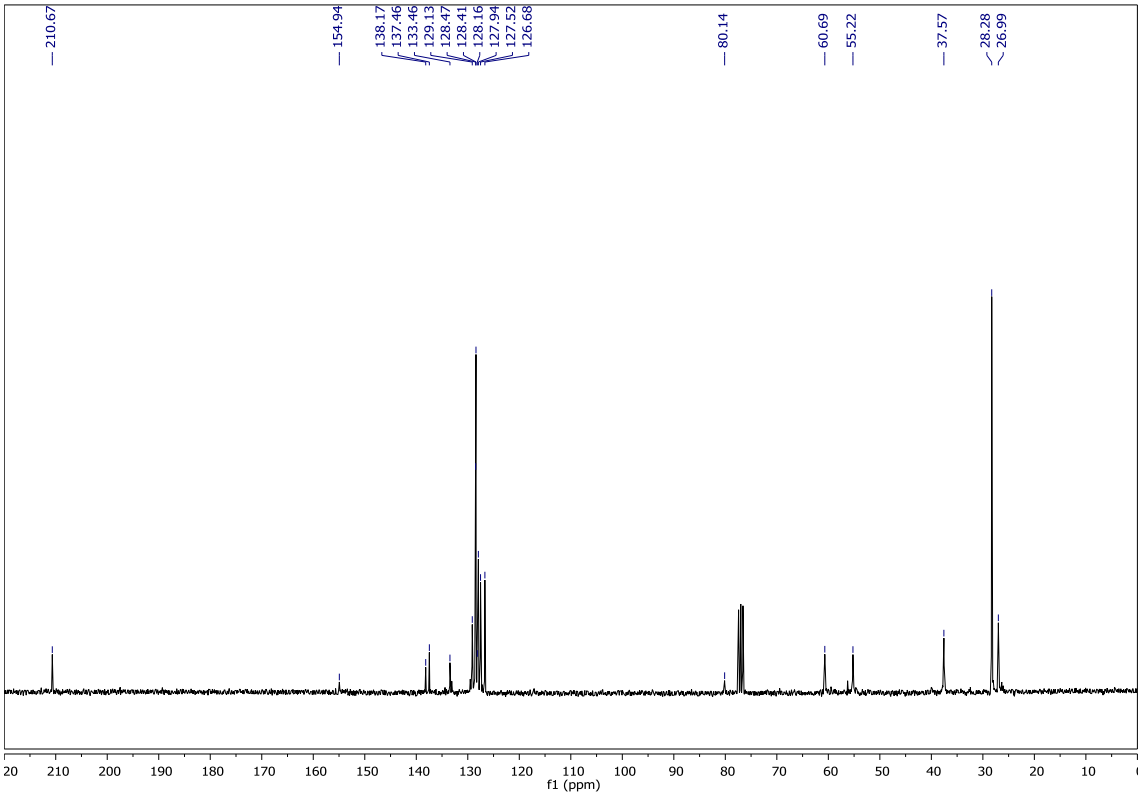
1.73
0.99
0.83
1.01
0.96
1.86
1.01
1.25
9.00
f1 (ppm)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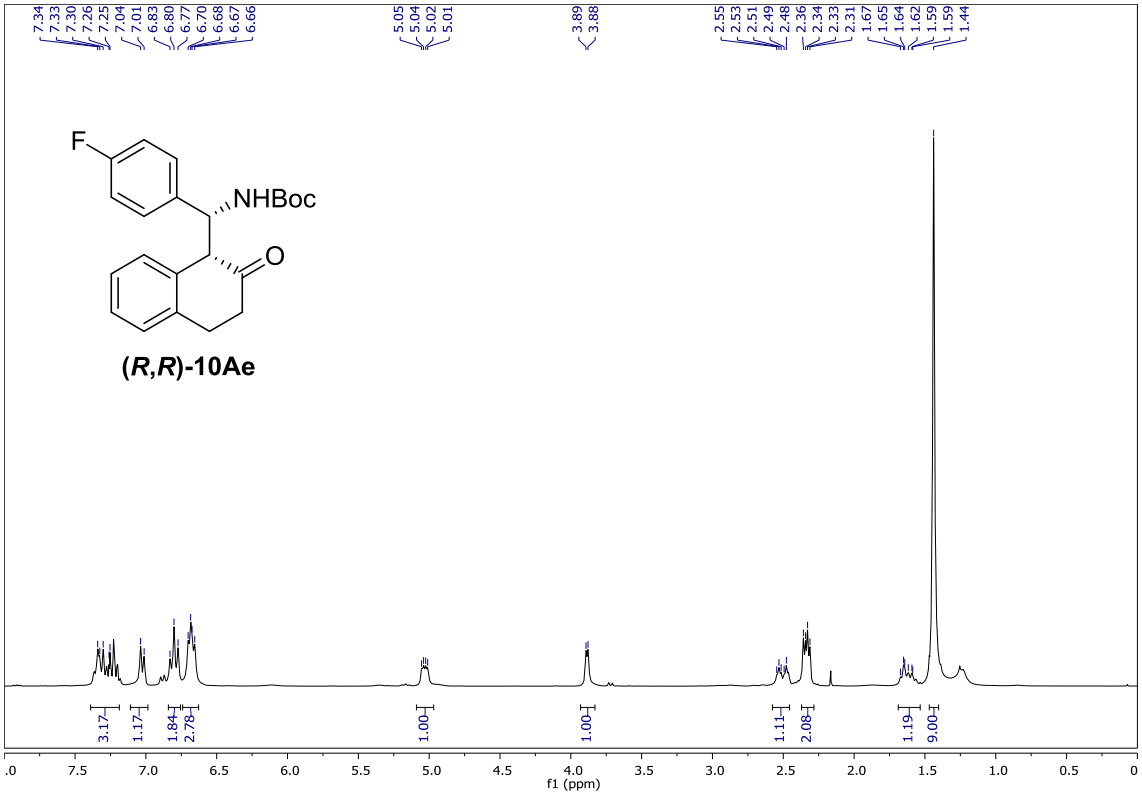
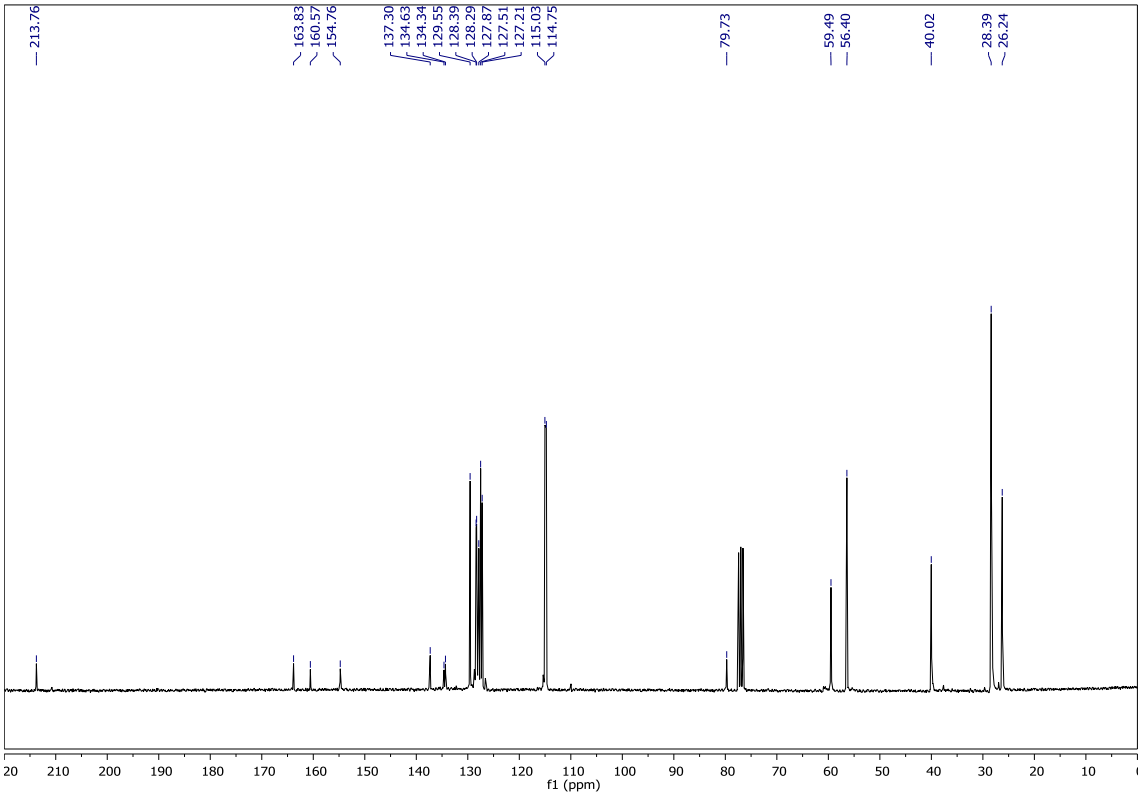
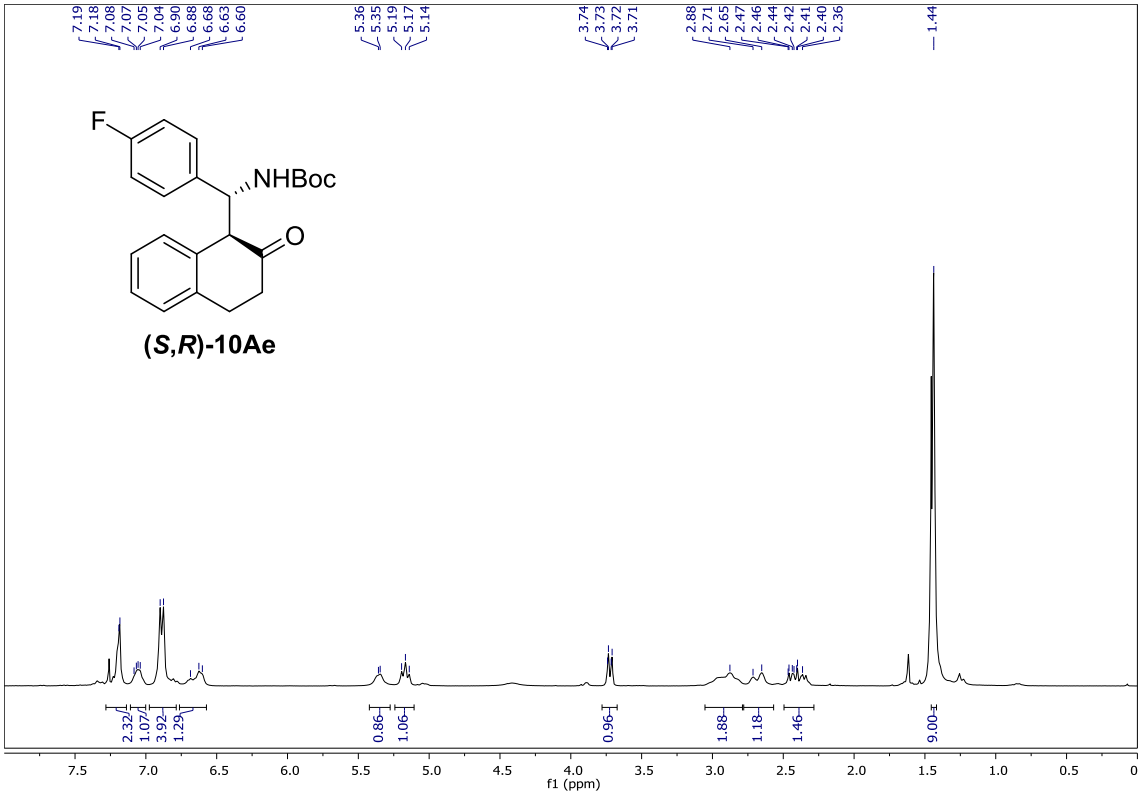
138.17
137.46
133.46
129.13
128.47
128.41
128.16
127.94
127.52
126.68
80.14
60.69
55.22
37.57
28.28
26.99
f1 (ppm)


F
NHBoc
O
(R,R)-10Ae
f1 (ppm)


f1 (ppm)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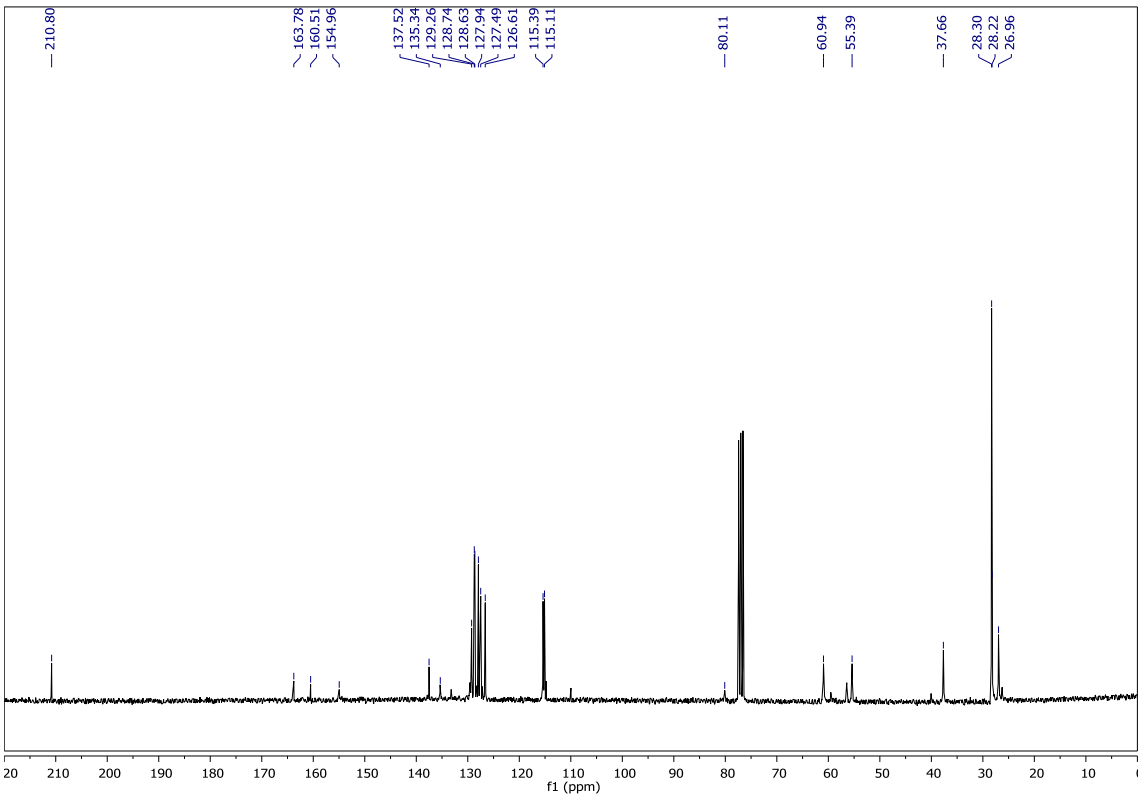
7.18
7.08
7.07
7.05
7.04
6.90
6.88
6.68
6.63
6.60
5.36
5.35
5.19
5.17
5.14
3.74
3.73
3.72
3.71
2.88
2.71
2.65
2.47
2.46
2.44
2.42
2.41
2.40
2.36
1.44
F
NHBoc
O
(S,R)-10Ae
2.32
1.07
3.92
1.29
0.86
1.06
0.96
1.88
1.18
1.46
9.00
f1 (ppm)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163.78
160.51
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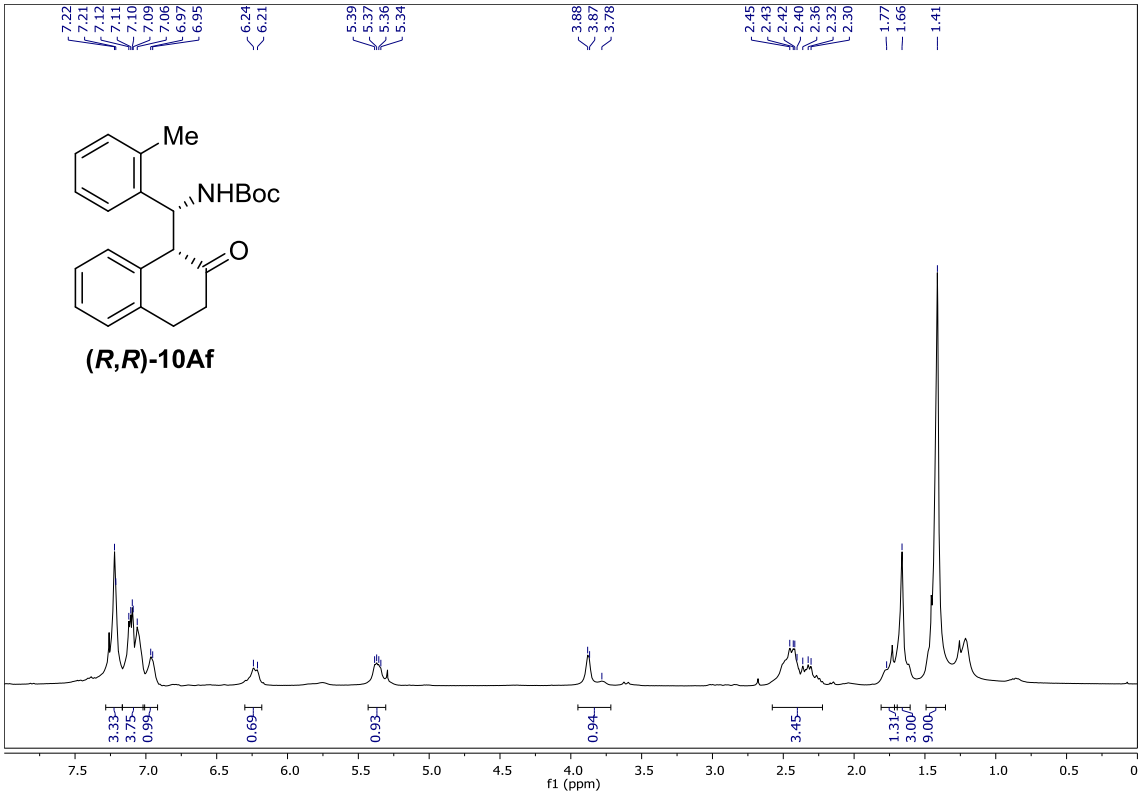
137.52
135.34
129.26
128.74
128.63
127.94
127.49
126.61
115.39
115.11
80.11
60.94
55.39
37.66
28.30
28.22
26.96
f1 (ppm)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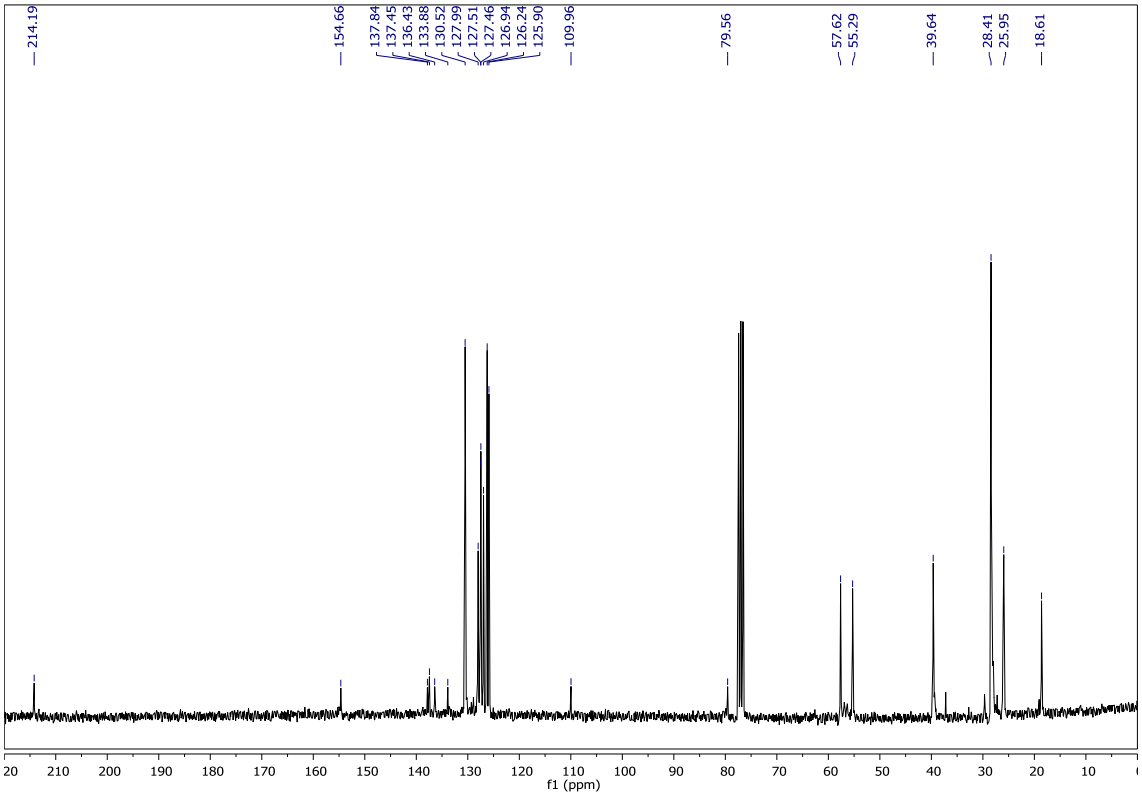
7.21
7.12
7.11
7.10
7.09
7.06
6.97
6.95
6.24
6.21
5.39
5.37
5.36
5.34
3.88
3.87
3.78
2.45
2.43
2.42
2.40
2.36
2.32
2.30
1.77
1.66
1.41
Me
NHBoc
O
(R,R)-10Af
3.33
3.75
0.99
0.69
0.93
0.94
3.45
1.31
3.00
9.00
f1 (ppm)


214.19
154.66
137.84
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136.43
133.88
130.52
127.99
127.51
127.46
126.94
126.24
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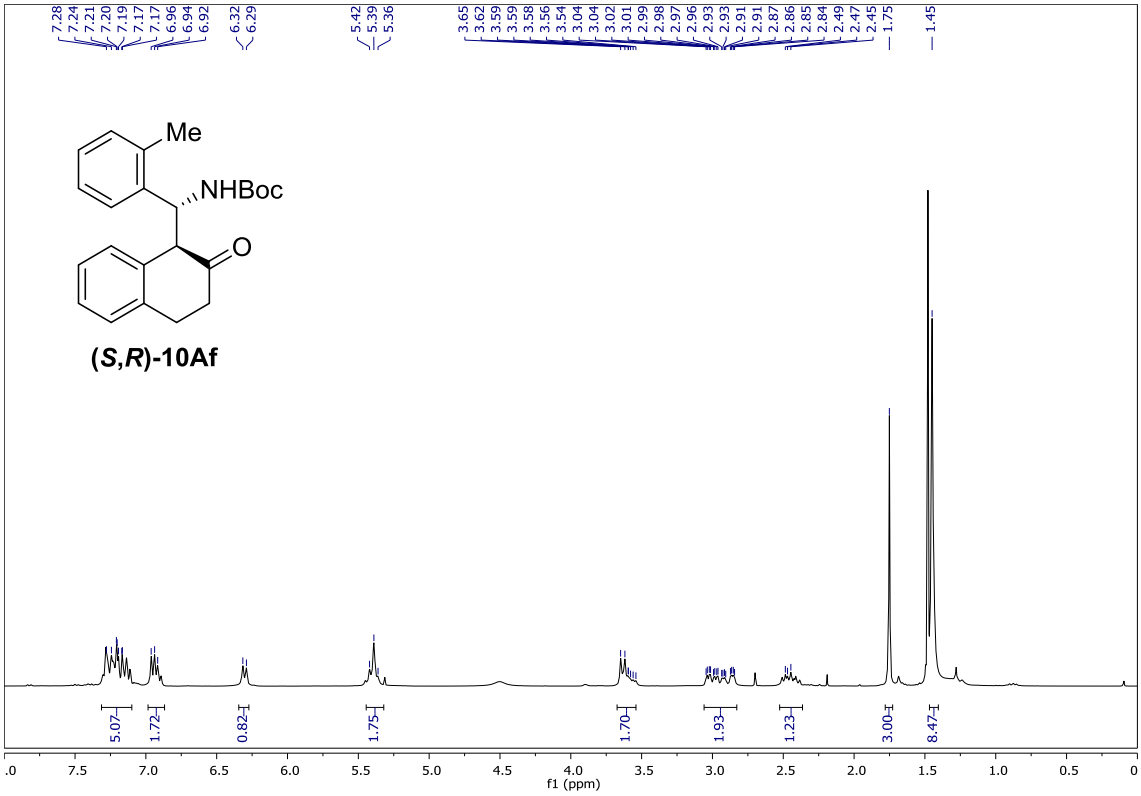
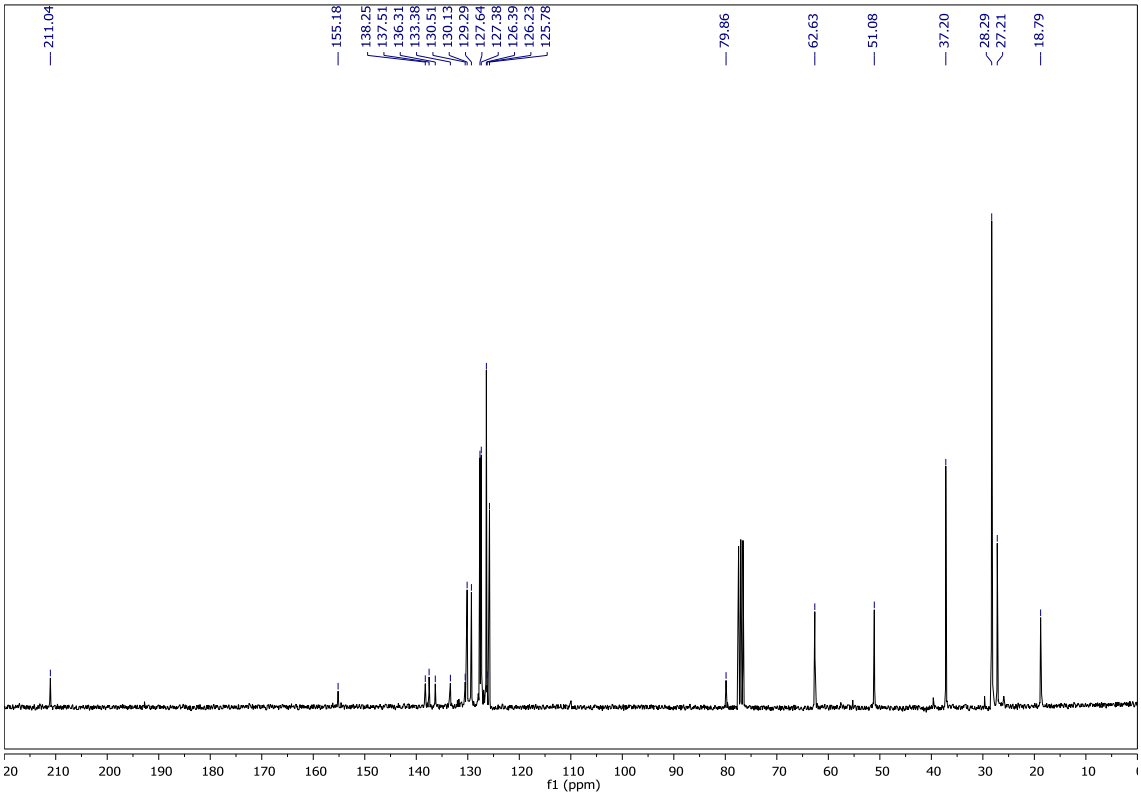
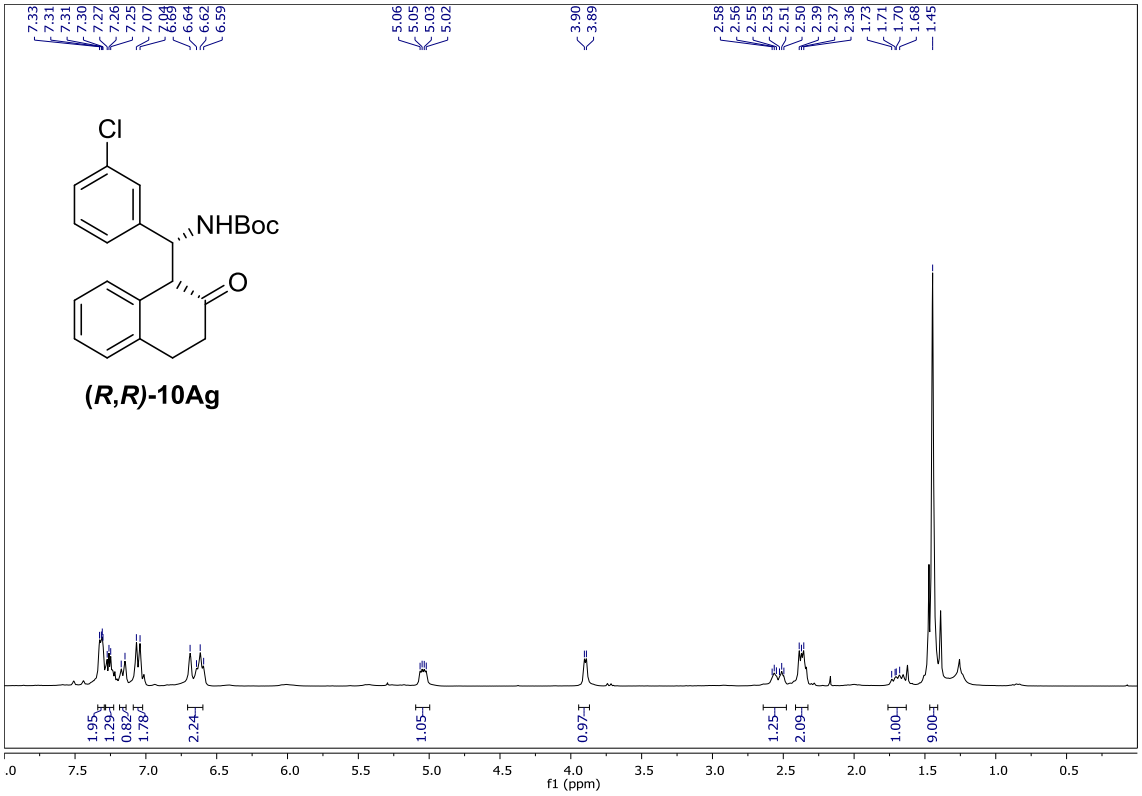
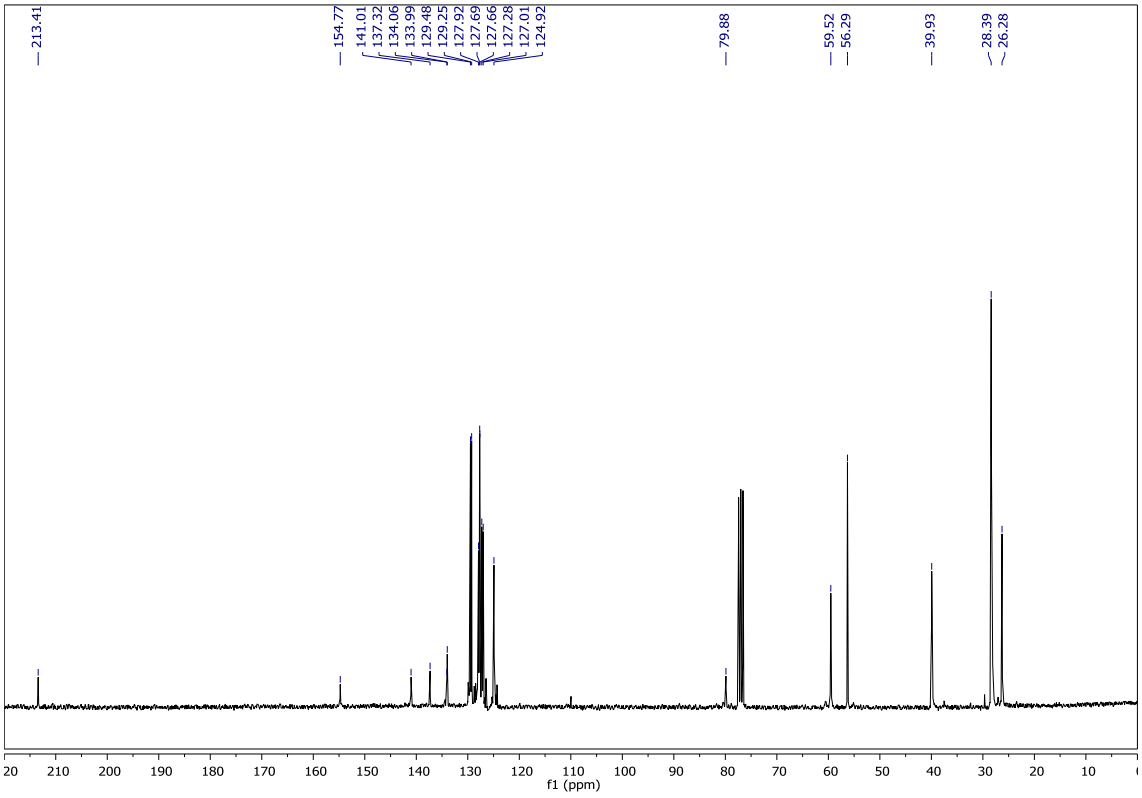
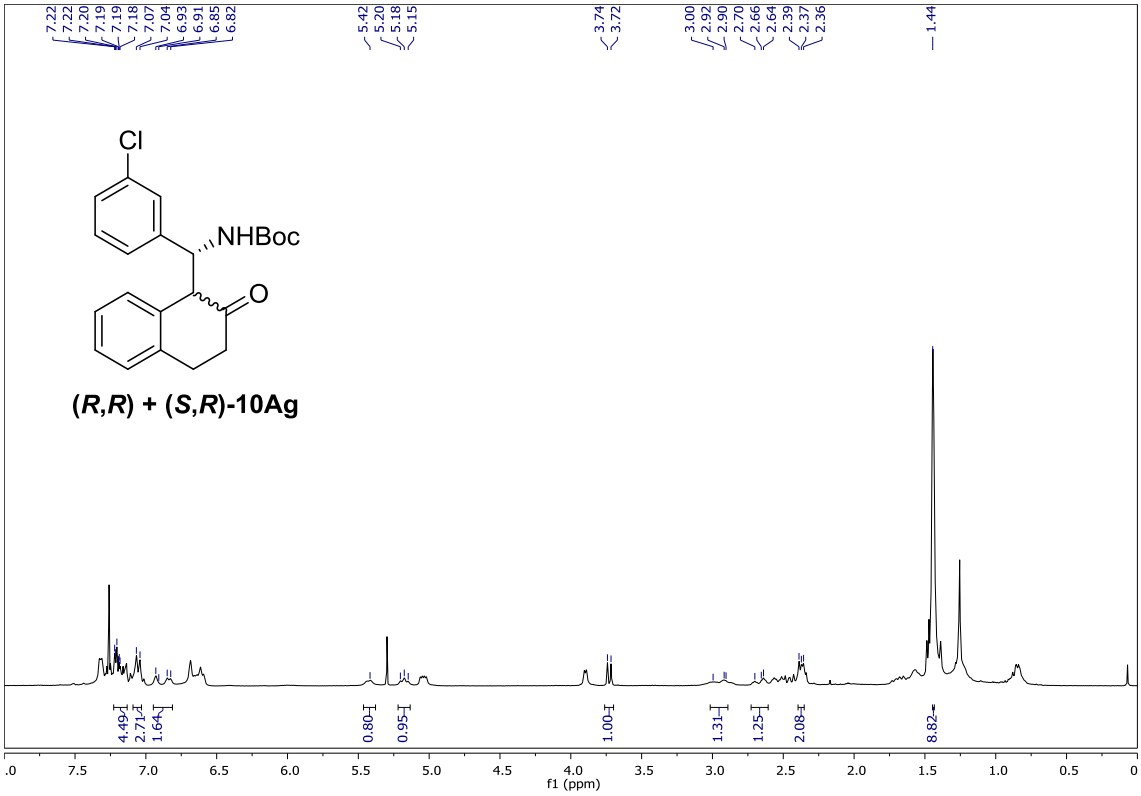
39.64
28.41
25.95
18.61
f1 (ppm)

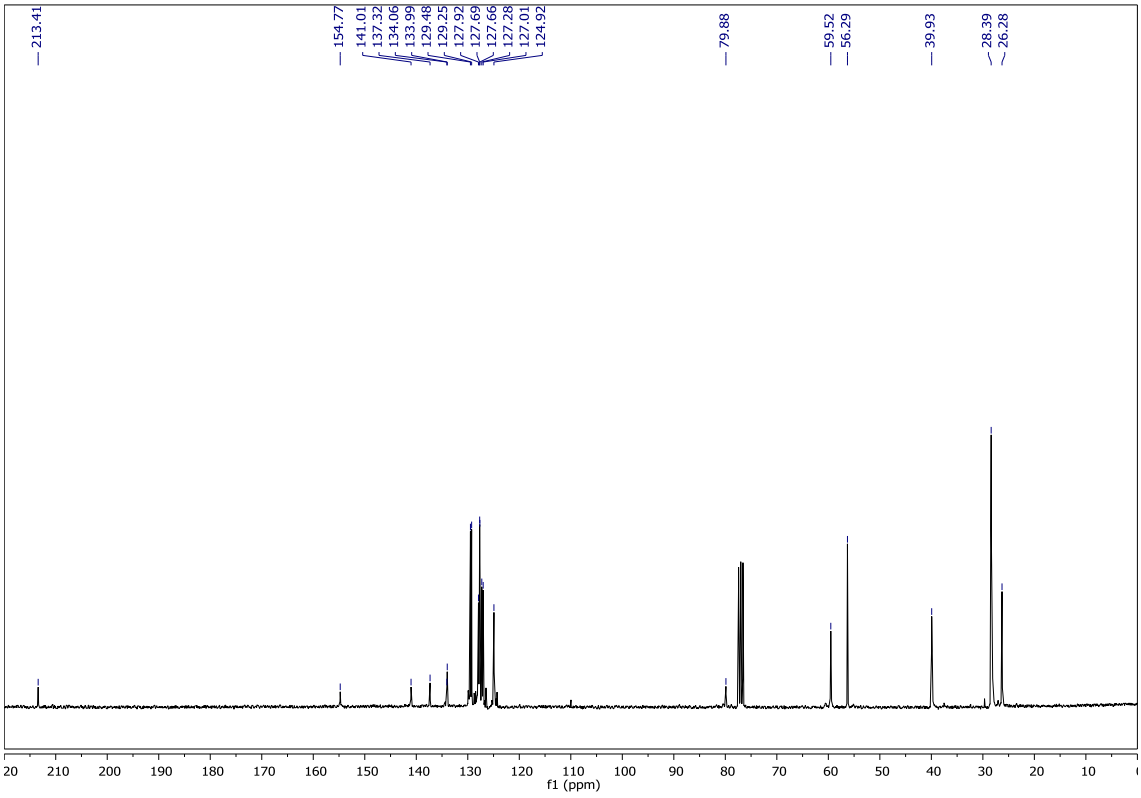

Me
NHBoc
O
(S,R)-10Af
f1 (ppm)


f1 (ppm)

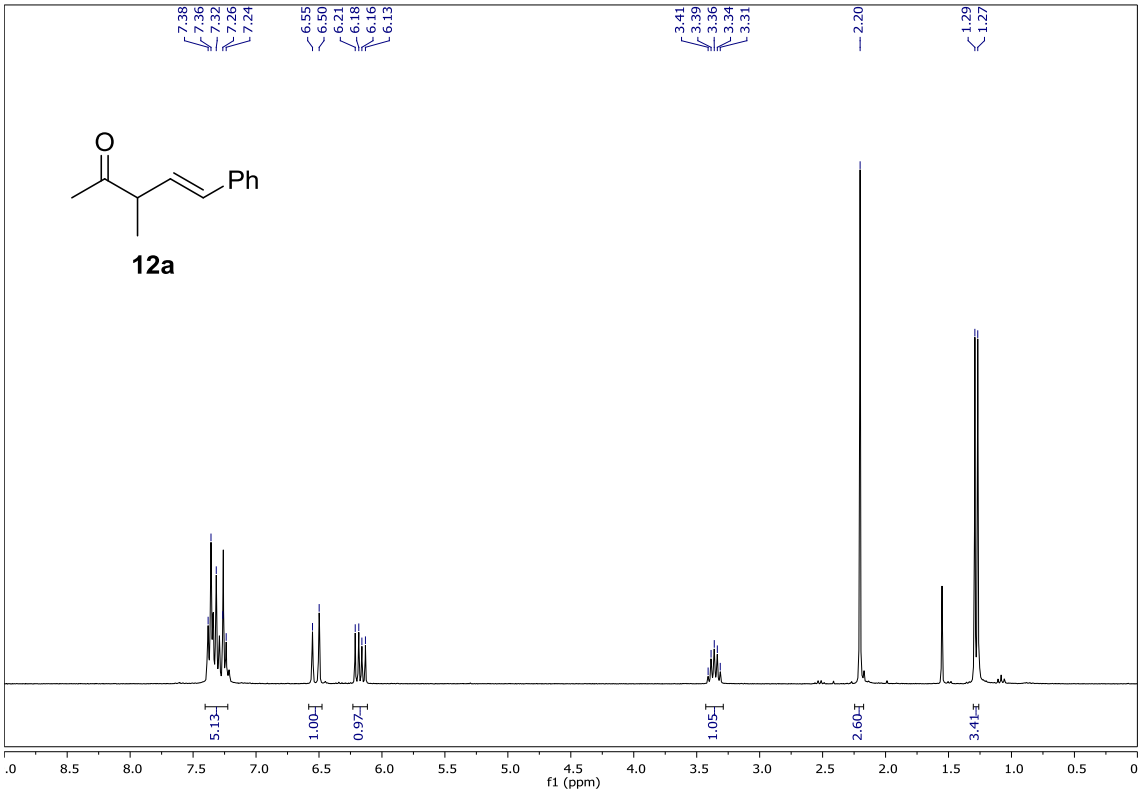

Cl
NHBoc
O
(R,R)-10Ag
f1 (ppm)

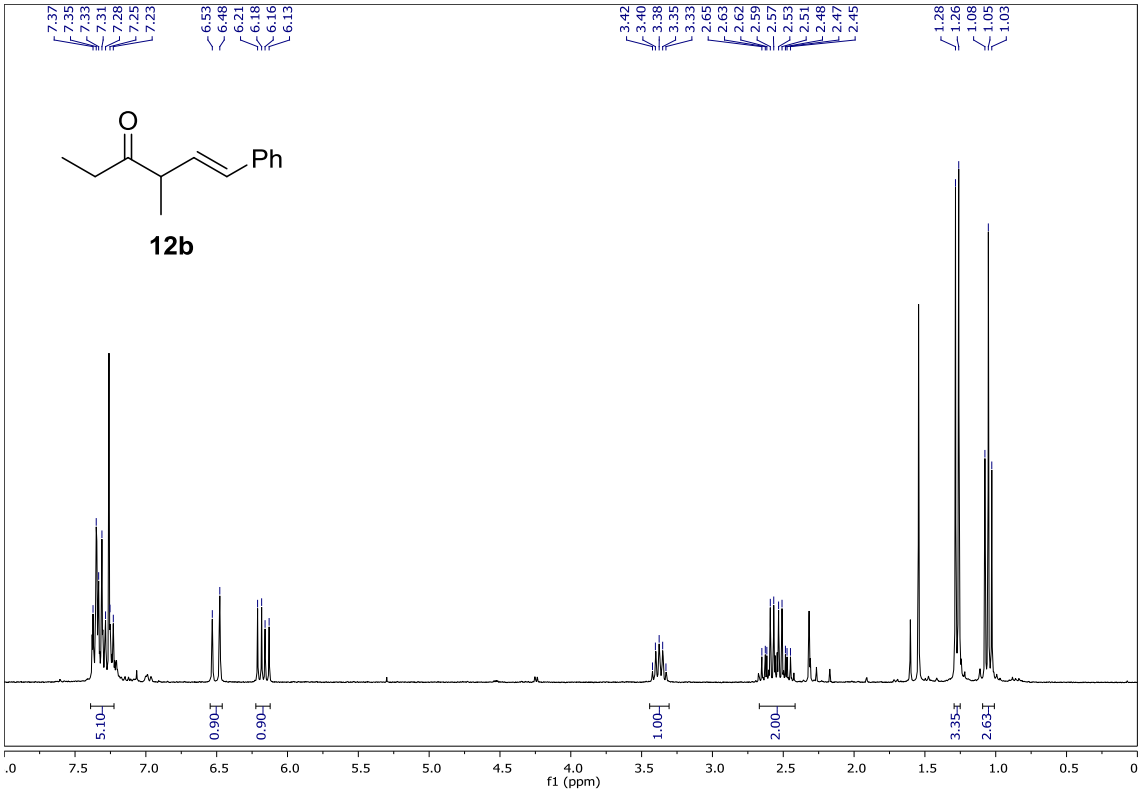

f1 (ppm)


7.22
7.22
7.20
7.19
7.19
7.18
7.07
7.04
6.93
6.91
6.85
6.82
5.42
5.20
5.18
5.15
3.74
3.72
3.00
2.92
2.90
2.70
2.66
2.64
2.39
2.37
2.36
1.44
Cl
NHBoc
O
(R,R) + (S,R)-10Ag
4.49
2.71
1.64
0.80
0.95
1.00
1.31
1.25
2.08
8.82
f1 (ppm)


213.41
154.77
141.01
137.32
134.06
133.99
129.48
129.25
127.92
127.69
127.66
127.28
127.01
124.92
79.88
59.52
56.29
39.93
28.39
26.28
f1 (ppm)

5.5.3. NMR spectra for Chapter 3

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7.35
7.33
7.31
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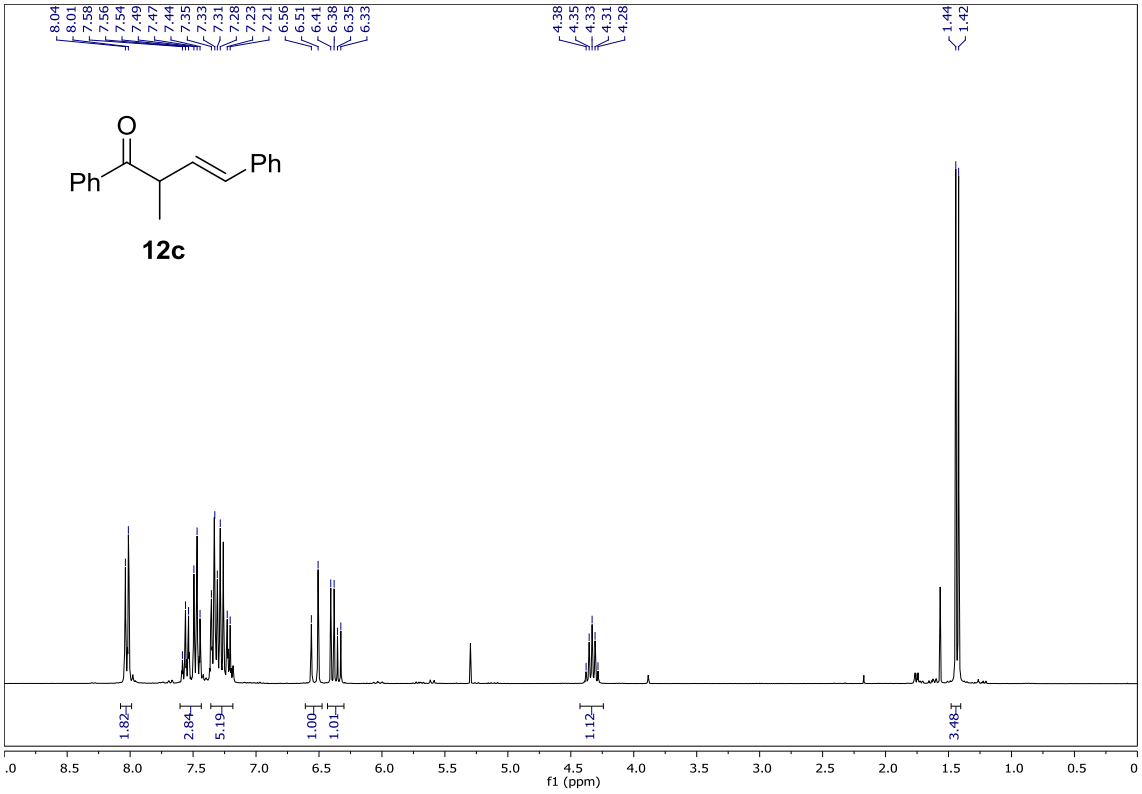
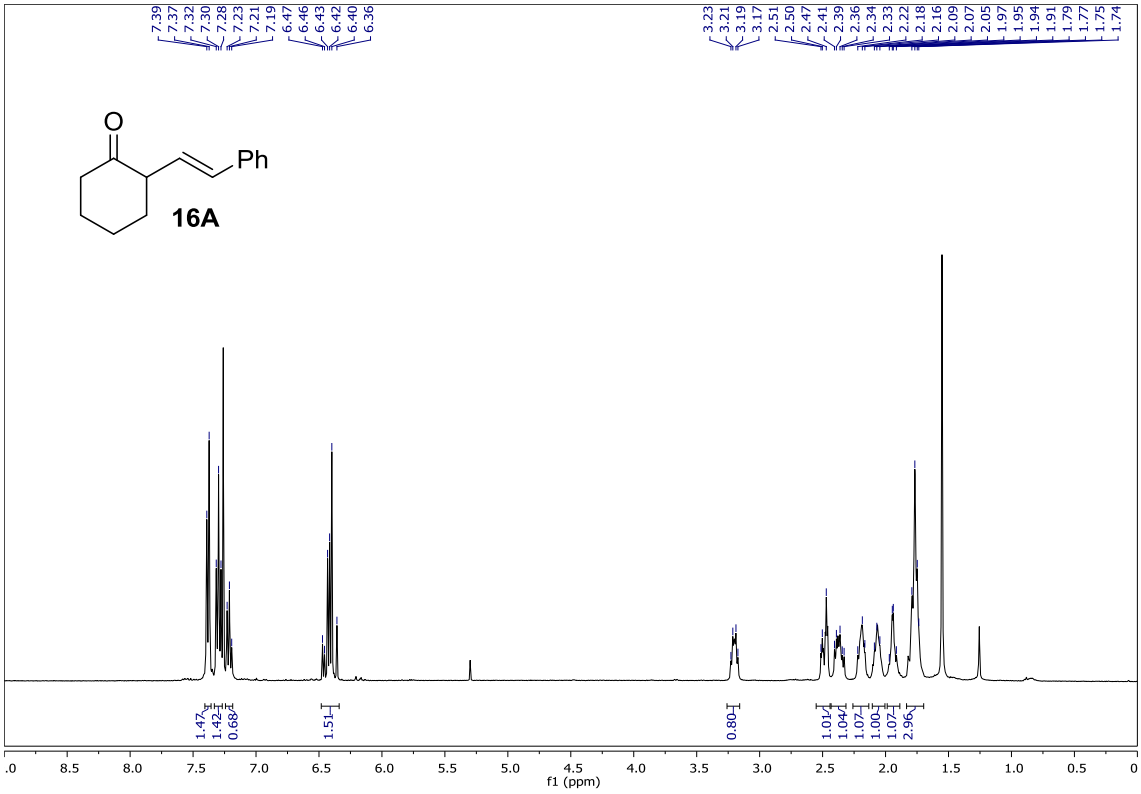
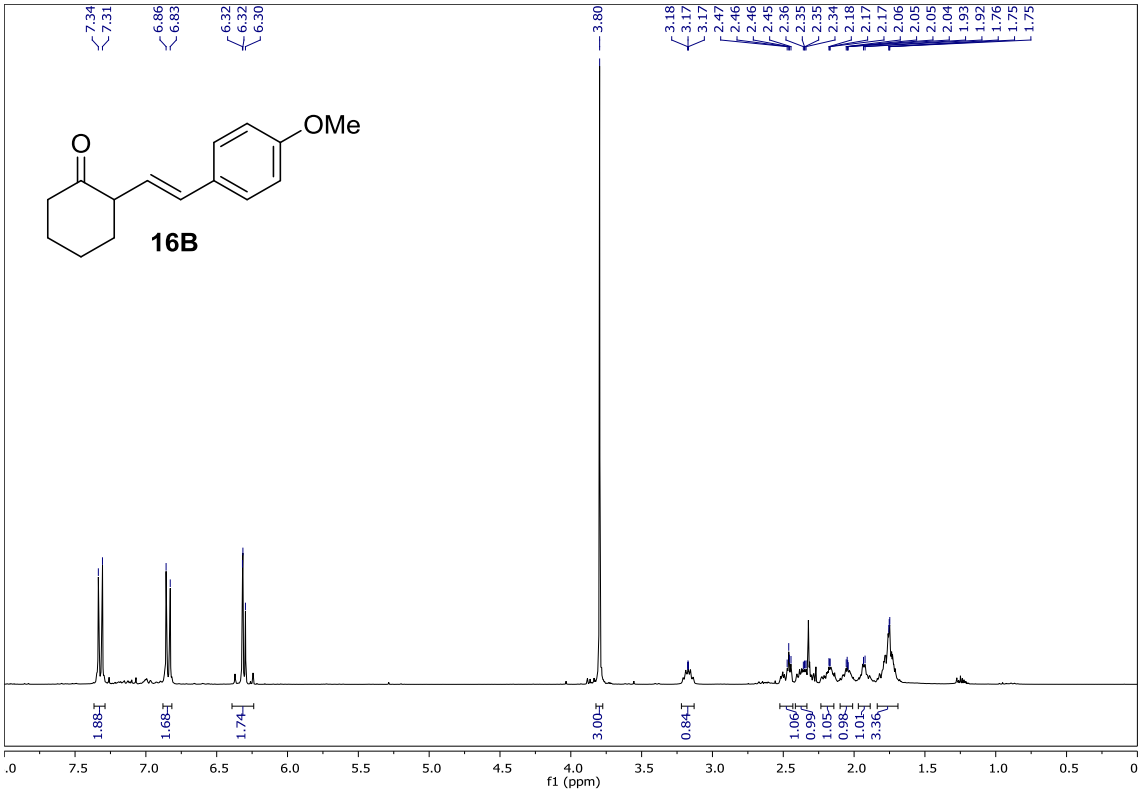
7.25
7.23
6.53
6.48
6.21
6.18
6.16
6.13
3.42
3.40
3.38
3.35
3.33
2.65
2.63
2.62
2.59
2.57
2.53
2.51
2.48
2.47
2.45
1.28
1.26
1.08
1.05
1.03
O
Ph
12b
5.10
0.90
0.90
1.00
2.00
3.35
2.63
f1 (ppm)


8.04
8.01
7.58
7.56
7.54
7.49
7.47
7.44
7.35
7.33
7.31
7.28
7.23
7.21
6.56
6.51
6.41
6.38
6.35
6.33
4.38
4.35
4.33
4.31
4.28
1.44
1.42
O
Ph
Ph
12c
1.82
2.84
5.19
1.00
1.01
1.12
3.48
f1 (ppm)


7.39
7.37
7.32
7.30
7.28
7.23
7.21
7.19
6.47
6.46
6.43
6.42
6.40
6.36
3.23
3.21
3.19
3.17
2.51
2.50
2.47
2.41
2.39
2.36
2.34
2.33
2.22
2.18
2.16
2.09
2.07
2.05
1.97
1.95
1.94
1.91
1.79
1.77
1.75
1.74
O
Ph
16A
1.47
1.42
0.68
1.51
0.80
1.01
1.04
1.07
1.00
1.07
2.96
f1 (ppm)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7.31
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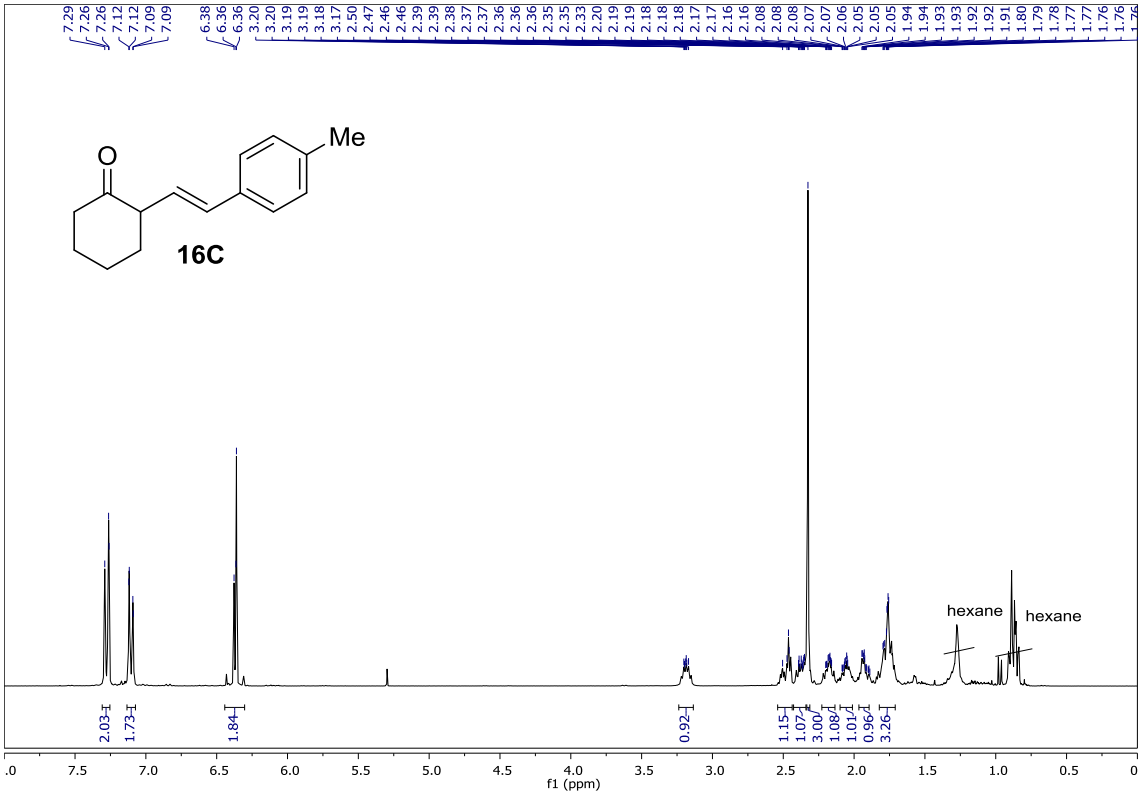
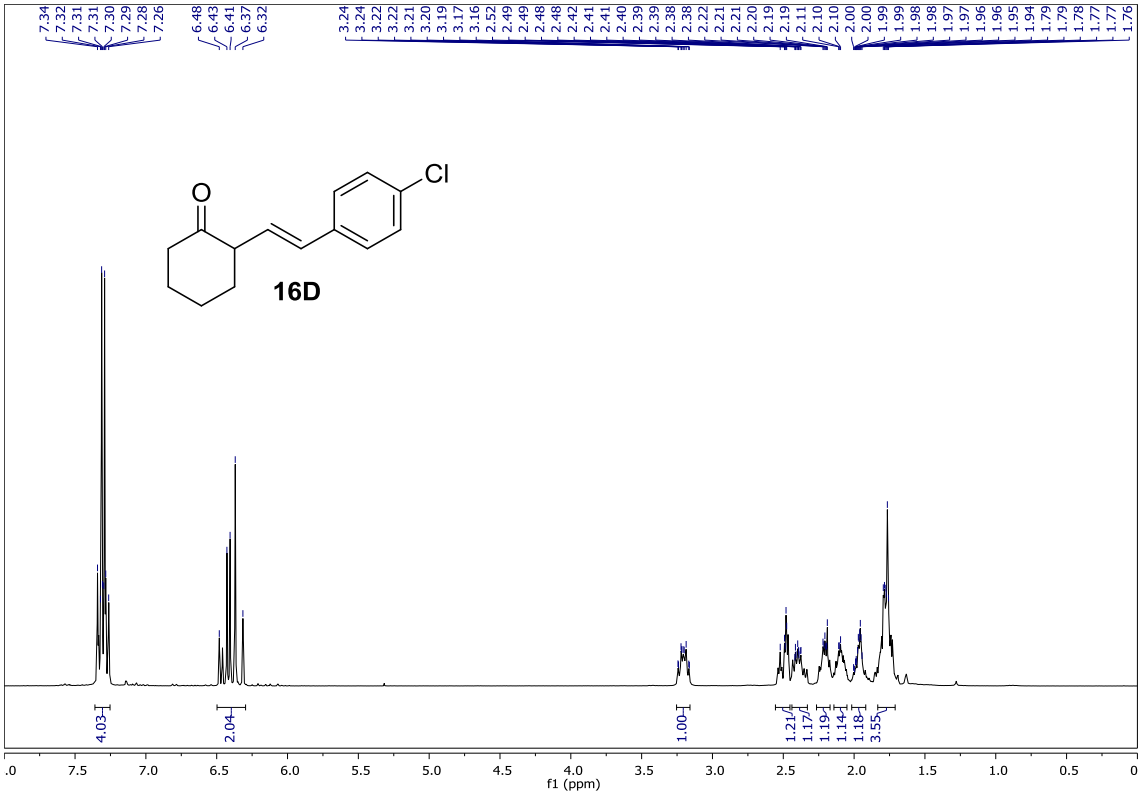
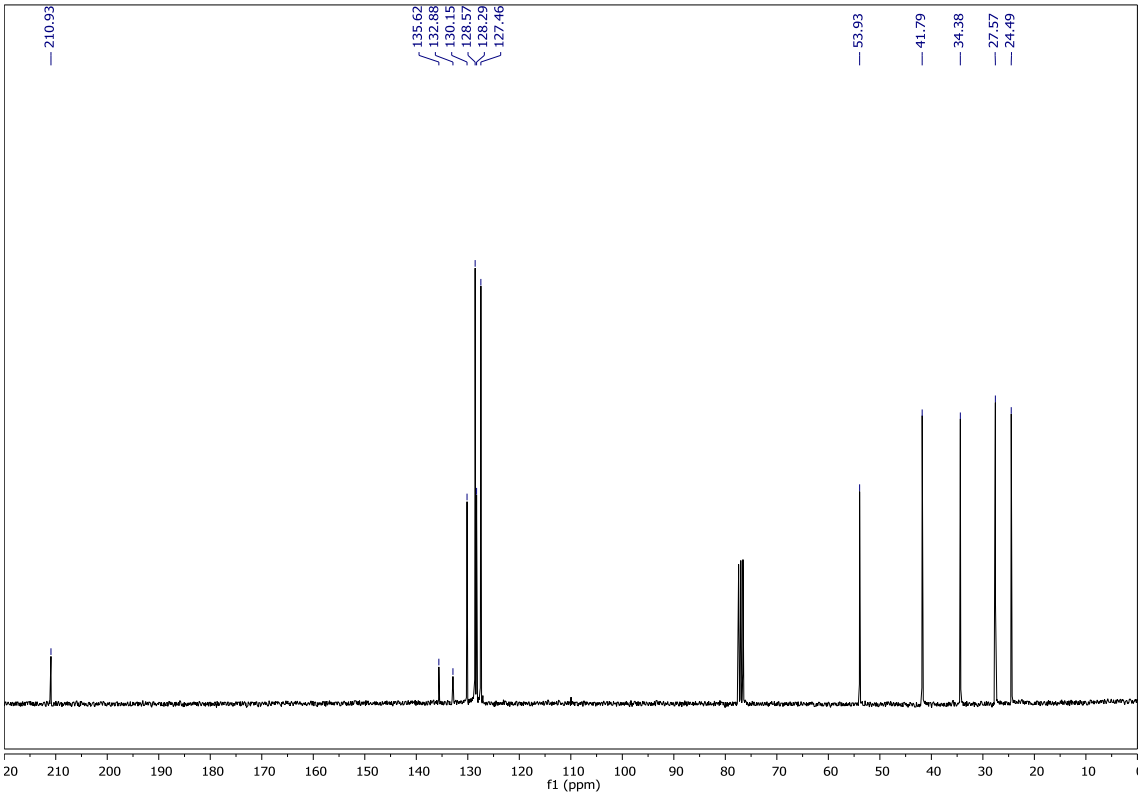
6.32
6.30
3.80
3.18
3.17
3.17
2.47
2.46
2.46
2.45
2.36
2.35
2.35
2.34
2.18
2.17
2.17
2.06
2.05
2.05
2.04
1.93
1.92
1.76
1.75
1.75
O
OMe
16B
1.88
1.68
1.74
3.00
0.84
1.06
0.99
1.05
0.98
1.01
3.36
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


O
Me
16C
hexane
hexane
f1 (ppm)


O
Cl
16D
f1 (ppm)


210.93
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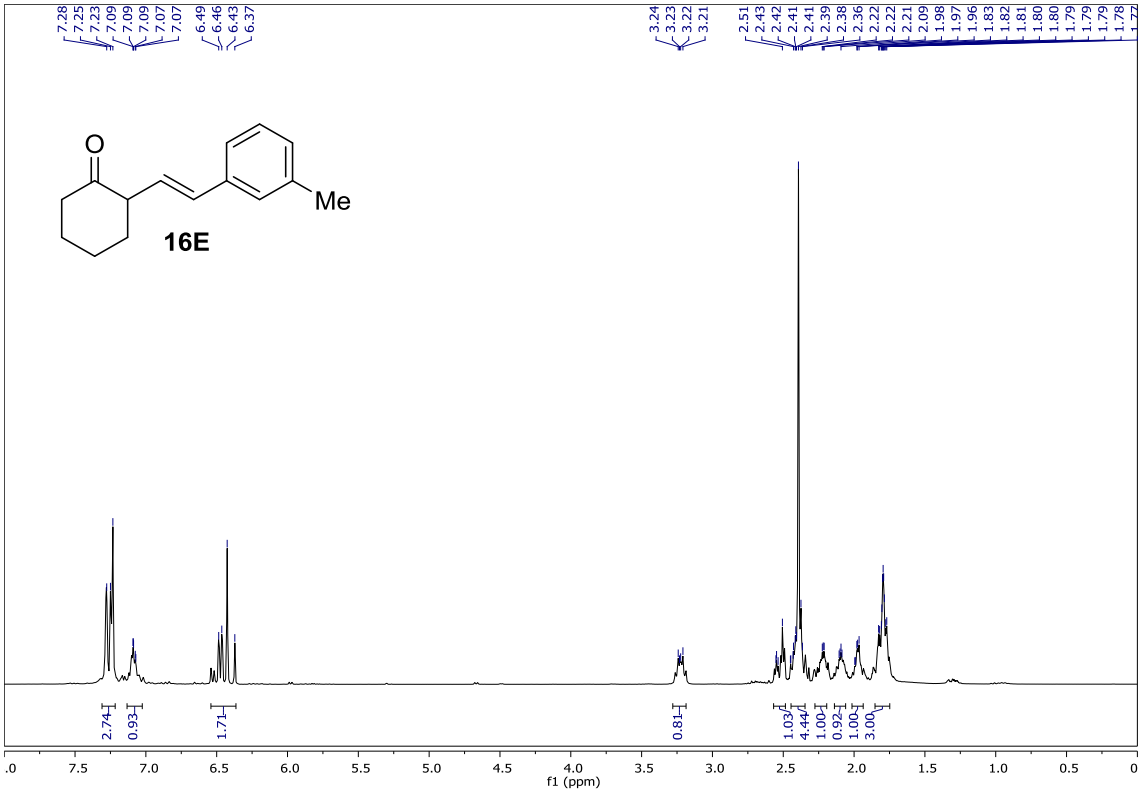
128.57
128.29
127.46
53.93
41.79
34.38
27.57
24.49
f1 (ppm)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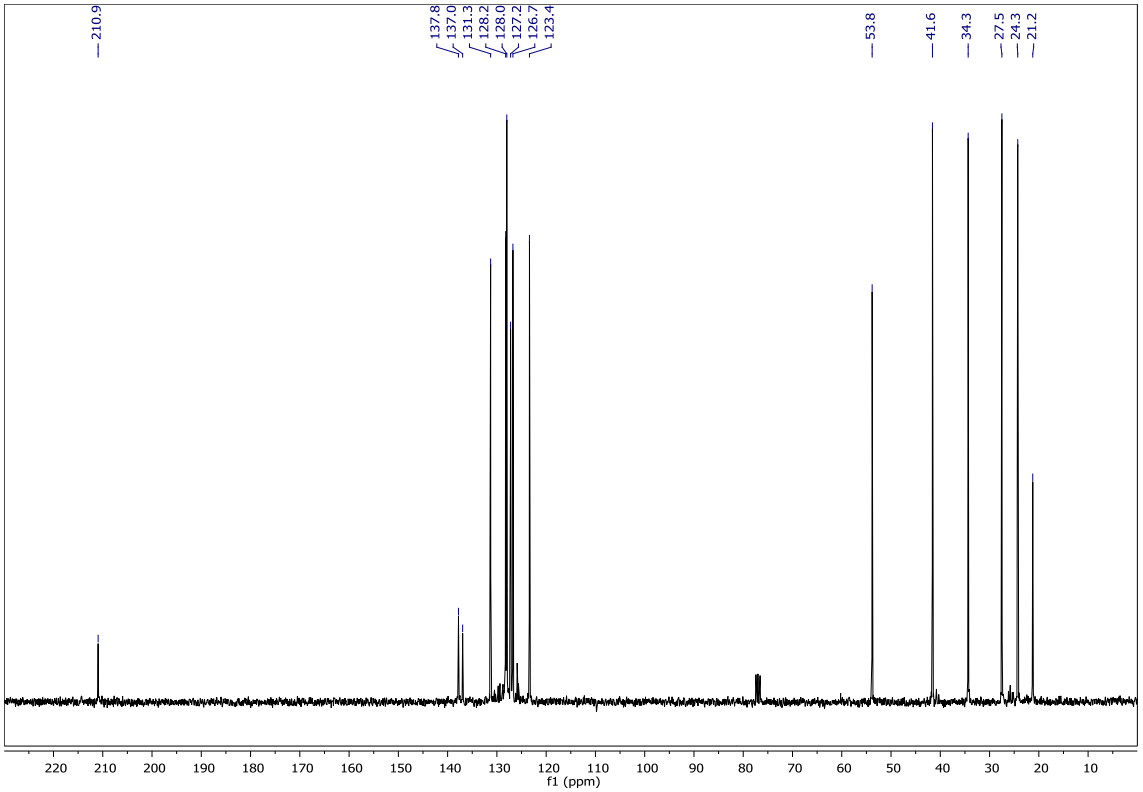
7.09
7.09
7.07
7.07
6.49
6.46
6.43
6.37
3.24
3.23
3.22
3.21
2.51
2.43
2.42
2.41
2.41
2.39
2.38
2.36
2.22
2.22
2.21
2.09
1.98
1.97
1.96
1.83
1.82
1.81
1.80
1.80
1.79
1.79
1.79
1.78
O
Me
16E
2.74
0.93
1.71
0.81
1.03
4.44
1.00
0.92
1.00
3.00
f1 (ppm)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126.7
123.4
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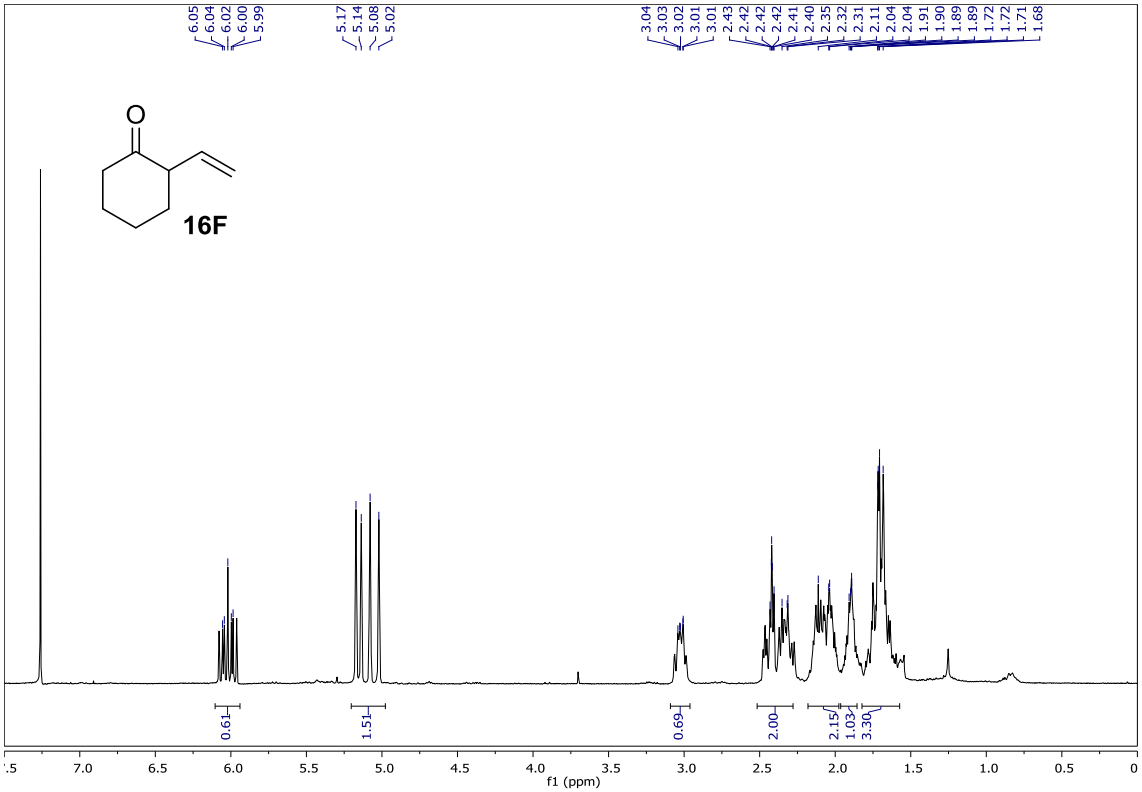
41.6
34.3
27.5
24.3
21.2
f1 (ppm)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6.02
6.00
5.99
5.17
5.14
5.08
5.02
3.04
3.03
3.02
3.01
3.01
2.43
2.42
2.42
2.42
2.41
2.40
2.35
2.32
2.31
2.11
2.04
2.04
1.91
1.90
1.89
1.89
1.72
1.72
1.71
1.68
O
16F
0.61
1.51
0.69
2.00
2.15
1.03
3.30
7.0
6.5
6.0
5.5
5.0
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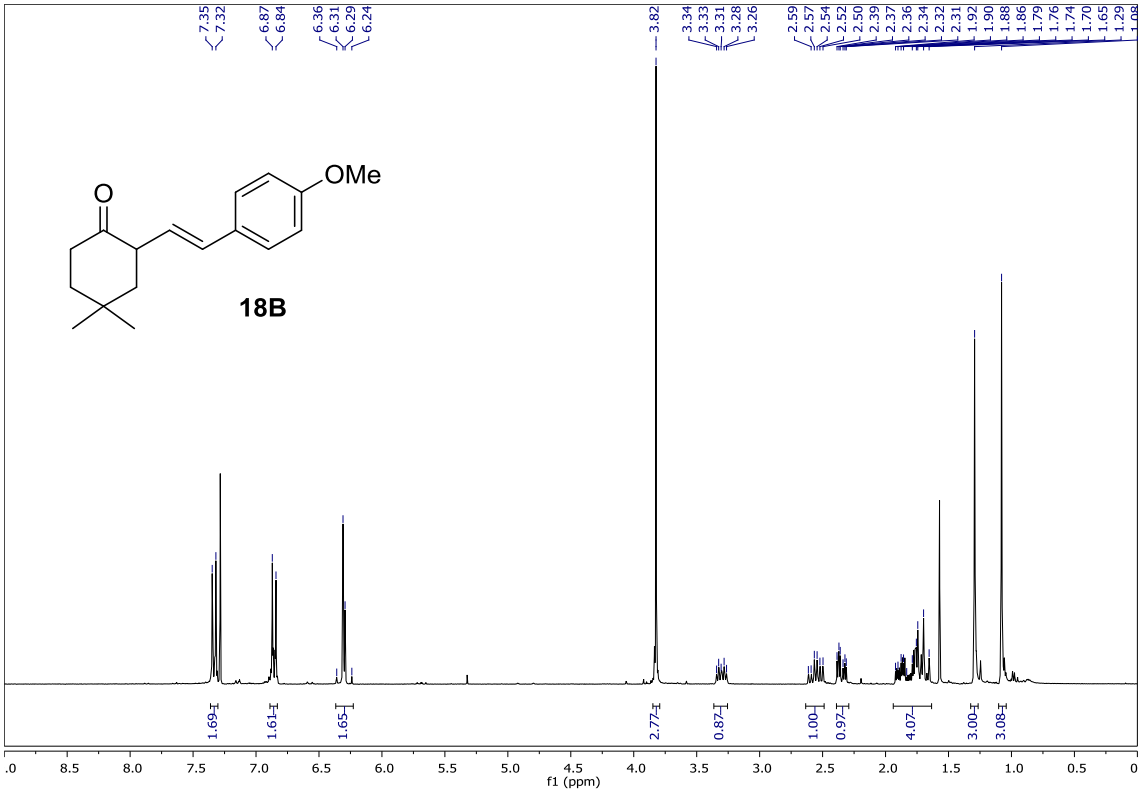
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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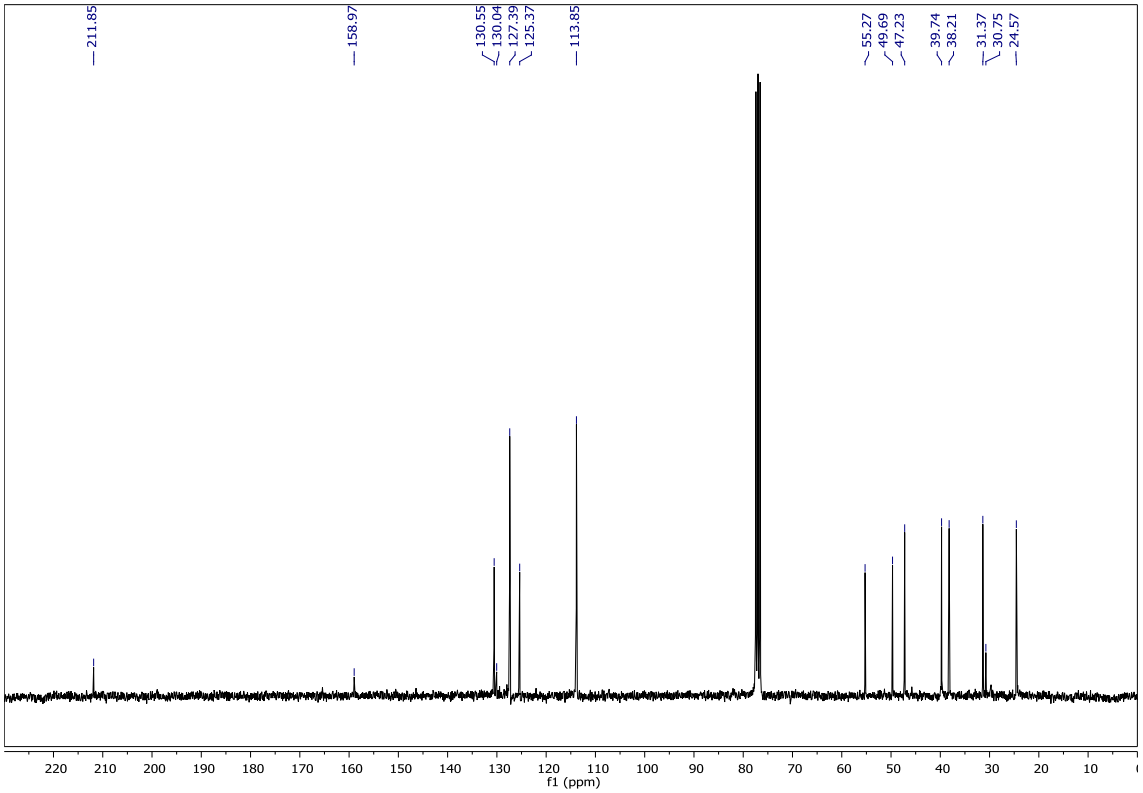
6.31
6.29
6.24
3.82
3.34
3.33
3.31
3.28
3.26
2.59
2.57
2.54
2.52
2.50
2.39
2.37
2.36
2.34
2.32
2.31
1.92
1.90
1.88
1.86
1.79
1.76
1.74
1.70
1.65
1.29
O
OMe
18B
1.69
1.61
1.65
2.77
0.87
1.00
0.97
4.07
3.00
3.08
f1 (ppm)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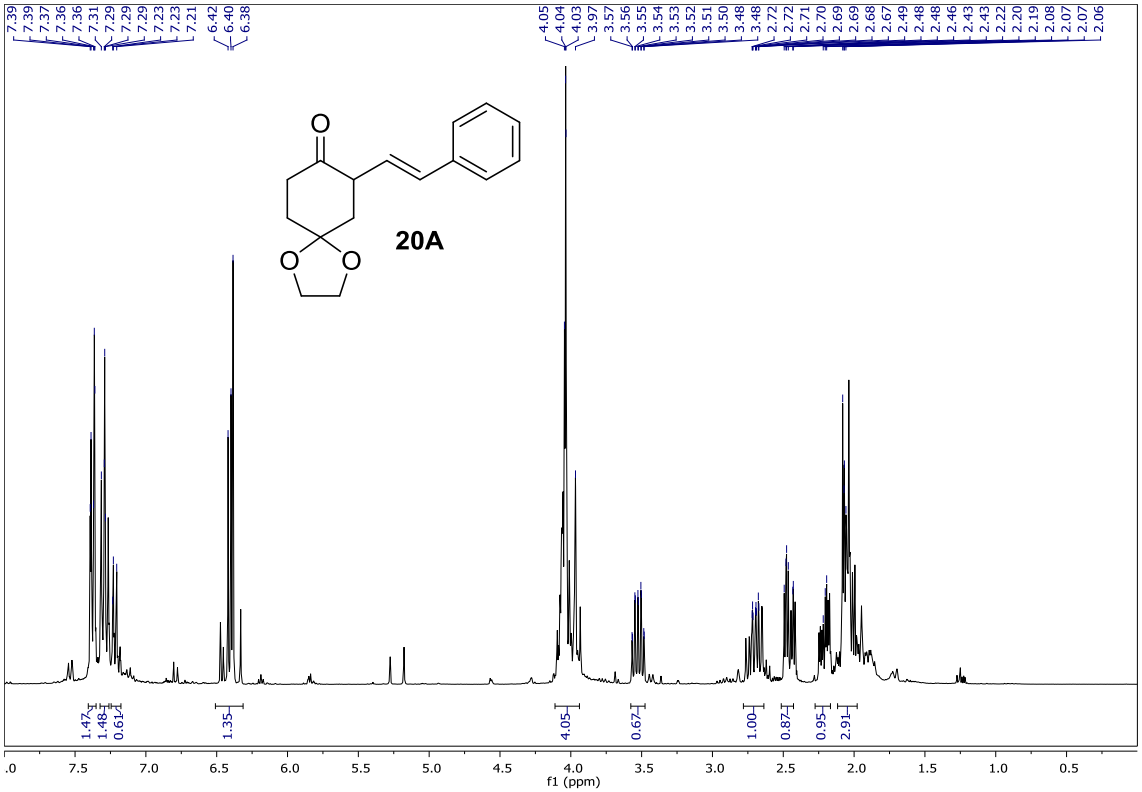
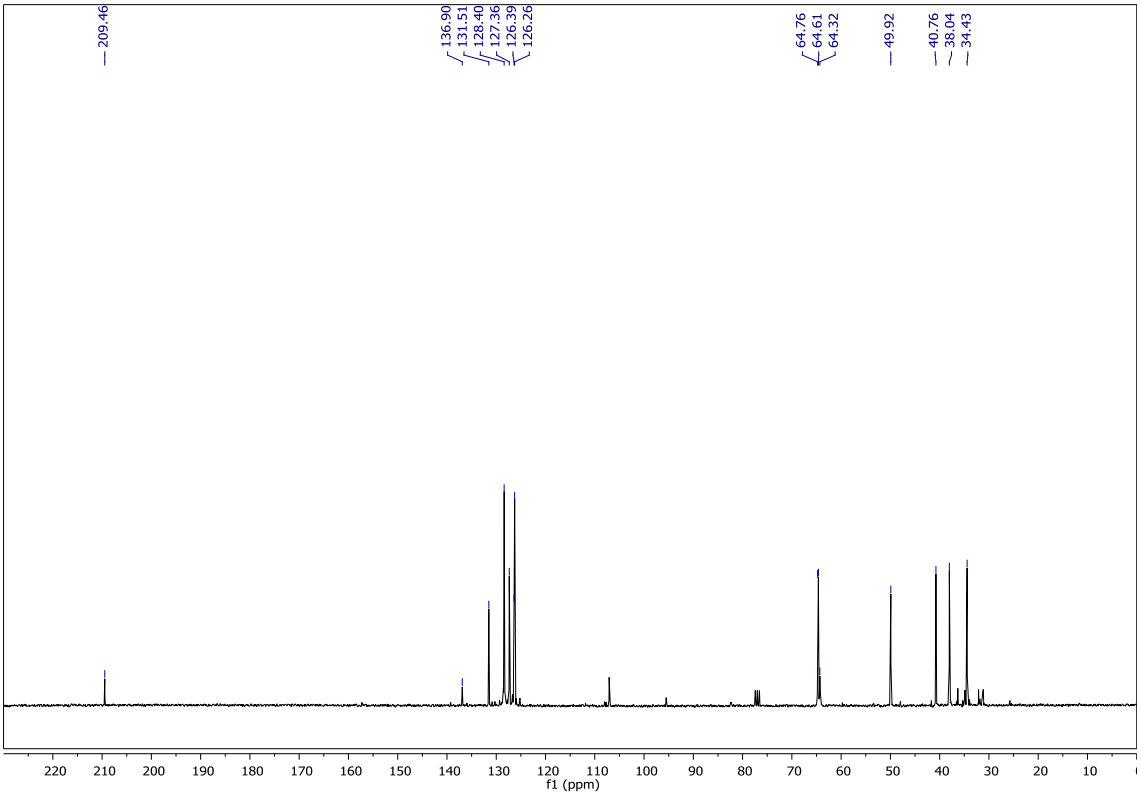
130.04
127.39
125.37
113.85
55.27
49.69
47.23
39.74
38.21
31.37
30.75
24.57
f1 (ppm)


20A
f1 (ppm)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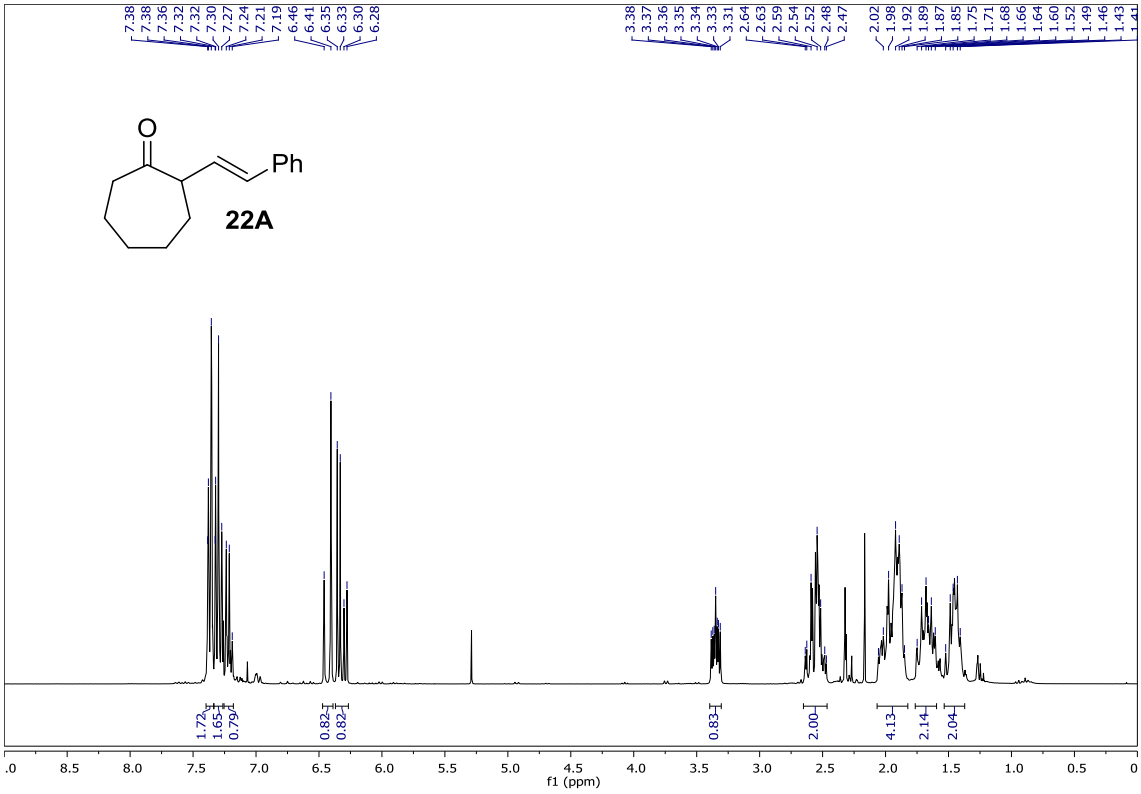
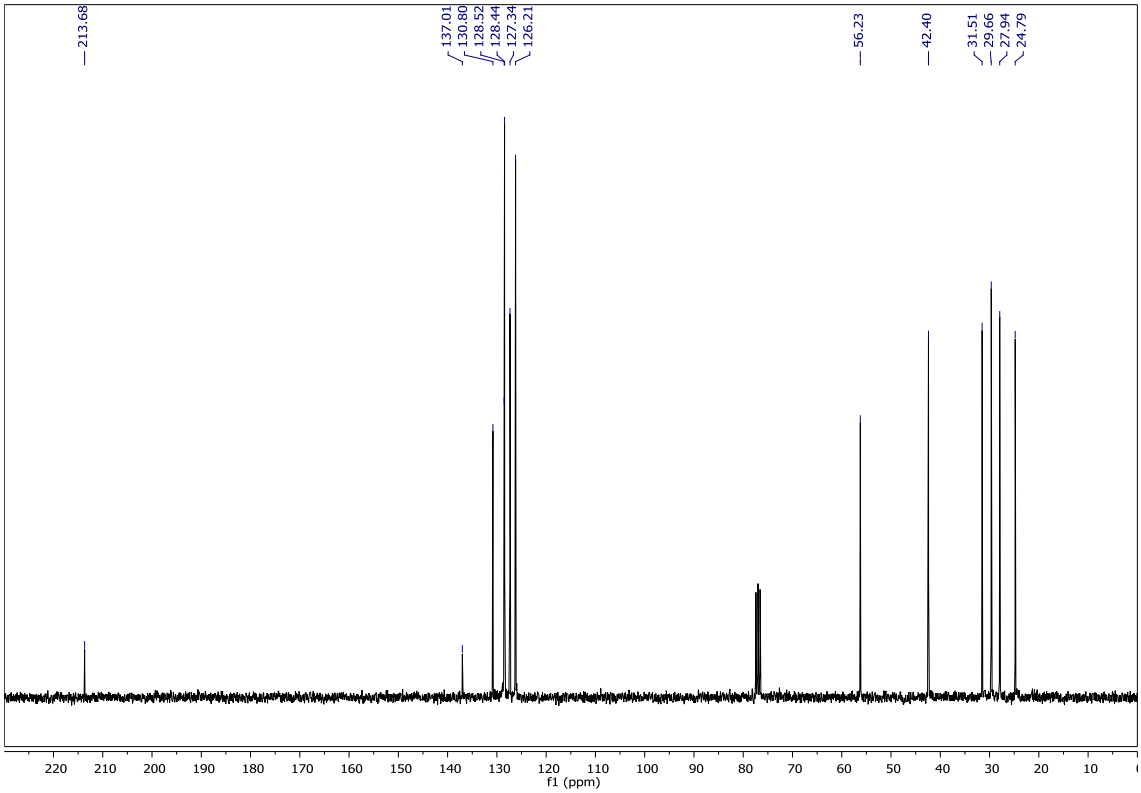

O
Ph
22A
f1 (ppm)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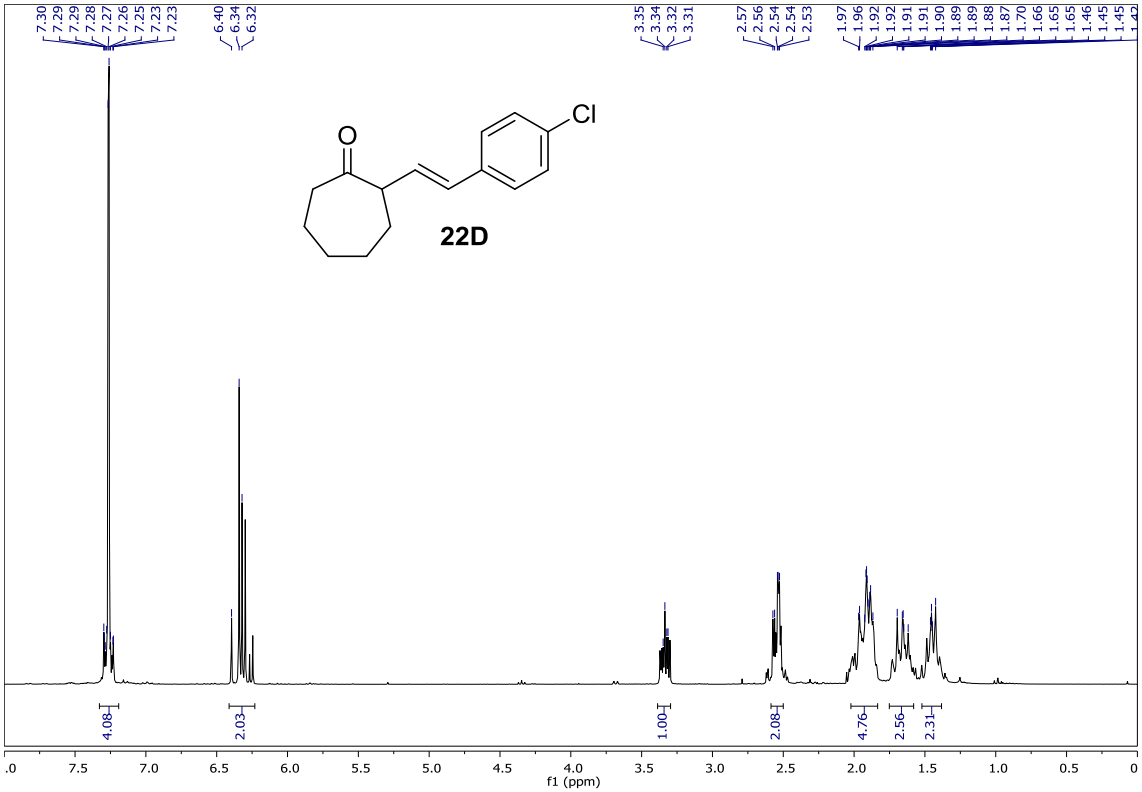
127.34
126.21
56.23
42.40
31.51
29.66
27.94
24.79
f1 (ppm)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3.32
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1.96
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1.92
1.91
1.91
1.90
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1.89
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1.65
1.46
1.45
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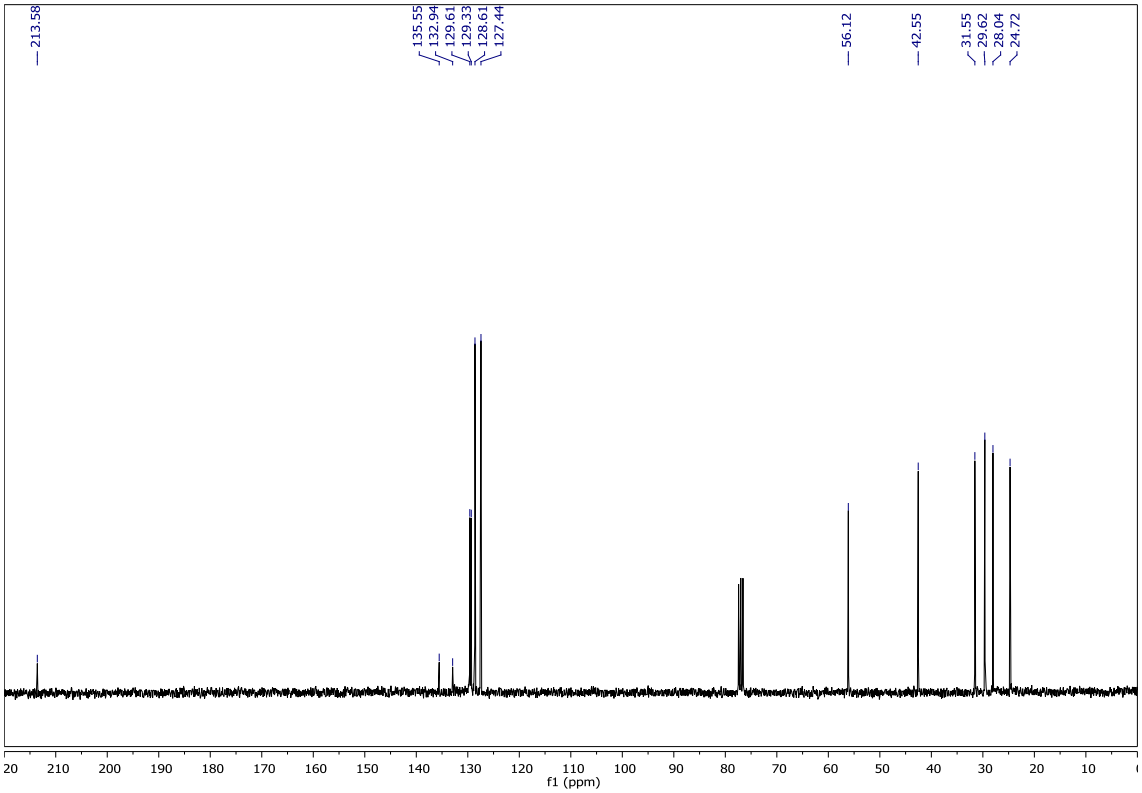
f1 (ppm)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29.62
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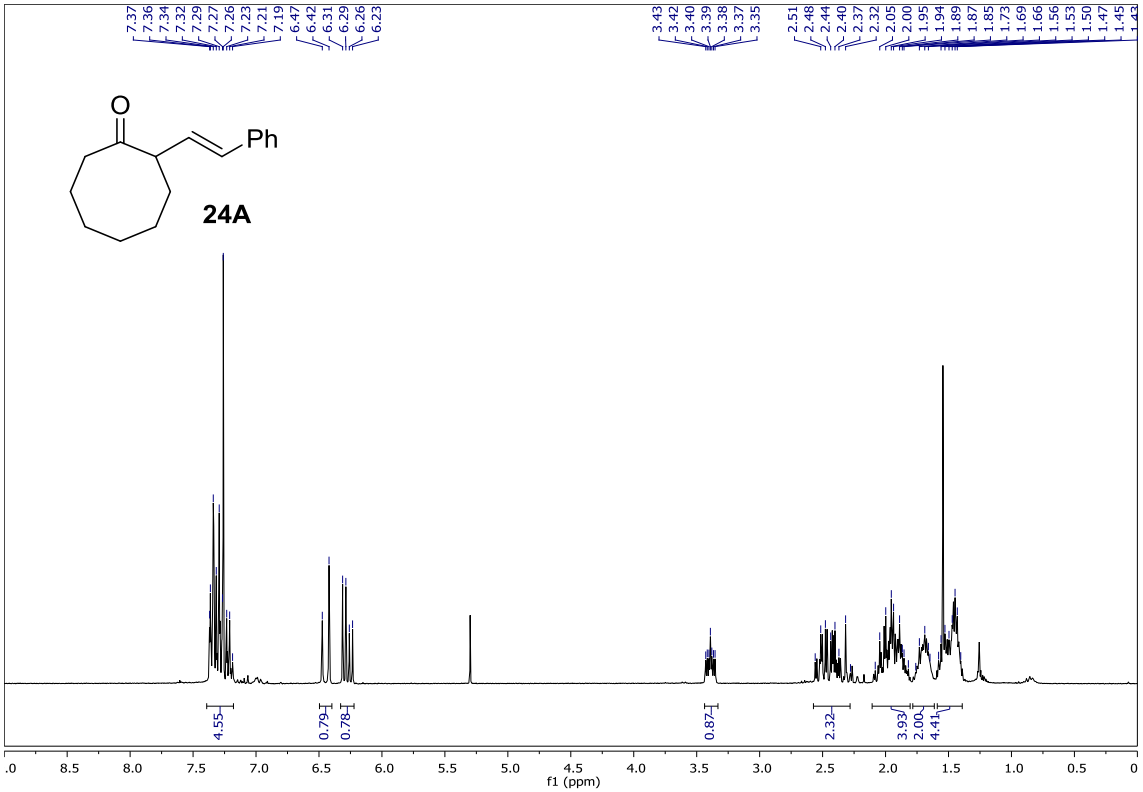
24.72
f1 (ppm)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Ph
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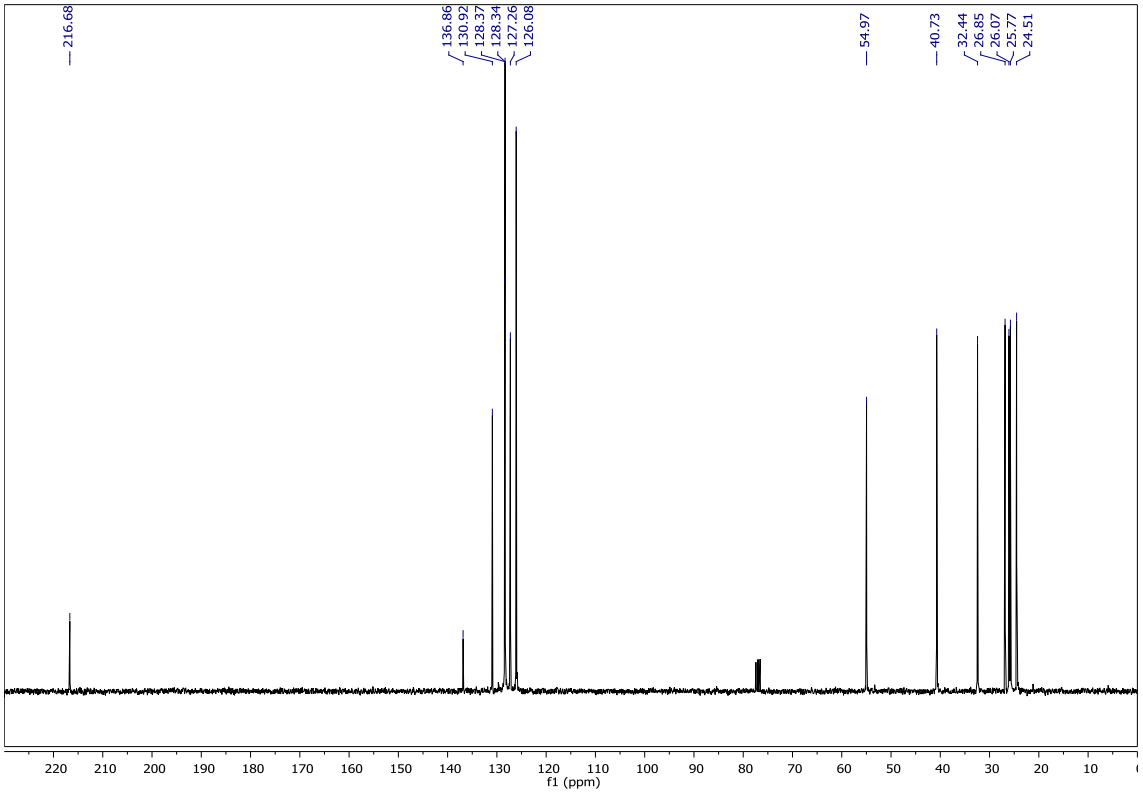
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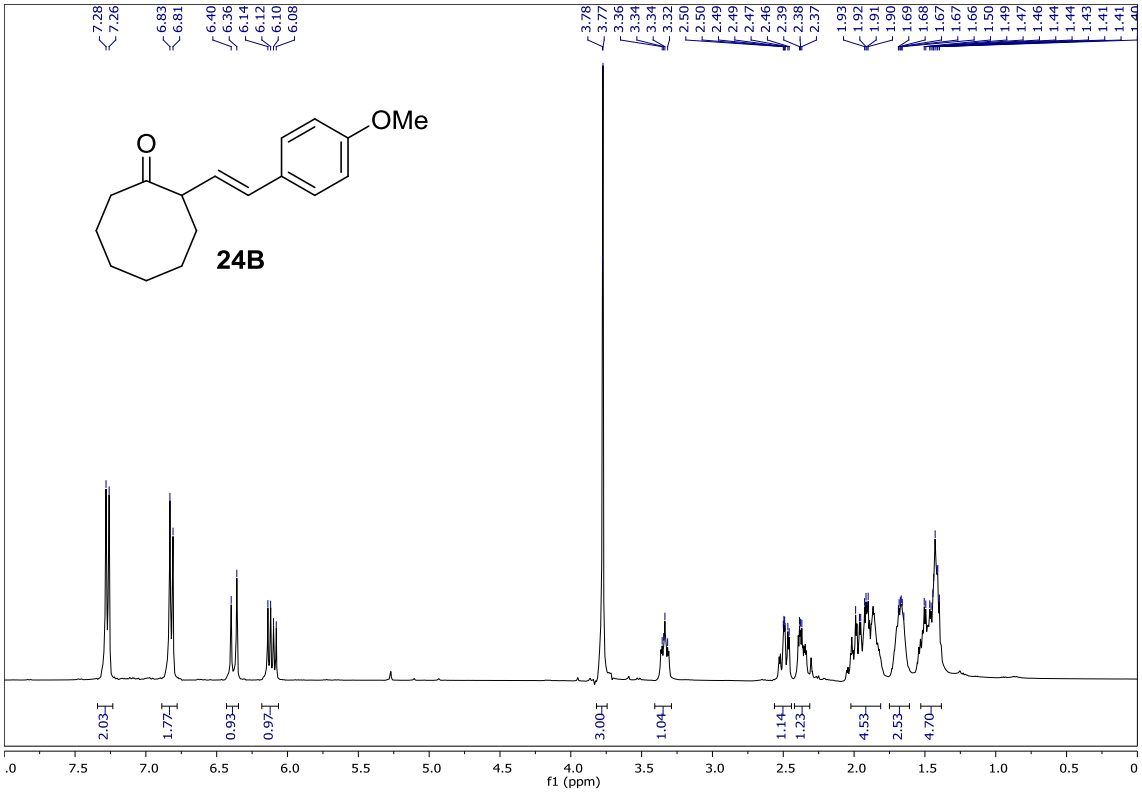
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1.44
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1.41
1.41
1.40
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OMe
24B
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4.70
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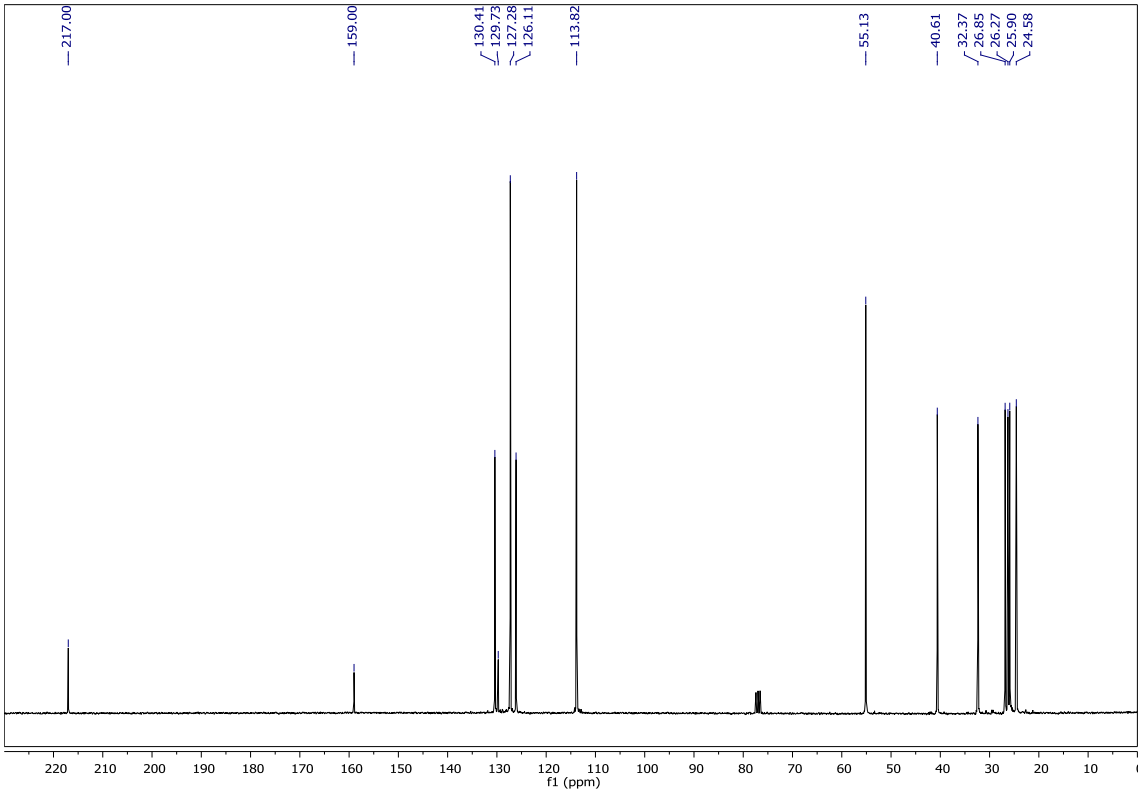
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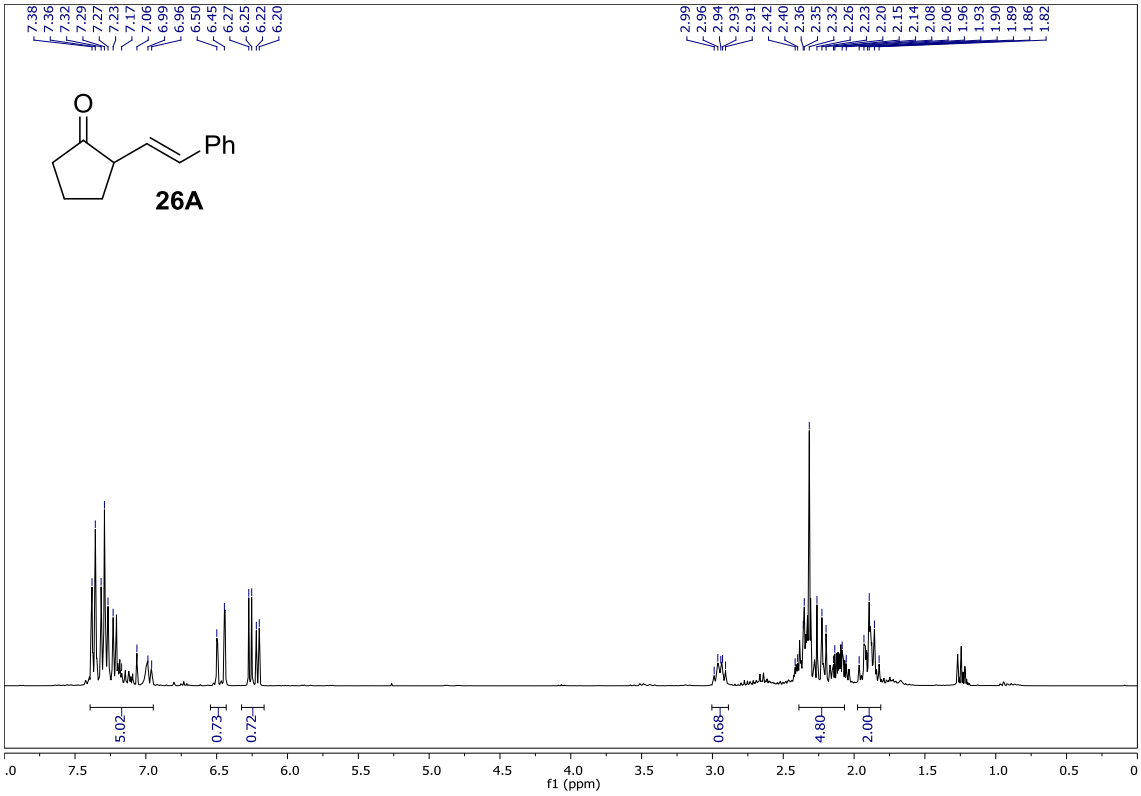
24.58
f1 (ppm)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2.08
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Ph
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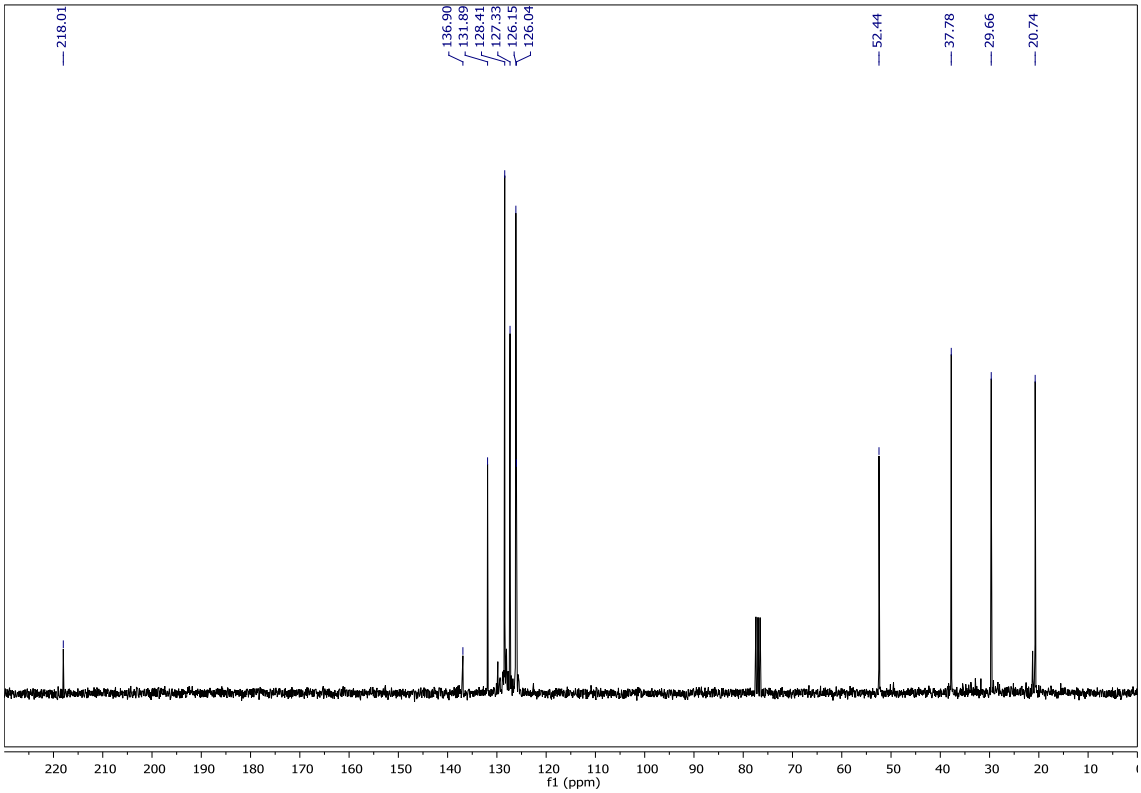
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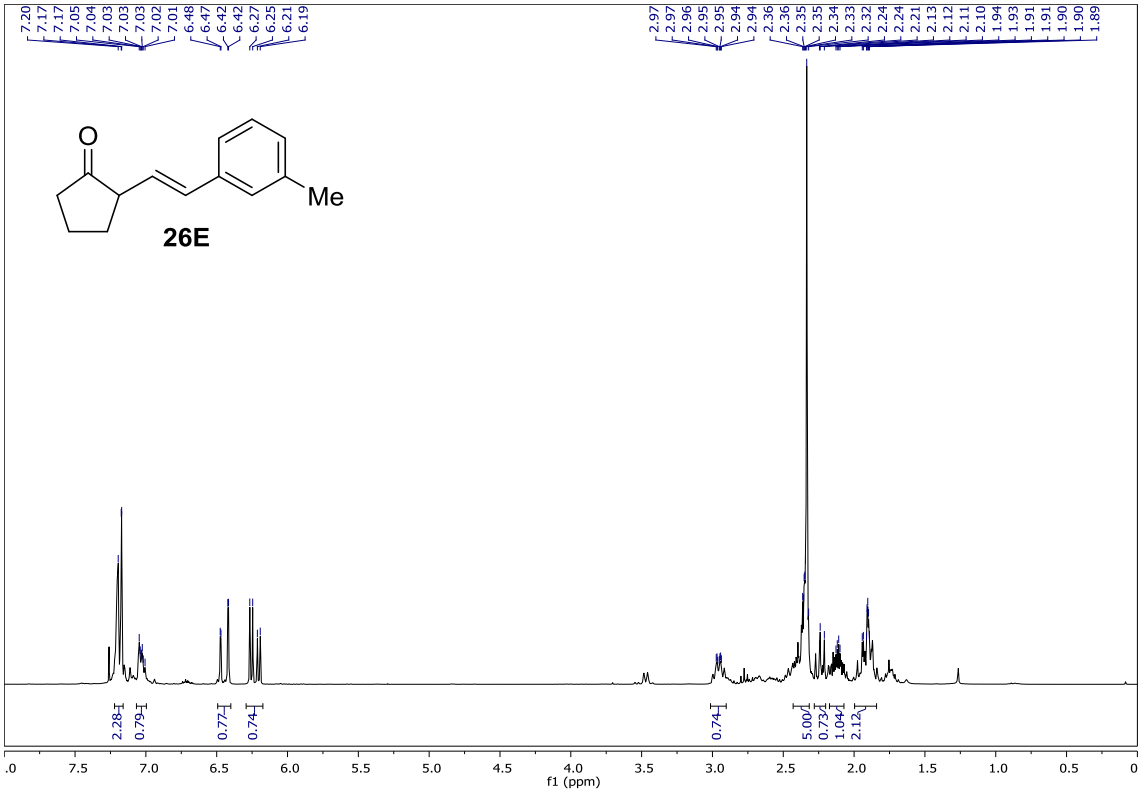
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2.94
2.94
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2.12
2.11
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1.94
1.93
1.91
1.91
1.90
1.90
1.90
1.89
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0.74
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0.73
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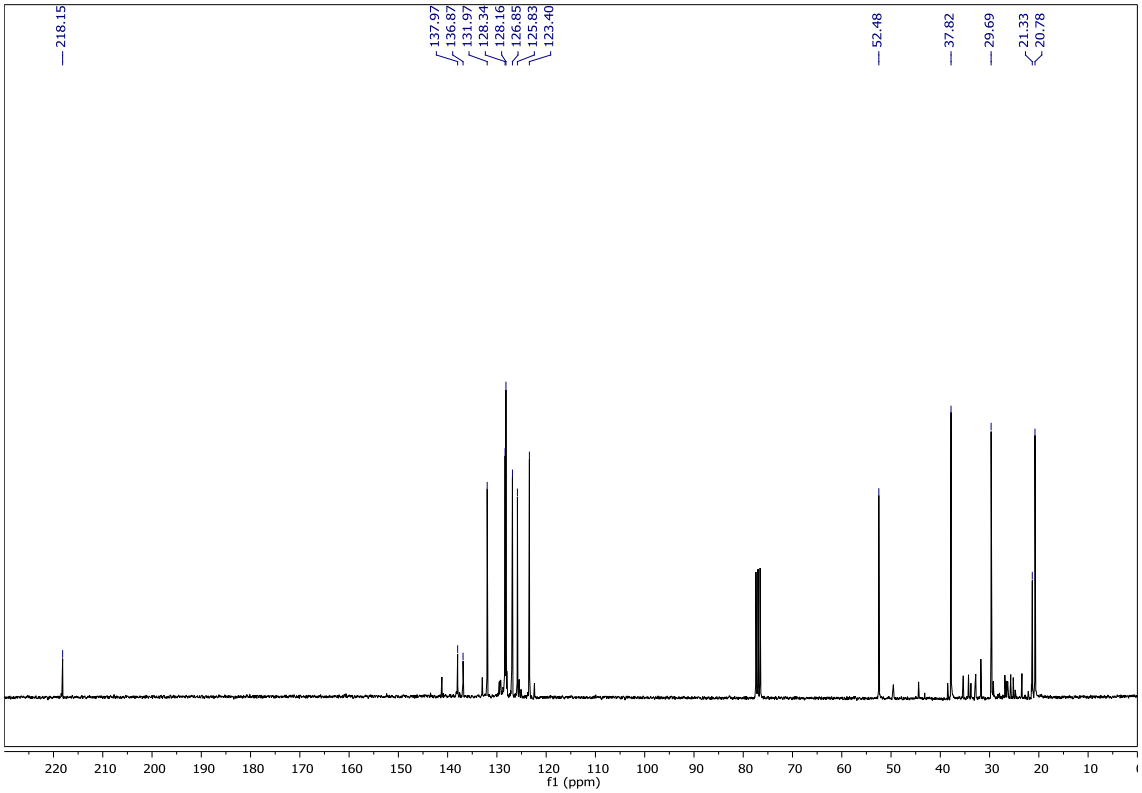
2.12
f1 (ppm)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37.82
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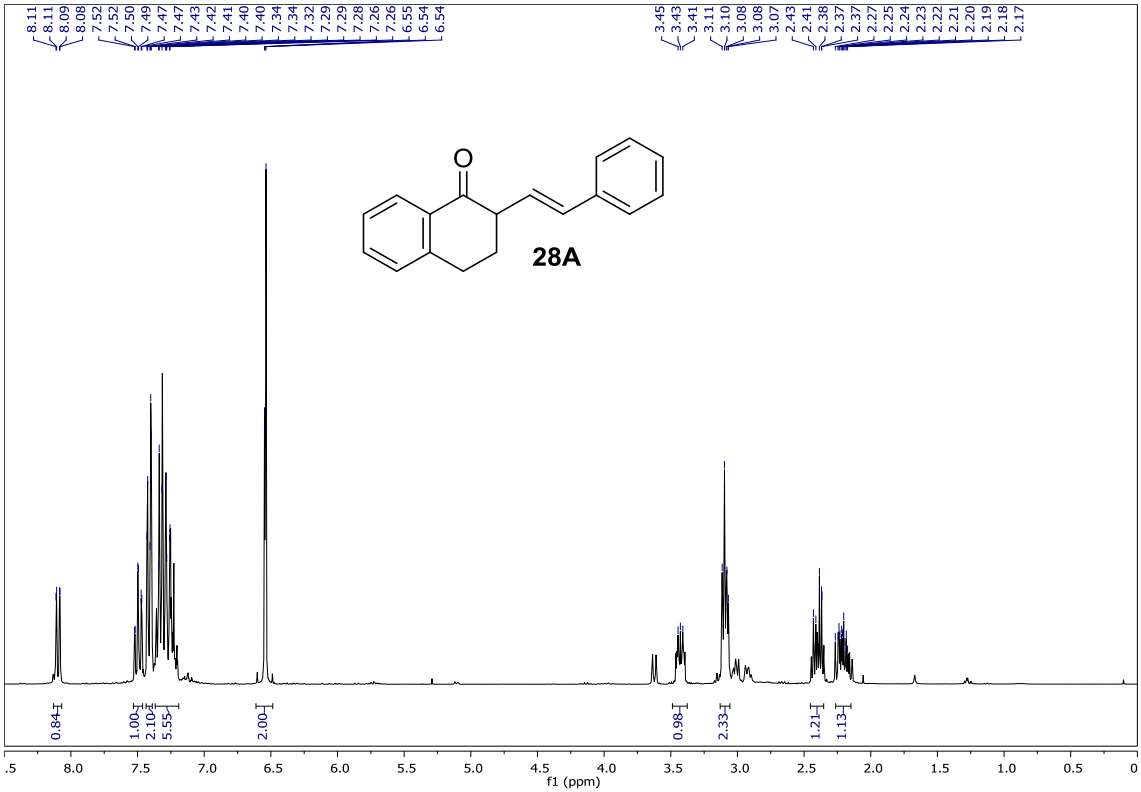
21.33
20.78
f1 (ppm)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2.37
2.27
2.25
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2.23
2.22
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2.20
2.19
2.18
2.17
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1.13
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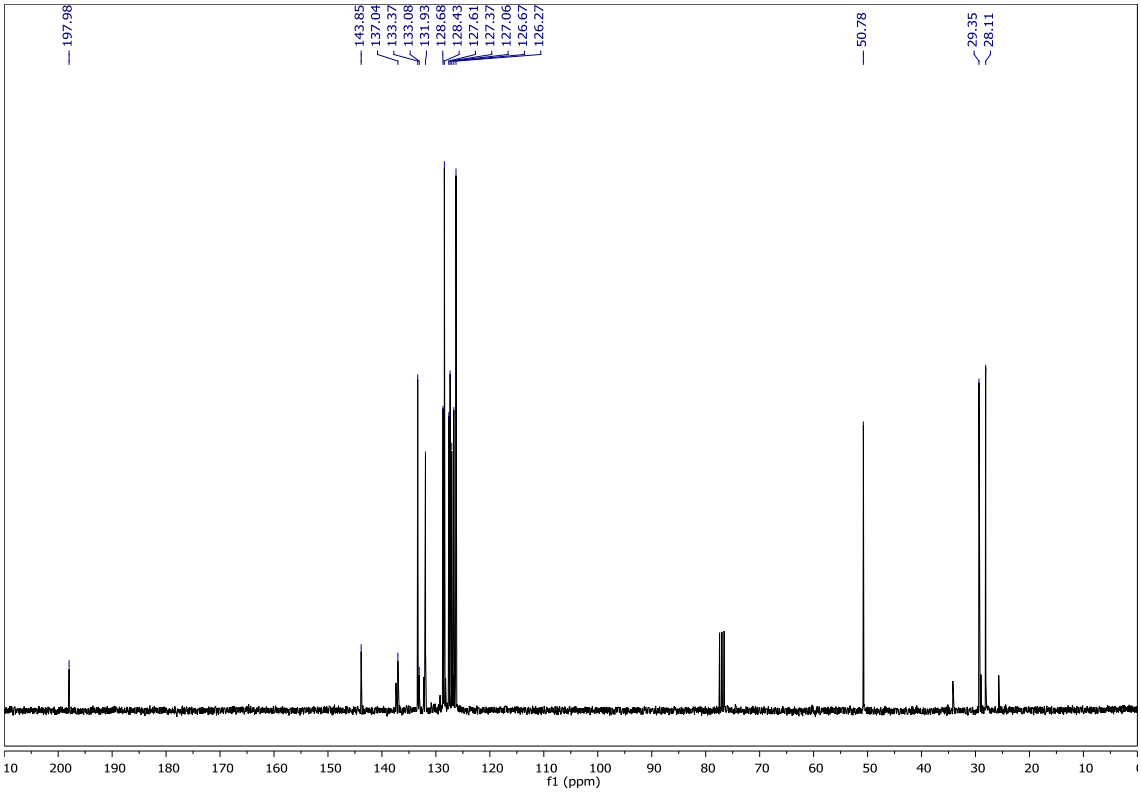
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126.27
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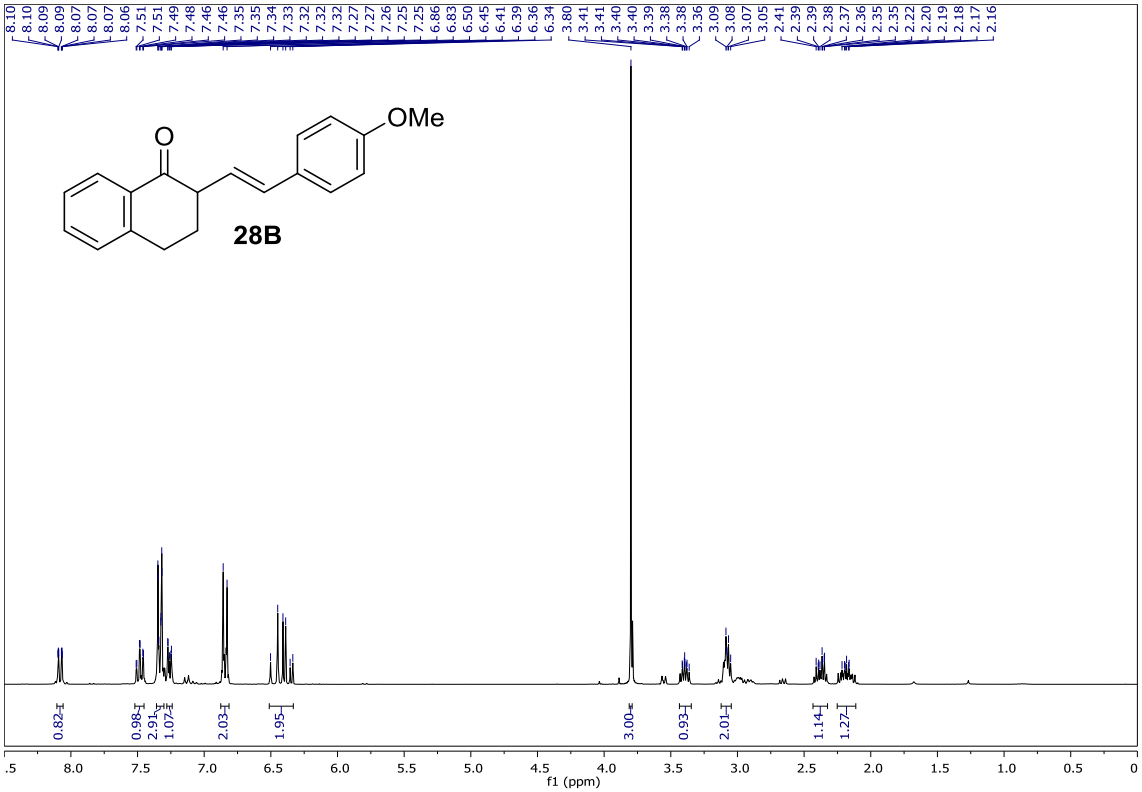
28.11
f1 (ppm)


