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Universidad del País Vasco
Euskal Herriko Unibertsitatea

α'-OXY ENONES AND PYRROLIDIN-2,3-DIONES AS EFFICIENT NEW TEMPLATES IN ASYMMETRIC ORGANOCATALYTIC MICHAEL REACTIONS

DOCTORAL THESIS

Eider Badiola Aramendi

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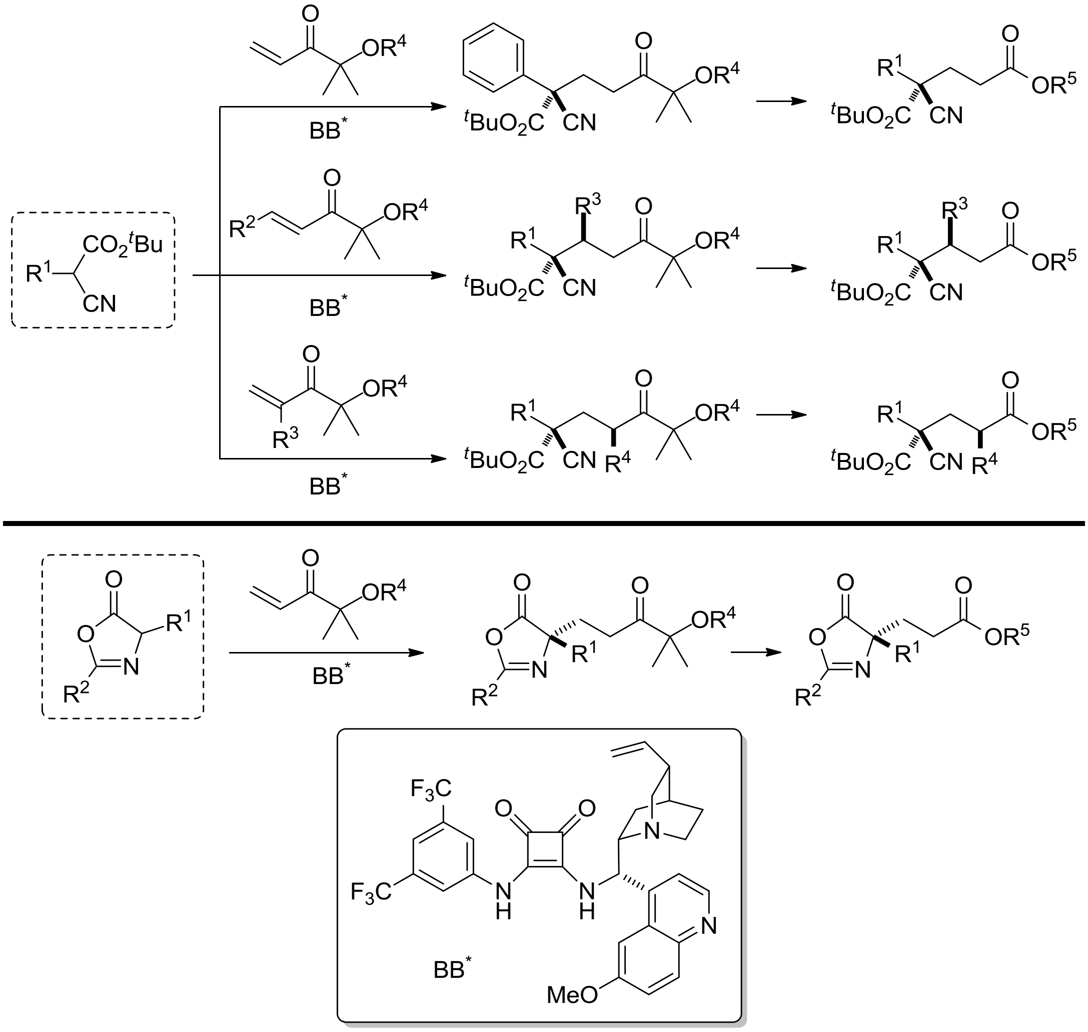
Summary

The objective of this PhD Thesis has been the search for new electrophiles and/or pronucleophiles for organocatalytic Michael reactions in which tetrasubstituted stereocenters are created. More specifically, interest has been focused in enolizable ester and α,β-unsaturated ester surrogates which are challenging substrates in organocatalysis due to their low reactivity.

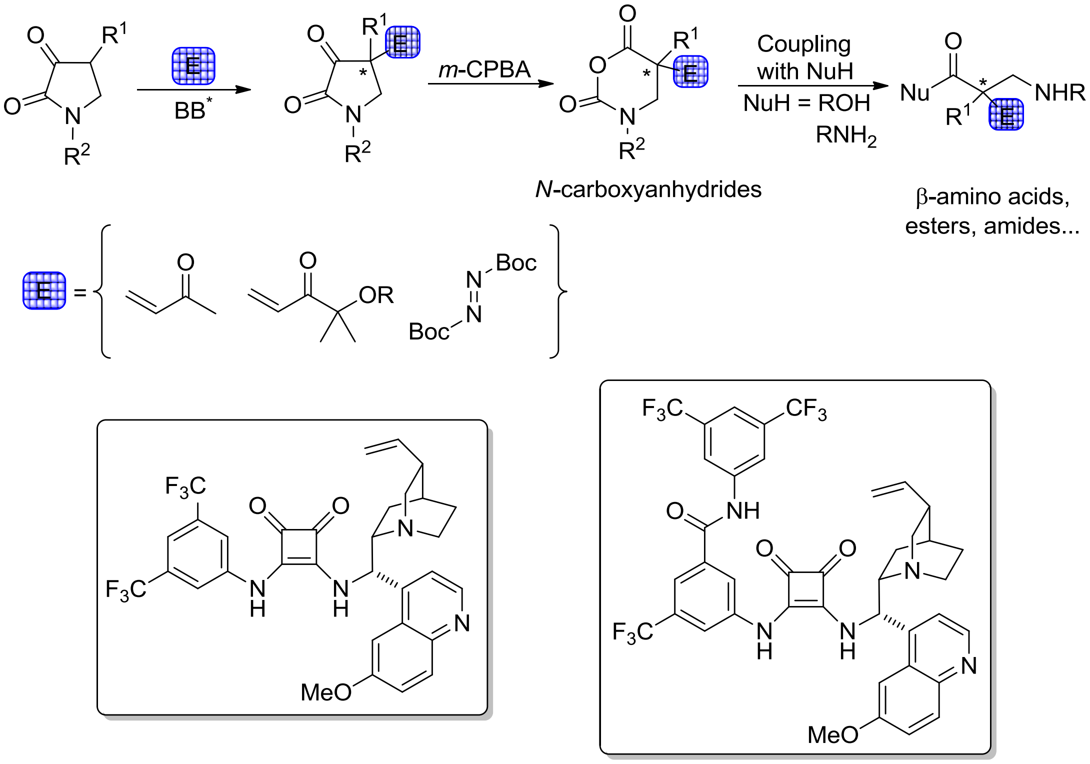
α'-Oxy enones have been widely employed in metal-catalyzed reactions as α,β-unsaturated carboxylic acid surrogates as the resulting α'-oxy ketone adducts can smoothly be converted into the correspoding aldehyde, ketone or carboxylic acid derivatives through simple oxidative cleavage of the ketol unit. However, these Michael acceptors had not been previously employed in organocatalysis. In this Thesis we show that these templates are also efficient electrophiles in the organocatalytic Michael addition of α-substituted cyanoacetates and azlactones (Scheme A) promoted by bifunctional chiral Brønsted bases.



Scheme A.

Moreover, the addition of cyanoacetates is also efficient with β-substituted and α-substituted α’-oxy enones. The corresponding Michael adducts are easily transformed into the corresponding esters, thus showning the efficiency of α’-oxy enones as α,β-unsaturated ester surrogates.

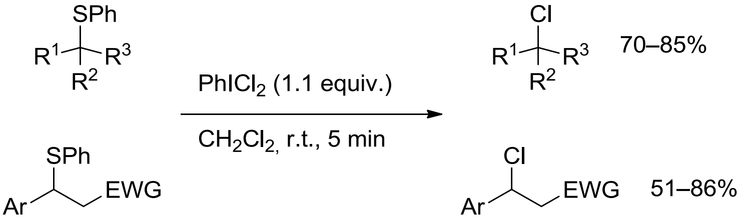
On the other hand, the efficiency of pyrrolidin-2,3-diones as Michael donors has been demonstrated for the first time in enantioselective organocatalytic conjugate additions catalyzed by bifunctional Brønsted bases with different electrophiles (Scheme B). For instance, the Michael reaction of these substrates with vinyl ketones, α’-oxy enones and di-*tert*-butyl azodicarboxylates has been explored. The resulting adducts are obtained in very good yields and stereoselectivities and, apart from being biologically interesting, are precursors of $\beta^{2,2}$-amino acids. Specifically, through their transformation into the NCAs followed by ring opening β-amino acids, ester and amides are easily affordable. This represents a new catalytic approach to $\beta^{2,2}$-amino acids, that allows for the first time their direct coupling with nucleophiles.



Scheme B.

Finally, and under the guidance of Prof. Mauro F. A. Adamo from the Department of Pharmaceutical and Medicinal Chemistry in the Royal College of

Surgeons in Ireland a quick methodology has been established for the synthesis of benzylic chlorides and β-chloro(thio)esters through oxidative desulfurative chlorination of tertiary alkyl phenyl sulfides and β-thio carbonyl compounds (Scheme C). The reaction occurs with high stereospecifity, thus being a valuable tool for the synthesis of optically active chlorides from enantioenriched sulfa-Michael adducts.

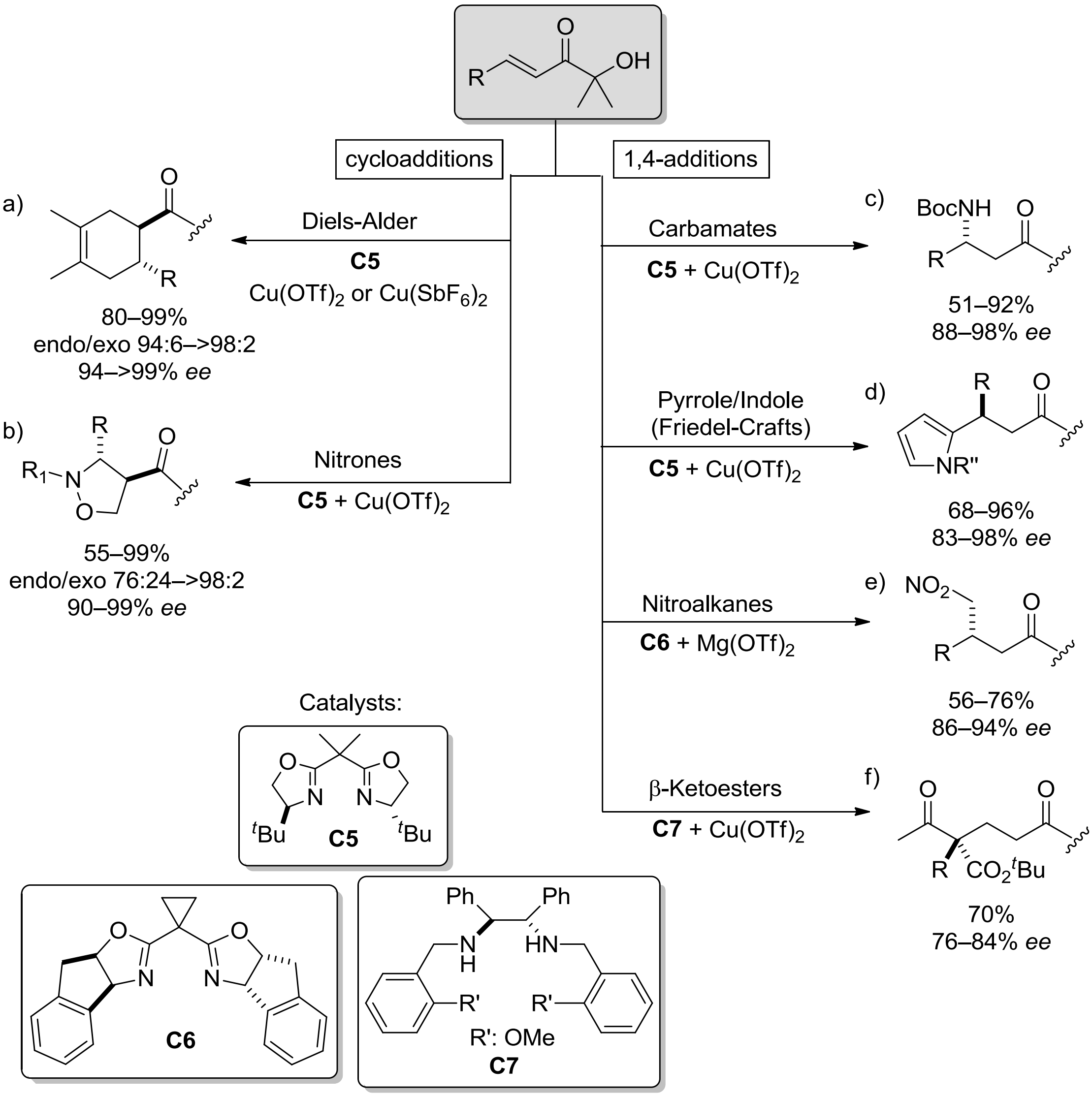


Scheme C.

Resumen

El objetivo de esta Tesis Doctoral ha sido la búsqueda de nuevos electrófilos y nucleófilos para reacciones de Michael organocatalíticas en las cuales se crean centros tetrasustituídos. En concreto, el interés se ha centrado en ésteres enolizables y equivalentes sintéticos de ésteres α,β-insaturados que son sustratos que presentan problemas en organocatálisis debido a su baja reactividad.

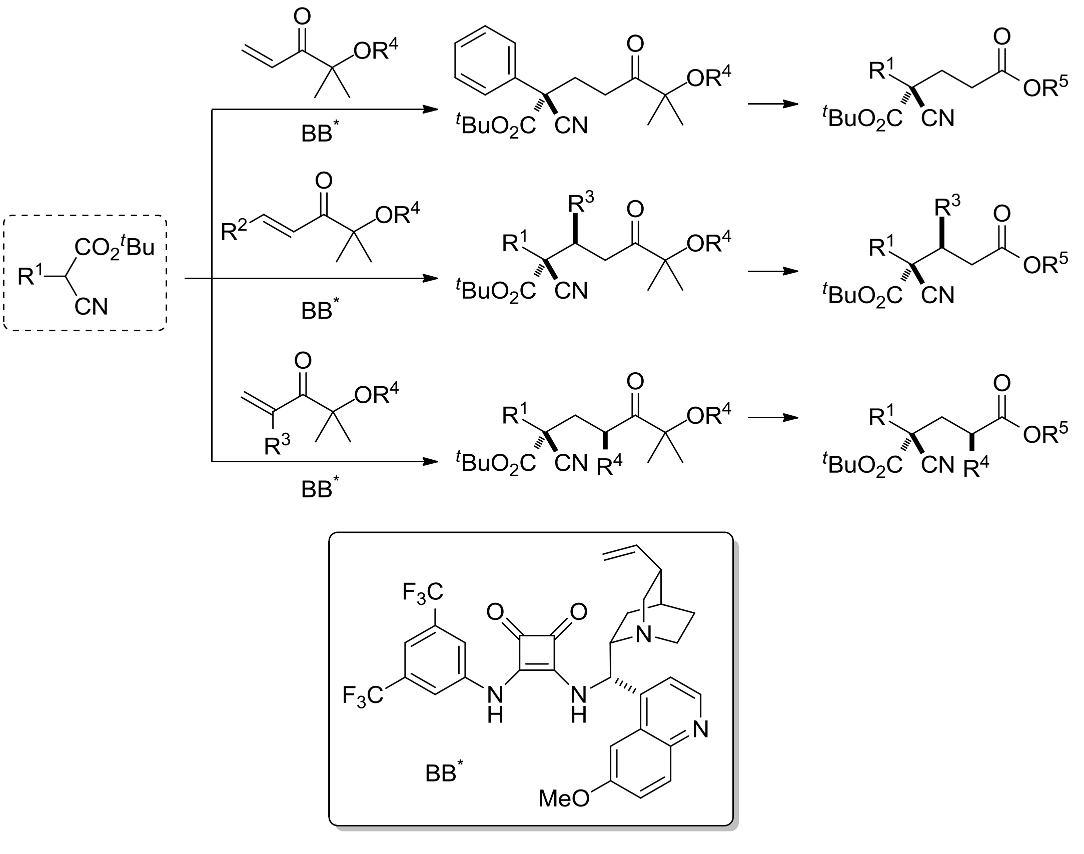
Son conocidas las dificultades que presentan los ésteres y derivados de ácidos carboxílicos α,β-insaturados como aceptores de Michael, particularmente debido a su relativamente baja reactividad y problemas de estereocontrol. Nuestro grupo de investigación ha demostrado con anterioridad que las α'-oxi enonas mostradas en el Esquema A son sustratos eficientes en diversas reacciones catalizadas por metales (tanto



Esquema A.

cicloadiciones como adiciones de Michael). Más significativamente, son equivalentes sintéticos de derivados de ácidos carboxílicos α,β-insaturados ya que el aducto resultante se puede convertir fácilmente en aldehído, cetona o ácido carboxílico mediante una escisión oxidativa de la unidad cetólica.

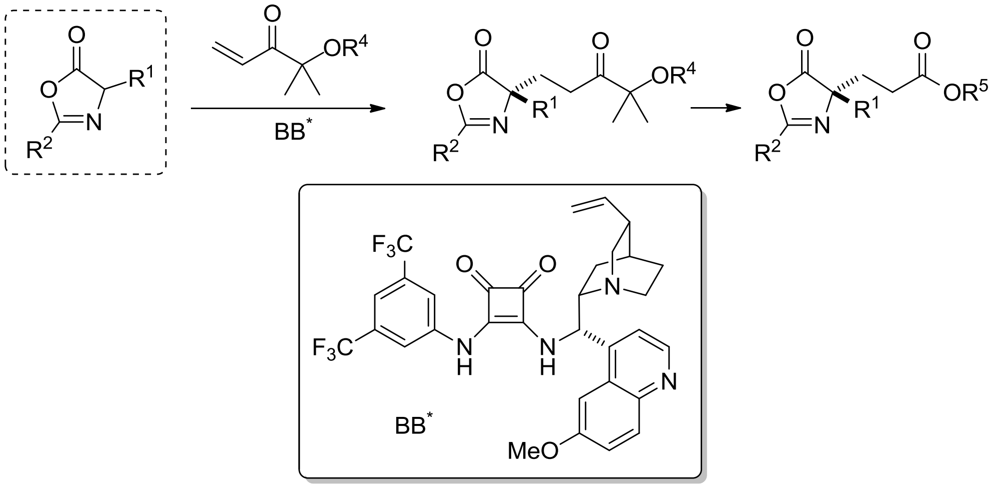
Sin embargo, estos aceptores de Michael no se habían empleado antes en organocatálisis. En esta Tesis Doctoral se demuestra que estas plantillas son electrófilos eficientes en reacciones de Michael organocatalíticas tanto de cianoacetatos α-sustituídos (Esquema B) como de azalactonas (Esquema C) promovidas por bases de Brønsted bifuncionales y quirales.



Esquema B.

Concretamente, se ha estudiado el comportamiento de α’-oxi enonas con diferentes patrones de sustitución en el doble enlace (no-sustituídas, β- y α-sustituídas). Los correspondientes aductos de Michael se obtienen con altos rendimientos con un excelente estereocontrol. En estos casos también se han conseguido las trasformaciones a ácidos carboxílicos, cetonas y aldehídos, corroborando de esta manera que son equivalentes sintéticos eficientes de derivados de ácidos carboxílicos α,β-insaturados.

La misma metodología se ha aplicado a otro tipo sustratos heterocíclicos. Mas concretamente, se han empleado azalactonas en la reacción de Michael con α’-oxi enonas generando un centro estereogénico tetrasustituído que contiene un nitrógeno en presencia como catalizador de la misma base Brønsted bifuncional y quiral empleada anteriormente (Esquema C). Se han obtenido resultados satisfactorios con la α’-oxi enona no sustituída, sin embargo, con enonas sustitudas la reacción no tiene lugar y se recuperan los productos de partida.



Esquema C.

Por otro lado, las pirrolidin-2,3-dionas de estructura como la mostrada en la Figura A son sustratos apenas explorados como pronucleófilos en reacciones organocatalíticas, a pesar de su gran interés sintético. Mientras la síntesis asimétrica y reactividad de las γ-butirolactamas **126**, y sus análogos **127** y **128** han sido ampliamente investigadas dada su presencia en diferentes compuestos biológicamente activos, las pirrolidin-2,3-dionas no han sido objeto de investigación. Desde el punto de vista sintético, la unidad de cetoamida cíclica combina caraterísticas nucleofílicas y electrofílicas, lo que permitiría llevar a cabo varios tipos de transformaciones de forma secuencial o en cascada con electrófilos y nucleófilos adecuados.

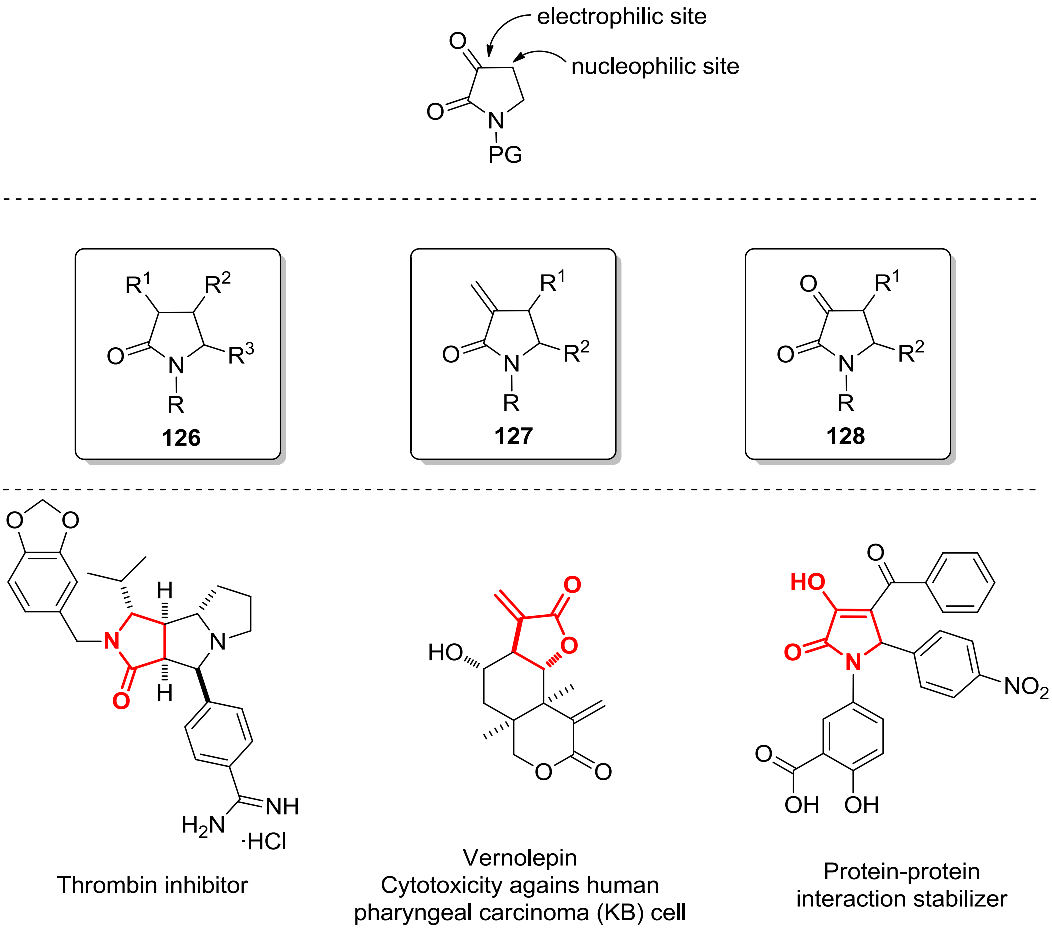
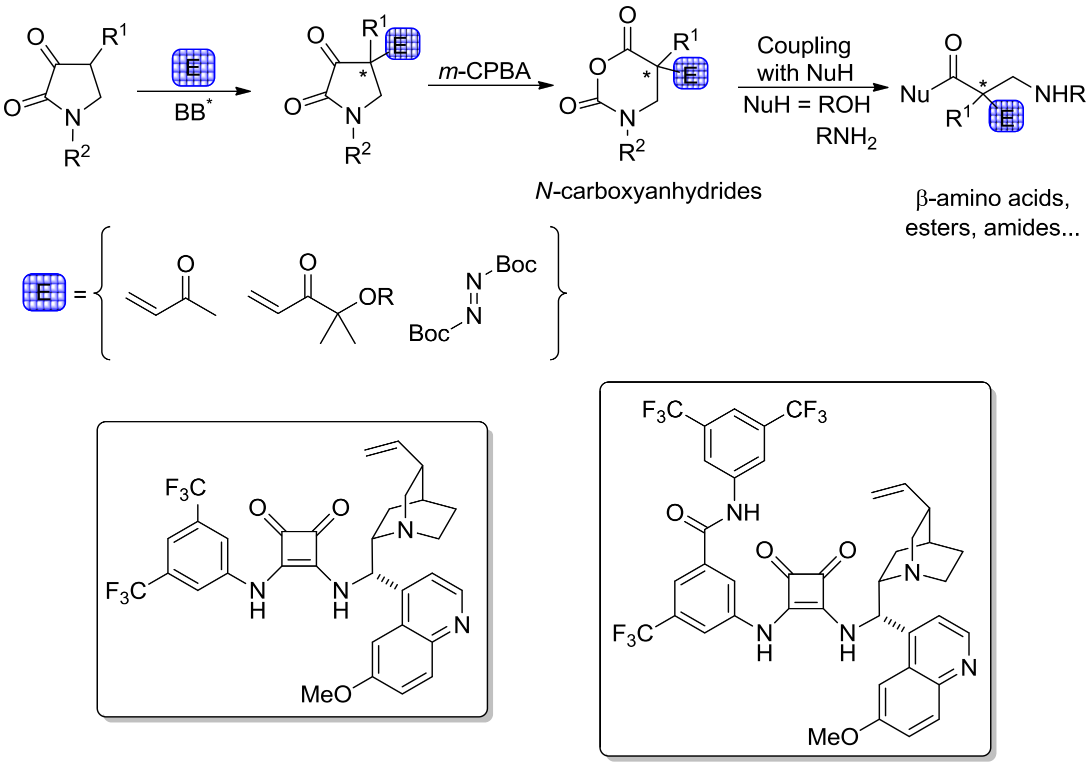


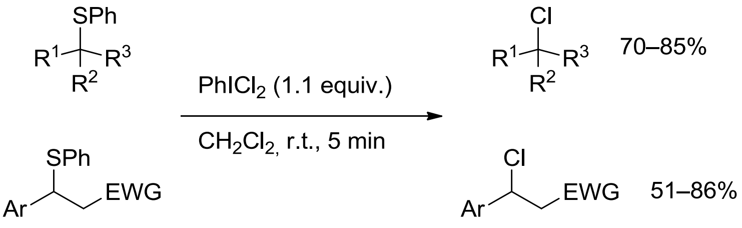
Figura A

En la presente Tesis Doctoral se demuestra por vez primera la eficiencia de pirrolidin-2,3-dionas como dadores de Michael con diferentes electrófilos en reacciones de Michael organocatalíticas y enantioselectivas catalizadas por bases de Brønsted bifuncionales. Se ha estudiado la adición conjugada de estos sustratos a vinil cetonas, α’-oxi enonas y azodicarboxilatos de *tert*-butilo (Esquema D). Los aductos resultantes, que son biológicamente interesantes, se han conseguido con buenos rendimientos y enantioselectividades. Además también son precursores de $\beta^{2,2}$-aminoácidos, ya que mediante su transformación al NCA correspondiente seguido de la apertura del anillo, se pueden conseguir β-aminoácidos, ésteres, amidas y derivados.



Esquema D.

Finalmente, bajo la supervisión del Prof. Mauro F. A. Adamo del Departamento de Química Farmacéutica y Médica de Royal College of Surgeon in Ireland se ha desarrollado una metodología rápida para la obtención de cloruros bencílicos y β-chloro(tio)ésteres mediante una cloración desulfurativa (Esquema E).



Esquema E.

Abbreviations and acronyms

AA	Amino acid
Ac	Acetyl
aq.	Aqueous
Ar	Aryl
Å	Åmstrong
BB*	Chiral Brønsted base
BIMP	Bifunctional iminophosphorane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOX	Bisoxazoline
^{i}Bu	Isobutyl
*t*Bu	*tert*-Butyl
Cat*	Chiral catalyst
DBU	1,8-Diazabicycloundec-7-ene
DCE	Dichloroethane
(DHQD)$_2$PYR	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
*m*CPBA	*meta*-Chloroperbenzoic acid
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
EPC	Enantiomerically pure compound
equiv.	Equivalent
Et	Ethyl
EWG	Electron-withdrawing group
h	Hour(s)

HPLC	High-performance liquid chromatograpy
LDA	Lithium diisopropylamide
LUMO	Lowest unocuppied molecular orbital
MBH	Morita-Baylis-Hillman
Me	Methyl
min	Minutes
MS	Molecular sieves
MVK	Methyl vinyl ketone
Napht	Naphthyl
NCA	*N*-Carboxyanhydride
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NPA	Natural population analysis
Nu	Nucleophile
ORTEP	Oak ridge thermal ellipsoid plot
P	Product
PEG	Polyethylene glycol
PG	Protecting group
Ph	Phenyl
PHN	Phenanthrene
PMP	*para*-Methoxyphenyl
^{n}Pr	*n*-Propyl
^{i}Pr	Isopropyl
quant.	Quantitative
Ref.	Reference
r.t.	Room temperature
SOMO	Singly occupied molecular orbital
t	Time
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TMS	Trimethyl silyl
TS	Transition state

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CHAPTER 1

INTRODUCTION

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1. Introduction

Life is based on a large number of reactions catalyzed by enzymes. This type of reactions are responsible for the origin of asymmetry and chirality in life. The concept of chirality was first formulated by Lord Kelvin (Figure 1, a) more than one century ago: “I call any geometrical figure, or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself”.[1] One example of a chiral object is a hand; a left hand cannot be superposed with a right hand. In the case of molecules, the pair of non superimposable mirror images are called enantiomers and in chiral environments, such as biological systems, they can exhibit different biological activity. The most representative example of this is thalidomide whose two enantiomers show very different biological properties (Figure 1, b).

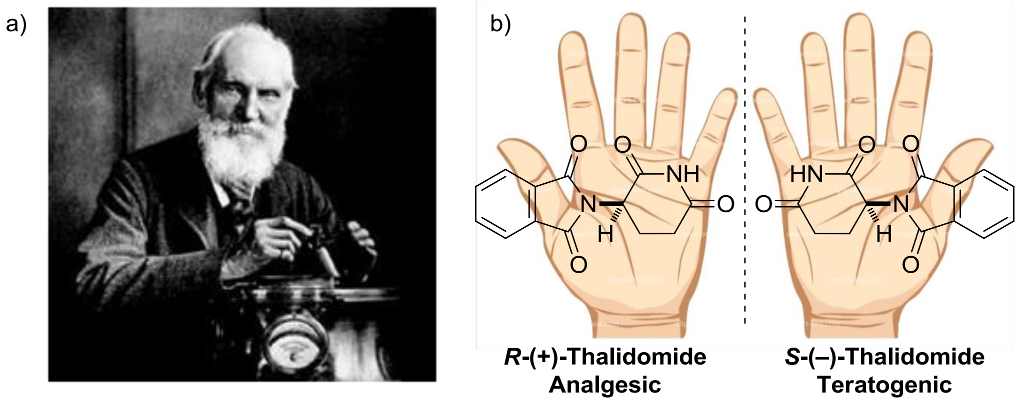

Figure 1. a) Lord Kelvin, who first defined the concept of chirality. b) Both enantiomers of thalidomide and their biological properties.

Since the tragedy of thalidomide,[2] the demand of enantiomerically pure compounds (EPC)[3] has growth sharply in the pharmaceutical industry but also in other areas including agricultural chemicals, flavors, fragances and new materials. Historically, the best way to obtain enantiomerically pure compounds was to isolate them from natural sources. However, there was a considerable dependence on natural products for the production of enantiomerically pure pharmaceuticals. Owing to the importance of the chiral molecules in life, synthetic chemists have made great efforts in

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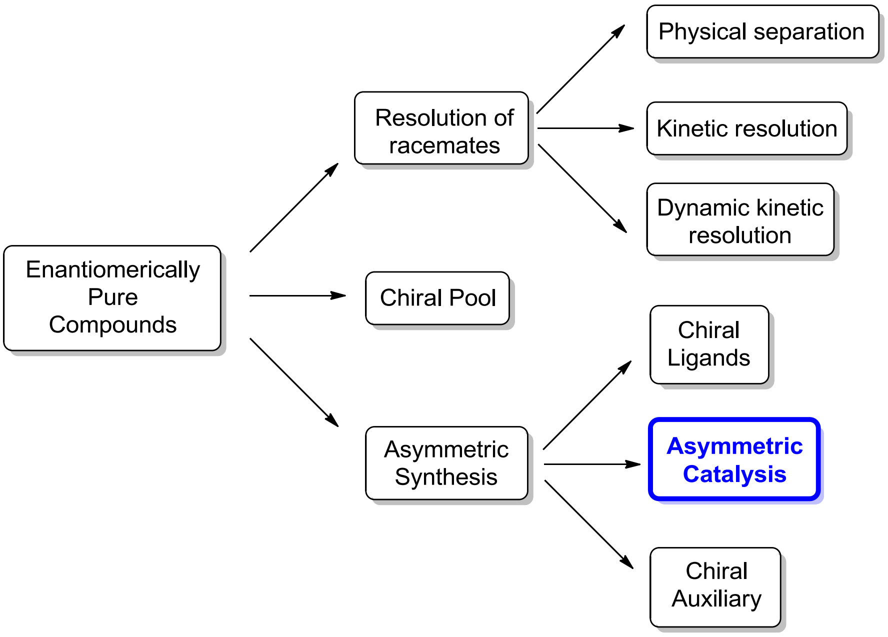
[1] Lord Kelvin: C. J. Clay and Sons, *Baltimore Lectures on Molecular Dynamics and the Wave of Theory of Light*, **1904**, Cambridge University Press Warehouse, London (UK).

[2] Stephens, T.; Brynner, R. *Dark Remedy: The impact of Thalidomide and Its Revival as a Vital Medicine*, **2001**, Perseus, Cambridge, MA.

[3] Seebach, D.; Hungerbühler, E. *Synthesis of Enantiomerically Pure Compounds (EPC-Synthesis)* in *Modern Synthetic Methods*, Scheffold, R., Ed., **1980**, p 94, Salle + Sauerländer, Frankfurt.

developing protocols to obtain enantiomerically enriched compounds. In general, there are three strategies for this purpose (Scheme 1).



Scheme 1. Strategies for the synthesis of Enantiomerically Pure Compounds (EPC).

One option is the *resolution of racemates* which consists of synthesizing the molecule in its racemic form and then resolve it by means of adequate physical or chemical methods.[4] In *dynamic kinetic resolution*[5] the enantiomers of a racemic substrate are induced to equilibrate at a rate that is faster than that of the slow-reacting enantiomer. Both enantiomers are converted into a single stereoisomeric product with a combination of a standard *kinetic resolution* and *in situ* racemisation of the less reactive enantiomer. Another alternative, known as *chiral pool*,[6] makes use of enantiopure natural products as a source of chirality and all transformations are carried out starting from these compounds and without altering the initial stereogenic elements. Among the most used natural compounds of this type are amino acids, amino alcohols, hydroxy acids, alkaloids, terpenes or sugars. Both options require stoichiometric amounts of a suitable precursor.

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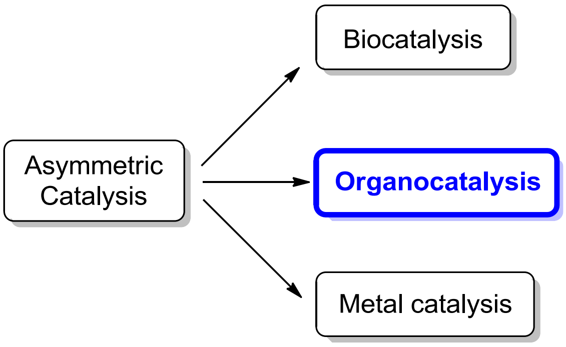
[4] For general reviews on resolution methods, see: a) Synoradzki, L.; Bernás, U.; Ruśkowski, P. *Org. Prep. Proced. Inc.* **2008**, *40*, 163–200. b) Anderson, N. G. *Org. Proc. Res. Dep*. **2005**, *9*, 800–813.

[5] For general reviews on the kinetic dynamic resolution, see: a) Pellissier, H. *Chirality from Dynamic Kinetic Resolution*, **2011**, RSC, Cambridge. b) Matute, B. M. *An. Quim*. **2006**, *102*, 46–52.

[6] For reviews about chiral pool, see: a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*, **2003**, Wiley-VCH. b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, **1996**, Wiley-VCH. c) Hanessian, S. *Pure Appl. Chem*. **1993**, *65*, 1189–1204.

Finally, *asymmetric synthesis*[7] makes use of an achiral substrate as starting material and the asymmetric induction can come from a chiral ligand,[8] a chiral auxiliary[9] or a chiral catalyst.[10] While the two formers require the use of stoichiometric amounts of those compounds, *asymmetric catalysis* which is based on the use of substoichiometric quantities of a chiral enantiopure substance that accelerates the reaction and controls the stereochemistry of the products, has growth sharply during the last decades.



Scheme 2. Strategies of asymmetric catalysis.

In the field of asymmetric catalysis three different groups can be distinguished: *biocatalysis*, *organocatalysis* and *metal catalysis* (Scheme 2). Catalytic asymmetric methods have expanded their application from the enzymes (biocatalysis),[11] which have been the prime catalysts in academia and industry for over a century. In the last decades of 20th century, metal catalysis dominated the field;[12] however, since the beginning of

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[7] For more information about asymmetric synthesis, see: a) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis 2nd Edition*, **2012**, Pergamon Press, Oxford. b) *Asymmetric Synthesis II: More Methods and Applications*, Eds. Christmann, M.; Bräse, S., **2012**, Wiley-VHC, Weinheim, Germany. c) Christmann, M.; Bräse, S. *Asymmetric Synthesis: The Essentials*, **2007**, Wiley-VCH, New York.

[8] For more information about chiral ligands, see: a) *Privileged chiral ligands and catalyst*, Ed. Zhou, Q.-L. **2011**, Wiley-VCH, Weinheim. b) Schütz, T. *Synlett* **2003**, *6*, 901–902.

[9] For more information about chiral auxiliaries, see: a) Roos, G. *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York. b) Glorious, F.; Gnass, Y. *Syntesis*, **2006**, *12*, 1899–1930. c) Roos, G. *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York.

[10] For general references on asymmetric catalysis, see: a) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*, **2007**, Wiley-VCH, Weinhelm. b) Trost, B. M. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5348–5355.

[11] For general reviews on enzymatic catalysis, see: a) De Gonzalo, G.; Lavandera, I.; Gotor, V. *Catalytic Methods in Asymmetric Synthesis. Advanced material, techniques, and applications*, **2011**, 391–527, Ed. M. Gruttadauria, F. Giacalone, John Wiley & Sons. b) Zagrebelny, N. *Russ. Chem. Rev*. **2005**, *74*, 285–296. c) Reetz, M. T.; Brunner, B.; Schnerider, F.; Schulz, C. M.; Clouthier, M. M.; Kayser, M. *Angew. Chem. Int. Ed*. **2004**, *43*, 4075–4078.

[12] For general reviews on organometallic catalysis, see: a) Leenders, S. H. A. M.; Gramage-Doria, R.; de Bruin, B.; Reek, J. N. H. *Chem. Soc. Rev*. **2015**, *44*, 433–448. b) Steinborn, D. *Fundamentals of*

2000, *organocatalysis*, which implies the use of small organic molecules to catalyze organic transformations, has become the third pillar of asymmetric catalysis. Although in 1975 Wynberg described the first asymmetric Brønsted base catalyzed reaction which consists of the Michael addition of α-ketoesters to vinyl ketones (Figure 2, a),[13] in 2000 two publications appeared almost simustaneously launching the field of aminocatalysis: one from Barbas III, Lerner and List[14] on enamine-mediated catalysis and the other from MacMillan's group[15] on iminium-mediated catalysis (Figure 2, b). These reports described two activation modes for aldehydes and α,β-unsaturated aldehydes to provide enamine and iminium ion intermediates, respectively. From this point, many types of organocatalysts have been developed, most of them sharing identical characteristics (Figure 2, c).

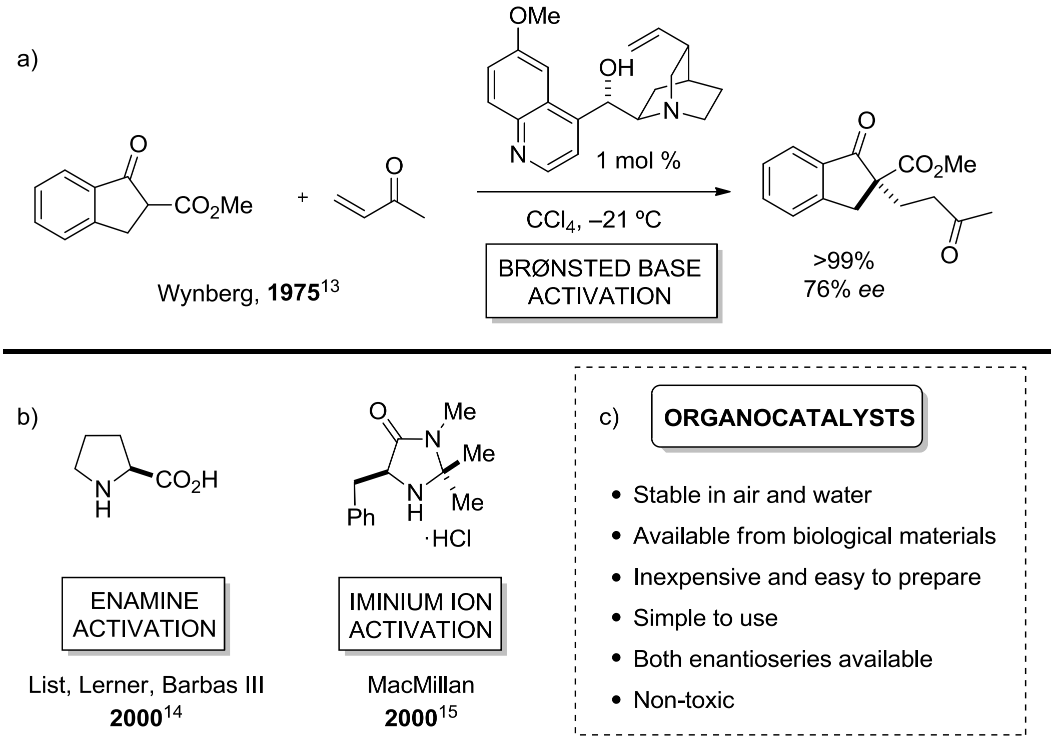

Figure 2. a) First asymmetric example of a Brønsted base catalyzed reaction. b) Catalysts employed in the first two significant reports on organocatalysis. c) General characteristics of organocatalysts.

From a mechanistic point of view, interactions between the catalyst and the substrates in asymmetric organocatalytic reactions are different to those implicated in

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Organometallic Catalysis, **2011**, Wiley-VCH, Germany. c) Astruc, D. *Organometallic Chemistry and Catalysis*, **2007**, Springer-Verlag Berlin Heidelberg.

[13] a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057–4060. b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238–2244.

[14] List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[15] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

metal-catalyzed processes. One way to classify organocatalysts is taking into account the type of interaction between the catalyst and the electrophile.[16] In general terms, if the interaction is between 4 and 15 Kcal/mol, the catalyst and substrate are said to form covalent bonds affording activated complexes. Appropriate catalysts for this type of reactions with carbonyl compounds are primary/secondary chiral amines,[17] *N*-heterocyclic carbenes[18] and some tertiary amines and analogous[19] such as alkyl pyridines, trialkylphosphines and trialkyl amines.[20] Chiral amines, known as aminocatalysts, react with carbonyl compounds such as aldehydes and ketones, to generate reactive species through different activation modes (iminium ion,[21] enamine,[22] dienamine,[23] trienamine[24] and SOMO[25]).

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[16] This classification was outlined by Langebeck in 1949 in his book "Organic Catalysts and Their Relations with Enzymes". For a more recent classification, see: a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2001**, *40*, 3726–3748. For an alternative classification based on the acid/base reactivity of organocatalysts, see: c) Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719–724.

[17] The aminocatalysis term was first mentioned in 2001: a) List, B. *Synlett* **2001**, 1675–1686. For reviews on aminocatalysis, see: b) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 358–368. c) Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Chem. Sci*. **2013**, *4*, 2287–2300. d) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgenesen, K. A. *Chem. Commun*. **2011**, *47*, 632–649. e) Alemán, J.; Cabrera, S. *An. Quím*. **2009**, *105*, 189–197. f) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, *38*, 2178–2189. g) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79–87. h) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed*. **2006**, *45*, 7876–7880.

[18] For reviews on *N*-heterocyclic carbenes, see: a) Bugaut, X.; Glorius, F. *Chem. Soc. Rev*. **2012**, *41*, 3511–3522. b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606–5655. c) Marion, N.; Diez-González, S; Nolan, S. P. *Angew. Chem. Int. Ed*. **2007**, *46*, 2988–3000.

[19] For a review on reactions promoted by chiral dialkylamino pyridines in asymmetric synthesis, see: Wurz, R. P. *Chem. Rev*. **2007**, *107*, 5570–5595.

[20] For reviews on trialkyl amines catalyzed reactions, see: a) Declerck, V.; Martínez, J.; Lamaty, F. *Chem. Rev*. **2009**, *109*, 1–48. b) Krishna, P. R.; Sachwani, R.; Reddy, P. S. *Synlett* **2008**, 2897–2912. c) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev*. **2007**, *36*, 1581–1588. d) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614–4628. e) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem*. **2007**, 2905–2916.

[21] For general reviews on iminium ion catalysis, see: a) Brazier, J. B.; Tomkinson, N. C. O. *Top. Curr. Chem*. **2010**, *291*, 281–347. b) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, *12*, 1759–1772. c) Pihko, P.M.; Majander, I.; Erkkila, A. *Chem. Rev*. **2007**, *107*, 5416–5470.

[22] For general reviews on enamine catalysis, see: a) Pihko, P. M.; Majander, I.; Erkkila, A. *Top. Curr. Chem*. **2010**, *291*, 29–75. b) Mukherjee, S.; Woon, J.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471–5569. c) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. d) Marigo, M.; Jørgensen, K. A. *Chem. Commun*. **2006**, 2001–2011.

[23] For general reviews on dienamine catalysis, see: a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem*. **2012**, 865–887. b) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

In the cases where the energy of the interaction is less than 4 Kcal/mol the process is said to be controlled by weak interactions which can involve the formation of either hydrogen bonds or ionic pairs, as in the case of phase transfer catalysis[26] or Brønsted base catalysis.[27]

During the last years the contributions in the field of asymmetric catalysis have growth considerably, and nowadays, different methodologies are available to efficiently perform many synthetically useful transformations. However, some of them are still unrealized, and or need further improvements regarding reactivity and/or selectivity. In this field, an additional challenge is the construction of tetrasubstituted stereocenters, which has proven to be quite difficult.[28] With the aim of solving these problems, recent efforts in the field are being devoted to the development of more efficient catalysts in combination with new appropriate (pro)nucleophiles and electrophiles.

In this context soft enolization[29] constitutes an attractive tool for the deprotonation of some carbonyl compounds.[30] In this strategy a relatively weak amine is generally used to reversively deprotonate a relatively acidic substrate. However, to date, the carbonyl compounds for these reactions are restricted to 1,3-diones, β-ketoesters,

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[24] For general reviews on trienamine catalysis, see: a) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem*. **2013**, *11*, 709–716. b) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, *133*, 5053–5061.

[25] For general reviews on SOMO catalysis, see: a) Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 1360–1363. b) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 7356–7359. c) Young, H.-Y.; Hung, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2007**, *129*, 7004–7005.

[26] For general reviews on phase transfer catalysis, see: a) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed*. **2013**, *52*, 4312–4348. b) Maruoka, K. *Asymmetric Transfer Catalysis*, **2008**, Wiley-VCH, Weinheim. c) Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2007**, *107*, 5656–5682. d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed*. **2007**, *46*, 4222–4266.

[27] For reviews on organocatalytic reactions promoted by chiral Brønsted bases, see: a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev*. **2009**, *38*, 632–653. b) Maruoka, K *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*; Ed.; Thieme: Stuttgart, **2012**. c) Ting, A.; Gross, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem*. **2010**, *291*, 145–200.

[28] For general reviews on the formation of tetrasubstituted stereocenters, see: a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Ed. Christoffers, J.; Baro, A., **2005**, Wiley-VCH, Weinheim, Germany. b) Liu, Y.; Han, S.-J.; Liu, W.-R.; Stoltz, B. M. *Acc. Chem. Res*. **2015**, *48*, 740–751. For organocatalytic formation of tetrasubstituted stereocenters: b) Bella, M.; Casperi, T. *Synthesis* **2009**, 1583–1614. For metal catalyzed formation of tetrasubstituted stereocenters: c) Hawner, C.; Alexakis, A. *Chem. Commun*. **2010**, *46*, 7295–7306.

[29] For pioneering examples of soft enolization, see: a) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622–2624. b) Rathke, M. W.; Nowak, M. *J. Org. Chem*. **1985**, *50*, 2624–2626. c) Tirpak, R. E.; Olsen. R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877–4879.

[30] For some representative examples, see: a) Yost, J. M.; Garnsey, M. R.; Kohler, M. C.; Coltart, D. M. *Synthesis* **2008**, 56–58. b) Zhou, G.; Lim, D.; Coltart, D. M. *Org. Lett*. **2008**, *10*, 3809–3812.

malonates, α-cyanoacetates, 3-substituted oxindoles and related systems; all of them being easily deprotonated by relatively weak chiral Brønsted bases.

1.1. Chiral Brønsted bases as organocatalysts

Among the organocatalysts working through non covalent interactions chiral Brønsted bases have been thoroughly explored.[27] According to the IUPAC, a Brønsted base (BB) can be defined as a molecular entity capable of accepting a hydron (or proton) from an acid or the corresponding chemical species. From the perspective of organic transformations, proton transfer is often considered a key activation step of one of the reaction components that precedes the new bond creation in the coupling of reactants through the formation of a chiral ionic pair. Figure 3 shows the catalytic cycle followed in this type of reactions.

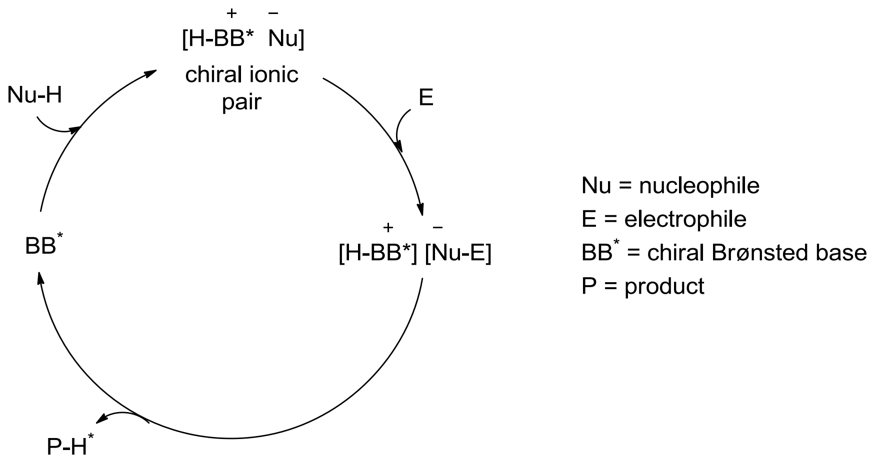

Figure 3. Catalytic cycle promoted by Brønsted bases.

Various nitrogen-containing functionalities have been used for the design of chiral BB catalysts. Among them, tertiary amines, guadinines,[31] amidines and imidazoles are the most prominent (Figure 4, a). In this context, alkaloids, particularly those of cinchone family are a source of enantiopure BB catalyst candidates providing access to various BBs which display reasonable constitutional and stereochemical diversity (Figure 4, b). Another type of BB catalysts are derived from α-amino acids which are cheap starting materials. Other non-natural sources, such as synthetic 1,2-diamines and binaphthols, have also been employed as enantiopure material precursors for the design of Brønsted base catalysts (Figure 4, c).

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[31] For reviews on guanidines in asymmetric synthesis, see: a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752. b) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553–557.

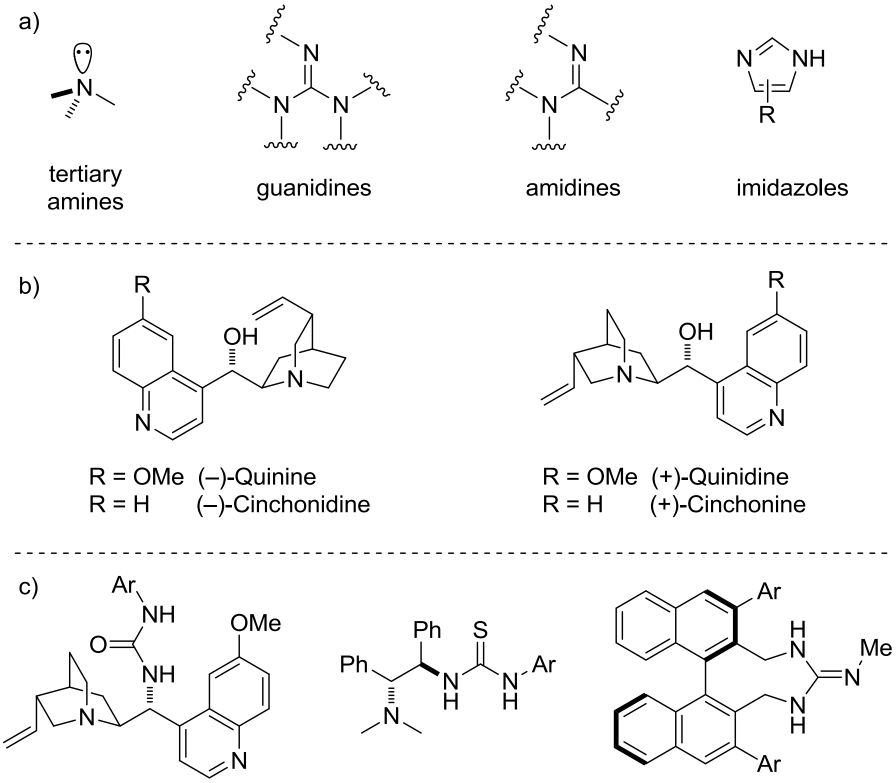

Figure 4. a) Chiral BB catalysts' basic core functions. b) Alkaloids from the cinchone family. c) Some representative chiral Brønsted base catalysts.

1.1.1. The concept of "bifunctionality"

Enzymes are examples of polyfunctional catalysts since they are able to combine multiple interactions in the transition states or intermediates to lower the activation energy increasing reaction rates and specifity. Considering these principles of enzymes, many chemists have designed bifunctional catalysts which include two different reacting functional sites (Figure 5).[32] Bifunctional chiral catalysts are able to simultaneously bind and activate two reacting partners because of the presence of two

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[32] For a general review on bifunctional catalysis promoted by Brønsted-base thiourea catalysts, see: a) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197. For a general review on bifunctional organocatalysis, see: b) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, 23, 490–508. For a general review on multiple catalysis with two chiral units, see: c) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6216–6232. For a mechanistic study of bifunctional catalysis promoted by cinchona alkaloids, see: d) Cucinotta, C.S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. *Chem. Eur. J.* **2009**, *15*, 7913–7921. For a general review on bifunctional catalysis promoted by α,α-diarylprolinol catalysts, see: e) Lattanzi, A. *Chem. Commun.* **2009**, 1452–1463. For a general review on bifunctional catalysis promoted by Brønsted-base thiourea/urea catalysts, see: f) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510. For a general review on bifunctional catalysis promoted by Cupreine and Cupreidine catalysts, see: g) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, 45, 7496–7504.

catalytic units which can work as Lewis acid/base or Brønsted acid/base centers improving reaction efficiency and/or selectivity.

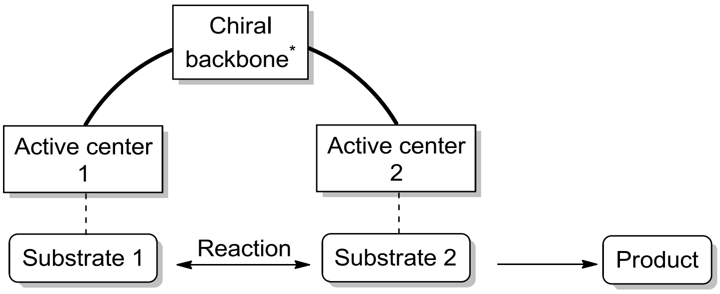

Figure 5. General structural pattern of bifunctional catalysts.

Cinchona alkaloids such as quinine and quinidine are simple molecules of Nature (Figure 6, a). In the first example of a Brønsted base catalyzed reaction published in 1975 by Wynberg,[13] it was shown that cinchona alkaloids promote the enantioselective addition of α-ketoesters to vinyl ketones operating as bifunctional catalysts (the tertiary amine moiety was proposed to deprotonate the α-ketoester pronucleophile and the hydrogen-bond donating hydroxyl group to activate the enone electrophile). However it was not until 1997 that Shibasaki employed for the first time the same bifunctional activation strategy efficiently with metal catalysts in the aldol reaction of aldehydes with ketones (Figure 6, b).[33] Later, this metal catalytic concept was extended to other transformations.[34] In 2003, Takemoto and co-workers developed 1,2-*trans*-cyclohexyldiamine-derived thiourea catalysts for enantioselective Michael additions of dimethylmalonate to nitroalkenes (Figure 6, c).[35] The authors propose that the Lewis acidic thiourea moiety activates the nitroalkene electrophile by hydrogen-bonding while the basic amine deprotonates the pronucleophile.[36] In view of the precedent set by Takemoto's catalyst, since 2005 many research groups have described

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[33] Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed*. **1997**, *36*, 1871–1873.

[34] For some reviews on this type of metal catalysts, see: a) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117–1127. b) Matsunaga, S.; Shibasaki, M. *Bull. Chem. Soc. Jpn*. **2008**, *81*, 60–75. c) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev*. **2006**, *35*, 269–279. d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev*. **2002**, *102*, 2187–2209.

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

[36] However, later Pápai and Zhong proposed that the malonate was coordinated to the *NH*-bonds of the thiourea moiety and the nitrostyrene was activated by the protonated tertiary amine based on DFT and ^{1}H-NMR studies: a) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc*. **2006**, *128*, 13151–13160. b) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett*. **2010**, *12*, 2682–2685.

different transformations promoted by thiourea-substituted cinchona alkaloid catalysts with excellent results.[37]

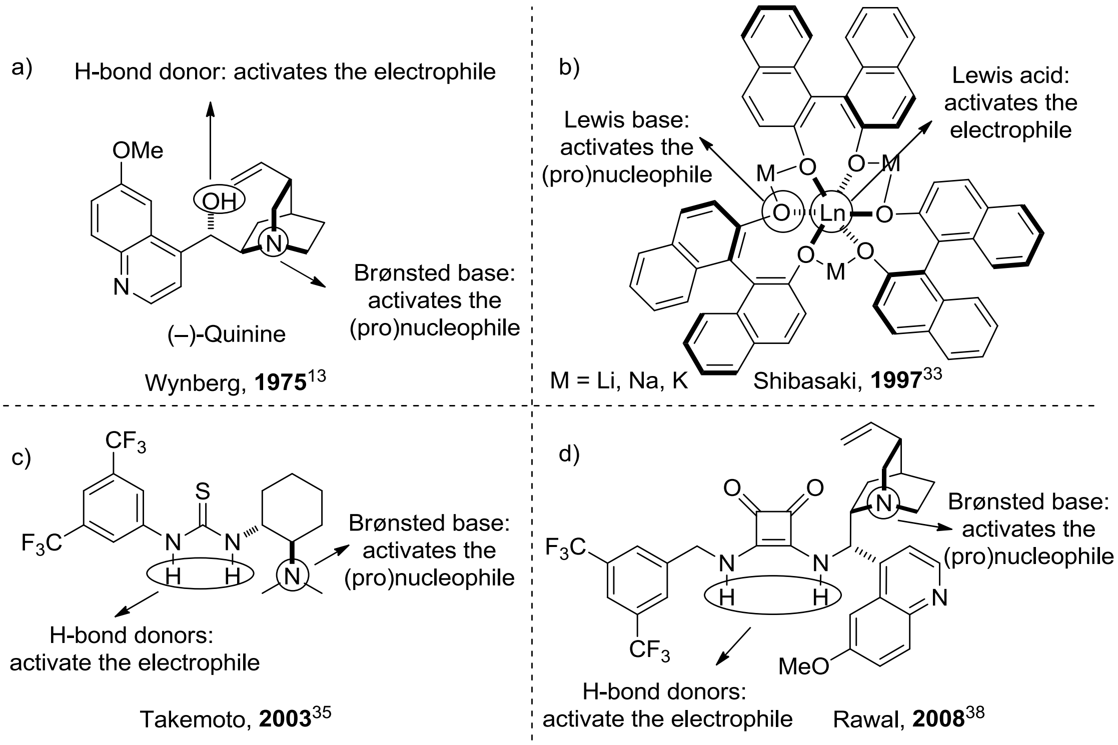

Figure 6. Representative examples of first developed bifunctional catalysts.

In 2008, Rawal's group described a new type of bifunctional catalysts based on the squaramide functionality (Figure 6, d).[38] Before, squaramides had been used as artificial anion receptors in molecular recognition studies due to their ability to interact with negatively charged species such as carboxylates and nitrates.[39] Since then,

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[37] For pioneering examples, see: a) Li, B. J.; Jiang, L.; Liu, M.; Cheng, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603–606. b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969. c) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370. d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. For some recent examples, see: e) Han, W.-Y.; Zhao, J.-Q.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2013**, *78*, 10541–10547. f) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 6320–6324.

[38] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14418.

[39] a) Prohens, R.; Tomàs, S.; Morey, J.; Deyá, P. M.; Ballester, P.; Costa, A. *Tetrahedron Lett.* **1998**, *39*, 1063–1066. b) Frontera, A.; Morey, J.; Oliver, A.; Piña, N. M.; Quiñonero, D.; Costa, A.; Ballester, P.; Deyá, P. M.; Anslyn, E. V. *J. Org. Chem.* **2006**, *71*, 7185–7195.

squaramide catalysts have emerged as an effective alternative to the urea/thiourea- and guanidine-base catalysts.[40]

1.1.2. Squaramides *vs* thioureas

Squaramides are remarkable four-membered ring systems derived from squaric acid that are able to perform up to four hydrogen bonds. They contain two hydrogen-bond donors (*N–H*) and two carbonyl acceptors (*C*=*O*). Compared to thioureas, squaramides are more "bifunctional" because they offer three possible *H*-bonding patterns as shown in Figure 7, a. Both (thio)urea and squaramides are structurally rigid, although, there are some structural differences between them. The distance between the two *N–H* groups in thioureas has been calculated to be approximately 2.13 Å;[41] whereas Rawal estimated the distance for squaramides to be 2.71 Å[38] (Figure 7, b). Furthermore, the "square geometric" structure of the cyclobutenedione ring induces a convergent orientation of the *N–H* groups. Both functionalities have the possibility of delocalizing the nitrogen lone pair through the carbon-oxygen double bond; however, only in the case of squaramides further delocalization can occur through the partially aromatic cyclobutenedione system.[42] Thus, the *N–H* acidity of the squaramide is higher compared to thiourea due to their vinylogous amide nature (Figure 7, c). Cheng calculated a number of popular squaramide organocatalysts' acidities and compared them to thioureas.[43] He found that the pK_a values of squaramides are lower than their thiourea analogues, in which 0.13–1.97 pK_a gap units are obtained. The fact that squaramide is more acidic indicates that it engages in stronger hydrogen bonds than the corresponding thiourea. These results may explain why lower loadings of squaramide catalysts can perform with even higher reactivity in a broad range of asymmetric transformations.

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[40] For reviews on squaramides, see: a) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253–281. b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899. c) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346.

[41] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

[42] Tomàs, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deyá, P. M.; Ballester, P.; Costa, A. *J. Org. Chem.* **1996**, *61*, 9394–9401.

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

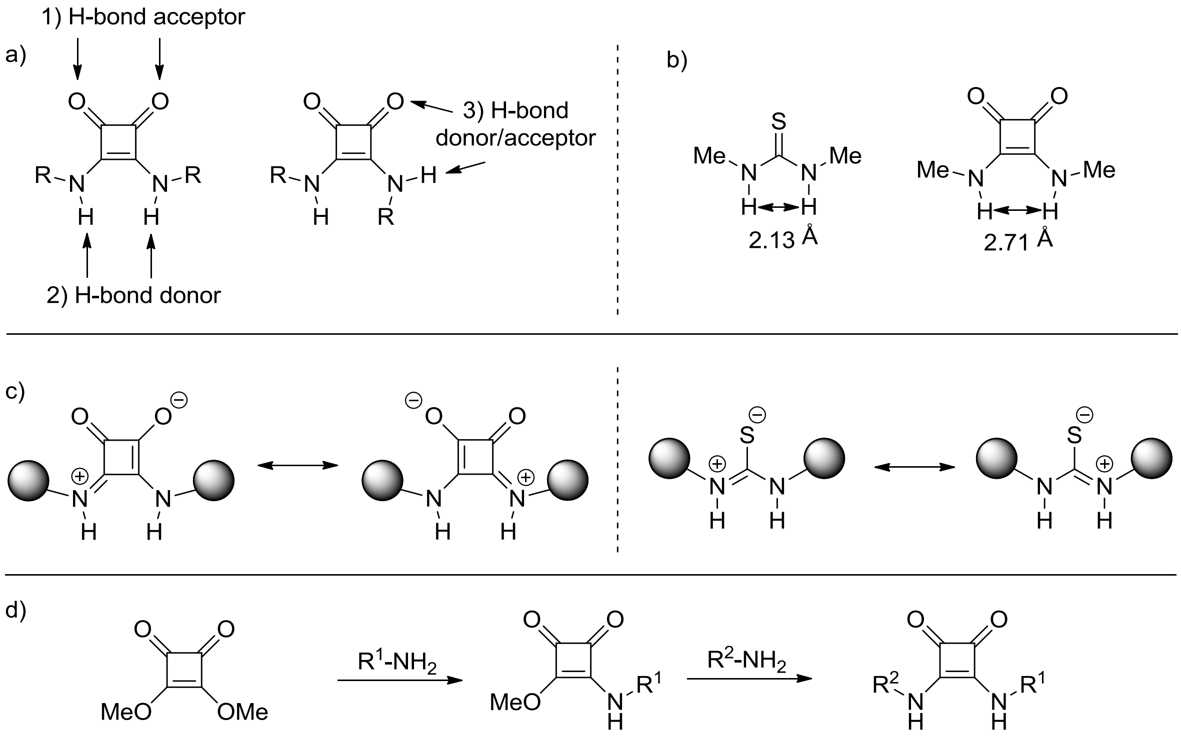

Figure 7. a) Possible *H*-bonding patterns of squaramides. b) Calculated distances between *N–H* groups. c) Comparison of the zwitterionic forms of the thiourea and squaramide skeletons. d) General preparation scheme for the squaramide catalysts.

The additional advantage of these squaramide catalysts is their facile preparation from easily available or commercially starting materials. The first step involves a substitution reaction of dimethyl squarate which is followed by a similar substitution reaction with a chiral primary amine (Figure 7, d). In most cases the catalyst precipitates out of solution making chromatographic purification unnecessary.[40c]

1.2. Organocatalytic asymmetric Michael reactions

Among all the organic reactions the Michael addition or conjugate reaction of nucleophiles to electron-poor alkenes is one of the most frequently used *C–C* and *C*–heteroatom bond forming reactions in organic synthesis.[44] The first example of a Michael reaction was described by Arthur Michael in 1887.[45] In general, the Michael reaction involves the addition of a nucleophile (Nu) or Michael donor to an electron deficient olefin known as Michael acceptor (Figure 8). The electron withdrawing group

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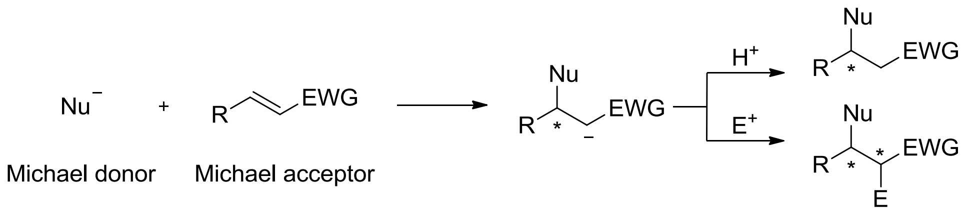
[44] For a general review on asymmetric Michael additions, see: Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC, **2010**.

[45] Michael, A. *Prakt. J. Chem*. **1887**, *36*, 349–356.

(EWG) of the Michael acceptor stabilizes the carbanionic intermediate of the addition and this intermediate can either be protonated or react with another electrophile, to create up to two new stereocenters. Therefore in these reactions the control of both, the enantio- and diastereoselectivity are of considerable significance and a broad range of chiral metal-based[46] and metal-free catalysts[47] have been described in this field.



Nu^- = Nucleophile (nucleophilic atom C, O, N, S or P)
EWG = Electronwithdrawing group (CHO, COR', CO_2R', $CONR'_2$, SO_2R', SOR', NO_2 ...)

Figure 8. General scheme of the Michael reaction.

A wide range of Michael acceptors and donors have been reported for this reaction. Commonly employed Michael acceptors are α,β-unsaturated carbonyl compounds (aldehydes, ketones, esters, amides, etc.), but it is also usual the use of other activating groups such as nitro, sulfonate, sulfoxide, phosphate or phosphonate. Moreover, the nucleophilic atom of the donor can be a carbon or a heteroatom such as *O, N, S* and *P* (oxa-, aza-, sulfa- and phospha-Michael reaction).[48]

As said before, reactions under proton transfer conditions promoted by soft enolization have demonstrated to provide a mild and operationally simple approach to the deprotonation of certain types of carbonyl compounds; and this strategy has also

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[46] For reviews on asymmetric Michael additions promoted by metal-ligand complexes, see: a) Kanemasa, S.; Hasegawa, M.; Ono, F. *The Chemical Record* **2007**, *7*, 137–149. b) Comelles, J.; Moreno-Mañas, M.; Vallribera, A. *Arkivoc* **2005**, *ix*, 207–238. c) Jha, S. C.; Joshi, N. N. *Arkivoc* **2002**, *vii*, 167–196. d) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171–196.

[47] For reviews on asymmetric organocatalytic Michael additions, see: a) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis*, **2007**, *14*, 2065–2092. b) Almasi, D.; Alonso, D.; Nájera, D. C. *Tetrahedron: Asymmetry*, **2007**, *18*, 299–365. c) Tsogoeva, S. B. *Eur. J. Org. Chem*. **2007**, 1701–1716.

[48] For more information about general and asymmetric hetero-Michael reactions, see: a) Helmchen, G.; Hoffmann, R. W.; Muzler, J.; Schaumann, E. *Stereoselective Synthesis [Houben-Weyl]*, **1996**, Thieme, Stuttgart, New York, vols. E21c y E21e. For reviews on aza-Michael reactions, see: b) Enders, D.; Wang, X.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076. c) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron*, **2009**, *65*, 9657–9672. d) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem*. **2005**, 633–639. For a review of oxa-Michael reactions, see: e) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218–1228. For a review of sulfa-Michael reactions, see: f) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem*. **2011**, *7*, 582–595. g) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis*, **2007**, 959–980. For a review of phospha-Michael reactions, see: h) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem*. **2006**, 29–49.

been thoroughly investigated in asymmetric Michael additions. However, as previously mentioned, the carbonyl substrates for these reactions are generally restricted to relatively acidic compounds such as 1,3-dicarbonyl compounds, 3-substituted oxindoles and related systems (13–18 pK_a range).[49] Generally, enolizable esters or carboxylic acid derivatives have been challenging in this strategy, because their pK_a values (approximately 19 in DMSO)[49] are much higher. Although recently it has been shown that the problem of this low reactivity may be addressed through the development of Brønsted base catalysts with increased basicity,[50] most efforts still focus on the development of new pronucleophiles suitable for soft enolization. On the other hand, among Michael acceptors, simple α,β-unsaturated esters and amides still also are challenging substrates in direct Michael additions and have only been employed in few successful conjugate reactions, mainly due to their inherent lower reactivity and the limitations associated to the activation/coordination of these compounds to a suitable catalyst. As an alternative, different efficient unsaturated ester/amide surrogates have been described to solve this problem.

1.3. Templates for asymmetric Michael organocatalytic reactions

Ideally, strongly biased achiral templates may decrease otherwise observed substrate-catalyst dependence, attenuating undesired fluctuations on the catalyst efficiency. The proper design of templates may result crucial in many difficult transformations, such as, the enantioselective generation of tetrasubstituted carbon stereocenters.[28] The challenge of controlling the configuration of asymmetric tetrasubstituted centers is crucial in organic synthesis since they can be found not only in a range of important and useful compounds in pharmaceutical and medicinal contexts, but also in a large variety of natural products. Tetrasubstituted carbons can be prepared routinely by the face selective addition of a nucleophile to carbon-carbon or a carbon-heteroatom double bond. Stereochemical induction may be achieved through neighboring functional groups in the substrate and/or in a chiral catalyst.

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

[50] For references related to stronger Brønsted bases, see: a) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Wiley: New York, **2009**. For reviews on chiral guanidines, see: b) Selig, P. *Synthesis* **2013**, *45*, 703–718. c) Fu, X.; Tan, C.-H. *Chem. Commun*. **2011**, *47*, 8210–8222. d) Ishikawa, T. *Chem. Pharm. Bull*. **2010**, *58,* 1555–1564. e) Leow, D.; Tan, C.-H. *Synlett* **2010**, 1589–1605. f) Leow, D.; Tan, C.-H. *Chem. Asian. J.* **2009**, *4,* 488–507. g) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752. For a review on chiral iminophosphoranes, see: h) Krawcyk, H.; Dziegielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, L. *Chem. Eur. J.* **2015**, *21,* 10268–10277.

In this field during the last years various types of useful templates have been described, and a number of Michael acceptors and heterocyclic pronucleophiles (Michael donors) have been found efficient templates in asymmetric conjugate reactions under proton transfer conditions with the simultaneous creation of tetrasubstituted carbons. The most representative examples of known templates for Michael reactions are summarized below.

1.3.1. Michael acceptor templates

Among several categories of Michael acceptors, α,β-unsaturated carbonyl compounds are of great synthetic significance. Adducts obtained from the conjugate reaction of a nucleophilic reagent to α,β-unsaturated aldehydes, ketones or carboxylic acid derivatives have been really useful in many applications. However, Michael addition to carboxylic acid derivatives is not well suited for iminium ion activation catalysis and the most common activation mechanism relies on the coordination of the carbonyl group to a Lewis acid (metal catalysis) or a *H*-bond donor species (organocatalysis).

To solve this problem in these difficult transformations, on the one hand some properly designed templates have been developed. Attractive α,β-unsaturated carboxylic acid surrogates are expected to posses certain qualities: i) enhanced activation of the substrate towards nucleophilic attack; ii) improved coordination to the chiral catalyst; and, iii) easy and mild replacement upon demand of the activating group.

On the other hand, as previously mentioned, a less developed alternative to overcome the low inherent electrophilicity of this type of Michael acceptors in Brønsted base catalysis is to raise the Brønsted basicity of the catalyst. Increased Brønsted basicity in the catalyst increases the concentration of the nucleophilic conjugate base and, as a consequence, the rate of the addition step. Recently, Dixon and co-workers reported a highly enantioselective sulfa-Michael addition of alkyl thiols to unactivated α-substituted acrylate esters catalyzed by the bifunctional iminophosphorane (BIMP) superbase organocatalyst **C1** (Scheme 3).[51] The strong Brønsted basicity of the iminophosphorane moiety provides the necessary activation of the alkyl thiol pronucleophile, while the two *tert*-leucine residues and thiourea hydrogen-bond donor facilitate high enantiofacial selectivity in the protonation of the transient enolate intermediate.

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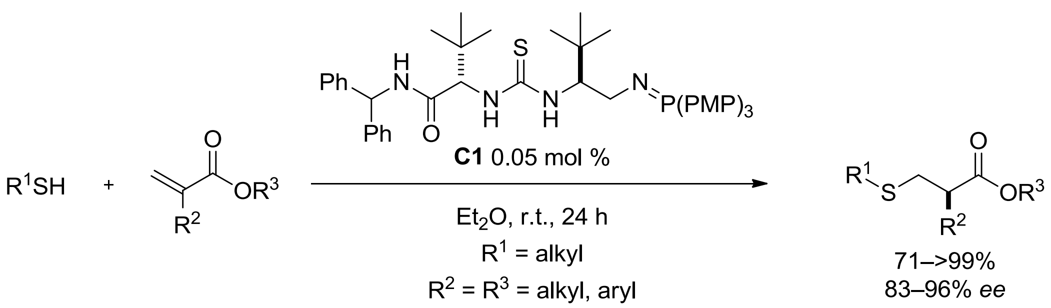
[51] Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995.



Scheme 3. Organocatalytic sulfa-Michael addition of thiols to α-substituted acrylates catalyzed by BIMP **C1**. **Dixon, 2015**.

The basic mode of activation of α,β-unsaturated carbonyl compounds assumes that the lone electron pair of the carbonyl oxygen atom coordinates to the Lewis acid or is involved in hydrogen-bonding interactions. Thus, the activation of the substrate is the result of a lowered energy of its LUMO, which induces an easier reaction with a nucleophilic reagent. In this field, several two-point binding acyl templates bearing an additional coordination site have been developed (Figure 9). Monodentate templates may lead to two degenerate *C*=*O*···metal complex geometries complicating stereocontrol. Nevertheless, bidentate templates can form cyclic chelates with metals due to the presence of an extra coordination site, thus facilitating stereocontrol.

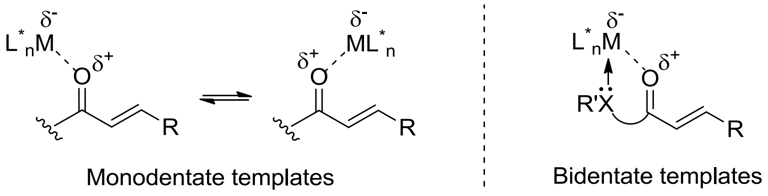


Figure 9. Monodenate *vs* bidentate acyl templates.

Following this idea, different activated carboxylated bidentate templates have been reported for stereoselective Michael additions. These templates can be classified in heteroatom-linked and carbon-linked templates depending on their structural differences (Figure 10). Among heteroatom-linked templates representative examples are α,β-unsaturated imides, α,β-unsaturated *N*-acyl heterocycles (pyrroles, pyrazoles and bentzotriazoles) and β,γ-unsaturated α-oxophosphonates (Figure 10, a). Regarding carbon-linked templates worth of mention are β,γ-unsaturated α-ketoesters, 3-methyl-4-nitro-5-alkenyl-isoxazoles and α'-hydroxy enones (Figure 10, b). The latter were introduced by our group in the realm of metal catalysis and now have been extended to the area of organocatalysis as will be outlined later.

LUMO energy values (eV) of some representative Michael acceptors are outlined in Figure 10, c. As more negative the LUMO value, more favored is the attack of the nucleophile affording the desired addition product.

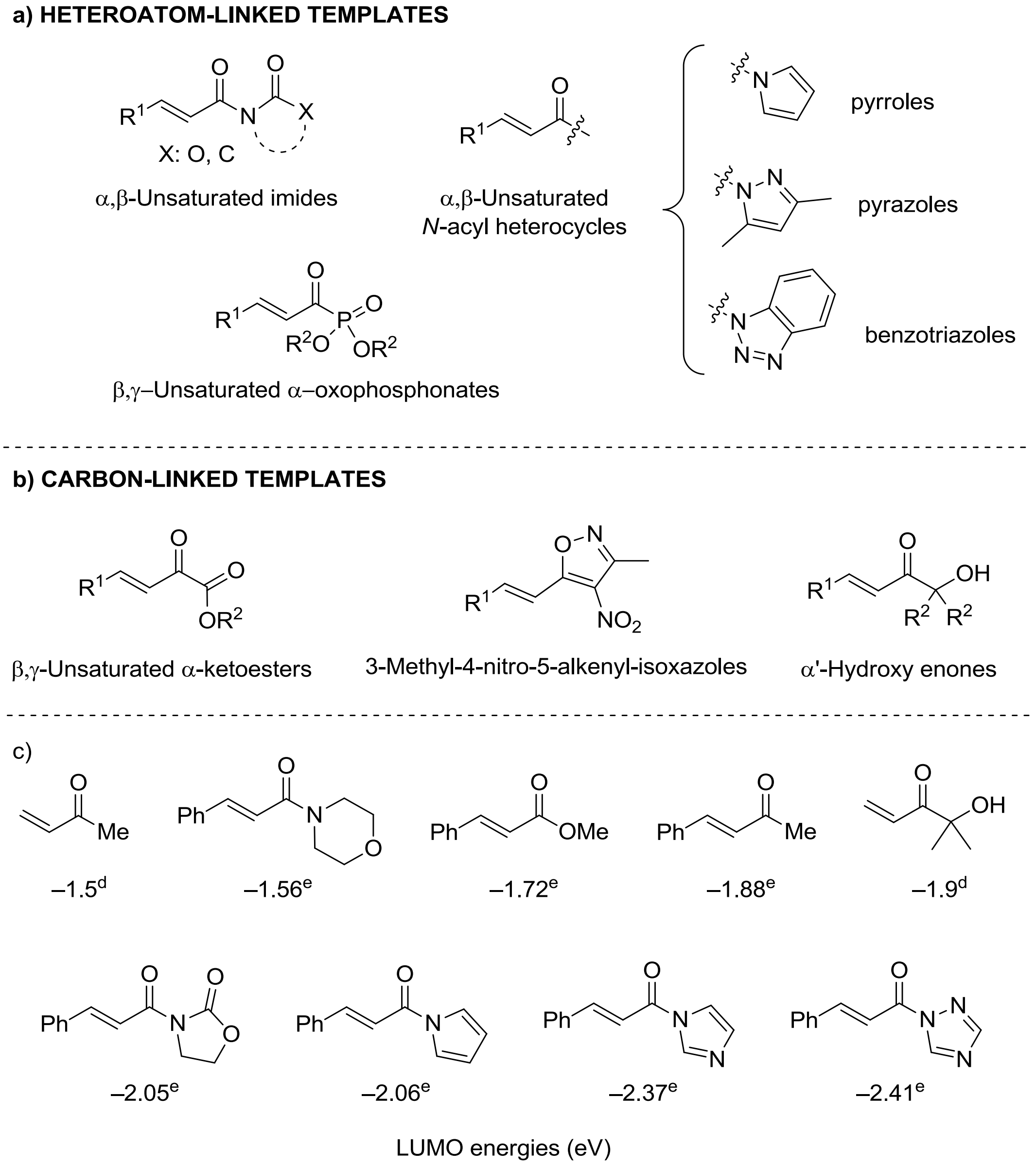


Figure 10. Examples of acyl bidentate Michael acceptor templates. a) Heteroatom-linked templates. b) Carbon-linked templates. c) LUMO energy values (eV) of some representive Michael acceptors calculated by our group (d)[52] and Shibasaki (e).[53]

The synthesis of both type of templates attached to the carboxylic *C=O* group involves a common two-step procedure from carboxylic acids and aldehydes, and/or

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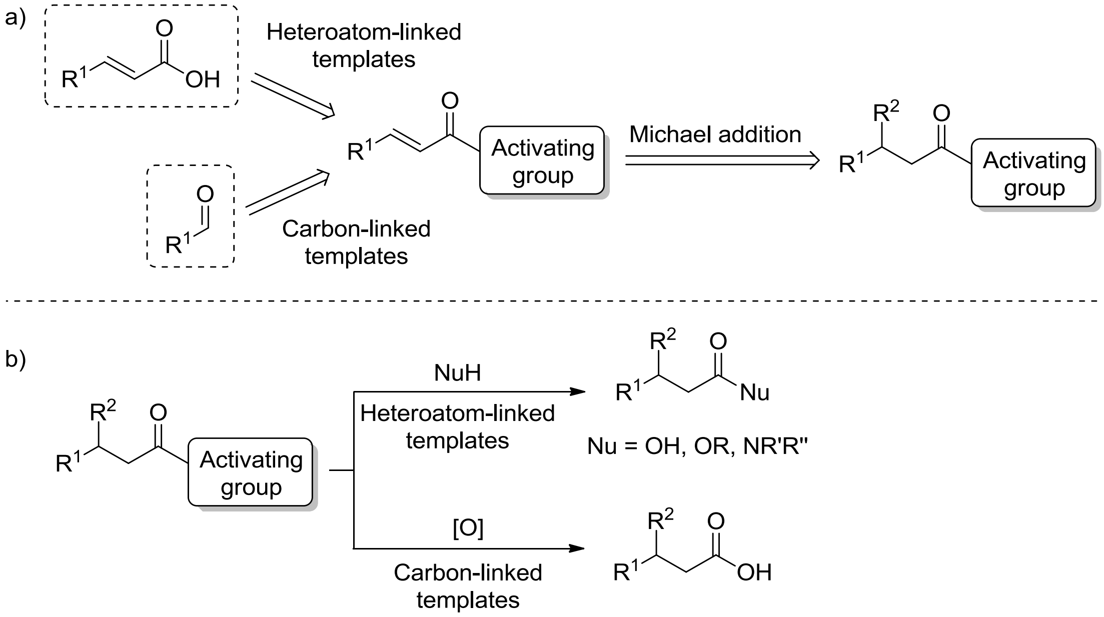
[52] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.

[53] Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559–7570.

other simple starting materials (Scheme 4, a). After performing the asymmetric conjugate addition, a simple replacement of the activating group in the final Michael adducts can be achieved by acyl substitutions in the presence of a suitable nitrogen- and oxygen-centered nucleophile in the case of heteroatom-linked templates or by *C–C* cleavage under oxidative conditions in the case of carbon-linked templates (Scheme 4, b).[54]



Scheme 4. a) General retrosynthesis of templates. b) Template transformation through activating group replacement in the final Michael adducts.

1.3.1.1. Heteroatom-linked acceptor templates

1.3.1.1.1. α,β-Unsaturated imides and α,β-unsaturated N-acyl heterocycles

Among α,β-unsaturated imides *N*-acyl oxazolidinones showed to be very useful chiral auxiliaries in asymmetric reactions after the pioneering work by the Evans group.[55] Later, further investigation of these derivatives led to the successful implementation of several metal-catalyzed enantioselective processes through the use of achiral *N*-acyl oxazolidinone templates (Figure 11). The first example of the use of

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[54] For a review on carboxylic acid surrogate templates in organocatalysis, see: a) Monge, D.; Jiang, H.; Alvarez-Casao, Y. *Chem. Eur. J.* **2015**, *21*, 4494–4504. For some reviews on α,β-unsaturated amides and related compounds in asymmetric catalytic reactions: b) Byrd, K. M. *Beilstein J. Org. Chem.* **2015**, *11*, 530–562. c) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2015**, *115*, 9922–9980.

[55] a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127. For a general review, see: b) Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Bevola, L.; Botta, B. *Current Organic Synthesis* **2007**, *4*, 81–135.

these templates in metal-catalyzed Michael reactions was reported by Evans in 1999 in the copper-mediated conjugate addition of enolsilanes and the corresponding adducts were obtained in very good yields and stereoselectivities.[56] Following this work the same group described other metal-promoted reactions with these templates.[57]

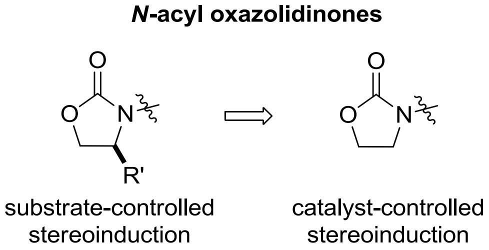

Figure 11. Evolution from a chiral auxiliary to an achiral template in Evans group.

However, the first use of α,β-unsaturated imides in organocatalysis was not reported until the year 2000 when Miller and co-workers published the enantioselective aza-Michael reaction of trimethylsilylazide[58] to α,β-unsaturated imides.[59] After this work, Takemoto reported in 2005 the highly enantioselective organocatalytic Michael addition of several soft carbon-nucleophiles (malononitrile, methyl α-cyanoacetate and nitromethane) to α,β-unsaturated imides using the bifunctional thiourea **C2** as catalyst (Figure 12, a, 1).[60] It was demonstrated that the 2-methoxybenzamide moiety was key for reactivity and stereoselectivity in the reaction, which was attributed to a self-activation of the imide by intramolecular *H*-bonding. The proposed way of action of the bifunctional catalyst **C2** is shown in Figure 12, a, 1, wherein the two imide carbonyl oxygens are proposed to coordinate to the two *N–H* groups of the thiourea based catalyst.

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[56] Evans, D.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865–868.

[57] For a review on asymmetric cycloadditions, conjugate additions and aldol reactions to achiral α,β-unsaturated imides catalyzed by Cu (II) bisoxazoline (BOX) Lewis acids, see: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.,* **2000**, *33*, 325–335.

[58] Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem. Int. Ed*. **2000**, *39*, 3635–3638.

[59] For a sulfa-Michael addition of alkyl thiols to α,β-unsaturated oxazolidinones catalyzed by thioureas, see: a) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc*. **2009**, *131*, 418–419. For a sulfa-Michael reaction of thiols to α,β-unsaturated *N*-acylated succinimides catalyzed by squaramides, see: b) Zhao, B. L.; Du, D. M. *Org. Biomol. Chem*. **2014**, *12*, 1585–1594. For a sulfa-Michael reaction of thiols to β-trifluoromethyl substituted oxazolidinones catalyzed by squaramides, see: c) Chen, W.; Jing, Z.; Chin, K. F.; Quiao, B.; Zhao, Y.; Yan, L.; Tan, C. H.; Jiang, Z. *Adv. Synth. Catal*. **2014**, *356*, 1292–1300.

[60] a) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed*. **2005**, *44*, 4032–4035. b) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2006**, *128*, 9413–9419.

α,β-Unsaturated *N*-acyl heterocycles (Figure 12, b) have also been described as efficient Michael acceptor templates in organocatalytic reactions. These templates offer diverse coordination facilities for the engagement with *H*-bonding organocatalysts. Moreover, these *N*-based heterocycles are usually good leaving groups and as such, highly suitable for subsequent acyl substitutions. Among these templates *N*-acyl pyrroles (Figure 12, b, I), pyrazoles (Figure 12, b, II) and benzotriazoles (Figure 12, b, III) have been described.

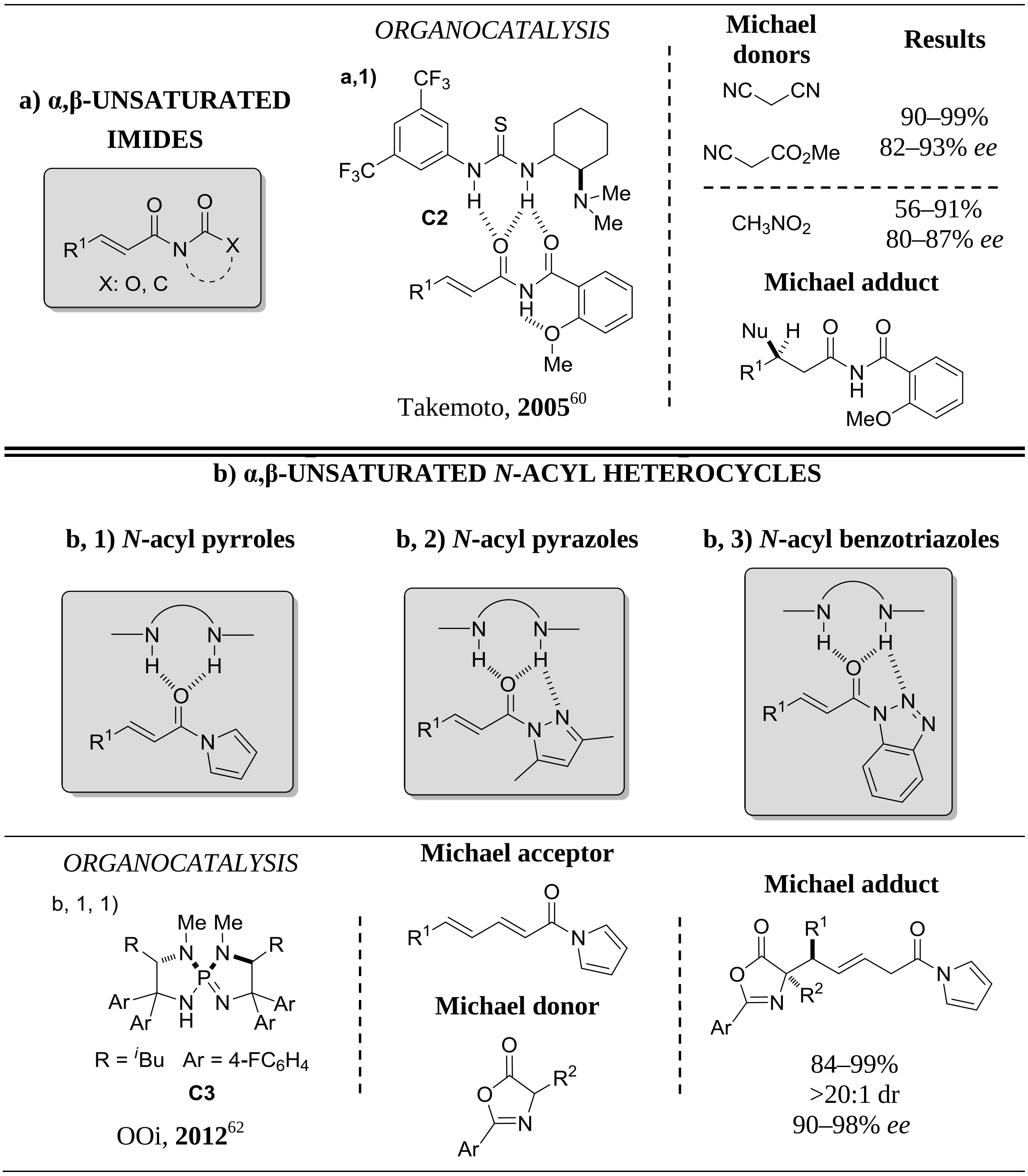

Figure 12. Representative examples of the use of *N*-acyl templates in Michael addition reactions.

In 2004 Shibasaki and co-workers demostrated for the first time the utility of α,β-unsaturated *N*-acylpyrroles as monodentate ester surrogates in metal-promoted catalytic asymmetric epoxidation and conjugate additions.[53] It has been calculated that the nitrogen lone pair in these substrates is delocalized, thus affording a similar level of LUMO energy as in simple enones. Later, Soós developed the first organocatalytic example in the Michael addition of nitroalkanes to α,β-unsaturated acylpyrroles.[61] Inspired by these results, the efficiency of these templates for the generation of tetrasubstituted stereocenters was extended to polyconjugated systems in the 1,6-conjugate reaction by Ooi in 2012 (Figure 12, b, 1, 1).[62] A highly diastereo- and enantioselective 1,6-addition of azlactones to simple δ-monosubstituted dienyl *N*-acylpyrroles promoted by the chiral iminophosphorane catalyst **C3** was described to afford Michael adducts with a tetrasubstituted stereogenic center. To the best of our knowledge, this represents the only example of the use of *N*-acyl templates involving the generation of a stereocenter of this type.

An additional *N*-centered coordination site in the pyrrol template plays a crucial role providing *H*-bond acceptor sites for better organization and higher levels of selectivity with bifunctional *H*-bond donor catalysts. Therefore, the exchange of the pyrrol ring by a pyrazole or benzotriazol gives bidentate substrates which are templates with properly positioned hydrogen bond acceptors for activation by chiral organocatalysts. The efficiency of *N*-acyl pyrazoles has been demonstrated in the conjugate addition of *O*-benzylhydroxylamine[63] and in cascade sulfa-Michael aldol reactions.[64] α,β-Unsaturated acylbenzotriazoles have also been successfully applied as useful ester surrogates in the 1,4-addition of azlactones.[65]

As mentioned before, the main characteristic of all these templates is that replacement of the activating group in the final Michael adducts can be easily performed under the appropriate reaction conditions to afford different products such as ketones, esters and amides as shown in Scheme 6.

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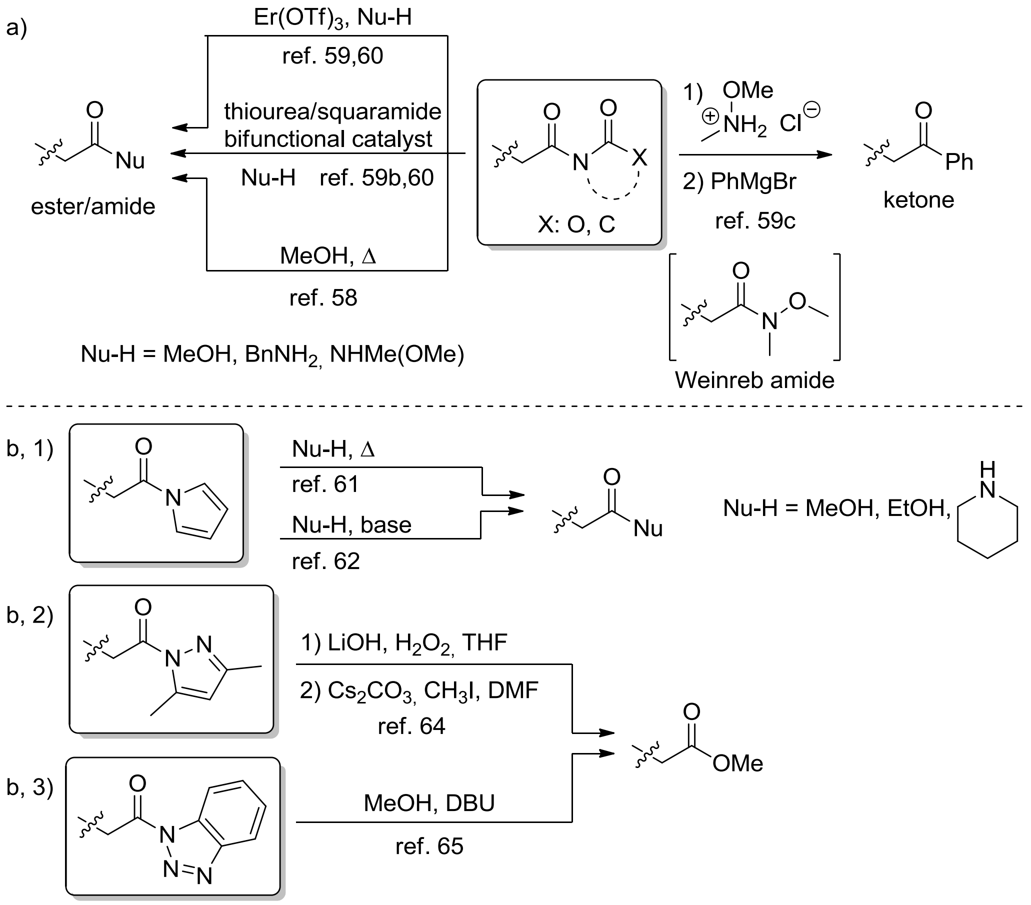
[61] Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475–3480.

[62] Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370–19373.

[63] Itoh, K.; Sibi, M. P. *J. Am Chem. Soc.* **2007**, *129*, 8064–8065.

[64] Dong, X. Q.; Fang, X.; Tao, H. T.; Zhou, X.; Wang, C. J. *Chem. Commun.* **2012**, *48*, 7238–7240.

[65] Uraguchi, D.; Ueki, Y.; Ooi, T. *Science*, **2009**, *326*, 120–123.



Scheme 5. Transformation of the Michael adducts. a) Michael adducts coming from α,β-unsaturated imides. b) Michael adducts coming from α,β-unsaturated *N*-acyl heterocycles.

1.3.1.1.2. β,γ-Unsaturated α-oxophosphonates

β,γ-Unsaturated α-oxophosphonates are also activated ester/amide surrogates which exhibit unique characteristics: i) the electron-withdrawing phosphonate group activates the substrate towards nucleophilic attack, ii) the catalyst can bind to the phosphoryl and carbonyl oxygens leading to further activation and constraining to a well-defined orientation; and iii) the lability of the *C–P* bond of **1** enables a facile nucleophilic cleavage for the transformation into the corresponding ester or amide **2** under mild conditions (Figure 13, a). The adjacent *C=O* and *P=O* groups have usually a dihedral angle of 180º; however, reorientation is possible in the presence of favorable interactions. Breuer *et al*. calculated the energy difference between the s-*trans* and s-*cis* conformations of the *C–P* bond of dimethyl benzoylphosphonate **3** which was only of 1.8 kcal (Figure 13, b).[66] All these characteristics make β,γ-unsaturated α-oxophosphonates good Lewis/Brønsted acid acceptors and/or *H*-bond acceptors.

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[66] Karaman, R.; Goldblum, A.; Breuer, E.; Leader, H. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 765–774.

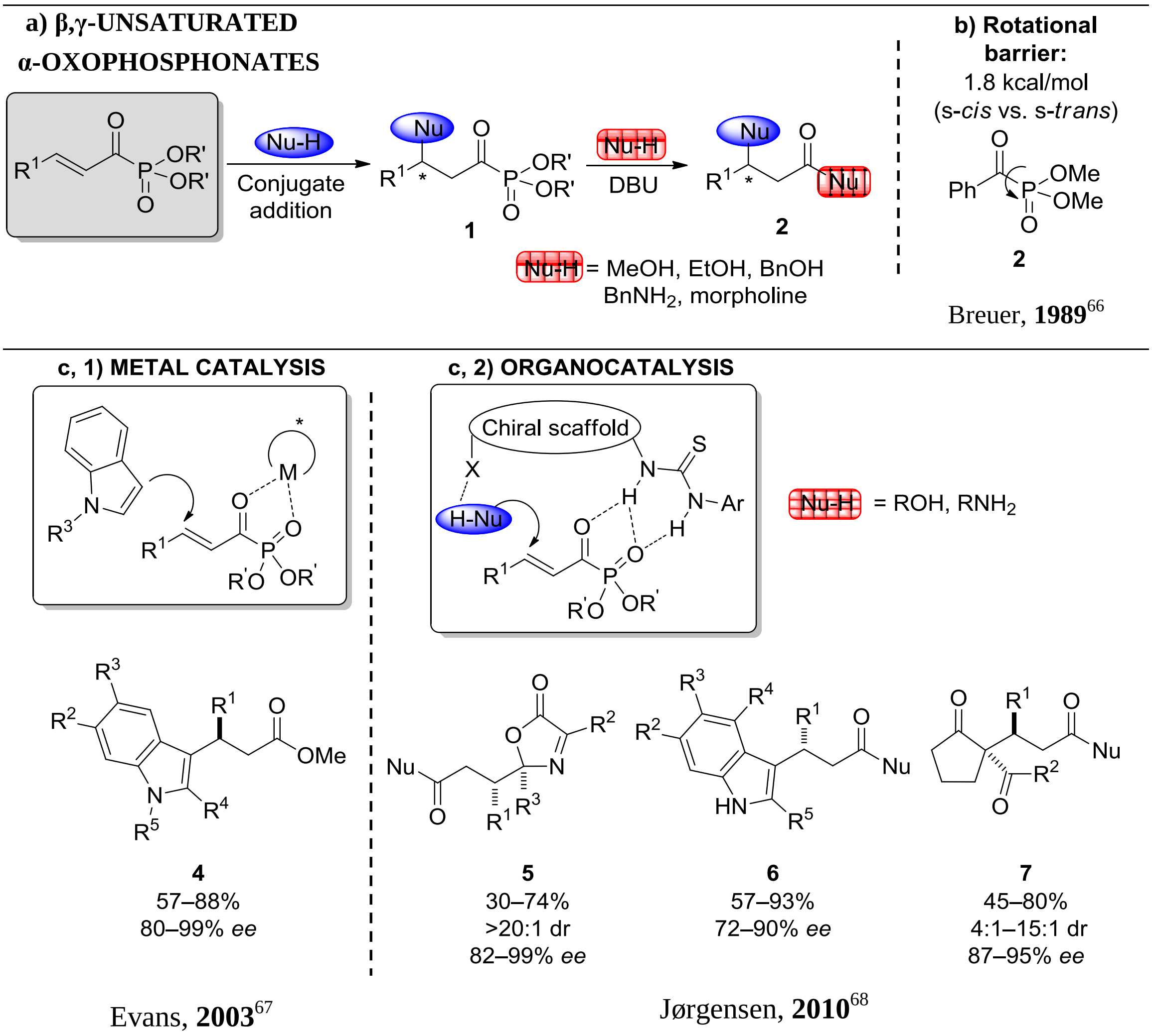

Figure 13. a) β-Functionalization of β,γ-unsaturated α-oxophosphonates and subsequent simple *C–P* bond cleaveage. b) Rotational barrier of acyl phophonates (Breuer). c) First examples of phosphonates in metal catalysis (c, 1) and bifunctional thiourea promoted catalysis (c, 2).

Acyl phosphonates were introduced as activated ester surrogates in asymmetric catalysis in 2003 by Evans in the Friedel-Crafts alkylation reaction of indoles promoted by organometallic complexes affording adducts **4** (Figure 13, c, 1).[67] After this work, many groups reported the utility of these templates through an alternative activation strategy using bifunctional chiral catalysts. Jørgensen used for the first time these unsaturated acylphosphonates in asymmetric organocatalytic reactions promoted by bifunctional thioureas with three different carbon-centered nucleophiles (oxazolones, 1,3-dicarbonyls and indoles), followed by acyl substitution with alcohols or amines to give esters and amides **5**–**7** in one pot and very good stereoselectivity (Figure 13, c, 2).[68] It is remarkable that the use of azlactones and 1,3-dicarbonyl compounds as

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[67] Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10780–10781.

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

pronucleophiles provides Michael adducts **5** and **7** wherein a tetrasubstituted stereocenter is generated efficiently, being this the only example of the creation of tetrasubstituted stereocenters with acyl phosphonates as templates.

This strategy has been extended to other nucleophiles, such as naphthoquinones[69] and 4–hydroxylcoumarins[70] which provide novel optically active chemicals with potent pharmacological properties. The usefulness of these templates has also been demonstrated in other organocatalytic reactions.[71]

1.3.1.2. Carbon-linked templates

Efficient carbon-linked templates have also been reported as acceptor in Michael addition reactions. The most representative ones are described below.

1.3.1.2.1. β,γ-Unsaturated α-ketoesters and 3-methyl-4-nitro-5-alkenyl-isoxazoles

β,γ-Unsaturated α-ketoesters (Figure 14, a) have a specific advantage as templates due to the presence of a further carboxylic function attached to the carbonyl group which enables a robust coordination to a Lewis acid or a hydrogen donor catalyst. This coordination increases the reactivity which makes them a recurring class of substrates in many types of asymmetric reactions in both metal-based and organocatalysis.[72] Among them, Michael and aldol reactions, Diels-Alder reactions, several type of cycloadditions, intramolecualr reactions, carbonyl reduction, alkylation and arylation reactions are found. Several chiral complex catalysts (Lewis acids) and organocatalysts ((thio)-urea, pyrrolidine derivatives, cinchona-based structures, Binol- or Binap-based Brønsted acids) have been reported to induce enantioselectivity in a variety of reactions with these templates.

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[69] Liu, T.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *J. Org. Chem*. **2011**, *76*, 4119–4124.

[70] Chang, X.; Wang, Q.; Wang, Y.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem*. **2013**, 2164–2171.

[71] For an inverse-electron demand hetero-Diels-Alder reaction of α,β-unsaturated aldehydes and acyl aldehydes promoted by a *H*-bond donor catalyst via dienamine formation, see: a) Albrecht, L.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2012**, *51*, 13109–13113. For an asymmetric Michael addition/lactonization of aryl- and alkenylacetic acids catalyzed by an isothiourea, see: b) Smith, S. R.; Leckie, S. M.; Holmes, R.; Douglas, J.; Fallan, C.; Shapland, P.; Pryde, D.; Slawing, A. M. Z.; Smith, A. D. *Org. Lett*. **2014**, *16*, 2506–2509.

[72] For a review on β,γ-unsaturated α-ketoesters in asymmetric organocatalytic reactions, see: Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev*. **2013**, *113*, 5924–5988.

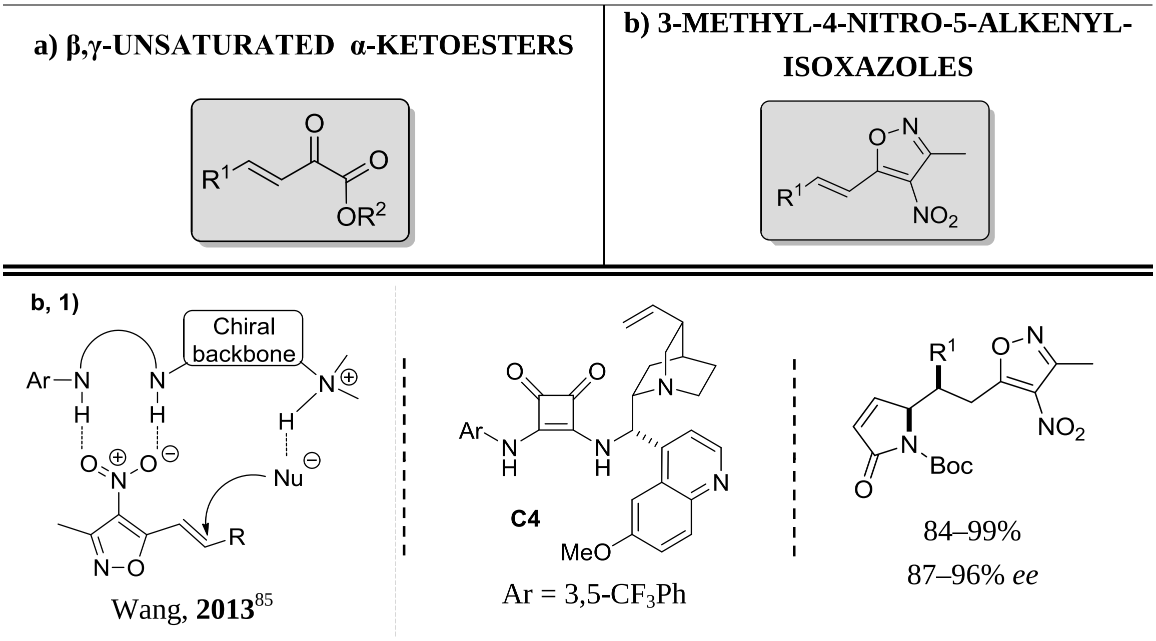

Figure 14. β,γ-Unsaturated α-ketoesters and 3-methyl-4-nitro-5-alkenyl-isoxazoles as Michael acceptor templates.

The first use of β,γ-unsaturated α-ketoesters was reported by Jørgensen in 2003 in the metal-promoted Michael addition of 4-hydroxycoumarins.[73] Seven years later, Wang described the same reaction but making use of a thiourea-based organocatalyst[74] and soon after, many groups published the use of different thiourea[75] and squaramide[76] bifunctional quinine derivatives[77] for the same reaction due to the importance of 3-substituted 4-hydroxycoumarins as biologically active compounds. Bifunctional thiourea catalysts were also found to efficiently promote the Michael addition of various carbon-nucleophiles such as 3-oxo-3-phenylpropanenitrile,[78] malonitrile,[79] trifluoroacetyl-β-oxo derivatives,[80] 1,2-cyclohexandione[81] and *N*-(pyrrolidin-1-

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[73] Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem*. **2003**, *68*, 5067–5074.

[74] Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.* **2010**, *16*, 13068–13071.

[75] a) Wang, J.-J.; Lao, J.-H.; Hu, Z.-P.; Lu, R.-J.; Nie, S.-Z.; Du, Q.-S.; Yan, M. *Arkivoc* **2010**, 229–243. b) Chen, X.-K.; Zheng, C.-W.; Zhao, S.-L.; Chai, Z.; Yang, Y.-Q.; Zhao, G.; Cao, W.-G. *Adv. Synth. Catal.* **2010**, *352*, 1648–1652. c) Gao, Y.; Ren, Q.; Ang, S.-M.; Wang, J. *Org. Biomol. Chem*. **2011**, *9*, 3691–3697.

[76] a) Xu, D-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, 4177–4180. b) Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhang, G.-C.; Xia, A.-B.; Xu, X.-S.; Xu, D.-Q. *Eur. J. Org. Chem.* **2010**, 4981–4985.

[77] Calter, M. A.; Wang, J. *Org. Lett*. **2009**, *11*, 2205–2208.

[78] Zhao, S.-L.; Zheng, C.-W.; Wang, H.-F.; Zhao, G. *Adv. Synth. Catal*. **2009**, 2811–2816.

[79] Zhao, S.-L.; Zheng, C.-W.; Zhao, G. *Tetrahedron: Asymmetry* **2009**, *20*, 1046–1051.

[80] Wang, J.-J.; Hu, Z.-P.; Lou, C.-L.; Liu, J.-L.; Li, X.-M.; Yan, M. *Tetrahedron* **2011**, *67*, 4578–4583.

[81] Ren, Q.; Gao, Y.; Wang, J. *Org. Biomol. Chem*. **2011**, *9*, 5297–5302.

yl)methanimine[82] to β,γ-unsaturated α-ketoesters. Although, β,γ-unsaturated α-ketoesters have been exploited with a variety of nucleophiles, to the best of our knowledge, the creation of tretrasubstituted stereocenters in β- and/or γ-position remains unrealized.

3-Methyl-4-nitro-5-alkenyl-isoxazoles (Figure 14, b) constitute a valuable synthetic alternative to esters in procedures that require a tuning of the acceptor electrophilicity. These substrates posses a rigid heterocyclic framework linked to an exocyclic nitro group and may be considered as a nitrodiene system, which have been employed as cinnamate equivalents showing high reactivity towards stabilized (soft) nucleophiles. The first example of the use of 3-methyl-4-nitro-5-alkenyl-isoxazoles as Michael acceptors was reported by Adamo and Bernardi in the 1,4-addition of nitromethane under phase transfer catalysis conditions.[83]

Later, various groups envisaged the utilization of hydrogen bonding-tertiary amine type bifunctional catalysts (thioureas and squaramides) for the activation of both electrophile and nucleophile.[84] With this methodology Wang demonstrated that the bifunctional squaramide **C4** was also efficient in the asymmetric vinylogous 1,6-Michael addition of α,β-unsaturated γ-butyrolactams obtaining adducts with excellent yields and enantioselectivities (Figure 14, b, 1).[85] Other examples of the use of these Michael acceptors in a domino Michael/cyclization reaction[86] and in [4+2] cycloadditions with dienals have also been reported.[87]

The final Michael adducts obtained from α-ketoesters and 3-methyl-4-nitro-isoxazoles can be converted into a variety of compounds (Scheme 6). The resulting γ- or β,γ-functionalized α-ketoesters **8** can be subjected to different transformations such as

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[82] Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303–3306.

[83] Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9342–9345. For an example of the use of the same type of chincona derived phase-transfer catalyst for the obtention of heavily substituted cyclopropane esters, see: Del Fiandra, C.; Piras, L.; Fini, F.; Disetti, P.; Moccia, M.; Adamo, M. F. A. *Chem. Commun.* **2012**, *48*, 3863–3865.

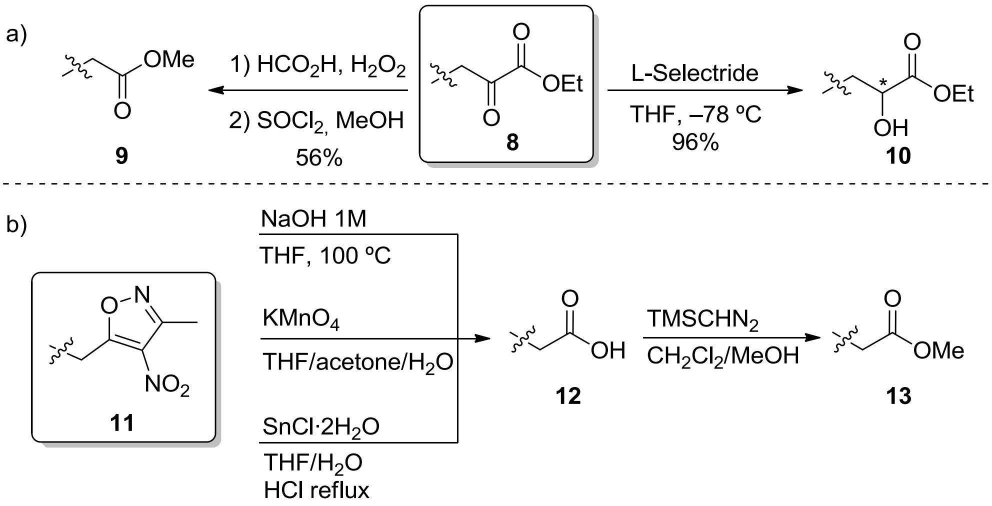
[84] For the 1,6-Michael addition of anthrone to 3-methyl-4-nitro-alkenyl-isoxazoles catalyzed by bifunctional thiureas, see: a) Sun, H. W.; Liao, Y. H.; Wu, Z. J.; Wang, H. Y.; Zhang, X. M.; Yuan, W. C. *Tetrahedron*, **2011**, *67*, 3991–3996. For the 1,6-Michael addition of aryl-thiols to 3-methyl-4-nitro-alkenyl-isoxazoles catalyzed by bifunctional thiureas, see: b) Pei, Q. L.; Sun, H. W.; Wu, Z. J.; Du, X. L.; Zhang, X. M.; Yuan, W. C. *J. Org. Chem.* **2011**, *76*, 7849–7859.

[85] Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329–9331.

[86] Liu, X. L.; Han, W. Y.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2013**, *15*, 1246–1249.

[87] Li, Y.; López-Delgado, F. J.; Jørgensen, D. K. B.; Nielsen, R. P.; Jiang, H.; Jørgensen, K. A. *Chem. Commun.* **2014**, *50*, 15689–15691.

the diastereoselective reduction of the α-carbonyl[88] or oxidative decarboxylation[89] to afford the corresponding esters **9** and **10** (Scheme 6, a). Additionally, the presence of a carboxylate group attached to the carbonyl carbon atom enables also cyclization reactions. The 3-methyl-4-nitro-isoxazol moiety in adducts **11** can also be easily removed under mild conditions to provide carboxylic acids **12** and/or esters **13** (Scheme 6, b).



Scheme 6. Transformation of the Michael adducts: a) Michael adducts coming from the reaction with β,γ-unsaturated α-ketoesters. b) Michael adducts coming from the reaction with 3-methyl-4-nitro-5-alkenyl-isoxazoles.

1.3.1.2.2. α'-Hydroxy enones

Research from this laboratory has revealed that achiral α'-oxy ketones, and particularly α'-hydroxy enones, are outstanding bidentate achiral templates for efficient asymmetric catalysis.[90] The presence of a pendant hydroxyl group in α'-hydroxy enones is the key for successful applications of such substrates as carboxylate equivalents in asymmetric synthesis. This unique scaffold enables a bidentate coordination with the catalyst and furthermore, provides a readily cleavable *C–C* ketol/diol system which under suitable conditions releases the corresponding carboxylic acid, aldehyde or ketone depending on the reaction conditions.

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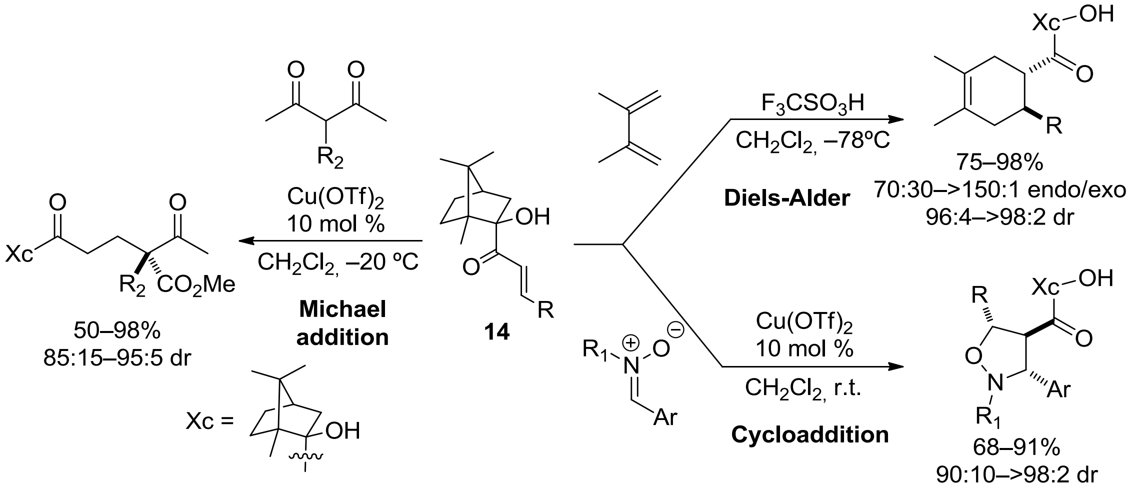
[88] Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942–4945.

[89] Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303–3306.

[90] For a review on α'-hydroxy ketones as templates, see: Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150–4164.

Heathcock[91] and Masamune[92] employed for the first time α-hydroxy enones in asymmetric *C–C* bond forming reactions as chiral auxiliaries in early 80's. Complementing previous work, our group designed the camphor-derived α'-hydroxy enones **14** which efficiently participate in diastereoselective Michael,[93] Diels-Alder[94] and cycloaddition reactions (Scheme 7).[95]



Scheme 7. Michael, Diels-Alder and cycloaddition reactions described by our group with camphor-derived α'-hydroxy enone **14**.

Later, our group also demonstrated the efficiency of the α-hydroxy ketone moiety in various metal catalytic asymmetric transformations which are depicted in Scheme 8. These involve on the one hand, copper promoted cycloaddition reactions as Diels-Alder[96] and nitrone-alkene 1,3-dipolar cycloadditions[95] (Scheme 8, a and b). On

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[91] a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc*. **1979**, *101*, 7077–7079. b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300. c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 2499–2506.

[92] a) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557–558. b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc*. **1981**, *103*, 1566–1568. c) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc*. **1982**, *104*, 5521–5523.

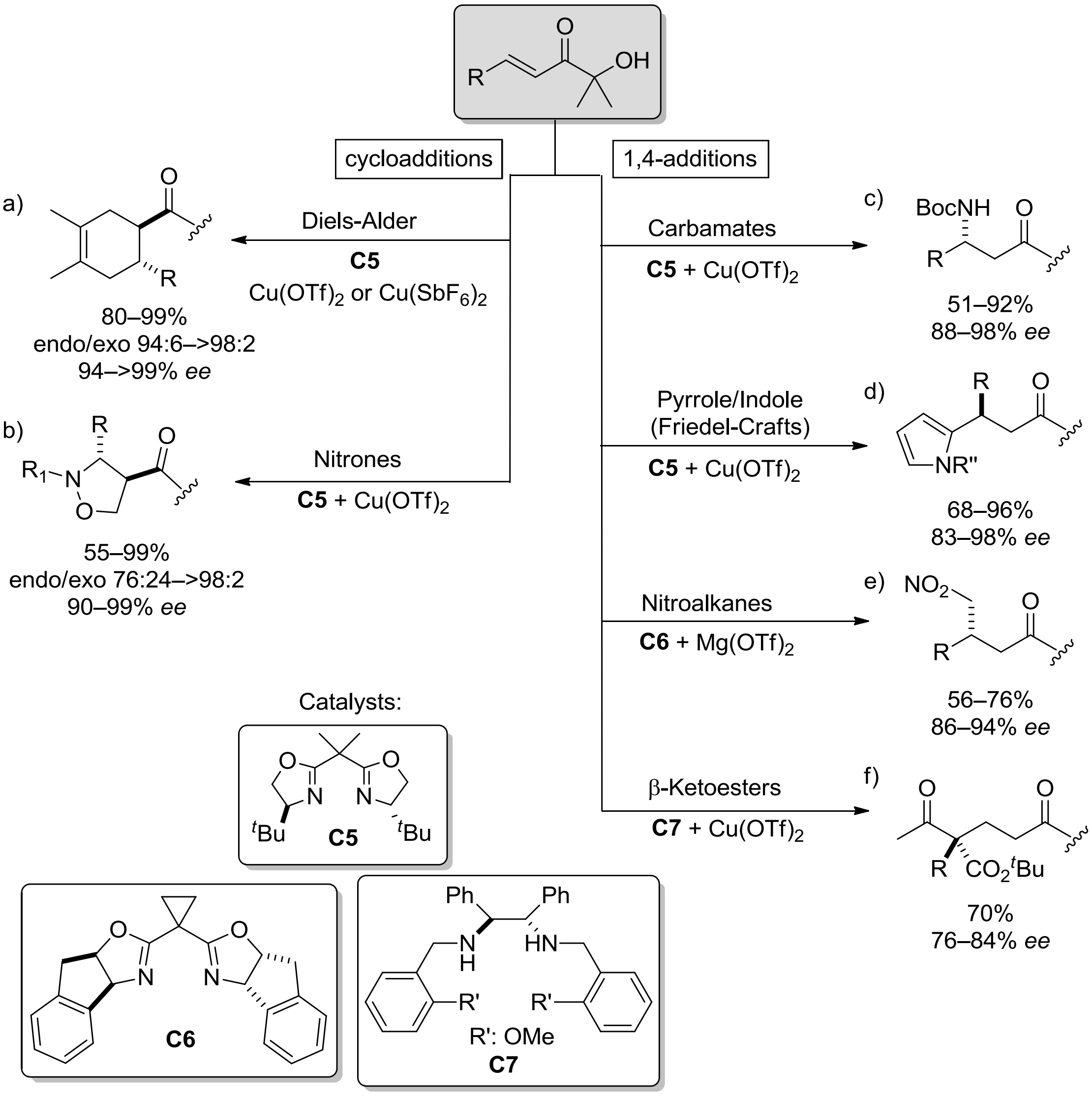
[93] Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.* **2008**, *10*, 2637–2640.

[94] a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288–10289. b) Bañuelos, P.; García, J. M.; Gómez-Bengoa, E.; Herrero, A.; Odriozola, J. M.; Oiarbide, M.; Palomo, C.; Razkin, J. *J. Org. Chem*. **2010**, *75*, 1458–1473.

[95] Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 6187–6190.

[96] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc*. **2003**, *125*, 13942–13943.

the other hand, different efficient 1,4-additions of several nucleophiles as carbamates,[97] pyrroles/indoles (Friedel-Crafts),[98] nitroalkanes[99] and β-ketoesters[100] (Scheme 8, c, d, e and f) have also been described.



Scheme 8. Metal-catalyzed asymmetric transformations using α'-hydroxy enones as Michael acceptors.

After this work other metal-catalyzed reactions which make use of α'-hydroxy enones in Michael reactions of diethyl zinc[101] and *N*,*N*-dialkylhydrazones as source of

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[97] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 9188–9189.

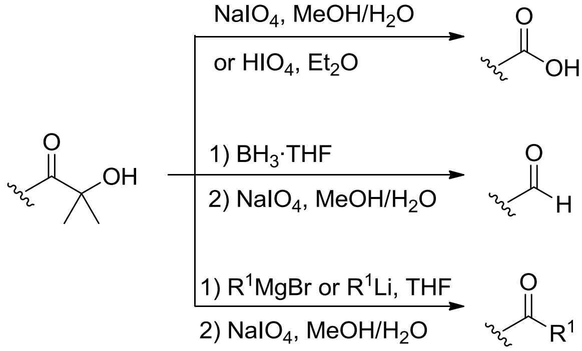
[98] a) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc*. **2005**, *127*, 4154–4155. For an efficient Friedel-Crafts alkylation of indoles with β-aryl α'-hydroxy enones, see: b) Yang, L.; Zhu, Q.; Guo, S.; Quian, B.; Xia, C.; Huang, H. *Chem. Eur. J*. **2010**, *16*, 1638–1645.

[99] Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal*. **2006**, *348*, 1161–1164.

[100] Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett*. **2008**, *10*, 2637–2640.

acyl anions (umpolung) or cyanide equivalents have also been reported.[102] α'-Hydroxy enones have also been investigated in catalytic asymmetric reactions promoted by chiral NHC catalysts[103] and in Michael additions following a radical pathway.[104]

Another interesting aspect of these achiral templates is that the elaboration of the Michael adducts can be performed under smooth oxidative conditions as shown in Scheme 9. These transformations are compatible with a variety of organic functionalities affording interesting products such as carboxylic acids, aldehydes and ketones.



Scheme 9. Transformation of the Michael adducts coming from the reaction with α,β-unsaturated α'-hydroxy enones.

With these precedents it is clear the excellent hability of the ketol moiety for both 1,4-metal and 1,4-proton bidentate binding in metal and Brønsted acid catalyzed asymmetric reactions (Figure 15).[105] One structural feature of the 1,4-chelate (five-membered ring) in α'-hydroxy enones is that the most probable conformation is highly planar with both *C–O* bonds eclipsed, thereby permitting optimum intramolecular

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[101] García, J. M.; González, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14*, 8768–8771.

[102] Monge, D.; Martín-Zamora, E.; Vázquez, J.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 2867–2870.

[103] a) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J Am. Chem. Soc*. **2009**, *131*, 8714–8718. b) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378–5381. c) Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun*. **2009**, 4566–4568. d) Kaeobamrung, J.; Bode, J. W. *Org Lett.* **2009**, *11*, 677–680.

[104] Lee, S.; Lim, C. J.; Kim, S.; Subramaniam, R.; Zimmerman, J.; Sibi, M. P. *Org. Lett.* **2006**, *8*, 4311–4313.

[105] It has been reported that in the presence of metal or Brønsted acids the intramolecular oxa-Michael cyclisation of α'-hydroxy enones is a side reaction under forcing conditions: a) Bradley, J. P.; Jarvis, T. C.; Johnson, C. D.; McDonnell, P. D.; Weatherstone, T. A. P. *Tetrahedron Lett.* **1983**, *24*, 2851–2854; b) Hong, Y. M.; Shen, Z. L.; Hu, X. Q.; Mo, W. M.; He, X. F.; Hu, B. X.; Sun, N. *ARKIVOC*, **2009**, *xiv*, 146–155.

hydrogen bonding.[106] However, when the work for this PhD Thesis started no precedent on the efficiency of these α'-hydroxy enones in organocatalysis had been described.

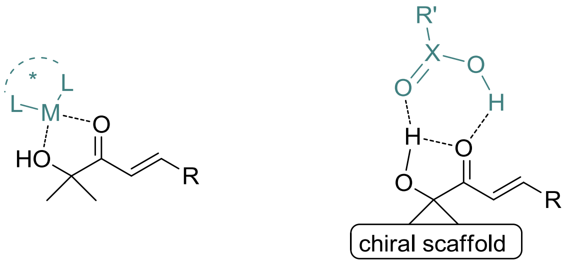
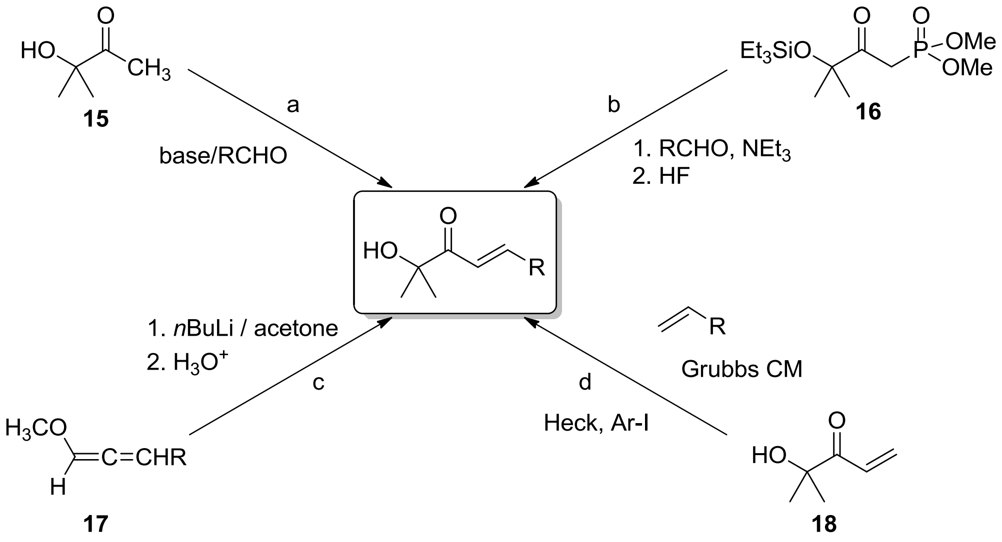


Figure 15. 1,4-Metal and 1,4-proton binding patterns of the ketol moiety.

Another relevant aspect of a potentially useful template is its accessibility. In this respect, there are several routes to synthesize α'-hydroxy enones from raw materials following straight and robust procedures. Among them are: aldol condensation of commercially available 3-hydroxy-3-methyl-2-butanone **15** and aldehydes (Scheme 10, a);[107] Horner-Wadsworth-Emmons olefination from β-keto phosphonates **16** (Scheme 10, b);[108] nucleophilic addition of a lithium methoxyallene **17** to acetone followed by a smooth hydrolysis (Scheme 10, c);[96] and Heck reaction and cross metathesis from **18** using Grubbs catalysts (Scheme 10, d).



Scheme 10. General methods for the preparations of α'-hydroxy enones.

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[106] Joris, L.; Schleyer, P. R. *J. Am. Chem. Soc*. **1968**, *90*, 4599–4611.

[107] Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun*. **2010**, *46*, 1715–1717.

[108] a) See ref. 97. b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc*. **2005**, *127*, 4154–4155.

1.3.2. Michael donor templates

Many efforts have also been devoted to the search for appropriate Michael donor templates, especially for suitable pronucleophiles for soft enolization. In this context, catalytic asymmetric synthesis based on simple esters or carboxylic acid derivatives as nucleophiles is still challenging. Direct asymmetric transition-metal based Michael approaches are well developed for carbonyl compounds bearing activating electron-withdrawing groups at the α-position. However, organocatalytic approaches rely on pronucleophiles such as simple ketones and aldehydes via *in situ* enamine formation or relatively acidic carbonyl compounds for soft enolization in Brønsted base-promoted catalysis.

One option to solve this problem has been the introduction of electronwithdrawing groups in the α-position to an ester or equivalent functionality, as for instance the use of α-cyanoacetates[109] and half-thioesters.[110] Other alternative is the use of activated ester surrogates as masked equivalents of the desired products. In this context, some strategies have been recently developed for the asymmetric construction of α-substituted carboxylic acid derivatives by using various acyclic and cyclic activated ester/amide surrogates.

1.3.2.1. Acyclic Michael donors

With the aim of searching mild reaction conditions for the direct asymmetric *C*–*C* bond formation involving carboxylic acid equivalents, various new pronucleophiles have been designed. In these studies some features for the development of efficient Michael donors are considered (Figure 16); on the one hand, the introduction of an appropriate activating group is of great importance since it should engender an amide/ester surrogate of low pK_a that would facilitate enolization. On the other hand, this activating group should also serve as director for enhancing stereocontrol and reactivity; and finally it should also act as a good leaving group for subsequent transformations.

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[109] Reviews on asymmetric synthesis of α-substituted cyanoacetates: a) Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261–3288. b) Jautza, S.; Peters, R. *Synthesis* **2010**, 365–388.

[110] For the use of malonic acid half thioester as thioester equivalents in asymmetric organocatalysis, see: a) Lubkoll, J.; Wennemers, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6841–6844. b) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Perez-Herrera, R.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037–1040.

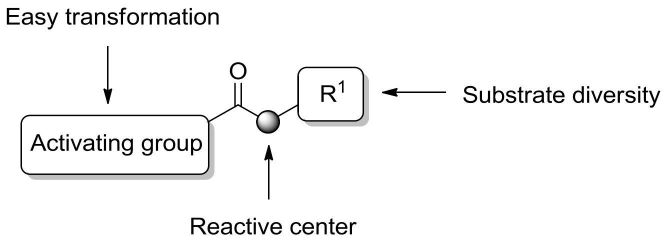

Figure 16. General characteristics of activated ester/amide surrogates.

Direct organocatalytic methods based on amine catalysis under proton-transfer conditions have a functional pK_a barrier for nucleophile activation that lies between the pK_a values of 16 and 17 (Figure 17). It is known that a malonate diester with a pK_a value of 16.4 can be activated by amine bases to act as a nucleophile, but ketones with α-carbon pK_a values of ca. 18 require amine activation by enamine formation. Some experiments carried out by Um and Drueckhammer[111] showed that the change from an oxyphenol ester to a thiophenol ester results in a reduction in the pK_a value of the α-carbon of an ester by approximately 2 units, just at the borderline for nucleophile activation using the currently available amine organocatalysts.[112] Moreover, experiments carried out with trifluoroethyl thioesters suggested that the pK_a value might be close to those of malonate diesters, making them candidate ester nucleophiles.

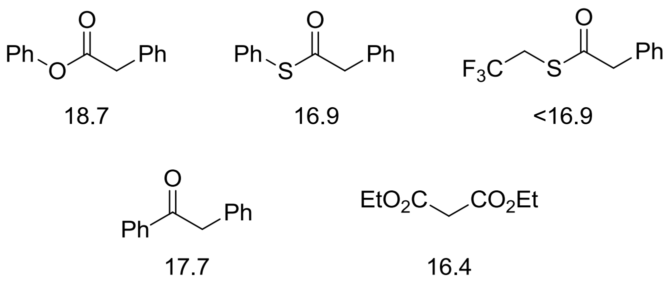

Figure 17. pK_a Values of the α-carbons of some pronucleophiles in DMSO.[113]

The most representative acyclic activated ester/amide surrogates described in the literature are depicted in Scheme 11 and involve trifluoroethyl thioesters **19**, pyrazoleamides **21**, α-ketophosphonates **24** and acylsilanes **26**. Their main characteristics and properties are described below.

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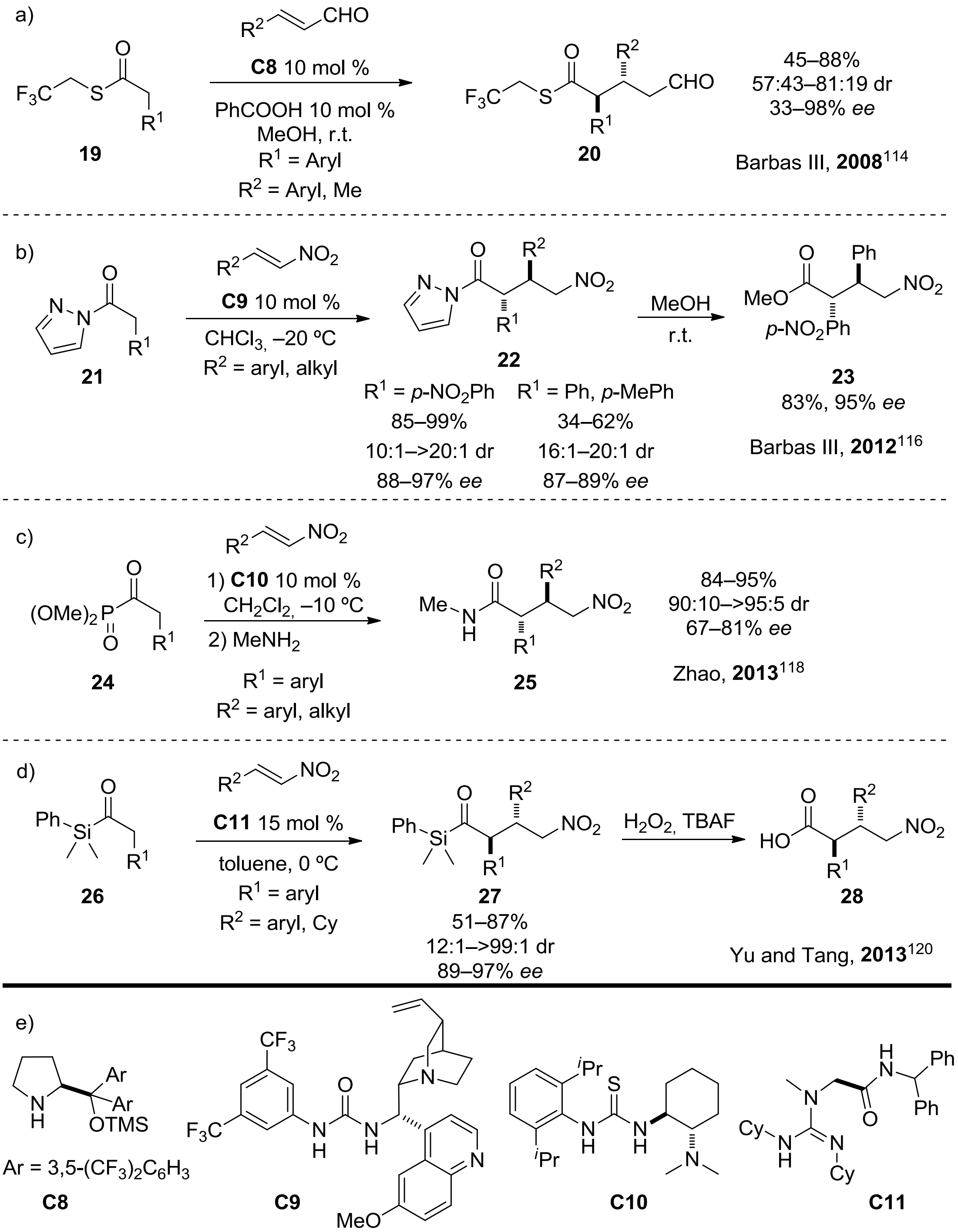
[111] Um, P.-J.; Drueckhammer, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 5605–5610.

[112] For the use of thiophenol esters in asymmetric organocatalytic Mannich reactions, see: a) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 3376–3379.

[113] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.



Scheme 11. Representative reactions carried out with acyclic ester/amide surrogates. a) Trifluoroethyl thioesters. b) Pyrazoleamides. c) α-Ketophosphonates. d) Acylsilanes. e) Structure of the catalysts employed in the above examples.

Taking advantage of the lower pK_a value of trifluoroethyl thioesters **19**, Barbas III reported for the first time strategies based on the use of this type of Michael donors as pronucleophiles in organocatalytic reactions (Scheme 11, a).[114] The versatility of the

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[114] Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591.

trifluoroethyl thioester system was explored in organocatalytic asymmetric Michael reactions involving α,β-unsaturated aldehydes. The trialkylsilyl-protected diaryprolinol catalyst **C8** together with benzoic acid as co-catalyst provided the Michael adducts **20** from α,β-unsaturated aldehydes in good chemical yield, moderate diastereoselectivity and good enantioselectivity.[115] Nevertheless, one of the drawbacks of this approach is the cost of the trifluoroethanethiol amount that is required for the synthesis of the starting material and the fact that diastereoselectivity of these reactions is modest.

Some years later, the same group reported the use of pyrazoleamides **21** as amide pronucleophiles for the Michael reaction with nitrostyrenes catalyzed by the quinine derived bifunctional urea **C9** (Scheme 11, b).[116] They hypothesized that the aromatic properties of the pyrazoleamide would provide a relatively low pK_a value facilitating enolization with weak amine bases. Furthermore, the pyrazoleamide moiety served as a directing group through hydrogen bonding to the catalyst for enhancing stereocontrol and as a good leaving group for subsequent transformations.[117] In this case, the Michael adducts **22** were obtained with excellent and very good diastereo- and enantioselectivities and were then transformed into the corresponding esters **23** while maintaining the stereoselectivity. Despite the fact that excellent results were achieved, the electronic nature of the α-substituent on the nucleophile (R^1) has a major influence on the reactivity of this reaction. Whenever there is an electron-donating group, the yield is modest.

On the other hand, it is known that the α-ketophosphonate group can be easily converted into an ester or amide group. Taking advantage of this fact, in 2013 Zhao reported the first organocatalyzed asymmetric Michael reaction of β-aryl-α-ketophosphonates **24** with nitroalkenes using the chiral bifunctional Brønsted base catalyst **C10** (Scheme 11, c).[118] The α-ketophosphonate group in the final Michael adducts was *in situ* converted into an amide group through aminolysis to give the corresponding α,β-disubstituted γ-nitroamides **25** in high yields and good stereoselectivities. The same group employed α-ketophosphonates **24** for aldol reactions leading to isatins.[119]

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[115] For the extension of this strategy to racemic versions of the conjugate reaction to nitrostyrenes, aldol, amination and Mannich reactions, see: a) See ref. 114. b) Utsumi, N.; Kitagaki, S.; Barbas III, C. F. *Org. Lett.* **2008**, *10*, 3405–3408.

[116] Tan, B.; Hernández-Torres, G.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 5381–5385.

[117] For a one-pot Michael-cyclization of pyrazoleamides with α,β-unsaturated aldehydes to afford δ-lactones, see: Agrawal, S.; Molleti, N.; Singh, V. *Chem. Commun.* **2015**, *51*, 9793–9796.

[118] Guang, J.; Zhao, J. C.-G. *Tetrahedron Lett.* **2013**, *54*, 5703–5706.

[119] Guang, J.; Guo, Q.; Zhao, J. C.-G. *Org. Lett.* **2012**, *14*, 3174–3177.

A stronger activation strategy of carboxylic acid surrogates has been employed by Yu and Tang in the Michael addition of acylsilanes **26** to nitroalkenes (Scheme 11, d).[120] Due to their slightly higher pK_a values compared with aldehydes, ketones and 1,3-dicarbonyl compounds, the α-alkylation of acylsilanes **26** is more difficult. To overcome this problem the use of a stronger base is necessary. This formal acylsilane α-alkylation in the presence of the chiral guanidine **C11** affords products **27** in good yields and high diastereoselectivity although in modest enantioselectivity. The corresponding adducts **27** can be converted into carboxylic acids **28** whose further reaction with thionyl chloride affords the corresponding esters.

Remarkably, all the examples reported with these acyclic Michael donor templates involve the creation of a tertiary stereocenter. To the best of our knowledge, no examples of the creation of a tetrasubstituted stereocenter have been described.

1.3.2.2. Heterocyclic Michael donors

Apart from acyclic substrates several different heterocyclic compounds containing enolizable ester/amide groups have been described. Some of them are part of biologically active compounds, and others have also been employed as carboxylic acid surrogate pronucleophiles involving the creation of a new tetrasubstituted stereocenter. The most representative heterocycles of this type are shown in Figure 18.

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[120] Wu, L.; Li, G.; Fu, Q.; Yu, L.; Tang, Z. *Org. Biomol. Chem.* **2013**, *11*, 443–447.

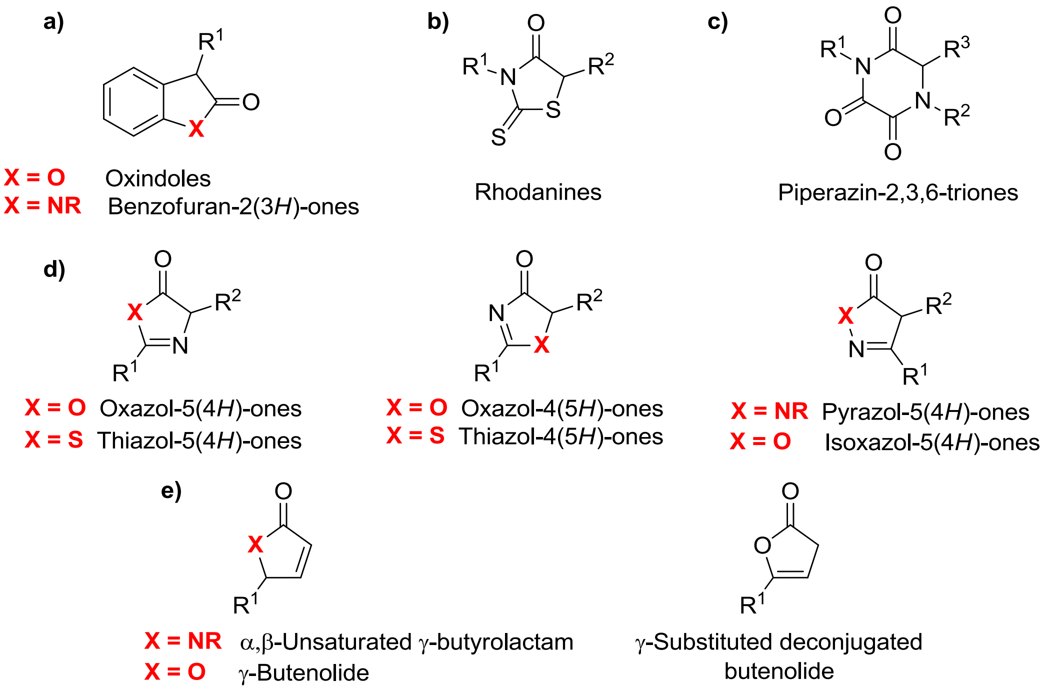

Figure 18. Heterocyclic substrates as Michael donors for the construction of tetrasubstituted stereocenters. a) Oxindoles and benzofuran-2(3*H*)-ones. b) Rhodanines. c) Piperazin-2,3,6-triones. d) Oxazolone, thiazolone and pyrazolone analogs. e) α,β-Unsaturated γ-butyrolactams, γ-butenolides and γ-substituted deconjugated butenolides.

In general, these heterocycles show very interesting characteristics: i) easy deprotonation under soft enolization conditions (aromatic enolate formation, except for rhodanines and piperazin-2,3,6-triones); ii) the geometry of the resulting starting enolate or equivalent is fixed due to their cyclic nature, thus facilitating the control of the stereoselectivity; iii) they are substituted at the α-position of the carbonyl and therefore after reaction with an electrophile a new tetrasusbtituted stereocenter is created; and iv) some of them after the enantioselective reaction with an electrophile, can be opened under appropriate conditions to afford α-mercapto, α-hydroxy and α- or β-amino acid derivatives with a tetrasubstituted stereocenter.

1.3.2.2.1. Oxindoles and benzofuran-2(3H)-ones

Among the most used heterocycles as pronucleophiles are oxindoles[121] and benzofuran-2(3*H*)-ones.[122] Both structures have an ester or amide functionality but their pK_a values are much lower than their parent ester or amide acyclic compounds. In both

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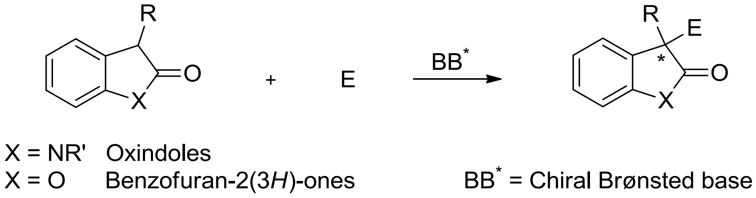
[121] For some reviews on the synthesis of 3,3-disubstituted oxindoles, see: a) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343–356. b) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. c) Zhou, F.; Liu, Y.-L; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.

[122] For a review on catalytic asymmetric reactions with benzofuranones, see: Li, Y.; Li, X.; Cheng, J.-P. *Adv. Synth. Catal.* **2014**, *356*, 1172–1198.

cases, the depronation of the α-carbon is favored due to the formation of an aromatic enolate. The most versatile methodology to construct the tetrasubstituted carbon stereocenter at the *C*-3 position of the oxindole or benzofuranone framework is based on the reaction of these prochiral 3-substituted substrates with different electrophiles (Scheme 12). This methodology allows the generation of the desired tretrasubstituted carbon stereocenter with all carbon substituents or with a heteroatom substituent.



Scheme 12. Construction of a tetrasubstituted stereocenter in oxindoles and benzofuran-2(3H)-ones by Brønsted base catalyst.

The ionization of oxindoles in organic solvents may occur readily at both nitrogen and carbon, suggesting potentially similar reactivity of nitrogen and carbon in unsubstituted oxindoles.[123] Regarding the pK_a values of this type of substrates, unsubstituted oxindole **30** (Figure 19) has a pK_a value of 18.2 and the pK_a values of 3-alkyl-substituted oxindoles are expected to be substantially higher. Nevertheless, the pK_a value of 3-alkyl substituted oxindoles might be significantly influenced by the *N*-protecting group. As shown in Figure 19, the pK_a value of *N*-methyloxindole **29** can be lowered down from 18.2 to 13.0 by the introduction of a carbonyl group (*N*-acetoxy derivative **31**). In the light of this, most employed methods use *N*-Boc-3-substituted oxindoles as substrates in base-promoted reactions for three reasons: i) they exhibit suitable pK_a value for deprotonative activation; ii) this group suppresses nucleophilic attack from the *N*; and, iii) they show bulkier steric hindrance and bidentate coordination to the catalyst for better stereocontrol. On the other hand, benzofuran-2(3*H*)-one (**32**, Figure 19) has a relatively lower pK_a value (13.5) comparing with oxindoles, thus allowing easy deprotonation.

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[123] For an example of *N*- and *O*-selectivity issues with *N*-protected oxindoles, see: Zhou, F.; Ding, M.; Liu, Y.-L.; Wang, C.-H.; Ji, C.-B.; Zhang, Y.-Y.; Zhou, J. *Adv. Synth. Catal*. **2011**, *353*, 2945–2952.

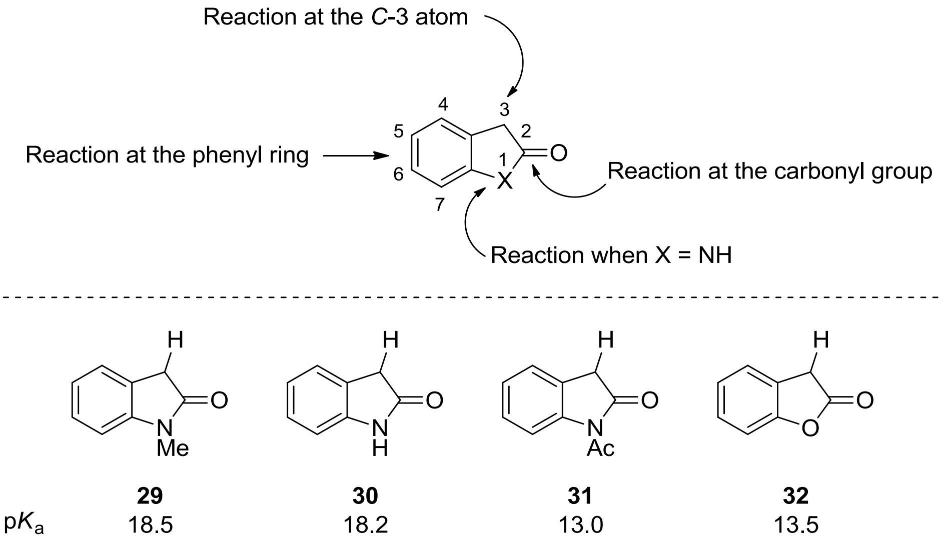

Figure 19. Reactivity patterns and pK_a values in DMSO[113] of oxindoles **29**–**31** and benzofuran-2(3*H*)-one **32**.

Many methods have been developed with 3-susbtituted oxindoles as pronucleophiles for the stereoselective construction of tetrasubstituted carbons. The main reason of this development is that the oxindole framework bearing a tetrasubstituted carbon stereocenter at the 3-position is the core of a large family of bioactive natural products and a series of pharmaceutically active compounds.[124] These substrates have been employed in many asymmetric catalytic reactions which have been comprehensively reviewed[121] and will not be discussed here.

Furthermore, the Michael addition of 3-substituted oxindoles to electron-deficient olefins not only provides an efficient method to construct a quaternary stereocenter at the 3-position, but can also be used in the synthesis of 3,3'-spirooxindoles because the electron-withdrawing group of the acceptor can be further utilized for ring formation.[125] However, Brønsted base promoted reaction of 3-oxindoles **33** to enones **34** has met with limited success (Scheme 13) except when the benzylic substituent was tested in *C*-3 (Scheme 13, c). For example, Luo and Cheng reported that methyl vinyl ketone (MVK), ethyl vinyl ketone and phenyl vinyl ketone all provide

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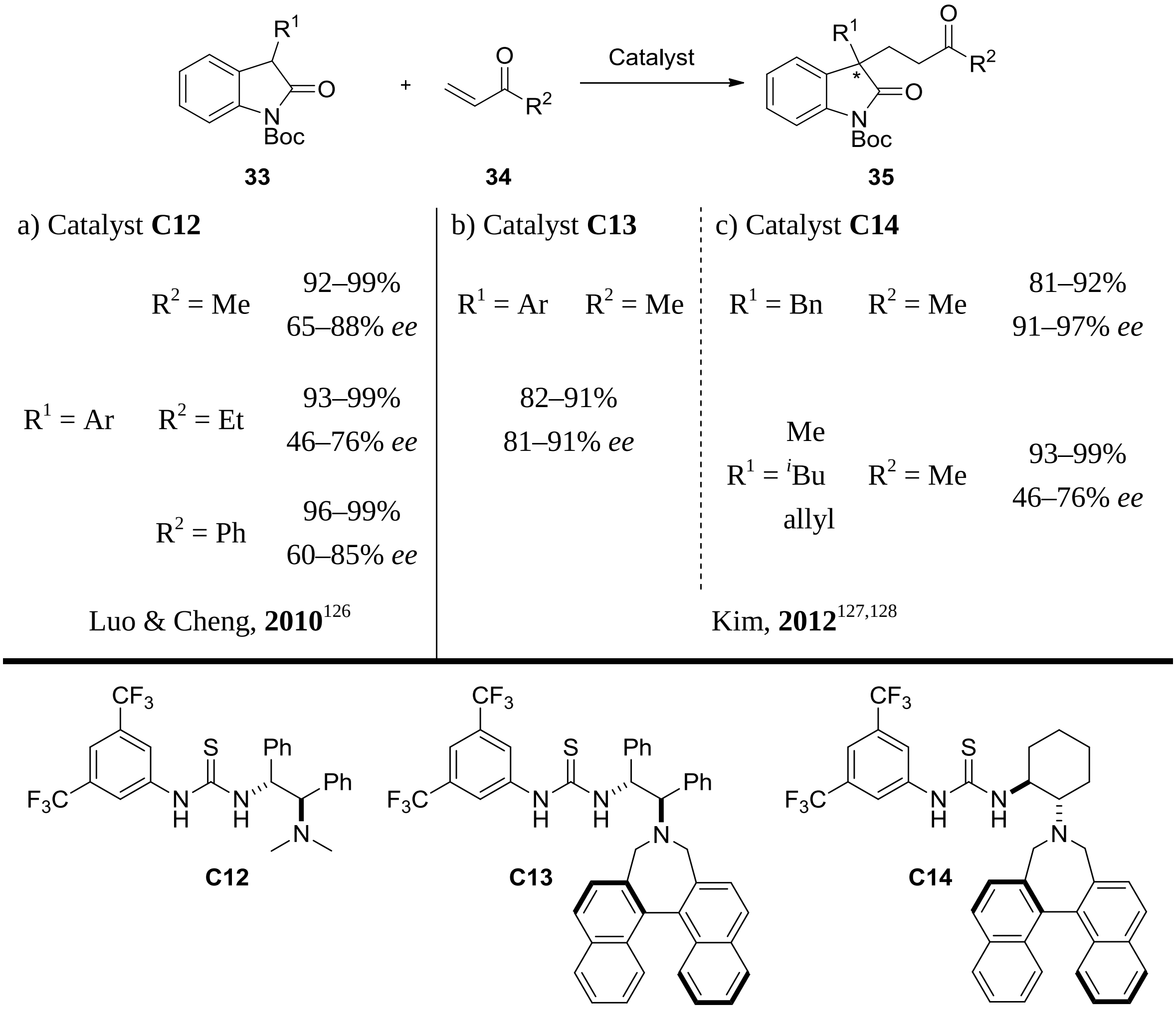
[124] a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 8748–8758. b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219. c) Lin, H.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **2003**, *42*, 36–51.

[125] For reviews on spirooxindoles synthesis, see: a) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas III, C. F. *ACS Catal*. **2014**, *4*, 743–762. b) Hong, L.; Wang, R. *Adv. Synth. Catal*. **2013**, *355*, 1023–1052. c) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *18*, 3003–3025.

enantiomeric excess values in the range of 46–88% *ee* in the Michael addition of 3-aryl oxindoles promoted by the bifunctional thiourea based catalyst **C12** (Scheme 13, a).[126]



33 **34** **35**

a) Catalyst **C12**			b) Catalyst **C13**		c) Catalyst **C14**		
	R^2 = Me	92–99% 65–88% *ee*	R^1 = Ar	R^2 = Me	R^1 = Bn	R^2 = Me	81–92% 91–97% *ee*
R^1 = Ar	R^2 = Et	93–99% 46–76% *ee*	82–91% 81–91% *ee*		Me R^1 = ^{i}Bu allyl	R^2 = Me	93–99% 46–76% *ee*
	R^2 = Ph	96–99% 60–85% *ee*					
Luo & Cheng, **2010**[126]			Kim, **2012**[127,128]				

C12 **C13** **C14**

Scheme 13. Michael additions of 3-substituted oxindoles to enones under different conditions.

Later, Kim improved slightly the enantioselectivities with MVK modifying the thiourea catalyst.[127] Therefore, as shown in Scheme 13, catalyst **C13** provided enantiomeric excess values in the range 81–91% (Scheme 13, b). Moreover, the same group investigated the same reaction with MVK promoted by catalyst **C14**; however, satisfactory results were only obtained with 3-benzyl substituted oxindoles (Scheme 13, c).[128] More examples of the Michael addition of 3-substituted oxindoles to enones have been described through different modes of activation.[129]

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[126] Li, X.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Org. Biomol. Chem*. **2010**, *8*, 77–82.

[127] Lee, H.-J.; Woo, S.-B.; Kim, D.-Y. *Molecules* **2012**, *17*, 7523–7532.

[128] Lee, H.-J.; Kim, D.-Y. *Bull. Korean Chem. Soc*. **2012**, *33*, 3171–3172.

[129] For a Michael addition to enones promoted by chiral amines via iminium ion catalysis, see: a) Pesciaioli, F.; Tian, X.; Bencivenni, G.; Bartoli, G.; Melchiorre, P. *Synlett* **2010**, 1704–1708. b) Sun, W.;

Benzofuran-2(3*H*)-ones have been less exploited than oxindoles in Michael addition reactions; however, the enantioselective synthesis of chiral benzofuran-2(3*H*)-ones has attracted great attention among synthetic chemists because this scaffold bearing a quaternary stereogenic center at the *C*-3 position can be found in a number of biologically active heterocyclic compounds.[130]

The most versatile methodology to construct the quaternary carbon center at the *C*-3 position of the benzofuranone framework is based on the reaction of 3-substituted prochiral benzofuranones with different electrophiles,[122] including aldol[131] and Mannich[132] reactions, allylic alkylations,[133] aminations,[134] fluorinations,[135] Michael[136] and domino reactions.[137] However, here again, as in the case of 3-substituted oxindoles, the Michael addition to enones, which involves the generation of a tetrasubstituted stereocenter, has met limited success. In 2010, Cheng and co-workers reported the first

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Hong, L.; Liu, C.; Wang, R. *Tetrahedron: Asymmetry* **2010**, *21*, 2493–2497. For the Michael addition of 3-aryl oxindoles to enones and enals under phase-transfer conditions, see: c) He, R.; Ding, C.; Maruoka, K. *Angew. Chem. Int. Ed*. **2009**, *48*, 4559–4561. d) Shirakawa, S.; Kasai, A.; Tokuda, T.; Maruoka, K. *Chem. Sci*. **2013**, *4*, 2248–2252. For the Michael addition of oxindoles to enones promoted by a chiral phosphine catalyst, see: e) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 943–947. For a metal-catalyzed Michael addition of 3-aryl oxindoles to MVK, see: f) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc*. **2011**, *133*, 3339–3341.

[130] For some selected biologically active heterocyclic compounds containing chiral benzofuran-2(3*H*)-ones, see: a) Nicolaou, K. C.; Wu, T.-R.; Kang, Q.; Chen, D. Y.-K. *Angew. Chem. Int. Ed*. **2009**, *48*, 3440–3443. b) Ramírez, M. L. G.; Trejo, A.; Navarro, V.; Bye, R.; Linares, E.; Delgado, G. J. *J. Nat. Prod*. **2001**, *64*, 432–435. c) Su, B.-N.; Takaishi, Y.; Tori, M.; Takaoka, S.; Honda, G.; Itoh, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *Org. Lett*. **2000**, *2*, 493–496. d) Li, W.; Asada, Y.; Yoshikawa, T. *Phytochemistry* **2000**, *55*, 447–456.

[131] Li, X.; Han, Y.; Tan, B.-X.; Wang, B.; Cheng, J.-P. *Chem. J. Chin. Univ*. **2014**, *35*, 1908–1911.

[132] Zhu, Y.; Zhang, E.; Luo, C.; Li, X.; Cheng, J.-P. *Tetrahedron* **2015**, *71*, 4090–4097.

[133] a) Liu, C.; Tan, B.-X.; Jin, J.-L.; Zhang, Y.-Y.; Dong, N.; Li, X.; Cheng, J.-P. *J. Org. Chem*. **2011**, *76*, 5838–5845. b) Zhu, C.-L.; Yang, L.-J.; Nie, J.; Zheng, Y.; Ma, J.-A. *Chin. J. Chem*. **2012**, *30*, 2693–2702. c) Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 590–593.

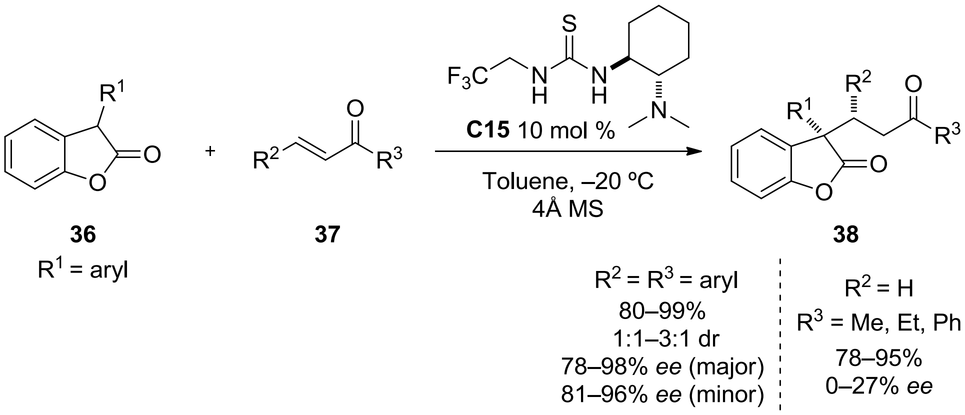
[134] Zhu, C.-L.; Zhang, F.-G.; Meng, W.; Nie, J.; Cahard, D.; Ma, J.-A. *Angew. Chem. Int. Ed*. **2011**, *50*, 5869–5872.

[135] Zhu, C.-L.; Fu, X.-Y.; Wei, A.-J.; Cahard, D.; Ma, J.-A. *J. Fluorine Chem*. **2013**, *150*, 60–66.

[136] For the conjugate addition to maleimides promoted by bifunctional thioureas, see: a) Li, X.; Hu, S.; Xi, Z.; Zhang, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem*. **2010**, *75*, 8697–8700. For the conjugate addition to vinyl bis(sulfone)s catalyzed by bifunctional thioureas, see: b) Li, X.; Zhang, Y. Y.; Xue, X. S.; Jin, J. L.; Tan, B. X.; Liu, C.; Dong, N.; Cheng, J. P. *Eur. J. Org. Chem*. **2012**, *2*, 1774–1782. For the conjugate addition to nitroolefins in the presence of bifunctional thioureas, see: c) Li, X.; Xue, X.-S.; Liu, C.; Wang, B.; Tan, B.-X.; Jin, J.-L.; Zhang, Y.-Y.; Dong, N.; Cheng, J.-P. *Org. Biomol. Chem*. **2012**, *10*, 413–420.

[137] a) Companyó, X.; Zea, A.; Alba, A. N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun*. **2010**, 6953–6955. b) Cassani, C.; Tian, X.; Escudero-Adan, E. C.; Melchiorre, P. *Chem. Commun*. **2011**, 233–235. c) Li, X.; Yang, C.; Jin, J.-L.; Xue, X.-S.; Cheng, J.-P. *Chem. Asian. J.* **2013**, *8*, 997–1003.

asymmetric Michael addition reaction of 3-substituted benzofuran-2(3*H*)-ones **36** to chalcones **37** catalyzed by the bifunctional tertiary-amine thiourea **C15** (Scheme 14).[138] Excellent yields and enantioselectivities but regular diastereoselectivities were obtained with 3-aryl benzofuran-2(3*H*)-ones. However, the addition reactions to vinyl ketones, including MVK, ethyl vinyl ketone and phenyl vinyl ketone worked well to give the desired products **38** in high yields but with low enantioselectivities. Later, Melchiorre reported the addition of these substrates to α,β-unsaturated aldehydes with a chiral secondary amine obtaining excellent enantioselectivities (86–99% *ee*), but poor control of diastereoselectivity (1.1:1–1.5:1 dr).[139]



Scheme 14. First asymmetric organocatalytic Michael addition of benzofuran-2(3*H*)-ones to enones. **Cheng, 2010**.

1.3.2.2.2. Rhodanines

Rhodanines **39** are heterocycles which have been scarcely used as pronucleophiles in asymmetric catalysis.[140] Only few examples have been reported which involve the use of enones **40**,[141] enals **42**[142] and azodicarboxylates **44**[143] as electrophiles (Scheme 15). The reaction with enones **40** is promoted by the chiral primary amine **C16** and the corresponding Michael adducts **41** are obtained from moderate to excellent yields and enantioselectivities (Scheme 15, a); in the case of enals **42**, Hayashi's catalyst **C17** has been employed for the construction of sulfur-containing spirocyclic compounds **43** with good results (Scheme 15, b). Moreover, the α-amination

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[138] Li, X.; Xi, Z.; Luo, S.; Cheng, J.-P. *Adv. Synth. Catal.* **2010**, *352*, 1097–1101.

[139] Bergonzini, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 971–974.

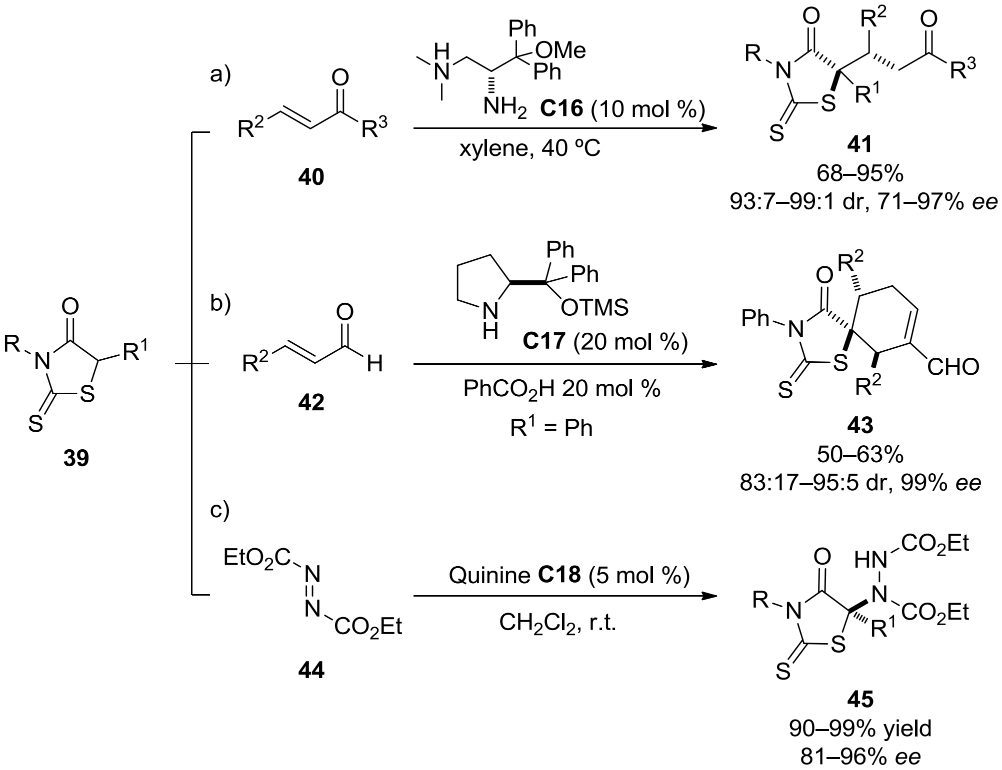
[140] For the use of rhodanine derivatives in tandem reactions, see: a) Wu, W.; Huang, H.; Yuan, X.; Zhu, K.; Ye, J. *Chem. Commun.* **2012**, *48*, 9180–9182. b) Zhu, K.; Huang, H.; Wu, W.; Wei, Y.; Ye, J. *Chem. Commun.* **2013**, *49*, 2157–2159.

[141] Yu, F.; Hu, H.; Gu, X., Ye, J. *Org. Lett.* **2012**, *14*, 2038–2041.

[142] Géant, P.-Y.; Urban, M.; Remeš, M.; Císařová, I.; Veselý, J. *Eur. J. Org. Chem.* **2013**, 7979–7988.

[143] Zhang, H.; Wang, B.; Cui, L.; Li, Y.; Qu, J.; Song, Y. *Org. Biomol. Chem.* **2014**, *12*, 9097–9100.

reaction with azodicarboxylates **44** promoted by quinine **C18** afford adducts **45** with excellent yields and enantioselectivities (Scheme 15, c).



Scheme 15. Rhodanines **46** in asymmetric catalytic reactions. Reactions of rhodanines with a) enones; b) enals; and, c) azodicarboxylates.

1.3.2.2.3. Piperazin-2,3,6-triones

2,5-Diketopiperazines (Figure 20) are useful starting materials for the generation of structural diversity and complexity in the field of heterocyclic compounds. There are broad applications of these heterocycles in the synthesis of many types of bioactive compounds such as several families of alkaloids[144] which, in turn, are also valuable precursors of α-amino acids derivatives.[145] Olenyuk's group reported the only two enantioselective examples of 2,5-diketopiperazines as pronucleophiles; an α-

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[144] For reviews on 2,5-diketopiperazines, see: a) Borthwick, A. D. *Chem. Rev.* **2012**, *112*, 3641–3716. b) González, J. F.; Ortín, I.; de la Cuesta, E.; Menéndez, J. C. *Chem. Soc. Rev.* **2012**, *41*, 6902–6915.

[145] For a selected example of synthesis of quaternary α-amino acids from diketopiperazines, see: a) Davies, S. G.; Garner, A. C.; Ouzman, J. V. A.; Roberts, P. M.; Smith, A. D.; Snow, E. J.; Thomson, J. E.; Tamayo, J. A.; Vickers, R. J. *Org. Biomol. Chem.* **2007**, *5*, 2138–2147. For a selected example of synthesis of peptides from diketopiperazines, see: b) Robertz, B.; Keul, H.; Höcker, H. *Macromol. Chem. Phys.* **1999**, *200*, 1034–1040.

sulfenilation reaction[146] and an alkylation reaction.[147] However, in both cases activated 2,5-diketopiperazines are needed and total stereocontrol of the reaction is not achieved.

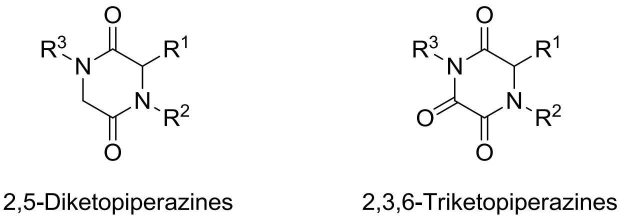
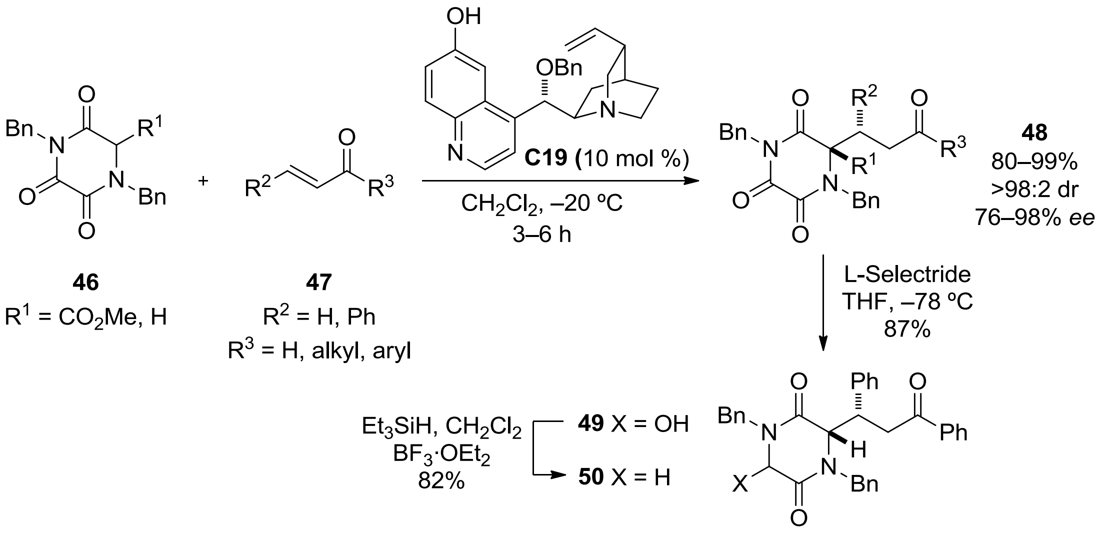


Figure 20. General structure of 2,5-diketopiperazines and 2,3,6-triketopiperazines.

Recently, Simpkins and co-workers employed under-explored triketopiperazines **46** (Figure 20) to access diketopiperazines **50** in high enantioselectivity in a cinchona alkaloid catalyzed **C19** Michael addition to enones **47** (Scheme 16).[148] However, the reaction is only efficient with 5-unsubstituted and 5-methoxycarbonyl triketopiperazines (R^1 = H, CO_2Me). No examples involving aliphatic or aromatic R^1 substituents have been reported to date. Reaction with chalcones also demonstrated to be efficient and adducts were transformed into 2,5-diketopiperazine derivatives **50** in high yields.



Scheme 16. Enantioselective Michael addition of triketopiperazines to enones, an approach to the synthesis of tetrasubstituted chiral 2,5-diketopiperazines. **Simpkins, 2015**.

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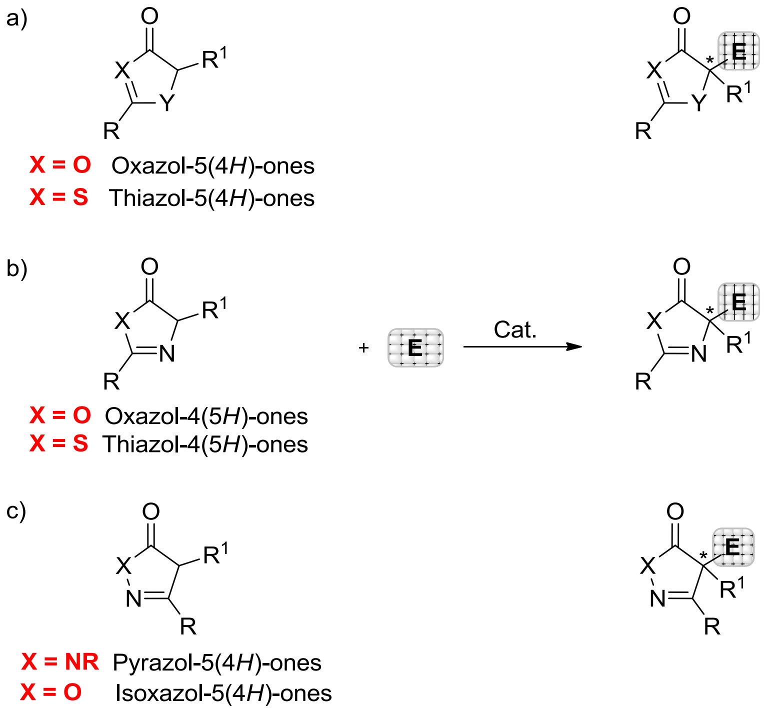
[146] Polaske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2742–2750.

[147] Dubey, R.; Olenyuk, B. *Tetrahedron Lett.* **2010**, *51*, 609–612.

[148] Cabanillas, A.; Davies, C. D.; Male, L.; Simpkins, N. S. *Chem. Sci.* **2015**, *6*, 1350–1354.

1.3.2.2.4. Oxazolone, Thiazolone and Pyrazolone analogs

Many more examples of heterocyclic compounds of type of Scheme 17 have been described as pronucleophiles during the last years in asymmetric reactions with the simultaneous creation of tetrasubstituted carbons.



Scheme 17. Oxazolones/thiazolones (a, b) and pyrazolones/isoxazolones (c) as pronucleophiles in asymmetric reactions.

In this context, examples of this type of heterocycles are oxazol-5(4*H*)-ones (or azlactones) and their thiazol-5(4*H*)-one analogs (Figure 21, a), as well as oxazol-4(5*H*)-ones and their thiazol-4(5*H*)-one analogues (Figure 21, b). The addition adducts can be easily hydrolyzed to provide carboxylic acids or their derivatives carrying different functionalities (α-amino acids **51**, α-hydroxy acids **52** and α-mercapto acids **53**).

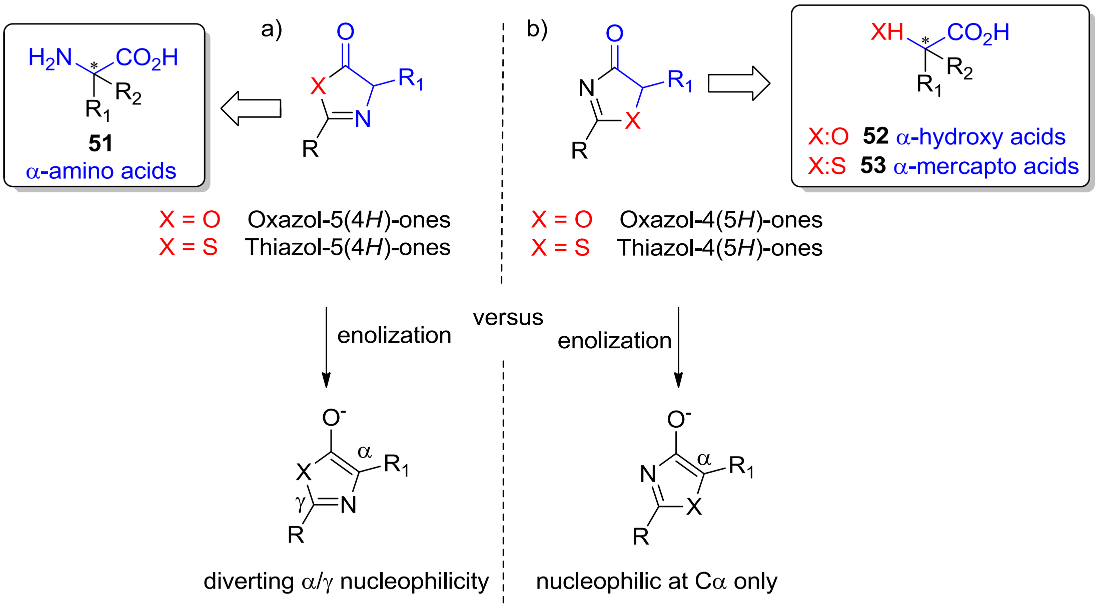


Figure 21. Some α-susbtituted oxazolone and thiazolone derivatives for asymmetric catalysis, their reactivity patterns against enolization, and resulting adducts after catalytic reaction and hydrolysis.

Oxazol-5(4*H*)-ones or azlactones (Figure 21, a, X = *O*) and their sulfur analogs thiazol-5(4*H*)-ones (Figure 21, a, X = *S*) exhibit multiple reactive sites, which make them excellent substrates for the synthesis of highly substituted scaffolds. The acidity of *C*-4 ($pK_a \approx 9$)[149] allows the easy formation of an oxazole enolate, which can react with a range of electrophiles. Upon enolization the reaction with an electrophile can occur either at the α- or γ-position. This can generate problems of regioselectivity depending on the reaction conditions and/or type of substituents. However, oxazol-4(5*H*)-ones (Figure 21, b, X = *O*) and their sulfur analogs thiazol-4(5*H*)-ones (Figure 21, b, X = *S*) upon enolization only exhibit one nucleophilic position at the α-carbon to the carbonyl. Here the regioselectivity problem is avoided. All these types of heterocycles have been used in asymmetric catalysis promoted by chiral Brønsted bases in reactions which generate tetrasubstituted carbons.

The first developed pronucleophiles of this type are oxazol-5-(4*H*)-ones or azlactones, which have been deeply investigated and reviewed.[150] Michael reactions concerning these substrates will be discussed in Chapter 2. Structurally related thiazol-5(4*H*)-ones are associated with several biological active compounds[151] and the first

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[149] Goodman, M.; Levine, L. *J. Am. Chem. Soc*. **1964**, *86*, 2918–2922.

[150] a) Alba, A.-N.; Ríos, R. *Chem. Asian J.* **2011**, *6*, 720–734. b) Hewlett, N. M.; Hupp, C. D.; Tepe, J. J. *Synthesis* **2009**, *17*, 2825–2839. c) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry*, **2008**, *19*, 2755–2762. d) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev*. **2007**, 1432–1440.

[151] a) Biron, E.; Chatterjee, J.; Kessler, H. *Org. Lett*. **2006**, *8*, 2417–2420. b) Deng, S.; Taunton, J. *Org. Lett*. **2005**, *7*, 299–301. c) Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc*. **1998**, *120*, 591–592.

organocatalytic asymmetric reaction with these substrates was described by Ooi in a highly stereoselective Mannich-type reaction.[152] Later, more examples of Mannich[153] and Michael reactions to nitroalkenes[154] and electron-deficient alkynes[155] have been developed.

On the other hand, since the pionnering work by Trost in 2004,[156] several examples of the utility of the structurally related oxazol-4(5*H*)-ones (Figure 21, b, X = *O*) have also been published, which involve mainly Michael additions (to enones,[157] nitroalkenes,[158] alkynones[159] and vinyl sulfones[160]), γ-additions to allenoates,[161] 1,6-

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d) Mulzer, J.; Mantoulider, A.; Ohler, E. *Tetrahedron Lett*. **1997**, *38*, 7725–7728. e) Badorc, A.; Bordes, M. F.; Herbert, J. M. *J. Med. Chem*. **1997**, *40*, 3393–3401.

[152] For the asymmetric Mannich reaction of thiazol-5(4*H*)-ones to *N*-Boc imines catalyzed by C_1-symmetric chiral ammonium betaine, see: Uraguchi, D.; Koshimoto, K.; Ooi, T. *Chem. Commun*. **2010**, *46*, 300–302.

[153] For the asymmetric Mannich reaction of thiazol-5(4*H*)-ones to *N*-tosyl imines catalyzed by cinchona derived alkaloids, see: Liu, X.; Deng, L.; Song, H.; Jia, H.; Wang, R. *Org. Lett*. **2011**, *13*, 1494–1497.

[154] For the asymmetric Michael addition of thiazol-5(4*H*)-ones to nitroalkenes catalyzed by a bifunctional thiourea, see: Liu, X.; Song, H.; Chen, Q.; Li, W.; Yin, W.; Kai, M.; Wang, R. *Eur. J. Org. Chem*. **2012**, 6647–6655.

[155] For the asymmetric Michael addition of thiazol-5(4*H*)-ones to internal alkynes catalyzed by iminophosphorane, see: Uraguchi, D.; Yamada, K.; Ooi, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 9954–9957.

[156] Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc*. **2004**, *126*, 1944–1945.

[157] For the asymmetric Michael addition of oxazol-4(5*H*)-ones to ketones catalyzed by a bifunctional thiourea, see: a) Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. *Chem. Commun*. **2012**, *48*, 461–463. For the asymmetric Michael addition of oxazol-4(5*H*)-ones to vinyl ketones catalyzed by guanidines, see: b) Misaki, T.; Sugimura, T. *Tetrahedron Lett*. **2015**, *56*, 264–267.

[158] For the asymmetric Michael addition of oxazol-4(5*H*)-ones to nitroalkenes catalyzed by a dinuclear Zn complex, see: a) Trost, B. M.; Hirano, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 6480–6483. For the asymmetric Michael addition of oxazol-4(5*H*)-ones to nitroalkenes catalyzed by a bifunctional thiourea, see: b) Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett*. **2013**, *15*, 2358–2361.

[159] For the asymmetric Michael addition of oxazol-4(5*H*)-ones to alkynes catalyzed by chiral guanidines, see: a) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc*. **2011**, *133*, 5695–5697. For a theoretical study of asymmetric Michael addition of oxazol-4(5*H*)-ones to alkynes catalyzed by chiral guanidines, see: b) Lu, N.; Wang, H. *Int. J. Quant. Chem*. **2013**, *113*, 2267–2276.

[160] For the asymmetric Michael addition of oxazol-4(5*H*)-ones to vinyl sulfones catalyzed by a bifunctional thiourea, see: Liu, Q.; Qiao, B.; Chin, K. F.; Tan, C.-H., Jiang, Z. *Adv. Synth. Catal*. **2014**, *356*, 3777–3783.

[161] For the asymmetric Michael addition of oxazol-4(5*H*)-ones to allenic ketones and esters catalyzed by guanidines, see: a) Jin, N.; Misaki, T.; Sugimura, T. *Chem. Lett*. **2013**, *42*, 894–896. For the asymmetric Michael addition of oxazol-4(5*H*)-ones to allenic esters catalyzed by phosphines, see: b) Wang, T.; Yu, Z.; Hoon, D.-L.; Huang, K.-W.; Lan, Y., Lu, Y. *Chem. Sci*. **2015**, *6*, 4912–4922.

additions to conjugated dienones,[162] aldol/Mannich reactions,[163] α-sulfenylation reactions[164] and alkylations.[165] Concerning the Michael reaction to enones, Ye reported in 2012 a highly diastereo- and enantioselective addition of 4-alkyl oxazol-4(5*H*)-ones **54** to β-substituted α,β-unsaturated ketones **55** promoted by the thiourea-tertiary amine bifunctional catalyst derived from *L*-*tert*-leucine **C20** (Scheme 18, a).[157a] Recently, Sugimura employed chiral guadinine **C21** to catalyze the addition to vinyl ketones with very good results (Scheme 18, b).[157c] To the best of our knowledge, only 5-alkyl 2-aryl oxazol-4(5*H*)-ones have been employed in these reactions and no examples of the use of 5-aryl derivatives as pronucleophiles have been reported.

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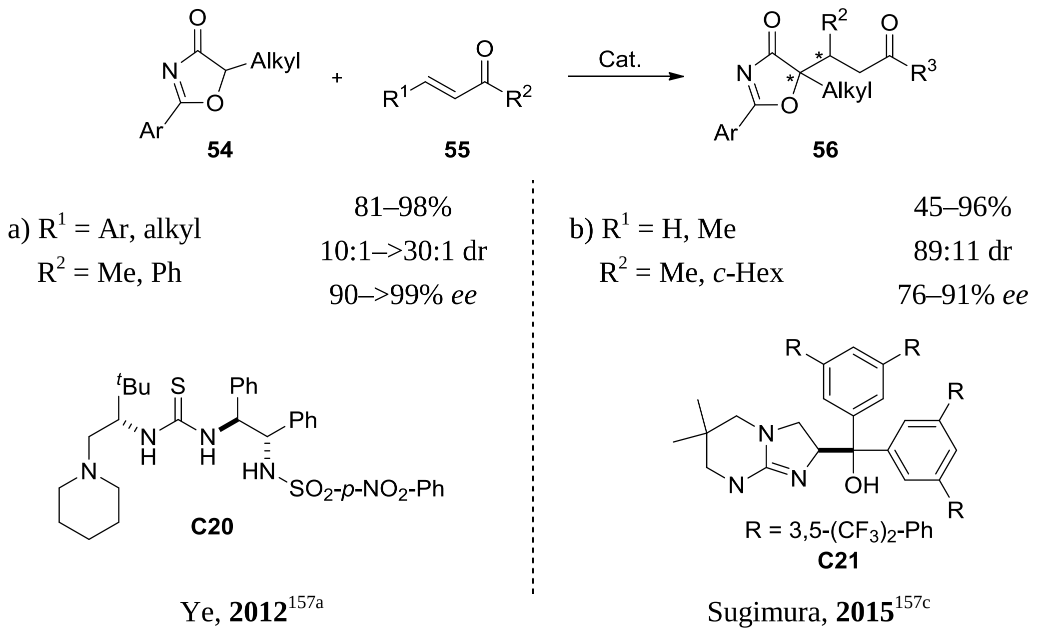
[162] For the asymmetric Michael addition of oxazol-4(5*H*)-ones to dienones and esters catalyzed by guanidines, see: Morita, A.; Misaki, T.; Sugimura, T. *Chem. Lett.* **2014**, *43*, 1826–1828.

[163] For the asymmetric Mannich reaction of oxazol-4(5*H*)-ones to diphenylphosphinoyl imines catalyzed by Zn complexes, see: a) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527. For the asymmetric Mannich reaction of oxazol-4(5*H*)-ones to *N*-TIPBs-arylimines catalyzed by a bifunctional urea, see: b) Han, Z.; Yang, W.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2013**, *355*, 1505–1511. For the asymmetric aldol reaction of oxazol-4(5*H*)-ones to aldehydes catalyzed by chiral guanidines, see: c) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.

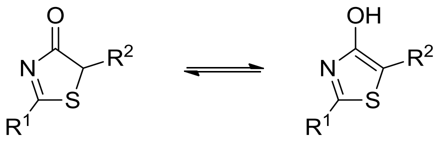
[164] For the asymmetric sulfenylation of oxazol-4(5*H*)-ones with *N*-(phenylthio)succinimide catalyzed by a bifunctional squaramide, see: Xu, M.; Qiao, B.; Duan, S.; Liu, H., Jiang, Z. *Tetrahedron* **2014**, *70*, 8696–8702.

[165] For the asymmetric alkylation of oxazol-4(5*H*)-ones promoted by Ir complexes, see: a) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc*. **2014**, *136*, 377–382. For the asymmetric alkylation of oxazol-4(5*H*)-ones through phase-transfer catalysis, see: b) Duan, S.; Li, S.; Du, N.-N.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 7770–7778.



Scheme 18. Examples of Michael reactions of 4-alkyl oxazol-4(5*H*)-ones to α,β-unsaturated ketones.

Sulfur (thiazol-4(5*H*)-ones, Scheme 19) analogues of these oxazol-4(5*H*)-ones have been well known for a long time and have found several applications in pharmaceutical and medicinal chemistry.[166] These compounds are readily accessible and in turn, can be suitable donors for asymmetric catalytic reactions. In these cases the hydrolysis of the adducts coming from an asymmetric reaction can provide α-mercapto acids. It has been shown by ^{1}H-NMR that these compounds exist as an equilibrium in solution between the two tautomeric forms (Scheme 19),[167] and therefore this could facilitate deprotonation at the 5-position to further react with various electrophiles.



Scheme 19. Equilibrium between enol and keto form of thiazolones.

In spite of this, and although structurally related to oxazol-4(5*H*)-ones and oxazol-5(4*H*)-ones, this thiazol-5(4*H*)-ones have been rarely used until now in

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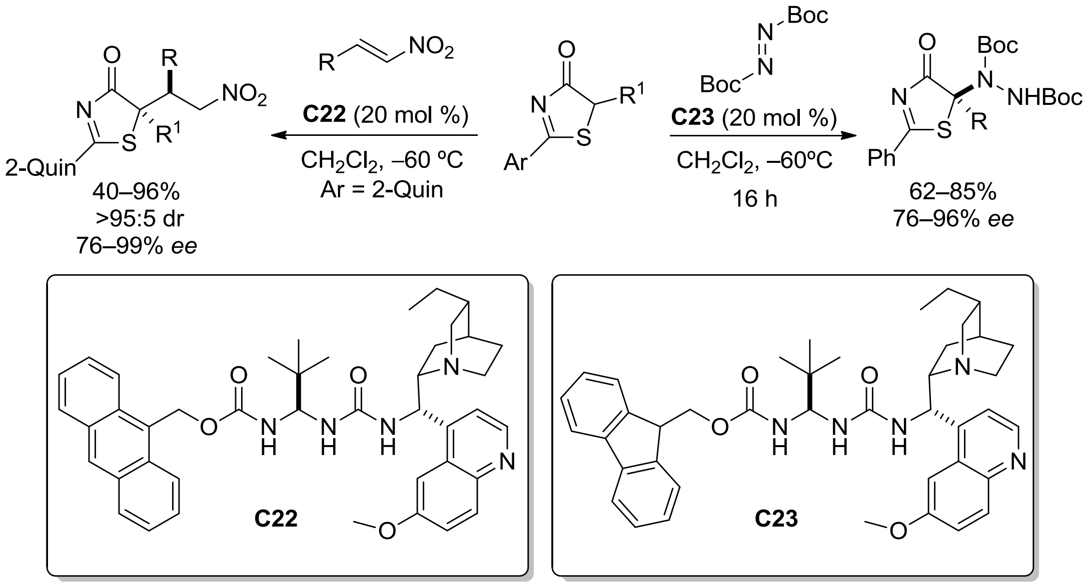
[166] a) Khalil, N. A.; Ahmed, E. M.; El-Nassan, H. B. *Med. Chem. Res.* **2013**, *22*, 1021–1027. b) Grummt, U. V.; Weiss, D.; Birckner, E.; Beckert, R. *J. Phys. Chem. A* **2007**, *111*, 1104–1110. c) Véniant, M. M.; Hale, C.; Hungate, R. W.; Gahm, k.; Emery, M. G.; Jona, J.; Joseph, S.; Adams, J.; Hague, A.; Moniz, G.; et al. *J. Med. Chem.* **2010**, *53*, 4481–4487.

[167] Täuscher, E.; Weib E.; Beckert, R.; Fabian, J.; Assumpçao, A.; Görls, H. *Tetrahedron Lett.* **2011**, *52*, 2292–2294.

asymmetric catalysis, and only very recently four interesting examples describing their applications in this area have been reported.[168] Our group described the first application of these compounds in the conjugate addition to nitroalkenes which worked efficiently in the presence of the new ureidopeptide-like Brønsted base catalyst **C22**.[169] The α-amination reaction of these substrates with *tert*-butyl azodicarboxylate in the presence of ureidopeptide-like catalyst **C23** also afforded very good results.



Scheme 20. Highly enantioselective reactions of thiazol-4(5*H*)-ones as pronucleophiles promoted by ureidopeptide-like bifunctional Brønsted base catalysts. a) Michael addition to nitroalkenes. b) α-Amination.

Another type of heterocyclic scaffolds are pyrazol-5(4*H*)-ones[170] (Figure 22, X = *NR*^{3}) and isoxazol-5(4*H*)-ones (Figure 22, X = *O*) and their tautomerism has been investigated by various groups.[171] Both compounds have attractive pharmacological properties[172] and are valuable building blocks which would permit a rapid access to β-

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[168] For phosphine-catalyzed asymmetric γ-additions to allenoates and alkynes, see: a) Wang, T.; Yu, Z.; Long Hoon, D.; Huang, K.-W.; Lan, Y.; Lu, Y. *Chem. Sci.* **2015**, *6*, 4912–4922. For iridium-catalyzed allylation substitution reactions, see: b) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc*. **2014**, *136*, 377–382.

[169] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Olaizola, I; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

[170] For a review on pyrazol-5(4*H*)-ones in asymmetric catalysis, see: Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun*. **2015**, *51*, 12890–12907.

[171] For pyrazol-5(4*H*)-ones, see: a) Holzer, W.; Kautsch, C.; Laggner, C.; Claramunt, R. M.; Pérez-Torralba, M.; Alkorta, I.; Elguero, J. *Tetrahedron* **2004**, *60*, 6791–6805. For isoxazol-5(4*H*)-ones, see: b) De Sarlo, F. *Tetrahedron* **1967**, *23*, 831–840.

[172] For antibacterial activity of pyrazol-5(4*H*)-ones, see: a) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4501–4503. For antitumor activity of pyrazol-5(4*H*)-ones: b) Casas, J. S.; Castellano, E. E.; Ellena, J.; García-Tasende, M.

amino acids.[173] Despite the value of these compounds for pharmaceutical sciences and organic synthesis, little is known about the enantioselective preparation of chiral derivatives. One reason seems to be that alkylation of isoxazolinones via the corresponding enolates suffers from low regioselectivity due to the competition of nucleophilic *C*, *N* and *O* centers, which all of them can react with electrophiles (Figure 22).[174]

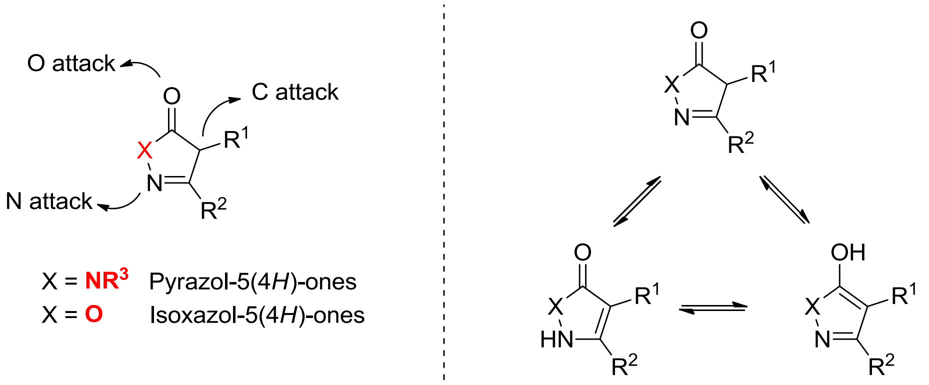

Figure 22. General structure scheme and tautomerism of pyrazol-5(4*H*)-ones and isoxazol-5(4*H*)-ones.

The first use of pyrazol-5(4*H*)-ones as pronucleophiles in organocatalytic asymmetric reaction was described by Yuan and co-workers in the Michael addition to nitroolefins.[175] After this example some more reports on these substrates in Michael addition,[176] amination[177] and alkylation[178] reactions have been published. In the case of

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S.; Peres-Paralle, M. L.; Sanchez, A.; Sanchez-González, A.; Sordo, J.; Touceda, A. *J. Inorg. Biochem.* **2008**, *102*, 33–45. For anticancer and antibacterial activity of isoxazol-5(4*H*)-ones, see: c) Chande, M. S.; Verma, R. S.; Barve, P. A.; Khanwelkar, R. R.; Vaidya, R. B.; Ajaikumar, K. B. *Eur. J. Med. Chem.* **2005**, *40*, 1143–1148.

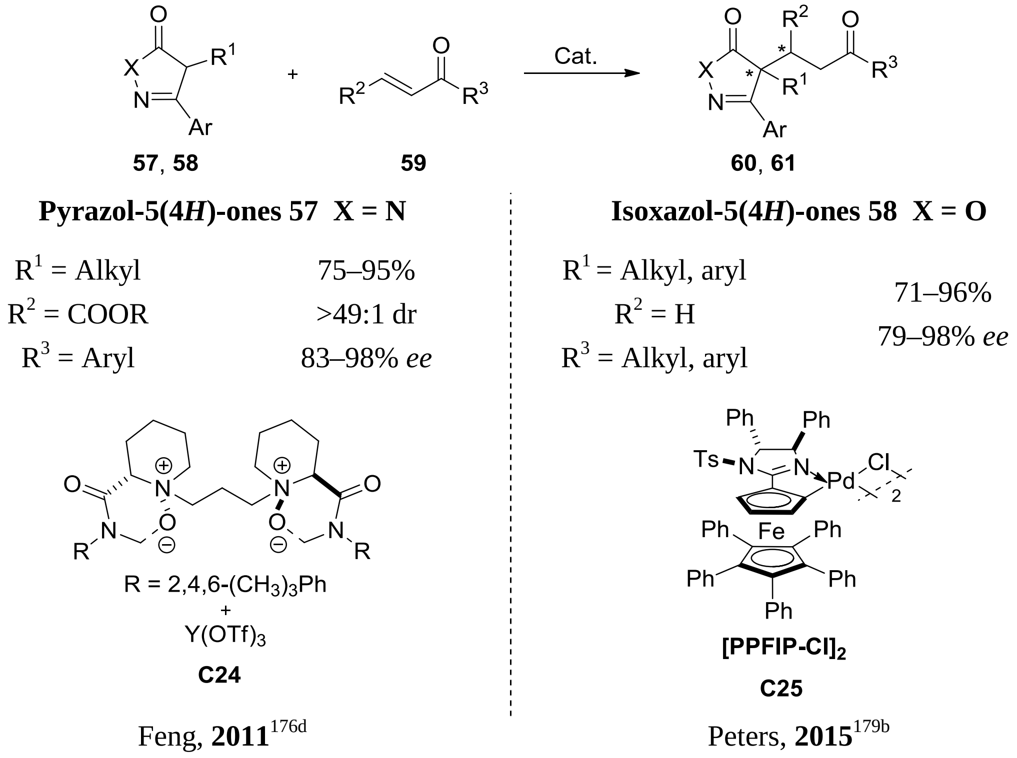
[173] For the *N–O* bond cleavage of isoxazolidin-5-ones to give β-amino acids, see: a) Tite, T.; Sabbah, M.; Levacher, V.; Brière, J.-F. *Chem. Commun*. **2013**, *49*, 11569–11571. b) Postikova, S.; Tite, T.; Levacher, V.; Brière, J.-F. *Adv. Synth. Catal*. **2013**, *355*, 2513–2517.

[174] a) Moreno-Manas, M.; Pérez, M.; Pleixats, R. *Tetrahedron* **1994**, *50*, 515–528. b) Atfani, M.; Lubell, W. D. *J. Org. Chem*. **1995**, *60*, 3184–3188.

[175] Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827–832.

[176] For a Michael addition to aldehydes catalyzed by secondary amines, see: a) Alba, A. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem*. **2011**, 1318–1325. For a Michael addition to alkynones promoted by metal complexes, see: b) Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed*. **2012**, *51*, 2776–2779. For a Michael addition to maleimides promoted by bifunctional thiourea catalysts, see: c) Mazzanti, A.; Calbet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem*. **2012**, *10*, 1645–1652. For a Michael addition to enones promoted by a metal catalyst, see: d) Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed*. **2011**, *50*, 4928–4932.

isoxazol-5(4*H*)-ones there are only three reports on their use as pronucleophiles.[179] However, it is worth to mention that regarding the Michael addition of pyrazol-5(4*H*)-ones **57**[176d] and isoxazol-5(4*H*)-ones **58**[179b] to α,β-unsaturated ketones **59** two examples have been only reported both promoted by metal catalysts **C24** and **C25** (Scheme 21). In both cases, adducts **60** and **61** are obtained with excellent results but in the case of pyrazol-5(4*H*)-ones activated enones are required.



Scheme 21. Metal catalyzed Michael addition examples of pyrazol-5(4*H*)-ones and isoxazol-5(4*H*)-ones to enones.

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[177] For the asymmetric α-amination with azodicarboxylates catalyzed by Gd complexes, see: Yang, Z.; Wang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 596–599.

[178] For the asymmetric allylic alkylation with allylic alcohols catalyzed by Pd complexes, see: Tao, Z.-L.; Zhang, W.-Q.; Chen, D.-F.; Adele, A.; Gong, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 9255–9258.

[179] For one-pot sequential 1,4-addition/dearomative fluorination, see: a) Meng, W.-T.; Zheng, Y.; Nie, J.; Xiong, H.-Y.; Ma, J.-A. *J. Org. Chem.* **2013**, *78*, 559–567. For a Michael addition to enones promoted by a metal catalyst, see: b) Hellmuth, T.; Frey, W.; Peters, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 2788–2791. For a domino Michael-cyclization reaction for the synthesis of spirocyclic oxindoles catalyzed by quinine, see: c) Cui, B.-D.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2014**, *70*, 1895–1902.

1.3.2.2.5. *α,β-Unsaturated γ-butyrolactams and butenolides*

α,β-Unsaturated γ-butyrolactams and butenolides have emerged as the most attractive reactants in asymmetric organometallic or organocatalytic reactions for the synthesis of chiral β- and γ-functionalized pyrrolidin-2-ones and furan-2-ones. These structural motifs are present in a variety of bioactive compounds and are prodigious building blocks (Figure 23).[180]

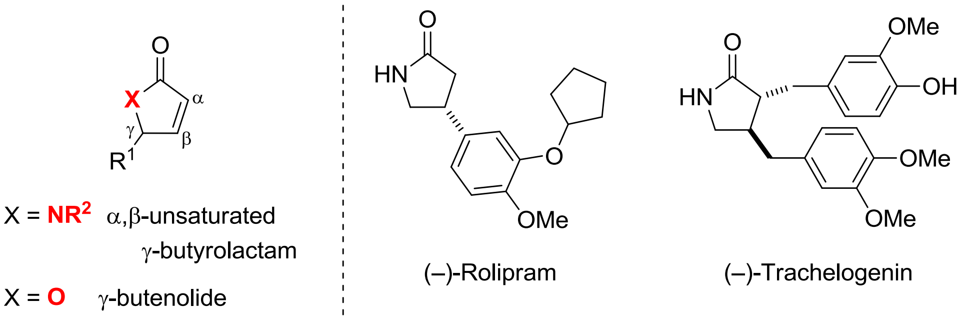

Figure 23. General structure of α,β-unsaturated γ-butyrolactams and γ-butenolides and some biologically active compounds.

Owing to their synthetic significance, intense efforts have been made to extend the structurally diverse substituted butyrolactams (Scheme 22). α,β-Unsaturated γ-butyrolactams have been mainly employed as vinylogous nucleophiles to perform Michael additions to form tertiary stereocenters as has been collected in various extensive reviews.[181] Moreover, there are some examples involving the asymmetric catalyzed 1,4-addition introducing *C*-4 chirality at the β position, but in all cases these heterocycles are acting as electrophiles.[182] In contrast, the reaction at the α-position of α,β-unsaturated γ-butyrolactam with electrophiles is rare and only a few examples have been reported.[183]

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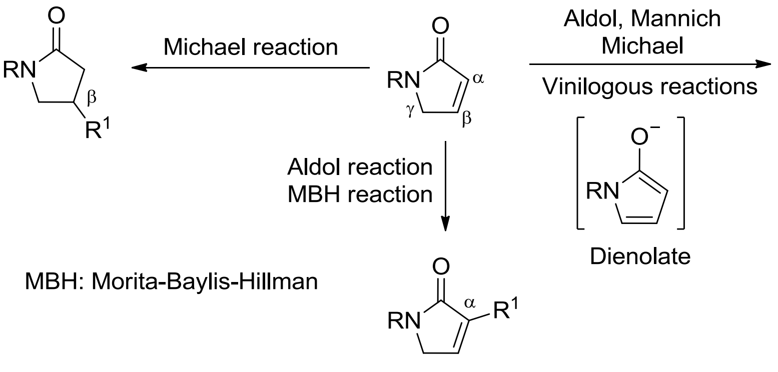
[180] For selected reviews on natural or non-natural compounds with remarkable biological activities, see: a) Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 139–165. b) Ordónez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3–99.

