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Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions: Divergent Access to α-Quaternary Δ^4- and Δ^5-Dehydroprolines

DOCTORAL THESIS

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ESKERRAK

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Ciencias Químicas de Donostia, Universidad del País Vasco (UPV-EHU), bajo la dirección del Dr. Claudio Palomo Nicolau y el Dr. Mikel Oiarbide Garmendia, a quienes expreso mi más sincero agradecimiento primero por darme la oportunidad de desarrollar esta tesis doctoral en este departamento y por su dedicación y esfuerzo durante el desarrollo de este trabajo. También me gustaría agradecer al resto de profesores que forman parte del departamento y al personal de la Universidad por estar siempre dispuestos a prestar su ayuda. Debo agradecer, además, la necesaria financiación proveniente de la beca predoctoral de la UPV-EHU.

Ofizialtasunak alde batera, aspektu pertsolanago batean ezinbesteko izan zareten guztiei eskertu nahiko nizueke, urte hauetan lortutakoa zentzu handi batean zuei esker izan baita. Zuek alboan edukitzeak zorioneko sentiarazten nau.

Lehenik eta behin nire labokide kuttunei!! Pixkanaka hutsunea uzten joan zaretenei ere… beti laguntzeko eta entzuteko prest egon zaretelako. Oso harro, urte hauetako nire bigarren familia zaretela esan dezaket. Beti jakin duzue nire irriparra ateratzen, nik uste det zirko on bat montatu genezakela “empresa” moduan! Zuek bezain lankide-lagun onak aurkitzea ez da batere erraza izango.

A mis compis de piso y mi familia donostiarra que ha ido creciendo poco a poco, por hacerme tan amena la vuelta a casa después de una dura jornada. Por hacer incluso de un martes más, un día para recordar. Planes improvisados que surgen demostrando que el tiempo es oro o momentos de sofá, relax y risas, tan esenciales en esta etapa. Todo un gusto encontrarme a gente como vosotros por el camino.

Nola ez, nire lagartatxoei!! Pilak kargatzen lagundu didazuelako beti, zuen bizipozarekin dena errexagoa baita. Zuentzat garrantzitsua nahizela erakutsi didazue eta bukatzen dudan lekuan bukatzen dudala, badakit beti edukiko zaituztedala. Kuadrilla bat ez dela aukeratzen esaten da, tokatu egiten dela diote, ba guri zoologiko ona tokatu zaigu!! Zuekin edonora ;-)

Eta azkenik familiari, bereziki nire gurasoei. Beti nitan sinisteagatik, garrantzitsua eta indartsua nahizela erakusteagatik, zuen maitasunari esker naizelako gaur egun naizena. Nire altxorrik preziatuena zatere. Asko maite zaituztet!

Summary

α-Quaternary prolines are considered structurally unique α-amino acids of great importance in peptide chemistry, as well as in the area of natural products and biologically active substances. The most widely employed strategy for their asymmetic synthesis is based on metal catalyzed [3 + 2] cycloadditions of azomethine ylides and electron-deficient olefins. In contrast, the synthesis of α-quaternary prolines through cycloadditions involving the use of isocyanoacetates has been much less developed. In addition, the use of isocyanoacetates in [3+2] cycloadditions has required very reactive dipolarophiles as reaction partner and with few exceptions, the presence of metal to promote the reaction (Figure 1). However, isocyanoacetates have demonstrated in the last decades their great synthetic potential, particularly due to the chemical diversity conferred by the isonitrile (isocyano) group and, thus, the reactions involving their use are considered interesting alternative routes and worthy of being studied.

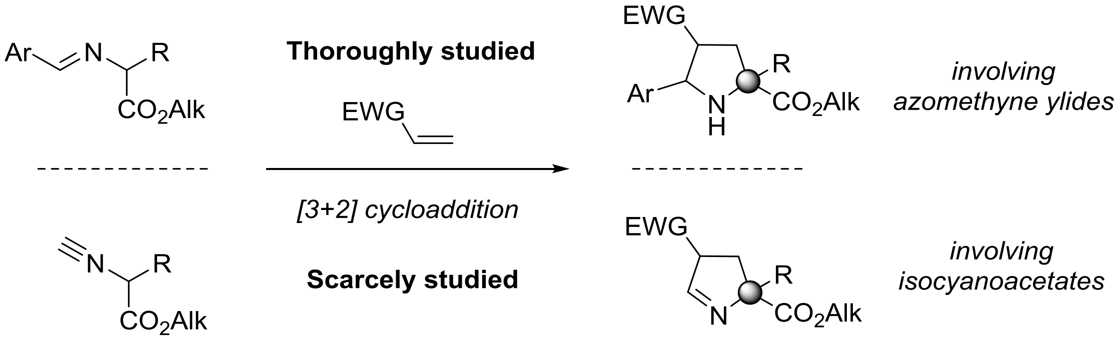
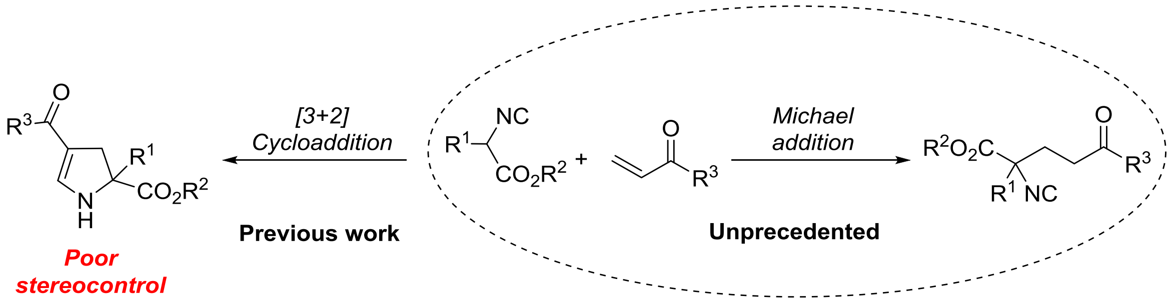


Figura 1.

The aim of this thesis has been to contribute to the enantioselective synthesis of α-quaternary prolines and other α-quaternary amino acid derivatives through reactions with isocyanoacetates. With this purpose, the organocatalytic asymmetric Michael reaction between α-substituted isocyanoacetates and vinyl ketones has been studied for the first time, whose corresponding cycloaddition reaction previously reported had provided unsatisfactory stereochemical results.

Summary



Scheme 1.

The results obtained with the commonly known bifunctional organocatalysts could be successfully improved thanks to the design of a new family of squaramide/tertiary amine type catalysts (Figure 2). The key for the success of these catalysts relies in the steric hindrance generated by the gem,gem-(bis) diaryl bulky group which, in addition to providing an excellent stereocontrol, prevents the frequent self-aggregate through hydrogen-bonding between different squaramide molecules that usually hinders the activity as a catalyst. On the other hand, the polyaryl group increases the solubility of the catalyst in both polar and apolar solvents.

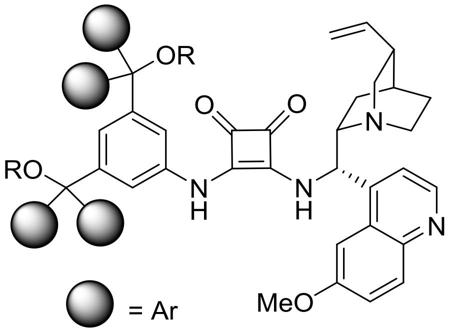
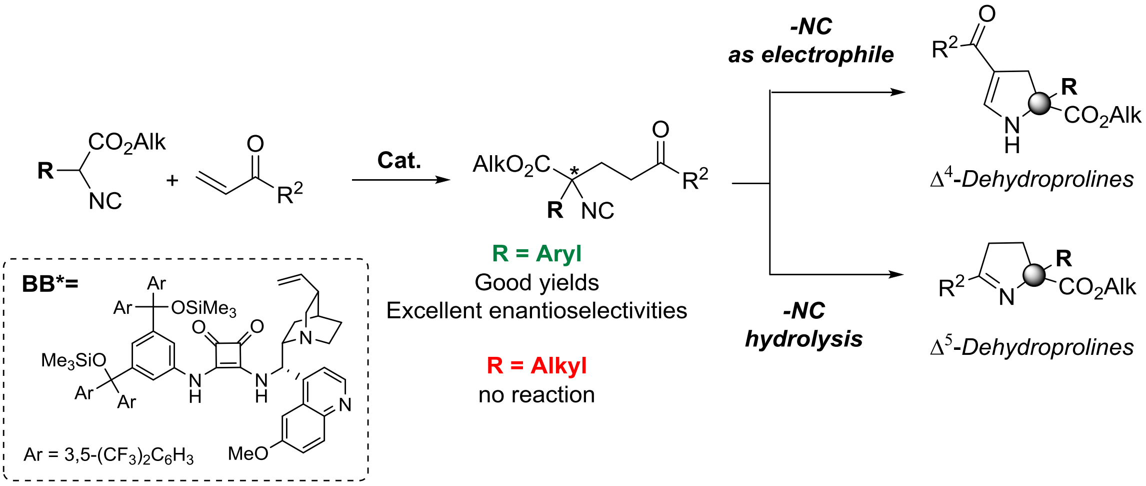


Figure 2.

By catalyzing the reaction in the absence of a metal, it has been possible to favor the protonation of the carbanionic Michael adduct and avoid the intramolecular cyclization step that commonly follows to this type of 1,4-addition reactions giving rise to [3+2] cycloaddition process. This has allowed us to take full advantage of the chemical diversity of the isonitrile group in the enantioenriched Michael addition products and to design a new divergent route for the synthesis of α-quaternary Δ^5-dehydroprolines and Δ^4-dehydroprolines, which formally derive from [3 + 2] cycloadditions (Scheme 2). However, while the asymmetric Michael reaction gives very good results when α-aryl substituted isocyanoacetates are used, when the substitution is α-alkyl, the nucleophile is not sufficiently reactive and no reaction occurs.



Scheme 2. Enantioselective Michael addition of α-substituted isocyanoacetates to vinyl ketones.

Inspired by how Nature has found an elegant solution using thioesters as active oxo-esters surrogates in the synthetic route of polyketides and fatty acids, we proposed to address the Michael addition to vinyl ketones with α-alkyl isocyanothioesters, substrates never before used in asymmetric catalytic reactions.

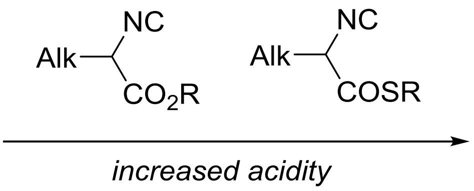
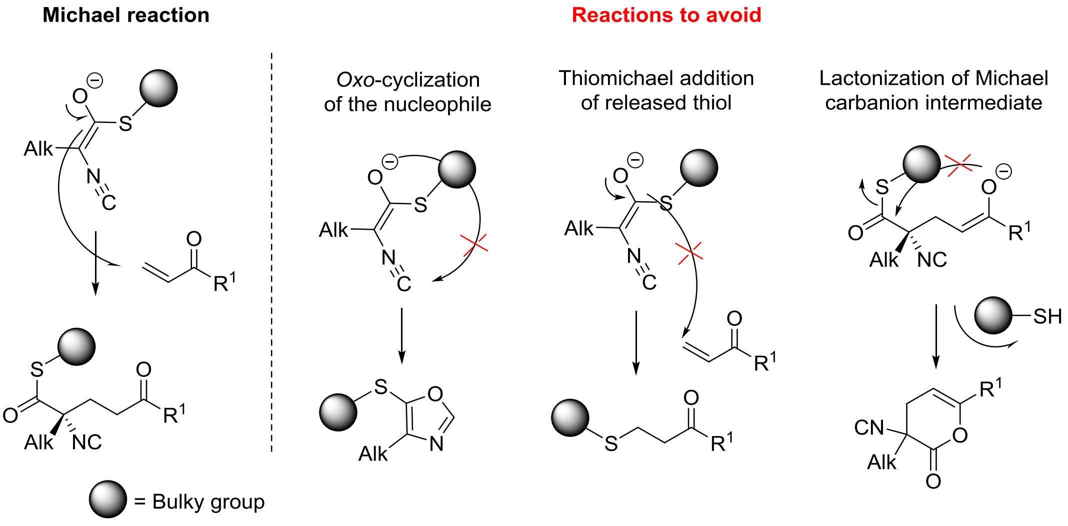


Figure 3.

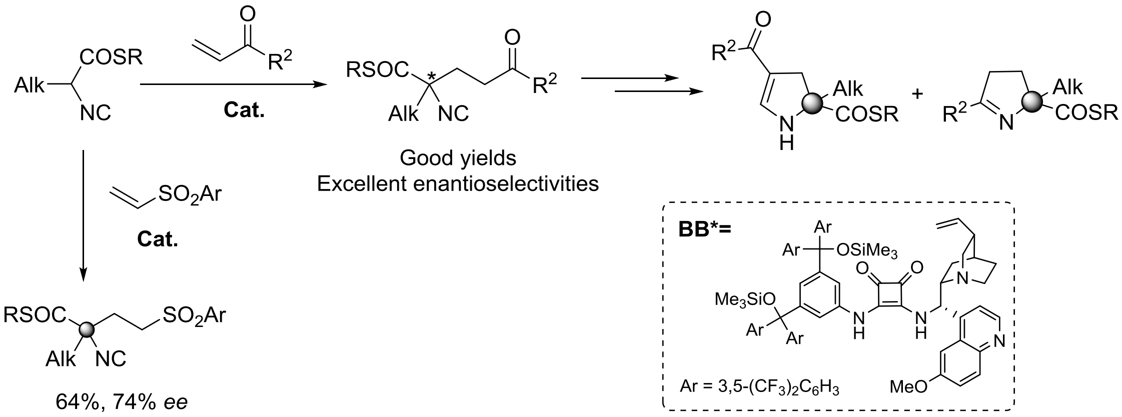
Although these nucleophiles prove to be sufficiently reactive to give the Michael addition to vinyl ketones in a stereocontrolled manner, the reaction pathway is strongly dependent on the thioester nature. In this sense, the best results are produced using isocyanothioacetates with sterically more demanding thioester group such as *ortho*-disubstituted aryl thioesters (Scheme 3).



Scheme 3. Desired Michael reaction vs unwanted reaction pathways.

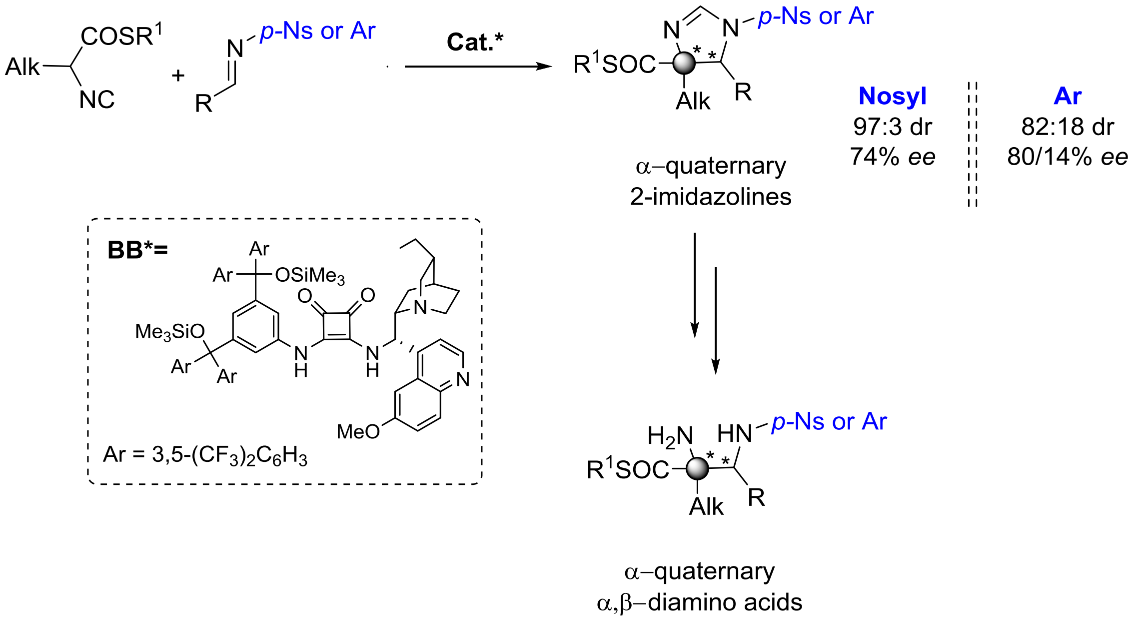
As a result, asymmetric Michael reaction with vinyl ketones promoted by the new catalyst and using isocyanothioacetates bearing a variety of α-alkyl substituents provides the desired Michael products with good yields and excellent enantiomeric excesses. Thus obtained Michael products can be easily transformed into Δ^4- and Δ^5-dehydroprolines. On the whole, asymmetric Michael reaction to vinyl ketones provides a new divergent synthetic route for the enantioselective synthesis of various α-aryl and α-alkyl substituted quaternary prolines.

Based on these α-alkyl isocyanothioacetates, it has been possible to address for the first time the stereocontrolled Michael addition between an α-alkyl substituted isocyanoacetate equivalent and a vinyl sulfone. In this latter case the reaction stereoselectivities were a little bit lower than with vinyl ketones as acceptor.



Scheme 4. Enantioselective Michael reactions with α-alkyl isocyanoacetates.

On the other hand, the Mannich reaction involving α-substituted isocyanoacetates still has many limitations, especially when we refer to the α-alkyl substituted isocyanoacetates in combination with the use of organocatalysts. Nevertheless, this reaction provides a route for the synthesis of α-quaternary 2-imidazolines, structural subunits of biologically active compounds and ideal precursors of α,β-diamino acids. Accordingly, the organocatalytic asymmetric Mannich reaction of α-alkyl isocyanothioacetates with activated aldimines (*N*-Tosyl) and less active aldimines (*N*-Aril) has also been explored. The preliminary results indicated, as in the previous case, that the reaction takes place even though the products were obtained with low enantiomeric excess.



Scheme 5. Enantioselective Mannich reactions with α-alkyl isocyanoacetates.

Resumen

Las prolinas α-cuaternarias son α-aminoácidos estructuralmente únicos de gran importancia en química de péptidos, así como en el área de productos naturales y sustancias biológicamente activas. La estrategia más utilizada para la síntesis catalítica asimétrica de prolinas α-cuaternarias se basa en las cicloadiciones [3+2] con iluros de azometino y olefinas deficientes en electrones haciendo uso de catalizadores metálicos. En comparación, la síntesis de prolinas α-cuaternarias a través de cicloadiciones que implican el uso de isocianoacetatos ha sido mucho menos desarrollada. Estos métodos además han requerido dipolarófilos muy reactivos y salvo alguna excepción, la presencia de metal para promover la reacción (Figura 1). No obstante, a lo largo de la historia los isocianoacetatos han demostrado su potencial sintético, en gran medida gracias a la diversidad química que le confiere el grupo isonitrino (isociano) y en consequencia, las reacciones que implican su uso son consideradas rutas alternativas de gran interés.

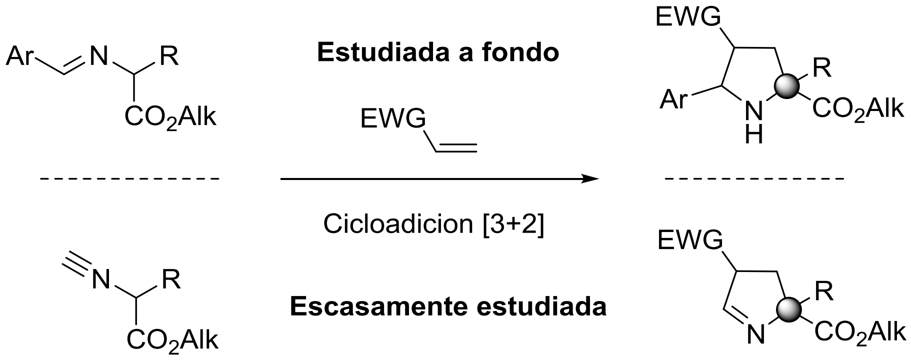
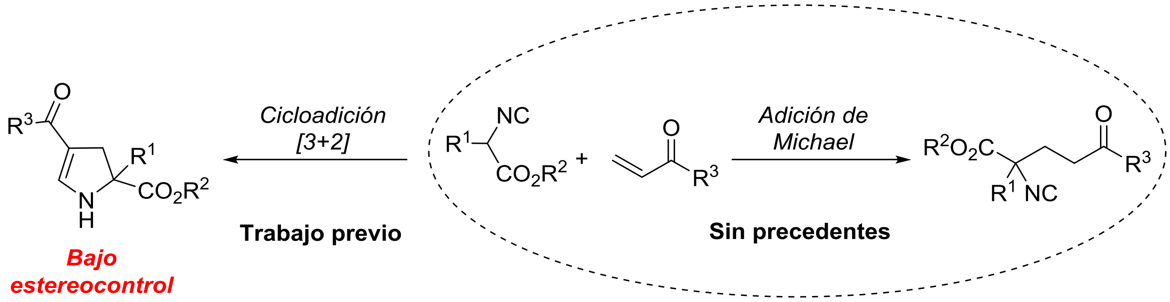


Figura 1.

Por lo tanto, el objetivo de esta tesis ha sido contribuir a la síntesis de prolinas α-quaternarias y otros derivados de amino ácidos α-cuaternarios a través de reacciones con isocianoacetatos. Para ello se ha estudiado por primera vez la reacción organocatalítica asimétrica de Michael entre isocianoacetatos α-sustituidos y vinyl cetonas, cuya correspondiente reacción de cicloadición estudiada previamente había proporcionado resultados estereoquímicos insatisfactorios.



Esquema 1.

Los resultados obtenidos con los organocatalizadores bifuncionales comunmente conocidos se pudieron mejorar con éxito gracias al diseñó de una nueva familia de catalizadores del tipo escuaramida/amina terciaria (Figura 2). La clave del éxito de estos catalizadores reside en el impedimento estérico generado por el grupo voluminoso *gem,gem*-(bis)diaril que, además de proporcionar un estereocontrol excelente, impide la frecuente auto-agregación entre distintas moléculas de escuaramidas que suele dificultar las reacciones. Por otro lado, el grupo poliarilo favorece la solubilidad del catalizador en disolventes tanto polares como apolares.

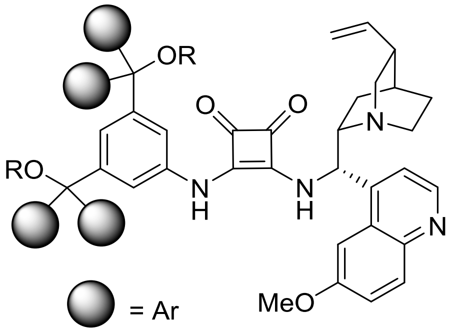
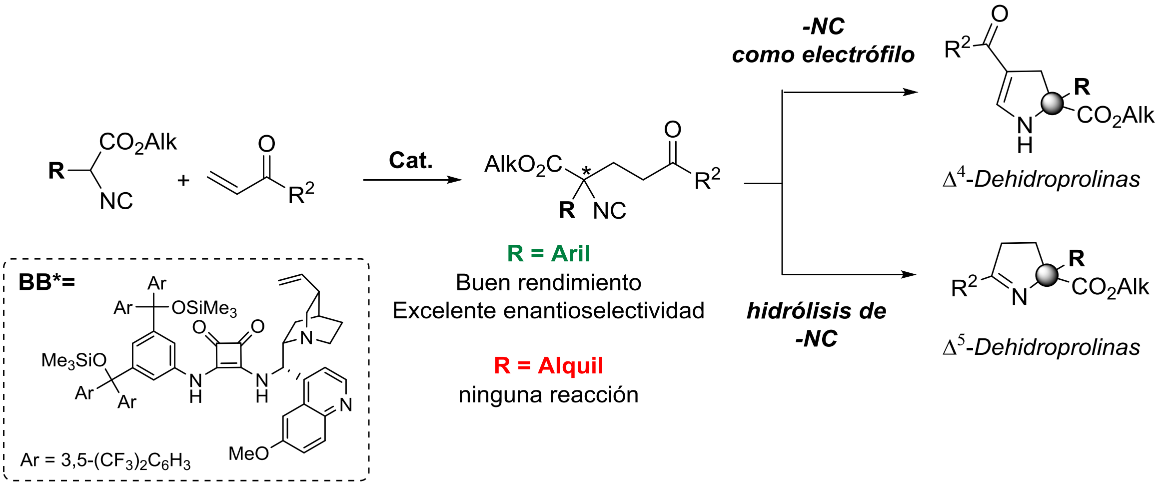


Figura 2.

Al catalizar la reacción en ausencia del metal se ha conseguido favorecer la protonación del aducto de Michael carbaniónico frente a la ciclación intramolecular que comúnmente ocurre en estas reacciones de adición 1,4 dando lugar a cicloadiciones [3+2]. Esto ha permitido sacar partido a la diversidad química del grupo funcional isonitrilo en los productos enantioenriquecidos de la reacción de Michael y diseñar una ruta sintética divergente para la síntesis de Δ^4-dehidroprolinas que formalmente derivan de las cicloadiciones [3+2] y Δ^5-dehidroprolinas con un estereocentro cuaternario en la posición α (Esquema 2). Sin embargo, mientras que la reacción asimétrica de Michael da muy buenos resultados cuando se emplean isocianoacetatos α-aril sustituidos, cuando la sustitución es α-alquílica, el nucleófilo no resulta lo suficientemente reactivo y no se produce reacción.



Esquema 2. Adición de Michael enantioselectiva de isocianoacetatos α-sustituidos a vinil cetonas.

Inspirados en como la naturaleza ha encontrado una solución elegante utilizando tioesteres como sustitutos activos de oxo-ésteres en la ruta sintética de policétidos y ácidos grasos, propusimos abordar la adición de Michael a vinyl cetonas con isocianotioésteres α-alquílicos, sustratos nunca antes empleados en reacciones de catálisis asimétrica.

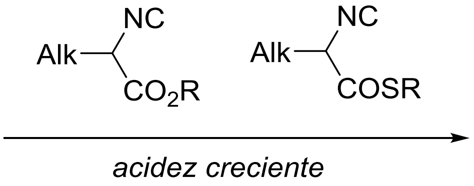
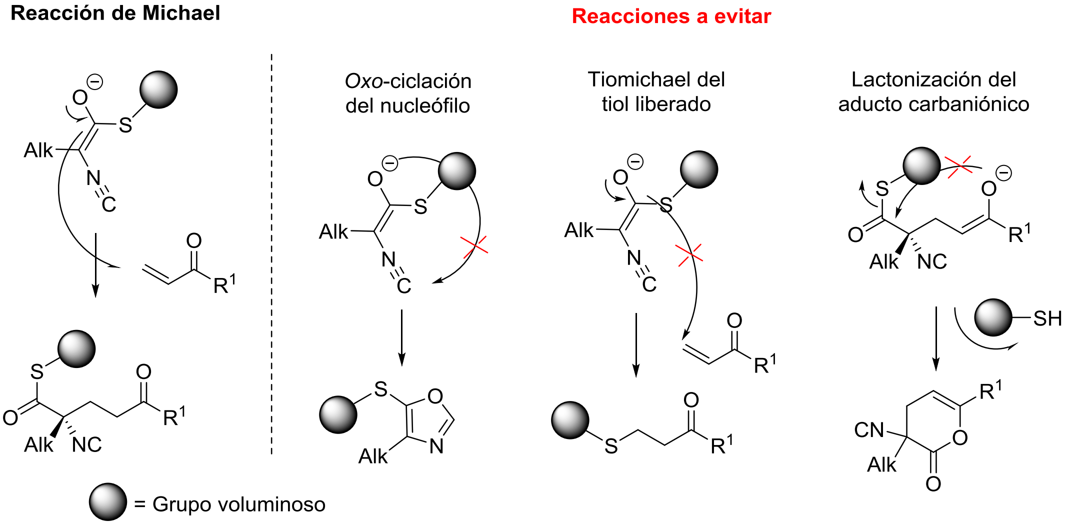


Figura 3.

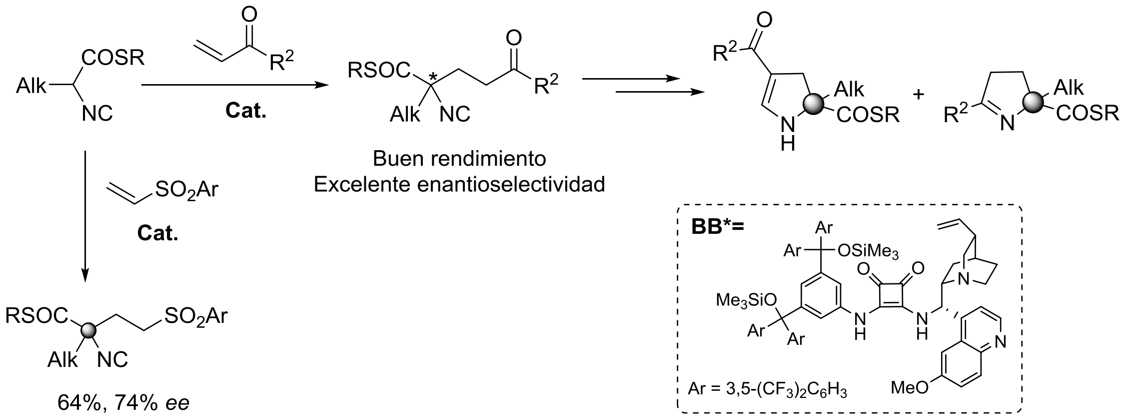
Aunque estos nuevos nucleófilos demuestran ser lo suficientemente reactivos para dar la adición a vinil cetonas de forma perfectamente estereocontrolada, el transcurso de la reacción está estrechamente relacionado con la naturaleza del tioester. En este sentido, los mejores resultados se producen empleando isocianotioacetatos con un grupo tioester con demanda estérica, como por ejemplo tioesteres con grupos aril *orto*-disustituidos (Esquema 3).



Esquema 3. Reacción de Michael vs reacciones secundarias no deseadas.

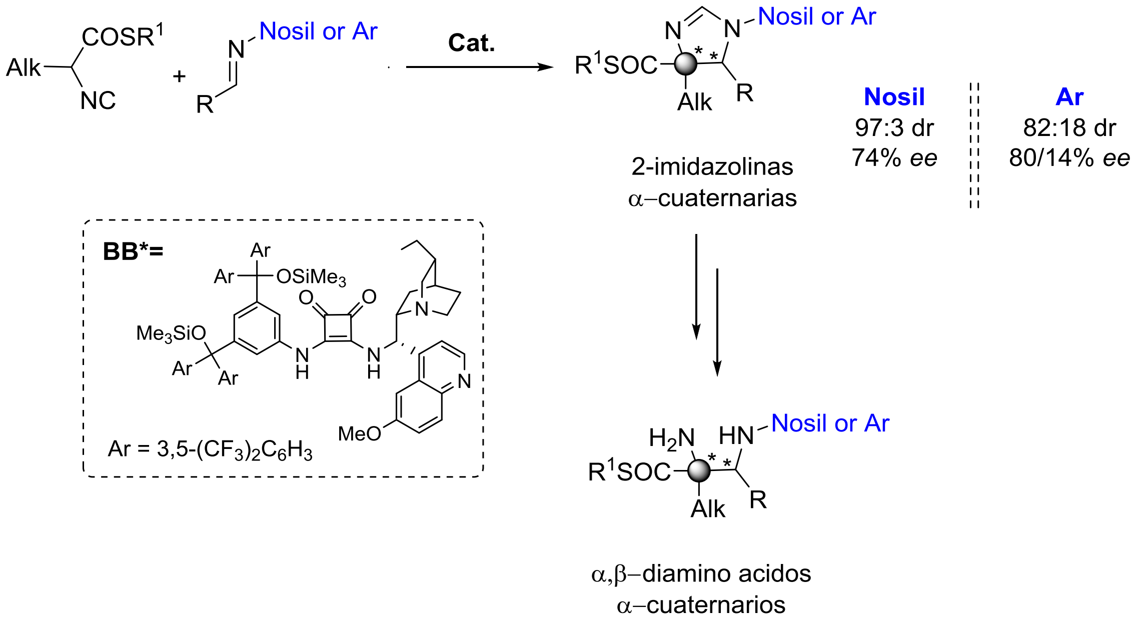
De este modo, la reacción asimétrica asistida por el nuevo catalizador y empleando isocianotioacetatos con una variedad de sustituyentes alquílicos en la posición alfa y diversas vinyl cetonas proporciona los productos de Michael deseados con buenos rendimientos y excelentes excesos enantioméricos. Los productos de Michael obtenidos pueden ser fácilmente transformados en Δ^4- y Δ^5-dehidroprolinas. En conjunto, la reacción asimétrica de Michael a vinyl cetonas proporciona una nueva ruta sintética para la síntesis enantioselectiva de diversas prolinas cuaternarias α-aril y α-alquil sustituidas.

Gracias a estos nuevos nucleófilos, se ha podido realizar por primera vez la adición de Michael estereocontrolada entre un equivalente de isocianoacetato α-alquil sustituido y una vinil sulfona, aunque empleando el mismo catalizador la reacción da resultados inferiores a los logrados con las vinil cetonas.



Esquema 4. Isocianotioacetatos α-alquilados en adiciones de Michael enantioselectivas.

Por otro lado, la reacción de Mannich de isocianoacetatos α-sustituidos aun presenta muchas limitaciones, sobre todo cuando se trata de nucleófilos α-alquil sustituidos en combinación con el uso de organocatalizadores. No obstante, esta reacción proporciona una vía para la síntesis de 2-imidazolinas α-cuaternarias, subunidades estructurales de compuestos biológicamente activos y precursores ideales de α,β-diamino ácidos. Por consiguiente, la reacción de Mannich asimétrica de isocianotioacetatos α-alquilados con aldiminas activadas (*N*-Tosyl) y aldiminas menos activas (*N*-Aril) también ha sido explorada mediante el uso de organocatalizadores. Los resultados preliminares indicaron, igual que en el caso anterior, que la reacción tiene lugar si bien los productos se obtuvieron con bajos excesos enantioméricos.



Esquema 5. Isocianotioacetatos α-alquilados en reacciones de Mannich enantioselectivas.

ABBREVIATIONS AND ACRONYMS

Standard abbreviations and acronyms has been used as recommended is *"Guidelines for authors"* (*J. Org. Chem.,* January 2017).

Å	Amstrong
AA	Amino acid
Ac	Acetyl group
Alk	Alkyl group
Ar	Aryl group
BA	Brønsted acid
BB	Brønsted base
BINOL	1,1´-Bi-naphtol
Bn	Benzyl group
Boc	*tert*-Butyloxycarbonyl group
*i*Bu	Isobutyl (group)
*n*Bu	*n*-Butyl (group)
*t*Bu	*tert*-Butyl (group)
Cat.*	Chiral catalyst
calcd.	Calculated
Cbz	Benzyloxycarbonyl group
m-CPBA	*Meta*-Chloroperbenzoic acid
Cy	Cyclohexyl group
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
$(DHQ)_2PYR$	Hydroquinine 2,5-diphenyl-4,6-pyridineyl ether
DIBALH	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl group
equiv.	Equivalent

EWG	Electron withdrawing group
h	Hour(s)
Hal	Halogen
HPLC	Highperformance liquid chromatography
HOBt	1-hydroxybenzotriazole
L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
M	Metal
m-	*meta-*
MBH	Morita-Baylis-Hillman
Me	Methyl (group)
MeIm	1-Methylimidazole
Mes	Mesityl (2,4,6-Me_3-C_6H_2-)
MOM	Methoxymethyl (CH_3OCH_2-)
m.p.	Melting point
MS	Molecular sieves
Ms	Mesyl ($MeSO_2$-)
MTBE	Methyl *tert*-butyl ether
Naphth	Naphthyl group
n.d.	No determined
n.r.	No reaction
NMM	*N*-methyl morpholine
NMR	Nuclear magnetic resonance
Ns	Nosyl group
Nu	Nucleophile
o-	*ortho-*
p-	*para-*
PG	Protecting group
Ph	Phenyl group
PMP	*para*-Methoxyphenyl (4-MeO-C_6H_4-)
*i*Pr	Isopropyl group
Pyr	Piridine
PTC	Phase-transfer catalysis
quant.	Quantitative
Rac.	Racemic
ref.	Reference
r.t.	Room temperature
SOMO	Singly occupied molecular orbital

t	time
TBAF	Tetrabutylammonium floride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl group
TLC	Thin layer chromatography
TMS	Trimethyl silyl group
*p*Tol	*para*-Tolyl (4-Me-C_6H_4-)
Ts	Tosyl (4-Me-C_6H_4-SO_2-)
*p*TSA	*para*-Toluenesulfonic acid
*	Chiral

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Chapter 1

Introduction

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1. Introduction

1.1. Asymmetric (Organo)Catalysis

Chirality[1] is a property of certain three-dimensional objects by virtue of which they cannot be superposed onto its mirror image. The first investigations in relation to the molecular chirality date back to the XIX century, with the studies of the optical activity *vs* molecular asymmetry carried out by Luis Pasteur.[2] These studies helped to better understand what is known today by stereochemistry, even before Kekulé proposed the tetravalence of carbon.[3] As a result of these findings, in 1874 the tetrahedral three-dimensional model for the carbon atom was proposed[4] in such a way that a tetravalent carbon (stereocenter) joined to four different substituents could generate two molecules of identical composition and constitution (connectivity) but different spatial distribution of atoms, which are known as enantiomers (Figure 1).

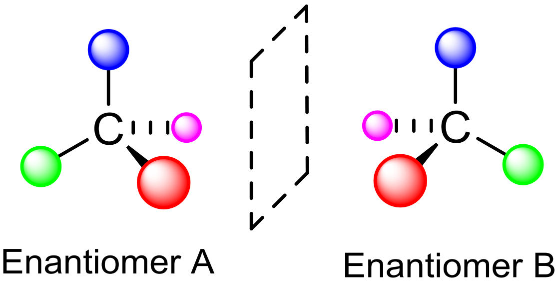

Figure 1. Both enantiomers of a chiral molecule containing a stereogenic carbon.

When a chiral compound is in an achiral environment, the two enantiomers of it behave chemically and physically in an almost identical way. However, both enantiomers may have different response to a chiral environment, as happens in most biochemical processes.[5] The thalidomide scandal case in the 60´s 70´s was a social event that

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[1] a) Riehl, J. P.; *Mirror-Image Asymmetry. An Introduction to the Origin and Consequences of Chirality* (John Wiley & Sons, New Jersey) 2009. b) Bentley, R. *Chirality* **2010**, *22*, 1–2.

[2] a) Pasteur, L. *C. R. Acad. Sci. Paris* **1848,** *26*, 535–538. b) Pasteur, L. *Ann. de Chim. et. de Phys.* **1848**, *24*, 442–459. c) Pasteur, L. *Ann. de Chim. et. de Phys.* **1853**, *38*, 437–483. d) Vallery-Radot, R.; *La vie de Pasteur* (Hachette et cie., Paris) 1900.

[3] Kekulé, A. *Annals* **1858**, *106*, 154.

[4] a) Van´t Hoff, J. H. *Arch. Neerl. Sci. Exacles. Nat.* **1874**, *4*, 445–454. b) Le Bel, J. A. *Bull. Soc. Chim. Fr.* **1874**, *22*, 337–347.

[5] Triggle, D. J., *Chirality in Natural and Applied Science*; Lough, W. J., Wainer, I. W., Eds.; Blackwell Science, Ltd. Bodwin, Cornwall, 2002; pp. 108–138.

unconversed this phenomenon leading to thousands of personal victims. [6] To avoid this undesired responses, pharmaceutical-, agricultural- and food-chemistry have set as synthetic goal the obtaining of enantiomerically pure molecules, and as a consequence, in 2006, more than 80% of the drugs approved by the FDA were enantiomerically pure.[7]

Chemical transformations involving new carbon-carbon and carbon-heteroatom bond formations lead to a racemic chiral product in the absence of an asymmetric inductor. Conversely, the synthesis of enantiomerically pure compounds requires a chiral inductor. Furthermore, to be used on an industrial scale, they must be economically viable and compatible with the environment. As shown in Figure 2, the strategies for obtaining enantiopure products can be divided into three main groups: 1) racemic resolution, 2) chiral-pool and 3) asymmetric synthesis.

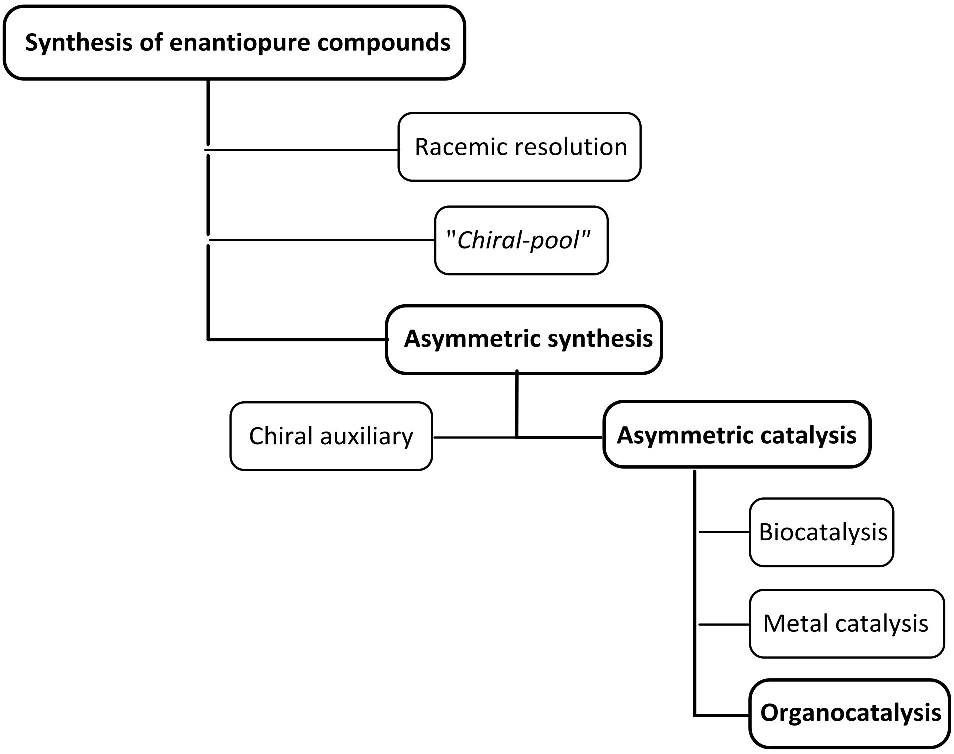

Figure 2. The strategies for obtaining enantiopure compounds.

Today, the most used strategy in the pharmaceutical industry[8] to obtain enantiopure compounds is the resolution of racemates.[9] The enantiopure compound is separated

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

[7] Thayler, A. N. *Chem. Eng. News* **2007**, *9*, 105–110.

[8] Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[9] Anderson, N. G. *Org. Proc. Res. Dev.* **2005**, *9*, 800–813.

from an initially racemic mixture by crystallization, chromatographical resolution, kinetic resolution or dynamic kinetic resolution techniques. As a general limitation, the total yield of the process can be at most 50%, having to discard the unwanted enantiomer, except in the case of dynamic kinetic resolution,[10] which combines kinetic resolution with an *in situ* racemization process allowing the formation desired enantiomer with a theoretical 100% yield.

The chiral pool strategy consists of generating the desired enantioenriched products through stereoselective transformations starting from enantiomerically pure products obtained from diverse natural sources.[11] Therefore, it is necessary to find in Nature a chiral compound with the desired configuration and that can be efficiently transformed into the desired product, which sometimes is not easy. In addition, although Nature offers a variety of enantiopure amino acids,[12] carbohydrates,[13] hydroxyacids,[14] terpenes and alkaloids, their abundance may be another limitation for use in industrial processes.[15]

The third strategy for obtaining enantiopure compounds is the asymmetric synthesis,[16] which encompasses all the processes in which at least one new stereogenic element is generated stereoselectively. Within the asymmetric synthesis, one of the alternatives is the use of a chiral auxiliary,[17] which is temporarily anchored to the substrate to control the stereochemical outcome of the reaction and thus the

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[10] a) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490. b) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331. c) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769–3802.

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[12] a) Coppola, G. M.; Shuster, H. F.; *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids* (John Wiley, New York) 1982. b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872.

[13] a) Diéguez, M.; Pamies, O.; Ruiz, A.; Diaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165–2192. b)Lehnert, T.; Özüduru, G.; Grugel, H.; Albrecht, F.; Telligmann, S. M.; Boysen, M. M. K. *Synthesis* **2011**, *17*, 2685–2708.

[14] Coppola, G. M.; Shuster, H. F.; *α-Hydroxy Acids in Enantioselective Synthesis*, (Wiley-VCH, Weinheim) 2009.

[15] Hannessian, S. *Total Synthesis of Natural Products* (Pergamon Press, Oxford) 1983.

[16] a) Hassner, A.; *Advances in Asymmetric Synthesis* (JAI Press, Greenwich) 1995. b) Gawley, R. E.; Aube, J.; Baldwin, J. E.; Magnus, P. D.; *Principles of Asymmetric Synthesis* (Pergamon Press, Oxford) 1996. c) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis* (John Wiley & Sons, New York) 2001. d) Christmann, M.; Brase, S.; *Asymmetric Synthesis: The Essentials* (Wiley-VCH, New York) 2007.

[17] a) Seyden-Penne, J.; *Chiral Auxiliaries and Ligands in Asymmetric Synthesis* (Willey, New York) 1995. b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875. X) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92–138. c) Paquette, L. A.; *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis* (Willey, New York) 2003. d) Glorious, F.; Gnass, Y. *Synthesis* **2006**, *12*, 1899–1930.

configuration of the new stereogenic elements generated during the process. In addition, the obtained diastereomeric mixture can be enriched by physical processes, whereby the auxiliary cleavage would lead to an enantiomerically enriched compound.

Asymmetric catalysis[18] is a major third approach to enantioenriched chiral products. As compared to chiral auxiliaries, in this latter approach the auxiliary anchoring and release stages are avoided. In addition, subestequiometric (catalytic) quantity of the chiral source of information is sufficient to control the stereochemistry of the product. Depending on the catalyst used, three areas are distinguished: biocatalysis, organometallic catalysis and organocatalysis.

Biocatalysis[19] is mainly based on high regio-, chemo- and stereoselective enzymatic processes which are commonly limited to certain substrates and reaction categories. Organometallic catalysis[20] and organocatalysis[21] are more compatible with the development of numerous asymmetric transformations with a great variety of structurally different substrates. In this context, organocatalytic methods have attracted much interest in the last two decades, since they are cheaper and more harmless to the environment than those involving the use of organometallic catalysts, besides being usually stable so they do not require inert or anhydrous conditions.

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[18] Trost, B M. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5348–5355. b) Mikami, K.; Lautens, M.; *New Fronteries in Asymmetric Catalysis* (Wiley-VCH, Weinhelm) 2007. c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chemistry* **2012**, *4*, 603–614.

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1.1.1. Asymmetric bifunctional organocatalysis

The term organocatalysis refers to a form of catalysis whereby the rate of a chemical reaction is increased by an organic catalyst referred to as an "organocatalyst" consisting of carbon, hydrogen, sulfur and other nonmetal elements found in organic compounds. Organocatalysts can activate the nucleophiles, electrophile or both reagents (bifunctional catalysis) through strong covalent bonding or weaker non-covalent interactions such as hydrogen bonding or ion pairing (Figure 3).

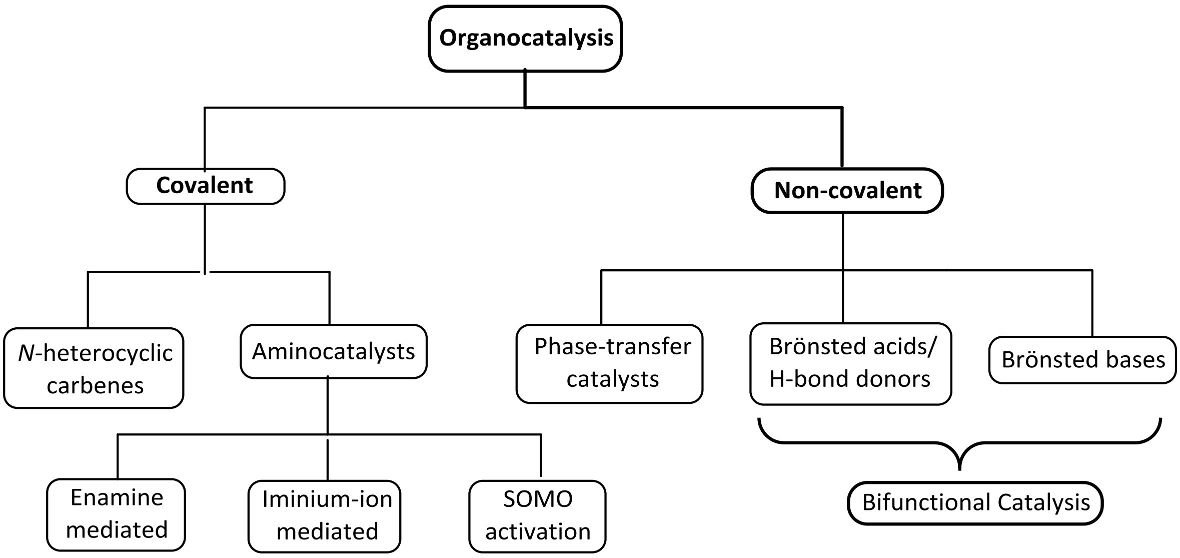

Figure 3. Organocatalysis.

Covalent-based activation is based on the ability of a catalyst to covalent bind a substrate in a reversible fashion to form a chiral reactive intermediate. In this context, aminocatalysis has been the most developed strategy;[22] primary or secondary chiral amines are used to promote the reaction by activation of carbonyl substrate through iminium,[23] enamine,[24] dienanime[25] and trienamine[26] intermediate or through SOMO

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[22] For a general reviews related to the aminocatalysis, see: a) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046. b) Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47. c) Aleman, J.; Cabrera, S. *An. Quím.* **2009**, *105*, 189–197. d) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734. e) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632–649. f) Marqués-López, E.; Herrera, R. P. *Curr. Org. Chem.* **2011**, *15*, 2311–2327. g) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264. h) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 358–368.

[23] a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79–87. b) Pihko, P. M.; Majander, I.; Erkkila, A. *Chem. Rev.* **2007**, *107*, 5416–5470. c) Bartoli, G.; Melchiorre, P. *Synlett*, **2008**, *12*, 1759–1772. d) Brazier, J. B.; Tomkinson, N. C. O. *Top. Curr. Chem.* **2010**, *291*, 281–347.

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

activation.[27] Other types of catalysts, such as *N*-heterocyclic carbenes[28] or less frequently used tertiary amines,[29] alkyl pyridines[30] and trialkylphosphines[31] are also employed in covalent organocatalysis. These activation modes enable the stereoselective functionalization of unmodified carbonyl compounds at the *ipso*, *α* and *β* positions.

Non-covalent approaches are based on the cooperation of weak interactions between the catalyst and a basic functional group on the substrate, through π stacking, polar-, ion pair- and H-bond associations, remembering the ways in which many enzymes activate their substrates. In chiral phase-transfer catalysis (PTC),[32] the chiral catalyst (generally a chiral ammonium salt) and the substrate form a chiral ion pair (being the responsible of asymmetric induction in a biphasic reaction) (Figure 4, a).

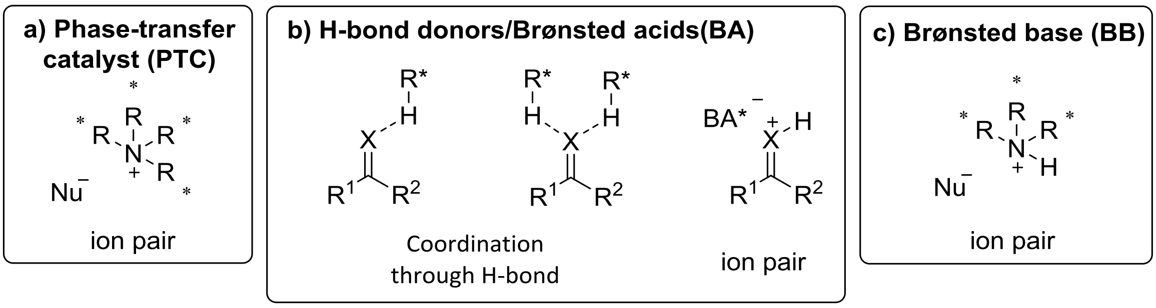

Figure 4. Substrate activation in non-covalent catalysis.

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[25] a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865–887. b) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49,* 4869–4883.

[26] a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061. b) Jiang, H.; Gschwend, B.; Albrecht, L.; Hansen, S. G.; Jorgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032–9036. c) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638–8641. d) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709–716.

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[30] Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595.

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[32] a) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266. b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. c) Maruoka, K.; *Asymmetric Transfer Catalysis* (Wiley-VCH, Weinheim) 2008. d) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *526*, 4312–4348. e) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, *14*, 5367–5376.

On the other hand, chiral Brønsted acid catalysts[33] (commonly organophosphoric acids and derivatives) increase the substrate electrophilicity by protonation at the same time that the chiral ion pair is formed. However, catalysis by H-bond donors (diols, biphenols, ureas, thioureas, squaramides, etc)[34] is effected decreasing the electron-density of an acceptor (typically a π system) or increasing the acidity of the carbon nucleophiles upon coordination of a heteroatom through H-bond forming. Thanks to this coordination a chiral environment is generated close to the reagent (Figure 4, b).

Finally, catalysis by chiral Brønsted bases (BB),[35] relies on the activation of the substrate by deprotonation leading to a chiral ion pair (Figure 4, c). Tertiary amines, guanidines, amidines and imidazoles are the most prominent nitrogen-containing functionalities used for the design of chiral BB catalysts. In this context, natural cinchona alkaloids constitute very popular source of enantiopure BB which provide diversity in stereochemical and constitutional terms (Figure 5).

R^1 = OMe, R^2 = vinyl (–)-Quinine
R^1 = OMe, R^2 = ethyl (–)-Dihydroquinine
R^1 = H, R^2 = vinyl (–)-Cinchonidine

R^1 = OMe, R^2 = vinyl (+)-Quinidine
R^1 = OMe, R^2 = ethyl (+)-Dihydroquinidine
R^1 = H, R^2 = vinyl (+)-Cinchonine

Figure 5. Alkaloids from the cinchona family.

As a result of the non-directional nature of the electrostatic interactions of the formed ionic complexes, it is difficult to predict the stereochemical course of the BB-catalyzed reactions. Incorporating some hydrogen donor group into the BB catalyst structure (bifunctional catalyst) would allow to simultaneously activate the pronucleophile and the electrophile of the reaction providing greater stereochemical control of the process

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[33] a) Akiyama, T.; Itoh, J.; Fuchible, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. b) Terada, M. *Chem. Comm.* **2008**, 4097–4112. c) Lv, F.; Liu, S.; Hu, W. *Asian J. Org. Chem.* **2013**, *2*, 824–836.

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(Figure 6).[36] Within bifunctional catalysts, those based on Brønsted bases are especially useful tool on asymmetric catalysis due to the availability of alkaloids usually employed in BB in Nature.

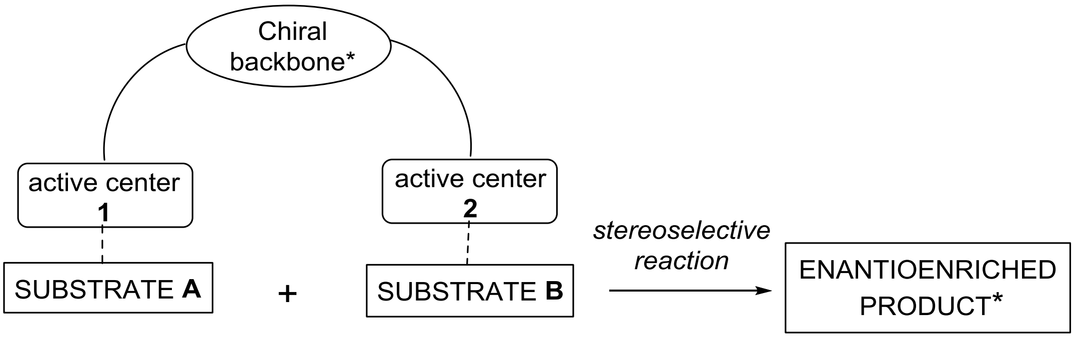

Figure 6. Bifunctional catalysis.

Although previous examples of cinchona alkaloids-based catalytic transformation were seldom documented, in 1975 Wynberg published the first example of Brønsted base catalyzed reaction in which cinchona alkaloids operated as bifunctional catalyst in enantioselective addition of α-ketoesters to vinyl ketones (Figure 7, a).[37] The tertiary amine activates the pronuclephile by deprotonation while the hydroxyl group activates the electrophile by hydrogen-bond.[38] In 2003, Takemoto and co-workers developed cyclohexyldiamine derived thiourea catalysts, in which they proposed that the thiourea moiety activated the nitroalkenes by H-bond forming, while the tertiary amine deprotonated the dimethylmalonate in the Michael addition (Figure 7, b).[39] Since 2003, a variety of thiourea-subtituted cinchona alkaloid catalyst systems have been developed, demonstrating their effectiveness in many transformations.[40] More recently, since in

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[36] For reviews related to bifunctional organometallic catalysts, see: a) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, *10*, 1491–1508. b) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117–1127. c) Cao, Z.-Y.; Brittain, W. D. G.; Fossey, J. S.; Zhou, F. *Cat. Sci. Technol* **2015**, *5*, 3441–3451. For reviews related to bifunctional organocatalysts, see: d) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504. e) Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 6145–6158. f) Wang, S.-X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, *19*, 2766–2778. g) Tsakos, M.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 10199–10222.

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[40] For a reviews on bifunctional catalysis promoted by urea/thiourea Brønsted base catalysts, see: a) Connon, S. J.; *Chem. Commun.* **2008**, 2499–2510. b) Fang, X.; Wang, C.-G. *Chem. Commun.* **2015**, *51*, 1185–1197. For pionering examples, see: c) Li, B. J.; Jiang, L.; Liu, M.; Cheng, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603–606. d) Vaculya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969. e) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370. f) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. For some recent examples, see: g) Montesinos-Magraner, M.; Vila, C.;

2008 Rawal´s group demonstrated the capacity of the squaramides as bifunctional catalysts (Figure 7, c)[41], they have been the focus of much attention.[42]

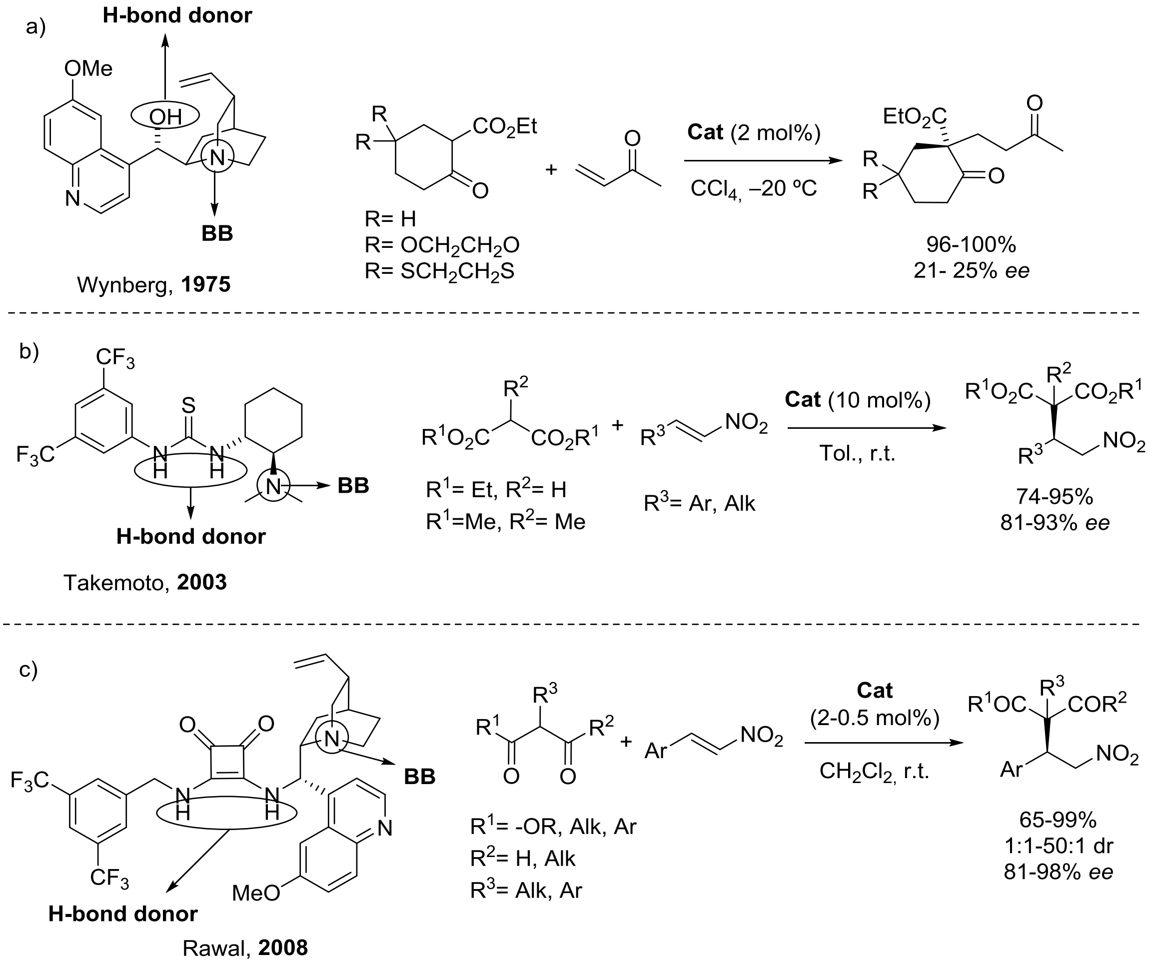

Figure 7. Representative first reported reaction using bifunctional Brønsted base organocatalysts.

1.1.1.1. *Squaramides vs thioureas*

As mentioned above, several H-bond donors such as diols, biphenols, ureas, thioureas, squaramides, etc. have been employed in asymmetric catalysis, of which the thioureas and squaramides are the most common in bifunctional Brønsted base catalysts so far.

Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 6320–6324. h) Wang, J.-J.; Yang, H.; Gou, B.-B.; Zhou, L.; Chen, J. *J. Org. Chem.* **2018**, *83*, 4730–4738.

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

[42] For reviews on bifunctional catalysis promoted by squaramides Brønsted base catalysts, see: a) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346. b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899. c) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253–281. d) Held, F. E.; Tsogoeva, S. B. *Catal. Sci. Technol.* **2016**, *6*, 645–667. e) Rouf, E.; Tanyel, C. *Curr. Org. Chem.* **2016**, *20*, 2996–3013.

In general, squaramides have demonstrated higher reactivity than thiourea catalysts in asymmetric transformations, and hence, the catalyst loading needed to complete the full conversion of the substrate is lower. This extraordinary performance is due to the special characteristics that the squaramide skeleton gives to these catalysts. The additional advantage of squaramides is their facile preparation from easily available starting materials, besides that in many cases, as the catalyst is formed, it precipitates in the reaction solution, so is available by filtration and the chromatographic purification is not nesesary.

In terms of structural differences, squaramide posses four-membered ring with two hydrogen-bond acceptors at the carbonyl groups and two N-H hydrogen-bond donor groups (Figure 8, a). In addition, crystallographic structure reported by Rawal has demonstrated that these N–H groups are coplanar with the cyclobutendione rigid unit and that the distance between them is longer than in case of thioureas.[43] The square geometric also induces the disposition of N–H groups with an angle of approximately 6° (Figure 8, b).

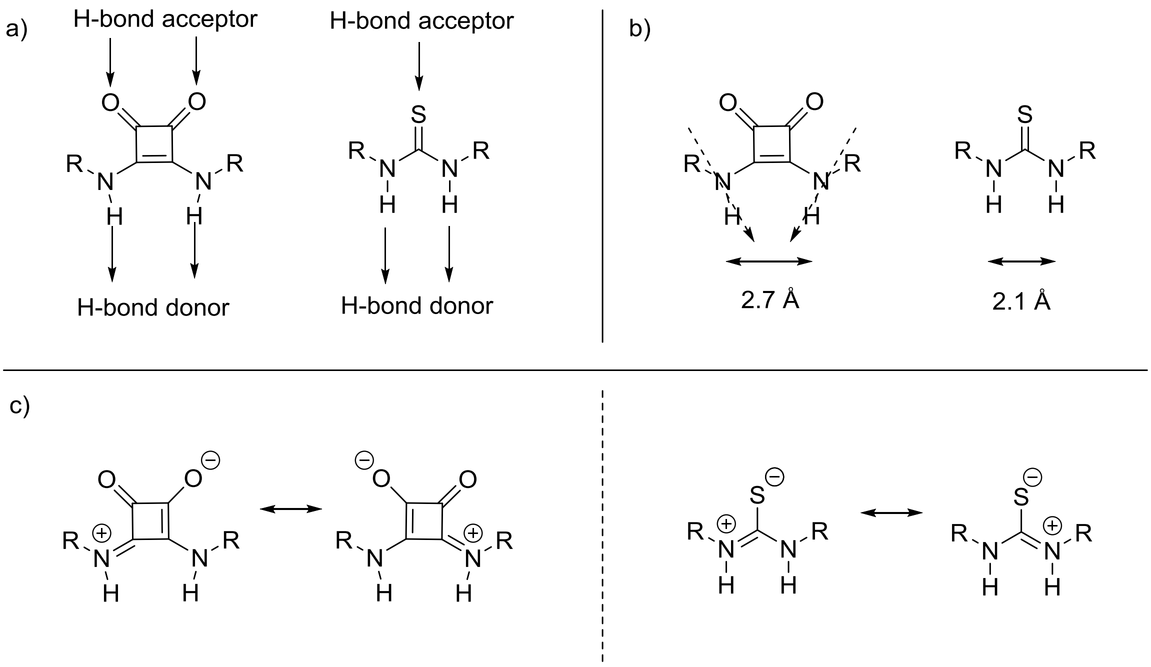

Figure 8. Structural differences between squaramide and thiourea skeletons.

Even so, probably the structural difference that justifies its greater reactivity than the thioureas is their further capacity to delocate the nitrogen lone pair through the partially

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

aromatic cyclobutenedione system (Figure 8, c).[44] Thus, as Cheng's study confirmed,[45] the acidity of squaramides is higher compared to thiourea and the hydrogen bonds that are formed with the substrates are stronger.

Accordingly, in this thesis work special interest has been placed on the design of new squaramide-based bifunctional Brønsted base catalysts, particularly, to be employed in the stereoselective synthesis of α- quaternary amino acid derivatives.

1.2. α-Quaternary Amino Acids

The design and synthesis of polyfunctionalized molecules not present in Nature have caused much interest among organic, bioorganic, peptide and medicinal chemists in the 21st century. One category of such rationally functionalized molecules might be foldamers (firstly named by Gellman),[46] that are polymers with a strong tendency to adopt a specific compact conformation. The last foldamers designed and developed by evolution in Nature might be the natural enzymes and receptors, which can adopt a three-dimensional defined form and have specific biological functions.[47]

In this context, naturally occurring L-α-amino acids have an essential role as building blocks of oligopeptides and proteins, and the synthesis of these building blocks has attracted considerable interest.[48] The diverse functionalities of peptides are conditioned by physical and chemical properties of specific side chain of the amino acid residues and their three-dimensional structures (secondary structures). However, oligopeptides composed by natural L-α-amino acids often form unstable or unordered

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

[45] For study related to the pKa of thioureas, see: a) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S. Z.; Cheng, J.-P. *Chem. Eur. J.* **2010**, *16*, 450–455. b) Jakab, G.; Tancon, C.; Zhang, Z. G.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724–1727. For study related to the pKa of squaramides, see: c) Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16*, 1786–1789.

[46] Gellman, S. H.; *Acc. Chem. Res.* **1998**, 173–181.

[47] a) Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J. *Chem. Rev.* **2000**, *100*, 235–349. b) Champoux, J. J. *Annu. Rev. Biochem.* **2001**, *70*, 369–413. c) Vieille, C.; Zeikus, G. J. *Microbiol. And Molec. Biol. Rev.* **2001**, *65*, 1–43.

[48] For selected reviews on the asymmetric synthesis of α-amino acids, see: a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. b) Martens, J. *ChemCatChem* **2010**, *2*, 379–381. c) Luo, Y.-C.; Zhang, H.-H.; Wang, Y.; Xu, P.-F. *Acc. Chem. Res.* **2010**, *43*, 1317–1330. d) Jakubowska, A.; Kulig, K. *Curr. Org. Synth.* **2013**, *10*, 547–563. e) Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. *Amino Acids* **2013**, *45*, 1017–1033. f) Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. *Amino Acids* **2014**, *46*, 2047–2073. For leading books on the topic, see: g) R. M. Williams, *Synthesis of Optically Active α-Amino Acids* (Pergamon, Oxford) 1989. h) *Asymmetric Synthesis and Application of α-Amino Acids* (V. A. Soloshonok & K. Izawa ed., American Chemical Society, Washington DC) 2009.

secondary structures and can adopt several conformations in solution, particularly in the case of short peptides due to their flexible nature. Only a few conformers are responsible for their diverse biological properties, so this instability in the secondary structure is a drawback in the use of the oligopeptides as drug candidates and functionalized-deviced molecules.[49] In addition, α-amino acids are employed as chiral source in chemical catalysis and synthesis.[50]

The modification of native peptides constitutes a powerful means to modulate the biological properties and conformation of peptides. Thus, organic chemists have demonstrated great interest in the design of non-proteinogenic α-amino acids.[51] α-Quaternary α-amino acids, which derive from the replacement of the α-hydrogen atom of L-α-amino acids with an alkyl or aryl substituent, change the properties of the native L-α-amino acids and derived peptides as follow:[52] 1) increasing the stability against chemical and enzymatic hydrolysis, 2) increasing hydrophobicity, and 3) increasing helix-inducing potencial (Scheme 1). These effects have been attributed to the loss of conformational freedom due to the steric constraint, which restricts the secondary

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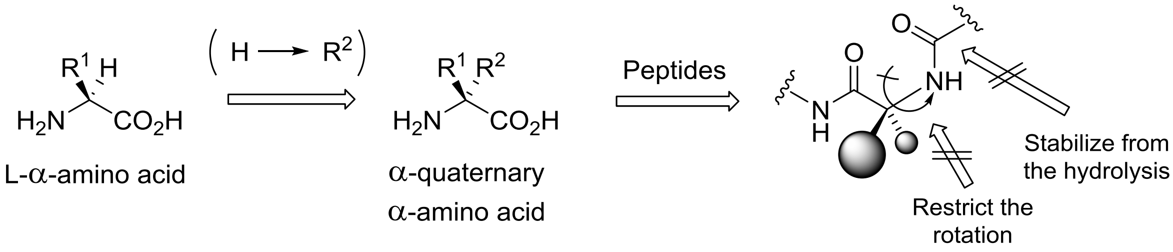
[49] Adessi, C.; Soto, C.; *Curr. Med. Chem.* **2002**, *9*, 963–975.

[50] For application in asymmetric synthesis of biodegradable polymers, see: a) Sun, H.; Meng, F.; Dias, A. A.; Hendriks, M.; Feijen, J.; Zhong, Z. *Biomacromolecules* **2011**, *12*, 1937–1955. For their use as chiral auxiliaries, see: b) W. Maison, *Comprehensive Chirality* (E. M. Carreira & K. Yamamoto ed., Elsevier B.V., Amsterdam) **2012**. For application in asymmetric synthesis of heterocycles: c) Singh, P.; Samanta, K.; Das, S. K.; Panda, G. *Org. Biomol. Chem.* **2014**, *12*, 6297–6339.

[51] For selected reviews on the synthesis of unnatural α-amino acids, see: a) Hanessian, S.; McNaughton-Smith, G; Lombart, H.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. b) Michaux, J.; Niel, G.; Campagne, J.-M. *Chem. Soc. Rev.* **2009**, *38*, 2093–2116. c) Tarui, A.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Adv. Synth. Catal.* **2010**, *352*, 2733–2744. d) Johansson, H.; Pedersen, D. S. *Eur. J. Org. Chem.* **2012**, 4267–4281. e) Popkov, A.; Elsinga, P. *Curr. Org. Chem.* **2013**, *17*, 2127–2137. f) Kotha, S.; Goyal, D.; Chavan, A. S. *J. Org. Chem.* **2013**, *78*, 12288–12313. g) Kotha, S.; Bandarugattu, V. B.; Krishna, N. G. *Tetrahedron* **2014**, *70*, 5361–5384. h) Harkiss, A. H.; Sutherland, A. *Org. Biomol. Chem.* **2016**, *14*, 8911–8921. For leading book on the topic, see: i) J. Vidal, *Amino Acids, Peptides and Proteins in Organic Chemistry* (A. B. Hughes ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2009. j) M. Ikunaka & K. Maruoka, *Asymmetric Catalysis on Industrial Scale* (H.-U. Blaser & H.-J. Federsel ed., Wiley-VCH Verlag GmbH & Co. KGaA 2nd ed.) 2010.

[52] For some reviews on the biological properties of quaternary α-amino acids, see: a) Karle I. L; Balaram P.; *Biochemistry* **1990**, *29*, 6747—6756. b) Heimgartner H., *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238—264. c) Crisma, M.; Valle, G.; Bonora, G. M.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternall, F.; Hardy, P. M.; Maia, H. L. S. *Biopolymers* **1991**, *31*, 637–641. c) Gante, J. *Angew. Chem. Int. Ed.* **1994**, *33*, 1699–1720. d) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048–12054. e) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152. f) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. *Synlett* **2006**, *2006*, 1295–1310. g) Tanaka, M. *Chem. Pharm. Bull. (Tokyo).* **2007**, *55*, 349–358. h) Guichard, G.; Huc, I. *Chem. Commun.* **2011**, *47*, 5933–5941.

structure of peptides. Besides the application in peptide chemistry, quaternary α-amino acids are found in many natural and biologically active compounds as well (Figure 9).[53,54]



Scheme 1. General structure of the L-α-amino acids, quaternary α-amino acids and derived peptide.

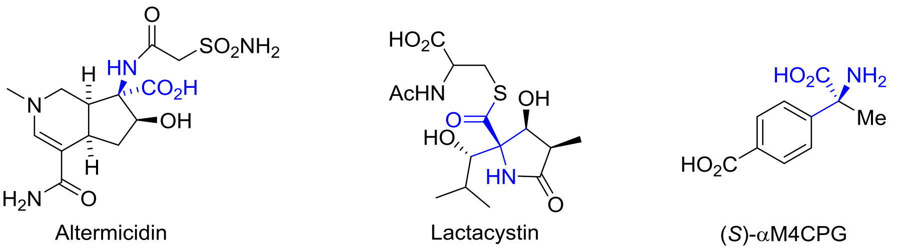


Figure 9. Examples of biologically active quaternary α-amino acids.

Due to the great importance of α,α-disubstituted amino acids, a variety of approaches to their stereoselective synthesis have been developed.[55,56] Here, we should distinguish those based on the stoichiometric of a chiral source, either an auxiliary or a molecule

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[53] a) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, *117*, 10597–10598. b) Yano, H.; Nakanishi, S.; Ikuina, Y.; Ando, K.; Yoshida, M.; Saitoh, Y.; Matsuda, Y. *J. Antibiot. (Tokyo).* **1997**, *50*, 992–997. c) Becker, D.; Kiess, M.; Brückner, H. *Liebigs Ann.* **1997**, *1997*, 767–772.

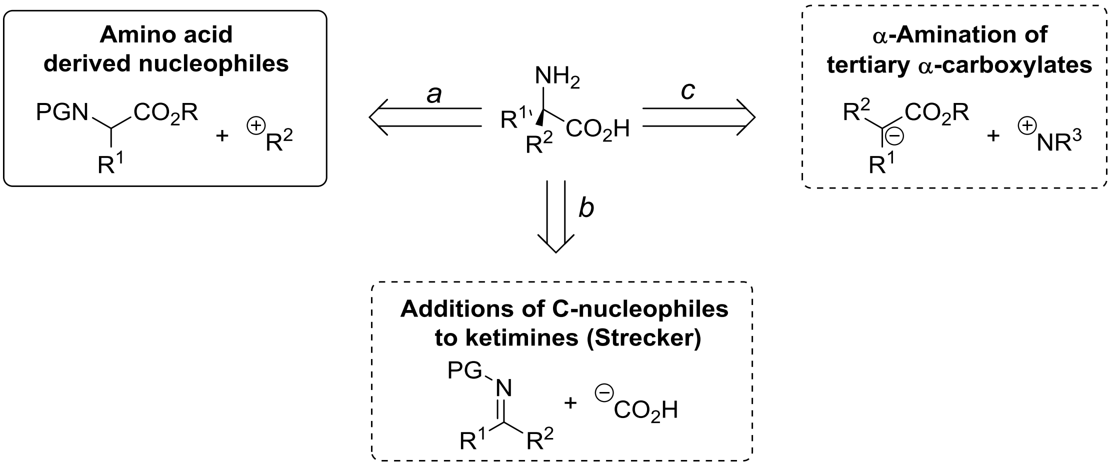
[54] For selected examples of bioactive quaternary α-aminoacids, see: a) Altermicidin: Takahashi, A.; Kurasawa, S.; Ikeda, D.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 1556–1561. b) Lastacystin: Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726–731. c) (S)α-M4CPG: Kingston, A. E.; Burnett, J. P.; Mayne, N. G.; Lodge, D.; *Pergamon* **1995**, *34*, 887–894.