OMe
O
28B
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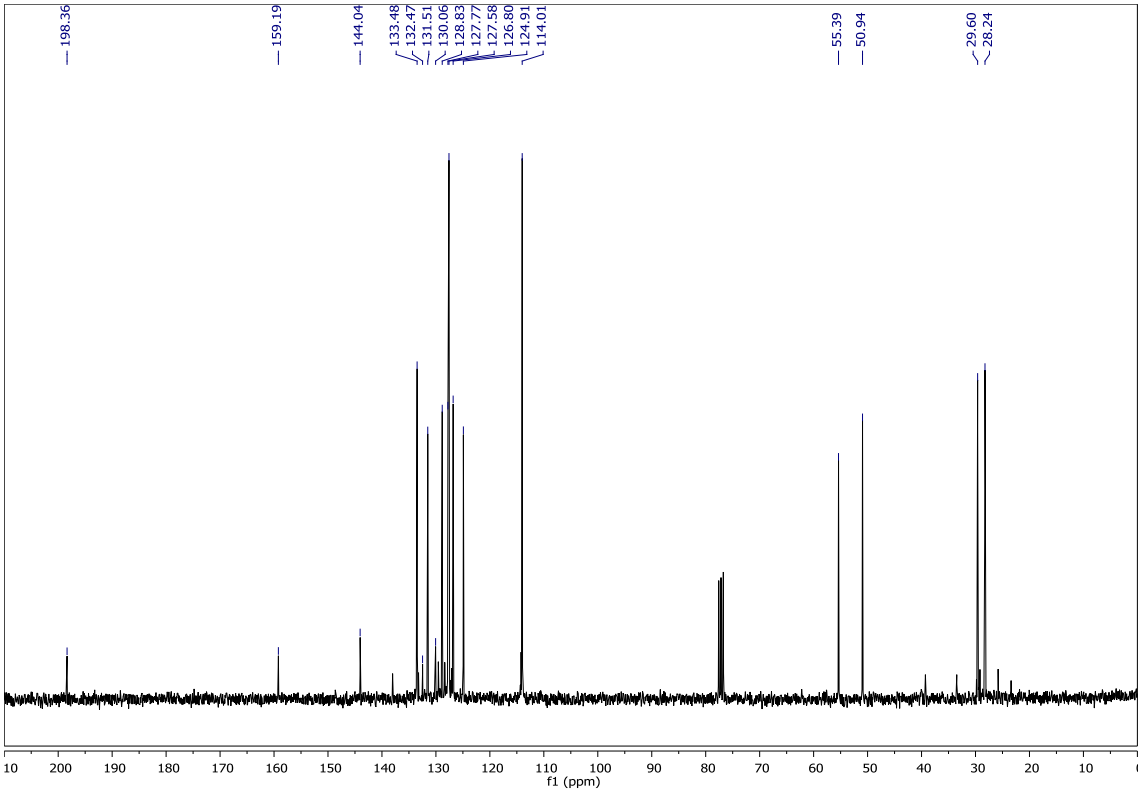
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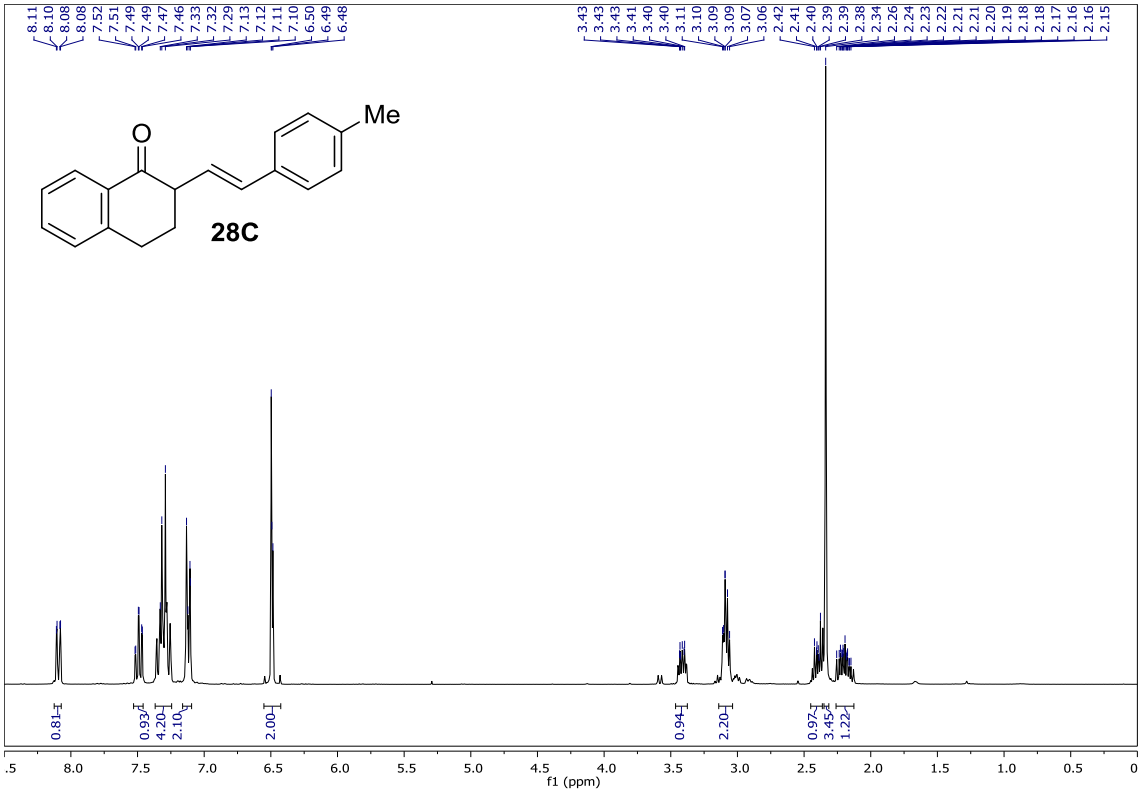
28.24
f1 (ppm)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3.43
3.41
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3.40
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2.16
2.15
O
Me
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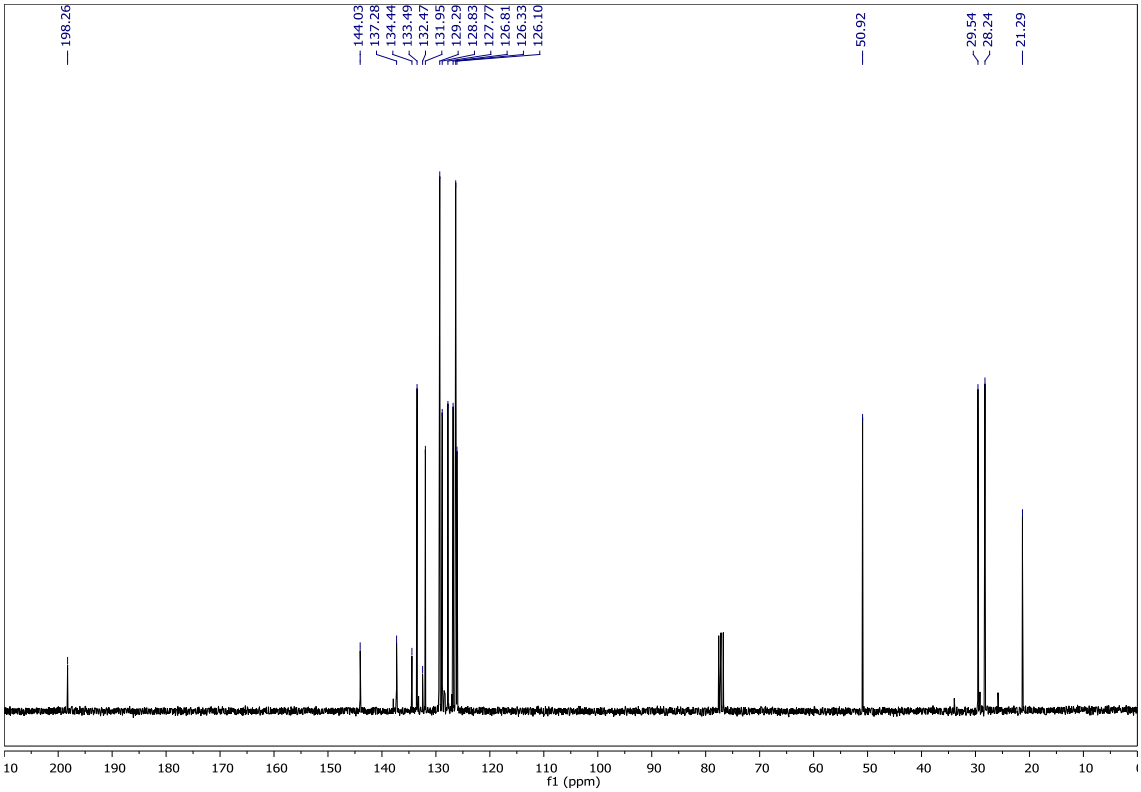
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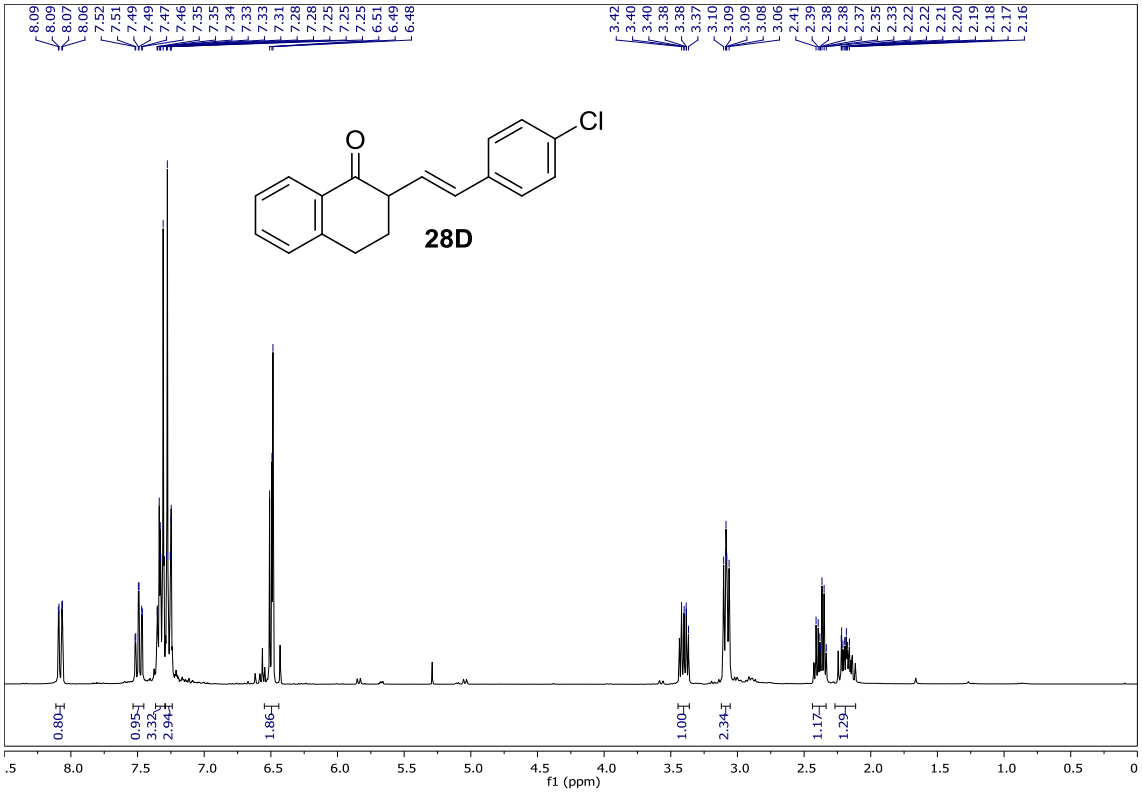
f1 (ppm)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3.40
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3.38
3.37
3.10
3.09
3.09
3.08
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2.16
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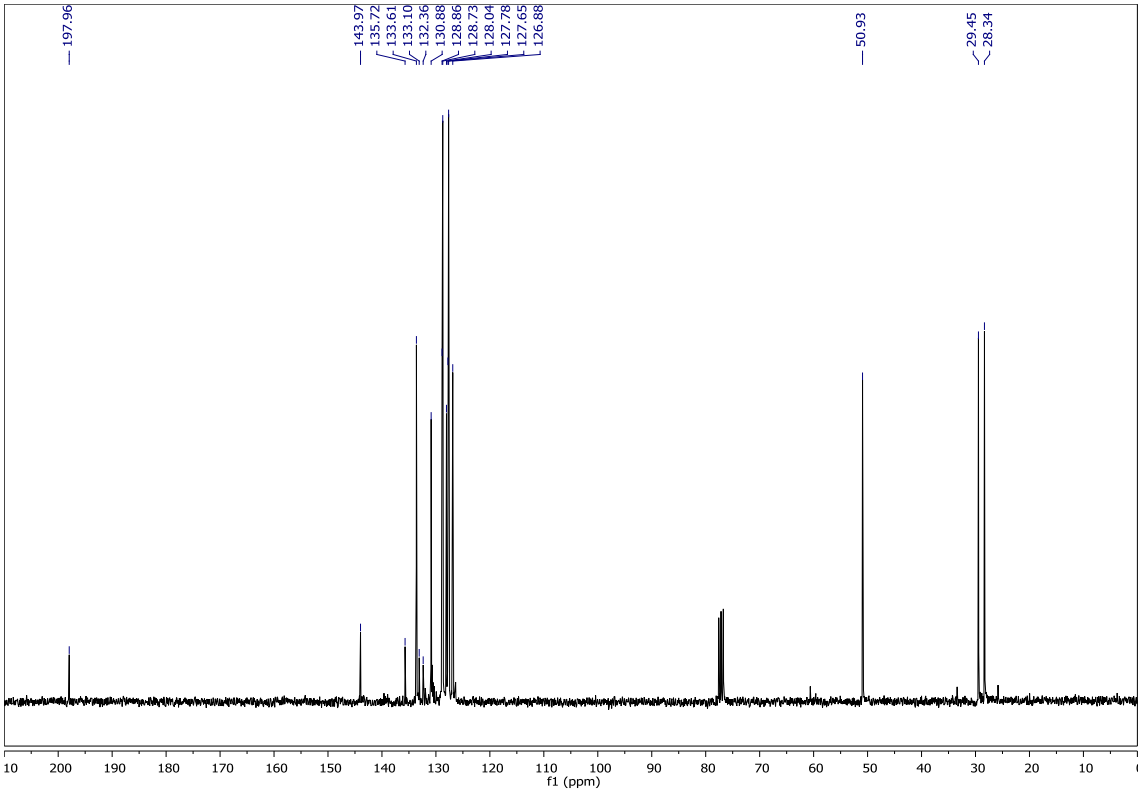
1.29
f1 (ppm)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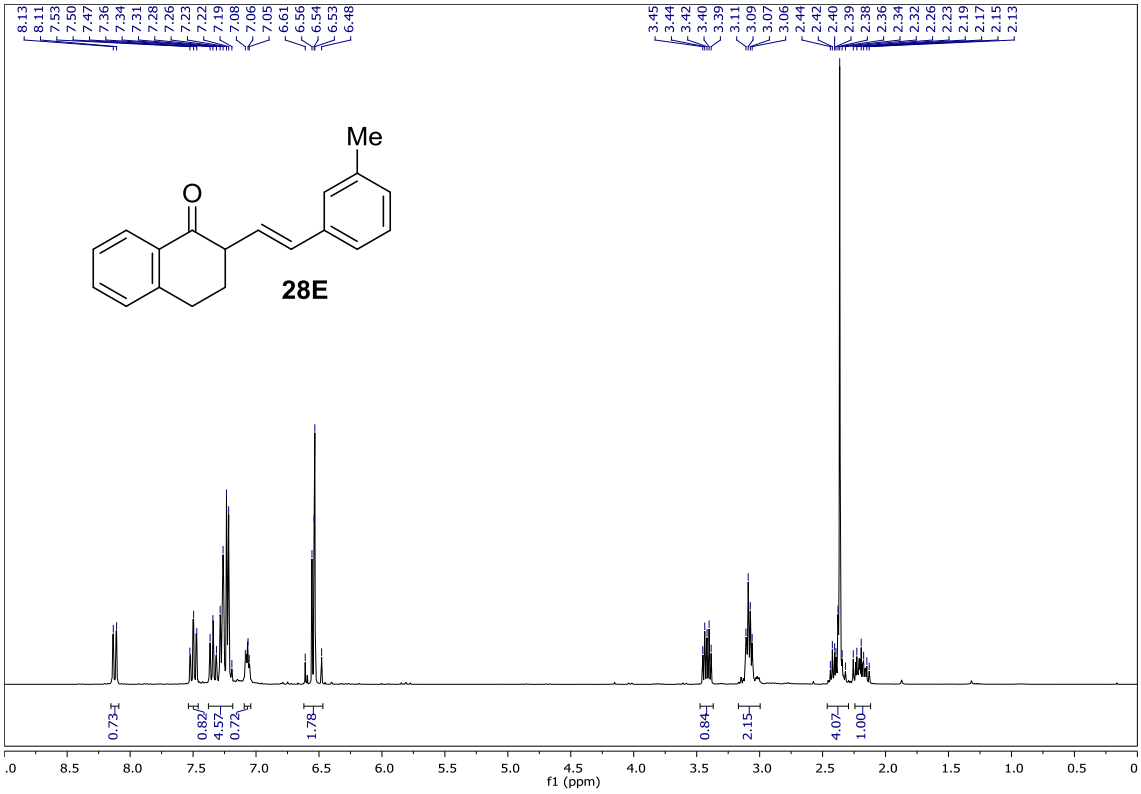
f1 (ppm)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2.17
2.15
2.13
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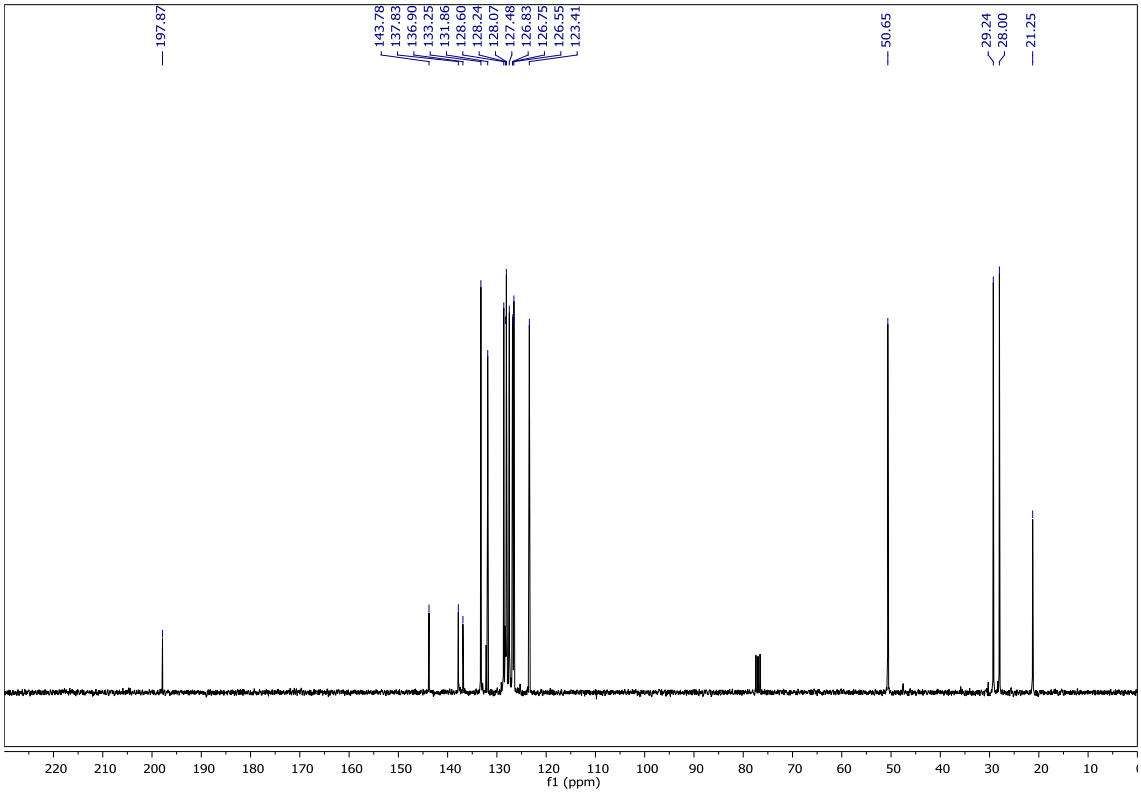
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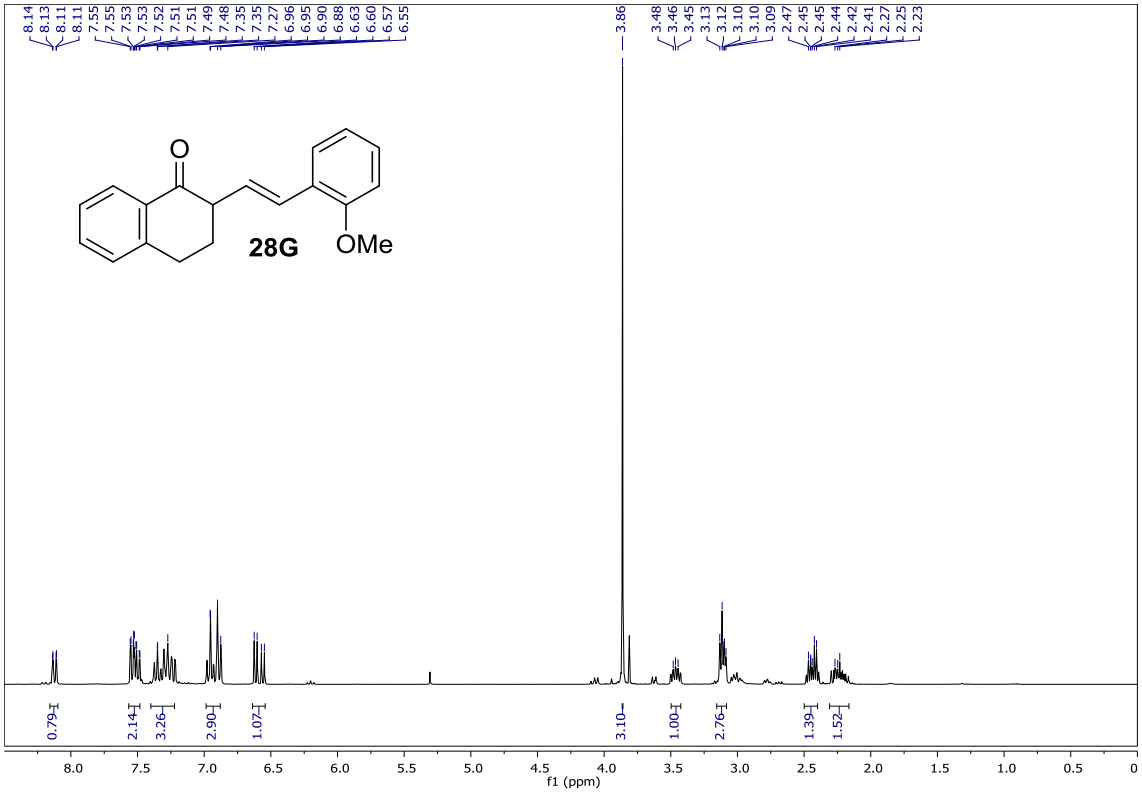
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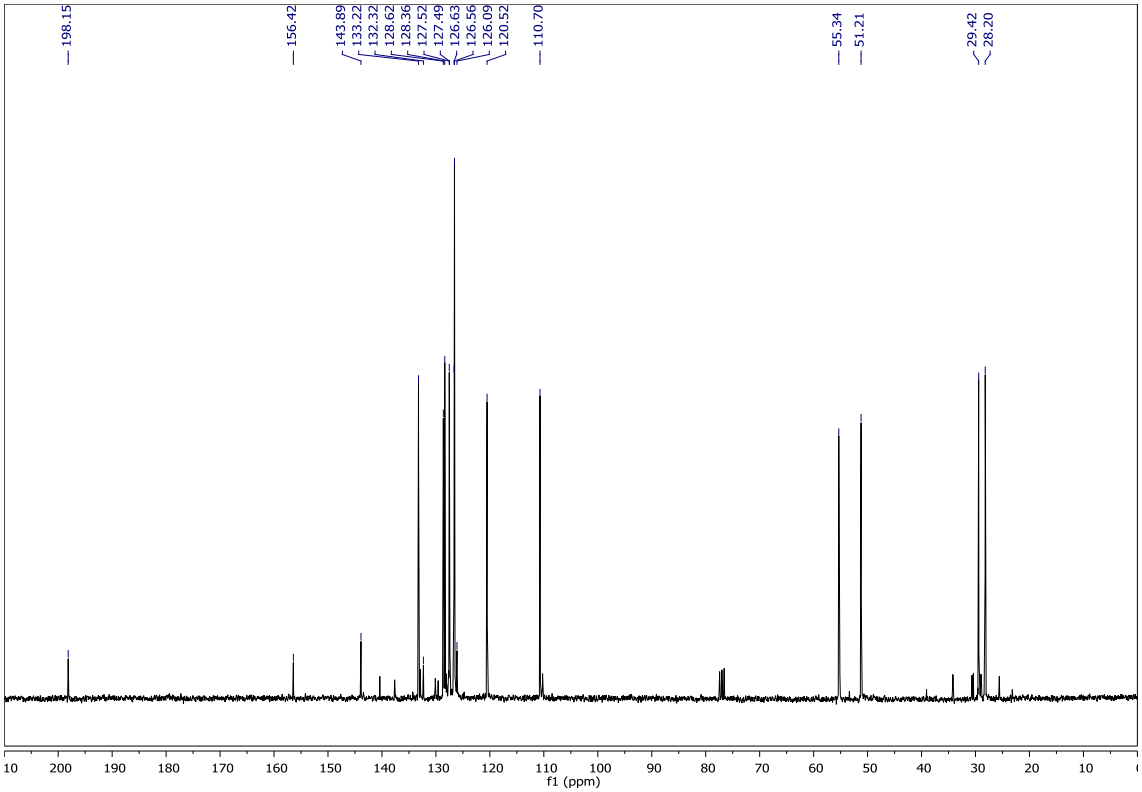
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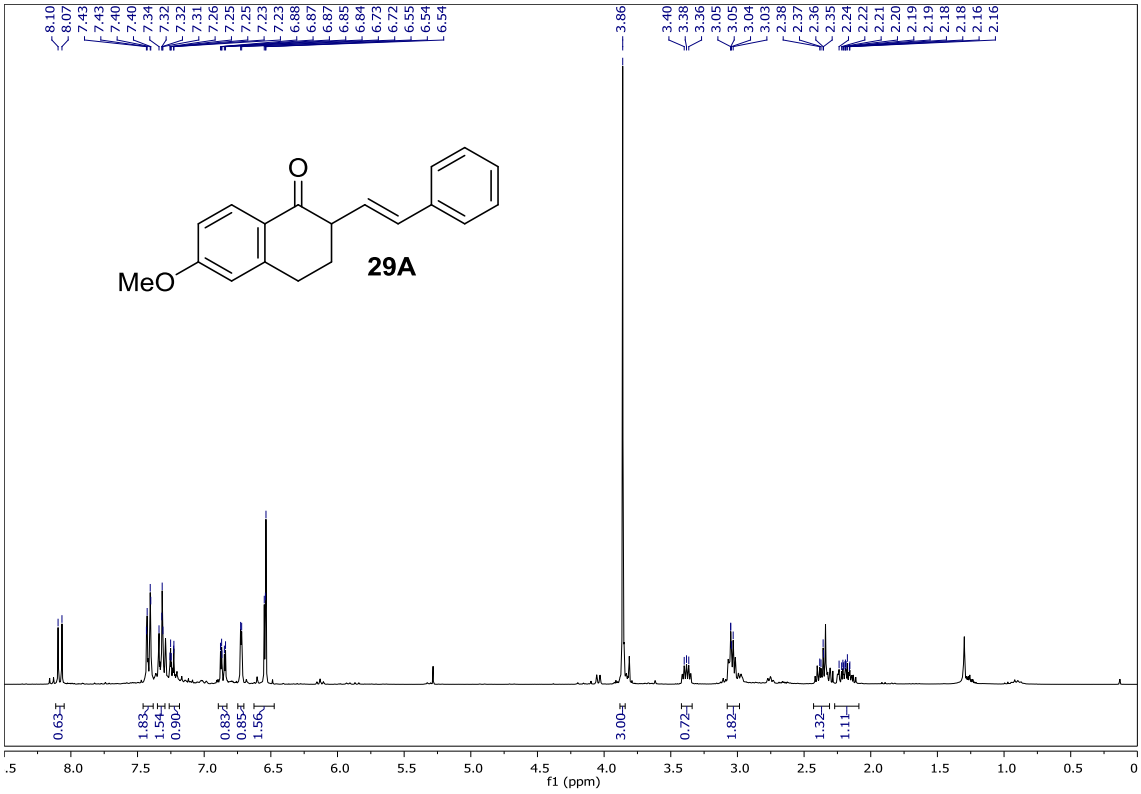
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2.16
2.16
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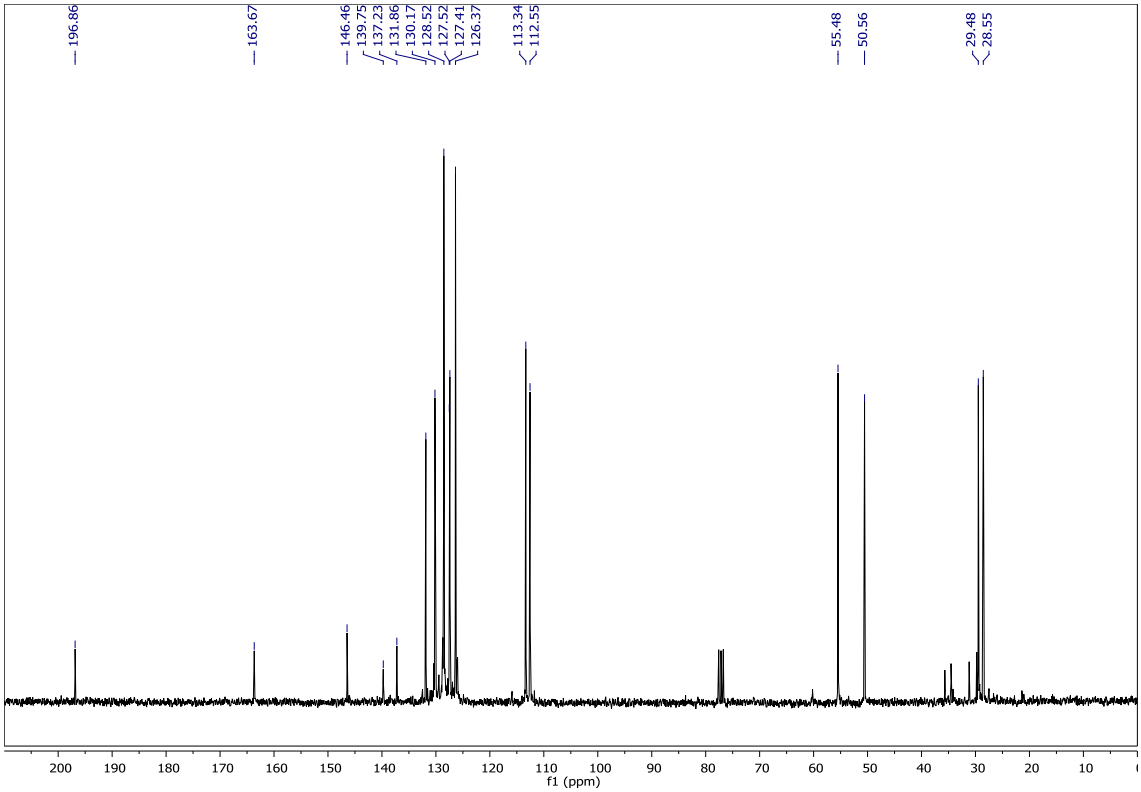
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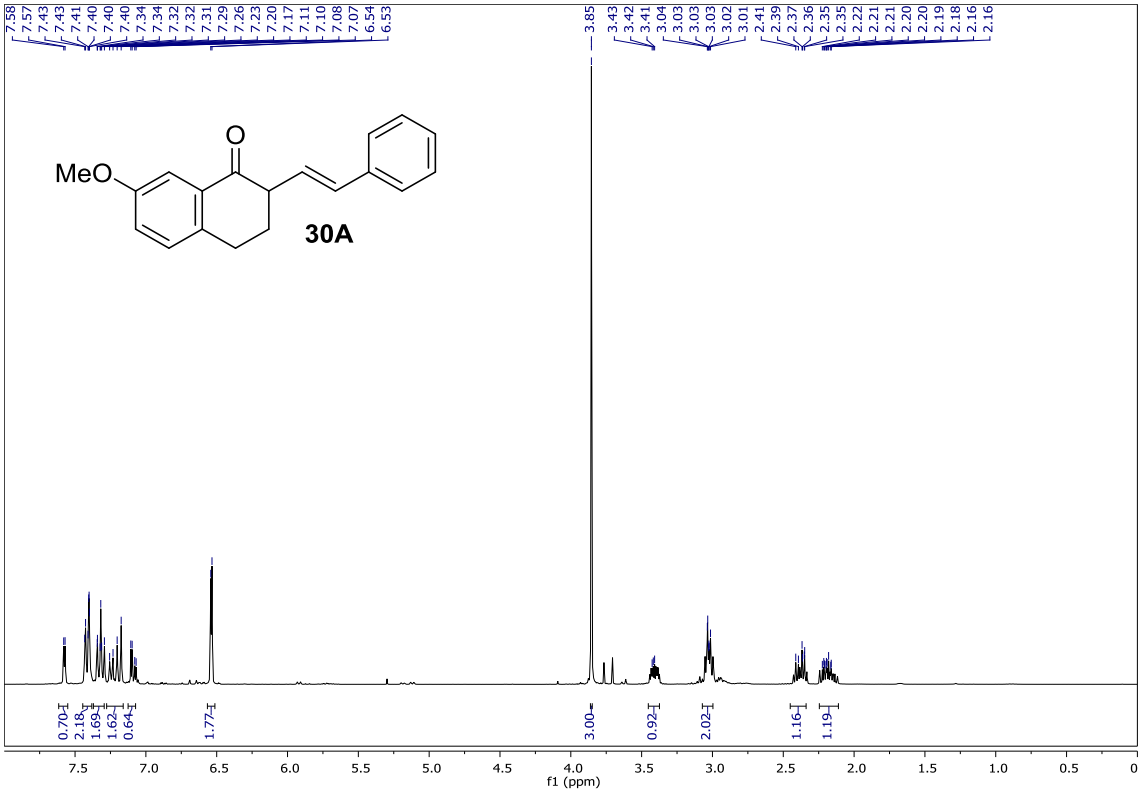
f1 (ppm)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O
30A
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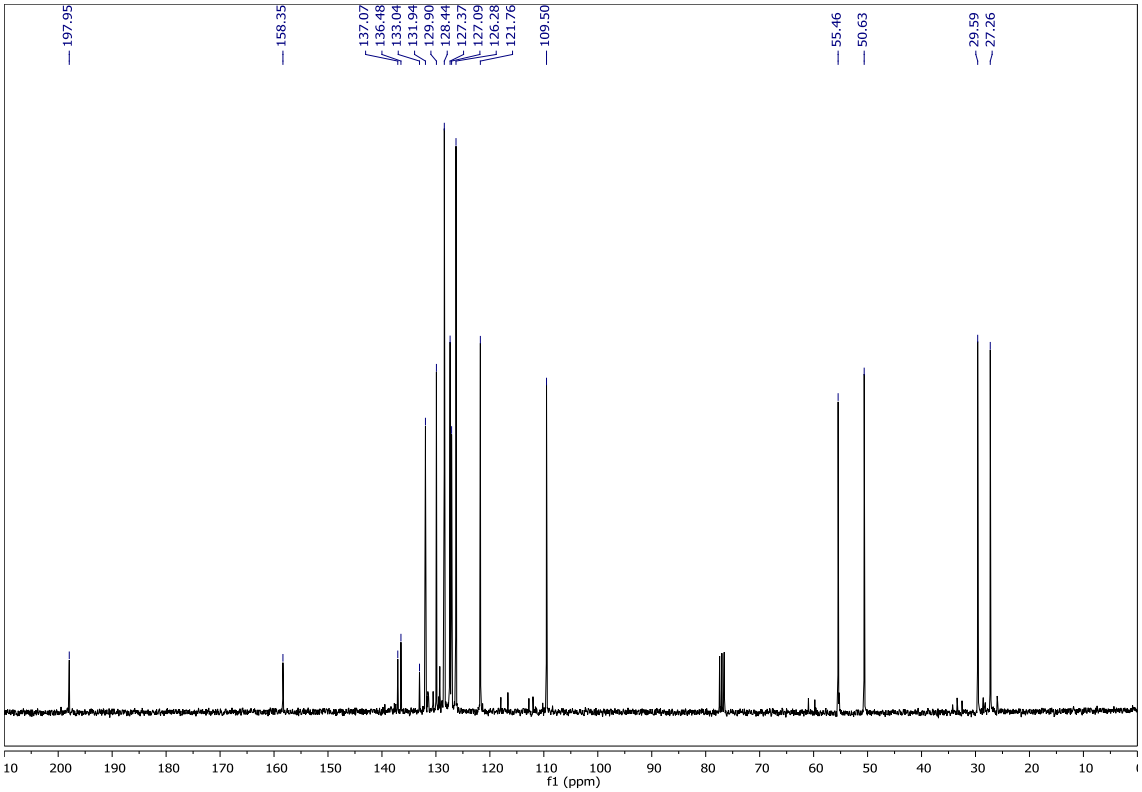
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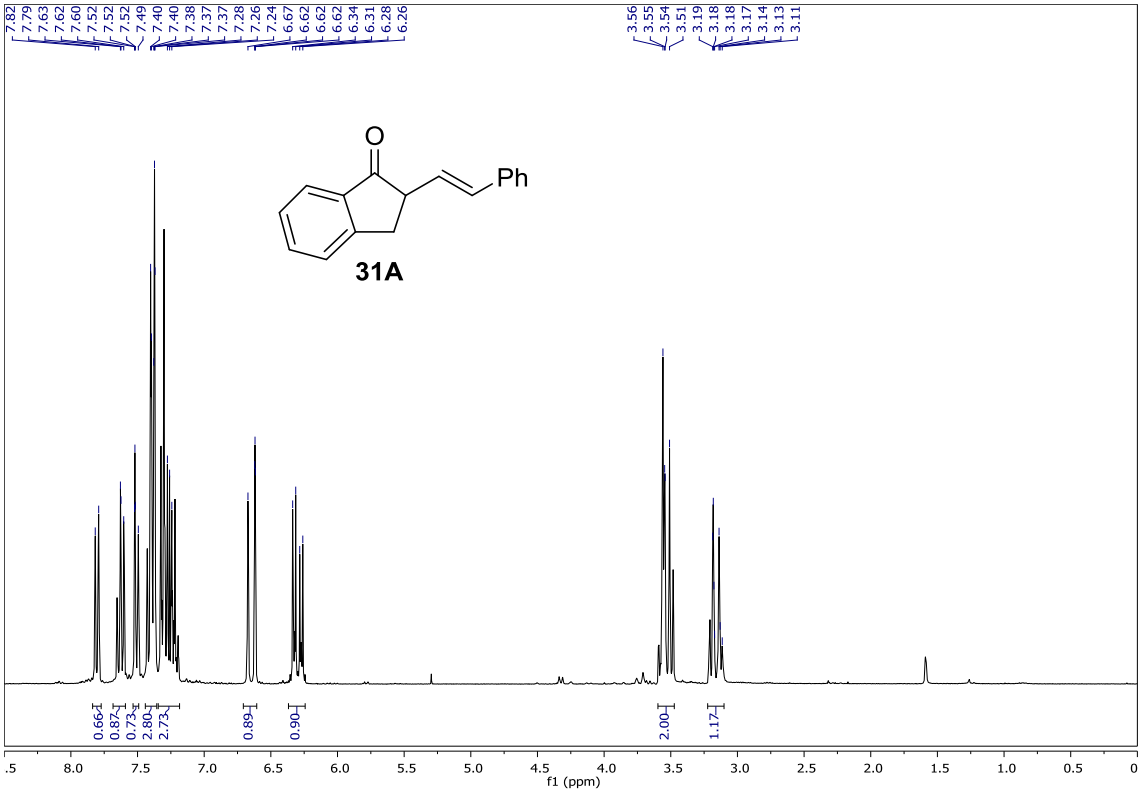
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3.13
3.11
O
Ph
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2.73
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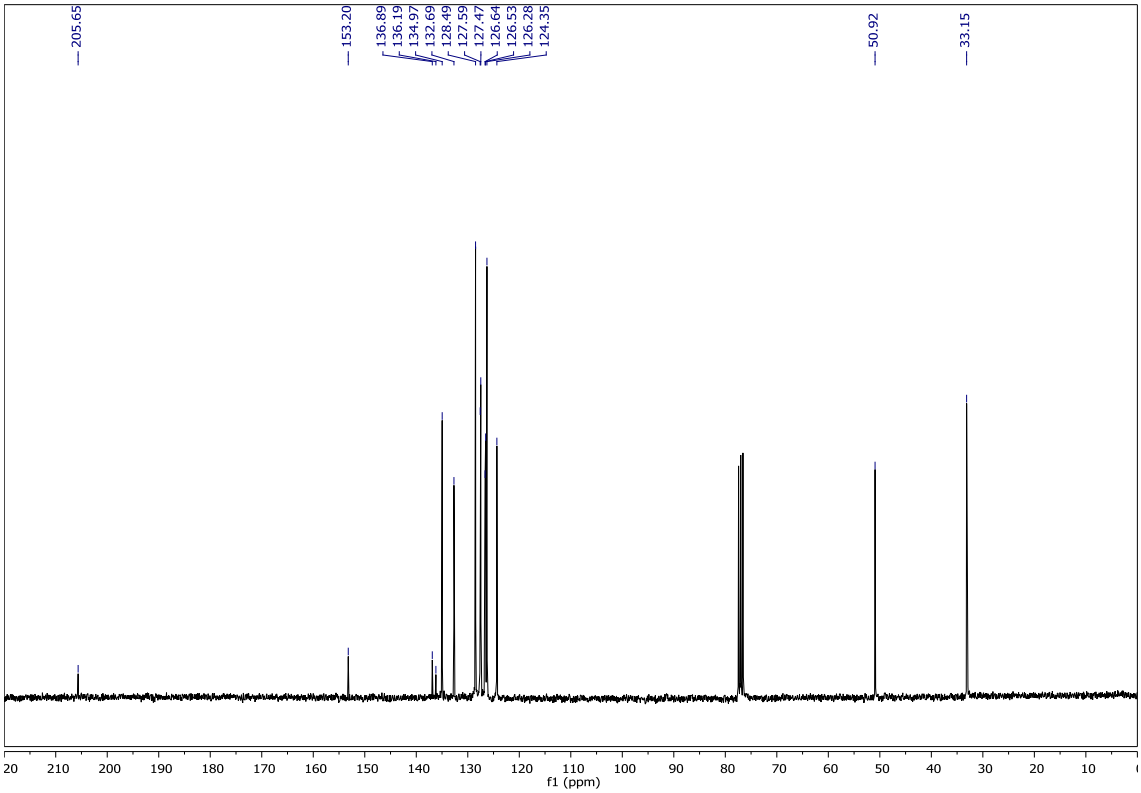
0.90
2.00
1.17
f1 (ppm)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126.53
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124.35
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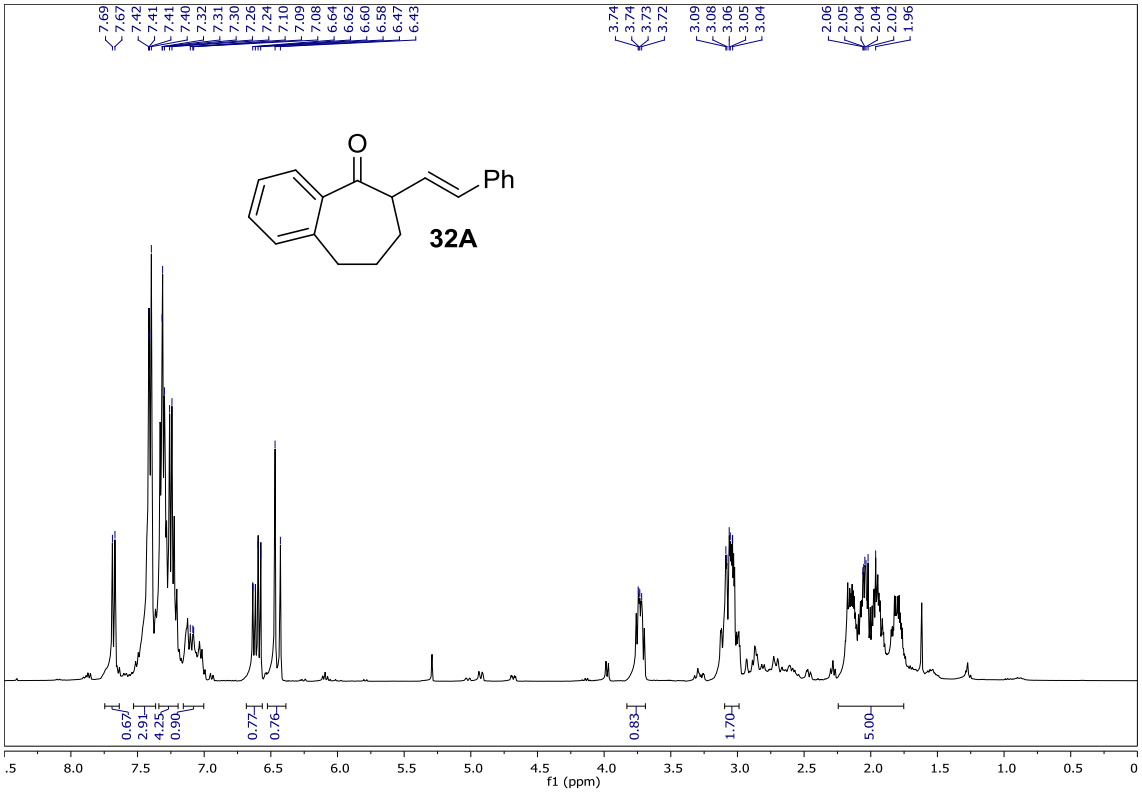
33.15
f1 (ppm)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7.31
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7.26
7.24
7.10
7.09
7.08
6.64
6.62
6.60
6.58
6.47
6.43
3.74
3.74
3.73
3.72
3.09
3.08
3.06
3.05
3.04
2.06
2.05
2.04
2.04
2.02
1.96
O
Ph
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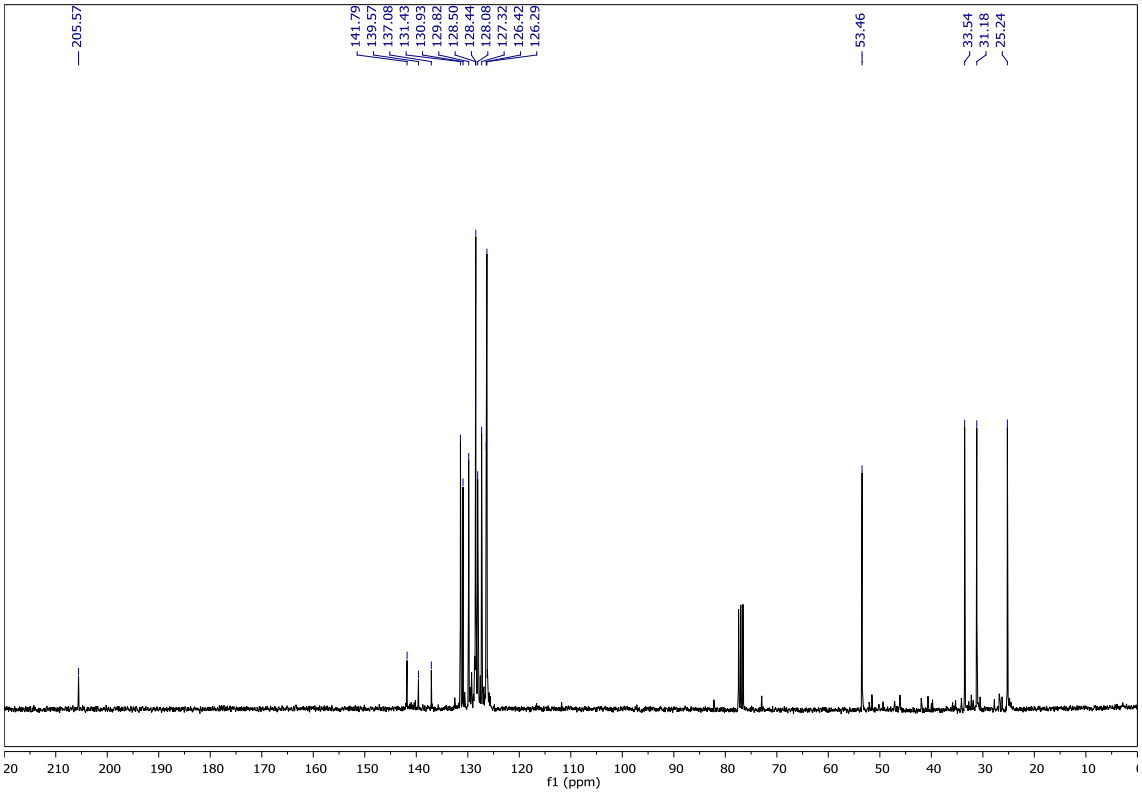
2.91
4.25
0.90
0.77
0.76
0.83
1.70
5.00
f1 (ppm)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128.50
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128.08
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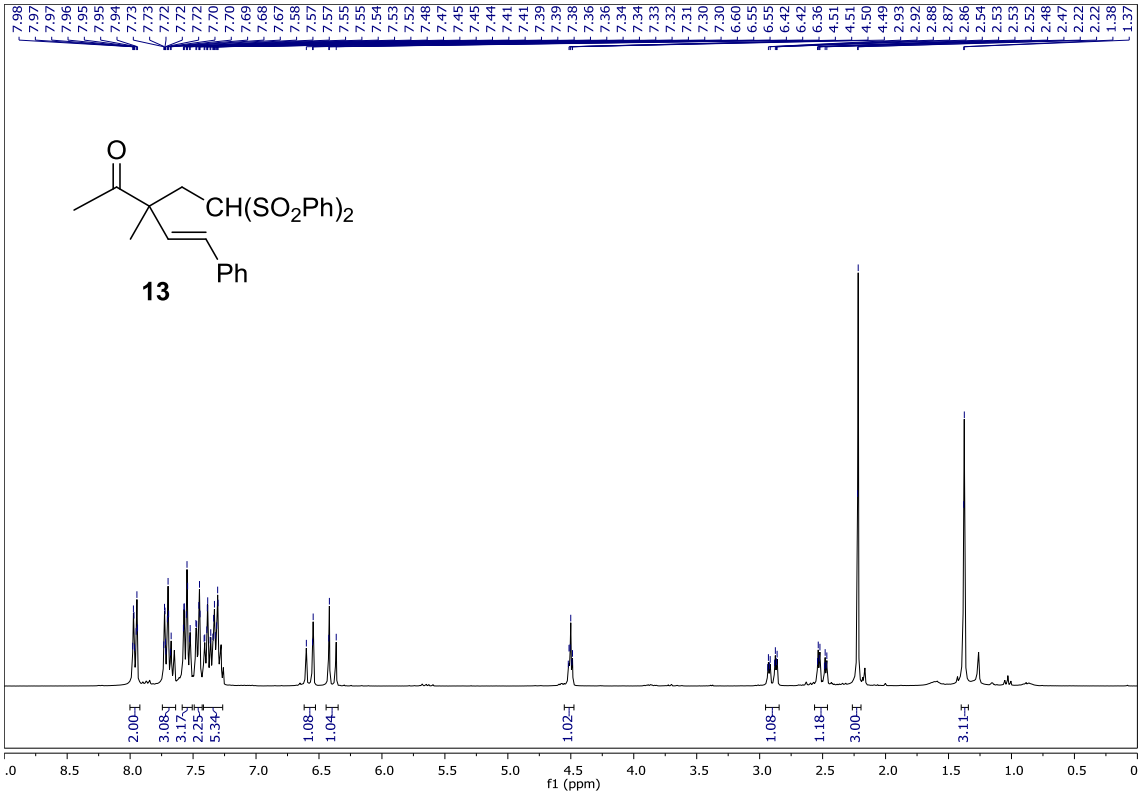
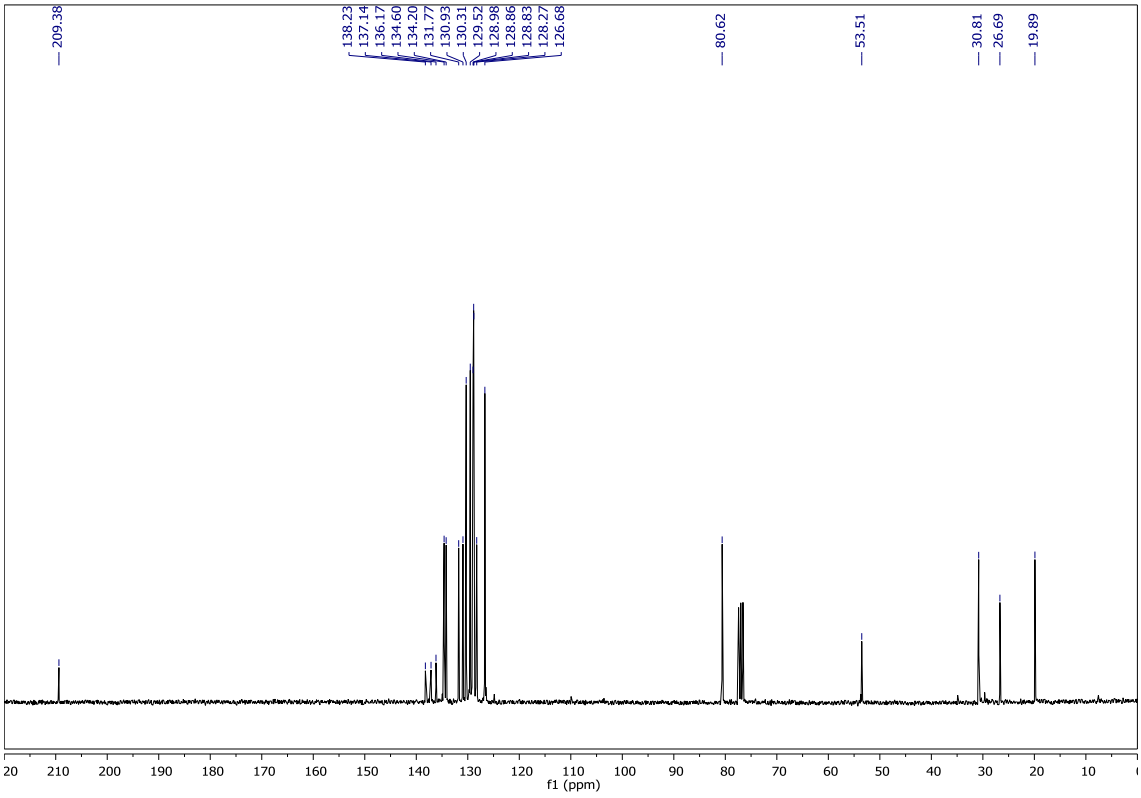
126.42
126.29
53.46
33.54
31.18
25.24
f1 (ppm)


O
CH(SO2Ph)2
Ph
13
f1 (ppm)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128.83
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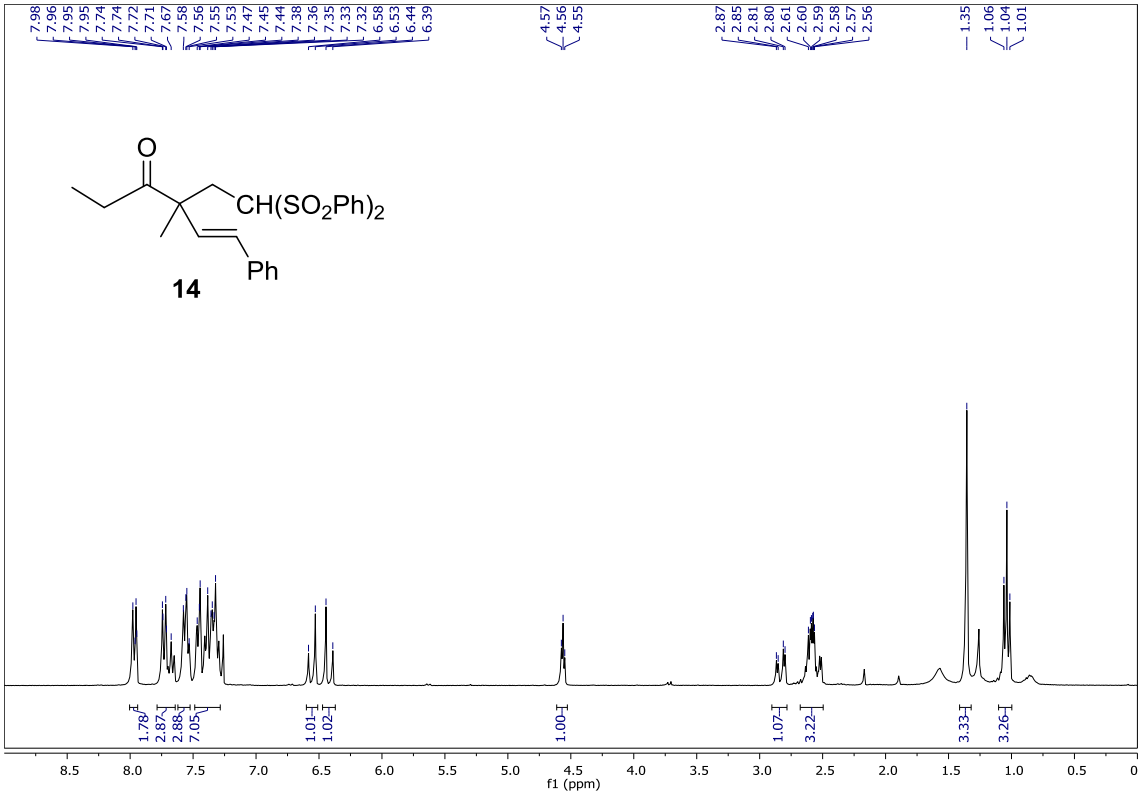
126.68
80.62
53.51
30.81
26.69
19.89
f1 (ppm)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7.95
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7.72
7.71
7.67
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7.56
7.55
7.53
7.47
7.45
7.44
7.38
7.36
7.35
7.33
7.32
6.58
6.53
6.44
6.39
4.57
4.56
4.55
2.87
2.85
2.81
2.80
2.61
2.60
2.59
2.58
2.57
2.56
1.35
1.06
1.04
1.01
O
CH(SO2Ph)2
Ph
14
1.78
2.87
2.88
7.05
1.01
1.02
1.00
1.07
3.22
3.33
3.26
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
2.0
1.5
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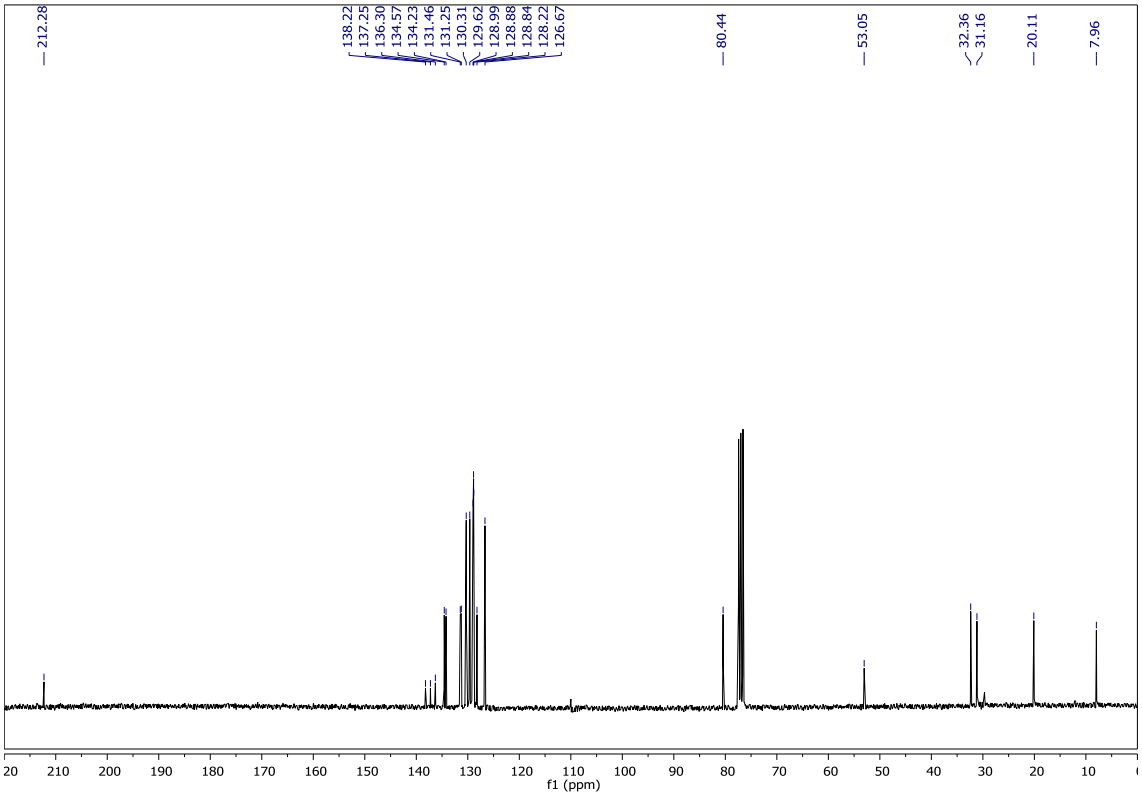
0.5
0
f1 (ppm)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131.25
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129.62
128.99
128.88
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128.22
126.67
80.44
53.05
32.36
31.16
20.11
7.96
20
210
200
190
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150
140
130
120
110
100
90
80
70
60
50
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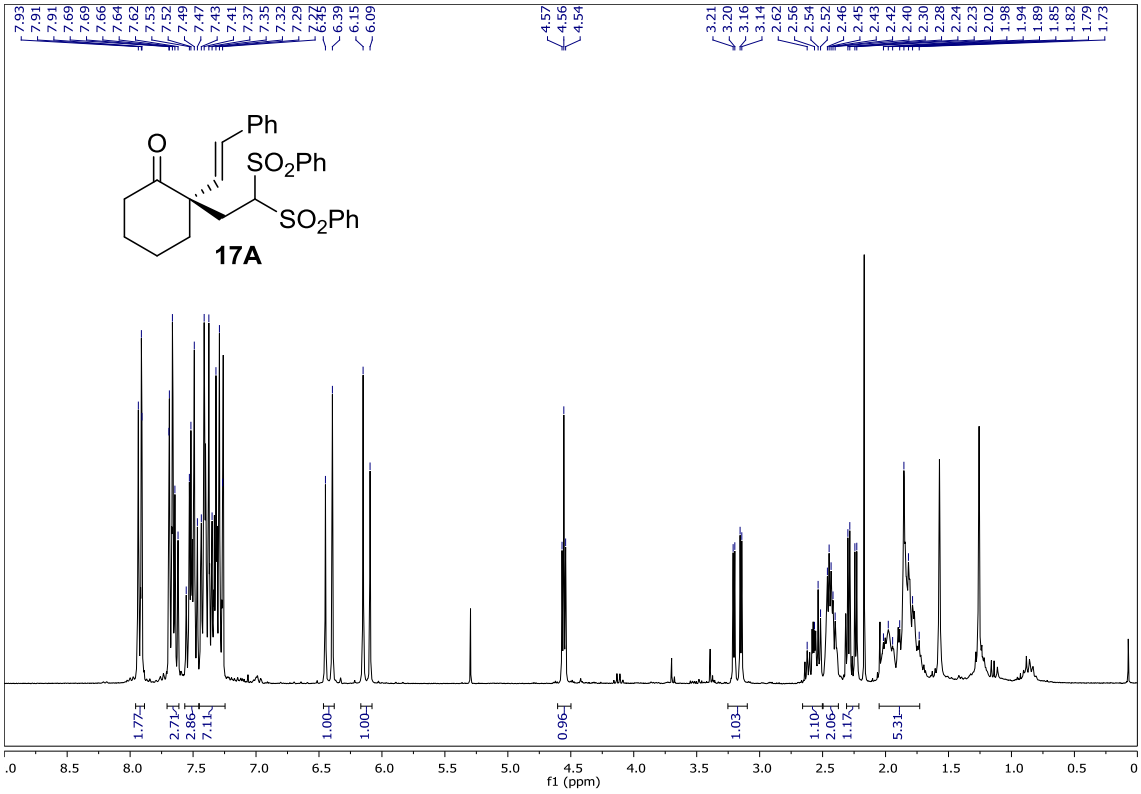
30
20
10
f1 (ppm)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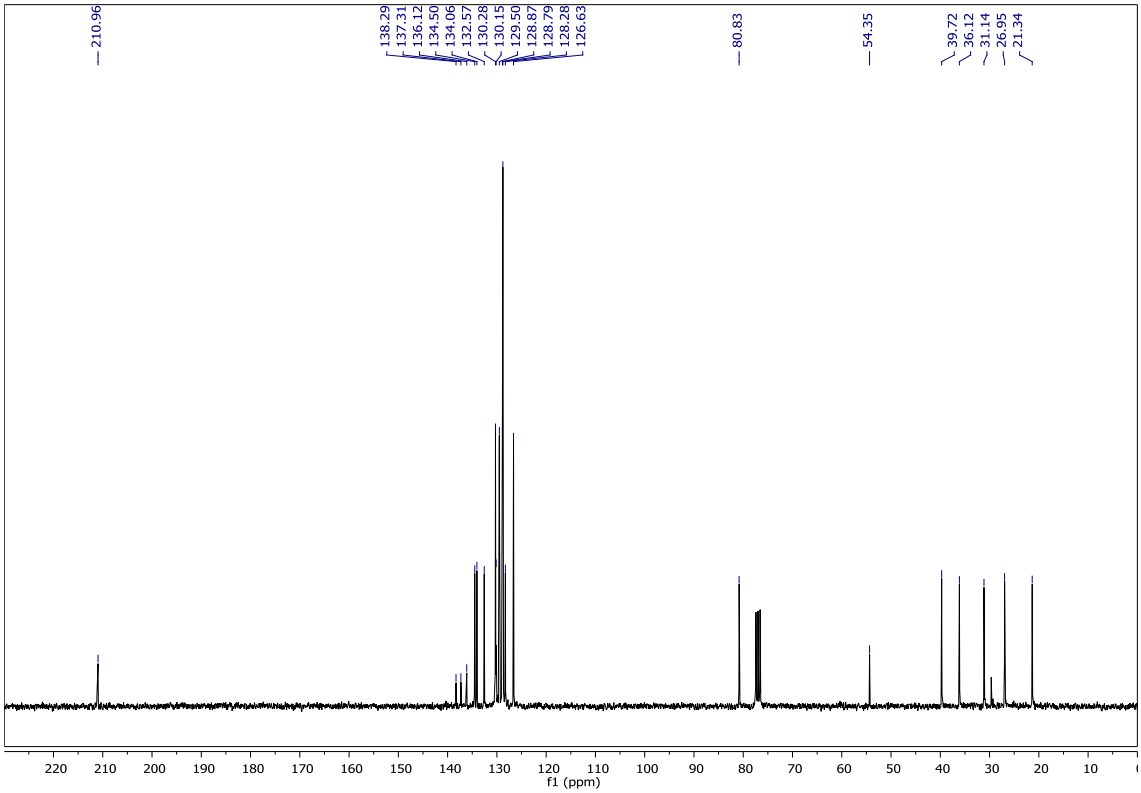
7.91
7.91
7.69
7.69
7.66
7.64
7.62
7.53
7.52
7.49
7.47
7.43
7.41
7.37
7.35
7.32
7.29
6.45
6.39
6.15
6.09
4.57
4.56
4.54
3.21
3.20
3.16
3.14
2.62
2.56
2.54
2.52
2.46
2.45
2.43
2.42
2.40
2.30
2.28
2.24
2.23
2.02
1.98
1.94
1.89
1.85
1.82
1.79
1.73
Ph
O
SO2Ph
SO2Ph
17A
1.77
2.71
2.86
7.11
1.00
1.00
0.96
1.03
1.10
2.06
1.17
5.31
f1 (ppm)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134.06
132.57
130.28
130.15
129.50
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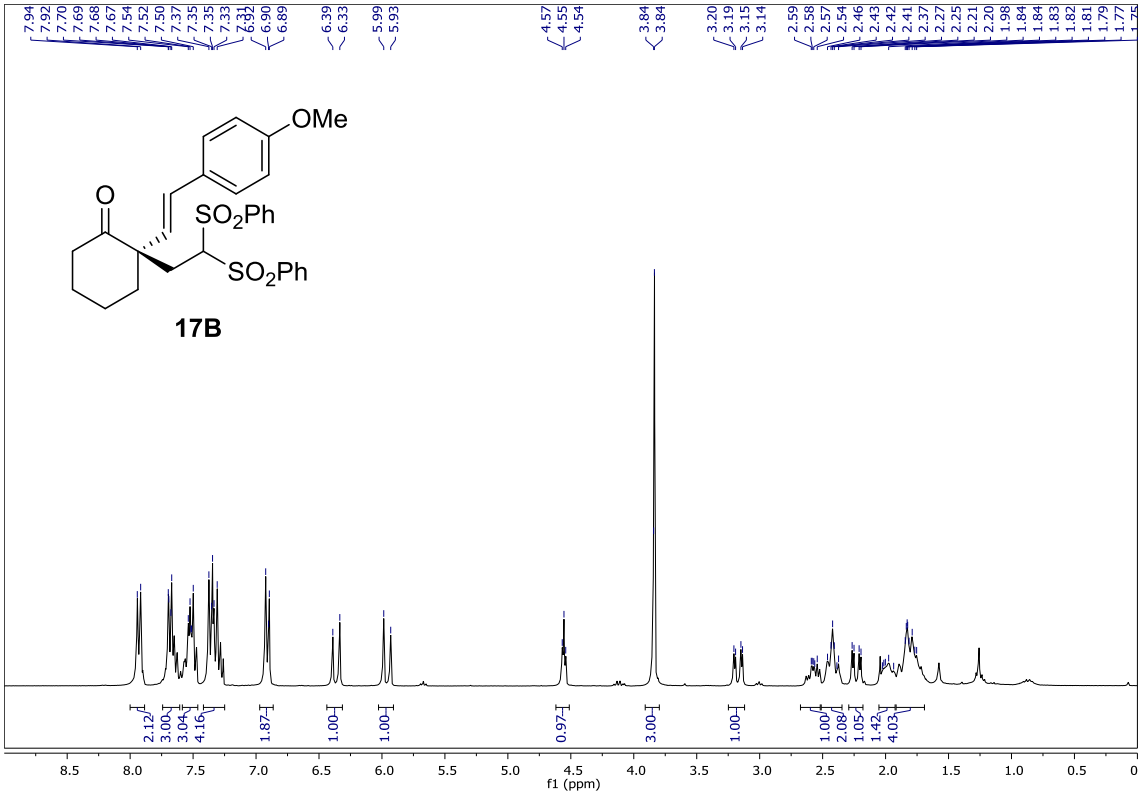
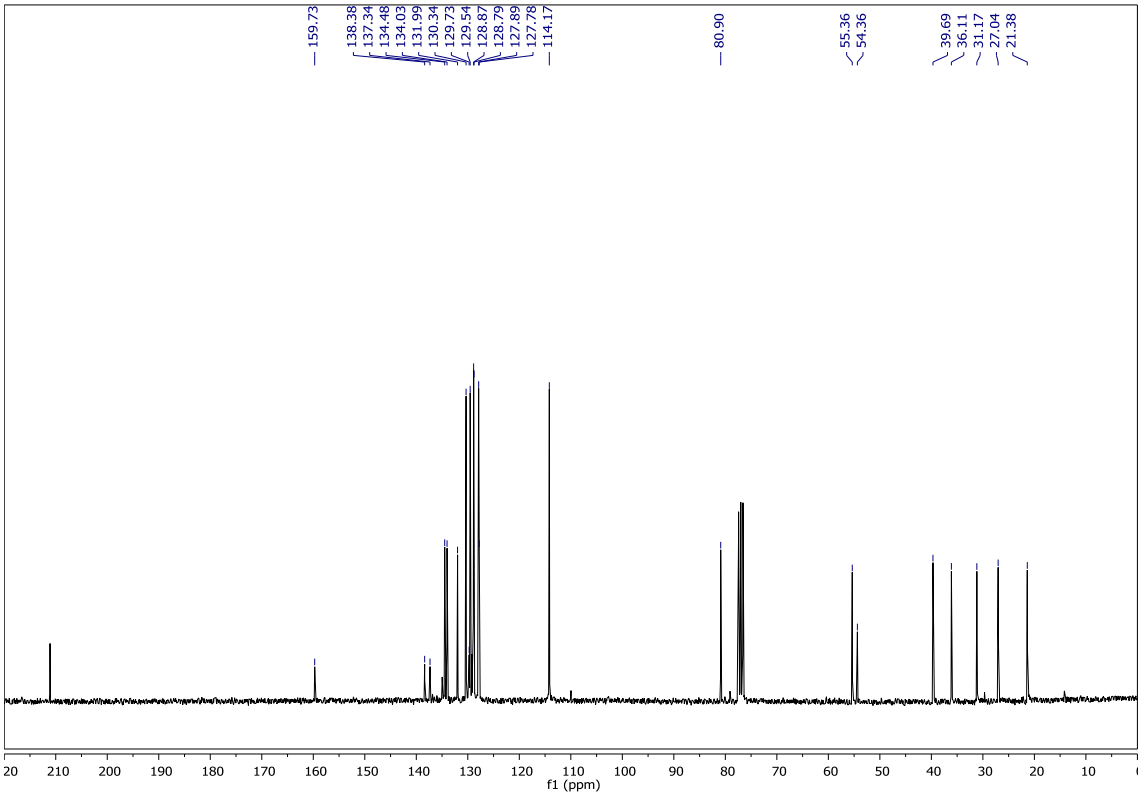
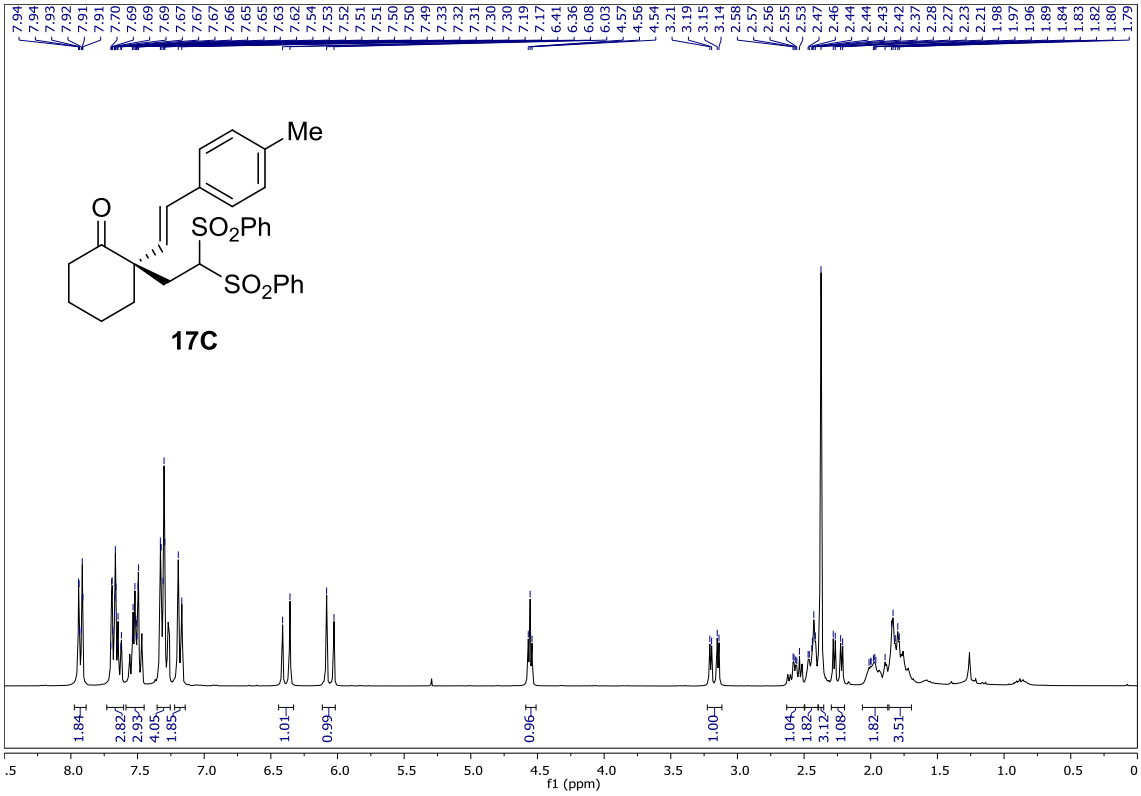
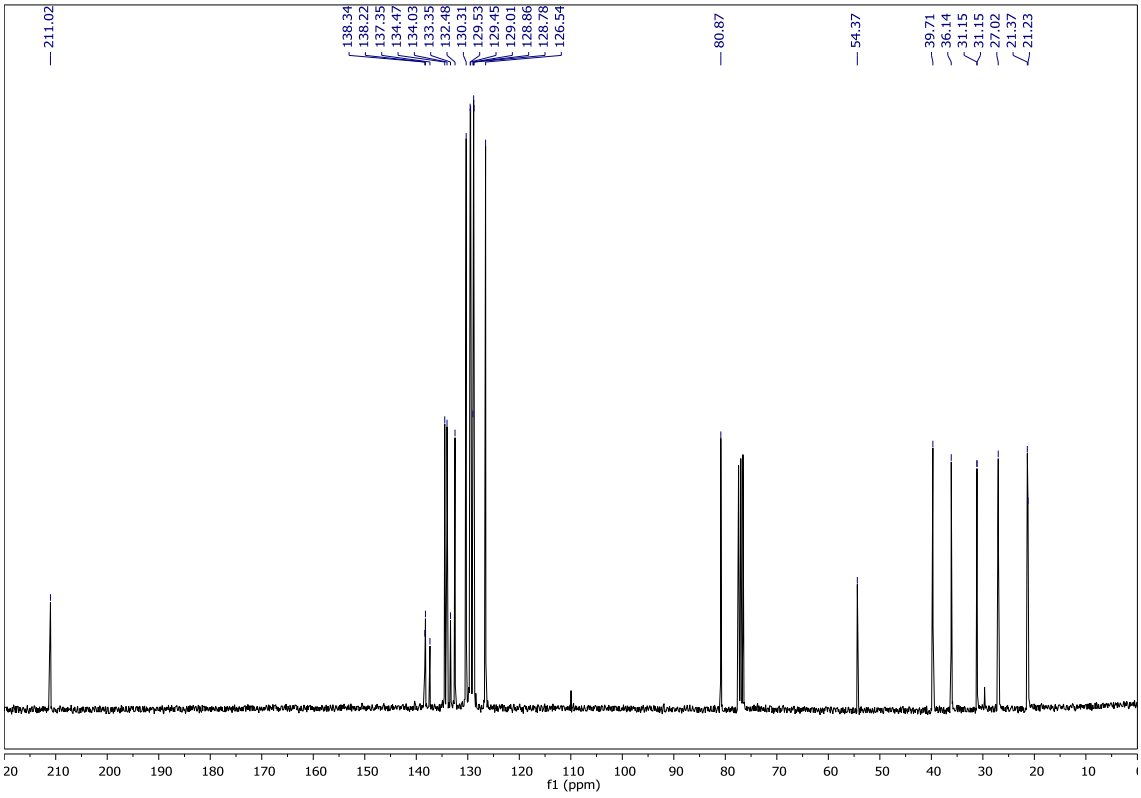
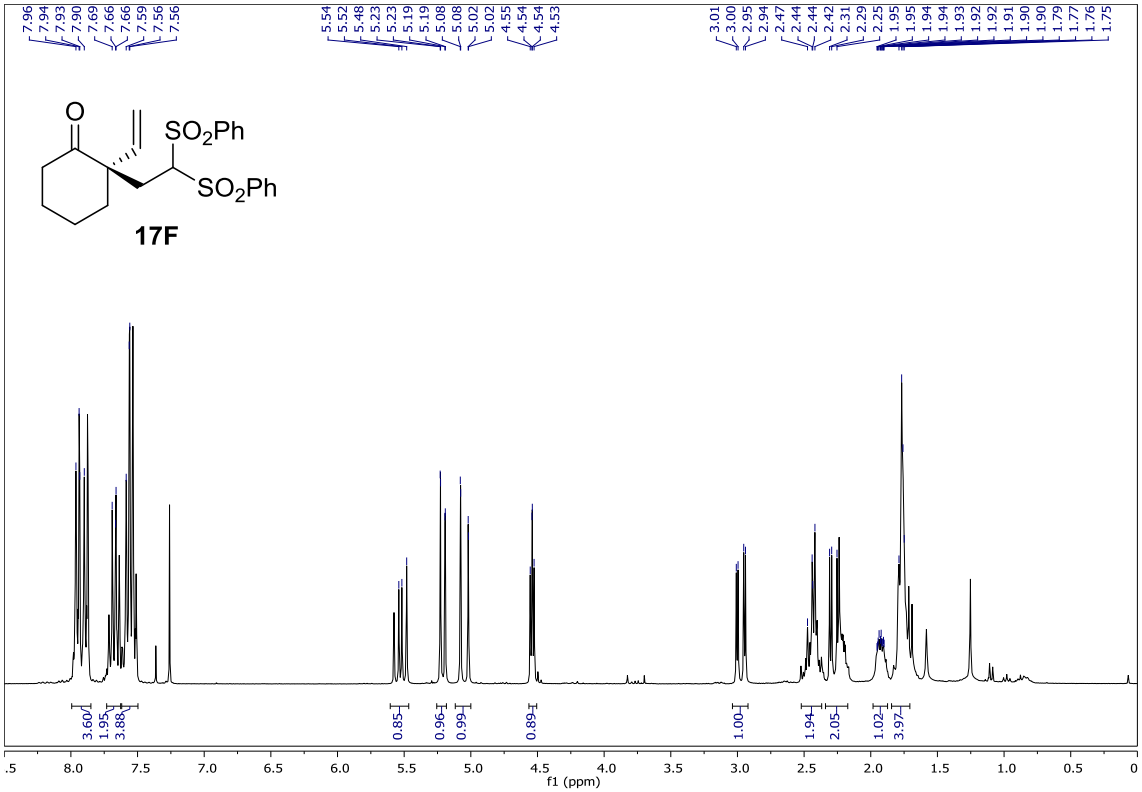
128.79
128.28
126.63
80.83
54.35
39.72
36.12
31.14
26.95
21.34
f1 (ppm)


OMe
O
SO2Ph
SO2Ph
17B
f1 (ppm)


f1 (ppm)


Me
O
SO2Ph
SO2Ph
17C
f1 (ppm)


f1 (ppm)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7.90
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7.59
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7.56
5.54
5.52
5.48
5.23
5.23
5.19
5.19
5.08
5.08
5.02
5.02
4.55
4.54
4.54
4.53
3.01
3.00
2.95
2.94
2.47
2.44
2.44
2.42
2.31
2.29
2.25
1.95
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.90
1.90
1.79
1.77
1.76
1.75
O
SO2Ph
SO2Ph
17F
3.60
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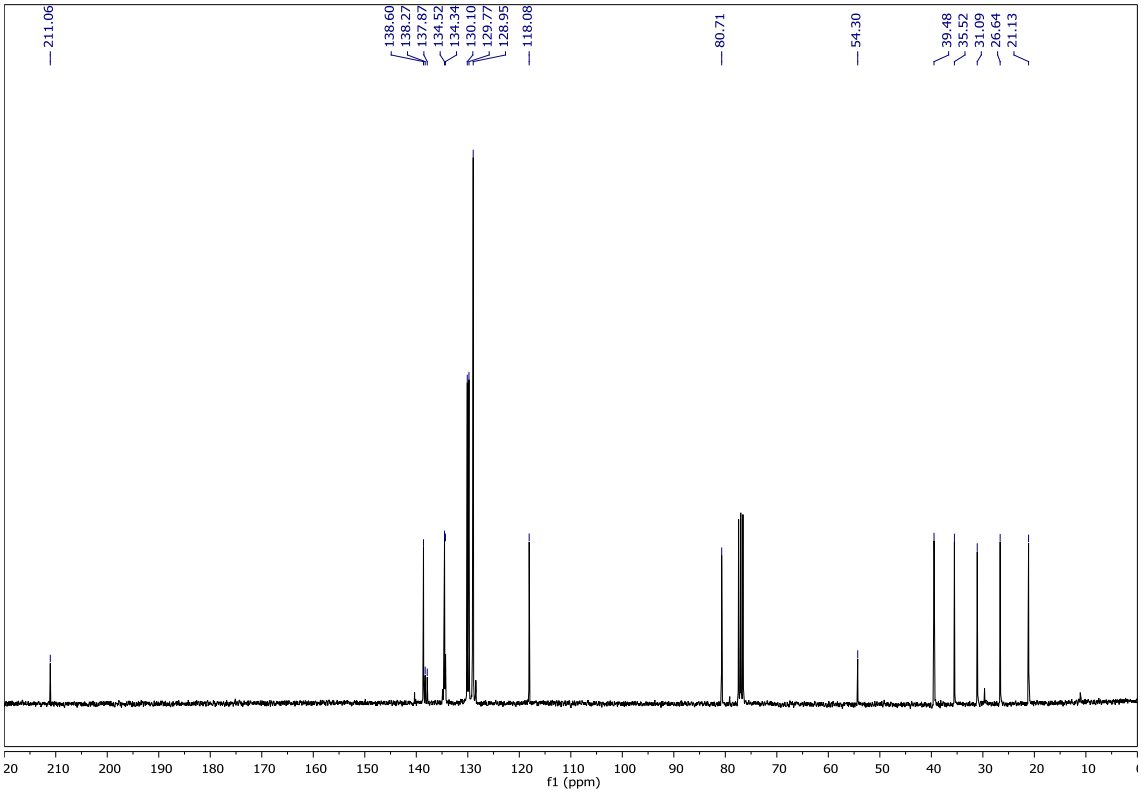
0.96
0.99
0.89
1.00
1.94
2.05
1.02
3.97
f1 (ppm)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129.77
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54.30
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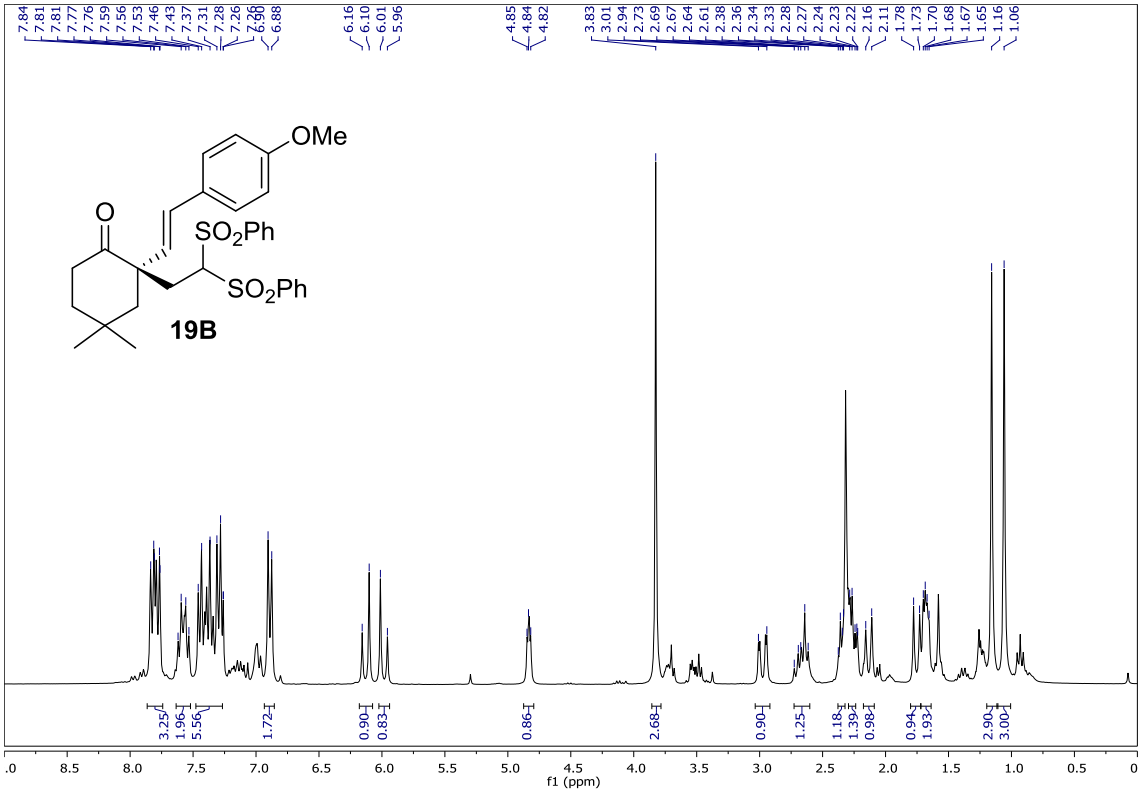
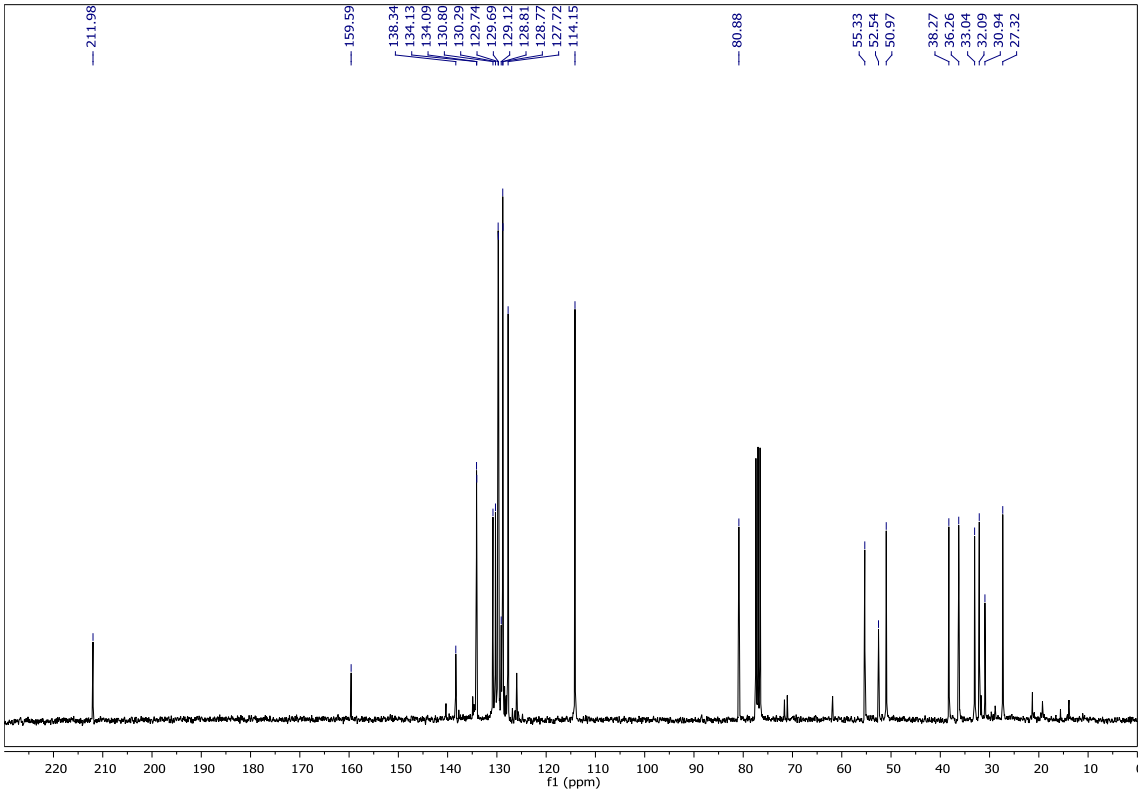
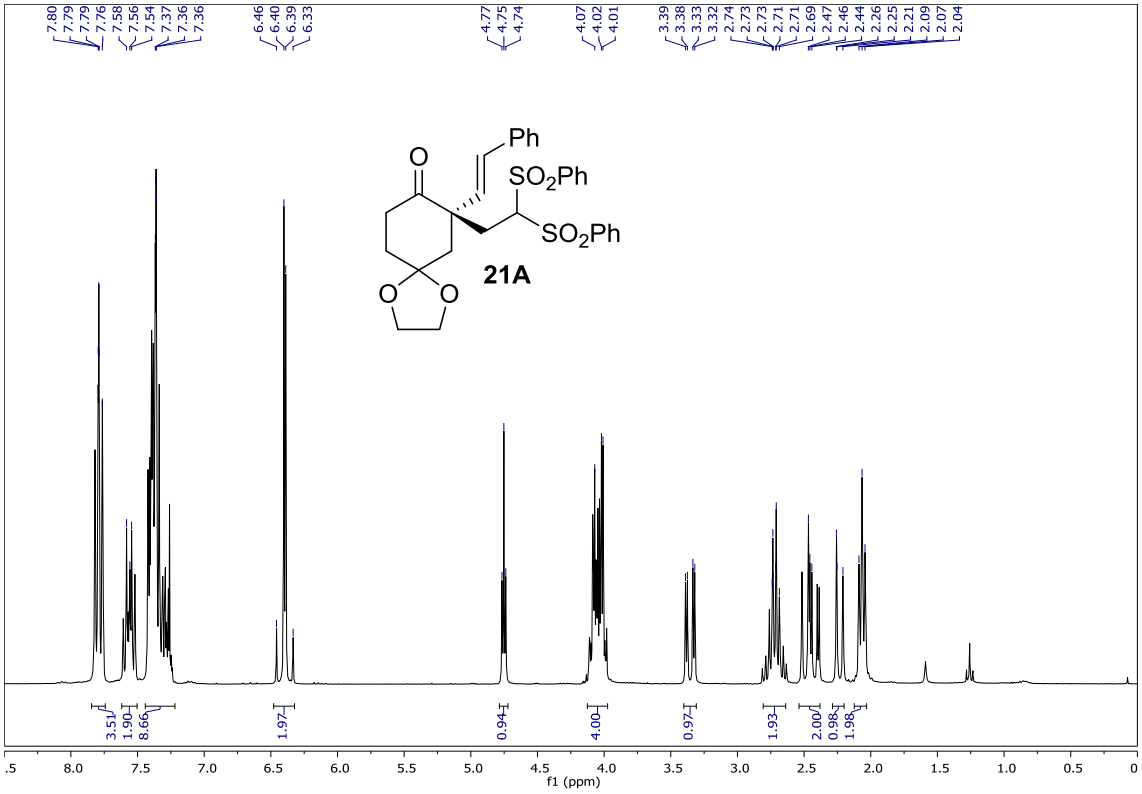
35.52
31.09
26.64
21.13
f1 (ppm)


OMe
O
SO2Ph
SO2Ph
19B
f1 (ppm)


f1 (ppm)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6.40
6.39
6.33
4.77
4.75
4.74
4.07
4.02
4.01
3.39
3.38
3.33
3.32
2.74
2.73
2.73
2.71
2.71
2.69
2.47
2.46
2.44
2.26
2.25
2.21
2.09
2.07
2.04
Ph
O
SO2Ph
SO2Ph
21A
O
O
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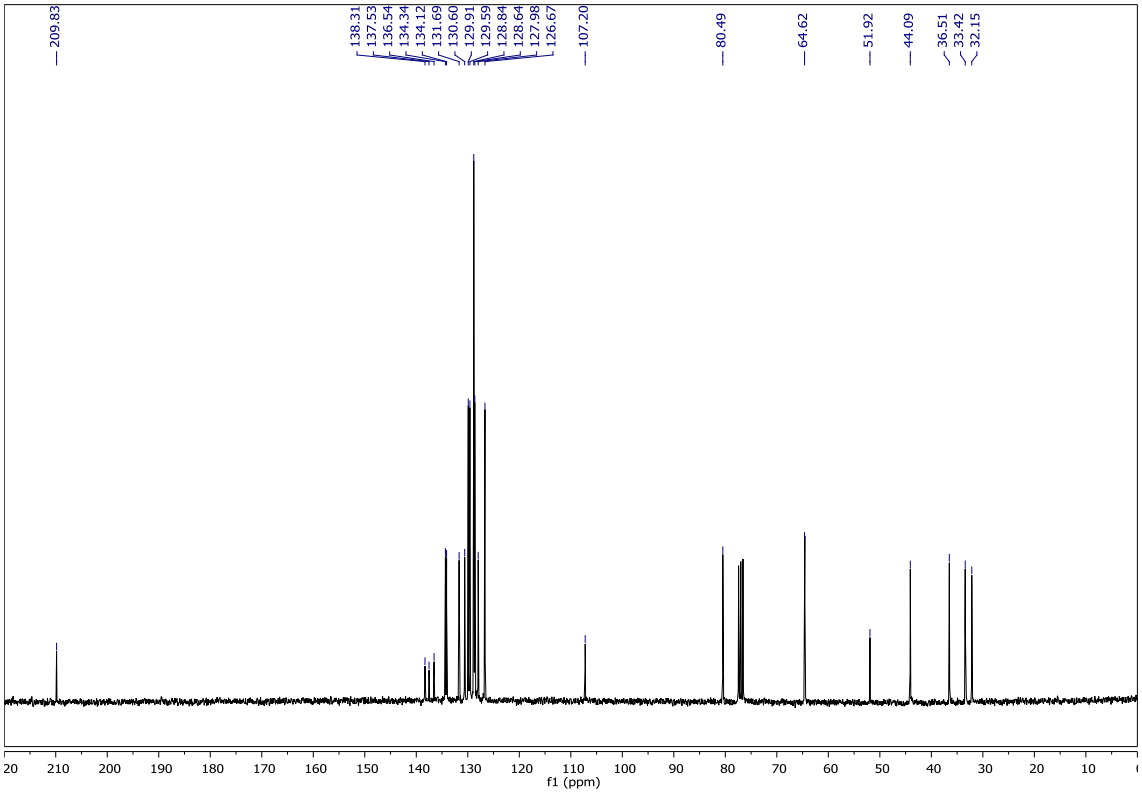
1.97
0.94
4.00
0.97
1.93
2.00
0.98
1.98
f1 (ppm)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129.59
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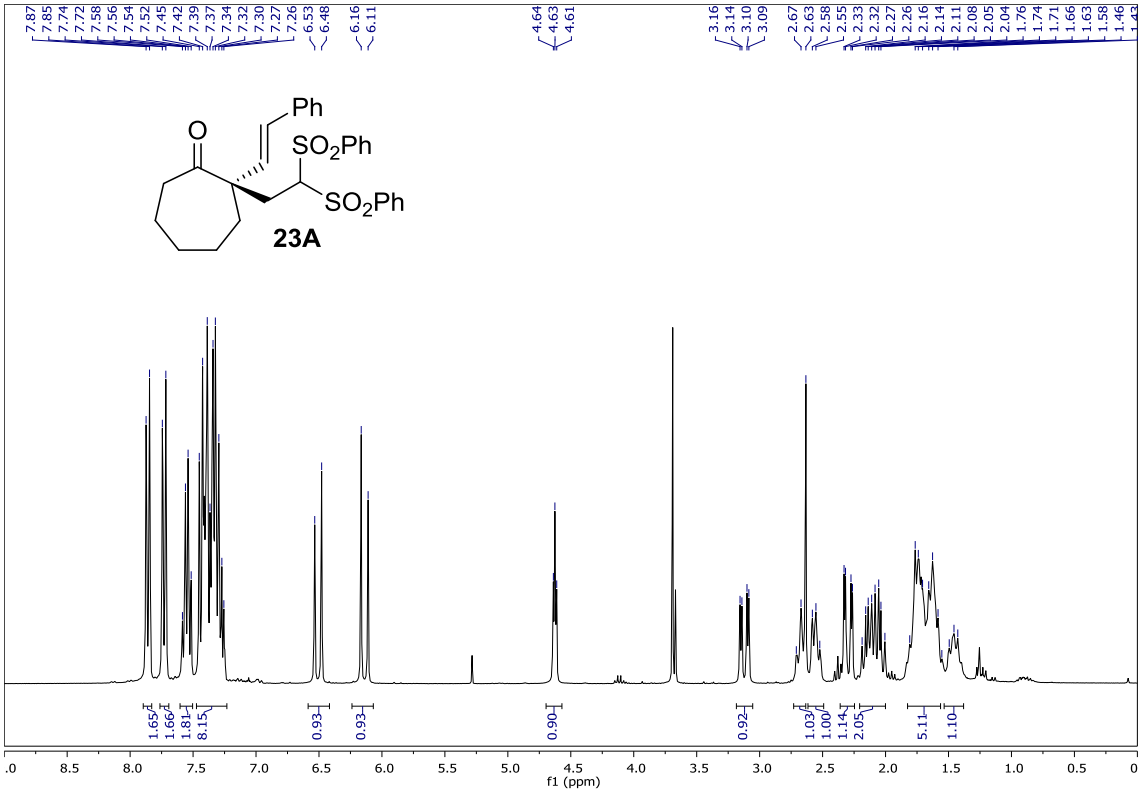
64.62
51.92
44.09
36.51
33.42
32.15
f1 (ppm)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7.30
7.27
7.26
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6.48
6.16
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4.63
4.61
3.16
3.14
3.10
3.09
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2.63
2.58
2.55
2.33
2.32
2.27
2.26
2.16
2.14
2.11
2.08
2.05
2.04
1.76
1.74
1.71
1.66
1.63
1.58
1.46
Ph
O
SO2Ph
SO2Ph
23A
1.65
1.66
1.81
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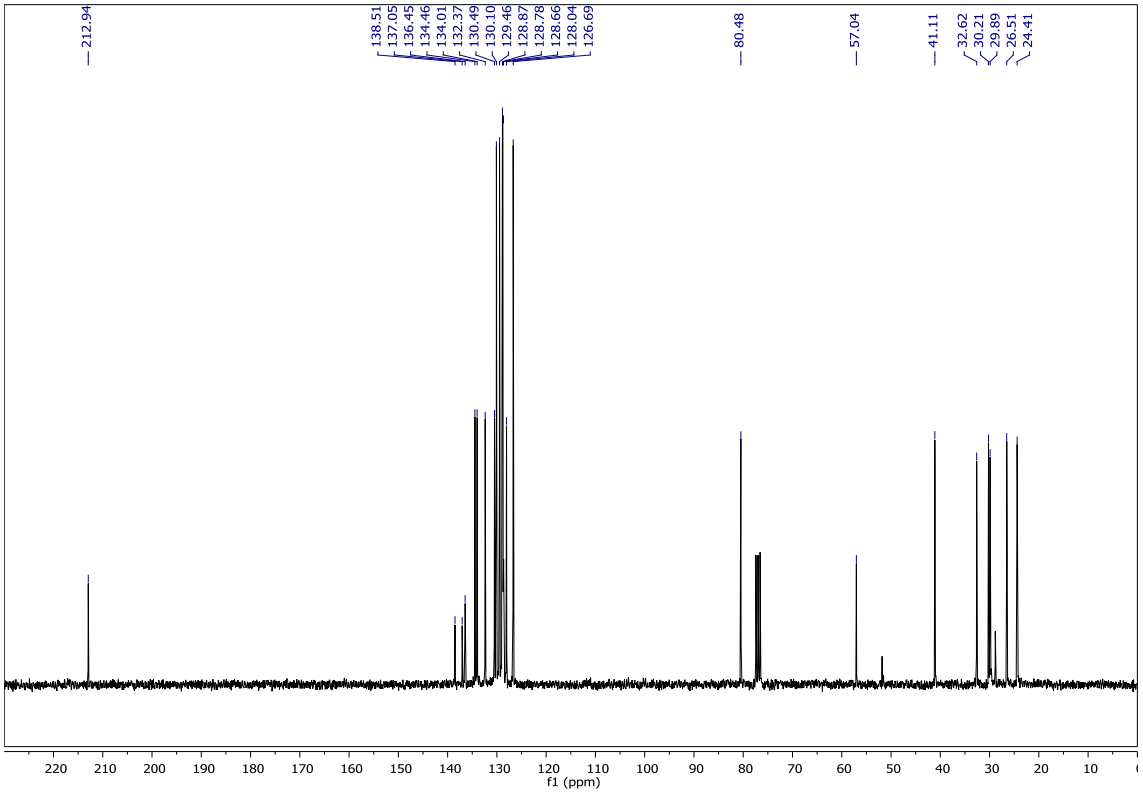
0.93
0.90
0.92
1.03
1.00
1.14
2.05
5.11
1.10
f1 (ppm)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130.49
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129.46
128.87
128.78
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41.11
32.62
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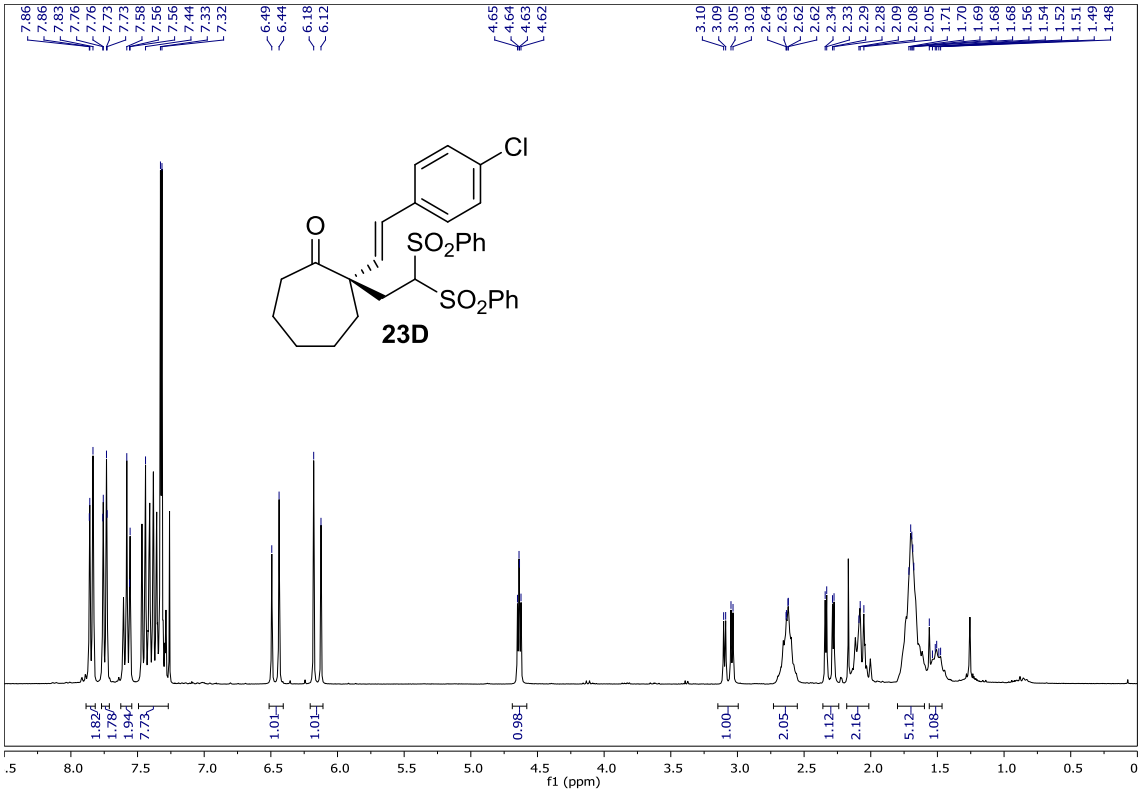
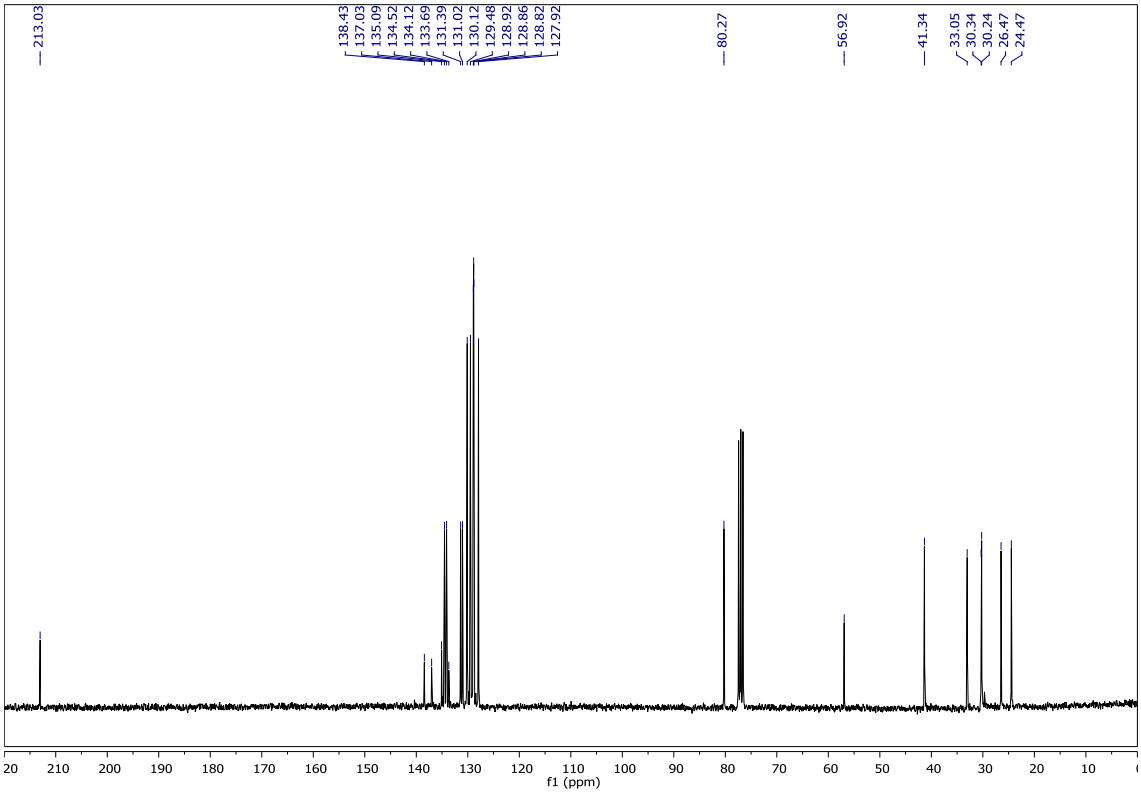
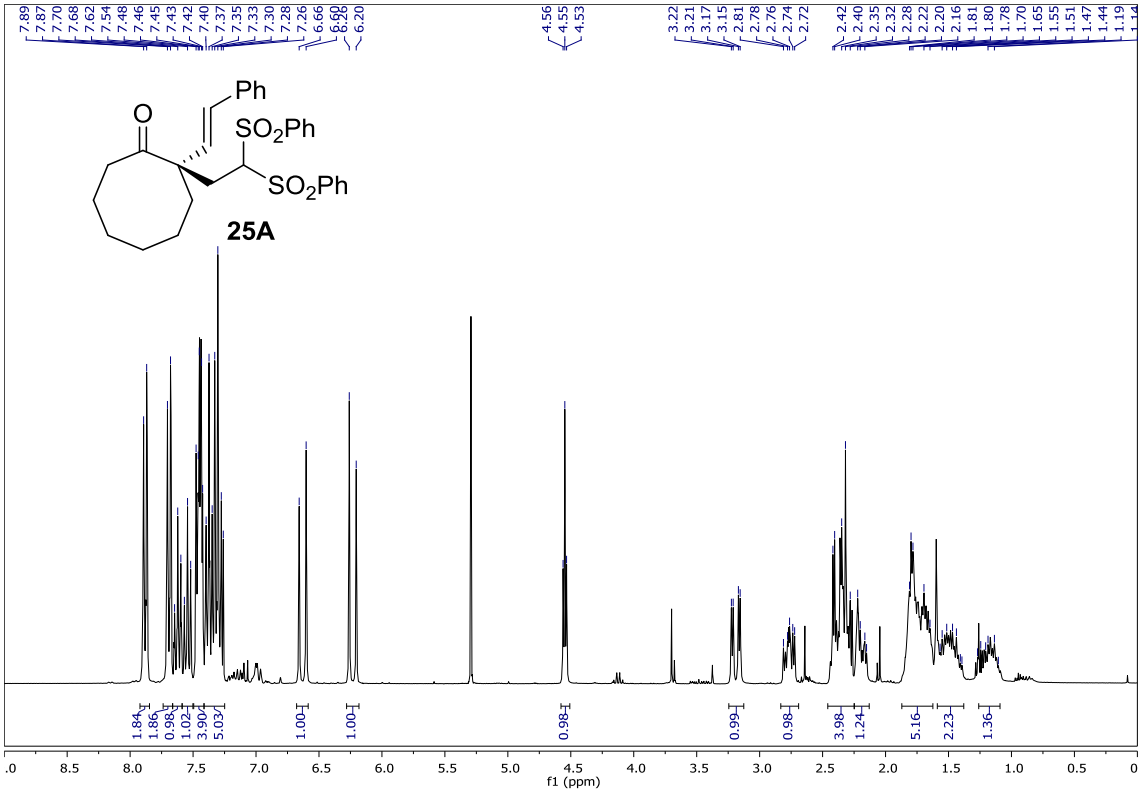
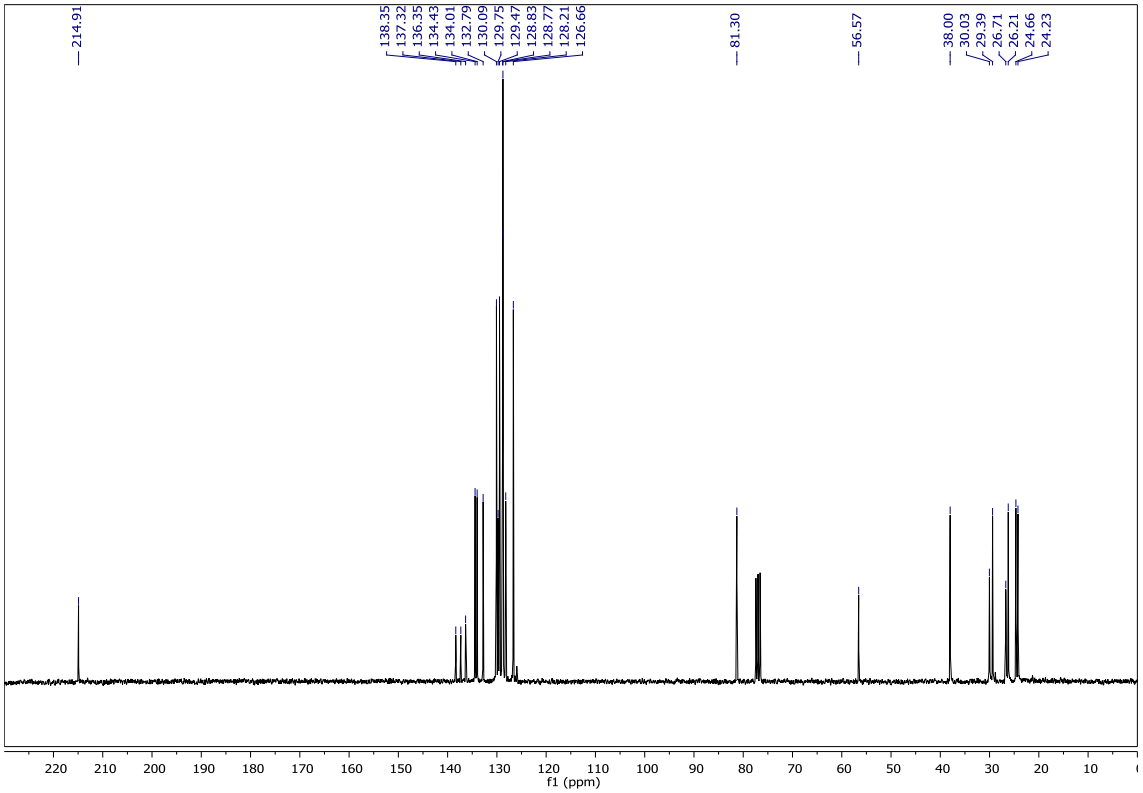
29.89
26.51
24.41
f1 (ppm)