[181] For some recent reviews, see: a) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595–2615. b) Schneider, C.; Abels, F. *Org. Biomol. Chem*. **2014**, *12*, 3531–3543. c) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev*. **2011**, *111*, 3076–3154. d) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed*. **2005**, *44*, 4682–4698.

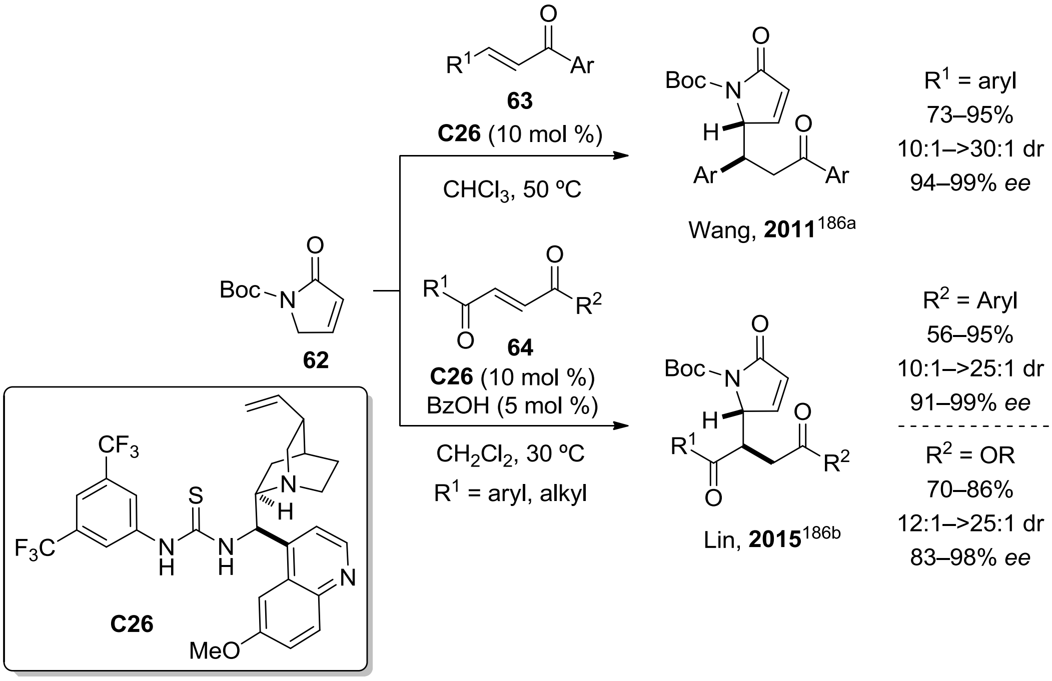
[182] a) Pace, V.; Rae, J. P.; Procter, D. J. *Org. Lett*. **2014**, *16*, 476–479. b) Kuuloja, N.; Vaismaa, M.; Franzén, R. *Tetrahedron* **2012**, *68*, 2313–2318. c) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett*. **2011**, *13*, 788–791.

[183] a) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun*. **2013**, *49*, 3300–3302. b) Duan, Z.; Zhang, Z.; Quian, P.; Han, J.; Pan, Y. *RSC Adv*. **2013**, *3*, 10127–10130. c) Ma, Y.; Zhang, G.; Zhang, J.; Yang, D.; Wang, R. *Org. Lett*. **2014**, *16*, 5358–5361.



Scheme 22. Different reaction positions of α,β-unsaturated butyrolactams.

Two groups have described the Michael addition of α,β-unsaturated butyrolactams to enones and β-activated acrylates in organocatalysis.[184] In 2011 Wang reported the vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams **62** to chalcones **63** promoted by the bifunctional thiourea catalyst **C26**. Excellent results were obtained but the methodology failed with enones with R^1 = Me and ^{t}Bu substituents. Later, Lin employed the same catalyst **C26** for the conjugate addition to enones and β-acyl acrylates **64** affording adducts with good stereocontrol.



Scheme 23. Michael addition of α,β-unsaturated butyrolactams to enones described by Wang (a) and Lin (b).

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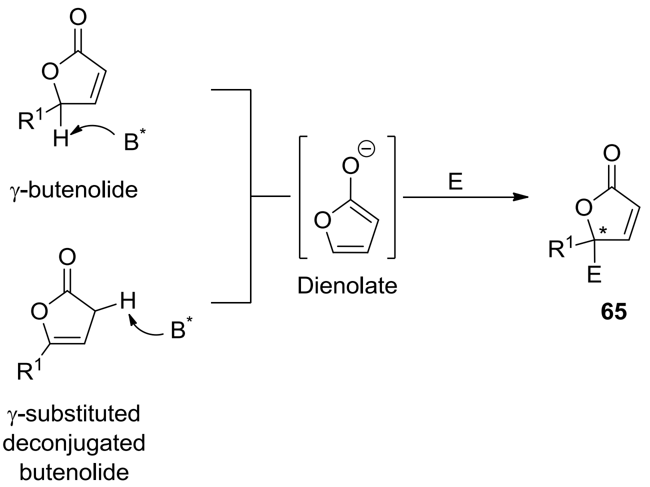
[184] a) Zhang, Y.; Shao, Y.-L.; Xu, H.-S.; Wang, W. *J. Org. Chem.* **2011**, *76*, 1472–1474. b) Chen, Y.-R; Das, U.; Liu, M.-H.; Lin, W. *J. Org. Chem.* **2015**, *80*, 1985–1992.

Many different vinylogous reactions have been developed with γ-butenolides that have also been collected in a review.[185] Structurally similar γ-substituted deconjugated butenolides have gained attention due to their potential for the construction of the same products **65** obtained from γ-butenolides containing a γ-quaternary stereocenter (Scheme 24). It is noteworthy to mention that at the outset of this research area instead of using directly γ-butenolides as pronucleophiles, many reactions were described with 2-silyloxyfurans,[186] probably because of their higher reactivity.



Scheme 24.

Asymmetric allylic alkylation[187] and vinylogous Mannich reaction[188] have been achieved under either metal or organocatalytic conditions with these γ-substituted deconjugated butenolides. Direct organocatalytic Michael additions of these heterocycles to various electrophiles such as enals,[189] nitroolefins[190] and enoyl

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[185] For a review on the synthesis of butenolides by direct vinylogous reactions, see: Yan, L.; Wu, X.; Liu, H.; Xie, L.; Jiang, Z. *Mini-Reviews Med. Chem.* **2013**, *13*, 845–853.

[186] a) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414–1415. b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053. c) Yadav, J. S.; Subba Reddy, B. V.; Narasimhulu, G.; Satheesh, G. *Tetrahedron Lett.* **2008**, *49*, 5683–5686. d) Zhang, Q.; Xiao, X.; Lin, L.; Liu, X.; Feng, X. *Org. Biomol. Chem.* **2011**, *9*, 5748–5754. e) Fraile, J. M.; García, N.; Herrerías, C. I. *ACS Catal.* **2013**, *3*, 2710–2718. f) Silverio, D. L.; Fu, P.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Tetrahedron Lett.* **2015**, *56*, 3489–3493.

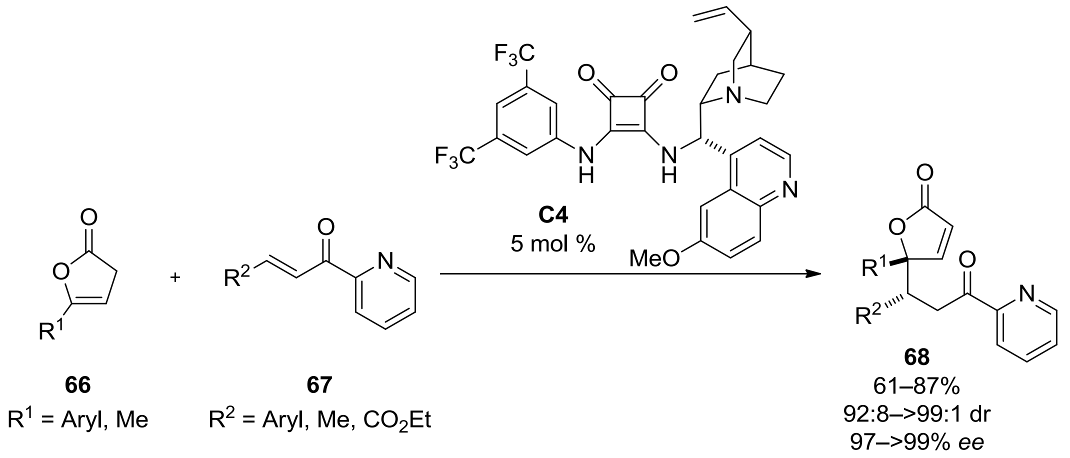
[187] a) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720–723. b) Huang, X.; Peng, J.; Dong, L.; Chen, Y.-C. *Chem. Commun.* **2012**, *48*, 2439–2441.

[188] Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056–3059.

[189] Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540–1543.

[190] a) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193–5195. b) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026–3029.

pyridines[191] have also been reported. The vinylogous Michael addition of γ-substituted deconjugated butenolides **66** to 2-enoylpyridines **67** has been reported by Xu and Yuan (Scheme 25), and the corresponding adducts **68** are obtained in good yield and excellent diastereo- and enantiocontrol in the presence of the squaramide-based bifunctional catalyst **C4**. In this approach the 2-pyridyl moiety has been found to be key for the obtention of high yields. Additionally, when the γ-methyl butenolide (R^1 = Me) was used with β-methyl enone (R^2 = Me) no reaction was observed.



Scheme 25. Michael addition of γ-substituted deconjugated butenolides to 2-enoyl pyridines catalyzed by the bifunctional squaramide **C4**. **Xu &Yuan, 2015**.

1.4. Objectives

The previous precedents show that the use of carboxylic acid derivatives as Michael acceptors and donors in organocatalysis is challenging. There are not many examples of asymmetric catalytic reactions involving these substrates. The low acidity of the α-carbon of the ester group complicates efficient deprotonation with typical weak chiral amines. Additionally, the low reactivity of α,β-unsaturated ester/amides as Michael acceptors, further illustrates the need of new surrogates. On the other hand, Michael additions of carbon nucleophiles to enones or α,β-unsaturated esters involving the generation of a tetrasubstituted stereocenter have also found limited success.

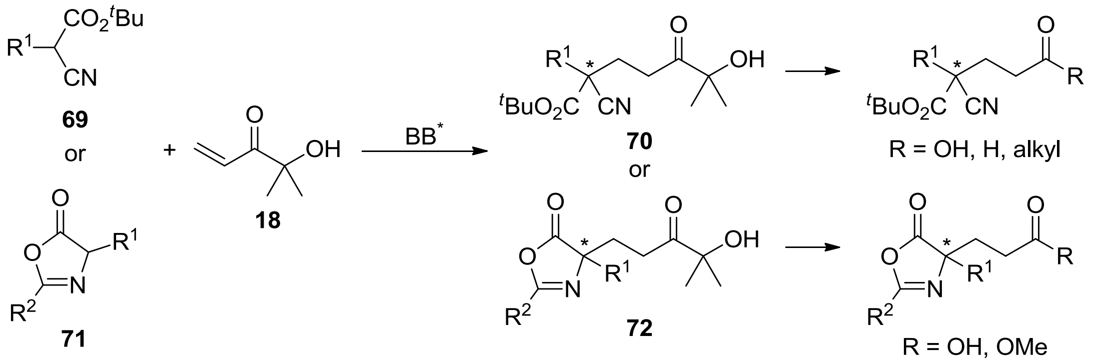
In this context and, as mentioned before, our group reported the efficiency of α'-oxy enones as Michael acceptor templates in various metal catalyzed asymmetric reactions. They showed higher innate reactivity than most ester surrogates and the resulting addition adducts were easily converted into carboxylic acids, aldehydes and

---

[191] Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun*. **2015**, *51*, 15835–15838.

ketones. However, at the beginning of the research work for this Thesis, the use of these types of acceptors had not been investigated in organocatalysis.

Inspired by these precedents, we hypothesized that α’-oxy enones could be efficient ester surrogates in asymmetric reactions promoted by Brønsted base organocatalysts. So the first goal of this work was to check the efficiency of these templates as Michael acceptors in the reaction with carbon-nucleophiles promoted by bifunctional Brønsted base catalysts, while simultaneously generating tretrasubstituted stereocenters. The corresponding Michael adducts could then be converted into the analog esters and ketones, thus given access to derivatives otherwise not accessible through direct conjugate addition. More specifically, the pronucleophiles chosen for this first objective were α-substituted cyanoacetates **69** and azlactones **71** (Scheme 26). The reasons of this choice as well as the corresponding results of this research are outlined in Chapter 2.



Scheme 26. First exploration of the utility of α’-oxy enones as Michael acceptors in organocatalysis.

On the other hand, the search of new efficient pronucleophiles in asymmetric catalysis still is another focus of interest. More specifically the finding of new heterocyclic pronucleophiles for organocatalytic reactions that promote simple access to carbonylic compounds with quaternary α-*C* (sp^3) moieties has been the goal of several research groups throughout decades. In this context, the second goal of this work was to check the validity of pyrrolidin-2,3-diones as pronucleophiles in Brønsted base promoted catalytic reactions (Scheme 27). Specifically, pyrrolidin-2,3-diones **73** were selected as promising substrates since this heterocyclic scaffold is biologically interesting and precursor of β-amino acids, *vide infra*. To the best of our knowledge, these substrates have only been used in an iminium based asymmetric catalytic reaction to generate tertiary stereocenters.[192] Due to the tautomerism of 4-substituted pyrrolidin-2,3-diones bifunctional Brønsted bases were envisaged as ideal catalysts to depronОnate

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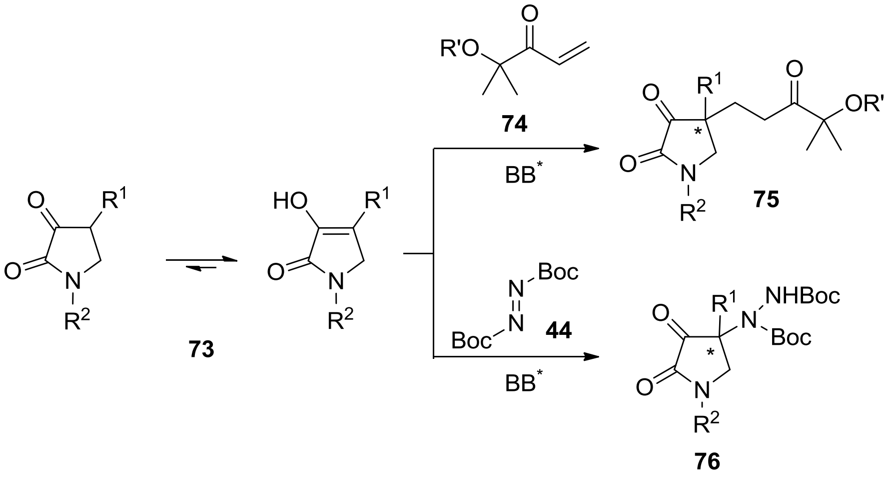
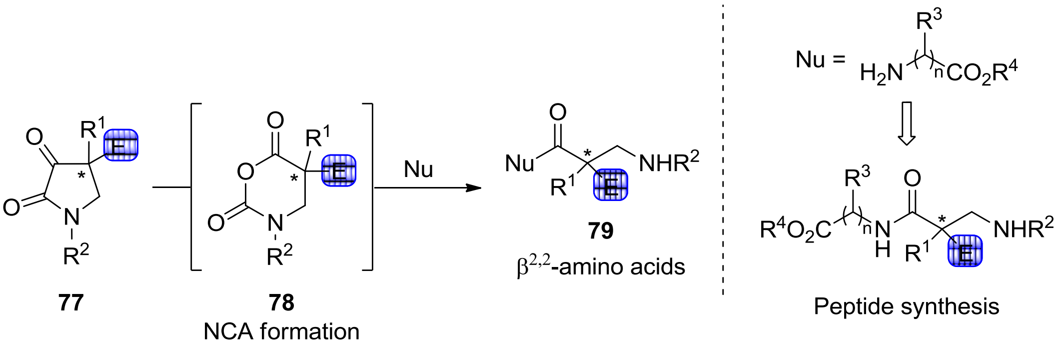
[192] Zhu, H.-L.; Ling, J.-B.; Xu, P.-F. *J. Org. Chem*. **2012**, *77*, 7737–7743.

them and provide chiral environment. In this instance, both α’-oxy enones **74** and azodicarboxylates **44** were the electrophiles of choice for this study.



Scheme 27. First investigations on the utility of 4-substituted pyrrolidin-2,3-diones as pronucleophiles in organocatalysis.

This synthetic plan presents some challenges because pyrrolidin-2,3-diones exhibit more than one reacting sites and there are some evidences of regioselectivity problems in alkylation reactions.[193] The most interesting characteristic of the addition adducts **77** coming from these substrates is that they can be easily converted into the corresponding NCAs **78** for their direct incorporation into peptidic sequences and/or reaction with different nucleophiles (Scheme 28). All the results concerning the use of pyrrolidin-2,3-diones as pronucleophiles as well as the applications of the resulting adducts are collected in Chapter 3.



Scheme 28. Applications of the Michael adducts coming from pyrrolidin-2,3-diones in peptide synthesis.

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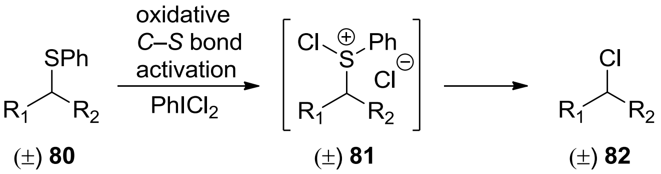
[193] Southwick, P. L.; Barnas, E. F. *J. Org. Chem.* **1962**, *27*, 98–106.

Finally, a short stay was carried out under the supervision of Prof. Mauro Adamo in the Royal Collegue of Surgeons in Ireland in the Pharmaceutical and Medicinal Department. The research project there was focused on the preparation of racemic benzylic chlorides **82** from racemic benzylic sulfides **80** with stoichiometric amounts of hypervalent iodine (Scheme 29). The corresponding results are presented in Chapter 4.



Scheme 29. Synthesis of racemic benzyl chlorides from benzylic sulfides through oxidative *C–S* bond activation.

CHAPTER 2

α'-Oxy enones as Michael acceptors in organocatalytic reactions

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2. α’-Oxy enones as Michael acceptors in organocatalytic reactions

As mentioned in the previous chapter, one of the goals of this Thesis was to investigate the efficiency of α’-oxy enones as Michael acceptor substrates in organocatalytic asymmetric reactions. For that purpose, two types of enolizable carbonyl compounds (cyanoacetates **69** and azlactones **70**) that have previously demonstrated to be challenging were selected. Moreover, a variety of α’-oxy enones with different substitution patterns (non-substituted, β-substituted and α-substituted enones, Figure 24) were chosen as bidentate templates to investigate the Michael addition promoted by chiral bifunctional Brønsted base catalysts.

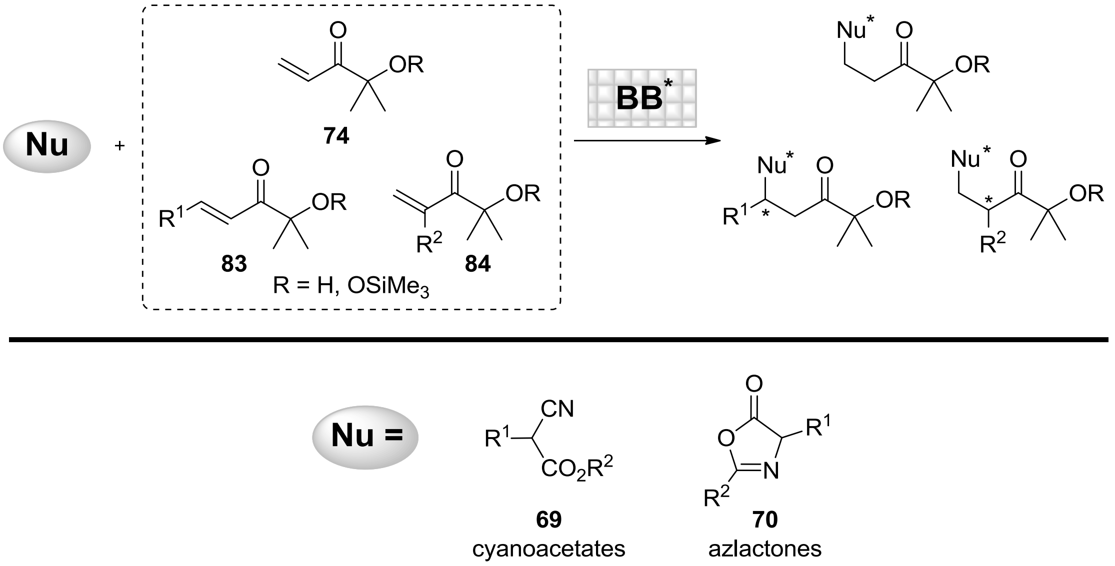
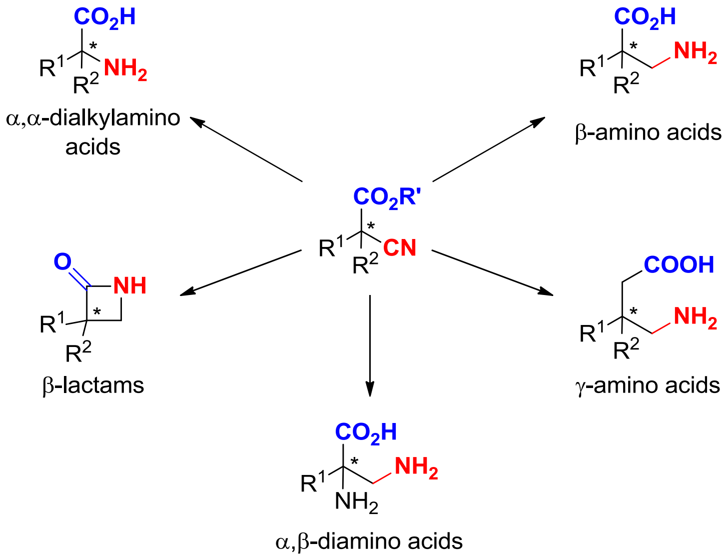


Figure 24. Proposed pronucleophiles to check the efficiency of α’-oxy enones in asymmetric Brønsted base catalyzed Michael reactions.

2.1. α-Substituted cyanoacetates as Michael donors

The use of 2-cyano esters as pronucleophiles in asymmetric reactions provides direct access to highly functionalized chiral building blocks with different structural features. The versatility of both the carboxy and cyano group as precursors of different functional groups makes possible the enantioselective synthesis of different products such as α,α-dialkylamino acids,[194] β-amino acids and β-lactams,[195] α,β-diamino acids,[196] γ-amino acids[197] and others[198] (Scheme 30).



Scheme 30. Diversity of products obtained from chiral cyanoacetates.

Several different types of asymmetric reactions have been carried out with 2-cyano esters which afford α-functionalized derivatives with a new tetrasubstituted stereocenter.[199] Among the reactions involving α-carbon functionalization of the substrates, alkylations,[200] allylic substitutions,[201] Mannich[202] and multicomponent

---

[194] For some selected examples, see: a) Terada, M.; Tsushima, D.; Nakano, M. *Adv. Synth. Catal*. **2009**, *351*, 2817–2821. b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599, and references cited therein.

[195] For some selected examples, see: a) Inaba, Y.; Yano, S.; Mikata, Y. *Bull. Chem. Soc. Jpn*. **2008**, *81*, 606–616. b) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Gil, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2209-2214. c) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2787–2796. d) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *J. Org. Chem*. **1994**, *59*, 2497–2505.

[196] Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1996**, *52*, 687–694.

[197] Aguirre, D.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **2006**, *62*, 8142–8146.

[198] a) Nagata, K.; Sano, D.; Shimizu, Y.; Miyazaki, M.; Kanemitsu, T.; Itoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2530–2536. b) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2005**, *127*, 1313–1317. c) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 706–707. c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2003**, *125*, 11204–11205.

[199] Reviews on asymmetric catalytic reactions of α-substituted cyanoacetates, see ref. 109

[200] For the asymmetric alkylation of cyanoacetates under phase transfer conditions, see: a) Nagata, K.; Sano, D.; Itoh, T. *Synlett* **2007**, 547–550. b) Ref. 198a.

[201] For Pd catalyzed allylic alkylation of 2-cyano esters, see: a) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3309–3310. For Mo catalyzed allylic alkylation of α-cyano esters, see: b) Trost, B. M.; Miller, J. R.; Hoffman, C. M. *J. Am. Chem. Soc*. **2011**, *133*, 8165–8167. For organocatalytic β-

reactions[203] have been reported, most of them promoted by chiral organocatalysts. Regarding α-heteroatom functionalization of these substrates, significant progress has been made in the organocatalytic α-amination,[204] α-phosphination[205] and α-fluorination[206] reactions. However, the development of other α-heteroatom functionalizations (oxidation, chlorination, bromination or sulfenylation) remains unexplored.

Cyanoacetates are incapable of two-point binding to the catalyst because of the linear geometry of the cyano group which affords less rigid and less organized transition states and hampers the differentiation of prochiral enol(ate) faces. To overcome this difficulty the most efficient methodology with these substrates has been a bifunctional activation mode (for example, dinuclear Lewis acid catalysis or a well-defined hydrogen-bonding network) to activate both the cyanoacetate nucleophile and the electrophile.

Apart from a study by Wymberg and Helder in 1975[207] about the Michael addition of ethyl 2-phenyl-2-cyanoacetate to methyl vinyl ketone catalyzed by quinine, metal complexes were the only catalysts used to promote the conjugate addition of 2-cyano esters to activated olefins until 2005. Since then organocatalysts have taken the place of metal catalysts and some of the most representative results are summarized in Table 1.

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isocupreidine catalyzed allylic alkylation of α-cyano esters, see: c) van Steenis, D. J.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal*. **2007**, *349*, 281–286.

[202] For (DHQD)$_2$PYR catalyzed Mannich reaction of α-substituted cyanoacetates, see: Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2005**, *44*, 2896–2899.

[203] For three-component cascade reactions of α-cyano esters catalyzed by thioureas, see: Yang, G.; Luo, C.; Mu, X.; Wang, T.; Liu, X.-Y. *Chem. Commun*. **2012**, *48*, 5880–5882.

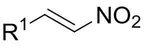
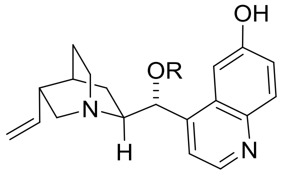
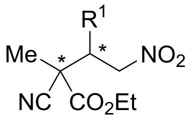
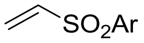
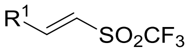
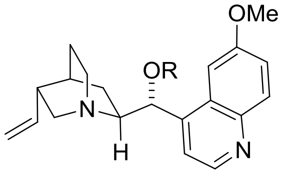
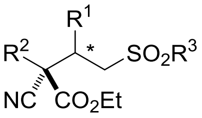
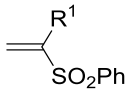
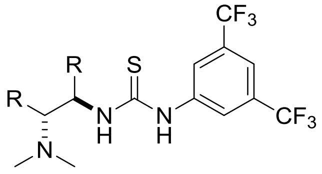
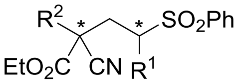
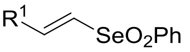
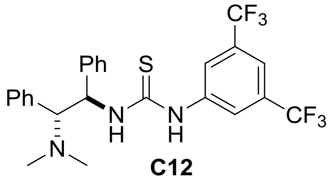
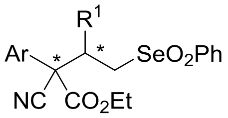
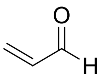
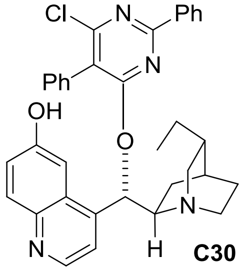
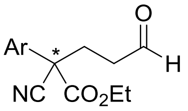
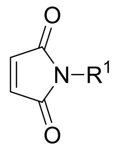
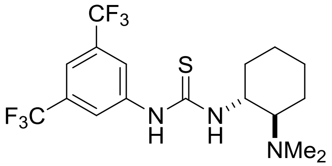
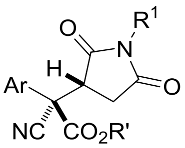
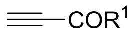
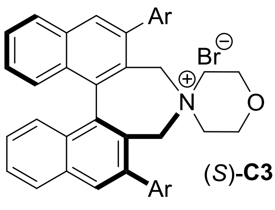
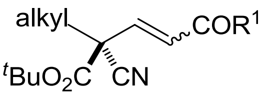
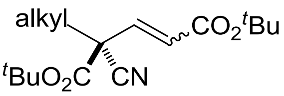
[204] For the metal-catalyzed amination of cyanoacetates with azodicarboxylates, see: a) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc*. **2008**, *130*, 2158–2159. For the organocatalyzed amination of cyanoacetates with azodicarboxylates, see: b) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2004**, *126*, 8120–8121. c) Liu, X.; Li, H.; Deng, L. *Org. Lett*. **2005**, *7*, 167–169. d) Liu, Y.; Melgar-Fernández, R.; Juaristi, E. *J. Org. Chem*. **2007**, *72*, 1522–1525.

[205] For the organocatalyzed phosphination reaction of α-cyano esters, see: Nielsen, M.; Jacobsen, C. B.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2011**, *50*, 3211–3214.

[206] For cinchona alkaloid/Selectfluor combination promoted fluorination of α-substituted cyanoacetates, see: a) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc*. **2000**, *122*, 10728–10729. b) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc*. **2001**, *123*, 7001–7009. For the Pd-complexes catalyzed fluorination of α-cyano esters, see: c) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett*. **2005**, *46*, 3115–3117. d) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc*. **2007**, *28*, 2435–2441. e) Jacquet, O.; Clément, N. D.; Blanco, C.; Martínez-Belmonte, M.; Benet-Buchholz, J. B.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem*. **2012**, 4844–4852.

[207] See ref. 13.

Table 1. Representative examples of organocatalyzed Michael additions of α-substituted cyanoacetates.

Author	Michael acceptors	Catalyst	Product	Results
a) Deng **2005**[208]		 **C27** R = H, Bn	 R^1 = Ph, *n*-pentyl	75–77% 93:7–>98:2 dr 98–>99% *ee*[a]
b) Deng **2005**[209]	 	 **C28** R = PHN	 R^1 = alkyl R^2 = aryl, alkyl	76–96% 5.6:1–49:1 dr 81–97% *ee*[a]
c) Chen **2006**[210]		 **C29** R = Ph, (-CH_2-)$_4$	 R^1 = H, SO_2Ph R^2 = aryl, alkyl	73–98% 72–96% *ee*[a]
d) Marini **2009**[211]		 **C12**	 R^1 = H, Ph	75–97% 3:1 dr 74–90% *ee*[a]
e) Deng **2006**[212]		 **C30**		90–100% 80–95% *ee*[a]
f) Yan Yuan **2011**[214,215]		 **C2**		65–99% 75:25–98:2 dr 81–98% *ee*
g) Maruoka **2007**[217]	 	 (*S*)-**C31** Ar = 3,5-[3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3	 	70–99% 1.6:1–5.0:1 *E/Z* 71–93% *ee* 80–99% 3.3:1–7.5:1 *E/Z* 92–97% *ee*

[a] Absolute configuration not specified

Deng and co-workers described the first efficient organocatalyzed Michael addition of 2-methyl cyanoacetates to nitroalkenes (Table 1, a).[208] Two contiguous stereogenic centers were created with excellent levels of enantio- and diastereoselectivity promoted by the cinchona derived catalyst **C27**. In light of the discovery of this type of catalysts as highly efficient in the reaction with nitroalkenes, the same group reported the enantioselective conjugate addition of 2-aryl-2-cyanoacetates to vinyl sulfones (Table 1, b).[209] Nevertheless, 2-alkyl cyanoacetates were significantly less active and to overcome this lack of reactivity, the more electrophilic 3,5-bis-(trifluoromethyl)-phenyl vinyl sulfone was used as Michael acceptor. Furthermore, the efficiency of β-substituted α,β-unsaturated sulfones as Michael acceptors was also demonstrated as the corresponding adducts were obtained in good yields and good to excellent levels of enantio- and diastereoselectivity.

Similar results were described by Chen in the addition reaction of 2-substituted cyanoacetates to vinyl sulfones catalyzed by the chiral bifunctional thiourea **C29** (Table 1, c).[210] From good to excellent yields and excellent enantioselectivities were observed in the reaction of 2-aryl cyanoacetates with phenyl vinyl sulfone; however, 2-alkyl cyanoacetates required a more electrophilic sulfone (1,1-bis(phenylsulfonyl)ethane) to observe good reactivity (73–96%, 91–96% *ee*).

Another type of Michael acceptor was studied later by Marini and co-workers (Table 1, d). Vinyl selenones turned out to be efficient substrates in the addition of 2-aryl-2-cyanoacetates catalyzed by **C12** affording the Michael adducts in good to excellent yields, diastereo- and enantioselectivities.[211] However, the reaction could not be extended to 2-alkyl cyanoacetates due to their low reactivity. The reaction was also performed using β-substituted α,β-unsaturated selenones as Michael acceptors and the corresponding adducts were obtained with enantioselectivity from moderate to good. The synthetic versatility of the selenone moiety allowed its conversion into synthetically valuable chiral functional groups such as azide, bromide, iodide and alkene.

Deng and co-workers were also the first to describe the organocatalytic asymmetric conjugate addition of 2-substituted cyanoacetates to enals (Table 1, e).[212]

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[208] Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed*. **2005**, *44*, 105–108.

[209] a) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc*. **2005**, *127*, 8948–8949. b) Li, H.; Song, J.; Deng, L. *Tetrahedron* **2009**, *65*, 3139–3148.

[210] Liu, T.- Y.; Long, J.; Li, B.- J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.- S.; Chen, Y.- C. *Org. Biomol. Chem*. **2006**, *4*, 2097–2099.

[211] Marini, F.; Sternativo, S.; Del Verme, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal*. **2009**, *351*, 103–106.

[212] Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem. Int. Ed*. **2006**, *45*, 4301–4305.

The corresponding Michael adducts coming from the reaction of 2-aryl and 2-heteroaryl cyanoacetates with acrolein[213] were obtained with excellent yields and enantioselectivities employing the modified cinchona catalyst **C30.**

In 2011, Yan[214] and Yuan[215] and co-workers reported almost at the same time the organocatalytic asymmetric Michael reaction of 2-aryl cyanoacetates with maleimides[216] promoted by the thiourea-based catalyst **C2** (Table 1, f) demonstrating that this was a useful tool for the asymmetric synthesis of chiral succinimide derivatives. However, in the same reaction aliphatic cyanoacetates reacted with decreased stereoselectivity (52:48–69:41 dr; 68–71% *ee*).

Organocatalytic phase-transfer conditions have also been checked in the conjugate reaction of α-alkyl cyanoacetates with alkynyl ketones and alkynyl esters by Maruoka (Table 1, g).[217] High enantioselectivity and moderate *E/Z* selectivity was observed under the influence of the binaphthyl derived phase transfer catalyst **C31**.

2.1.1. Michael addition of α-substituted cyanoacetates to α,β-unsaturated ketones

Acyclic carbonyl compounds possessing multiple stereocenters are important building-blocks for the construction of complex natural products and bioactive molecules. The Michael addition of α-substituted cyanoacetates to α,β-unsaturated ketones may provide derivatives of type **A**, **B** and **C** depending on the substitution pattern of the ketone Michael acceptor (Figure 25). In this regard, very few examples of these additions have been reported for type **A** and type **B** structures, and, to the best of our knowledge, no examples leading to structures of type **C** bearing two non-adjacent stereocenters can be found in the literature.[218,219] These units are of a great synthetic

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[213] For a related example of the Michael addition of alkylidene cyanoacetates to acrolein catalyzed by a cinchona alkaloid, see: Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407–5410.

[214] Wang, J.- J.; Dong, X.- J.; Wei, W.- T.; Yan, M. *Tetrahedron: Asymmetry* **2011**, *22*, 690–696.

[215] Liao, Y.- H.; Liu, X.- L.; Wu, Z.- J.; Du, X.- L.; Zhang, X.- M.: Yuan, W.- C. *Adv. Synth. Catal.* **2011**, *353*, 1720–1728.

[216] For the Michael addition of methyl 2-cyanoacetate to 2-methoxybenzimides promoted by a thiourea catalyst, see: Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419.

[217] a) Lan, Q.; Wang, X.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 4675–4678. b) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038–1039.

[218] For classic examples of multistep approaches to α,γ-substituted carbonyl patterns en route to erythromycins, see: a) Corey, E. J.; Hopkins, P. B.; Sung-eun, S. K.; Krishnan, Y.; Nambiar, P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131–7134. b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chtnevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee,

significance since they are present in many biological active compounds such as erythromycins and related macrolide antibiotics.[220] The corresponding precedents of these reactions are explained below.

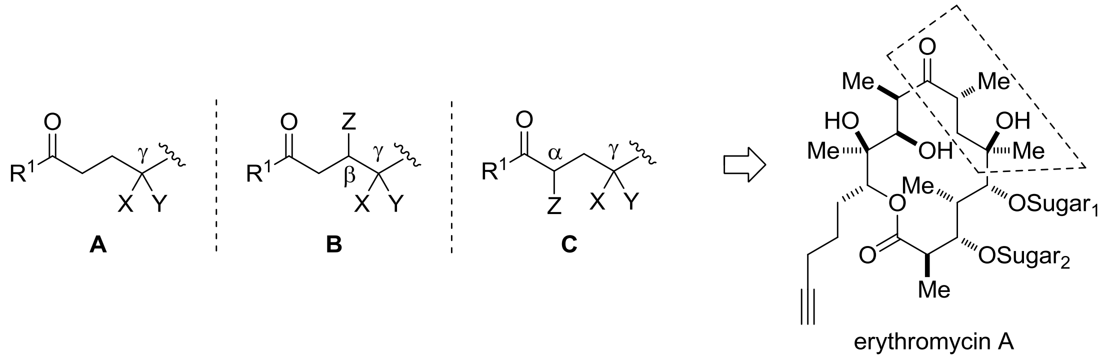

Figure 25. Acyclic carbonyl compounds with different stereoarrays.

2.1.1.1. *Unsubstituted α,β-unsaturated ketones as acceptors*

As mentioned previously, the use of metal complexes dominated the field of enantioselective conjugate additions of 2-cyano esters to α,β-unsaturated ketones until 2005.[221] The first and, to the best of our knowledge, the only efficient organocatalyzed Michael addition of 2-substituted cyanoacetates to α,β-unsaturated ketones was described in 2007. Chen and co-workers reported the highly enantioselective reaction of these substrates with vinyl ketones in the presence of the simple bifunctional

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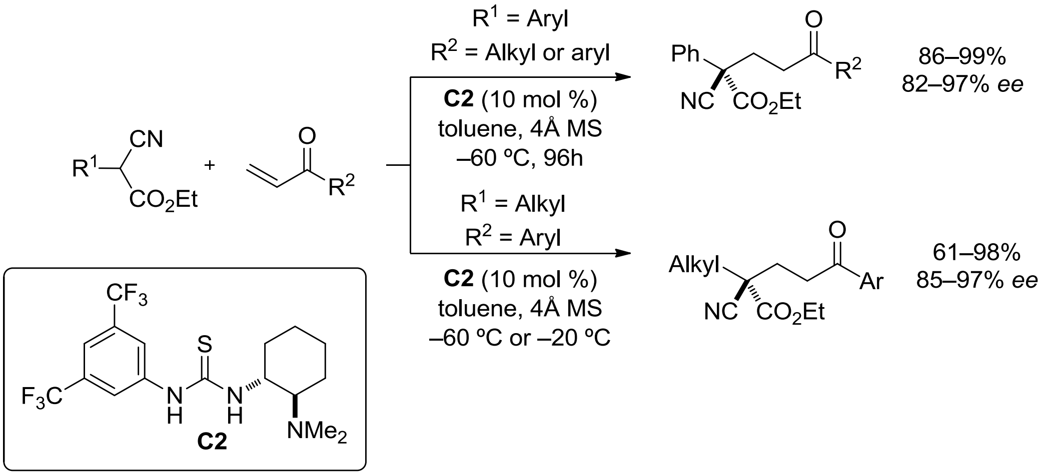
V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong H. N.-C. *J. Am. Chem. Soc*. **1981**, *103*, 3215–3217. c) Stork, G.; Rychnovsky, D. R. *J. Am. Chem. Soc*. **1987**, *109*, 1565–1567. d) Mulzer, J. *Angew. Chem. Int. Ed*. **1991**, *30*, 1452–1454. e) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 101–103.

[219] For a racemic synthesis of a α,γ-substituted carbonyl pattern with all-carbon quaternary/tertiary nonadjacent stereocenters, see: Fan, J.-H.; Wei, W.-T.; Zhou, M.-B.; Song, R.-J.; Li, J.-H. *Angew. Chem. Int. Ed*. **2014**, *53*, 6650–6654.

[220] For the activity of erythromycin A against Gram-Negative Bacteria, see: a) Cochrane, S. A.; Li, X.; He, S.; Yu, M.; Wu, M.; Vederas, J. C. *J. Med. Chem*. **2015**, *58*, 9779–9785. For the activity of erythromycin related compounds as anti-bacterial agents, see: Arsic, B.; Awan, A.; Brennan, R. J.; Aguilar, J. A.; Ledder, R.; McBain, A. J.; Regan, A. C.; Barber, J. *Med. Chem. Commun*. **2014**, *5*, 1347–1354.

[221] For some selected examples of metal-catalyzed Michael reactions to α,β-unsaturated ketones, see: a) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439–4454. b) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc*. **1992**, *114*, 8295–8296. c) Inagaki, K.; Nozaki, K.; Takaya, H. *Synlett* **1997**, 119–120. d) Stark, M. A.; Richards, C. J. *Tetrahedron Lett*. **1997**, *38*, 5881–5884. e) Takenaka, K.; Minakawa, M.; Uozumi, Y. *J. Am. Chem. Soc*. **2005**, *127*, 12273–12281.

thiourea/tertiary amine organocatalyst **C2** (Scheme 31).[222] A number of α-aryl substituted cyanoacetates were successfully employed in the addition to methyl vinyl ketone with the simultaneous formation of a quaternary stereocenter. Nevertheless, α-alkyl cyanoacetates showed poor reactivity against this ketone but provided good results when aryl vinyl ketones were used as Michael acceptors.



Scheme 31. First organocatalyzed example of the Michael addition α-substituted cyanoacetates to vinyl ketones. **Chen, 2007**.

2.1.1.2. *β-Substituted α,β-unsaturated ketones as acceptors*

Chen and co-workers also reported a catalytic and highly enantioselective addition of α-unsubstituted cyanoacetates to β-substituted chalcone derivatives in the presence of the bifunctional thiourea organocatalyst **C32** derived from hydroquinine (Scheme 32).[223] Although the *syn/anti* diastereoselectivity was moderate, both adducts were obtained with excellent enantioselectivity. In this case no quaternary stereocenters are created.

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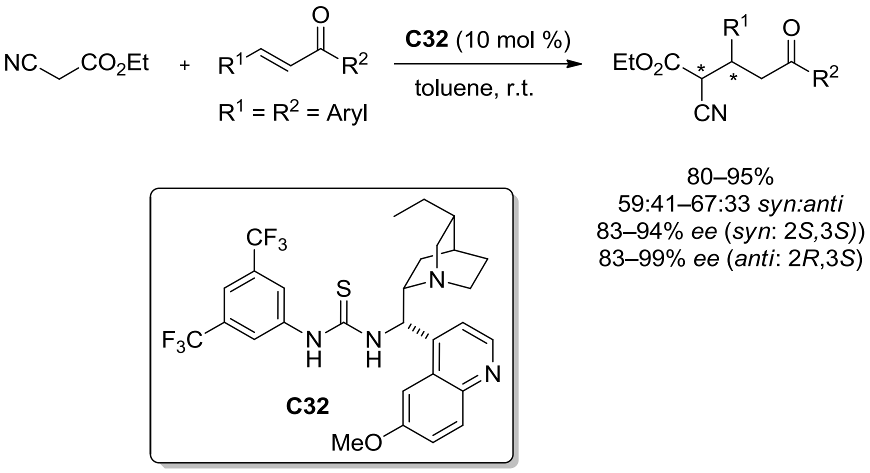
[222] Liu, T.- Y.; Li, R.; Chai, Q.; Long,, J.; Li, B.- J.; Wu, Y.; Ding, L.- S.; Chen, Y.- C. *Chem. Eur. J.* **2007**, *13*, 319–327.

[223] Gu, C.- L.; Liu, L.; Sui, Y.; Zhao, J.- L.; Wang, D.; Chen, Y.- J. *Tetrahedron: Asymmetry* **2007**, *18*, 455–463.



Scheme 32. Conjugate addition of cyanoacetates to β-substituted chalcones promoted by a bifunctional thiourea organocatalyst. **Chen, 2007**.

Adjacent quaternary and tertiary stereocenters are common structural motifs in complex natural products. In principle, the stereocontrolled conjugate addition of a trisubstituted carbon nucleophile to a β-substituted Michael acceptor could provide a one-step construction of such motifs. The simultaneous *C–C* bond formation of sterically demanding both quaternary and tertiary stereocenters has proven to be a great challenge. In this context, Jørgensen and co-workers described the use of activated β-chloroalkenones as Michael acceptors in the enantioselective conjugate addition of α-substituted cyanoacetates promoted by the phase-transfer catalyst **C33** (Scheme 33).[224] The resulting β-halo substituted enolate gave rapid elimination of the halide and this turned out to be the substitution of the vinylic halide with good control in the formation of the double bond.

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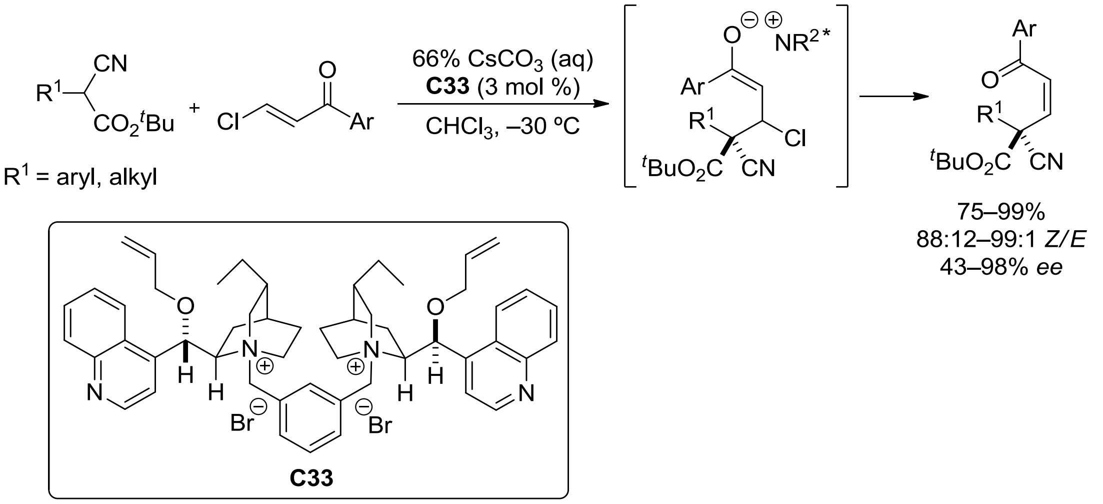
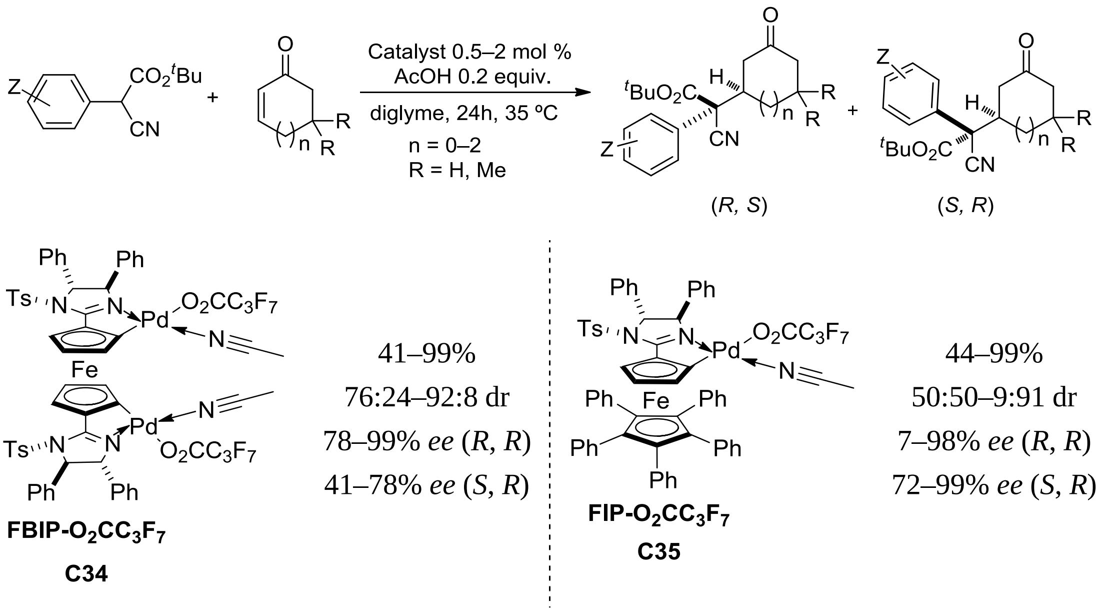
[224] Bell, M.; Poulsen, T. B.; Jørgensen, K. A. *J. Org. Chem*. **2007**, *72*, 3053–3056.



Scheme 33. Michael reaction of α-substituted cyanoacetates to β-chloroalkenones promoted by a phase-transfer catalyst. **Jørgensen, 2007**.

Peters addressed this issue and provided a solution to this problem involving cyclic enones as acceptors and using metal catalysis.[225] Different diastereomers as major products can be formed with high enantioselectivity depending on the use of a mono- or a bimetallic catalyst (Scheme 34). The planar chiral ferrocene based mono-palladacycle **C34** in general furnishes the (*S*,*R*) diastereomers with high enantioselectivity and the structurally related bis-palladacycle **C35** gives predominantly access to the (*R*,*R*) diastereomers with high enantiopurity.



Scheme 34. Michael addition of α-aryl cyanoesters to cyclic enones promoted by metal catalysts. **Peters, 2013**.

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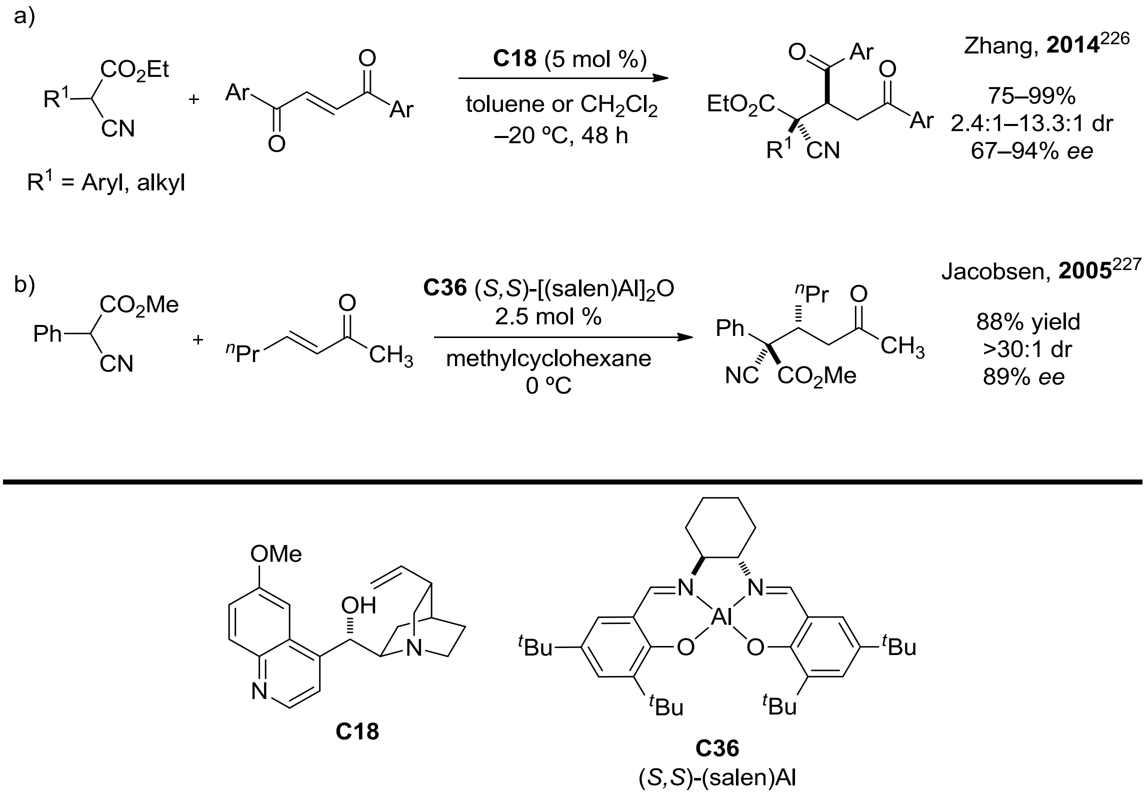
[225] Eitel, S. H.; Jautze, S.; Frey, W.; Peters, R. *Chem. Sci.* **2013**, *4*, 2218–2233.

On the other hand, Zhang reported the Michael addition of α-substituted cyanoacetates to β-acyl activated enones catalyzed by quinine **C18** generating a quaternary stereocenter (Scheme 35, a).[226] Both α-aryl and alkyl substituted cyanoacetates provided adducts with good diastereo- and enantioselectivities. Furthermore, only one example of the Michael reaction of α-substituted cyanoacetates with β-substituted alicyclic enones has been documented. As shown in Scheme 35b, the reaction is catalyzed by the Jacobsen salen complex catalyst **C36** and proceeds with excellent yields, diastereomeric ratios and *ee*’s.[227]



Scheme 35. Michael addition of α-cyanoacetates to activated enones (a) and acyclic enones (b) promoted by quinine (a) and a salen catalyst (b).

2.1.1.3. *α-Substituted α,β-unsaturated ketones as acceptors*

To the best of our knowledge there are no reports involving the Michael addition of α-substituted cyanoacetates to α-substituted α,β-unsaturated enones. Only a few examples of the addition of other Michael donors to other α-substituted Michael acceptors have been published. For instance, Pihko described the Mukaiyama-Michael

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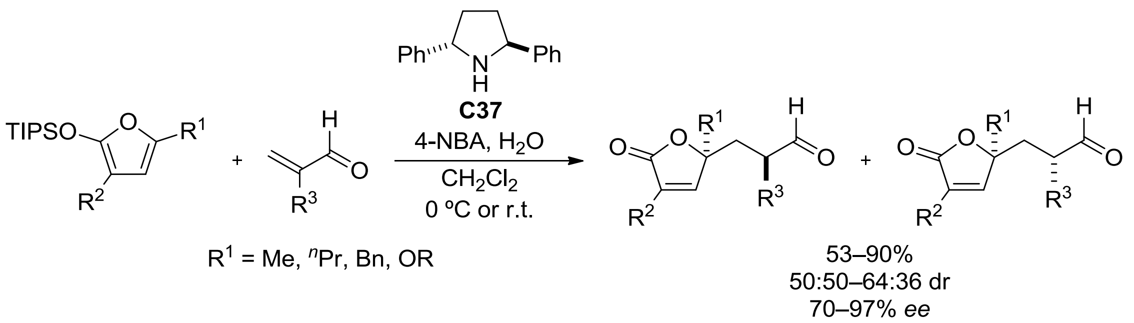
[226] Liu, L.; Liao, Y.; Lian, C.; Yuan, W.; Zhang, X. *Tetrahedron* **2014**, *70*, 5919–5927.

[227] Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317.

reaction between silyloxyfurans and methacrolein via iminium activation (Scheme 36).[228] The addition adducts were afforded with enantioselectivities from good to excellent, but led to an approximately 1:1 mixture of the two possible diastereomers.



Scheme 36. Mukaiyama-Michael addition of silyloxyfurans to methacrolein catalyzed by a secondary amine. **Pihko, 2012**.

Moreover, Deng described the Michael addition of α-substituted cyanoketones and β-ketoesters to activated α-chloroacrylonitrile as Michael acceptor affording the corresponding adducts in the presence of the bifunctional Brønsted base/*H*-bond organocatalysts **C38** and **C15**, with excellent stereocontrol (Scheme 37).[229] Then Chen extended the same methodology to 2-oxindoles as pronucleophiles to give adducts with excellent results.[230]

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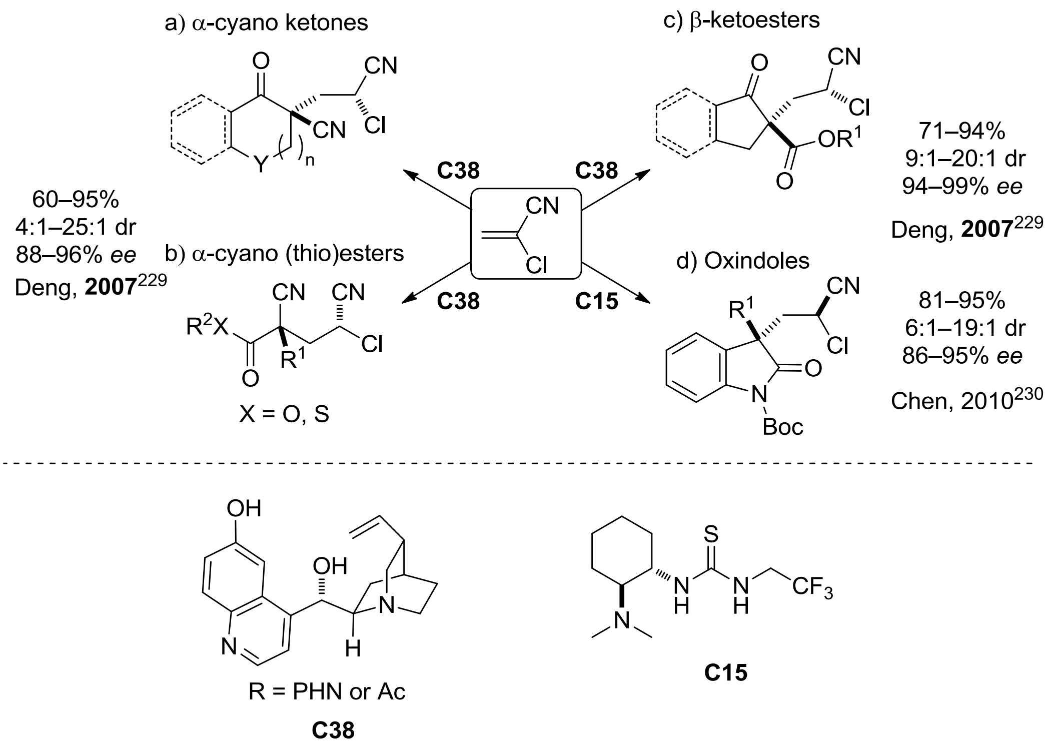
[228] a) Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M. *Org. Lett.* **2012**, *14*, 1086–1089. b) Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza, A.; Kótai, B.; Pápai, I.; Pihko, P. M. *Chem. Eur. J.* **2014**, *20*, 5983–5993.

[229] a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930. b) Wang, B.; Wu, F.; Wang, Y.; Liu, X., Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768–769.

[230] Li, X.; Luo, S.; Cheng, J.-P. *Chem. Eur. J.* **2010**, *16*, 14290–14294.



Scheme 37. Michael addition of a) α-cyanoketones, b) α-cyano(thio)esters, c) β-ketoesters and d) oxindoles to α-chloroacrylonitrile promoted by Brønsted base catalysts.

All the previous precedents clearly show the difficulties involved in the Michael addition of α-subsituted 2-cyano esters to enones with different substitution patterns. These are mainly associated to reactivity and stereocontrol problems. But not only enones, also α,β-unsaturated esters are still challenging Michael acceptors in general and more specifically in the addition of α-substituted cyano esters as shown below.

2.1.2. Michael addition of α-substituted cyanoacetates to α,β-unsaturated esters

The extension of this methodology to less reactive Michael acceptors, such as esters, remains challenging. Most of the reported Michael additions of α-cyanoacetates to fully unsubstituted α,β-unsaturated esters are racemic and among them the most employed promoters are metal-based and phosphine-based catalysts.[231] In addition, and

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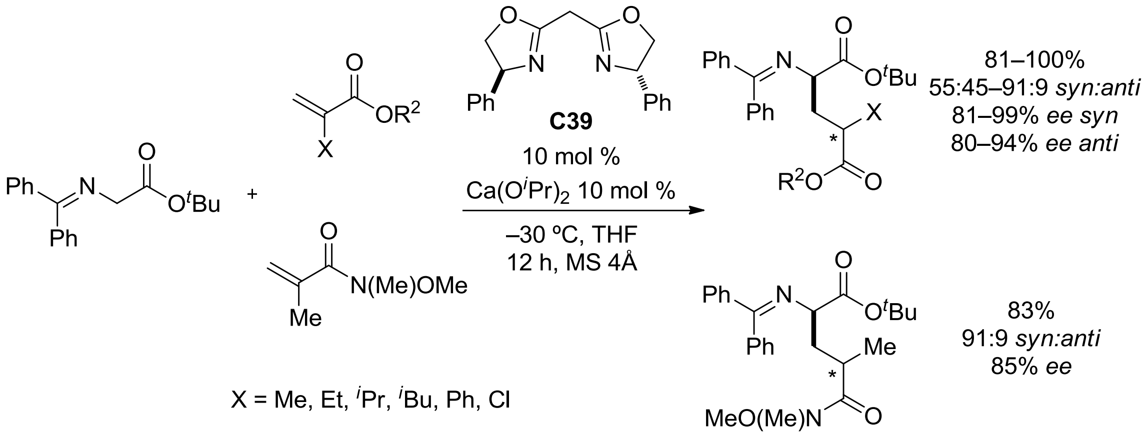
[231] For the racemic phosphine-catalyzed Michael addition of cyanoacetates to allenoates, see: a) Gandi, V. R.; Lu, Y. *Chem. Commun*. **2015**, *51*, 16188–16190. For the racemic phosphine-catalyzed bis-Michael addition of cyanoacetates to ethyl acrylate, see: b) Xu, D-Z.; Zhan, M.-Z.; Huang, Y. *Tetrahedron* **2014**, *70*, 176–180. For the racemic DBU-catalyzed Michael addition of cyanoacetates to *tert*-butyl acrylate, see: c) Chen, X.; Chen, F. *Synthesis* **2014**, 1506–1510. For the racemic Michael addition of cyanoacetates to α,β-unsaturated esters catalyzed by Ni complexes, see: d) Ray, S.; Shaikh, M. M.; Ghosh, P. *Eur. J. Inorg. Chem*. **2009**, 1932–1941.

to the best of our knowledge, no additions of α-substituted cyanoacetates to β-substituted esters have been reported.

2.1.2.1. α-Substituted α,β-unsaturated esters

It is evident the problematic which implies the use of α,β-unsaturated esters in Michael additions, and to the best of our knowledge, no examples of conjugate additions of α-substituted cyano esters to α-substituted α,β-unsaturated esters have been described. More specifically additions of other nucleophiles to this type of acceptors still are limited. A remarkable precedent was described by Kobayashi in which a Ca(BOX)$_2$ **C39** catalyzed the conjugate addition of glycine Schiff bases to α-substituted acrylate methyl esters and amides (Scheme 38).[232] The products were obtained with good enantioselectivity but moderate diastereoselectivity (*syn*/*anti* ratio below 67:33 for α-alkyl substituted acrylate esters). The *syn*/*anti* ratio was improved up to 91:9 by using the acrylamide, but the enantioselectivity decreased.



Scheme 38. Michael addition of glycine Schiff bases to α-substituted acrylate esters and acrylamide under metal catalysis. **Kobayashi, 2008**.

In 2011, the group of Chen and Xiao reported the tandem Michael/α-protonation reaction of 2-oxindoles to activated acceptors as ethyl α-phthalimidoacrylate[233] and ethyl α-phosphonoacrylate[234] under similar catalysis conditions (Table 2). In both cases remarkable stereoselectivities are obtained in the presence of catalysts **C40** and **C41**, but the methods are restricted to doubly activated Michael acceptors (α-

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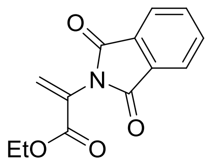
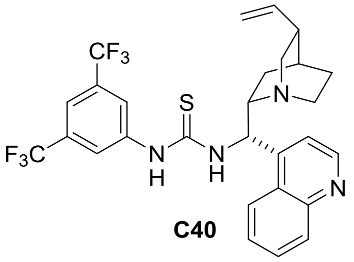
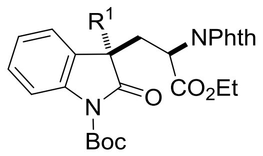
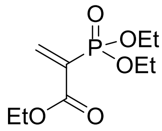
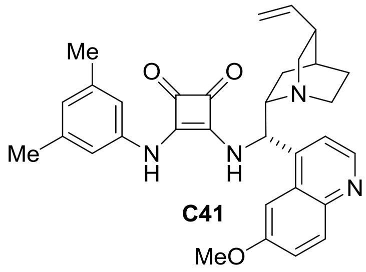
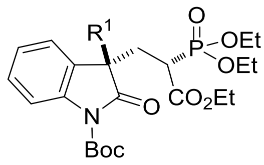
[232] Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130,* 13321–13332.

[233] Duan, S.-W.; An, J.; Chen, J. R.; Xiao, W.J. *Org. Lett.* **2011**, *13*, 2290–2293.

[234] Duan, S.-W.; Liu, Y.-Y.; Ding, W.; Li, T.-R.; Shi, D.-Q.; Chen, J. R.; Xiao, W.J. *Synthesis* **2013**, *45,* 1647–1653.

chloroacrylonitrile and α-phthalimidoacrylate). Therefore, only α-heterosubstituted carbonyl and nitrile products are afforded.

Table 2. Examples of Michael additions of 2-oxindoles to activated α-substituted α,β-unsaturated esters.

Michael acceptor	Catalyst	Product	Results
	 **C40**		90–96% 89:11–94:6 dr 93–99% *ee*
	 **C41**		90–97% 84:16–94:6 dr 92–>99% *ee*

On the basis of all these precedents, it seems that the Michael addition of α-substituted 2-cyano esters to different α,β-unsaturated ketones and esters is difficult due to both reactivity and stereoselectivity problems. In view of the previously demonstrated efficiency of α’-hydroxy enones as α,β-unsaturated ester and ketone surrogates in metal-catalyzed reactions, we hypothesized that these Michael acceptors would be good candidates for the conjugate reaction with α-substituted cyanoacetates. Therefore, fully unsubstituted, β-substituted and α-substituted α’-hydroxy enones were prepared and their potential in the Michael addition of α-substituted cyanoacetates was investigated. These results are discussed in section 2.4.

2.2. Azlactones as Michael donors

Michael additions of heteroatom-bearing soft carbon nucleophiles are interesting and yet difficult processes to get products as single enantiomers. As mentioned before, azlactones can be used as general templates for the stereoselective synthesis of natural/unnatural amino acids and highly substituted heterocyclic scaffolds.[235] They exhibit a dual behavior, as they present a nucleophilic and electrophilic nature.

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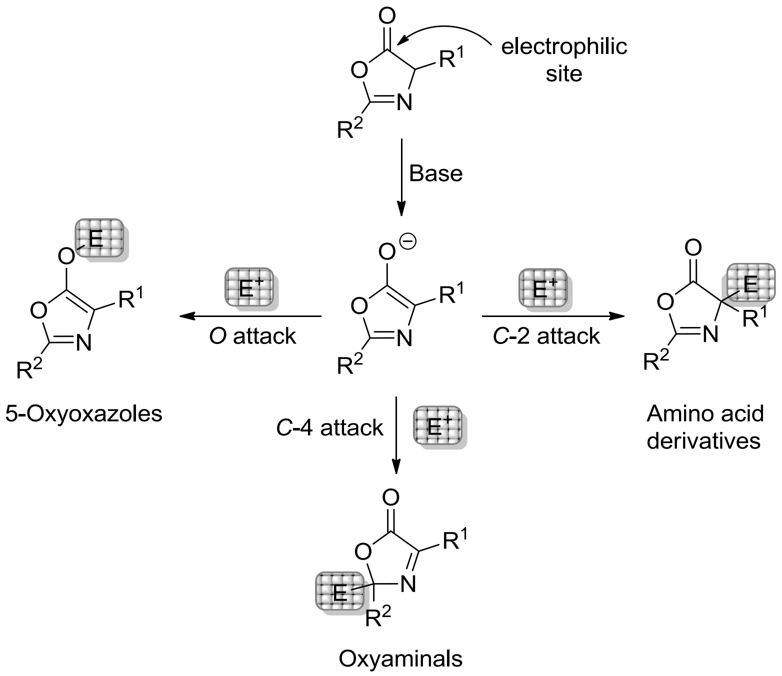
[235] For the reviews of azlactones in asymmetric catalytic reactions, see: Ref. 150

Furthermore, as shown in Scheme 39, there are three different nucleophilic sites which make azlactone reactivity rich and interesting.



Scheme 39. Reactive sites of azlactones.

The use of azlactones as precursors for asymmetric synthesis of quaternary α-amino acid derivatives was pioneered by the groups of Fu and Trost promoted by metal catalysts in dynamic kinetic resolution[236] and allylation reactions,[237] respectively. However, the efficiency of azlactones as nucleophiles in enantioselective Michael additions was reported ten years later by Jørgensen and co-workers (Scheme 40).[238] An efficient organocatalytic conjugate addition of 4-substituted azlactones to α,β-unsaturated aldehydes catalyzed by diarylprolinol silyl ether **C17** was described with complete *C*-4 regioselectivity. Shortly, Hayashi reported a similar enantioselective transformation with slightly different reaction conditions.[239]

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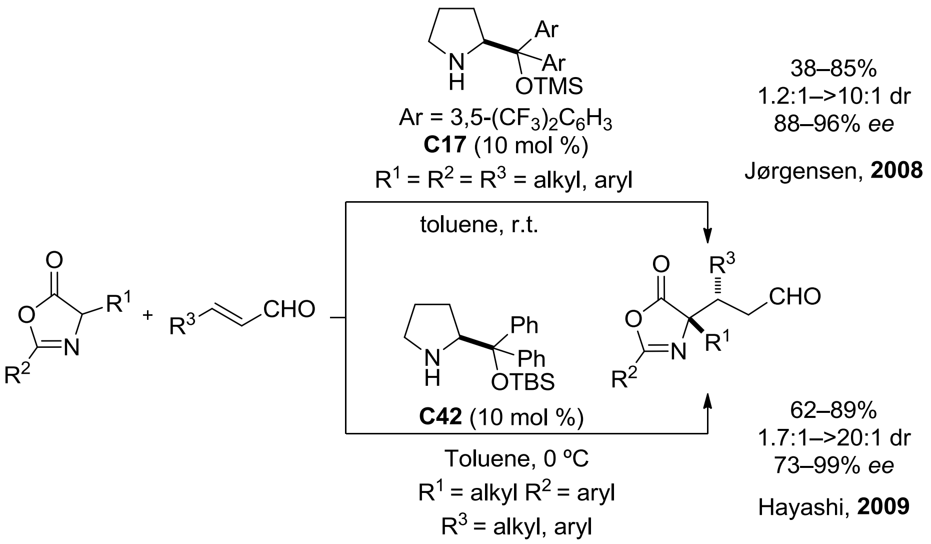
[236] Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154–3155.

[237] Trost, B. N.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.

[238] Cabrera, S.; Reyes, E.; Alemán, J. Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037.

[239] Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem. Asian. J.* **2009**, *4*, 246–249.



Scheme 40. First examples of Michael reactions of azlactones with enals promoted by diarylprolinol silyl ethers.

Subsequently, many groups reported organocatalyzed Michael additions of 4-substituted azlactones to various electrophiles to provide masked quaternary α-amino acid derivatives or chiral oxyaminals depending on the *C*-4 or *C*-2 regioselectivity, respectively. Jørgensen employed nitroalkenes as electrophiles in the conjugate addition of oxazolones using thiourea cinchona derivative **C43** as promoter with good yields, excellent diastereoselectivities and from moderate to good enantioselectivities (Scheme 41).[240] It is remarkable that when R^1 is a phenyl group the reaction takes place at the *C*-4 position; however, the reaction is *C*-2 specific with alkyl substituents which afford *N*,*O*-aminal compounds.

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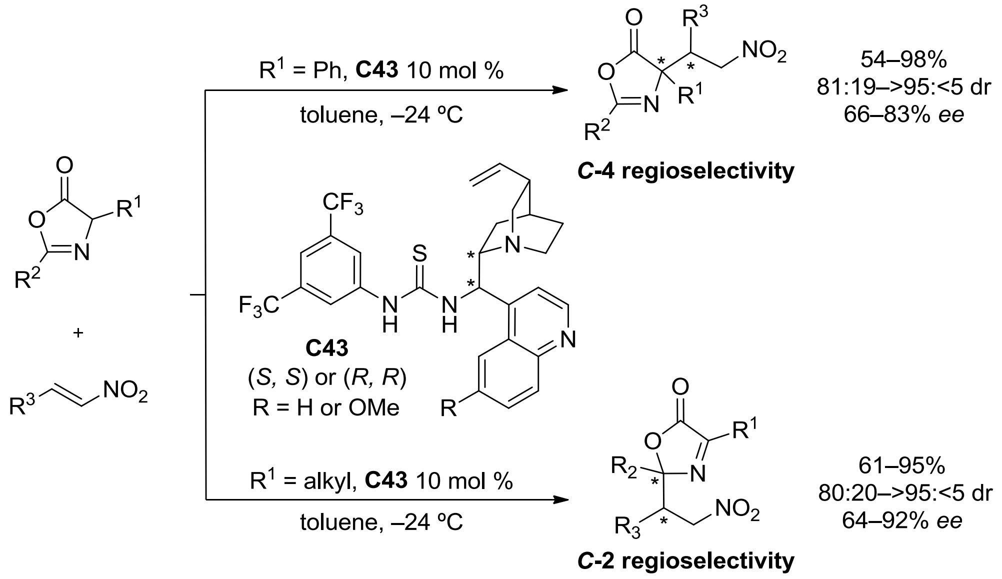
[240] Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 10958–10966.



Scheme 41. Michael addition of azlactones to nitroalkenes promoted by a thiourea catalyst affording *C*-4 or *C*-2 substituted products. **Jørgensen, 2008**.

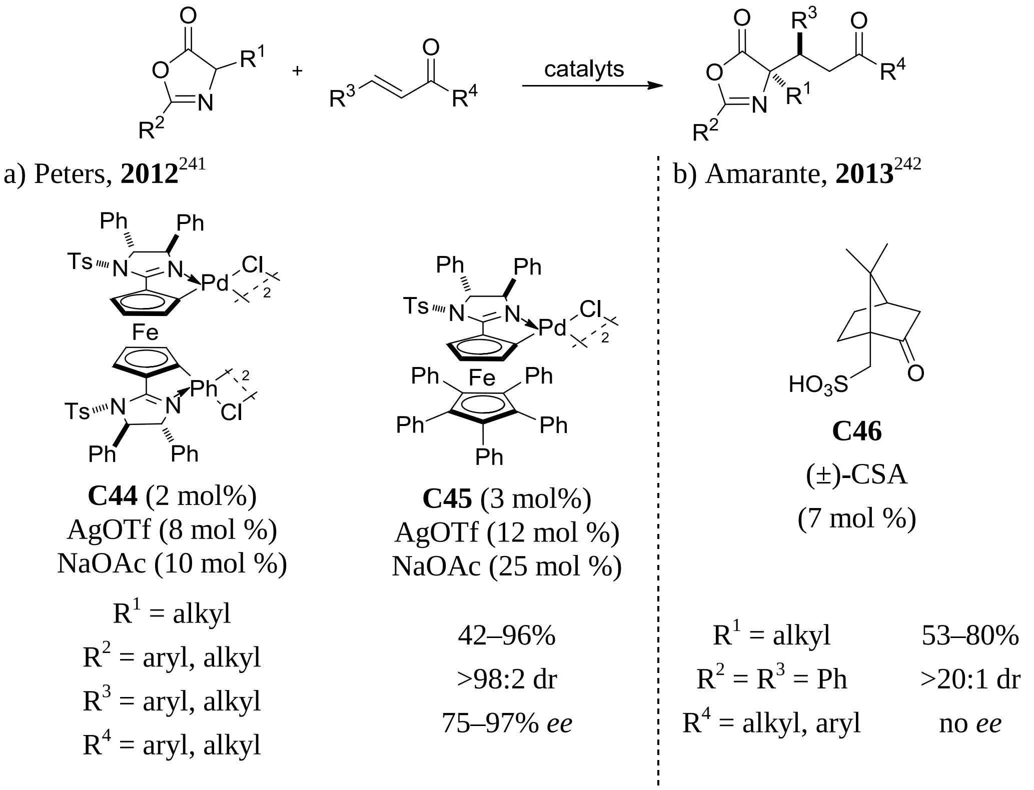
2.2.1. α,β-Unsaturated ketones as Michael acceptors

The use of α,β-unsaturated ketones as Michael acceptors in organocatalyzed conjugate additions of azlactones has been limited. Peters and co-workers reported the Michael addition of azlactones to enones promoted by metal mono- or bispalladiumcycle catalyst **C44**/**C45** and excellent results were obtained (Scheme 42, a).[241] Later, Amarante developed a (±)-camphorsulfonic acid **C46** catalyzed methology for this transformation with high diastereoselectivities but without any enantioselectivity control (Scheme 42, b).[242] In both cases the products obtained were only the *anti* isomers.

---

[241] a) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *Chem. Eur. J.* **2012**, *18*, 14792–14804. b) Weber, M.; Peters, R. *J. Org. Chem.* **2012**, *77*, 10846–10855. c) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *J. Am. Chem. Soc.* **2010**, *132*, 12222–12225.

[242] Ávila, E. P.; de Mello, A. C.; Diniz, R.; Amarante, G. W. *Eur. J. Org. Chem.* **2013**, 1881–1883.



Scheme 42. Michael addition of azlactones to enones developed by Peters and Amarante.

R. Wang and co-workers described the Michael addition of azlactones to activated α,β-unsaturated trichloromethyl ketones in the presence of the bifunctional thiourea catalyst **C47** (Scheme 43, a).[243] The trichloromethyl motif is a good electron-withdrawing group that activates the enone and after some transformations can be transformed into the corresponding ester or amide. The reaction was developed for alkyl and aromatic substituents on both substrates and the corresponding *syn* adducts were afforded in good yields and in high to excellent diastereo- and enantioselectivities. Then, Y. Wang and X. W. Wang used *o*-hydroxy chalcone derivatives as Michael acceptors and the experimental results show that an *o*-hydroxy group on the aryl motif plays a crucial role in the regioselectivity of the reaction because *N*,*O*-aminals are exclusively obtained from the *C*-2 addition (Scheme 43, b).[244]

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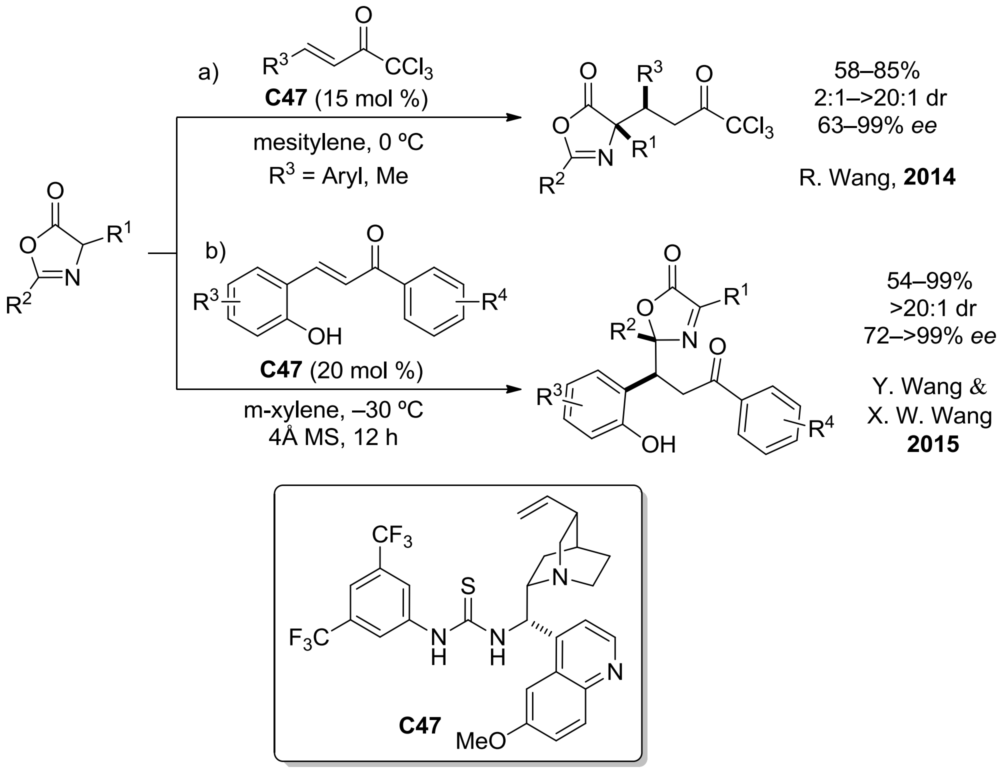
[243] Zhang, J.; Liu, X.; Wu, C.; Zhang, P.; Chen, J.; Wang, R. *Eur. J. Org. Chem.* **2014**, 7104–7108.

[244] Zhang, S. Y.; Ruan, G. Y.; Geng, Z. C.; Li, N. K.; Lv, M.; Wang, Y.; Wang, X. W. *Org. Biomol. Chem.* **2015**, *13*, 5698–5709.



Scheme 43. Michal addition of azlactones to β-substituted enones catalyzed by a bifunctional thiourea catalyst.

2.2.2. α,β-Unsaturated esters as Michael acceptors

Concerning the Michael addition of azlactones to α,β-unsaturated esters, only a few examples have been reported. It is worth to mention the only catalytic enantioselective example of the conjugate reaction of azlactones to acrylic esters developed by Kobayashi (Scheme 44).[245] The chiral coordinative Pybox calcium catalyst **C48** was found to be effective for these reactions and the desired adducts were obtained in relatively good yields and enantioselectivities.

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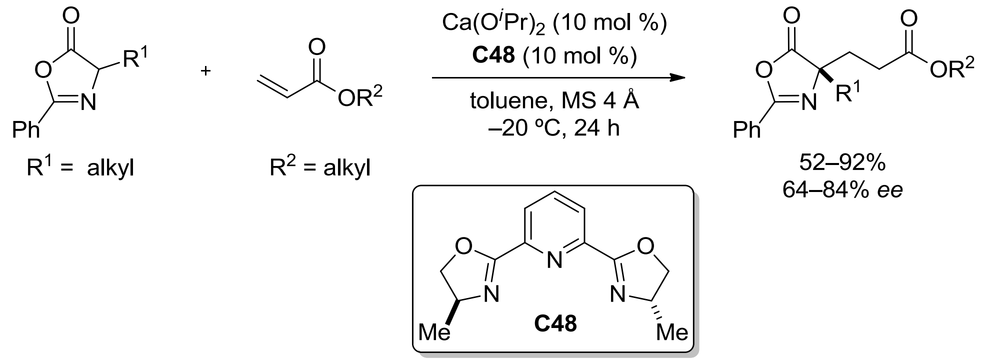
[245] Tsubogo, T.; Kano, Y.; Ikemoto, K.; Yamashita, Y.; Kobayashi, S. *Tetrahedron: Asymmetry* **2010**, *21*, 1221–1225.



Scheme 44. Michael addition of azlactones to acrylic esters promoted by a calcium catalyst **C48**. **Kobayashi, 2010**.

Another type of α,β-unsaturated esters are ynoates and allenoates; Ooi described the conjugate addition of azlactones to methyl propiolate catalyzed by an iminophosphorane.[246] Recently, Fu[247] and Lan and Lu[248] employed the same type of methodology based on phosphine-catalysts to promote γ-additions of azlactones to allenoates with excellent diastereo- and enantiocontrol.

In view of the limited success in the Michael addition of azlactones to α,β-unsaturated ketones and esters, α’-hydroxy enones were again considered as masked enones and α,β-unsaturated esters. On this basis the reaction of azlactones with α’-hydroxy enones in the presence of BB catalyst was selected. The corresponding results are presented in the following sections.

2.3. Precedents and synthetic plan

As said in the Introduction, α’-hydroxy enones have shown to be very efficient acryloyl and ketone/aldehyde equivalents in diastereoselective reactions and metal-catalyzed enantioselective reactions such as Cu promoted cycloadditions and 1,4-conjugate additions to various electrophiles. The resulting adducts can be converted into carboxylic acid derivatives, aldehydes or ketones upon oxidative cleavage of the ketol moiety (Scheme 45).[249]

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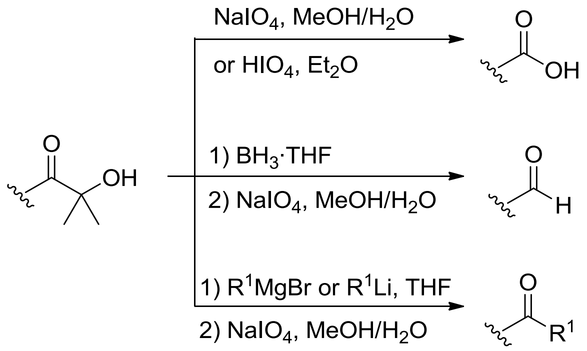
[246] Uraguchi, D.; Ueki, Y.; Sugiyama, A.; Ooi, T. *Chem. Sci.* **2013**, *4*, 1308–1311.

[247] Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438–9442.

[248] Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 265–271.

[249] a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079. b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300. c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 2499–2506.



Scheme 45. Transformation of α’-hydroxy ketone moiety into carboxylic acid, aldehyde and ketone.

In the reported metal-promoted catalytic reactions the ability of the ketol moiety for both 1,4-metal and 1,4-proton binding revealed to be crucial for success (Figure 26, a). Based on these precedents it was hypothesized that the *H*-bonding ability of the ketol moiety in α’-hydroxy enone could participate as two-point *H*-bond donor/acceptor and acceptor/acceptor partner in the transition state (Figure 26, b). To the best of our knowledge, α’-hydroxy enones had not been previously studied in the context of organocatalytic asymmetric bond construction processes.

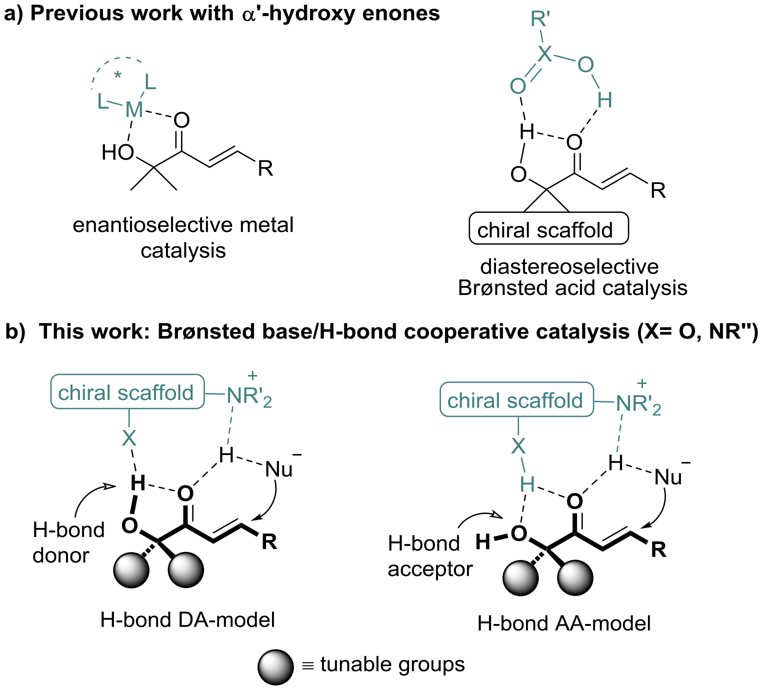
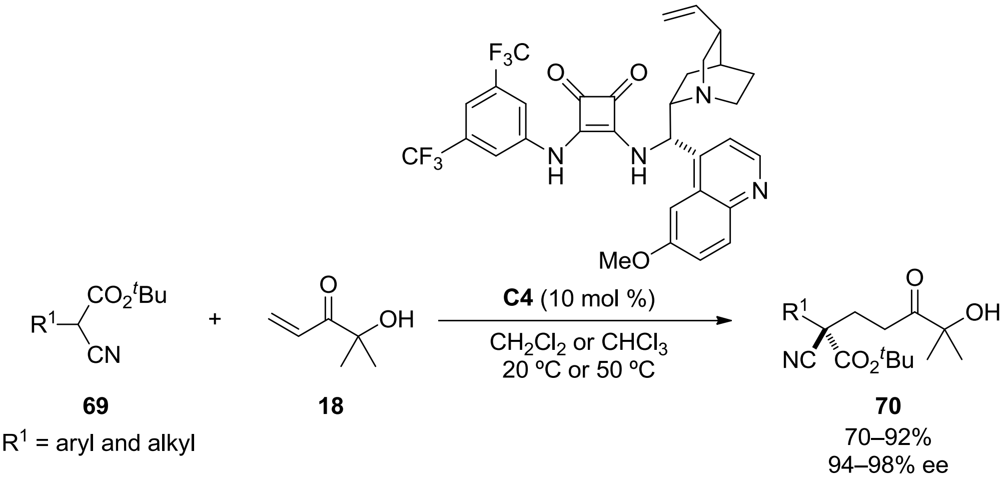


Figure 26. Different activation modes of α’-oxy enones.

On this basis and, as previously said, one of the goals of this Thesis was to investigate the efficiency of α’-hydroxy enones as Michael acceptors and ester/ketone surrogates in Brønsted base-promoted addition reactions with α-substituted cyanoacetates and azlactones as pronucleophiles. Both reactions would involve the creation of a quaternary stereocenter.

This project was started in collaboration with Professors Jesús M. García, José M. Odriozola and Jesús Razkin from the Department of Applied Chemistry (Universidad Pública de Navarra). To first explore the reactivity of these α’-hydroxy enones in Brønsted base catalysis, the research group from Navarra initiated this study by checking the reaction of cyanoacetates **69** and α’-hydroxy enone **18**. They found that this enone was an effective Michael acceptor with not only α-aryl, but also α’-alkyl cyanoacetates, a subclass of substituted cyanoacetates previously documented to be poorly reactive substrates particularly against alkyl vinyl ketones (Scheme 46). The squaramide family of catalysts proved to be the most effective in these instances. Catalyst **C4** resulted optimal for the reaction between **18** and a range of both α-aryl and α-alkyl *tert*-butyl cyanoacetates **69**.

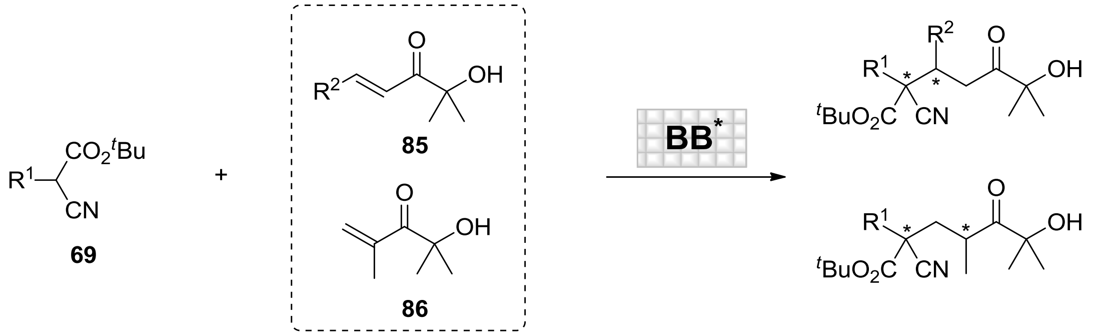


Scheme 46. Michael addition of α-substituted *tert*-butyl cyanoacetates **69** to α’-hydroxy enone **18** promoted by **C4**.

2.4. Results and discussion

We reasoned that the problems associated with the lack of efficient chirality transfer with α-substituted cyanoacetates in conjugate additions could be solved by the capacity of α’-hydroxy enones for two-point binding.

For this purpose the reaction of both α-aryl and α-alkyl cyanoacetates **69** with α’-hydroxy enones **85** and **86** promoted by chiral bifunctional Brønsted bases was selected (Scheme 47). The corresponding results are presented in the next sections.



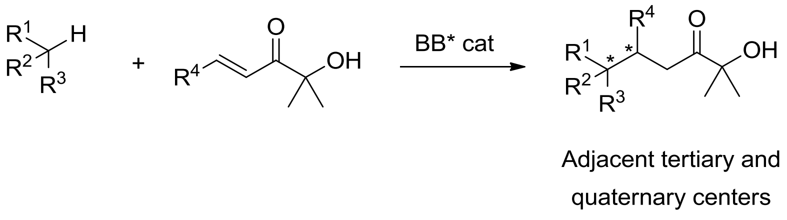
a R^1 = Ph
b R^1 = 4-MePh
c R^1 = 4-MeOPh
d R^1 = 4-BrPh
e R^1 = 4-ClPh
f R^1 = 3-MePh
g R^1 = 2-MePh
h R^1 = Me

A R^2 = $PhCH_2CH_2$
B R^2 = CH_3CH_2
C R^2 = $CH_3CH_2CH_2$
D R^2 = $CH_3(CH_2)_3CH_2$
E R^2 = $CH_2{=}CHCH_2CH_2$
F R^2 = $(CH_3)_2CHCH_2$
G R^2 = *c*-C_6H_{11}
H R^2 = Ph

Scheme 47. Employed α-aryl and α-alkyl cyanoacetates **69** for the Brønsted base catalyzed Michael addition to α'-hydroxy enones **85** and **86**.

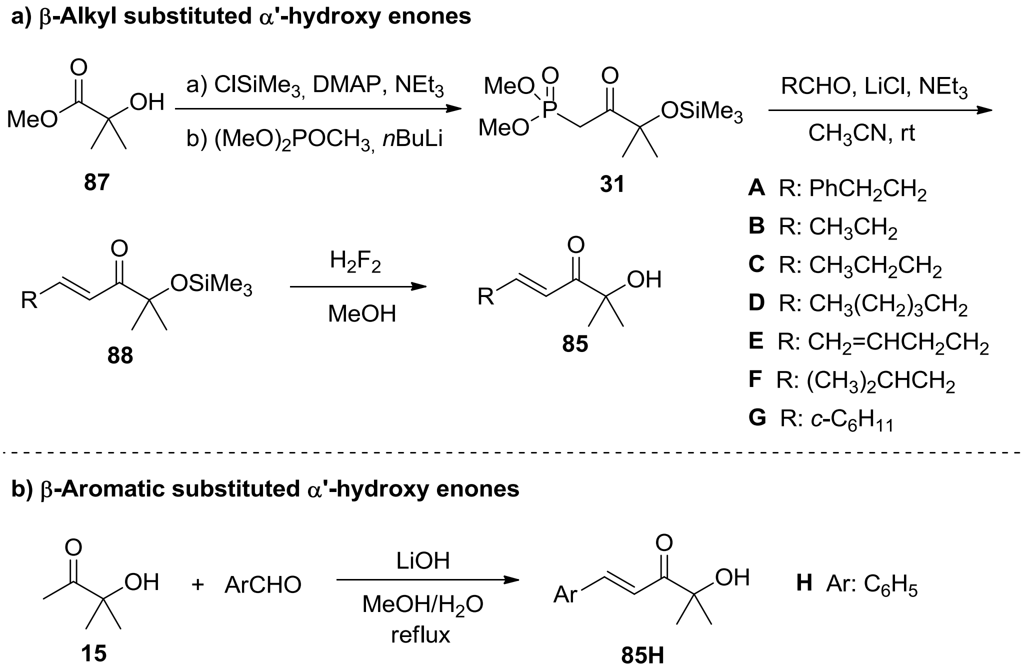
2.4.1. Michael reaction of α-substituted cyanoacetates 69 with β-substituted α'-oxy enones 85

Taking into account the previous results obtained with α'-hydroxy vinyl ketone **18**, we wondered whether this template model would be effective to generate a quaternary carbon adjacent to a tertiary stereogenic center, a synthetic task that generally presents difficulties as shown in the previous precedents.



Scheme 48. Proposed synthetic plan.

For that purpose several β-aryl and alkyl substituted α'-hydroxy enones were synthesized according to procedures previously described (Scheme 49). The classical Horner-Wadsworth-Emmons olefination protocol from the β-keto phosphonate **31** was used to afford alkyl substituted α'-hydroxy enones **85** (Scheme 49, a). This phosphonate was prepared from commercial hydroxyester **87**.[250] Likewise, for β-aryl substituted α’-hydroxy enones **85** aldol condensation of **15** with benzaldehydes was employed (Scheme 49. b).[251]



Scheme 49. General procedures for the synthesis of β-alkyl and β-aromatic substituted α’-hydroxy enones.

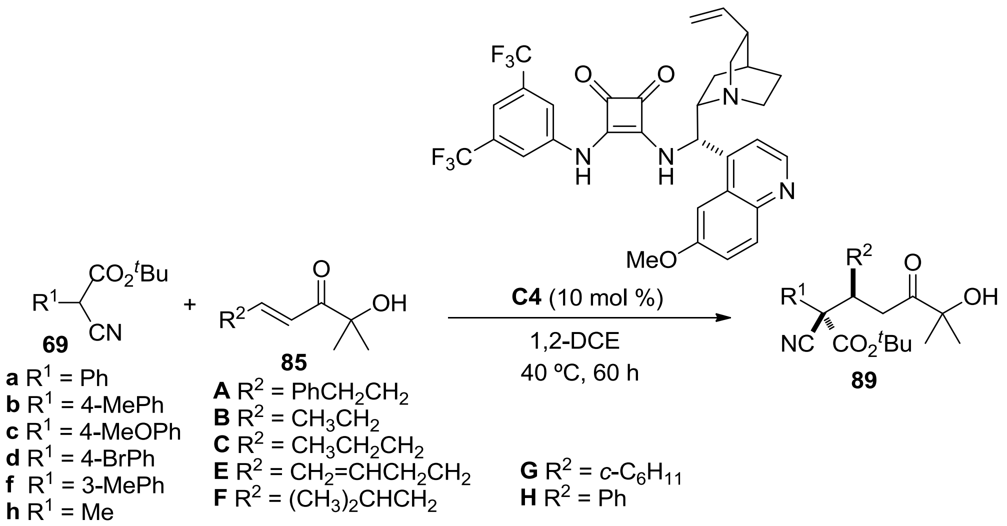
It was gratifying to observe that α-aryl cyanoacetates **69a–d** and **69f** reacted with β-alkyl substituted α’-hydroxy enones **85A–C** and **85E–F** in the presence of **C4** catalyst to furnish adducts **89** in good yields (Table 3). The reactions were carried out in 1,2-dichloromethane at 40 ºC and generally essentially one diastereomer was produced in excellent enantiomeric excess. As exceptions, β-substituted enones **85G** and **85H**, bearing the cyclohexyl and phenyl groups, respectively, were ineffective and did not react under these conditions. Enone **85F** provided **89Fa** in good yields but with lower stereoselectivity.

---

[250] Adapted from: a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525–2529. b) McCarthy, D. G.; Collins, C. C.; O’Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667–3675.

[251] a) See ref. 98. b) See ref. 108b.

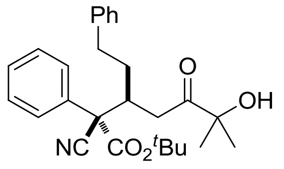
Table 3. Conjugate additions of cyanoacetates **69** to β-substituted α'-hydroxy enones **85**.



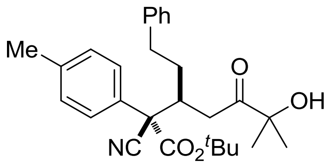
a R^1 = Ph
b R^1 = 4-MePh
c R^1 = 4-MeOPh
d R^1 = 4-BrPh
f R^1 = 3-MePh
h R^1 = Me

A R^2 = $PhCH_2CH_2$
B R^2 = CH_3CH_2
C R^2 = $CH_3CH_2CH_2$
E R^2 = CH_2=$CHCH_2CH_2$
F R^2 = $(CH_3)_2CHCH_2$

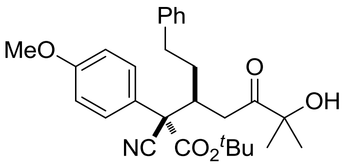
G R^2 = c-C_6H_{11}
H R^2 = Ph



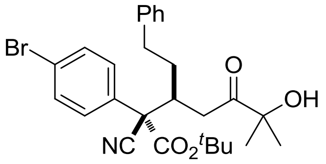
89Aa
90%[b], 98:2 dr , 96% *ee*



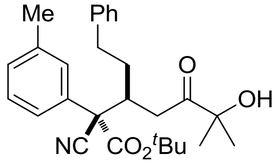
89Ab
95%, 99:1 dr, 99% *ee*



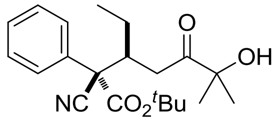
89Ac
92%, 98:2 dr, 96% *ee*



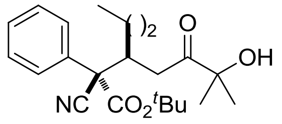
89Ad
89%, >99:1 dr, 94% *ee*



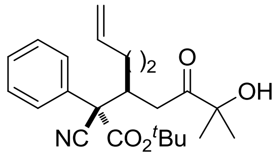
89Af
89%, >99:1 dr, 98% *ee*



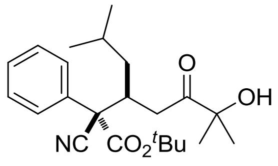
89Ba
95%[b], 96:4 dr, 92% *ee*



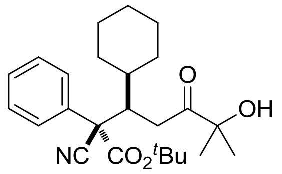
89Ca
90%, >99:1 dr, 92% *ee*



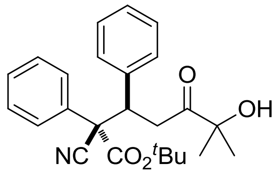
89Ea
93%, >99:1 dr, 96% *ee*



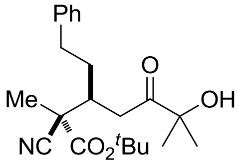
89Fa
82%, 95:5 dr, 83% *ee*



89Ga
0% conv.



89Ha
0% conv.

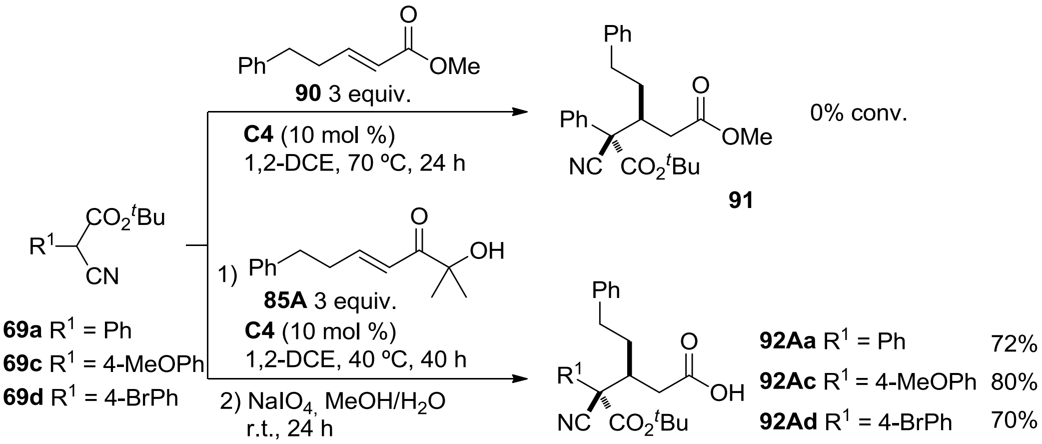


89Ah
0% conv.

[a] Reaction conditions: **69** (0.3 mmol), enone **85** (3 equiv., 0.9 mmol) and catalyst **C4** (10 mol %) in 1,2-DCE (1.2 mL) at 40 ºC otherwise stated. Yield of isolated products after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] Reaction carried out at 50 ºC.

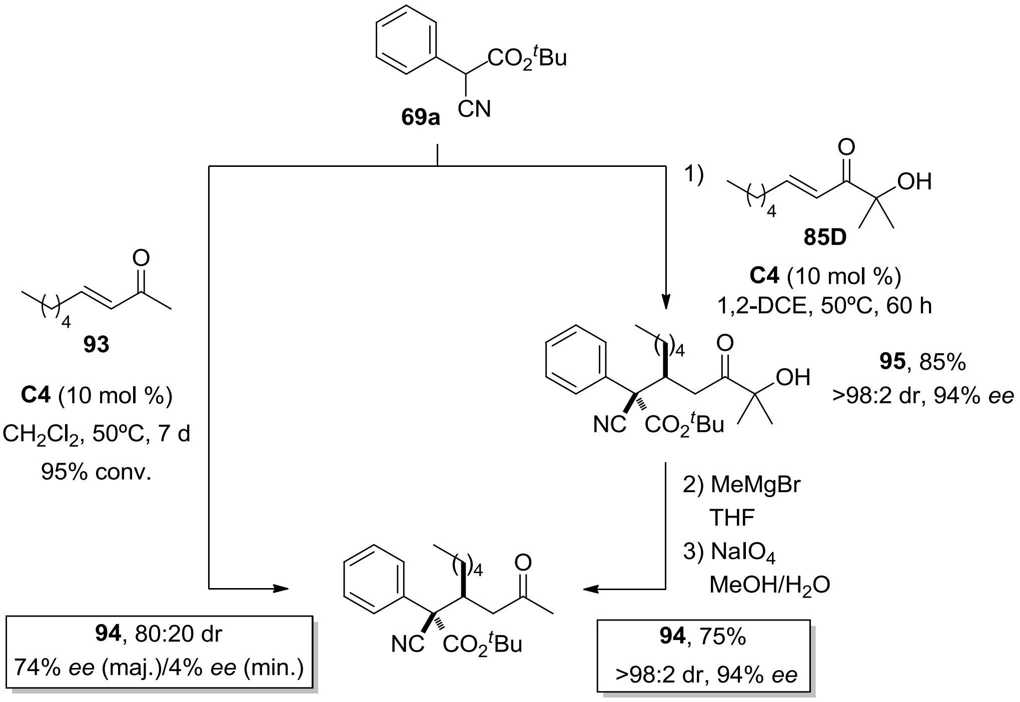
On the other hand, α-alkyl cyanoacetate **69h** was unreactive and did not provide the corresponding adduct. Despite these limitations, which confirms the difficulties associated to these problematic pronucleophiles, the method represents the first Michael addition of α-substituted cyanoacetates to β-alkyl enones catalyzed by a chiral Brønsted base. Once more, the excellent behavior of α’-hydroxy enones as Michael acceptors is confirmed.

Then the behavior of β-substituted α,β-unsaturated simple esters was analyzed. No reaction was observed from cyanoacetates **69a**, **69c** and **69d** with methyl 5-phenylpent-2-enoate **90** in the presence of **C4** (Scheme 50). However, the Michael addition of these substrates to β-substituted α’-oxy enone **85A** followed by oxidative cleavage provided the desired corresponding carboxylic acids **92**.



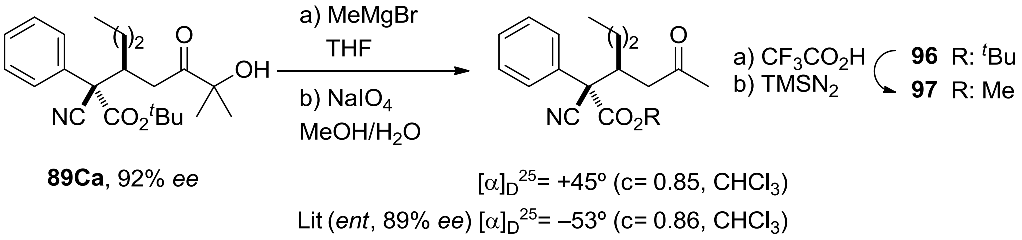
Scheme 50. Michael addition of α-substituted cyanoacetates to β-substituted α,β-unsaturated simple esters and an indirect solution to the low reactivity.

The reaction between cyanoacetate **69a** and *trans*-3-nonen-2-one **93**, which lacks the α’-hydroxy group, catalyzed by **C4** was also examined (Scheme 51). The reaction proceeded, but it required 7 days to reach 95% of conversion and the product was formed as a 80:20 mixture of diastereomers with only modest enantioselectivity for the major isomer **94**. In contrast, the reaction between **69a** and α’-hydroxy enone **85D** gave essentially **95** as essentially single diastereomer in 94% *ee*. This method enables an alternative and highly enantioselective entry to product **94** via usual alkylation and oxidative scission.



Scheme 51. Conjugate addition of α-substituted cyanoacetates to simple enone *trans*-3-nonen-2-one **93** and indirect solution to the low inherent stereoselectivity.

In order to confirm the stereochemical assignments of the adducts, compound **89Ca** was converted into the methyl ketone **96** and upon subsequent transesterification, afforded the corresponding methyl ester **97** (Scheme 52). This compound exhibited essentially identical ^{1}H and ^{13}C NMR spectra to those reported in the literature[252] but opposite optical activity confirming the stereochemistry.



Scheme 52. Stereochemical assignment of the Michael adducts.

2.4.2. Michael reaction of α-substituted cyanoacetates 69 with α-substituted α'-oxy enone 86

To the best of our knowledge, no direct, catalytic and highly both diastereo- and enantioselective approach has been described for the construction of α-alkyl carbonyl structures. After the excellent results obtained with non-substituted and β-substituted α'-

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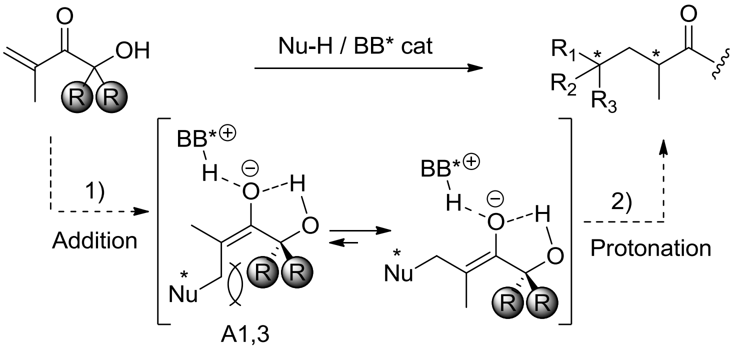
[252] See reference 227.

hydroxy enones, we proposed α-substituted α’-hydroxy enones as Michael acceptors for the construction of α,γ-branched carbonyl analogs through Michael reactions promoted by Brønsted base catalysts.



Scheme 53. Proposed synthetic plan for the construction of α,γ-branched carbonyl compounds.

In comparison to the earlier approach to construct β,γ-branched carbonyls, two major problems related to the construction of α,γ-branched carbonyl analogs are: (i) the low electrophilicity of most Michael acceptors bearing an α-methyl substituent against neutral *C*-pronucleophiles[253] and (ii) the complications associated to the face-selective α-protonation of the *in situ* formed enolates. Concerning the last problem, one of the issues is how to control the E/Z configuration of the enolate.[254] Moreover, the small size of the proton and the need that both elements of the stereoinduction (the initially generated γ-stereocenter and the chiral catalyst), work in concert are additional concerns.

Initial attempts to carry out the Brønsted base-catalyzed reaction of 2-phenyl cyanoacetate **69a** with representative carbonyl Michael acceptors confirmed the above difficulties. For instance, as shown in Table 4, attempts to react **69a** with methyl methacrylate **98** in the presence of several mono- and bifunctional Brønsted base catalysts all led to the recovery of starting materials. With catalyst **C4**, the reaction of

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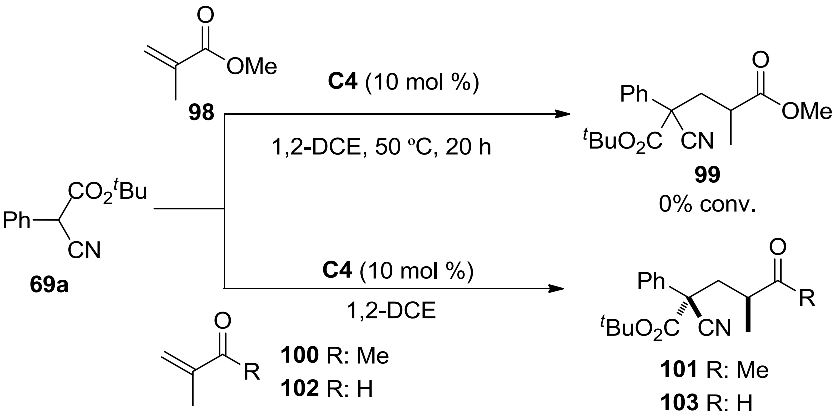
[253] The large majority of catalyst-controlled tandem conjugate addition/enantioselective α-protonation protocols involve *N*-, *S*- and *O*-heteronucleophiles. For examples, see: Oudeyer, S.; Briére, J.-F.; Levacher, V. *Eur. J. Org. Chem*. **2014**, 6103–6119.

[254] Cyclic unsaturated carbonyls are commonly used as Michael acceptors in stereoselective enolate-trapping reactions because only one (*E* or *Z*) enolate can be formed. For exceptions involving acyclic carbonyl Michael acceptors, see: a) Fu, N.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem. Eur. J.* **2013**, *19*, 15669–15681. b) Cui, L.; Zhang, L.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2014**, 3540–3545. c) Fu, N.; Zhang, L.; Luo, S. *Org. Lett.* **2015**, *17*, 382–385. d) Sibi, N. P.; Coulomb, J.; Stanley, L. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 9913–9915. e) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390–2391. f) Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159–6169.

69a and 3-methylbutenone **100** took place slowly and higher temperatures (50 ºC) were needed for significant progress (60% conversion after 90h), affording 45% isolated yield, moderate diastereoselectivity (80:20 dr) and good enantioselectivity (92% *ee*) for the major diastereomer **101**. Finally, aldehyde **102** resulted more reactive, but led to essentially uncontrolled stereoselectivity.

Table 4. Difficulties in the addition of α-cyanoacetate **69a** to simple α-methyl substituted carbonyl Michael acceptors.

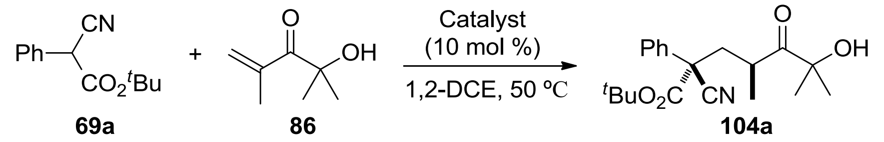


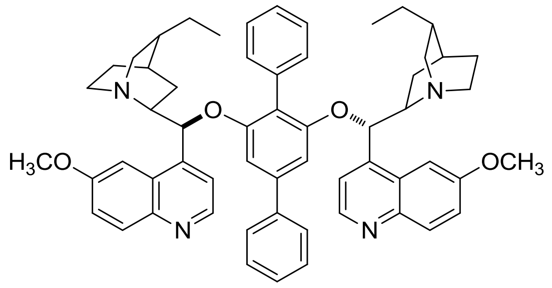
Entry	R	Conditions	Yield (%)	dr	*ee* (major/minor)
1	Me	50 ºC, 60% conv., 90 h	45 **101**	80:20	92% / 42%
2	H	r.t., 100% conv., 24 h	83 **103**	60:40	14% / 10%

Previous work with non-substituted and β-substituted α'-oxy enones as an acrylate surrogate, encouraged us to try α'-substituted α'-hydroxy enones as Michael acceptors. On this basis, we speculated that α-methyl α'-hydroxyenone **4** might serve as an efficient novel methacrylate surrogate in BB/*H*-bond catalyzed conjugate additions helping to solve the problems mentioned before.

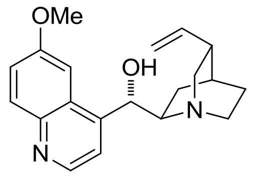
The initial catalyst screening, Table 5, showed us that once again catalyst **C4** was the most efficient in promoting the conjugate addition of 2-phenyl cyanoacetate **69a** to α-methyl α'-hydroxy enone **86**. In order to get full conversions, the reactions were run at 50 ºC. Interestingly, almost perfect enantio- and diastereocontrol were observed, indicating that not only the conjugate addition step that forms a γ-stereocenter, but also the subsequent α-protonation, proceeded with remarkable face selectivity. Surprisingly, catalyst **C51** showed lower reactivity with α-substituted α'-hydroxy enone **86** and afforded **104a** with only 23% conversion after 72 h at 50 ºC.

Table 5. Catalyst screening for the conjugate addition of 2-phenyl cyanoacetate **69a** to α-methyl α’-hydroxy enone **86**.

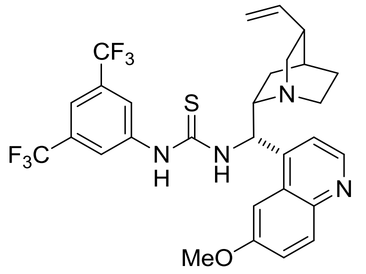




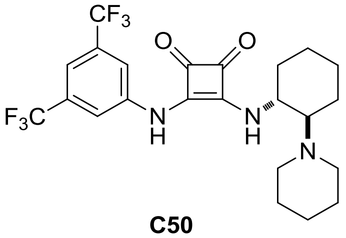
C49 $(DHQD)_2PYR$
72h, 100% conv., 72%
70:30 dr, 30% *ee*



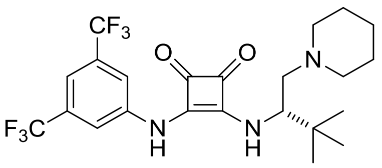
C18 Quinine
72h, 65% conv., 49%
75:25 dr, 16% *ee*



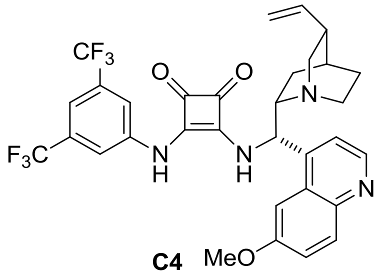
C47
72h, 70% conv., 46%
80:20 dr, 68% *ee*



C50
40h, 100% conv., 75%
75:25 dr, –12% *ee*



C51
72h, 23% conv., n.d.%
n.d. dr, n.d. *ee*

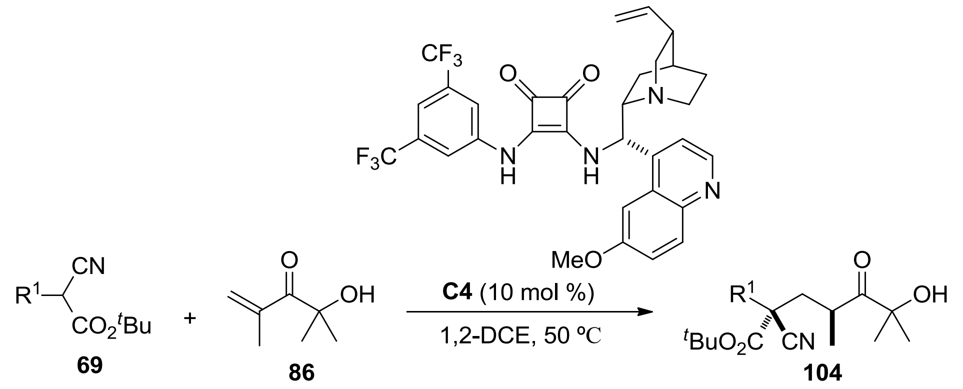


C4
24h, 100% conv., 81%
>99:1 dr, 98% *ee*

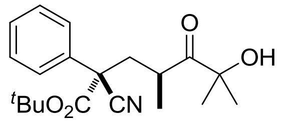
[a] Reaction conditions: **69a** (0.2 mmol), **86** (1.5 equiv., 0.3 mmol), catalyst (10 mol %), in 1,2-DCE (0.4 mL). Conversion related to the disappearance of the starting material. Yield of isolated products after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Next, the reaction scope was explored with different α-substituted cyanoacetates (Table 6). Under optimized conditions which involve 1.5 equivalents of cyanoacetate and 10 mol % of **C4** in 1,2-DCE at 50 ºC, the reaction of **86** worked equally well with other 1-aryl cyanoacetates **69a**–**f** to afford the corresponding addition adducts **104a**–**f** as essentially single diastereomer in yields within the range from 69% to 95% and *ee* values greater than 95% in all every case. However, the reaction was unsuccessful with *ortho*-methyl aryl substituted or methyl substituted cyanoacetates **69g** and **69h** and only starting materials were recovered even when the reaction was heated up to 70 ºC.

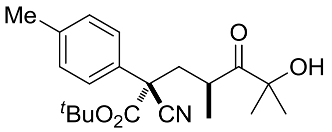
Table 6. Scope of the conjugate addition of cyanoacetates **69** to α-methyl α'-hydroxy enone **86**.[a]



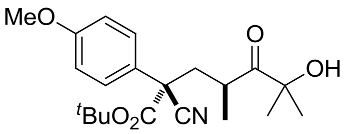
a R^1 = Ph
b R^1 = 4-MePh
c R^1 = 4-MeOPh
d R^1 = 4-BrPh
e R^1 = 4-ClPh
f R^1 = 3-MePh
g R^1 = 2-MePh
h R^1 = Me



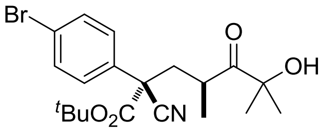
104a
24 h, 81%
>99:1 dr, 98% *ee*



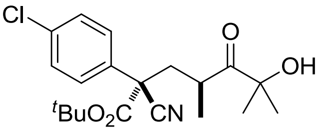
104b
40 h, 67%
>99:1 dr, 97% *ee*



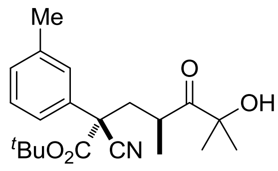
104c
40 h, 70%
>99:1 dr, 98% *ee*



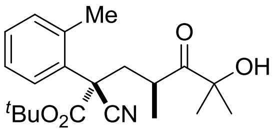
104d
24h, 69%
98:2 dr, 98% *ee*



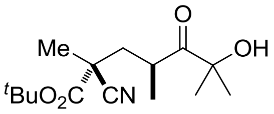
104e
24h, 95%
98:2 dr, 96% *ee*



104f
40h, 83%
>99:1 dr, 97% *ee*



104g
40h[b], 0% conv.



104h
40h[b], 0% conv.

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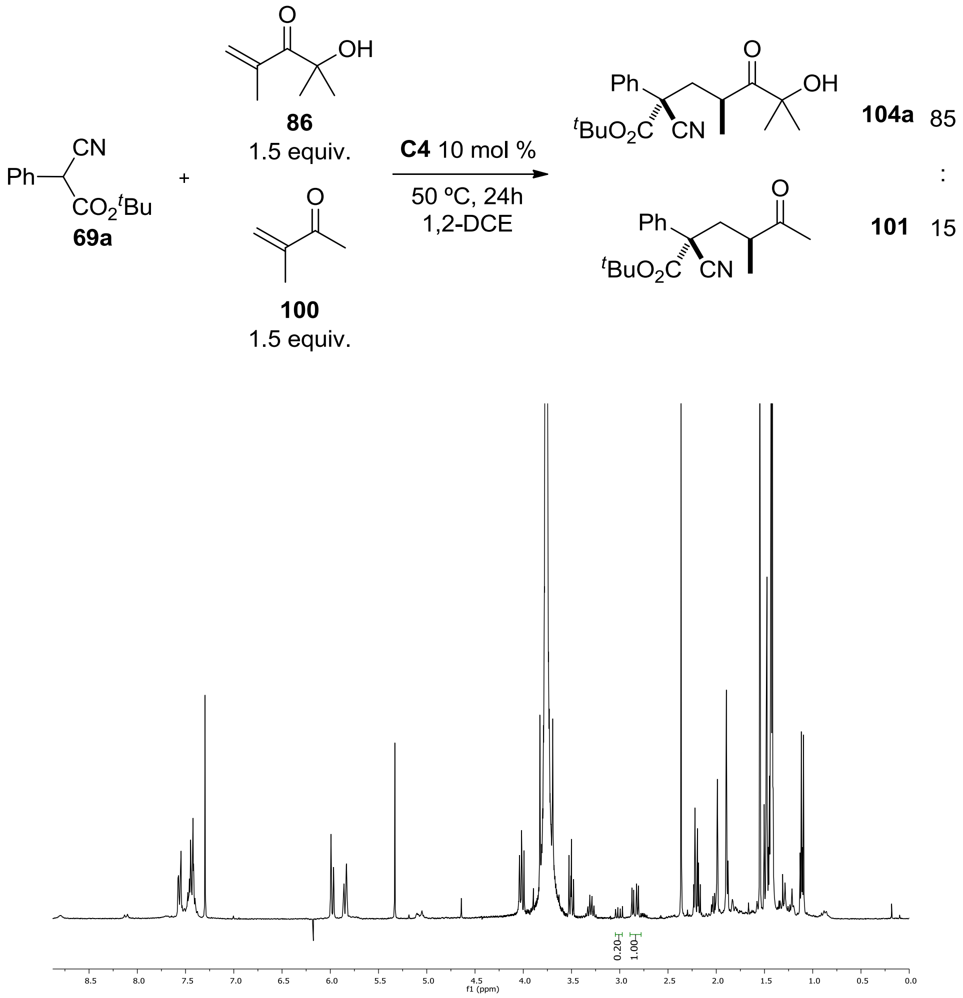
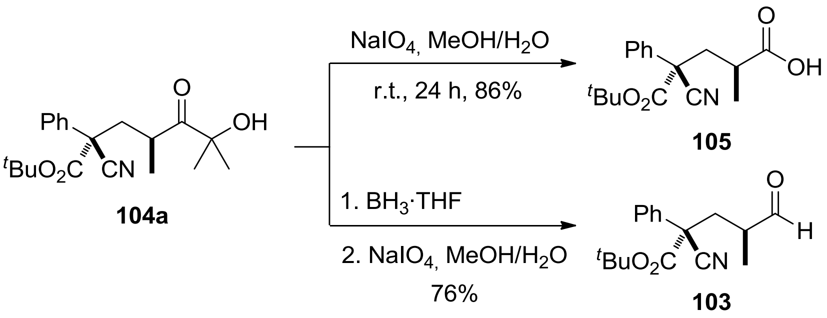
[a] Reaction conditions: **86** (0.2 mmol), **69** (1.5 equiv., 0.3 mmol), catalyst **C4** (10 mol %), in 1,2-DCE (0.4 mL). Conversion related to the disappearance of the starting material. Yield of isolated products after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase.[b] Reaction carried out at 70 ºC.

The reactivities of α’-hydroxy enone **86** and 3-methylbutenone **100** were compared in the presence of α-phenyl cyanoacetate **69a** and catalyst **C4** in 1,2-DCE and at 50 ºC. Once more, the design of enone **86** demonstrated to be instrumental in achieving these levels of reactivity. For example, when an equimolecular mixture of enone **86** and 3-methylbutenone **100** was stirred with α-phenyl cyanocacetate at 50 ºC for 24 h in the presence of 10 mol % **C4**, a 85:15 mixture of **104a** and **27**, respectively, was obtained (Scheme 54).



Scheme 54. ^{1}H-NMR spectra on an aliquote after 24 h at 50 ºC of the conjugate addition of α-cyanoacetate to a mixture of α’-hydroxy enone **86** and 3-methylbutenone **100**, showing the relation between the two addition products **104a** and **101**.

With these adducts in hand, diverse carbonyl compounds (carboxylic acids and aldehydes) are easily affordable following the procedures described before (Scheme 55). For example, treatment of adduct **104a** with $NaIO_4$ in $MeOH/H_2O$ provided carboxylic acid **105** in 86% yield along with acetone as the only organic side product formed. Alternatively, reduction of the carbonyl group followed by diol cleavage as above furnished the aldehyde **103** in 76% yield over the two steps. Thus, this methodology overcomes the reactivity issue of methacrylate ester **98** and enal **102** noted above.



Scheme 55. Conversion of the ketol moiety into carboxy and aldehyde functionalities.

The relative and absolute configuration of adduct **104b** were established by a single crystal X-ray analysis (Figure 27) and the configuration of the remaining adducts was assigned by assuming a uniform reaction mechanism.

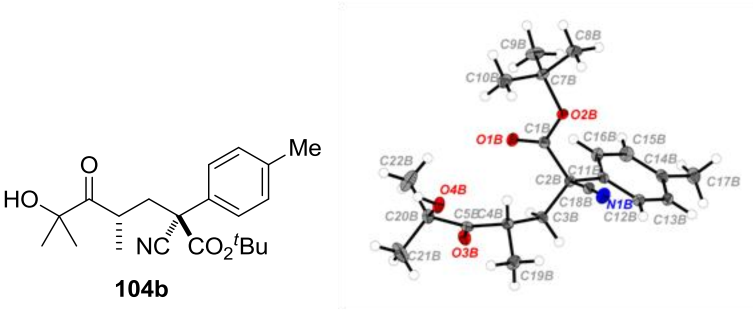
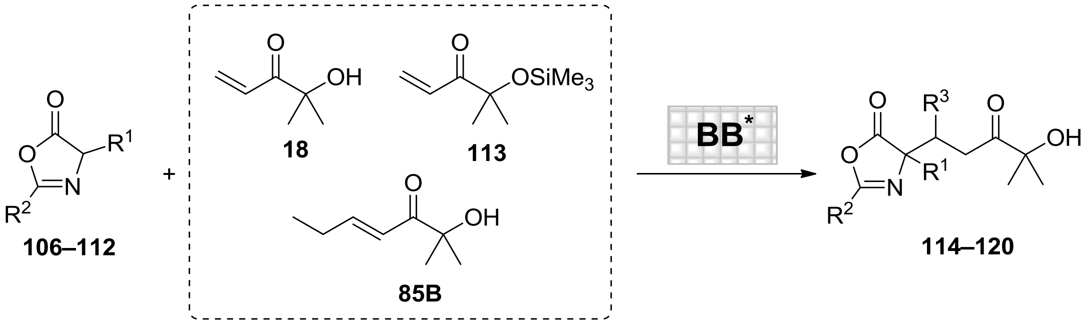


Figure 27. ORTEP diagram of compound **104b**.

2.4.3. Michael reaction of azlactones with α'-oxy enones

After the excellent results obtained from α-substituted cyanoacetates, we considered the extension of the methodology to other nucleophiles. Products containing tetrasubstituted stereogenic carbons bearing a sulfur, oxygen or nitrogen heteroatom are also interesting but difficult compounds to obtain as single enantiomers. In this context, we decided to investigate the efficiency of our template model in Brønsted base-catalyzed conjugate additions of several heteroatom-bearing soft carbon nucleophiles. For this study 4*H*-oxazol-5-ones (azlactones) were selected. More specifically the azlactones and α'-hydroxy enones shown in Scheme 56 were investigated.



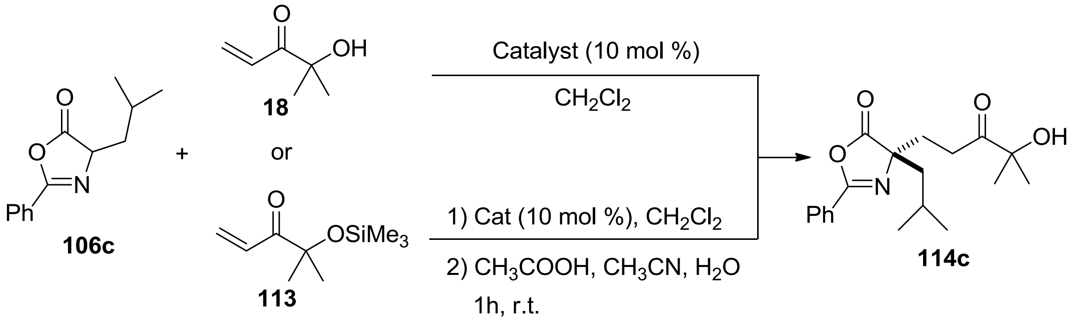
a R^1 = Me
b R^1 = ^{i}Pr
c R^1 = ^{i}Bu
d R^1 = Bn
e R^1 = Ph

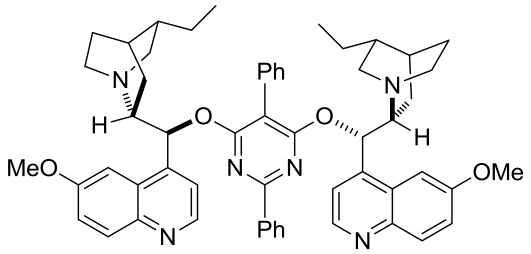
106 R^2 = Ph
107 R^2 = ^{t}Bu
108 R^2 = 4-ClPh
109 R^2 = 2,6-Cl_2Ph
110 R^2 = 4-MeOPh
111 R^2 = 3-MePh
112 R^2 = 2-Naphthyl

Scheme 56. Employed azlactones **106–112** for the Brønsted base catalyzed Michael addition to α’-hydroxy enones **18**, **113** and **85B** with different substitution patterns.

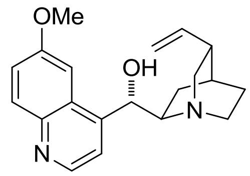
First, a catalyst screening with different bifunctional Brønsted bases was carried out for the reaction of the azlactone **106c** with α’-hydroxy enones **18** and **113** (Table 7). We found out that reaction with α’-hydroxy enone **18** proceeds in the presence of catalyst **C4**, but without any stereocontrol. Further exploration led us to obtain better enantioselectivities with the modified enoyl template **113**, prepared by simple silylation of the hydroxyl group in enone **18**. The reaction of azlactone **106c** and enone **113** catalyzed by either **C4** or **C51** in dichloromethane at –20 ºC provided, after desilylation of the resulting intermediate, the corresponding addition product **114c** in good yields and enantioselectivities.

Table 7. Catalyst screening for the conjugate addition of 4-isobutyl-2-phenyloxazol-5(4*H*)-one **106c** to α'-oxy enones **18** and **113**[a].

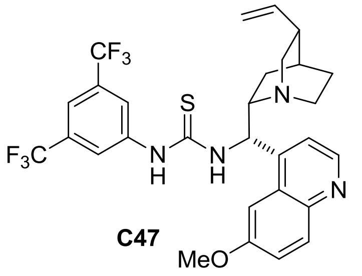




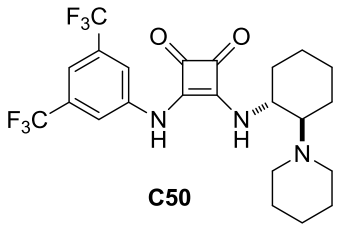
(DHQD)$_2$PYR, **C49**
with **18**: –40 °C, 0% *ee*
with **113**: –20 °C, 20% *ee*



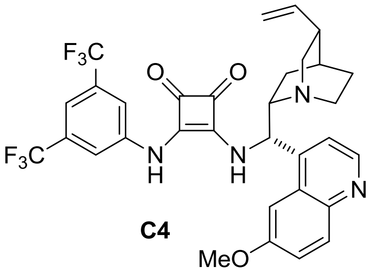
C18 Quinine
with **113**: –40 °C, 3% *ee*



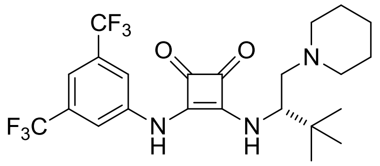
C47
with **113**: –40 °C, 74% *ee*



C50
with **113**: –20 °C, 82% *ee*



C4
with **18**: –40 °C, 88% *ee*
–20 °C, 88% *ee*
r.t., 80% *ee*
with **113**: –20 °C, 88% *ee*



C51
with **113**: 0 °C, 90% *ee*

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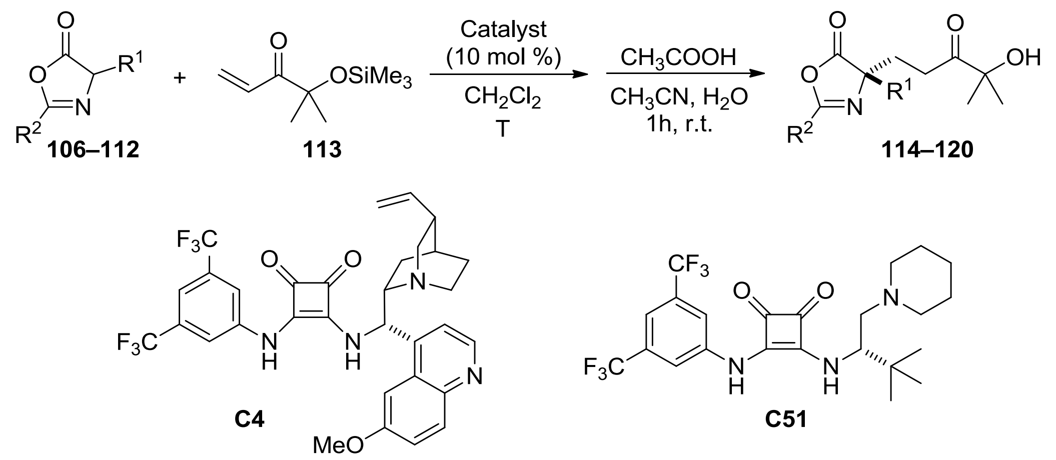
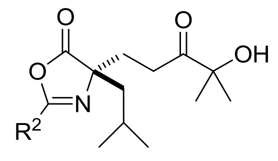
[a] Reaction conditions: **106c** (0.3 mmol), enone (3 equiv., 0.9 mmol), catalyst (10 mol %), in CH_2Cl_2 (0.9 mL). The *ee* values were determined by HPLC analysis on a chiral stationary phase.

The scope of the azlactone was then explored by modifying the R^2 group. The reactions were carried out in the presence of catalysts **C4** and **C51** (Table 8) and all proceeded with high site selectivity as no products from reaction at the *C*-2 position of the azlactone ring were observed when R^2 was an aromatic group. In general, similar enantioselectivities were obtained with electron-donor and electron-withdrawing substituents in the aromatic ring. However, when R^2 was an aliphatic group (^{t}Bu) the reaction did not take place and only the starting materials were detected.

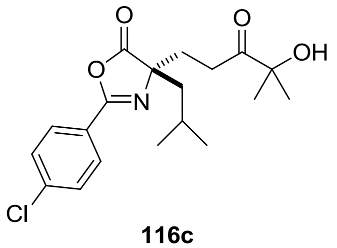
Table 8. Azlactone screening for the conjugate addition to α’-silyloxy enone **113**.[a]



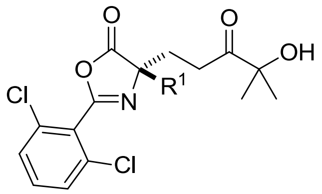


R^2 = Ph **114c** — **C1**, –20 ºC, 20 h — XX%, 88% *ee*

R^2 = ^{t}Bu **115c** — **C1**, r.t., 20 h — 0% conv., n.d. *ee*

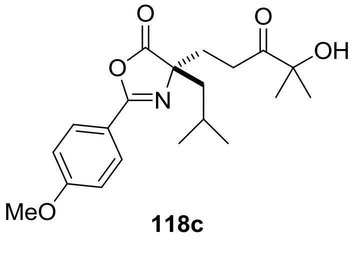


116c — **C1**, –20 ºC, 20 h — 72%, 86% *ee*

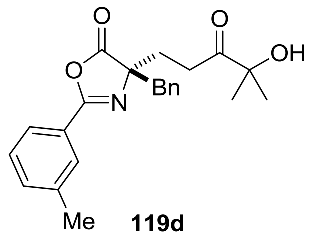


R^1 = ^{i}Bu **117c** — **C1**, –20 ºC, 20 h — 69%, 70% *ee*

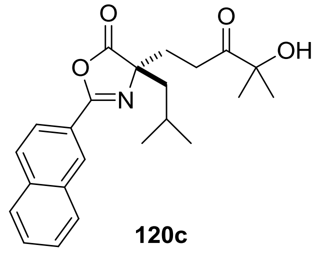
R^1 = Bn **117d** — **C1**, –20 ºC, 20 h — 35%, 88% *ee*



118c — **C2**, 0 ºC, 40 h — 70%, 90% *ee*



119d — **C1**, r.t., 6 h — 65%, 86% *ee*

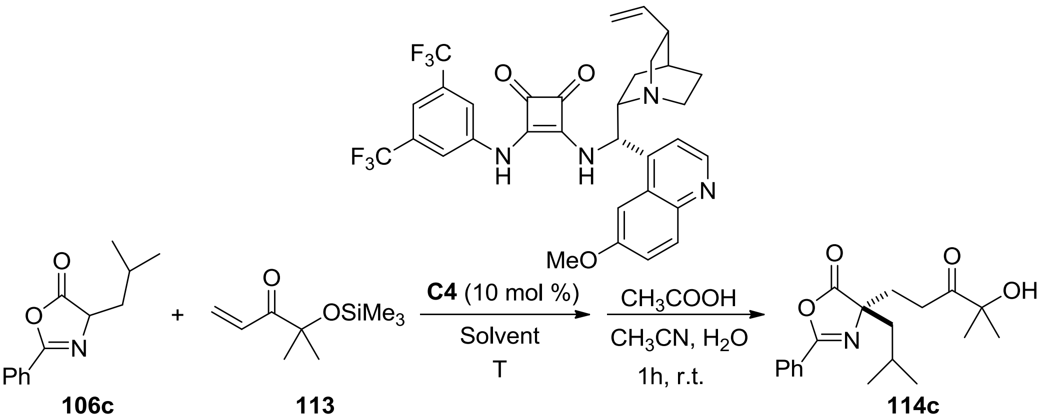


120c — **C1**, –20 ºC, 20 h — 84%, 66% *ee*

[a] Reaction conditions: **106**–**112** (0.3 mmol), **113** (1.5 equiv., 0.45 mmol) and catalyst (10 mol%) in CH_2Cl_2 (0.6 mL). Complete conversion related to the disappearance of the starting material. Yield of the adduct after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Solvent and temperature screening was also carried out. The best results were obtained with chlorinated solvents, as dichoromethane and 1,2-dichloroethane (Table 9, entries 3,4). Temperature influence was investigated in CH_2Cl_2 as solvent and enantioselectivities decreased as temperature decreased. The best enantiomeric excess was obtained in CH_2Cl_2 at room temperature (entry 6) with 1.5 equivalents of enone.

Table 9. Solvent and temperature screening for the conjugate addition of 4-isobutyl-2-phenyloxazol-5(4*H*)-one **106c** to α'-silyloxy enone **113**.[a]

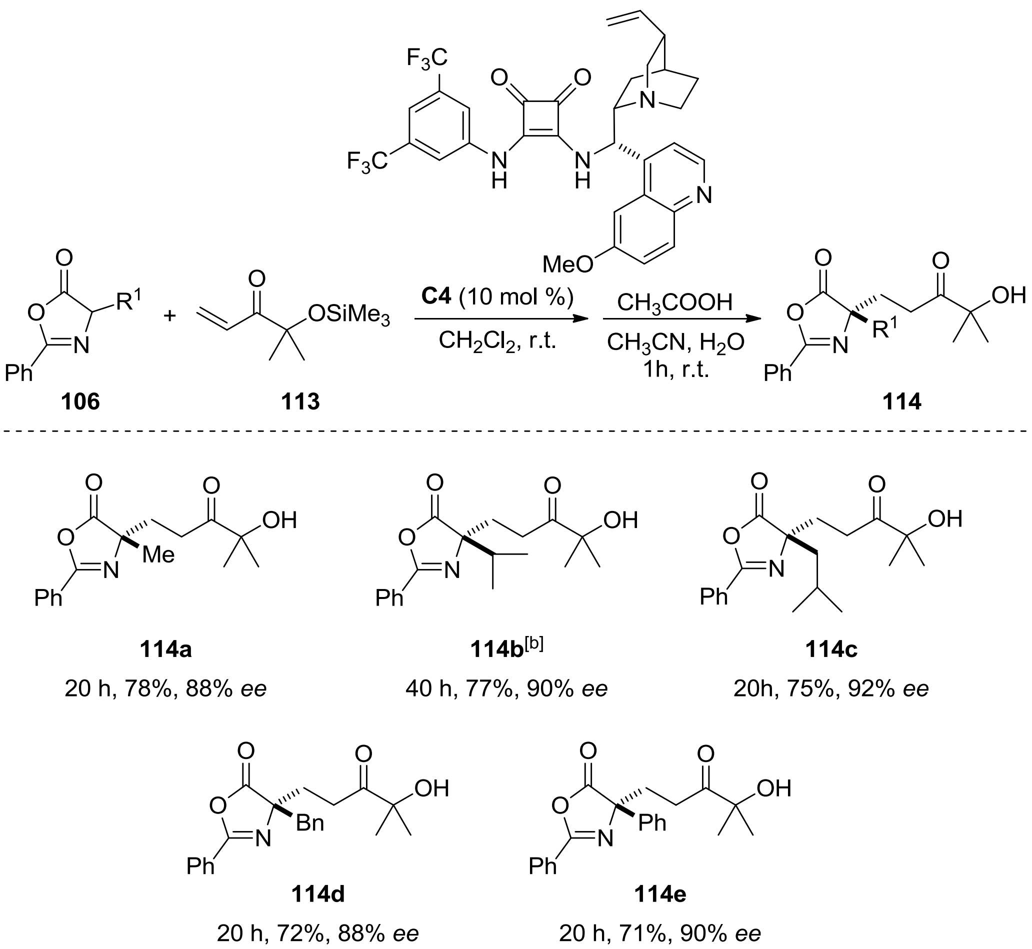


Entry	Solvent	Enone equiv.	T	t (h)	Conv. (%)[b]	*ee*[c]
1	Toluene	3	–20	40	100	40
2	$CHCl_3$	1.5	–20	20	100	70
3	$ClCH_2CH_2Cl$	1.5	–20	20	100	80
4	CH_2Cl_2	1.5	–20	20	100	88
5		3	–40	20	100	90
6		1.5	r.t.	20	100	92

[a] Reaction conditions: **106c** (0.3 mmol), **113** and catalyst **C4** (10 mol %) in a solvent (0.6 mL). [b] Related to the disappearance of the starting material. [c] Determined by HPLC analysis on a chiral stationary phase.

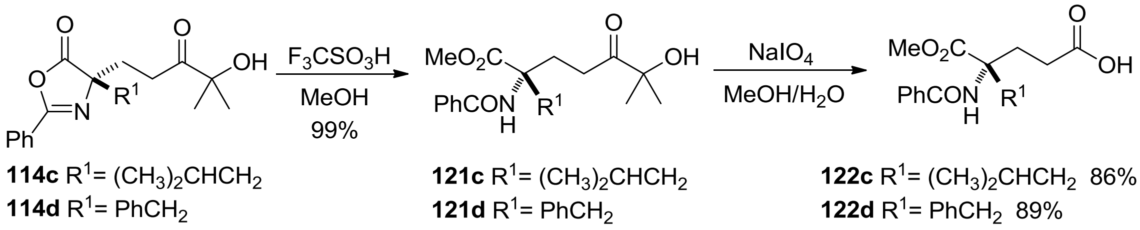
After optimization, we found that the best conditions for the conjugate addition of azlactones to α'-silyloxy enone **113**, involved the use of 1.5 equivalents of enone, 10 mol % of squaramide **C4** in dichloromethane at room temperature or –20 ºC. In this way, very good yields and excellent enantioselectivities were obtained after desilylation with several alkyl and aryl substituents at the *C*-4 position of the azlactone (Table 10). Nevertheless, it was necessary to increase the equivalents of enone and catalyst loading up to 3 equiv. and 20 mol%, respectively, for full conversion in the case of **114b** that bears the bulky isopropyl substituent.

Table 10. Azlactone reaction scope for the conjugate addition to α’-silyloxy enone **113**.[a]



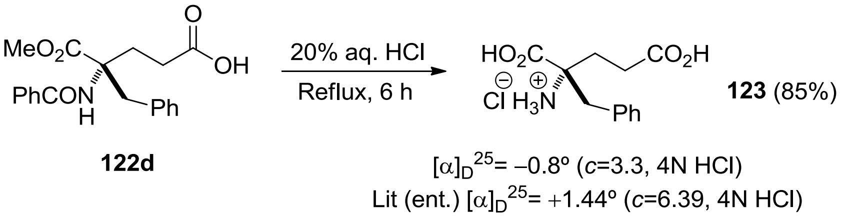
[a] Reaction conditions: **106** (0.3 mmol), **113** (1.5 equiv., 0.45 mmol) and catalyst **C4** (10 mol %) in CH_2Cl_2 (0.6 mL). [b] For complete conversion it was necessary 3 equivalents of enone and 20% mol of catalyst. Complete conversion related to the disappearance of the starting material. Yield of the adduct after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Elaboration of the obtained azlactone adducts afforded useful building blocks (Scheme 57). For instance, azlactone ring can be opened by treatment with triflic acid in methanol with quantitative yield. Subsequent ketol elaboration, following the same procedure as for cyanoacetates, provided the corresponding carboxylic acids with excellent yields.



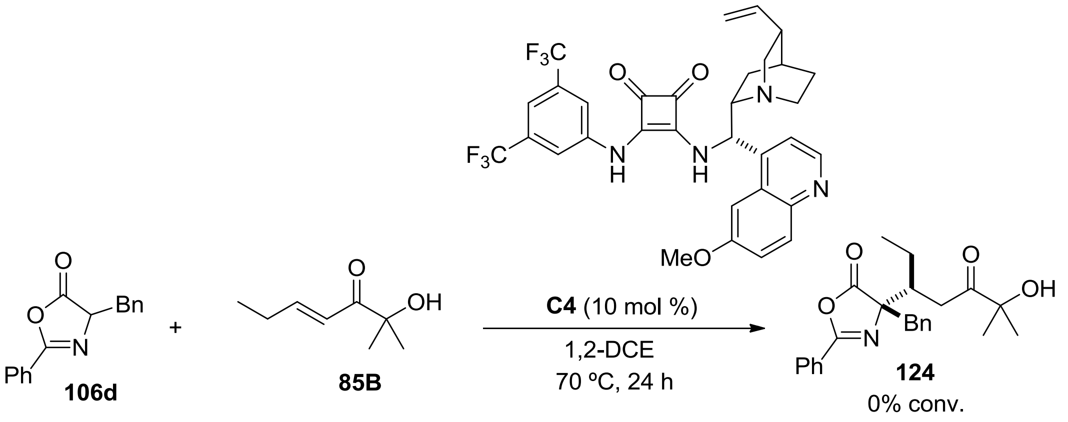
Scheme 57. Elaboration of adducts **114c** and **114d**.

The carboxylic acid **122d** was then transformed into the known glutamic acid derivative **123**[255] and the comparison of optical rotation values set the stereochemical course of the catalytic reaction (Scheme 58).



Scheme 58. Elaboration of adduct to α,α-disubstituted glutamic acid derivative.

In contrast to the case of cyanoacetates noted above, the reaction of azlactones with β-alkyl α'-hydroxy enones did not provide the corresponding addition products even at higher temperatures. For instance, when azlactone **106d** was treated with the β-substituted α'-hydroxy enone **85B** in the presence of squaramide catalyst **C4** in 1,2-dichloromethane at 70 ºC no addition product was detected (Scheme 59).



Scheme 59. Conjugate addition of 4-benzyl-2-phenyloxazol-5(4*H*)-one **106d** to the β-substituted α'-hydroxy enone **85B** promoted by squaramide catalyst **C4**.

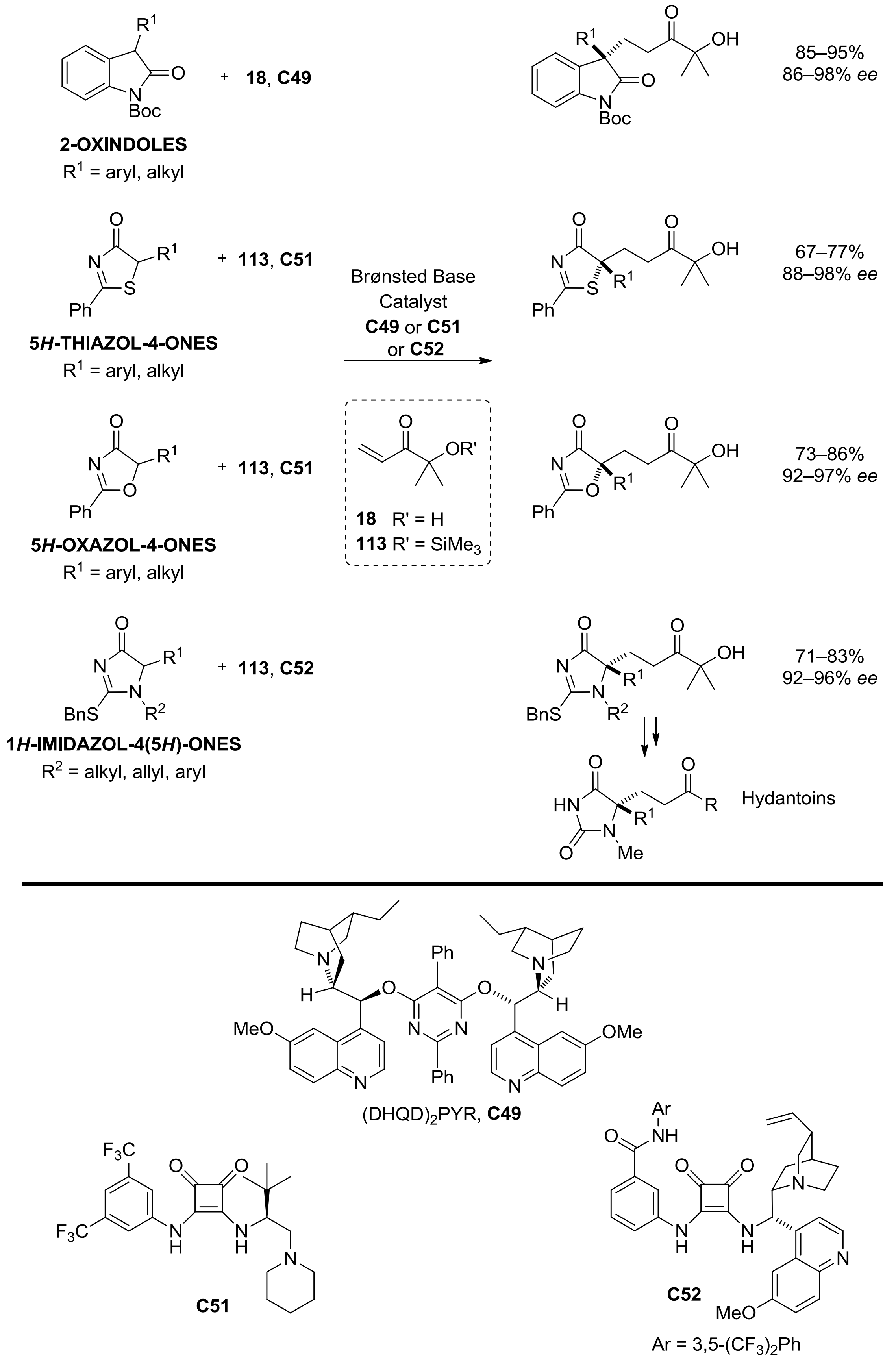
---

[255] Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507–1518.

Finally, the efficiency of α'-oxy enones in Brønsted base catalyzed reactions was corroborated by our group from the Michael addition using different pronucleophiles (Scheme 60).[256] Excellent yields and enantioselectivities were observed in the addition of 2-oxindoles, 5*H*-thiazol-4-ones, 5*H*-oxazol-4-ones and 1*H*-imidazol-4(5*H*)-ones to α'-oxy enones. The latter ones showed to serve as effective equivalents of *N*-substituted quaternary α-amino acids and medicinally interesting 5,5-disubstituted hydantoins.[256b]

---

[256] a) See ref. 52. b) Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.



Scheme 60. Different pronucleophiles employed by our group in the Brønsted base catalyzed Michael addition to α’-oxy enones.

2.4.4. Computational studies

With all the results obtained, it was clear that α’-oxy enones exhibit some unique reactivity compared to ordinary enones, such as, MVK. Both higher reactivity and enantioselectivity have been observed in the BB-catalyzed reactions studied.

Similarly, our experimental results indicate a distinct behavior of α’-oxy enones as compared with other typical enoyl templates previously reported for the BB-catalyzed enantioselective generation of quaternary stereogenic carbon centers. More specifically, the catalyst controlled conjugate addition of α-substituted cyanoacetates is, as mentioned before, sluggish with the majority of Michael acceptors, while it works well with α’-oxy enones.

With the aim to understand better such distinguishing behavior, we decided to study computationally[257] the case of the conjugate additions of cyanoacetates. A DFT investigation was carried out in our department by Dr. Enrique Gómez-Bengoa and Béla Fiser selecting methyl vinyl ketone (MVK) and the two α’-oxy enones **18** and **125** as the model Michael acceptors and examining the relationship between their reactivity and structure. Calculations show that the intramolecular *H*-bond activation in **18** and **125** induces a change in a series of electronic parameters (Figure 28), explaining their higher reactivity in comparison with MVK.

---

[257] All calculations were performed with Gaussian 09, Revision D.01: Frisch, M. J. et al. *Gaussian 09, revision D.01*; Gaussian, Inc., Wallingford, CT, 2013. The geometries of the stationary points were optimized by using DFT with the B3LYP functional and 6-311++G** basis set in a dichloromethane solvent system.

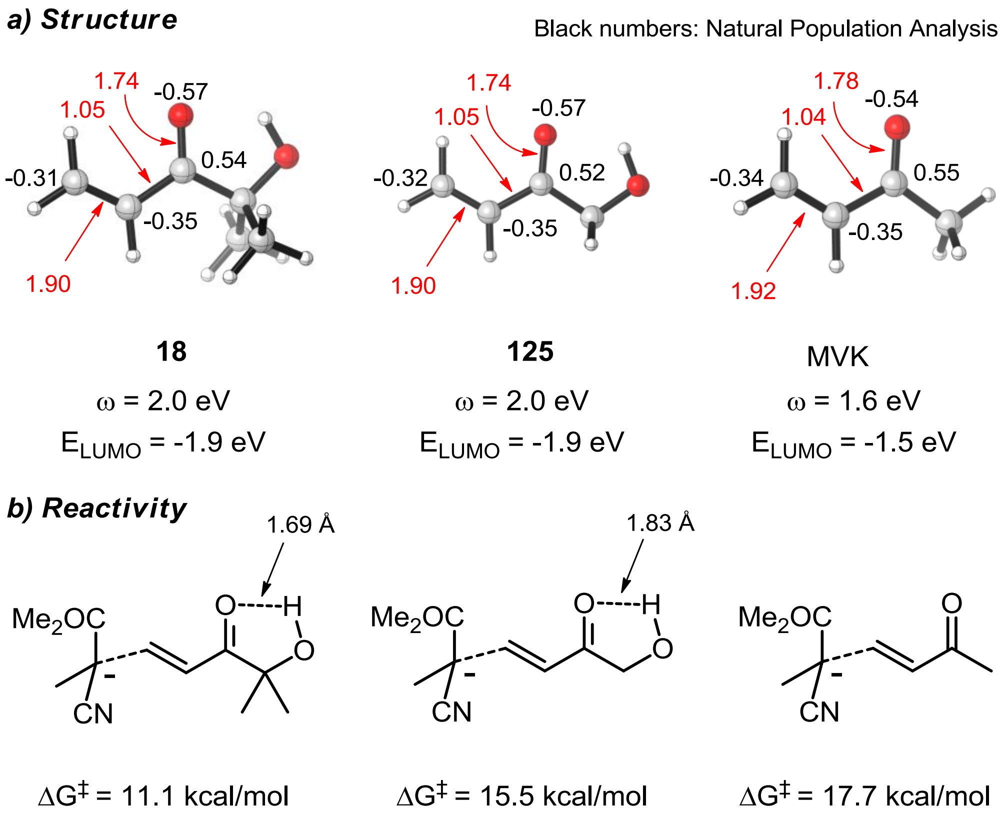


Figure 28. Structure-reactivity relationship.

In particular, the electrophilicity index ω[258] for both **18** and **125** (ω = 2.0 eV) is higher than for MVK (ω = 1.6 eV), which is consistent with the lower energy LUMO for **18** and **125** (–1.9 eV) as compared to LUMO of MVK (–1.5 eV). In the same way, the character of the β-carbon of **18** is more positive (*Natural Population Analysis*, NPA charge of –0.31) than the corresponding β-carbon of MVK (–0.34). These values correlate well with the Wiberg bond index for **18** (1.90) and MVK (1.92), respectively, indicating the lower double bond character of the enone *C*=*C* bond in **18**.

Subsequently, the activation energy of the reaction of these three Michael acceptors with methyl α-methylcyanoacetate **69h** was calculated (Figure 28, b). This barrier resulted significantly lower for α'-hydroxy enone **18** (11.1 kcal/mol) than for MVK (17.7 kcal/mol). On the other hand, although the electronic parameters of both α'-hydroxy enones **18** and **125** do not differ significantly from one another, the reaction involving the latter presents an activation energy 4.4 kcal/mol higher than the reaction with **18**. This additional stabilization of the transition state (TS) for the reaction with **18** as compared with **125** is consistent with the shorter intramolecular hydrogen bond in the

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[258] Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc*. **1999**, *121*, 1922–1924.

first case (1.69 vs 1.83 Å) and might be attributed to a Thorpe-Ingold effect[259] imparted by the two germinal methyl substituents in **18**.

The origin of the stereoselectivity in the **C4**-catalyzed reaction between α'-hydroxy enone **18** and α-cyanoacetates was studied next. Firstly, the *H*-bond pattern formed between the catalyst and both substrates in the TS corresponding to the *C–C* bond-forming step was examined. In this respect, up to three different ternary complexes (**A**–**C**, Figure 29) have been proposed for reactions involving noncovalent cooperative activation of the nucleophile and electrophile, typically described in a bifunctional thiourea (or squaramide)-tertiary amine catalysis.[260] Therefore, the question of whether or not a unified *H*-bond network model (**A**, **B**, **C**, other) could be applied to different reactions within this catalysis category seems to be still open and more data are desirable.

---

[259] a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc*. **1915**, *107*, 1080–1106. b) Jung, M. E.; Piizzi, G. *Chem. Rev*. **2005**, *105*, 1735–1766.

[260] For studies describing type **A** transition structures, see: a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672–12673. b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119–125. c) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2007**¸ *129*, 15872–15883. d) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2009**, *131*, 15358–15374. e) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal*. **2007**, *349*, 2537–2548. For type **B**: f) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc*. **2006**, *128*, 13151–13160. g) Almasi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem*. **2009**, *74*, 6163–6168. h) Tan, B., Lu, Y., Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett*. **2010**, *12*, 2682–2685. i) Han, X.; Lee, R.; Chen, T.; Luo, J.; Lu, Y.; Huang, K. W. *Sci. Rep*. **2013**, *3*, 2557. j) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**¸ *20*, 5631–5639. k) Azuma, T.; Kobayashi, Y.; Sakata, K.; Sasamori, T.; Tokitoh, N.; Takemoto, Y. *J. Org. Chem.* **2014**, *79*, 1805–1817. For type **C**: l) Zhu, J.-L.; Zhang, Y.; Liu, C., Zheng, A.-M.; Wang, W. *J. Org. Chem*. **2012**, *77*, 9813–9825.

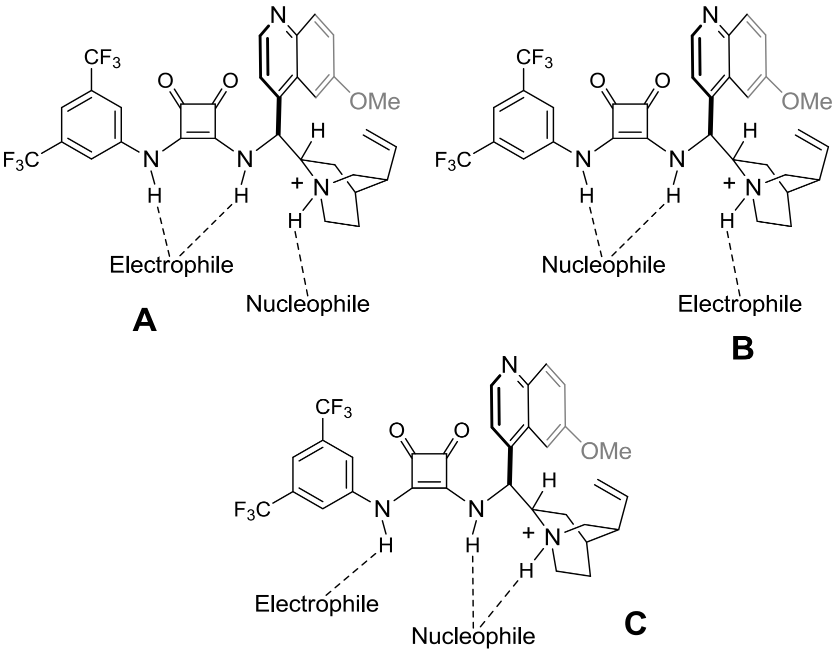


Figure 29. Three alternative substrate-catalyst combinations.

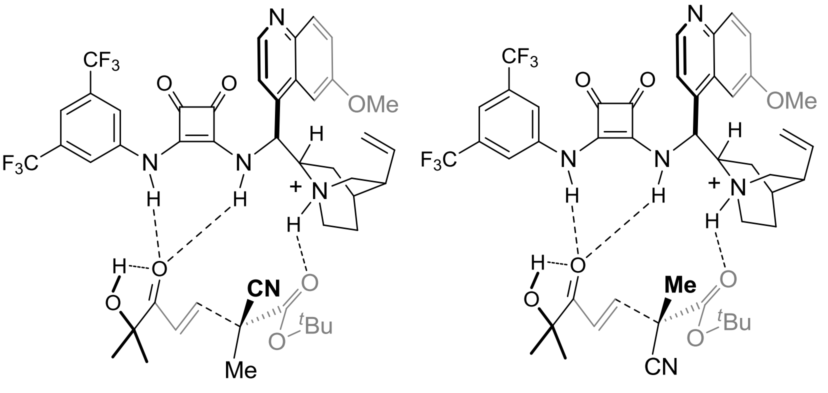
In our case, despite much effort, any plausible transition structure of type **B** was not found among the several *H*-bond combinations studied.[261] From a look to the geometries of the resulting complexes, it seemed that once cyanoacetate is *H*-bonded to the catalyst there is no space available for the electrophile to interact with the same catalyst molecule. Therefore, the structure closest to **B** found involves an approach of the *H*-bonded cyanoacetate anion to the non complexed enone.[262] On the other hand, a single structure similar to model **C** was also found; however, it was predicted to be unrealistic due to its high activation energy.

In its turn, four possible structures of type **A** (**TS-R$_1$**, **TS-S$_1$**, **TS-R$_2$**, **TS-S$_2$**, Figure 30) were located, in which the α'-hydroxy enone carbonyl is double *H*-bonded to the squaramide *NH* groups, while the protonated quinuclidine NH^+ might bind to either the *CN* or the ester group of the cyanoacetate moiety.

---

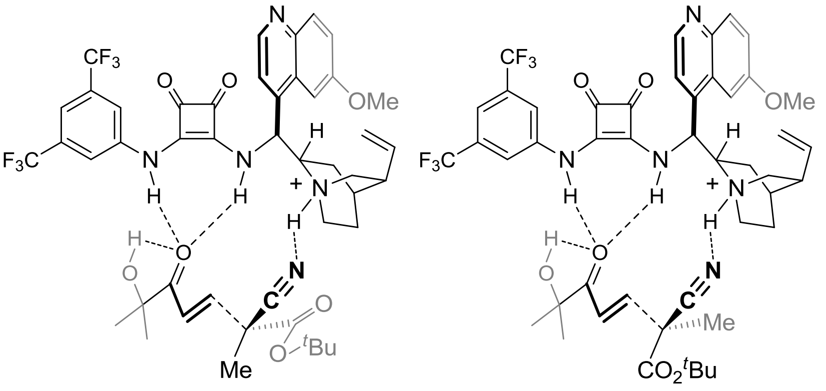
[261] In our calculations we have considered the chiral cinchonine moiety of **C4** addopting either a *syn*-open or *anti*-open conformations. The prevalence of such conformations in similar bifunctional catalysts as well as in the native cinchona alkaloids has been studied both experimental and theoretically: a) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537–2548. b) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas*, **1989**, *108*, 95. c) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069–8076. d) Bürgi, T.; Baiker, A. *J. Am. Chem. Soc*. **1998**, *120*, 12920–12926.

[262] While the intramolecular *H*-bond present in our α'-hydroxy enone would help the occurrence of such a transition state, its energy is exceedingly high and this pathway may be discarded.



TS-R$_1$
ΔΔG = 0 kcal/mol

TS-S$_1$
ΔΔG = 2.8 kcal/mol



TS-R$_2$
ΔΔG = 6.1 kcal/mol

TS-S$_2$
ΔΔG = 6.4 kcal/mol

Figure 30. Located TSs for the catalytic addition reaction.

TS-R$_1$ is the lowest in energy and correctly explains the formation of the major isomer observed experimentally. Extrapolation of this TS model to the reaction between β-substituted enones and cyanoacetates would also correctly predict the (*S*,*S*) relative configuration of these adducts obtained in Table 3. The other TS structure **B** predicts products of wrong relative stereochemistry upon a similar extrapolation. The next most feasible structure is **TS-S$_1$**. Interestingly, in both cases, the $CO_2{}^t$Bu is involved in *H*-bonding with the catalyst *NH*$^+$ moiety, while the methyl (**TS-S$_1$**) and the cyano group (**TS-R$_1$**) are, respectively, almost eclipsed with the enone double bond. The energy difference between them is 2.8 kcal/mol at the M06-2X/6-311+G** computational level[263] and the preference of **TS-R$_1$** is attributed to a larger destabilizing effect of pseudoeclipsed methyl (dihedral angle 21.9º) than pseudoeclipsed cyano (dihedral angle 33.5º). The remaining two structures, **TS-R$_2$** and **TS-S$_2$**, both involving a *NH*$^+$···*NC* interaction, are 6.1 and 6.4 kcal/mol higher in energy than **TS-R$_1$**, respectively.

---

[263] Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc*. **2008**¸*120*, 215–241.

From these results some conclusions can be obtained: (i) in the studied catalytic reactions, the ketol moiety of the acceptor α'-hydroxy enone plays a key role in decreasing reaction energy barriers; (ii) among several possible *H*-bond combinations for the nucleophile-catalyst-electrophile complex, type **A** is preferred, with the squaramide group interacting with the α'-hydroxy enone (electrophile activation), and the protonated quinuclidine interacting with the cyanoacetate anion (nucleophile activation); (iii) given the previous data in the literature in favor of models of type **B** and **C** for related catalytic reactions, a unified model cannot be proposed for all reactions involving this type of noncovalent bifunctional catalysis; (iv) calculations for our system confirms that *H*-bond with the nitrile group contributes poorly to TS stabilization as compared with *H*-bond to a ester group, probably due to the fact that linear arrangements (as in $C{\equiv}N{\cdots\cdots}H$X) are more difficult to fit in the TS than angular arrangements (as in $C{=}O{\cdots}H$X).[264] Eventually, the combination of these factors leads to the highly stereoselective formation of the new quaternary stereocenter in addition adducts.

---

[264] It seems that the preference of the nitrile versus the ester group to get coordinated to a metal center does not correlate with the ability of each group for engaging in H-bonding. Thus most TS models invoked in the literature for the metal-catalyzed conjugate addition reactions of α-cyanoacetates consider metal-coordinated nitrile and uncoordinated ester groups, respectively, In contrast, and in agreement with our own calculations, previously reported qualitative activation models for related reactions involving H-bond catalysis assume the preference of the ester group over the nitrile for H-bonding. To further illustrate this divergency, the structure of a cyanoacetate-metal catalyst complex has been elucidated in which both the metal-CN and the ester-H-bond interaction are identified.

CHAPTER 3

Pyrrolidin-2,3-diones as pronucleophiles in organocatalytic asymmetric reactions

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3. Pyrrolidin-2,3-diones as pronucleophiles in organocatalytic asymmetric reactions

3.1. Pyrrolidin-2,3-diones: General characteristics

The search for new pronucleophiles which effectively participate in asymmetric catalytic reactions and provide diverse functionalities for subsequent elaborations is of a great interest. In this field, pyrrolidin-2,3-diones (Figure 31) are synthetic scaffolds which are present in a variety of biologically important compounds.[265] From the synthetic point of view, this cyclic α-ketoamide combines both nucleophilic and electrophilic characteristics, which can enable various types of reactions and sequential or cascade transformations with suitable nucleophiles or electrophiles.

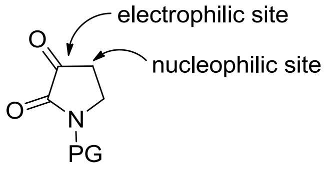

Figure 31. Structure of pyrrolidin-2,3-diones, and their nucleophilic and electrophilic character.

Compared to 1,3-dicarbonyl compounds,[266] there are not many organocatalytic examples of the use of 1,2-dicarbonyl compounds (1,2-diketone, α-ketoester and α-ketoamide)[267] as carbon-centered nucleophiles despite their diverse reactivity and synthetic value. Utilization of 1,2-dicarbonyl compounds in asymmetric organocatalytic transformations has been limited to the increased electrophilic ketone reactivity by the presence of an adjacent carbonyl group.[268] This highlights the importance of the

---

[265] a) Meyers, A. I.; Snyder, L. *J. Org. Chem*. **1993**, *58*, 36–42. b) Moody, C. M.; Young, D. W. *Tetrahedron Lett*. **1994**, *35*, 7277–7280. c) Rigo, B.; Fasseur, D.; Cherepy, N.; Couturier, D. *Tetrahedron Lett*. **1989**, *30*, 7057–7060. d) Poli, G.; Baffoni, S. C.; Giambastiani, G.; Renginato, G. *Tetrahedron* **1998**, *54*, 10403–10418.

[266] For some selected examples of 1,3-dicarbonyl compounds as pronucleophiles, see: a) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc*. **2006**, *128*, 1454–1455. b) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed*. **2005**, *44*, 6367–6370. c) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc*. **2004**, *126*, 9906–9907. d) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672–12673.

[267] For a review of 1,2-dicarbonyl compounds in organocatalysis, see: Raimondi, W.; Bonne, D.; Rodriguez, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 40–42.

[268] For some selected examples of the utilization of 1,2-dicarbonyl compounds as electrophiles in organocatalytic transformations, see: a) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Chem. Commun*. **2010**, *46*, 904–906. b) Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluhácková, K.; Kocovský, P. *Org. Lett*. **2007**, *9*, 5473–5476. c) Procuranti, B.; Connon, S. J. *Chem. Commun*. **2007**, 1421–1423. d) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 732–733.

development of suitable selective organocatalyzed activation modes for enhancing the nucleophilic potential of 1,2-dicarbonyl compounds towards cross-condensation instead of competitive self-condensation.

3.2. Biological relevance of pyrrolidinone skeletons

Enantioenriched pyrrolidinone skeletons are of great biological and pharmaceutical interest[265] and many efforts have been made in the development of their synthesis with diverse structural features.[269] Among them, γ-butyrolactams or 2-pyrrolidinones **126** (Figure 32) are a class of versatile core structures found in many natural products with important biological properties as cytotoxicity, antitumor and anti-inflammatory activities.[270] They are also excellent precursors for the synthesis of biologically active pyrrolidine derivatives.[271]

Other interesting modified skeletons are α-methylene derivatives **127**[272] and the structurally related α-keto-γ-butyrolactams or pyrrolidin-2,3-diones **128** (Figure 32). Both of them are the core of many natural products and drugs displaying diverse activities. For instance, the pyrrolidin-2,3-dione scaffold has been demonstrated to be a privileged structure in the design of protein-protein interactions.[273]

---

[269] For some selected examples, see: a) Marino, J. P.; Zou, N. *Org. Lett.* **2005**, *7*, 1915–1917. b) Schobert, R.; Bieser, A.; Mullen, G.; Gordon, G. *Tetrahedron Letters* **2005**, *46*, 5459–5462. c) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem. Int. Ed.* **2002**, *41*, 4526–4529. d) Yoon, C. H.; Flanigan, D. L.; Chong, B.-D.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 6582–6584 and references therein.

[270] For some representative examples, see: a) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 4907–4916. b) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257–4259. c) Aslanian, R.; Lee, G.; Iyer, R. V.; Shih, N.-Y.;. Piwinski, J. J; Draper, R. W.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 3867–3871. d) Xu, L.; Liu, S.-L.; Zhang, J.-T. *Chirality* **2005**, *17*, 239–244. e) Gouliaev, A. H.; Senning, A. *Brain Res. Rev.* **1994**, *19*, 180–222. f) Khuong-Huu, F.; Monseur, X.; Ratle, G.; Lukacs, G.; Goutarel, R. *Tetrahedron Lett.* **1973**, *14*, 1757–1760.

[271] For some selected examples, see: a) Obst, U.; Betschmann, P.; Lerner, C.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 855–909. b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667. c) Puschl, A.; Tedeschi, T.; Nielsen, P. E. *Org. Lett.* **2000**, *2*, 4161–4163. d) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616–9617. e) Alvarez-Ibarra, C.; Csákÿ, A. G.; López de Silanes, I.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 479–484. f) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149–4174 and references therein.

[272] For a selected recent review, see: Albrecht, A.; Albrecht, L.; Janecki, T. *Eur. J. Org. Chem.* **2011**, 2747–2766.

[273] a) Thiel, P.; Kaiser, M.; Ottmann, C. *Angew. Chem. Int. Ed.* **2012**, *54*, 2012–2018. b) Rose, R.; Erdmann, S.; Bovens, S.; Wolf, A.; Rose, M.; Hennig, S.; Waldmann, H.; Ottmann, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 4129–4132. c) Zhuang, C.; Miao, Z.; Zhu, L.; Dong, G.; Guo, Z.; Wang, S.; Zhang, Y.; Wu, Y.; Yao, J.; Sheng, C.; Zhang, W. *J. Med. Chem.* **2012**, *55*, 9630–9642. d) Reddy, T. R. K.; Li, C.; Guo, X.; Myrvang, H. K.; Fischer, P. M; Dekker, L. V. *J. Med. Chem.* **2011**, *54*, 2080–2094.

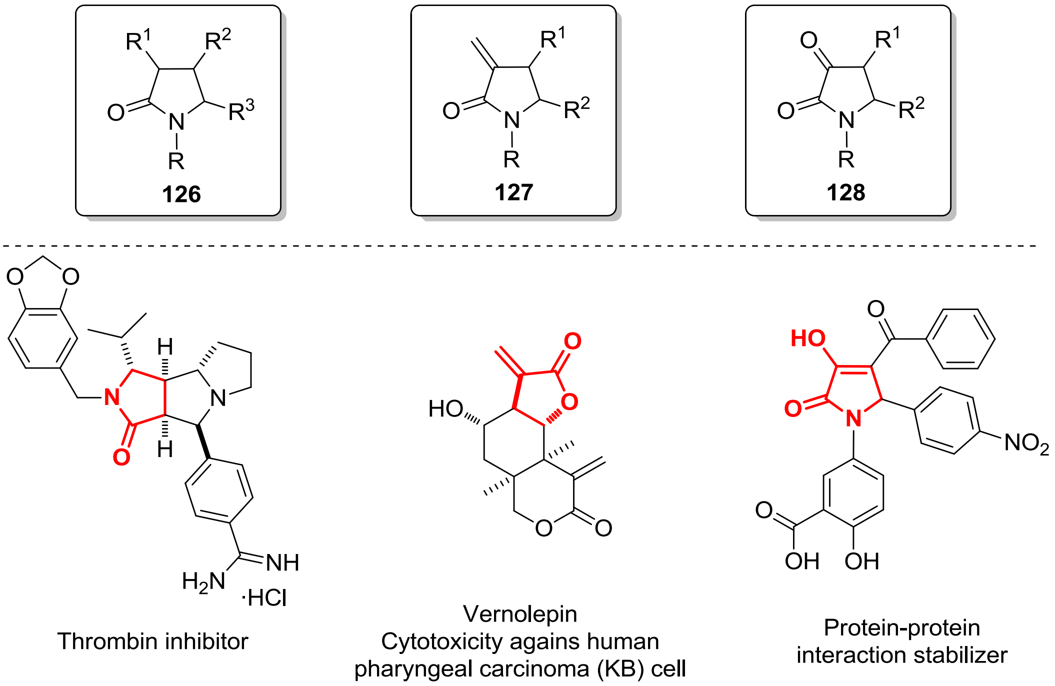

Figure 32. General structure of γ-butyrolactams or 2-pyrrolidinones **126**, α-methylene derivatives **127** and pyrrolidin-2,3-diones **128** and some biologically active examples.

Despite their interest, little is known about the asymmetric synthesis and reactions of chiral pyrrolidin-2,3-diones. There is only one example about the use of this type of substrates in organocatalysis reported by Xu and co-workers exploring their dual reactivity in a one-pot Michael/Pictet-Spengler sequence (Scheme 61).[274] Synthetically interesting and medicinally important pentacyclic butyrolactam-fused indoloquinolizidines are efficiently constructed in a highly stereocontrolled manner. The reaction is proposed to be initiated by iminium ion activation by the secondary amine catalyst in the Michael addition of **129** to **130** to produce the chiral hemiacetal **131**. Under acidic conditions, the activated hemiacetal reacts with tryptamine to generate the iminium ion **132**, which undergoes a diastereoselective Pictet-Spengler reaction[275] to afford the butyrolactam-fused indoloquinolizidines **133**.

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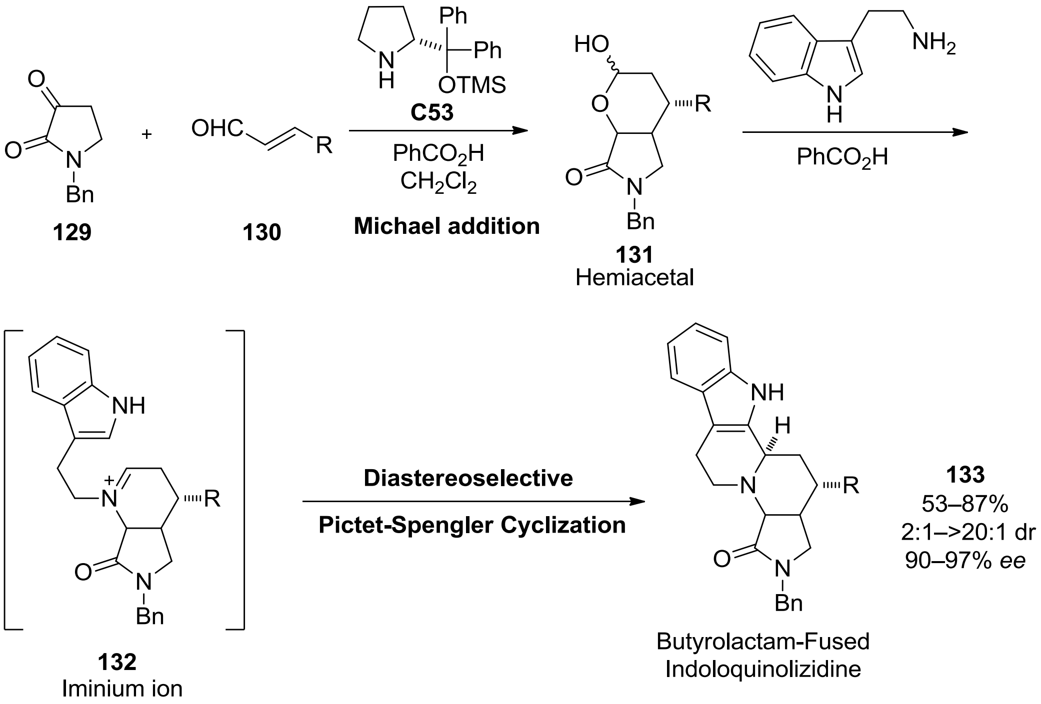
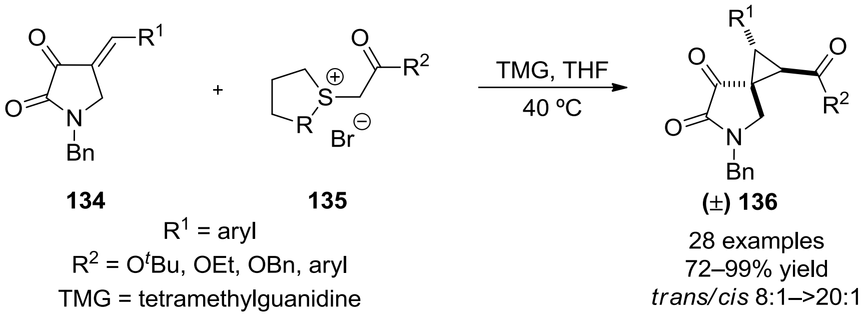
[274] Zhu, H.-L.; Ling, J.-B.; Xu, P.-F. *J. Org. Chem*. **2012**, *77*, 7737–7743.

[275] For selected examples of organocatalytic Pictet-Spengler reactions, see: a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 10558–10559. b) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc*. **2009**, *131*, 10796–10797.



Scheme 61. Only example of the use of pyrrolidin-2,3-diones in asymmetric organocatalysis: sequential Michael addition/Pictet-Spengler cyclization. **Xu, 2012**.

More recently, the utility of 4-alquiliden pyrrolidin-2,3-diones **134** as Michael acceptors has been demonstrated in a reaction with sulfur ylides **135** to provide spiro-cyclopropanes **136** (Scheme 62).[276] Despite of not being an asymmetric reaction, the corresponding adducts **136** are obtained with very good yields and excellent *cis/trans* diastereoselectivity.



Scheme 62. Spiro-cyclopropane synthesis from 4-alquiliden pyrrolidin-2,3-diones **134**. **Xu, 2015**.

3.3. β-Amino acids from pyrrolidin-2,3-diones

Apart from biological properties, pyrrolidin-2,3-diones can also be precursors of β-amino acids, which are present in a variety of natural products, pharmaceutical agents

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[276] Zhang, S.; Hu, X.-Q.; Wang, Z.-Y.; Xu, P.-F. *Synthesis* **2015**, *47*, 2529–2537.

and mimics of protein structural motifs.[277] The substitution pattern and configuration at the *C*-4 and/or *C*-3 position of β-amino acids (Figure 33) strongly influence the structural, chemical and biological characteristics of β-amino acids and their oligomers (β-peptides). Therefore, the development of efficient protocols for the enantioselective synthesis of β-amino acids with different substitution patterns has been of great interest.

Although a number of methods have been successfully developed for the synthesis of β^{2}-, β^{3}-, $\beta^{3,3}$-, $\beta^{2,3}$- amino acids,[278] the stereoselective preparation of or $\beta^{2,2}$-derivatives (Figure 33) still remains challenging,[279] especially with catalytic strategies, since an all-carbon substituted quaternary stereocenter has to be generated.

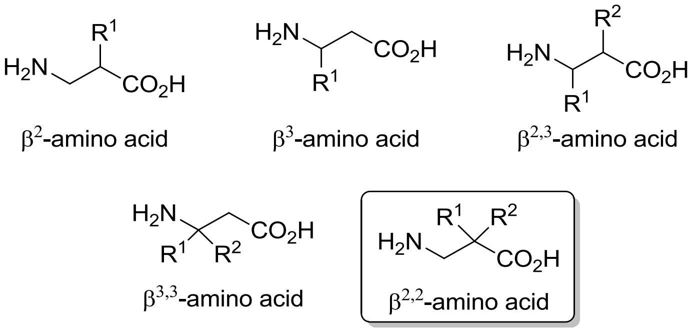

Figure 33. Different substitution patterns in β-amino acids.

Most of the methods for the synthesis of $\beta^{2,2}$-amino acids are based on diastereoselective approaches,[280] and catalytic enantioselective examples are currently

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[277] For some reviews on synthesis, structures and functions of β-amino acids and β-peptides, see: a) Seebach, D.; Gardiner, J. *Acc. Chem. Res*. **2008**, *41*, 1366–1375. b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev*. **2001**, *101*, 3219–3232.

[278] For general reviews on the synthesis of β-amino acids, see: a) Lui, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. b) Juaristi, E. *Enantioselective Synthesis of β-amino acids*; Wiley-VCH: New York, **1997**. c) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem*. **2007**, *16*, 5797–5815. d) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891. For general reviews on the synthesis of β^{3}-amino acids, see: e) Bruneau, C.: Renaud, J.-L.; Jerphagnon, T. *Coord. Chem. Rev*. **2008**, *252*, 532–544. f) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannerberg, A.; Heller, D. *Org. Proccess. Res. Dev*. **2003**, *7*, 355–361. For a general review on the synthesis of β^{2}-amino acids, see: g) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Groselj, U.; Zass, E. *Synthesis* **2009**, 1–32.

[279] For a general review on the synthesis of geminally disubstituted β-amino acids, see: a) Abele, S.; Seebach, D. *Eur. J. Org. Chem*. **2000**, 1–15.

[280] For a diastereoselective approach for synthesis of $\beta^{2,2}$-amino acids from *tert*-butanesulfinyl imines, see: a) Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **2002**, *67*, 7819–7832. For a diastereoselective approach for synthesis of $\beta^{2,2}$-amino acids from 1-benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one, see: b) Juaristi, E.; Balderas, M.; Ramírez-Quirós, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3881–3888. For a diastereoselective approach for synthesis of $\beta^{2,2}$-amino acids from Fischer boroxyl alkenyl carbine

very limited. These involve Michael additions of carbon centered nucleophiles to β-nitroacrylates, conjugate reactions of α-substituted cyanoacetates to different electrophiles, enantioselective Henry reaction of nitromethane with α-keto esters and the catalytic asymmetric acylation of (silyloxy)nitrile anions. The contributions and limitations of these protocols are summarized below.

One of the approaches makes use of β-nitroacrylates as Michael acceptors. After the conjugate addition, the nitro group can be reduced to generate the corresponding $\beta^{2,2}$-amino ester (Scheme 63). This strategy has been explored with different carbon-centered nucleophiles. For instance, Meggers[281] and Jia[282] developed the asymmetric Friedel-Crafts alkylation of indoles with α-substituted β-nitroacrylates catalyzed by the iridium and niquel complexes **C54** and **C55**, respectively (Scheme 63, a). In both cases the corresponding adducts containing a quaternatery stereocenter were synthesized with excellent results even from α-alkyl substituted β-nitroacrylates. Later, Bencivenni reported the efficient γ-functionalization of oxindoles bearing nonsymmetric 3-alkylidene groups via vinylogous Michael reaction catalyzed by the cinchona derived thiourea **C56** with only α-aryl β-nitroacrylates (Scheme 63, b).[283] Making use of a similar type of catalyst, Hu and Zhao optimized the enantioselective Michael reaction of malononitrile with α-aryl substituted β-nitroacrylates producing adducts in high yield and enantioselectivities promoted by the thiourea-based bifunctional Brønsted base **C57** (Scheme 63, c).[284] In the same context, Jørgensen disclosed a new activation concept for polycyclic π-systems by using aminocatalysis (Scheme 63, d). In this case, an example of Diels-Alder reaction of an anthracene aldehyde was developed using α-methyl β-nitroacrylates in the presence of the bifunctional aminocatalyst **C58** with excellent results.[285] A similar type of activation strategy has been reported by Wennemers in the Michael addition of aliphatic aldehydes to α-aryl β-nitroacrylates promoted by the peptide-base catalyst **C59** affording adducts with high yields and stereoselectivity (Scheme 63, e).[286] Finally, Melchiorre descrided the vinylogous Michael addition of a

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complexes, see: c) Barluenga, J.; Canteli, R. M.; Flórez, J.; García-Granda, S.; Gutiérrez-Rodríguez, A.; Martín, E. *J. Am. Chem. Soc*. **1998**, *120*, 2514–2522.

[281] Chen, L.-A.; Tang, X.; Xi, J.; Xu, W.; Gong, L.; Meggers, E. *Angew. Chem. Int. Ed*. **2013**, *52*, 14021–14025.

[282] Weng, J.-Q.; Deng, Q.-M.; Wu, L.; Xu, K.; Wu, H.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. *Org. Lett*. **2014**, *16*, 776–779.

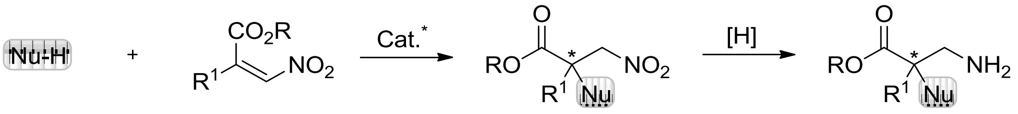
[283] Iorio, N. D.; Righi, P.; Ranieri, S.; Mazzanti, A.; Margutta, R. G.; Bencivenni, G. *J. Org. Chem*. **2015**, *80*, 7158–7171.

[284] Chen, S.; Lou, Q.; Ding, Y.; Zhang, S.; Hu, W.; Zhao, J. *Adv. Synth. Catal*. **2015**, *357*, 2437–2441.

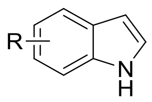
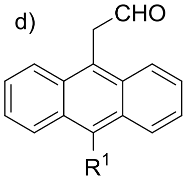
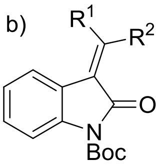
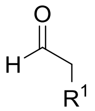
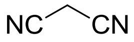
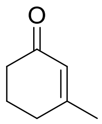
[285] Jiang, H.; Rodríguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2012**, *51*, 10271–10274.

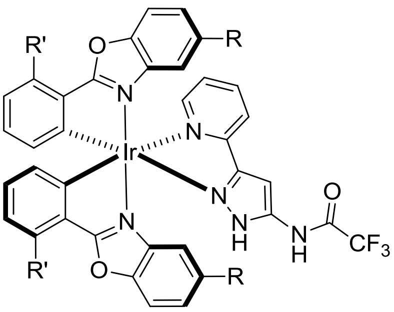
[286] Kastl, R.; Wennemers, H. *Angew. Chem. Int. Ed*. **2013**, *52*, 7228–7232.

cyclic enone to α-phenyl β-nitroacrylate via dienamine catalysis promoted by 6′-hydroxy-9-amino-9-deoxyepiquinine **C60** with moderate yield but good enantioselectivity (Scheme 63, f).[287]

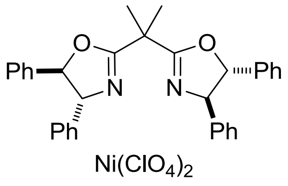


C-centered pronucleophiles:

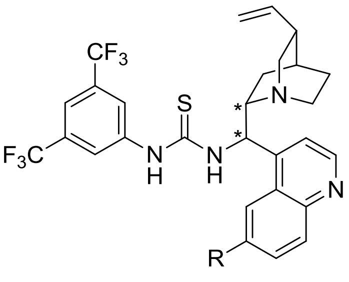
a) 	Meggers, **2013**[281] **C54** (1 mol %) 72–97% 93–98% *ee*	Jia, **2014**[282] **C55** (1 mol %) 87–98% 88–97% *ee*	d) 	Jørgensen, **2012**[285] **C58** (2 mol %) 96% 92% *ee*
b) 	Bencivenni, **2015**[283] **C56** (20 mol %) 50–87% >99:1 dr >99:1 *ee*		e) 	Wennemers, **2013**[286] **C59** (10 mol %) 72–90% 3:1–10:1 dr 89–97% *ee*
c) 	Hu & Zhao, **2015**[284] **C57** (10 mol %) 70–98% 73–93% *ee*		f) 	Melchiorre, **2010**[287] **C60** (30 mol %) 58% 90% *ee*



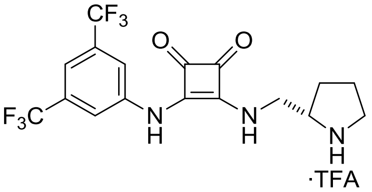
C54 R = CONEt$_2$ R' = *N*-carbazolyl



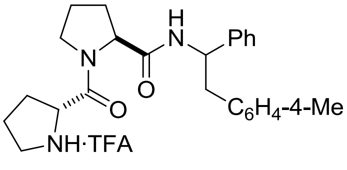
C55



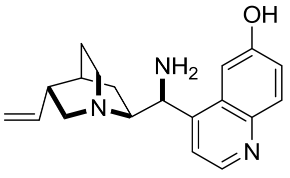
C56 R = OH (*S*,*S*)
C57 R = H (*R*,*R*)



C58



C59



C60

Scheme 63. Different *C*-centered pronucleophiles employed in the Michael addition to β-nitroacrylates for the enantioselective synthesis of $\beta^{2,2}$-amino acids.

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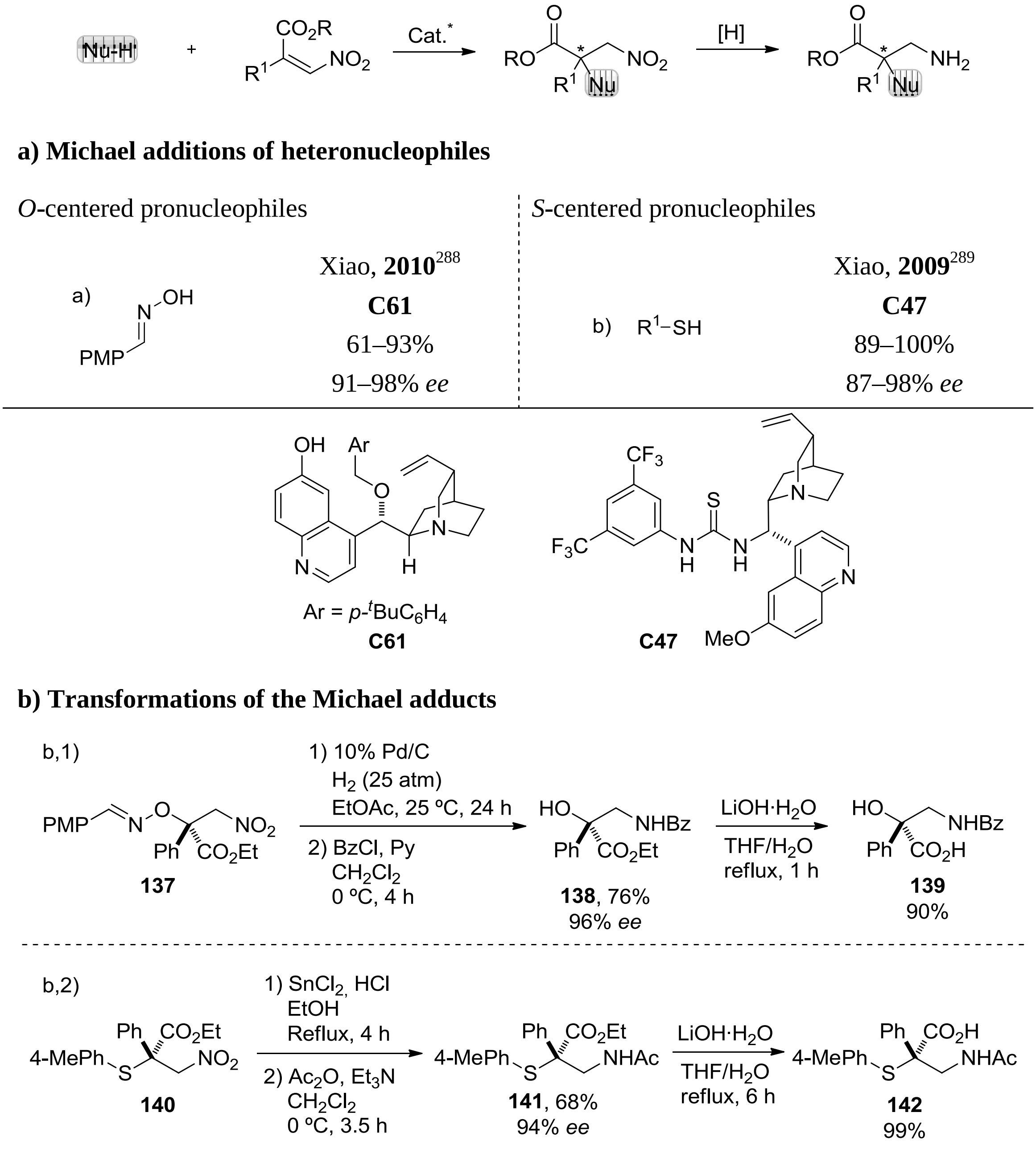
[287] Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *PNAS* **2010**, *107*, 20642–20647.

This strategy has been extended to other heteronucleophiles (Scheme 64, a). More specifically, oximes[288] and thiols[289] have also been used as pronucleophiles in the Michael addition to β-nitroacrylates promoted by the bifunctional thiourea **C61** and the cinchona alkaloid **C47** generating tetrasubstituted stereocenters with high enantioselectivity.



Scheme 64. a) Different *O*- and *S*-centered pronucleophiles employed in the Michael addition to β-nitroacrylates for the enantioselective synthesis of $\beta^{2,2}$-amino acids. b) Transformation of the Michael adducts into $\beta^{2,2}$-amino acids. **Xiao, 2009–2010**.

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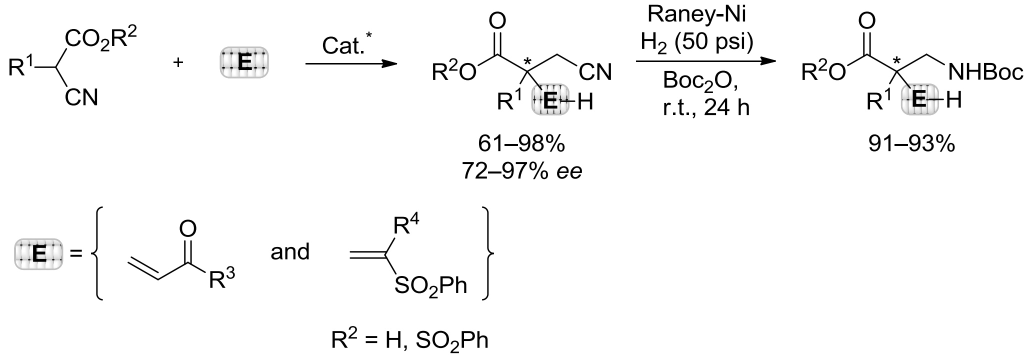
[288] Zhang, F.-G.; Yang, Q.-Q.; Xuan, J.; Lu, H.-H.; Duan, S.-W.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 5636–5639.

[289] Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946–3949.

The addition adducts from these type of heteronucleophiles are valuable building blocks as they are highly functionalized. For example, cleavage of the weak *N–O* bond and simultaneous reduction of the nitro group under mild condition with 10% $Pd/C/H_2$ afforded α-hydroxy β-amino ester **138** (Scheme 64, b, 1).[288] Subsequent protection with benzoyl chloride and hydrolysis of the ester group provided the $\beta^{2,2}$-amino acid derivative **139**. In a similar way, the corresponding *p*-tolylthio $\beta^{2,2}$-amino acids **142** were obtained through a three-step sequence which involves nitro-reduction/amine acylation/ester hydrolysis in high yield and with retention of optical purity (Scheme 64, b, 2).[289]

Another strategy for the enantioselective production of $\beta^{2,2}$-amino acids is the Michael addition of α-substituted cyanoacetates to different electrophiles (Scheme 65). In this case, the corresponding adducts can also be hydrogenated to give the corresponding $\beta^{2,2}$-amino derivatives. As previously exposed in Chapter 2, Chen reported the addition of this type of pronucleophiles to vinyl ketones[290] and vinyl sulfones;[291] however, the strategy is limited to the more reactive α-aryl cyanoacetates.



Scheme 65. Michael addition of α-substituted cyanoacetates to vinyl ketones and vinyl sulfones for the synthesis of $\beta^{2,2}$-amino acids. **Chen, 2006**–**2007**.

A further approach is the Henry reaction of nitromethane to various α-keto esters which gives access to enantioenriched β-nitro-α-hydroxy esters (Table 11). The latter compounds can be easily transformed into β-amino-α-hydroxy esters by a simple hydrogenation. Several groups have described this reaction promoted by metal-based and organocatalysts. For instance, Jørgensen employed copper (II) triflate salt in combination with the chiral bisoxazoline ligand **C62** to afford adducts in yields and enantioselectivities from moderate to excellent (Table 11, a).[292] Later, Blay and Pedro changed the ligand to iminopyridines; however, little improvement was observed in the

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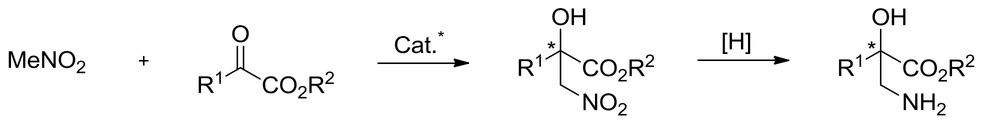
[290] See ref. 222.

[291] See ref. 210.

[292] Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881.

results (Table 11, b).[293] Sohtome and Nagasawa obtained similar results with the thiourea-guanidine bifunctional organocatalyst **C64** (Table 11, c);[294] but Deng made a substantial progress in this reaction observing excellent yields and enantioselectivities with all alkyl and aryl substituted α-ketoesters in the presence of the cinchona alkaloid **C65** as catalyst (Table 11, d).[295]

Table 11. Enantioselective Henry reaction of nitromethane with α-keto esters for the synthesis of $\beta^{2,2}$-amino acids promoted by different catalysts.



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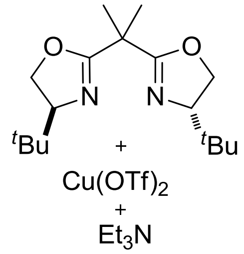
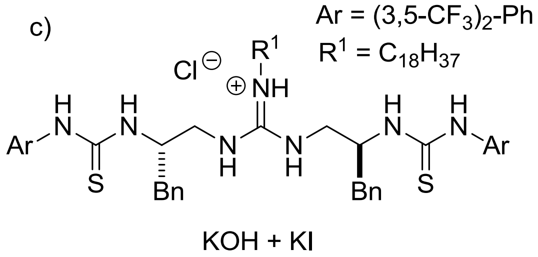
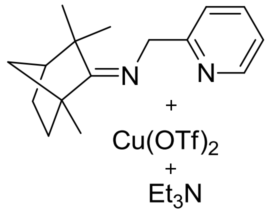
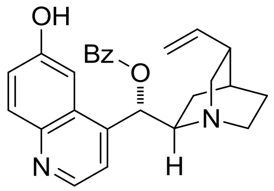


C62
Jørgensen, **2002**[292]
47–99%
57–94% *ee*</td><td>c)


C64
Sohtome & Nagasawa, **2008**[294]
60–90%
78–93% *ee*</td></tr>
<tr><td>b)


C63
Blay & Pedro, **2008**[293]
73–99%
52–82% *ee*</td><td>d)


C65
Deng, **2006**[295]
86–98%
93–97% *ee*</td></tr>
</table>

Finally, Johnson developed an asymmetric cyanation/1,2-Brook rearrangement/*C*-acylation reaction of acylsilanes with cyanoformates catalyzed by the

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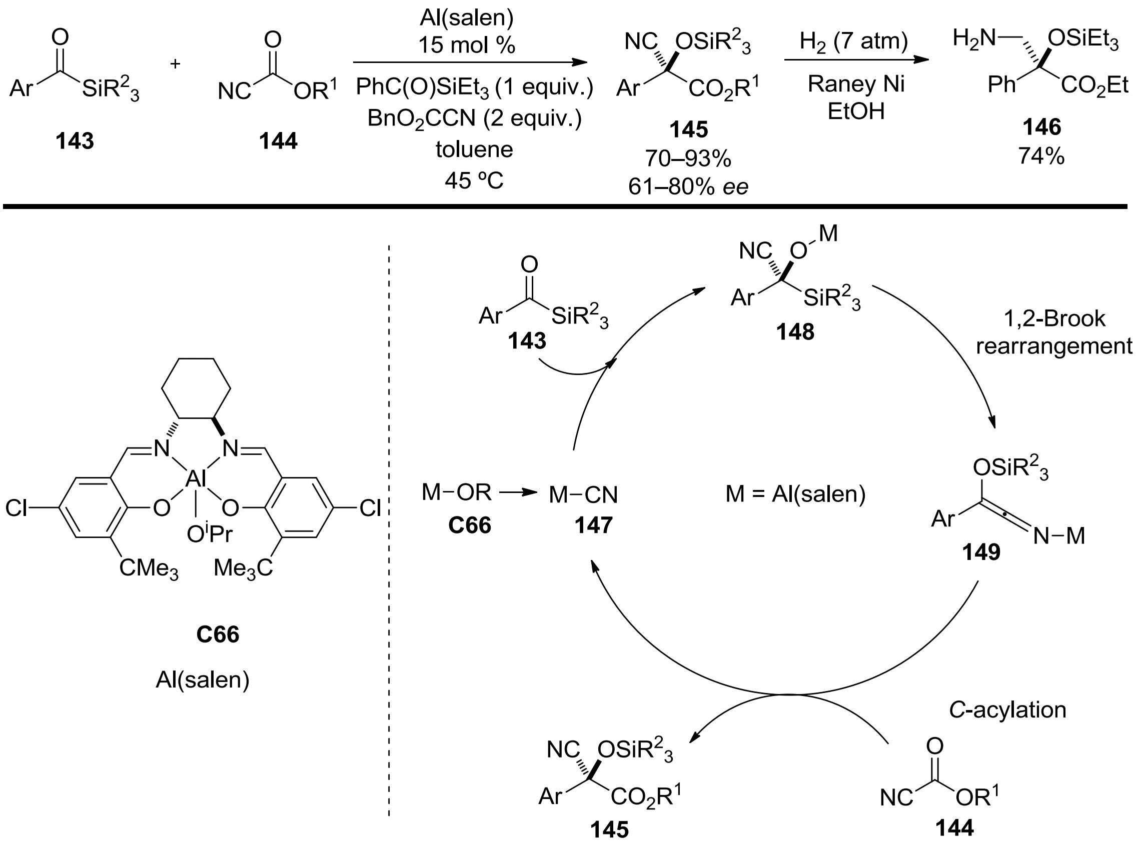
[293] Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Biomol. Chem.* **2008**, *6*, 468–476.