[55] For selected reviews on the synthesis of quaternary α-amino acids, see: a) Cativiela, C.; Díaz-de-Villegas M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, *2005*, 5127–5143. c) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430. d) Tanaka, M. *Chem. Pharm. Bull. (Tokyo).* **2007**, *55*, 349–358. d) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623. e) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63. f) Soloshonok, V.; Sorochinsky, A. *Synthesis* **2010**, 2319–2344. g) Baer, K.; Dückers, N.; Hummel, W.; Gröger, H. *ChemCatChem* **2010**, *2*, 939–942. h) Bera, C.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234–1260.

[56] Review on the Self-Regeneration of Stereocentres (SRS), see: a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2708–2748. For a recent example employing chiral auxiliaries to synthesize quaternary α- amino acids, see: b) Netz, I.; Kucukdisly, M; Opatz, T. *J. Org. Chem*. **2015**, *80*, 6864–6869. For a review on Memory of Chirality (MOC), see: c) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16. For an example of MOC of tertiary aromatic amides, see: d) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711–10718. For a recent example of the synthesis of β-hydroxy quaternary α-amino acids through MOC, see: e) Viswambharan, B.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Org. Lett.* **2014**, *16*, 788–791.

from the chiral pool, from the catalytic methods. Methods based on chiral catalysts are more attractive and atom-economic than stoichiometric methods.

Catalytic asymmetric methods for the synthesis of α,α-disubstituted amino acids can be classified in four main groups, based on the type of reaction disconnection (Scheme 2). The strategy based on the nucleophilic addition of masked amino acids is the most obvious and Figure 10 shows the most useful α-amino acid derivatives within this strategy. This thesis is focused on the use of α-substituted isocyano(thio)acetates, particularly, their Michael addition to α,β-unsaturated ketones as a route to α-quaternary proline derivatives. A preliminary study of the Mannich reaction to several imines has also been carried out, a very useful reaction commonly used for the synthesis of α-quaternary α, β-diamino acids.



Scheme 2. Retrosynthetic analysis of quaternary α-amino acids.

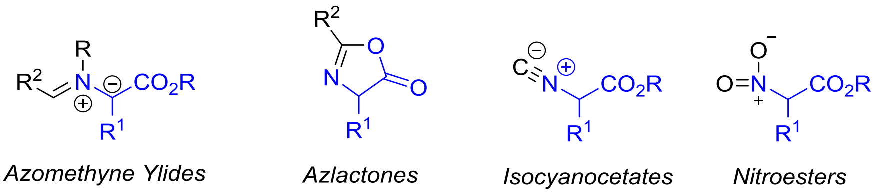


Figure 10. Most common α-amino acid derived nucleophiles.

1.3. α-Quaternary Prolines

Among all the α-amino acids, proline analogues are of special interest given their ability to constrain the conformation of peptides once incorporated in their backbone structure. Such significance is due to the exceptional rigidity conferred by its cyclic structure and the hinge behaviour thanks to the participation of pyrrolidine nitrogen in peptide bonds (Figure 11).[57] The interest of proline analogues is also due to protein-protein interactions mediated by link domains rich in these amino acids[58] and to their capacity to generate β-turn secondary structures in peptidomimetics.[59] α-Quaternary proline analogues constitute a particularly relevant subclass. The number of studies carried out in relation to the incorporation of α-methylated proline into peptides and other biologically active compounds demonstrates the relevance of these proline analogues.[60] Although many aspects of the α-quaternary prolines conformational preference are still unknown, their use as templates in studies of the structure-function relationship of biologically active conformations is widespread.[61] In addition, α-quaternary prolines are valuable building blocks for the design and construction of organic catalysts and chiral auxiliaries for asymmetric synthesis.[62]

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[57] For selected reviews and articles related to proline analogues, see: a) MacArthur, M. W.; Thornton, J. M.; *J. Mol. Biol.* **1991**, *218*, 397–412. b) Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205–1211. c) Reiersen, H.; Rees, A. R. *Trends. Biochem. Sci.* **2001**, *26*, 679–684. d) Bach, T. M. H.; Takagi, H. *Appl. Microbiolog. Biotecnolog* **2013**, *97*, 6623–6634. For leading book on the topic, see: e) Karoyan, P.; Sagan, S.; Lequin, O.; Quancard, J.; Lavielle, S.; Chassaing, G. *Susbtituted Prolines: Syntheses and Applications in Structure-Activity Relationship Studies of Biologically Active Peptides.* In *Targets in Heterocyclic Systems-Chemistry and Properties*; Attanasi, O.A., Spinelli, D., Eds.; Royal Society of Chemistry: Cambridge, UK, 2004; Volume 8, pp. 216–273.

[58] *Handbook of Biologically Active Peptides*; Kastin, A. J., Ed.; Academic Press, Elsevier: London, 2006.

[59] a) Aubry, A.; Vitoux, B.; Marraud, *Biopolymers* **1985**, *24*, 1089–1100. b) M.Kee, S.; Jois, S. *Curr. Pharm. Des.* **2003**, *9*, 1209–1224.

[60] For selected articles related to the relevance of α-methylated proline, see: a) Thaisrivongs, S.; Pals, D. T.; Lawson, J. A.; Turner, S. R.; Harris, D. W. *J. Med. Chem.* **1987**, *30*, 536–541. b) Hinds, M. G.; Welsh, J. H.; Brennand, D. M.; Fisher, J.; Glennie, M. J.; Richards, N. G. J.; Turner, D. L.; Robinson, J. A. *J. Med. Chem.* **1991**, *34*, 1777–1789. c) Bisang, C.; Weber, C.; Inglis, J.; Schiffer, C. A.; van Gunsteren, W. F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7904–7915. d) Doherty, G. A.; Yang, G. X.; Borges, E.; Tong, S.; McCauley, E. D.; Treonz, K. M.; Riper, G. V.; Pacholok, S.; Si, Q.; Koo, G. C.; Shah, K.; Mumford, R. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1891–1895 and references cited therein. e) Coleman VI, D. R.; Ren, Z.; Mandal, P. K.; Cameron, A. G.; Dyer, G. A.; Muranjan, S.; Campbell, M.; Chen, X.; McMurray, J. S. *J. Med. Chem.* **2005**, *48*, 6661–6670.

[61] a) Delaney, N. G.; Madison, V. *J. Am. Chem. Soc.* **1982**, *104*, 6635–6641. b) Flippen-Anderson, J. L.; Gilardi, R.; Karle, I. L.; Frey, M. H.; Opella, S. J.; Gierasch, L. M.; Goodman, M.; Madison, V.; Delaney, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6609–6614. c) Baures, P. W.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L. *J. Pept. Res.* **1997**, *50*, 1–13. d) Paradisi, M. P.; Mollica, A.; Cacciatore, I.; Di Stefano, A.; Pinnen, F.; Caccuri, A. M.; Ricci, G.; Duprè, S.; Spirito, A.; Luccente, G. *Bioorg. Med. Chem.* **2003**, *11*, 1677–1683. e) Sugase, K.; Horikawa, M.; Sugiyama, M.; Ishiguro, M. *J. Med. Chem.* **2004**, *47*, 489–492.

[62] *Enantioselective Organocatalysis;* Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007.

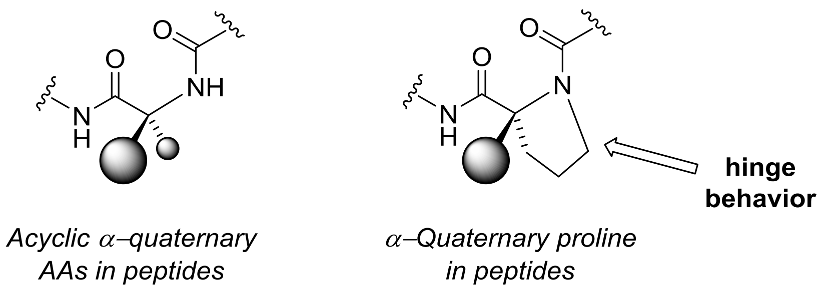

Figure 11. Peptides composed by α-quaternary acyclic AAs VS α-quaternary proline analogues.

Besides this, according to the study carried out by Njardarson *et al.* in relation to the relevance of the nitrogen heretocycles in the pharmaceutical industry,[63] among the nitrogen heterocycle containing drugs approved by the US Food and Drug Administration, pyrrolidine is ranked number five, appearing in 37 drugs. Among all these drugs the proline core is the most commonly employed pyrrolidine structural fragment (Figure 12). Also, this structure can be found in many natural products and biologically active substances (Figure 13).[64,65,66]

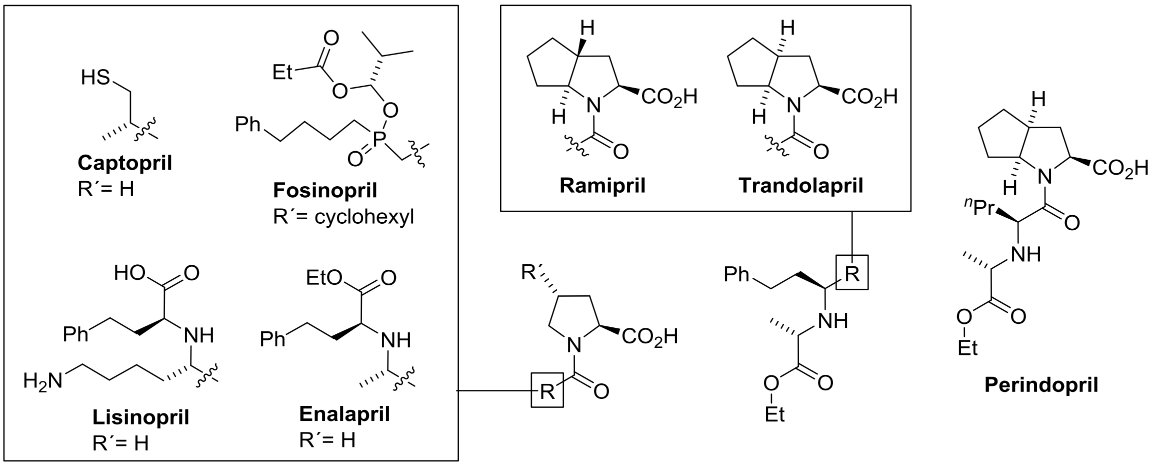

Figure 12. Pharmaceuticals containing proline core.

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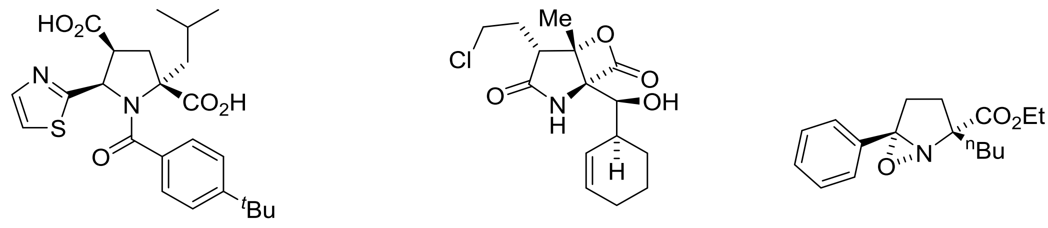
[63] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

[64] Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R.-T.; Lin-Goerke, J.; Hofmann, G. A.; Slater, M. J.; Haigh, D.; Dhanak, D.; Johnson, V. K.; Parry, N. R.; Thomes, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1930–1933.

[65] a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113–116. b) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 355–357.

[66] Ningsanont, N.; Black, D. S. C.; Chanphen, R.; Thebtaranonth, Y. *J. Med. Chem.* **2003**, *46*, 2397–2403.



GSK polymerase inhibitor [64] **Salinosporamide A** [65] **Antimalarial** [66]

Figure 13. Examples of biologically active α-quaternary prolines

For all these reasons, in recent years, special interest has been paid to the asymmetric synthesis of prolines containing an α-quaternary stereocenter.[67] The strategies can be classified according to two main groups as depicted in Figure 14: 1) α-functionalization of proline analogues and 2) nucleophilic addition of α-substituted amino acid derivatives to electron-deficient olefins. An alternative classification would distinguish whether the chiral inductor is used in stoichiometric or catalytic amount. In this thesis, emphasis will be made in catalytic asymmetric approaches which are, as said before, more attractive and atom-economic.

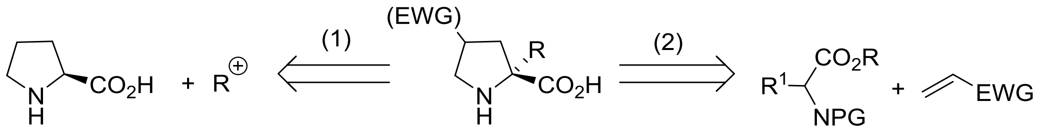


Figure 14. Strategies to complete the α-quaternary proline skeleton.

1.3.1. Estereoselective synthesis of α-quaternary prolines

1.3.1.1. α-Functionalization of a proline analogue

The α-functionalization of a chiral proline analogue, frequently by reaction with an electrophilic alkylating reagent, is one of the general approaches to optically active α-quaternary proline derivatives. In this context, in 1981 Seebach developed the self-regeneration of stereocentres strategy (SRS),[68] which consists of a chirality rely on a temporary formed stereogenic center (auxiliary) via diastereoselective formation of a bicyclic hemiaminal (Scheme 3). Then, the diastereoselective alkylation at the Cα followed by aminal hydrolysis provides α-quaternary prolines with retention of the

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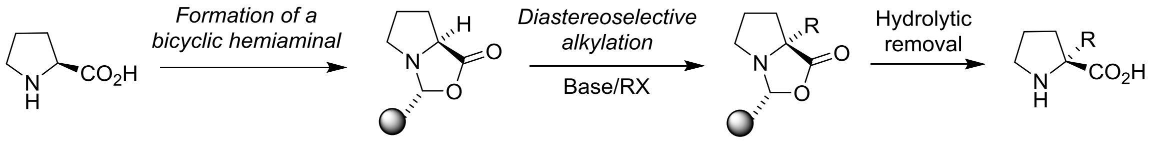
[67] For selected reviews of α-quaternary proline synthesis, see: a) Calaza, M. I.; Cavitiela, C. *Eur. J. Org. Chem.* **2008**, 3427–3448. b) ref.55a page 17. c) ref.55e page 17. d) ref.55h page 17.

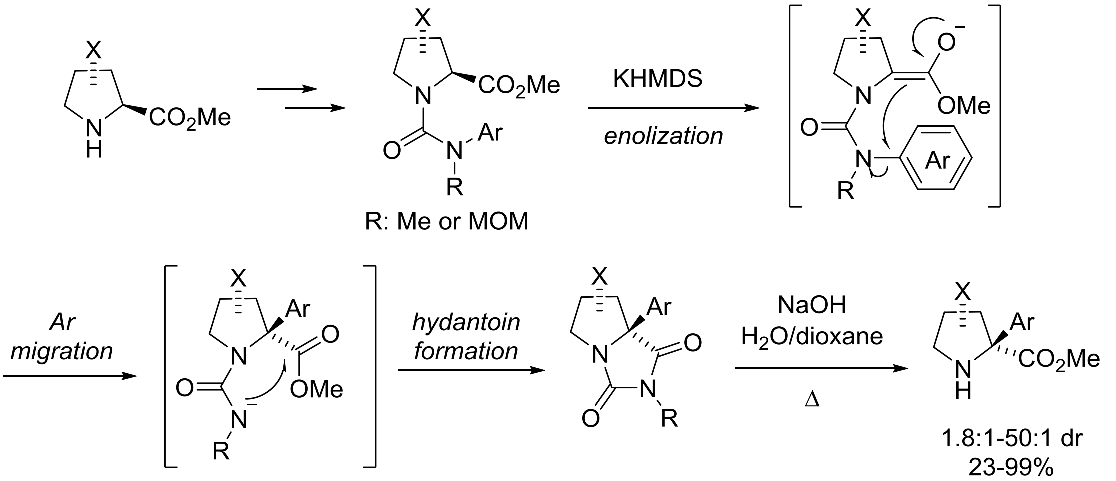
[68] a) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704–2708. b) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398. c) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708–2748.

configuration. The strategy has been further developed, to broaden the scope of the reaction, modulate the diastereoselectivity and explore new variations.[69]



Scheme 3. Seebach´s self-regenation of stereocenters strategy

Alternatively, the diastereoselective Cα alkylation of substituted L-proline esters can be achieve if the initial proline contains a second stereocenter with the set configuration.[70] The spatial orientation of the substituents on the second stereocenter determines the approach of the incoming group R. Based on this strategy, recently the diastereoselective Cα arylation of L-proline derivatives have also been achieved by Claiden (Scheme 4).[70e]



Scheme 4. Diastereoselective Cα arylation of L-proline derivatives.

On the other hand, there is one example of catalytic asymmetric construction of α-quaternary stereocentre from racemic 3-oxoproline analogue, developed by Maruoka in

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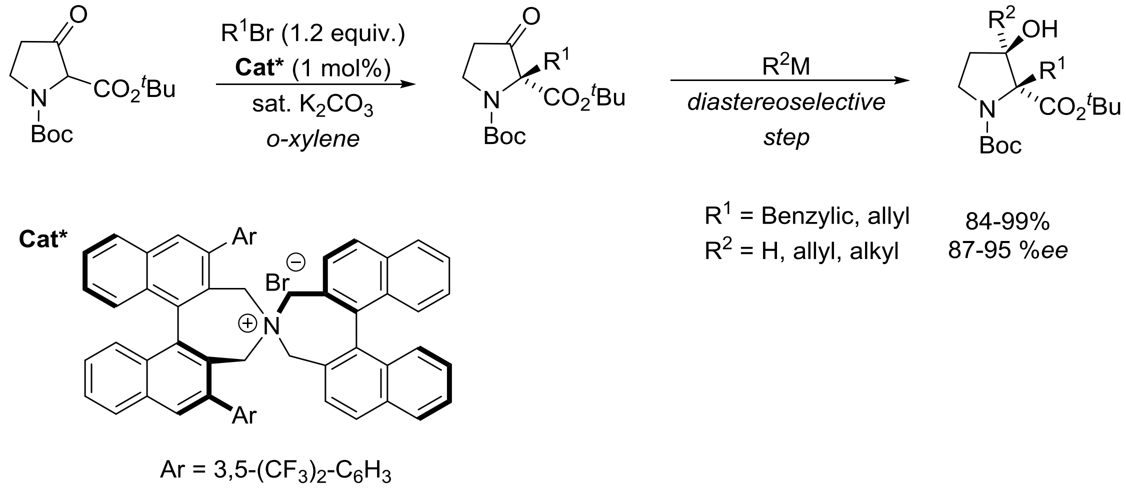
[69] For recent examples employing SRS to synthesize quaternary prolines, see: a) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Org. Lett.* **2014**, *16*, 432–435. b) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Tetrahedron* **2015**, *71*, 5814–5823. c) Temizsoy, M.; Sethi, W.; Reinholt, A.; Schau-Magnussen, M.; Bendix, J.; Hammershøi, A. *Dalton Trans.* **2015**, *44*, 18438–18446.

[70] For selected examples related to diastereoselective Cα-alkylation of substituted L-proline esters, see: a) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Perkin Trans.* **1995**, *1*, 1801–1808. b) Nagumo, S.; Mizukami, M.; Akutsu, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209–3212. c) Hussaini, S. R.; Moloney, M. G. *Org. Biomol. Chem.* **2006**, *4*, 2600–2615. d) Filosa, R.; Holder, C.; Auberson, Y. P. *Tetrahedron Lett.* **2006**, *47*, 8929–8932. e) Maury, J.; Clayden, J *J. Org. Chem.* **2015**, *80*, 10757–10768.

2005.[71] α-Quaternary proline analogues were enantioselectively obtained by asymmetric allylic alkylation of the precursor 3-oxoproline under phase-transfer condition using binaphthyl-derived spiranic chiral ammoniun bromide as catalyst (Scheme 5).



Scheme 5. Phase-transfer-catalyzed alkylation of racemic 3-oxo proline analogue.

1.3.1.2. Nucleophilic (cyclo)additions of α-amino acid derivatives

Methods involving *de novo* formation of the pyrrolidine ring have been developed to a relatively larger extent based primarily on the use of the chiral pool or chiral auxiliaries,[72] but also asymmetric catalysis. Within all strategies, asymmetric [3+2] cycloaddition (also known as 1,3-dipolar cycloaddition) of α-amino acid derivatives has been extensively studied for the stereoselective synthesis of α-quaternary pyrrolidines.[73] Both strategies, the use of chiral dipole[74]/dipolarophile[75] as starting material or the

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[71] Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191–193.

[72] See ref. 67, page 21.

[73] For general reviews on asymmetric 1,3-dipolar cycloadditions, see: a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909. b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285. c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902. d) T. Hashimoto, K. Maruoka, *Chem. Rev*. **2015**, *115*, 5366–5412; e) M. S. Singh, S. Choudhury, S. Koley, *Tetrahedron* **2016**, *72*, 1603–1644.

[74] For selected examples related to the use of chiral dipoles on the asymmetric catalytic [3+2] cycloadditions, see: a) Anslow, A. S.; Hardwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 997–1000. b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707–1710. c) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Eur. J. Org. Chem.* **2001**, 3133–3140. d) Alcaide, B.; Almendros, P.; Alonso, J. M.; Redondo, M. C. *J. Org. Chem.* **2003**, *68*, 1426–1432. e) Alcaide, B.; Almendros, P.; Redondo, M. C.; Ruiz, M. P. *J. Org. Chem.* **2005**, *70*, 8890–8894.

[75] For selected examples related to the use of chiral dipolarophiles on the asymmetric catalytic [3+2] cycloadditions, see: a) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791–7808. b) Waldmann, H.; Bläser, E.; Jansen, M; Letschert, H.-P. *Chem. Eur. J.* **1995**, *1*, 150–154. c) García-Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981–987. d) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vanaclocha, F.; Cossío, F. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 2903–2907. e) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1985–1989.

reaction between achiral starting materials under the control of a chiral catalyst, are plausible.

With respect to the strategies focused on the use of chiral catalysts, most of the progress relies on the Lewis acid type catalysts, formed by complexation of a transition metal and a coordinating chiral ligand. However, in recent years, protocols based on organocatalysts have become popular.[76]

The majority of examples of organocatalytic [3+2] cycloadditions so far reported involve α-unsubstituted glycine derivatives as 1,3-dipoles (ylides); ylides derived from α-substituted amino acids, especially α-alkyl substituted, have been much less used. In general, dipoles derived from α-substituted α-amino acids require very reactive dipolarophiles for the cycloadditions to proceed conveniently. Commonly, this is achieved by employing α-iminoesters (azomethine ylide precursors) with an additional activating group at α-position to increase the acidity of this Cα,[77] most commonly two ester groups.[78] However, in the resulting prolines the cleavage of one of the electron-withdrawing group would require in order to prepare biologically and catalytically important proline scaffolds, hence, the quaternary centre is lost. In short, the most persecuted strategy for the synthesis of α-quaternary proline has been [3+2] cycloaddition involving α-aryl or α-alkyl substituted amino acid derivatives (Figure 15).

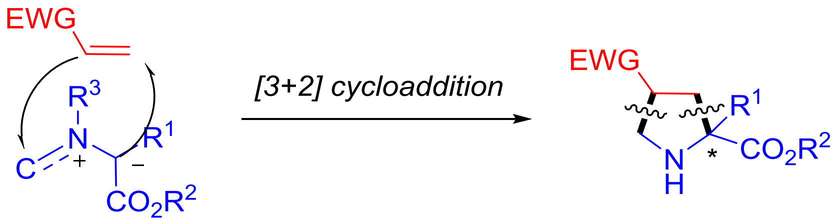

Figure 15. General [3+2] cycloaddition involving α-aryl or α-alkyl substituted amino acid derivatives.

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[76] For reviews of organocalytic [3+2] cycloadditions: a) Held, F. E.; Tsogoeva, S. B.; *Catal. Sci. Technol.* **2016**, *6*, 645–667. c) Vicario, J. L. *Synlett* **2016**, *27*, 1006–1021.

[77] For examples involving dipoles bearing different EWG groups, see: a) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307–3312. b) Lin, S.; Deiana, L.; Zhao, G.-L.; Sun, J.; Córdova, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 7624–7630.

[78] For examples involving α-diester dipoles, see: a) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168–5170. b) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130,* 5652–5653. c) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946–4949. d) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825. e) Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275–1277. f) Tian, L.; Xu, G.-Q.; Li, Y.-H.; Liang, Y.-M.; Xu, P.-F. *Chem. Commun.* **2014**, *50*, 2428–2430.

Below are collected the main studies carried out with α-aryl or α-alkyl substituted amino acid derivatives, namely: 1) azomethyne ylide precursors, 2) α-nitroesters and 3) α-isocyanoacetates.

1.3.1.2.1. Azomethine ylides

1.3.1.2.1.1. [3+2] Cycloadditions

Definitely, one major thoroughly investigated approach for the synthesis of polyfunctionalized prolines relies on the metal-catalyzed[79] [3+2] cycloaddition involving azomethine ylides and electron-deficient olefins.[80] In this context, α-alkyl or α-aryl substituted azomethine ylides have been applied in [3+2] cycloadditions reactions with many types of dipolarophiles (Table 1, entry 1). In addition to the best-known azomethine ylides, azlactones also have been used as cyclic azomethine equivalents in some catalytic asymmetric [3+2] cycloadditions for the synthesis of α-quaternary prolines (entry 2).[81]

Acrylates,[82,] fumarates/maleates[,83] maleimides,[84] nitroalkenes[85] and enones[86] have been the most used dipolarophiles in these reactions. To a lesser extent,

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[79] For metal-catalyzed [3+2] cycloaddition involving azomethine ylides, see: Adrio, J; Carretero, C *Chem. Commun.* **2011**, *47*, 6784–6784.

[80] For selected reviews related to the catalytic [3+2] cycloaddition involving azomethine ylides, see: a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809. b) J. Adrio, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 12434–12446; c) K. Jiang, Y.-C. Chen, *Tetrahedron Lett*. **2014**, *55*, 2049–2055; d) R. Narayan, M. Potowski, Z.-J. Ja, A. P. Antonchick, H. Waldman, *Acc. Chem. Res.* **2014**, *47*, 1296–1310; e) C. Nájera, J. M. Sansano, M. Yus, *Org. Biomol. Chem*. **2015**, *13*, 8596.

[81] For [3+2] cycloadditions involving azlactones, see: a) Melhado, A. D.; Luparia, M.; Toste, D. *J. Am. Chem. Soc.* **2007**, *129*, 12638−12639. b) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517−3527. c) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M. *Synlett* **2012**, *23*, 62−65. d) Sun, W.; Zhu, G.; Wu, C.; Li, G.; Hong, L.; Wang, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8633−8637. e) Zhang, Z.; Sun, W.; Zhu, G.; Yang, J.; Zhang, M.; Hong, L.; Wang, R. *Chem. Commun.* **2016**, *52*, 1377−1380.

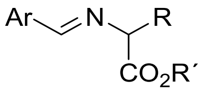
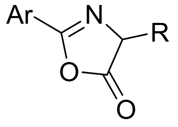
[82] For [3+2] cycloadditions between azomethine ylides and acrylates, see: a) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332. b) Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; Cózar, A.; Cossío F. P. *Eur. J. Org. Chem.* **2009**, 5622–5634. c) Tong, M.-C.; Li, J.; Tao, H.-Y.; Li, Y.-X.; Wang, C.-J. *Chem. Eur. J.* **2011**, *17*, 12922–12927. d) Li, Q.-H.; Tong, J.; Li, H.-Y.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 11110–11112. e) Li, Q.-H.; Liu, T.-L.; Wei, Zhou, X.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 9642–9644.

[83] For [3+2] cycloadditions between azomethine ylides and fumarates/maleates, see: a) Wang, C.-G.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250−17251. b) He, L.; Chen, X.-H.; Wang, D.-N.; Lou, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc* **2011**, *133*, 13504−13518. c) Liu, T.-L.; He, Z-L.; Tao, H.-Y.; Wang, C.-J. *Chem. Eur. J* **2012**, *18*, 8042−8046. d) Guo, C.; Song, J.; Gong, L.-X. *Org. Lett.* **2013**, *15,* 2676−2679. e) Wang, H.; Deng, Q.; Zhou, Z.; Hu, S.; Liu, Z.; Zhou, L.-Y. *Org . Lett.* **2016**, *18*, 404−407.

[84] For [3+2] cycloadditions between azomethine ylides and maleimides, see: a) Nájera, C.; Retamosa, M. De G.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025−4028. b) Martin-Rodriguez, M.; Nájera, C.; Sansano, J. M.;

allenoates,[87] alkylidene malonates,[88] methyleneindolinones[83d,89] and vinyl sulfones[90] have also been studied.

Table 1.

Entry	Ylide precursors	Dipolarophiles
1		acrylates, fumarates/maleates, maleimides, allenoates, alkylidene malonates, methyleneindolinones, nitroalkenes, vinyl sulfones, enones
2	 (azlactones)	acrylates, fumarates/maleates, maleimides, methyleneindolinones

Among the great variety of works reported, one of the works to be highlighted from the point of view of the substrate could be the Cu(I)-Fesulphos-catalyzed [3+2] cycloaddition

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Cozar, A.; Cossio, F. P. *Chem. Eur. J.* **2011**, *17*, 14224–14233. c) Mancebo-Aracil, J.; Martín-Rodriguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596–1606. d) Tada, A.; Watanabe, S.; Kimura, M.; Tokoro, Y.; Fukuzawa, S.-i. *Tetrahedron Lett*. **2014**, *55*, 6224–6226. e) Xue, Z.-Y.; Xiong, Y.; Wang, C.-J. *Synlett* **2014**, *25*, 2733–2737. f) Molina, A.; Pascual-Escudero, A.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2017**, *82*, 11238–11246.

[85] For [3+2] cycloadditions between azomethine ylides and nitroalkenes, see: a) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, 132, 5338–5339. b) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Cozar, A.; Cossío, F. P. *Org. Lett.* **2013**, *15*, 2902–2905. c) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; Cozar, A.; Cossío, F. P. *Adv. Synth. Catal.* **2014**, *356*, 3861–3870. d) Narayan, R.; Bauer, J. O.; Strohmann, C.; Antonchick, A P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, *52,* 12892–12896. e) Narayan, R.; Bauer, J. O.; Strohmann, C.; Antonchick, A P.; Waldmann, H. *Angew. Chem.* **2013**, *125,* 13130–13134. f) Castello, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; Cózar, A.; Cossío, F. P. *Synthesis* **2015**, *47*, 934–943. g) Gerten, A. L.; Stanley, L. M. *Org. Chem. Front.* **2016**, *3*, 339–343. h) Esteban, F.; Ciéslik, W.; Arpa, E. M.; Guerrero-Corella, A.; Díaz-Tendero, S.; Perles, J.; Fernández-Salas, J. A.; Fraile, A.; Alemán, J. *ACS Catal.* **2018**, *8*, 1884–1890.

[86] For [3+2] cycloadditions between azomethine ylides and enones, see: a) see ref 82b. b) Robles-Machín, R.; González-Esguevillas, M.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2010**, *75*, 233–236. c) Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275–1277. d) Liu, K.; Teng, H.-L.; Yao, L.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 2250–2253. e) Liu, H.-C.; Liu, K.; Xue, Z.-Y.; He, Z.-L.; Wang, C.-J. *Org. Lett.* **2015**, *17*, 5440–5443. f) Li, J.-Y.; Kim, H. Y.; Oh, K. *Adv, Synth. Catal.* **2016**, *358*, 984–993. g) Xu, S.; Zhang, Z.-M.; Xu, B.; Liu, B.; Liu, Y.; Zhang, J. *J. Am. Chem. Soc.* **2018**, *140,* 2272–2283.

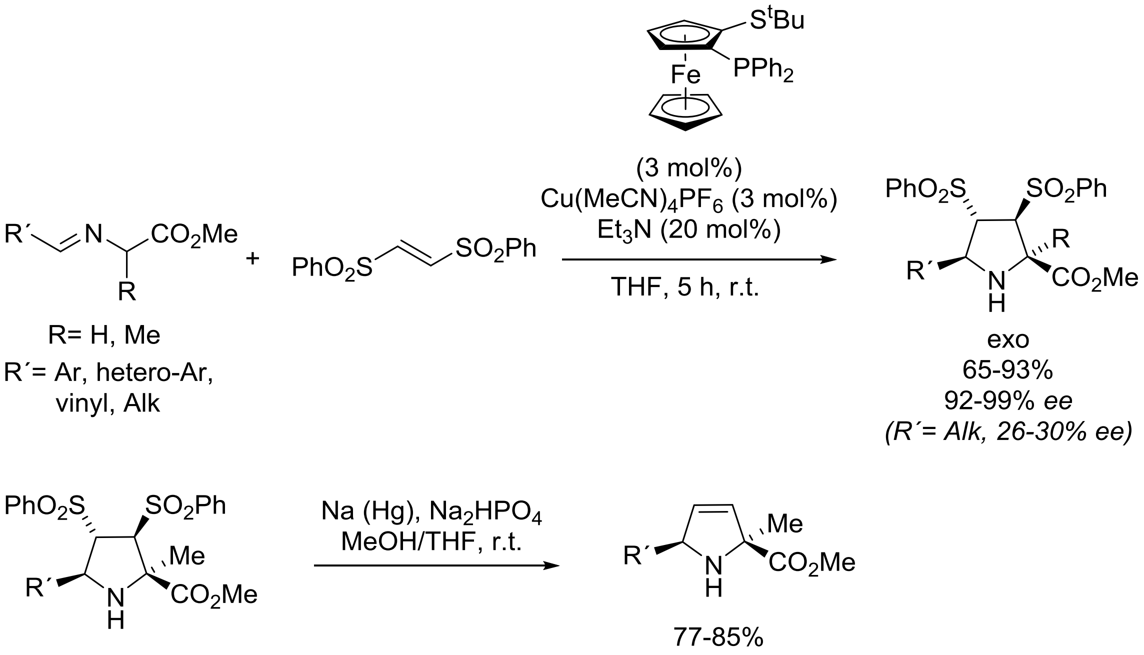
[87] For [3+2] cycloaddition between azomethine ylides and allenoates, see: Xue, Z.-Y.; Fang, X.; Wang, C.-J.; *Org. Biomol. Chem.* **2011**, *9*, 3622–3624.

[88] For [3+2] cycloadditions between azomethine ylides and alkylidene malonates, see: a) Xue, Z.-Y.; Liu, T.-L.; Lu, Z.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, *46*, 1727–1729. b) Xue, Z.-Y.; Fang, X.; Wang, C.-J. *Org. Biomol. Chem.* **2011**, *9*, 3622–3624.

[89] For [3+2] cycloadditions between azomethine ylides and methyleneindolinones, see: Wang, L.; Shi, X.-M.; Dong, W.-P.; Zhu, L.-P.; Wang, R. *Chem. Commun.* **2013**, *49*, 3458–3460.

[90] For [3+2] cycloadditions between azomethine ylides and vinyl sulfones, see: a) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Synthesis* **2007**, *6*, 950–956. b) Fukuzawa, S.-I.; Oki, H. *Org. Lett.* **2008**, *10*, 1747–1750. c) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085. d) Liang, G.; Tong, M.-C.; Wang, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 3101–3106.

of azomethine ylides and bis-sulfonyl ethylene reported by Carretero and colaborators in 2008.[91] The reductive elimination of both sulfonyl groups resulted in 3-pyrrolines, and hence, bis-sulfonyl ethylene acted as masked acetylene, unreactive dipolarophile in this reaction (Scheme 6).



Scheme 6. The synthesis of α-quaternary 3-pyrrolidines through the [3+2] cycloaddition between azomethine ylides and bis-sulfonyl ethylene.

Another work to highlight could be one that recently Liu, Zhang and co-workers reported based on Cu(I)-Fesulphos-catalyst.[92] They have developed for the first time a regiodivergent method in which the regioselectivity of the cycloaddition involving β-fluoromehtyl β,β-disubstituted enones may be modulated by the ligand used (Scheme 7). According to the theoretical DFT calculations, the formation of a Cu−O^{enone} bond with the amine nitrogen of **L2** (dissociated from the Cu(I) center) results in a swich on the regioselectivity.

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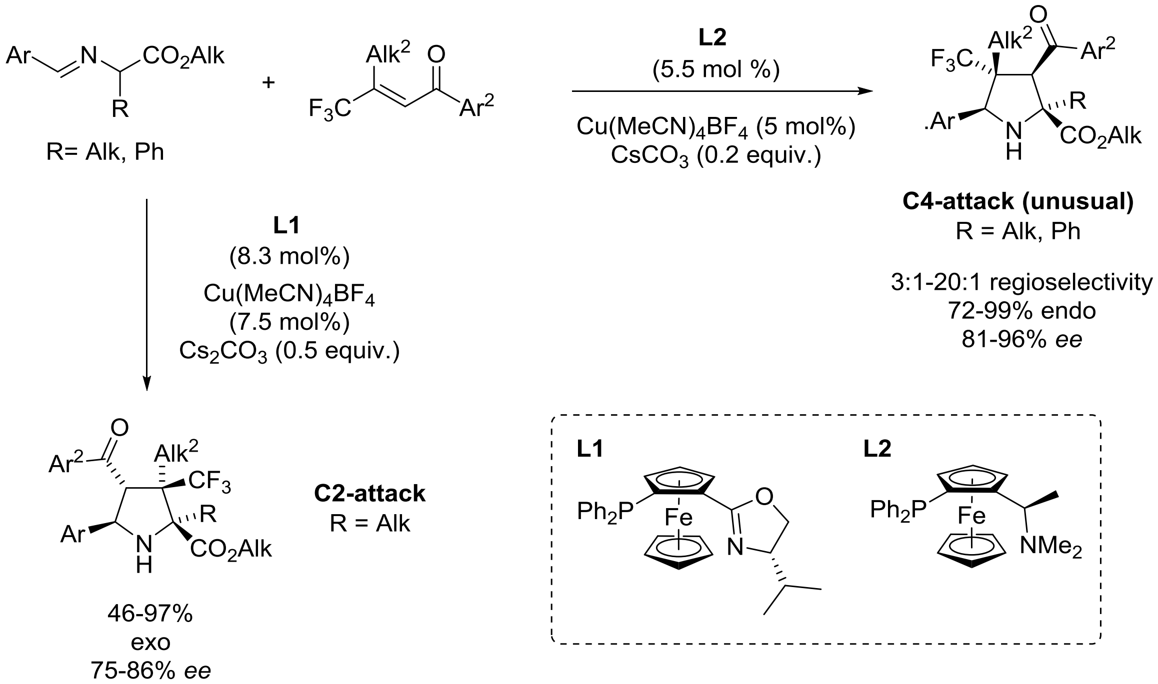
[91] See ref. 90c. page 26.

[92] See ref. 86g, page 26.



Scheme 7. Ligand-controlled regiodivergent Cu(I)-Fesulphos-catalyzed asymmetric [3+2] cycloaddition.

A feature of these methods is that metal catalysis is required in most cases with few exceptions.[93] In addition, in the organocatalytic methods the scope of the reaction has been limited by the reactivity of the reagents, requiring highly reactive olefins and azomethine ylides, as reflected for example in the reaction shown in the Scheme 8. Gong and co-workers reported the sole example of organocatalytic [3+2] cycloaddition of azomethine ylides to enones, which was promoted by phosphoric acid (Brønsted acid) catalyst employing α-iminoesters with an additional activating group at α-position as nucleophiles and quinone derivatives (highly reactive enone) as dipolarophiles.[93a]

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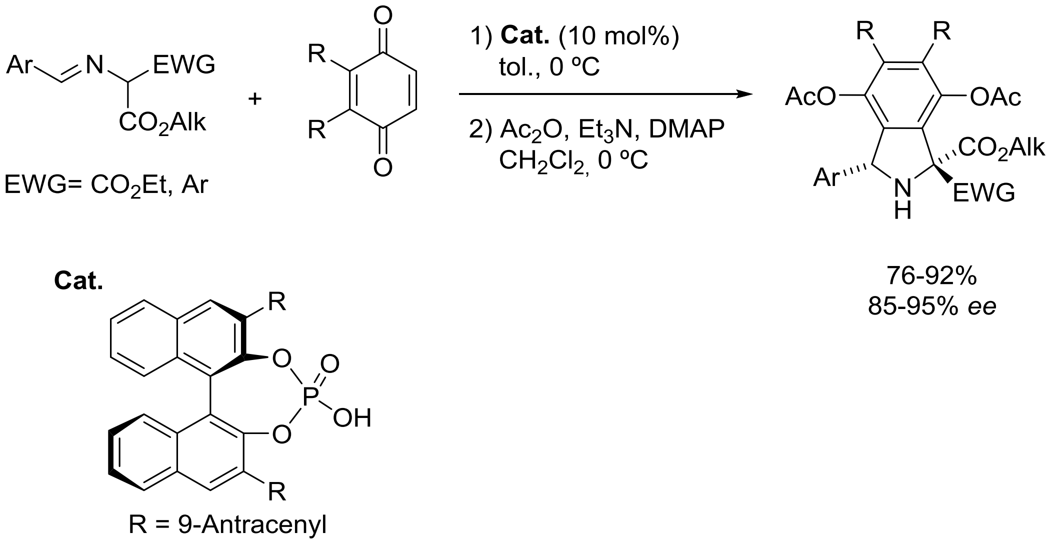
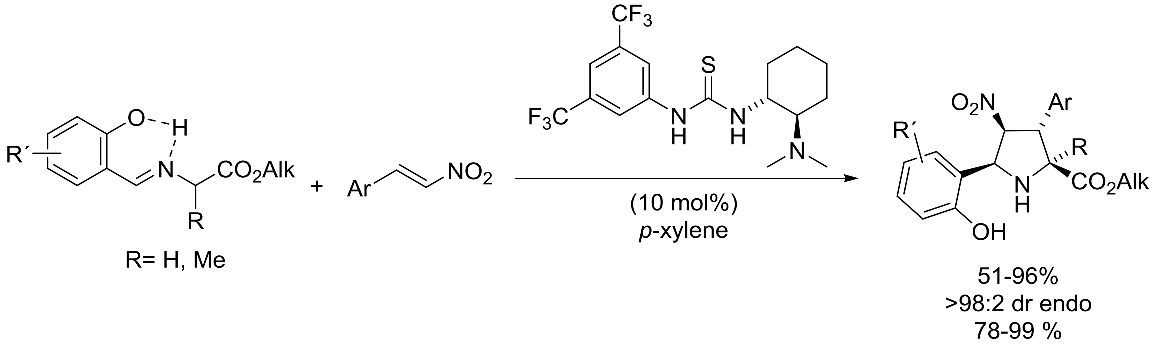
[93] For organocatalytic [3+2] cycloadditions involving azomethine ylides, see: a) see ref. 86c, page 26. b) see ref. 83b, page 25. c) see ref. 81d, page 25. d) see ref. 81e, page 25. e) see ref. 85h, page 26.



Scheme 8. The organocatalytic [3+2] cycloaddition between highly reactive azomethine ylides and enones.

In the above context, a reamarkable advance has been achieved very recently by Fraile and Alemán.[93e] They were able to develop an organocatalytic strategy for the synthesis of tetrasubstituted proline derivatives from β-substituted nitroalkenes and azomethine ylides bearing only one activating group, even with α-methyl substitution (Scheme 9). The key for success is the intramolecular activation of the azomethine ylide precursor via hydrogen bond.



Scheme 9. The organocatalytic [3+2] cycloaddition between azomethine ylides bearing only one activating group and β-substituted nitroalkenes.

While α-substituted azomethine ylides are commonly prepared via deprotonation of imino esters, the last years alternative protocols have been devised. Carretero *et. al* reported the first catalytic asymmetric synthesis of α-quaternay prolines through [3+2] cycloadditions to maleimide and alkenyl sulfones using α-silylimines as azomethine ylides precursors (Table 2).[94] It is interesting to note that the 2,3-dicarboxylate ester

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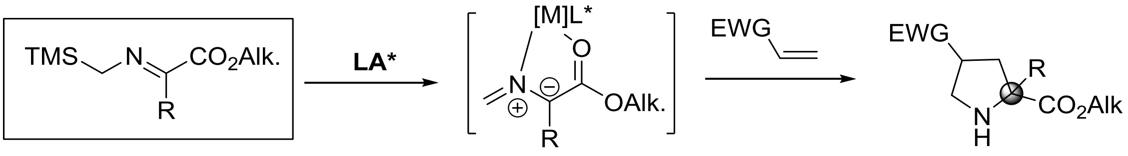
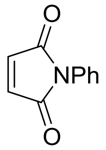
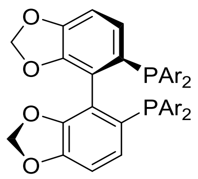
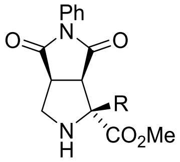
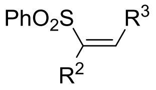
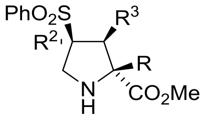
[94] Hernández-Toribio, J.; Padilla, S.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 8854–8858.

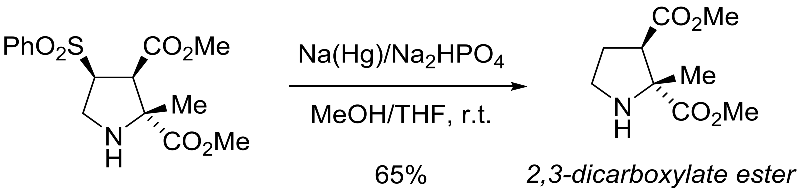
pyrrolidine that coming from the desulfonylation of the 2,3-dicarboxy-4-sulfonyl pyrrolidine displayed the opposite regioselectivity to what would be obtained using typical acrylate dipolarophiles (see desulfonylation step, Table 2). More recently, Kumar and collaborators have extended the use of these α-silylimines to the asymmetric [3+2] cycloaddition with benzopyrone derivatives.[95]

Table 2. The [3+2] cycloaddition of α-silylimines to different activated olefins developed by Carretero.



Dipolarophile	LA*	Product	Results
	 Ar = 4-MeO-3,5-^{t}Bu$_2$C$_6$H$_2$ / Cu(MeCN)$_4$PF$_6$ (10 mol%)	 R = Alk., Ar.	58-80% *trans* 92-98% *ee* (R = 2-ClPh, no reaction)
 R^2 = H, R^3 = H R^2 = H, **R^3 = CO_2Me** R^2 = SO_2Ph, R^3 = H		 R = Alk.	48-89% *trans* 55-99% *ee*

Desulfonylation

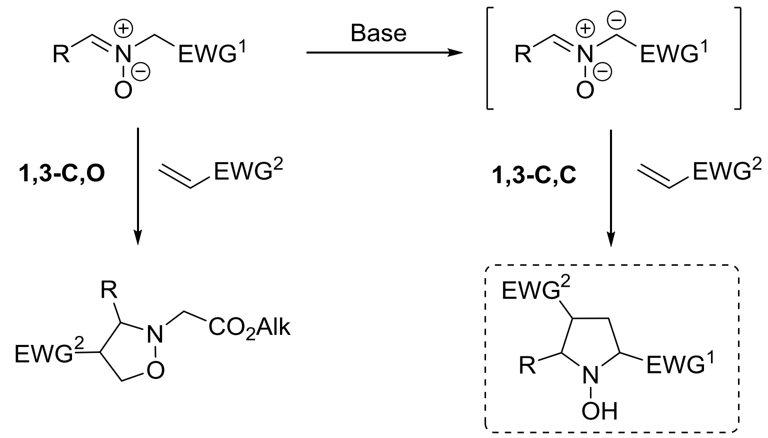


On the other hand, the use of nitrone ylides in [3+2] cycloadditions has also provided a new entry to pyrrolidine scaffold synthesis.[96] The change of the nitrone standard 1,3-C,O conventional reactivity into a less conventional 1,3-C,C reactivity has been achieved enhancing the acidity of the α-position with electron-withdrawing groups (Scheme 10).

---

[95] Kesava-Reddy, N.; Golz, C.; Strohmann, C.; Kumar, K. *Chem. Eur. J.* **2016**, *22*, 18373−18377.

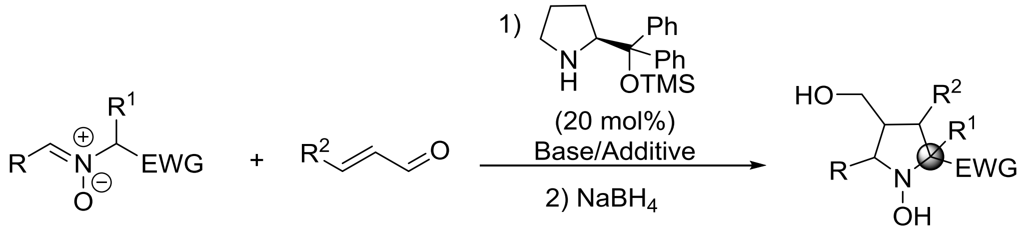
[96] a) Hanessian, S.; Bayrakdarian, M. *Tetrahedron Lett.* **2002**, *43*, 967−971. b) Merino, P.; Tejero, T.; Díez-Martínez, A.; Gültekin, Z. *Eur. J. Org. Chem.* **2011**, 6567−6573.

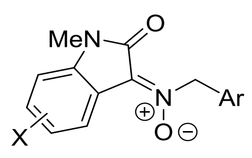
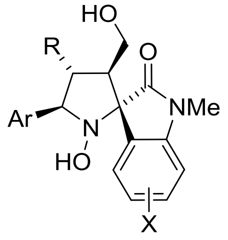
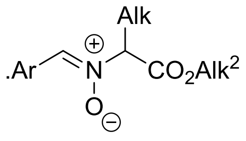
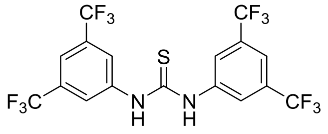
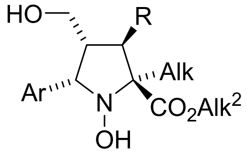


Scheme 10. General dipolar cycloadditions of nitrones and nitrone ylides.

Following this strategy, nitrone ylides have been applied in organocatalytic asymmetric [3+2] cycloadditions with enals under iminiun activation to obtain α-quaternary prolines (Table 3).[97]

Table 3. α-Quaternary prolines synthesis by [3+2] cycloadditions involving nitrone ylides.



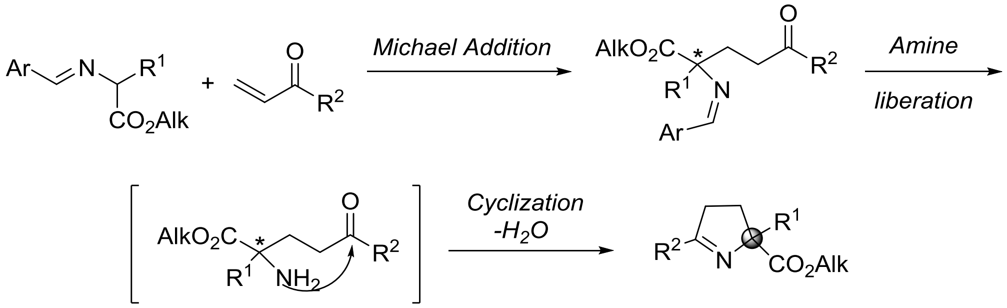
Nitrone	Base/Additive	Product	Results	Ref.
	Et_3N (20 mol%)	 R = Alk, Ar	45-90% *endo* 89-99% *ee*	97a
	Et_3N (20 mol%)/  (20 mol%)	 R = Alk	45-96% *exo* 90-99% *ee*	97b

---

[97] a) Chen, Y.-R.; Zhan, G.; Du, W.; Chen, Y.-C. *Adv. Synth. Catal.* **2016**, *358*, 3759–3764. b) Prieto, L.; Juste-Navarro, V.; Uria, U.; Delso, I.; Reyes, E.; Tejero, T.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2017**, *23*, 2764–2768.

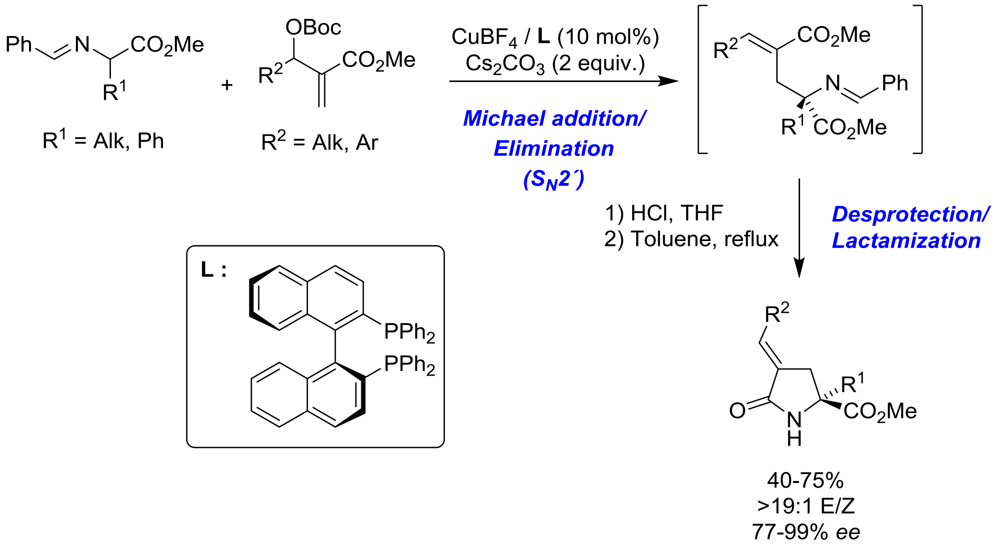
1.3.1.2.1.2. Michael additions

In most cases, the Michael addition of azomethine ylides is followed by the intramolecular cyclization step leading to a [3+2] cycloadditions. However, sometimes the reaction stops in the 1,4-addition, providing the possibility of releasing the amine and thus preparing another type of prolines as shown in Scheme 11.



Scheme 11. Synthesis of α-quaternary prolines through the Michael adducts coming from azomethine ylide precursors.

Wang and co-workers could synthesize α-quaternary pyroglutamates via Cu (I)/BINAP-catalyzed tandem Michael addition-elimination of azomethine ylide with Morita-Baylis-Hillman (MBH) carbonates followed by deprotection/lactamization (Scheme 12).[98] In this case, the conventional [3+2] cycloaddition was avoided thanks to the elimination step that occurred after the Michael addition.

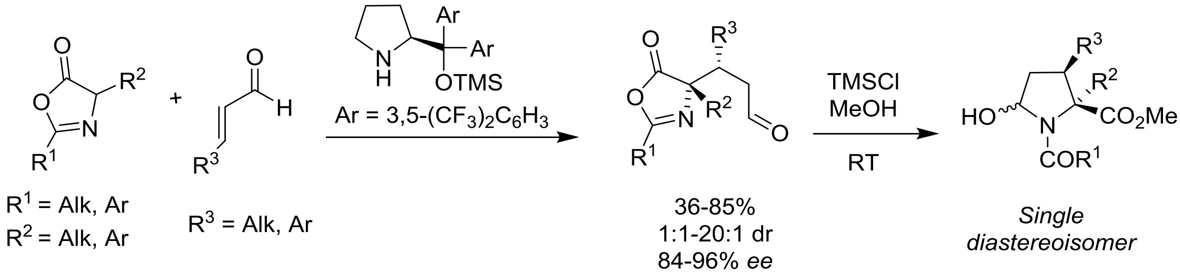


Scheme 12. Tandem Michael addition-elimination followed by deprotection/lactamization.

---

[98] Teng, H.-L.; Luo, F.-L.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2011**, *20*, 5600–5603.

Even so, azlactones have turned out to be more suitable nucleophiles for catalytic asymmetric Michael addition to α,β-unsaturated aldehydes and ketones. Jørgensen *et al.* developed the first method for the stereocontrolled addition of azlactones to α,β-unsaturated aldehydes which relies on an iminium ion activation strategy, catalyzed by diarylprolinol ethers (Scheme 13). The products of the reaction could be transformed diastereoselectively into α-quaternary proline derivatives via hemiaminal formation.[99]



Scheme 13.

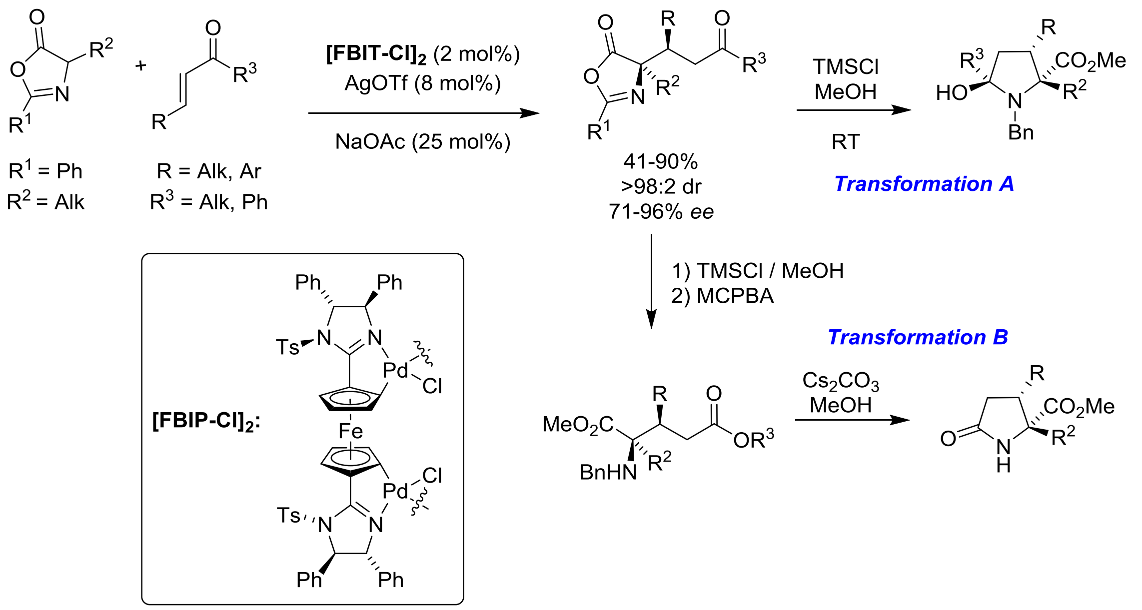
Afterward, Peter *et al.* reported the first catalytic asymmetric conjugate addition of azlactones to enones and the subsequent estereoselective transformation to the proline derivatives (Scheme 24, Transformation A).[100a] Two years later, they extended the reaction to the ¨*in situ*¨ formation of azlactone from unprotected α-amino acids[100b,c] and they could make a new transformation to obtain the *N*-unprotected pyroglutamic acid (Scheme 24, Transformation B). More recently, other studies have been carried out dealing with the conjugate addition of azlactones to enones,[101] expanding the reaction to different enones and the use of organocatalysts.

---

[99] For organocatalytic Michael addition of azlactones to α,β-unsaturated aldehydes, see: a) Cabrera, S.; Reyes, E.; Aleman, J.; Milelli, A.; Kobbelgaard, S; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037. b) Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem. Asian J.* **2009**, *4*, 246–249.

[100] For the first catalytic asymmetric Michael additions of azlactones to α,β-unsaturated ketones, see: a) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *J. Am. Chem. Soc.* **2010**, *132*, 12222–12225. b) Weber, M.; Frey, W.; Peters. R. *Adv. Synth. Catal.* **2012**, *354*, 1443–1449. c) Weber, M.; Peters, R. *J. Org. Chem.* **2012**, *77*, 10846–10855.

[101] For the conjugate additions of azlactones to trichloromethyl enones, see: a) Zhang, J.; Liu, X.; Wu, C.; Zhang, P.; Chen, J.; Wang, R. *Eur. J. Org. Chem.* **2014**, 7104–7108. For organocatalytic conjugate additions of azlactones to different enones, see: b) Avila, E.; Mello, A.; Diniz, R.; Amarante, G. W. *Eur. J. Org. Chem.* **2013**, 1881–1883. c) Wang, C.-H.; Xiao, J.-A.; Wang, J.; Wang, S.-S.; Deng, Z.-X.; Yang, H. *J. Org. Chem.* **2016**, *81*, 8001–8008.



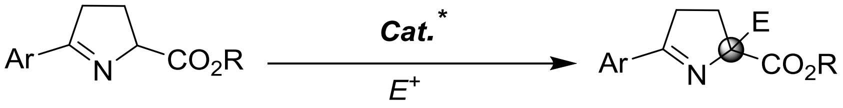
Scheme 14.

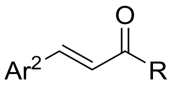
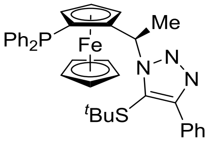
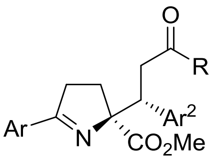
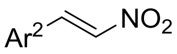
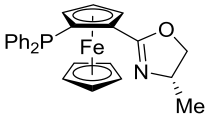
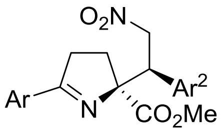
Finally, in recent years, the use of azomethine ylides with preformed pyrrolidine structures has allowed the stereocontrolled α-functionalization of pyrrolidines through Michael additions (Table 4).[102] In this particular case, the Michael additions provide directly α-quaternary proline scaffolds without needing a second cyclization step. Furthermore, the reduction of the resulting imine moiety of the products can be carried out in a diastereoselective manner.[102]

---

[102] To nitroalkenes: a) Li, C.-Y.; Yang, W.-L.; Luo, X.; Deng, W.-P. *Chem. Eur. J.* **2015**, *21*, 19048–19057. b) Koizumi, A.; Kimura, M.; Arai, Y.; Tokoro, Y.; Fukuzawa, S.-i. *J. Org. Chem*. **2015**, *80*, 10883–10891. To enones, see: c) Koizumi, A.; Harada, M; Haraguchi, R.; Fukuzawa S.-i. *J. Org. Chem*. **2017**, *82*, 8927–8932.

Table 4. Catalytic asymmetric Michael additions using azomethine ylide precursors with preformed pyrrolidine structures.

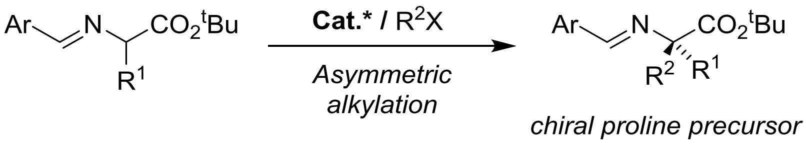


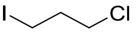
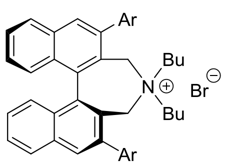
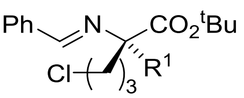
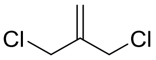
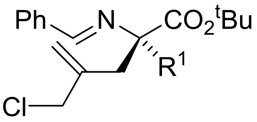
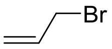
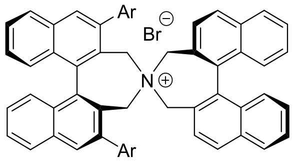
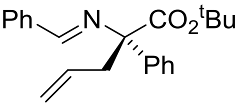
Electrophile (E^+)	**Cat.***	**Product**	**Results**	**Ref.**
 R = Ar, Alk	 (5.5 mol%) AgOAc (5 mol%)/DBU (20 mol%)		*syn* >50% >95:5 dr 83-99% *ee*	102c
	 (5.5 mol%) CuOAc (5 mol%)/Py (5 mol%)		74:26–92:8 *syn/anti* 94–99% *ee* (1:99 *anti* with AgOAc)	102b

1.3.1.2.1.3. Alkylation

In few cases, the catalytic asymmetric C-alkylation of azomethine ylides has also served for the formation of chiral α-quaternary proline precursors (Table 5).[103]

Table 5. Catalytic asymmetric C-alkylation of azomethine ylides



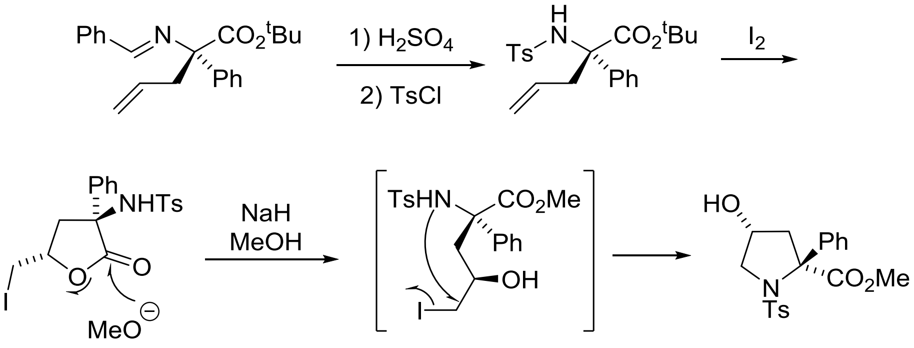
	R^1	R^{2}X	Cat.*	Product	Results	Ref.
1	Alk Ph		 Ar = 3,4,5-F$_3$C$_6$H$_2$ (1 mol%)/CsOH.H$_2$O (5 equiv.)		75-94% 98-99% *ee* (R^1=Ph 64% *ee*)	103b
2	Alk				44-64% 96–97% *ee*	
3	Ph		 Ar = 3,4,5-F$_3$C$_6$H$_2$ (1 mol%)/CsOH.H$_2$O (5 equiv.)		81% 97% *ee*	103a

The hydrolysis of the imine moiety in the acyclic chiral compound directly leads to an intramolecular *N*-alkylation providing the corresponding α-quaternary proline in cases of entry 1 and entry 2. Nevertheless, in case of entry 3 more steps are required to get the cyclic product (Scheme 15).[104]

---

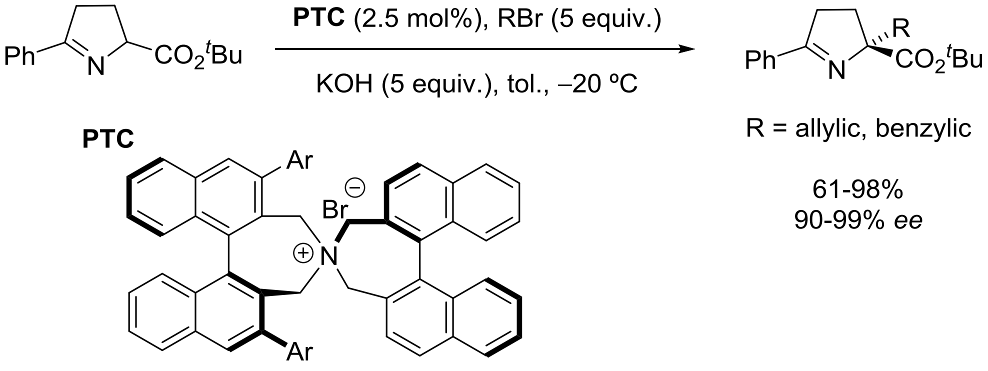
[103] a) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, *7*, 1185–1187. b) Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.-G.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900–4904.

[104] Maeda, K.; Miller, R. A.; Szumigala, R. H.; Shafiee, A.; Karady, S.; Armstrong, J. D. *Tetrahedron Letters* **2005**, *46*, 1545–1549.



Scheme 15. Transformation from chiral α-allyl functionalized compound to proline.

Finally, there is one example in which the catalytic enantioselective Cα-alkylation of azomethine ylides with preformed pyrrolidine has also allowed the synthesis of α-quaternary proline derivatives (Scheme 16).[105] The reduction of the imine moiety even could be modulated according to the reducing agent used.



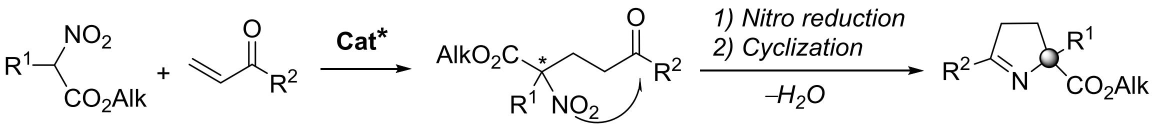
Scheme 16. The catalytic enantioselective Cα-alkylation of azomethine ylides with preformed pyrrolidine.

1.3.1.2.2. *α-Nitroesters*

Since the nitro group can be converted into amine very easily, the asymmetric Michael additions of α-nitroesters has provided an alternative route for the enantioselective synthesis of α-quaternary prolines as shown in Scheme 17.

---

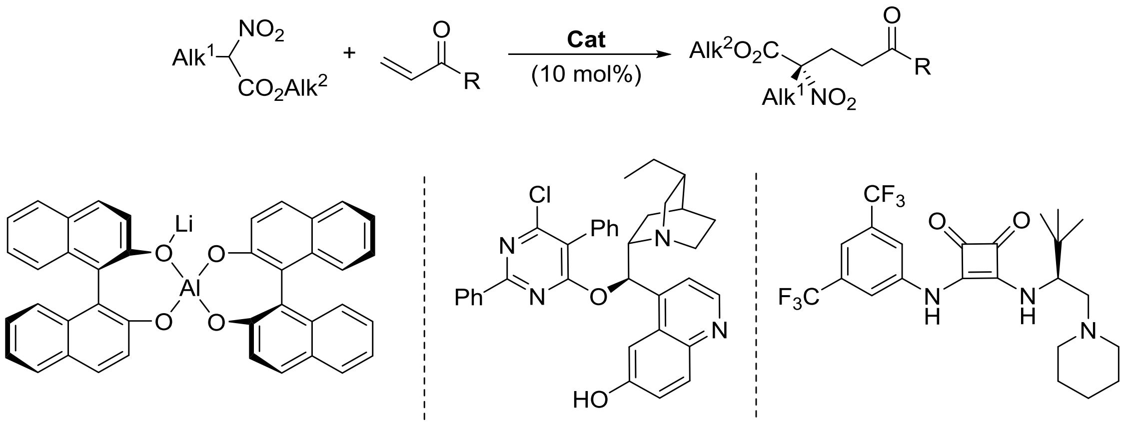
[105] Lee, M.; Lee, Y.; Park, E; Park, Y.; Ha, M. W.; Hong, S; Lee, Y.; Kim, T.; Kim, M.; Park, H. *Org. Biomol. Chem.* **2013**, *11*, 2039–2046.



Scheme 17. Synthesis of α-quaternary prolines through the Michael addition of α-nitroesters.

Several catalytic Michael reactions have been developed where α-nitroesters was enantioselectively added to vinyl ketones, even using organocatalysts; nevertheless, the scope of the reaction remains limited in most to α-alkyl nitroesters (Table 6).[106]

Table 6. Michael addition of α-alkyl nitroacetates to vinyl ketones.



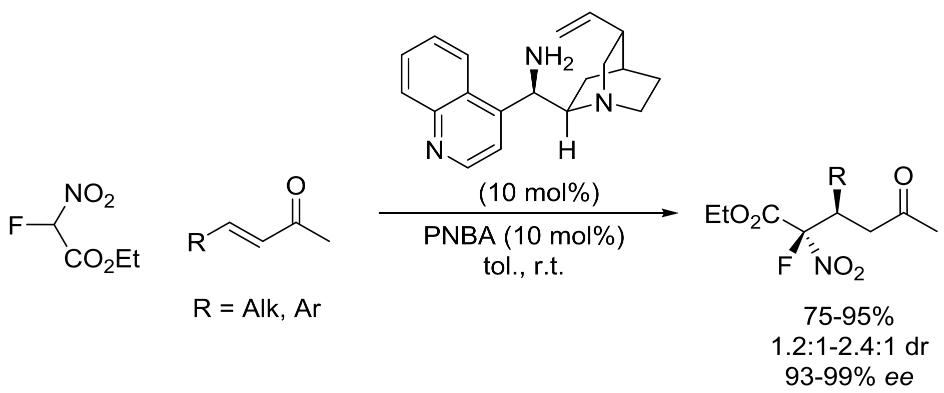
Feringa 1997[ref]	**Snider 2006[ref]**	**Namboothiri 2016[ref]**
R = Me, Et 81-86% 33-80% *ee* (R = Ph) 87%, 5% *ee* (R = OMe, H) n. r.	R = Me (Alk^1 = only Me) 90% 90% ee	R = Ar 76-97% 71-86% *ee*

Only one example is known in which it was possible to carry out the asymmetric catalytic 1,4-addition between α-fluoro nitroesters and β-substituted enones, although the diastereoselectivity of the reaction was no good (Scheme 18).[107]

---

[106] a) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403–3413. b) Keller, E.; Feringa, B. L. *Synlett* **1997**, 842–844. c) Duvall, J. R.; Wu, F.; Snider, B. B. *J. Org. Chem.* **2006**, *71*, 8579–8590. d) Bera, K.; Satam, N. S.; Namboothiri, N. N. *J. Org. Chem.* **2016**, *81*, 5670–5681.

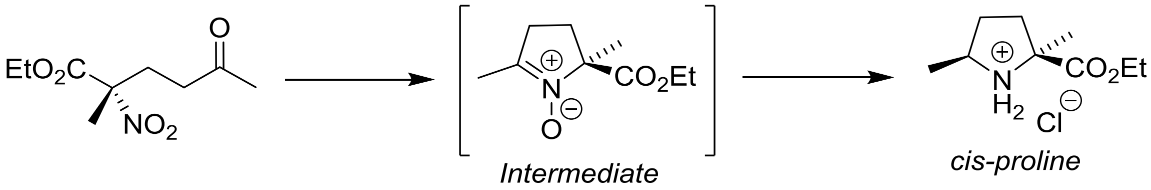
[107] Cui, H.-F.; Li, P.; Wang, X.-W.; Chai, Z.; Yang, Y.-Q.; Cai, Y.-P.; Zhu, S.-Z.; Zhao, G. *Tetrahedron* **2011**, *67*, 312–317.



Scheme 18. Asymmetric Michael addition between α-fluoro nitroesters and β-substituted enones.

The cyclization step of these adducts for obtaining reduced proline scaffolds consists of an intramolecular reductive amination involving an intermediate nitrone for which optimized conditions are described in Table 7.

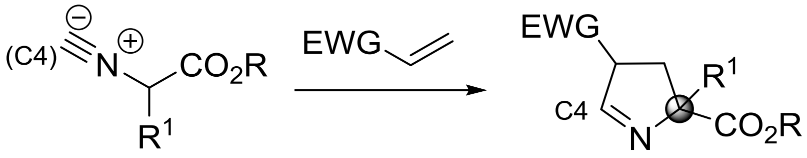
Table 7. Optimization of the reduction-cyclization step.



	Cyclization conditions	Results	Ref.
1	1 atm H_2, Pd/C EtOH, 72 h	2:1 dr (cis/trans)	106b
2	1) 1 atm H_2, Pd/C, EtOH, 15 h 2) 3 equiv. HCl, 3.3 atm H_2, 36h	>20:1 dr (cis/trans)	106c

1.3.1.2.3. α-Isocyanoacetates

The catalyst-controlled [3+2] cycloaddition involving isocyanoacetates has been much less developed than those based on azomethine ylides. However, the acidic α-carbon atom and the electrophilicity of the isocyanide group make these amino acid derivatives perfect dipole precursors for α-quaternary proline scaffold synthesis through [3+2] cycloadditions. In addition, isocyanoacetates allow the C_4-unsubstituted proline synthesis, what is not feasible with conventional azomethine ylides because the aryl-substitution in the iminic carbon is mandatory (Scheme 19).



Scheme 19. α-Quaternary prolines derivated from isocyanoacetates.