Cl
O
SO2Ph
SO2Ph
23D
f1 (ppm)


f1 (ppm)


Ph
O
SO2Ph
SO2Ph
25A
f1 (ppm)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128.77
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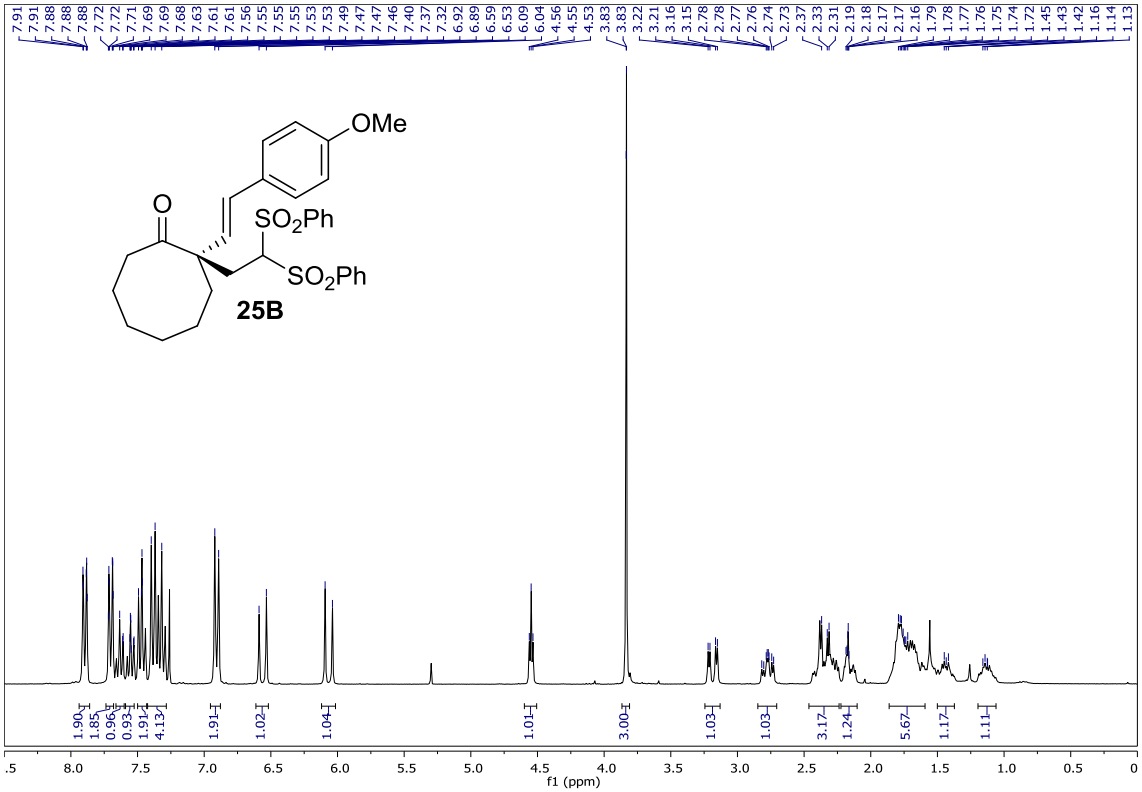
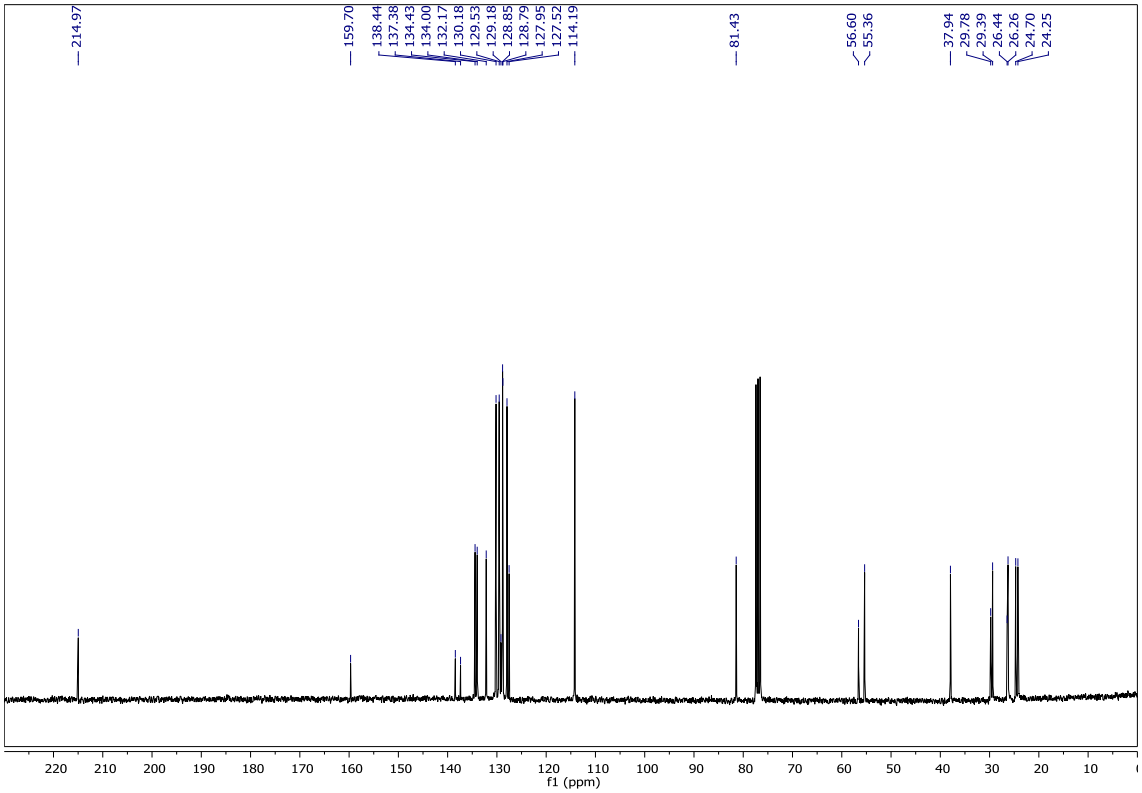
26.71
26.21
24.66
24.23
f1 (ppm)


OMe
O
SO2Ph
SO2Ph
25B
f1 (ppm)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132.17
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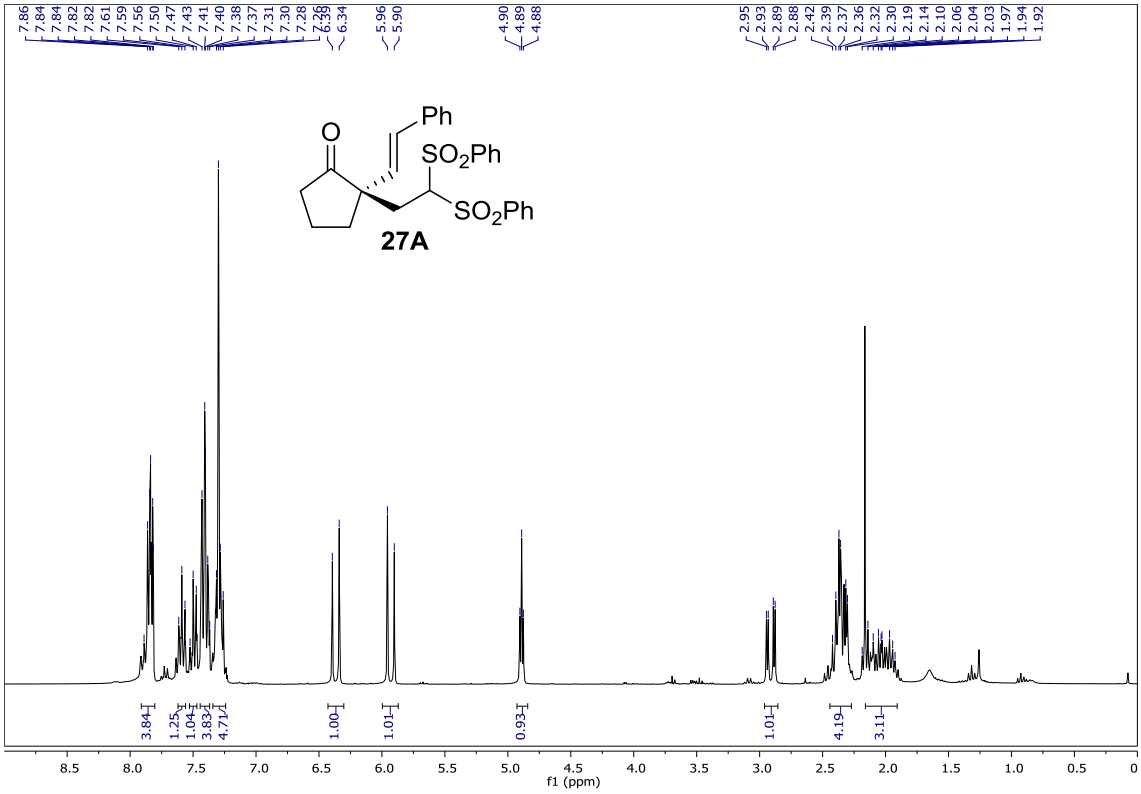
129.18
128.85
128.79
127.95
127.52
114.19
81.43
56.60
55.36
37.94
29.78
29.39
26.44
26.26
24.70
24.25
f1 (ppm)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7.43
7.41
7.40
7.38
7.37
7.31
7.30
7.28
6.38
6.34
5.96
5.90
4.90
4.89
4.88
2.95
2.93
2.89
2.88
2.42
2.39
2.37
2.36
2.32
2.30
2.19
2.14
2.10
2.06
2.04
2.03
1.97
1.94
1.92
O
Ph
SO2Ph
SO2Ph
27A
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1.04
3.83
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1.00
1.01
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1.01
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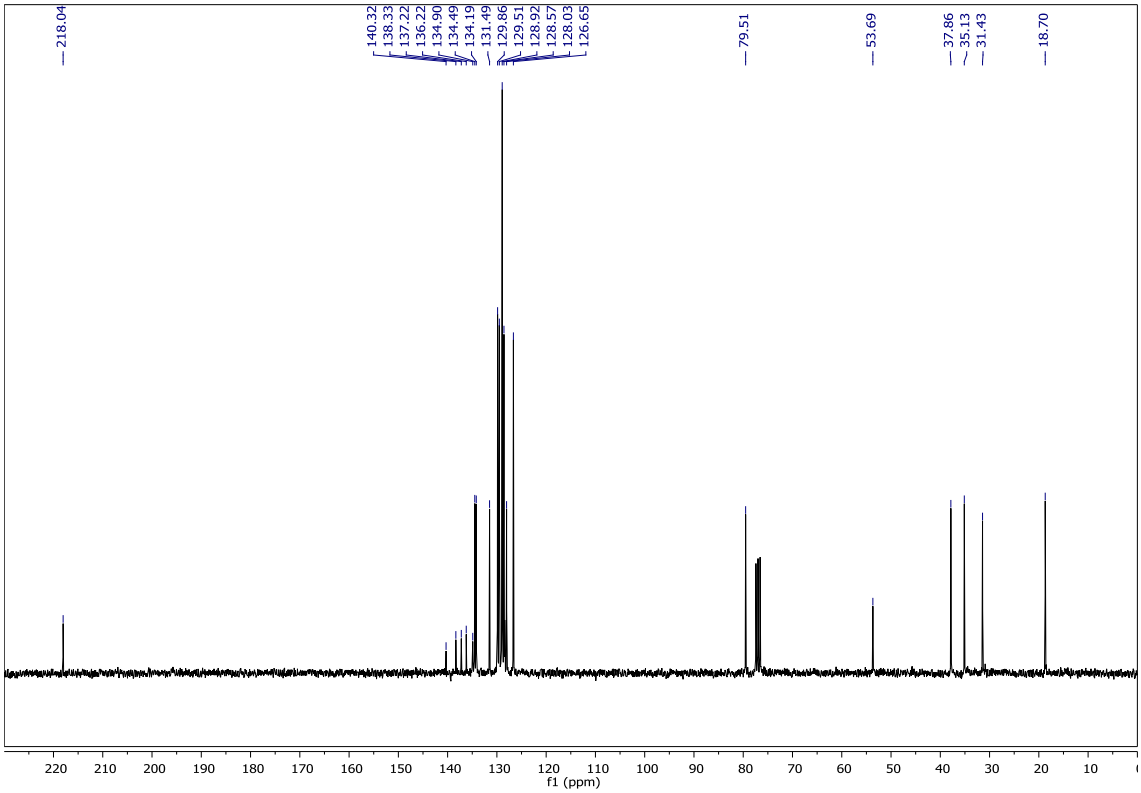
3.11
f1 (ppm)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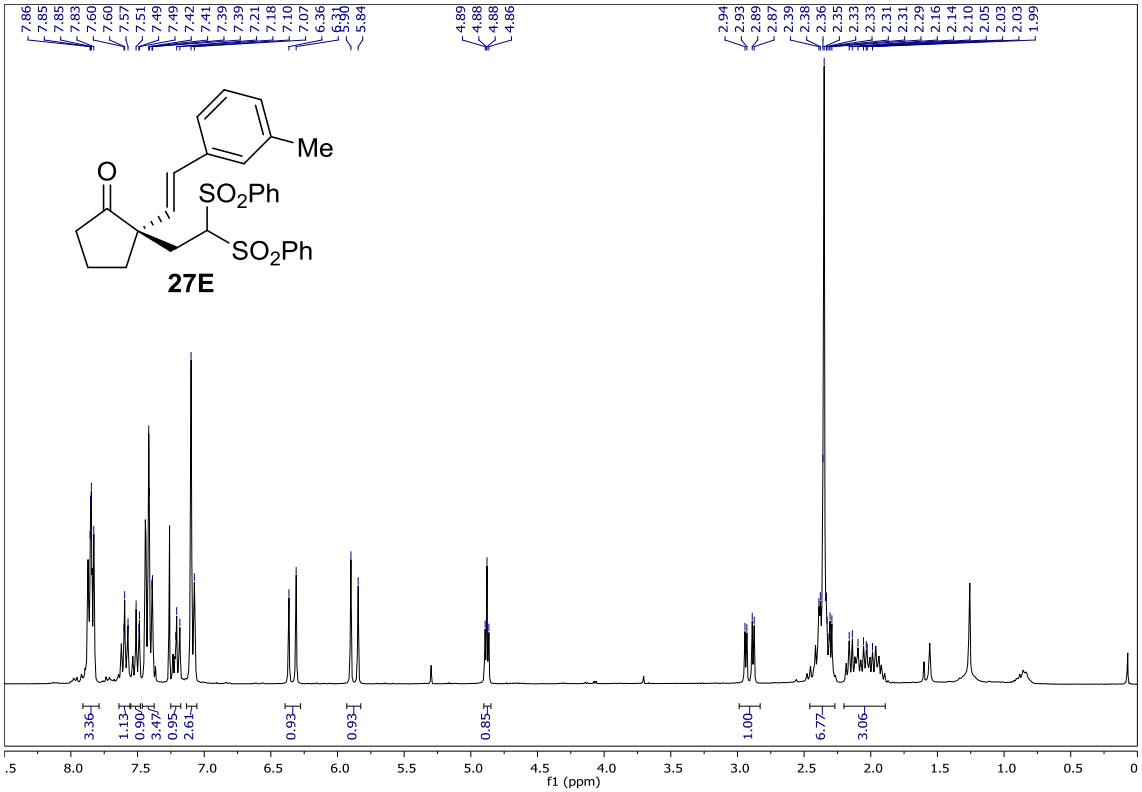
129.86
129.51
128.92
128.57
128.03
126.65
79.51
53.69
37.86
35.13
31.43
18.70
f1 (ppm)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7.85
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7.60
7.57
7.51
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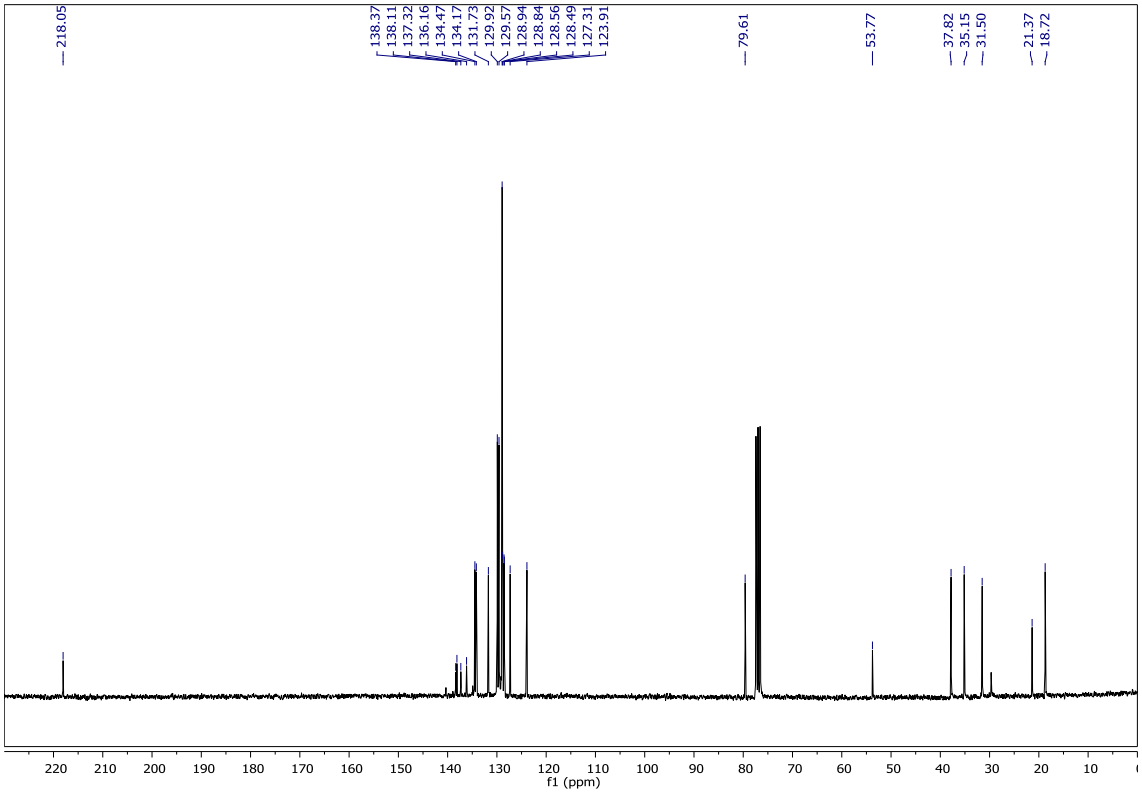
7.49
7.42
7.41
7.39
7.39
7.21
7.18
7.10
7.07
6.36
6.31
5.90
5.84
4.89
4.88
4.88
4.86
2.94
2.93
2.89
2.87
2.39
2.38
2.36
2.35
2.33
2.33
2.31
2.31
2.29
2.16
2.14
2.10
2.05
2.03
2.03
1.99
Me
O
SO2Ph
SO2Ph
27E
3.36
1.13
0.90
3.47
0.95
2.61
0.93
0.93
0.85
1.00
6.77
3.06
f1 (ppm)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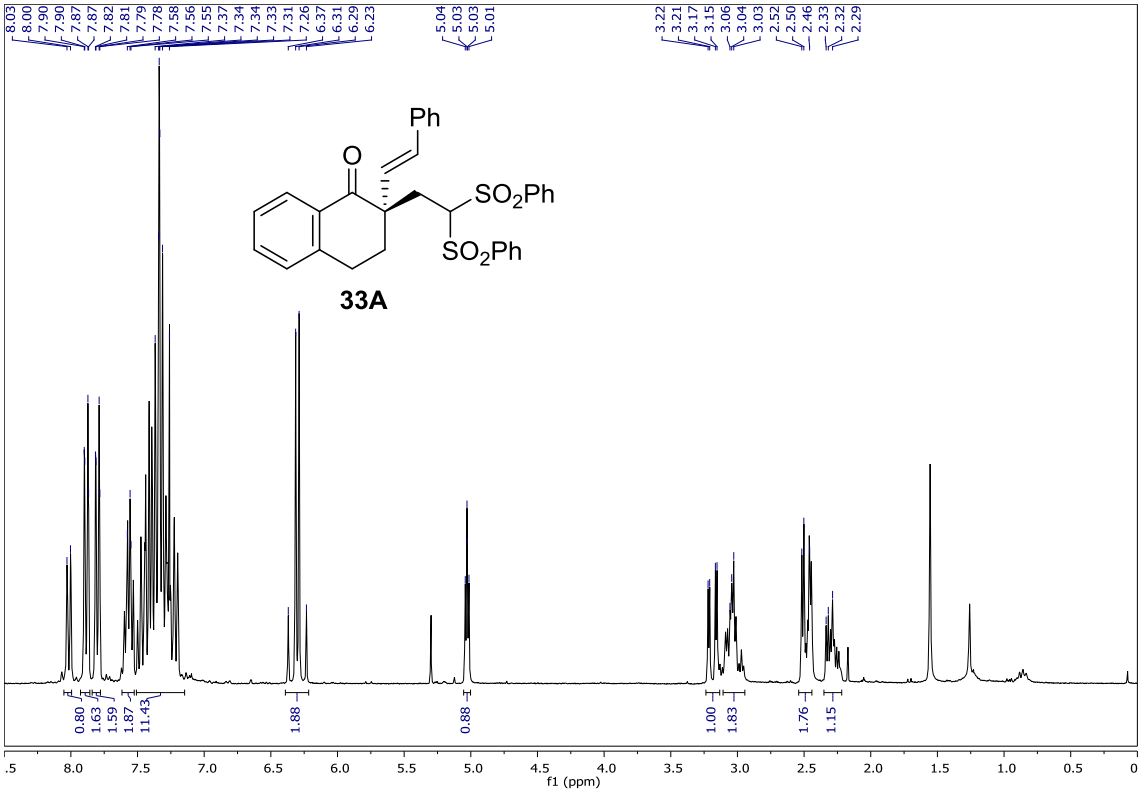
134.47
134.17
131.73
129.92
129.57
128.94
128.84
128.56
128.49
127.31
123.91
79.61
53.77
37.82
35.15
31.50
21.37
18.72
f1 (ppm)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8.00
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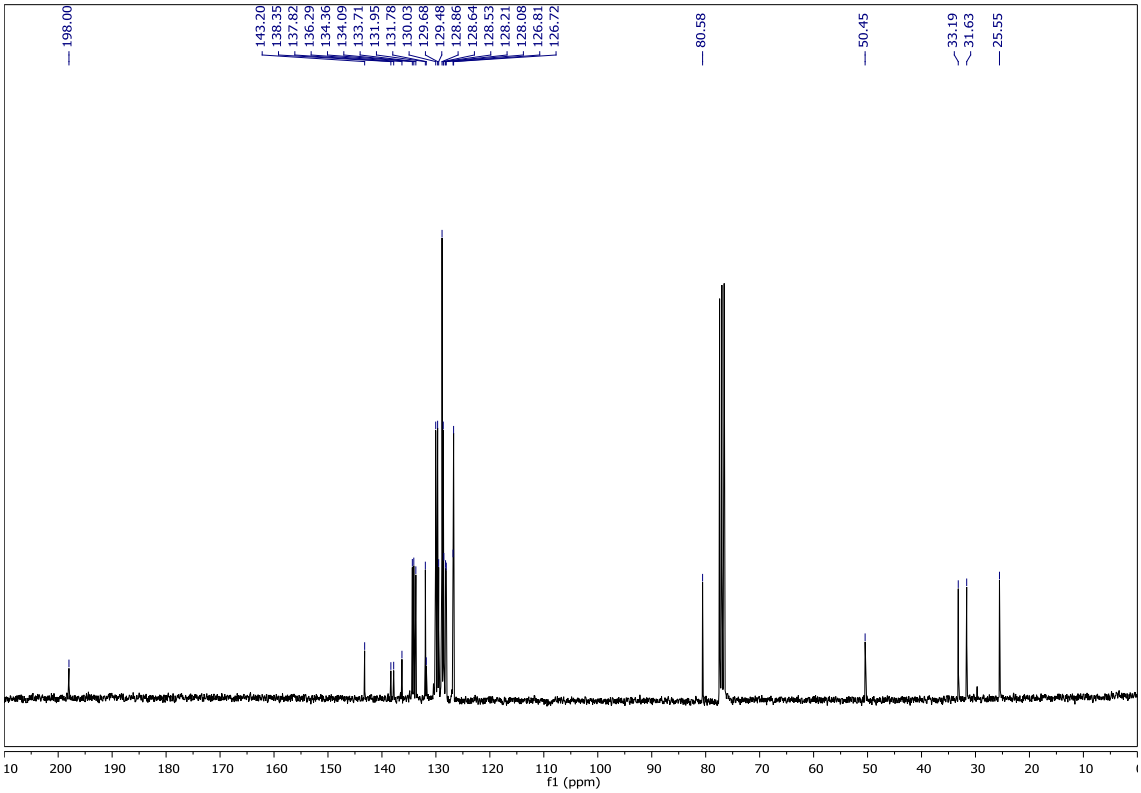
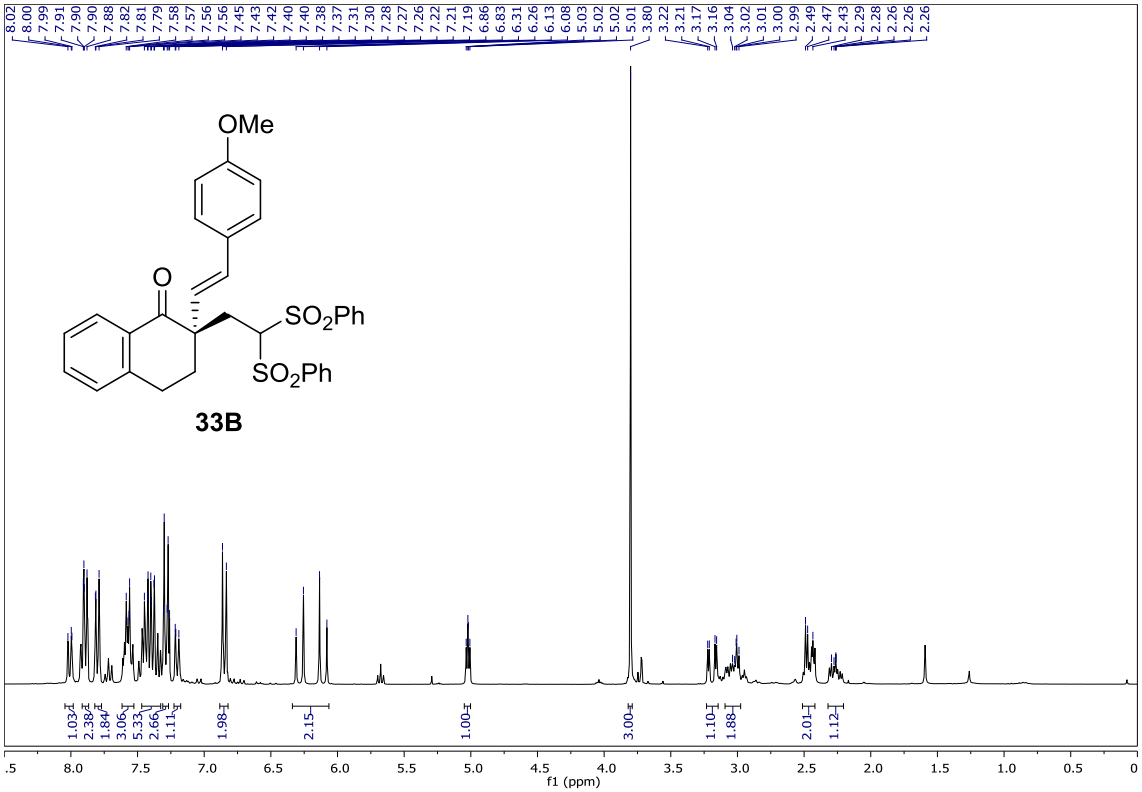
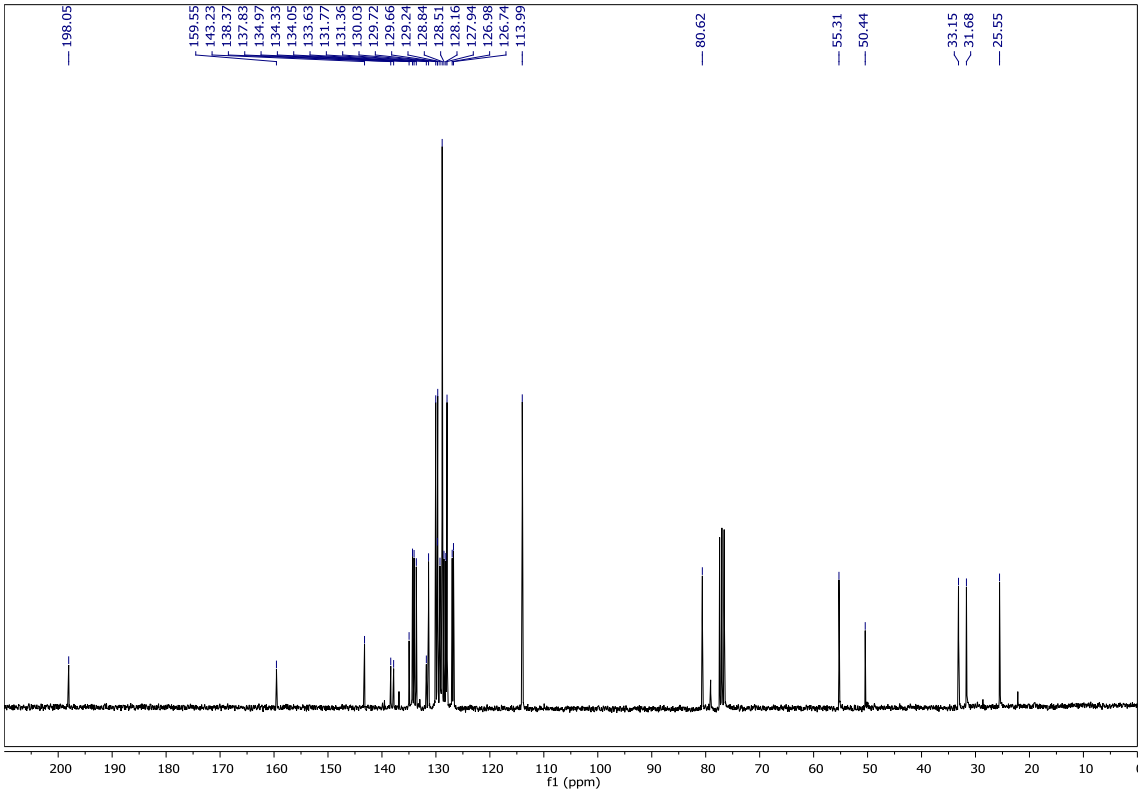
7.87
7.82
7.81
7.79
7.78
7.58
7.56
7.55
7.37
7.34
7.34
7.33
7.31
7.26
6.37
6.31
6.29
6.23
5.04
5.03
5.03
5.01
3.22
3.21
3.17
3.15
3.06
3.04
3.03
2.52
2.50
2.46
2.33
2.32
2.29
Ph
O
SO2Ph
SO2Ph
33A
0.80
1.63
1.59
1.87
11.43
1.88
0.88
1.00
1.83
1.76
1.15
f1 (ppm)


198.00
143.20
138.35
137.82
136.29
134.36
134.09
133.71
131.95
131.78
130.03
129.68
129.48
128.86
128.64
128.53
128.21
128.08
126.81
126.72
80.58
50.45
33.19
31.63
25.55
f1 (ppm)


OMe
O
SO2Ph
SO2Ph
33B
f1 (ppm)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134.97
134.33
134.05
133.63
131.77
131.36
130.03
129.72
129.66
129.24
128.84
128.51
128.16
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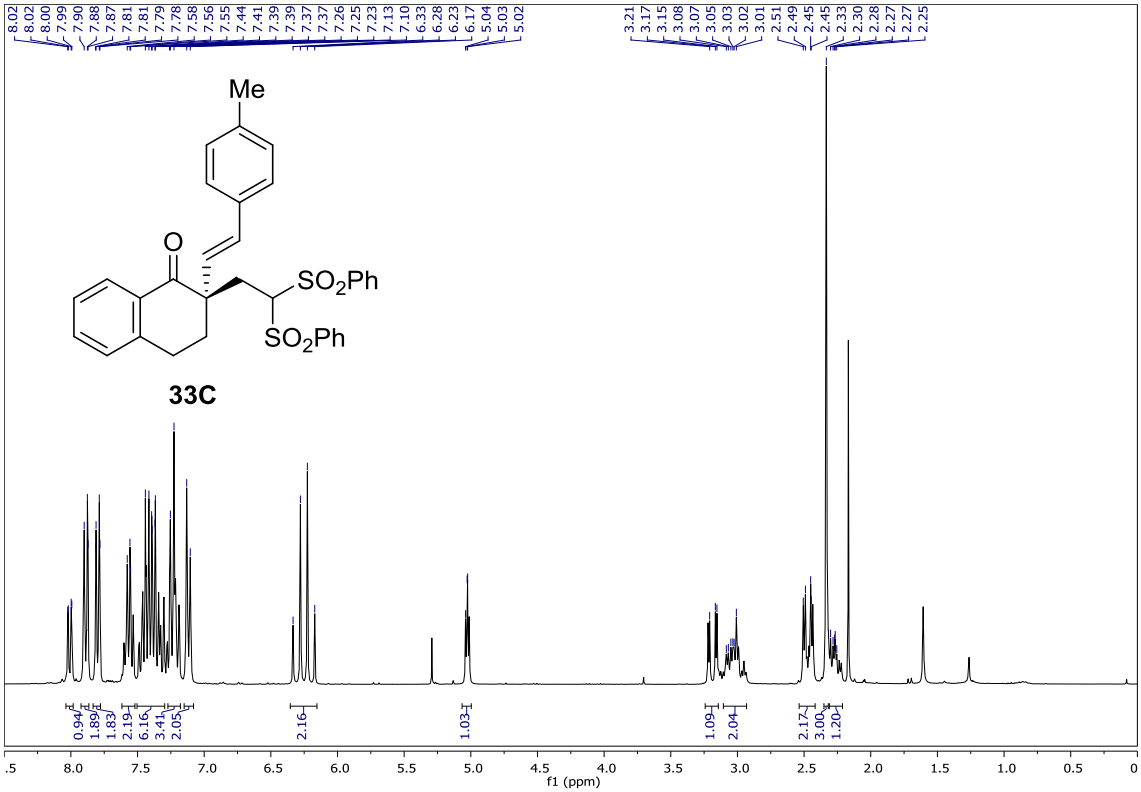
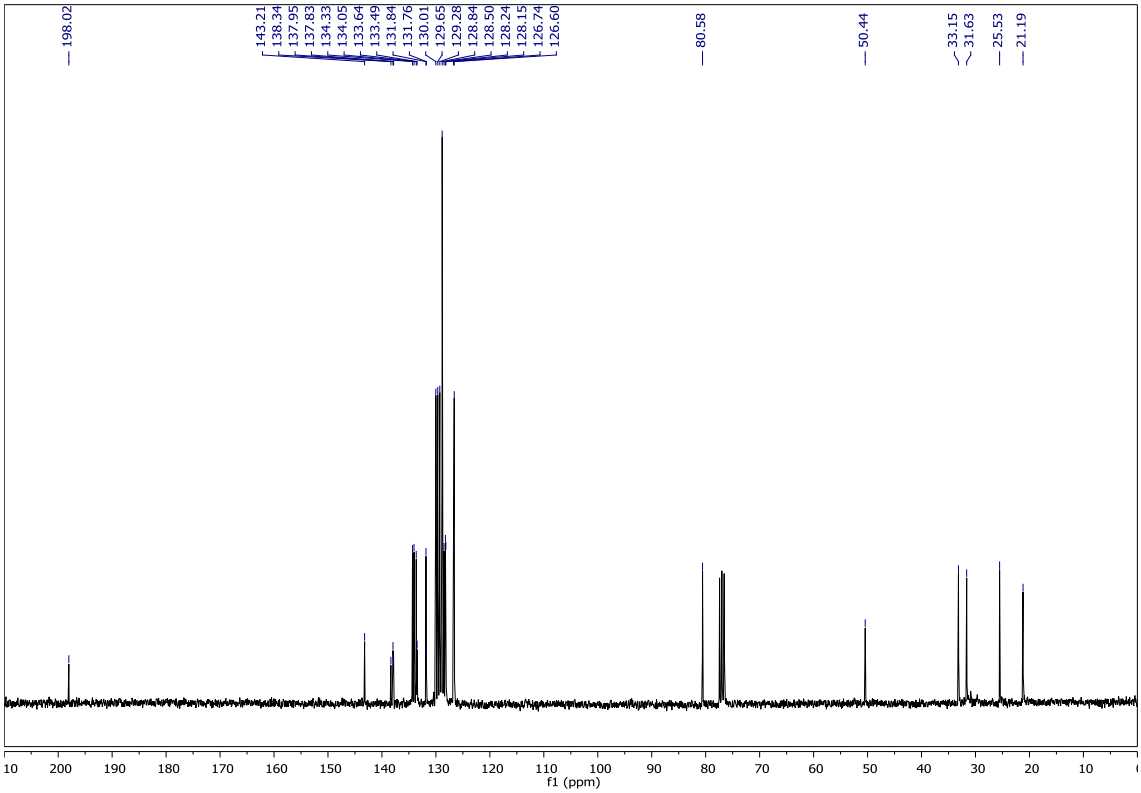
126.74
113.99
80.62
55.31
50.44
33.15
31.68
25.55
f1 (ppm)


Me
O
SO2Ph
SO2Ph
33C
f1 (ppm)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133.64
133.49
131.84
131.76
130.01
129.65
129.28
128.84
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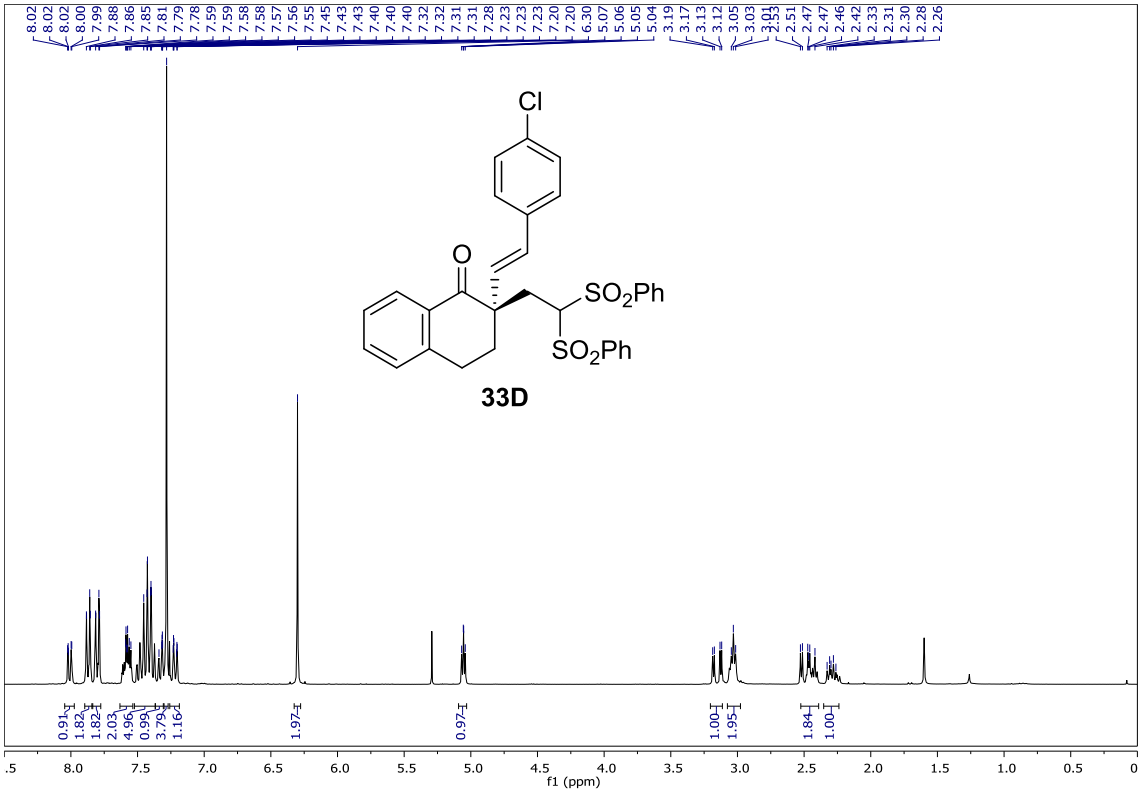
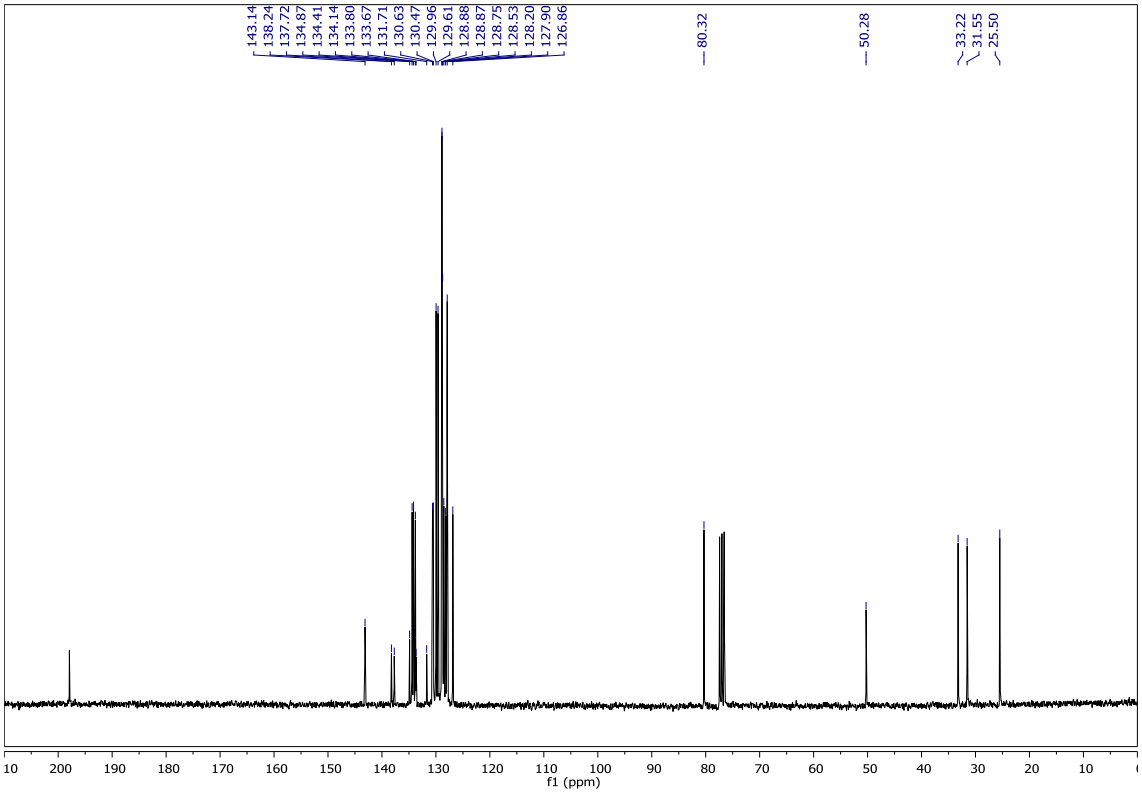
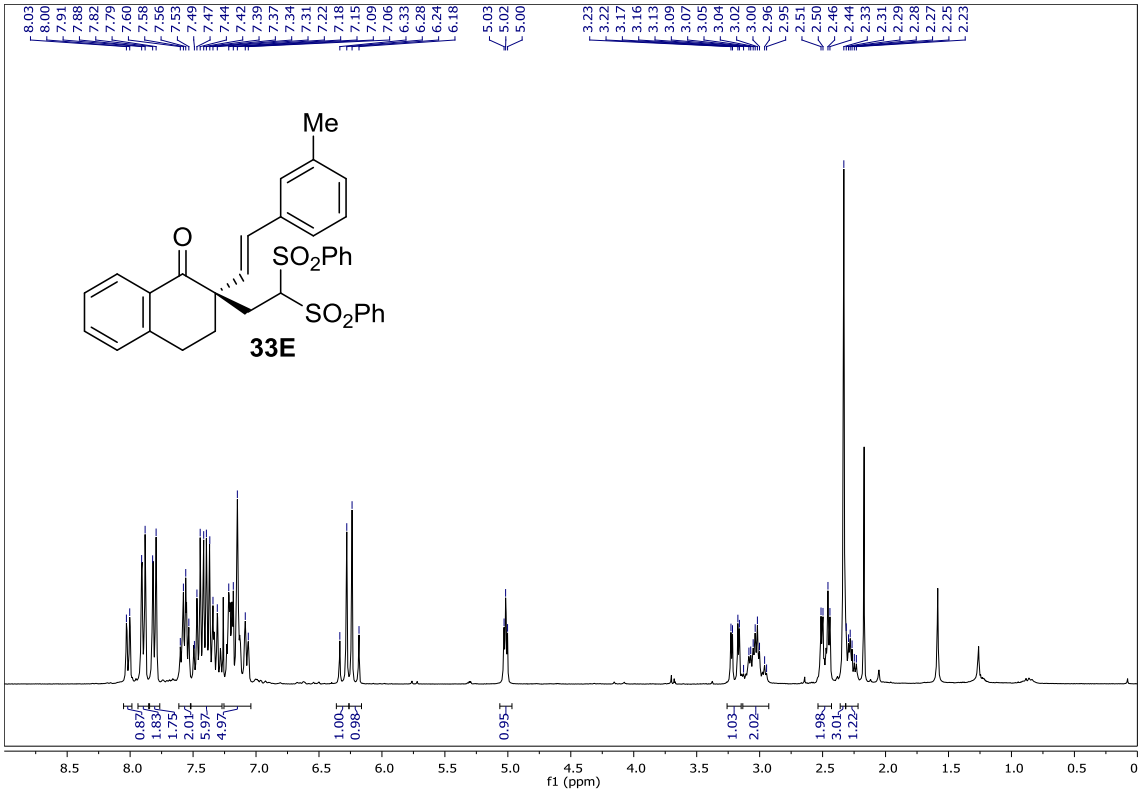
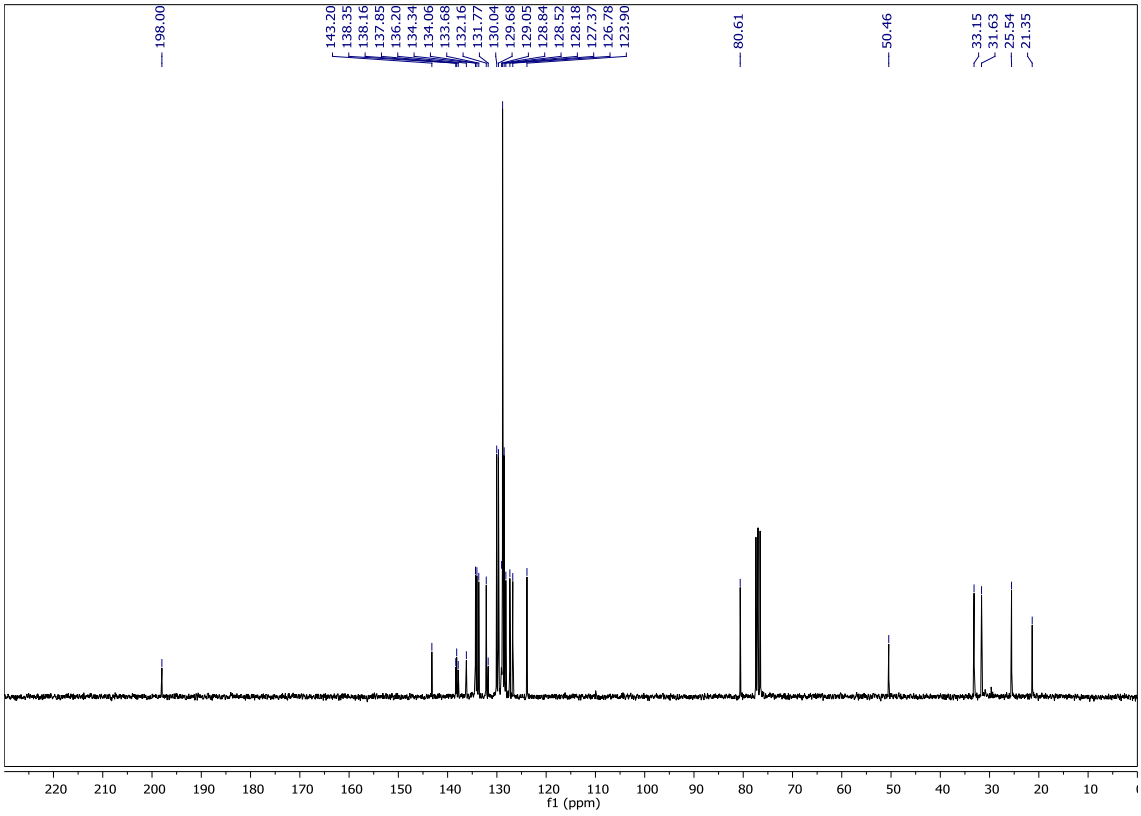
33.15
31.63
25.53
21.19
f1 (ppm)



33D




Me
O
SO2Ph
SO2Ph
33E
f1 (ppm)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143.20
138.35
138.16
137.85
136.20
134.34
134.06
133.68
132.16
131.77
130.04
129.68
129.05
128.84
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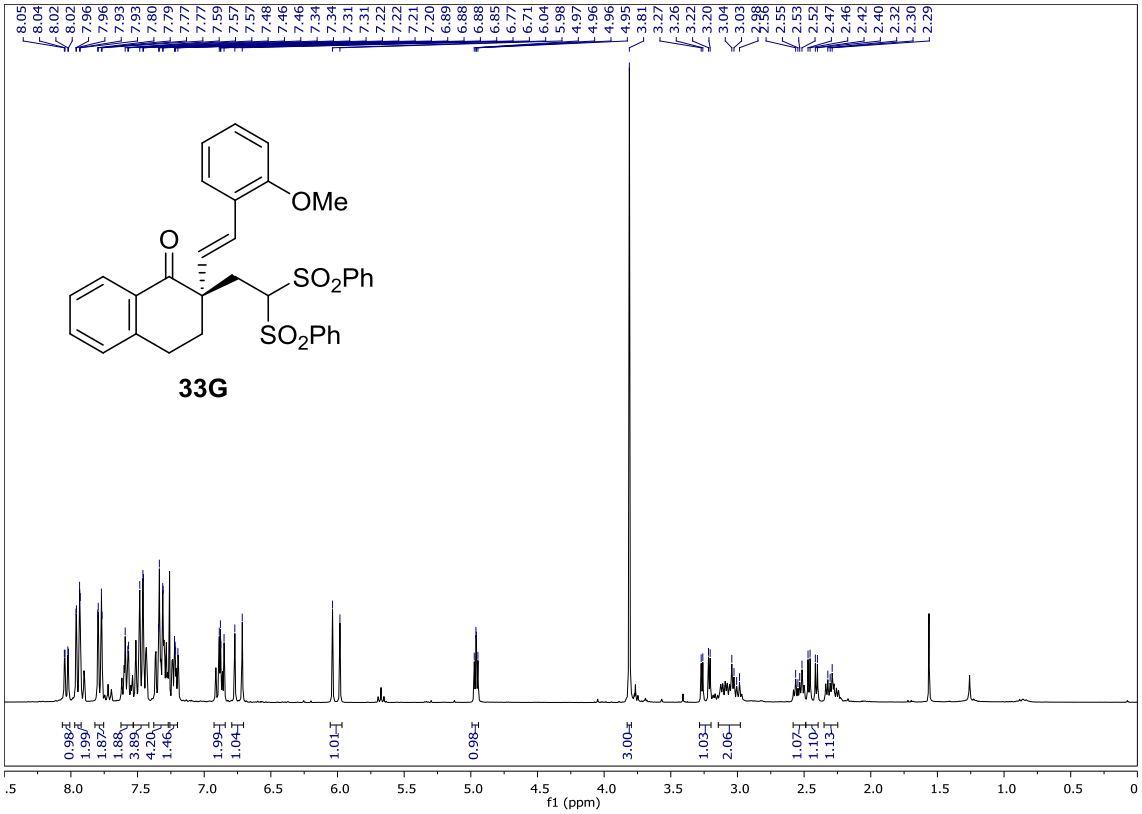
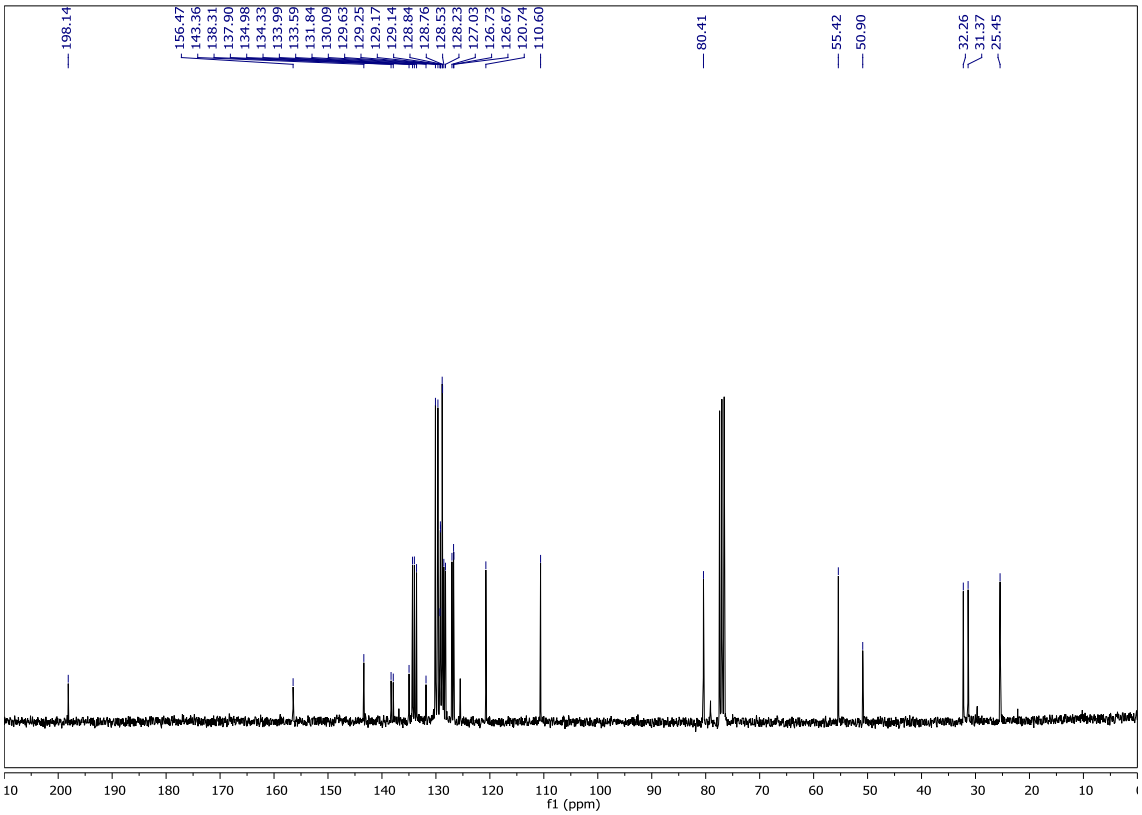
33.15
31.63
25.54
21.35
f1 (ppm)


OMe
O
SO2Ph
SO2Ph
f1 (ppm)

33G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156.47
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134.33
133.99
133.59
131.84
130.09
129.63
129.25
129.17
129.14
128.84
128.76
128.53
128.23
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126.73
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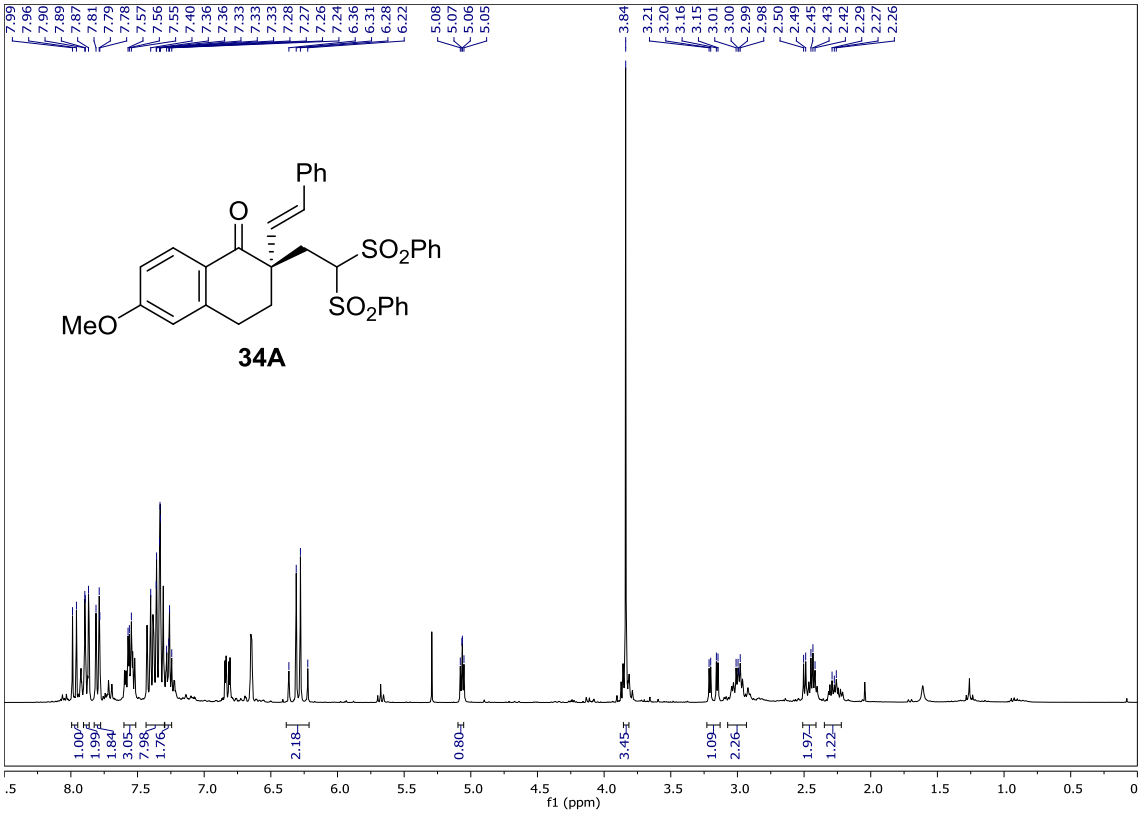
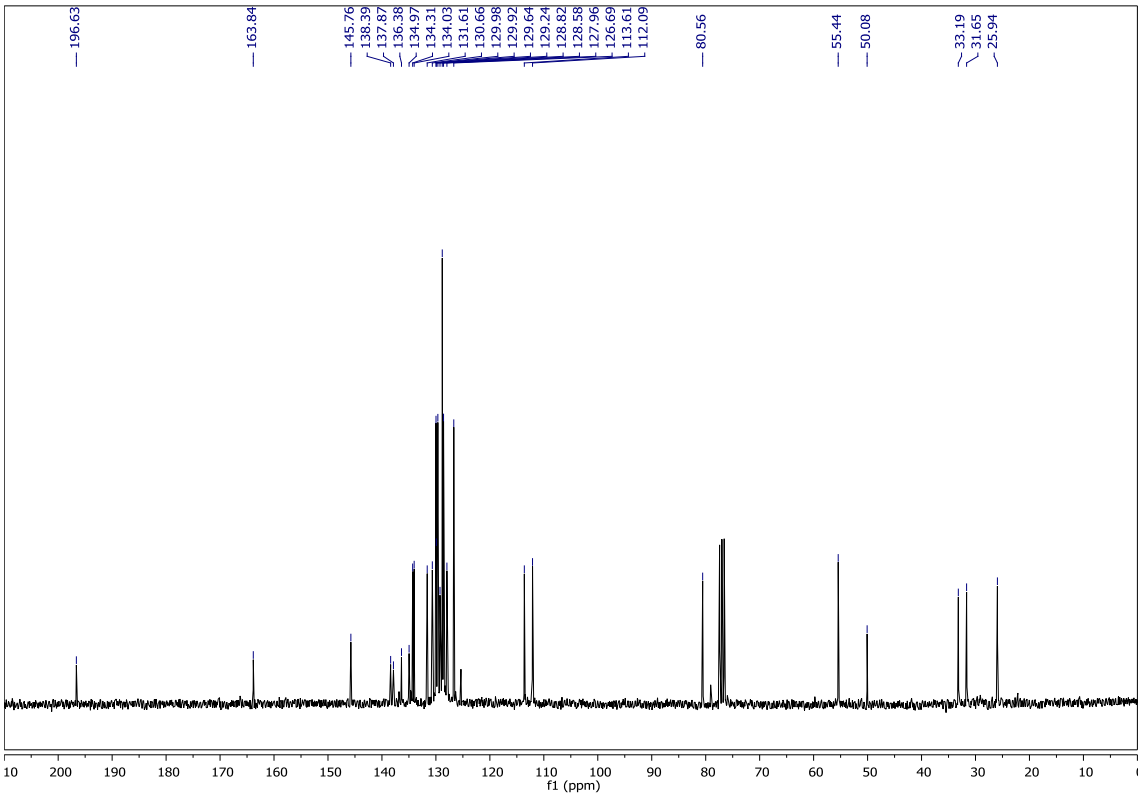
120.74
110.60
80.41
55.42
50.90
32.26
31.37
25.45
f1 (ppm)


Ph
O
SO2Ph
SO2Ph
MeO
34A
f1 (ppm)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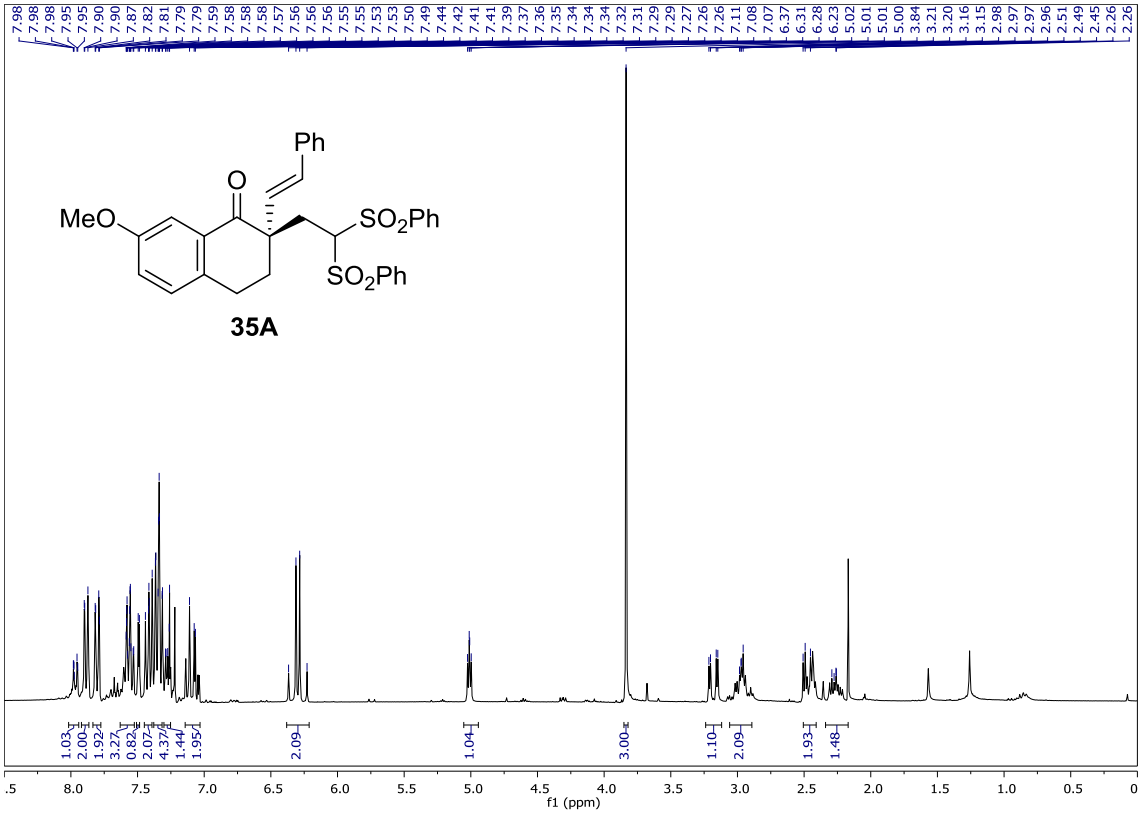
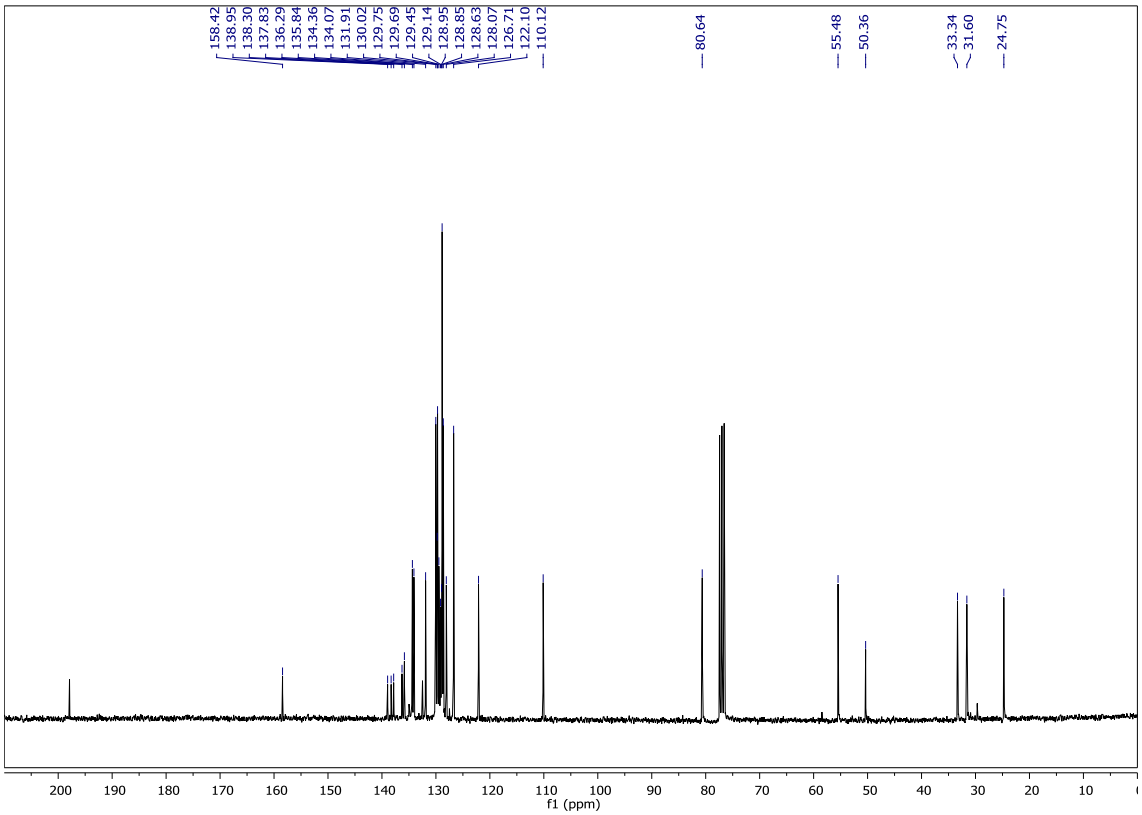

Ph
O
MeO
SO2Ph
SO2Ph
35A
f1 (ppm)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135.84
134.36
134.07
131.91
130.02
129.75
129.69
129.45
129.14
128.95
128.85
128.63
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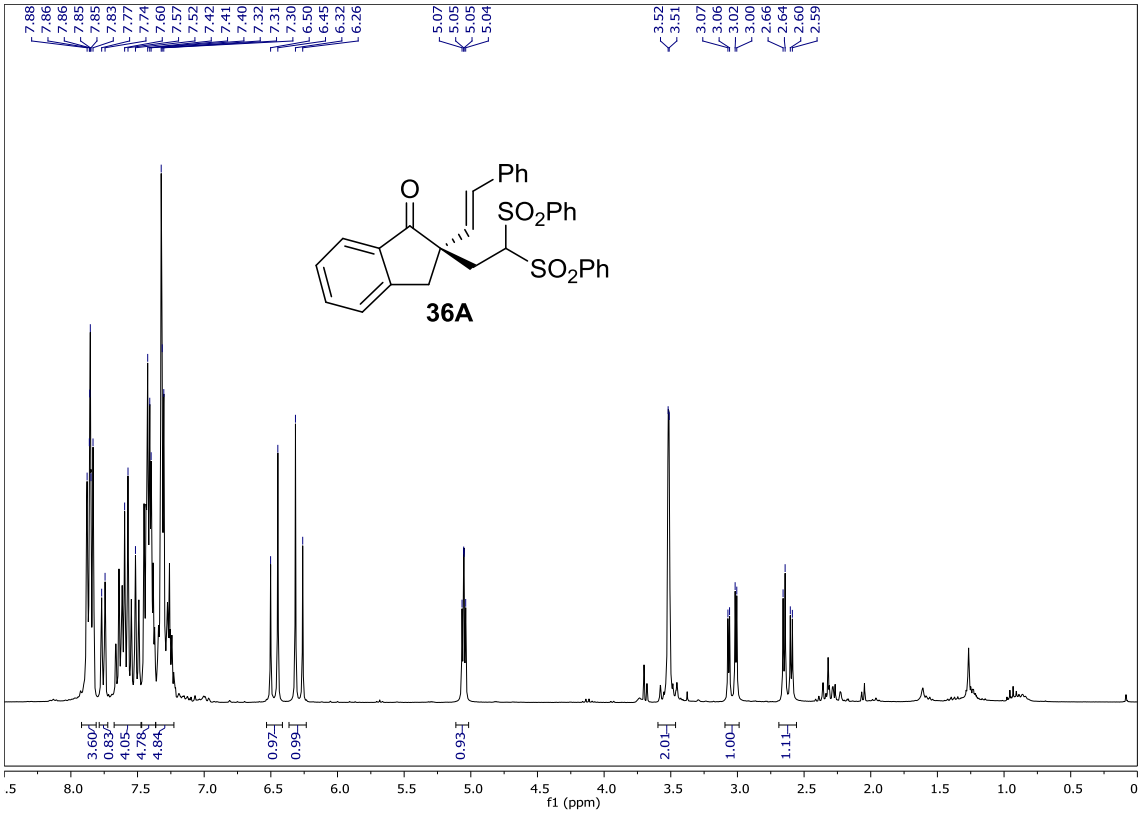
122.10
110.12
80.64
55.48
50.36
33.34
31.60
24.75
f1 (ppm)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7.60
7.57
7.52
7.42
7.41
7.40
7.32
7.31
7.30
6.50
6.45
6.32
6.26
5.07
5.05
5.05
5.04
3.52
3.51
3.07
3.06
3.02
3.00
2.66
2.64
2.60
2.59
O
Ph
SO2Ph
SO2Ph
36A
3.60
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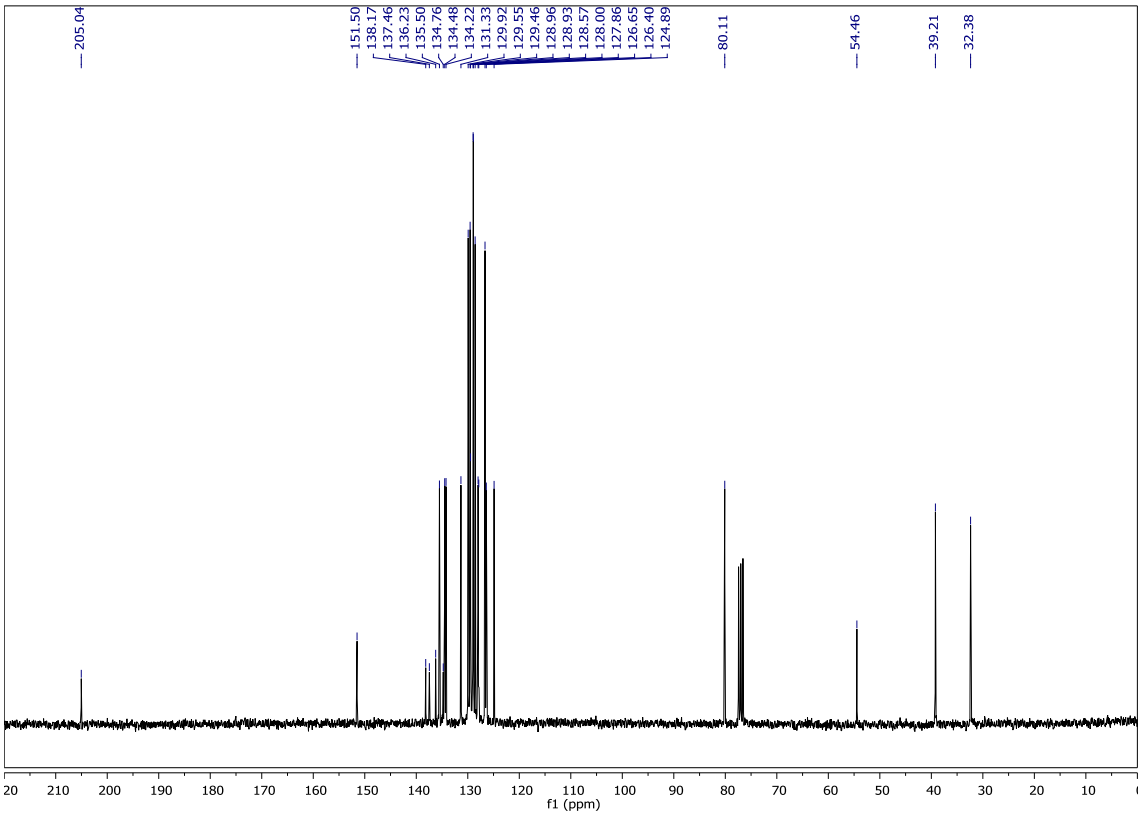
4.78
4.84
0.97
0.99
0.93
2.01
1.00
1.11
f1 (ppm)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129.55
129.46
128.96
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80.11
54.46
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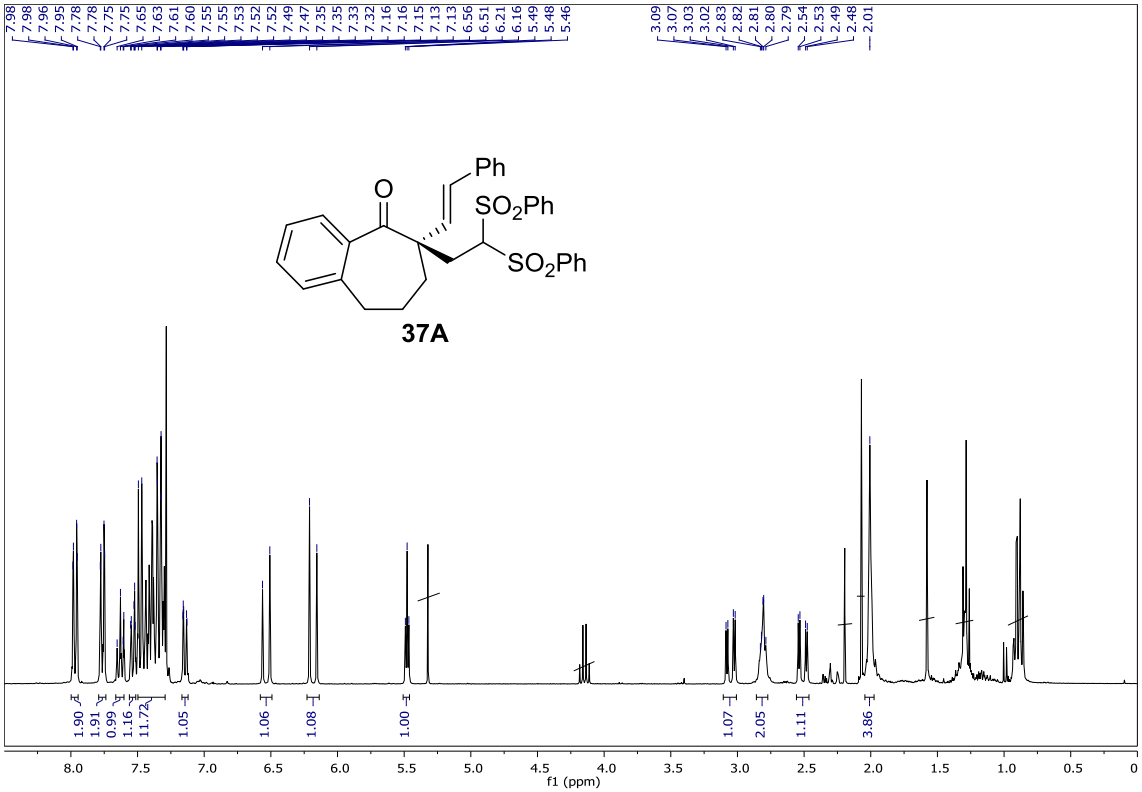
32.38
f1 (ppm)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7.61
7.60
7.55
7.55
7.53
7.52
7.52
7.49
7.47
7.35
7.35
7.33
7.32
7.16
7.15
7.13
7.13
6.56
6.51
6.21
6.16
5.49
5.48
5.46
3.09
3.07
3.03
3.02
2.83
2.82
2.81
2.80
2.79
2.54
2.53
2.49
2.48
2.01
Ph
O
SO2Ph
SO2Ph
37A
1.90
1.91
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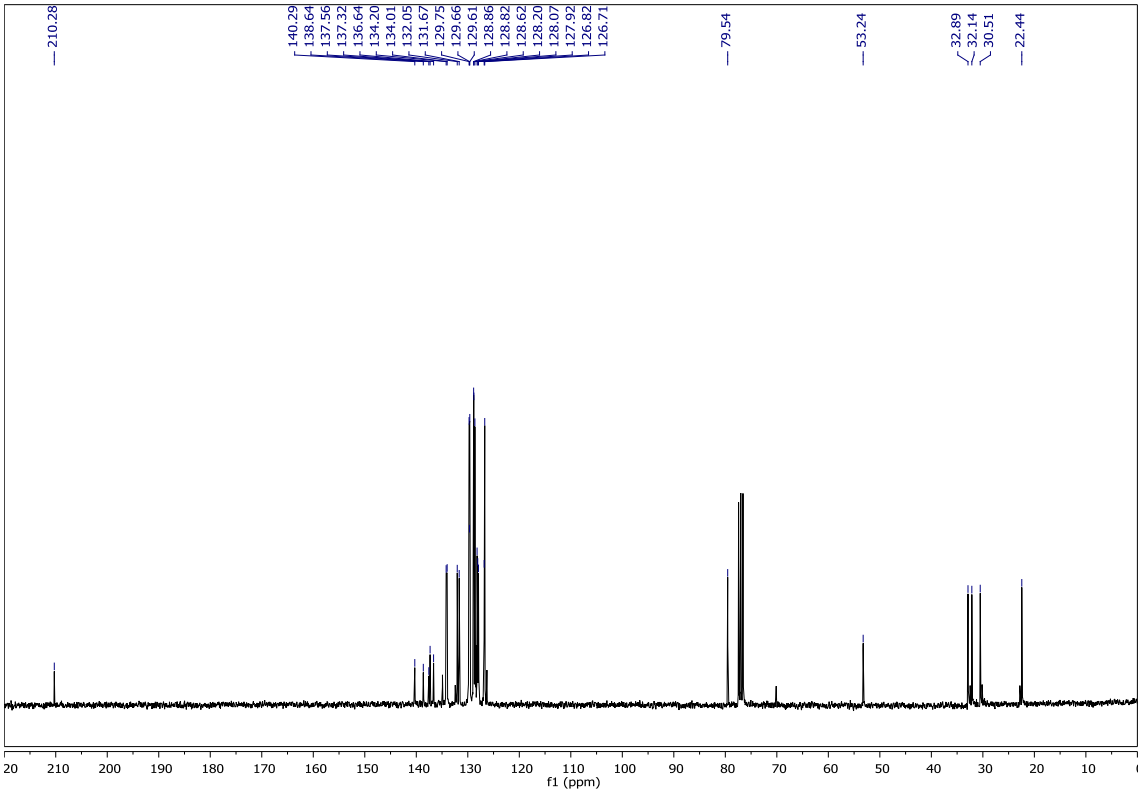
1.05
1.06
1.08
1.00
1.07
2.05
1.11
3.86
f1 (ppm)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129.66
129.61
128.86
128.82
128.62
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128.07
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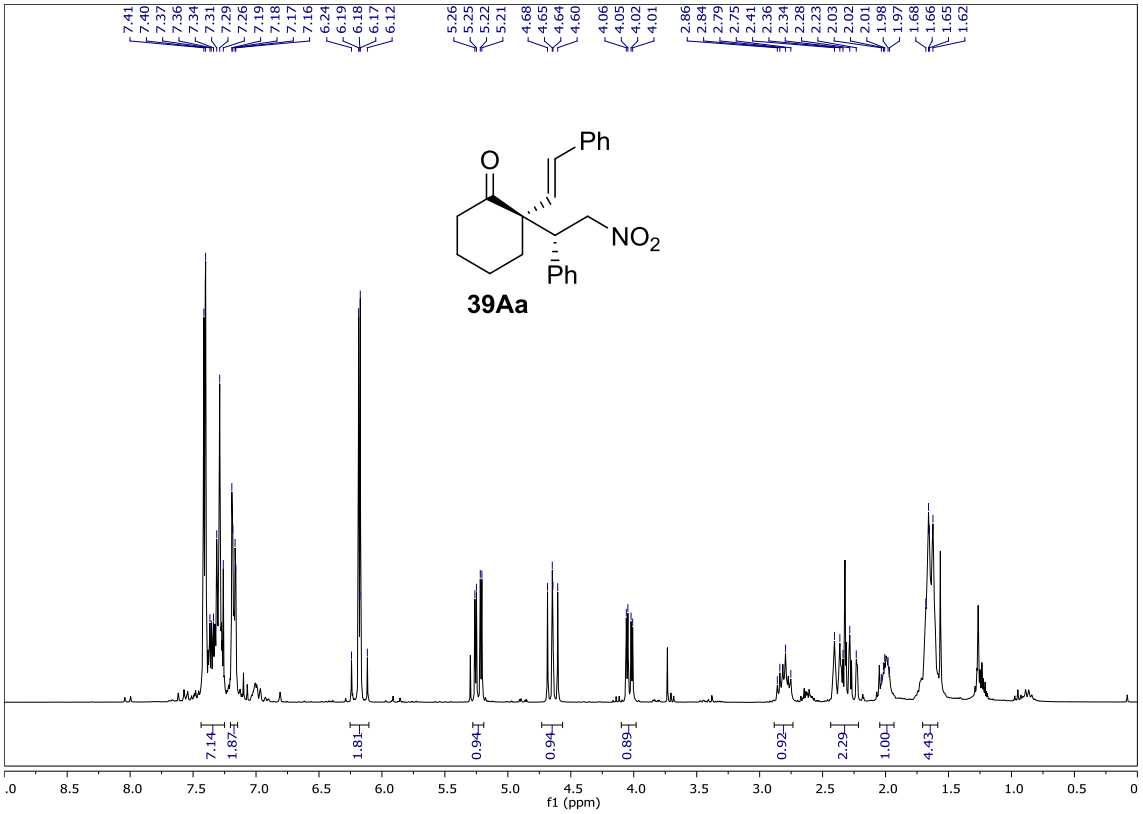
126.82
126.71
79.54
53.24
32.89
32.14
30.51
22.44
f1 (ppm)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7.26
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7.16
6.24
6.19
6.18
6.17
6.12
5.26
5.25
5.22
5.21
4.68
4.65
4.64
4.60
4.06
4.05
4.02
4.01
2.86
2.84
2.79
2.75
2.41
2.36
2.34
2.28
2.23
2.03
2.02
2.01
1.98
1.97
1.68
1.66
1.65
1.62
O
Ph
NO2
Ph
39Aa
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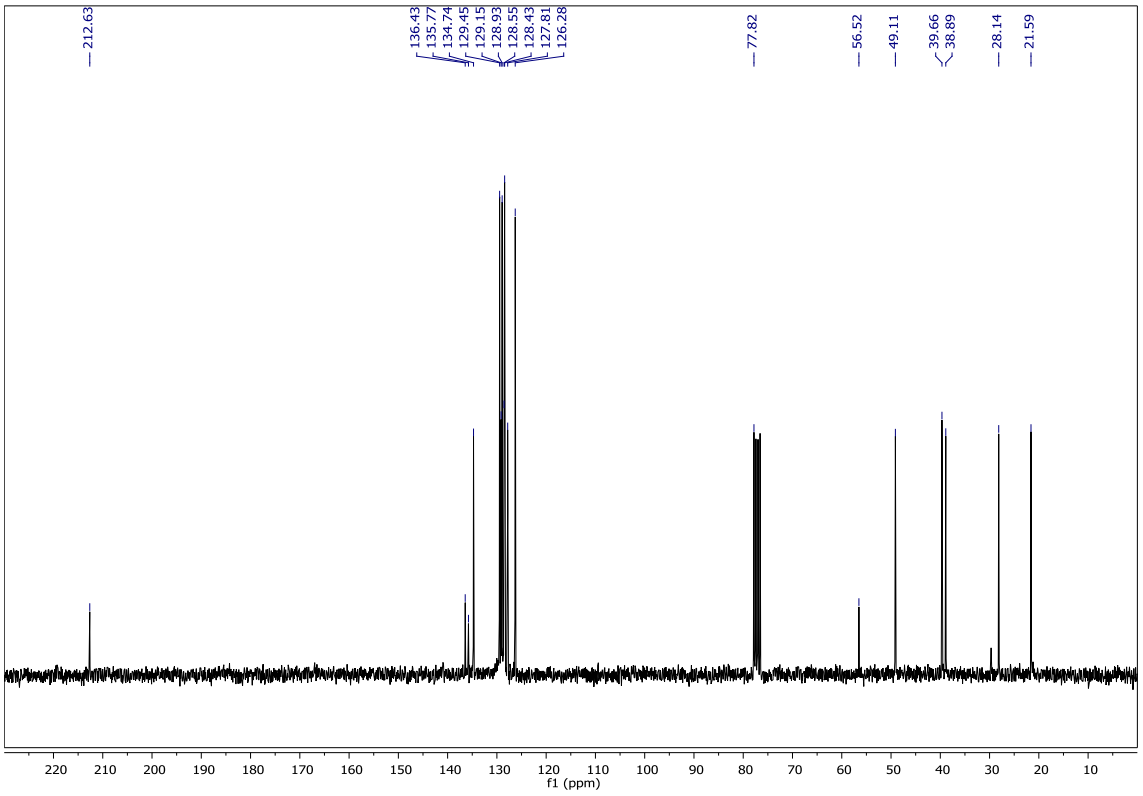
1.81
0.94
0.94
0.89
0.92
2.29
1.00
4.43
f1 (ppm)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129.45
129.15
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128.43
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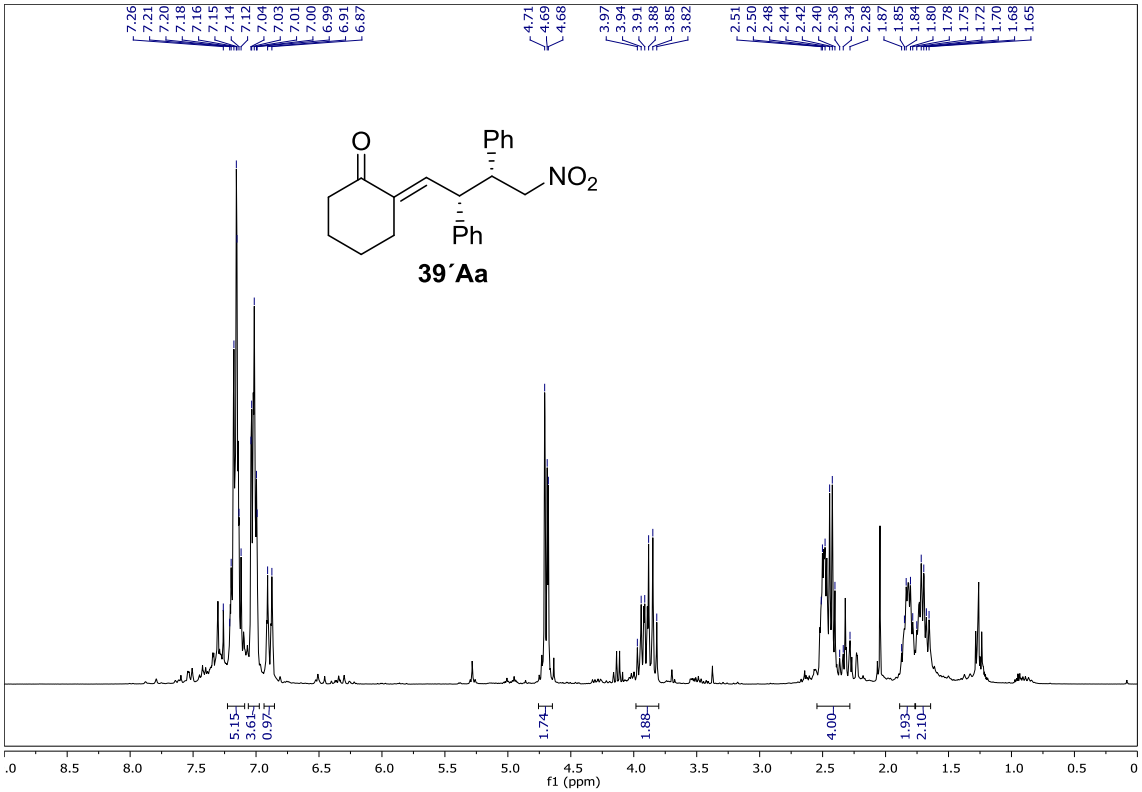
126.28
77.82
56.52
49.11
39.66
38.89
28.14
21.59
f1 (ppm)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7.21
7.20
7.18
7.16
7.15
7.14
7.12
7.04
7.03
7.01
7.00
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6.91
6.87
4.71
4.69
4.68
3.97
3.94
3.91
3.88
3.85
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2.51
2.50
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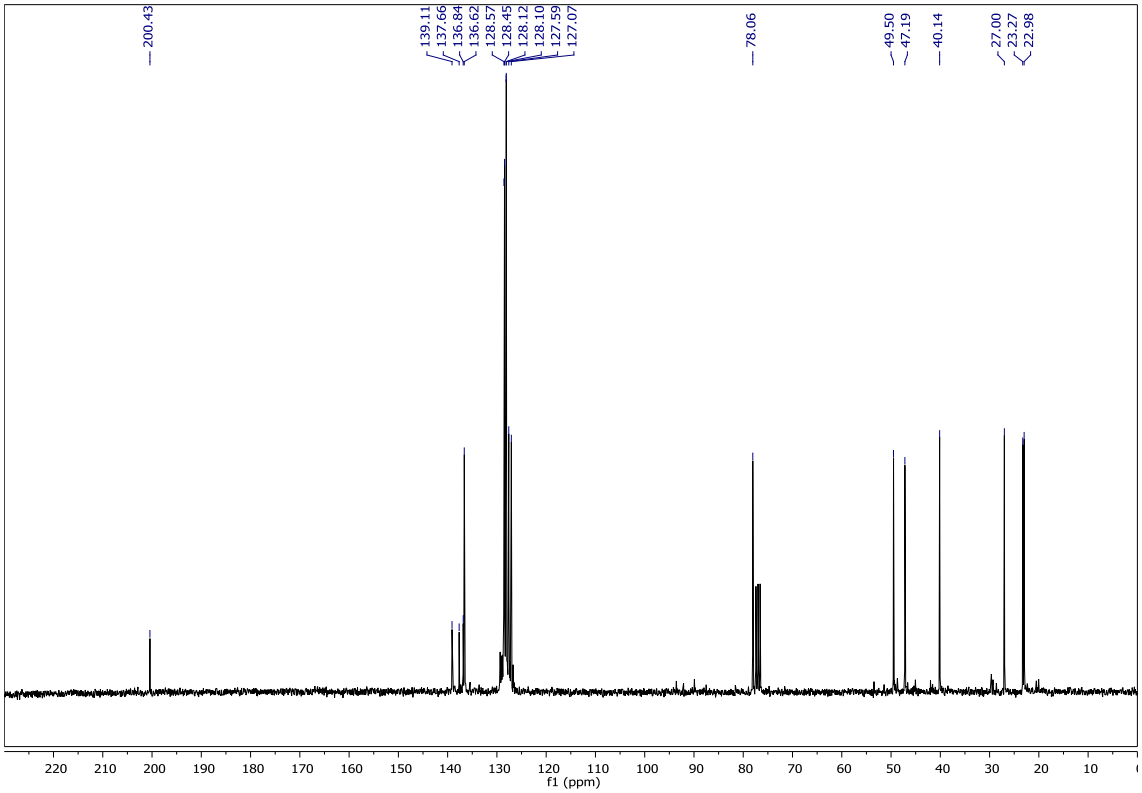
2.36
2.34
2.28
1.87
1.85
1.84
1.80
1.78
1.75
1.72
1.70
1.68
1.65
O
Ph
NO2
Ph
39´Aa
5.15
3.61
0.97
1.74
1.88
4.00
1.93
2.10
f1 (ppm)


200.43
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136.84
136.62
128.57
128.45
128.12
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127.07
78.06
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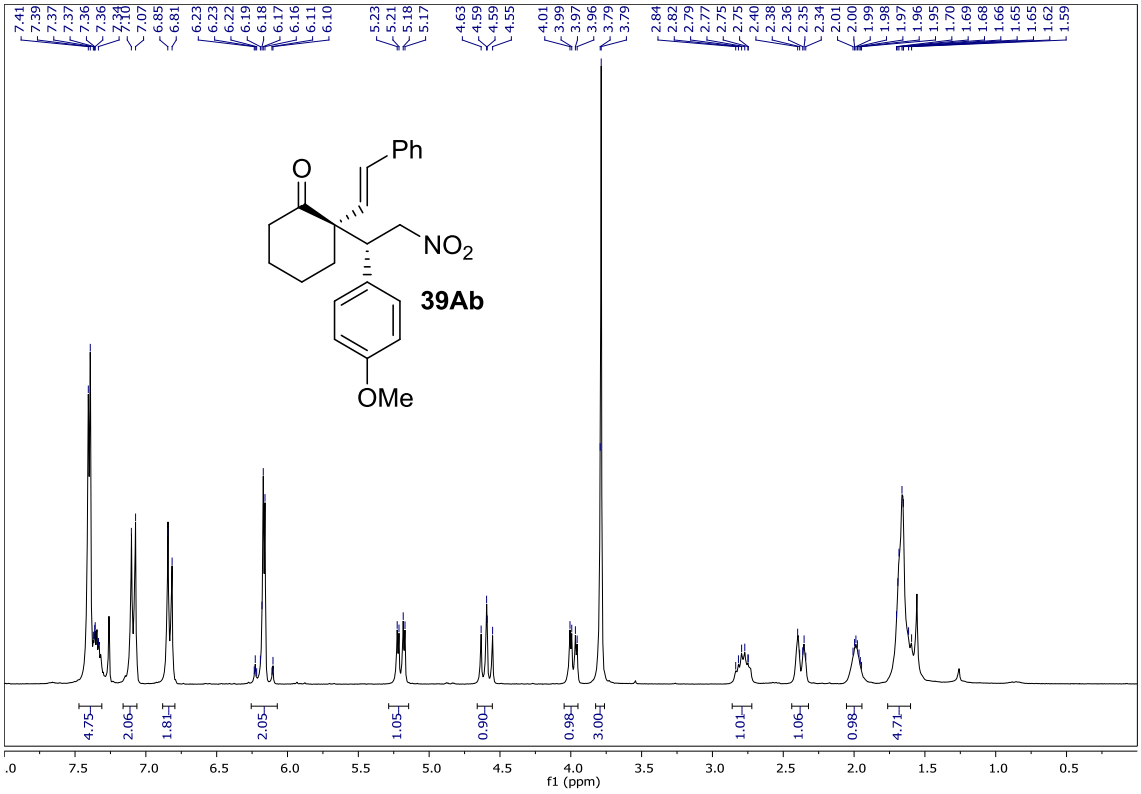
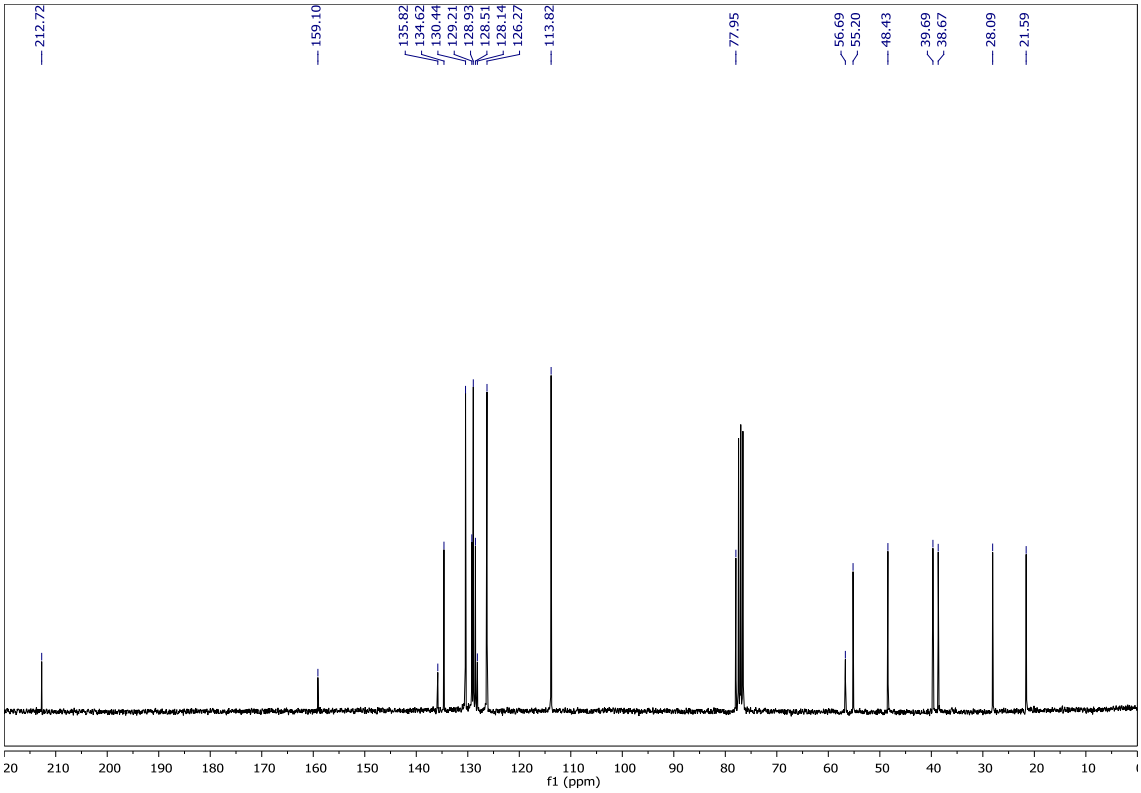
40.14
27.00
23.27
22.98
f1 (ppm)