[294] Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623–1626.

[295] Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733.

(salen)aluminum alkoxide **C66** (Scheme 66).[296] ^{1}H-NMR spectroscopy suggests that the metal alkoxide **C66** reacts with benzyl cyanoformate to form the catalytically active (cyano)aluminum complex **147** which would react with acylsilanes **143** generating protected cyanohydrins anions **148**. Then 1,2-Brook rearrangement would provide species **149** which after subsequent *C*-acylation with cyanoformate **144** would led to the adduct **145**, precursor of $\beta^{2,2}$-amino-α-hydroxy esters.



Scheme 66. Catalytic asymmetric acylation of (silyloxy)nitrile anions to provide masked α-hydroxy α-substituted $\beta^{2,2}$-amino esters. **Johnson, 2004**.

Besides the narrow range of enantioselective methods for the synthesis of $\beta^{2,2}$-amino acids, there is also the fact that the common tactic for the incorporation and/or derivatization of $\beta^{2,2}$-amino acids into peptide segments involves *N*-protection, subsequent carboxyl group activation and final coupling (Scheme 67, a), thus complicating somewhat the process. In this context, β-amino acid *N*-carboxyanhydrides constitute a very attractive option as they offer simultaneously *N*-protection and carboxyl group activation (Scheme 67, b). To follow this strategy $\beta^{2,2}$-amino acids have to be transformed into the corresponding *N*-carboxyanhydrides.

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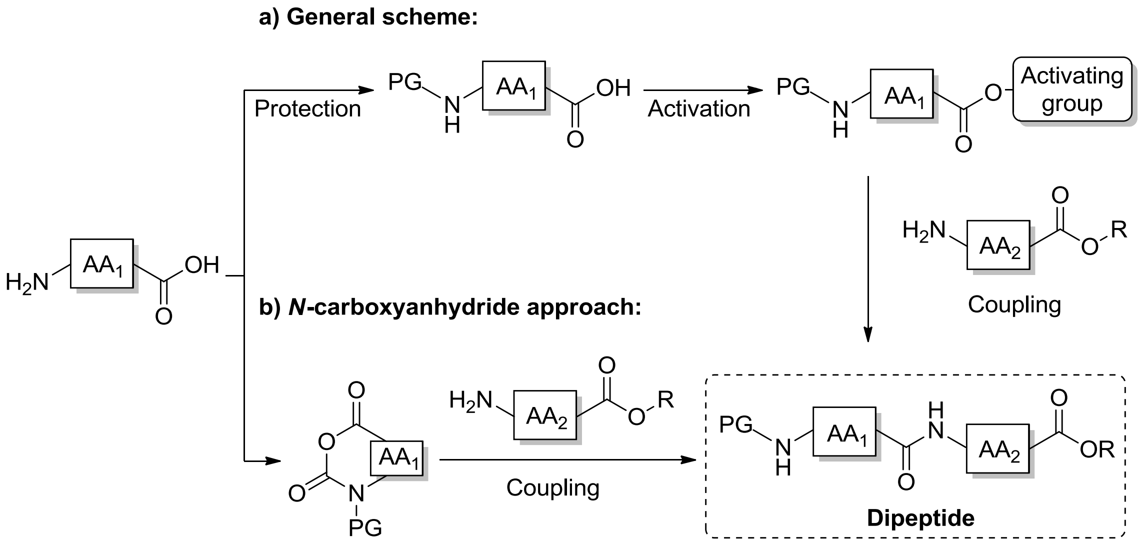
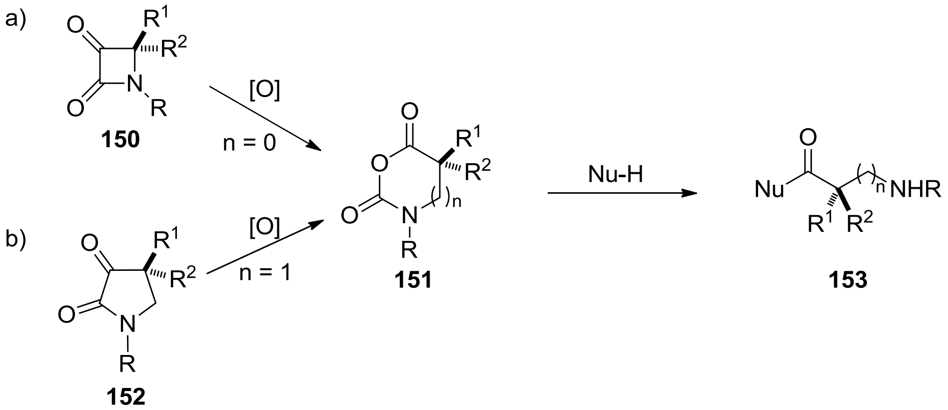
[296] Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem. Int. Ed*. **2004**, *43*, 2652–2655.



Scheme 67. a) General scheme for the incorporation and/or derivatization of amino acids into peptidic sequences and b) *N*-carboxyanhydride approach.

Our group has previously synthesized directly β-amino acid *N*-carboxyanhydrides of type **151** containing a quaternary stereocenter starting from disubstituted β-lactams of type **150** (Scheme 68, a).[297] This protocol provides an attractive and short route for the incorporation of $\beta^{2,2}$-amino acids into peptides. On this basis, we considered 4,4-disubstituted pyrrolidin-2,3-diones **152** could be suitable substrates for this purpose (Scheme 68, b). Therefore, an enantioselective protocol for the synthesis of 4,4-disubstituted pyrrolidin-2,3-diones would be required.



Scheme 68. a) Previous work for the synthesis of $\beta^{2,2}$-amino acid *N*-carboxyanhydrides from β-lactams and b) Approach for the synthesis of $\beta^{2,2}$-amino acid *N*-carboxyanhydrides from pyrrolidin-2,3-diones.

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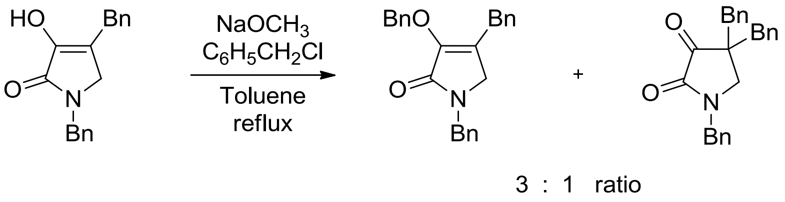
[297] For a review on the use of β-lactams in α- and β-amino acid synthesis, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, *12*, 1813–1826.

3.4. Synthetic plan

Catalytic enantioselective construction of pyrrolidin-2,3-diones with an all-carbon quaternary stereocenter at *C*-4 is an objective still unrealized. Probably, one reason that justifies this situation is that the alkylation reaction of pyrrolidin-2,3-diones by alkyl halides provides mainly *O*-alkylated products (Scheme 69).[298] Experiments carried out by Southwick and Barnas demonstrated that sodium enolates obtained from the 4-benzyl-pyrrolidin-2,3-diones give a mixture of 3:1 of *O*-alkylated and *C*-alkylated products.



Scheme 69. Alkylation reaction of sodium enolates of 4-substituted pyrrolidin-2,3-diones providing both *O*- and *C*-alkylation products.

Experimental data (IR and NMR analysis) corroborate that 4-substituted pyrrolidin-2,3-diones are enolized to a large extent as will be explained later. On this basis, we hypothesized that in the presence of a chiral Brønsted base the reaction of these substrates with an appropriate Michael acceptor would proceed to give *C*-4-dialkyl derivatives otherwise inaccessible through direct reaction with the corresponding alkyl halides (Scheme 70, a). It was also expected that any background racemic reaction should be suppressed by the proper choice of the catalyst. Additionally, Baeyer-Villiger oxidation of Michael products would give *N*-carboxyanhydrides and after subsequent coupling with a nucleophile β-amino acids, esters or amides. (Scheme 70, b).

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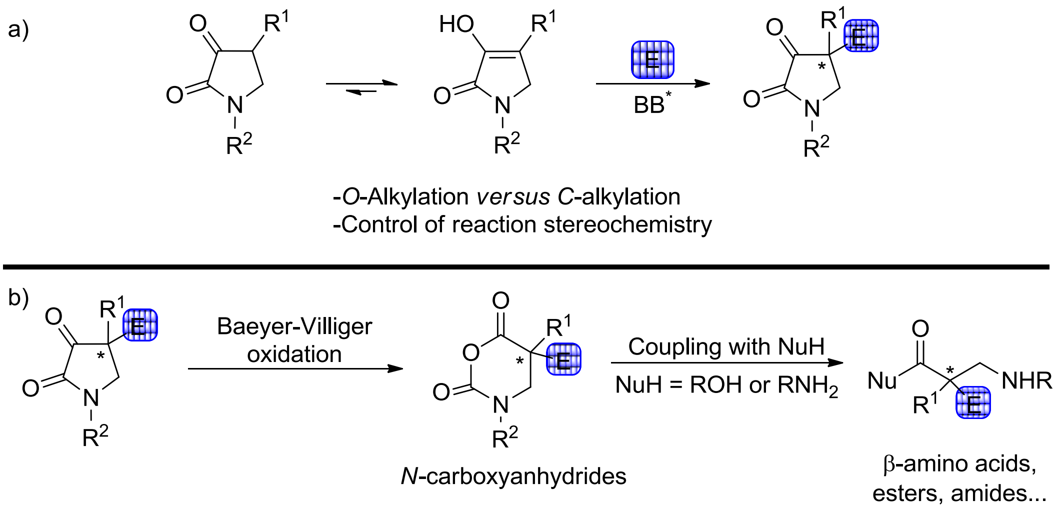
[298] Southwick, P. L.; Barnas, E. F. *J. Org. Chem.* **1962**, *27*, 98–106.

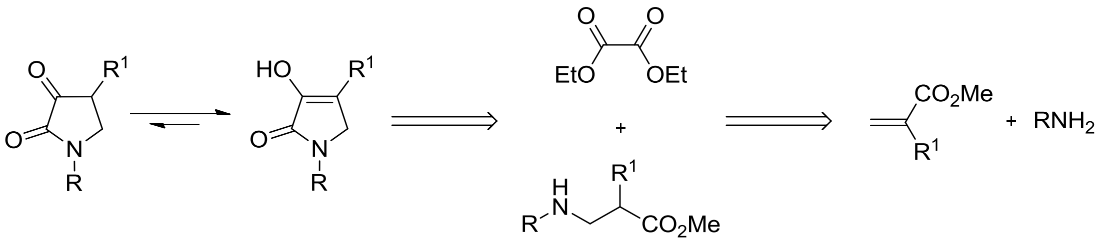


Scheme 70. a) Current challenges in the asymmetric reaction of 4-substituted pyrrolidin-2,3-diones. b) Transformation of the Michael adducts into $\beta^{2,2}$-amino acid derivatives.

This constitutes a part of a more general project in our group on the potential of 4-substituted pyrrolidin-2,3-diones as new pronucleophiles in the realm of asymmetric catalysis. In the following sections the preliminary results of this study are presented and further investigations are currently underway in our laboratory.

3.5. General synthesis of pyrrolidin-2,3-diones

The synthesis of 2,3-pyrrolidin-2,3-diones was outlined according to the following retrosynthetic scheme (Scheme 71).



Scheme 71. Retrosynthetic scheme of pyrrolidin-2,3-diones.

This synthetic procedure was previously described in the literature for non-substituted pyrrolidin-2,3-diones (Scheme 72, a).[299] The first step of the proposal is the reaction of the corresponding β-amino ester with ethyl oxalate followed by an *in situ* decarboxylation. The conjugate addition of the corresponding amine to the α-substituted acrylate was considered for the preparation of the β-amino esters (Scheme 72, b).

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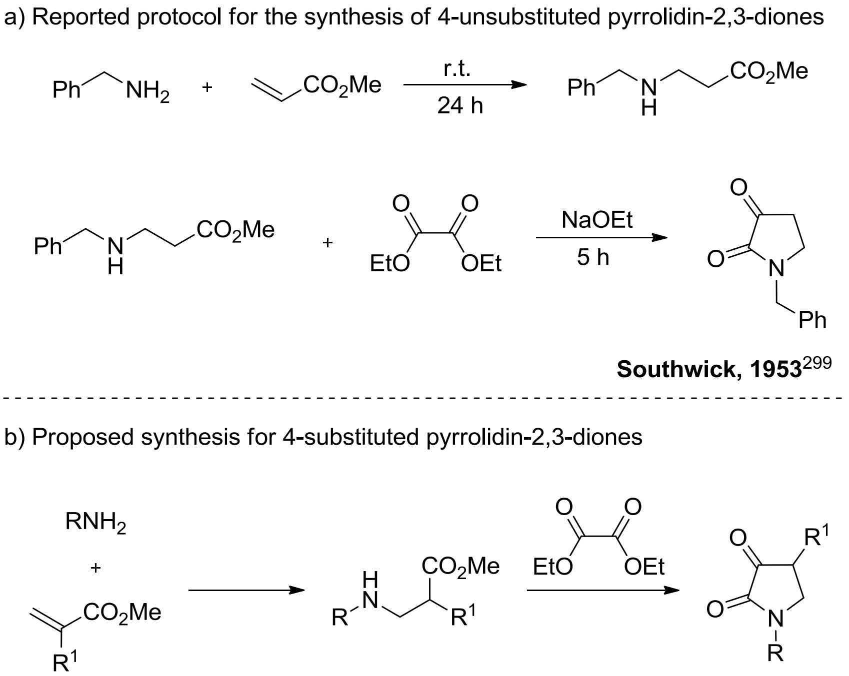
[299] Southwick, P. L.; Crouch, R. T. *J. Am. Chem. Soc.* **1953**, *75*, 3413–3417.



Scheme 72. a) Reported protocol for the synthesis of 1-benzylpyrrolidine-2,3-dione and b) proposed synthesis for 4-substituted pyrrolidin-2,3-diones.

Thus, in a first instance we focused on the preparation of both α-alkyl and aryl acrylates according to the procedure outlined below.

3.5.1. Preparation of acrylates

α-Substituted methyl acrylates were synthesized following protocols described in the literature. Two different synthetic approaches were considered for alkyl and aryl substituted acrylates. The formers were prepared via retro-Claisen reaction of the corresponding β-keto derivatives **155** and these were synthesized by methyl acetoacetate **154** alkylation (Scheme 73).[300] Methyl methacrylate **156a** is commercially available and the yields of the synthesized α-alkyl acrylates are summarized in Scheme 73.

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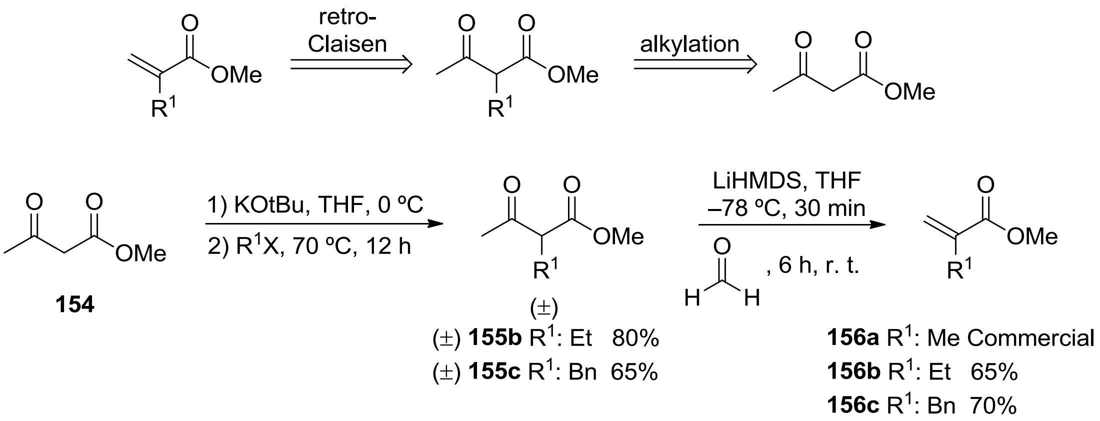
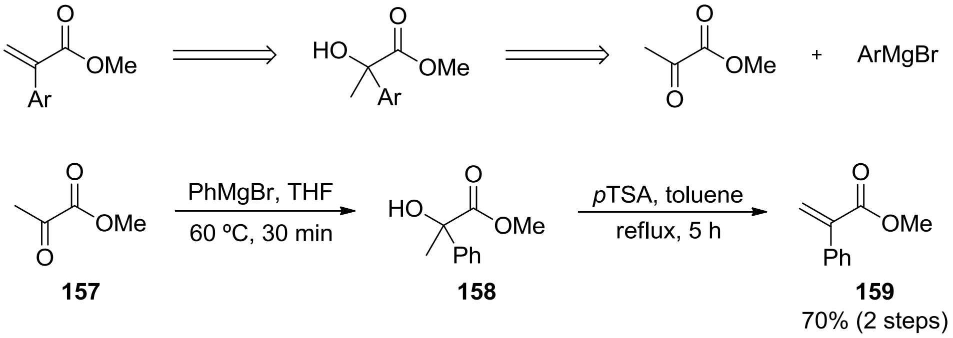
[300] Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812–2825.



Scheme 73. Retrosynthesis and synthetic procedure for the preparation of α-alkyl substituted acrylates.

α-Susbtituted aryl acrylates can be obtained through the addition of the corresponding Grignard reagent to methyl pyruvate **157**.[300] Reaction conditions for the synthesis of the α-phenyl acrylate **159** are described in Scheme 74, which was obtained in 70% yield over the two steps.



Scheme 74. Retrosynthesis and synthetic procedure for the preparation of α-aryl substituted acrylates.

3.5.2. Preparation of β-amino esters

β-Amino esters were synthesized via the addition of the corresponding amine to the α-substituted acrylate (Table 12). Initially the reactions were performed in the presence of manganese chloride (Table 12, method A).[301] Under these conditions β-amino esters **22Aa**, **22Ac**, **22Ae**, **22Ba** and **22Ca** were obtained in good yields (entries 1–5). However, under the same conditions isopropyl amine did not react. In this case, the use of ruthenium (III) chloride as catalyst and polyethylene glycol as solvent provided better results (entry 6).[302]

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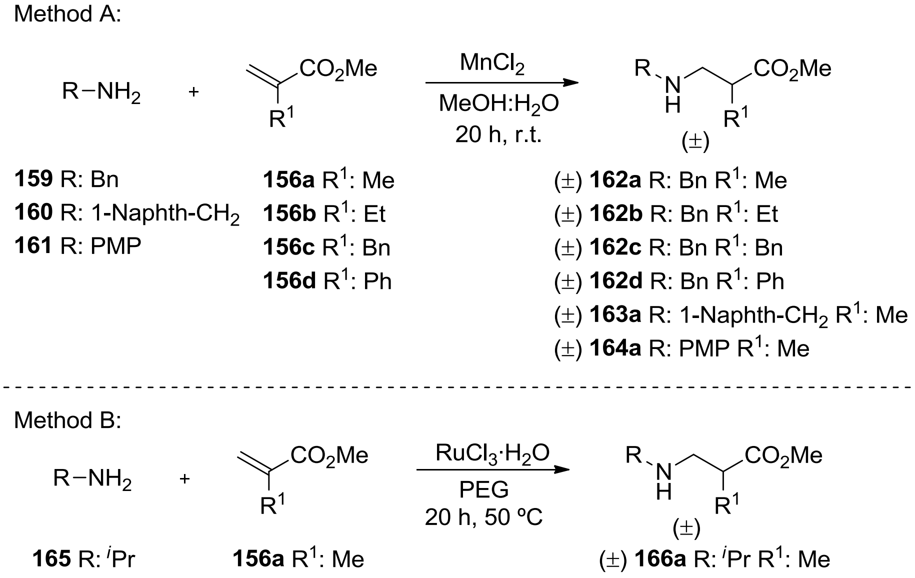
[301] Roy, A.; Kundu, D.; Kundu, S. K.; Majee, A.; Hajra, A. *Open Catal. J.* **2010**, *3*, 34–39.

[302] Zhang, H.; Zhang, Y.; Liu, L.; Xu, H.; Wang, Y. *Synthesis* **2005**, *13*, 2129–2136.

Table 12. Preparation of β-amino esters.[a]



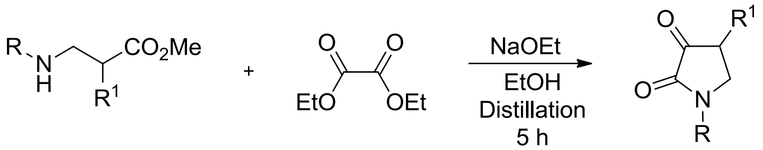
Entry	Product	Method	R	R^1	Yield (%)
1	**162a**	A	Bn	Me	80
2	**162b**	A	Bn	Et	65
3	**162c**	A	Bn	Bn	61
4	**162d**	A	Bn	Ph	92
5	**163a**	A	1-Naphth-CH_2	Me	58
6	**164a**	A	PMP	Me	60
7	**166a**	B	^{i}Pr	Me	76

Method A:[301] A mixture of the amine (1 equiv.) and the acrylate (1 equiv.) was stirred in the presence of $MnCl_2$ (10 mol%) in $MeOH:H_2O$ (1:1) at room temperature for 20 h. Method B:[302] A mixture of the amine (1 equiv.) and the acrylate (1.5 equiv.) was stirred in the presence of $RuCl_3·H_2O$ (5 mol%) in PEG (average Mw 2000) at 50 ºC for 24 h.

3.5.3. Cyclization/decarboxylation reaction

Pyrrolidin-2,3-diones were synthesized by reaction of the β-amino esters with ethyl oxalate in the presence of sodium ethoxide in absolute ethanol.[299] Ethanol is distilled to facilitate cyclization and decarboxylation occurs simultaneously in these reaction conditions affording the cyclic addults from good to excellent yields (Table 13).

Table 13. Cyclization reaction for the formation of pyrrolidin-2,3-diones.[a]



(±) **162a** R: Bn R^1: Me
(±) **162b** R: Bn R^1: Et
(±) **162c** R: Bn R^1: Bn
(±) **162d** R: Bn R^1: Ph
(±) **163a** R: 1-Naphth-CH_2 R^1: Me
(±) **164a** R: PMP R^1: Me
(±) **166a** R: ^{i}Pr R^1: Me

167

(±) **168a** R: Bn R^1: Me
(±) **168b** R: Bn R^1: Et
(±) **168c** R: Bn R^1: Bn
(±) **168d** R: Bn R^1: Ph
(±) **169a** R: 1-Naphth-CH_2 R^1: Me
(±) **170a** R: PMP R^1: Me
(±) **171a** R: ^{i}Pr R^1: Me

Entry	Product	R	R^1	Yield (%)
1	**168a**	Bn	Me	86
2	**168b**	Bn	Et	65
3	**168c**	Bn	Bn	93
4	**168d**	Bn	Ph	92
5	**169a**	1-Naphth-CH_2	Me	65
6	**170a**	PMP	Me	71
7	**171a**	^{i}Pr	Me	80

[a]A solution of the β-amino ester (1 equiv.) and ethyl oxalate (1.2 equiv.) in EtOH was added to a solution of NaOEt (1.2 equiv.) in EtOH. The ethanol was removed by distillation.

Previous studies by Southwick and Barnas, supported by IR spectroscopy showed that 4-substituted pyrrolidin-2,3-diones are fully enolized.[298] This was also corroborated by IR analysis of our synthesized pyrrolidin-2,3-diones. Infrared spectrum of non-substituted pyrrolidin-2,3-dione **172** shows two bands of *C*=*O* stretch related to the ketone and the amide (Figure 34). However, the presence of the OH stretch and the lack of *C*=*O* stretch in the spectrum of 4-methyl substituted compound **168a** explains the tendency to enolization of these compounds. Further support it is also given by the ^{1}H-NMR spectrum of compound **168a**, which shows that the compound is fully enolized (Figure 35).

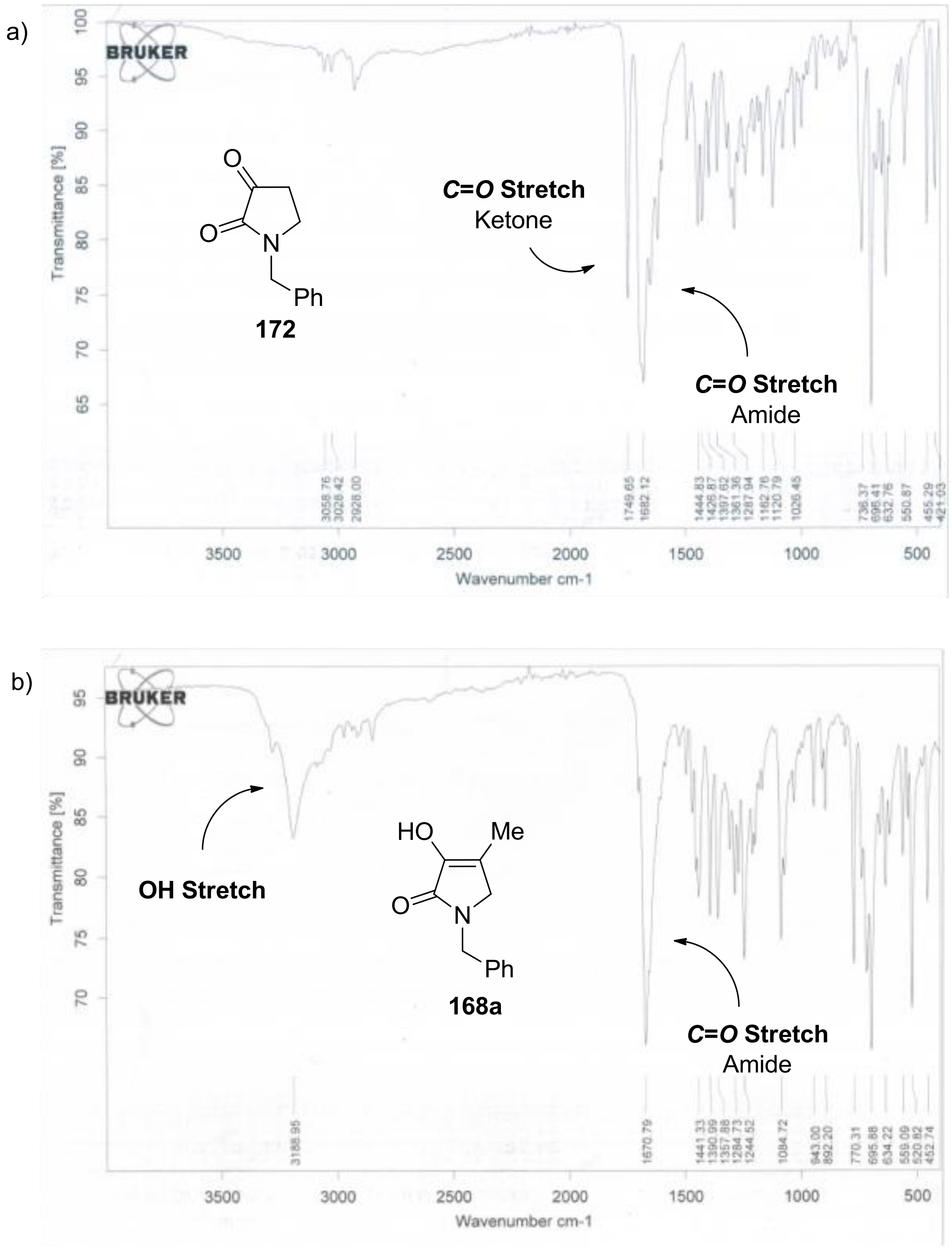


Figure 34. IR spetra of pyrrolidin-2,3-diones: a) *C*-4 unsubstituted pyrrolidin-2,3-dione **172**. b) 4-Methyl pyrrolidin-2,3-dione **168a**.

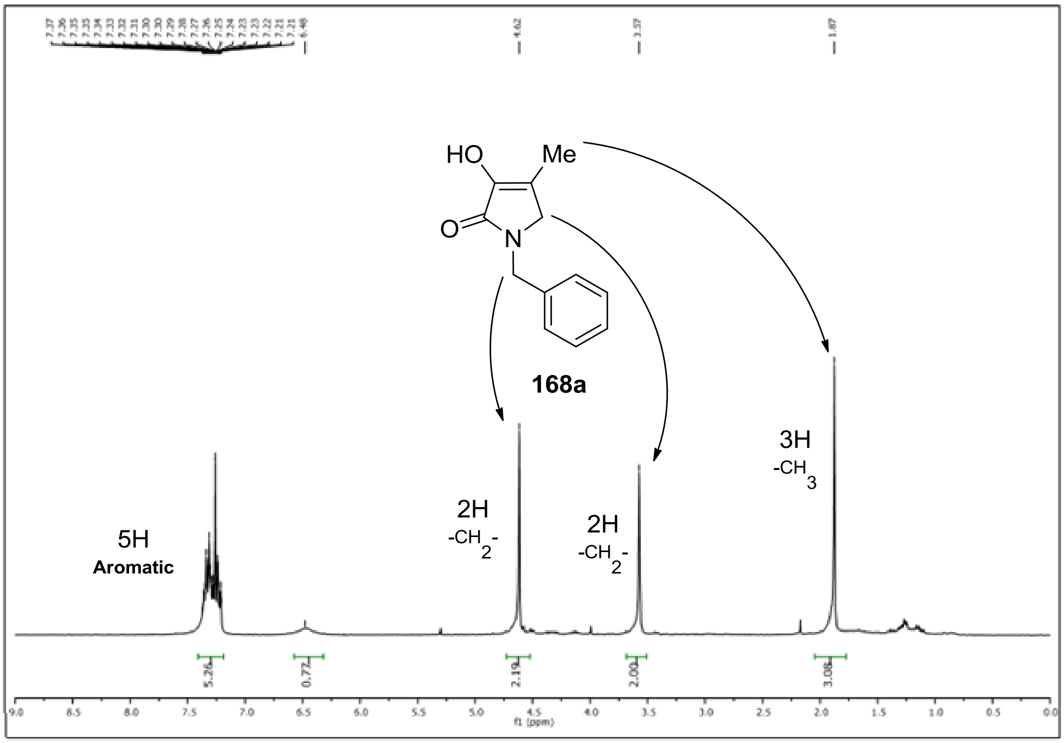
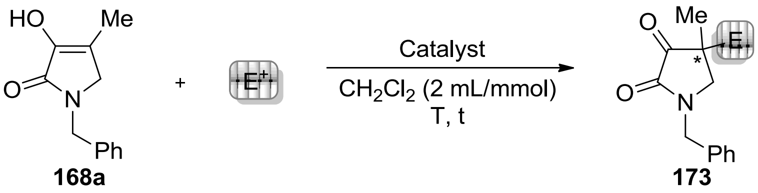


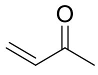
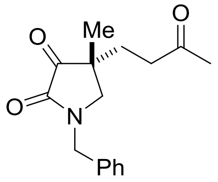
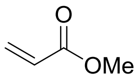
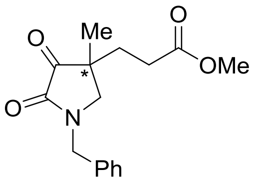
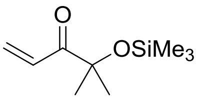
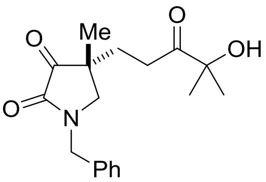
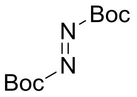
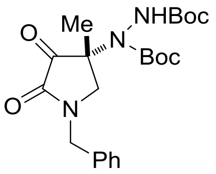
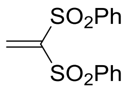
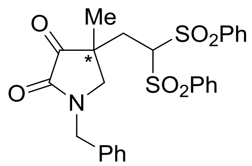
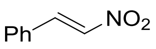
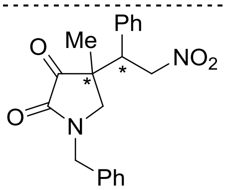
Figure 35. ^{1}H-NMR spectrum of 4-methyl pyrrolidin-2,3-dione **168a**.

3.6. Results and discussion

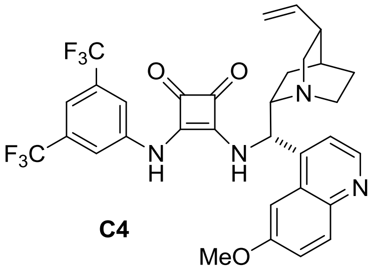
We began our study by exploring the reaction of *N*-benzyl 4-methyl pyrrolidin-2,3-dione **168a** with different electrophiles promoted by the Brønsted base catalysts **C4** and **C67** (Table 14). For that purpose methyl vinyl ketone, methyl acrylate, α'-hydroxy enone, di-*tert*-butyl azodicarboxylate, 1,1-bis(phenylsulfonyl)ethylene and nitrostyrene were selected. The corresponding results are shown in Table 14. The conjugate addition to methyl vinyl ketone in the presence of **C4** at –10 ºC provided after 16 h the corresponding adduct in full conversion, good yield and excellent enantioselectivity (Table 14, entry 1). However, only 50% of conversion was observed with methyl acrylate as Michael acceptor and catalyst **C4** at room temperature in 24 h (Table 14, entry 2). This result corroborates once more the lower reactivity of acrylates as Michael acceptors in these reactions. In view of the good results obtained in Chapter 2 with α'-oxy enones as ester surrogates, we also checked the reaction with these acceptors, which after 16 h at –10 ºC in the presence of catalyst **C4** reacted in total conversion, good yield and excellent enantioselectivity (Table 14, entry 3). The α-amination of these substrates was also checked with di-*tert*-butyl azodicarboxylates. A rapid reaction was observed even at –40 ºC catalyzed by **C4** providing in 1 h the adduct in high yield and enantioselectivity (Table 14, entry 4). Moreover, the Michael addition to vinyl (bis)sulfone showed this to be a reactive acceptor, nevertheless, the adduct was afforded with lower enantiomeric excess (Table 14, entry 5). Finally, the reaction of pyrrolidin-2,3-dione and nitrostyrene was carried out in the presence of **C67**, which was available in the laboratory and belongs to a family of catalysts recently developed in our group. The corresponding Michael adducts were obtained in good results (Table 14, entry 6).

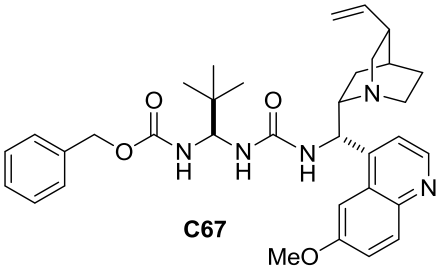
Table 14. Michael reaction of 4-methyl pyrrolidin-2,3-dione **168a** to different electrophiles.[a]



Entry	Electrophile	Catalyst	T (°C), t, Conv.[b] (%)	Product	Results
1	 2 equiv.	**C4** (10 mol %)	–10 °C, 16 h, 100%		75% 92% *ee*
2	 2 equiv.	**C4** (10 mol %)	r.t., 24 h, 50%		Yield n.d. *ee* n.d.
3	 3 equiv.	**C4** (20 mol %)	–10 °C, 16 h, 100%		60% 90% *ee*
4	 1.5 equiv.	**C4** (10 mol %)	–40 °C, 1 h, 100%		89% 94% *ee*
5	 1.2 equiv.	**C4** (10 mol %)	–60 °C, 30 min, 100%		93% 60% *ee*[c]
6	 1.5 equiv.	**C67** (20 mol %)	–60 °C, 40 h, 100%		65% 91:9 dr[c] 92% *ee*[c]

[a] Reaction conditions: **168a** (0.2 mmol), Michael acceptor (XX mmol) and the catalyst (10 or 20 mol %) in CH_2Cl_2 (0.4 mL). Yield of isolated products after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] Conversion related to the disappearance of the pyrrolidin-2,3-dione. [c] Absolute configuration not determined.

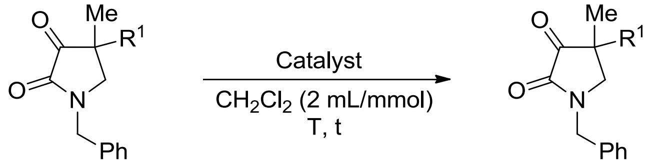

C4

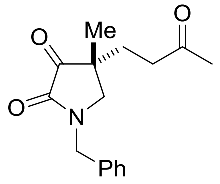
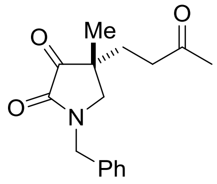
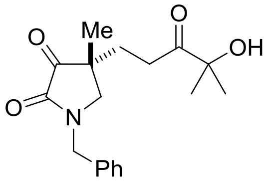
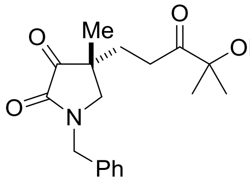
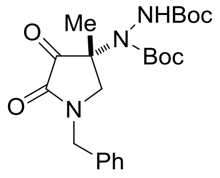
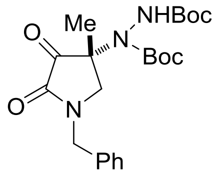
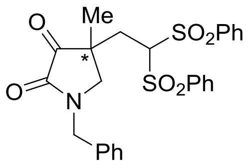
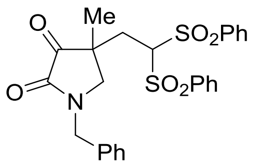
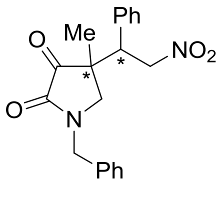
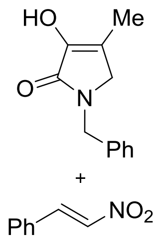

C67

We then envisaged that depending on the nature of the electrophile retro-addition could also occur. On this basis, the stability of the addition adducts previously obtained was studied under different conditions (Table 15). Adducts obtained from methyl vinyl ketone, α'-hydroxy enone and di-*tert*-butyl azodicarboxylate showed excellent stability in the presence of 10 mol % catalyst **C4** for 24 h at room temperature and no decrease in the enantioselectivity was observed in any case (Table 15, entries 1–3). However, after the treatment of the adduct coming from vinyl (bis)sulfone with catalyst **C4** for 2 h at room temperature, the enantioselectivity was considerably affected (from 60% *ee* to 12% *ee*) (Table 15, entry 4). This is an evidence of the racemisation of the adduct in the presence of the catalyst most probably due to the retro-Michael reaction. The same behavior was confirmed in the case of the adduct coming from the reaction with nitrostyrene since after treatment with TEA or acid silica only the starting materials were recovered (Table 15, entry 5).

These data clearly show that the selection of the appropriate electrophile for the Michael addition of 4-substituted pyrrolidin-2,3-diones is key for success, not only regarding reactivity and stereocontrol, but considering also the retro-addition probability. Therefore, first exploration of the Michael reaction was undertaken with methyl ketones, α'-oxy enones and azo-dicarboxylates as acceptors. The corresponding results are presented in the following sections.

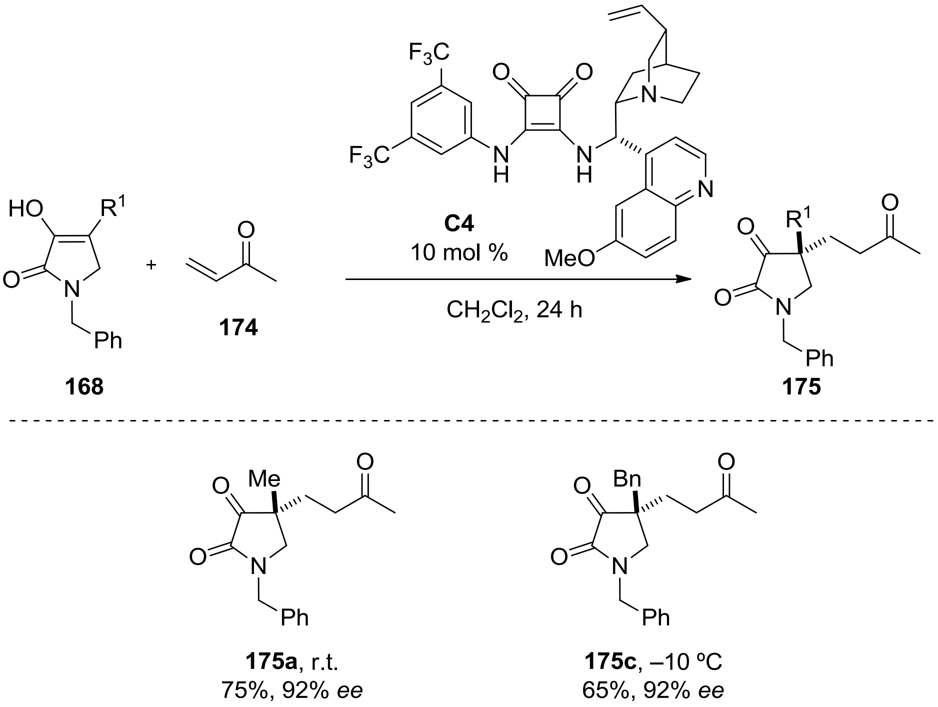
Table 15. Experiments carried out to check the stability of the addition adducts and retro-Michael reaction.



Entry	Adduct	Catalyst	T (ºC), t (h)	Results
1	 92% *ee*	**C4** (10 mol %)	r.t., 24 h	 92% *ee*
2	 86% *ee*	**C4** (10 mol %)	r.t., 24 h	 86% *ee*
3	 99% *ee*	**C4** (10 mol %)	r.t., 24 h	 99% *ee*
4	 60% *ee*	**C4** (10 mol %)	r.t., 2 h	 12% *ee*
5	 80% *ee*	Acid silica (Si$_2$O) TEA	r.t., 3 h r.t., 16 h	

3.6.1. Michael addition to methyl vinyl ketone and α'-oxy enones

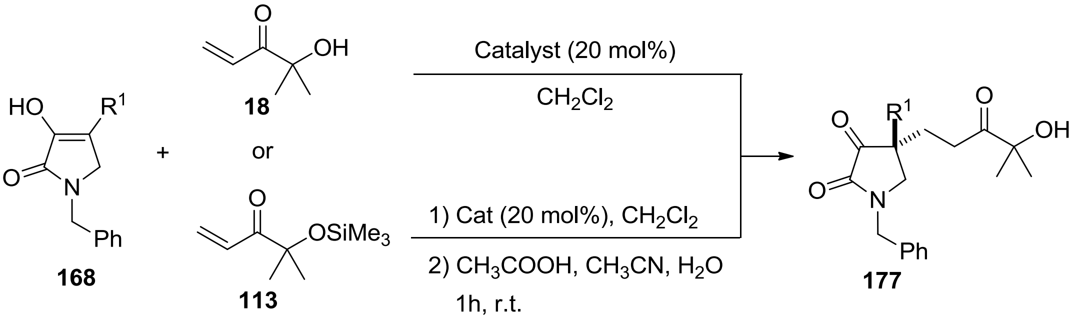
In a first instance, the reaction of pyrrolidin-2,3-diones **168** with methyl vinyl ketone **174** in the presence of catalyst **C4** was explored (Scheme 75). 4-Methyl and 4-benzyl substituted pronucleophiles **168a** and **168c** were reacted with 2 equiv. of the enone **174** in the presence of 10 mol % of catalyst in CH_2Cl_2. Full conversions were observed in both cases after 24 h and the adducts were obtained in good yield and excellent enantioselectivities. Further results from our group have shown that the reaction is equally efficient with other pyrrolin-2,3-diones and enones.

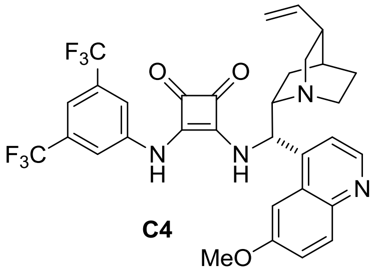


Scheme 75. Michael reaction of pyrrolidin-2,3-diones **168** with methyl vinyl ketone **174** promoted by catalyst **C4**.

After these preliminary results and taking into account the low conversion (50%) obtained in the Michael reaction of pyrrolidin-2,3-dione **168a** with methyl acrylate promoted by **C4** at room temperature in 24 h (Table 14, entry 2), the utility of α'-oxy enones as acrylate surrogates was thought to solve this reactivity problem. After examining several common bifunctional Brønsted bases, it was gratifying to observe that the best results were obtained with quinine derived squaramide catalyst **C4** and the silylated hydroxyl enone **113** (Table 16), although improvement was still needed. Enantioselectivity was measured in the desilylated adducts **177** and the same procedure for azlactones, acetic acid in acetonitrile and water for 1 h at room temperature, was applied for the desilylation.

Table 16. Catalyst screening for the conjugate addition of pyrrolidin-2,3-diones **168** to α’-oxy enones **18** and **113**[a].

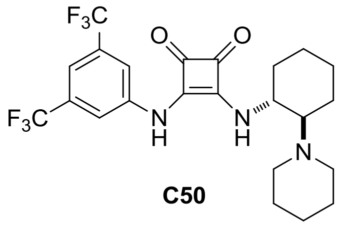




C4

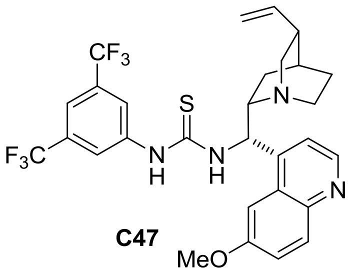
R^1 = Bn with **18**: –50 °C, 28% *ee*

R^1 = Bn with **113**: –10 °C, 84% *ee*



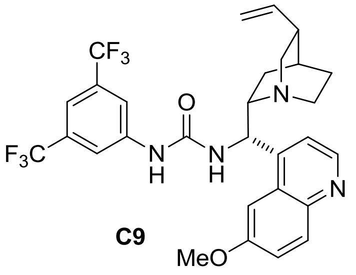
C50

R^1 = Bn with **113**: 0 °C, 24% *ee*



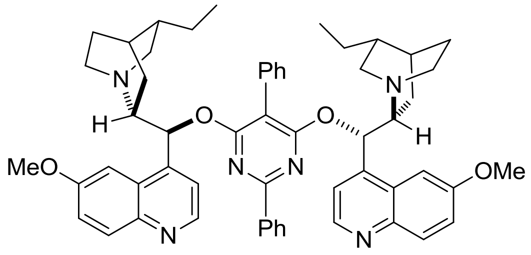
C47

R^1 = Me with **113**: –10 °C, 80% *ee*



C9

R^1 = Me with **113**: –10 °C, 70% *ee*



$(DHQD)_2PYR$, **C49**

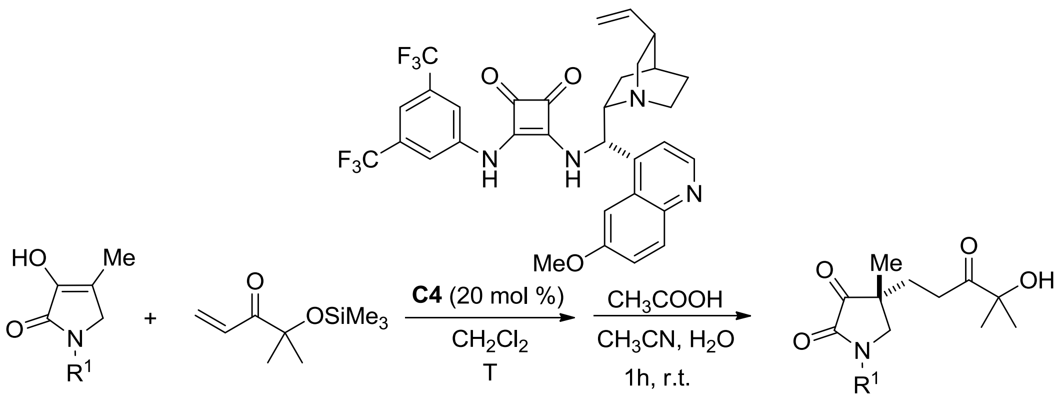
R^1 = Bn with **18**: –30 °C, 6% *ee*

---

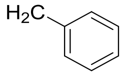
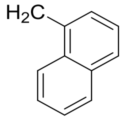
[a] Reaction conditions: **168** (0.3 mmol), enone (3 equiv., 0.9 mmol), catalyst (20 mol %, 0.06 mmol), in CH_2Cl_2 (0.9 mL). The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Then temperature screening was carried out with pyrrolidin-2,3-diones **168a** and **169a** in the presence of squaramide **C4** (Table 17). Optimal reaction temperature for substrate **168a** was found to be –10 ºC (90% *ee*, entry 2) because lower temperatures the enantiolectivity is depleted (86% *ee*, entry 3). However, with substrate **169a**, excellent enantioselectivities are obtained even at room temperature (90% *ee*, entry 4) and decreasing the temperature to –10 ºC the enantiomeric excess slightly improves (96% *ee*, entry 6).

Table 17. Temperature screening for the conjugate addition of pyrrolidin-2,3-diones **168a** and **169a** to α'-silyloxy enone **113**.[a]



168a, **169a** **113** **177**, **178**

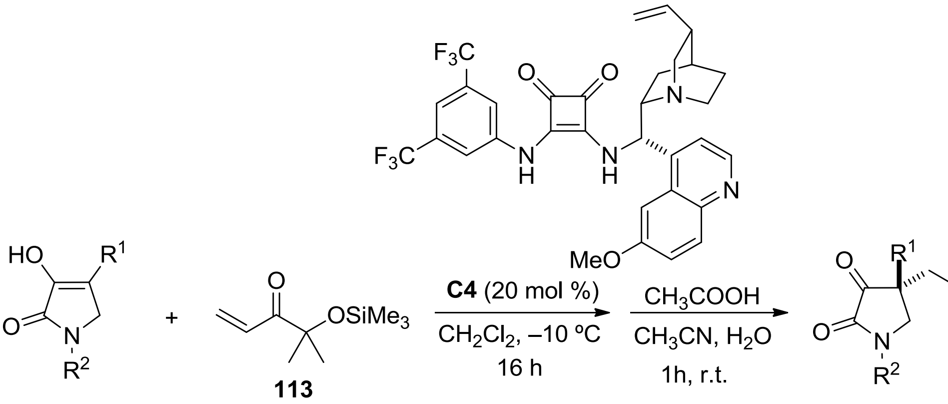
Entry	R^1	T	t (h)	Conv. (%)[b]	*ee*[c]
1		r.t.	16	100	80
2		–10	16	100	90
3	**168a**	–20	16	100	86
4		r.t.	16	100	90
5		0	16	100	92
6		–10	16	100	96
7	**169a**	–20	16	100	96

[a] Reaction conditions: **168a** or **169a** (0.3 mmol), **113** (3 equiv., 0.9 mmol) and catalyst **C4** (20 mol %, 0.06 mmol) in dichloromethane (0.6 mL). [b] Related to the disappearance of the starting material. [c] Determined by HPLC analysis on a chiral stationary phase.

For both substrates –10 ºC was chosen as optimal temperature and then the reaction scope was investigated with different pyrrolidin-2,3-dione derivatives. As Table 18 shows, after the conjugate addition and desylilation good yields and enantioselectivities were afforded with *N*-benzyl pyrrolidin-2,3-diones **168** and **169**. In the case of **168d** carrying a phenyl substituent at *C*-4 longer reaction times (40 h) are required for complete conversion. The reaction was more efficient with naphthalene-1-

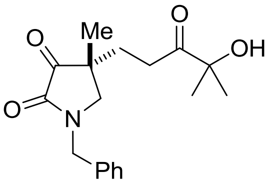
yl-methyl derivative **169a** providing the corresponding adduct **178a** in excellent yield and enantioselectivity.

Table 18. Pyrrolidin-2,3-diones reaction scope for the conjugate addition to α'-silyloxy enone **113**.[a]



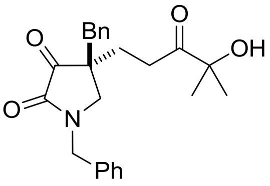
168a R^1 = Me R^2 = Bn
168c R^1 = Bn R^2 = Bn
168d R^1 = Ph R^2 = Bn
169a R^1 = CH_2-1-Napht R^2 = Me

177, 178



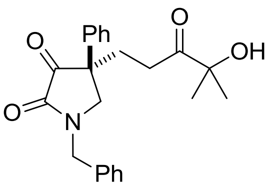
177a

74%, 90% *ee*



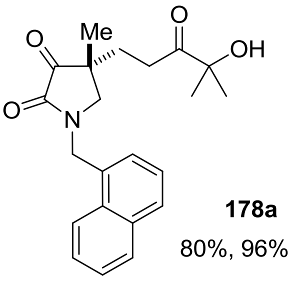
177c

70%, 84% *ee*



177d

60%, 80% *ee*



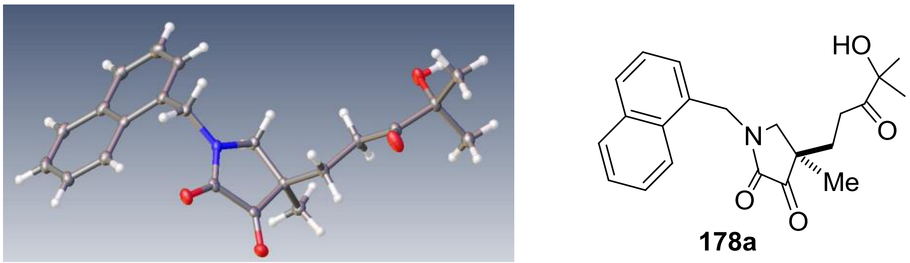
178a

80%, 96% *ee*

---

[a] Reaction conditions: **168** or **169** (0.3 mmol), **113** (3 equiv., 0.9 mmol) and catalyst **C4** (20 mol %, 0.06 mmol) in dichloromethane (0.6 mL). Enantioselectivities determined by HPLC analysis on a chiral stationary phase.

The absolute configuration was determined for compound **178a** by X-ray single crystal structure analysis and that of the remaining adducts was established by assuming a uniform reaction mechanism (Figure 36).



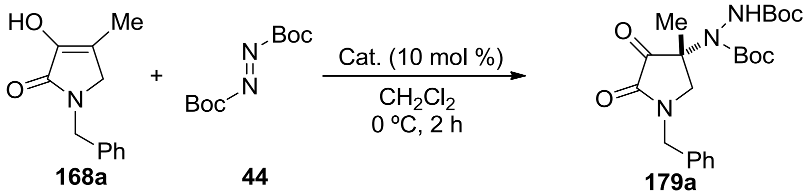
178a

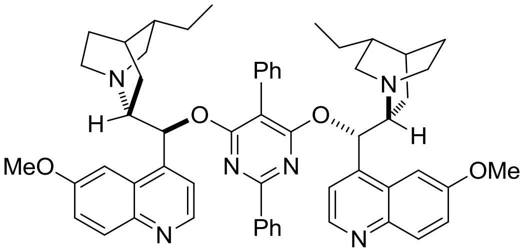
Figure 36. X-Ray structure for compound **178a**.

3.6.2. α-Amination of pyrrolidin-2,3-diones with *tert*-butyl azodicarboxylate

In order to demonstrate the efficiency of this type of pronucleophiles in Brønsted base catalysis, reaction of pyrrolidin-2,3-dione **168a** and *tert*-butyl azodicarboxylate **44** was carried out in presence of different bifunctional catalysts (Table 19). Once more, the best results were obtained with quinine derived squaramide catalyst **C4** with 1.5 equivalents of azodicarboxylate **44** at 0 ºC in dichloromethane and, in all cases, reaction conversions were completed in 2 h, but enantioselectivity still needed improvement.

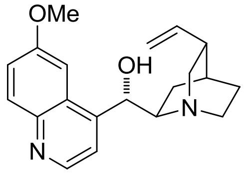
Table 19. Brønsted base catalyst screening for the reaction of pyrrolidin-2,3-dione **168a** and *tert*-butyl azodicarboxylate **44**.





(DHQD)$_2$PYR, **C49**

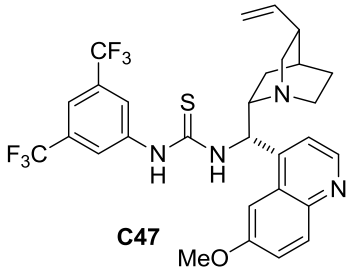
68% *ee*



C18

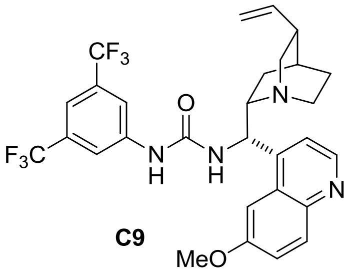
Quinine

–40% *ee*



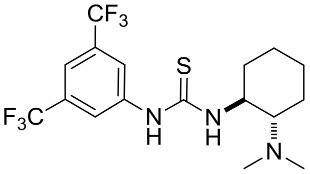
C47

16% *ee*



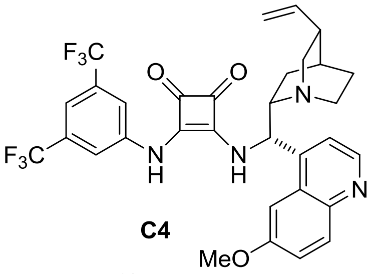
C9

20% *ee*



C2

–13% *ee*



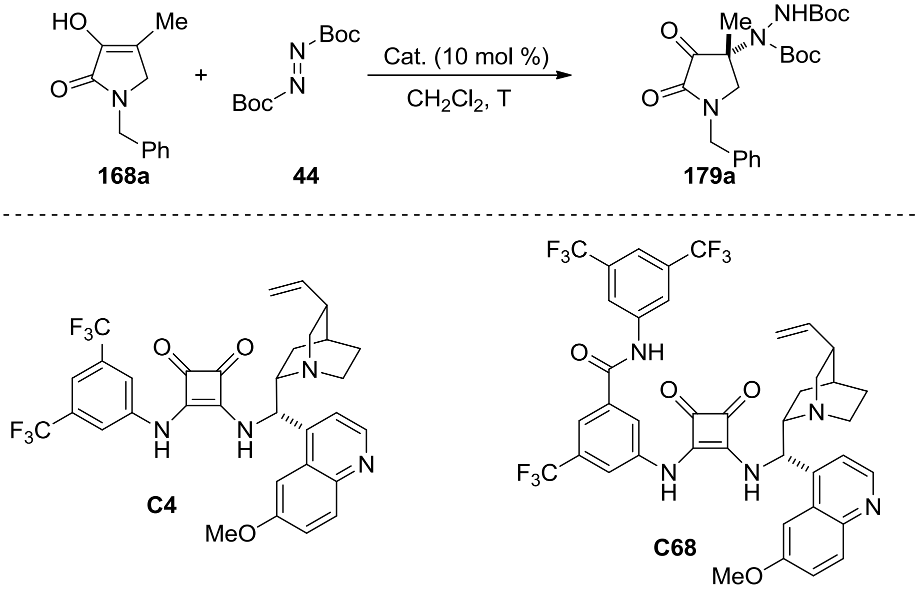
C4

80% *ee*

To a mixture of the α-ketoamide **168a** (41 mg, 0.2 mmol, 1 equiv.) and catalyst (0.02 mmol, 10 mol %) in dichloromethane (0.4 mL) at 0 °C, di-*tert*-butyl azodicarboxylate **44** (69 mg, 0.3 mmol, 1.5 equiv.) was added. The resulting mixture was stirred at the same temperature until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was directly purified by flash column chromatography on silica gel (eluent hexane/ ethyl acetate 80/20) without previous work-up to afford the expected adduct **179a**.

In this instance, we thought that a modification of the catalyst might improve the enantioselectivity value of 80% obtained with **C4**. Catalyst **C68**, which is easily affordable by tuning the carboxylic moiety, provided better results than catalyst **C4** (Table 20). Excellent enantioselectivities were obtained in all cases with catalyst **C68** changing the temperature from 0 ºC to –40 ºC, whilst with **C4** enantioselectivity gradually improved by decreasing temperature.

Table 20. Temperature screening for the reaction of 4-methyl pyrrolidin-2,3-diones **168a** and *tert*-butyl azodicarboxylate **44** catalyzed by **C4** and **C68**.

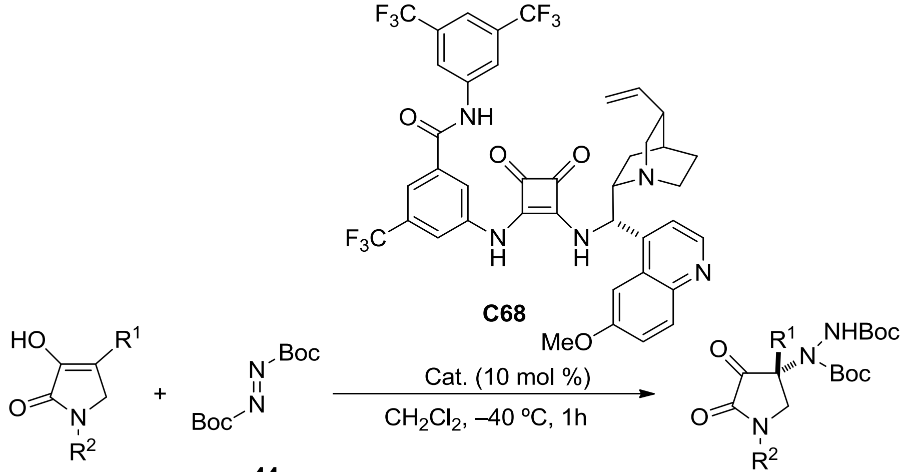


Entry	Catalyst	T (ºC)	t (h)	Conv. (%)	Yield (%)	*ee* (%)
1	**C1**	0	1	100	92	80
2	**C2**	0	1	100	93	99
3	**C1**	–20	2	100	98	86
4	**C2**	–20	1	100	94	99
5	**C1**	–40	2	100	89	94
6	**C2**	–40	1	100	92	99
7	**C1**	–60	2	100	98	94

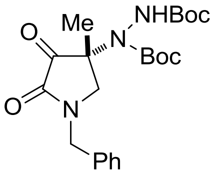
To a mixture of the α-ketoamide **168a** (41 mg, 0.2 mmol, 1 equiv.) and catalyst (0.02 mmol, 10 mol%) in dichloromethane (0.4 mL), di-*tert*-butyl azodicarboxylate **44** (69 mg, 0.3 mmol, 1.5 equiv.) was added. The resulting mixture was stirred until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was directly purified by flash column chromatography on silica gel (eluent hexane/ ethyl acetate 80/20) without previous work-up to afford the expected adduct **179a**.

Once in hand the best catalyst and optimal conditions, we proceeded to explore the reaction scope with different *N* protecting groups and substituents in *C*-4 (Table 21). In general, the amination reaction of **168**–**171** with **44** promoted by **C68** at –40 ºC give products **179**–**182** with very good yields and enantioselectivities between 96–99% with alkyl and aryl groups at *C*-4. Moreover, the reaction seems to be independent of the substituent R^2 and both **169a** and **170a** led to **180a** and **181a** with excellent yields and 96% *ee*. However, the reaction of pyrrolidin-2,3-dione **171a** bearing the bulky isopropyl group needed longer reaction time (16 h) for completion and provided essentially a single enantiomer.

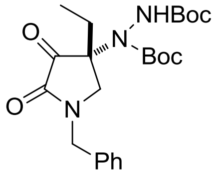
Table 21. Pyrrolidin-2,3-diones reaction scope for the conjugate addition to di-*tert*-butyl azodicarboxylate **44**.[a]



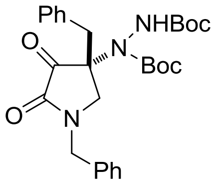
168a R^1 = Me R^2 = Bn
168b R^1 = Et R^2 = Bn
168c R^1 = Bn R^2 = Bn
168d R^1 = Ph R^2 = Bn
169a R^1 = CH_2-1-Napht R^2 = Me
170a R^1 = PMP R^2 = Me
171a R^1 = ^{i}Pr R^2 = Me



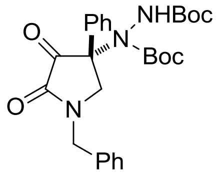
179a
92%, 99% *ee*



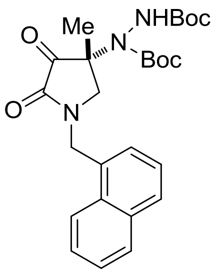
179b
89%, 96% *ee*



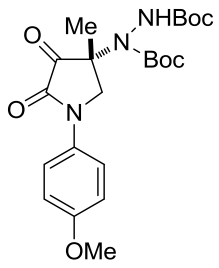
179c
86%, 96% *ee*



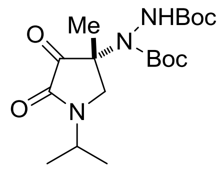
179d
75%, 96% *ee*



180a
97%, 99% *ee*



181a
95%, 96% *ee*



182a
80%[b], 99% *ee*

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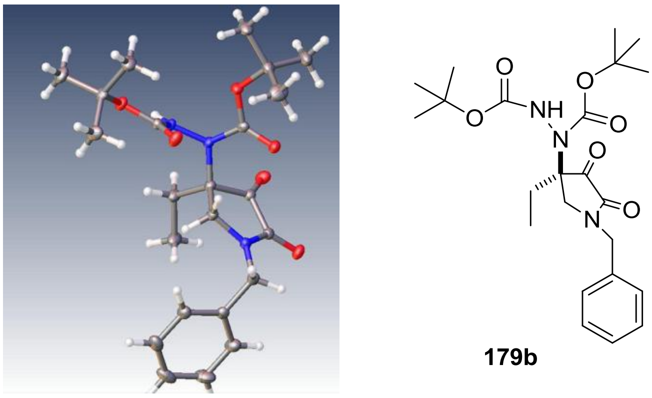
[a] To a mixture of the α-ketoamide **168**–**171** (41 mg, 0.2 mmol, 1 equiv.) and catalyst **C68** (0.02 mmol, 10 mol%) in dichloromethane (0.4 mL), di-*tert*-butyl azodicarboxylate **44** (69 mg, 0.3 mmol, 1.5 equiv.) was added. The resulting mixture was stirred until consumption of the α-ketoamide (1 h, monitored by ^{1}H-NMR). The reaction mixture was directly purified by flash column chromatography on silica gel (eluent hexane/ ethyl acetate 80/20) without previous work-up to afford the expected adducts **179**–**182**. [b] 16 h for the completion of the reaction.

The absolute configuration was determined for compound **179b** by X-ray single crystal structure analysis and that of the remaining adducts was established by assuming a uniform reaction mechanism (Figure 37).



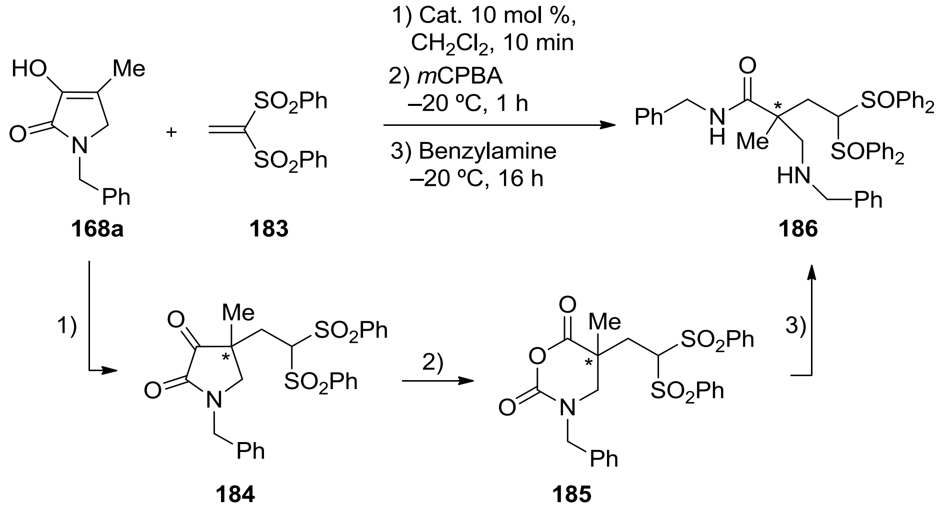
179b

Figure 37. X-Ray structure for compound **179b**.

3.6.3. Michael addition to vinyl (bis)sulfones

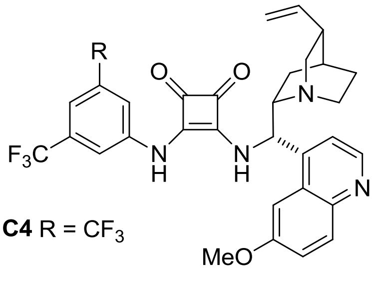
Taking into account the retro-Michael addition that suffer the addition adducts **184** coming from 1,1-bis(phenylsulfonyl)ethylene **183**, we decided to transform the adducts into compounds less probable to give the retro-Michael addition. For that purpose, we designed the synthetic pathway shown in Table 22. After the conjugate addition, the resulting adduct **184** would be converted into the corresponding NCA **185** at low temperature to avoid the retro-Michael reaction and then subsequently opened with benzylamine. For that purpose first the lower temperature at which the retro-addition occurs was determined and it was found that at –20 ºC or lower temperatures it did not take place. Therefore, the asymmetric reaction was carried out first at –20 ºC in the presence of catalyst **C4** and the β-amino amide **186** was obtained in 80% *ee* (Table 22, entry 1). Lowering the temperature to –60 ºC did not improve that value (Table 22, entry 2), neither by using the other squaramide-type catalysts (Table 22, entries 3–5).

Table 22. The Michael addition of 4-substituted pyrrolidin-2,3-dione **168a** to 1,1-bis(phenylsulfonyl)ethylene **183**[a].



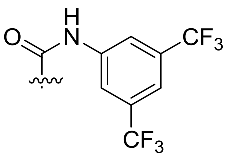
Entry	Catalyst	T (ºC)	t (min)	Conv. (%)	Yield (%)	*ee* (%)
1	**C4**	–20	15	100	68	80
2	**C4**	–60	15	100	75	62
3	**C68**	–20	15	100	60	36
4	**C69**	–20	15	100	68	–32
5	**C51**	–20	15	100	65	–18

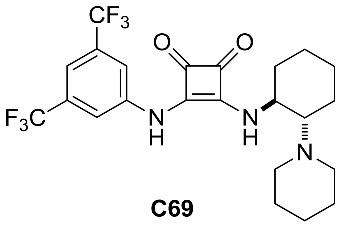
[a] To a mixture of the α-ketoamide **168a** (41 mg, 0.2 mmol, 1 equiv.) and catalyst (0.02 mmol, 10 mol %) in dichloromethane (0.4 mL), bis(phenylsulfonyl)ethylene **183** (93 mg, 0.3 mmol, 1.5 equiv.) was added. The resulting mixture was stirred until consumption of the α-ketoamide and *m*CPBA (75 mg, 0.3 mmol, 1.5 equiv.) was *in situ* slowly added. After reaction completion (1 h) benzylamine (26 µL, 0.24 mmol, 1.2 Eq) in CH_2Cl_2 (1 mL) was added dropwise and it was stirred for 16 h. The reaction was quenched with aqueous 10% $NaHSO_3$ and it was extracted with CH_2Cl_2. All organic phases were washed with NaOH 1N, dried over $MgSO_4$ and evaporated under reduced pressure.



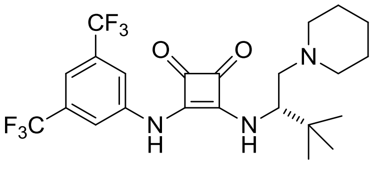
C4 R = CF_3

C68 R =



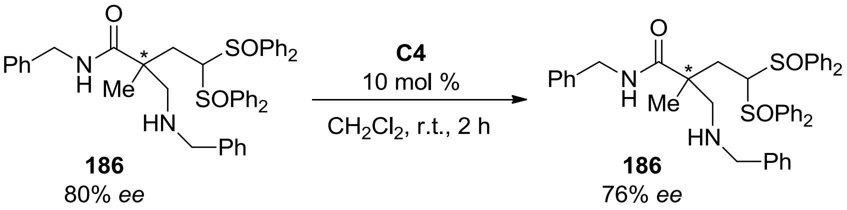


C69



C51

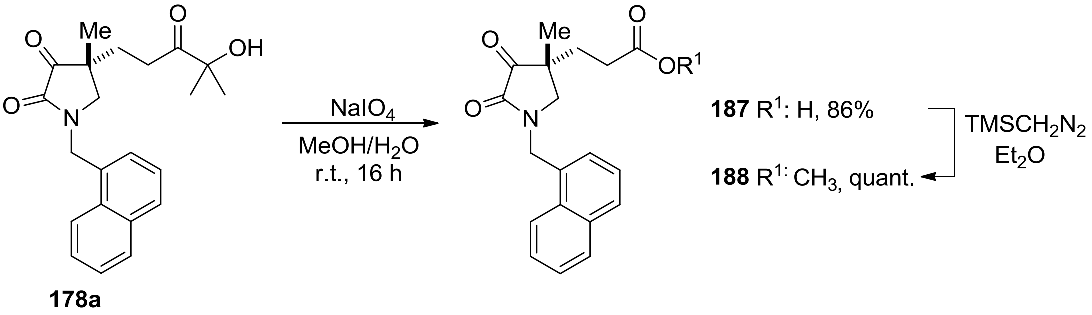
In this case the retro-Michael reaction was also evaluated by treating adduct **186** with catalyst **C4** at room temperature for 2 h (Scheme 76). Nevertheless, the final acyclic adduct seems not to racemize under these conditions.



Scheme 76. Control experiment carried out to evaluate the retro-Michael reaction in adduct **186**.

3.7. Elaboration of the adducts

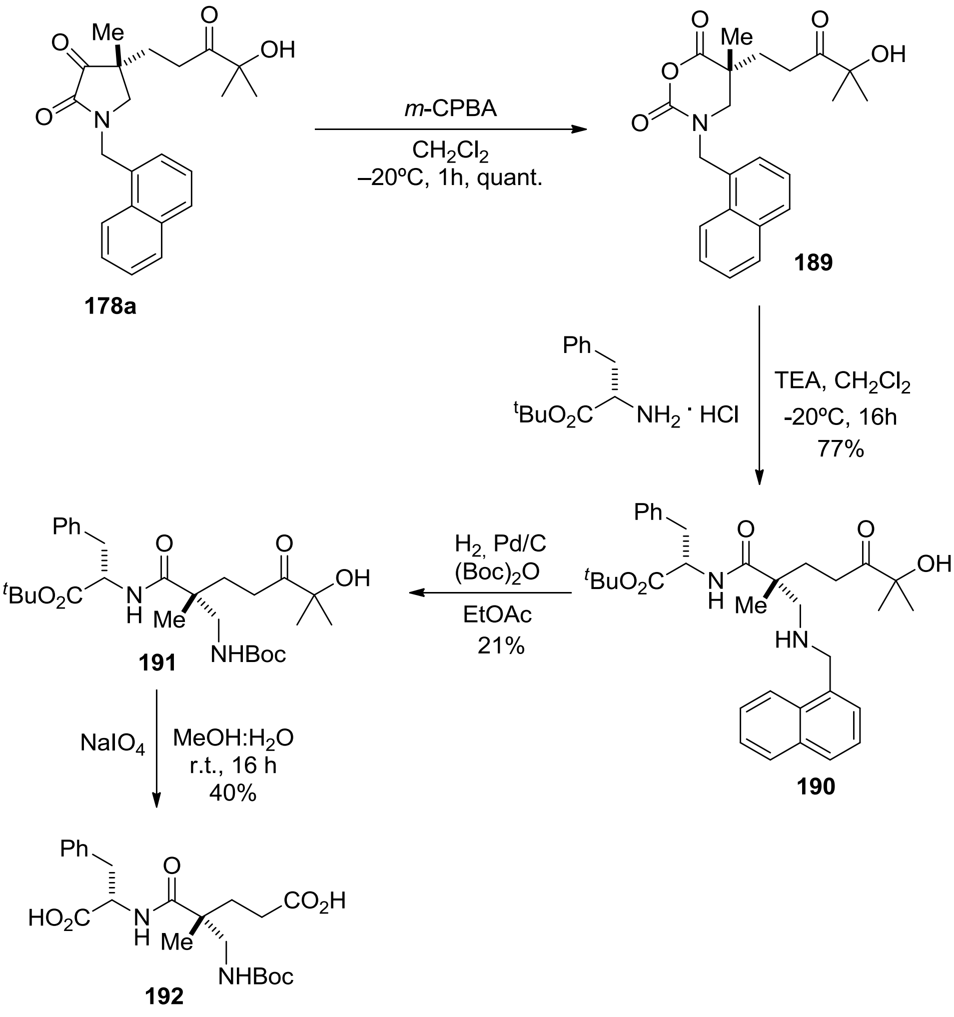
These densely functionalized adducts can be transformed into different functionalities. Oxidative cleavage of the ketol moiety proceed without affecting the 1,2-diketo functionality with the same reaction conditions reported before for the adducts coming from the reaction with cyanoacetates and azlactones (Scheme 77). Carboxylic acid **187** was afforded in 86% yield and its transformation into the corresponding methyl ester **188** with trimethyl silyl diazomethane was quantitative. These adducts are formally derived from the addition to the unreactive methyl acrylate. Once more, the synthetic utility of α'-oxy enones as ester surrogates is demonstrated.



Scheme 77. Ketol scission to carboxylic acid and ester.

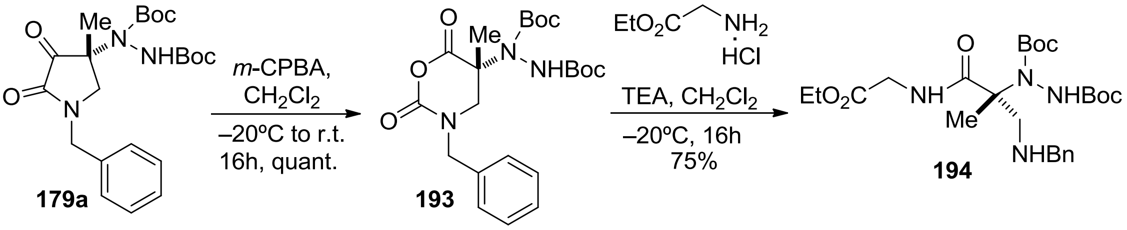
In addition to the above transformation, it was also found that treatment of pyrrolidin-2,3-diones with *m*-chloroperbenzoic acid (*m*-CPBA) furnished β-amino acids *N*-carboxyanhydrides ($\beta^{2,2}$-NCAs) with excellent yields. To the best of our knowledge, this is the first approach to enantiomerically enriched $\beta^{2,2}$-NCAs from non α,α-disubstituted β-amino acids precursors. Coupling of these NCAs with appropriate nucleophiles provides a quick entry to more elaborated containing $\beta^{2,2}$-amino acid products.

For example, **189**, obtained by treatment of **178a** with 1.5 equivalents of *m*-CPBA, followed by the addition of *tert*-butyl ester of *L*-phenylalanine, Scheme 78, furnished the coupling product **190** in 77% yield. This intermediate was transformed into the *N*-Boc derivative **191** by hydrogenation carried out in the presence of $(Boc)_2O$ and further elaboration of the ketol moiety provided the dicarboxylic acid **192**. Although major improvement is needed for these last two steps, the approach could be clearly advantageous.



Scheme 78. Elaboration into $\beta^{2,2}$ amino acid N-carboxyanhydride pyrrolidin-2,3-diones and derivatives.

Similarly, ring expansion of **179a** upon coupling with glycine ethyl ester afforded the α-tetrasubstituted β-amino α-hydrazino acid derived peptide **194** in 75% of yield.



Scheme 79. Elaboration of adduct **179a**.

CHAPTER 4

(Dichloroiodo)benzene-mediated desulfurative chlorination of alkyl phenyl sulfides

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4. (Dichloroiodo)benzene-mediated desulfurative chlorination of alkyl phenyl sulfides

This part of the work was carried out in the group of Prof. Mauro Adamo in The Royal College of Surgeons in Ireland (RCSI). In this project the chlorination of alkyl phenyl sulfides promoted by (dichloroiodo)benzene has been explored. This work has been carried out together with Dr. Stefano Lancianesi, Chiara Strinna and Daniele Canestrari under the supervision of Dr. Hasim Ibrahim and Prof. Mauro Adamo.

A novel chlorination reaction from secondary/tertiary alkyl phenyl sulfides, as well as, sulfa-Michael derived sulfides, promoted by (dicloroiodo)benzene ($PhICl_2$) has been developed. This mild and rapid oxidative reaction affords elimination sensitive benzylic chlorides in good yields.

4.1. Introduction

Alkyl chlorides are of great synthetic interest as building blocks and these motifs are present in a variety of natural products (Figure 38).[303] Chlorinated molecules have attracted attention in drug discovery and the development of new methods for the formation of carbon-chlorine bonds is a relevant area of research nowadays.

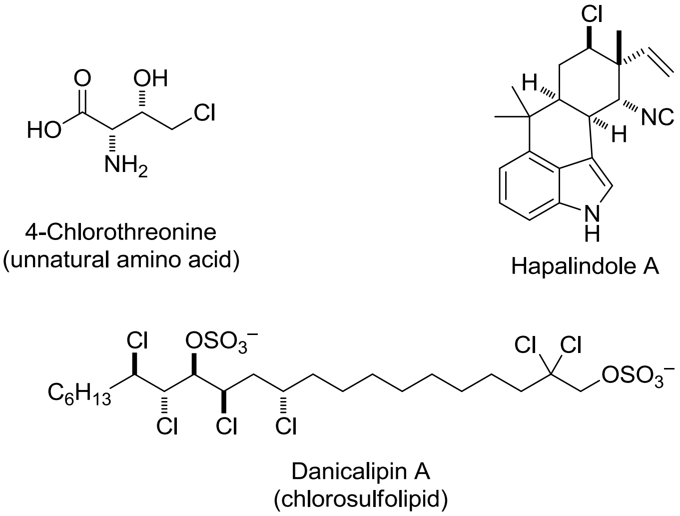

Figure 38. Biologically interesting alkyl chlorides.

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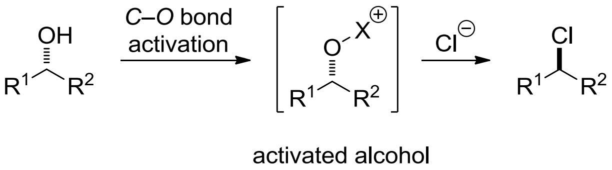
[303] For reviews and selected examples, see: a) Chung, W.-J.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 2–41. b) Chung, W.-J.; Vanderwal, C. D. *Acc. Chem. Res*. **2014**, *47*, 718–728. c) Umezawa, T.; Matsuda, F. *Tetrahedron Lett*. **2014**, *55*, 3003–3012. d) Bucher, C.; Deans, R. M.; Burns, N. Z. *J. Am. Chem. Soc*. **2015**, *137*, 12784–12787. e) D. C. Braddock, A. X. Gao, A. J. P. White, M. Whyte, *Chem. Commun*. **2014**, *50*, 13725–13728.

A general procedure for obtaining alkyl chlorides is the S_N2 displacement of carbinols with chloride ion.[304] However, this strategy needs the activation of the strong sp^3 hybridized *C–O* bond towards chloride ion reaction and traditionally conversion of alkyl alcohols, for instance, into the corresponding sulfonated esters has been employed.[305] One important drawback is the atom efficiency of these reactions since by-products are generated along with product and nowadays the interest is focused on the development of chemical reactions that consume the minimum amount of raw material and generate the minimum amount of waste.

In this context, chlorodehydration of alcohols by *in situ* activation of the *C–O* bond in which the hydroxyl group is activated and the formation of X–OH bond compensates for *C–O* cleavage has been extensively studied (Scheme 80).[306]



Scheme 80. Conventional strategy for the synthesis of alkyl chlorides: chlorodehydration of alcohols by S_N2 substitution.

A range of transformations have been developed in this field and among them, the Appel reaction is highlighted which makes use of triphenylphosphine and tetrahalomethanes (CCl_4, CBr_4) with alcohols to convert them into the corresponding alkyl halides under mild conditions (Scheme 81).[307] Recently, some catalytic variants of the Appel reaction[308] and some other innovative catalytic chlorodehydration platforms

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[304] Bohlmann, R. *Comprehensive Organic Transformations* (Ed.: R. C. Larock), Wiley-VCH, New York, 2nd ed., **1999**, pp. 689–702.

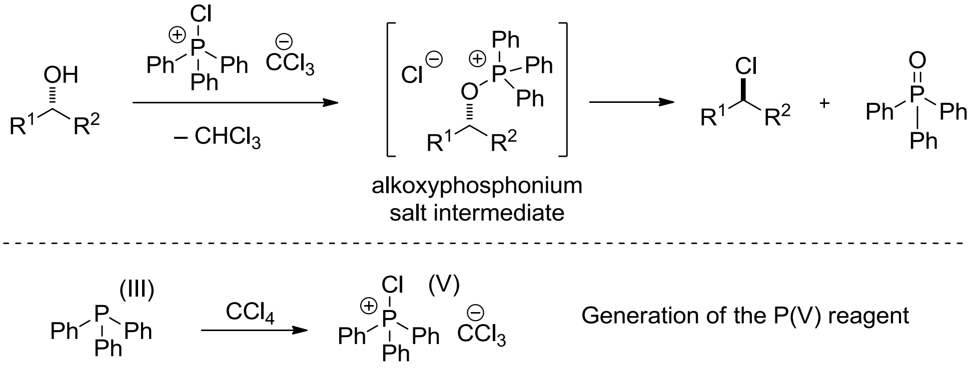
[305] For some selected examples, see: a) Cahiez, G.; Lefèvre, N.; Poizat, M.; Moyeux, A. *Synthesis* **2013**, *45*, 231–236. b) Liu, Y.; Xu, Y.; Jung, S. H.; Chae, J. *Synlett* **2012**, *23*, 2663–2666. c) Braddock, D. C.; Pouwer, R. H.; Burton, J. W.; Broadwith, P. *J. Org. Chem*. **2009**, *74*, 6042–6049.

[306] For some selected examples, see: a) Moerdyk, J. P.; Bielawski, C. W. *Chem. Eur. J*. **2014**, *20*, 13487–13490. b) Nguyen, T. V.; Bekensir, A. *Org. Lett*. **2014**, *16*, 1720–1730. c) Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T.; Kartika, R. *Org. Lett*. **2012**, *14*, 3676–3679. d) Villalpando, A.; Ayala, C. E.; Watson, C. B.; Kartika, R. *J. Org. Chem*. **2013**, *78*, 3989–3996. e) Sun, L.L.; Peng, G.; Niu, H.; Wang, Q.; Li, C. *Synthesis* **2008**, 3919–3924. f) Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc*. **2004**, *126*, 7186–7187.

[307] a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811. b) Pluempanupat, W.; Chantarasriwong, O.; Taboonpong, P.; Jang, D. O.; Chavasiri, W. *Tetrahedron Lett.* **2007**, *48*, 223–226.

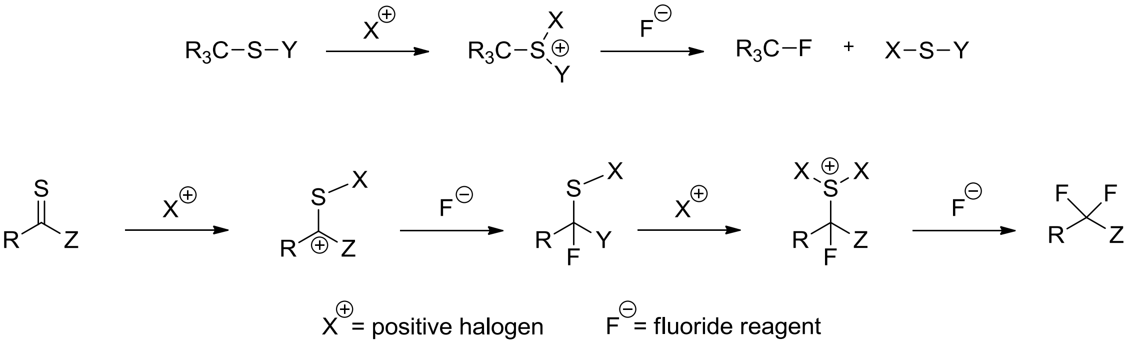
[308] a) Denton, R. M.; Jie, A.; Adeniran, B. *Chem. Commun*. **2010**, *46*, 3025–3027. b) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *J. Org. Chem*. **2011**, *76*, 6749–6767.

have been reported.[309] Nevertheless, some limitations remain in these strategies such as the formation of side products, narrow substrate scope, reactivity issues and the use of multiple reagents.



Scheme 81. The Appel reaction.

sp^3 Hybridized *C–S* bonds are generally weaker than the corresponding *C–O* bonds and furthermore, can be more reactive towards nucleophiles by sulfur oxidation to sulfonium ions. This methodology has been employed in the desulfurative fluorination of thioacetals, dithioacetals and trithioorthoesters affording mono- or di-flurorinated compounds following the mechanism shown in Scheme 82.[310] The basic idea involves the activation of the *C–S* bond by an electrophile, followed by a nucleophilic substitution with fluoride to form the *C–F* bond. In the case of a substrate having a *C*=*S* double bond, double desulfurization-fluorination occurs to give difluoromethylene compounds.



Scheme 82. Oxidative desulfurization-fluorination of organosulfur compounds.

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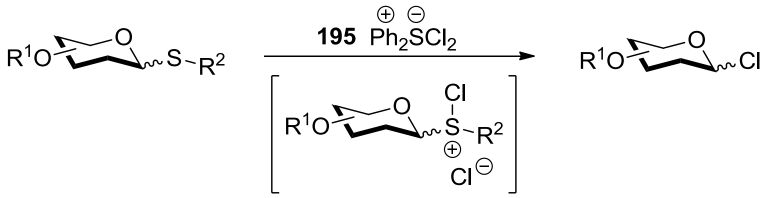
[309] An, J.; Denton, S. M.; Lambert, T. H.; Nacsa, E. D. *Org. Biomol. Chem.* **2014**, *12*, 2993–3003 and references therein.

[310] For reviews on desulfurative fluorination, see: a) Hugenberg, V.; Haufe, G. *J. Fluorine Chem.* **2012**, *143*, 238–262. b) Kuroboshi, M.; Kanie, K.; Hiyama, T. *Adv. Synth. Catal.* **2001**, *343*, 235–250.

The analogous desulfurative chlorination has been less developed; as an example Diakur and co-workers reported the chlorination of thioglycosides to glycosyl chlorides via chlorosulfonium salts (Scheme 83).[311] The salt from phenyl sulfoxide/oxalyl chloride **195** was found to be an efficient chlorine transfer reagent and yields of glycosyl chlorides were typically >90% according to ^{1}H-NMR analysis of the crude product.



Scheme 83. Desulfurative chlorination of thioglycosides to glycosyl chlorides.

However, direct halogenative *C–S* bond cleavage without neighbouring group participation or anchimeric assistance, which involves the interaction of an electron pair of geminal heteroatoms, has been little studied. In most cases activated alkyl aryl sulfides have been used in desulfurative fluorinations wherein the *C–S* bond is activated through oxidative *S*-methylation,[312] *S*-nitrosylation[313] or *S*-halogenation.[310]

In contrast, very few examples of the analogous chlorination have been reported. Cordts described the addition of chlorine to propylene sulfide **196** causing ring cleavage at the primary carbon-sulfur bond to give access to bis-(1-methyl-2-haloethyl) disulfides **198** (Scheme 84, a).[314] The mechanistic proposal is the addition of one molecule of chlorine to a molecule of sulfide **196** to form 1-halo-2-propanesulfenyl halide **197**. Subsequently, a rapid reaction of this compound with another molecule of propylene sulfide provides the final disulfides **198**. Likewise, ring opening chlorinolysis of thiacyclobutane **199** was reported to occur with sulfuryl chloride (SO_2Cl_2) affording γ-chloropropanesulfenyl chloride **200** (Scheme 84, b).[315]

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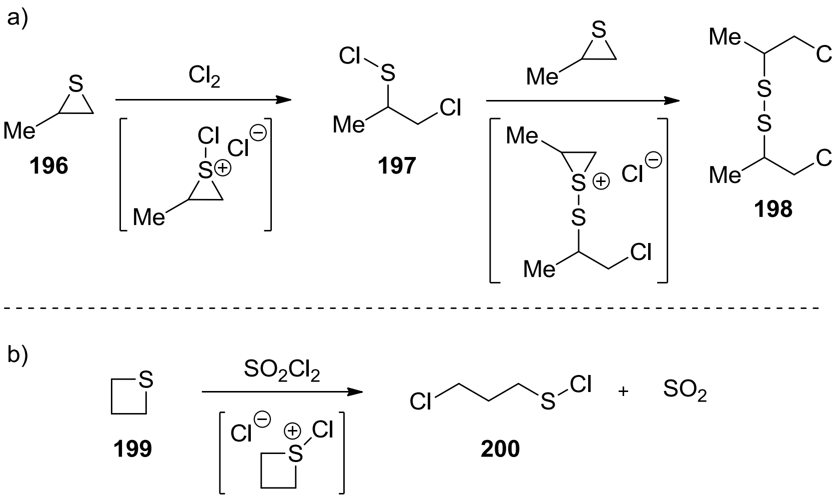
[311] Sugiyama, S.; Diakur, J. M. *Org. Lett.* **2000**, *2*, 2713–2715.

[312] Ichikawa, J.; Sugimoto, K.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1987**, 1985–1988.

[313] York, C.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **1996**, *52*, 9–14.

[314] Stewart, J. M.; Cordts, H. P. *J. Am. Chem. Soc.* **1952**, *74*, 5880–5884.

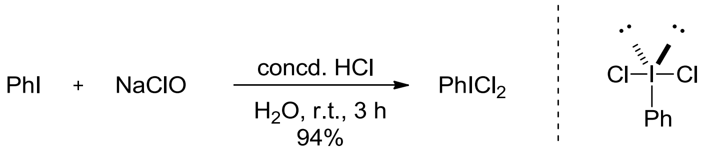
[315] Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572–577.



Scheme 84. Direct chlorination of *C–S* bonds a) in propylene sulfide and b) in thiacyclobutane.

4.2. Hypervalent iodine reagents

Hypervalent iodine reagents have shown to possess a broad oxidative reactivity profile since their discovery in the 1880s.[316] Among (dichloroiodo)arenes, (dichloroiodo)benzene is the most commonly used reagent which can be conveniently prepared by direct chlorination of iodobenzene (Scheme 85).[317] Their reactions typically occur under mild and environmentally benign conditions, and have been well documented by Stang and Zhdankin.[318] The overall geometry of molecule RIL_2 is a distorted trigonal bipyramid with two heteroatom ligands (L=Cl) occupying the apical positions and the least electronegative carbon ligand (R=Ph) and both electron pairs reside in equatorial positions.



Scheme 85. General procedure for the synthesis of (dichloroiodo)benzene and its trigonal bipyramid geometry.

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[316] Willgerodt, C. *J. Prakt. Chem*. **1886**, *33*, 154–160.

[317] Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, *4*, 551–557.

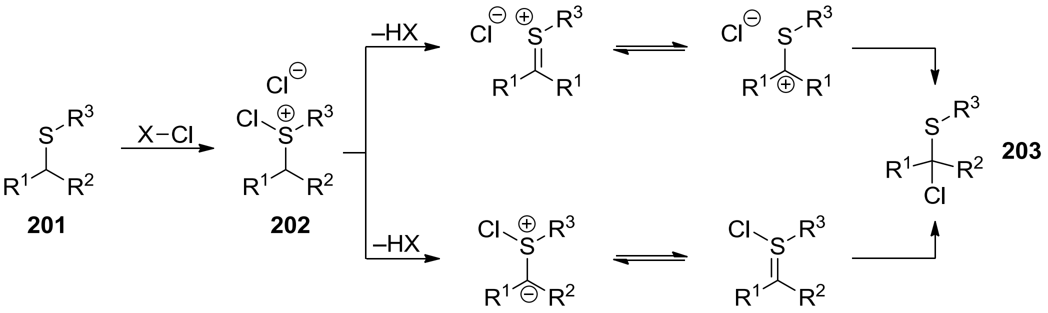
[318] a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev*. **1996**, *96*,1123–1178. b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2002**, *102*, 2523–2584. c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2008**, *108*, 5299–5358.

4.3. Working hypothesis and synthetic plan

It is known that reaction of primary alkyl phenyl sulfides with chlorinating agents forms phenyl α-chlorosulfides from chloro-Pummerer rearrangement.[319]

Scheme 86. Chloro-Pummerer rearrangement of alkyl sulfides.

The Pummerer rearrangement is the transfer of functionality from sulfur to carbon, in this case a migration of a chloride atom. Initial attack on sulfide produces the *S*-chlorosulfonium ion **202** whose conversion to chlorosulfide **203** has been described by Bordwell and Pitt[315] as "riding downhill from sulfur to carbon on an electron cloud". Two mechanistic extremes of how this may be brought about are illustrated in Scheme 87. Which pathway will be favored in any particular situation will be influenced by structural considerations, such as the acidity of the α-carbon atom, and the choice of chlorinating agent since the basicity of the anion Cl⁻ is also implicated.



Scheme 87. Mechanistic proposal for the chloro-Pummerer rearrangement.

To the best of our knowledge, the few other examples make use of activated phenyl sulfides capable of generating stable carbenium ion intermediates.

The reaction of (dichloro)iodobenzene with sulfides was reported by Schreiber and Fernández for the first time in which two different reactivity patterns were described depending on the starting sulfides.[320] Decomposition of the chlorosulfonium chloride intermediate **202** can occur in one of two ways depending on the nature of the organic groups attached to the sulfur atom. When one group is phenyl, benzyl or methyl, and the other is methyl or benzyl, the intermediate reacts with the evolution of

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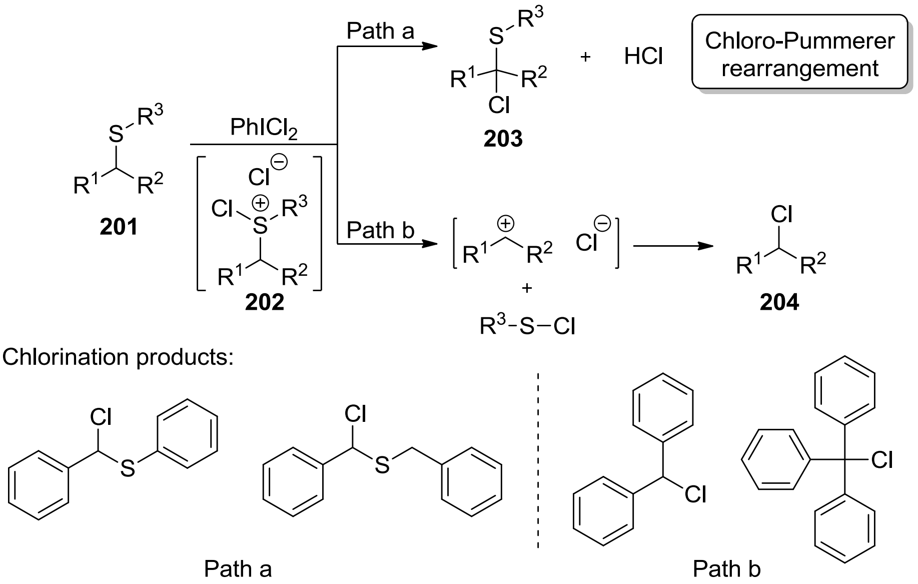
[319] Dilworth, B. M.; McKervey, M. A. *Tetrahedron* **1986**, *42*, 3731–3752.

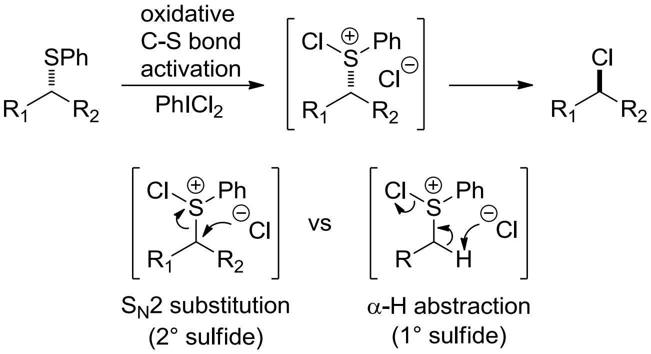
[320] a) Schreiber, K. C.; Fernandez, V. P. *J. Org. Chem.* **1961**, *26*, 2910–2916. b) Schreiber, K. C.; Fernandez, V. P. *J. Org. Chem.* **1961**, *26*, 2478–2479.

hydrogen chloride to give the α-chloro sulfide **203** (Scheme 88, path a). A second path by which the chlorosulfonium ion **202** could decompose is by ionization of the intermediate to the sulfenyl halide and the carbonium ion (Scheme 88, path b). Here, there are factors that stabilize a carbonium ion greatly favoring this path. It is for this reason that trityl sulfide gives almost quantitative yields of trityl chloride since one of the group is triphenylmethyl group which contributes a large steric effect and stabilizes by resonance.



Scheme 88. Two paths of the decomposition of the chlorosulfonium chloride intermediate.

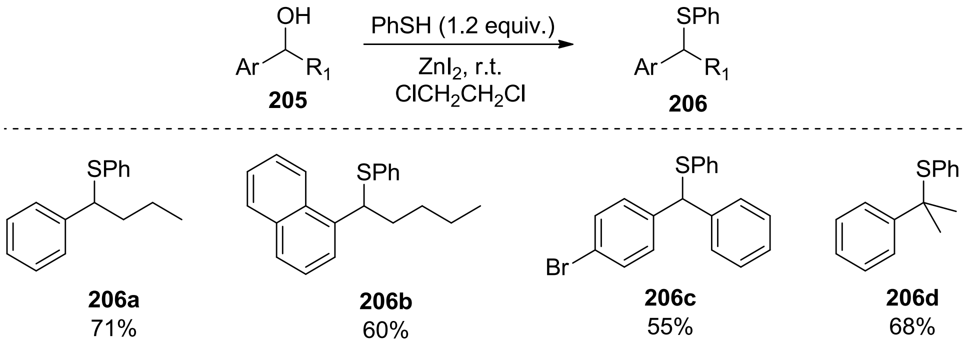
We reasoned that (dichloroiodo)benzene ($PhICl_2$) could be a suitable chlorinating agent for its capacity to act as both the oxidant and the source of weakly basic chloride ion. This chlorinating agent would *in situ* generate a chlorosulfonium intermediate in which a chloride displacement through S_N2 substitution or α-proton abstraction to the thionium ion (or Pummerer) intermediate could occur.



Scheme 89. Proposed chlorination strategy of sulfides with (dichloroiodo)benzene.

4.4. Results and discussion

We start our studies with activated secondary alkyl phenyl sulfides. For that purpose some alkyl phenyl sulfides were prepared from the corresponding alcohols with thiophenol and zinc iodide following a described procedure (Scheme 90).[321]



Scheme 90. Preparation of alkyl phenyl sulfides.

It was gratifying to observe that **206a** reacted with $PhICl_2$ **207** (1.1 equiv.) in dry dichloromethane at room temperature (Table 23). A color change from yellow to orange occurred within 5 minutes indicating the rapid consumption of the starting material.

(Dichloroiodo)arenes are generally light and heat sensitive yellow crystalline solids which are insufficiently stable for extended storage even at low temperatures. Therefore their quality could affect the experiments, so $PhICl_2$ samples were freshly prepared or used within two weeks of preparation in order to ensure lower traces of HCl.

Once known optimized conditions for chlorination reaction, a range of secondary alkyl sulfides were tested and complete conversions to the chlorinated products within 5 minutes were obtained (Table 23). Chloride **208a** was isolated in good yield (71%) after column chromatography; however, attempts to purify crude chlorides **208b** and **208c** by column chromatography on silica gel or neutral alumnia resulted in partial hydrolysis or decomposition. Being so sensitive these chlorides to column chromatography, we decided to isolate them as their corresponding trifluoroethyl ether derivatives **209**.[322] It was gratifying to observe that solvolysis of

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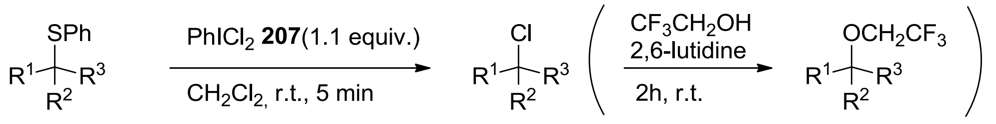
[321] Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357–1359.

[322] a) Shi, L.; Horn, M.; Kobayashi, S.; Mayr, H. *Chem. Eur. J.* **2009**, *15*, 8533–8541. b) Mihel, I.; Orlović, M.; Polla, E.; Borčić, S. *J. Org. Chem.* **1979**, *44*, 4086–4090. c) Orlović, M.; Polla, E.; Borčić, S. *J. Org. Chem.* **1983**, *48*, 2278–2280. d) Jurić, S.; Filipović, A.; Kronja, O. *J. Phys. Org. Chem.* **2003**, *16*, 900–904.

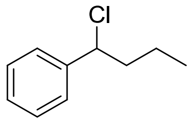
crude chlorides **208b** and **208c** in 2,2,2-trifluoroethanol gave good yields (70–79%) of trifluoroethyl ethers **209b**-OCH_2CF_3 and **209c**-OCH_2CF_3.

Table 23. Desulfurative chlorination of alkyl phenyl sulfides **1** with $PhICl_2$.[a]

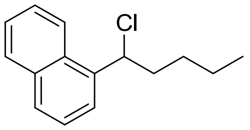


(±) 206 **(±) 208** **(±) 209**

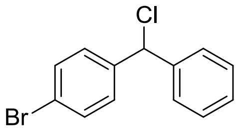
a R^1 = Ph R^2 = Pr R^3 = H
b R^1 = 1-Nathph R^2 = Bu R^3 = H
c R^1 = 4-BrPh R^2 = Ph R^3 = H
d R^1 = Ph R^2 = Me R^3 = Me



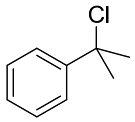
(±) 208a, 71%



(±) 208b, 70%[b]



(±) 208c, 79%[b]

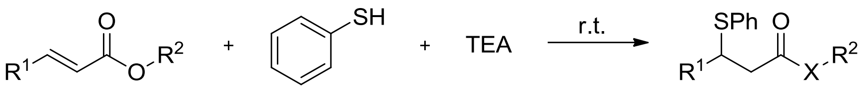


(±) 208d, 85%

[a] Reactions performed on 0.5 mmol scale at 0.17 M (3 mL). Isolated yield after column chromatography. [b] Isolated yield of the corresponding trifluoroethyl ether derivative.

Moreover, it is remarkable that chlorination reaction of sulfide **206d** worked satisfactorily with 85% yield demonstrating that reaction scope includes tertiary phenyl sulfides (Table 23).

Having established that simple phenyl sulfides **206** underwent desulfurative chlorination, we proceeded to examine sulfa-Michael derived phenyl sulfides. A variety of β-sulfido (thio)ester compounds **212** were prepared through simple sulfa-Michael reaction between acrylates **210** and thiol **211** promoted by triethylamine at room temperature.

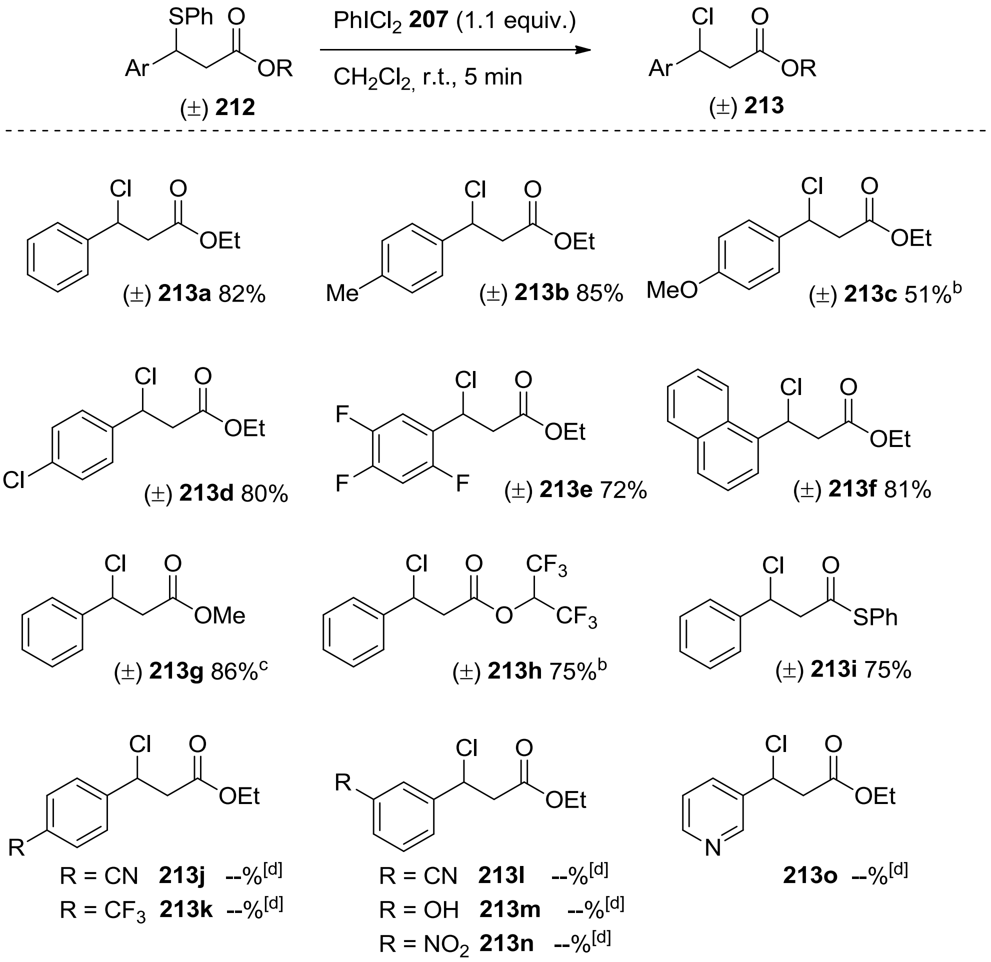


210 **211** **212**
X = O, S

Scheme 91. Preparation of β-sulfido (thio)esters.

According to conditions on Table 23, chlorination reaction of these substrates also turned out to be rapid and in high yields (Table 24). Reaction scope included β-sulfido esters **212a-h** with some electron-withdrawing and donors groups, and β-sulfido thioester **212i**. Interestingly, thioester **212i** having two electronically modified phenylsulfenyl groups also underwent the chlorination in 78% yield. Finally, the chlorination of sulfide **212g** was conducted on a 5.0 mmol scale and, gratifyingly, gave a comparable yield of chloride **213g**. However, the chlorination of substrates **212j-o** carrying -CN, -CF_3, -OH and -NO_2 groups in the aromatic ring provided a mixture of different compounds making impossible the isolation of the corresponding chlorinated products **213j-o**.

Table 24. Desulfurative chlorination of sulfa-Michael derived sulfides **212** with $PhICl_2$.[a]



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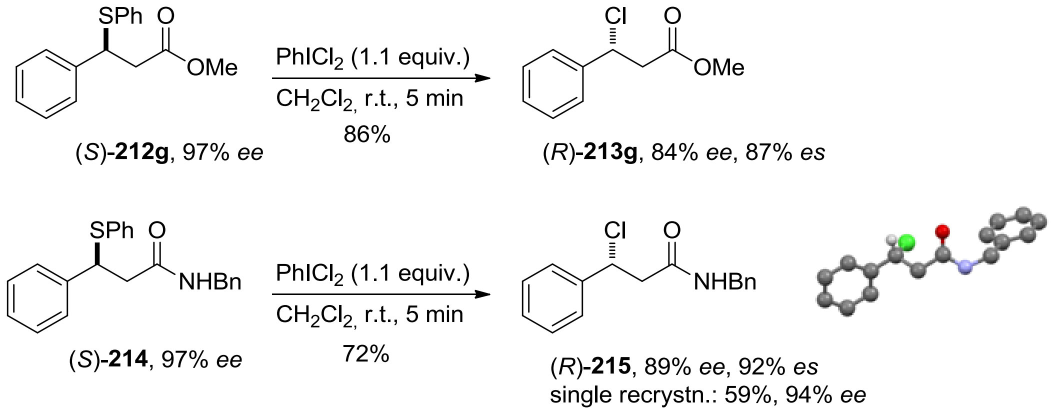
[a] Reactions performed on 0.5 mmol scale at 0.17 M (3 mL). Isolated yield after column chromatography. [b] Isolated yield of the corresponding trifluoroethyl ether derivative. [c] Reaction performed on 5.0 mmol scale. [d] Yield not determined, messy crude.

Given the importance of chiral chlorinated products, interest was then focused on the development of methods that deliver aryl chlorides with high enantiopurity. For this purpose we selected β-sulfido ester **212g** as substrate, which was synthesized by sulfa-Michael addition to α,β-unsaturated ester following reported protocols.[323] Initial experiments carried out by S. Lancianesi involving β-sulfido ester (*S*)-**212g**[324] of 97% *ee*, gave the corresponding inverted chloride (*R*)-**213g** in 86% yield and 84% *ee*, determining that reaction proceeded with high stereoespecificity (87%) (Scheme 92). Likewise, β-sulfido amide (S)-**214** was converted into β-chloro amide (*R*)-**215** in 89% *ee* and 92% *es*. Moreover, a single recrystallization allowed the isolation of (*R*)-**215** in 59% yield and 94% *ee*. The absolute configuration was confirmed by X-ray analysis to be *R* indicating that the chlorination proceeded with inversion at the sulfide stereocenter.



Scheme 92. Chlorination of enatioenriched phenyl sulfides (*S*)-**212g** and (*S*)-**214**.

Mechanistic hypothesis for the presented desulfurative chlorination is outlined in Scheme 93. The capacity of aryl-λ^3-iodanes to oxidize organoelement compounds of groups 15 and 16 transfering one[325] or both[326] heteroatom ligands is well established.[327] The latter case is favored when both ligands are the same and of moderate *trans*-influence on hypervalent bonding[328] and it is applied for reactions with $PhICl_2$.[329] A

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[323] Fang, X.; Li, J. Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448–3451.

[324] Fang, X.; Li, J. Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448–3451.

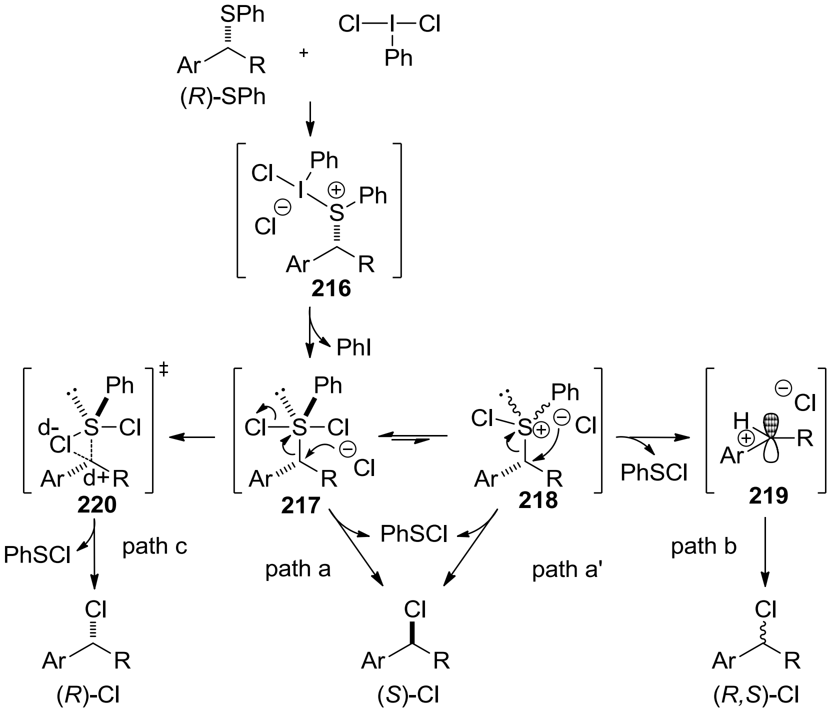
[325] a) Ray III, D. G.; Koser, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 5672–5673. b) Koser, G. F.; Kokil, P. B.; Shah, M. *Tetrahedron Lett.* **1987**, *28*, 5431–5434.

[326] a) Liu, Z.-D.; Chen, Z.-C. *Heteroatom Chem.* **1992**, *3*, 559–561. b) Combes, S.; Finet, J.-P.; *Tetrahedron* **1998**, *54*, 4313–4318. c) Kang, S.-K.; Ryu, H.-C.; Lee, S.-W. *J. Organomet. Chem.* **2000**, *610*, 38–41. c) Burford, N.; Clyburne, J. A. C.; Gates, D. P.; Schriver, M. J.; Richardson, J. F. *J. Chem. Soc. Dalton Trans.* **1994**, 997–1001.

[327] a) Zhdankin, V. V. *Hypervalent Iodine Chemistry*, Wiley, Chichester, **2014**. b) “Hypervalent Iodine Chemistry”: *Topics Current Chemistry*, *Vol. 224* (Ed.: T. Wirth), Springer, Berlin, **2003**.

[328] Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 8203–8206.

generation of highly reactive dichloro-λ^4-sulfurane **217** in equilibrium with its diastereomeric chlorosulfonium salt **218**[330] as key intermediates is proposed.[331] In principle iodosulfonium adduct **216** can serve as a precursor to intermediates **217** and **218**. However, to the best of our knowledge, such intermediates have never been characterized. Due to the absence of Lewis acids capable of binding chloride ion, this equilibrium is likely displaced to the side of sulfurane **217**.[332]



Scheme 93. Mechanistic hypothesis for the desulfurative chlorination.

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[329] For oxidative dichlorination of late transition metal complexes with $PhCl_2$, see: a) Hofer, M.; Nevado, C. *Eur. J. Inorg. Chem*. **2012**, 1338–1341. b) Racowski, J. M.; Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc*. **2011**, *133*, 18022–18025. c) McCall, A. S.; Wang, H.; Desper, J. M.; Kraft, S. *J. Am. Chem. Soc*. **2011**, *133*, 1832–1848. d) Pearson, S. L.; Sanford, M. S.; Arnold, P. *J. Am. Chem. Soc*. **2009**, *131*, 13912–13913. e) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 15142–15143. f) Lagunas, M.-C.; Gossage, R. A.; Spek, A. L.; van Koten, G. *Organometallics* **1998**, *17*, 731–741.

[330] For ReactNMR characterization of an alkyl phenyl sulfide derived diastereomeric chlorosulfonium salt generated with NCS, see: Foley, D. A.; Doecke, C. W.; Buser, J. Y.; Merritt, J. M.; Murphy, L.; Kissane, M.; Collins, S. G.; Maguire, A. R.; Kaerner, A. *J. Org. Chem*. **2011**, *76*, 9630–9640.

[331] For proposed participation of such adducts in Pummerer type reactions, see: a) Motherwell, W. B.; Greaney, M. F.; Edmunds, J. J.; Steed, J. W. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2816–2826. b) Motherwell, W. B.; Greaney, M. F.; Tocher, D. A. *J. Chem. Soc,. Perkin Trans. 1*, **2002**, 2809–2815. c) Tohma, H.; Egi, M.; Ohtsubo, M.; Watanabe, H.; Takizawa, S.; Kita, Y. *Chem. Commun*. **1998**, 173–174. d) Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J.-I. *Chem. Pharm. Bull*. **1986**, *34*, 1061–1066.

[332] Brucks, A. P.; Treitler, D. S.; Liu, S.-A.; Snyder, S. A. *Synthesis* **2013**, *45*, 1886–1898.

Chloride ion displacement of PhSCl from intermediates **217** or **218** by S_N2 mechanism furnishes the desired inverted chloride (*S*)-Cl (path **a** or **a'**). Alternative pathways from carbenium ion **219** (path **b**), or concerted ligand coupling (1,2-chloride shift) from sulfurane **217** via **220** (path **c**), which is expected to proceed with retention of configuration, would generate the undesired chloro-enantiomer (*R*)-Cl.

In conclusion, a novel chlorination reaction from phenyl sulfides and β-sulfido (thio)esters has been developed. This rapid transformation enables the preparation of activated alkyl chlorides and β-chloride (thio)esters under very mild reaction conditions. Moreover, preliminary results show that the reaction proceeds with high stereoespecifity, making it possible for the synthesis of optically active benzylic chlorides from easily accessible enantioenriched sulfa-Michael adducts.

CHAPTER 5

CONCLUSIONS

5. CONCLUSIONS

A highly stereoselective generation of all-carbon quaternary and *C–N* tetrasubstituted carbons has been developed via bifunctional Brønsted base catalyzed Michael reaction of two types of challenging *C*-nucleophiles as α-substituted cyanoacetates and azlactones with α’-oxy enones as key enoate surrogates. Parallel experiments using simple enones or esters and the respective α’-oxy enones indicate that the α’-oxy ketone moiety is crucial for achieving high levels of reactivity and stereoselectivity. The resulting α’-oxy ketone adducts can smoothly be converted into the corresponding carboxylic acid derivative, ketone or aldehyde.

Excellent results have been observed in the Michael addition of α-substituted cyanoacetates to α’-oxy enones with different substitution patterns (β- and α-substituted). The corresponding adducts containing adjacent tertiary quaternary stereocenters or non-adjacent tertiary quaternary stereocenters have been satisfactorily constructed through a Brønsted base catalyzed Michael reaction. Furthermore, azlactones have also demonstrated to be adequate substrates for this type of reaction with non-substituted α’-oxy enones. The present methodology provides access to synthetically relevant building blocks bearing a fully substituted stereogenic carbon atom in enantioenriched form.

On the other hand, 4-substituted pyrrolidin-2,3-diones have been employed as efficient new Michael donor templates with various electrophiles in the conjugated addition promoted by Brønsted base catalysts. Moreover, an approach to obtain $\beta^{2,2}$-amino acid derivatives has been described which is suitable for the incorporation of these unit into peptides through previous transformation into *N*-carboxyanhydrides.

Finally, a mild and rapid methodology has been established for the obtention of alkyl benzylic chlorides and β-chloro (thio)esters carrying out the oxidative desulfurative chlorination with (dichloroiodo)benzene. The reaction proceeds with high stereospecificity, making it useful for the synthesis of optically active species from enantioenriched sulfa-Michael adducts.

All these protocols provide interesting products for further transformations and open the way to the development of other related protocols.

CHAPTER 6

EXPERIMENTAL SECTION

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6. EXPERIMENTAL SECTION

6.1. MATERIAL AND TECHNIQUES

6.1.1. Reagents and solvents

Reagents were purchased from different commercial suppliers (Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated.

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

When anhydrous solvents were required, they were dried following established procedures.[333] Dichloromethane was dried over CaH_2, and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma aldrich) columns.

6.1.2. General experimental

All non-aqueous reactions were performed 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 a 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-110, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (~0.5 mmHg) was employed.

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[333] Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory Chemicals* 3rd Edition Butterworth-Heinemann, Oxford **1988**.

6.1.3. 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 Bioblock lamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 ml of water (limited lifetime), followed by heating.

Chromatographic purification was performed on Merck 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. Optical rotations

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).

6.1.4. Melting points

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

6.1.5. 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) 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 8.1 program was used to process and edit the registered spectra.

6.1.6. 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) or in the Royal Collegue of Surgeons of Ireland (RCSI).

6.1.7. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported.

6.1.8. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on either a Waters 600 (equipped with Photodiode Array Detector Waters 2996). The used columns were AD-H, AD-3, AY-H, AS-H, IA, IC and Phenomenex Lux 3µ Cellulose-4; and flow/solvent conditions are given for each compound.

6.1.9. 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.

6.1.10. Computational studies

All structures were optimized using the functional B3LYP39[334] and the 6-31G* basis set as implemented in Gaussian 09.[335] All energy minima and transition structures were characterized by frequency analysis. The stationary points were characterized by

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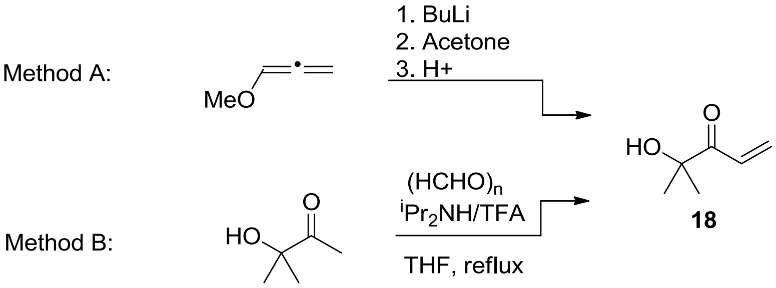
[334] a) Becke, A. D. J. *Chem. Phys*. **1993**, *98*, 5648–5652. b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

[335] Gaussian 09, Revision B.01; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian, Inc., Wallingford CT, **2009**.

frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinates (IRC)[336] were followed to verify the energy profiles connecting each transition state to the correct associated local minima. The energies reported in this work include single-point calculations at M06-2X/6-311++G** level on the IEF-PCM solvation model (solvent = dichloromethane),[337] using the previously optimized gas-phase structures (B3LYP/6-31G*).

6.2. GENERAL PROCEDURE FOR THE SYNTHESIS OF α'-OXY ENONES

6.2.1. Preparation of α'-hydroxy enone 18



METHOD A:[338] To a solution of methoxypropadiene (3.50 g, 50 mmol) in dry Et_2O (100 mL) at –40 °C, *n*BuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at –40 °C for 10 min. Then, acetone (4.04 mL, 55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-methyl-3-methoxy-3,4-pentadien-2-ol as a yellow liquid (5.65 g, 41.0 mmol, 82%) that was employed in the next step without further purification.

The material from previous step (2-methyl-3-methoxy-3,4-pentadien-2-ol, 5.65 g, 44 mmol) was added dropwise to 5% aq H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 h. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et_2O (5 x 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4.

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[336] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem*. **1990**, *94*, 5523–5527.

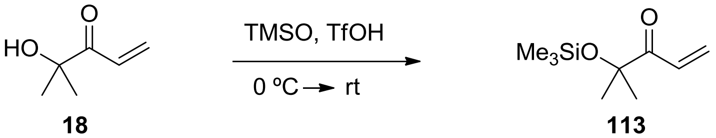
[337] a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys*. **1997**, *107*, 3032-3047. b) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct. (Theochem)* **1999**, *464*, 211–226.

[338] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc*. **2003**, *125*, 13942–13943.

The solvent was removed to give a yellow oil which upon distillation afforded the enone as a colorless liquid (4.42 g, 38.7 mmol, 88%) b.p. 45 ºC (13 mmHg); IR (neat, cm^{-1}) 3445 (OH), 1693 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.73 (dd, *J* = 9.5, 16.8 Hz, 1H), 6.50 (dd, *J* = 2.2, 16.8 Hz, 1H), 5.82 (dd, *J* = 2.2, 10.3 Hz, 1H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.3, 131.1, 128.8, 75.4, 26.1.

METHOD B:[339] Commercially available 3-hydroxy-3-methyl-2-butanone (1 equiv., 5.3 mL, 50 mmol) and paraformaldehyde (2 equiv., 3 g, 100 mmol) were added to a solution of $^{i}Pr_2NH$ (2 equiv., 14.0 mL, 100 mmol) and TFA (2.5 equiv., 9.6 mL, 125 mmol) in THF (250 mL). The mixture was refluxed and paraformaldehyde (2 equiv., 3 g, 100 mmol) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH_2Cl_2 (100 mL) was added and the mixture was washed with 1N HCl (75 mL), 1N NaOH (75 mL) and brine (75 mL), and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure (230 mbar/ bath 40 ºC). The residue was purified by flash column chromatography on silica gel (eluent: diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one as colorless oil. Yield: 5.0 g, 44.5 mmol, 89%.

6.2.2. Preparation of 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one 113[340]



18 **113**

3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (1.5 equiv., 3.4 mL, 22.5 mmol) and 3 drops of trifluoromethanesulfonic acid were added to enone 1 (1 equiv., 1.68 g, 15 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL). The organic phase was then dried over with $MgSO_4$ and concentred under reduced pressure to afford the title compound **113** as a colorless oil. Yield: 2.6 g, 14.0 mmol, 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3, 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 130.7, 129.2, 79.3, 27.2, 2.3.

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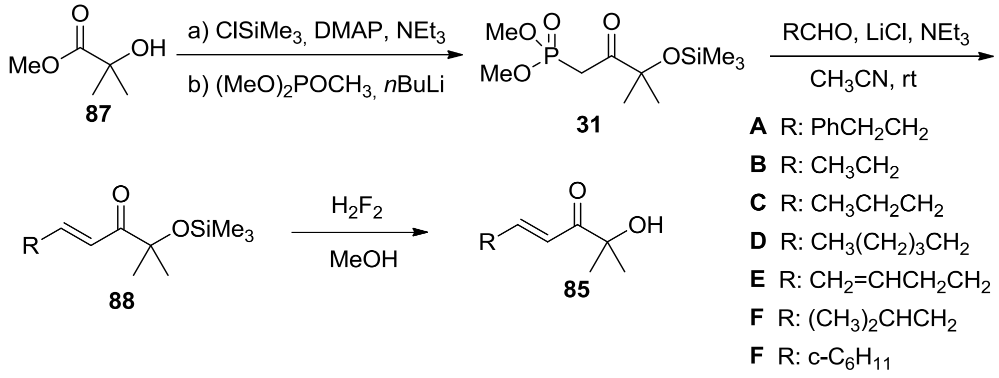
[339] Adapted from: Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715–1717.

[340] Adapted from: Aizpurua, J. M.; Palomo, C.; Palomo, A. L. *Can. J. Chem.* **1984**, *62*, 336–340.

6.2.3. Preparation of alkyl-substituted α’-hydroxy enones 85A-F[341]



A R: $PhCH_2CH_2$
B R: CH_3CH_2
C R: $CH_3CH_2CH_2$
D R: $CH_3(CH_2)_3CH_2$
E R: $CH_2{=}CHCH_2CH_2$
F R: $(CH_3)_2CHCH_2$
F R: c-C_6H_{11}

*6.2.3.1. Preparation of (3-methyl-2-oxo-3-trimethylsilyloxybutyl)phosphonic acid dimethyl ester **31**[342]*

Methyl 2-hydroxyisobutyrate (6.9 mL, 60 mmol) was added under a nitrogen atmosphere to a solution of dimethyl amino pyridine (1.22 g, 10 mmol), triethylamine (10 mL, 50 mmol) and trimethylchlorosilane (6.3 mL, 50 mmol) in 50 mL of dichloromethane. The reaction mixture was stirred at room temperature for 24 hours. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1 x 50 mL) and water (1 x 50 mL). The solvent was removed under reduced pressure to give the corresponding triethylsilyl ether which was used as such without further purification. Yield: 12.6 g (92%). Dimethyl methyl phosphonate (13.8 mL, 130 mmol, 2.5 eq) in dry THF (40 mL) was added dropwise to a cold solution of *n*BuLi (1.6 M in hexanes, 79 mL, 130 mmol) in dry THF (80 mL) at –78 °C under a nitrogen atmosphere. After 30 min of stirring at the same temperature, a solution of the crude trimethylsilyl ether prepared above (12 g, 51 mmol) in dry THF (100 mL) was added dropwise at –78 °C. The mixture was stirred at the same temperature (–78 °C) for 3 h and then quenched at this temperature with a saturated ammonium chloride solution (200 mL). The reaction mixture was allowed to reach room temperature, it was extracted with diethyl ether (3 x 250 mL) and dried over $MgSO_4$. The solvent was then evaporated under reduced pressure to get the title compound which was used for the next step without further purification. Yield: 14.6 g (99%).

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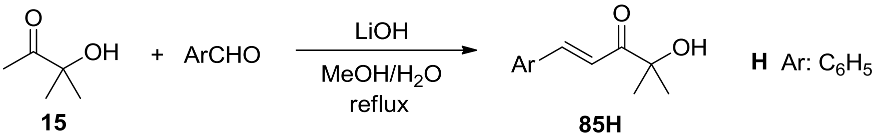
[341] a) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189. b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

[342] Adapted from: a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525–2529. b) McCarthy, D. G.; Collins, C. C.; O’Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667–3675.

*6.2.3.2. Preparation of enones **88** and their desilylation to **85***

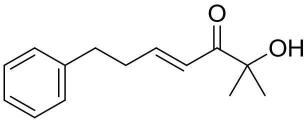
Dried LiCl (1.17 g, 27 mmol) and Et_3N (3.8 mL, 27 mmol) were added successively to a solution of (3-methyl-2-oxo-3-trimethylsilyloxybutyl)phosphonic acid dimethyl ester (7.95 g, 27 mmol) in dry MeCN (67 mL). The resulting milky suspension was stirred for 15 min at room temperature and the corresponding aliphatic aldehyde (27 mmol) was added dropwise. The mixture was stirred for 40 h, diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was dissolved in methanol (200 mL) and a solution of hydrofluoric acid (HF) (48% in water, 5 mL) was added. The resulting mixture was stirred for 0.5 h at room temperature and then was neutralized by addition of a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude desilylated product that was purified by flash silica gel chromatography (hexane-EtOAc, 40:1).

6.2.4. Preparation of aryl-substituted α’-hydroxy enone 85H[343]



3-Hydroxy-3-methyl-2-butanone 7 (5.0 g, 49 mmol) was dissolved in a mixture of MeOH (120 mL) and H_2O (40 mL). Freshly distilled aldehyde (87.5 mmol) was then added followed by $LiOH{\cdot}H_2O$ (10.28 g, 245 mmol). The reaction mixture was stirred at reflux for 3 h, and after removal of MeOH under reduced pressure, the aqueous residue was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The CH_2Cl_2 extracts were combined, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (hexane-EtOAc, 50:1).

(*E*)-2-Hydroxy-2-methyl-7-phenyl-hept-4-en-3-one 85A[343a]



The general procedure for alkyl-substituted α’-hydroxy enones was followed using hydrocinnamaldehyde (15.2 mL, 240 mmol). Colourless oil. Yield 7.7 g, 177 mmol, 74%. All

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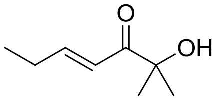
[343] a) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189. b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

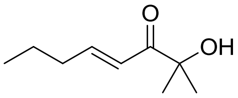
spectroscopic data were consistent with those previously reported. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.28-7.21 (m, 6H), 6.41 (d, *J* = 15.5Hz, 1H), 3.98 (s, 1H), 2.8 (t, *J* = 8Hz, 2H), 2.59 (m, 2H), 1.34 (s, 6H).

(*E*)-2-Hydroxy-2-methylhept-4-en-3-one 85B[343a]



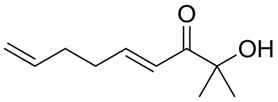
The general procedure for alkyl-substituted α'-hydroxy enones was followed using *n*-propanal (17.5 mL, 240 mmol). Colourless oil. Yield 6.6 g, 134 mmol, 56%. All spectroscopic data were consistent with those previously reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (m, 1H), 6.38 (d, *J* = 15Hz, 1H), 4.0 (s, 1H), 2.27 (m, 2H), 1.36 (s, 6H), 1.08 (t, *J* = 6.0 Hz, 3H).

(*E*)-2-Hydroxy-2-methyloct-4-en-3-one 85C[344]



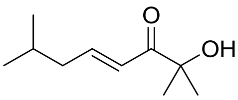
The general procedure for alkyl-substituted α'-hydroxy enones was followed using n-butanal (25.7 mL, 240 mmol). Colourless oil. Yield 7.78 g, 180 mmol, 75%. All spectroscopic data were consistent with those previously reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 1H), 6.46 (d, *J* = 15.4 Hz, 1H), 4.09 (s, 1H), 2.30 –2.20 (m, 2H), 1.55 – 1.43 (m, 2H), 1.40 (s, 6H), 0.97 (t, *J* = 7.4 Hz, 3H).

(*E*)-2-Hydroxy-2-methylnona-4,8-dien-3-one 85E



The general procedure for alkyl-substituted α'-hydroxy enones was followed using 4-pentenal (16.5 mL, 240 mmol). Colourless oil. Yield 6.6 g, 156 mmol, 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dt, *J* = 15.4, 6.7 Hz, 1H), 6.43 (dt, *J* = 15.3, 1.5 Hz, 1H), 5.80 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H), 5.13 – 4.97 (m, 2H), 3.96 (s, 1H), 2.45 – 2.32 (m, 2H), 2.32 – 2.14 (m, 2H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 145.0, 137.0, 122.8, 115.9, 75.3, 32.1, 26.5. HRMS (ESI): $C_{10}H_{17}O_2$ $[M+H]^+$ calcd.: 169.1229, found: 169.1216.

(*E*)-2-Hydroxy-2,7-dimethyloct-4-en-3-one 85F[343a]



The general procedure for alkyl-substituted α'-hydroxy enones was followed using isopentanaldehyde (25.7 mL, 240 mmol). Colourless oil. Yield 7.78 g, 132 mmol, 55%. All spectroscopic data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dt, *J* = 15.1, 7.5 Hz, 1H), 6.40 (dt, *J* = 15.3, 1.4 Hz, 1H), 3.98 (s, 1H), 2.15 (ddd, *J* = 7.4, 6.8, 1.4 Hz, 2H), 1.80 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.39 (s, 6H), 0.94 (d, *J* = 6.7 Hz, 6H).

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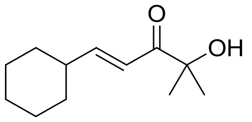
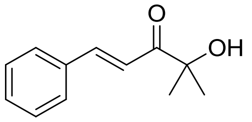
[344] Katritzky, A. R.; Feng, D.; Lang, H. *J. Org. Chem.* **1997**, *62*, 706–714.

(*E*)-1-Cyclohexyl-4-hydroxy-4-methylpent-1-en-3-one 85G[343a]



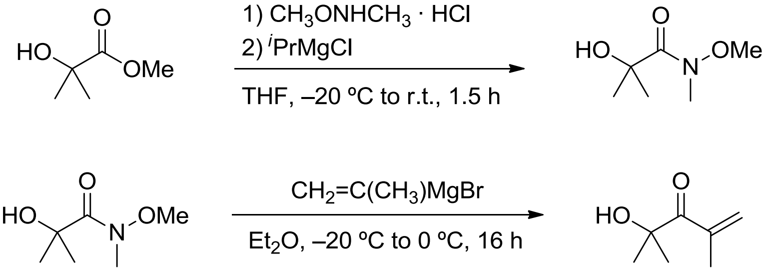
The general procedure for alkyl-substituted α'-hydroxy enones was followed using cyclohexylcarbaldehyde (29 mL, 240 mmol). Colourless oil. Yield 7.0 g, 103.2 mmol, 43%. All spectroscopic data were consistent with those previously reported. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.10 (dd, *J* = 15.5, 7.0 Hz, 1H), 6.36 (dd, *J* = 15.5, 1.4 Hz, 1H), 4.00 (s, 1H), 2.18 (m, 1H), 1.85 – 1.64 (m, 4H), 1.38 (s, 6H), 1.33 – 1.10 (m, 4H), 0.91 – 0.81 (m, 2H).

(*E*)-2-Hydroxy-2-methyl-5-phenylpent-4-en-3-one 85H[345]



The general procedure for aryl-substituted α'-hydroxy enones was followed using benzaldehyde (25 mL, 240 mmol). Colourless oil. Yield 7.0 g, 140 mmol, 60%. All spectroscopic data were consistent with those previously reported.^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (d, *J* = 15.7 Hz, 1H), 7.58 (m, 2H), 7.40 (m, 3H), 7.02 (d, *J* = 15.4 Hz, 1H), 4.00 (s, 1H), 1.45 (s, 6H).

6.2.5. Preparation of 4-hydroxy-2,4-dimethylpent-1-en-3-one 86



1st step: To a solution of methyl 2-hydroxy-2-methylpropanoate (1.77 g, 15 mmol, 1 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv.) in THF (50 mL), a 2M solution of ^{i}PrMgCl in THF (60 mmol, 4 equiv.) was added at –20 ºC. The reaction mixture was stirred for 1.5 h at room temperature. The reaction was then quenched with an aqueous saturated solution of NH$_4$Cl (30 mL) and extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic phases were dried over MgSO$_4$ and filtered and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography (eluent hexane/ethyl acetate, 80/20) to obtain the desired amide product as colourless oil. Yield 1.99 g, 13.5 mmol, 90%. ^{1}H and ^{13}C

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[345] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

NMR spectra were coincident with those reported in the literature.[346] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (s, 1H), 3.73 (s, 3H), 3.28 (s, 3H), 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 72.1, 61.0, 33.6, 26.5.

2nd step: To a solution of the starting amide (1.85 g, 10 mmol, 1 equiv.) in Et_2O (20 mL), a solution of isopropenyl magnesium bromide (0.5 M, 60 mL, 3 equiv.) was added at –20 ºC, and the resulting mixture was stirred at 0 ºC for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O, 95/5) to obtain the desired product as a colourless oil. Yield: 833 mg, 6.5 mmol, 65%. ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[347] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.75 (s, 1H), 4.11 (s, 1H), 1.86 (s, 3H), 1.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3, 140.3, 125.6, 72.0, 28.3, 19.9.

6.3. Preparation of catalysts

Catalysts $(DHQD)_2$Pyr **C49** and **C2** are commercially available and were purchased from commercial suppliers. Catalysts **C4**, **C9, C47**, **C50**, **C51** and **C68** were prepared as follows.

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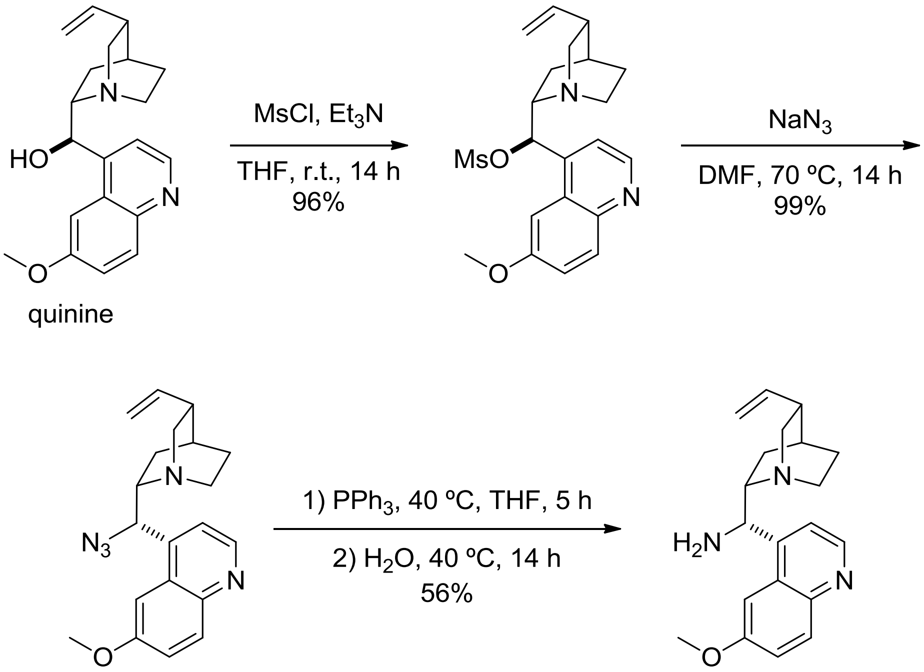
[346] Miege, F.; Trost, B. M. *J. Am. Chem. Soc*. **2014**, *136*, 3016–3019.

[347] Basheer, A.; Mishima, M.; Marek, I. *Org. Lett*. **2011**, *13*, 4076–4079.

6.3.1. Preparation of 9-amino-(9-deoxy)epiquinine[348]



1st step:[349] A mixture of quinine (1 equiv., 16.2 g, 50 mmol) and triethylamine (3.6 equiv., 25.1 mL, 180 mmol) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (1.8 equiv., 7.0 mL, 90 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford crude productwith 96% yield, which was used in the next step without further purification.

2nd step:[350] The crude product (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 ºC and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 70 ºC for 16 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl thoroughly (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield which was used in the next step without further purification.

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[348] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

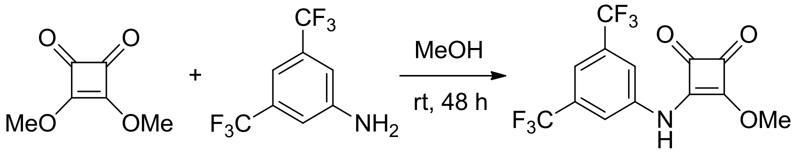
[349] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.

[350] Adapted from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality*, **2003**, *15*, 127–134.

3rd step:[350] The crude product was dissolved in THF (250 mL) and PPh_3 (1 equiv., 12.6 g, 48 mmol) was added. The reaction mixture was heated to 40 ºC and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 ºC. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 ºC and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 8.7 g, 26.9 mmol, 56%. All data were consistent with those previously reported. ^1H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, J = 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, J = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

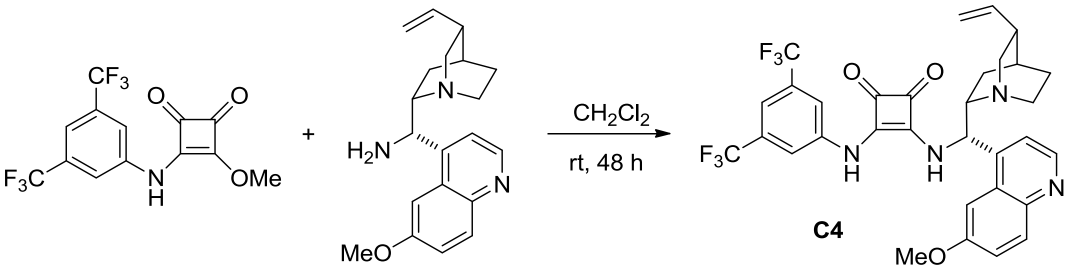
6.3.2. Preparation of squaramide-based Brønsted catalysts C4, C50 and C51

6.3.2.1. Preparation of common squaric ester monoamide intermediate[351]



To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1.42 g, 10.0 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1.56 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give desired product (2.25 g, 6.6 mmol, 66%). m.p. 179-181 °C. All spectroscopic data were identical to those reported in literature. ^1H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

*6.3.2.2. Preparation of Catalyst **C4***[351]



C4

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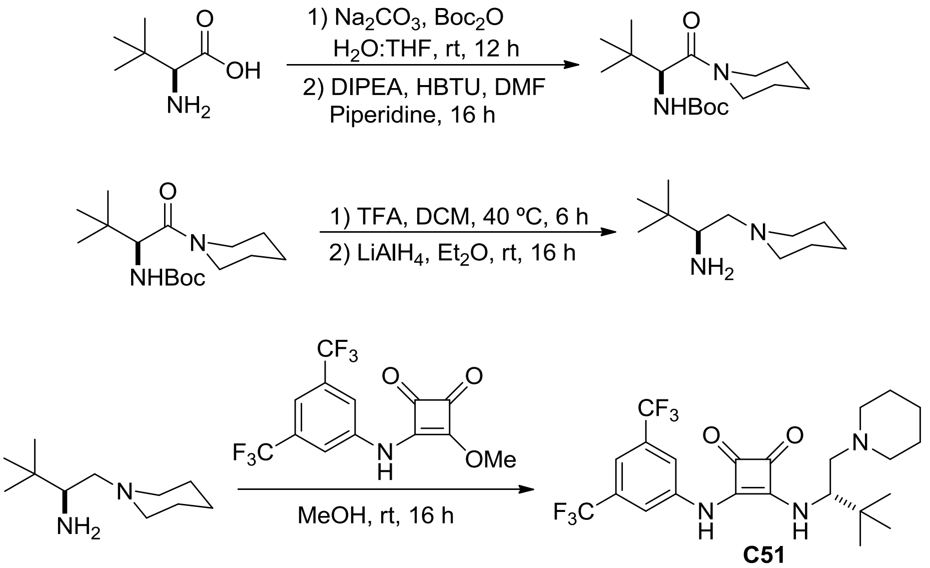
[351] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

To a solution of squaric ester monoamide prepared as above (339 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) 9-amino-(9-deoxy)epiquinine (323 mg, 1.0 mmol) was added. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography. White solid (441 mg, 0.70 mmol, 70% yield); m.p. 224–225 °C. All spectroscopic data were identical to those reported in literature. ^1H NMR (300 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.80 (d, J = 4.5 Hz, 1H), 8.36 (br s, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, J = 10.0 Hz, 1H), 7.67 (d, J = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s, 3H), 3.52-3.42 (m, 1H), 3.30- 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H).

*6.3.2.3. Preparation of Catalyst **C51***



C51

1st step:[352] Na_2CO_3 (2.12 g, 20 mmol, 2 equiv.) and Boc_2O (3.3 g, 15 mmol, 1.5 equiv.) were added to a solution of *t*-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL) and THF (5 mL) at 0 °C. After stirring for 12 h at room temperature HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The aqueous phases were united and washed with brine (50 mL) and dried over $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was then redissolved in dry DMF dissolution (20 mL) and DIPEA (2.58 g, 20 mmol, 2 equiv.) and HBTU (5.7 g, 15 mmol, 1.5 equiv.) were added. After stirring for 1 h piperidine (0.94 g, 11 mmol, 1.1 equiv.) was added and the mixture was stirred for further 16 h. The reaction was quenched adding HCl 1 M (20 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were united and washed with HCl 1 M and brine (20 mL) and dried over $MgSO_4$, after which the solvent was removed under

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[352] Adapted from: Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.* **2010**, *16*, 13068–13071.

reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 85/15) to afford *tert*-butyl (S)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate as a white solid. Yield: 2.5 g, 8.3 mmol, 83%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.43 (s, 9H), 1.52 – 1.62 (m, 6H), 3.46 – 3.69 (m, 4 H), 4.54 (d, *J* = 9.7 Hz, 1H), 5.38 (d, *J* = 9.6 Hz, 1H).

2nd step: Previously obtained amide (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 ^oC until no more starting material was observed by TLC (eluting with hexane/ EtOAc 70/30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40 %), dried over $MgSO_4$ and the solvent was removed under reduced pressure obtaining the aminoamide as a yellow oil. The aminoamide was then dissolved in dry diethyl ether (10 mL) and was added dropwise over a suspension of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 ^oC under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 h. The reaction was quenched adding water (1.2 mL), NaOH 15 % (1,2 mL) and water (3.6 mL) at 0 ^oC. The result was filtered and the liquid was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 1/1) to afford (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine as yellow oil. Yield: 1.16 g, 6.8 mmol, 92%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.52 (d, *J* = 12.3 Hz, 4H), 2.28 (dd, *J* = 12.3, 2.8 Hz, 3H), 2.13 (dd, *J* = 12.1, 11.2 Hz, 1H), 1.61-1.53 (m, 4H), 1.44 – 1.42 (m, 2H), 0.90 (s, 9H).

3rd step:[353] To a solution of the diamine (780 mg, 4.6 mmol, 1 equiv.) in methanol (30 mL) the squaric ester monoamide obtained above (1.56 g, 4.6 mmol, 1 equiv.) was added and the mixture was stirred until complete disappearance of the starting amide as monitored by TLC (16 h). The formed white precipitate was filtered and washed with CH_2Cl_2 to afford essentially pure **C51** as a white solid. m.p. 246‒248 ^oC. Yield: 1.29 g, 2.6 mmol, 59%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.08 (s, 2H), 7.64 (s, 1H), 4.07 – 3.93 (m, 1H), 2.49 – 2.04 (m, 5H), 1.51 – 1.22 (m, 6H), 0.93 (s, 9H).

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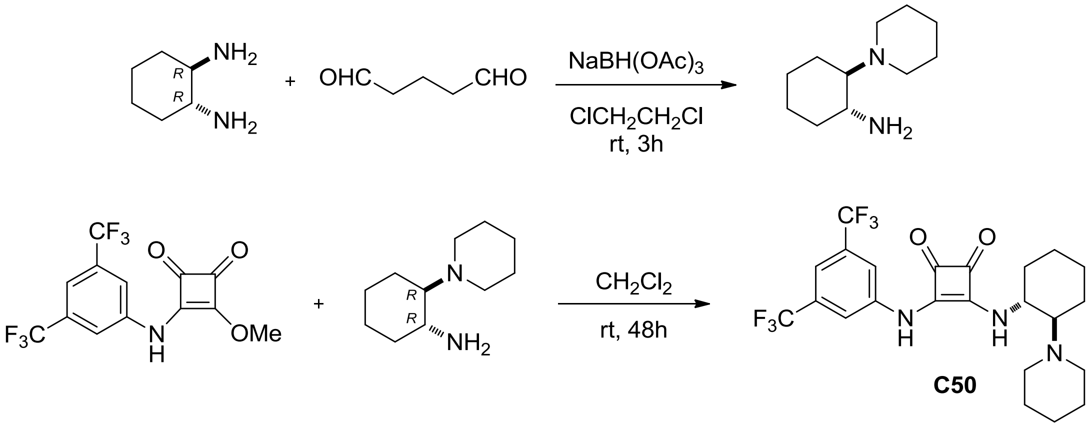
[353] Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.

6.3.2.4. Preparation of Catalyst ***C50***



1st step:[354] Glutaraldehyde (50 wt% in H_2O, 1.90 mL, 10.4 mmol) was added dropwise into a mixture of diamine (1.140 g, 10 mmol) and $NaBH(OAc)_3$ (8.500 g, 40 mmol) in $ClCH_2CH_2Cl$ (60 mL) at room temperature. The resulting mixture was stirred at room temperature for 3h, and quenched with NaOH aq solution (6M, 30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were concentrated. The residue was dissolved in 50 mL CH_2Cl_2, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give 1.622 g product as a yellow liquid (89% yield). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 – 2.68 (m, 1H), 2.67 – 2.49 (m, 3H), 2.41 – 2.19 (m, 2H), 2.16 – 1.92 (m, 2H), 1.88 – 1.34 (m, 8H), 1.31 – 0.97 (m, 4H).

2nd step:[355] To a solution of squaramide (339 mg, 1.0 mmol) in 5 mL CH_2Cl_2 was added 2-(piperidin-1-yl)cyclohexanamine (379 mg, 1.0 mmol). The reaction mixture was stirred for 48 h at room temperature. After solvent evaporation the desired product was obtained by silica gel column chromatography. White solid (347 mg, 0.71 mmol, 71% yield). m.p. 134–136 °C. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.43 (s, 1H), 4.00 – 3.80 (m, 1H), 2.66 – 2.49 (m, 2H), 2.39 – 2.14 (m, 3H), 1.93 – 1.59 (m, 4H), 1.48 – 0.98 (m, 10H).

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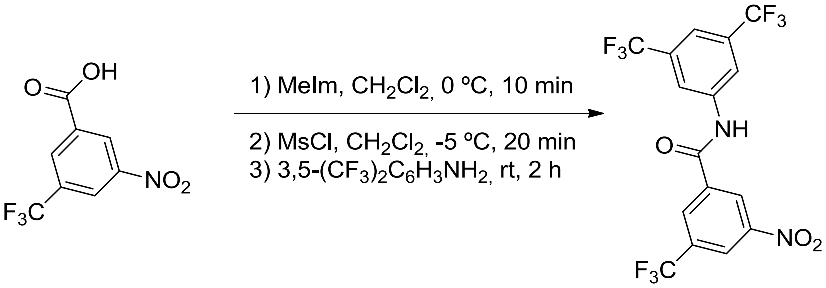
[354] Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

[355] Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241–1246.

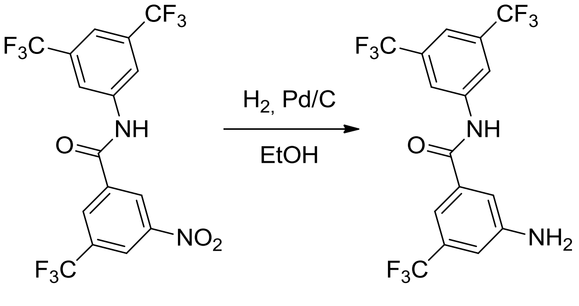
6.3.2.5. Preparation of catalyst ***C68***

_N_-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide[356]



1-Methylimidazole (1.99 mL, 25 mmol, 2.5 equiv.) was added to a slurry of the 3-nitro-5-(trifluoromethyl)benzoic acid (2.351 g, 10 mmol, 1 equiv.) in CH_2CL_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.16 mL, 15 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL) was added to the mixture under –5 °C. After the mixture was stirred under that temperature for 20 min, 3,5-bis(trifluoromethyl)aniline (1.56 mL, 10 mmol, 1 equiv.) was added. Then the mixture was stirred at room temperature for 2 h. H_2O (100 mL) was added to the mixture and a solid precipitated, which was solved with EtOAc (100 mL). The organic layer was washed with brine (3 x 50 mL) and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the title product as a white solid. Yield: 4.5 g, 10 mmol, >99%. ^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (s, 1H), 8.72 (s, 2H), 8.43 (s, 2H), 7.72 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 164.9, 150.3, 141.9, 138.7, 134.3 (q), 133.3 (q), 131.6, 131.5, 127.5, 124.8, 124.7, 121.7, 121.6, 118.7. UPLC-DAD-QTOF: $C_{16}H_6F_9N_2O_3$ $[M-H]^-$ calcd.: 445.0235, found: 445.0233.

3-Amino-N-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide



To a solution of the protected aniline (4.5 g, 10 mmol) in EtOH (20 mL) and EtAc (2 mL) under inert atmosphere, Pd/C was added (450 mg, Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20h. After that the solution was filtered over celite and the

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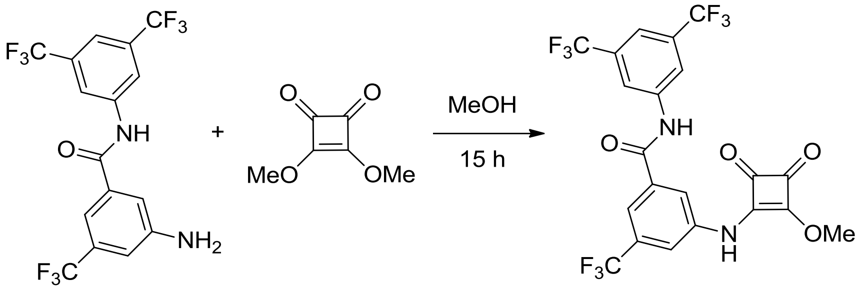
[356] Adapted from: Mao, L.; Wang, Z.; Li, Y.; Han, X.; Zhou, W. *Synlett* **2011**, *1*, 129–133.

filtrate was concentrated under reduced pressure to afford the hydrogenated product. Yield: 4.2 g, 10 mmol, >99%. ^{1}H NMR (300 MHz, CD_3OD) 8.40 (s, 2H), 7.77 (s, 1H), 7.68 (s, 1H), 7.49 – 7.42 (m, 1H), 7.42 – 7.38 (m, 1H), 7.12 (s, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 168.4, 151.1, 142.3, 137.4, 133.3 (q), 132.4 (q), 121.5, 118.2, 117.8, 115.0, 115.0, 113.1, 113.1. UPLC-DAD-QTOF: $C_{16}H_{10}N_2OF_9$ $[M+H]^+$ calcd.: 417.0649, found: 417.0638.

N-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide[357]



To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (711 mg, 5.0 mmol, 1 equiv.) in MeOH (10 mL) was added the free aniline (2.29 g, 5.5 mmol, 1.1 equiv.) at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtrated and washed with MeOH. Obtained white solid was dried in vacuo to give the title product as a white solid. Yield: 2.27 g, 4.4 mmol, 88%. ^{1}H NMR (300 MHz, Acetone-*d*$_6$) δ 10.71 (s, 1H), 10.52 (s, 1H), 8.03 (s, 2H), 7.73 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.39 (s, 1H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 187.5, 184.4, 179.6, 169.2, 164.2, 140.7, 139.5, 136.0, 130.5 (q), 129.5 (q), 125.0, 122.6, 121.4, 120.1, 119.1, 118.7, 116.8, 60.8. UPLC-DAD-QTOF: $C_{21}H_{12}F_6N_2O_4F_9$ $[M+H]^+$ calcd.: 527.0653, found: 527.0655.

N-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C68)[358]

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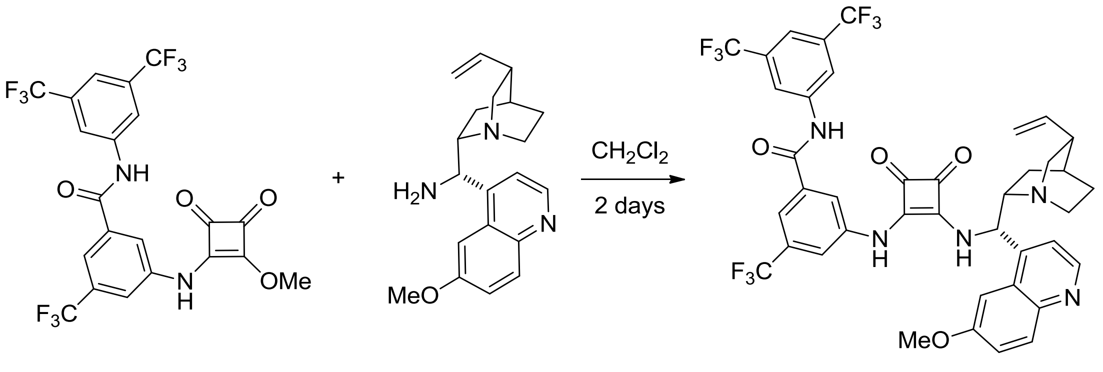
[357] Adapted from: Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 3004–3006.

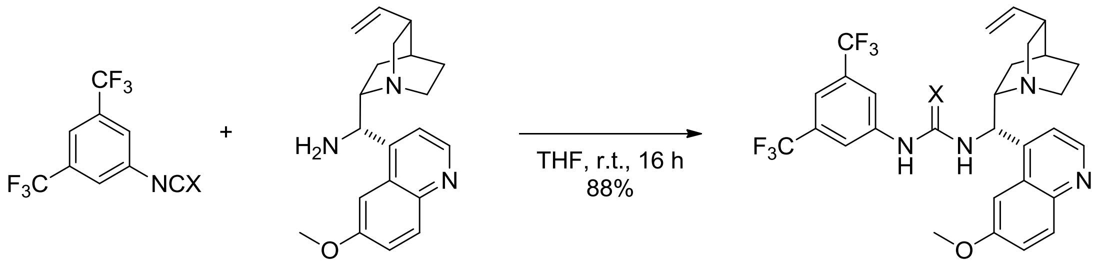
[358] Adapted from: see ref. 351, page 184.



C68

To a suspension of the squarate (1.05 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was added (*R*,*R*)-9-deoxy-9-epiaminoquinine (646 mg, 2.0 mmol, 1 equiv.) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was evaporated and purified by silica column chromatography (CH_2Cl_2:MeOH, 98:2) to give the pure **C68** catalyst as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, *J* = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.22 – 5.82 (m, 2H), 5.30 – 4.81 (m, 2H), 3.96 (s, 3H), 3.56 – 3.06 (m, 4H), 2.85 – 2.55 (m, 2H), 2.28 (q, J = 8.0, 7.2 Hz, 1H), 1.84 – 1.34 (m, 4H), 0.68 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.6, 180.1, 168.5, 164.4, 163.0, 157.9, 147.8, 144.3, 143.1, 142.1, 140.7, 140.3, 136.0, 131.5, 130.9, 130.5, 127.5, 125.1, 121.2, 120.0, 118.0, 117.5, 116.8, 114.3, 101.5, 58.9, 55.7, 27.3, 26.0. UPLC-DAD-QTOF: $C_{40}H_{33}N_5O_4F_9$ $[M+H]^+$ calcd.: 818.2389, found: 818.2398.

6.3.3. Thiourea and urea containing Brønsted base catalysts C47[359] and C9[360]



X = S
X = O

C9 X = O 82%
C47 X = S 88%

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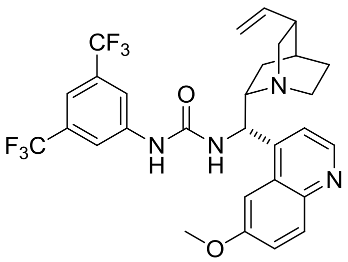
[359] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A. Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

[360] Greenaway, K.; Dambruoso, P.; Ferrali, A.; Hazelwood, A. J.; Sladojevich, F.; Dixon, D. J. *Synthesis* **2011**, *12*, 1880–1886.

General procedure[359]

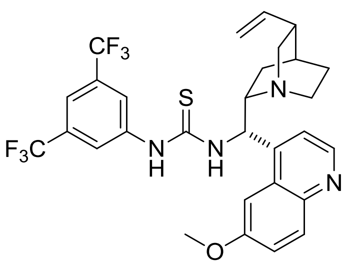
To a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 1.6 g, 5 mmol) in dry THF (7.5 mL) at 0 ºC, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.1 equiv., 1.5 g, 5.5 mmol) or bis(trifluomethyl)phenyl isocyanate (1.1 equiv., 0.6 mL, 5.5 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford the title compounds **C9** and **C47**.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea C9



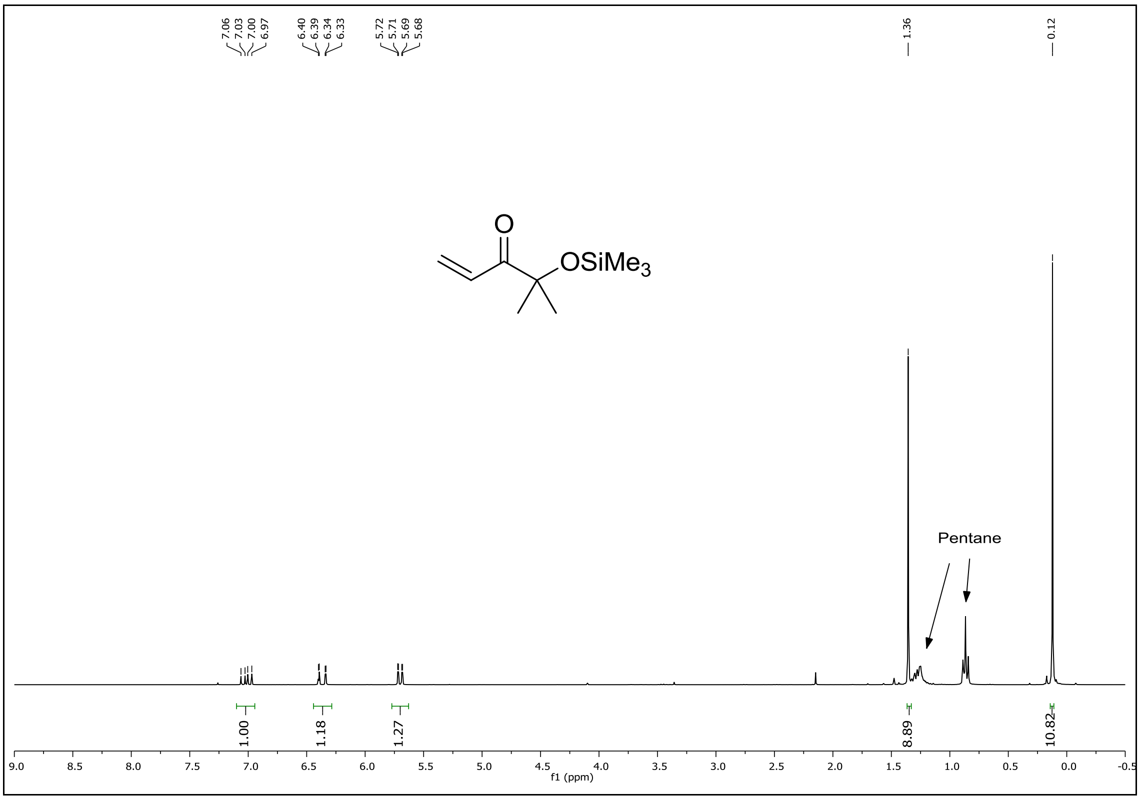
The title compound **C9** was prepared from bis(trifluomethyl)phenyl isocyanate (0.6 mL, 5.5 mmol) according to the general procedure. White solid, yield: 2.4 g, 4.1 mmol, 82%. m. p. 132–134 ºC. All data were consistent with those previously reported.^{1}H NMR (300 MHz, CD_3OD) δ 8.58 (d, *J* = 4.5 Hz, 1H), 7.84–7.90 (m, 3H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 5.83–5.89 (m, 1H), 5.65 (bs, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.91 (s, 3H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 3.03–3.15 (m, 4H), 2.41–2.43 (m, 1H), 1.40–1.73 (m, 3H), 1.17–1.25 (m, 3H).

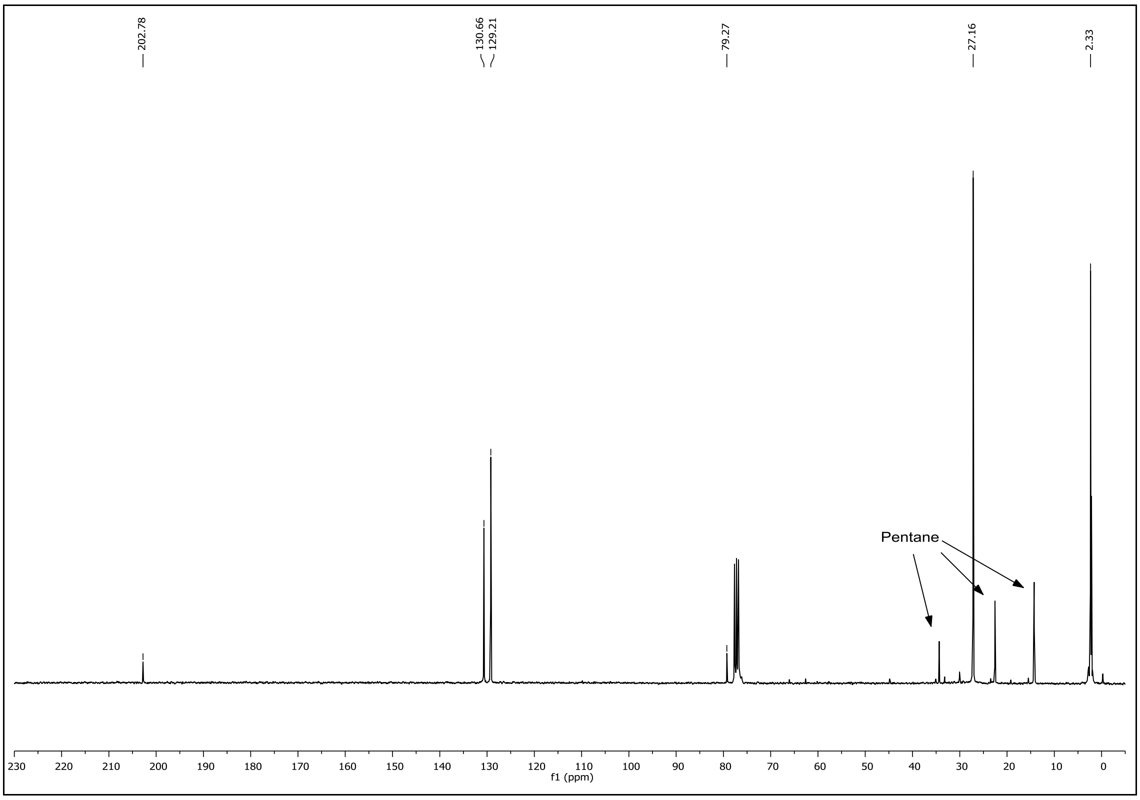
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea C47

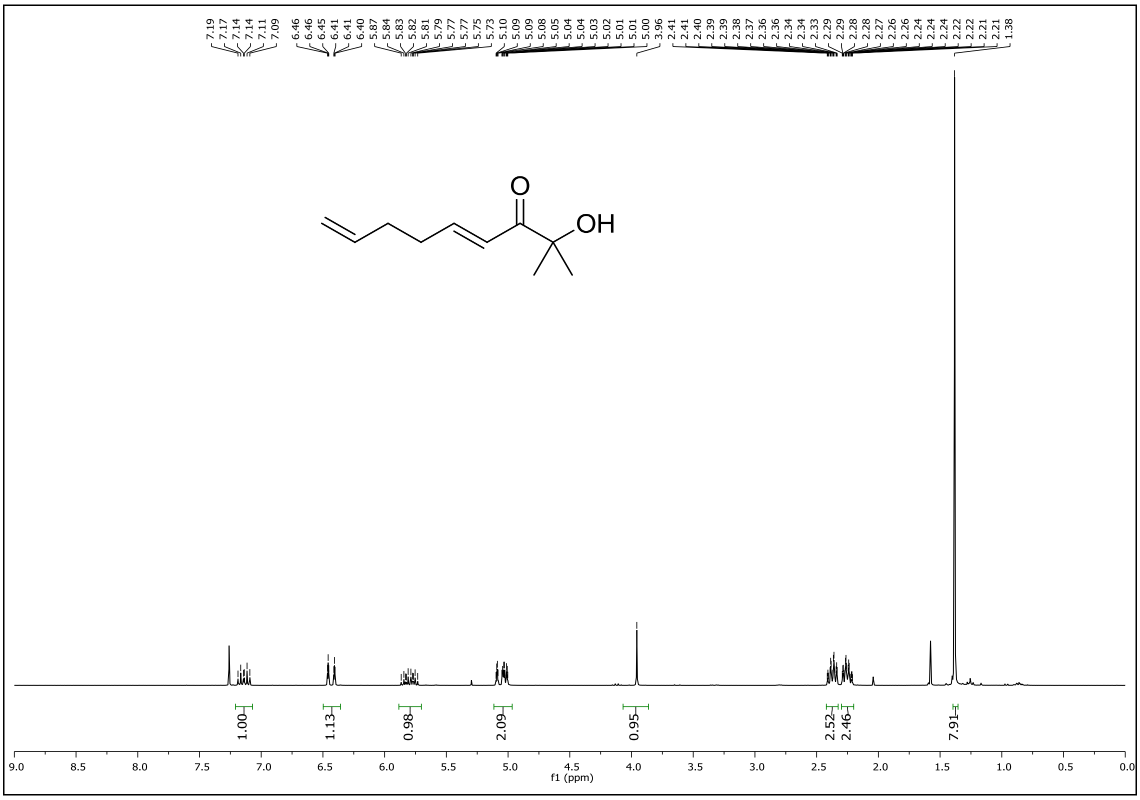


The title compound **C47** was prepared from bis(trifluomethyl)phenyl isothiocyanate (1.5 g, 5.5 mmol) according to the general procedure . White solid, yield: 2.6 g, 4.4 mmol, 88%. m. p. 123–125 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CD_3OD) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56–3.53 (m, 1H), 3.39–3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38–2.35 (m, 1H), 1.71–1.68 (m, 2H), 1.64–1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

6.3.4. Representative NMR spectra



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OH
1.00
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0.98
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0.95
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2.46
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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1.0
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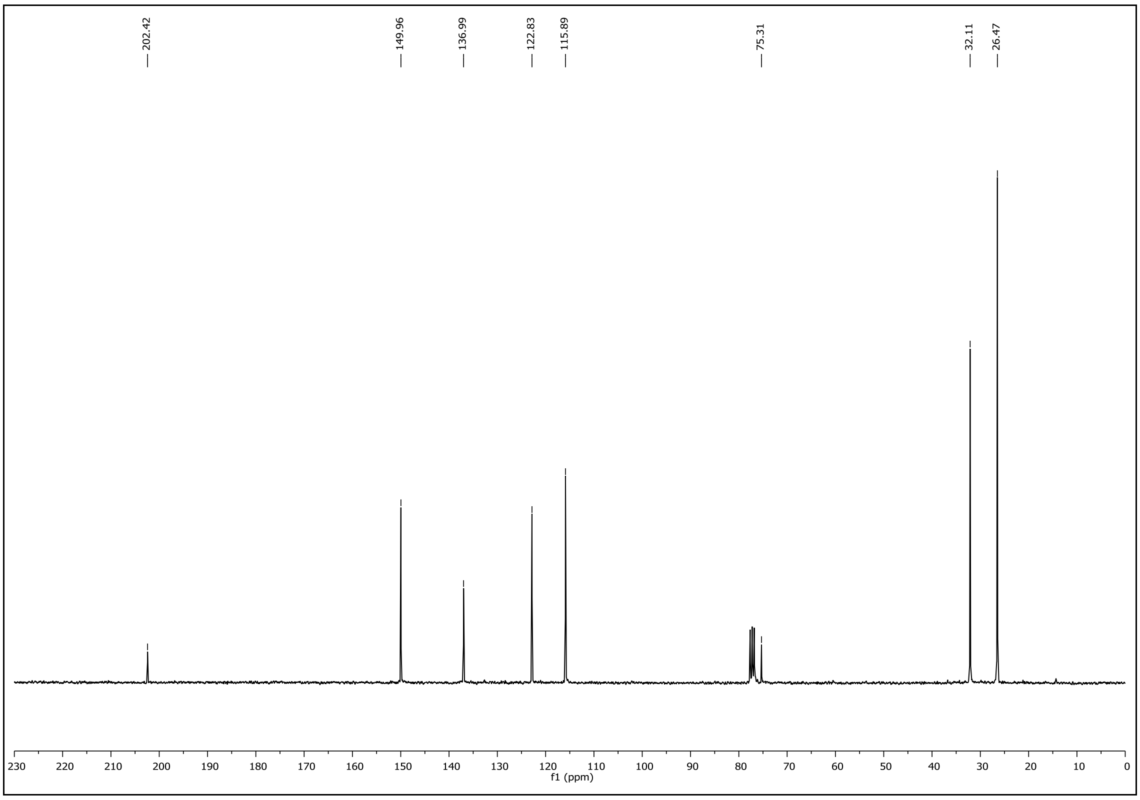
0.0
f1 (ppm)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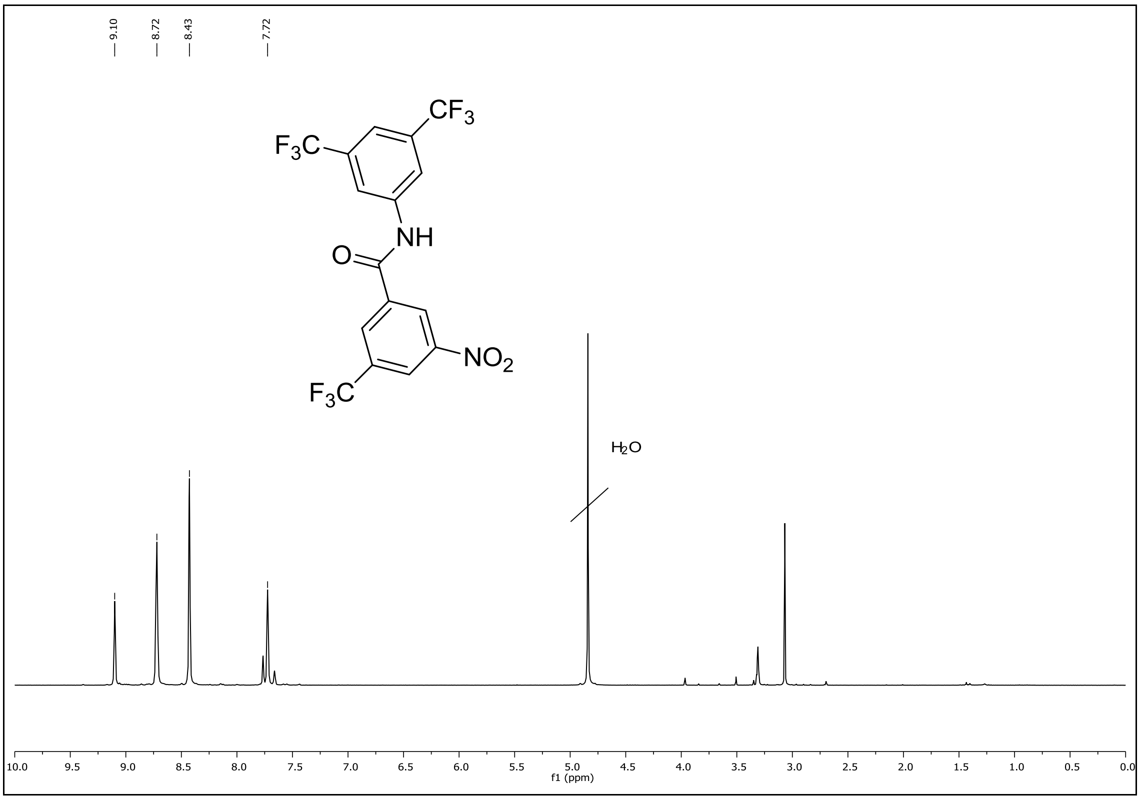
f1 (ppm)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8.0
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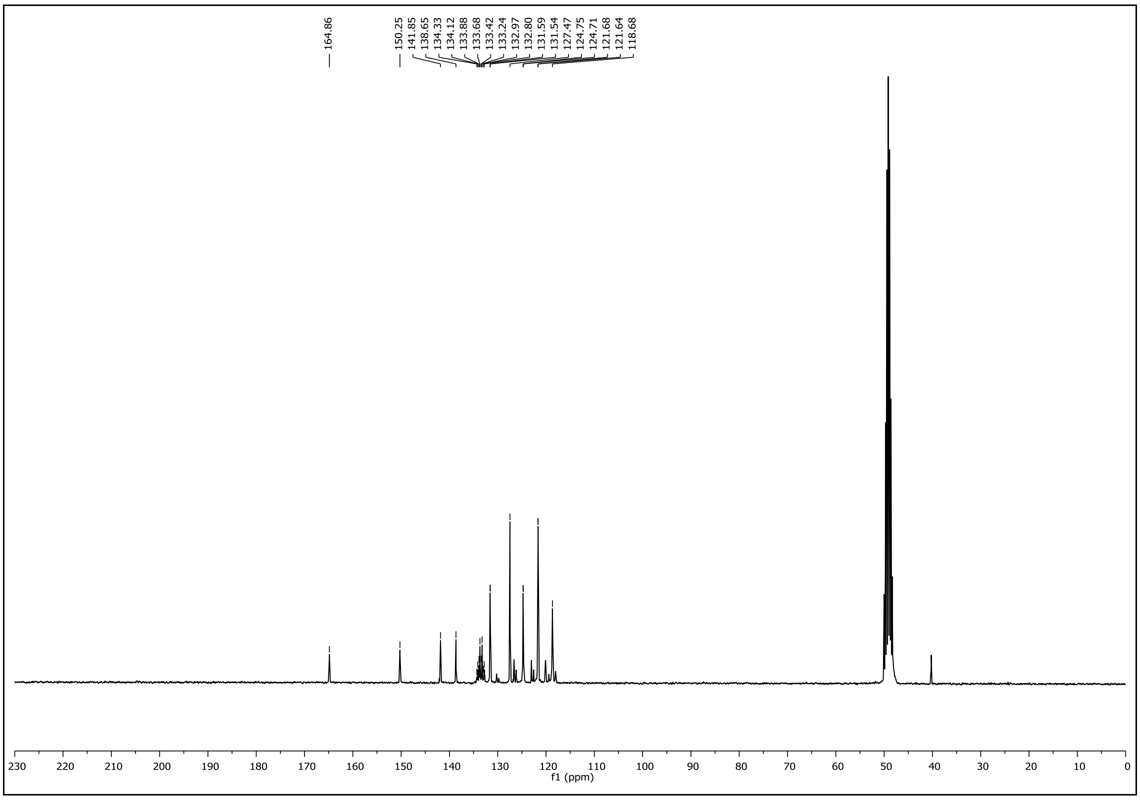
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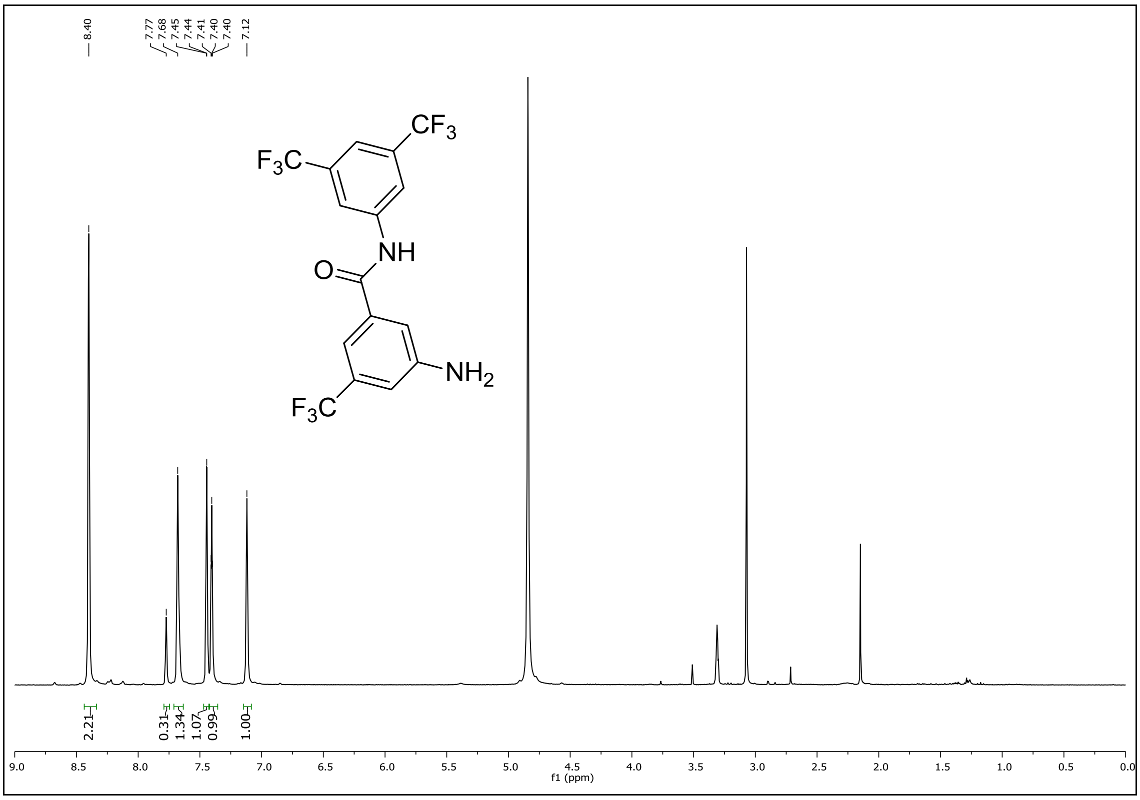
f1 (ppm)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F3C
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0.99
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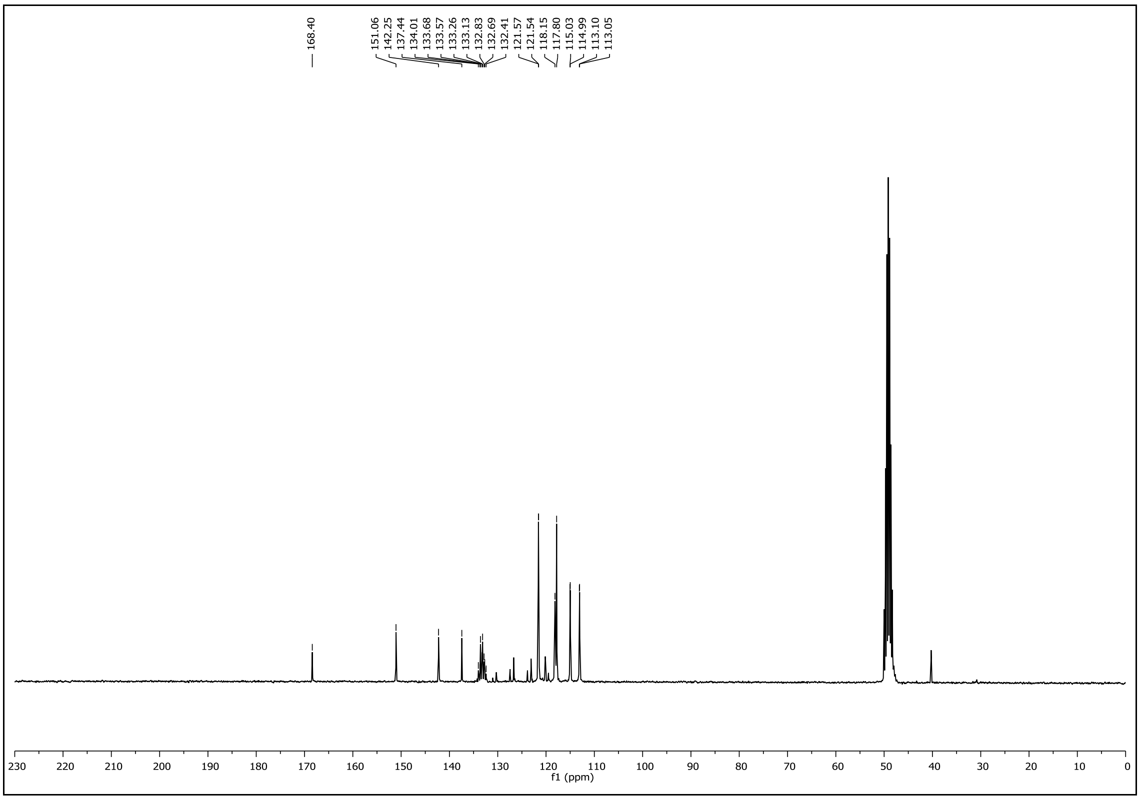
1.0
0.5
0.0
f1 (ppm)


168.40
151.06
142.25
137.44
134.01
133.68
133.57
133.26
133.13
132.83
132.69
132.41
121.57
121.54
118.15
117.80
115.03
114.99
113.10
113.05
230
220
210
200
190
180
170
160
150
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110
100
90
80
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60
50
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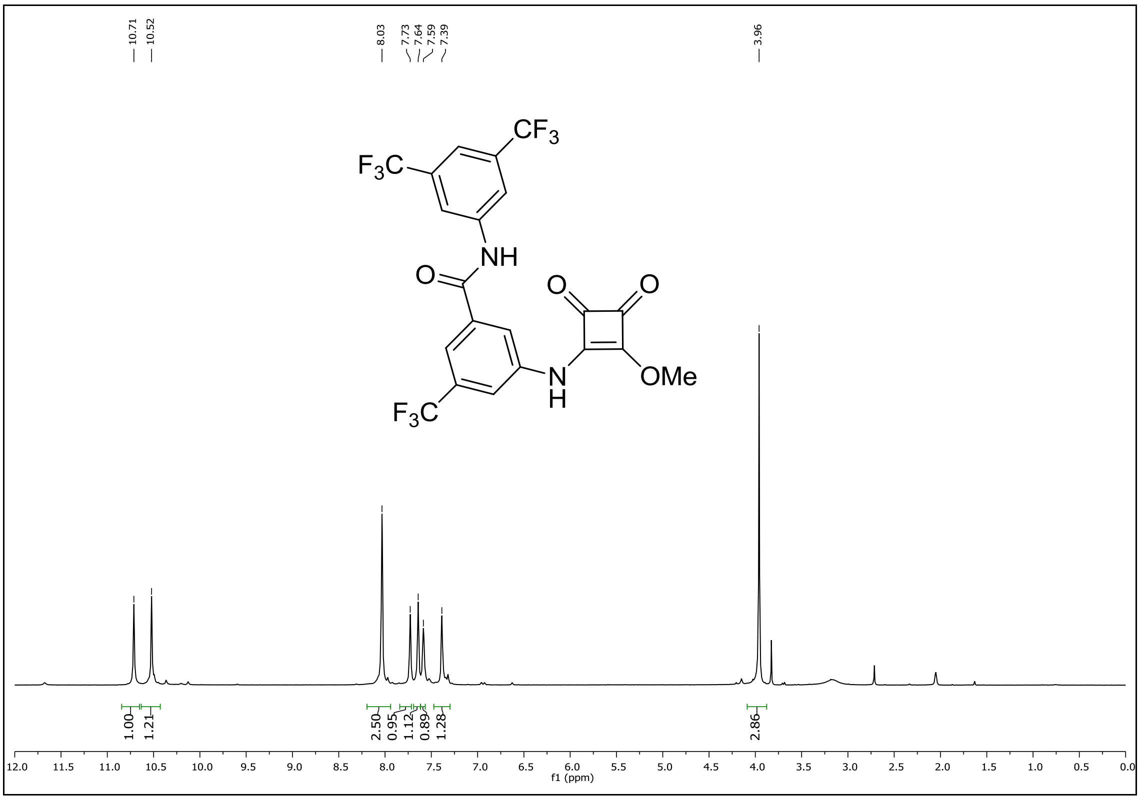
f1 (ppm)


10.71
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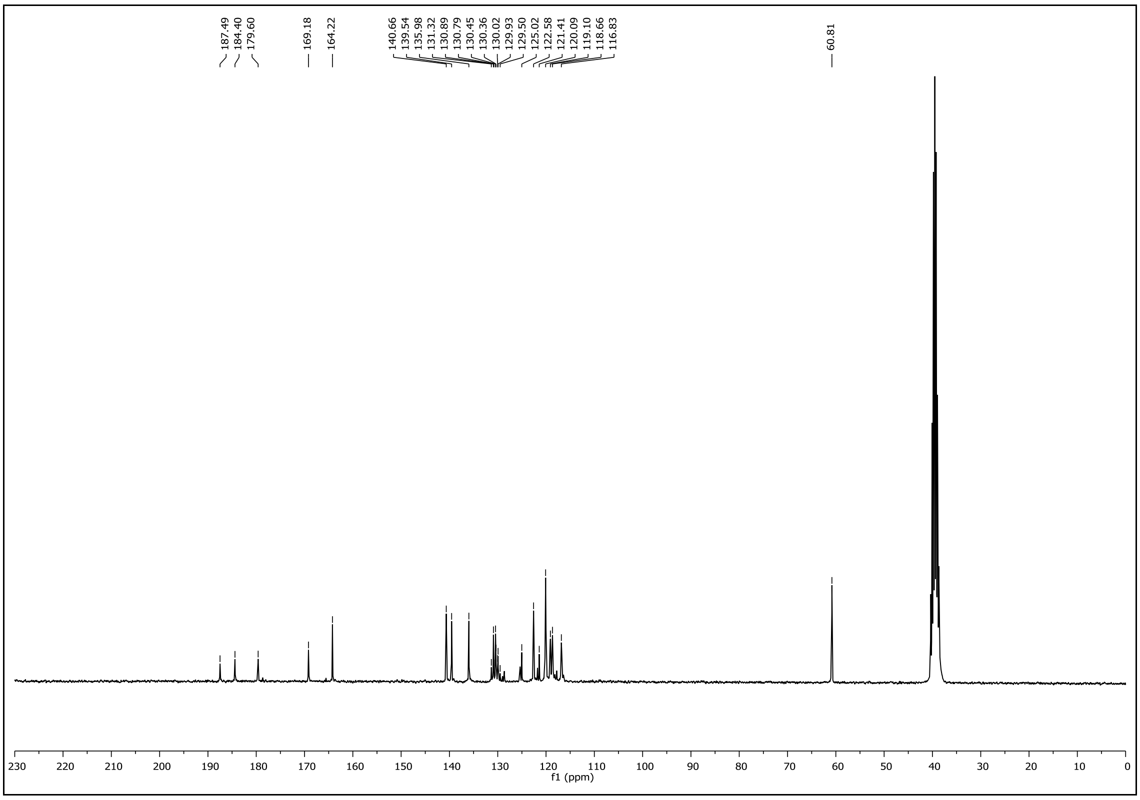
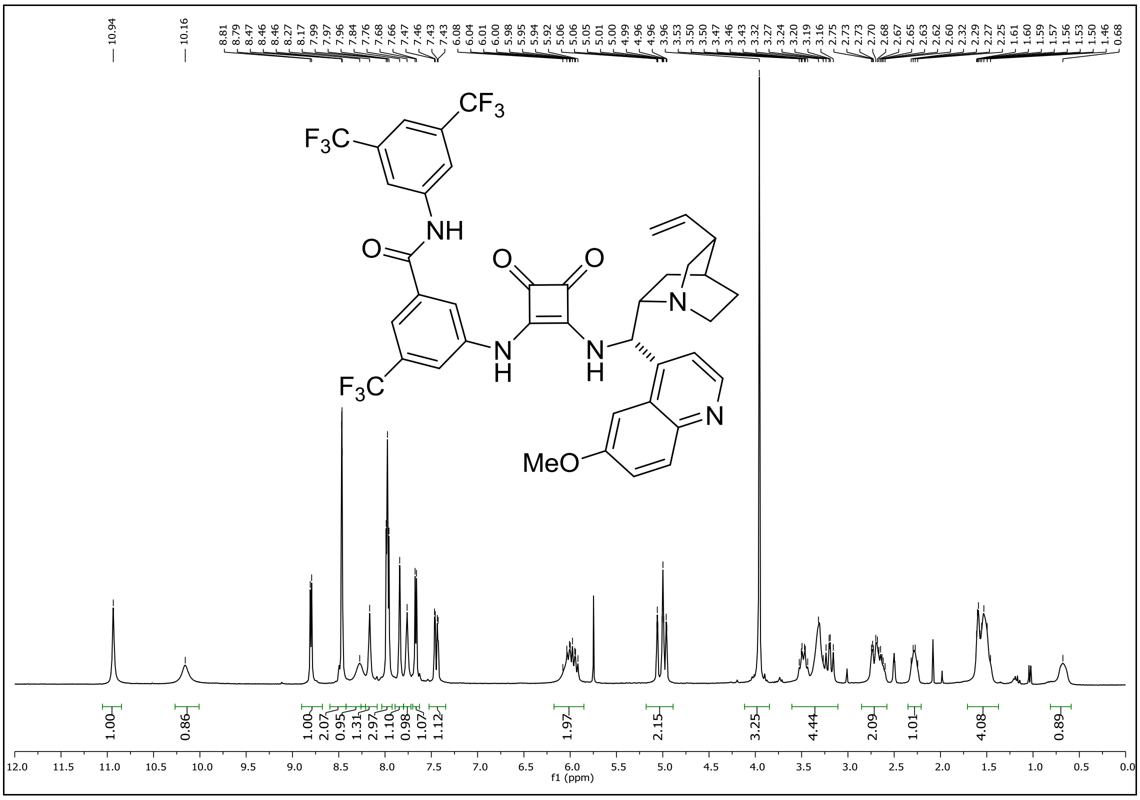
7.73
7.64
7.59
7.39
3.96
CF3
F3C
NH
O
O
O
N
H
OMe
F3C
1.00
1.21
2.50
0.95
1.12
0.89
1.28
2.86
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


187.49
184.40
179.60
169.18
164.22
140.66
139.54
135.98
131.32
130.89
130.79
130.45
130.36
130.02
129.93
129.50
125.02
122.58
121.41
120.09
119.10
118.66
116.83
60.81
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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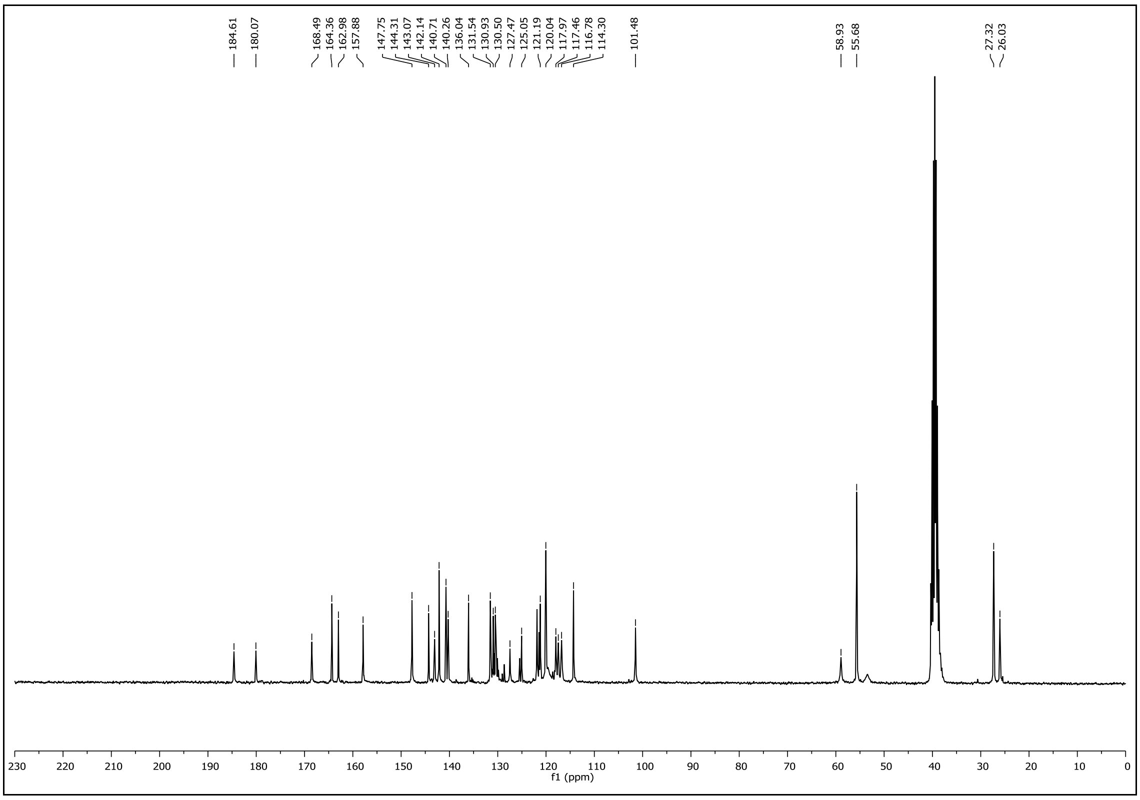
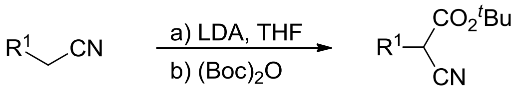
10.16
8.81 8.79 8.47 8.46 8.46 8.27 8.17 7.99 7.97 7.96 7.84 7.76 7.68 7.66 7.47 7.46 7.43 7.43 6.08 6.04 6.01 6.00 5.98 5.95 5.94 5.92 5.06 5.06 5.05 5.01 5.00 4.99 4.96 4.96 3.96 3.53 3.50 3.50 3.47 3.46 3.43 3.32 3.27 3.24 3.20 3.19 3.16 2.75 2.73 2.73 2.70 2.68 2.67 2.65 2.63 2.62 2.60 2.32 2.29 2.27 2.25 1.61 1.60 1.59 1.57 1.56 1.53 1.50 1.46 0.68
CF_3
F_3C
NH
O
O
O
N
H
N
H
N
F_3C
N
MeO
1.00 0.86 1.00 2.07 0.95 1.31 2.97 1.10 0.98 1.07 1.12 1.97 2.15 3.25 4.44 2.09 1.01 4.08 0.89
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 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 0.0
f1 (ppm)


184.61 180.07 168.49 164.36 162.98 157.88 147.75 144.31 143.07 142.14 140.71 140.26 136.04 131.54 130.93 130.50 127.47 125.05 121.19 120.04 117.97 117.46 116.78 114.30 101.48 58.93 55.68 27.32 26.03
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

6.4. EXPERIMENTAL SECTION OF CHAPTER 2

6.4.1. Preparation of pronucleophiles

6.4.1.1. General procedure for the preparation of cyanoacetates ***69a-h***[361]

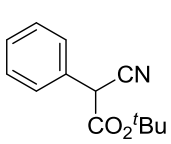


69a-h

a R^1: C_6H_5
b R^1: 4-MeC_6H_4
c R^1: 4-$MeOC_6H_4$
d R^1: 4-BrC_6H_4
e R^1: 4-ClC_6H_4
f R^1: 3-MeC_6H_4
g R^1: 1-MeC_6H_4
h R^1: Me

A solution of nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) cooled to −78 ºC. The reaction mixture was allowed to stir at –78 ºC for 45 min. and then at room temperature for an additional 45 minutes. The reaction mixture was then cooled to −78 ºC and a solution of di-*tert*-butyl dicarbonate (2.62 g, 12 mmol, 1.2 equiv.) in THF (10 mL) was added *via* syringe. The reaction mixture was stirred at −78 ºC for 16 hours. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 1N HCl (30 mL), brine (30 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography (EtOAc:hexane 1:20) to yield the desired cyanoester **69**.

***tert*-Butyl 2-cyano-2-phenylacetate 69a**[361]



It was obtained as a clear oil (1.402 g, 6.4 mmol, 64%) from benzyl cyanide (1.15 mL, 10 mmol) whose characterization data were coincident with the reported ones. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 5H), 4.61 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 130.7, 129.4, 129.1, 127.9, 116.14, 84.6, 45.0, 27.8. HRMS (ESI): $C_{13}H_{16}NO_2$ $[M+H]^+$ calcd.: 218.1181, found: 218.1196.

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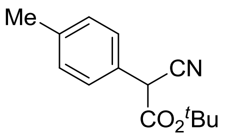
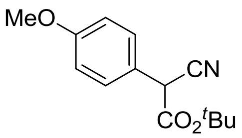
[361] Trost, B. M.; Miller, J. R.; Hoffman Jr., C. M. *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.

***tert*-Butyl 2-cyano-2-(*p*-tolyl)acetate 69b**[362]



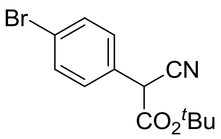
It was obtained as a clear oil (1.734 g, 7.5 mmol, 75%) from 4-methylbenzyl cyanide (1.33 mL, 10 mmol) whose characterization data were coincident with the reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.56 (s, 1H), 2.36 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 139.1, 130.1, 127.8, 116.3, 84.5, 44.6, 27.8, 21.3. HRMS (ESI): $C_{14}H_{18}NO_2$ $[M+H]^+$ calcd.: 232.1338, found: 232.1330.

***tert*-Butyl 2-cyano-2-(4-methoxyphenyl)acetate 69c**



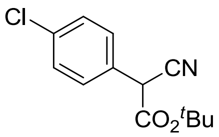
It was obtained as a clear oil (1.826 g, 7.4 mmol, 74%) from 4-methoxybenzyl cyanide (1.31 mL, 10 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 2H), 6.99 – 6.85 (m, 2H), 4.55 (s, 1H), 3.82 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 160.2, 129.2, 122.6, 116.4, 114.8, 84.5, 55.5, 44.2, 27.8. HRMS (ESI): $C_{14}H_{18}NO_3$ $[M+H]^+$ calcd.: 248.1287, found: 248.1282.

***tert*-Butyl 2-cyano-2-(4-bromophenyl)acetate 69d**[361]



It was obtained as a yellow oil (2.141 g, 7.23 mmol, 72%) from 4-bromobenzyl cyanide (1.960 g, 10 mmol) whose characterization data were coincident with the reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 7.36 – 7.29 (m, 2H), 4.57 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 132.6, 129.7, 123.5, 115.7, 85.1, 44.5, 27.8. HRMS (ESI): $C_{13}H_{15}BrNO_2$ $[M+H]^+$ calcd.: 296.0286, found: 296.0292.

***tert*-Butyl 2-(4-chlorophenyl)-2-cyanoacetate 69e**[362]



It was obtained as a yellow oil (1.701 g, 6.75 mmol, 68%) from 4-chlorobenzyl cyanide (1.515 g, 10 mmol) whose characterization data were coincident with the reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 4H), 4.58 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz,

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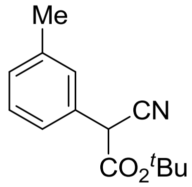
[362] Jautze, S.; Peters, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 9284–9288.

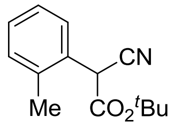
$CDCl_3$) δ 163.6, 135.3, 129.6, 129.3, 115.7, 85.0, 44.3, 27.8. UPLC-DAD-QTOF (ESI): $C_{13}H_{13}NO_2Cl$ $[M-H]^-$ calcd.: 250.0635, found: 250.0632.

***tert*-Butyl 2-cyano-2-(*m*-tolyl)acetate 69f**[362]



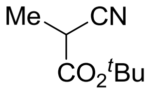
It was obtained as a clear oil (1.693 g, 7.32 mmol, 73%) from 3-methylbenzyl cyanide (1.31 mL, 10 mmol) whose characterization data were coincident with the reported ones. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.08 (m, 4H), 4.59 (s, 1H), 2.38 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 139.2, 130.5, 129.9, 129.2, 128.5, 125.0, 116.3, 84.5, 44.8, 27.8, 21.5. HRMS (ESI): $C_{14}H_{18}NO_2$ $[M+H]^+$ calcd.: 232.1338, found: 232.1331.

***tert*-Butyl 2-cyano-2-(*o*-tolyl)acetate 69g**



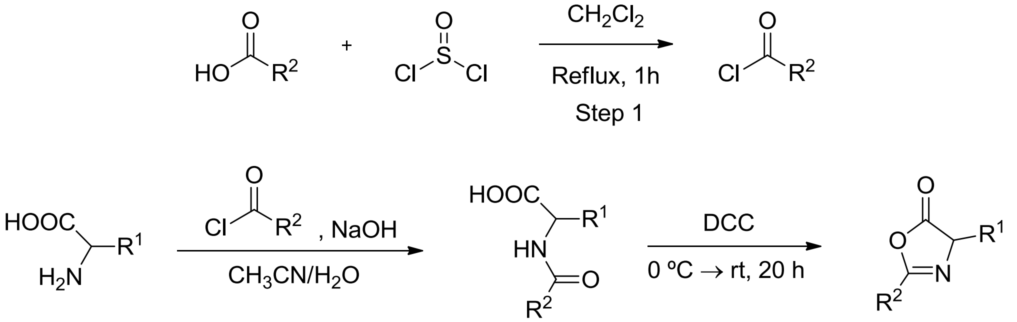
It was obtained as a clear oil (1.274 g, 5.50 mmol, 55%) from 2-methylbenzyl cyanide (1.24 mL, 10 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.38 (m, 1H), 7.35 – 7.17 (m, 4H), 4.79 (s, 1H), 2.40 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 136.2, 131.3, 129.6, 129.2, 128.6, 127.0, 116.3, 84.6, 42.2, 27.8, 19.5. HRMS (ESI): $C_{14}H_{18}NO_2$ $[M+H]^+$ calcd.: 232.1338, found: 232.1333.

***tert*-Butyl 2-cyanopropanoate 69h**[361]



It was obtained as a clear oil (1.253 g, 8.1 mmol, 81%) from propionitrile (0.71 mL, 10 mmol) whose characterization data were coincident with the reported ones. ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (q, J = 7.4 Hz, 1H), 1.55 (d, J = 7.4 Hz, 3H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 117.9, 83.9, 32.6, 27.8, 15.3. HRMS (ESI): $C_8H_{14}NO_2$ $[M+H]^+$ calcd.: 156.1025, found: 156.1024.

6.4.1.2. *Preparation of racemic azlactones* ***106–112***[363]



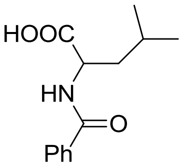
106–112

Azlactones were prepared from the corresponding acyl chloride as shown above. When the acyl chloride was not commercial it was prepared according to the following procedure:

1st step: Synthesis of the acyl chloride. To a suspension of the carboxylic acid (1 eq.) in CH_2Cl_2 (1 mL/mmol) thionyl chloride (10 eq.) was added and the mixture was refluxed for 1 h. All volatiles were evaporated to afford the acyl chloride which was used without further purification.