Most examples of [3+2] cycloadditions of isocyanoacetates, involve very reactive dipolarophiles such as nitroalkenes,[108] α,β-unsaturated ketoesters,[109] maleimides,[110] methyleneindolinones,[111] allenoates,[112] cyclopentenediones[113] and activated acrylates[114], and aside from Brønsted base, the presence of a metal is required in most cases with few exceptions (Table 8, entry 1 and 3). Generalization of metal Lewis acid/Brønsted base cooperative catalysis is often hampered by self-quenching problem, which obstructs the proper coordination of catalyst and thus stereocontrol is lost, especially during the formation of α-quaternary alkyl stereocenters as entry 2 clearly shows. Furthermore, while the reactions are commonly compatible with a wide variety of α-aryl isocyanoacetates (active), the use of α-alkyl isocyanoacetates has been much more restricted (see entry 1, 3 and 6). Meanwhile, a sole example is known regarding the cycloaddition involving simple vinyl ketone as the reaction partner, which has a close relationship with this thesis (Table 8, entry 7),[115] affording the corresponding proline derivatives with poor enantioselectivity, especially in case of the α-quaternary prolines (≤36% ee).

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[108] Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 3414–3417.

[109] Song, J.; Guo, C.; Chen, P.-H.; Yu, J.; Luo, S.-W.; Gong, L.-Z. *Chem. Eur. J.* **2011**, *17*, 7786–7790.

[110] a) Zhao, M.-X.; Wei, D-K.; Ji, F.-H.; Zhao, X.-L.; Shi, M. *Chem. Asian J.* **2012**, *7*, 2777–2781. b) Padilla, S.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2012**, *77*, 4161–4166.

[111] a) Wang, L.-L.; Bai, J.-F.; Peng, L; Qi, L.-W.; Jia, L.-N.; Guo, Y.-L.; Luo, X.-Y.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2012**, *48*, 5175–5177. b) Peng, X.-J.; Ho, Y. A.; Wang, Z.-P.; Shao, P.-L.; Zhao, Y.; He, Y. *Org. Chem. Front.* **2017**, *4*, 81–85.

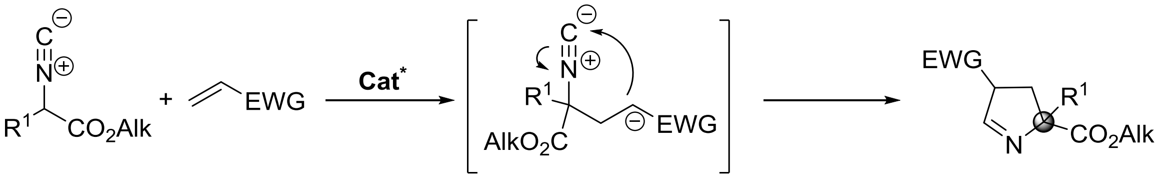
[112] Liao, J.-Y.; Shao, P.-L.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137*, 628–631.

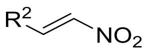
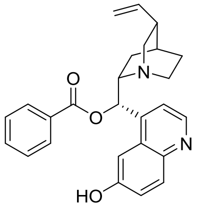
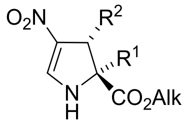
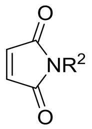
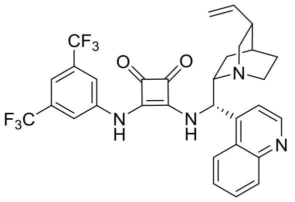
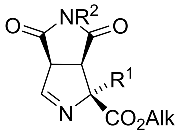
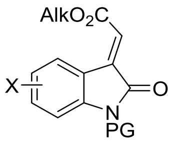
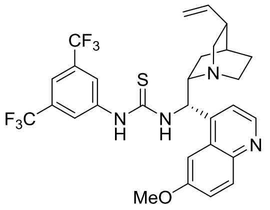
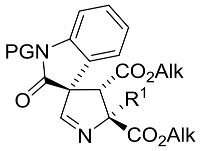
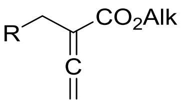
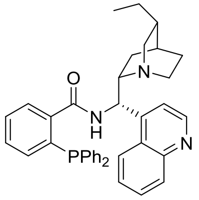
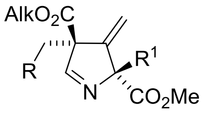
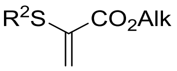
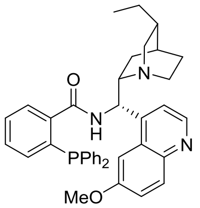
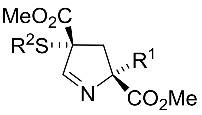
[113] George, J.; Kim, H. Y.; Oh, K. *Org. Lett.* **2018**, *20*, 2249–2252.

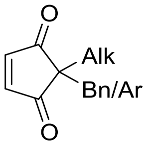
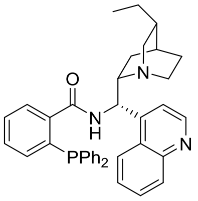
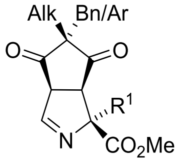
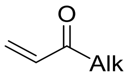
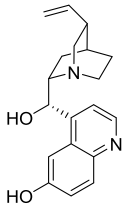
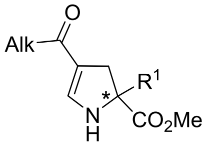
[114] a) Cheng, H.; Zhang, R.; Yang, S.; Wang, M.; Zeng, X.; Xie, L.; Xie, C.; Wu, J.; Zhong, G. *Adv, Synth, Catal.* **2016**, *358*, 970–976. b) Wang, Z.-P.; Wu, Q.; Jiang, J.; Li, Z.-R.; Peng, X.-J.; Shao, P.-L.; He, Y. *Org. Chem. Front.* **2018**, *5*, 36–40.

[115] Arroniz, C.; Gil-González, A.; Semak, V.; Escolano, C.; Bosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, 3755–3760.

Table 8. Selected examples of [3+2] cycloaddition between isocyanoacetates and reactive olefins.



	Electrophile	Cat.*	Product	Results	Ref.
1	 R^2 = Alk, Ar	 (20 mol%)	 R^1 = Ar, **only Bn**	51-99% 4:1->20:1 dr 90-99% *ee*	108
2	 R^2 = Ar, Alk	 (5 mol%)/AgSbF$_6$ (10 mol%)	 R^1 = Ar, ^{i}Pr, Bn, H	(R^1 = Ar) 76-98% >20:1 dr 53-92% *ee* **(R^1 ≠ Ar)** 67-85% >20:1 dr **10-13% *ee***	110a
3	 PG = Boc, phenylamide	 (10 mol %)	 R^1 = **only Ph**	41-65% 1.9:1-8:1 dr 90–99% *ee*	111a
4	 R = Ar, vinyl	 (20 mol%)/ Ag$_2$O (10 mol%)	 R^1 = Me, Bn	58-90% 4:1-11:1 dr 82-96% *ee*	112
5	 R^2 = Alk, Ar, Ts	 (20 mol%)/ Ag$_2$O (10 mol%)	 R^1 = Alk, Ar	86-99% 52:48-75:25 dr 92-98% *ee*	114b

	Electrophile	Cat.*	Product	Results	Ref.
6		 (10 mol%)/ $AgNO_3$ (10 mol%)	 R^1 = Ar, **only ^{i}Pr**	63-91% >84:16 dr 80-98% *ee*	113
7	 Alk = Me, Et	 (10 mol%)/ $AgNO_3$ (5 mol%)	 R^1 = H, Bn	(R^1 = H) 20-59% 52-89% *ee* **(R^1 = Bn)** 68-85% **16-36% *ee***	115

As a conclusion for this section, the development of organocatalytic methods for the synthesis of α-quaternary prolines through cycloaddition reaction with isocyanoacetates is still a challenge, especially with α-alkyl isocyanoacetate derivatives. In this context, the use of simple vinyl ketone as dipolarophile is virtually unexplored.

1.4. α-Quaternary α,β-diamino acids

α,β-Diamino acids have played a central role in replacing natural amino acids in peptidic structures to modify their biological activities and stabilities to peptidases. For example, the specific substitution of Lys (essential α,ε-diamino acid) by Dpr (an α,β-diamino acid) attenuates the hydrophobic mismatched effects with phospholipids in some peptides[116] and the α-helix propensity is decreased.[117] Besides the application in peptide chemistry, nonproteinogenic α,β-diaminoacids or small peptidomimetics constitute a key structutral frangments in many natural and biologically active compounds (Figure 16).[118]

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[116] a) Liu, F.; Lewis, R. N. A. H.; Hodges, R. S.; McElhaney, R. N. *Biochemistry* **2002**, *41*, 9197–9207. b) Liu, F.; Lewis, R. N. A. H.; Hodges, R. S.; McElhaney, R. N. *Biophys. J.* **2004**, *87*, 2470–2482.

[117] a) Padmanabhan, S.; York, E. J.; Stewart, J. M.; Baldwin, R. L. *J. Mol. Biol.* **1996**, *257*, 726–734. b) Gibson, T. J.; Murphy, R. M. *Biochemistry* **2005**, *44*, 8898–8907. c) Virdee, S.; Macmillan, D.; Waksman, G. *Chem. Biol.* **2010**, *17*, 274–284.

[118] To articles related to the L-mimosine, see: a) Dobbin, P. S.; Hider, R. C.; Hall, A. D.; Taylor, P. D.; Sarpong, P.; Porter, J. B.; Xiao, G.; van der Helm, D. *J. Med. Chem.* **1993**, *36*, 2448–2458. b) Dong, Z.; Zhang, J.-T. *Molecular Biology of cell* **2003**, *14*, 3942–3951. To articles related to the BMAA, see: c) Vega, A.; Bell, E. A. *Phytochemistry* **1967**, *6*, 759–762. d) Murch, S. J.; Cox, P. A.; Banack, S. A.; Steele, J. C.; Sacks, O. W. *Acta Neurol. Scand.* **2004**, *110*, 267–269. To articles related to imidapril, see: e) Hosoya, K.; Ishimitsu, T. *Cardiovasc. Drug. Rev.* **2002**, *20*, 93–110. f) Wang, J.-m.; Wang, Y.; Zhu, Z.-S.; Zhang, M.-c.;

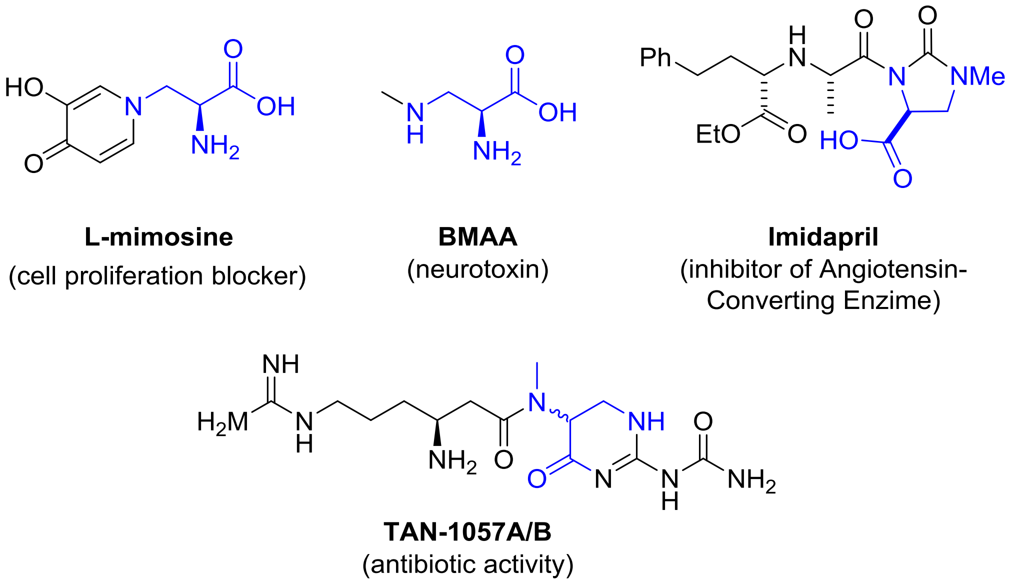


Figure 16. Biologically active compounds containing α,β-diaminoacid frangments.

Within α,β-diaminoacids those that contain α-quaternary stereocenters are considered particularly relevant owing to their unique structural biases, but their synthesis still presents limitations in many aspects. The principal approaches developed for the α,β-diaminoacids asymmetric synthesis can be classified depending on the bond formed to complete de skeleton (Scheme 20).[119] The first approach consists in the addition of nucleophilic synthetic equivalent of carboxyl group to electrophilic Cα (pathway a), commonly by Strecker reaction (cyanation of imines).[120] Second approach is focused in the introduction of the nitrogen atoms in the carbon backbone (pathway b), those proceed mostly through β-amination from readily available α-amino acids[121], diamination of α,β-unsaturated alkanoates[122] or electrophilic amination of enolates.[123]

Zou, Y.; Li, J.-j.; Li, M.-J.; Jiang, X.-j.; Li, X.-Y. *Life Sci.* **2004**, *75*, 407–420. To articles related to TAN-1057A/B, see: g) Brands, M.; Endermann, R.; Gahlmann, R.; Krüger, J.; Raddatz, S.; Stoltefuss, J.; Belov, V. N.; Nizamov, S.; Sokolov, V. V.; de Meijere, A. *J. Med. Chem.* **2002**, *45*, 4246–4253. h) Zhang, L.; Kim, C. U.; Xu, L. *Tetrahedron Lett.* **2007**, *48*, 3273–3275.

[119] Viso, A.; de la Pradilla, R. F.; Tortosa, M.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1–PR42, and references cited therein.

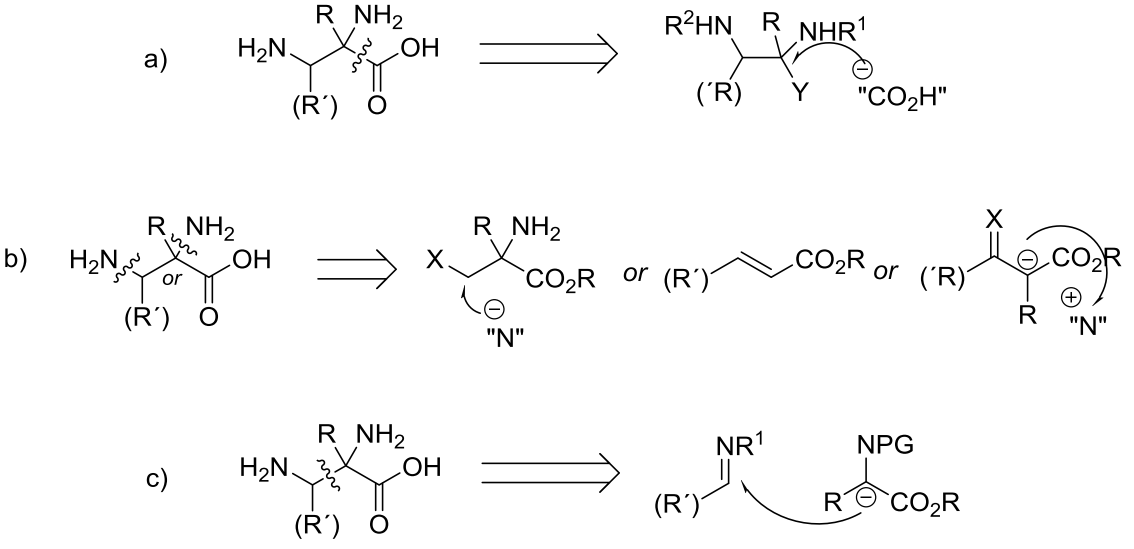
[120] For representative examples, see: a) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402. b) Fondekar, K. P. P.; Volk, F.-J.; Khaliq-uz-Zaman, S. M.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2241–2249. c) Hazelard, D.; Fadel, A.; Guillot, R. *Tetrahedron: Asymmetry* **2008**, *19*, 2063–2067.

[121] For representative examples, see: a) Baldwin, J. E.; Adlington, R. M; Mellor, L. C. *Tetrahedron* **1994**, *50*, 5049–5066. b) Strazzolini, P.; Dall´ Arche, M. G.; Zossi, M.; Pavsler, A. *Eur. J. Org. Chem.* **2004**, 4710–4716. c) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183–2186.

[122] For representative examples, see: a) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045–2048. b) Li, G.; Kim, S. H.; Wei, H.-X. *Tetrahedron Lett.* **2000**, *41*, 8699–8703. c) Muñiz, K.; Nieger, M. *Synlett* **2003**, 211–214.

[123] For representative examples, see: a) Badorrey, R.; Cavitiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2787–2796. b) Capone, S.; Guaragna, A.; Palumbo, G.; Pedatella, S.

However, for the total synthesis of optically pure α,β-diaminoacids, many steps and chiral source or chiral auxiliary are required in both approaches, besides being little explored the methods involving the formation of α-quaternary stereocenters. In this sense, the majority of catalytic asymmetric methods developed so far are based on the Mannich addition of masked aminoacids (pathway c),[124] requiring less steps for the synthesis of α,β-diaminoacids and even providing in much cases the products with α-quaternary stereocenter. Even so, owing to the congestion provided by the additional substituent in Cα, the studies carried out with α-subtituted amino acids still show important limitation; in special when α-alkyl nucleophiles and organocatalysts are used.



Scheme 20. Principal approaches for α,β-diaminoacids asymmetric synthesis.

To facilitate the compression of the reader, the analysis of these precedents is developed in the section corresponding to the Mannich reaction, with emphasis on the catalytic asymmetric Mannich reaction of isocyanoacetates (Chapter 3, section 3.5., page 125).

Tetrahedron **2005**, *61*, 6575–6579. c) Makino, K.; Kubota, S.; Hara, S.; Sakaguchi, M.; Hamajima, A.; Hamada, Y. *Tetrahedron* **2009**, *65*, 9468–9473.

[124] For review on catalytic asymmetric Mannich reaction toward α,β-diamino acids synthesis, see: Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940–1948.

1.5. Isocyanoacetates

1.5.1. General considerations

The isocyano (isonitrile) group was obtained for the first time by Lieke in 1859[125] and hundred years later its synthesis became available from primary amines by dehydration of formamides.[126] The most relevant knowledge acquired about the exceptional nature of the isocyano group are attributed to Ugi, who appreciated the diverse possibilities of this functional group for the first time.

Being stable carbene, isonitrile is an unusual functionality that can react with almost any type of compounds: electrophiles, nucleophiles and radicals (Figure 17, a). As a consequence, isonitriles are very versatile building blocks in organic chemistry, especially for the synthesis of various heterocycles[127] as well as interesting ligands to form metal complexes.[128] In addition, the isocyano group can undergo various transformations such as isocyanide-cyanide rearrangement and different types of oxidations/reductions, enhancing their synthetic potential (Figure 17, b).[129]

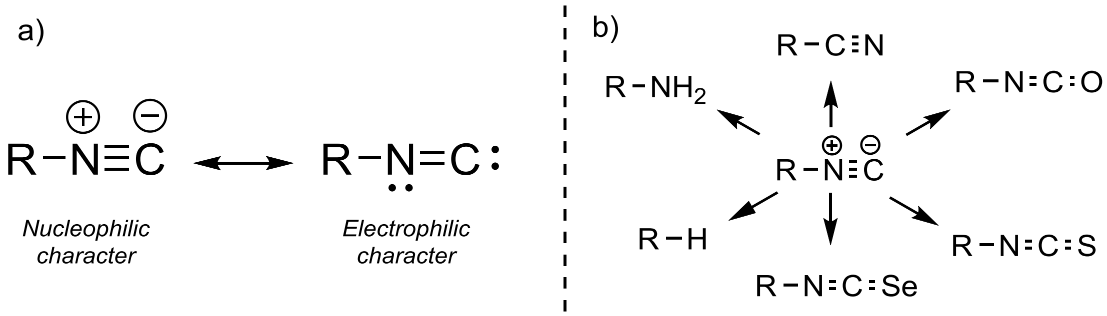


Figure 17. General resonance structure of an organo isocyanide and its possible transformations.

The carbon acidity of CH units attached to an isocyanide is enhanced by the moderate electron-withdrawing effect imparted by the isocyanide. Because of this effect, isocyanoacetates are good candidates for base-promoted nucleophilic additions through

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[125] Lieke, W; *Justus Liebigs Ann. Chem.* **1859**, *112*, 316–321.

[126] Ugi, I.; Meyr, R. *Angew. Chem.* **1958**, *70*, 702–703.

[127] a) Ono, N. *Heterocycles* **2008**, *75,* 243–284. b) Lygin, A. V.; de Meijere, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124.

[128] Malatesta , L.; in *Progress in Inorganic Chemistry*, (ed. F.A. Cotton), John Wiley & Sons, Inc , Hoboken, New York, 1959; Vol. 1, pp. 283 – 379 .

[129] For leading book related to isocyanide, see: a) *Isocyanide Chemistry: Applications in Synthesis and Material Science* (Nenajdenko, V. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2012, and references therein. For reviews related to isocyanide, see: b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698–2779. c) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F.-Q.; Mohan, R.; Ravindra, M. P.; Shah, D.; Yang, X.; Fleming, F. F. *Adv. Synth. Catal.* **2014**, *356*, 2135–2196.

Cα and cycloadditions reactions. However, due to the electrophilic character of the isonitrile group, many times the cycloaddition reaction that follows to the nucleophilic addition cannot be avoided or even the presence of certain functional groups can disturb the desired reaction pathway.

Since the first isocyanoacetate was obtained by Ugi in 1961,[130] these compounds have received much attention and nowadays are commonly available. Due to their interesting structure isocyanoacetates are especially attractive among other isocyanides (Figure 18).[131]

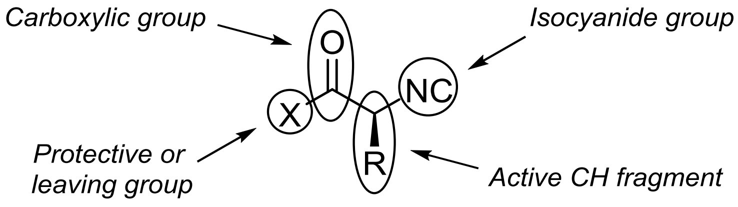

Figure 18. Reactivity centers of α-isocyanoacetate derivatives.

Each of these molecules contains four reaction centers:

1. Isocyanide group: multicomponent reaction, nucleophilic addition, electrophilic attacks, metal coordination, etc.
2. Active CH fragment: Michael, alkylation, Mannich, etc.
3. R substituent: also can handle functional groups.
4. Carboxylic acid: acylation, etc.

Thanks to the combination of these potential reaction centers, isocyanoacetates are very attractive in different branches of organic, inorganic, coordination, polymeric, combinatorial and medicinal chemistry. Multicomponents reactions[132] with isocyanoacetates are used for the synthesis of a variety of biochemically relevant compounds such as peptides and peptide mimetics. In addition, such molecules are efficient building blocks for the synthesis of biologically active molecules,[133] nitrogen

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[130] Ugi, I.; Betz, W.; Fetzer, U.; Offerman, K.; *Chem. Ver.* **1961**, *94*, 2814.

[131] Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331.

[132] a) Dömling, A.; Ugi, I *Angew. Chem. Int. Ed* **2000**, *39*, 3168–3210. b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. c) Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634. d) Hulme, C.; Dietrich, J. *Mol. Divers.* **2009**, *13*, 195–207. e) Berkel, S. S.; Bögels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, 3543–3559. f) Alemán, J.; Cabrera, S.; Alvarado, C. *Recent Advances in the Ugi Multicomponent Reactions,* Herrera, R. P., Marqués-López, E., Eds.; Wiley; 2015; pp 247–282.

[133] For some examples related to amino sugar compound synthesis: a) Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1982**, *23*, 1193–1196. b) Hamada, Y.; Kawai, A.; Matsul, T.; Hara, O.; Shioiri, T. *Tetrahedron* **1990**, *46*, 4823–4846.

heterocycles[134] and in total synthesis of complex natural products.[135] In this context and closely related to this thesis, isocyanoacetaes have proven to be perfect candidates for the synthesis of amino acid derivatives.

1.5.2. Synthesis of α-amino acids involving isocyanoacetates

The isocyano group stabilizes effectively the negative charge eventually formed at the α-position in α-isocyanoacetates and also can be easily transformed into an amino group, commonly by treatment with protic acid. Therefore, α-isocyanoacetates may serve as convenient synthetic equivalents of amino acids carbanion.[136] As such they have been demonstrated useful for the synthesis of different kinds of α-amino acids through reaction with carbonyl compounds, imines, activated olefin and acylating and alkylating agents (Scheme 21).

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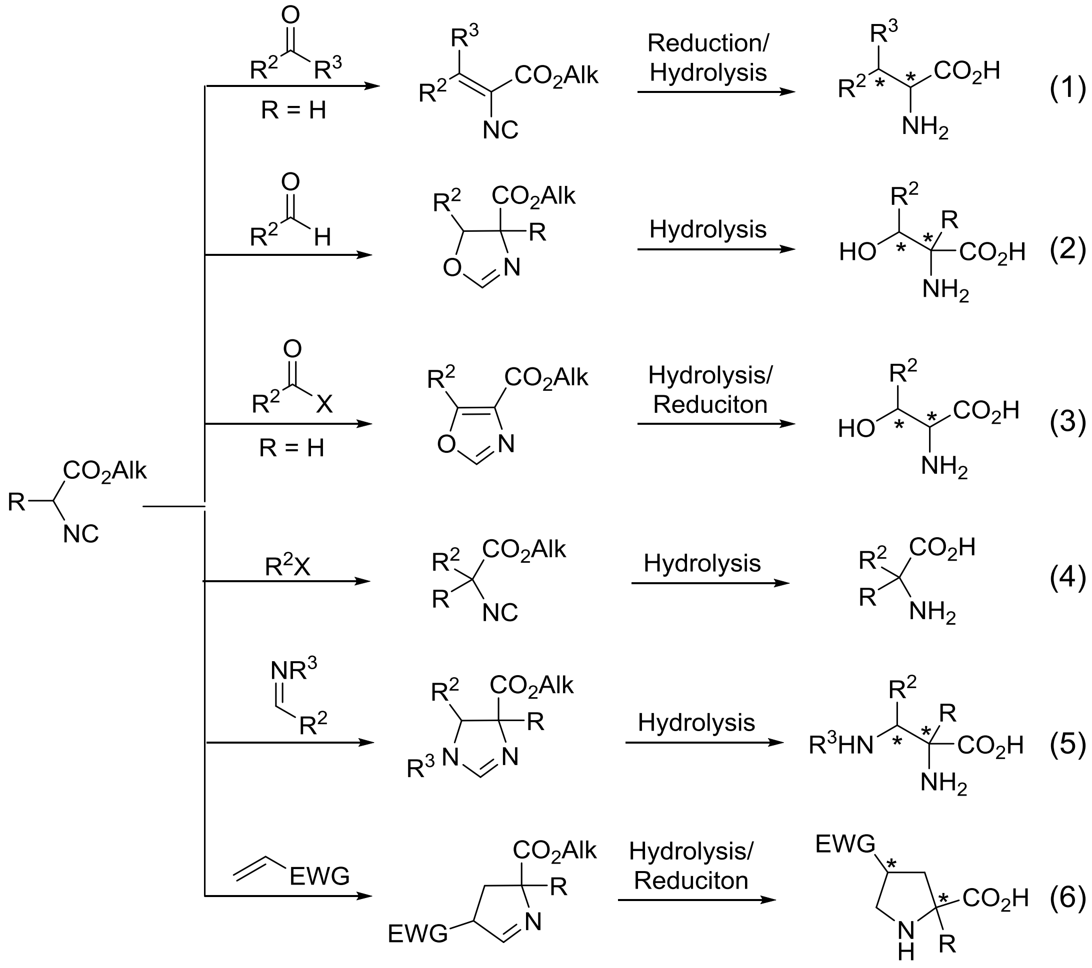
[134] See ref 127, page 45.

[135] For some examples related to the total synthesis of complex natural products: a) Ortuno, J.-C.; Langlois, Y. *Tetrahedron Lett.* **1991**, *32*, 4491–4494. b) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Angew. Chem. Int. Ed.* **1999,** *38*, 3537–3539. c) Dömling, A.; Beck, B.; Eichelberg, U.; Sakamuri, S.; Menon, S.; Chen, Q.-Z.; Lu, Y.; Wessjohann, L. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7235–7239. d) Faure, S.; Hjelmgaard, T.; Roche, S. P.; Aitken, D. J. *Org. Lett.* **2009**, *11*, 1167–1170.

[136] For review related to the synthesis of amino acid derivatives from glycine equivalents, see: a) Kotha, S.; Halder, S. *Synlett* **2010**, *3*, 337–354. For selected reviews on the synthesis of amino acids, see: b) see ref 48, page 15 y 51, page 16.



Scheme 21. Synthesis of α-amino acids based on the α-functionalization of α-isocyanoacetates.

As mentioned in the previous section, α-quaternary amino acids are of especial interest, but their synthesis involves α-substituted isocyanoacetates which present decreased reactivity and therefore increased challenge.

In this context, a comparison of the carbon acidities of several common masked α-amino acid equivalents would be informative. As data in Figure 19 show, among a series of N-containing functional group, isocyanide is the weakest EWG, inducing a limited enhancement of Cα acidity.[137] Thus, isocyanoacetates are among the less acidic α-amino acid equivalents which causes the necessity of using stronger bases or larger amount of metal promoter to perform the reaction with the corresponding electrophile, especially when the isocyanoacetates have no-activating α-substituents (i.e. an alkyl chain).

---

[137] For pKa values of common organic compounds, see: a) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van Der Pui, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321–325. b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

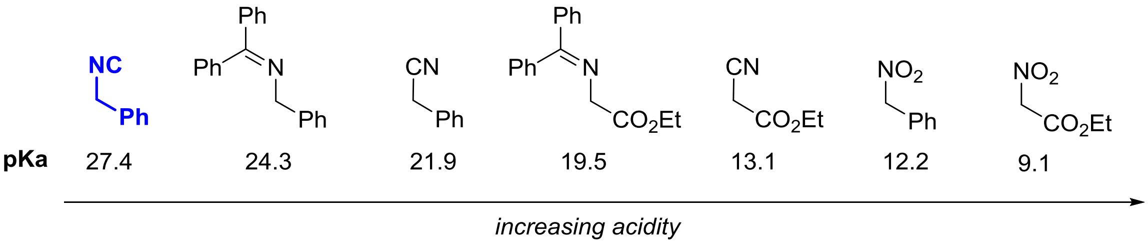


Figure 19. The effect of the amine precursor group in the acidity of α-position.

These characteristics justify the limitations in the scope indicated in the section on α-quaternary prolines synthesis (see Table 8, page 41), and equally, precedents regarding to the Mannich addition that are analyzed later (chapter 3, page X-X) reflect that these limitations are not exclusive to the synthesis of prolines.

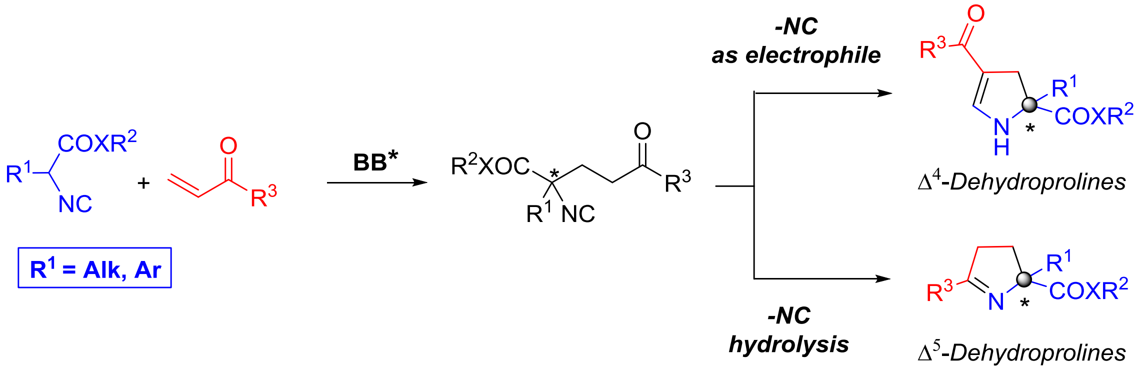
Nevertheless, due to the synthetic diversity that confers the structure of isocyanoacetates, reactions involving them for the synthesis of α-quaternary amino acids are considered valuable alternatives to those involve other masked α-amino acids. So, in order to extend α-substituted isocyanoacetates application, especially in metal-free methods, the design of a more active structure of isocyanoacetates is a field that deserves to be further studied.

1.6. Objetives

As mentioned in the general introduction, α-quaternary prolines are structurally unique α-amino acids of great significance in peptide chemistry as well as the fields of natural products and biologically active substances. Besides, their unique structural bias makes them particularly relevant within the α-amino acids family.

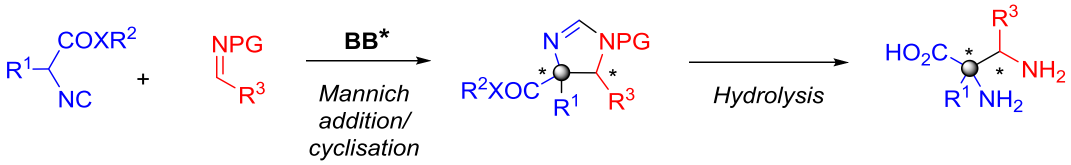
The most widely investigated approach for the enantioselective synthesis of α-quaternary prolines relies on the catalytic [3+2] cycloadditions reaction between azomethine ylides and electron-deficient olefins, involving in most cases metal catalysis (page 25-37). In this context, α-substituted isocyanoacetates have been seldom employed owing to the low acidity of Cα, despite this approach would be a complement alternative. Most studies dealing with catalytic enantioselective cycloadditions of α-substituted isocyanoacetates involve very reactive olefins as reaction counterparts and require combined metal/Brønsted base catalysis. In addition, the use of α-alkyl isocyanoacetates is still a challenge (section 1.3.1.2.3, page 39).

The overall aim of this Thesis investigation consists of the development of a new approach for the organocatalytic asymmetric synthesis of α-aryl and α-akyl substituted prolines from α-substituted isocyanoacetates and simple vinyl ketones, a transformation that has been scarcely explored. If successful, one feature of the approach is that, thanks to the chemical diversity of the isocyanide group, the eventually formed Michael adduct would allow a divergent route to either Δ^4- and Δ^5-Dehydroprolines (Scheme 22).



Scheme 22. Divergent synthesis of quaternary Δ^4- and Δ^5-Dehydroprolines.

The two main challenges to overcome are the reactivity for BB-based activation and control of stereochemistry during the formation of the quaternary stereocenter, especially when the reaction is performed with α-alkyl (least reactive) isocyanoacetates. To address these challenges we planned the screen of several common bifunctional BB/H-bond catalysts and eventually the development of novel catalysts that best fit this particular transformation. Once the optimal conditions for this objective were found, the idea was to see the scope of these reaction conditions with another type of electrophiles, such as other Michael acceptors or imines. The catalytic asymmetric Mannich addition of these nucleophiles would provide α-quaternary 2-imidazolines, commonly used for the synthesis of α,β-diamino acid precursors.



Scheme 23. Synthesis of α-quaternary α,β-diamino acids via Mannich addition of isocyanoacetates.

Chapter 2

Bifunctional Brønsted base/H-bond catalysis assisted Michael addition of α-aryl isocyanoacetates to vinyl ketones: divergent synthesis of Δ^4- and Δ^5-dehydroprolines

2. *Bifunctional Brønsted base/H-bond catalysis assisted Michael addition of α-aryl isocyanoacetates to vinyl ketones: divergent synthesis of Δ^4- and Δ^5-Dehydroprolines* *55*

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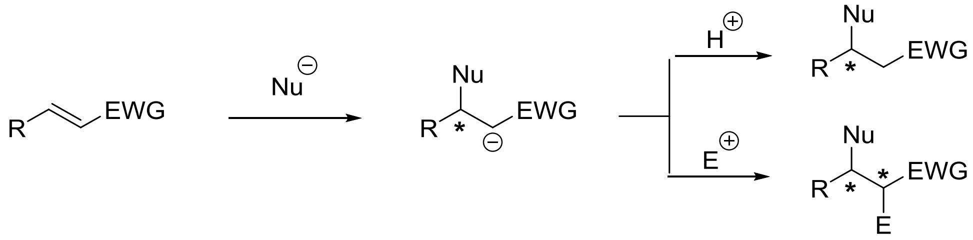
2. Bifunctional Brønsted base/H-bond catalysis assisted Michael addition of α-aryl isocyanoacetates to vinyl ketones: divergent synthesis of Δ^4- and Δ^5-Dehydroprolines.

2.1. Introduction

2.1.1. Organocatalytic asymmetric Michael additions

The asymmetric Michael addition or conjugate addition is one of the most powerful methods in organic chemistry for C–C or C–heteroatom bond formation and thus for the preparation of chiral complex molecules.[138] In this process, the nucleophile or Michael donor attacks to the β-carbon of an electron-deficient olefin or Michael acceptor, giving rise a stabilized carbanionic intermediate. This anionic intermediate can either capture a proton or another electrophile. So, up to two new stereocenters at α- and β-position may be created (Scheme 24). Thus, the control of enantio- and diastereoselectivity in the processes is of considerable significance.



Scheme 24. General scheme of the Michael addition reaction.

Considering that Michael reactions may be part of a tandem, domino or cascade process[139] and the variety of donors and acceptors that can be used, this approach offers great synthetic utility/versatility often constituting a key strategic transformation in the synthesis of bioactive compounds of high complexity. The Michael acceptors are

---

[138] For reviews on asymmetric conjugate addition, see: a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806. b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061. c) Krause, N.; Hoffmann-Röder, A. *Synthesis*, **2001**, *2*, 171–196. For a leading book on the topic, see: d) Perlmutter, P.; *Conjugate Addition Reactions in Organic Chemistry* (Pergamon, Oxford) 1992.

[139] For general reviews related to Michael addition in cascade reactions, see: a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186. b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. c) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chemistry* **2010**, *2*, 167–178. d) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390–2431. For leading book on the topic, see: e) Tietze, L. F.; Brasche, G.; Gerike, K. *Domino Reactions in Organic Chemistry* (Wiley-VCH, Weinheim).

usually α,β-unsaturated carbonyl compounds (aldehydes, ketones, esters, amides, etc.) but other electron-poor olefins with activating groups such as nitro, nitrile, sulfonate, sulfoxide, phosphate and phosphonate have also been employed successfully. Additionally, the nucleophilic atom can be either carbon or heteroatom (oxa-, aza-, sulfa- and phospha-Michael reaction).[140]

Arthur Michael reported the first racemic example of Michael reaction in 1887[141] and since them, the reaction has been investigated and applied to organic synthesis with no interruption. In the last decades, focus has been in the development of catalyst-controlled asymmetric versions involving metal-based [138,142] and organocatalysis.[143] Interactions between the catalyst and the substrates in organocatalytic asymmetric Michael reactions are different from those involving metal catalysis. As shown in the introduction (section 1.1.1, page 9), the chiral organocatalysts can activate the nucleophile, the electrophile or both the reagents through covalent bonding or non-covalent bonding.[144] In this sense, different approaches have been studied for the asymmetric Michael addition (Figure 20).

---

[140] For reviews on aza-Michael reactions, see: a) Xu, L.-W.; XIa, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639. 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. For a review of oxa-Michael reactions, see: d) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37,* 1218–1228. For a reviews of sulfa-Michael reactions, see: e) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, 959–980. f) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582–595. For a review of phospha-Michael reactions, see: g) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29–49.

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

[142] For general reviews on general metal-catalized asymmetric conjúgate addition, see: a) Hayashi, T.; Yamasaki, K. *Chem. Rev*. **2003**, *103*, 2829–2844. b) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295–7306. c) Hui, C.; Pu, F.; Xu, J. *Chem. Eur. J.* **2017**, *23*, 4023–4036.

[143] For reviews on organocatalyzed asymmetric conjúgate addition, see: a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716. b) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365. c) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065–2092. d) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42–53. For leading books on the topic, see: e) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions* (RSC Publishing, Cambridge) 2010. f) Zhang, Y.; Wang, W. *Stereoselective Organocatalysis,* Rios, R., Eds.; Wiley: Hoboken; 2013; pp 147–203.

[144] Marcus, Y:; Hefter, G. *Chem Rev.* **2006**, *103*, 4585–4621.

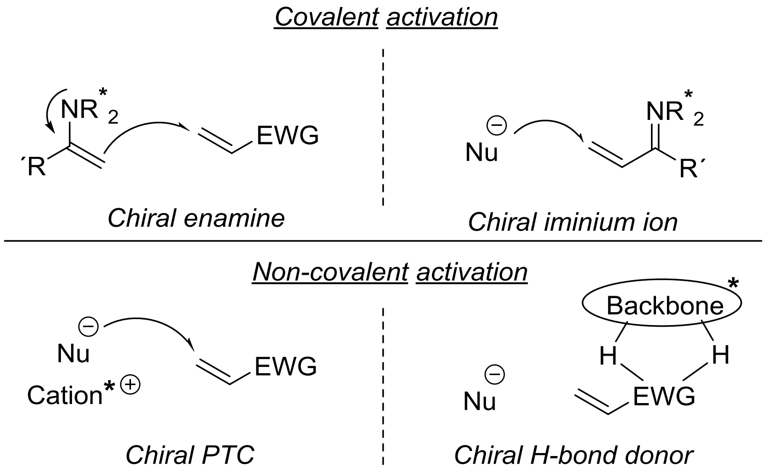


Figure 20. Organocatalytic activations in asymmetric Michael additions.

With respect to covalent activation, chiral aminocatalysts in Michael addition can operate through two mechanisms, namely: enamine activation (Nu reagent activated)[145] and iminium activation (E reagent activated).[146] Regarding to non-covalent activations, chiral phase-transfer catalysis (PTC)[147] can be used in conjugate additions for enantioface discrimination. In addition to this non-covalent activation pathway, chiral H-bond donors (diols, biphenols, ureas, thioureas, squaramides, etc.)[148] are useful tools for substrate activation in asymmetric Michael additions.

At the same time, soft deprotonation/enolization promoted by proton transfer is often the key step to the activation of certain types of carbonyl compounds in asymmetric Michael additions. However, deprotonation of esters and other carboxylic acid derivatives, such as amino acid derivatives, by soft bases have been challenging due to the low acidity of such species. Although stronger Brønsted base catalysts have been developed to overcome this reactivity issue,[149,150] the main problem with these bases often is the proton transfer from the protonated Brønsted base leading the product and regenerating the catalyst (catalyst turnover). Likely for this reason most efforts still focus

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[145] Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135.

[146] See Chapter 1, ref. 23a, page 9.

[147] a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. b) Maruoka, K. *Organic Process Research & Development* **2008**, *12*, 679–697.

[148] a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543. b) Nishikawa, Y. *Tetrahedron Letters* **2018**, *59*, 216–223.

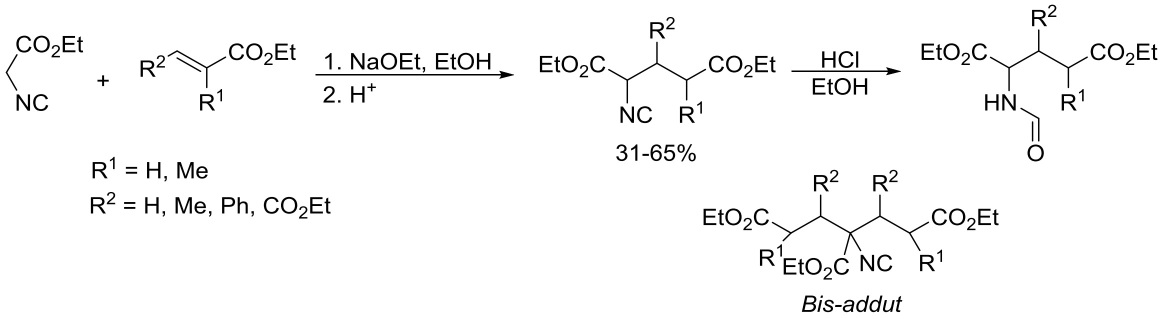
[149] See Chapter1, ref. 35, page 11.

[150] For reviews in chiral guanidines, see: a) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553–557. b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752. c) Leow, D.; Tan, C.-H. *Chem. Asian. J* **2009**, *4*, 488–507. d) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555–1564. e) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210–8222. f) Selig, P. *Synthesis* **2013**, *45*, 703–718. For reviews in chiral iminophosphoranes, see:) Krawcyk, H.; Dzigielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, L. *Chem. Eur. J.* **2015**, *21*, 10268–10277.

on the development of more effective bifunctional Brønsted base catalysts or new pronucleophilic templates suitable for soft enolization.

2.1.2. Isocyanoacetates in catalytic asymmetric Michael additions

Conjugate additions of isocyanoacetates have been used for the synthesis of nitrogen-containing compounds such as branched amino acids. The first non-asymmetric variant was reported by Schöllkopf in 1970, in which the conjugate addition of ethyl isocyanoacetates to acrylates and their derivatives was successfully implemented. One of the problems in this method is the formation of the bis-adduct sideproduct (Scheme 25).[151]



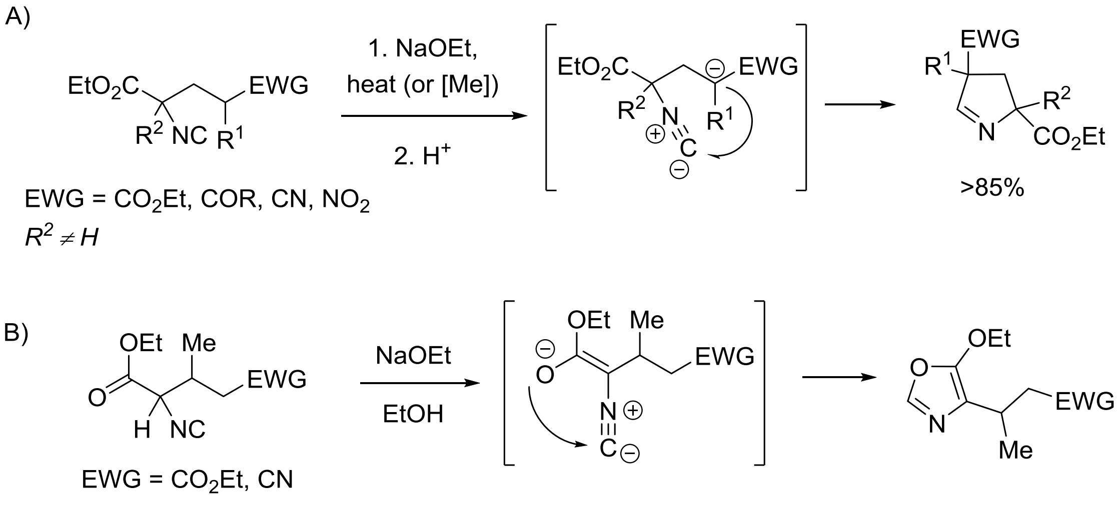
Scheme 25. The first non-asymmetric Michael addition of isocyanoacetates.

After this first racemic version, similar racemic reactions were studied with Michael acceptors other than acrylates and the reaction adducts were submitted to ulterior transformations, demonstrating the synthetic versatility of thus obtained adducts (Scheme 26).[152] While the transformation A provides the product that would derive from the corresponding [3+2] cycloaddition, the transformation B is a pathway to avoid in asymmetric Michael additions if we want to conserve the Cα stereocenter.

---

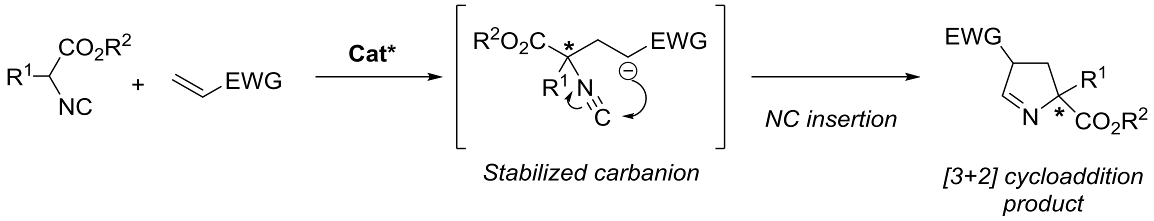
[151] Schöllkopf, U.; Hantke, K. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 896–897.

[152] a) Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316–3323. b) Schöllkopf, U.; Porsch, P.-H. *Angew. Chem. Int. Ed.* **1972**, *11*, 429–431. c) Schöllkopf, U.; Hantke, K. *Liebigs Ann. Chem.* **1973**, 1571–1582. d) Schöllkopf, U.; Porsch, P.-H. *Chem. Ber.* **1973**, *106*, 3382–3390. e) Murakami, M.; Hasegawa, N.; Tomita, I.; Inouye, N.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 1257–1260. f) Murakami, M.; Hasegawa, N.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1991**, *56*, 7356–7360.



Scheme 26. Subsequent elaboration of the isocyanoacetate adducts.

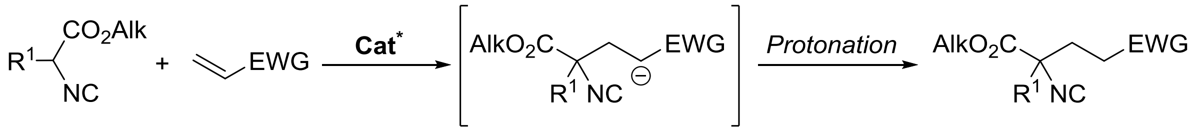
Nowadays, in contrast to the long history of non-asymmetric variants, catalytic enantioselective Michael additions of isocyanoacetates have been much less developed. One of the problems is that, the carbanionic Michael adducts spontaneously cyclize by subsequent intramolecular nucleophilic addition to the isocyano group. So obtaining the acyclic product has been possible in very few cases (Scheme 27). The electron-withdrawing group stabilizes the negative charge in the Cα of the intermediate, making the isocyano group insertion more favorable than the α-protonation. In addition, as has been shown in the introduction (see page 39), in most developments very reactive olefins in conjunction with metal catalysts are required. In the presence of the metal (Lewis acid) catalyst, the electrophilicity of the isocyano group is increased by coordination, so the cyclization process of the intermediate carbanion is faster than in the absence of the metal.

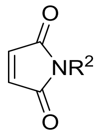
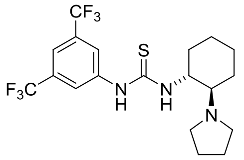
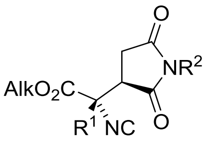
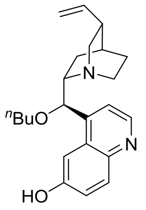
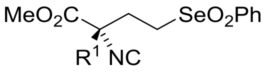


Scheme 27. The most common reaction pathway involving asymmetric Michael additions of isocyanoacetates leads to cyclization products.

In this context, if the cyclization step could be avoided, and so the isocyano group preserved, in the products then full advantage of its synthetic potential would be realized (being practically necessary to overcome the use of metals for it). However, the organocatalytic Michael additions of this type of nucleophiles still remains a challenge in part because of the relative low acidity of α-substituted isocyanoacetates and also the steric constrains imposed by the formation of a quaternary stereocenter. The few studies dealing with Michael reaction leading to acyclic adducts are collected in (Table 9).[153]

Table 9. Reported asymmetric Michael additions of α-substituted isocyanoacetates that stop at the acyclic adduct.



	Electrophile	Cat.*	Product	Results	Ref
1	 R^2 = Ar, Alk	 (10 mol%)	 R^1 = Ar, Me, Bn	**R^1/R^2 = Ar/Ar** 91-98% 80:20-99:1 dr 86-98% *ee* **R^1 = Me, Bn** 65-71% 55:45 dr 54-58% *ee* **R^2 = Me, Bn** 72-77% 70:30-75:25 dr 72-77% *ee*	153a
2		 (10 mol%)	 R^1 = Ar	62-96% 75-96% *ee*	153b

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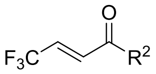
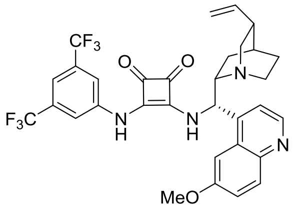
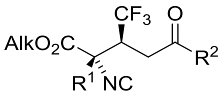
[153] a) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947–2953. b) Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718. c) Zhao, M.-X.; Ji, F.-H.; Wei, D.-K.; Shi, M. *Tetrahedron* **2013**, *69*, 10763–10771. d) Zhao, M.-X.; Zhu, H.-K.; Dai, T.-L.; Shi, M. *J. Org. Chem.* **2015**, *80*, 11330–11338.

	Electrophile	Cat.*	Product	Results	Ref
3	 R^2 = Ar, -CH_2CH_2Ph	 (20 mol %)	 R^1 = Ar, Bn	**R^1/R^2 = Ar/Ar** 45-97% >21:1 dr 79–99% *ee* **R^1 = Bn, 2-MeC_6H_4** No reaction **R^2 = -CH_2CH_2Ph** No reaction	153d

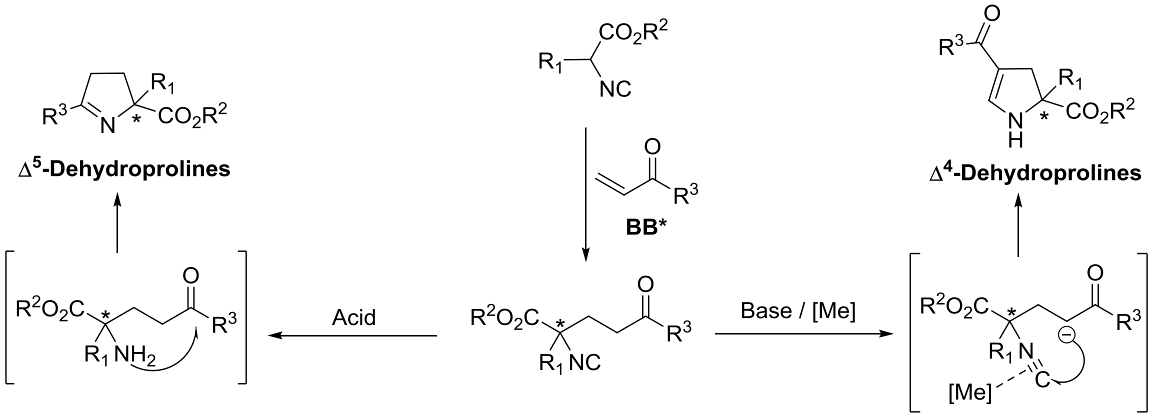
In these works, only very specific Michael acceptor have been employed and mainly with α-aryl isocyanoacetates. Shi and collaborators extended the addition to N-aryl maleimides employing squaramide bifunctional bronsted bases,[153c] even so, they did not improve the results of entry 1. Closely related to this thesis, once our work was in progress, Zhao and co-workers reported the first asymmetric Michael addition of isocyanoacetates to enones (Table 9, entry 3). One limitation of this method is that the Michael reaction did not work with α-alkyl isocyanoacetates. The same happened with α-aryl isocyanoacetates bearing an *orto*-substituted aryl group, probably by steric reasons. Furthermore, the reaction worked only with enones bearing an aryl group at R^2 postition.

Looking at these precedents, it is reflected that the enantioselective Michael addition of isocyanoacetates still presents challenges in many aspects and deserves to be studied more thoroughly.

2.2. Synthetic plan

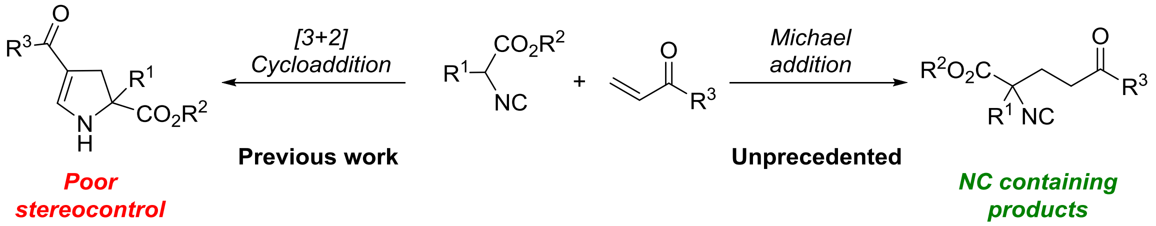
As mentioned above, commonly, the conjugate addition of isocyanoacetates to electron-deficient olefin is followed by the subsequent intramolecular cyclization giving rise to [3+2] cycloaddition products. This phenomenon has caused that the synthesis of acyclic adducts by asymmetric Michael addition had been scarcely developed. However, the linear products offer great synthetic possibilities since they contain the isocyano group intact which would allow performing a variety of ulterior transformations (see Figure 17, page 45).

Significally, a brief review of the precedents reported related to the possible transformations with this type of compounds (Scheme 25 and Scheme 26, page 58-59), we envisioned that these chiral Michael addition products could be a common intermediate for the synthesis of different types of α-quaternary proline derivatives (Scheme 28). On the one hand, the hydrolysis of the isocyano group would release the amine which would cause the cyclization by intramolecular nucleophilic addition to the carbonyl group, providing Δ^5-dehydroprolines. On the other hand, the electrophile character of the isocyano group would allow us to perform the intramolecular nucleophilic addition of the relatively acidic Cα to this isocyano, giving rise Δ^4-dehydroprolines by means of a two-step [3+2] cycloaddition.



Scheme 28. Synthetic plan.

As a result, we set out to study the catalytic asymmetric Michael addition of α-substituted isocyanoacetates to simple vinyl ketones which had not previously been documented (Scheme 29, right). In addition, a sole example was known related to the [3+2] cycloaddition variant of these substrate partners affording the corresponding dihydroproline products with moderate (52-74% *ee*, R^1 = H) or poor (16-36% *ee*, R^1 = Bn) enantioselectivity (Scheme 29, left).[154]



Scheme 29. State of the art.

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[154] See ref. 115, Chapter 1, page 40.

Considering that the absence of a metal catalyst would slow down the subsequent intramolecular cyclization step, we envisaged to study metal-free organocatalytic approach. The previous studies proved that the bifunctional Brønsted bases were suitable candidates to catalyze the reaction, but we would probably have to design a more effective catalyst than those reported to date, owing to the low reactivity of simple vinyl ketones as compared with N-aryl maleimides (entry 1, Table 9) and vinyl selenones (entry 2, Table 9). In this context, bifunctional squaramides have demonstrated higher reactivity than thiourea catalysts, so in this thesis work special interest has been placed in the development of more effective squaramide catalysts.

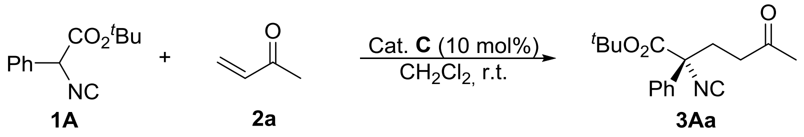
Summarizing, we envisaged developing a general asymmetric bifunctional Brønsted base catalyzed Michael addition of α-substituted isocyanoacetates to vinyl ketones, which could be applicable to the synthesis of different type of enantioenriched α-quaternary proline derivatives.

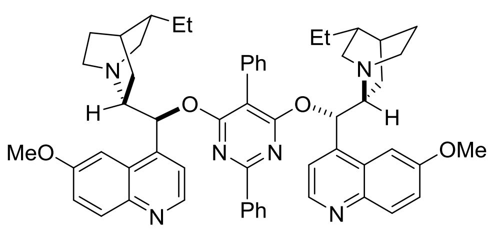
2.3. Catalyst screening and design

2.3.1. Preliminary studies

The study began by assessing the behaviour of some bifunctional BB/H-bond catalysts on the reaction of α-phenyl *tert*-butyl isocyanoacetate **1A** and methyl vinyl ketone **2a** to produce **3Aa**. The preliminary screening with previously known bifunctional Brønsted base organocatalysts demonstrated that tertiary amine/squaramide were the best catalysts (Table 10). While **C1**-**C4** catalysts (DHQ$_2$Pyr, (–)-Quinine, thiourea and ureidopeptide) gave essentially no stereocontrol, the squaramide **C5** provided the product with good enantiopurity (86% *ee*).

Table 10. Screening of H-bond donors.

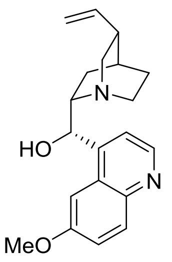




C1

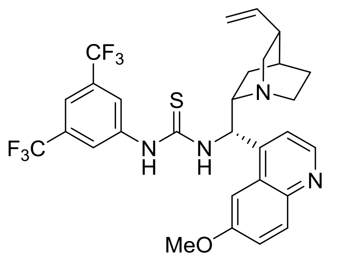
14h, conv. 85%, --

20h, conv. 95%, 0% *ee*



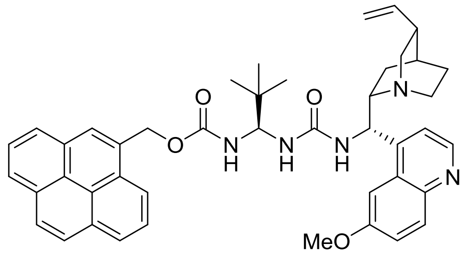
C2

14h, conv. 100%, 5% *ee*



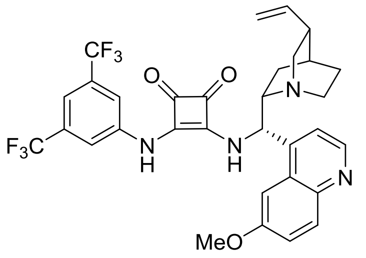
C3

14h, conv. 95%, 10% *ee*



C4

60h 100%, 0% ee



C5

14h, conv. 95%, 84% *ee*

80h, conv. 100%, 86% *ee*[b]

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Conversion into the corresponding adduct determined by ^{1}H-RMN spectroscopy and the *ee* values by chiral HPLC on the reaction crude. [b] Reaction carried out at 0 °C.

Then, a series of bifunctional tertiary amine/squaramide catalysts were tested. Here two strategic variations were studied: the structure of the basic amine site and the structure of the side group attached to the squaramide. In order to evaluate the basic motif, 3,5-bis(trifluromethyl)phenyl group was chosen as achiral activating group of squaramides. This group seems to be a key structural motif for the success in most of (thio)urea and squramide-based bifunctional Brønsted bases, introduced by Schreiner and Wittkop for the first time (Figure 21).[155]

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[155] a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.

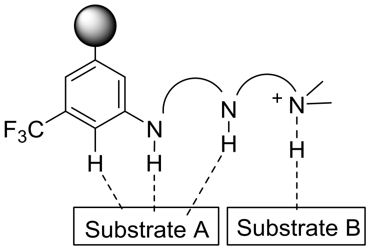

Figure 21. Activation model proposed by Zhong and Schreiner.

From the results using squaramide bases **C5**-**C8**, the first one was the most appropriate given product **3Aa** with 84% *ee* (Table 11, up). In order to improve the *ee*, we tested next the Rawal´s squaramide **C9** and the silylated catalysts **C10** and **C11** designed in our group for the Michael addition reactions involving cyanomethyl azaarene *N*-oxides.[156] However, in our Michael addition these catalysts gave **3Aa** with moderated stereocontrol (50-60% *ee*). In addition, catalysts **C12** and **C13**, which had already been used successfully in other asymmetric Michael additions in our group, were also tested.[157] The results indicated that catalyst **C13** was more effective than **C12** in terms of enantioselectivity (**C12**: 56% *ee* vs **C13**: 80% *ee*), giving very similar result to that obtained with **C5** (84% *ee*). Since the latter cannot be modified easily, catalyst **C13** was elected for further improvements.

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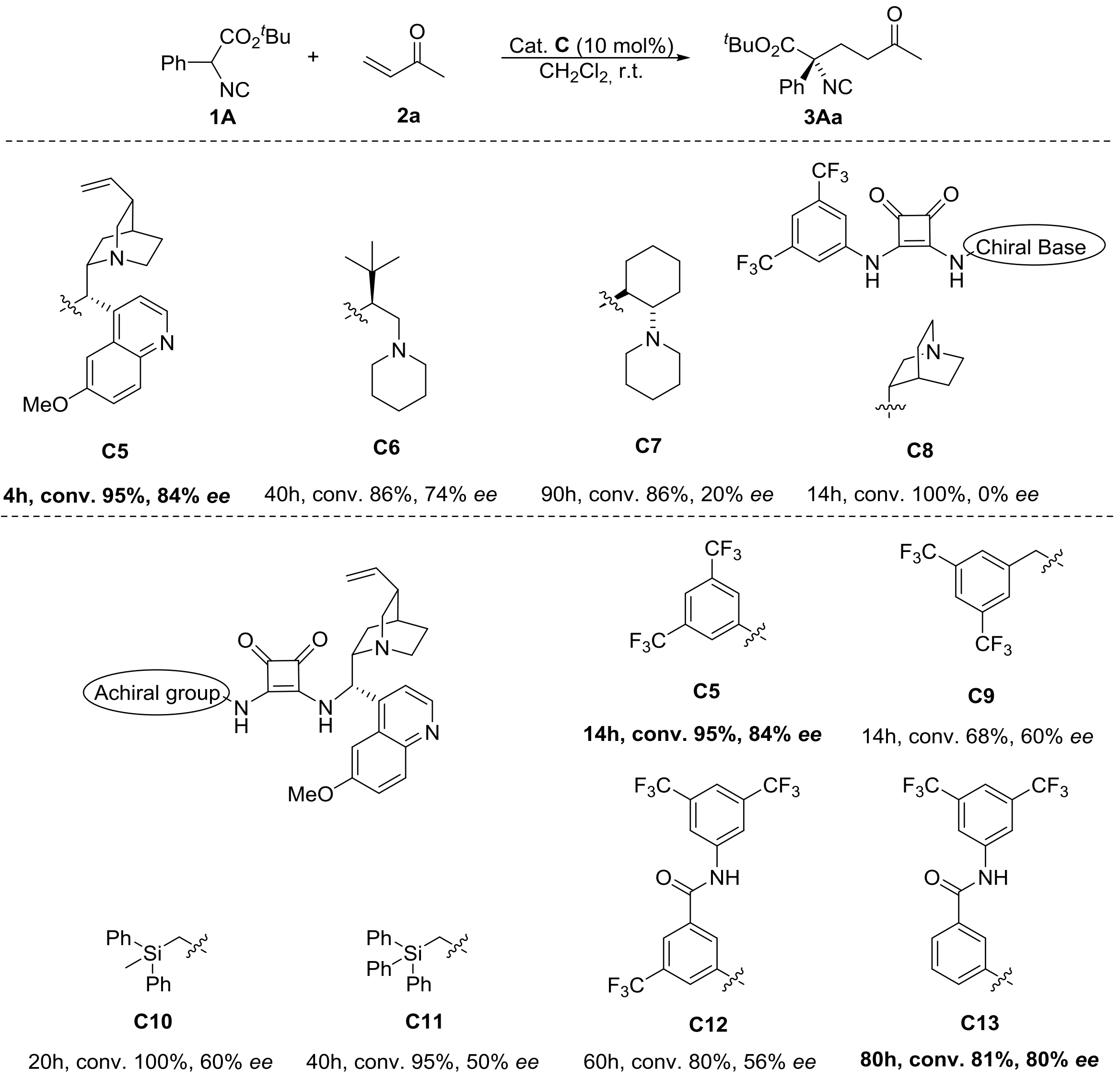
[156] Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138,* 3282–3285.

[157] a) Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886. b) Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185–8195.

Table 11. Screening of the chiral Brønsted base and the achiral motif.



C5 **14h, conv. 95%, 84% *ee***

C6 40h, conv. 86%, 74% *ee*

C7 90h, conv. 86%, 20% *ee*

C8 14h, conv. 100%, 0% *ee*

C5 **14h, conv. 95%, 84% *ee***

C9 14h, conv. 68%, 60% *ee*

C10 20h, conv. 100%, 60% *ee*

C11 40h, conv. 95%, 50% *ee*

C12 60h, conv. 80%, 56% *ee*

C13 **80h, conv. 81%, 80% *ee***

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Conversion into the corresponding adduct determined by ^{1}H-RMN spectroscopy and the *ee* values by chiral HPLC on the reaction crude.

2.3.2. Development of a new tertiary amine/squaramide catalyst having a polyaryl bulky groups

The desing of catalyst **C13** in this laboratory had been guided by assumption that the amide NH would give an internal H- bond interaction with the carbonyl group of the squarate (Figure 22), which would provide greater rigidity and H-bond donor ability to the catalyst.[158] However, the conformational analysis carried out by Julen Etxabe during his tesis in our group could not find direct evidences of the existence of this internal link yet.[159]

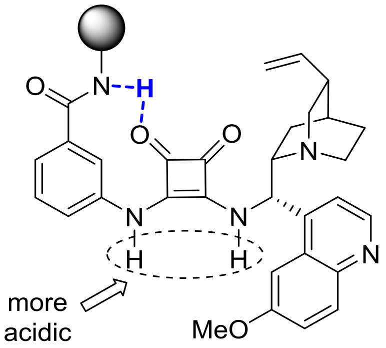


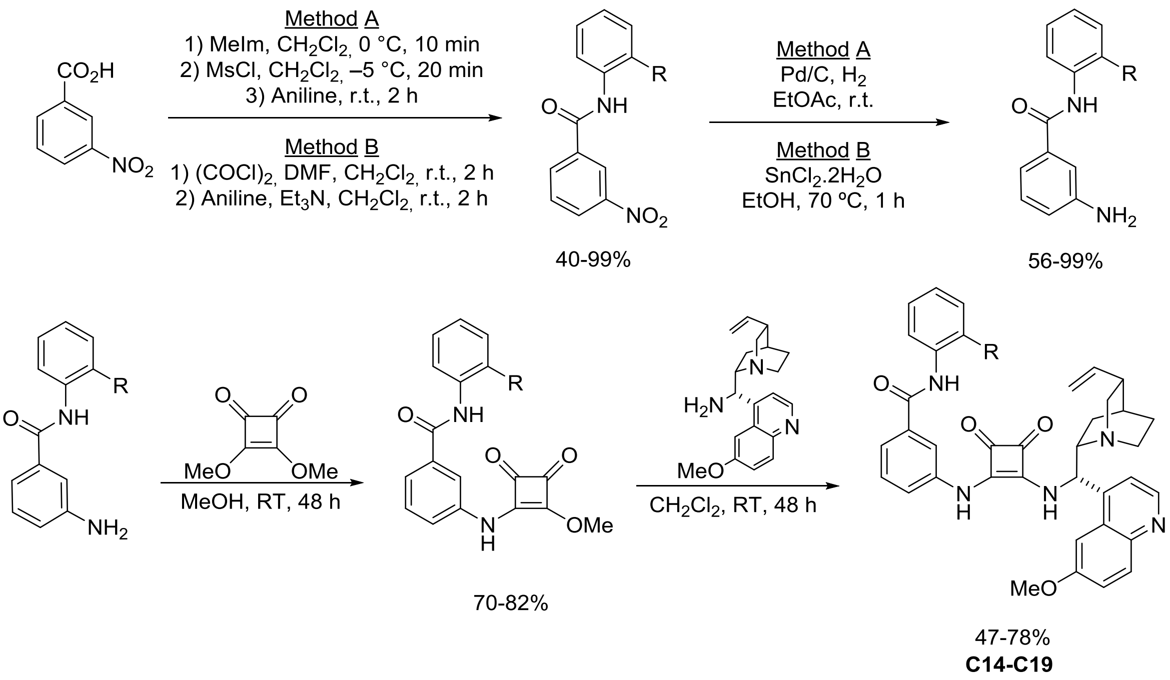
Figure 22. Internal H- bond interaction.

Our idea was to investigate if bulky groups near the squaramide could improve the stereocontrol of the reaction. The synthesis of these catalysts was planned to carry out by a modification of the previously described procedure for **C13** type catalysts (Scheme 30). Amide-bond formation (step 1) was firstly performed using methyl imidazole/methanesulfonyl chloride as coupling reagent, but in the case of *ortho*-hydroxy arylamine was unsuccessful. Coupling conditions using oxalyl chloride in combination with triethylamine (method B) were more effective, even improving some yields that were obtained with the method A. The reduction of the nitro group (step 2) was performed successfully using standard reduction conditions, except in the case of *ortho*-chloro substitution in which method B had to use. Once the desired amines were obtained, the tertiary amine/squaramide catalysts **C14**-**C19** were prepared using the standard procedure.

---

[158] For studies in relation to catalysts with similar internal coordinations, see: a) Jones, C. R.; Pantos, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 7391–7394. b) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J Org. Chem.* **2014**, 2633–2646.

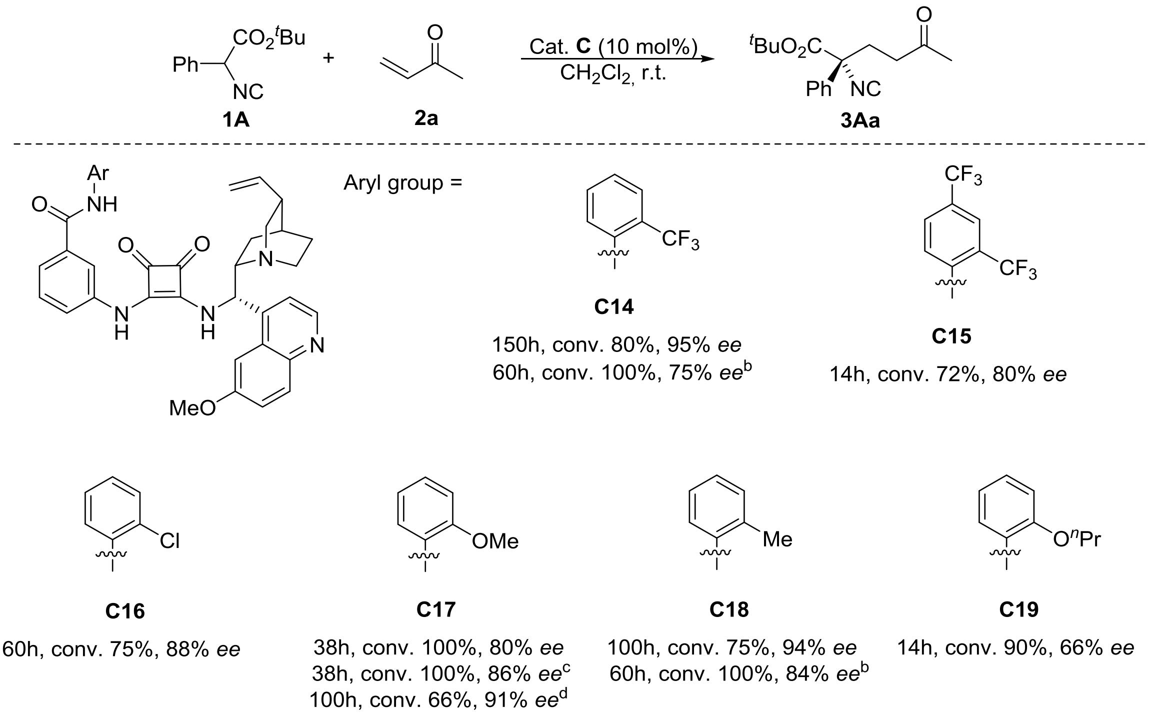
[159] For doctoral thesis related to the conformational analysis of **C13**, see: Etxabe, J. *Catalytic Asymmetric Synthesis of α,α-Disubtituted α-Thio and α-Amino Acid Derivatives* EHU/UPV; 2016; pp 290–292.



Scheme 30. Synthesis of *ortho*-substitued amide catalysts **C14**-**C19**.

Results with the newly prepared catalysts **C14**-**C19** are collected in Table 12. One general feature of these catalysts was the low solubility in non polar solvents such as dichloromethane, which compromises catalyst activity forcing long reaction times for practical conversion (up to 6 days at r.t.): **C14:** 6 days, conv. 80%, **C16:** 60h, conv. 75% and **C18:** 4 days, conv. 75%. However, **C14** and **C18** gave the product with excellent enantiopurity (95% and 94% *ee,* respectively), but when the temperature increased to 40 °C, the enantiomeric excess dropped considerably (75% and 84% *e,e* respectively) although the conversion was complete. The most promising catalyst in solubility and reactivity terms was **C17.** Even so, the stereocontrol of the reaction was lower (80% *ee*) than in case of **C14** and **C18**. Performing the same experiment at 0 °C and -20 °C the enantiomeric excess increased to 86% and 91% *ee* respectively, but the reaction rate dramatically decreases at -20 °C. We also tried catalyst **C19** with a longer alkoxy chain in but the result was worse (66% *ee*).

Table 12. Screening of *ortho*-substitued amide catalysts.



C14
150h, conv. 80%, 95% *ee*
60h, conv. 100%, 75% *ee*[b]

C15
14h, conv. 72%, 80% *ee*

C16
60h, conv. 75%, 88% *ee*

C17
38h, conv. 100%, 80% *ee*
38h, conv. 100%, 86% *ee*[c]
100h, conv. 66%, 91% *ee*[d]

C18
100h, conv. 75%, 94% *ee*
60h, conv. 100%, 84% *ee*[b]

C19
14h, conv. 90%, 66% *ee*

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Conversion into the corresponding adduct determined by ^{1}H-RMN spectroscopy and the *ee* values by chiral HPLC on the reaction crude. [b] Reaction carried out at 40 °C. [c] Reaction carried out at 0 °C. [d] Reaction carried out at -20 °C.