Ph
O
NO2
39Ab
OMe
f1 (ppm)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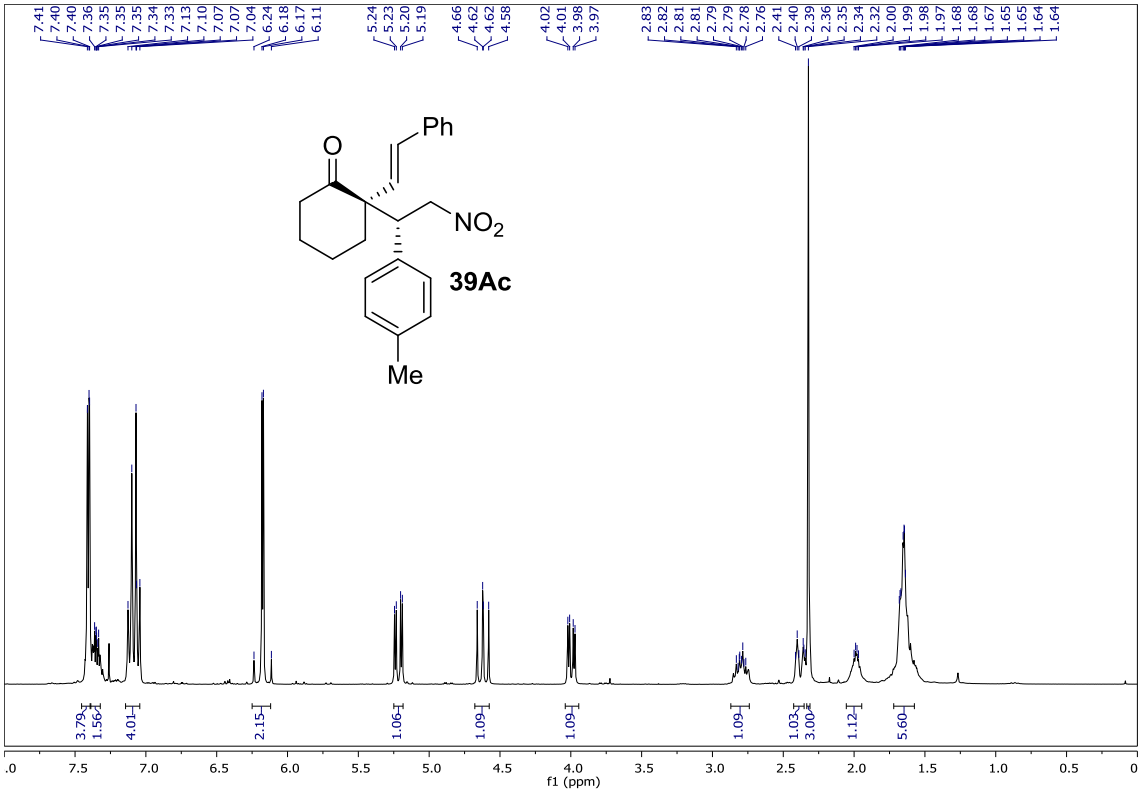
Ph
O
NO2
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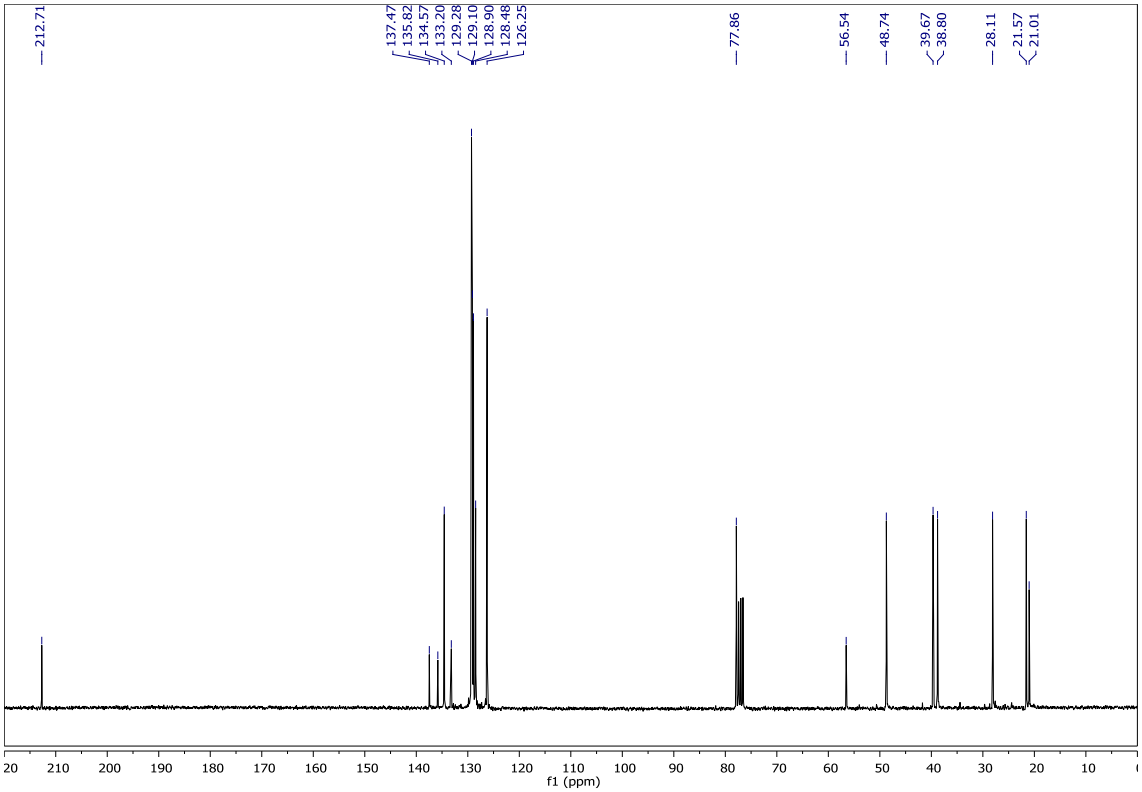
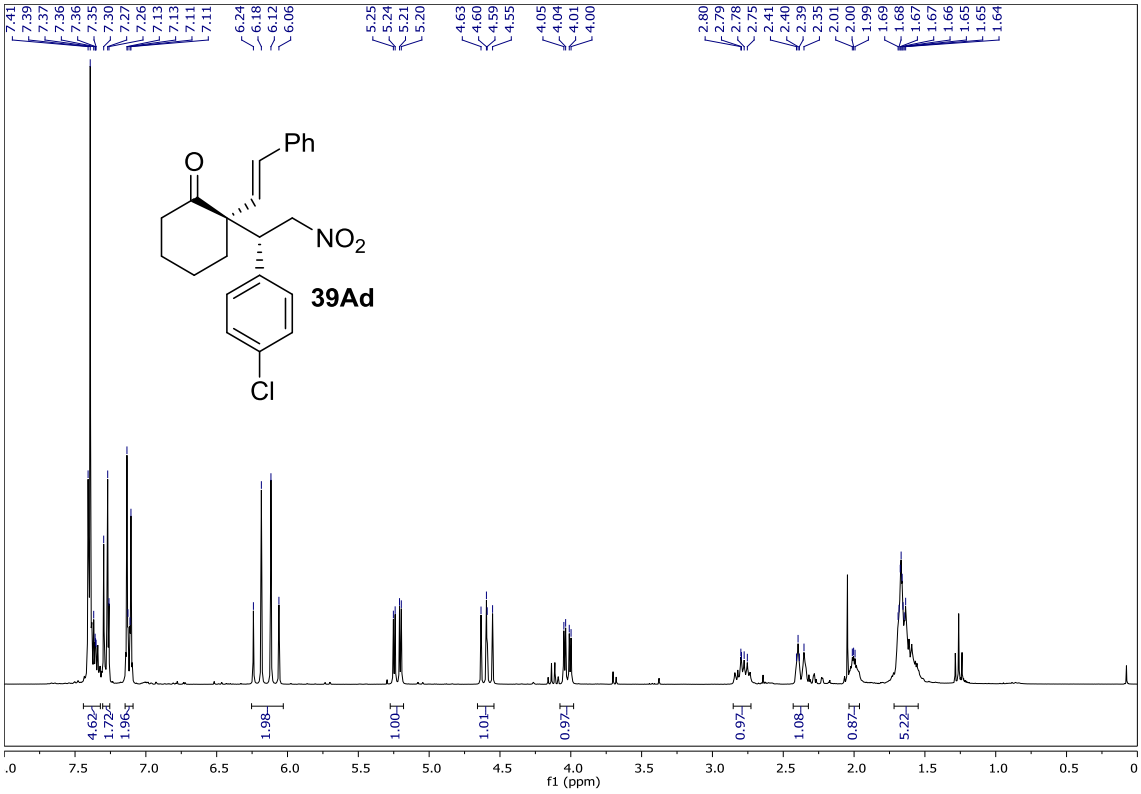
Me
f1 (ppm)


f1 (ppm)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6.12
6.06
5.25
5.24
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4.60
4.59
4.55
4.05
4.04
4.01
4.00
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2.79
2.78
2.75
2.41
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2.00
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1.65
1.64
O
Ph
NO2
39Ad
Cl
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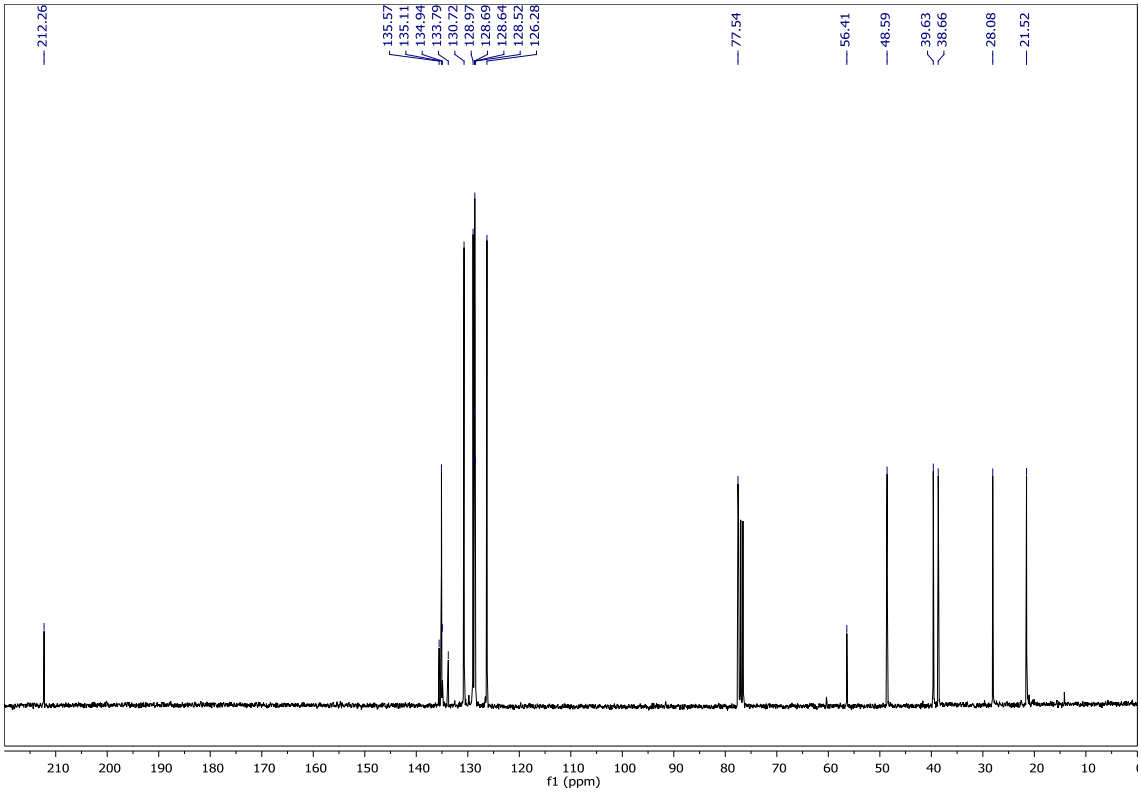
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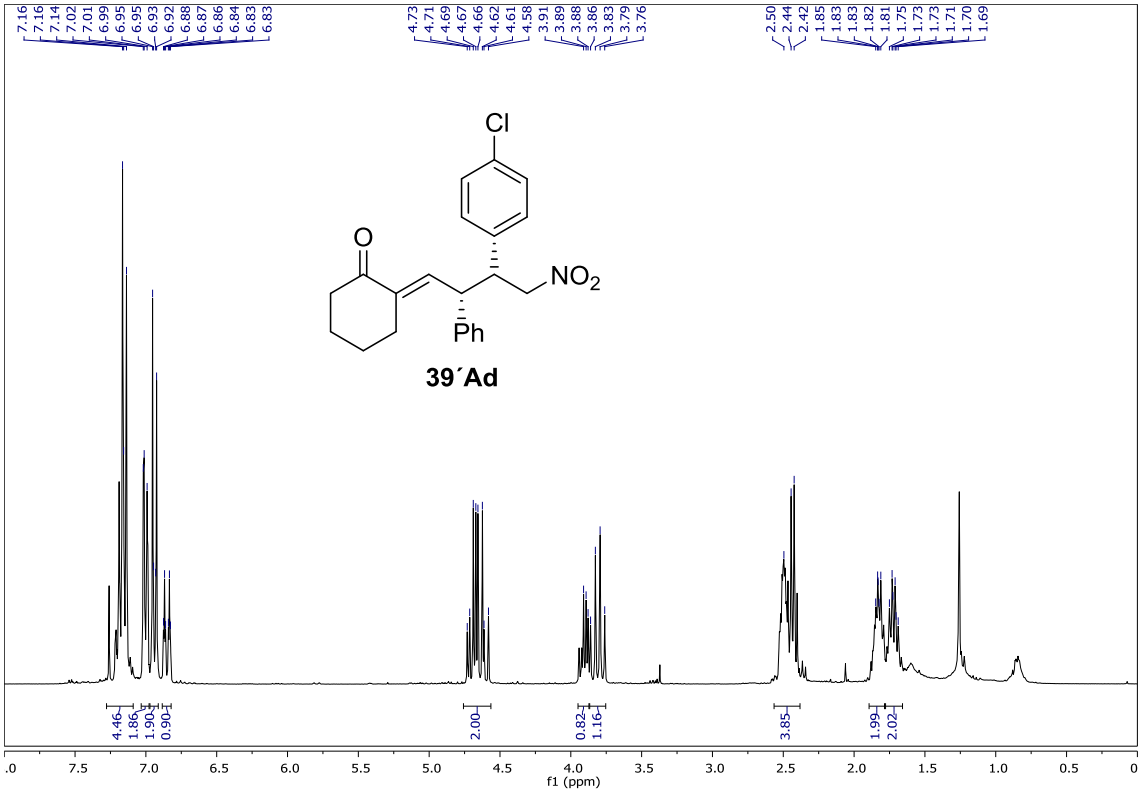
21.52
f1 (ppm)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1.70
1.69
Cl
O
NO2
Ph
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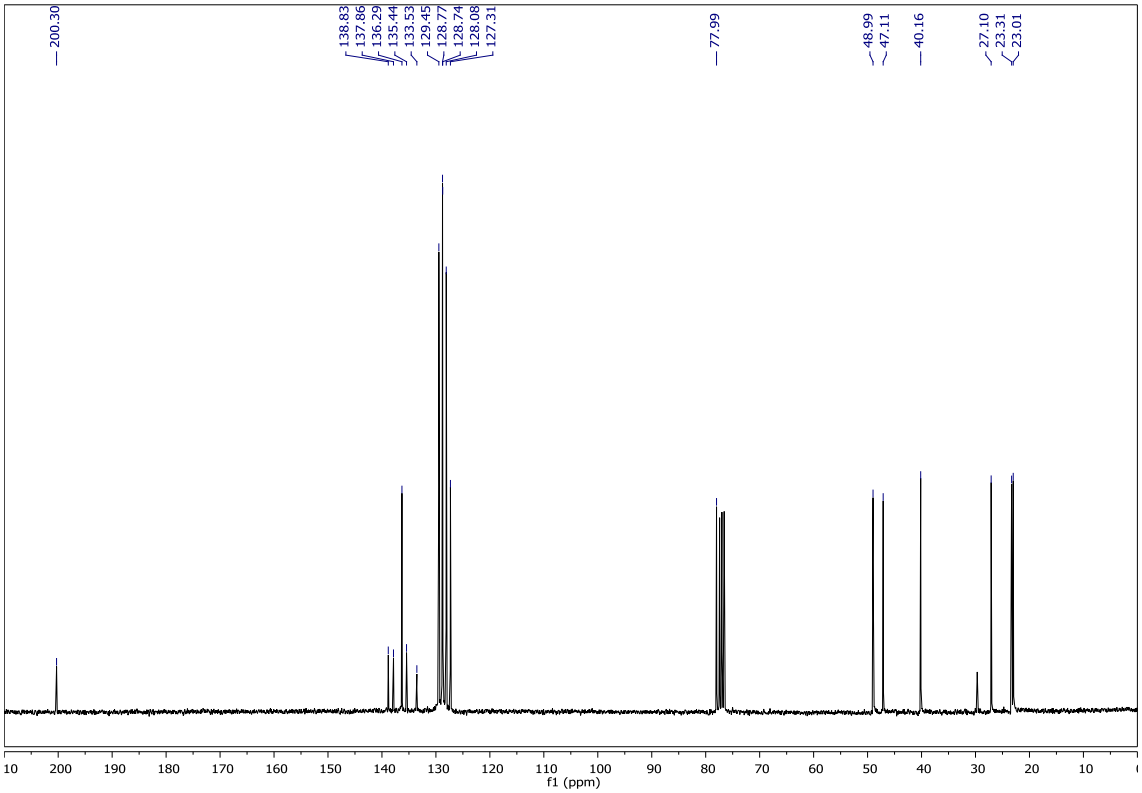
f1 (ppm)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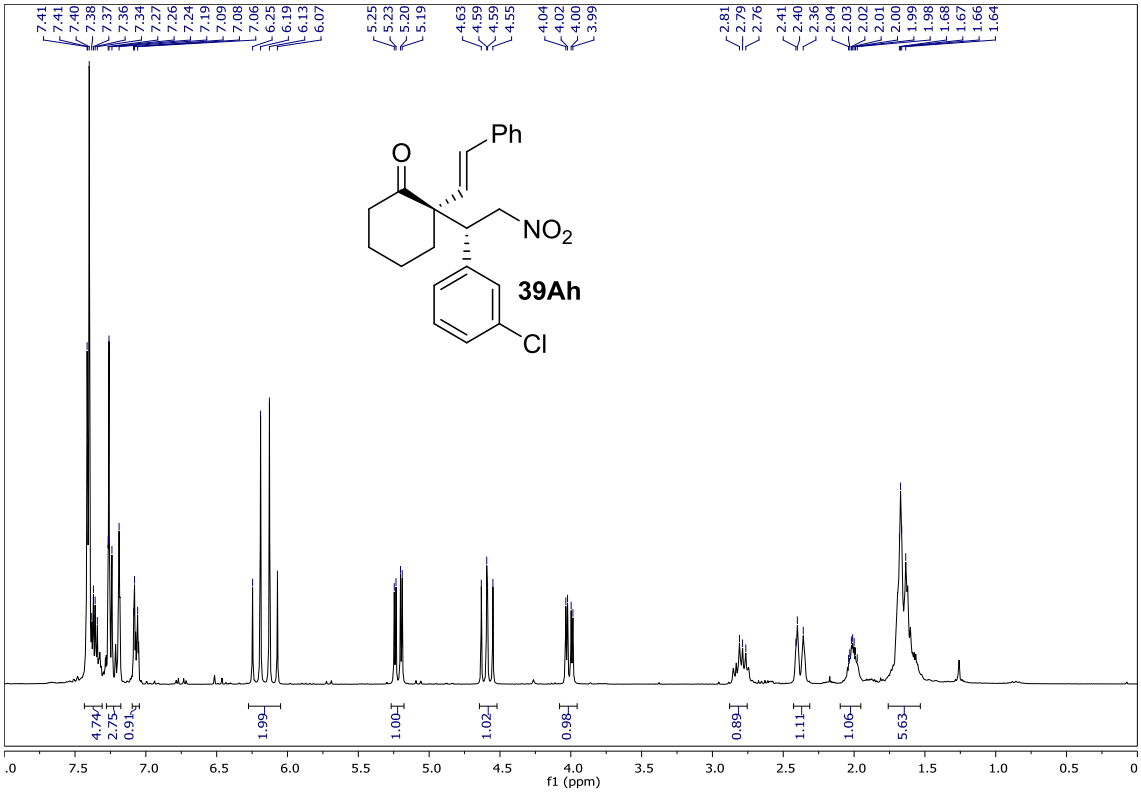
23.31
23.01
f1 (ppm)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6.19
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4.59
4.55
4.04
4.02
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3.99
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2.79
2.76
2.41
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2.36
2.04
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2.01
2.00
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1.98
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1.67
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Ph
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Cl
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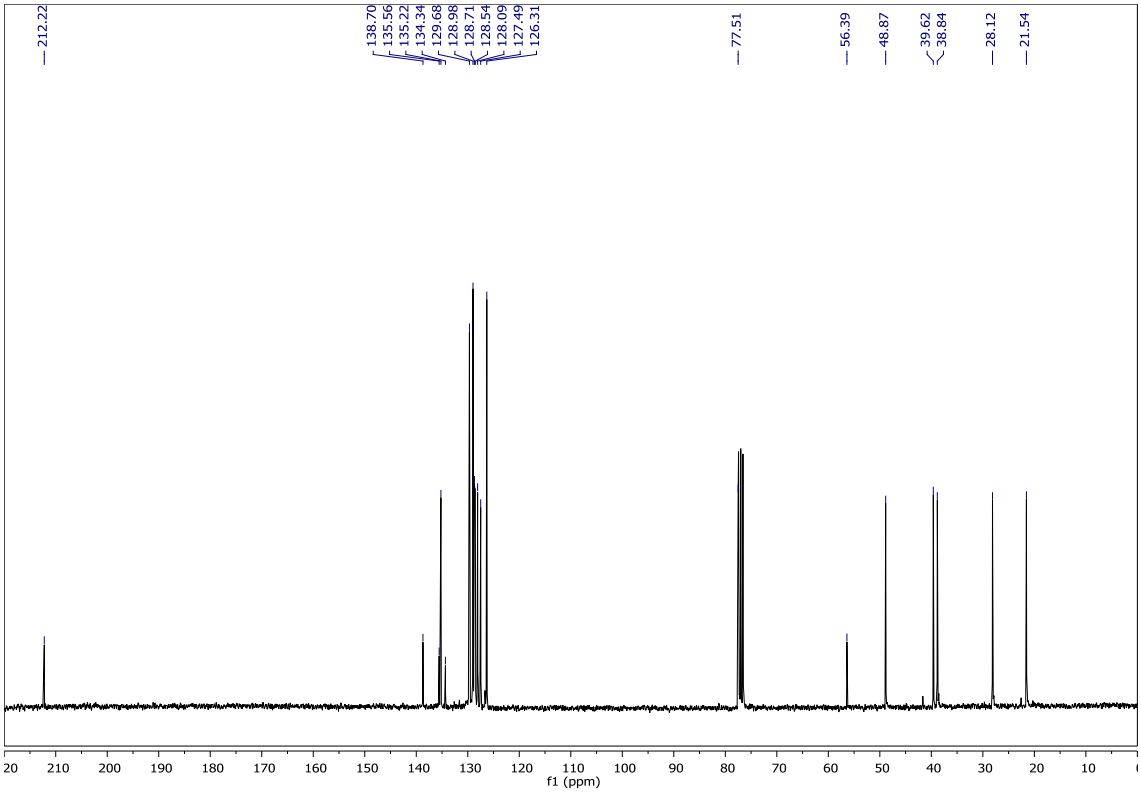
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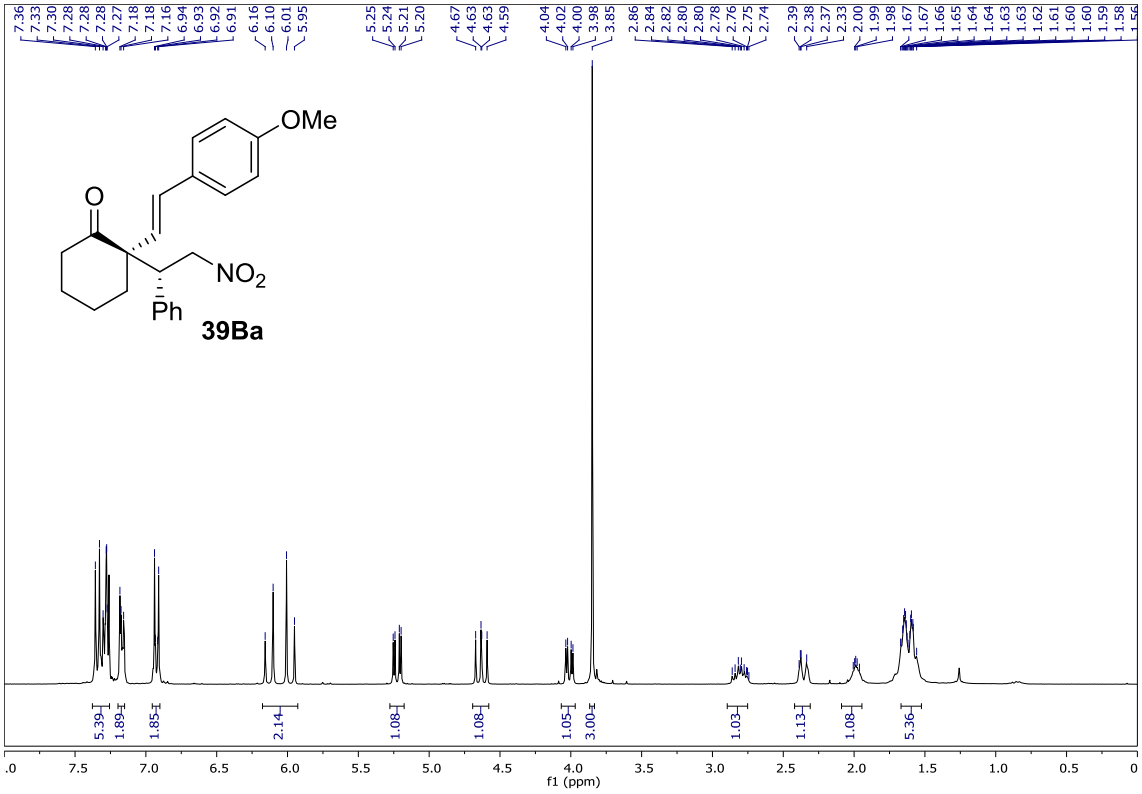
28.12
21.54
f1 (ppm)


OMe
O
NO2
Ph
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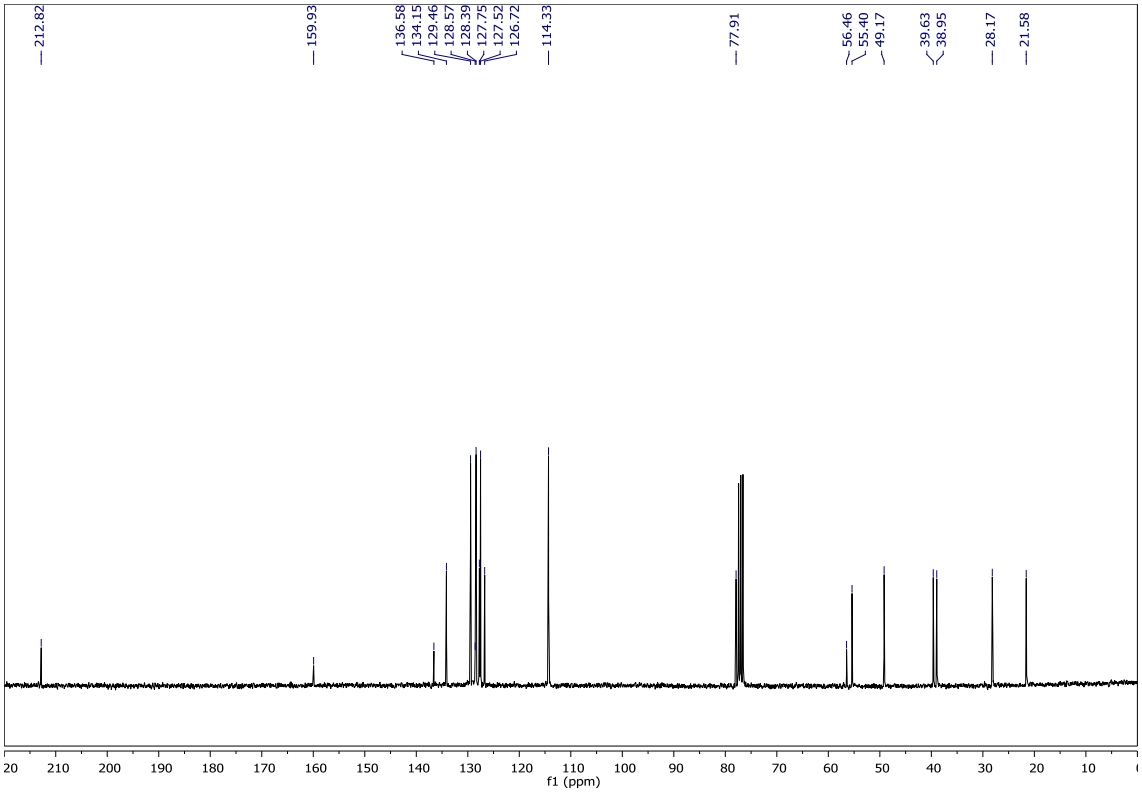
f1 (ppm)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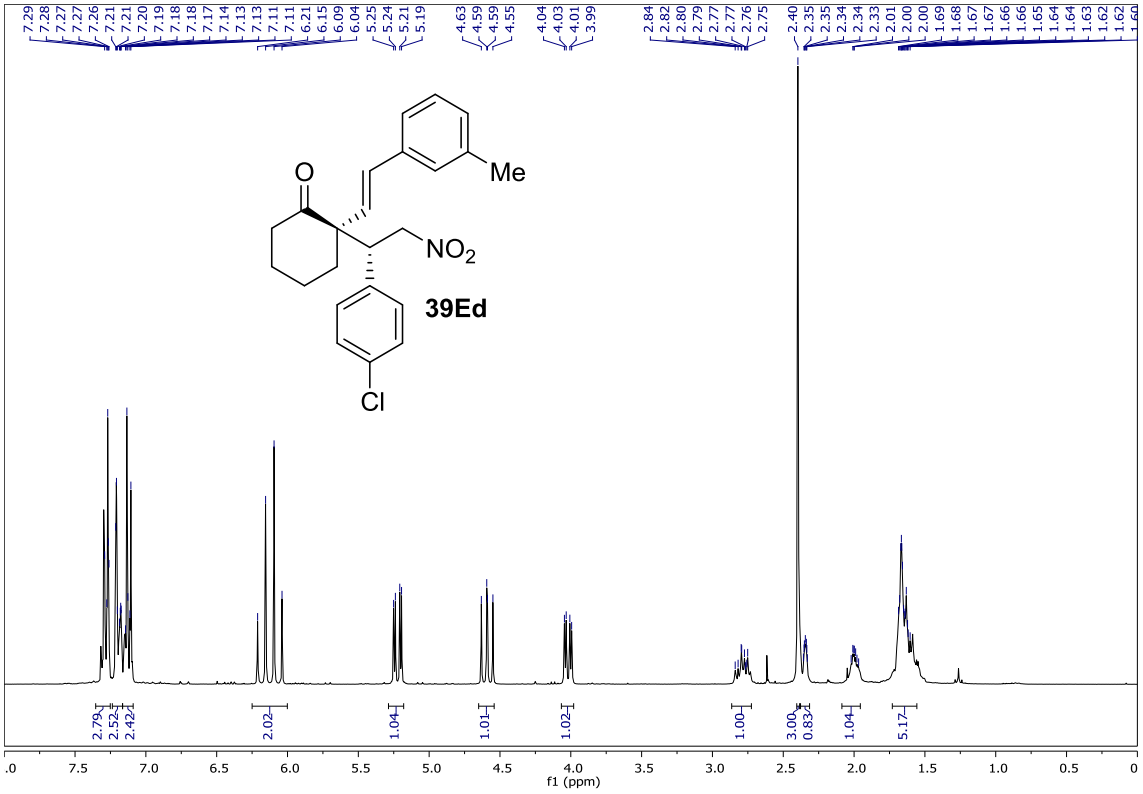
39.63
38.95
28.17
21.58
f1 (ppm)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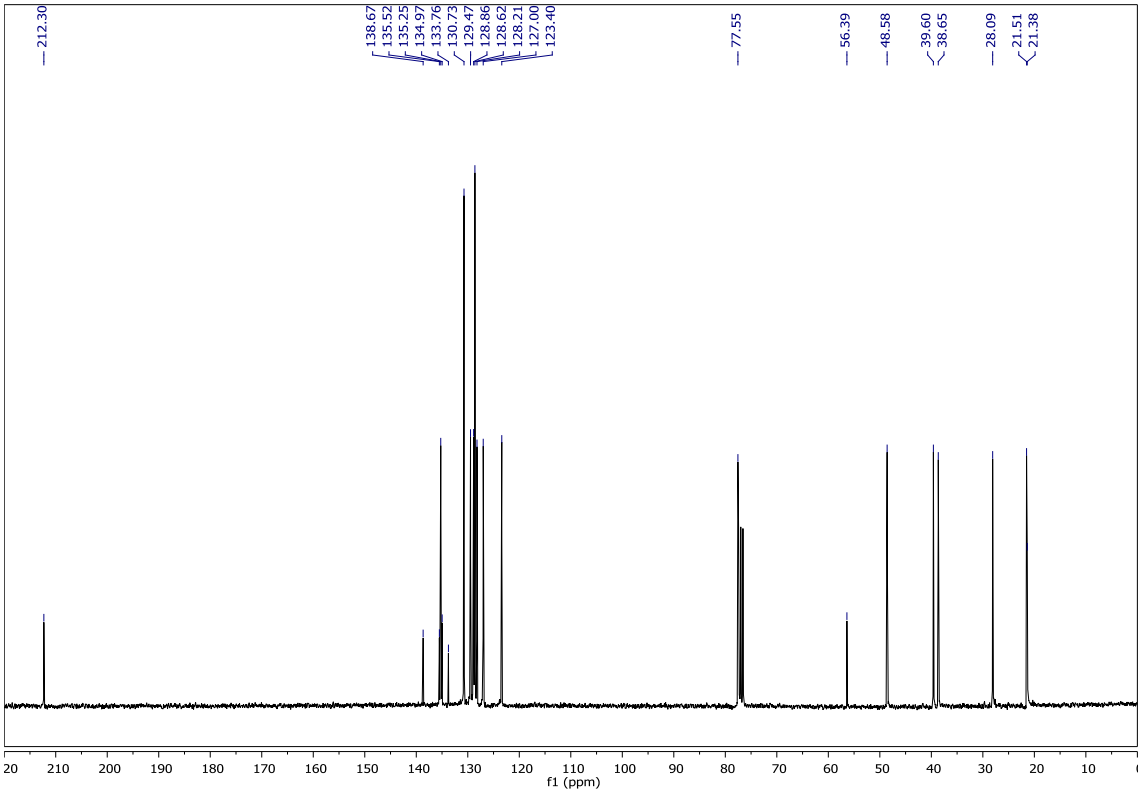
Me
NO2
39Ed
Cl
f1 (ppm)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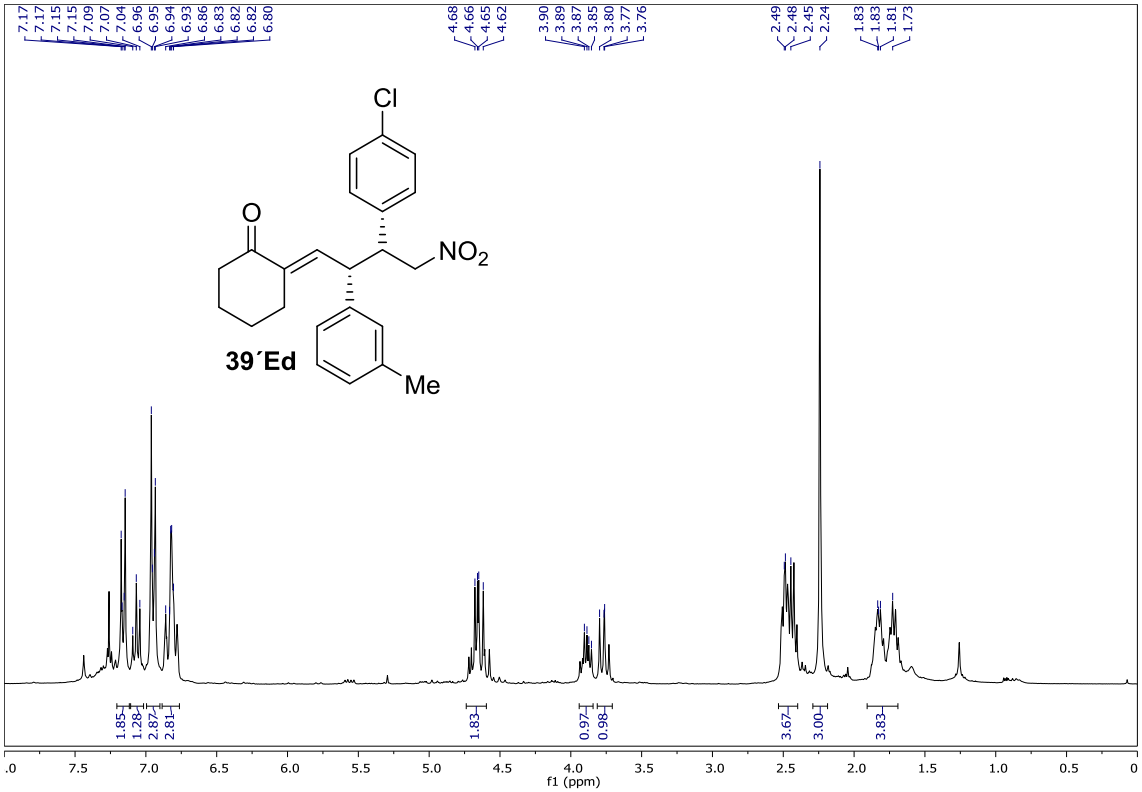
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6.94
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6.83
6.82
6.82
6.80
4.68
4.66
4.65
4.62
3.90
3.89
3.87
3.85
3.80
3.77
3.76
2.49
2.48
2.45
2.24
1.83
1.83
1.81
1.73
Cl
O
NO2
39´Ed
Me
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0.98
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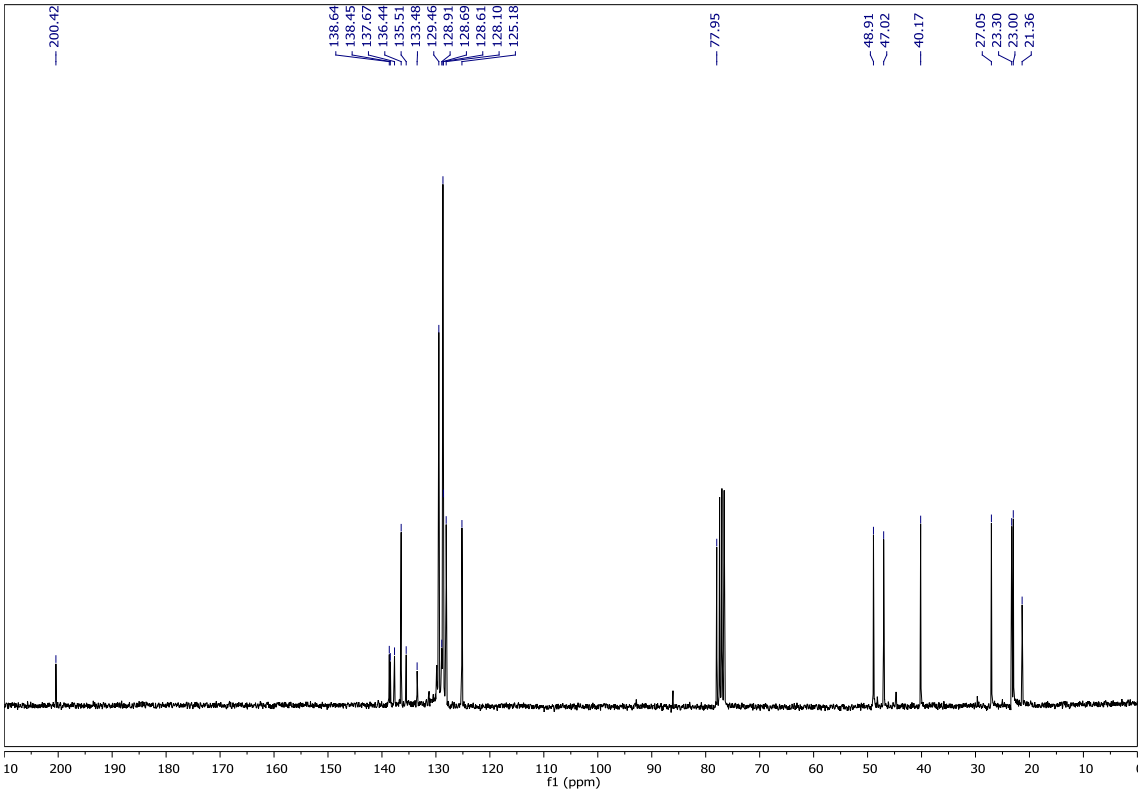
3.83
f1 (ppm)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128.69
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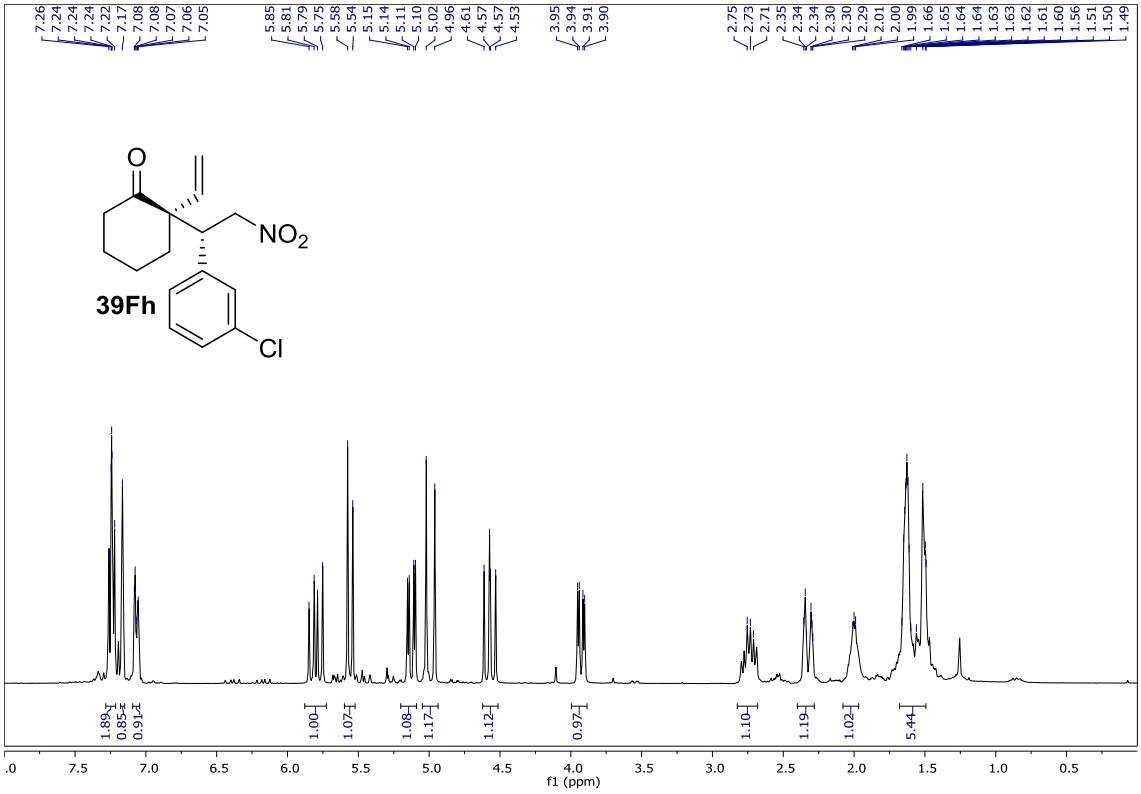
27.05
23.30
23.00
21.36
f1 (ppm)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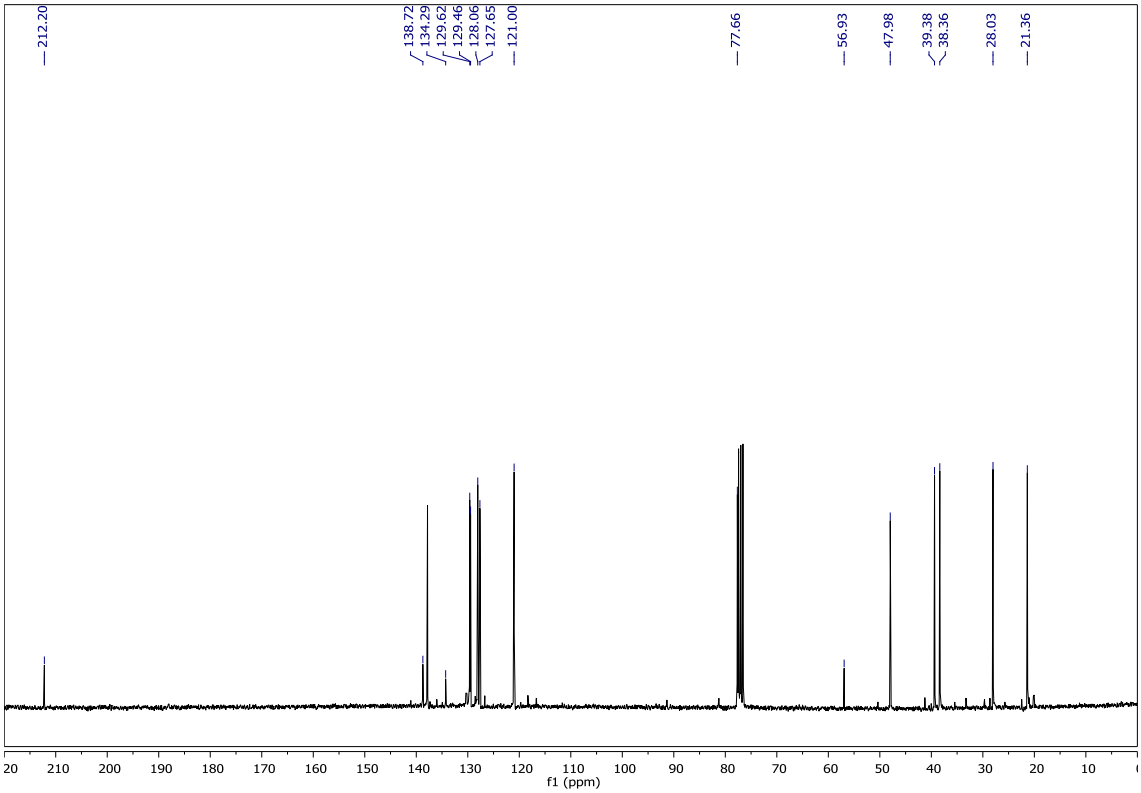
5.85 5.81 5.79 5.75 5.58 5.54 5.15 5.14 5.11 5.10 5.02 4.96 4.61 4.57 4.57 4.53
3.95 3.94 3.91 3.90
2.75 2.73 2.71 2.35 2.34 2.34 2.30 2.30 2.29 2.01 2.00 1.99 1.66 1.65 1.64 1.64 1.63 1.63 1.62 1.61 1.60 1.56 1.51 1.50 1.49
O
NO2
39Fh
Cl
1.89 0.85 0.91 1.00 1.07 1.08 1.17 1.12 0.97 1.10 1.19 1.02 5.44
f1 (ppm)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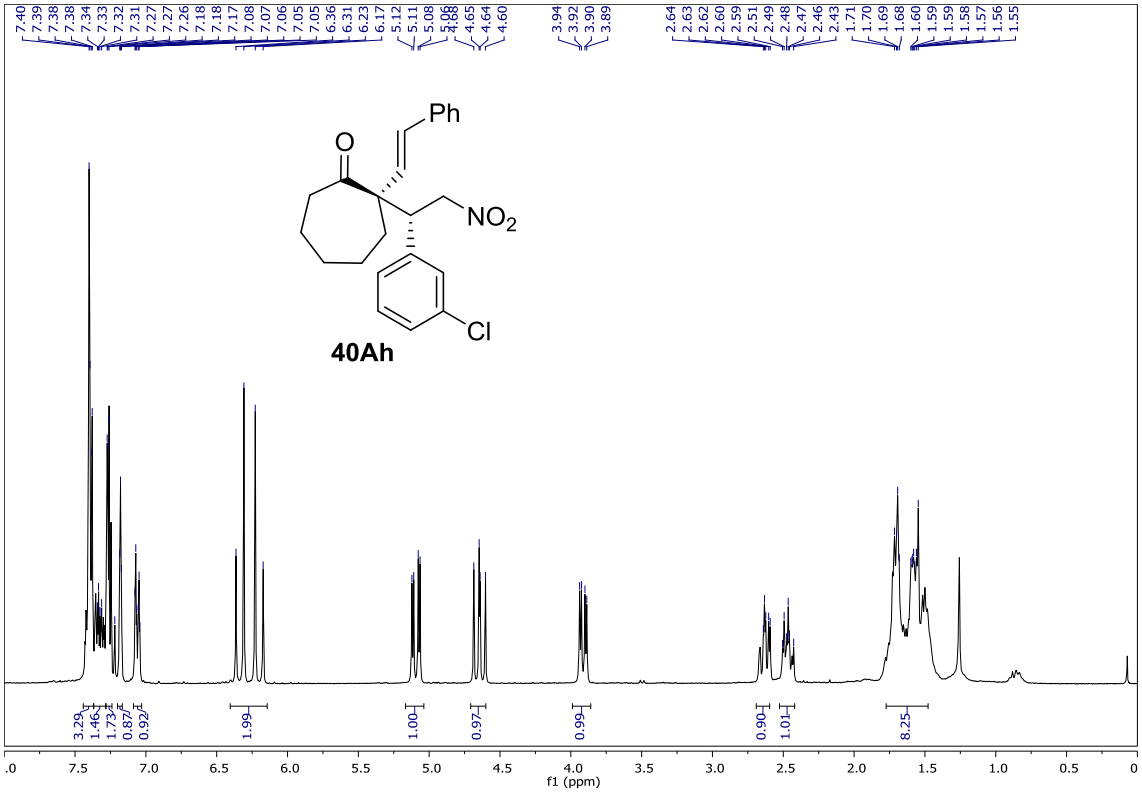
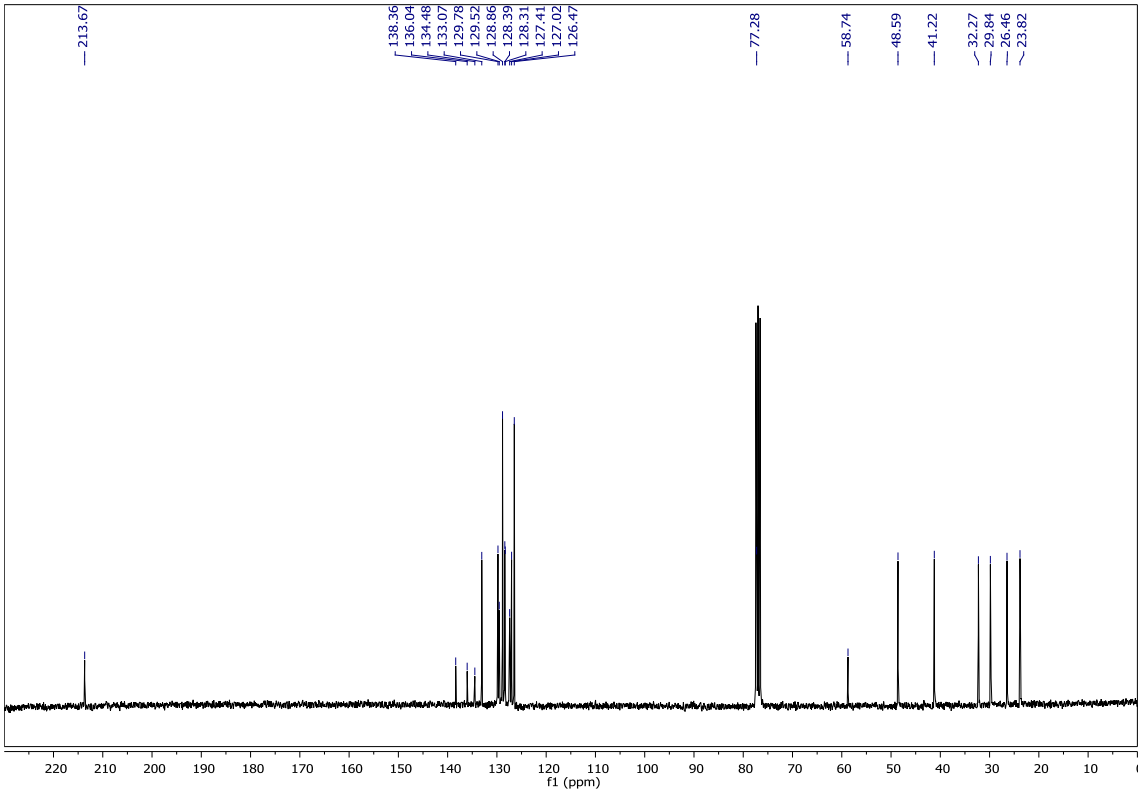
138.72 134.29 129.62 129.46 128.06 127.65 121.00
77.66
56.93 47.98 39.38 38.36 28.03 21.36
f1 (ppm)


Ph
O
NO2
Cl
40Ah
f1 (ppm)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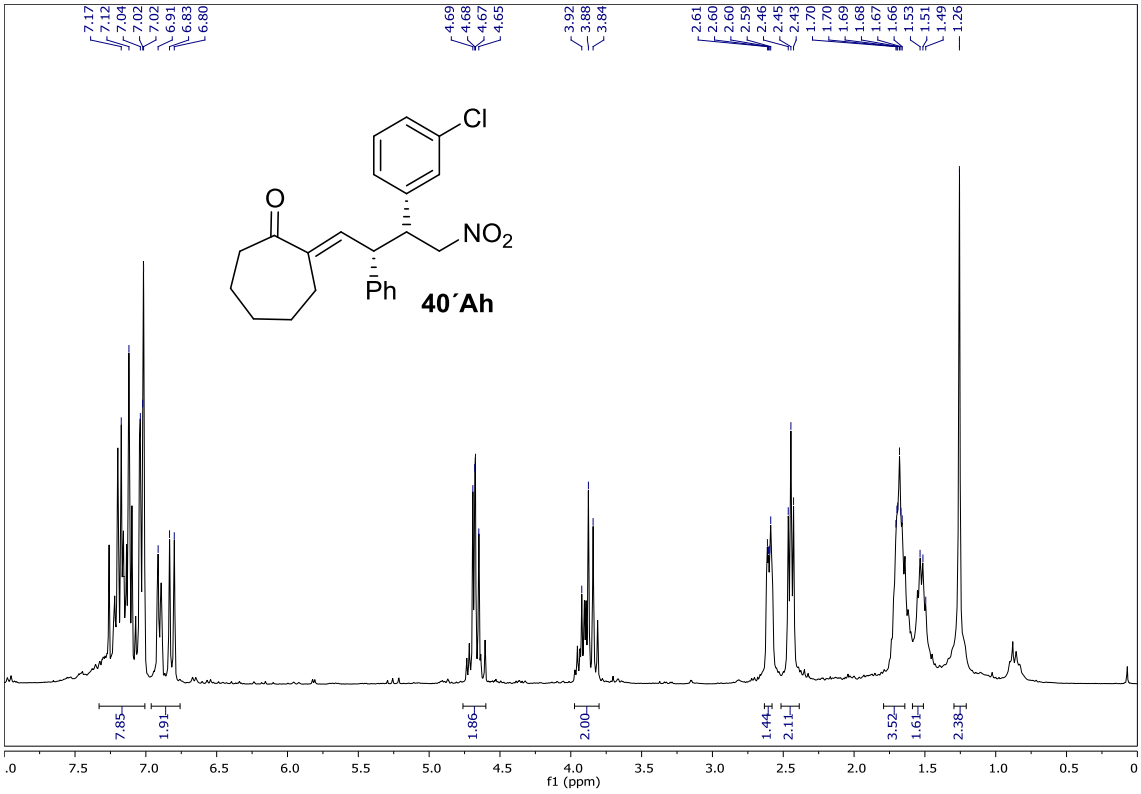
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4.68
4.67
4.65
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3.88
3.84
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2.60
2.59
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2.43
1.70
1.70
1.69
1.68
1.67
1.66
1.53
1.51
1.49
1.26
Cl
O
NO2
Ph
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1.91
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2.00
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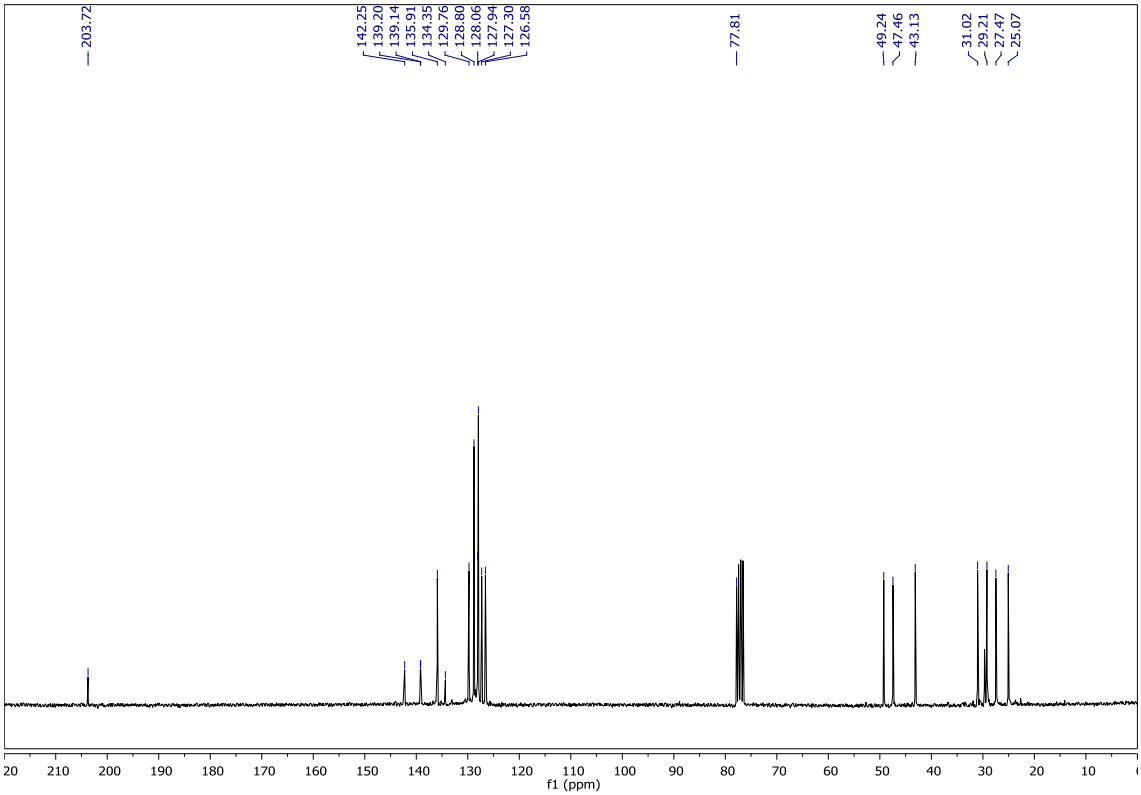
2.11
3.52
1.61
2.38
f1 (ppm)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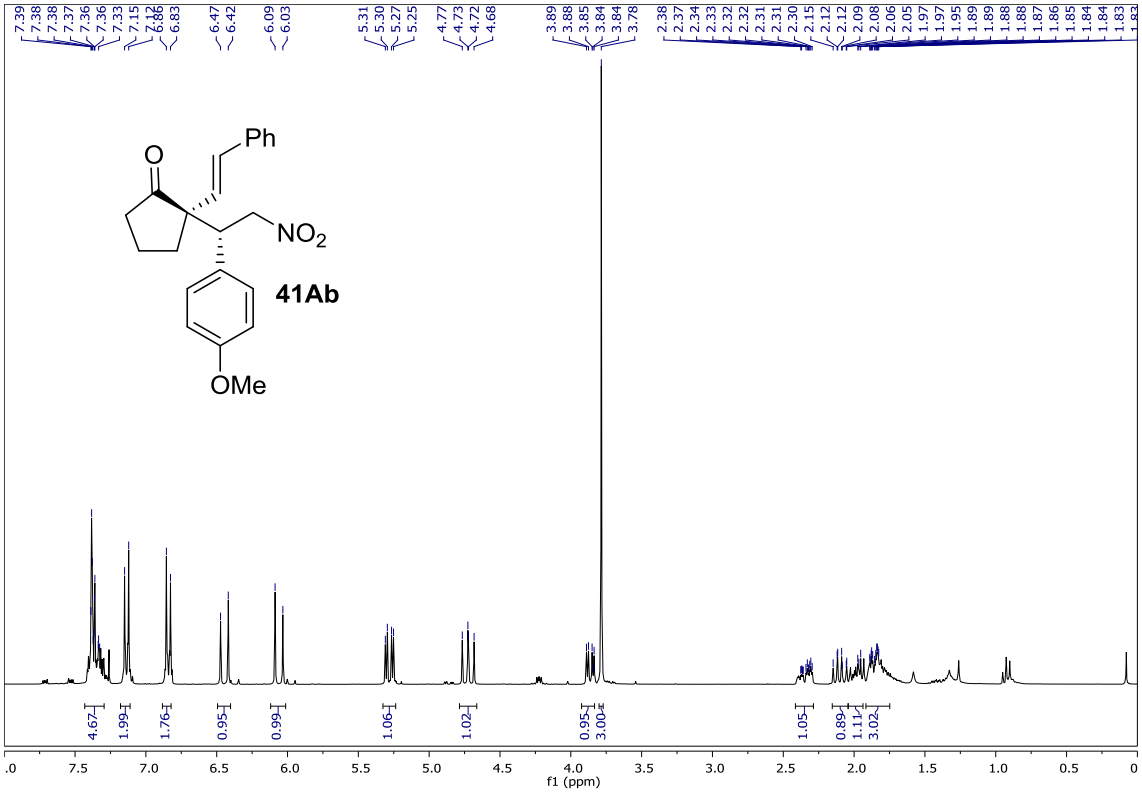
31.02
29.21
27.47
25.07
f1 (ppm)


Ph
O
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41Ab
OMe
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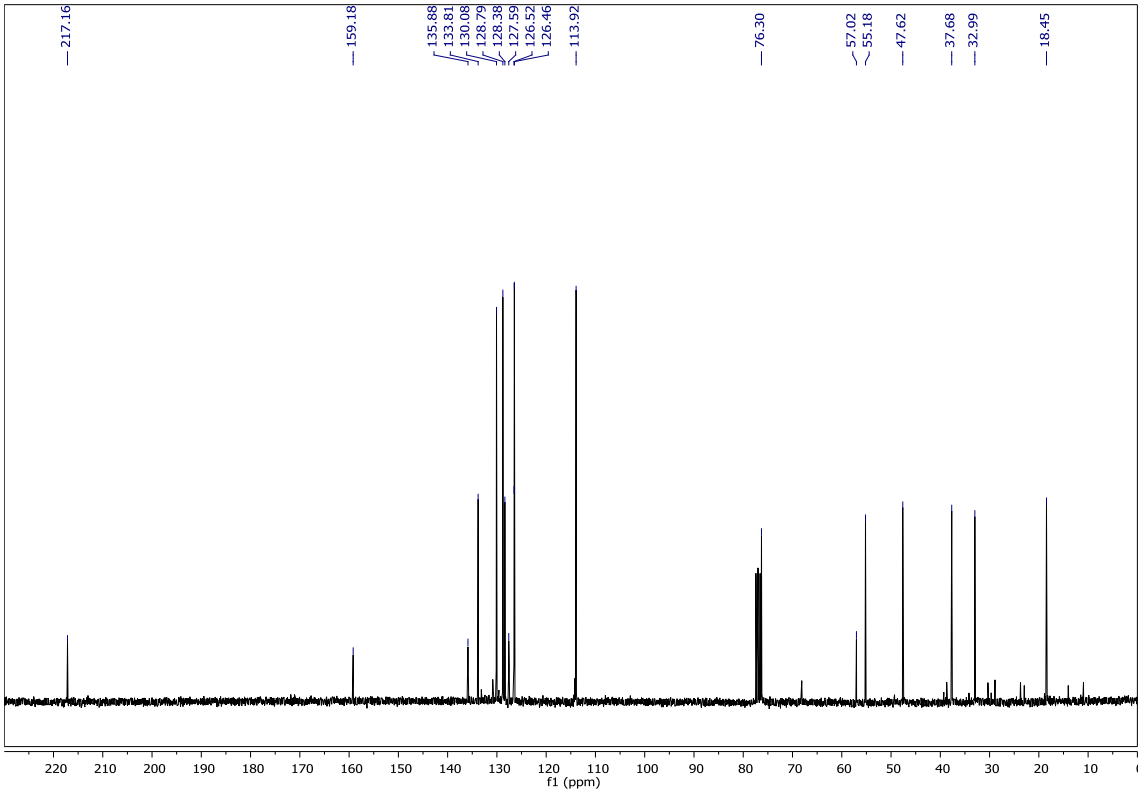
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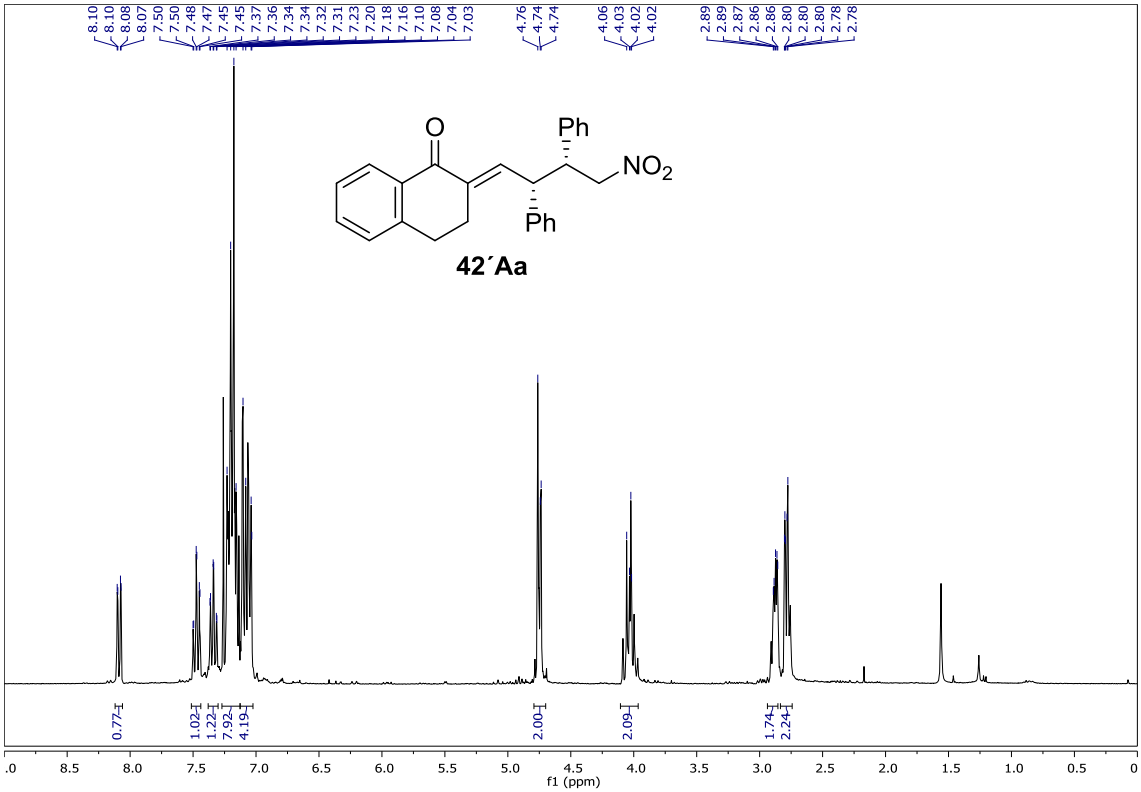
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8.07
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7.50
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7.45
7.37
7.36
7.34
7.34
7.32
7.31
7.23
7.20
7.18
7.16
7.10
7.08
7.04
7.03
4.76
4.74
4.74
4.06
4.03
4.02
4.02
2.89
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2.87
2.86
2.86
2.80
2.80
2.80
2.78
2.78
O
Ph
NO2
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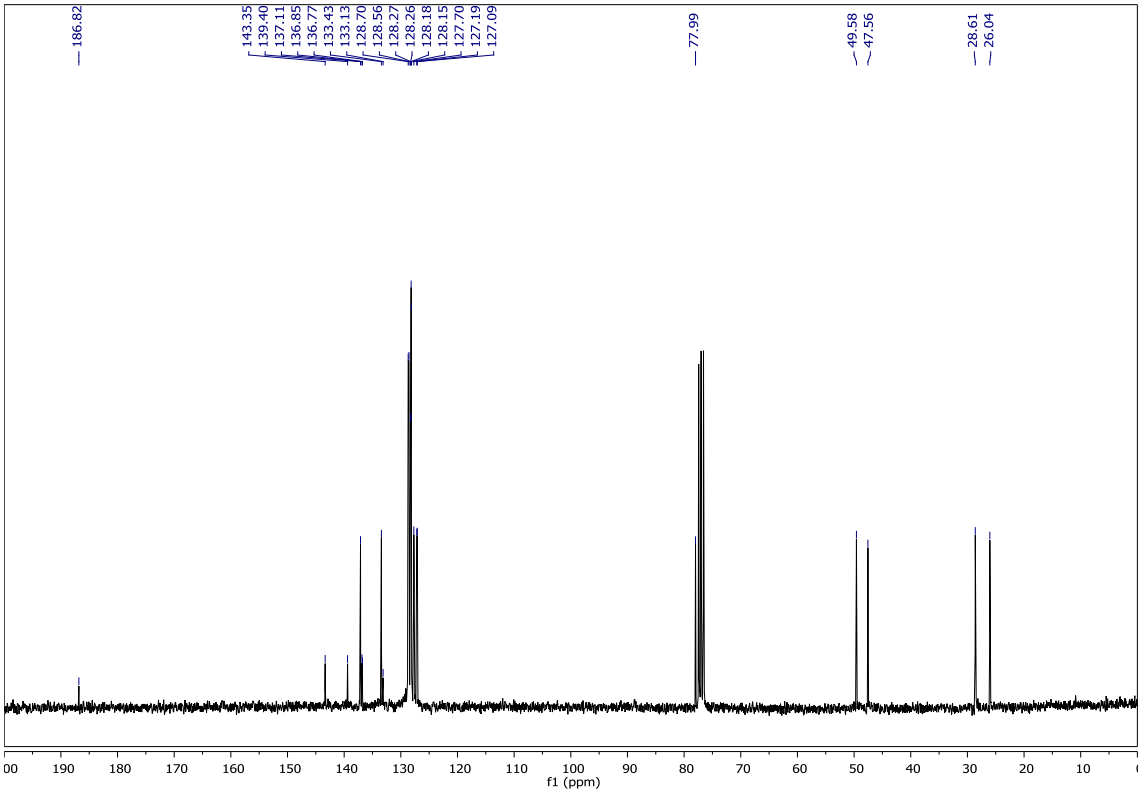
2.24
f1 (ppm)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127.19
127.09
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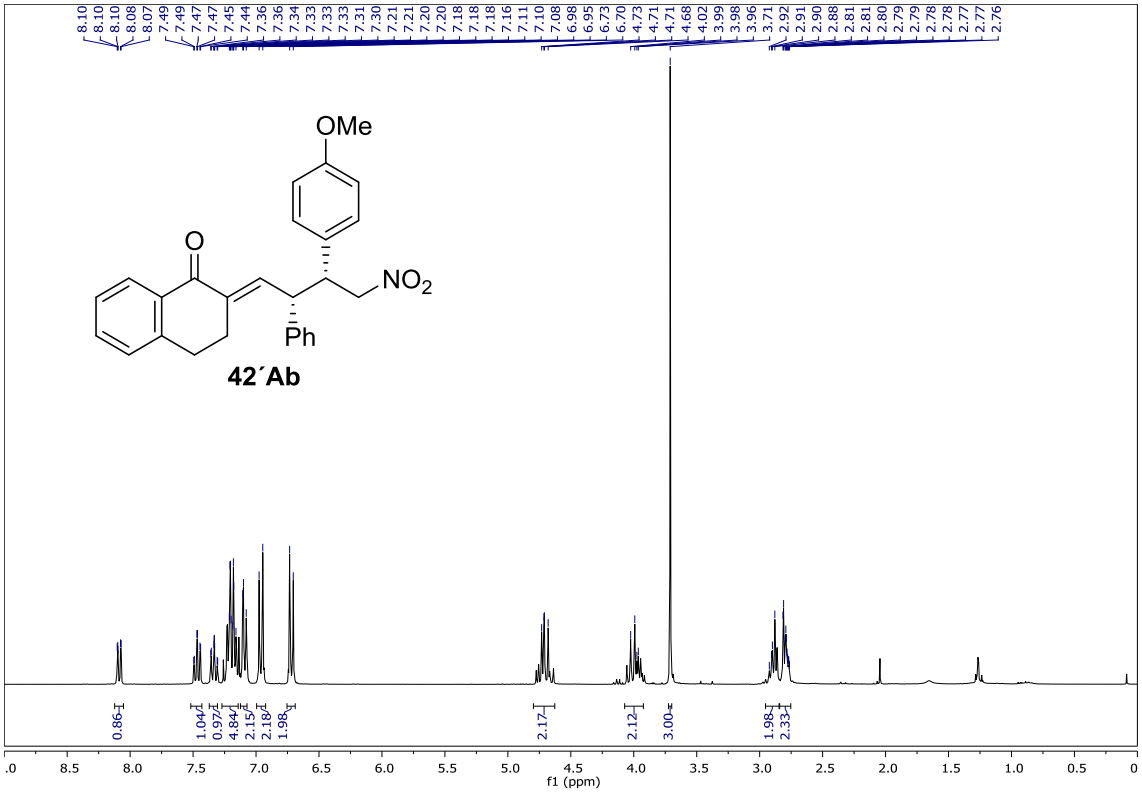
47.56
28.61
26.04
f1 (ppm)


OMe
O
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Ph
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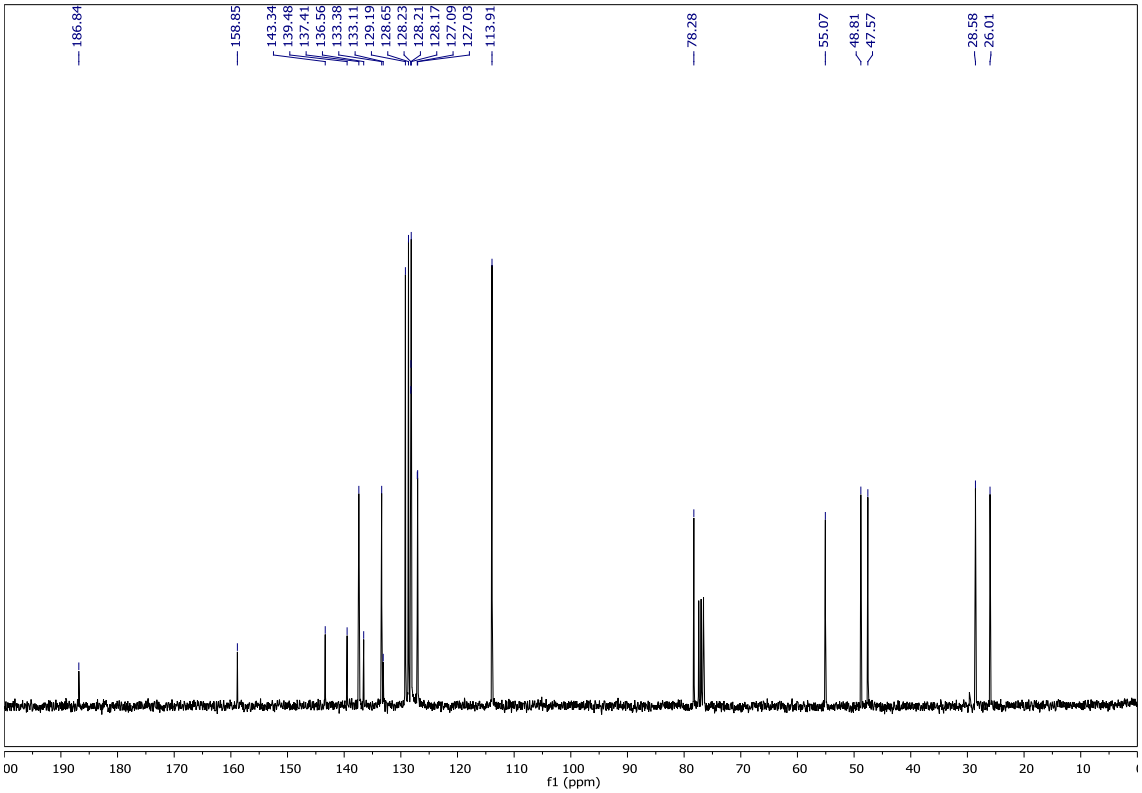
f1 (ppm)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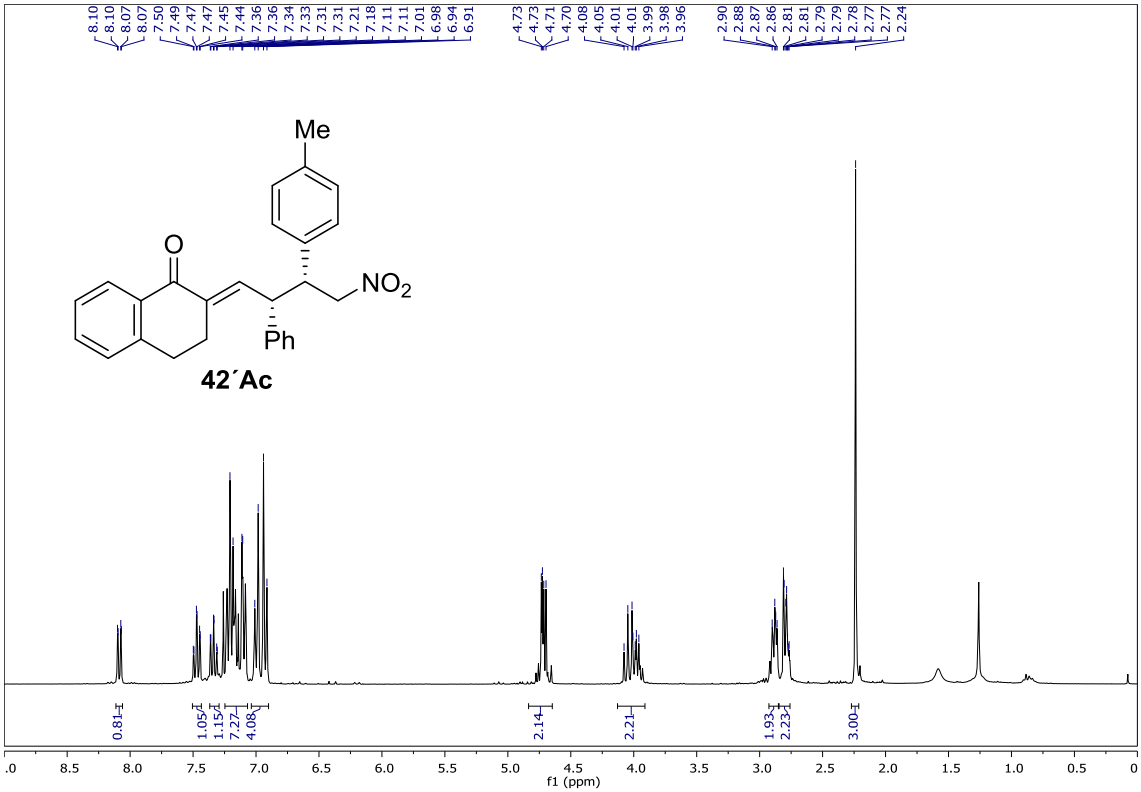
Me
O
NO2
Ph
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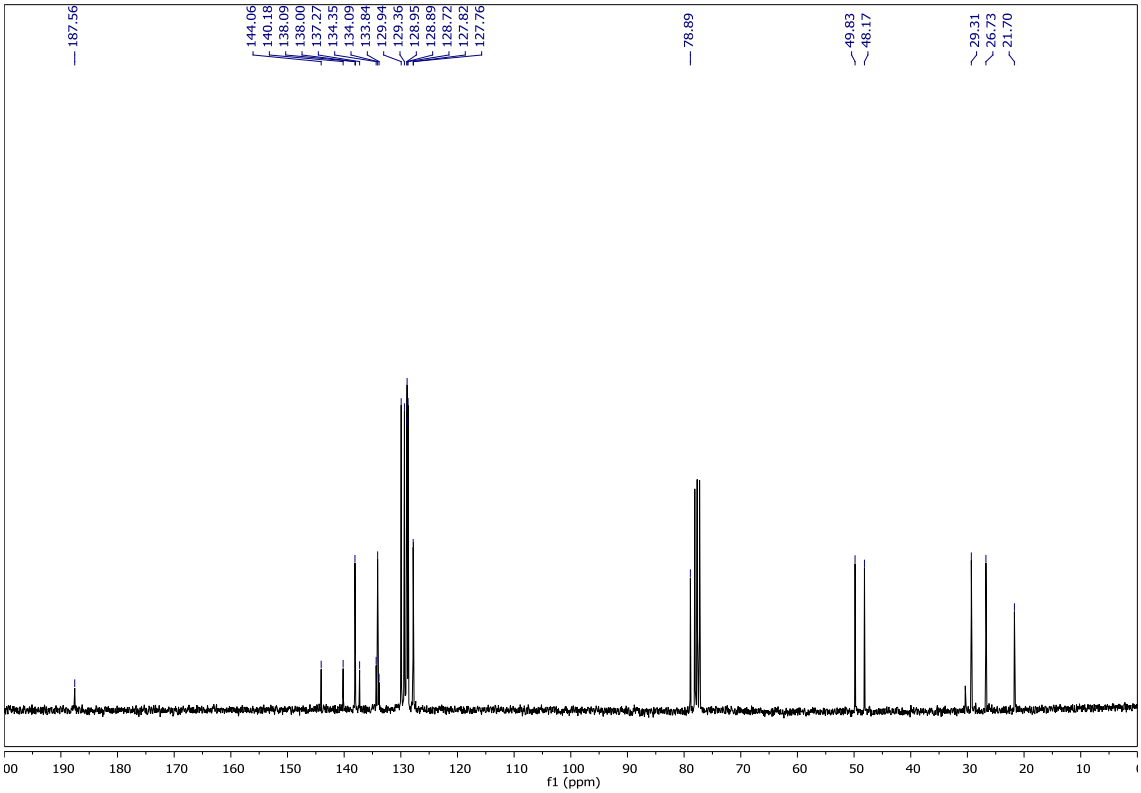
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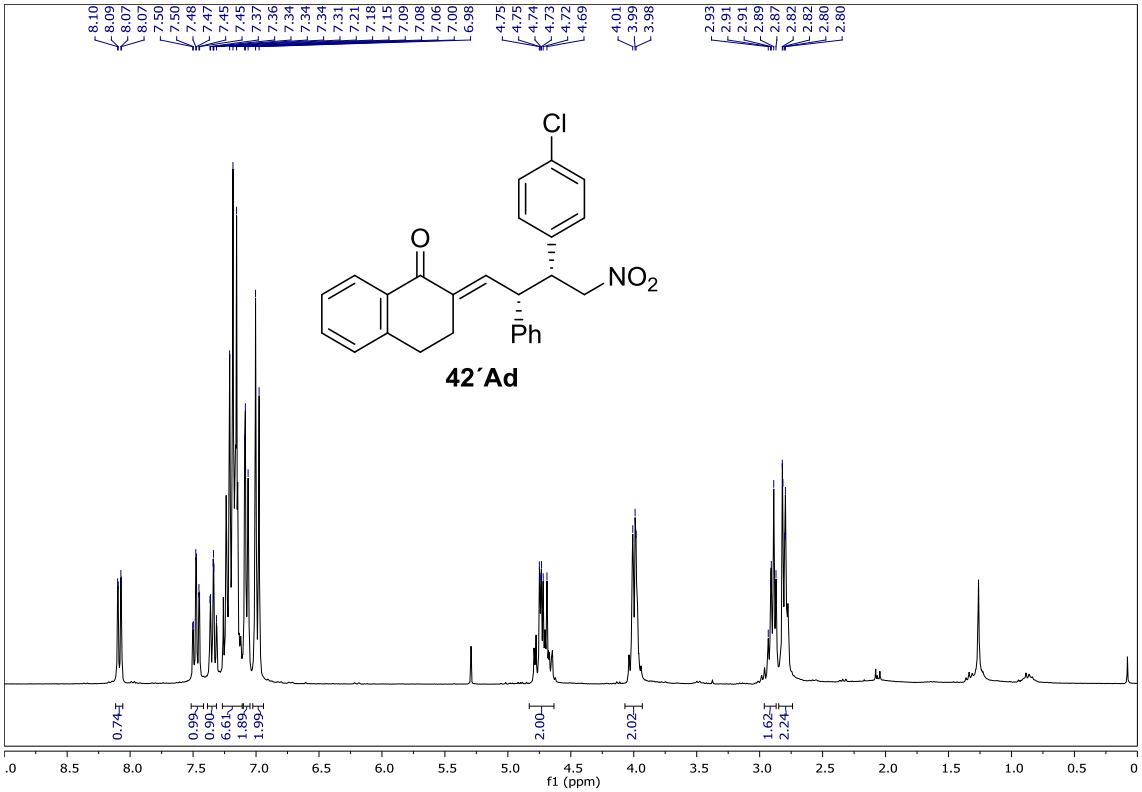
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2.91
2.89
2.87
2.82
2.82
2.80
2.80
Cl
O
NO2
Ph
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1.99
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2.02
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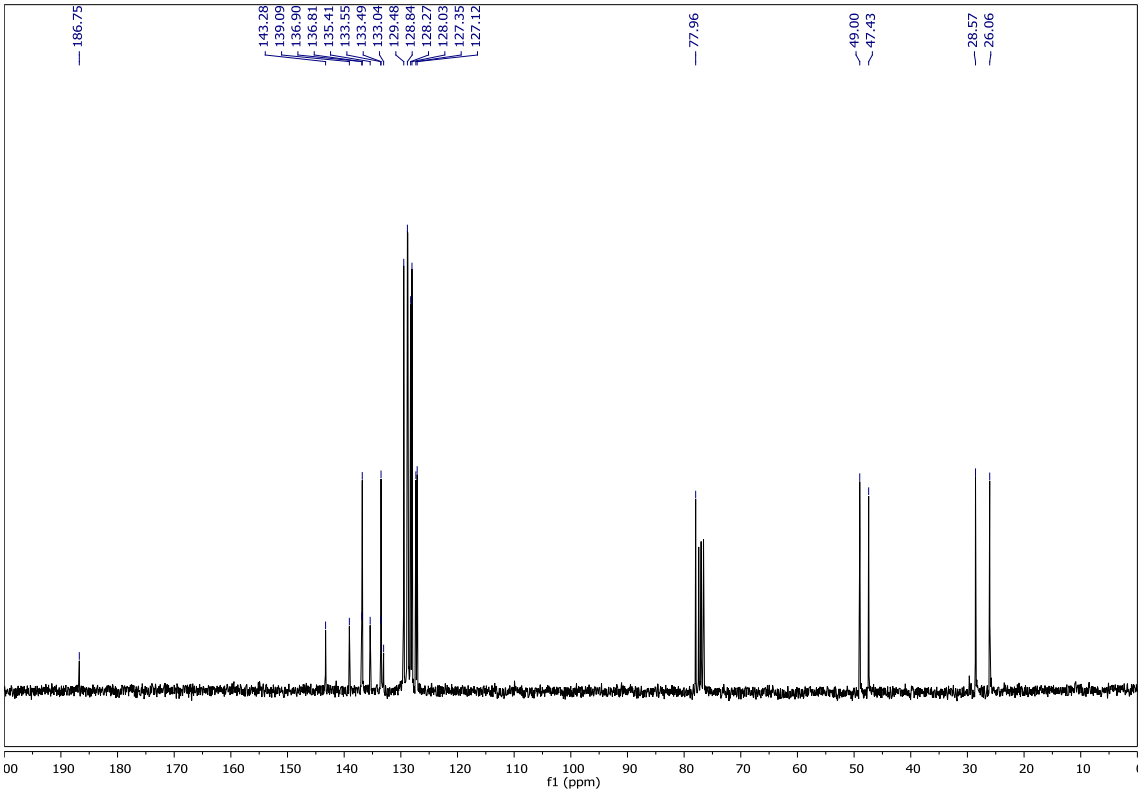
2.24
f1 (ppm)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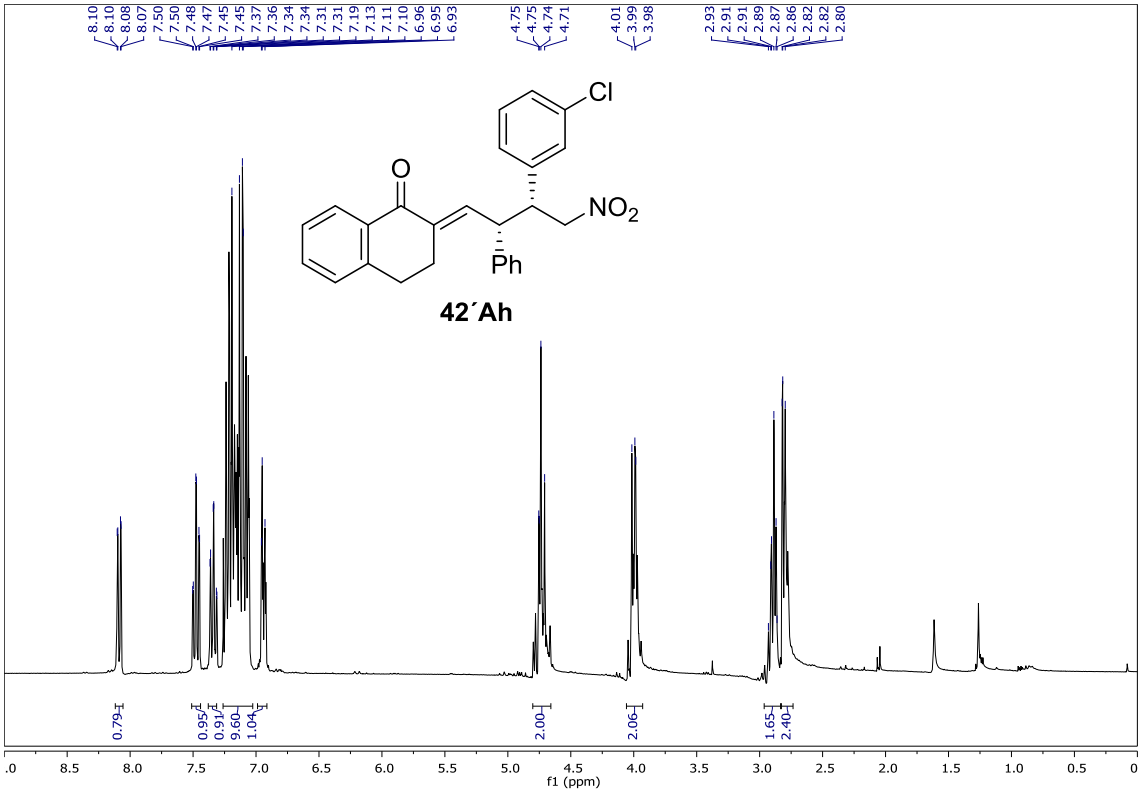
f1 (ppm)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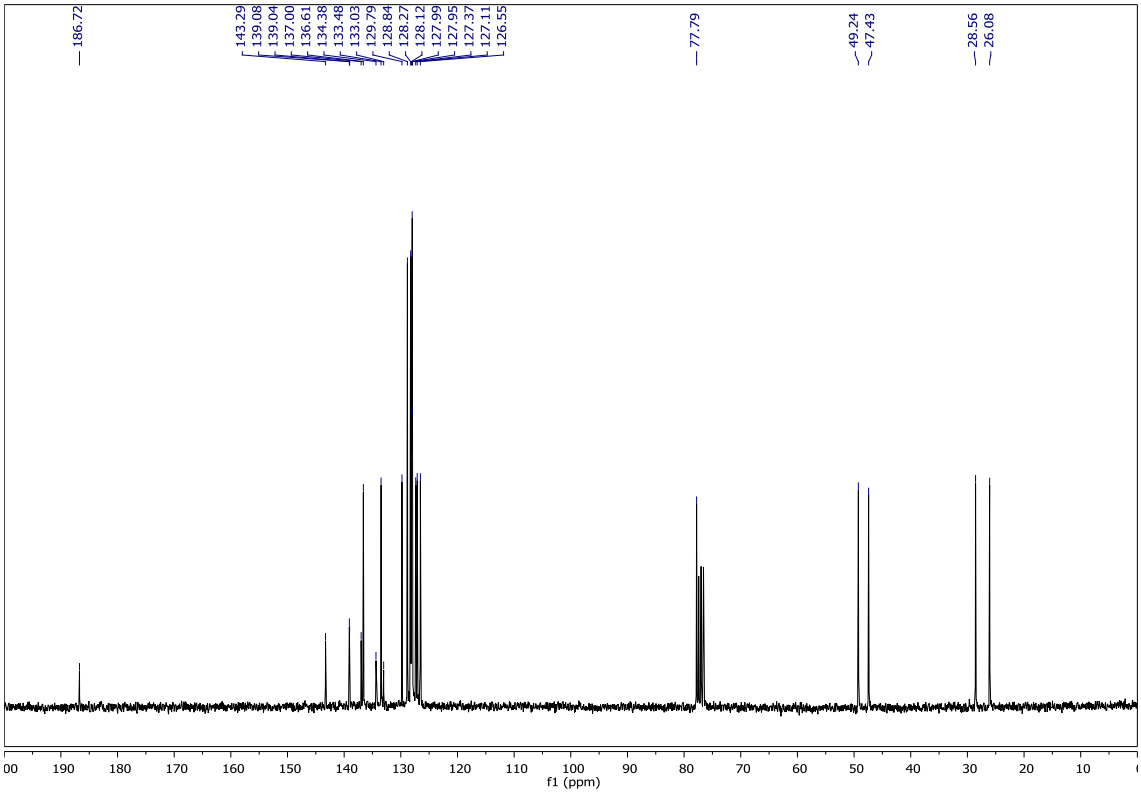
2.91
2.89
2.87
2.86
2.82
2.82
2.80
Cl
O
NO2
Ph
42´Ah
0.79
0.95
0.91
9.60
1.04
2.00
2.06
1.65
2.40
f1 (ppm)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47.43
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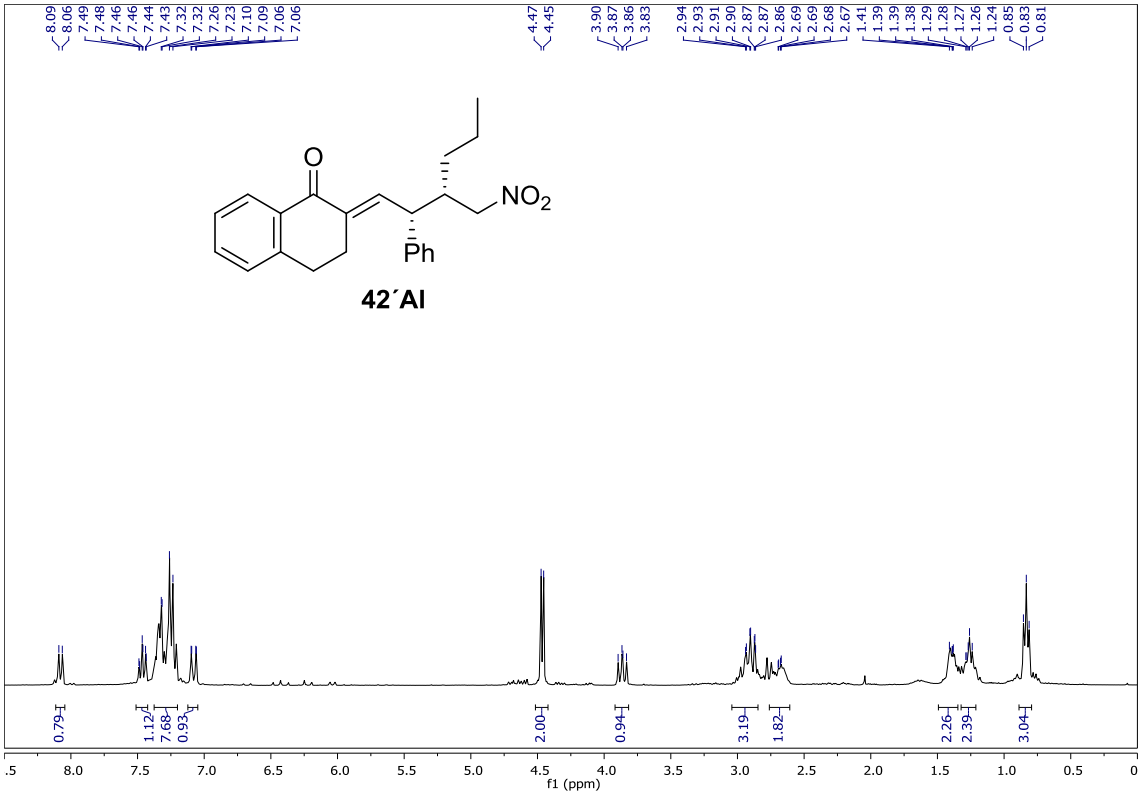
f1 (ppm)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7.43
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7.26
7.23
7.10
7.09
7.06
7.06
4.47
4.45
3.90
3.87
3.86
3.83
2.94
2.93
2.91
2.90
2.87
2.87
2.86
2.69
2.69
2.68
2.67
1.41
1.39
1.39
1.38
1.29
1.28
1.27
1.26
1.24
0.85
0.83
0.81
O
NO2
Ph
42´AI
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0.94
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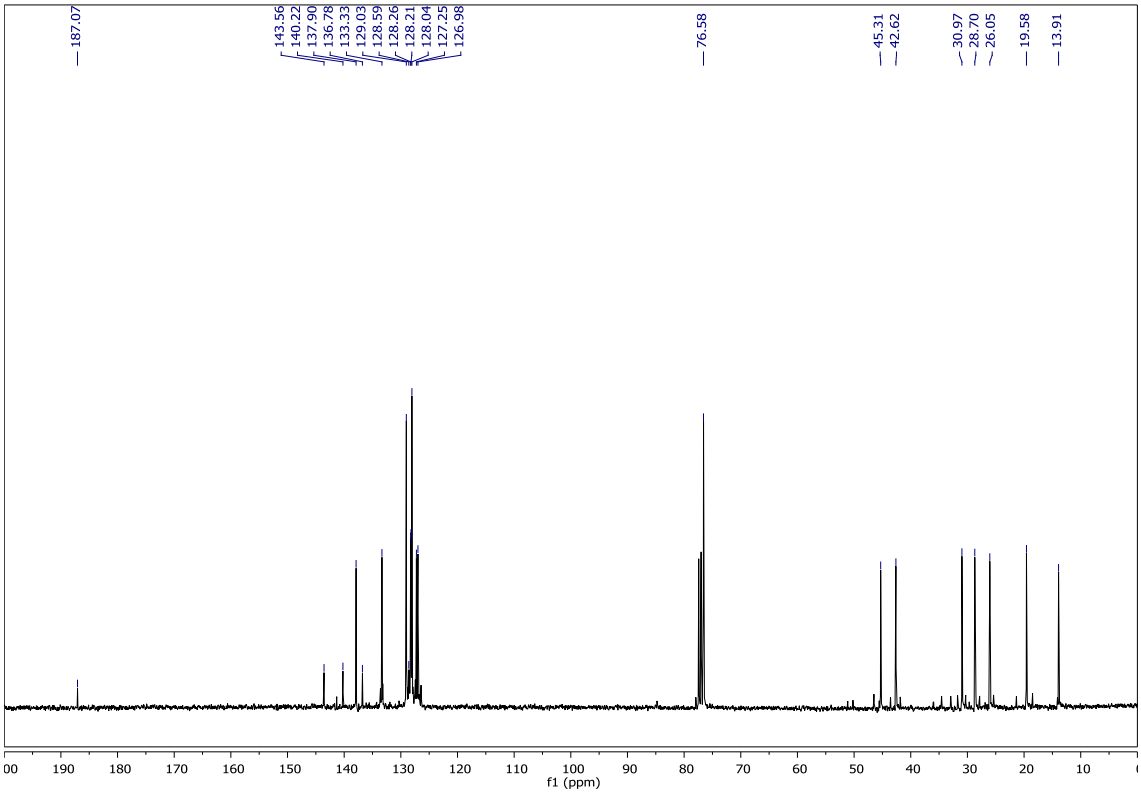
2.26
2.39
3.04
f1 (ppm)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128.59
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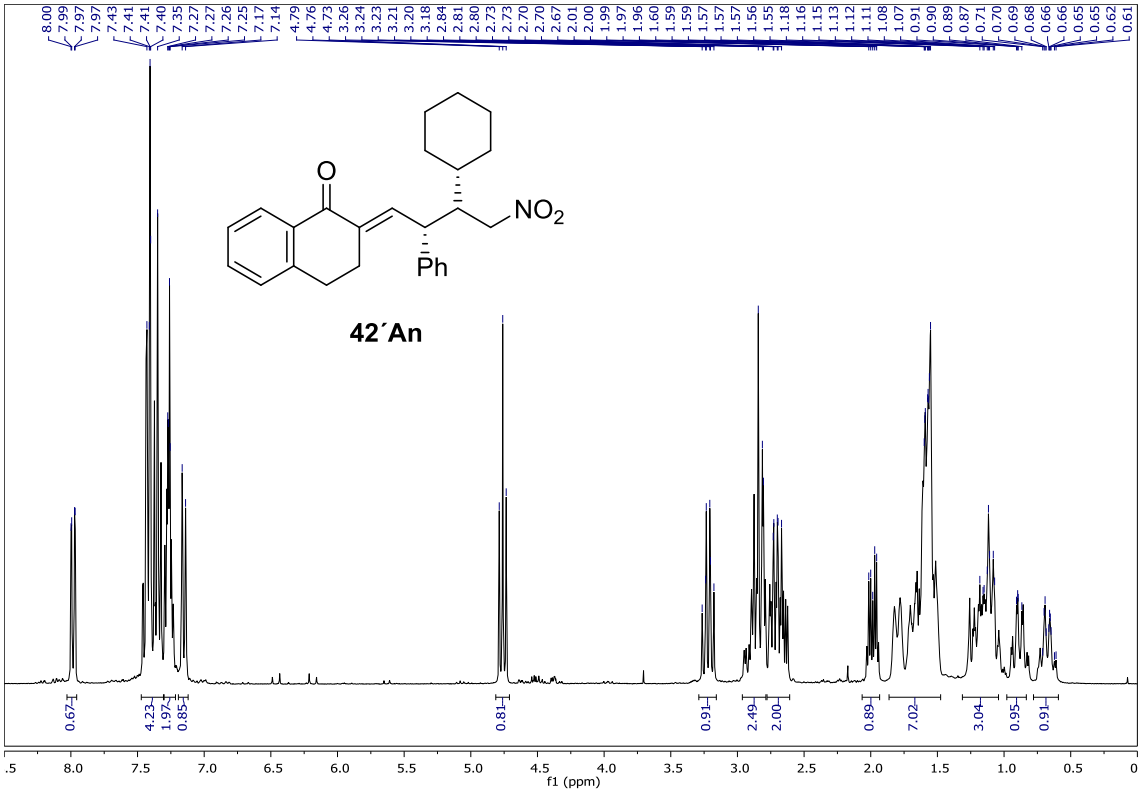
42.62
30.97
28.70
26.05
19.58
13.91
f1 (ppm)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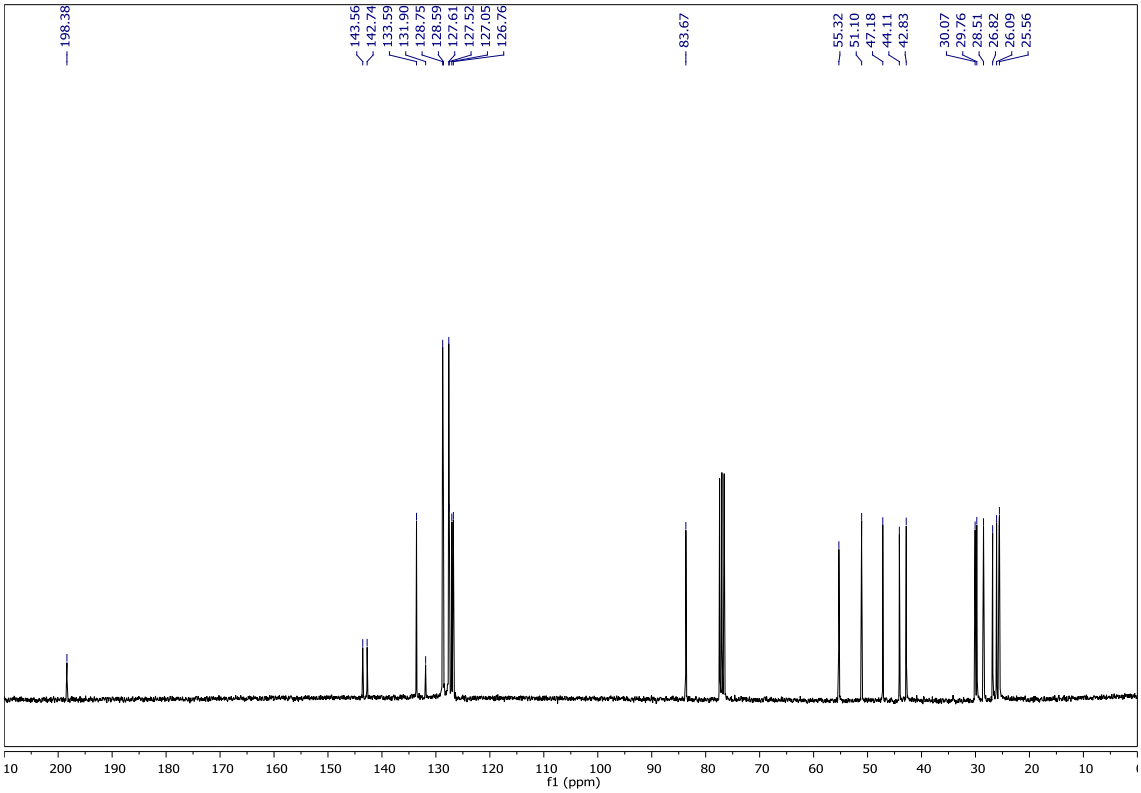
NO2
Ph
42´An
f1 (ppm)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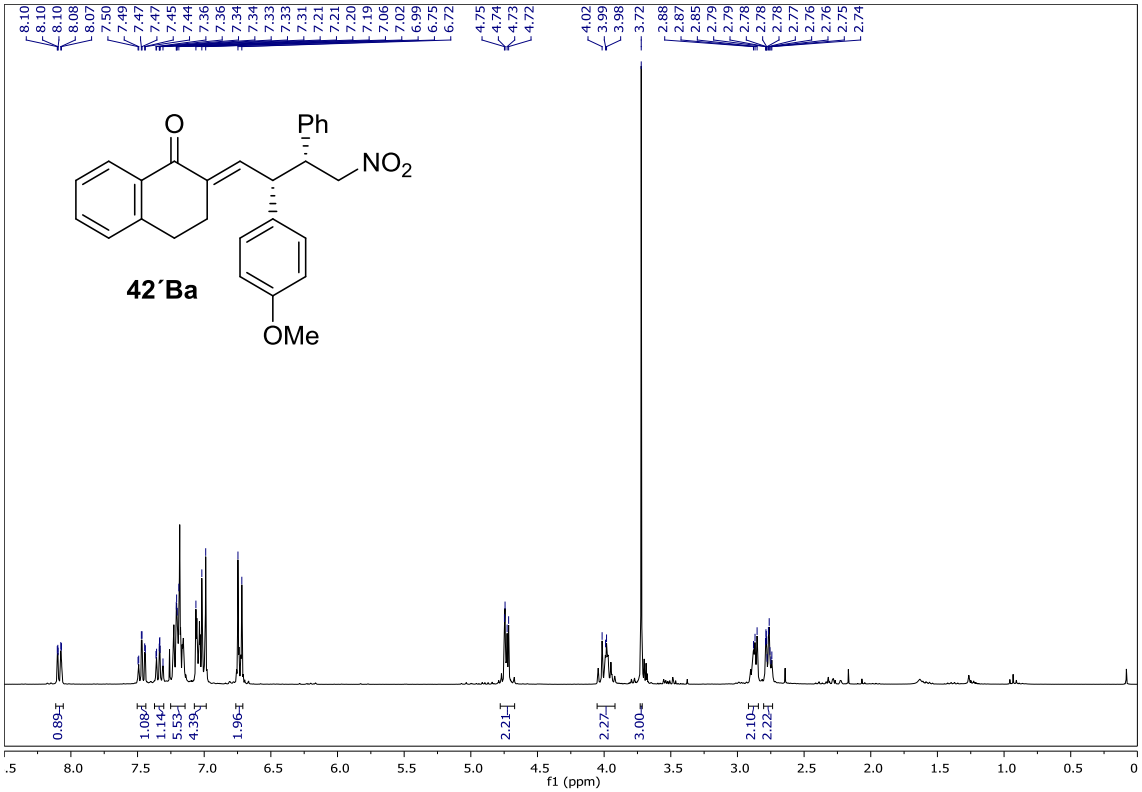
30.07
29.76
28.51
26.82
26.09
25.56
f1 (ppm)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Ph
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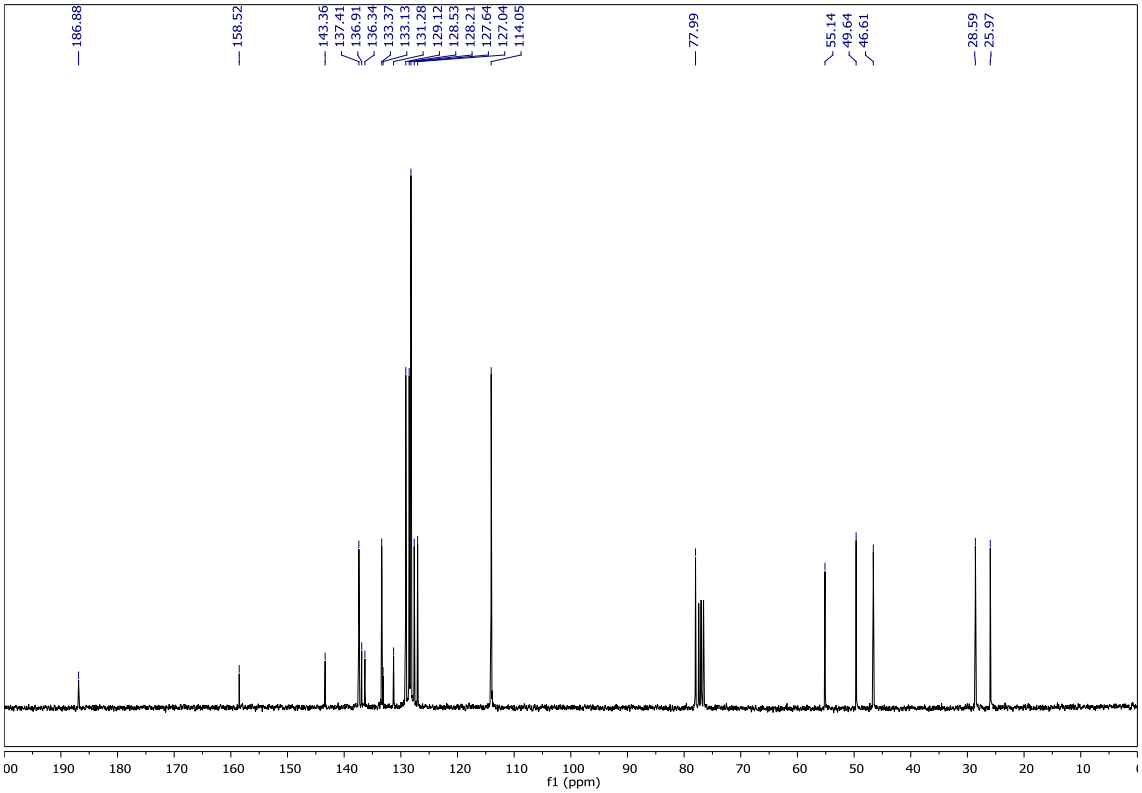
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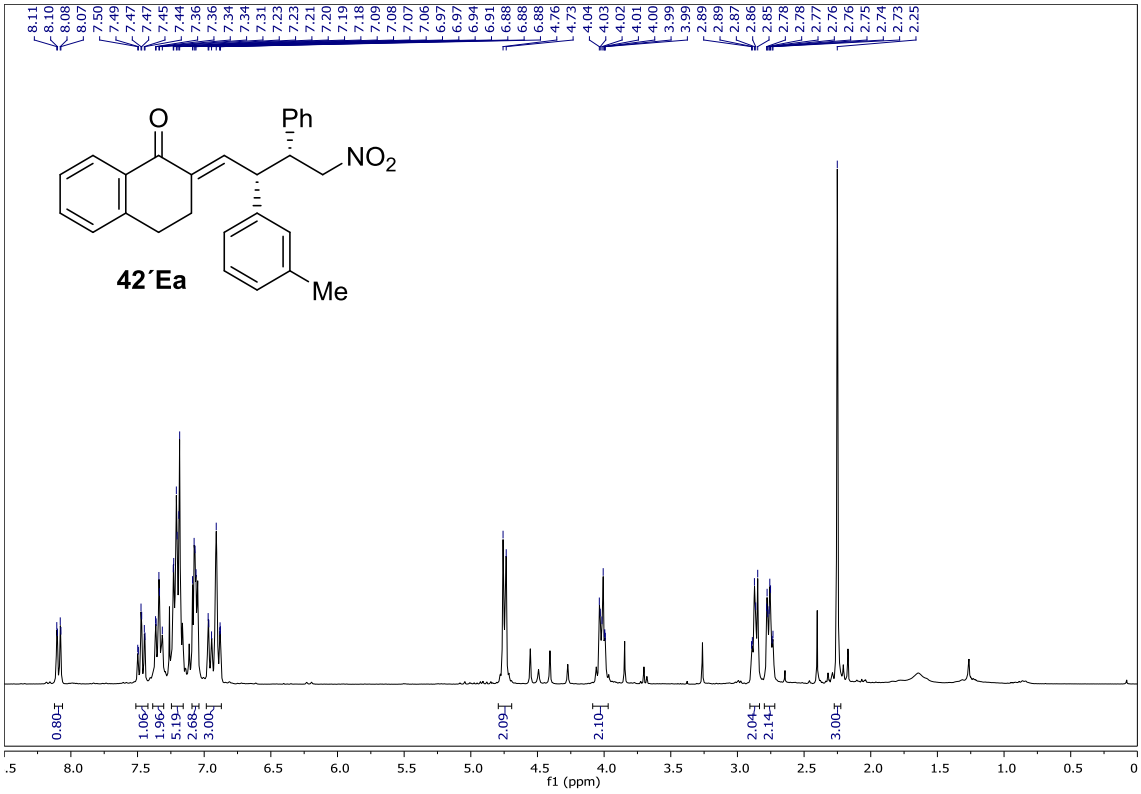
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O
Ph
NO2
42´Ea
Me
0.80 1.06 1.96 5.19 2.68 3.00 2.09 2.10 2.04 2.14 3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
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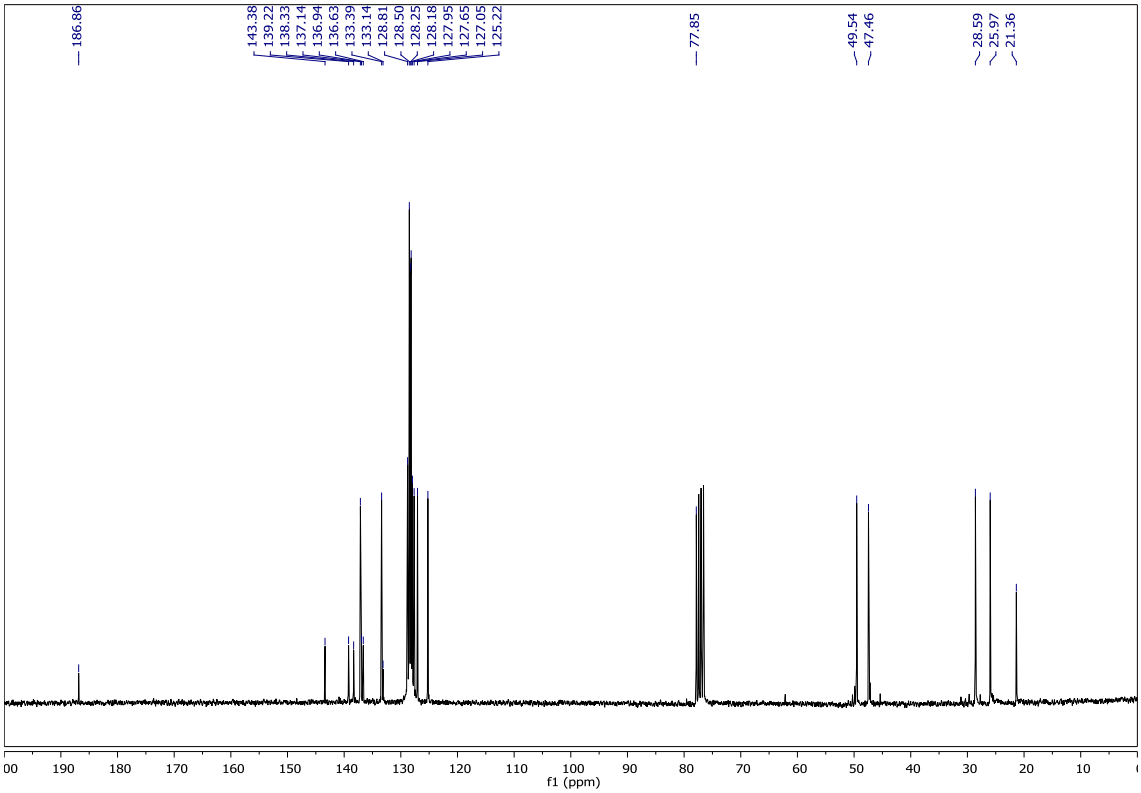
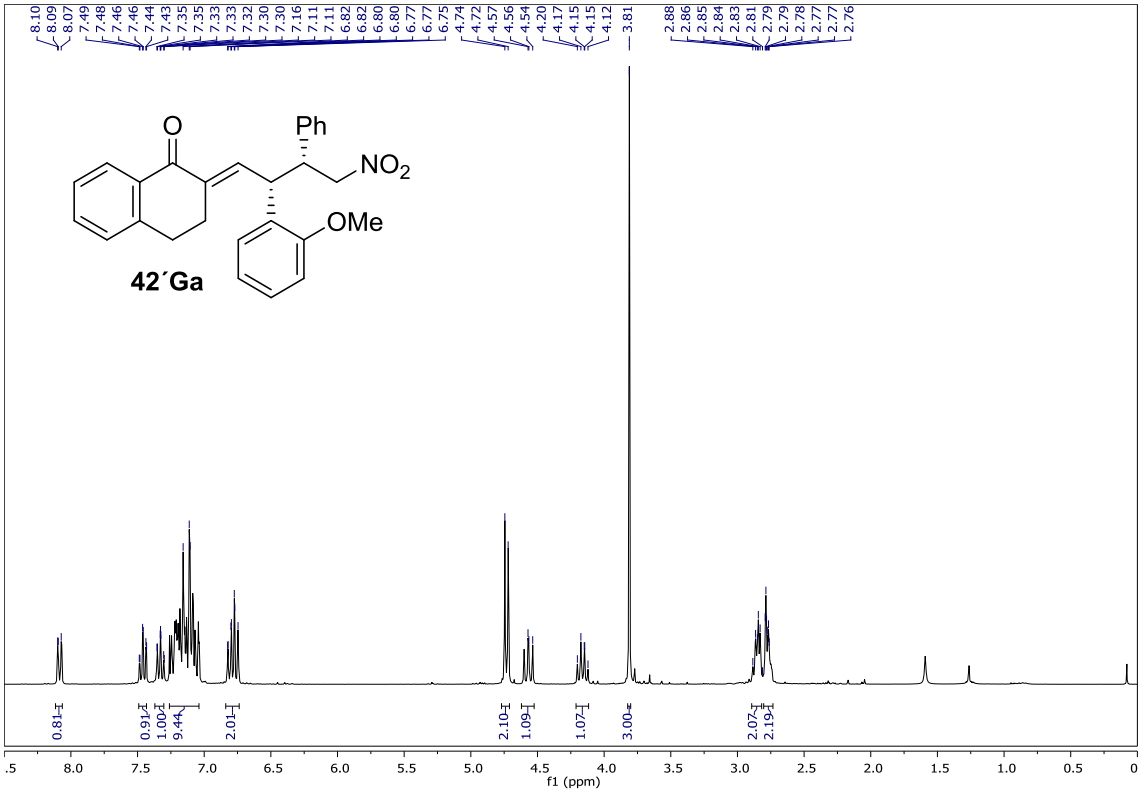