2nd step: Synthesis of the *N*-substituted amino acid. The corresponding racemic amino acid (1 equiv.) and NaOH (4 eq.) were dissolved in H_2O/CH_3CN (75/25, 0.3 M). After cooling to 0 °C, the corresponding acyl chloride (1.05 equiv.) was added dropwise at this temperature. After the addition was complete, the mixture was stirred for additional 2 h at 0 °C. Subsequently, the mixture was allowed to warm to room temperature and was stirred for one additional hour. All volatiles were then removed under reduced pressure before conc. HCl was added to cause precipitation. The mixture was filtered and the filter cake was washed with ice-cold diethylether.

(±) *N*-Benzoyl-*D,L*-leucine[364]



D,L-Leucine (1.31 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (2.01 g, 8.51 mmol, 85%). The characterization data were coincident with the previously

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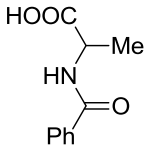
[363] Adapted from: Weber, M.; Jautze, S.; Frey, W.; Peters, R. *J. Am. Chem. Soc.*, **2010**, *132*, 12222–12225.

[364] Beller, M.; Eckert, M.; Vollmüller, F. *J. Mol. Catal. A-Chem.* **1998**, *135*, 23–33.

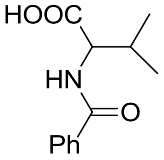
reported ones. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.87 – 7.75 (m, 2H), 7.63 – 7.41 (m, 3H), 6.49 (d, *J* = 7.8 Hz, 1H), 4.91 – 4.77 (m, 1H), 1.93 – 1.63 (m, 3H), 1.00 (d, *J* = 6.1 Hz, 6H).

(±) *N*-Benzoyl-*D,L*-alanine[364]



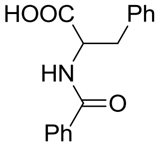
D,L-Alanine (0.89 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (1.68 g, 8.71 mmol, 87%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 – 8.01 (m, 1H), 7.91 – 7.76 (m, 2H), 7.68 – 7.54 (m, 1H), 7.55 – 7.37 (m, 2H), 6.65 (s, 1H), 4.83 (p, *J* = 7.1 Hz, 1H), 1.61 (d, *J* = 7.2 Hz, 3H).

(±) *N*-Benzoyl-*D,L*-valine[365]



D,L-Valine (1.17 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (1.99 g, 9.01 mmol, 90%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$), δ 9.03 (s, 1H), 7.85 – 7.77 (m, 2H), 7.63 – 7.40 (m, 3H), 6.69 (d, *J* = 8.5 Hz, 1H), 4.82 (dd, *J* = 8.5, 4.8 Hz, 1H), 2.45 – 2.28 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 6H).

(±) *N*-Benzoyl-*D,L*-phenylalanine[365]



D,L-Phenylalanine (1.65 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (2.38 g, 8.82 mmol, 88%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.14 – 8.06 (m, 2H), 7.73 – 7.57 (m, 2H), 7.53 – 7.38 (m, 2H), 7.35 – 7.19 (m, 5H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.16 – 5.03 (m, 1H), 3.34 (ddd, *J* = 30.5, 13.8, 5.5 Hz, 2H).

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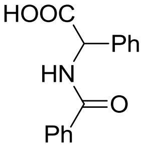
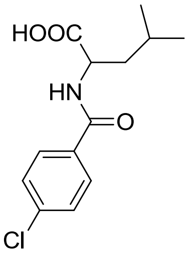
[365] Metrano, A. J.; Miller, S. J. *J. Org. Chem.* **2014**, *79*, 1542–1554.

(±) *N*-Benzoyl-*D,L*-phenylglycine[366]



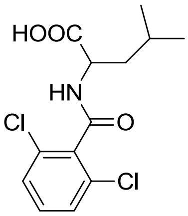
D,L-Phenylglycine (1.51 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (2.03 g, 7.97 mmol, 80%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.86 – 7.77 (m, 2H), 7.57 – 7.32 (m, 8H), 7.08 (d, *J* = 7.0 Hz, 1H), 5.80 (d, *J* = 6.7 Hz, 1H).

(±) *N*-4-Chlorobenzoyl-*D,L*-leucine[367]



D,L-Leucine (1.31 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and 4-chlorobenzoyl chloride (1.35 mL, 10.5 mmol) to yield a white solid (2.56 g, 9.51 mmol, 95%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.78 – 7.70 (m, 2H), 7.48 – 7.37 (m, 2H), 6.50 (d, *J* = 7.9 Hz, 1H), 4.95 – 4.73 (m, 1H), 1.98 – 1.57 (m, 3H), 1.00 (d, *J* = 5.7 Hz, 6H).

(±) *N*-2,6-Dichlorobenzoyl-*D,L*-leucine



2,6-Dichlorobenzoyl chloride was prepared from 2,6-dichlorobenzoic acid (2.01 g, 10.5 mmol) and thionyl chloride (7.62 mL, 105 mmol). *D,L*-Leucine (1.31 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and 2,6-dichlorobenzoyl chloride to yield a white solid (2.80 g, 9.20 mmol, 92%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.13 (m, 4H), 6.20 (d, J = 8.3 Hz, 1H), 5.02 – 4.74 (m, 1H), 1.98 – 1.60 (m, 3H), 1.02 (dd, J = 11.7, 6.3 Hz, 6H).

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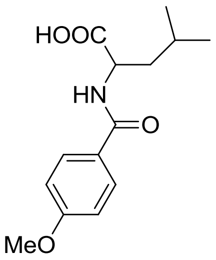
[366] Koen, M. J.; Morgan, J.; Pinhey, J. T.; Sherry, C. J. *J. Chem. Soc., Perkin Trans. 1*, **1997**, *4*, 487–491.

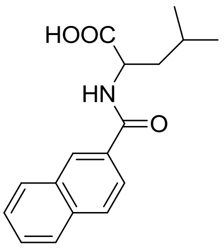
[367] Snyder, S. E.; Huang, B.-S.; Chu, Y. W.; Lin, H.-S.; Carey, J. R. *Chem. Eur. J.* **2012**, *18*, 12663–12671.

(±) *N*-4-Methoxybenzoyl-*D,L*-leucine[367]



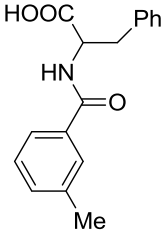
4-Methoxybenzoyl chloride was prepared from 4-methoxybenzoic acid (1.60 g, 10.5 mmol) and thionyl chloride (7.62 mL, 105 mmol). Then *D,L*-leucine (1.31 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and 4-methoxybenzoyl chloride to yield a white solid (2.61 g, 9.82 mmol, 98%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.77 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.46 (d, *J* = 7.3 Hz, 1H), 4.95 – 4.68 (m, 1H), 3.85 (s, 3H), 2.01 – 1.63 (m, 3H), 0.99 (d, *J* = 5.6 Hz, 6H).

(±) *N*-2-Naphthoyl-*D,L*-leucine[368]



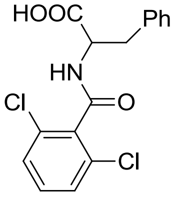
D,L-leucine (1.31 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and 2-naphthoyl chloride (2.00 g, 10.5 mmol))to yield a white solid (1.86 g, 6.52 mmol, 65%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 – 8.24 (m, 1H), 8.02 – 7.76 (m, 4H), 7.69 – 7.42 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.91 (td, *J* = 8.2, 4.4 Hz, 1H), 1.96 – 1.66 (m, 3H), 1.16 – 0.82 (m, 6H).

(±) *N*-*m*-Toluoyl-*D,L*-phenylalanine



D,L-Phenylalanine (1.65 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and *m*-toluoyl chloride (1.39 mL, 10.5 mmol) to yield a white solid (2.22 g, 7.83 mmol, 78%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 – 7.91 (m, 1H), 7.68 – 7.50 (m, 1H), 7.39 – 7.12 (m, 7H), 6.48 (d, *J* = 7.1 Hz, 1H), 5.06 (dt, *J* = 7.1, 5.8 Hz, 1H), 3.38 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.27 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.39 (s, 3H).

(±) *N*-2,6-Dichlorobenzoyl-*D,L*-phenylalanine



2,6-Dichlorobenzoyl chloride was prepared from 2,6-dichlorobenzoic acid (2.01 g, 10.5 mmol) and thionyl chloride (7.62 mL, 105 mmol). *D,L*-Phenylalanine (1.65 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and 2,6-dichlorobenzoyl chloride to yield a white solid (2.83 g, 8.37 mmol, 84%). The characterization data were coincident

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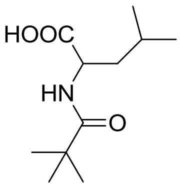
[368] Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344–16347.

with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 8H), 6.23 (d, *J* = 7.7 Hz, 1H), 5.24 (dt, *J* = 8.2, 5.7 Hz, 1H), 3.43 – 3.18 (m, 2H).

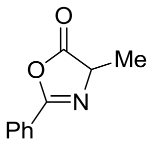
(±) 4-Methyl-2-pivalamidopentanoic acid[369]



D,L-Leucine (1.31 g, 10 mmol) was treated with with NaOH (1.62 g, 40 mmol) and trimethylacetyl chloride (1.29 mL, 10.5 mmol) to yield a white solid (1.19 g, 5.51 mmol, 55%). The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J* = 7.5 Hz, 1H), 4.63 – 4.42 (m, 1H), 1.88 – 1.47 (m, 3H), 1.22 (s, 9H), 1.07 – 0.82 (m, 6H).

3rd step: The corresponding *N*-substituted amino acid (5 mmol, 1 equiv.) was suspended in CH_2Cl_2 (50 mL, 10 mL/mmol), the mixture was cooled to 0 °C and DCC (1.08 g, 5.25 mmol, 1.05 equiv.) was added portionwise. After complete addition the mixture was allowed to warm to RT and was stirred for additional 20 h at this temperature. A precipitate was filtered off and the filtrate was concentrated *in vacuo*. The product was purified by silica gel column chromatography using hexane/ethyl acetate (95:5).

(±) 4-Methyl-2-phenyloxazol-5(4*H*)-one 106a[370]



The title compound was prepared from *N*-benzoyl-*D,L*-alanine (0.97 g, 5 mmol) according to the general procedure. White solid; yield: 630 mg, 3.60 mmol, 72%. m.p. 39–40 °C. The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.6, 2.1 Hz, 2H), 7.62 – 7.53 (m, 1H), 7.53 – 7.45 (m, 2H), 4.45 (q, *J* = 7.6 Hz, 1H), 1.59 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 161.5, 132.7, 128.8, 127.9, 125.9, 61.0, 16.9. UPLC-DAD-QTOF: $C_{10}H_{10}NO_2$ $[M+H]^+$ calcd.: 176.0712, found: 176.0710.

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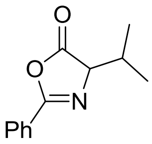
[369] Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2008**, *47*, 4882–4886.

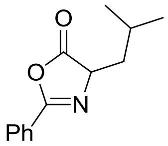
[370] Melhado, D. A.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc*. **2007**, *129*, 12638.

(±) 4-Isopropyl-2-phenyloxazol-5(4*H*)-one 106b[365]



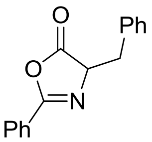
The title compound was prepared from *N*-benzoyl-*D,L*-valine (2.21 g, 10 mmol) according to the general procedure. White solid; yield: 1.56 g, 7.65 mmol, 77%. m.p. 44–47 °C. The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 2H), 7.62 – 7.54 (m, 1H), 7.53 – 7.44 (m, 2H), 4.29 (d, *J* = 4.5 Hz, 1H), 2.59 – 2.24 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 161.8, 132.8, 128.9, 128.0, 126.1, 70.8, 31.4, 18.9, 17.7. UPLC-DAD-QTOF: $C_{12}H_{14}NO_2$ $[M+H]^+$ calcd.: 204.1025, found: 204.1025.

(±) 4-Isobutyl-2-phenyloxazol-5(4*H*)-one 106c[365]



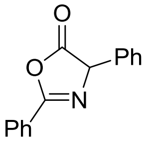
The title compound was prepared from *N*-benzoyl-*D,L*-leucine (1.35 g, 5 mmol) according to the general procedure. White solid; yield: 944 mg, 3.75 mmol, 75%. m.p. 53–55 °C. The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.62 – 7.44 (m, 3H), 4.41 (dd, *J* = 8.9, 5.7 Hz, 1H), 2.07 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.85 (ddd, *J* = 13.5, 7.7, 5.7 Hz, 1H), 1.68 (ddd, *J* = 13.7, 8.9, 6.4 Hz, 1H), 1.03 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 161.6, 134.8, 132.8, 128.9, 128.0, 64.1, 40.9, 25.4, 22.9, 22.3. UPLC-DAD-QTOF: $C_{13}H_{16}NO_2$ $[M+H]^+$ calcd.: 218.1181, found: 218.1182.

(±) 4-Benzyl-2-phenyloxazol-5(4*H*)-one 106d[370]



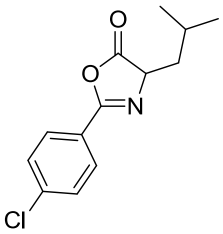
The title compound was prepared from *N*-benzoyl-*D,L*-phenylalanine (1.35 g, 5 mmol) according to the general procedure. White solid; yield: 759 mg, 3.02 mmol, 60%. m.p. 69–71 °C. The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 2H), 7.59 – 7.40 (m, 3H), 7.32 – 7.17 (m, 5H), 4.69 (dd, *J* = 6.7, 5.0 Hz, 1H), 3.38 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.19 (dd, *J* = 14.0, 6.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 161.9, 135.5, 132.9, 129.8, 128.9, 128.6, 128.1, 127.4, 125.9, 66.7, 37.5. UPLC-DAD-QTOF: $C_{16}H_{14}NO_2$ $[M+H]^+$ calcd.: 252.1025, found: 252.1029.

(±) 2,4-Diphenyloxazol-5(4*H*)-one 106e[370]



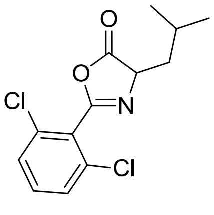
The title compound was prepared from *N*-benzoyl-*D,L*-phenylglycine (1.28 g, 5 mmol) according to the general procedure. Yellow solid; yield: 737 mg, 3.11 mmol, 62%. m.p. 104–105 °C. The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 7.94 (m, 2H), 7.67 – 7.49 (m, 3H), 7.48 – 7.34 (m, 5H), 5.53 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 162.8, 133.6, 133.3, 129.1, 129.1, 128.9, 128.8, 128.3, 127.6, 127.4, 127.0, 68.3. UPLC-DAD-QTOF: $C_{15}H_{12}NO_2$ [M+H]$^+$ calcd.: 238.0863, found: 238.0860.

(±) 2-(4-Chlorophenyl)-4-isobutyloxazol-5(4*H*)-one 107



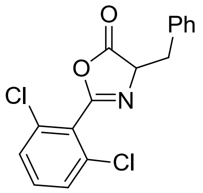
The title compound was prepared from *N*-4-chlorobenzoyl-*D,L*-leucine (2.70 g, 10 mmol) according to the general procedure. White solid; yield: 1.90 g, 7.53 mmol, 75%. m.p. 53–55 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.84 (m, 2H), 7.57 – 7.38 (m, 2H), 4.40 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.04 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.84 (ddd, *J* = 13.5, 7.8, 5.6 Hz, 1H), 1.67 (ddd, *J* = 13.7, 9.0, 6.3 Hz, 1H), 1.02 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 160.8, 139.2, 129.4, 124.7, 64.2, 41.0, 25.5, 22.9, 22.2. UPLC-DAD-QTOF: $C_{13}H_{15}ClNO_2$ [M+H]$^+$ calcd.: 252.0791, found: 252.0792.

(±) 2-(2,6-Dichlorophenyl)-4-isobutyloxazol-5(4*H*)-one 108



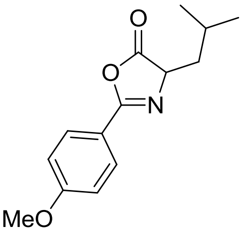
The title compound was prepared from *N*-2,6-dichlorobenzoyl-*D,L*-leucine (1.52 g, 5 mmol) according to the general procedure. Colourless oil; yield: 0.92 g, 3.22 mmol, 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.33 (m, 3H), 4.48 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.15 – 2.00 (m, 1H), 1.98 – 1.84 (m, 1H), 1.83 – 1.66 (m, 1H), 1.04 (dd, *J* = 6.6, 5.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 158.0, 134.9, 132.5, 128.2, 63.9, 40.5, 25.3, 22.8, 22.1. UPLC-DAD-QTOF: $C_{13}H_{14}Cl_2NO_2$ [M+H]$^+$ calcd.: 286.0402, found: 286.0400.

(±) 4-Benzyl-2-(2,6-dichlorophenyl)oxazol-5(4*H*)-one 109



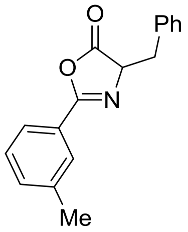
The title compound was prepared from *N*-2,6-dichlorobenzoyl-*D,L*-phenylalanine (1.33, 5 mmol) according to the general procedure. White solid; yield: 1.20 g, 3.75 mmol, 75%. m.p. 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.01 (m, 8H), 4.86 – 4.59 (m, 1H), 3.43 (dd, *J* = 14.0, 5.1 Hz, 1H), 3.28 (dd, *J* = 14.0, 6.6 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 158.6, 135.3, 135.1, 132.6, 130.0, 128.9, 128.2, 127.5, 66.7, 37.0. UPLC-DAD-QTOF: $C_{16}H_{12}Cl_2NO_2$ $[M+H]^+$ calcd.: 320.0245, found: 320.0239.

(±) 4-Isobutyl-2-(4-methoxyphenyl)oxazol-5(4*H*)-one 110



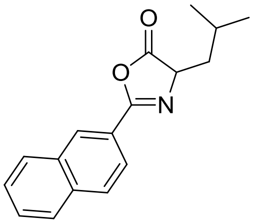
The title compound was prepared from *N*-4-methoxybenzoyl-*D,L*-leucine (2.65 g, 10 mmol) according to the general procedure. White solid; yield: 1.26 g, 5.11 mmol, 51%. m.p. 68-69 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.89 (m, 2H), 7.06 – 6.92 (m, 2H), 4.38 (d, *J* = 14.5 Hz, 1H), 3.88 (s, 3H), 2.04 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.83 (ddd, *J* = 13.5, 7.7, 5.7 Hz, 1H), 1.67 (ddd, *J* = 13.7, 8.8, 6.4 Hz, 1H), 1.02 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 163.3, 161.3, 129.9, 118.6, 114.4, 64.1, 55.7, 41.1. UPLC-DAD-QTOF: $C_{14}H_{18}NO_3$ $[M+H]^+$ calcd.: 248.1287, found: 248.1291.

(±) 4-Benzyl-2-(*m*-tolyl)oxazol-5(4*H*)-one 111



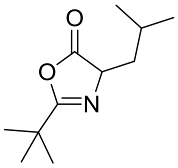
The title compound was prepared from *N*-*m*-toluoyl-*D,L*-phenylalanine (1.42 g, 5 mmol) according to the general procedure. White solid; yield: 0.81 g, 3.21 mmol, 64%. m.p. 58–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 6.3 Hz, 7H), 4.67 (dd, *J* = 6.6, 5.0 Hz, 1H), 3.36 (dd, *J* = 13.9, 4.9 Hz, 1H), 3.18 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.41 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 161.9, 143.6, 135.6, 129.8, 129.7, 128.6, 128.1, 127.4, 123.2, 66.7, 37.6, 21.9. UPLC-DAD-QTOF: $C_{17}H_{16}NO_2$ $[M+H]^+$ calcd.: 266.1181, found: 266.1185.

(±) 4-Isobutyl-2-(naphthalen-2-yl)oxazol-5(4*H*)-one **112**



The title compound was prepared from *N*-2-naphthoyl-*D,L*-leucine (1.43 g, 5 mmol) according to the general procedure. White solid; yield: 0.67 g, 2.50 mmol, 50%. m.p. 52–54 ºC. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.49 (s, 1H), 8.07 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.92 (dt, *J* = 10.3, 6.9 Hz, 3H), 7.71 – 7.46 (m, 2H), 4.48 (dd, *J* = 8.9, 5.7 Hz, 1H), 2.10 (dq, *J* = 13.1, 6.6 Hz, 1H), 1.89 (ddd, *J* = 13.5, 7.7, 5.7 Hz, 1H), 1.73 (ddd, *J* = 13.7, 8.9, 6.3 Hz, 1H), 1.05 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 179.2, 161.7, 135.5, 132.8, 129.5, 129.3, 128.9, 128.5, 128.1, 127.2, 123.6, 64.3, 41.1, 25.5, 23.0, 22.3. UPLC-DAD-QTOF: $C_{17}H_{18}NO_2$ $[M+H]^+$ calcd.: 268.1338, found: 268.1342.

(±) 2-(*tert*-Butyl)-4-isobutyloxazol-5(4H)-one **113**[371]



The title compound was prepared from 4-methyl-2-pivalamidopentanoic acid (1.08 g, 5 mmol) according to the general procedure. Colourless oil; yield: 828 mg, 4.21 mmol, 84%. The characterization data were coincident with the previously reported ones. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.17 (dd, *J* = 8.0, 6.1 Hz, 1H), 1.95 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.74 (ddd, *J* = 13.5, 7.2, 6.1 Hz, 1H), 1.57 (ddd, *J* = 13.8, 8.1, 6.8 Hz, 1H), 1.28 (s, 9H), 0.97 (t, *J* = 6.5 Hz, 6H).^{13}C NMR (75 MHz, CDCl$_3$) δ 179.6, 171.5, 63.4, 40.5, 27.5, 26.8, 25.0, 22.6, 22.4. UPLC-DAD-QTOF: $C_{11}H_{20}NO_2$ $[M+H]^+$ calcd.: 198.1494, found: 198.1490.

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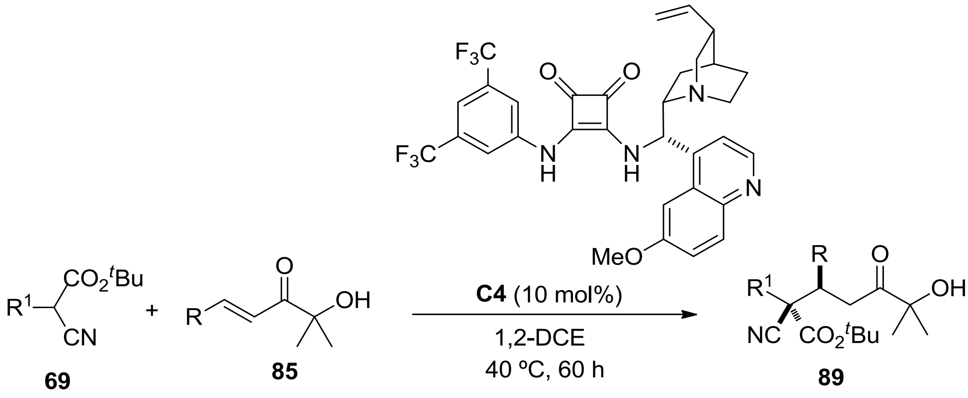
[371] Kalek, M.; Fu, G. C. *J. Am. Chem. Soc*. **2015**, *137*, 9438–9442.

6.4.2. General procedure for the conjugate addition of α-cyanoacetates 69 to β-substituted α’-hydroxy enones 85

6.4.2.1. Asymmetric reaction



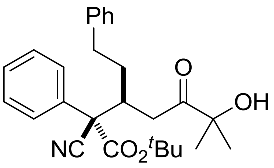
To a mixture of the corresponding cyanoacetate (0.1 mmol, 1 equiv.) and α’-hydroxy enone **85** (0.3 mmol, 3 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C4** (6.31 mg, 0.01 mmol) was added. The resulting mixture was stirred at 40°C, unless otherwise stated, until consumption of the cyanoacetate (monitored by ^{1}H-NMR). The reaction was treated with HCl 1N and the product was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product as a mixture of diastereomers in all cases higher than 95:5. After purification by flash column chromatography (eluent hexane/ ethyl acetate 95/5) the product was isolated in essentially diastereomerically pure form.

6.4.2.2. Racemic reaction

Racemic reactions were conducted following the procedure for the asymmetric version, but using as catalyst DBU (20 mol%) and running the reaction at 70 °C.

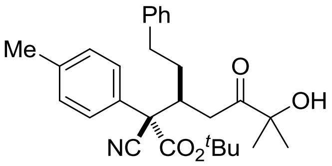
*6.4.2.3. Characterization data for compounds **89***

(2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-phenylheptanoate 89Aa



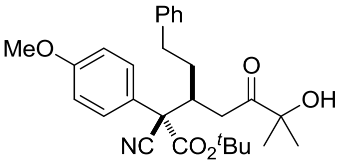
The title compound was prepared from (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **85A** (65 mg, 0.3 mmol) and *tert*-butyl 2-cyano-2-phenylacetate **69a** (22 mg, 0.1 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 98:2. Yield of pure major diastereomer after column chromatography purification (colourless oil): 90% (39 mg). $[\alpha]_D^{25}$ = +44.8º (c=1.00, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 2H), 7.42 – 7.36 (m, 3H), 7.20 – 7.10 (m, 3H), 6.92 – 6.90 (m, 2H), 3.60 (brs, 1H), 3.40 – 3.35 (m, 1H), 2.95 (dd, *J* = 18.8 Hz and 7.6 Hz, 1H), 2.83 (dd, *J* = 18.8 Hz and 2.6 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.21 – 2.12 (m, 1H), 1.60 – 1.46 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 166.0, 141.12, 133.4, 129.1, 129.0, 128.3, 128.1, 126.4, 125.9, 117.7, 84.7, 76.4, 60.7, 39.5, 39.2, 33.7, 33.4, 27.4, 26.8, 26.7. MS (ESI, *m*/*z*): calcd for $C_{27}H_{34}NO_4$ $(M+H^+)$, 436.2488; found, 436.2485. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3, hexane/isopropanol 90/10, flow rate= 0.5 mL/min at 10 ºC, retention times: 23.5 min (minor.) and 24.7 min (major.)).

(2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-(*p*-tolyl)heptanoate 89Ab



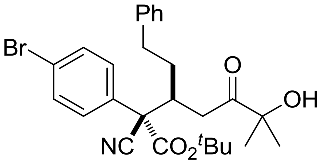
The title compound was prepared from *tert*-butyl 2-cyano-2-(*p*-tolyl)acetate **69b** (23 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **85A** (65 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 95% (43 mg). $[\alpha]_D^{24}$= +40.0° (c=1.9, 99% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.39 (m, 2H), 7.22 – 7.07 (m, 5H), 7.02 – 6.80 (m, 2H), 3.59 (s, 1H), 3.40 – 3.28 (m, 1H), 2.92 (dd, *J* = 18.6, 7.6 Hz, 1H), 2.79 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.53 – 2.39 (m, 1H), 2.19 (m, 1H), 1.59 (m, 1H), 1.53 – 1.45 (m, 1H) 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 166.4, 141.4, 139.1, 130.6, 123.0, 128.5, 128.4, 126.5, 126.1, 118.0, 84.8, 76.6, 60.6, 39.8, 39.4, 33.9, 33.7, 27.7, 27.0, 26.9, 21.2. UPLC-DAD-QTOF: $C_{28}H_{36}NO_4$ $[M+H]^+$ calcd.: 450.2344, found: 450.2347. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralcel AD-H, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 49.9 min (minor.) and 57.5 min (major.)). Channel Descr.: PDA 210 nm.

(2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-6-methyl-5-oxo-3-phenethylheptanoate 89Ac



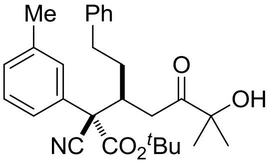
The title compound was prepared from *tert*-butyl 2-cyano-2-(4-methoxyphenyl)acetate **69c** (25 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **85A** (65 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 98:2. Yield of pure major diastereomer after column chromatography purification (colourless oil): 92% (43 mg). $[\alpha]_D^{24}$= +37.0° (c=1.4, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.36 (m, 2H), 7.17 (m, 3H), 7.04 – 6.72 (m, 4H), 3.82 (s, 3H), 3.58 (s, 1H), 3.36 – 3.26 (m, 1H), 2.92 (dd, *J* = 18.6, 7.6 Hz, 1H), 2.78 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.47 – 2.34 (m, 1H), 2.27 – 2.13 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 166.5, 160.1, 141.4, 128.5, 127.9, 126.2, 125.5, 118.1, 114.6, 84.8, 76.6, 60.3, 55.5, 39.8, 39.4, 33.9, 33.7, 27.7, 27.1. UPLC-DAD-QTOF: $C_{28}H_{36}NO_5$ $[M+H]^+$ calcd.: 466.2593, found: 466.2589. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralcel AD-3, hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 25.4 min (minor.) and 31.4 min (major.)). Channel Descr.: PDA 210 nm.

(2*S*,3*S*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethylheptanoate 89Ad



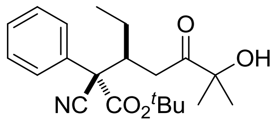
The title compound was prepared from *tert*-butyl 2-cyano-2-(4-bromophenyl)acetate **69d** (30 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **85A** (65 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 89% (46 mg). $[\alpha]_D^{24}$= +32.1° (c=1.0, 94% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.24 – 7.14 (m, 3H), 6.97 – 6.90 (m, 2H), 3.50 (s, 1H), 3.33 (m, 1H), 2.94 (dd, *J* = 18.7, 7.3 Hz, 1H), 2.80 (dd, *J* = 18.7, 2.8 Hz, 1H), 2.50 – 2.37 (m, 1H), 2.22 (m, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 165.8, 141.0, 132.7, 132.4, 128.5, 128.4, 128.3, 126.2, 123.4, 117.4, 85.3, 76.6, 60.6, 39.7, 39.1, 33.9, 33.4, 27.6, 27.0, 26.9. UPLC-DAD-QTOF: $C_{27}H_{33}NO_4Br$ $[M+H]^+$ calcd.: 514.1593, found: 514.1594. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralcel AD-H, hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 11.1 min (minor.) and 13.9 min (major.)). Channel Descr.: PDA 210 nm.

(2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-(*m*-tolyl)heptanoate 89Af



The title compound was prepared from *tert*-butyl 2-cyano-2-(*m*-tolyl)acetate **69f** (23 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **85A** (65 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 89% (40 mg). $[\alpha]_D^{24}$= +30.6° (c=2.5, 98% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.27 (m, 2H), 7.22 – 7.11 (m, 3H), 6.95 – 6.87 (m, 2H), 3.58 (s, 1H), 3.39 – 3.29 (m, 1H), 2.93 (dd, *J* = 18.6, 7.5 Hz, 1H), 2.81 (dd, *J* = 18.6, 2.8 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.36 (s, 3H), 2.17 (ddd, *J* = 13.7, 10.7, 6.3 Hz, 1H), 1.63 – 1.54 (m, 1H), 1.53 – 1.45 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 166.3, 141.4, 139.2, 133.4, 129.9, 129.2, 128.5, 128.4, 127.2, 126.1, 123.6, 118.0, 84.9, 76.6, 60.9, 39.8, 39.4, 33.9, 33.6, 27.7, 27.0, 27.0, 21.7. UPLC-DAD-QTOF: $C_{28}H_{36}NO_4$ $[M+H]^+$ calcd.: 450.2644, found: 450.2640. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Phenomenex Lux 3μ Cellulose-4, hexane/isopropanol 96/4, flow rate= 1.0 mL/min, retention times: 9.9 min (minor.) and 10.9 min (major.)). Channel Descr.: PDA 207 nm.

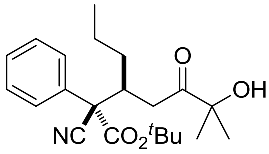
(2*S*,3*S*)-*tert*-Butyl 2-cyano-3-ethyl-6-hydroxy-6-methyl-5-oxo-2-phenylheptanoate 89Ba



The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **69a** (22 mg, 0.1 mmol) and *(E)*-2-hydroxy-2-methylhept-4-en-3-one **85B** (43 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio as determined in the crude material 96:4. Yield of pure major diastereomer after column chromatography purification (colourless oil): 95% (35 mg). $[\alpha]_D^{23}$= +19.4° (c=1.15, 92% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.55 (m, 2H), 7.46 – 7.32 (m, 3H), 3.62 (s, 1H), 3.33 – 3.22 (m, 1H), 2.86 (dd, *J* = 18.8, 7.6 Hz, 1H), 2.71 (dd, *J* = 18.7, 2.5 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.37 (s, 9H), 1.31 – 1.13 (m, 2H), 0.67 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 166.3, 133.8, 129.3, 129.1, 126.6, 118.0, 84.8, 76.6, 61.0, 40.6, 38.9, 27.7, 27.1, 27.0, 24.6, 11.6. UPLC-DAD-QTOF: $C_{21}H_{30}NO_4$ $[M+H]^+$ calcd.: 360.2175, found: 360.2171. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Phenomenex Lux 3μ Cellulose-4, hexane/isopropanol 99/01, flow rate=

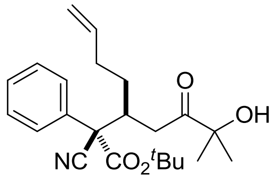
1.0 mL/min, retention times: 26.8 min (minor.) and 27.8 min (major.)). Processed Channel Descr.: PDA 207 nm.

(2*R*,3*S*)-*tert*-Butyl 6-hydroxy-2-isocyano-6-methyl-5-oxo-2-phenyl-3-propylheptanoate 89Ca



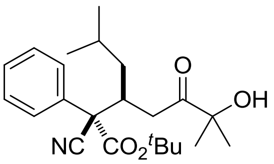
The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **69a** (22 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyloct-4-en-3-one **85C** (47 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 90% (33 mg). $[\alpha]_D^{24}$= +27.9° (c=1.4, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.52 (m, 2H), 7.52 – 7.33 (m, 3H), 3.62 (s, 1H), 3.33 (qd, *J* = 7.2, 2.7 Hz, 1H), 2.84 (dd, *J* = 18.7, 7.2 Hz, 1H), 2.72 (dd, *J* = 18.7, 2.7 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 9H), 1.27 – 1.13 (m, 2H), 1.10 – 0.92 (m, 2H), 0.71 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 166.3, 133.9, 129.3, 129.1, 126.6, 118.0, 84.8, 76.5, 61.1, 39.5, 39.1, 34.1, 27.7, 27.0, 27.0, 20.3, 14.2. UPLC-DAD-QTOF: $C_{22}H_{32}NO_4$ $[M+H]^+$ calcd.: 374.2331, found: 374.2339. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralcel AD-H, hexane/isopropanol 98/2, flow rate= 1.0 mL/min, retention times: 22.2 min (major.) and 29.7 min (minor.)).

(2*S*,3*S*)-*tert*-Butyl 2-cyano-3-(3-hydroxy-3-methyl-2-oxobutyl)-2-phenylhept-6-enoate 89Ea



The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **69a** (22 mg, 0.1 mmol) and *(E)*-2-hydroxy-2-methylnona-4,8-dien-3-one **85E** (50 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): Yield: 93% (36 mg). $[\alpha]_D^{23}$= +29.4° (c=1.7, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.51 – 7.34 (m, 3H), 5.62 – 5.49 (m, 1H), 4.93 – 4.77 (m, 1H), 3.58 (s, 1H), 3.39 – 3.26 (m, 1H), 2.94 – 2.73 (m, 2H), 1.84 – 1.61 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 9H), 1.33 – 1.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 166.2, 137.5, 133.7, 129.3, 129.2, 127.1, 126.6, 117.9, 115.4, 85.0, 76.6, 61.0, 39.6, 39.0, 31.3, 31.2, 27.7, 27.0, 27.0. UPLC-DAD-QTOF: $C_{23}H_{32}NO_4$ $[M+H]^+$ calcd.: 386.2331, found: 386.2320. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralcel AD-3, hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 19.4 min (major.) and 21.9 min (minor.)). Channel Descr.: PDA 207 nm.

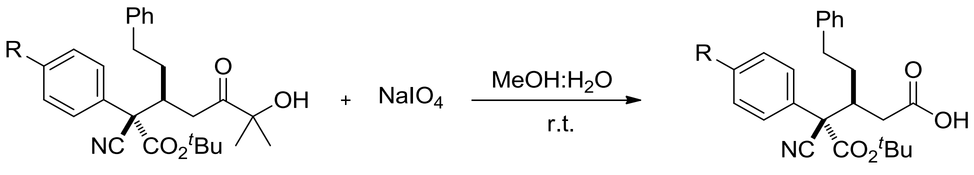
(2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-3-isobutyl-6-methyl-5-oxo-2-phenylheptanoate 89Fq



The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **69a** (22 mg, 0.1 mmol) and (*E*)-2-hydroxy-2,7-dimethyloct-4-en-3-one **85F** (51 mg, 0.3 mmol) according to the general procedure. The diastereomeric ratio was determined in the crude material 95:5. Yield of pure major diastereomer after column chromatography purification (colourless oil): 82% (32 mg). $[\alpha]_D^{23}$= +32.6° (c=1.2, 83% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.46 – 7.35 (m, 3H), 3.62 (s, 1H), 3.41 (m, 1H), 2.81 – 2.74 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 1.36 (s, 9H), 1.23 – 1.18 (m, 1H), 1.10 (m, 1H), 0.96 (m, 1H), 0.74 (t, *J* = 6.7 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 166.4, 134.0, 129.2, 129.1, 126.7, 84.9, 76.5, 61.5, 41.8, 40.3, 37.4, 27.7, 27.0, 27.0, 25.4, 24.0, 21.4. UPLC-DAD-QTOF: $C_{23}H_{34}NO_4$ $[M+H]^+$ calcd.: 388.2488, found: 388.2491. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Phenomenex Lux 3µ Cellulose-2, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 10.3 min (minor.) and 12.7 min (major.)). Channel Descr.: PDA 207 nm.

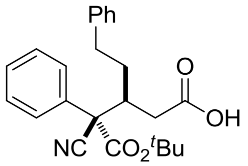
*6.4.2.4. Elaboration of adducts **92**, **96** and **97***

*6.4.2.4.1. To carboxylic acids **92***



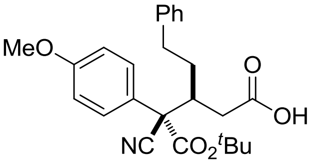
A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of the corresponding α’-hydroxy ketone adduct **89** (0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 48 h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid **92**.

(3*S*,4*S*)-5-(*tert*-Butoxy)-4-cyano-5-oxo-3-phenethyl-4-phenylpentanoic acid 92Aa



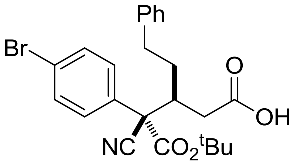
The title compound was prepared from (2*S*,3*S*)-*tert*-butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-phenylheptanoate **89Aa** (87 mg, 0.2 mmol) following the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 57 mg, 0.14 mmol, 72%. $[\alpha]_D^{23}$= +24.1° (c=0.4, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.44 – 7.31 (m, 3H), 7.16 (m, 3H), 6.99 – 6.86 (m, 2H), 3.17 (dq, *J* = 10.1, 5.6 Hz, 1H), 2.75 – 2.69 (m, 2H), 2.61 (ddd, *J* = 13.8, 10.3, 5.6 Hz, 1H), 2.31 (ddd, *J* = 13.7, 10.1, 7.0 Hz, 1H), 1.67 – 1.51 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 166.1, 141.1, 133.5, 129.3, 129.2, 128.5, 128.5, 126.6, 126.2, 117.5, 85.1, 60.7, 41.0, 37.9, 33.5, 33.4, 27.7 UPLC-DAD-QTOF: $C_{24}H_{28}NO_4$ $[M+H]^+$ calcd.: 394.2018, found: 394.2022.

(3*S*,4*S*)-5-(*tert*-Butoxy)-4-cyano-4-(4-methoxyphenyl)-5-oxo-3-phenethylpentanoic acid 92Ac



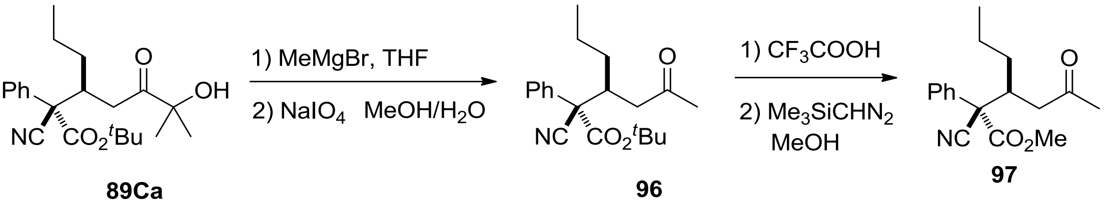
The title compound was prepared from (2*S*,3*S*)-*tert*-butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-6-methyl-5-oxo-3-phenethylheptanoate **89Ac** (93 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 48 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 68 mg, 0.16 mmol, 80%. $[\alpha]_D^{24}$= +26.8° (c=1.05, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.17 (m, 3H), 6.98 – 6.83 (m, 4H), 3.82 (s, 3H), 3.15 – 3.04 (m, 1H), 2.71 – 2.65 (m, 2H), 2.64 – 2.54 (m, 1H), 2.32 (ddd, *J* = 13.7, 9.5, 7.5 Hz, 1H), 1.64 – 1.53 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 166.1, 159.9, 141.0, 128.3, 127.7, 125.9, 125.1, 117.4, 114.4, 84.8, 59.8, 55.3, 40.8, 37.5, 33.2, 27.5. UPLC-DAD-QTOF: $C_{25}H_{30}NO_5$ $[M+H]^+$ calcd.: 424.2124, found: 424.2122.

(3*S*,4*S*)-4-(4-Bromophenyl)-5-(*tert*-butoxy)-4-cyano-5-oxo-3-phenethylpentanoic acid 92Ad

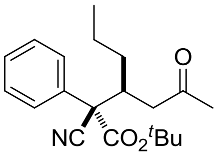


The title compound was prepared from (2*R*,3*S*)-*tert*-butyl 2-(4-bromophenyl)-6-hydroxy-2-isocyano-6-methyl-5-oxo-3-phenethyl-heptanoate **89Ad** (103 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 48 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 66 mg, 0.14 mmol, 70%. $[\alpha]_D^{24}$= +30.1° (c=0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.37 (m, 2H), 7.26 – 7.12 (m, 3H), 7.00 – 6.90 (m, 2H), 3.12 (dq, *J* = 9.1, 6.1, 5.7 Hz, 1H), 2.76 – 2.67 (m, 2H), 2.68 – 2.56 (m, 1H), 2.36 (ddd, *J* = 13.7, 9.7, 7.2 Hz, 1H), 1.65 (dq, *J* = 13.4, 4.1 Hz, 1H), 1.56 – 1.46 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 165.7, 140.8, 132.6, 132.4, 128.6, 128.5, 128.3, 126.3, 123.5, 117.0, 85.5, 60.3, 40.9, 37.7, 33.4, 33.2, 27.6. UPLC-DAD-QTOF: $C_{24}H_{27}NO_4Br$ $[M+H]^+$ calcd.: 472.1123, found: 472.1126.

6.4.2.4.2. *To ketones* ***96–97***

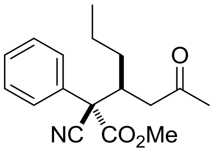


(2*S*,3*S*)-*tert*-Butyl 2-cyano-5-oxo-2-phenyl-3-propylhexanoate 96



MeMgBr (3.2 M in MeTHF, 0.67 mL, 2.15 mmol) was added to a solution of the α'-hydroxy ketone **89Ca** (159 mg, 0.43 mmol) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at room temperature until the reaction was finished (monitored by TLC). Then NH_4Cl (saturated solution, 3 mL) was added at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 x 5 mL). The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 25/1 to 10/1) to afford an oil. Yield: 90 mg, 0.27 mmol, 64%. $[\alpha]_D^{23}$= +35.4° (c=0.85, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.47 (m, 2H), 7.37 (m, 3H), 3.33 – 3.12 (m, 1H), 2.68 (dd, *J* = 17.8, 7.0 Hz, 1H), 2.58 (dd, *J* = 17.8, 3.2 Hz, 1H), 2.17 (s, 3H), 1.35 (s, 9H), 1.12 (m, 3H), 1.00 – 0.87 (m, 1H), 0.68 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 166.3, 133.9, 129.1, 128.9, 126.6, 117.9, 84.6, 61.2, 47.1, 39.4, 33.9, 30.3, 27.6, 20.3, 14.2. UPLC-DAD-QTOF: $C_{20}H_{28}NO_3$ $[M+H]^+$ calcd.: 330.2069, found: 330.2072.

Determination of the stereochemistry. Conversion of *tert*-butyl ester 96 into methyl ester 97



A solution of *tert*-butyl ester **96** (70 mg, 0.21 mmol) in trifluoroacetic acid (1.0 mL) was stirred for 1 h at room temperature. After evaporating all volatile compounds carboxylic acid was obtained and the residue was dissolved in MeOH (1 mL). Trimethylsilyldiazomethane (2M in diethyl ether, 0.8 mL) was added and the reaction mixture was stirred for 30 min at room temperature. Then all volatile compounds were evaporated and the crude material was purified by flash column chromatography (eluting with hexane/ethyl acetate 95:5) to afford the desired methyl ester. Yield: 43 mg, 0.15 mmol, 71%. $[\alpha]_D^{23}$= +45.0° (c=0.85, $CHCl_3$). Literature data for the opposite enantiomer (2*S*,3*R*): $[\alpha]_D^{25}$= –53° (c=0.85, $CHCl_3$).[372] Spectroscopic data were essentially identical to those reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.41 (qd, *J* = 6.3, 5.8, 2.4 Hz, 3H), 3.73 (s, 3H), 3.32 – 3.22 (m, 1H), 2.70 (dd, *J* = 17.8, 6.8 Hz, 1H), 2.61 (dd, *J* = 17.7, 3.9 Hz, 1H), 2.19 (s, 3H), 1.15 (m, 3H), 1.03 – 0.96 (m, 1H), 0.71 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 168.2, 133.4, 129.4, 129.3, 126.9, 117.6, 60.1, 54.1, 47.0, 40.0, 33.7, 30.3, 20.4, 14.2. UPLC-DAD-QTOF: $C_{17}H_{22}NO_3$ $[M+H]^+$ calcd.: 288.1600, found: 288.1605.

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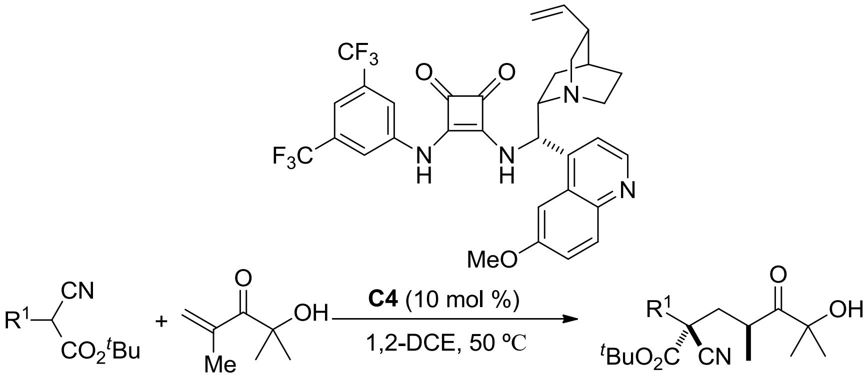
[372] Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2005**, *127*, 1313–1317.

6.4.3. General procedure for the conjugate addition of α-cyanoacetates 69 to α-substituted α'-hydroxy enone 86

6.4.3.1. Asymmetric reaction



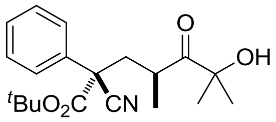
To a mixture of the corresponding cyanoacetate (0.3 mmol, 1.5 equiv.) and α'-hydroxy enone **86** (0.2 mmol, 1 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C4** (13 mg, 0.02 mmol) was added. The resulting mixture was stirred until consumption of the enone (monitored by ^{1}H-NMR). The reaction was treated with HCl 1N and the product was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product as a mixture of diastereomers in all cases higher than 98:2. After purification by flash column chromatography (eluent hexane/ethyl acetate 95/5) the product was isolated in essentially diastereomerically pure form.

6.4.3.2. Racemic reaction

Racemic reactions were conducted following the procedure for the asymmetric version, but using as catalyst DBU (20 mol %) and running the reaction at room temperature.

6.4.3.3. Characterization data for compounds 104a-f

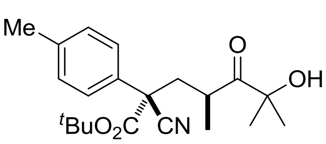
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-phenylheptanoate 104a



Prepared according to the general procedure starting from hydroxyketone **86** (26 mg, 0.2 mmol) and *tert*-butyl 2-cyano-2-phenylacetate **69a** (65 mg, 0.3 mmol). The diastereomeric ratio was determined in the crude material >99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 81% (84 mg). $[\alpha]_D^{25}$ = +27.6°

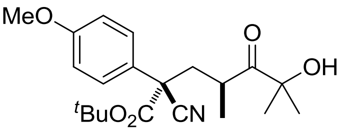
(c=0.7, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 2H), 7.48 – 7.34 (m, 3H), 3.33 – 3.20 (m, 2H), 2.81 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.17 (dd, *J* = 14.6, 5.9 Hz, 1H), 1.41 (d, *J* = 1.6 Hz, 6H), 1.39 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 166.2, 135.1, 129.3, 129.1, 126.1, 118.8, 84.9, 53.8, 40.6, 36.9, 27.7, 27.2, 27.0, 19.9. UPLC-DAD-QTOF: $C_{20}H_{27}NO_4Na$ $[M+Na]^+$ calcd.: 368.1838, found: 368.1836. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 19.6 min (major.) and 24.5 min (minor.)).

(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(*p*-tolyl)heptanoate 104b



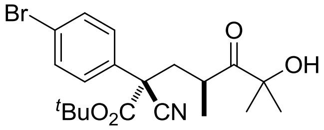
Prepared according to the general procedure starting from hydroxyketone **86** (26 mg, 0.2 mmol) and *tert*-butyl 2-cyano-2-(*p*-tolyl)acetate **69b** (69 mg, 0.3 mmol). The diastereomeric ratio was determined in the crude material >99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 67% (72 mg). $[\alpha]_D^{25}$ = +28.7° (c=0.85, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.21 – 7.17 (m, 2H), 3.32 (s, 1H), 3.25 (q, *J* = 6.3, 5.8 Hz, 1H), 2.78 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.35 (s, 3H), 2.14 (dd, *J* = 14.6, 5.9 Hz, 1H), 1.40 (d, *J* = 1.5 Hz, 6H), 1.38 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 166.4, 139.0, 132.0, 130.0, 126.0, 119.0, 84.8, 53.5, 40.6, 36.9, 27.7, 27.2, 27.0, 21.2, 20.0. UPLC-DAD-QTOF: $C_{21}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 382.1994, found: 382.1998. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 1 mL/min, retention times: 10.2 min (major.) and 12.1 min (minor.)).

(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-4,6-dimethyl-5-oxoheptanoate 104c



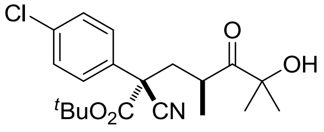
Prepared according to the general procedure starting from hydroxyketone **86** (26 mg, 0.2 mmol) and *tert*-butyl 2-cyano-2-(4-methoxyphenyl)acetate **69c** (74 mg, 0.3 mmol). The diastereomeric ratio was determined in the crude material >99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 70% (79 mg). $[\alpha]_D^{25}$ = +25.4° (c=0.85, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.35 (m, 2H), 6.97 – 6.84 (m, 2H), 3.82 (s, 3H), 3.32 (s, 1H), 3.26 (q, *J* = 6.3, 5.8 Hz, 1H), 2.77 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.19 – 2.05 (m, 1H), 1.40 (d, *J* = 2.0 Hz, 6H), 1.39 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.9, 166.3, 139.2, 135.0, 129.8, 129.2, 126.7, 123.1, 119.0, 84.8, 53.8, 40.7, 37.0, 27.7, 27.2, 27.0, 21.7, 19.9. UPLC-DAD-QTOF: $C_{21}H_{29}NO_5Na$ $[M+Na]^+$ calcd.: 398.1943, found: 398.1942. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 36.7 min (minor.) and 40.9 min (major.)).

(2*S*,4*S*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate 104d



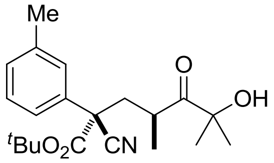
Prepared according to the general procedure starting from hydroxyketone **86** (26 mg, 0.2 mmol) and *tert*-butyl 2-cyano-2-(4-bromophenyl)acetate **69d** (88 mg, 0.3 mmol). The diastereomeric ratio was determined in the crude material 98:2. Yield of pure major diastereomer after column chromatography purification (colourless oil): 69% (88 mg). $[\alpha]_D^{25}$ = +18.5° (c=1.15, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.44 – 7.38 (m, 2H), 3.27 (q, *J* = 6.3, 5.9 Hz, 1H), 3.21 (s, 1H), 2.81 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.10 (dd, *J* = 14.6, 5.7 Hz, 1H), 1.40 (s, 6H), 1.39 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.6, 165.8, 134.2, 132.5, 127.9, 123.5, 118.4, 85.4, 53.5, 40.6, 36.9, 27.7, 27.3, 27.1, 20.0. UPLC-DAD-QTOF: $C_{20}H_{26}NO_4BrNa$ $[M+Na]^+$ calcd.: 446.0943, found: 446.0945. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 27.1 min (minor.) and 29.3 min (major.)).

(2*S*,4*S*)-*tert*-Butyl 2-(4-chlorophenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate 104e



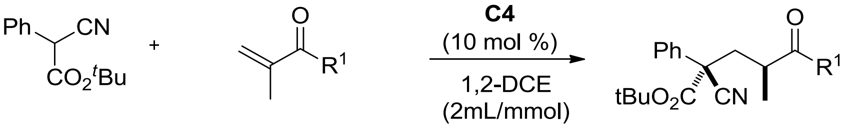
Prepared according to the general procedure starting from hydroxyketone **86** (26 mg, 0.2 mmol) and *tert*-butyl 2-(4-chlorophenyl)-2-cyanoacetate **69e** (76 mg, 0.3 mmol). The diastereomeric ratio was determined in the crude material 98:2. Yield of pure major diastereomer after column chromatography purification (colourless oil): 95% (108 mg). $[\alpha]_D^{25}$ = +17.8° (c=4.2, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.39 – 7.33 (m, 2H), 3.34 – 3.20 (m, 2H), 2.80 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.09 (dd, *J* = 14.6, 5.7 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.6, 165.8, 135.2, 133.7, 129.5, 127.6, 118.4, 85.2, 53.4, 40.5, 36.9, 27.7, 27.2, 27.0, 19.9. UPLC-DAD-QTOF: $C_{20}H_{26}NO_4ClNa$ [M+Na]$^+$ calcd.: 402.1448, found: 02.1447. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 30.9 min (minor.) and 34.9 min (major.)).

(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(*m*-tolyl)heptanoate 104f



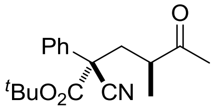
Prepared according to the general procedure starting from hydroxyketone **86** (26 mg, 0.2 mmol) and *tert*-butyl 2-cyano-2-(*m*-tolyl)acetate **69f** (69 mg, 0.3 mmol). The diastereomeric ratio was determined in the crude material >99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 83% (89 mg). $[\alpha]_D^{25}$ = +22.7° (c=2.35, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 3H), 7.19 – 7.12 (m, 1H), 3.34 (s, 1H), 3.31 – 3.22 (m, 1H), 2.78 (dd, *J* = 14.6, 5.5 Hz, 1H), 2.37 (s, 3H), 2.12 (dd, *J* = 14.6, 6.0 Hz, 1H), 1.40 (s, 6H), 1.38 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.9, 166.3, 139.2, 135.0, 129.8, 129.2, 126.7, 123.1, 119.0, 84.8, 53.8, 40.7, 37.0, 27.7, 27.2, 27.0, 21.7, 19.9. UPLC-DAD-QTOF: $C_{21}H_{29}NO_4Na$ [M+Na]$^+$ calcd.: 382.1994, found: 382.1991. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 99/1, flow rate= 1 mL/min, retention times: 30.4 min (major.) and 43.1 min (minor.)).

6.4.3.4. General procedure for the addition to 3-methylbut-3-en-2-one as Michael acceptor



To a mixture of the cyanoacetate (65 mg, 0.3 mmol, 1.5 equiv.) and a Michael acceptor (17 mg, 0.2 mmol, 1 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C4** (13 mg, 0.02 mmol) was added. The resulting mixture was stirred until consumption of the electrophile (monitored by ^{1}H-NMR). The reaction was treated with HCl 1N and the product was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product. After purification by flash column chromatography (eluent hexane/ ethyl acetate, 95/5) the product was isolated.

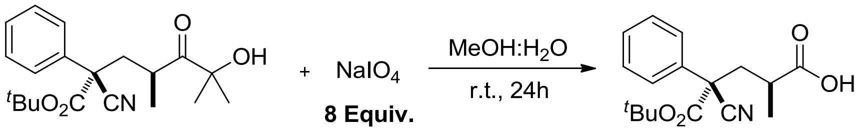
(2*S*,4*S*)-*tert*-Butyl 2-cyano-4-methyl-5-oxo-2-phenylhexanoate 101



Prepared according to the general procedure starting from 3-methyl-3-buten-2-one (17 mg, 0.2 mmol) and *tert*-butyl 2-cyano-2-phenylacetate **69a** (69 mg, 0.3 mmol). Diastereomeric ratio as determined in the crude material 80:20. Yield of mixture of diastereomers after column chromatography purification (colourless oil): 45% (27 mg). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 – 7.45 (m, 2H), 7.45 – 7.30 (m, 3H), 2.97 (dd, *J* = 14.4, 6.9 Hz, 1H), 2.85 – 2.60 (m, 1H), 2.18 (s, 3H), 2.04 – 1.90 (m, 1H), 1.41 (minor., s, 3H), 1.39 (s, 3H), 1.19 (minor., d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H).^{13}C NMR (75 MHz, CDCl$_3$) δ 10.3, 166.3, 135.3, 129.3, 129.2, 129.0, 126.4, 126.2, 118.7, 84.7, 54.1, 44.3, 44.2, 39.7, 39.3 (minor.), 28.7 (minor.), 27.7, 18.6, 18.2 (minor.). UPLC-DAD-QTOF: $C_{18}H_{24}NO_3$ $[M+H]^+$ calcd.: 302.1756, found: 302.1750. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 99/1, flow rate= 1 mL/min, retention times: 15.5 min (major.) and 17.2 min (minor.)).

6.4.3.5. Elaboration of adducts

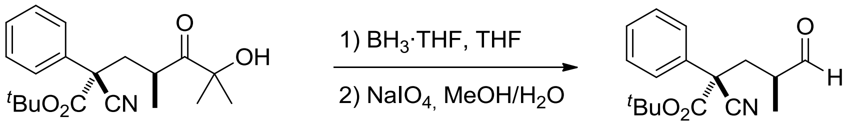
*6.4.3.5.1. To carboxylic acid **105***



(2*S*,4*S*)-5-(*tert*-Butoxy)-4-cyano-2-methyl-5-oxo-4-phenylpentanoic acid 105

A suspension of sodium periodate NaIO$_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of the α’-hydroxy ketone (0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 24h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et$_2$O (3 x 6 mL). The combined organic extracts were dried over MgSO$_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid. After purification by flash column chromatography (80:20 Hex: EtOAc) the acid was obtained as a colorless oil (46 mg, 0.15 mmol, 76% yield). $[\alpha]_D^{25}$ = +34.9° (c=2.45, CH$_2$Cl$_2$).^{1}H NMR (300 MHz, CDCl$_3$) δ 7.57 – 7.49 (m, 2H), 7.45 – 7.32 (m, 3H), 2.93 (dd, *J* = 14.4, 7.5 Hz, 1H), 2.68 (tt, *J* = 7.3, 3.5 Hz, 1H), 2.09 (dd, *J* = 14.5, 4.7 Hz, 1H), 1.40 (s, 9H), 1.21 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 181.3, 166.0, 135.2, 129.3, 129.0, 126.1, 118.3, 84.9, 53.9, 40.8, 37.1, 27.7, 18.8. UPLC-DAD-QTOF: $C_{17}H_{22}NO_4$ $[M+H]^+$ calcd.: 304.1549, found: 304.1553.

*6.4.3.5.2. To aldehyde **103***

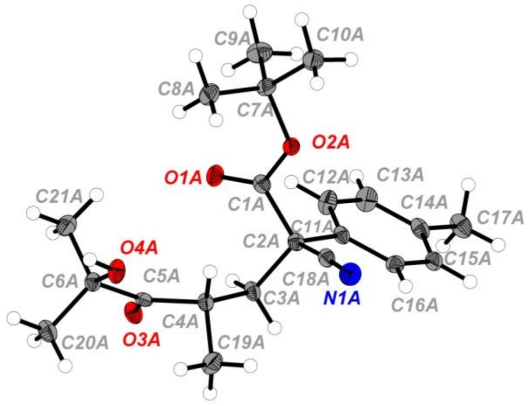


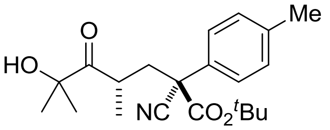
(2*S*,4*S*)-*tert*-Butyl 2-cyano-4-methyl-5-oxo-2-phenylpentanoate 103

BH_3·THF complex (1 M, 0.4 mL, 0.4 mmol) was added to a solution of α'-hydroxy ketone (69 mg, 0.2 mmol) in dry THF (0.9 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 95/5) to give the title compound as an oil (38 mg, 0.13 mmol, 66% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, *J* = 2.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.45 – 7.36 (m, 3H), 2.97 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.67 – 2.51 (m, 1H), 1.98 (dd, *J* = 14.5, 5.1 Hz, 1H), 1.41 (s, 9H), 1.11 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 180.6, 135.2, 129.4, 129.1, 129.0, 126.1, 85.1, 53.9, 40.8, 38.5, 27.7, 15.4. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.6 mL/min, retention times: 18.7 min (major.) and 22.2 min (minor.)).

6.4.4. ORTEP diagram of compound 104b

CCDC-1470018 contains the supplementary crystallographic data for the structural analysis of **104b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

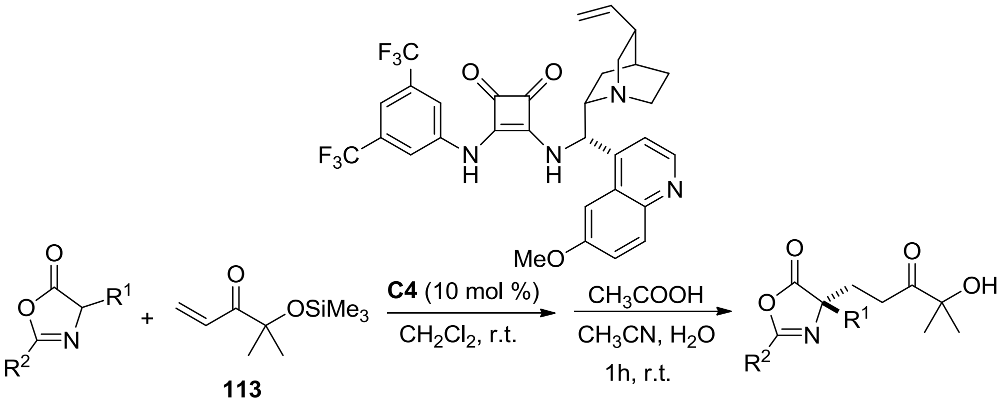




104b

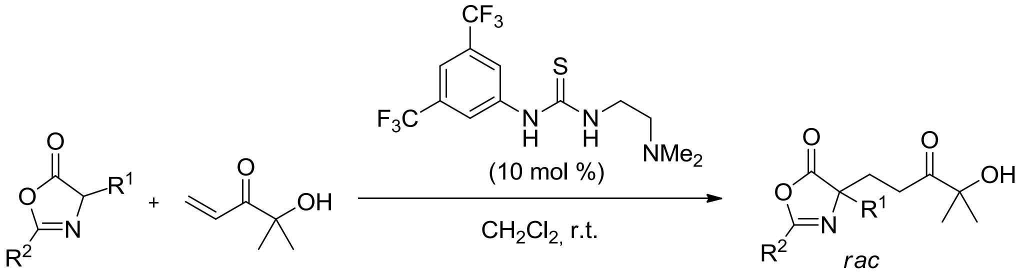
6.4.5. General procedure for the conjugate addition of azlactones to α'-trimethylsilyloxy enone 113

6.4.5.1. Asymmetric reaction



To a mixture of the corresponding azlactone (1 equiv., 0.2 mmol) and the α'-silyloxyenone **113** (1.5 equiv., 0.3 mmol) in dichloromethane (0.4 mL) catalyst **C4** was added at room temperature. The mixture was stirred at the same temperature, until consumption of the azlactone (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. For the desilylation the resulting crude was dissolved in CH_3CN (1 mL) and, H_2O (0.5 mL) and glacial acetic acid (0.3 mL) were added. The reaction mixture was stirred for 1 h at room temperature and it was quenched with $NaHCO_3$ saturated aqueous solution (20 mL). The organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

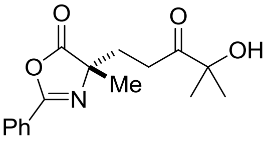
6.4.5.2. Racemic reaction



To a mixture of the corresponding azlactone **106**–**112** (1 equiv., 0.2 mmol) and the α'-hidroxy enone **113** (1.5 equiv., 0.3 mmol) in dichloromethane (0.4 mL) the achiral thiourea catalyst was added at room temperature. The mixture was stirred at the same temperature until consumption of the azlactone (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

*6.4.5.3. Characterization data for compounds **114**–**120***

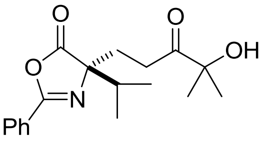
(*S*)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-methyl-2-phenyloxazol-5(4*H*)-one 114a



The title compound was prepared from 4-methyl-2-phenyloxazol-5(4*H*)-one **106a** (35 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 46 mg, 0.16 mmol, 78%. $[\alpha]_D^{25}$= –23.4º (c= 1.1, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.89 (m, 2H), 7.69 – 7.55 (m, 1H), 7.55 – 7.41 (m, 2H), 3.56 (s, 1H), 2.72 – 2.45 (m, 2H), 2.33 – 2.11 (m, 2H), 1.55 (s, 3H), 1.33 (d, *J* = 4.2 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 180.5, 160.5, 133.1, 129.1, 128.2, 126.0, 76.6, 68.5, 32.0, 30.3, 26.8, 23.9. UPLC-DAD-QTOF: $C_{16}H_{20}NO_4$ $[M+H]^+$ calcd.: 290.1392, found: 290.1396. The enantiomeric purity was determined by

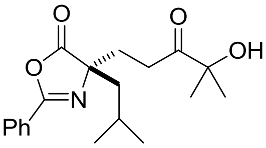
HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 8.3 min (major.) and 10.1 min (minor.)).

(*R*)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-isopropyl-2-phenyloxazol-5(4*H*)-one 114b



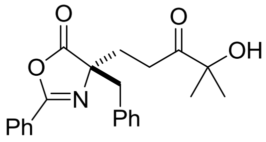
The title compound was prepared from 4-isopropyl-2-phenyloxazol-5(4*H*)-one **106b** (41 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 49 mg, 0.15 mmol, 77%. $[\alpha]_D^{25}$= +0.7º (c= 0.65, 90% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.63 – 7.56 (m, 1H), 7.54 – 7.47 (m, 2H), 3.50 (s, 1H), 2.54 – 2.45 (m, 2H), 2.39 – 2.28 (m, 1H), 2.26 – 2.13 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 180.1, 160.7, 133.1, 129.1, 128.2, 125.7, 76.5, 75.6, 35.2, 30.3, 28.9, 26.8, 16.9. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calcd.: 318.1700, found: 318.1705. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 7.4 min (major.) and 8.3 min (minor.)).

(*R*)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one 114c



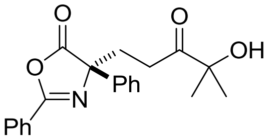
The title compound was prepared from 4-isobutyl-2-phenyloxazol-5(4*H*)-one **106c** (43 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 51 mg, 0.15 mmol, 75%. $[\alpha]_D^{25}$= –28.7º (c= 2.2, 92% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 – 7.89 (m, 2H), 7.64 – 7.56 (m, 1H), 7.55 – 7.47 (m, 2H), 3.55 (s, 1H), 2.62 – 2.44 (m, 2H), 2.29 – 2.11 (m, 2H), 1.97 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.82 (dd, *J* = 14.0, 7.1 Hz, 1H), 1.62 (dq, *J* = 12.6, 6.7 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 0.88 (dd, *J* = 10.4, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 180.7, 160.3, 133.1, 129.1, 128.6, 125.8, 76.6, 72.0, 46.2, 32.5, 29.9, 26.7, 25.0, 24.3, 23.3. UPLC-DAD-QTOF: $C_{19}H_{26}NO_4$ $[M+H]^+$ calcd.: 332.1856, found: 332.1860. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 99/1, flow rate= 1.0 mL/min, retention times: 43.3 min (major.) and 52.4 min (minor.)).

(***R***)-4-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-5(4*H*)-one 114d



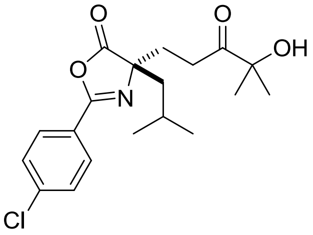
The title compound was prepared from 4-benzyl-2-phenyloxazol-5(4*H*)-one **106d** (50 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 41 mg, 0.14 mmol, 72%. $[\alpha]_D^{25}$= –70.5º (c= 2.2, 88% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.58 – 7.50 (m, 1H), 7.47 – 7.40 (m, 2H), 7.16 (m, 5H), 3.56 (s, 1H), 3.31 – 3.12 (m, 2H), 2.71 – 2.51 (m, 2H), 2.45 – 2.28 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 179.4, 160.6, 134.0, 133.0, 130.3, 128.9, 128.4, 128.0, 127.6, 125.5, 76.6, 73.8, 43.9, 31.2, 30.4, 26.8. UPLC-DAD-QTOF: $C_{22}H_{24}NO_4$ $[M+H]^+$ calcd.: 366.1700, found: 366.1709. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min, retention times: 22.5 min (minor.) and 25.9 min (major.)).

(***R***)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-2,4-diphenyloxazol-5(4*H*)-one 114e



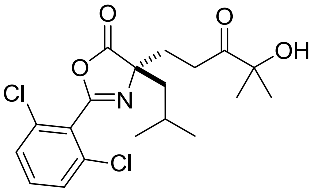
The title compound was prepared from 2,4-diphenyloxazol-5(4*H*)-one **106e** (48 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 50 mg, 0.14 mmol, 71%. $[\alpha]_D^{25}$= –108.0º (c= 2.3, 90% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 2H), 7.69 – 7.59 (m, 3H), 7.56 – 7.50 (m, 2H), 7.39 (m, 3H), 3.57 (s, 1H), 2.80 – 2.38 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 178.5, 160.9, 137.3, 133.3, 129.1, 129.1, 128.8, 128.4, 126.0, 125.8, 76.6, 73.2, 34.6, 30.5, 26.7. UPLC-DAD-QTOF: $C_{21}H_{22}NO_4$ $[M+H]^+$ calcd.: 352.1549, found: 352.1551. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 8.8 min (minor.) and 12.7 min (major.)).

(*R*)-2-(4-Chlorophenyl)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyloxazol-5(4*H*)-one 116c



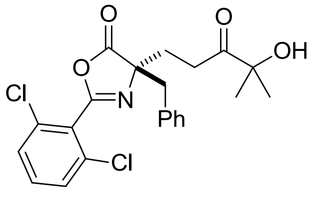
The title compound was prepared from 2-(4-chlorophenyl)-4-isobutyloxazol-5(4*H*)-one **108c** (50 mg, 0.2 mmol) and α'-silyloxyenone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 51 mg, 0.14 mmol, 72%. $[\alpha]_D^{25}$= –16.2º (c= 2.9, 86% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 2H), 7.52 – 7.44 (m, 2H), 3.49 (s, 1H), 2.60 – 2.48 (m, 2H), 2.25 – 2.15 (m, 2H), 1.96 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.81 (dd, *J* = 14.0, 7.1 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 0.88 (dd, *J* = 9.6, 6.6 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 212.99, 180.34, 159.48, 139.51, 129.48, 129.42, 129.08, 127.50, 124.22, 76.57, 72.10, 46.07, 32.41, 29.95, 26.75, 25.03, 24.24, 23.30. UPLC-DAD-QTOF: $C_{19}H_{25}ClNO_4$ $[M+H]^+$ calcd.: 366.1472, found: 366.1474. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 98/2, flow rate= 1.0 mL/min, retention times: 26.2 min (minor.) and 30.7 min (major.)).

(*R*)-2-(2,6-Dichlorophenyl)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyloxazol-5(4*H*)-one 117c



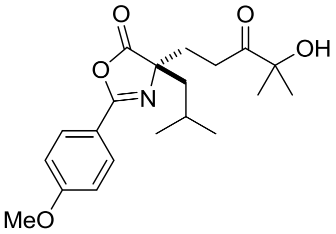
The title compound was prepared from 2-(2,6-dichlorophenyl)-4-isobutyloxazol-5(4*H*)-one **109c** (48 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 56 mg, 0.14 mmol, 69%. $[\alpha]_D^{25}$= +12.9º (c= 1.1, 70% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.33 (m, 3H), 3.52 (s, 1H), 2.97 – 2.69 (m, 1H), 2.69 – 2.44 (m, 1H), 2.25 (d, J = 15.3 Hz, 2H), 2.03 (d, J = 12.9 Hz, 1H), 1.97 – 1.69 (m, 2H), 1.36 (s, 6H), 0.97 (t, *J* = 6.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 180.0, 157.2, 135.0, 132.8, 128.7, 127.0, 76.5, 72.3, 46.1, 32.0, 30.4, 26.8, 24.9, 23.3. UPLC-DAD-QTOF: $C_{19}H_{24}Cl_2NO_4$ $[M+H]^+$ calcd.: 400.1082, found: 400.1079. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 7.7 min (major.) and 15.5 min (minor.)).

(*R*)-4-Benzyl-2-(2,6-dichlorophenyl)-4-(4-hydroxy-4-methyl-3-oxopentyl)oxazol-5(4*H*)-one 117d



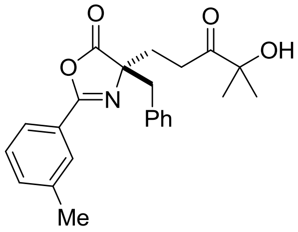
The title compound was prepared from 4-benzyl-2-(2,6-dichlorophenyl)oxazol-5(4*H*)-one **109d** (64 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 76 mg, 0.18 mmol, 88%. $[\alpha]_D^{25}$= +20.5º (c= 0.8, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.31 – 7.19 (m, 6H), 3.51 (s, 1H), 3.38 – 3.18 (m, 2H), 2.86 (ddd, *J* = 17.8, 8.8, 7.2 Hz, 1H), 2.72 – 2.51 (m, 1H), 2.35 (dd, *J* = 8.9, 7.2 Hz, 2H), 1.35 (d, *J* = 4.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 179.2, 157.4, 135.0, 134.1, 132.7, 130.8, 128.8, 128.4, 127.7, 76.5, 73.8, 43.3, 31.3, 30.6, 26.8, 26.8. UPLC-DAD-QTOF: $C_{22}H_{22}Cl_2NO_4$ $[M+H]^+$ calcd.: 434.0926, found: 434.0919. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 13.5 min (major.) and 27.0 min (minor.)).

(*R*)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-(4-methoxyphenyl)oxazol-5(4*H*)-one 118c



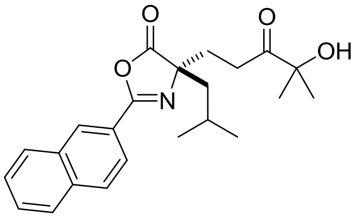
The title compound was prepared from 4-isobutyl-2-(4-methoxyphenyl)oxazol-5(4*H*)-one **110c** (50 mg, 0.2 mmol) and α'-silyloxyenone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 51 mg, 0.14 mmol, 70%. $[\alpha]_D^{25}$= –24.4º (c= 1.9, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.99 – 7.90 (m, 2H), 7.03 – 6.96 (m, 2H), 3.88 (s, 3H), 3.62 (s, 1H), 2.65 – 2.45 (m, 2H), 2.27 – 2.11 (m, 2H), 1.95 (dd, *J* = 14.0, 5.6 Hz, 1H), 1.80 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.70 – 1.51 (m, 1H), 1.32 (s, 3H), 1.29 (s, 3H), 0.88 (dd, *J* = 11.2, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, CDCl3), δ: 213.16, 180.88, 163.53, 160.01, 130.04, 118.02, 114.51, 76.54, 71.84, 55.71, 46.21, 32.68, 29.98, 26.74, 26.72, 25.04, 24.27, 23.33. UPLC-DAD-QTOF: $C_{20}H_{28}NO_5$ $[M+H]^+$ calcd.: 362.1967, found: 362.1972. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 10.2 min (minor.) and 12.2 min (major.)).

(*R*)-4-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-5(4*H*)-one 119d



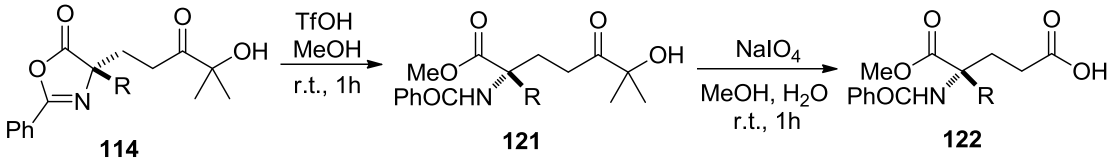
The title compound was prepared from 4-benzyl-2-(*m*-tolyl)oxazol-5(4*H*)-one **111d** (53 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 49 mg, 0.13 mmol, 65%. $[\alpha]_D^{25}$= –80.7º (c= 2.2, 86% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.52 (m, 2H), 7.40 – 7.23 (m, 2H), 7.22 – 7.06 (m, 5H), 3.62 (s, 1H), 3.30 – 3.09 (m, 2H), 2.72 – 2.48 (m, 2H), 2.37 (s, 3H), 2.37 – 2.27 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 179.4, 160.8, 138.8, 134.0, 133.8, 130.3, 128.8, 128.5, 128.4, 127.5, 125.4, 125.2, 76.6, 73.7, 43.8, 31.3, 30.4, 26.8, 26.7, 21.4. UPLC-DAD-QTOF: $C_{23}H_{26}NO_4$ $[M+H]^+$ calcd.: 380.1862, found: 380.1870. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min, retention times: 14.1 min (minor.) and 22.6 min (major.)).

(*R*)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-(naphthalen-2-yl)oxazol-5(4*H*)-one 120c



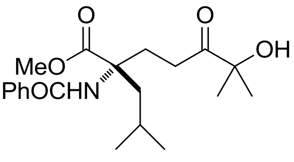
The title compound was prepared from 4-isobutyl-2-(naphthalen-2-yl)oxazol-5(4*H*)-one **112c** (53 mg, 0.2 mmol) and α'-silyloxy enone **113** (56 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 50 mg, 0.13 mmol, 66%. $[\alpha]_D^{25}$= +5.3º (c= 2.7, 66% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 – 8.43 (m, 1H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.01 – 7.80 (m, 3H), 7.69 – 7.35 (m, 2H), 3.55 (s, 1H), 2.72 – 2.44 (m, 2H), 2.37 – 2.16 (m, 2H), 2.08 – 1.92 (m, 1H), 1.91 – 1.77 (m, 1H), 1.78 – 1.59 (m, 1H), 1.31 (d, *J* = 8.9 Hz, 6H), 0.90 (dd, *J* = 9.4, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 180.7, 160.5, 135.5, 132.8, 129.7, 129.3, 129.1, 128.7, 128.1, 127.3, 123.6, 122.9, 76.6, 72.2, 46.3, 32.6, 30.0, 26.7, 25.1, 24.3, 23.3. UPLC-DAD-QTOF: $C_{23}H_{28}NO_4$ $[M+H]^+$ calcd.: 382.2018, found: 382.2024. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 10.4 min (minor.) and 13.1 min (major.)).

*6.4.5.4. Elaboration of adducts **114** into carboxylic acids **122***



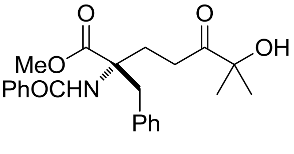
1st step: To a solution of α-hydroxy ketone **114** (0.5 mmol) in MeOH (2.5 mL, 5 mL/mmol) 2 drops of triflic acid were added and the solution was stirred at room temperature until completion of reaction (1 h). After that the solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel.

(*R*)-Methyl 2-benzamido-6-hydroxy-2-isobutyl-6-methyl-5-oxoheptanoate 121c



The title compound **121c** was prepared from (*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **114c** (166 mg, 0.5 mmol). The reaction mixture was stirred for 1 h until completion of reaction. After evaporating the organic solvent the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 174 mg, 0.48 mmol, 95%. $[\alpha]_D^{25}$= +4.5º (c= 0.75, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2H), 7.55 – 7.43 (m, 3H), 7.33 (s, 1H), 3.83 (s, 3H), 3.55 (s, 1H), 2.97 – 2.85 (m, 1H), 2.73 – 2.51 (m, 2H), 2.38 – 2.21 (m, 2H), 1.83 (dd, *J* = 14.2, 7.6 Hz, 1H), 1.60 (dd, *J* = 13.6, 7.1 Hz, 1H), 1.29 (s, 6H), 0.85 (dd, *J* = 26.6, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 175.6, 166.2, 134.9, 131.9, 128.9, 126.9, 76.5, 63.9, 53.2, 43.8, 30.8, 30.6, 26.8, 26.7, 25.1, 23.9, 22.8. UPLC-DAD-QTOF: $C_{20}H_{30}NO_5$ $[M+H]^+$ calcd.: 364.2124, found: 364.2124.

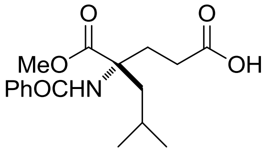
(*R*)-Methyl 2-benzamido-2-benzyl-6-hydroxy-6-methyl-5-oxoheptanoate 121d



The title compound **121d** was prepared from (*R*)-4-(4 hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **114d** (183 mg, 0.5 mmol) following the general procedure. The reaction mixture was stirred for 1 h until completion of reaction. After evaporating the organic solvent the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 199 mg, 0.5 mmol, >99%. $[\alpha]_D^{25}$= –52.3º (c= 1.01, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H), 7.54 – 7.38 (m, 3H), 7.19 (m, 2H), 7.04 – 6.96 (m, 3H), 3.87 (d, *J* = 13.8 Hz, 1H), 3.84 (s, 3H), 3.26 (d, *J* = 13.5 Hz, 1H), 3.10 – 2.96 (m, 1H), 2.77 – 2.57 (m, 1H), 2.50 – 2.32 (m, 2H), 1.29 (d, *J* = 3.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 173.7, 166.9, 136.1, 134.9, 131.9, 129.9, 128.9, 128.5, 127.3, 126.9, 76.5, 65.7, 53.2, 40.9, 30.9, 29.9, 26.7, 26.7. UPLC-DAD-QTOF: $C_{23}H_{28}NO_5$ $[M+H]^+$ calcd.: 398.1962, found: 398.1967.

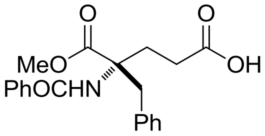
2nd step: The residue obtained in the previous step was dissolved in MeOH and to this solution a suspension of sodium periodate $NaIO_4$ (535 mg, 2.5 mmol, 5 equiv.) in water (1.5 mL) was added. The reaction mixture was stirred at room temperature until completion of reaction (1 h). The solvent was then removed under reduced pressure, water (4.5 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid. The crude was purified by flash column chromatography on silica gel.

(*R*)-4-Benzamido-4-(methoxycarbonyl)-6-methylheptanoic acid 122c



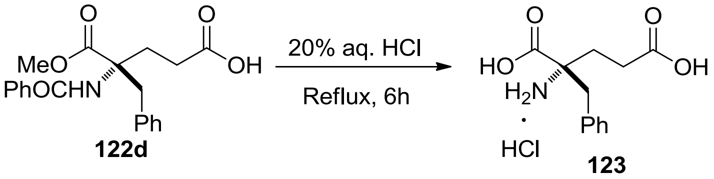
The title compound **122c** was prepared from (*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **121c** (182 mg, 0.5 mmol) and $NaIO_4$ (535 mg, 2.5 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 60/40) to give the title compound as a white foam. Yield: 138 mg, 0.43 mmol, 86% over two steps. $[\alpha]_D^{25}$= –77.0° (c= 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H), 7.53 – 7.32 (m, 3H), 3.80 (s, 3H), 3.02 – 2.88 (m, 1H), 2.67 (dd, *J* = 14.2, 5.3 Hz, 1H), 2.38 – 2.03 (m, 3H), 1.78 (dd, *J* = 14.2, 7.6 Hz, 1H), 1.57 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 175.3, 166.5, 134.7, 131.9, 128.9, 127.1, 63.9, 53.2, 43.7, 31.2, 29.3, 25.0, 23.9, 22.7. UPLC-DAD-QTOF: $C_{17}H_{24}NO_5$ $[M+H]^+$ calcd.: 322.1649, found: 322.1653.

(*R*)-4-Benzamido-4-benzyl-5-methoxy-5-oxopentanoic acid 122d

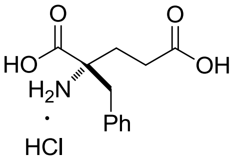


The title compound **122d** was prepared from (*R*)-4-benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-5(4*H*)-one **122c** (199 mg, 0.5 mmol) and $NaIO_4$ (535 mg, 2.5 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 60/40) to give the title compound as a white foam. Yield: 160 mg, 0.45 mmol, 89% over two steps. $[\alpha]_D^{25}$= –14.8° (c= 2.6, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 2H), 7.55 – 7.43 (m, 1H), 7.40 (m, 2H), 7.22 – 7.15 (m, 2H), 7.09 – 6.99 (m, 3H), 3.91 (d, *J* = 13.6 Hz, 2H), 3.82 (s, 3H), 3.23 (d, *J* = 13.5 Hz, 2H), 3.15 – 3.05 (m, 1H), 2.51 – 2.31 (m, 2H), 2.26 – 2.14 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 173.5, 167.3, 136.0, 134.8, 131.9, 129.8, 128.8, 128.5, 127.2, 127.1, 65.7, 53.1, 40.7, 30.4, 29.5. UPLC-DAD-QTOF: $C_{20}H_{22}NO_5$ $[M+H]^+$ calcd.: 356.1492, found: 356.1496.

6.4.5.5. *Synthesis of glutamic acid analogue **123***[373]



2-(*R*)-Benzylglutamic acid hydrochloride 123



(*R*)-4-Benzamido-4-benzyl-5-methoxy-5-oxopentanoic acid **122d** (355 mg, 0.75 mmol) was treated with 5 mL of 20% HCl for 4 h at reflux. After standing overnight in the refrigerator, the resulting crystals of benzoic acid were removed by filtration and the filtrate was washed twice with diethyl ether. The solution was evaporated to dryness in vaccuo. The residue was dissolved in a small amount of water and the solution was evaporated to dryness again in order to remove any trace of HCl. Finally, the product was dried overnight in the lyophilizator to obtain a white solid. Yield: 151 mg, 0.64 mmol, 85 %. m.p. 195–199 °C. $[\alpha]_D^{25}$= –0.98° (c= 3.3, 4N HCl); Literature data for the opposite enantiomer: $[\alpha]_D^{25}$= +1.44° (c= 6.39, 4N HCl).[374] ^1H NMR (300 MHz, D_2O) δ 7.50 – 7.38 (m, 3H), 7.36 – 7.30 (m, 2H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.14 (d, *J* = 14.4 Hz, 1H), 2.70 – 2.50 (m, 2H), 2.46 – 2.32 (m, 1H), 2.30 – 2.16 (m, 1H).^{13}C NMR (75 MHz, D_2O) δ 174.9, 172.5, 132.8, 130.6, 129.6, 128.7, 63.9, 41.3, 30.7, 28.6.

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[373] Izumi, Y.; Tatsumi, S.; Imaida, M.; Fukuda, Y.; Akabori, S. *Bull. Chem. Soc. Jpn.*, **1965**, *38*, 1338–1340.

[374] Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507–1518.

6.4.6. Computational studies

We carried out an extensive search for different H-bond combination patterns in line with the proposed activation ternary complexes **A**, **B**, and **C**.

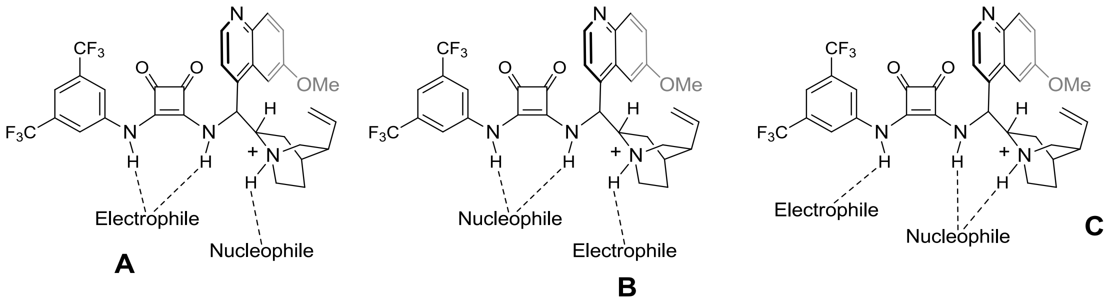
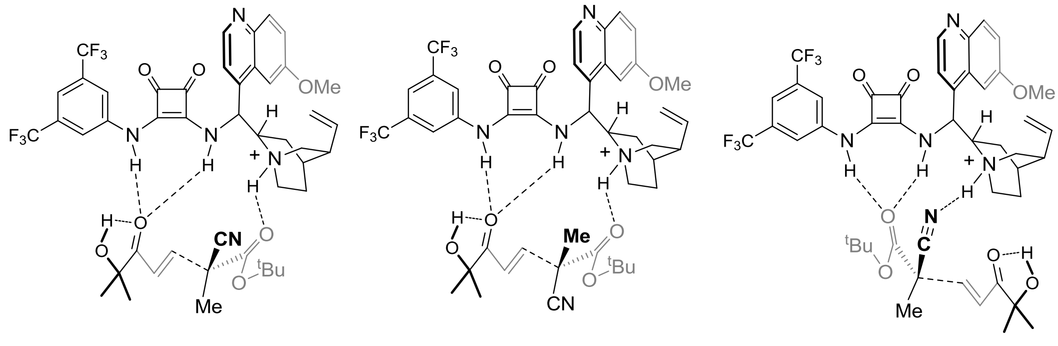


Figure 39. Previously proposed activation ternary complexes.

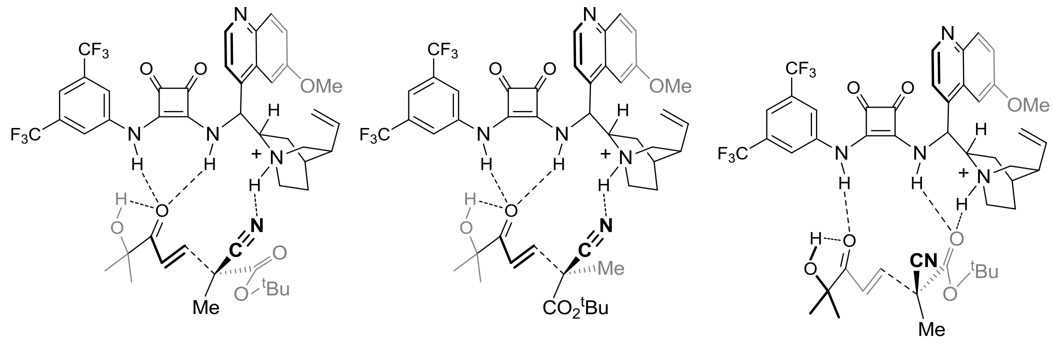
Only transition structures belonging to **A**-type activation (**TS-R$_1$**, **TS-S$_1$**, **TS-R$_2$** and **TS-S$_2$**) are predicted to have feasible energies (Figure 40), whereas a single structure of too high energy presented pattern **C** (**TS-R$_C$**), and no plausible structure of type **B** was located. In what can be considered the saddle point closest to **B** (**TS-S$_{B'}$**), the cyanoacetate is activated by three H-bonds, while the electrophilic hydroxyenone remains non-bonded. This structure can be discarded, as it presents too high energy, and predicts the formation of the wrong S enantiomer. The corresponding TS for the formation of the R enantiomer could not be located.



TS-R$_1$ ΔΔG = 0 kcal/mol

TS-S$_1$ ΔΔG = 2.8 kcal/mol

TS-S$_{B'}$ ΔΔG = 8.1 kcal/mol



TS-R$_2$ ΔΔG = 6.1 kcal/mol

TS-S$_2$ ΔΔG = 6.4 kcal/mol

TS-R$_C$ ΔΔG = 5.4 kcal/mol

Figure 40. Lowest in energy transition states located in this study. Relative Gibbs energies (kcal/mol) for the solvent model (CH_2Cl_2) are shown.

Table 25. Energies of the structures involved in the computational study.

	G (M06-2X/6-311++G**, IEF-PCM, CH_2Cl_2)	relative **G**	Frequency
Transition States			
TS-R$_1$	-3104.470112	0	-311.6
TS-S$_1$	-3104.465609	2.83	-194.0
TS-R$_2$	-3104.460460	6.06	-195.2
TS-S$_2$	-3104.459971	6.36	-104.4
TS-S$_{B'}$	-3104.457132	8.15	-371.1
TS-R$_C$	-3104.451775	11.51	-198.1
Structures			
69h	-360.071203		
125	-306.353223		
18	-384.917547		
MVK	-231.138280		
TS-69h+125	-666.399678	15.5	-276.4
TS-69h+18	-744.970910	11.1	-155.5
TS-69h+MVK	-591.181233	17.7	-315.5

Cartesian Coordinates of the structures involved in the computational study:

TS-R_1

```
                 Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          1           0        2.752133    2.548579    3.131656
      2          1           0       -1.320494   -0.563770   -0.767164
      3          1           0       -3.335417   -0.618065   -1.789669
      4          1           0        2.732683    0.849815    2.654112
      5          1           0       -2.904747   -2.297886    2.162326
      6          1           0        1.864390    2.309027    0.967437
      7          1           0        2.867820    4.295130    1.563310
      8          1           0        3.144057    3.951759   -0.147687
      9          1           0        3.212474    1.817859   -0.935043
     10          1           0        0.960763    0.195135   -0.843144
     11          1           0       -6.708089   -2.448173    0.147230
     12          1           0        5.529383    1.701661   -0.726278
     13          1           0        5.408601    0.337385    0.372643
     14          1           0        5.194792    4.340889    1.953104
     15          1           0        5.457597    4.105899    0.228178
     16          1           0        5.060745    2.324682    3.522252
     17          1           0        5.054361    0.699302    2.847777
     18          1           0        6.522923    2.247670    1.506178
     19          7           0        1.428496   -0.026552    0.041839
     20          6           0       -2.954194   -1.416011    0.182229
     21          6           0       -3.759236   -1.130498   -0.932630
     22          6           0       -3.510908   -2.072478    1.289607
     23          6           0       -5.436003   -3.201122    2.421071
     24          6           0        1.039792   -1.263533    2.273476
     25          6           0       -0.407565   -1.748638    2.380561
     26          6           0        0.712265   -0.721981    0.945690
     27          6           0       -0.624827   -1.152200    1.022832
     28          7           0       -1.614469   -1.011049    0.115131
     29          6           0       -5.665133   -2.158441    0.154740
     30          6           0       -4.857918   -2.433836    1.258172
     31          6           0       -5.965931   -1.129260   -2.113494
     32          6           0       -5.100075   -1.501403   -0.938618
     33          6           0        2.896175   -0.070825    0.066283
     34          6           0        3.505122    1.348173    0.006454
     35          6           0        3.218089    1.809808    2.476888
     36          7           0        2.905820    2.259335    1.068992
     37          6           0        3.423741    3.665738    0.865867
     38          6           0        5.048084    1.354399    0.192373
     39          6           0        4.950879    3.692806    1.105434
     40          6           0        4.752640    1.733179    2.654696
     41          6           0        5.436594    2.258026    1.378254
     42          9           0       -5.263460   -4.533733    2.267699
     43          9           0       -4.859169   -2.857267    3.589780
     44          9           0       -6.766706   -2.989851    2.545771
     45          9           0       -5.254944   -1.050855   -3.259870
     46          9           0       -6.555795    0.076287   -1.933538
     47          8           0        2.049387   -1.272703    2.968597
     48          8           0       -1.076405   -2.337694    3.205616
     49          9           0       -6.957445   -2.025059   -2.308594
     50          6           0        3.450825   -0.919624   -1.078107
     51          7           0        4.431032   -2.421726   -3.282445
     52          6           0        4.257129   -2.081733   -0.841485
     53          6           0        3.159232   -0.582677   -2.383520
     54          6           0        3.658436   -1.369033   -3.450222
     55          6           0        4.734217   -2.783976   -2.002830
     56          1           0        2.525870    0.263868   -2.629759
     57          1           0        3.391479   -1.101482   -4.470102
     58          1           0        3.168854   -0.523216    1.018290
     59          6           0        4.605271   -2.573528    0.440522
     60          1           0        4.227141   -2.125321    1.352622
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    61          6           0        5.406914   -3.695267    0.578699
    62          6           0        5.893908   -4.376005   -0.567043
    63          1           0        6.521073   -5.253161   -0.462820
    64          6           0        5.554933   -3.924699   -1.821592
    65          1           0        5.902440   -4.432787   -2.714830
    66          8           0        5.679276   -4.078514    1.857804
    67          6           0        6.436791   -5.260693    2.074277
    68          1           0        5.946999   -6.141581    1.641478
    69          1           0        6.496377   -5.380918    3.156605
    70          1           0        7.451803   -5.174581    1.666299
    71          6           0       -0.608283    3.995497   -0.540560
    72          6           0       -0.594892    3.632154    0.868481
    73          6           0       -1.956416    3.804977    2.937213
    74          8           0        0.251814    2.895108    1.408910
    75          8           0       -1.661672    4.122919    1.525598
    76          6           0       -2.190012    2.300595    3.101105
    77          1           0       -2.970594    1.959295    2.414525
    78          1           0       -2.525025    2.091136    4.121758
    79          1           0       -1.278623    1.733838    2.911132
    80          6           0       -3.250092    4.584930    3.184722
    81          1           0       -4.039399    4.247266    2.507471
    82          1           0       -3.092992    5.655560    3.025554
    83          1           0       -3.588738    4.432591    4.213493
    84          6           0       -0.832831    4.324821    3.839370
    85          1           0       -1.125914    4.213081    4.887950
    86          1           0       -0.652140    5.387385    3.648918
    87          1           0        0.091156    3.770755    3.674346
    88          6           0        0.579384    3.647108   -1.230314
    89          7           0        1.516893    3.316785   -1.847544
    90          6           0       -1.312218    5.258689   -1.013126
    91          1           0       -2.288166    5.347148   -0.532677
    92          1           0       -1.459428    5.227813   -2.096878
    93          1           0       -0.741338    6.165603   -0.779614
    94          6           0       -0.414809    0.777223   -4.443686
    95          1           0        0.993923    2.428523   -4.520087
    96          1           0        0.552939    1.747167   -6.102569
    97          1           0       -0.579799    2.808334   -5.247549
    98          1           0       -1.342948   -0.004413   -6.236077
    99          1           0       -2.032500   -0.655957   -4.739858
   100          1           0       -2.449201    0.989201   -5.258819
   101          1           0       -2.007877    2.764378   -3.437436
   102          1           0       -2.802580    3.102412   -1.100478
   103          1           0       -1.732797    1.725343   -0.542774
   104          8           0        0.601674   -0.219805   -4.449800
   105          6           0        0.171524    2.025006   -5.115241
   106          6           0       -1.643572    0.250055   -5.215326
   107          1           0        0.493666   -0.670094   -3.591331
   108          8           0       -0.400496    0.168925   -2.132390
   109          6           0       -0.820448    1.035787   -2.970780
   110          6           0       -1.663088    2.118672   -2.636911
   111          6           0       -1.965659    2.447610   -1.317153
 ---------------------------------------------------------------------
```

TS-S$_1$

```
                          Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          1           0        2.803653    2.307325    3.270735
      2          1           0       -1.357903   -0.503435   -0.742645
      3          1           0       -3.407083   -0.459620   -1.689837
      4          1           0        2.719144    0.654355    2.659859
      5          1           0       -2.777406   -2.694005    1.948525
      6          1           0        1.832028    2.266518    1.113512
      7          1           0        2.843443    4.175842    1.833859
      8          1           0        3.159719    3.969813    0.114303
      9          1           0        3.158030    1.893242   -0.856236
     10          1           0        0.943140    0.239686   -0.843180
     11          1           0       -6.632986   -2.715722    0.031133
     12          1           0        5.469896    1.875641   -0.696697
     13          1           0        5.419035    0.378702    0.218453
```

14	1	0	5.159847	4.141304	2.304566
15	1	0	5.454507	4.141223	0.569489
16	1	0	5.102817	1.936600	3.606970
17	1	0	5.044646	0.418649	2.718953
18	1	0	6.519680	2.131528	1.574057
19	7	0	1.432931	-0.052288	0.004852
20	6	0	-2.930297	-1.521162	0.131837
21	6	0	-3.781330	-1.109111	-0.905785
22	6	0	-3.422785	-2.358829	1.141862
23	6	0	-5.290990	-3.628468	2.211808
24	6	0	1.121353	-1.492307	2.121473
25	6	0	-0.314809	-2.014151	2.220365
26	6	0	0.745719	-0.832479	0.863289
27	6	0	-0.582185	-1.285667	0.935361
28	7	0	-1.604121	-1.064835	0.081523
29	6	0	-5.607293	-2.371739	0.063279
30	6	0	-4.755137	-2.770476	1.092330
31	6	0	-6.016663	-1.044655	-2.028658
32	6	0	-5.104762	-1.536238	-0.934590
33	6	0	2.899056	-0.067340	0.003385
34	6	0	3.478081	1.367180	0.047600
35	6	0	3.228809	1.610881	2.545604
36	7	0	2.893156	2.183202	1.187923
37	6	0	3.415884	3.597543	1.106926
38	6	0	5.027971	1.398948	0.183068
39	6	0	4.938366	3.609411	1.374191
40	6	0	4.763782	1.475323	2.674677
41	6	0	5.431795	2.153845	1.464030
42	9	0	-6.373635	-4.338662	1.823316
43	9	0	-4.368609	-4.503532	2.659707
44	9	0	-5.671280	-2.875404	3.269279
45	9	0	-5.338119	-0.784906	-3.169335
46	9	0	-6.644257	0.099743	-1.675008
47	8	0	2.151560	-1.545190	2.783252
48	8	0	-0.947379	-2.701238	2.994637
49	9	0	-6.977027	-1.946824	-2.322199
50	6	0	-0.578009	1.114184	-4.383849
51	1	0	0.796427	2.795778	-4.465691
52	1	0	0.255345	2.200934	-6.043353
53	1	0	-0.834836	3.186181	-5.052178
54	1	0	-1.538369	0.379440	-6.177657
55	1	0	-2.155015	-0.362818	-4.691491
56	1	0	-2.645117	1.287268	-5.120813
57	1	0	-2.215540	3.000579	-3.231194
58	1	0	-2.921367	3.239954	-0.870231
59	1	0	-1.839164	1.821978	-0.402845
60	8	0	0.480161	0.165297	-4.469777
61	6	0	-0.065003	2.411741	-5.018846
62	6	0	-1.813810	0.576518	-5.137602
63	1	0	0.389028	-0.370274	-3.661132
64	8	0	-0.474716	0.405810	-2.107446
65	6	0	-0.949899	1.283536	-2.890601
66	6	0	-1.828830	2.326219	-2.474773
67	6	0	-2.144057	2.541908	-1.152601
68	6	0	-0.585984	4.184898	-0.216161
69	6	0	-0.541431	3.548153	1.063523
70	6	0	-1.792518	3.349364	3.205033
71	8	0	0.326028	2.715415	1.435548
72	8	0	-1.590998	3.874728	1.848790
73	6	0	-1.981097	1.829345	3.168384
74	1	0	-2.787969	1.564898	2.478133
75	1	0	-2.257195	1.466408	4.163512
76	1	0	-1.067073	1.326441	2.852851
77	6	0	-3.087830	4.044035	3.635074
78	1	0	-3.907231	3.777604	2.962148
79	1	0	-2.967536	5.130420	3.611371
80	1	0	-3.359146	3.742041	4.651024
81	6	0	-0.632170	3.769975	4.114027
82	1	0	-0.856006	3.493709	5.149254
83	1	0	-0.493072	4.854665	4.073212
84	1	0	0.295533	3.280594	3.815518
85	6	0	0.558878	4.043457	-1.182671
86	1	0	1.084117	3.102463	-1.001826
87	1	0	1.278961	4.871151	-1.118403
88	1	0	0.192501	4.013622	-2.215224
89	6	0	-1.432622	5.312037	-0.394879

```
     90          7           0       -2.119370    6.231449   -0.613249
     91          6           0        3.459612   -0.814694   -1.208211
     92          7           0        4.474945   -2.106080   -3.528471
     93          6           0        4.354380   -1.926568   -1.067413
     94          6           0        3.100365   -0.427326   -2.482584
     95          6           0        3.620844   -1.107854   -3.609765
     96          6           0        4.844568   -2.520236   -2.282988
     97          1           0        2.393728    0.376845   -2.663412
     98          1           0        3.305075   -0.799269   -4.604043
     99          1           0        3.195043   -0.584624    0.914686
    100          6           0        4.778043   -2.467039    0.171427
    101          1           0        4.392857   -2.108111    1.119304
    102          6           0        5.666384   -3.529848    0.217946
    103          6           0        6.167272   -4.100124   -0.981330
    104          1           0        6.862800   -4.929905   -0.948995
    105          6           0        5.754759   -3.602928   -2.195539
    106          1           0        6.111015   -4.028229   -3.127663
    107          8           0        6.006359   -3.966347    1.461596
    108          6           0        6.854420   -5.100540    1.586649
    109          1           0        6.417015   -5.987584    1.112872
    110          1           0        6.953425   -5.279420    2.657765
    111          1           0        7.848006   -4.914380    1.160176
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TS-R_2

```
                         Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          1           0        2.885818   -2.529393   -3.329381
      2          1           0       -0.834701    0.116328    1.168095
      3          1           0       -2.614922    0.289236    2.529317
      4          1           0        2.940030   -0.874970   -2.720777
      5          1           0       -2.508595    2.532867   -1.153223
      6          1           0        2.212945   -2.493440   -1.072313
      7          1           0        3.151197   -4.397152   -1.914019
      8          1           0        3.588068   -4.187485   -0.220899
      9          1           0        3.762039   -2.122266    0.712428
     10          1           0        1.526841   -0.620874    0.948327
     11          1           0       -6.004588    2.661408    1.361267
     12          1           0        6.050455   -1.960110    0.286343
     13          1           0        5.810496   -0.531202   -0.704522
     14          1           0        5.434616   -4.425872   -2.514043
     15          1           0        5.859509   -4.303495   -0.810193
     16          1           0        5.153185   -2.308379   -3.926480
     17          1           0        5.235417   -0.730688   -3.151946
     18          1           0        6.809952   -2.365439   -2.062995
     19          7           0        1.900671   -0.215760    0.089935
     20          6           0       -2.406221    1.348136    0.658756
     21          6           0       -3.090605    0.960944    1.822900
     22          6           0       -3.023295    2.221260   -0.249079
     23          6           0       -5.013940    3.540161   -0.999373
     24          6           0        1.269446    1.233621   -1.938260
     25          6           0       -0.144034    1.799778   -1.800661
     26          6           0        1.083070    0.570935   -0.644456
     27          6           0       -0.234951    1.038611   -0.509986
     28          7           0       -1.115774    0.834006    0.488123
     29          6           0       -5.003214    2.296621    1.170510
     30          6           0       -4.313441    2.678229    0.019834
     31          6           0       -5.075043    1.066883    3.350983
     32          6           0       -4.375527    1.434146    2.069377
     33          6           0        3.354105   -0.164517   -0.099920
     34          6           0        3.957603   -1.579766   -0.216284
     35          6           0        3.428991   -1.849330   -2.669984
     36          7           0        3.254644   -2.404738   -1.278117
     37          6           0        3.775497   -3.818608   -1.231052
     38          6           0        5.475806   -1.562154   -0.554852
     39          6           0        5.275481   -3.834041   -1.607481
     40          6           0        4.939521   -1.772567   -2.996574
     41          6           0        5.741125   -2.383638   -1.831006
     42          9           0       -5.913606    4.368028   -0.419250
     43          9           0       -4.153563    4.301697   -1.701095
     44          9           0       -5.699958    2.786211   -1.893345
     45          9           0       -4.606100   -0.088141    3.873261
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46	9	0	-6.406145	0.919293	3.168911
47	8	0	2.186646	1.271611	-2.754227
48	8	0	-0.857395	2.541838	-2.442251
49	9	0	-4.913607	2.020950	4.297372
50	6	0	0.977652	-3.122865	3.132458
51	1	0	1.770250	-4.235212	1.445719
52	1	0	2.425681	-4.713574	3.036557
53	1	0	0.800577	-5.221097	2.547076
54	1	0	1.287649	-3.770235	5.176087
55	1	0	0.119349	-2.445689	5.016008
56	1	0	-0.356741	-4.097086	4.580832
57	1	0	-1.282567	-4.303835	2.232661
58	1	0	-3.185390	-3.405049	0.953676
59	1	0	-2.335477	-1.782116	0.789922
60	8	0	2.057924	-2.187171	3.183058
61	6	0	1.524785	-4.404552	2.497096
62	6	0	0.468569	-3.379438	4.564791
63	1	0	1.610468	-1.323381	3.106642
64	8	0	-0.029303	-1.233392	2.084939
65	6	0	-0.157760	-2.475629	2.293378
66	6	0	-1.271621	-3.269851	1.902617
67	6	0	-2.278087	-2.825517	1.073593
68	1	0	-1.822312	-5.459461	-0.578624
69	1	0	-2.255921	-5.268722	-2.285495
70	1	0	-3.430544	-4.867046	-1.035475
71	6	0	-1.870100	-3.395784	-1.220198
72	6	0	-2.610373	-2.288106	-1.823042
73	6	0	-4.806513	-1.759408	-2.832961
74	8	0	-2.182790	-1.142522	-1.934580
75	8	0	-3.855802	-2.685357	-2.197829
76	6	0	-2.368200	-4.827515	-1.286645
77	6	0	-0.491720	-3.202022	-1.120128
78	7	0	0.662198	-3.095154	-0.938497
79	6	0	-5.164036	-0.622385	-1.872124
80	1	0	-4.295887	0.002997	-1.670993
81	1	0	-5.539132	-1.026936	-0.926384
82	1	0	-5.947825	0.003536	-2.309359
83	6	0	-4.228470	-1.237909	-4.153358
84	1	0	-3.939211	-2.074545	-4.797606
85	1	0	-3.356377	-0.608224	-3.977355
86	1	0	-4.988035	-0.650307	-4.679129
87	6	0	-6.022070	-2.654051	-3.090623
88	1	0	-5.756272	-3.489089	-3.745495
89	1	0	-6.819044	-2.077035	-3.569238
90	1	0	-6.407210	-3.062169	-2.151474
91	1	0	3.513254	0.346457	-1.048448
92	6	0	4.056750	0.627869	1.007843
93	7	0	5.333259	2.041130	3.122881
94	6	0	4.561834	1.952518	0.776586
95	6	0	4.203018	0.088714	2.270388
96	6	0	4.841360	0.833068	3.291851
97	6	0	5.201439	2.605896	1.888406
98	1	0	3.828068	-0.900738	2.513560
99	1	0	4.947034	0.394688	4.283070
100	6	0	5.728035	3.908387	1.707775
101	1	0	6.204791	4.374216	2.563588
102	6	0	4.475074	2.643207	-0.456508
103	1	0	3.973985	2.225486	-1.322707
104	6	0	5.000620	3.918798	-0.595150
105	6	0	5.637416	4.558832	0.499404
106	1	0	6.048340	5.555520	0.393329
107	8	0	4.862722	4.487500	-1.823946
108	6	0	5.308361	5.822137	-2.020072
109	1	0	4.794626	6.523514	-1.351290
110	1	0	5.061327	6.067805	-3.053397
111	1	0	6.392556	5.914904	-1.878138

TS-S_2

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

```
---------------------------------------------------------------------
   1       7       0      1.866753   -0.204416    0.065180
   2       6       0     -1.726528    2.677886    0.131748
   3       6       0     -2.616895    2.580037    1.214369
   4       6       0     -1.913803    3.679844   -0.831361
   5       6       0     -3.232149    5.590133   -1.769839
   6       6       0      1.988922    1.305740   -2.017778
   7       6       0      0.825275    2.296181   -2.043203
   8       6       0      1.452115    0.775201   -0.756421
   9       6       0      0.349050    1.647404   -0.779026
  10       7       0     -0.680195    1.745350    0.089939
  11       6       0     -3.882446    4.465457    0.370435
  12       6       0     -2.989332    4.558390   -0.696336
  13       6       0     -4.597346    3.393695    2.518830
  14       6       0     -3.682713    3.467053    1.324409
  15       6       0      3.200924   -0.802238   -0.053990
  16       6       0      3.105980   -2.333712   -0.217985
  17       6       0      2.858587   -2.369530   -2.731303
  18       7       0      2.233553   -2.713500   -1.401041
  19       6       0      1.949105   -4.194089   -1.349577
  20       6       0      4.487720   -3.016909   -0.410288
  21       6       0      3.280370   -4.978880   -1.411716
  22       6       0      4.178824   -3.161605   -2.891955
  23       6       0      4.434976   -3.980065   -1.611692
  24       6       0     -0.315503   -2.616661    2.904684
  25       6       0     -0.357484   -4.014936    2.280259
  26       6       0     -0.861843   -2.624405    4.345454
  27       6       0     -1.095307   -1.575854    2.059966
  28       6       0     -2.428663   -1.880762    1.666938
  29       6       0     -3.142901   -1.156993    0.742519
  30       6       0     -2.927031   -2.095051   -1.472787
  31       6       0     -1.530875   -2.054362   -1.540539
  32       7       0     -0.360386   -1.997562   -1.561751
  33       6       0     -3.731885   -1.105835   -2.291724
  34       6       0     -3.458011   -3.384103   -1.057616
  35       6       0     -5.590247   -4.627834   -0.903448
  36       6       0     -5.508342   -4.924543    0.598984
  37       6       0     -5.114624   -5.815253   -1.749154
  38       6       0     -7.014502   -4.223590   -1.294969
  39       6       0      4.104151   -0.422223    1.123645
  40       7       0      5.725917    0.266034    3.359608
  41       6       0      5.083786    0.621841    0.999778
  42       6       0      3.981468   -1.054467    2.344418
  43       6       0      4.809304   -0.674212    3.428858
  44       6       0      5.871597    0.914286    2.168360
  45       6       0      6.857494    1.928700    2.095125
  46       6       0      5.321291    1.367015   -0.180138
  47       6       0      6.294004    2.354750   -0.213891
  48       6       0      7.073670    2.638339    0.937048
  49       6       0      7.371688    4.072000   -1.493666
  50       1       0      3.429646   -5.547930   -0.488960
  51       1       0      2.111713   -2.630173   -3.483796
  52       1       0     -0.715003    1.007617    0.806499
  53       1       0     -2.471697    1.810305    1.964490
  54       1       0      2.999249   -1.287961   -2.773544
  55       1       0     -1.231419    3.776228   -1.671065
  56       1       0      1.275005   -2.247631   -1.359647
  57       1       0      1.282022   -4.405670   -2.186579
  58       1       0      1.389258   -4.377969   -0.431540
  59       1       0      2.575032   -2.742696    0.646216
  60       1       0      1.270149   -0.460089    0.853336
  61       1       0     -4.712475    5.155150    0.457504
  62       1       0      4.765406   -3.548696    0.503571
  63       1       0      5.259465   -2.258645   -0.579568
  64       1       0      3.254627   -5.700828   -2.233361
  65       1       0     -0.274304   -3.319627    4.952672
  66       1       0      4.122439   -3.825997   -3.759905
  67       1       0      5.008437   -2.470907   -3.069786
  68       1       0      5.384571   -4.516410   -1.695719
  69       9       0     -4.010126    5.095412   -2.760333
  70       9       0     -3.867974    6.678751   -1.278856
  71       9       0     -2.085052    6.009843   -2.337524
  72       9       0     -4.234818    4.276712    3.477670
  73       9       0     -4.590641    2.168276    3.088072
  74       8       0      2.947304    1.018553   -2.727111
  75       8       0      0.453323    3.192295   -2.773352
```

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    76        9         0      -5.874799    3.680967    2.185358
    77        1         0      -0.129025   -3.972856    1.212572
    78        1         0       0.373534   -4.652648    2.787169
    79        1         0      -1.343319   -4.473142    2.376877
    80        1         0      -0.780103   -1.627178    4.789341
    81        1         0      -1.911692   -2.928555    4.378994
    82        1         0      -2.854682   -2.805626    2.038838
    83        1         0      -4.197899   -1.347978    0.588530
    84        1         0      -2.771032   -0.212236    0.365964
    85        8         0       1.057614   -2.211086    2.928779
    86        1         0       1.013067   -1.238408    2.903800
    87        8         0      -0.484788   -0.493007    1.822305
    88        1         0      -3.949452   -1.475961   -3.301609
    89        1         0      -3.196329   -0.157517   -2.394153
    90        1         0      -4.693270   -0.902403   -1.811845
    91        8         0      -2.795280   -4.289939   -0.555415
    92        8         0      -4.812212   -3.430479   -1.233204
    93        1         0      -4.493569   -5.202632    0.883231
    94        1         0      -6.187518   -5.745796    0.851464
    95        1         0      -5.813701   -4.045878    1.176648
    96        1         0      -4.093438   -6.093079   -1.488185
    97        1         0      -5.152215   -5.560203   -2.812974
    98        1         0      -5.771841   -6.675157   -1.582368
    99        1         0      -7.064956   -3.974001   -2.358637
   100        1         0      -7.338424   -3.349672   -0.722220
   101        1         0      -7.709885   -5.044940   -1.096831
   102        1         0       3.249385   -1.838100    2.509046
   103        1         0       4.698487   -1.181573    4.386036
   104        1         0       3.634023   -0.393370   -0.966006
   105        1         0       7.435430    2.124800    2.991909
   106        1         0       4.747282    1.217234   -1.087740
   107        1         0       7.834511    3.409130    0.912602
   108        8         0       6.436470    3.006759   -1.399875
   109        1         0       7.139901    4.878613   -0.787334
   110        1         0       7.285387    4.452815   -2.511818
   111        1         0       8.399731    3.727444   -1.324717
 ---------------------------------------------------------------------
```

TS-S$_B$'

```
                         Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          9           0       -8.408690   -1.804267    0.634717
      2          9           0       -7.452620   -2.881644   -0.992277
      3          9           0       -5.843494    3.316405    0.411370
      4          6           0        3.096709   -4.462648   -2.689798
      5          6           0        4.264616   -3.618100   -2.130125
      6          6           0        3.913896   -3.134901   -0.702275
      7          6           0        4.428091   -2.381105   -3.031166
      8          8           0        0.092948   -4.577735   -0.031663
      9          9           0       -6.834505   -3.249697    1.058312
     10          9           0       -7.338305    2.633237   -1.014000
     11          8           0       -3.118484   -4.056962    0.162759
     12          1           0        2.784837   -1.055794   -3.708036
     13          1           0       -1.916886    0.113309    0.177875
     14          1           0       -4.543719   -2.537046    0.415857
     15          1           0        0.944753   -3.987335   -2.558457
     16          1           0       -7.663633    0.344421   -0.294255
     17          1           0       -3.549920    1.571357   -0.434161
     18          1           0        3.442669   -0.635236   -2.126625
     19          1           0        4.494144   -2.685883   -4.081501
     20          1           0        5.183051   -4.210947   -2.113975
     21          1           0        1.805689   -3.550472   -0.518454
     22          1           0        0.378932   -0.280720    0.289298
     23          9           0       -5.302730    3.050016   -1.673303
     24          1           0        1.274216   -1.649962   -2.157461
     25          1           0        1.749380   -3.248972   -3.962999
     26          1           0        4.033967   -3.935711    0.030961
     27          1           0        4.582396   -2.319305   -0.404788
     28          1           0        3.383087   -4.927846   -3.637373
     29          1           0        2.835666   -5.268824   -1.997621
     30          1           0        5.334066   -1.814493   -2.802408
     31          7           0        0.613235   -1.271578    0.221979
```

32	6	0	-3.877961	-0.509693	0.031995
33	6	0	-4.289023	0.794388	-0.274650
34	6	0	-4.841761	-1.515193	0.203174
35	6	0	-7.222121	-2.286641	0.199770
36	6	0	-0.627641	-3.595806	0.112484
37	6	0	-2.126695	-3.354311	0.164719
38	6	0	-0.425170	-2.129176	0.221877
39	6	0	-1.819813	-1.897573	0.194547
40	7	0	-2.496296	-0.730522	0.159803
41	6	0	-6.610939	0.109099	-0.210092
42	6	0	-6.191298	-1.191390	0.076639
43	6	0	-6.040642	2.520121	-0.671417
44	6	0	-5.644444	1.096011	-0.386904
45	6	0	2.053521	-1.591573	0.320315
46	6	0	2.440858	-2.681326	-0.697757
47	6	0	3.213213	-1.466625	-2.792791
48	7	0	2.105701	-2.269318	-2.135870
49	6	0	1.872446	-3.539577	-2.917548
50	8	0	5.830939	0.688767	-2.358547
51	6	0	4.825739	1.943710	-4.132143
52	6	0	2.980706	3.032876	-1.860857
53	8	0	3.794475	1.022366	-0.901213
54	6	0	1.919626	3.174312	-0.949973
55	6	0	3.892928	1.966615	-1.744613
56	6	0	6.107620	3.084380	-2.266687
57	6	0	5.168555	1.920998	-2.637324
58	1	0	4.375464	2.894202	-4.431003
59	1	0	3.134584	3.780124	-2.632098
60	1	0	1.510016	4.167539	-0.785400
61	1	0	6.353883	3.042376	-1.201463
62	1	0	7.038047	2.997356	-2.836837
63	1	0	5.654384	4.057723	-2.477038
64	1	0	5.740054	1.797621	-4.716105
65	1	0	4.127826	1.140003	-4.384288
66	1	0	1.988867	2.562835	-0.054145
67	1	0	5.417784	0.424989	-1.509371
68	6	0	-0.564683	2.473203	-0.284189
69	6	0	-1.316984	4.007655	1.525384
70	1	0	-0.404705	4.531733	-2.143252
71	6	0	-0.298378	3.558291	-2.624640
72	6	0	0.299211	1.198948	-2.125558
73	8	0	-0.633152	1.456040	0.437385
74	6	0	0.088370	2.507202	-1.590745
75	7	0	0.499353	0.138698	-2.569517
76	1	0	-1.244582	3.320881	-3.123047
77	8	0	-0.976305	3.683627	0.116212
78	1	0	0.480984	3.630175	-3.389369
79	6	0	-0.114835	3.708846	2.425247
80	1	0	0.776310	4.230768	2.064413
81	1	0	0.095278	2.639634	2.468619
82	1	0	-0.327456	4.061356	3.439369
83	6	0	-2.571727	3.253412	1.968805
84	1	0	-2.391263	2.179788	2.018863
85	1	0	-3.409607	3.449687	1.295006
86	1	0	-2.862143	3.599484	2.966055
87	6	0	-1.587572	5.511750	1.451235
88	1	0	-0.702548	6.048266	1.098052
89	1	0	-1.851106	5.892727	2.442057
90	1	0	-2.415601	5.721627	0.768640
91	1	0	2.560331	-0.665174	0.043085
92	6	0	2.453836	-1.988910	1.747227
93	7	0	3.053657	-2.768457	4.419220
94	6	0	2.111183	-3.228922	2.247808
95	6	0	3.138422	-1.075007	2.619331
96	6	0	3.404209	-1.533483	3.958202
97	6	0	2.433977	-3.572054	3.582761
98	1	0	1.581866	-3.956149	1.640260
99	1	0	2.158409	-4.555398	3.961082
100	6	0	4.066539	-0.667196	4.861902
101	1	0	4.251772	-1.041884	5.862928
102	6	0	3.558020	0.227229	2.253501
103	1	0	3.423525	0.621800	1.252042
104	6	0	4.199911	1.046991	3.168267
105	6	0	4.457429	0.597477	4.488499
106	1	0	4.959972	1.237514	5.203595
107	8	0	4.553266	2.284347	2.713290

108	6	0	5.266569	3.154312	3.578235
109	1	0	6.221268	2.718247	3.898392
110	1	0	4.678660	3.422120	4.465671
111	1	0	5.464015	4.055993	2.996909

TS-R$_C$

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-6.015958	-3.083934	-1.035057
2	1	0	-4.850953	-1.210937	-2.118057
3	1	0	-5.068960	-4.002936	1.171943
4	1	0	-3.897959	-3.673940	-2.351057
5	1	0	-4.286963	-4.856939	-1.108057
6	1	0	-1.736955	-2.067945	0.583943
7	1	0	-2.570954	-1.432943	-1.733057
8	1	0	-1.796959	-3.481945	-1.315057
9	1	0	-2.332961	-4.349944	0.125943
10	6	0	5.062058	2.780037	-0.008057
11	6	0	0.770055	1.692048	0.124943
12	6	0	-0.581946	1.328052	0.147943
13	6	0	5.411052	0.667036	-1.087057
14	6	0	-3.122953	-1.191942	-0.820057
15	6	0	-3.610956	-2.386940	1.345943
16	9	0	6.896061	3.996032	0.867943
17	9	0	5.562063	5.040036	-0.493057
18	8	0	-2.031942	2.926056	1.386943
19	9	0	5.732047	-1.154965	-2.570057
20	9	0	4.902062	4.580037	1.525943
21	8	0	1.146060	3.902047	1.281943
22	1	0	-3.705953	-1.388940	1.776943
23	1	0	-3.098958	-3.012942	2.074943
24	1	0	-5.780956	-2.398935	1.322943
25	1	0	-5.226952	-0.689936	-0.483057
26	1	0	6.996056	2.064032	-0.646057
27	1	0	1.562051	0.108046	-0.838057
28	1	0	3.036059	3.265042	0.548943
29	1	0	3.657049	-0.533959	-1.404057
30	1	0	-0.696951	-0.451948	-0.813057
31	9	0	7.425051	0.176031	-2.231057
32	6	0	0.496058	2.961049	0.873943
33	6	0	-0.981943	2.524053	0.913943
34	6	0	5.604061	4.101035	0.478943
35	6	0	3.690057	2.539041	0.076943
36	6	0	4.047051	0.402040	-1.017057
37	6	0	3.175054	1.339042	-0.436057
38	6	0	6.340049	-0.377966	-1.646057
39	6	0	-2.704949	0.234057	-0.412057
40	7	0	-2.671956	-2.265943	0.167943
41	7	0	1.815053	1.007045	-0.404057
42	7	0	-1.248949	0.252054	-0.309057
43	6	0	5.935055	1.859035	-0.587057
44	6	0	-5.011957	-2.847937	-0.672057
45	6	0	-4.959958	-2.958937	0.863943
46	9	0	6.797047	-1.205968	-0.677057
47	6	0	-3.977960	-3.820939	-1.270057
48	6	0	-4.635953	-1.404938	-1.065057
49	6	0	-2.609959	-3.579943	-0.593057
50	1	0	-1.793953	-1.382945	4.289943
51	1	0	1.147052	0.741047	3.266943
52	1	0	1.739038	-4.647954	3.934943
53	1	0	2.737037	-4.926957	2.499943
54	1	0	-1.461951	-0.473946	5.776943
55	1	0	1.403046	-1.521953	6.251943
56	1	0	-0.964955	-2.169947	5.652943
57	1	0	0.961051	0.196048	6.349943
58	1	0	2.274049	-0.321956	5.275943
59	6	0	-1.072953	-1.234947	5.093943
60	7	0	-0.253963	-5.212949	0.723943
61	6	0	2.175039	-4.168955	3.050943
62	6	0	0.324044	-2.416951	2.660943

```
    63          1           0        2.872041   -3.404957    3.400943
    64          6           0        1.294049   -0.598953    5.675943
    65          6           0        0.174051    0.484050    3.695943
    66          6           0        0.343038   -4.461951    1.389943
    67          8           0       -0.713955   -1.983948    2.136943
    68          6           0        0.283048   -0.782951    4.542943
    69          6           0        1.115041   -3.543953    2.152943
    70          1           0       -0.547949    0.356052    2.891943
    71          1           0       -0.146946    1.320051    4.324943
    72          8           0        0.885045   -1.880952    3.757943
    73          1           0        2.474039   -4.104956   -0.928057
    74          1           0        2.875042   -3.130957   -3.755057
    75          1           0        1.977046   -1.580955    0.786943
    76          1           0        1.588042   -3.223954   -4.983057
    77          1           0        1.861046   -1.714955   -4.088057
    78          1           0        0.162037   -5.114950   -2.017057
    79          1           0        1.765036   -5.225954   -2.758057
    80          1           0        3.207043   -2.890958    1.113943
    81          6           0        0.770038   -4.785952   -2.864057
    82          8           0       -0.465957   -2.803949   -3.332057
    83          1           0       -0.451955   -1.876949   -3.032057
    84          1           0        0.331037   -5.167951   -3.790057
    85          6           0        0.841042   -3.260952   -2.946057
    86          6           0        2.303043   -2.596956    0.590943
    87          6           0        2.049042   -3.137955   -0.682057
    88          6           0        1.178043   -2.555953   -1.608057
    89          8           0        0.638047   -1.391951   -1.482057
    90          6           0        1.861043   -2.806955   -4.009057
    91          6           0       -3.246947    1.214059   -1.461057
    92          7           0       -4.238942    2.870061   -3.546057
    93          6           0       -4.393944    2.039062   -1.226057
    94          6           0       -2.637946    1.284057   -2.697057
    95          6           0       -3.168944    2.122059   -3.706057
    96          6           0       -4.845942    2.848063   -2.326057
    97          1           0       -1.741948    0.707055   -2.903057
    98          1           0       -2.684944    2.159057   -4.681057
    99          1           0       -3.117948    0.492058    0.564943
   100          6           0       -5.981940    3.677066   -2.142057
   101          1           0       -6.302939    4.274067   -2.989057
   102          6           0       -6.650940    3.725068   -0.942057
   103          1           0       -7.515938    4.369070   -0.835057
   104          6           0       -6.194942    2.939067    0.147943
   105          6           0       -5.090944    2.117064    0.002943
   106          1           0       -4.756946    1.582063    0.882943
   107          8           0       -6.785942    2.934068    1.374943
   108          6           0       -7.863940    3.828071    1.620943
   109          1           0       -7.563937    4.873070    1.476943
   110          1           0       -8.141940    3.676072    2.664943
   111          1           0       -8.729940    3.607073    0.983943
 ---------------------------------------------------------------------
```

69h

```
                          Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -0.860457   -0.756678    0.000151
      2          1           0       -0.757704   -1.835118    0.000161
      3          6           0       -2.140962   -0.204768    0.000063
      4          7           0       -3.231969    0.239601   -0.000076
      5          6           0        0.290563    0.061641   -0.000012
      6          8           0        0.371392    1.299144   -0.000009
      7          8           0        1.458092   -0.710626   -0.000228
      8          6           0        2.670060    0.034034    0.000084
      9          1           0        2.756430    0.672400    0.886121
     10          1           0        2.756155    0.673632   -0.885067
     11          1           0        3.477813   -0.701636   -0.000513
 ---------------------------------------------------------------------
```

125

```
                          Standard orientation:
 ---------------------------------------------------------------------
```

```
Center     Atomic      Atomic             Coordinates (Angstroms)
Number      Number       Type             X           Y           Z
---------------------------------------------------------------------
     1          6           0        -1.355684   -0.630496   -0.000071
     2          1           0        -1.326651   -1.717317   -0.000191
     3          6           0        -0.056651    0.078034   -0.000037
     4          6           0         1.207512   -0.767689    0.000070
     5          1           0         1.178099   -1.428796    0.881987
     6          1           0         1.178151   -1.428998   -0.881717
     7          6           0        -2.516981    0.032952    0.000051
     8          1           0        -3.470789   -0.483828    0.000021
     9          1           0        -2.530442    1.118788    0.000156
    10          8           0         0.054891    1.301216   -0.000022
    11          8           0         2.356419    0.037844   -0.000022
    12          1           0         2.011979    0.950868    0.000018
---------------------------------------------------------------------
```

18

```
                         Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic             Coordinates (Angstroms)
Number      Number       Type             X           Y           Z
---------------------------------------------------------------------
     1          6           0         1.588316   -0.658893    0.000067
     2          1           0         1.292091   -1.702848    0.000145
     3          6           0         0.520147    0.370135    0.000026
     4          6           0        -0.956295   -0.072504   -0.000015
     5          6           0         2.881531   -0.316282   -0.000022
     6          1           0         3.669004   -1.062535   -0.000023
     7          1           0         3.174951    0.729200   -0.000135
     8          8           0         0.769341    1.573770    0.000003
     9          8           0        -1.762381    1.095851   -0.000201
    10          1           0        -1.124583    1.834855   -0.000103
    11          6           0        -1.262067   -0.884303   -1.272844
    12          1           0        -1.037969   -0.292558   -2.164997
    13          1           0        -2.328029   -1.129653   -1.283562
    14          1           0        -0.695755   -1.818554   -1.318014
    15          6           0        -1.262172   -0.884017    1.272983
    16          1           0        -0.695811   -1.818231    1.318454
    17          1           0        -2.328121   -1.129422    1.283635
    18          1           0        -1.038216   -0.292046    2.165015
---------------------------------------------------------------------
```

MVK

```
                         Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic             Coordinates (Angstroms)
Number      Number       Type             X           Y           Z
---------------------------------------------------------------------
     1          6           0         2.014340   -0.104129    0.000052
     2          1           0         2.923060   -0.697049   -0.000079
     3          1           0         2.114600    0.977454   -0.000145
     4          6           0         0.801409   -0.665308    0.000012
     5          1           0         0.682582   -1.746039   -0.000059
     6          6           0        -0.442398    0.161928   -0.000075
     7          8           0        -0.404771    1.386460    0.000020
     8          6           0        -1.751810   -0.596953    0.000002
     9          1           0        -1.809439   -1.248949   -0.879386
    10          1           0        -2.592232    0.097942   -0.000346
    11          1           0        -1.809655   -1.248264    0.879905
---------------------------------------------------------------------
```

TS-69h+125

```
                         Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic             Coordinates (Angstroms)
Number      Number       Type             X           Y           Z
---------------------------------------------------------------------
     1          6           0        -0.004886   -1.037000    1.041866
```

```
    2      1      0      0.743115   -0.966015    1.824866
    3      1      0     -0.183906   -2.038996    0.665866
    4      6      0     -1.069869   -0.139979    1.023866
    5      1      0     -1.009851    0.790020    1.583866
    6      6      0     -2.219873   -0.355957    0.223866
    7      8      0     -2.413892   -1.331953   -0.544134
    8      6      0     -3.367853    0.671066    0.286866
    9      1      0     -2.987834    1.656058   -0.029134
   10      1      0     -3.703851    0.783072    1.329866
   11      6      0      1.476120   -0.707029   -0.508134
   12      1      0      0.782120   -0.720015   -1.340134
   13      6      0      2.325098   -1.833045   -0.395134
   14      7      0      2.972079   -2.799058   -0.259134
   15      6      0      2.024145    0.578960   -0.126134
   16      8      0      2.985149    0.781942    0.612866
   17      8      0      1.272165    1.601975   -0.634134
   18      6      0      1.668191    2.915967   -0.224134
   19      1      0      2.675196    3.151948   -0.580134
   20      1      0      1.652193    3.010968    0.864866
   21      1      0      0.945204    3.597982   -0.672134
   22      8      0     -4.424861    0.243086   -0.542134
   23      1      0     -4.051878   -0.589921   -0.911134
---------------------------------------------------------------------
```

TS-69h+18

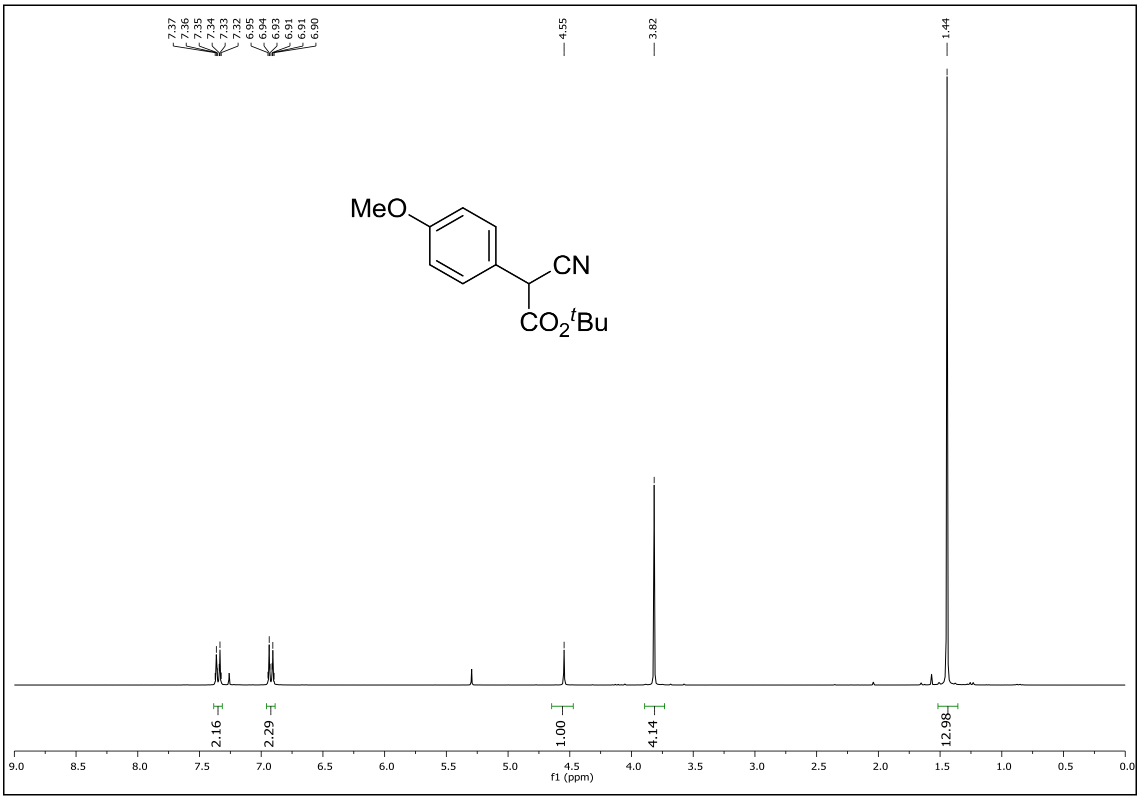
```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number       Type              X           Y           Z
---------------------------------------------------------------------
    1      1      0      2.641887   -1.789084   -1.762088
    2      1      0      4.251907   -1.094130   -1.482088
    3      1      0      3.526876   -2.169110   -0.272088
    4      1      0      1.642957    0.645944   -2.037088
    5      1      0      3.295974    1.260897   -1.820088
    6      1      0      1.991990    1.831934   -0.765088
    7      1      0      3.068944    0.218903    1.495912
    8      1      0      0.363902   -1.258019   -1.220088
    9      1      0     -0.670110   -1.672990    1.646912
   10      1      0     -1.303134   -2.509972    0.191912
   11      8      0      3.620947    0.324888    0.673912
   12      6      0      3.309899   -1.379103   -0.998088
   13      6      0      2.381965    0.956923   -1.294088
   14      6      0      2.690933   -0.164086   -0.289088
   15      8      0      1.501928   -0.356052    1.778912
   16      6      0      1.405922   -0.568049    0.518912
   17      6      0      0.323906   -1.130018   -0.142088
   18      6      0     -0.858107   -1.589984    0.575912
   19      1      0     -0.621962    3.495009    1.020912
   20      1      0     -0.251984    2.743998   -0.563088
   21      1      0     -1.857963    3.459044   -0.275088
   22      1      0     -2.551071   -0.325936    1.613912
   23      6      0     -1.024978    2.923020    0.185912
   24      8      0     -1.477014    1.679033    0.750912
   25      8      0     -2.045034    0.983050   -1.324088
   26      6      0     -1.960040    0.781047   -0.128088
   27      7      0     -4.238114   -1.815888   -0.604088
   28      6      0     -3.399096   -1.192912   -0.090088
   29      6      0     -2.315076   -0.498943    0.563912
---------------------------------------------------------------------
```

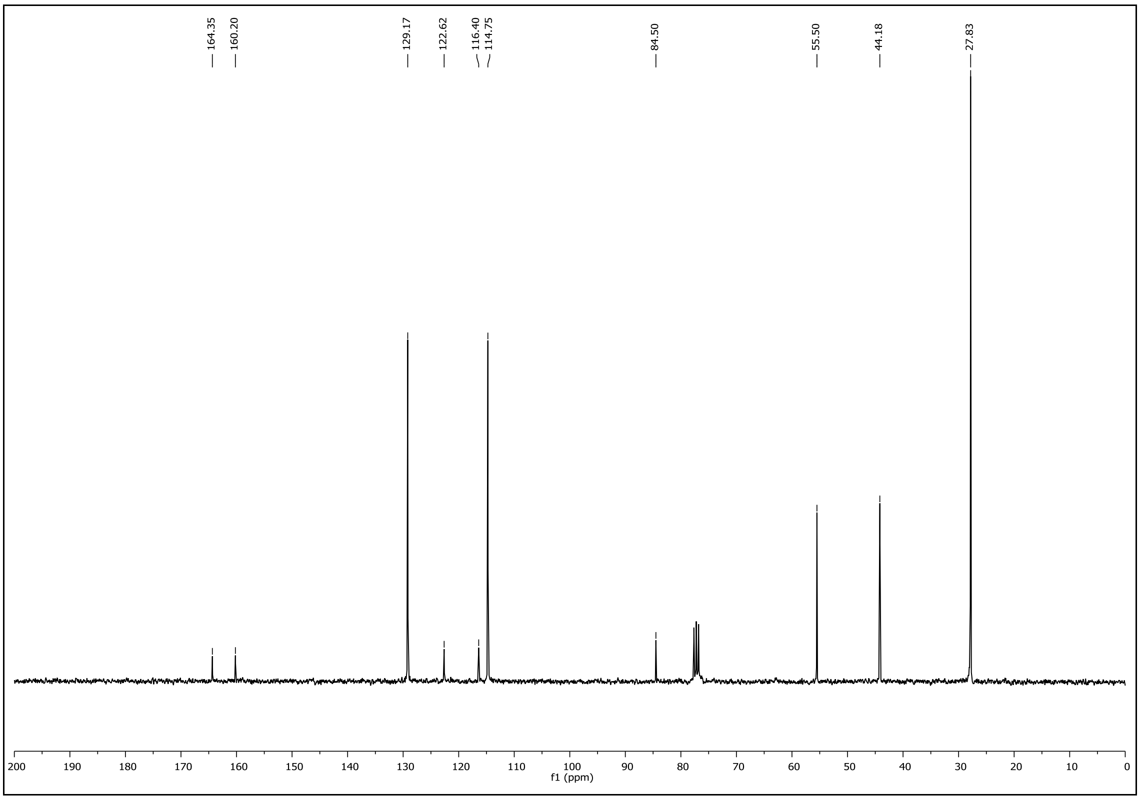
TS-69h+MVK

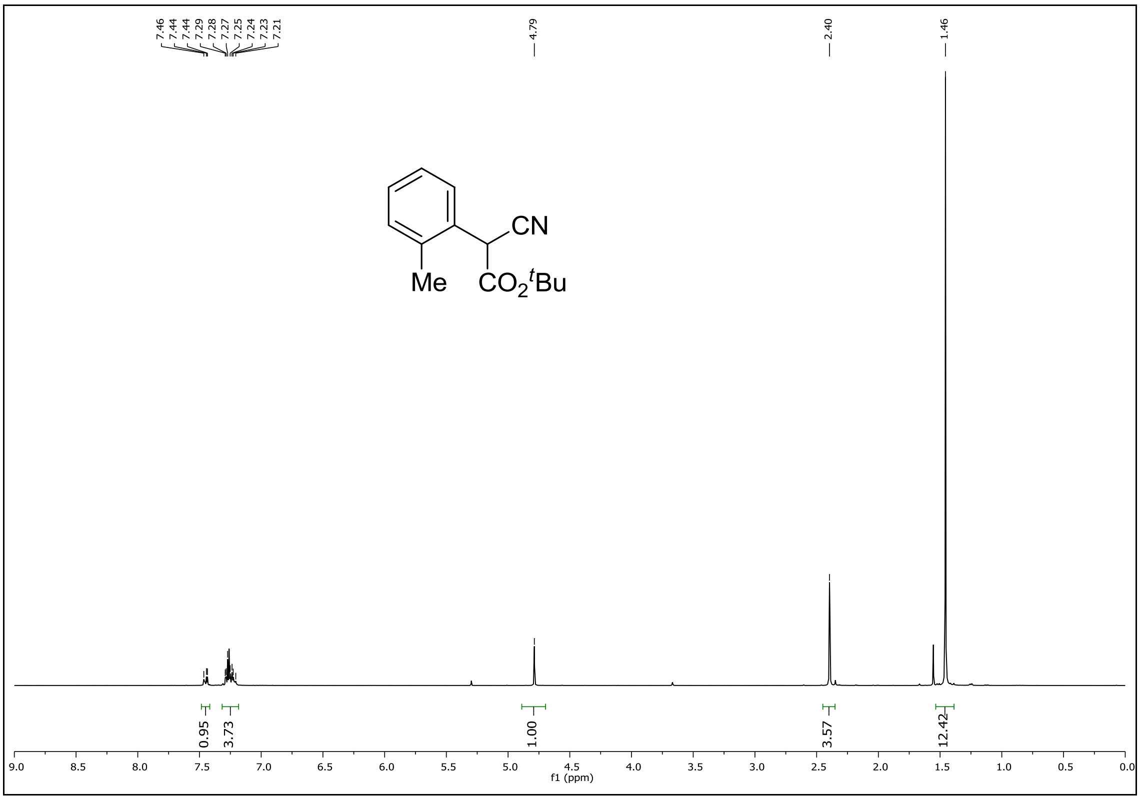
```
                      Standard orientation:
---------------------------------------------------------------------
Center     Atomic      Atomic              Coordinates (Angstroms)
Number     Number       Type              X           Y           Z
---------------------------------------------------------------------
    1      6      0     -0.461041   -1.016998    0.968022
    2      1      0      0.219956   -0.986935    1.815022
    3      1      0     -0.666949   -2.015017    0.592022
```