In brief, these experiments were conditioned by the low reaction rate, as consequence of the low solubility of the catalysts. In cases in which the time required for a total conversion was acceptable, the enantiomeric excess of the final product decreased and *vice versa*. However, the data obtained reflect that the steric hindrance around the squarate improved the stereocontrol of the reaction.

With these data in hand, the idea was to find more soluble catalysts that would catalyze the reaction more effectively, whereas increasing the steric congestion around the squarate might be favorable for the enantiocontrol. Also, although the existence of the internal H-bond in amide-type catalysts has not been confirmed, initially the idea was to design a new type of catalysts in which this coordination could be possible. Based on these ideas, we decided to install a bulky tertiary alcohol in place of the N-H amide. In addition, these alcohols would be in principle accessible via nucleophilic addition of the corresponding Grignard reagents to a common ester intermediate, making the preparation highly versatile for structural variation.

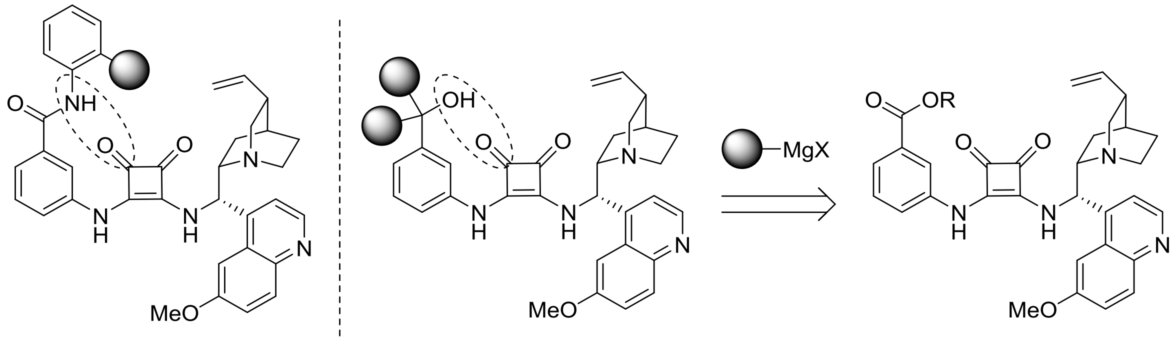
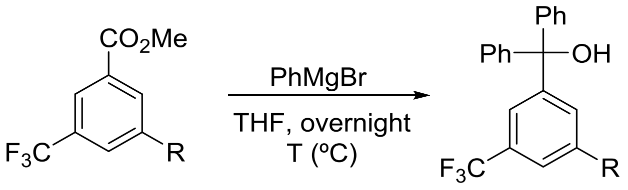


Figure 23. Design of the new catalysts and their preparation.

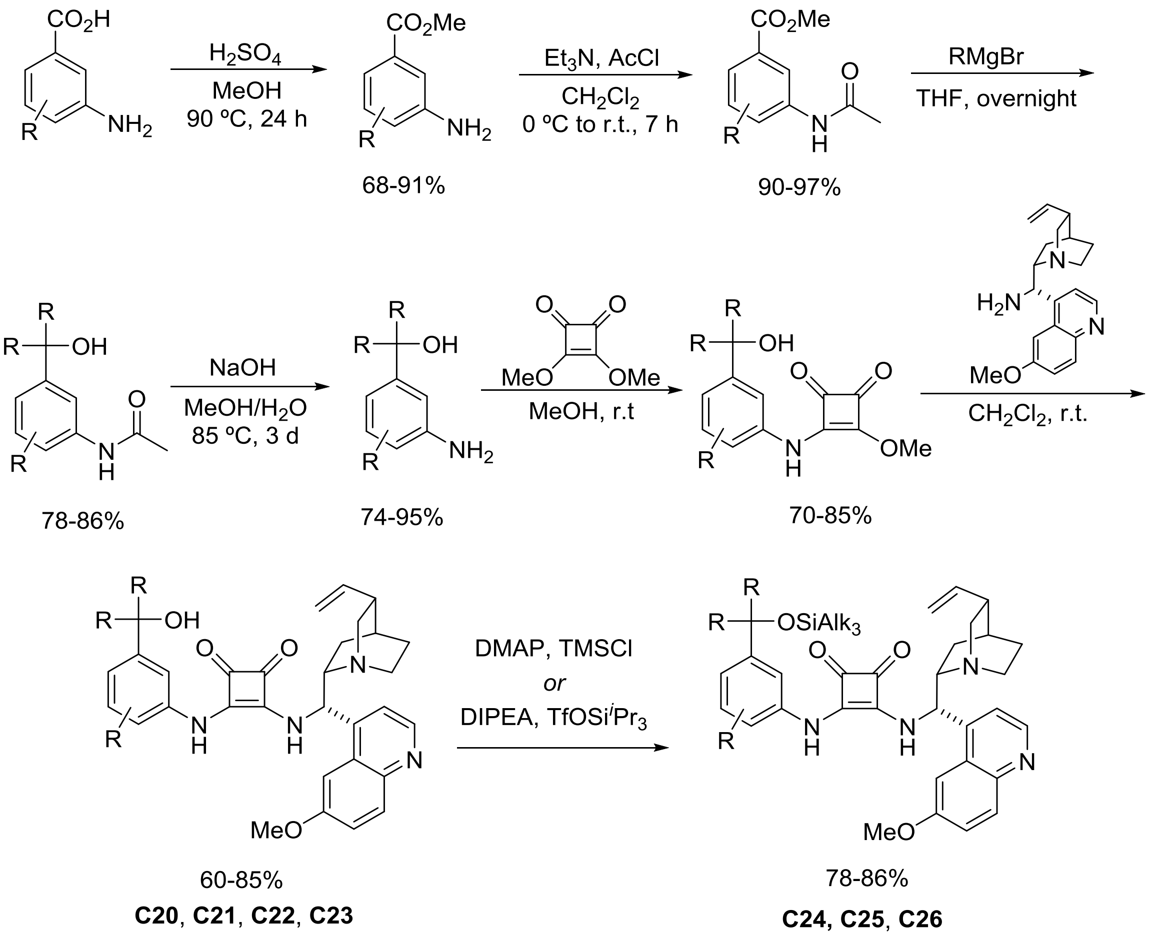
After several failed attempts (Table 13), it was discovered that for a successful addition of the Grignard reagent to the ester group, the amine had to be acetylated previously.



R	T	Result
NH_2	reflux	Messy crude (similar ^{1}H NMR)
NH_2	r.t.	
NO_2	reflux	
NO_2	r.t.	
NHAc	r.t.	86% of product

Table 13. Assays of the addition of the Grignard reagent to the ester group.

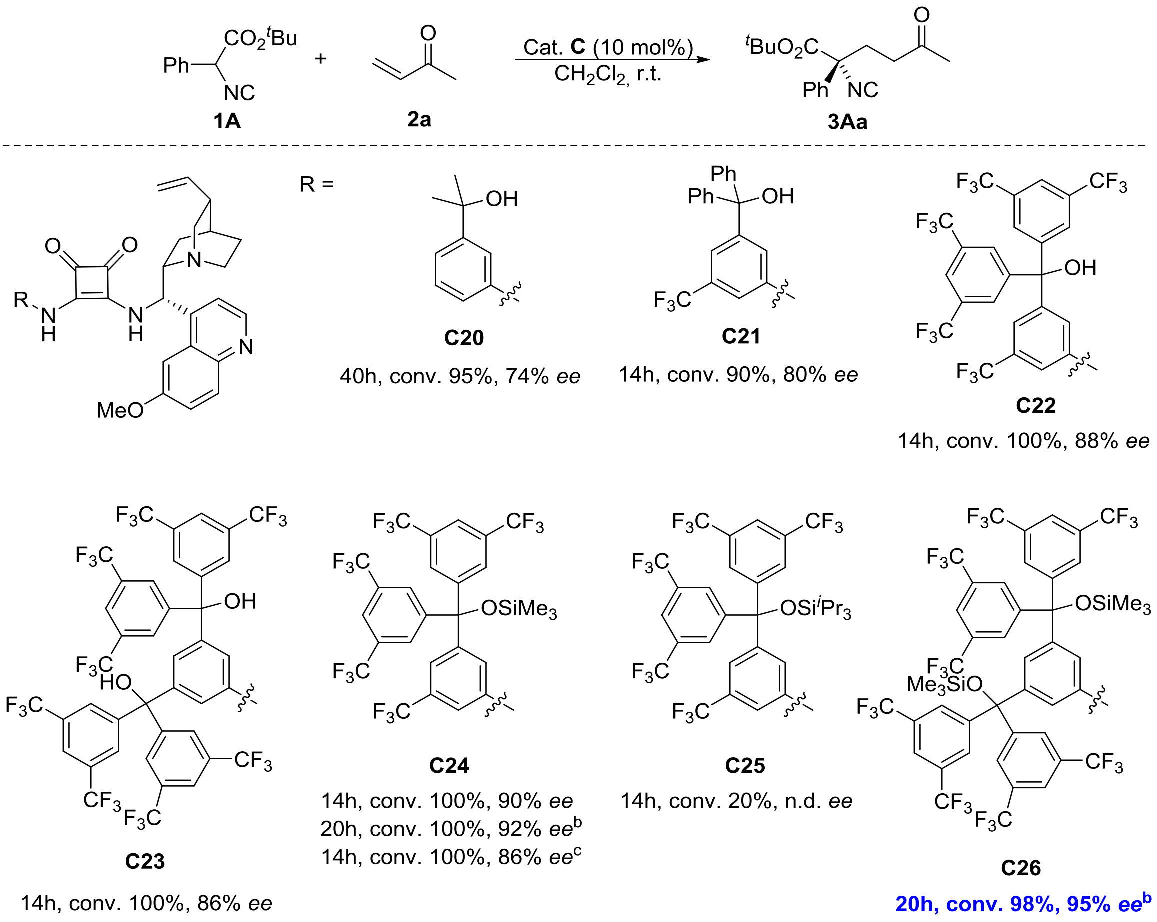
The full synthetic sequence for the preparation of catalysts **C20**-**C26** is shown in Scheme 31. Although 6 steps are required from commercial or simply accessible *meta*-benzoic acids to reach the final catalysts, the yields of each step in general are good and in many cases, the steps are clean enough to continue without a prior purification of the intermediates. As general features, these catalysts are solid and have high molecular weight (1500 mg/mmol approximately), so very low catalyst amount can be weighed accurately for the catalytic reactions. In addition, they showed excellent solubility in both polar and non-polar solvents allowing their use in a broad range of solvents.



Scheme 31. General procedure for synthesis of new catalysts.

As shown in the Table 14 the newly prepared catalysts resulted more active allowing the reation between isocyanoacetate **1A** and vinyl ketone **2a** to be essentially complete after 14 h. First we evaluated the influence of the groups around the hydroxyl group; among methyl (**C20**: 74% *ee*), phenyl (**C21**: 80% *ee*) and bistrifuoromethylphenyl (**C22**: 88% *ee*), the latter gave the best stereochemical results. So, we took the *gem*-diaryl **C22** as a reference to further development. Suprisingly, the trimethylsilyl derivative **C24** worked as well as **C22** even improving the enantiomeric excess when the catalyst loading was lower (5 mol%, 92% *ee*). However, a more bulky alkylsilyl group (TIPS) drastically affected the reactivity (**C25**: 14h conv. 20%). Finally, the *gem,gem*-(bis)diaryl congener **C23** and its silylated derivative **C26** were tested, being this last one, with 5 mol% of catalyst loading, the most selective (95% *ee*).

Table 14. Screening of catalysts containing tertiary alkoxy groups.



C20
40h, conv. 95%, 74% *ee*

C21
14h, conv. 90%, 80% *ee*

C22
14h, conv. 100%, 88% *ee*

C23
14h, conv. 100%, 86% *ee*

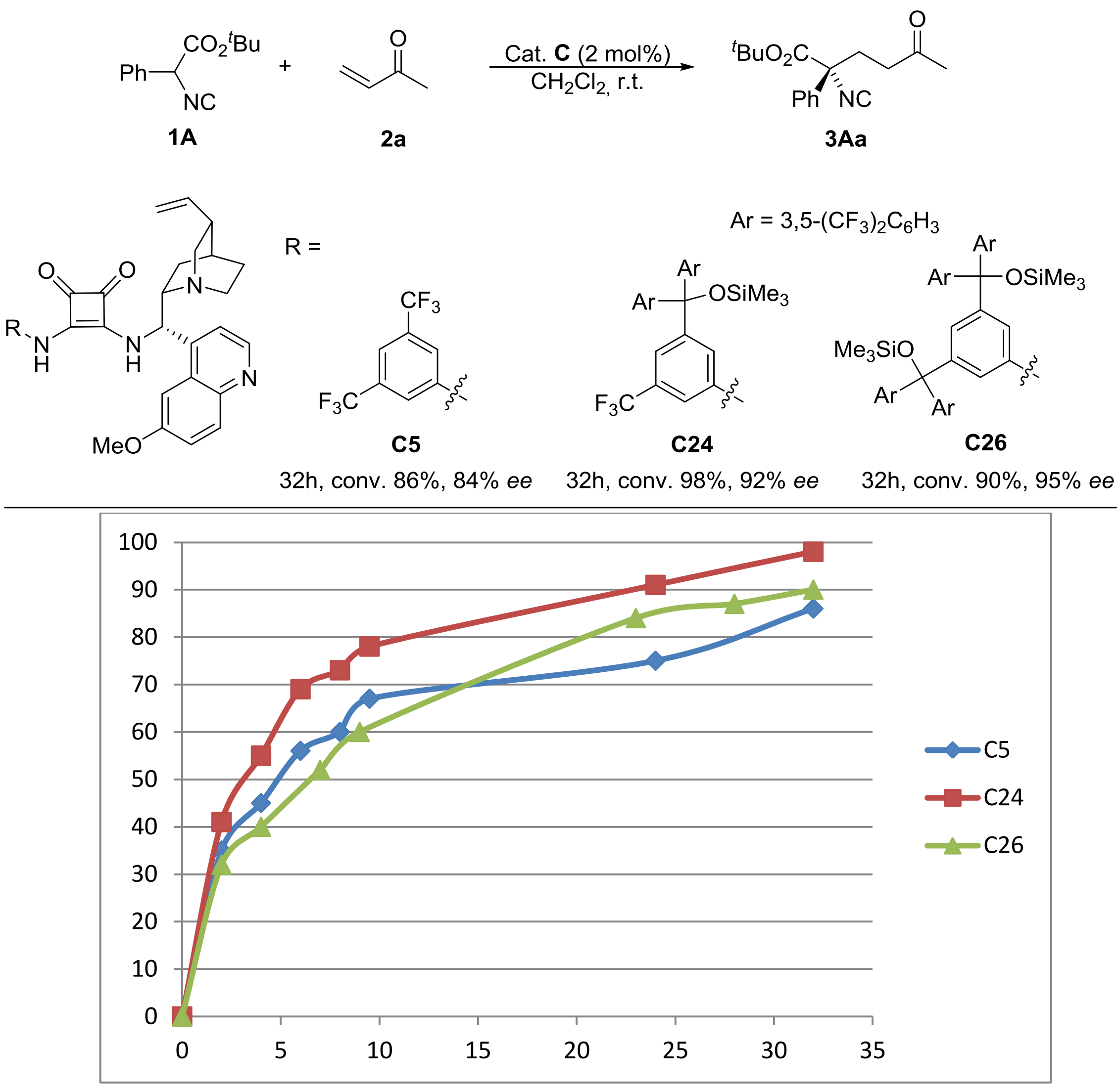
C24
14h, conv. 100%, 90% *ee*
20h, conv. 100%, 92% *ee*[b]
14h, conv. 100%, 86% *ee*[c]

C25
14h, conv. 20%, n.d. *ee*

C26
20h, conv. 98%, 95% *ee*[b]

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Conversion into the corresponding adduct determined by ^{1}H-RMN spectroscopy and the *ee* values by chiral HPLC on the reaction crude. [b] Reaction with 5 mol% of catalyst. [c] Reaction in 0.2 mL of toluene.

A comparison of the reaction progress using 2 mol% of catalysts **C5**, **C24** and **C26** demonstrated that both **C26** and **C24** were a little more active than **C5** (Figure 24). Although the reaction catalyzed by **C24** was faster, 2 mol% of catalyst **C26** was enough to obtain 90% of conversion in 32h (maintaining the *ee* values at 95%).



[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1A**/**2b**/catalyst 1:2:0.02). Conversion into the corresponding adduct determined by ^{1}H-RMN spectroscopy and the *ee* values by chiral HPLC on the reaction crude.

Figure 24. Reaction rate study.

Crystalls of catalyst **C26** of enough quality for X-ray analysis could be obtained and the solved solid structure is worth of coment (Figure 25). The interatomic diamine H--H distance is unusually short (2.446 Å) comparing with the typical values previously reported for related squaramide catalysts (see Figure 8, Chapter 1, page 14). This feature would enhance the resultant dipolar moment and hence, the activation by H-bonds should be more effective. In addition, squaramide solid structure does not self-aggregate through dual hydrogen-bonding as normally happen in squaramides and which usually hinders its activity (left structure).[160] This phenomenon was attributed to the bulky polyaryl moiety near the squaramide framework which prevents the approximation of different squaramide units, causing both N-H bonds of each squaramide unit to point toward the quinoline nitrogen of a contiguous molecule. Based on these structural information/data, it also seems that there is not any intramolecular interaction between the silicon atom and the carbonyl group of squaramide.

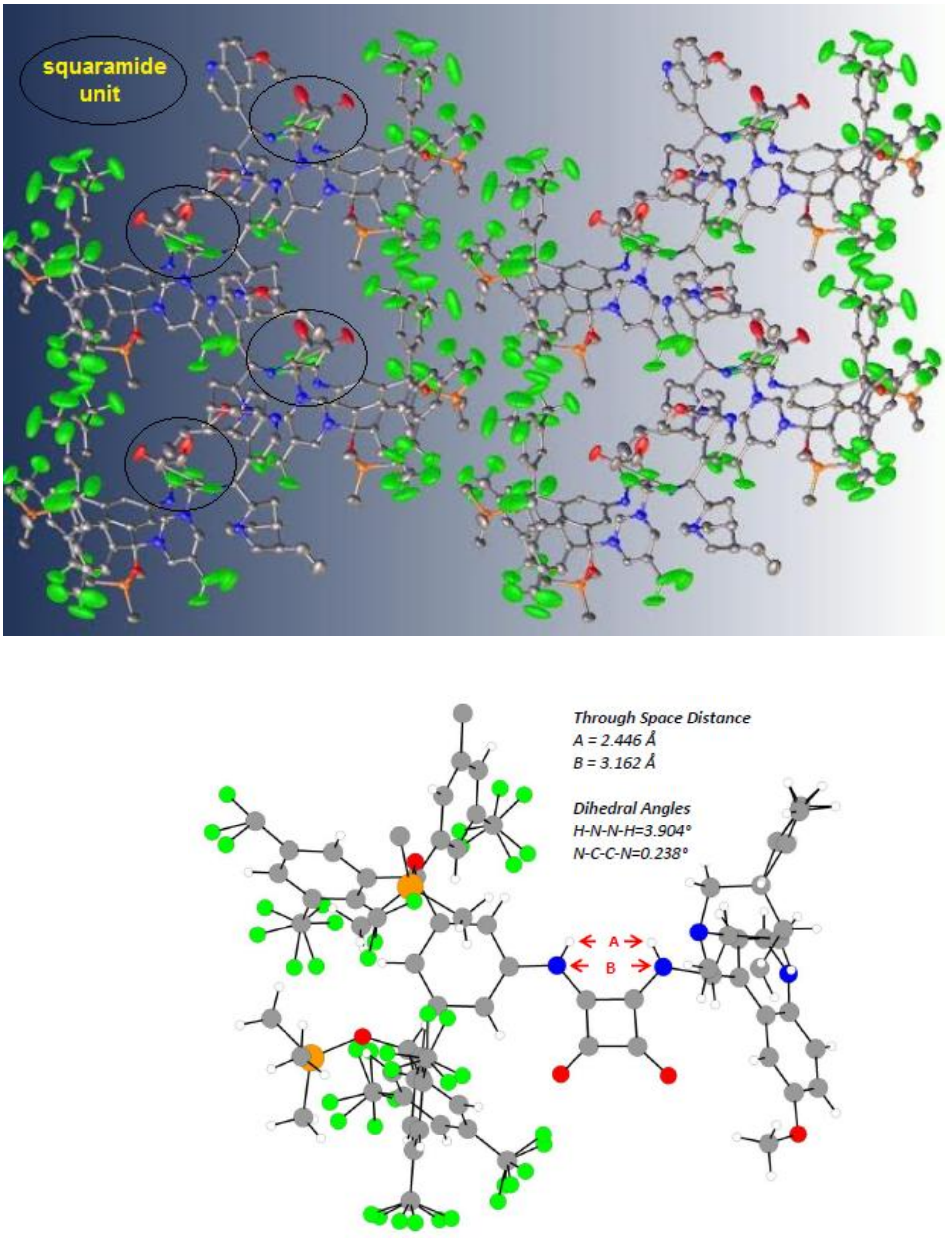


Figure 25. X-ray structure and extracted datas of the catalyst **C26**.

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[160] See ref 42, Chapter 1, page 13.

Concluding, the *gem,gem*-(bis)diaryl *oxo*-silylated catalyst **C26** demonstrated to be an excellent catalyst for this Michael addition in terms of enantioselectivity, solubility and reactivity, so was selected to follow with the study.

2.4. Scope of the reaction

2.4.1. Vinyl ketones as Michael acceptors

Due to the good results obtained with the methyl vinyl ketone **2a**, it was considered that vinyl ketones deserved to be studied more thoroughly. To explore the scope of the reaction, a 5% catalyst loading was used and a range isocyanoacetates/vinyl ketones were combined (Table 15).

As can be seen, the reaction perfectly tolerated *meta*, *para* and unsubstituted α-aryl isocyanoacetates, even decreasing the catalyst load to 2 mol% (**3Ac** and **3Dd**) or using electron donating substituent in whichever of the two aryl groups. Also, less reactive alkyl vinyl ketone provided de Michael adducts with very good yields and enantioselectivities (**3Aa**, **3Ab** and **3Ca**). Nevertheless, as in the work reported by Zhao *et* al.[161] this reaction also did not tolerate α-alkyl substitution pattern in the nucleophiles (**3Ee**).

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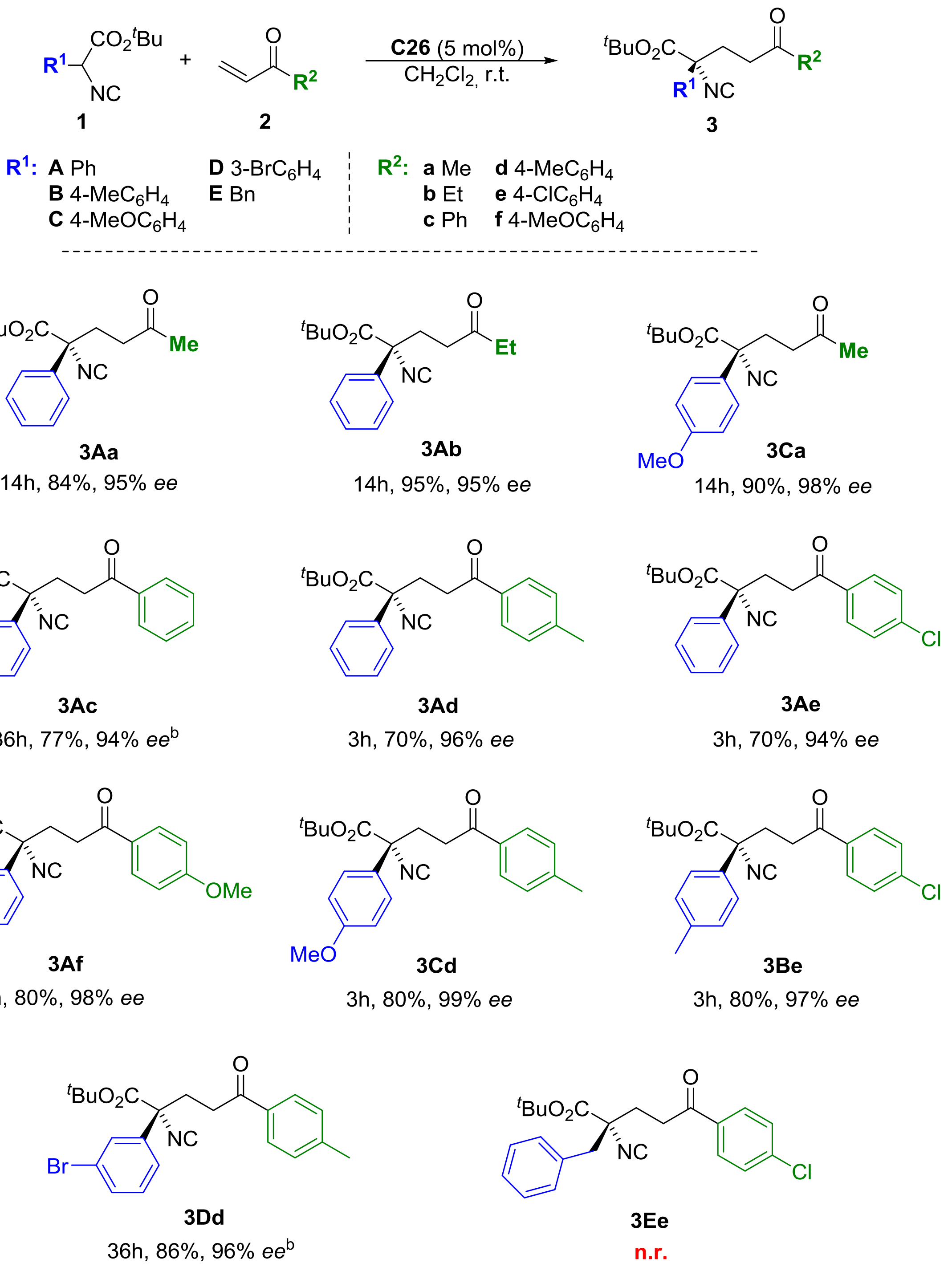
[161] See ref. 153d, page 60.

Table 15. Scope of the Michael addition involving vinyl ketones as Michael acceptor.



R^1: **A** Ph, **B** 4-MeC$_6$H$_4$, **C** 4-MeOC$_6$H$_4$, **D** 3-BrC$_6$H$_4$, **E** Bn

R^2: **a** Me, **b** Et, **c** Ph, **d** 4-MeC$_6$H$_4$, **e** 4-ClC$_6$H$_4$, **f** 4-MeOC$_6$H$_4$

3Aa
14h, 84%, 95% *ee*

3Ab
14h, 95%, 95% *ee*

3Ca
14h, 90%, 98% *ee*

3Ac
36h, 77%, 94% *ee*[b]

3Ad
3h, 70%, 96% *ee*

3Ae
3h, 70%, 94% *ee*

3Af
3h, 80%, 98% *ee*

3Cd
3h, 80%, 99% *ee*

3Be
3h, 80%, 97% *ee*

3Dd
36h, 86%, 96% *ee*[b]

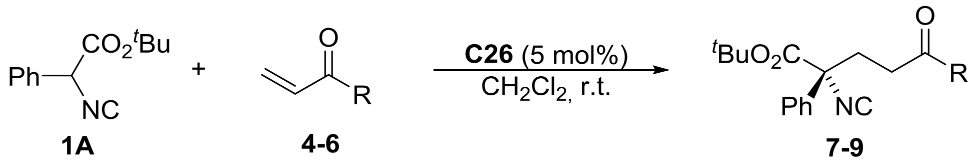
3Ee
n.r.

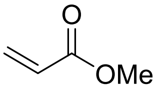
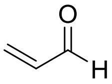
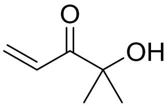
n.r.: no reaction

[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.05). Yields of isolated product after column chromatography. The enantioselectivity determined by chiral HPLC. [b] 2 mol% of **C26** used.

Subsequently, we wanted to explore the scope of the reaction to other α,β-unsaturated carbonyl compounds (Table 16). The Michael addition of isocyanoacetate **1A** using methyl acrylate (**4**) as Michael's acceptor proved to be very slow (entry 1), whereas the reaction with acrolein almost finished in 2 h leading to product **8** with low enantioselectivity (entry 2). Hence, it seems that α,β-unsaturated esters too poor electrophiles for these reactions, while the selectivity control with enals is challenging. In view of the good results provided by vinyl ketones, the possibility of using the α´-hydroxyenones as acrolein and acrylate equivalents was considered. The ketol moety in these adducts is easily transformable to aldehyde or ester group through simple oxidative cleavage.[162] Fortunately, the enantioselective Michael reaction with the α-hydroxyenone **6a** could be successfully carried out affording product **9Aa** in good yield and 98% *ee* (entry 3), what encouraged us to see the scope of the reaction.

Table 16. Michael addition to different α,β-unsaturated carbonyl compounds.



Entry	Acceptor	t (h)	Product	Conversion (%)	Yield (%)	*ee* (%)
1	 **4**	40	**7**	15	n.d.	n.d.
2	 **5**	2	**8**	85	n.d.	34
3	 **6a**	3	**9Aa**	90	70	98

[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.05). Conversion into the corresponding adduct determined by ^{1}H-RMN spectroscopy and the *ee* values by chiral HPLC on the reaction crude.

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[162] Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garía, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

2.4.2. α´-Hydroxyenones as Michael acceptors

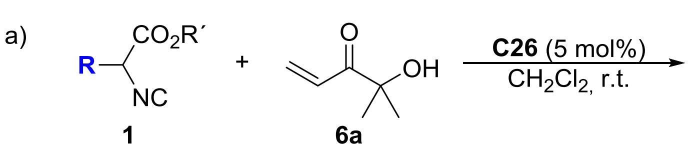
Studies from this laboratory had shown that α´-oxy enones, and particularly α´-hydroxy-enones are useful achiral bidentate templates in asymmetric catalysis.[163] However, to date they have never been used as acceptors in the Michael addition with isocyanoacetates.

We explored the scope of the reaction employing α´-hydroxy vinyl-ketone **6a** as Michael acceptor, **C26** (5 mol%) as catalyst and a variety of α-substituted isocyanoacetates. As the data in Table 17 show, α-aryl substituted isocyanoacetates were competent reaction partners providing the products **9** with good isolated yields and *ee´s* up to 92%, except *ortho*-substituted aryl isocyanoacetates (**1F** and **1G**), which did not react probably due to the steric hindrance around the nucleophilic carbon. Once again, the α-alkyl substituted isocyanoacetates (**1E**) or unsubstituted isocyanoacetates (**1H**) were nonreactive under the present catalytic conditions owing, probably, to their lower acidity.

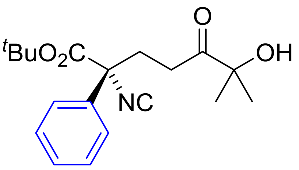
---

[163] 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.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161–1164. c) Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Chem.* **2008**, *10*, 2637–2640. d) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150–4164. e) Badiola, E.; Flser, 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.

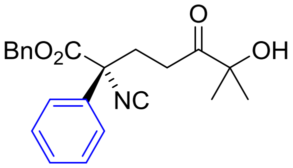
Table 17. Scope of the Michael addition involving α´-hydroxyeones as Michael acceptor.



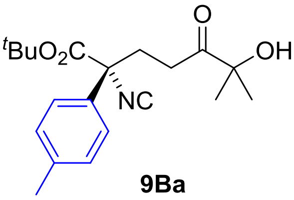
R: **A** Ph
A´ Ph (R´=Bn)
B 4-MeC_6H_4
C 4-$MeOC_6H_4$
D 3-BrC_6H_4
E Bn
F 2-MeC_6H_4
G 2-ClC_6H_4
H H



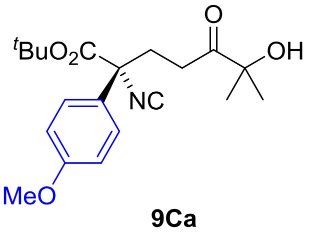
9Aa
4h, 70%, 98% *ee*



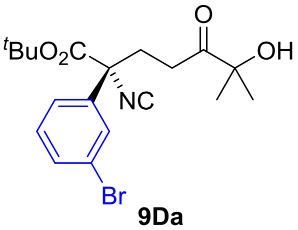
9A´a
5h, 74%, 92% *ee*



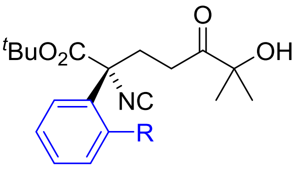
9Ba
16h, 70%, 99% *ee*



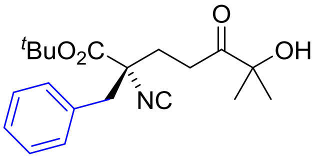
9Ca
80h, 72%, 98% *ee*



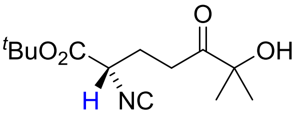
9Da
6h 86%, 96% *ee*



9Fa **n.r.**
9Ga **n.r.**[b]



9Ea
n.r.[b]



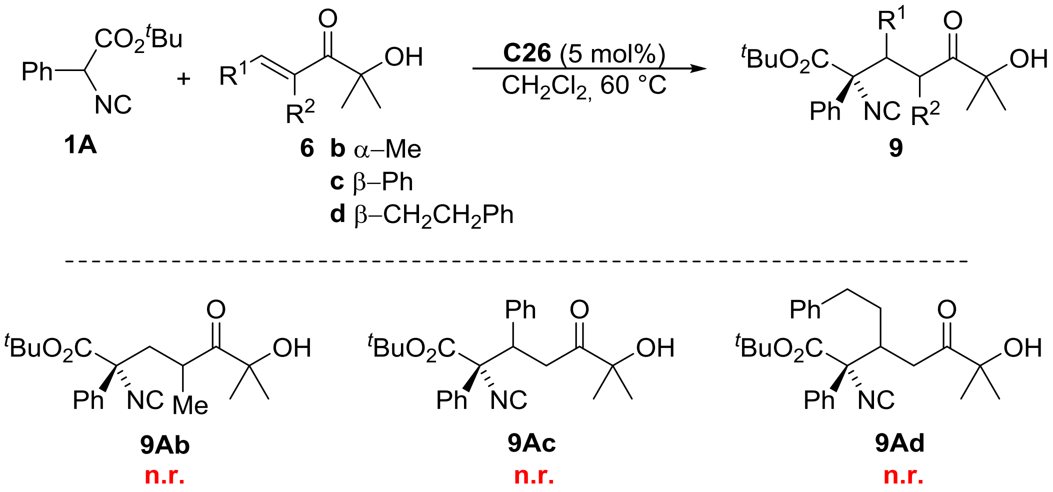
9Ha
n.r.[c]

n.r.: no reaction

[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2g**/catalyst 1:2:0.05). Yields of isolated product after column chromatography. The enantioselectivity determined by chiral HPLC. [b] The reaction carried out at 40 °C. [c] Reaction carried out at 60 °C.

Some α- and β-substituted α´-hydroxyenones (**6b-d**) were also tested, but not surprisingly the addition reaction did not work, even heating at 60 °C (Table 18). Taking into account that α´-hydroxyenones showed the same or greater reactivity than vinyl ketones, we assumed that the vinyl ketones would present these same limitations in the reactivity, as it reflected the experiment that was carried out with α-benzyl isocyanoacetate **1E** and aryl vinyl ketone **2e** (see Table 15, compound **3Ee**).

Table 18. Attempts of the Michael reaction with α- and β-substituted α´-hydroxyeones.



n.r.: no reaction

[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.05).

Summarizing, the **C26**-catalyzed asymmetric Michael addition of α-aryl isocyanoacetates with alkyl- and aryl-vinyl ketones **2a-f** and α´-hydroxy vinyl-ketone **6a** could be performed with very good yields and excellent enantioselectivities. As exception, isocyanoacetates with α-alkyl groups or *ortho*-substituted α-aryl groups were unreactive (also see Zhao's work Table 9, entry 3, page 60).

2.4.3. Transition-state model

Although the mechanism of the reaction remains to be clarified, based on the stereochemical result determined by X-ray crystallographic analysis of the product **26** (Scheme 36, page 88**),** we could propose a dual plausible transition-state model. One of the possibilities considered was the double coordination of the nucleophiles with the catalyst through the enol group and the isocyanide group, in a similar manner to that assumed for a metal-mediated process.[164] While in second cases the metal coordinated the isocyanide group, in bifunctional BB catalysts mediated process this coordination could be given through one of the N-H bond donor group, which forces the formation of a *Z* enolate of the isocyanoacetate. However, as can be seen in Figure 26, pathway a, this transition-state would favor the attack by the *Re* face of the nucleohile to the enone providing the enantiomer of opposite configuration (S), hence, this model was rejected.

---

[164] For selected examples, see: a) See ref. 109, page 40. b) See ref. 113, page 40.

The other possibility was to consider the coordination of the isocyanide with the protonated quinuclidine moiety instead with the N-H bond donor group of the squaramide (Figure 26, pathway b), in similar manner to the model proposed by Zhu and co-workers in the reaction of isocyanoacetates to vinyl selenones.[165] In this case, the squaramide motif forced the direction of the nucleophilic attack from the *Si* face of the *Z* enolate to the enone, providing the corresponding adduct with R configuration. Therefore, this transition-state model is plausible.

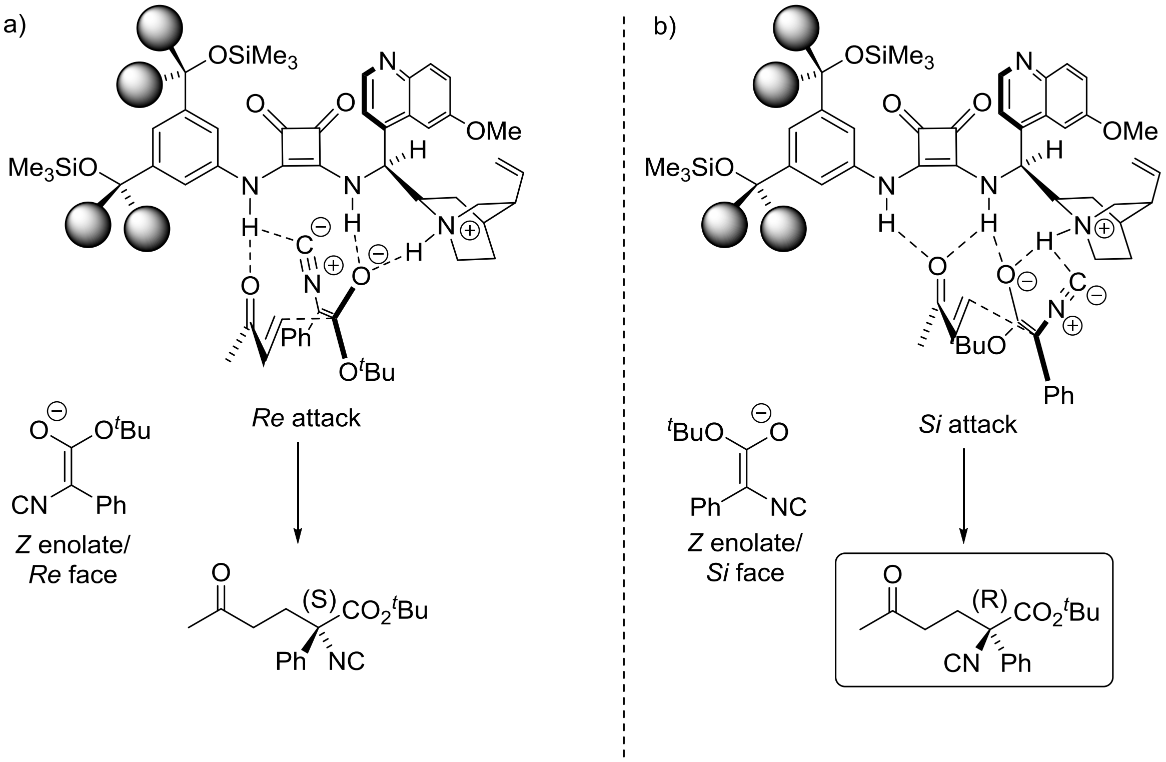


Figure 26. Possible transition-state models for the Michael addition.

2.5. Elaboration of adducts

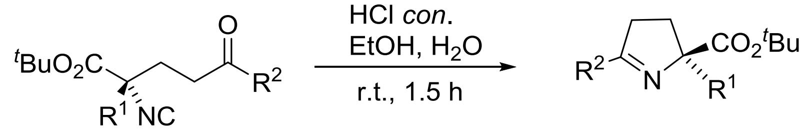
Having developed an organocatalytic and highly enantioselective method for the Michael reaction of α-isocyanoacetates to different enone reagents, the potential of the resulting enantioenriched adducts in synthesis was briefly explored.

---

[165] See ref. 153b, page 60.

2.5.1. Synthesis of α-quaternary Δ⁵-dehydroprolines and derivatives

The release of the amine group upon hydrolysis of the isonitrile group and the subsequent cyclization to provide the corresponding α-quaternary Δ^5-dehydroprolines was performed one pot (Scheme 32). Thus treatment of adducts with concentrated hydrochloride acid, led in all cases tested, the corresponding product **10-13** in good yields.



3Ad, 3Af, 3Aa, 3Ab

10	R^1: Ph, R^2: Me	80%
11	R^1: Ph, R^2: Et	83%
12	R^1: Ph, R^2: p-MeC_6H_4	80%
13	R^1: Ph, R^2: p-$OMeC_6H_4$	Quantit.

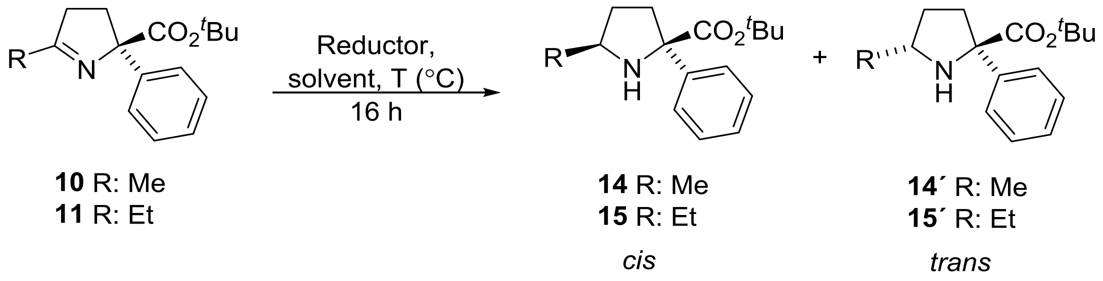
Scheme 32. Synthesis of α-quaternary Δ^5-dehydroprolines.

Transformation of these dehydroprolines into the parent α-quaternary prolines is easily conceivable through reduction of the imine moiety.[166] Based on this idea, compound **10** was first subjected to reduction with L-Selectride. Despite this reagent is rather bulky, under these conditions diastereocontrol was really poor and the pirrolidine product was obtained as an equimolar mixture of diastereomers (Table 19, entry 1). Instead, exposure of **10** to H_2 over Pd on charcoal gave product **14** with an excellent diastereomeric ratio and good yield (Table 19, entry 2). The X-ray single crystal structure analysis of a compound derived from N-acylation of **14** served to determine the configuration of both stereocenters, confirming the *syn* disposition of the methyl group with respect to the ester group (Figure 27). These reduction conditions were employed to each of the Δ^5-dehydroprolines **10**-**13**. In case of **11,** product **15** was obtained again with very good diastereocontrol (>20:1 dr) and good yield (Table 19, entry 3).

---

[166] a) Strohmeier, M.; Leach, K.; Zajak, M. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 12335–12338. b) see ref. 102, page 34.

Table 19. Reduction of dehydroprolines **10**-**11** to α-quaternary prolines **14**-**15**.



Entry	R	Reductor	Solvent	Temp. (°C)	*cis*:trans	Product	Yield (%)
1	Me	L-Selectride	THF	–78→r.t.	1:1	**14**	--
2		Pd/C, H_2	EtOH	r.t.	>20:1		80
3	Et	Pd/C, H_2	EtOH	r.t.	>20:1	**15**	75

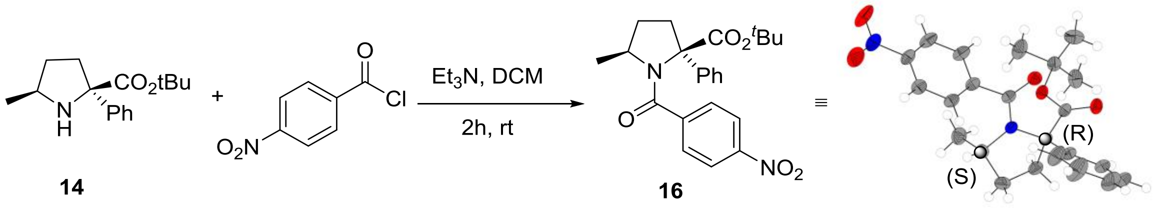
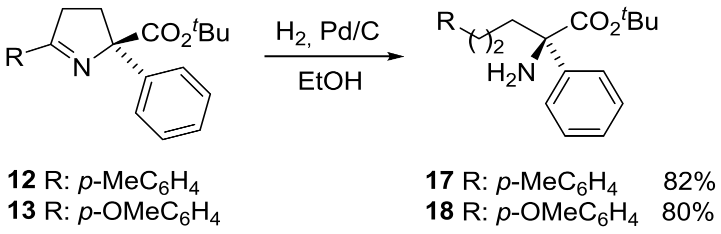


Figure 27. The X-ray single crystal structure analysis.

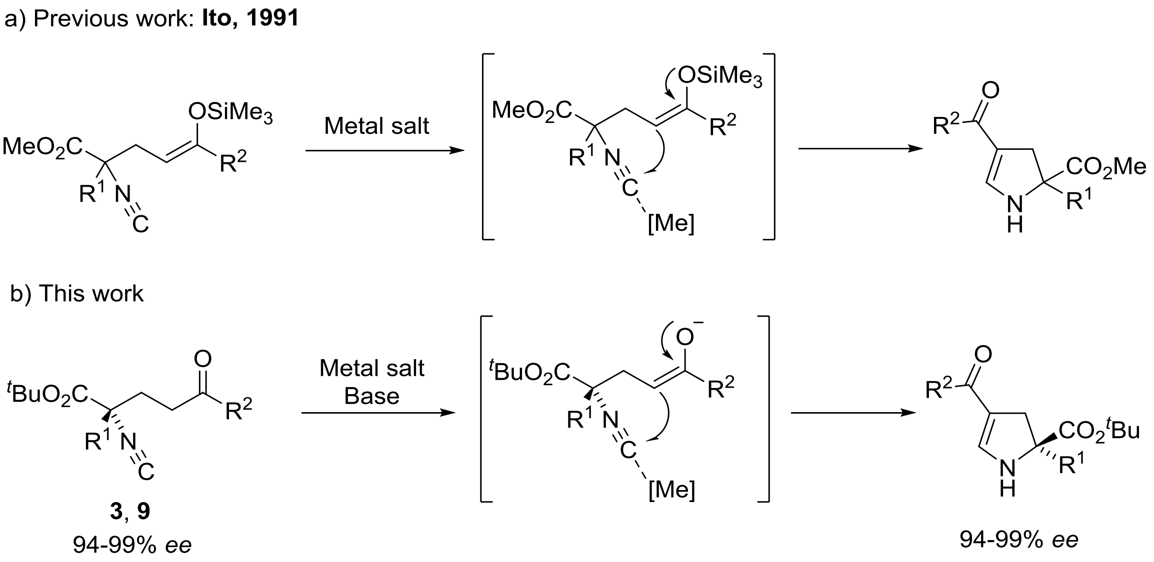
However, starting from Δ^5-dehydroprolines containing aromatic R substitution (**12**-**13**) the reduction proceeded with concomitant hydrogenolytic cleavage of the benzylic C-N bond giving rise open chain α,α-disubstituted α-amino esters **17** and **18** respectively, which are equally interesting compounds.



Scheme 33. Reduction of α-quaternary Δ^5-dehydroprolines.

2.5.2. Synthesis of α-quaternary Δ⁴-dehydroprolines

Inspired by the transformation reported by Ito and collaborators in 1991,[167] we foreesed that Δ^4-dehydroproline skeleton could be created starting from enantiopure lineal Michael adducts **3** by using a base to generate de corresponding enolate and a metal complex to promote the cyclization (Scheme 34).



Scheme 34. Synthetic plan for the α-quaternary Δ^4-dehydroprolines synthesis.

The search of optimal conditions for this transformation was focused on the use of silver (I) complexes (Table 20) owing to the success of these reagents on other cycloadditions reactions.[168] Experiments revealed the dramatic dependence of the silver source on the reaction outcome. For example, whereas with AgF formation of **19** was completed within 5 h, with AgOAc the conversion was lower, and using $AgNO_3$ or AgOTf not even traces of products were observed. Thus, AgF was chosen to explore the effect of the base. As it was expected, the stronger the base employed the faster was the reaction. Thus, while using both Et_3N and DIPEA the reaction was incompleted after 5 h, in DBU and $P_4{}^t$Bu phosphazene base, 100% conversion was reached. However, among the both latter, DBU was the best in terms of clean reaction product. In addition, we could verify that the transformation could be executed one pot by adding the AgF and the base once the Michael addition reaction was complete.

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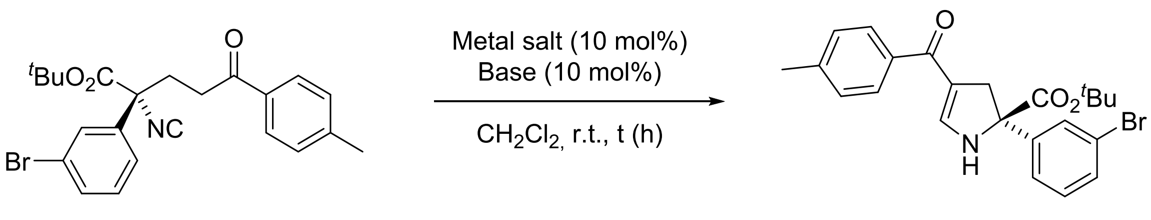
[167] See ref. 152f, page 58.

[168] See Table 8, Chapter 1, page 41.

Table 20. Screening of reaction conditions for the synthesis of Δ^4-dehydroproline scaffold.

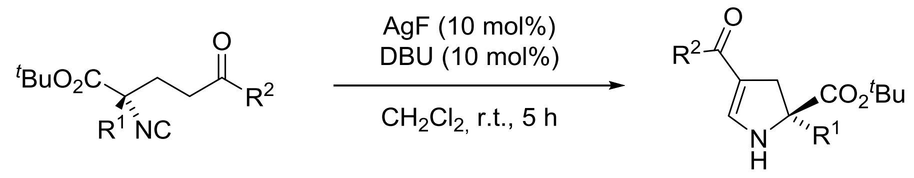


3Dd **19**

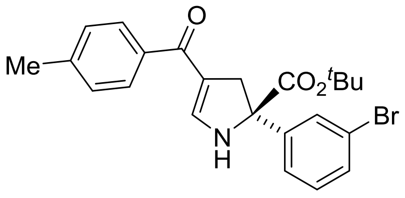
Entry	Metal salt	Base	t (h)	Conversion (%)
1	AgF	$P_4{}^t Bu$	5	100
2	AgOAc	$P_4{}^t Bu$	5	75
3	$AgNO_3$	$P_4{}^t Bu$	5	0
4	AgOTf	$P_4{}^t Bu$	5	0
5	AgF	DIPEA	5 24	35 95
6	AgF	Et_3N	5 24 100	25 50 95
7	AgF	DBU	5	100

Once the combination of AgF and DBU was selected optimun, different Michael adducts were subjected to the same conditions demonstrating the scope of the transformation (Table 21). The reaction worked perfectly with adducts that came from the conjugate addition involving simple vinyl ketones (**3**) providing the corresponding α-quaternary Δ^4-dehydroprolines **19**-**23** with good yields. However, the reaction that involved adduct containing α´-hydroxyketone functionalization (**9Aa**) gave a messy reaction crude and only traces of product **24** were observed, regardless the base employed.

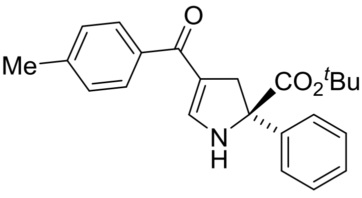
Table 21. Scope of the transformation of adducts into α-quaternary Δ^4-dehydroprolines.



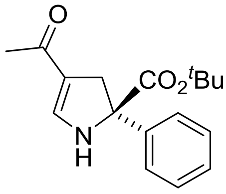
3Dd, 3Ad, 3Aa, 3Ca, 3Ab, 9Aa **19-24**



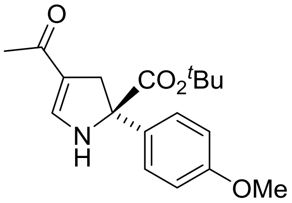
19
92%



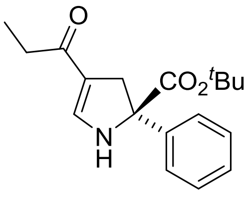
20
85%



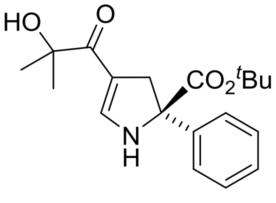
21
85%



22
88%



23
78%



24
messy reaction

It should be noted that the resulting α-quaternary Δ^4-dehydroprolines were not completely stable to regular silica-gel column purification. Instead, a rapid filtration through a pad of silica-gel was sufficient to remove traces of impurities and excess reactants. In general, it is recommended to prepare the products when they are going to be used and in any case, store them at low temperature (-40 °C).

2.5.3. Synthesis of α-quaternary pyroglutamate ester

Pyroglutamates[169] bearing α-quaternary stereocenter serve as the core structures in many natural alkaloids and bioactive molecules, as for example Oxazolomycin A[170] or previously mentioned Salinosporamide A[171] and Lactacystin.[172] Due to the broad array of

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[169] a) Smith, M. B. *Alkaloids: Chem. Biol. Perspect.* **1998**, *12*, 229–287. b) Panday, S. K.; Prasad, J.; Dikshit, D. K. *Tetrahedron: Asymmetry* **2009**, *20*, 1581–1632.

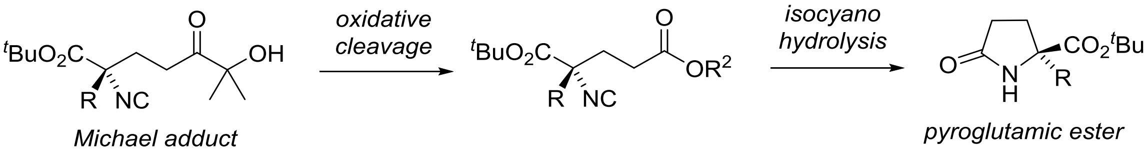
[170] a) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D. *Tetrahedron Lett.* **1985**, *26*, 1073–1076.

[171] See ref. 65, Chapter 1, page 20.

[172] See ref. 54, Chapter 1, page 41.

biological and pharmaceutical properties that exhibit, organic chemists have pursued efficient synthetic methods for those compounds.[173]

Previous works developed in our group have demonstrated the synthetic potential of α′-hydroxy ketone moiety as a precursor to the corresponding acid/ester, aldehyde or ketone products which could be obtained through different oxidative cleavages.[174] Accordingly, we anticipated that these Michael adducts subjected to the appropriate oxidative conditions would yield the corresponding ester which upon isocyanate hydrolysis, could provide the corresponding α-quaternary pyroglutamic esters (Scheme 35).



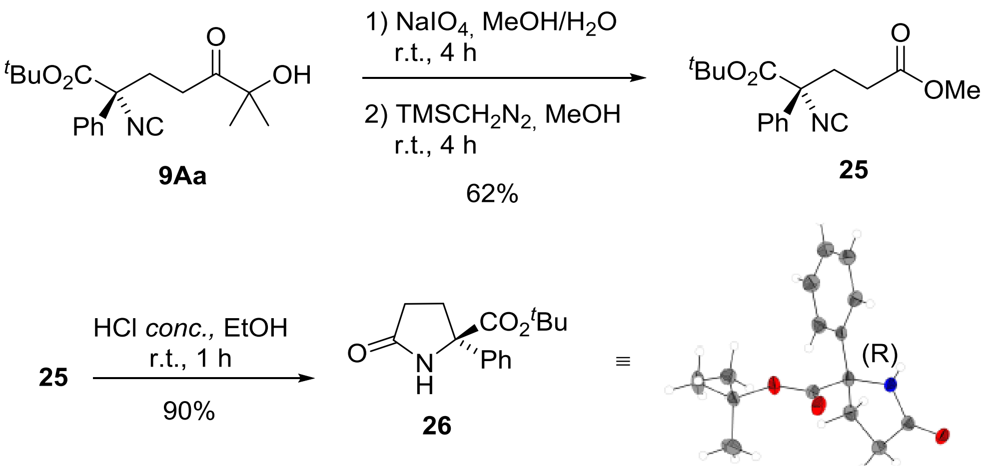
Scheme 35. Synthesis of pyroglutamic esters from Michael adducts.

We observe that the treatment of adduct **9Aa** with sodium periodate proceed as usual to produce a carboxylic acid, which upon methylation with $TMSCH_2N_2$, provided the ester **25** with moderate isolated yield (35%). We observed that the acid intermediate was not very stable probably due to interferences between the isocyanide and the carboxylic acid groups. Then we modified the conditions by submitting the crude material obtained upon the $NaIO_4$ oxidation to the next methylation as soon as possible. This way, the overall yield of the two steps was improved to 62%. Of practical interest, acetone is the only by-product formed during this two-step transformation and in addition, as demonstrated in the preliminary studies, this ester cannot be obtain enantioselectively from a direct Michael addition to methyl acrylate under these catalytic conditions (see Table 16, page 77). Once the stable ester is obtained, the hydrolysis of the isocyano group and the subsequent clycization was carried out by treatment with concentrated hydrochloride acid which afforded pyroglutamate ester **26** in 90% yield (Scheme 36).

---

[173] a) Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003**, *1*, 3726–3737. b) Onyango, E. O.; Tsurunoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6703–6705. c) Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem. Asian J.* **2007**, *2*, 20–38. d) Yamada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2008**, *19*, 2789–2795. e) Moore, B. S.; Guilder, T. A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9346–9367. f) See ref. 98, Chapter 1, page 56. g) See ref. 99, Chapter 1, page 57.

[174] a) ref. 162, page 77. b) ref. 163, page 78.



Scheme 36. Synthesis of α-quaternary pyroglutamate ester.

The absolute configuration of product **19** was determined by X-ray crystallographic analysis, which coincides with the X-ray result of the compound **16** (Figure 27, page 83). Configuration of the remaining adducts was assigned by analogy and by assuming a uniform reaction mechanism.

On the whole, the chemical transformations with these Michael addition adducts allowed the enantioselective synthesis of a variety of α-quaternary proline derivatives, demonstrating the synthetic potential of this approach.

Chapter 3

Catalytic addition reactions of α-alkyl isocyanothioacetates: enantioselective synthesis of α-quaternary dehydroprolines and imidazolines

3. Catalytic addition reactions of α-alkyl isocyanothioacetates: enantioselective synthesis of α-quaternary dehydroprolines and imidazolines. 93

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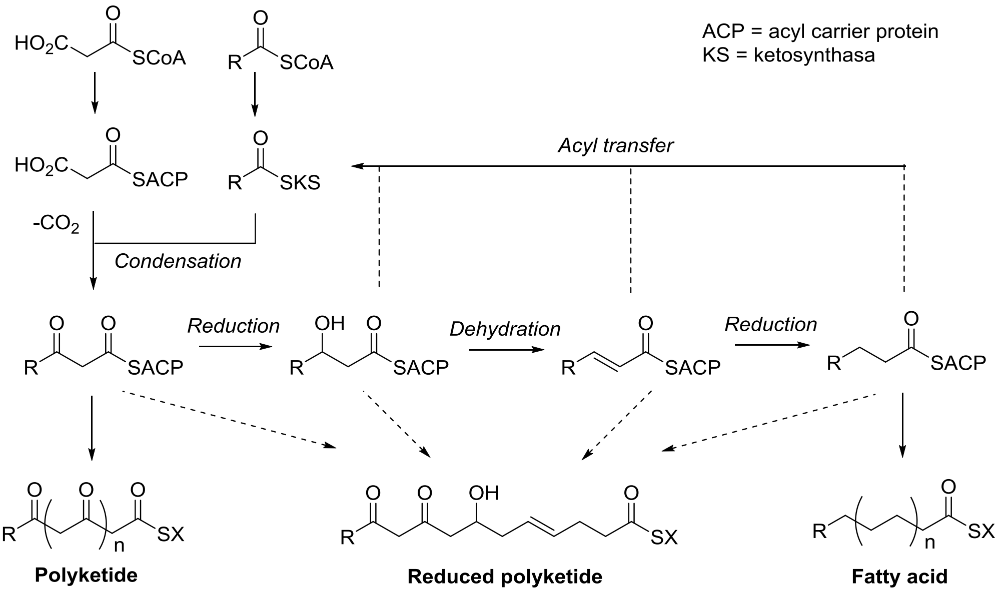
3. Catalytic addition reactions of α-alkyl isocyanothioacetates: enantioselective synthesis of α-quaternary dehydroprolines and imidazolines.

3.1. Introduction

3.1.1. Thioesters in catalytic asymmetric C-C bond forming reactions

As reflected in the precedent discussions, catalytic asymmetric reactions involving the use of simple ester as nucleophiles remains challenging. This situation is justified in part by the relatively low acidity of simple ester compounds, which has led scientists to develop metal-based approaches and also the design of more active ester equivalents susceptible for enolization under mild conditions.

In this context, nature has found an elegant solution to this problem by using thioesters as active ester surrogates for the synthesis of medicinally and metabolically important polyketides and fatty acid molecules (Scheme 37).[175] Polyketide synthase enzymes effectively catalyze the reaction of a variety of thioesters like acetyl-CoA, propionyl-CoA or malonyl-CoA, giving the desired products.



Scheme 37. The basic pathway of fatty acid and polyketide biosynthesis.

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[175] a) Hopwood, D. *Chem. Rev.* **1997**, *97*, 2465–2497. b) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380–416. c) Reeves, C. D.; Murli, S.; Ashley, G. W.; Piagentini, M.; Hutchinson, C. R.; McDaniel, R. *Biochemistry* **2001**, *40*, 15464–15470. d) Pfeifer, B. A.; Khosla, C. *Microbiol. Mol. Biol. Rev.* **2001**, *65*, 106–118. e) Hill, A. M. *Nat. Prod. Rep.* **2006**, *23*, 256–320.

Inspired by these biosynthetic pathways, chemists have long been wondering biomimetic approaches based on the use of thioesters as equivalent of oxoesters with enhanced reactivity, especially in catalytic settings. The rationale behind the unique behaviour of thioesters is their increased α-acidity as compared with parent esters. Bordwell has quantified this difference in about 2 pKa units[176]. In addition, thioesters are also rather reactive acyl-transfer agents[177], so thioesters-based reaction has turned out to be an interesting alternative to methods involving *oxo*-esters giving access to a much wider array of compounds (Figure 28).

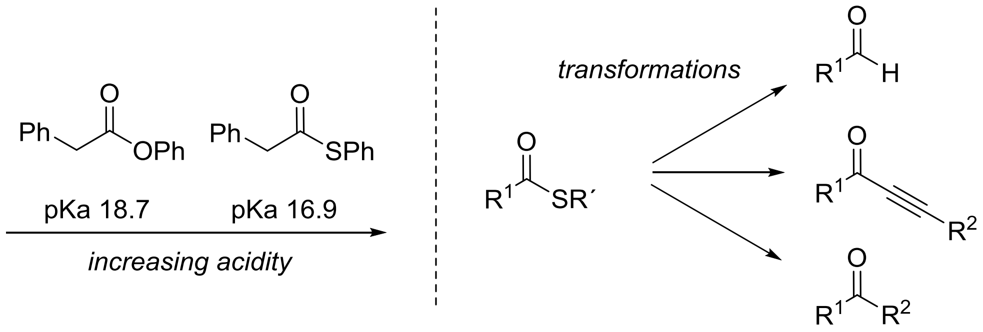

Figure 28. The effect in the acidity and transformations allowed with thioesters.

However, only a few classes of thioesters have been successfully employed so far in catalytic asymmetric carbon-carbon bond forming reactions. The most representative cases are described below.

3.1.1.1. Malonic acid derivatives as nucleophiles

Decarboxylative Claisen condensation with malonic acid half thioester (MAHTs) is a key step in the biosynthesis of polyketides and fatty acids (Scheme 38, a). This transformation, which involves a decarboxylative enolate generation followed by a C-C bond forming reaction, has served as inspiration to scientists for the development of the first catalytic asymmetric nucleophilic additions of thioester compounds (Scheme 38, b).

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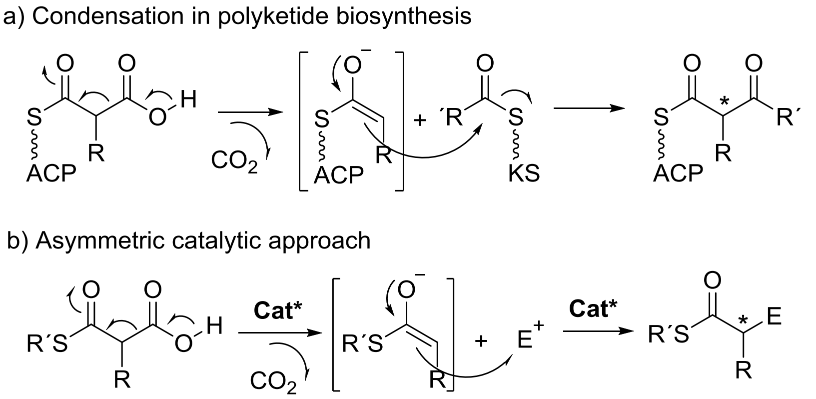
[176] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *13*, 4218–4223.

[177] Miyazaki, T.; Han-ja, X.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477–480.



Scheme 38. Decarboxylative Claisen condensation with malonic acid half thioesters and its implementation into asymmetric C-C bond technologies.

Based on this approach catalytic asymmetric aldol,[178] Michael,[179] and Mannich[180] reactions involving addition of MAHTs, including organocatalytic methods, have been developed (Table 22). However, the low reactivity of the thioester enolate precursors typically forces the use of relatively large amounts of the catalyst (up to 30 mol%) and long reaction time.

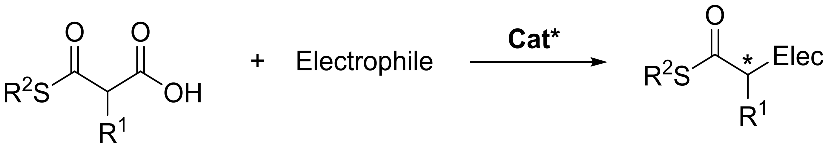
---

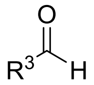
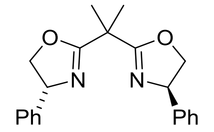
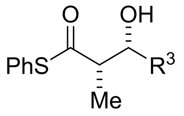
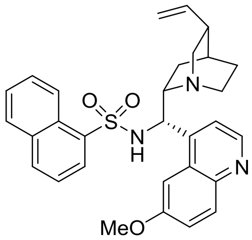
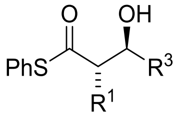
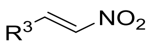
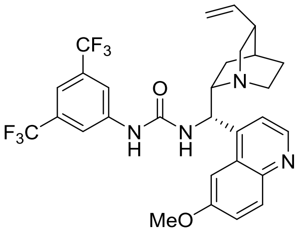
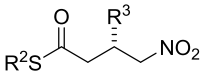
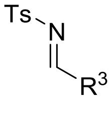
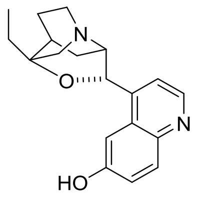
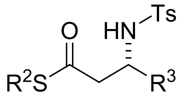
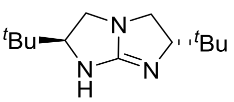
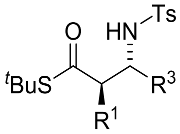
[178] a) Orlandi, S.; Benaglia, M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747–1749. b) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284–7285. c) Bae, H. Y.; Sim, J. H.; Lee, J.-W.; List, B.; Song, C. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 12143-12147.

[179] Lubkoll, J.; Wennemers, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6841–6844.

[180] a) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Herrera, R. P.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037–1040. b) Pan, Y.; Kee, C. W.; Jiang, Z.; Ma, T.; Zhao, Y.; Yang, Y.; Xue, H.; Tan, C.-H. *Chem. Eur. J.* **2011**, *17*, 8363–8370. c) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem. Eur. J.* **2012**, *18*, 9276–9280. d) Zhong, F.; Jiang, C.; Yao, W.; Xu, L.-W.; Lu, Y. *Tetrahedron Lett.* **2013**, *54*, 4333–4336.

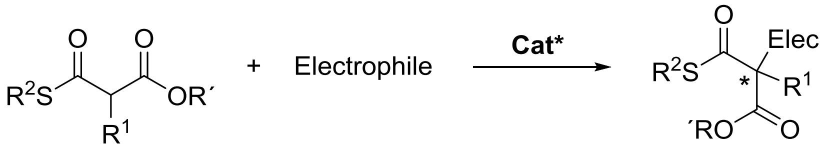
Table 22. Representative catalytic asymmetric addition of MAHTs.

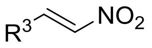
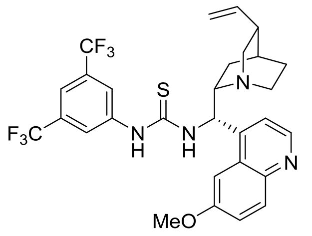
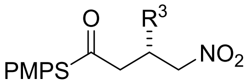
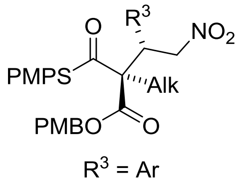
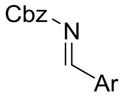
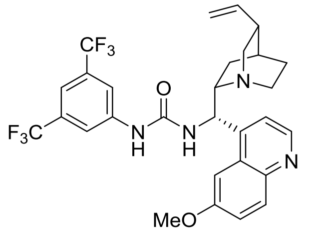
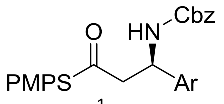
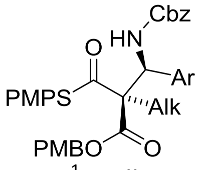
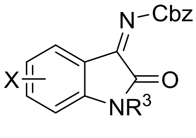
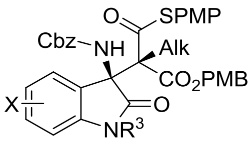


	Electrophile	Cat.*	Product	Results	Ref.
1		 (13 mol%) Cu(OTf)$_2$ (10 mol%)	 R^3 = Ar, Alk	59-83% 2.2:1-36:1 dr 89-96% *ee*	178b
2		 (30 mol%)	 R^1 = Me, H R^3 = Ar, Alk, Allyl	R^1=H/R^3=Ar 61-96% 89-96% *ee* R^1 = Me/R^3=Ar **31%, 5:1 dr** 97% *ee* R^3 ≠ Ar **16-32%** 73-91% *ee*	178c
3		 (20 mol%)	 R^1 = H R^2 = *p*-OMeC$_6$H$_4$ R^3 = Ar, Alk	23-93% 61-90% *ee*	179
4		 (20 mol%)	 R^1 = H R^2 = *p*-OMeC$_6$H$_4$, *p*-ClC$_6$H$_4$ R^3 = Ar, Ph(CH$_2$)$_2$	47-84% 51-79% *ee* (**R^3=*o*-BrC$_6$H$_4$**: 21-38% *ee*)	180a
5		 (10 or 20 mol%)	 R^1 = H, Alk, allyl R^3 = Ar	R^1 = H 43-85% >20:1 dr 85-97% *ee* R^1 ≠ H 37-70% **1:1-7:3 dr** 90-98% *ee*	180b

More recently, the use of mono thiomalonates (MTMs) as thioester (or thioesters enolate precursor) equivalents has emerged. In these cases, the decarboxylation step is obviated and lower catalyst loadings are needed. Following this strategy, MTMs have been employed in catalytic asymmetric Michael[181] and Mannich[182] reactions giving rise products containing a α-quaternary stereocenter in several instances (Table 23).

Table 23. Representative catalytic asymmetric addition of MTMs.



	Electrophile	Cat.*	Product	Results	Ref.
1		 (<5 mol%) (R^3 = Alk: 20 mol%)	after decarboxylation:  R^3 = Ar, Alk	82-98% 91-99% *ee*	181a
2			 R^3 = Ar	70-87% 3:1-10:1 dr 92-99% *ee*	181c
3		 (<5 mol%)	after decarboxylation:  R^1 = H	62-93% 90-99% *ee*	182a
			 R^1 = Alk	51-99% 6:1->20:1 dr 90-99% *ee*	
4			 R^3 = H, Me, Ac, Allyl, Boc	42-96% 4:1->20:1 dr 73-99% *ee*	182b

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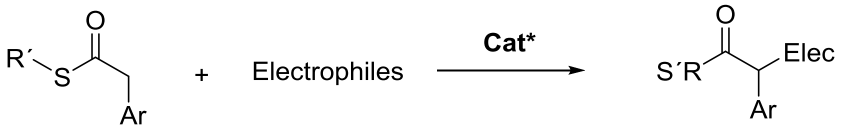
[181] a) Clerici, P.; Wennemers, H. *Org. Biomol. Chem.* **2012**, *10*, 110–113. b) Kolarovic, A.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 4236–4239. c) Arakawa, Y.; Fritz, S. P.; Wennemers, H. *J. Org. Chem.* **2014**, *79*, 3937–3945. d) Eng, O. D.; Fritz, S. P.; Käsling, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 5454–5457.

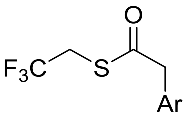
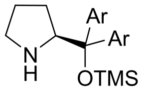
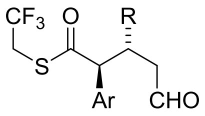
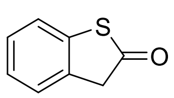
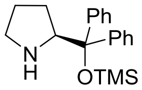
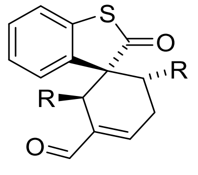
[182] a) Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 8779–8783. b) Engl, O. D.; Fritz, S. P.; Wennemers, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 8193–8197. c) Cosimi, E.; Engl, O. D.; Saadi, J.; Elbert, M.-O.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 13127–13131.

3.1.1.2. *Arylacetic derivatives as nucleophiles*

With the aim of developing more atom economical method that does not require waste-producing decarboxylation as a driving force or an additional activating group at the α-position of the thioester, it aroused the idea of using arylacetic thioesters (Table 24). These reagents could be applied as donors in asymmetric Michael additions involving α,β-unsaturated aldehydes[183] and in Mannich additions involving sulphonyl imines[184]. For example, the Michael reaction of benzothiophen-2-one and enals, proceeded through via iminium ion activation affording a double Michael addition, followed by intramolecular aldol reaction, giving rise to spirocyclic compounds (entry 2). Later, the reaction was expanded to 3-substituted benzothiophen-2-ones.[183e] The reaction could also be carried out with α-alkyl-substituted thioesters using enolsilanes as starting material in a Mukaiyama-Michael variant via enamine intermediate (entry 3).

Table 24. Representative catalytic asymmetric addition of arylacetic thioesters.