186.86
143.38 139.22 138.33 137.14 136.94 136.63 133.39 133.14 128.81 128.50 128.25 128.18 127.95 127.65 127.05 125.22
77.85
49.54 47.46
28.59 25.97 21.36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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Ph
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OMe
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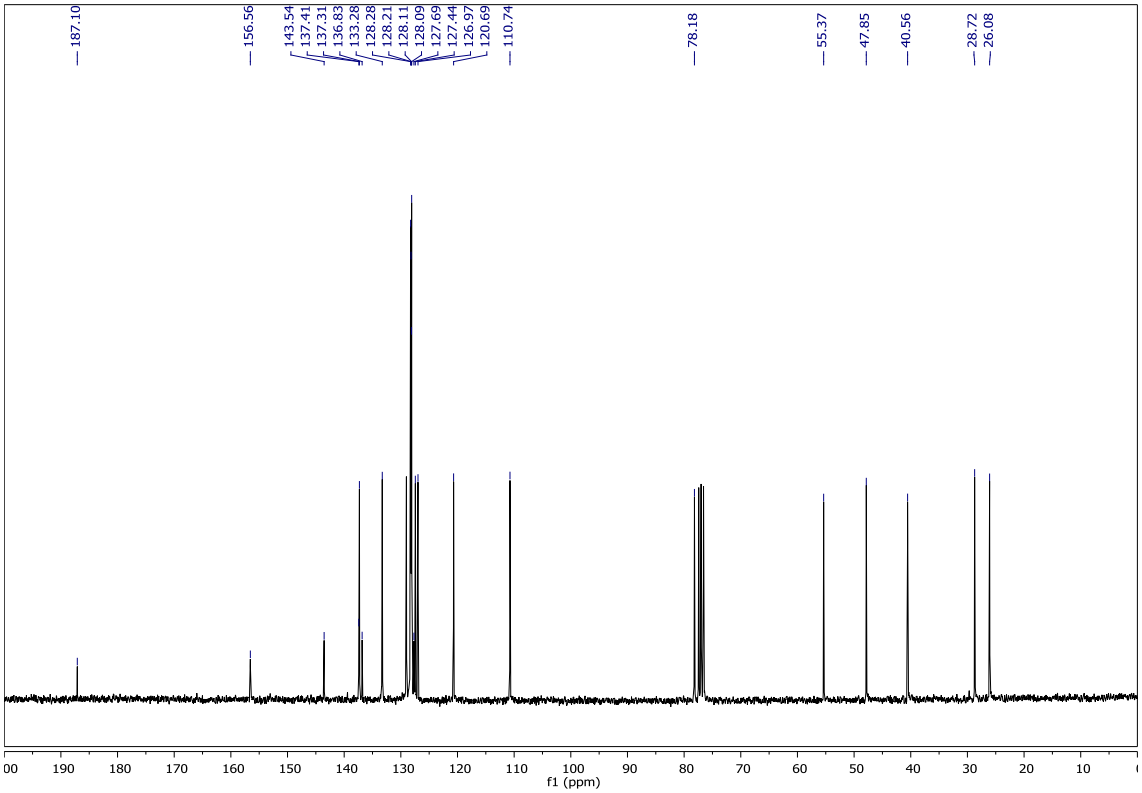
f1 (ppm)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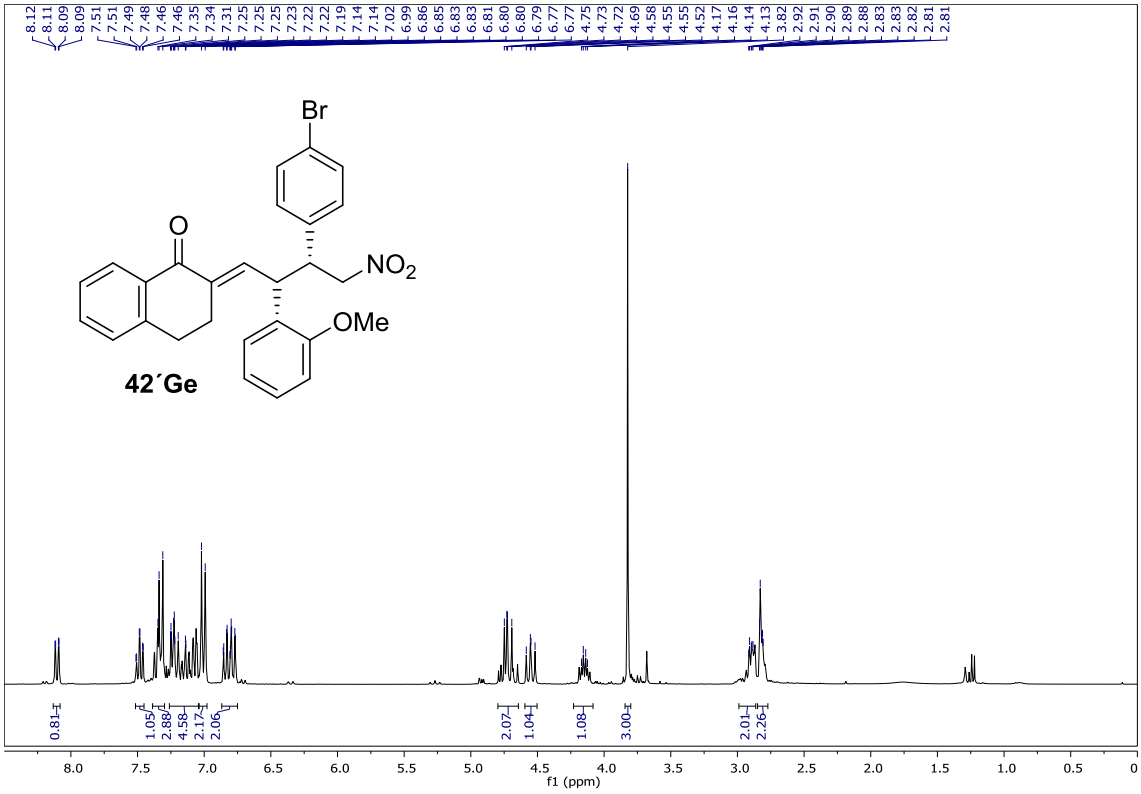
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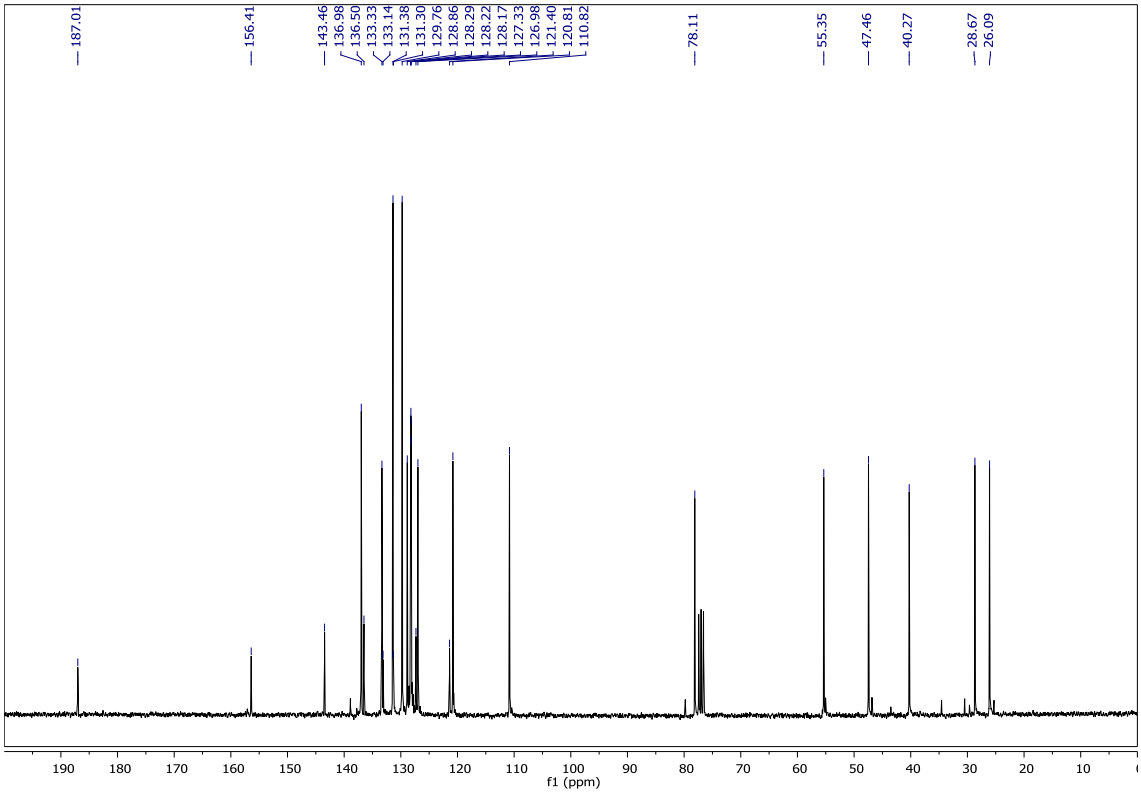
NO2
OMe
42´Ge
f1 (ppm)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128.22
128.17
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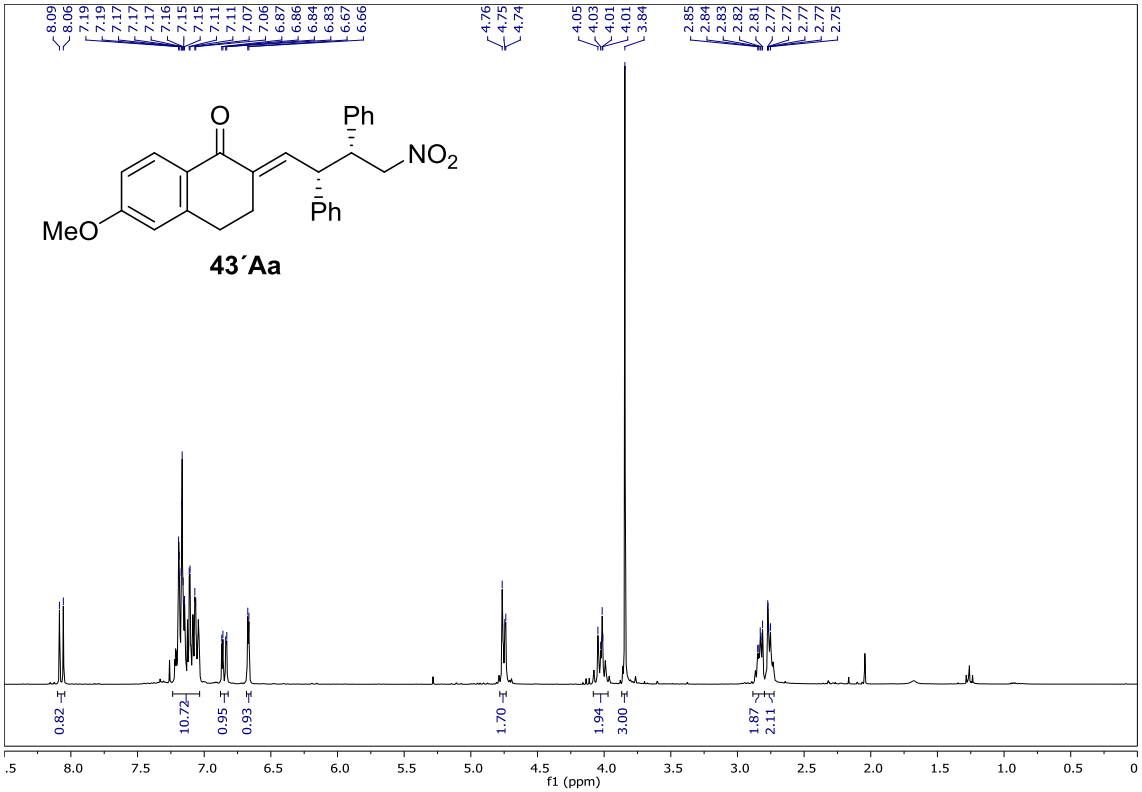
40.27
28.67
26.09
f1 (ppm)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2.77
2.77
2.77
2.77
2.75
O
Ph
NO2
Ph
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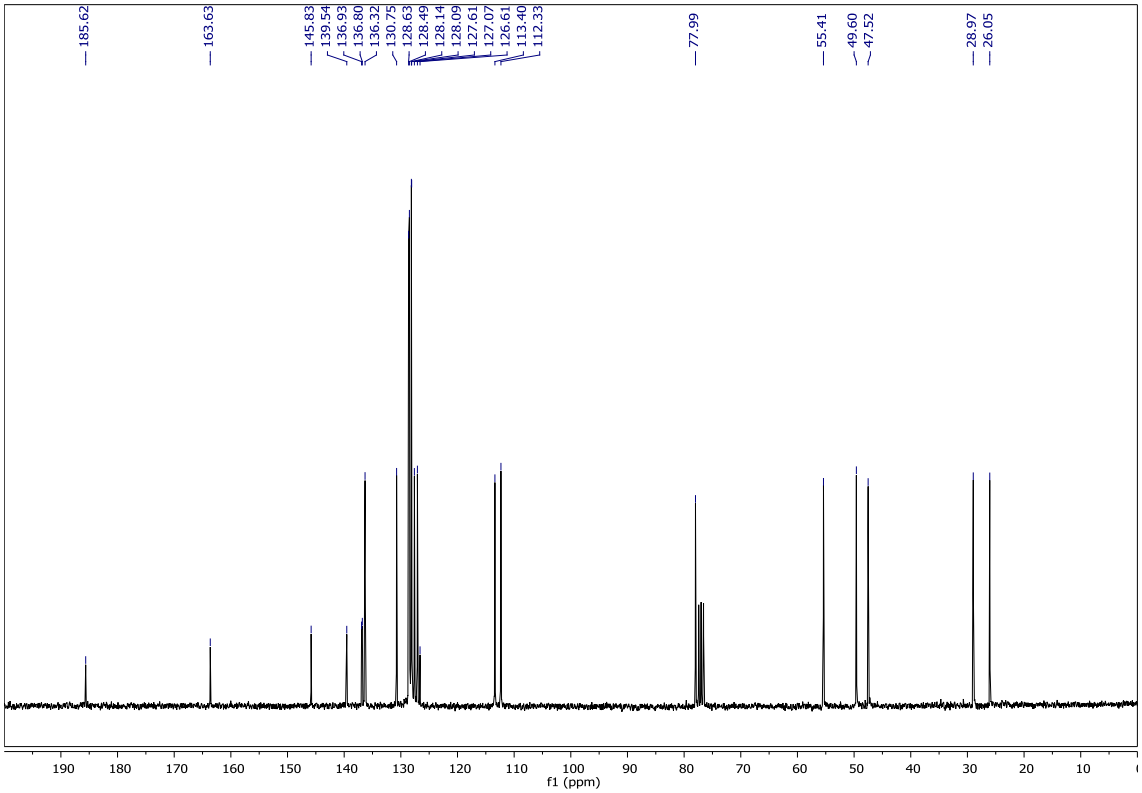
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77.99
55.41
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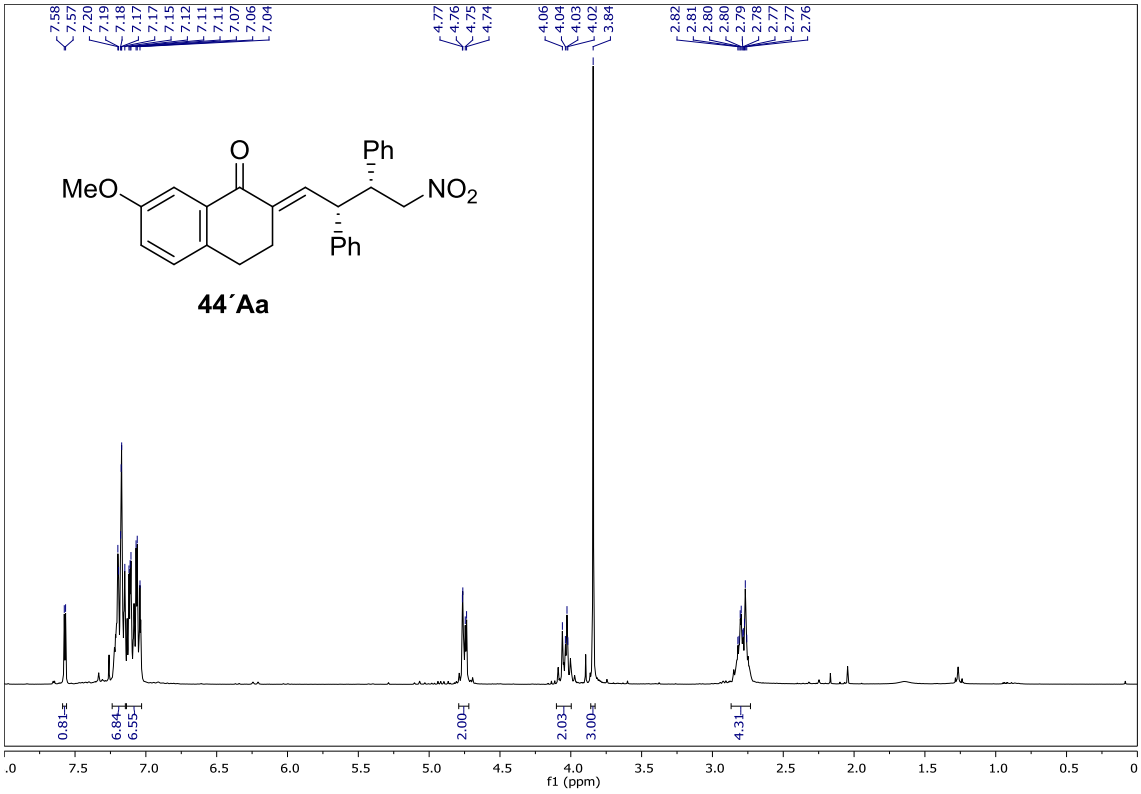
47.52
28.97
26.05
f1 (ppm)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7.04
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4.06
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2.80
2.80
2.79
2.78
2.77
2.77
2.76
O
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Ph
44´Aa
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6.55
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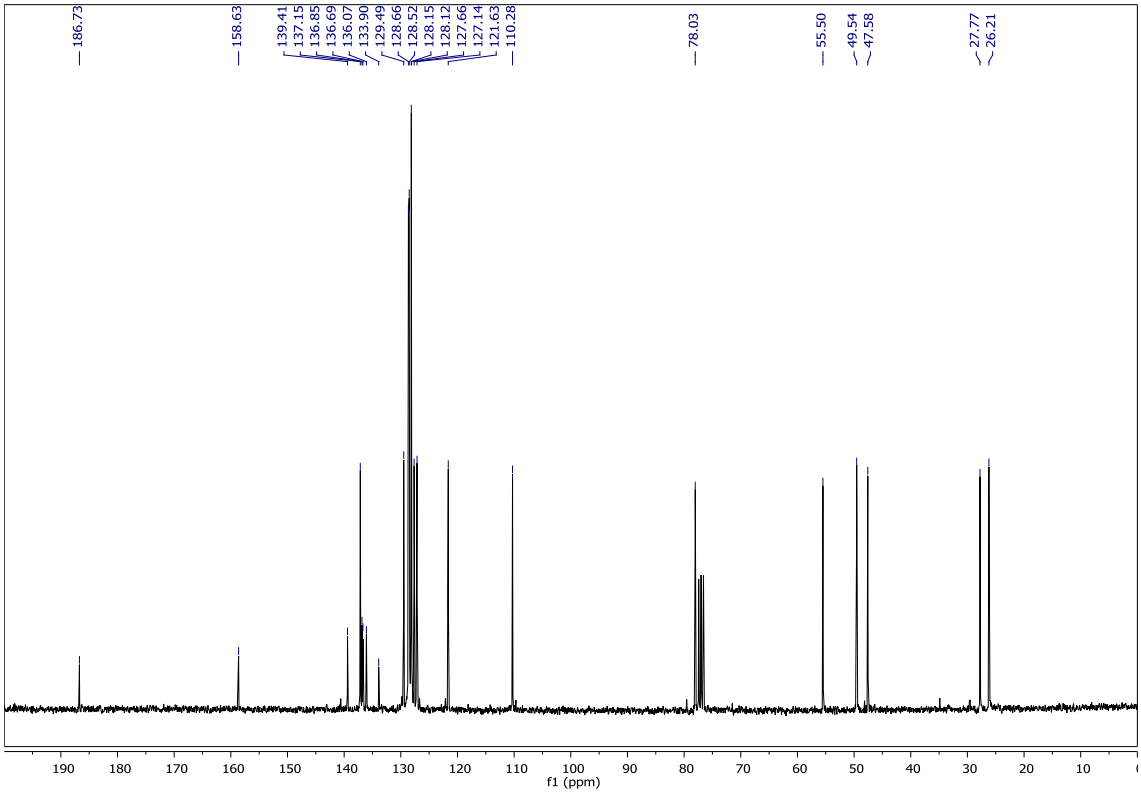
2.03
3.00
4.31
f1 (ppm)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128.52
128.15
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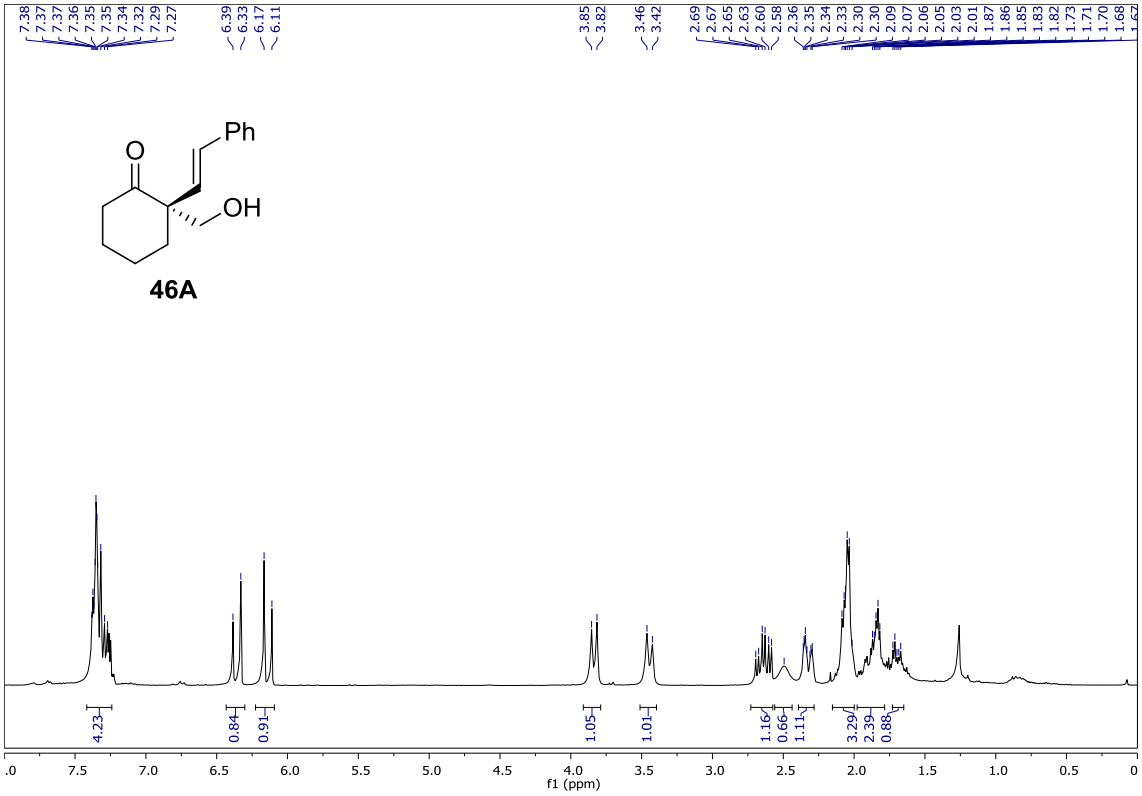
121.63
110.28
78.03
55.50
49.54
47.58
27.77
26.21
f1 (ppm)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6.11
3.85
3.82
3.46
3.42
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2.67
2.65
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2.60
2.58
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2.34
2.33
2.30
2.30
2.09
2.07
2.06
2.05
2.03
2.01
1.87
1.86
1.85
1.83
1.82
1.73
1.71
1.70
1.68
O
Ph
OH
46A
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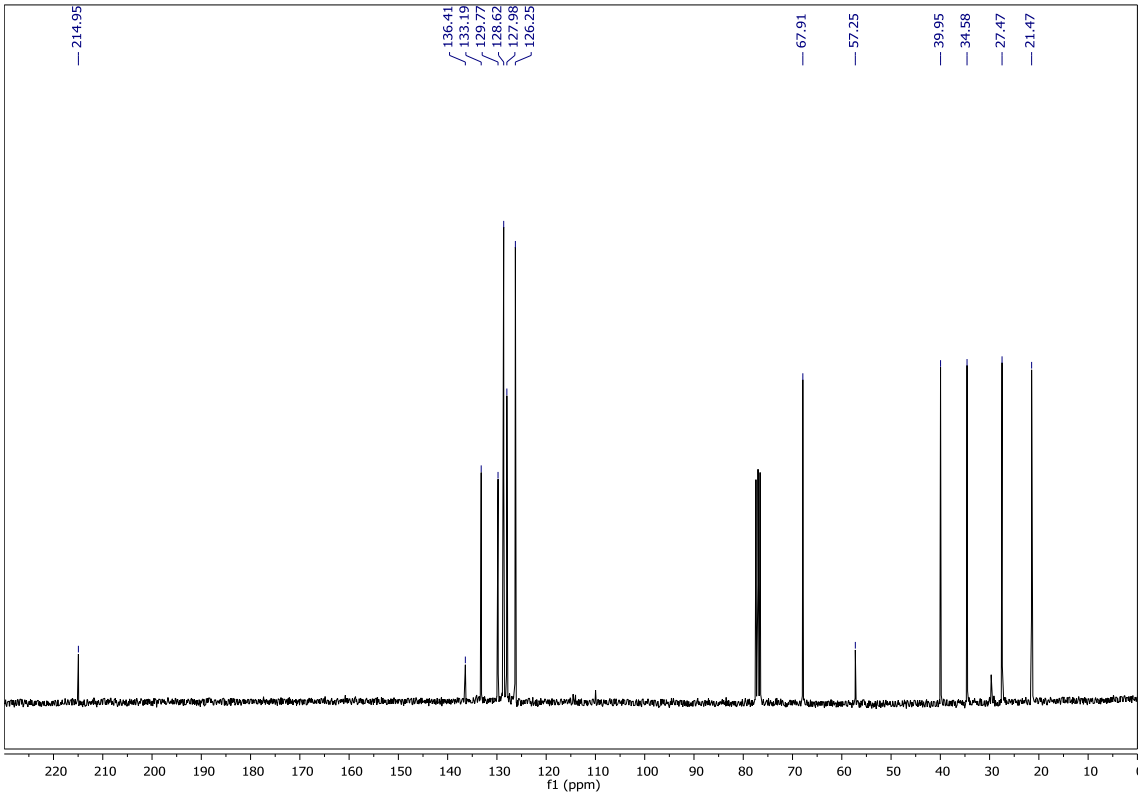
0.91
1.05
1.01
1.16
0.66
1.11
3.29
2.39
0.88
f1 (ppm)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67.91
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34.58
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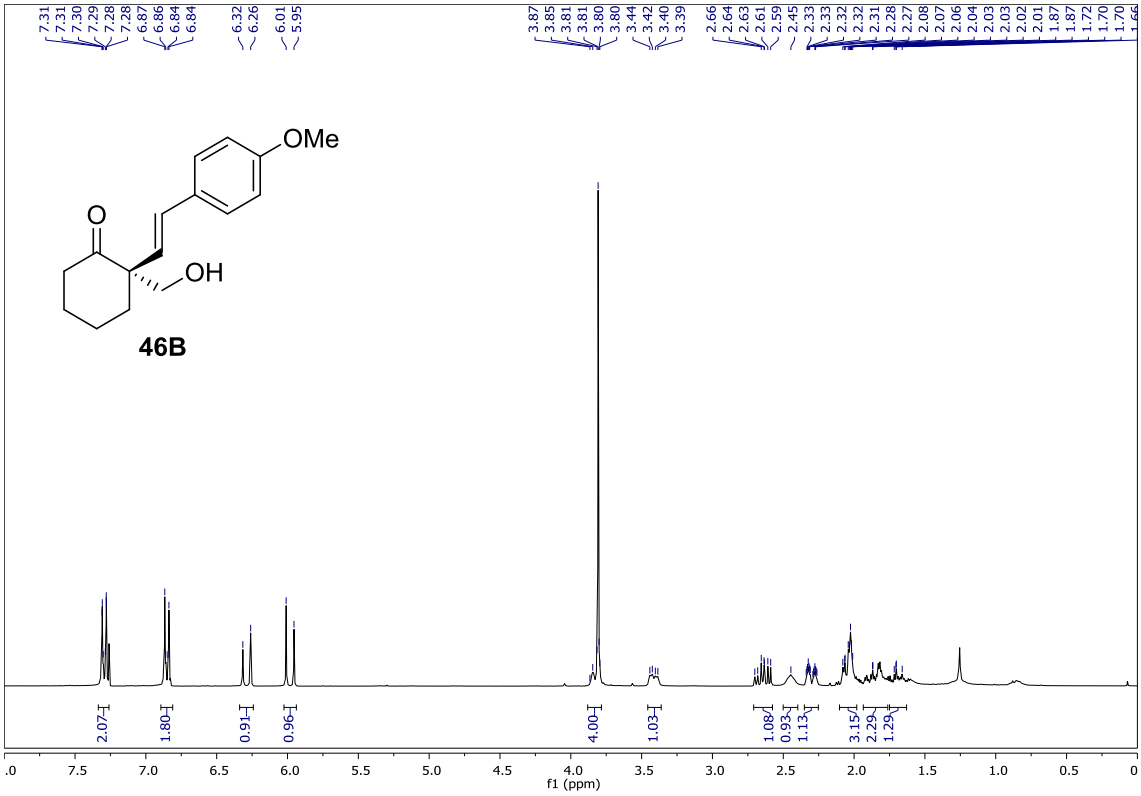
21.47
f1 (ppm)


OMe
O
OH
46B
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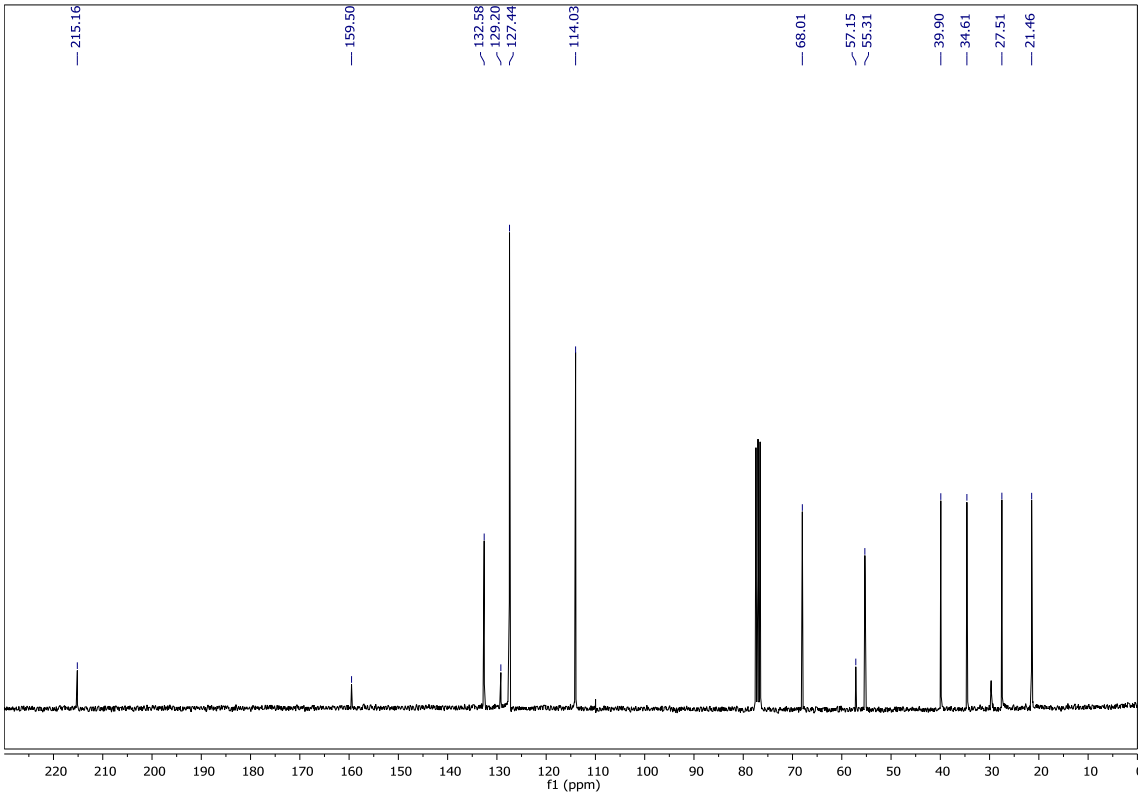
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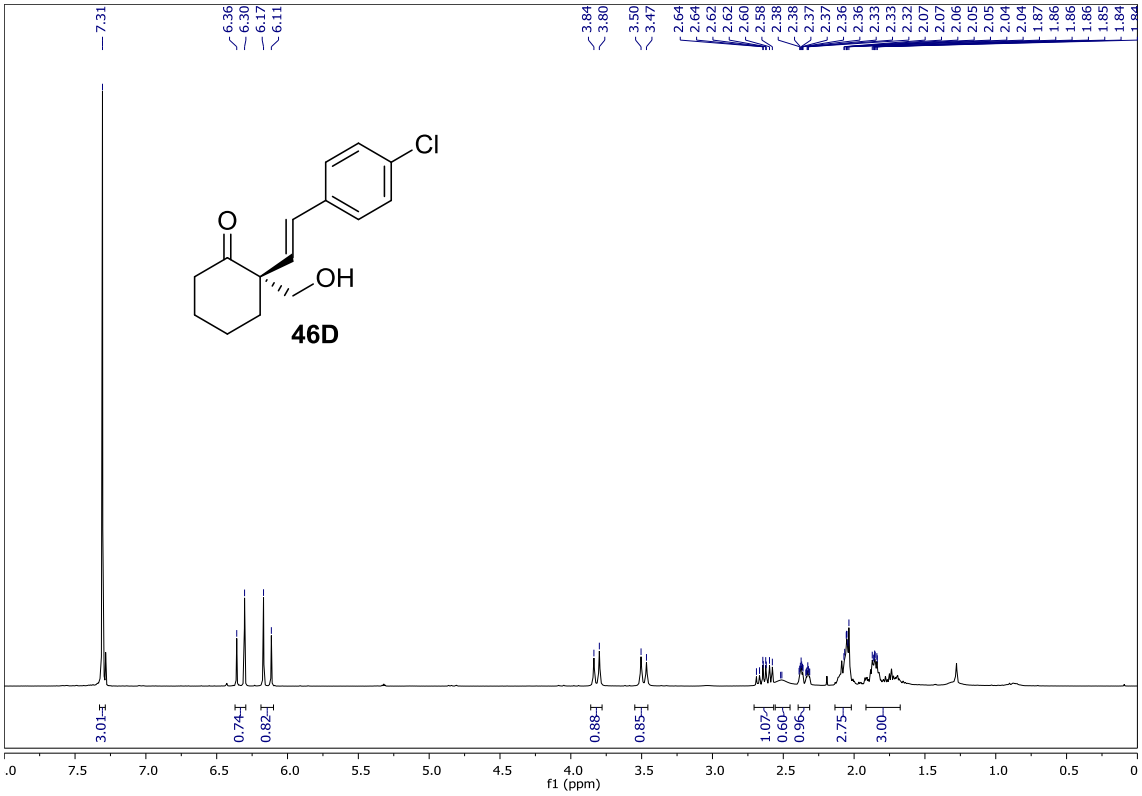
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2.37
2.36
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2.06
2.05
2.05
2.04
2.04
1.87
1.86
1.86
1.86
1.85
1.84
Cl
O
OH
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2.75
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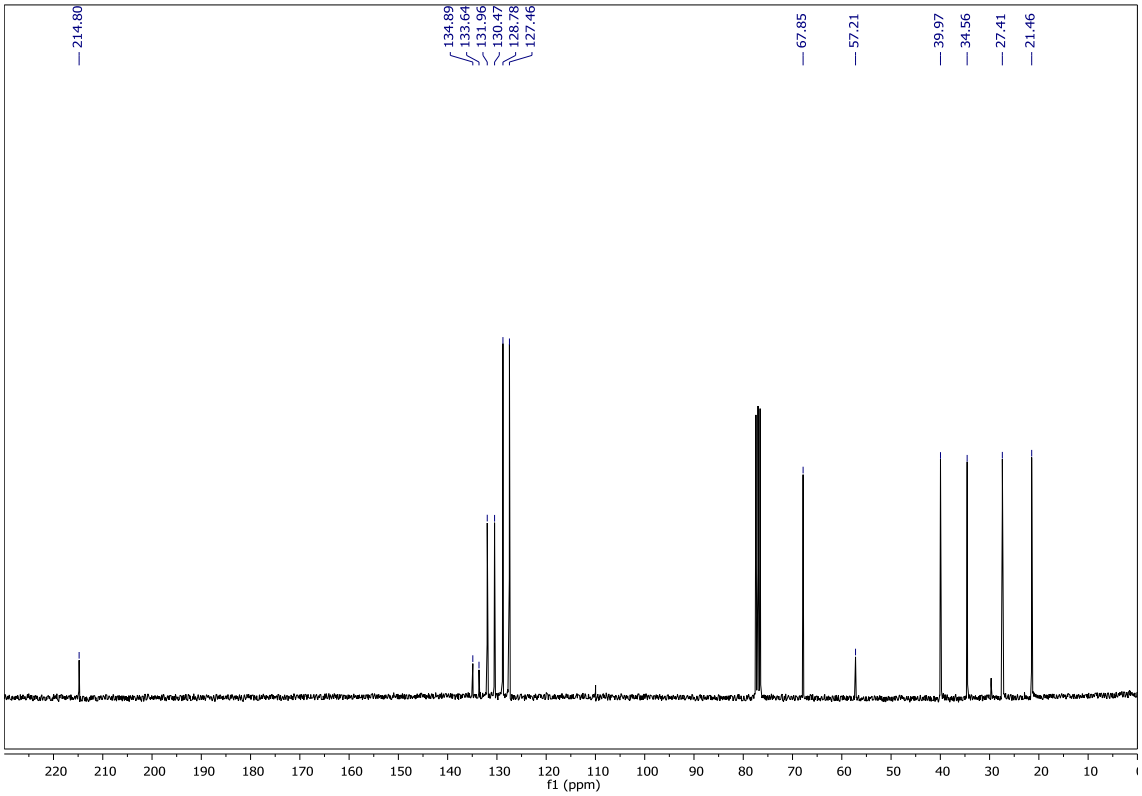
f1 (ppm)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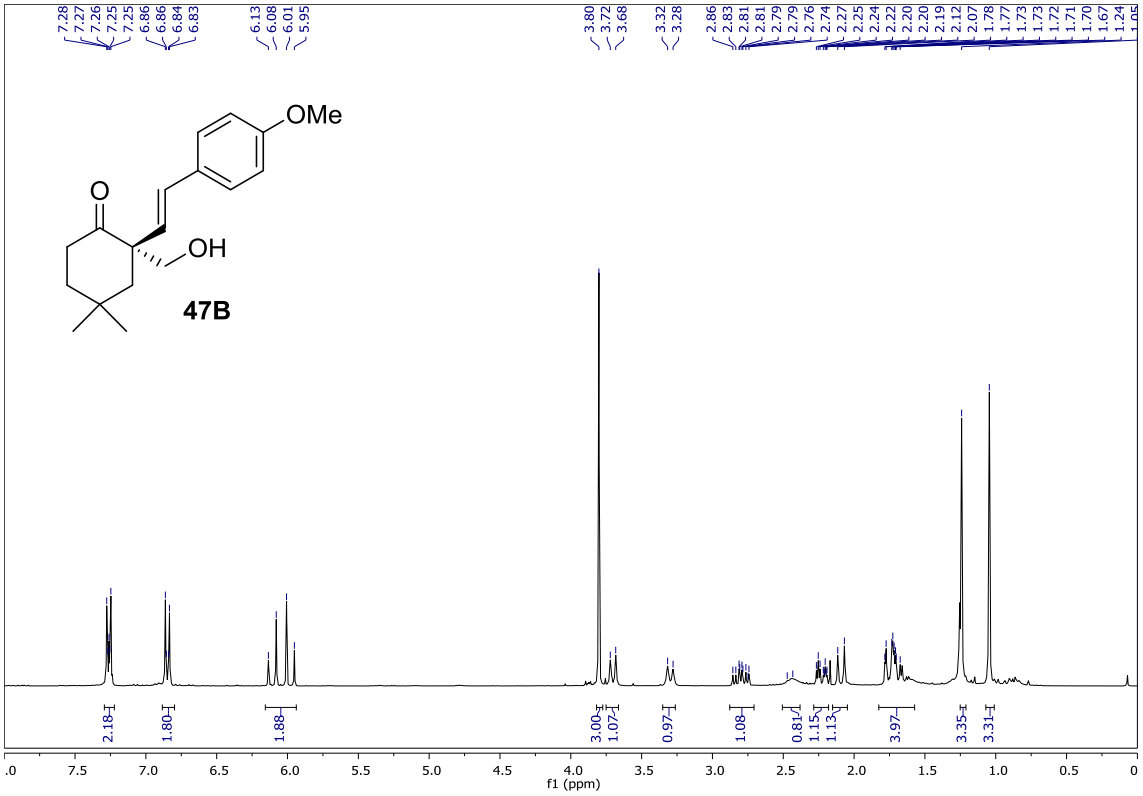
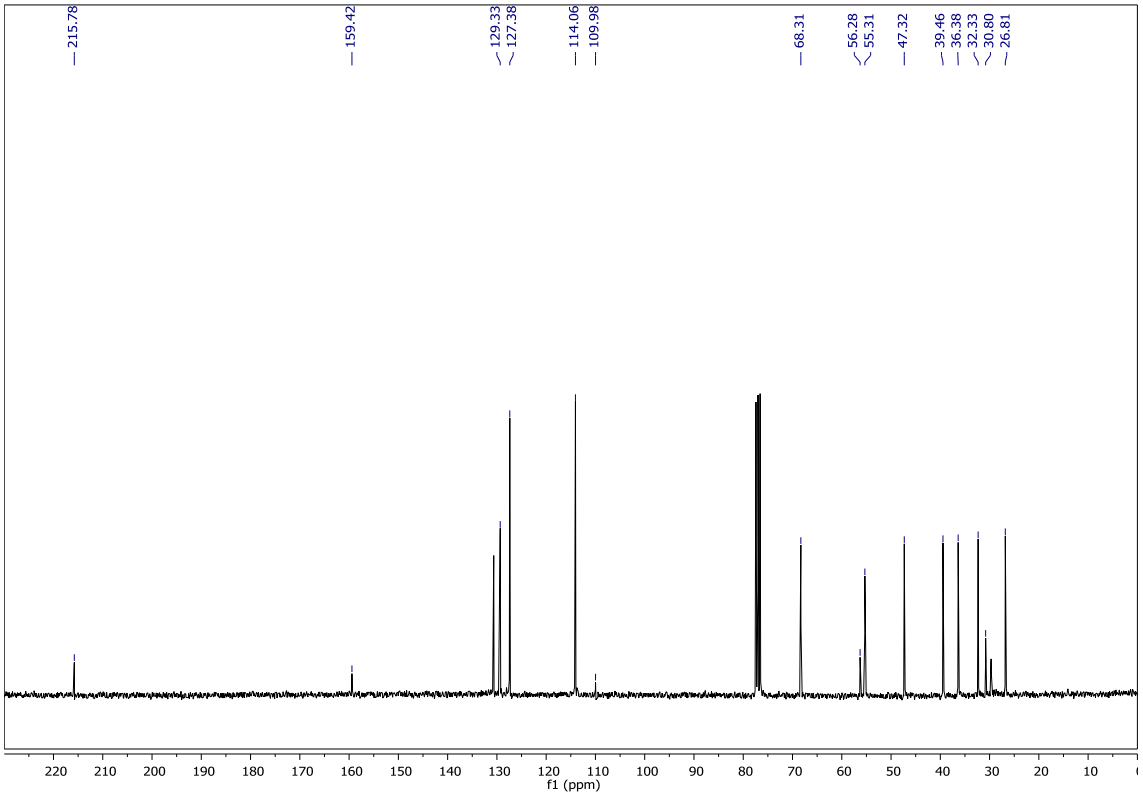
34.56
27.41
21.46
f1 (ppm)


OMe
O
OH
47B
f1 (ppm)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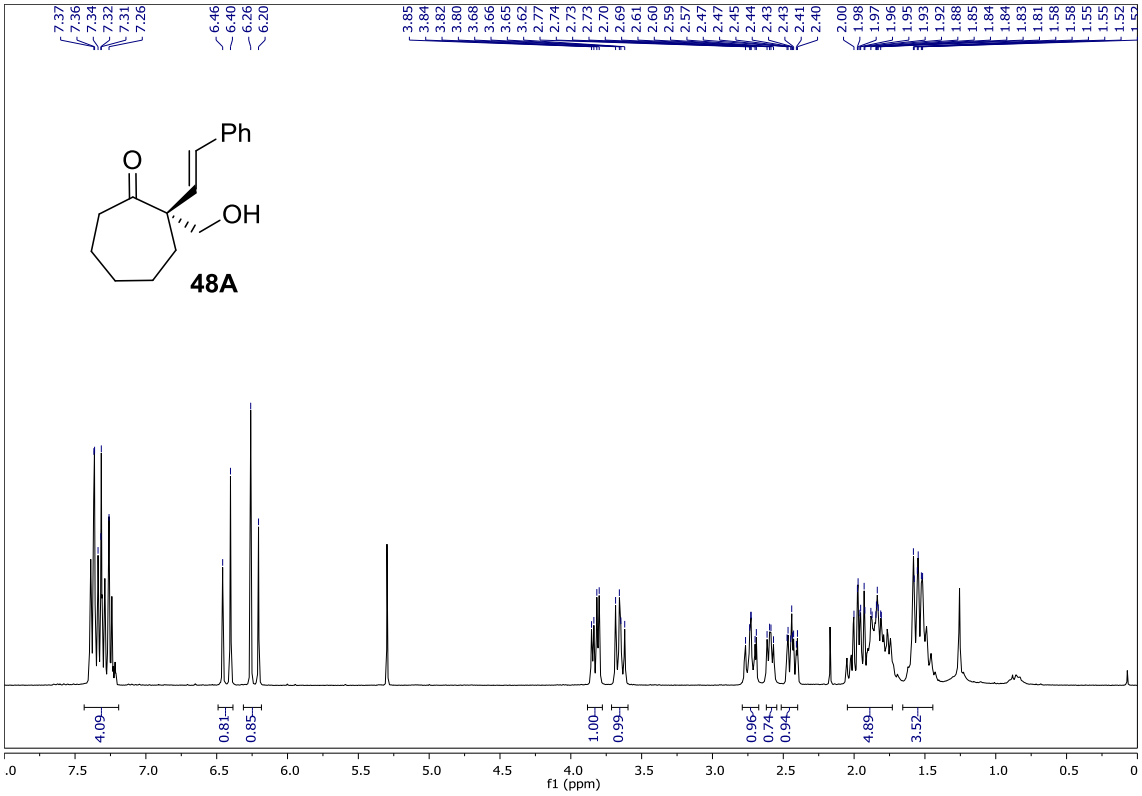
Ph
O
OH
48A
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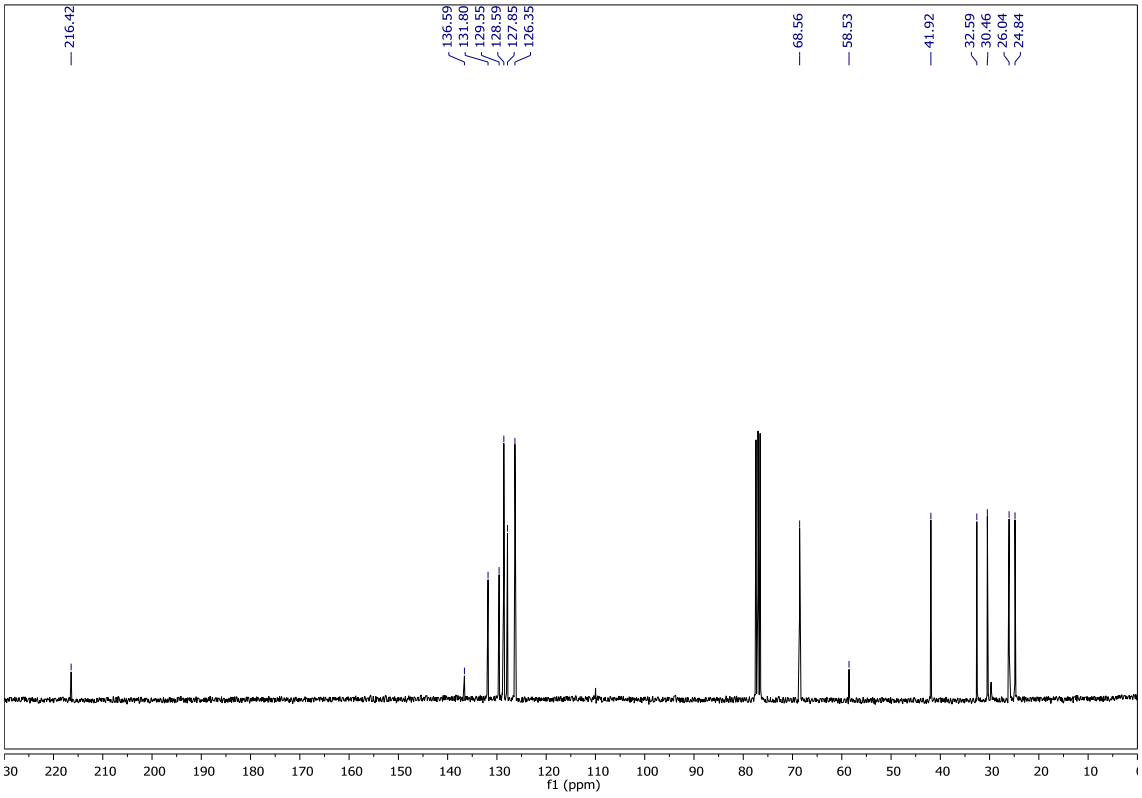
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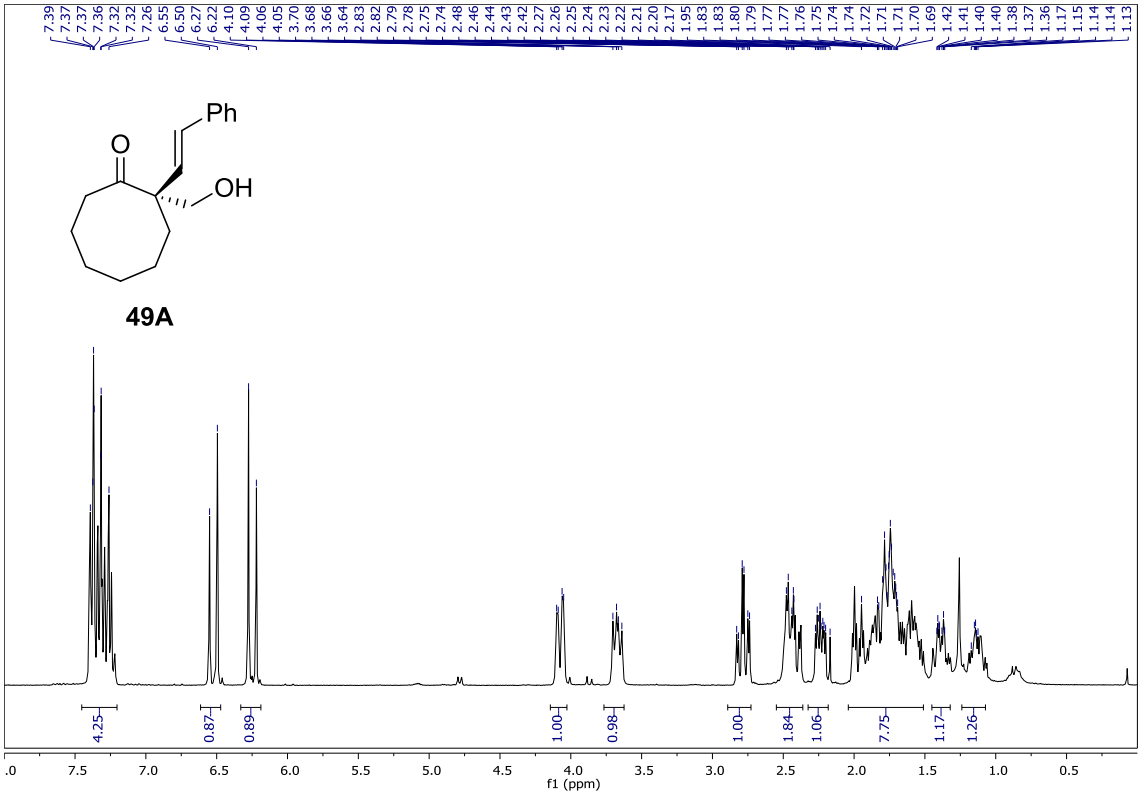
Ph
O
OH
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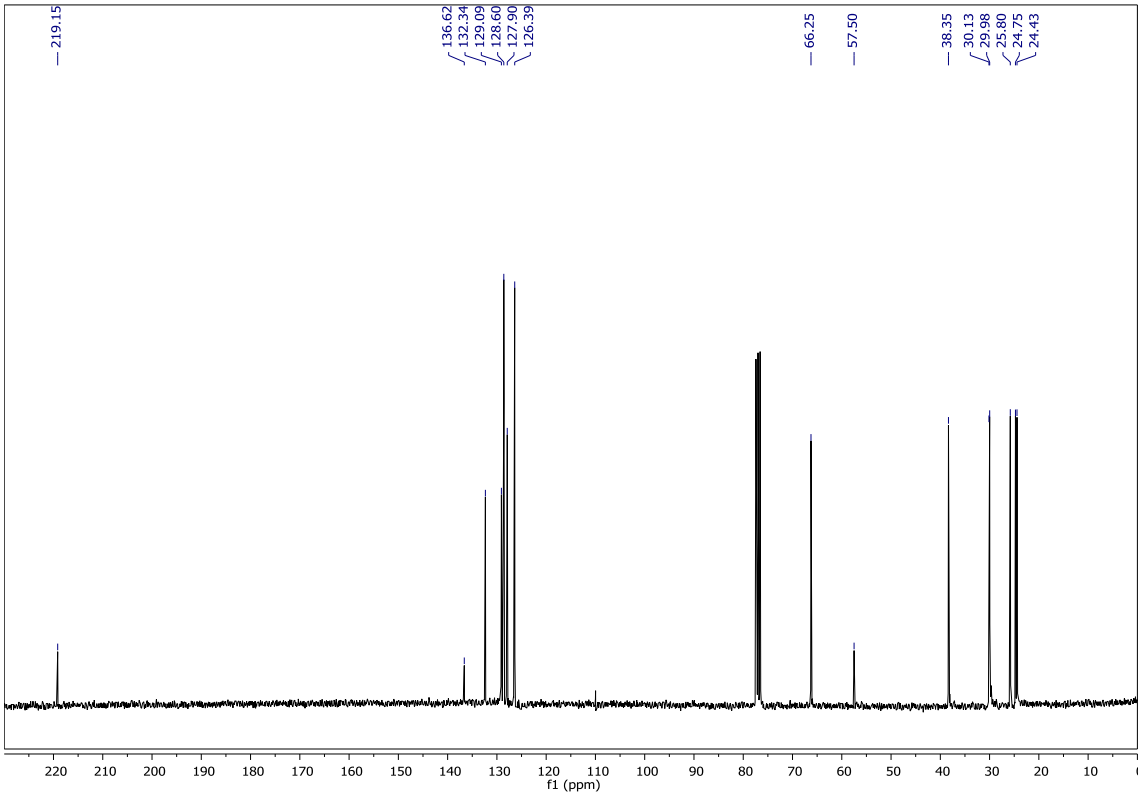
f1 (ppm)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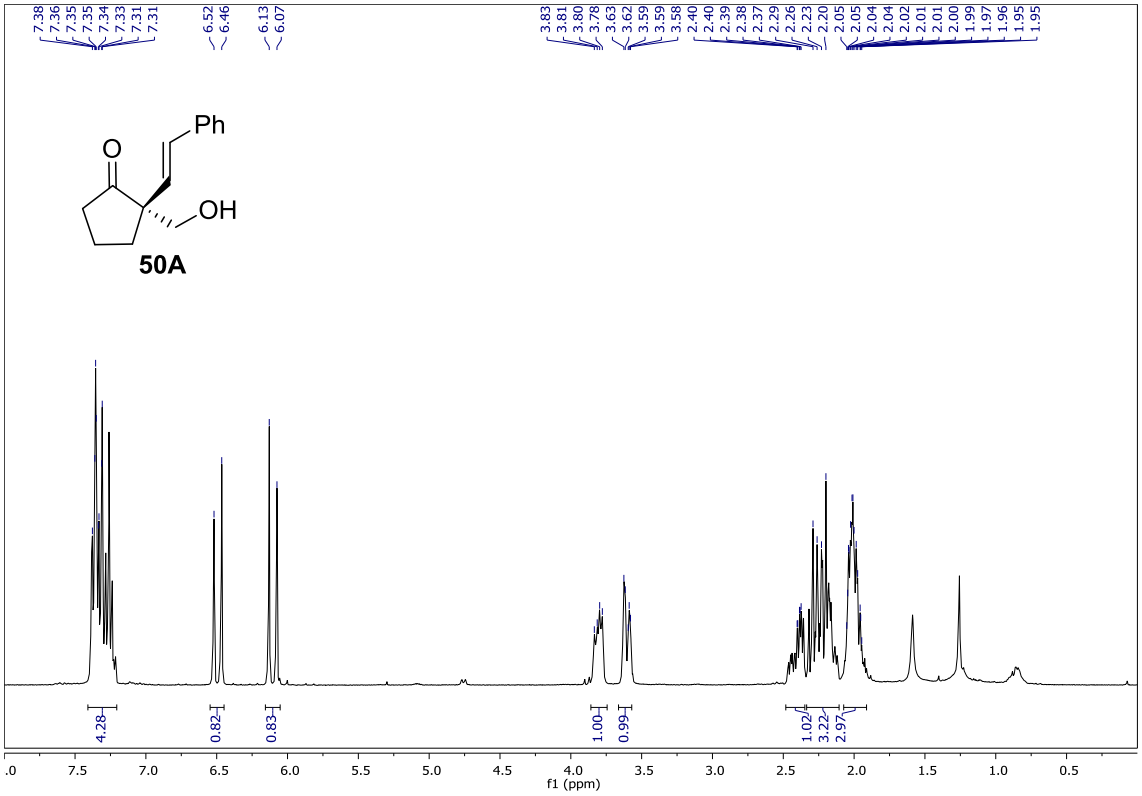
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3.81
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2.38
2.37
2.29
2.26
2.23
2.20
2.05
2.05
2.04
2.04
2.02
2.01
2.01
2.00
1.99
1.97
1.96
1.95
1.95
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1.02
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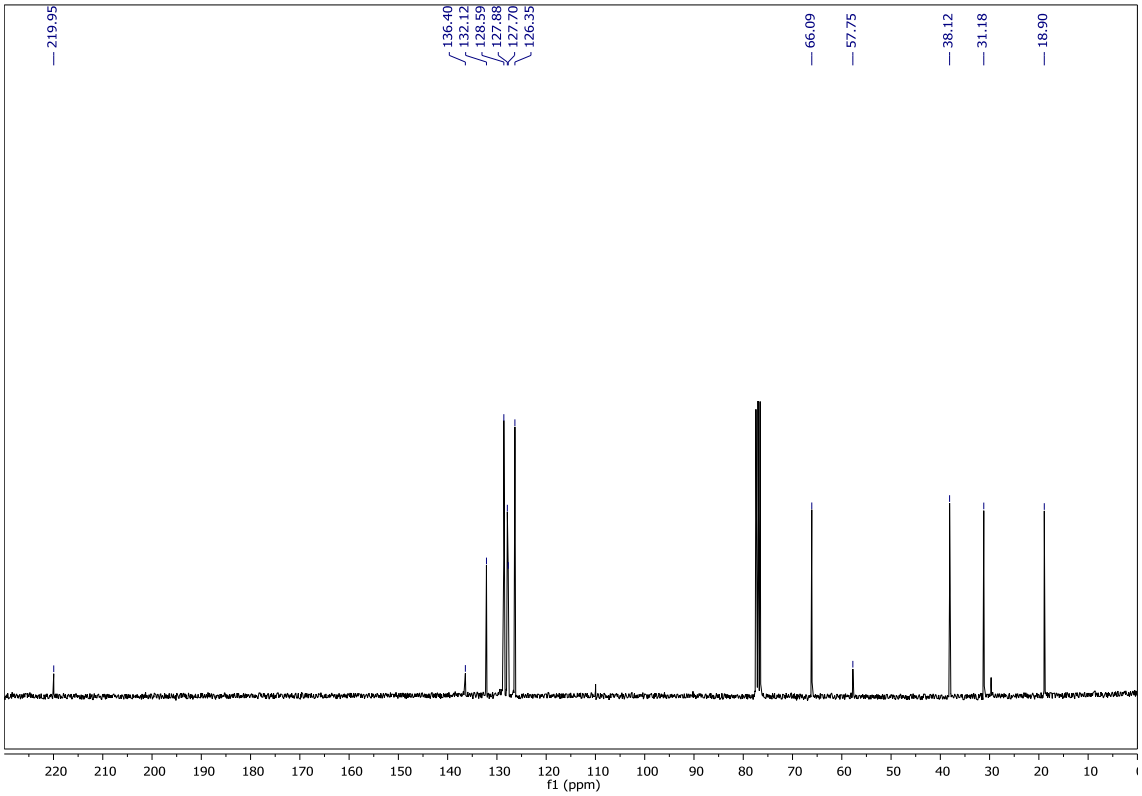
2.97
f1 (ppm)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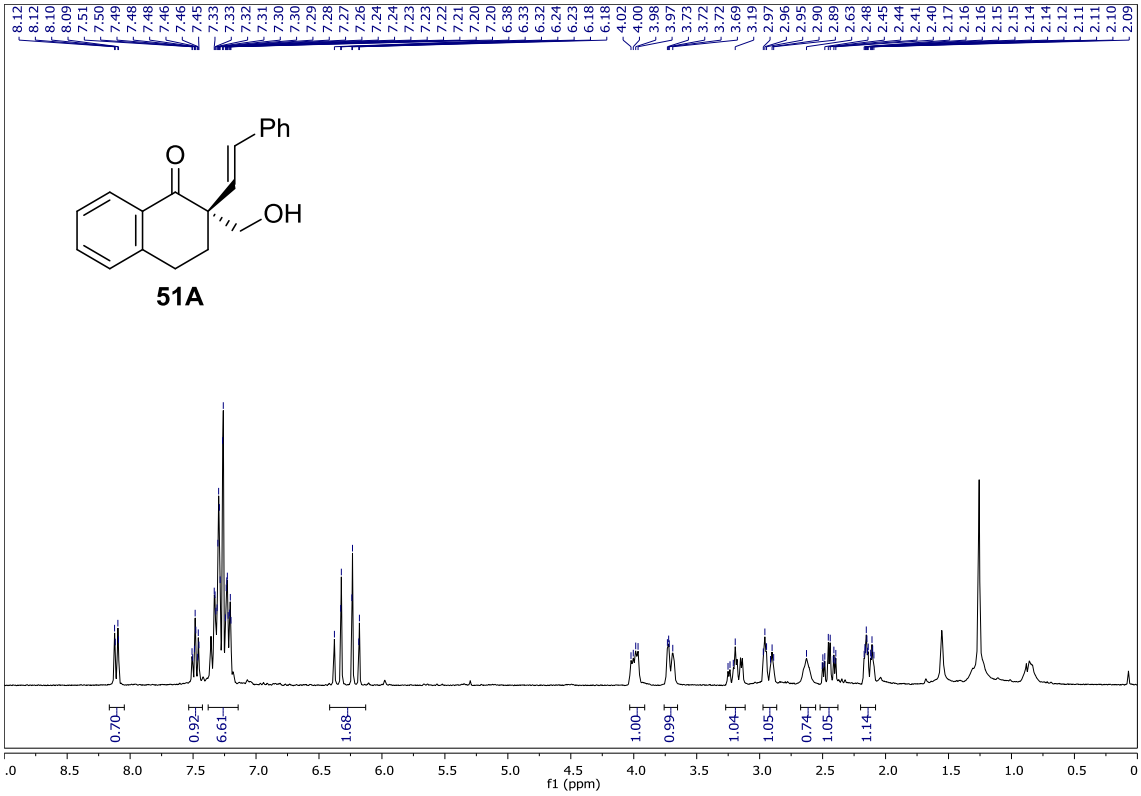
18.90
f1 (ppm)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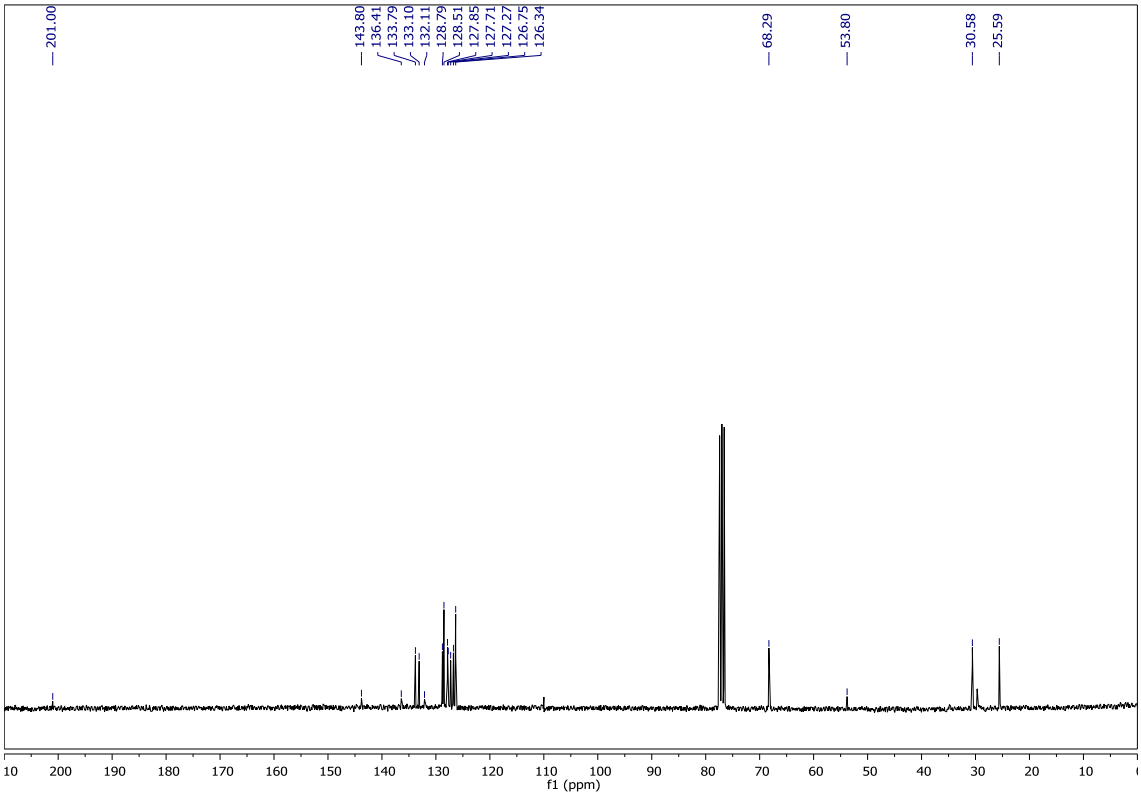
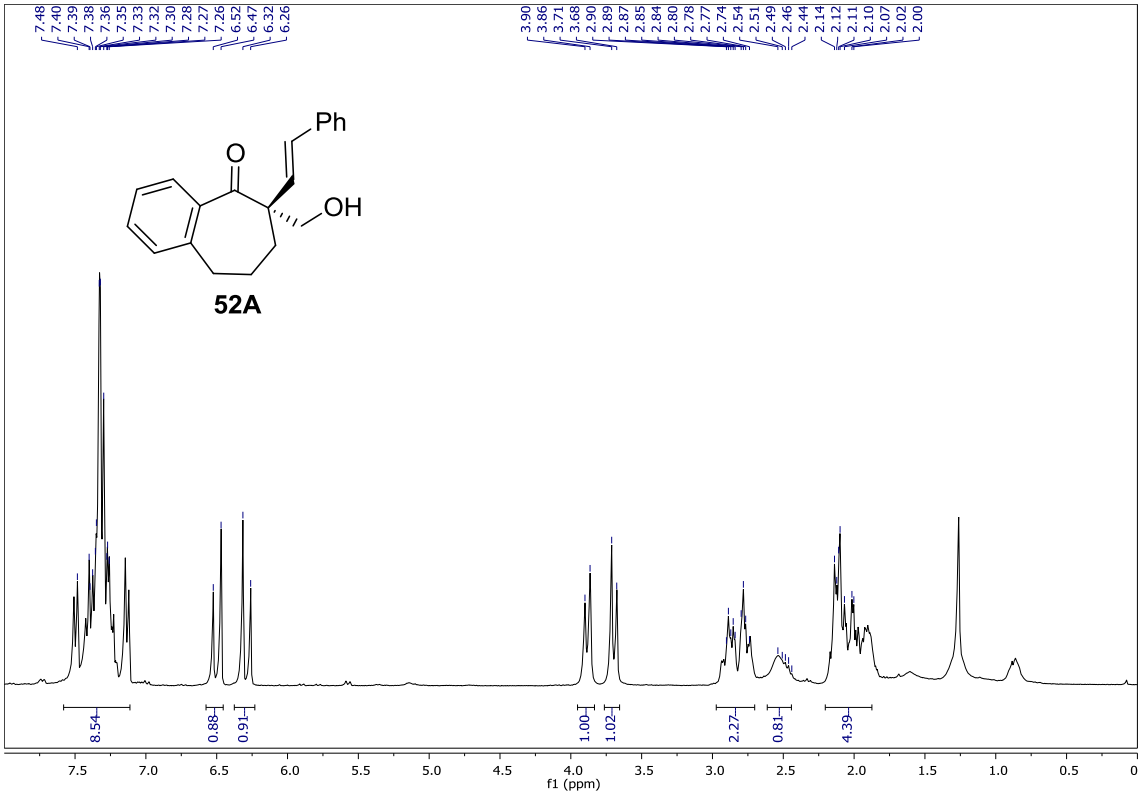
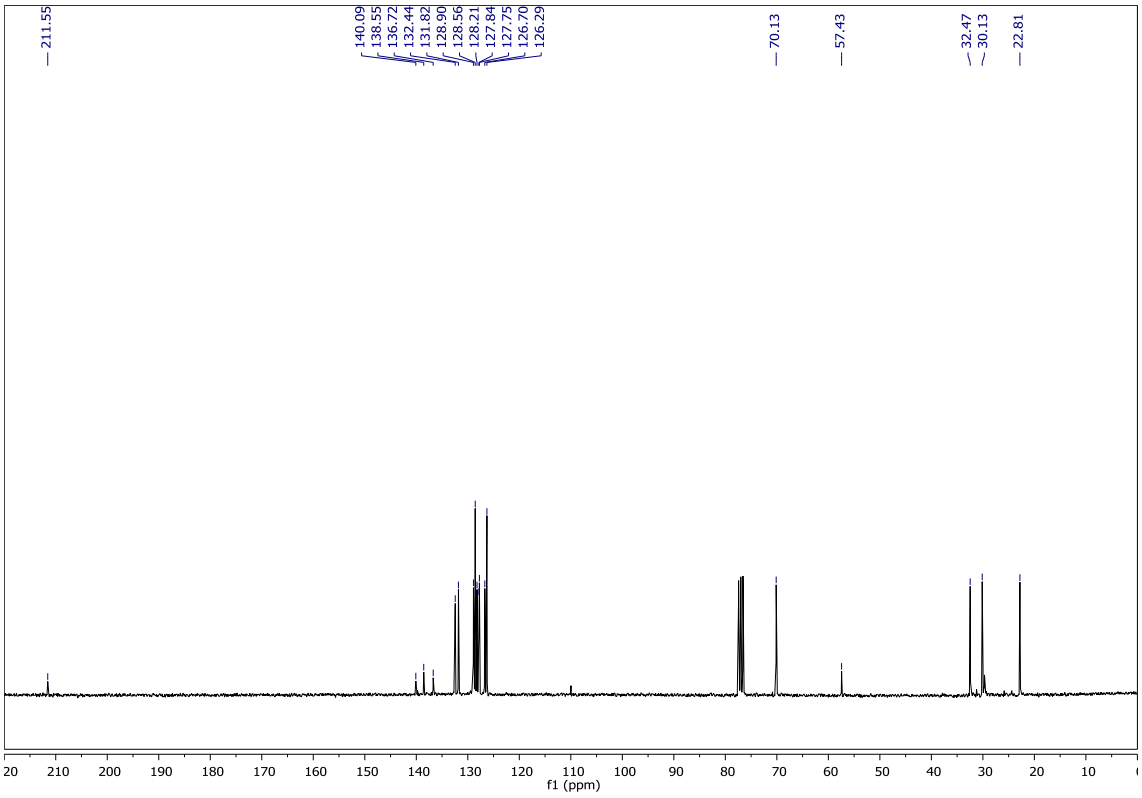
OH
51A
f1 (ppm)


f1 (ppm)

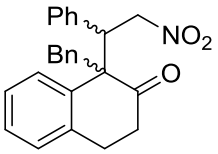

7.48
7.40
7.39
7.38
7.36
7.35
7.33
7.32
7.30
7.28
7.27
7.26
6.52
6.47
6.32
6.26
3.90
3.86
3.71
3.68
2.90
2.89
2.87
2.85
2.84
2.80
2.78
2.77
2.74
2.54
2.51
2.49
2.46
2.44
2.14
2.12
2.11
2.10
2.07
2.02
2.00
Ph
O
OH
52A
8.54
0.88
0.91
1.00
1.02
2.27
0.81
4.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


211.55
140.09
138.55
136.72
132.44
131.82
128.90
128.56
128.21
127.84
127.75
126.70
126.29
70.13
57.43
32.47
30.13
22.81
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

5.6. Determination of Enantiomeric Excesses of Representative Compounds

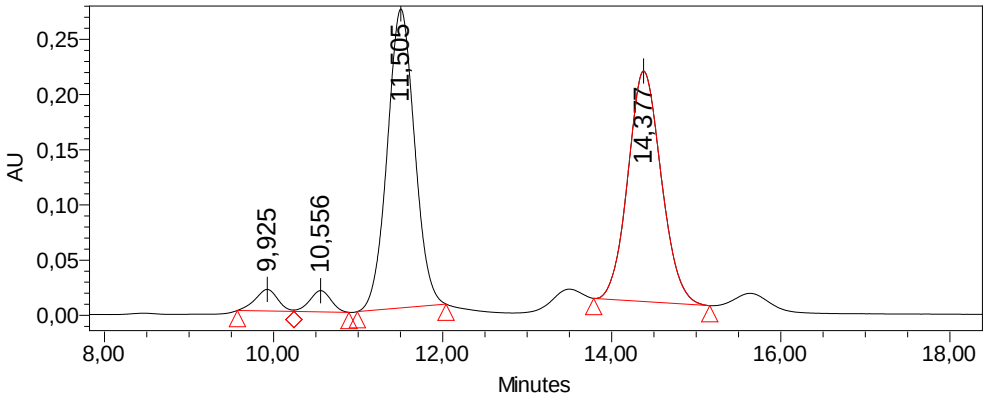
5.6.1. HPLC chromatograms for Chapter 2

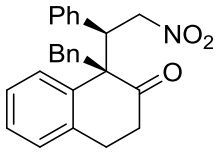
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



***rac*-4Aa**

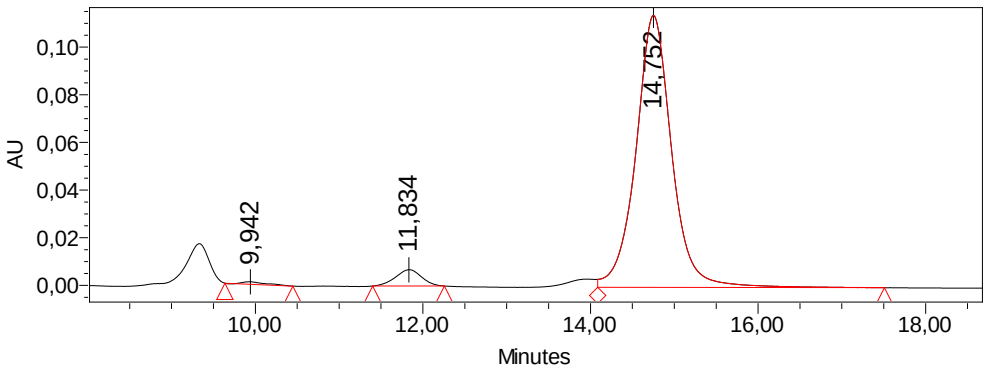
Retention Time	% Area
9,925	2,89
10,556	2,68
11,505	48,56
14,377	45,86



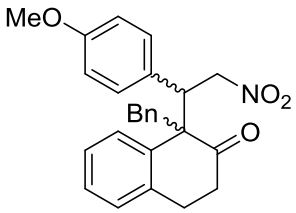


4Aa

Retention Time	% Area
9,942	0,64
11,834	4,14
14,752	95,22

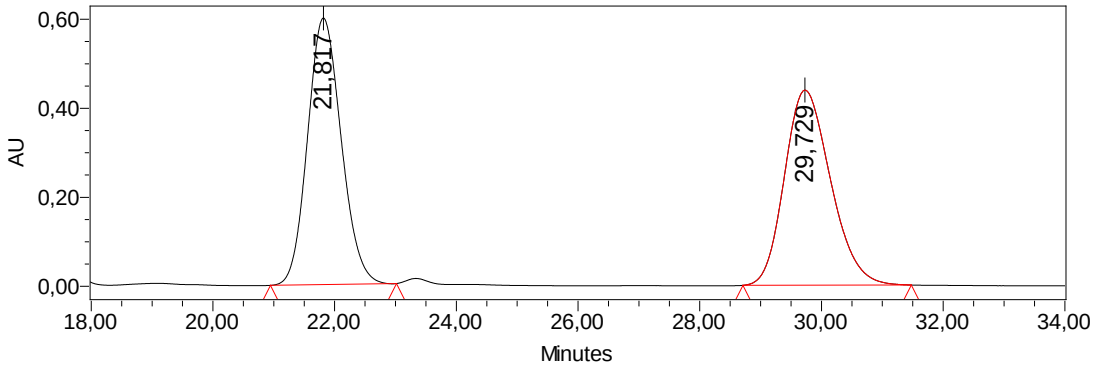


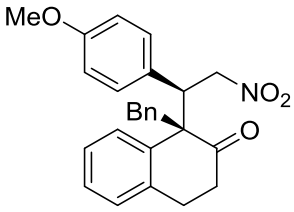
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Ab**

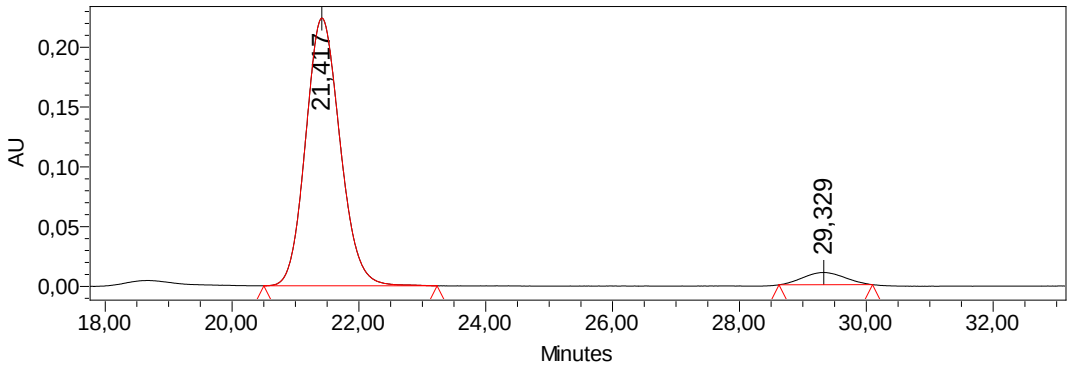
Retention Time	% Area
21,817	49,96
29,729	50,04



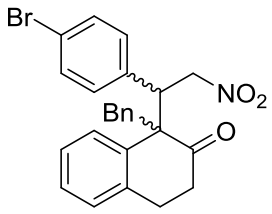


4Ab

Retention Time	% Area
21,417	94,76
29,329	5,24

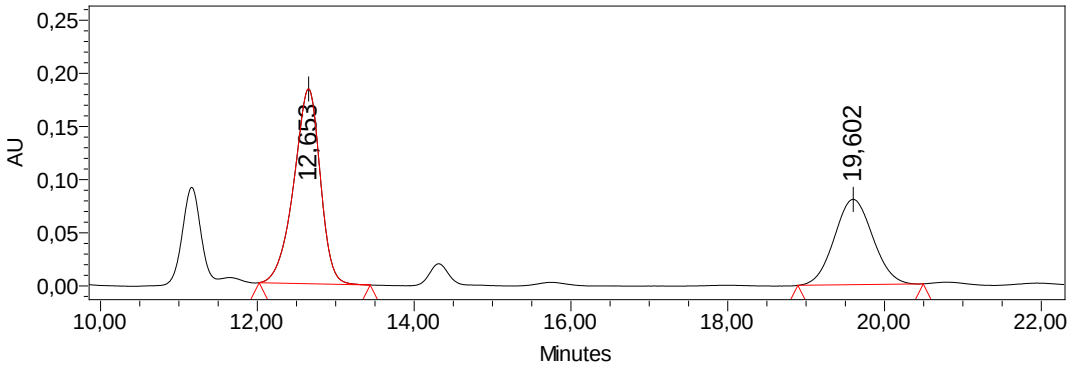


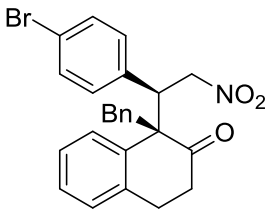
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Ae**

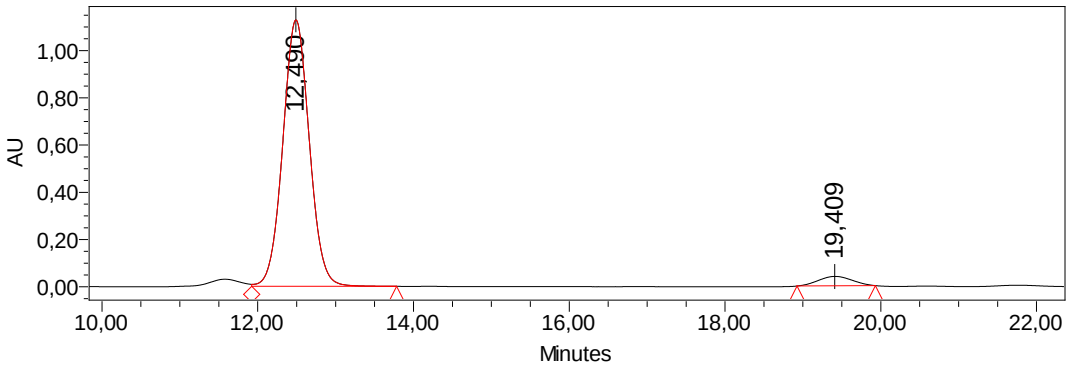
Retention Time	% Area
12,653	51,09
19,602	48,91



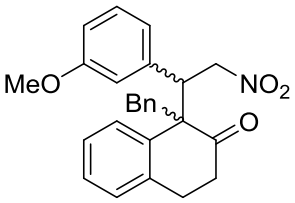


4Ae

Retention Time	% Area
12,490	95,70
19,409	4,30

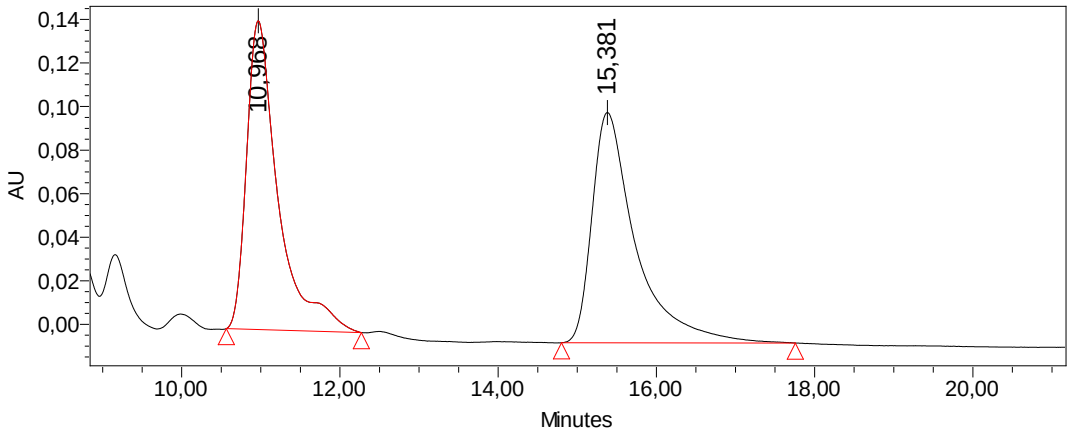


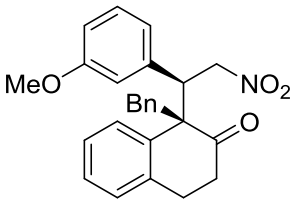
Chiralpack IA 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Af**

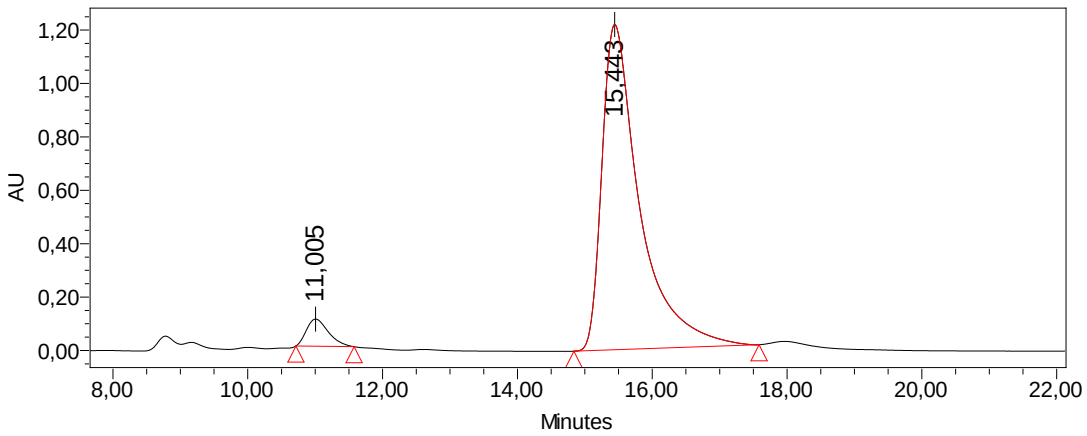
Retention Time	% Area
10,968	49,24
15,381	50,76



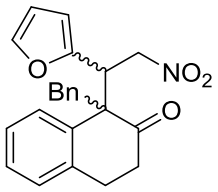


4Af

Retention Time	% Area
11,005	4,64
15,443	95,36

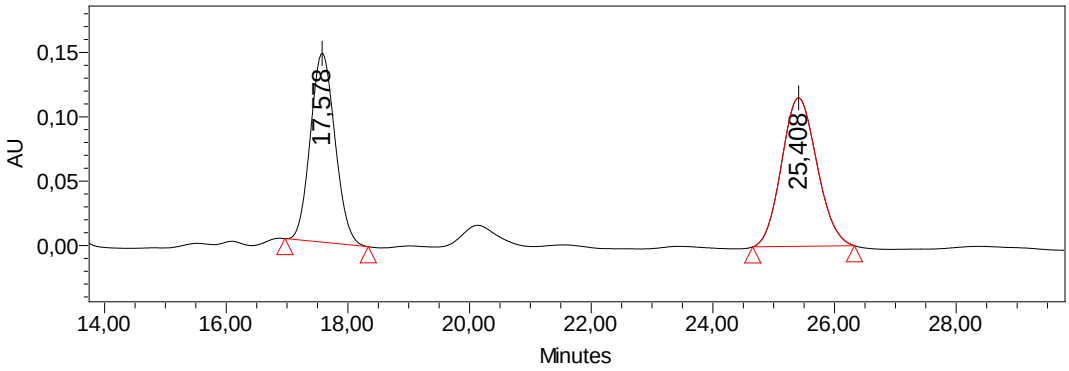


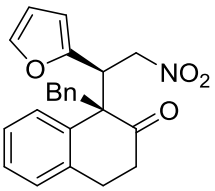
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Aj**

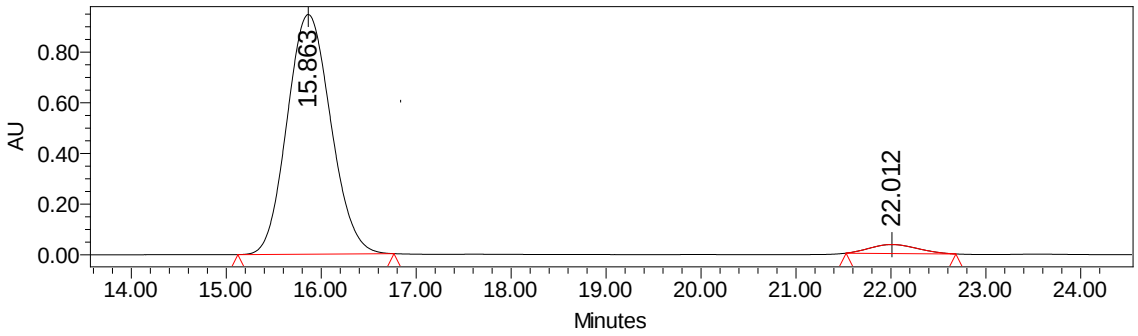
Retention Time	% Area
17,578	47,01
25,408	52,99



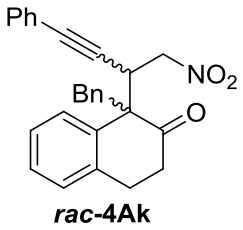


4Aj

Retention Time	% Area
15.863	96.12
22.012	3.88

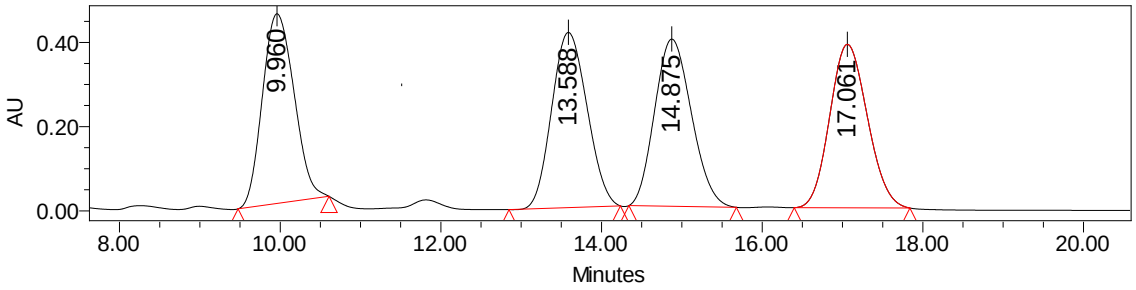


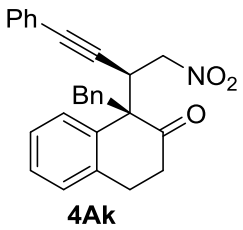
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 252 nm



***rac*-4Ak**

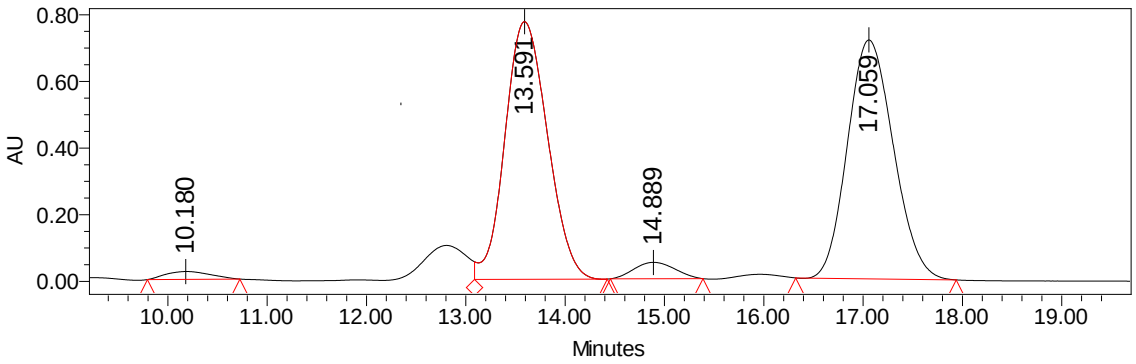
Retention Time	% Area
9,960	24,50
13,588	25,28
14,875	25,13
17,061	25,10



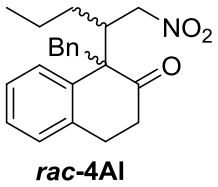


4Ak

Retention Time	% Area
10,180	1,53
13,591	47,76
14,889	2,91
17,059	47,80

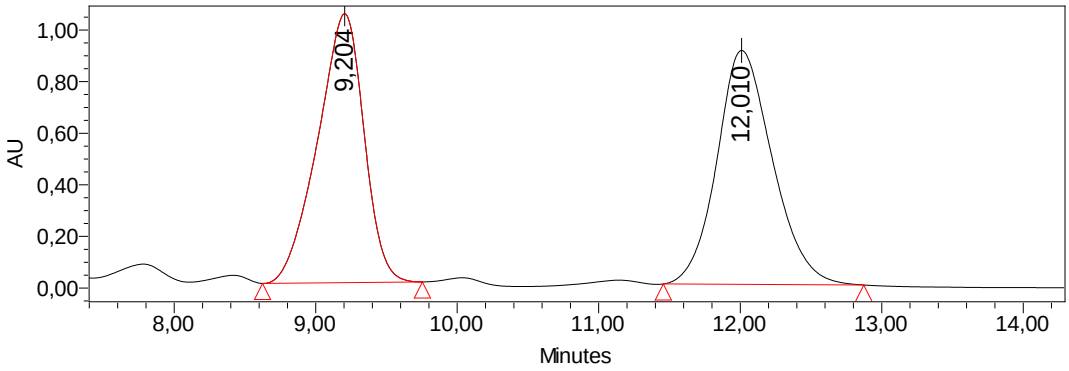


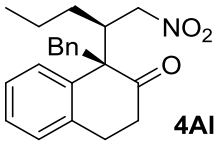
Chiralpack IA 1 mL/min, hexane/isopropanol 98:2, λ = 210 nm



***rac*-4Al**

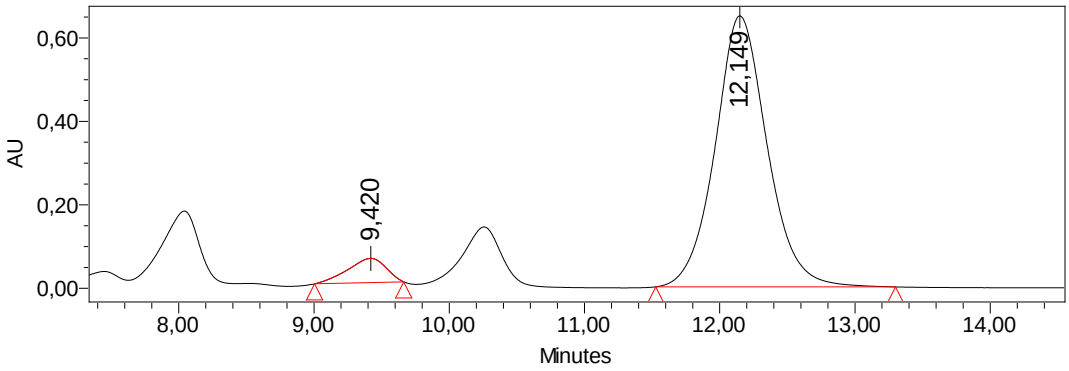
Retention Time	% Area
9,204	48,90
12,010	51,10



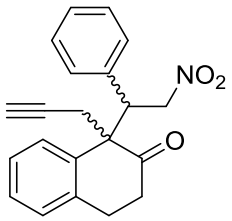


4Al

Retention Time	% Area
9,420	6,16
12,149	93,84

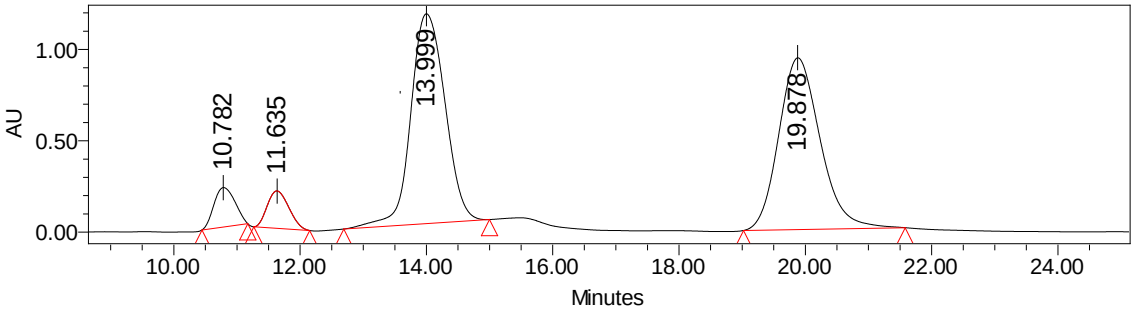


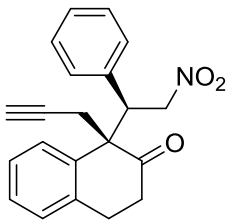
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



***rac*-4Ba**

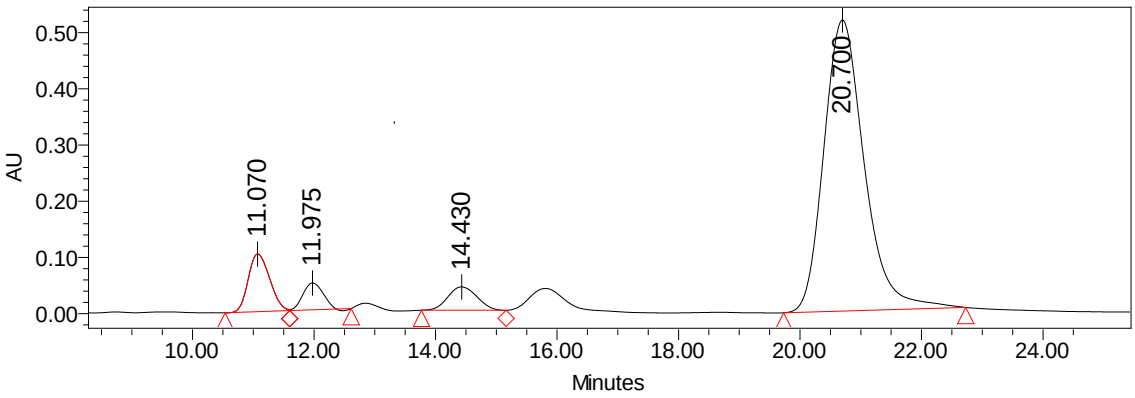
Retention Time	% Area
10,782	5,20
11,635	5,08
13,999	45,13
19,878	44,59



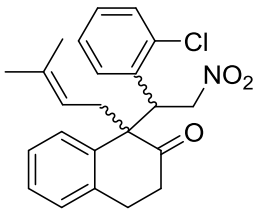


4Ba

Retention Time	% Area
11,070	8,67
11,975	3,95
14,430	4,77
20,700	82,61

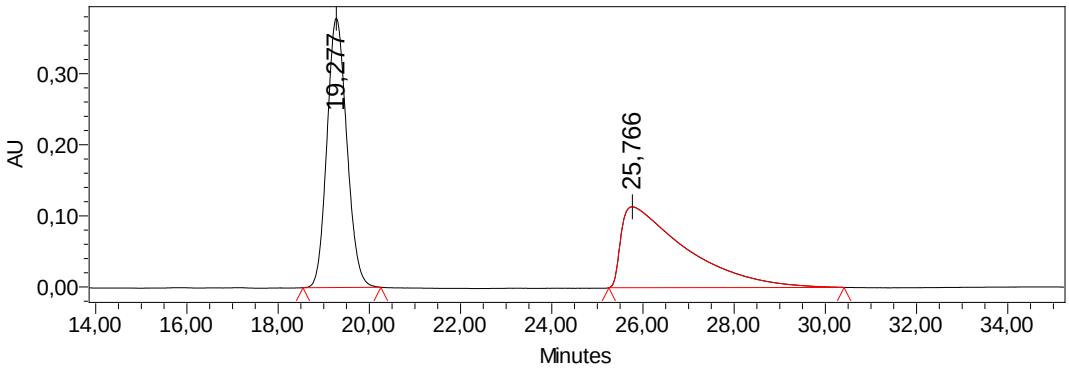


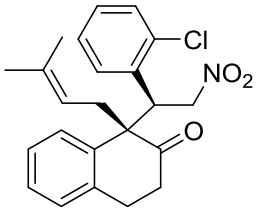
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Ci**

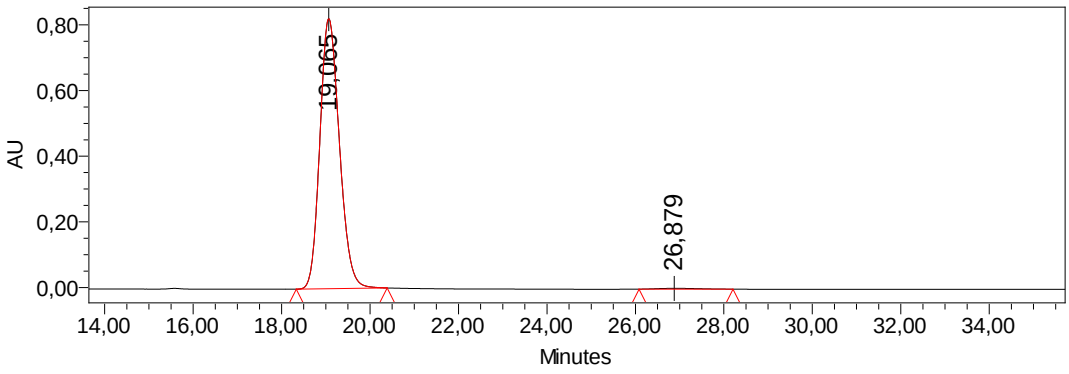
Retention Time	% Area
19,277	50,68
25,766	49,32



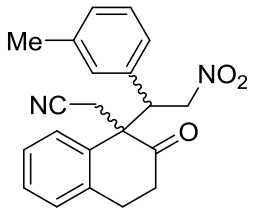


4Ci

Retention Time	% Area
19,065	99,39
26,879	0,61

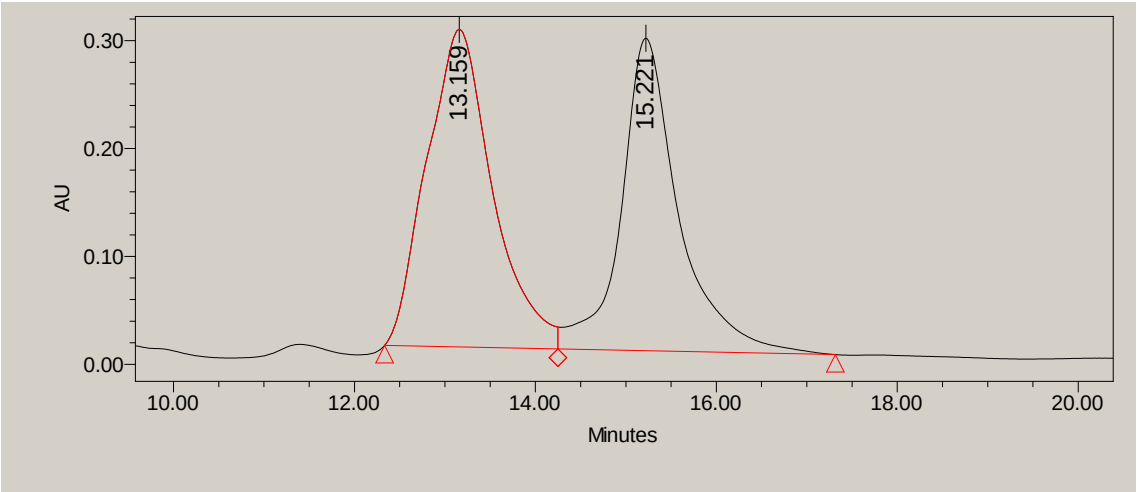


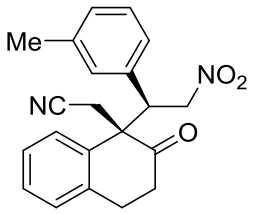
Chiralpack IA 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Dg**

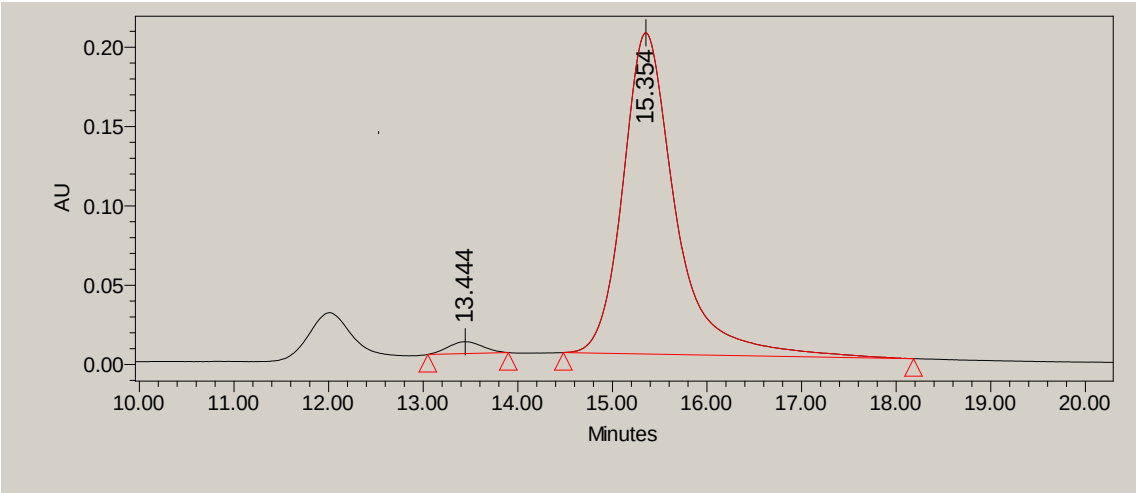
Retention Time	% Area
13.159	52.74
15.221	47.26



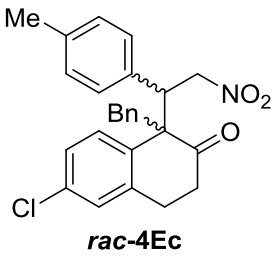


4Dg

Retention Time	% Area
13.444	2.35
15.354	97.65

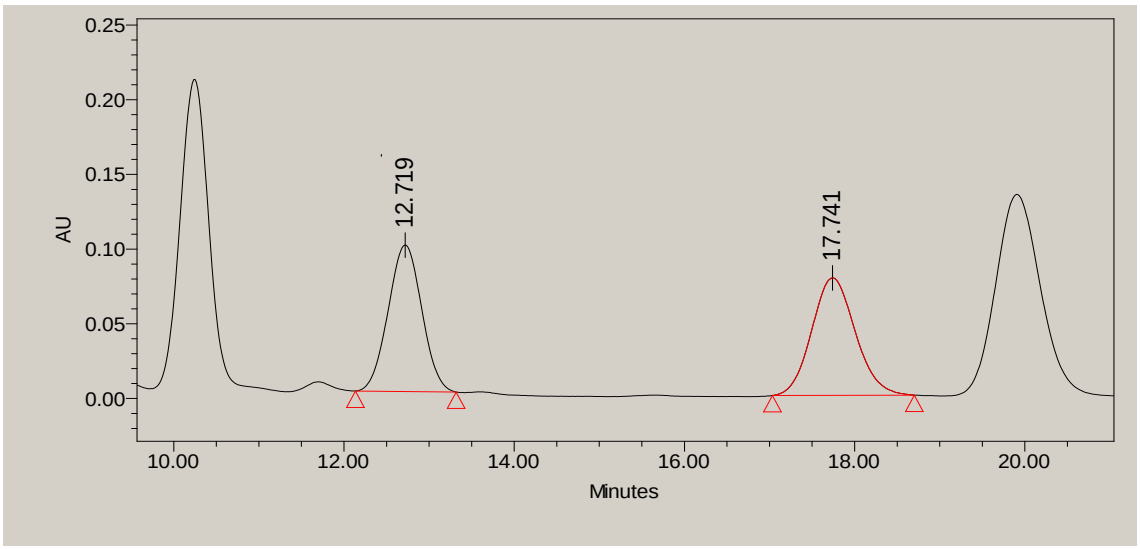


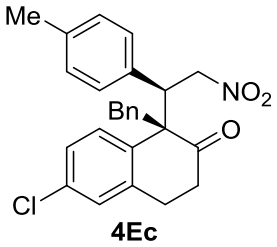
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Ec**

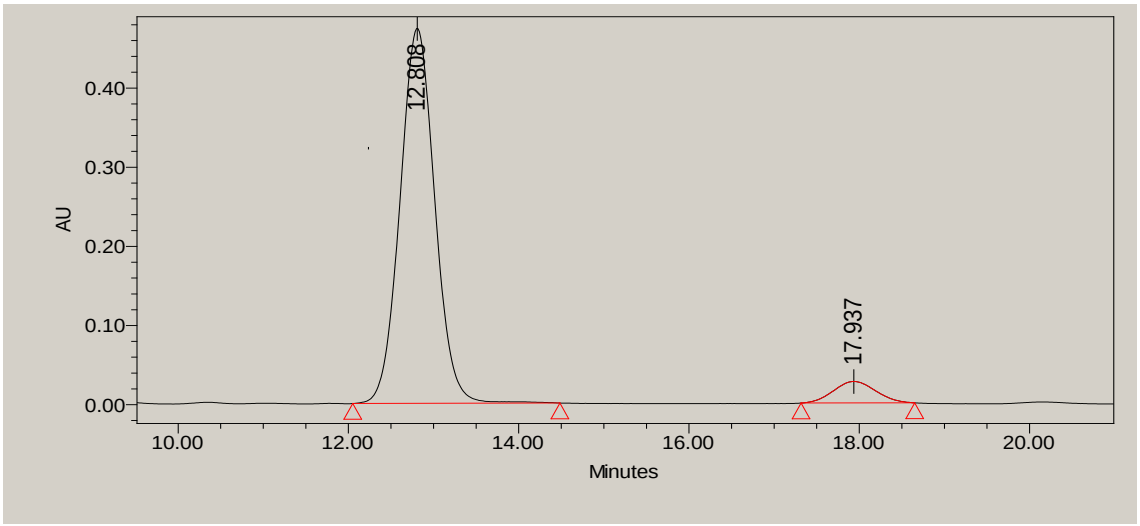
Retention Time	% Area
12.719	49.11
17.741	50.89



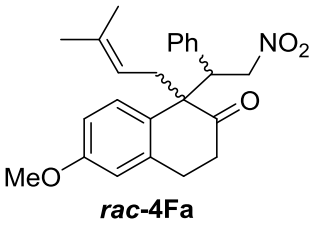


4Ec

Retention Time	% Area
12.808	94.81
17.937	5.19

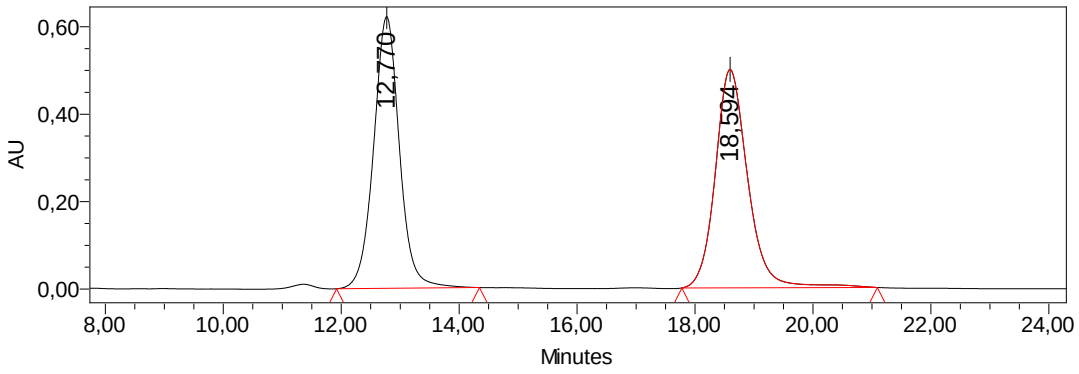


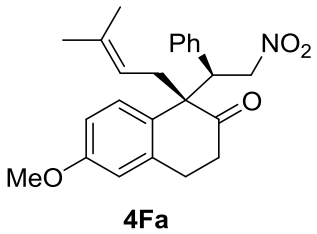
Chiralpack IC 1 mL/min, hexane/isopropanol 98:2, λ = 210 nm



***rac*-4Fa**

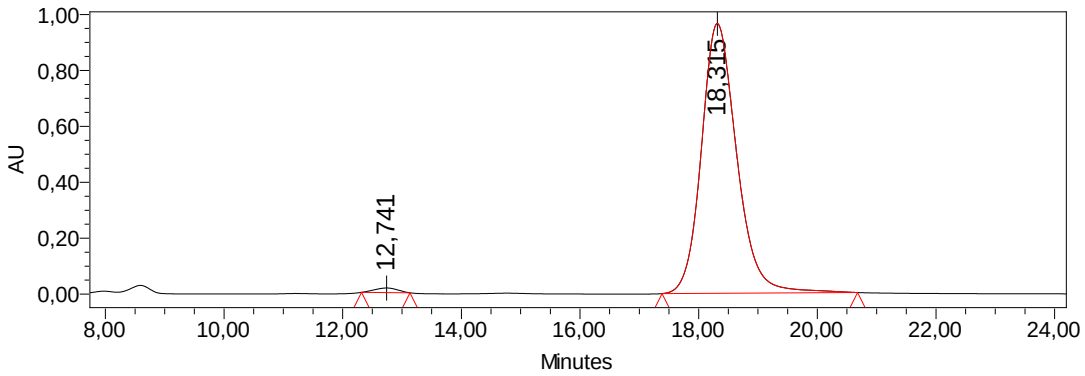
Retention Time	% Area
12,770	49,70
18,594	50,30



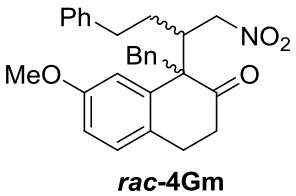


4Fa

Retention Time	% Area
12,741	1,09
18,315	98,91

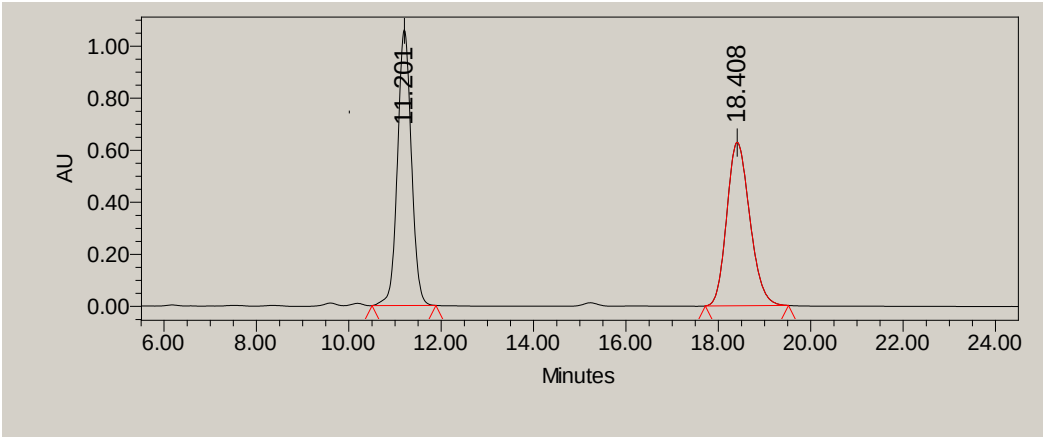


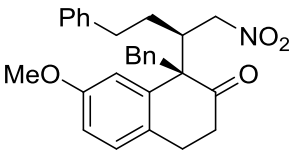
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-4Gm**

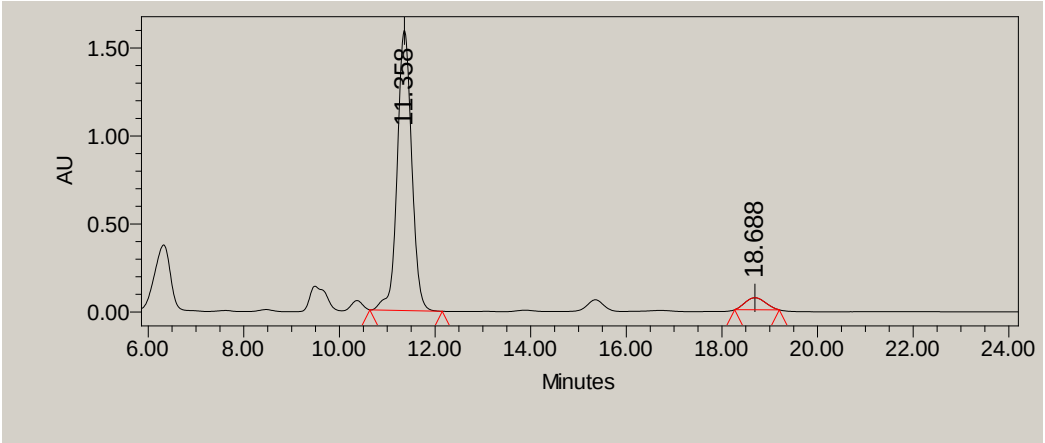
Retention Time	% Area
11.201	50.39
18.408	49.61



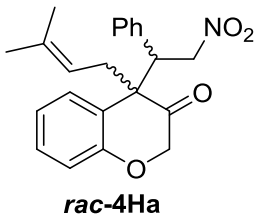


4Gm

Retention Time	% Area
11.358	95.37
18.688	4.63

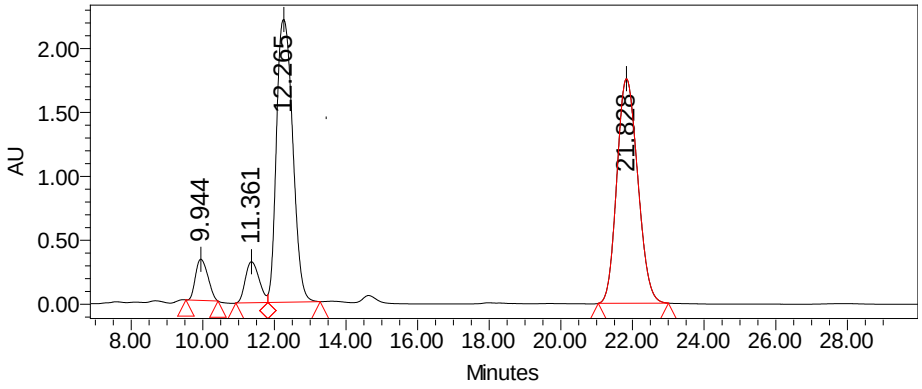


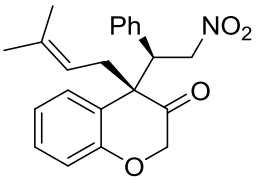
Chiralpack IC, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



***rac*-4Ha**

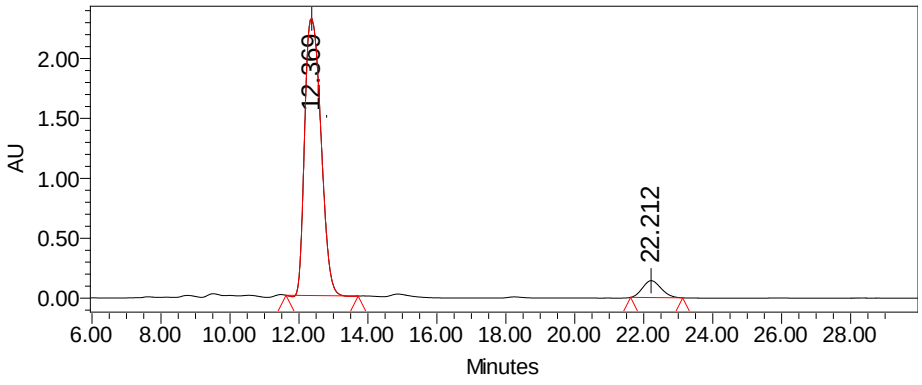
Retention Time	% Area
9,944	4,95
11,361	5,51
12,265	44,24
21,828	45,31



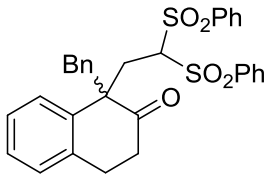


4Ha

Retention Time	% Area
12,369	95,03
22,212	4,97

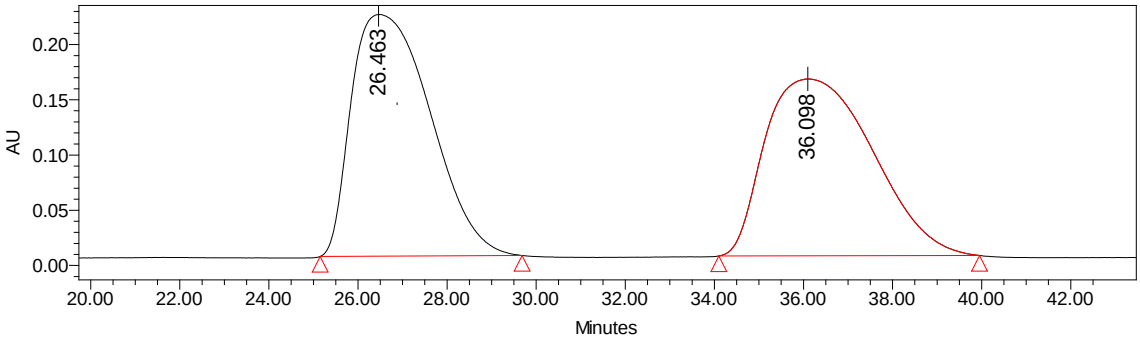


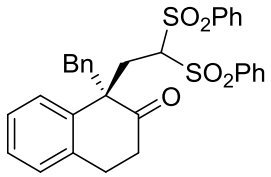
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-5A**

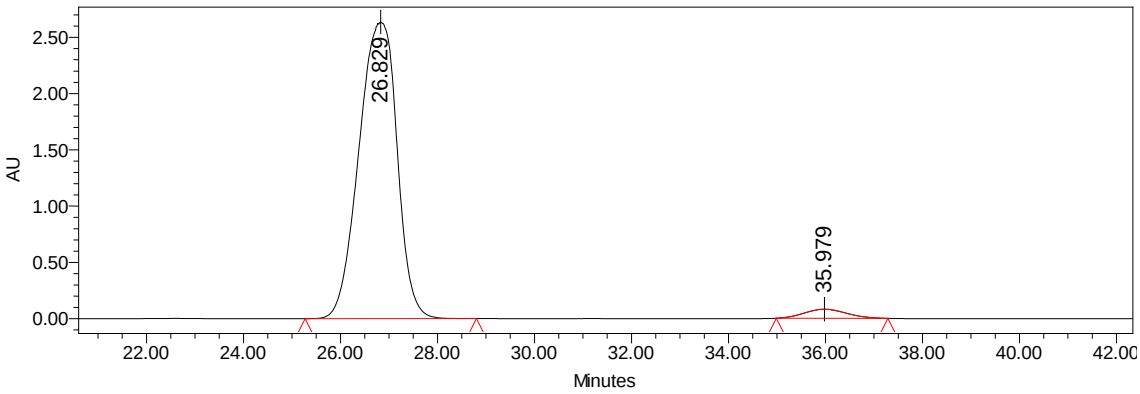
Retention Time	% Area
26.463	50.11
36.098	49.89



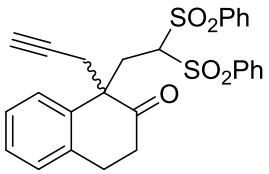


5A

Retention Time	% Area
26.829	96.72
35.979	3.28

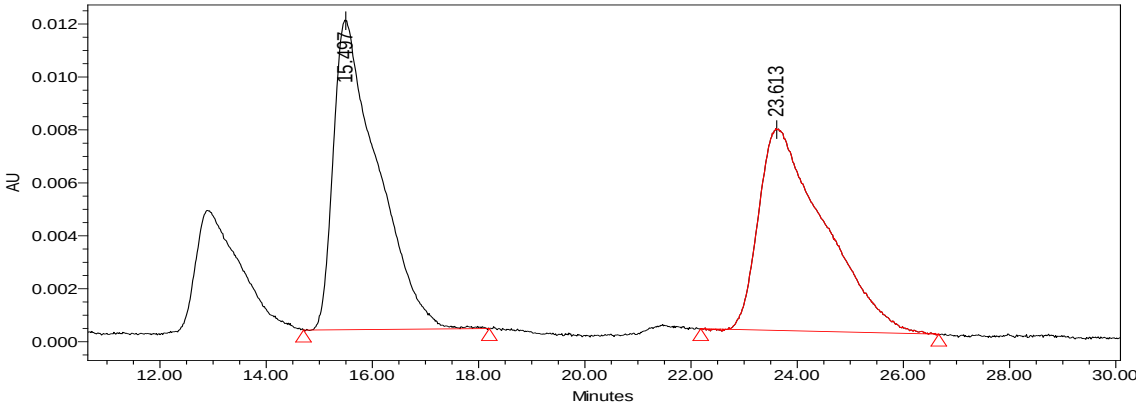


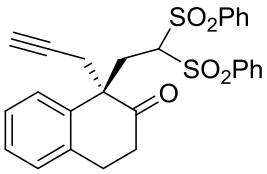
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-5B**

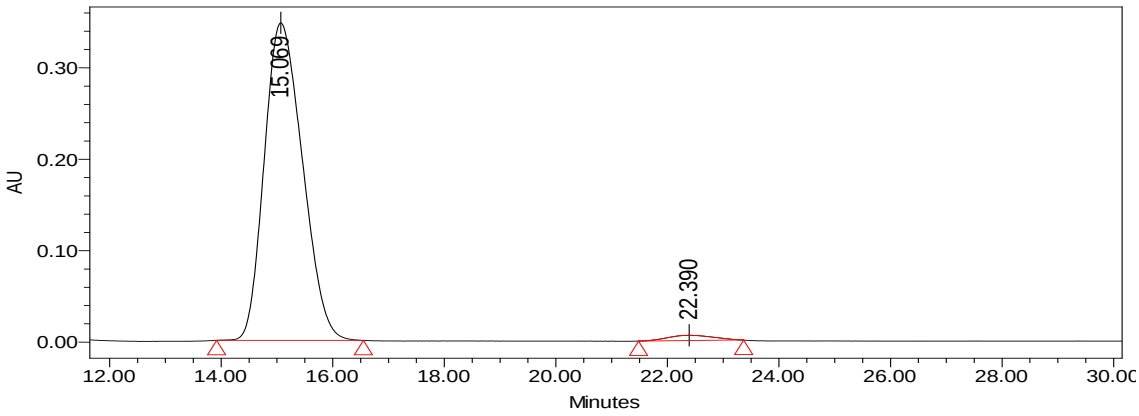
Retention Time	% Area
15.497	50.77
23.613	49.23