```
    4          6           0       -1.513126   -0.095095    0.904022
    5          1           0       -1.467211    0.820910    1.487022
    6          6           0       -2.601109   -0.279195    0.002022
    7          8           0       -2.704020   -1.240204   -0.797978
    8          6           0       -3.725205    0.759701    0.020022
    9          1           0       -4.684159    0.257613    0.198022
   10          1           0       -3.797249    1.236695   -0.963978
   11          1           0       -3.588277    1.537714    0.776022
   12          6           0        1.037932   -0.725859   -0.450978
   13          1           0        0.391932   -0.725919   -1.321978
   14          6           0        1.876037   -1.863782   -0.321978
   15          7           0        2.507127   -2.836724   -0.170978
   16          6           0        1.619814    0.552194   -0.076978
   17          8           0        2.559797    0.736281    0.692022
   18          8           0        0.923719    1.588130   -0.630978
   19          6           0        1.346598    2.896169   -0.225978
   20          1           0        2.382581    3.082265   -0.520978
   21          1           0        1.263587    3.018162    0.857022
   22          1           0        0.680534    3.595108   -0.734978
 ---------------------------------------------------------------------
```

6.4.7. Representative NMR spectra



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7.24
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7.21
4.79
2.40
1.46
CN
Me
CO2tBu
0.95
3.73
1.00
3.57
12.42
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
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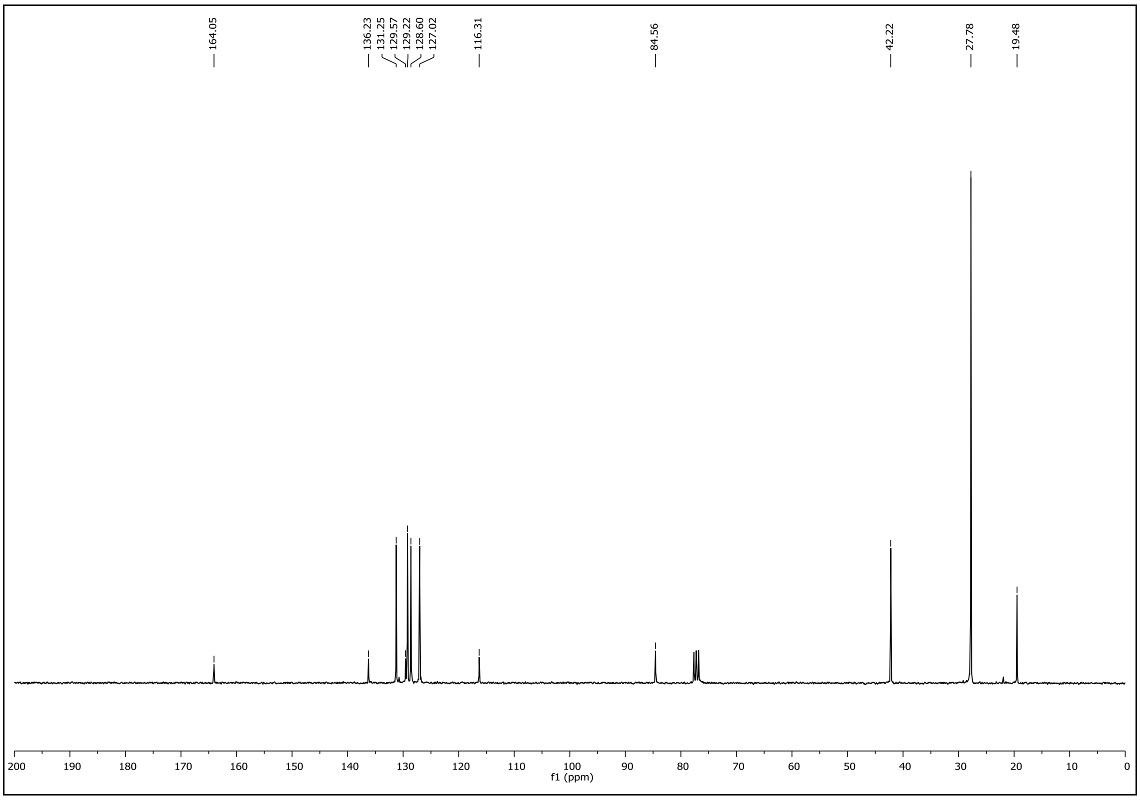
f1 (ppm)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129.22
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127.02
116.31
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42.22
27.78
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200
190
180
170
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130
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110
100
90
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30
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10
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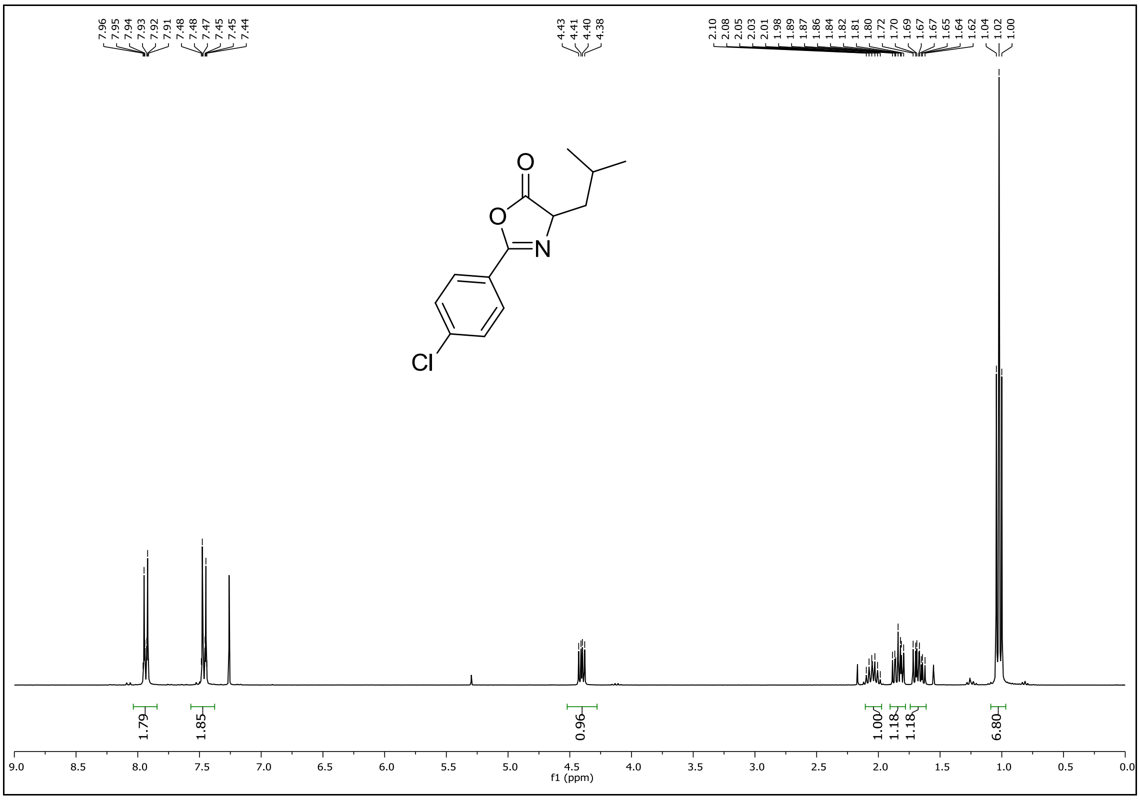
f1 (ppm)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7.45
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4.41
4.40
4.38
2.10
2.08
2.05
2.03
2.01
1.98
1.89
1.87
1.86
1.84
1.82
1.81
1.80
1.72
1.70
1.69
1.67
1.67
1.65
1.64
1.62
1.04
1.02
1.00
O
O
N
Cl
1.79
1.85
0.96
1.00
1.18
1.18
6.80
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7.5
7.0
6.5
6.0
5.5
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3.0
2.5
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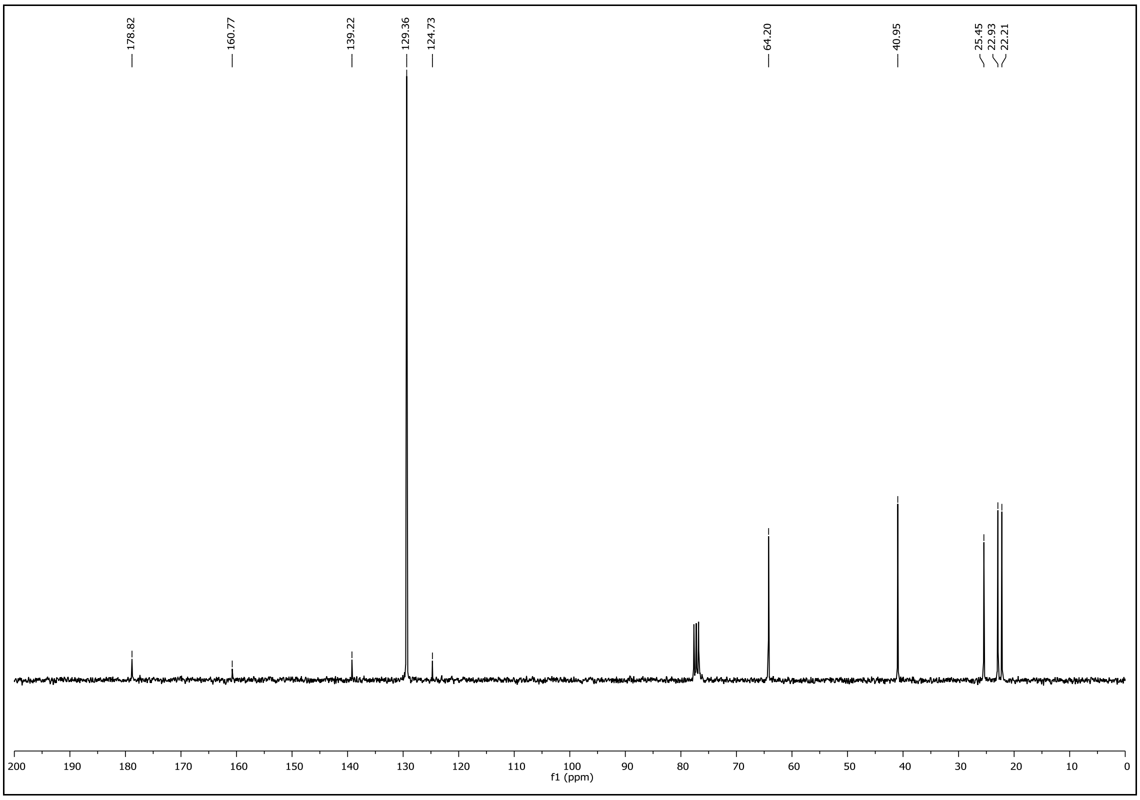
f1 (ppm)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22.21
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180
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150
140
130
120
110
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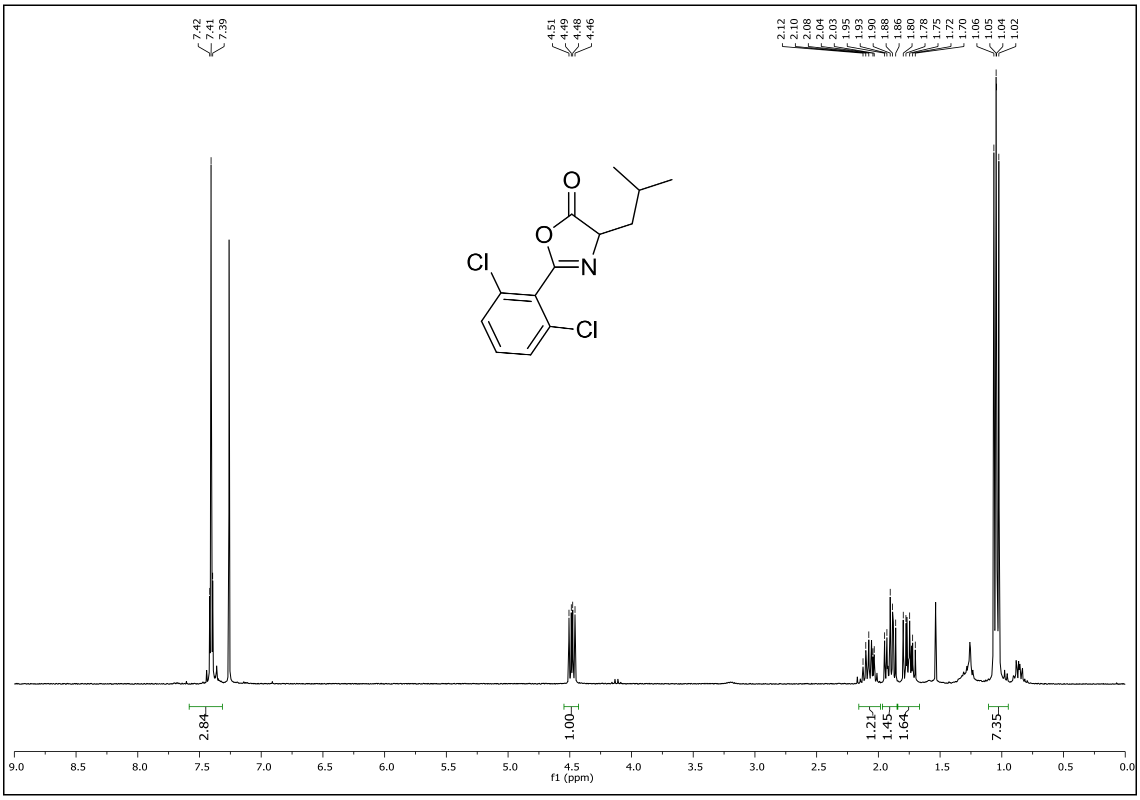
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1.80
1.78
1.75
1.72
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1.04
1.02
O
O
N
Cl
Cl
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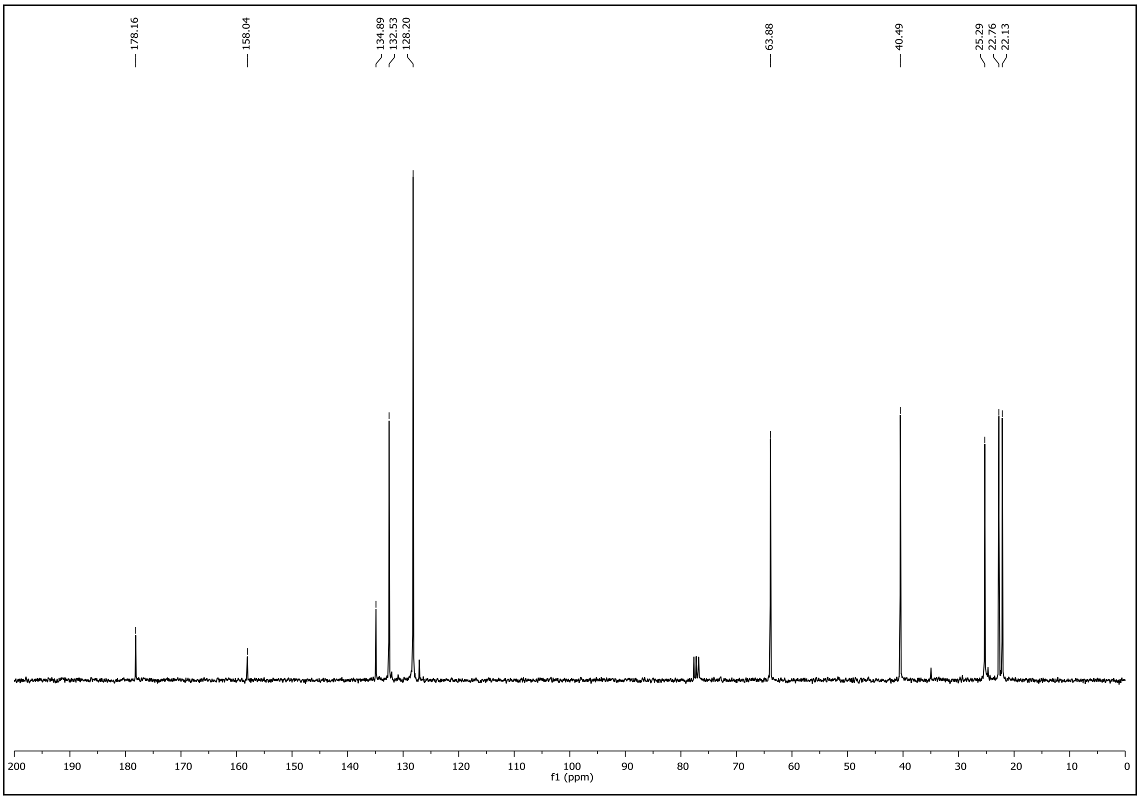
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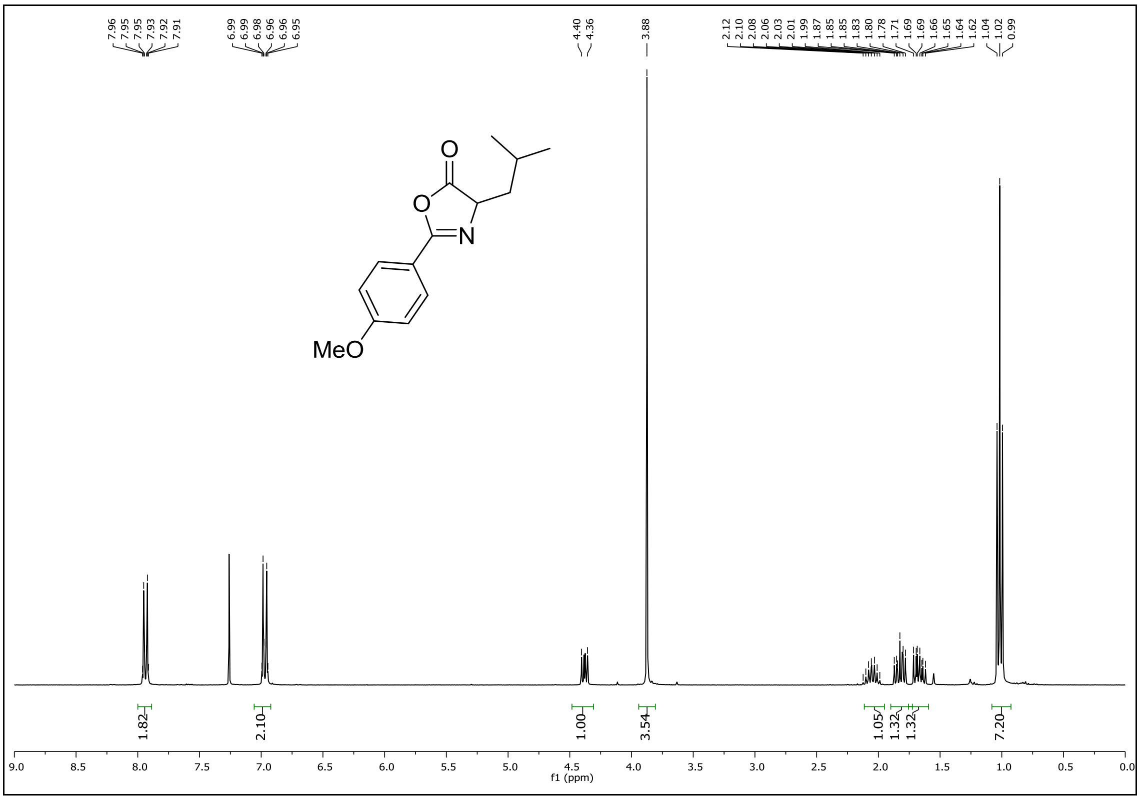
f1 (ppm)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4.36
3.88
2.12
2.10
2.08
2.06
2.03
2.01
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1.87
1.85
1.85
1.83
1.80
1.78
1.71
1.69
1.69
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1.65
1.64
1.62
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1.02
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O
N
MeO
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6.0
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2.5
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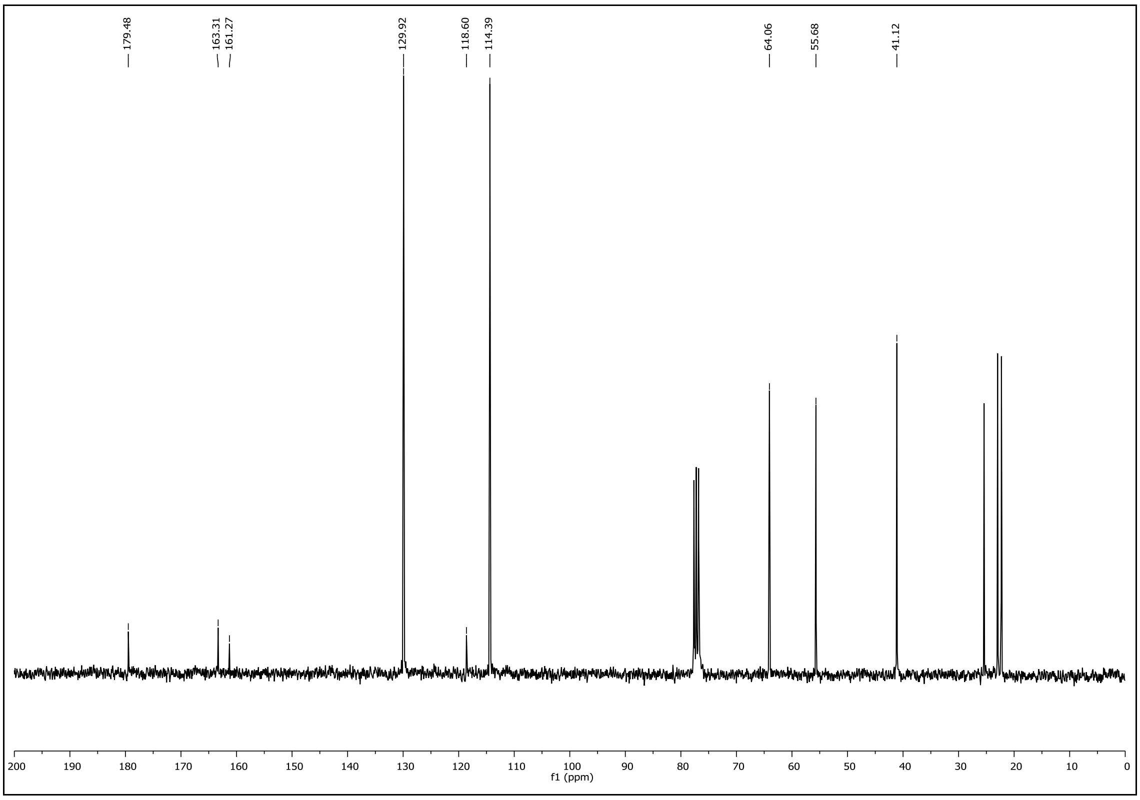
f1 (ppm)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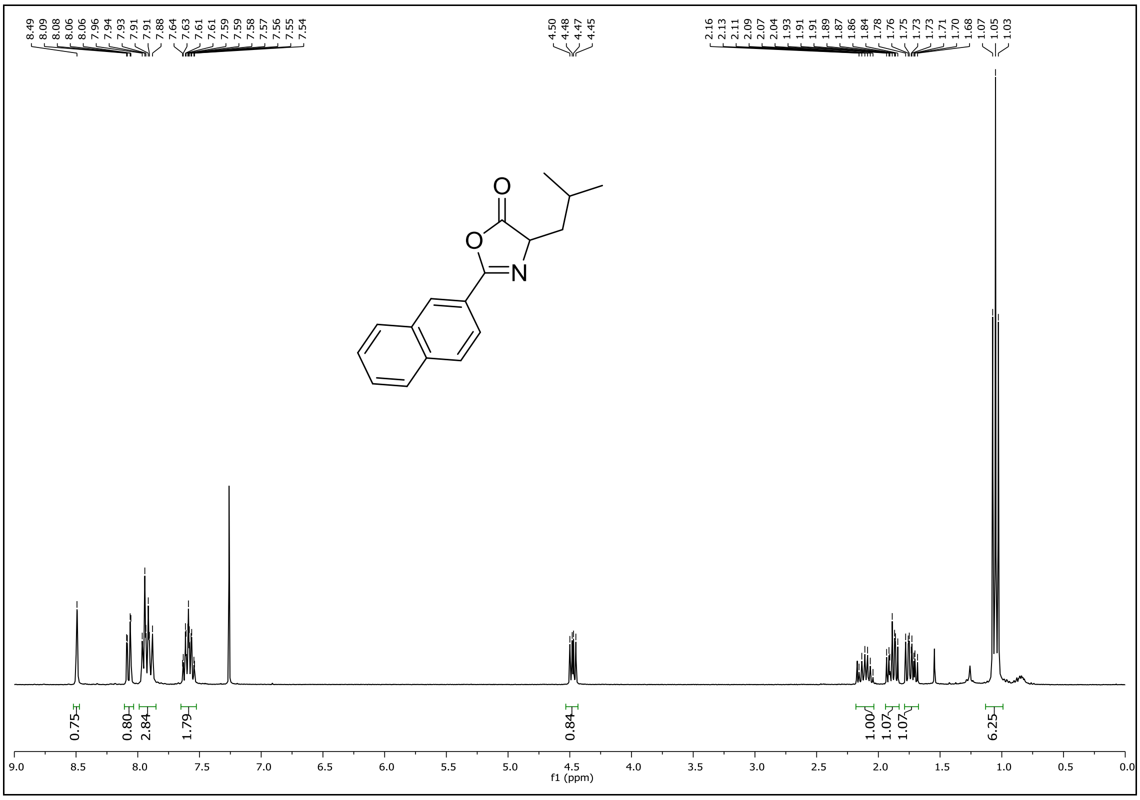
f1 (ppm)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7.56
7.55
7.54
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4.47
4.45
2.16
2.13
2.11
2.09
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2.04
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1.91
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1.86
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1.73
1.71
1.70
1.68
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1.05
1.03
O
O
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7.0
6.5
6.0
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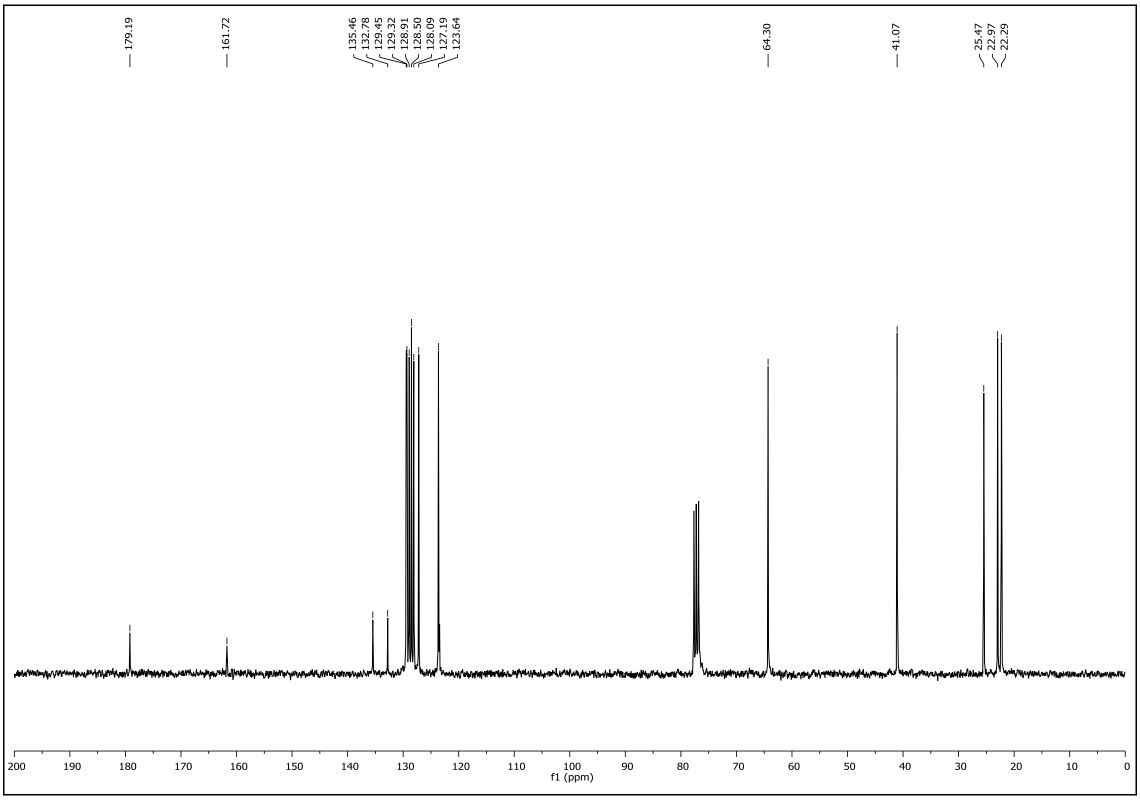
0.0
f1 (ppm)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200
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180
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120
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70
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50
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10
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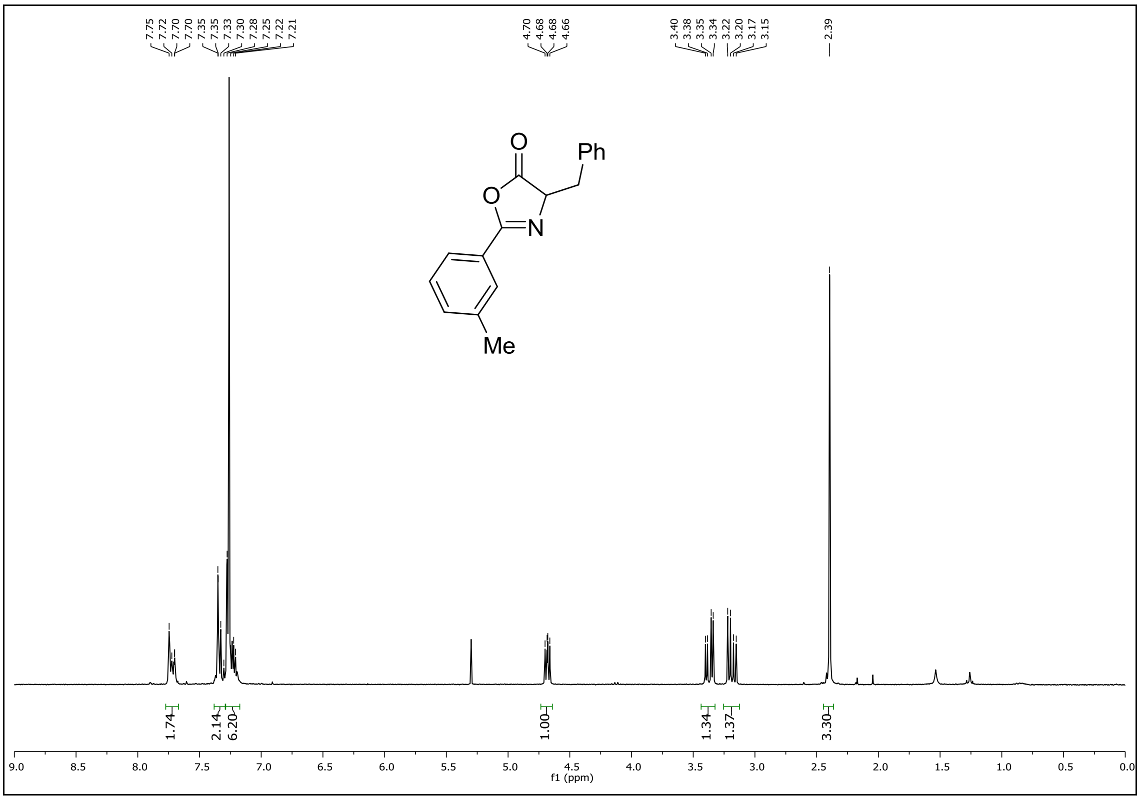
f1 (ppm)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3.34
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3.20
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2.39
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Ph
O
N
Me
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1.34
1.37
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8.0
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7.0
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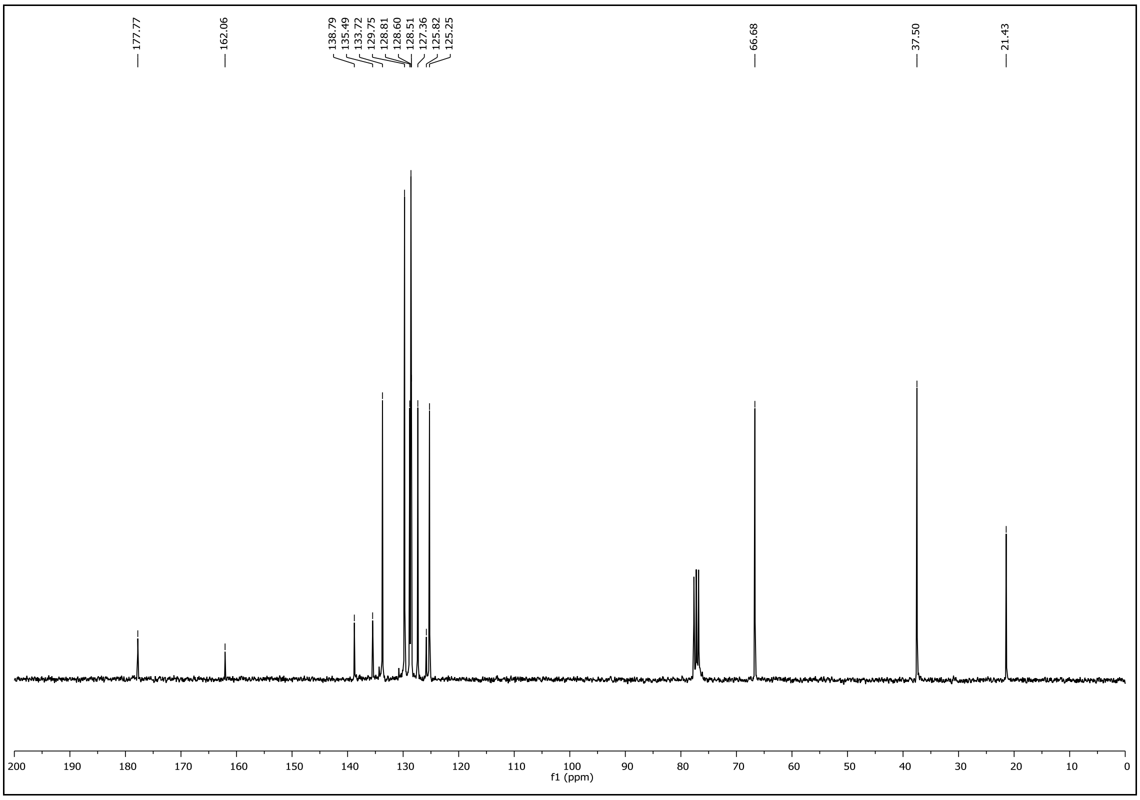
f1 (ppm)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37.50
21.43
200
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180
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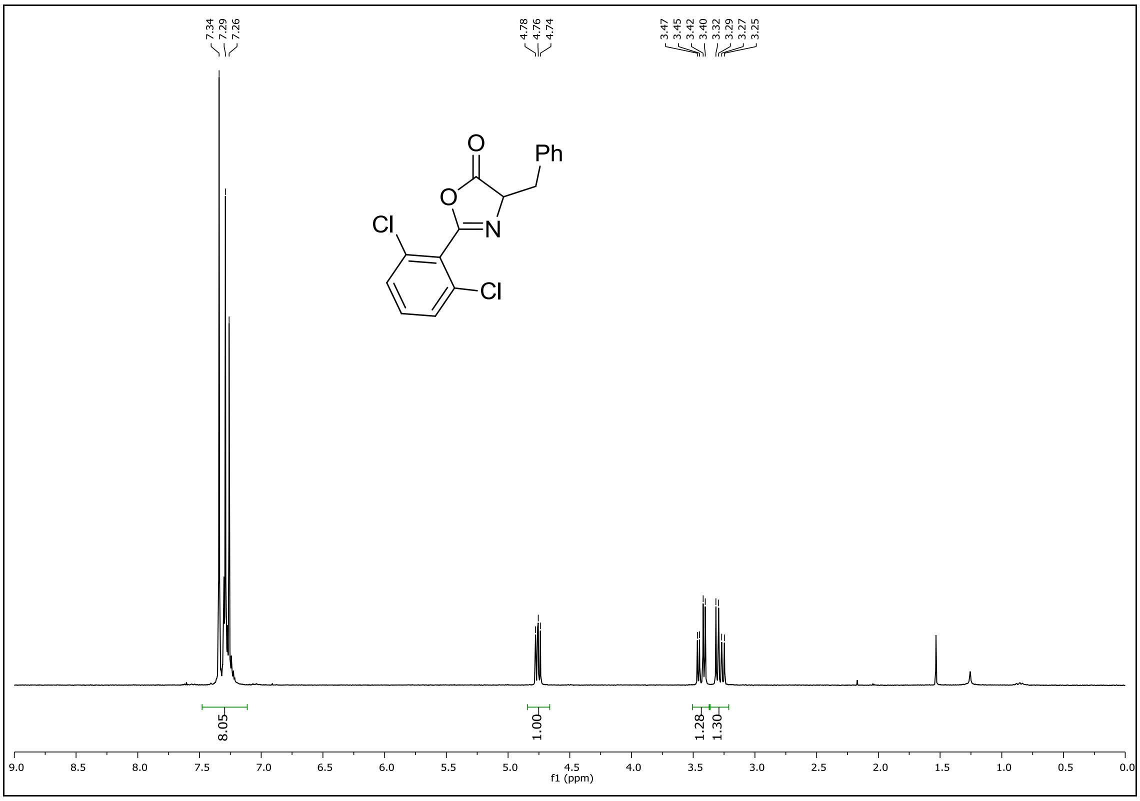
f1 (ppm)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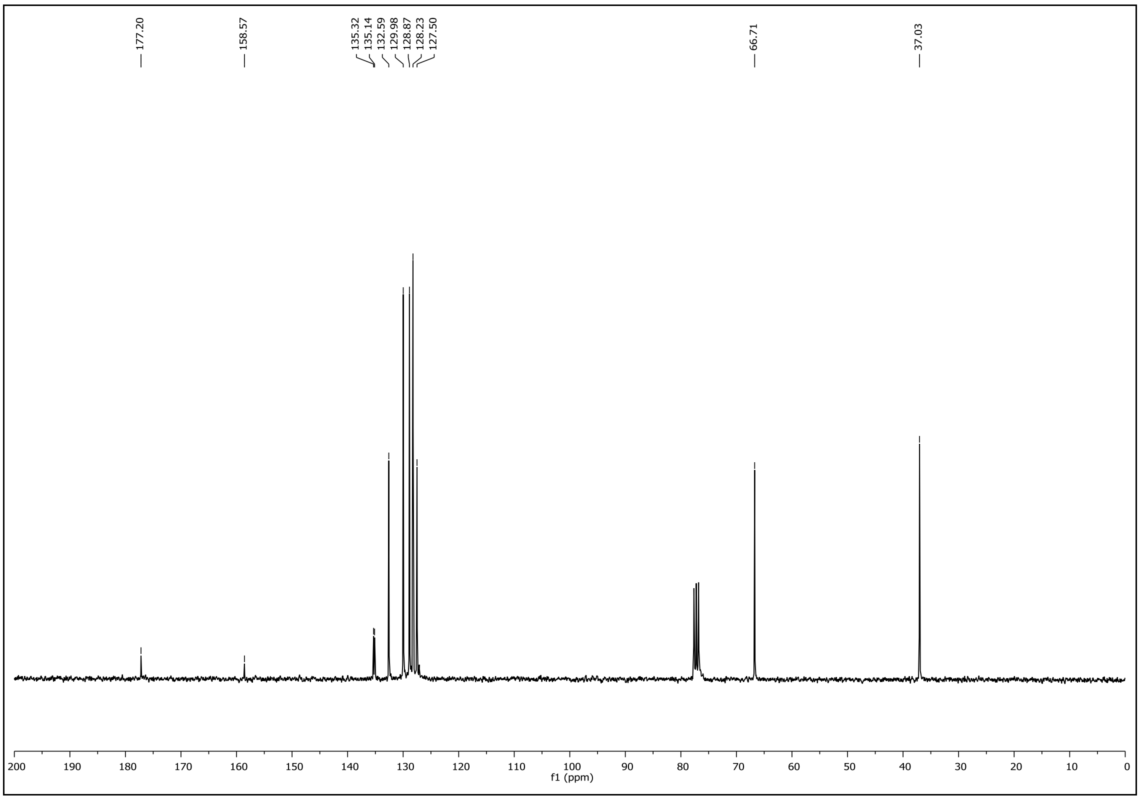
3.27
3.25
O
Ph
O
N
Cl
Cl
8.05
1.00
1.28
1.30
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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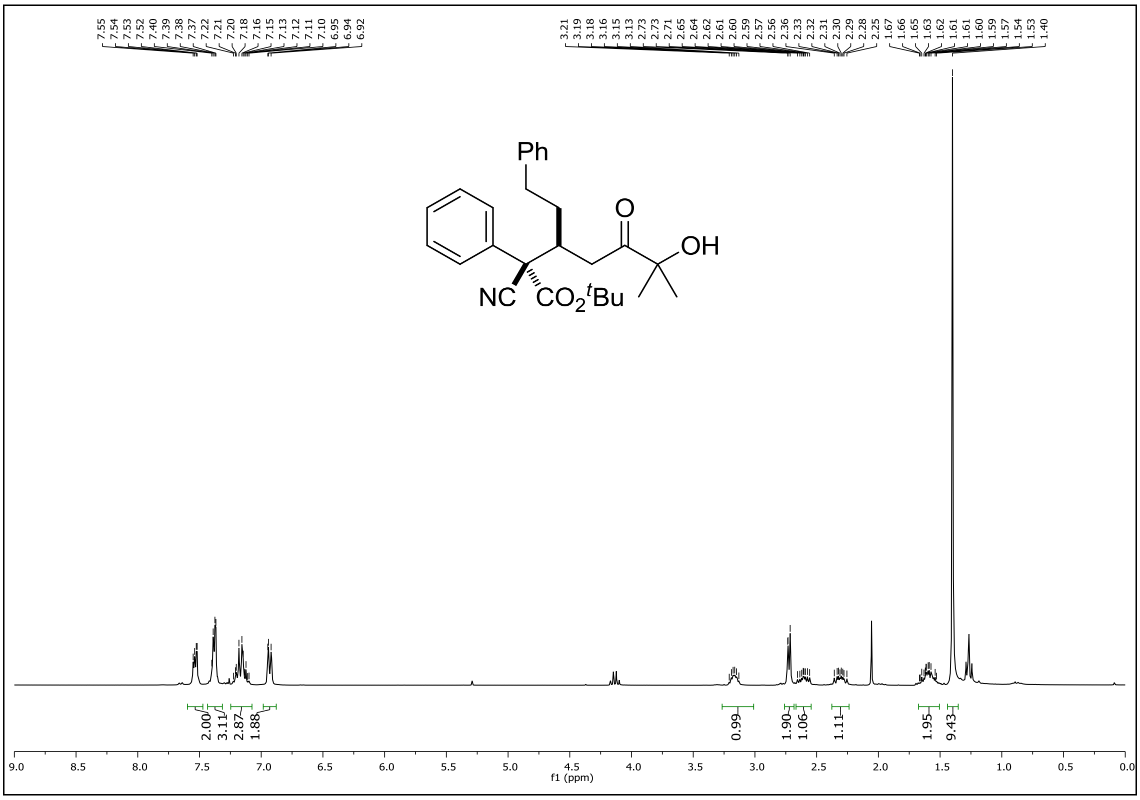
f1 (ppm)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3.18
3.16
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2.56
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1.54
1.53
1.40
Ph
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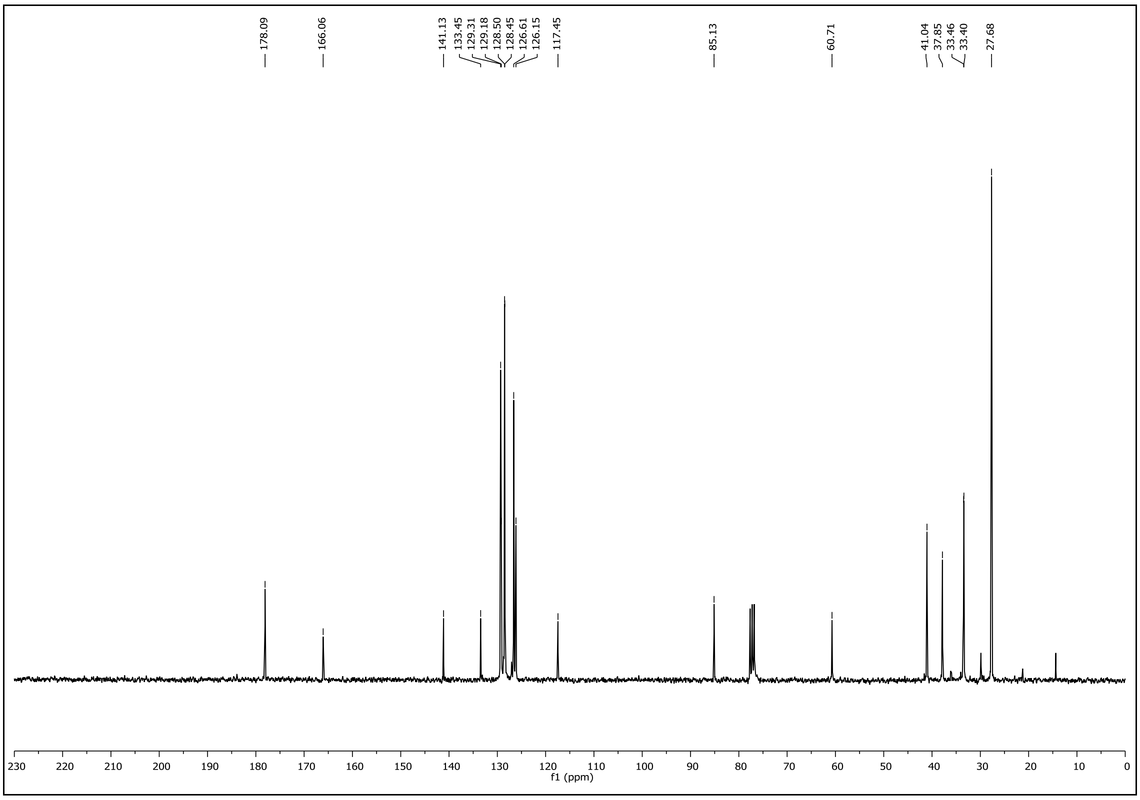
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41.04
37.85
33.46
33.40
27.68
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220
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200
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180
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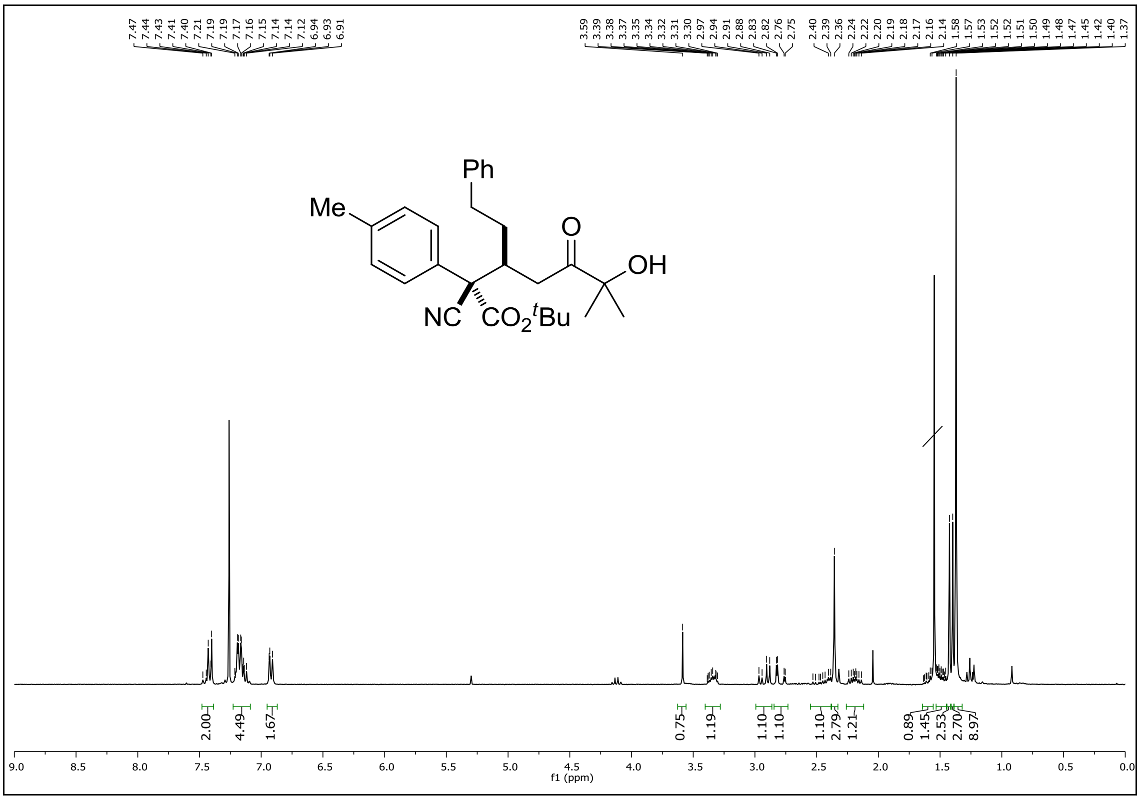
f1 (ppm)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7.14
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6.91
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3.38
3.37
3.35
3.34
3.32
3.31
3.30
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2.91
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2.36
2.24
2.22
2.20
2.19
2.18
2.17
2.16
2.14
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1.57
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1.52
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Ph
Me
O
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CO2tBu
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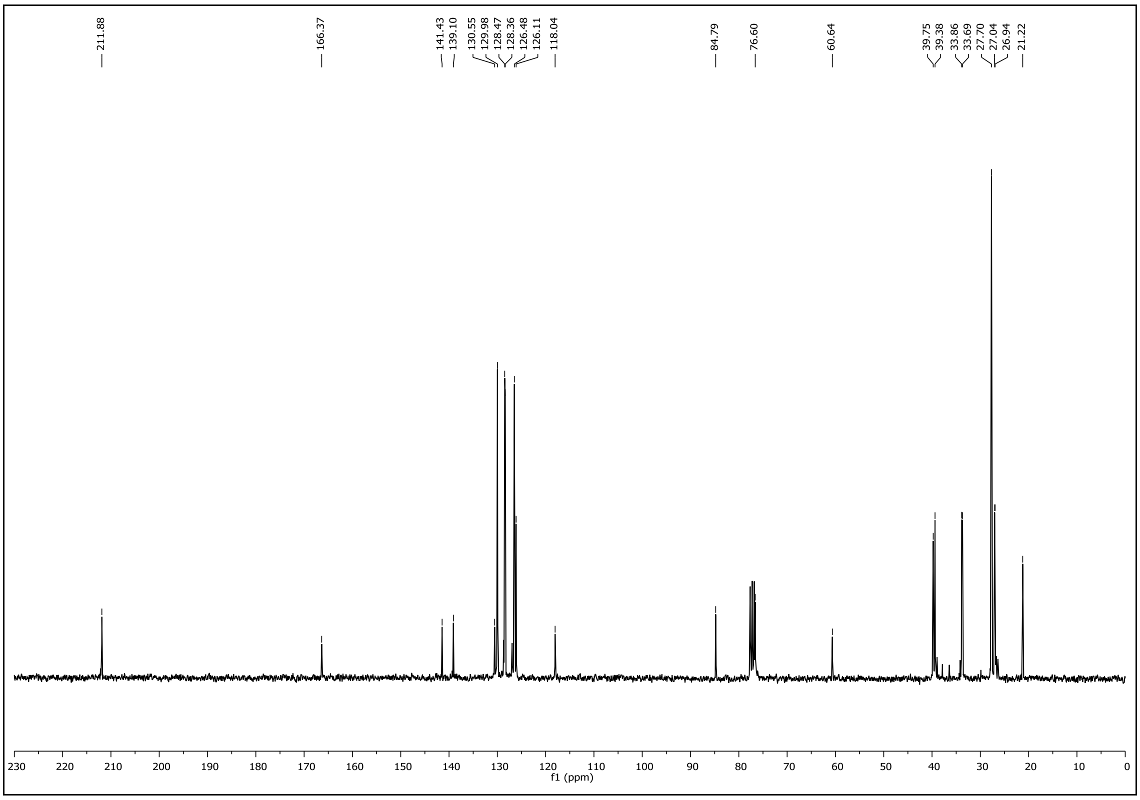
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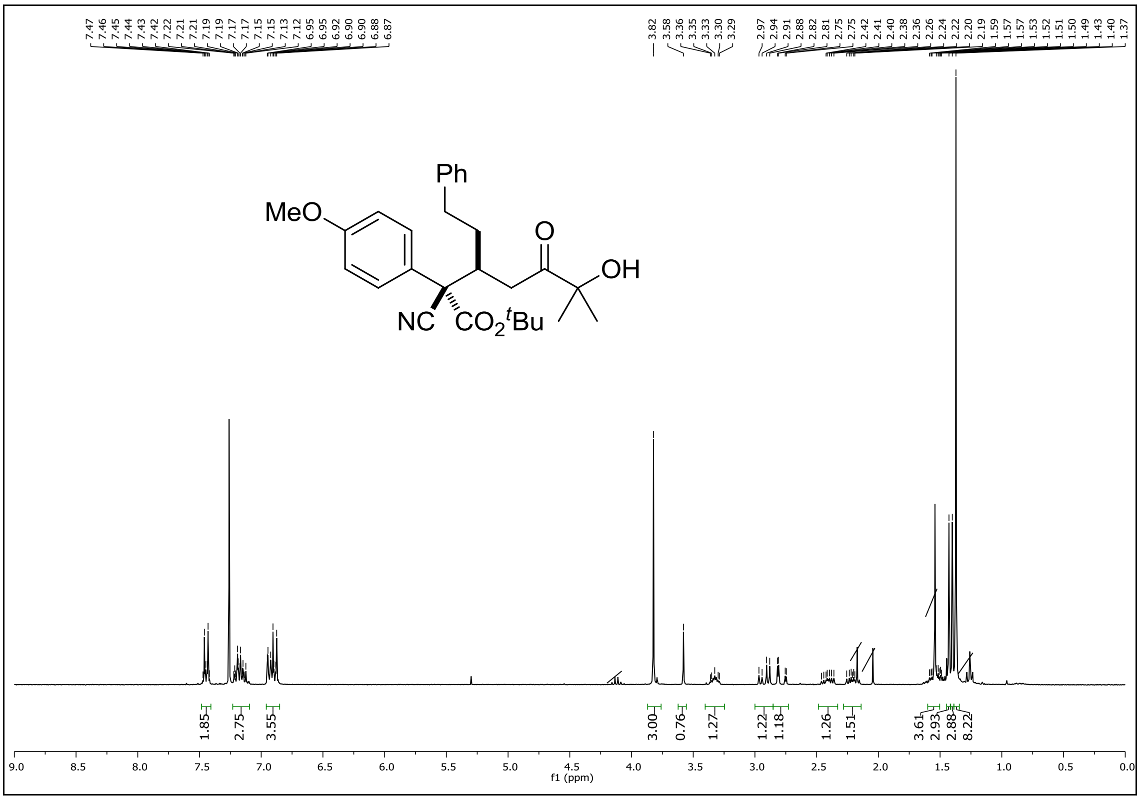
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3.29
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2.94
2.91
2.88
2.82
2.81
2.75
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1.40
1.37
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MeO
O
OH
NC
CO2tBu
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3.61
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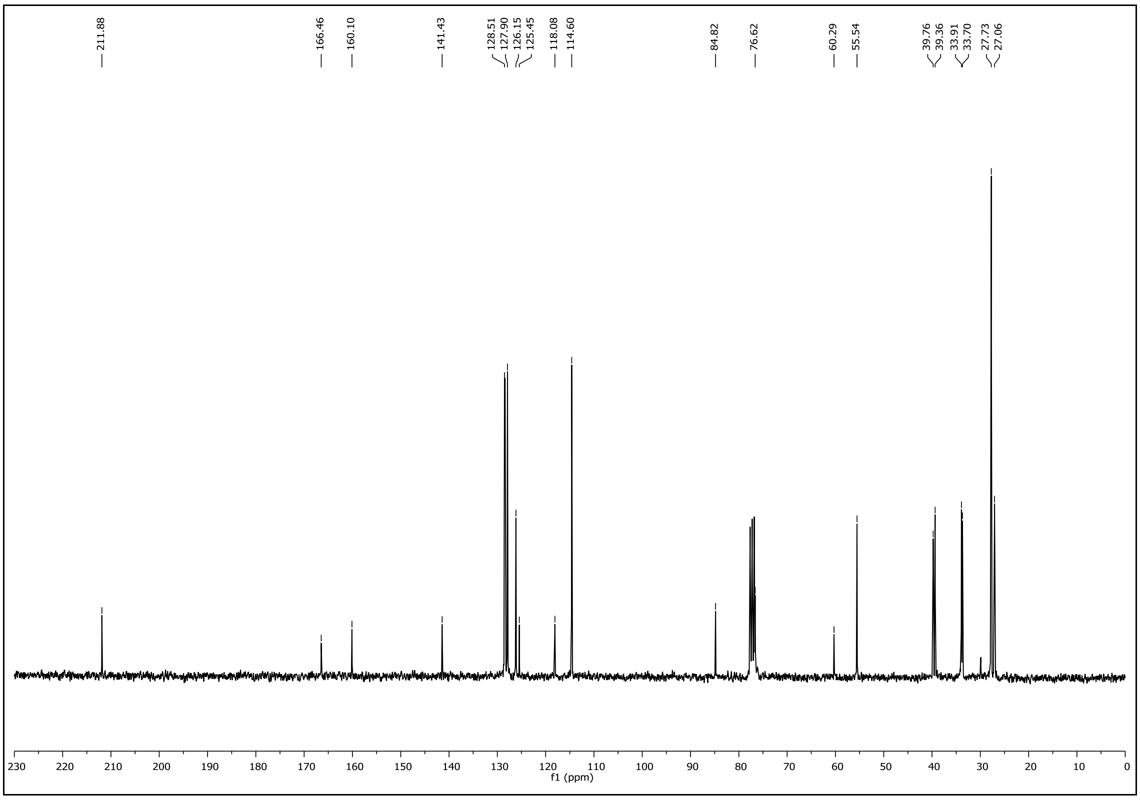
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27.06
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220
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200
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180
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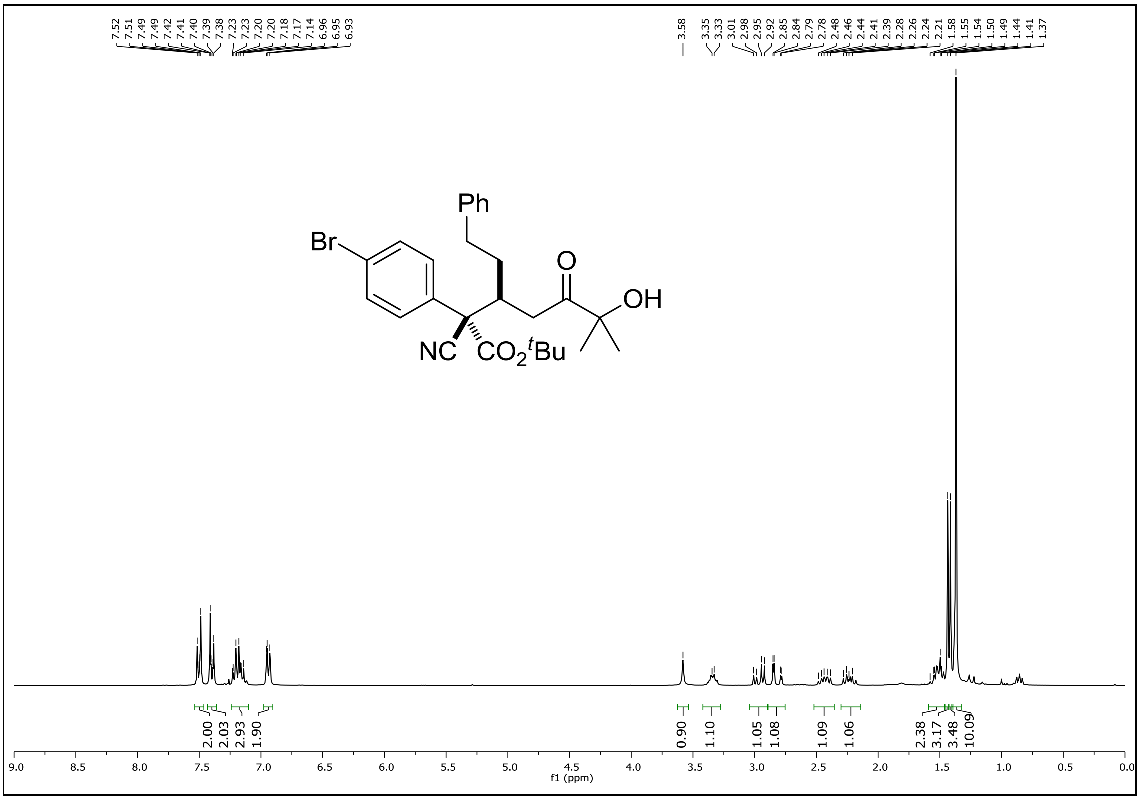
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1.41
1.37
Ph
Br
O
OH
NC
CO2tBu
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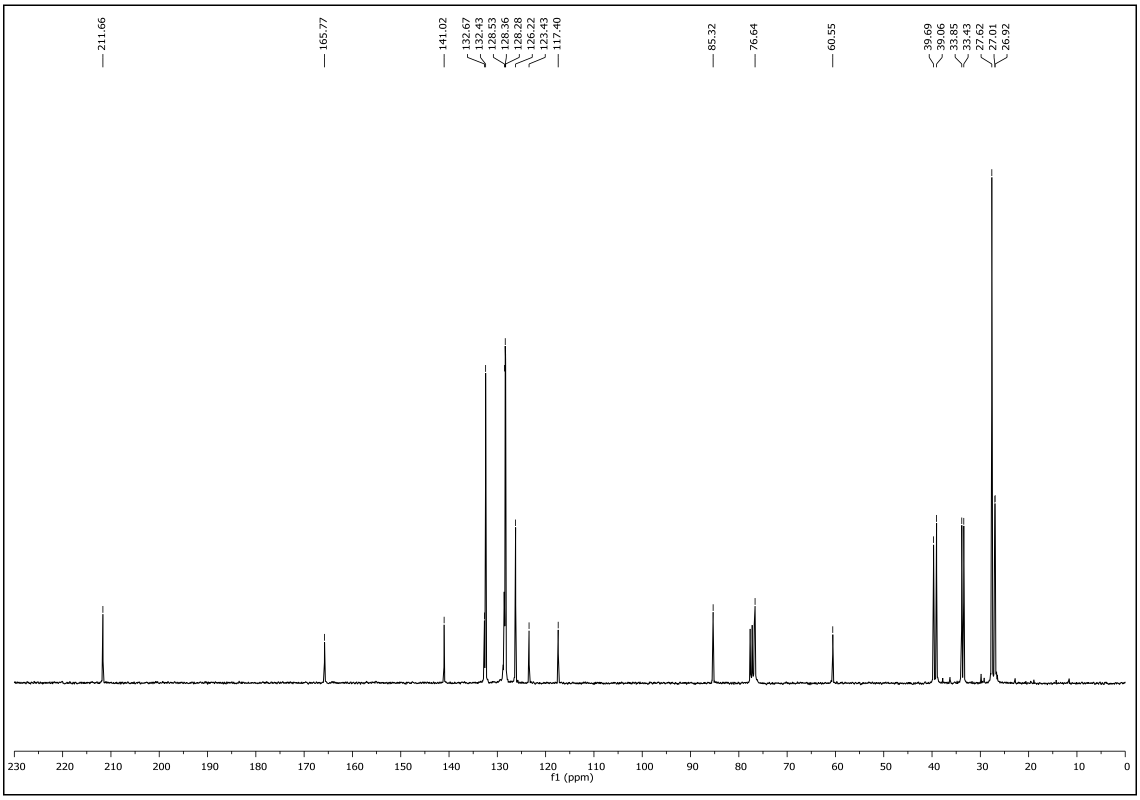
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33.85
33.43
27.62
27.01
26.92
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200
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180
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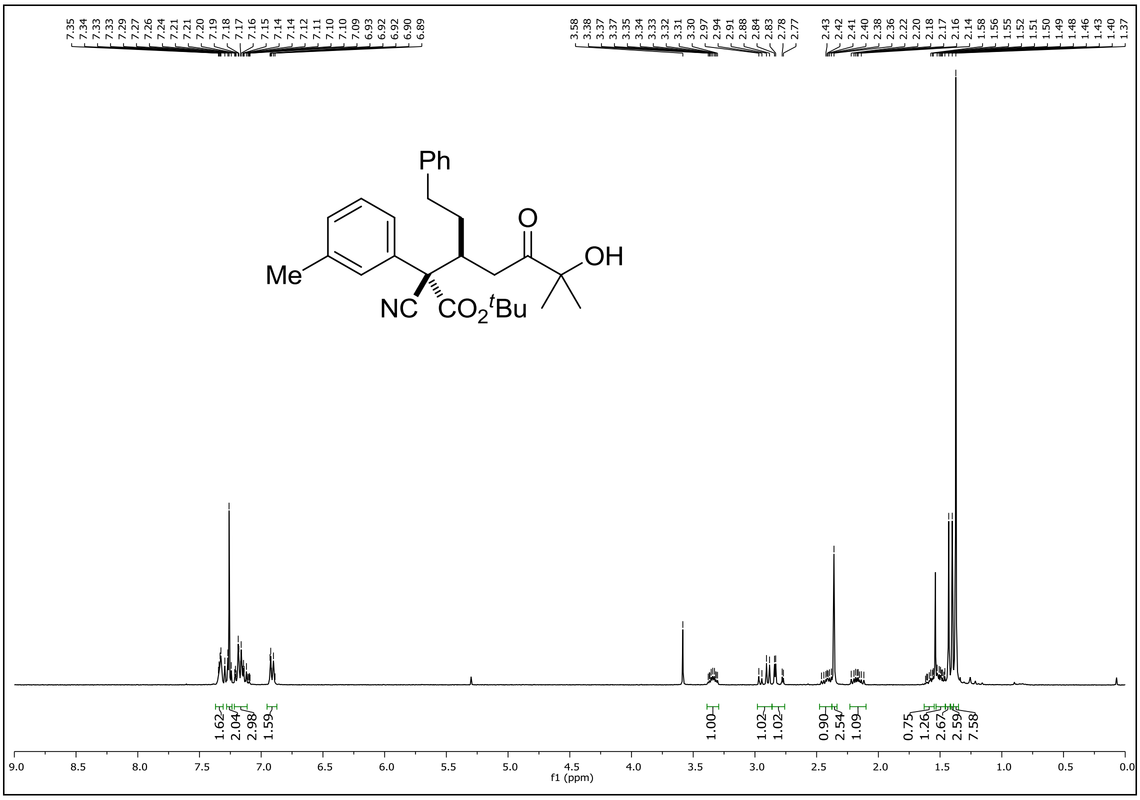
f1 (ppm)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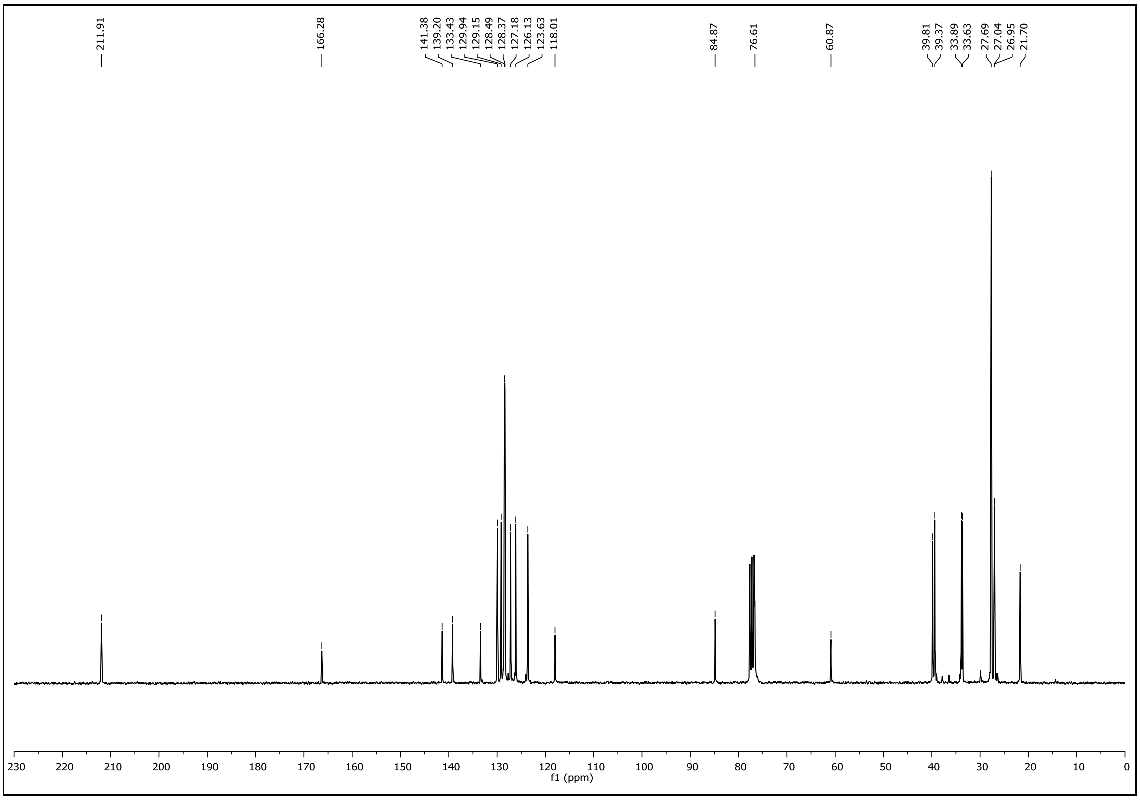
3.58 3.38 3.37 3.35 3.34 3.33 3.32 3.31 3.30 2.97 2.94 2.91 2.88 2.84 2.83 2.78 2.77
2.43 2.42 2.41 2.40 2.38 2.36 2.22 2.20 2.18 2.17 2.16 2.14 1.58 1.56 1.55 1.52 1.51 1.50 1.49 1.48 1.46 1.43 1.40 1.37
Ph
O
OH
Me
NC
CO2tBu
1.62 2.04 2.98 1.59
1.00
1.02 1.02
0.90 2.54 1.09
0.75 1.26 2.67 2.59 7.58
9.0 8.5 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 0.0
f1 (ppm)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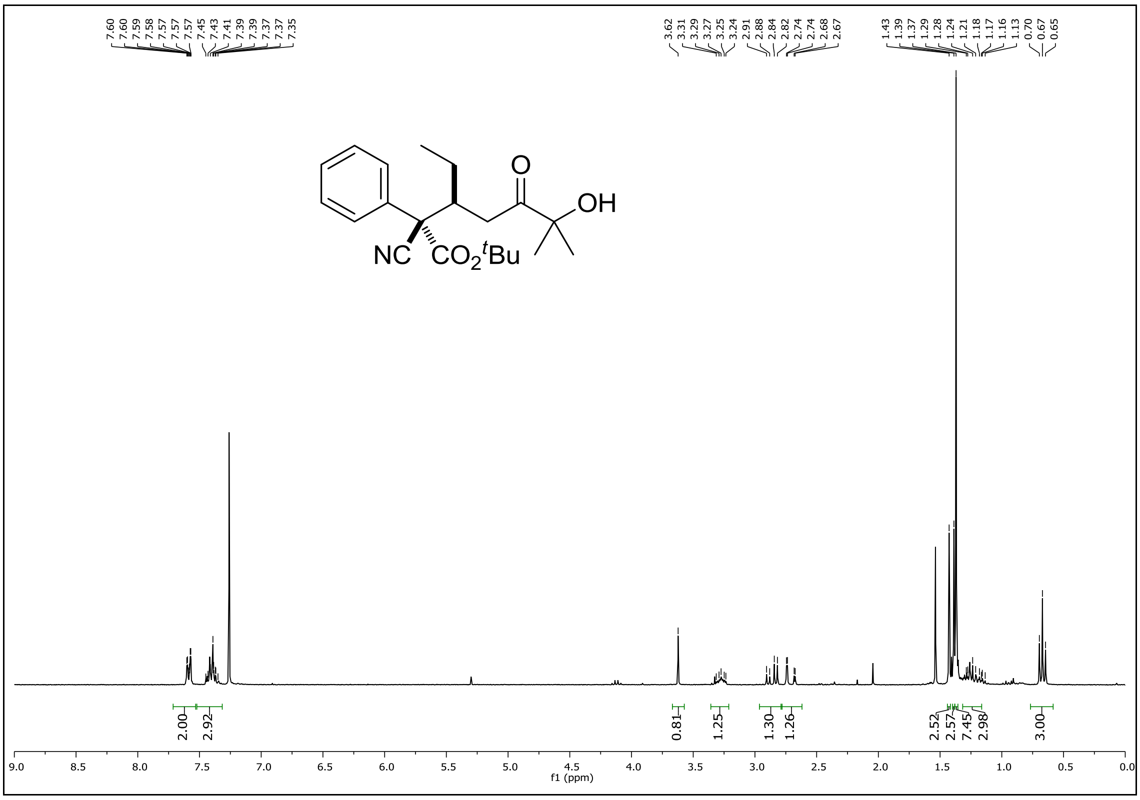
84.87
76.61
60.87
39.81 39.37 33.89 33.63 27.69 27.04 26.95 21.70
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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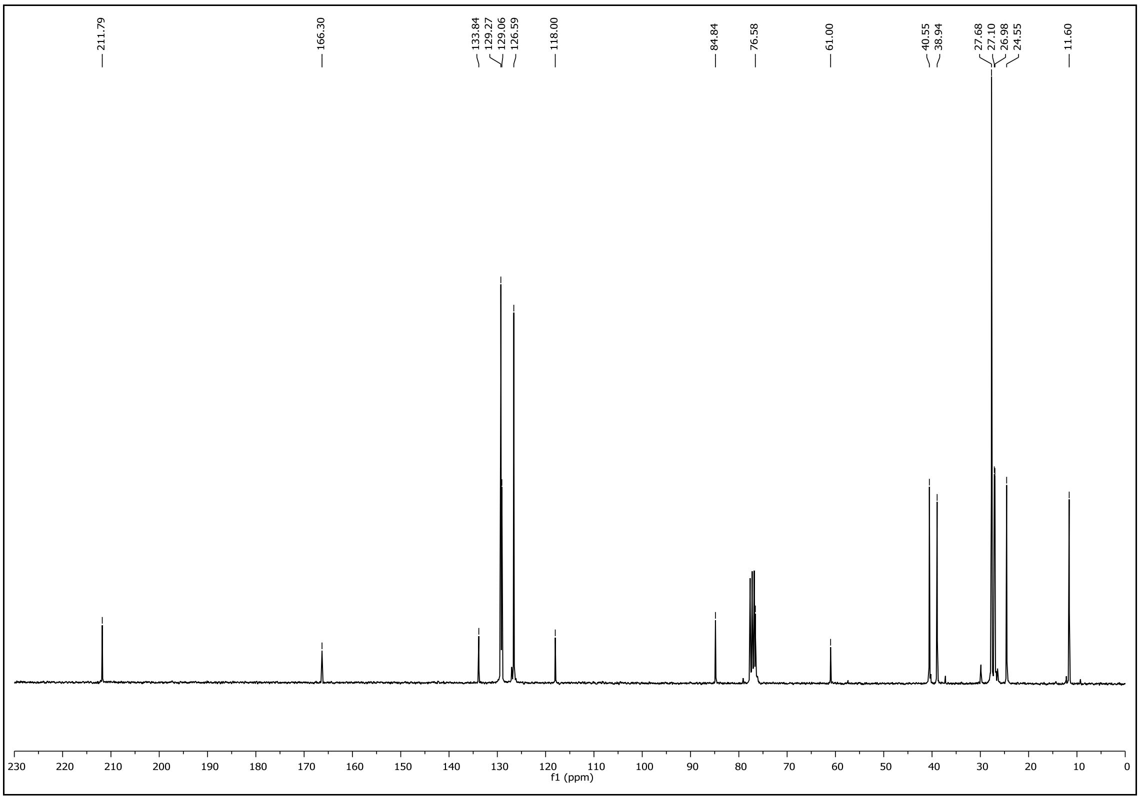
3.62 3.31 3.29 3.27 3.25 3.24 2.91 2.88 2.84 2.82 2.74 2.74 2.68 2.67
1.43 1.39 1.37 1.29 1.28 1.24 1.21 1.18 1.17 1.16 1.13 0.70 0.67 0.65
O
OH
NC
CO2tBu
2.00
2.92
0.81
1.25
1.30
1.26
2.52
2.57
7.45
2.98
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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76.58
61.00
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27.68 27.10 26.98 24.55
11.60
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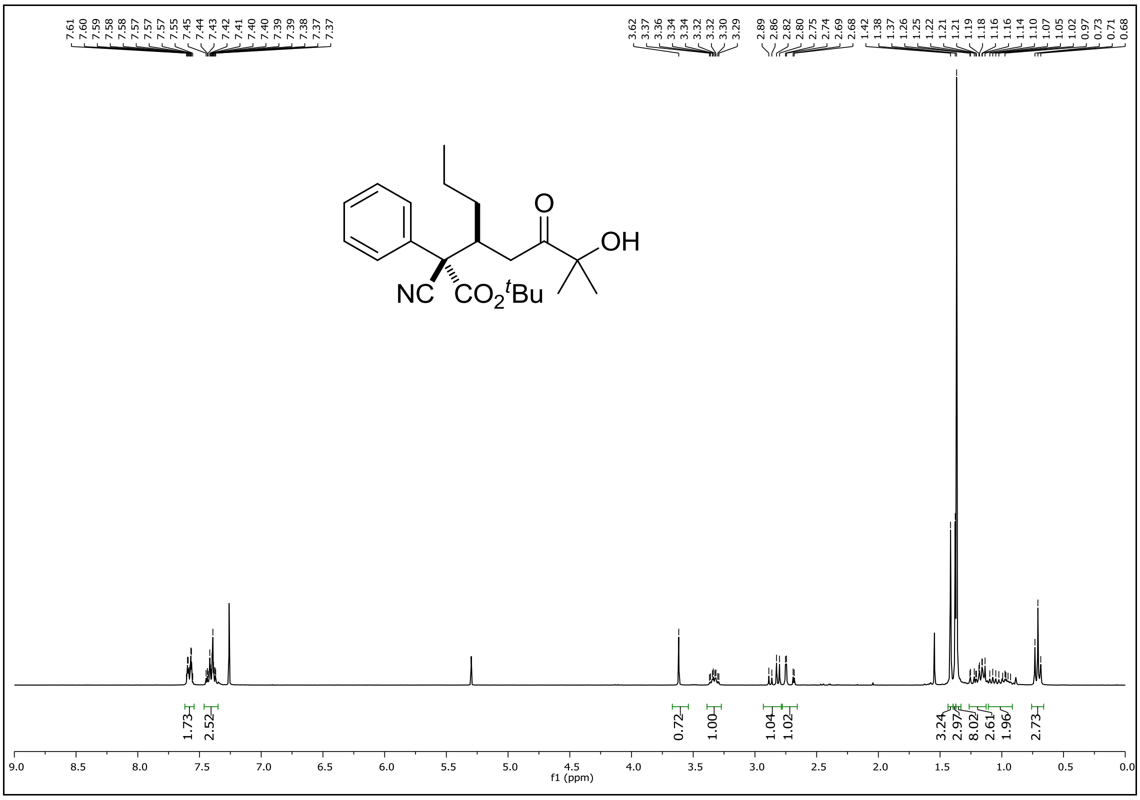
f1 (ppm)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7.38
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3.30
3.29
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2.82
2.80
2.75
2.74
2.69
2.68
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1.25
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1.19
1.18
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1.16
1.14
1.10
1.07
1.05
1.02
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0.73
0.71
0.68
O
OH
NC
CO2tBu
1.73
2.52
0.72
1.00
1.04
1.02
3.24
2.97
8.02
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8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
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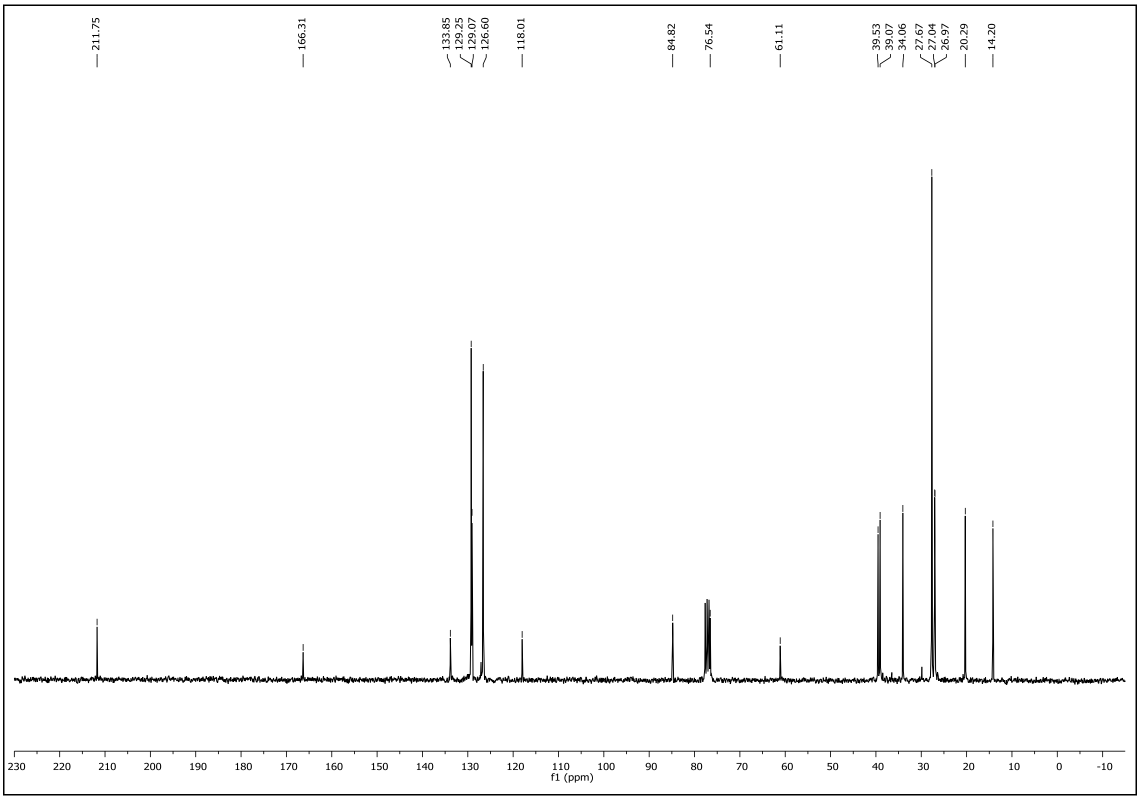
0.0
f1 (ppm)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39.07
34.06
27.67
27.04
26.97
20.29
14.20
230
220
210
200
190
180
170
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100
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80
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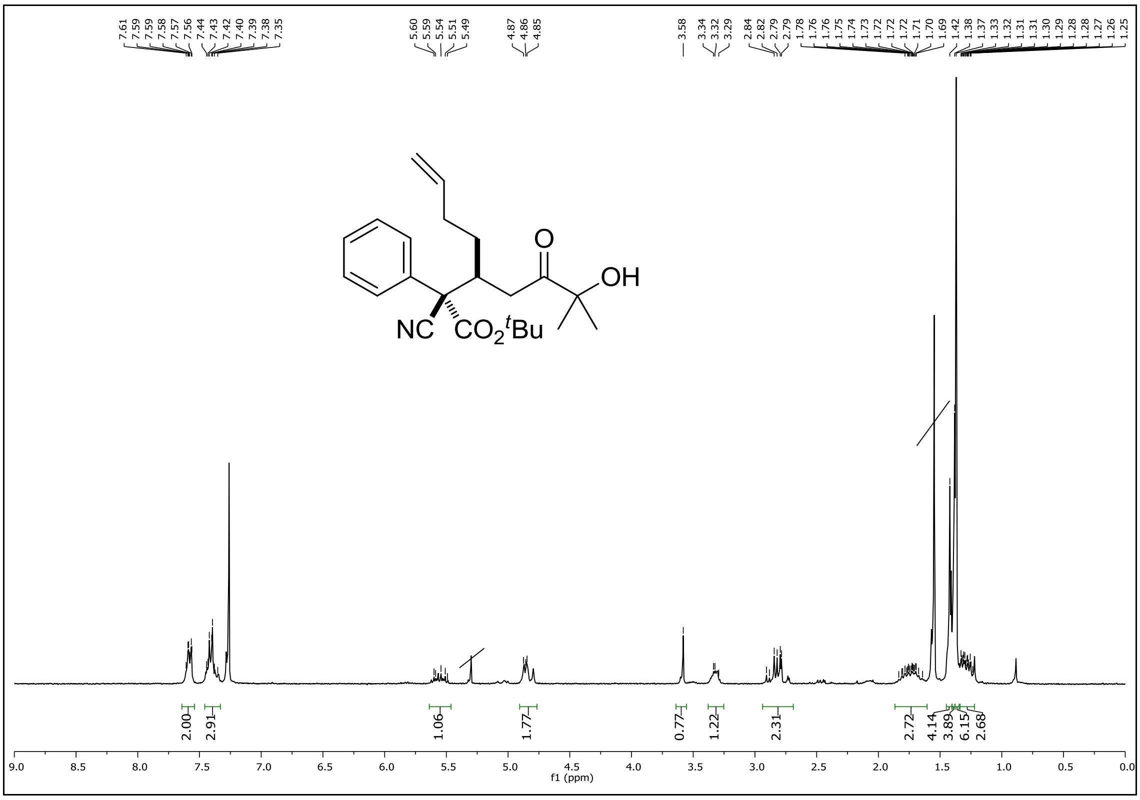
f1 (ppm)



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4.87 4.86 4.85
3.58
3.34 3.32 3.29
2.84 2.82 2.79 2.79
1.78 1.76 1.76 1.75 1.74 1.73 1.72 1.72 1.72 1.71 1.70 1.69
1.42 1.38 1.37 1.33 1.32 1.31 1.30 1.29 1.28 1.27 1.26 1.25
O
OH
NC
CO2tBu
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2.91
1.06
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0.77
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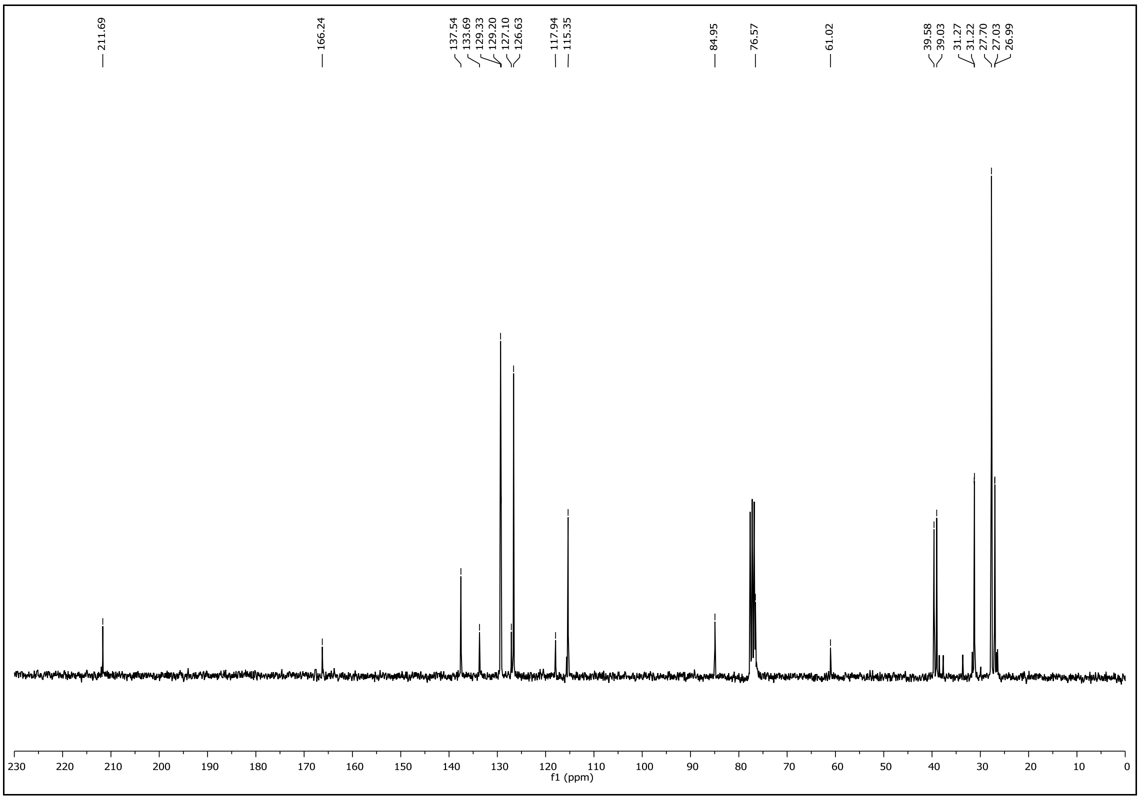
2.31
2.72
4.14
3.89
6.15
2.68
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



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76.57
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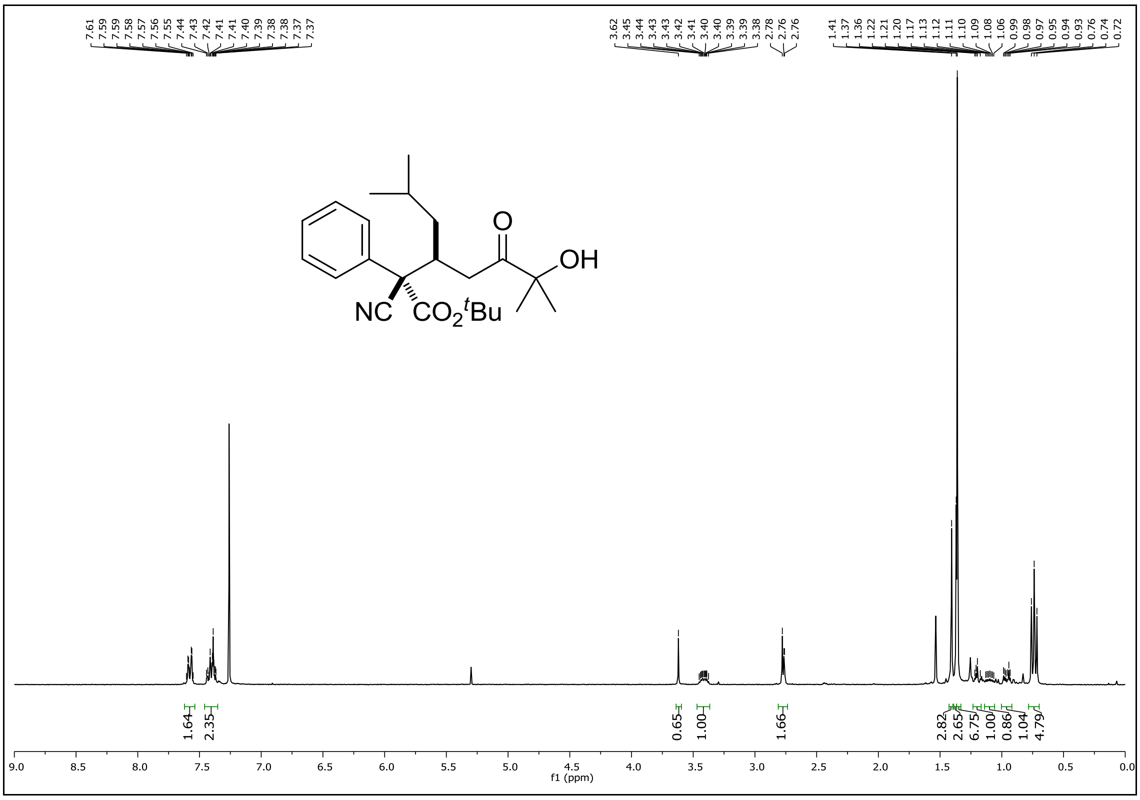

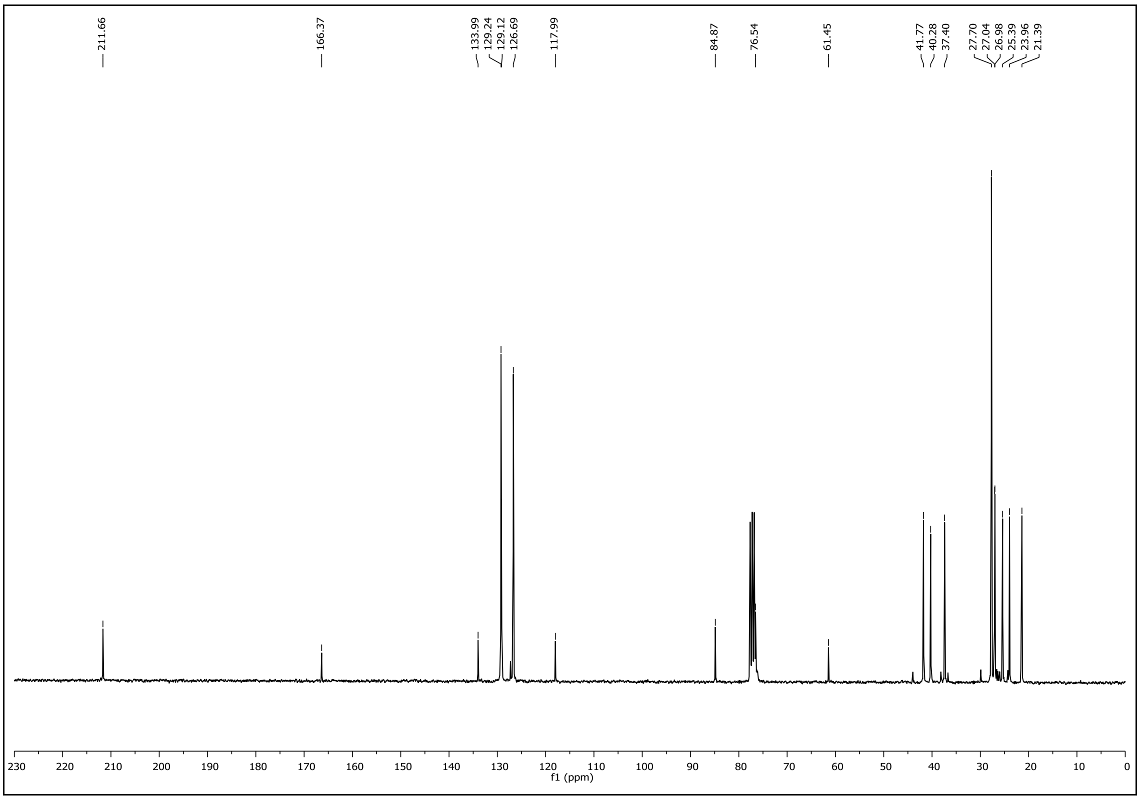

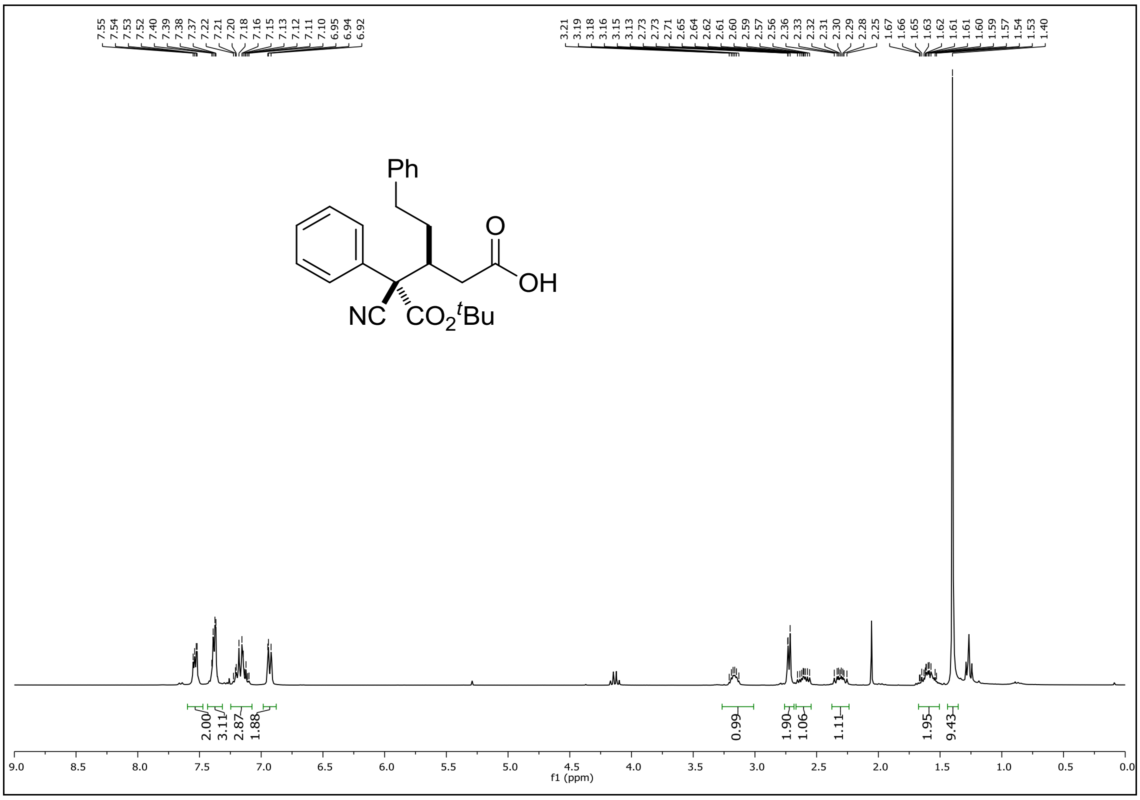
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3.21 3.19 3.18 3.16 3.15 3.13 2.73 2.73 2.71 2.65 2.64 2.62 2.61 2.60 2.59 2.57 2.56 2.36 2.33 2.32 2.31 2.30 2.29 2.28 2.25 1.67 1.66 1.65 1.63 1.62 1.61 1.61 1.60 1.59 1.57 1.54 1.53 1.40
Ph
O
OH
NC
$CO_2{}^tBu$
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1.90
1.06
1.11
1.95
9.43
9.0 8.5 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 0.0
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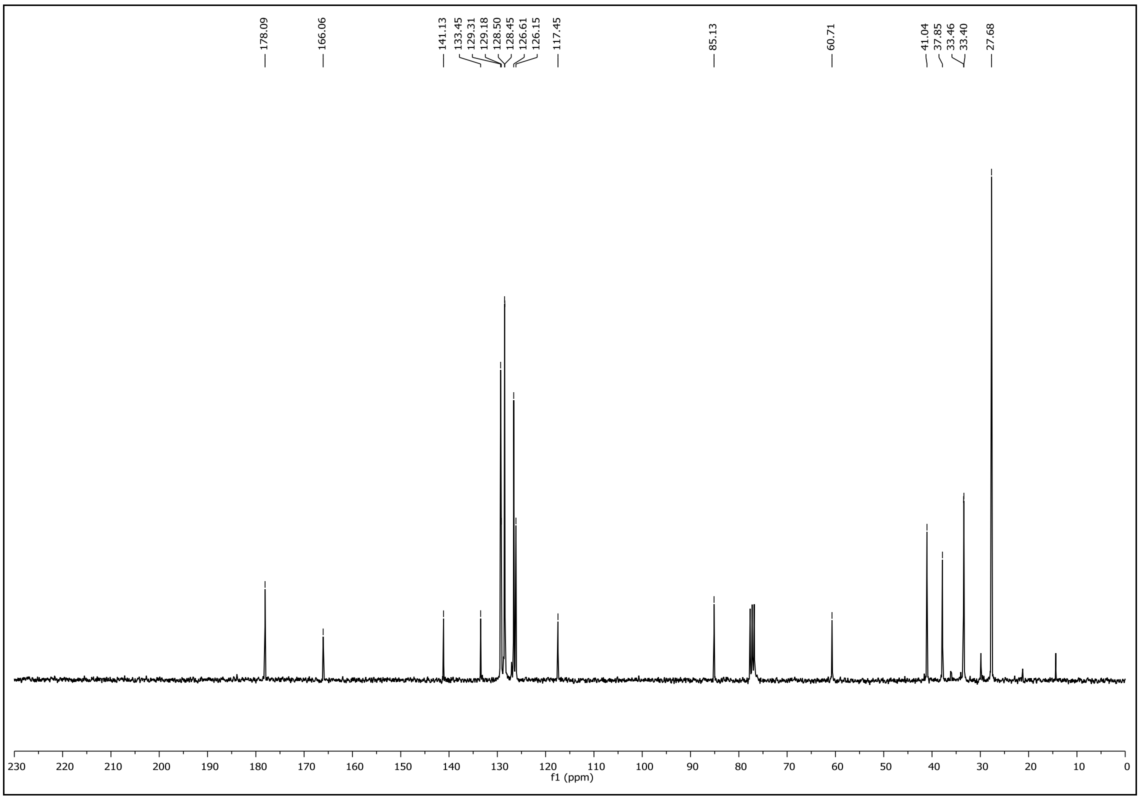
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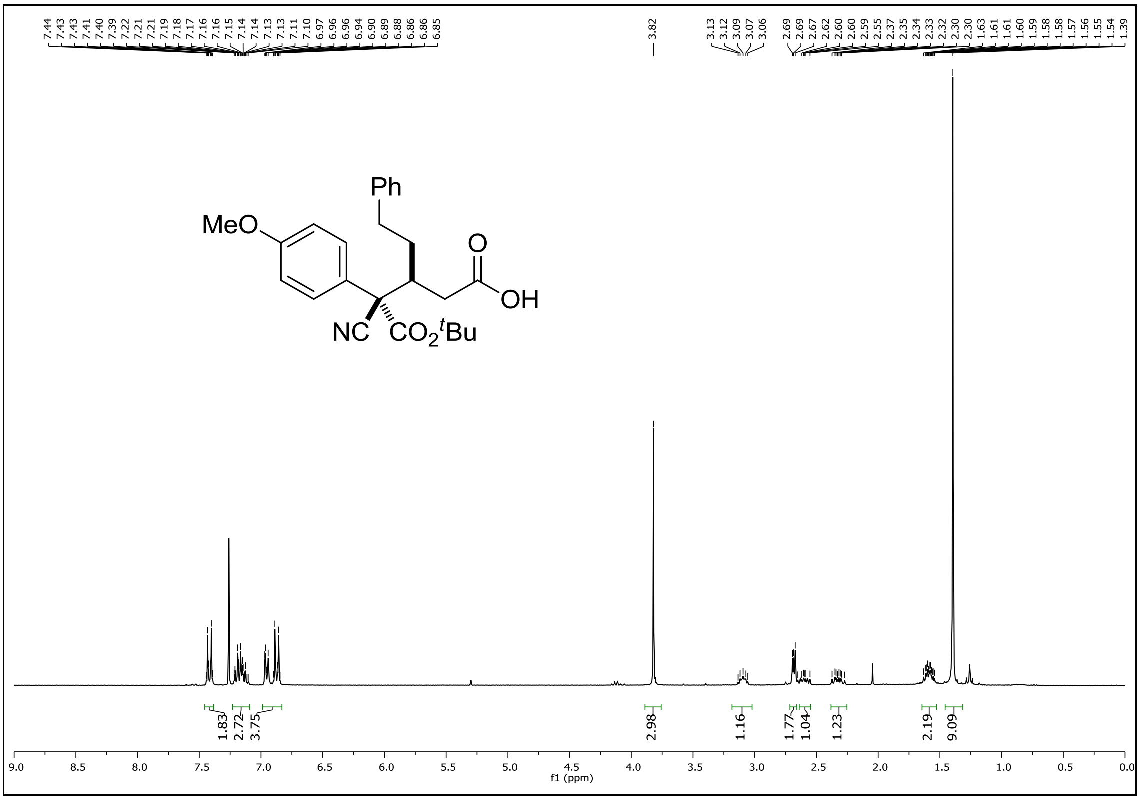
f1 (ppm)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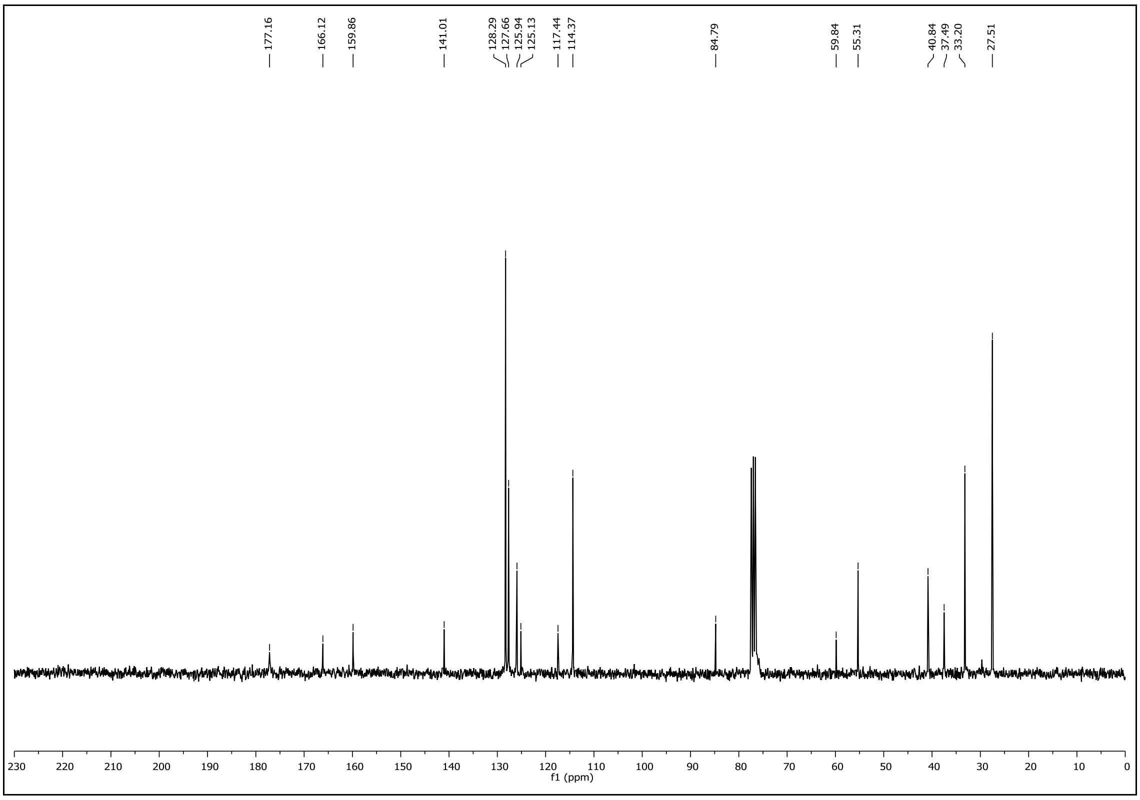
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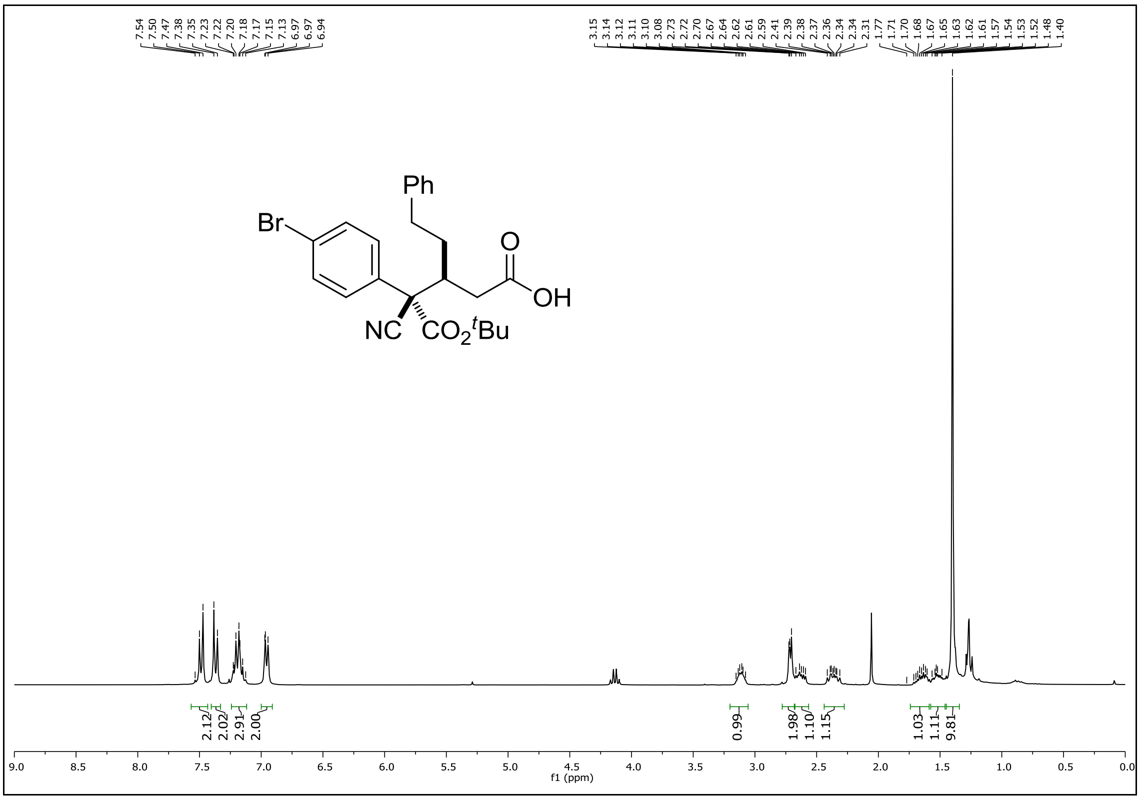
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Ph
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OH
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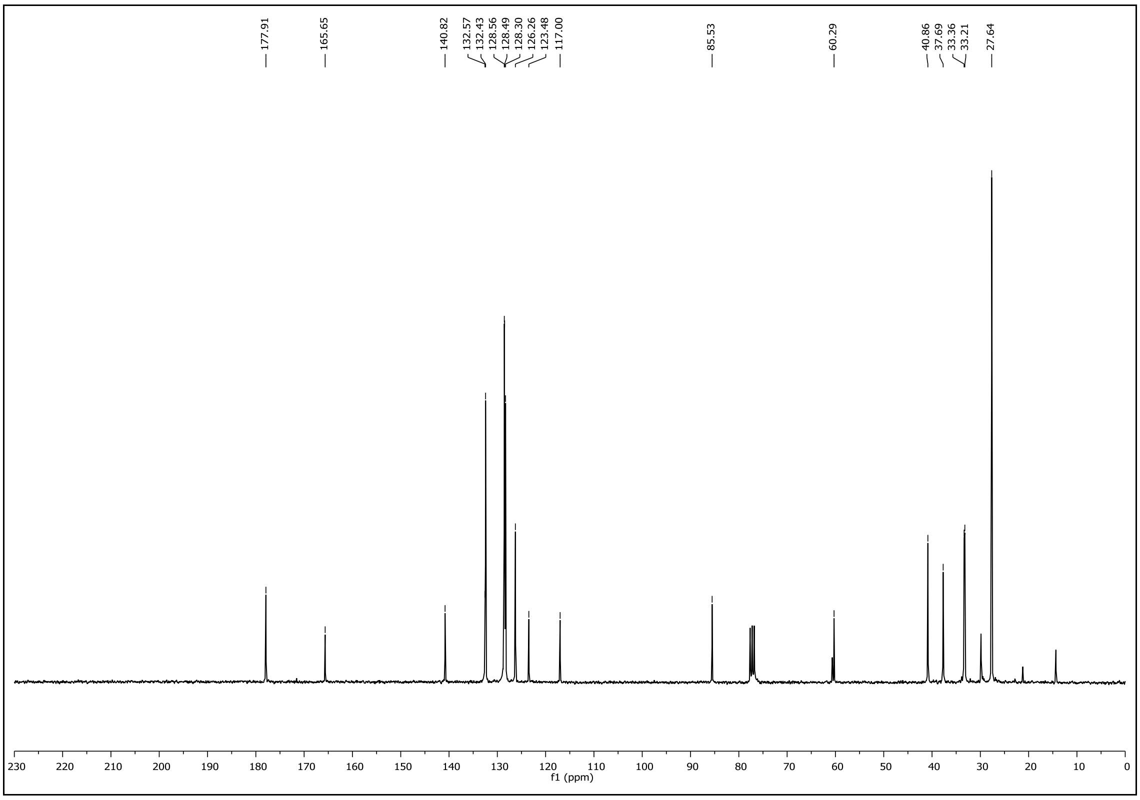
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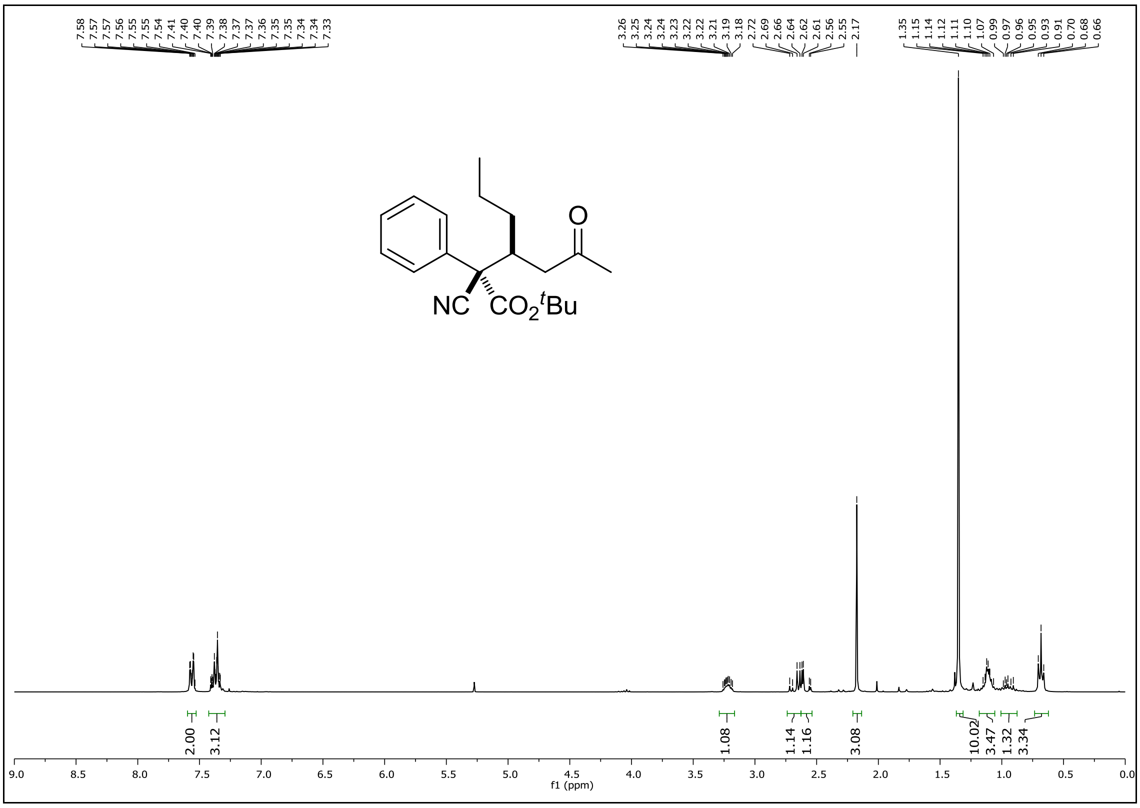
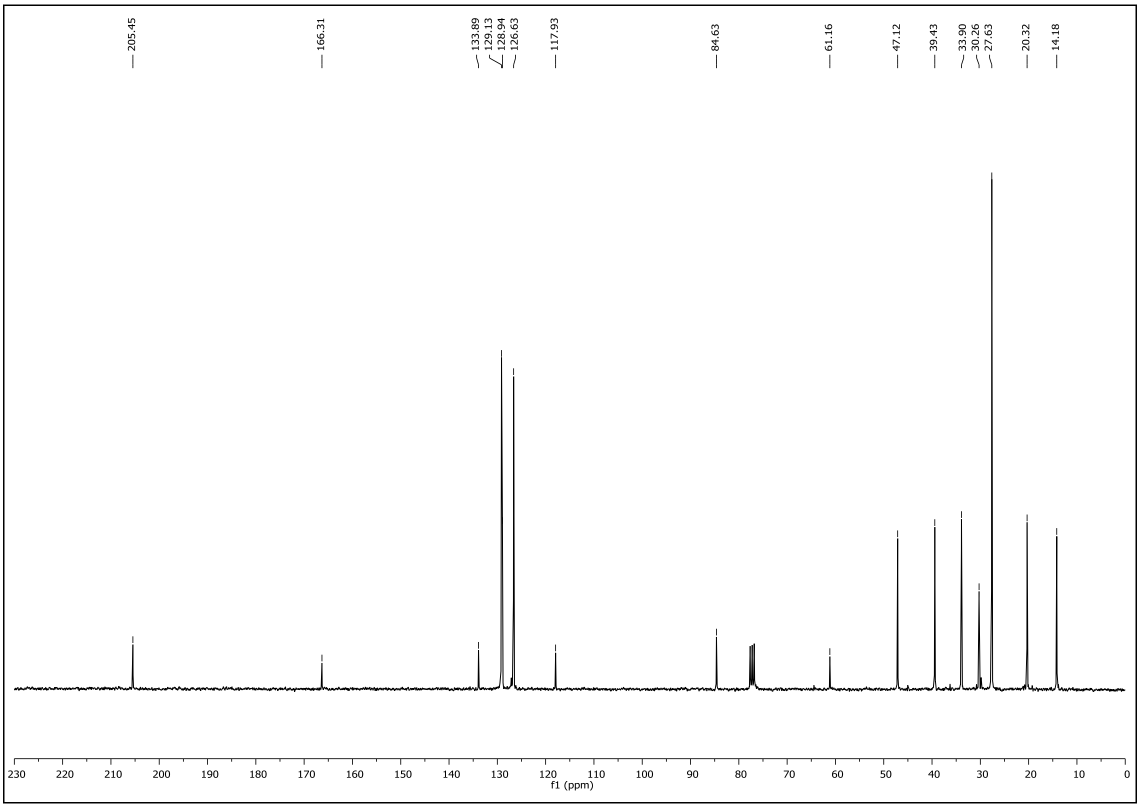
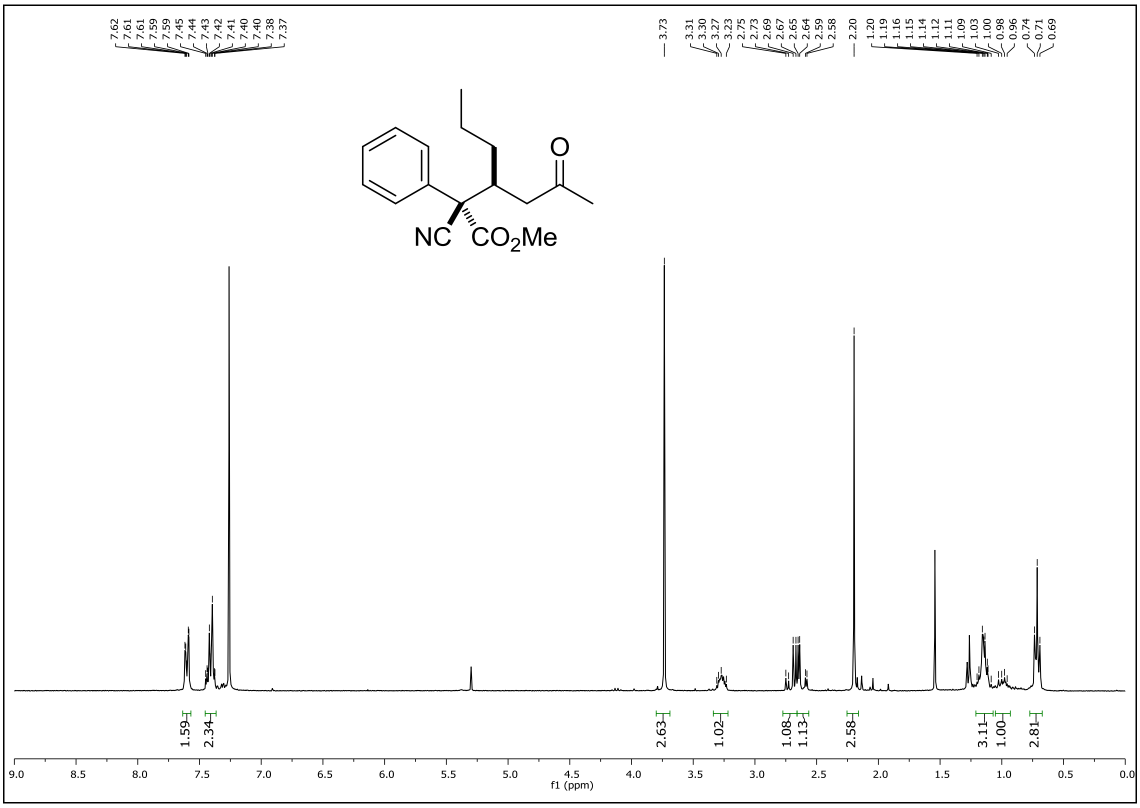
f1 (ppm)



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3.0
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2.0
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1.0
0.5
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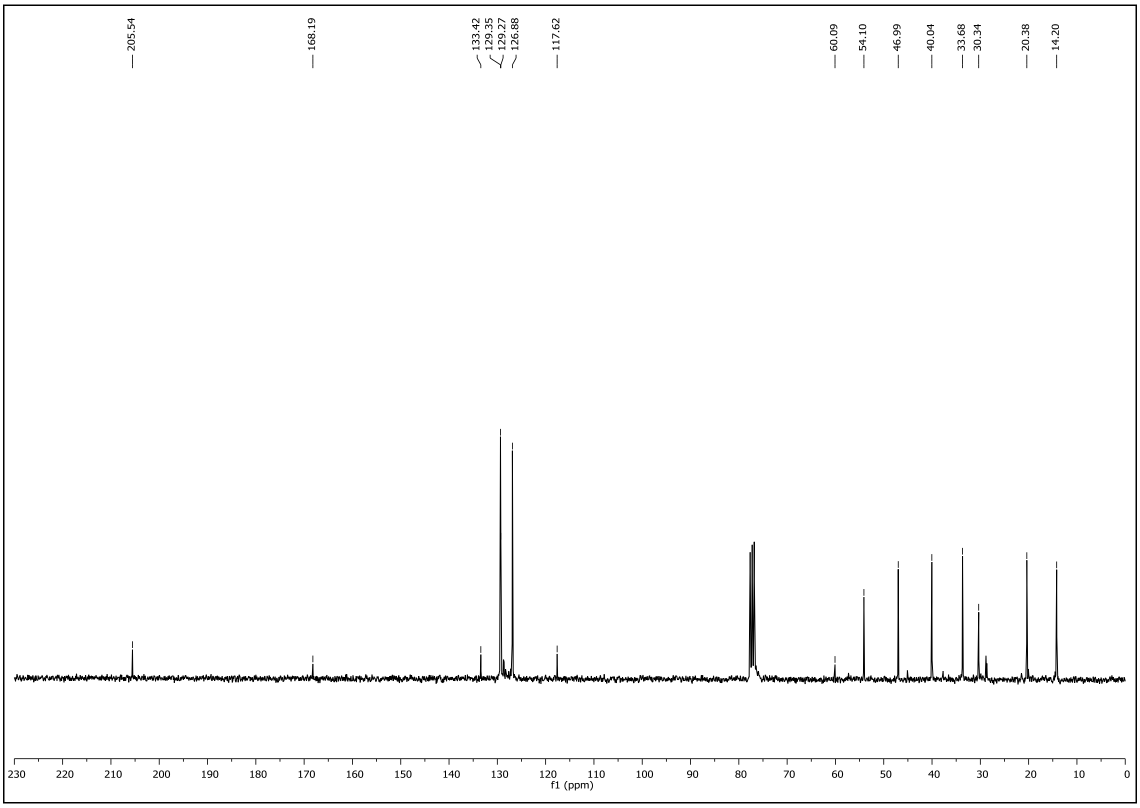
f1 (ppm)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180
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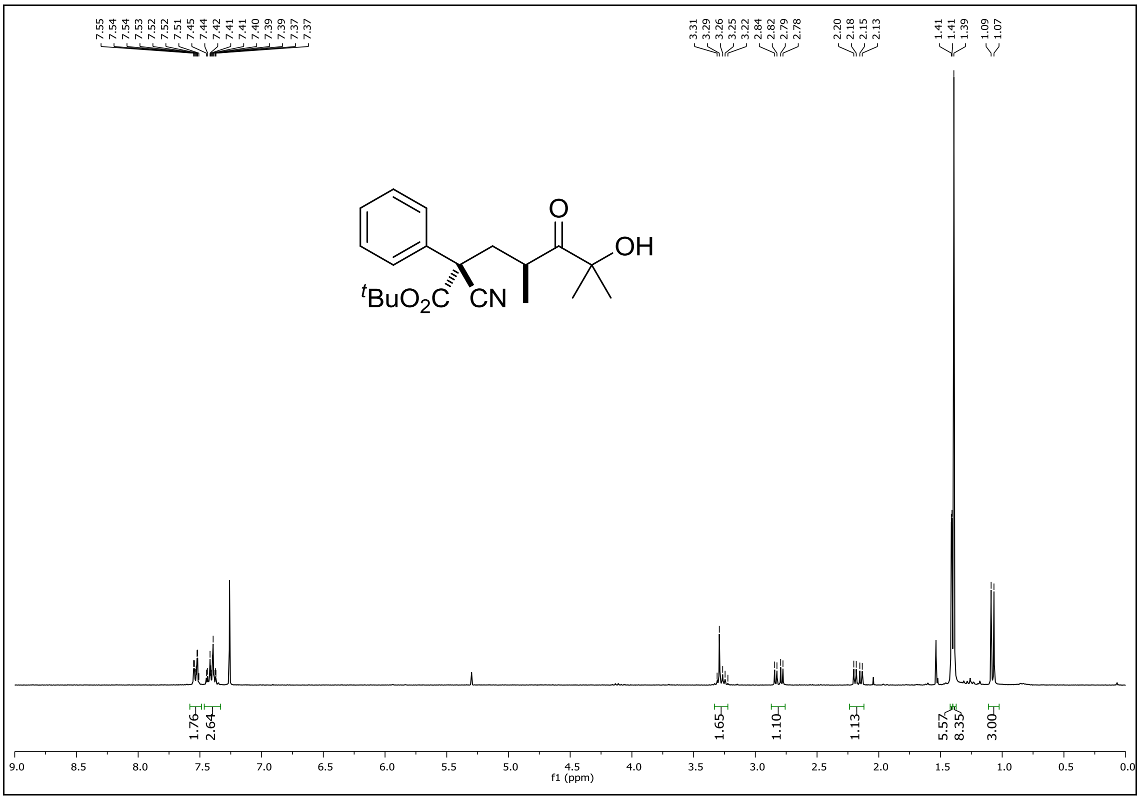
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7.37
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3.29
3.26
3.25
3.22
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2.82
2.79
2.78
2.20
2.18
2.15
2.13
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1.41
1.39
1.09
1.07
O
OH
^{t}BuO$_2$C
CN
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1.10
1.13
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3.00
9.0
8.5
8.0
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7.0
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6.0
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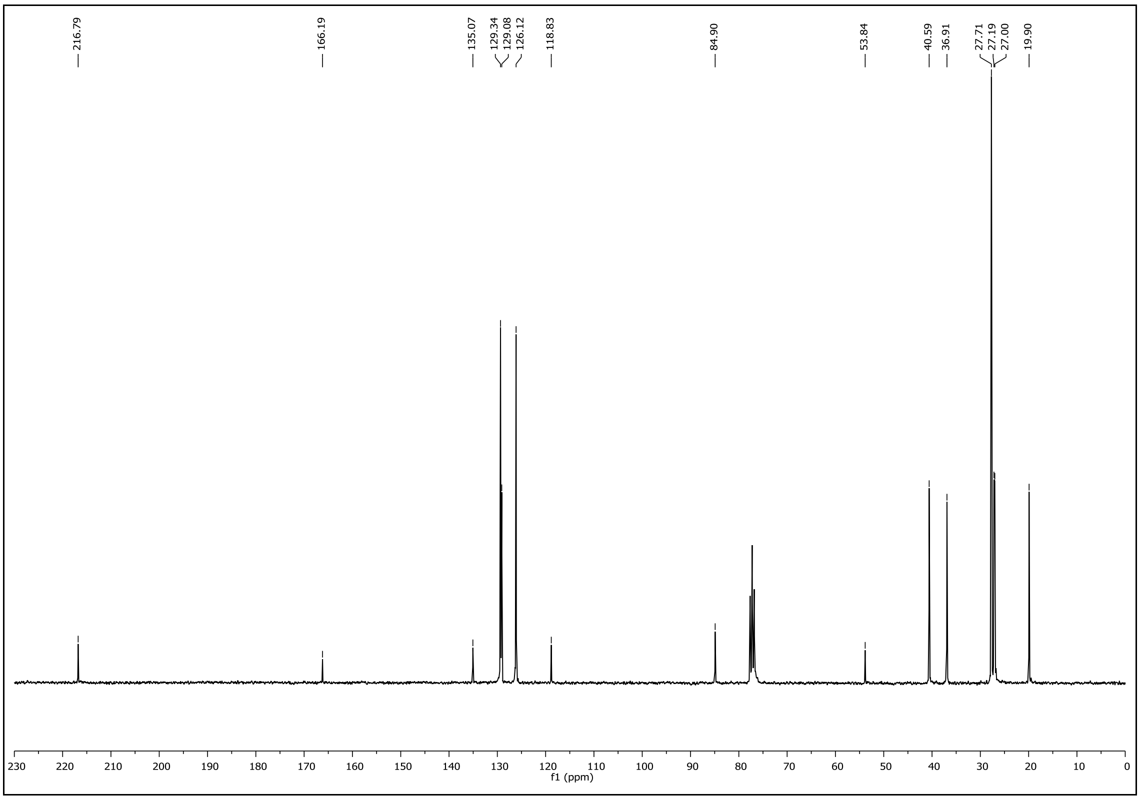
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180
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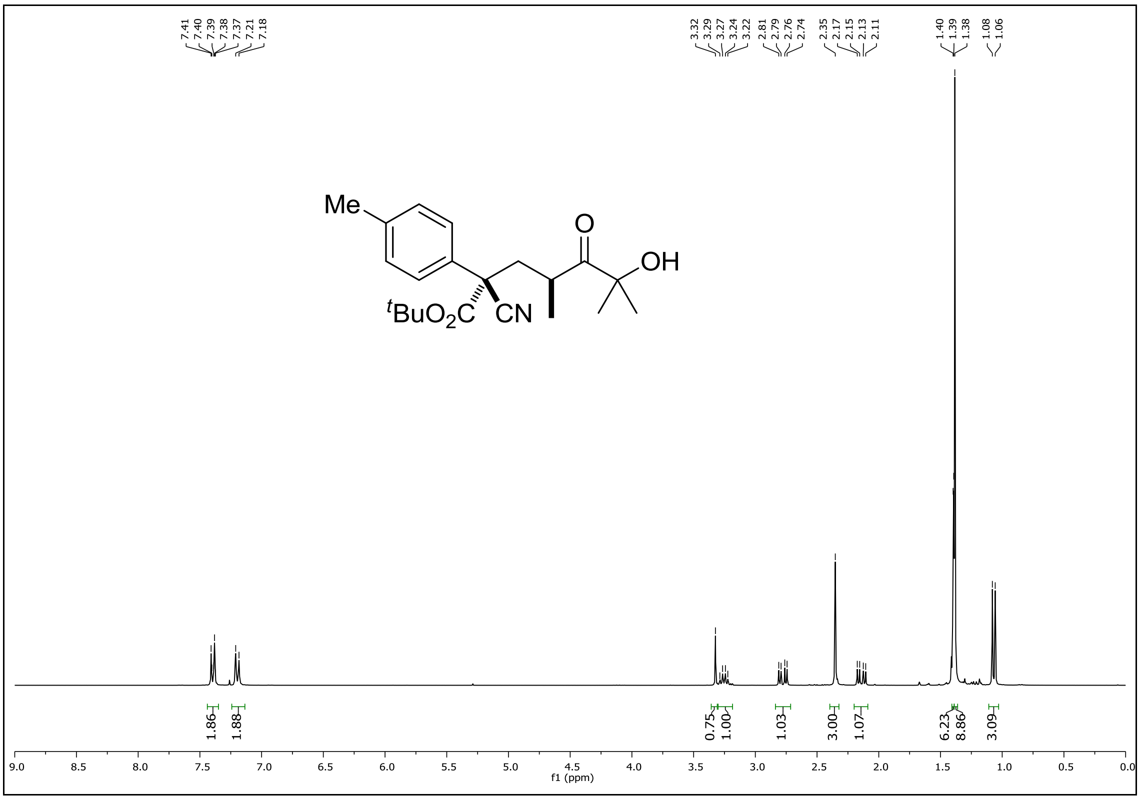
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2.79
2.76
2.74
2.35
2.17
2.15
2.13
2.11
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1.39
1.38
1.08
1.06
Me
O
OH
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CN
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3.00
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6.23
8.86
3.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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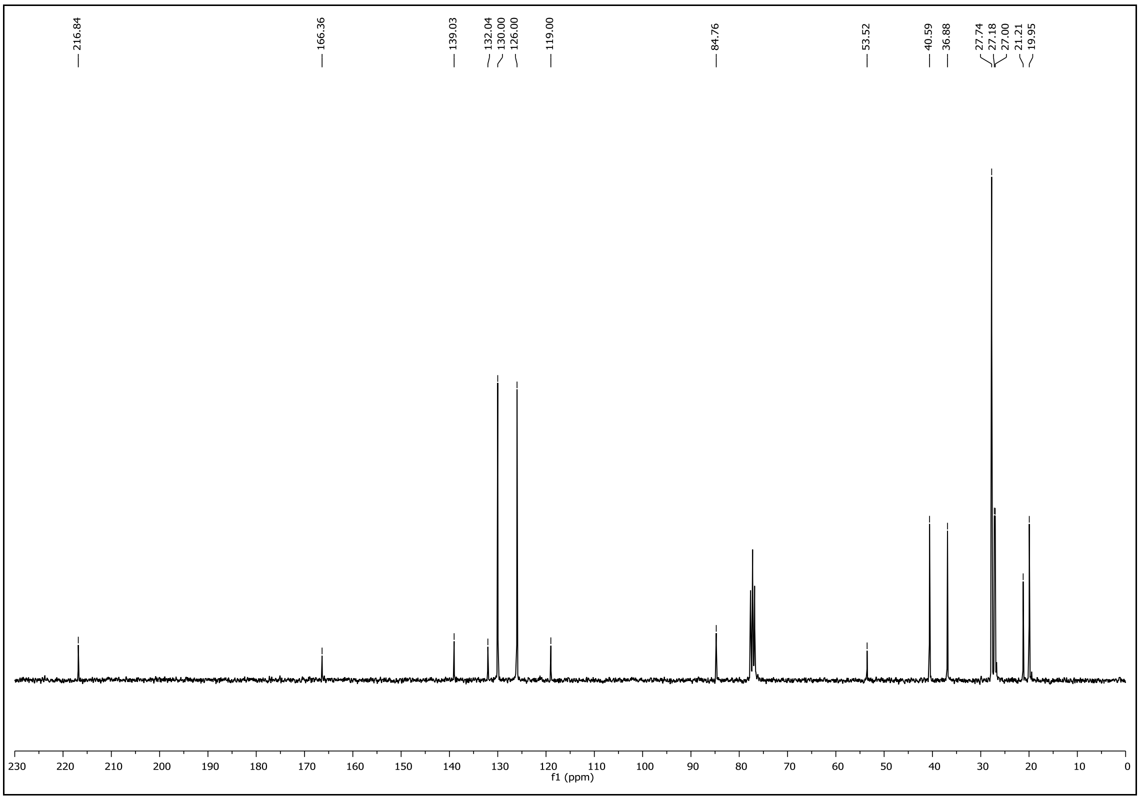
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200
190
180
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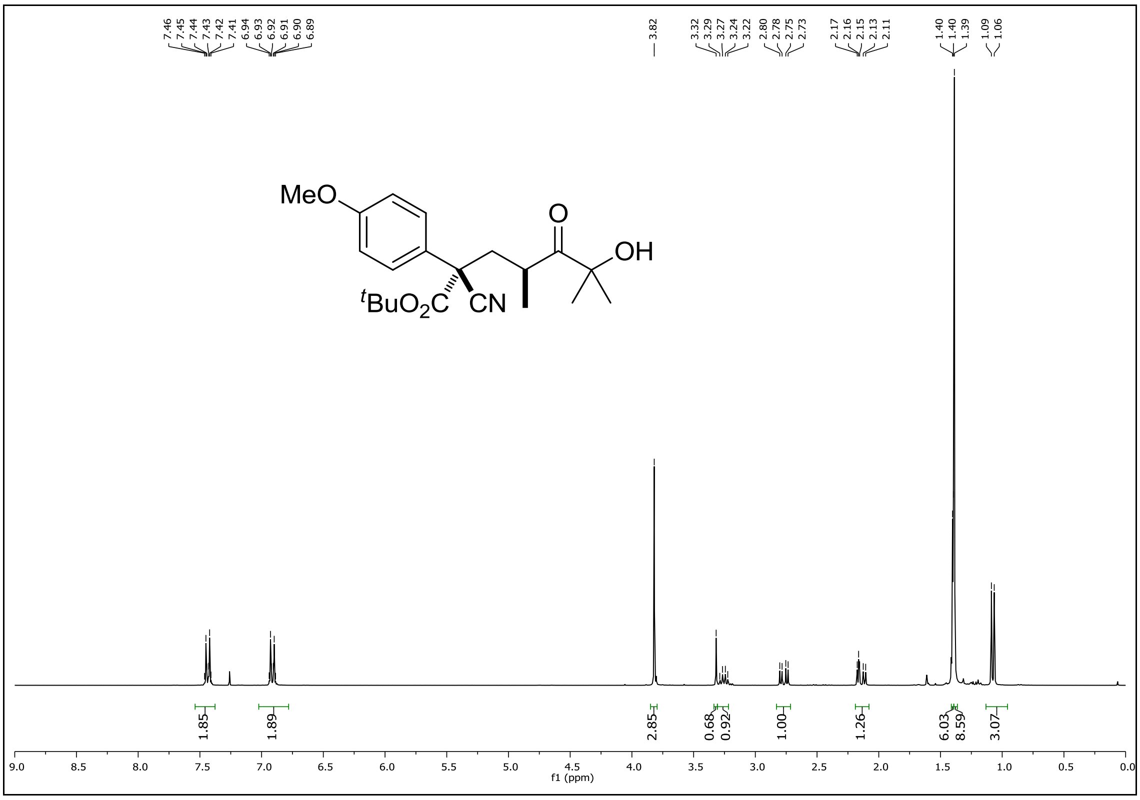
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3.32
3.29
3.27
3.24
3.22
2.80
2.78
2.75
2.73
2.17
2.16
2.15
2.13
2.11
1.40
1.40
1.39
1.09
1.06
MeO
O
OH
$^tBuO_2C$
CN
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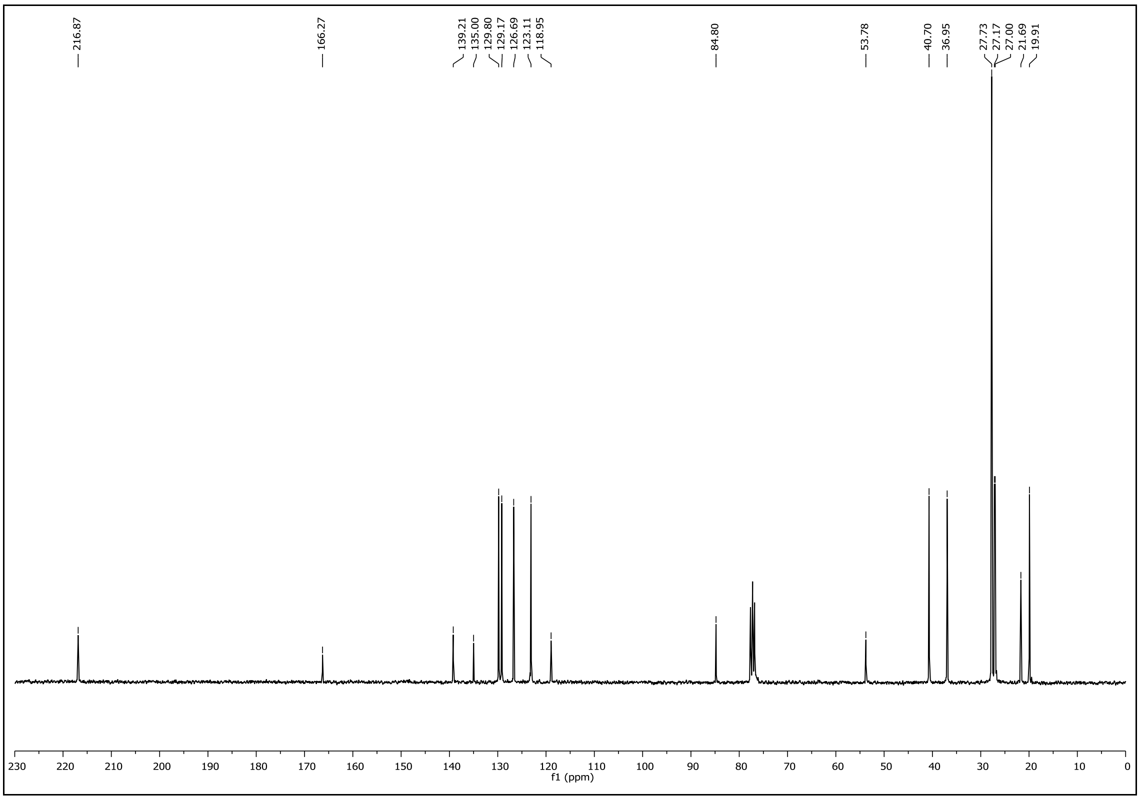
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200
190
180
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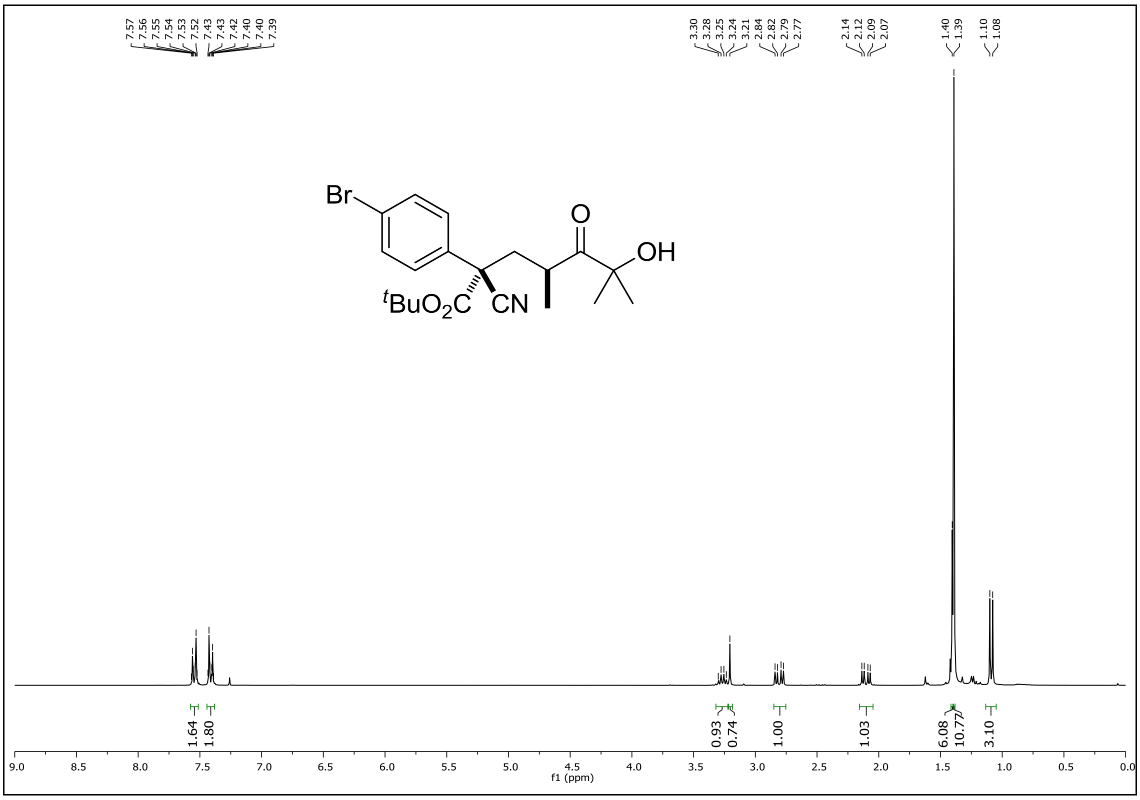
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3.28
3.25
3.24
3.21
2.84
2.82
2.79
2.77
2.14
2.12
2.09
2.07
1.40
1.39
1.10
1.08
Br
O
OH
^{t}BuO$_2$C
CN
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1.80
0.93
0.74
1.00
1.03
6.08
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8.0
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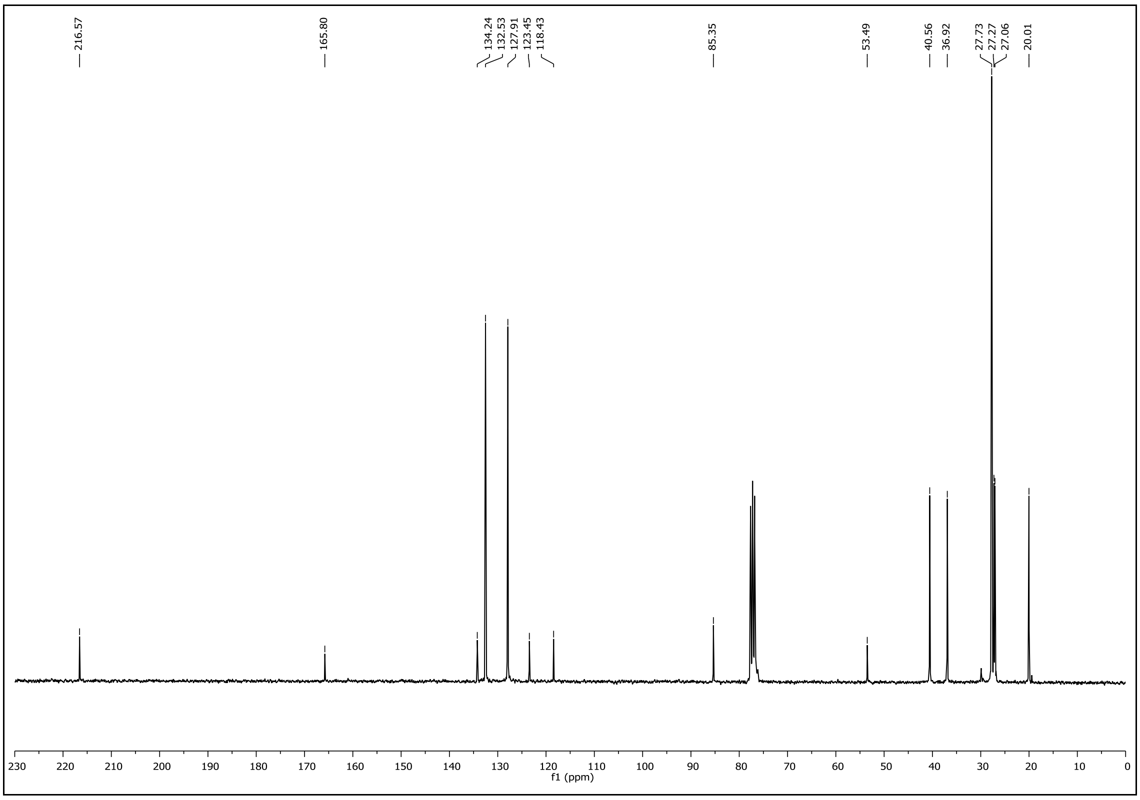
f1 (ppm)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20.01
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180
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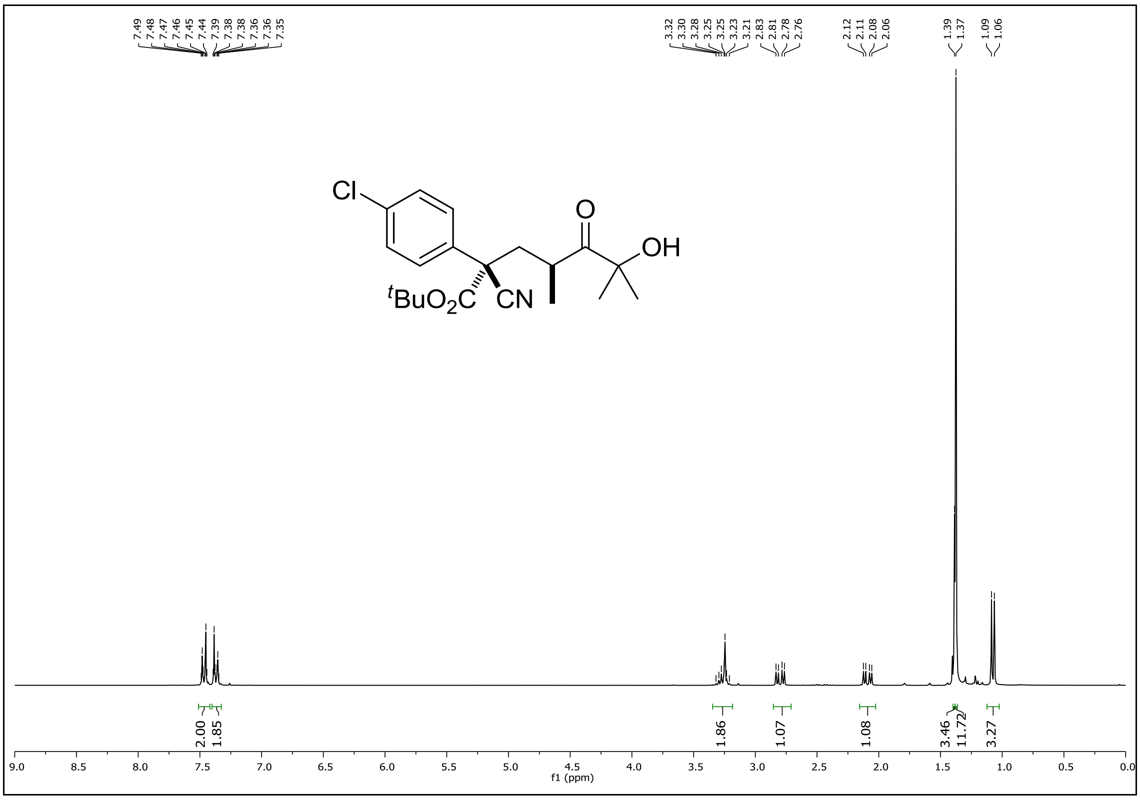
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3.25
3.25
3.23
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2.78
2.76
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2.11
2.08
2.06
1.39
1.37
1.09
1.06
Cl
O
OH
tBuO2C
CN
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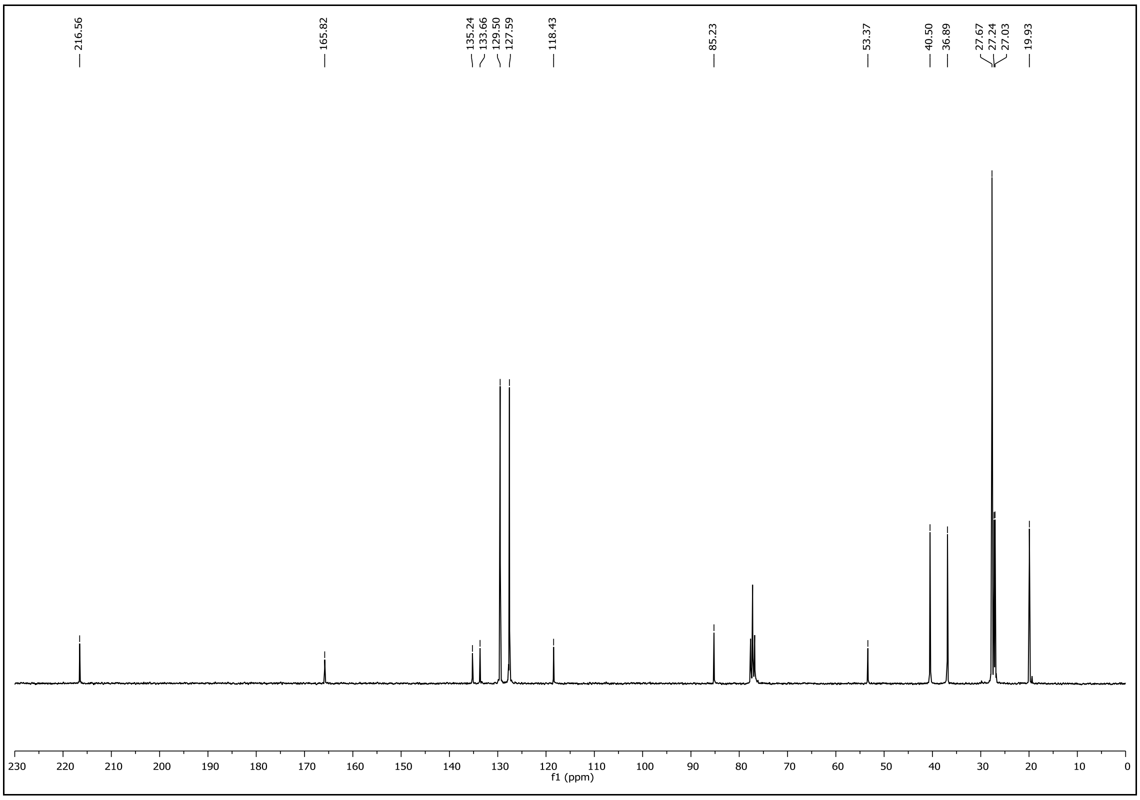
f1 (ppm)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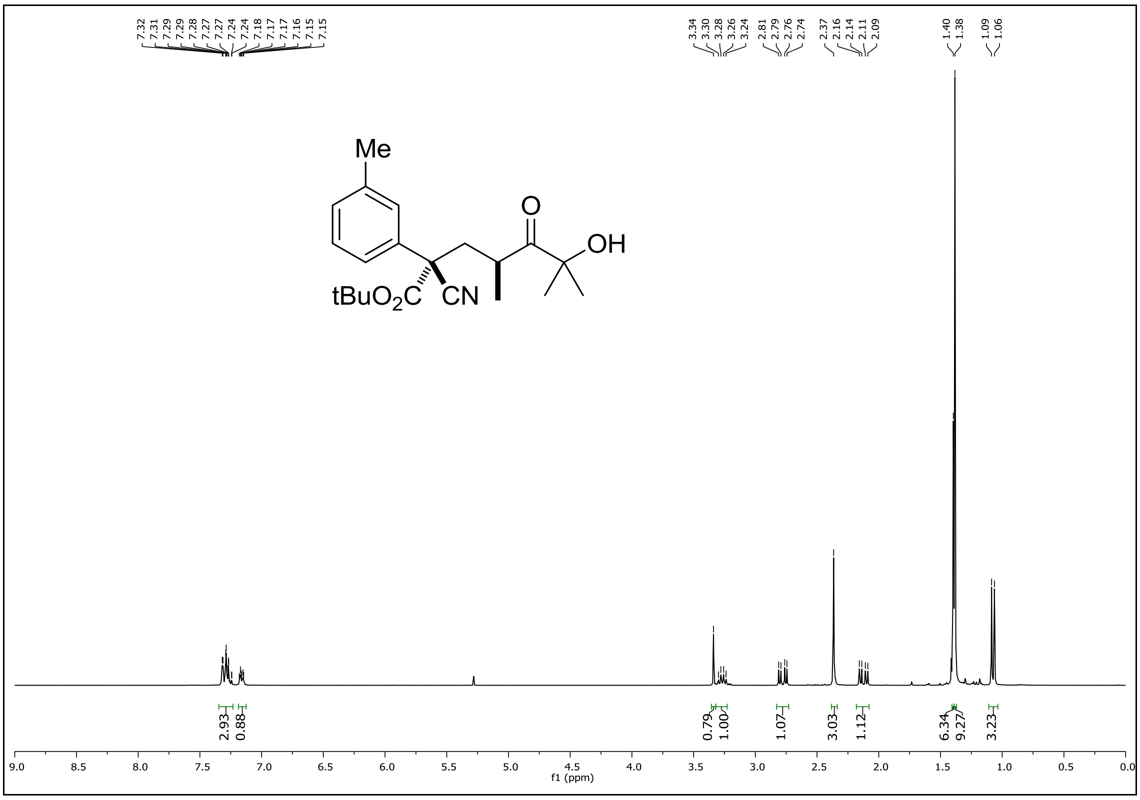
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3.24
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1.09
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OH
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CN
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1.07
3.03
1.12
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3.23
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6.0
5.5
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2.0
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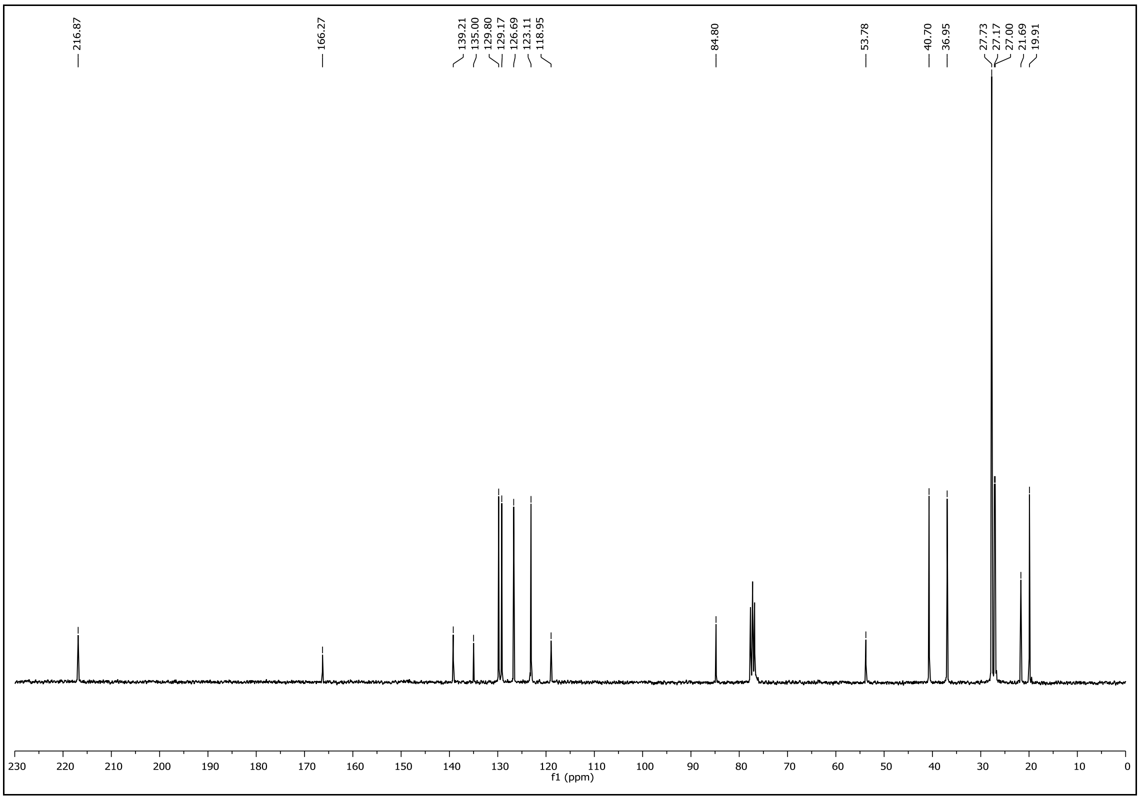
f1 (ppm)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200
190
180
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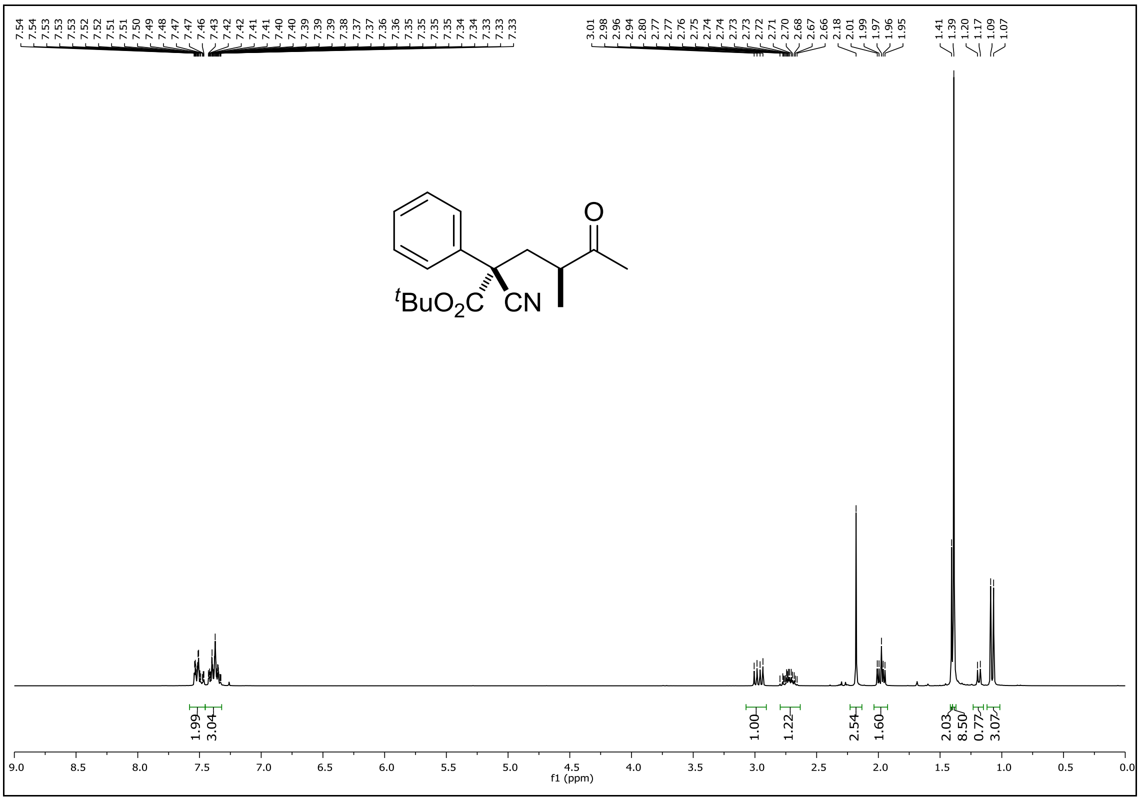
f1 (ppm)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1.95
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1.09
1.07
O
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CN
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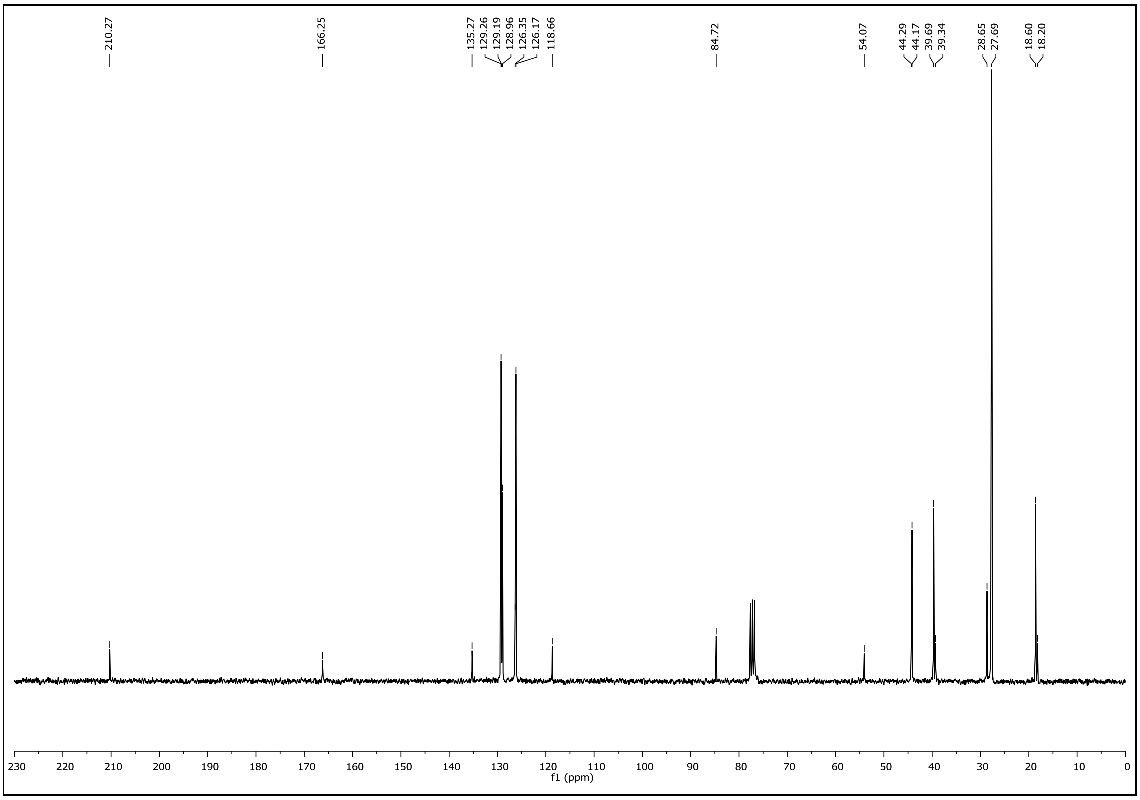
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200
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180
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50
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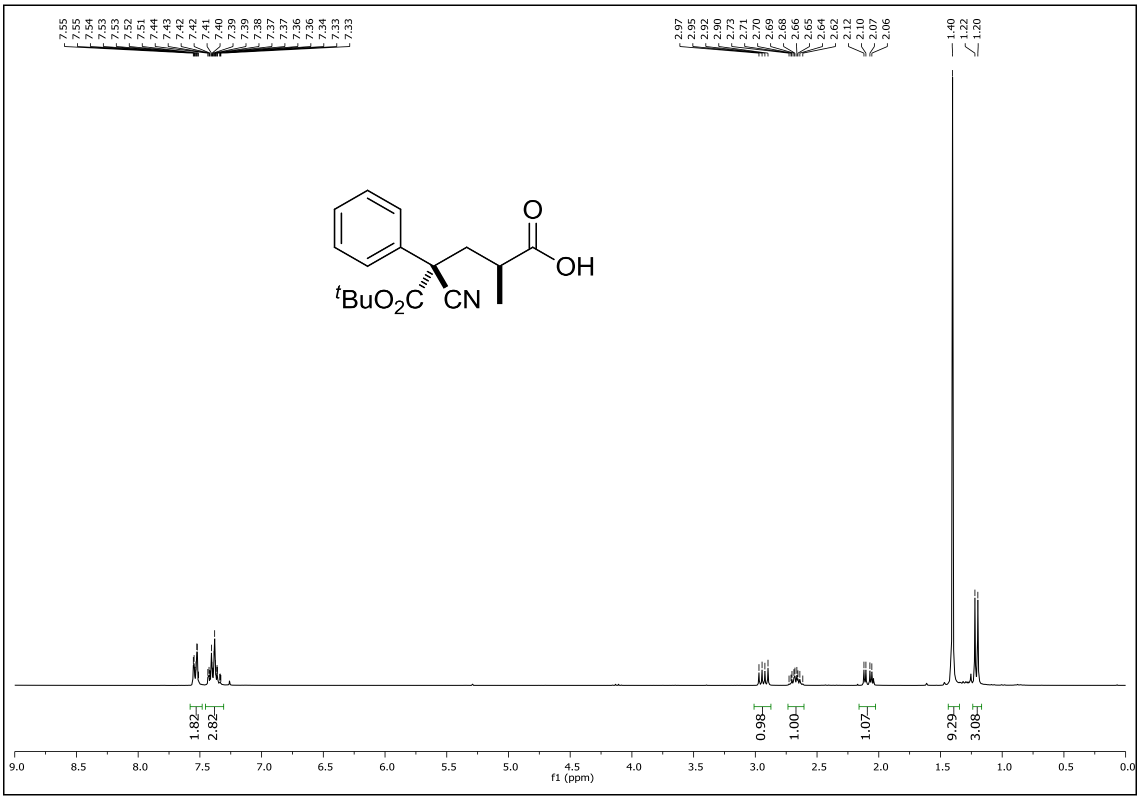
f1 (ppm)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7.39
7.39
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7.37
7.37
7.36
7.34
7.33
7.33
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2.95
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2.90
2.73
2.71
2.70
2.69
2.68
2.66
2.65
2.64
2.62
2.12
2.10
2.07
2.06
1.40
1.22
1.20
O
OH
^{t}BuO$_2$C
CN
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2.82
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1.00
1.07
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3.08
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7.5
7.0
6.5
6.0
5.5
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2.0
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1.0
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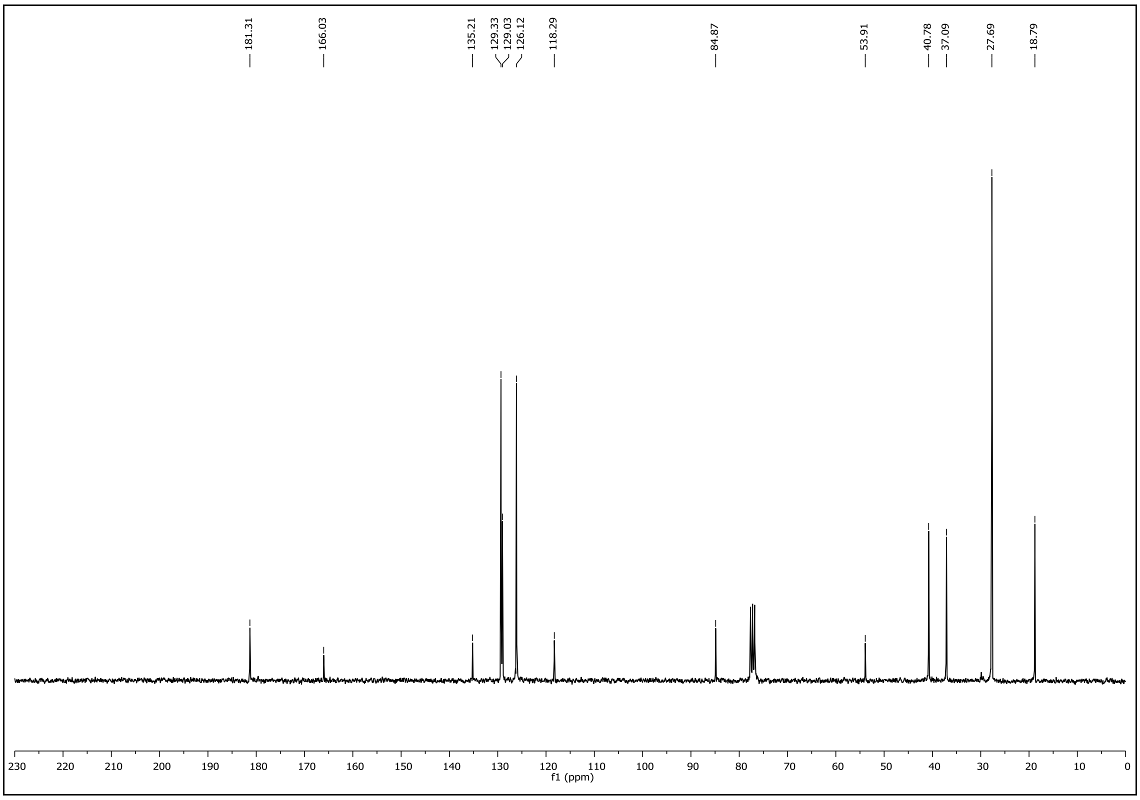
0.0
f1 (ppm)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230
220
210
200
190
180
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70
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50
40
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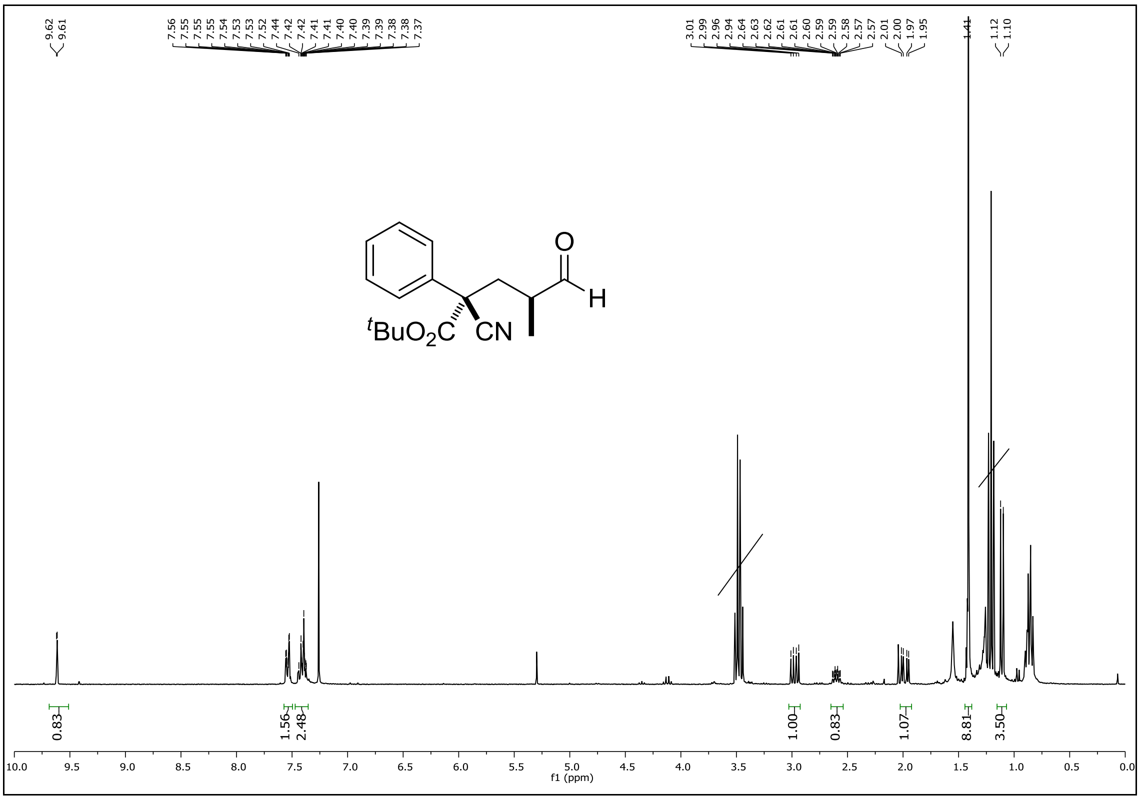
10
0
f1 (ppm)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7.40
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7.39
7.38
7.38
7.37
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2.99
2.96
2.94
2.64
2.63
2.62
2.61
2.61
2.60
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2.58
2.57
2.57
2.01
2.00
1.97
1.95
1.41
1.12
1.10
O
H
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8.81
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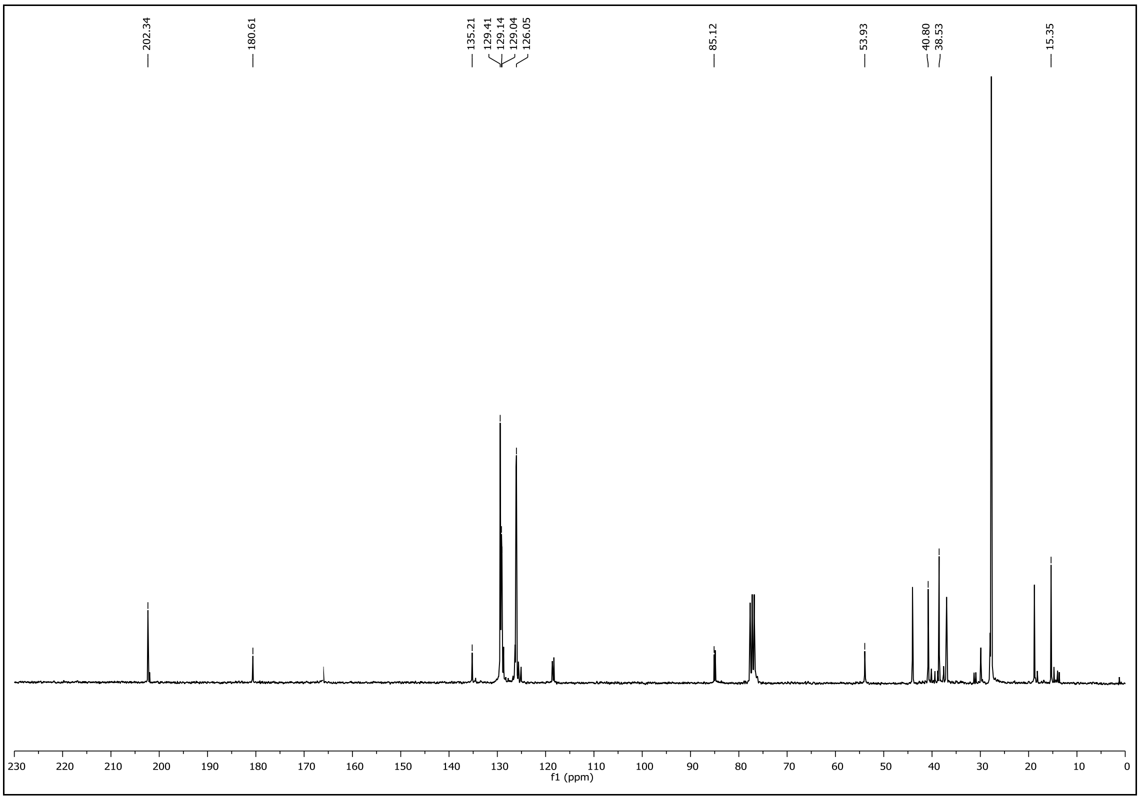
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85.12
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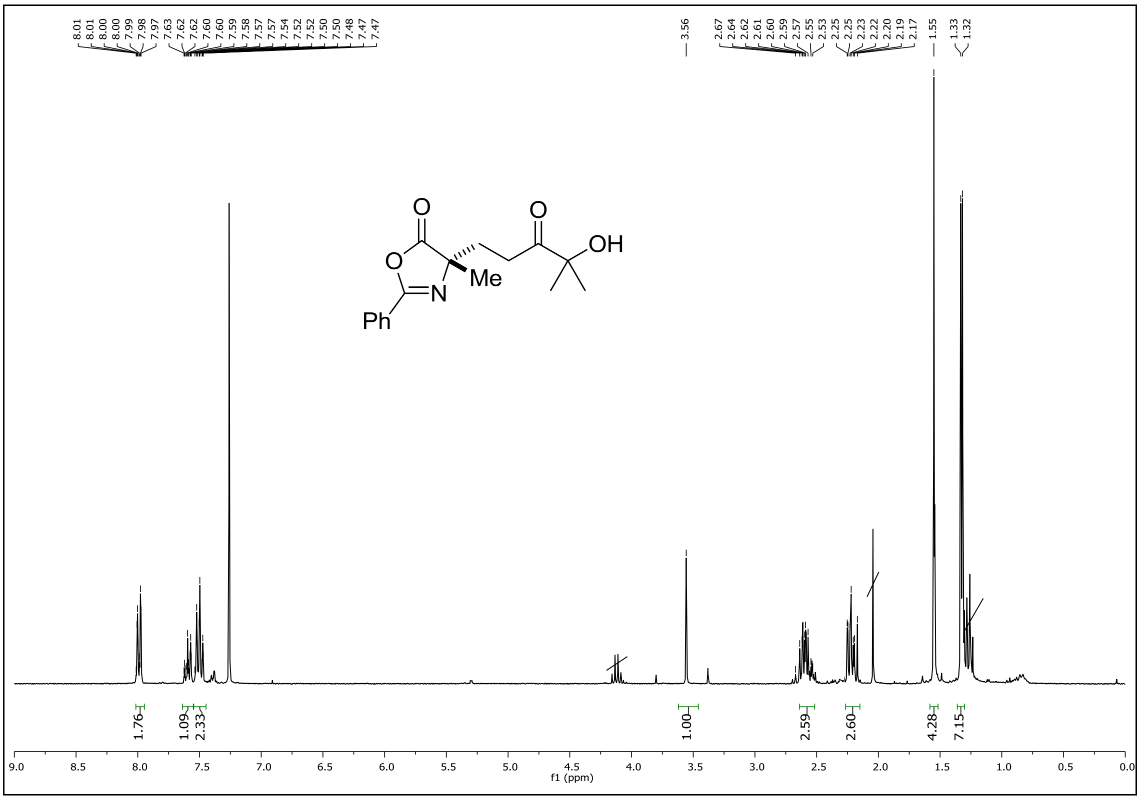
38.53
15.35
f1 (ppm)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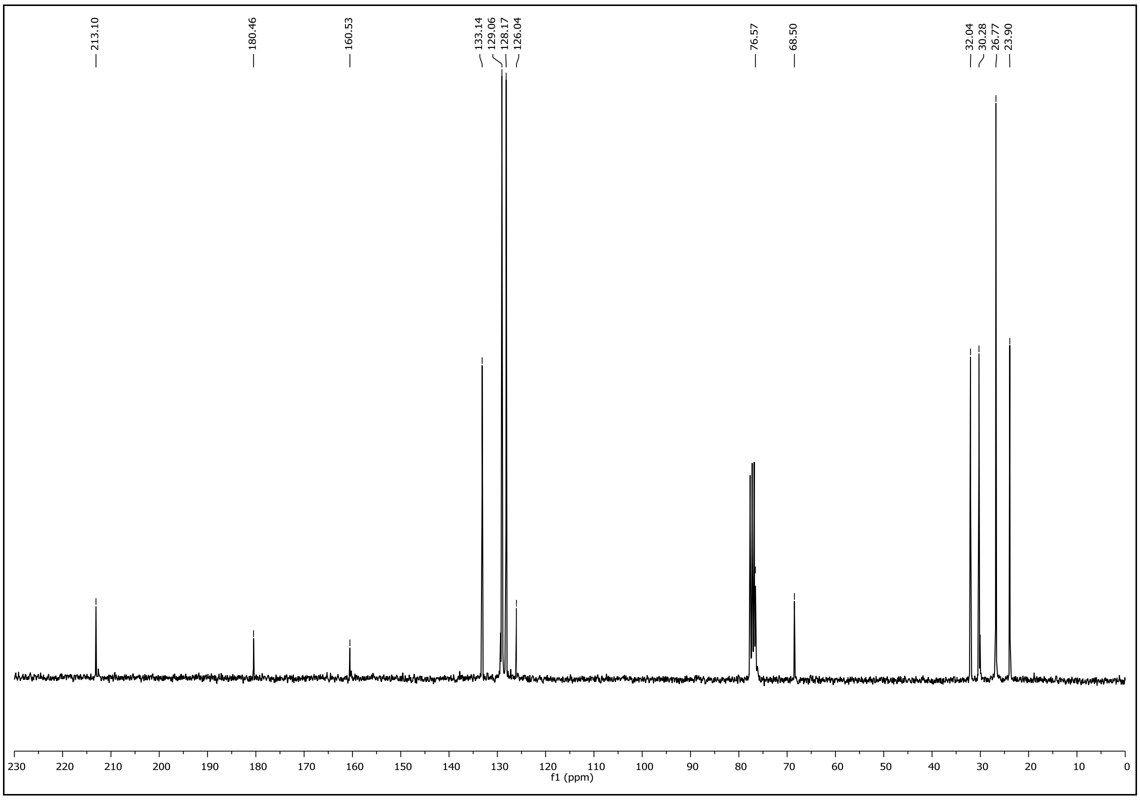
3.56
2.67 2.64 2.62 2.61 2.60 2.59 2.57 2.55 2.53 2.25 2.25 2.23 2.22 2.20 2.19 2.17
1.55
1.33 1.32
O
O
OH
O
N
Me
Ph
1.76
1.09
2.33
1.00
2.59
2.60
4.28
7.15
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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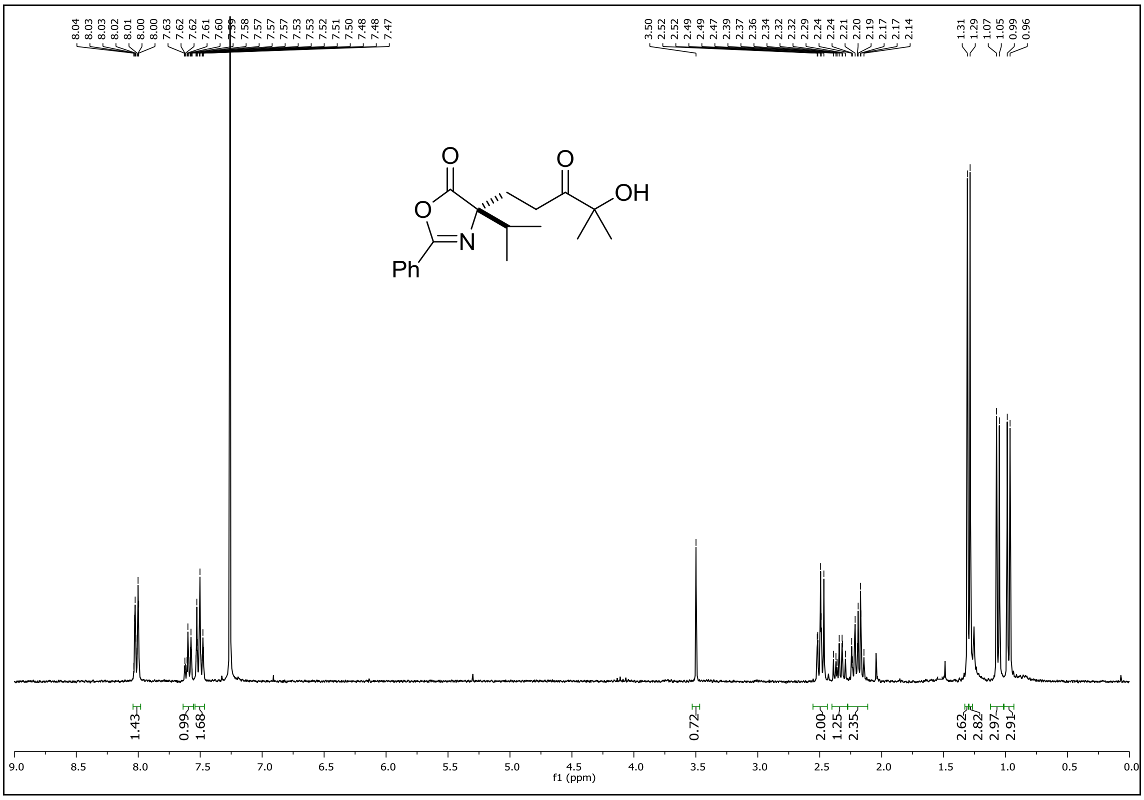
133.14 129.06 128.17 126.04
76.57
68.50
32.04 30.28 26.77 23.90
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.62
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7.58
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7.52
7.51
7.50
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3.50
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2.52
2.49
2.49
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2.32
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2.24
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2.19
2.17
2.17
2.14
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1.29
1.07
1.05
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0.96
O
O
OH
O
N
Ph
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9.0
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7.5
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6.5
6.0
5.5
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4.5
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3.5
3.0
2.5
2.0
1.5
1.0
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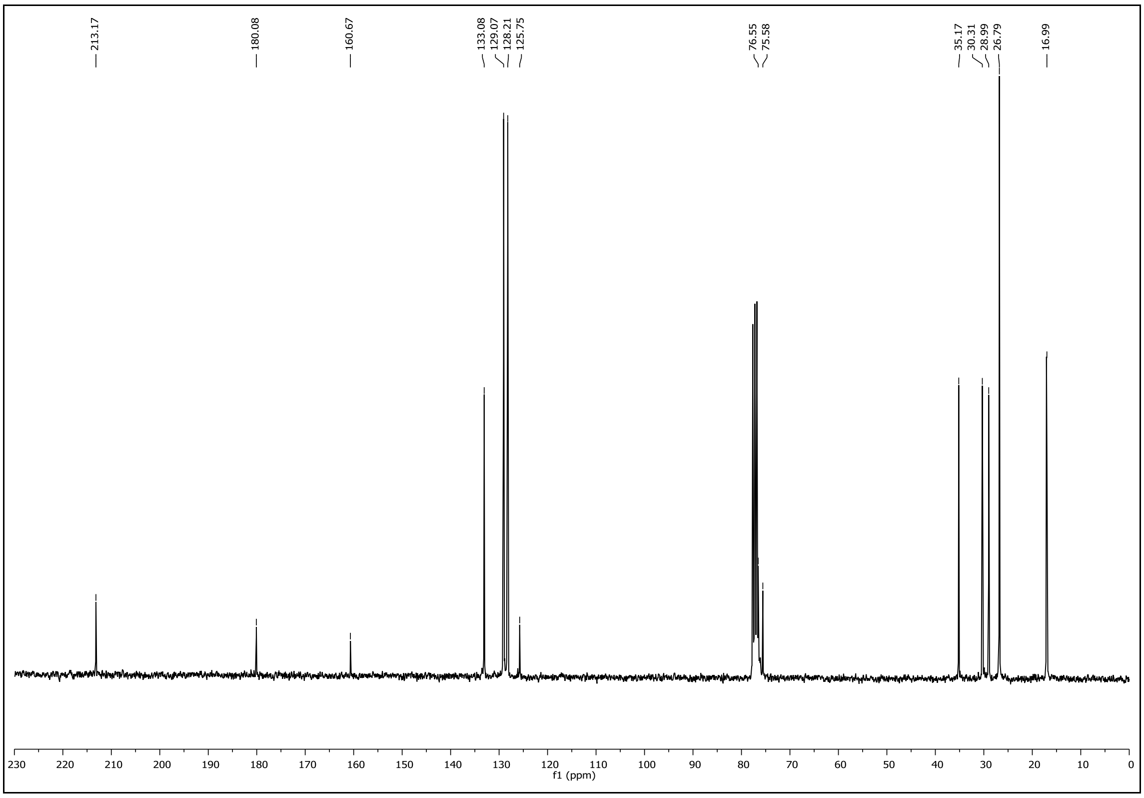
0.0
f1 (ppm)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200
190
180
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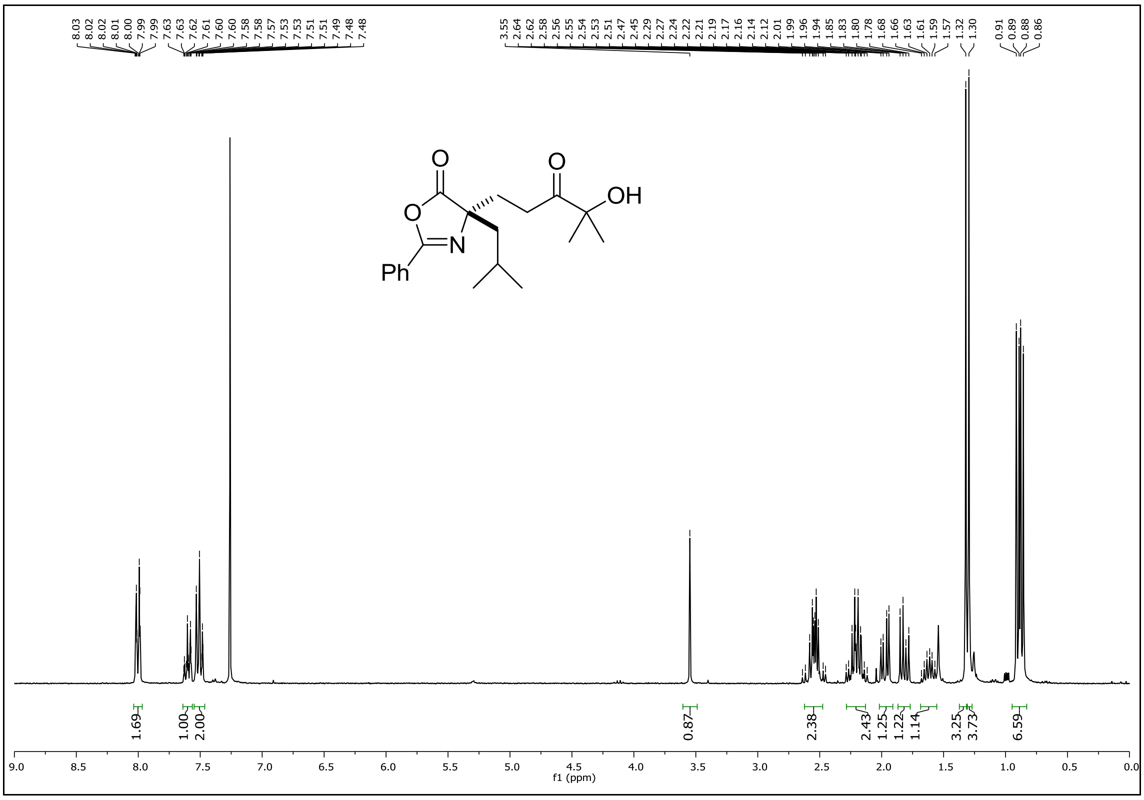
0
f1 (ppm)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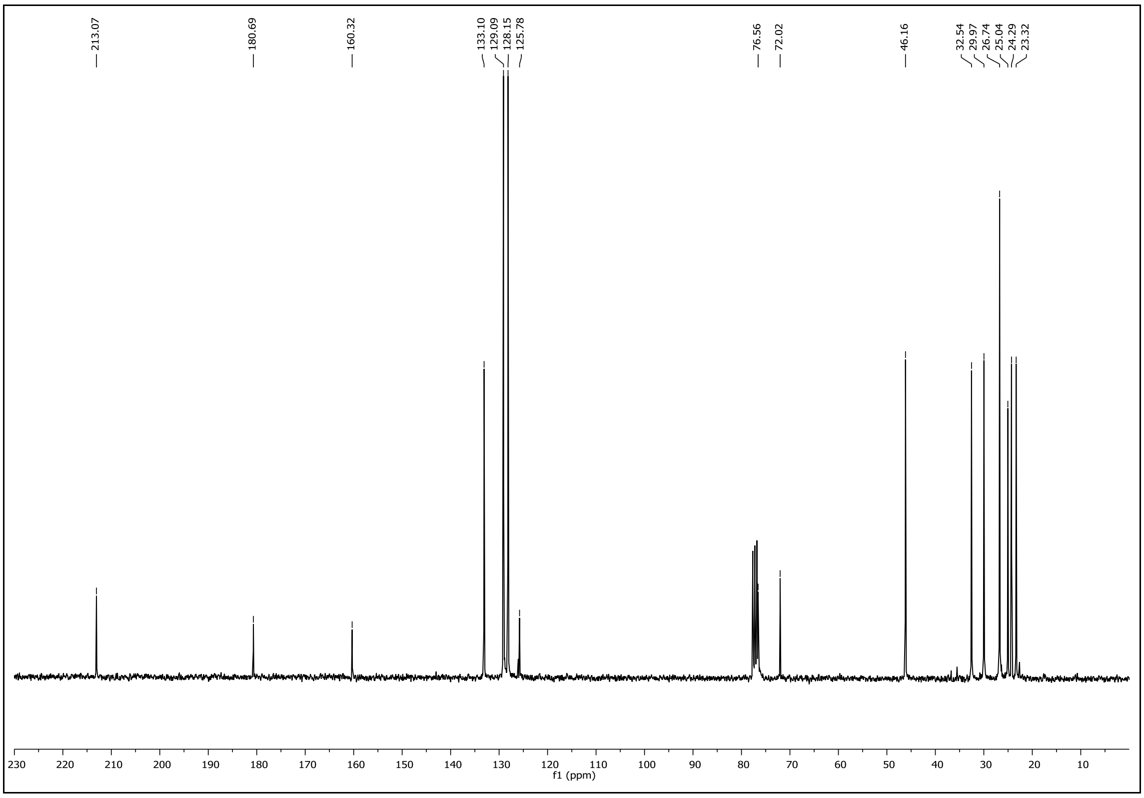
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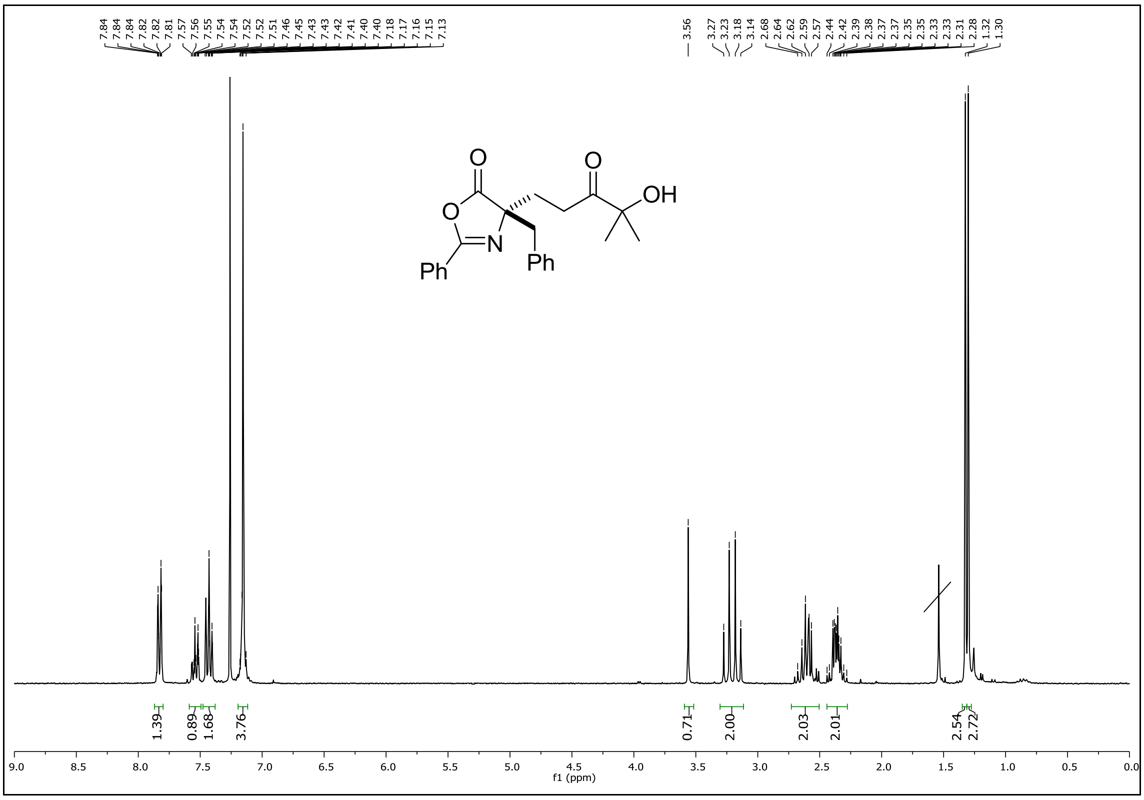
f1 (ppm)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3.56
3.27 3.23 3.18 3.14 2.68 2.64 2.62 2.59 2.57 2.44 2.42 2.39 2.38 2.37 2.37 2.35 2.35 2.33 2.33 2.31 2.28 1.32 1.30
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Ph
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2.01
2.54
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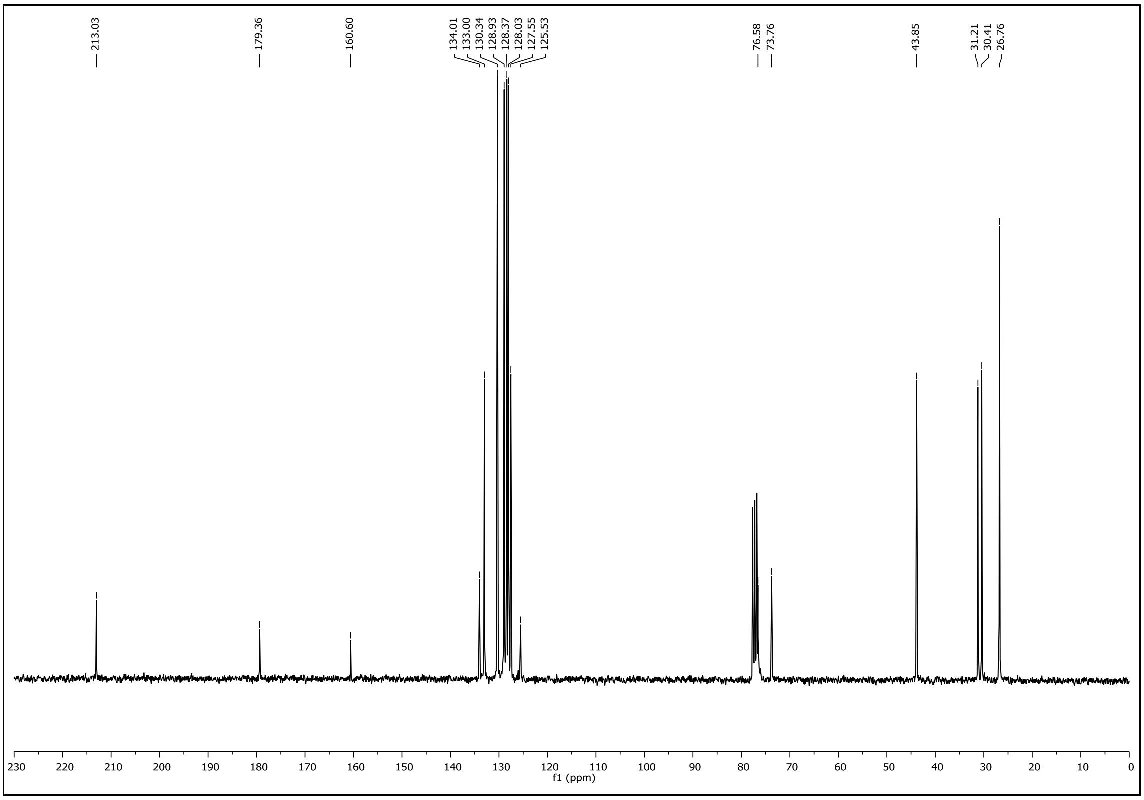
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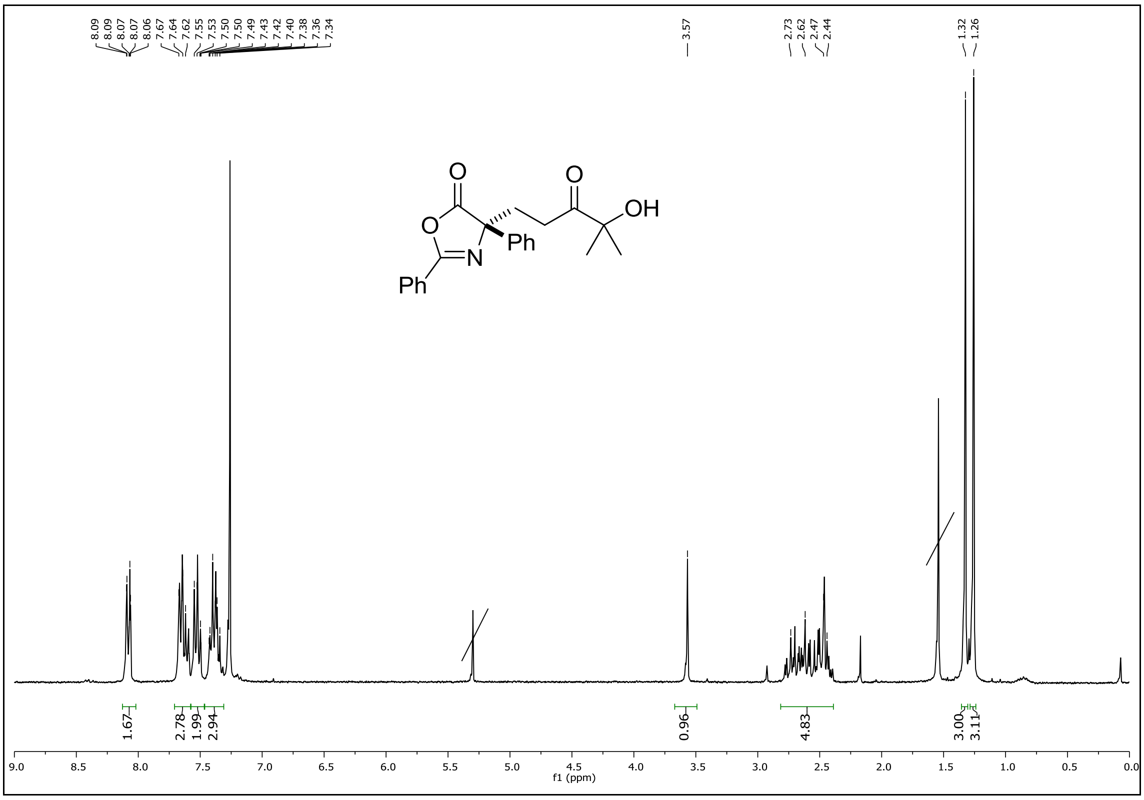
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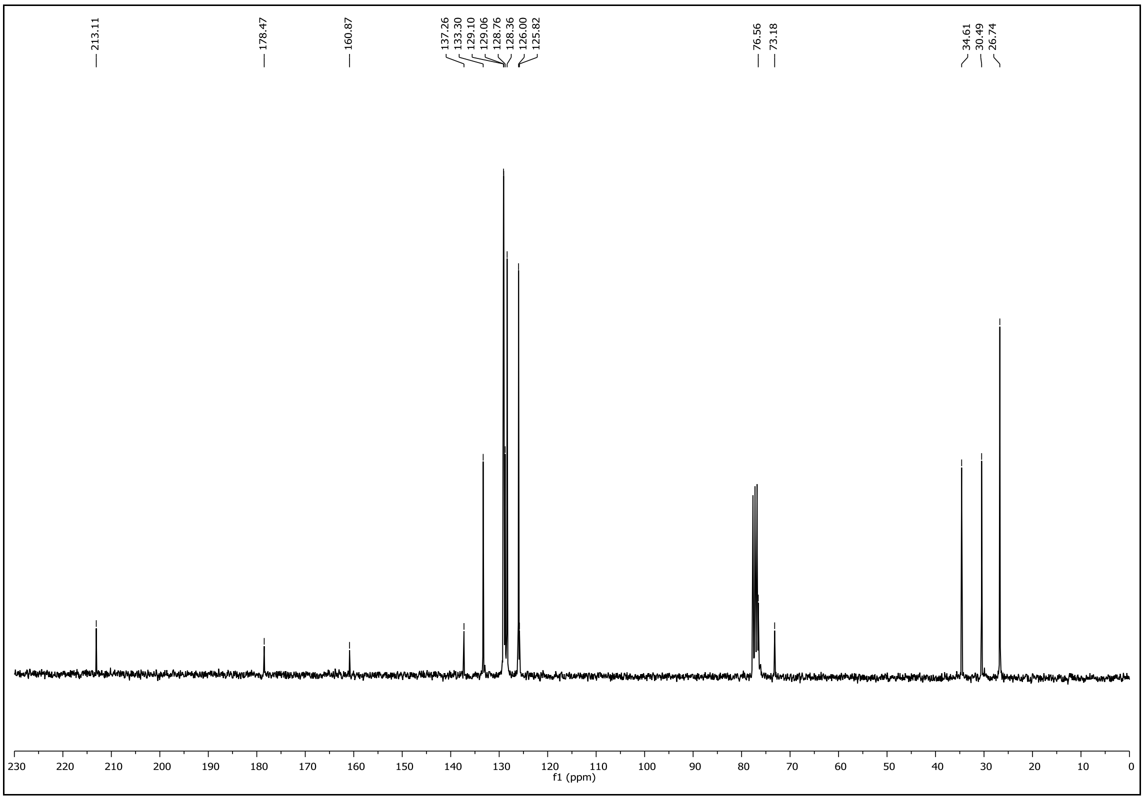
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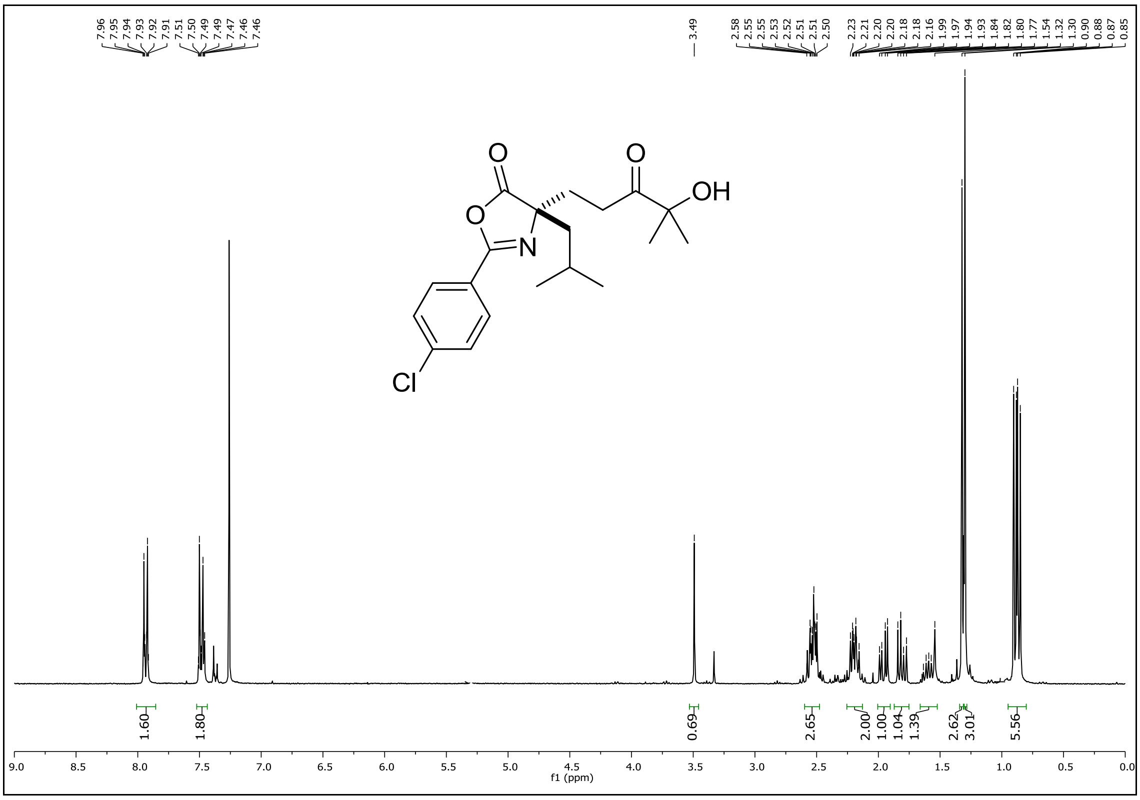
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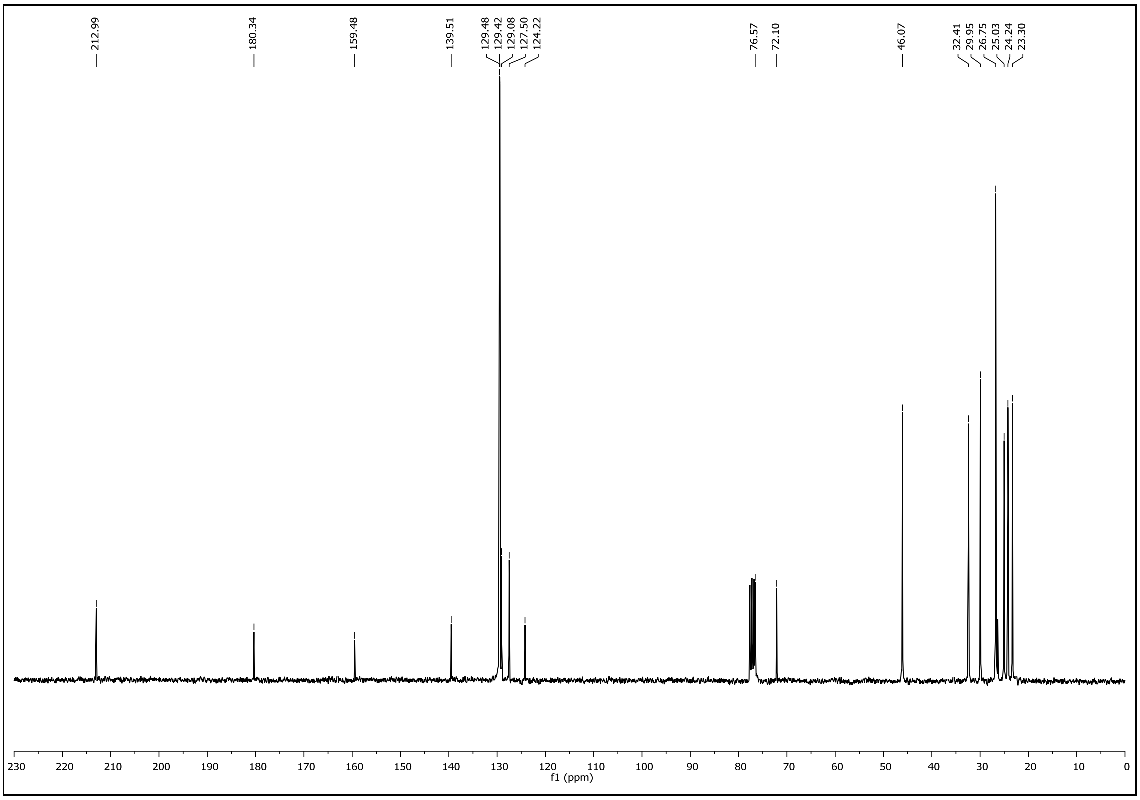
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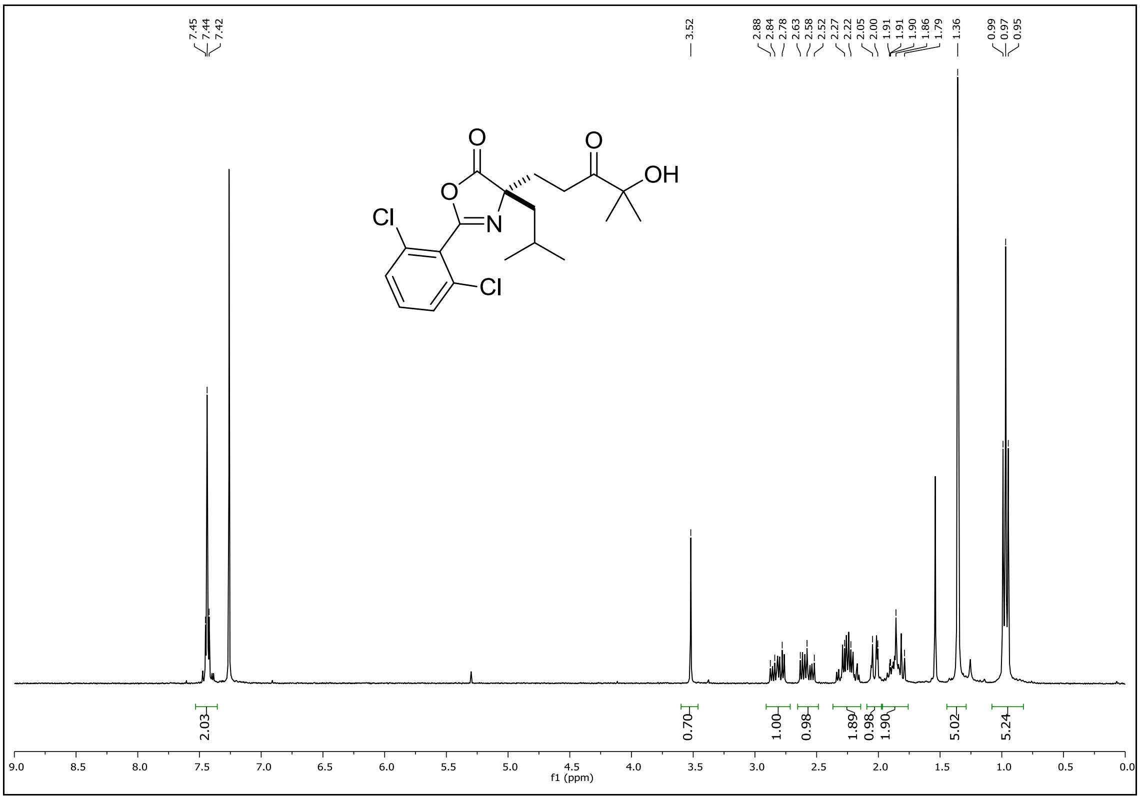
f1 (ppm)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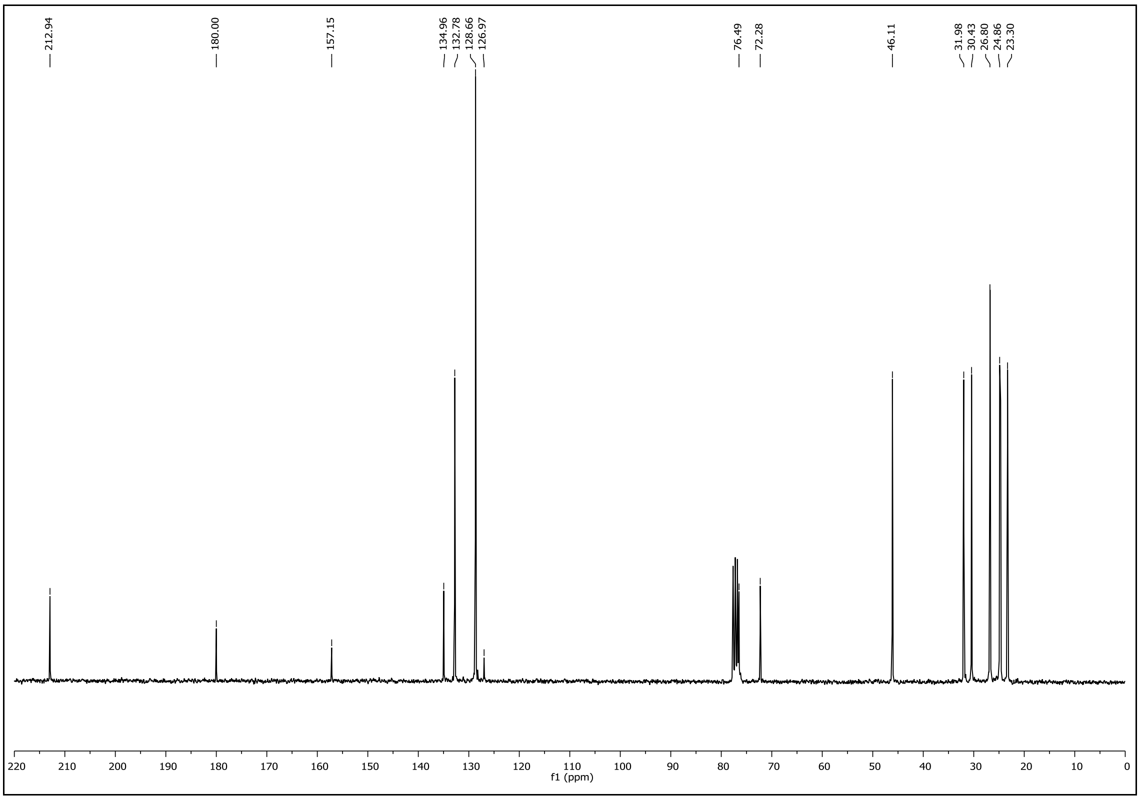
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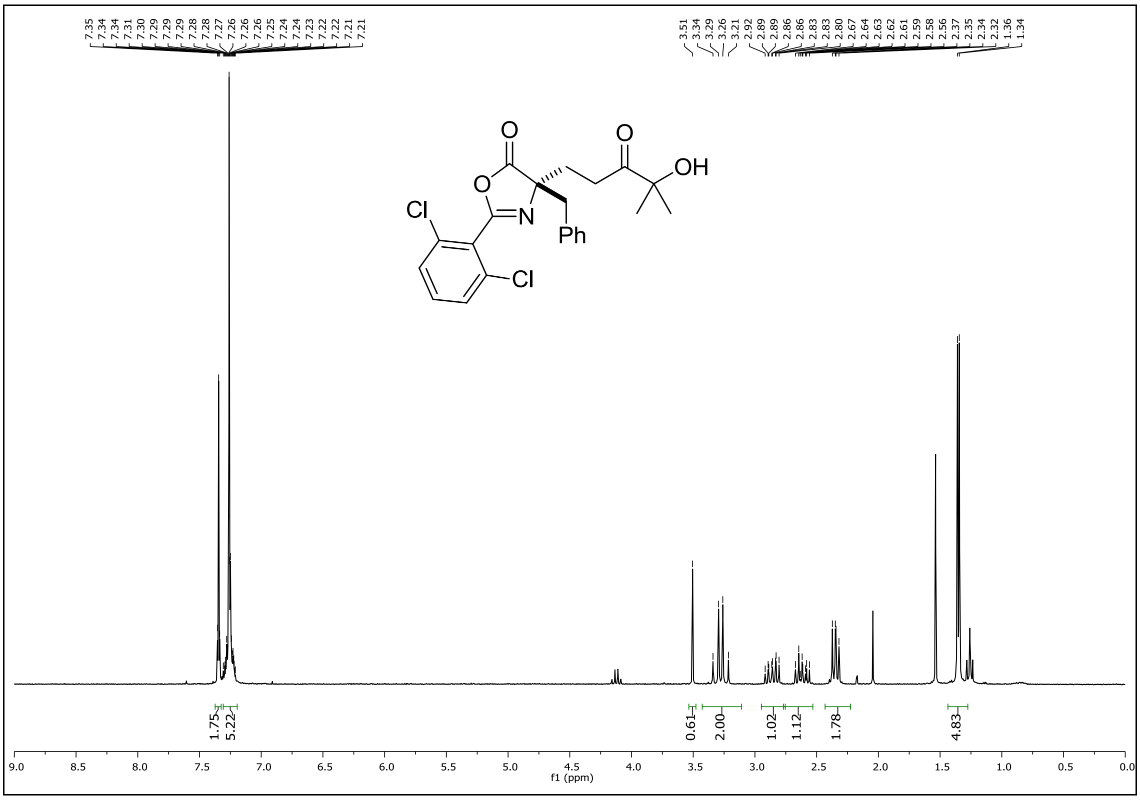
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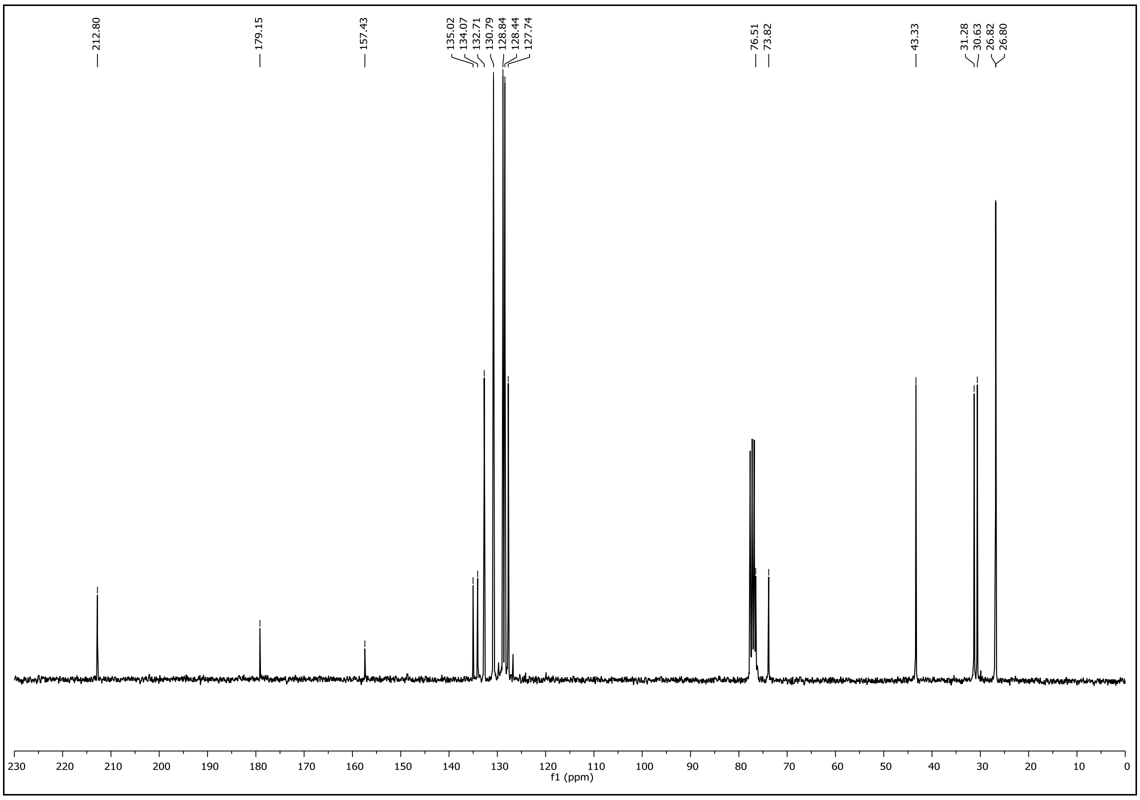
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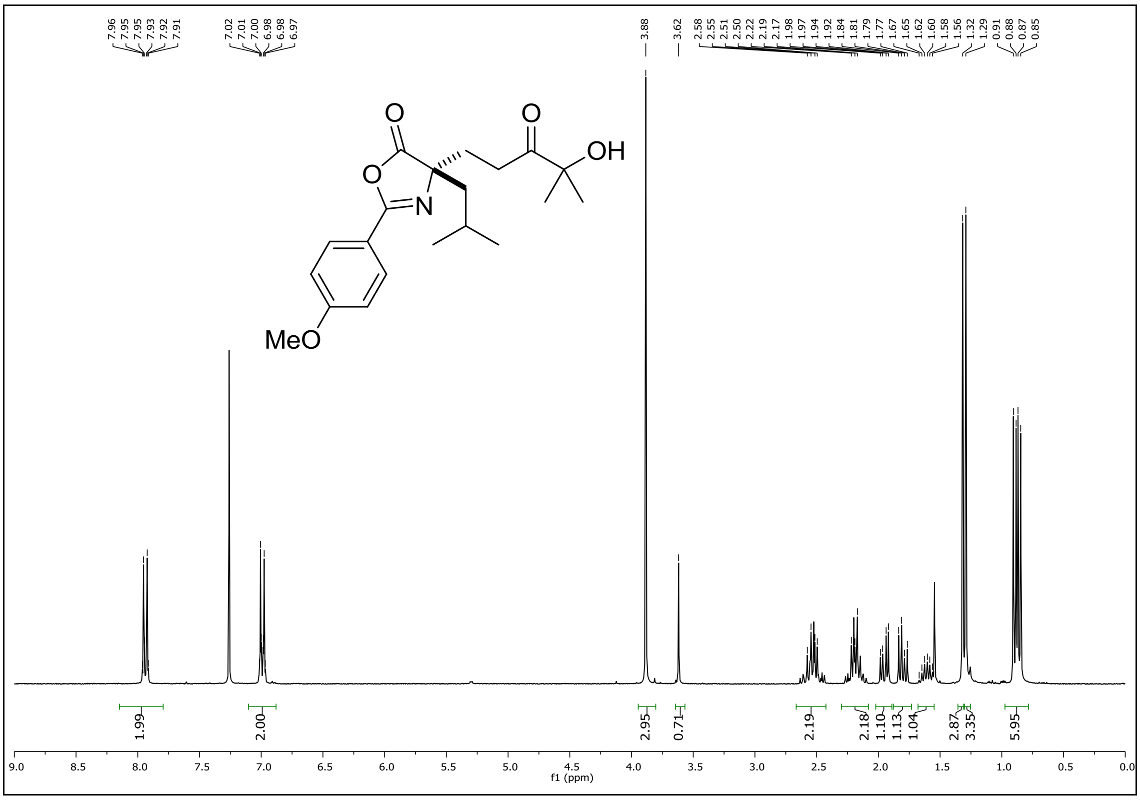
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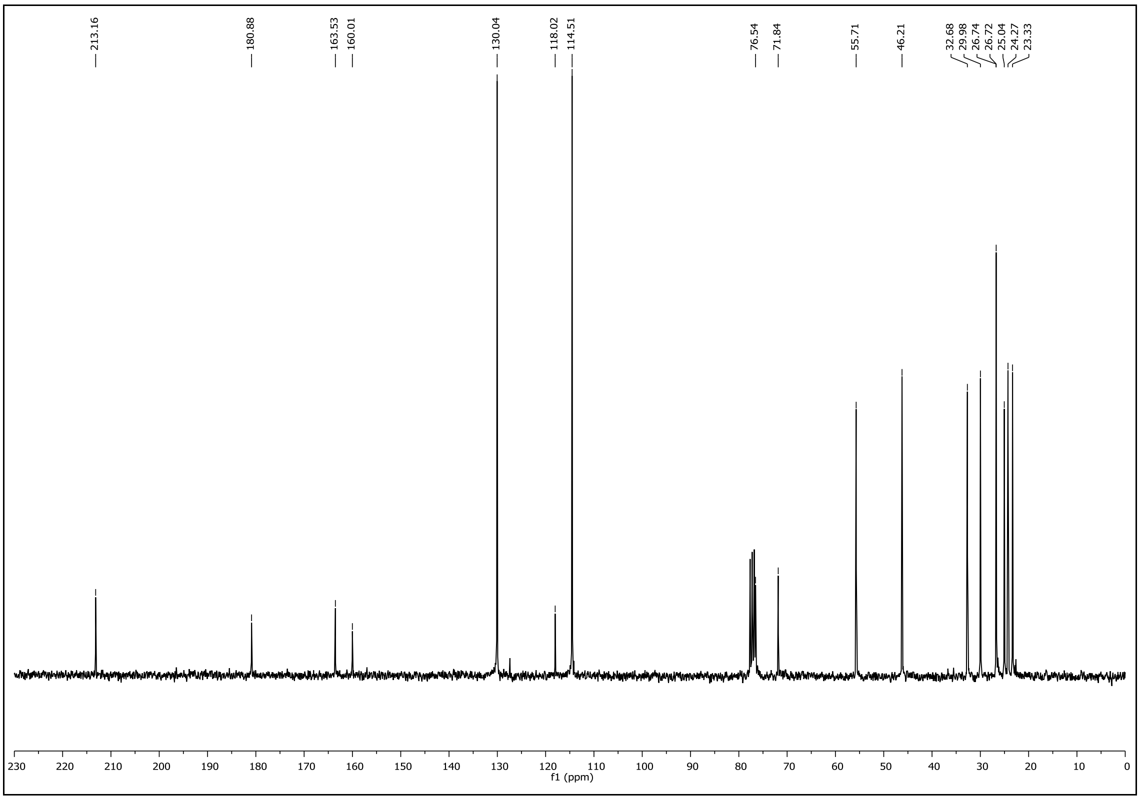
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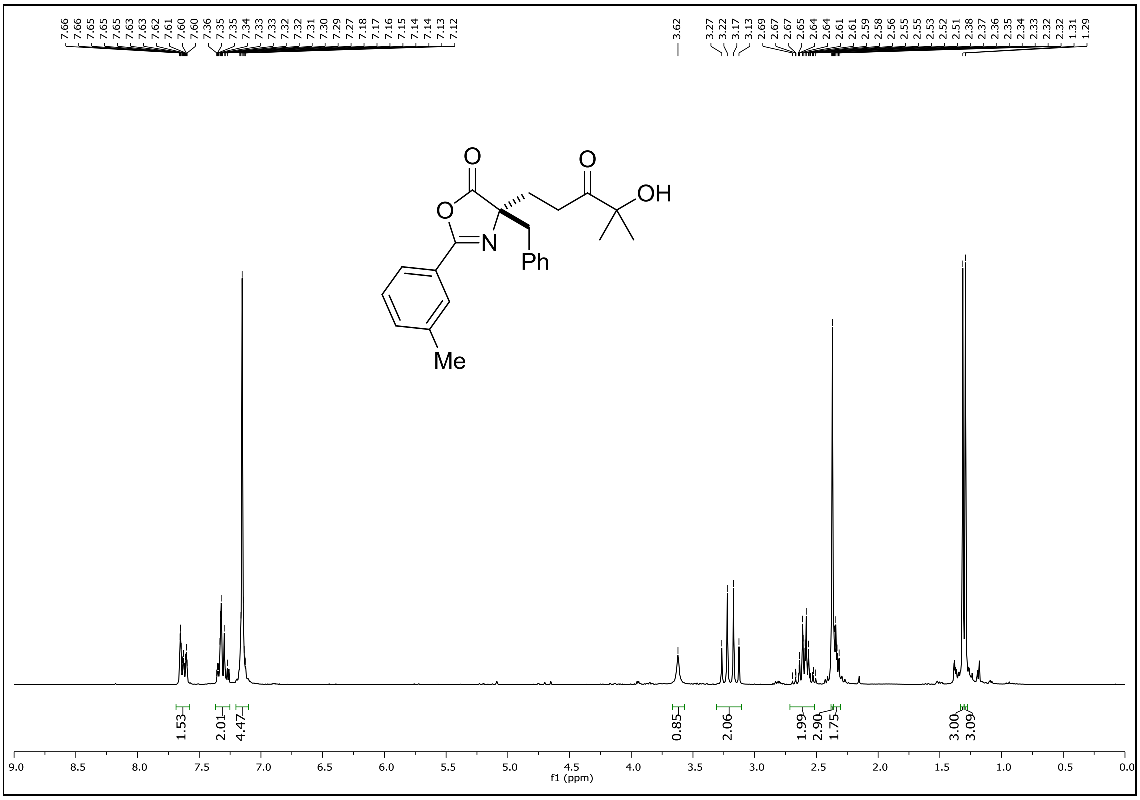
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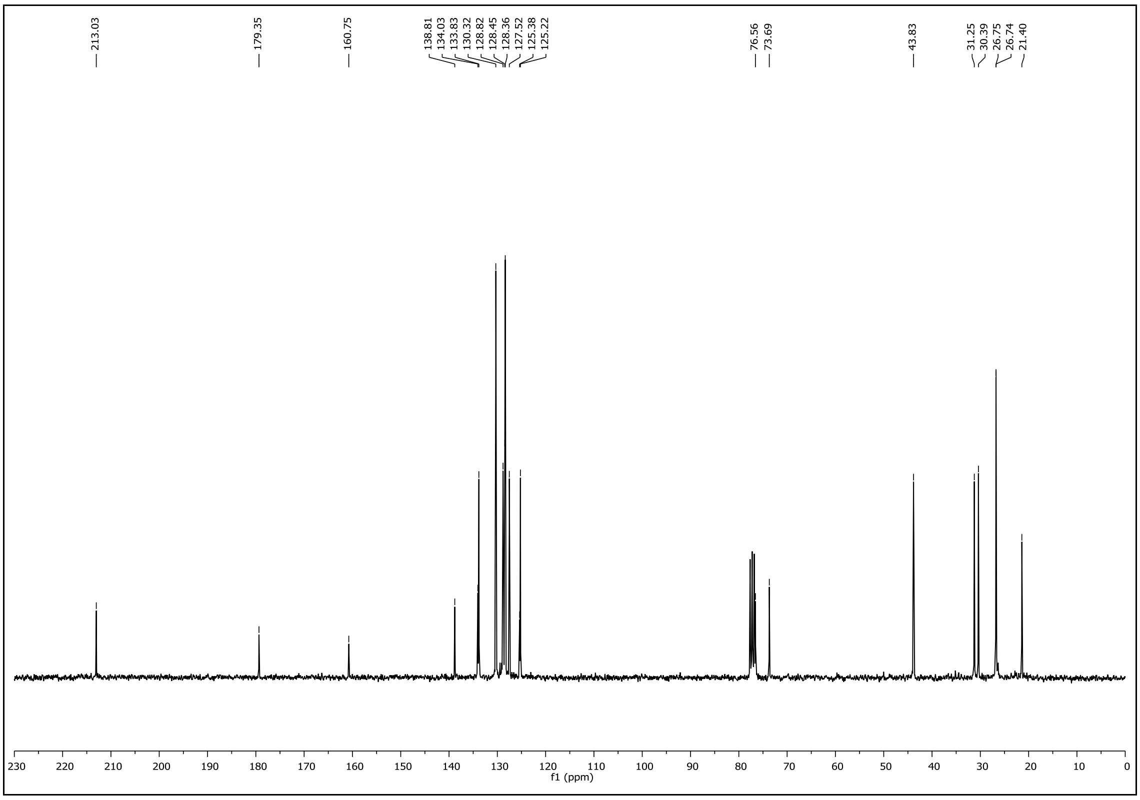
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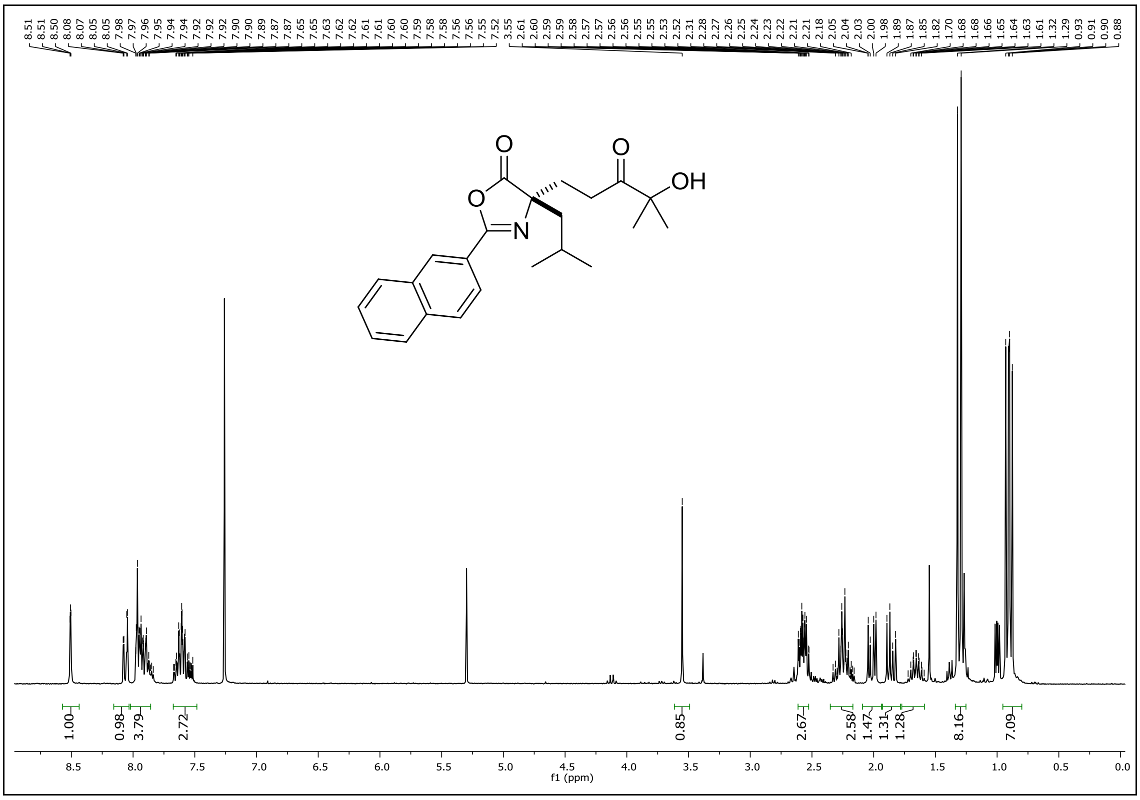
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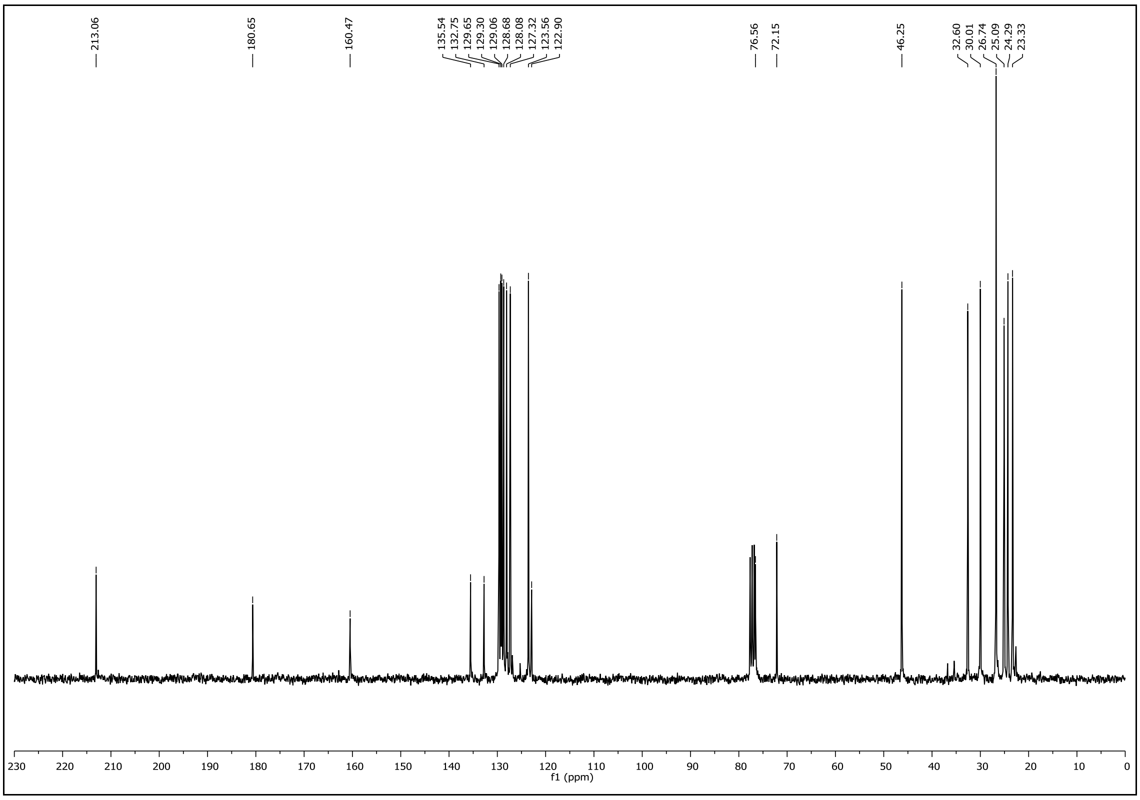
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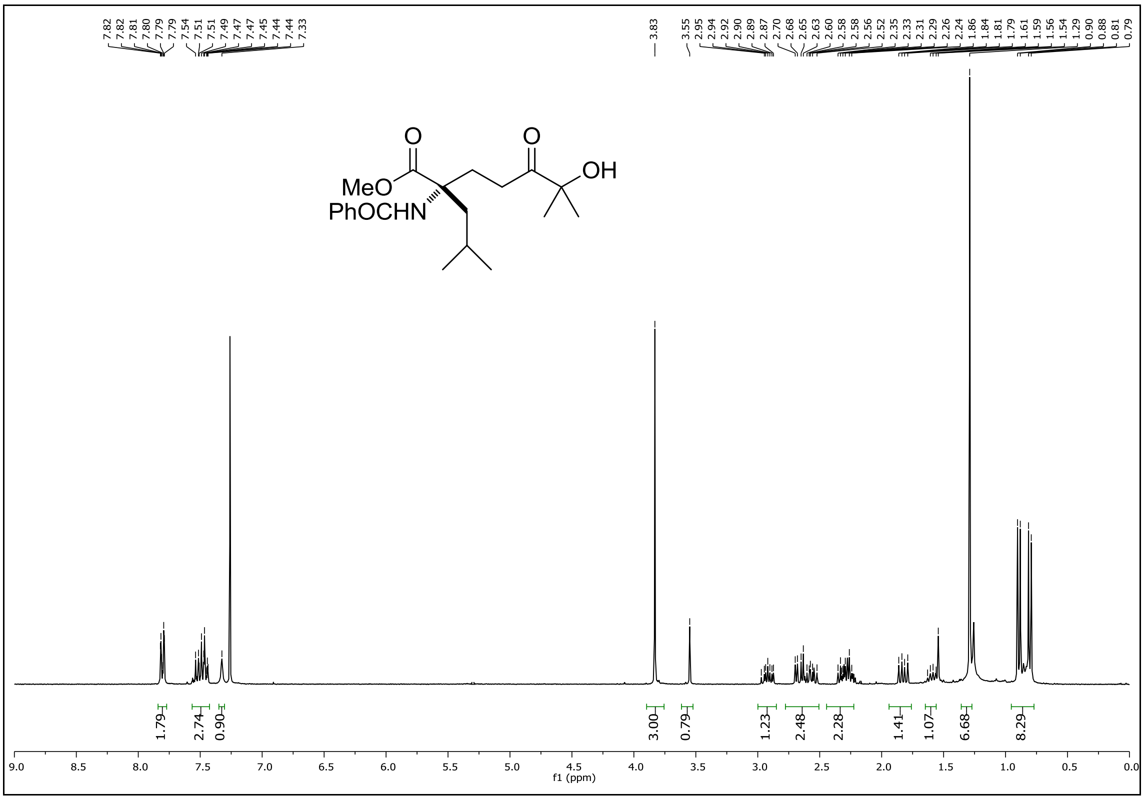
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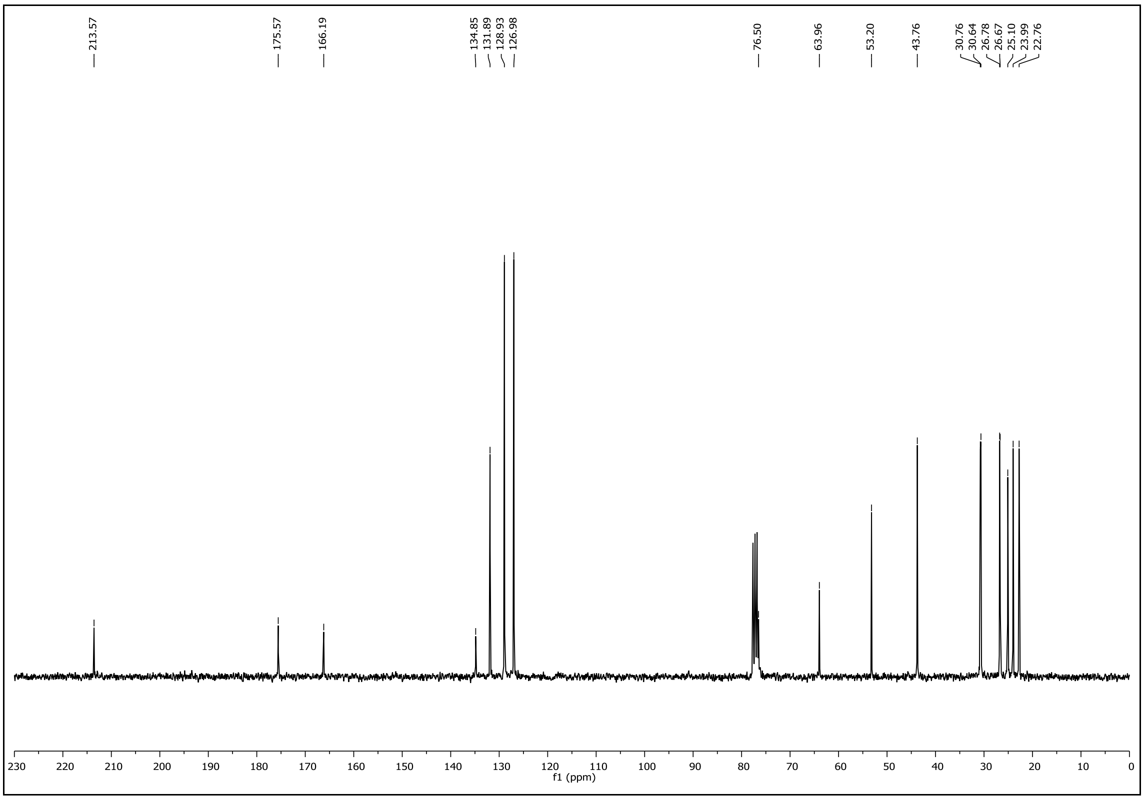
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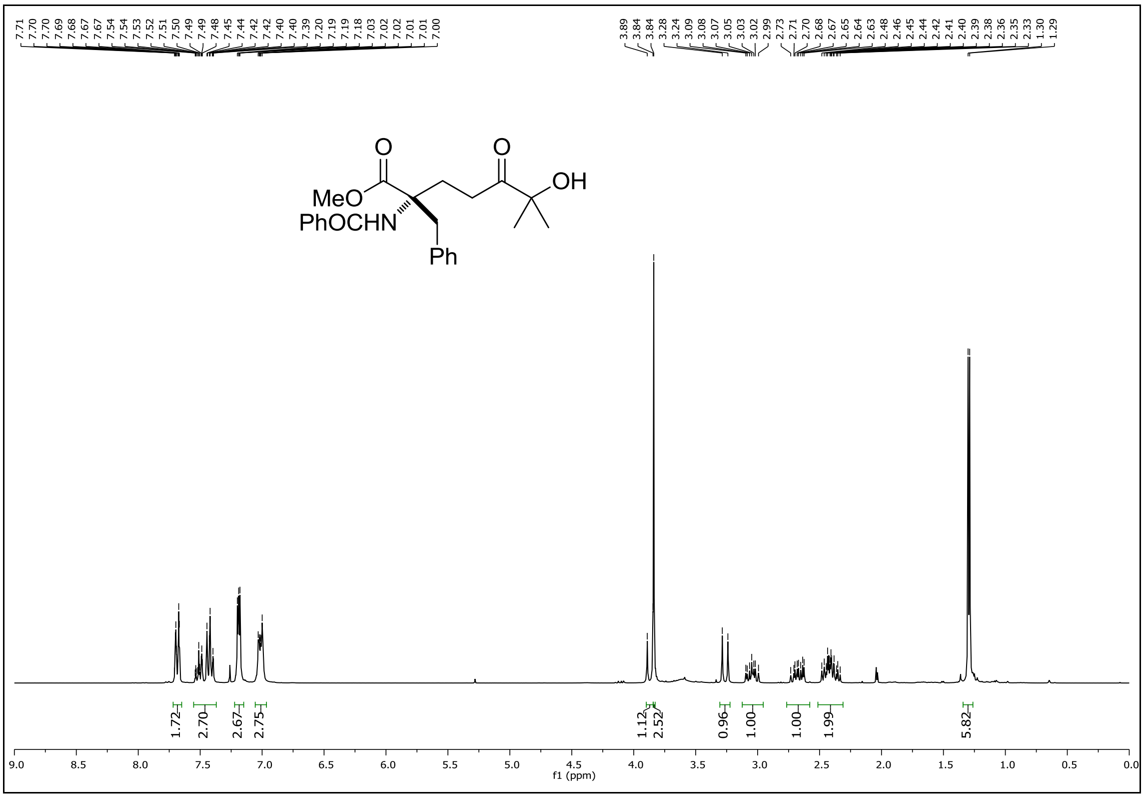
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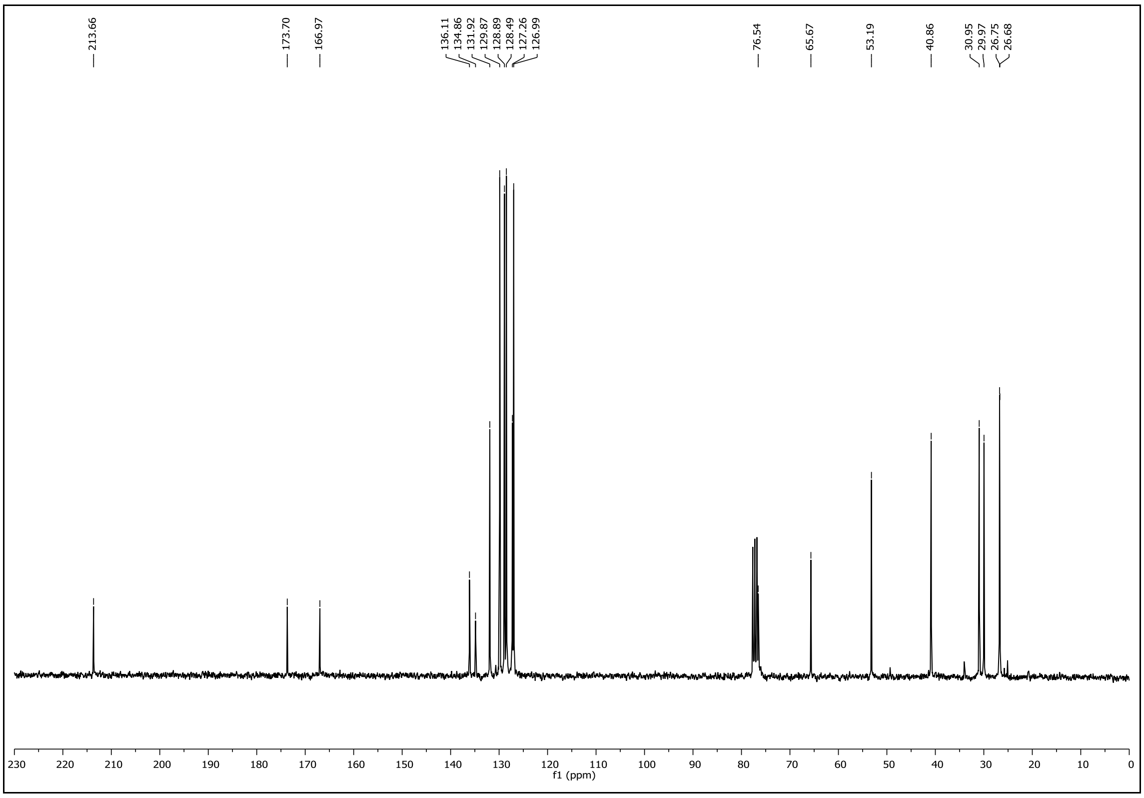
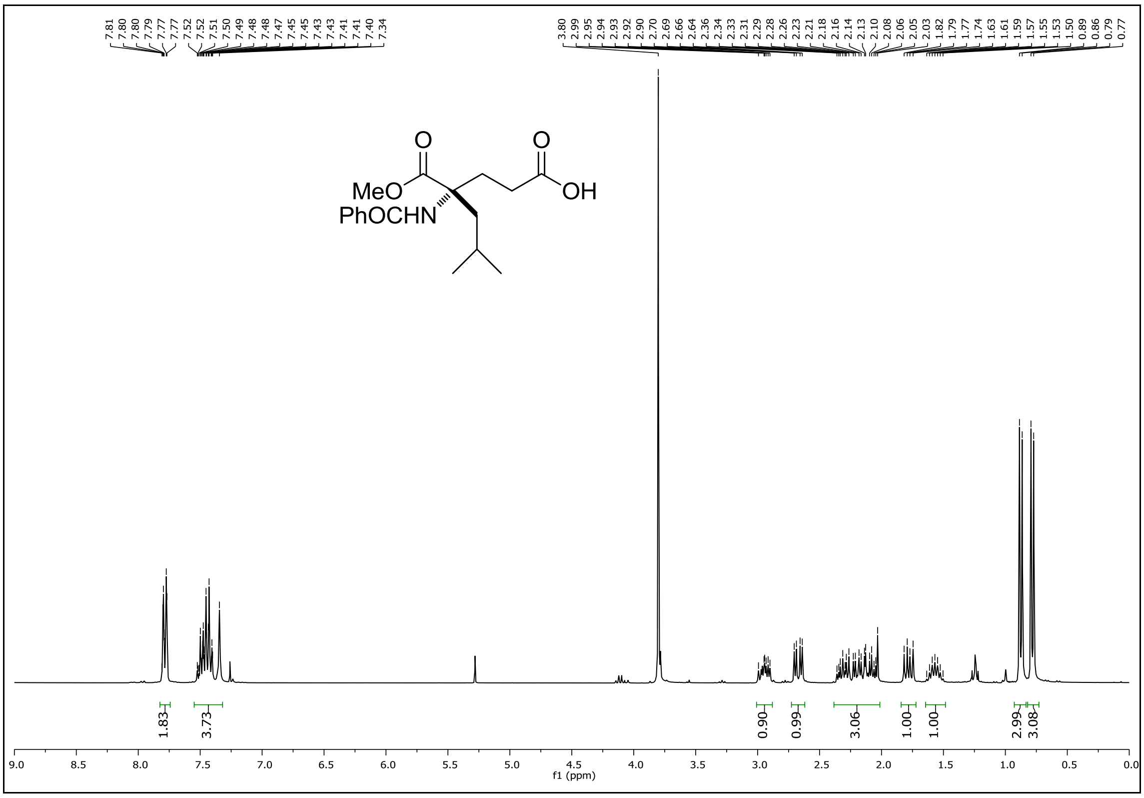
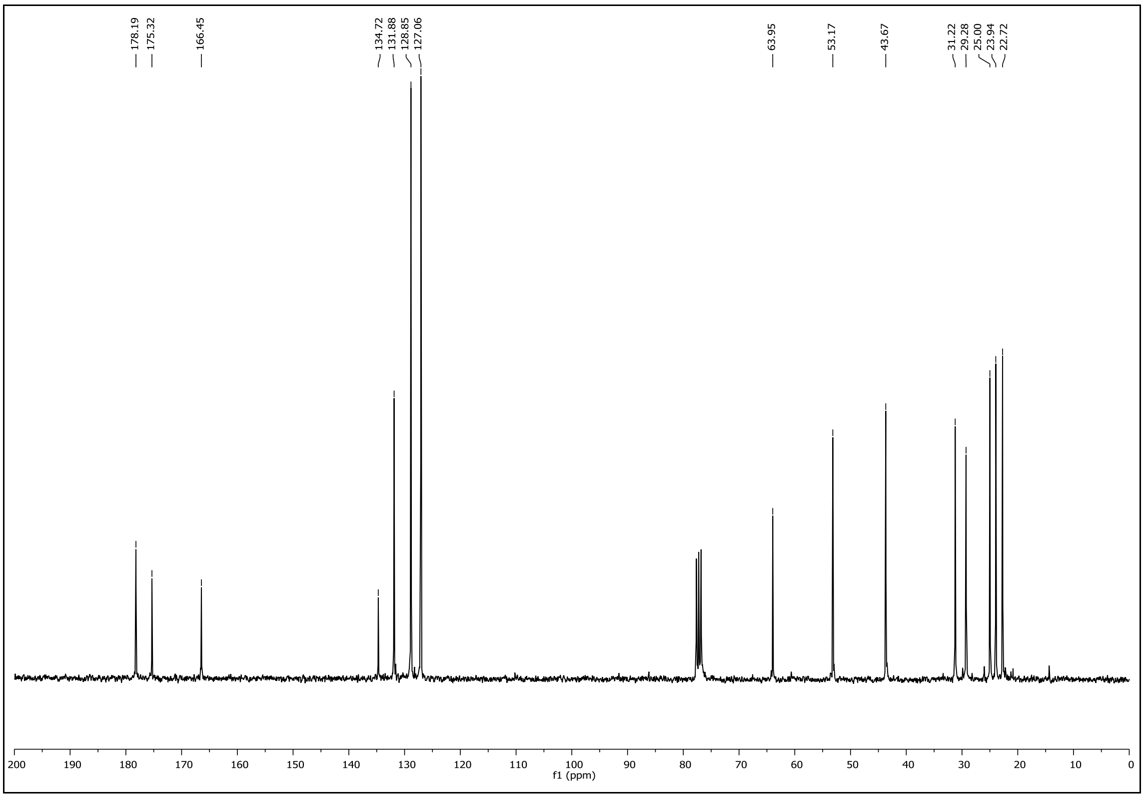
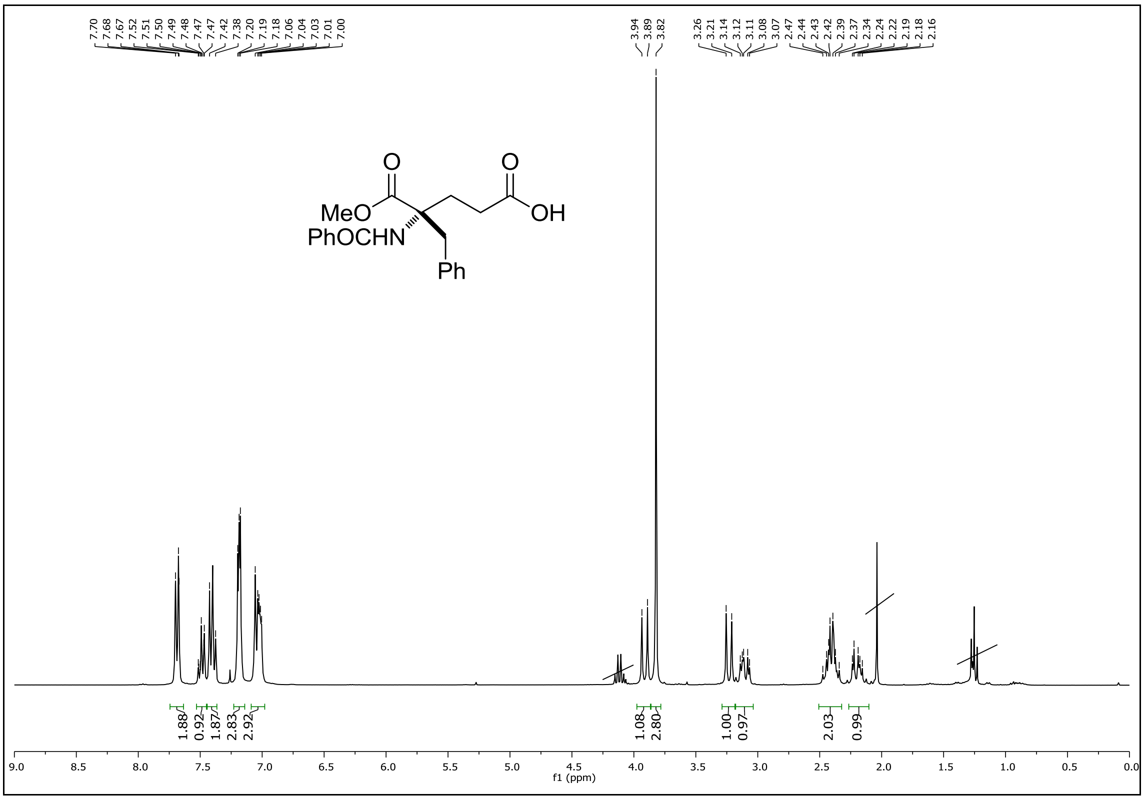
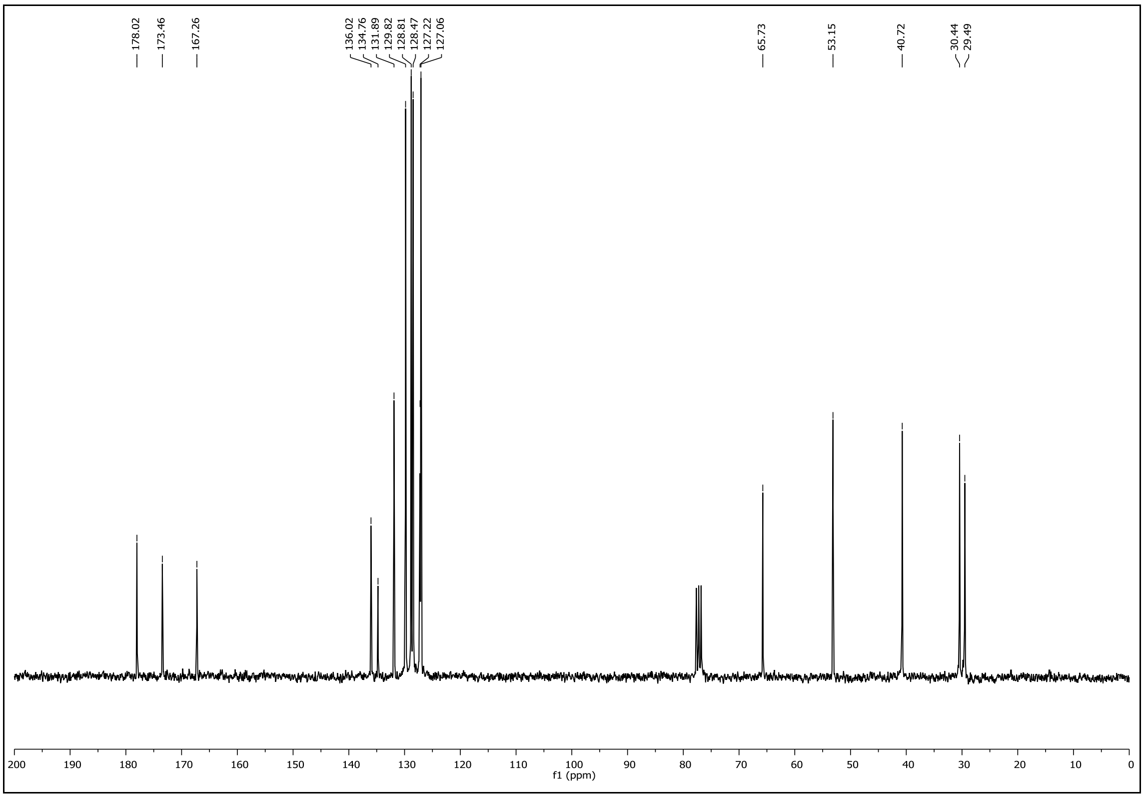
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

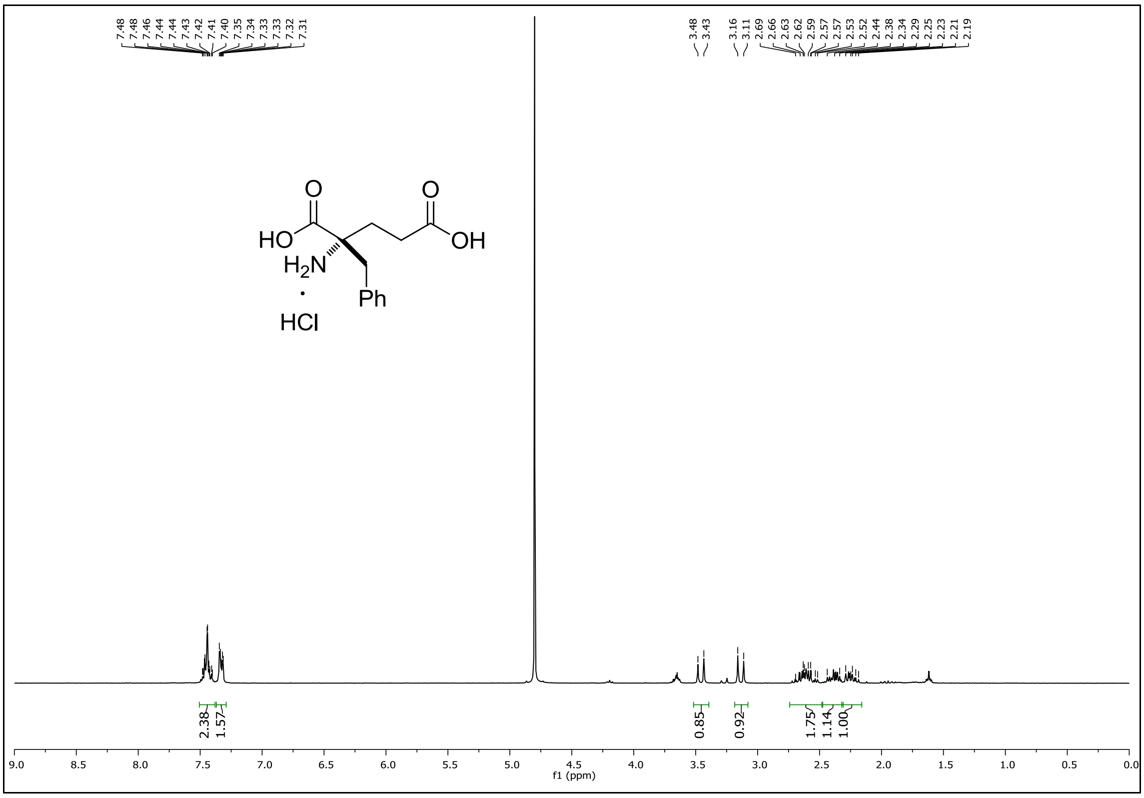

213.66
173.70
166.97
136.11
134.86
131.92
129.87
128.89
128.49
127.26
126.99
76.54
65.67
53.19
40.86
30.95
29.97
26.75
26.68
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

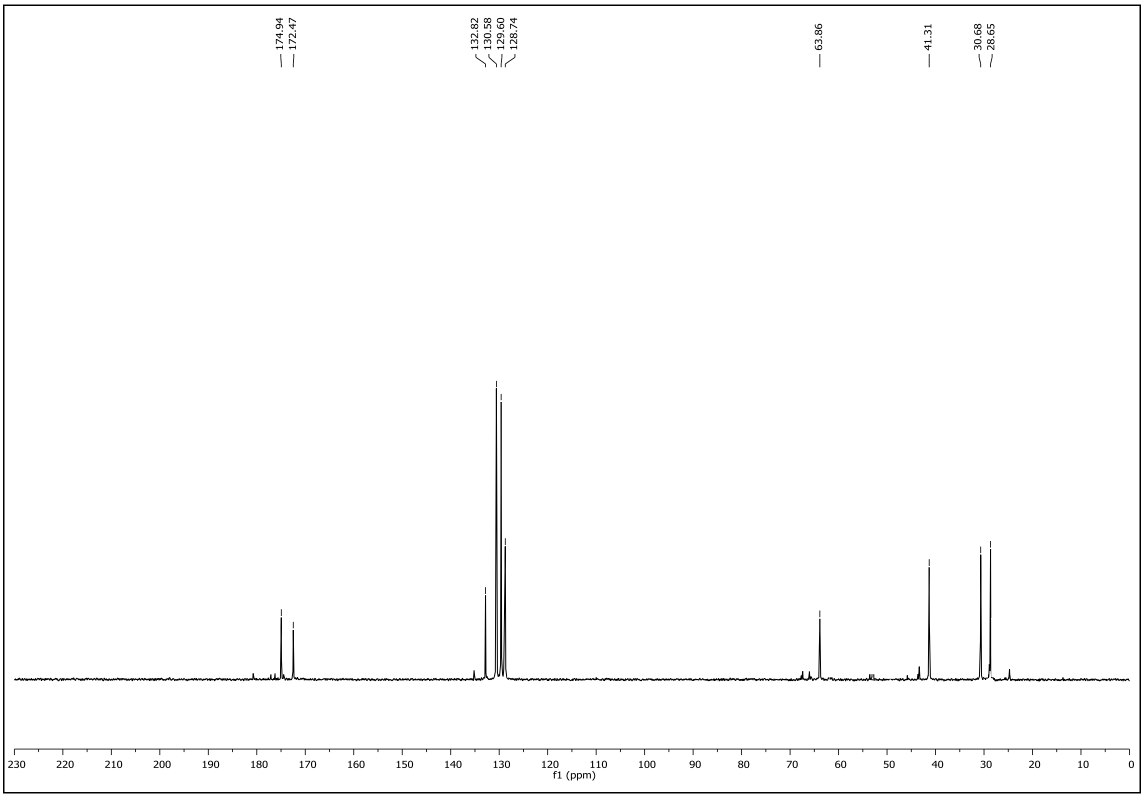

7.81
7.80
7.79
7.77
7.77
7.52
7.51
7.50
7.49
7.48
7.47
7.45
7.45
7.43
7.43
7.41
7.40
7.34
3.80
2.99
2.95
2.94
2.93
2.92
2.90
2.70
2.69
2.66
2.64
2.36
2.34
2.33
2.31
2.29
2.28
2.26
2.23
2.21
2.18
2.16
2.14
2.13
2.10
2.08
2.06
2.05
2.03
1.82
1.79
1.77
1.74
1.63
1.61
1.59
1.57
1.55
1.50
0.89
0.86
0.79
0.77
O
O
MeO
OH
PhOCHN
1.83
3.73
0.90
0.99
3.06
1.00
1.00
2.99
3.08
9.0
8.5
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
0.0
f1 (ppm)


178.19
175.32
166.45
134.72
131.88
128.85
127.06
63.95
53.17
43.67
31.22
29.28
25.00
23.94
22.72
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

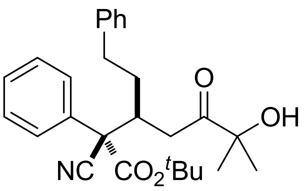

7.70 7.68 7.67 7.52 7.51 7.50 7.49 7.48 7.47 7.47 7.42 7.38 7.20 7.19 7.18 7.06 7.04 7.03 7.01 7.00
3.94 3.89 3.82
3.26 3.21 3.14 3.12 3.11 3.08 3.07 2.47 2.44 2.43 2.42 2.39 2.37 2.34 2.24 2.22 2.19 2.18 2.16
O
O
MeO
OH
PhOCHN
Ph
1.88 0.92 1.87 2.83 2.92
1.08 2.80
1.00 0.97
2.03 0.99
9.0 8.5 8.0 7.5 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 0.0
f1 (ppm)


178.02
173.46
167.26
136.02 134.76 131.89 129.82 128.81 128.47 127.22 127.06
65.73
53.15
40.72
30.44 29.49
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.48
7.48
7.46
7.44
7.44
7.43
7.42
7.41
7.40
7.35
7.34
7.33
7.33
7.32
7.31
3.48
3.43
3.16
3.11
2.69
2.66
2.63
2.62
2.59
2.57
2.57
2.53
2.52
2.44
2.38
2.34
2.29
2.25
2.23
2.21
2.19
O
O
HO
OH
H2N
HCl
Ph
2.38
1.57
0.85
0.92
1.75
1.14
1.00
9.0
8.5
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
0.0
f1 (ppm)


174.94
172.47
132.82
130.58
129.60
128.74
63.86
41.31
30.68
28.65
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

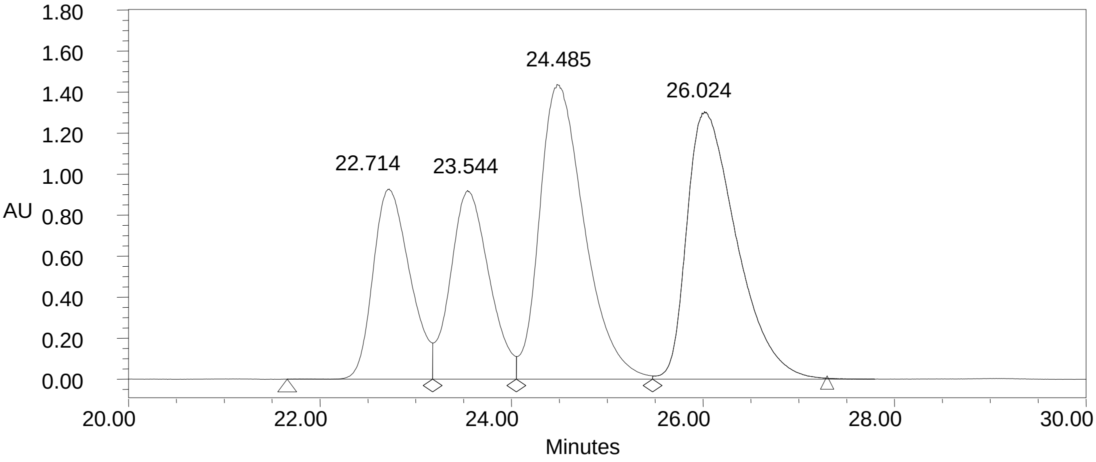
6.4.8. HPLC chromatograms



89Aa

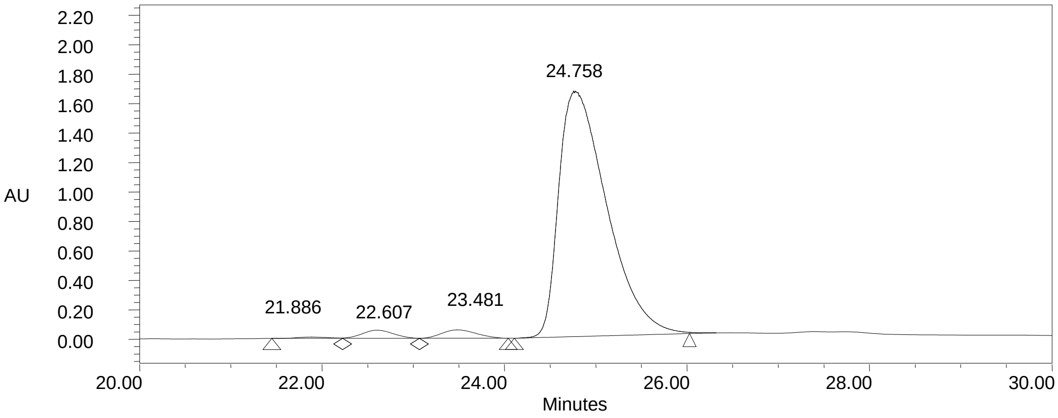
Column: AD3
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 0.5 mL/min
λ = 210 nm T = 10 ºC

rac-**89Aa**



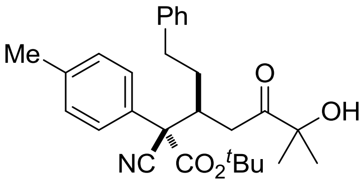
	Retention Time	Area	% Area	Height
1	22.714	24775154	17.14	926316
2	23.544	25841902	17.88	917248
3	24.485	46819083	32.39	1434780
4	26.024	47133939	32.60	1301938

89Aa



	Retention Time	Area	% Area	Height
1	21.886	210126	0.33	9214
2	22.607	1304069	2.03	55276
3	23.481	1503226	2.34	56833
4	24.758	61188267	95.30	1669002

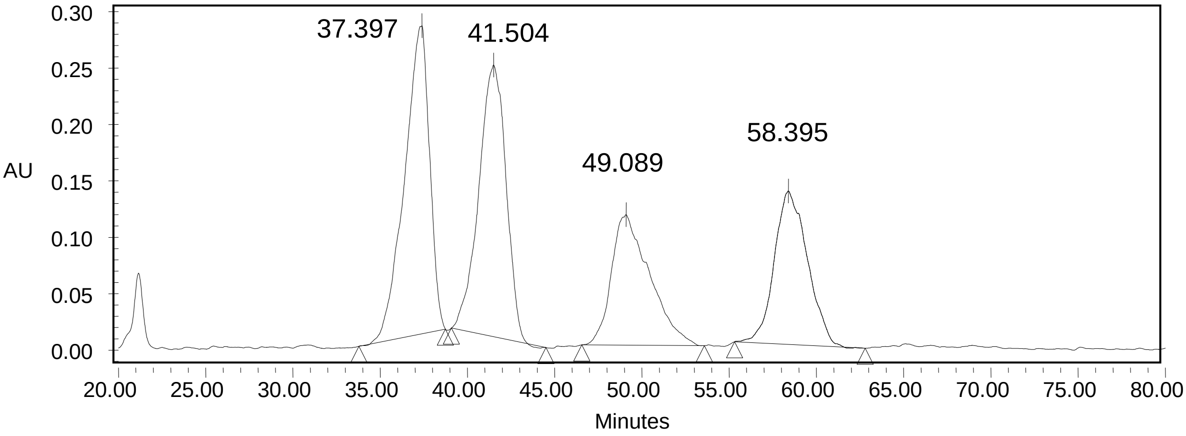
98:2 *dr*   96% *ee*



89Ab

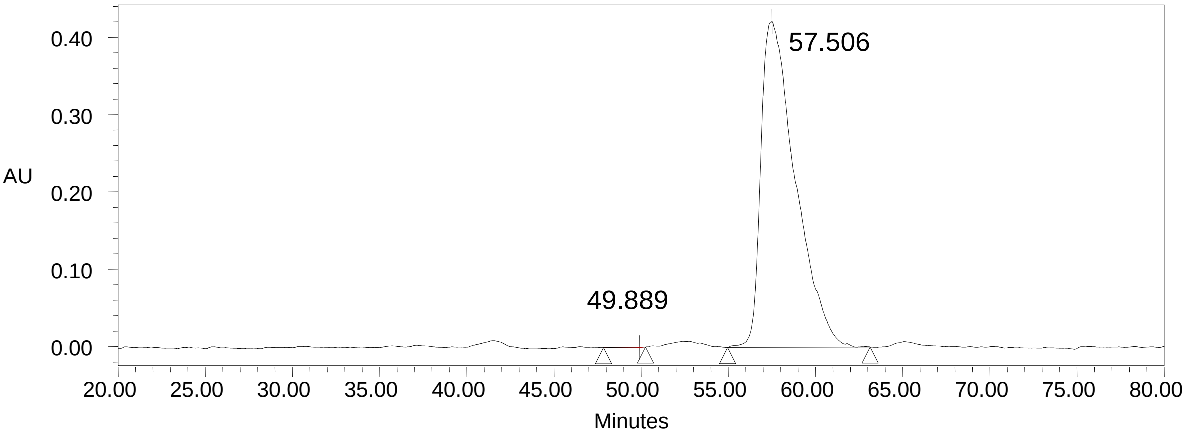
Column: AD-H
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**89Ab**



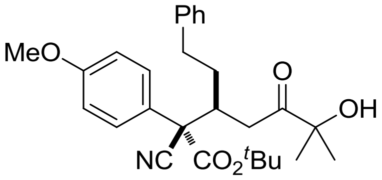
	Retention Time	% Area
1	37.397	30.58
2	41.504	29.48
3	49.089	19.74
4	58.395	20.19

89Ab



	Retention Time	% Area
2	57.506	99.95
1	49.889	0.05

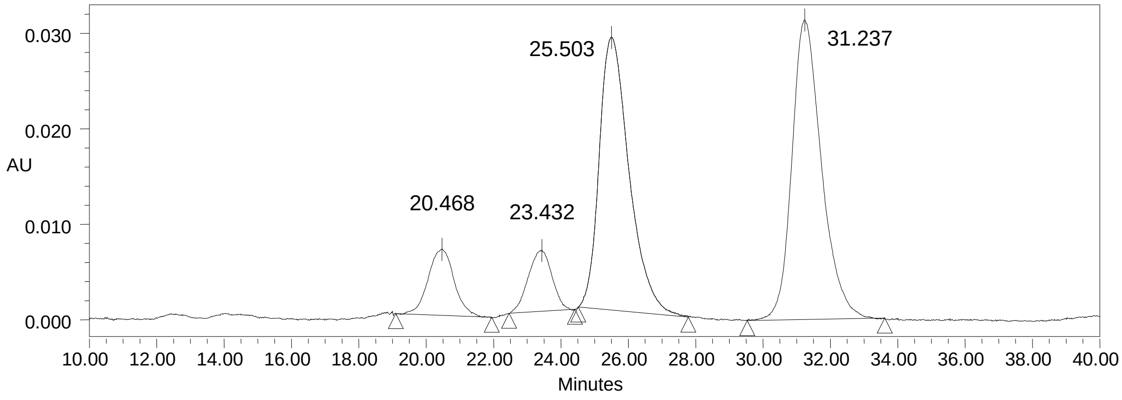
99:1 *dr* 99% *ee*



89Ac

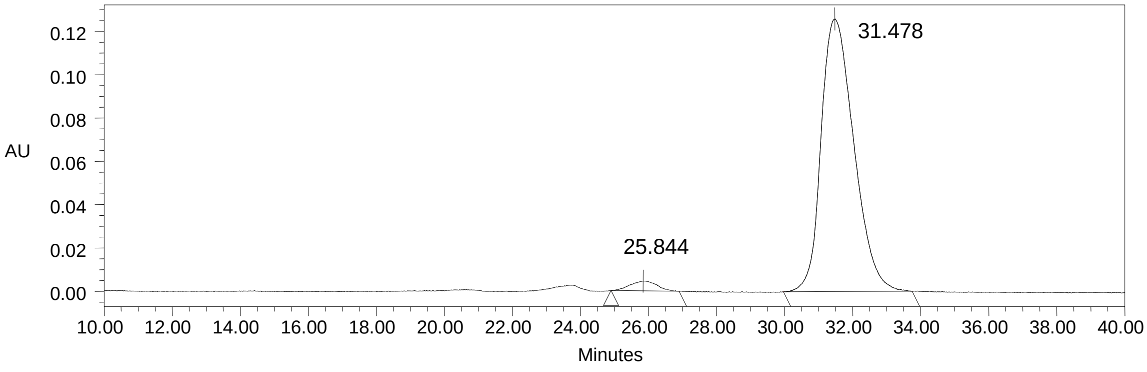
Column: AD-3
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 0.5 mL/min
λ = 210 nm

rac-**89Ac**



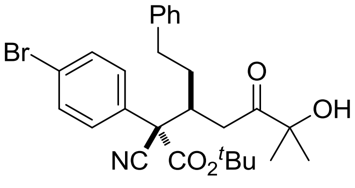
	Retention Time	% Area
1	20.468	8.49
2	23.432	7.15
3	25.503	40.40
4	31.237	43.95

89Ac



	Retention Time	% Area
2	31.478	97.17
1	25.844	2.83

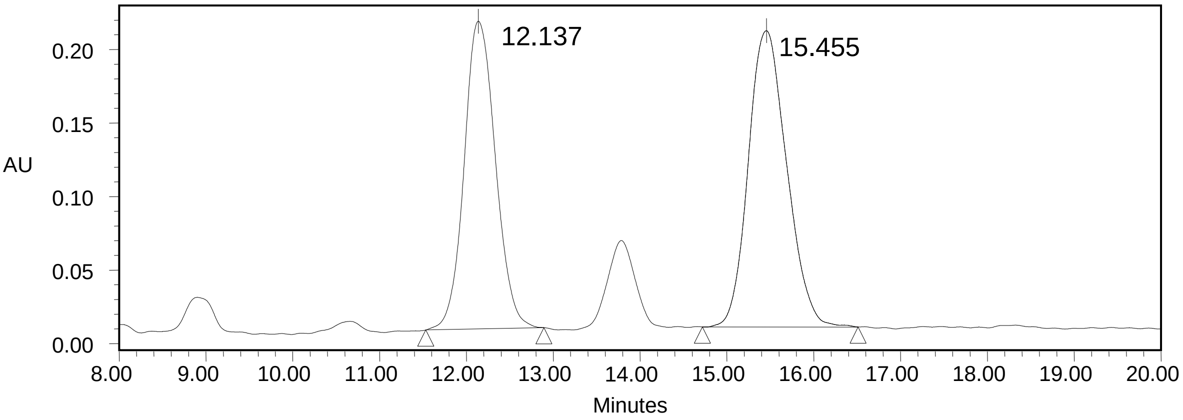
98:2 *dr* 96% *ee*



89Ad

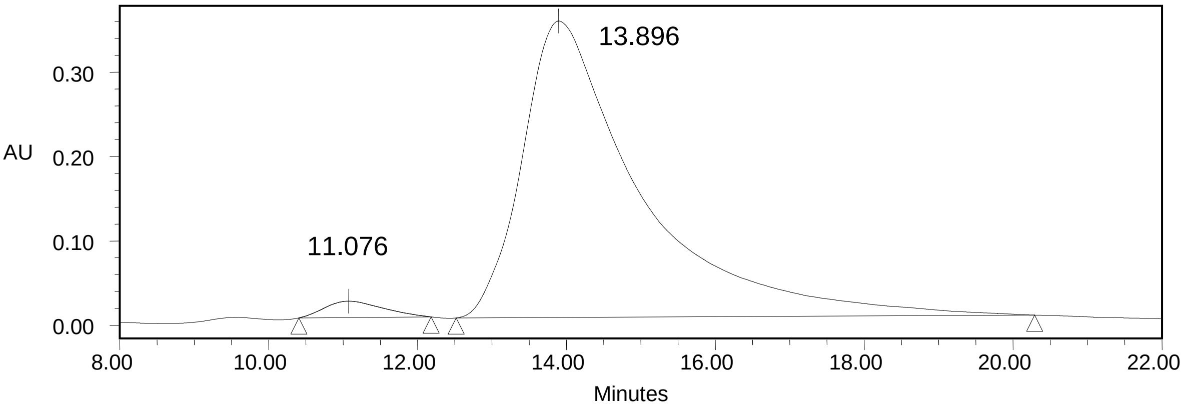
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**89Ad**



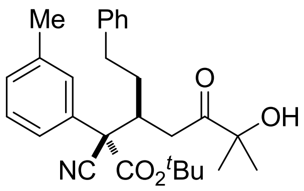
	Retention Time	% Area
2	15.455	54.15
1	12.137	45.85

89Ad



	Retention Time	% Area
2	13.896	97.23
1	11.076	2.77

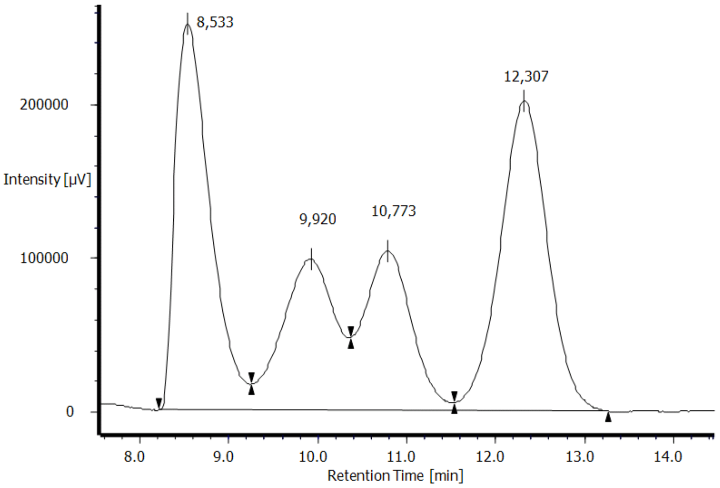
>99:1 *dr* 94% *ee*



89Af

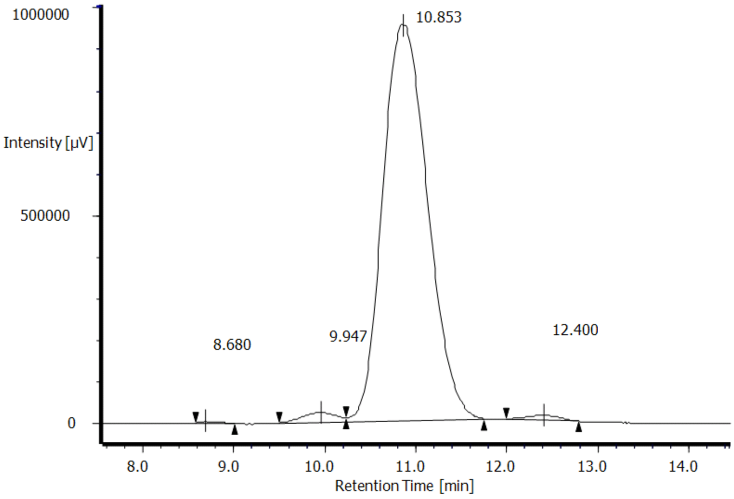
Column: Phenomenex Lux
3μ Cellulose-4
Eluent: Hex:*i*PrOH, 96:4
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**89Af**



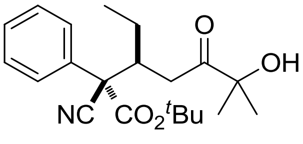
	Retention Time	% Area
1	8.533	30.82
2	9.920	18.33
3	10.773	17.36
4	12.307	33.49

89Af



	Retention Time	% Area
1	8.680	0.19
2	9.947	1.81
3	10.853	97.15
4	12.400	0.85

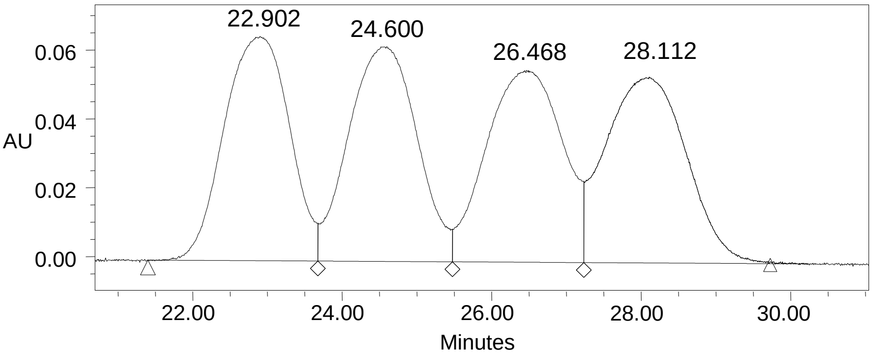
>99:1 *dr*   98% *ee*



89Ba

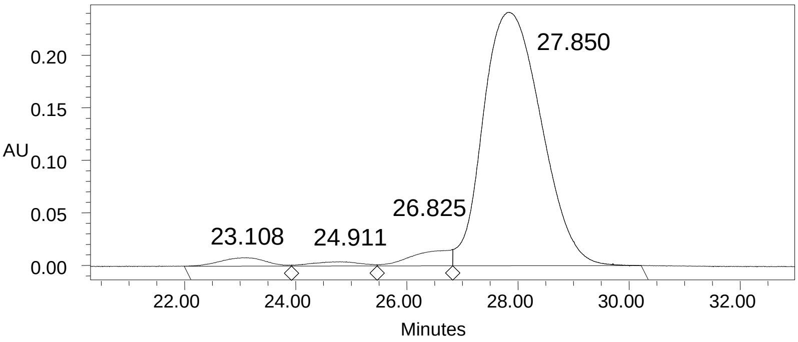
Column: Phenomenex Lux
3μ Cellulose-4
Eluent: Hex:*i*PrOH, 99:1
Flow rate = 1.0 mL/min
λ = 210 nm

Rac-**89Ba**



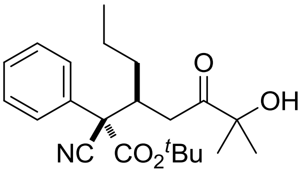
	Retention Time	% Area
1	22.902	24.80
2	24.600	24.96
3	26.468	24.74
4	28.112	25.50

89Ba



	Retention Time	% Area
1	23.108	2.40
2	24.911	1.28
3	26.825	3.86
4	27.850	92.46

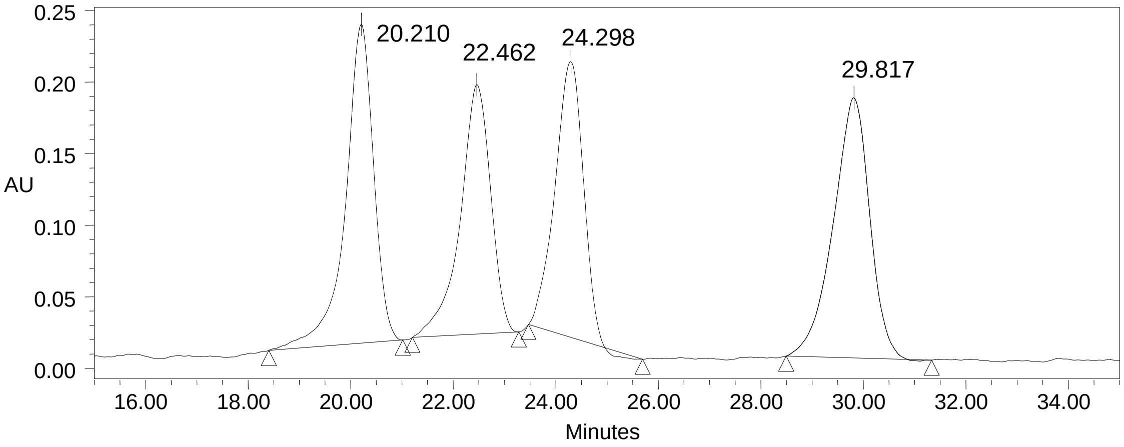
96:4 *dr* 92% *ee*



89Ca

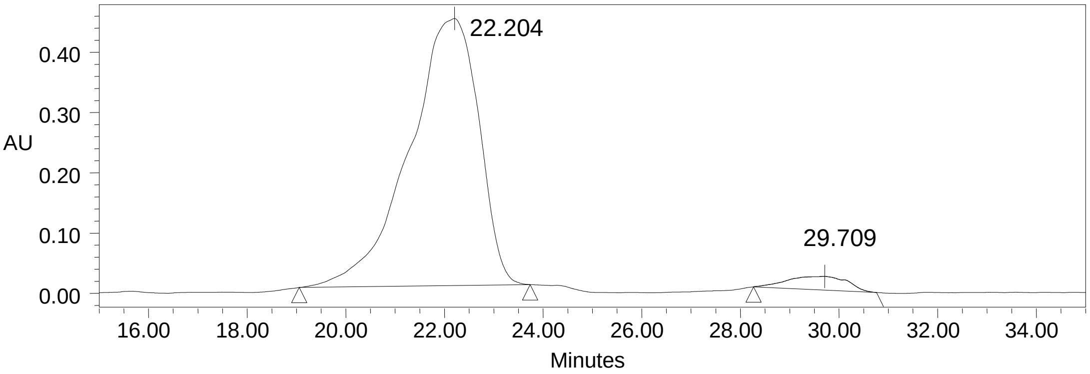
Column: AD-H
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

Rac-**89Ca**



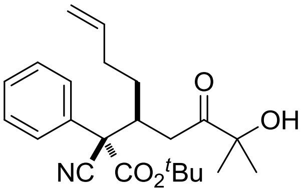
	Retention Time	% Area
1	20.210	26.37
2	22.462	22.26
3	24.298	23.42
4	29.817	27.95

89Ca



	Retention Time	% Area
2	29.709	4.15
1	22.204	95.85

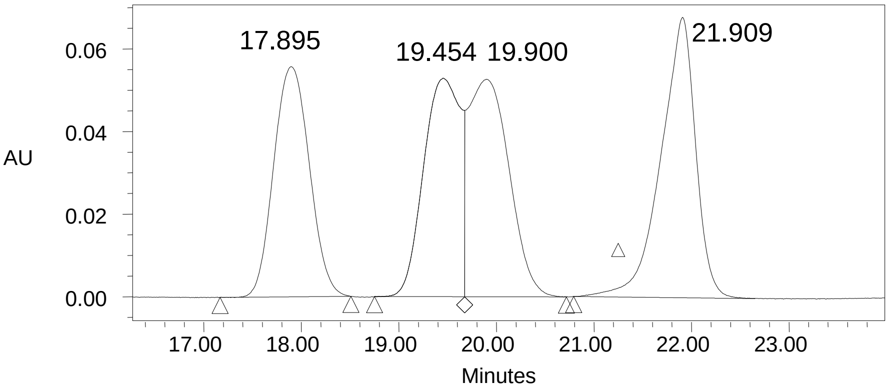
>99:1 *dr* 92% *ee*



89Ea

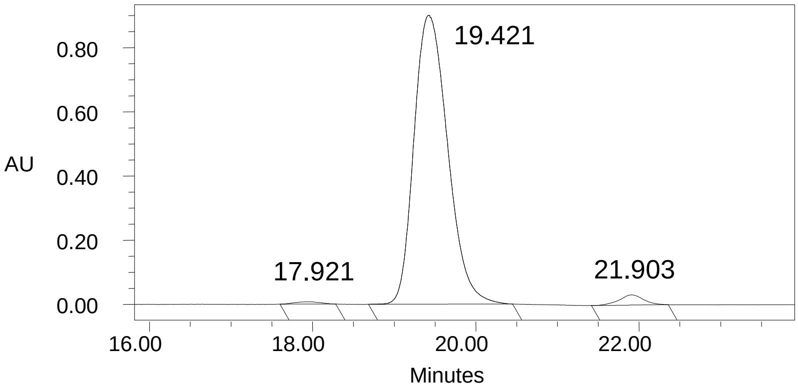
Column: AD-3
Eluent: Hex:*i*PrOH, 95:5
Flow rate = 0.5 mL/min
λ = 210 nm

Rac-**89Ea**



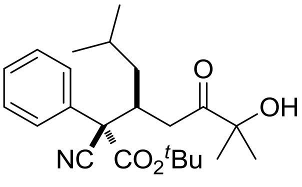
	Retention Time	% Area
1	17.895	23.63
2	19.454	23.08
3	19.900	25.35
4	21.909	27.93

89Ea



Retention Time	% Area
17.921	0.59
19.421	96.96
21.903	2.46

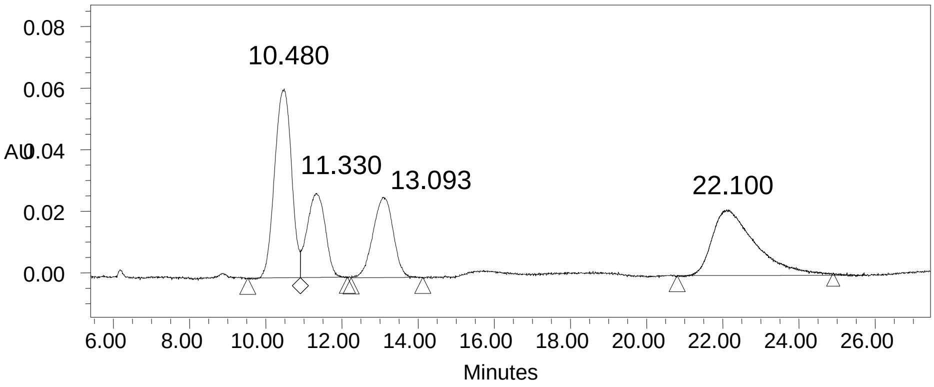
>99:1 *dr*   96% *ee*



89Fa

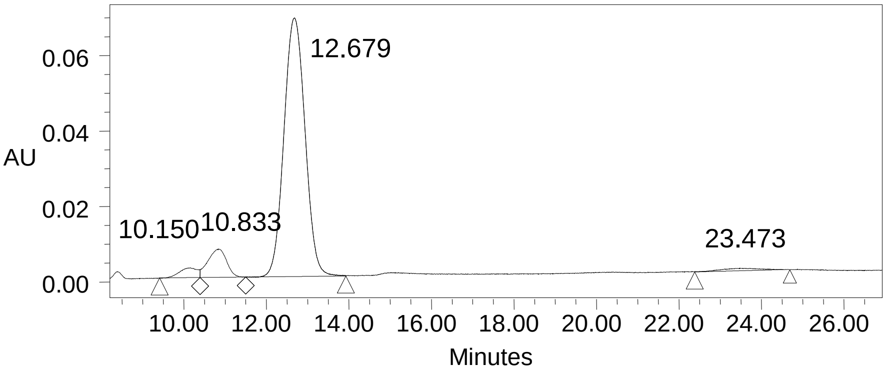
Column: AD-3
Eluent: Hex:*i*PrOH, 95:5
Flow rate = 0.5 mL/min
λ = 210 nm

Rac-**89Fa**



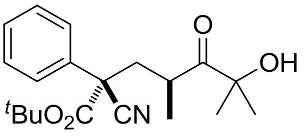
Retention Time	Area	% Area	Height
10.480	1891116	34.63	61128
11.330	909383	16.65	27227
13.093	962892	17.63	26106
22.100	1697485	31.08	21292

89Fa



	Retention Time	Area	% Area	Height
1	10.150	78393	2.81	2583
2	10.833	233367	8.37	7495
3	12.679	2435231	87.29	68521
4	23.473	42748	1.53	623

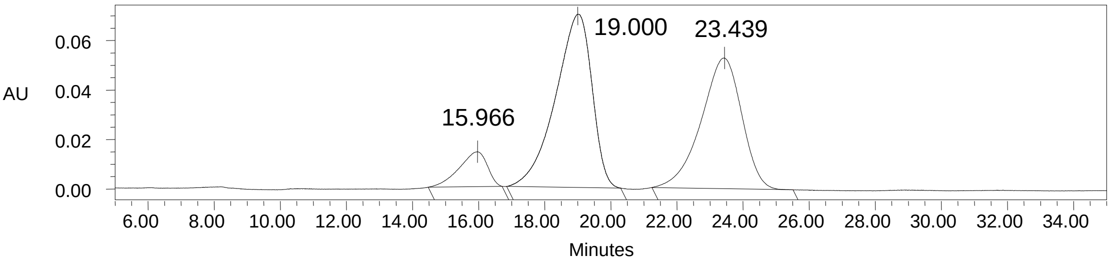
95:5 *dr* 83% *ee*



104a

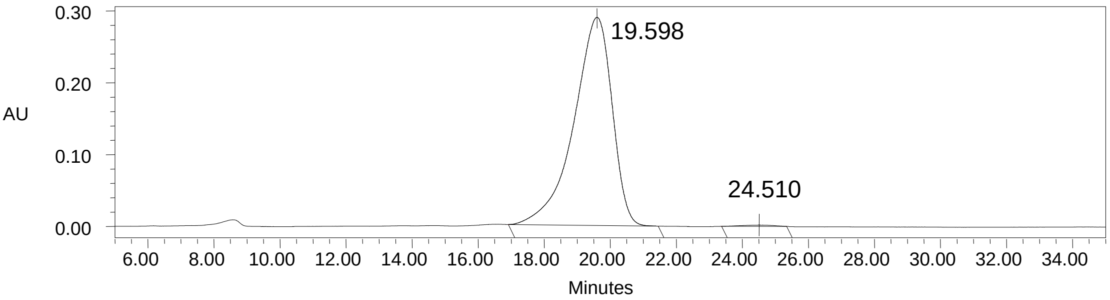
Column: IC
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**104a**



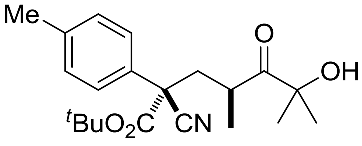
	Retention Time	Area	% Area	Height
1	15.966	837575	7.81	14122
2	19.000	5381088	50.18	70135
3	23.439	4504790	42.01	52851

104a



	Retention Time	Area	% Area	Height
1	19.598	23362803	99.45	289755
2	24.510	128192	0.55	1887

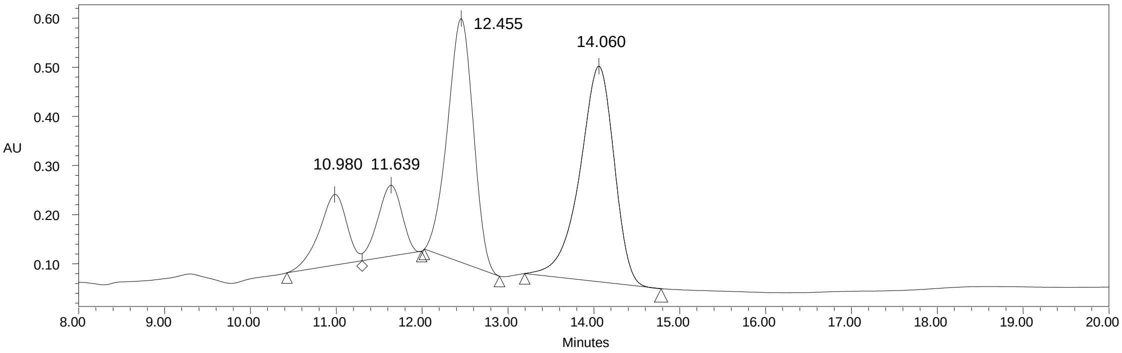
>99:1 *dr* 99% *ee*



104b

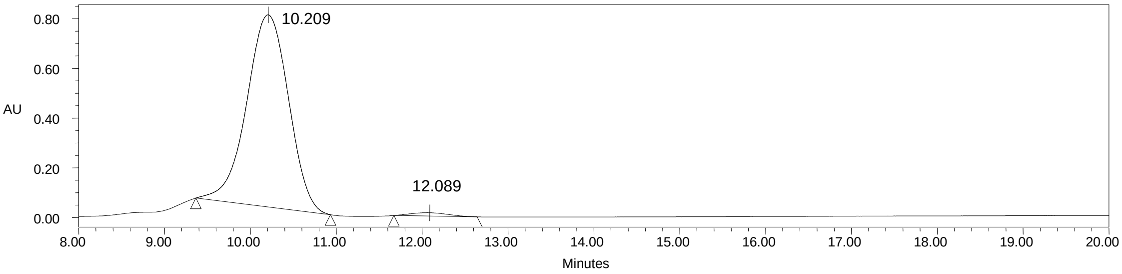
Column: IC
Eluent: Hex:*i*PrOH, 85:15
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**104b**



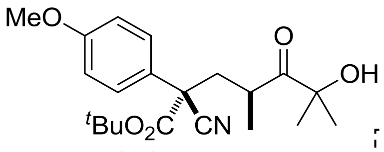
	Retention Time	Area	% Area	Height
4	14.060	12213367	42.68	438711
3	12.455	10395302	36.32	495986
2	11.639	2812315	9.83	144101
1	10.980	3197850	11.17	143683

104b



	Retention Time	Area	% Area	Height
2	12.089	395670	1.49	13281
1	10.209	26248711	98.51	772819

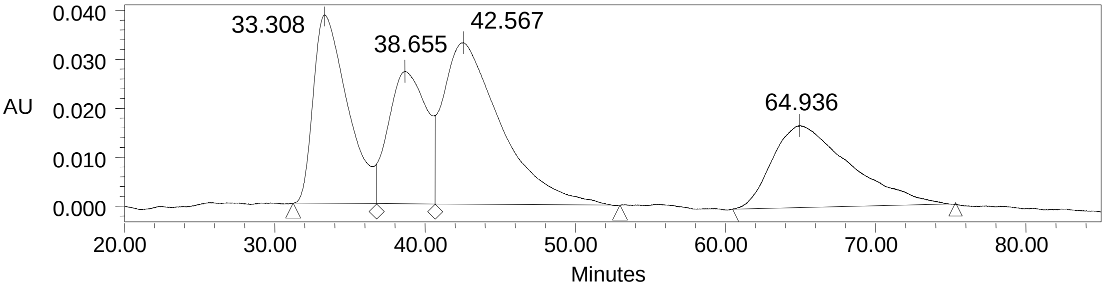
>99:1 *dr* 97% ee



104c

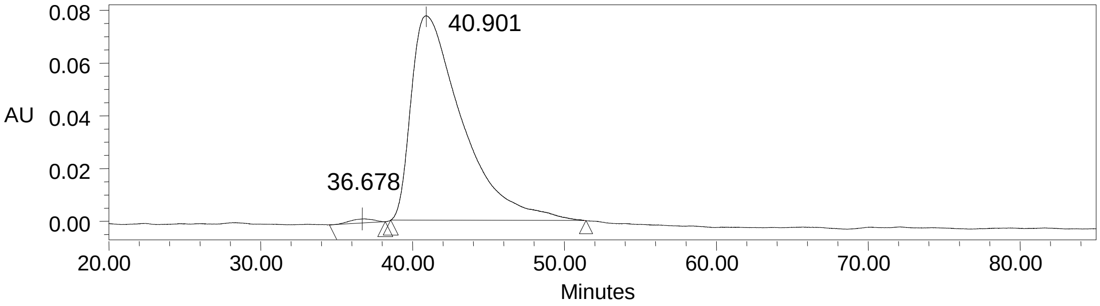
Column: AY-H
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**104c**



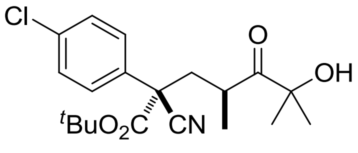
	Retention Time	Area	% Area	Height
4	64.936	6017265	23.38	16754
3	42.567	8833842	34.32	32995
2	38.655	4775763	18.55	27054
1	33.308	6113472	23.75	38484

104c



	Retention Time	Area	% Area	Height
2	40.901	18121094	99.10	77559
1	36.678	164964	0.90	1578

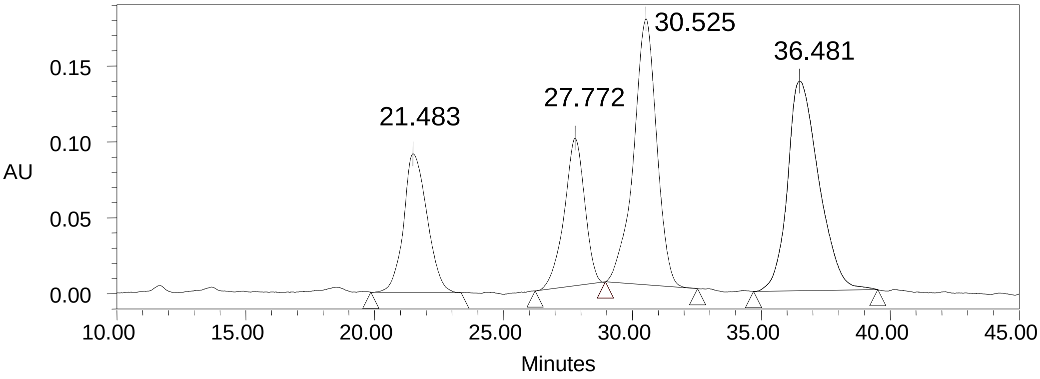
>99:1 *dr* 98% *ee*



104e

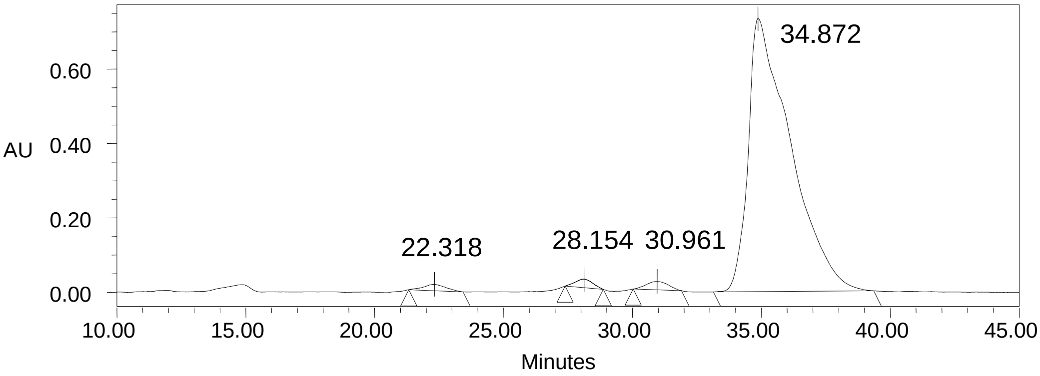
Column: IA
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**1044**



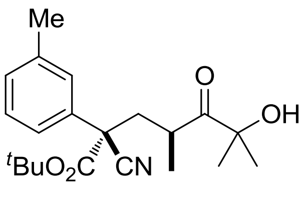
	Retention Time	Area	% Area	Height
1	21.483	5762780	17.07	91140
2	27.772	5378653	15.93	97241
3	30.525	10944371	32.42	175296
4	36.481	11675291	34.58	138092

104e



	Retention Time	Area	% Area	Height
1	22.318	1019460	1.17	17217
2	28.154	1095755	1.25	22859
3	30.961	1346425	1.54	22596
4	34.872	84031295	96.04	734174

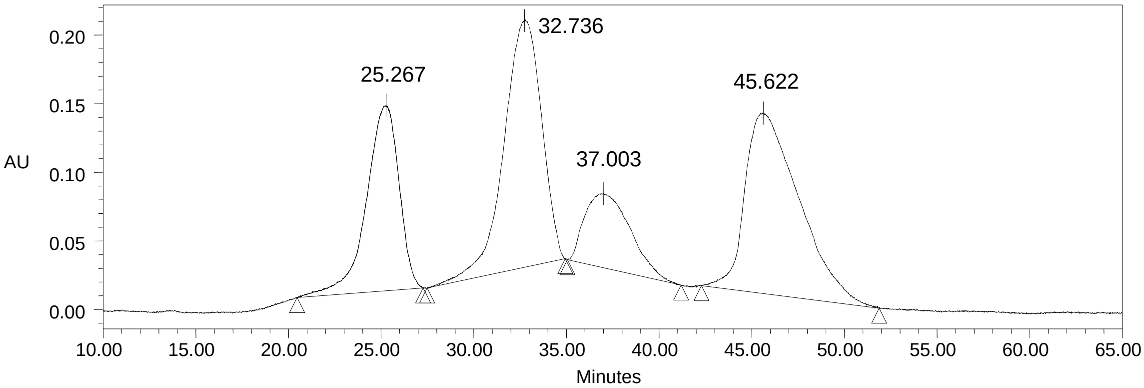
98:2 *dr*   96% *ee*



104f

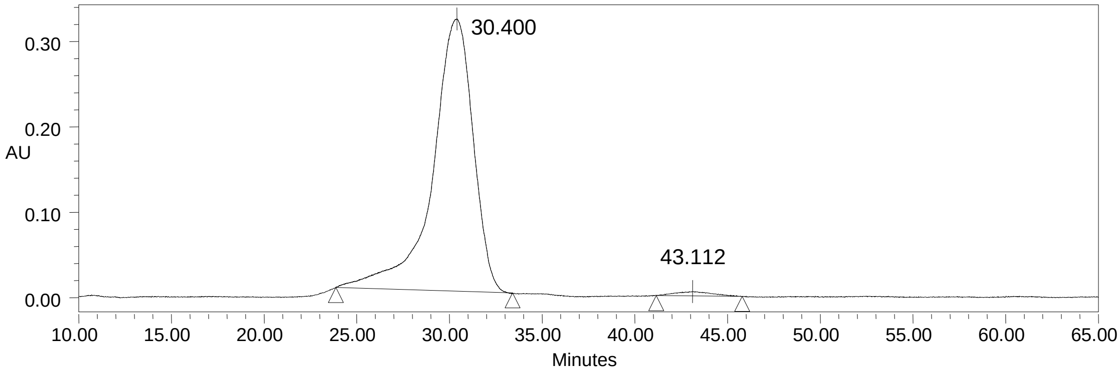
Column: IC
Eluent: Hex:*i*PrOH, 99:1
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**104f**



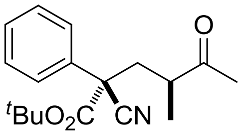
	Retention Time	Area	% Area	Height
4	45.622	26889132	34.34	131594
3	37.003	9316343	11.90	53895
2	32.736	25504192	32.57	180199
1	25.267	16586096	21.18	134673

104f



	Retention Time	Area	% Area	Height
1	30.400	48766610	98.61	318693
2	43.112	686201	1.39	5069

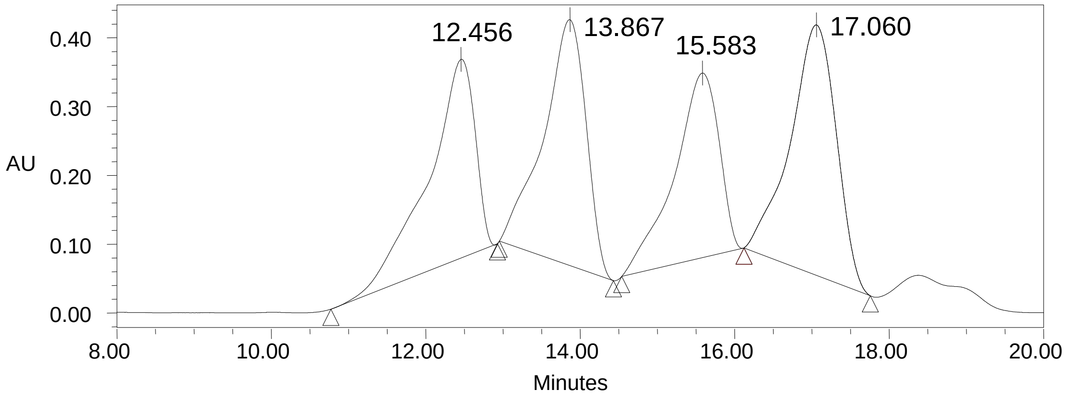
>99:1 *dr* 97% *ee*



101

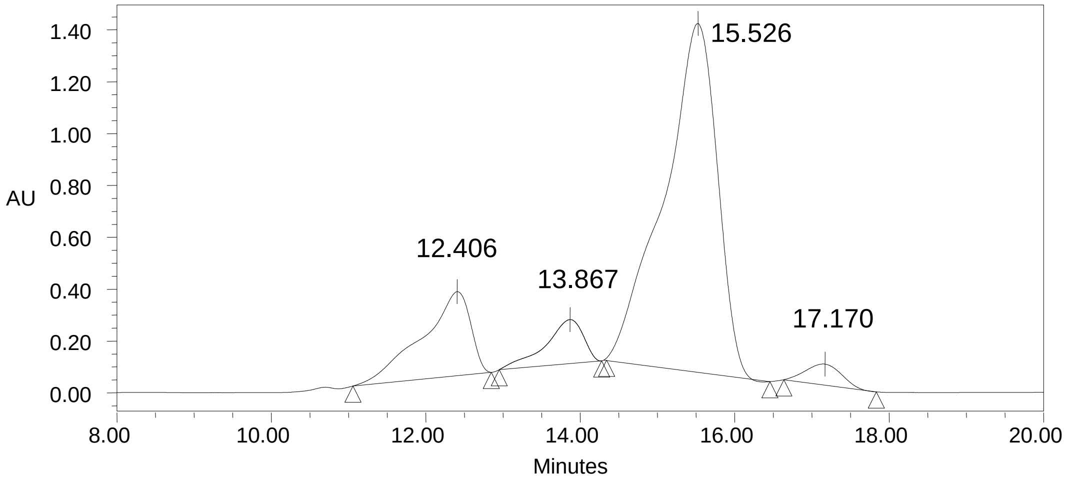
Column: AD-H
Eluent: Hex:*i*PrOH, 99:1
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**101**



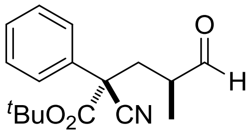
	Retention Time	Area	% Area	Height
1	12.456	12163732	23.48	288662
2	13.867	13714389	26.47	357393
3	15.583	10810537	20.86	268153
4	17.060	15126763	29.19	364032

101



	Retention Time	Area	% Area	Height
2	13.867	5761668	6.61	169616
1	12.406	14165292	16.25	323895
4	17.170	2606201	2.99	80843
3	15.526	64637491	74.15	1345565

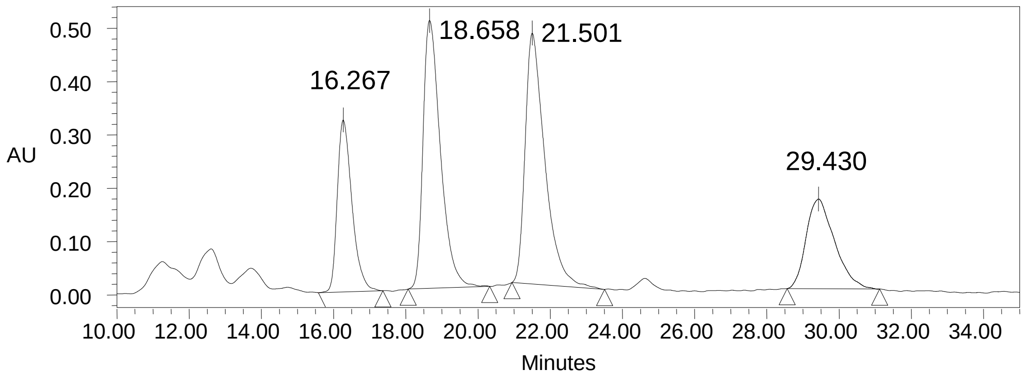
80:20 *dr* 92% *ee* (major.) 42% *ee* (minor.)



103

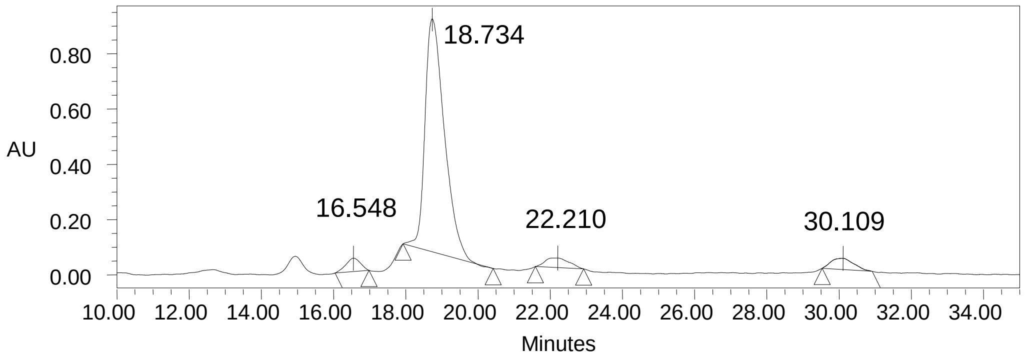
Column: AY-H
Eluent: Hex:*i*PrOH, 95:5
Flow rate = 0.6 mL/min
λ = 210 nm

Rac-**103**



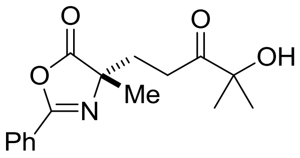
	Retention Time	Area	% Area	Height
1	16.267	9103329	17.17	322348
2	18.658	16850925	31.79	502337
3	21.501	17846964	33.67	470486
4	29.430	9206326	17.37	168054

103



	Retention Time	Area	% Area	Height
1	16.548	1376800	3.31	48689
2	18.731	38142958	91.73	894624
3	22.231	1191685	2.87	28830
4	30.123	869363	2.09	26716

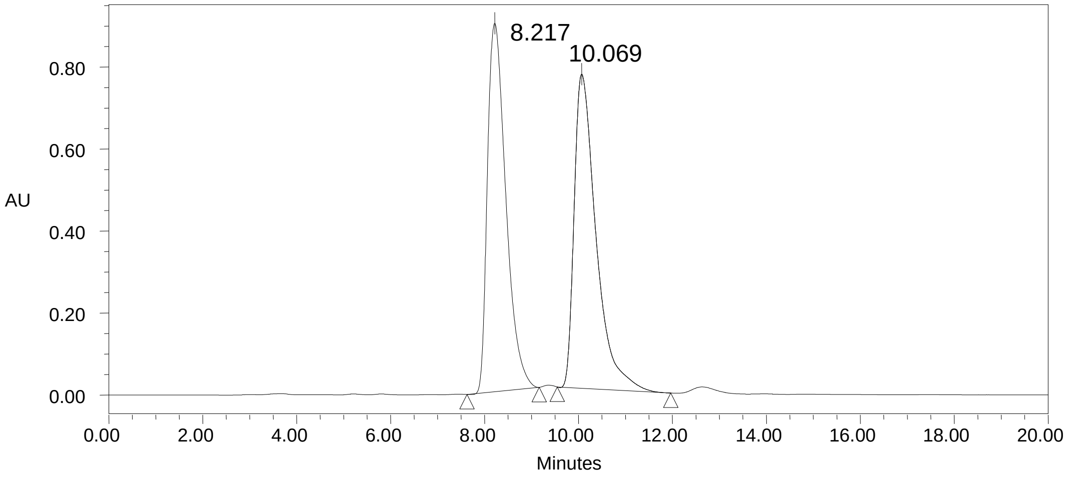
95:5 *dr* 94% *ee*



114c

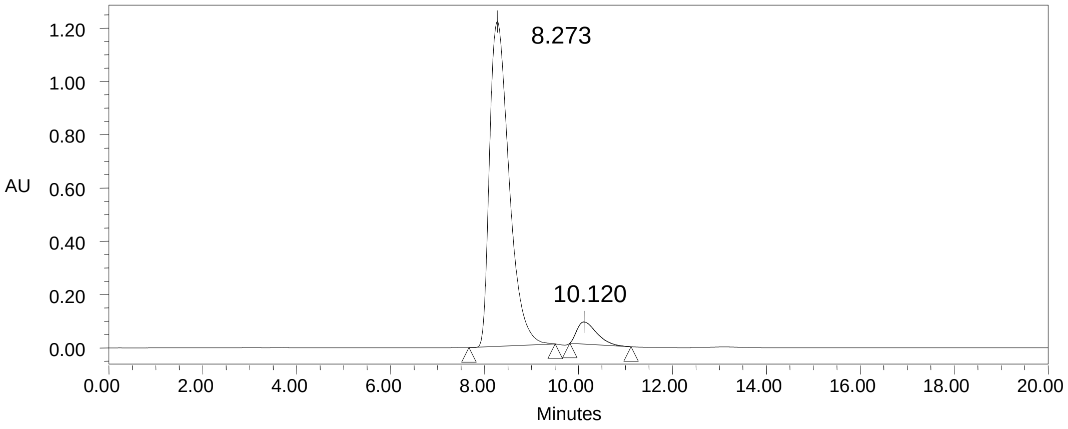
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**114c**



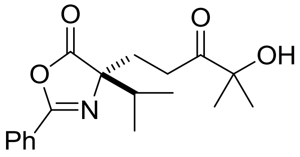
	Retention Time	% Area
2	10.069	50.25
1	8.217	49.75

114c



	Retention Time	% Area
2	10.120	6.49
1	8.273	93.51

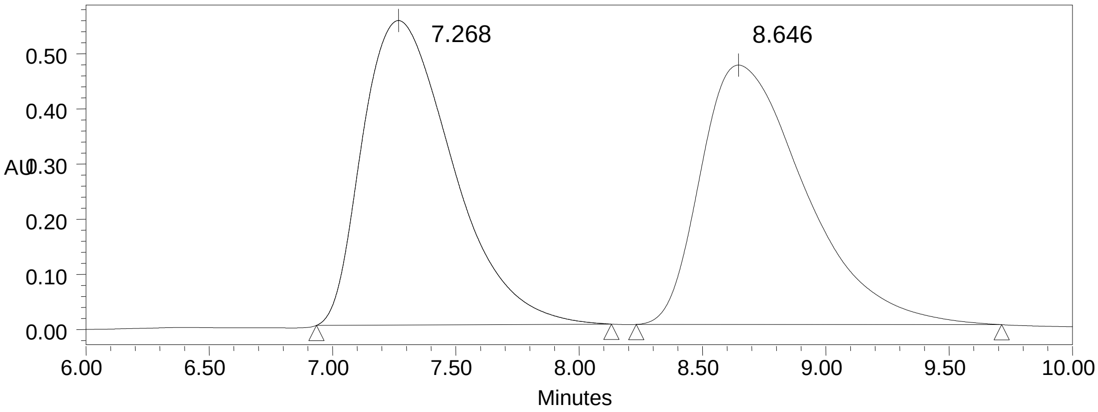
88% *ee*



114b

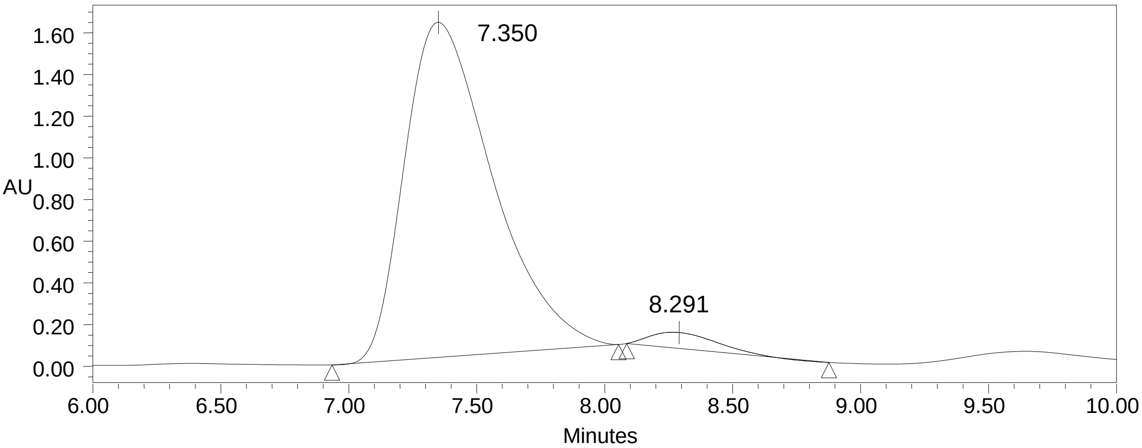
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**114b**



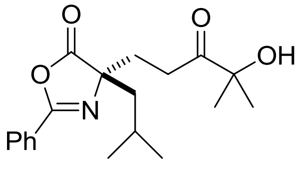
	Retention Time	% Area
2	8.646	49.48
1	7.268	50.52

114b



	Retention Time	% Area
2	8.290	4.82
1	7.350	95.18

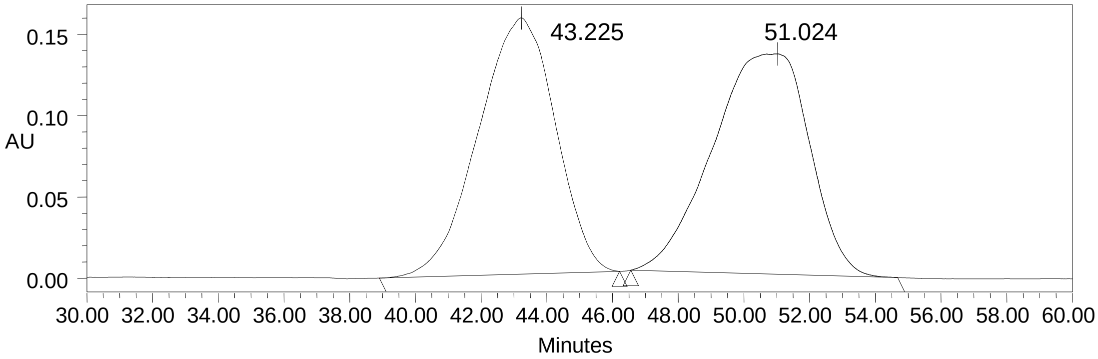
90% *ee*



114c

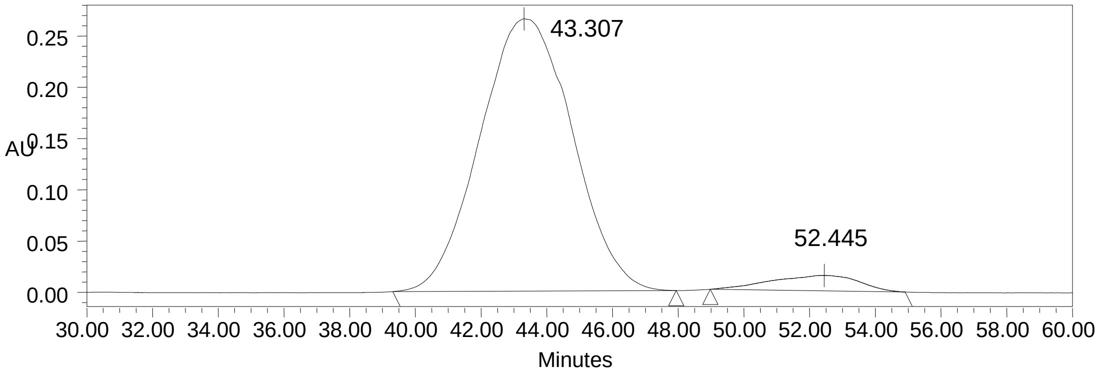
Column: IC
Eluent: Hex:*i*PrOH, 99:1
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**114c**



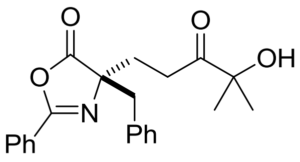
	Retention Time	% Area
2	51.024	51.95
1	43.225	48.05

114c



	Retention Time	% Area
2	52.491	4.37
1	43.307	95.63

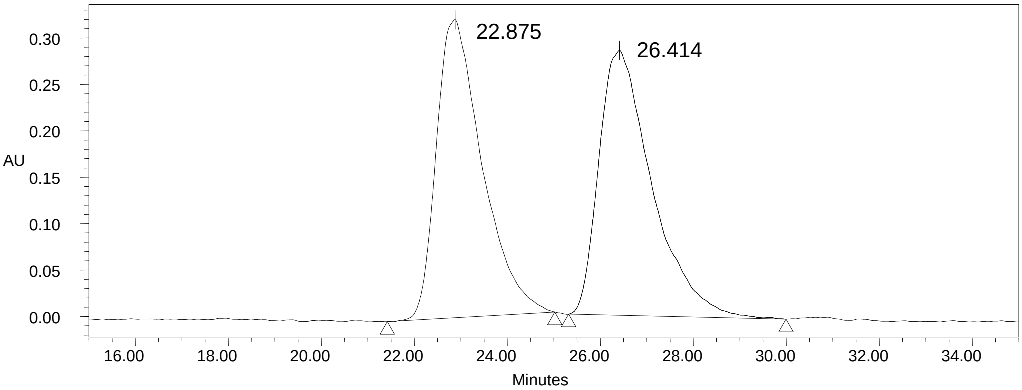
92% *ee*



114d

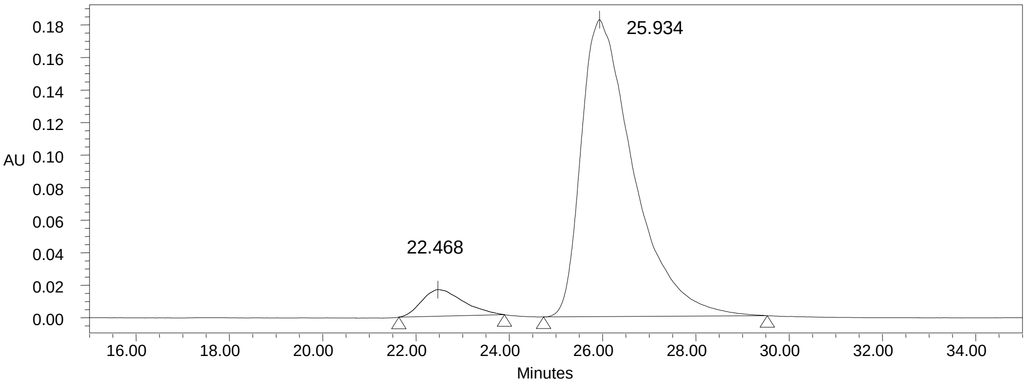
Column: AD-H
Eluent: Hex:*i*PrOH, 95:5
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**114d**



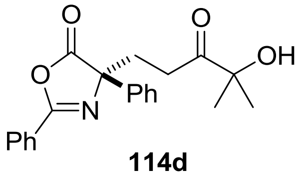
	Retention Time	% Area
2	26.414	50.65
1	22.875	49.35

114d



	Retention Time	% Area
1	22.468	6.15
2	25.934	93.85

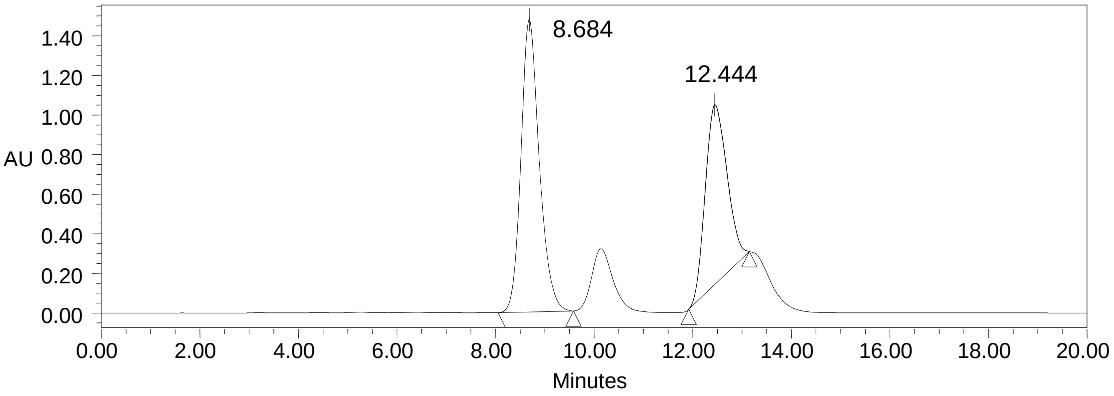
88% *ee*



114d

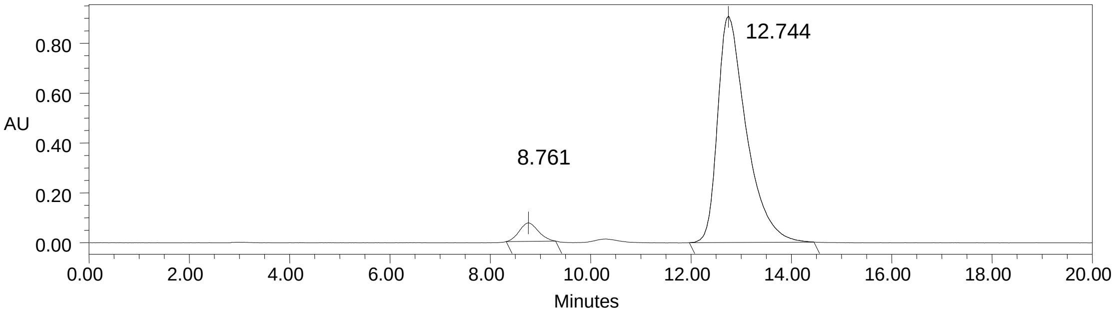
Column: IA
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**114d**



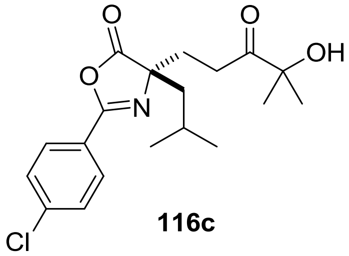
	Retention Time	% Area
2	12.444	42.07
1	8.684	57.93

114d



	Retention Time	% Area
2	12.744	94.90
1	8.761	5.10

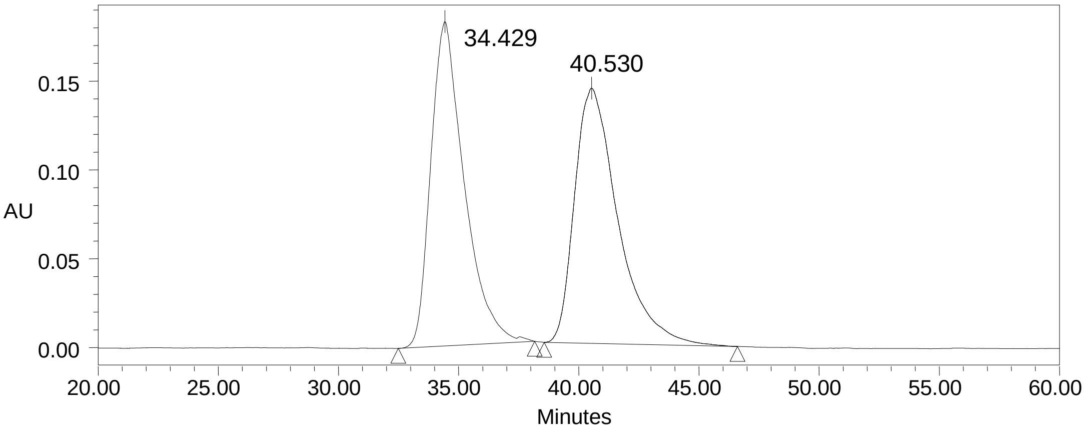
90% *ee*



116c

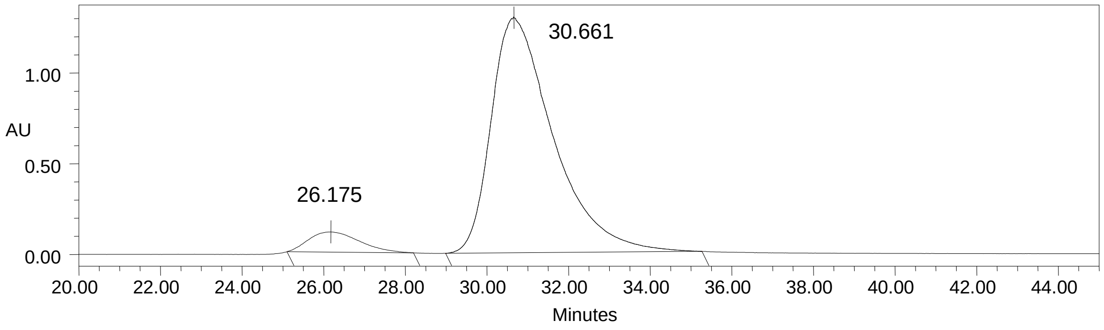
Column: AD-H
Eluent: Hex:*i*PrOH, 98:2
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**116c**



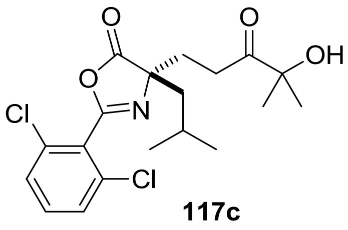
	Retention Time	% Area
2	40.530	50.50
1	34.429	49.50

116c



	Retention Time	% Area
2	30.661	93.45
1	26.175	6.55

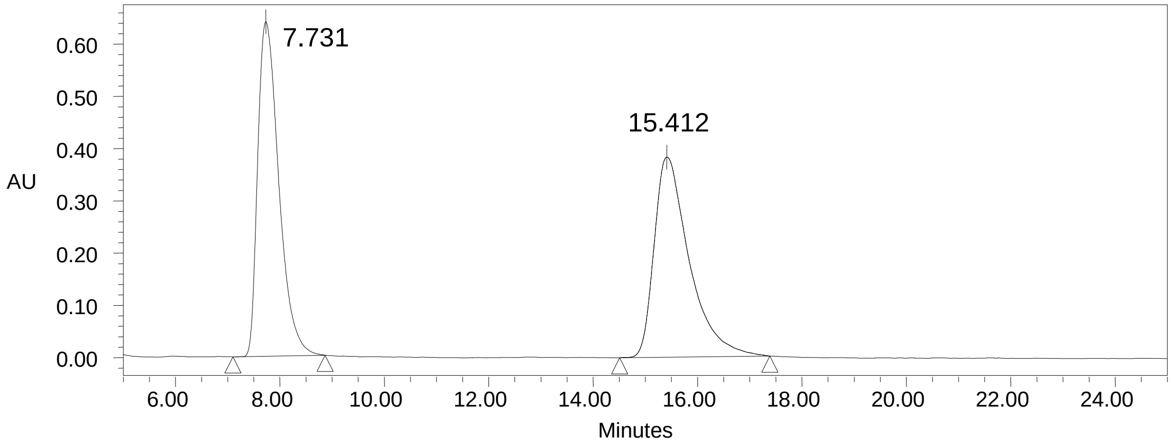
86% *ee*



117c

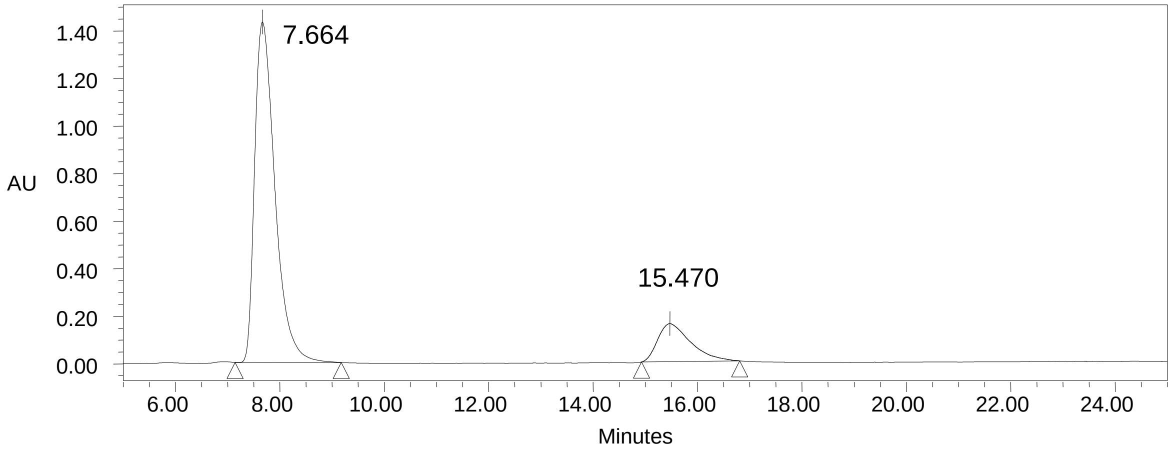
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**117c**



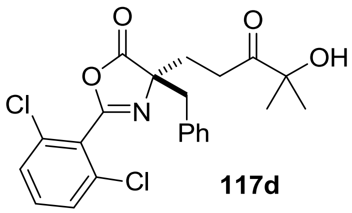
	Retention Time	% Area
2	15.412	49.82
1	7.731	50.18

117c



	Retention Time	% Area
2	15.470	15.25
1	7.664	84.75

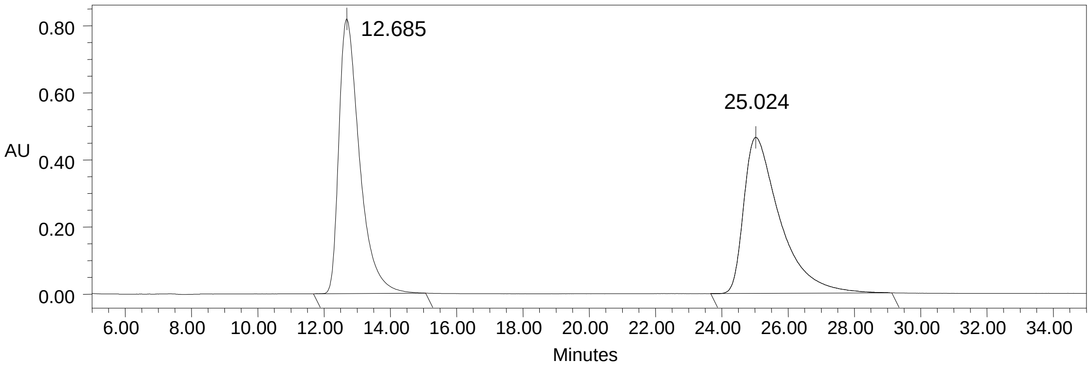
70% *ee*



117d

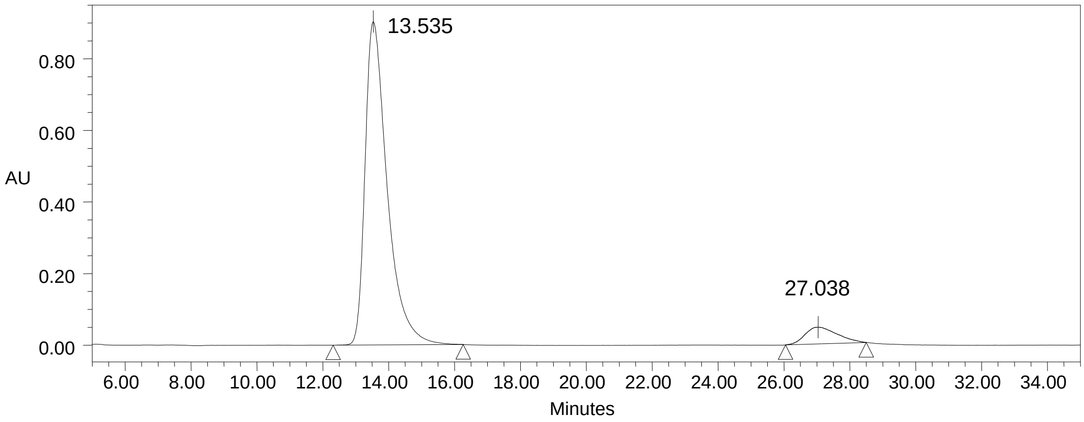
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**117d**



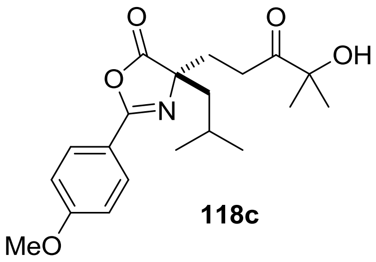
	Retention Time	% Area
2	25.024	49.89
1	12.685	50.11

117d



	Retention Time	% Area
2	27.038	6.31
1	13.535	93.69

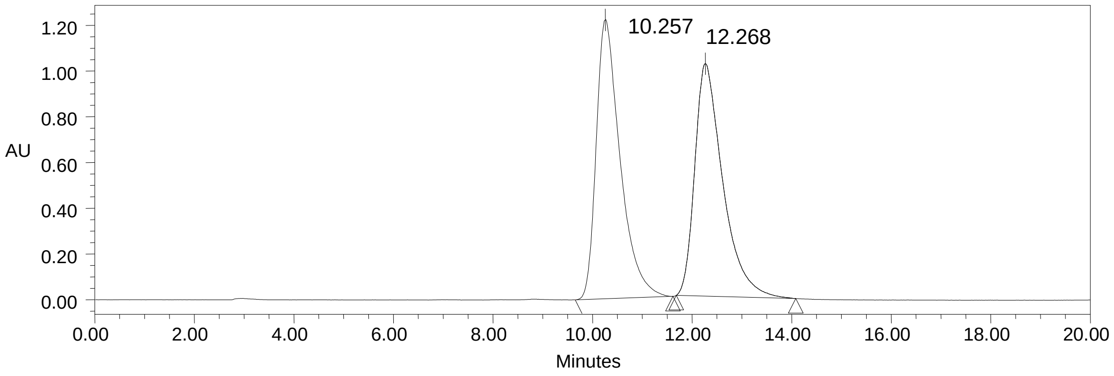
88% *ee*



118c

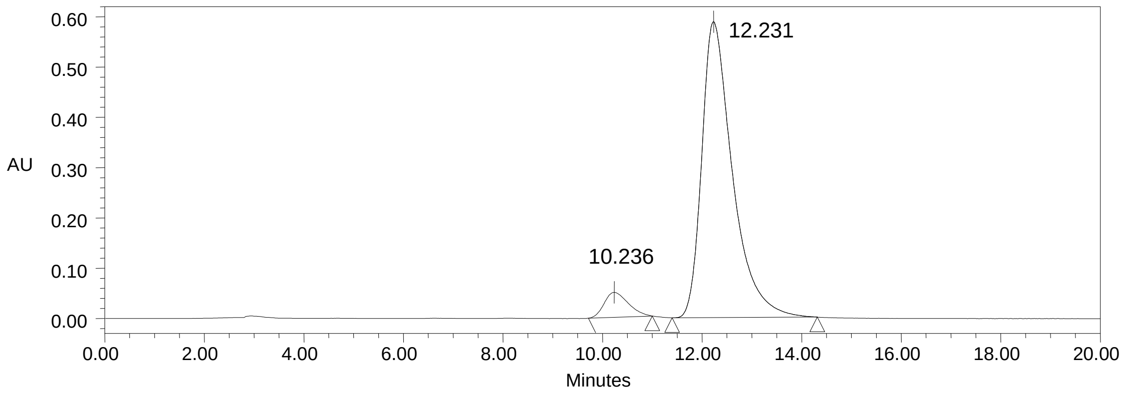
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**118c**



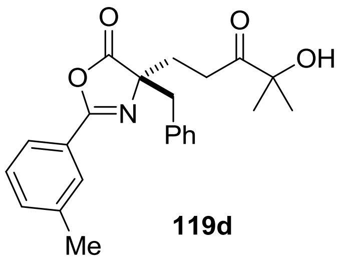
	Retention Time	% Area
2	12.268	49.39
1	10.257	50.61

118c



	Retention Time	% Area
2	12.231	95.07
1	10.236	4.93

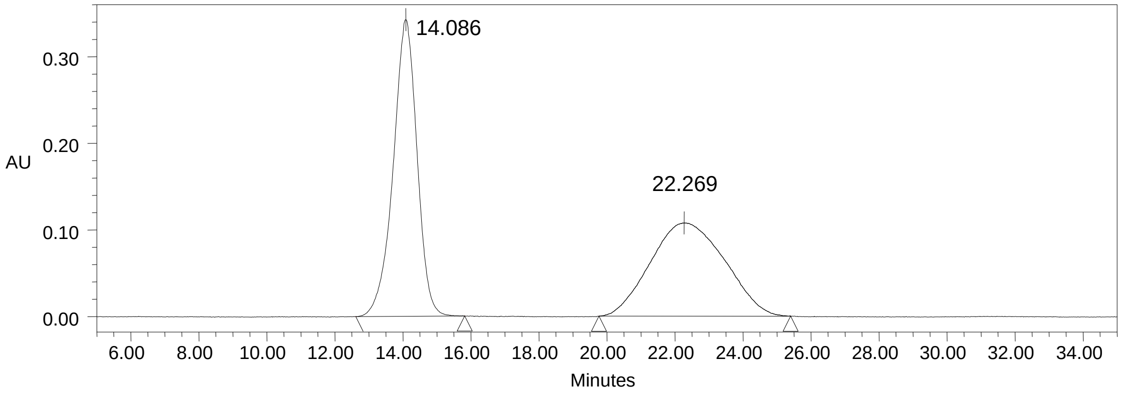
90% *ee*



119d

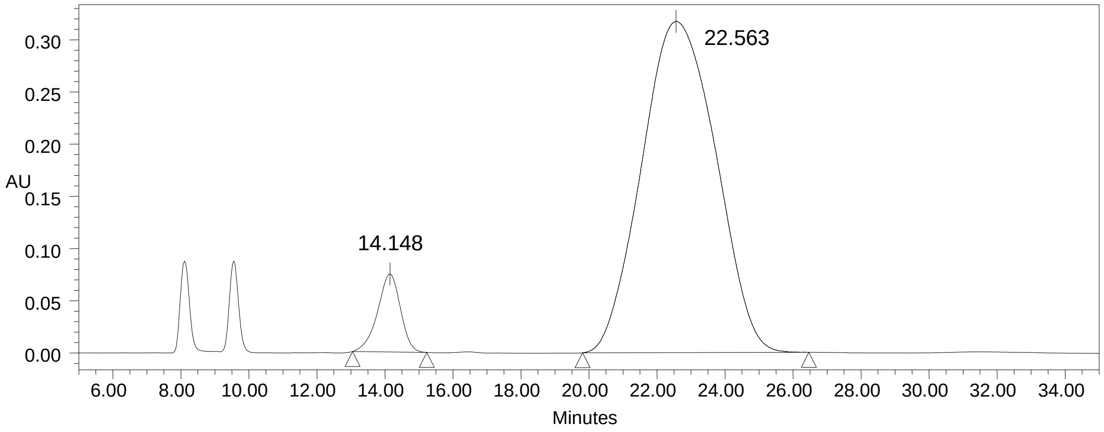
Column: AS-H
Eluent: Hex:*i*PrOH, 95:5
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**119d**



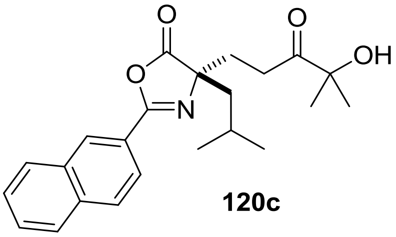
	Retention Time	% Area
2	22.269	49.49
1	14.086	50.51

119d



	Retention Time	% Area
2	22.563	93.25
1	14.148	6.75

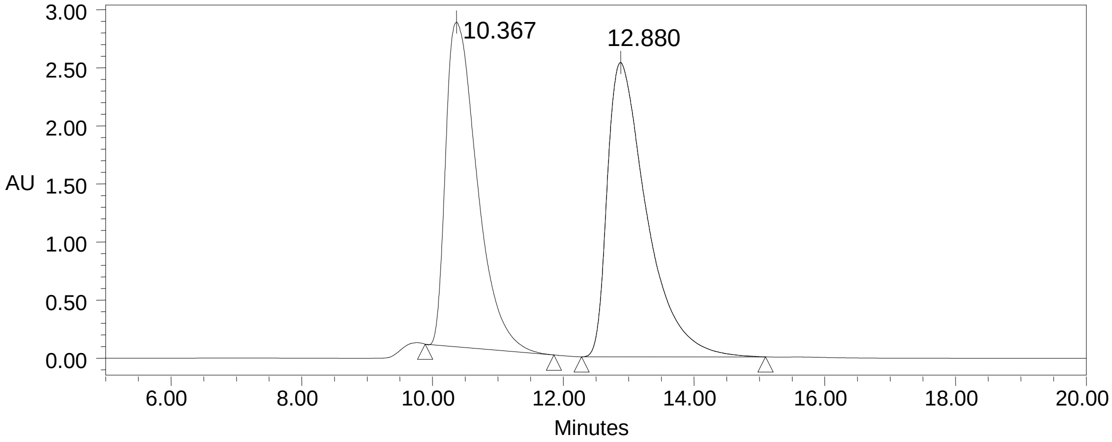
86% *ee*



120c

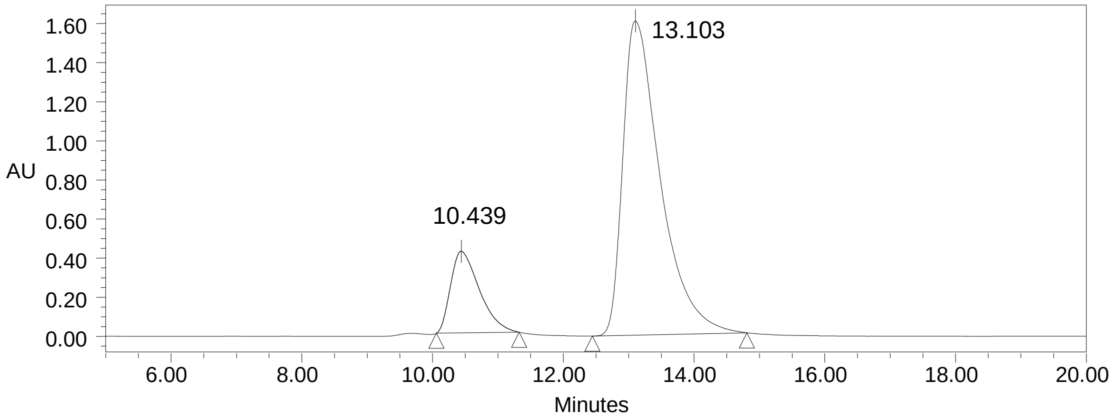
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 1.0 mL/min
λ = 254 nm

rac-**120c**



	Retention Time	% Area
2	12.880	52.69
1	10.367	47.31

120c

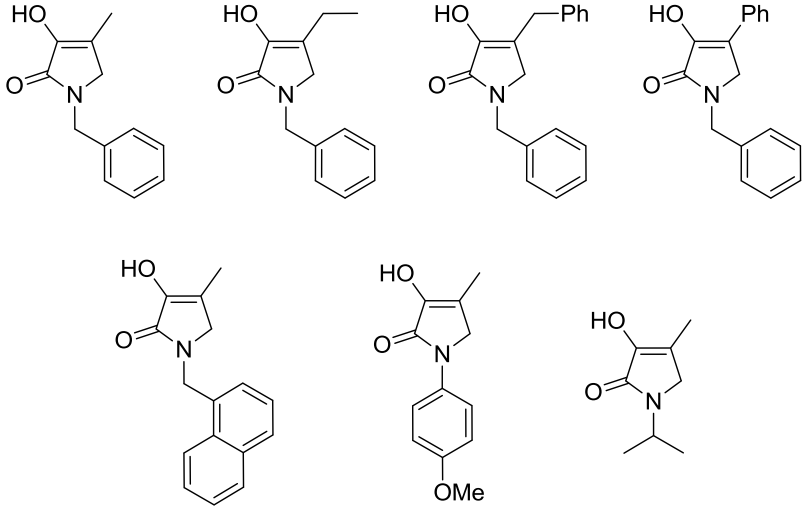


	Retention Time	% Area
2	13.103	83.39
1	10.439	16.61

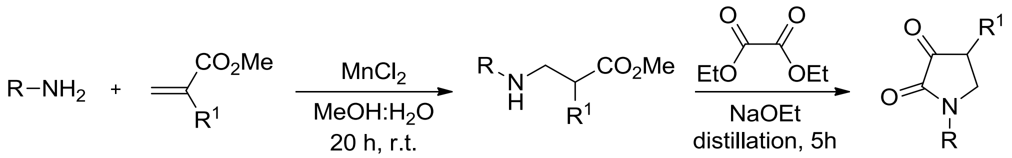
66% *ee*

6.5. EXPERIMENTAL SECTION OF CHAPTER 3

6.5.1. Synthesis of 4-substituted pyrrolidin-2,3-diones



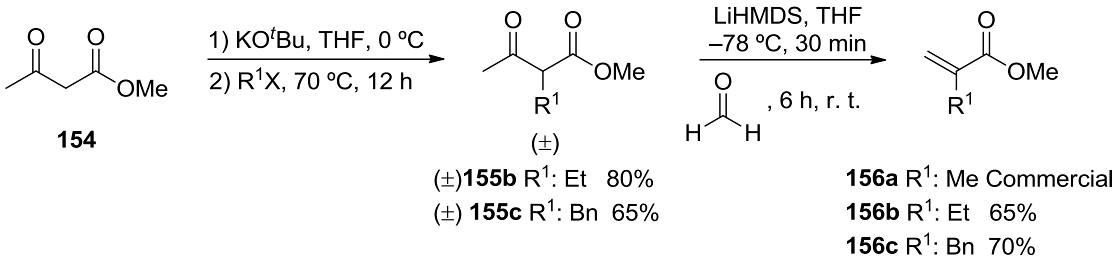
General procedure for the synthesis of 4-substituted pyrrolidin-2,3-diones:



6.5.1.1. Synthesis of acrylates

Methyl acrylate **156a** is commercial and others were prepared according to the following procedure.

Preparation of alkyl acrylates:[375]



1st step: To a suspension of potassium *tert*-butoxide (1.2 equiv.) in THF (2.5 mL/mmol) methyl acetate (1 equiv.) and *tert*-butanol (0.1 equiv.) were added at 0 ºC. The resulting mixture was stirred for 30 min at 0 ºC and then alkyl halide (0.99 equiv.)

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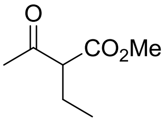
[375] Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem*. **2007**, *5*, 2812–2825.

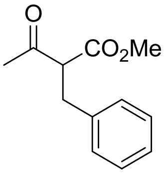
was added. The mixture was warmed up to 70 ºC for 12 h. The reaction was quenched with $NaHCO_3$ (4 mL/mmol) and extracted with Et_2O (3 x 5 mL/mmol). The organic layers were combined and dried over $MgSO_4$. The mixture was concentrated under reduced pressure to afford the desired product which was purified by flash column chromatography.

(±) Methyl 2-ethyl-3-oxobutanoate 155b



The title compound was prepared according the general procedure from methyl acetoacetate (6.48 mL, 60 mmol, 1 equiv.) and ethyl iodide (4.8 mL, 59.4 mmol, 0.99 equiv.). The crude was purified by flash column chromatography (hexane/EtOAc, 90:10) affording a colourless oil (6.92 g, 48 mmol, 80%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.35 (t, *J* = 7.4 Hz, 1H), 2.21 (s, 3H), 1.89 (dd, *J* = 12.2, 4.9 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

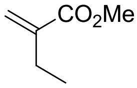
(±) Methyl 2-benzyl-3-oxobutanoate 155c



The title compound was prepared according the general procedure from methyl acetoacetate (6.48 mL, 60 mmol, 1 equiv.) and benzyl bromide (7.1 mL, 59.4 mmol, 0.99 equiv.). The crude was purified by flash column chromatography (hexane/EtOAc, 95:5) affording a colourless oil (8.04 g, 39 mmol, 65%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 –7.10 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 3.17 (d, *J* = 7.6 Hz, 2H), 2.18 (s, 3H).

2nd step: Retro-Claisen Reaction. LiHMDS (1.1 equiv.) was added dropwise to a solution of alkyl acetoacetate (1 equiv.) in THF (8 mL/mmol) at –78 ºC. After 30 min, paraformaldehyde (1 equiv.) was added and the resultant mixture was warmed to r.t. over 6 h. Then reaction mixture was filtered over celite and all organic solvents were removed under reduced pressure. The resulting crude was purified by flash column chromatography.

Methyl 2-methylenebutanoate 156b[376]



The title compound was prepared according the general procedure from methyl 2-ethyl-3-oxobutanoate (6.92 g, 48 mmol). The crude was purified by flash column chromatography (hexane/EtOAc, 90:10) affording a colourless oil (3.6 g, 31.2 mmol, 65%). All the spectroscopic data were identical to reported in the literature. ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (d, *J* = 1.2 Hz, 1H), 5.53 (d, *J* = 1.5 Hz, 1H), 3.76 (s, 3H), 2.52 – 2.19 (m, 2H), 1.08 (t, *J* = 7.4 Hz, 3H).

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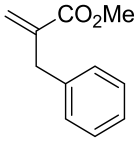
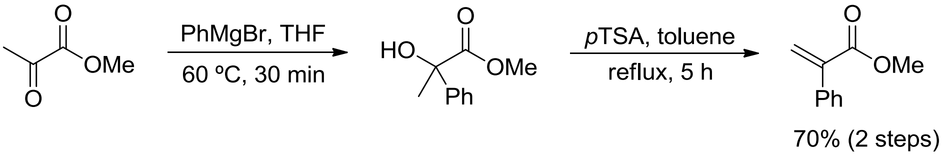
[376] Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc*. **2015**, *137*, 15992–15995.

Methyl 2-benzylacrylate 156c[377]



The title compound was prepared according the general procedure from methyl 2-benzyl-3-oxobutanoate (8.04 g, 39 mmol). The crude was purified by flash column chromatography (hexane/EtOAc, 98:2) affording a colourless oil (4.82 g, 27.3 mmol, 70%). All the spectroscopic data were identical to the reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 5H), 6.24 (d, *J* = 1.1 Hz, 1H), 5.46 (q, *J* = 1.4 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 2H).

Preparation of the aromatic acrylate 159:[375]



The Grinard reagent (1 M in THF, 1.01 equiv.) was added dropwise to a solution of methyl pyruvate (1 equiv.) in THF (4 mL/mmol). After the addition was complete, the mixture was heated to 60 ºC with stirring for 1 h, then cooled, hydrolyzed by the addition of water (1 mL/mmol) and subsequently treated with 1M HCl (2 mL/mmol) to dissolve the precipitate that had been formed. The mixture was filtered and extracted with ethyl acetate (3 x 2 mL/mmol). The combined organic layers were washed with brine (2 x 1 mL/mmol), dried over $MgSO_4$, filtered and evaporated. Without purification, the resulting alcohol was added to a stirred solution of *p*-toluenesulfonic acid (0.1 equiv.) in toluene (10 mL/mmol) and the reaction mixture was stirred at refluxed temperature under a Dean-Stark trap for 4 h. The cooled reation mixture was diluted with ether (30 mL) and washed successively with $NaHCO_3$ solution (1 mL/mmol). The combined organic layers were washed with brine (1 mL/mmol), dried with $MgSO_4$, filtered and evaporated. Purification on flash column chromatography (hexane/EtOAc, 98:2) produced the corresponding ester.

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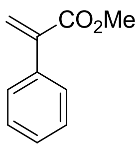
[377] Frlan, R.; Sova, M.; Gobec, S.; Stavber, G.; Casar, Z. *J. Org. Chem*. **2015**, *80*, 7803–7809.

Methyl 2-phenylacrylate[378]

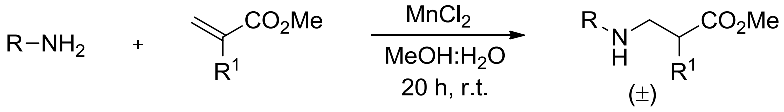


The title compound was prepared according the general procedure from methyl pyruvate (1.36 ml, 15 mmol, 1 equiv.) phenyl magnesium bromide (1M in THF, 15.15 mL, 1.01 equiv.). The crude was purified by flash column chromatography (hexane/EtOAc, 98:2) affording a colourless oil (1.70 g, 10.5 mmol, 70%). All the spectroscopic data were identical to the reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.34 (m, 5H), 6.37 (d, *J* = 1.2 Hz, 1H), 5.90 (d, J = 1.2 Hz, 1H), 3.83(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 141.4, 136.8, 128.4, 128.3, 128.2, 127.0, 52.3.

6.5.1.2. Addition of amines to acrylates: β-Amino esters synthesis

β-Amino esters were afforded through the addition of the corresponding amine to the α-substituted acrylate. The best results were obtained with the catalytic amount of manganese chloride (METHOD A) but with hindered amines, such as isopropyl amine, the use of ruthenium (III) chloride as catalyst and poly ethylene glycol as solvent were necessary (METHOD B).

METHOD A[379]



159 R: Bn
160 R: 1-Naphth-CH$_2$
161 R: PMP

156a R^1: Me
156b R^1: Et
156c R^1: Bn
156e R^1: Ph

(±) **162a** R: Bn R^1: Me
(±) **162b** R: Bn R^1: Et
(±) **162c** R: Bn R^1: Bn
(±) **162e** R: Bn R^1: Ph
(±) **163a** R: 1-Naphth-CH$_2$ R^1: Me
(±) **164a** R: PMP R^1: Me

A mixture of the amine (1 equiv.), acrylate (1 equiv.) and manganese salt (10 mol %) in H_2O (0.6 mL/mmol) and MeOH (0.6 mL/mmol) was kept at r.t. under vigorous stirring for 20 h. After completion of the reaction, methanol was evaporated and the residue dissolved in EtOAc (20 mL/mmol). All salts were filtered, the organic phase was washed with H_2O (2 x 5 mL/mmol) and brine (2 x 5 mL/mmol), dried over $MgSO_4$ and evaporated. The crude product was purified by flash column chromatography on silica gel.

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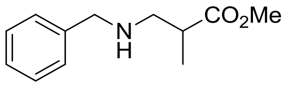
[378] Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed*. **2011**, *50*, 8412–8415.

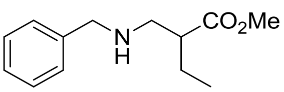
[379] Anupam, R.; Dhiman, K.; Shrishnu, K.; Adinath, M.; Alakananda, H. *The Open Catalysis Journal* **2010**, *3*, 34–39.

(±) Methyl 3-(benzylamino)-2-methylpropanoate 162a[380]



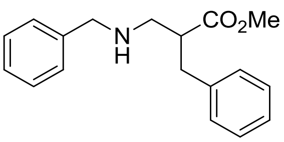
Prepared according to METHOD A starting from benzylamine (2.18 mL, 20 mmol) and methyl methacrylate (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (2.522 g, 12.2 mmol, 66%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 – 7.28 (m, 3H), 7.27 – 7.19 (m, 2H), 3.79 (s, 2H), 3.69 (s, 3H), 2.88 (td, *J* = 9.9, 3.6 Hz, 1H), 2.75 – 2.61 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H).

(±) Methyl 2-((benzylamino)methyl)butanoate 162b



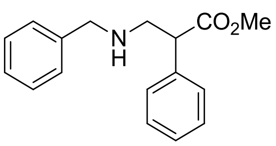
Prepared according to METHOD A starting from benzylamine (2.18 mL, 20 mmol) and methyl 2-methylenebutanoate (2.28 g, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (2.43 g, 11.3 mmol, 55%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 – 7.18 (m, 5H), 3.89 – 3.71 (m, 2H), 3.69 (s, 3H), 2.88 (dd, *J* = 11.9, 8.8 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.51 (dddd, *J* = 8.8, 8.0, 5.9, 4.9 Hz, 1H), 1.74 – 1.45 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H).

(±) Methyl 2-benzyl-3-(benzylamino)propanoate 162c[381]



Prepared according to METHOD A starting from benzylamine (2.18 mL, 20 mmol) and methyl 2-benzylacrylate (3.52 g, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (3.68 g, 13.0 mmol, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 – 7.16 (m, 10H), 3.90 – 3.82 (m, 2H), 3.67 (s, 3H), 3.29 (dd, *J* = 12.0, 8.6 Hz, 4H), 2.93 (dd, *J* = 12.0, 6.5 Hz, 1H).

(±) Methyl 3-(benzylamino)-2-phenylpropanoate 162d[382]



Prepared according to METHOD A starting from benzylamine (2.18 mL, 20 mmol) and methyl 2-phenylacrylate (3.244 g, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (3.501 g, 13.0 mmol, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 – 7.16 (m, 10H), 3.90 – 3.82 (m, 1H), 3.81 (s, 2H), 3.67 (s, 3H), 3.29 (dd, *J* = 12.0, 8.6 Hz, 1H), 2.93 (dd, *J* = 12.0, 6.5 Hz, 1H).

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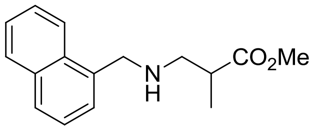
[380] Escalante, J.; Carrillo-Morales, M.; Linzaga, I. *Molecules* **2008**, *13*, 340–347.

[381] Bartrum, H. E.; Adams, H.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 3701–3712.

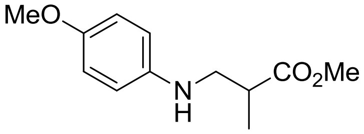
[382] Rangel, H.; Carrillo-Morales, M.; Galindo, J. M.; Castillo, E.; Obregón-Zúñiga, A.; Juaristi, E.; Escalante, J. *Tetrahedron: Asymmetry* **2015**, *26*, 325–332.

(±) Methyl 2-methyl-3-((naphthalen-1-ylmethyl)amino)propanoate 163a



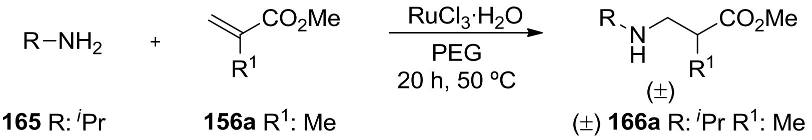
Prepared according to METHOD A starting from 1-naphthylmethylamine (2.93 mL, 20 mmol) and methyl methacrylate (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (2.98 g, 11.6 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 1H), 7.89 – 7.82 (m, 1H), 7.80 – 7.73 (m, 1H), 7.56 – 7.37 (m, 4H), 4.24 (s, 2H), 3.66 (s, 3H), 3.01 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.85 – 2.63 (m, 3H), 1.19 (d, *J* = 6.9 Hz, 3H).

(±) Methyl 3-((4-methoxyphenyl)amino)-2-methylpropanoate 164a



Prepared according to METHOD A starting from *p*-anisidine (2.46 g, 20 mmol) and methyl methacrylate (2.13 mL, 20 mmol). The title compound was purified by flash column chromatography (hexane/EtOAc, 80:20) and isolated as a yellow oil (2.456 g, 11.0 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 – 6.72 (m, 2H), 6.62 – 6.49 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.37 (dd, *J* = 12.9, 7.9 Hz, 1H), 3.17 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.86 – 2.72 (m, 1H), 1.23 (d, *J* = 7.1 Hz, 3H).

METHOD B[383]



$RuCl_3{\cdot}H_2O$ (0.022 g, 0.1 mmol) was added to a mixture of PEG (average MW 2000, 8 g), amine (20 mmol, 1 equiv.) and methyl acrylate (20 mmol, 1 equiv.). The reaction mixture was kept at 50 °C for 16h by magnetic stirring and then cooled to r.t. After the reaction, the solution was poured into Et_2O (40 mL), then the solution was kept cooling in a refrigerator for 30 min to aid precipitation. The precipitate was filtered and washed with further portions of Et_2O, and the washings were combined with the initial filtrate. The combined organic phases were washed several times with H_2O and dried ($MgSO_4$). After filtration and removal of the solvent, the product was purified by flash column chromatography (eluent 1:1 Hex:EtOAc) affording colourless oil.

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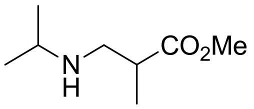
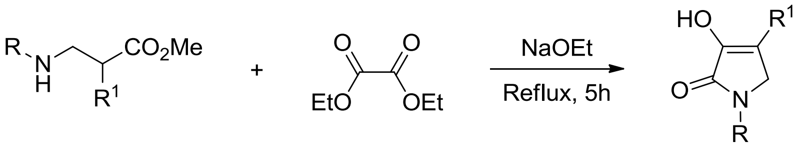
[383] Zhang, H.; Zhang, Y.; Liu, L.; Xu, H.; Wang, Y. *Synthesis* **2005**, *13*, 2129–2136.

(±) Methyl 3-(isopropylamino)-2-methylpropanoate 166a[383]



Prepared according to METHOD B starting from isopropylamine (1.72 mL, 20 mmol) and methyl methacrylate (2.13 mL, 20 mmol). The title compound was isolated as a yellow oil (2.420 g, 15.2 mmol, 76%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.69 (s, 3H), 2.91 – 2.82 (m, 1H), 2.82 – 2.72 (m, 1H), 2.68 – 2.55 (m, 2H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.03 (dd, *J* = 6.2, 1.1 Hz, 6H).

6.5.1.3. Cyclization/decarboxylation reaction[384]

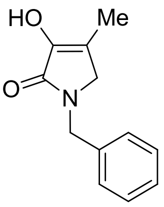


(±) **162a** R = Bn, R^1 = Me
(±) **162b** R = Bn, R^1 = Et
(±) **162c** R = Bn, R^1 = Bn
(±) **162d** R = Bn, R^1 = Ph
(±) **163a** R = 1-Napht-CH$_2$, R^1 = Me
(±) **164a** R = PMP, R^1 = Me
(±) **166a** R = ^{i}Pr, R^1 = Me

168a R = Bn, R^1 = Me
168b R = Bn, R^1 = Et
168c R = Bn, R^1 = Bn
168d R = Bn, R^1 = Ph
169a R = 1-Napht-CH$_2$, R^1 = Me
170a R = PMP, R^1 = Me
171a R = ^{i}Pr, R^1 = Me

To a solution of the β-amino ester compound (10 mmol, 1 equiv.) and ethyl oxalate (1.63 mL, 12 mmol, 1.2 equiv.), sodium ethoxide (817 mg, 12 mmol, 1.2 equiv.) was added. The mixture was heated under reflux for 5 hours and etanol was removed by distillation leaving a liquid residue which was dissolved in a 50 mL of warm water. Acidification with 20% HCl precipitated a solid and the resulting decarboxilated product was collected by filtration which was then purified by using column chromatography on silica gel.