	Nucleophile	Cat.*	Product	Results	Ref.
1		 Ar = 3,5-$(CF_3)_2$-C_6H_3 (10 mol%)/ $PhCO_2H$ (10 mol%)	 R = Ar, Me	46-88% 57:43-81:19 dr 66-98% *ee* (R = Me, **54% *ee***)	183a
2		 (20 mol%)/ Acid (20 mol%)	 R = Ar, Alk, H	42-77% >20:1 dr 99% *ee* (R = H, **60% *ee***)	183c

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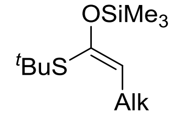
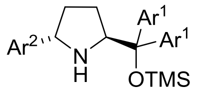
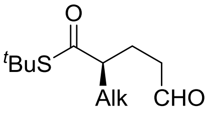
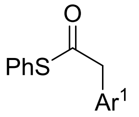
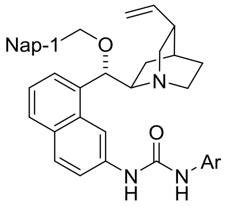
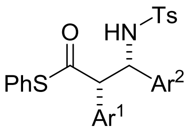
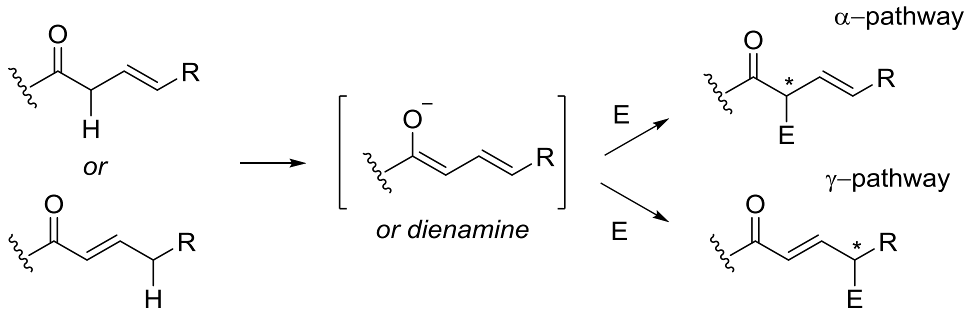
[183] a) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591. b) Duce, S.; Jorge, M.; Alonso, I.; Ruano, J. L. G.; Cid, M. B. *Eur. J. Org. Chem.* **2013**, 7067–7075. c) Géant, P.-Y.; Urban, M.; Remes, M; Císarova, I.; Veselý, J. *Eur. J. Org. Chem.* **2013**, 7979–7988. d) Claraz, A.; Sahoo, G.; Berta, D.; Madarász, A.; Pápai, I.; Pikho, P. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 669–673. e) Li, S.; Zhang, E.; Feng, J.; Li, X. *Org. Chem. Front.* **2017**, *4*, 2301–2305.

[184] a) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Caltart, D. M. *Org. Lett.* **2010**, *12*, 3376–3379. b) Guang, J.; Larson, A. J.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2015**, *357*, 523–529.

	Nucleophile	Cat.*	Product	Results	Ref.
3		 Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 4-OMe-3,5-(Me)$_2$C$_6$H (20 mol%)/ 4-nitrobenzoic acid (20 mol%)		60-76% 88-96% *ee*	183d
4		 Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$ (10 mol%)		82-97% 19:9-98:2 dr 90-98% *ee*	184b

3.1.1.3. β,γ-Unsaturated carboxylic acid derivatives as nucleophiles

Reactions involving dienolate (or equivalent dienamine) intermediates constitute a particular case owing to bidentate nature of these nucleophiles (Scheme 39).[185] While these transformations thus require additional control over the α- vs. γ-competitive reaction pathways, the resulting adducts are of great synthetic versatility. Enamine catalysis (dienamine/trienamine) and metal catalysis have been employed recently to some extent, typically leanding to γ-addition compounds. The alternative α-reaction pathway implies the disruption of the π-conjugation at some point along the reaction, and hence, the regioselective formation of α-addition product is less favorable.



Scheme 39. Reaction pathways of β,γ-unsaturated carboxylic acid nucleophiles additions.

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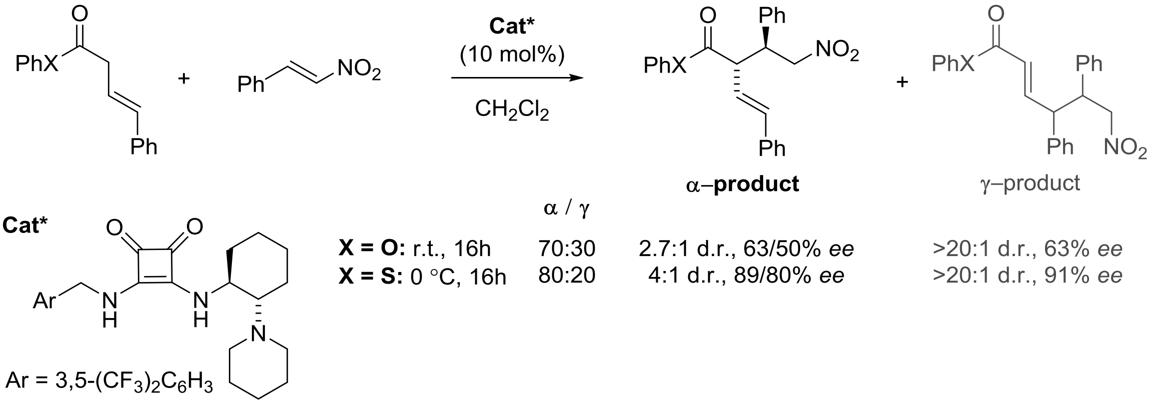
[185] For reviews on vinylogous addition reactions, see: a) Casiraghi, G.; Battistini, L.; Curti, C; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154. b) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531–3543. c) Denmark, S. E.; Heemstra, J. R.; Beuter, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698.

In this context, Brønsted base catalyzed α-site functionalization of vinylogous enolates remains little explored, and in general the reported examples featured moderated enantioselectivities or were restricted to specific substrates. There are only few examples where in Brønsted base catalyzed α-functionalization of β,γ-unsaturated carbonyl compounds with three potentially reactive sites (α, β and α´) has proceeded in a stereocontrolled manner.[186] Our group accomplished the asymmetric α-addition of a β,γ-unsaturated esters and equivalents to nitrostyrene and could be demonstrated that thioesters are more reactive and regioselective to α-addition compounds than the parent esters (Scheme 40).[186b] In the study previously carried out by Tan and collaborators, the asymmetric addition of β,γ-unsaturated thioester to azodicarboxylate compounds was γ-selective.[187]



Scheme 40. Asymmetric addition of β,γ-unsaturated thioester to nitrostyrene.

In consequence, the use of thioesters as activated ester equivalents has enabled to expand the inherently difficult α-reactivity of the parent ester.

3.1.2. Isocyanothioacetates in asymmetric synthesis

Until the starting of this thesis, a single precedent was known involving isocyanothioacetates as reagents in the synthesis of chiral compounds. Rotstein et al. reported a reactions secuence between isocyanoacetates and other enantiopure starting materials for the synthesis of chiral macrocycles (Scheme 41).[188]

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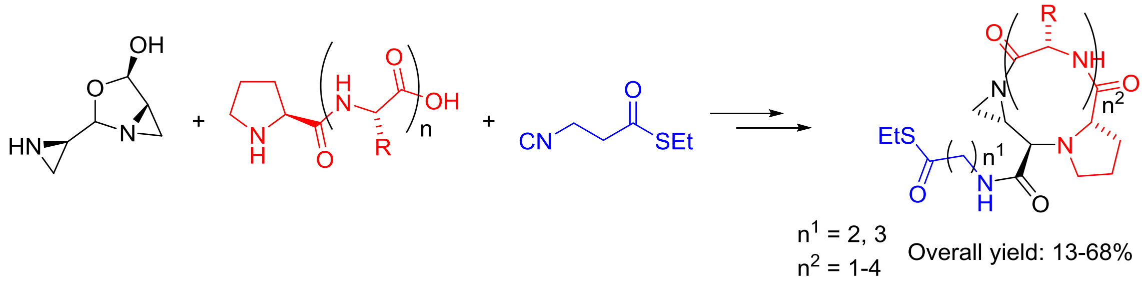
[186] a) Frias, M.; Mas-Ballesté, R.; Arias, S.; Alvarado, C.; Alemán, J. *J. Am. Chem. Soc.* **2017**, *139,* 672–679. b) Iriarte, I.; Olaizola, O.; Vera, S.; Gamboa, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864.

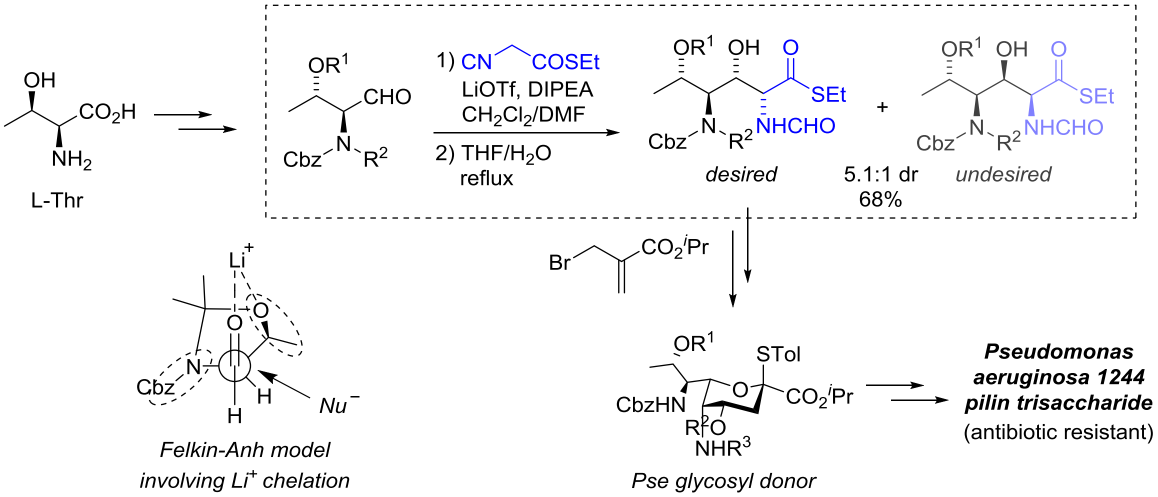
[187] Wang, J.; Chen, J.; Kee, C. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 2382–2386.

[188] Rotstein, B. H.; Winternheimer, D. J.; Yin, L. M.; Deber, C. M.; Yudin, A. K. *Chem. Commun.* **2012**, *48*, 3775–3777.



Scheme 41. Isocyanothioacetates in chiral macrocycles synthesis.

More recently and during the progress of our investigations, Li *et. all* carried out a diastereoselective α-addition of glycine-thioester isonitrile to chiral aldehydes, as a key step for the synthesis of pseudaminic acid (Pse) saccharide and its functionalized derivatives from L-threonine (Scheme 42).[189] The diastereoselectivity of the aldol addition under this condition could be rationalized by the lithium cation chelation stabilized Felkin-Anh model, which resulted in the formation of a *cis*-oxazoline that was hydrolyzed one-pot to give the desired aldol products. Finally, the aldol products could be transformed in Pse glycosyl donors, which were used for the synthesis of biologically active *Pseudomonas aeruginosa* 1244 pilin trisaccharide.



Scheme 42. The synthesis of *Pseudomonas aeruginosa* 1244 pilin through diastereoselective aldol reaction involving glycine-thioester isonitrile.

Therefore, to the best our knowledge, thioester-isocyanides had never been used as nucleophiles in catalytic asymmetric reactions; their used in asymmetric synthesis have been limited to substrate-controlled reactions involving quiral starting materials.

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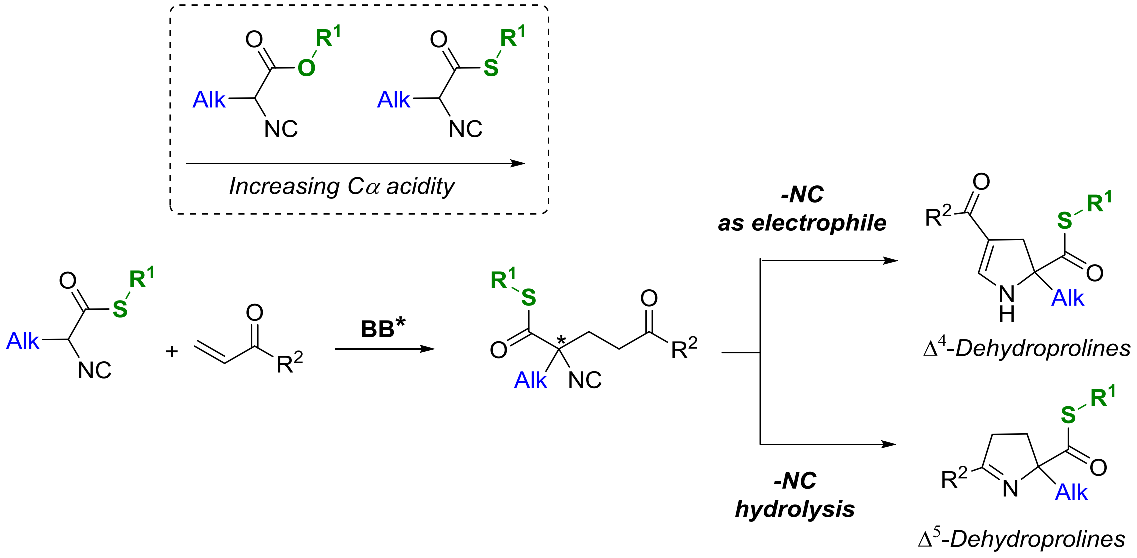
[189] Liu, H.; Zhang, Y.; Wei, R.; Andolina, G.; Li, X. *J. Am. Chem. Soc.* **2017**, *139*, 13420–13428.

3.2. Working hypothesis

As explained before, isocyanoacetates have aroused a great interest among synthetic chemists due to the structural richness they provide in such a small portion of the molecule (see Chapter 1, Figure 18, page 46). The carboxyl group in the α-position of the molecule and the unique reactivity of the isocyano group open a wide range of possibilities that no other amino acid equivalent offers. However, to date, their use as nucleophiles in the branch of asymmetric organocatalysis has been very limited, in part because the low acidity of Cα, as demonstrated in our results with α-alkyl isocyanoacetates (see Chapter 2, section 2.4, page 75). Thus, it would be interesting to find more active isocyanoacetate equivalents that may serve to considerably expand its use in synthesis.

Our rationale was that employing thioesters-isocyanides as activated isocyanoacetate equivalents could expand their use to reactions difficult to perform with the parent esters. So, we decided to explore thioester-isocyanides in catalytic asymmetric nucleophilic additions, particularly the α-alkyl substituted ones. α-Alkyl substituents, compromise reactivity in part because of stereic stress and also because a lowering of the Cα acidity.

Ultimatelly, finding suitable conditions to carry out Brønsted base catalyzed enantioselective additions of thioester-isocyanides is not only challenge, but also would constitute a new approach for the synthesis of α-quaternary amino acids from the most active isocyanide containing AA-derivative nucleophiles found to date. If successful, the eventually formed Michael adduct would allow a divergent route to Δ^4- and Δ^5-Dehydroprolines with a quaternary α-alkyl stereocenter (Scheme 43). Finally, to demonstrate thioester isocyanides generality and synthetic utility, several electrophiles, such as vinyl sulphones and imines with different reactivity would be studied.



Scheme 43. Synthetic plan for α-alkyl quaternary Δ^4- and Δ^5-dehydroprolines asymmetric synthesis.

The intrinsic nature of these new nucleophiles can be very similar to conventional isocyanoacetates, so the new squaramide family (**C20**-**C26**) designed and essayed successfully in the previous setion were the first BB catalyst candidates to evaluate.

3.3. Synthesis of isocyanothioacetates

We first focused our efforts in the development of an efficient and robust methology to prepare a variety of isocyanothioacetates.

3.3.1. Isocyano phenyl-thioacetates

The synthetic route to reach these compounds is different from that used with conventional isocyanoacetates because the amine must be protected prior to the formation of the thioester. According to the literature, thiol esters could be prepared using classical peptidic coupling conditions from Boc-protected amino acids in excellent yields.[190] Hence, we started with the preparation of thiophenylester-isocyanides following the reactions sequence shown in Scheme 44 for the thioester formation. These steps were developed with good overall yields (65-97%), but the steps from amine hydrochloride to isocyanide required a deeper study.

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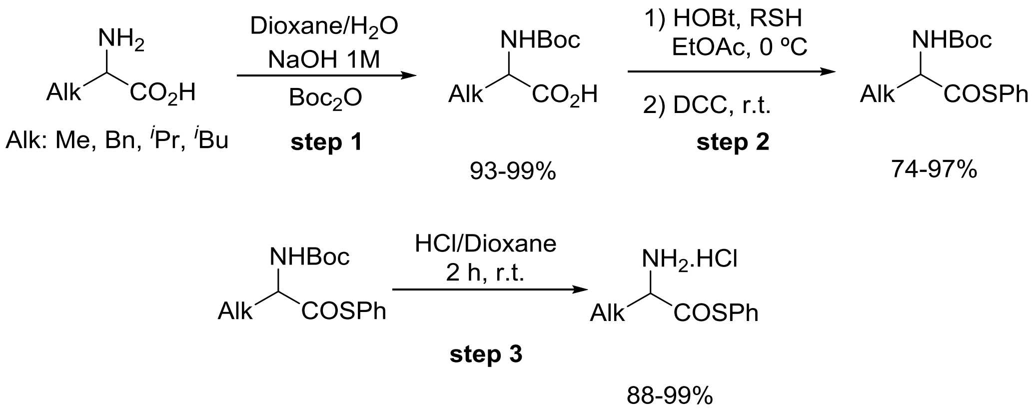
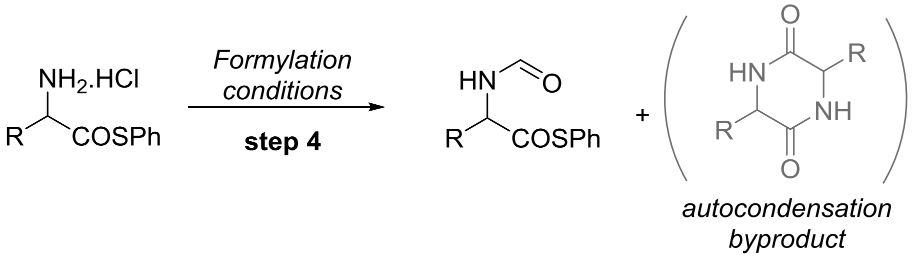
[190] Garnier-Amblard, E. C.; Mays, S. G.; Arrendale, R. F.; Baillie, M. T.; Bushnev, A. S.; Culver, D. G.; Evers, T. J.; Holt, J. J.; Howard, R. B.; Liebeskind, L. S. *Med. Chem. Lett.* **2011**, *2*, 438–443.



Scheme 44. Reactions sequence for (phenyl)thioesters formation.

After releasing the amine from the amine hydrochloride, it was attempted to perform the formylation under the same conditions as with isocyanoacetates **1** (Table 25, entry 1), but in all cases (except when Alk= ^{i}Pr, yield 90%) autocondensation byproduct was observed harming the yields of the reaction. Therefore, a variety of reaction conditions were studied taking as reference the formylation of amine hydrochloride with R= Me. Under conditions of entry 2 and 3 desired product was hardly observed. Nevertheless, under conditions of entry 4 the reaction was effective, without formation of the byproduct and giving the fomyl-thioesters in 85% isolated yield. These reaction conditions could also be used successfully for the formylation of α-Bn and α-^{i}Bu amino thioesters (yields of 85-94%).

Table 25. Conditions for the formylation step.



Entry	R	Formylation conditions	Yield of formyl products (%)	Byproduct
1	Me	1. $NaHCO_3$ sat. 2. HCO_2Et, 6 h ,reflux	16%	Yes
2	Me	1. $NaHCO_3$ sat. 2. HCO_2H, I_2, 6 h ,reflux[191]	Messy	Yes
3	Me	HCO_2H, $Si(OEt)_4$, Et_3N CH_3CN, r.t. [192]	Messy	Yes
4	Me	1. HCO_2H/EDCI, CH_2Cl_2 2. NMM, 5 °C, 16 h[193]	85	No
	Bn		94	No
	^{i}Bu		85	No

The subsequent dehydration step was also not effective under the conditions employed with isocyanoacetates, and very complex product mixtures were obtained instead (Table 26, entry 1). Similar results were obtained with SO_2Cl/DMAP system (entry 2). However, using triphosgene and N-methyl molpholine as dehydrating system the reaction was clean, allowing the formation of the desired isocyano product **27A-D** in acceptable yields (60-75%). The isonitrile group of isocyanothioacetates **27** is easily detectable by infrared spectroscopy as in the case of isocyanoacetates **1**.

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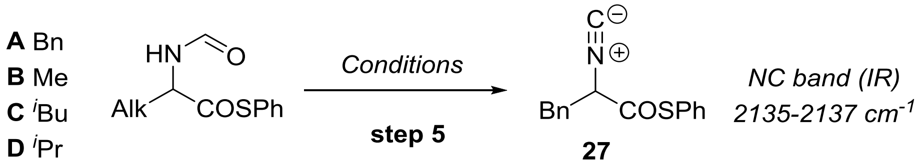
[191] Kim, J.-G.; Jang, D. O. *Synlett* **2010**, *14*, 2093–2096.

[192] Nishikawa, Y.; Nakamura, H.; Ukai, N.; Adachi, W.; Hara, O. *Tetrahedron Lett.* **2017**, *58*, 860–863.

[193] Chem, F. M. F.; Benoitton, N. L. *Synthesis* **1979**, *9*, 709–710.

Table 26. Conditions for the dehydration step.



Entry	Alk	Conditions	Product	Yield (%)
1	Bn	$POCl_3$, DIPA CH_2Cl_2, –30 °C, 2 h[194]	**27A**	Messy
2	Bn	SO_2Cl, DMAP CH_2Cl_2, –30 °C, 2 h[195]	**27A**	Messy
3	Bn	Triphosgene/NMM –78 °C, 2 h[196]	**27A**	60
	Me		**27B**	62
	^{i}Bu		**27C**	75
	^{i}Pr		**27D**	71

3.3.2. Isocyano aryl- or benzyl-thioacetates (2nd generation route)

For reasons that will be commented later, isocyanothioacetates with benzyl or aryl thioesters group other than phenyl were required as well. With this objective, we prepared several isocyanothioesters containing *ortho*- or elsewhere substituted aryl groups. However, the formation of these thioesters was not possible by applying the previous methodology, probably because the *N*-Boc is too bulky and prevents the attack of thiol to the carbonyl group. So, we designed another route starting from *N*-formyl α-amino acids instead (Figure 29).

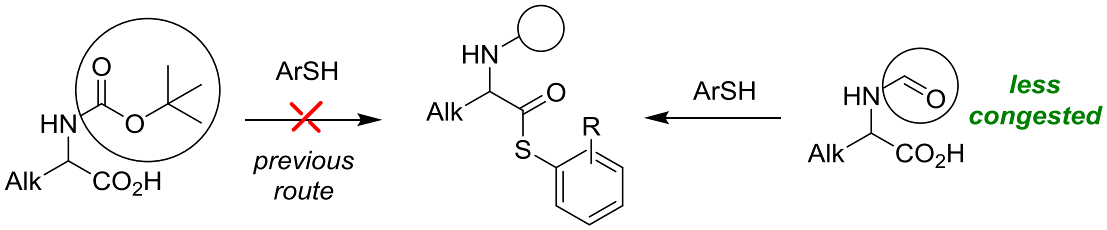


Figure 29. Strategy for the formation of the thioester group.

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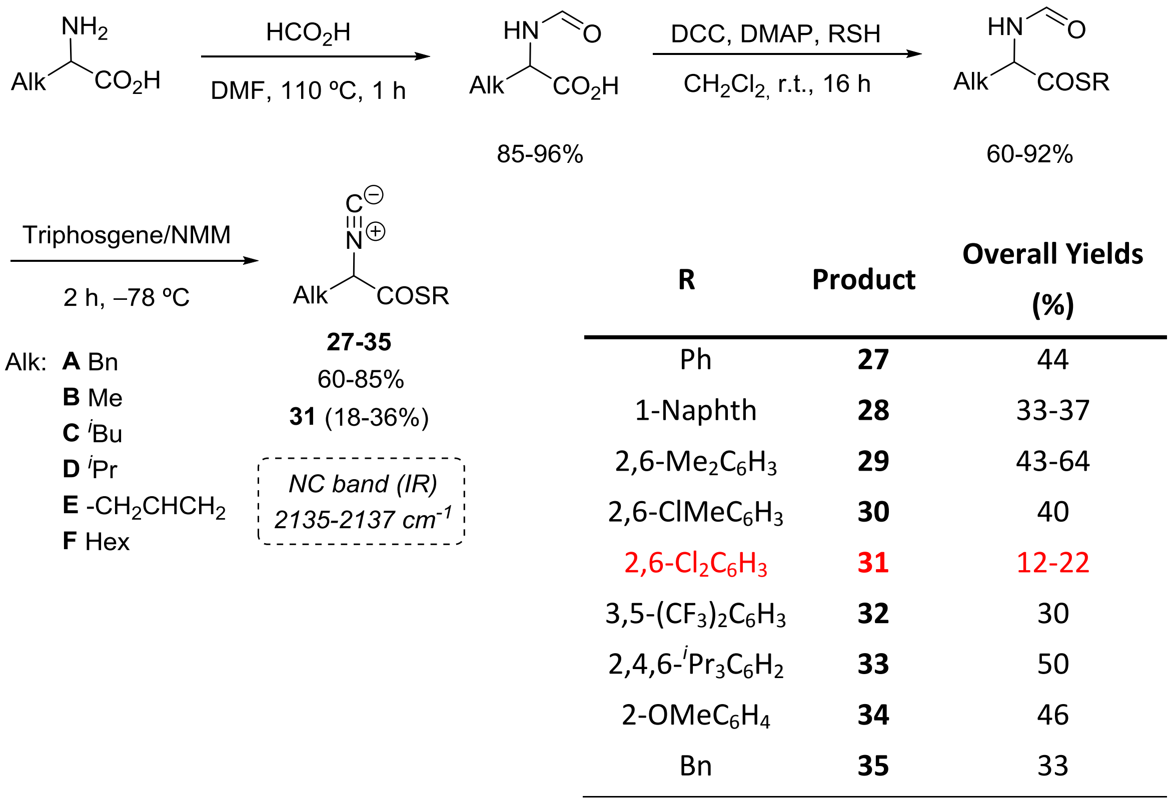
[194] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.
[195] Arrieta, A.; García, T.; Palomo, C. *Synth. Commun.* **1982**, *12*, 1139–1146.
[196] Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.*, **2009**, *50*, 577–579.

Following the reactions sequence shown in Scheme 45 the synthesis of desired isocyanothioacetates have been possible with moderate overall yields and in fewer steps than in the previous methology. Once the formamides were obtained following a simple procedure[197], the thioesterification with an array of aryl and benzyl thiols could be carried out effectively by employing dicyclohexylcarbodiimide and dimethylamino pyridine as coupling activation reagents.[198] Finally, the dehydration step was accomplished under the same conditions as before. In general, yields of isolated compounds over the three steps were good, with the exception of isocyanothioacetates bearing 2,6-dichlorophenyl thioester; the final product **31** was hardly observed in any of the conditions tested for the last step.



R	Product	Overall Yields (%)
Ph	**27**	44
1-Naphth	**28**	33-37
2,6-$Me_2C_6H_3$	**29**	43-64
2,6-$ClMeC_6H_3$	**30**	40
2,6-$Cl_2C_6H_3$	**31**	12-22
3,5-$(CF_3)_2C_6H_3$	**32**	30
2,4,6-$^{i}Pr_3C_6H_2$	**33**	50
2-$OMeC_6H_4$	**34**	46
Bn	**35**	33

Scheme 45. Synthetic route for α-substituted aryl isocyano thioacetates.

Eventually it was found that this route was also applicable to α-benzyl phenylthioester-isocyanide (**27A**), which could be obtained from DL-phenylalanine in total 3 steps and a global 44% isolated yield (methodology 1: global 23% isolated yield). It should be noted

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[197] Aizpurua, J. M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 745–752.

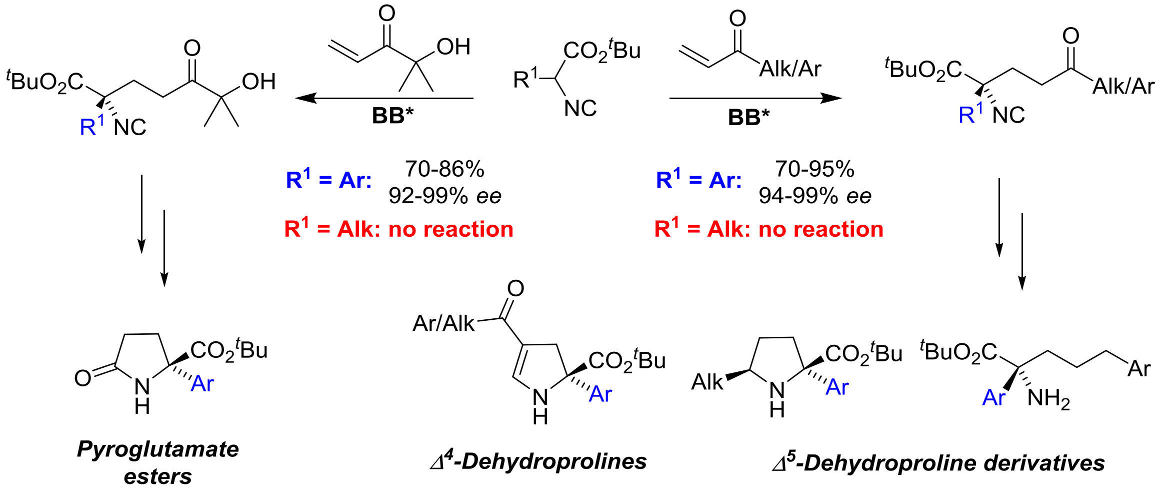
[198] See ref. 184, page 98.

that compounds **27-35** are stable enough to be stored at low temperature (–30 °C) for months.

3.4. Michael reaction with enones: synthesis of α-alkyl α-quaternary dehydroprolines

3.4.1. Synthetic plan

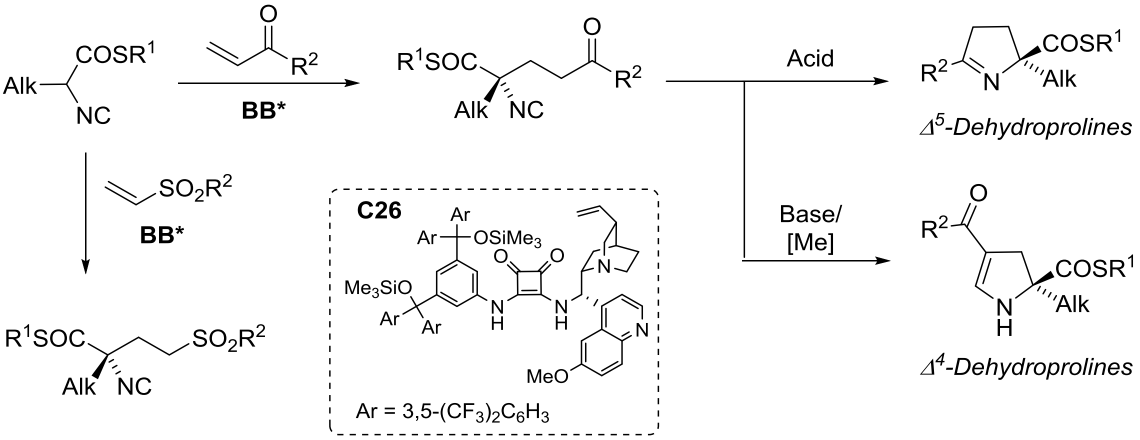
As can be seen in the introduction, the nucleophilic conjugate additions of α-substituted isocyanoacetates to Michael acceptors involve most often very reactive olefins or require the presence of a metal complex to catalyze the reaction (see Chapter 1, Table 8, page 41). In addition, in these instances, the initially formed Michael adduct tends to cyclisize intramolecularly to exclusively lead to α-quaternary Δ^4-dehydroprolines. However, as shown in the previous chapter the linear Michael adducts of this reaction offer a greater synthetic diversity, allowing the synthesis of proline derivatives of different nature (Scheme 46). Nevertheless, as it reflected experimentally in the Chapter 2 of this thesis, the low reativity of isocyanoacetates is accentuated in α-alkyl isocyanoacetates, and thus, the stereocontrolled additions that involve them suppose a greater challenge.



Scheme 46. Summary of the study carried out in chapter 2

Therefore, we set out to explore the catalytic asymmetric Michael addition of α-alkyl isocyanothioacetates to vinyl ketones. It was our expectation that the α-isonitrile thioacetate esters would be more acidic and so deprotonation by Brønsted-base catalyst to form reactive enolate intermediate would be more effective. In addition, also in this way (absence of metal) the intramolecular cyclization step would be less likely to occur (Scheme 47).

It should be noted that there was a single example in which α-substituted isocyanoacetates are used as nucleophiles in the catalytic asymmetric conjugate addition to vinyl selenones, which act as the equivalent of vinyl sulfone (see Chapter 2, Table 9, page 60, entry 2). However, although vinyl selenones are more active than vinyl sulfones, the reaction is limited only to α-aryl isocyanoacetates. Hence, once the appropriate conditions for the previous reaction were found, α-alkyl isocyanothioacetates would be applied in the conjugate addition to vinylsulfones, an unexplored reaction to date.



Scheme 47. Synthetic plan for catalytic asymmetric Michael addition of.α-akyl isocyanothioacetates

If successful, the overall Michael addition of α-substituted isocyano(thio)acetates would allow the enantioselective synthesis of a great variety of α-akyl and α-aryl substituted quaternary amino acids.

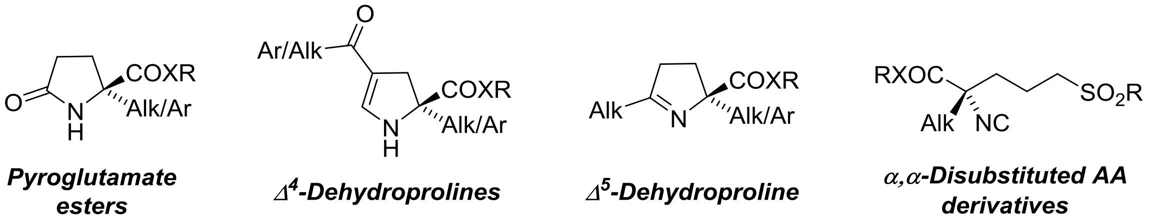
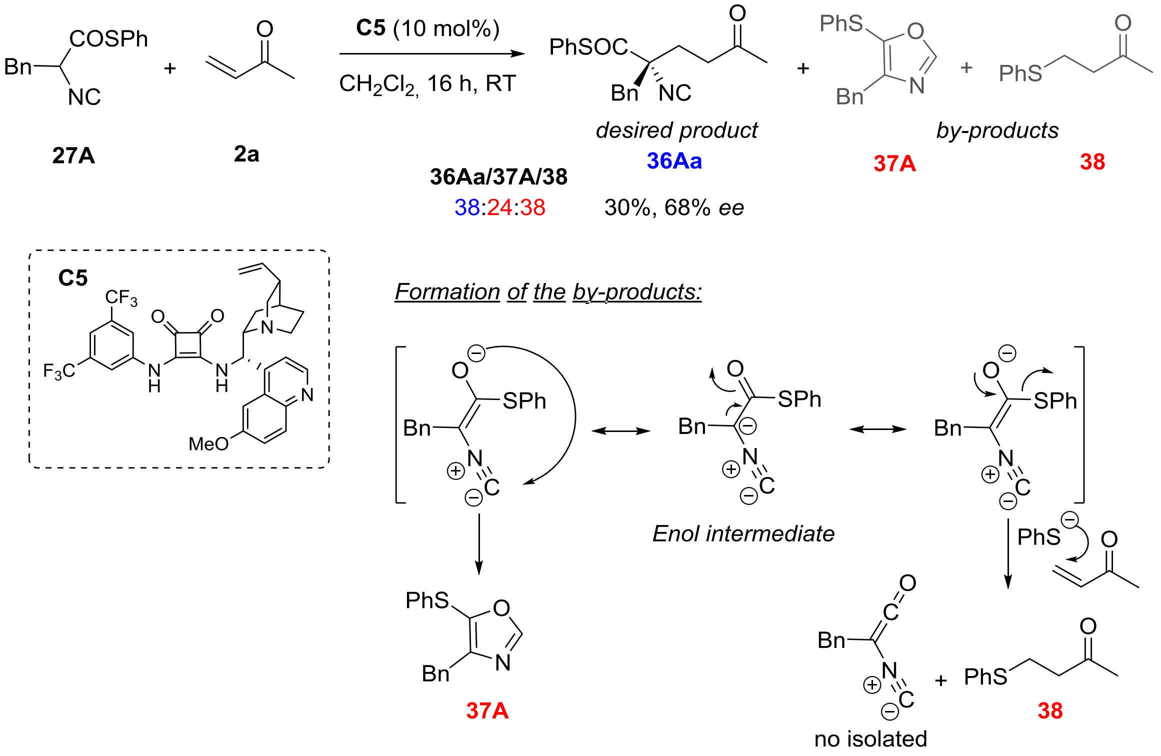


Figure 30. α-Akyl and α-aryl substituted quaternary amino acids.

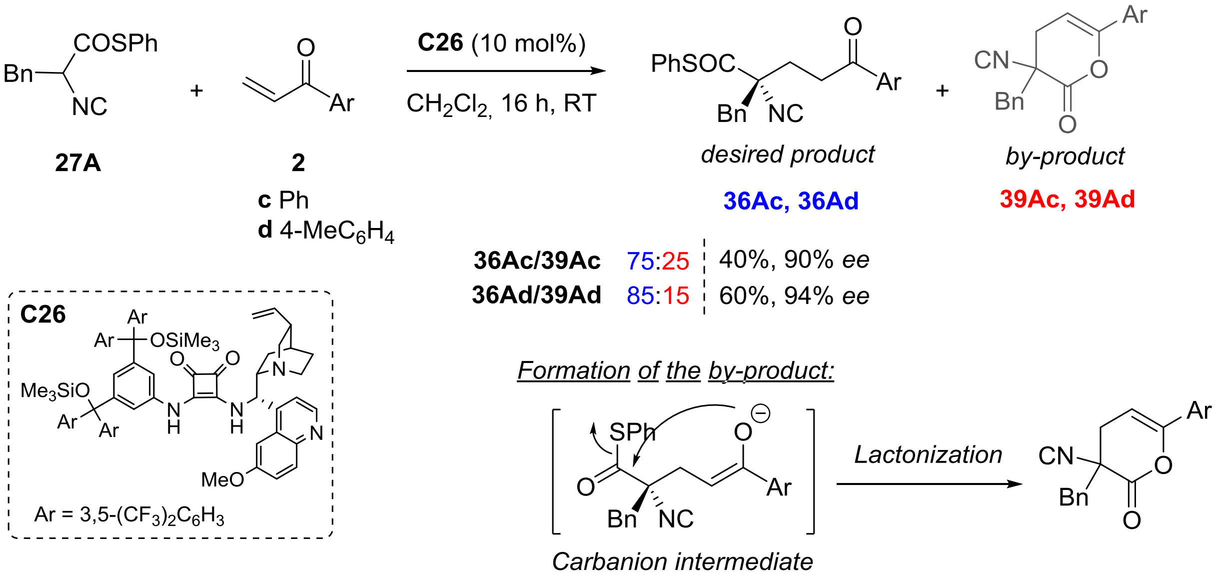
3.4.2. Catalytic Michael reaction with enones

The initial study was carried out using the isocyanothio(phenyl)acetate **27A** and methyl vinyl ketone **2a** (Scheme 48). We observed that the squaramide **C5** could catalyze the reaction giving Michael adduct **36Aa** with low yield and moderate enantiocontrol. Besides desired adduct **36Aa**, the formation of several by-products was observed, which could be isolated and indentified as the oxazole **37A** and the thio-Michael adduct **38**. Palusible routes to both byproducts via intermediate enolate are shown in Scheme 48. In order to improve the yield of the desired product **36Aa** it was convenient to find a way to avoid these undesired reaction pathways.



Scheme 48. Catalytic asymmetric Michael addition of **27A** to methyl vinyl ketone **2a.**

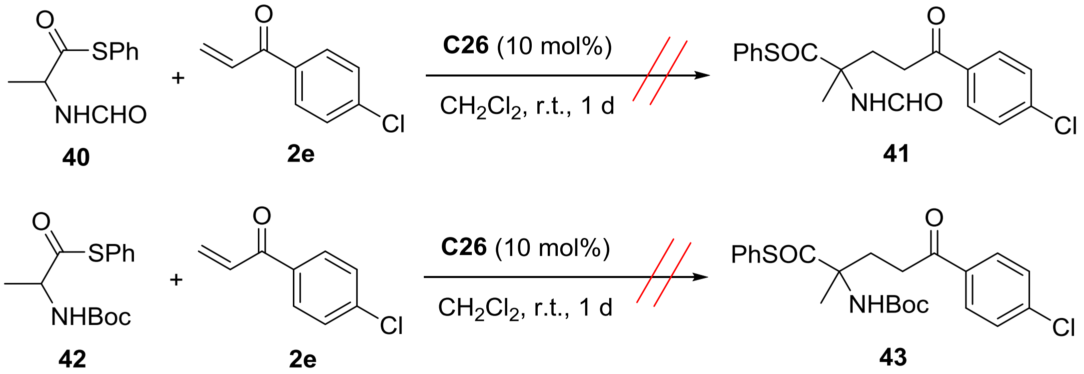
In subsequent experiments it was observed that the reaction of **27A** with aryl vinyl ketones **2c**/**2d** in the presence of catalyst **C26** effectively provided Michael adducts **36Ac** and **36Ad** with moderate yields and excellent enantiocontrol (Scheme 49). In these instances by products analogs to **37A** and **38** were not observed. Instead, a new by-product **39** was isolated. The divergent behaviour of aryl enones as compared with alkyl enones might be explained base on the: 1) higher reactivity of the former 2) additional stabilization of both the Michael adduct enolate and the enol lactone by-product. In addition, the carbonyl group in thioesters is more susceptible to a nucleophilic attack than in a parent oxoester, making possible the formation of the corresponding lactone **39** for the first time. Thus, to avoid the formation of the lactone was essential to improve the yield of the desired Michael adducts (40-60%).



Scheme 49. Catalytic asymmetric Michael addition of **27A** to aryl vinyl ketones **2c-d**.

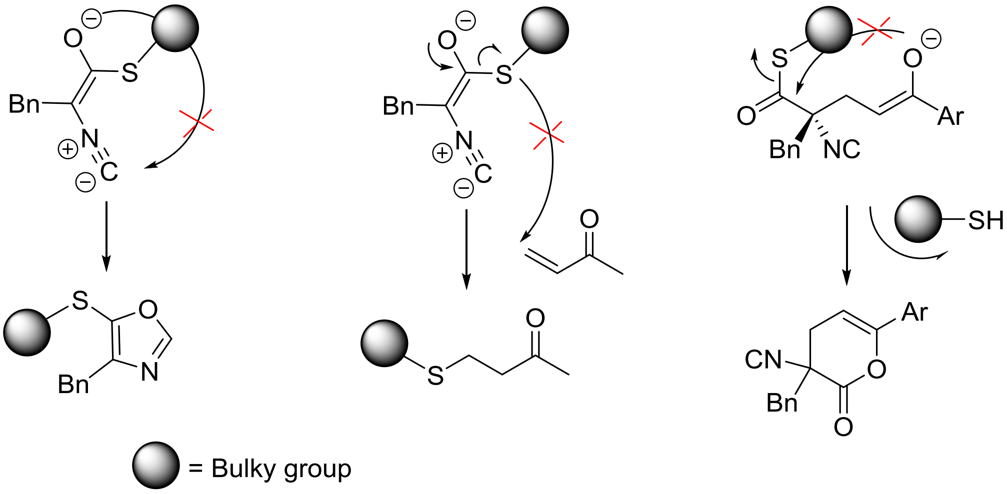
3.4.2.1. *Substrate optimization*

We set out to explore the most appropriate conditions to improve the yield of the reaction towards the acyclic Michael addition product. To that end, some precursors of α-isocyanothioesters, such as α-formamido **40** and *N*-Boc α-amido thioester **42**, were also evaluated for their reactions with enones, but these attempts were completely unsuccessful and unreacted starting material was recovered (Scheme 50).



Scheme 50. Catalytic asymmetric Michael addition involving precursors of α-isocyanothioesters.

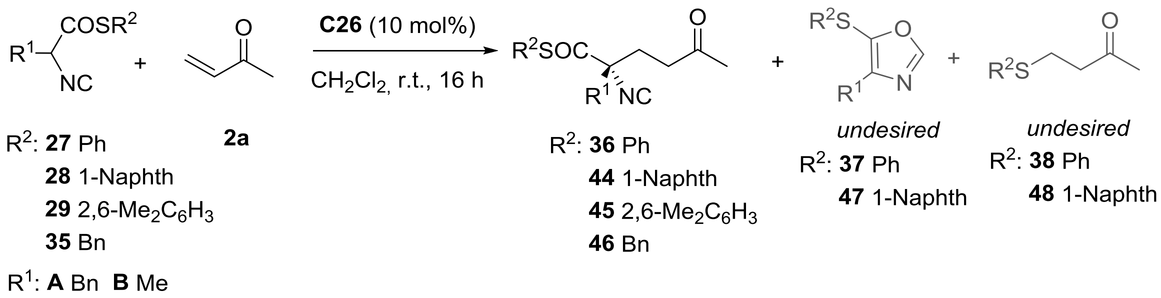
Our next focus was on the nature of the thioesters and how the nature of the S-subtituent may affect the course of the reaction. In this respect we envisaged bulky thioester groups could probably prevent formation of these by-products (Scheme 51).

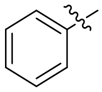
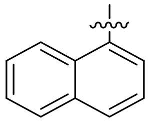
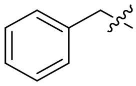
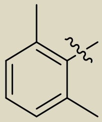


Scheme 51. Strategy to avoid the formation of by-products.

For that purpose, α-akylisocyanothioacetates with more sterically demanding thiols, namely 1-naphthyl, 2,6-$Me_2C_6H_3$ and Bn groups, were prepared and evaluated (Table 27). The reaction of **28B** with methyl vinyl ketone (**2a**) in the presence of 10 mol% **C26** did not produce even traces of product **44** (entry 2). On the contrary, both isocyanoacetates **29** and **35** reacted cleanly to produce the corresponding adducts **45** and **46** essentially as sole reaction product (entry 3, 4 and 5). Within these isocyano thioester compounds, the one containing *ortho*-dimethyl-substituted aryl group (**29**) was better in enantioselectivity terms (entry 3: 88% *ee*, entry 4: 91% *ee*), and thus, it was selected to continue with the study. We could also observe the effectiveness of the new catalyst **C26** in stereochemical terms compared to the common squaramide **C5** (entry 5).

Table 27. Substrate optimization for the Michael addition to methyl vinyl ketone **2a**.[a]

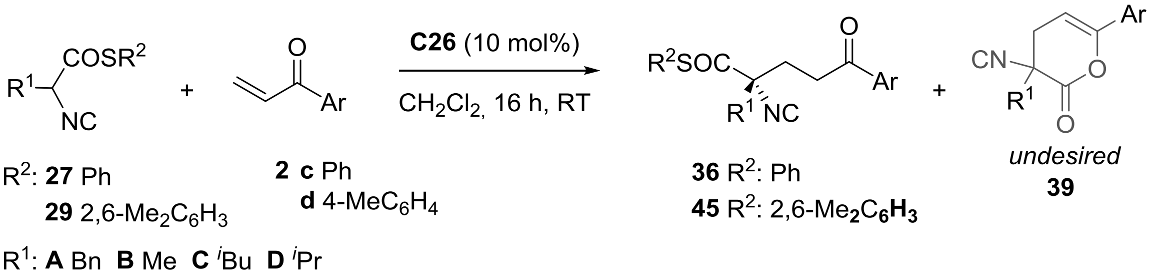


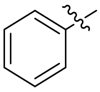
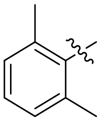
	Isocyanothioacetate R^2		Products	Products ratio	Yield (%)[b]	*ee* (%)
1		**27A**	**36Aa:37A:38**	38:24:38	30	68[b]
2		**28B**	**44Ba:47B:48**	0:57:43	--	--
3		**35B**	**46Ba**	100:0:0	62	88
4		**29B**	**45Ba**	100:0:0	90	91
5		**29A**	**45Aa**	100:0:0	74	92/80[c]

[a] Reaction conduced on a 0.1 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio isocyanothioacetate/**2**/catalyst 1:2:0.1). The enantioselectivity determined by chiral HPLC. [b] Yields of isolated Michael adducts after complete conversion. [c] Reaction carried out using **C5** (10 mol%).

To see the generality of this reaction, the Michael addition of isocyano thioacetates **27** and **29** to aryl vinyl ketones **2c-d** (Table 28) was evaluated. Whereas in the reactions with **27** the formation of the corresponding lactone **39** was always observed (entry 1-5), with **29** only the desired product **45** was observed (entry 6-7). However, the reactivity decreased considerably especially with *p*-methylaryl enone partner (**2d**), hence, we used 3 equivalents of enone **2d** (entry 7).

Table 28. Substrate optimization for the Michael addition to aryl vinyl ketones **2c-d**.[a]



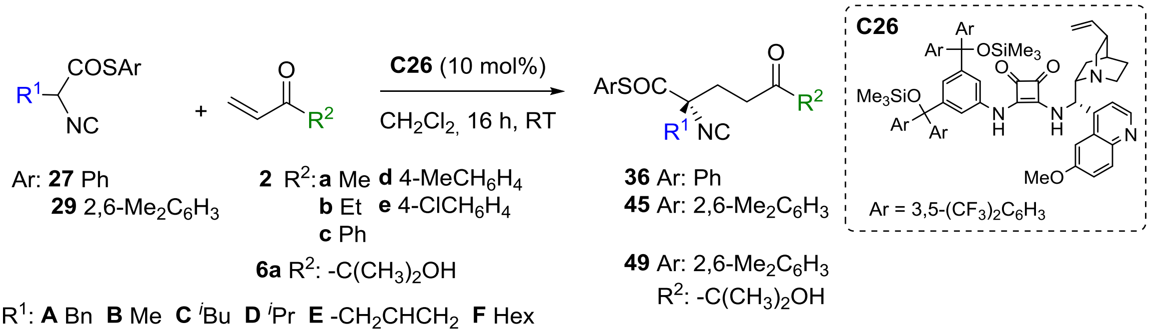
	Isocyanothioacetate		Vinyl ketone	Products	Products ratio	Yield (%)[b]	*ee* (%)
	R^2						
1		**27A**	**2c**	**36Ac:39Ac**	75:25	40	90
2		**27A**	**2d**	**36Ad:39Ad**	85:15	60	94
3		**27B**	**2d**	**36Bd:39Bd**	75:25	41	93
4		**27C**	**2c**	**36Cc:39Cc**	80:20	52	96
5		**27D**	**2c**	**36Dc:39Dc**	90:10	74	98
6		**29A**	**2c**	**45Ac**	100:0	77	94
7		**29A**	**2d**	**45Ad**	100:0	70	92[c]

[a] Reaction conduced on a 0.1 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio isocyanothioacetate/**2**/catalyst 1:2:0.1). The enantioselectivity determined by chiral HPLC. [b] Yields of isolated Michael adducts after complete conversion. [c] Reaction run for 2 days and using 3 equiv. of **2d**.

3.4.2.2. Scope of the reaction

With the *o,o*-dimethylphenyl thioesters isocyanide selected as optimum, the substrate scope of the catalytic reaction was studied (Table 29). This reactivity pattern was general for an array of vinyl ketones, including the α′-hydroxy enone **6a**. Regarding the α-alkyl isocyanide, isocyanoacetates **29** bearing short, medium, longer and branched α-alkyl chains, all provided the Michael acyclic adducts in good yields and excellent enantioselectivities and without any detectable main by-product. Furthermore, as the production of compound **45Fe** illustrates, the reaction can be run at 3 mmol scale without any detriment in yield or stereoselectivity.

Table 29. Reaction scope of α-alkyl isocyanothioacetates asymmetric Michael addition to vinyl ketone.[a]



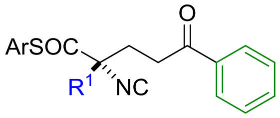
Ar: **27** Ph
29 2,6-$Me_2C_6H_3$

2 R^2: **a** Me **d** 4-$MeCH_6H_4$
b Et **e** 4-$ClCH_6H_4$
c Ph
6a R^2: -$C(CH_3)_2OH$

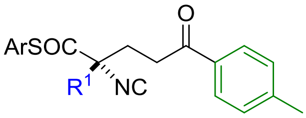
36 Ar: Ph
45 Ar: 2,6-$Me_2C_6H_3$

49 Ar: 2,6-$Me_2C_6H_3$
R^2: -$C(CH_3)_2OH$

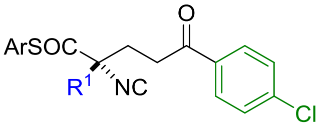
R^1: **A** Bn **B** Me **C** *ⁱ*Bu **D** *ⁱ*Pr **E** -CH_2CHCH_2 **F** Hex



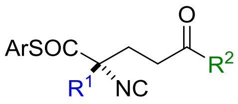
36Dc R^1: *ⁱ*Pr 77%, 94% *ee*
45Ac R^1: Bn 77%, 94% *ee*
45Cc R^1: ⁱBu 70%, 99% *ee*



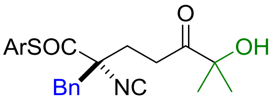
45Ad R^1: Bn 60%, 92% *ee*
45Bd R^1: Me 68%, 94% *ee*



45Be R^1: Me 88%, 90% *ee*
45Ce R^1: ⁱBu 86%, 97% *ee*
45Ee R^1: -$CH_2CH{=}CH_2$ 63%, 97% *ee*
45Fe R^1: ⁿHex 86%, 98% *ee*[b]



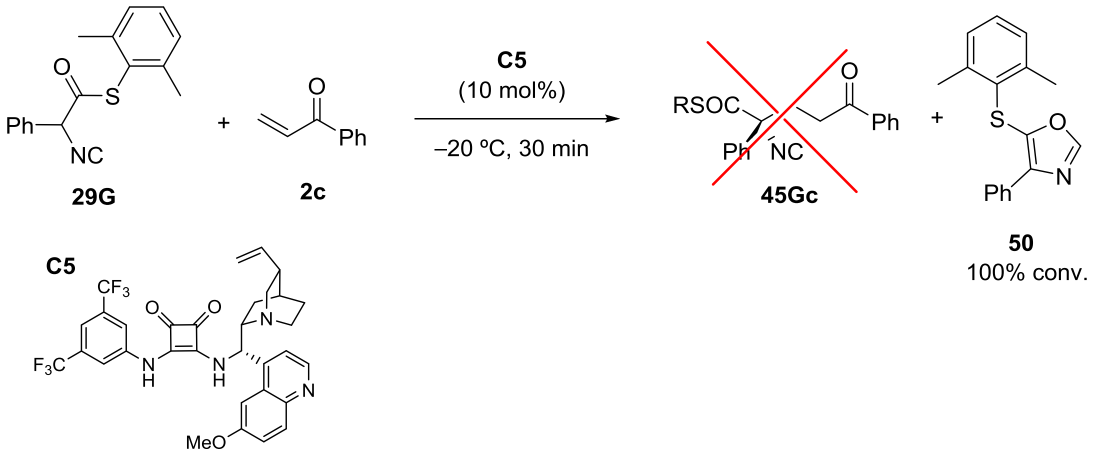
45Aa R^1: Bn, R^2: Me 74%, 92% *ee*
45Ba R^1: Me, R^2: Me 90%, 91% *ee*
45Bb R^1: Me, R^2: Et 82%, 96% *ee*



49Aa
73%, 96% *ee*

[a] Reaction conduced on a 0.1 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Yields of isolated product after column chromatography. The enantioselectivity determined by chiral HPLC. [b] Reaction run at 3 mmol scale using 1.3 equiv. of **2e**.

We next considered applying the α-aryl substituted thioesters series as well, which would be of great interest to increase the reactivity as, for example, of *ortho*-substituted aryl isocyanoacetates (see Chapter 2, Table 17, page 79, compounds **9Fa** and **9Ga**). However, as shown in Scheme 52, reaction between **29G** and **2c** in the presence of **C5** failed, and instead of Michael adduct **45Gc**, product **50** coming from intramolecular *oxo*-cyclization was exclusively formed, even cooling the experiment at –20 °C. Therefore, the use of thioesters as active oxoester surrogates, a priori, does not seem possible in the case of α-aryl isocyanides.



Scheme 52.

Concluding, the substitution of the ester group in isocyanoacetates by a thioester allowed to perform the catalytic asymmetric Michael addition of α-alkyl isocyano(thio)acetates to vinyl ketones, providing acyclic Michael adducts bearing α-alkyl quaternary stereocenters with good isolated yields and excellent enantioselectivities.[199]

3.4.3. Elaboration of adducts

The Michael adduct **45Be** was submitted to several transformations to demonstrate the synthetic potential of these adducts. In each case the corresponding Δ^4-dehydroproline and Δ^5-dehydroproline were formed, thus paralleling the results obtained with the isocyanoacetate adducts (see Chapter 2, section 2.5, page 81-113).

For example, when the isocyano ketone **45B** was subjected to hydrolysis in hydrochloric acid solution for two hours the corresponding Δ^5-dehydroproline **51** was obtained in good yield (Scheme 53).

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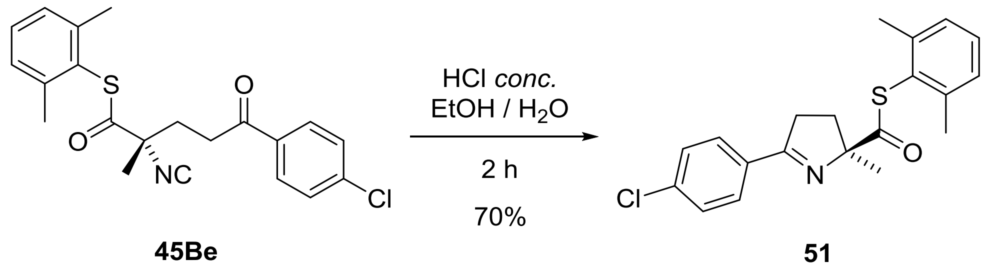
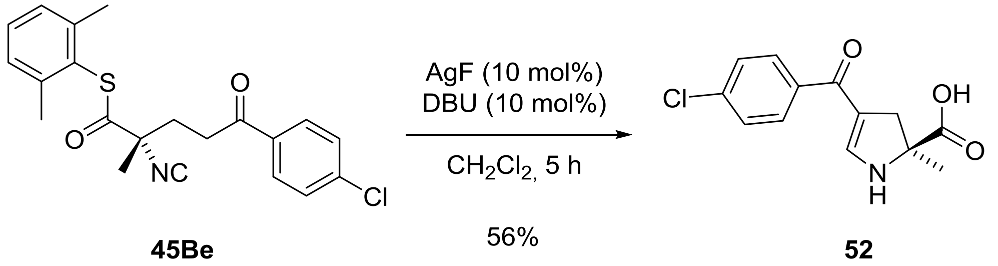
[199] This reactivity pattern appears to be independent of the acceptor. For example, although *N*-phenyl maleimide hardly reacts with α-benzyl and α-methyl isocyanoacetate methyl ester through Brønsted base catalysis (Chaper 2, Table 9, entry 1, page 60), the reaction with isocyanothioacetate **29A** proceeded smoothly (10 mol% **C26**, r.t., overnight) to produce the correspondig adduct in 70% isolated yield, albeit as a mixture of diastereomers (dr= 70:30, 68%/80% *ee*).



Scheme 53. Synthesis of α-alkyl quaternary Δ^5-dehydroproline **51**.

On the other hand, treatment of **45Be** to silver(I) fluoride and DBU, afforded the corresponding Δ^4-dehydroproline **52**. In this instance, at some point in the reaction course or during aqueous workup, the thioester gets also hydrolized to give the free carboxylic acid.



Scheme 54. Synthesis of α-alkyl quaternary Δ^4-dehydroproline **52**.

3.4.4. Reaction with vinyl sulfones as acceptor

Vinyl sulfones have demonstrated their value as building blocks in organic chemistry involving very different reactions,[200] including asymmetric versions.[201] They have been used mainly in Michael addition reactions, being the desulfonilation the most common aftermath transformation. Accordingly, the Michael addition of α-amino acid derivatives to vinyl sulfones gives access to interesting α-alkyl substituted amino acids. Likewise, by using α-alkyl amino acid derivatives as nucleophiles α,α-dialkyl amino acids would be obtained (Scheme 55). As alternative routes to enantiopure α,α-dialkyl amino acids, the

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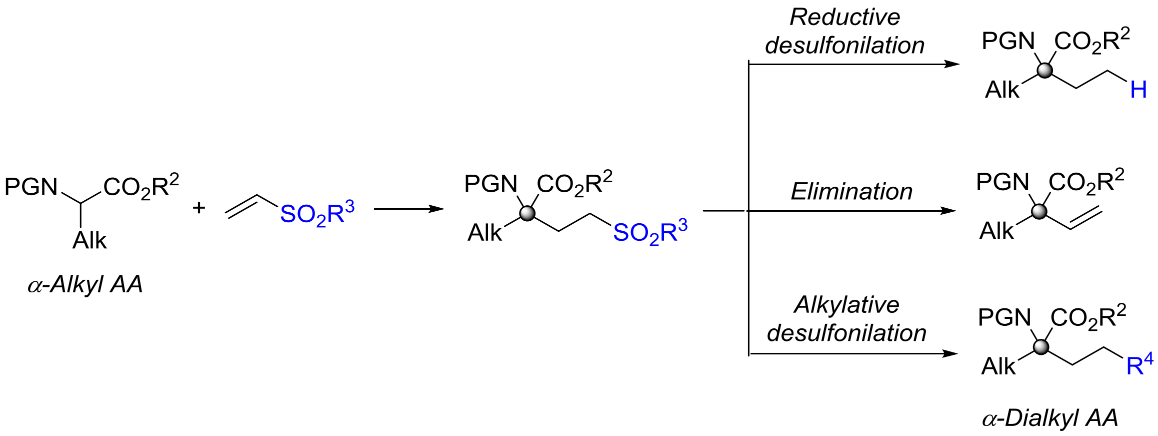
[200] a) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951–6984. b) Simpkins, N. S. *Sulphones in Organic Synthesis* (Pergamon, Oxford) 1993. c) Forristal, I. *J. Sulfur Chem.* **2005**, *26*, 163–195. d) El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315–2349. d) Alba, A.-N. R.; Compayó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018–2033.

[201] Carretero, J. C.; Arrayás, R. G.; Adrio, J. *Organosulfur Chemistry in Asymmetric Synthesis,* Toru, B., Bolm, C., Eds.; Wiley, 2008; pp 291.

catalytic alkylation of α-alkyl amino acid derivatives (or glycine)[202] and the Strecker reaction involving ketimines[203] are the most commonly employed.



Scheme 55. Synthesis of α,α-dialkyl AAs through the Michael addition to vinyl sulfones.

Nevertheless, in the presence of a metal to catalyze the asymmetric Michael addition of α-alkyl AA derivatives to vinyl sulfones, the intramolecular cyclization of the Michael adduct occurs spontaneously in most instaces resulting in cycloaddition products.[204] Studies describing isolation of the respective acyclic Michael adducts have been limited, and usually involve organocatalytic methods. Deng and co-workers developed the first highly enantioselective catalytic conjugate addition to vinyl sulfones, involving the use of O-phenantrenyl quinine as a monofunctional Brønsted base catalyst and using α-substituted cyanoacetates as nucleophiles (Scheme 56).[205] Nevertheless, the transformation of the nitrile group into amine is not direct, so the adduts were elaborated through a 3 steps sequence providing α-amino acids with modest overall yield.

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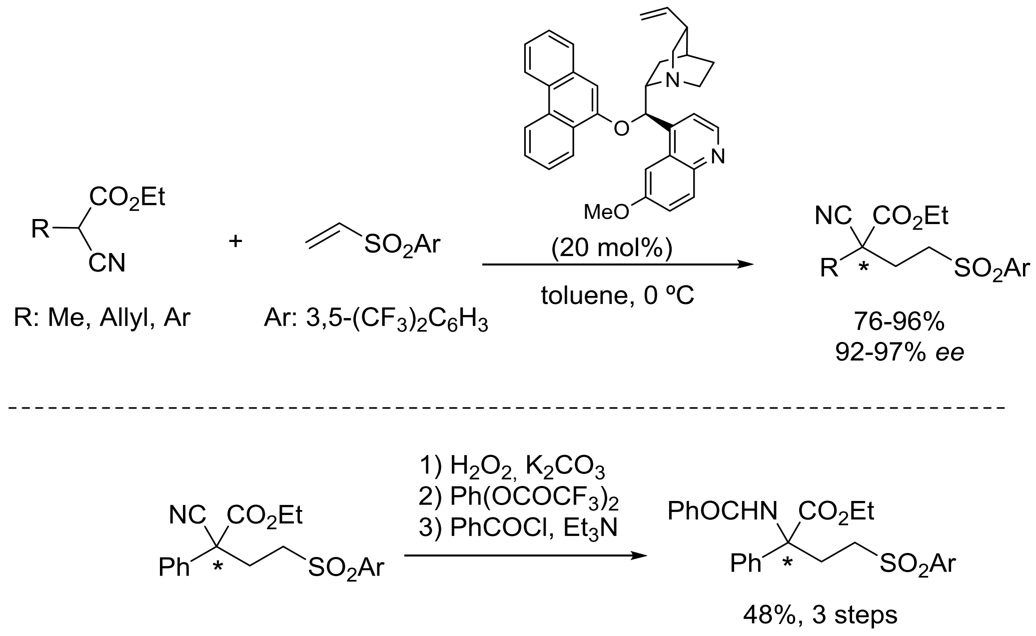
[202] a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *8*, 3013–3028. b) see Chapter 1, ref 103b, page 59.

[203] For selected articles, see: a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014. b) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635. c) Wang, J.; Wang, W.; Li, W.; Hu, X.; Shen, K.; Tan, C.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 11642–11659.

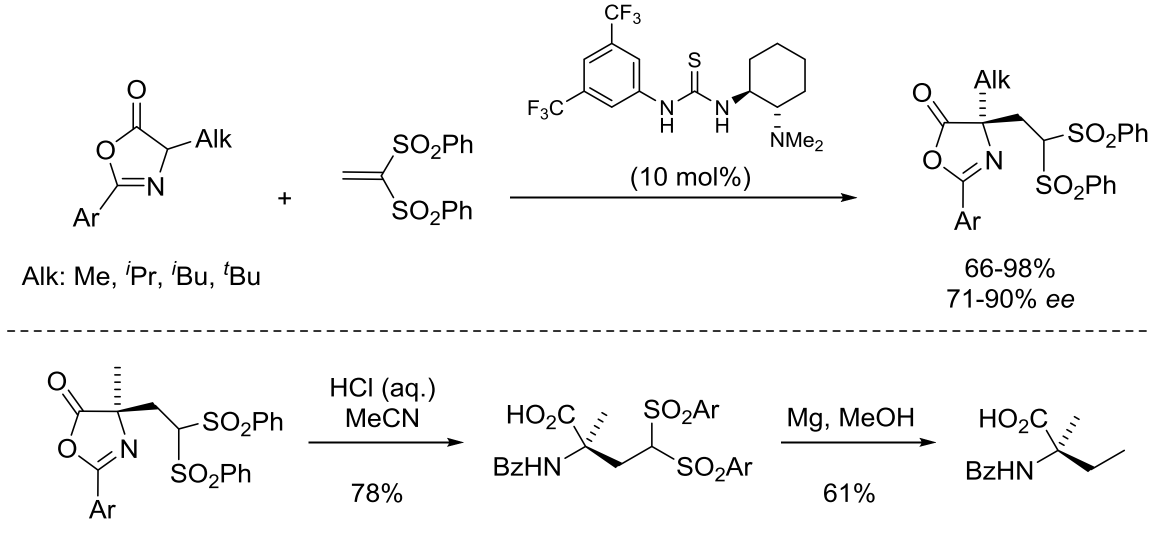
[204] See Chapter 2, ref. 90, page 26.

[205] a) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949. For more recent examples, see: b) Liu, T. Y.; Long, J.; Li, B.; Jiang, L.; Li, R.; Wu, Y.; Ding, L. S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006, 4,** 2097–2099. c) Li, H.; Song, J.; Deng, L. *Tetrahedron* **2009**, *65*, 3139–3148.



Scheme 56. Enantioselective catalytic conjugate addition of α-substituted cyanoacetates to vinyl sulfones.

More recently, azlactones were used as α-AA surrogates in their reaction with vinyl bis-sulfones[206] in the presence of a thiourea catalyst. α,α-Dialkyl amino acid derivatives were obtained upon hydrolysis and subsequent double desulfonation of adducts, which makes the method hardly atom economic.



Scheme 57. Enantioselective catalytic conjugate addition of α-alkyl azlactones to vinyl sulfones.

It is remarkably that no study is known regarding the catalytic asymmetric Michael addition of α-substituted isocyanoacetates to vinyl sulfones. As mentioned earlier (see

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[206] Alba, A.-N. R.; Compayó, X.; Valero, G.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2010**, *16*, 5354–5361.

Chapter 2, Table 9, page 60),[207] a single example is known of catalytic addition of isocyanoacetates to vinyl selenones acting as vinyl sulfone equivalents; but even vinyl selenones are proven more active olefins than vinyl sulfones, the α-alkyl isocyanoacetates still turn out to be too little reactive to give the conjugate addition.

In view of this gap in the use of α-isocyanoacetates, the catalytic asymmetric Michael addition of α-alkyl isocyano thioesters to vinyl sulfones was considered for study. At the outset, both reactivity as well as stereocontrol during formation of quaternary stereocenters remained considerable challenges.

3.4.4.1. Study of the catalytic reaction

A series of selected vinyl sulfones were tested against their reaction with isocyanothioacetate **29A** under the catalytic conditions previously optimized for the enones (Table 30). Phenylsulfonylethylene was initially selected as model acceptor,[208] but it displayed very low reactivity (entry 1). Then the comparatively more reactive geminal bis-sulfone group was tested,[209] but under this reaction conditions messy reaction crude was obtained even at –20 °C (entry 2). Recently, heteroaryl vinyl sulfones have been used as acceptor olefins with increased reactivity.[210] Specifically, it has been demonstrated that sulfones with a phenyltetrazole ring at the sulfur atom are more reactive and show interesting sythetic possibilities, [211] so we decided to test them. We found that this vinyl sulfone reacted with the isocyano(thio)acetate **29A** using the *gem,gem*-(bis)diaryl **C26** as catalyst (entry 3), without formation of undesired byproducts. Nevertheless, the enantioselectivity of the reaction was low and the reaction proceeded too slowly, so further study of the reaction conditions and catalyst was undertaken. We reproduced the reaction of entry 3 using toluene as solvent, which led to product **58** with an increased enantioselectivity (from 30% to 44% *ee*).

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[207] See: a) ref 153b, page 60. For recently reported transformations of phenylselenonyl group, see: b) Buyck, T.; Wang, Q; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 11524–11528. c) Torres-Ochoa, R. O.; Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 5679–5683.

[208] See ref. 200, page 117.

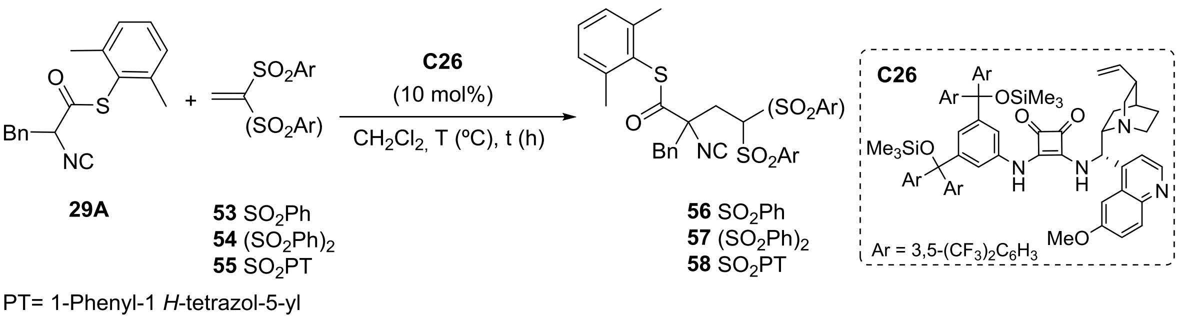
[209] For some representative examples, see: a) Mossé, S.; Alexakis, A. *Org. Let.* **2005**, *7*, 4361–4364. b) Zhu, Q.; Cheng, L. L.; Lu, Y. *Chemm. Commun.* **2008**, *44*, 6315–6317. c) Zhu, Q.; Lu, Y. *Org. Lett.* **2009**, *11*, 1721–1724. d) Zhu, Q.; Lu, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756. e) Quitard, A.; Alexakis, A. *Chem. Commun.* **2011**, *47*, 7212–7214. For articles involving amino acid derivatives as nucleophiles, see: f) see ref. 205b, page 118. g) see ref. 206, page 119.

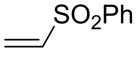
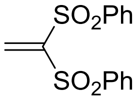
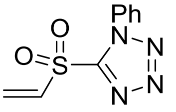
[210] a) Mauleón, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924–9935. b) Desrosiers, J.-N.; Bechara, W. S.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2315–2318.

[211] a) Rodrigo, E.; Morales, S.; Duce, S.; Ruano, J. L. G.; Cid, M. B. *Chem. Commun.* **2011**, *47*, 11267–11269. b) Uraguchi, D.; Nakamura, S.; Sasaki, H.; Konakade, Y.; Ooi, T. *Chem. Commun.* **2014**, *50*, 3491–3493. c) Simlandy, A. K.; Mukherjee, S. *Org. Biomol. Chem.* **2016**, *14*, 5659–5664. d) Rodrigo, E.; Alonso, I.; Ruano, J. L. G.; Cid, M. B. *J. Org. Chem.* **2016**, *81*, 10887–10899.

Accordingly, toluene was adopted as the solvent of choice for the remaining experiments which include variation of the nature of the thioester group.

Table 30. Screening of vinyl sulfones.[a]

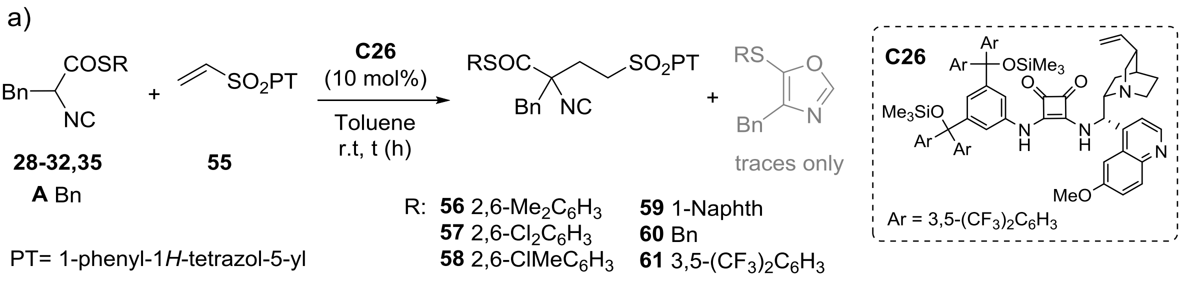


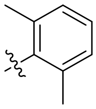
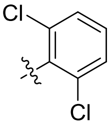
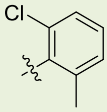
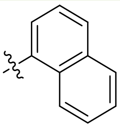
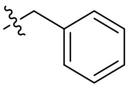
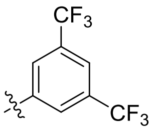
Entry	Vinyl sulfone	Conditions	Product	Results
1	 **53**	r.t., 16 h	**56**	No reaction
2	 **54**	–20 °C, 2 h	**57**	Messy crude
3	 **55**	r.t., 48 h	**58**	70% conversion 47%, 30% *ee* (44% *ee*)[b]

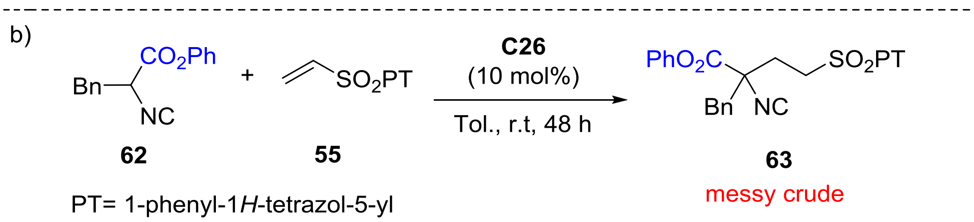
[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Yields of isolated product after column chromatography. The enantioselectivity determined by chiral HPLC. [b] Reaction carried out using toluene as solvent.