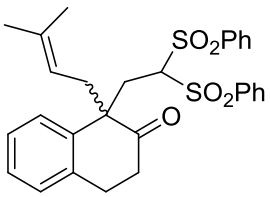


5B

Retention Time	% Area
15.069	98.02
22.390	1.98

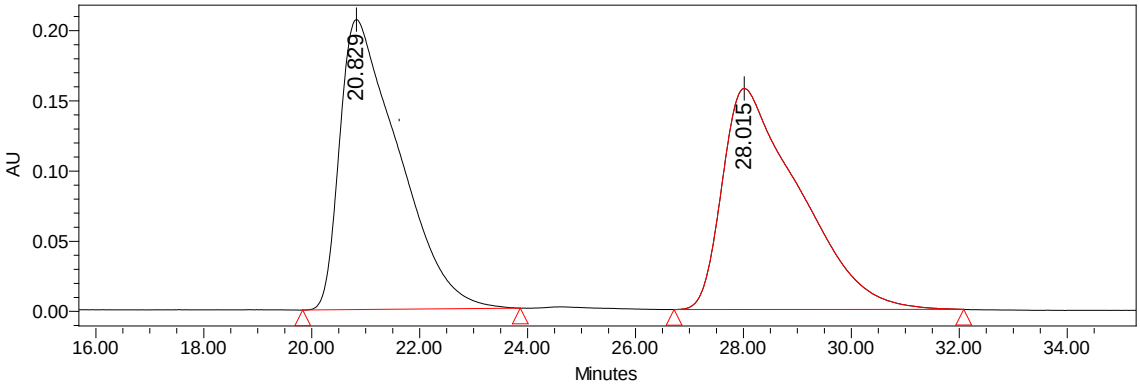


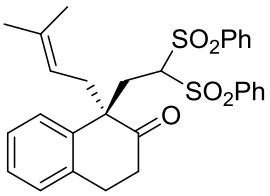
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-5C**

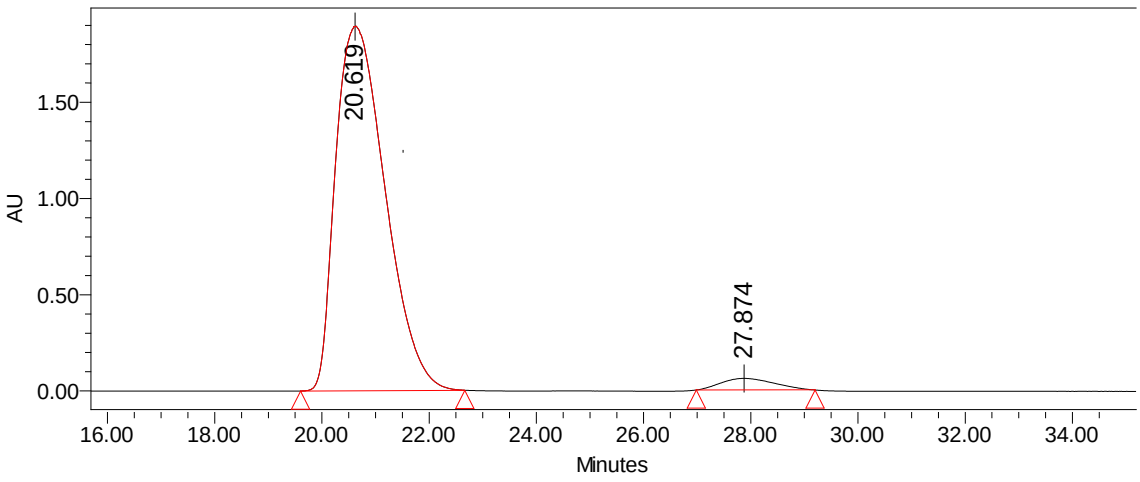
Retention Time	% Area
20.829	50.08
28.015	49.92



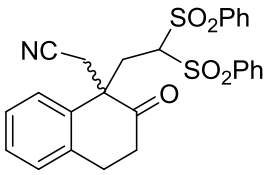


5C

Retention Time	% Area
20.619	96.68
27.874	3.32

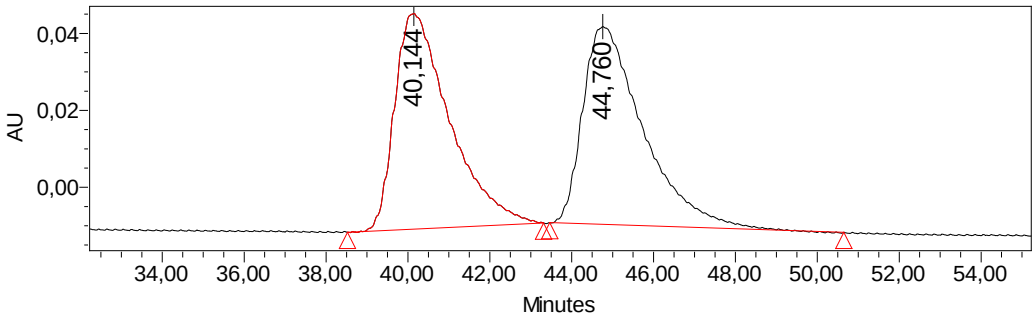


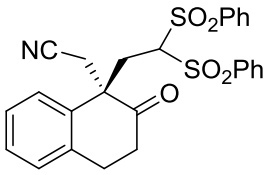
Chiralpack IB, 1 mL/min, hexane/isopropanol 80:20, λ = 210 nm



***rac*-5D**

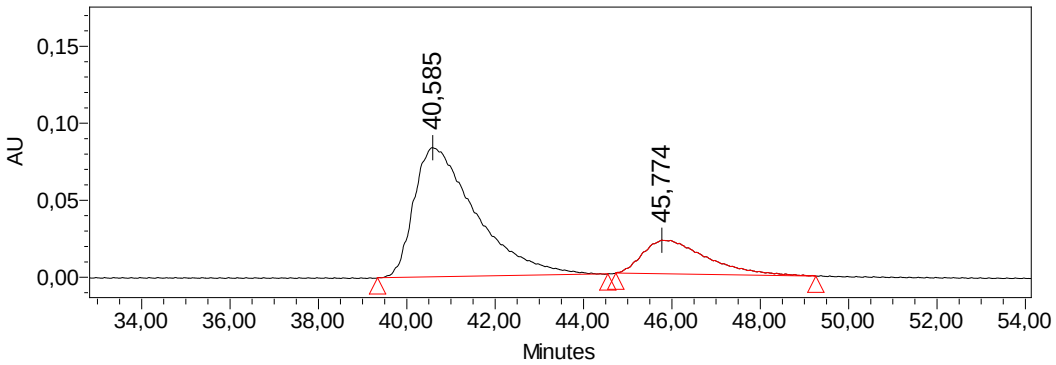
Retention Time	% Area
40.144	49.82
44.760	50.18



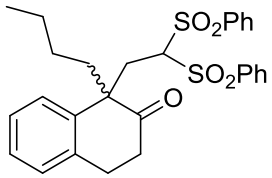


5D

Retention Time	% Area
40.585	78.78
45.774	21.22

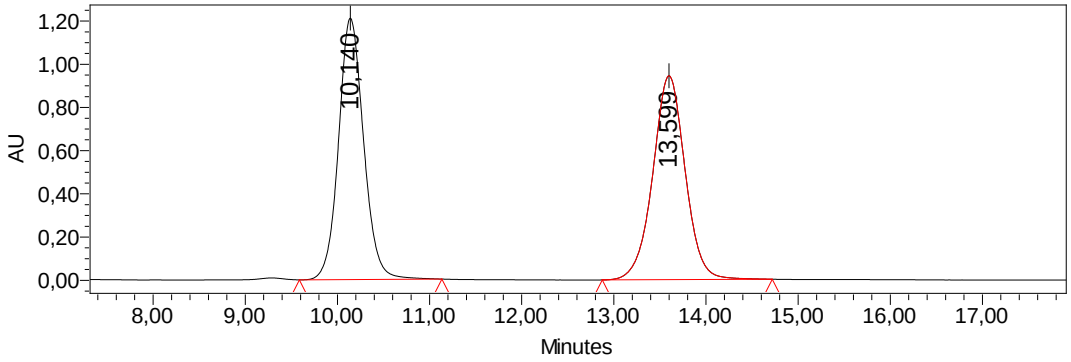


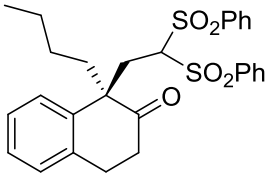
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 210 nm



***rac*-5l**

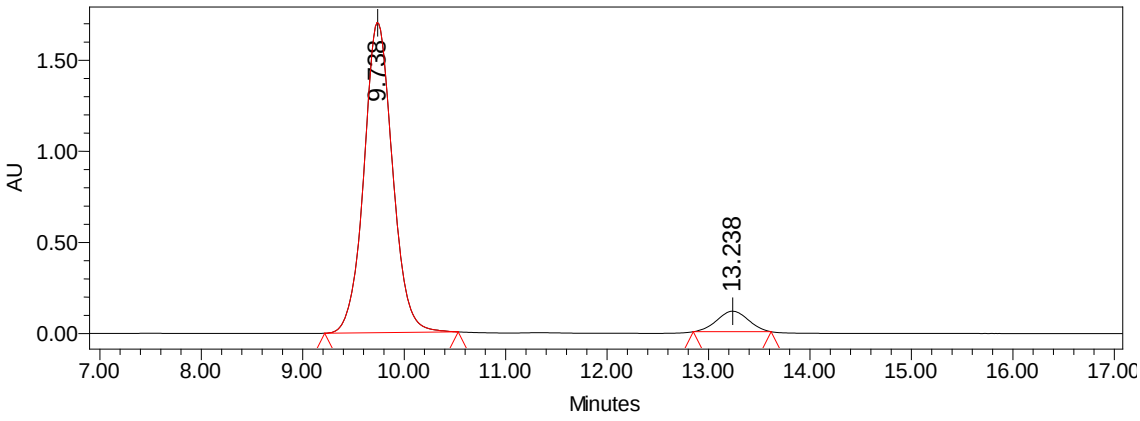
Retention Time	% Area
10.140	49.85
13.599	50.15



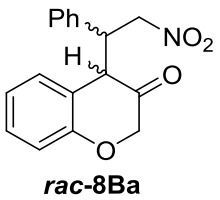


5l

Retention Time	% Area
9.738	93.27
13.238	6.73

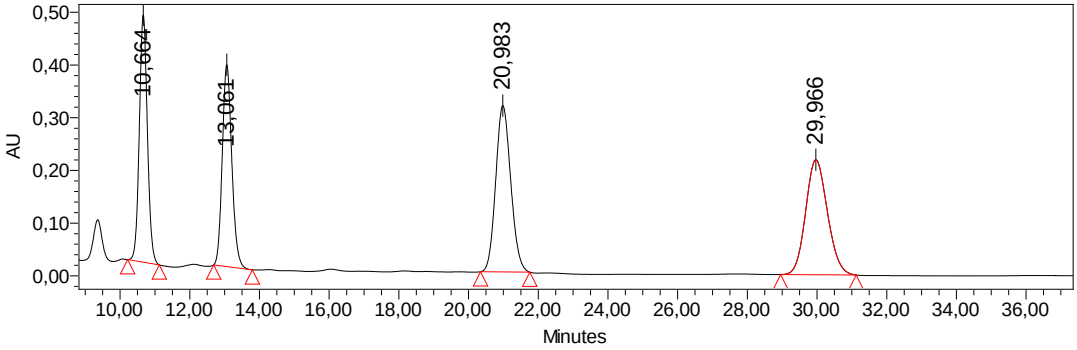


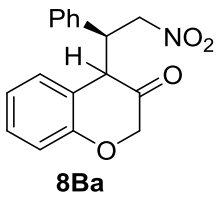
Chiralpack IC, 1 mL/min, hexane/isopropanol 80:20, λ = 210 nm



***rac*-8Ba**

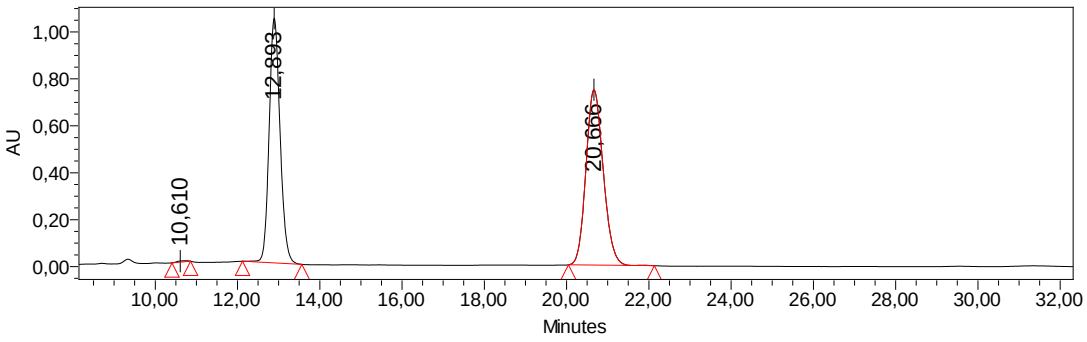
Retention Time	% Area
10,664	22,31
13,061	21,55
20,983	28,04
29,966	28,10



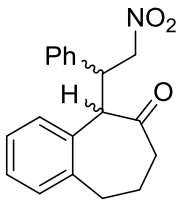


8Ba

Retention Time	% Area
10,610	0,21
12,893	46,79
20,666	53,00

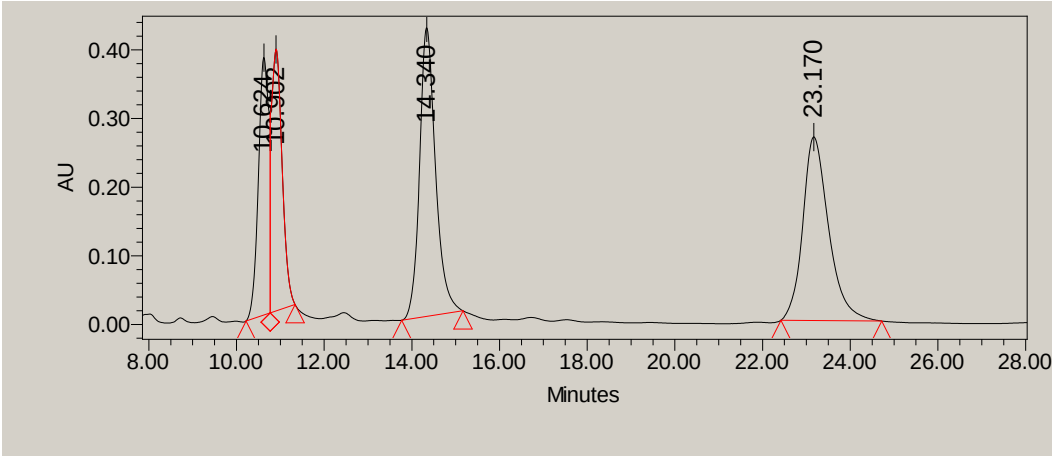


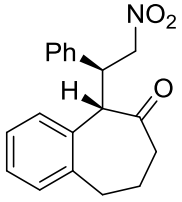
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



***rac*-8Ca**

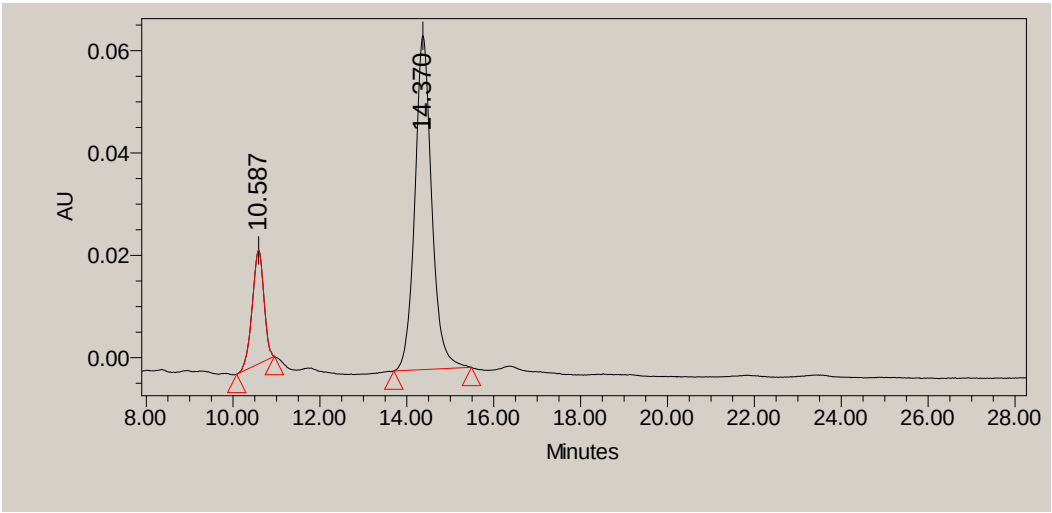
Retention Time	% Area
10.624	17.80
10.902	18.88
14.340	31.21
23.170	32.11



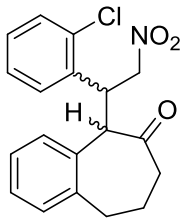


8Ca

Retention Time	% Area
10.587	19.05
14.370	80.95

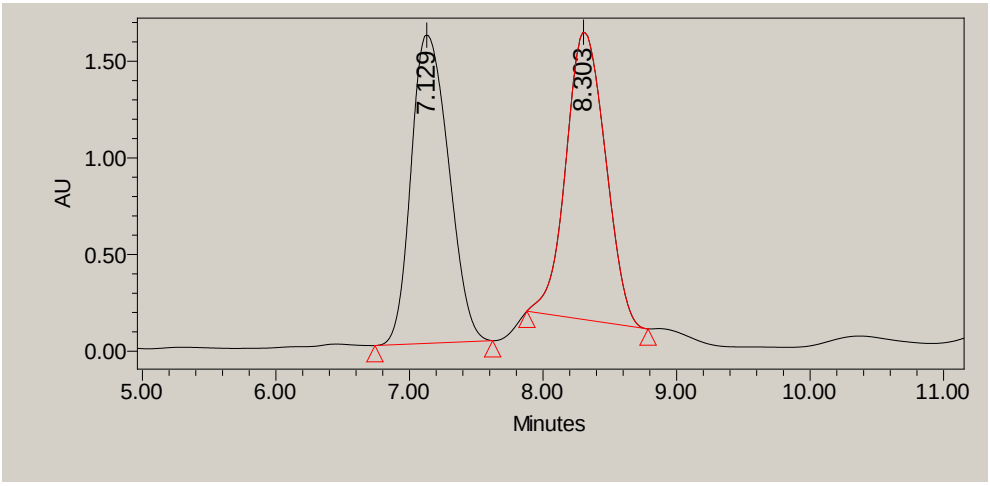


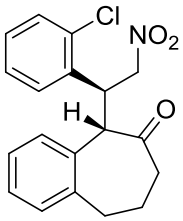
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-8Ci**

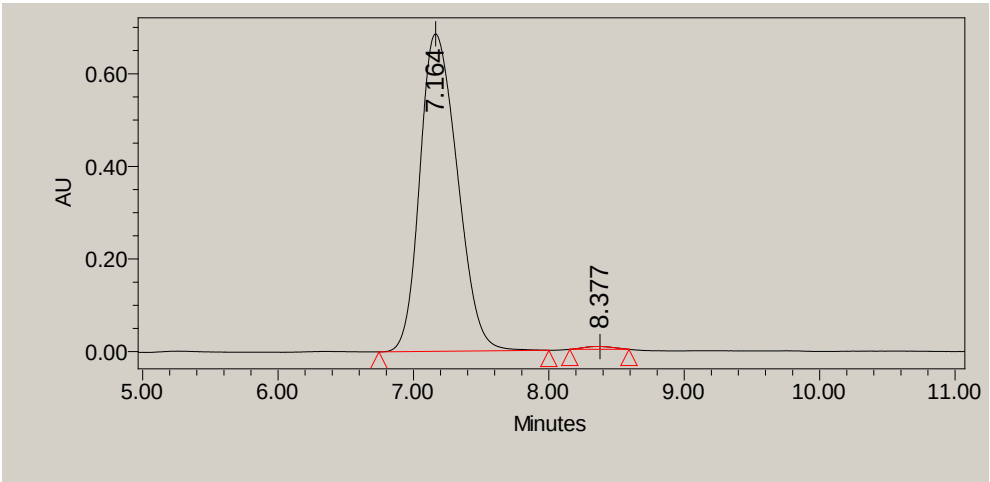
Retention Time	% Area
7.129	50.43
8.303	49.57



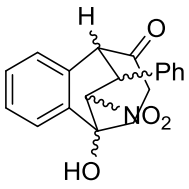


8Ci

Retention Time	% Area
7.164	99.29
8.377	0.71

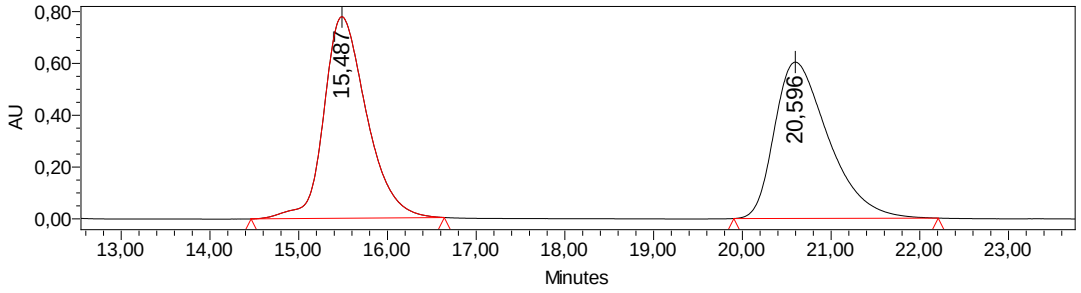


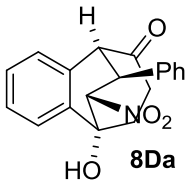
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-8Da**

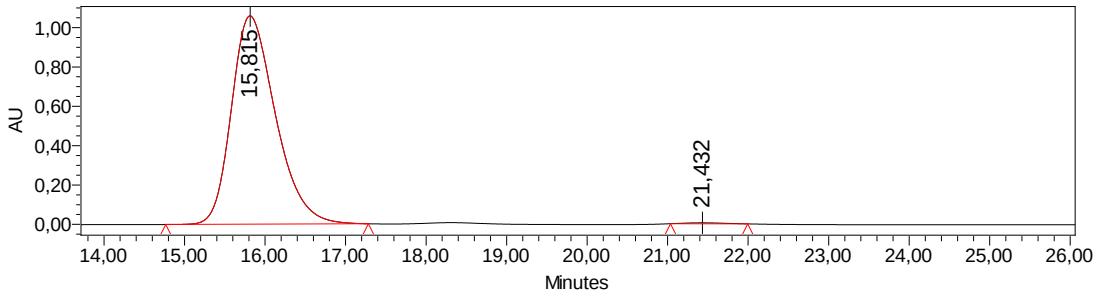
Retention Time	% Area
15,487	50,61
20,596	49,39



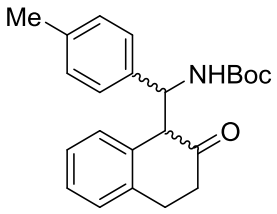


8Da

Retention Time	% Area
15,815	99,58
21,432	0,42

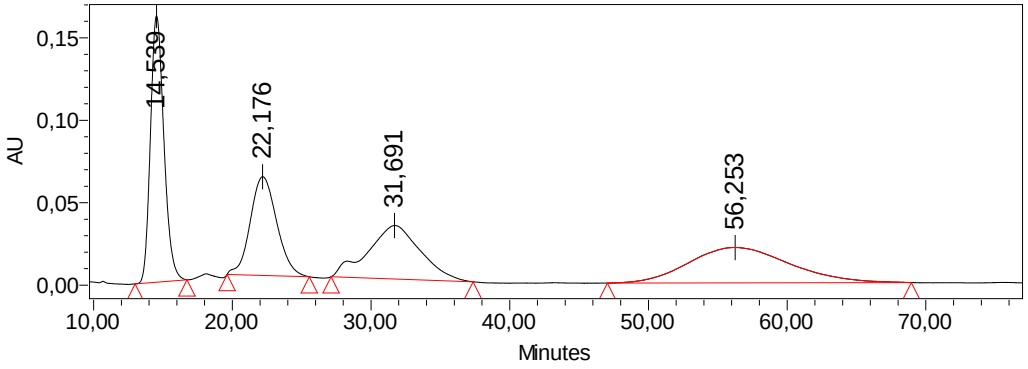


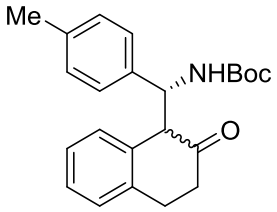
Chiralpack AY-H, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



***rac*-10Aa**

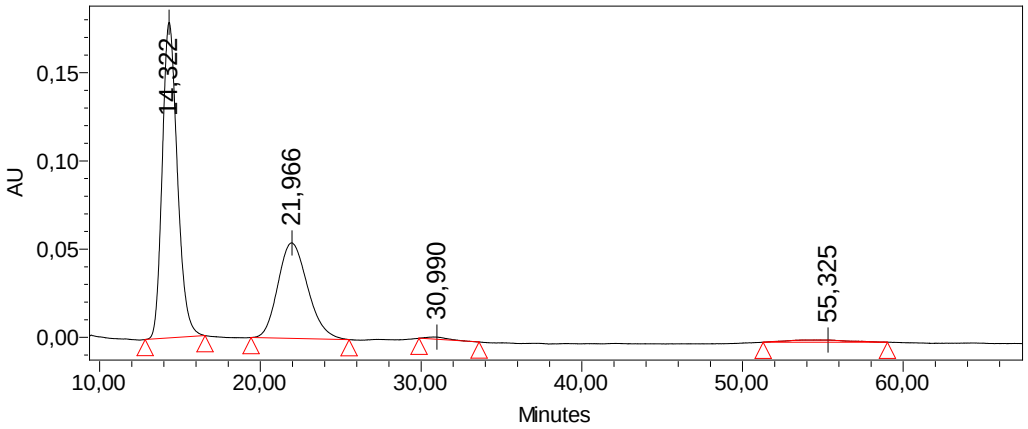
Retention Time	% Area
14.539	28.44
22.176	20.74
31.691	22.33
56.253	28.49



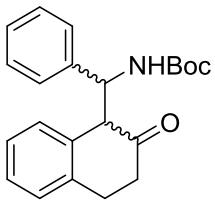


10Aa

Retention Time	% Area
14.322	61.17
21.966	36.56
30.990	0.57
55.325	1.69

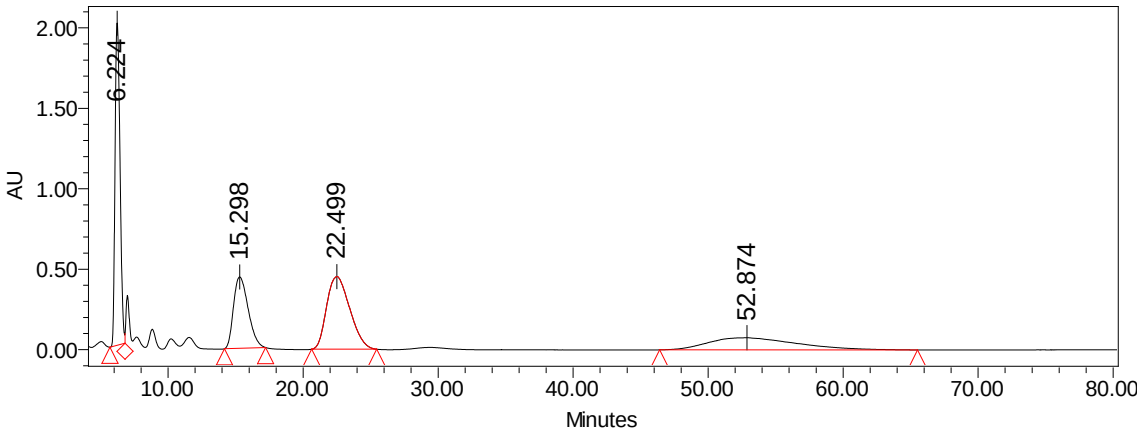


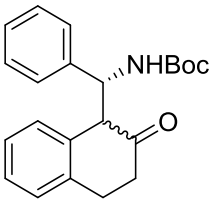
Chiralpack AS-H, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-10Ab**

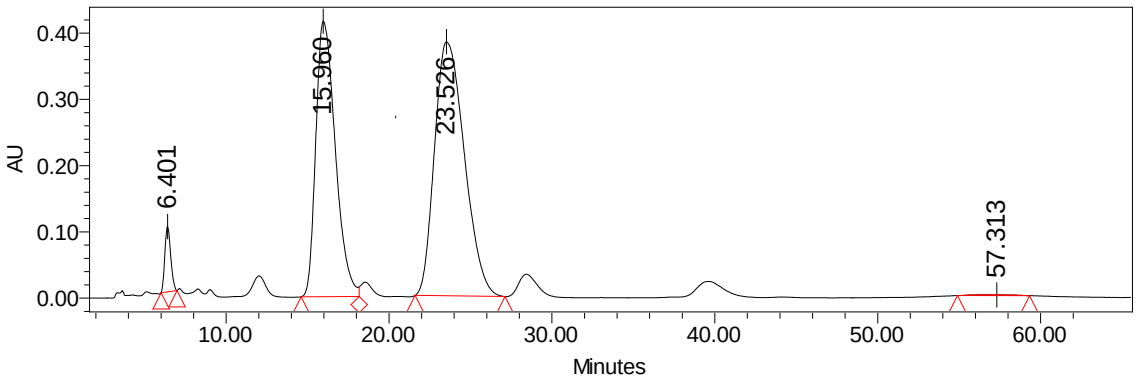
Retention Time	% Area
6.224	29.71
15.298	19.35
22.499	31.07
52.874	19.87



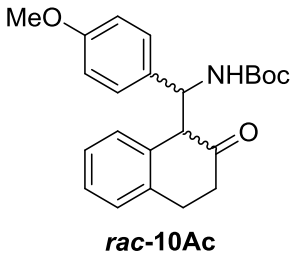


10Ab

Retention Time	% Area
6.401	2.88
15.960	40.20
23.526	56.69
57.313	0.23

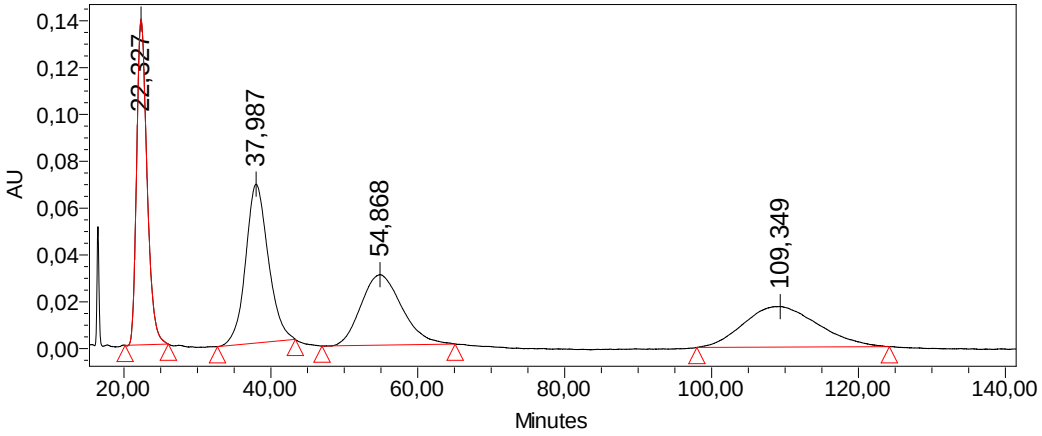


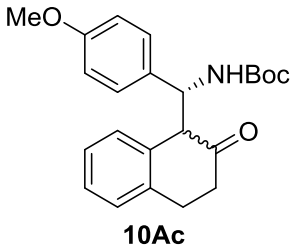
Chiralpack AY-H, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



***rac*-10Ac**

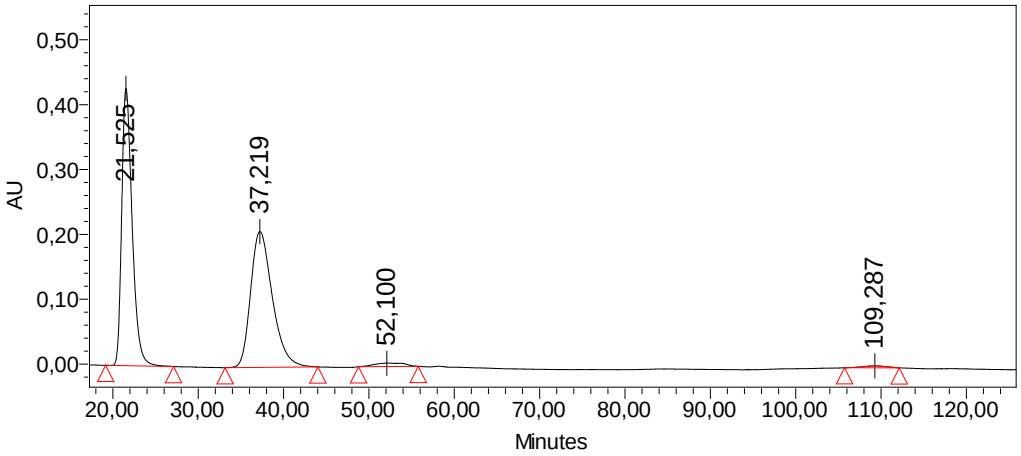
Retention Time	% Area
22.327	22.35
37.987	27.95
54.868	26.27
109.349	23.43



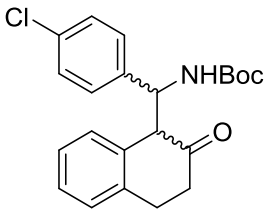


10Ac

Retention Time	% Area
21.525	48.25
37.219	49.22
52.100	1.78
109.287	0.74

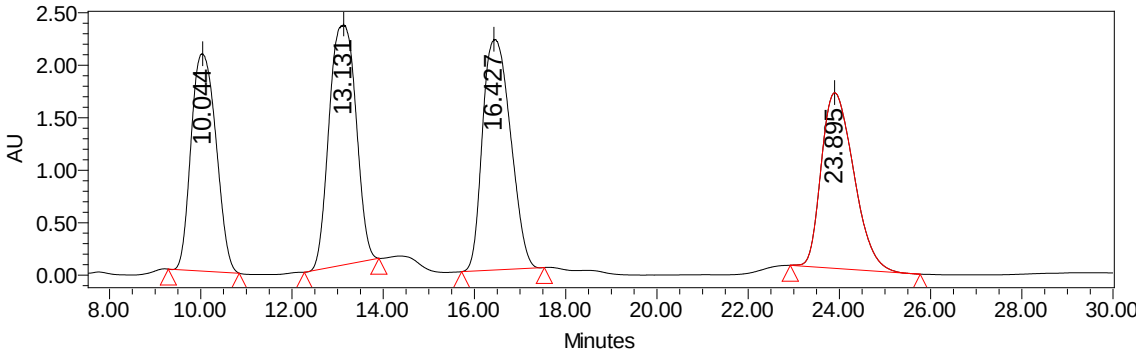


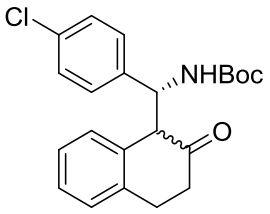
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



***rac*-10Ad**

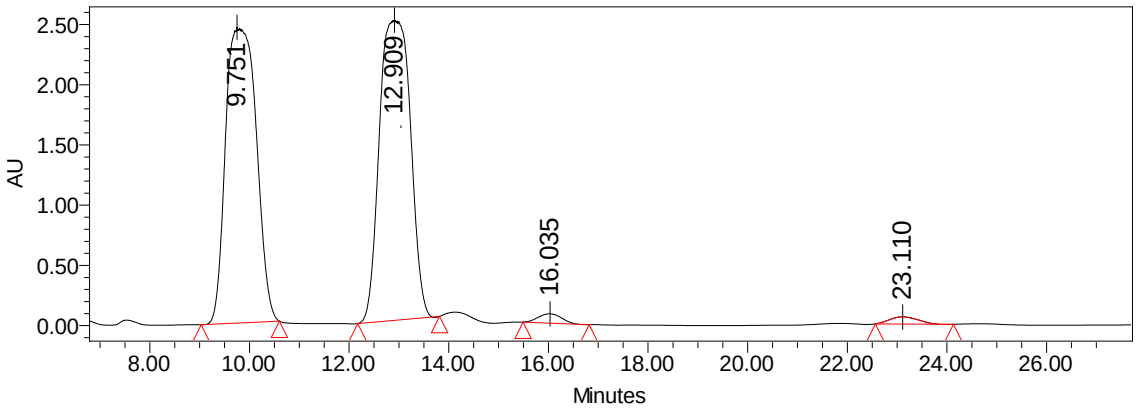
Retention Time	% Area
10.044	22.56
13.131	26.87
16.427	26.85
23.895	23.72



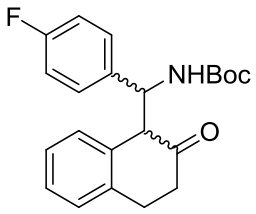


10Ad

Retention Time	% Area
9.751	48.17
12.909	49.58
16.035	1.16
23.110	1.09

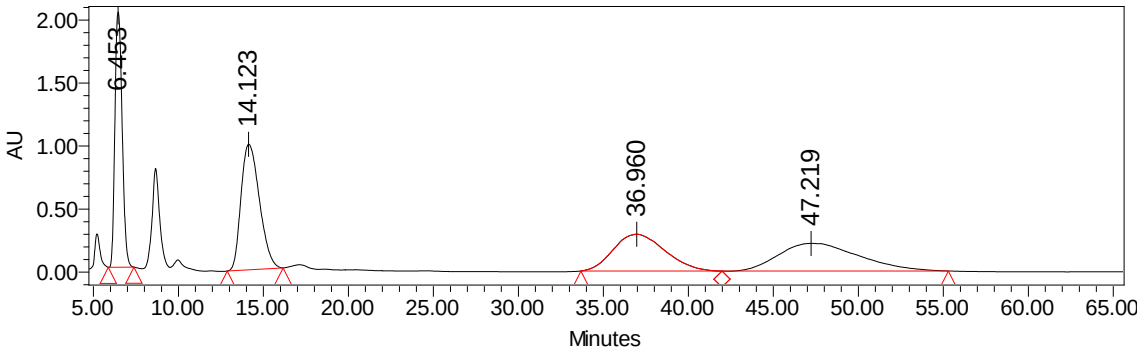


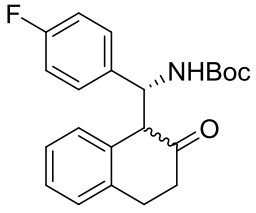
Chiralpack AS-H, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-10Ae**

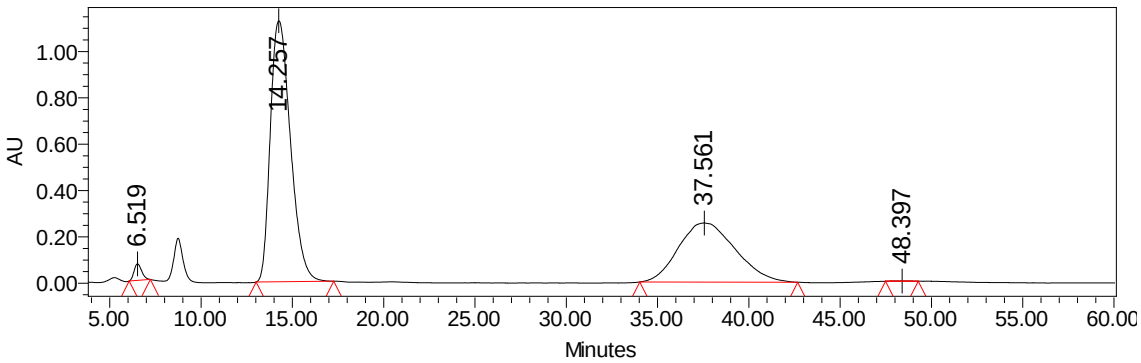
Retention Time	% Area
6.453	22.36
14.123	27.98
36.960	22.82
47.219	26.84



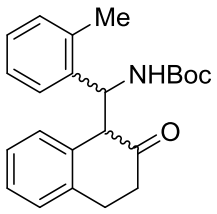


10Ae

Retention Time	% Area
6.519	1.47
14.257	60.10
37.561	38.38
48.397	0.05

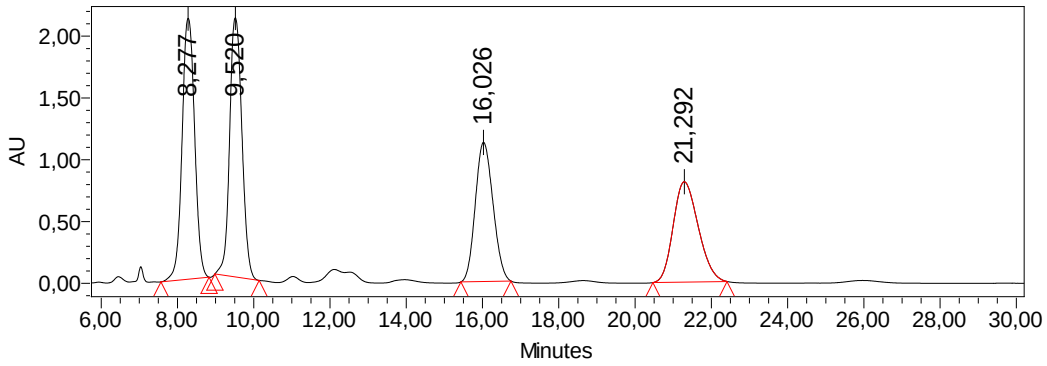


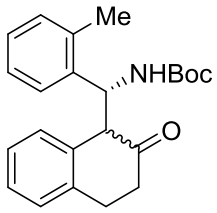
Chiralpack IC, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



***rac*-10Af**

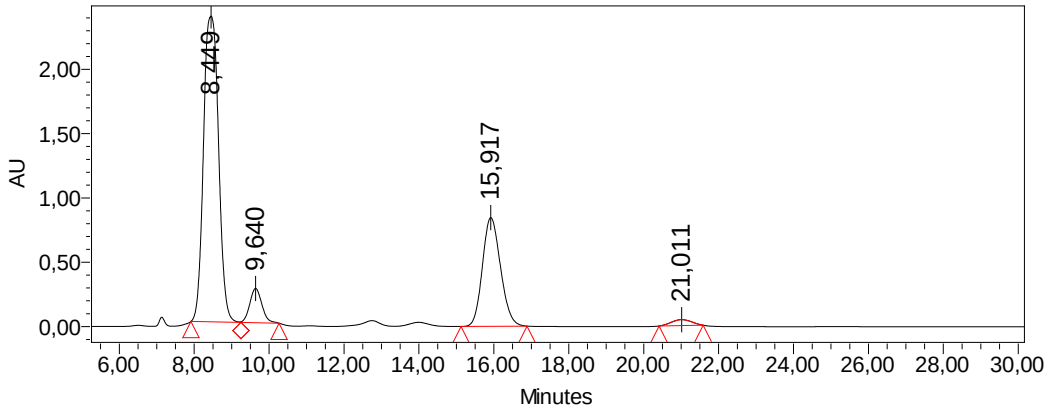
Retention Time	% Area
8.277	28.66
9.520	27.84
16.026	21.51
21.292	21.99



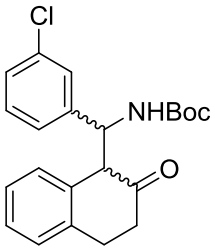


10Af

Retention Time	% Area
8.449	64.72
9.640	5.86
15.917	27.73
21.011	1.70

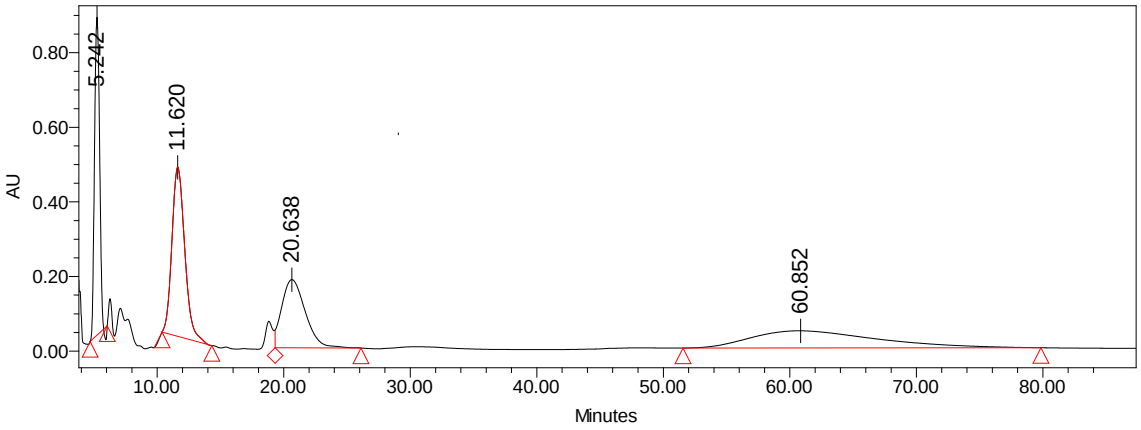


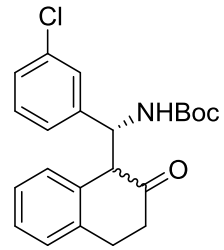
Chiralpack AS-H, 1 mL/min, solvent gradient: 1) hexane/isopropanol 90:10 for 15 min; 2) hexane/isopropanol 80:20 for 20 min; 3) hexane/isopropanol 70:30 for 3 min; 4) hexane/isopropanol 60:40 for 3 min; 5) hexane/isopropanol 50:50, λ = 210 nm



***rac*-10Ag**

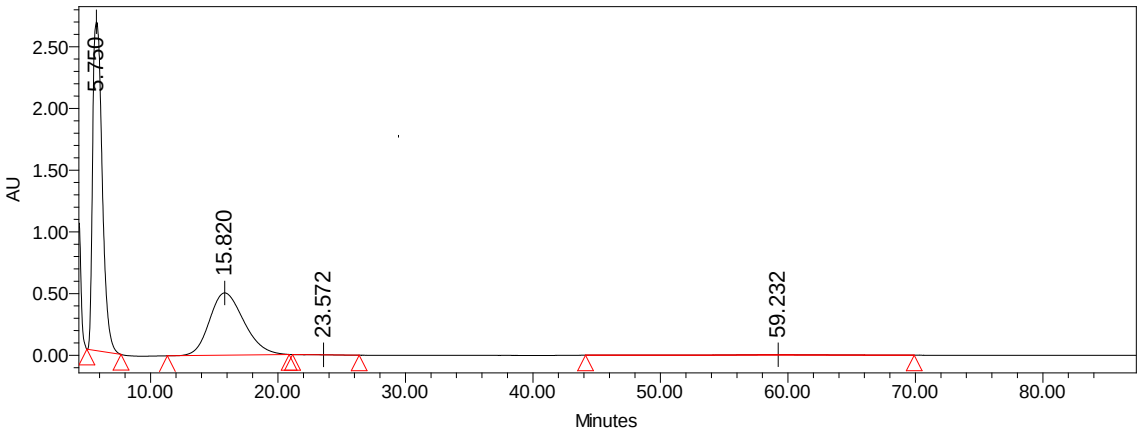
Retention Time	% Area
5.242	21.71
11.620	28.69
20.638	21.14
60.852	28.46





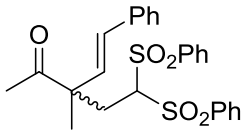
10Ag

Retention Time	% Area
5.750	58.83
15.820	40.18
23.572	0.05
59.232	0.95



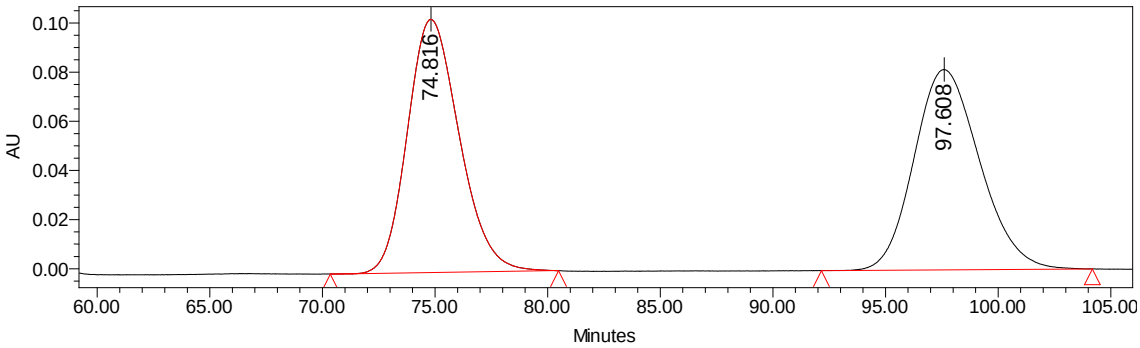
5.6.2. HPLC chromatograms for Chapter 3

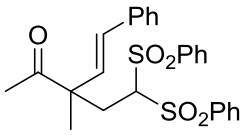
Chiralpack IC mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-13**

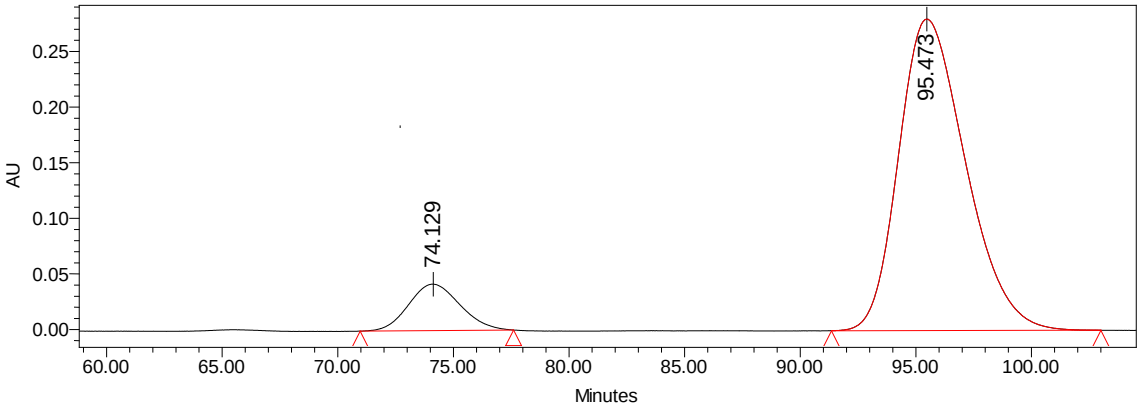
Retention Time	% Area
74.816	50.05
97.608	49.95



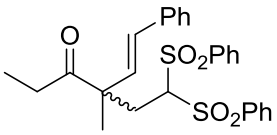


13

Retention Time	% Area
74.129	10.27
95.473	89.73

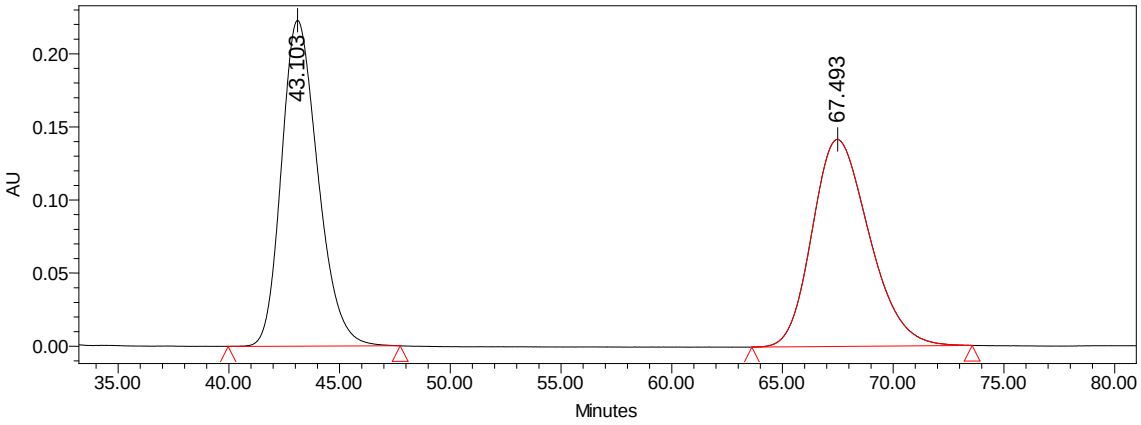


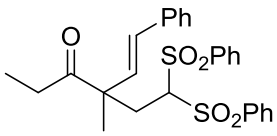
Chiralpack IC mL/min, hexane/isopropanol 60:40, λ = 210 nm



***rac*-14**

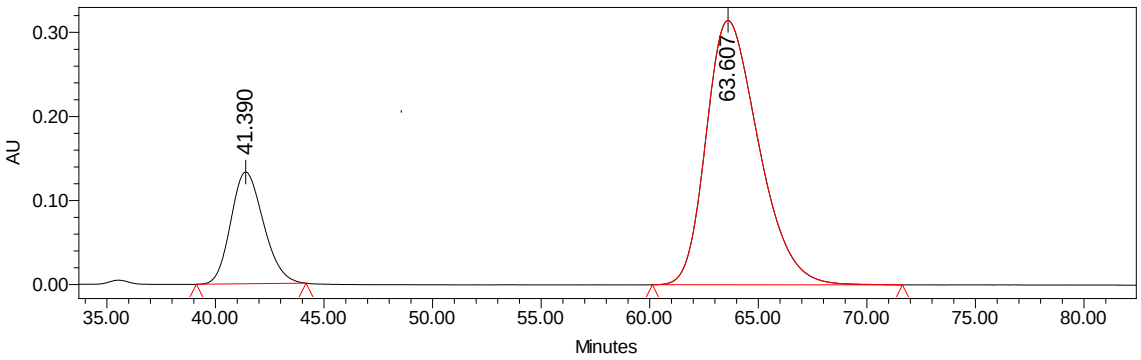
Retention Time	% Area
43.103	50.14
67.493	49.86



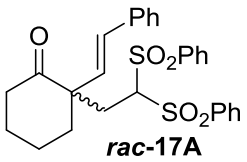


14

Retention Time	% Area
41.390	20,86
63.607	79.14

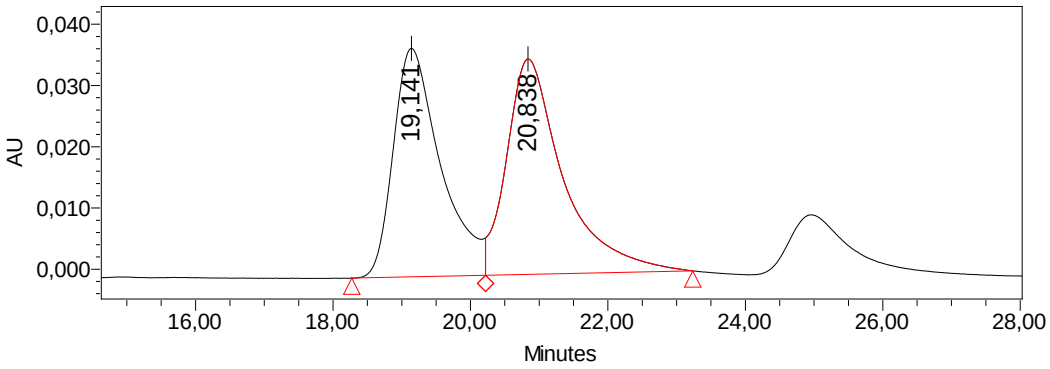


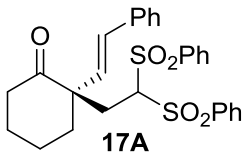
Chiralpack IA, 1 mL/min, hexane/isopropanol 70:30, λ = 250 nm



***rac*-17A**

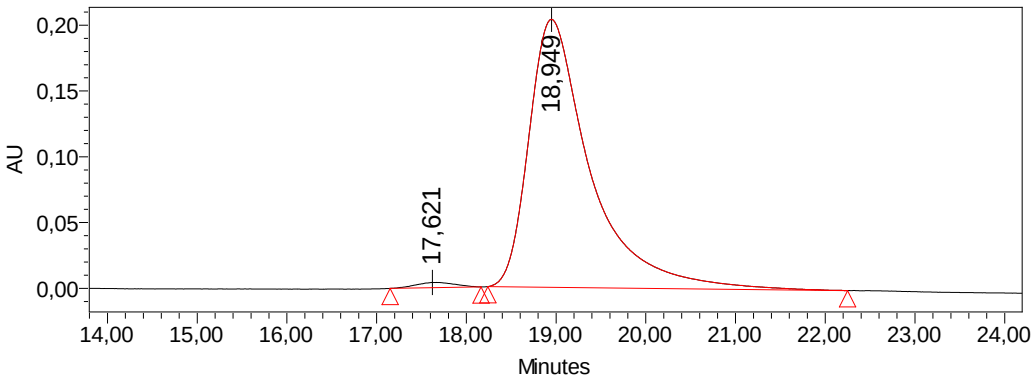
Retention Time	% Area
19,141	48,09
20,838	51,91



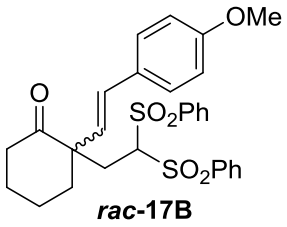


17A

Retention Time	% Area
17,621	1,21
18,949	98,79

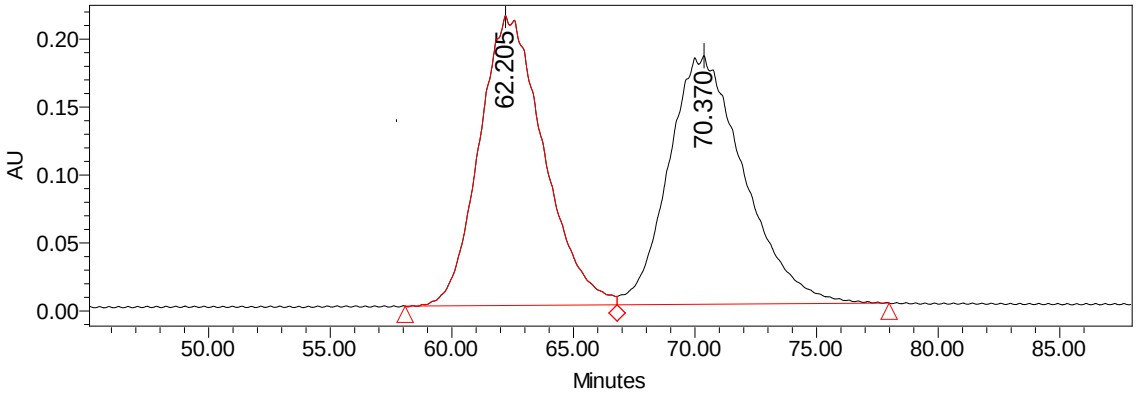


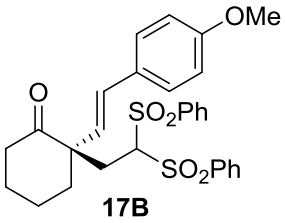
Chiralpack IC mL/min, hexane/isopropanol 50:50, λ = 210 nm



***rac*-17B**

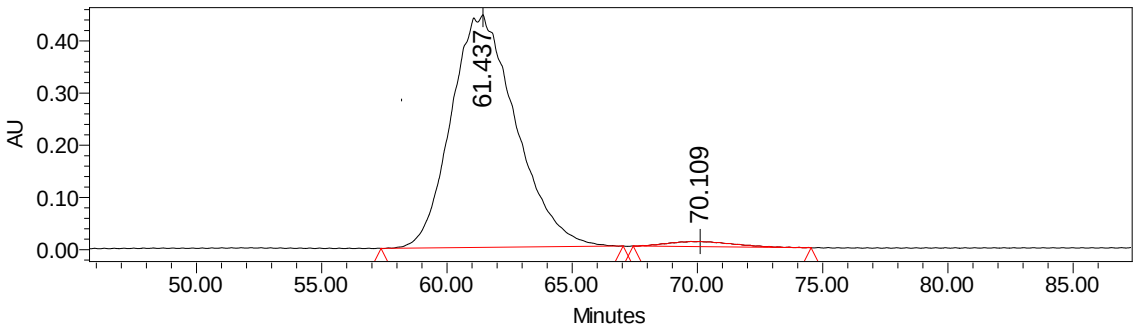
Retention Time	% Area
62.205	49.86
70.370	50.14



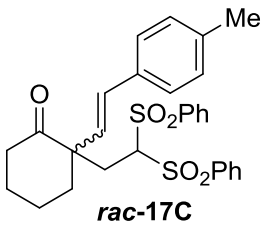


17B

Retention Time	% Area
61.437	97.86
70.109	2.14

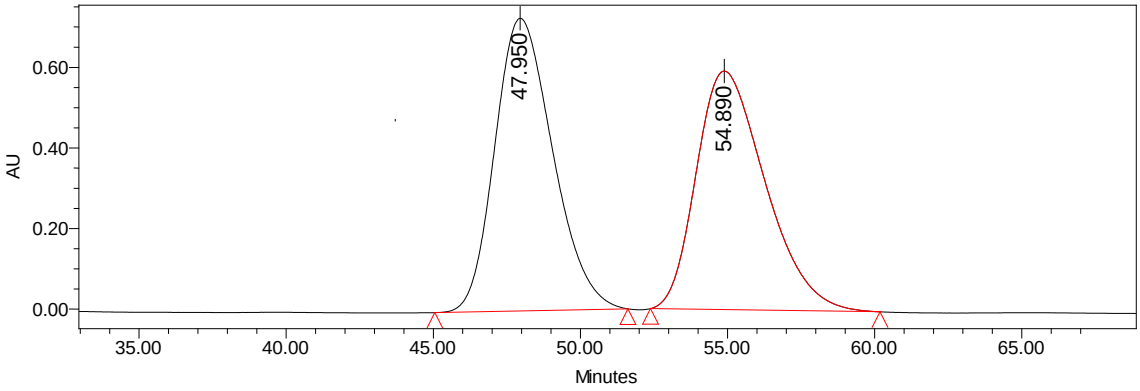


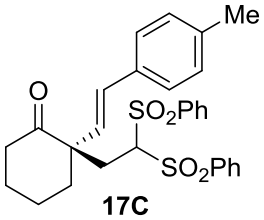
Chiralpack IC mL/min, hexane/isopropanol 50:50, λ = 210 nm



***rac*-17C**

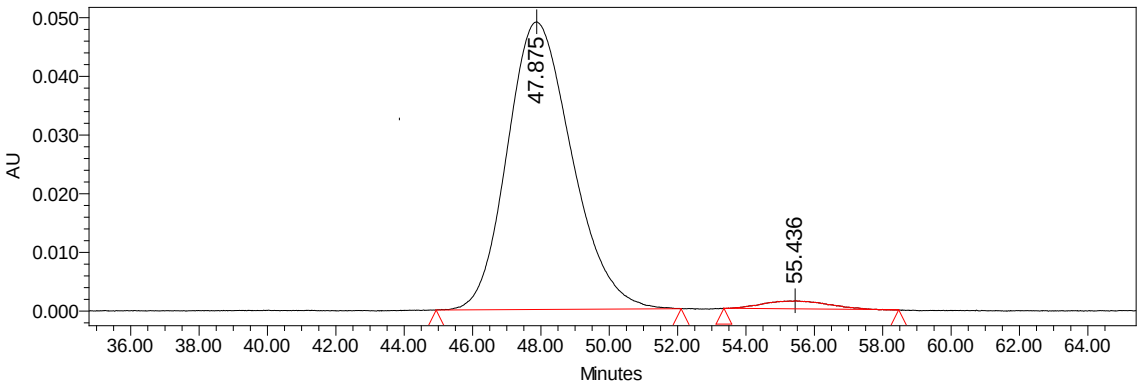
Retention Time	% Area
47.950	50.79
54.890	49.21



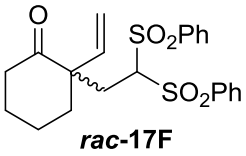


17C

Retention Time	% Area
47.875	97.26
55.436	2.74

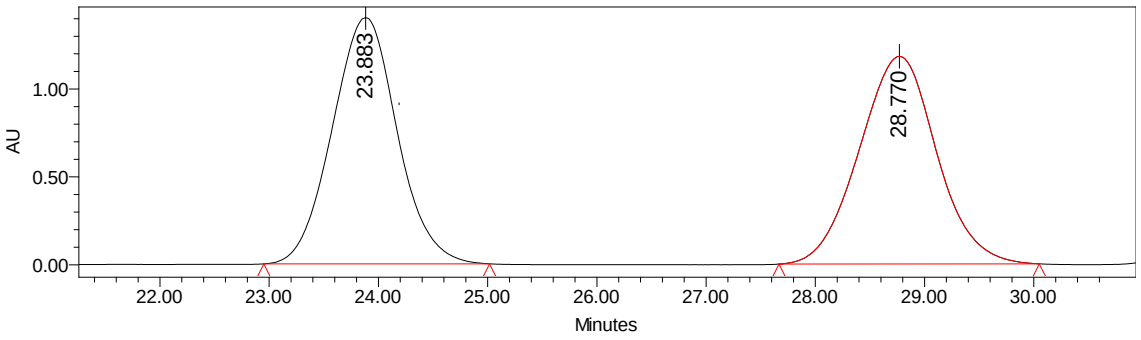


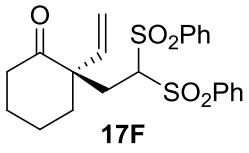
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 80:20, λ = 210 nm



***rac*-17F**

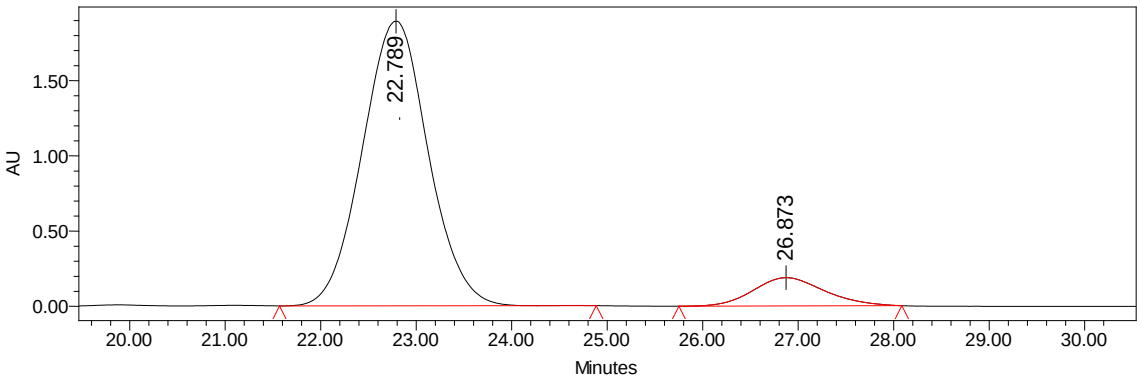
Retention Time	% Area
23.883	49.93
28.770	50.07



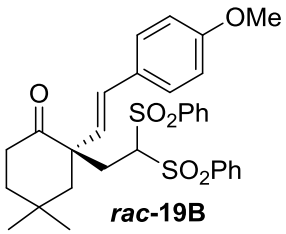


17F

Retention Time	% Area
22.789	90.31
26.873	9.69

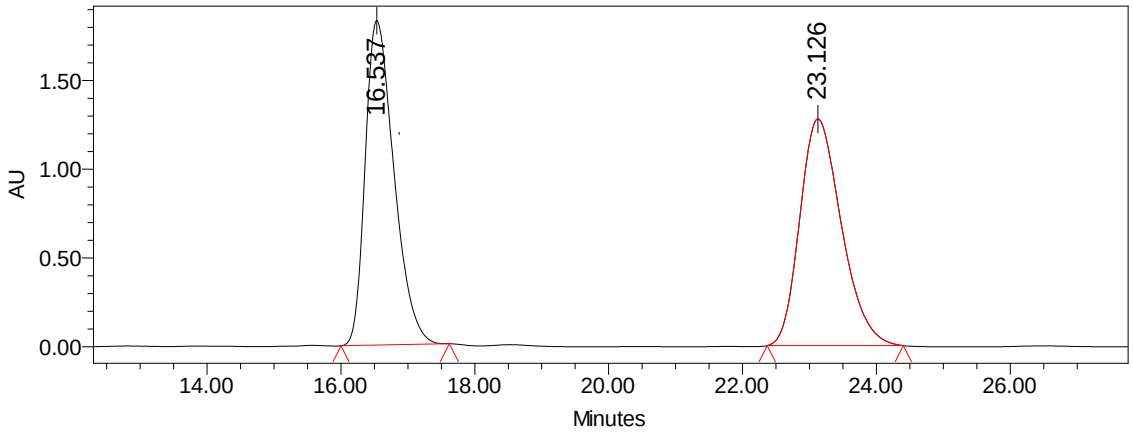


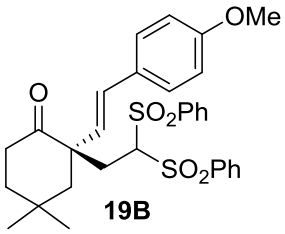
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 30:70, λ = 250 nm



***rac*-19B**

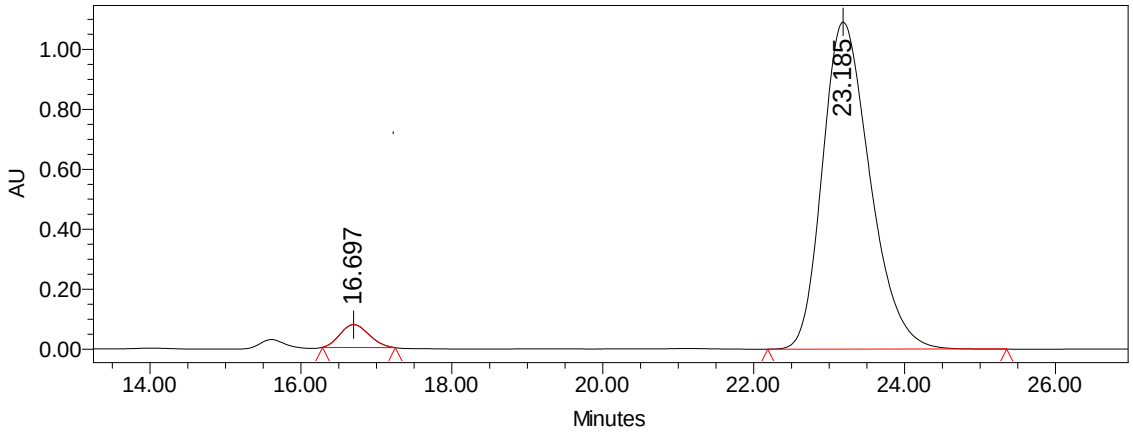
Retention Time	% Area
16.537	49.80
23.126	50.20



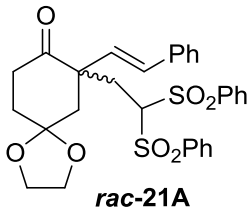


19B

Retention Time	% Area
16.697	4.09
23.185	95.91

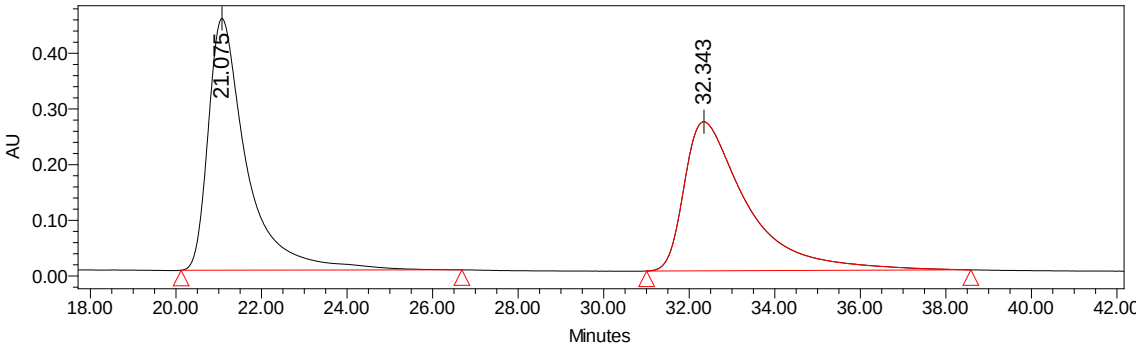


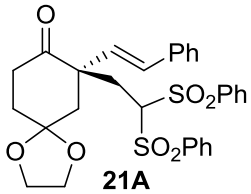
Chiralpack IA mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-21A**

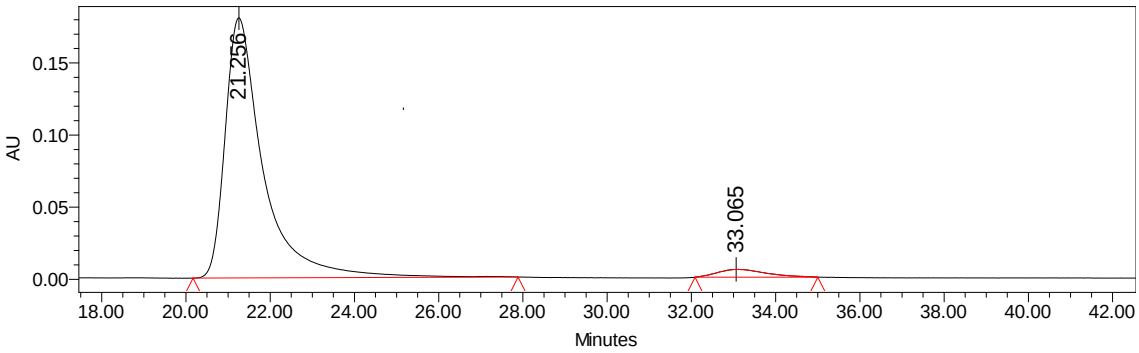
Retention Time	% Area
21.075	50.78
32.343	49.22



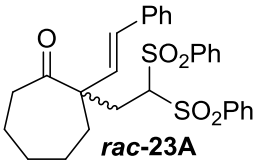


21A

Retention Time	% Area
21.256	96.33
33.065	3.67

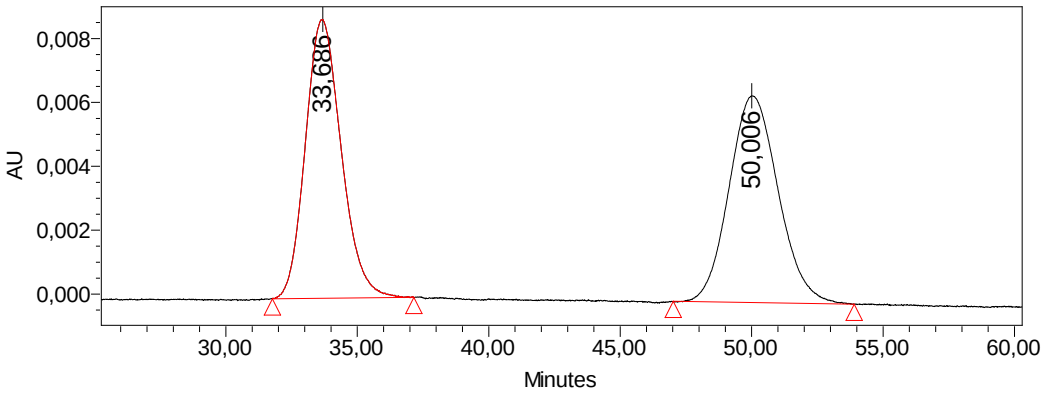


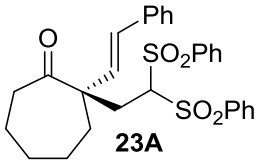
Chiralpack IC, 1 mL/min, hexane/isopropanol 50:50, λ = 250 nm



***rac*-23A**

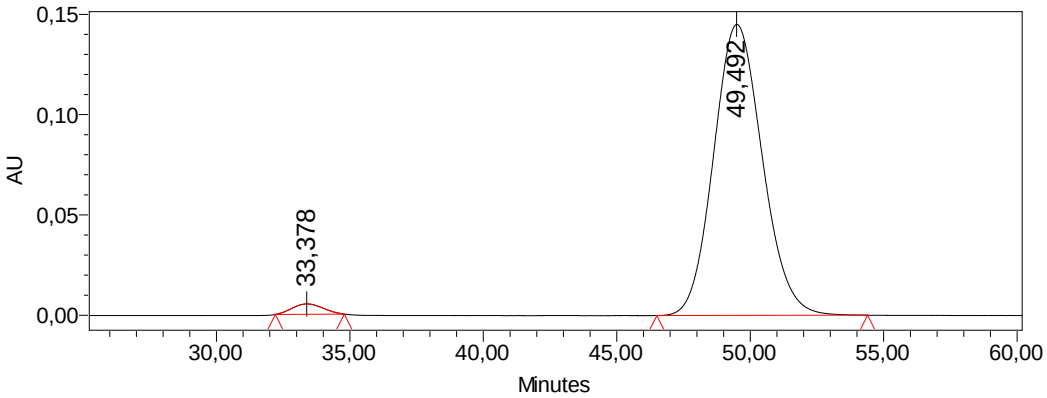
Retention Time	% Area
33,686	49,64
50,006	50,36



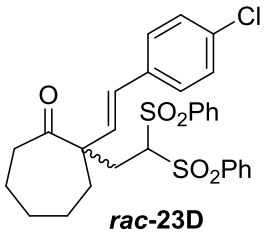


23A

Retention Time	% Area
33,378	2,19
49,492	97,81

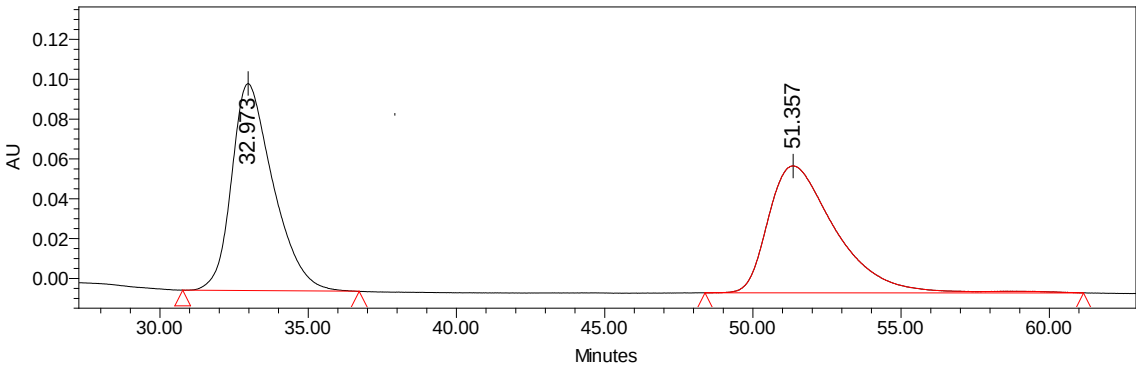


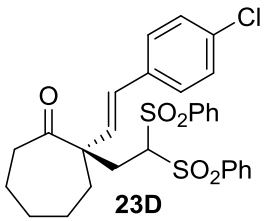
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-23D**

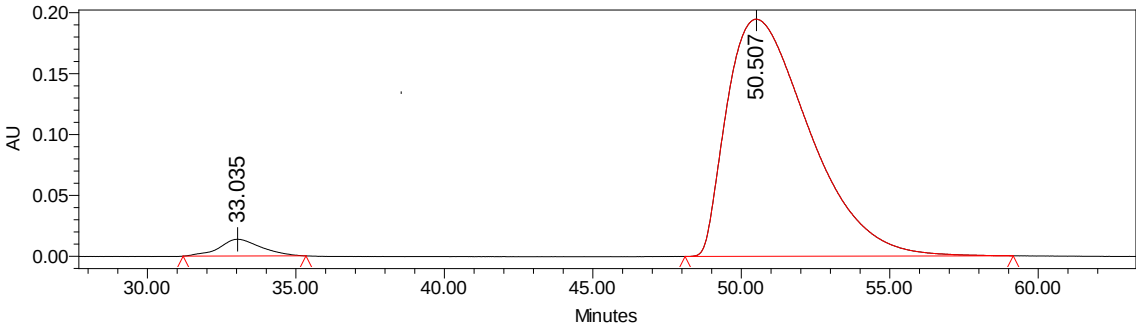
Retention Time	% Area
32.973	49.89
51.357	50.11



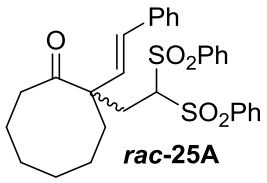


23D

Retention Time	% Area
33.035	3.46
50.507	96.54

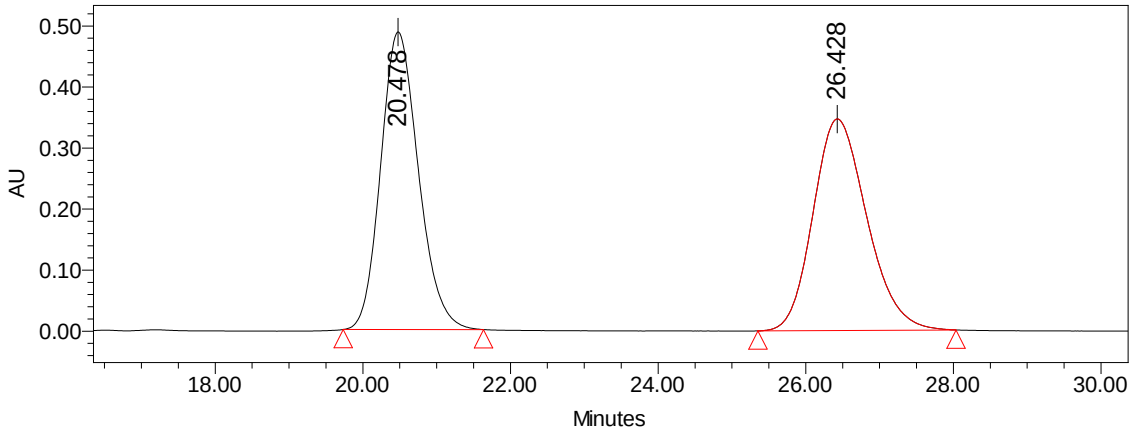


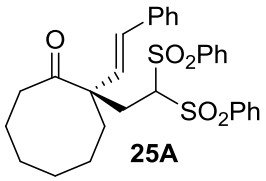
Chiralpack AD-H, 0.5 mL/min, hexane/isopropanol 30:70, λ = 250 nm



***rac*-25A**

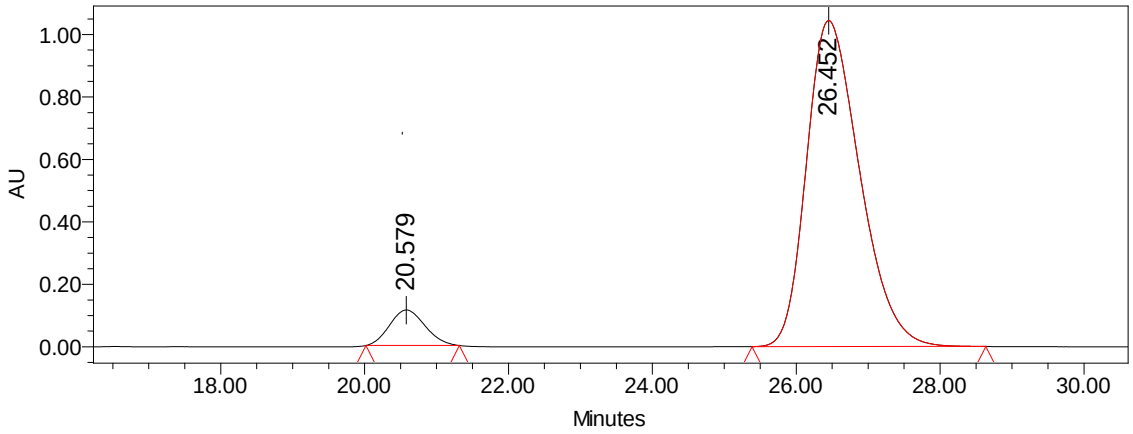
Retention Time	% Area
20.478	49.70
26.428	50.30



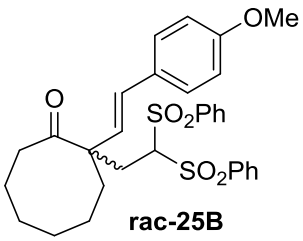


25A

Retention Time	% Area
20.579	6.07
26.452	93.93

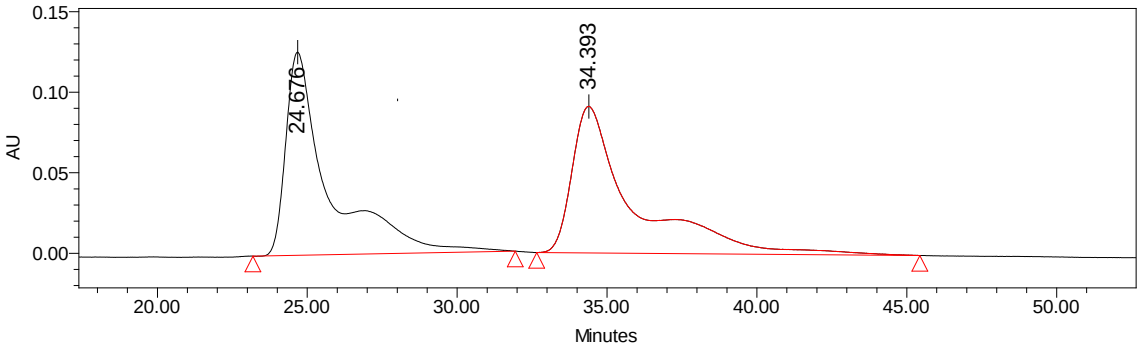


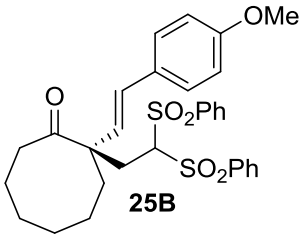
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 60:40, λ = 210 nm



rac-25B

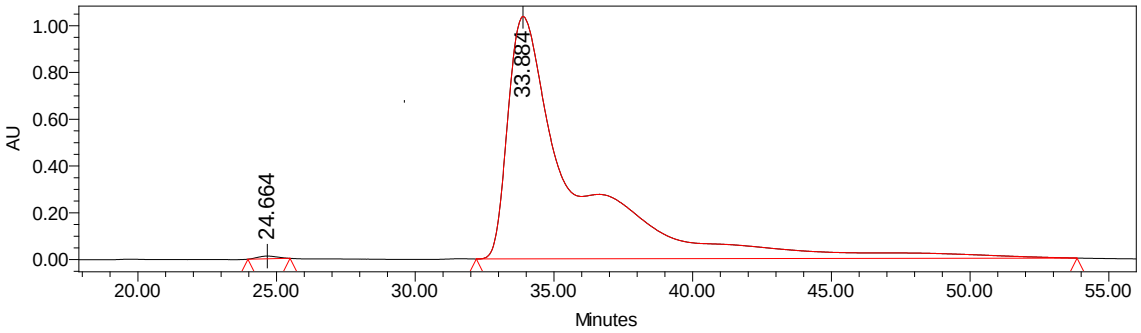
Retention Time	% Area
24.676	49.20
34.393	50.80



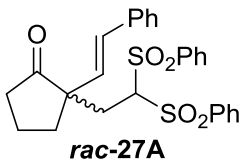


25B

Retention Time	% Area
24.664	0.32
33.884	99.68

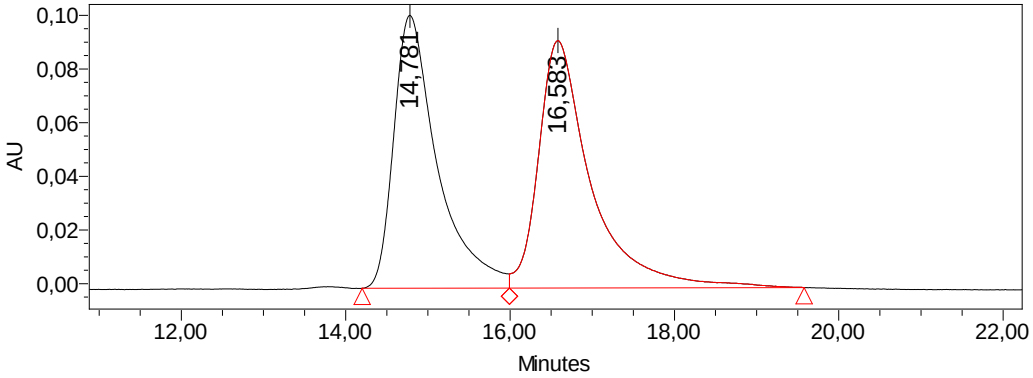


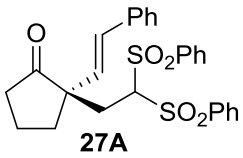
Chiralpack IA, 1 mL/min, hexane/isopropanol 70:30, λ = 260 nm



***rac*-27A**

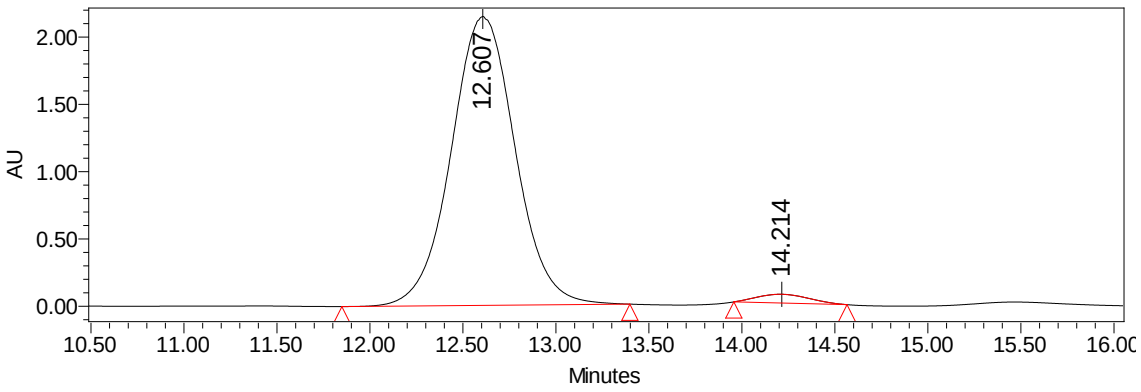
Retention Time	% Area
14,781	47,81
16,583	52,19



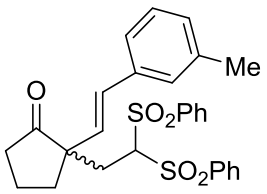


27A

Retention Time	% Area
12,607	97,57
14,214	2,43

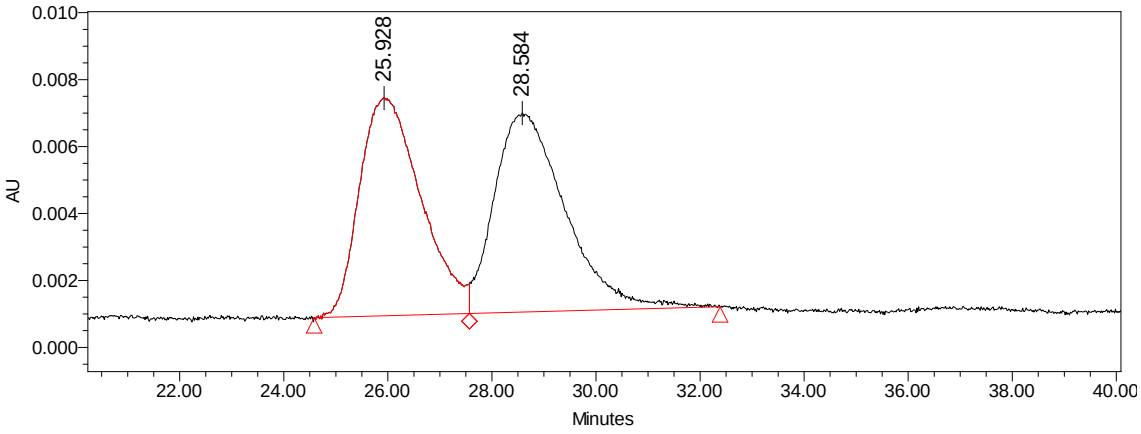


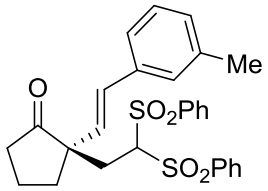
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 85:15, λ = 210 nm



***rac*-27E**

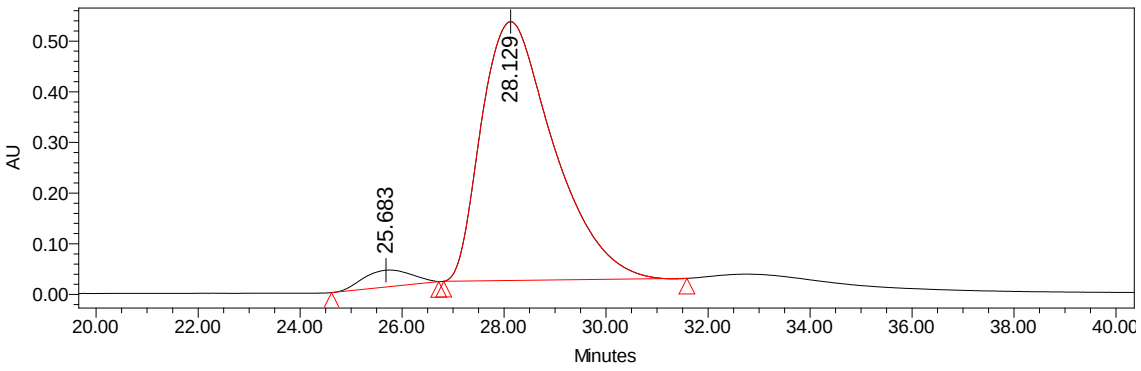
Retention Time	% Area
25.928	48.71
28.584	51.29



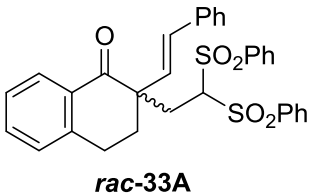


27E

Retention Time	% Area
25.683	4.16
28.129	95.84

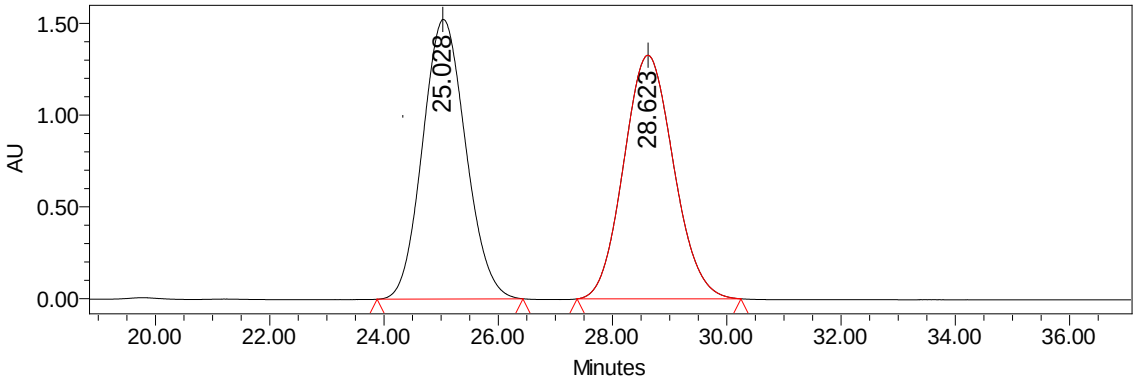


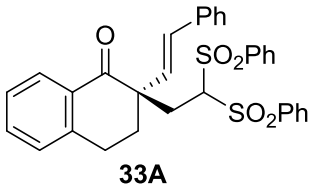
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-33A**

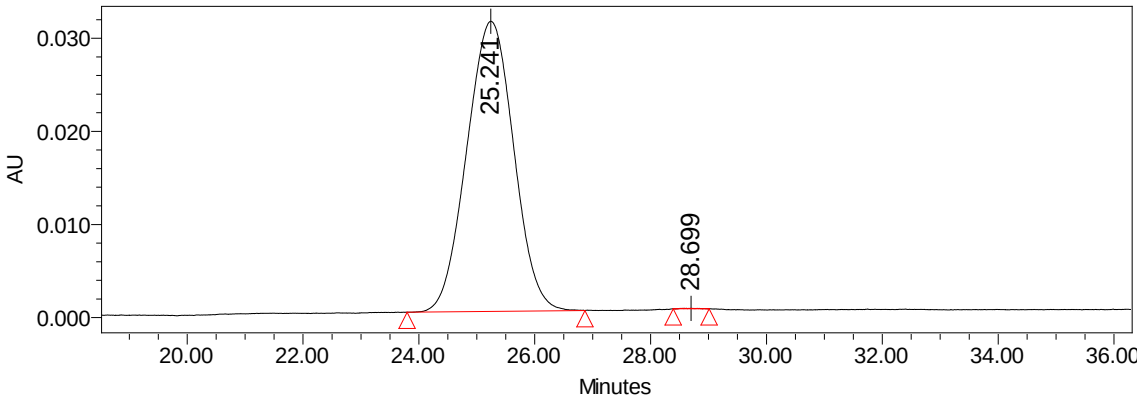
Retention Time	% Area
25.028	49.80
28.623	50.20



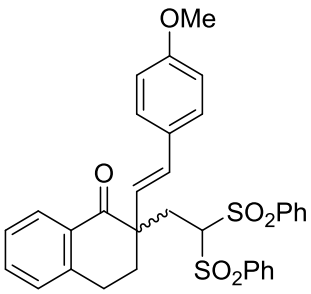


33A

Retention Time	% Area
25.241	99.95
28.699	0.05

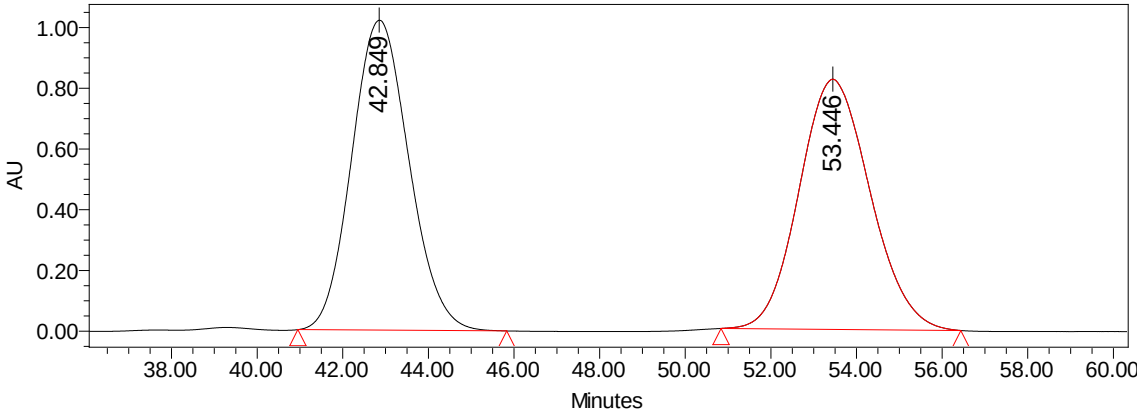


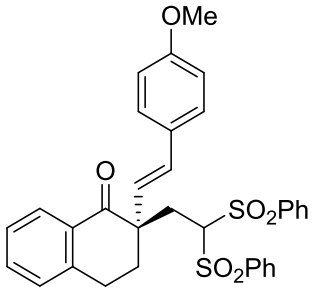
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-33B**

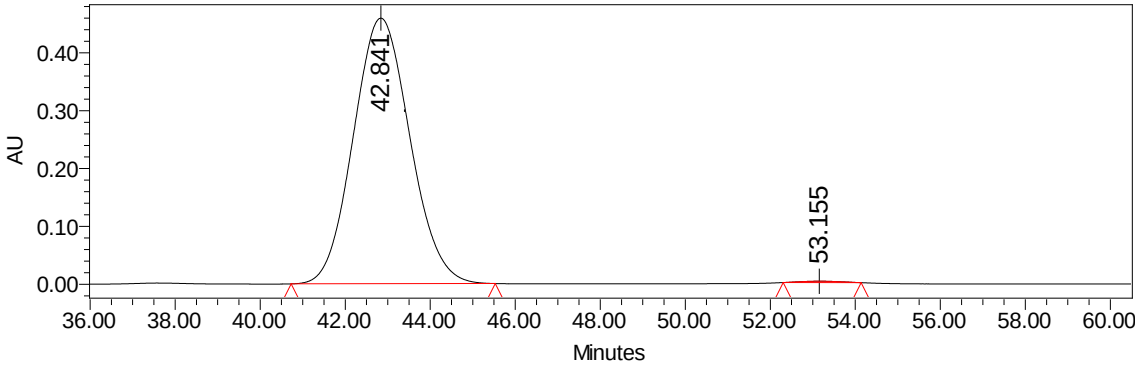
Retention Time	% Area
42.849	49.98
53.446	50.02



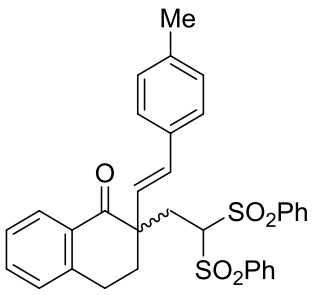


33B

Retention Time	% Area
42.841	99.62
53.155	0.38

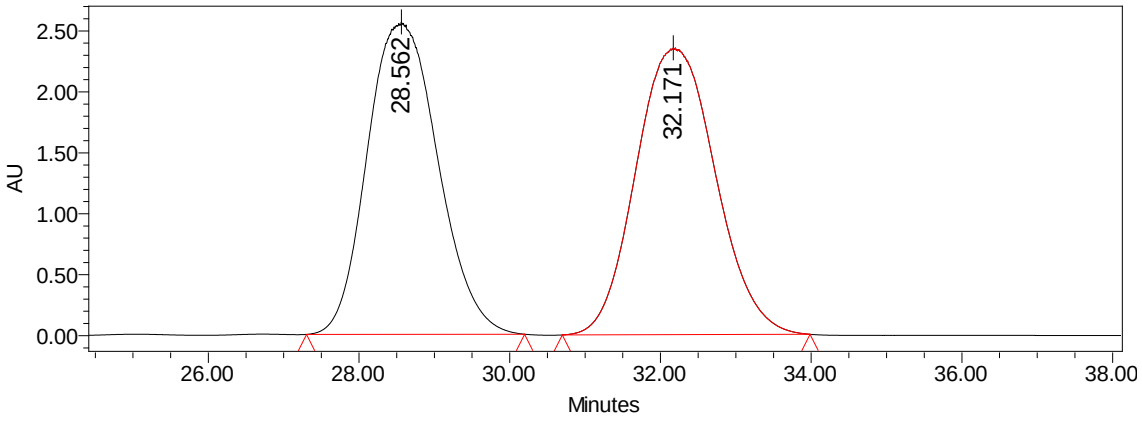


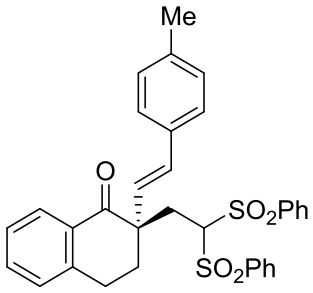
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-33C**

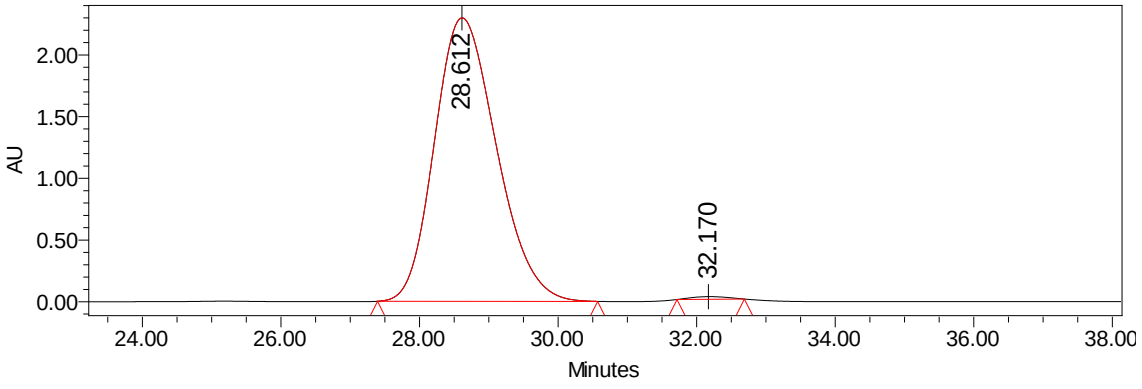
Retention Time	% Area
28.562	49.13
32.171	50.87



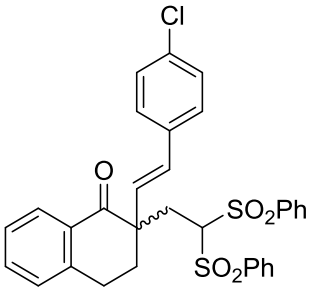


33C

Retention Time	% Area
28.612	99.46
32.170	0.54

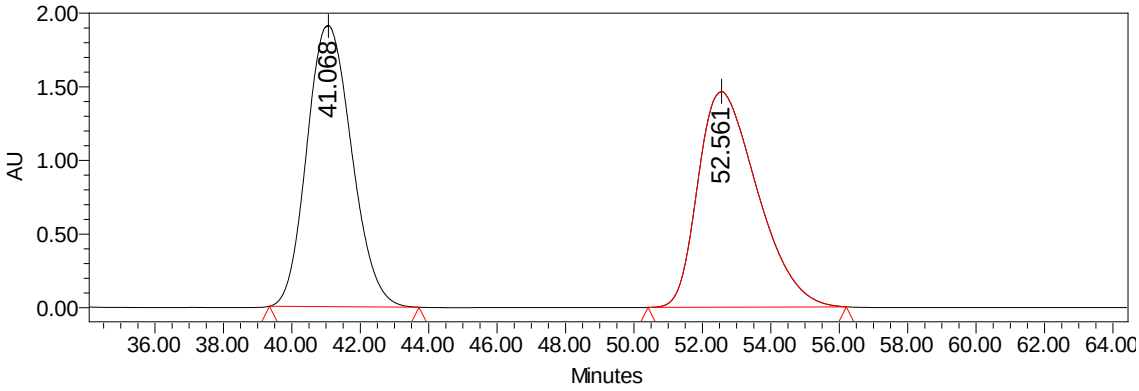


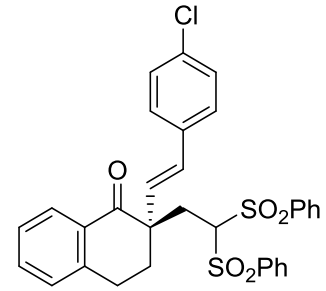
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-33D**

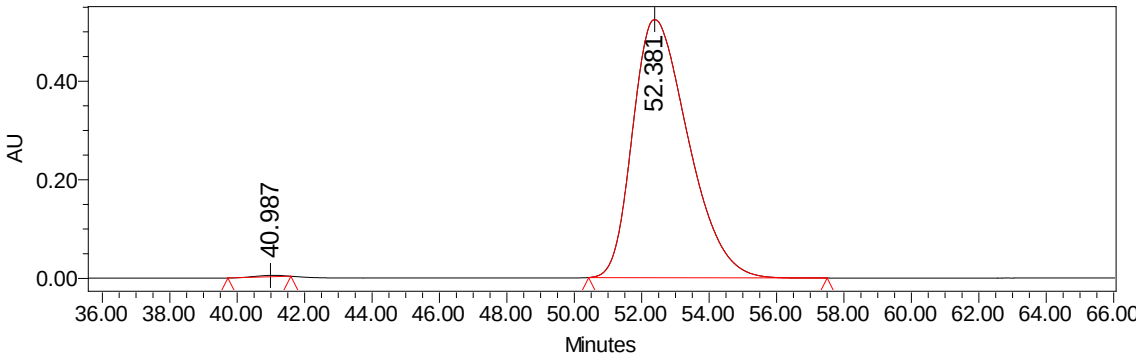
Retention Time	% Area
41.068	49.63
52.561	50.37



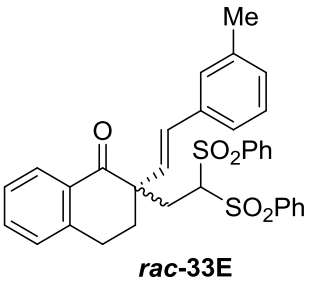


33D

Retention Time	% Area
40.987	0.26
52.381	99.74

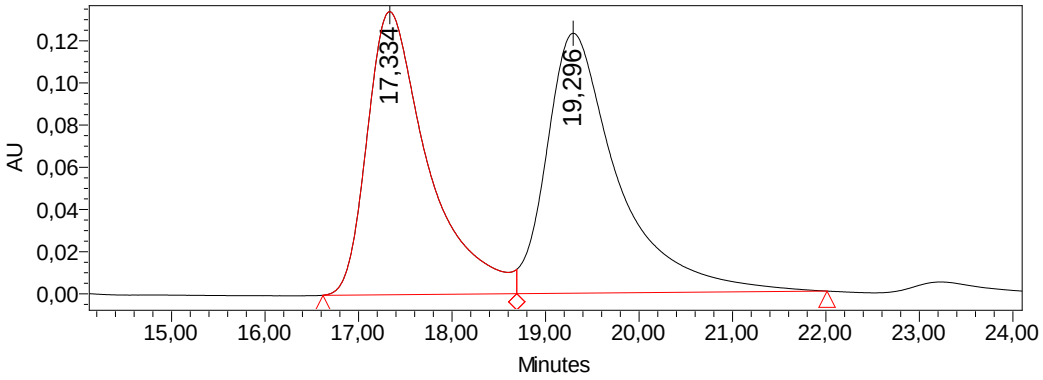


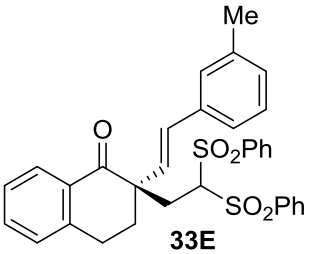
Chiralpack IA, 1 mL/min, hexane/isopropanol 70:30, λ = 260 nm



***rac*-33E**

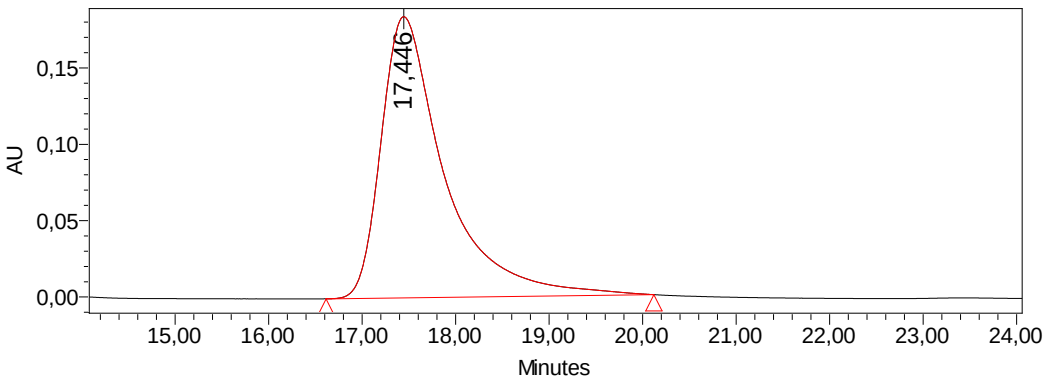
Retention Time	% Area
17,334	48,25
19,296	51,75



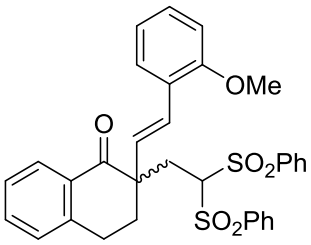


33E

Retention Time	% Area
17,446	100,00

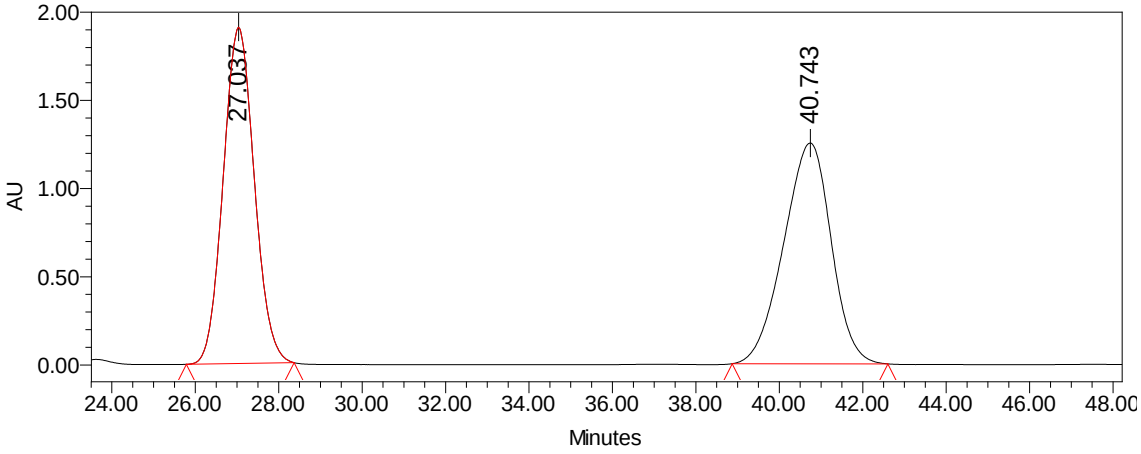


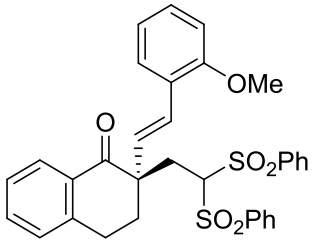
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-33G**

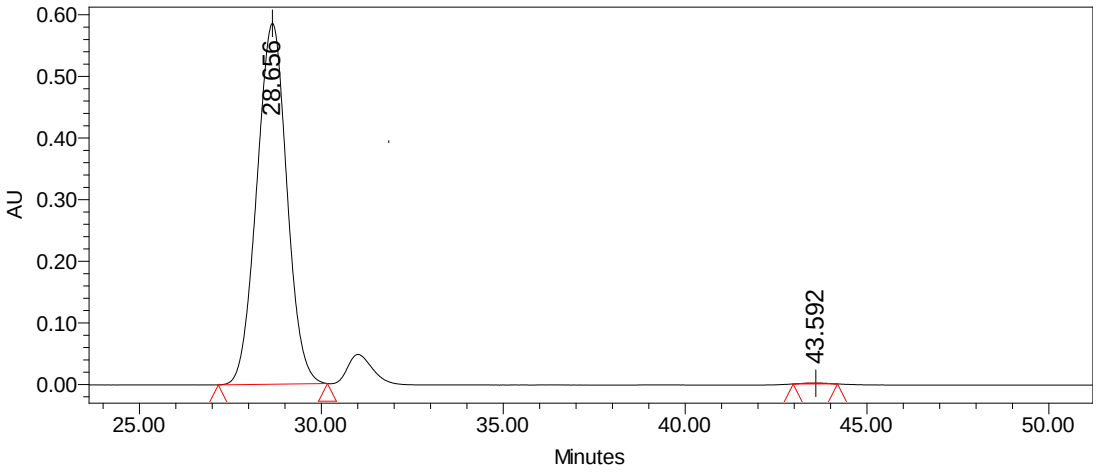
Retention Time	% Area
27.037	49.88
40.743	50.12



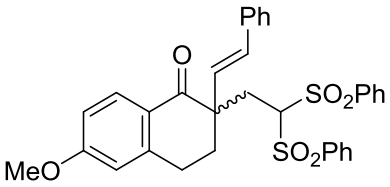


33G

Retention Time	% Area
28.656	99.81
43.592	0.19

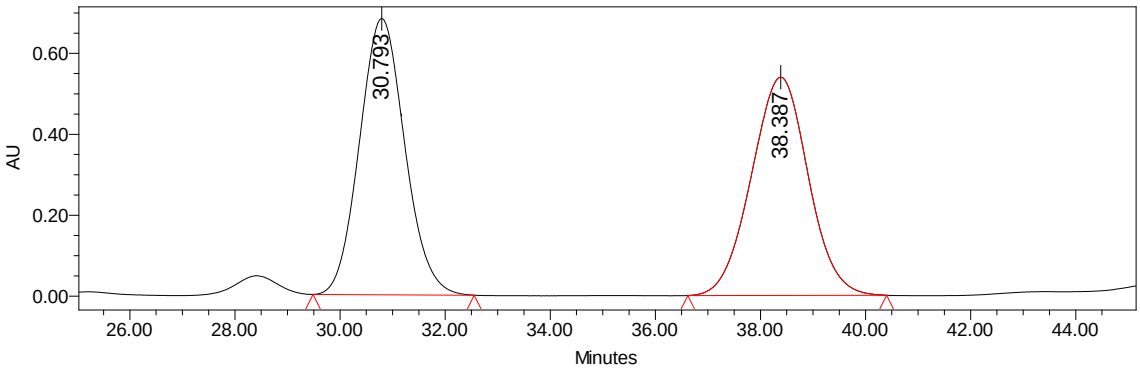


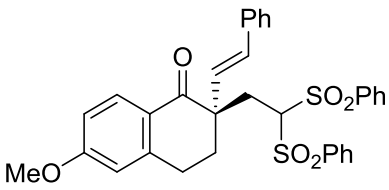
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-34A**

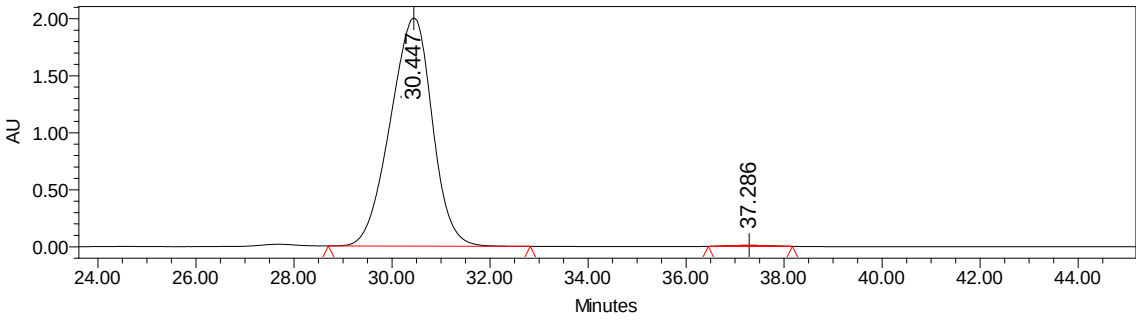
Retention Time	% Area
30.793	50.22
38.387	49.78