1-Benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one 168a



Prepared according to the general procedure starting from methyl 3-(benzylamino)-2-methylpropanoate (2.073 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtAc, 80:20). The title compound was isolated as a white solid (2.75 g, 8.6 mmol, 86%). m.p. = 140–144 ºC. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55 – 7.06 (m, 5H), 6.48 (s,

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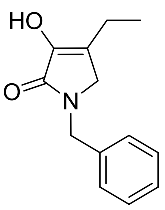
[384] Southwick, P. L.; Crouch, R. T. *J. Am. Chem. Soc.* **1953**, *75*, 3413–3417.

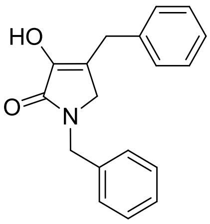
1H), 4.62 (s, 2H), 3.57 (s, 2H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 142.0, 137.0, 128.9, 128.2, 127.8, 118.2, 50.7, 46.9, 10.3. UPLC-DAD-QTOF: $C_{12}H_{14}NO_2$ $[M+H]^+$ calcd.: 204.1025, found: 204.1023.

1-Benzyl-4-ethyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one 168b



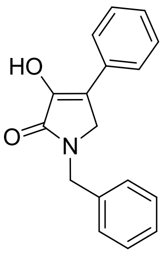
Prepared according to the general procedure starting from methyl 2-((benzylamino)methyl)butanoate (2.21 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtAc, 80:20). The title compound was isolated as a white solid (1.41 g, 6.51 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 5H), 5.99 (s, 1H), 4.62 (s, 2H), 3.60 (s, 2H), 2.34 (qt, *J* = 7.7, 1.0 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 141.1, 136.8, 128.7, 128.0, 127.6, 124.2, 48.8, 46.7, 18.4, 12.4. UPLC-DAD-QTOF: $C_{13}H_{16}NO_2$ $[M+H]^+$ calcd.: 218.1181, found: 218.1180.

1,4-Dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one 168c



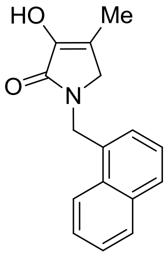
Prepared according to the general procedure starting from methyl 2-benzyl-3-(benzylamino)propanoate (2.79 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtAc, 1:1). The title compound was isolated as a yellow solid (2.60 g, 9.32 mmol, 93%). m.p. = 149–151 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.11 (m, 10H), 4.59 (s, 2H), 3.66 (s, 2H), 3.51 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 142.1, 138.9, 136.9, 129.0, 128.9, 128.8, 128.2, 127.9, 126.7, 120.8, 49.1, 47.0, 31.6. UPLC-DAD-QTOF: $C_{18}H_{18}NO_2$ [M+H]+ calcd.: 280.1338, found: 280.1335.

1-Benzyl-3-hydroxy-4-phenyl-1*H*-pyrrol-2(5*H*)-one 168d



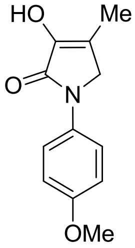
Prepared according to the general procedure starting from methyl 3-(benzylamino)-2-phenylpropanoate (2.693 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtAc, 1:1). The title compound was isolated as a white solid (2.43 g, 9.2 mmol, 92%). m.p. = 240–244 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 – 7.47 (m, 2H), 7.41 – 7.01 (m, 8H), 4.63 (s, 2H), 4.12 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 143.2, 137.5, 132.7, 128.7, 128.5, 127.6, 127.4, 127.1, 125.7, 116.6, 47.1, 45.8. UPLC-DAD-QTOF: $C_{28}H_{36}NO_5$ $[M+H]^+$ calcd.: 266.1181, found: 266.1173.

3-Hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1*H*-pyrrol-2(5*H*)-one 169a



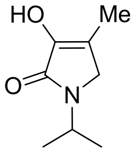
Prepared according to the general procedure starting from methyl 2-methyl-3-((naphthalen-1-ylmethyl)amino)propanoate (2.573 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtAc, 80:20). The title compound was isolated as a white solid (1.65 g, 6.5 mmol, 65%). m.p. = 158–161 ºC. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.17 – 8.09 (m, 1H), 7.92 – 7.79 (m, 2H), 7.60 – 7.35 (m, 4H), 6.73 (s, 1H), 5.07 (s, 2H), 3.45 (s, 2H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.9, 141.8, 134.1, 132.3, 131.6, 129.1, 128.8, 127.5, 127.1, 126.3, 125.4, 123.9, 118.2, 50.7, 45.1, 10.3. UPLC-DAD-QTOF: $C_{16}H_{16}NO_2$ [M+H]+ calcd.: 254.1181, found: 254.1181.

3-Hydroxy-1-(4-methoxyphenyl)-4-methyl-1*H*-pyrrol-2(5*H*)-one 170a



Prepared according to the general procedure starting from methyl 3-((4-methoxyphenyl)amino)-2-methylpropanoate (2.233 g, 10 mmol) and purified by flash silica column chromatography (hexane/EtAc, 1:1). The title compound was isolated as a yellow solid (1.55 g, 7.1 mmol, 71%). m.p. = 173–175 ºC. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 – 7.49 (m, 2H), 6.93 – 6.82 (m, 2H), 6.32 (s, 1H), 4.08 (s, 2H), 3.77 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.4, 156.7, 141.8, 132.6, 120.5, 116.2, 114.6, 55.7, 51.9, 10.4. UPLC-DAD-QTOF: $C_{12}H_{14}NO_3$ [M+H]$^+$ calcd.: 220.0974, found: 220.0973.

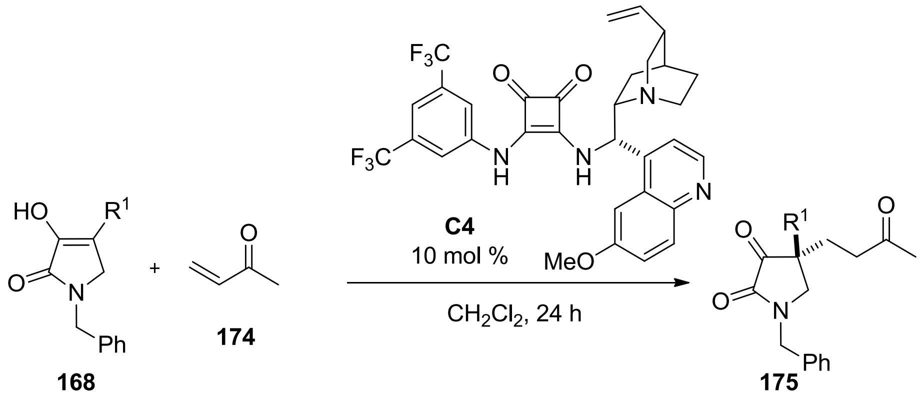
3-Hydroxy-1-isopropyl-4-methyl-1*H*-pyrrol-2(5*H*)-one 170a



Prepared according to the general procedure starting from methyl 3-(isopropylamino)-2-methylpropanoate (1.59 g, 10 mmol) purified by flash silica column chromatography (hexane/EtAc, 80:20). The title compound was isolated as a yellow solid (1.11 g, 7.13 mmol, 71%). m.p. = 138–140 ºC. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.39 (hept, J = 6.8 Hz, 1H), 3.61 (s, 2H), 1.89 (s, 3H), 1.16 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 142.2, 117.2, 46.4, 43.3, 21.0, 10.3. UPLC-DAD-QTOF: $C_8H_{14}NO_2$ [M+H]$^+$ calcd.: 156.1025, found: 156.1011.

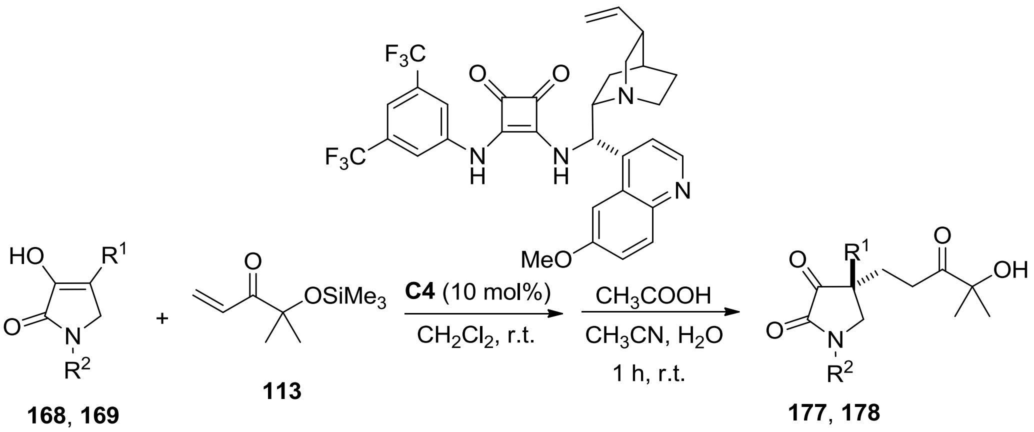
6.5.2. General procedure for the conjugate addition of 4-substituted pyrrolidin-2,3-diones to methyl vinyl ketone and α’-oxy enones

6.5.2.1. Asymmetric reaction to vinyl ketones



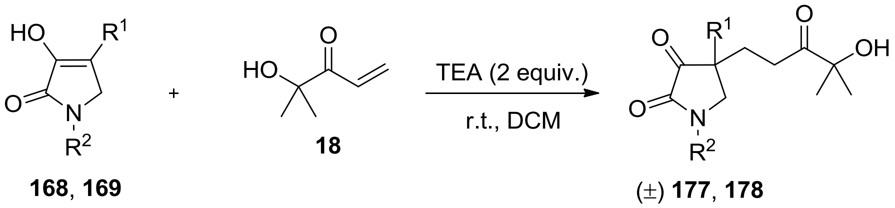
To a mixture of the corresponding α-ketoamide **168** (1 equiv., 0.2 mmol) and methyl vinyl ketone **174** (74 mg, 2 equiv., 0.4 mmol) in dichloromethane (0.4 mL) catalyst **C4** (0.02 mmol, 10 mol%) was added. The mixture was stirred until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

6.5.2.2. Asymmetric reaction to α’-oxy enones



To a mixture of the corresponding α-ketoamide **168** or **169** (1 equiv., 0.2 mmol) and the α’-silyloxyenone **113** (74 mg, 2 equiv., 0.4 mmol) in dichloromethane (0.4 mL) catalyst **C4** (0.02 mmol, 10 mol%) was added. The mixture was stirred until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. For the desilylation step, the reaction crude was dissolved in CH_3CN (1mL) and, H_2O (0.5 mL) and glacial acetic acid (0.3 mL) were added. The reaction mixture was stirred for 1 h at room temperature and it was quenched with $NaHCO_3$ saturated aqueous solution (20 mL). The organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

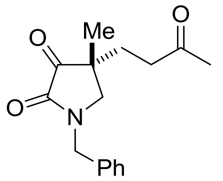
6.5.2.3. Racemic reaction



To a mixture of the corresponding α-ketoamide **168** or **169** (1 equiv., 0.2 mmol) and α'-hydroxy enone **18** (34 mg, 1.5 eq., 0.3 mmol) in dichloromethane (0.4 mL) TEA (56 µL, 0.4 mmol, 2 equiv.) was added at room temperature. The mixture was stirred at the same temperature, until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

*6.5.2.4. Characterization data for compounds **175**, **177** and **178***

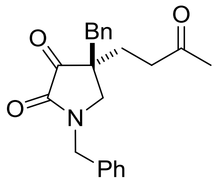
(*R*)-1-Benzyl-4-methyl-4-(3-oxobutyl)pyrrolidine-2,3-dione 175a



The title compound was prepared from 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one **168a** (41 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (41 mg, 0.15 mmol, 75%). $[\alpha]_D^{23}$ = – 1.0° (c=1.75, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) 7.40 – 7.18 (m, 5H), 4.71 (d, *J* = 14.3 Hz, 1H), 4.61 (d, *J* = 14.3 Hz, 1H), 3.29 (d, *J* = 10.9 Hz, 1H), 3.20 (d, *J* = 10.9 Hz, 1H), 2.33 (dd, *J* = 8.7, 6.8 Hz, 2H), 2.05 (s, 3H), 1.86 – 1.73 (m, 2H), 1.15 (s, 3H). ^{13}C NMR

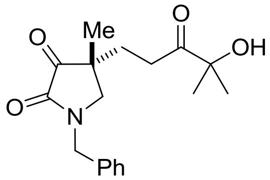
(75 MHz, $CDCl_3$) δ 207.0, 203.6, 159.2, 134.6, 129.2, 128.7, 128.6, 54.0, 48.6, 42.5, 37.8, 30.9, 30.1, 21.8. UPLC-DAD-QTOF: $C_{16}H_{20}NO_3$ $[M+H]^+$ calcd.: 274.1443, found: 274.1453. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 80/20, flow rate= 0.7 mL/min, retention times: 38.1 min (minor.) and 41.3 min (major.)).

(*S*)-1,4-Dibenzyl-4-(3-oxobutyl)pyrrolidine-2,3-dione 175c



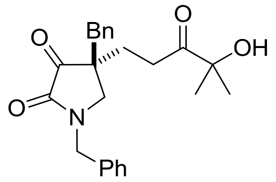
The title compound was prepared from 1,4-dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one **168c** (59 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (59 mg, 0.17 mmol, 84%). $[\alpha]_D^{23}$ = – 15.3° (c=2.0, 92% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 3H), 7.24 – 7.15 (m, 3H), 7.05 – 6.98 (m, 2H), 6.95 – 6.89 (m, 2H), 4.50 (s, 2H), 3.48 (d, *J* = 11.2 Hz, 1H), 3.17 – 3.06 (m, 2H), 2.64 (d, *J* = 13.6 Hz, 1H), 2.49 – 2.22 (m, 2H), 2.08 (s, 3H), 2.04 – 1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 204.4, 159.1, 135.0, 134.4, 129.9, 129.2, 128.9, 128.4, 128.4, 127.5, 49.8, 48.4, 46.9, 41.9, 37.6, 30.8, 30.1. UPLC-DAD-QTOF: $C_{22}H_{24}NO_3$ $[M+H]^+$ calcd.: 350.1756, found: 350.1769. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 21.5 min (minor.) and 40.4 min (major.)).

1-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-methylpyrrolidine-2,3-dione 177a



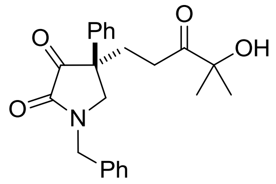
The title compound was prepared from 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one **168a** (41 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (53 mg, 0.17 mmol, 84%). $[\alpha]_D^{23}$ = + 18.9° (c=1.15, 90% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.22 (m, 5H), 4.77 (d, *J* = 14.3 Hz, 1H), 4.61 (d, *J* = 14.3 Hz, 1H), 3.34 (s, 1H), 3.31 (d, *J* = 10.9 Hz, 1H), 3.24 (d, *J* = 10.9 Hz, 1H), 2.53 – 2.43 (m, 2H), 1.92 – 1.82 (m, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 203.5, 159.2, 134.6, 129.3, 128.7, 128.6, 76.6, 53.9, 48.6, 42.5, 31.1, 30.2, 26.7, 21.9. UPLC-DAD-QTOF: $C_{18}H_{24}NO_4$ $[M+H]^+$ calcd.: 318.1705, found: 318.1705. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 40/60, flow rate= 0.7 mL/min, retention times: 23.1 min (major.) and 27.9 min (minor.)).

1,4-Dibenzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)pyrrolidine-2,3-dione 177c



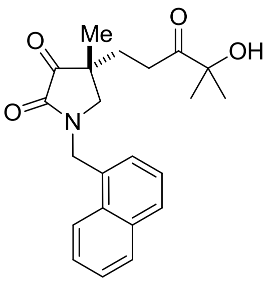
The title compound was prepared from 1,4-dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one **168b** (59 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (55 mg, 0.14 mmol, 70%). $[\alpha]_D^{23}$ = + 17.6° (c=1.45, 84% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 7H), 7.08 – 6.90 (m, 3H), 4.54 (d, *J* = 14.4 Hz, 1H), 4.47 (d, *J* = 14.4 Hz, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 3.30 (s, 1H), 3.17 – 3.06 (m, 2H), 2.66 (d, *J* = 13.7 Hz, 1H), 2.63 – 2.34 (m, 2H), 2.04 (ddd, *J* = 14.2, 9.9, 5.9 Hz, 1H), 1.90 (ddd, *J* = 14.3, 10.3, 5.4 Hz, 1H), 1.33 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 204.3, 159.1, 134.9, 134.4, 123.0, 129.3, 129.0, 128.5, 128.5, 127.7, 76.7, 49.9, 48.6, 46.9, 42.0, 31.0, 30.0, 26.8. UPLC-DAD-QTOF: $C_{24}H_{28}NO_4$ $[M+H]^+$ calcd.: 394.2018, found: 394.2007. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 70/30, flow rate= 1.0 mL/min, retention times: 25.9 min (minor.) and 31.2 min (major.)).

1-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-phenylpyrrolidine-2,3-dione 177d



The title compound was prepared from 1-benzyl-3-hydroxy-4-phenyl-1*H*-pyrrol-2(5*H*)-one **168d** (53 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (45 mg, 0.12 mmol, 60%). $[\alpha]_D^{23}$ = – 0.14° (c=1.25, 80% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 6.94 (m, 10H), 4.71 (q, *J* = 14.4 Hz, 2H), 3.82 (d, *J* = 10.9 Hz, 1H), 3.61 (d, *J* = 11.0 Hz, 1H), 3.40 (s, 1H), 2.64 – 2.45 (m, 1H), 2.36 – 2.20 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 200.4, 159.0, 137.4, 134.4, 129.4, 129.3, 128.8, 128.8, 128.2, 126.5, 76.5, 54.5, 50.5, 48.7, 31.8, 30.5, 26.7, 26.6. UPLC-DAD-QTOF: $C_{23}H_{26}NO_4$ $[M+H]^+$ calcd.: 380.1862, found: 380.1870. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 40/60, flow rate= 0.6 mL/min, retention times: 12.7 min (minor.) and 28.3 min (major.)).

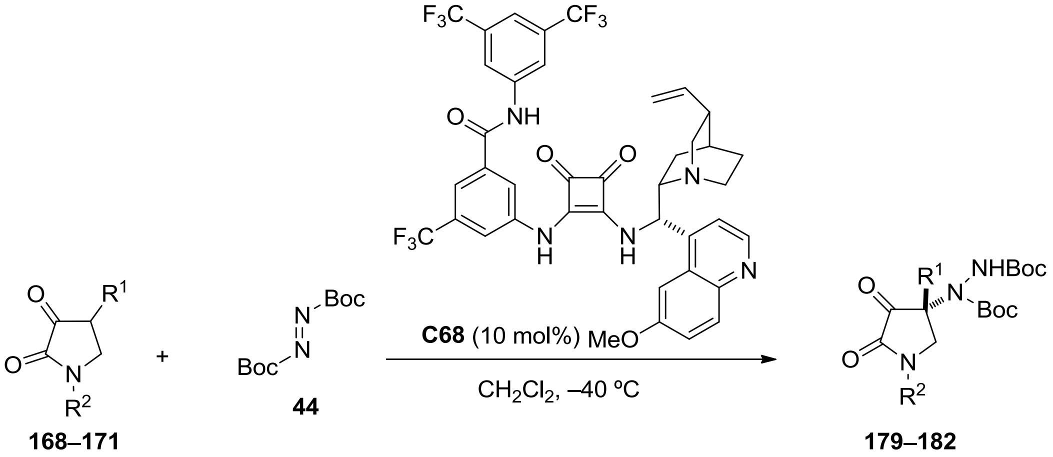
4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-(naphthalen-1-ylmethyl)pyrrolidine-2,3-dione 178a



The title compound was prepared from 3-hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1*H*-pyrrol-2(5*H*)-one **169a** (51 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (63 mg, 0.17 mmol, 86%). $[\alpha]_D^{23}$ = + 18.3° (c=1.6, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 – 7.97 (m, 1H), 7.96 – 7.76 (m, 2H), 7.67 – 7.36 (m, 4H), 5.31 (d, *J* = 14.4 Hz, 1H), 4.98 (d, *J* = 14.4 Hz, 1H), 3.32 (s, 1H), 3.19 – 3.04 (m, 2H), 2.40 – 2.09 (m, 2H), 1.85 – 1.61 (m, 2H), 1.16 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 203.6, 158.8, 134.1, 131.5, 130.0, 129.9, 129.1, 128.9, 127.6, 126.7, 125.3, 123.5, 76.5, 53.6, 46.9, 42.5, 31.2, 23.0, 26.6, 22.2. UPLC-DAD-QTOF: $C_{22}H_{26}NO_4$ $[M+H]^+$ calcd.: 368.1862, found: 368.1861. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/ethanol 50/50, flow rate= 0.5 mL/min, retention times: 13.6 min (minor.) and 15.7 min (major.)).

6.5.3. General procedure for the α-amination of pyrrolidin-2,3-diones with di-*tert*-butyl azodicarboxylate

6.5.3.1. Asymmetric reaction



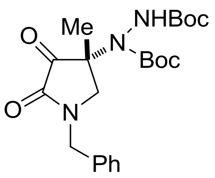
To a mixture of the corresponding α-ketoamide (0.2 mmol, 1 equiv.) and catalyst **C68** (16 mg, 0.02 mmol, 10 mol %) in dichloromethane (0.4 mL), di-*tert*-butyl azodicarboxylate **44** (69 mg, 0.3 mmol, 1.5 equiv.) was added at –40 ºC. The resulting mixture was stirred at the same temperatura until consumption of the α-ketoamide (monitored by ^{1}H-NMR). The reaction mixture was directly purified by flash column chromatography on silica gel (eluent hexane/ ethyl acetate 80/20) without previous work-up to afford the expected adducts.

6.5.3.2. Racemic reaction

Racemic reactions were conducted following the procedure for the asymmetric version, but using as catalyst TEA (2 equiv.) and running the reaction at room temperature.

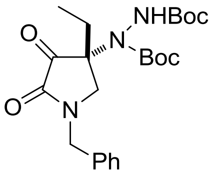
*6.5.3.3. Characterization data for compounds **179–182***

Di-*tert*-butyl 1-(1-benzyl-3-methyl-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 179a



Prepared according to the general procedure starting from 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrrol-2(5*H*)-one **168a** (41 mg, 0.2 mmol). The title compound was isolated as a white foam (80 mg, 0.18 mmol, 92%). [α]$_D^{23}$ = + 54.2° (c=1.16, 99% *ee*, CH$_2$Cl$_2$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.54 – 7.14 (m, 5H), 6.45 (s, 1H), 4.81 (d, *J* = 14.6 Hz, 1H), 4.60 (d, *J* = 15.9 Hz, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 3.29 (d, *J* = 7.3 Hz, 1H), 1.52 (s, 3H), 1.49 – 1.22 (m, 18H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 195.3, 158.6, 155.9, 154.5, 134.8, 128.9, 128.6, 128.1, 83.4, 82.1, 60.0, 54.6, 48.0, 28.2, 28.1, 21.1. UPLC-DAD-QTOF: C$_{22}$H$_{31}$N$_3$O$_6$Na [M+Na]$^+$ calcd.: 456.2111, found: 456.2117. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 85/15, flow rate= 0.7 mL/min, retention times: 10.5 min (major.) and 13.9 min (minor.)).

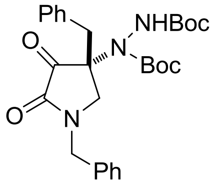
Di-*tert*-butyl 1-(1-benzyl-3-ethyl-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 179b



Prepared according to the general procedure starting from 1-benzyl-4-ethyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one **168b** (43 mg, 0.2 mmol). The title compound was isolated as a white foam (80 mg, 0.178 mmol, 89%). [α]$_D^{23}$ = + 83.1° (c=1.01, 96% *ee*, CH$_2$Cl$_2$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42 – 7.18 (m, 5H), 6.54 (s, 1H), 4.85 (d, *J* = 14.5 Hz, 1H), 4.49 (d, *J* = 15.4 Hz, 1H), 3.92 (d, *J* = 11.4 Hz, 1H), 3.29 (d, *J* = 11.1 Hz, 1H), 1.61 (q, *J* = 7.4 Hz, 2H), 1.42 (s, 9H), 1.35 (s, 9H), 0.70 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 195.5, 159.3, 156.0, 154.8, 134.9, 129.2, 128.9, 128.5, 128.2, 128.1, 83.4, 62.6, 53.1, 48.1, 28.5, 28.3, 28.1, 7.2. UPLC-DAD-QTOF: C$_{23}$H$_{33}$N$_3$O$_6$Na [M+Na]$^+$

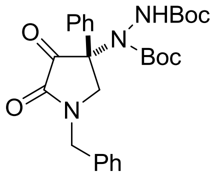
calcd.: 470.2267, found: 470.2269. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 85/15, flow rate= 0.7 mL/min, retention times: 8.9 min (major.) and 13.3 min (minor.)).

Di-*tert*-butyl 1-(1,3-dibenzyl-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 179c



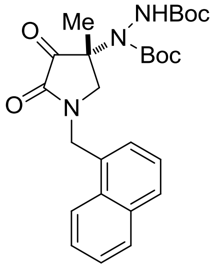
Prepared according to the general procedure starting from 1,4-dibenzyl-3-hydroxy-1*H*-pyrrol-2(5*H*)-one **168c** (59 mg, 0.2 mmol). The title compound was isolated as a white foam (88 mg, 0.17 mmol, 86%). $[\alpha]_D^{24}$ = + 68.0° (c=1.08, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.06 (m, 6H), 7.03 – 6.79 (m, 4H), 6.66 (s, 1H), 4.39 – 4.12 (m, 2H), 3.87 (d, *J* = 11.5 Hz, 1H), 3.56 (d, *J* = 10.1 Hz, 1H), 3.12 (d, *J* = 12.7 Hz, 1H), 2.86 (d, *J* = 12.6 Hz, 1H), 1.47 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 159.0, 156.0, 154.6, 134.4, 131.7, 130.3, 128.9, 128.8, 128.1, 127.9, 127.7, 83.7, 82.3, 62.2, 51.8, 47.8, 41.0, 28.3, 28.1. UPLC-DAD-QTOF: $C_{28}H_{35}N_3O_6Na$ $[M+Na]^+$ calcd.: 532.2424, found: 532.2426. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 0.7 mL/min, retention times: 31.6 min (minor.) and 36.1 min (major.)).

Di-*tert*-butyl 1-(1-benzyl-4,5-dioxo-3-phenylpyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 179d



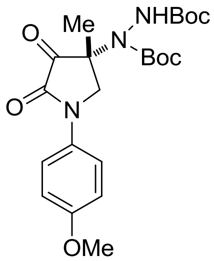
Prepared according to the general procedure starting from 1-benzyl-3-hydroxy-4-phenyl-1*H*-pyrrol-2(5*H*)-one **168d** (53 mg, 0.2 mmol). The title compound was isolated as a white foam (78 mg, 0.15 mmol, 75%). $[\alpha]_D^{24}$ = – 8.8° (c=1.05, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 10H), 6.26 (s, 1H), 4.98 (d, *J* = 14.1 Hz, 1H), 4.49 (d, *J* = 14.2 Hz, 1H), 4.32 (d, *J* = 10.7 Hz, 1H), 4.15 (d, *J* = 9.7 Hz, 1H), 1.40 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 158.4, 155.3, 134.7, 131.8, 129.4, 129.1, 129.0, 128.6, 128.2, 128.0, 125.4, 83.7, 81.9, 67.5, 51.0, 48.2, 28.1. UPLC-DAD-QTOF: $C_{27}H_{33}N_3O_6Na$ $[M+Na]^+$ calcd.: 518.2267, found: 518.2266. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol, 80/19/1, flow rate= 0.5 mL/min, retention times: 14.5 min (minor.) and 21.2 min (major.)).

Di-*tert*-butyl 1-(3-methyl-1-(naphthalen-1-ylmethyl)-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 180a



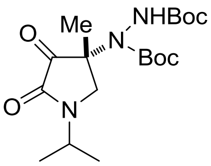
Prepared according to the general procedure starting from 3-hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1*H*-pyrrol-2(5*H*)-one **169a** (51 mg, 0.2 mmol). The title compound was isolated as a white foam (94 mg, 0.19 mmol, 97%). $[\alpha]_D^{25}$ = + 56.8° (c=1.06, 99% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.72 (m, 2H), 7.54 – 7.30 (m, 5H), 6.63 (s, 1H), 5.54 (d, *J* = 14.7 Hz, 1H), 4.71 (d, *J* = 14.7 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 1H), 3.07 (d, *J* = 11.1 Hz, 1H), 1.38 (s, 9H), 1.33 (s, 9H), 1.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 158.3, 155.8, 154.5, 133.9, 131.4, 123.0, 129.3, 128.8, 127.9, 127.0, 126.3, 125.3, 123.5, 83.4, 82.0, 60.1, 54.1, 46.4, 28.2, 28.0, 21.0. UPLC-DAD-QTOF: $C_{26}H_{33}N_3O_6Na$ $[M+Na]^+$ calcd.: 506.2267, found: 506.2270. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 30.9 min (major.) and 45.7 min (minor.)).

Di-*tert*-butyl 1-(1-(4-methoxyphenyl)-3-methyl-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 181a



Prepared according to the general procedure starting from 3-hydroxy-1-(4-methoxyphenyl)-4-methyl-1*H*-pyrrol-2(5*H*)-one **170a** (44 mg, 0.2 mmol). The title compound was isolated as a white foam (85 mg, 0.19 mmol, 95%). $[\alpha]_D^{25}$ = + 44.4° (c=1.00, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.55 (s, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 3.77 – 3.85 (m, 4H), 1.40 – 1.51 (m, 21H).^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 158.0, 156.9, 156.1, 154.5, 132.0, 121.5, 114.3, 83.5, 82.2, 60.0, 55.9, 55.6, 28.3, 28.10, 21.5. UPLC-DAD-QTOF: $C_{22}H_{31}N_3O_7Na$ $[M+Na]^+$ calcd.: 472.2060, found: 472.2068. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 12.3 min (minor.) and 15.5 min (major.)).

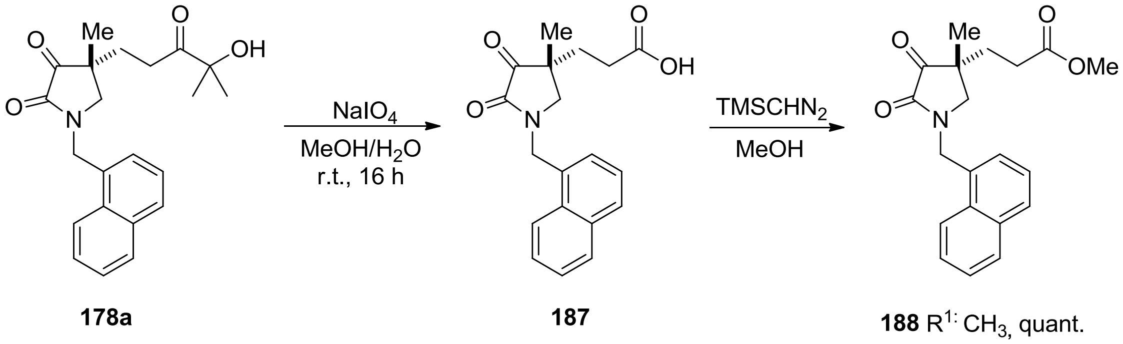
Di-*tert*-butyl 1-(1-isopropyl-3-methyl-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate 182a



Prepared according to the general procedure starting from methyl 3-(isopropylamino)-2-methylpropanoate **171a** (31 mg, 0.2 mmol). The title compound was isolated as a white foam (60 mg, 0.16 mmol, 80%). $[\alpha]_D^{23}$ = + 50.1° (c=1.8, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1H), 4.73 – 4.48 (m, 1H), 3.91 (d, *J* = 11.4 Hz, 1H), 3.34 (d, *J* = 12.7 Hz, 1H), 1.47 (s, 9H), 1.36 (s, 9H), 1.29 (s, 3H), 1.27 – 1.13 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 158.0, 156.1, 154.4, 83.3, 82.2, 60.6, 49.9, 44.4, 28.3, 21.3, 19.3. UPLC-DAD-QTOF: $C_{18}H_{31}N_3O_6Na$ $[M+Na]^+$ calcd.: 408.2111, found: 408.2114. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 0.7 mL/min, retention times: 10.8 min (minor.) and 13.0 min (major.)).

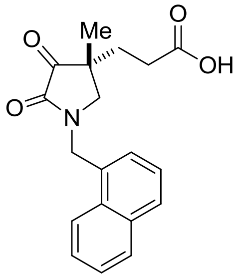
6.5.4. Elaboration of the adducts

*6.5.4.1. To carboxylic acid **187** and ester **188***



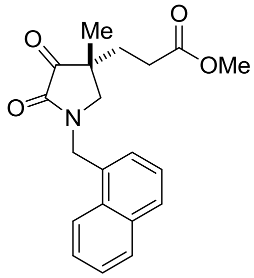
A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of the α'-hydroxy ketone **178a** (0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 16h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid. For the obtention of the ester, the carboxylic acid was dissolved in MeOH (1 mL/mmol) and $TMSCHN_2$ (2M in Et_2O, 2 equiv.) was added dropwise. The reaction mixture was stirred for 5 h and then all organic solvents were evaporated under reduced pressure. The resulting crude was purified by flash column chromatography to afford the desired methyl ester.

3-(3-Methyl-1-(naphthalen-1-ylmethyl)-4,5-dioxopyrrolidin-3-yl)propanoic acid 187



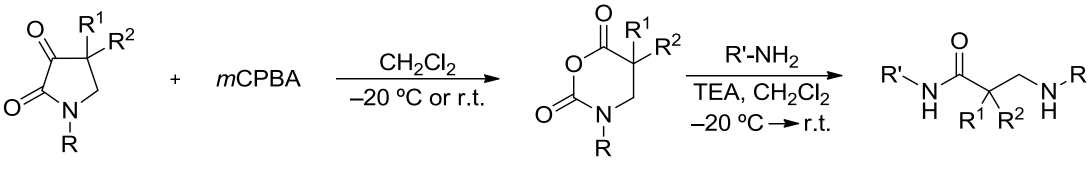
The title compound was prepared from 4-(4-hydroxy-4methyl-3-oxopentyl)-4-methyl-1-(naphthalen-1-ylmethyl)pyrrolidine-2,3-dione **178a** (74 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 16h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 50/50) to give the title compound as a white foam (55 mg, 0.17 mmol, 86%). $[\alpha]_D^{23}$ = + 10.2° (c=1.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 – 7.83 (m, 3H), 7.68 – 7.42 (m, 4H), 5.18 (q, *J* = 14.5 Hz, 2H), 3.21 (d, *J* = 11.0 Hz, 1H), 3.07 (d, *J* = 11.0 Hz, 1H), 2.28 – 2.13 (m, 2H), 1.91 – 1.68 (m, 2H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 176.9, 159.1, 134.1, 131.5, 123.0, 129.8, 129.1, 128.7, 127.5, 126.7, 125.3, 123.5, 53.5, 47.0, 42.7, 31.6, 28.7, 21.8. UPLC-DAD-QTOF: $C_{19}H_{20}NO_4$ $[M+H]^+$ calcd.: 326.1392, found: 326.1401.

Methyl 3-(3-methyl-1-(naphthalen-1-ylmethyl)-4,5-dioxopyrrolidin-3-yl)propanoate 188



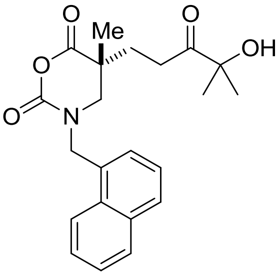
The title compound was prepared from 3-(3-methyl-1-(naphthalen-1-ylmethyl)-4,5-dioxopyrrolidin-3-yl)propanoic acid **187** (55 mg, 0.17 mmol) following the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (56 mg, 0.17 mmol, 99%). $[\alpha]_D^{25}$ = + 10.9° (c=0.7, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 – 7.78 (m, 3H), 7.69 – 7.43 (m, 4H), 5.16 (s, 2H), 3.57 (s, 3H), 3.16 (d, *J* = 11.0 Hz, 1H), 3.03 (d, *J* = 11.0 Hz, 1H), 2.15 – 2.04 (m, 2H), 1.84 – 1.68 (m, 2H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 172.9, 158.9, 134.1, 131.5, 130.0, 129.9, 129.1, 128.8, 127.5, 126.7, 125.3, 123.5, 53.4, 52.0, 47.0, 42.7, 31.9, 28.8, 21.9. UPLC-DAD-QTOF: $C_{20}H_{22}NO_4$ $[M+H]^+$ calcd.: 340.1549, found: 340.1541.

6.5.4.2. To NCAs and ring opening with amines



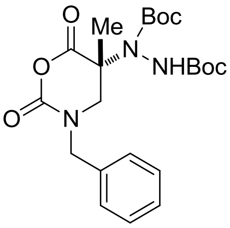
1st step: To a solution of the Michael adduct (0.2 mmol, 1 equiv.) in CH_2Cl_2 (1 mL), *m*CPBA (67 mg, 0.3 mmol, 1.5 equiv.) was slowly added at –20 ºC. The reaction mixture was stirred at –20 ºC or warmed up to room temperature. The reaction was quenched with aqueous 10% $NaHSO_3$ and it was extracted with CH_2Cl_2. All organic phases were combined, washed with NaOH 1 N, dried over $MgSO_4$ and evaporated under reduced pressure to afford the corresponding NCAs.

(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-3-(naphthalen-1-ylmethyl)-1,3-oxazinane-2,6-dione 189



The title compound was prepared starting from 4-(4-hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-(naphthalen-1-ylmethyl)pyrrolidine-2,3-dione **178a** (73 mg, 0.2 mmol) and following the general procedure at –20 ºC for 1 h. The crude material was pure enough for the next step (77 mg, 0.2 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.05 (m, 1H), 8.03 – 7.84 (m, 2H), 7.67 – 7.35 (m, 4H), 5.15 (d, *J* = 14.5 Hz, 1H), 5.08 (d, *J* = 14.5 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.41 (ddd, *J* = 18.1, 9.3, 5.9 Hz, 1H), 2.26 (ddd, *J* = 18.1, 9.1, 5.8 Hz, 1H), 1.79 (ddd, *J* = 14.9, 9.1, 6.0 Hz, 1H), 1.50 (ddd, *J* = 14.7, 9.2, 5.7 Hz, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 0.99 (s, 3H).

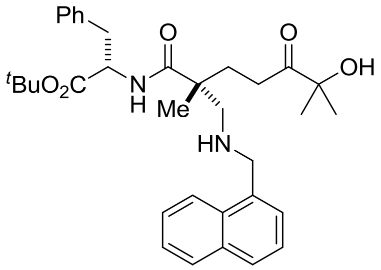
(*R*)-Di-*tert*-butyl 1-(3-benzyl-5-methyl-2,6-dioxo-1,3-oxazinan-5-yl)hydrazine-1,2-dicarboxylate 193



The title compound was prepared starting from di-tert-butyl 1-(1-benzyl-3-methyl-4,5-dioxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate **179a** (87 mg, 0.2 mmol) and following the general procedure adding *m*-CPBA at –20 ºC, warming up slowly and stirring at room temperature for 6 h. The crude material was pure enough for the next step (90 mg, 0.2 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.09 (m, 5H), 4.95 – 4.72 (m, 1H), 4.33 (dd, *J* = 16.1, 9.2 Hz, 1H), 4.19 – 3.81 (m, 1H), 3.53 (d, *J* = 13.6 Hz, 1H), 3.22 – 3.01 (m, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 1.36 (s, 3H).

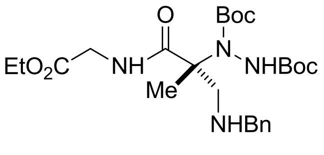
2nd step: The corresponding amino ester hydrochloride (1.1 equiv.) was dissolved in CH_2Cl_2 (2 mL/mmol) and TEA (2 equiv.) was added. The mixture was stirred for 30 min and then it was cooled to –20 ºC. At this temperature the crude NCA (0.2 mmol, 1 equiv.) was dissolved in CH_2Cl_2 was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with HCl 1N, extracted with CH_2Cl_2, washed with $NaHCO_3$, dried over $MgSO_4$ and the organic layer was evaporated under reduced pressure.

(*S*)-*tert*-Butyl 2-((*R*)-6-hydroxy-2,6-dimethyl-2-(((naphthalen-1-ylmethyl)amino)methyl)-5-oxoheptanamido)-3-phenylpropanoate 190



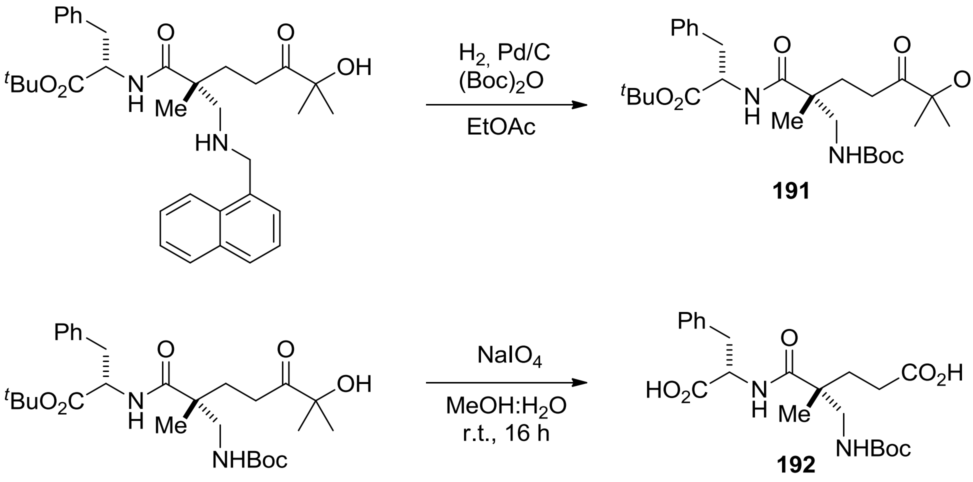
The title compound was prepared from (*R*)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-3-(naphthalen-1-ylmethyl)-1,3-oxazinane-2,6-dione **189** (77 mg, 0.2 mmol), (*S*)-*tert*-butyl 2-amino-3-phenylpropanoate (53 mg, 0.24 mmol) and triethylamine (56 μL, 0.4 mmol) following the general procedure. The reaction mixture was stirred for 16h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20) to give the title compound as a white foam (86 mg, 0.15 mmol, 77% yield). $[\alpha]_D^{23}$ = + 1.8° (c=0.8, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.4 Hz, 1H), 8.12 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.94 – 7.75 (m, 2H), 7.56 – 7.34 (m, 5H), 7.12 – 7.03 (m, 2H), 6.89 – 6.79 (m, 2H), 4.70 – 4.59 (m, 1H), 4.32 (d, *J* = 13.0 Hz, 1H), 4.05 (d, *J* = 13.0 Hz, 1H), 2.98 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.76 (d, *J* = 12.2 Hz, 1H), 2.70 (d, *J* = 12.2 Hz, 1H), 2.54 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.43 – 2.15 (m, 3H), 1.72 – 1.61 (m, 2H), 1.44 (s, 9H), 1.26 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 176.0, 171.3, 137.2, 134.2, 132.0, 129.4, 129.1, 128.5, 128.3, 127.0, 126.8, 126.7, 126.0, 125.6, 123.9, 81.8, 76.5, 56.6, 53.5, 52.3, 44.2, 38.0, 31.8, 28.2, 26.7, 26.6, 22.1. UPLC-DAD-QTOF: $C_{34}H_{45}N_2O_5$ [M+H]+ calcd.: 561.3328, found: 561.3331.

(*R*)-Di-*tert*-butyl 1-(3-(benzylamino)-1-((2-ethoxy-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)hydrazine-1,2-dicarboxylate 194

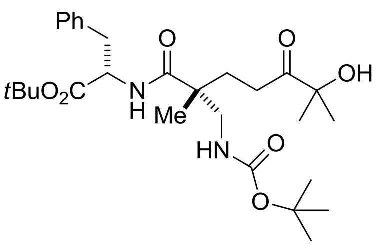


The title compound was prepared from (*R*)-di-*tert*-butyl 1-(3-benzyl-5-methyl-2,6-dioxo-1,3-oxazinan-5-yl)hydrazine-1,2-dicarboxylate 193 (90 mg, 0.2 mmol), ethyl 2-amino acetate (25 mg, 0.24 mmol) and triethylamine (56 μL, 0.4 mmol) following the general procedure. The reaction mixture was stirred for 16h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 50/50) to give the title compound as a white foam (76 mg, 0.15 mmol, 75% yield). $[\alpha]_D^{23}$ = + 15.5° (c=0.75, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.38 – 7.15 (m, 5H), 6.69 (d, *J* = 32.7 Hz, 1H), 4.25 – 4.07 (m, 3H), 3.88 – 3.75 (m, 3H), 3.45 – 3.15 (m, 1H), 3.01 (dd, *J* = 25.7, 12.6 Hz, 1H), 1.90 (s, 1H), 1.49 (d, *J* = 5.0 Hz, 9H), 1.46 (s, 3H), 1.39 (d, *J* = 6.6 Hz, 9H), 1.30 – 1.21 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 169.9, 157.7, 154.0, 140.3, 128.6, 128.3, 127.3, 82.4, 82.1, 81.8, 67.3, 61.2, 54.8, 41.6, 28.4, 28.3, 22.6, 14.3. UPLC-DAD-QTOF: $C_{25}H_{41}N_4O_7$ $[M+H]^+$ calcd.: 509.6156, found: 509.6150.

6.5.4.3. *To dicarboxylic acid **192***

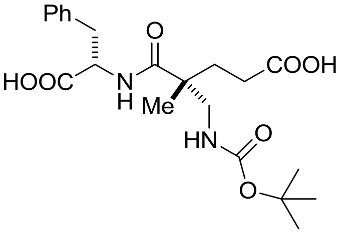


(*S*)-*tert*-Butyl 2-((*R*)-2-(((tert-butoxycarbonyl)amino)methyl)-6-hydroxy-2,6-dimethyl-5-oxoheptanamido)-3-phenylpropanoate 191



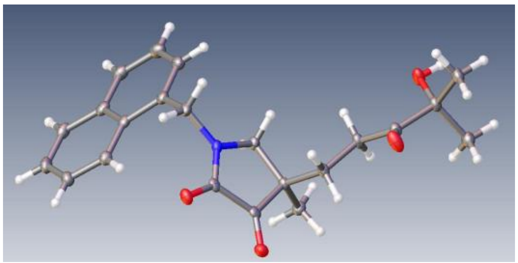
To a solution of (*S*)-*tert*-butyl 2-((*R*)-6-hydroxy-2,6-dimethyl-2-(((naphthalen-1-ylmethyl)amino)methyl)-5-oxoheptanamido)-3-phenylpropanoate (151 mg, 0.3 mmol, 1 equiv.) and di-tert-butyl dicarbonate (130 mg, 0.6 mmol, 2 equiv.) in EtOAc (1 mL, 5 mL/mmol) Pd/C (30 mg, 20 mol % on weight) was added and the resulting mixture was stirred under hydrogen for 16 h. Then resulting mixture was filtered through celite and all volatiles were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 50/50) to give the title compound as a white foam (32 mg, 0.06 mmol, 21% yield). $[\alpha]_D^{23}$ = + 10.1° (c=0.75, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 3H), 7.15 – 7.09 (m, 2H), 6.03 (d, *J* = 7.5 Hz, 1H), 4.78 – 4.65 (m, 1H), 3.91 (t, *J* = 7.7 Hz, 1H), 3.84 – 3.67 (m, 1H), 3.44 – 3.35 (m, 1H), 3.19 – 3.00 (m, 2H), 2.26 – 2.08 (m, 1H), 1.77 – 1.62 (m, 2H), 1.57 (s, 3H), 1.47 (s, 9H), 1.43 (s, 9H), 1.19 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.4, 176.0, 171.0, 136.4, 129.7, 128.6, 127.2, 82.7, 80.7, 75.6, 60.5, 53.4, 47.5, 43.0, 38.1, 31.6, 28.6, 28.2, 28.1, 21.5.

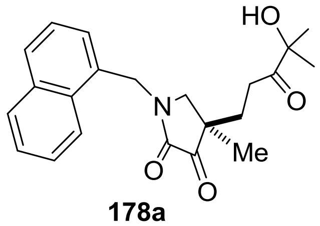
(*R*)-4-(((*tert*-Butoxycarbonyl)amino)methyl)-5-(((*S*)-1-carboxy-2-phenylethyl)amino)-4-methyl-5-oxopentanoic acid 192



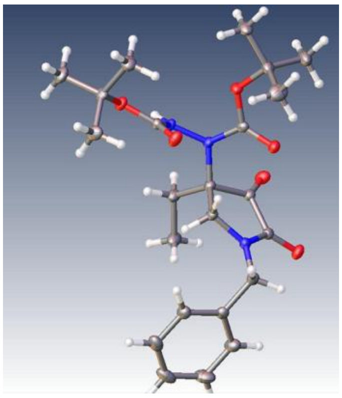
The title compound was prepared from (*S*)-*tert*-butyl 2-((*R*)-2-(((tert-butoxycarbonyl)amino)methyl)-6-hydroxy-2,6-dimethyl-5-oxoheptanamido)-3-phenylpropanoate **191** (32 mg, 0.06 mmol) following the synthetic previously described for the transformation of the ketol moiety to carboxylic acid with $NaIO_4$ in MeOH and H_2O. The reaction mixture was stirred for 16h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 50/50) to give the title compound as a white foam (10 mg, 0.024 mmol, 40% yield). $[\alpha]_D^{23}$ = + 8.2° (c=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 1H), 7.79 – 7.70 (m, 1H), 7.53 – 7.45 (m, 1H), 7.44 – 7.37 (m, 1H), 7.27 – 7.11 (m, 3H), 6.71 – 6.45 (m, 1H), 4.81 – 4.61 (m, 1H), 3.60 – 3.46 (m, 1H), 3.41 – 3.28 (m, 1H), 3.17 – 2.96 (m, 2H), 2.38 – 2.19 (m, 1H), 2.20 – 2.11 (m, 1H), 2.05 – 1.87 (m, 1H), 1.41 (s, 9H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 176.3, 175.2, 170.9, 133.4, 129.5, 128.8, 127.4, 80.8, 54.1, 50.1, 47.5, 38.2, 23.0, 29.6, 28.5, 28.2.

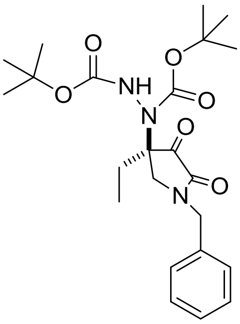
6.5.5. ORTEP diagram for compounds 178a and 179b





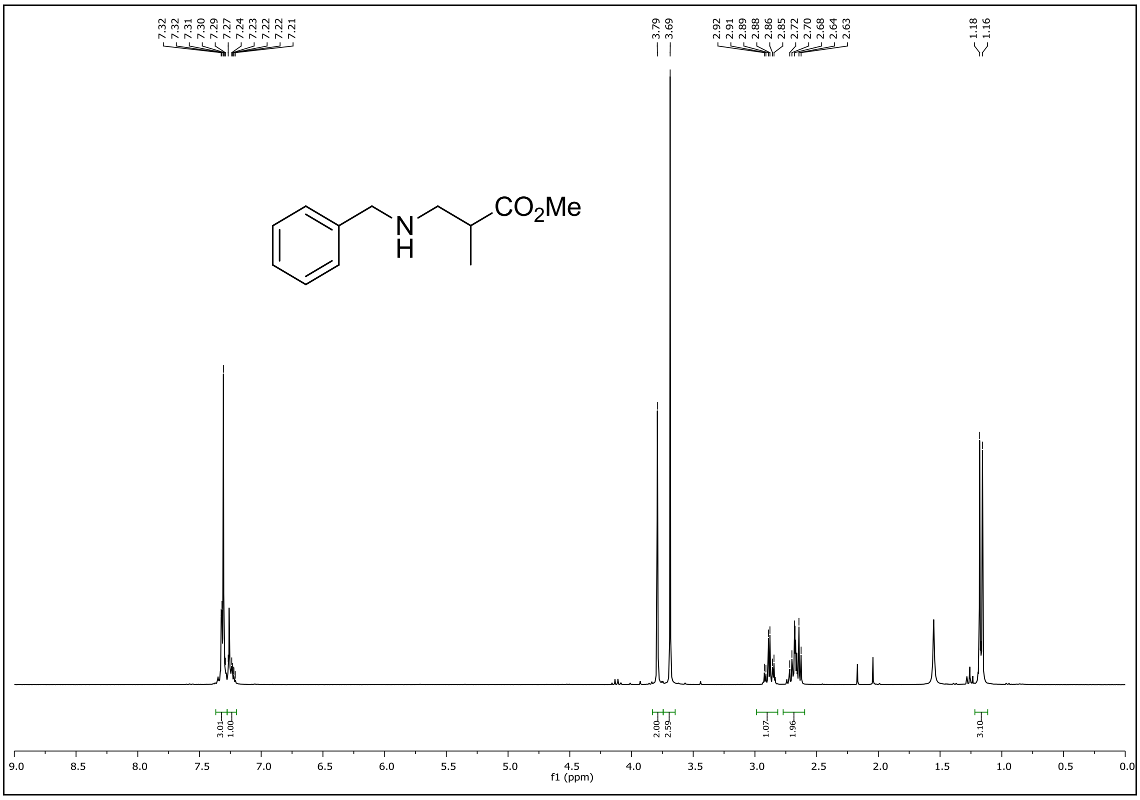
178a

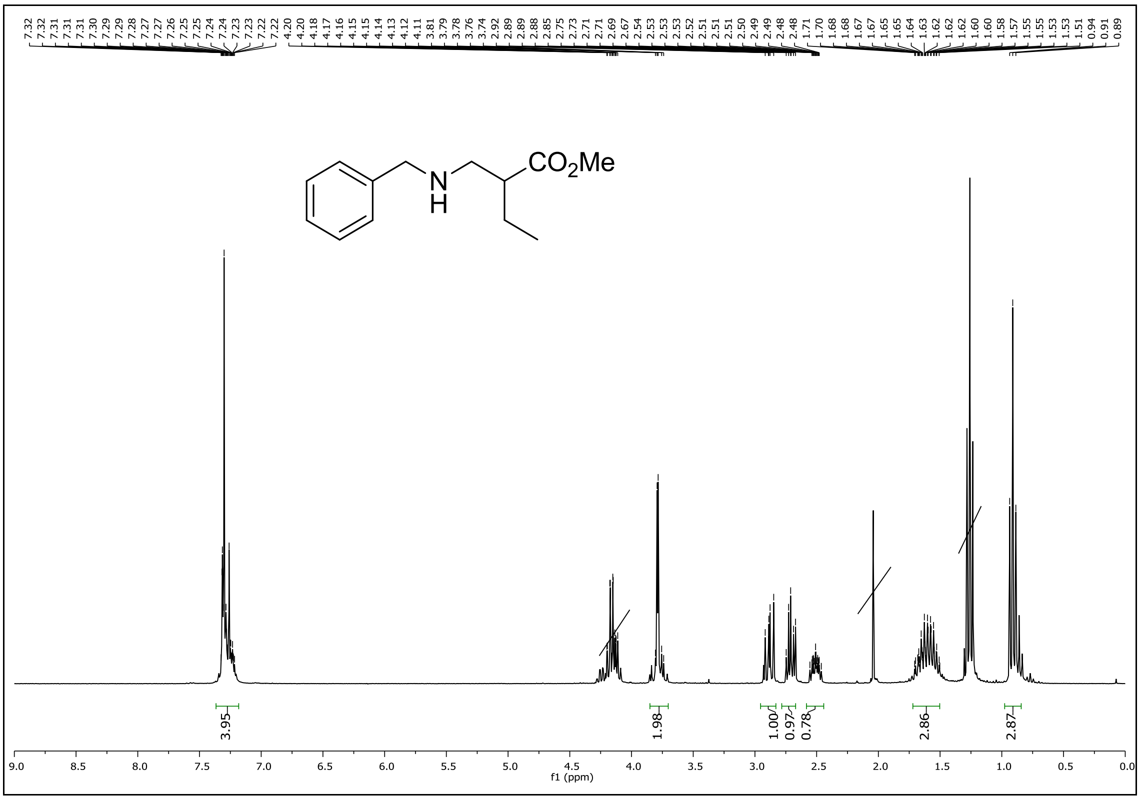


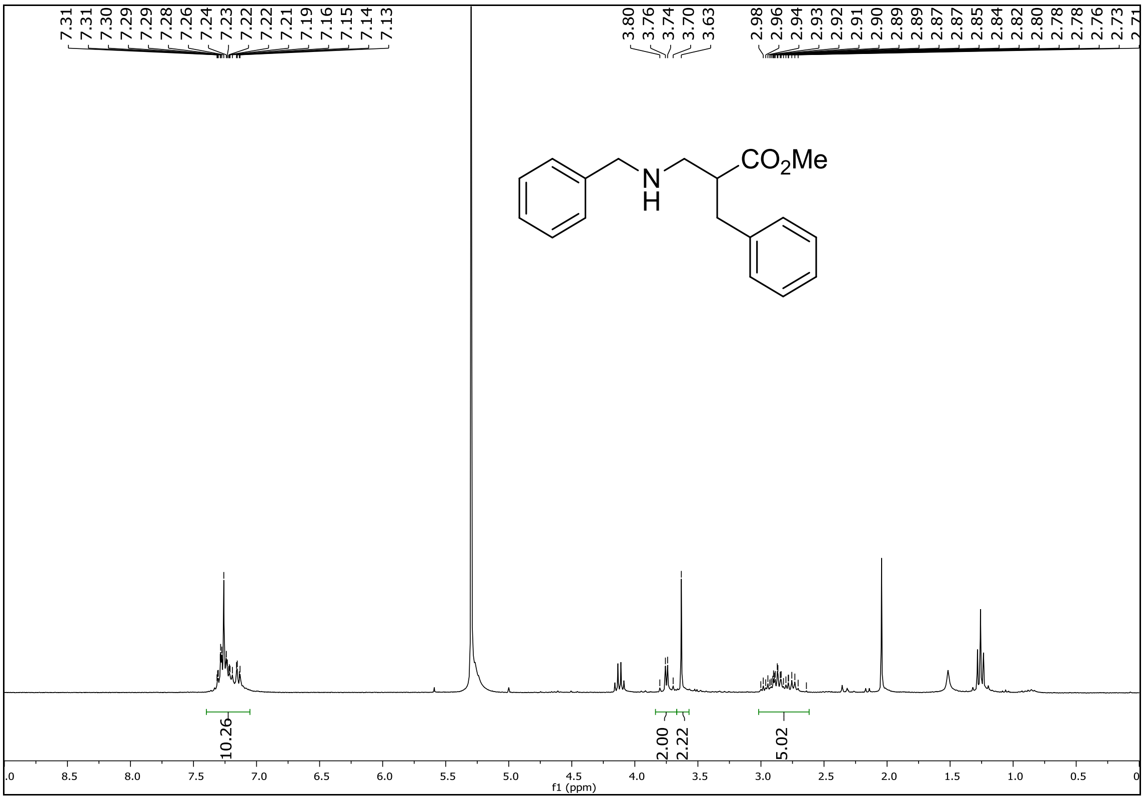


179b

6.5.6. Representative NMR



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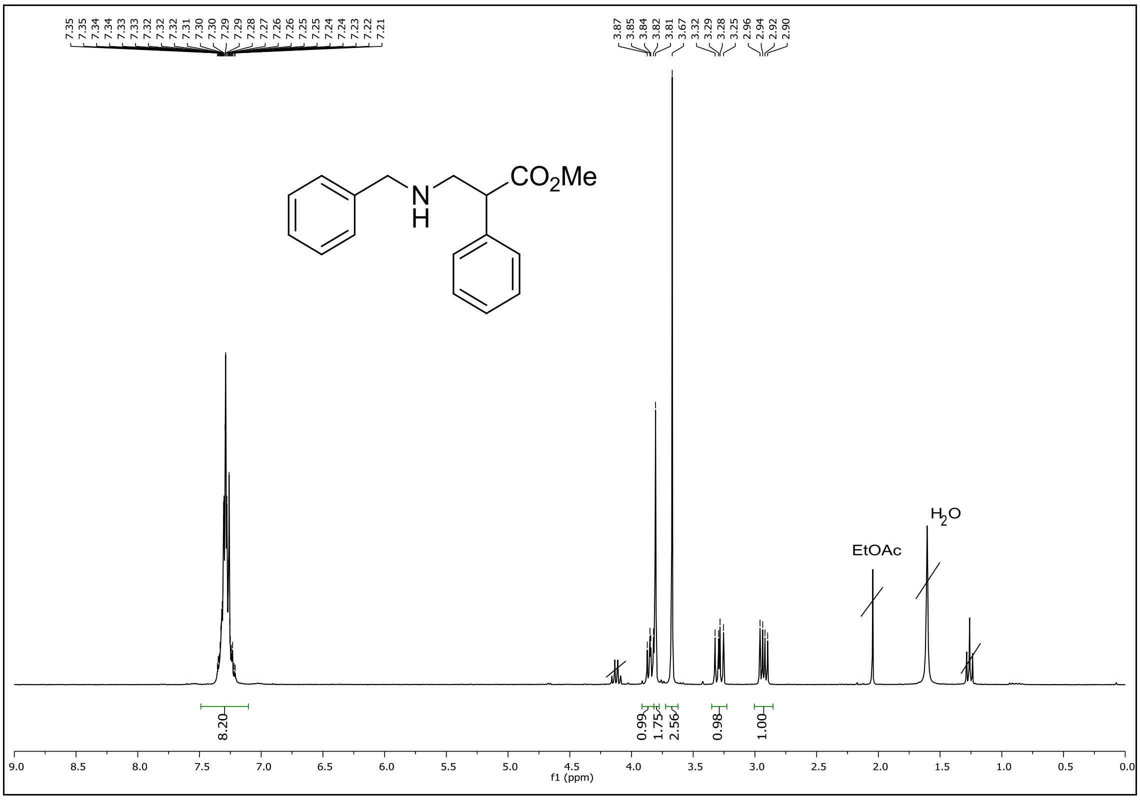
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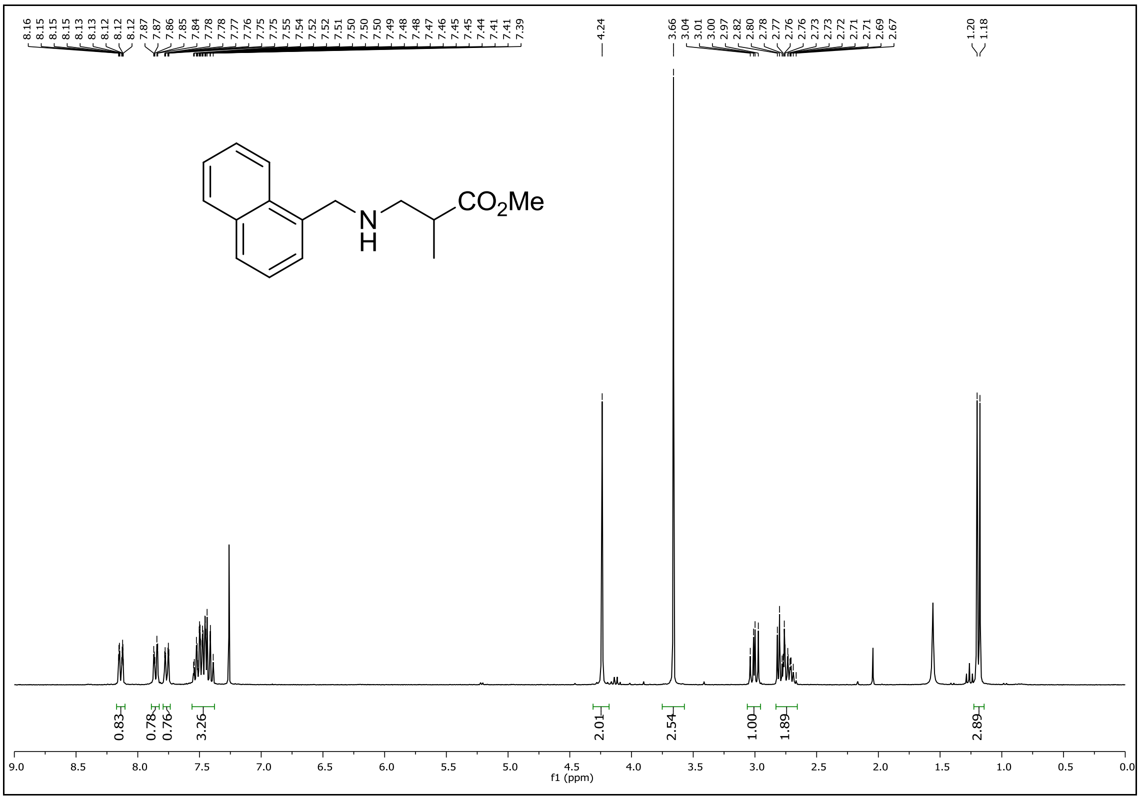
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4.24
3.66 3.04 3.01 3.00 2.97 2.82 2.80 2.78 2.77 2.76 2.76 2.73 2.73 2.72 2.71 2.69 2.67
1.20 1.18
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H
CO2Me
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0.76
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2.01
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9.0 8.5 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 0.0
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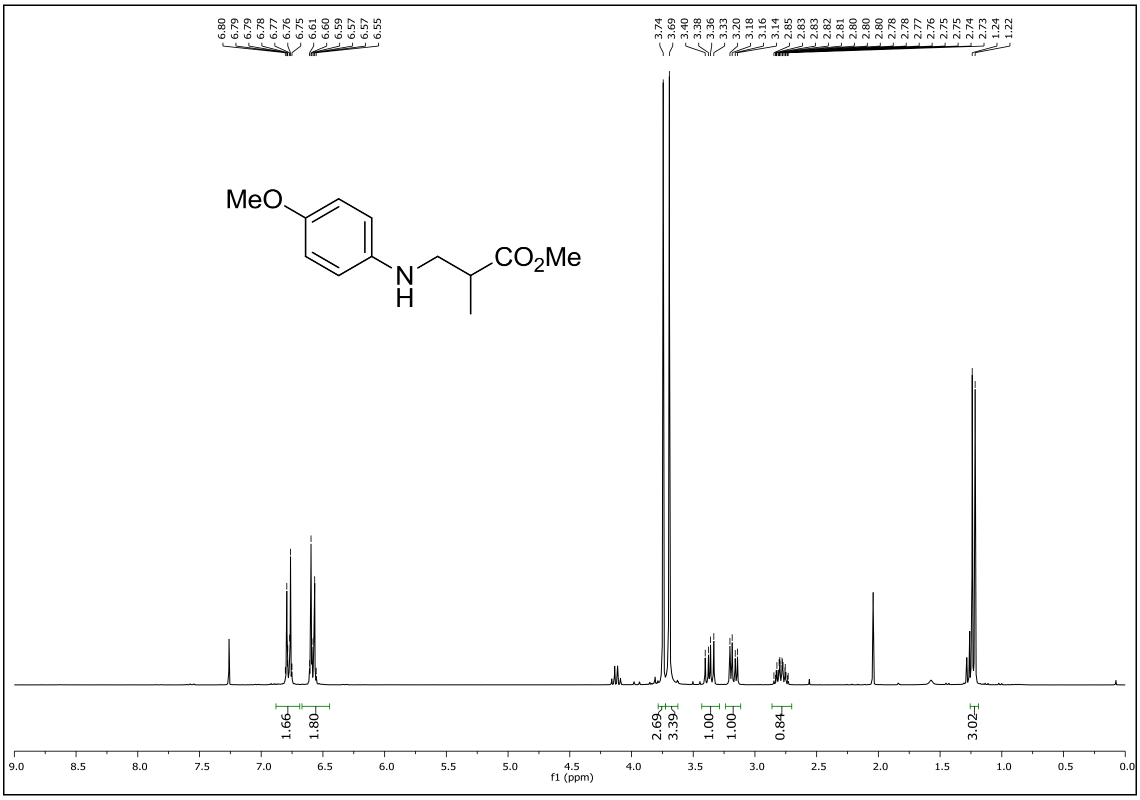
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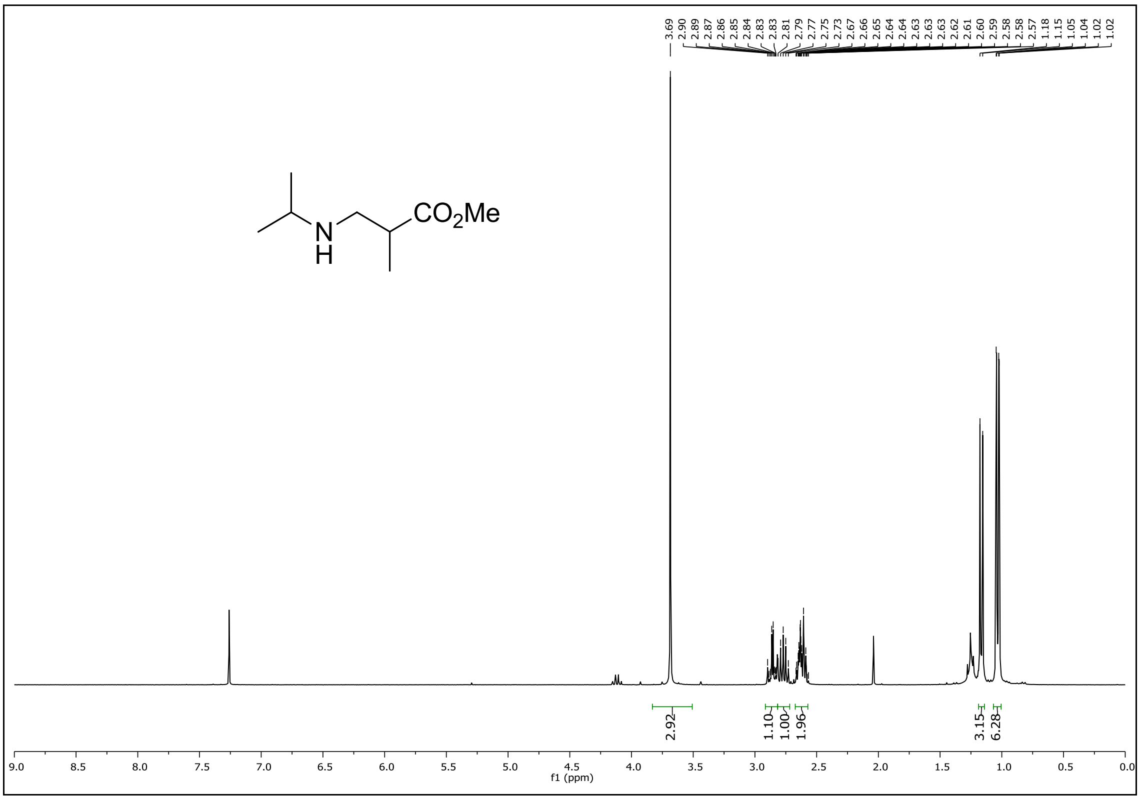
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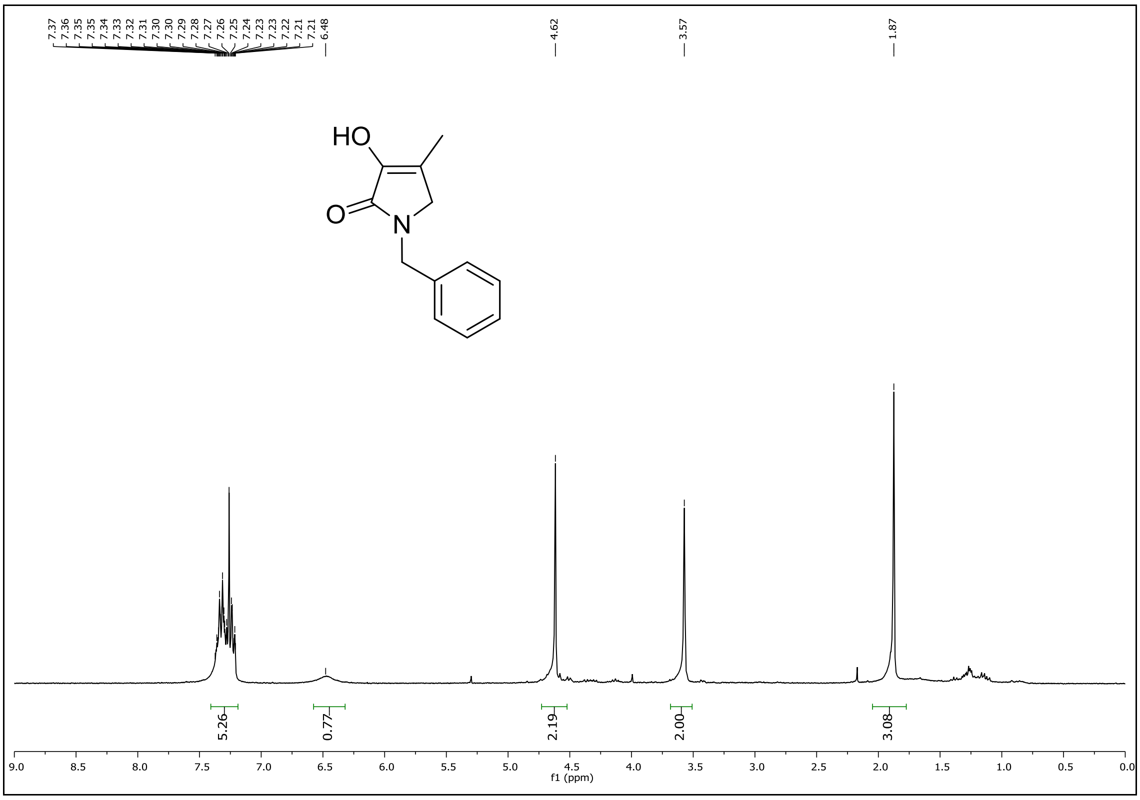
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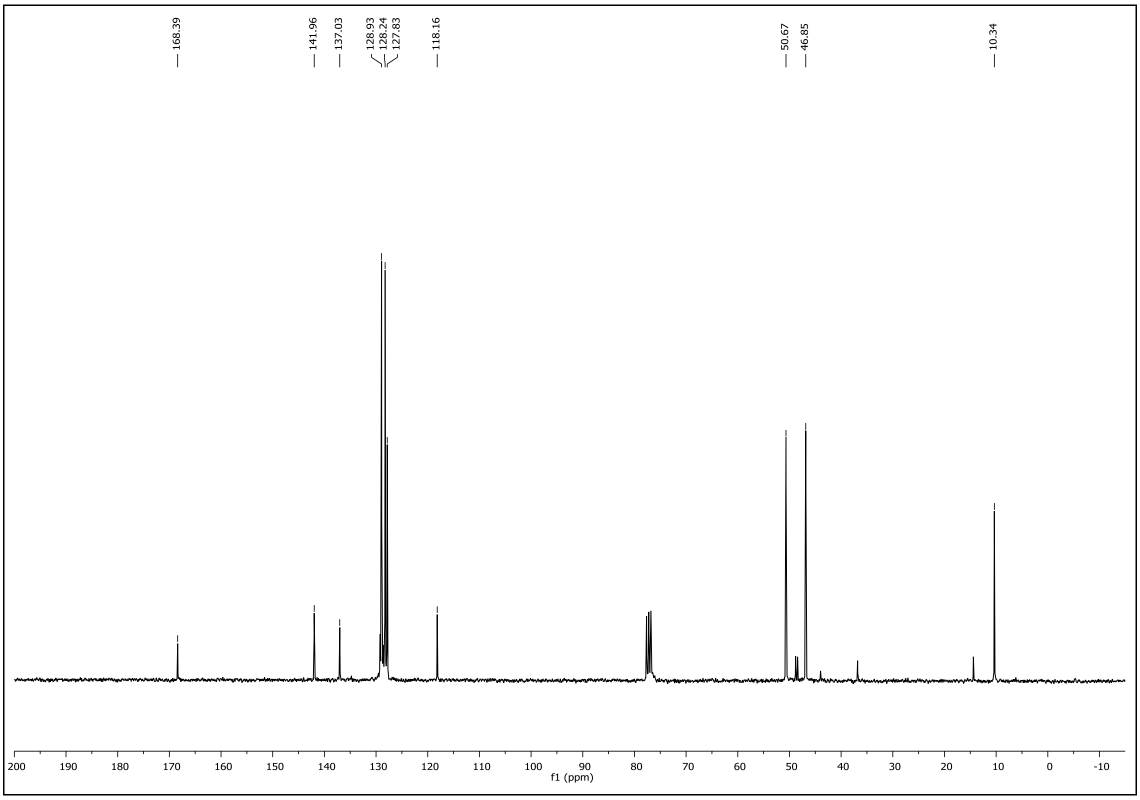
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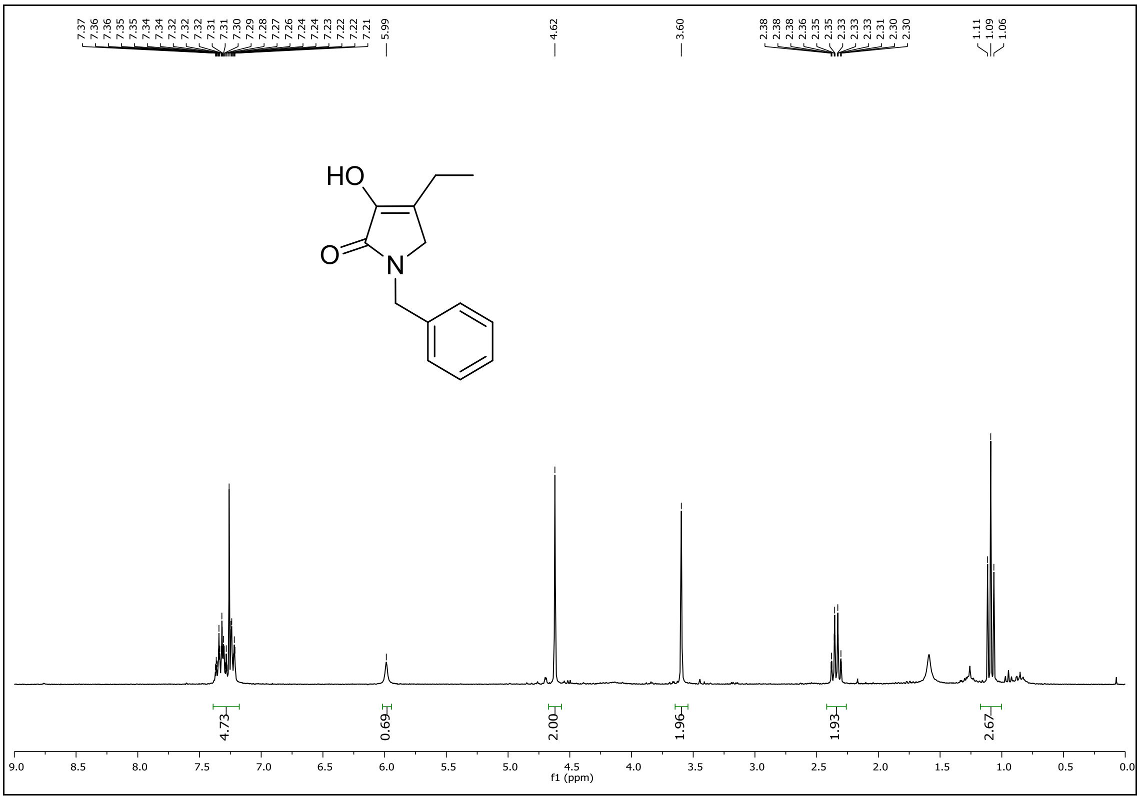
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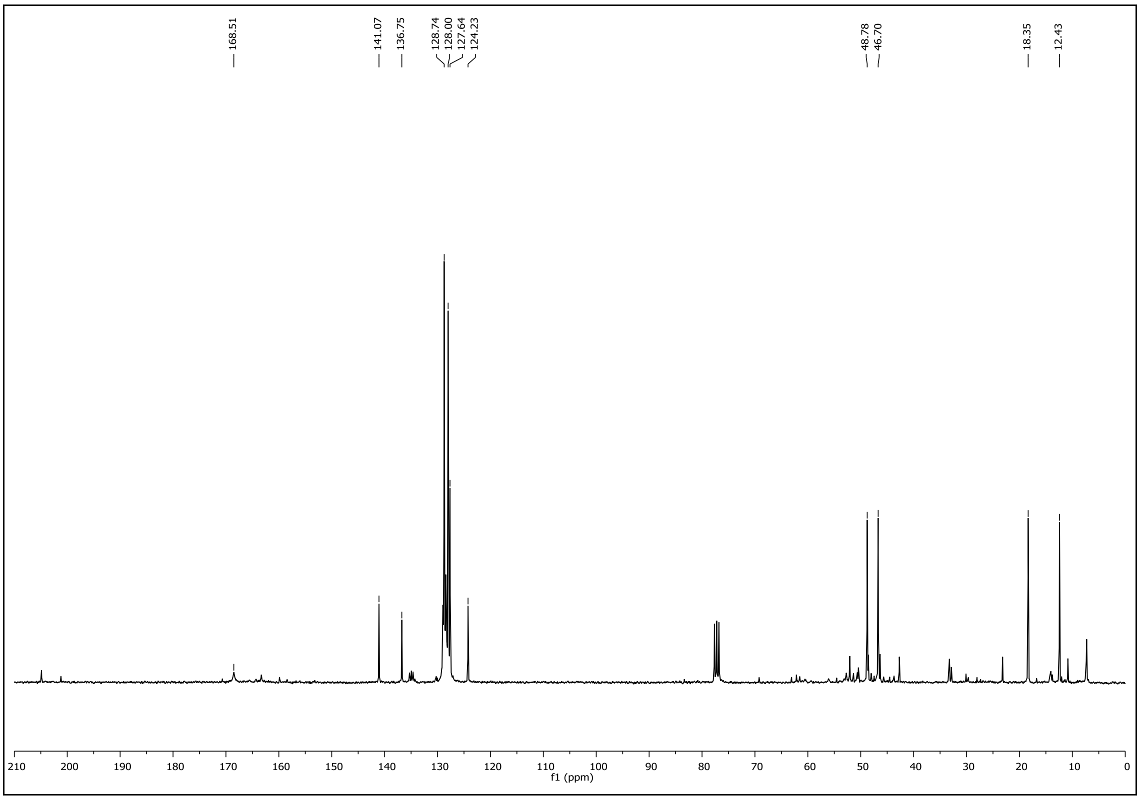
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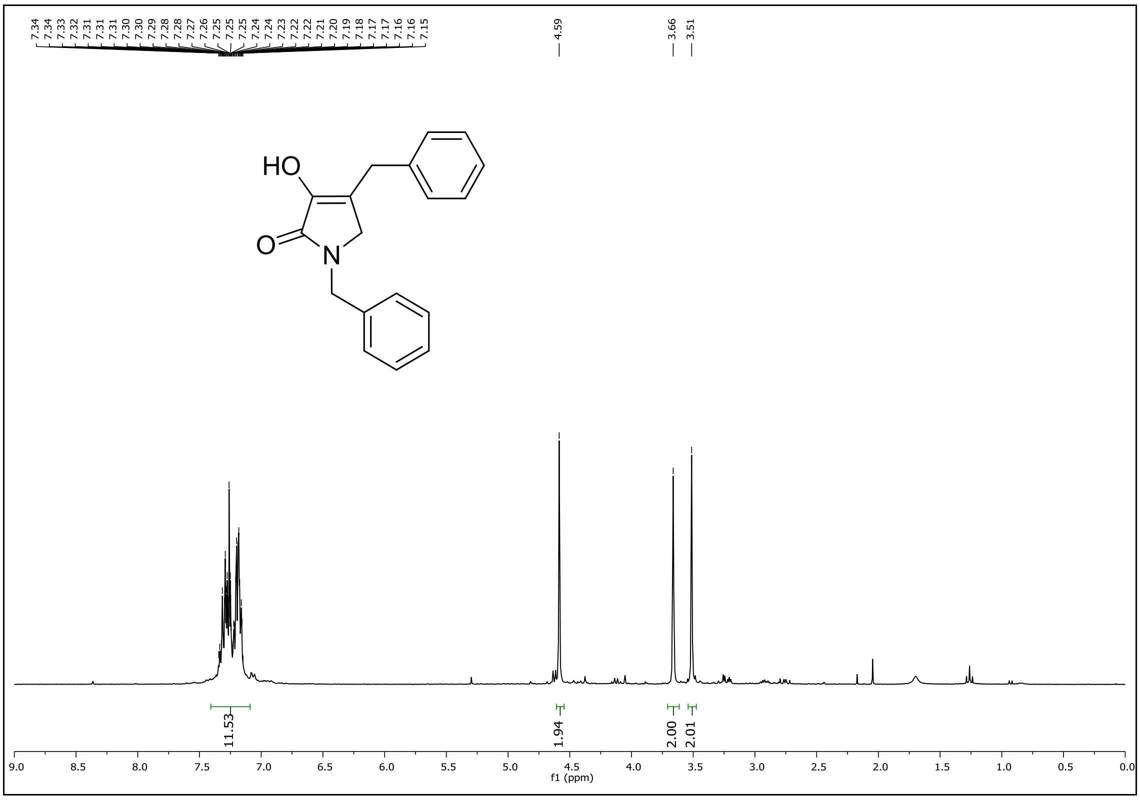
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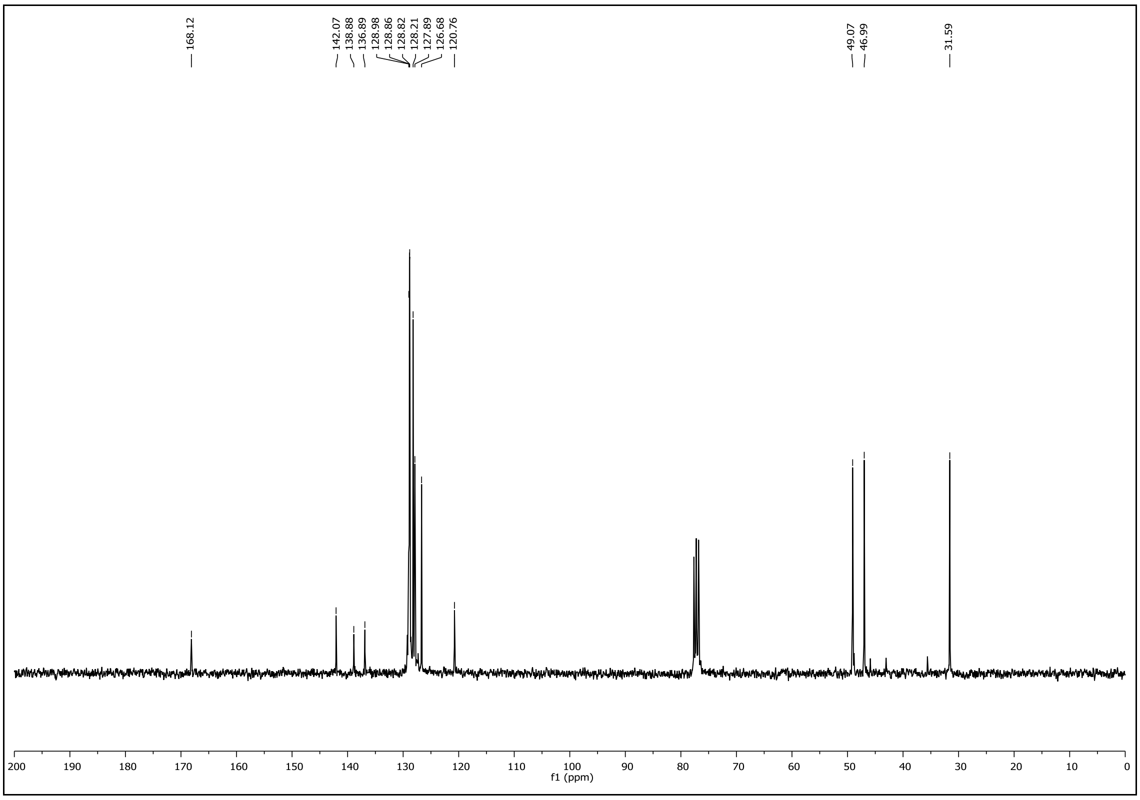
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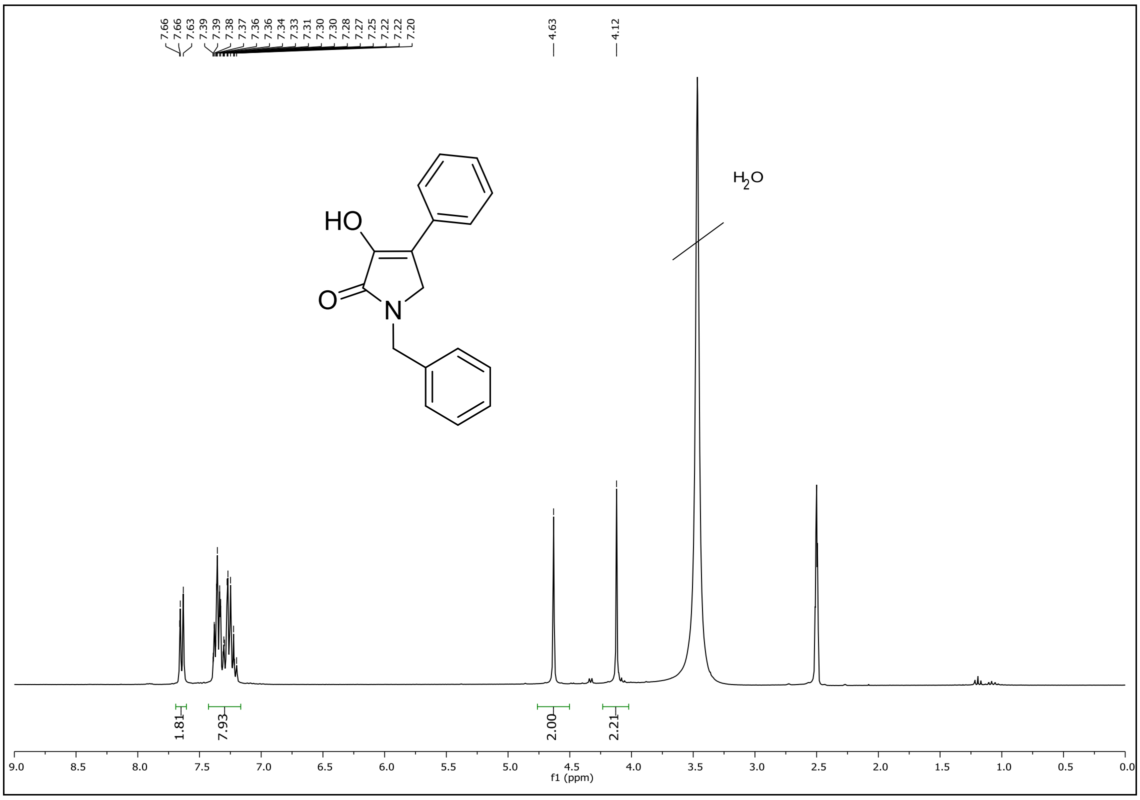
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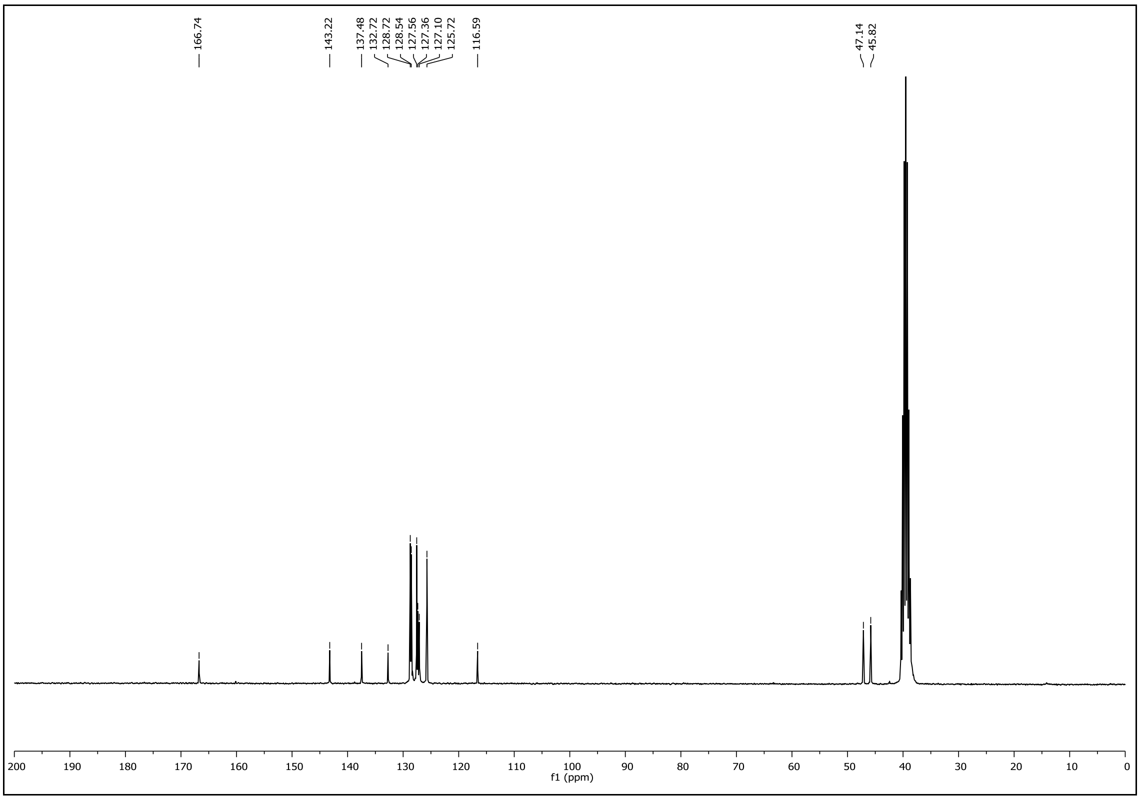
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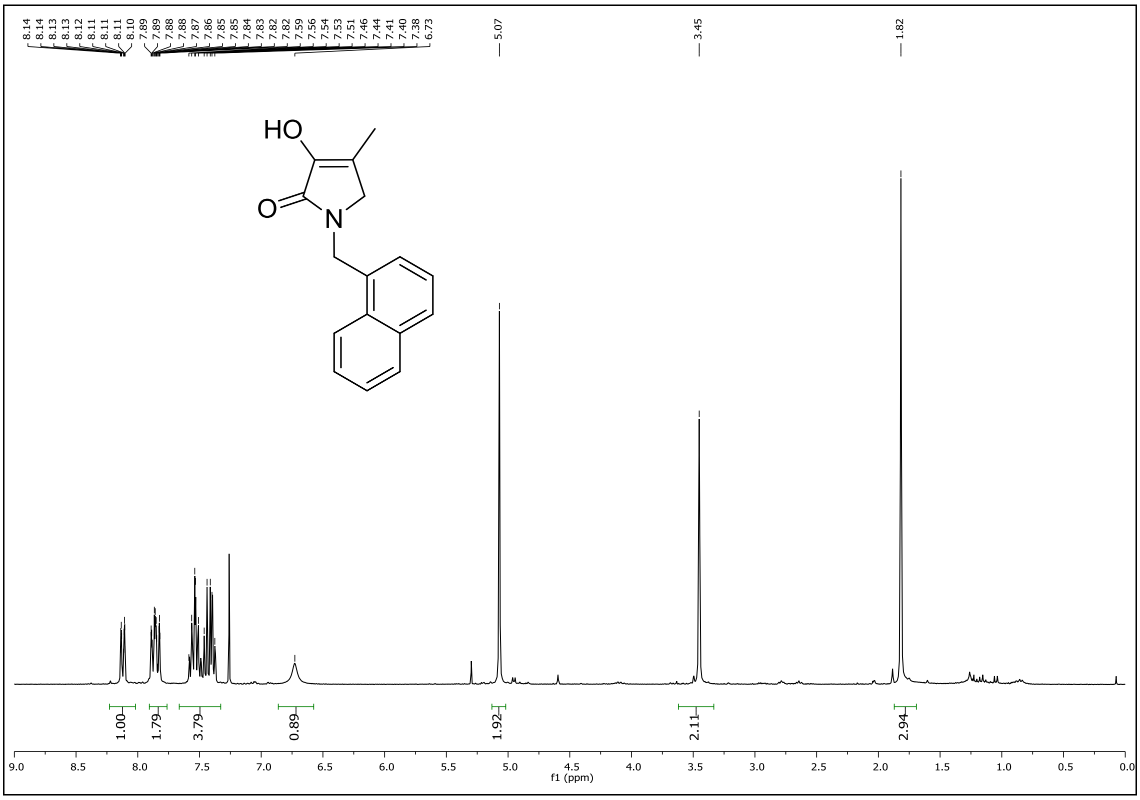
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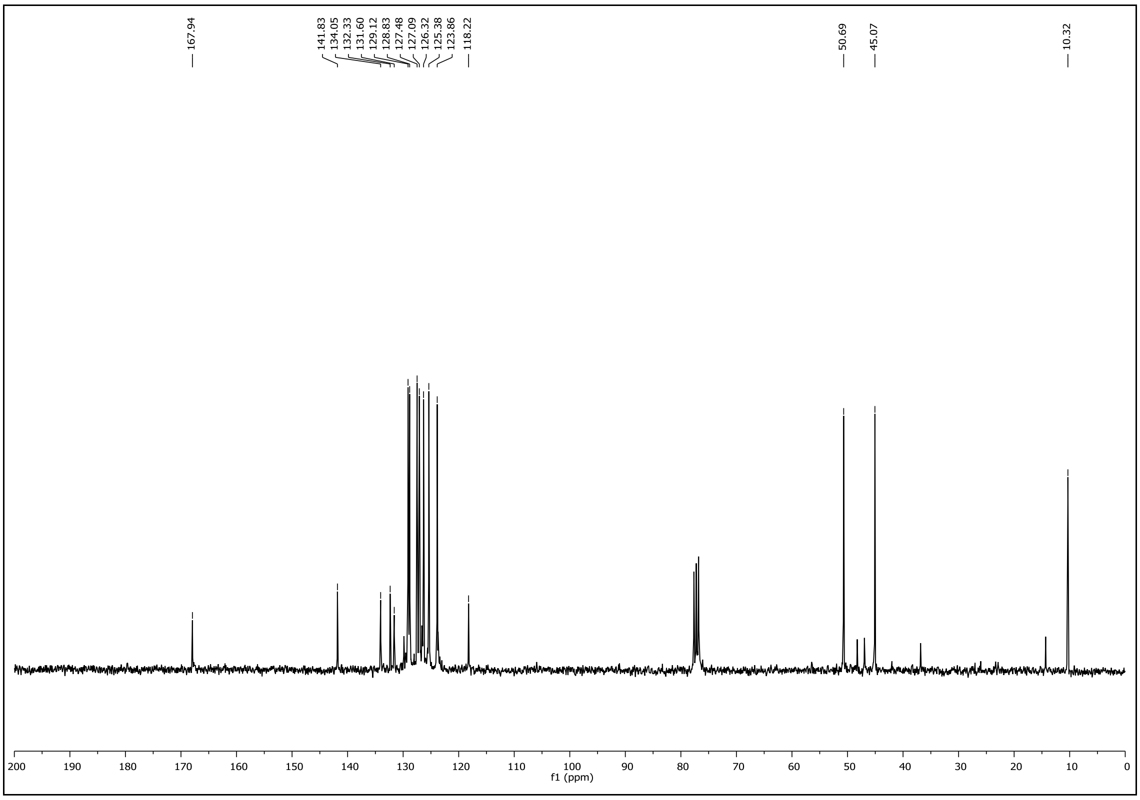
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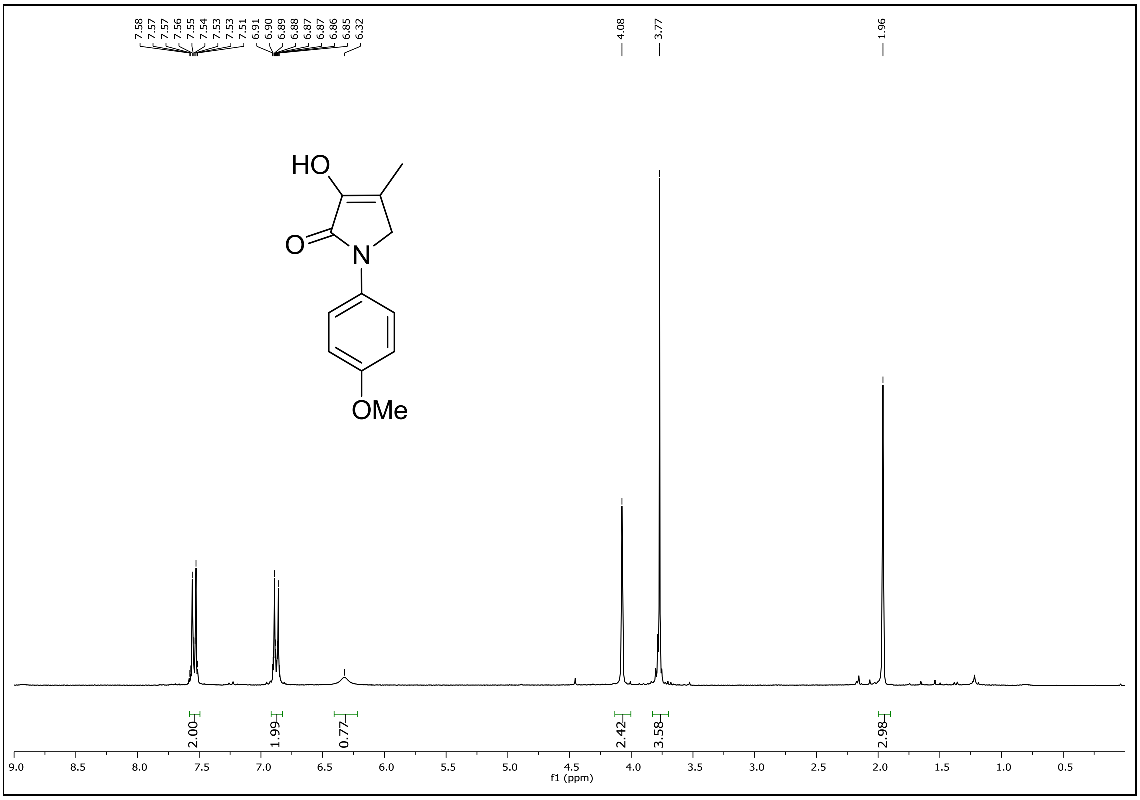
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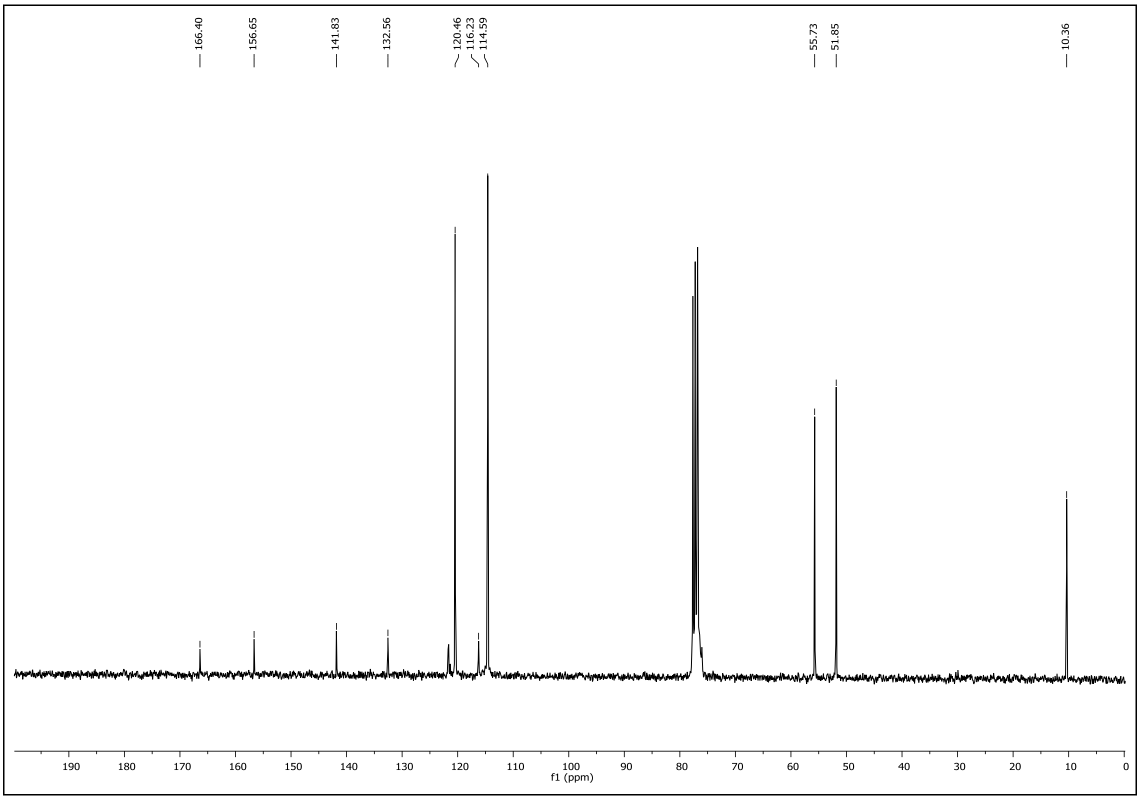
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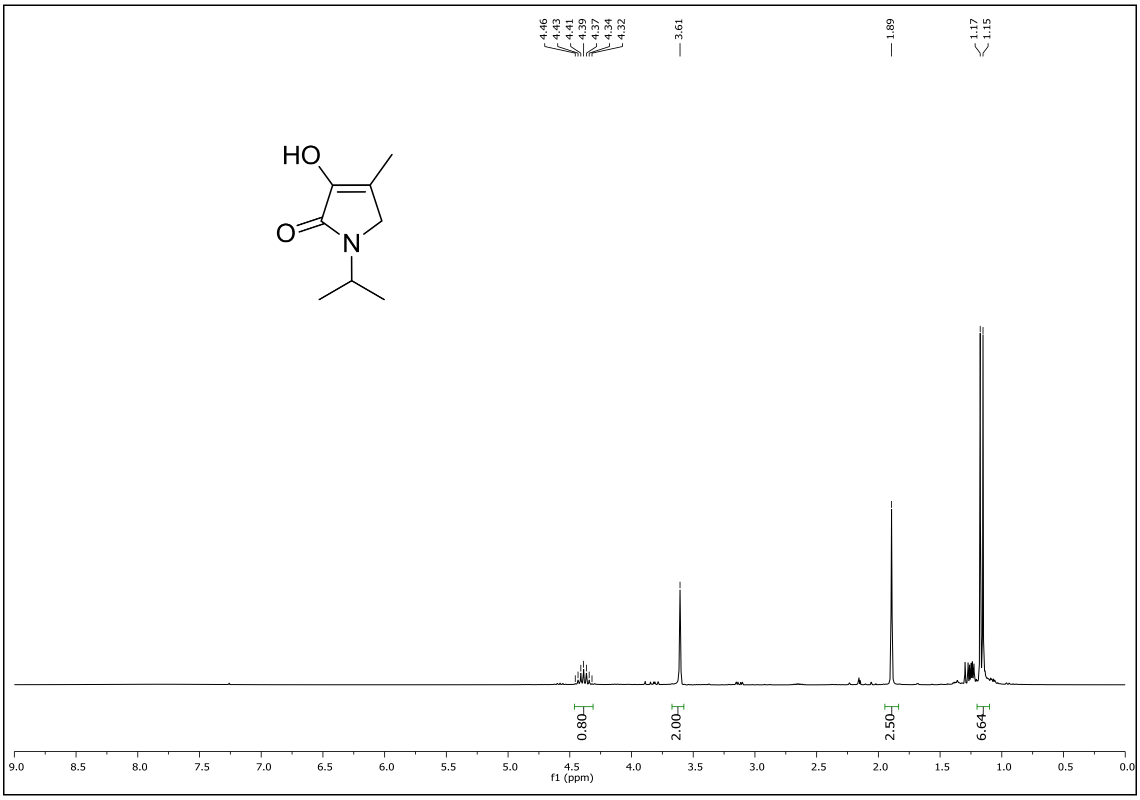
f1 (ppm)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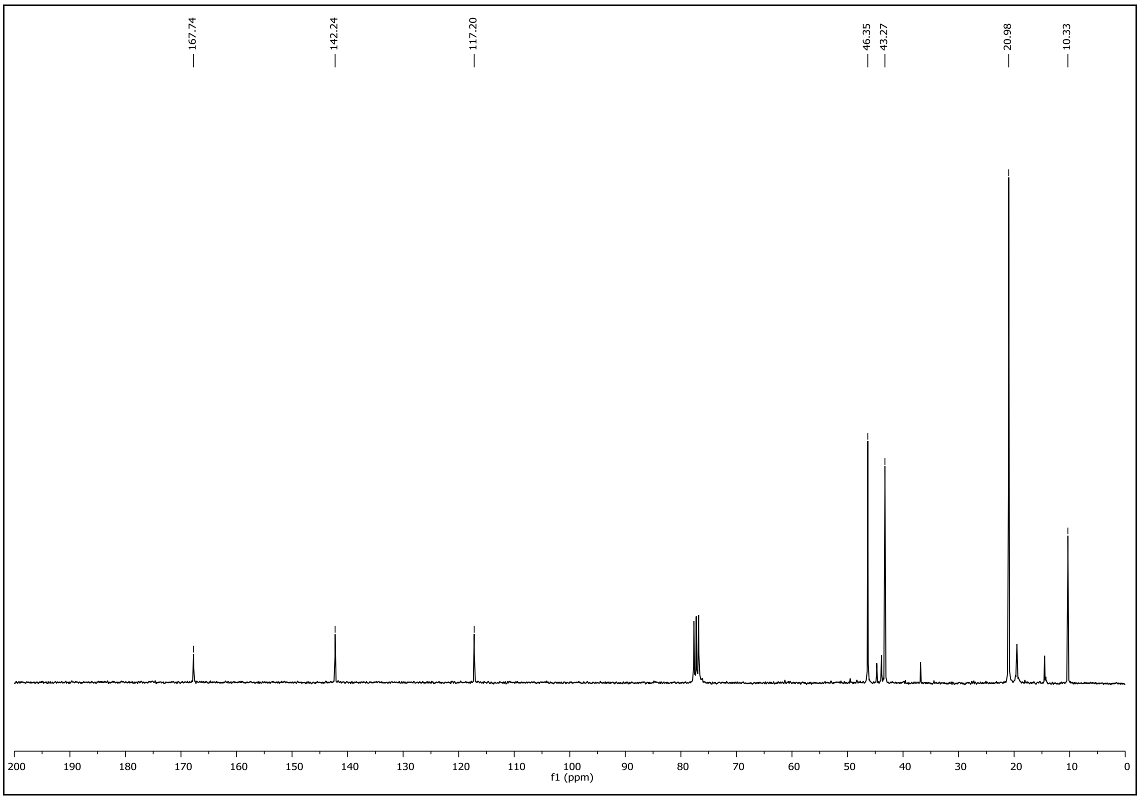
f1 (ppm)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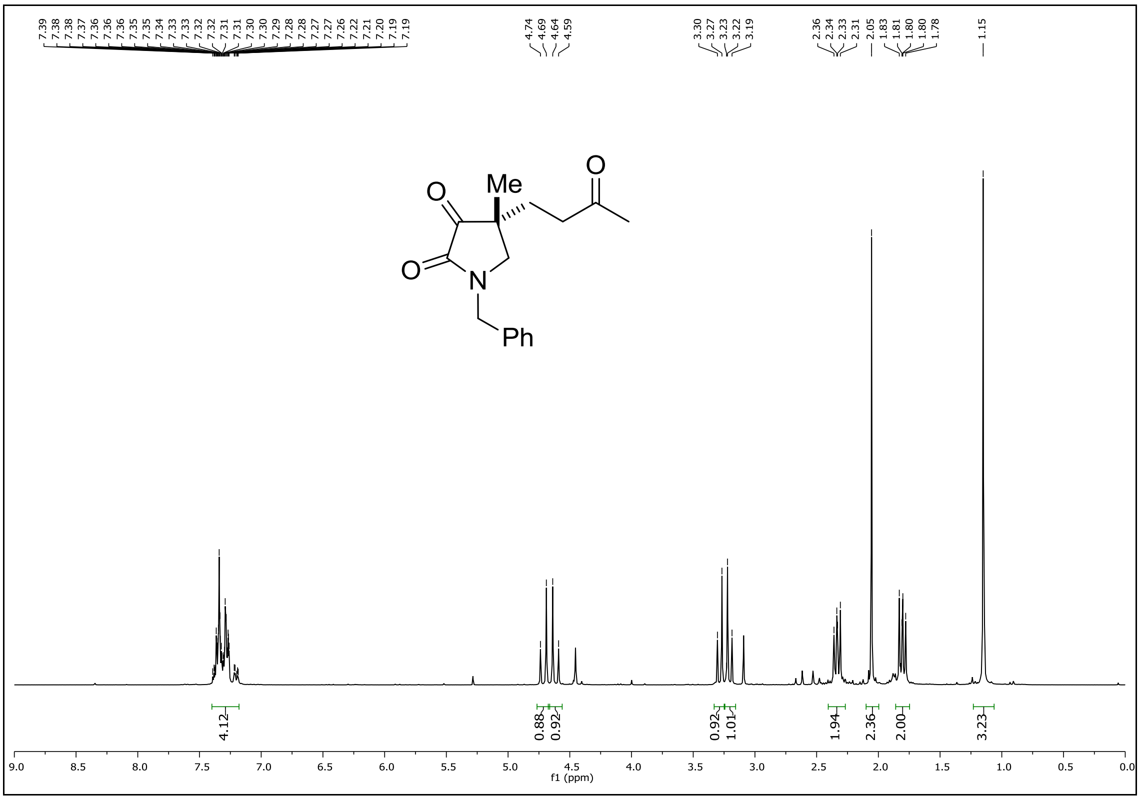
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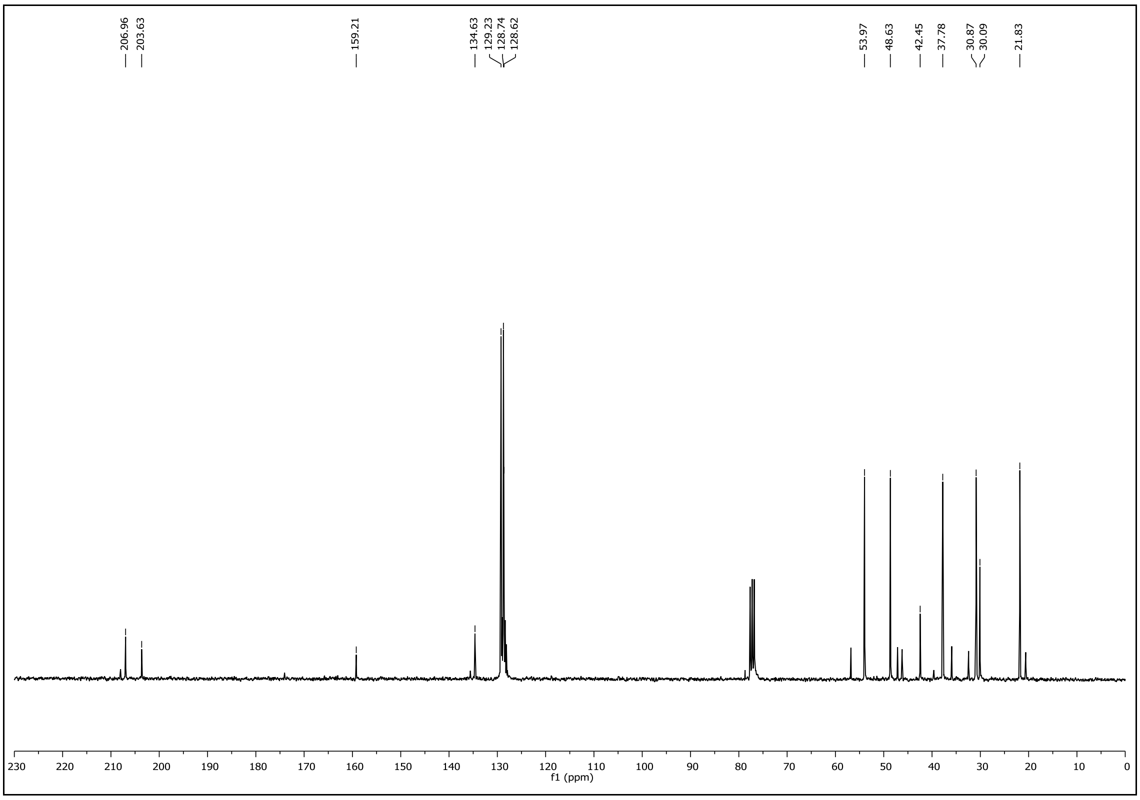
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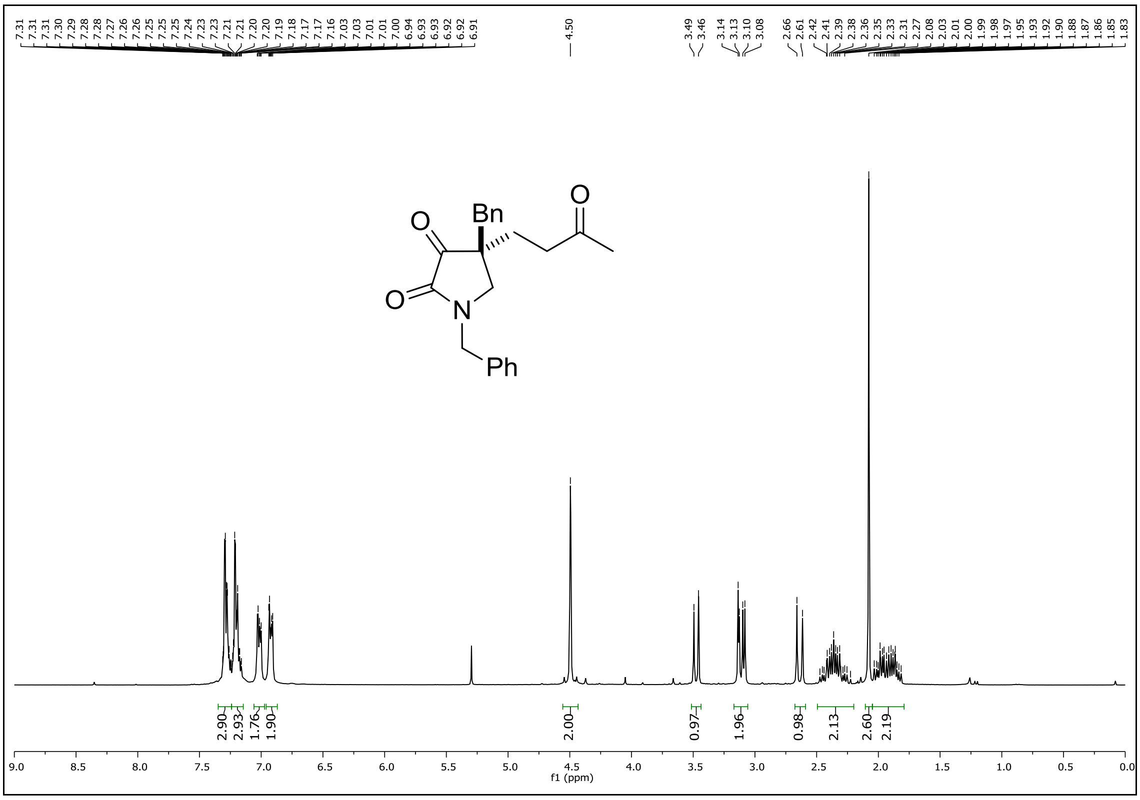
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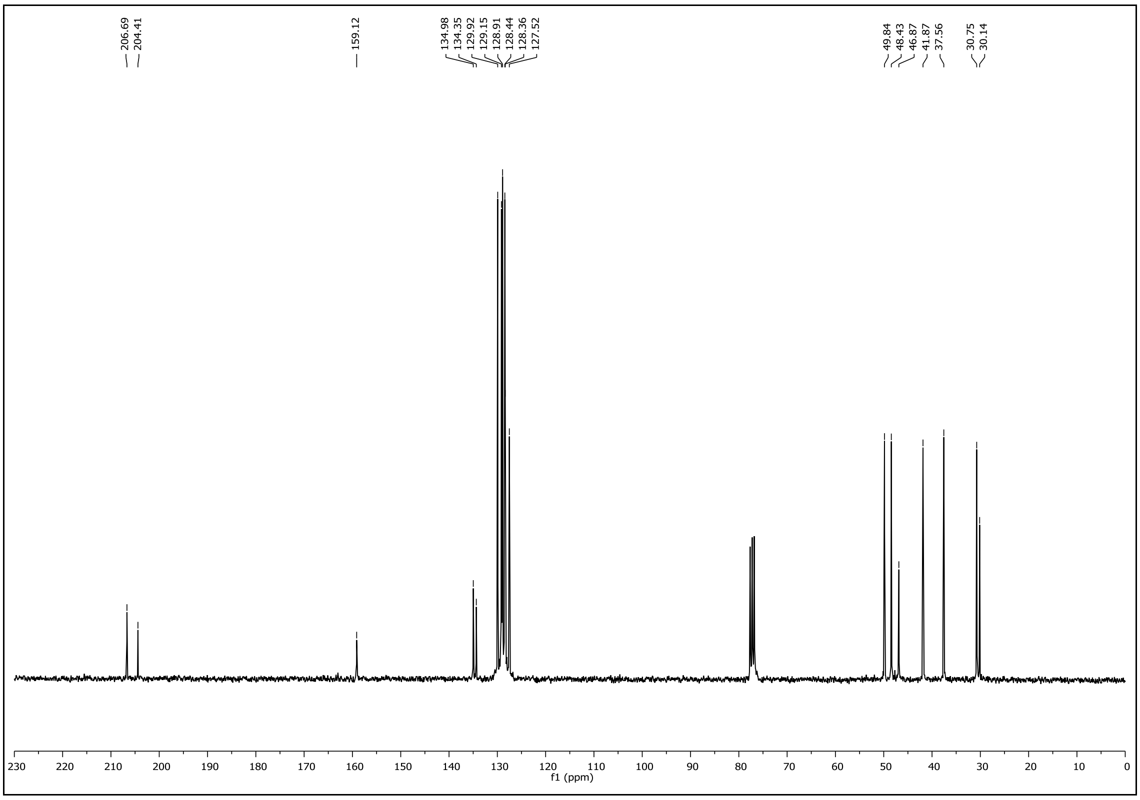
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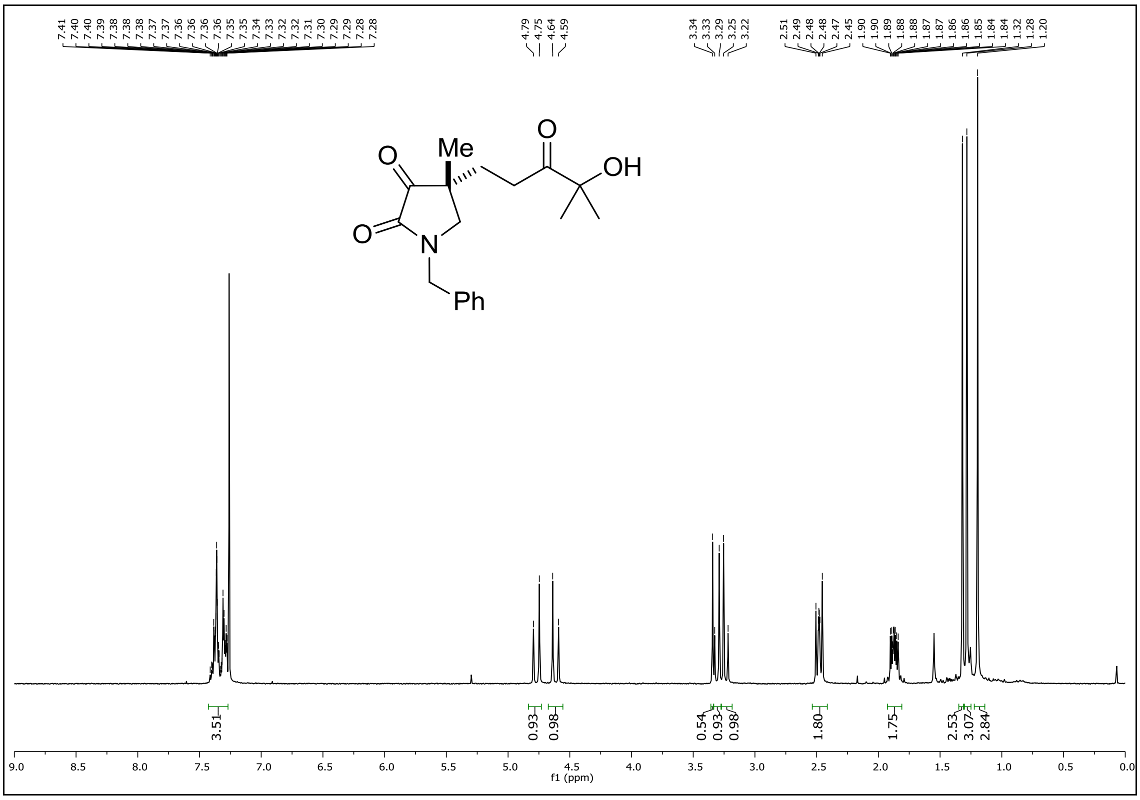
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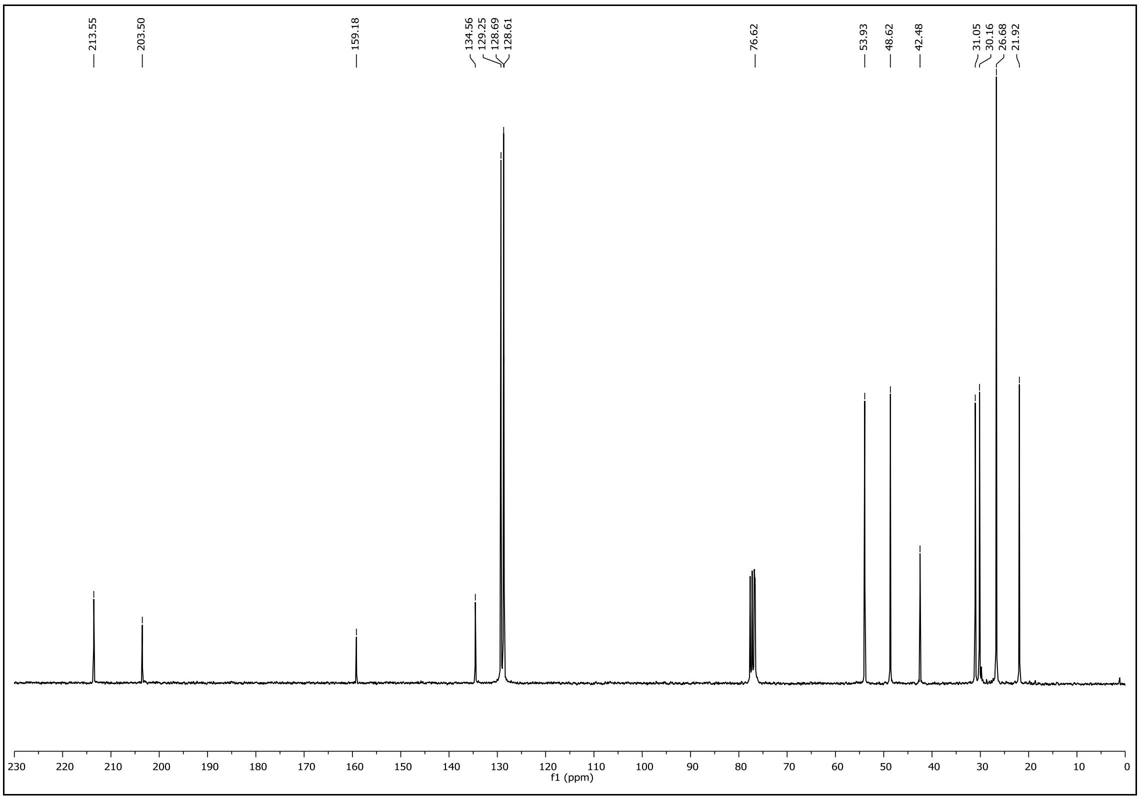
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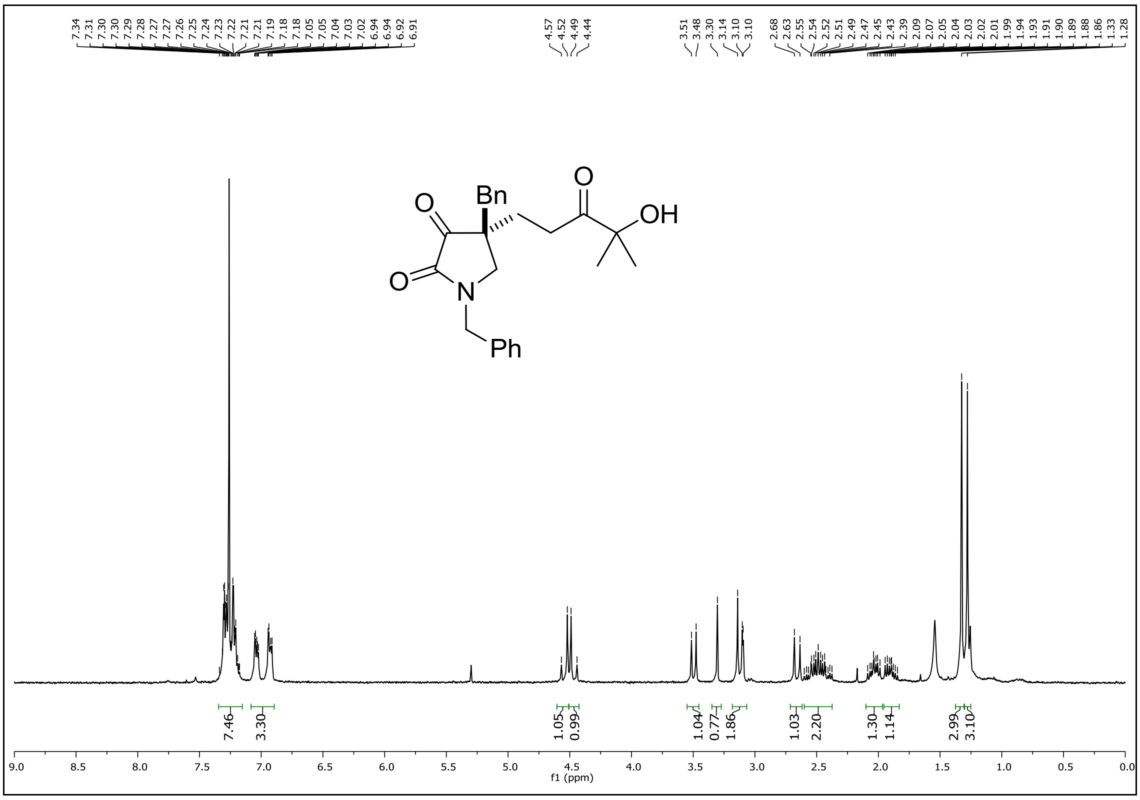
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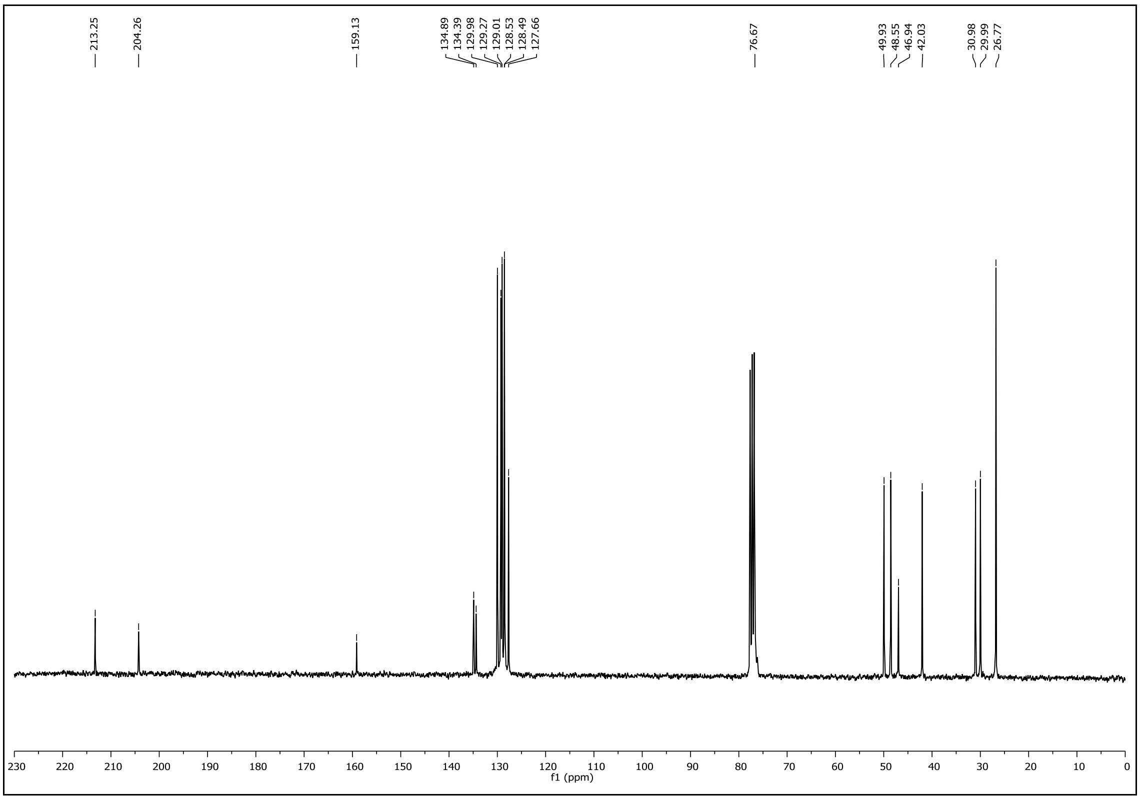
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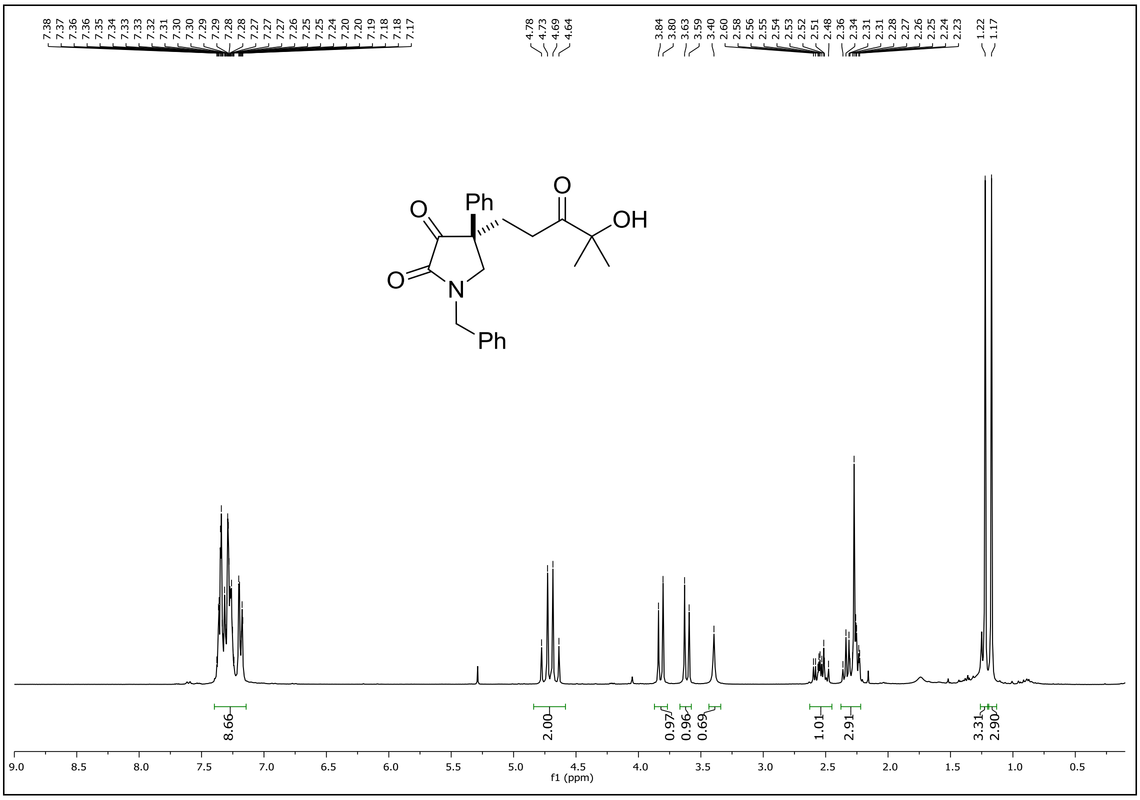
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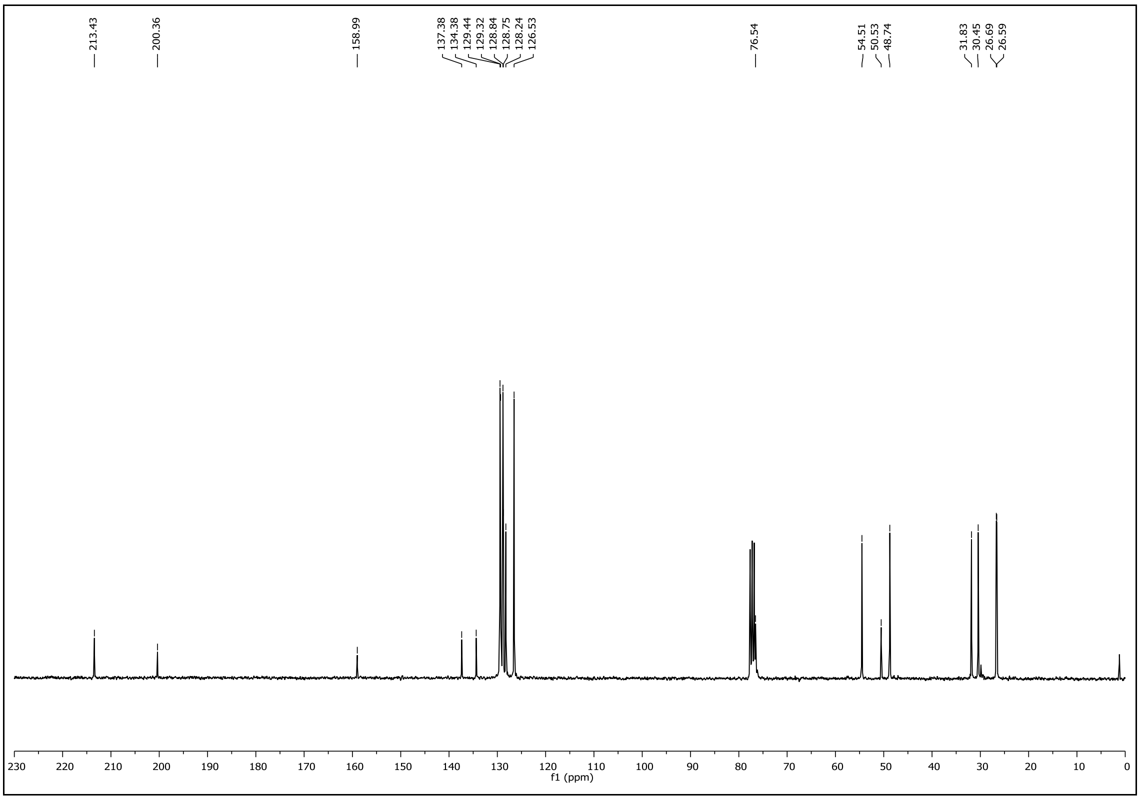
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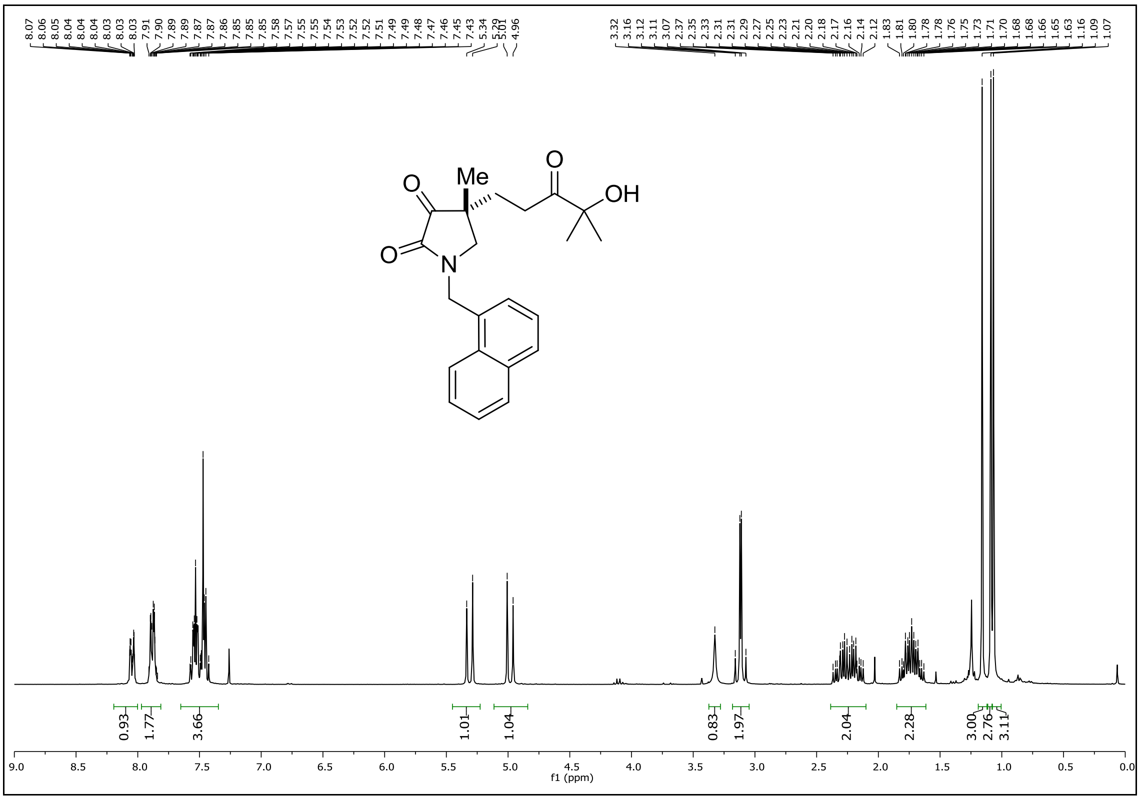
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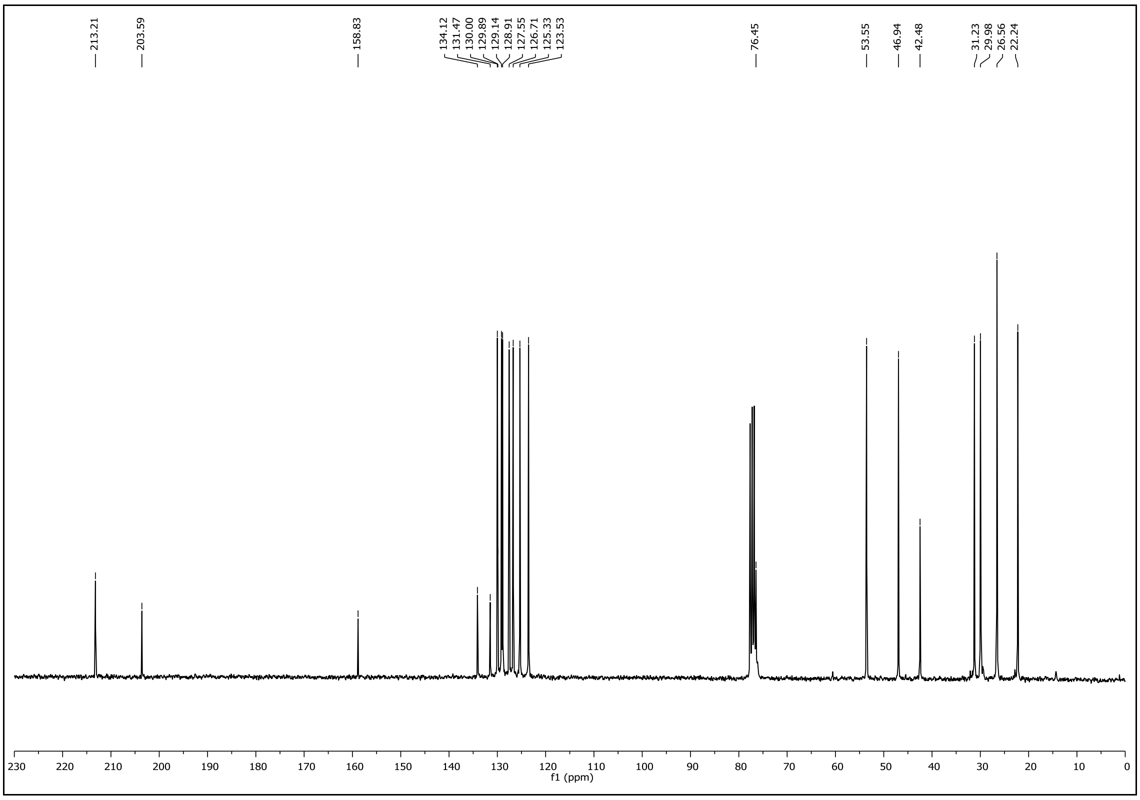
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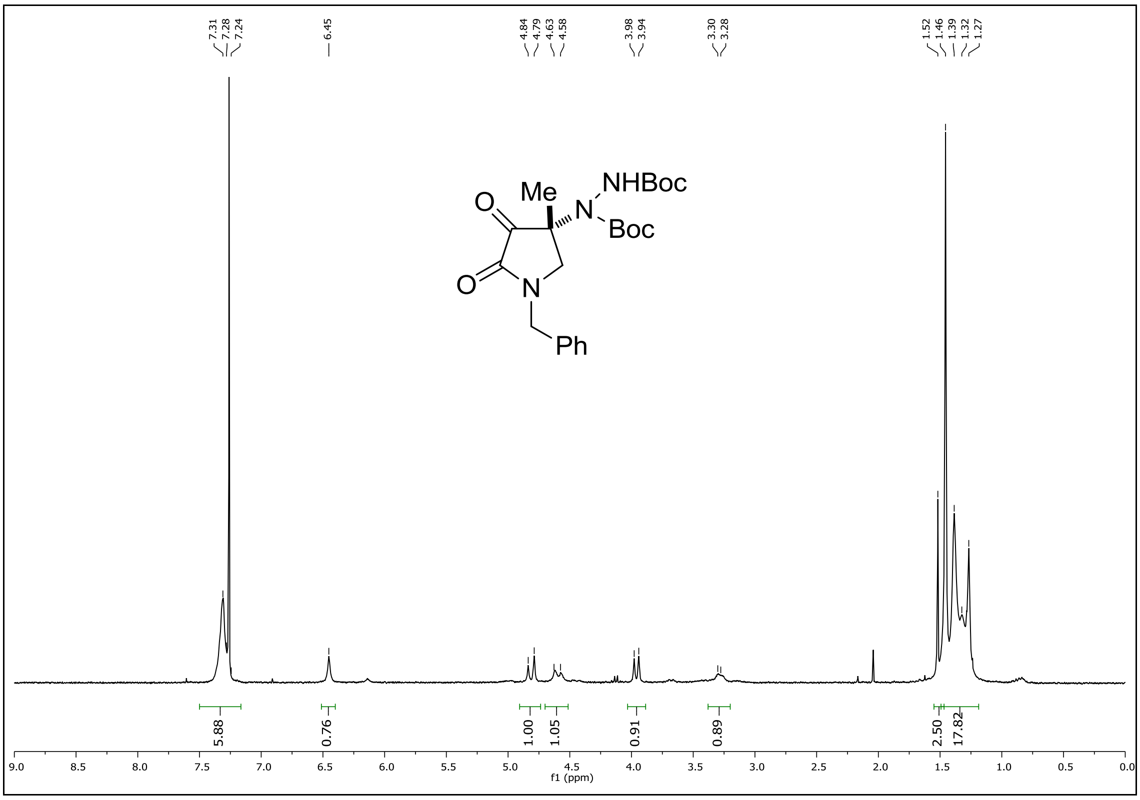
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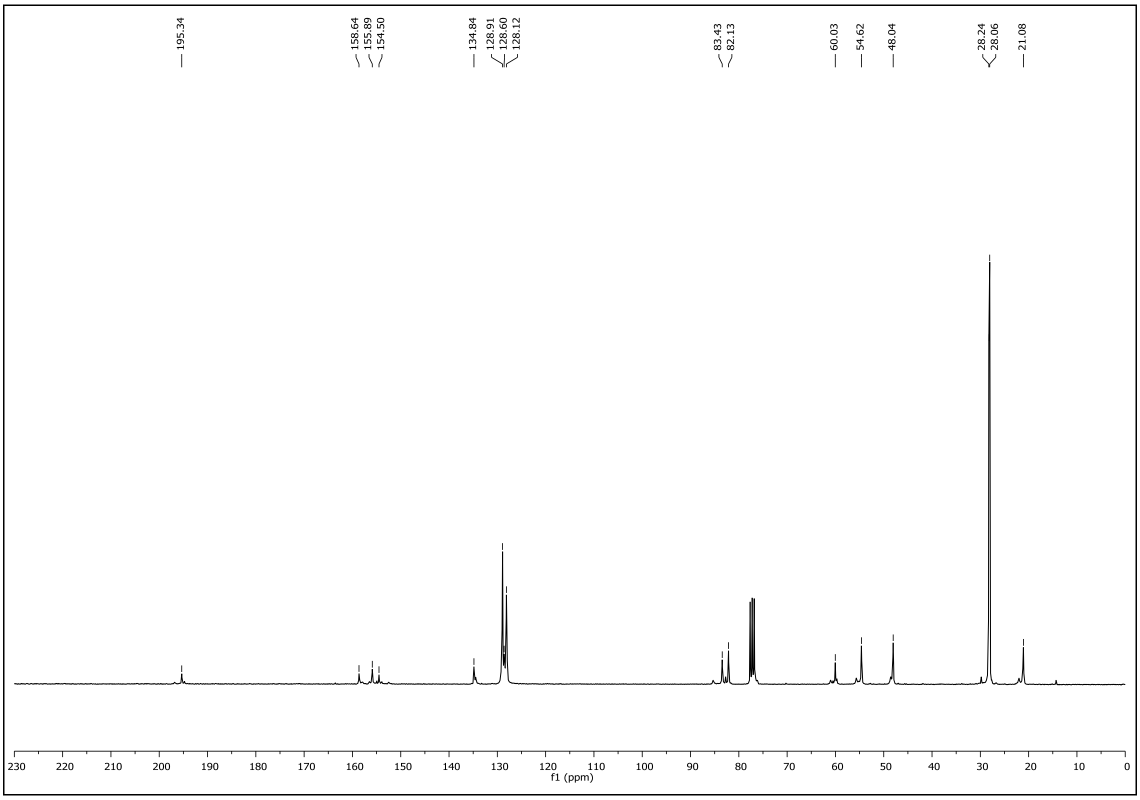
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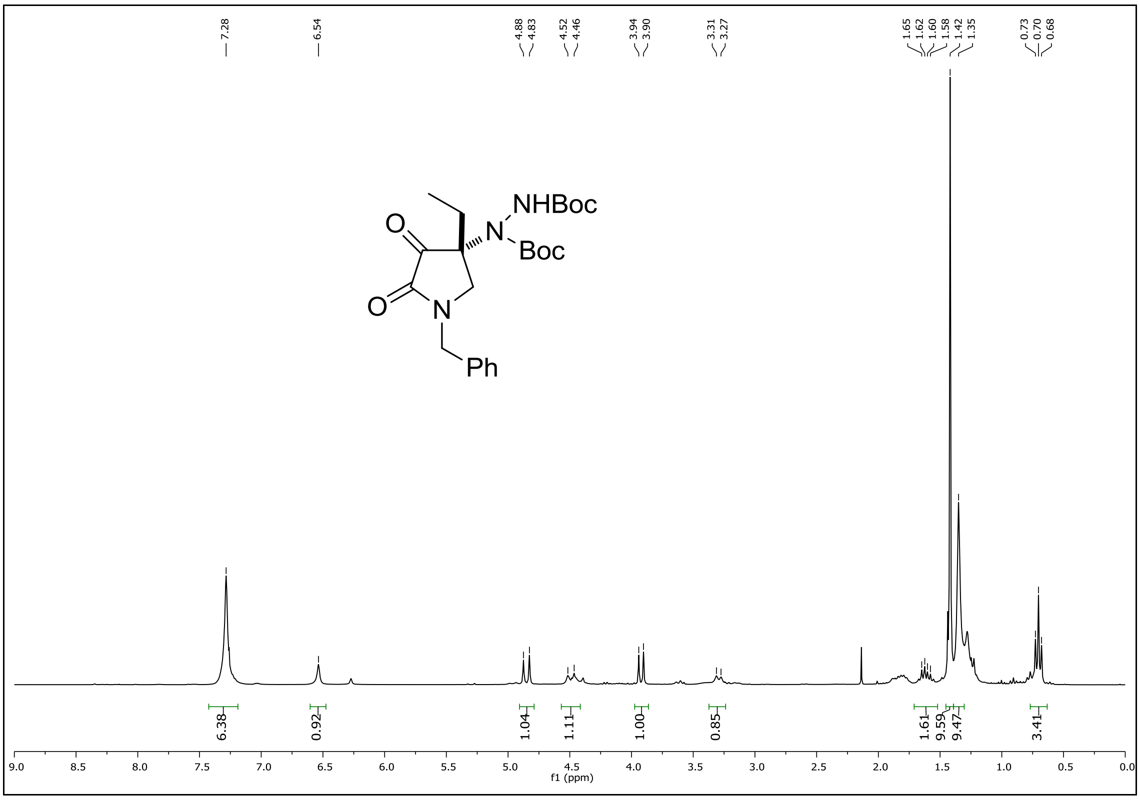
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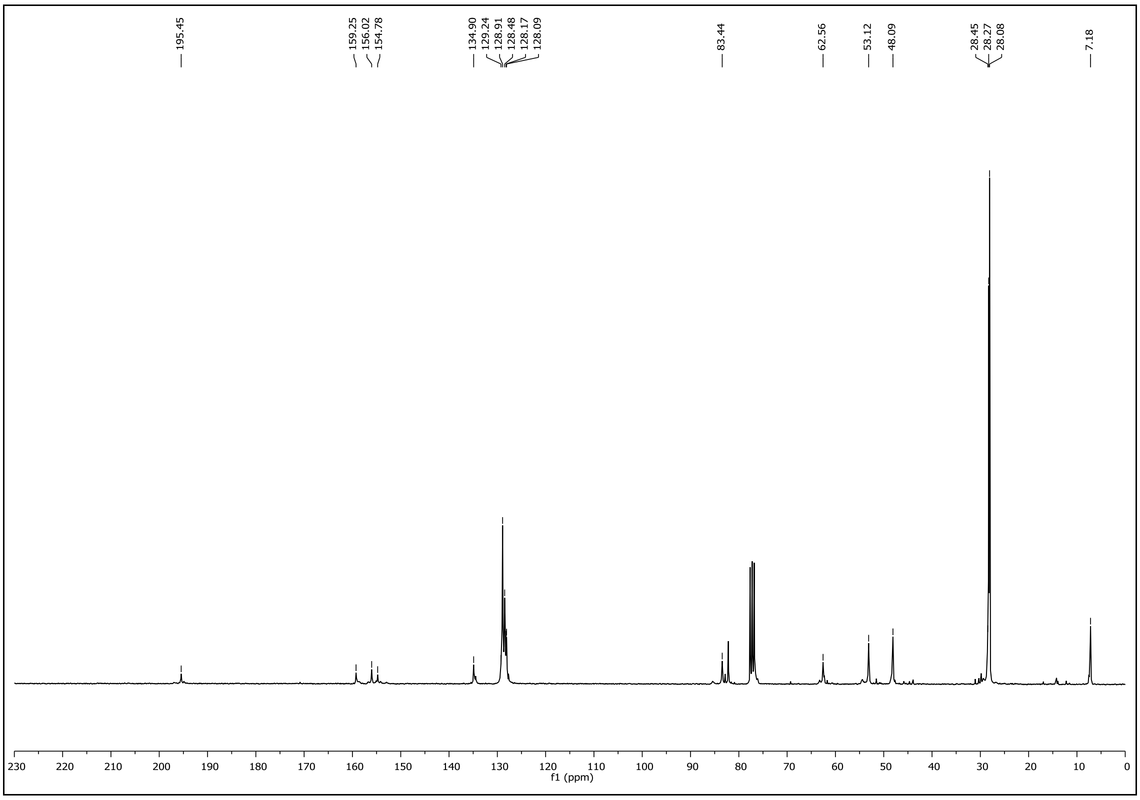
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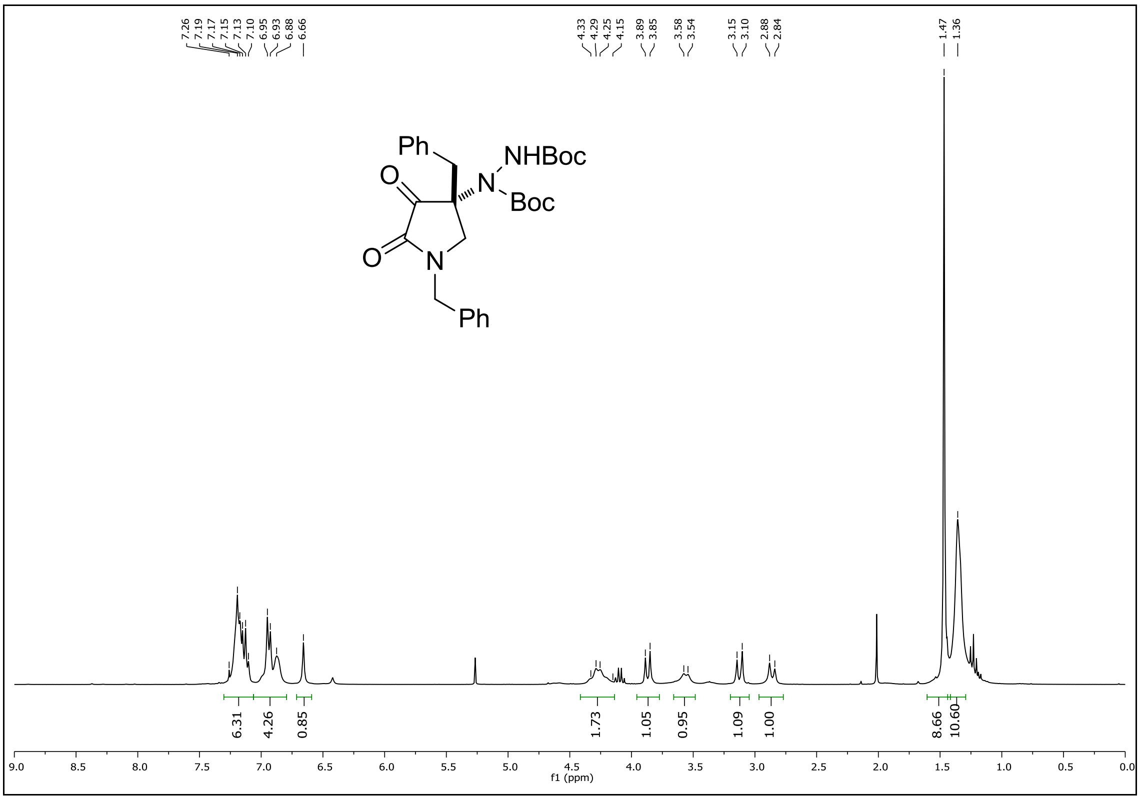
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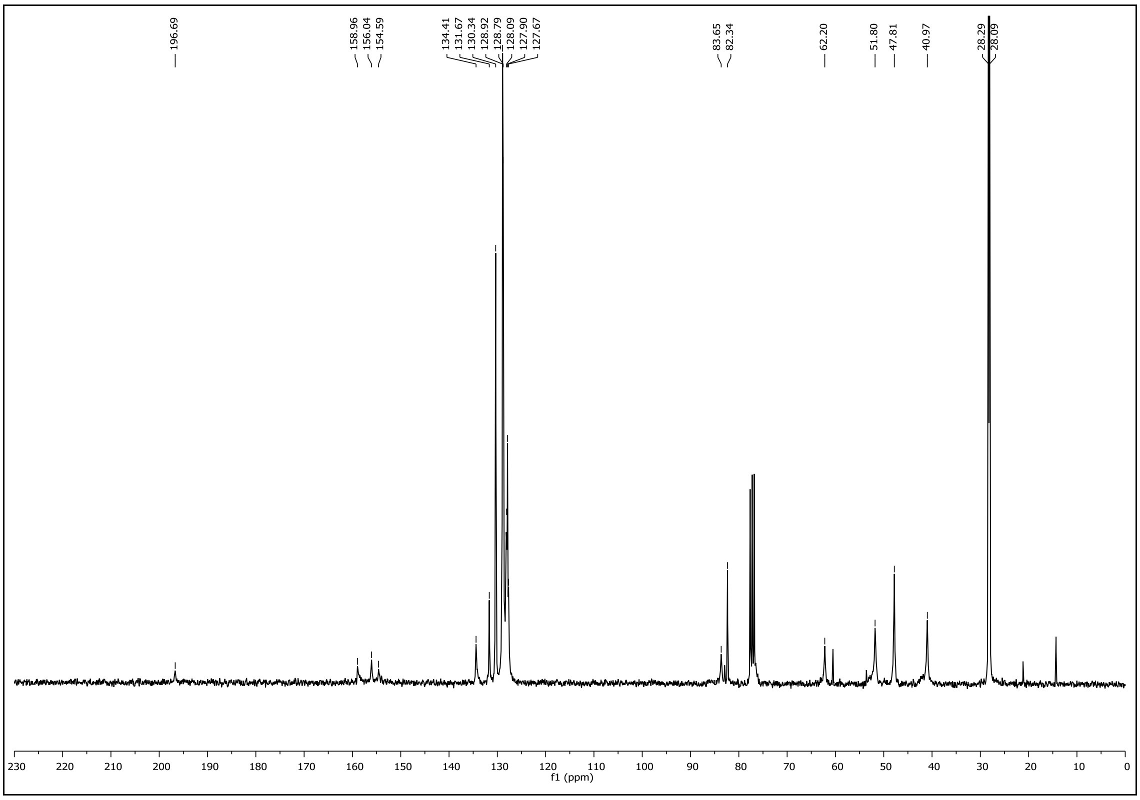
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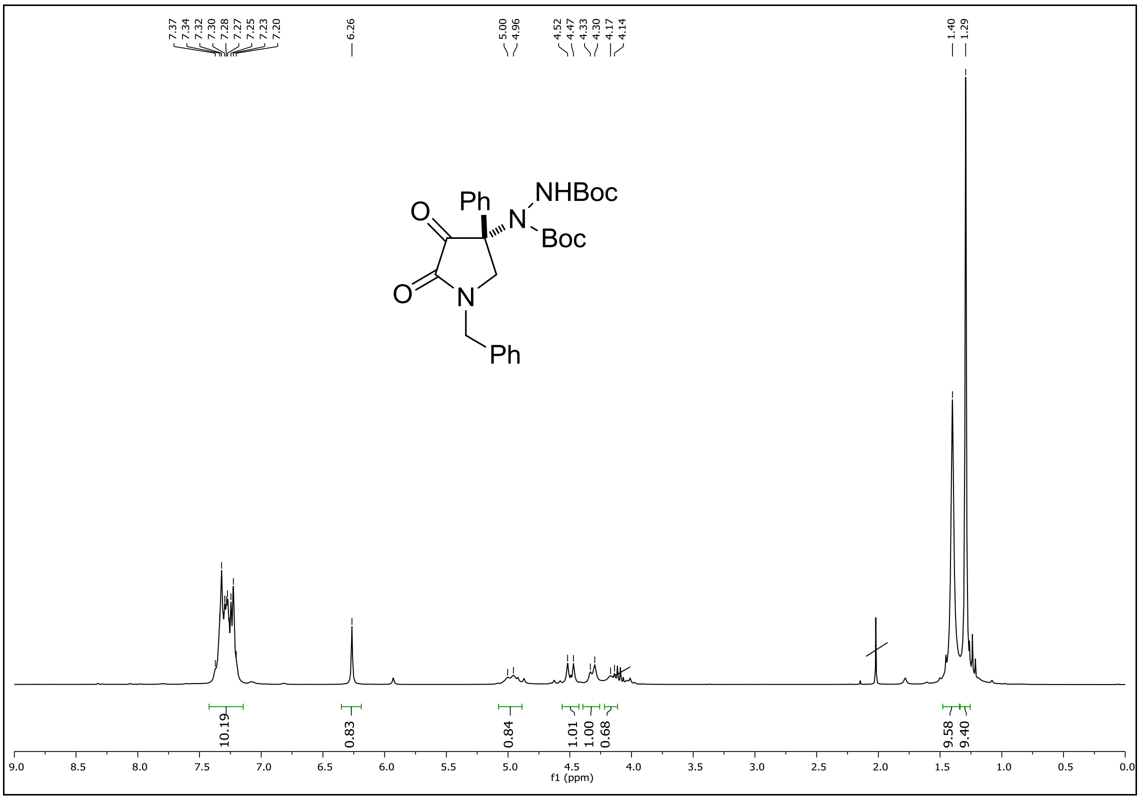
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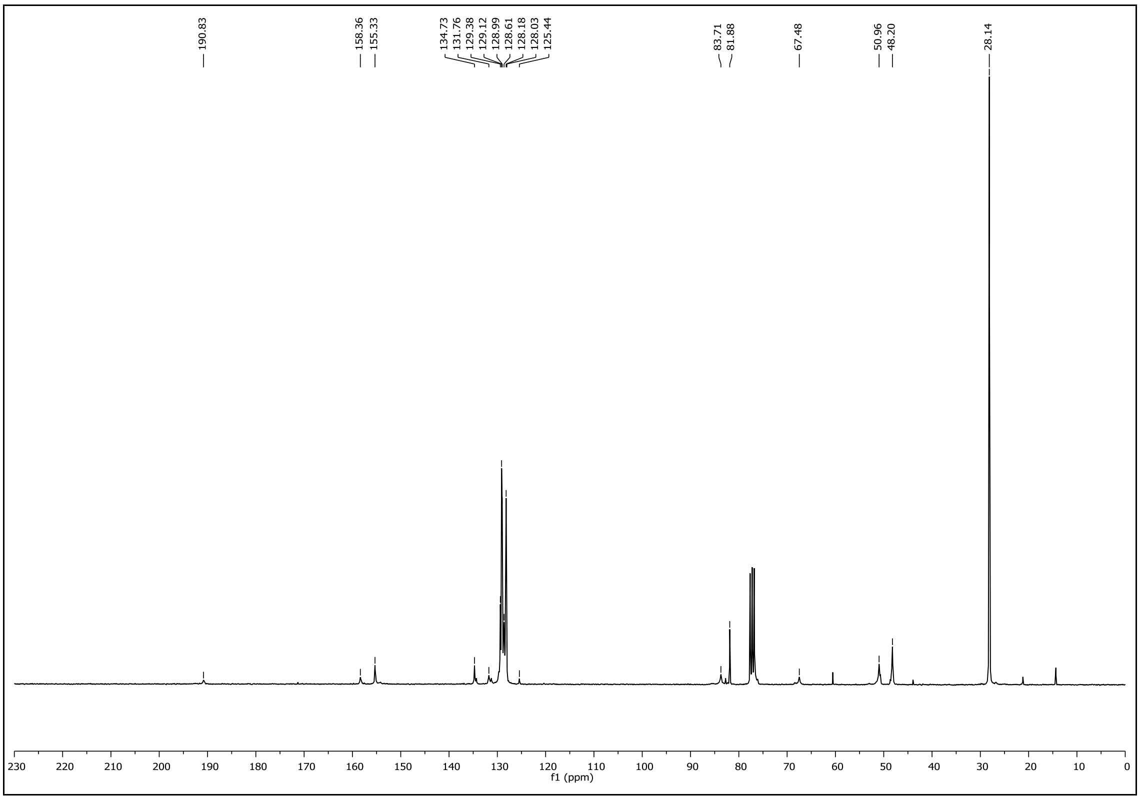
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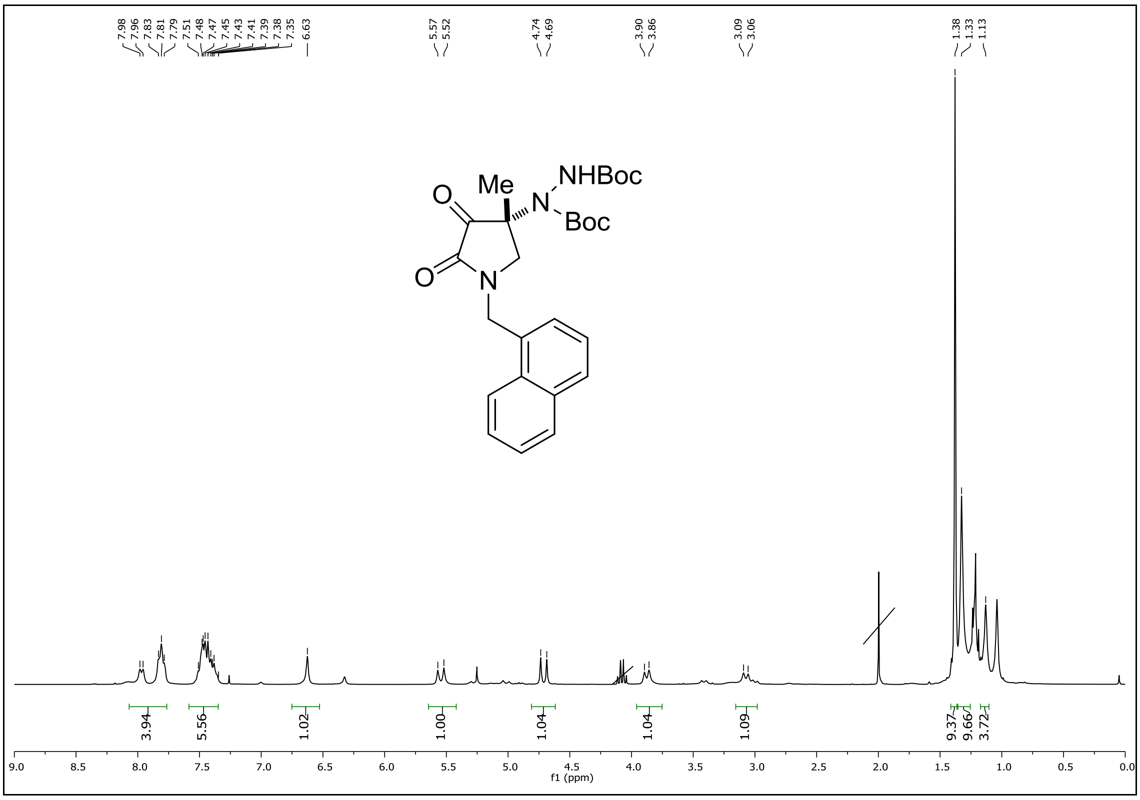
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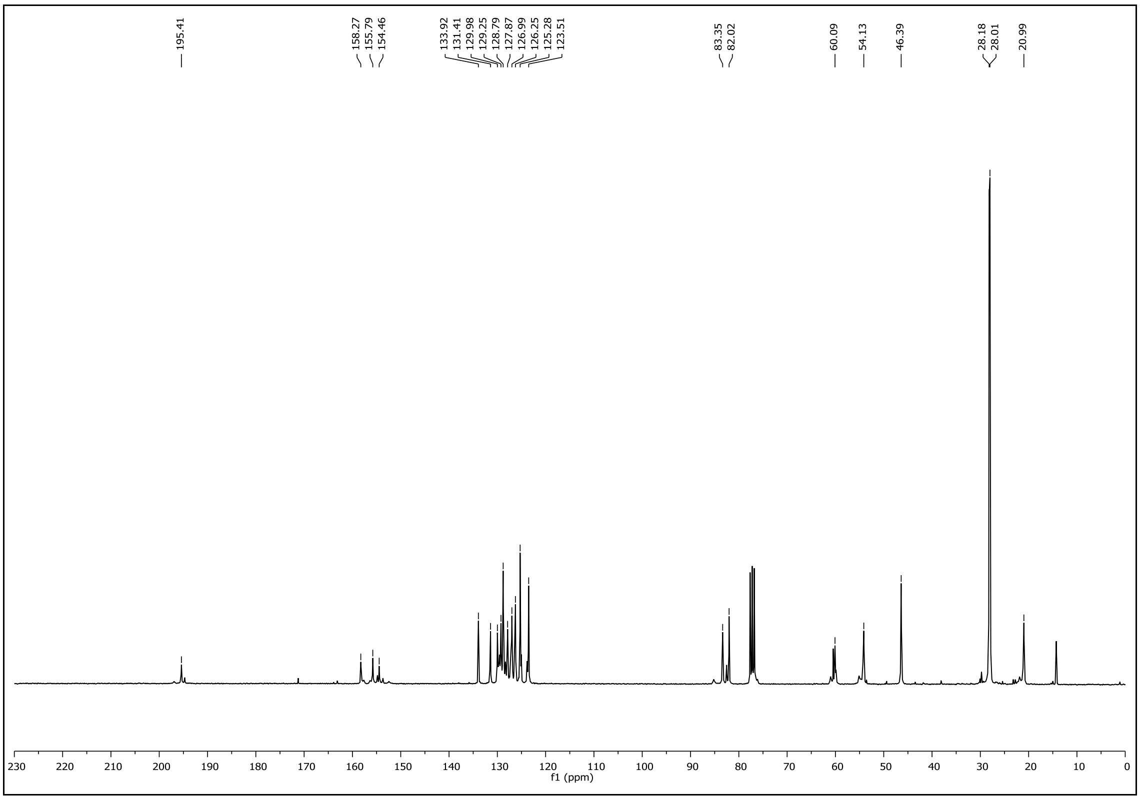
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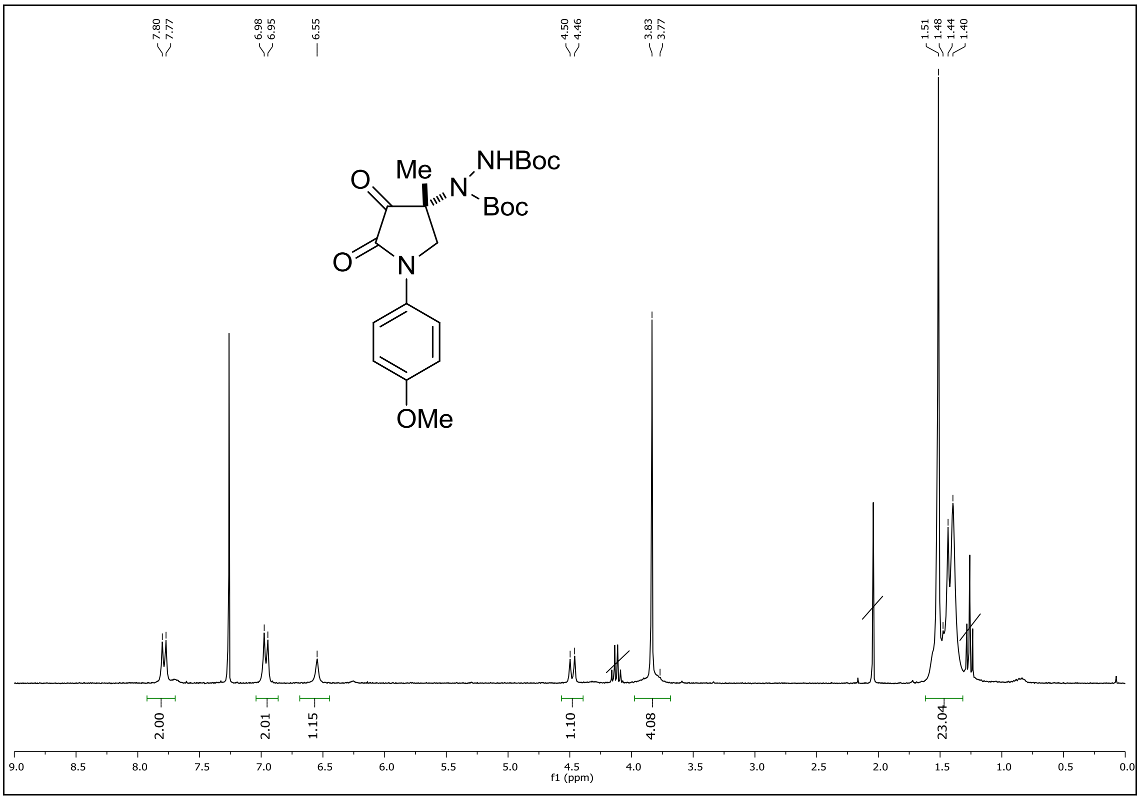
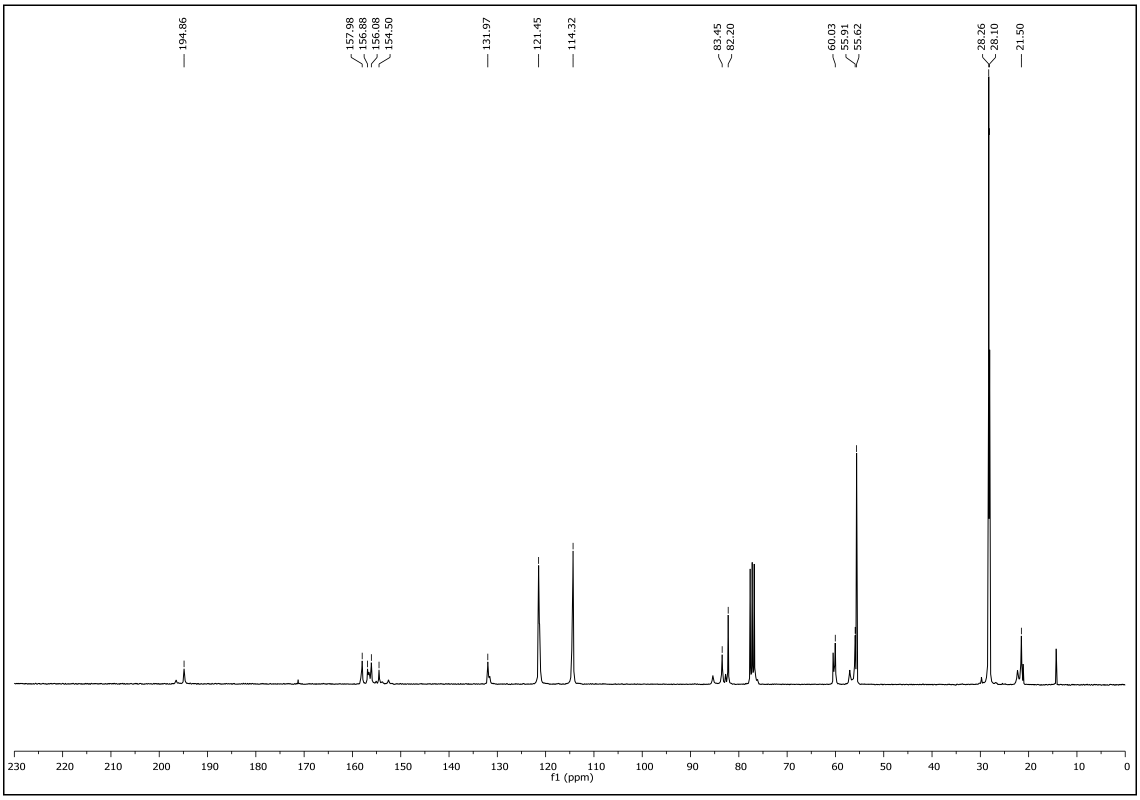
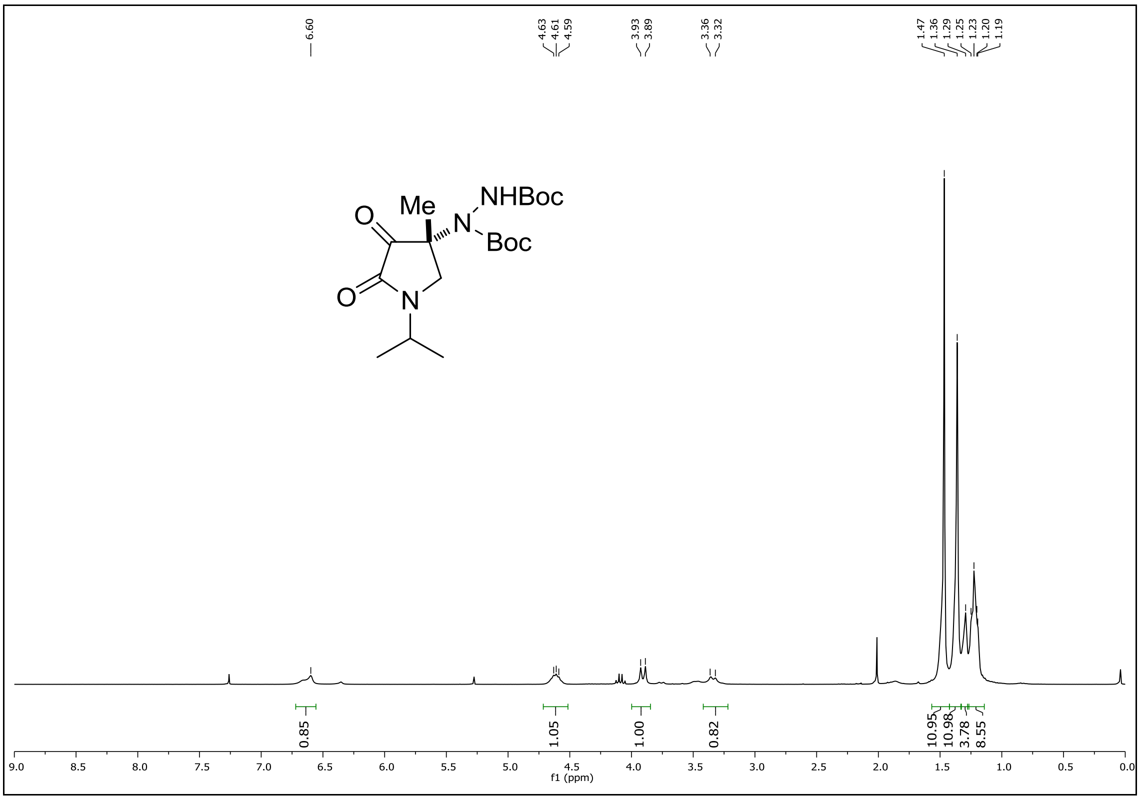
f1 (ppm)


7.80
7.77
6.98
6.95
6.55
4.50
4.46
3.83
3.77
1.51
1.48
1.44
1.40
Me
NHBoc
O
N
Boc
O
N
OMe
2.00
2.01
1.15
1.10
4.08
23.04
9.0
8.5
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
0.0
f1 (ppm)


194.86
157.98
156.88
156.08
154.50
131.97
121.45
114.32
83.45
82.20
60.03
55.91
55.62
28.26
28.10
21.50
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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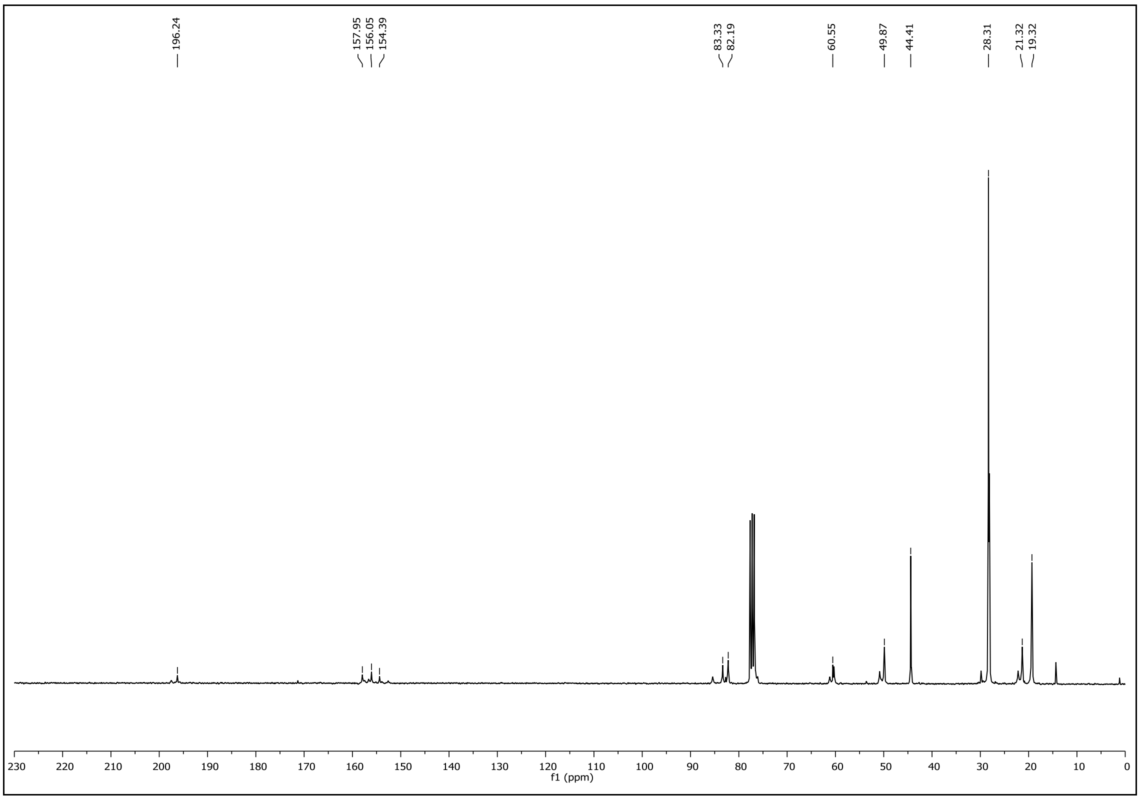
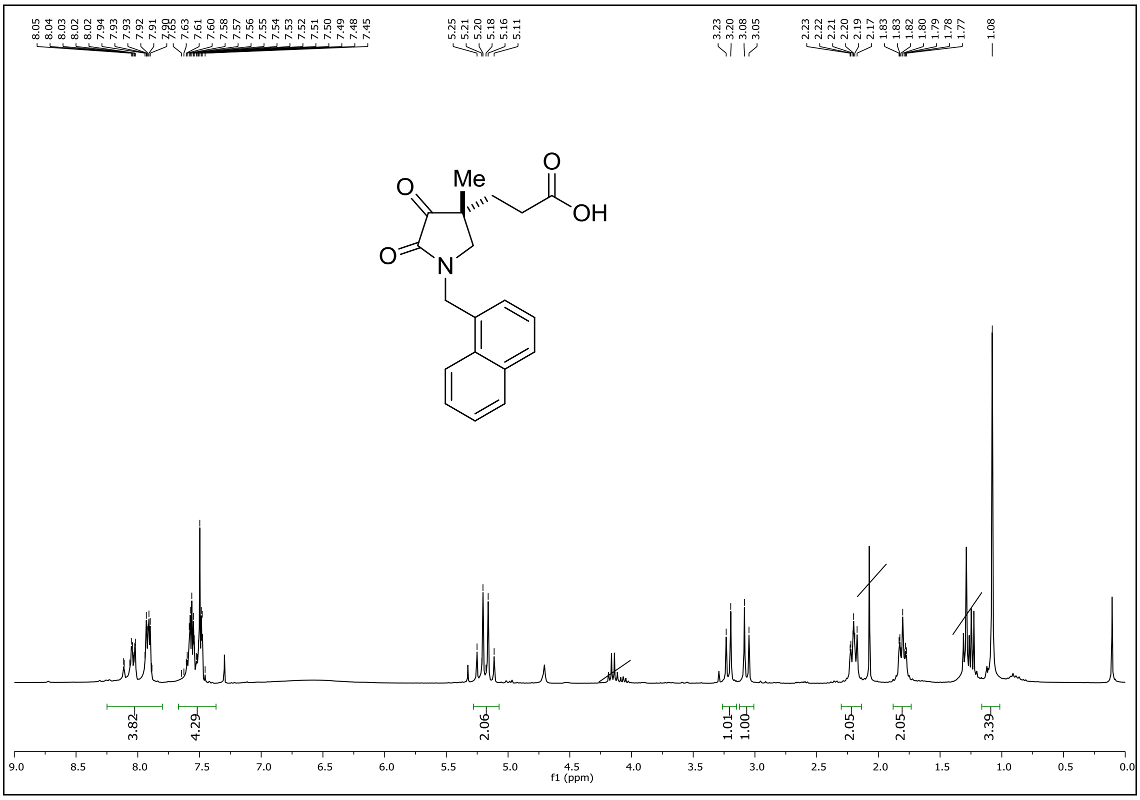
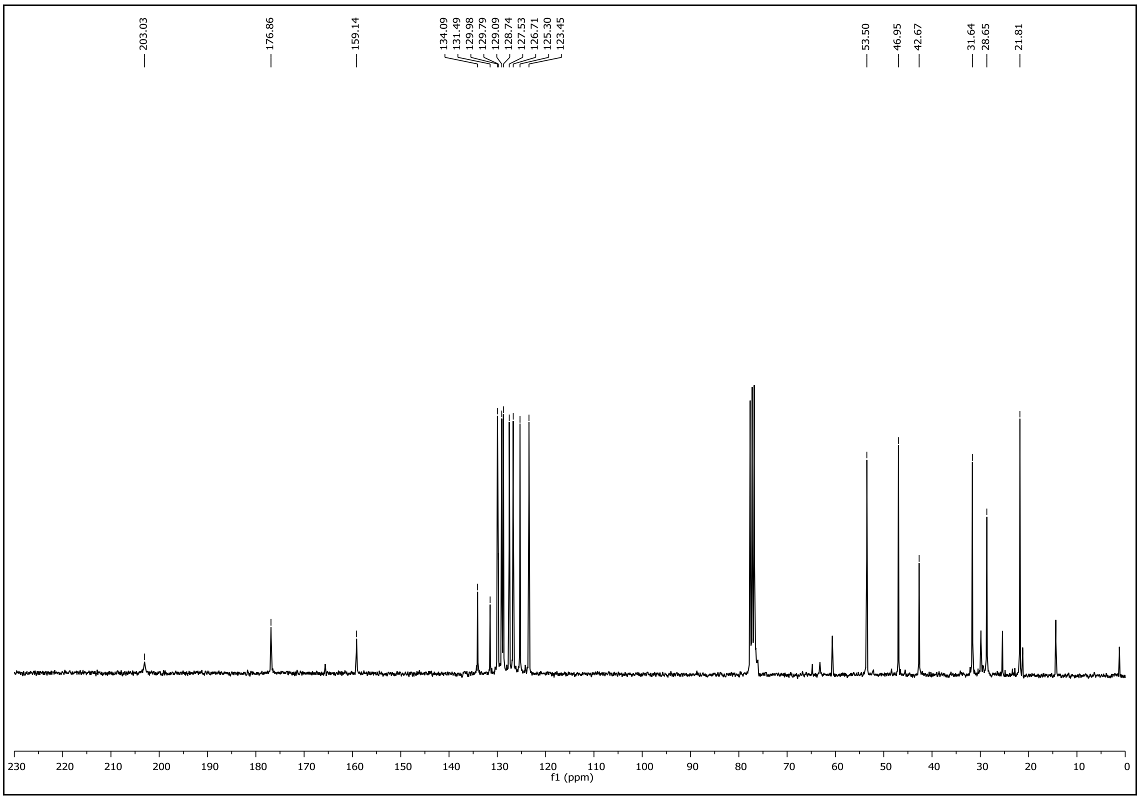
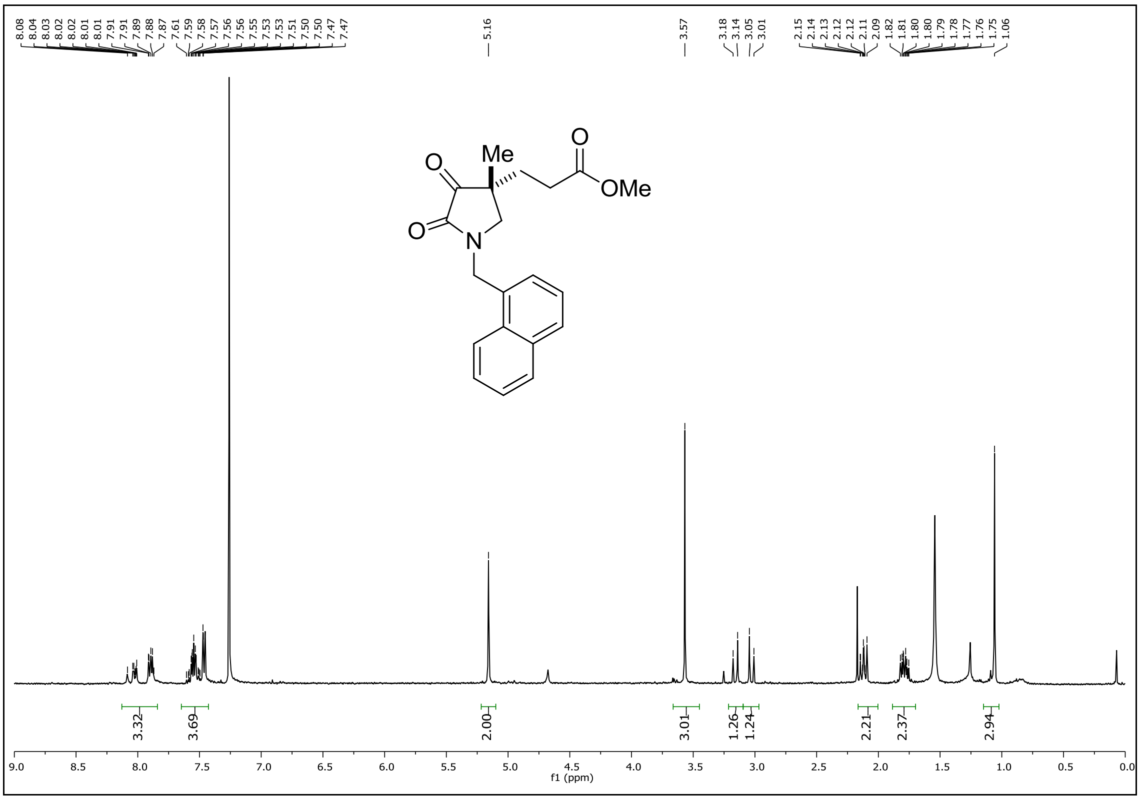
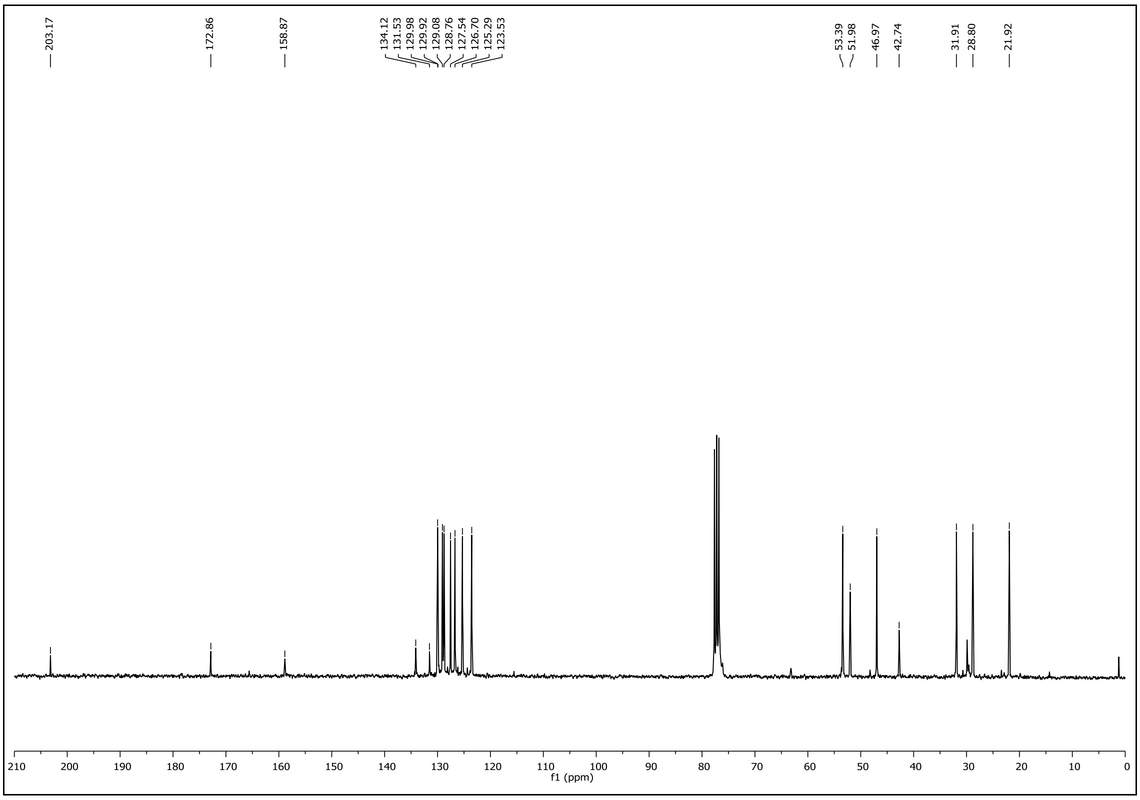
4.63
4.61
4.59
3.93
3.89
3.36
3.32
1.47
1.36
1.29
1.25
1.23
1.20
1.19
O
Me
NHBoc
N
Boc
O
N
0.85
1.05
1.00
0.82
10.95
10.98
3.78
8.55
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

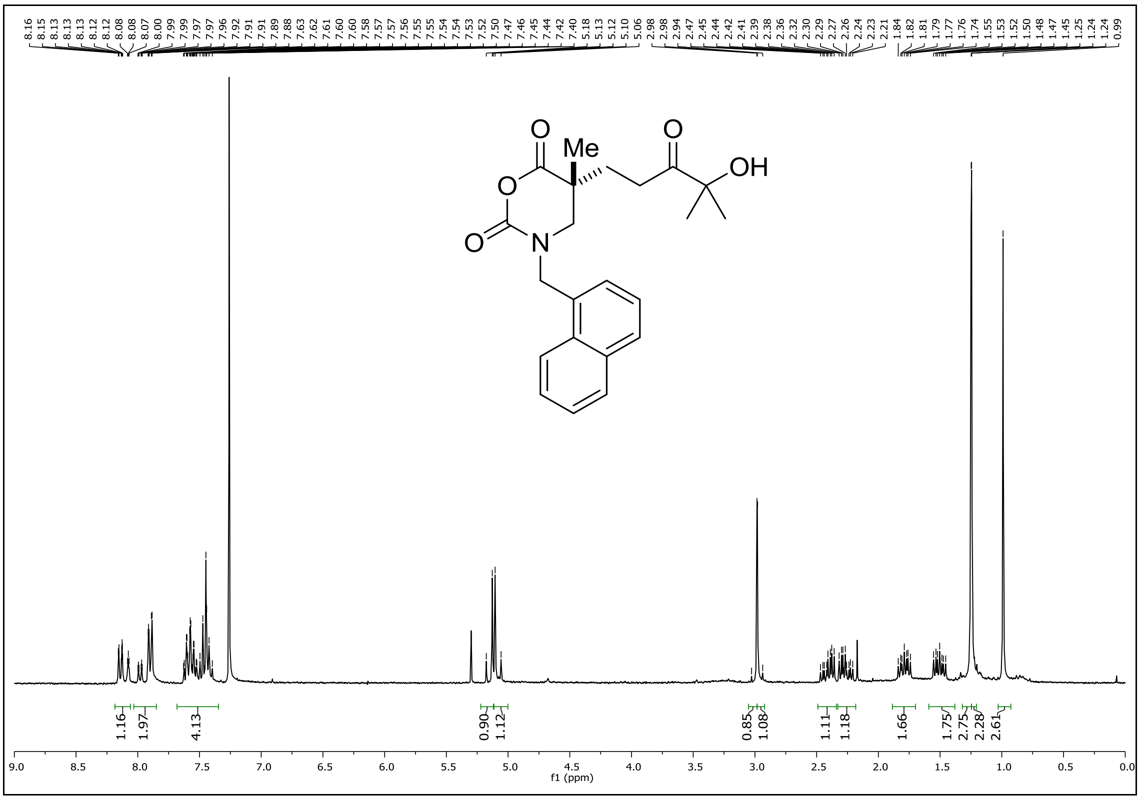

196.24
157.95
156.05
154.39
83.33
82.19
60.55
49.87
44.41
28.31
21.32
19.32
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

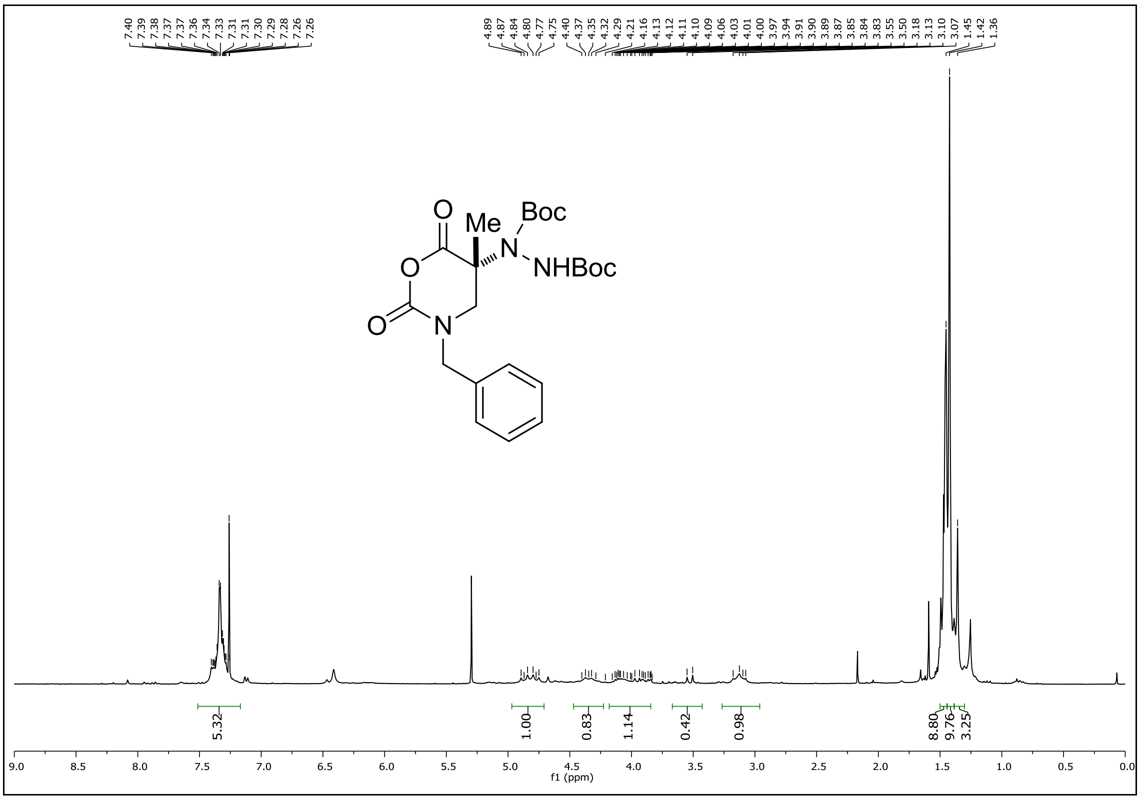

8.05
8.04
8.03
8.02
8.02
7.94
7.93
7.93
7.92
7.91
7.90
7.65
7.63
7.61
7.60
7.58
7.57
7.56
7.55
7.54
7.53
7.52
7.51
7.50
7.49
7.48
7.45
5.25
5.21
5.20
5.18
5.16
5.11
3.23
3.20
3.08
3.05
2.23
2.22
2.21
2.20
2.19
2.17
1.83
1.83
1.82
1.80
1.79
1.78
1.77
1.08
Me
O
O
OH
O
N
3.82
4.29
2.06
1.01
1.00
2.05
2.05
3.39
9.0
8.5
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
0.0
f1 (ppm)

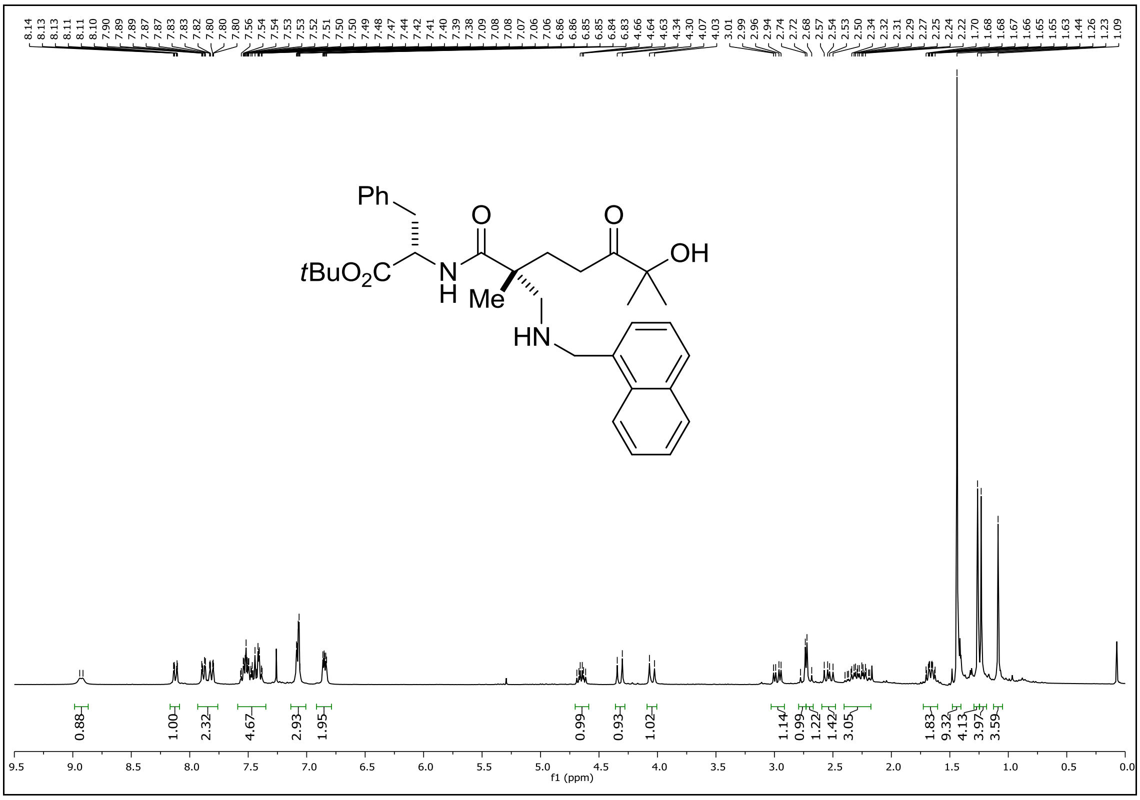

203.03
176.86
159.14
134.09
131.49
129.98
129.79
129.09
128.74
127.53
126.71
125.30
123.45
53.50
46.95
42.67
31.64
28.65
21.81
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

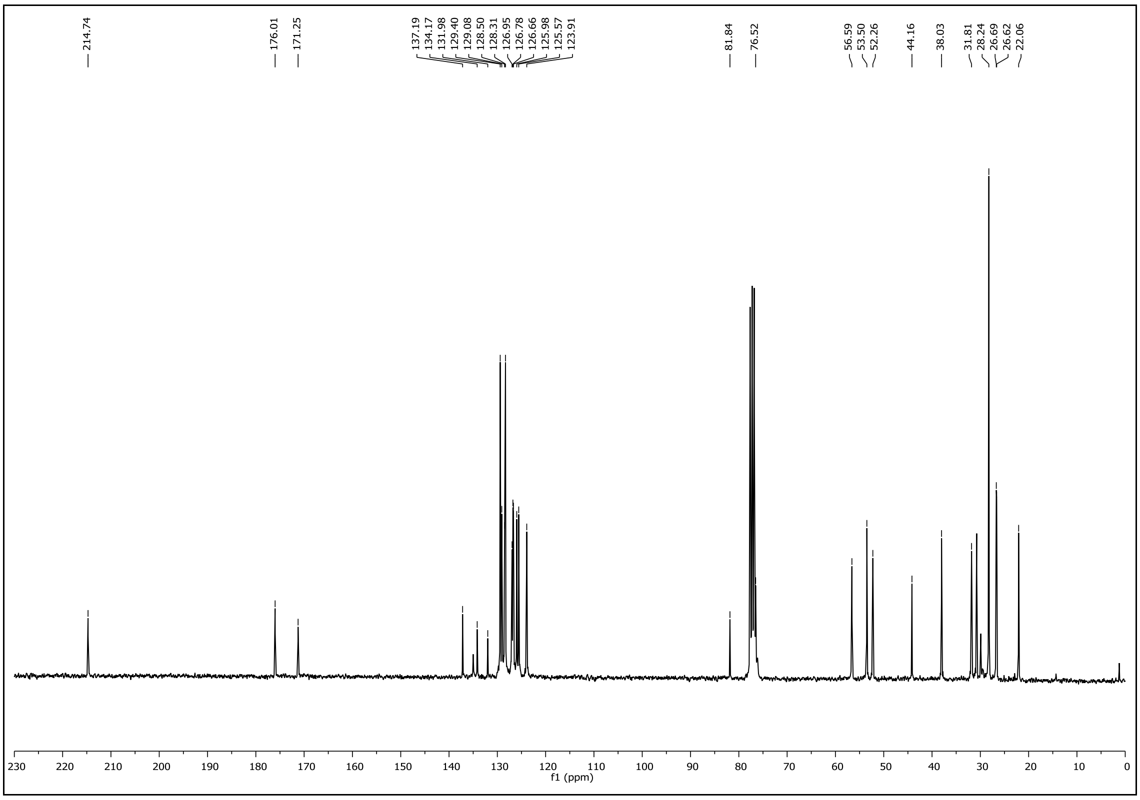

8.08
8.04
8.03
8.02
8.02
8.01
8.01
7.91
7.91
7.89
7.88
7.87
7.61
7.59
7.58
7.57
7.56
7.56
7.55
7.53
7.53
7.51
7.50
7.50
7.47
7.47
5.16
3.57
3.18
3.14
3.05
3.01
2.15
2.14
2.13
2.12
2.12
2.11
2.09
1.82
1.81
1.80
1.80
1.79
1.78
1.77
1.76
1.75
1.06
Me
O
O
OMe
O
N
3.32
3.69
2.00
3.01
1.26
1.24
2.21
2.37
2.94
9.0
8.5
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
0.0
f1 (ppm)

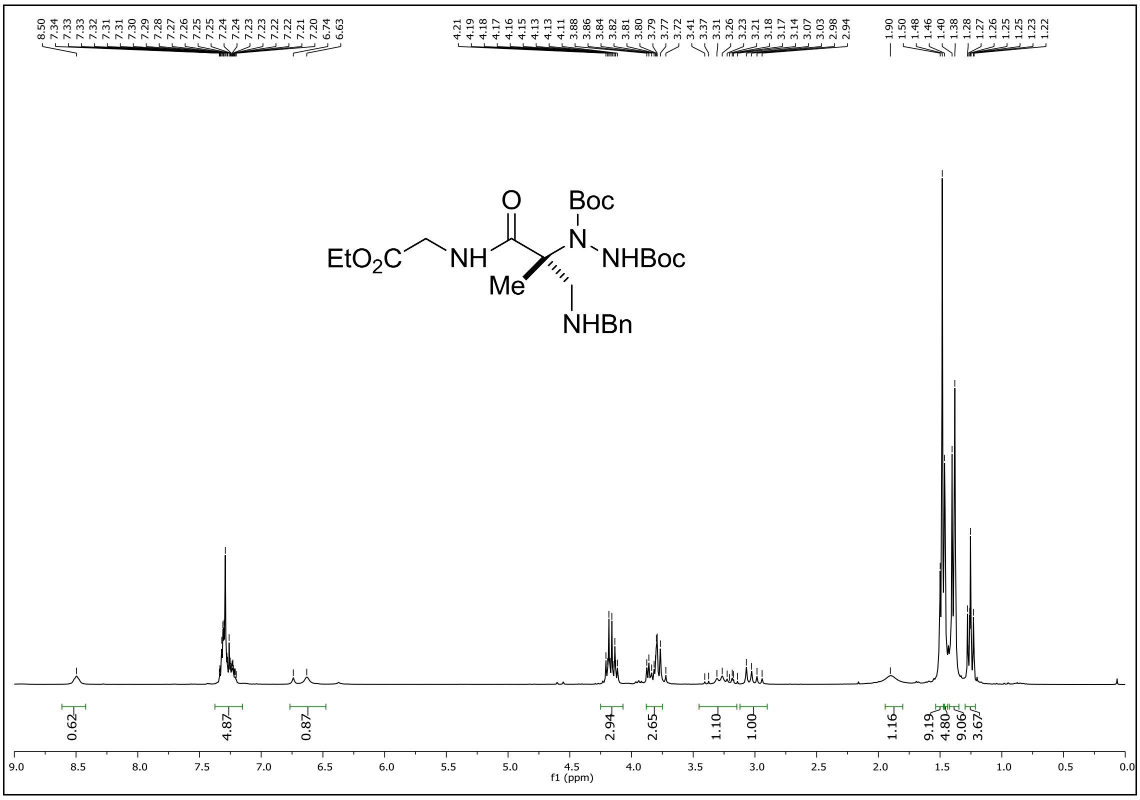

203.17
172.86
158.87
134.12
131.53
129.98
129.92
129.08
128.76
127.54
126.70
125.29
123.53
53.39
51.98
46.97
42.74
31.91
28.80
21.92
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

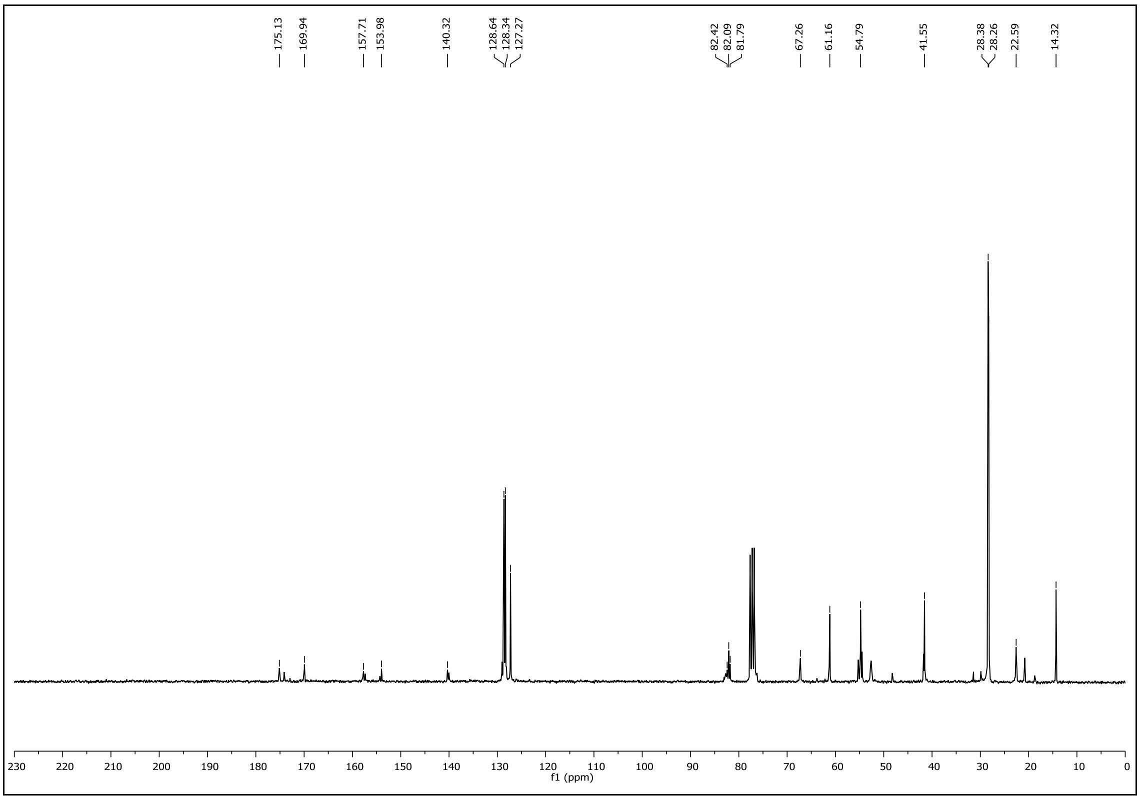

8.16 8.15 8.13 8.13 8.13 8.12 8.12 8.08 8.08 8.07 8.00 7.99 7.99 7.97 7.97 7.96 7.92 7.91 7.91 7.89 7.88 7.63 7.62 7.61 7.60 7.58 7.57 7.56 7.55 7.55 7.54 7.54 7.53 7.52 7.50 7.47 7.46 7.45 7.44 7.42 7.40 5.18 5.13 5.12 5.10 5.06 2.98 2.94 2.47 2.45 2.44 2.42 2.41 2.39 2.38 2.36 2.32 2.30 2.29 2.27 2.26 2.24 2.23 2.21 1.84 1.82 1.81 1.79 1.77 1.76 1.74 1.55 1.53 1.52 1.50 1.48 1.47 1.45 1.25 1.24 0.99
O
Me
O
OH
O
O
N
1.16
1.97
4.13
0.90
1.12
0.85
1.08
1.11
1.18
1.66
1.75
2.75
2.28
2.61
9.0 8.5 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 0.0
f1 (ppm)

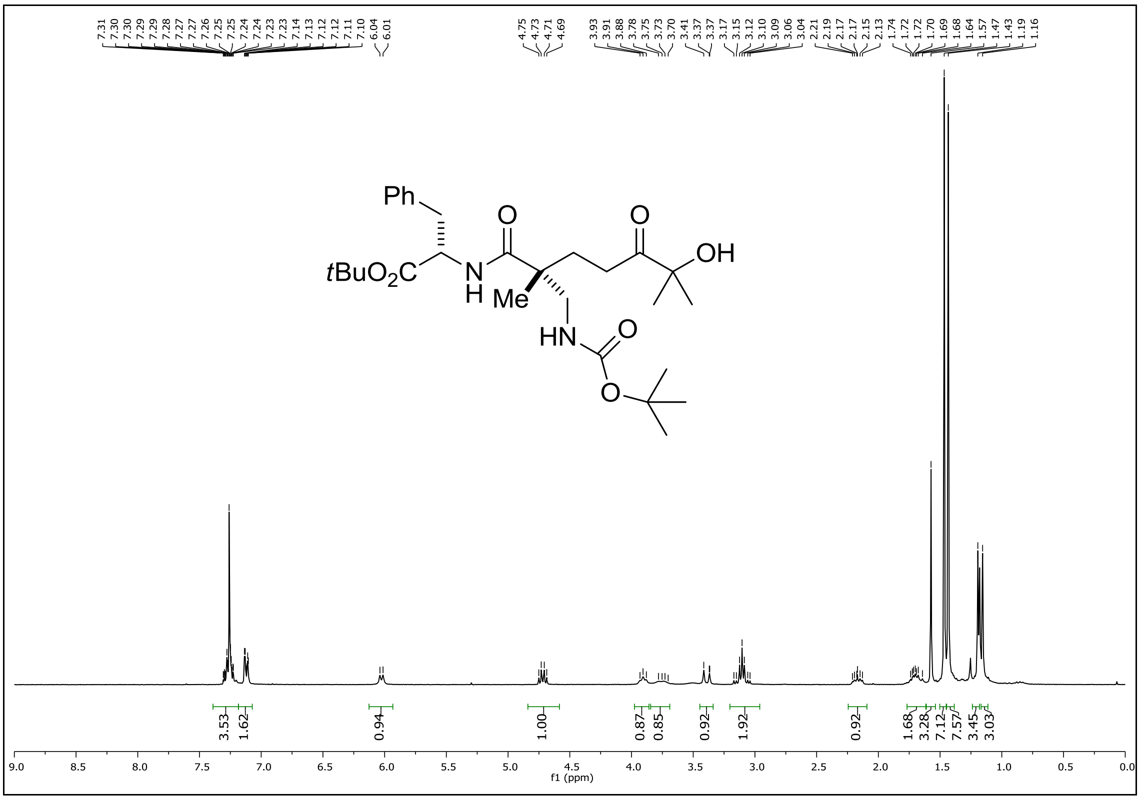

7.40 7.39 7.38 7.37 7.37 7.36 7.34 7.33 7.31 7.31 7.30 7.29 7.28 7.26 7.26
4.89 4.87 4.84 4.80 4.77 4.75 4.40 4.37 4.35 4.32 4.29 4.21 4.16 4.13 4.12 4.11 4.10 4.09 4.06 4.03 4.01 4.00 3.97 3.94 3.91 3.90 3.89 3.87 3.85 3.84 3.83 3.55 3.50 3.18 3.13 3.10 3.07 1.45 1.42 1.36
O
Me
Boc
N
NHBoc
O
O
N
5.32
1.00
0.83
1.14
0.42
0.98
8.80
9.76
3.25
9.0 8.5 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 0.0
f1 (ppm)

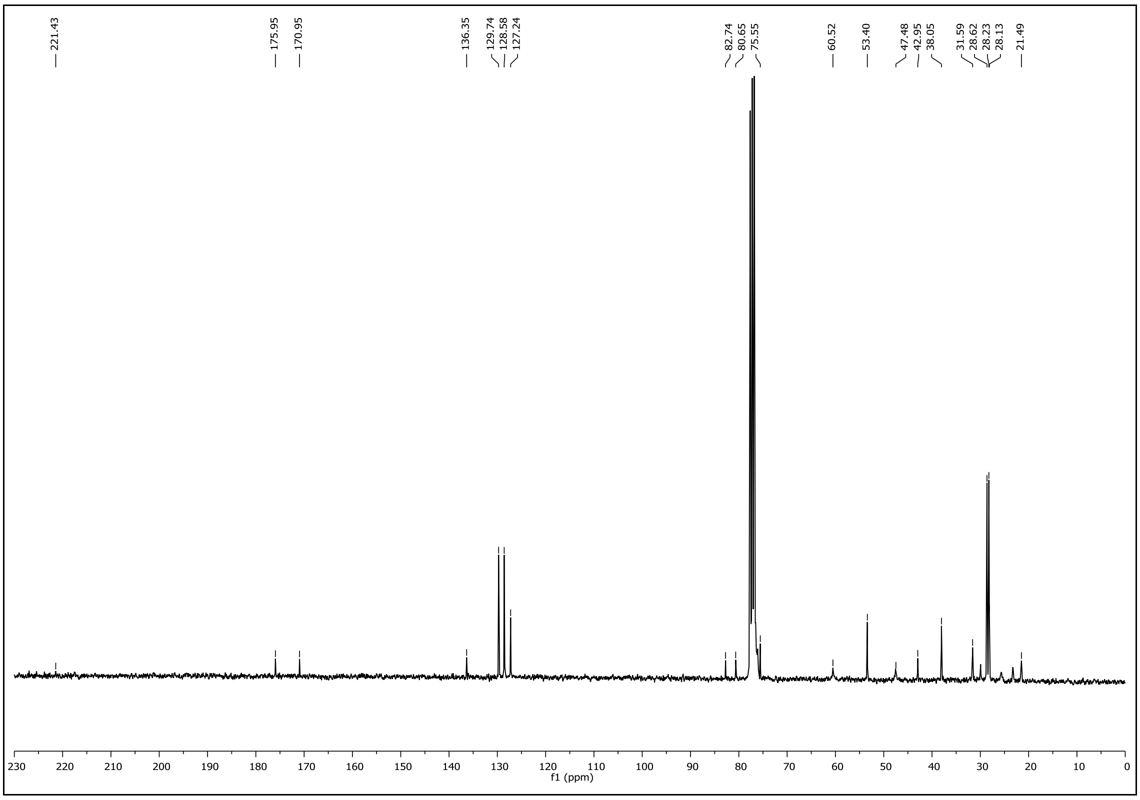

8.14 8.13 8.13 8.11 8.11 8.10 7.90 7.89 7.89 7.87 7.87 7.83 7.83 7.82 7.80 7.80 7.56 7.54 7.54 7.53 7.53 7.52 7.51 7.50 7.50 7.49 7.48 7.47 7.44 7.42 7.41 7.40 7.39 7.38 7.09 7.08 7.08 7.07 7.06 7.06 6.86 6.86 6.85 6.85 6.84 6.83 4.66 4.64 4.63 4.34 4.30 4.07 4.03 3.01 2.99 2.96 2.94 2.74 2.72 2.68 2.57 2.54 2.53 2.50 2.34 2.32 2.31 2.29 2.27 2.25 2.24 2.22 1.70 1.68 1.67 1.66 1.65 1.63 1.44 1.26 1.23 1.09
Ph
O
O
OH
tBuO2C
N
H
Me
HN
0.88
1.00
2.32
4.67
2.93
1.95
0.99
0.93
1.02
1.14
0.99
1.22
1.42
3.05
1.83
9.32
4.13
3.97
3.59
9.5 9.0 8.5 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 0.0
f1 (ppm)

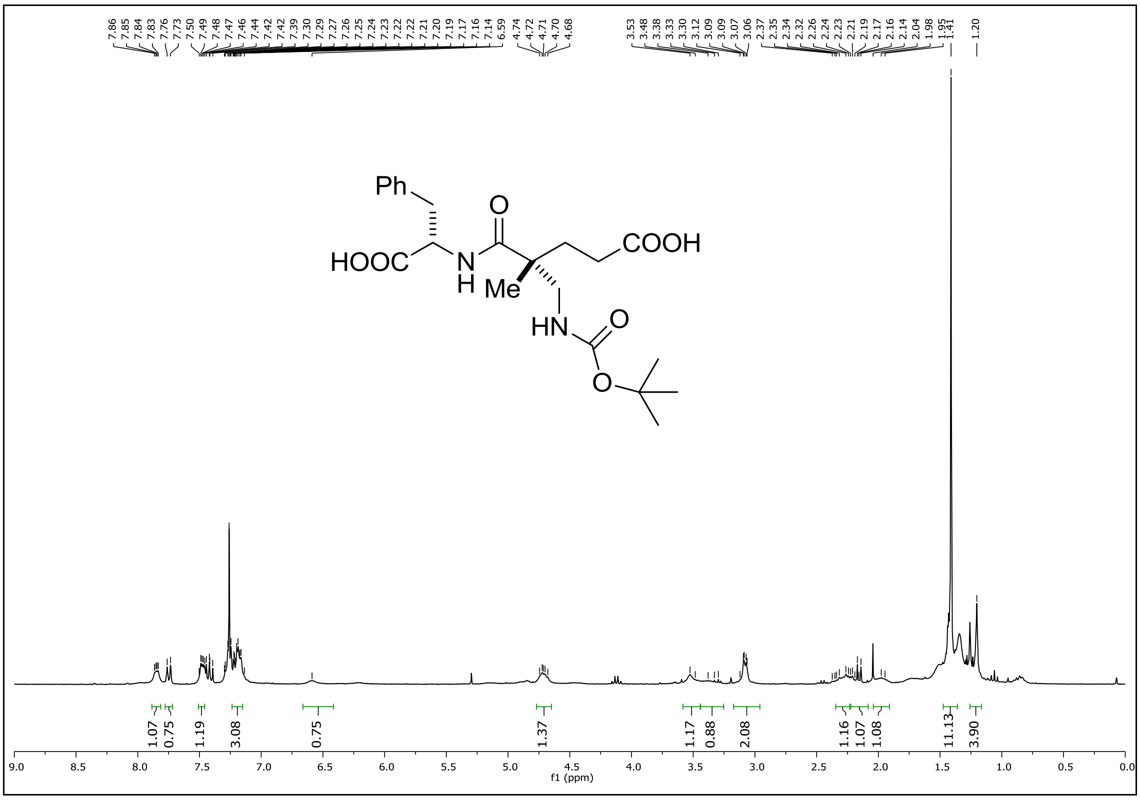

214.74
176.01
171.25
137.19 134.17 131.98 129.40 129.08 128.50 128.31 126.95 126.78 126.66 125.98 125.57 123.91
81.84
76.52
56.59 53.50 52.26
44.16
38.03
31.81 28.24 26.69 26.62 22.06
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

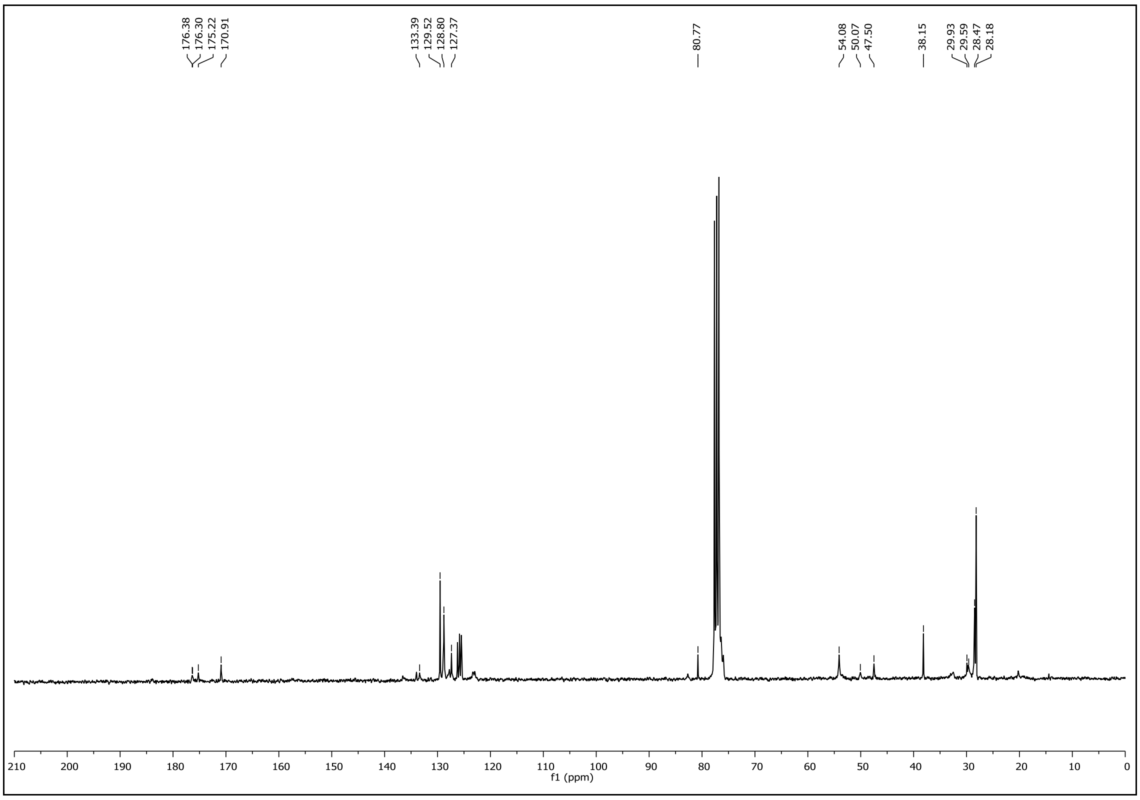

8.50
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.25
7.24
7.24
7.23
7.23
7.22
7.22
7.21
7.20
6.74
6.63
4.21
4.19
4.18
4.17
4.16
4.15
4.13
4.13
4.11
3.88
3.86
3.84
3.82
3.81
3.80
3.79
3.77
3.72
3.41
3.37
3.31
3.26
3.23
3.21
3.18
3.17
3.14
3.07
3.03
2.98
2.94
1.90
1.50
1.48
1.46
1.40
1.38
1.28
1.27
1.26
1.25
1.25
1.23
1.22
O
Boc
N
EtO2C
NH
NHBoc
Me
NHBn
0.62
4.87
0.87
2.94
2.65
1.10
1.00
1.16
9.19
4.80
9.06
3.67
9.0
8.5
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
0.0
f1 (ppm)


175.13
169.94
157.71
153.98
140.32
128.64
128.34
127.27
82.42
82.09
81.79
67.26
61.16
54.79
41.55
28.38
28.26
22.59
14.32
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

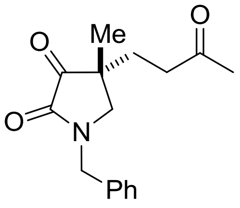

7.31 7.30 7.29 7.29 7.28 7.27 7.27 7.26 7.25 7.25 7.24 7.24 7.23 7.23 7.14 7.13 7.12 7.12 7.11 7.10 6.04 6.01
4.75 4.73 4.71 4.69
3.93 3.91 3.88 3.78 3.75 3.73 3.70 3.41 3.37 3.37 3.17 3.15 3.12 3.10 3.09 3.06 3.04
2.21 2.19 2.17 2.17 2.15 2.13 1.74 1.72 1.72 1.70 1.69 1.68 1.64 1.57 1.47 1.43 1.19 1.16
Ph
O
O
OH
tBuO2C
N
H
Me
HN
O
O
3.53
1.62
0.94
1.00
0.87
0.85
0.92
1.92
0.92
1.68
3.28
7.12
7.57
3.45
3.03
9.0 8.5 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 0.0
f1 (ppm)


221.43
175.95
170.95
136.35
129.74
128.58
127.24
82.74
80.65
75.55
60.52
53.40
47.48
42.95
38.05
31.59
28.62
28.23
28.13
21.49
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.86 7.85 7.84 7.83 7.76 7.73 7.50 7.49 7.48 7.47 7.46 7.44 7.42 7.42 7.39 7.30 7.29 7.27 7.26 7.25 7.24 7.23 7.22 7.22 7.21 7.20 7.19 7.17 7.16 7.14 6.59 4.74 4.72 4.71 4.70 4.68 3.53 3.48 3.38 3.33 3.30 3.12 3.09 3.09 3.07 3.06 2.37 2.35 2.34 2.32 2.26 2.24 2.23 2.21 2.19 2.17 2.16 2.14 2.04 1.98 1.95 1.41 1.20
Ph
O
COOH
HOOC
N
H
Me
HN
O
O
1.07 0.75 1.19 3.08 0.75 1.37 1.17 0.88 2.08 1.16 1.07 1.08 11.13 3.90
9.0 8.5 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 0.0
f1 (ppm)


176.38 176.30 175.22 170.91 133.39 129.52 128.80 127.37 80.77 54.08 50.07 47.50 38.15 29.93 29.59 28.47 28.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

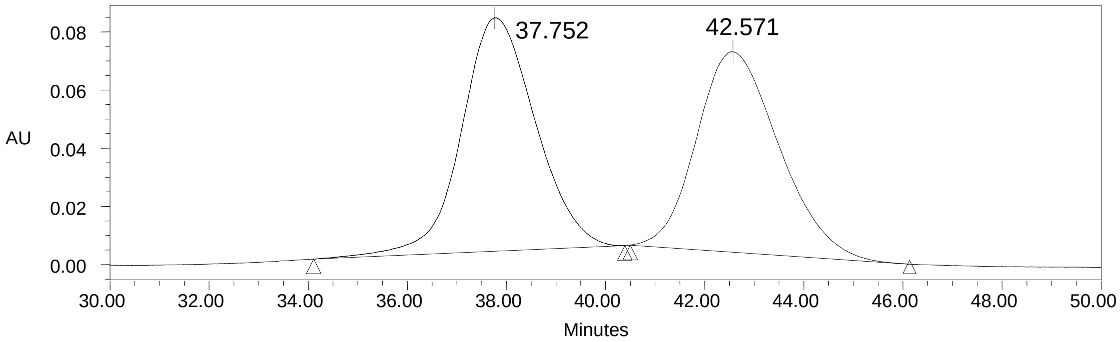
6.5.7. HPLC chromatograms



175a

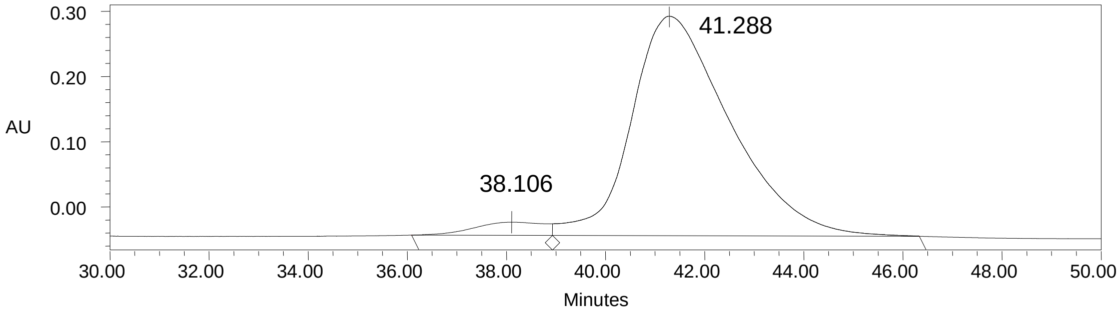
Column: OD-H
Eluent: Hex: *i*PrOH, 80:20
Flow rate = 0.7 mL/min
λ = 210 nm

rac-**175a**



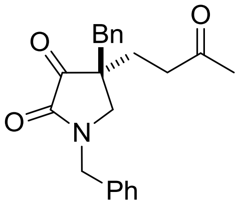
	Retention Time	Area	% Area	Height
1	37.752	8342884	51.13	80249
2	42.571	7973303	48.87	68928

175a



	Retention Time	Area	% Area	Height
1	38,106	1977722	4,07	20154
2	41,288	46626263	95,93	336572

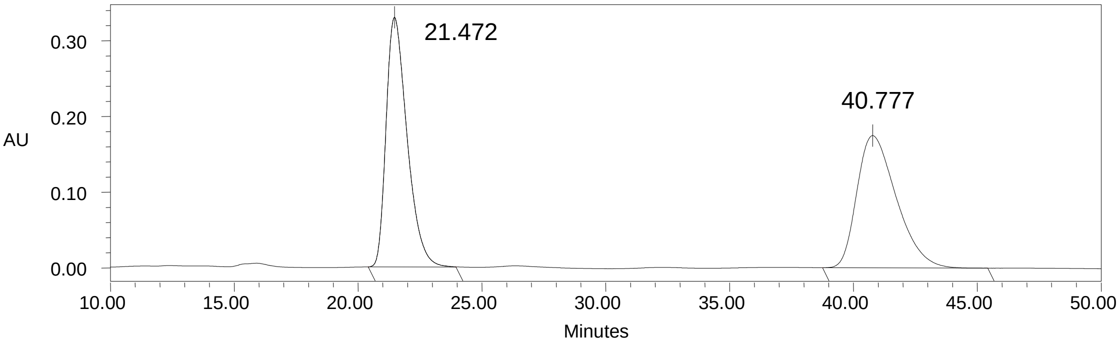
92% *ee*



175c

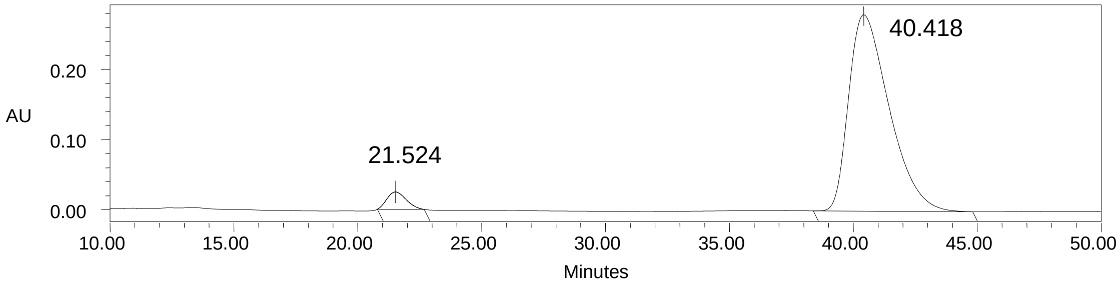
Column: OD-H
Eluent: Hex: *i*PrOH, 50:50
Flow rate = 0.5 mL/min
λ = 210 nm

rac-**175c**



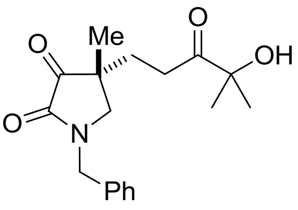
	Retention Time	Area	% Area	Height
1	21,472	19421974	50,17	329536
2	40,777	19293528	49,83	174663

175c



	Retention Time	Area	% Area	Height
1	21,524	1336108	4,02	24782
2	40,418	31859260	95,98	280217

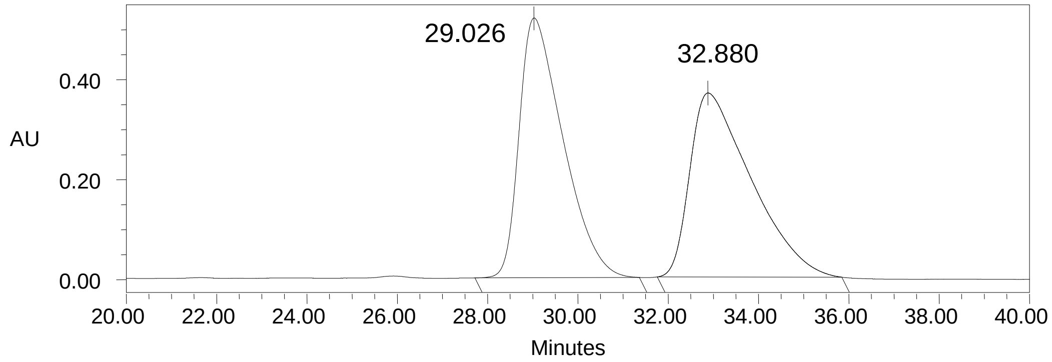
92% *ee*



177a

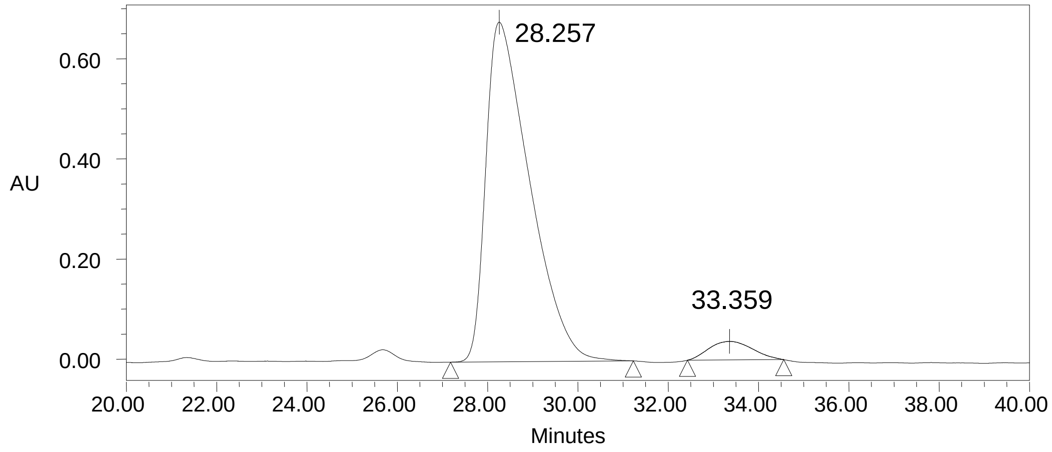
Column: AY-H
Eluent: Hex:*i*PrOH, 40:60
Flow rate = 0.6 mL/min
λ = 210 nm

rac-**177a**



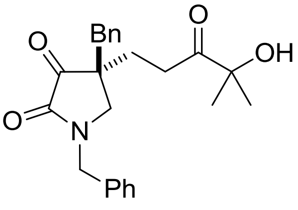
	Retention Time	Area	% Area	Height
1	29.026	35060217	50.30	519519
2	32.880	34640780	49.70	367940

177a



	Retention Time	Area	% Area	Height
1	28.257	45765470	94.83	678627
2	33.359	2497607	5.17	37150

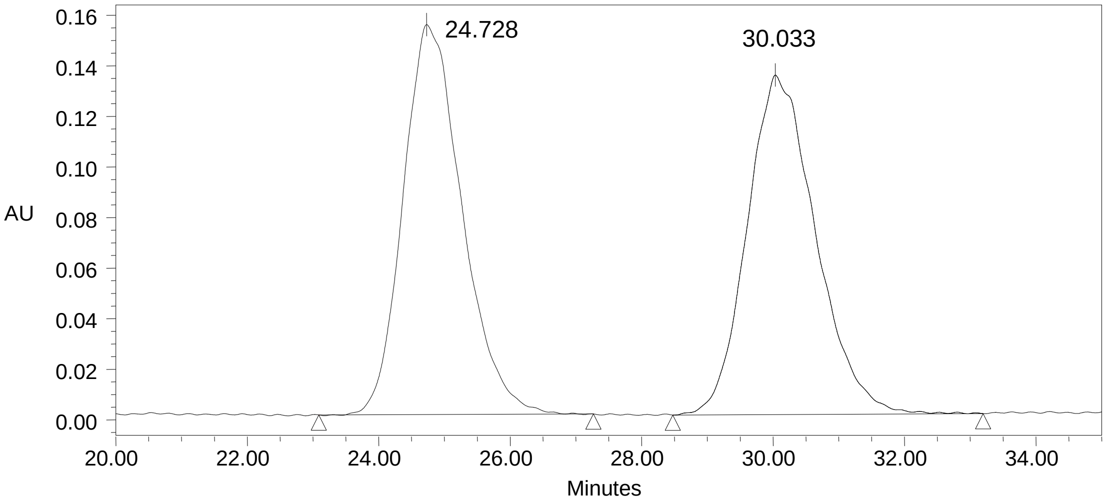
90% *ee*



177c

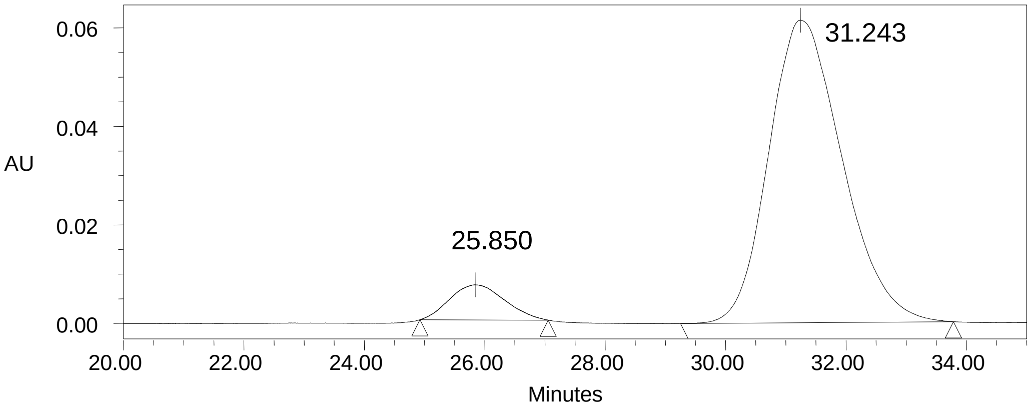
Column: IC
Eluent: Hex:*i*PrOH, 70:30
Flow rate = 1.0 mL/min
λ = 210 nm

rac-**177c**



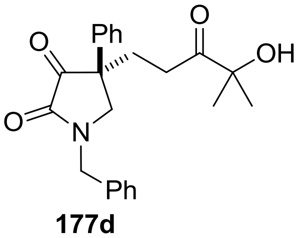
	Retention Time	Area	% Area	Height
1	24.728	9415088	49.79	153130
2	30.033	9494185	50.21	133221

177c



	Retention Time	Area	% Area	Height
1	25.850	450106	7.95	7121
2	31.243	5212830	92.05	61431

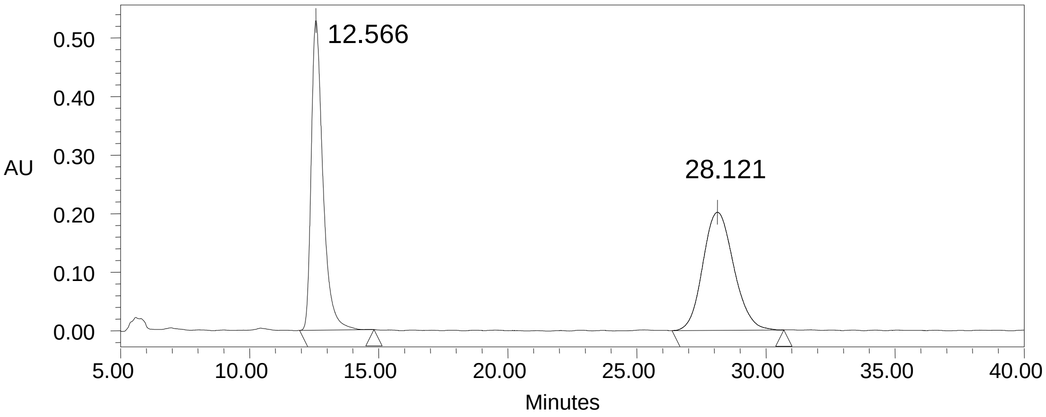
84% *ee*



177d

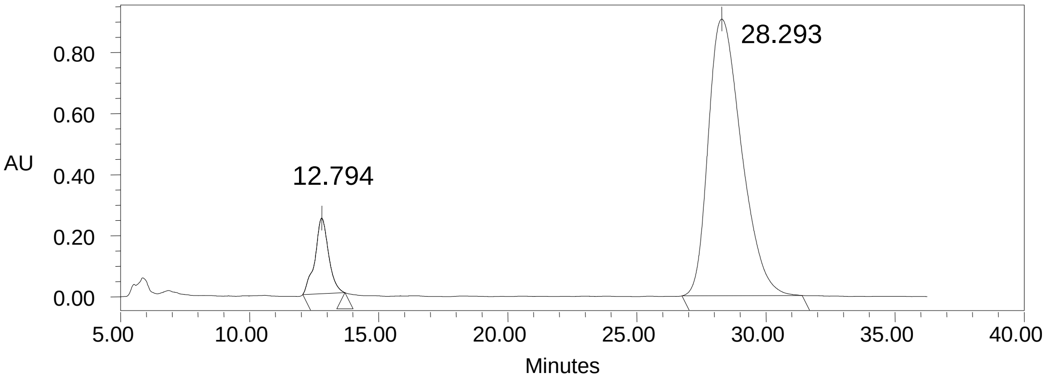
Column: AY-H
Eluent: Hex:*i*PrOH, 40:60
Flow rate = 0.6 mL/min
λ = 210 nm

rac-**177d**



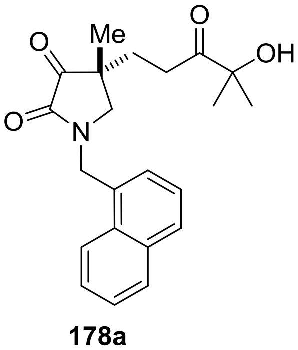
	Retention Time	Area	% Area	Height
1	12.566	16722479	49.93	528818
2	28.121	16772249	50.07	201648

177d



	Retention Time	Area	% Area	Height
1	12.794	9123076	10.10	247630
2	28.293	81205565	89.90	906374

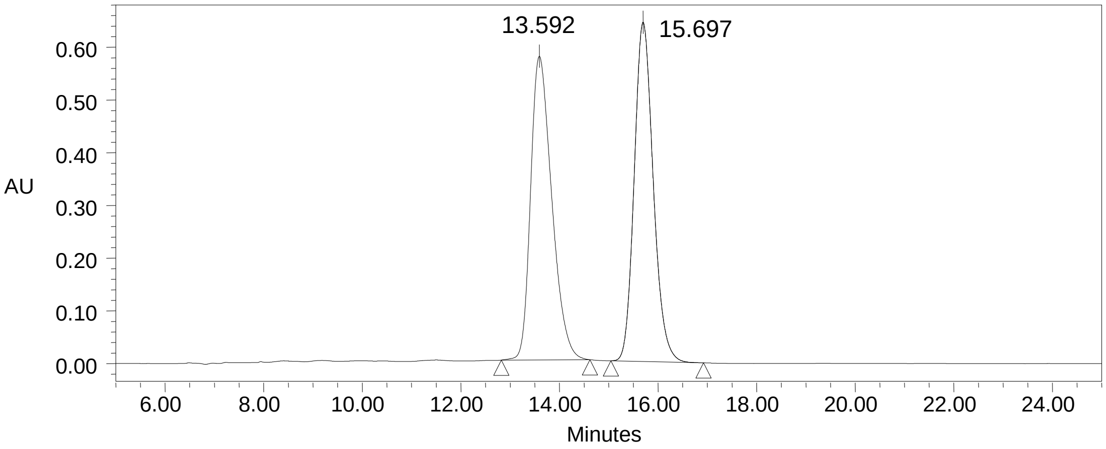
80% *ee*



178a

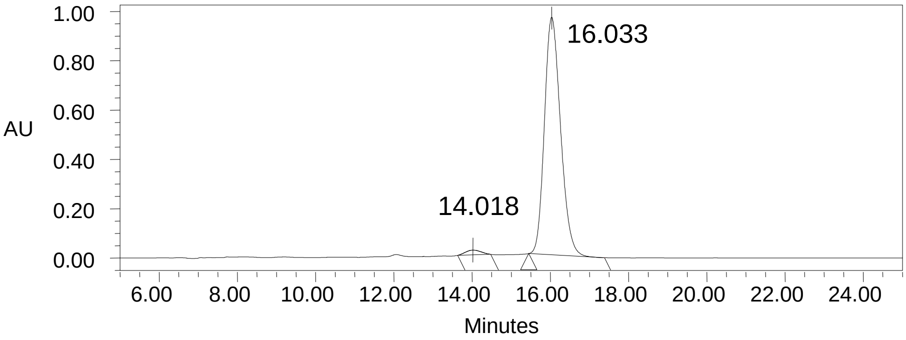
Column: AY-H
Eluent: Hex:EtOH, 50:50
Flow rate = 0.5 mL/min
λ = 210 nm

rac-**178a**



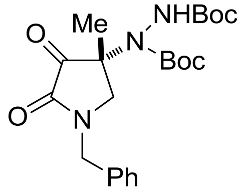
	Retention Time	Area	% Area	Height
2	15.697	17291962	50.18	643571
1	13.592	17169147	49.82	575983

178a



	Retention Time	Area	% Area	Height
1	14.018	532959	1.89	19415
2	16.033	27640192	98.11	963936

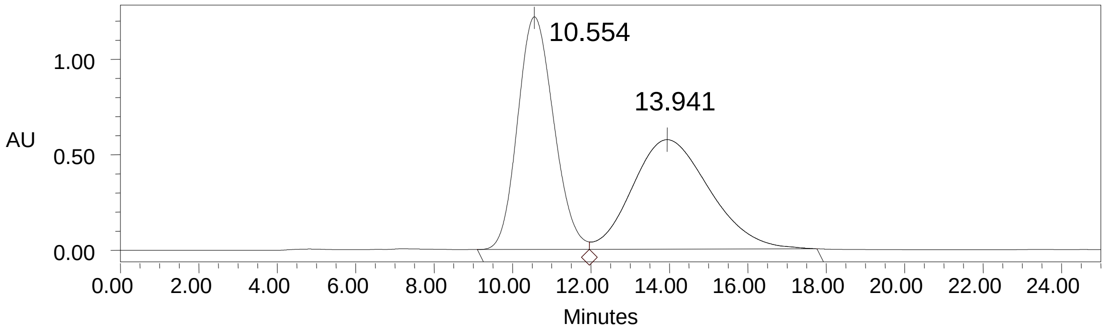
96% *ee*



179a

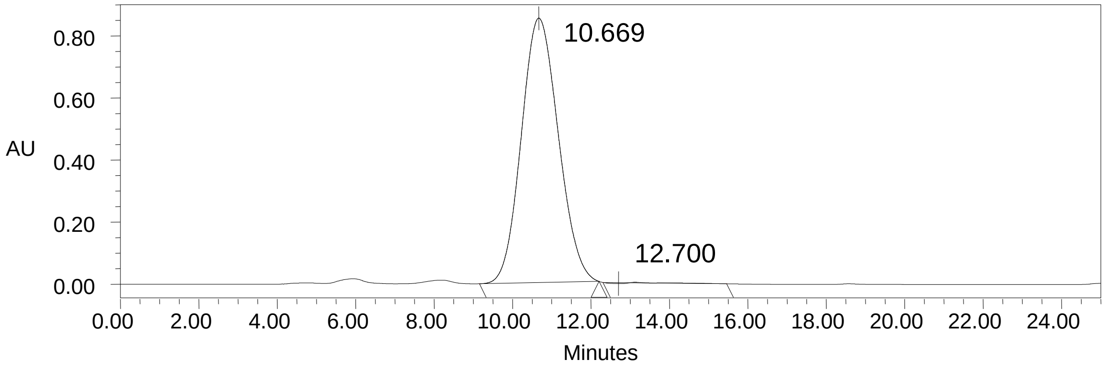
Column: AD-H
Eluent: Hex:*i*PrOH, 85:15
Flow rate = 0.7 mL/min
λ = 210 nm

rac-**179a**



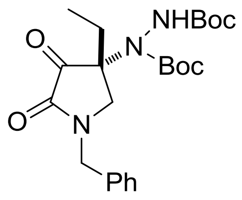
	Retention Time	Area	% Area	Height
2	13.941	78271835	50.12	573027
1	10.554	77896125	49.88	1217688

179a



	Retention Time	Area	% Area	Height
1	10.669	55985240	99.65	852346
2	12.700	195441	0.35	-3335

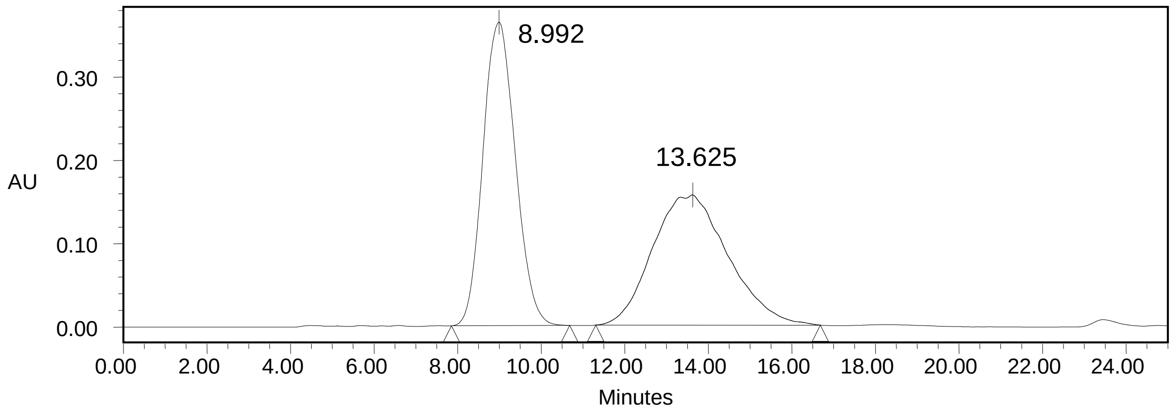
99% *ee*



179b

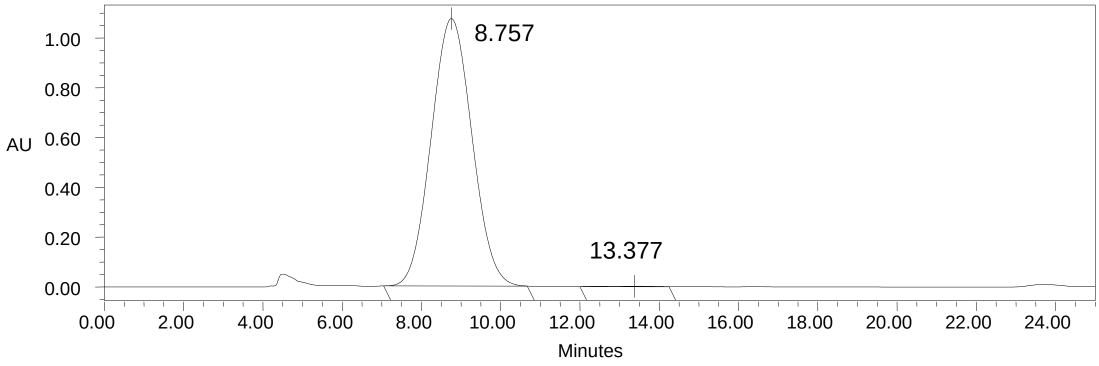
Column: AD-H
Eluent: Hex:*i*PrOH, 85:15
Flow rate = 0.7 mL/min
λ = 210 nm

rac-**179b**



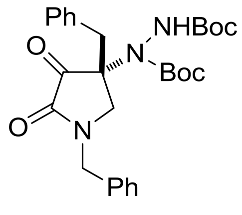
	Retention Time	Area	% Area	Height
2	13.625	19638537	49.97	156180
1	8.992	19665185	50.03	364089

179b



	Retention Time	Area	% Area	Height
2	13.377	119433	0.16	1775
1	8.757	76890138	99.84	1074094

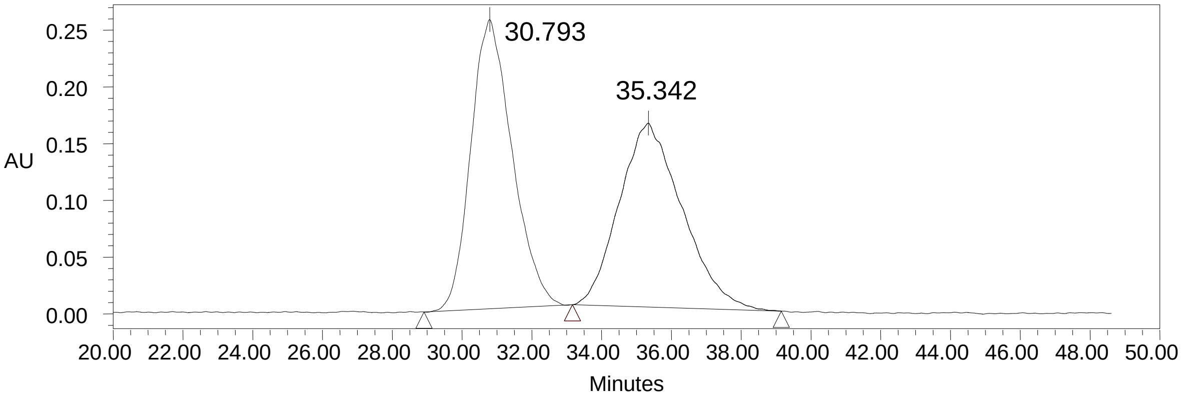
99% *ee*



179c

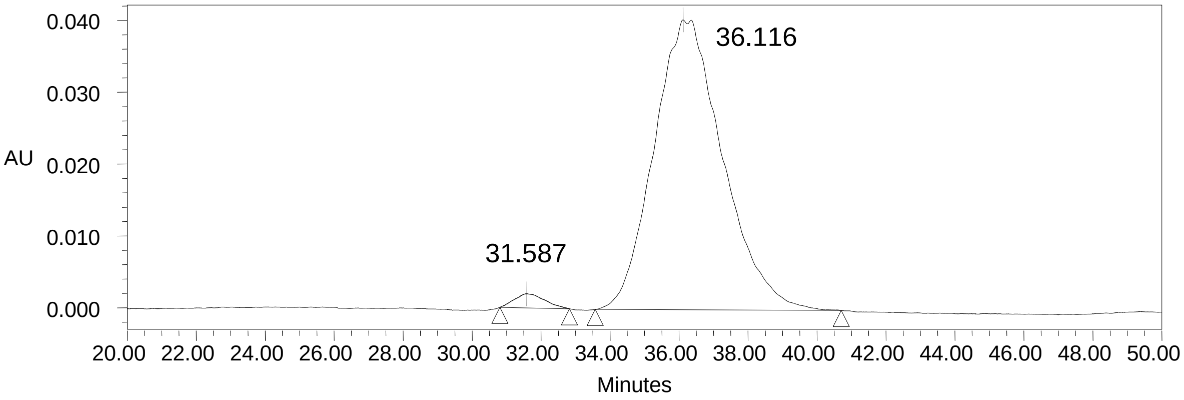
Column: IC
Eluent: Hex:*i*PrOH, 85:15
Flow rate = 0.7 mL/min
λ = 210 nm

rac-**179c**



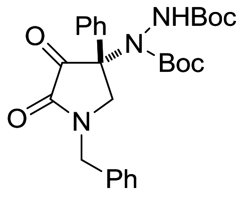
	Retention Time	Area	% Area	Height
2	35.342	20306434	49.12	162007
1	30.793	21031349	50.88	254814

179c



	Retention Time	Area	% Area	Height
1	31.587	120540	2.11	1963
2	36.116	5602756	97.89	40358

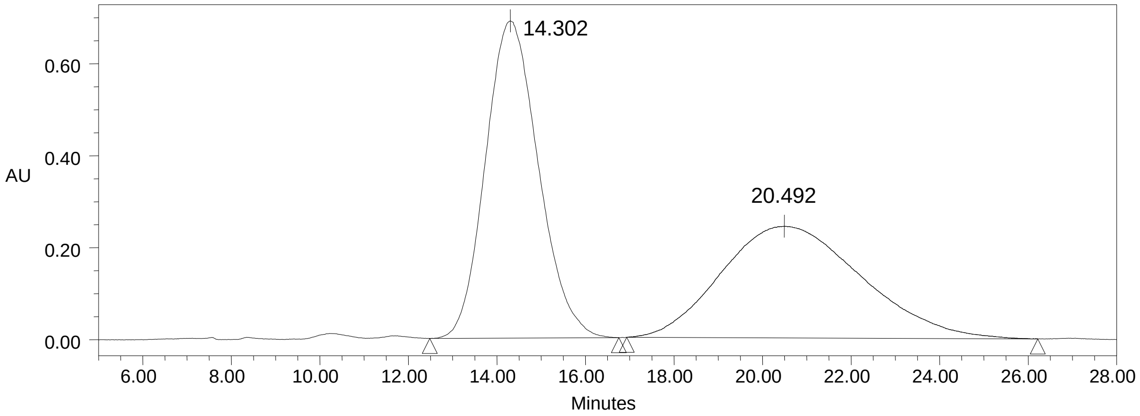
96% *ee*



179d

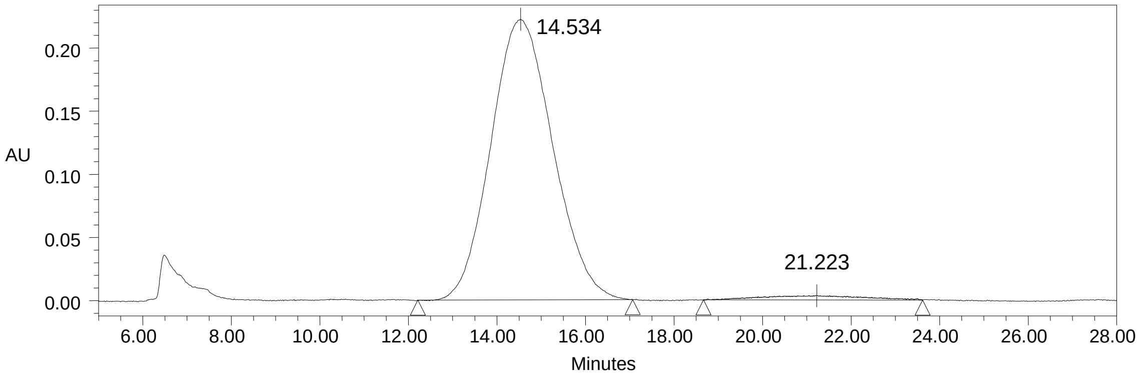
Column: AD-H
Eluent: Hex:*i*PrOH:EtOH, 80:19:1
Flow rate = 0.5 mL/min
λ = 210 nm

rac-**179d**



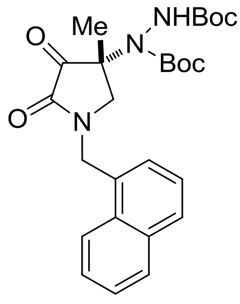
	Retention Time	Area	% Area	Height
2	20.492	53517272	48.23	242849
1	14.302	57435749	51.77	689460

179d



	Retention Time	Area	% Area	Height
2	21.223	539138	2.43	3386
1	14.534	21649603	97.57	222004

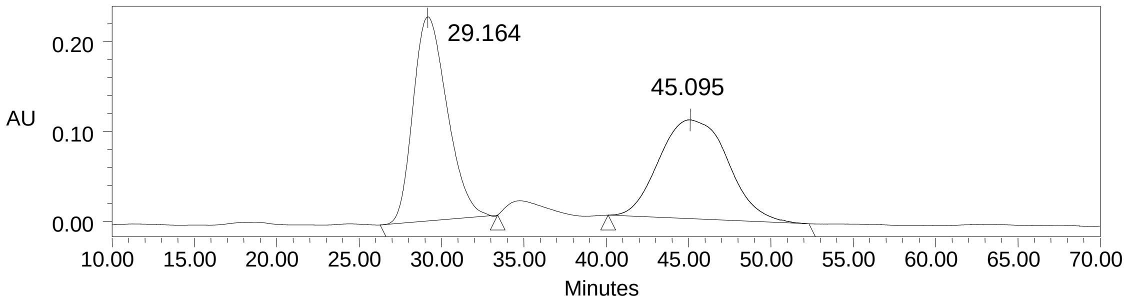
96% *ee*



180a

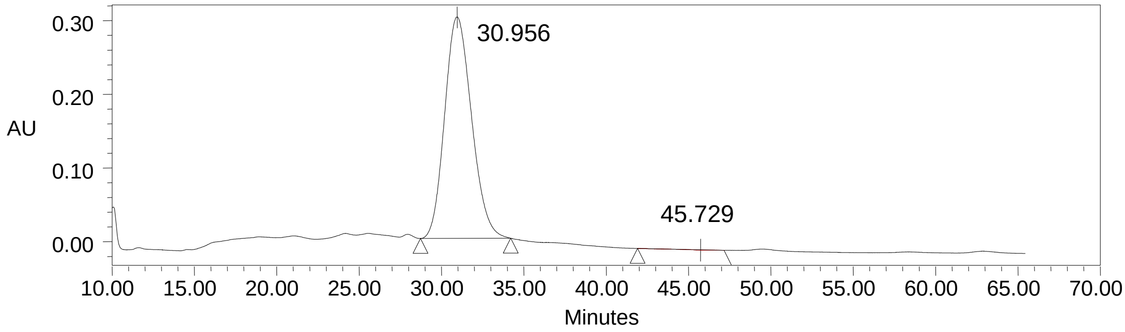
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 0.5 mL/min
λ = 210 nm

rac-**180a**



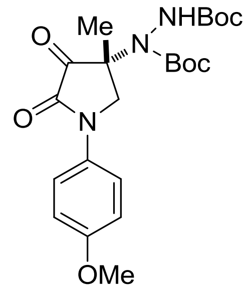
	Retention Time	Area	% Area	Height
2	45.095	32090868	49.50	109948
1	29.164	32739873	50.50	227429

180a



	Retention Time	Area	% Area	Height
2	47.442	147237	0.43	-790
1	30.956	34257318	99.57	300651

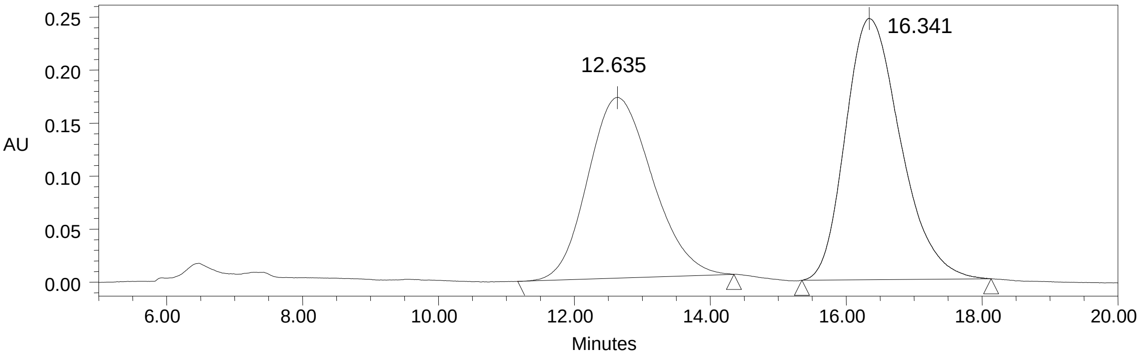
99% *ee*



181a

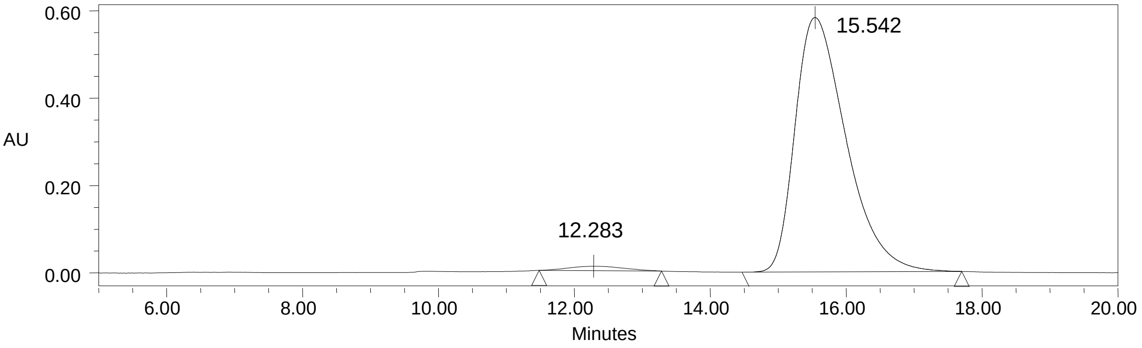
Column: IA
Eluent: Hex:*i*PrOH, 80:20
Flow rate = 0.5 mL/min
λ = 210 nm

rac-**181a**



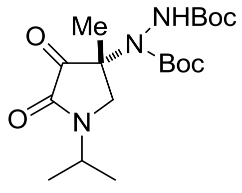
	Retention Time	Area	% Area	Height
2	16.341	12589814	51.49	234721
1	12.635	11859932	48.51	172899

181a



	Retention Time	Area	% Area	Height
2	15.542	30421068	98.13	582419
1	12.283	580046	1.87	10279

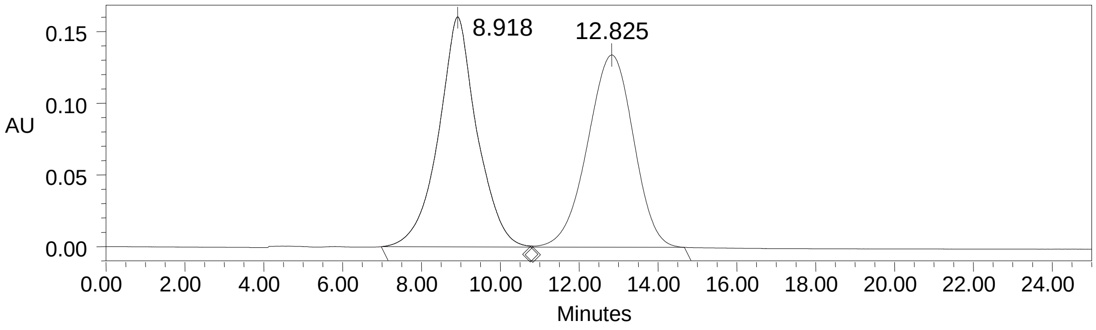
96% *ee*



182a

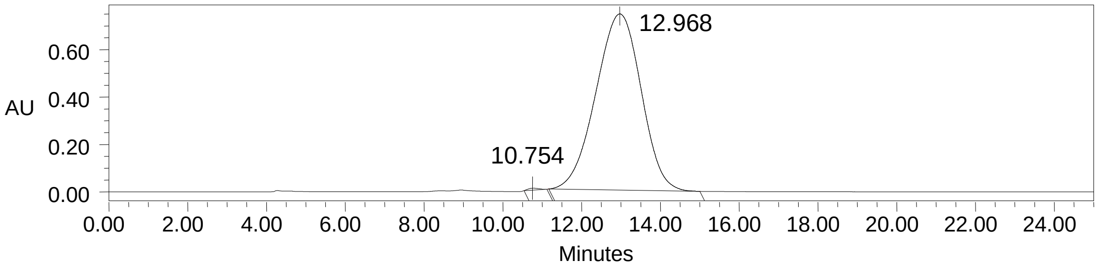
Column: AD-H
Eluent: Hex:*i*PrOH, 90:10
Flow rate = 0.7 mL/min
λ = 210 nm

rac-**182a**



	Retention Time	Area	% Area	Height
1	8.918	10863850	50.04	160406
2	12.825	10848112	49.96	134051

182a

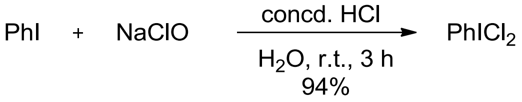


	Retention Time	Area	% Area	Height
2	12.968	59399823	99.75	743248
1	10.754	150643	0.25	8370

99% *ee*

6.6. EXPERIMENTAL SECTION OF CHAPTER 4

6.6.1. Preparation of (dichloro)iodobenzene $PhICl_2$[385]

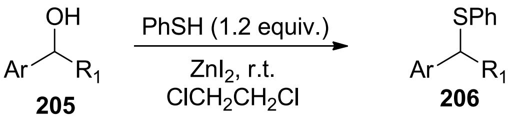


$$PhI + NaClO \xrightarrow[H_2O,\ r.t.,\ 3\ h]{concd.\ HCl} PhICl_2$$

94%

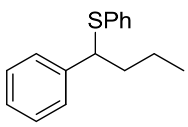
Aq 5.84% NaOCl soln (32 mL) was added dropwise over 1 h to a vigorously stirred soln of iodobenzene (0.90 mL, 8 mmol) in concd HCl (8 mL) at r.t. Stirring was continued for a further 2 h when the addition of NaOCl was complete. The precipitated yellow solid was collected by filtration, washed with H_2O and light petroleum ether, and dried at r.t. in the dark overnight. The solid was identified to be $PhCl_2$ by comparison of its m.p. with that reported in the literature. Yield: 2.16 g, 7.86 mmol, 98%.

6.6.2. Preparation alkyl sulfides[386]



Dried zinc iodide (5 mmol) was added to a solution of alcohol **205** (10 mmol) in dry 1,2-dichloroethane (20 mL). To the obtained suspension thiophenol (12 mmol) was addes and the reaction mixture was stirred at room temperature until the consumption of the alcohol. The reaction was quenched with water (50 mL) and the reaction products worked up by extraction with dichloromethane (2 x 30 mL). The combined organic extracts were washed with brine and dried over NaSO4 from which solvent was evaporated at reduced pressure. The residue was purified by silica gel column chromatography (hex:EtOAc, 98:2).

Phenyl(1-phenylbutyl)sulfane 206a[387]



Prepared according to the general procedure starting from 1-phenylbutan-1-ol (451 mg, 3 mmol). The title compound was isolated as a colourless oil after short silica column chromatography (98:2, Hex:EtOAc). Yield: 71% (516 mg, 2.13 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 7.3 – 6.9 (m, 10H), 4.10 (t, *J* = 7 Hz, 1H), 2.1 – 1.7 (m, 2H), 1.6 – 1.0 (m, 2H), 0.85 (t, *J* = 6.8 Hz, 3H).

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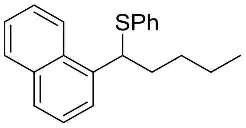
[385] Zhao, X-F.; Zhang, C. *Synthesis* **2007**, *4*, 551–557.

[386] Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357–1359.

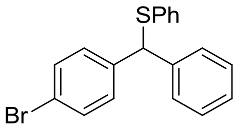
[387] Miyake, H.; Yamamura, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 89–91.

(1-(Naphthalen-1-yl)pentyl)(phenyl)sulfane 206b



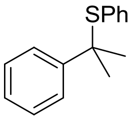