Knowing that Michael reaction to vinyl ketones was closely conditioned by the thioester nature, we performed a screening of thioester groups in the reaction with vinyl sulfone **55** (Table 31, reaction a). We wanted to see the effect of the incorporation of halide groups in the thioesters using **31A**. As expected, the reaction was much faster, with a full conversion at 16h, and also it showed a positive effect in the stereoselectivity of the reaction (62% *ee*, entry 2). In its turn, the thioester **30A**, a kind of hybrid of **29** and **31**, behaved similar to **31A** in terms of reactivity (entry 3), with the advantage that the isocyanoacetate **30A** could be synthesized more effectively than **31A**. The thioesters **28A**, **32A** and **35A** were also tested, but whilst the reactions proceeded equally well, the stereocontrol diminished considerably (entry 4-5), and with the new nucleophile **32A** stereoselectivity was neglectable (entry 6). In all experiments carried out with these nucleophiles, the reactions were clean and only traces of intramolecular *oxo*-cyclization byproduct could be observed (<5%). Finally, the reaction did not work well using a relatively active oxoester **62** (Table 31, reaction b), so the thioester group at the nucleophile resulted essential.

Table 31. Screening of the (thio)ester group.[a]



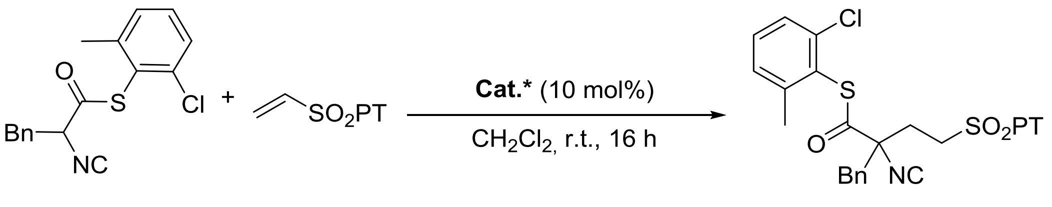
Entry	Nucleophile	R	t (h)	Product	Yield (%)	*ee* (%)
1	**29A**		48	**56**	47 (70)[b]	44
2	**31A**		16	**57**	90	62
3	**30A**		16	**58**	60	65
4	**28A**		16	**59**	61	40
5	**35A**		48	**60**	43	28
6	**32A**		16	**61**	50	0



[a] Reaction conduced on a 0.1 mmol scale in 0.4 mL toluene (molar ratio **1**/**2**/catalyst 1:2:0.1). Yields of isolated product after column chromatography. The enantioselectivity determined by chiral HPLC. [b] The results in parentheses indicate the conversion value when the total conversion was not achieved.

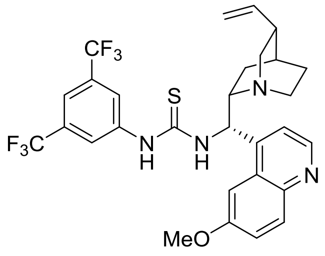
Once the suitable nucleophile was selected, other types of bifunctional Brønsted base catalysts were tested (Table 32). In all cases the conversion was total upon 16 h of reaction, but with lower levels of stereocontrol (essentially 0% *ee* with thiourea **C3**). The Rawal´s squaramide **C9** also gave a low enantiomeric excess compared to the *gem,gem*-(bis)diaryl squaramide catalyst **C26**. However, surprisingly the catalyst **C27**, analogous to **C26** which contained (–)-dihydroquinine as a Brønsted base, improved the enantiomeric excess, providing the product **58** in moderated yield and enantioselectivity (64%, 74% *ee*).

Table 32. Screening of catalysts.



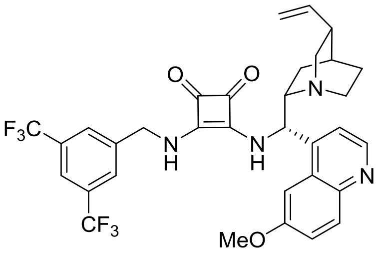
30A **55** **58**

PT= 1-phenyl-1*H*-tetrazol-5-yl



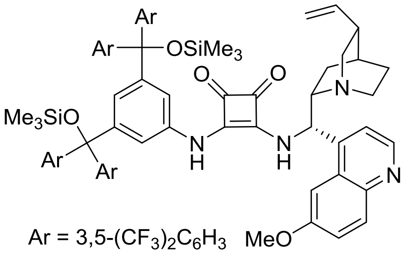
C3

60%, 0% *ee*



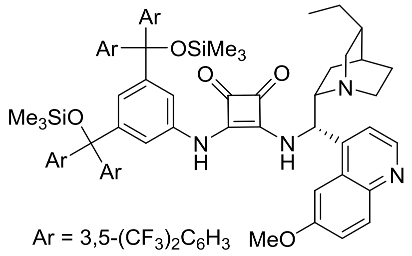
C9

68%, 24% *ee*



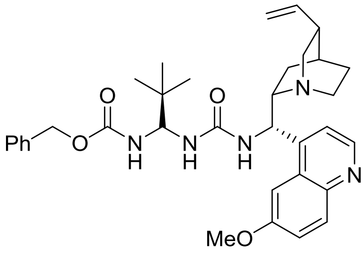
C26

60%, 65% *ee*[b]



C27

64%, 74% *ee*[b]



C28

72%, 20% *ee*

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[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio **1**/**2**/catalyst 1:2:0.1). Yields of isolated product after column chromatography. The enantioselectivity determined by chiral HPLC. [b] Reaction carried out using toluene as solvent.

During this preliminary study it was demonstrated that the isocyanothioesters work correctly in the Michael addition with vinylsulfones, giving solution for the first time to the reactivity problem shown by the α-alkyl isocyanoesters in similar reactions. It has also been possible to see the compatibility of the new squaramide catalysts with these AA-derivative nucleophiles to give several conjugate additions in a stereocontrolled fashion. However, we eventually decided to stop here the study with vinyl sulfones, and we moved to study a different class of acceptor reagents.

3.5. Mannich reaction: synthesis of α-alkyl α-quaternary imidazolines

In this section, our purpose was to expand the application of α-alkyl isocyanothioacetates to asymmetric Mannich reactions using the newly designed bifunctional Brønsted base catalysts.

The Mannich reaction is one of the most powerful methods for the preparation of chiral nitrogen containing molecules with concominant formation of a new C-C bond.[212] Along the process, imines work as electrophilic reagents and β-amino carbonyl compound with up to two new stereogenic centers can be generated (Figure 31).

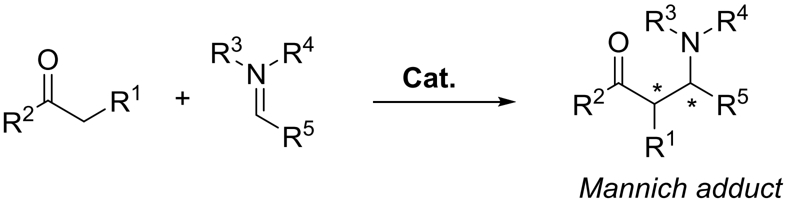

Figure 31. General Mannich reaction.

Many approaches have been developed to afford asymmetric Mannich reactions. Some of them are based on the use of chiral auxiliaries,[213] but in the last decades catalytic asymmetric Mannich methodologies have been developed based on the use of metal catalysts[214] or organocatalysts, particularly enamine mediated methods using aldehydes and ketones as donor carbonyl components.[215,216]

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[212] For general reviews on the asymmetric Mannich reaction, see: a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070. b) Syamala, M. *Org. Prep. Procc. Int.* **2009**, *41*, 1–68. c) Greco, S. J.; Lacerda, V.; Bezerra dos Santos, R. *Aldrichimica Acta* **2011**, *44*, 15–23. d) Bhadury, P. S.; Song, B.-A. *Curr. Org. Chem.* **2010**, *14*, 1989–2006. e) Xiao-Hua, C.; Hui, G.; Bing, X. *Eur. J. Chem.* **2012**, *3*, 258–266.

[213] For some pioneer stereoselective Mannich reaction using chiral auxiliaries, see: a) Broandley, K.; Davies, S. G. *Tetrahedron Lett.* **1984**, *25*, 1743–1744. b) Hart, D. J.; Lee, C.-S. *J. Am. Chem. Soc.* **1986**, *108*, 6054–6056. c) Gennari, C.; Venturini, I.; Gilson, G.; Shimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227–230. For more recent representative examples, see: a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *308*, 5603–5606. b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. c) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 981–984. d) Palomo, C.; Oiarbide, M; González-Rego, M. C.; Sharma, A. K.; García, J. M.; Landa, C.; Linden, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1063–1065.

[214] For selected reviews on metallocatalyzed approaches, see: a) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089–2100. b) Kazmaier, U. *Angew. Chem. Int. Ed.* **2009**, *48*, 5790–5792. c) Tsubogo, T.; Yamashita, Y.; Kobayashi, S. *Top. Organomet. Chem.* **2013**, *45*, 243–270. d) Karimi, B.; Enders, D.; Jafari, E. *Synthesis* **2013**, 2769–2812.

[215] For selected reviews on organocatalyzed approaches, see: a) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas III, C. F. *J. Org. Chem.* **2003**, *68*, 9624–9634. b) Marques, M. M. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352. c) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.*

The Mannich reaction involving α-amino acid equivalents constitutes one of the most practical routes towards the preparation of α,β-diamino acids stereoselectively,[217] important structural motifs that are contained in many biologically active compounds (see Chapter 1, section 1.4, page 42). The common approach consists on the catalytic asymmetric direct Mannich reaction between a prochiral α-amino acid derivative and an imine, which results in the construction of a C-C bond and the two neighbouring nitrogen containing stereocenters simultaneously in a single step (Scheme 58). Several α-AA surrogates (particularly α-carboxy azomethine ylides,[218] α-nitroesters,[219] azlactones,[220] and isothiocyanates[221]) have been employed in this context, with methods employing α-isocyanoacetates being underdeveloped to date. The Mannich reaction between α-carboxy azomethine ylides and imines is perhaps the most thoroughly investigated approach.

2007, 5797–5815. d) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, P. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. e) Hayashi, Y. *J. Synth. Org. Chem.* **2014**, *72*, 1228–1238.

[216] For selected reviews on both metallocatalyzed and organocatalyzed approaches, see: a) Córdova, A. *Acc. Chem. Rev.* **2004**, *37*, 102–112. b) Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *387*, 1940–1948; c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.

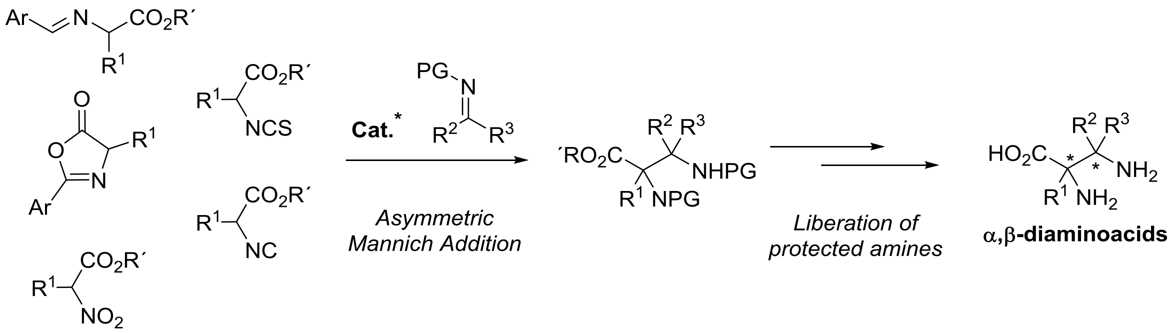
[217] See Chapter 1, ref. 124, page 44.

[218] For catalytic asymmetric Mannich reaction of azomethine yilides, see: a) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583–2591. b) Ooi, T.; Kameda, M.; Fujii, J.-I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397–2399. c) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564–4567. d) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas III, C. F. *Org. Lett.* **2006**, *8*, 2839–2842. e) Kobayashi, S.; Yazaki, R.; Seki, K.; Yamashita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 5613–5615. f) Hernández-Toribio, J.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150–16151. g) Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc*. **2008**, *130*, 14362–14363. h) Shang, D.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 3678–3681. i) Zhang, H.; Syed, S.; Barbas, C. F. *Org. Lett.* **2010**, *12*, 708–711. j) Hernández-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 1153–1157. k) Liang, G.; Tong, M.-C.; Tao, H.; Wang, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1851–1855. l) Hernando, E.; Arrayás, E. R.; Carretero, J. C. *Chem. Commun*. **2012**, *48*, 9622–9624. m) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799–11802.

[219] For catalytic asymmetric Mannich reaction of nitroesters, see: a) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem*. **2005**, *3*, 1362–1364. b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171. c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867. d) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 8094–8097. e) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879. f) Puglisi, A.; Raimondi, L.; Benaglia, M.; Bonsignore, M.; Rossi, S. *Tetrahedron Lett.* **2009**, *50*, 4340–4342. g) Uraguchi, D.; Koshimoto, K.; Sanada, C.; Ooi, T. *Tetrahedron: Asymmetry* **2010**, *21*, 1189–1190.

[220] For catalytic asymmetric Mannich reaction of azlactones, see: a) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088–14089. b) Liu, X.; Deng, L; Jiang, X.; Yan, W.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 876–879. c) Shi, S.-H.; Huang, F.-P.; Zhu, P.; Dong, Z.-W.; Hui, X.-P. *Org. Lett.* **2012**, *14*, 2010–2013. d) Zhang, W.-Q.; Cheng, L.-F.; Yu, J.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 4085–4088.

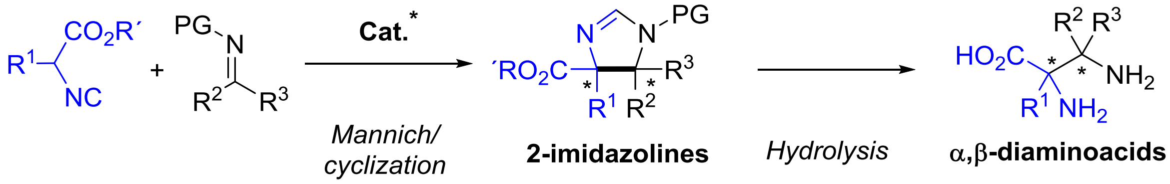
[221] For catalytic asymmetric Mannich reaction of isothiocyanates, see: a) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Kçhn, G.; Willis, M. C. *J. Am. Chem. Soc*. **2007**, *129*, 10632–10633. b) Li, L.; Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 11648–11649. c) Chen, X.; Dong, S.; Qiao, Z.; Zhu, Y.; Xie, M.; Lin, L.; Liu, X.; Feng, X. *Chem. Eur. J.* **2011**, *17*, 2583–2586. d) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 4382–4385.



Scheme 58. Mannich addition of α-amino acid precursors on route to α,β- diamino acids products.

3.5.1. Isocyanoacetates in catalytic asymmetric Mannich reactions

An attractive route to enantiopure α,β-diamino acids starting from isocyanates proceeds via 2-imidazoline formation and subsequent standard hydrolytic or reductive manipulation.[222] 2-Imidazolines may be formed by catalytic asymmetric Mannich addition/cyclization reactions between isocyanoacetates and imines (Scheme 59).



Scheme 59. General approach for α, β-diamino acids synthesis based on catalytic asymmetric Mannich reaction of isocyanoacetates.

On the other hand, substituted imidazolines are structural subunits of biologically active compounds[223] and they are useful for the synthesis of cyclopalladated complexes, chiral catalysts and chiral solvating agents as well.[224] Due to these practical interests, chemists

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[222] a) Sang-Hun, J.; Harold, K. *Tetrahedron Lett.* **1984**, *25*, 399–402. b) Meyer, R.; Schöllkopf, U.; Bohme, P. *Liebigs Ann. Chem.* **1977**, 1183–1193.

[223] For example, see: a) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc*. **1992**, *114*, 5010–5017. b) Rondu, F.; Le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lamaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J. *J. Med. Chem.* **1997**, *40*, 3793 –3803. c) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586–3591.

[224] For example, see: a) Xu, J.; Guan, Y.; Yang, S.; Ng, Y.; Peh, G.; Tan, C.-H. *Chem. Asian J.* **2006**, *1*, 724–729. b) Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2009**, *351*, 489–519. c) Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2010**, *352*, 1113–1118.

have made great efforts in developing methodologies for their enantioselective synthesis.

The racemic Mannich-type reaction of isocyanoacetates with imines was first reported by Schöllkoptf et al. in 1977.[225] In 1996 Hayashi et al. reported the Au(I)-catalyzed *cis*-diastereoselective Mannich reaction of isocyanoacetates with *N*-sulfonylimines[226] and the following studies showed that the diastereoselectivity depends closely on the catalyst used.[227] As far as the enantioselective Mannich versions of these substrates are concerned, the majority of the methods are based on combined use of chiral ligands and metal; the transition metal is assumed to coordinate to isocyano group during activation.

Metal-catalyzed methods reported to date are collected in Table 33.[228] In 1999, Lin et al. found that the reaction between ethyl isocyanoacetate and *N*-Tosyl aldimines can be catalyzed by Me_2SAuCl and ferrocene-derived diphosphine ligand (entry 1). Later, it was found that the same reaction could be promoted by chiral palladium-pincer complex catalyst with similar levels of selectivity (entry 2). Ulterior studies demonstrated that Ag, Cu and Ni salts in combination with multi(three)dentate cinchona-alkaloid-derived ligands are able to promote the reaction between isocyanoacetates and several imines (entry 3-7), such as phosphinoyl ketimines (entry 4-7), even using α-alkyl substituted isocyanoacetates (entry 6-7). However, in all these examples activated imines, bearing activating groups attached at N, C or both were employed.

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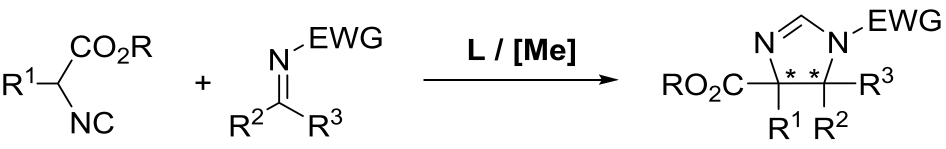
[225] Meyer, R.; Schöllkoptf, U.; Bohme, P. *Justus Liebigs Ann. Chem.* **1977**, 1183–1193.

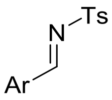
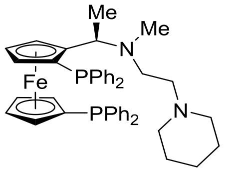
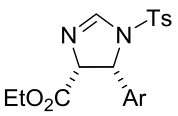
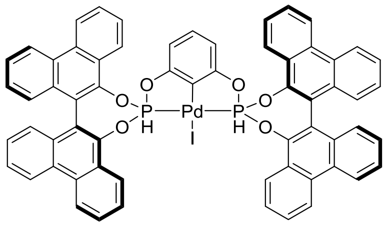
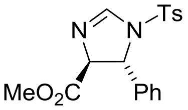
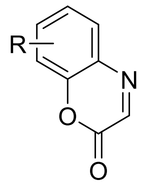
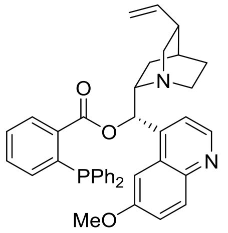
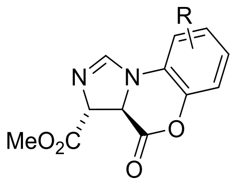
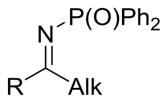
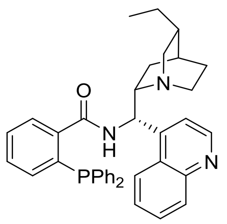
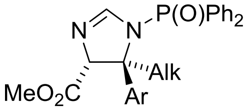
[226] Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969–4972.

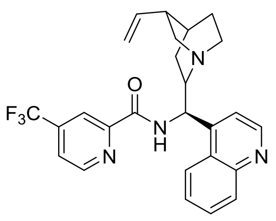
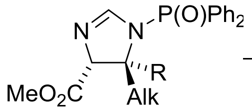
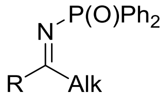
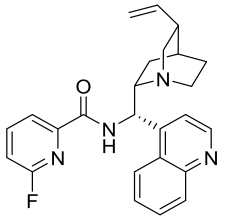
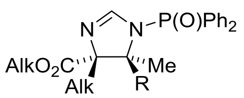
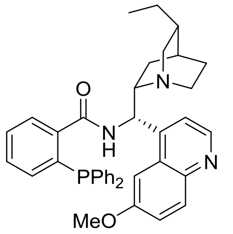
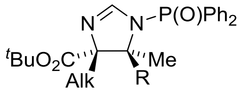
[227] a) Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799–1803. b) Benito-Garagorri, D.; Bocokic, V.; Kirchner, K. *Tetrahedron Lett.* **2006**, *47*, 8641–8644. c) Aydin, J.; Kumar, K. S.; Eriksson, L.; Szabó, K. *Adv, Synth. Catal.* **2007**, *349*, 2585–2594.

[228] For metallocatalyzed asymmetric Mannich reactions of isocyanoacetates, see: a) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331–1334. b) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855–862. c) Aydin, J.; Rydén, A.; Szabó, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1867–1870. d) Ortín, I.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3462–3465. e) Shao, P.-L.; Liao, J.-Y.; Ho, Y. A.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 5435–5439. f) Hayashi, M.; Iwanaga, M.; Shiomi, N.; Nakane, D.; Masuda, H.; Nakamura, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 8411–8415. g) Nakamura, S.; Yamaji, R.; Iwanaga, M. *Chem. Commun.* **2016**, *52*, 7462–7465. h) de la Campa, R.; Yamagata, A. D. G.; Ortín, I.; Franchino, A.; Thompson, A. L.; Odell, B.; Dixon, D. J. *Chem. Commun.* **2016**, *52*, 10632–10635.

Table 33. Asymmetric Mannich reactions of isocyanoacetates with imines promoted by metal catalysts.



	Electrophile	Cat.*	Product	Results	Ref
1		 (0.5 mol%)/ Me_2SAuCl (0.5 mol%)		79-91% 85:15-96:4 dr 46-88% *ee*	228a
2		 (1 mol%)		98% 1:4 dr 75% *ee*	228c
3		 (20 mol%)/ Ag_2O (10 mol%)		84-92% 20:1 dr 93-91% *ee*	228e
4		 (20 mol%)/ Ag_2O (5 mol%)		70-98% 73:27-99:1 dr 90-99% *ee*	228d

	Electrophile	Cat.*	Product	Results	Ref
5		 (10 mol%)/ $Cu(OTf)_2$ (10 mol%)/ Cs_2CO_3 (20 mol%)	 *syn*	R: Ar (*syn)* 44-68% 81:19-92:8 dr 91-99% *ee* R: Alk *(anti)* 54-78% 40:60-28:72 dr 93-95% *ee*	228f
6		 (10 mol%)/ $NiCl_2$ (10 mol%)/ Cs_2CO_3 (20 mol%)	 R= Alk, Ar	68-99% 85:15-99:1 dr 80--92% *ee*	228g
7		 (10 mol%)/ AgOAc (5 mol%)	 R= Ar, CH_2CH_2Ph	48-90% 98:2 dr 87-95% *ee*	228h

The asymmetric Mannich reaction of isocyanoacetates in the absence of metals still remains a scarcely explored area. As far as we are aware, only the works shown in the Table 34 are known,[229] all involving aldimines with *N*-activating groups such as sulfonyl (entries 1 and 2) or *tert*-butoxycarbonyl (entry 4), or specially reactive ketimines, such as isatin-derived cyclic ketimines showed in entry 3. Furthermore, while α-aryl substituted isocyanoacetates have been applied in several reactions (entry 2-4), those with an α-alkyl substituent still remain a challenge due to their attenuated reactivity. The only

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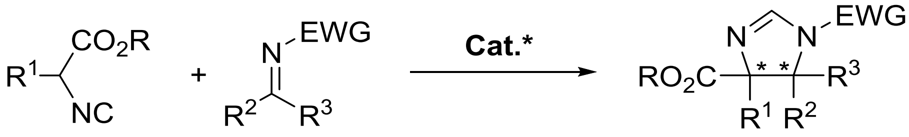
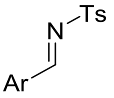
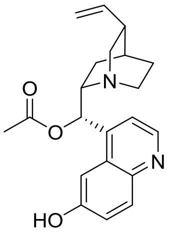
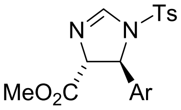
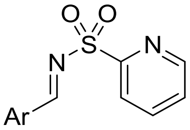
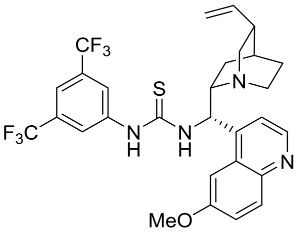
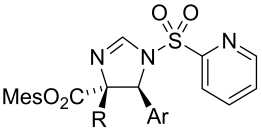
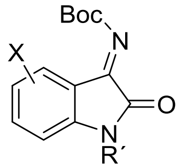
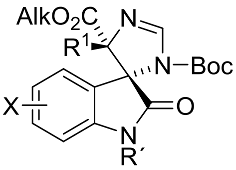
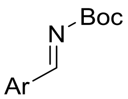
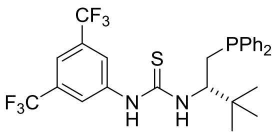
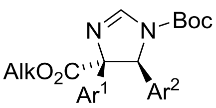
[229] For organocatalyzed asymmetric Mannich reactions of isocyanoacetates, see: a) Zhang, Z.-W.; Lu, G.; Chen, M.-M.; Lin, N; Li, Y.-B.; Hayashi, T.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2010**, *21*, 1715–1721. b) Nakamira, S.; Maeno, Y.; Ohara, M.; Yamamura, A.; Funahashi, Y.; Shibata, N. *Org. Lett.* **2012**, *14*, 2960–2963. c) Zhao, M.-X.; Jing, L.; Zhou, H.; Shi, M. *RSC Adv.* **2015**, *5*, 75648–75652. d) Ji, X.; Cao, W.-G.; Zhao, G. *Tetrahedron* **2017**, *73*, 5983–5992.

example by Nakamura, Shibata et al. using *N*-azaarenesulfonyl imines is remarkable although it failed with the bulky α-isopropyl group (entry 2).

Table 34. Asymmetric Mannich reactions of isocyanoacetates with imines promoted by organocatalysts.



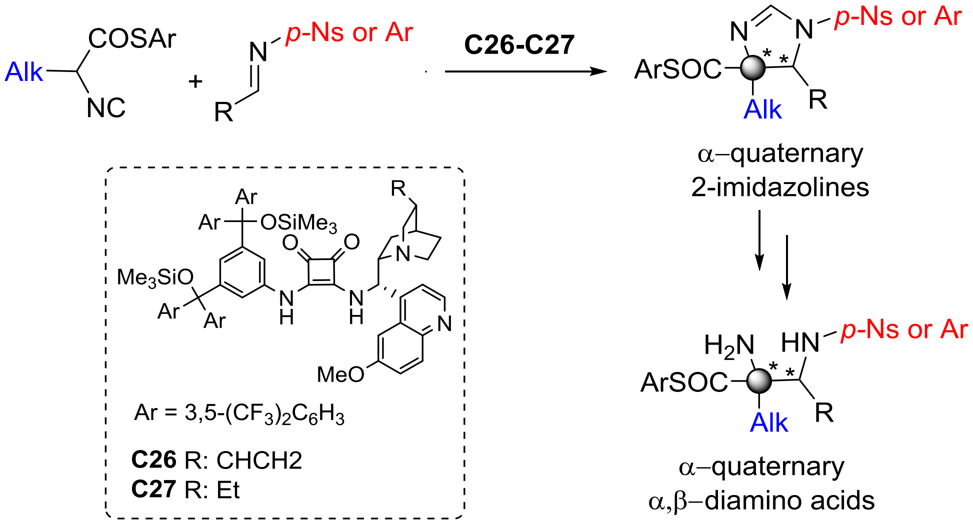
	Electrophile	Cat.*	Product	Results	Ref.
1		 (10 mol%)		34-79% 91:9-99:1 dr 5-70% *ee*	229a
2		 (10 mol%)	 Mes: 2,4,6-MeC_6H_2 R= Alk, Ar	R= Ar 71-99% 81:19-99:1 dr 74-96% *ee* R= Alk 73:27-99:1 dr 78-88 % *ee* (R= ^{i}Pr: no reaction)	229b
3			 R^1= Ar	55-90% 20:1 dr 69-98% *ee* **R^1= Bn, 2-BrC_6H_4**: no reaction	229c
4		1) Mannich reaction:  (0.5 mol%)/ Methyl acrylate (0.5 mol%) 2) Cyclization: AgOAc (10 mol%)/ PPh_2Me (20 mol%)		85-98% 1.1:1-9:1 dr 50-93% *ee*	229d

In summary, the organocatalytic asymmetric synthesis of α-quaternary 2-imidazolines, particularly those containing α-alkyl quaternary stereocenters, remains underdeveloped as yet. The low reactivity of the α-alkyl isocyanoacetates compared to α-aryl analogs is one of the major obstacles.

3.5.2. Objetive

In view of the good results obtained with *gem,gem*-(bis)diaryl squaramide catalysts **C26-C27** in various Michael addition reactions of α-alkyl isocyano(thio)acetates, our goal was to explore that catalytic system in the context of the Mannich reactions. The attenuated reactivity of isocyanoacetates has limited their use in organocatalytic Mannich reactions, and to date, squaramide catalysts have never been successfully employed in this type of reaction.

At the beginning the reaction of α-alkyl isocyano(thio)acetates to activated aldimines was explored, and then the study was extended to other less activated aldimines (Scheme 60).

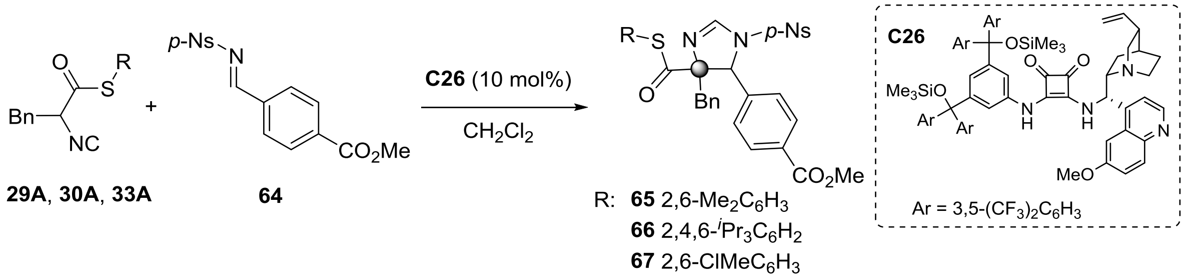


Scheme 60. Synthetic plan.

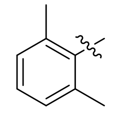
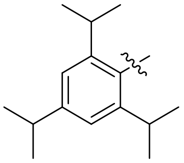
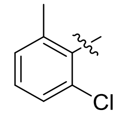
3.5.3. Reaction of α-alkyl isocyano(thio)acetates with activated (*N*-nosyl) aldimines

The study was initiated by comparing the behavior of several isocyanothioacetates in the reaction with the *N*-nosyl imine **64**, using 10 mol% of catalyst **C26** and dichloromethane as solvent (Table 35). The reaction with **29A** as nuclephile proceeded in a stereocontrolled manner (entry 1). However, the reaction was too slow and before total consumption of the nucleophile the imine hydrolyzed extensively, so the product was obtained in a low yield. In addition, although the diastereocontrol of the reaction was good, the enantiocontrol was poor (36% *ee*). We decided to test thioesters **33A** and **30A** which exhibit clearly congested sterics and electron-poor character respectively, adding molecular sieve at the reaction to avoid the hydrolysis of the imine. The reaction with **33A** did not go at room temperature and it was necessary to heat up to 50 °C to give the product in good yield but low stereocontrol (entry 2). In its turn, the isocyanothioacetate **30A** gave product **67** with total conversion in 3 h at room temperature, and with improved stereocontrol (entry 3). Thus, **30A**, bearing *ortho*-chloro-*ortho*-methylphenyl thioester group, was selected for further optimization of the reaction conditions.

Table 35. Substrate optimization for the Mannich reaction with *N*-*p*-Nosyl aldimines.[a]



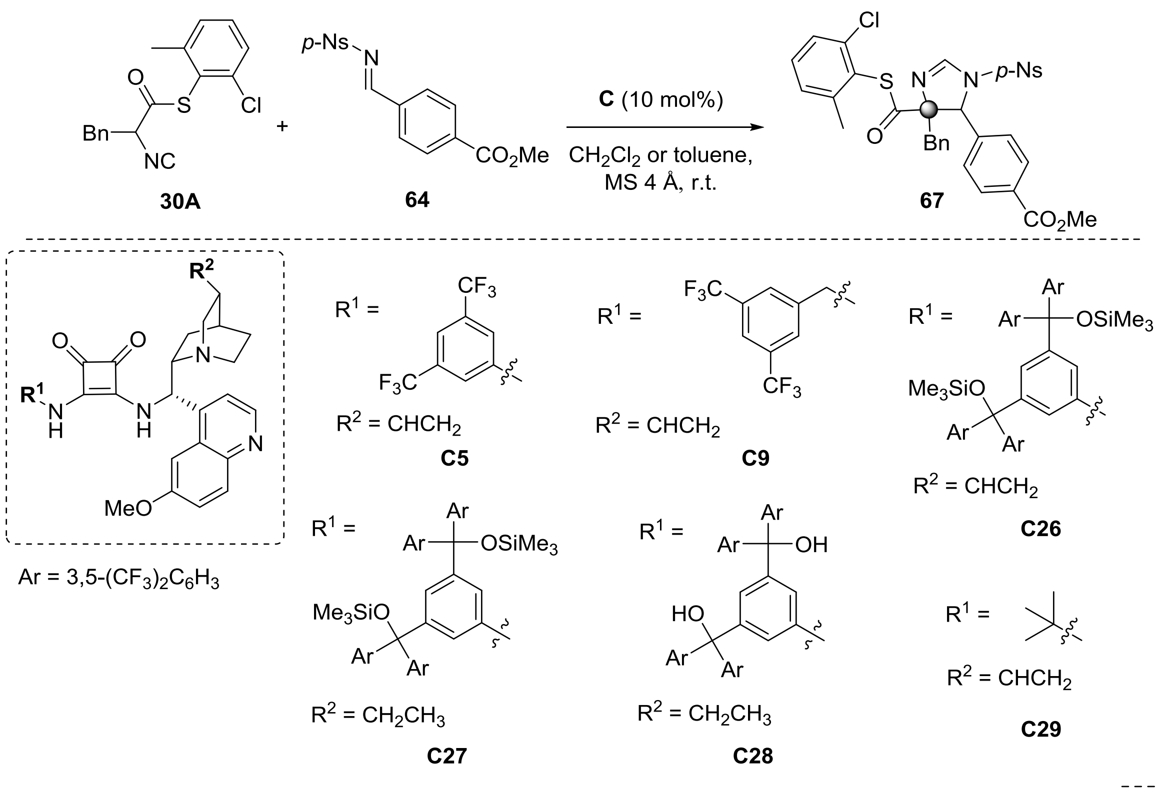
29A, **30A**, **33A** **64**

Entry	R	T (°C)	t (h)	Product	Yield (%)	dr	*ee* (%)
1	 **29A**	r.t.	16	**65**	47	90:10	36
2[b]	 **33A**	r.t.	16	**66**	n.r.	--	--
		50	16		82	70:30	10
3[b]	 **30A**	r.t.	3	**67**	75	90:10	56

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio isocyanothioacetate/**64**/catalyst 1:1.5:0.1). Yields of isolated product after column chromatography. The diastereoselectivity and the enantioselectivity of the major diastereomer determined by chiral HPLC. [b] MS 4 Å was added.

Next we analyzed the best conditions for the reaction with **30A**, varying the catalyst, solvent and temperature (Table 36). The Mannich reaction with catalyst **C26** in toluene as solvent (97:3 dr and 70% e*e*) was superior as compared with the reaction in CH_2Cl_2 (entry 3). On the other hand, the (–)-dihydroquinine catalyst **C27** promoted the reaction in toluene faster that catalyst **C26** yielding essentially a single diastereomer of compound **67** at 0 °C with a 72% *ee* (entry 4). However, catalyst **28** containing two tertiary alcohol groups provided product **67** with very poor enantiocontrol (entry 5, 10% *ee*) as in case of the commonly known squaramides (**C5**, **C9** and **C29**).

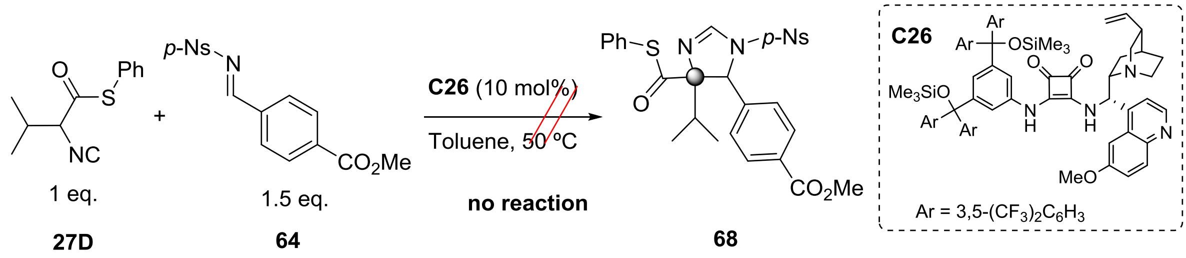
Table 36. Study of reaction conditions for the addition of **30A** to **64**.



Entry	C	Solvent	T (°C)	t (h)	Conversion (%)	dr	*ee* (%)
1	**5**	CH_2Cl_2	r.t.	3	100	85:15	3
2	**9**	CH_2Cl_2	0	16	100	85:15	10
3	**26**	CH_2Cl_2	r.t.	3	100	90:10	56
		Toluene	r.t.	16	90	97:3	70
4	**27**	Toluene	r.t.	3	100	**97:3**	**74**
			0	3	100	**100:0**	**72**
5	**28**	CH_2Cl_2	r.t.	24	90	85:15	10
			0	16	0	--	--
6	**29**	Toluene	r.t.	16	98	80:20	32

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 or toluene (molar ratio **30A**/**64**/catalyst 1:1.5:0.1) at room temperature. The diastereo- and enantioselectivity determined by chiral HPLC.

Unfortunately, the bulkier α-^{i}Pr isocyanothioacetate **27D** resulted inactive under the present catalytic conditions (Scheme 61), even heating at 50 °C.



Scheme 61.

In summary, the asymmetric Mannich reaction of isocyano(thio)acetates has been promoted by a squaramide catalyst for the first time, giving access to α-alkyl quaternary *N-(p-*Nosyl) imidazolines with excellent diastereoselectivity and moderate enantioselectivity.

3.5.4. α-Alkyl isocyano(thio)acetates with unactivated (*N*-aryl) aldimines

As far as non-activated imines are concerned (Figure 32), to date they have never been used in asymmetric Mannich reactions with α-isocyanoacetates, and imines with *N*- or *C*-activating groups are generally required even in the reactions promoted by metal catalysts (see Table 33, page 129 and Table 34, page 131).

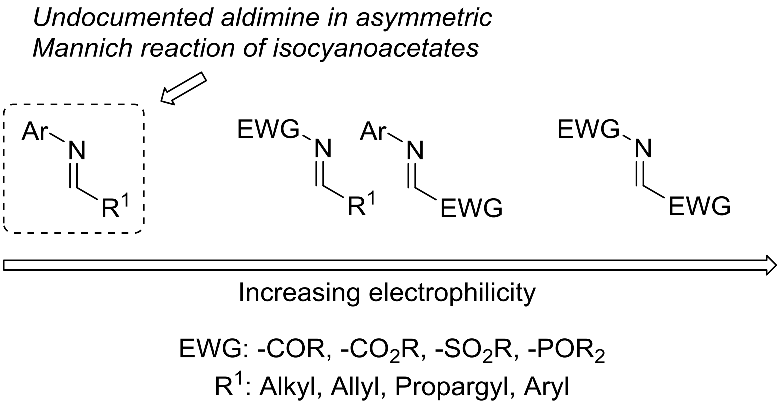


Figure 32. Classification of aldimines according to their electrophilicity/reactivity.

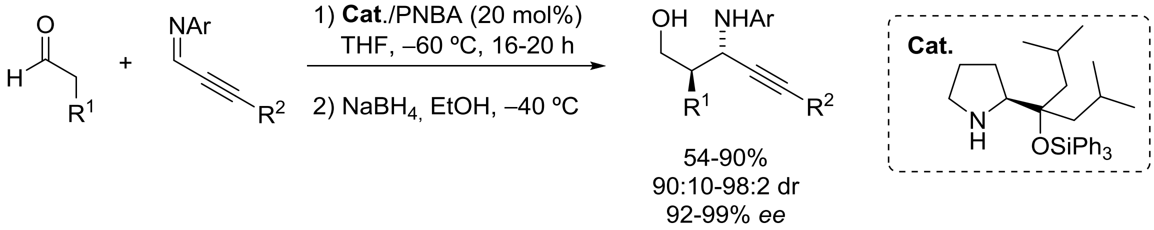
N-aryl propargylic imines are a particular type of non-activated imines with great synthetic versatility: the alkynyl moiety in the Mannich adducts may participate in several intramolecular cyclization processes,[230] or alternatively can be partially or totally

---

[230] a) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230–12231. b) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3503–3507. c) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. c) Gudoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980. d) Gómez-Bengoa,

reduced, providing adducts formally derived from recalcitrant imines (little reactive and enolizable).[230b] In addition, the removal of the N-aryl group if desired, can be carried out easily in some instances to produce the NH amine by a simple oxidative procedure.[231] These features make the resulting propargylamine adducts potentially versatile building-blocks in the synthesis of natural products,[232] drugs[233] and pesticides,[234] as well as a number of bioactive compounds.[235]

Enamine-mediated Mannich methodology involving propargylic imines has been previously developed in our laboratory using a new type of α,α-dialkylprolinol catalysts (Scheme 62).[230d]



Scheme 62. Precedent of our group related to the use of propargylic imines as Mannich acceptor.

The aim was now to explore the asymmetric Mannich addition of α-alkyl isocyanothioacetates to *N*-aryl propargylic imines using our newly developed *gem,gem*-(bis)diaryl squaramide catalyst **C27** (Scheme 63).

E.; Jiménez, J.; Lapuerta, I.; Mielgo, A.; Oiarbide, M.; Otazo, I.; Velilla, I.; Vera, S.; Palomo, C. *Chem. Sci.* **2012**, *3*, 2949–2957.

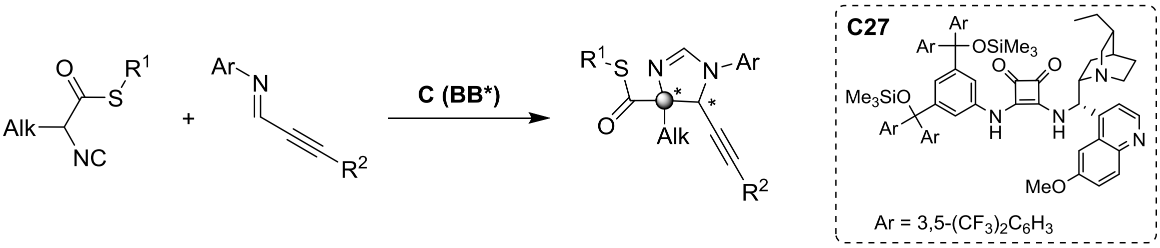
[231] a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410. b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735.

[232] a) Yoon, T.; Shair, M.D.; Danishefsky, S. J.; Shulte, G. K. *J. Org. Chem.* **1994**, *59*, 3752–3754. b) Jiang, B.; Xu, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2543–2546. c) Fleming, J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926–3927.

[233] For selected examples, see: a) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Limori, T. *J. Org. Chem.* **1987**, *52*, 3488–3489. b) Miyachi, N.; Kanda, F.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3511–3513. c) Hoepping, A.; Johnson George, K. M.; Flippen-Anderson, J.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 2064–2071.

[234] Swithenbank, C.; McNulty, P. J.; Viste, K. L. *Agric. Food. Chem.* **1971**, *19*, 417–423.

[235] For selected examples, see: a) Gupta, P.; Qiu, Y.; Adjei, A. *Int. J. Pharm.* **1997**, *147*, 207–218. b) Aungst, B. J.; Nguyen, N. H.; Taylor, N. J.; Bindra, D. S. *J. Pharm. Sci.* **2002**, *91*, 1390–1395. c) Suzuki, T.; Fujii, A.; Ohya, J.; Amano, Y.; Kitano, Y.; Abe, D.; Nakamura, H. *Cancer Sci.* **2007**, *98*, 1977–1984.

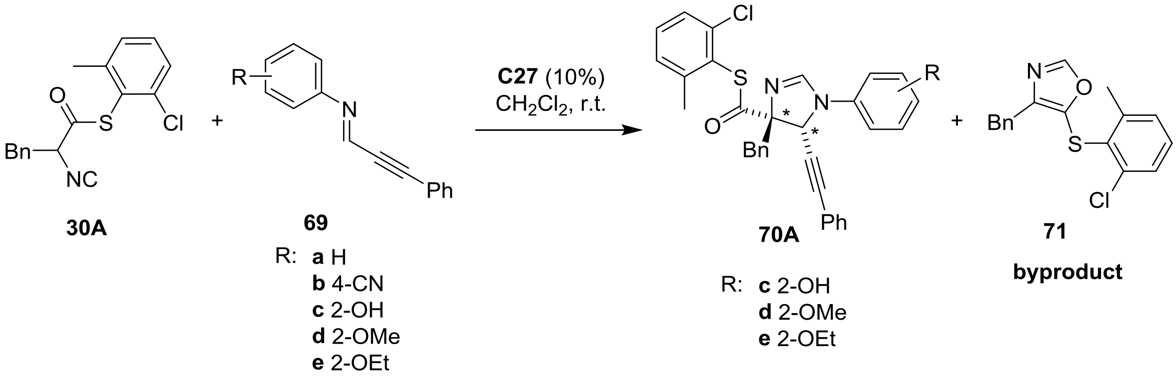


Scheme 63. Asymmetric Mannich reaction between α-alkyl isocyanothioacetates and *N*-aryl propargylic imines.

3.5.4.1. *Study of reaction conditions and scope*

The reaction study began testing different propargylic *N*-aryl imines with the aim to assess the impact of the *N*-aryl group on the reaction outcome (Table 37). The reaction of isocyanothioacetate **30A** with the *N*-phenyl or *para*-nitrile substituted *N*-aryl imines (**69a** and **69b**) in the presence of *gem,gem*-(bis)diaryl squaramide **C27** as catalyst gave no imidazoline (entry 1 and 2) and only byproduct **71** was observed in both cases. This byproduct, which is analogue to the previously identify **37A** (see Scheme 48, page 110), derived from the intramolecular hydroalkoxylation of the isonitrile group.

Table 37. Screenig of propargylic *N*-aryl imines.[a]



Entry	Imine	t (h)	Products	Products ratio	Yield of 70 (%)	dr	*ee* (%)
1	**69a**	20	**71**	0:100	--	--	--
2	**69b**	20	**71**	0:100	--	--	--
3	**69c**	16	**70Ac:71**	40:60	20	40:60	20/20
4	**69d**	48	**70Ad:71**	60:40	54	40:60	54/0
[5]	**69e**	20	messy	--	--	45:55	4/3

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio **30A**/imine/catalyst 1:1.5:0.1) at room temperature. The diastereo- and enantioselectivity determined by chiral HPLC on the reaction crude. The compound with the entry in brackets cannot be isolated and characterized..

Imine **69c**, bearing an *ortho*-OH group, demonstrated to be more reactive and led to the formation of the desired imidazoline product (entry 3). However, the stereoselectivity of the reaction and the yield of imidazoline **70Ac** were low. It should be noted that imine **69c** is of limited solubility in CH_2Cl_2, a circumstance that can justify the poor results. The higher reactivity of imine **69c** as compared to both **69a** and **69b** might be explained by assuming an intramolecular H-bond activation as depicted in Figure 33, model a. On the other hand, the corresponding methyl ether analog **69d** participated well in the Mannich reaction, affording adduct **70Ad** in higher yield and with lower amount of byproduct **71** formed (entry 4). This behaviour indicates that the methoxy group at the *ortho* position can also participate during the reaction probably by facilitating the substrate quelation through H-bonding (postulated in section b of the Figure 33). It should be noted that this imine was soluble in CH_2Cl_2 thus facilitating the reaction. Finally, the corresponding *ortho*-ethoxy imine **69e** was tested and although **71** was not observed, the stereoselectivity of the reaction crude was very bad and the reaction turned out to be very dirty (entry 5). Hence, the imines **69c** and **69d** were selected as the best to continue with the study.

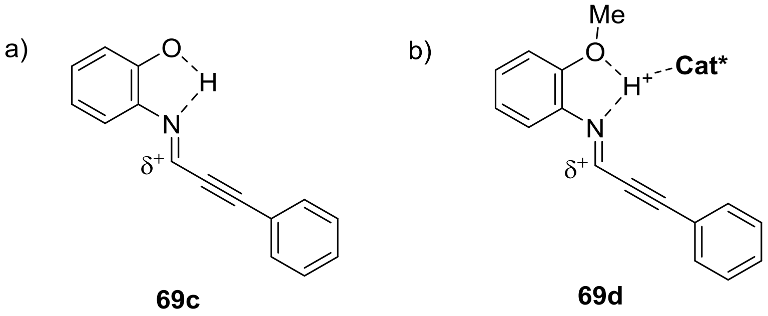
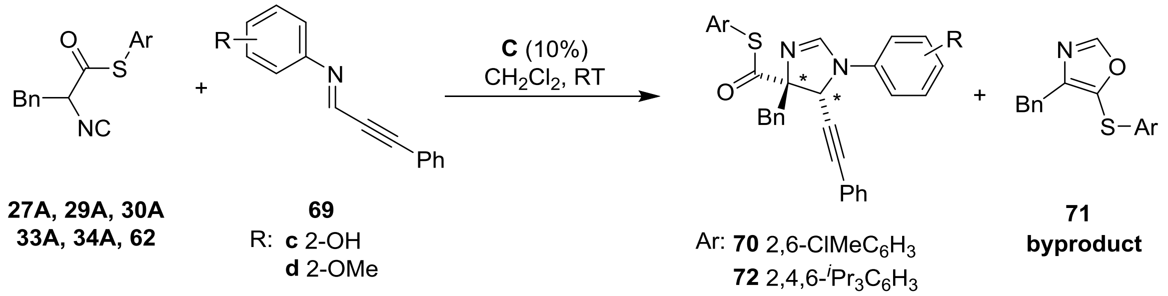
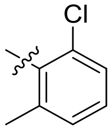
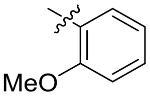
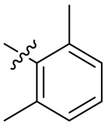
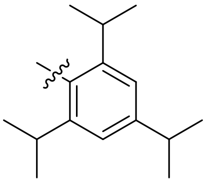


Figure 33. Speculative models to justify the increase of reactivity in **69c** and **69d** imines.

Subsequent attempts to improve the Mannich reaction outcome by varying the nature of the thioesters group as before were unsuccellful. Thus, as results in Table 38 show, while the phenyl oxoester isocyanide **62** gave no reaction and starting materials were recovered (entry 3), with the rest of the thioesters isocyanides the reactions were dirty (entry 4-9), besides that in most cases, the formation of by-product **71** was observed.

Table 38. Screenig of the thioester group.



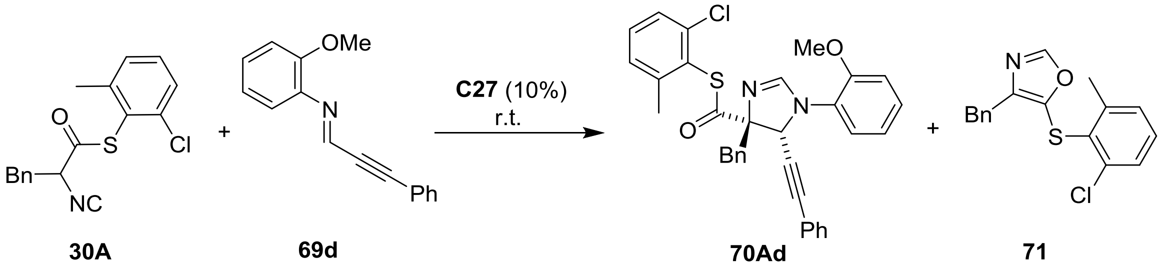
Entry	Isocyano thioacetate	Imine	C	t (h)	70:71	Yield of 70 (%)	dr	*ee* (%)
1	 **30A**	**69c**	**27**	16	60:40	20	40:60	20/20
2		**69d**	**27**	48	40:60	56	40:60	54/0
3	-OPh **62**	**69d**	**27**	72	Starting materials	--	--	--
4	-SPh **27A**	**69d**	**27**	4	0:100	--	--	--
5	 **34A**	**69c**	**27**	16	Messy + **71** traces	--	--	--
6			**5**	16	Messy + **71** traces	--	--	--
7	 **29A**	**69d**	**27**	16	Messy + **71** traces	--	--	--
8	 **33A**	**69c**	**5**	72	Messy + **72Ac** traces	--	--	--
9		**69d**	**27**	72	Messy + **72Ad** traces	--	--	--

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio isocyanothioacetate/imine/catalyst 1:1.5:0.1) at room temperature. The diastereo- and enantioselectivity determined by chiral HPLC on the reaction crude. The compound with the entry in brackets cannot be isolated and characterized.

Then, a brief survey of reaction conditions and solvent was carried out for the reaction between **30A** and **69d** catalyzed by **27**(Table 39). Surprisingly, we could observe by ^{1}H-

NMR that changing the solvent from CH_2Cl_2 to toluene the diastereoselectivity was reversed (entry 1 vs entry 2). On the other hand, employing toluene as solvent better enantiomeric excess was obtained for the major diastereomer (85% *ee*) but more byproduct was formed, probably because the reaction was slower (entry 2). To decrease the formation of byproduct, we concentrated the reaction (entry 3); and although under these conditions less amount of byproduct is observed at the end of the reaction, the stereochemical results were worse both diastereoselectively (65:35 dr) and enantioselectively (70% *ee* for the major diastereomer). Thus, we decided to carry out the reaction employing the imine as limiting reagent. In this way, we could obviate the formation of **71** and achieve a total consumption of **69b** to give the desired product. As observed in entry 4, following this strategy **70Ad** was obtained with the best results to date: 58% yield, moderated diastereoselectivity (82:18) and good enantiomeric excess (80%) for the major diastereomer. In all cases using toluene as solvent, the enantiopurity of the major diastereomer was much better than that for the minor isomer.

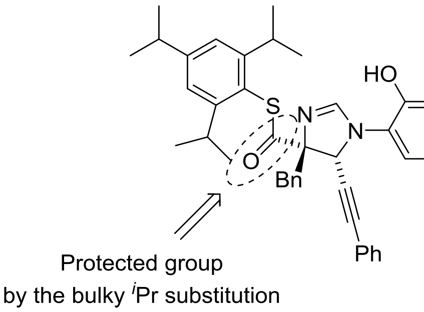
Table 39. Study of reaction conditions for the addition of **30A** to **69d**.



Entry	30A equiv.	69d equiv.	Solvent (mL/mmoL)	t (h)	70Ad:71	Yied of 70Ad (%)	dr	*ee* (%)
1	1	1.5	CH_2Cl_2 (2)	48	60:40	54	40:60	54/0
2	1	1.5	Tol. (2)	20	15:85	15	85:15	85/15
3	1	2	Tol. (1)	16	45:55	36	65:35	70/0
4	2	1	Tol. (2)	72	--	58	82:18	80/14

[a] Reaction conduced on a 0.1 mmol scale at room temperature. The diastereo- and enantioselectivity determined by chiral HPLC on the reaction crude.

Eventually, during the purification of the reaction crudes by column chromatography we observed that the resulting Mannich adducts were not completely stable to silica gel conditions. Indeed adduct **72Ac** with the bulky tris-isopropylphenyl group was the only fully stable congener (Figure 34). According to this observation, we believe that the low chemical stability of adducts may be one of the causes of the unsatisfactory yields.

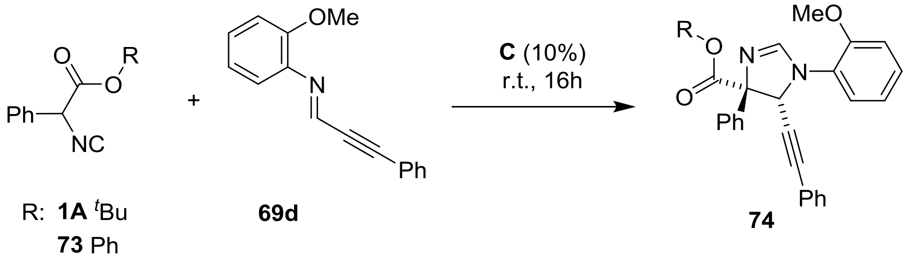


72Ac

Figure 34.

Then, the reaction was extended to the corresponding α-aryl isocyanoacetates (Table 40). The tert-butyl ester isocyanide **1A** was not sufficiently reactive (entry 1) and a phenylester group (more electron-withdrawing) was required for the reaction to proceed (entry 2). In addition, with **73** no *oxo*-cyclization byproducts were produced, although other uncharacterized byproducts were observed in small quantities, which caused the yields to be moderated. As it happened with the thioester analogues, the selectivity towards one or another diastereomer varied depending on the solvent used (entry 2 and 3). In addition, toluene turned out to be better than dichloromethane in enantioselectivity terms, at least as regards the major diastereoisomer (entry 2: 10% *ee* *vs* entry 3: 56% *ee*). In this instance, product **74** was perfectly stable to regular silica-gel column purification and in the reaction medium.

Table 40. Reaction conditions for the corresponding Mannich addition of α-aryl isocyanoacetates.



Entry	Isocyanoacetate	Cat. (mol%)	Solvent (mL/mmoL)	Yied 74 (%)	dr	*ee* (%)
1	**1A**	**5**	DCM (2)	--	--	--
2	**73**	**5**	DCM (2)	57	70:30	10:10
3	**73**	**27**	Tol. (2)	51	40:60	0:56

[a] Reaction conduced on a 0.1 mmol scale in 0.2 mL of solvent (molar ratio isocyanoacetate/imine/catalyst 1:1.5:0.1) at room temperature. The diastereo- and enantioselectivity determined by chiral HPLC on the reaction crude.

The absolute configuration of compound **74** was established by a single crystal X-ray analysis (Figure 35) and that for the remaining adducts including those derived from α-akyl isocyanothioacetates (**70** and **72**) was assumed based on a uniform mechanism.

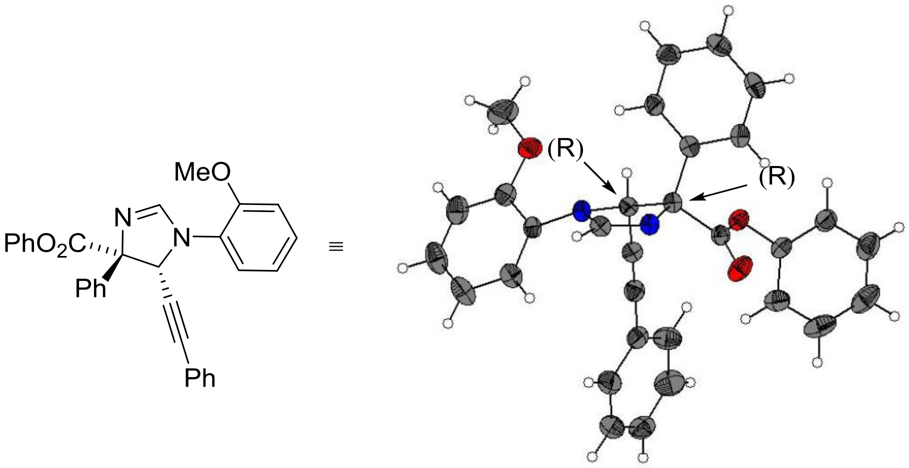


Figure 35. ORTEP diagram of compound **74**.

In summary, preliminary results indicate that these new squaramide catalysts can catalyze the Mannich reaction between α-aryl and α-alkyl isocyano(thio)acetates and propargyl *N*-aryl imines although with yet unsatisfactory stereoselectivities. There is additional room for further reaction optimization as the variability of the thioester or the N-aryl group.

Chapter 4

Conclusions

4. Conclusions

A divergent method for the asymmetric synthesis of α-quaternary prolines and derivatives has been developed starting from isocyano(thio)acetates as key reaction partners and under bifunctional Brønsted base/H-bond catalysis activation. The key step for the formation of the chiral common intermediate has been the enantioselective Michael addition of isocyano(thio)acetates to vinyl ketones, for which a new squaramide/tertiary amine catalyst has been designed, more effective than those known to date.

The lack of reactivity shown by α-alkyl isocyanoacetates in this Michael addition reaction has been solved by employing thioesters-isocyanides as activated isocyanoacetates equivalents. Following this strategy, the Michael adducts containing α-aryl and α-alkyl quaternary stereocenters have been obtained with excellent results.

Isocyanothioacetates had never been used as nucleophiles in catalytic asymmetric reaction; hence, their reaction with vinyl sulfones and imines with different reactivity has been described for the first time. Preliminary experiments show their generality and synthetic utility to expand the inherently difficult α-reactivity of the parent *oxo*ester.

Chapter 5

Experimental section

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5. Experimental section

5.1. Material and Techniques

5.1.1. Reagents and solvents

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

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

Anhydrous solvents were dried following established procedures.[236] Dichloromethane was dried over CaH_2, diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder 150 mesh, pore size 58 Å, basic Sigma Aldrich) columns.

5.1.2. General experimental

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

Heat requiring reactions were performed using a hotplate with a sand bath and 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-100, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller. For the complete removal of solvents vacuum pump Telstar Top-3 ($P \approx 0.5$ mmHg) was employed.

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

5.1.3. Chromatography

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

Purification by column chromatography was performed on 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.

5.1.4. Optical rotation

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

5.1.5. Melting points

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

5.1.6. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer, Bruker 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) Varian 400 MR (400 MHz for ^{1}H, 100 MHz for ^{13}C) or Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (HZ).

MestrReNova Mnova 8.1 program was used to process and edit the registered spectra.

5.1.7. Mass spectra

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

5.1.8. Infrared spectra

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

5.1.9. X-Ray diffraction analysis

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

5.2. Preparation of catalysts

(DHQ)$_2$Pyr (**C1**) was purchased from Sigma Aldrich, quinine (**C2**) was purchased from Alfa Aesar and catalysts **C3**,[237] **C4**,[238] **C5**,[239] **C6**,[240] **C7**,[241] **C9**,[242] **C10**,[243] **C11**,[243] **C12**[244] and **C13**[244] were prepared following the procedures described in the literature. Catalyst **C8** was prepared starting from (*S*)-(−)-3-aminoquinuclidine dihydrochloride and the corresponding squaric amide-ester. Catalysts **C14-C26** were prepared starting from

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[237] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

[238] Adapted from: 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. b) Diosdado, S. *Adición de Fosfonoacetatos, Malonatos y Sulfonilacetonitrilos a Iminas. Desarrollo de Bases de Brønsted Bifuncionales, Ureidopétido-Cinchona* EHU/UPV; Doctoral thesis; 2013; pp 186–201.

[239] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

[240] Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.

[241] Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241–1246.

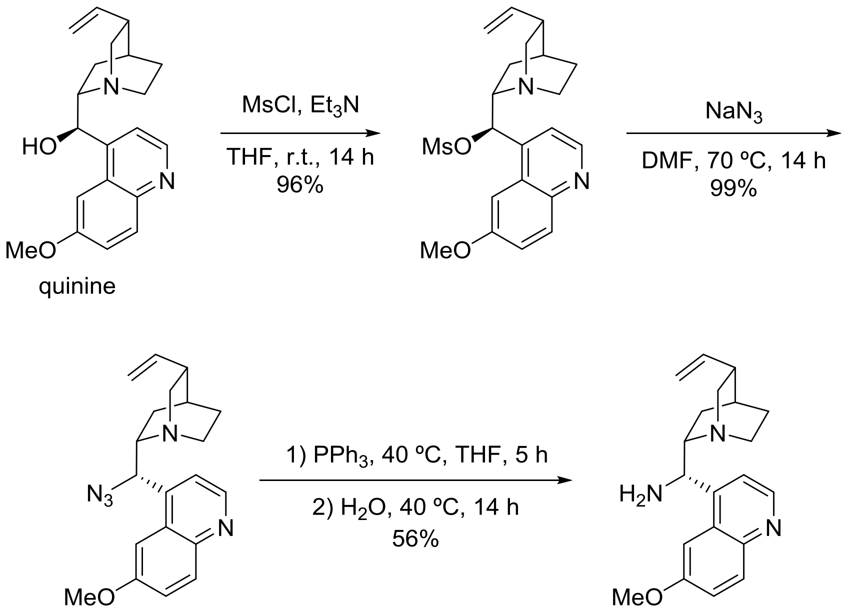
[242] See ref. 41, Chapter 1, page 13.

[243] a) See ref. 156, Chapter 2, page 65. b) Izquierdo, J. *New Approaches to Optically Active 2-tert-Alkyl Azaaryl Compounds and 5,5-Disubstituted Hydantoyns* EHU/UPV; Doctoral thesis; 2018; pp 149–156.

[244] a) See ref. 157a, Chapter 2, page 65. b) Etxabe, J. *Catalytic Asymmetric Synthesis of α,α-Disubtituted α-Thio and α-Amino Acid Derivatives* EHU/UPV; Doctoral thesis; 2016; pp 259–261.

(*R,R*)-9-deoxy-9-epiaminoquinine or (*R,R)*-9-amino-(9-deoxy)epihydroquinine and the corresponding squaric amide-ester.

Preparation of 9-amino-(9-deoxy)epiquinine[245]



1st step:[246] 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 °C 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 mesylated product with 96% yield, which was used in the next step without further purification.

2nd step:[247] The crude mesylated product (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 70 °C 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

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[245] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

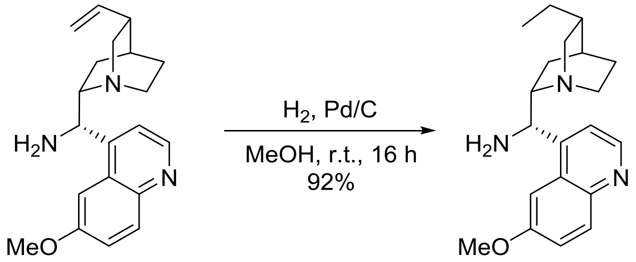
[246] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.

[247] Adapted from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality*, **2003**, *15*, 127–134.

crude azide derived product in quantitative yield which was used in the next step without further purification.

3rd step:[247] The azide derived 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 °C and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 °C. 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 °C 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: 56% (8.7 g, 26.9 mmol). All data were consistent with those previously reported. ^{1}H 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).

Preparation of 9-amino-(9-deoxy)epihydroquinine[248]



10% Palladium on carbon (10% w/w, 0.32 g) was added to a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 3.2 g, 10 mmol) in methanol (10 mL). The reaction mixture was stirred overnight under H_2 atmosphere, and then was filtered over celite and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*hydroquinine as a yellow viscous oil. Yield: 92% (3.0 g, 9.2 mmol). All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CD_3OD), δ: 8.69 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.69 (brs, 1H), 7.61 (d, *J* = 4.7 Hz, 1H,), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.00 (s, 3H), 3.36–3.24 (m, 1H), 3.28 (dd, *J* = 13.6, 9.9 Hz, 1H), 3.16 (q, *J* = 10.7 Hz, 1H), 2.79 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.56 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 1.62–1.58 (m, 1H), 1.60 (dd, *J* = 13.3, 10.4 Hz, 1H), 1.58–1.47 (m, 4H), 1.37–1.34 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

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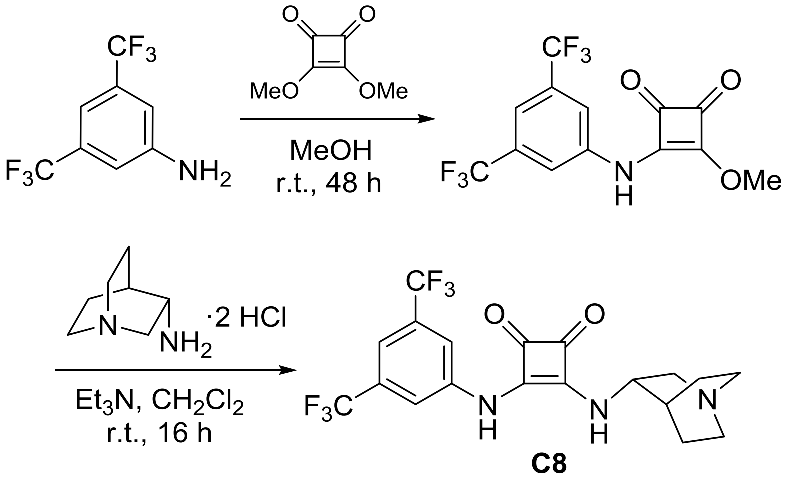
[248] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A. Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

5.2.1. Preparation of catalyst C8

Catalyst **C8** was prepared according to the following procedure:



C8

1st step:[249] To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 1.42 g, 10 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1 equiv., 1.56 mL, 10 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vacuum to give title compound as a white solid. Yield: 66% (2.25 g, 6.6 mmol). M.p. = 179–181 °C. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

2nd step: To a suspension of the corresponding squaric ester monoamide prepared above (3.6 mmol, 1.2 equiv.) in CH_2Cl_2 (6 mL) was added (*S*)-(−)-3-aminoquinuclidine dihydrochloride (597 mg, 3.0 mmol, 1 equiv.) and triethylamine (0.3 mL, 6.6 mmol, 2.2 equiv.). The reaction mixture was stirred for 16 h at room temperature. Then, CH_2Cl_2 (15 mL) was added and the mixture was washed with water (3 x 10 mL), dried with anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was submitted to purification by silica gel column chromatography (CH_2Cl_2/MeOH, 95:5), affording the catalyst **C8** as white solid (936 mg, 2.16 mmol, 72%). ^{1}H NMR (300 MHz, MeOD) δ 8.09 (s, 2H), 7.51 (s, 1H), 4.47 – 4.30 (m, 1H), 3.51 (ddd, *J* = 14.3, 9.6, 2.1 Hz, 1H), 3.14 – 2.77 (m, 5H), 2.17 – 2.10 (m, 1H), 2.10 – 1.96 (m, 1H), 1.95 – 1.76 (m, 2H), 1.76 – 1.61 (m, 1H). ^{13}C NMR (75 MHz, MeOD) δ 185.5, 182.3, 171.1, 164.6, 142.6, 133.8 (q), 124.3 (q), 119.2, 116.4, 55.9, 52.3, 47.9, 47.1, 28.6, 25.4, 19.6.

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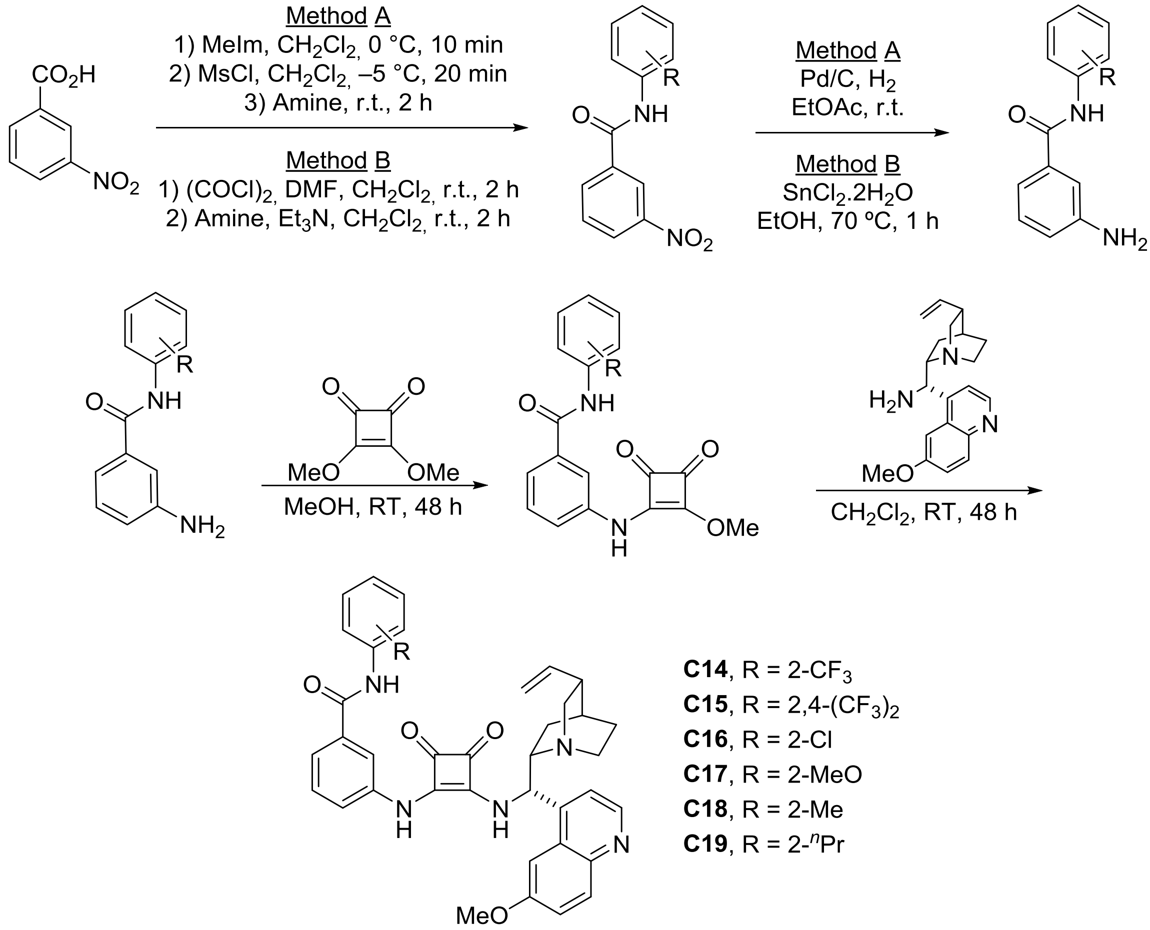
[249] Yang, W.; Du, D. M. *Org. Lett.*, **2010**, *12*, 5450–5453.

5.2.2. Preparation of catalysts C14-C19

Amide group-bearing squaramide-based catalysts **C14**-**C19** were prepared for the first time adapting the previously described procedure for **C12**-**C13**.[250]



C14, R = 2-CF_3
C15, R = 2,4-$(CF_3)_2$
C16, R = 2-Cl
C17, R = 2-MeO
C18, R = 2-Me
C19, R = 2-^{n}Pr

1st step: METHOD A:[251] 1-Methylimidazole (2.2 mL, 27.6 mmol, 2.5 equiv.) was added to the 3-nitrobenzoic acid (3 g, 11 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.3 mL, 16.5 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, the corresponding aniline derivative (11 mmol, 1 equiv) was added. Then the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, H_2O (100 mL) was added to the mixture and a solid precipitated, which was solved with ethyl acetate (100 mL). The organic layer was washed with brine (3 × 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.

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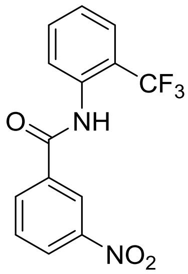
[250] See ref. 244, page 157.
[251] Adapted from: Mao, L.; Wang, Z.; Li, Y.; Han, X.; Zhou, W. *Synlett* **2011**, *1*, 129–133.

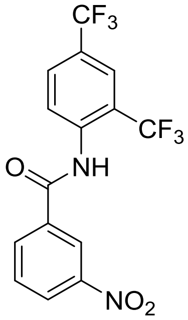
METHOD B: Oxalyl chloride (0.52 mL, 6 mmol, 1.2 equiv.) was added to a suspension of the corresponding 3-nitrobenzoic acid (836 mg, 5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen atmosphere. DMF (1 drop) was then added and the mixture was allowed to stir at room temperature for 2 h, observing the complete dissolution of the solid. The resulting crude was concentrated under reduced pressure and slowly added to a solution of the corresponding aniline derivative (10 mmol, 2 equiv.) and triethylamine (0.84 mL, 6 mmol, 1.2 equiv.) in dichloromethane (2.5 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and CH_2Cl_2 (30 mL) was added. The organic phase was washed with aqueous HCl (1 M) (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure affording the desired amide.

N-(2-(Trifluoromethyl)phenyl)-3-nitrobenzamide



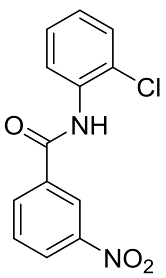
Yield: 56% (method A).^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.33 (t, *J* = 2.0 Hz, 1H), 8.02 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1H), 7.93 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.48 – 7.27 (m, 3H), 7.13 (t, *J* = 7.1 Hz, 2H).