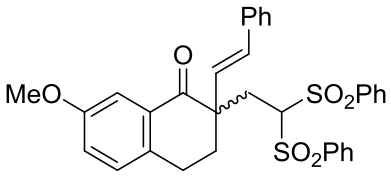


34A

Retention Time	% Area
30.447	99.54
37.286	0.46

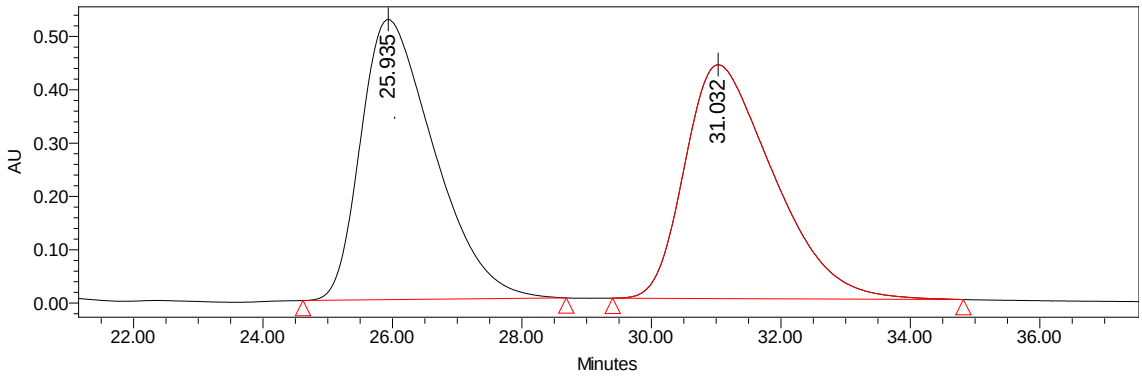


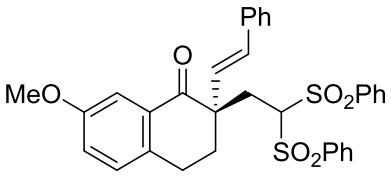
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



***rac*-35A**

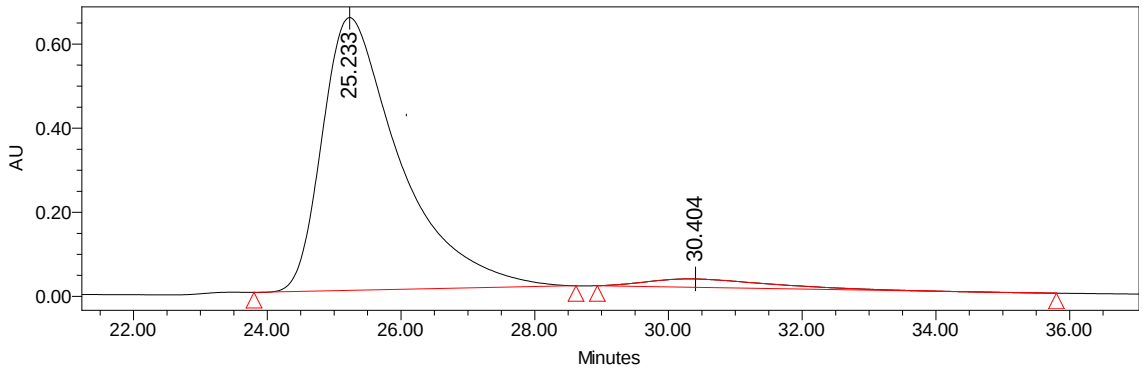
Retention Time	% Area
25.935	49.85
31.032	50.15



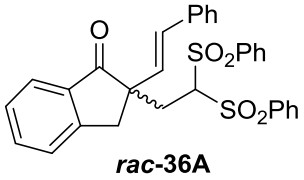


35A

Retention Time	% Area
25.233	95.29
30.404	4.71

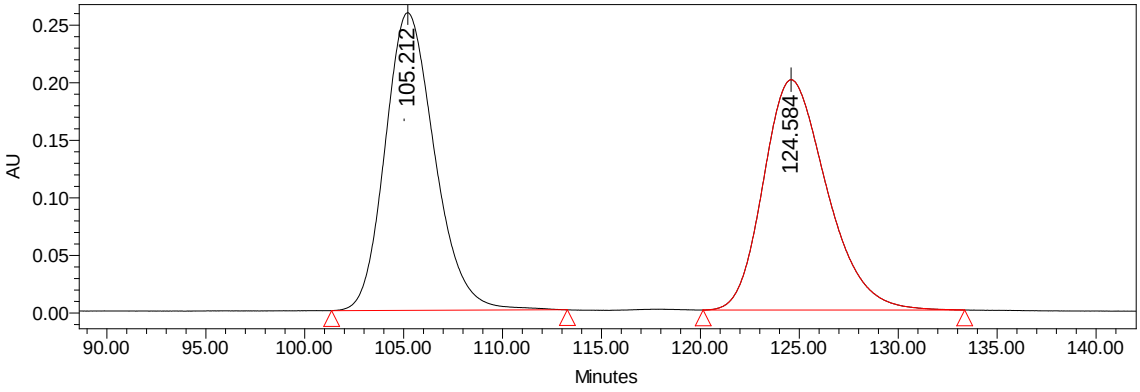


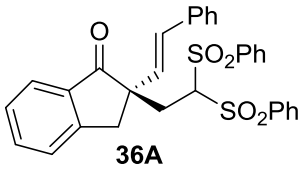
Chiralpack AD-H, 1 mL/min, solvent gradient: 1) hexane/isopropanol 80:20 for 63 min; 2) hexane/isopropanol 70:30, λ = 210 nm



***rac*-36A**

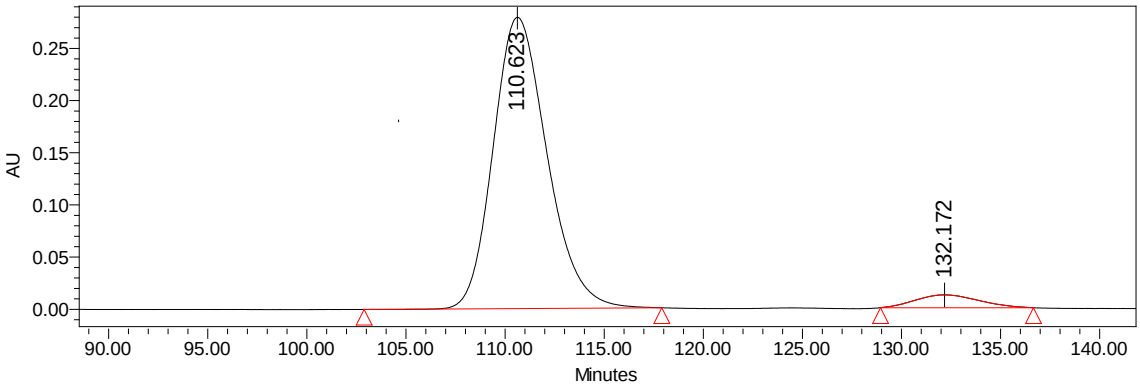
Retention Time	% Area
105.212	50.26
124.584	49.74



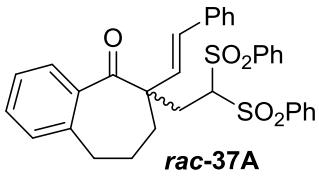


36A

Retention Time	% Area
110.623	95.06
132.172	4.94

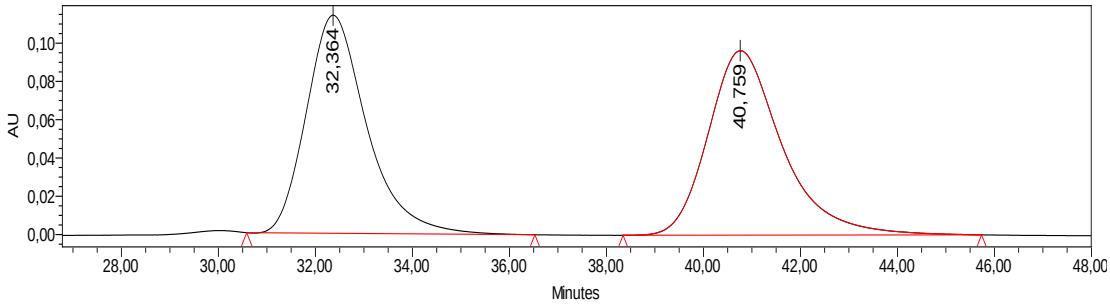


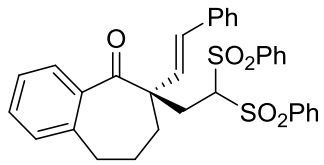
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 230 nm



***rac*-37A**

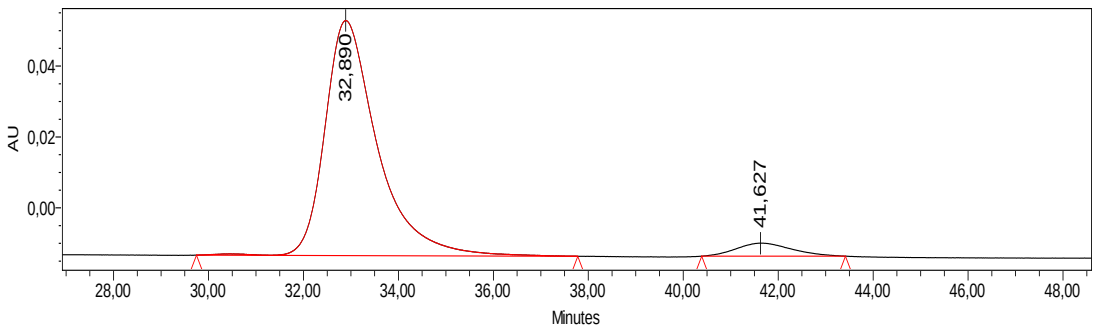
Retention Time	% Area
32.364	49.10
40.759	50.90



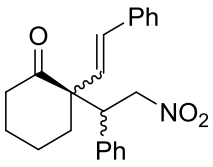


37A

Retention Time	% Area
32.890	94.47
41.627	5.53

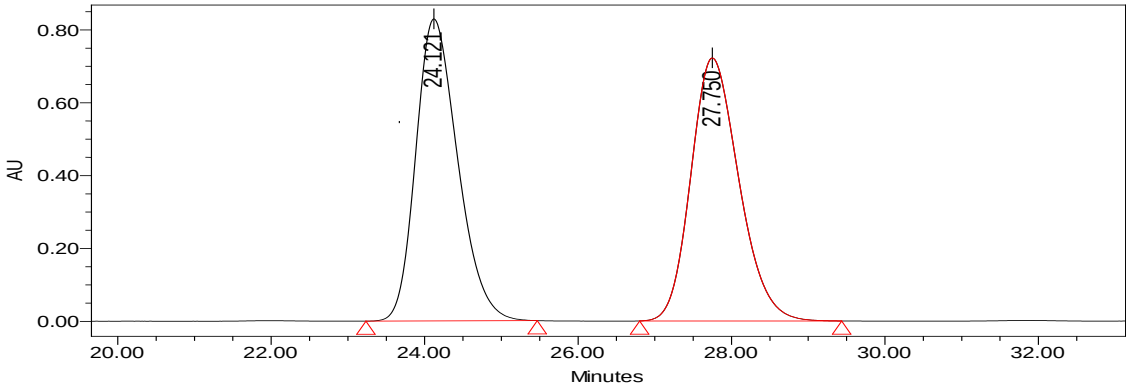


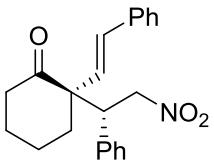
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 250 nm



***rac*-39Aa**

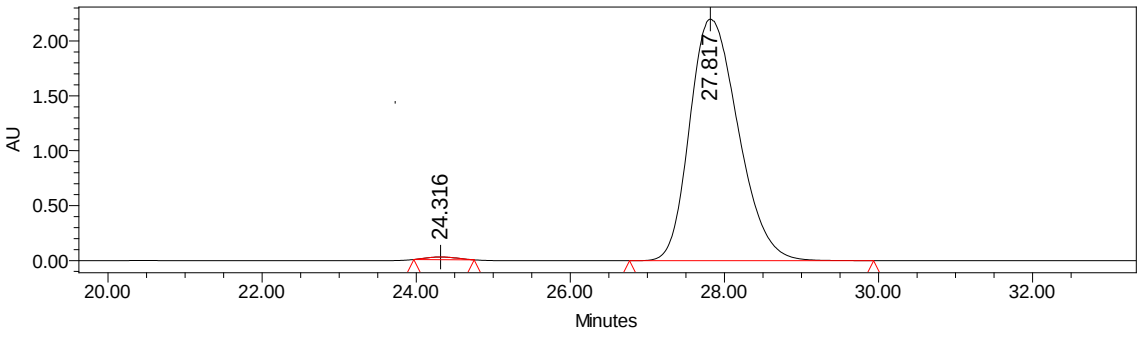
Retention Time	% Area
24.121	49.95
27.750	50.05



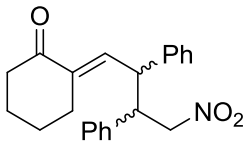


39Aa

Retention Time	% Area
24.316	0.68
27.817	99.32

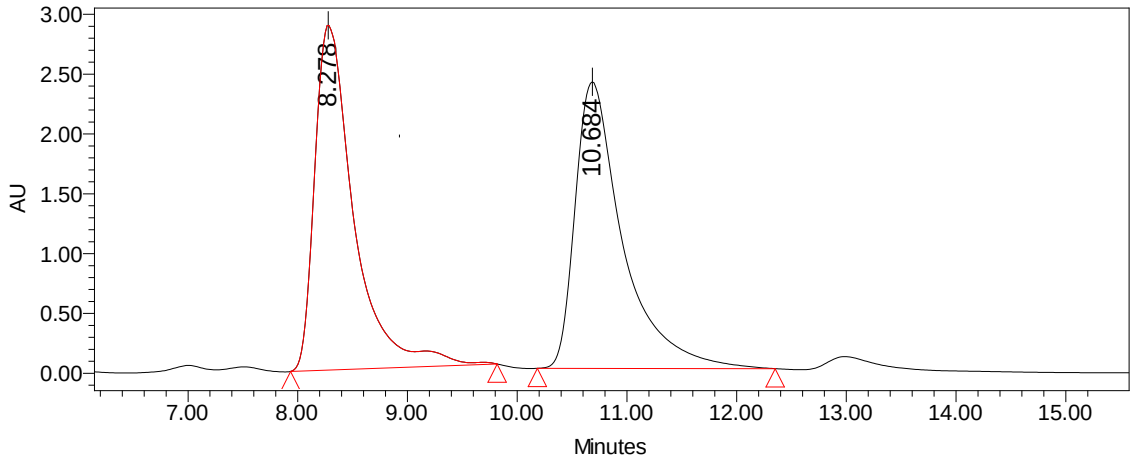


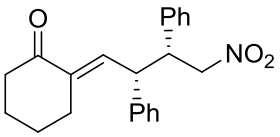
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 250 nm



***rac*-39´Aa**

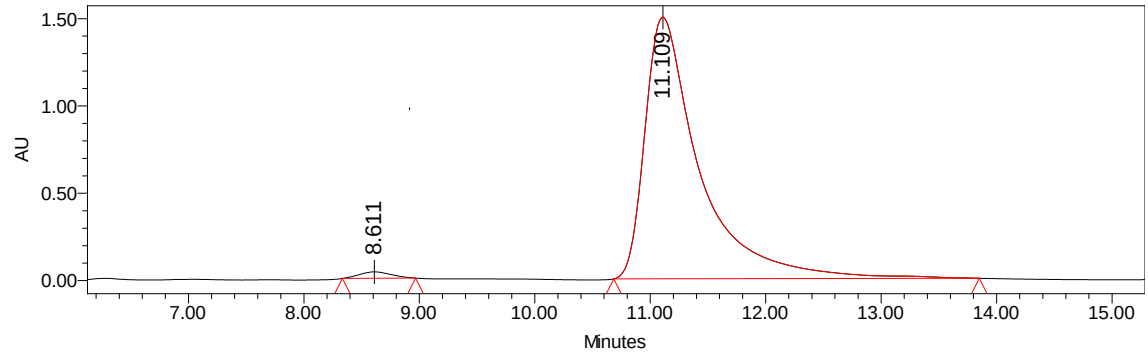
Retention Time	% Area
8.278	49.88
10.684	50.12



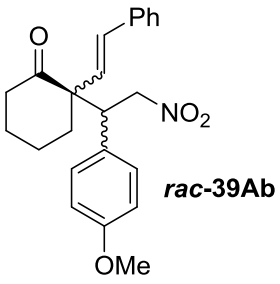


39´Aa

Retention Time	% Area
8.611	1.40
11.109	98.60

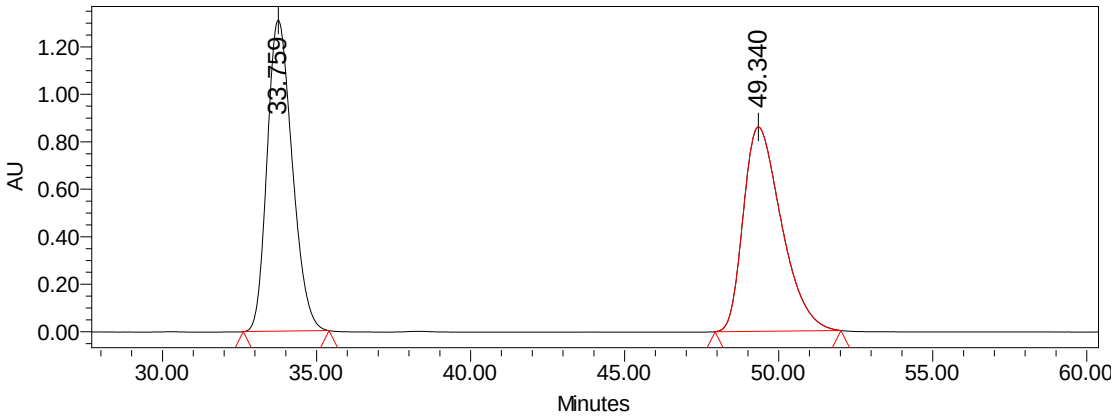


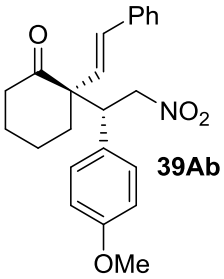
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39Ab**

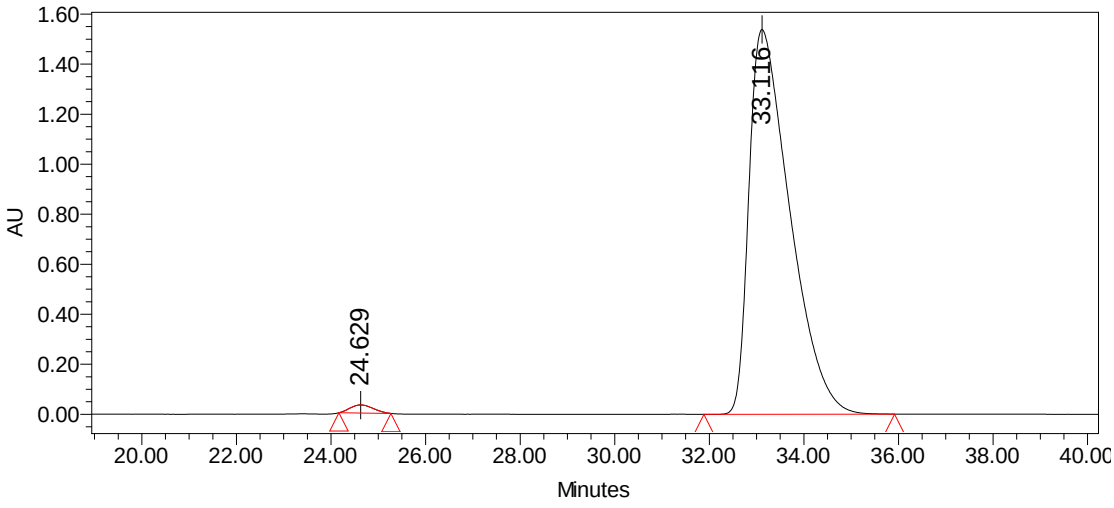
Retention Time	% Area
33.759	50.04
49.340	49.96



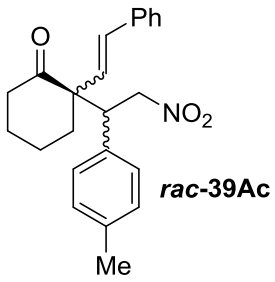


39Ab

Retention Time	% Area
35.277	1.91
51.141	98.09

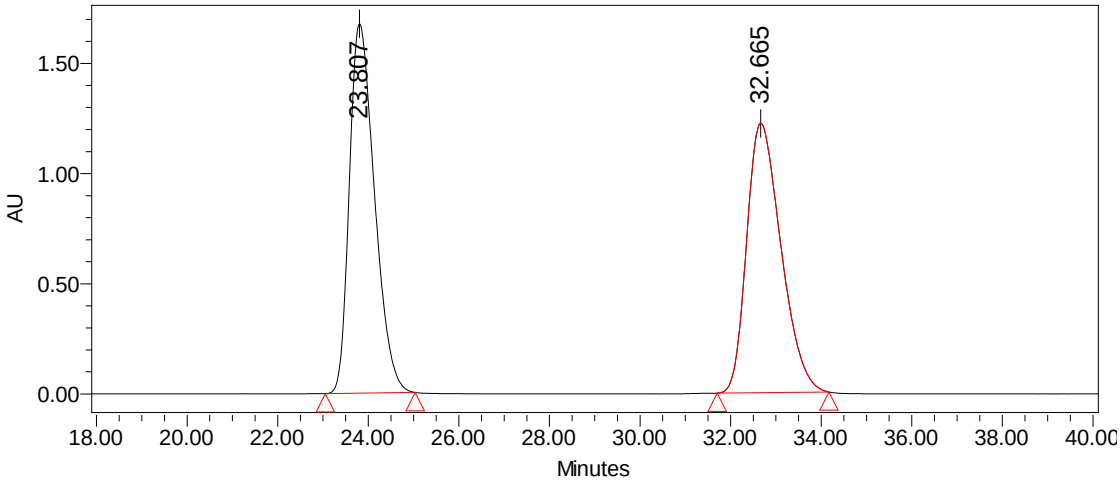


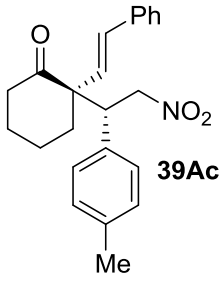
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 260 nm



***rac*-39Ac**

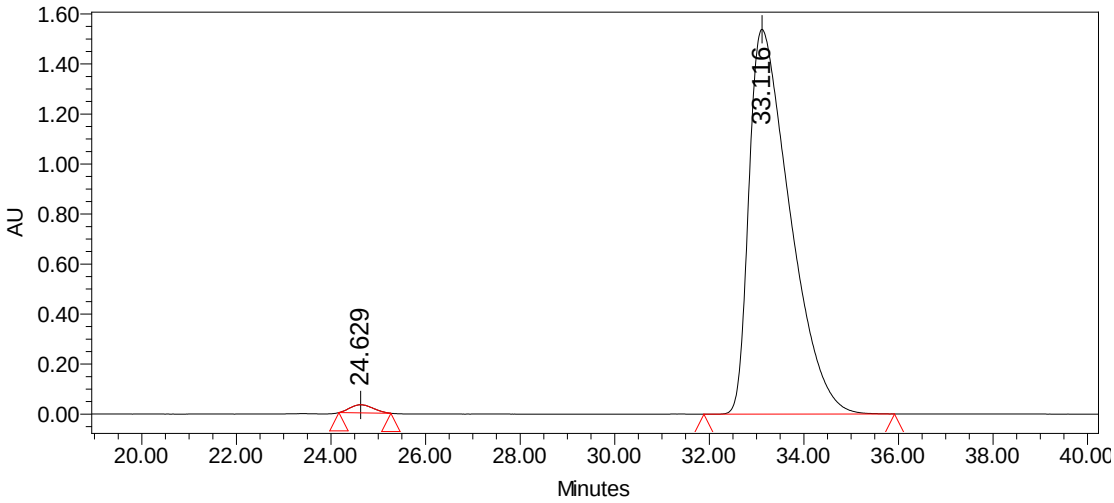
Retention Time	% Area
23.807	50.16
32.665	49.84



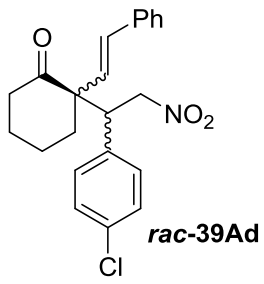


39Ac

Retention Time	% Area
24.629	1.18
33.116	98.82

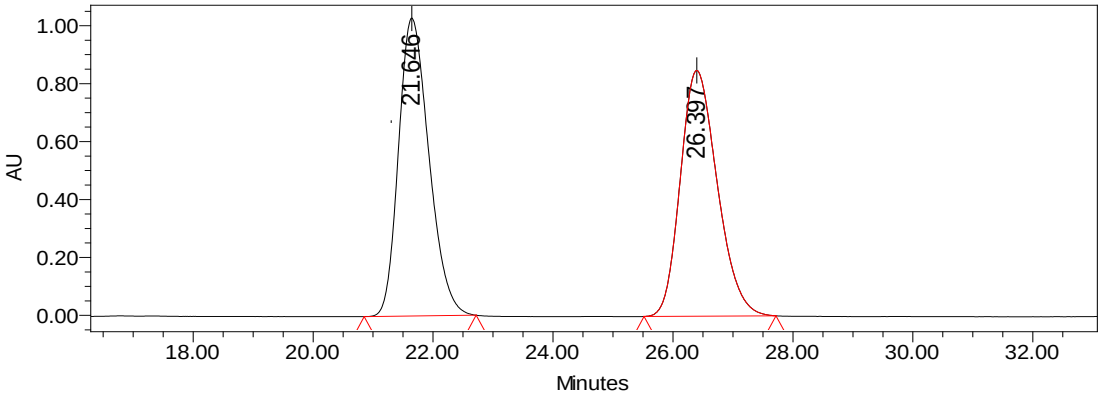


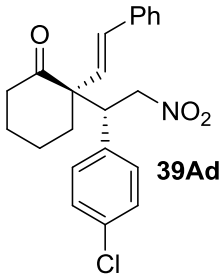
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39Ad**

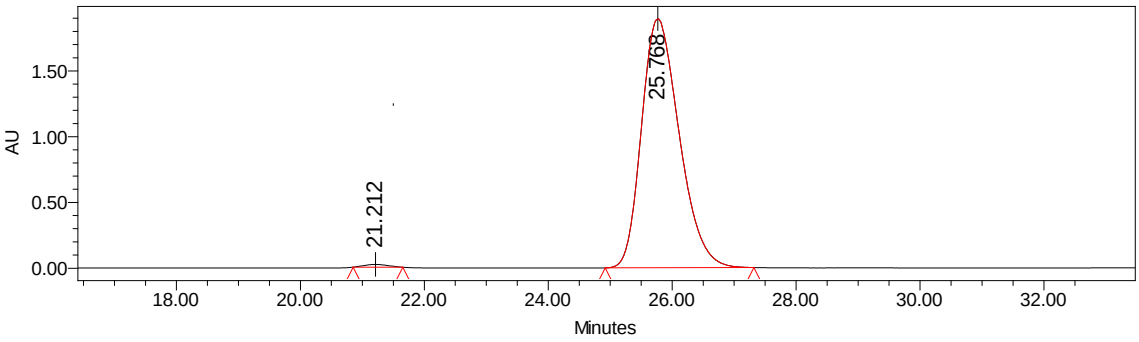
Retention Time	% Area
21.646	49.94
26.397	50.06



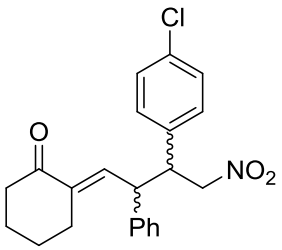


39Ad

Retention Time	% Area
21.212	0.69
25.768	99.31

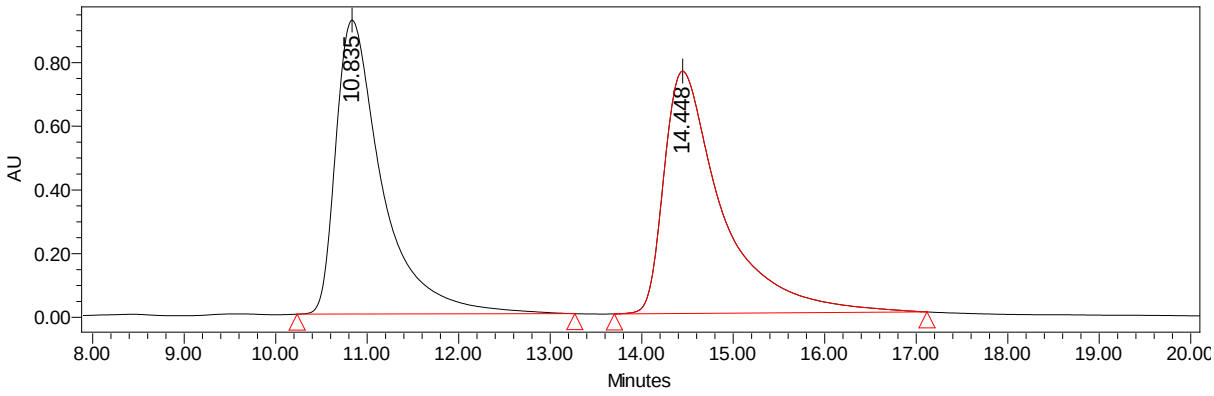


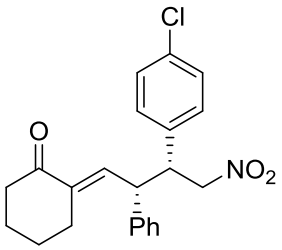
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39´Ad**

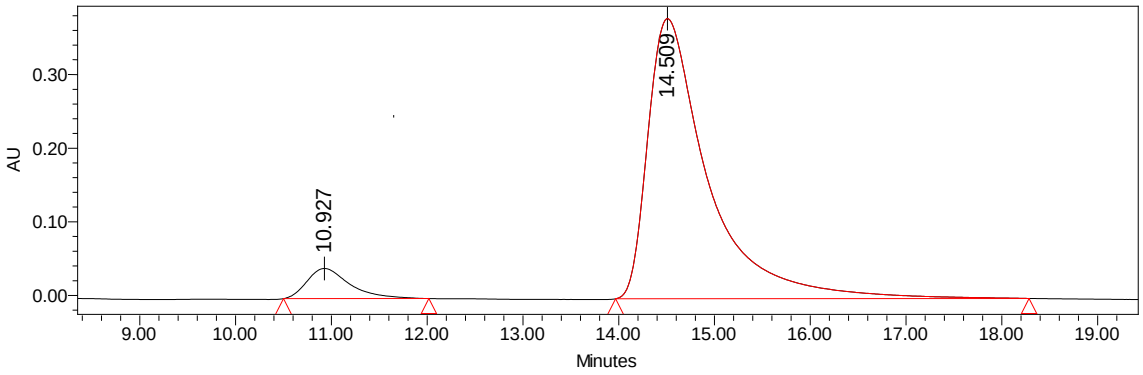
Retention Time	% Area
10.835	49.10
14.448	50.90



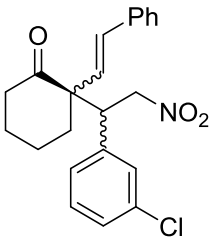


39´Ad

Retention Time	% Area
10.927	7.05
14.509	92.95

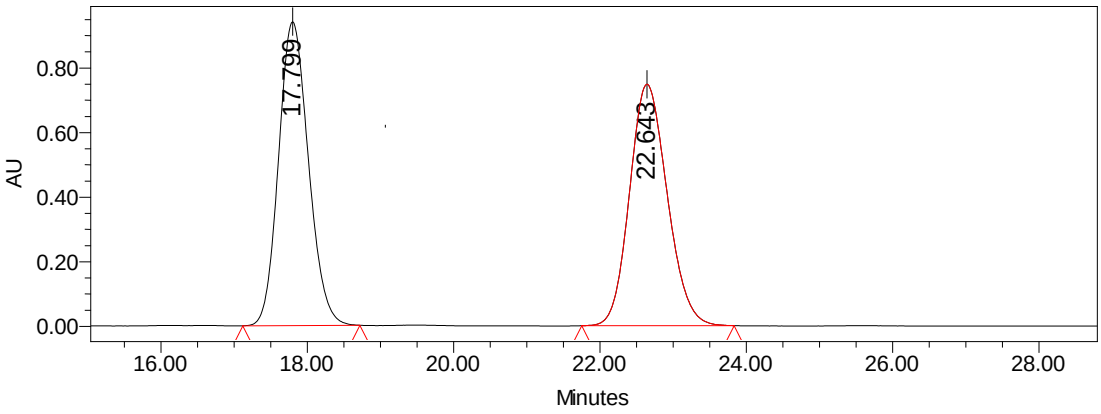


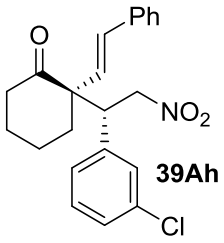
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39Ah**

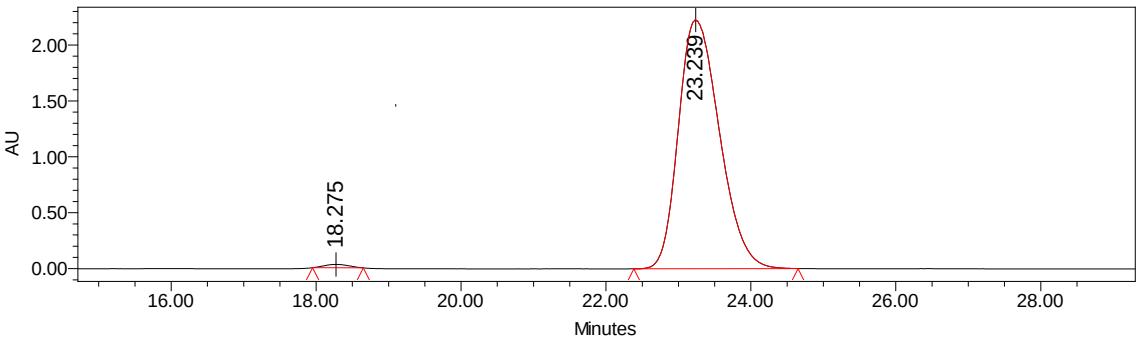
Retention Time	% Area
17.799	49.95
22.643	50.05



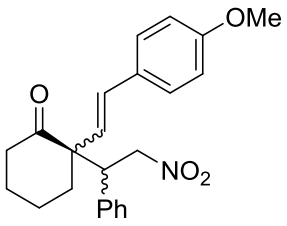


39Ah

Retention Time	% Area
18.275	0.79
23.239	99.21

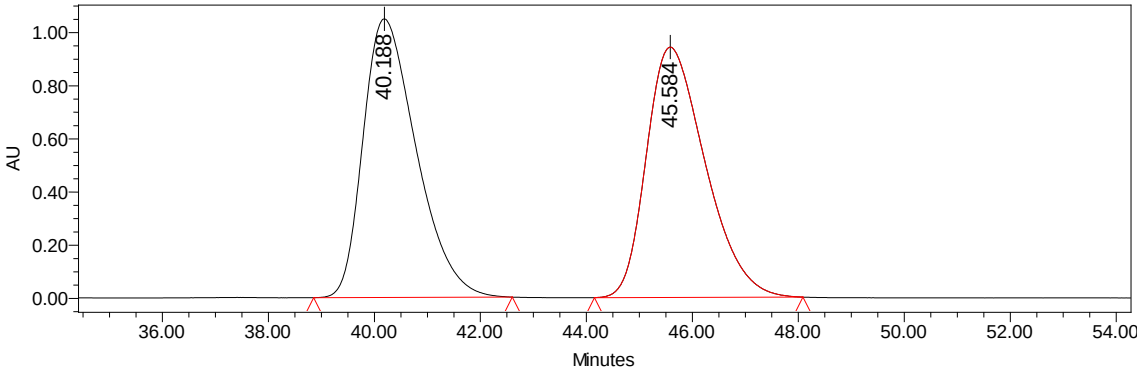


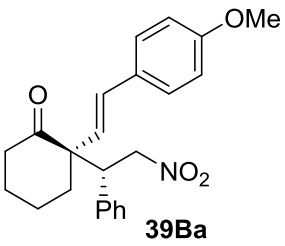
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39Ba**

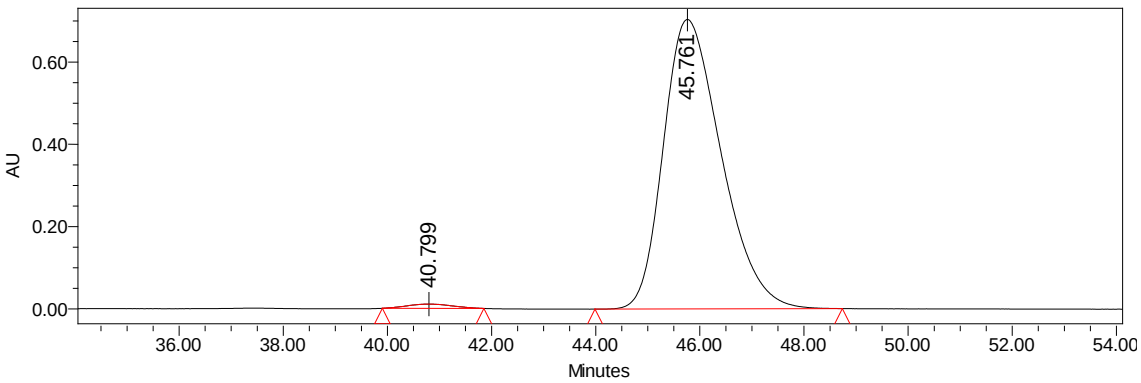
Retention Time	% Area
40.188	50.17
45.584	49.83



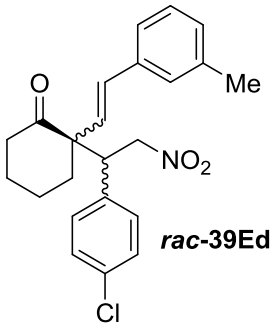


39Ba

Retention Time	% Area
40.799	1.14
45.761	98.86

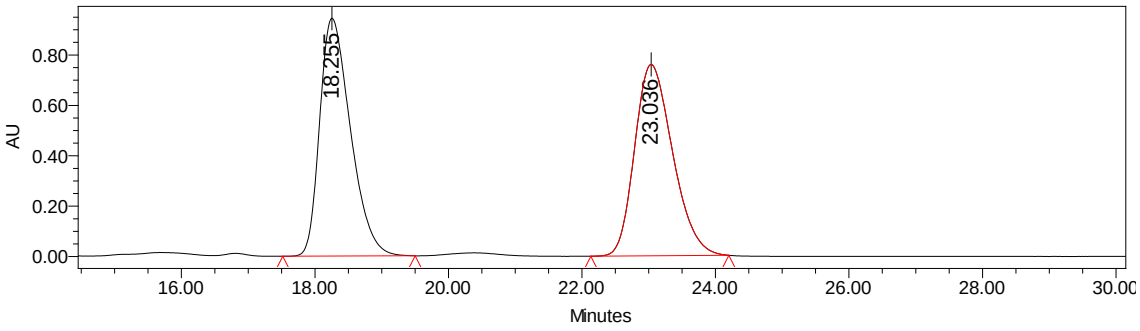


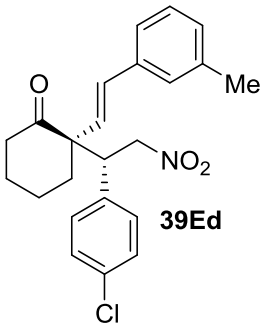
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39Ed**

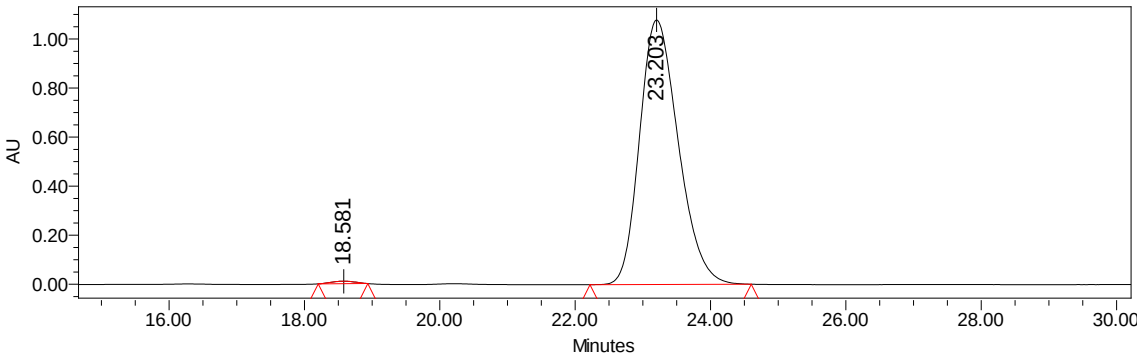
Retention Time	% Area
18.255	50.14
23.036	49.83



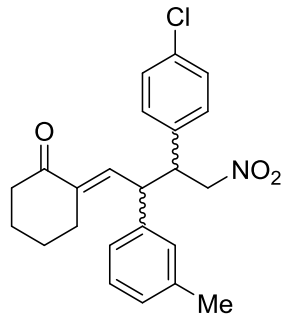


39Ed

Retention Time	% Area
18.581	0.59
23.203	99.41

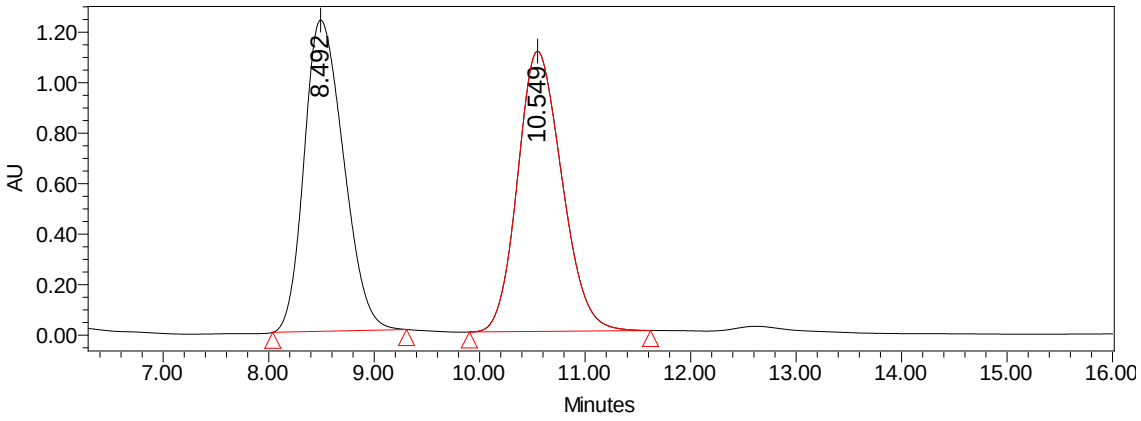


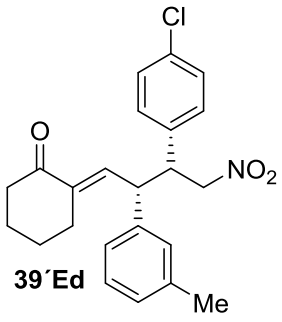
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-39´Ed**

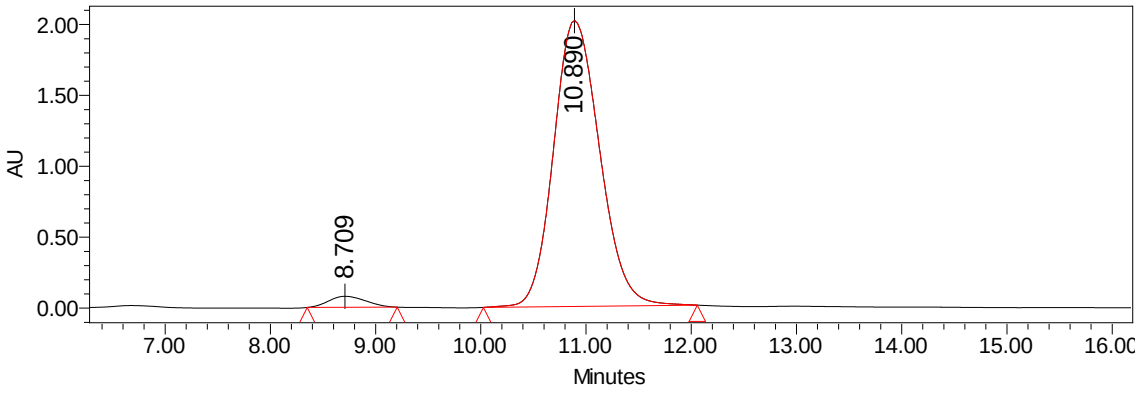
Retention Time	% Area
8.492	49.72
10.549	50.28



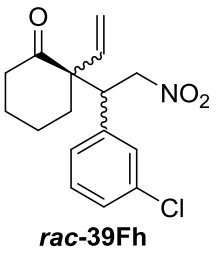


39´Ed

Retention Time	% Area
8.709	3.00
10.890	97.00

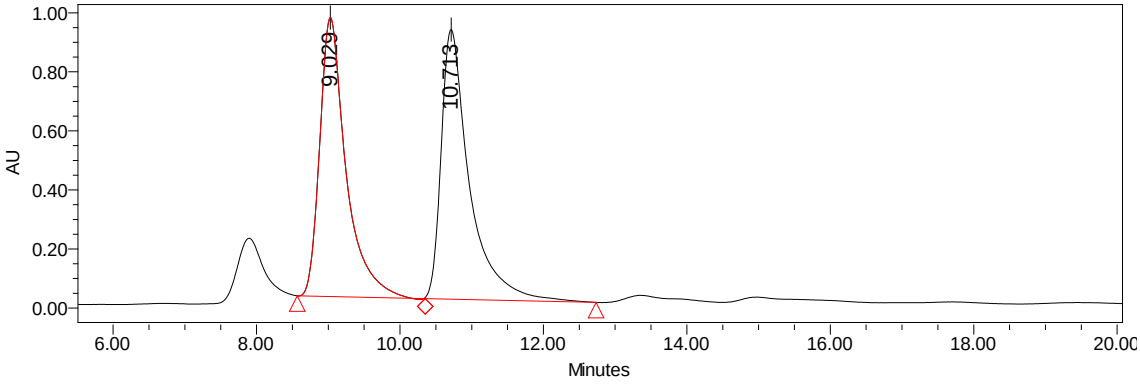


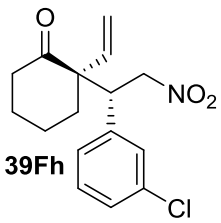
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



***rac*-39Fh**

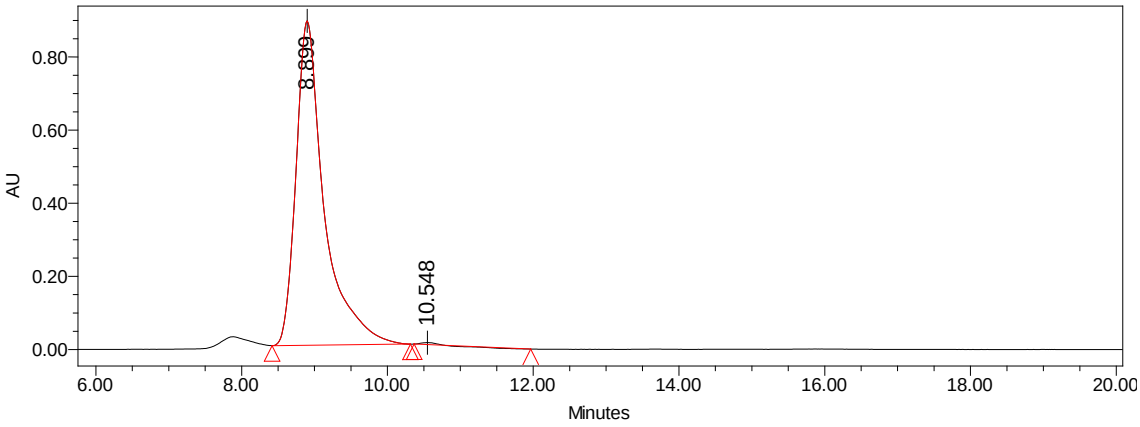
Retention Time	% Area
9.029	49.04
10.713	50.96



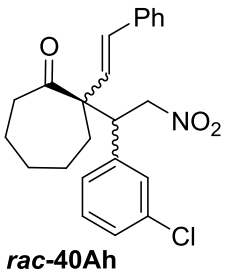


39Fh

Retention Time	% Area
8.899	99.39
10.548	0.61

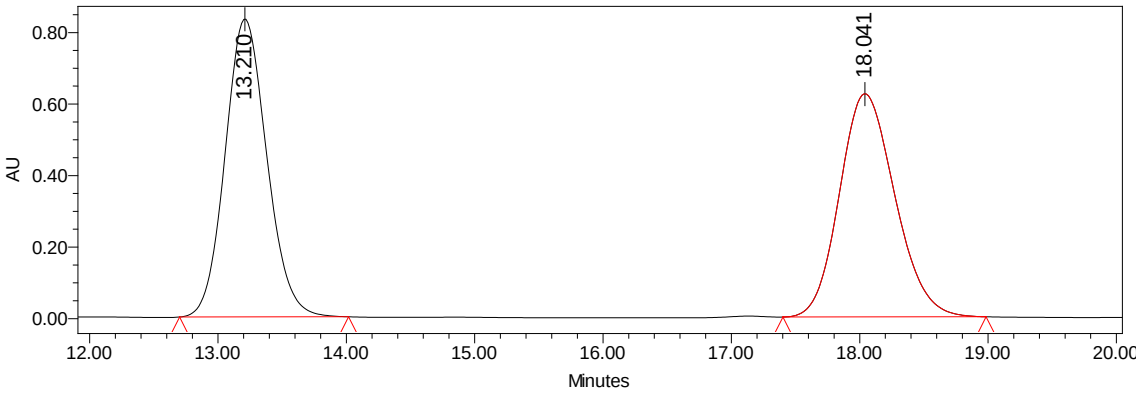


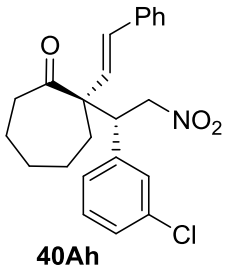
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 250 nm



***rac*-40Ah**

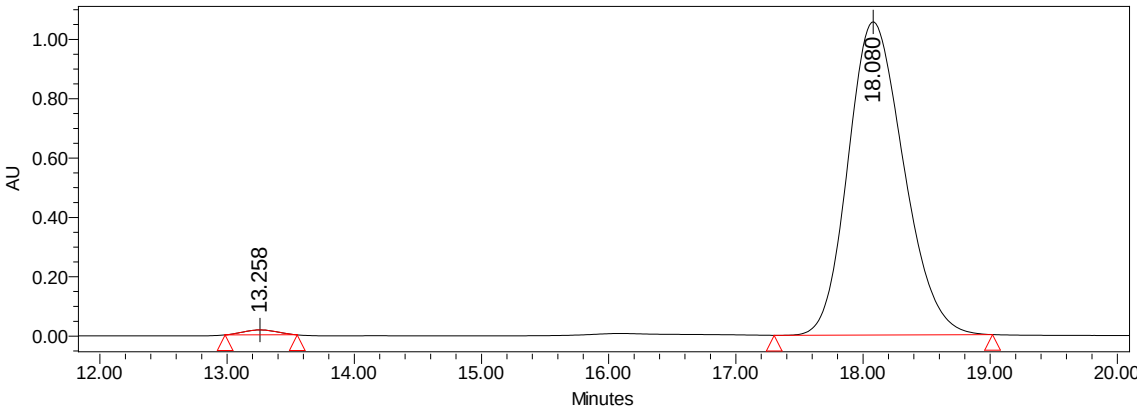
Retention Time	% Area
13.210	50.17
18.041	49.83



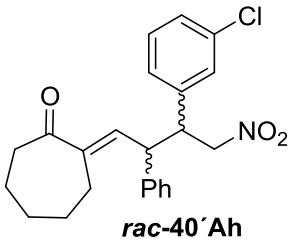


40Ah

Retention Time	% Area
13.258	0.95
18.080	99.05

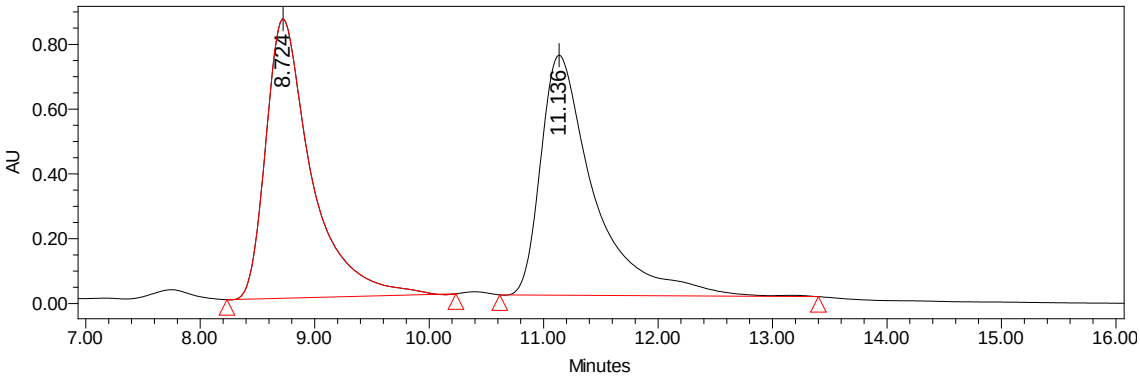


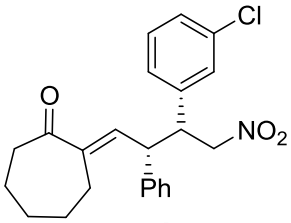
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-40´Ah**

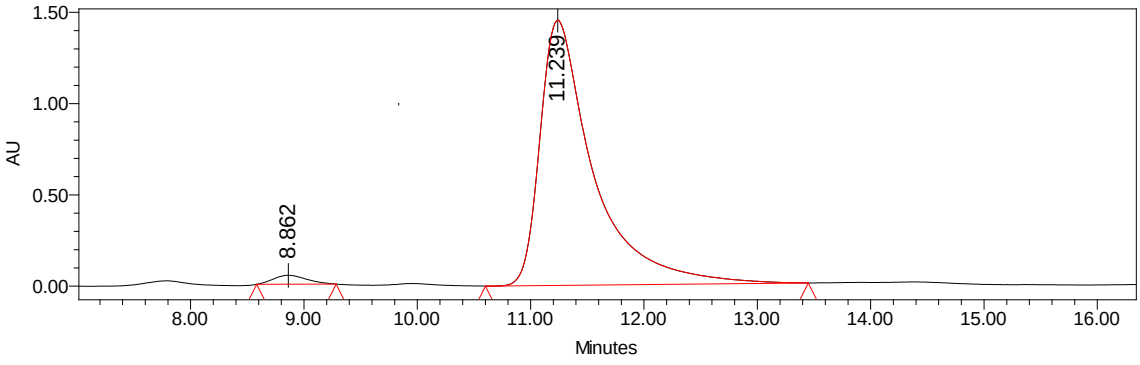
Retention Time	% Area
8.724	49.83
11.136	50.17



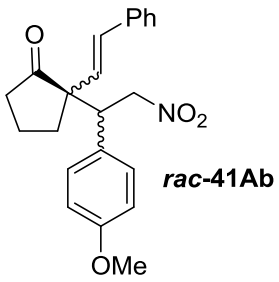


40´Ah

Retention Time	% Area
8.862	2.05
11.239	97.95

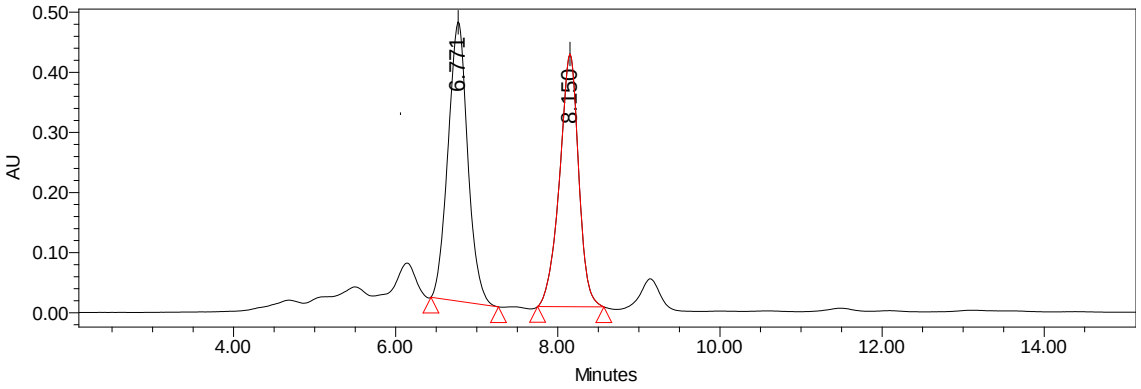


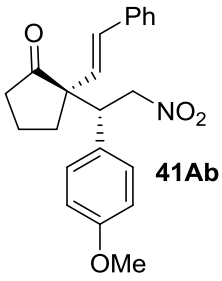
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 210 nm



***rac*-41Ab**

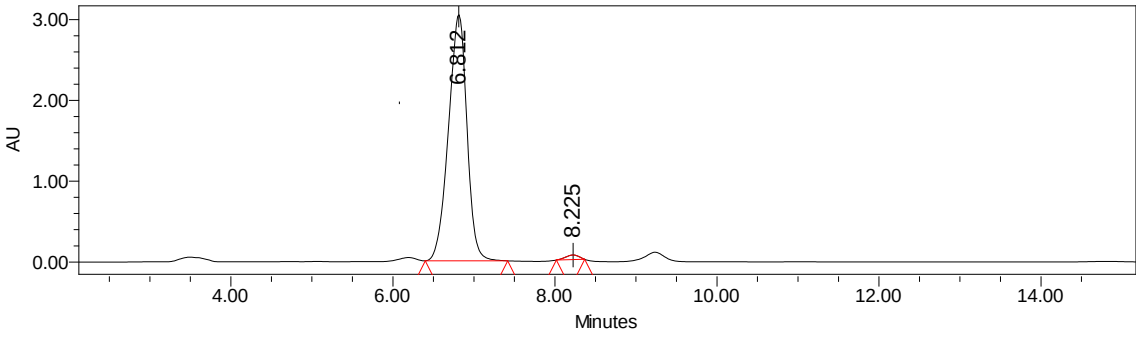
Retention Time	% Area
6.771	52.50
8.150	49.83



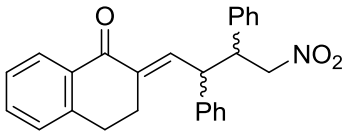


41Ab

Retention Time	% Area
6.812	98.67
8.225	1.33

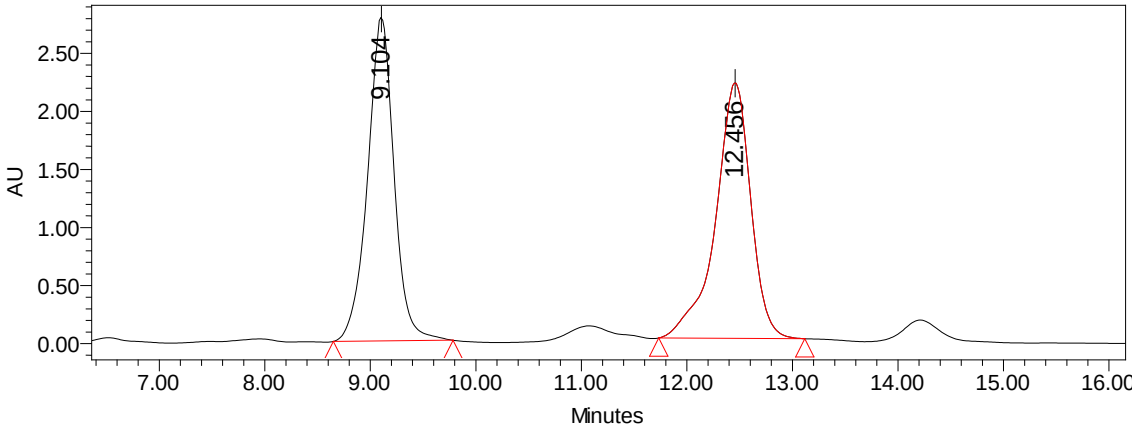


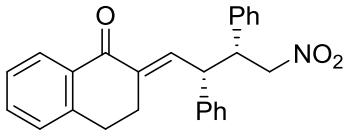
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 250 nm



***rac*-42´Aa**

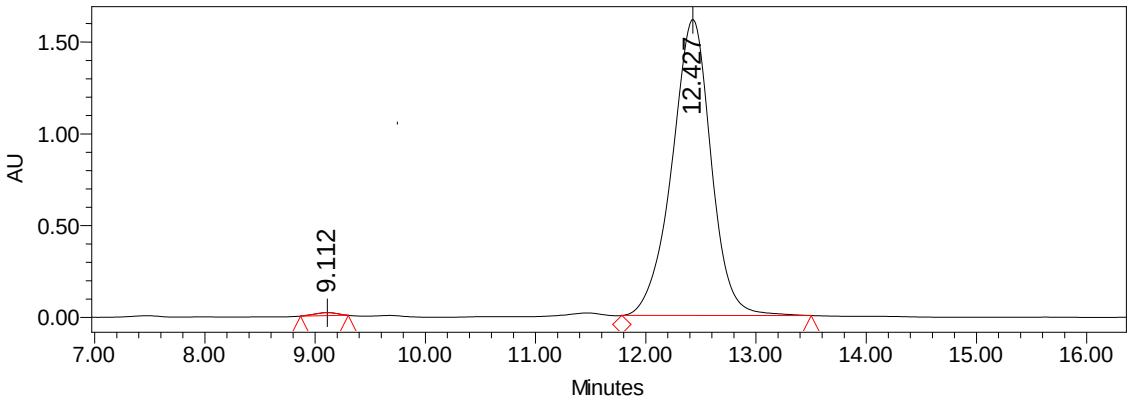
Retention Time	% Area
9.104	48.73
12.456	51.27



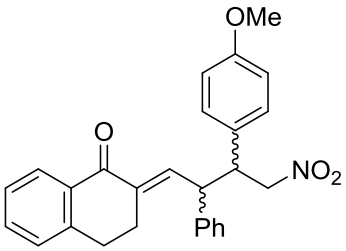


42´Aa

Retention Time	% Area
9.112	0.59
12.427	99.41

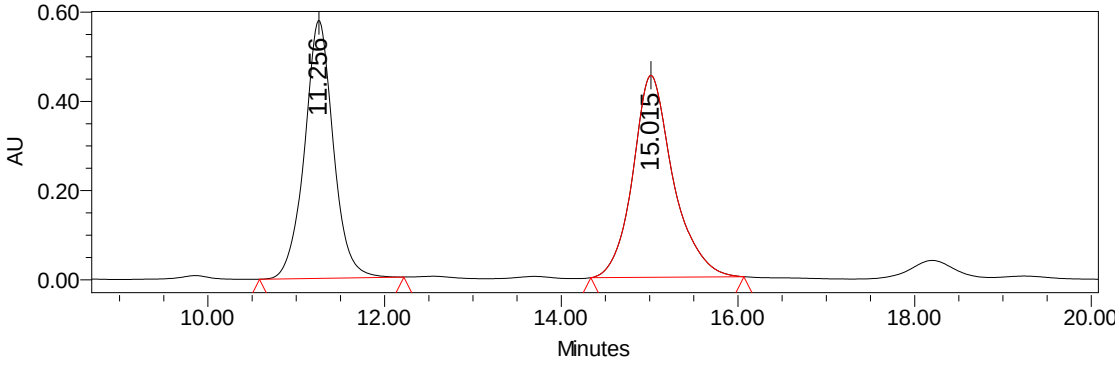


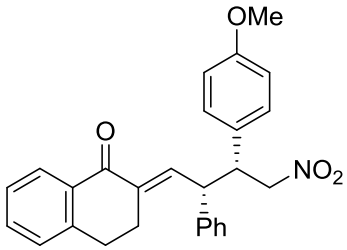
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 280 nm



***rac*-42´Ab**

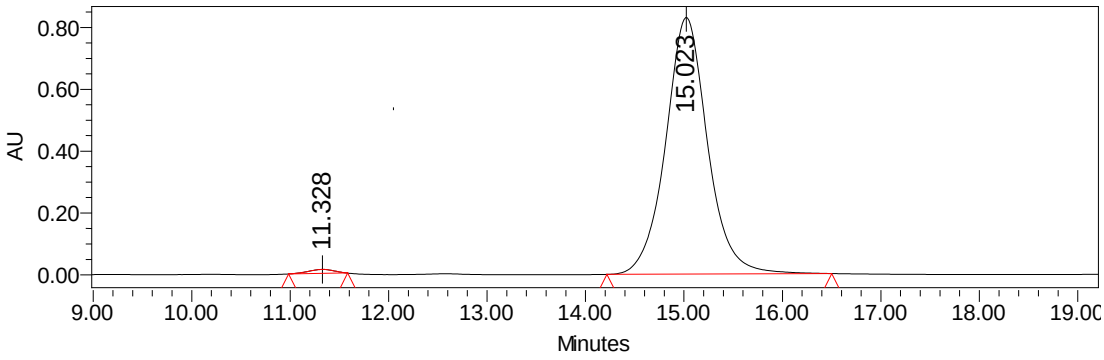
Retention Time	% Area
11.256	47.66
15.015	52.345



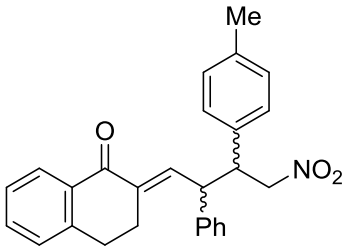


42´Ab

Retention Time	% Area
11.328	0.97
15.023	99.03

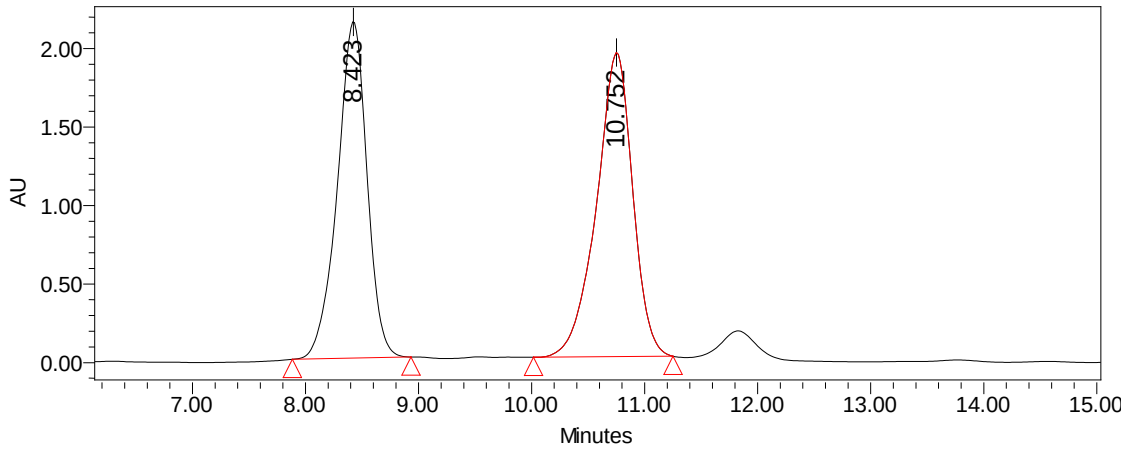


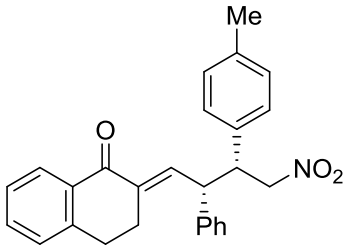
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 280 nm



***rac*-42´Ac**

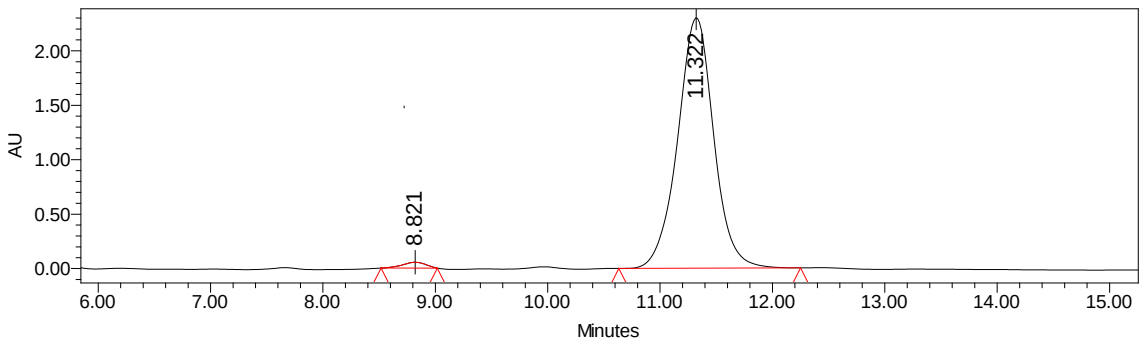
Retention Time	% Area
8.432	47.55
10.752	52.45



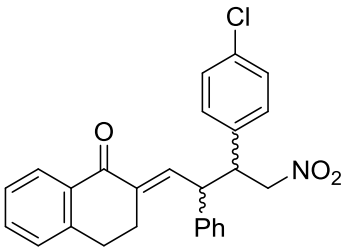


42´Ac

Retention Time	% Area
8.821	1.48
11.322	98.52

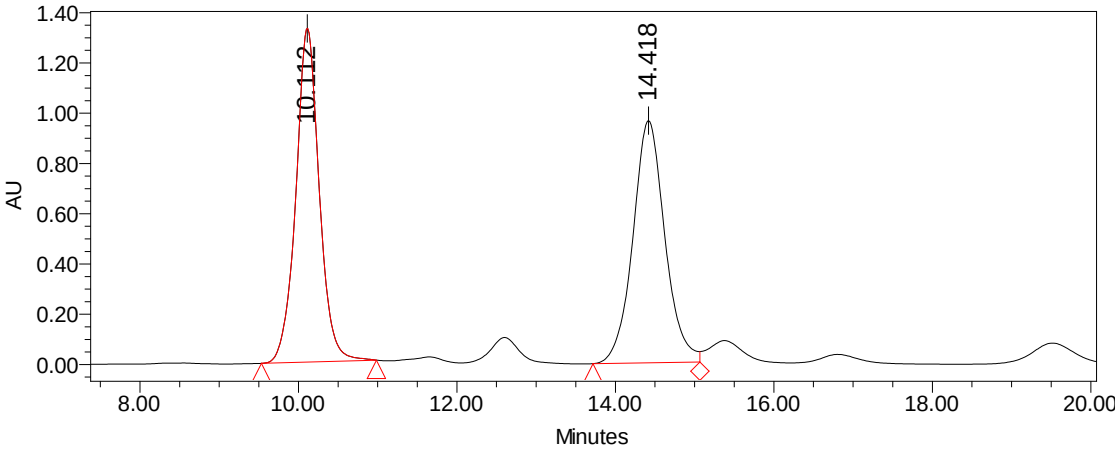


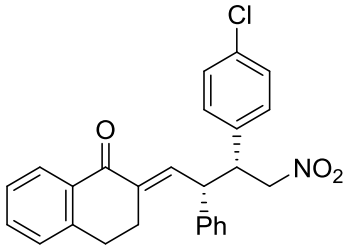
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 270 nm



***rac*-42´Ad**

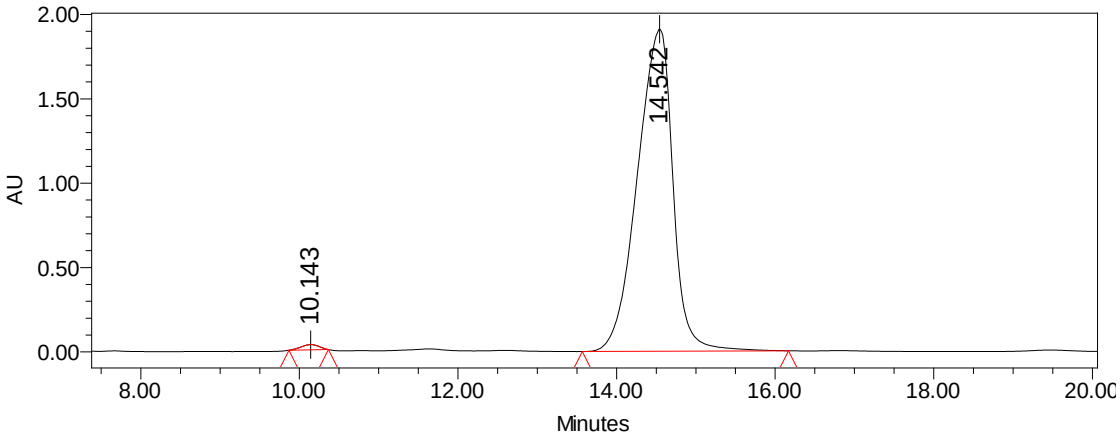
Retention Time	% Area
10.112	50.15
14.418	49.85



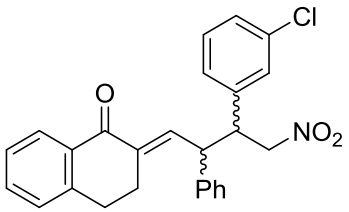


42´Ad

Retention Time	% Area
10.143	0.83
14.542	99.17

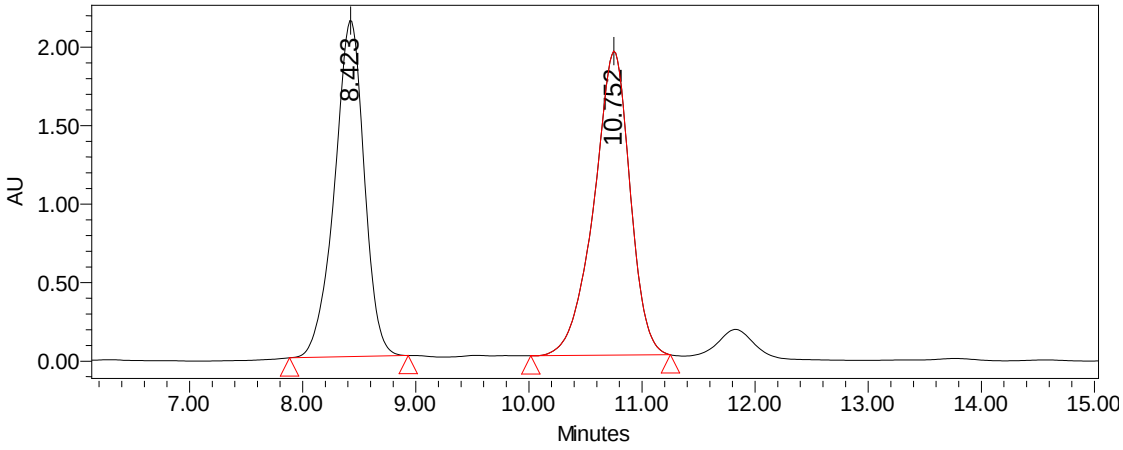


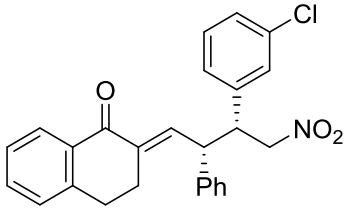
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 280 nm



***rac*-42´Ah**

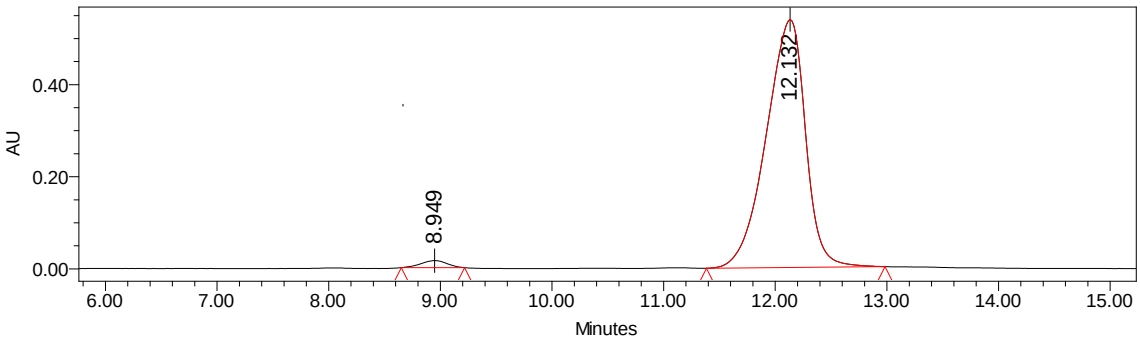
Retention Time	% Area
8.423	50.14
10.752	49.86



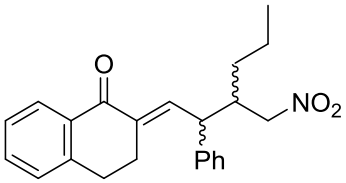


42´Ah

Retention Time	% Area
8.949	1.68
12.132	98.14

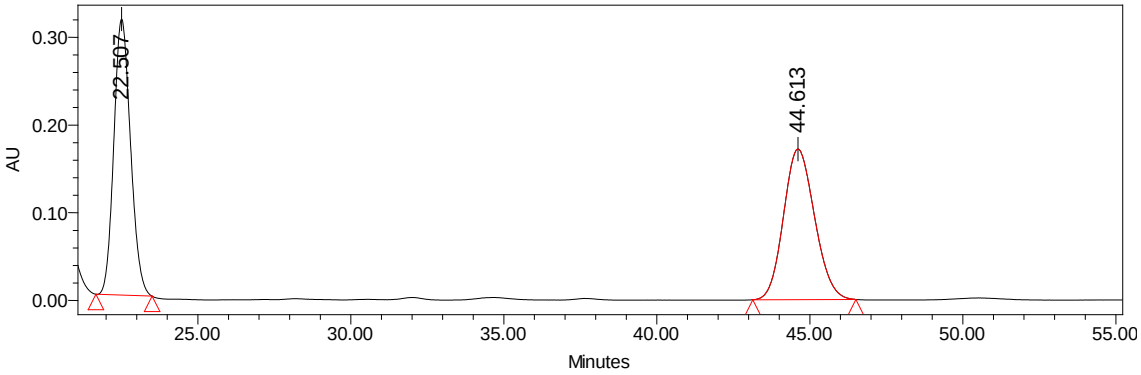


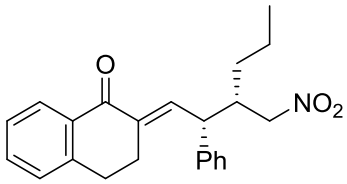
Chiralpack IC, 1 mL/min, hexane/isopropanol 95:5, λ = 265 nm



***rac*-42´Al**

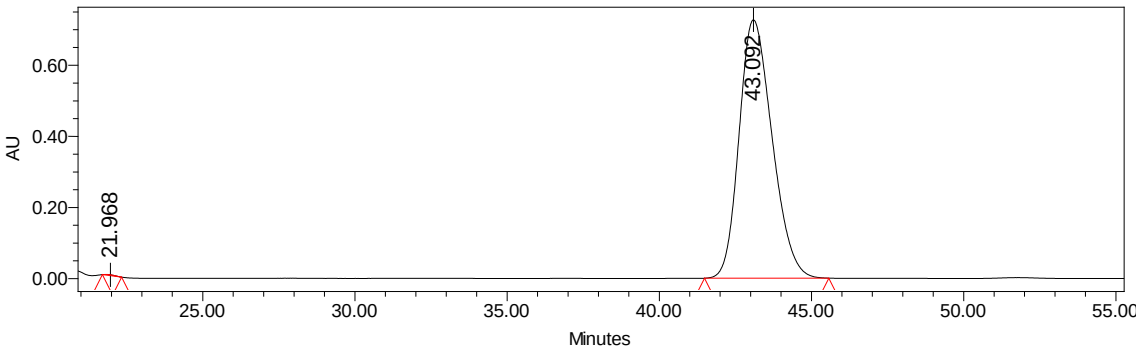
Retention Time	% Area
22.507	49.69
44.613	50.31



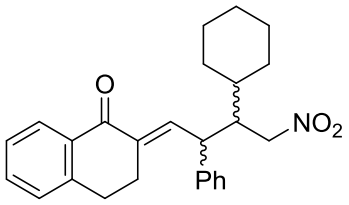


42´Al

Retention Time	% Area
21.968	0.10
43.092	99.90

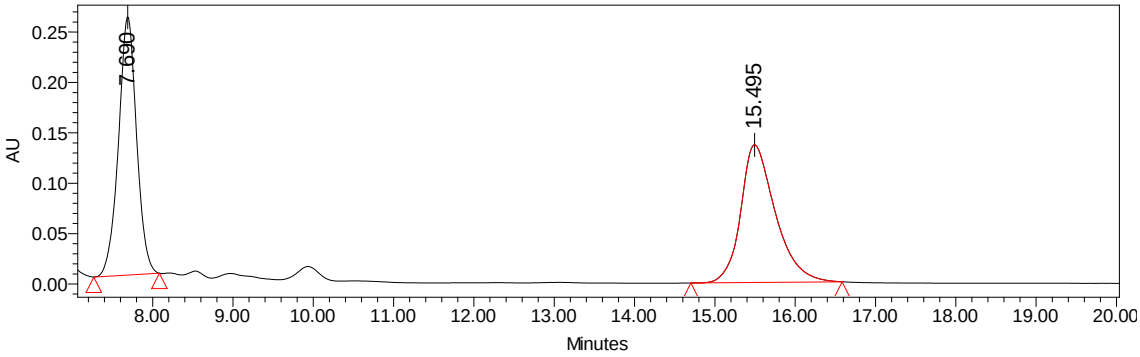


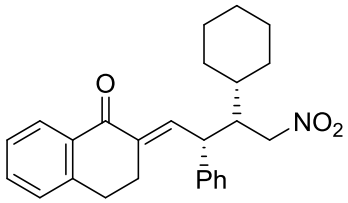
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 280 nm



***rac*-42´An**

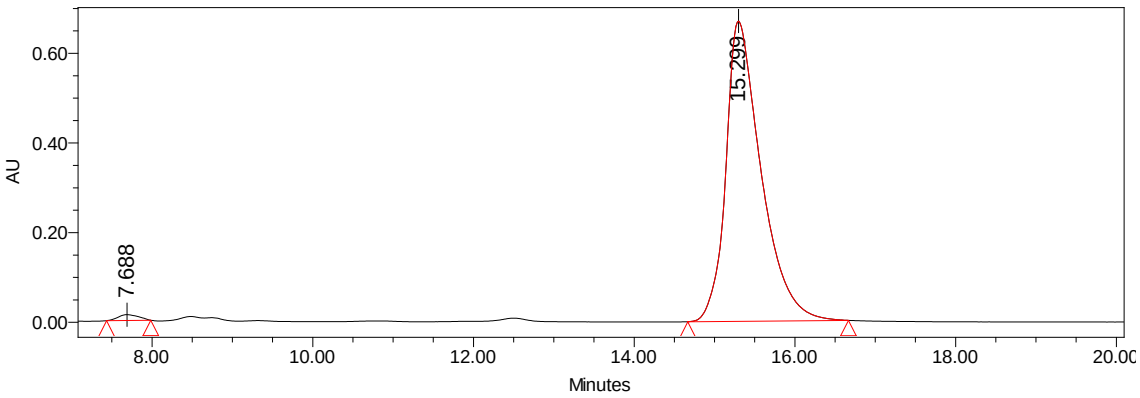
Retention Time	% Area
7.690	49.51
15.495	50.49



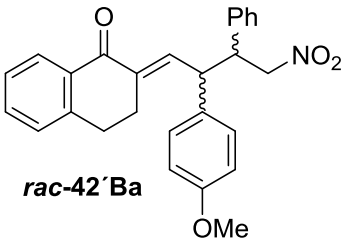


42´An

Retention Time	% Area
7.688	1.11
15.293	98.89

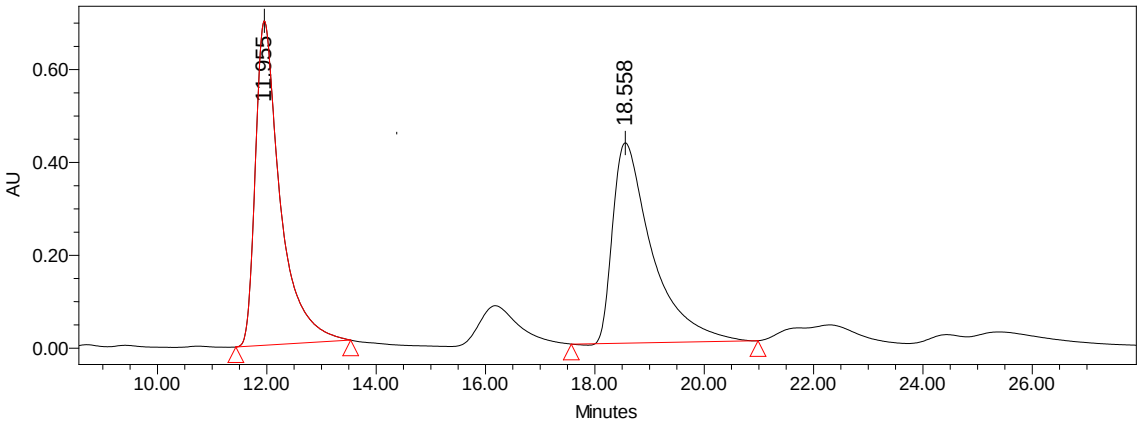


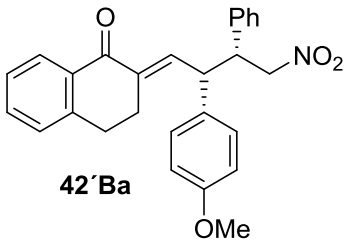
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 250 nm



***rac*-42´Ba**

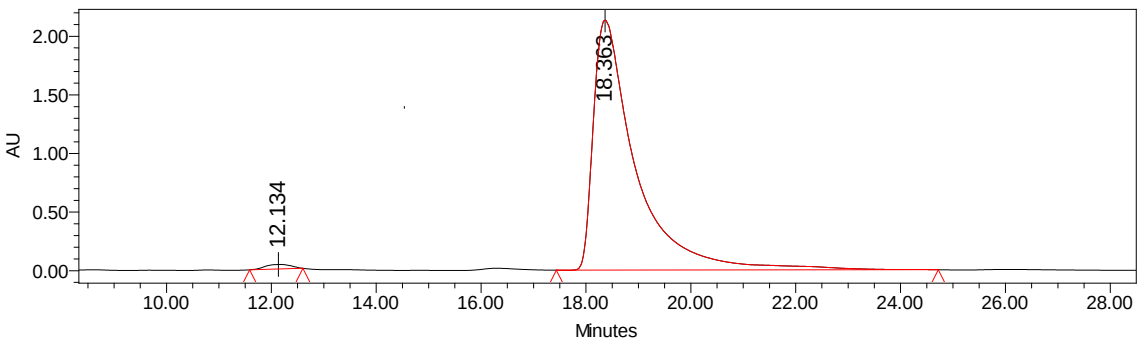
Retention Time	% Area
11.955	50.46
18.558	49.54



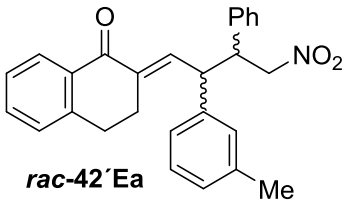


42´Ba

Retention Time	% Area
12.134	1.09
18.363	98.91

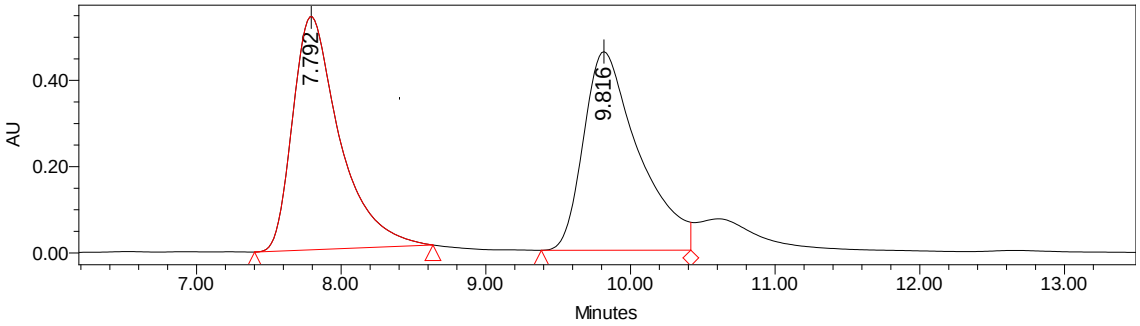


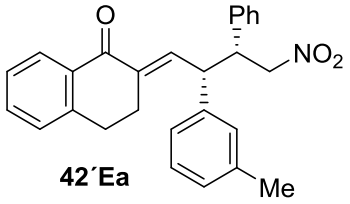
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 250 nm



***rac*-42´Ea**

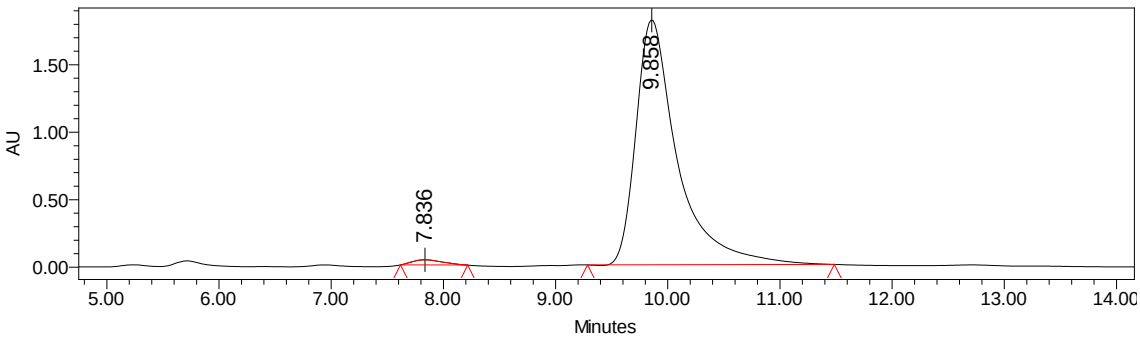
Retention Time	% Area
7.792	50.02
9.816	49.98



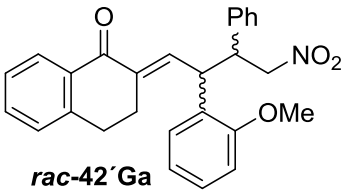


42´Ea

Retention Time	% Area
7.836	1.56
9.858	98.44

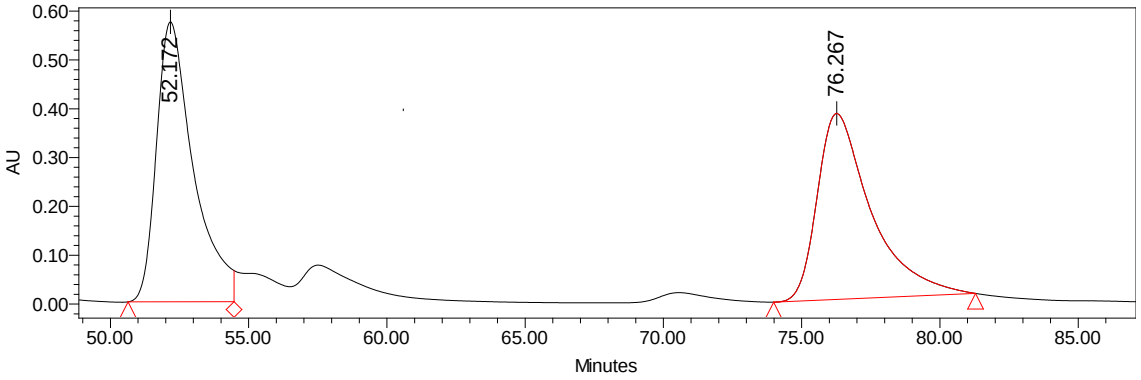


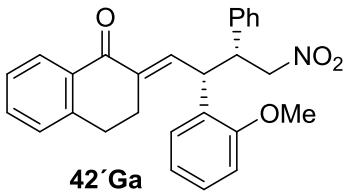
Chiralpack IA - IA, 1 mL/min, hexane/isopropanol 95:5, λ = 250 nm



***rac*-42´Ga**

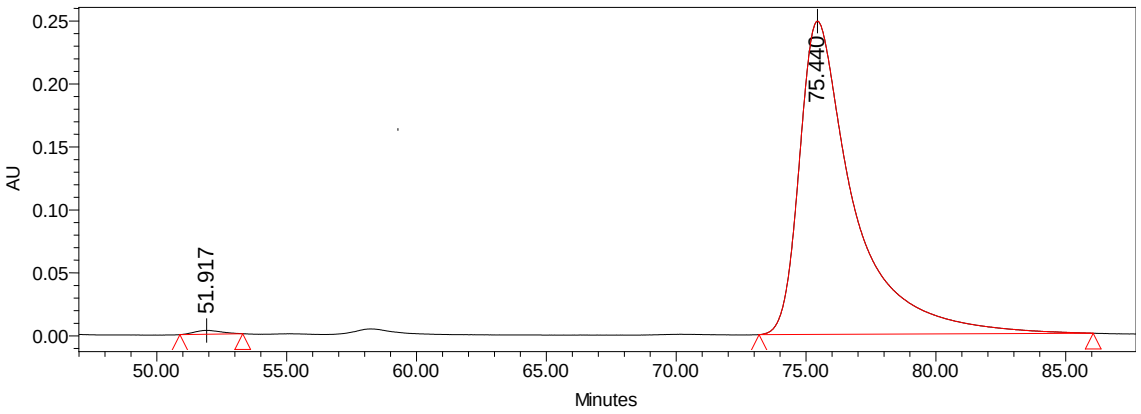
Retention Time	% Area
52.172	50.78
76.267	49.22



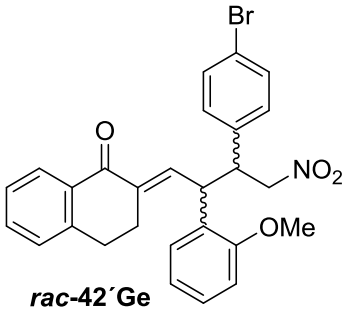


42´Ga

Retention Time	% Area
51.917	0.60
75.440	99.40

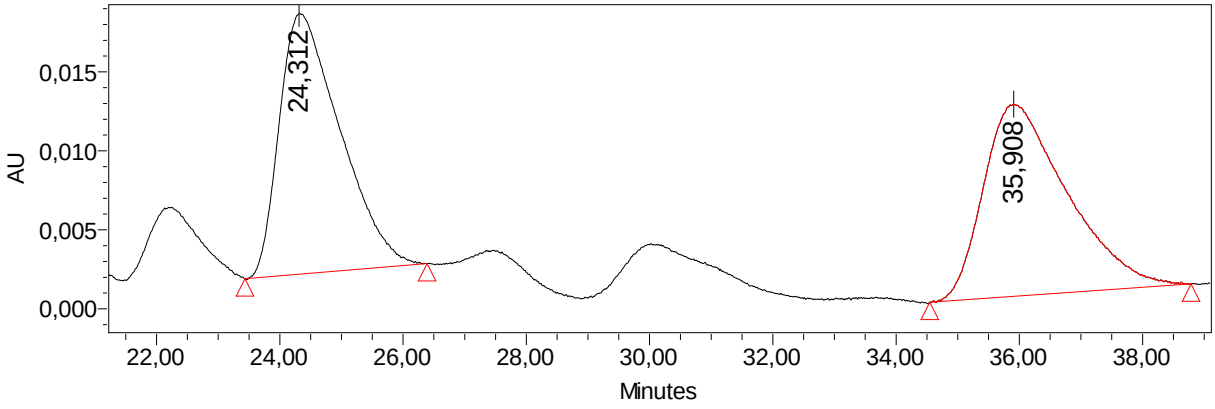


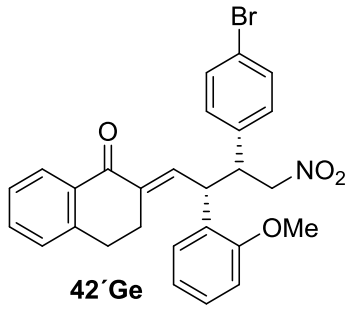
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 250 nm



***rac*-42´Ge**

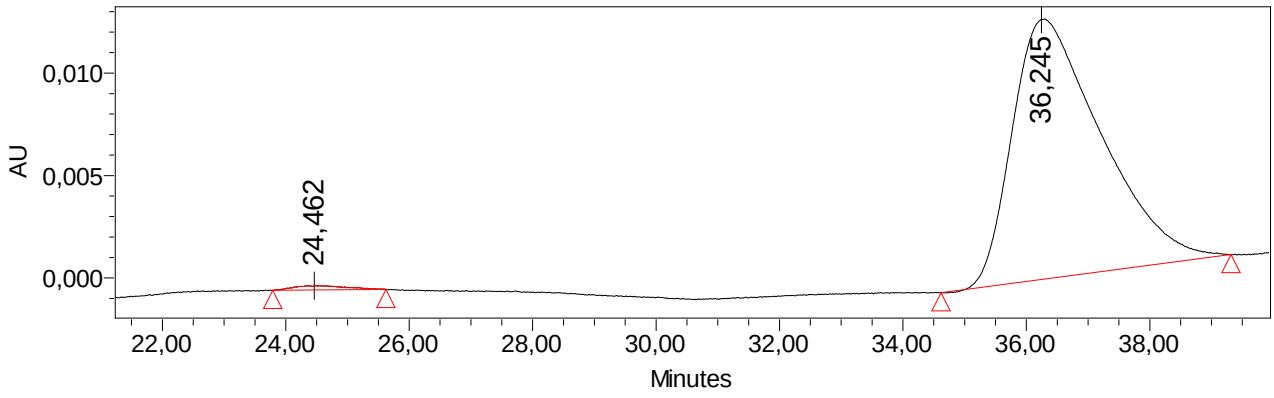
Retention Time	% Area
24.312	49.97
35.908	50.03



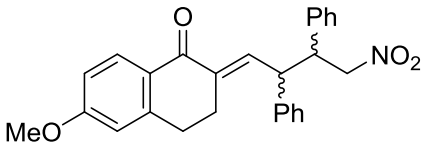


42´Ge

Retention Time	% Area
24.462	0.95
36.245	99.05

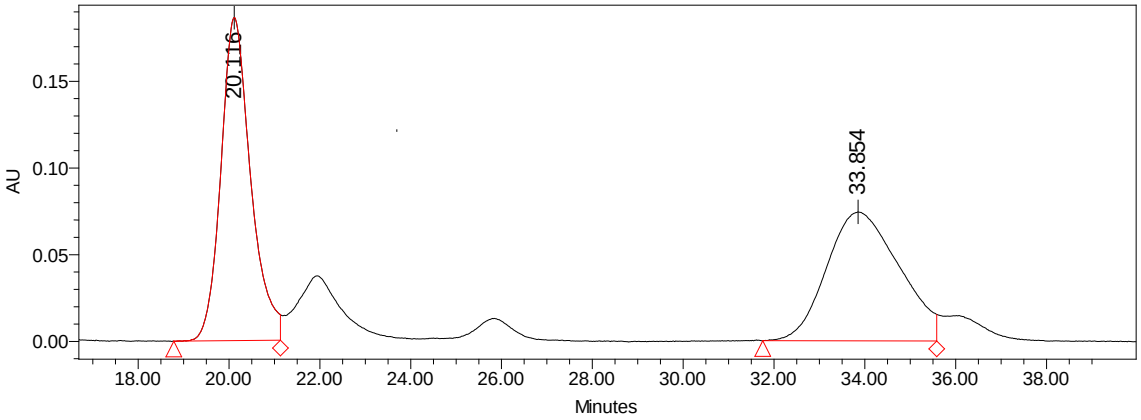


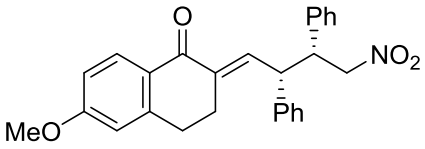
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 333 nm



***rac*-43´Aa**

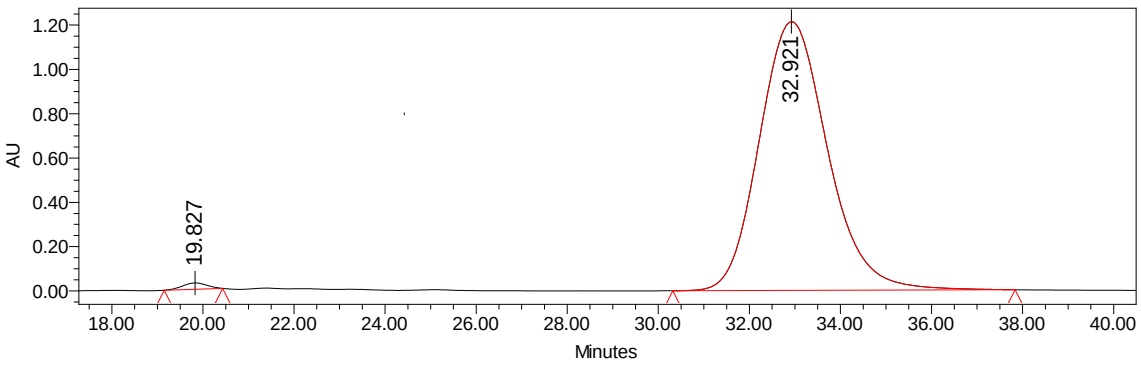
Retention Time	% Area
20.116	50.77
33.854	49.23



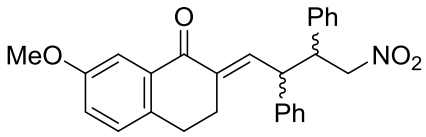


43´Aa

Retention Time	% Area
19.827	0.61
32.921	99.39

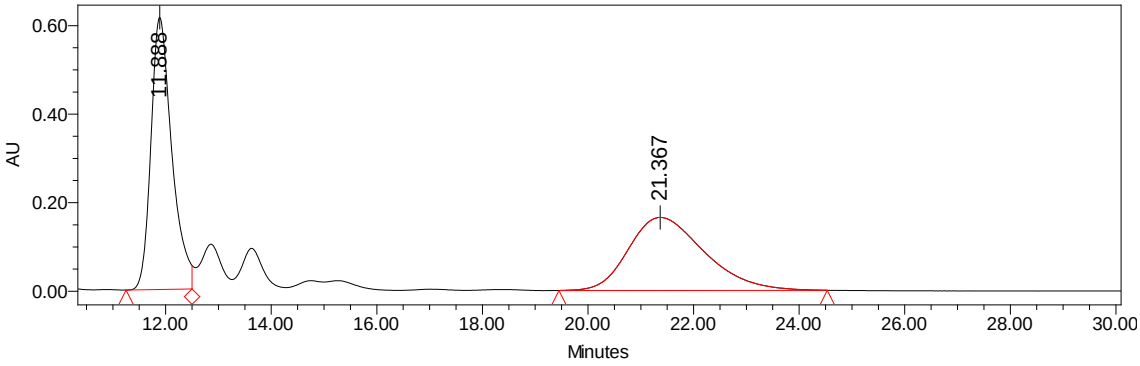


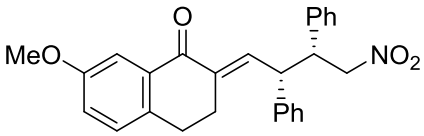
Chiralpack IA, 1 mL/min, hexane/isopropanol 80:20, λ = 250 nm



***rac*-44´Aa**

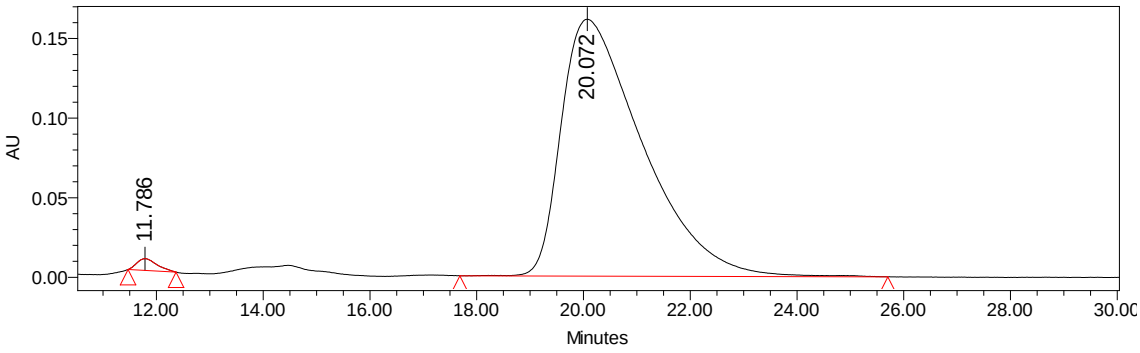
Retention Time	% Area
11.888	50.68
21.367	49.32



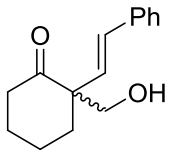


44´Aa

Retention Time	% Area
11.786	1.14
20.072	98.86

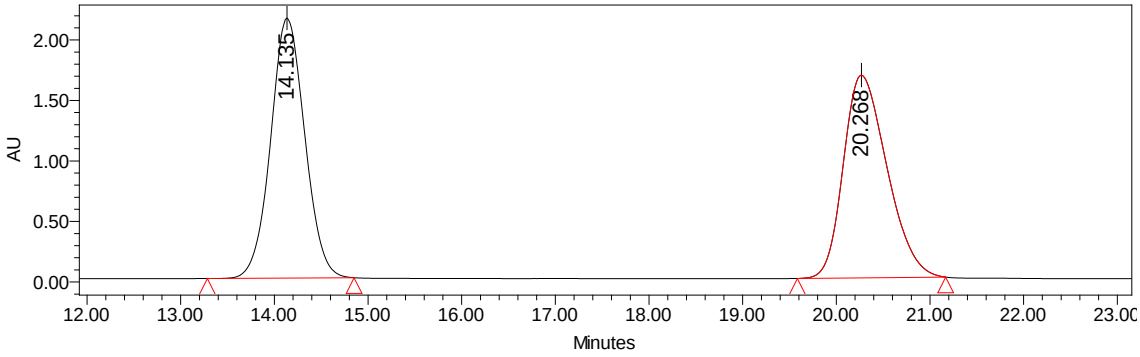


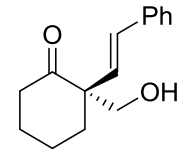
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-46A**

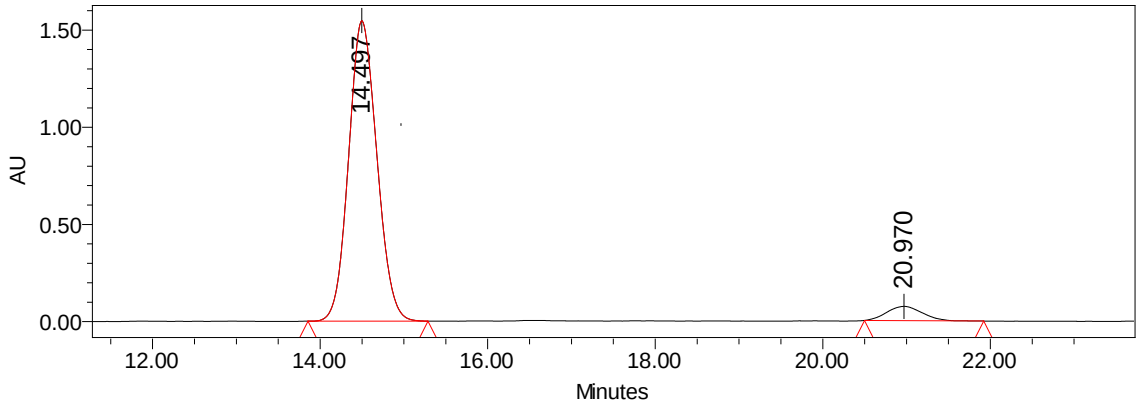
Retention Time	% Area
14,135	50,13
20,268	49,87



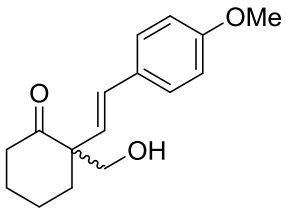


46A

Retention Time	% Area
14,497	94,40
20,970	5,60

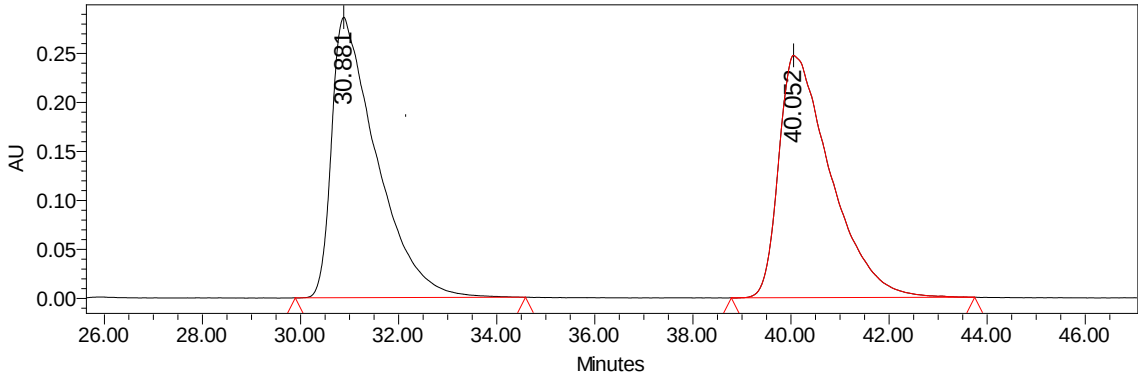


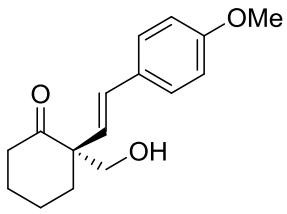
Chiralpack ID, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-46B**

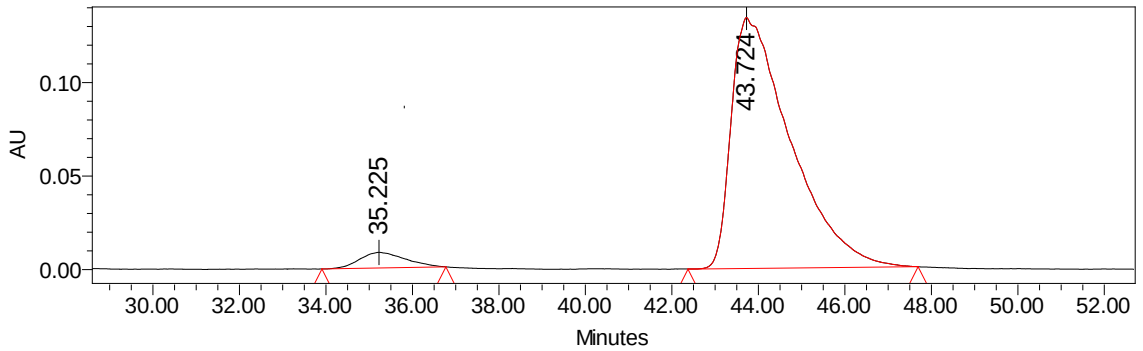
Retention Time	% Area
30,881	50,07
40,052	49,93



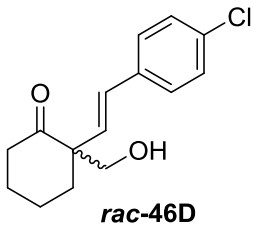


46B

Retention Time	% Area
35,225	4,54
43,724	95,46

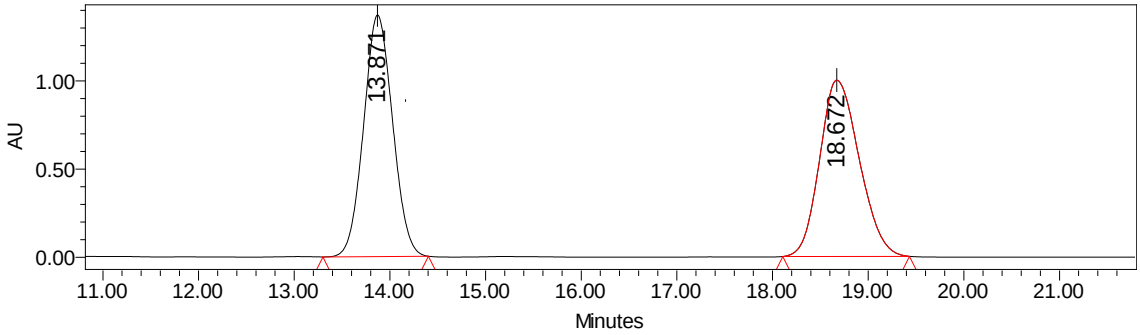


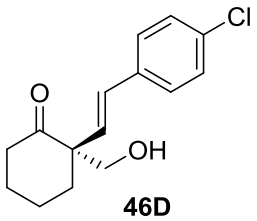
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-46D**

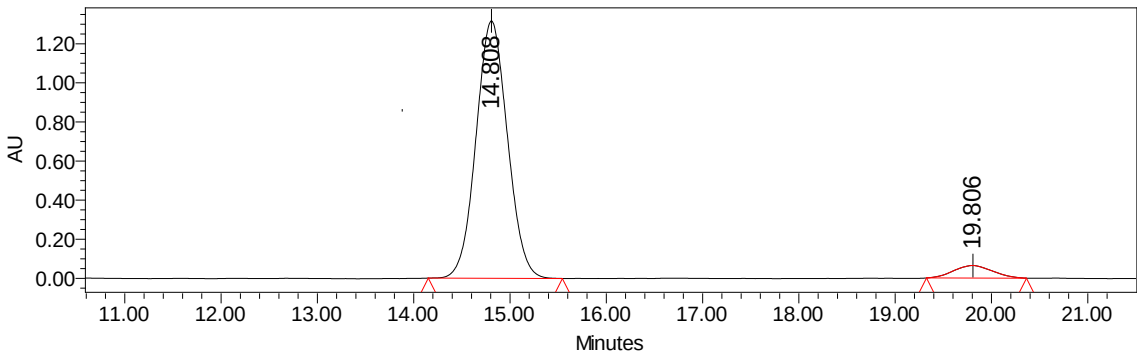
Retention Time	% Area
13,871	50,08
18,672	49,92



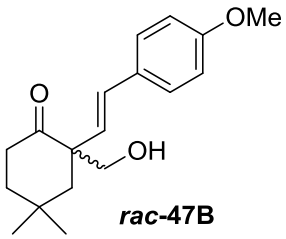


46D

Retention Time	% Area
14,808	94,31
19,806	5,69

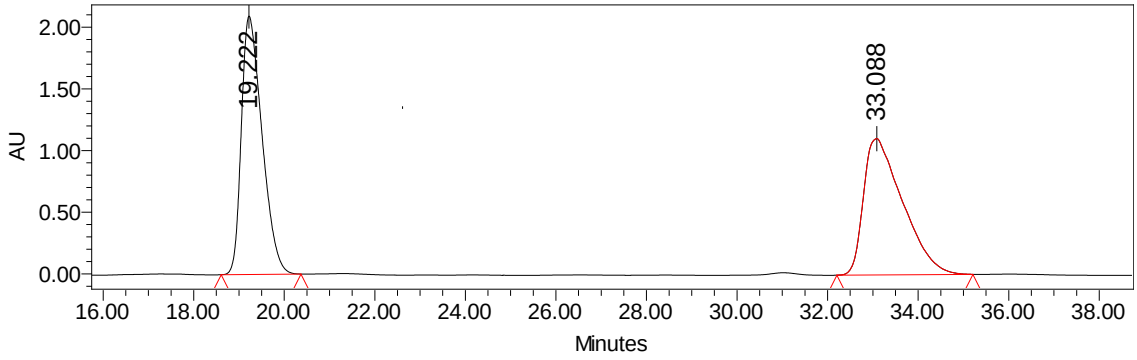


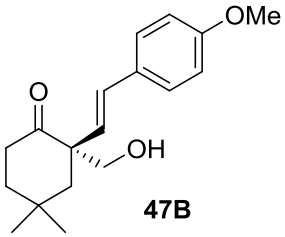
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-47B**

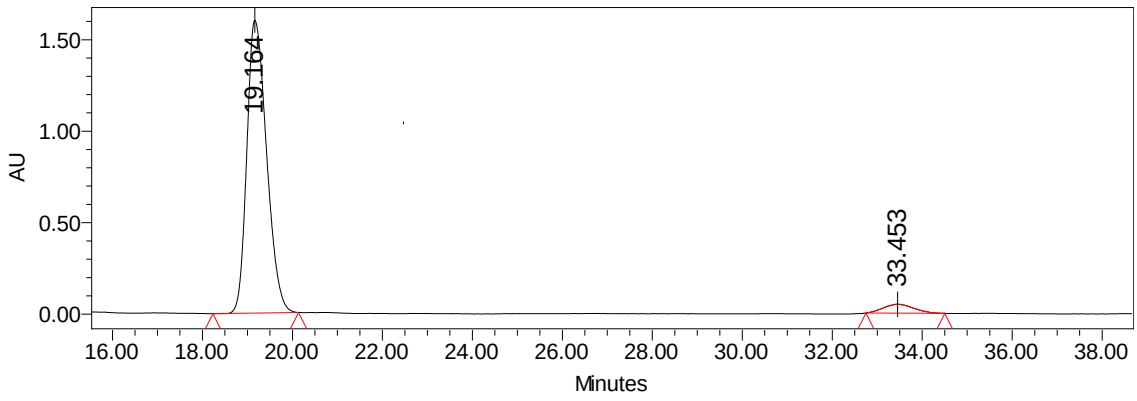
Retention Time	% Area
19,222	50,07
33,088	49,93