Prepared according to the general procedure starting from 1-(naphthalen-1-yl)pentan-1-ol (643 mg, 3 mmol). The title compound was isolated as a colourless oil after short silica column chromatography (98:2, Hex:EtOAc). Yield: 60% (551 mg, 1.80 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, CDCl3) δ 8.17 – 8.05 (m, 1H), 7.84 (dd, J = 7.9, 1.8 Hz, 1H), 7.76 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.53 – 7.39 (m, 3H), 7.28 – 7.14 (m, 1H), 5.08 (dd, *J* = 8.2, 4.9 Hz, 1H), 3.72 (dq, *J* = 12.2, 9.0 Hz, 1H), 3.58 (dq, *J* = 12.2, 8.6 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.93 – 1.79 (m, 1H), 1.60 – 1.45 (m, 1H), 1.43 – 1.26 (m, 3H), 0.85 (t, J = 7.1 Hz, 3H).

((4-Bromophenyl)(phenyl)methyl)(phenyl)sulfane 206c



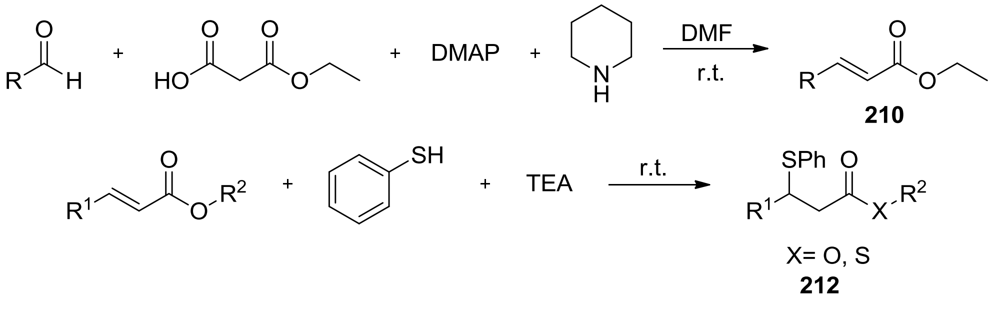
Prepared according to the general procedure starting from (4-bromophenyl)(phenyl)methanol (790 mg, 3 mmol). The title compound was isolated as a colourless oil after short silica column chromatography (98:2, Hex:EtOAc). Yield: 55% (586 mg, 1.65 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.34 – 7.23 (m, 5H), 7.21 – 7.15 (m, 2H), 5.10 (s, 1H), 3.76 (q, *J* = 8.6 Hz, 2H).

Phenyl(2-phenylpropan-2-yl)sulfane[388]



Prepared according to the general procedure starting from 2-phenylpropan-2-ol (409 mg, 3 mmol). The title compound was isolated as a colourless oil after short silica column chromatography (98:2, Hex:EtOAc). Yield: 68% (466 mg, 2.04 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.25 – 7.03 (m, 8H), 1.61 (s, 6H).

6.6.3. Preparation β-sulfido (thio)esters compounds



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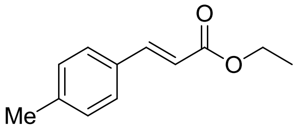
[388] Cabrero-Antonino, J. R.; Leyva-Pérez, A.; Corma, A. *Adv. Synth. Catal.* **2012**, *354*, 678–687.

*6.6.3.1. Preparation of acrylates **210***[389]

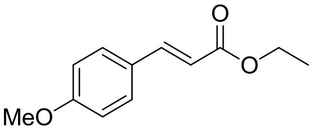
4-Dimethylaminopyridine (37 mg, 0.3 mmol, 10 mol%) was dissolved in DMF (7 mL). The malonic acid half ester (0.53 mL, 4.5 mmol, 1.5 equiv.), the aldehyde (3 mmol, 1 equiv.) and piperidine (30 µL, 0.3 mmol, 10 mol%) were added. The reaction mixture was stirred at room temperature until the aldehyde was consumed. Water (20 mL) was added and the mixture was extracted with Et_2O and the organic layer was washed successively with NH_4Cl, water, $NaHCO_3$ and once again with water. After drying (Na_2SO_4) and filtering, all volatiles were evaporated under vacuum. All the spectroscopic data of synthetized acrylates was identical to reported in the literature.

(*E*)-Ethyl 3-(*p*-tolyl)acrylate 210[390]



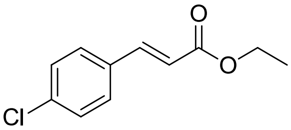
Prepared according to the general procedure starting from *p*-tolualdehyde (0.35 mL, 3 mmol). The reaction was completed in 72h. The title compound was isolated as a colourless oil after short silica column chromatography (95:5, Hex:EtOAc). Yield: 96% (548 mg, 2.88 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(4-methoxyphenyl)acrylate 210c[389]



Prepared according to the general procedure starting from *p*-anisaldehyde (0.36 mL, 3 mmol). The reaction was completed in 72h. The title compound was isolated as a yellow oil after short silica column chromatography (90:10, Hex:EtOAc). Yield: 96% (591 mg, 2.87 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(4-chlorophenyl)acrylate 210d[391]



Prepared according to the general procedure starting from 4-chlorobenzaldehyde (422 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after short silica column chromatography (90:10, Hex:EtOAc). Yield: 77% (488 mg, 2.31 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 16.0 Hz, 1H),

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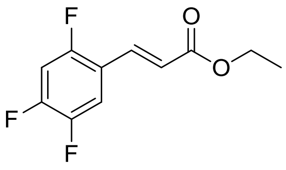
[389] List, B.; Doehring, A.; Hechavarria-Fonseca, M. T.; Wobser, K.; van Thienen, H.; Rios Torres, R.; Llamas Galilea, P. *Adv. Synth. Catal*. **2005**, *347*, 1558–1560.

[390] Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc*. **1990**, *112*, 4324–4330.

[391] Cao, P.; Li, C.-Y.; Kang, Y.-B.; Xie, Z.; Sun, X.-L.; Tang, Y. *J. Org. Chem*. **2007**, *72*, 6628–6630.

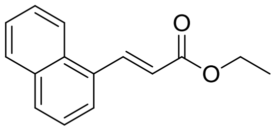
7.51 – 7.38 (m, 2H), 7.41 – 7.32 (m, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(2,4,5-trifluorophenyl)acrylate 210e[392]



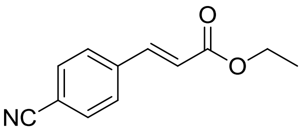
Prepared according to the general procedure starting from 2,4,5-trifluorobenzaldehyde (0.34 mL, 3 mmol). The reaction was completed in 72h. The title compound was isolated as a colourless oil after short silica column chromatography (95:5, Hex:EtOAc). Yield: 71% (490 mg, 2.13 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 – 7.63 (m, 1H), 7.35 (ddd, *J* = 10.5, 8.6, 6.7 Hz, 1H), 6.98 (td, *J* = 9.8, 6.5 Hz, 1H), 6.44 (d, *J* = 16.2 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(naphthalen-1-yl)acrylate 210f[389]



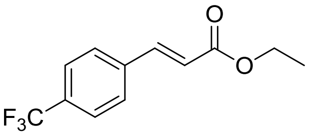
Prepared according to the general procedure starting from 1-naphthaldehyde (0.41 mL, 3 mmol). The reaction was completed in 72h. The title compound was isolated as a colourless oil after short silica column chromatography (95:5, Hex:EtOAc). Yield: 95% (649 mg, 2.87 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.53 (d, *J* = 15.8 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.75 (m, 2H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.65 – 7.40 (m, 3H), 6.53 (d, *J* = 15.8 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

(*E*)-ethyl 3-(4-cyanophenyl)acrylate 210j[393]



Prepared according to the general procedure starting from 4-cyanobenzaldehyde (393 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a white solid after short silica column chromatography (95:5, Hex:EtOAc). Yield: 72% (435 mg, 2.16 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 – 7.65 (m, 3H), 7.65 – 7.57 (m, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(4-(trifluoromethyl)phenyl)acrylate 210k[391]



Prepared according to the general procedure starting from 4-(trifluoromethyl)benzaldehyde (0.41 mL, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a white solid after short silica column

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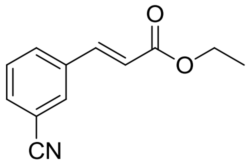
[392] Ishikawa, H.; Honma, M.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 2824–2827.

[393] List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Job, A.; Rios Torres, R. *Tetrahedron* **2006**, *62*, 476–482.

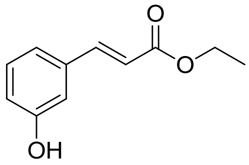
chromatography (95:5, Hex:EtOAc). Yield: 98% (719 mg, 2.94 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.68 – 7.56 (m, 4H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(3-cyanophenyl)acrylate 210l[394]



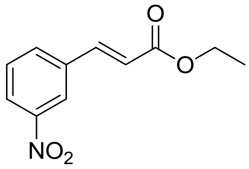
Prepared according to the general procedure starting from 3-cyanobenzaldehyde (393 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a white solid after short silica column chromatography (80:20, Hex:EtOAc). Yield: 95% (572 mg, 2.84 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (t, *J* = 1.7 Hz, 1H), 7.74 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.69 – 7.59 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(3-hydroxyphenyl)acrylate 210m[395]



Prepared according to the general procedure starting from 3-hydroxybenzaldehyde (366 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a white solid after short silica column chromatography (80:20, Hex:EtOAc). Yield: 98% (565 mg, 2.94 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 16.0 Hz, 1H), 7.32 – 7.18 (m, 1H), 7.09 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.06 – 6.97 (m, 1H), 6.87 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 5.45 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(3-nitrophenyl)acrylate 210n[396]



Prepared according to the general procedure starting from 3-nitrobenzaldehyde (453 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a white solid after short silica column chromatography (90:10, Hex:EtOAc). Yield: 95% (630 mg, 2.95 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (t, *J* = 1.8 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 16.1 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 4.36 – 4.24 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H).

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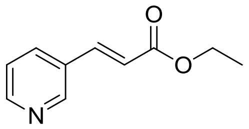
[394] Wadhwa, K.; Verkade, J. G. *J. Org. Chem*. **2009**, *74*, 4368–4371.

[395] Bera, R.; Dhananjaya, G.; Singh, S. N.; Kumar, R.; Mukkanti, K.; Pal, M. *Tetrahedron* **2009**, *65*, 1300–1305.

[396] Cheng, G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2003**, *22*, 1468–1474.

(*E*)-Ethyl 3-(pyridin-3-yl)acrylate 210o[397]

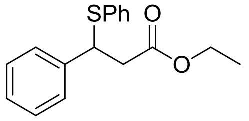


Prepared according to the general procedure starting from 3-pyridinecarboxaldehyde (0.29 mL, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after short silica column chromatography (80:20, Hex:EtOAc). Yield: 79% (418 mg, 2.37 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.74 (d, *J* = 2.1 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.83 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.50 (d, *J* = 16.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 2H).

6.6.3.2. *Sulfa-Michael addition of thiophenyl to acrylates* ***210***

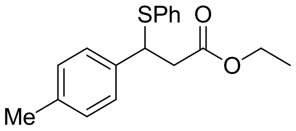
To a corresponding acrylate, thiophenol (1.1 equiv.) and triethylamine (10 mol%) were added and the reaction mixture was stirred at room temperature until the consumption of the starting material.

Ethyl 3-phenyl-3-(phenylthio)propanoate 212a[398]



Prepared according to the general procedure with ethyl cinnamate (529 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (95:5, Hex:EtOAc). Yield: 91% (781 mg, 2.73 mmol). All the spectroscopic data was identical to reported in the literature. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 – 7.35 (m, 2H), 7.36 – 7.20 (m, 8H), 4.72 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.09 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.03 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.97 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7, 140.7, 133.8, 133.4, 128.9, 128.5, 127.8, 127.8, 127.6, 60.7, 49.3, 41.1, 14.2.

Ethyl 3-(phenylthio)-3-(p-tolyl)propanoate 212b



Prepared according to the general procedure with (*E*)-ethyl 3-(*p*-tolyl)acrylate (548 mg, 2.88 mmol). The reaction was completed in 72h. The title compound was isolated as a colourless oil after silica column chromatography (95:5, Hex:EtOAc). Yield: 79% (684 mg, 2.28 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 7.13 – 7.09 (m, 2H), 7.04 – 6.98 (m, 2H), 4.60 (dd, *J* = 8.4, 7.1 Hz, 1H), 4.06 – 3.91 (m, 2H), 2.95 – 2.87 (m, 1H), 2.87 – 2.80 (m, 1H), 2.24 (s, 3H), 1.09 (t, *J* = 7.1 Hz,

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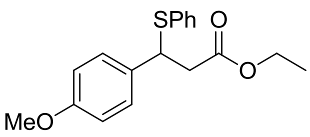
[397] Cong, X.; Tang, H.; Wu, C.; Zeng, X. *Organometallics* **2013**, *32*, 6565–6575.

[398] Has-Becker, S.; Bodmann, K.; Kreuder, R.; Santoni, G.; Rein, T.; Reiser, O. *Synlett* **2001**, 1395–1398.

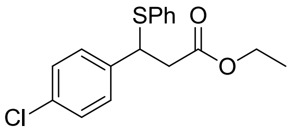
3H). NMR (101 MHz, CDCl$_3$) δ 170.8, 137.6, 137.2, 134.1, 133.2, 129.2, 128.9, 127.7, 127.6, 60.7, 48.9, 41.3, 21.2, 14.2.

Ethyl 3-(4-methoxyphenyl)-3-(phenylthio)propanoate 212c



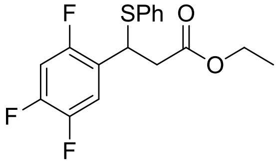
Prepared according to the general procedure with (*E*)-ethyl 3-(4-methoxyphenyl)acrylate (591 mg, 2.87 mmol). The reaction was completed in 72h. The title compound was isolated as a colourless oil after silica column chromatography (95:5, Hex:EtOAc). Yield: 80% (736 mg, 2.32 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 7.19 – 7.10 (m, 2H), 6.80 – 6.71 (m, 2H), 4.60 (dd, *J* = 8.6, 6.9 Hz, 1H), 3.99 (qd, *J* = 7.1, 4.4 Hz, 2H), 3.71 (s, 3H), 2.96 – 2.78 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, CDCl$_3$) δ 170.8, 159.0, 134.0, 133.3, 132.6, 128.9, 128.9, 127.8, 113.9, 60.7, 55.3, 48.7, 41.3, 14.2.

Ethyl 3-(4-chlorophenyl)-3-(phenylthio)propanoate 212d



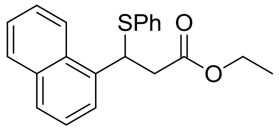
Prepared according to the general procedure with (*E*)-ethyl 3-(4-chlorophenyl)acrylate (488 mg, 2.31 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (98:2, Hex:EtOAc). Yield: 94% (699 mg, 2.18 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.23 (m, 2H), 7.28 – 7.18 (m, 5H), 7.20 – 7.12 (m, 2H), 4.59 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 4.04 (qd, *J* = 7.1, 3.9 Hz, 2H), 2.94 (dd, *J* = 15.8, 6.8 Hz, 1H), 2.85 (dd, *J* = 15.7, 8.8 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.6, 139.4, 133.8, 133.4, 133.4, 129.2, 129.1, 128.8, 128.2, 61.0, 48.8, 41.0, 14.3.

Ethyl 3-(phenylthio)-3-(2,4,5-trifluorophenyl)propanoate 212e



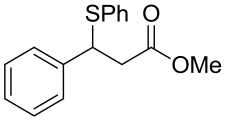
Prepared according to the general procedure with (*E*)-ethyl 3-(2,4,5-trifluorophenyl)acrylate (490 mg, 2.13 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (95:5, Hex:EtOAc). Yield: 60% (435 mg, 1.28 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.26 (m, 2H), 7.26 (qd, *J* = 4.3, 1.4 Hz, 3H), 7.02 (ddd, *J* = 10.7, 8.6, 6.6 Hz, 1H), 6.84 (td, *J* = 9.7, 6.5 Hz, 1H), 4.86 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 4.07 (qd, *J* = 7.1, 4.9 Hz, 2H), 2.95 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.85 (dd, *J* = 16.0, 8.7 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, CDCl$_3$) δ 170.1, 155.4 (ddd), 150.9 – 147.6 (m), 148.4 – 144.9 (m), 133.9, 132.7, 129.2, 128.6, 124.8 (dt), 116.6 (ddd), 105.7 (dd), 61.1 , 41.6, 40.1, 14.2.

Ethyl 3-(naphthalen-1-yl)-3-(phenylthio)propanoate 212f



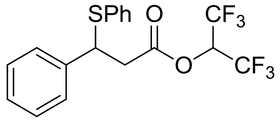
Prepared according to the general procedure with (*E*)-ethyl 3-(naphthalen-1-yl)acrylate (649 mg, 2.87 mmol). The reaction was completed in 40h. The title compound was isolated as a colourless oil after silica column chromatography (98:2, Hex:EtOAc). Yield: 80% (774 mg, 2.30 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.74 (dd, *J* = 5.9, 3.6 Hz, 1H), 7.57 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.49 (ddd, *J* = 7.9, 6.7, 1.1 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.31 – 7.23 (m, 2H), 7.25 – 7.16 (m, 3H), 5.50 (t, *J* = 7.6 Hz, 1H), 4.14 – 3.89 (m, 2H), 3.11 (d, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 136.0, 134.2, 133.7, 131.0, 129.1, 129.0, 128.4, 128.0, 126.5, 125.9, 125.2, 124.8, 123.4, 60.9, 41.1, 14.2.

Methyl 3-phenyl-3-(phenylthio)propanoate 212g[399]



Prepared according to the general procedure with methyl cinnamate (487 mg, 3 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (95:5, Hex:EtOAc). Yield: 92% (751 mg, 2.76 mmol). All the spectroscopic data was identical to reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.28 – 7.19 (m, 8H), 4.70 – 4.60 (m, 1H), 3.59 (s, 3H), 2.98 (dd, *J* = 14.1, 5.5 Hz, 1H), 2.92 (dd, *J* = 14.1, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 140.5, 133.7, 133.3, 128.9, 128.5, 127.8, 127.6, 127.6, 51.8, 49.1, 40.8.

1,1,1,3,3,3-Hexafluoropropan-2-yl 3-phenyl-3-(phenylthio)propanoate 212h[400]



Prepared according to the general procedure with 1,1,1,3,3,3-hexafluoropropan-2-yl cinnamate (596 mg, 2.00 mmol). The reaction was completed in 40h. The title compound was isolated as a colourless oil after silica column chromatography (98:2, Hex:EtOAc). Yield: 60% (490 mg, 1.20 mmol). All the spectroscopic data was identical to reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.28 (m, 10H), 5.66 (hept, *J* = 6.0 Hz, 1H), 4.61 (t, *J* = 7.8 Hz, 1H), 3.14 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 139.2, 133.8, 132.8, 129.0, 128.6, 128.3, 127.9, 127.5, 120.2 (q), 66.5 (hept), 48.7, 39.9.

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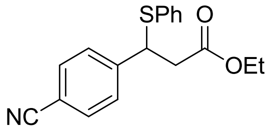
[399] Sharma, G.; Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2008**, *49*, 4272–4275.

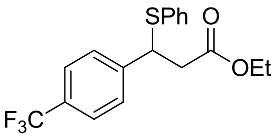
[400] Fang, X.; Li, J.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448–3451.

Ethyl 3-(4-cyanophenyl)-3-(phenylthio)propanoate 212j



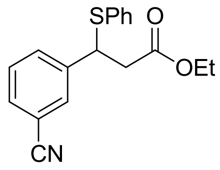
Prepared according to the general procedure with (*E*)-ethyl 3-(4-cyanophenyl)acrylate (435 mg, 2.16 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (90:10, Hex:EtOAc). Yield: 83% (558 mg, 1.79 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.33 – 7.19 (m, 7H), 4.62 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.05 (qd, *J* = 7.1, 4.7 Hz, 2H), 2.98 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.88 (dd, *J* = 16.0, 8.8 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, $CDCl_3$) δ 170.3, 146.4, 134.1, 132.5, 132.3, 129.2, 128.6, 118.8, 111.4, 61.1, 49.1, 40.3, 14.2.

Ethyl 3-(phenylthio)-3-(4-(trifluoromethyl)phenyl)propanoate 212k



Prepared according to the general procedure with (*E*)-ethyl 3-(4-(trifluoromethyl)phenyl)acrylate (719 mg, 2.94 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (98:2, Hex:EtOAc). Yield: 81% (844 mg, 2.38 mmol).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.22 (m, 2H), 7.25 – 7.16 (m, 3H), 4.65 (dd, *J* = 8.7, 6.9 Hz, 1H), 4.03 (qq, *J* = 7.2, 3.7 Hz, 2H), 2.97 (dd, *J* = 15.9, 6.9 Hz, 1H), 2.88 (dd, *J* = 15.9, 8.6 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 145.0 (q), 129.8 (q), 129.1, 128.4, 128.2, 125.5 (q), 122.9, 61.0, 49.0, 40.7, 14.2.

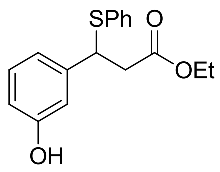
Ethyl 3-(3-cyanophenyl)-3-(phenylthio)propanoate 212l



Prepared according to the general procedure with (*E*)-ethyl 3-(3-cyanophenyl)acrylate (572 mg, 2.84 mmol). The reaction was completed in 24h. The title compound was isolated as a colourless oil after silica column chromatography (90:10, Hex:EtOAc). Yield: 65% (575 mg, 1.85 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 3H), 7.33 (td, *J* = 7.3, 1.6 Hz, 1H), 7.30 – 7.17 (m, 5H), 4.61 (dd, *J* = 8.8, 6.7 Hz, 1H), 4.04 (qd, *J* = 7.1, 3.7 Hz, 2H), 2.97 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.87 (dd, *J* = 16.0, 8.9 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, $CDCl_3$) δ 170.2, 142.5, 133.9, 132.5, 132.3, 131.3, 131.2, 129.3, 129.1, 128.5, 118.6, 112.5, 61.0, 48.6, 40.4, 14.2.

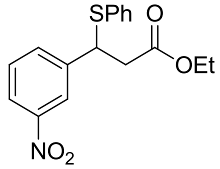
Ethyl 3-(3-hydroxyphenyl)-3-(phenylthio)propanoate 212m

Prepared according to the general procedure with (*E*)-ethyl 3-(3-hydroxyphenyl)acrylate (565 mg, 2.94 mmol). The reaction was completed in 24h. The title compound was



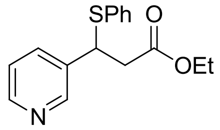
isolated as a white solid after silica column chromatography (90:10, Hex:EtOAc). Yield: 59% (524 mg, 1.73 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 6.8, 3.6, 2.1 Hz, 2H), 7.27 – 7.19 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.81 (dt, *J* = 7.9, 1.2 Hz, 1H), 6.77 (t, *J* = 2.1 Hz, 1H), 6.70 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 6.09 (s, 1H), 4.60 (t, *J* = 7.8 Hz, 1H), 4.06 (qd, *J* = 7.1, 4.2 Hz, 2H), 2.99 – 2.92 (m, 1H), 2.92 – 2.86 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, $CDCl_3$) δ 171.5, 171.5, 156.1, 142.3, 133.8, 133.4, 129.8, 129.0, 128.0, 120.0, 114.9, 114.8, 61.2, 49.1, 41.3, 14.2.

Ethyl 3-(3-nitrophenyl)-3-(phenylthio)propanoate 212n



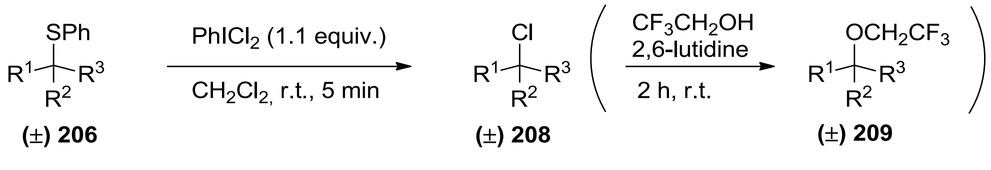
Prepared according to the general procedure with (*E*)-ethyl 3-(3-nitrophenyl)acrylate (630 mg, 2.95 mmol). The reaction was completed in 24h. The title compound was isolated as a white solid after silica column chromatography (90:10, Hex:EtOAc). Yield: 74% (723 mg, 2.18 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.02 (m, 2H), 7.54 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.31 – 7.18 (m, 5H), 4.69 (dd, *J* = 8.9, 6.7 Hz, 1H), 4.06 (qd, *J* = 7.1, 4.9 Hz, 2H), 3.01 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.92 (dd, J = 16.0, 8.9 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, $CDCl_3$) δ 170.3, 148.4, 143.2, 134.1, 134.1, 132.5, 129.5, 129.3, 128.7, 122.8, 122.7, 61.2, 48.8, 40.6, 14.3.

Ethyl 3-(phenylthio)-3-(pyridin-3-yl)propanoate 212o



Prepared according to the general procedure with (*E*)-ethyl 3-(pyridin-3-yl)acrylate (418 mg, 2.37 mmol). The reaction was completed in 24h. The title compound was isolated as a yellow oil after silica column chromatography (80:20, Hex:EtOAc). Yield: 73% (497 mg, 1.73 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.36 (m, 2H), 7.54 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.32 – 7.17 (m, 5H), 7.20 – 7.12 (m, 1H), 4.61 (dd, *J* = 8.8, 6.9 Hz, 1H), 4.04 (qq, *J* = 7.1, 3.7 Hz, 2H), 2.98 (dd, *J* = 15.8, 6.9 Hz, 1H), 2.89 (dd, *J* = 15.8, 8.8 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). NMR (101 MHz, $CDCl_3$) δ 170.3, 149.4, 148.9, 136.4, 135.0, 134.0, 132.6, 129.1, 128.4, 123.4, 61.0, 46.8, 40.5, 14.2.

6.6.4. Desulfurative chlorination of alkyl phenyl sulfides with $PhICl_2$



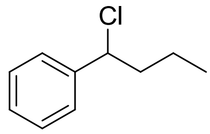
The corresponding alkyl phenyl sulfide **206** (0.5 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and $PhICl_2$ (151 mg, 0.55 mmol, 1.1 equiv.) was added in one portion.

The reaction mixture was stirred in the dark until the color from yellow to orange (5 min). The solvent was evaporated under reduced pressure and the adducts were purified by silica gel column chromatography.

Sensitive chlorides towards column chromatography on silica gel were isolated as their corresponding trifluoroethyl ether derivatives **209**.[401] To a mixture of the crude benzyl chloride (0.5 mmol) and 2,6-lutidine (0.17 mL, 1.5 mmol, 3 equiv.), TFE (5 mL) was added during stirring and ice cooling. The mixture was stirred for 2 h, added HCl (5%, 30 mL) and diluted with pentane (20 mL). The aqueous layer was extracted with pentane (2 x 20 mL), the combined organic layers washed with HCl (5%, 2 x 30 mL) and brine (3 x 30 mL). After drying over Na_2SO_4 and evaporation of solvent, trifluoroethyl ether derivatives were obtained.

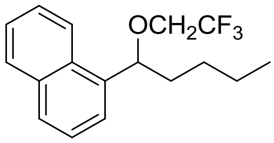
*6.6.4.1. Characterization data for compounds **208–209***

(1-Chlorobutyl)benzene 208a



The title compound was preprared according the general procedure from phenyl(1-phenylbutyl)sulfane (121 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 60 mg, 0.36 mmol, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 5H), 4.87 (dd, *J* = 8.2, 6.4 Hz, 1H), 2.13 (dddd, *J* = 13.6, 9.8, 8.2, 5.4 Hz, 1H), 2.01 (ddt, *J* = 13.9, 9.6, 6.1 Hz, 1H), 1.50 (dddd, *J* = 15.1, 9.5, 5.2, 2.3 Hz, 1H), 1.44 – 1.28 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 128.8, 128.4, 127.2, 63.8, 42.3, 20.5, 13.7.

1-(1-(2,2,2-Trifluoroethoxy)pentyl)naphthalene 209b



The title compound was preprared according the general procedure from (1-(naphthalen-1-yl)pentyl)(phenyl)sulfane (153 mg, 0.5 mmol) and the product was isolated as trifluoroethyl ether derivative (colourless oil). Yield: 104 mg, 0.35 mmol, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.05 (m, 1H), 7.84 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.76 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.53 – 7.39 (m, 3H), 7.28 – 7.14 (m, 1H), 5.08 (dd, *J* = 8.2, 4.9 Hz, 1H), 3.72 (dq, *J* = 12.2, 9.0 Hz, 1H), 3.58 (dq, *J* = 12.2, 8.6 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.93 – 1.79 (m, 1H), 1.60 – 1.45 (m, 1H), 1.43 – 1.26 (m, 3H), 0.85 (t, *J* = 7.1 Hz, 3H).

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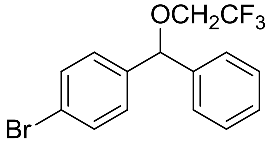
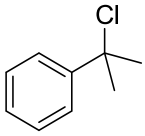
[401] Shi, L.; Horn, M.; Kobayashi, S.; Mayr, H. *Chem. Eur. J.* **2009**, *15*, 8533–8541.

1-Bromo-4-(phenyl(2,2,2-trifluoroethoxy)methyl)benzene 209c



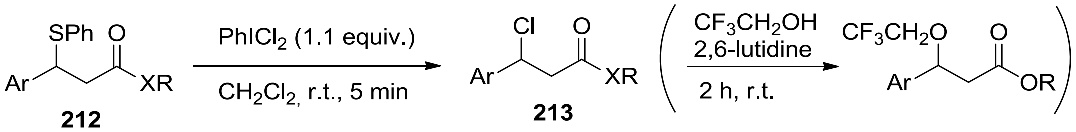
The title compound was preprared according the general procedure from ((4-bromophenyl)(phenyl)methyl)(phenyl)sulfane (178 mg, 0.5 mmol) and the product was isolated as trifluoroethyl ether derivative (colourless oil). Yield: 117 mg, 0.34 mmol, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.34 – 7.23 (m, 5H), 7.21 – 7.15 (m, 2H), 5.44 (s, 1H), 3.76 (q, J = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 139.9, 131.9, 129.0, 128.8, 128.6, 127.3, 124.2 (q), 122.2, 84.1, 66.2 (q).

(2-Chloropropan-2-yl)benzene 208d[402]



The title compound was preprared according the general procedure from phenyl(2-phenylpropan-2-yl)sulfane (114 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 66 mg, 0.43 mmol, 85%. All the spectroscopic data was identical to reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.15 (m, 5H), 5.13 (q, J = 7.0 Hz, 1H), 2.83 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 128.4, 125.9, 125.1, 69.2, 34.0.

6.6.5. Desulfurative chlorination of sulfa-Michael derived sulfides with $PhICl_2$



The corresponding β-sulfido (thio)ester **212** (0.5 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and $PhICl_2$ (151 mg, 0.55 mmol, 1.1 equiv.) was added in one portion. The reaction mixture was stirred in the dark until the color from yellow to orange (5 min). The solvent was evaporated under reduced pressure and the adducts **213** were purified by silica gel column chromatography.

Sensitive chlorides towards column chromatography on silica gel were isolated as their corresponding trifluoroethyl ether derivatives.[401] To a mixture of the crude benzyl chloride (0.5 mmol) and 2,6-lutidine (0.17 mL, 1.5 mmol, 3 equiv.), TFE (5 mL) was added during stirring and ice cooling. The mixture was stirred for 2 h, added HCl (5%, 30 mL) and diluted with pentane (20 mL). The aqueous layer was extracted with pentane (2 x 20 mL), the combined organic layers washed with HCl (5%, 2 x 30 mL)

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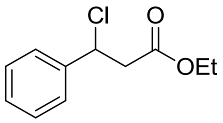
[402] Strazzolini, P.; Giumanini, A. G.; Verardo G. *Tetrahedron* **1994**, *50*, 217–254.

and brine (3 x 30 mL). After drying over Na_2SO_4 and evaporation of solvent, trifluoroethyl ether derivatives were obtained.

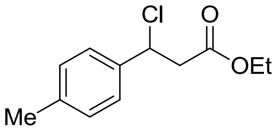
*6.6.5.1. Characterization data for compounds **213a-i***

Ethyl 3-chloro-3-phenylpropanoate 213a[403]



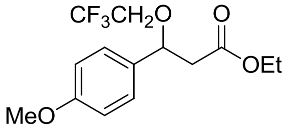
The title compound was preprared according the general procedure from ethyl 3-phenyl-3-(phenylthio)propanoate (143 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 87 mg, 0.41 mmol, 82%. All the spectroscopic data was identical to reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 5H), 5.35 (dd, *J* = 9.0, 5.8 Hz, 1H), 4.25 – 4.09 (m, 2H), 3.18 (dd, *J* = 15.9, 9.0 Hz, 1H), 3.03 (dd, *J* = 15.9, 5.8 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 140.4, 128.8, 128.7, 127.0, 61.0, 58.2, 45.0, 14.2.

Ethyl 3-chloro-3-(*p*-tolyl)propanoate 213b



The title compound was preprared according the general procedure from ethyl 3-(phenylthio)-3-(*p*-tolyl)propanoate (150 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 96 mg, 0.43 mmol, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.20 – 7.14 (m, 2H), 5.33 (dd, *J* = 9.0, 5.9 Hz, 1H), 4.16 (qd, *J* = 7.1, 2.7 Hz, 2H), 3.17 (dd, *J* = 15.9, 9.0 Hz, 1H), 3.01 (dd, *J* = 15.9, 5.9 Hz, 1H), 2.35 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 138.8, 137.6, 129.7, 127.0, 61.2, 58.3, 45.1, 21.4, 14.3.

Ethyl 3-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)propanoate 213c-OCH_2CH_3



The title compound was preprared according the general procedure from ethyl 3-(4-methoxyphenyl)-3-(phenylthio)propanoate (158 mg, 0.5 mmol) and the product was isolated as trifluoroethyl ether derivative (colourless oil). Yield: 78 mg, 0.26 mmol, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.34 – 7.23 (m, 5H), 7.21 – 7.15 (m, 2H), 5.44 (s, 1H), 3.76 (q, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 139.9, 131.9, 129.0, 128.8, 128.6, 127.3, 124.2 (q), 122.2, 84.1, 66.2 (q).

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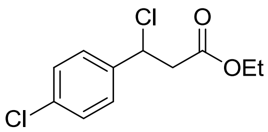
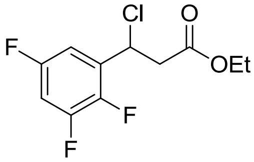
[403] Yasuda, M., Yamasaki, S., Onishi Y., Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186–7187.

Ethyl 3-chloro-3-(4-chlorophenyl)propanoate 213d



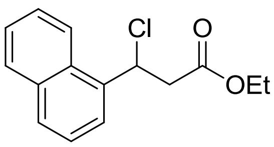
The title compound was preprared according the general procedure from ethyl 3-(4-chlorophenyl)-3-(phenylthio)propanoate (160 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 99 mg, 0.40 mmol, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.28 (m, 4H), 5.31 (dd, *J* = 8.6, 6.3 Hz, 1H), 4.31 – 3.96 (m, 2H), 3.15 (dd, *J* = 16.0, 8.6 Hz, 1H), 3.00 (dd, *J* = 16.0, 6.3 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 138.9, 134.6, 129.1, 128.5, 61.2, 57.2, 44.9, 14.2.

Ethyl 3-chloro-3-(2,3,5-trifluorophenyl)propanoate 213e



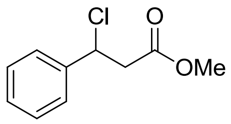
The title compound was preprared according the general procedure from ethyl 3-(phenylthio)-3-(2,4,5-trifluorophenyl)propanoate (170 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 96 mg, 0.36 mmol, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 10.6, 8.5, 6.7 Hz, 1H), 6.94 (td, *J* = 9.7, 6.5 Hz, 1H), 5.55 (ddd, *J* = 8.3, 6.2, 1.0 Hz, 1H), 4.16 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.13 (dd, *J* = 16.2, 8.5 Hz, 1H), 3.02 (dd, *J* = 16.2, 6.3 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 154.9 (ddd), 150.3 (ddd), 147.2 (ddd), 124.2 (dt), 116.7 (ddd), 106.2 (dd), 61.5, 50.1 (d), 43.7, 14.3.

Ethyl 3-chloro-3-(naphthalen-1-yl)propanoate 213f



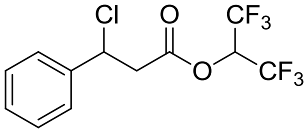
The title compound was preprared according the general procedure from ethyl 3-(naphthalen-1-yl)-3-(phenylthio)propanoate (168 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 106 mg, 0.41 mmol, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.59 – 7.43 (m, 2H), 6.22 (dd, *J* = 9.4, 5.0 Hz, 1H), 4.29 – 4.16 (m, 2H), 3.40 (dd, *J* = 16.0, 9.4 Hz, 1H), 3.26 (dd, *J* = 16.0, 5.0 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 135.6, 134.1, 130.4, 129.7, 129.2, 126.9, 126.2, 125.4, 124.5, 123.1, 61.3, 54.6, 44.0, 14.3.

Methyl 3-chloro-3-phenylpropanoate 213g[404]



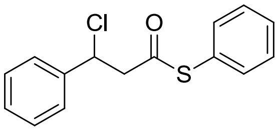
The title compound was preprared according the general procedure from methyl 3-phenyl-3-(phenylthio)propanoate (136 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 85 mg, 0.43 mmol, 86%. All the spectroscopic data was identical to reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 5H), 5.35 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.71 (s, 3H), 3.19 (dd, *J* = 16.0, 9.1 Hz, 1H), 3.04 (dd, *J* = 16.0, 5.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 140.4, 129.0, 128.9, 127.0, 58.2, 52.2, 44.8.

1,1,1,3,3,3-Hexafluoropropan-2-yl 3-chloro-3-phenylpropanoate 213h



The title compound was preprared according the general procedure from 1,1,1,3,3,3-hexafluoropropan-2-yl 3-phenyl-3-(phenylthio)propanoate (204 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 125 mg, 0.38 mmol, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H), 5.76 (hept, *J* = 6.1 Hz, 1H), 5.34 (dd, *J* = 9.2, 5.7 Hz, 1H), 3.40 (dd, *J* = 16.3, 9.2 Hz, 1H), 3.25 (dd, *J* = 16.3, 5.7 Hz, 1H).

S-Phenyl 3-chloro-3-phenylpropanethioate 213i



The title compound was preprared according the general procedure from *S*-phenyl 3-phenyl-3-(phenylthio)propanethioate (175 mg, 0.5 mmol) and the chlorinated product was isolated as a colourless oil. Yield: 108 mg, 0.39 mmol, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.26 (m, 10H), 5.39 (dd, *J* = 8.6, 5.9 Hz, 1H), 3.50 (dd, *J* = 15.6, 8.7 Hz, 1H), 3.31 (dd, *J* = 15.6, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 140.0, 134.5, 129.8, 129.4, 128.9, 128.9, 127.1, 57.7, 52.8.

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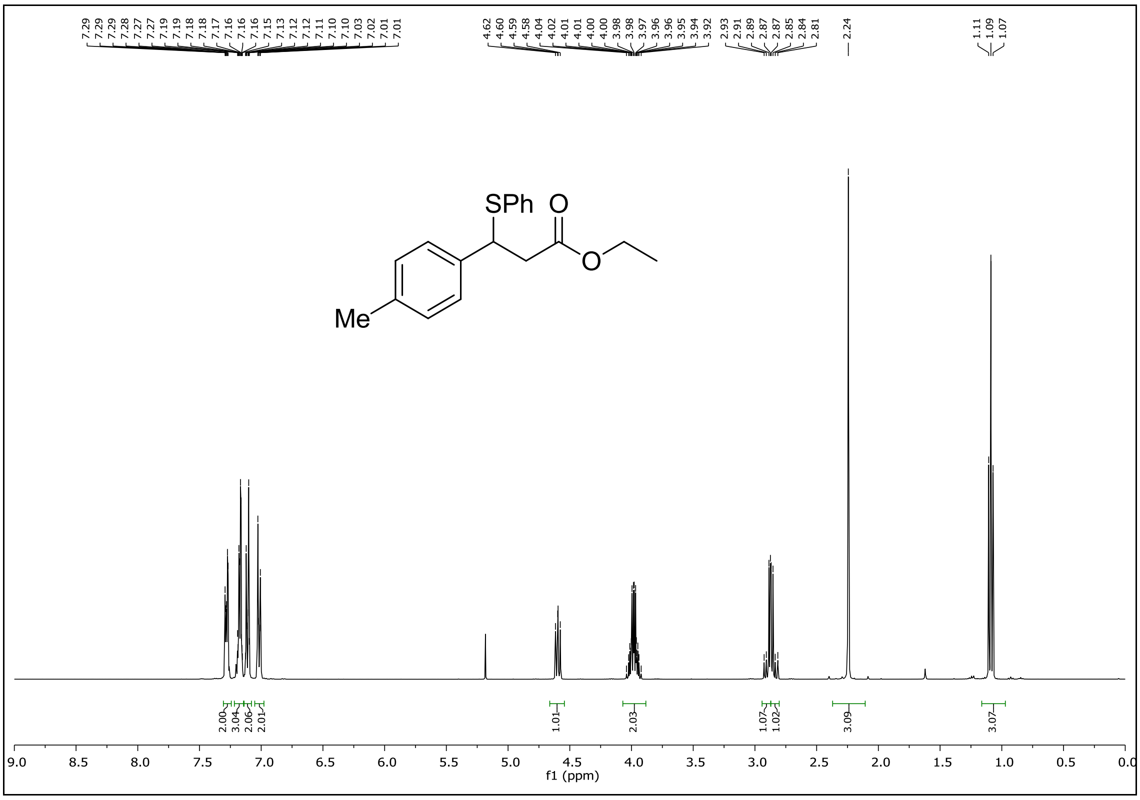
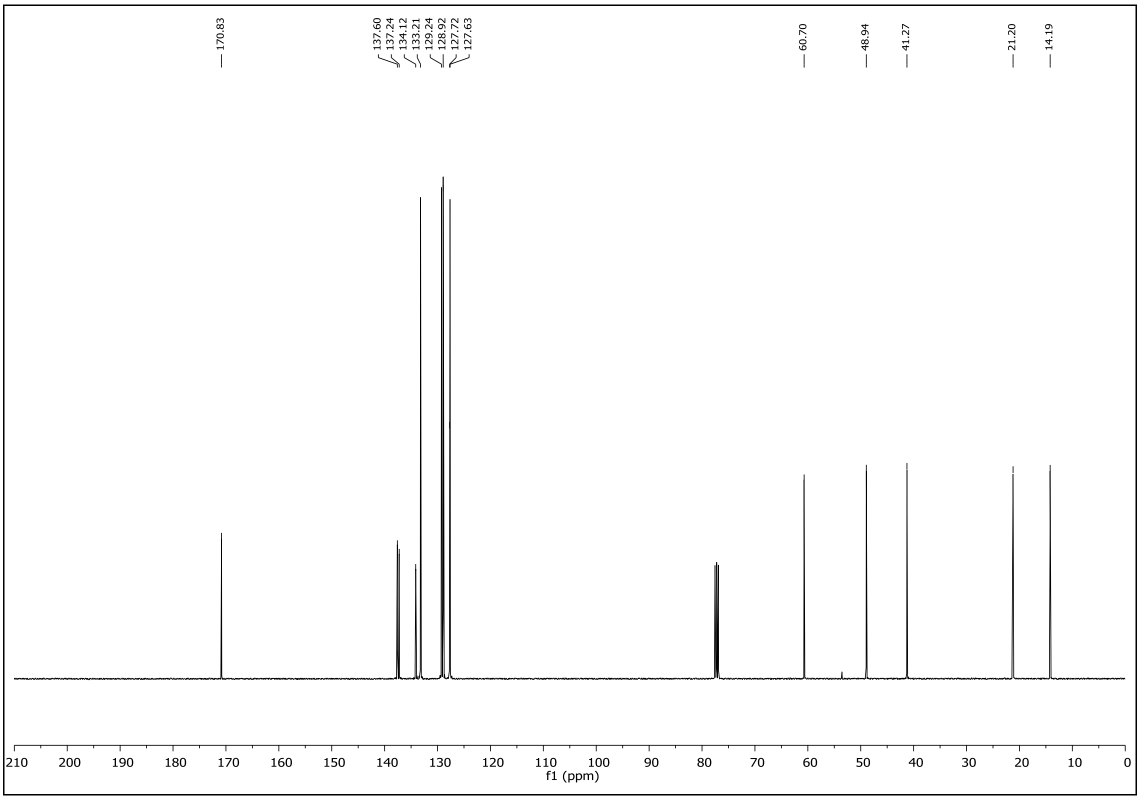
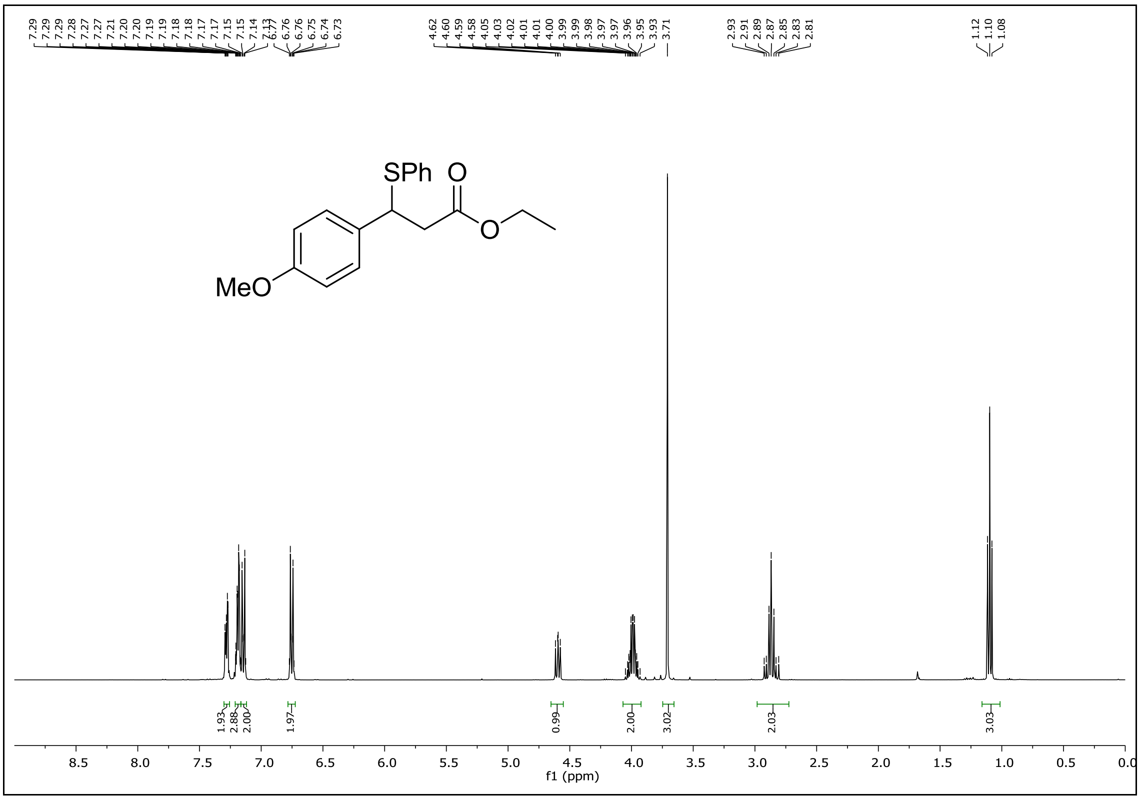
[404] Tan, E. W., Chan B., Blackman, A. G. *J. Am. Chem. Soc*. **2002**, *124*, 2078–2079.

6.6.6. Representative NMR spectra



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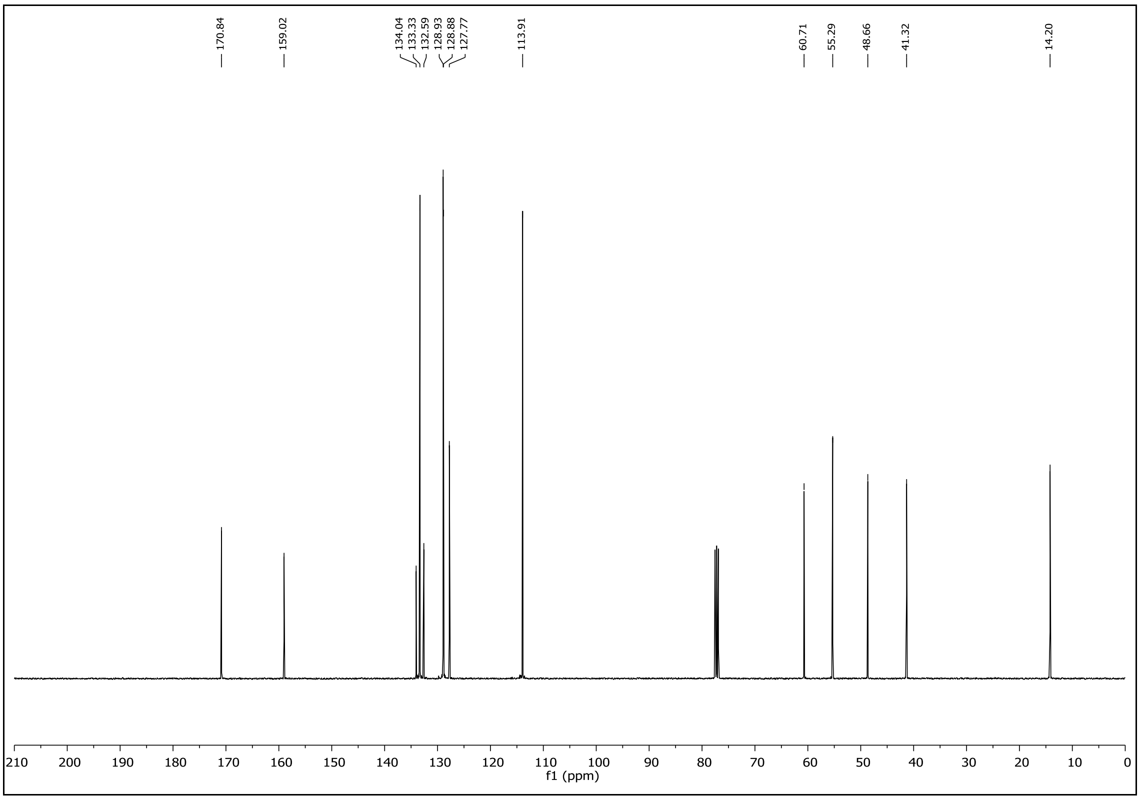
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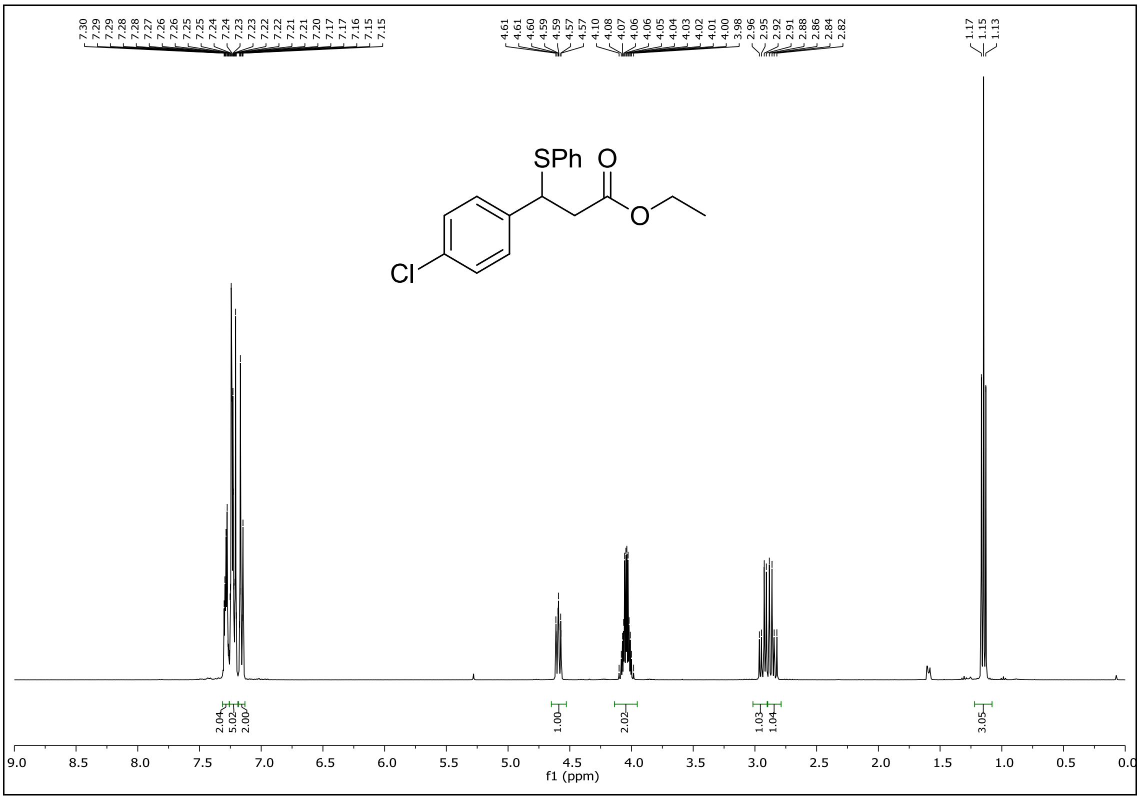
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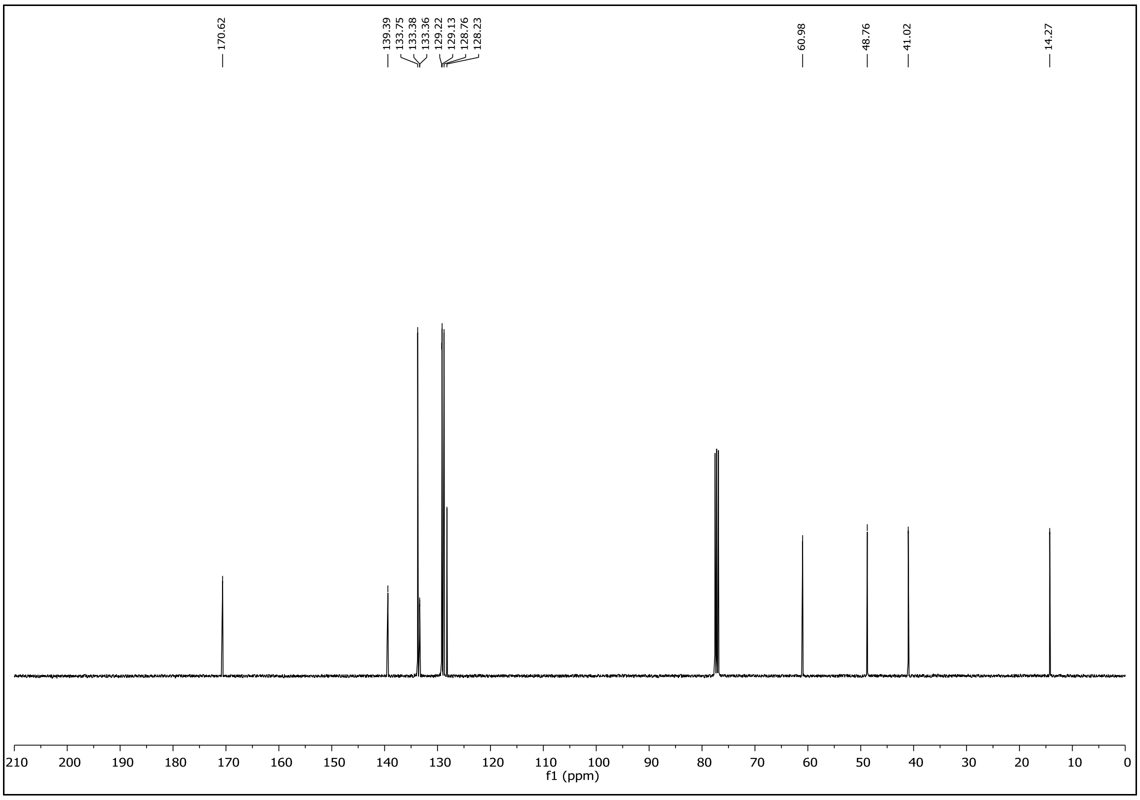
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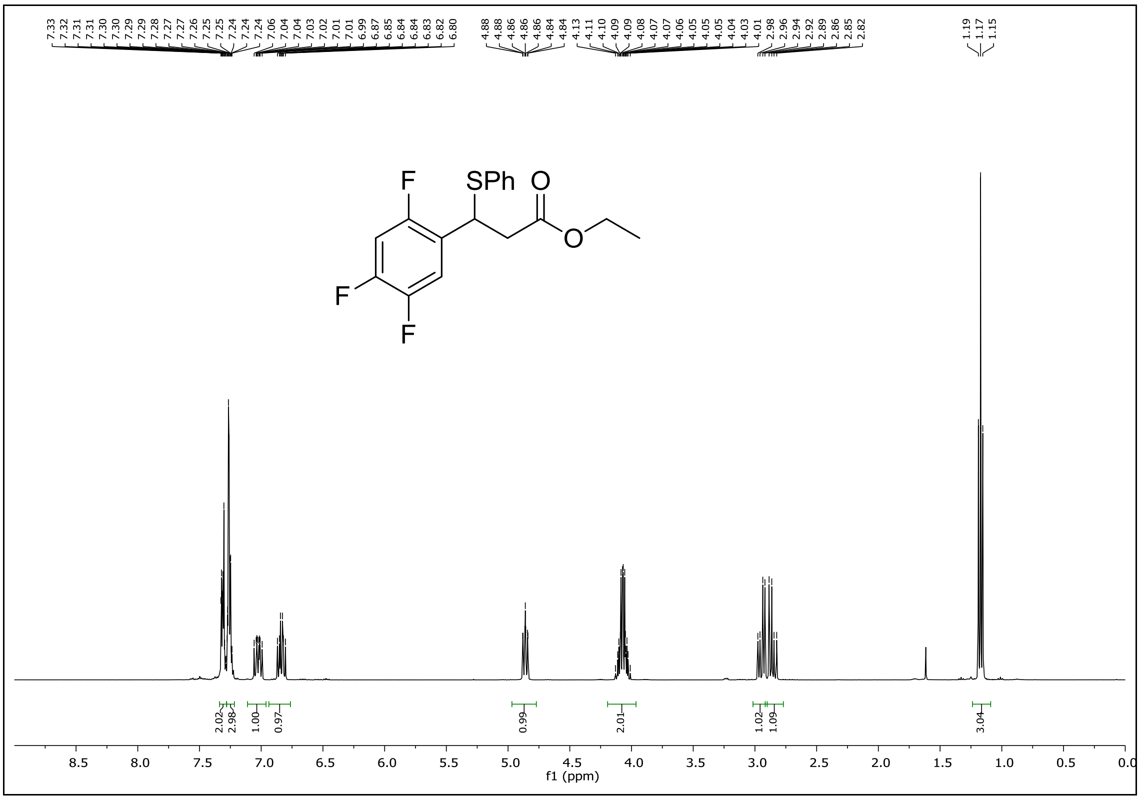
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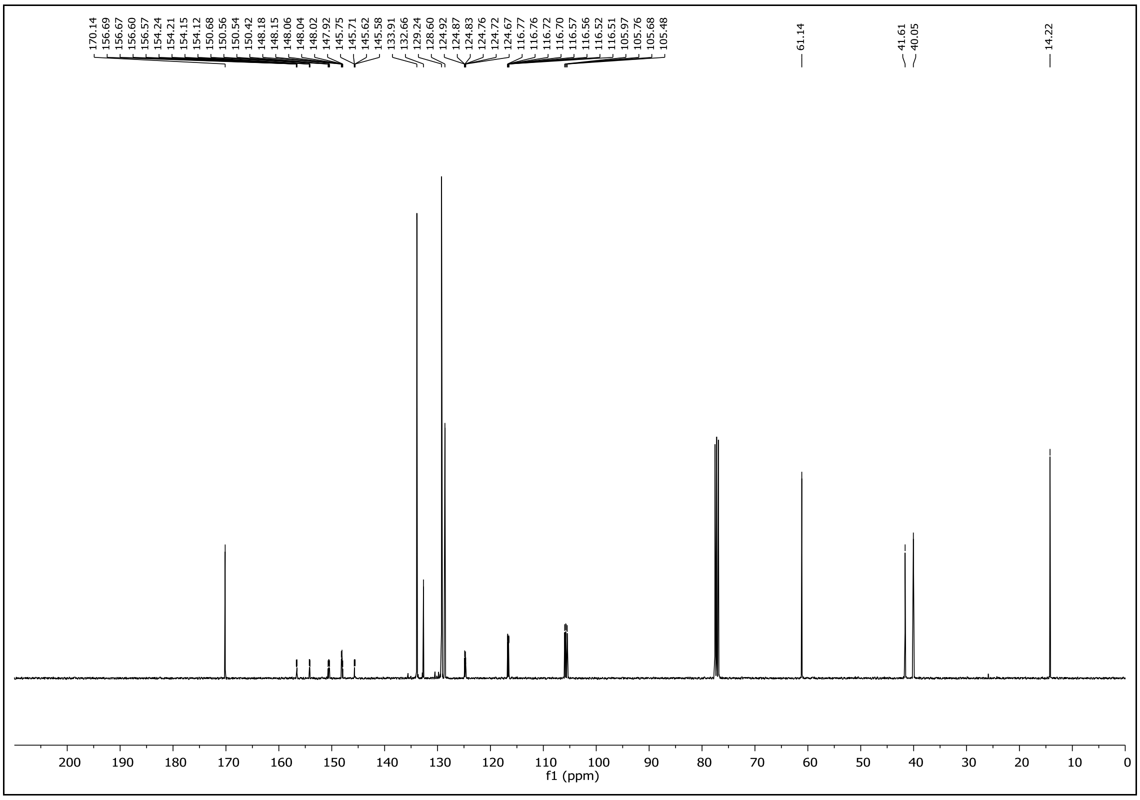
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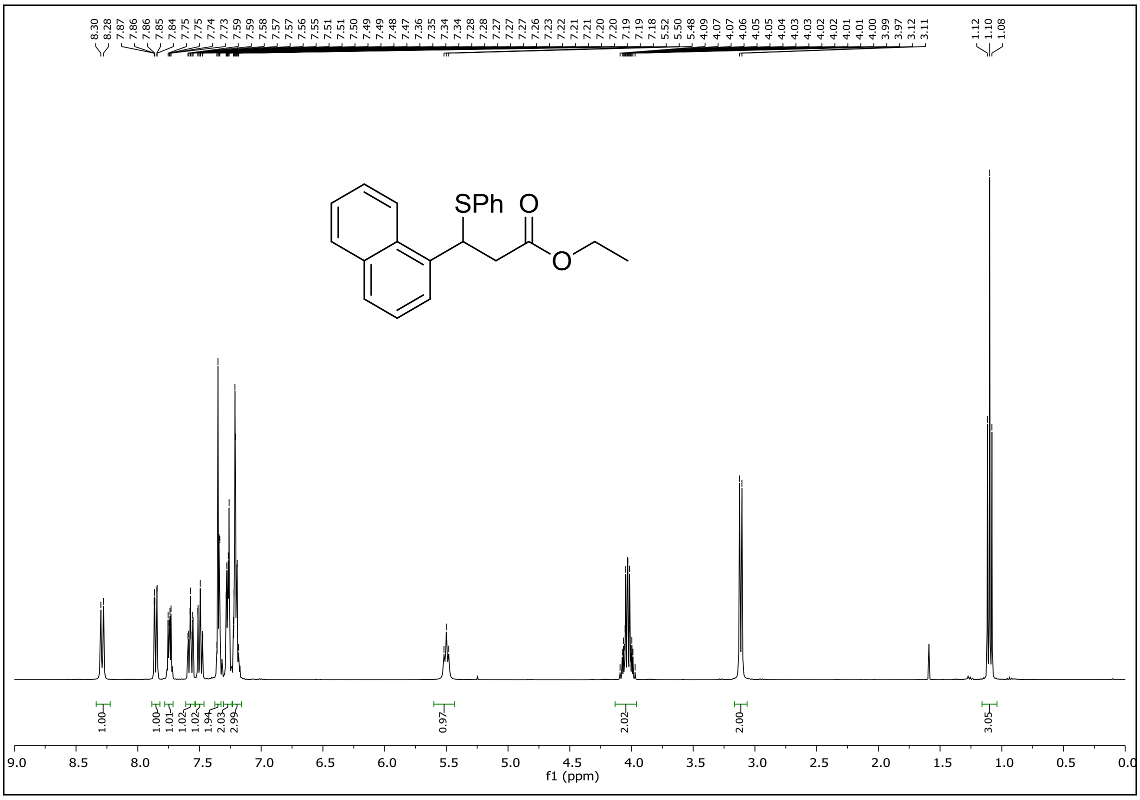
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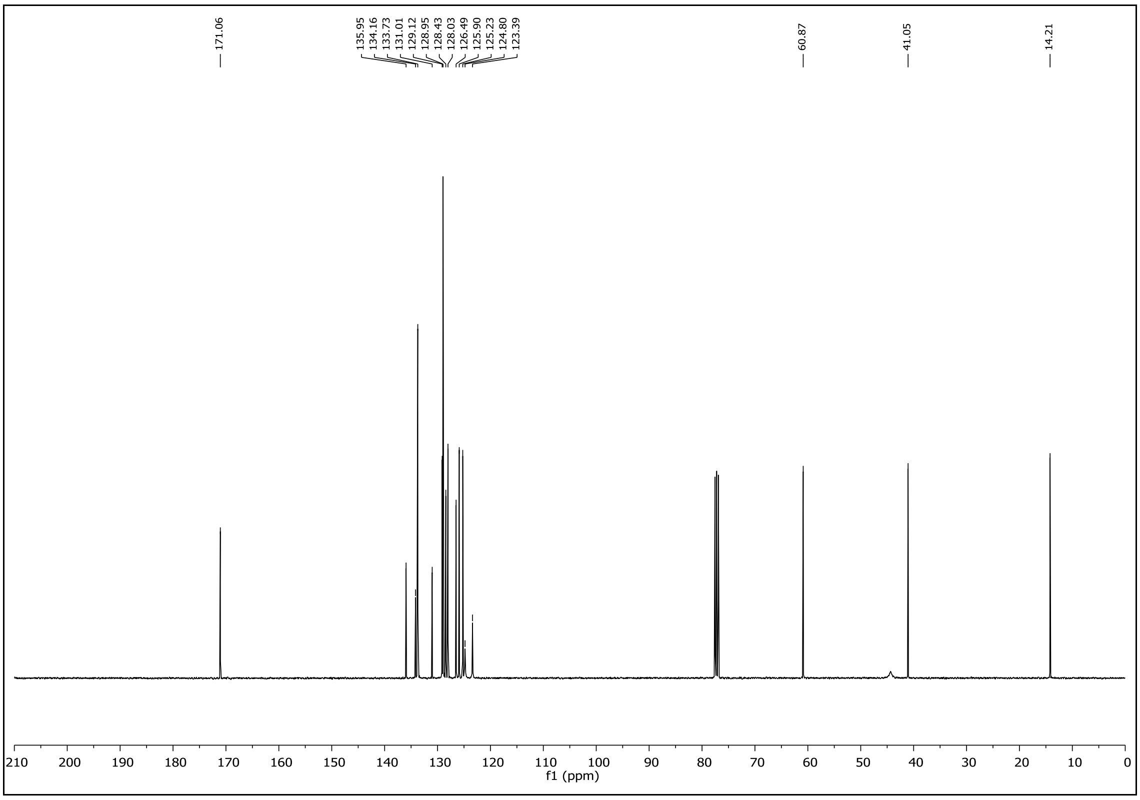
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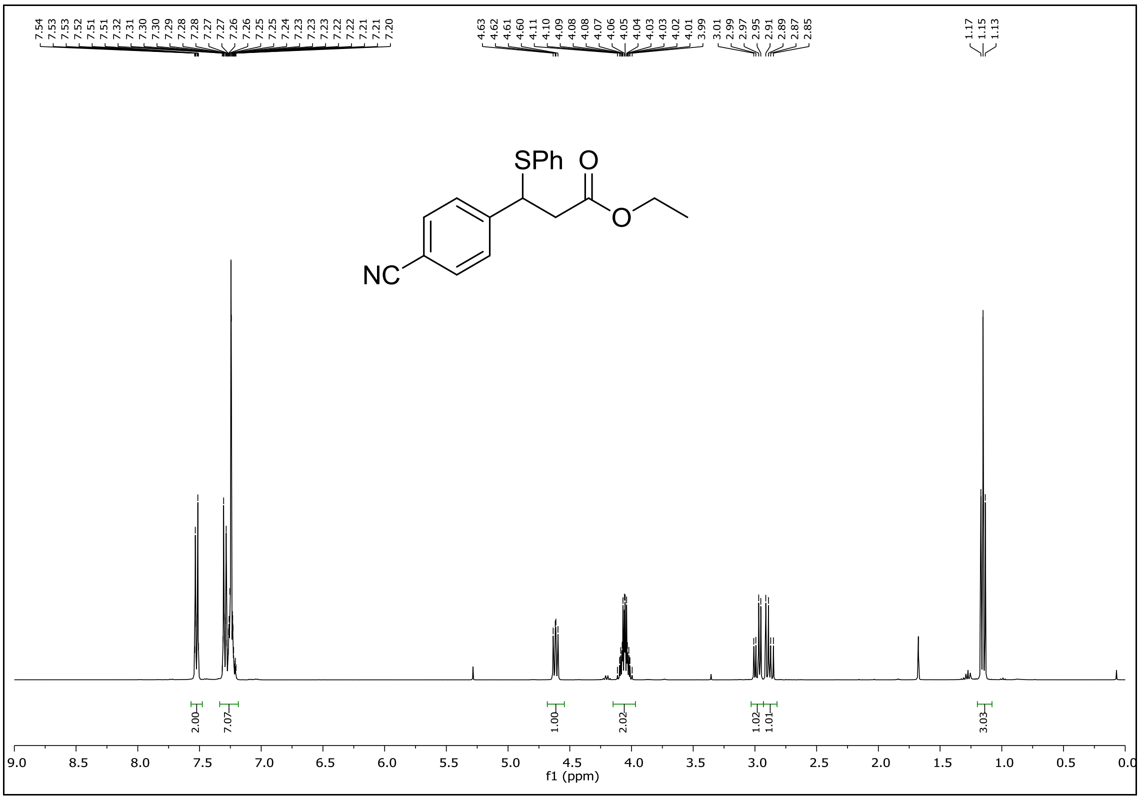
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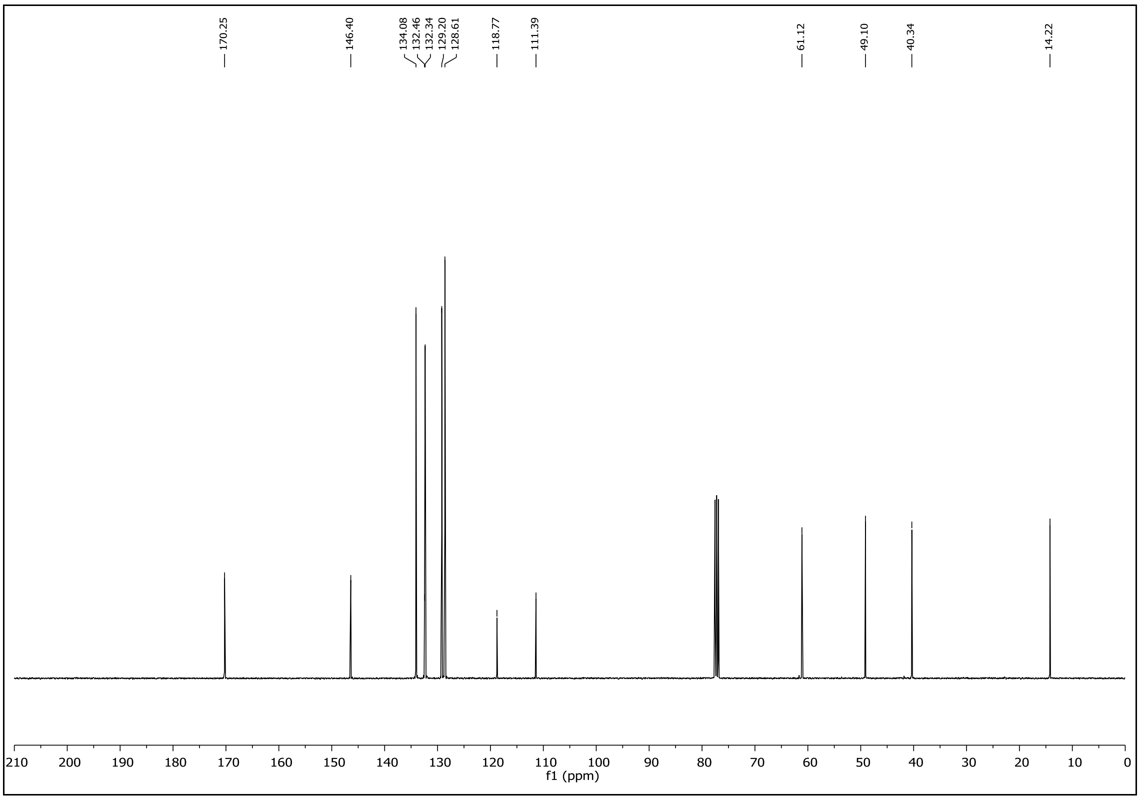
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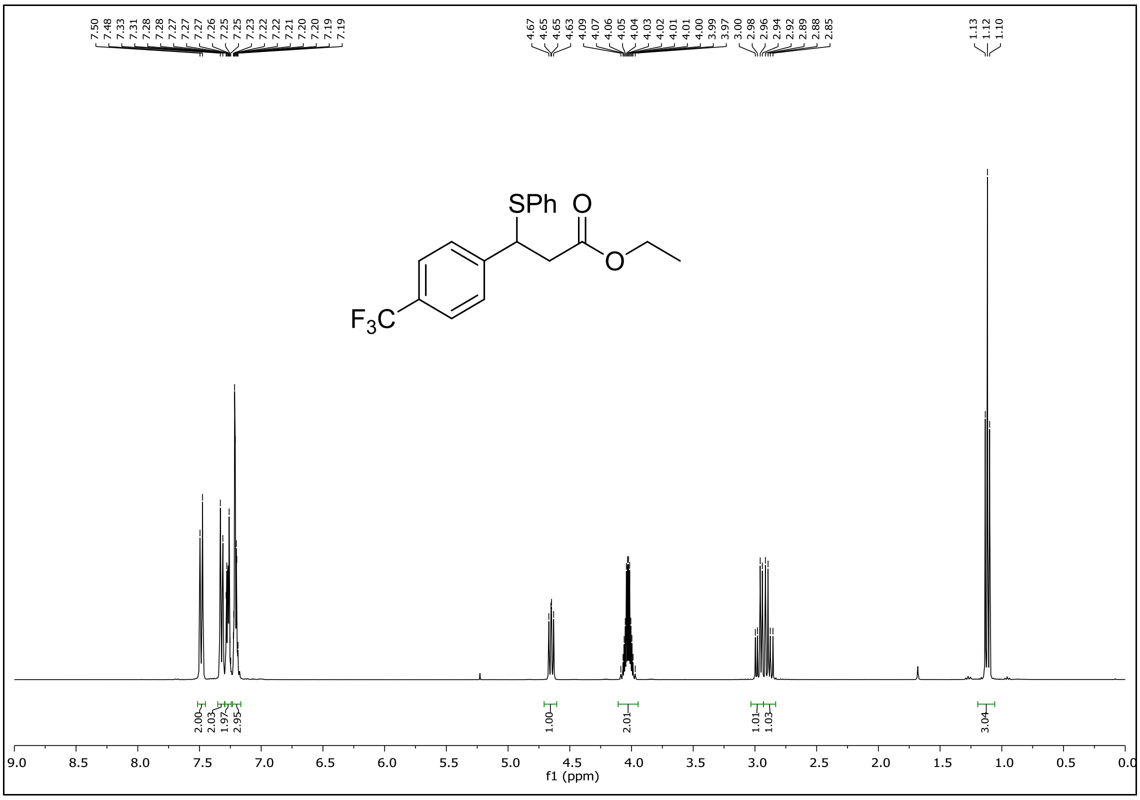
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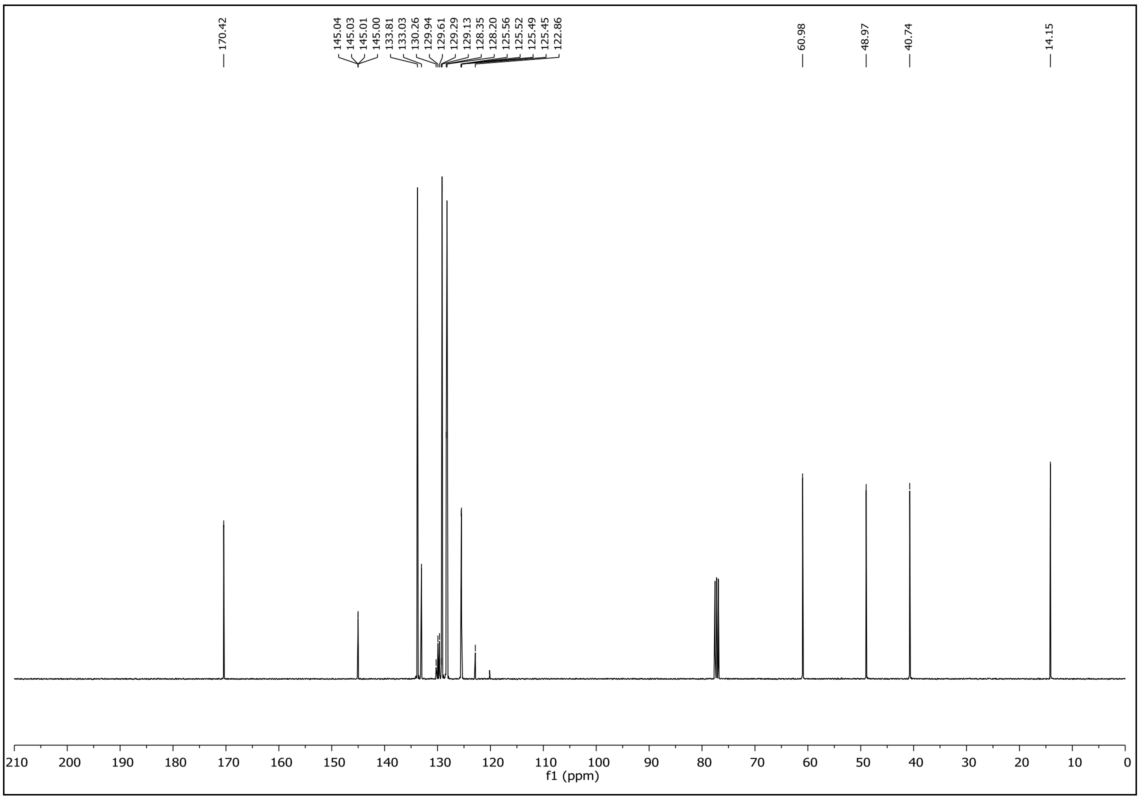
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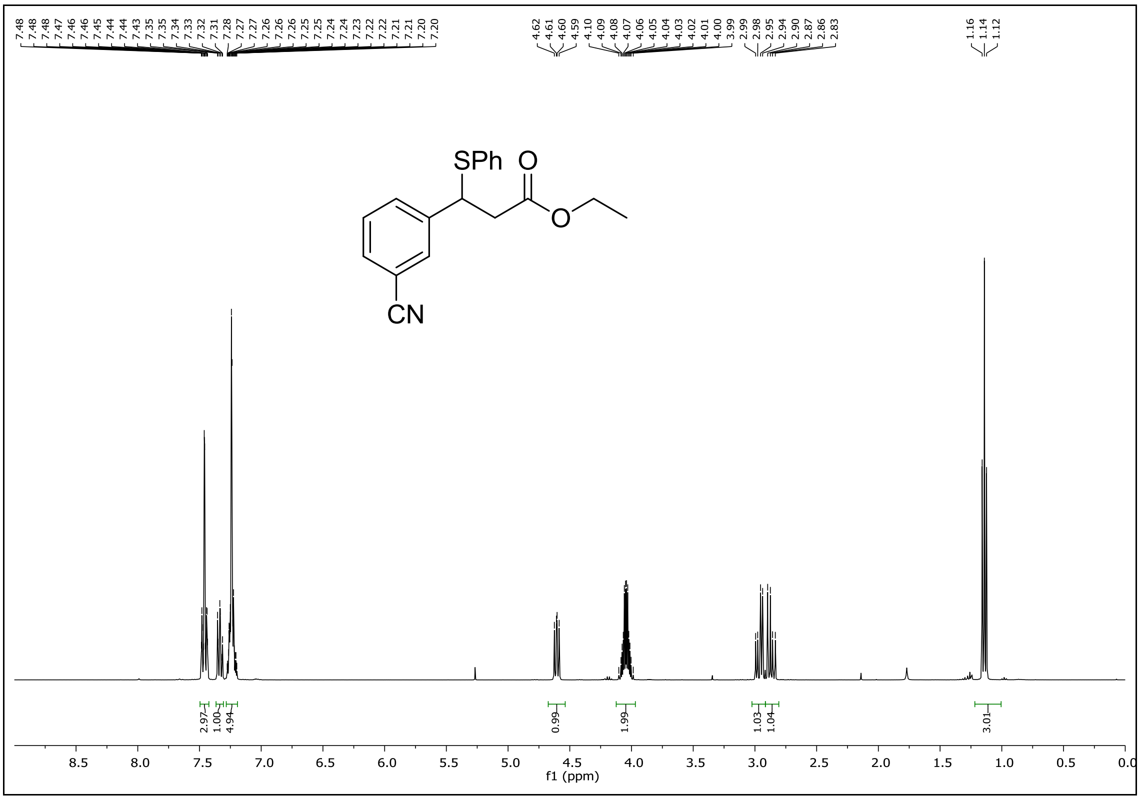
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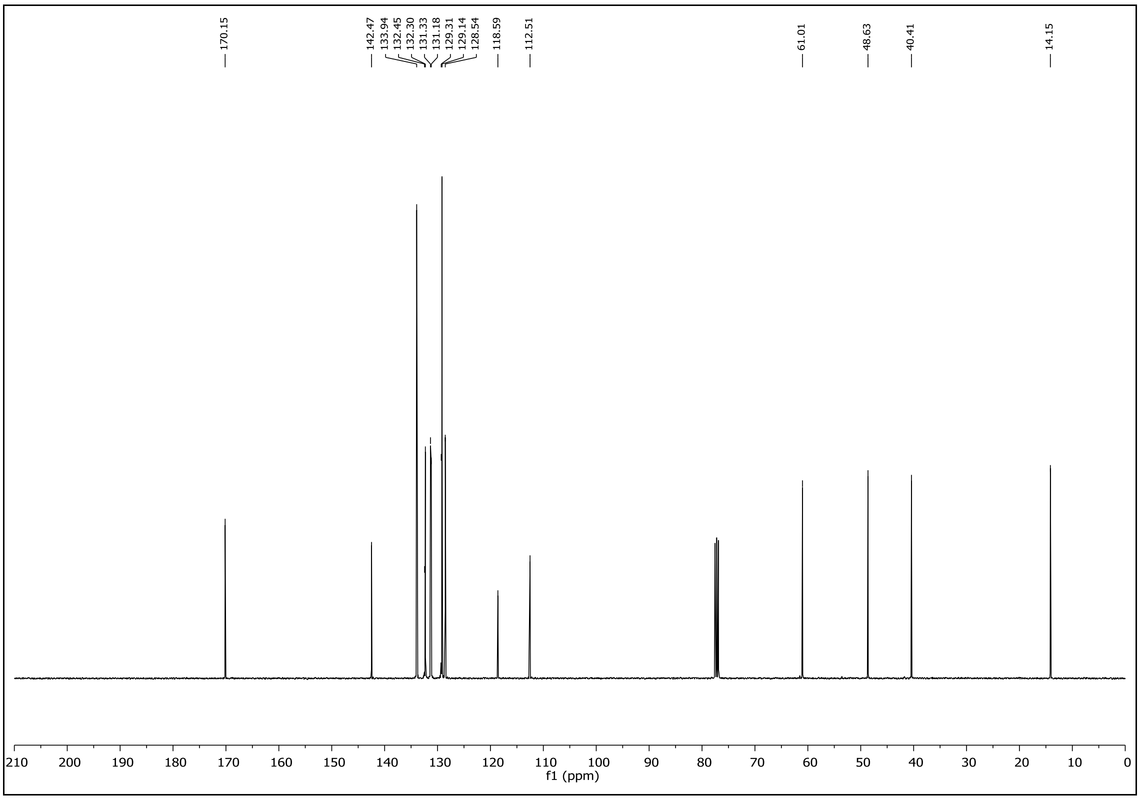
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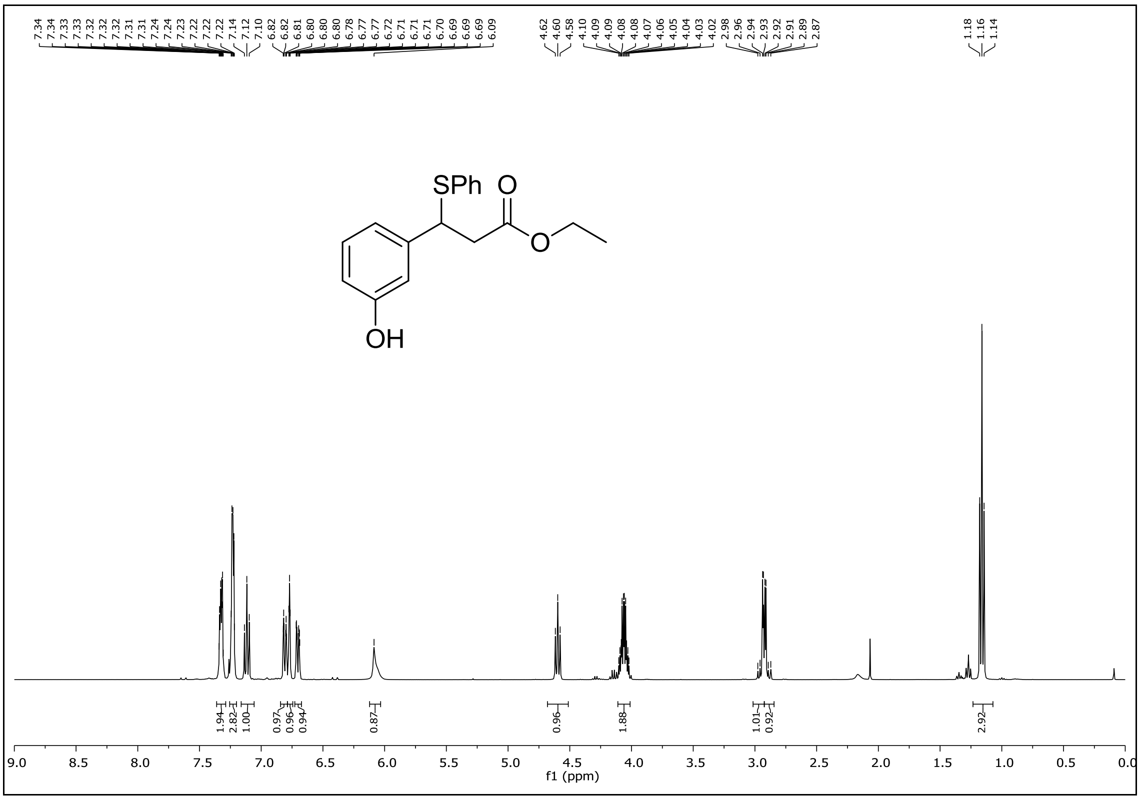
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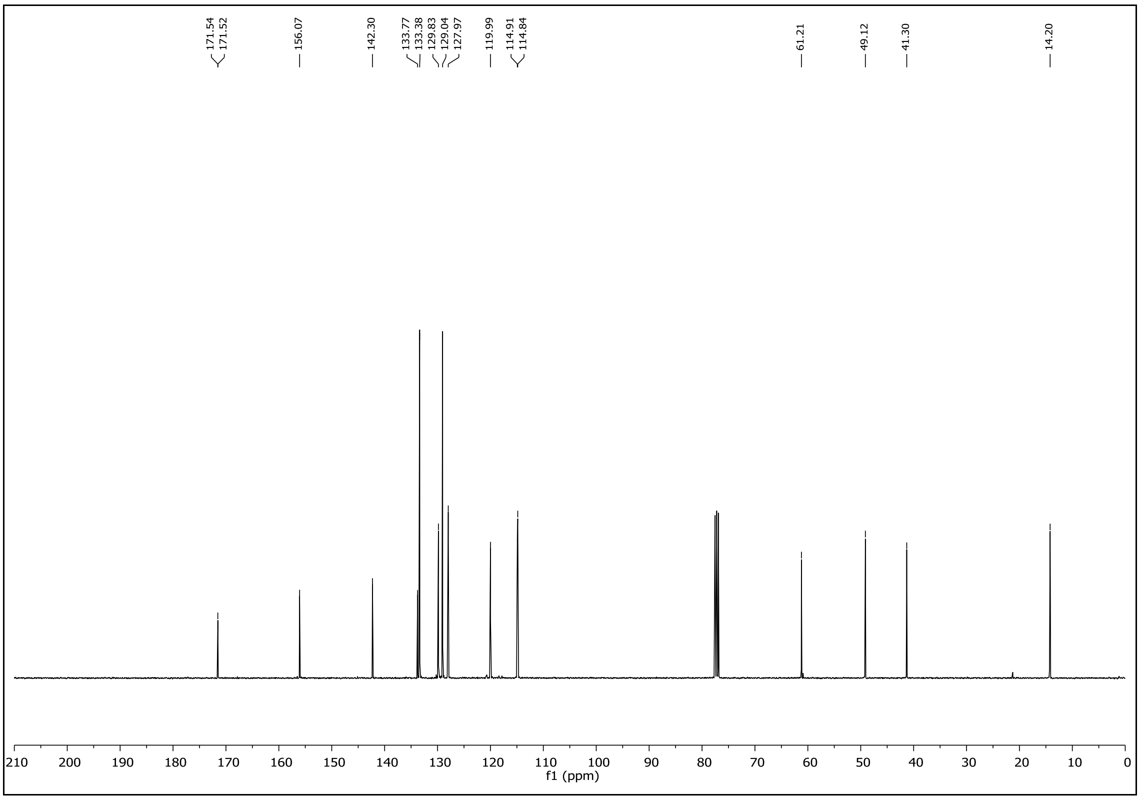
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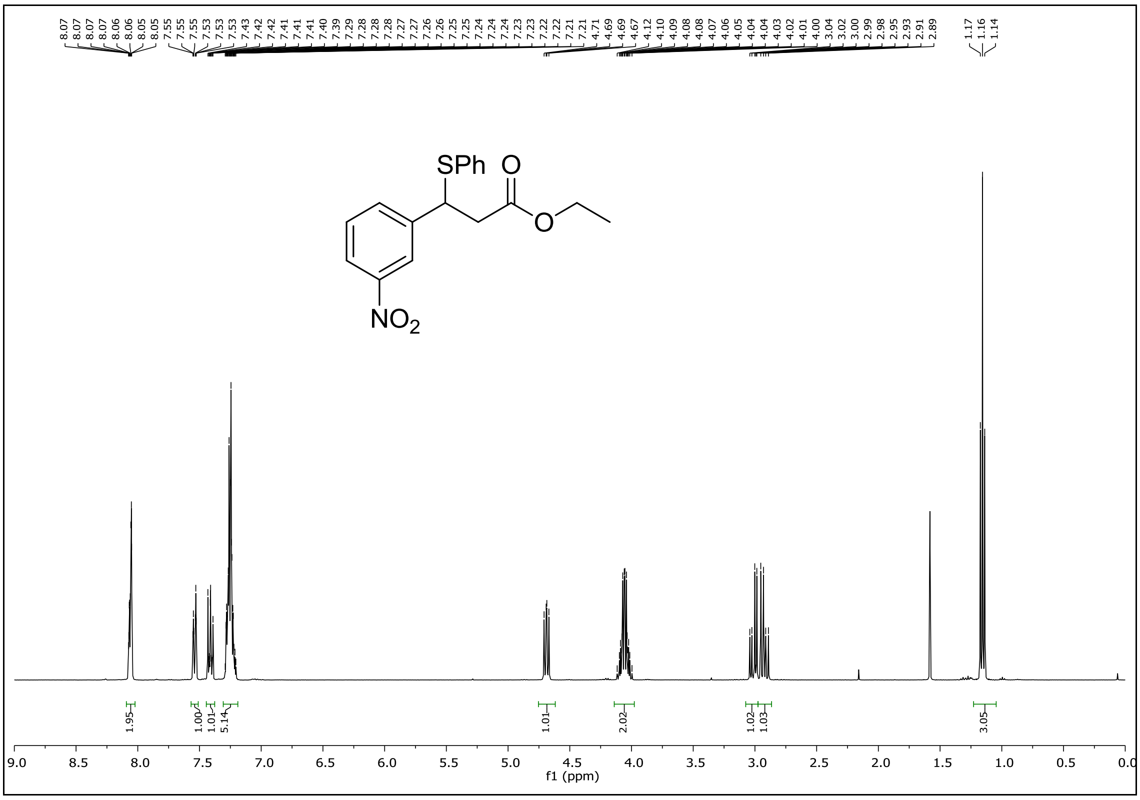
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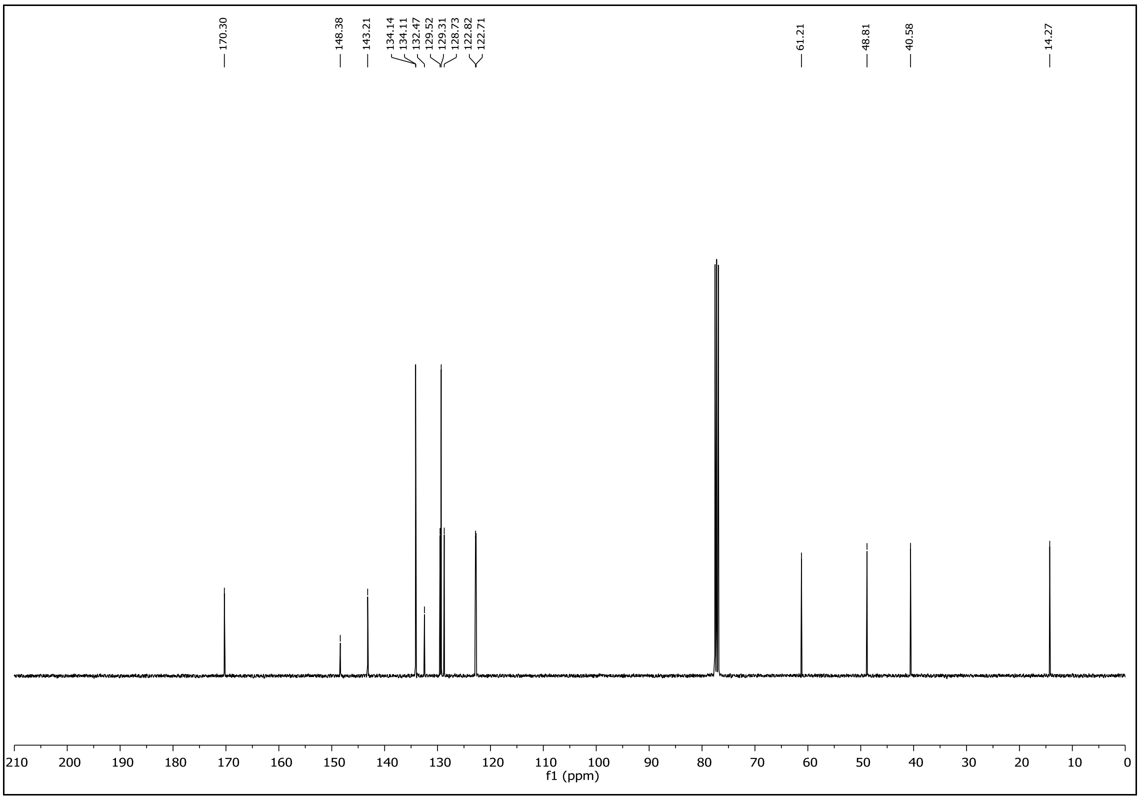
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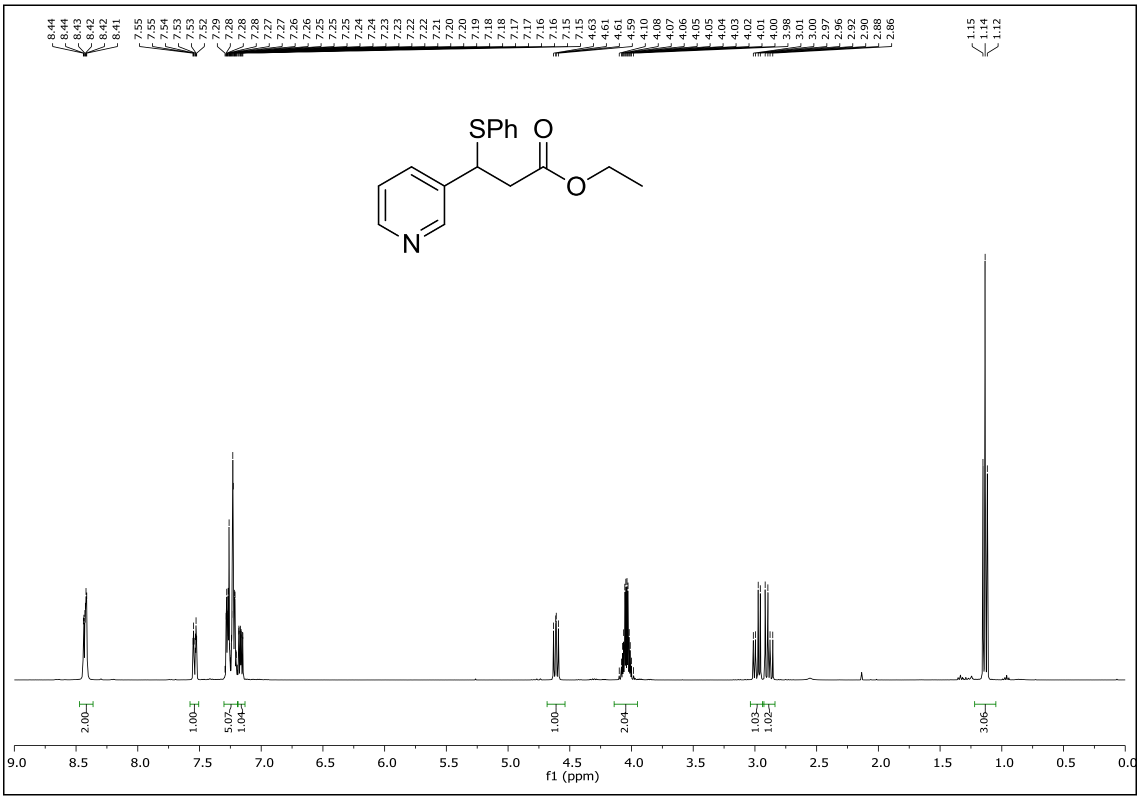
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1.00
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1.02
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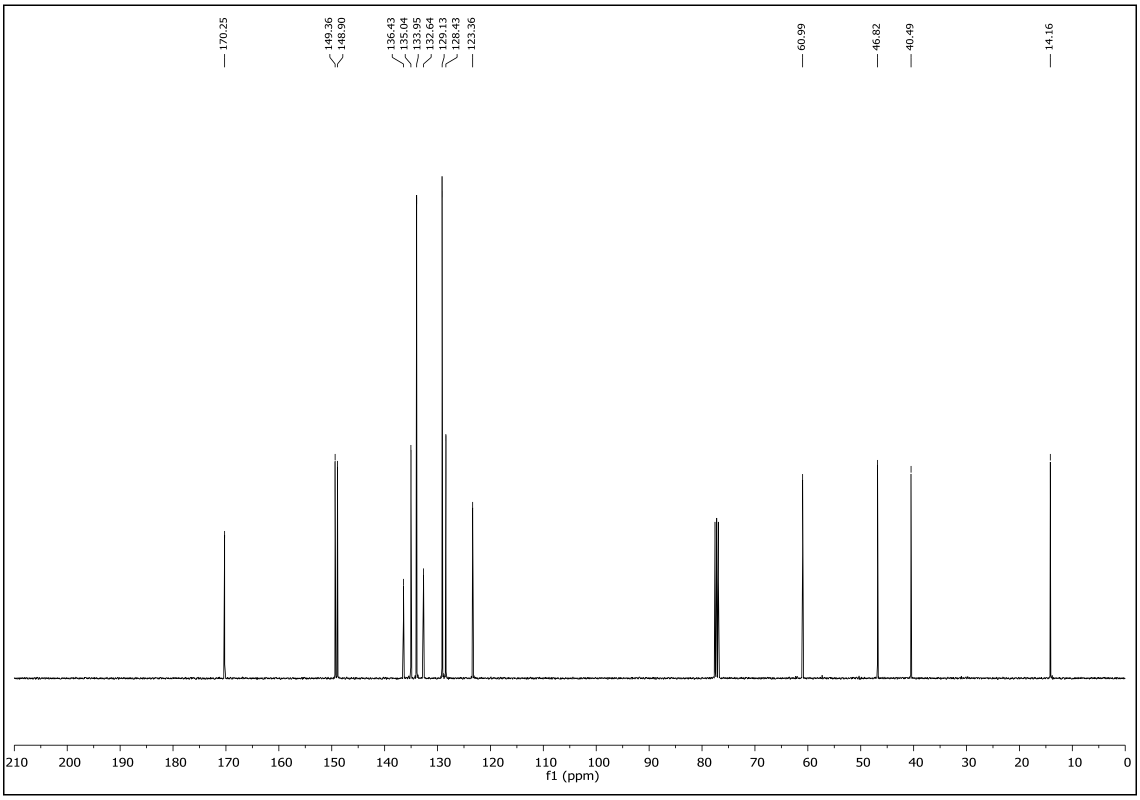
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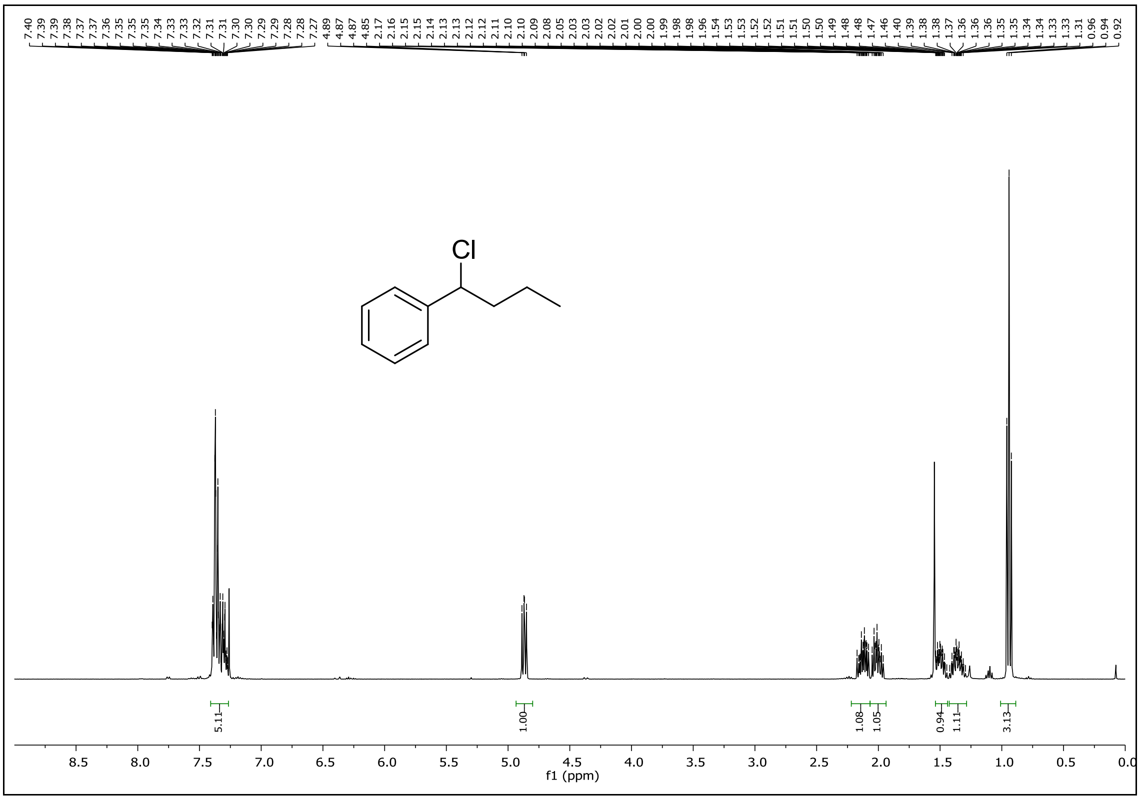
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4.89 4.87 4.85
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1.54 1.53 1.53 1.52 1.52 1.51 1.51 1.50 1.50 1.49 1.48 1.48 1.47 1.46 1.40 1.39 1.38 1.38 1.37 1.36 1.36 1.36 1.35 1.35 1.34 1.34 1.33 1.33 1.31
0.96 0.94 0.92
Cl
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1.00
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1.05
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1.11
3.13
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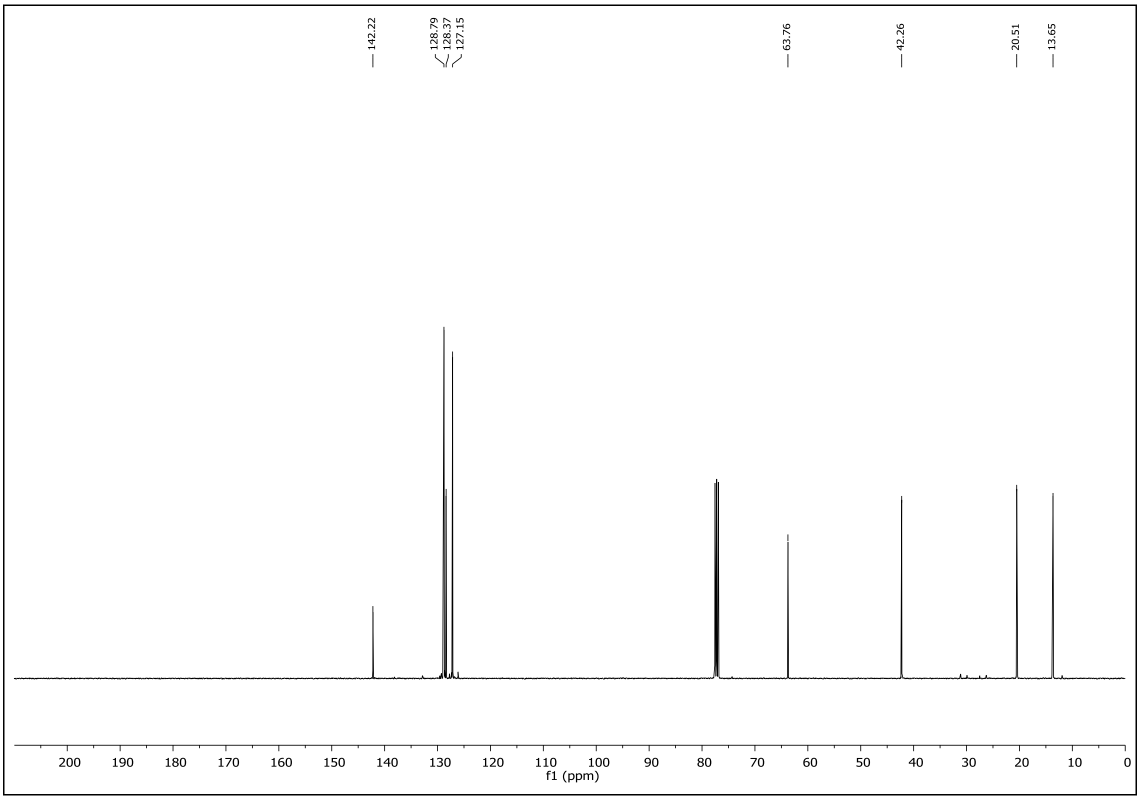
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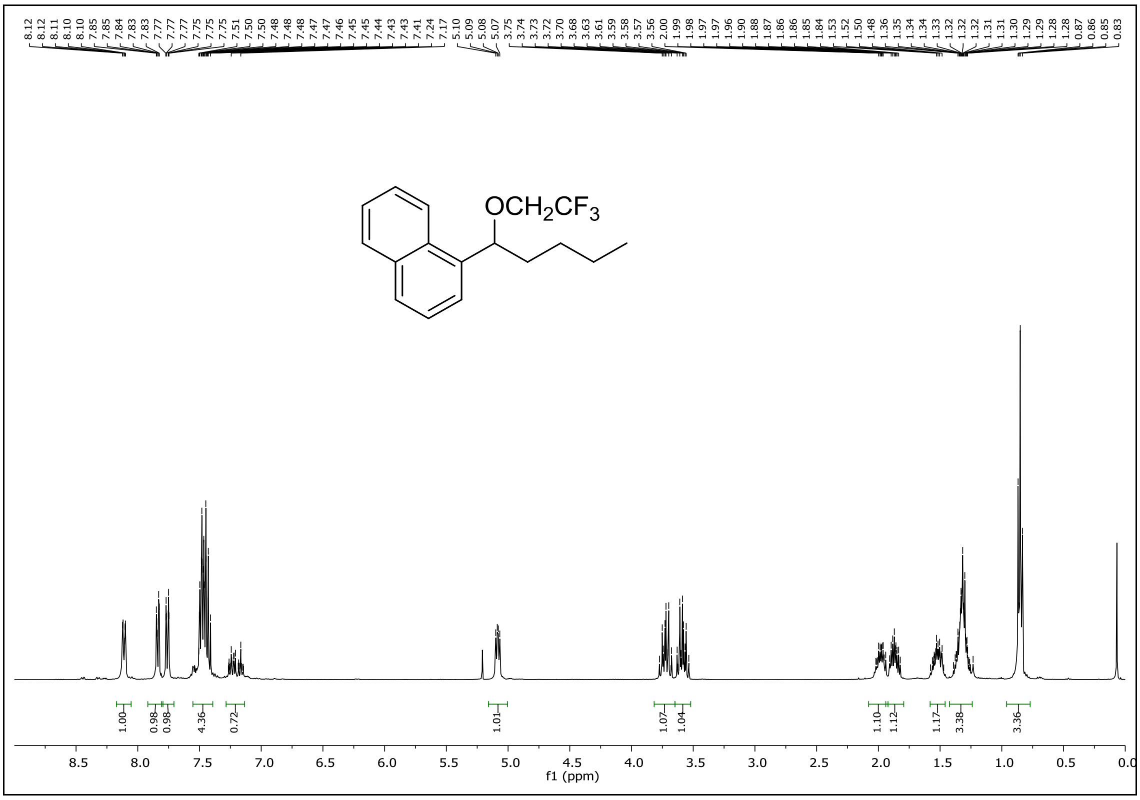
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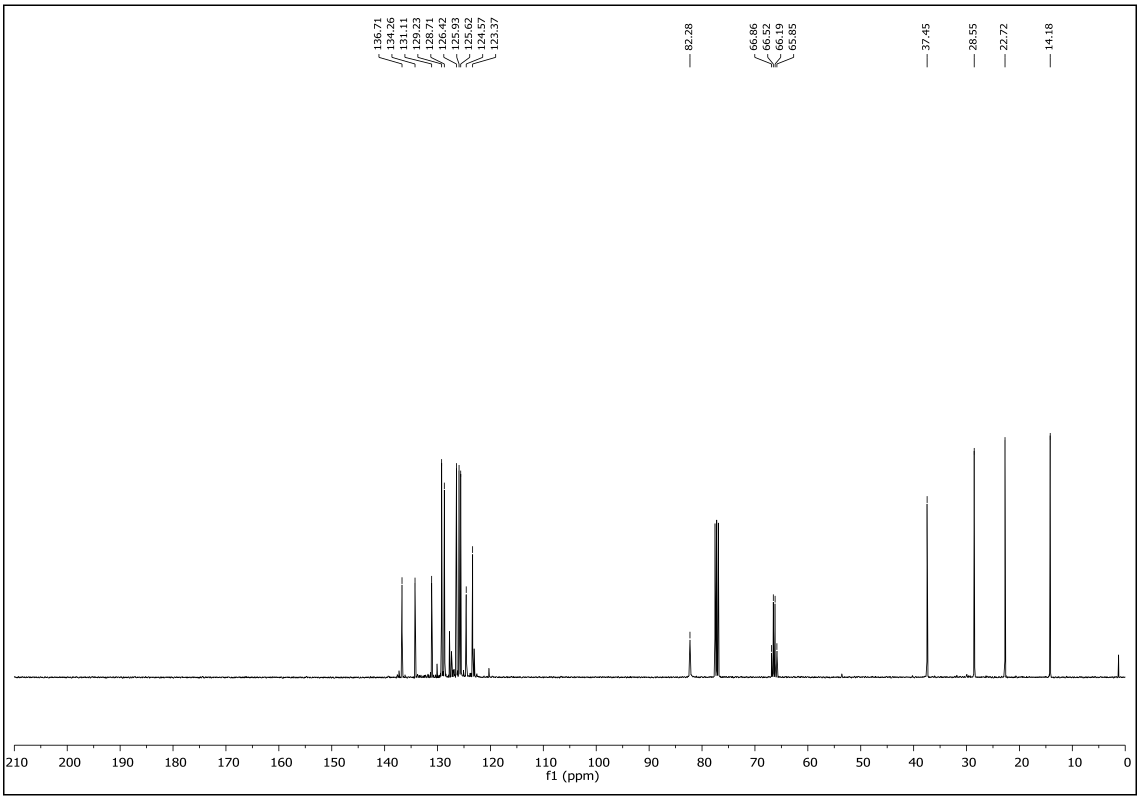
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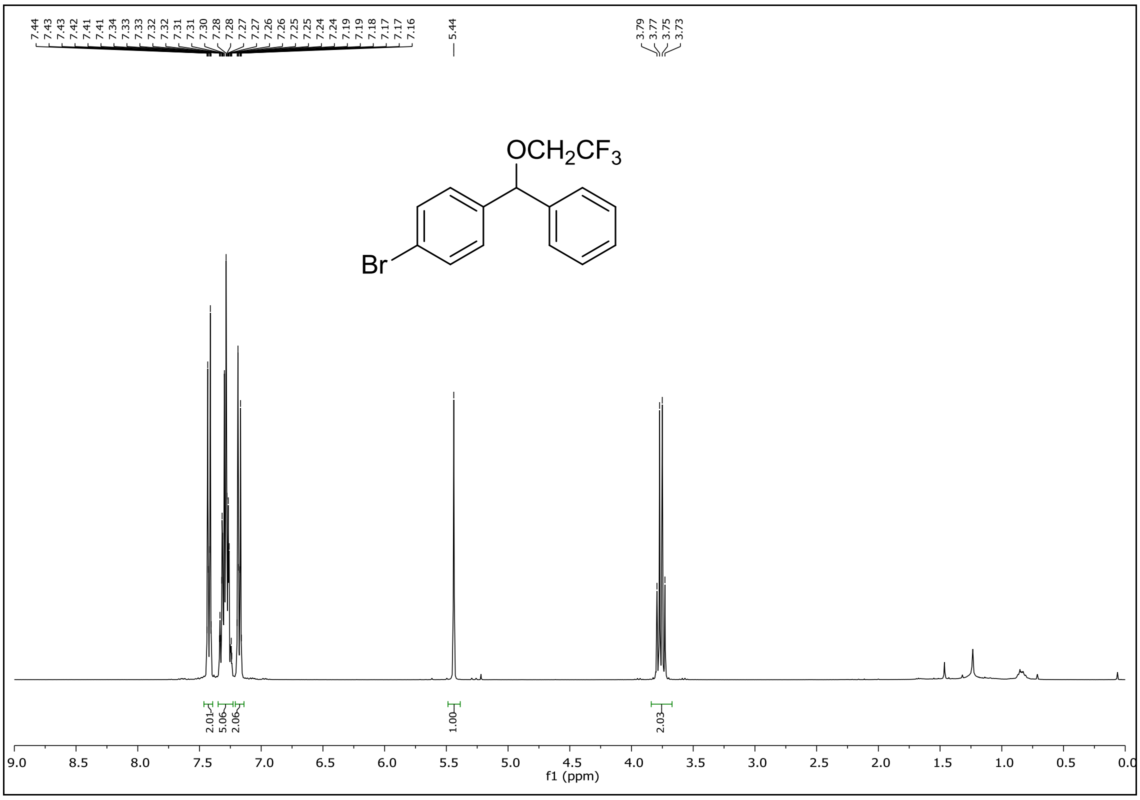
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2.06
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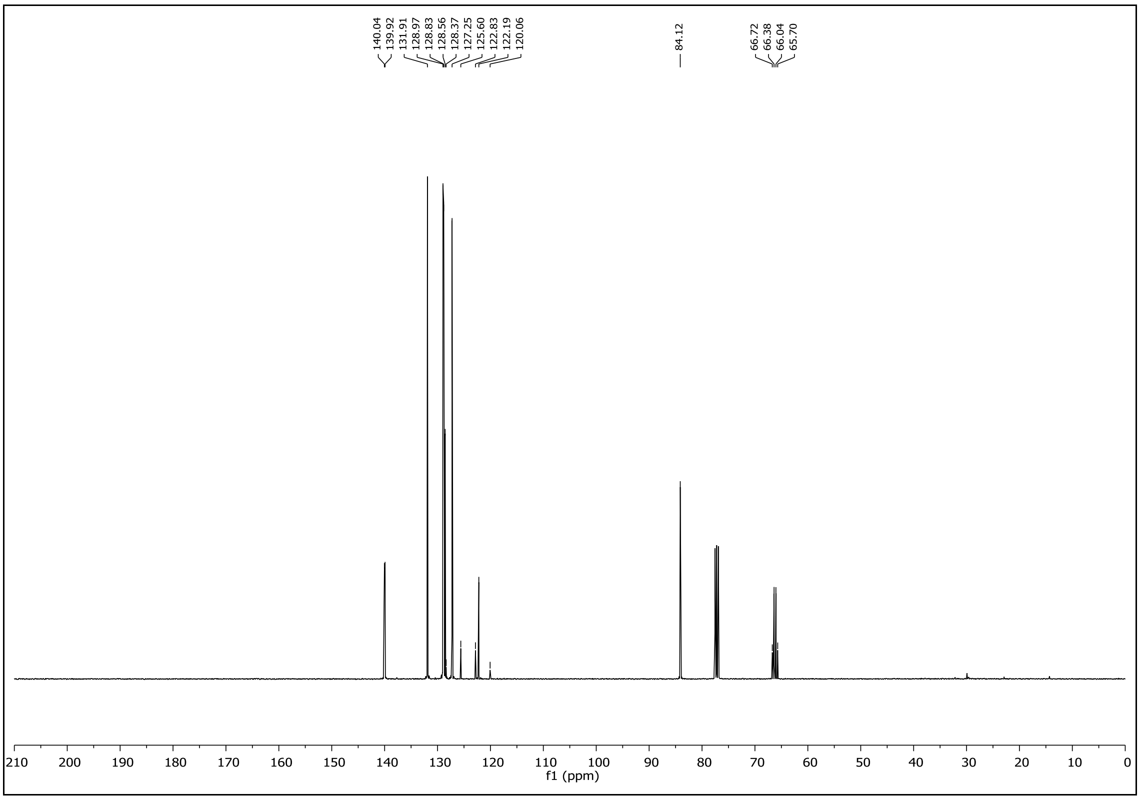
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66.04
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180
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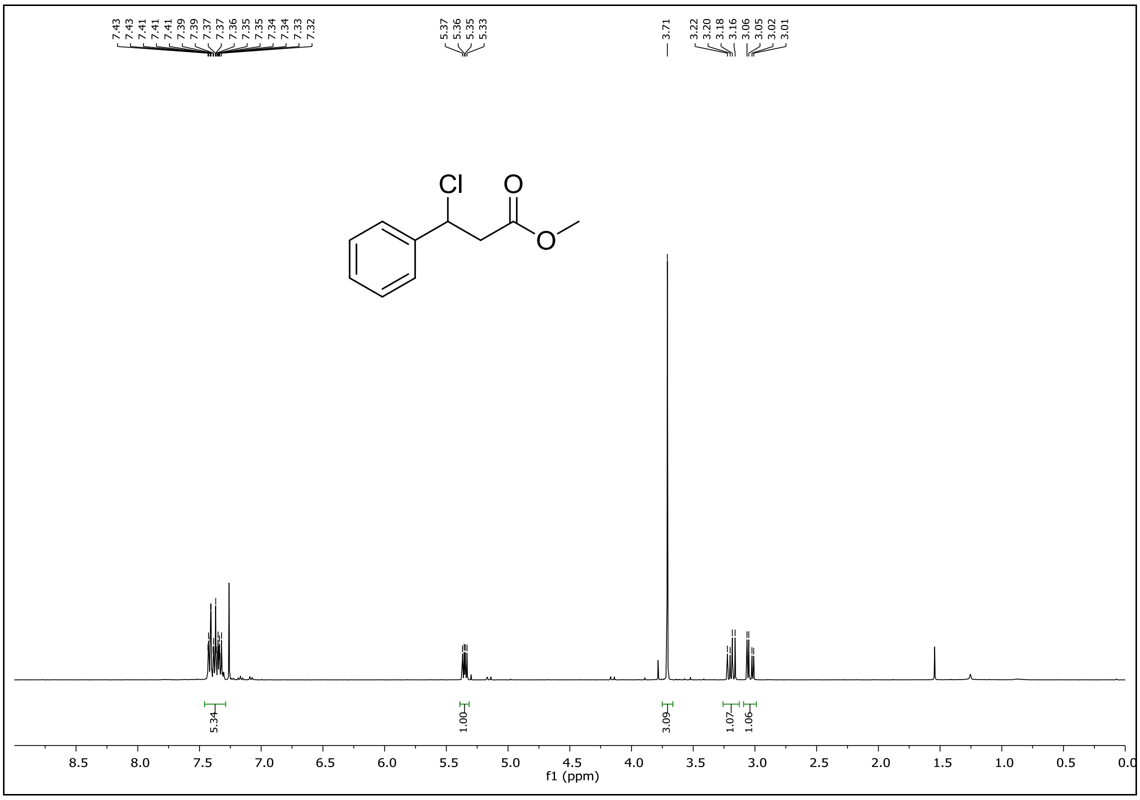
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3.05
3.02
3.01
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O
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1.07
1.06
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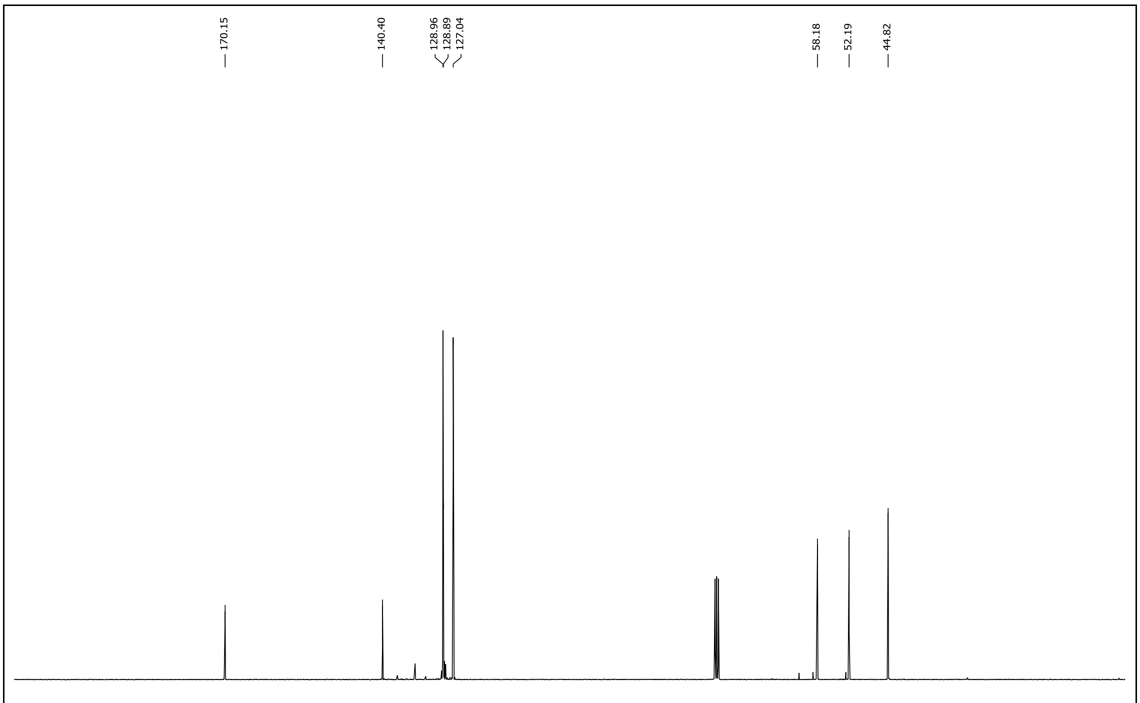
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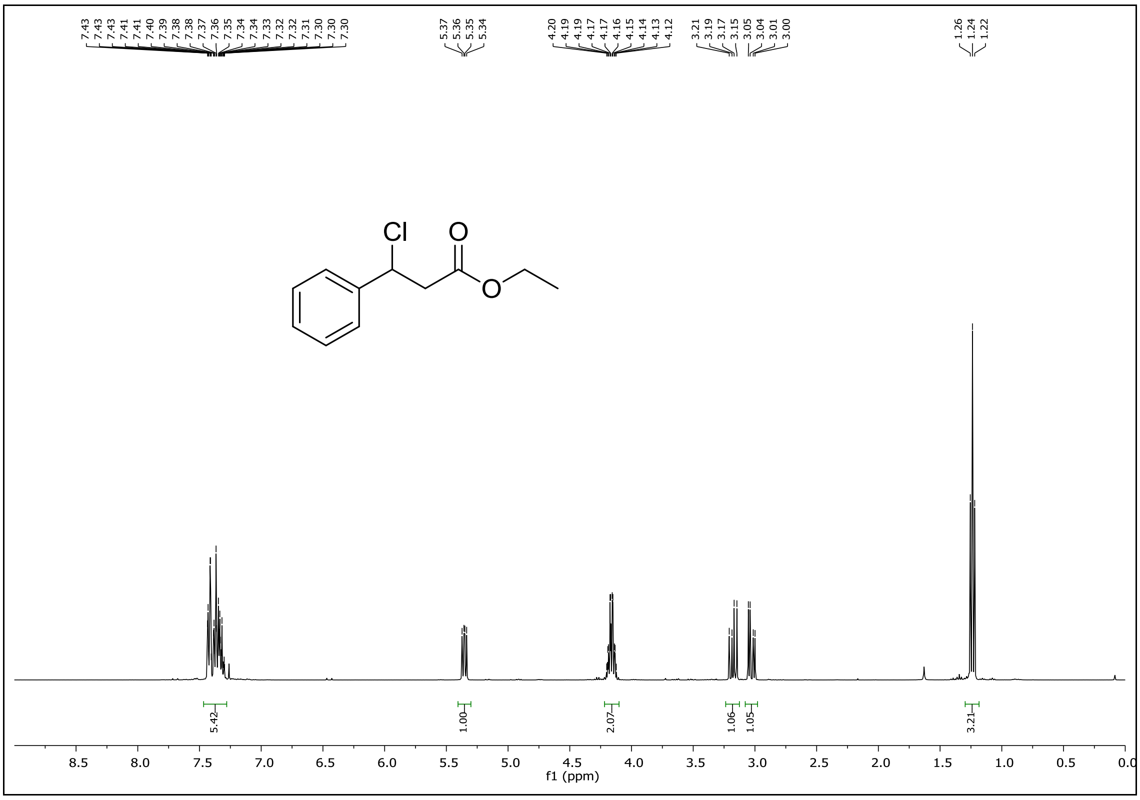
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4.17
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3.17
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3.05
3.04
3.01
3.00
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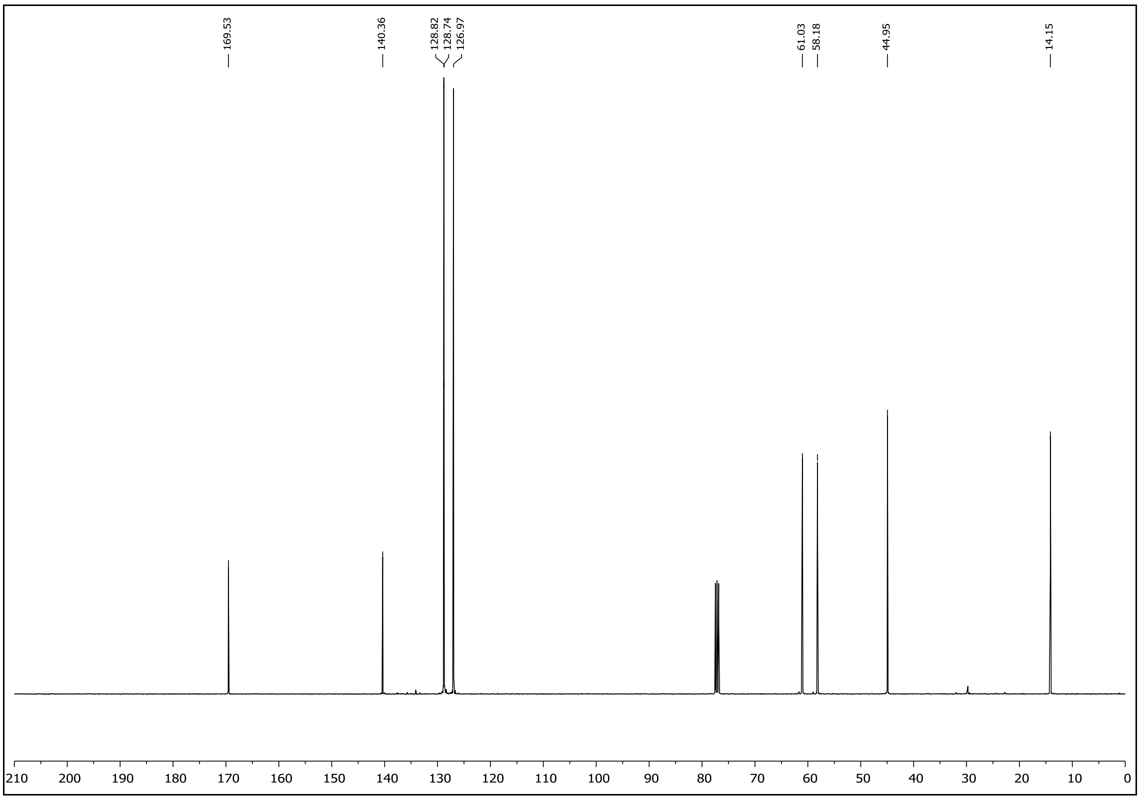
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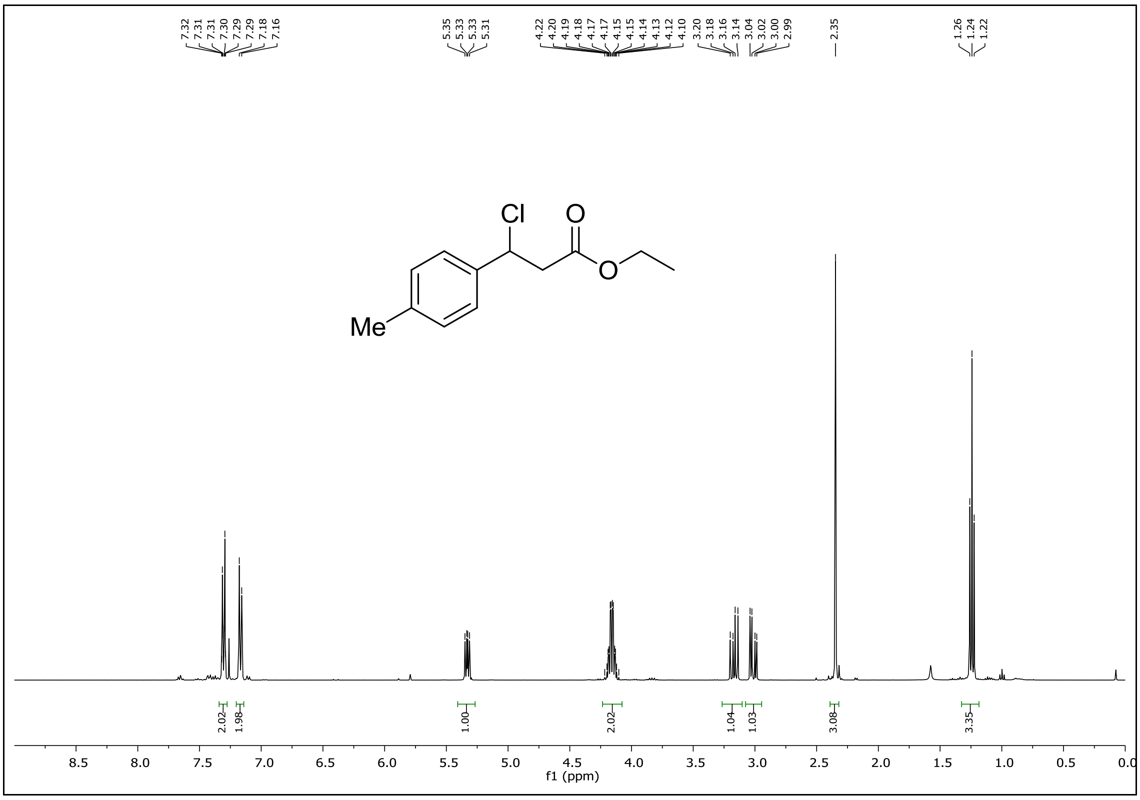
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3.20
3.18
3.16
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1.26
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1.22
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O
O
Me
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2.02
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1.03
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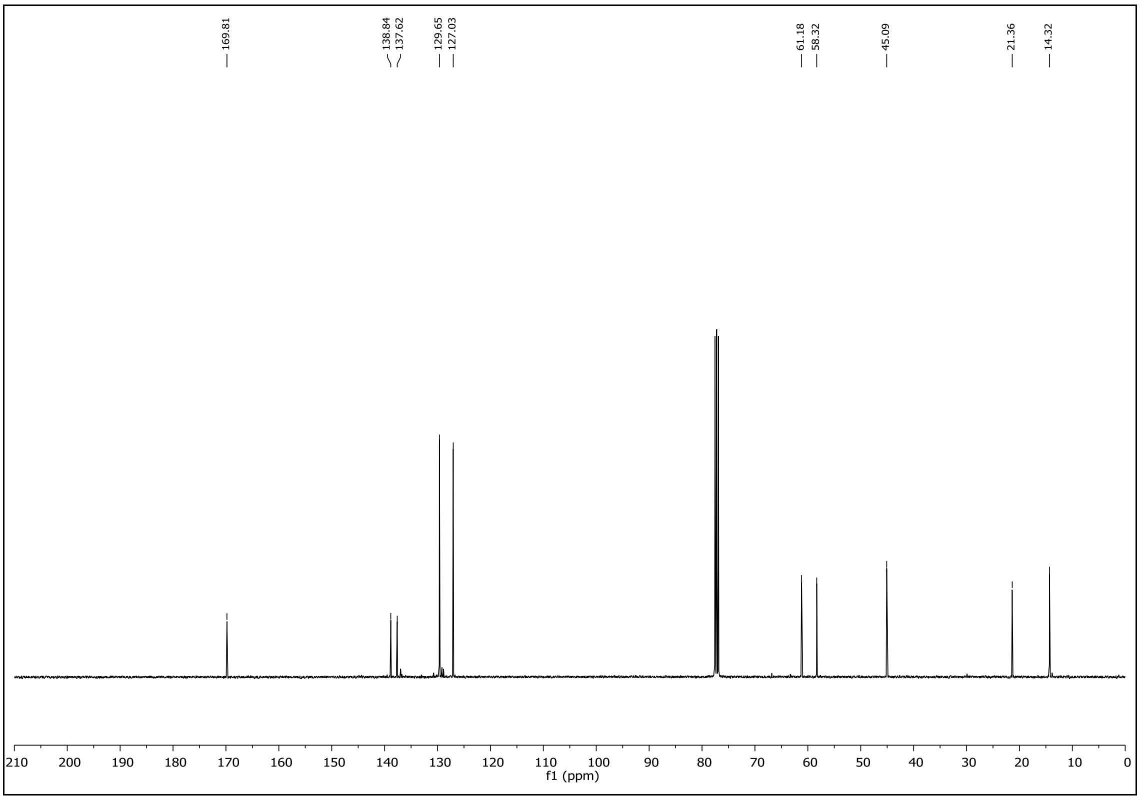
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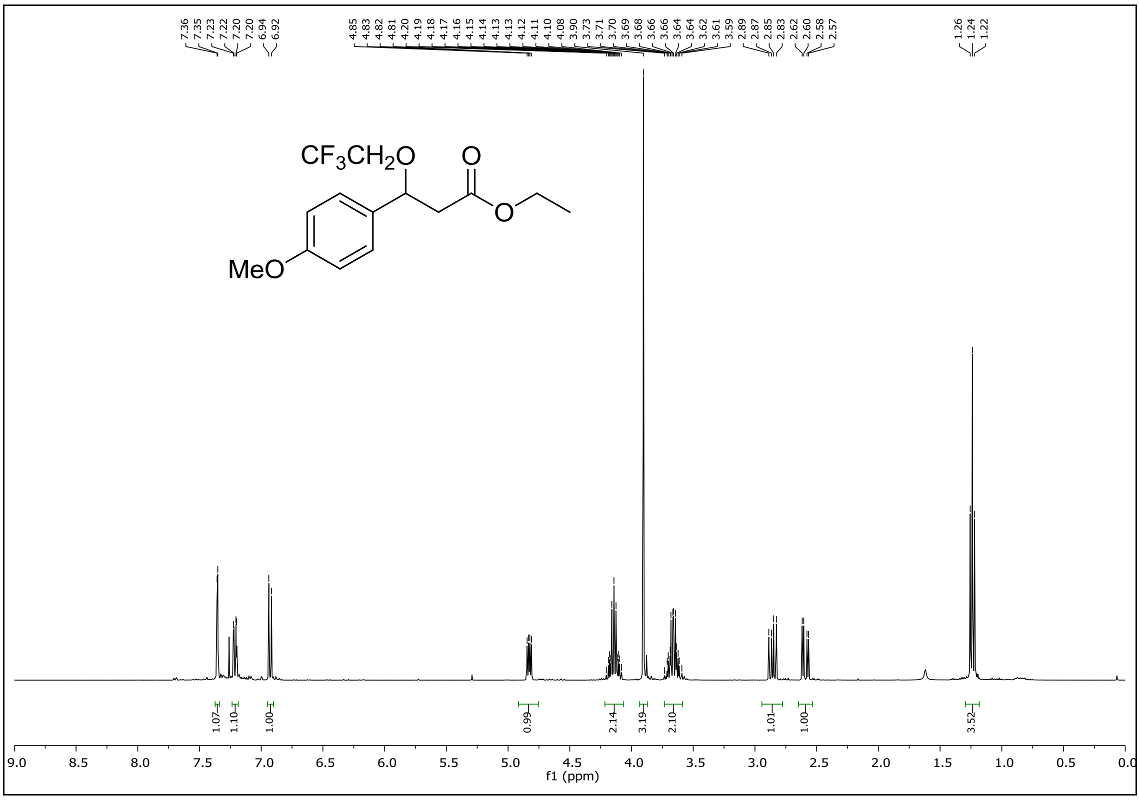
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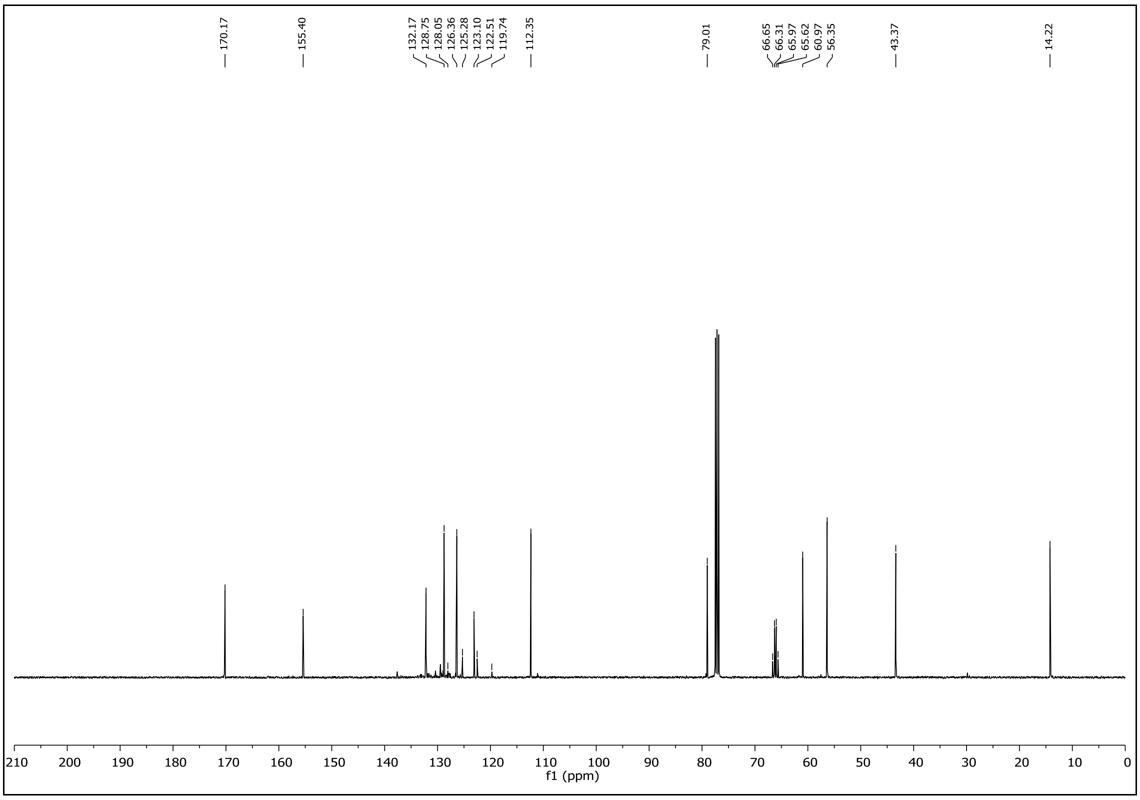
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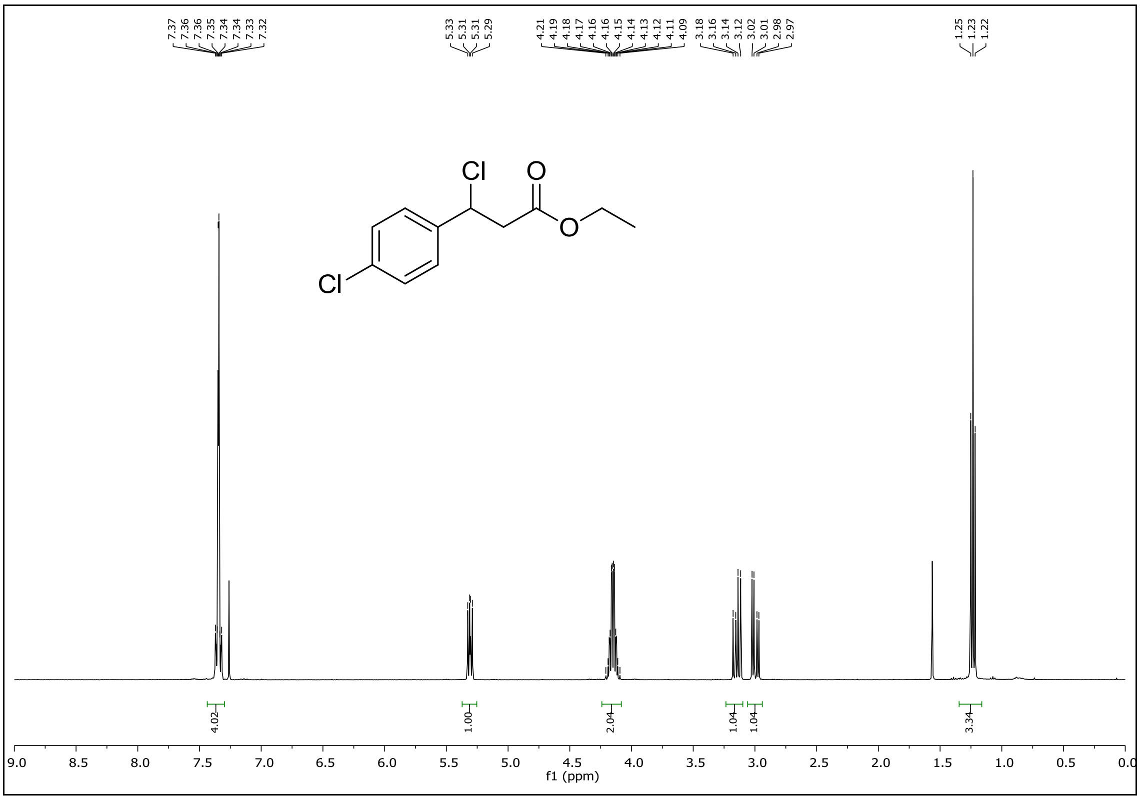
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Cl
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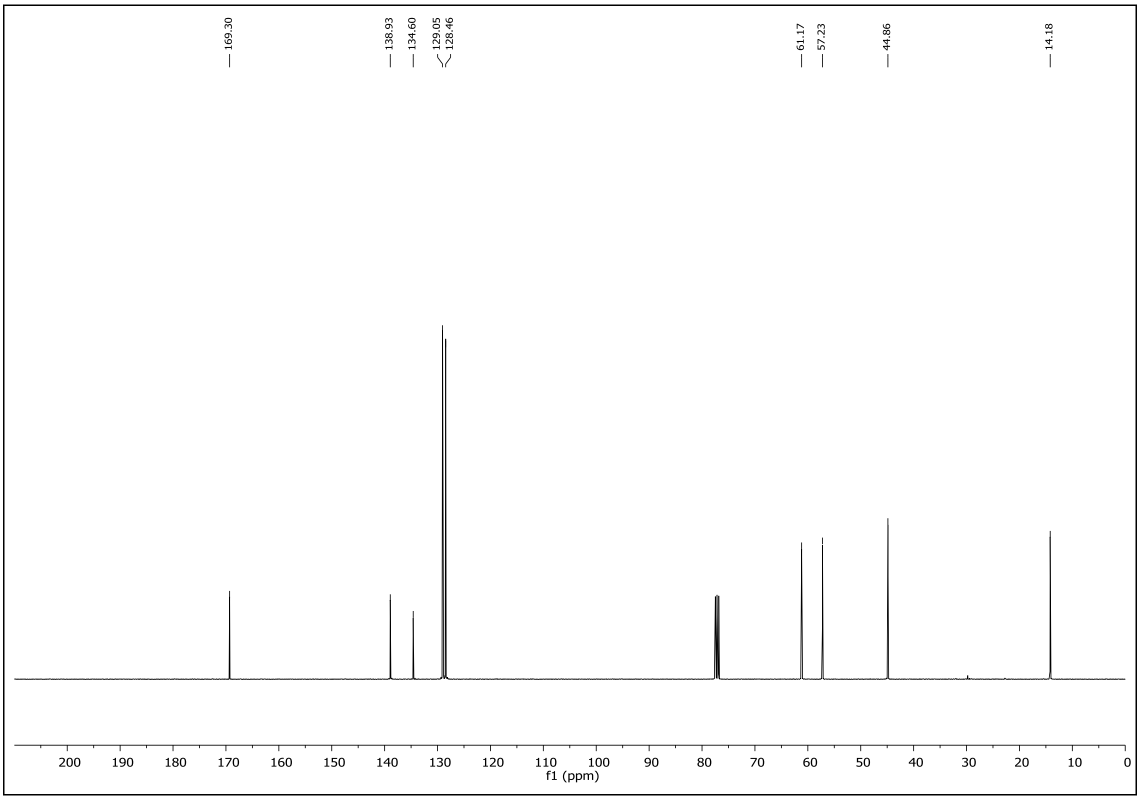
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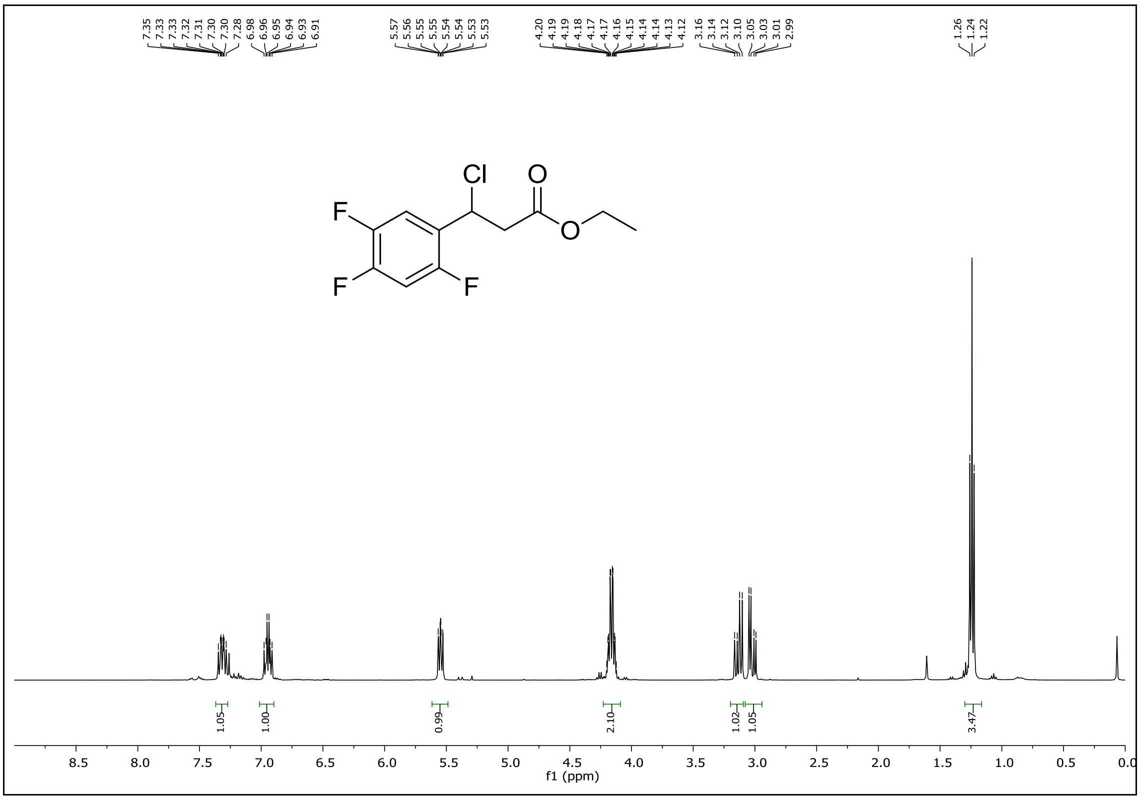
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F
F
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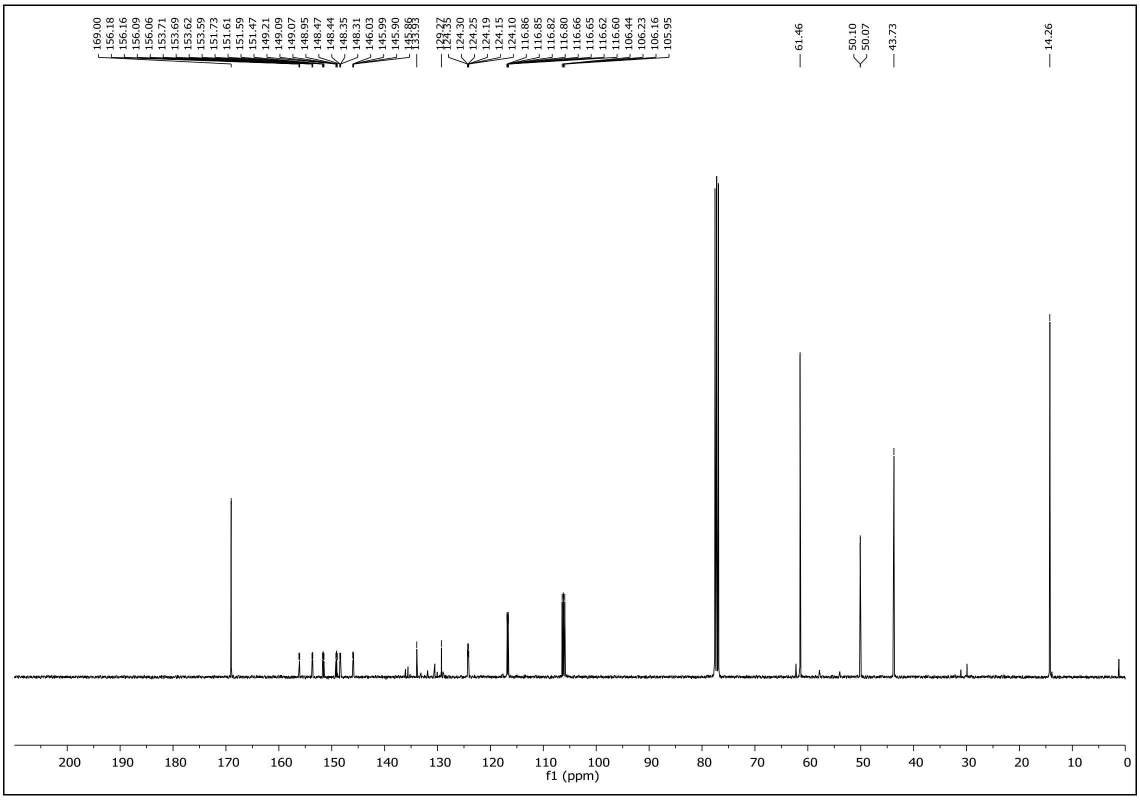
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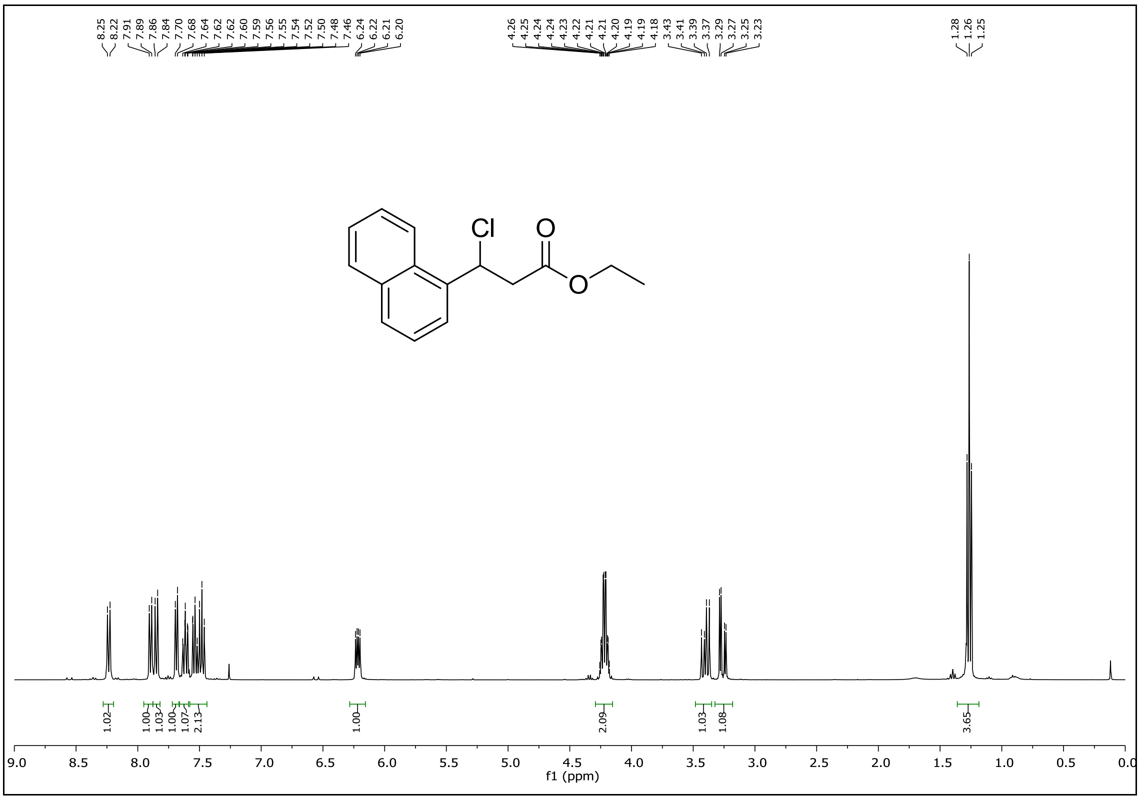
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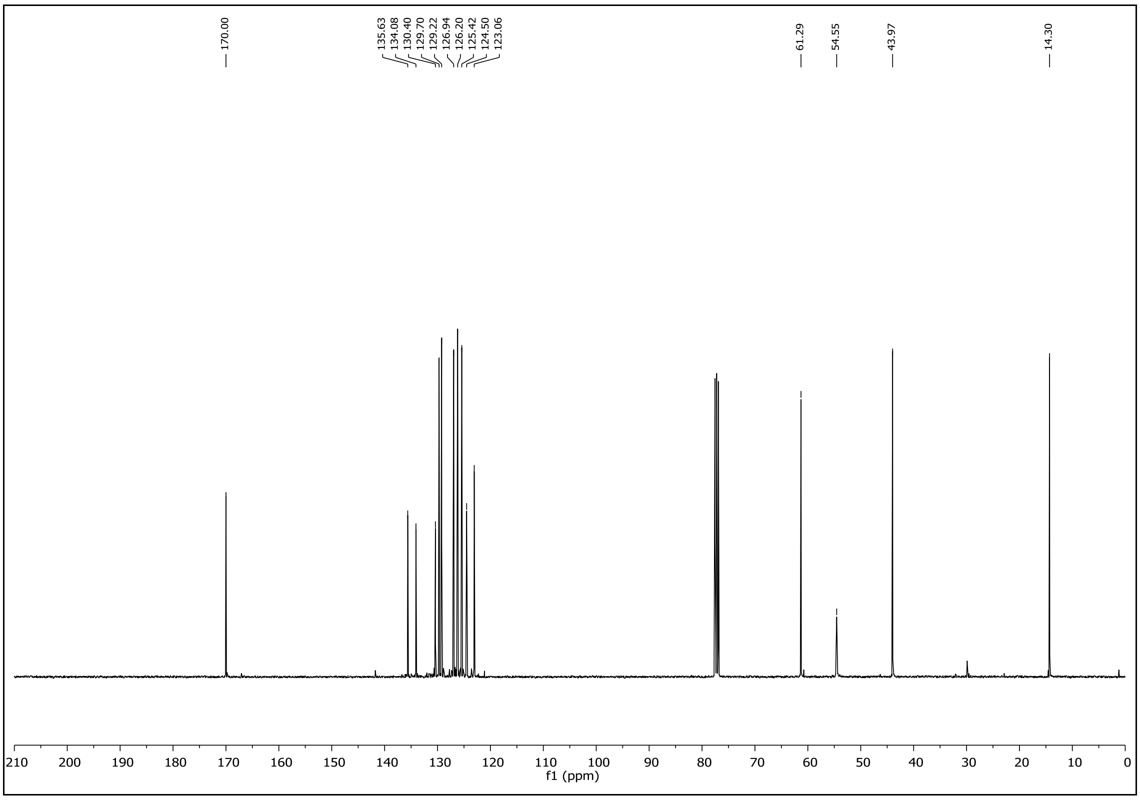
f1 (ppm)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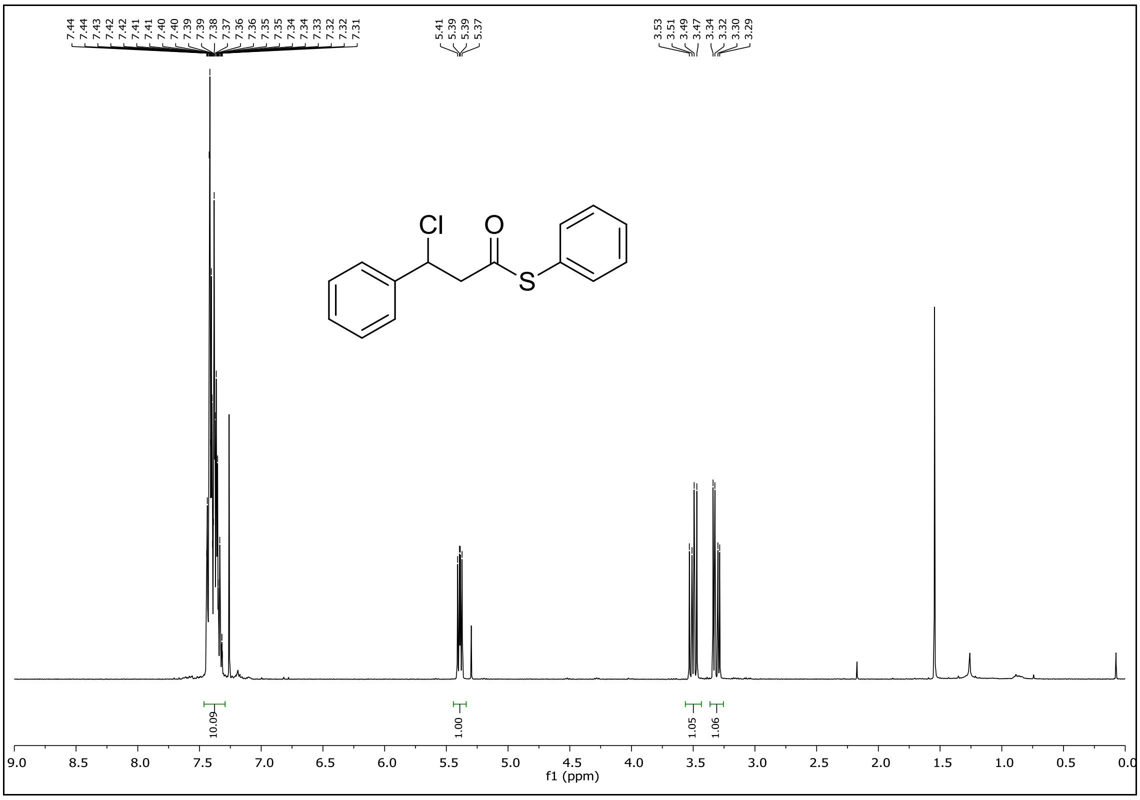
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3.29
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1.0
0.5
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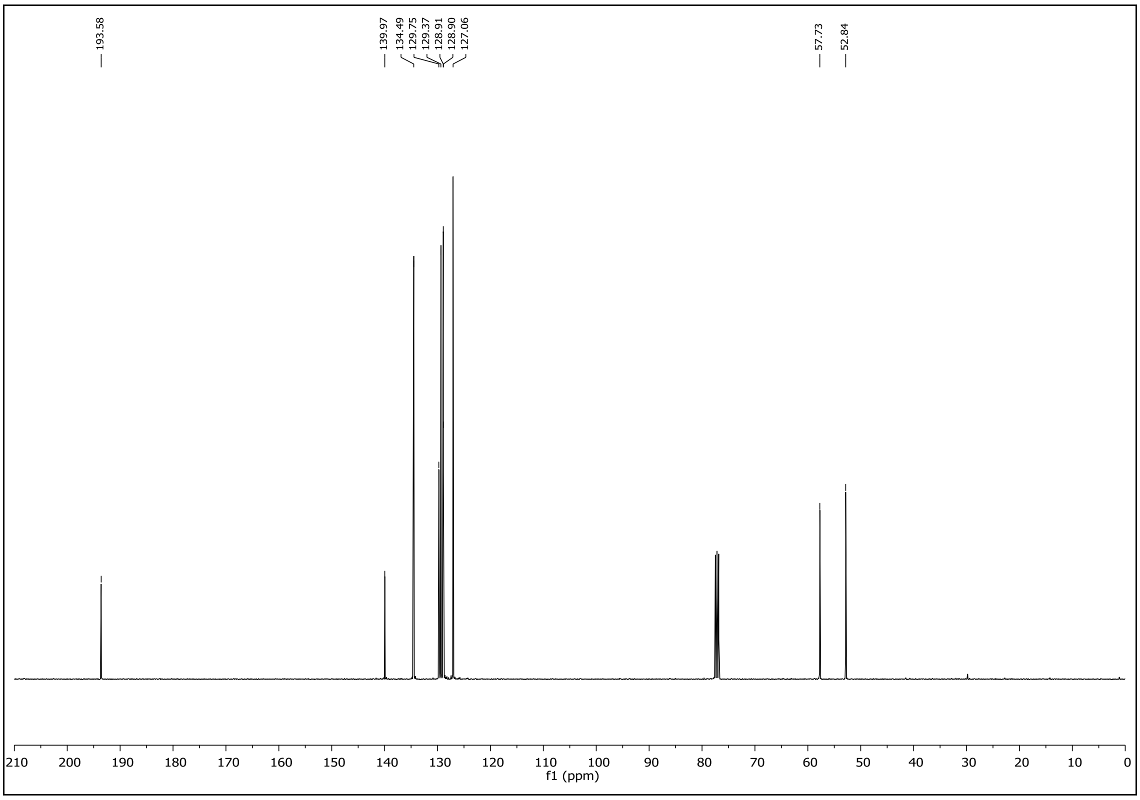
f1 (ppm)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Enantioselective Construction of Tetrasubstituted Stereogenic Carbons through Brønsted Base Catalyzed Michael Reactions: α′-Hydroxy Enones as Key Enoate Equivalent

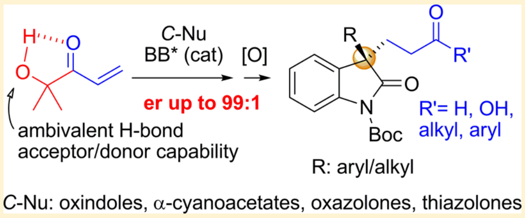
Eider Badiola,[†] Béla Fiser,[†] Enrique Gómez-Bengoa,[†] Antonia Mielgo,[†] Iurre Olaizola,[†] Iñaki Urruzuno,[†] Jesús M. García,*[,‡] José M. Odriozola,[‡] Jesús Razkin,[‡] Mikel Oiarbide,*[,†] and Claudio Palomo*[,†]

[†]Departamento de Química Orgánica I, Universidad del País Vasco, Manuel Lardizábal 3, 20018-San Sebastián, Spain

[‡]Departamento de Química Aplicada, Institute of Advanced Materials (INAMAT), Universidad Pública de Navarra, 31006-Pamplona, Spain

Ⓢ *Supporting Information*

ABSTRACT: Catalytic and asymmetric Michael reactions constitute very powerful tools for the construction of new *C*−*C* bonds in synthesis, but most of the reports claiming high selectivity are limited to some specific combinations of nucleophile/electrophile compound types, and only few successful methods deal with the generation of all-carbon quaternary stereocenters. A contribution to solve this gap is presented here based on chiral bifunctional Brønsted base (BB) catalysis and the use of *α*′-oxy enones as enabling Michael acceptors with ambivalent H-bond acceptor/donor character, a yet unreported design element for bidentate enoate equivalents. It is found that the Michael addition of a range of enolizable carbonyl compounds that have previously demonstrated challenging (i.e., *α*-substituted 2-oxindoles, cyanoesters, oxazolones, thiazolones, and azlactones) to *α*′-oxy enones can afford the corresponding tetrasubstituted carbon stereocenters in high diastereo- and enantioselectivity in the presence of standard BB catalysts. Experiments show that the *α*′-oxy ketone moiety plays a key role in the above realizations, as parallel reactions under identical conditions but using the parent *α*,*β*-unsaturated ketones or esters instead proceed sluggish and/or with poor stereoselectivity. A series of trivial chemical manipulations of the ketol moiety in adducts can produce the corresponding carboxy, aldehyde, and ketone compounds under very mild conditions, giving access to a variety of enantioenriched densely functionalized building blocks containing a fully substituted carbon stereocenter. A computational investigation to rationalize the mode of substrate activation and the reaction stereochemistry is also provided, and the proposed models are compared with related systems in the literature.



INTRODUCTION

Catalytic asymmetric conjugate addition reactions account as one of the most useful and atom economic approaches for the construction of new *C*−*C* and *C*−*X* bonds stereoselectively.[1] Major advances in the field have been triggered by the design and discovery of new chiral catalysts, both metal catalysts and organocatalysts, often in conjunction with the development of appropriate Michael acceptor templates.[2] The templates not only should provide gained chemical versatility to the resulting conjugate addition adducts, but also should contribute to attain optimal performance by the intervening catalyst in terms of reactivity and stereoselectivity. Ideally, strongly biased achiral templates may override otherwise observed substrate-dependent catalyst behavior, thus attenuating undesired fluctuations on the catalyst efficiency. This aid from properly design templates may result instrumental when difficult transformations, such as the enantioselective generation of tetrasubstituted carbon stereocenters, are pursued.

Among several categories of Michael acceptors, *α*,*β*-unsaturated carbonyl compounds are of prime synthetic significance. Adducts resulting from the conjugate addition of a nucleophilic reagent to *α*,*β*-unsaturated aldehydes, ketones, or carboxylic acid derivatives have all found a myriad of applications. In particular, certain carboxylic acid derivatives may afterward be converted into the corresponding aldehyde or ketone derivatives smoothly, making the former very versatile compounds. However, while both the addition reactions to *α*,*β*-unsaturated aldehydes and to ketones are well suited for iminium ion activation catalysis,[3] conjugate addition to the corresponding carboxylic acids and their derivatives is not. In this latter case, the most common activation mechanism relies upon coordination of the carbonyl group of the *α*,*β*-unsaturated carboxylic acid derivative to a Lewis acid (metal catalysis) or a H-bond donor species (organocatalysis). In this context, several two-point binding enoyl templates bearing an additional coordinating site (X, Figure 1a) tethered to the enoyl system have been developed. Compared with monodentate templates, which may lead to two degenerate C═O···metal complex geometries, thus complicating stereocontrol, bidentate templates can form chelates upon coordination to the metal as key organizational/activation element.[4] Similarly, bidentate enoyl

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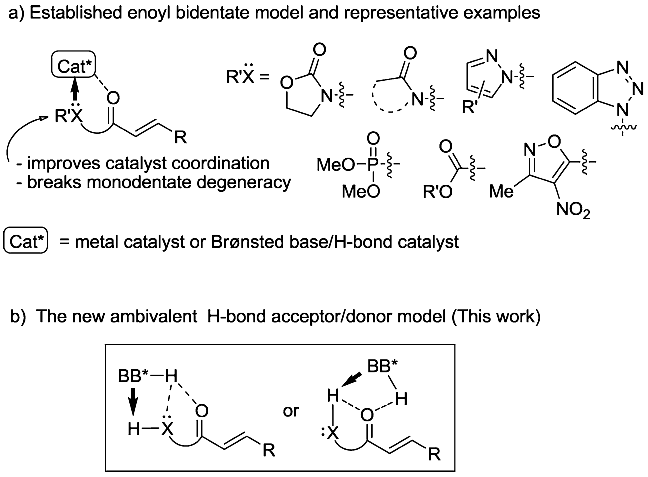

a) Established enoyl bidentate model and representative examples

b) The new ambivalent H-bond acceptor/donor model (This work)

Figure 1. Bidentate enoyl templates for asymmetric catalysis: (a) previously established and (b) the new proposal. (BB* = chiral Brønsted base.)

templates may perform superiorly in conjugate addition reactions triggered by bifunctional Brønsted base−H-bond catalysts, because of the likely occurrence of double H-bond interactions between the substrate and the catalyst (Figure 1a).[1,5] This type of Brønsted base catalysis has emerged as very advantageous, not only because many Brønsted bases (BB) are commercially available and/or readily accessible, but also because the pronucleophilic reagent (NuH) does not generally need to be preactivated in a separate step.[6] However, successful BB-catalyzed enantioselective *C*−*C* bond forming conjugate addition reactions are often limited to certain inherently reactive nucleophiles (particularly 1,3-dicarbonyl compounds) and/or electrophiles (particularly nitroalkenes),[7] while in many other instances, α,β-unsaturated esters being a notable example, sluggish reactivity or poor enantiocontrol is achieved. This situation becomes more problematic when generation of all-carbon quaternary stereocenters is pursued.[8] Both reactivity attenuation by steric constraints and difficulties in controlling face selectivity in prostereogenic trisubstituted trigonal centers make this goal to be a hot topic yet.

In this study, we describe a new enoyl template model for asymmetric organocatalysis in which the bidentate substrate might engage as either H-bond donor or acceptor or both (ambivalency) during activation by the bifunctional catalyst (Figure 1b). As representatives of such a model, we show that α'-hydroxy enones perform exceedingly well in the Brønsted base-catalyzed asymmetric conjugate addition of a range of soft *C*-nucleophiles leading to tetrasubstituted carbon stereocenters in very high enantioselectivity. The chemical versatility of thus obtained adducts is also illustrated and a theoretical interpretation of the results provided.

■ RESULTS AND DISCUSSION

Background and Working Hypothesis. While being a prominent synthetic operation toward 1,5-dicarbonyl frameworks, successful catalytic and asymmetric methods for the constructive assembly of all-carbon quaternary centers from monodentate α,β-enones are usually restricted to 1,3-dicarbonyl substrates and related active pronucleophiles. In this context, metal-catalyzed[9] enantioselective conjugate addition of 1,3-diketones, β-ketoesters, and α-aryl cyanoesters to acrolein or vinyl ketones (mainly methyl vinyl ketone) as the Michael acceptor have been reported by the groups of Ito,[10] Shibasaki,[11] Sodeoka,[12] and Jacobsen,[13] among others.[9]

In concurrent efforts under metal-free conditions, chiral Brønsted base-catalyzed conjugate additions of enolizable carbonyl compounds have also been explored after the pioneering work by Wynberg and co-workers.[6,14] Deng and co-workers have reported conjugate additions of α-substituted β-dicarbonyl compounds and α-aryl cyanoacetates to acrolein or methyl vinyl ketone promoted by a bifunctional Cinchona based catalyst,[15,16] while Jørgensen and co-workers documented the reaction of cyclic β-keto esters with both acrolein and methyl vinyl ketone using a nonbiaryl atropisomeric Cinchona-based catalyst.[17] More recently, Rodriguez, Constantieux, and co-workers[18] extended the Brønsted base catalysis approach to cyclic β-ketoamides as nucleophiles against methyl vinyl ketone. Notwithstanding these achievements, the realization of BB-catalyzed asymmetric conjugate additions involving more reluctant substrate combinations, such as less reactive enolizable carbonyl compounds and acryloyl equivalents, remains challenging. Thus, while some ester surrogates have been applied to Brønsted base-catalyzed conjugate addition reactions,[5] to the best of our knowledge, only in three cases the generation of all-carbon quaternary centers has been documented. In a significant work, Dixon and Rigby[5m] described highly enantioselective conjugate additions of cyclic β-keto esters to naphthyl thioacrylate and *N*-acryloyl pyrrol, respectively, using a modified cinchona alkaloid as bifunctional Brønsted base catalyst. When acyclic keto esters were used as nucleophiles, yields and selectivity diminished, a limitation also noticed by Bartoli, Melchiorre and co-workers[5n] who used maleimides as competent Michael acceptors. Also, β,γ-unsaturated acyl phosphonates[5f] have been reported to be effective enoate surrogates against reactive pronucleophiles including azlactones and 1,3-dicarbonyl compounds.

In the early 1980s Heathcock and co-workers demonstrated that α'-hydroxy ketones are convenient enoate equivalents in the context of aldol addition reactions,[19] since oxidative cleavage of the ketol moiety in the corresponding aldol adducts affords β-hydroxy carboxylic acids. Focused on this observation, research from these laboratories has led to the development of metal-catalyzed conjugate addition and cycloaddition reactions of simple α'-hydroxy enones,[20] as well as Brønsted acid-catalyzed Diels−Alder reactions of chiral α'-hydroxy enones,[21,22] methods that provide, after cleavage of the ketol moiety, products in the carboxylic acid oxidation state. In these developments, the ability of the ketol moiety for both 1,4-metal and 1,4-proton binding (Figure 2a)[23] revealed to be critical for success. Based on these precedents, we hypothesized that the H-bonding ability of the ketol moiety in α'-hydroxy enones may decisively influence reactions initiated by a proton-transfer event, such as the BB-catalyzed Michael reactions (Figure 2b).[24] Specifically, the substrate α'-hydroxy enone might participate as a two-point H-bond donor/acceptor (DA-model) or acceptor/acceptor (AA-model) partner in the transition state, a diverting design element that is lacking in previous enoyl templates.[5] To the best of our knowledge, α'-hydroxy enones have not been studied within the context of organocatalytic asymmetric bond-construction processes.[25,26]

Preparation of α'-Hydroxy Enones. The α-oxy enones **1** and **3** were readily prepared[27] from the addition of lithium methoxyallene **6** to acetone and 1,3-diphenylacetone **8**, respectively, and subsequent smooth one-pot hydrolysis of the resulting intermediates, as shown in Scheme 1. Alter-

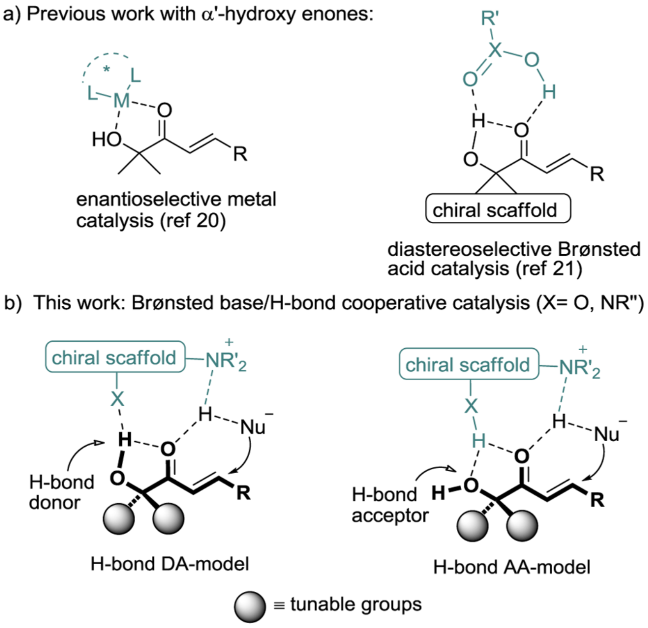
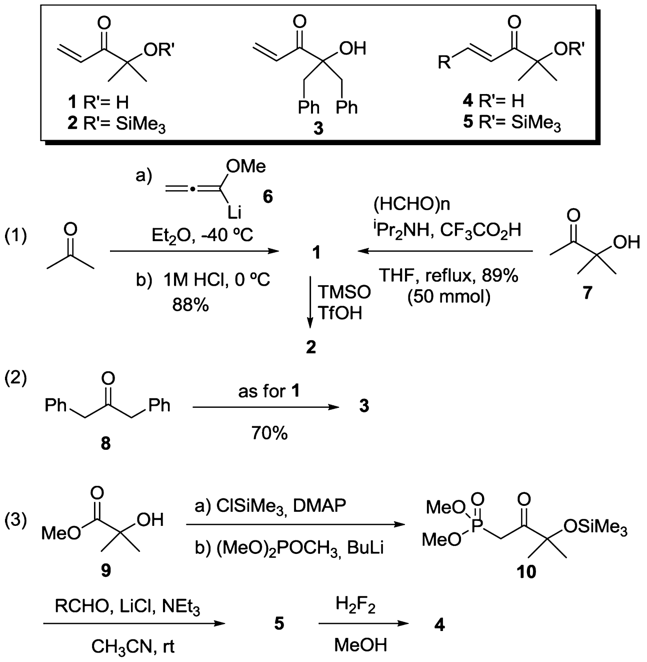


Figure 2. Two point binding α′-hydroxy enone templates for asymmetric catalysis.

Scheme 1. Preparation of α′-Hydroxy Enones[a]



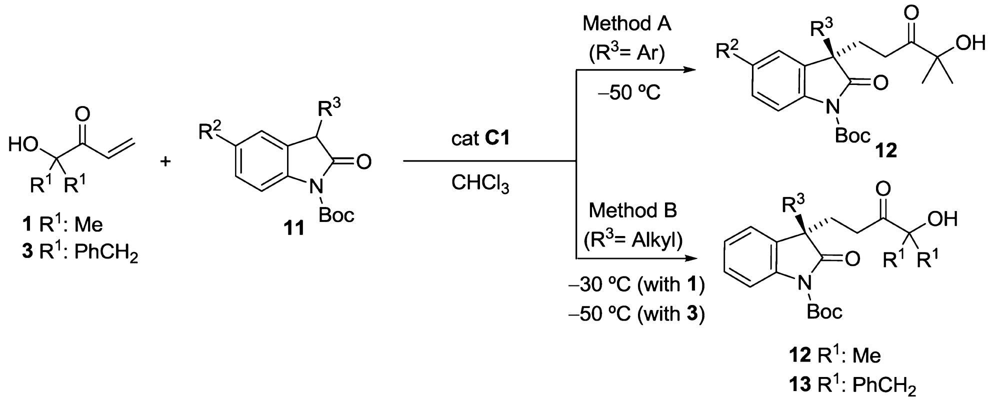
A R: $PhCH_2CH_2$
B R: CH_3CH_2
C R: $CH_2{=}CHCH_2CH_2$
D R: $CH_3CH_2CH_2$
E R: $CH_3(CH_2)_3CH_2$
F R: c-C_6H_{11}
G R: $(CH_3)_2CHCH_2$
H R: C_6H_5
I R: 4-MeC_6H_4
J R: 4-BrC_6H_4
K R: 3-$MeOC_6H_4$

[a] TMSO: *N*-(trimethylsilyl)-oxazolidin-2-one.

natively, enone **1** could also be prepared by the method of Connell et al.,[28] starting from the commercially available α-hydroxy ketone **7**. In both cases, compound **1** was obtained in yields between the range 80−90% at 50 mmol scale. Preparation of **2** from **1** is straightforward and quantitative by silylation with commercial *N*-trimethylsilyl oxazolidin-2-one (TMSO). For β-substituted enones **5**, the classical Horner−Wadsworth−Emmons olefination protocol from the β-keto phosphonate **10** was used. This phosphonate was in its turn prepared from commercial hydroxyester **9**.[29] Likewise, for β-aryl substituted α-hydroxy enones **4** (R = Ar), an aldol condensation of **7** with benzaldehydes may also be employed.[27]