N-(2,4-bis(Trifluoromethyl)phenyl)-3-nitrobenzamide



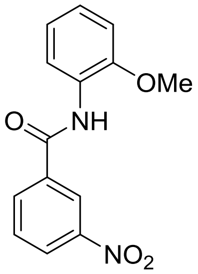
Yield: 50% (method B).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (t, *J* = 2.0 Hz, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 8.54 – 8.46 (m, 1H), 8.36 (s, 1H), 8.19 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.78 (t, *J* = 8.0 Hz, 1H).

N-(2-Chlorophenyl)-3-nitrobenzamide



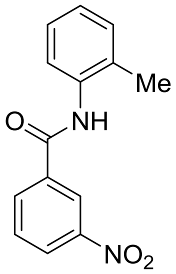
Yield: Quantit (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (t, *J* = 2.0 Hz, 1H), 8.54 – 8.49 (m, 1H), 8.48 – 8.42 (m, 2H), 8.26 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.38 (td, *J* = 8.4, 7.9, 1.5 Hz, 1H), 7.15 (td, *J* = 7.8, 1.6 Hz, 1H).

N-(2-Methoxyphenyl)-3-nitrobenzamide



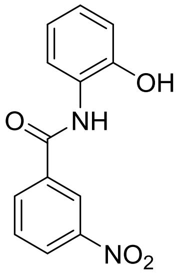
Yield: 70% (method A). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.73 (t, *J* = 2.0 Hz, 1H), 8.57 (s, 1H), 8.49 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.41 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H), 8.25 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.14 (td, *J* = 7.8, 1.7 Hz, 1H), 7.05 (td, *J* = 7.8, 1.5 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.5 Hz, 1H), 3.96 (s, 3H).

3-Nitro-N-(o-tolyl)benzamide



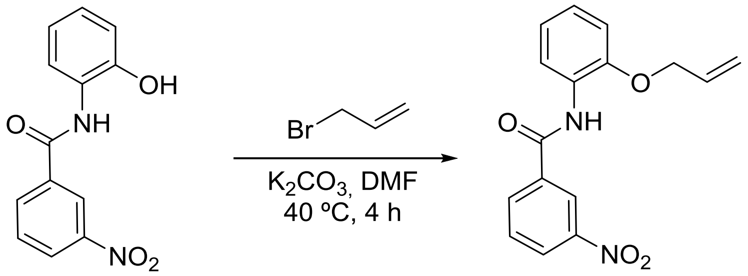
Yield: Quantit (method B). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.75 (t, *J* = 2.0 Hz, 1H), 8.46 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.36 – 7.30 (m, 2H), 7.27 – 7.17 (m, 1H), 2.40 (s, 3H).

N-(2-Hydroxyphenyl)-3-nitrobenzamide



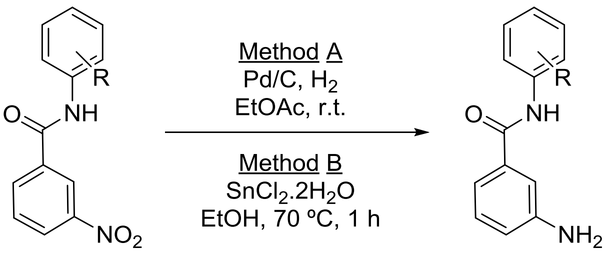
Yield: 40% (method B). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.83 – 8.70 (m, 1H), 8.48 – 8.34 (m, 2H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.06 (td, *J* = 7.7, 1.7 Hz, 1H), 6.93 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.88 – 6.76 (m, 1H).

N-(2-(Allyloxy)phenyl)-3-nitrobenzamide



To a solution of nitrobenzamide (516 mg, 2 mmol, 1 equiv.) and K$_2$CO$_3$ (836 mg, 6 mmol, 3 equiv.) in DMF (5 mL) was added allyl bromide (0.44 mL, 5 mmol, 2.5 equiv.). After 4 h at room temperature, the reaction mixture was filtered over celita, and EtOAc (10 mL) was added. The organic phase was washed with brine (10 × 5 mL), dried over MgSO$_4$ and the solvent was eliminated under reduced pressure affording the desired product. Yield: 84%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.76 (t, *J* = 2.1 Hz, 1H), 8.49 – 8.33 (m, 2H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.22 (ddd, *J* = 8.7, 7.4, 1.7 Hz, 1H), 7.11 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.99 (td, *J* = 7.6, 1.4 Hz, 1H), 6.14 – 5.97 (m, 1H), 5.42 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.23 (dq, *J* = 10.6, 1.6 Hz, 1H), 4.64 (dt, *J* = 5.0, 1.7 Hz, 2H).

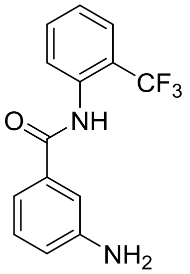
2nd step:



METHOD A: To a solution of the previous 3-nitrobenzamide (5 mmol) in EtOAc (15 mL) under inert atmosphere, Pd/C was added (Pd 10% in activated carbon, 10% in weight). In the cases that benzamide was insoluble, DMF was added until complete dissolution of the solid. The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. After that the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product, which was used for the preparation of the corresponding squaric ester monoamide without further purification.

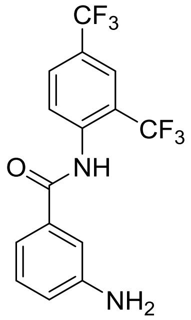
METHOD B: To a solution of the previous 3-nitrobenzamide (1 mmol) in EtOH (2 mL) $SnCl_2{\times}H_2O$ (1.13 g, 5 mmol, 5 equiv.) was added, and the reaction mixture was refluxed for 6 h. After cooling to room temperature, a saturated solution of sodium bicarbonate (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the hydrogenated product, which was used for the preparation of the corresponding squaric ester monoamide without further purification.

3-Amino-N-(2-(trifluoromethyl)phenyl)benzamide



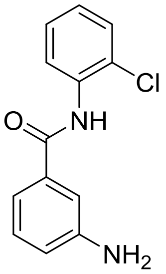
Yield: 75% (method A). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.3 Hz, 1H), 8.19 (s, 1H), 7.74 – 7.54 (m, 2H), 7.32 – 7.26 (m, 2H), 7.24 – 7.20 (m, 1H), 7.16 (ddt, *J* = 7.6, 1.5, 0.8 Hz, 1H), 6.87 (ddt, *J* = 7.9, 2.4, 0.8 Hz, 1H), 3.88 (brs, 2H).

3-Amino-N-(2,4-bis(trifluoromethyl)phenyl)benzamide



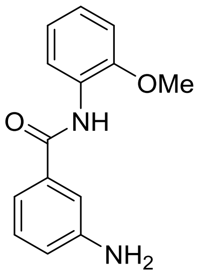
Yield: 56% (method A).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.7 Hz, 1H), 8.36 (s, 1H), 7.93 – 7.81 (m, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 2.1 Hz, 1H), 7.15 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H), 6.90 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H), 3.90 (brs, 2H).

3-Amino-N-(2-chlorophenyl)benzamide



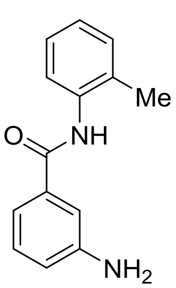
Yield: 88% (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.40 (s, 1H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.26 – 7.20 (m, 2H), 7.07 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 6.87 (ddd, *J* = 7.7, 2.4, 1.3 Hz, 1H), 3.87 (brs, 2H).

3-Amino-N-(2-methoxyphenyl)benzamide



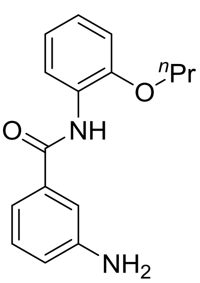
Yield: Quantit (method A). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 7.9, 2.0 Hz, 2H), 7.28 – 7.17 (m, 3H), 7.13 – 6.97 (m, 2H), 6.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.84 (ddd, *J* = 7.6, 2.4, 1.2 Hz, 1H), 3.92 (s, 3H), 3.84 (brs, 2H).

3-Amino-N-(o-tolyl)benzamide



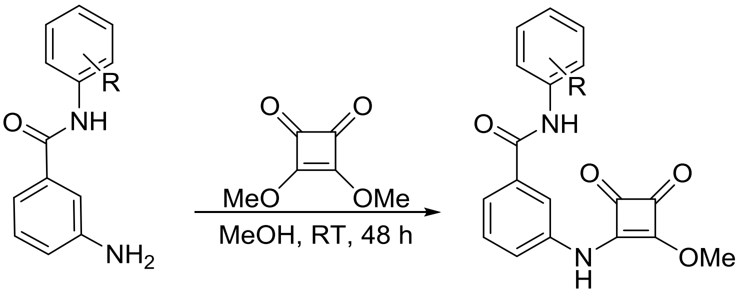
Yield: 93% (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 1H), 7.67 (s, 1H), 7.36 – 7.10 (m, 6H), 6.88 (ddd, *J* = 7.8, 2.5, 1.1 Hz, 1H), 3.88 (brs, 2H), 2.37 (s, 3H).

3-Amino-N-(2-butoxyphenyl)benzamide



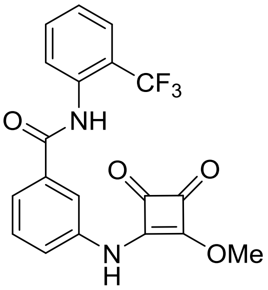
Yield: Quantit. (method A). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.53 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.20 – 7.13 (m, 1H), 7.09 – 6.96 (m, 2H), 6.90 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.84 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 1H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.83 (brs, 2H), 1.89 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

3rd step :



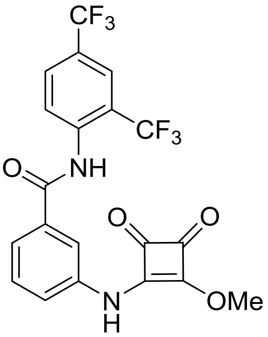
To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (308 mg, 2.2 mmol, 1.1 equiv.) in MeOH (8 mL) was added the corresponding amine (2.0 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature until the amine is consumed. The formed precipitate was filtered and in few cases, the solid was submitted to purification by silica gel column chromatography (CH_2Cl_2/MeOH, 95:5), affording the the squaric ester monoamide as pale yellow solid.

3-((2-Methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(2-(trifluoromethyl)phenyl) benzamide



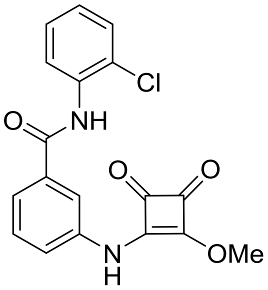
Yield: 80%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.78 (s, 1H), 9.07 (s, 1H), 8.05 (t, *J* = 2.0 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.83 – 7.70 (m, 4H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 4.47 (s, 3H).

N-(2,4-bis(Trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino) benzamide



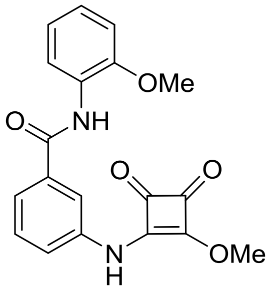
Yield: 82%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.35 (s, 1H), 8.20 – 8.10 (m, 2H), 7.91 – 7.82 (m, 2H), 7.70 (dt, *J* = 7.3, 1.5 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.58 – 7.51 (m, 1H), 4.39 (s, 3H).

N-(2-Chlorophenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide



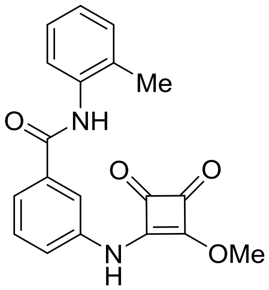
Yield: 73%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.78 (s, 1H), 9.02 (s, 1H), 8.25 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.17 – 8.10 (m, 1H), 7.82 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.75 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.42 (td, *J* = 7.7, 1.6 Hz, 1H), 7.30 – 7.19 (m, 1H), 4.50 (s, 3H).

3-((2-Methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(2-methoxyphenyl)benzamide



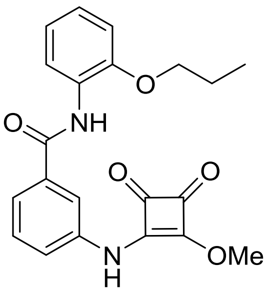
Yield: 72%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.34 (s, 1H), 7.91 (t, *J* = 1.8 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.69 (dt, *J* = 7.3, 1.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.18 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.02 – 6.94 (m, 1H), 4.40 (s, 3H), 3.85 (s, 3H).

3-((2-Methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(o-tolyl)benzamide



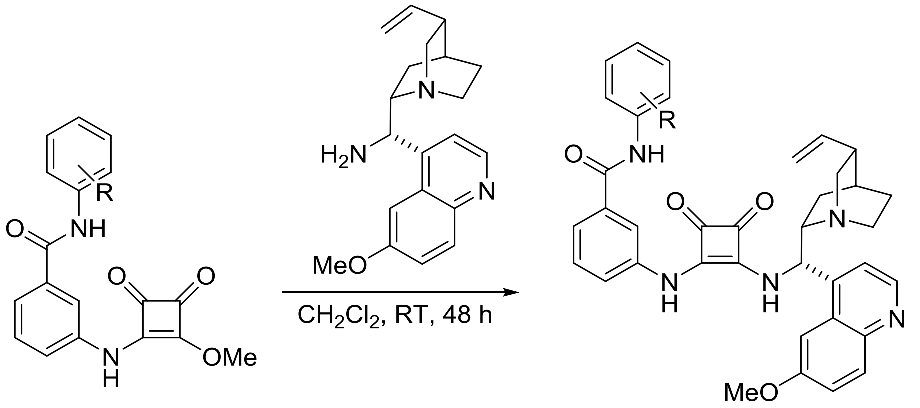
Yield: 70%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.72 (s, 1H), 8.95 (s, 1H), 8.14 – 8.07 (m, 1H), 7.78 (dt, J = 7.8, 1.3 Hz, 1H), 7.69 (ddd, J = 8.0, 2.3, 1.1 Hz, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.32 – 7.18 (m, 2H), 7.14 (td, J = 7.4, 1.5 Hz, 1H), 4.47 (s, 3H), 2.37 (s, 3H).

3-((2-Methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(2-propoxyphenyl)benzamide



Yield: 76%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.28 (s, 1H), 7.89 (t, J = 1.9 Hz, 1H), 7.86 (s, 1H), 7.66 (dt, J = 7.0, 1.7 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.22 – 7.05 (m, 2H), 6.96 (td, J = 7.5, 1.6 Hz, 1H), 4.39 (s, 3H), 4.01 (t, J = 6.5 Hz, 2H), 1.86 – 1.67 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

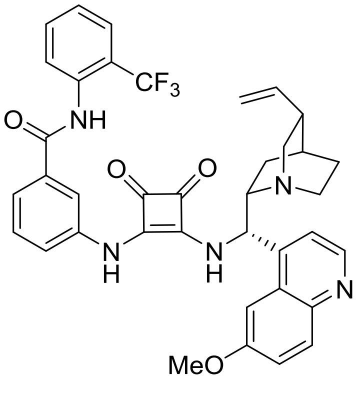
4rd step :



C14, R = 2-CF_3
C15, R = 2,4-$(CF_3)_2$
C16, R = 2-Cl
C17, R = 2-MeO
C18, R = 2-Me
C19, R = 2-^{n}PrO

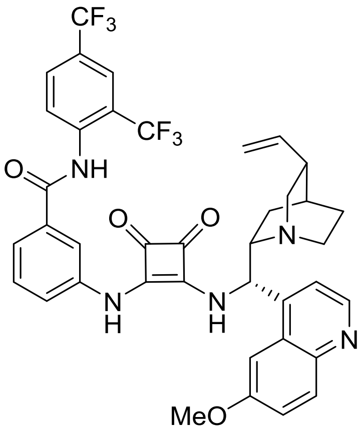
To a suspension of the corresponding squaric ester monoamide prepared above (1.0 mmol, 1 equiv.) in CH_2Cl_2 (8 mL) was added 9-amino-(9-deoxy)*epi*quinine (323 mg, 1.0 mmol, 1 equiv.) and the reaction mixture was stirred for 48 h at room temperature. Then, the solvent was evaporated, and the product submitted to purification by silica gel column chromatography (CH_2Cl_2/MeOH, 95:5), affording the corresponding squaramide product.

3-((2-(((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl) amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(2-(trifluoromethyl)phenyl)benzamide (C14)



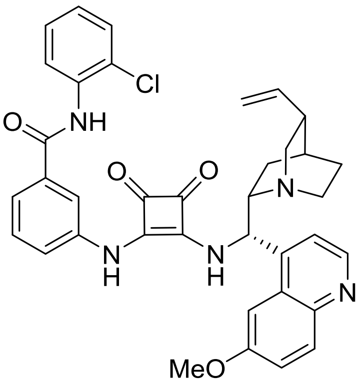
White solid (532 mg, 0.78 mmol, 78%). M.p.= 180-190 °C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.02 (s, 1H), 8.74 (d, *J* = 4.5 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.92 (td, *J* = 6.1, 3.5 Hz, 2H), 7.82 – 7.75 (m, 1H), 7.71 (dd, *J* = 7.9, 2.6 Hz, 2H), 7.68 – 7.60 (m, 2H), 7.49 (td, *J* = 7.8, 2.3 Hz, 2H), 7.41 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.25 (s, 1H), 5.93 (ddd, *J* = 17.6, 10.3, 7.7 Hz, 1H), 5.09 – 4.89 (m, 2H), 4.03 (s, 3H), 3.70 – 3.43 (m, 2H), 3.28 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.44 – 2.29 (m, 1H), 1.74 – 1.52 (m, 4H), 0.94 – 0.78 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 184.2, 179.7, 168.2, 165.9, 163.6, 157.9, 147.8, 144.3, 143.1, 142.1, 139.1, 135.6, 135.2, 133.1, 131.5, 131.1, 129.5, 127.4, 126.5, 126.1, 124.9, 122.2, 121.9, 121.5, 121.3, 119.5, 117.4, 114.3, 101.5, 58.9, 55.7, 55.6, 53.6, 39.0, 38.9, 27.3, 27.0, 26.0. UPLC-DAD-QTOF: $C_{38}H_{35}N_5O_4F_3$ $[M+H]^+$ calcd.: 682.2641, found: 682.2658.

N-(2,4-bis(Trifluoromethyl)phenyl)-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C15)



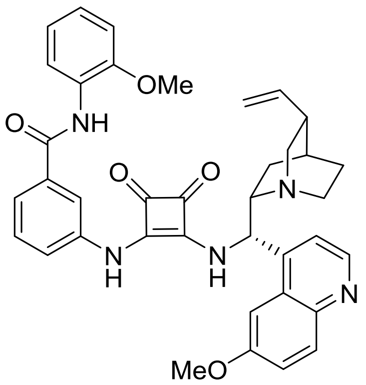
White solid (532 mg, 0.71 mmol, 71%). M.p.= 195-197 °C ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.65 (d, *J* = 4.5 Hz, 1H), 8.37 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.87 (t, *J* = 3.4 Hz, 1H), 7.84 – 7.72 (m, 3H), 7.59 – 7.50 (m, 1H), 7.36 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.33 – 7.21 (m, 2H), 7.21 – 7.09 (m, 1H), 6.25 (s, 1H), 5.94 – 5.69 (m, 1H), 5.18 – 4.92 (m, 2H), 3.98 (s, 3H), 3.93 – 3.73 (m, 1H), 3.76 – 3.53 (m, 1H), 3.44 – 3.17 (m, 1H), 3.09 – 2.72 (m, 2H), 2.42 (s, 1H), 1.94 – 1.49 (m, 4H), 0.99 – 0.79 (m, 1H). ^{13}C NMR (75 MHz, CD_2Cl2) δ 184.3, 181.6, 168.9, 165.2, 164.3, 159.0, 147.8, 145.1, 142.7, 140.1, 139.5, 138.9, 134.8, 131.9, 130.1, 130.0, 128.0, 126.7 (q), 125.4, 125.2, 124.0, 123.9, 122.8, 122.7, 121.8, 121.4, 118.0, 115.7, 101.5, 60.5, 56.3, 55.60, 4.38, 38.8, 27.5, 26.8, 25.6. UPLC-DAD-QTOF: $C_{39}H_{34}N_5O_4F_6$ $[M+H]^+$ calcd.: 750.2515, found: 750.2518.

N-(2-Chlorophenyl)-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinyl quinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C16)



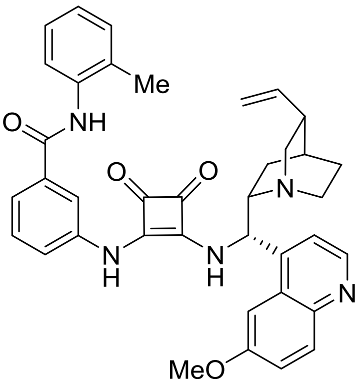
Yellow solid (305 mg, 0.47 mmol, 47%). M.p.= 183-189 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.74 (d, *J* = 4.5 Hz, 1H), 8.22 (dt, *J* = 8.2, 2.5 Hz, 1H), 8.07 – 7.91 (m, 2H), 7.65 (q, *J* = 4.1 Hz, 3H), 7.55 – 7.33 (m, 3H), 7.21 (td, *J* = 7.7, 1.6 Hz, 1H), 5.94 (ddd, *J* = 17.6, 10.2, 7.4 Hz, 1H), 5.13 – 4.92 (m, 2H), 4.03 (s, 3H), 3.83 – 3.67 (m, 1H), 3.58 (d, *J* = 12.1 Hz, 1H), 3.46 – 3.24 (m, 1H), 2.96 – 2.74 (m, 1H), 2.41 (s, 1H), 1.83 – 1.57 (m, 4H), 0.96 – 0.83 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.3, 179.7, 168.2, 165.1, 163.8, 157.8, 147.8, 144.2, 143.3, 141.8, 139.4, 135.1, 134.9, 131.5, 129.5, 129.3, 128.8, 127.7, 127.4, 127.2, 121.9, 121.5, 121.4, 120.2, 117.6, 114.4, 101.4, 58.9, 55.7, 55.4, 54.8, 39.1, 38.7, 29.6, 27.2, 27.1, 25.8. UPLC-DAD-QTOF: $C_{37}H_{35}N_5O_4Cl$ $[M+H]^+$ calcd.: 648.2378, found: 648,2380.

N-(2-Methoxyphenyl)-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinyl quinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C17)



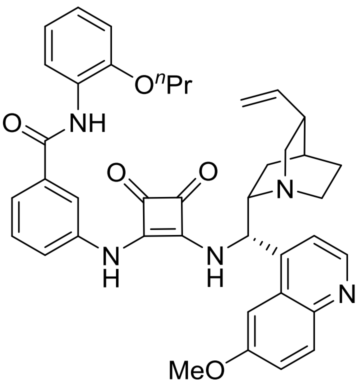
Yellow solid (412 mg, 0.64 mmol, 64%). M.p.= 188-198 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 – 9.90 (m, 1H), 9.30 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.39 – 8.27 (m, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.77 (s, 1H), 7.72 – 7.63 (m, 2H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.19 – 7.12 (m, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 5.99 (tt, *J* = 17.4, 9.3 Hz, 2H), 5.01 (dd, *J* = 22.3, 13.7 Hz, 2H), 3.95 (s, 3H), 3.82 (s, 3H), 3.55 (s, 2H), 3.60 – 3.39 (m, 2H), 3.29 – 3.11 (m, 1H), 2.83 – 2.60 (m, 3H), 2.30 (d, *J* = 10.4 Hz, 1H), 1.70 – 1.40 (m, 4H), 0.75 – 0.59 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.1, 179.9, 168.1, 164.4, 163.6, 157.9, 150.8, 147.8, 144.3, 143.0, 142.0, 139.0, 135.7, 131.5, 129.6, 127.4, 126.8, 125.4, 123.2, 121.9, 121.5, 121.0, 120.2, 117.1, 114.4, 111.3, 101.5, 58.9, 55.7, 55.7, 55.5, 53.1, 38.9, 38.9, 27.2, 25.9. UPLC-DAD-QTOF: $C_{38}H_{38}N_5O_5$ $[M+H]^+$ calcd.: 644.2873, found: 644.2888.

3-((2-(((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl) amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(o-tolyl)benzamide (C18)



Pale yellow solid (389 mg, 0.62 mmol, 62%). M.p.= 185-200 °C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.93 (s, 1H), 8.73 (d, *J* = 4.6 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.99 (dd, *J* = 9.2, 1.9 Hz, 1H), 7.93 (d, *J* = 2.7 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.69 – 7.63 (m, 2H), 7.63 (s, 1H), 7.46 – 7.38 (m, 2H), 7.30 – 7.16 (m, 2H), 7.16 – 7.09 (m, 1H), 6.29 (d, *J* = 10.8 Hz, 1H), 5.92 (ddd, *J* = 17.5, 10.3, 7.6 Hz, 1H), 5.12 – 4.90 (m, 2H), 4.03 (s, 3H), 3.80 – 3.62 (m, 1H), 3.62 – 3.47 (m, 1H), 3.31 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.79 – 2.68 (m, 2H), 2.45 – 2.36 (m, 1H), 2.35 (s, 3H), 1.78 – 1.53 (m, 3H), 0.96 – 0.81 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.1, 179.8, 168.1, 164.9, 163.6, 157.8, 147.7, 144.3, 143.0, 142.0, 138.9, 136.3, 135.8, 133.4, 131.5, 130.3, 129.5, 127.4, 126.3, 126.0, 121.9, 121.6, 120.9, 119.7, 117.5, 114.4, 101.5, 59.7, 58.9, 55.7, 55.6, 54.9, 27.2, 26.0, 20.7, 17.8, 14.1. UPLC-DAD-QTOF: $C_{42}H_{22}NO_3F_{24}$ [M+H]$^+$ calcd.: 628.2924, found: 628.2919.

3-((2-(((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl) amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-N-(2-propoxyphenyl)benzamide(C19)

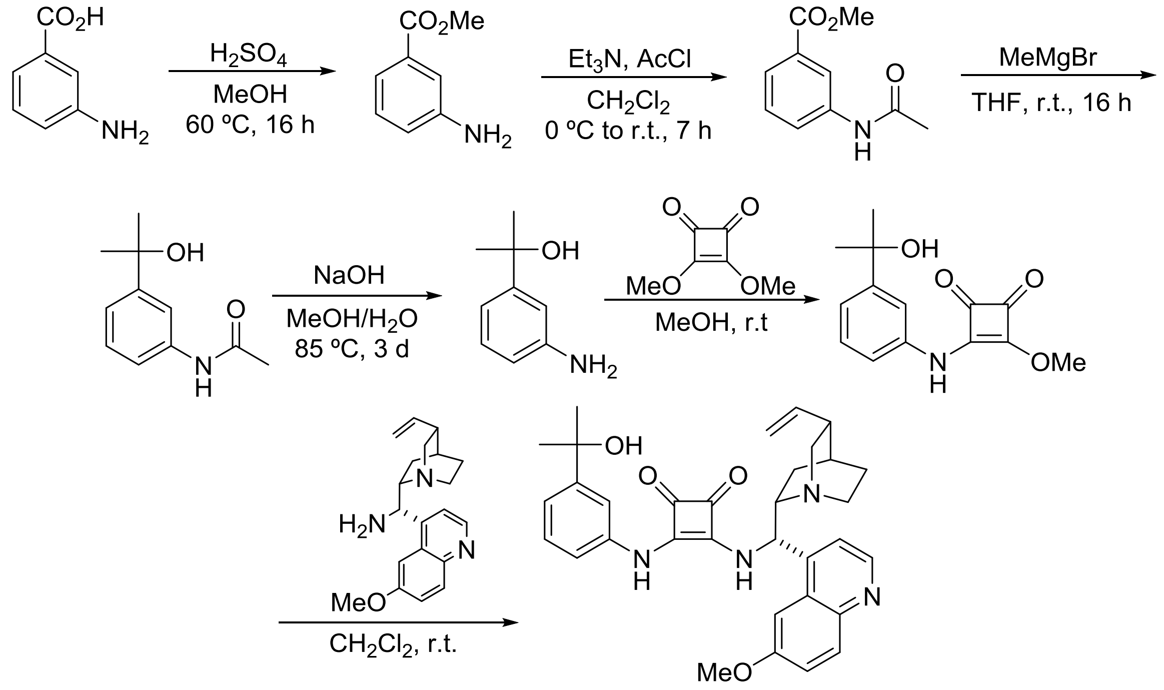


Orange solid (417 mg, 0.62 mmol, 62%). M.p.= 166-172 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.22 (s, 1H), 8.81 (d, *J* = 4.5 Hz, 1H), 8.36 – 8.21 (m, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.82 – 7.75 (m, 1H), 7.71 – 7.61 (m, 2H), 7.59 – 7.53 (m, 1H), 7.52 – 7.41 (m, 2H), 7.13 (td, *J* = 7.7, 7.3, 1.7 Hz, 1H), 7.05 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.94 (td, *J* = 7.6, 1.5 Hz, 1H), 6.18 – 5.89 (m, 2H), 5.12 – 4.93 (m, 2H), 4.05 – 3.92 (m, 6H), 3.60 – 3.48 (m, 1H), 3.29 – 3.14 (m, 1H), 2.82 – 2.62 (m, 2H), 2.39 – 2.21 (m, 1H), 1.72 (h, *J* = 7.1 Hz, 3H), 1.65 – 1.45 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.78 – 0.61 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.1, 179.9, 168.1, 164.3, 163.6, 157.9, 150.1, 147.8, 144.3, 143.0, 142.0, 139.0, 135.8, 131.5, 129.7, 127.4, 127.0, 125.4, 123.1, 121.9, 121.3, 121.1, 120.2, 117.1, 114.4, 112.2, 101.5, 69.7, 58.9, 55.7, 55.5, 53.4, 38.7, 38.2, 27.3, 27.3, 26.0, 21.9, 10.3. UPLC-DAD-QTOF: $C_{40}H_{42}N_5O_5$ [M+H]$^+$ calcd.: 672.3115, found: 672.3108.

5.2.3. Preparation of catalysts C20-C27

New catalysts **C20**-**C27** were synthesised as follows:

*5.2.3.1. Preparation of catalyst **C20***



C20

1st step: To a solution 3-aminobenzoic acid (1.37 g, 10 mmol, 1.0 equiv.) in MeOH (10 mL) was added concentrated H_2SO_4 (1.5 mL, 40 mmol, 4.0 equiv.). The reaction mixture was stirred for 16 h and then, the solvent was removed under reduced pressure. NaOH 2M was added at 0 °C to reach pH 7 and the product was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was obtained as yellow solid (1.18 g, 7.80 mmol, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 3.83 (bs, 2H).

2nd step:[252] To a solution of the obtained aniline (1.51 g, 10 mmol) and Et_3N (1.40 mL, 10 mmol) in CH_2Cl_2 (50 mL) acetyl chloride (0.757 mL, 10.5 mmol) was added dropwise at 0 °C. After 7 h at room temperature, the reaction mixture was washed with water and brine, dried over $MgSO_4$ and concentrated to provide the title compound as white solid (1.70 g, 8.8 mmol, 80%) which was used in the next step without further purification. ^{1}H-

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[252] Adapted from: Yang, H.; Zhou, L.; Wang, P. *Photochem. Photobiol. Sci.***2012**, *11,* 514–517.

RMN (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.7 Hz, 1H), 7.67 (s, 1H), 7.34 (t, *J* = 5.8 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 1H), 3.92 (s, 3H), 2.03 (s, 3H).

3rd step: [252] A solution of the acetylated ester (966 mg, 5 mmol, 1 equiv.) in THF (25 mL) was treated with MeMgBr (10 mL, 2 M in THF, 4 equiv.) dropwise at 0 °C under argon atmosphere. The reaction was stirred overnight at room temperature, quenched by NH_4Cl saturated solution and the solvent was evaporated under reduced pressure. The mixture was extracted with dichloromethane (3 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. After recrystallization from petroleum ether and CH_2Cl_2 the trityl alcohol was obtained as a brown solid (754 mg, 3.9 mmol, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 2.18 (s, 3H), 1.57 (s, 6H).

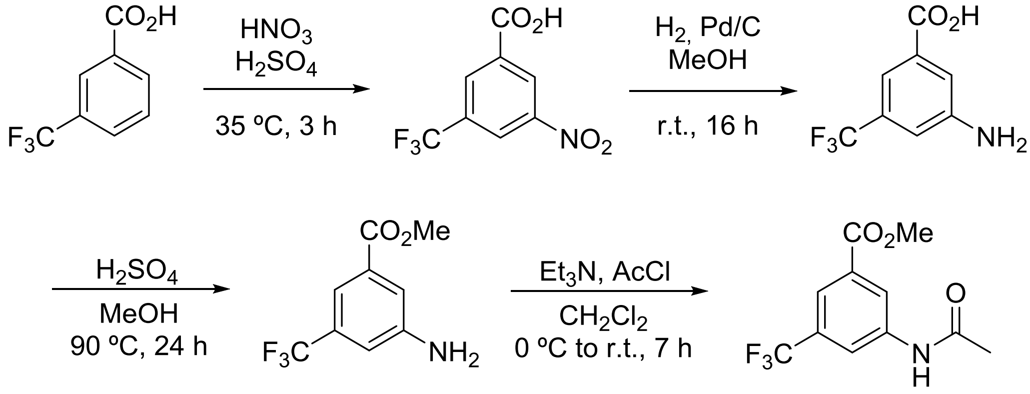
4th step: A solution of the obtained trityl alcohol (580 g, 3 mmol, 1 equiv.) was treated with NaOH (2.4 g, 60 mmol, 20 equiv.) in methanol (17 mL) and water (2.4 mL) and heated at 85 °C for 3 d. The reaction mixture was neutralized with HCl 1M until pH 7, extracted with DCM (3 × 10 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to obtain the title compound as a white solid (334 mg, 2.21 mmol, 74%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 1H), 6.88 – 6.82 (m, 2H), 6.61 – 6.54 (m, 1H), 1.55 (s, 6H).

5th step: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (170 mg, 1.2 mmol, 1 equiv.) in MeOH (4.8 mL) was added the free aniline (181 mg, 1.2 mmol, 1 equiv.) at room temperature. The mixture was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluting with DCM/MeOH 98/2) to give the title compound as a yellow solid (201 mg, 0.92 mmol, 77%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 1.4 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 4.51 (s, 3H), 1.59 (s, 6H).

6th step: To a suspension of the squarate (130 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added (*R,R*)-9-deoxy-9-epiaminoquinine (162 mg, 0.5 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 (DCM/MeOH, 98/2) to give pure **C20** as a yellow solid (235 mg, 0.43 mmol, 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.51 (d, *J* = 4.5 Hz, 2H), 7.34 (dd, *J* = 9.3, 2.3 Hz, 1H), 6.98 – 6.74 (m, 3H), 6.41 – 6.18 (m, 1H), 5.87 – 5.66 (m, 1H), 5.12 – 4.91 (m, 2H), 3.96 (s, 3H), 3.85 – 3.48 (m, 2H), 3.31 – 3.13 (m, 1H), 3.08 – 2.70 (m, 2H), 2.48 – 2.28 (m, 1H), 1.63 (d, *J* = 40.5 Hz, 5H), 1.36 (d, *J* = 13.5 Hz, 6H), 0.90 – 0.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8, 181.6, 168.9, 163.9, 158.9, 150.9, 147.7, 144.7, 142.8, 140.1, 137.9, 131.7, 129.0, 127.8, 122.7, 120.1, 119.3, 117.2, 115.7, 115.5, 101.2, 77.4, 72.2, 60.4, 56.2, 55.5, 53.5, 41.2, 38.8, 31.8, 31.3, 27.4, 27.0, 25.7. UPLC-DAD-QTOF: $C_{33}H_{37}N_4O_4$ $[M+H]^+$ calcd.: 553.2815, found: 553.2813.

5.2.3.2. *Preparation of catalysts* ***C21-C22*** *and* ***C24-C25***

Preparation of methyl 3-acetamido-5-(trifluoromethyl)benzoate (common intermediate)



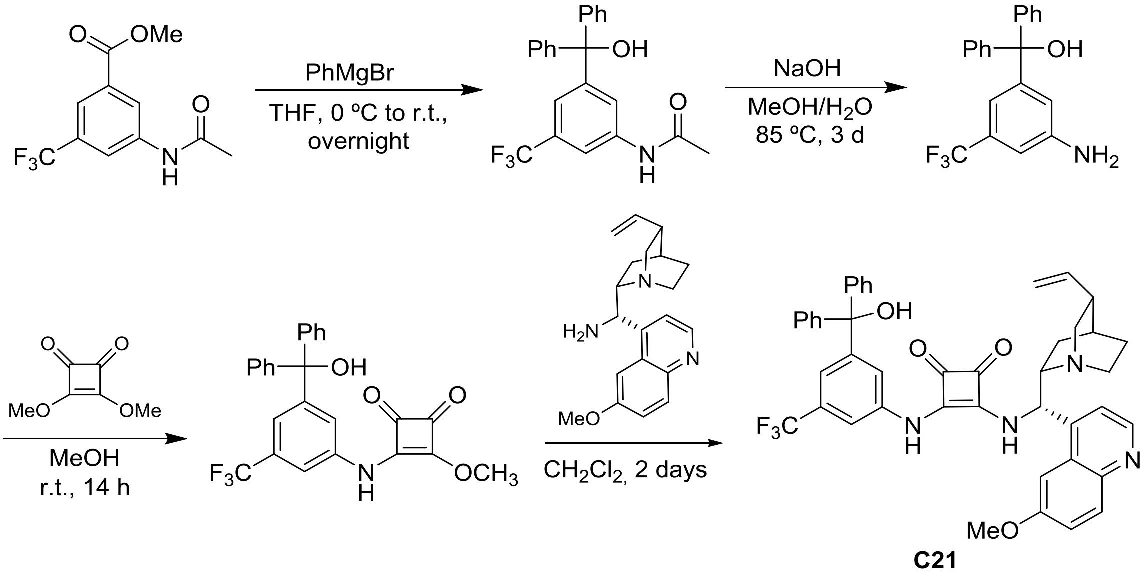
1st step: To a solution of 3-trifluoromethylbenzoic acid (2 g, 10 mmol) in concentrated sulfuric acid (10 mL) was added nitric acid (2 mL) at 0 ºC over 15 min. The mixture was stirred at 35 °C for 3 h, and slowly poured onto ice. The precipitate was filtrated with water (100 mL), and dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water, and dried, and the solvent was evaporated under reduced pressure to give 3-nitro-5-(trifluoromethyl) benzoic acid. Yield: 91 % (2.14 g, 9.12 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.74 (s, 1H), 8.69 (s, 1H).

2nd step: To a solution of nitro compound (1.31 g, 5.6 mmol) in MeOH (20 mL) under inert atmosphere, Pd/C was added (Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 16 h. After that the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product as a white solid (1.18 g, 5.4 mmol, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.54 (s, 1H), 7.11 (s, 1H).

3rd step: To a solution 3-amino-5-(trifluoromethyl)benzoic acid (1.17 g, 5.74 mmol, 1.0 equiv.) in MeOH (8.0 mL) was added concentrated H_2SO_4 (1.24 mL, 23.0 mmol, 4.0 equiv.). The reaction mixture was stirred for 24 h and then, the solvent was removed under reduced pressure. NaOH 2M was added at 0 °C to reach pH 7 and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was obtained as yellow solid (1.14 g, 5.20 mmol, 91 %). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.05 (dt, *J* = 1.7, 0.9 Hz, 1H), 3.98 (s, 2H), 3.92 (s, 3H).

4th step: To a solution of the obtained aniline (2.192 g, 10 mmol) and Et_3N (1.40 mL, 10 mmol) in CH_2Cl_2 (50 mL) acetyl chloride (0.757 mL, 10.5 mmol) was added dropwise at 0 °C. After 7 h at room temperature, the reaction mixture was washed with water and brine, dried over $MgSO_4$ and concentrated to provide the title compound as white solid (2.534 g, 9.7 mmol, 97%) which was used in the next step without further purification. ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 5.4 Hz, 2H), 8.03 (s, 1H), 7.44 (s, 1H), 3.95 (s, 3H), 2.23 (s, 3H).

Preparation of catalyst C21



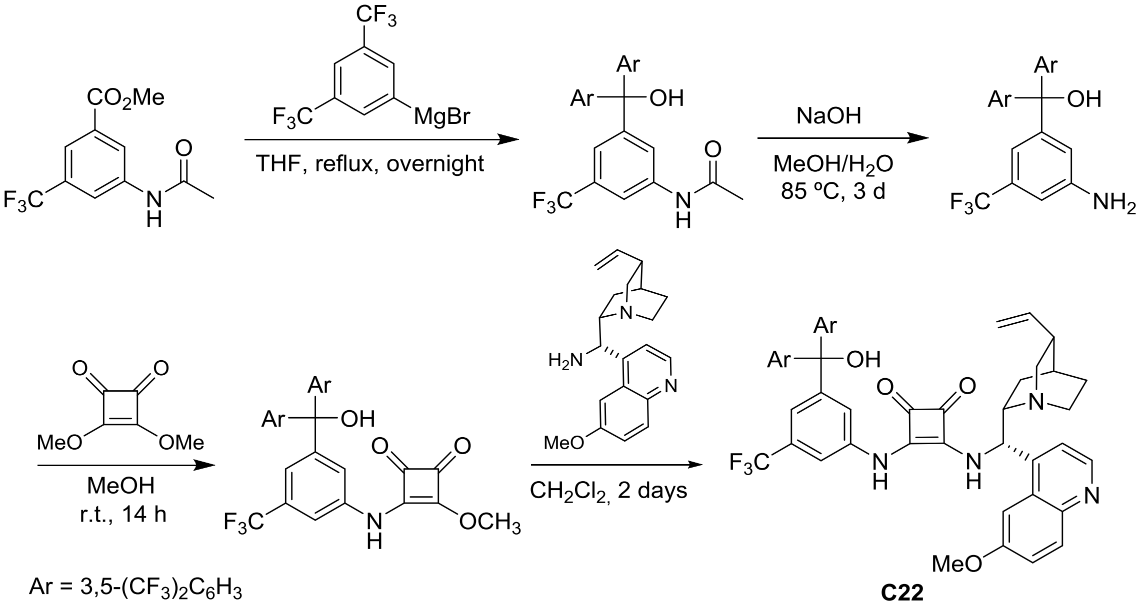
1st step: A solution of the crude material of the previous reaction (5.0 mmol, 1.31 g) in THF (10 mL) was added dropwise at 0 °C to a solution of phenyl magnesium bromide (0.5M in THF, 15 mmol). The mixture was stirred at room temperature overnight. The reaction was quenched with NH_4Cl saturated solution, the solvent was evaporated under reduced pressure and diluted with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 7/3) to give the title compound as a yellow solid (1.67 g, 4.3 mmol, 86%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.39 (d, *J* = 1.8 Hz, 2H), 7.36 – 7.30 (m, 5H), 7.27 – 7.21 (m, 5H), 2.87 (s, 1H), 2.13 (s, 3H).

2nd step: To a solution of the acetamide obtained above (770 mg, 2.0 mmol) was added in MeOH (15 mL) and water (2 mL) NaOH (1.60 g, 40 mmol, 20 equiv.) and the mixture was heated at 85 °C for 3 d. The reaction mixture was neutralized with HCl 1M until pH 7, extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound as a yellow solid (651 mg, 1.9 mmol, 95%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ δ 7.35 – 7.23 (m, 10H), 6.97 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.81 (s, 1H), 6.76 (s, 1H), 3.87 (s, 3H).

3rd step: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (142 mg, 1.0 mmol, 1 equiv.) in MeOH (4 mL) was added the free aniline obtained above (343 mg, 1.0 mmol, 1 equiv.) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluting with Hexane/ ethyl acetate 7/3) to give the title compound as a yellow solid (316 mg, 0.7 mmol, 70%). M.p.= 100-110 °C. ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.48 (s, 2H), 7.39 – 7.32 (m, 5H), 7.27 – 7.23 (m, 5H), 4.37 (s, 3H), 2.89 (s, 1H). UPLC-DAD-QTOF: $C_{25}H_{19}NO_4F_3$ $[M+H]^+$ calcd.: 454.1266, found: 454.1260.

4th step: To a suspension of the hemisquaramide obtained above (227 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added (*R,R*)-9-deoxy-9-epiaminoquinine (162 mg, 0.5 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature for 2 days. The solvent was evaporated in the rotary evaporator and the oil residue was submitted to purification by silica column chromatography (CH2Cl2/MeOH, 98/2) to give the pure **C21** catalyst as a yellow solid (253 mg, 0.34 mmol, 68%). M.p.= 185-198 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.63 (d, *J* = 4.7 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.82 – 7.71 (m, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.29 – 7.10 (m, 10H), 6.20 (d, *J* = 11.1 Hz, 1H), 5.84 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 5.09 – 4.93 (m, 2H), 3.93 (s, 3H), 3.54 (ddd, *J* = 21.8, 17.1, 8.7 Hz, 2H), 3.29 – 3.26 (m, 1H), 3.26 – 3.19 (m, 1H), 2.91 – 2.67 (m, 2H), 2.43 – 2.26 (m, 1H), 1.71 – 1.50 (m, 4H), 0.77 – 0.63 (m, 1H). ^{13}C NMR (75 MHz, MeOD) δ 185.3, 181.9, 169.6, 165.5, 160.4, 152.1, 148.3, 147.8, 145.4, 145.0, 141.9, 140.1, 131.7, 129.3, 129.1, 128.9, 128.3, 124.4, 122.8, 120.4, 120.3, 115.5, 114.9, 102.0, 82.3, 61.1, 56.7, 54.7, 41.8, 40.2, 28.6, 27.9, 27.0. UPLC-DAD-QTOF: $C_{44}H_{40}N_4O_4F_3$ $[M+H]^+$ calcd.: 745.3002, found: 745.2998.

Preparation of catalysts C22



C22

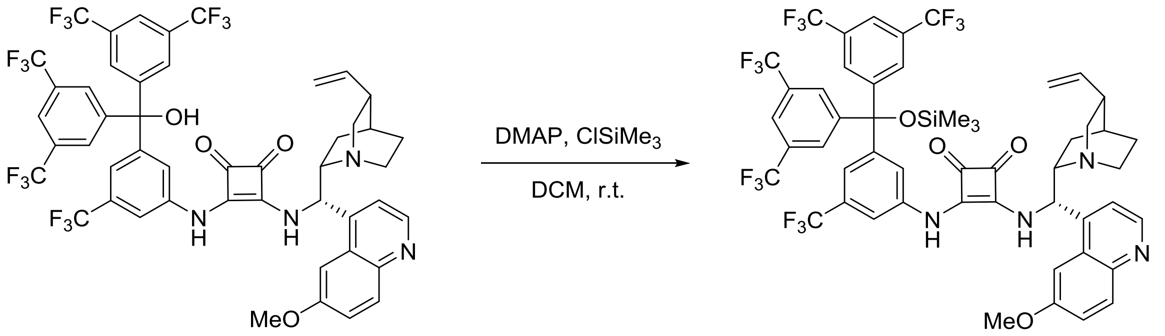
1st step: A solution of the crude material of the previous reaction (5.0 mmol, 1.31 g) in THF (10 mL) was added dropwise at 0 °C to a solution of 3,5-bis(trifluoromethyl)-phenyl magnesium bromide (0.5M in THF, 15 mmol). The mixture was stirred at reflux overnight. The reaction was quenched with NH_4Cl saturated solution, the solvent was evaporated under reduced pressure and diluted wit water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 7/3) to give the title compound as a brown solid (2.70 g, 4.1 mmol, 82%). M.p.= 190-198 °C. ^1H NMR (300 MHz, MeOD) δ 8.08 – 8.04 (m, 1H), 8.01 – 7.96 (m, 2H), 7.91 – 7.85 (m, 4H), 7.63 (t, *J* = 1.8 Hz, 1H), 7.40 – 7.35 (m, 1H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ 172.1, 150.0, 148.2, 141.2, 133.2, 129.2, 126.4, 123.4, 123.0, 120.2, 120.2, 117.0, 117.0, 81.3, 23.9. UPLC-DAD-QTOF: $C_{26}H_{15}NO_2F_{15}$ $[M+H]^+$ calcd.: 658.0863, found: 658.0859.

2nd step: To a solution of the acetamide obtained above (1.31 g, 2.0 mmol) was added in MeOH (15 mL) and water (2 mL) NaOH (1.60 g, 40 mmol, 20 equiv.) and the mixture was heated at 85 °C for 3 d. The reaction mixture was neutralized with HCl 1M until pH 7, extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 98:2) to give the title compound as a brown solid (1.14 g, 1.9 mmol, 93%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.85 – 7.78 (m, 4H), 6.92 (t, *J* = 1.8 Hz, 1H), 6.78 (td, *J* = 1.6, 0.8 Hz, 1H), 6.53 (t, *J* = 1.9 Hz, 1H), 3.98 (s, 2H), 2.96 (s, 1H).

3rd step: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (142 mg, 1.0 mmol, 1 equiv.) in MeOH (4 mL) was added the free aniline obtained above (615 mg, 1.0 mmol, 1 equiv.) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluting with Hexane/ ethyl acetate 7/3) to give the title compound as a yellow solid (616 mg, 0.85 mmol, 85%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.80 (s, 4H), 7.55 (s, 2H), 7.22 (s, 1H), 4.42 (s, 3H), 4.02 (s, 1H).

4th step: To a suspension of the hemisquaramide obtained above (363 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added (*R,R*)-9-deoxy-9-epiaminoquinine (162 mg, 0.5 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature for 2 days. The solvent was evaporated in the rotary evaporator and the oil residue was submitted to purification by silica column chromatography (CH_2Cl_2/MeOH, 98/2) to give the pure **C22** catalyst as a yellow solid (346 mg, 0.34 mmol, 68%). M.p.= 175-183 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 – 9.71 (m, 1H), 8.78 (d, *J* = 4.5 Hz, 1H), 8.13 – 8.03 (m, 2H), 8.03 – 7.89 (m, 5H), 7.79 (s, 1H), 7.74 – 7.65 (m, 2H), 7.62 (d, *J* = 4.6 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.33 (s, 1H), 6.03 – 5.88 (m, 1H), 5.11 – 4.88 (m, 2H), 3.90 (s, 3H), 3.23 – 3.10 (m, 2H), 2.75 – 2.54 (m, 2H), 2.36 – 2.19 (m, 1H), 1.65 – 1.39 (m, 4H), 0.63 (d, *J* = 14.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.4, 179.6, 168.3, 163.0, 157.9, 148.3, 147.7, 147.4, 144.3, 142.9, 142.1, 139.7, 131.5, 130.3 (q), 128.6, 128.2, 127.4, 125.5, 124.9, 121.9, 121.3, 120.8, 117.7, 117.6, 114.4, 114.1, 101.4, 79.5, 64.9, 58.8, 55.6, 38.5, 38.2, 27.3, 26.0. UPLC-DAD-QTOF: $C_{48}H_{36}N_4O_4F_{15}$ $[M+H]^+$ calcd.: 1017.2497, found: 1017.2518.

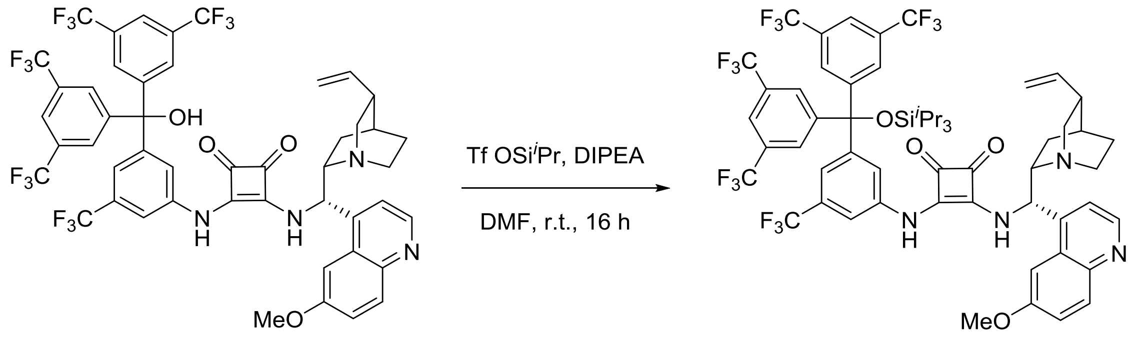
Preparation of catalyst C24



C22 **C24**

To a suspension of catalyst **C22** (102 mg, 0.1 mmol, 1 equiv.) and DMAP (20 mg, 0.15 mmol, 1.5 equiv.) in CH_2Cl_2 (0.2 mL) was added dropwise chlorotrimethylsilane (20 µL, 0.15 mmol, 1.5 equiv.) and the reaction mixture was stirred for 14 h at r.t. Then, CH_2Cl_2 (2 mL) was added and the organic layer was washed twice with water and HCl 1M, dried over $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography on silica gel (Hexane/EtOAc, 70:30) to give pure catalyst **C24** as a yellow solid (93.6 mg, 0.086 mmol, 86%). M.p.= 160-165 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.74 (d, *J* = 4.6 Hz, 1H), 8.07 (t, *J* = 1.8 Hz, 1H), 8.00 (s, 6H), 7.98 – 7.92 (m, 2H), 7.76 (d, *J* = 2.6 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.41 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.32 (s, 1H), 6.34 (d, *J* = 11.4 Hz, 1H), 5.96 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.04 (d, *J* = 10.3 Hz, 1H), 3.97 (s, 3H), 3.82 – 3.67 (m, 1H), 3.52 (dd, *J* = 13.4, 10.2 Hz, 1H), 3.25 – 2.98 (m, 2H), 2.71 – 2.57 (m, 1H), 1.37 – 1.11 (m, 2H), 1.02 – 0.87 (m, 1H), -0.12 (s, 9H). ^{13}C NMR (75 MHz, MeOD) δ 185.8, 181.3, 169.5, 166.0, 160.7, 149.1, 148.4, 145.5, 143.8, 141.6, 140.7, 133.1 (q), 132.8, 131.8, 129.4, 129.1, 126.3, 124.6, 123.3, 122.7, 122.3, 120.4, 119.6, 119.1, 116.4, 115.9, 115.9, 101.7, 84.6, 61.2, 56.7, 56.1, 54.4, 42.2, 39.4, 28.4, 26.8, 26.3, 1.4. UPLC-DAD-QTOF: $C_{51}H_{44}N_4O_4F_{15}Si$ $[M+H]^+$ calcd.: 1089.2876, found: 1089.2873.

Preparation of catalyst C25



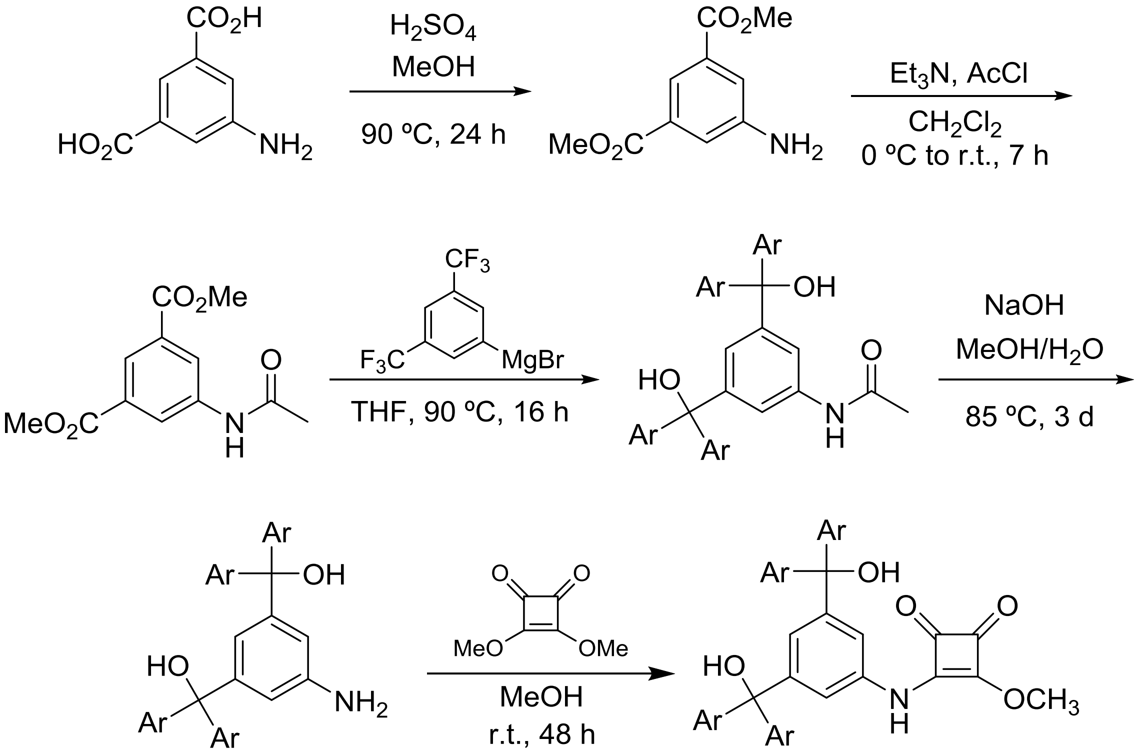
C22 **C25**

To a suspension of catalyst **C22** (102 mg, 0.1 mmol, 1 equiv.) and DIPEA (26 mg, 0.2 mmol, 2 equiv.) in DMF (0.2 mL) was added dropwise triisopropylsilyl trifluoromethanesulfonate (46 mg, 0.15 mmol, 1.5 equiv.) and the reaction mixture was stirred for 14 h at r.t.. Then, EtOAc (5 mL) was added and the organic layer was washed with HCl 1M (2 x 5 mL) and brine (10 x 5 mL), dried over $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography on silica gel (Hexane/EtOAc, 70:30) to give pure catalyst **C25** as a white solid (91.5 mg, 0.078 mmol, 78%). M.p.= 145-152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.5 Hz, 1H), 8.04 (d, *J* =

9.2 Hz, 1H), 7.95 – 7.87 (m, 3H), 7.83 (d, *J* = 5.3 Hz, 4H), 7.73 – 7.57 (m, 3H), 7.55 (s, 1H), 7.42 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.38 (s, 1H), 5.54 (dt, *J* = 17.1, 8.7 Hz, 1H), 5.17 – 4.95 (m, 2H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.00 (s, 3H), 3.95 – 3.84 (m, 1H), 3.68 – 3.51 (m, 2H), 3.37 – 3.10 (m, 2H), 2.69 (d, *J* = 10.5 Hz, 1H), 2.12 (d, *J* = 8.6 Hz, 1H), 2.04 (s, 2H), 1.82 (t, *J* = 12.9 Hz, 1H), 0.89 (d, *J* = 8.2 Hz, 18H), 0.84 – 0.73 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 180.1, 167.2, 166.2, 159.5, 147.9, 147.7, 147.6, 145.2, 139.9, 135.8, 132.5, 132.4, 131.8 (q), 128.6, 127.2, 125.3, 125.0, 124.9, 123.4, 122.4, 121.7, 121.4, 121.3, 121.2, 118.7, 118.2, 114.8, 100.3, 83.9, 60.7, 56.4, 54.4, 41.9, 36.3, 29.8, 26.4, 24.2, 24.0, 18.4, 13.7. UPLC-DAD-QTOF: $C_{57}H_{56}N_4O_4F_{15}Si$ $[M+H]^+$ calcd.: 1173.3840, found: 1173.3844..

*5.2.3.3. Preparation of catalysts **C23**, **C26** ad **C27***

Preparation of the squaric ester monoamide intermediate



1st step: To a solution 5-aminoisophthalic acid (1.81 g, 10 mmol, 1.0 equiv.) in MeOH (20 mL) was added concentrated H_2SO_4 (4.32 mL, 80 mmol, 8 equiv.). The reaction mixture was stirred for 24 h at 90 °C. After allowing the mixture to reach r.t. the solvent was removed under reduced pressure. Then, water (10 mL) and NaOH 2M was added until neutral pH and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was obtained as white solid and used without further purification (1.54 g, 6.84 mmol, 68 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (t, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 1.5 Hz, 2H), 3.92 (s, 6H).

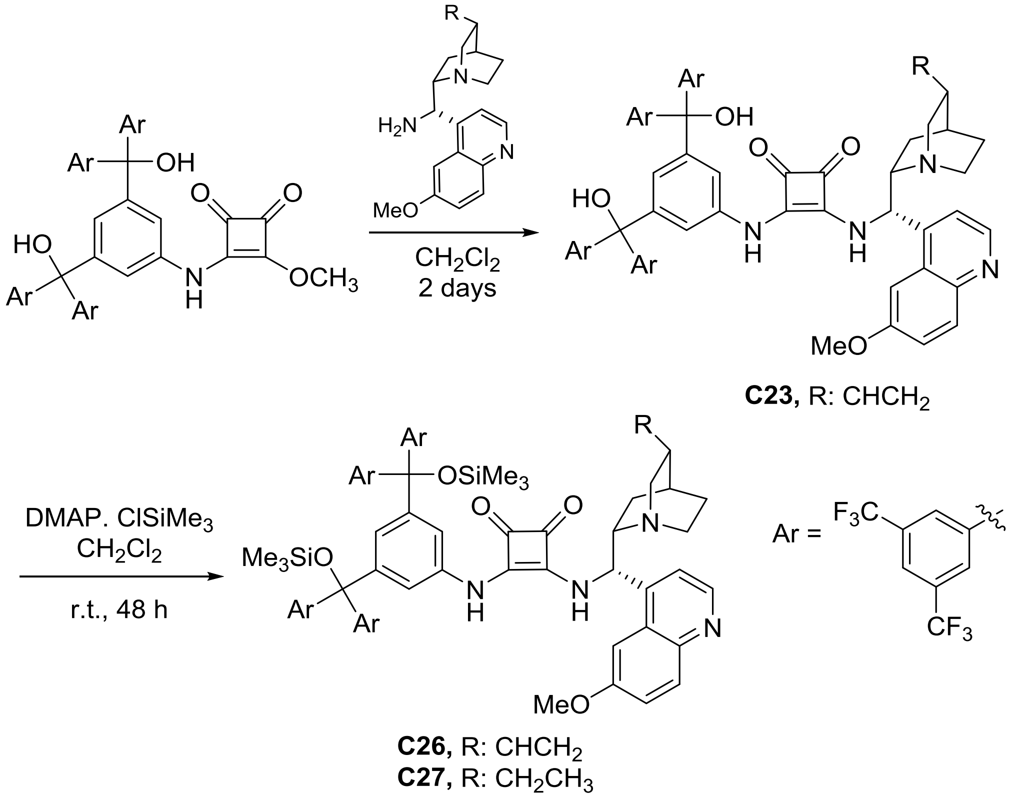
2nd step: To a solution of the crude dimethyl 3-aminophtalate (1.54 g, 6.84 mmol) and Et_3N (1.0 mL, 6.84 mmol) in CH_2Cl_2 (33 mL) was added dropwise at 0 °C acetyl chloride (0.54 mL, 7.52 mmol, 1.1 equiv.). After stirring for 7 h at room temperature, the reaction mixture was filtrated and the solid was washed with cool CH_2Cl_2 (2 × 10 mL) to provide the title compound as white solid (1.55 g, 6.16 mmol, 90%) which was used without further purification. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.39 (s, 1H), 8.46 (d, *J* = 1.4 Hz, 2H), 8.21 – 8.10 (m, 1H), 3.89 (s, 6H), 2.08 (s, 3H).

3rd step: A solution of the acetamide ester product obtained above (2.0 mmol, 522 mg) in THF (5 mL) was added dropwise at 0 °C to a solution of 3,5-bis(trifluoromethyl)phenyl magnesium bromide (0.5M in THF, 8 equiv., 32mL). The mixture was stirred at 90 °C 16 h. The reaction was cooled to room temperature, quenched with NH_4Cl saturated solution and solvent evaporated under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (3 × 5.0 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 7/3) to give the title compound as a brown solid (1.03 g, 1.57 mmol, 79%). M.p.= 195-205 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 4H), 7.64 (d, *J* = 1.7 Hz, 8H), 7.44 (d, *J* = 1.7 Hz, 2H), 7.34 (s, 1H), 2.03 (s, 3H). UPLC-DAD-QTOF: $C_{42}H_{22}NO_3F_{24}$ $[M+H]^+$ calcd.: 1044,1216, found: 1044,1239.

4th step: To a solution of the acetamide product obtained above (522 mg, 0.5 mmol) in MeOH (4.0 mL) and water (0.5 mL) was added NaOH (400 mg, 10 mmol, 20 equiv.) and the mixture was heated at 85 °C for 3 d. The reaction mixture was neutralized by adding dropwise HCl 1M until pH 7, and then, extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were ried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give the title compound as a brown solid (431 mg, 0.43 mmol, 85%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 4H), 7.68 (d, *J* = 1.7 Hz, 8H), 6.52 (d, *J* = 1.6 Hz, 2H), 6.08 (t, *J* = 1.7 Hz, 1H).

5th step: To a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (64 mg, 0.45 mmol, 1.05 equiv.) in MeOH (3 mL) was added the free aniline product obtained above (431 mg, 0.43 mmol, 1 equiv.) and the mixture was stirred at room temperature for 48 h. Then, the solvent was evaporated under reduced pressure and the oil residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate, 7:3) to give the title compound as a yellow solid (410 mg, 0.37 mmol, 82%). ^{1}H NMR (300 MHz, MeOD) δ 8.02 – 7.89 (m, 4H), 7.76 (d, *J* = 1.8 Hz, 8H), 7.49 (t, *J* = 2.4 Hz, 2H), 6.68 (s, 1H), 4.27 (s, 3H).

Preparation of the catalysts C23, C26 and C27



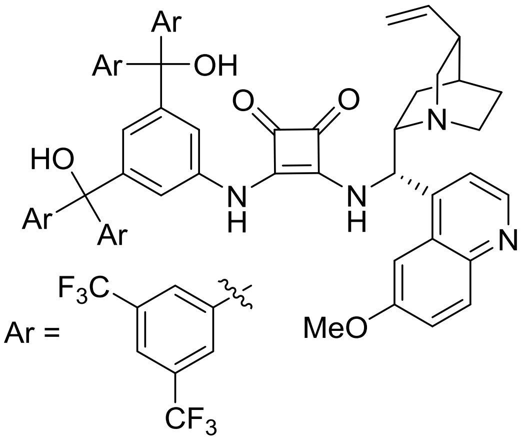
C23, R: CHCH$_2$

C26, R: CHCH$_2$
C27, R: CH$_2$CH$_3$

1st step: To a solution of the squaric ester monoamide prepared above (218 mg, 0.20 mmol) in CH$_2$Cl$_2$ (1 mL) was added the corresponding amine (0.20 mmol) and the reaction mixture was stirred for 48 h at room temperature. The resulting precipitate was filtered and washed with cold CH$_2$Cl$_2$ to give **C23** to use as catalyst, or the crude product was subsequently used in the second step without further purification.

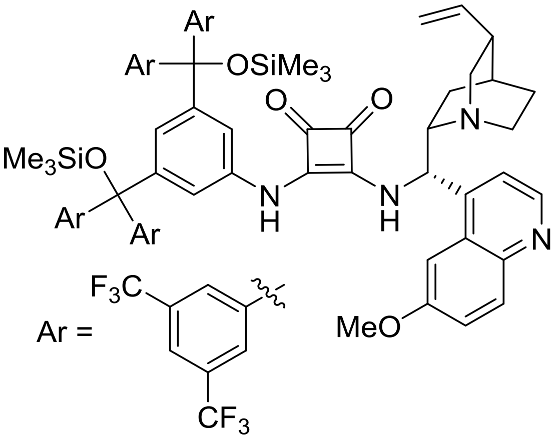
2nd step: To a suspension of the previously prepared diol-squaramide (0.20 mmol, 1 equiv.) and DMAP (80 mg, 0.60 mmol, 3 equiv.) in CH$_2$Cl$_2$ (0.8 mL) was added dropwise chlorotrimethylsilane (80 µL, 0.60 mmol, 3 equiv.) and the reaction mixture was stirred for 14 h at room temperature. Then, additional CH$_2$Cl$_2$ (4 mL) was added and the mixture was washed with water (2 × 4 mL) and HCl 1 M (2 × 4 mL). The organic layer was dried over MgSO$_4$ and the solvent was evaporated. The resulting residue was subjected to purification by flash column chromatography on silica gel (CH$_2$Cl$_2$/MeOH 98:2) affording the pure catalyst.

3-((3,5-bis(bis(3,5-bis(Trifluoromethyl)phenyl)(hydroxy)methyl)phenyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C23)



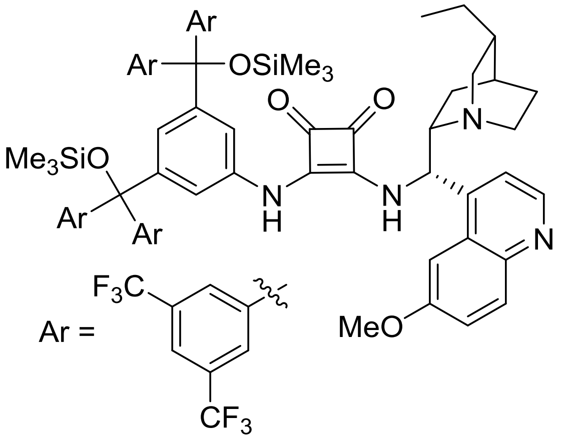
White solid (253 mg, 0.18 mmol, 60%). M.p.= 180-188 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.63 (d, *J* = 4.7 Hz, 1H), 7.92 – 7.80 (m, 5H), 7.80 – 7.68 (m, 9H), 7.55 – 7.41 (m, 3H), 7.31 (dd, *J* = 9.3, 2.5 Hz, 1H), 6.69 (t, *J* = 1.5 Hz, 1H), 6.16 (d, *J* = 10.9 Hz, 1H), 5.85 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1H), 5.06 – 4.91 (m, 2H), 3.91 (s, 3H), 3.43 (td, *J* = 9.6, 5.4 Hz, 2H), 3.29 – 3.15 (m, 2H), 2.87 – 2.61 (m, 2H), 2.40 – 2.25 (m, 1H), 1.69 – 1.43 (m, 4H), 0.72 – 0.56 (m, 1H). ^{13}C NMR (75 MHz, MeOD) δ 185.6, 181.3, 169.6, 165.6, 160.5, 150.1, 150.1, 148.2, 148.2, 145.4, 145.4, 142.4, 141.0, 132.8 (q) , 131.5, 129.9, 129.4, 129.1, 126.3, 124.4, 122.9, 122.7, 118.7, 115.2, 102.0, 81.4, 61.1, 56.9, 56.7, 54.8, 41.7, 40.6, 28.8, 28.3, 27.3. UPLC-DAD-QTOF: $C_{64}H_{43}N_4O_5F_{24}$ [M+H]$^+$ calcd.: 1403.2850, found: 1403.2844.

3-(3,5-bis[bis(3,5-bis(Trifluoromethyl)phenyl)(trimethylsilyloxy)methyl]phenyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C26)



Yellow solid. Yield after 2 steps: 47% (145 mg, 0.094 mmol). M.p.= 160–168 ºC. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.47 (d, *J* = 4.6 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 13H), 7.71 (s, 1H), 7.65 – 7.37 (m, 2H), 7.40 – 7.24 (m, 1H), 7.24 – 7.12 (m, 1H), 7.12 – 7.03 (m, 1H), 6.14 (s, 1H), 5.85 – 5.61 (m, 1H), 5.11 – 4.92 (m, 2H), 3.95 (s, 3H), 3.43 – 3.03 (m, 3H), 2.43 – 2.27 (m, 1H), 1.79 – 1.58 (m, 3H), 1.49 (t, *J* = 12.0 Hz, 1H), 1.37 – 1.21 (m, 1H), 0.78 (td, *J* = 17.3, 13.8, 6.5 Hz, 1H), -0.28 (s, 18H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 185.1, 180.5, 168.1, 164.9, 159.7, 148.2, 147.4, 147.0, 145.1, 140.8, 140.6, 132.5 (q), 132.4, 129.4, 129.0, 128.7, 125.4, 124.0, 122.7, 121.8, 118.2, 118.1, 115.9, 101.6, 84.0, 60.7, 59.4, 56.7, 56.3, 41.3, 39.2, 31.6, 30.4, 27.6, 26.5, 1.7. UPLC-DAD-QTOF: $C_{70}H_{59}N_4O_5F_{24}Si_2$ [M+H]$^+$ calcd.: 1547.3641, found: 1547.3595.

3-((3,5-bis(bis(3,5-bis(Trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)phenyl) amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C27)

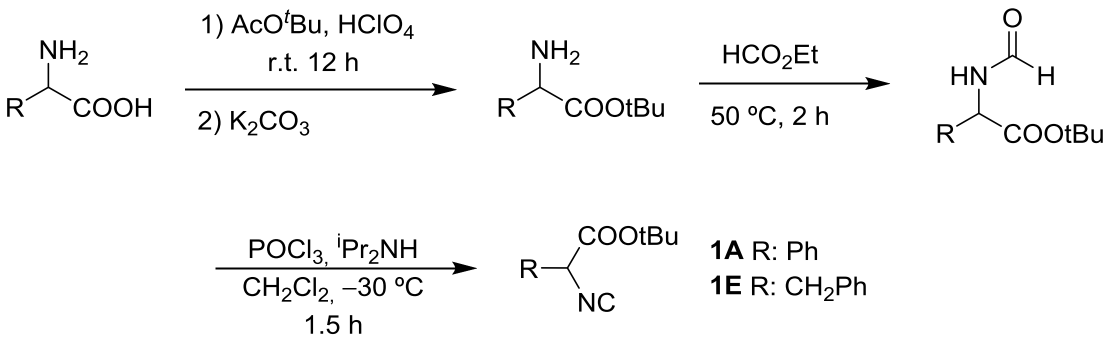


Yellow solid. Yield after 2 steps: 65% (202 mg, 0.13 mmol). M.p.= 155–160 ºC. ^{1}H-NMR (300 MHz, DMSO-*d$_6$*) δ 8.73 (d, *J* = 4.6 Hz, 1H), 8.21 (s, 1H), 7.96 (d, *J* = 3.9 Hz, 4H), 7.93 (s, 1H), 7.89 (d, *J* = 4.9 Hz, 8H), 7.72 – 7.63 (m, 1H), 7.59 – 7.54 (m, 1H), 7.46 (s, 2H), 7.36 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.85 (s, 1H), 5.96 (s, 1H), 3.88 (s, 3H), 3.53 – 3.45 (m, 1H), 3.27 – 3.06 (m, 2H), 2.62 – 2.53 (m, 1H), 2.39 (d, *J* = 13.4 Hz, 1H), 1.61 – 1.17 (m, 8H), 0.90 – 0.75 (m, 3H), 0.62 (s, 1H), -0.33 (s, 18H). ^{13}C NMR (75 MHz, DMSO) δ 183.9, 179.2, 168.1, 162.9, 157.8, 147.5, 147.5, 145.4, 144.3, 142.9, 140.1, 131.5, 130.7 (q), 128.2, 127.8, 124.6, 121.9, 120.9, 120.3, 117.3, 117.2, 101.1, 82.9, 78.4, 72.0, 70.0, 60.3, 57.2, 55.4, 36.7, 26.8, 25.8, 24.9, 11.8, 0.6. UPLC-DAD-QTOF: $C_{70}H_{61}N_4O_5F_{24}Si_2$ [M+H]$^+$ calcd.: 1549.3797, found: 1549.3822.

5.3. Experimental section of chapter 2

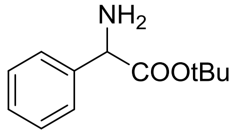
5.3.1. Synthesis of isocyanoacetates 1

*5.3.1.1. Synthesis of isocyanoacetates **1A** and **1E***



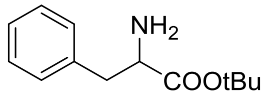
1st step:[253] To a solution of the aminoacid (30 mmol, 1 equiv.) in tert-butyl acetate (70 mL) at 0 °C, was added slowly $HClO_4$ (70% in water , 3.9 mL, 45 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 12 h. Then, the mixture was washed with H_2O (100 mL) and hydrochloric acid 1M (50 mL). The resulting combined aqueous solution was adjusted to pH 9 by addition of sat. K_2CO_3 solution, and then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered and concentrated to give an oil which was subjected to purification by flash chromatography on silica gel (ethyl acetate/hexane, 1:1) to give the pure tert-butyl aminoester.

tert-Butyl 2-amino-2-phenylacetate



Yield: 81%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 4.48 (s, 1H), 1.84 (brs, 2H), 1.39 (s, 9H).

tert-Butyl 2-isocyano-3-phenylpropanoate



Yield: 93%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 5H), 3.64 (dd, J = 7.8, 5.6 Hz, 1H), 3.07 (dd, J = 13.5, 5.6 Hz, 1H), 2.87 (dd, J = 13.5, 7.7 Hz, 1H), 1.46 (s, 9H).