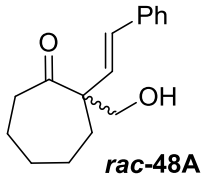


47B

Retention Time	% Area
19,164	95,54
33,453	4,46

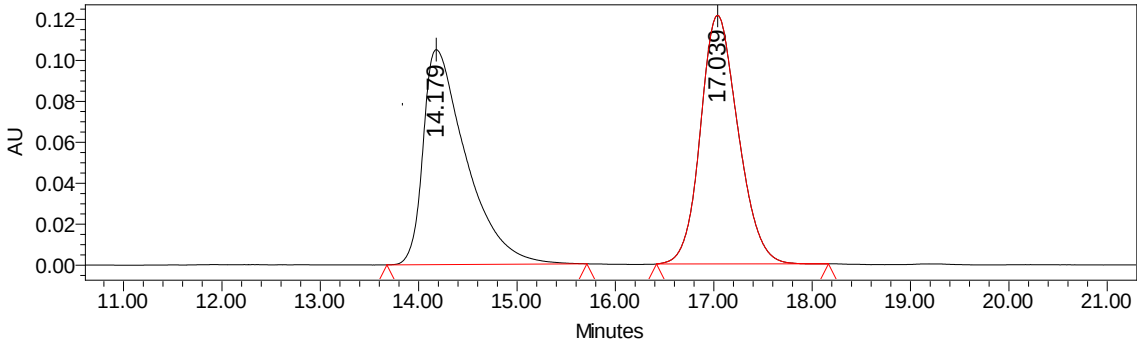


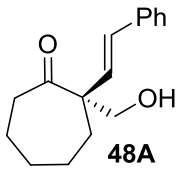
Chiralpack ID, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-48A**

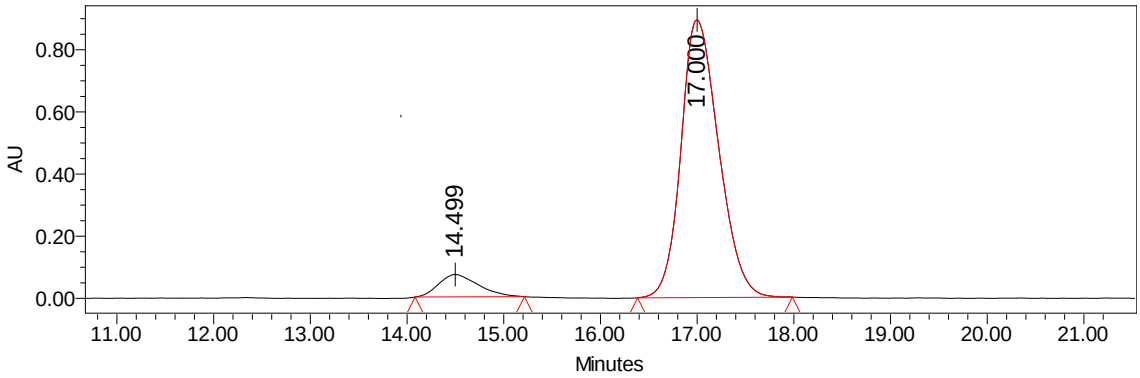
Retention Time	% Area
14,179	49,71
17,039	50,29



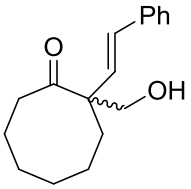


48A

Retention Time	% Area
14,499	7,79
17,000	92,21

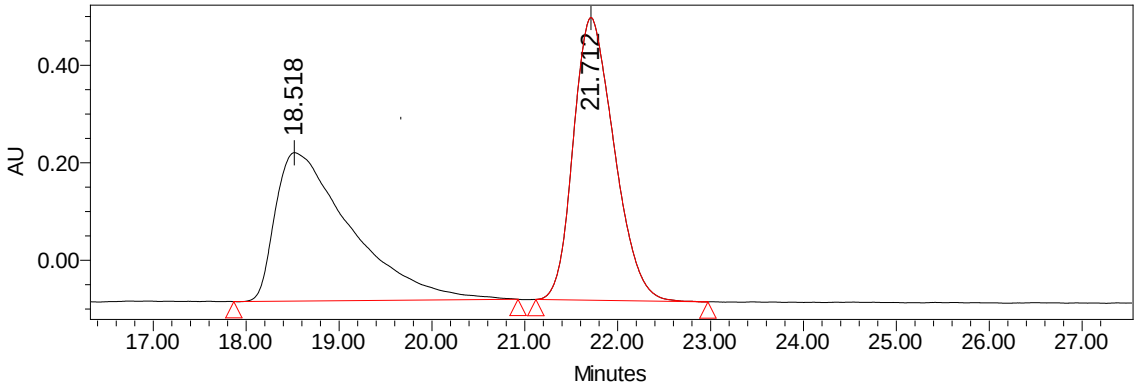


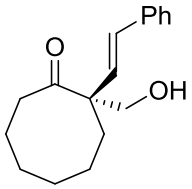
Chiralpack ID, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-49A**

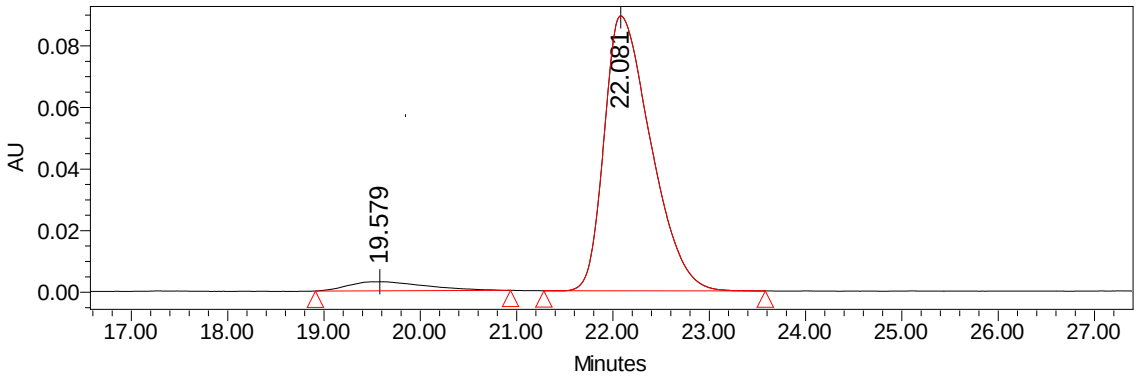
Retention Time	% Area
18,518	49,32
21,172	50,68



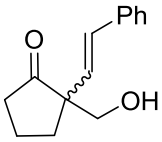


49A

Retention Time	% Area
19,579	5,15
22,081	94,85

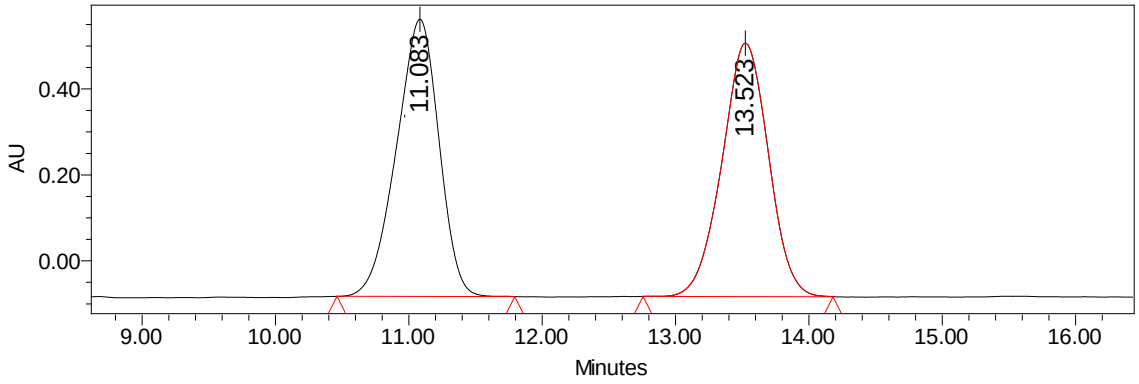


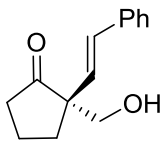
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-50A**

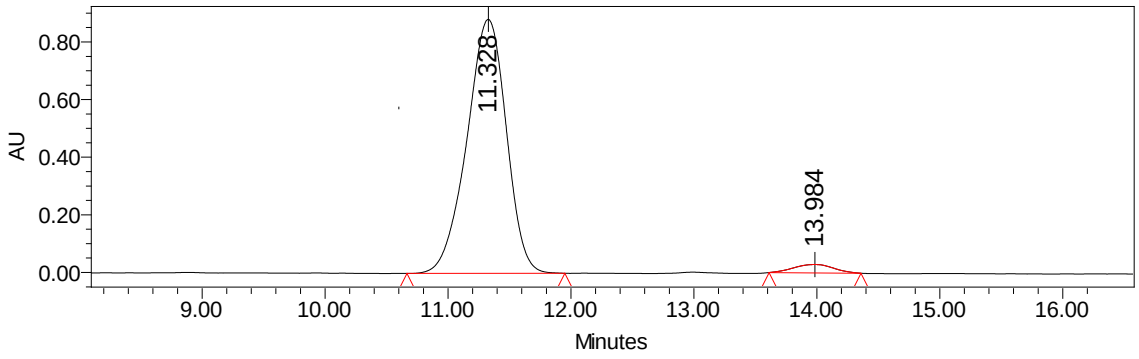
Retention Time	% Area
11,083	50,02
13,523	49,98



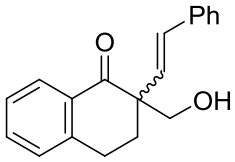


50A

Retention Time	% Area
11,328	96,79
13,984	3,21

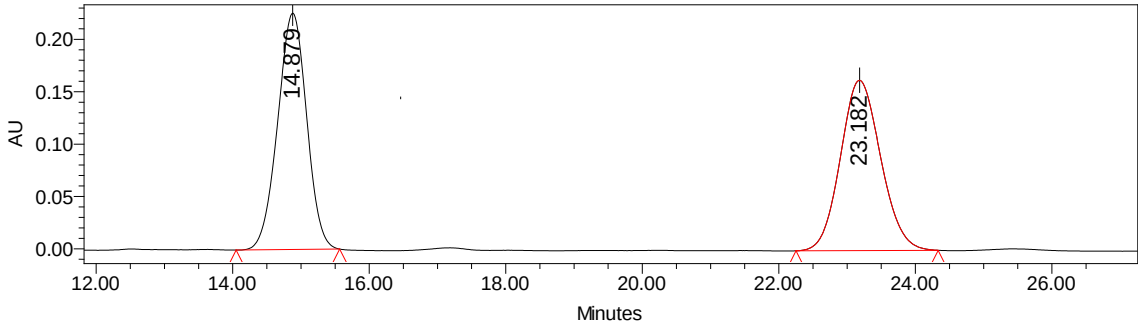


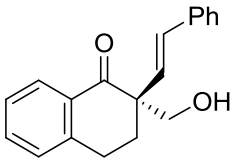
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-51A**

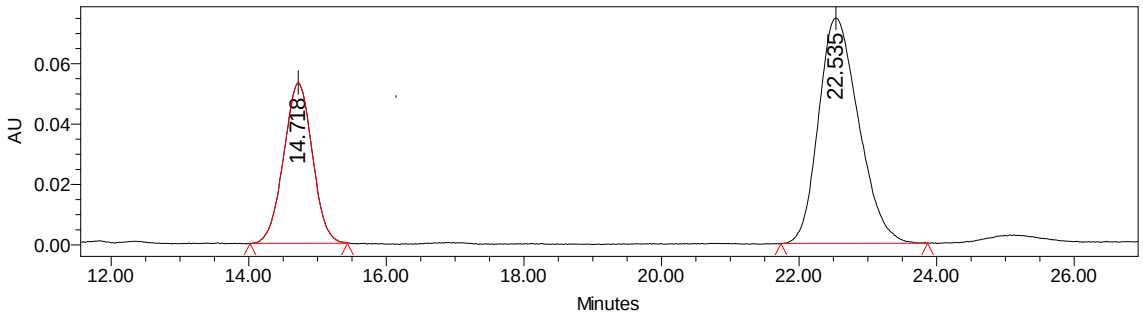
Retention Time	% Area
14.879	50,11
23.182	49,39



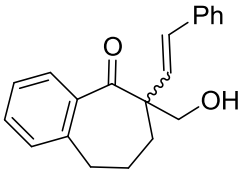


51A

Retention Time	% Area
14.718	33.76
22.535	66.24

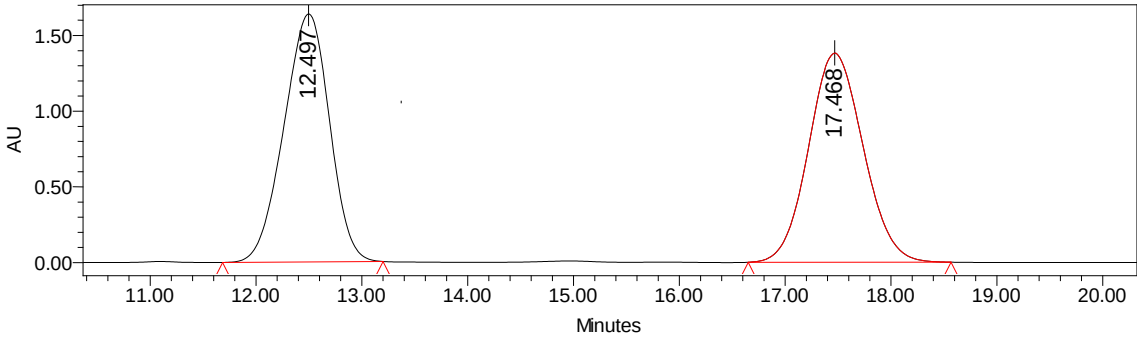


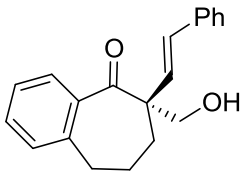
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



***rac*-52A**

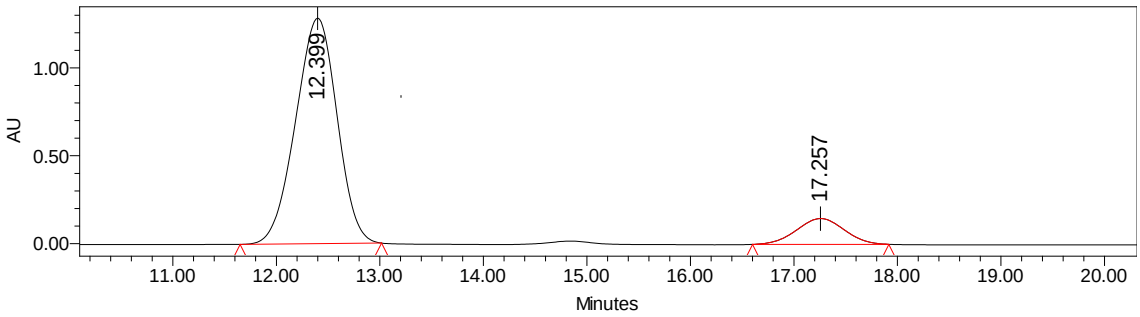
Retention Time	% Area
12.497	49.76
17.468	50.24





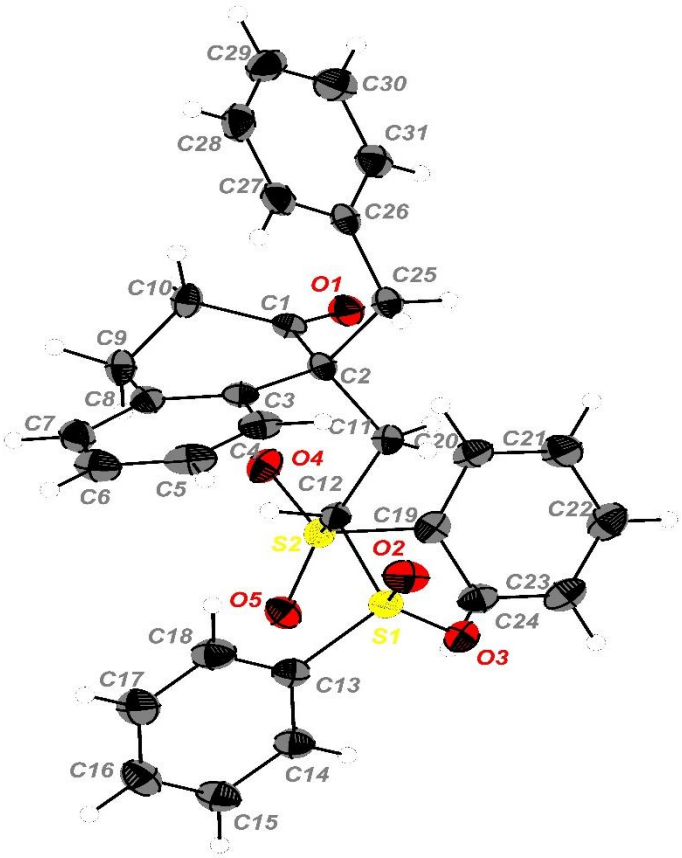
52A

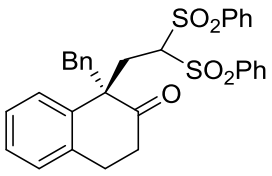
Retention Time	% Area
12.399	88.36
17.257	11.64



5.7. X-Ray Analysis

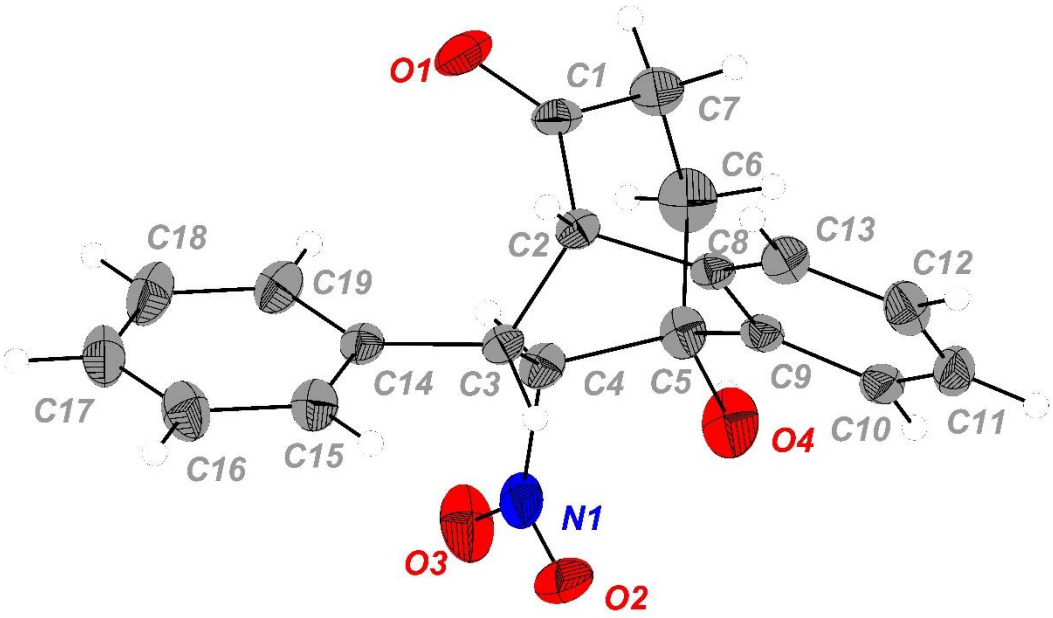
5.7.1. ORTEP diagram of compound 5A

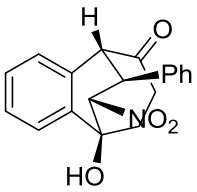




5A

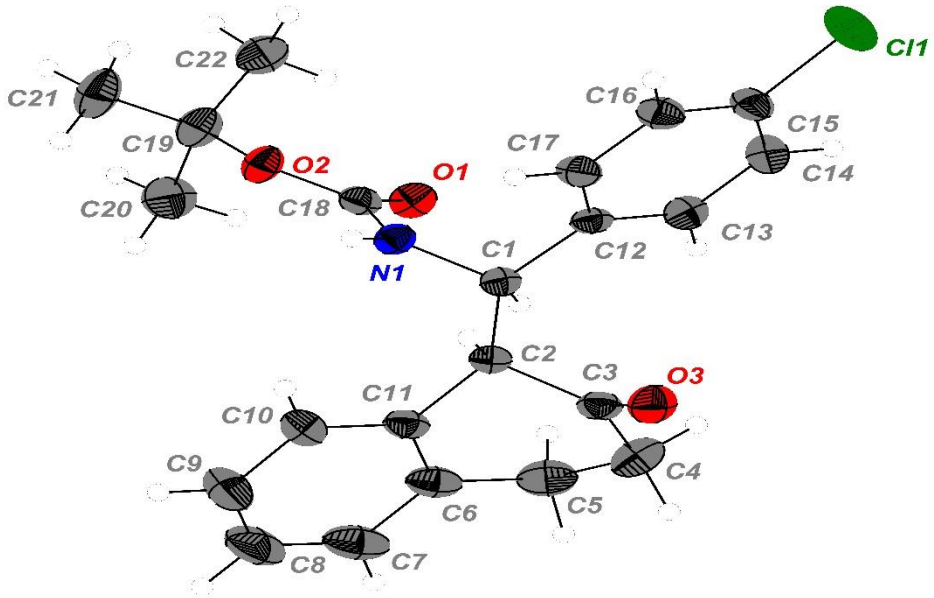
5.7.2. ORTEP diagram of compound 8Da

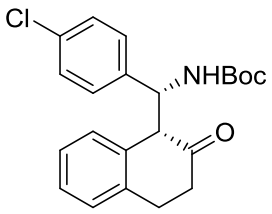




8Da

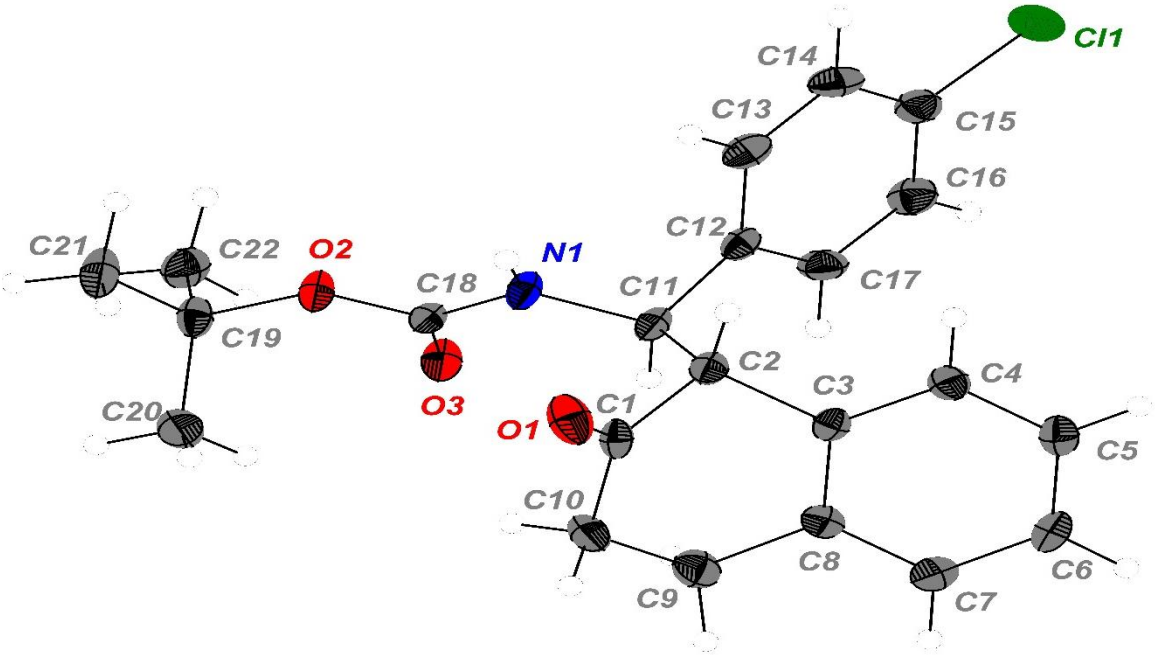
5.7.3. ORTEP diagram of compound (*R*,*R*)-10Ad

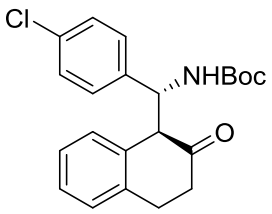




(*R*,*R*)-10Ad

5.7.4. ORTEP diagram of compound (*S*,*R*)-10Ad

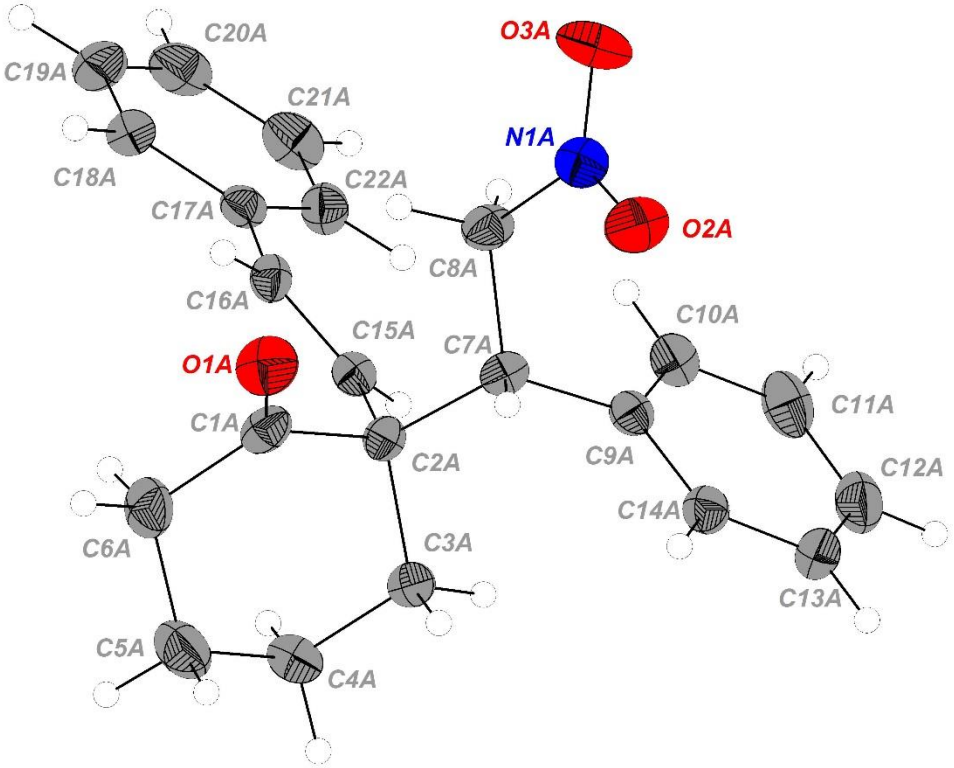


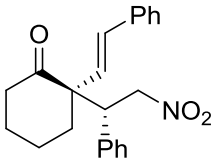


(*S*,*R*)-10Ad

5.7.5. ORTEP diagram of compound 39Aa

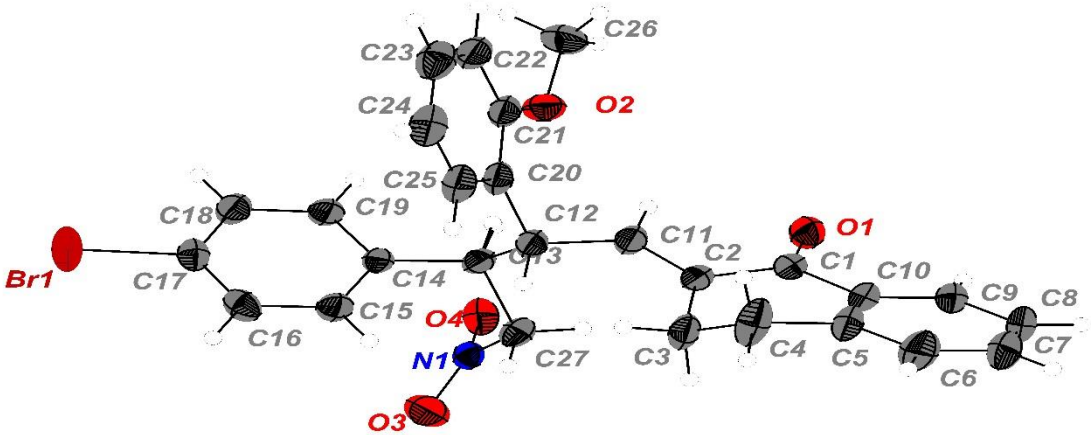
CCDC-1823074 contains the supplementary crystallographic data for the structural analysis of **39Aa**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

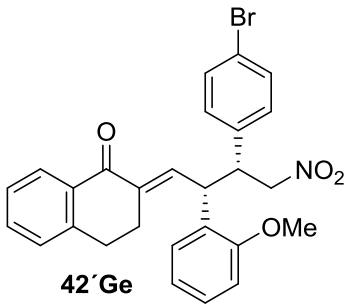




39Aa

5.7.6. ORTEP diagram of compound 42´Ge

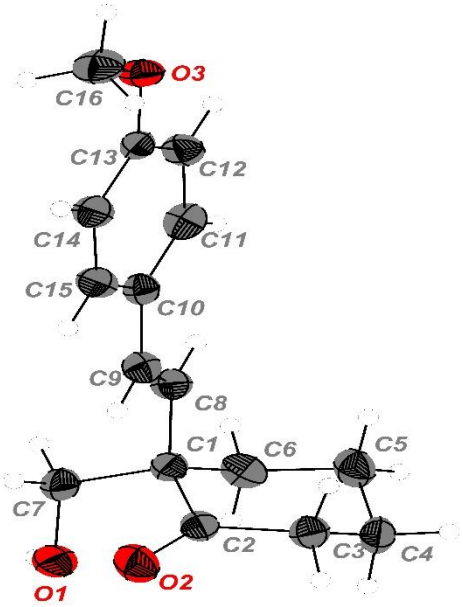


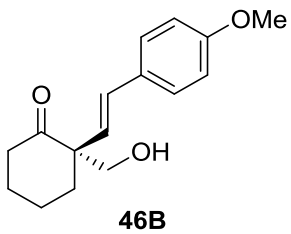


42´Ge

5.7.7. ORTEP diagram of compound 46B

CCDC-1903280 contains the supplementary crystallographic data for the structural analysis of **46B**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.





46B

Publications

Organocatalysis

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Bifunctional Brønsted Base Catalyst Enables Regio-, Diastereo-, and Enantioselective C_α-Alkylation of β-Tetralones and Related Aromatic-Ring-Fused Cycloalkanones

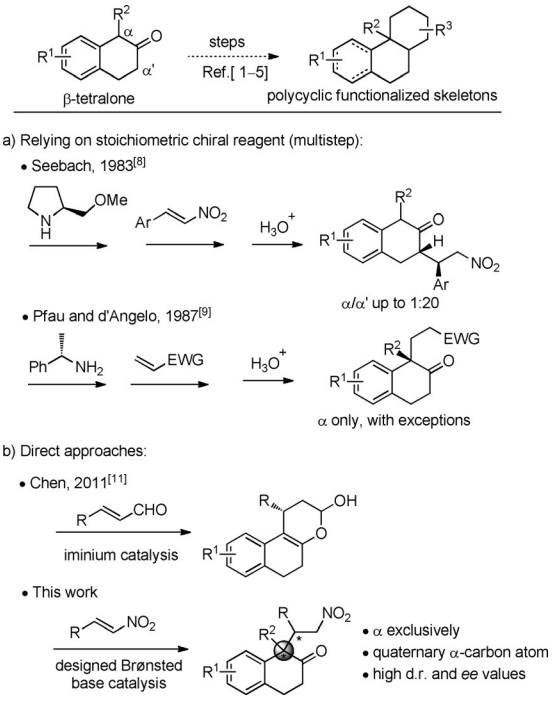
*Iñaki Urruzuno, Odei Mugica, Mikel Oiarbide, and Claudio Palomo**

In memory of José Barluenga

Abstract: *The catalytic asymmetric synthesis of both α-substituted and α,α-disubstituted (quaternary) β-tetralones through direct α-functionalization of the corresponding β-tetralone precursor remains elusive. A designed Brønsted base-squaramide bifunctional catalyst promotes the conjugate addition of either unsubstituted or α-monosubstituted β-tetralones to nitroalkenes. Under these reaction conditions, not only enolization, and thus functionalization, occurs at the α-carbon atom of the β-tetralone exclusively, but adducts including all-carbon quaternary centers are also formed in highly diastereo- and enantioselective manner.*

Syntheses of many bioactive compounds with polycyclic structures, including homoerythrina alkaloids,[1] morphan derivatives,[2] glucocorticoid receptors,[3] and stradiols,[4] among others,[5] have employed β-tetralones. However, this interest did not translate into a variety of approaches for the asymmetric synthesis of substituted β-tetralones. Most approaches for the α/α′-functionalization of β-tetralones so far documented exploit the idea of Stork et al.[6] which involves condensation with a chiral amine and subsequent C-alkylation of the resulting enamine, typically by addition to a Michael acceptor.[7] One complication, for any nonsymmetric cycloalkanone, is that enolization may occur at either the α or α′ site. In this context, Blarer and Seebach[8] reported that the reaction with nitrostyrenes of the enamine derived from (*S*)-2-methoxymethylpyrrolidine, and the respective β-tetralone produced in moderate yields the α′-adduct predominantly (α/α′ from 1:4 to 1:20) with generally good diastereo- and enantioselectivity after hydrolysis of the resulting iminium species (Scheme 1 a). Alternatively, the groups of Pfau and d'Angelo reported the condensation of β-tetralones with (*S*)-1-phenylethylamine and subsequent Michael reaction to afford the α-substituted adducts preferentially,[9] but with exceptions.[9a]

Apart from these stoichiometric multistep approaches, we are unaware of catalytic methods for the enantioselective α-functionalization of β-tetralones leading to an all-carbon quaternary stereocenter.[10] Chen and co-workers have reported direct reaction of β-tetralones with α,β-unsaturated aldehydes by iminium activation,[11] but stereogenicity at C_α is lost upon spontaneous hemiketal formation. Herein we report the direct site-, diastereo-, and enantioselective C_α-alkylation of β-tetralones by conjugate addition reaction enabled by newly designed Brønsted base catalysts. The new C–C bond is formed at the α-carbon atom exclusively, and adducts, including those with an α-quaternary center, are formed in a highly stereoselective manner.



Scheme 1. Enantioselective α/α′-functionalization of β-tetralones. EWG = electron-withdrawing group.

Our consideration was that the fused aromatic ring in β-tetralones might induce preferential enolization at C_α rather than C_α', and that in the presence of a Brønsted base relatively high concentrations of the enolic form would be expected, thus eventually driving the catalytic process forward. Nonetheless, this assumption was accompanied by a second significant challenge, namely the effective control of both the absolute and relative stereochemistry during con-

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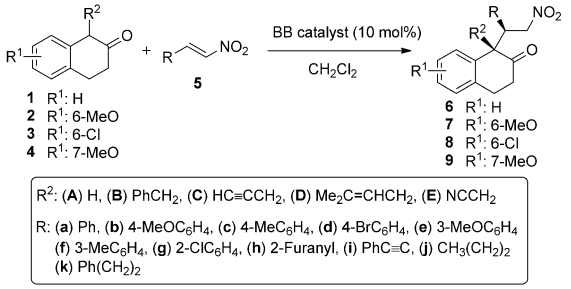
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201612332.

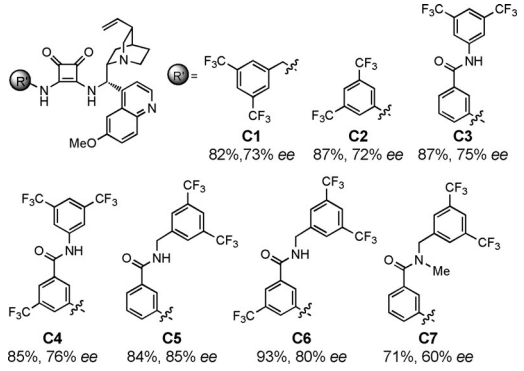
struction of the quaternary carbon stereocenter. In fact, while some success has been achieved in the enantioselective synthesis of α-quaternary carbonyl compounds by Brønsted base-catalyzed Michael reactions[12,13] of α-aryl cyclopentanones,[14a] the corresponding α-aryl cyclohexanones behaved sluggishly.[14,15] We started by screening a set of chiral bifunctional Brønsted base catalysts for the reaction of **1B** with the nitrostyrene **5a** (Scheme 2). It was found that while



Scheme 2. Catalytic addition of β-tetralones to nitroalkenes. BB = Brønsted base.

in each case the α,α-dialkyl β-tetralone **6Ba** was formed exclusively and with essentially perfect diastereoselectivity regardless of the chiral catalyst employed (Table 1),[16] the enantioselectivities were highly catalyst-dependent. The bifunctional squaramide-cinchona Brønsted base catalysts pioneered by Rawal and co-workers[17,18] were the most effective. Thus, by using the catalysts **C1**[17] and **C2**[19] the product **6Ba** was formed exclusively, albeit in moderate enantioselectivity (73 and 72% *ee*, respectively).

Table 1: Screening of catalysts for the reaction of **1B** with **5a**.[a]

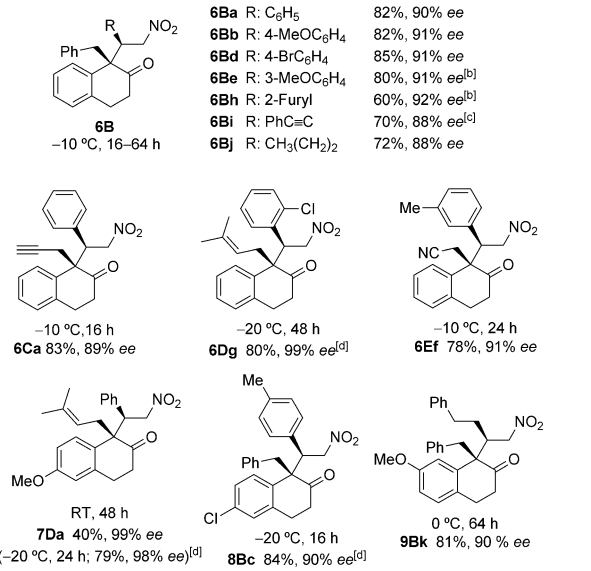


[a] Reactions carried out at 0.30 mmol scale, using 1.2 equiv of **5a** and 10 mol% catalyst in 0.6 mL CH_2Cl_2 at room temperature. Yield is that of the isolated product **6Ba** after chromatography. The *ee* value was determined by chiral-phase HPLC.

Next we examined the catalysts **C3**[20]/**C4** bearing an amide unit, which would provide a site not only for catalyst fine tuning, but also for additional hydrogen bonding (Table 1).[21] Both **C3** and **C4** catalyzed the reaction of **1B** with **5a**, but produced no improvement in the *ee* value. After several variations of the amide group, we were delighted to find that acceptable selectivity was achieved with the new catalysts **C5** and **C6** (85 and 80% *ee*, respectively). In contrast, the N-methylated catalyst **C7** led to a moderate 60% *ee*, thus indicating that the amide NH in the former catalysts is important. Lowering the reaction temperature allowed further improvement in the selectivity (90% *ee* at −10 °C for **C6**), although **C5** behaved sluggishly at subzero temperatures because of limited solubility. The same trend in the behavior of **C1**–**C7** was observed for the reaction of **1B** with the nitroalkene **5b**.[16]

As Table 2 illustrates, results with differently β-substituted nitroalkenes[22] were uniformly good when using **C6**. Thus, the stereoselectivity of the reactions seems to be independent of the electronic properties of the nitroalkene, and products **6Ba**, **6Bb**, **6Bd**, and **6Be** were formed from the respective nitrostyrenes **5** in yields around 80% and with *ee* values in the range of 90–91%. Nitroalkenes having heteroaromatic or alkynyl β-substituents (**5h**, **5i**) also led to the corresponding products (**6Bh**, **6Bi**) with similarly good yield and enantioselectivity. Remarkably, even the less reactive β-alkyl-substituted nitroalkenes, such as **5j** and **5k**, afforded the corresponding addition adducts (**6Bj**, **9Bk**) with equally good yields and *ee* values. The stereochemical outcome of the reaction is also independent of the α-substituent of the β-tetralone employed. The tetralones **1C**, **1D**, and **1E** reacted with the respective nitroalkenes **5** to afford the adducts **6Ca**, **6Dg**, and **6Ef**, respectively, in good yields and with *ee* values of up to 99%. The reaction also tolerates the β-tetralones **2D**, **3B**, and **4B**, bearing, respectively the 6-methoxy-, 6-chloro-,

Table 2: Scope of the reaction with respect to the α-substituted β-tetralones **1**–**4** with nitroalkenes **5** catalyzed by **C6**.[a]

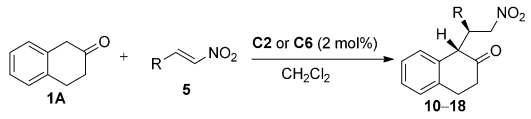


[a] Reactions carried out at 0.30 mmol scale, using 1.2 equiv of *trans*-nitroalkene **5** and 10 mol% **C6**, unless otherwise stated, in 0.6 mL CH_2Cl_2. d.r. > 20:1 in all entries as determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. Yield is that of the product isolated after chromatographic purification. The *ee* value was determined by chiral-phase HPLC. [b] Reaction conducted at −20 °C. [c] Obtained as a 1.5:1 mixture of diastereomers (94% *ee* for minor isomer). [d] Using catalyst **C4**.

and 7-methoxy groups at the aromatic ring, which were equally efficient (adducts **7Da**, **8Bc**, and **9Bk**). In the case of **7Da**, **C4** produced the best reaction outcome. Importantly, in every case no traces of products from the reaction at the α′-carbon atom of the β-tetralone were formed.

Next, the behavior of the α-unsubstituted β-tetralone **1A** was investigated and the reactions under similar reaction conditions were found, again, to be completely regioselective (Table 3). The products **10**–**18** were obtained from both aryl-

Table 3: Reaction of the β-tetralone **1A** with nitroalkenes catalyzed by either **C2** or **C6**.[a]



Product, R	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
10, Ph	−20	8	83	4:1	99
11, 4-MeOC_6H_4	−20	8	85	8:1	99
12, 4-BrC_6H_4	−20	8	88	4:1	99
13, 3-MeOC_6H_4	−20	8	80	4:1	99
14, 2-ClC_6H_4	−20	8	86	>20:1	99
15, 2-furyl	−20	8	84	1:1	98
16, $CH_3(CH_2)_2$	RT	16	81	5:1	99
17, C_6H_{11}	RT	24	80	4:1	99
18, $Ph(CH_2)_2$	RT	16	83	5:1	99

[a] Reactions carried out at 0.30 mmol scale, using 1.2 equiv of *trans*-nitroalkene and 2 mol% of either **C2** or **C6** in 0.6 mL CH_2Cl_2. [b] Yield of product isolated after chromatographic purification. [c] Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [d] Both diastereomers obtained with the same *ee* value as determined by chiral-phase HPLC.

and alkyl-substituted nitroalkenes in yields in the 80–88% range and, importantly, no products from a sequential addition of two equivalents of nitroalkene, either at $C_{\alpha/\alpha'}$ of the ketone or at C_α of the nitro group, were detected. With the exception of the 2-furyl-substituted nitroalkene **5h** (product **15**), in all other cases diastereoselectivity was good (d.r. ≥ 4:1) and enantioselectivity essentially perfect for both diastereomers. For these reactions both **C2** and **C6** were found to be equally effective at a 2 mol% loading. It should be noted that the thus obtained α-monosubstituted β-tetralones were prone toward epimerization under basic conditions at room temperature. For example, the compound **14**, which was isolated essentially as a single diastereomer (d.r. > 20:1), led, after exposure to 5 mol% of **C2** at room temperature in methylene chloride for 3 hours, to an almost equimolar mixture of diastereomers. In the absence of base, however, no epimerization was observed after a prolonged time (20 h) even at 80 °C.

Eventually, the suitability of this highly site- and stereoselective α-functionalization strategy was also investigated for related ketone substrates. As results in Figure 1 show, aromatic ring-fused cycloalkanones with an oxygen heteroatom in the cycle, or larger seven-membered cycloalkanones, were equally competent substrates undergoing the corresponding addition reaction at C_α exclusively, and with very high stereoselectivity. In particular cases, the enolizable

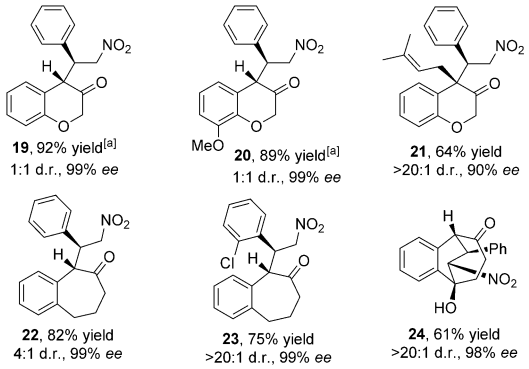
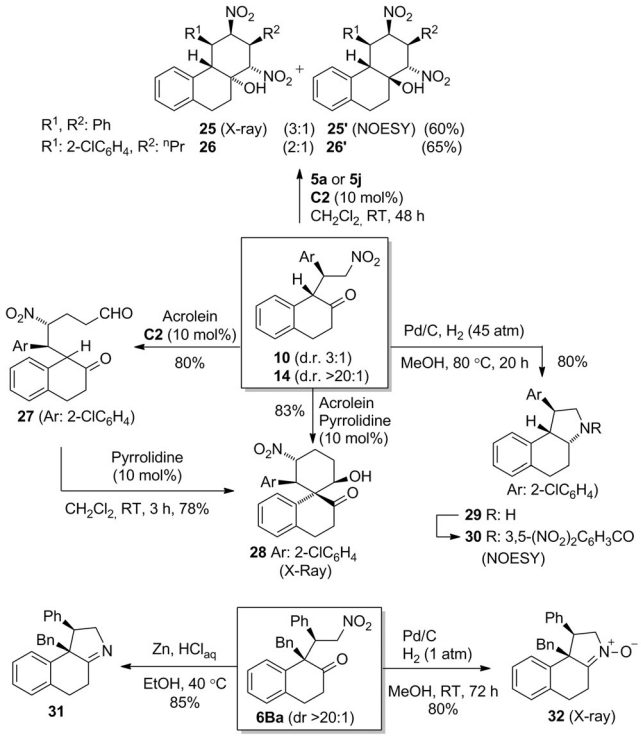


Figure 1. Adducts from the direct reaction of a survey of arene-fused cycloalkanones with nitroolefins in the presence of 10 mol% **C6** (for details, see the Supporting Information). [a] 2 mol% of catalyst **C2** used. Both diastereomers obtained with the same *ee* value.

compounds **19** and **20** were obtained as a mixture of two diastereomers, probably as a result of easy epimerization under the reaction conditions used. In contrast, in the case of employing a diketone substrate, the adduct **24** from a sequential Michael/intramolecular Henry reaction was obtained, again, as essentially a single diastereomer and very high enantioselectivity.

The excellent regio- and stereoselectivity achieved in the above reactions are of particular interest in that several options for further elaboration of the adducts are now made feasible. For instance (Scheme 3), the adduct **10** (3:1 ratio of diastereomers), upon treatment with **5a** in the presence of 10 mol% of **C2** provided the tricyclic systems **25**/**25′** in 60%



Scheme 3. Elaboration of adducts into a variety of polycyclic molecules.

combined yield. Remarkably, only two out of the possible 2^6 stereoisomers of **25** were formed.[23] An interesting aspect is that apparently no cyclization product derived from the minor isomer of **10** was detected. Moreover, the isomeric composition of isolated product **25**/**25′** was around 3:1 regardless of the initial mixture of starting **10** employed (3:1 in first run; 1:1 in second run). These results suggest that formation of the tricycles **25**/**25′** through a Michael/Henry cascade[24,25] not only proceeds in high stereoselectivity, but also involves some kinetic resolution process. Similarly, treatment of **14** (d.r. > 20:1) with **5j** in the presence of **C2** afforded the products **26**/**26′** in a 2:1 ratio. The absolute configuration of **25** was determined by single-crystal X-ray structure analysis,[26] and that of **25′** by NOESY experiments.[16] The configuration of **26**/**26′** was assigned by analogy. In a different example, when **14** was treated with acrolein in the presence of **C2** at room temperature, the Michael addition product **27** was isolated in 80% yield. The aldol-reaction-mediated cyclization of **27** to **28** could be carried out smoothly at room temperature by exposure to 10 mol% pyrrolidine. Alternatively, direct transformation of **14** into the spirocyclic aldol **28** was achieved by treatment with acrolein in the presence of 10 mol% pyrrolidine. In both cases **28** was produced as essentially a single diastereomer. The course of the above cascade reaction is quite surprising considering that cycloalkanones under similar reaction conditions are reported to furnish substituted decalins instead.[27] Importantly, as far as we know, no other catalytic enantioselective approach that allows regioselective production of tetralone-derived α-spirocycles are available until now.[5,28] In addition, hexahydro-benzo[*e*]indoles, heterocyclic cores present in various biologically active compounds,[29] could also be prepared. For example, reduction of the nitro group in adduct **6Ba** with either Zn/H^+ or H_2/Pd provided, respectively, **31** and **32**, whilst reduction of **14** led to **29**, all with good yields. The absolute configurations for the compounds **28** and **32** were determined by single-crystal X-ray structure analysis[26] and that of their precursor adducts was established by extrapolation.

In summary, we report the first examples of catalytic regio-, diastereo-, and enantioselective α-alkylation of both α-unsubstituted and α-substituted β-tetralones with Michael acceptors.[30] The synthetic utility of the method is demonstrated by easy conversion of adducts into diverse polycyclic compounds featuring up to six stereogenic centers or new spirocyclic system. This realization was feasible thanks to a readily available subclass of cinchona-alkaloid-derived bifunctional catalysts bearing a carboxamide group as an additional moiety for catalyst fine tuning. Importantly, the method proved to be applicable beyond β-tetralones, and the direct α-functionalization of other aromatic ring-fused cycloalkanones are equally affordable and selective. Investigations to further broadening the substrate scope of the approach are ongoing.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Brønsted bases · heterocycles · organocatalysis · polycycles · synthetic methods

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Angew. Chem. **2017**, *129*, 2091–2095

[1] Racemic synthesis: a) M. A. Le Dréau, D. Desmaele, F. Dumas, J. O'Angelo, *J. Org. Chem.* **1993**, *58*, 2933–2935.
[2] G. Lim, J. W. Hooper, US Patent 4, 017,497; Apr. 12, **1977**.
[3] B. P. Morgan, A. G. Swick, D. M. Hargrove, J. A. LaFlamme, M. S. Moynihan, R. S. Carrol, K. A. Martin, G. Lee, D. Decosta, J. Bordner, *J. Med. Chem.* **2002**, *45*, 2417–2424.
[4] a) Y. Bouali, F. Nique, J.-G. Teutsch, P. Van de Velde, US Patent 6, 207,657BI, Mar 27, **2001**; b) J. P. Larkin, C. Whrey, P. Boffelli, H. Lagraulet, G. Lamaitre, A. Nedelec, D. Prat, *Org. Process Res. Dev.* **2002**, *6*, 20–27.
[5] C. C. Silveira, A. L. Braga, T. S. Kaufman, E. J. Lenardão, *Tetrahedron* **2004**, *60*, 8295–8328.
[6] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207–222.
[7] J. d'Angelo, D. Desmaele, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.
[8] S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, *116*, 3086–3096.
[9] a) T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.* **1987**, *28*, 2367–2370; b) J. d'Angelo, G. Revial, T. Volpe, M. Pfau, *Tetrahedron Lett.* **1988**, *29*, 4427–4430. Also, see: c) M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273–274; d) Ref. [7].
[10] Selected reviews on stereoselective synthesis of quaternary centers: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745–2759; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593–4623; c) M. Bella, T. Caspery, *Synthesis* **2009**, 1583–1614; d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, *Eur. J. Org. Chem.* **2007**, 5969–5994; e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; f) *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; g) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; h) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.
[11] J.-H. Chen, C. Chang, H.-J. Chang, K. Chen, *Org. Biomol. Chem.* **2011**, *9*, 7510–7516.
[12] Reviews on Brønsted base catalysis: a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; b) *Asymmetric Organocatalysis 2*, *Brønsted Base and Acid Catalysis*, *and Additional Topics*: *Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**; c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200.
[13] Selected reviews on asymmetric organocatalytic conjugate additions: a) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselecive Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC Publishing, Cambridge, **2010**; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; c) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.

[14] a) X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 6840 – 6842; b) J. Deutsch, H.-J. Niclas, M. Ramm, *J. Prakt. Chem.* **1995**, *337*, 23 – 28.

[15] For catalytic asymmetric reactions of α-branched cyclic ketones using alternative activation strategies, see: (phosphoric acid catalysis) a) X. Yang, F. D. Toste, *Chem. Sci.* **2016**, *7*, 2653 – 2656; (phase-transfer catalysis) b) T. Kano, Y. Hayashi, K. Maruoka, *J. Am. Chem. Soc.* **2013**, *135*, 7134 – 7137; (enamine activation with primary amine-thiourea catalysis) c) J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178 – 3181; d) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, *81*, 3629 – 3637; e) R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457 – 4463.

[16] See the Supporting Information.

[17] a) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416 – 14417; b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153 – 156; *Angew. Chem.* **2010**, *122*, 157 – 160.

[18] For reviews on squaramides, see: a) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330 – 2346; b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890 – 6899; c) P. Chauhan, S. Mahahan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253 – 281.

[19] a) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137 – 2141; b) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450 – 5453.

[20] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 6883 – 6886; *Angew. Chem.* **2015**, *127*, 6987 – 6990.

[21] For more information on catalysts bearing multiple hydrogen-bonding donors, see: a) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185 – 1197; b) R. Kenny, F. Liu, *Eur. J. Org. Chem.* **2015**, 5304 – 5319. For selected reviews on dual or cooperative organocatalysis, see: c) L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, 490 – 508; d) *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis* (Ed.: R. Peters), Wiley-VCH, Weinheim, **2015**.

[22] Reviews on conjugate additions to nitroolefins: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; b) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561 – 2601; c) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, 2627 – 2628.

[23] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863.

[24] Selected reviews on organocatalytic cascade or domino reactions: a) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832 – 1844; b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390 – 2431; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167 – 178; d) H. Pellissier, *Asymmetric Domino Reactions*, RSC Publishing, Cambridge, **2013**.

[25] Nitroalkenes in the synthesis of carbocyclic compounds: a) A. Z. Halimehjani, I. N. N. Namboothiri, S. E. Hooshmanda, *RSC Adv.* **2014**, *4*, 31261 – 31299. Reviews on six-membered carbocycles: b) G. Koutoulogenis, N. Kaplaneris, C. G. Kokotos, *Beilstein J. Org. Chem.* **2016**, *12*, 462 – 495; c) X. Yang, J. Wang, P. Li, *Org. Biomol. Chem.* **2014**, *12*, 2499 – 2513; d) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, 1909 – 1930. For examples on catalytic Michael-Michael-Henry reactions, see: e) S. Varga, G. Jakab, L. Drahos, T. Holczbauer, M. Czugler, T. Soos, *Org. Lett.* **2011**, *13*, 5416 – 5419; f) O. Baslé, W. Raimondi, M.-M. Sánchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246 – 5249; g) Z. Mao, Y. Jia, Z. Xu, R. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1401 – 1406.

[26] CCDC 1511199 (**25**), 1511200 (**28**) and 1511201 (**32**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[27] S. Anwar, H.-J. Chang, K. Chen, *Org. Lett.* **2011**, *13*, 2200 – 2203.

[28] Reviews on spirocycles: a) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060 – 1074; b) B. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165 – 193. For examples on oxindoles, see: c) Ref. [10h]; d) B. Zhou, Y. Yang, J. Shi, Z. Luo, Y. Li, *J. Org. Chem.* **2013**, *78*, 2897 – 2907; e) X. Companyó, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano, R. Ríos, *Chem. Commun.* **2010**, *46*, 6953 – 6955.

[29] C. H. Lin, S. R. Haadsma-Svensson, G. Phillips, R. B. McCall, M. F. Piercey, M. W. Smith, K. Svensson, A. Carlsson, C. G. Chidester, P. F. Von Voigtlander, *J. Med. Chem.* **1993**, *36*, 2208 – 2218.

[30] Preliminary experiments show that vinyl sulfones are also competent reaction partners. See the Supporting Information.

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Cyclic Ketone Dienolates |*Hot Paper*|

α-Branched Ketone Dienolates: Base-Catalysed Generation and Regio- and Enantioselective Addition Reactions

Iñaki Urruzuno, Odei Mugica, Giovanna Zanella, Silvia Vera, Enrique Gómez-Bengoa, Mikel Oiarbide,* and Claudio Palomo*[a]

Abstract: In this study, the unique capacity of bifunctional Brønsted bases to generate α-branched ketone dienolates and control both site- and stereoselectivity of their addition reactions to representative classes of carbon electrophiles (i.e., vinyl sulfones, nitroolefins, formaldehyde) is documented. We demonstrate that by using selected chiral tertiary amine/squaramide catalysts, the reactions of β,γ-unsaturated cycloalkanones proceed through the dienolate Cα almost exclusively and provide all-carbon quaternary cyclic ketone adducts in good yields with very high enantioselectivities. A minor amount (<5%) of γ-addition is observed when nitroolefins are used as electrophiles. The parent acyclic ketone dienolates proved to be less reactive under these conditions, and thus still constitute a challenging class of substrates. Quantum chemical calculations correctly predict these differences in reactivity and explain the observed site-specificity and enantioselectivity.

Introduction

Over the years, the production of, and reactions with, ketone enolates and their equivalents have been basic operations in organic chemistry.[1] One of the most significant advances in this field has been the development of catalytic methods to control their generation and reaction outcomes.[2] In this context, ketone dienolates and their equivalents pose some unique challenges: while of great synthetic value, since they lead to adducts with a strategically positioned C=C double bond, dienolates may react through either the α or the γ nucleophilic carbon atom, thus demanding stringent reaction control. To date, the overwhelming majority of catalytic methods involving dienolate or equivalent intermediates have been applied to α-unsubstituted derivatives, and have proceeded mainly through the γ carbon atom (vinylogous reactivity; Figure 1 a).[3] These methods include catalyst-promoted addition reactions of preformed silyl dienol ethers (X: $OSiR'_3$)[4] as well as direct approaches based on metallic catalysis (X: O^-M^+),[5] dienamine activation (X: NR'_2),[6] and Brønsted acid-[7] and base-catalysed[8] activations. The γ-attack pathway would seem to be kinetically favourable because it involves no disruption of the π-conjugation along the reaction coordinate.

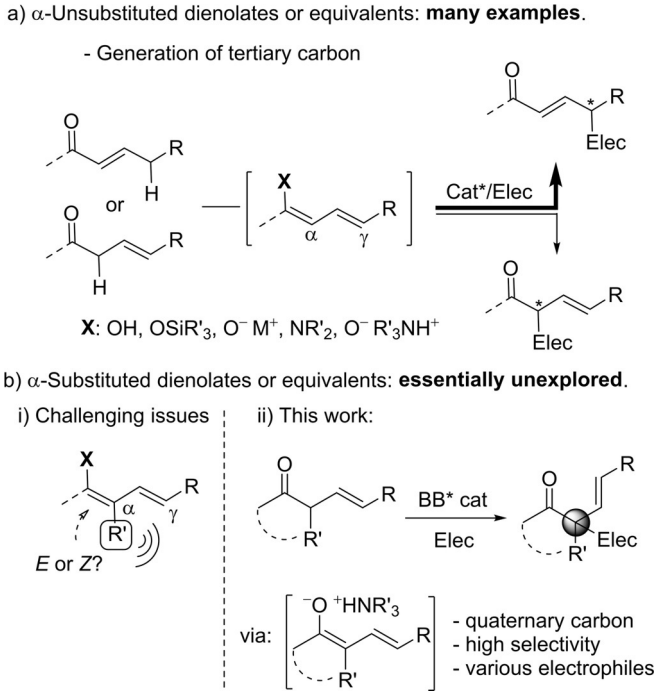

Figure 1. Divergent reaction pathways of dienolates or equivalents and the challenge to control reactions involving α-branched dienolates to obtain α-quaternary products.

Exceptions to this mainstream γ-selectivity involve concomitant isomerization of the C=C double bond to yield Morita–Baylis–Hillman-type adducts (no α-stereocentre is formed),[9] require specific substrate categories[10] or substrates with strong steric bias,[11] and/or lead to moderate enantioselectivity.[12] Moreover, none of these α-selective methods have proved to be useful for enantioselective generation of the α-quaternary ketone (or related carbonyl) products,[13] a process that would

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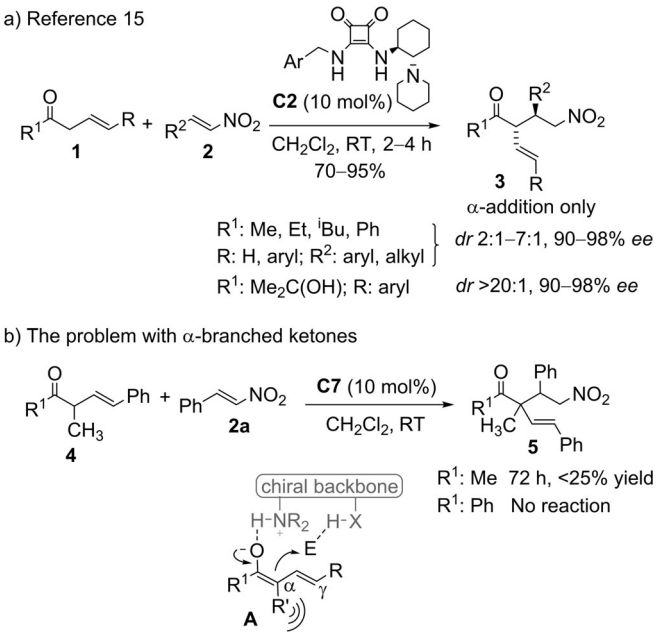
necessarily involve as intermediates α-substituted dienolates or equivalents (Figure 1b, i). Such an accomplishment would not only require stringent control over the *E*/*Z* enolate geometry and the face selectivity, but also retention of sufficient α-reactivity despite the steric congestion at Cα. This problem has recently been addressed by Toste through Brønsted acid catalysis,[14] but, to the best of our knowledge, no other solutions have been reported. Moreover, while the Brønsted acid activation approach is well suited for α-aminations,[14a] it apparently shows limitations with common carbon electrophiles such as conjugated olefins, with allenamides being a notable exception.[14b] Herein, we report another solution to this problem by documenting the first carbon-carbon bond-forming reactions of α-substituted β,γ-unsaturated ketones assisted by Brønsted base/H-bonding catalysis. This mode of activation tolerates several carbon electrophiles, including conjugated olefins and formaldehyde, and the reactions proceed with very high Cα site-selectivity, giving access to all-carbon α-quaternary ketone products with high enantioselectivity (Figure 1b, ii).

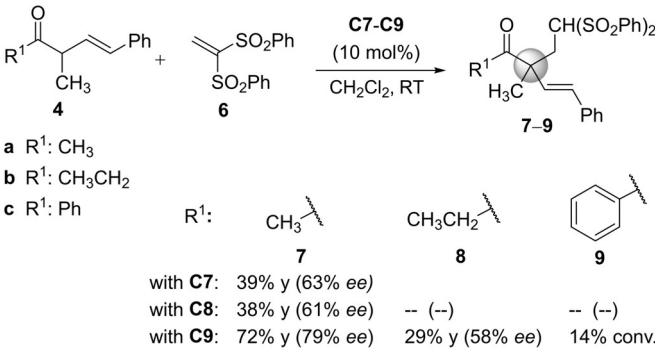
Results and Discussion

We have recently investigated the catalytic reactions of several in situ generated dienolate systems.[15] We found that chiral Brønsted base/H-bonding catalysts[16] are able to promote the smooth, enantioselective addition of β,γ-unsaturated ketones **1** to nitroolefins **2**, yielding α-addition adducts **3** as the exclusive products (Scheme 1a). It was noticed that on increasing the size of R^1 in **1**, the diastereoselectivity improved, and the highest selectivity was attained when using bulky hydroxyenones (R^1: $Me_2C(OH)$) in the presence of Rawal's[17] catalyst **C2**. The observed reaction outcome is compatible with model **A** ($R' = H$), in which the catalyst acts in a bifunctional manner, correctly orienting both reactants. Although extrapolation of model **A** to α-branched ketone dienolates is conceivable (i.e., **A**, $R' \neq H$), two apparent problems to overcome in this model are the steric shielding at Cα and the enolate *E*/*Z* configurational uncertainty. With regard to the former aspect, complications may be foreseen during both the enolate generation and the subsequent approach of the electrophilic reagent. In fact, with only two specific exceptions from this and another laboratory,[18] almost all of the organocatalytic approaches for the asymmetric α-functionalization of α-branched ketones assisted by Brønsted bases, including Michael additions, have been restricted to the use of active ketones bearing an adjacent electron-withdrawing group (EWG = carbonyl, nitrile, sulfonyl, or nitro).[13,19] Initial attempts to perform the reaction between nitrostyrene **2a** and α-branched ketones **4** using bifunctional catalyst **C7** confirmed the anticipated pitfalls, resulting in the recovery of unreacted enone (R^1: Ph) or very low conversions to product **5** (R^1: Me) as a mixture of α/γ isomers (Scheme 1b).



Scheme 1. Impact of α-substitution on the reactivity of transiently formed acyclic ketone dienolates.

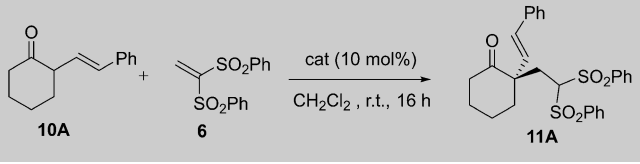
We reasoned that highly reactive and sterically less demanding Michael acceptors, such as 1,1-bis(phenylsulfonyl)ethylene **6**, might counterbalance the low reactivity of these ketones. Incidentally, the sulfonyl group in the adducts would be susceptible to several ulterior transformations, including reductive removal.[20] To our delight, as the results in Scheme 2 show, α-branched ketones **4** reacted with **6** in the presence of **C7**,[21] **C8**,[22] or **C9**[23] (formulas in Table 1) to afford adducts **7**–**9** from reaction exclusively at the α site, albeit in variable yields and with different enantioselectivities. For example, the reaction between methyl ketone **4a** and **6** in the presence of **C9** reached 81% conversion after 16 h at room temperature, and product **7** was obtained with 79% *ee*. Catalysts **C7** and **C8** were less efficient, leading to **7** in yields of 39% and 38% with 63/61% *ee*, respectively. The reaction with the ethyl ketone **4b** also proceeded, albeit much less effectively, giving product **8** with poor enantioselectivity, and the reaction of phenyl ketone **4c** to give **9** was sluggish.



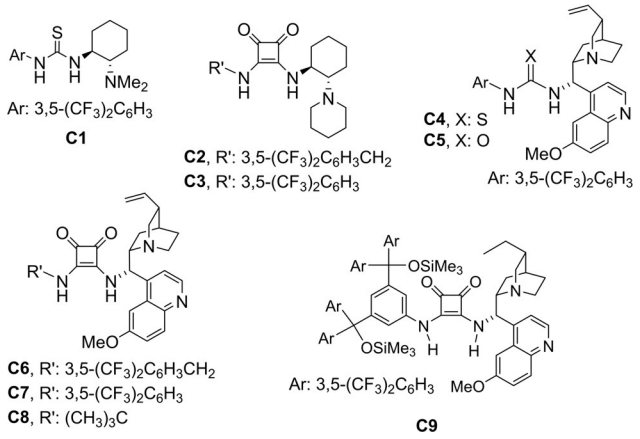
Scheme 2. Impact of ketone side-chain R^1 on the reactivity of derived dienolates.

These results, whilst promising, highlighted the two main problems of catalytically generated trisubstituted carbon nucleophiles: their attenuated reactivity and the difficulties in controlling enantioface selectivity. Moreover, the significant variations in the reaction outcome when switching from a methyl to an ethyl or phenyl ketone side-chain seem to indicate that slight structural changes in the substrate ketone may

Table 1. Catalyst screening for the reaction of cyclohexanone **10A** with vinyl sulfone **6** to give **11A**.[a]



Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**C1**	26	–
2	**C2**	NR	–
3	**C3**	NR	–
4	**C4**	72	10
5	**C5**	79	40
6	**C6**	83	60
7	**C7**	88	73
8	**C8**	87	98
9[d]	**C9**	89	98



[a] Reactions carried out at 0.15 mmol scale, using 2 equiv of vinyl disulfone and 10 mol% catalyst in CH_2Cl_2 (0.3 mL) at room temperature. No product from γ-addition was detected by ^{1}H NMR (Cα/Cγ > 95:5). [b] Yield after chromatography. [c] *ee* determined by chiral HPLC. [d] Reaction run at 0 °C.

have a huge impact on the reactivity and selectivity. The above observations also corroborate the multivariable origin of the Cα/Cγ selectivity in reactions involving dienolate systems.[24]

Hypothesis and working plan

To surmount the intrinsic difficulties mentioned above, cyclic ketones were adopted, in which the double bond is tethered at the Cα position with respect to the carbonyl function. The corresponding dienolates may be better suited based on: (i) the higher nucleophilicity of cyclic systems as compared with their more flexible, open-chain counterparts;[25] (ii) a more rigidified transition state and, thus, more efficient chirality transfer; (iii) the problem of enolate geometry (*E*/*Z* uncertainty) is annulled. For an initial assessment of the reactivity associated with these nucleophilic systems, we determined the charge distribution and Fukui nucleophilicity index (f^-)[26] at the α carbon atom of linear (**I**) and cyclic (**II**) dienolates (Figure 2). Computed data[27] showed the difference in negative charge at these respective carbon atoms to be negligible in the two enolates considered. Similarly, the evaluated Fukui indices of these enolates were essentially identical (−0.34 and −0.35, respectively). Accordingly, it appears that purely intrinsic electronic properties might not be decisive in dictating these reactivity trends, and that the role of the bifunctional catalyst as well as structural factors (steric hindrance, enolate rigidity) or α-CH acidity also need to be considered. For a more comprehensive analysis, energies for the reaction of each enolate system with bis-sulfone **6** were computed in the presence of a model achiral squaramide tertiary amine catalyst ($TS_{(I\text{-}II)}$). As shown by the data in Figure 2, the computed activation energy for the reaction of cyclic dienolate **II** (20.8 kcal mol^{-1}) is attainable at room temperature. In contrast, the activation barrier for the reaction involving acyclic species **I** is around 24.6 kcal mol^{-1}, implying much more sluggish reactivity, in good agreement with our preliminary experimental studies. Calculated data for this model reaction involving **II** also support the preference for the α-addition pathway over the γ-addition pathway, the latter being associated with a barrier that is about 6 kcal mol^{-1} higher. A preference for the α- over the γ-addition pathway was also found for the catalysed reaction involving acyclic enolate **I** (24.6 vs. 27.4 kcal mol^{-1}). These data were revealing, in view of the scarcity of mechanistic information concerning latent dienolate systems.[28]

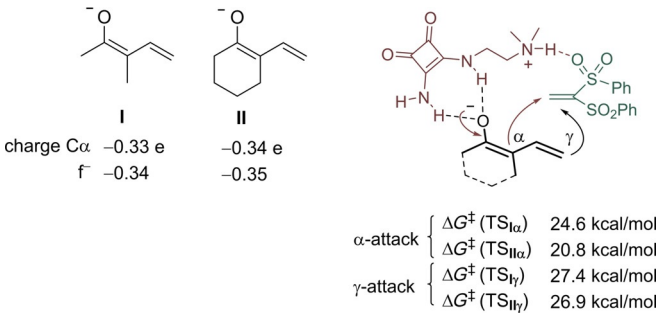


Figure 2. Reactivity parameters of two representative ketone dienolates.

Cyclic ketone dienolates

Catalyst screening and substrate scope: Encouraged by these theoretical predictions, the reaction between α-styryl cyclohexanone **10A** and bis(phenylsulfonyl)ethylene **6** was studied in the presence of an assortment of chiral bifunctional catalysts. By using Takemoto's catalyst **C1**[29] in CH_2Cl_2 as solvent at room temperature, product **11A** was formed in a poor 26% isolated yield (Table 1, entry 1).

Further screening showed that both the nature of the H-bond donor site and the structure of the tertiary amine in the catalyst were critical for reactivity as well as stereoselectivity. Thus, the reaction did not proceed at all with Rawal's[17] squaramides **C2** and **C3** (entries 2 and 3). The quinine-derived thiourea **C4**[30] and urea **C5**[30] were more active, although the enantioselectivities were poor (entries 4 and 5). Using squaramide **C6**, which has proved effective for reactions of α-unsubstituted dienolates with nitroolefins,[15] the reaction proceeded, but with a modest 60% *ee* (entry 6). With catalyst **C7**,[21] the

same level of reactivity and promising stereoselectivity were observed (entry 7). To our delight, with squaramide **C8**, a sterically congested catalyst developed by Connon,[22] the reaction between **10A** and **6** to afford **11A** proceeded to give a good isolated yield and, most significantly, with 98% *ee* (entry 8).

A similar result was obtained with catalyst **C9** (entry 9). Having established **C8** and **C9** as the best catalysts, the scope of suitable alkenyl cycloalkanone substrates was explored. As shown in Table 2, 4-substituted cyclohexanones **12B** and **14A** provided the corresponding addition products **13B** and **15A** in good yields with high enantioselectivity. Most importantly, the method proved to be equally effective with cycloalkanones of varying ring size. For instance, the **C9**-catalyzed reactions of α-branched cycloheptanones **16A** and **16D** afforded adducts **17A** and **17D** in yields of 86 and 79%, with selectivities of 96 and 93% *ee*, respectively. Likewise, reaction with branched cyclooctanone **18A** afforded product **19A** in high yield, albeit with diminished (88% *ee*) enantioselectivity. In this latter case, switching the solvent from CH_2Cl_2 to toluene led to an increase in enantioselectivity to 94% *ee*. Under these conditions, **18B** furnished **19B** in 88% yield essentially as a single enantiomer. The method also tolerates alkenyl cyclopentanones such as **20A** and **20E**, which furnished **21A** and **21E** with acceptable *ee* values. Cyclohexanone **10F** was an exception, giving to the corresponding adduct **11F** in good yield, but with a limited 65% *ee*.

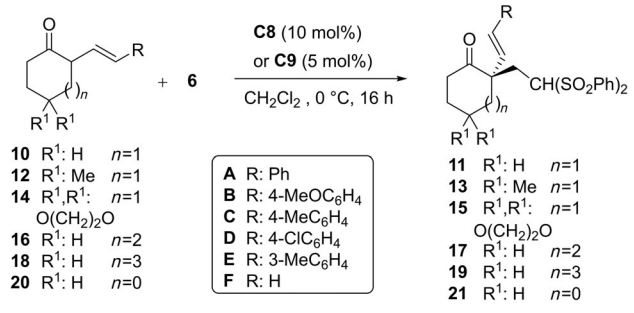
Eventually, the enantioselectivity could be increased to 80% *ee* by carrying out the reaction at −20 °C. In general, similar results were obtained with both catalysts **C8**/**C9**, although the latter led to better chemical yields for cycloalkanones bearing a *p*-methoxyphenylvinyl moiety (products **11B**, **13B**, and **19B**).

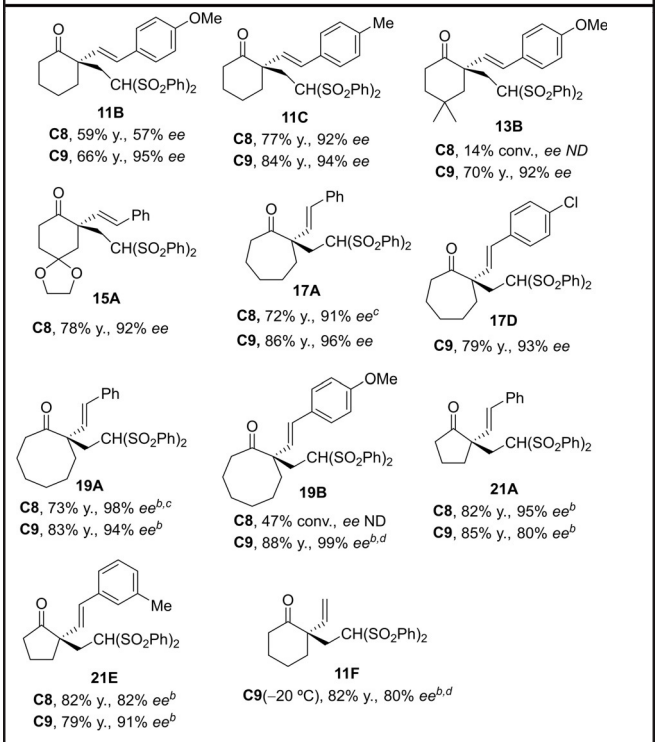
Benzo-fused cycloalkanones **22**–**26** were also excellent substrates for this catalytic reaction, affording the α-quaternary cycloalkanones **27**–**31**. As shown by the results in Table 3, using catalyst **C9**, adducts were obtained in good yields with remarkably high enantioselectivities, regardless of the nature of the substituents on the aromatic ring (R^2) and at the double bond (R). Once again, the method proved to be general with regard to the ketone ring size, and equally tolerated five-, six-, or seven-membered cycloalkanones.

Control experiments showed that for the above reactions the alternative Brønsted acid[14,31] and enamine activation[32] approaches were clearly inferior. For example, in the presence of 10 mol% (*R*)-TRIP (Scheme 3) in toluene at room temperature, no reaction occurred between **10A** and **6**, whereas the same reaction at 40 °C proceeded to give product **11A** in 45% yield, albeit essentially in racemic form. Likewise, whereas the addition of unsubstituted ketones to vinyl bis(sulfone) **6** has been reported to proceed selectively via an enamine intermediate,[33] attempts to react **10A** with **6** in the presence of chiral primary amines at room temperature were unfruitful. At 90 °C, product **11A** was formed (72% yield), albeit with very low (15% *ee*) selectivity, indicating that the amine catalyst probably acted as a base rather than by forming an enamine. This latter observation suggests that the enamine pathway is marginal with sterically congested ketones such as **10A**, in line with previous observations by Carter[32a,b] and Kotsuki,[32c] who showed that amine catalysis is impractical for branched ketones with α-substituents larger than methyl or ethyl.

Elaboration of adducts: The transformations in Scheme 4 illustrate the versatility of the adducts, as both groups, the alkene and the sulfone, are amenable to chemical elaboration. For instance, protection of the carbonyl as a ketal and subsequent reductive cleavage of the bis(sulfonyl) group proved feasible. Thus, ketalisation of **11A** and subsequent treatment of the resulting **32** with TMSCl/1,2-dimethoxyethane and Mg metal[34] afforded the α-ethyl product **34** in good overall yield. A similar reaction sequence applied to adduct **13B** gave product **35** satisfactorily. This sequence, if complemented with an intermediate bis(sulfone) α-alkylation step (e.g., methylation of **32**), allows access to higher α-alkyl systems (e.g., α-propyl ketone **36**). On the other hand, product **34** could be converted

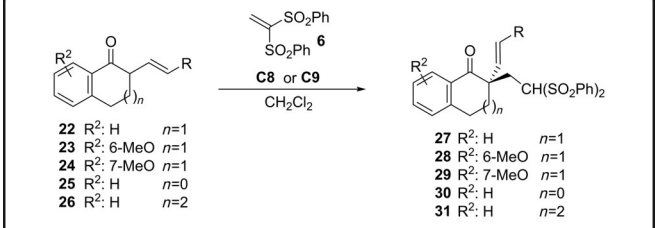
Table 2. Scope of the reaction of α-alkenyl cycloalkanones with **6** catalysed by **C8**/**C9**.[a]





[a] Reactions carried out at 0.15 mmol scale, using 10 mol% catalyst **C8** or 5 mol% catalyst **C9** in CH_2Cl_2 (0.3 mL) unless otherwise stated. Yield of isolated product after chromatography; *ee* determined by chiral HPLC. No product from γ-addition was detected by ^1H NMR (Cα/Cγ > 95:5). [b] Reaction carried out in toluene at RT. [c] With 3 equivalents of **6** and reaction for 48 h. [d] 10 mol% catalyst loading. ND = not determined.

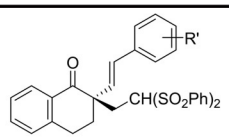
Table 3. Extension to benzo-fused cycloalkanones.[a]



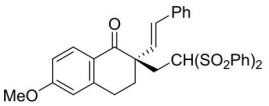
22 R^2: H n=1
23 R^2: 6-MeO n=1
24 R^2: 7-MeO n=1
25 R^2: H n=0
26 R^2: H n=2

27 R^2: H n=1
28 R^2: 6-MeO n=1
29 R^2: 7-MeO n=1
30 R^2: H n=0
31 R^2: H n=2

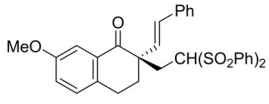
A R: Ph; **B** R: 4-MeOC$_6$H$_4$; **C** R: 4-MeC$_6$H$_4$; **D** R: 4-ClC$_6$H$_4$; **E** R: 3-MeC$_6$H$_4$; **G** R: 2-MeOC$_6$H$_4$



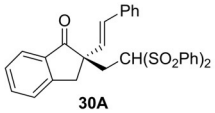
27A R': H 88% y., 99% *ee*
27B R': 4-MeO 79% y., 99% *ee*
27C R': 4-Me 93% y., 99% *ee*
27D R': 4-Cl 92% y., 99% *ee*
27E R': 3-Me 89% y., 99% *ee*
27G R': 2-MeO 71% y., 99% *ee*



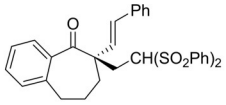
28A
C9 83% y., 99% *ee*



29A
C8 66% y., 82% *ee*
C9 54% y., 90% *ee*

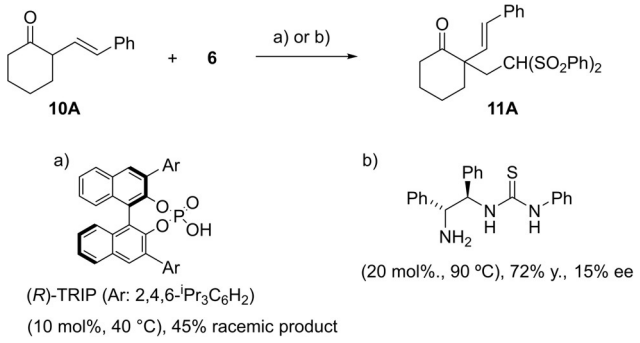


30A
C8 83% y., 69% *ee*
C9 82% y., 90% *ee*



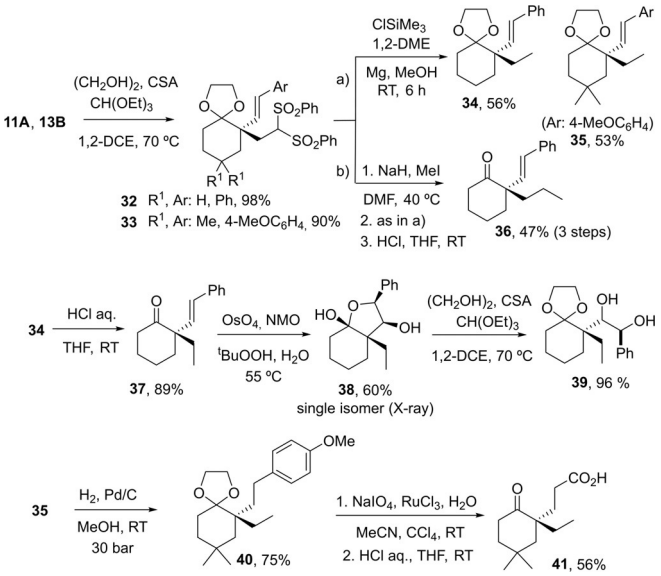
31A
C9 88% y., 89% *ee*

[a] Reactions carried out at 0.15 mmol scale, using 10 mol% catalyst **C8** or 5 mol% catalyst **C9** in CH_2Cl_2 (0.3 mL) unless otherwise stated. Yield of isolated product after chromatography; *ee* determined by chiral HPLC. No product from γ-addition was detected by ^{1}H NMR (Cα/Cγ > 95:5).



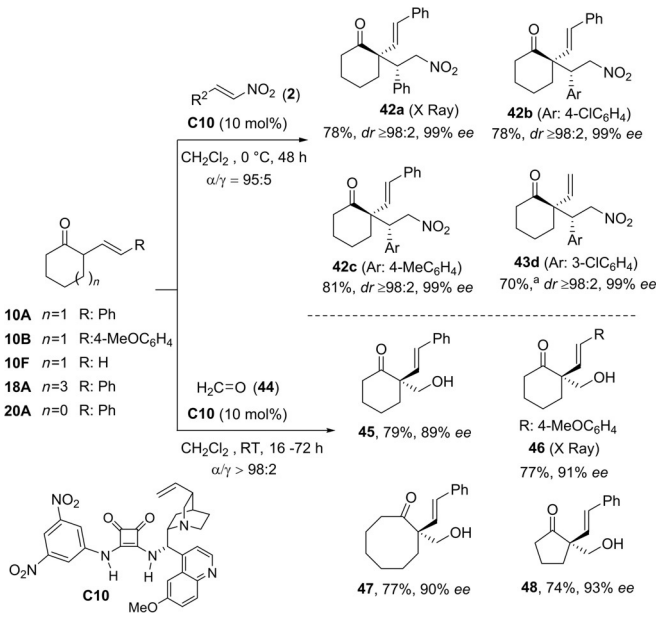
Scheme 3. Control experiments involving Brønsted acid- and enamine-based activation approaches for this reaction.

into diol **39** in a completely stereoselective manner. The transformation required some carbonyl deprotection/reprotection tactics, but eventually allowed determination of the crystal structure of intermediate **38**, which allowed us to define the configuration of the adducts.[35] Hydrogenation of **35** to give the α,α-dialkyl product **40** illustrates another possibility. In this case, further Sharpless oxidative scission of the *p*-methoxyphenyl moiety[36] afforded the quaternary ω-keto acid **41** in good overall yield. These are a few illustrative examples that demonstrate the potential of this approach to access functionalized cycloalkanones with an all-carbon quaternary Cα stereocentre.



Scheme 4. Chemical elaboration of the bis(sulfonyl) adducts.

Extension to other carbon electrophiles: Given the observations noted above, the suitability of carbon electrophiles other than the vinyl bis(sulfone) **6** was next explored. Initial attempts with some β-substituted Michael acceptors such as β-phenyl vinylsulfones and chalcones proved unsuccessful. However, it was gratifying to observe that β-substituted nitroolefins were competent reaction partners.[37] For instance, the reaction of 2-styryl cyclohexanone with nitroolefin **2a** in CH_2Cl_2 at room temperature catalysed by C7 afforded a mixture of the α- and γ-addition adducts in a 75:25 ratio, with essentially perfect diastereoselectivity and high enantioselectivity for each isomer. Further screening of the catalysts showed **C10**[38] to be superior, giving an 85:15 α/γ selectivity ratio and high *dr* and *ee*.[39] Finally, as indicated in Scheme 5, further improvement was achieved by carrying out the reaction at 0 °C, whereupon product **42a**[35] was obtained in 78% isolated yield with essentially perfect diastereo- and enantiocontrol (*dr* > 98:2, 99% *ee*). These results are in contrast to the poor behaviour of the parent open-chain α-branched allyl ketones (see above), which proved to be unreactive under the same conditions. Brief exploration of the reaction scope with nitroolefins (Scheme 5, top) demonstrated similar efficiency for related systems. Thus, good yields, an α/γ ratio of about 95:5, and excellent enantioselectivity for the major isomer were achieved, irrespective of the electron-donor (4-MeC$_6$H$_4$) or electron-acceptor (4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$) character of the aryl groups. Once again, control experiments with **10A** and **2a** under Brønsted acid catalysis and amine catalysis, respectively, aimed at obtaining adduct **42a**, failed or led to no selectivity,[39] reinforcing the unique capacity of the Brønsted base/H-bonding activation strategy. The utility of this catalytic activation could also be extended to α-hydroxymethylation.[40] In these instances, the reactions of various cycloalkanones with paraformaldehyde **44** using catalyst **C10** were perfectly site-selective and adducts **45**–**48** were formed



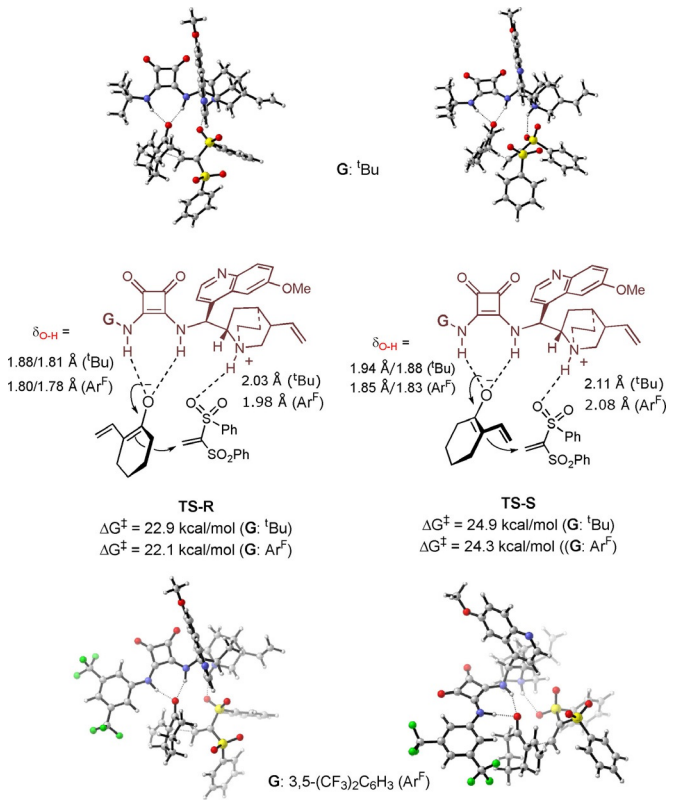
Scheme 5. Catalytic additions to nitroolefins and formaldehyde. [a] Reaction run for 72 h.

with *ee* values in the range 89–93 %, irrespective of the cycloalkanone ring size (Scheme 5, bottom).[41] These results suggest that this Brønsted base/H-bonding strategy might be applied to additional carbon electrophiles, considerably broadening the pool of accessible α,α-disubstituted cycloalkanones.

Origin of the stereoselectivity and plausible H-bond network

In order to shed light on the most favourable arrangement of the substrate and the catalyst during the transition state, we undertook DFT calculations on the model reaction between the vinyl cyclohexanone enolate **II**, vinyl bis-sulfone **6**, and either catalyst **C7** (R = Ar^F: 3,5-$(CF_3)_2C_6H_3$) or **C8** (R: *t*Bu).[27] As could be anticipated for this type of bifunctional Brønsted base/H-bonding catalysis, the located transition state (TS) structures each showed well-defined H-bond networks that strongly bias the spatial arrangement of reactants, determining the stereochemical outcome of the reaction. Calculations at the M06/def2tzvpp (IEFPCM, solvent: dichloromethane)//B3LYP/6-31 g(d,p) level of theory for the above reaction identified only two Papai-type[42] TSs, namely **TS-R**, leading to the *R*-configured product, and **TS-S**, leading to the *S* enantiomer, for each catalyst (Scheme 6).

In spite of extensive efforts, the alternative Takemoto-type activation mode,[29] with the sulfone oxygen atoms hydrogen-bonded to the squaramide NH groups, could not be found, probably due to the low H-bond acceptor character and high steric hindrance of the sulfone group. In agreement with the experimental observations, transition state **TS-R** is associated with the lowest activation energy (22.1 kcal mol^{-1} for catalyst **C7**), as compared to 24.3 kcal mol^{-1} predicted for **TS-S** (slightly higher values of 22.9 and 24.9 kcal mol^{-1}, respectively, for catalyst **C8**). The strongest H-bonds (shortest XH···Y bond) were



Scheme 6. TS structures and selected parameters for the model reaction between α-branched dienolate **II** and bis(phenylsulfonyl)ethene.

measured for the interaction between oxyanion **II** and the two squaramide NH moieties (1.80 and 1.78 Å for catalyst **C7**) in **TS-R**, in comparison to the values found for **TS-S** (1.85 and 1.83 Å). Similarly, the weak interaction between one oxygen atom of the bis-sulfone group and the protonated amine group in **C7** is less notable in **TS-S** as compared to **TS-R** (bond distances 2.08 and 1.98 Å, respectively). This same trend in H-bond strengths was calculated for the TS involving catalyst **C8**, although the slightly longer δ(O···H) values between the dienolate oxygen atom and squaramide NH groups (1.88/1.81 vs. 1.80/1.78 Å) in this latter case appear to indicate a less ideal accommodation of the large *t*Bu group. Summarizing, it seems that an optimally congested microenvironment is formed around protonated catalyst **C7** for best fitting of both reactants through an efficient H-bond network.

Conclusions

In summary, we have reported that bifunctional Brønsted base/H-bonding catalysis activation is able to generate dienolates from α-branched allylic ketones and induce their reaction with various carbon electrophiles mainly or exclusively at Cα. Under these catalytic conditions, reactions of α-branched cyclic ketone dienolates with vinyl bis(sulfone) afforded the corresponding all-carbon quaternary α-addition adducts with very high enantioselectivities. The parent acyclic dienolate systems are comparatively less reactive, but the reactions may still proceed to a small extent for α′-methyl ketones (not so for the α′-ethyl and α′-phenyl ketones). Quantum chemical calculations

on model α-substituted ketone dienolates correctly predicted the observed preference for α over γ-reactivity as well as the sense of enantioinduction based on a Pápai-type activation geometry. Importantly, the approach may be extended to additional carbon electrophiles, such as nitroolefins and formaldehyde, thus offering a robust platform for further development.

Experimental Section

Reactions of cyclic ketones 10–20 and 22–26 with 1,1-bis(phenylsulfonyl)ethylene (6): General procedure: Catalyst **C8** (10 mol%) or **C9** (5 mol%) was added to a solution of the corresponding cyclic α-alkenyl ketone (0.15 mmol) and 1,1-bis(phenylsulfonyl)ethylene (69 mg, 0.23 mmol) in CH_2Cl_2 at 0 °C (ketones **10**–**20**) or room temperature (ketones **22**–**26**). The resulting solution was stirred until the reaction was complete (typically 16 h), as monitored by TLC (hexane/EtOAc, 80:20). The mixture was then directly submitted to flash column chromatography, affording the corresponding adducts as essentially pure compounds.

Compound 11 A: Obtained from ketone **10 A** (30 mg, 0.15 mmol) using catalyst **C9**. Yield: 68 mg, 89%. White solid; m.p. 92 °C; $[\alpha]_D^{25} = -95.8^\circ$ ($c = 1.00$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.02–7.85$ (m, 2H), 7.71–7.61 (m, 3H), 7.57–7.45 (m, 3H), 7.45–7.25 (m, 7H), 6.42 (d, $J = 16.6$ Hz, 1H), 6.12 (d, $J = 16.6$ Hz, 1H), 4.56 (t, $J = 4.3$ Hz, 1H), 3.18 (dd, $J = 16.6$, 4.0 Hz, 1H), 2.64–2.51 (m, 1H), 2.49–2.37 (m, 2H), 2.26 (dd, $J = 16.6$, 4.6 Hz, 1H), 2.06–1.69 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.0$, 138.3, 137.3, 136.1, 134.5, 134.1, 132.6, 130.3, 130.2, 129.5, 128.9, 128.8, 128.3, 126.6, 80.8, 54.4, 39.7, 36.1, 31.1, 27.0, 21.3 ppm; MS (ESI): *m/z* calcd. for $C_{28}H_{32}N_2O_5S_2$: 526.6855 [$M+NH_4^+$]; found: 526.1727.

Compound 13 B: Obtained from ketone **12 B** (39 mg, 0.15 mmol) using catalyst **C9** (12 mg, 0.0075 mmol). White solid; m.p. 107 °C; yield: 70% (59 mg, 0.105 mmol); $[\alpha]_D^{25} = +10.8^\circ$ ($c = 1.00$, 92% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.86–7.72$ (m, 4H), 7.66–7.51 (m, 2H), 7.49–7.22 (m, 6H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.13 (d, $J = 16.7$ Hz, 1H), 5.98 (d, $J = 16.7$ Hz, 1H), 4.89–4.80 (m, 1H), 3.83 (s, 3H), 2.98 (d, $J = 20.0$ Hz, 1H), 2.74–2.54 (m, 1H), 2.42–2.32 (m, 1H), 2.32–2.21 (m, 1H), 2.13 (d, $J = 14.2$ Hz, 1H), 1.75 (d, $J = 14.2$ Hz, 1H), 1.68 (dd, $J = 9.1$, 4.6 Hz, 2H), 1.16 (s, 3H), 1.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 212.0$, 159.6, 138.3, 134.1, 134.1, 130.8, 130.3, 129.7, 129.7, 129.1, 128.8, 128.8, 127.7, 114.2, 80.9, 55.3, 52.5, 51.0, 38.3, 36.3, 33.0, 32.1, 30.9, 27.3 ppm; MS (ESI): *m/z* calcd. for $C_{31}H_{35}O_6S_2$: 567.1875 [$M+H^+$]; found: 567.1882.

Compound 32: Ketone **11 A** (125 mg, 0.25 mmol), ethylene glycol (60 μL, 1.0 mmol), and triethyl orthoformate (80 μL, 0.50 mmol) were dissolved in 1,2-dichloroethane (1,2-DCE, 0.6 mL), and then camphorsulfonic acid (16 mg, 0.07 mmol) was added. The resulting solution was stirred at 70 °C overnight. The mixture was then directly submitted to flash column chromatography on silica gel (hexane/EtOAc, 80:20) to give the title compound as a white solid; m.p. 67–69 °C; yield: 135 mg, 98%; $[\alpha]_D^{25} = -69.0^\circ$ ($c = 1.00$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05–7.99$ (m, 2H), 7.72–7.65 (m, 1H), 7.60–7.52 (m, 4H), 7.50–7.44 (m, 3H), 7.42–7.34 (m, 2H), 7.29 (d, $J = 7.2$ Hz, 1H), 7.20–7.12 (m, 2H), 6.37 (d, $J = 4.4$ Hz, 3H), 4.43 (t, $J = 4.0$ Hz, 2H), 4.04–3.80 (m, 4H), 2.79 (dd, $J = 16.2$, 4.0 Hz, 1H), 2.34 (dd, $J = 16.2$, 4.0 Hz, 2H), 2.05 (d, $J = 14.1$ Hz, 2H), 1.82–1.43 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.9$, 137.6, 137.3, 134.7, 134.1, 132.3, 131.2, 130.8, 129.6, 129.0, 128.9, 128.9, 127.9, 126.8, 111.7, 81.4, 65.2, 65.1, 49.5, 32.5, 30.4, 27.9, 23.5, 21.0 ppm; MS (ESI): *m/z* calcd. for $C_{30}H_{36}N_2O_5S_2$: 570.7385 [$M+NH_4^+$]; found: 570.1994.

Compound 34: Ketal **32** (138 mg, 0.25 mmol) was dissolved in MeOH (2 mL), and magnesium powder (61 mg, 2.5 mmol) was added. The resulting suspension was cooled to 0 °C and a drop of trimethylsilyl chloride and a drop of 1,2-dibromoethane were added. The resulting mixture was warmed to room temperature, observing the formation of hydrogen, and the reaction was monitored by TLC (hexane/EtOAc, 80:20). After completion of the reaction (2 h), the mixture was filtered through a pad of Celite, and the removed solid was washed with MeOH. The solvent was removed from the combined filtrate and washings under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The organic solution was washed with water (2×10 mL), dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The resulting crude compound was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to give the title compound as a colourless oil. Yield: 38 mg, 56%; $[\alpha]_D^{25} = -16.2^\circ$ ($c = 0.80$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 7.1$ Hz, 2H), 7.30 (t, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.2$ Hz, 1H), 6.34 (d, $J = 16.7$ Hz, 1H), 6.23 (d, $J = 16.7$ Hz, 1H), 4.03–3.82 (m, 4H), 1.94–1.82 (m, 1H), 1.74–1.51 (m, 8H), 1.51–1.38 (m, 1H), 0.74 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.9$, 134.4, 130.3, 129.1, 128.8, 127.4, 126.7, 126.1, 113.3, 65.9, 65.6, 49.0, 32.7, 29.8, 25.7, 24.2, 21.3, 8.4 ppm; MS (ESI): *m/z* calcd. for $C_{18}H_{25}O_2$: 273.3955 [$M+H^+$]; found: 273.1722.

Compound 37: Ketal **34** (16 mg, 0.6 mmol) was dissolved in a mixture of THF (0.5 mL) and aqueous 6 M HCl (0.5 mL) and the resulting mixture was stirred at room temperature overnight. The THF was then removed under reduced pressure and the remaining aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give the title compound as an essentially pure liquid. Yield: 12.2 mg, 89%; $[\alpha]_D^{25} = -30.3^\circ$ ($c = 0.50$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40–7.27$ (m, 4H), 7.26–7.22 (m, 1H), 6.30 (d, $J = 3.9$ Hz, 2H), 2.62–2.47 (m, 1H), 2.42–2.29 (m, 1H), 2.14–2.04 (m, 1H), 1.99–1.59 (m, 7H), 0.84 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 213.2$, 137.1, 133.2, 130.6, 128.6, 127.5, 126.1, 54.8, 39.6, 36.0, 30.3, 27.3, 21.6, 8.2 ppm.

Compound 38: Alkene **37** (62 mg, 0.25 mmol) and citric acid (72 mg, 0.75 mmol) were dissolved in a mixture of *t*BuOH (36 mL) and water (1 mL). *N*-Methylmorpholine *N*-oxide (136 mg, 0.75 mmol) and osmium tetraoxide (2.5 wt% in *t*BuOH; 1.2 mL, 0.1 mmol) were then added, and the reaction mixture was stirred at 55 °C for 24 h. Part of the solvent was removed under reduced pressure, and the aqueous phase was extracted with CH_2Cl_2 (3× 2 mL). The combined organic layers were dried over $MgSO_4$, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 85:15) to give the title compound as an oil. Yield: 38 mg, 60%; $[\alpha]_D^{25} = -18.1^\circ$ ($c = 1.00$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51–7.34$ (m, 4H), 7.34–7.24 (m, 1H), 5.49 (d, $J = 4.2$ Hz, 1H), 3.99 (d, $J = 2.5$ Hz, 2H), 2.12–1.78 (m, 3H), 1.70 (d, $J = 4.0$ Hz, 1H), 1.66–1.17 (m, 8H), 0.96 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.2$, 128.6, 127.7, 126.7, 107.7, 83.3, 79.1, 51.9, 31.9, 27.2, 22.5, 20.6, 18.8, 8.9 ppm; MS (ESI): *m/z* calcd. for $C_{16}H_{21}O_2$: 245.1536 [$M-OH^-$]; found: 245.1551.

Compound 39: Product **39** was obtained as a white foam following the same acetalization procedure as described above, starting from hemiketal **38** (25 mg, 0.10 mmol). Yield: 29 mg, 96%; $[\alpha]_D^{25} = +20.1^\circ$ ($c = 0.50$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41–7.19$ (m, 5H), 5.54 (d, $J = 4.7$ Hz, 1H), 4.04–3.87 (m, 2H), 3.73–3.61 (m, 3H), 2.80 (d, $J = 10.7$ Hz, 1H), 2.35–2.21 (m, 1H), 2.08–1.95 (m, 1H), 1.89 (d, $J = 13.3$ Hz, 2H), 1.74–1.67 (m, 1H), 1.62–1.50 (m, 2H), 1.49–1.36 (m, 3H), 1.32–1.20 (m, 2H), 0.98 ppm (t, $J = 7.4$ Hz,

3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.1, 128.0, 126.9, 126.4, 83.6, 79.0, 62.1, 61.7, 52.7, 28.7, 27.9, 22.7, 20.6, 18.8, 8.7 ppm; MS (ESI): *m/z* calcd. for $C_{18}H_{27}O_5$: 307.1904 [*M*+H$^+$]; found: 307.1917.

Reaction of 10A with nitrostyrene 2a to give 42a: Catalyst **C10** (9 mg, 0.015 mmol) was added to a solution of ketone **10A** (30 mg, 0.15 mmol) and nitroolefin **3a** (45 mg, 0.30 mmol) in CH_2Cl_2 at 0 °C. The resulting solution was stirred until the reaction was complete, as monitored by TLC (48 h). The mixture was then directly submitted to flash column chromatography (hexane/EtOAc, 95:5) to afford the title compound. Colourless oil. Yield: 41 mg, 78%; $[\alpha]_D^{25} = -123.4^\circ$ (*c* = 1.00, 99% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.25 (m, 8H), 7.18 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.18 (d, *J* = 4.0 Hz, 2H), 5.23 (dd, *J* = 13.0, 3.8 Hz, 1H), 4.64 (dd, *J* = 12.9, 11.4 Hz, 1H), 4.03 (dd, *J* = 11.3, 3.8 Hz, 1H), 2.88–2.73 (m, 1H), 2.45–2.21 (m, 2H), 2.08–1.91 (m, 1H), 1.76–1.57 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.6, 136.4, 135.8, 134.7, 129.5, 129.2, 128.9, 128.6, 128.4, 127.8, 126.3, 77.8, 56.5, 49.1, 39.7, 38.9, 28.1, 21.6 ppm; MS (ESI): *m/z* calcd. for $C_{22}H_{24}NO_3$: 350.1756 [*M*+H$^+$]; found: 350.1761.

Reaction of 10A with formaldehyde to give 45: Catalyst **C10** (9 mg, 0.015 mmol) was added to a solution of ketone **10A** (20 mg, 0.10 mmol) and paraformaldehyde (30 mg, 1 mmol) in CH_2Cl_2 at room temperature. The resulting solution was stirred until the reaction was complete, as monitored by TLC (16 h). The mixture was then directly submitted to flash column chromatography (hexane/EtOAc, 90:10) to afford the title compound in essentially pure form as a white foam. Yield: 18 mg, 79%; $[\alpha]_D^{25} = +20.7^\circ$ (*c* = 0.50, 89% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5H), 6.36 (d, *J* = 16.6 Hz, 1H), 6.14 (d, *J* = 16.6 Hz, 1H), 3.83 (d, *J* = 11.4 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 2.64 (td, *J* = 13.8, 6.0 Hz, 1H), 2.49 (br s, 1H), 2.38–2.28 (m, 1H), 2.04 (m, 3H), 1.84 (m, 2H), 1.70 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.9, 136.4, 133.2, 129.8, 128.6, 128.0, 126.3, 67.9, 57.3, 40.0, 34.6, 27.5, 21.5 ppm; MS (ESI): *m/z* calcd. for $C_{15}H_{19}O_2$: 231.1385 [*M*+H$^+$]; found: 231.1389.

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Conflict of interest

The authors declare no conflict of interest.

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[1] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reaction and Synthesis*, Springer, New York, **2007**.

[2] R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.* **2017**, *56*, 9278 – 9290; *Angew. Chem.* **2017**, *129*, 9406 – 9418.

[3] a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076 – 3154; b) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531 – 3543; c) Y. Yin, Z. Jiang, *ChemCatChem* **2017**, *9*, 4306 – 4318; d) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron* **2014**, *70*, 2595 – 2615; e) Q. Zhang, X. Liu, X. Feng, *Curr. Org. Synth.* **2013**, *10*, 764 – 785.

[4] Reviews: a) S. E. Denmark, J. R. Heemstra, G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682 – 4698; *Angew. Chem.* **2005**, *117*, 4760 – 4777; b) S. V. Pansare, E. K. Paul, *Chem. Eur. J.* **2011**, *17*, 8770 – 8779. For selected examples, see: c) S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800 – 7801; d) L. Ratjen, P. García-García, F. Lay, M. E. Beck, B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 754 – 758; *Angew. Chem.* **2011**, *123*, 780 – 784; e) V. Gupta, S. Sudhir, T. Mandal, C. Schneider, *Angew. Chem. Int. Ed.* **2012**, *51*, 12609 – 12612; *Angew. Chem.* **2012**, *124*, 12778 – 12781; f) S. Basu, V. Gupta, J. Nickel, C. Schneider, *Org. Lett.* **2014**, *16*, 274 – 277.

[5] Selected examples: a) B. M. Trost, J. Hitce, *J. Am. Chem. Soc.* **2009**, *131*, 4572 – 4573; b) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319 – 2322; c) L. Yin, H. Takada, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 7310 – 7313; *Angew. Chem.* **2013**, *125*, 7451 – 7454; d) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666 – 3667; e) X. Xiao, H. Mei, Q. Chen, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Commun.* **2015**, *51*, 580 – 583; f) D. Yang, L. Wang, F. Han, D. Zhao, B. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6739 – 6742; *Angew. Chem.* **2013**, *125*, 6871 – 6874; g) D. Yang, L. Wang, F. Han, D. Zhao, R. Wang, *Chem. Eur. J.* **2014**, *20*, 8584 – 8588; h) H.-J. Zhang, C.-Y. Shi, F. Zhong L. Yin, *J. Am. Chem. Soc.* **2017**, *139*, 2196 – 2199.

[6] Reviews: a) I. D. Jurberg, I. Chatterjee, R. Tannerta, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869 – 4883; b) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812 – 6832. Selected examples: c) G. Bencivenni, P. Galzeranoa, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642 – 20647 (correction: *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 4852 – 4853); d) V. Zhan, Q. He, X. Yuan, Y.-C. Chen, *Org. Lett.* **2014**, *16*, 6000 – 6003; e) Q. Guo, A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett.* **2016**, *18*, 2628 – 2631; f) M.-L. Shi, G. Zhan, S.-L. Zhou, W. Du, Y.-C. Chen, *Org. Lett.* **2016**, *18*, 6480 – 6483.

[7] a) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem. Int. Ed.* **2014**, *53*, 14128 – 14131; *Angew. Chem.* **2014**, *126*, 14352 – 14355; b) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479.

[8] Allyl ketones: a) B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6666 – 6670; *Angew. Chem.* **2013**, *125*, 6798 – 6802; b) Z. Jing, X. Bai, W. Chen, G. Zhang, B. Zhu, Z. Jiang, *Org. Lett.* **2016**, *18*, 260 – 263; c) B. Ray, S. Mukherjee, *J. Org. Chem.* **2018**, *83*, 10871 – 10880; d) M.-Y. Han, W.-Y. Luan, P.-L. Mai, P. Li, L. Wang, *J. Org. Chem.* **2018**, *83*, 1518 – 1524. Allyl pyrazoleamides: e) T.-Z. Li, Y. Jiang, Y.-Q. Guan, F. Sha, X.-Y. Wu, *Chem. Commun.* **2014**, *50*, 10790 – 10792. 1,1-Dicyanoalkylidenes: f) T. B. Poulsen, M. Bell, K. A. Jørgensen, *Org. Biomol. Chem.* **2006**, *4*, 63 – 70; g) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, *136*, 11107 – 11114. Alkylidene 2-oxindoles: h) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin, R. Wang, *Org. Lett.* **2014**, *16*, 1394 – 1397; i) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi, G. Casiraghi, *Angew. Chem. Int. Ed.* **2012**, *51*, 6200 – 6204; *Angew. Chem.* **2012**, *124*, 6304 – 6308; j) N. Di Iorio, P. Righi, S. Ranieri, A. Mazzanti, R. G. Margutta, G. Bencivenni, *J. Org. Chem.* **2015**, *80*, 7158 – 7171. Allyl thioesters: k) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2012**, *51*, 2382 – 2386; *Angew. Chem.* **2012**, *124*, 2432 – 2436. α-Aryl α,β-enals: l) J.-K. Xie, Y. Wang, J.-B. Lin, X.-R. Ren, P.-F. Xu, *Chem. Eur. J.* **2017**, *23*, 6752 – 6756; m) X. Bai, G. Zeng, T. Shao, Z. Jiang, *Angew. Chem. Int. Ed.* **2017**, *56*, 3684 – 3688; *Angew. Chem.* **2017**, *129*, 3738 – 3742.

[9] a) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387 – 3390; b) M. Frias, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, *J. Am. Chem. Soc.* **2017**, *139*, 672 – 679; c) M. Frias, A. C. Carrasco, A. Fraile, J. Alemán, *Chem. Eur. J.* **2018**, *24*, 3117 – 3121. For a proline-catalysed Mannich reaction leading to MBH-type aldehydes, see: d) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, *46*, 1878 – 1880; *Angew. Chem.* **2007**, *119*, 1910 – 1912.

[10] a) G. Tong, B. Zhu, R. Lee, W. Yang, D. Tan, C. Yang, Z. Han, L. Yan, K.-W. Huang, Z. Jiang, *J. Org. Chem.* **2013**, *78*, 5067 – 5072; b) B. Qiao, Y.-J. Huang, J. Nie, J.-A. Ma, *Org. Lett.* **2015**, *17*, 4608 – 4611.

[11] a) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70 – 73; b) E. Marqués-López, R. P. Her-

rera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, *Org. Lett.* **2009**, *11*, 4116 – 4119; c) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660 – 4663; d) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian J.* **2011**, *6*, 2255 – 2259; e) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 5474 – 5477; *Angew. Chem.* **2009**, *121*, 5582 – 5585.

[12] Ref. [6e] includes three examples of (essentially racemic) direct α-functionalization of α,β-unsaturated ketones.

[13] Reviews: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745 – 2759; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593 – 4623; c) M. Bella, T. Caspery, *Synthesis* **2009**, 1583 – 1614; d) P. G. Cozzi, R. Hilgraf, N. Zimmerman, *Eur. J. Org. Chem.* **2007**, 5969 – 1614; e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369 – 396; f) *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; g) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 – 5367; h) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181 – 191; i) T. Ling, F. Rivas, *Tetrahedron* **2016**, *72*, 6729 – 6777; j) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740 – 751.

[14] a) X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205 – 3208; b) X. Yang, F. D. Toste, *Chem. Sci.* **2016**, *7*, 2653 – 2656.

[15] I. Iriarte, O. Olaizola, S. Vera, I. Ganboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860 – 8864; *Angew. Chem.* **2017**, *129*, 8986 – 8990 .

[16] Selected reviews on bifunctional Brønsted bases: a) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621 – 631; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632 – 653; c) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145 – 200; d) *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*, (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 1 – 118; e) X. Fanga, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185 – 1197; f) H. B. Jang, J. S. Oh, C. E. Song, *Bifunctional Cinchona Alkaloid Organocatalysts, in Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 119 – 168.

[17] a) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153 – 156; *Angew. Chem.* **2010**, *122*, 157 – 160. For selected reviews on squaramide catalysts, see: b) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330 – 2346; c) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890 – 6899; d) P. Chauhan, S. Mahahan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253 – 281.

[18] a) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059 – 2063; *Angew. Chem.* **2017**, *129*, 2091 – 2095; b) X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Taoa, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 6840 – 6842.

[19] Selected reviews on Michael additions: a) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC Publishing, Cambridge, **2010**; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; c) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365; d) "The Catalytic Enantioselective Michael Reaction": E. Reyes, U. Uria, J. L. Vicario, L. Carrillo, in *Organic Reactions, Vol. 90* (Ed.: S. E. Denmark), Wiley, **2016**, pp. 1 – 898.

[20] Reviews on sulfones: a) N. S. Simpkins, *Tetrahedron* **1990**, *46*, 6951 – 6984; b) N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, **1991**. Sulphones in organocatalysis: c) A.-N. R. Alba, X. Companyó, R. Ríos, *Chem. Soc. Rev.* **2010**, *39*, 2018 – 2033; d) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 2668 – 2679; *Angew. Chem.* **2010**, *122*, 2726 – 2738; e) Q. Zhu, Y. Lu, *Aust. J. Chem.* **2009**, *62*, 951 – 955.

[21] a) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450 – 5453; b) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137 – 2141.

[22] F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed.* **2014**, *53*, 2628 – 2632; *Angew. Chem.* **2014**, *126*, 2666 – 2670.

[23] A. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 12758 – 12762.

[24] a) R. Gompper, H. U. Wagner, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 321 – 333; b) H. L. van Maanen, H. Kleijn, J. T. B. H. Jastrzebski, M. T. Lakin, A. L. Spek, G. van Koten, *J. Org. Chem.* **1994**, *59*, 7839 – 7848; c) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813 – 814.

[25] Nucleophilicity enhancement of cyclic vs. acyclic carbanions: E. P. Kündig, A. F. Cunningham Jr., *Tetrahedron* **1988**, *44*, 6855 – 6860.

[26] The Fukui functions were calculated from the NBO charge distribution: a) W. Yang, W. J. Mortier, *J. Am. Chem. Soc.* **1986**, *108*, 5708 – 5711; b) P. W. Ayers, W. Yang, L. J. Bartolotti, *The Fukui Function in Chemical Reactivity Theory: A Density Functional View*, Taylor & Francis, Boca Raton, **2009**, pp. 255 – 267.

[27] DFT calculations were carried out with the Gaussian 16 set of programs and the M06-2X functional. For computational details, see the Supplementary Information.

[28] For a theoretical justification of the preferred γ-addition pathway (vinylogous reactivity) of certain alkylidene 2-oxindoles against nitroolefins, see: C. Curti, L. Battistini, A. Sartori, G. Rassu, G. Pelosi, M. Lombardo, F. Zanardi, *Adv. Synth. Catal.* **2018**, *360*, 711 – 721.

[29] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672 – 12673; b) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119 – 125.

[30] a) S. M. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367 – 6370; *Angew. Chem.* **2005**, *117*, 6525 – 6528; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481 – 4483; c) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967 – 1969; d) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603 – 606.

[31] I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960 – 1964; *Angew. Chem.* **2015**, *127*, 1983 – 1987.

[32] a) J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178 – 3181; b) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, *81*, 3629 – 3637; c) R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457 – 4463.

[33] Q. Zhu, L. Cheng, Y. Lu, *Chem. Commun.* **2008**, 6315 – 6317.

[34] G. H. Lee, I. K. Youn, E. B. Choi, H. K. Lee, G. H. Yon, H. C. Yang, C. S. Pak, *Curr. Org. Chem.* **2004**, *8*, 1263 – 1287.

[35] CCDC 1821643 (**38**), 1823074 (**42a**), and 1903280 (**46**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[36] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936 – 3938.

[37] Reviews on conjugate additions to nitroolefins: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; b) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561 – 2601; c) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, 2627 – 2628.

[38] K. Ishihara, Y. Ogura, *Org. Lett.* **2015**, *17*, 6070 – 6073.

[39] See the Supporting Information for details.

[40] a) X.-L. Liu, Y.-H. Liao, Z.-J. Wu, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem.* **2010**, *75*, 4872 – 4875; b) S. De, M. K. Das, S. Bhunia, A. Bisai, *Org. Lett.* **2015**, *17*, 5922 – 5925. For a review, see: c) S. Meninno, A. Lattanzi, *Chem. Rec.* **2016**, *16*, 2016 – 2030.

[41] It should be noted that while the configuration of Cα in adducts **38** and **42a** is *S*, the configuration of Cα in adduct **46** is *R*. The origin of this enantioreversal is as yet unknown, although it might be related to the large difference in size and π-extension between the respective types of electrophiles, that is, Michael acceptors vs. formaldehyde.

[42] a) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631 – 5639; b) C. Trujillo, I. Rozas, A. Botte, S. J. Connon, *Chem. Commun.* **2017**, *53*, 8874 – 8877.

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