Conjugate Additions of 3-Substituted Oxindoles. To assess the reactivity profile of these α′-hydroxy enones in Brønsted base catalysis, our study was initiated with the reaction of α′-hydroxy enone **1** and 3-substituted oxindoles. The oxindole structural motif is widely present within natural and synthetic bioactive molecules;[30] however, Brønsted base promoted reaction of 3-substituted oxindoles with alkyl vinyl ketones has met with limited success so far.[31,32] For example, it has been reported that methyl vinyl ketone (MVK),[31a,b] ethyl vinyl ketone,[31a] and phenyl vinyl ketone[31a] all provided enantiomeric excess (ee) values in the range of 60−70% in the reactions with 3-aryl oxindoles; the reactions with 3-methyl-, 3-isobutyl-, and 3-allyl oxindoles proceed with even lower ee's (of about 55%).[31c] In addressing these issues, and after screening several Brønsted base catalysts,[27] we found that the above addition reactions using **1**, conducted in the presence of 10 mol % $(DHQD)_2PYR$ (**C1**), afforded the corresponding adducts **12** in excellent yields and enantioselectivities. As the data in Table 1 show, under these conditions (−50 °C in $CHCl_3$ as solvent), oxindoles **11A–F** bearing 3-aryl substituents with either electron donating or electron withdrawing groups are tolerated with almost equal efficiency. Oxindoles with substitution at the aromatic ring also provided adducts with excellent chemical and stereochemical results. Likewise, the 3-methyl oxindoles **11Ga**, **11Gc**, and **11Gd**, which are valuable precursors of natural products, vide infra, were competent reaction partners to give the respective adducts **12Ga**, **12Gc**, and **12Gd** in good yields and enantioselectivities, typically 90% ee. Nevertheless, attempts to further expand this reaction to oxindoles bearing larger alkyl chains at the C3 position failed. Oxindoles **11H**, **11I**, **11J**, **11K**, and **11M** all provided the corresponding adducts **12** with poor enantioselectivity, typically 50% ee. While these results seem to be quite common for reactions involving 3-alkyl substituted oxindoles, very few attempts to address this deficiency have resulted with success.[32] In fact, few catalytic systems work well for both aryl- and alkyl-substituted oxindoles.[32d] Given the ready availability of α′-hydroxy enones, we focused on the α′-disubstitution pattern as an additional element for steric tuning. We were pleased to observe that the enantioselectivity was notably increased, typically from 50% ee up to 90% ee, by using α′-hydroxy enone **3**. As the results in Table 1 show, the reactions were tolerant with oxindoles bearing short, large, and ramified alkyl chains as well as alkyl chains with functional groups. These results are of special interest in that diverse functionality may be generated from a single common adduct. Thus, treatment of adducts **12Aa** and **12Gc** with $NaIO_4$ in $MeOH/H_2O$ provided the corresponding carboxylic acids **14** in yields of 98% and 94%, respectively, along with acetone as the only organic side product formed, Scheme 2. Alternatively, oxidative cleavage of adducts **13La** and **13Oa**, by treatment with periodic acid in this case, led to acids **14La** and **14Oa** in 87% and 90% yield, along with dibenzyl ketone which could be recovered and reused. On the other hand, the addition of the corresponding Grignard reagent or reduction of the carbonyl group followed by diol cleavage as above furnished the methyl and aryl ketones **15**/**16** and the aldehyde **17**, respectively, in good yields. Importantly, during the above manipulations, configurational integrity of

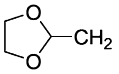
Table 1. Conjugate Additions of 3-Substituted Oxindoles to α′-Hydroxy Enones 1 and 3[a]

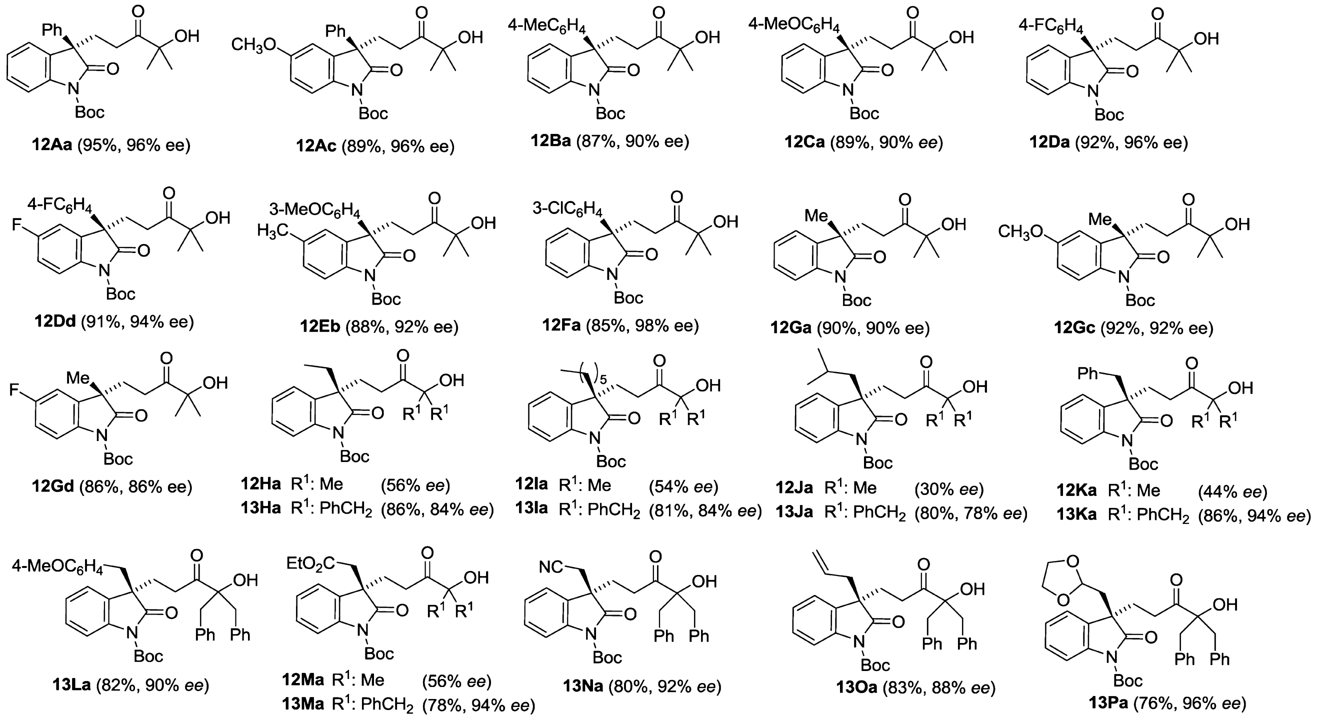


A R^3: Ph
B R^3: 4-MeC_6H_4
C R^3: 4-$MeOC_6H_4$
D R^3: 4-FC_6H_4
E R^3: 3-$MeOC_6H_4$
F R^3: 3-ClC_6H_4

a R^2: H
b R^2: Me
c R^2: MeO
d R^2: F

G R^3: Me
H R^3: CH_3CH_2
I R^3: $CH_3(CH_2)_5$
J R^3: $(CH_3)_2CHCH_2$
K R^3: $PhCH_2$
L R^3: 4-$MeOC_6H_4CH_2$
M R^3: EtO_2CCH_2
N R^3: $NCCH_2$
O R^3: CH_2=$CHCH_2$
P R^3:





12Aa (95%, 96% ee)
12Ac (89%, 96% ee)
12Ba (87%, 90% ee)
12Ca (89%, 90% *ee*)
12Da (92%, 96% ee)
12Dd (91%, 94% ee)
12Eb (88%, 92% ee)
12Fa (85%, 98% ee)
12Ga (90%, 90% ee)
12Gc (92%, 92% ee)
12Gd (86%, 86% ee)
12Ha R^1: Me (56% *ee*)
13Ha R^1: $PhCH_2$ (86%, 84% *ee*)
12Ia R^1: Me (54% *ee*)
13Ia R^1: $PhCH_2$ (81%, 84% *ee*)
12Ja R^1: Me (30% *ee*)
13Ja R^1: $PhCH_2$ (80%, 78% *ee*)
12Ka R^1: Me (44% *ee*)
13Ka R^1: $PhCH_2$ (86%, 94% *ee*)
13La (82%, 90% *ee*)
12Ma R^1: Me (56% *ee*)
13Ma R^1: $PhCH_2$ (78%, 94% *ee*)
13Na (80%, 92% *ee*)
13Oa (83%, 88% *ee*)
13Pa (76%, 96% *ee*)

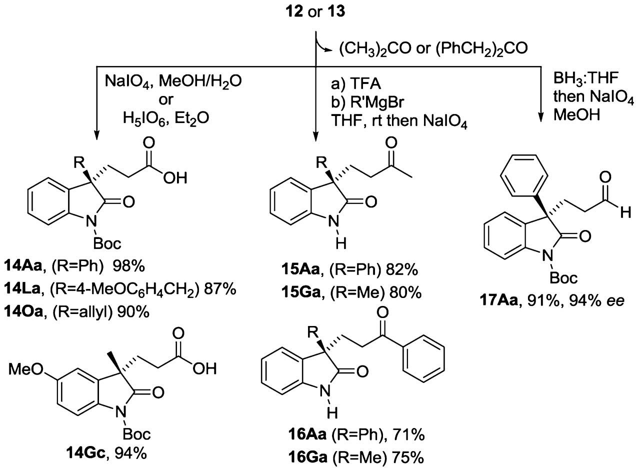
[a] The reactions were generally performed on a 0.30 mmol (for R^3 = Ar or Me) or 0.1 mmol (for R^3 = alkyl) scale in $CHCl_3$ (1.5 mL/mmol) using enone **1** (1.5 equiv) or **3** (3 equiv) and catalyst **C1** (10 mol % for **1**; 30 mol % for **3**). Yield of isolated product after chromatography. ee determined by HPLC analysis on chiral stationary phases.

newly generated tetrasubstituted stereogenic carbons in adducts was untouched as determined for aldehyde **17Aa** (94% ee) and acid **14Gc** (90% ee as determined in esermethole, vide infra). It is worth noting that the present method allows preparation of ketones such as **15Ga** and **16Ga**, formally derived from the less sterically demanding methyl-sustituted oxindoles, with enantioselectivities among the best reported until now.[31]

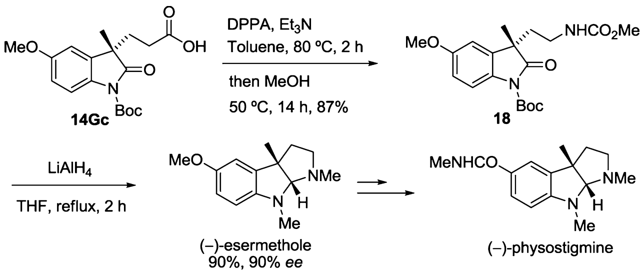
In addition, as far as we know, no asymmetric and catalytic conjugate addition of 3-substituted oxindoles to acrylate esters or their surrogates have been developed yet.[30,33] Our method may serve to remediate this deficiency by providing building blocks that can be easily transformed into biologically active compounds such as (−)-esermethole, Scheme 3,[34] an advanced intermediate for the synthesis of (−)-physostigmine.[35] Thus, Curtius rearrangement of carboxylic acid **14Gc** afforded carbamate **18**, which upon treatment with $LiAlH_4$ underwent reductive cyclization to (−)-esermethole of 90% ee.

The key role played by the $(CH_3)_2COH$ fragment of the template as a traceless activating group in the above reactions was clear from competitive experiments involving both **1** and methyl vinyl ketone (MVK), a simple enone lacking any group for additional H-bond coordination. Thus, when the reaction of oxindole **11Aa** was carried out with a 1:1 mixture of **1** and MVK in the presence of **C1** (10 mol %) at −50 °C, **12Aa** was the exclusive addition product obtained, without detecting any product from the addition reaction of **11Aa** to MVK. In

Scheme 2. Ketol Scission in Adducts 12



Scheme 3. Short Enantioselective Synthesis of (−)-Esermethole



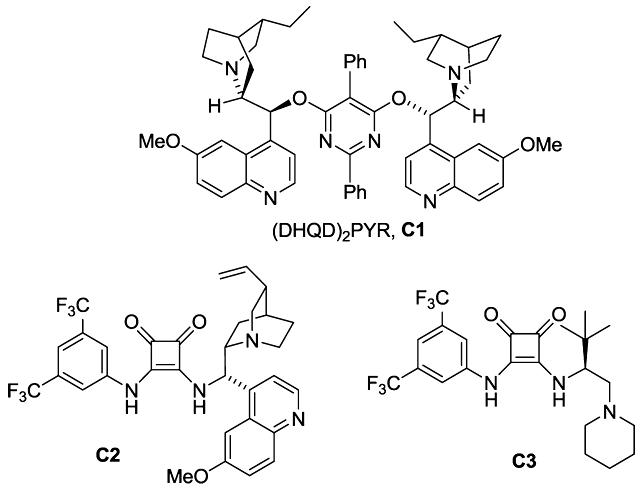


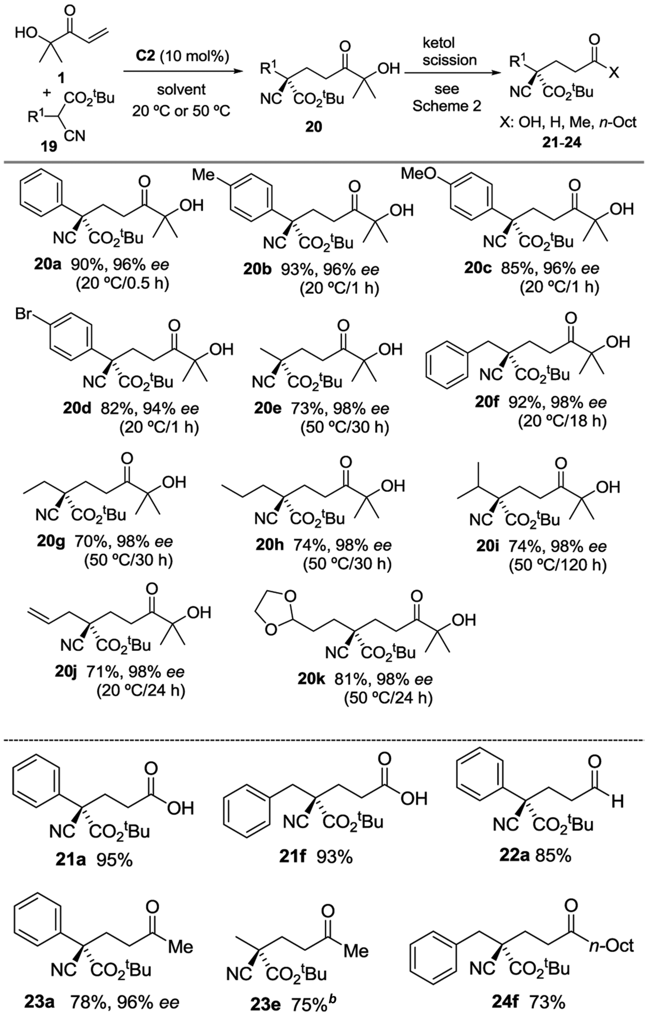
Figure 3. Catalysts employed within this work.

another experiment, the reaction between oxindole **11Aa** and MVK run at −30 °C in the presence of **C1** led, after 48 h, to 35% conversion only, with an isolated product of 50% ee.

Conjugate Additions of Cyanoacetates. Encouraged by these results, we next investigated the reaction of α'-hydroxy enones with α-substituted cyanoacetates.[36,37] The problems experienced in achieving efficient chirality transfer in metal catalyzed conjugate additions with these pronucleophiles have been ascribed to the fact that cyanoacetates are incapable of two-point binding.[38] We reasoned that the capacity of α'-hydroxy enones for two-point binding (Figure 2) may ameliorate this deficiency. Indeed, we found that **1** was effective in the Brønsted base catalyzed reaction with not only α-aryl, but also α-alkyl cyanoacetates, a subclass of substituted cyanoacetates previously documented to be poorly reactive substrates,[37] particularly against alkyl vinyl ketones.[37a] After evaluation of a survey of different Brønsted bases, including **C1**, the squaramide family of catalysts pioneered by Rawal and co-workers[39] probed the most effective in these instances. Among them, catalyst **C2**[40] (Figure 3) resulted optimal for the reaction between **1** and a range of both α-aryl and α-alkyl *tert*-butyl cyanoacetates **19**. In general, the reaction with α-aryl cyanoacetates **19a−d** was performed at room temperature using 3 equiv of enone **1** to afford, after 1 h, adducts **20a−d** with excellent yields independently of the nature of the aromatic ring substitution. In contrast, most α-alkyl cyanoacetates tested showed decreased reactivity with reaction times of about 120 h required for complete conversion under the above conditions. However, by using 3-fold excess of the latter and rising the temperature to about 50 °C, full conversions of products **19e−k** were attained within about 30 h or less, with very high yields of isolated product and essentially perfect enantioselectivity obtained. Again, chemical manipulation of the ketol unit in adducts **20** using simple Grignard technology and/or reduction/oxidation protocols, as in Scheme 2, provided a straightforward entry to the corresponding carboxylic acids **21**, aldehydes **22**, and ketones **23**/**24**. Comparison of optical rotation value of product **23e** (see Table 2, footnote b) with literature data[10] served to set the configuration of the products and hence the stereochemical course of the above catalytic reactions. As noted above enantioselective synthesis of products like **21−24** through direct catalytic Michael reactions remains challenging. Once more, the design enone **1** demonstrated to be instrumental in achieving these levels of reactivity and selectivity. For example, when an equimolar mixture of cyanoacetate **19a**, enone **1**, and MVK was stirred at 20 °C for 30 min in the presence of 10 mol % **C2**, a 12:1 mixture of **20a** and the addition adduct from MVK, respectively, was obtained. Likewise, parallel reactions of other typical Michael acceptor templates, i.e. *N*-acryloyl oxazolidinone or *N*-acryloyl pyrazole, with cyanoacetate **19e** under the above conditions were sluggish (less than 55% conversion after 120 h at room temperature for the two cases).

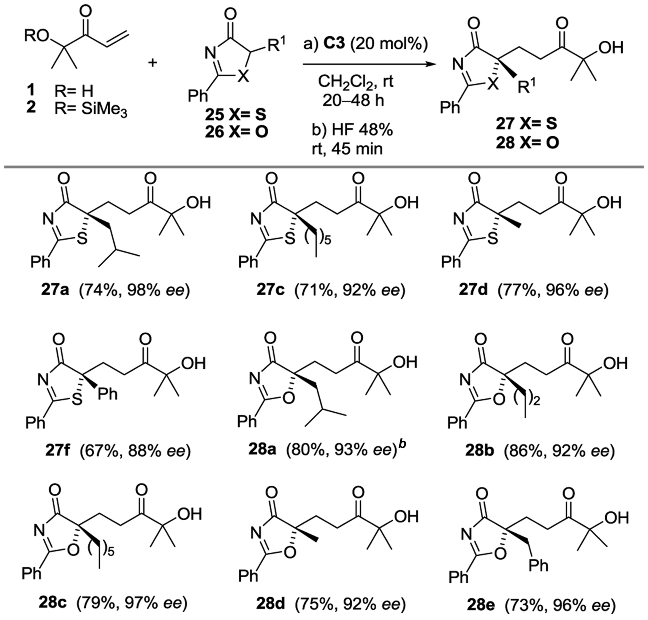
Conjugate Additions of Heteroatom-Bearing Soft Carbon Nucleophiles. Besides all-carbon quaternary stereocenters, tetrasubstituted stereogenic carbons bearing a sulfur, oxygen or nitrogen heteroatom are also interesting yet difficult products to obtain as single enantiomers. Therefore, we decided to investigate the capacity of our template model to participate in Brønsted base-catalyzed conjugate additions of several heteroatom-bearing soft carbon nucleophiles. For this study 5*H*-thiazol-4-ones **25**[41] and 5*H*-oxazol-4-ones **26**[42,43] were initially selected and we found that reaction of thiazolone **25a** and oxazolone **26a** with α'-hydroxy enone **1** did proceed in the presence of several Brønsted bases, including **C1** and **C2**, but with very poor enantioselectivity. Further exploration led us to examine the modified enoyl template **2**, prepared by simple silylation of the hydroxyl group in enone **1**. To our pleasure, the reaction of 5*H*-thiazol-4-ones **25** and enone **2** catalyzed by **C2** in dichloromethane at −20 °C provided, after desilylation of the resulting intermediates, the corresponding addition products **27** in good yields and ee's up to 98%. The parent 5*H*-oxazol-4-ones **26** participated with equal chemical efficiency in the reaction with enone **2**. For example, under the above conditions, **26a** provided **28a** in 85% yield albeit in 73% ee.

Table 2. Conjugate Addition of α-Substituted *tert*-Butyl Cyanoacetates 19 to α′-Hydroxy Enone 1 Promoted by C2^a



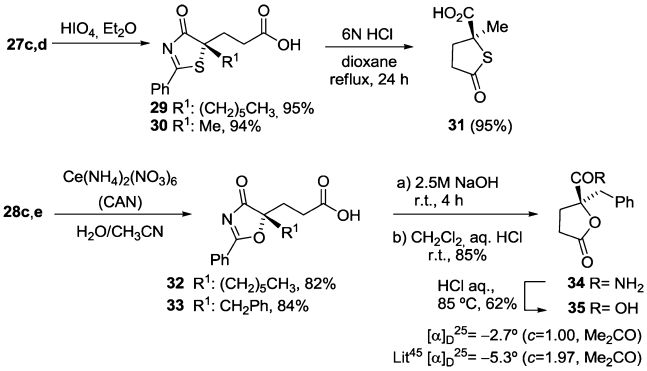
^{a}The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 at 20 °C or in $CHCl_3$ at 50 °C. Yield of isolated major isomer after chromatography. ee determined by HPLC. $^b[\alpha]_D^{22}$ = +3.9 (*c* = 1, $CHCl_3$); lit.[10] $[\alpha]_D^{20}$= +2.7 (*c* = 5, $CHCl_3$, 81% ee).

Table 3. Conjugate Addition of 5*H*-Thiazolones 25 and 5*H*-Oxazolones 26 to α′-Silyloxy Enone 2^a



^{a}The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.9 mL) using 1.5 equiv of enone **2**. For thiazolones **25**, reactions were conducted at −20 °C and for oxazolones **26** at rt. Yields after chromatography. ee determined by HPLC. ^{b}73% ee from catalyst **C2**.

Scheme 4. Elaboration of Thiazolone and Oxazolone Adducts 27 and 28



This result was further improved by using catalyst **C3**[44] (Figure 3), and the reaction between **2** and oxazolone **26a** performed at room temperature afforded, after desilylation of the resulting intermediate, adduct **28a** in 80% yield and 93% ee.

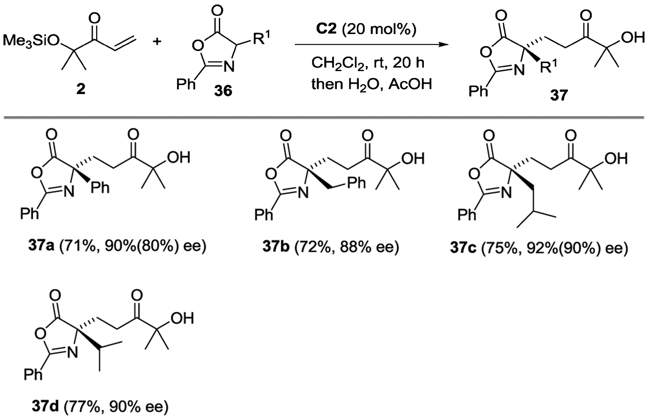
In general, excellent yields and enantioselectivities were achieved for a survey of thiazolones and oxazolones bearing either short, large, or ramified alkyl chains at the heterocyclic ring (Table 3). While these reactions were typically carried out in the presence of 20 mol % of catalyst, the catalyst loading could be reduced to 10 mol % provided the reactions were carried out at higher temperature. For example, products **28a** and **28b** were obtained in essentially same chemical yields and stereoselectivities as above when the corresponding reactions were performed in $CHCl_3$ at 40 °C during 30−40 h. Clearly, these results show that the α′−hydroxy enone template may be easily modified to better adapt to different substrate/catalyst combinations.

Transformation of adducts **27** and **28** into the corresponding carboxylic acids **29**, **30**, **32**, and **33**, Scheme 4, was easily achieved by treatment with periodic acid in the case of thiazolone adducts **27**, and with cerium ammonium nitrate (CAN) in the case of oxazolones **28**. Subsequent transformation of adduct **30** into the thiolactone **31**, as well as adduct **33** into the lactone derivative **34**, by simple ring opening under mild acid and/or basic conditions, illustrates the utility of the method. In addition, formation of known lactone **35**[45] from **34** served to establish the stereochemical course of the reactions. It should also be noted that both **25a** and **26a** upon treatment with either methyl acrylate or *tert*-butyl acrylate under the above conditions did not provided the corresponding Michael adducts.

Further exploration of the broad scope of α-silyloxy enone **2** showed that α-substituted azlactones, 4*H*-oxazol-5-ones, also fit well. For example, Table 4, the reaction between azlactones **36** and enone **2** in the presence of the catalyst **C2** or **C3** led, after desilylation of the intermediate adducts, to the corresponding products **37** with good yields and ee's. In each case, reactions proceeded with high site selectivity and no products from reaction at the C_2-position of the azlactone ring were observed.[46]

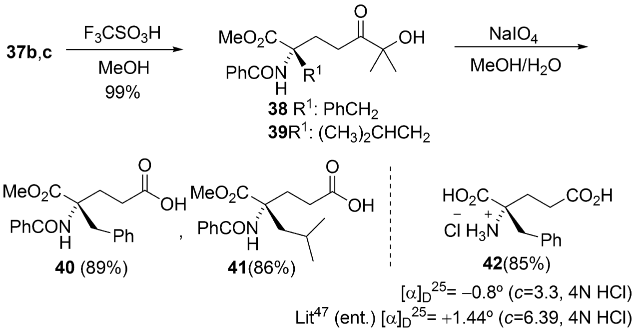
Elaboration of thus obtained azlactone adducts afforded useful building-blocks. For instance, Scheme 5, azlactone ring opening in **37b,c** to afford the corresponding compounds **38** and **39**, and subsequent ketol elaboration, provided acids **40** and **41**, respectively. The former was then transformed into the known glutamic acid derivative **42**[47] as a proof of the stereochemical course of the catalytic reaction.

Table 4. Conjugate Addition of Azlactones[a]



[a] The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.6 mL) using 3.0 equiv of enone **2**. Yield of isolated products after chromatography. ee determined by HPLC. In parentheses are ee's from catalyst **C3** (10 mol %).

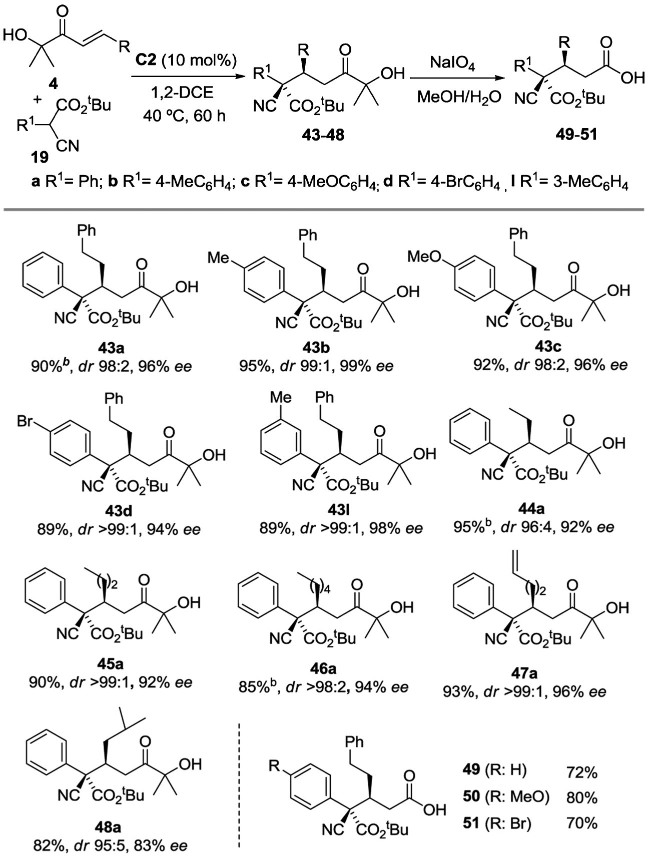
Scheme 5. Elaboration of Adducts to α,α-Disubstituted Glutamic Acid Derivatives



Reactions with β-Substituted α-Oxy Enones: Generation of Adjacent Quaternary/Tertiary Stereocenters. Given the results attained with the α-oxy vinyl ketones **1** and **2**, we wondered whether this template model would be effective to generate a quaternary carbon adjacent to a tertiary stereogenic center, a synthetic task that generally presents added difficulties. To this end, we selected the reaction of α-substituted cyanoacetates owing to the inherent challenges associated with this kind of pronucleophiles, vide supra. In this context, Peters has recently addressed this issue and provided a solution to the case of reactions involving cyclic enones, that is, cyclohexenone, using metal catalysis.[38a] On the other hand, only one example of Michael reaction of α-substituted cyanoacetates with β-substituted alicyclic enones has been documented, based on salen complex catalysis.[38d]

It was gratifying to observe that α-aryl cyanoacetates **19a–d** and **19l** reacted with β-alkyl substituted α-hydroxy enones **4A–E** to furnish adducts **43–47** in good yields, Table 5. The reactions were carried out in 1,2-dichloroethane at 40 °C, and generally essentially one diastereomer was produced in excellent enantiomeric excess. As exceptions, β-substituted enones **4F** and **4H**, bearing the cyclohexyl and phenyl groups, respectively, were ineffective under these conditions, while **4G** provided **48a** in good yield but diminished stereoselectivity. On the other hand, α-alkyl cyanoacetates were unreactive and did not provide the corresponding adducts. Despite these limitations, which, in their turn, confirm the difficulties associated with these problematic pronucleophiles, the method represents the first Michael addition of α-substituted cyanoacetates to β-alkyl enones catalyzed by a chiral Brønsted base, and confirms once more the excellent behavior of α′-hydroxy enones as Michael acceptors. In this respect, while no reaction was observed from **19a**, **19c**, and **19d** with methyl 5-phenylpent-2-enoate in the presence of **C2**, oxidative cleavage of **43a**, **43c**, and **43d** provided the desired carboxylic acids **49–51**. We also examined the **C2** catalyzed reaction between cyanoacetate **19a** and *trans*-3-nonen-2-one **52**, which lacks the α′-hydroxy group (Scheme 6). The reaction proceeded, but required 7 days to reach 95% of conversion and the product was formed as an 80:20 mixture of diastereomers with only modest enantioselectivity for the major isomer **53**. In sharp contrast, the reaction between **19a** and α′-hydroxy enone **4E**, as

Table 5. Conjugate Addition of Cyanoacetates to β-Substituted α-Hydroxy Enones[a]



[a] The reactions were performed on a 0.30 mmol scale in 1,2-DCE (1.2 mL) using 3.0 equiv of enone **4**, at 40 °C otherwise stated. Yield of isolated products after chromatography. ee determined by HPLC. dr determined by ^1H NMR or HPLC. [b] Reaction carried out at 50 °C.

Scheme 6. Conjugate Addition of α-Substituted Cyanoacetates to Simple Enones and an Indirect Solution to the Low Inherent Stereoselectivity

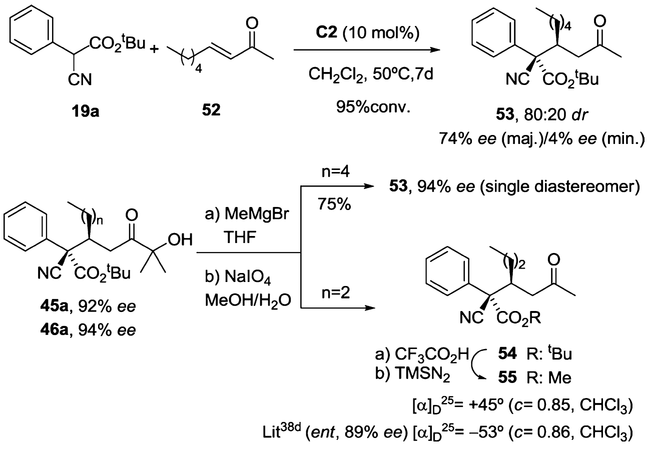
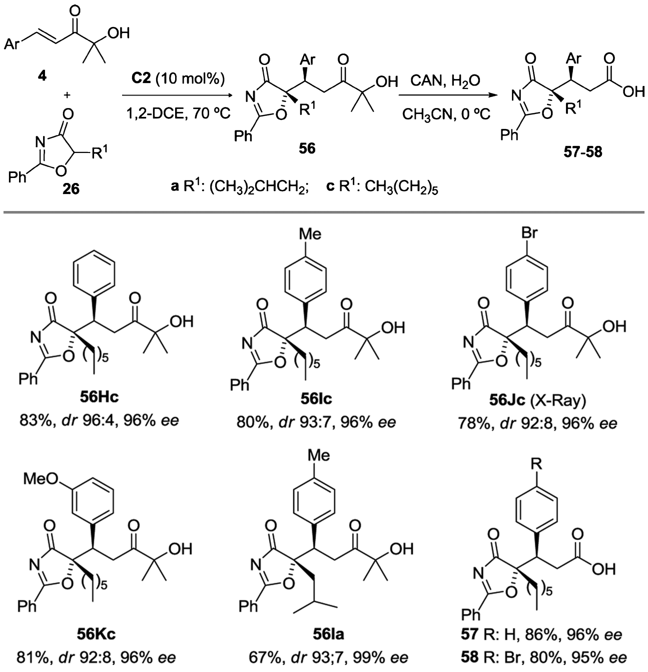


Table 6. Conjugate Addition of Oxazolones to β-Substituted α-Hydroxy Enones[a]



[a]The reactions were performed at 70 °C on a 0.15 mmol scale in dichloroethane (0.45 mL) using 3.0 equiv of enone **4**. Yield of isolated products after chromatography. Diastereomeric ratios determined by ^{1}H NMR (300 MHz) on the crude reaction products and confirmed by HPLC. ee determined by HPLC analysis on chiral stationary phases (for compounds **57** and **58**, after derivatization to their methyl esters).

mentioned above, gave **46a** as essentially single diastereomer in 94% ee (Table 5), which enables an alternative and highly stereoselective entry to product **53** via usual alkylation and oxidative scission. Similarly, **45a** could be converted into the methyl ketone **54** and, upon subsequent transesterification, the corresponding methyl ester **55**, which exhibited essentially identical ^{1}H and ^{13}C NMR spectra to those reported in the literature,[38d] but opposite optical activity, thus confirming the stereochemical assignments for the adducts.

Oxazolones **26** also participated in the reaction with β-substituted enones **4** to give the corresponding α,α-disubstituted α-hydroxy acid precursors with an adjacent tertiary stereocenter, Table 6. However, in contrast to the case of cyanoacetates noted above, the reactions of oxazolones **26** worked well only with β-aryl enones to afford the corresponding addition products **56**. The reactions with β-alkyl enones were unproductive and the starting materials could be recovered unchanged. From these results, it is clear that for these types of substrate combinations leading to adjacent quaternary/tertiary stereocenters, there might be strong steric interactions that may justify the observed variability. Configuration of adduct **56Jc** was established by a single crystal X-ray analysis and that of the remaining adducts by assuming a uniform reaction mechanism. Additionally, conversion of **56** into the carboxylic acids **57** and **58** could be accomplished by using CAN as the optimum oxidant.

Computational Studies. With these experimental data in hand, it seemed clear that α'-oxy enones exhibit some unique reactivity as compared with ordinary enones, that is, MVK. Both higher reactivity and improved levels of enantioselectivity are observed in the BB-catalyzed reactions studied. Similarly, our experimental results indicate a distinct behavior of α'-oxy enones as compared with other typical enoyl templates previously reported for the BB-catalyzed enantioselective generation of quaternary stereogenic carbon centers. More specifically, the catalyst-controlled conjugate addition of α-substituted cyanoacetates is, as mentioned before, sluggish with the majority of Michael acceptors, while it works well with α'-oxy enones. With the aim to bring some light on such distinguishing behavior, we decided to study computationally[48] the case of the conjugate addition reactions of cyanoacetates. MVK and the two α'-oxy enones **1** and **59** were selected as the model Michael acceptors, and the relationship between their reactivity and structure was examined first. In agreement with our working hypothesis, calculations show that the intramolecular H-bond activation in **1** and **59** induces a change in a series of electronic parameters (Figure 4), explaining their higher reactivity in comparison with MVK. In particular, the electrophilicity index ω[49] for both **1**/**59** (2.0 eV) is higher than that for MVK ($\omega = 1.6$ eV), which is consistent with the lower energy of LUMO for **1** and **59** (−1.9 eV) as compared with the LUMO of MVK (−1.5 eV), and also the more positive

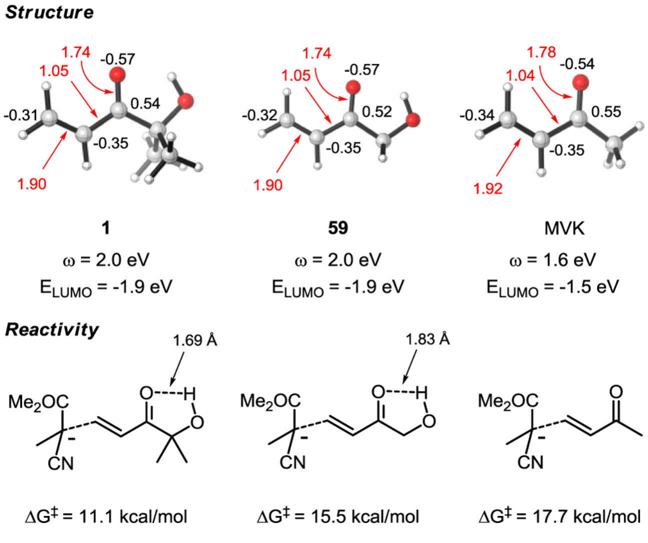


Figure 4. Structure−reactivity relationship.

character of the β-carbon of **1** (NPA charge of −0.31) than the corresponding β-carbon of MVK (−0.34). These values correlate well with the Wiberg bond index for **1** (1.90) and MVK (1.92), respectively, indicating the diminished double bond character of the enone C═C bond in **1**.

Subsequently, the activation energy of the reaction of these three Michael acceptors with methyl α-methylcyanoacetate was computed. This barrier resulted significantly lower for α′-hydroxy enone **1** (11.1 kcal/mol) than for MVK (17.7 kcal/mol). On the other hand, although the electronic parameters of both α′-hydroxy enones **1** and **59** do not differ significantly from one another (see above), the reaction involving the latter presents an activation energy 4.4 kcal/mol higher than the reaction with **1**. This additional stabilization of the transition state (TS) for the reaction with **1** as compared with **59** is consistent with the shorter intramolecular hydrogen bond in the former case (1.69 vs 1.83 Å, Figure 1) and might be ascribed to a favorable Thorpe−Ingold effect[50] imparted by the two geminal methyl substituents in **1**.

The origin of the stereoselectivity in the **C2**-catalyzed reaction between hydroxy enone **1** and α-cyanoacetates was addressed next, and the first question to elucidate was the preferred H-bond pattern formed between the catalyst and both substrates in the TS corresponding to the C−C bond-forming step. In this respect, up to (at least) three different ternary complexes (**A**−**C**, Figure 5) have been proposed for reactions involving noncovalent cooperative activation of the intervening nucleophile and electrophile, typically by a bifunctional thiourea (or squaramide)-tertiary amine catalyst.[51] Therefore, the question of whether or not a unified H-bond network model (**A**, **B**, **C**, other) could be applied to different reactions within this catalysis category seems to be still open and more data are desirable. In our case, we computed the reaction leading to adduct **20e** (Table 2), and despite much effort we were unable to find any plausible transition structure of type **B** among the several H-bond combinations studied.[52] From a look to the geometries of the resulting complexes, it seemed that once cyanoacetate is H-bonded to the catalyst there is not space available for the electrophile to interact with the same catalyst molecule. Thus, the structure closest to **B** we could find involves attack of the H-bonded cyanoacetate anion to the non complexed enone.[53] On the other hand, a single structure similar to model **C** was also found; however, it was predicted to be unrealistic due to its high activation energy.

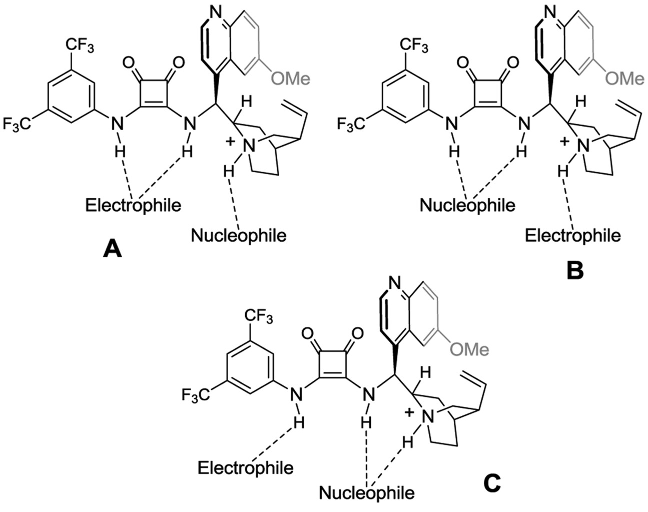


Figure 5. Three alternative substrate−catalyst combinations.

In its turn, four feasible structures of type **A** (**TS-R$_1$**, **TS-S$_1$**, **TS-R$_2$**, **TS-S$_2$**, Figure 6) were located, in which the α′-hydroxy enone carbonyl is double H-bonded to the squaramide NH groups, while the protonated quinuclidine NH$^+$ might bind to either the CN or the ester group of the cyanoacetate moiety. **TS-R$_1$** is the lowest in energy and correctly explains the formation of the major isomer observed experimentally.[54] The next most feasible structure is **TS-S$_1$**. Interestingly, in both cases, the CO$_2{}^t$Bu is involved in H-bonding with the catalyst NH$^+$ moiety, while the methyl (**TS-S$_1$**) and the cyano group (**TS-R$_1$**) are, respectively, almost eclipsed with the enone double bond. The energy difference between these two structures is 2.8 kcal/mol at the M06-2X/6-311+G** computational level,[55] with the preference of **TS-R$_1$** being attributable to a larger destabilizing effect of pseudoeclipsed methyl (dihedral angle 21.9°) than pseudoeclipsed cyano (dihedral angle 33.5°). The remaining two structures, **TS-R$_2$** and **TS-S$_2$**, both involving a NH$^+$···NC interaction, lye 6.1 and 6.4 kcal/mol higher in energy than **TS-R$_1$**, respectively. From these results, some tentative conclusions may be drafted: (i) in the studied catalytic reactions, the ketol moiety of the acceptor α′-hydroxy enone plays a key role in both decreasing reaction energy barriers; (ii) among the several possible H-bond combinations for the ternary nucleophile−catalyst−electrophile complex, type **A**[51a−e] is preferred, with the squaramide group interacting with the α′-hydroxy enone (electrophile activation), and the protonated quinuclidine interacting with the cyanoacetate anion (nucleophile activation); (iii) given previous data in the literature in favor of models of type **B**[51f−k] and **C**[51l] for related catalytic reactions, we believe that a unified model cannot accommodate

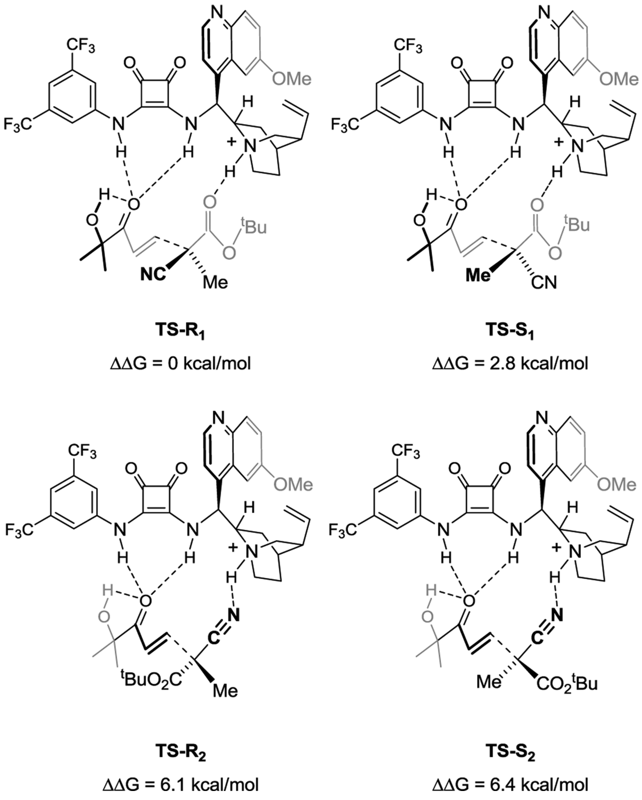


Figure 6. Located TSs for the catalytic addition reaction.

well for all reactions falling within this type of noncovalent bifunctional catalysis, and case to case analysis is required; (iv) calculations for our system confirms that H-bond with a nitrile group contributes poorly to TS stabilization as compared with H-bond to a ester group, probably due to the fact that linear arrangements, as in $C{\equiv}N\cdots HX$, are more difficult to fit in the TS than angular arrangements, as in $C{=}O\cdots HX$.[56] Eventually, the combination of these factors leads to the highly stereoselective formation of the new quaternary stereocenter in **20e**.

■ CONCLUSIONS

In summary, the highly stereoselective generation of tetrasubstituted carbons, including *C*−*N*, *C*−*O*, *C*−*S*, and all-carbon quaternary stereocenters, has been realized via bifunctional Brønsted base catalyzed Michael reaction of various types of hitherto challenging prostereogenic *C*-nucleophiles and α'-oxy enones as key enoate surrogates. Competitive and parallel experiments using simple enones (or esters) and the respective α'-oxy enones indicate that the α-oxy ketone moiety is crucial for achieving high levels of reactivity and stereoselectivity. The ability of α'-hydroxy enones to engage in H-bond networks as either donor or acceptor component (or both) was unknown in previous bidentate enoyl templates, and may in the future be exploited as a new design element in other organocatalytic asymmetric transformations. An additional noteworthy aspect of this design is that the *gem*-dialkylcarbinol framework of the template can be easily modified at both the carbon and oxygen sites, thus enabling easy template tuning for optimal performance. The resulting α-oxy ketone adducts can smoothly be converted into the corresponding aldehyde, ketone, or carboxylic acid derivatives through simple oxidative cleavage of the ketol unit. The present methodology thus provides access to synthetically relevant building-blocks bearing a fully substituted stereogenic carbon atom which were hitherto difficult to prepare in enantioenriched form. Studies toward broadening this methodology are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and characterization of compounds including NMR spectra, HPLC chromatograms, and X-ray ORTEP, as well as Cartesian coordinates of all computed stationary points, relative and absolute activation energies for all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

claudio.palomo@ehu.es

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Recent reviews on asymmetric conjugate additions. General: (a) *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, 2010. (b) Nguyen, B. N.; Hii, K. K.; Szymanski, W.; Jansen, D. B. In *Science of Synthesis Houben Weyl, Stereoselective Synthesis 1, Stereoselective Reactions of Carbon-Carbon Double Bonds*; de Vries, J. G., Ed.; Georg Thieme Verlag KG: Sttuttgart, NY, 2010; pp 571−688. Organocatalytic: (c) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42−53. (d) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselecive Conjugate Addition Reactions*; RSC Publishing: Cambridge, 2010. (e) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701−1716. (f) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299−365. (g) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065−2092. (h) Zhang, Y.; Wang, W. In *Stereoselective Organocatalysis*; Ríos, R., Ed; Wiley: Hoboken, New Jersey, 2013; pp 147−203.

(2) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol *I*−*III*. (b) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000, Vol *1*−*3*.

(3) Selected reviews: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79−87. (b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416−5470. (c) MacMillan, D. W. C.; Watson, A. J. B. In *Science of Synthesis: Asymmetric Organocatalysis Vol. 1*; List, B., Maruoka, K., Eds.; Thieme: Stuttgart, 2012; pp 309−401. (d) Liu, Y.; Melchiorre, P. In *Science of Synthesis: Asymmetric Organocatalysis Vol. 1*; List, B., Maruoka, K., Eds.; Thieme: Stuttgart, 2012; pp 403−438. (e) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748−9770. (f) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem.Commun.* **2011**, *47*, 632−649.

(4) Representative examples. *N*-Enoyl oxazolidinones: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480−4491. (c) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263−3296. and references therein. (d) Hird, A. W.; Hoveyda, A. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279. (e) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240−1241. *N*-Enoyl pyrazolidinones: (f) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718−719. and references therein. *N*-enoyl pyrazoles: (g) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. (h) Sibi, M. P.; Shay, J. J.; Liu, M.; Jarperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. *N*-Acyl pyrroles: (i) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943. (j) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559−7570. α,β-Unsaturated imides: (k) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724−14725. (l) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204−11205. and references therein. (m) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796−11797. β,γ-Unsaturated acyl phosphonates: (n) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Law, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780−10781. (o) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029−10041. β,γ-Unsaturated α-keto esters: (p) Jensen, K. B.; Thorhauge, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163. 2-Acyl imidazoles: (q) Coquière, D.; Feringa, B. L.; Roelfes, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 9308−9311. (r) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943.

(5) Examples of successful bidentate templates in Brønsted base catalysis. *N*-Enoyl oxazolidinones: (a) Zu, J.; Wang, J.; Li, H.; Xe, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036−1037. *N*-Acyl pyrazoles and pyrazoleamides: (b) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064−8065. (c) Tan, B.; Zeng, X.; Leong, W. W. Y.; Shi, Z.; Barbas, C. F., III; Zhong, G. *Chem.—Eur. J.* **2012**, *18*, 63−67. α,β-Unsaturated imides: (d) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J.*

Am. Chem. Soc. **2006**, *128*, 9413−9419. *N*-Acyl benzotriazoles: (e) Uraguchi, D.; Vek, Y.; Ooi, T. *Science* **2009**, *326*, 120−123. Acyl phosphonates: (f) Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775−2783. (g) Liu, T.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *J. Org. Chem.* **2011**, *76*, 4119−4124. Styryl isoxazoles: (h) Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9342−9345. (i) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329−9331. 2-Oxo-3-butenoates: (j) Gao, Y.; Ren, a.; Wang, L.; Wang, J. *Chem.—Eur. J.* **2010**, *16*, 13068−13071. (k) Xu, D.-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A. G.; Xia, A.-B.; Xu, Z.-Y. *Chem.—Eur. J.* **2010**, *16*, 4177−4180. (l) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266−8267. Thioesters and *N*-acryloyl pyrrol: (m) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798−3800. Maleimides: (n) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4966−4970.

(6) Reviews on Brønsted bases: (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632−653. (b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*; Maruoka, K., Ed.; Thieme: Stuttgart, 2012. (c) Ting, A.; Gross, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145−200.

(7) Reviews on nitroalkenes: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894. (b) Ballini, R.; Marcantoni, E.; Petrini, M. In *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 93−148. (c) Roca-López, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2562−2601.

(8) Recent reviews: (a) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745−2759. (b) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593−4623. (c) Bella, M.; Caspery, T. *Synthesis* **2009**, 1583−1614. (d) Cozzi, P. G.; Hilgraf, R.; Zimmerman, N. *Eur. J. Org. Chem.* **2007**, 5969−1614. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369−396. (f) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005. (g) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363−5367.

(9) For a review on metal-catalyzed conjugate additions leading to all-carbon quaternary stereocenters, see: Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295−7306.

(10) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295−8296.

(11) (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. (b) Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561−5564.

(12) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241.

(13) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313−1317.

(14) (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057−4060. (b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238−2244.

(15) (a) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947−950. (b) Wu, F.; Li, H.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301−4305.

(16) Reviews on Cinchona based catalysts: (a) Yeboah, E. M. O.; Yeboah, S. O.; Sing, G. S. *Tetrahedron* **2011**, *67*, 1725−1762. (b) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229−1279. (c) *Cinchona Alkaloids in Synthesis and Catalysis*; Song, C. E., Ed.; Wiley-VCH: Weinheim, 2009. (d) Reference 6.

(17) (a) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem.—Eur. J.* **2006**, *12*, 6039−6052. See also: (b) Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407−5410.

(18) Sanchez Duque, M. M.; Baslé, O.; Isambert, N.; Gaudel-Siri, A.; Génisson, Y.; Plaquevent, J.-C.; Rodriguez, J.; Constantieux, T. *Org. Lett.* **2011**, *13*, 3296−3299.

(19) (a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077−7079. (b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290−2300. (c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499−2506.

(20) Diels−Alder: (a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942−13943. Carbamate conjugate addition: (b) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188−9189. Friedel−Crafts: (c) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154−4155. Nitrone cycloaddition: (d) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187−6190.

(21) (a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288−10289. (b) Bañuelos, P.; García, J. M.; Gómez-Bengoa, E.; Herrero, A.; Odriozola, J. M.; Oiarbide, M.; Palomo, C.; Razkin, J. *J. Org. Chem.* **2010**, *75*, 1458−1473. Also, see: (c) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334−5335.

(22) Pioneering applications of chiral α'-hydroxy enones in synthesis: (a) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1139−1141. (b) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441−4444. (c) Stammen, B.; Berlage, U.; Kindermann, R.; Kaiser, M.; Günther, B.; Sheldrick, W. S.; Welzel, P.; Roth, P. W. R. *J. Org. Chem.* **1992**, *57*, 6566−6575.

(23) For spectroscopic proofs of intramolecular H−bonding in α-hydroxy ketones, see: (a) Joris, L.; Scheleyer, P.; von, R. *J. Am. Chem. Soc.* **1968**, *90*, 4599−4611. (b) Cho, T.; Kida, I.; Ninomiya, J.; Ikawa, S.-i. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 103−107. Also see reference 22.

(24) For reviews on direct catalytic asymmetric transformations under proton-transfer conditions, see: (a) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760−4772. (b) Yamashita, Y.; Tsubogo, T.; Kobayashi, S. *Chem.Sci.* **2012**, *3*, 967−975.

(25) For a review on the use of α'-hydroxy enones in asymmetric synthesis, see: Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150−4164.

(26) α'-Hydroxy enones as transiently protected forms of cinnamaldehydes (retrobenzoin reaction) in racemic nucleophilic catalysis by *N*-heterocyclic carbenes: (a) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714−8718. (b) Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 4566−4568. (c) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378−5381. For applications in kinetic resolution of cyclic secondary amines, see: (d) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698−19701.

(27) See the Supporting Information for details.

(28) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715−1717.

(29) (a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525−2529. (b) McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667−3675.

(30) For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209−2219. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127−139. (c) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36−51. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (e) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003−3025. (f) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381−1407.

(31) Bifunctional Brønsted base catalyzed additions of oxindoles to enones: (a) Li, X.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, *8*, 77−82. (b) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Molecules* **2012**, *17*, 7523−7532. (c) Lee, H. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 3171−3172.

(32) For a review on organocatalytic asymmetric conjugate addition of 3-substituted oxindoles, see reference 30f. For selected examples of

enantioselective Michael additions of oxindoles to enones, see: Metal catalysis: (a) Zheng, W.; Z-hang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339−3341. Phase transfer catalysis: (b) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559−4561. (c) Shirakawa, S.; Kasai, A.; Tokuda, T.; Maruoka, K. *Chem. Sci.* **2013**, *4*, 2248−2252. Chiral phosphine catalysis: (d) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 943−947. (e) Wang, T.; Yao, W.; Zhong, F.; Pang, G. H.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 2964−2968. Iminium ion catalysis: (f) Pesciaioli, F.; Tian, X.; Bencivenni, G.; Bartoli, G.; Melchiorre, P. *Synlett* **2010**, 1704−1708. (g) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Tetrahedron: Asymmetry* **2010**, *21*, 2493−2497. (h) Freund, M. H.; Tsogoeva, S. B. *Synlett* **2011**, 503−507.

(33) For advances in the catalytic enantioselective generation of all-carbon quaternary centers from Michael reactions of acrylic acid derivatives, see: Brønsted base catalysis: (a) Reference 5m. Covalent enamine catalysis:. (b) Kano, T.; Shiruzu, F.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 16068−16073. (c) Zhu, S.; Wang, Y.; Ma, D. *Adv. Synth. Catal.* **2009**, *351*, 2563−2566. Phase transfer catalysis with the assistance of overstoichiometric inorganic base: (d) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097−1100. (e) Andrus, M. B.; Ye, Z. *Tetrahedron Lett.* **2008**, *49*, 534−537. (f) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B. S.; Lee, J. H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.; Park, H. *Org. Lett.* **2005**, *7*, 3207−3209. (g) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348 and references therein..

(34) Node, M.; Hao, X.-j.; Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715−719.

(35) (a) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758−8759. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590−4591.

(36) Reviews on α-substituted cyanoacetates: (a) Jautza, S.; Peters, R. *Synthesis* **2010**, 365−388. (b) Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de Viu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261−3288.

(37) Asymmetric organocatalytic conjugate additions of α-substituted cyanoacetates. To enones: (a) Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem.—Eur. J.* **2007**, *13*, 319−327. (b) Bell, M.; Poulsen, T. B.; Jørgensen, A. K. *J. Org. Chem.* **2007**, *72*, 3053−3056. (c) Reference 14a. (d) Reference 15b. (e) Reference 17b. (f) Liu, L.; Liao, Y.; Lian, C.; Yuan, W.; Zhang, X. *Tetrahedron* **2014**, *70*, 5919−5927. To acetylenic carbonyls: (g) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871−874. (h) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038−1039. To maleimides: (i) Liao, Y.-H.; Liu, X.-L.; Wu, Z. J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2011**, *353*, 1720−1728. (j) Ma, Z.-W.; Wu, Y.; Sun, B.; Du, H.-L.; Shi, W.-m.; Tao, J.-c. *Tetrahedron: Asymmetry* **2013**, *24*, 7−13. To vinylsulfones: (k) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948−8949. (l) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097−2099. (m) Li, H.; Song, J.; Deng, L. *Tetrahedron* **2009**, *65*, 3139−3148. To vinyl selenones: (n) Marini, F.; Sternativo, S.; Del Verne, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2009**, *351*, 1801−1806. To acrylonitriles: (o) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768−769.

(38) For pertinent information, see: (a) Eitel, S. H.; Jautze, S.; Frey, W.; Peters, R. *Chem. Sci.* **2013**, *4*, 2218−2233. (b) Jautze, S.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9284−9288. and references therein. (c) Takenaka, K.; Minakawa, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 12273−12281. (d) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313−1317. (e) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810−6812. (f) Stork, M. A.; Jones, G.; Richards, C. J. *Organometallics* **2000**, *19*, 1282−1291. (g) Kawato, Y.; Takabashi, N.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 1484−1487. (h) Motoyama, Y.; Koga, Y.; Kobayashi, K.; Aoki, K.; Nishiyama, H. *Chem.—Eur. J.* **2002**, *8*, 2968−2975. (i) Hasegawa, Y.; Gridnev, I. D.; Ikariya, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 8157−8160.

(39) (a) Malerich, J. P.; Hagihara, K.; Rawal, V. R. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417. (b) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153−156. For reviews on squaramide catalysis, see: (c) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330−2346. (d) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890−6899.

(40) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450−5453.

(41) (a) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11846−11851. Also, see: (b) Chen, W.; Hartwig, J. H. *J. Am. Chem. Soc.* **2014**, *136*, 377−382.

(42) Trost, B. M.; Dogra, K.; Franzin, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944−1945.

(43) For the asymmetric conjugate addition of 5*H*-oxazol-4-ones, see: alkynyl carbonyl compounds: (a) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc.* **2011**, *133*, 5695−5697. β-Substituted α,β-enones: (b) Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. *Chem. Commun.* **2012**, *48*, 461−463. Nitroalkenes: (c) Trost, B. M.; Hirano, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 6480−6483. (d) Quiau, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett.* **2013**, *15*, 2358−2361. Use of 5*H*-oxazol-4-ones in other catalytic asymmetric reactions. Aldol: (e) Misaki, T.; Takimotoa, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286−6287. Mannich: (f) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7523−7527. (g) Han, Z.; Yang, W.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2013**, *355*, 1505−1511. Allylic substitution: (h) Reference 41b. α-Sulfenylation: (i) Xu, J.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696−8702.

(44) Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953−957.

(45) Paju, A.; Laos, M.; Jõgi, A.; Päri, M.; Jäälaid, P. T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.* **2006**, *47*, 4491−4493.

(46) For pertinent information, see: (a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432−1440. (b) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755−2762. (c) Alba, A.-N. R.; Rios, R. *Chem.—Asian J.* **2011**, *6*, 720−734.

(47) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507−1518.

(48) All calculations were performed with Gaussian 09, Revision D.01: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. The geometries of the stationary points were optimized by using DFT with the B3LYP functional and 6-311++G** basis set in a dichloromethane solvent system. For computational details and references, see the Supporting Information.

(49) Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922−1924.

(50) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080−1106. (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1736.

(51) For studies describing type **A** transition structures, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119−125. (c) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872−15883. (d) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358−15374. (e) Hammar, P.; Marcelli,

T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537−2548. For type **B**: (f) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151−13160. (g) Almasi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 6163−6168. (h) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682−2685. (i) Han, X.; Lee, R.; Chen, T.; Luo, J.; Lu, Y.; Huang, K. W. *Sci. Rep.* **2013**, *3*, 2557. (j) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem.—Eur. J.* **2014**, *20*, 5631−5639. (k) Azuma, T.; Kobayashi, Y.; Sakata, K.; Sasamori, T.; Tokitoh, N.; Takemoto, Y. *J. Org. Chem.* **2014**, *79*, 1805−1817. For type **C**: (l) Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813−9825.

(52) In our calculations we have considered the chiral cinchonine moiety of **C2** addopting either *syn*-open or *anti*-open conformations. The prevalence of such conformations in similar bifunctional catalysts as well as in the native *Cinchona* alkaloids has been studied both experimental and theoretically: (a) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. *Adv. Synth. Catal.* **2007**, *349*, 2537−2548. (b) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 95. (c) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069−8076. (d) Bürgi, T.; Baiker, A. *J. Am. Chem. Soc.* **1998**, *120*, 12920−12926.

(53) While the intramolecular H-bond present in our α'-hydroxy enone would help the occurrence of such a transition state, its energy is exceedingly high and this pathway may be discarded.

(54) Extrapolation of this TS model to the case of the reaction between β-substituted enones **4** and cyanoacetates **19** would also correctly predict the (*S*,*S*) relative configuration of adducts obtained in Table 5. In contrast, the structure closest to **B** we could find predicts products of wrong relative stereochemistry upon a similar extrapolation.

(55) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(56) It seems that the preference of the nitrile versus the ester group to get coordinated to a metal center does not correlate with the ability of each group for engaging in H-bonding. Thus, most TS models invoked in the literature for the metal-catalyzed conjugate addition reactions of α-cyanoacetates consider metal-coordinated nitrile and uncoordinated ester groups, respectively (see refs 10, 38a, 38b, 38h, and 38i). In contrast, and in agreement with our own calculations, previously reported qualitative activation models for related reactions involving H-bond catalysis assume the preference of the ester group over the nitrile for H-bonding (see refs 37a, 37f, and 37i). To further illustrate this divergency, the structure of a cyanoacetate−metal catalyst complex has been elucidated (reference 38i) in which both the metal−CN and the ester−H-bond interactions are identified.