2nd step: A solution of tert-butyl phenylglycine (2.07 g, 10 mmol) in ethyl formate (30 mL) was heated at 70 °C for 2 h and then, the reaction was concentrated under reduced pressure to afford formamide product in quantitative yield. The crude material was used in the next step without purification.

3rd step:[254] To a solution of previously obtained formamide (10 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) was added DIPA (5.19 mL, 37 mmol, 3.7 equiv.) and the mixture was cooled to -30 °C. $POCl_3$ (1.12 mL, 12 mmol, 1.2 equiv.) was added and the solution was stirred at -30 °C with TLC monitoring (around 1.5 h). A saturated aqueous solution of Na_2CO_3 (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), HCl 1M (2 × 20 mL), dried over $MgSO_4$ and was concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent ethyl acetate/hexane, 5:95) to give the isocyanide. Isonitrile NC band at IR: 2145 cm^{-1}.

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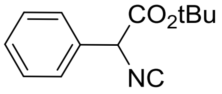
[253] Chen, H.; Feng, Y.; Xu, Z.; Ye, T. *Tetrahedron* **2005**, *61*, 1113-–11140.

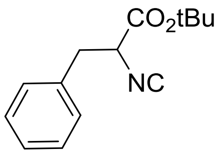
[254] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.

tert-Butyl 2-isocyano-2-phenylacetate (1A)



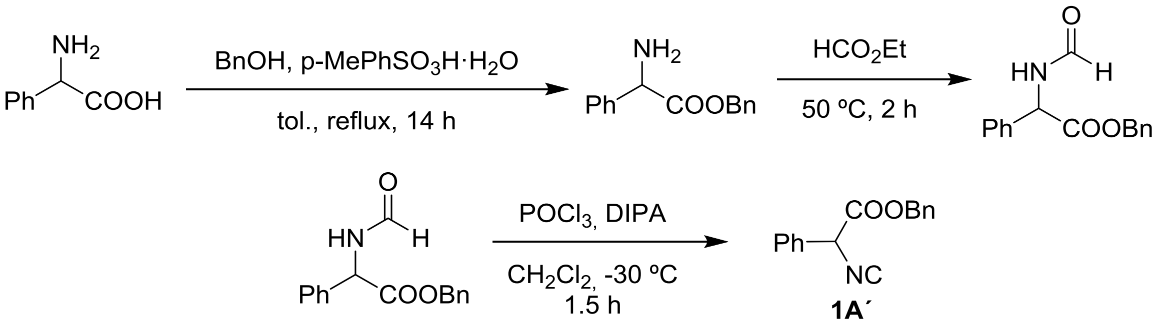
The isocyanoacetate **1A** was obtained following the general procedure. Yellow oil. Yield (last step): 87 % (1.89 g, 8.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.35 (m, 5H), 5.23 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 160.7, 132.4, 129.2, 129.0, 126.5, 84.1, 61.1, 27.6. UPLC-DAD-QTOF: calcd for $C_{13}H_{16}NO_2$ [M+H]$^+$, 218.1181; found, 218.1184.

tert-Butyl 2-isocyano-3-phenylpropanoate (1E)



The isocyanoacetate **1E** was obtained following the general procedure. Colourless oil. Yield (last step): 76 % (1.76 g, 7.6 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.34 (dd, *J* = 8.1, 5.3 Hz, 1H), 3.29 – 3.06 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 160.2, 134.8, 129.4, 128.7, 127.7, 83.9, 58.6, 38.9, 27.7. UPLC-DAD-QTOF: calcd for $C_{14}H_{17}NO_2$ [M+H]$^+$, 232.3035; found, 232.3031.

*5.3.1.2. Synthesis of isocyanoacetate **1A´***



1st step:[255] A mixture of phenylglycine (3.0 g, 20 mmol), p-toluene sulfonic acid monohydrate (4.14 g, 22 mmol) and benzyl alcohol (8.0 ml, 77 mmol) was refluxed in 30 ml toluene overnight. The solution was then cooled to room temperature and the resulting crystals filtered to yield a white solid. Those crystals was dissolved in dichloromethane (20 mL), washed with a saturated sodium bicarbonate solution (3 × 20 mL) and the organic layer was dried over magnesium sulphate and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel. Yield: 80%. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.17 (m, 10H), 5.14 (dd, *J* = 12.4 Hz, 2H), 4.66 (s, 1H), 1.84 (s, 2H).

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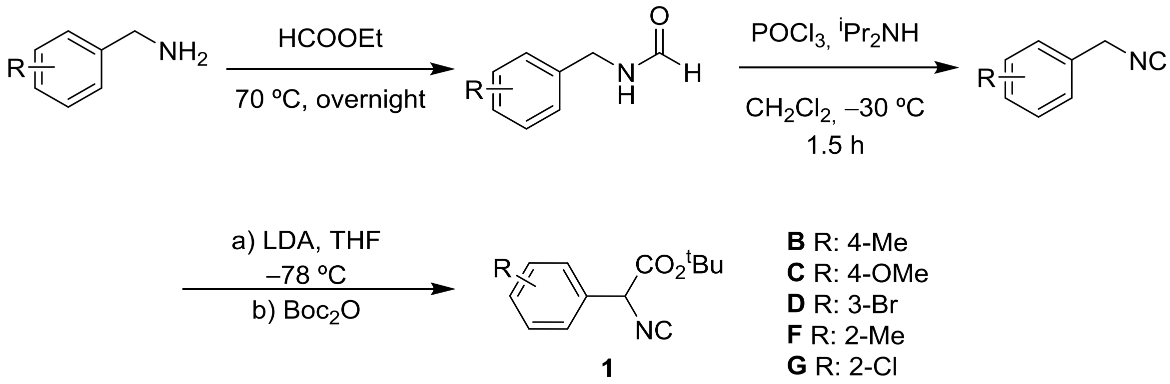
[255] Adapted from: Llewellyn, D. B.; Arndtsen, B. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1789–1799

2nd step: A solution of amine in ethyl formate (3 mL/mmol) was heated at 70ºC for 2h and the reaction was concentrated under reduced pressure to afford pure formamide in quantitative yield. The crude was used in the next step without purification.

3rd step:[256] To a solution of previously obtained formamide (10 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) was added DIPA (5.19 mL, 37 mmol, 3.7 equiv.) and the mixture was cooled to -30 °C. $POCl_3$ (1.12 mL, 12 mmol, 1.2 equiv.) was added and the solution was stirred at -30 °C with TLC monitoring (around 1.5 h). A saturated aqueous solution of Na_2CO_3 (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), HCl 1M (2 × 20 mL), dried over $MgSO_4$ and was concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent ethyl acetate/hexane, 5:95) to give the isocyanide **1A´**. Isonitrile NC band at IR: 2145 cm^{-1}. Yellow oil. Yield (last step): 74 % (1.86 g, 7.4 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 5H), 7.37 – 7.29 (m, 3H), 7.29 – 7.20 (m, 2H), 5.39 (s, 1H), 5.27 – 5.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 161.2, 134.1, 131.4, 129.2, 128.8, 128.4, 128.3, 127.8, 126.4, 68.1, 60.0. UPLC-DAD-QTOF: calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$, 252.0913; found, 222.0918.

*5.3.1.3. Synthesis of isocyanoacetates **1B-D** and **1F-G***



1st step: A solution of amine (10 mmol) in ethyl formate (30 mL) was heated at 70 °C for 2 h and then, the reaction was concentrated under reduced pressure to afford formamide product in quantitative yield. The crude material was used in the next step without purification.

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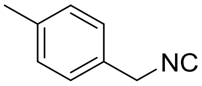
[256] Adapted form: see ref. 254, page 185.

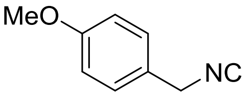
2nd step:[257] To a solution of previously obtained formamide (10 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) was added DIPA (5.19 mL, 37 mmol, 3.7 equiv.) and the mixture was cooled to -30 °C. $POCl_3$ (1.12 mL, 12 mmol, 1.2 equiv.) was added and the solution was stirred at -30 °C with TLC monitoring (around 1.5 h). A saturated aqueous solution of Na_2CO_3 (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), HCl 1M (2 × 20 mL), dried over $MgSO_4$ and was concentrated under reduced pressure at 0 °C. The crude was purified immediately by flash column chromatography on silica gel due to the instability of the products. NC band in IR: 2137-2147 cm^{-1}.

1-(Isocyanomethyl)-4-methylbenzene



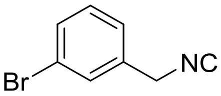
Yield (2 steps): 80%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 4H), 4.60 (s, 2H), 2.37 (s, 3H).

1-(Isocyanomethyl)-4-methoxybenzene



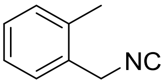
Yield (2 steps): 89%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 6.95 – 6.89 (m, 2H), 4.57 (s, 2H), 3.82 (s, 3H).

1-Bromo-3-(isocyanomethyl)benzene



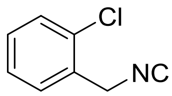
Yield (2 steps): 83%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 2H), 7.33 – 7.23 (m, 2H), 4.63 (s, 2H).

1-(Isocyanomethyl)-2-methylbenzene



Yield (2 steps): 66%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.33 – 7.17 (m, 3H), 4.59 (s, 2H), 2.34 (s, 3H).

1-Chloro-2-(isocyanomethyl)benzene



Yield (2 steps): 63%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 1H), 7.43 – 7.29 (m, 3H), 4.75 (s, 2H).

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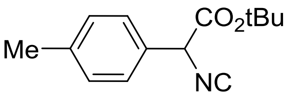
[257] Adapted from: see ref. 254, page 185.

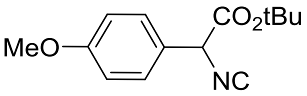
3rd step:[258] A solution of isonitrile (10 mmol) in THF (10 mL) was added dropwise to a cooled solution of LDA (25 mmol, 2.5 eq) in THF (30mL). The reaction mixture was allowed to stir at –78 °C for 45 min and then at room temperature for additional 45 min. The reaction mixture was cooled to −78 °C 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 °C for another 2 h. The reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 1M HCl (30 mL), brine (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude material was purified by flash column chromatography on silica gel (eluent, hexane/ethyl acetate, 9:1) to yield the desired product. Isonitrile NC band at IR: 2137-2147 cm^{-1}.

tert-Butyl 2-isocyano-2-(p-tolyl)acetate (1B)



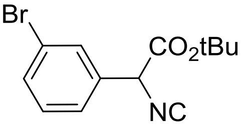
The isocyanoacetate **1B** was obtained following the general procedure. Yellow oil. Yield (last step): 80 % (1.85 g, 8.0 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.24 – 7.18 (m, 2H), 5.18 (s, 1H), 2.37 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 160.3, 139.2, 129.6, 129.4, 126.4, 84.0, 60.9, 27.6, 21.1. UPLC-DAD-QTOF: calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$, 232.1338; found, 232.1332.

tert-Butyl 2-isocyano-2-(4-methoxyphenyl)acetate (1C)



The isocyanoacetate **1C** was obtained following the general procedure. White solid. Yield (last step): 65 % (1.61 g, 6.5 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 6.97 – 6.89 (m, 2H), 5.16 (s, 1H), 3.83 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 160.4, 160.2, 127.9, 124.5, 114.4, 84.0, 60.6, 55.3, 27.6. UPLC-DAD-QTOF: calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$, 248.1287; found, 248.1282.

tert-Butyl 2-(3-bromophenyl)-2-isocyanoacetate (1D)



The isocyanoacetate **1D** was obtained following the general procedure. Yellow oil. Yield (last step): 80 % (2.37 g, 8.0 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, *J* = 1.8 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.44 – 7.38 (m, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 5.20 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz,

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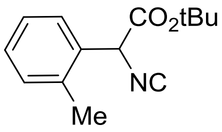
[258] Adapted from: a) Trost, B. M.; Miller, J. R.; Hoffman, C. M. *J. Am. Chem. Soc.,* **2011**, *133*, 8165-8167. b) Badiola, E.; Fiser, B.; Gonzalez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881.

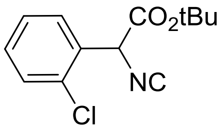
$CDCl_3$) δ 163.8, 161.7, 134.3, 132.5, 130.6, 129.7, 125.2, 122.9, 84.8, 60.4, 27.7. UPLC-DAD-QTOF: calcd for $C_{13}H_{15}NO_2Br$ $[M+H]^+$, 296.0286; found, 296.0287.

tert-Butyl 2-isocyano-2-(o-tolyl)acetate (1F)



The isocyanoacetate **1F** was obtained following the general procedure. Yellow oil. Yield (last step): 85 % (1.97 g, 8.5 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.18 (m, 1H), 5.43 (s, 1H), 2.42 (s, 3H), 1.42 (s, 9H). UPLC-DAD-QTOF: calcd for $C_{14}H_{17}NO_2$ $[M+H]^+$, 232.3076; found, 232.3080.

tert-Butyl 2-(2-chlorophenyl)-2-isocyanoacetate (1G)

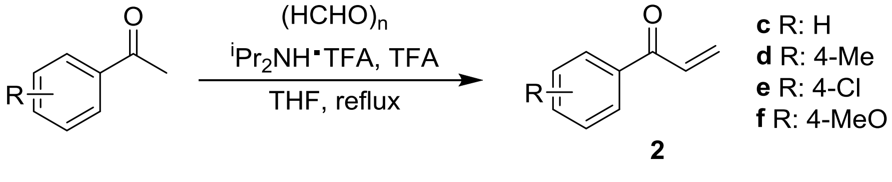


The isocyanoacetate **1G** was obtained following the general procedure. Yellow oil. Yield (last step): 87 % (2.19 g, 8.7 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 1H), 7.47 – 7.41 (m, 1H), 7.39 – 7.32 (m, 2H), 5.72 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 160.8, 133.1, 131.0, 130.7, 130.0, 128.4, 127.7, 84.6, 58.1, 27.7. UPLC-DAD-QTOF: calcd for $C_{13}H_{15}NO_2Cl$ $[M+H]^+$, 252.0791; found, 252.0799.

5.3.2. Synthesis of vinyl ketones 2 and 6a

Compounds **2a** and **2b** are commercially available. Compounds **2c-f** and **6a** were prepared according the following procedure:

5.3.2.1. *Synthesis of **2c-f***[259]



To a solution of the corresponding acetophenone (10 mmol) and paraformaldehyde (600 mg, 20 mmol, 2 equiv.) in dry THF (10 mL) were succesively added diisopropylammonium trifluoroacetate (2.15 g, 10 mmol, 1 equiv.) and trifluoroacetic acid (0.8 mL, 10 mmol, 1 equiv.). The reaction mixture was stirred at reflux for 2 h, then cooled down to room temperature and a second addition of paraformaldehyde (20

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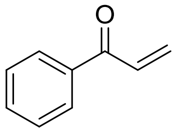
[259] Adapted from: Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715-1717.

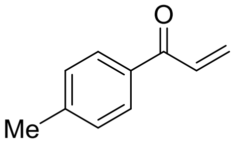
mmol) and ammonium salt (10 mmol) was performed. Next, the reaction mixture was stirred at reflux overnight. Then cooled down and the solvent was removed under reduced pressure. The crude material was dissolved in Et_2O and washed with HCl 1M, NaOH 1M and brine. The resulting organic solution was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel column chromatography (eluent hexane/ethyl acetate, 9:1). The spectroscopic data of thus obtained compounds were identical to those reported in the literature.[260]

1-Phenylprop-2-en-1-one (2c)



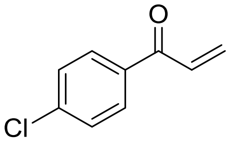
Colorless oil. Yield: 70%. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93 (2H, d, *J*= 9.2 Hz), 7.53-7.55 (1H, m), 7.43-7.47 (2H, m), 7.15 (1H, dd, *J*= 17.2, 10.8 Hz), 6.42 (1H, d, *J*= 17.2 Hz), 5.90 (1H, d, *J*= 10.8Hz).

1-(p-Tolyl)prop-2-en-1-one (2d)



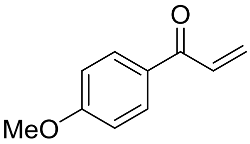
Colorless oil. Yield: 78%. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (2H, d, *J*= 8.0 Hz), 7.23 (2H, d, *J*= 8.0 Hz), 7.15 (1H, dd, *J*= 17.2, 10.4 Hz), 6.39 - 6.44 (1H, m), 5.84 - 5.87 (1H, m), 2.37 (3H, s).

1-(4-Chlorophenyl)prop-2-en-1-one (2e)



Colorless oil. Yield: 68%. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (2H, d, *J*= 8.4Hz), 7.43 (2H, d, *J*= 8.4 Hz), 7.12 (1H, dd, *J*= 16.8, 10.4 Hz), 6.42 - 6.46 (1H, m), 5.92 - 5.95 (1H, m).

1-(4-Methoxyphenyl)prop-2-en-1-one (2f)



Colorless oil. Yield: 75%. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (2H, d, *J*= 8.8 Hz), 7.18 (1H, dd, *J*= 16.8, 10.4 Hz), 6.95 (2H, d, *J*= 8.8 Hz), 6.42 (1H, d, *J*= 16.8Hz), 5.87 (1H, d, *J*= 10.4Hz), 3.86 (3H, s).

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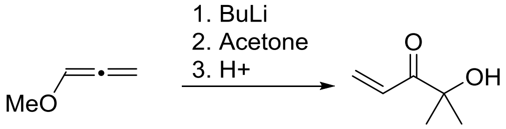
[260] Guo, S.-H.; Xing, S.-Z.; Mao, S.; Gao, Y.-R.; Chen, W.-L.; Wang, Y.-Q. *Tetrahedron Lett.* **2014**, *55*, 6718-6720.

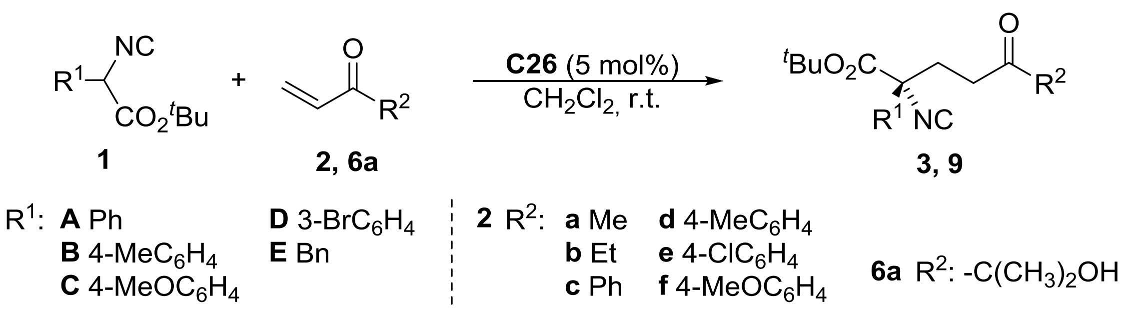
5.3.2.2. *Synthesis of α'-hydroxy enone **6a**.*[261]



To a solution of methoxypropadiene (3.50 g, 50 mmol, 1 equiv.) 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, 1.1 equiv.) 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 × 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 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 × 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation afforded the enone as a colorless liquid (4.42 g) (88%). ^1H NMR ($CDCl_3$) δ: 6.73 (1H, dd, *J*= 9.5 Hz, *J'*= 16.8 Hz), 6.50 (1H, dd, *J*= 2.2 Hz, *J'*= 16.8 Hz), 5.82 (1H, dd, *J*= 2.2 Hz, *J'*= 10.3 Hz), 1.38 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 202.3, 131.1, 128.8, 75.4, 26.1. IR (neat, cm^{-1}) 3445 (OH), 1693 (C=O).

5.3.3. General Procedure for the conjugate addition of isocyanoacetates 1 to vinyl ketones.



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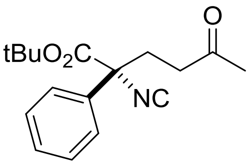
[261] Palomo, C.; Oiarbide, M.; García, J.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

Catalyst **C26** (5 mol%) was added to a solution of the corresponding isocyanoacetate **1** (0.2 mmol, 1 equiv.) and vinyl ketone **2** or **6a** (1–2 equiv.) in CH_2Cl_2 (0.4 mL) at room temperature and the resulting mixture was stirred at the same temperature until the reaction was completed (monitored by TLC). The solvent was removed under reduced pressure and the product was purified by column chromatography.

tert-Butyl (R)-2-isocyano-5-oxo-2-phenylhexanoate (3Aa)

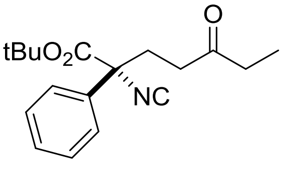


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **2a** (28 mg, 0.4 mmol). The title compound was obtained as a 97.5:2.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as a colorless oil. Yield: 85% (48.9 mg). $[\alpha]_D{}^{22}= -7.22°$ (*c*=1, 95% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.44 – 7.34 (m, 3H), 2.68 – 2.39 (m, 4H), 2.13 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 166.1, 160.9, 135.1, 129.0,129.0, 125.1, 84.4, 70.8, 38.6, 33.2, 30.1, 27.6. UPLC-DAD-QTOF: calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$, 288.1600; found, 288.1597.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 99:1; flux= 1 mL/min; retention times: 12.4 min (minor), 16.1 min (major)).

tert-Butyl (R)-2-isocyano-5-oxo-2-phenylheptanoate (3Ab)

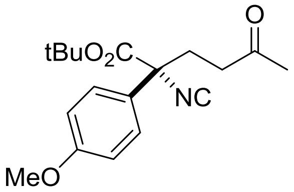


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **2b** (34 mg, 0.4 mmol). The title compound was obtained as a 97.5:2.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as a yellow oil. Yield: 95% (57.3 mg). $[\alpha]_D{}^{22}= -9.16°$ (*c*=1.95, 95% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.43 – 7.34 (m, 3H), 2.68 – 2.34 (m, 6H), 1.40 (s, 9H), 1.02 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 166.2, 160.8, 135.1, 129.0, 129.0, 125.1, 84.4, 70.9, 37.2, 36.2, 33.3, 27.6, 7.8. UPLC-DAD-QTOF: calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$, 302.1756; found, 302.1769.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 99:1; flux= 1 mL/min; retention times: 11.2 min (minor), 14.9 min (major)).

tert-Butyl (R)-2-isocyano-2-(4-methoxyphenyl)-5-oxohexanoate (3Ca)

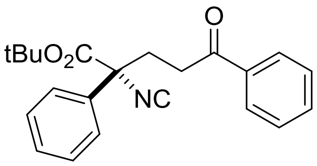


Prepared according to the general procedure starting from isocyanoacetate **1C** (49.5 mg, 0.2 mmol) and vinyl ketone **2a** (28 mg, 0.4 mmol). The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as a yellow oil. Yield: 90% (57.1 mg). $[\alpha]_D$ ^{22}= – 6.43° (*c*=0.85, 98% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.65 – 2.35 (m, 4H), 2.12 (s, 3H), 1.40 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 166.3, 160.5, 160.0, 127.0, 126.5, 114.2, 84.3, 70.4, 55.4, 38.6, 33.0, 30.2, 27.7. UPLC-DAD-QTOF: calcd for $C_{18}H_{23}NO_4Na$ $[M+H]^+$, 340.1525; found, 340.1536.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:isopropanol, 99:1; flux= 0.5 mL/min; retention times: 23.2 min (major), 29.2 min (minor)).

tert-Butyl (R)-2-isocyano-5-oxo-2,5-diphenylpentanoate (3Ac)

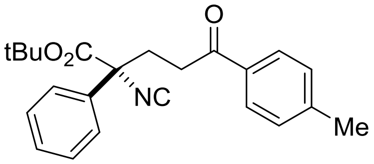


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **2c** (26.4 mg, 0.2 mmol). The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as a yellow oil. Yield: 77% (53.8 mg). $[\alpha]_D$ ^{22}= –10.90° (*c*= 3.4, 94% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H), 7.62 – 7.51 (m, 3H), 7.49 – 7.36 (m, 5H), 3.24 – 2.95 (m, 2H), 2.86 – 2.73 (m, 1H), 2.73 – 2.58 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 166.0, 160.9, 136.4, 135.0, 133.3, 128.9, 128.9, 128.6, 128.0, 125.0, 84.3, 70.9, 33.6, 33.6, 27.5. UPLC-DAD-QTOF: calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$, 350.1756; found, 350.1764.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 99:1; flux= 1 mL/min; retention times: 17.3 min (minor), 24.6 min (major)).

tert-Butyl (R)-2-isocyano-5-oxo-2-phenyl-5-(p-tolyl)pentanoate (3Ad)

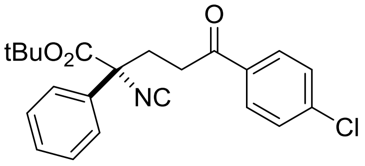


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **2d** (29.2 mg, 0.2 mmol). The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as a yellow oil. Yield: 70% (50.9 mg). $[\alpha]_D^{22} = -8.44°$ (*c*=1.5, 96% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.62 – 7.55 (m, 2H), 7.47 – 7.34 (m, 3H), 7.28 – 7.20 (m, 2H), 3.20 – 2.92 (m, 2H), 2.86 – 2.72 (m, 1H), 2.70 – 2.56 (m, 1H), 2.40 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 166.0, 160.8, 144.1, 135.0, 133.9, 129.3, 128.8, 128.5, 128.1, 125.1, 84.3, 70.9, 33.7, 33.5, 27.5, 21.6. UPLC-DAD-QTOF: calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$, 364.1913; found, 364.1910.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane:ethanol, 99:1; flux= 1 mL/min; retention times: 19.3 min (minor), 45.6 min (major)).

tert-Butyl (R)-5-(4-chlorophenyl)-2-isocyano-5-oxo-2-phenylpentanoate (3Ae)

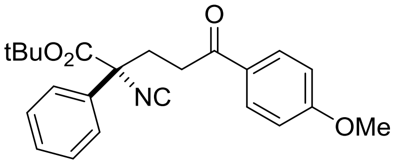


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **2e** (33.3 mg, 0.2 mmol). The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as a yellow oil. Yield: 70% (53.7 mg). $[\alpha]_D^{22} = -5.27°$ (*c*=1.45, 94% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.60 – 7.54 (m, 2H), 7.48 – 7.35 (m, 5H), 3.19 – 2.91 (m, 2H), 2.86 – 2.71 (m, 1H), 2.70 – 2.56 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 166.4, 161.4, 140.2, 135.3, 135.1, 129.8, 129.4, 129.4, 129.4, 125.4, 84.8, 71.3, 34.0, 34.0, 27.9. UPLC-DAD-QTOF: calcd for $C_{22}H_{23}NO_3Cl$ $[M+H]^+$, 384.1366; found,384.1354.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 97:3; flux= 1 mL/min; retention times: 9.6 min (minor), 14.6 min (major)).

tert-Butyl (R)-2-isocyano-5-(4-methoxyphenyl)-5-oxo-2-phenylpentanoate (3Af)

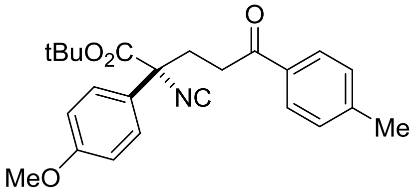


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **2f** (32.4 mg, 0.2 mmol). The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as colourless oil. Yield: 80% (60.7 mg). $[\alpha]_D{}^{22}$= –18.48° (*c*=0.6, 98% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.95 – 7.87 (m, 2H), 7.63 – 7.55 (m, 2H), 7.48 – 7.35 (m, 3H), 6.98 – 6.88 (m, 2H), 3.86 (s, 3H), 3.19 – 2.90 (m, 2H), 2.86 – 2.71 (m, 1H), 2.71 – 2.56 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 196.5, 166.2, 163.8, 160.9, 135.2, 130.7, 130.4, 129.6, 129.0, 125.2, 113.9, 84.4, 71.1, 55.6, 33.9, 33.4, 27.7. UPLC-DAD-QTOF: calcd for $C_{23}H_{26}NO_4$ $[M+H]^+$, 380.1862; found, 380.1856.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: 12.1 min (minor), 17.6 min (major)).

tert-Butyl (R)-2-isocyano-2-(4-methoxyphenyl)-5-oxo-5-(p-tolyl)pentanoate (3Cd)

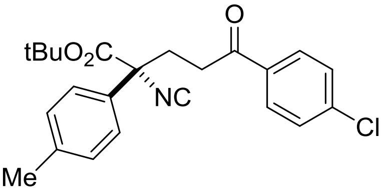


Prepared according to the general procedure starting from isocyanoacetate **1C** (49.5 mg, 0.2 mmol) and vinyl ketone **2d** (29.2 mg, 0.2 mmol). The title compound was obtained as a 99.5:0.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as colourless oil. Yield: 80% (63.0 mg). $[\alpha]_D{}^{22}$= –1.79° (*c*=3, 99% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 3.19 – 2.93 (m, 2H), 2.84 – 2.67 (m, 1H), 2.69 – 2.54 (m, 1H), 2.39 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 197.6, 166.4, 160.6, 160.0, 144.2, 134.1, 129.4, 128.2, 127.1, 126.6, 114.3, 84.2, 70.6, 55.4, 33.7, 33.6, 27.7, 21.7. UPLC-DAD-QTOF: calcd for $C_{24}H_{28}NO_4$ $[M+H]^+$, 394.2018; found, 394.2026.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 1 mL/min; retention times: 15.0 min (minor), 25.1 min (major)).

tert-Butyl (R)-5-(4-chlorophenyl)-2-isocyano-5-oxo-2-(p-tolyl)pentanoate (3Be)

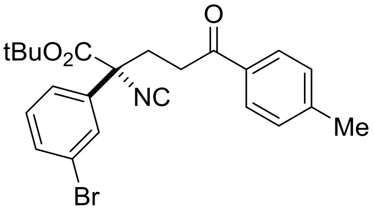


Prepared according to the general procedure starting from isocyanoacetate **1B** (46.3 mg, 0.2 mmol) and vinyl ketone **2e** (33.3 mg, 0.2 mmol). The title compound was obtained as a 98.5:1.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as yellow oil. Yield: 80% (63.7 mg). $[\alpha]_D{}^{22} = -6.89°$ (*c*=2.05, 97% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 2H), 7.48 – 7.38 (m, 4H), 7.21 (d, *J* = 8.1 Hz, 2H), 3.18 – 2.90 (m, 2H), 2.82 – 2.69 (m, 1H), 2.69 – 2.54 (m, 1H), 2.36 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 166.3, 160.8, 139.9, 139.0, 134.9, 132.1, 129.7, 129.6, 129.1, 125.1, 84.4, 70.8, 33.8, 33.7, 27.7, 21.1. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}NO_3Cl$ $[M+H]^+$, 398.1523; found, 398.1527.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 1 mL/min; retention times: 8.3 min (minor), 10.2 min (major)).

tert-Butyl (R)-2-(3-bromophenyl)-2-isocyano-5-oxo-5-(p-tolyl)pentanoate (3Dd)

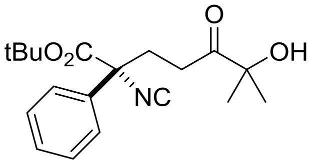


Prepared according to the general procedure starting from isocyanoacetate **1D** (59.2 mg, 0.2 mmol) and vinyl ketone **2d** (29.2 mg, 0.2 mmol). The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1) to give the title compound as a brown oil. Yield: 86% (76.1 mg). $[\alpha]_D{}^{22} = -3.00°$ (*c*=2.55, 96% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.75 (t, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.9 Hz, 2H), 7.34 – 7.26 (m, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.21 – 2.91 (m, 2H), 2.86 – 2.69 (m, 1H), 2.59 (dd, *J* = 19.0, 11.2 Hz, 1H), 2.40 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 197.3, 165.6, 161.8, 144.4, 137.4, 134.0, 132.3, 130.5, 129.5, 128.5, 128.2, 124.0, 123.2, 85.0, 70.6, 34.0, 33.5, 27.7, 21.7. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}NO_3Br$ $[M+H]^+$, 442.1018; found, 442.1021.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 12.6 min (minor), 23.4 min (major)).

tert-Butyl (R)-6-hydroxy-2-isocyano-6-methyl-5-oxo-2-phenylheptanoate (9Aa)

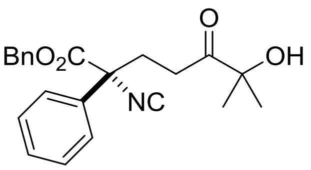


Prepared according to the general procedure starting from isocyanoacetate **1A** (43.4 mg, 0.2 mmol) and vinyl ketone **6a** (45.7 mg, 0.4 mmol). The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 7/3) to give the title compound as a yellow oil. Yield: 70% (46.4 mg). $[\alpha]_D{}^{22}$= –3.54° (*c*= 1, 98% *ee*, CH$_2$Cl$_2$).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.56 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.49 – 7.39 (m, 3H), 3.52 (s, 1H), 2.87 – 2.60 (m, 3H), 2.52 (m, 1H), 1.44 (s, 9H), 1.39 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 213.1, 166.4, 161.5, 135.4, 129.5, 129.5, 125.5, 85.0, 76.9, 71.3, 33.9, 31.4, 28.1, 27.1, 27.0. UPLC-DAD-QTOF: calcd for $C_{19}H_{26}NO_4$ $[M+H]^+$,332.1862; found, 332.1863.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 13.2 min (minor), 16.7 min (major)).

Benzyl (R)-6-hydroxy-2-isocyano-6-methyl-5-oxo-2-phenylheptanoate (9A´g)

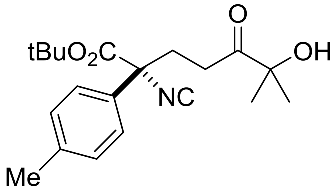


Prepared according to the general procedure starting from isocyanoacetate **1A´** (50.2 mg, 0.2 mmol) and vinyl ketone **6a** (45.7 mg, 0.4 mmol). The title compound was obtained as a 96:4 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 7/3) to give the title compound as yellow oil. Yield: 74% (54.1 mg). $[\alpha]_D{}^{22}$= – 10.60° (*c*= 2.11, 92% *ee*, CH$_2$Cl$_2$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.45 – 7.37 (m, 3H), 7.36 – 7.28 (m, 3H), 7.28 – 7.20 (m, 2H), 5.20 (s, 2H), 3.42 (s, 1H), 2.81 – 2.47 (m, 4H), 1.30 (s, 3H), 1.28 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 167.1, 162.0, 134.6, 134.4, 129.4, 129.2, 128.7, 128.7, 128.1, 125.2, 76.5, 70.4, 68.7, 33.6, 30.9, 26.6. UPLC-DAD-QTOF: calcd for $C_{22}H_{24}NO_4$ $[M+H]^+$, 366.1605; found, 366.1606.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 58.9 min (minor), 63.8 min (major)).

tert-Butyl (R)-6-hydroxy-2-isocyano-6-methyl-5-oxo-2-(p-tolyl)heptanoate (9Ba)

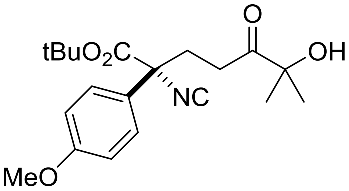


Prepared according to the general procedure starting from isocyanoacetate **1B** (46.3 mg, 0.2 mmol) and vinyl ketone **6a** (45.7 mg, 0.4 mmol). The title compound was obtained as a 99.5:0.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 7/3) to give the title compound as colourless oil. Yield: 70% (48.4 mg). $[\alpha]_D{}^{22} = -2.88°$ (*c*= 1.65, 99% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 3.50 (s, 1H), 2.78 – 2.43 (m, 4H), 2.35 (s, 3H), 1.41 (s, 9H), 1.35 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 166.2, 160.8, 139.1, 132.0, 129.7, 125.0, 84.4, 76.5, 70.7, 33.4, 31.0, 27.7, 26.7, 26.6, 21.1. UPLC-DAD-QTOF: calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$, 346.2018; found, 346.2023.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 26.1 min (major), 29.0 min (minor)).

tert-Butyl (R)-6-hydroxy-2-isocyano-2-(4-methoxyphenyl)-6-methyl-5-oxoheptanoate (9Ca)

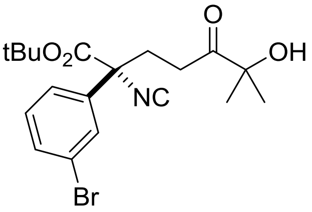


Prepared according to the general procedure starting from isocyanoacetate **1C** (49.5 mg, 0.2 mmol) and vinyl ketone **6a** (45.7 mg, 0.4 mmol). The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 7/3) to give the title compound as a yellow oil. Yield: 72% (52.2 mg). $[\alpha]_D{}^{22} = -4.84°$ (*c*=2.65, 98% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 6.96 – 6.88 (m, 2H), 3.81 (s, 3H), 3.49 (s, 1H), 2.77 – 2.43 (m, 4H), 1.41 (s, 9H), 1.36 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 166.3, 160.8, 160.1, 126.9, 126.5, 114.3, 84.4, 76.5, 70.5, 55.5, 33.4, 31.0, 27.7, 26.7, 26.6. UPLC-DAD-QTOF: calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$, 362.1961; found, 394.2018.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 21.3 min (minor), 31.8 min (major)).

tert-Butyl (R)-2-(3-bromophenyl)-6-hydroxy-2-isocyano-6-methyl-5-oxoheptanoate (9Da)



Prepared according to the general procedure starting from isocyanoacetate **1D** (59.2 mg, 0.2 mmol) and vinyl ketone **6a** (45.7 mg, 0.4 mmol). The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 7/3) to give the title compound as colourless oil. Yield: 86% (70.6 mg). $[\alpha]_D{}^{22} = -4.63°$ (*c*=3.15, 96% *ee*, CH_2Cl_2).

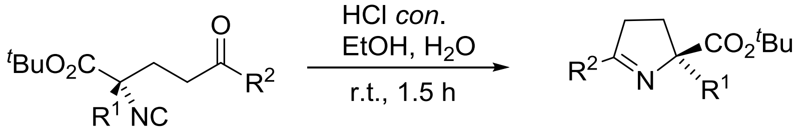
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (t, *J* = 1.6 Hz, 1H), 7.55 – 7.42 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 3.44 (s, 1H), 2.80 – 2.53 (m, 3H), 2.54 – 2.37 (m, 1H), 1.42 (s, 9H), 1.36 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 165.4, 161.9, 137.2, 132.3, 130.6, 128.4, 123.8, 123.2, 85.1, 76.6, 70.3, 33.6, 30.9, 27.6, 26.7, 26.7. UPLC-DAD-QTOF: calcd for $C_{19}H_{25}NO_4Br$ $[M+H]^+$, 410.0967; found, 410.0970.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 11.5 min (minor), 16.4 min (major)).

5.3.4. Elaboration of adducts

5.3.4.1. *Synthesis of Δ⁵-dehydroprolines **10-13** and corresponding derivatives **14-18***

Δ^5-Dehydroprolines **10-13** were prepared according to the following procedure:[262]

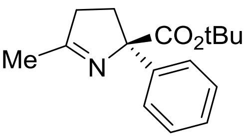


3Ad, 3Af, 3Aa, 3Ab

10	R^1: Ph, R^2: Me	80%
11	R^1: Ph, R^2: Et	83%
12	R^1: Ph, R^2: *p*-MeC_6H_4	80%
13	R^1: Ph, R^2: *p*-$OMeC_6H_4$	Quantit.

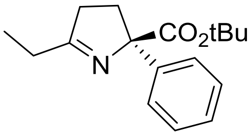
Concentrated HCl solution (0.5 mL) was dropwise added to a solution of the corresponding α-isonitrile ketone (1.0 mmol) in ethanol (10 mL). The mixture was stirred for 1 hour at room temperature. Then, the solvent was removed by reduced pressure. Water (10 mL) was added and the mixture was basified with NH_4OH (pH 9-10). The aqueous phase was extracted with dichloromethane (3 × 15 mL) and the combined organic layer was washed with water and sat. brine. The organic phase was dried over $MgSO_4$ and the solvent was evaporated to give Δ^5-dehydroprolines **10-13** which were submitted to the next hydrogenation step without further purification.

tert-Butyl (R)-5-methyl-2-phenyl-3,4-dihydro-2H-pyrrole-2-carboxylate (10)



Prepared according to the general procedure starting from adduct **3Aa** (287 mg, 1 mmol). The title compound was isolated as white foam. Yield: 80% (207 mg, 0.8 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H), 7.40 – 7.19 (m, 3H), 2.92 – 2.76 (m, 1H), 2.77 – 2.59 (m, 1H), 2.61 – 2.44 (m, 1H), 2.18 (s, 3H), 2.20 – 2.05 (m, 1H), 1.38 (s, 9H).

tert-Butyl (R)-5-ethyl-2-phenyl-3,4-dihydro-2H-pyrrole-2-carboxylate (11)



Prepared according to the general procedure starting from adduct **3Ab** (301 mg, 1 mmol). The title compound was isolated as colourless oil. Yield: 83% (227 mg, 0.81 mmol).^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H), 7.37 – 7.20 (m, 3H), 2.88 – 2.76 (m, 1H), 2.75 – 2.61 (m,

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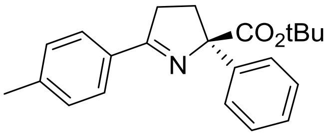
[262] Adapted from: Zhao, M.; Zhu, H.; Dai, T.; Shi, M. *J. Org. Chem* **2015**, *80*, 11330-11338.

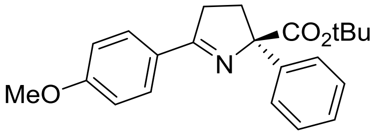
1H), 2.60 – 2.55 (m, 1H), 2.50 (q, *J* = 7.5 Hz, 2H), 2.16 – 2.03 (m, 1H), 1.38 (s, 9H), 1.22 (t, *J* = 7.5 Hz, 3H).

tert-Butyl (R)-2-phenyl-5-(p-tolyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (12)



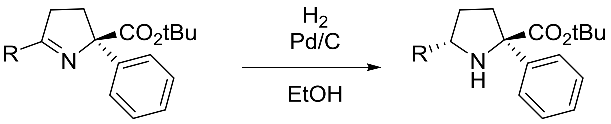
Prepared according to the general procedure starting from adduct **3Ad** (363 mg, 1 mmol). The title compound was isolated as white solid. m.p.= 120-125°C. Yield: 80% (268 mg, 0.8 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.94 – 7.85 (m, 2H), 7.58 – 7.50 (m, 2H), 7.38 – 7.28 (m, 2H), 7.25 – 7.21 (m, 3H), 3.19 – 2.91 (m, 3H), 2.40 (s, 3H), 2.32 – 2.19 (m, 1H), 1.40 (s, 9H).

tert-Butyl (R)-5-(4-methoxyphenyl)-2-phenyl-3,4-dihydro-2H-pyrrole-2-carboxylate (13)



Prepared according to the general procedure starting from adduct **3Af** (379 mg, 1 mmol). The title compound was isolated as yellow foam. Yield: Quantit. (351 mg, 1.0 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.02 – 7.93 (m, 2H), 7.60 – 7.49 (m, 2H), 7.40 – 7.31 (m, 2H), 7.32 – 7.24 (m, 1H), 7.00 – 6.93 (m, 2H), 3.88 (s, 3H), 3.21 – 2.91 (m, 3H), 2.38 – 2.16 (m, 1H), 1.42 (s, 9H).

Diastereoselective synthesis of α-quaternary proline esters 14 and 15

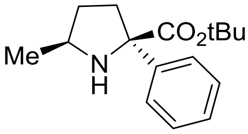


10 R: Me
11 R: Et

14 R: Me
15 R: Et

The corresponding dihydropyrrol **10/11** (0.5 mmol) was dissolved in ethanol (2.0 mL). Pd/C (50 mg) was added to this solution, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 16 h at room temperature. The reaction mixture was then passed through celite to remove Pd/C, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica (hexane/EtOAc 90/10) to give pyrrolidines **14** and **15**.

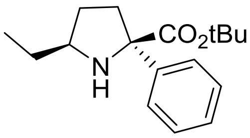
tert-Butyl (2R,5S)-5-methyl-2-phenylpyrrolidine-2-carboxylate (14)



Prepared according to the general procedure starting from the dihydropyrrol **10** (129.7 mg, 0.5 mmol). The title compound was isolated as a white foam. dr > 20:1. Yield: 80% (104.5 mg, 0.4 mmol). $[\alpha]_D^{22} = -5.6°$ (*c*=0.55, 98% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.34 – 7.16 (m, 3H), 3.38 – 3.24 (m, 1H), 2.74 (ddd, *J* = 12.5, 7.2, 2.9 Hz, 1H), 2.57 (s, 1H), 2.15 – 2.04 (m, 1H), 2.01 – 1.88 (m, 1H), 1.36 (s, 9H), 1.34 – 1.27 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 144.2, 128.0, 126.9, 126.4, 81.5, 72.9, 54.4, 38.1, 34.5, 27.9, 21.9. UPLC-DAD-QTOF: calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$, 262.1807; found, 262.1810.

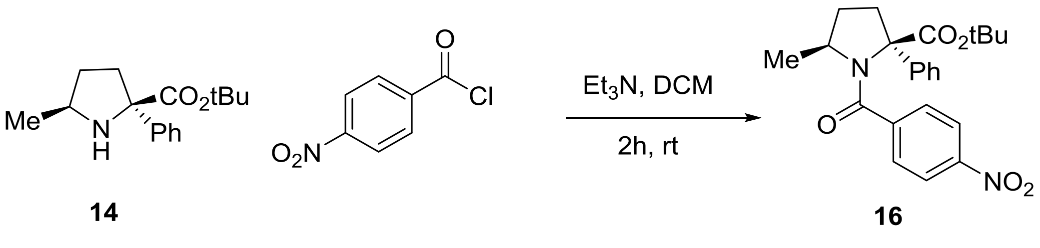
tert-Butyl (2R,5S)-5-ethyl-2-phenylpyrrolidine-2-carboxylate (15)



Prepared according to the general procedure starting from the dihydropyrrol **11** (136.7 mg, 0.5 mmol). The title compound was isolated as a white foam. dr > 20:1. Yield: 75% (103.3 mg, 0.38 mmol). $[\alpha]_D^{22} = -6.23°$ (*c*=1, 94% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H), 7.38 – 7.21 (m, 3H), 3.23 – 3.10 (m, 1H), 2.83 – 2.71 (m, 1H), 2.62 (s, 1H), 2.11 (ddd, *J* = 12.3, 10.5, 7.1 Hz, 1H), 2.04 – 1.93 (m, 1H), 1.71 (m, 1H), 1.57 – 1.43 (m, 1H), 1.40 (s, 9H), 1.39 – 1.27 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 144.2, 128.0, 126.9, 126.3, 81.4, 72.5, 60.6, 37.5, 32.0, 29.7, 27.8, 11.5. UPLC-DAD-QTOF: calcd for $C_{17}H_{26}NO_2$ $[M+H]^+$, 276.1964; found, 276.1970.

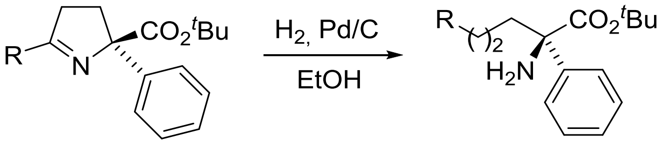
Derivatization of the quaternary proline esters 14 to 16 for X-ray analysis



To a solution of pyrrolidine **14** (52 mg, 0.2 mmoL, 1 equiv.) and Et_3N (42 µL, 0.3 mmol, 1.5 equiv.) in 2mL of dichloromethane was added 4-nitrobenzoyl chloride (56 mg, 0.3 mmoL, 1.5 equiv.) dropwise and the reaction was stirred at room temperature for

4h. After dilution with 5 mL dichloromethane, the mixture was washed with DCM (3 × 3 mL). The resulting solution was dried over $MgSO_4$, concentrated under reduced pressure and the crude was purified by flash column chromatography on silica (hexane/EtOAc 90/10). The title compound **16** was isolated as a white solid. m.p.= 200-204°C. Yield: 95% (78.0 mg, 0.19 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.42 – 7.23 (m, 3H), 4.39 – 4.29 (m, 1H), 2.74 (td, *J* = 12.4, 6.2 Hz, 1H), 2.43 – 2.29 (m, 1H), 2.13 – 1.95 (m, 1H), 1.71 – 1.60 (m, 1H), 1.55 (s, 9H), 1.05 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 167.3, 148.5, 143.6, 138.3, 127.8, 127.8, 127.5, 127.4, 124.0, 81.9, 73.9, 56.4, 39.1, 31.4, 28.1, 20.9.

Synthesis of α,α-disubtituted α-amino esters 17 and 18

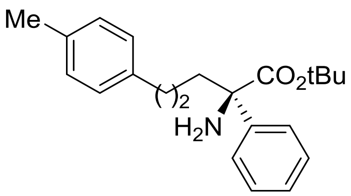


12 R: *p*-MeC_6H_4
13 R: *p*-$OMeC_6H_4$

17 R: *p*-MeC_6H_4 82%
18 R: *p*-$OMeC_6H_4$ 80%

The corresponding dihydropyrrol **12/13** (0.5 mmol) was dissolved in ethanol (2.0 mL). Pd/C (50 mg) was added to this solution, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 16 h at room temperature. The reaction mixture was then passed through celite to remove Pd/C, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica (hexane/EtOAc 90/10) to give amino esters **17** and **18**.

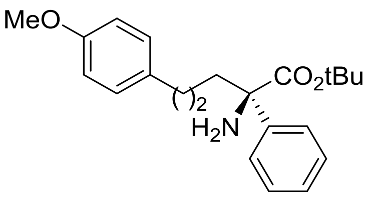
tert-Butyl (R)-2-amino-2-phenyl-5-(p-tolyl)pentanoate (17)



Prepared according to the general procedure starting from the dihydropyrrol **12** (167.7 mg, 0.5 mmol). The title compound was isolated as a white solid. m.p.= 45°C. Yield: 82% (139.2 mg, 0.41 mmol). $[\alpha]_D{}^{22}$= – 22.46° (*c*=0.65, 96% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.36 – 7.22 (m, 3H), 7.12 – 7.00 (m, 3H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 2.22 – 2.07 (m, 1H), 2.04 – 1.91 (m, 1H), 1.85 (s, 1H), 1.69 – 1.52 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 143.9, 139.1, 135.3, 129.1, 128.4, 128.3, 127.2, 125.5, 81.5, 64.1, 39.5, 35.8, 28.0, 26.3, 21.1. UPLC-DAD-QTOF: calcd for $C_{22}H_{30}NO_2$ $[M+H]^+$, 340.2277; found, 340.2281.

tert-Butyl (R)-2-amino-4-(4-methoxyphenyl)-2-phenylpentanoate (18)

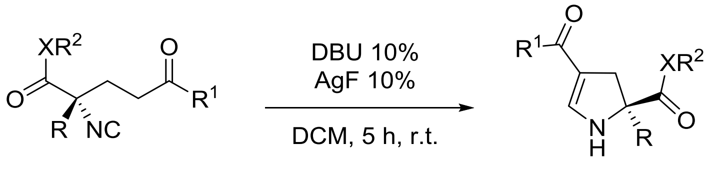


Prepared according to the general procedure starting from the dihydropyrrol **13** (176 mg, 0.5 mmol). The title compound was isolated as a yellow oil. Yield: 80% (142.2 mg, 0.4 mmol). $[\alpha]_D{}^{22}= -10.34°$ (*c*=1.65, 96% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.37 – 7.22 (m, 3H), 7.09 – 7.02 (m, 2H), 6.85 – 6.76 (m, 2H), 3.78 (s, 3H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.19 – 2.07 (m, 1H), 2.03 – 1.95 (m, 1H), 1.92 (brs, 2H), 1.67 – 1.51 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, CDCl3) δ 175.4, 158.4, 144.4, 134.8, 129.9, 128.9, 127.7, 126.0, 114.4, 82.1, 64.6, 55.9, 40.0, 35.9, 28.5, 26.9. UPLC-DAD-QTOF: calcd for $C_{22}H_{30}NO_2$ $[M+H]^+$, 356.2115; found, 356.2124.

5.3.4.2. Synthesis of Δ⁴-dehydroprolines ***19-23***

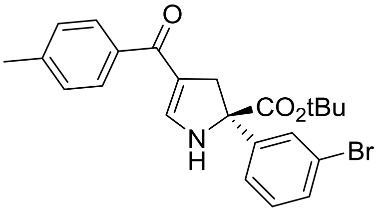
Δ^4-Dehydroprolines **19-23** were prepared according to the following procedure:



3Aa, 3Ab, 3Ad, 3Ca, 3Dd **19-23**

The corresponding adduct **3** (0.2 mmol) was dissolved in dichloromethane (0.4 ml), and AgF (2.5 mg, 0.1 equiv.) and DBU (3 mg, 0.1 equiv.) was added. The reaction mixture was stirred for 5 h at room temperature. Then, the reaction mixture was diluted in dichloromethane (2 mL), washed with HCl 1M and saturated NH_4Cl and the organic layer was dried with $MgSO_4$. The solvent was remove under reduced pressure to give the desired dehydroproline adduct. A rapid filtration through silica-gel pad (hexane/EtOAc 50/15) was sufficient to remove traces of impurities and excess reactants. These products were thermally instables unless at low temperature (–40 °C).

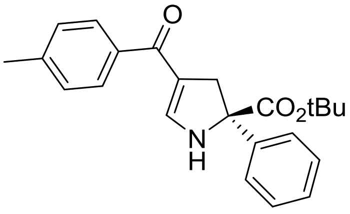
tert-Butyl (R) 2-(3-bromophenyl)-4-(4-methylbenzoyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (19)



Prepared according to the general procedure starting from **3Dd** (88.5 mg, 0.2 mmol). The title compound was isolated as a yellow foam. Yield: 92% (81.4 mg, 0.18 mmol).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59 (t, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.43 – 7.33 (m,2H), 7.17 (dd, *J* = 15.3, 7.7 Hz, 3H), 7.09 (d, *J* = 3.0 Hz, 1H), 6.25 (d, *J* = 2.6 Hz, 1H), 3.86 (dd, *J* = 15.9, 0.9 Hz, 1H), 3.14 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 190.0, 171.9, 149.7, 144.5, 140.8, 137.8, 130.9, 130.2, 128.8, 128.6, 128.0, 124.0, 122.8, 113.5, 83.5, 73.5, 40.4, 27.8, 21.5. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}NO_3Br$ [M+H]$^+$, 442.0101; found, 442.0105.

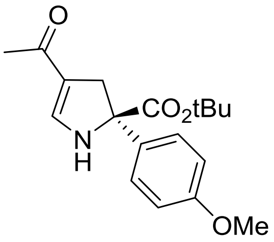
tert-Butyl (R) 4-(4-methylbenzoyl)-2-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate (20)



Prepared according to the general procedure starting from **3Ad** (72.7 mg, 0.2 mmol). The title compound was isolated as a white foam. Yield: 85% (61.8 mg, 0.17 mmol).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.44 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.41 – 7.22 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 3.1 Hz, 1H), 5.96 (d, *J* = 2.5 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.22 (d, *J* = 15.9 Hz, 1H), 2.37 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 190.2, 172.7, 149.7, 142.1, 140.8, 138.0, 128.9, 128.7, 128.1, 127.9, 125.3, 113.8, 83.2, 74.0, 40.0, 27.9, 21.5. UPLC-DAD-QTOF: calcd for $C_{23}H_{26}NO_3$ [M+H]$^+$, 364.1913; found, 364.1913.

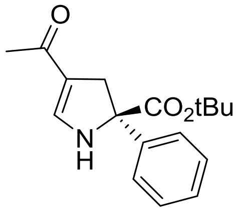
tert-Butyl (R) 4-acetyl-2-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (21)



Prepared according to the general procedure starting from **3Ca** (63.5 mg, 0.2 mmol). The title compound was isolated as a white foam. Yield: 88% (55.9 mg, 0.18 mmol).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34 – 7.25 (m, 2H), 7.26 (d, *J* = 2.7 Hz, 1H), 6.90 – 6.79 (m, 2H), 5.74 (s, 1H), 3.78 (s, 3H), 3.67 (d, *J* = 15.8 Hz, 1H), 2.99 (d, *J* = 15.9 Hz, 1H), 2.15 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 192.4, 173.2, 159.5, 147.5, 134.4, 126.8, 115.4, 114.3, 83.3, 74.0, 55.6, 39.5, 28.1, 25.7. UPLC-DAD-QTOF: calcd for $C_{18}H_{24}NO_4$ [M+H]$^+$, 318.1705; found, 318.1711.

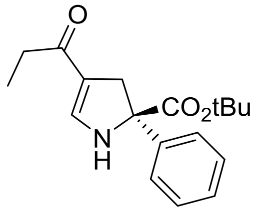
tert-Butyl (R) 4-acetyl-2-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate (22)



Prepared according to the general procedure starting from **3Aa** (57.5 mg, 0.2 mmol). The title compound was isolated as a yellow foam. Yield: 85% (48.9 mg, 0.17 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.23 (m, 6H), 5.74 (s, 1H), 3.72 (d, *J* = 15.1 Hz, 1H), 3.01 (d, *J* = 15.8 Hz, 1H), 2.16 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 172.6, 147.1, 141.9, 128.5, 127.7, 125.1, 115.0, 83.0, 74.1, 53.4, 39.1, 27.7, 25.3. UPLC-DAD-QTOF: calcd for $C_{17}H_{21}NO_3$ $[M+H]^+$, 288.1600; found, 288.1598.

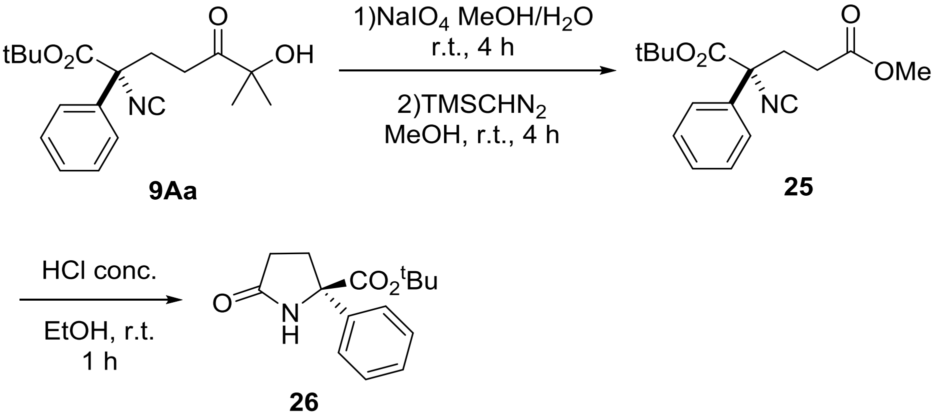
tert-Butyl (R) 2-phenyl-4-propionyl-2,3-dihydro-1H-pyrrole-2-carboxylate (23)



Prepared according to the general procedure starting from **3Ab** (60.3 mg, 0.2 mmol). The title compound was isolated as a white foam. Yield: 78% (47.0 mg, 0.16 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.8 Hz, 1H), 7.38 – 7.25 (m, 5H), 5.48 (s, 1H), 3.74 (dd, *J* = 15.8, 1.0 Hz, 1H), 3.02 (d, *J* = 15.8 Hz, 1H), 2.50 (q, *J* = 7.5 Hz, 2H), 1.41 (s, 9H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 172.9, 146.1, 142.2, 128.7, 127.9, 125.3, 114.4, 83.1, 74.0, 39.4, 31.2, 27.9, 9.8. UPLC-DAD-QTOF: calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$, 302.1756; found, 302.1760.

5.3.4.3. *Synthesis of pyroglutamate **26***



1st step: [263] A suspension of sodium periodate $NaIO_4$ (535 mg, 2.5 mmol, 5 equiv.) in water (1.5 mL) was added to a solution of the corresponding α-hydroxy ketone **9Aa** (166 mg, 0.5 mmol, 1 equiv.) in methanol (2.5 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TLC). Then the solvent was removed under reduced pressure. Water (7 mL) was added to the crude product, the resulting mixture was extracted with Et_2O (3 × 7 mL) and washed with water. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid as white solid. The crude product was used inmediately in the next step without further purification because its instability. ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.46 – 7.37 (m, 3H), 2.72 – 2.61 (m, 1H), 2.58 – 2.38 (m, 3H), 1.42 (s, 9H).

2nd step : (Trimethylsilyl)diazomethane (2M in hexane, 1.25 mL, 5 equiv.) was slowly added to a solution of the crude acid (0.5 mmol) in methanol (3.5 mL). The mixture was stirred at room temperature until the reaction was complete (about 2 h). The mixture was evaporated and purify by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 20/1) to give the compound **25** as colourless oil. Overall yield (step 1 and 2): 62% (94.0 mg, 0.31 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.48 – 7.33 (m, 3H), 3.66 (s, 3H), 2.76 – 2.58 (m, 1H), 2.59 – 2.31 (m, 3H), 1.42 (s, 9H).

3rd step: Concentrated HCl solution (0.1 mL) was dropwise added to a solution of the ester **25** (60.7 mg, 0.2 mmol) in ethanol (2 mL). The mixture was stirred for 1 hour at room temperature. Then, the solvent was removed by reduced pressure. Water (2 mL) was added and basify with NH_4OH (pH 9-10). The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic layer was washed with water and sat. brine. The organic phase was dried over $MgSO_4$, the solvent was evaporated and the crude was purify by flash column chromatography on silica gel (eluting hexane/ethyl acetate 8/2) to give the product **26**. Yield: 90% (54.5 mg, 0.18 mmol) $[\alpha]_D{}^{22}$= +84.04° (*c*=0.55, 97% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.26 (m, 5H), 6.55 (s, 1H), 3.04 – 2.88 (m, 1H), 2.43 – 2.33 (m, 2H), 2.33 – 2.21 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 170.6, 140.7, 128.4, 127.7, 124.2, 82.5, 68.5, 33.1, 29.6, 27.4. UPLC-DAD-QTOF: calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$, 262.1443; found, 262.1445.

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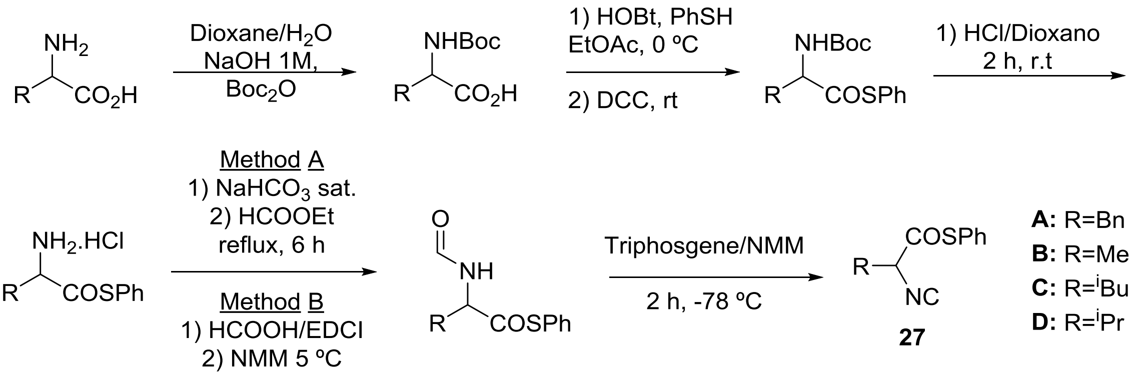
[263] Adapted from: Badiola, E.; Fiser, B.; Gomez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo C. *J. Am. Chem. Soc.* **2014,** *136*, 17869-17881.

5.4. Experimental section of chapter 3

5.4.1. Synthesis of isocyano(thio)acetates 27-35, 62 and 73

*5.4.1.1. Synthesis of isocyanothioacetates **27A-D***

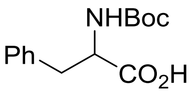
The isocyanothioacetates **27A-D** were prepared according to the following procedure:



EDCI = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
NMM = 4-Methylmorpholine

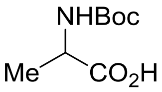
1st step: To a solution of the amino acid (10 mmol, 1 equiv.) in dioxane (40 mL) and water (20 mL) was added NaOH 1M (20 mL). The mixture was cooled to 0 °C, Boc_2O (2.4 g, 11 mmol, 1.1 equiv.) was slowly added and the reaction was stirred 6 h at room temperature. Then, the reaction mixture was diluted with ethyl acetate (20 mL), cooled in an ice-bath and acidified to pH 2-3 with $KHSO_4$ 1M. The layers were separated and the aqueous fraction was extracted with ethyl acetate (2 × 20 mL). Finally, the combined organic phases was dried over $MgSO_4$ and was concentrated under reduced pressure. The crude material was used in the next step without purification.

(tert-Butoxycarbonyl)phenylalanine



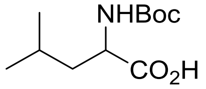
Yield: Quantit. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 3H), 7.22 – 7.14 (m, 2H), δ 4.94 (d, *J* = 8.1 Hz, 1H), 4.67 – 4.53 (m, 1H), 3.20 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.14 – 3.01 (m, 1H), 1.42 (s, 9H).

(tert-Butoxycarbonyl)alanine



Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.48 – 4.30 (m, 1H), 1.55 – 1.45 (m, 12H).

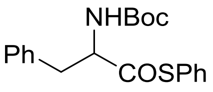
(tert-Butoxycarbonyl)leucine



Yield: Quantit. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 – 4.77 (m, 1H), 4.40 – 4.23 (m, 1H), 1.84 – 1.61 (m, 2H), 1.60 – 1.49 (m, 1H), 1.45 (s, 9H), 0.96 (d, *J* = 6.2 Hz, 6H).

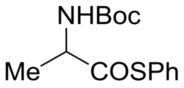
2nd step:[264] To a solution of Boc-aminoacid (5 mmol, 1 equiv.) and 1-hydroxibenzotriazole HOBt (676 mg, 5 mmol, 1.0 equiv.) in dry ethyl acetate (50 mL) under argon, at 0 °C, was added the corresponding thiol (10 mmol, 2 equiv.). After 5 min, 1,3-dicyclohexylcarbodiimide DCC (1.08 g, 5.5 mmol, 1.1 equiv.) was added by portions. After stirring overnight, a 50% solution of acetic acid in ethyl acetate (2 mL) was added. The reaction mixture was filtered through a pad of celite and solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel.

S-Phenyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanethioate



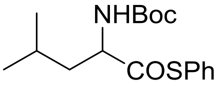
Yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.19 (m, 10H), 5.09 – 4.95 (m, 1H), 4.80 (q, *J* = 7.5, 7.1 Hz, 1H), 3.19 (t, *J* = 6.0 Hz, 2H), 1.48 (d, *J* = 2.3 Hz, 9H).

S-Phenyl 2-((tert-butoxycarbonyl)amino)propanethioate



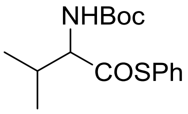
Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 5H), 5.06 – 4.95 (m, 1H), 4.59 – 4.45 (m, 1H), 1.49 (s, 9H), 1.44 (d, *J* = 7.2 Hz, 3H).

S-Phenyl 2-((tert-butoxycarbonyl)amino)-4-methylpentanethioate



Yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.35 (m, 5H), 4.94 (d, *J* = 8.8 Hz, 1H), 4.53 (td, *J* = 9.5, 3.9 Hz, 1H), 1.88 – 1.70 (m, 2H), 1.64 – 1.56 (m, 1H), 1.53 (s, 9H), 1.00 (dd, *J* = 6.3, 5.0 Hz, 6H).

S-Phenyl 2-((tert-butoxycarbonyl)amino)-3-methylbutanethioate



Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.3 Hz, 5H), 5.06 (d, *J* = 9.6 Hz, 1H), 4.45 (dd, *J* = 9.4, 4.6 Hz, 1H), 2.36 (dt, *J* = 13.1, 6.8 Hz, 1H), 1.53 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H).

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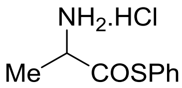
[264] Adapted from: a) Garnier-Amblard, E.-C.; Mays, S. G.; Arrendale, R. F.; Baillie, M. T.; Bushnev, A. S.; Culver, D. G.; Evers, T. J.; Holt, J. J.; Howard, R. B.; Liebeskind, L. S.; Menaldin, D. S.; Natchus, M. G.; Petros, G. A.; Ramaraju, H.; Reddy, G. P.; Liotta, D. C. *Med. Chem. Lett.* **2011**, *2*, 438-443. b) Rostein, B. H.; Winternheimer, D. J.; Yin, L. M.; Deber, C. M.; Yudin, A. K. *Chem. Commun.* **2012,** *48*, 3775–3777.

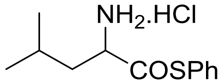
3rd step: To a solution of HCl 4M in dioxano (10 mL) Boc-protected aminothioester (4 mmol) was added and the mixture was stirred 2h. Then, the solvent was removed under reduced pressure, the solid was triturated with Et_2O and filtered. The title compound was obtained as a white solid.

S-Phenyl 2-aminopropanethioate hydrochloride



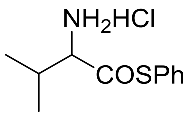
Yield: Quantit. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 3H), 7.53 – 7.36 (m, 5H), 4.31 (q, *J* = 7.2 Hz, 1H), 1.65 (d, *J* = 7.2 Hz, 3H).

S-Phenyl 2-amino-4-methylpentanethioate hydrochloride



Yield: 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 3H), 7.49 – 7.31 (m, 5H), 4.28 – 4.15 (m, 1H), 2.10 – 1.88 (m, 2H), 1.87 – 1.71 (m, 1H), 0.91 (t, *J* = 5.8 Hz, 6H).

S-Phenyl 2-amino-3-methylbutanethioate hydrochloride



Yield: Quantit. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 3H), 7.53 – 7.37 (m, 5H), 4.16 (d, *J* = 4.5 Hz, 1H), 2.59 – 2.43 (m, 1H), 1.17 (dd, *J* = 9.4, 6.9 Hz, 6H).

4th step: METHOD A: The amine hydrochloride (5 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with saturated $NaHCO_3$ (3 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. To the residue obtained above was added ethyl formate (15 mL) and the mixture was heated at 90 °C for 14 h, and then the reaction was concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel.

METHOD B[265]: To a solution of formic acid (9.3 mL, 8 mmol, 4 equiv.) in CH_2Cl_2 (15 mL) at 0 °C was added EDCI carbodiimide (766 mg, 4 mmol, 2 equiv.). After 15 min, a solution containing substrate (2 mmol, 1 equiv.) and *N*-methylmorpholine (0.44 mL, 4 mmol, 2 equiv.) in CH_2Cl_2 (15 mL) at 0 °C was added. The mixture was stirred at 5 °C for 20 h, washed successively twice with HCl 1M (20 mL), saturated $NaHCO_3$ (20 mL). The solution was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel giving the formamide compound.

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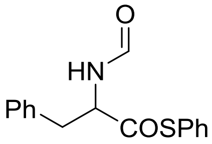
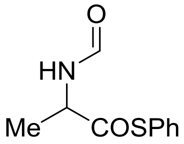
[265] Adapted from: Chem, F. M. F.; Benoitton, N. L. *Synthesis,* **1979**, *9*, 709-710.

S-Phenyl 2-formamido-3-phenylpropanethioate



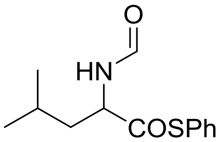
Yield: 94% (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.53 – 7.16 (m, 10H), 6.01 (d, *J* = 8.6 Hz, 1H), 5.31 – 5.19 (m, 1H), 3.25 (d, *J* = 6.3 Hz, 2H).

S-Phenyl 2-formamidopropanethioate



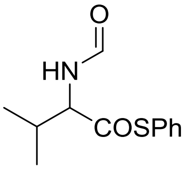
Yield: 85% (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.22 (m, 1H), 7.49 – 7.37 (m, 5H), 6.13 (s, 1H), 5.04 – 4.90 (m, 1H), 1.53 (d, *J* = 7.1 Hz, 3H).

S-Phenyl 2-formamido-4-methylpentanethioate



Yield: 94% (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 1H), 7.48 – 7.33 (m, 5H), 5.99 (d, *J* = 8.9 Hz, 1H), 5.07 – 4.89 (m, 1H), 1.88 – 1.69 (m, 2H), 1.68 – 1.52 (m, 1H), 0.98 (dd, *J* = 6.3, 4.2 Hz, 6H).

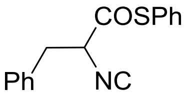
S-Phenyl 2-formamido-3-methylbutanethioate



Yield: 90% (method A). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 – 8.33 (m, 1H), 7.54 – 7.38 (m, 5H), 6.08 (s, 1H), 4.95 (ddd, *J* = 9.4, 4.8, 0.8 Hz, 1H), 2.50 – 2.32 (m, 1H), 1.10 (dd, *J* = 6.8, 1.9 Hz, 3H), 1.00 (m, 3H).

5th step:[266] To the corresponding *N*-formyl thioester (2 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added N-methylmorpholine (0.44 mL, 4 mmol, 2 equiv.) and the mixture was cooled to –78 °C. Triphosgene (207 mg, 0.7 mmol, 0.35 equiv.) was added in one portion and the reaction mixture was stirred at -78 °C with TLC monitoring (around 2 h). The reaction was quenched by slow addition of water, quickly extracted with CH_2Cl_2 (2 × 20 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure (Keep bath temp below 23 °C). The reaction crude was purified by flash column chromatography on silica gel. The product exhibited the characteristic isonitrile NC band at IR: 2135-2137 cm^{-1}.

S-Phenyl 2-isocyano-3-phenylpropanethioate (27A)



The isocyanothioate **4B** was obtained following the general procedure. Yellow oil. Yield (last step): 60 % (321 mg, 1.2 mmol). ^{1}H

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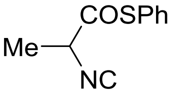
[266] Adapted from: Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.*, **2009**, *50*, 577-579.

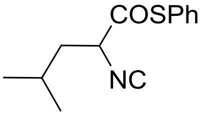
NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 3H), 7.43 – 7.33 (m, 4H), 7.33 – 7.25 (m, 3H), 4.56 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.32 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.19 (dd, *J* = 13.9, 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 164.0, 134.5, 133.9, 130.1, 129.5, 129.5, 128.7, 127.8, 125.6, 64.2, 39.3. UPLC-DAD-QTOF: $C_{16}H_{14}NOS$ $[M+H]^+$ calcd.: 268.0796, found: 268.0795.

S-Phenyl 2-isocyanopropanethioate (27B)



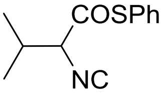
The isocyanothioate **4A** was obtained following the general procedure. Yellow oil. Yield (last step): 62 % (237 mg, 1.24 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.35 (m, 5H), 4.46 (q, *J* = 7.1 Hz, 1H), 1.72 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 162.5, 134.6, 130.1, 129.5, 125.6, 58.2, 20.0. UPLC-DAD-QTOF: $C_{10}H_{10}NOS$ $[M+H]^+$ calcd.: 192.0483, found: 192.0486.

S-Phenyl 2-isocyano-4-methylpentanethioate (27C)



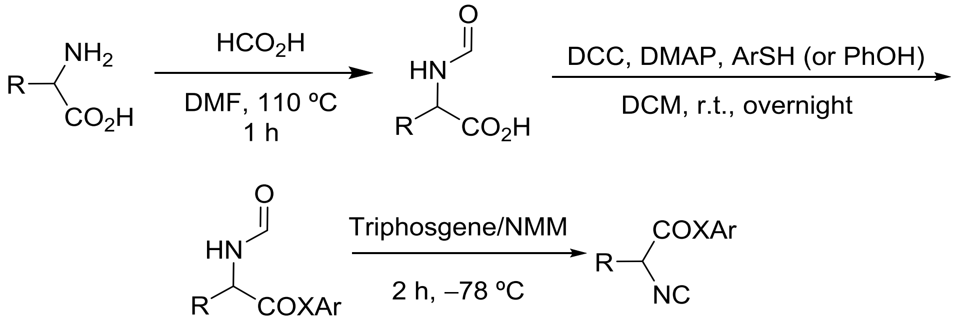
The isocyanothioate **4C** was obtained following the general procedure. Yellow oil. Yield (last step): 75 % (350 mg, 1.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.40 (m, 5H), 4.45 (dd, *J* = 9.9, 4.5 Hz, 1H), 2.09 – 1.91 (m, 2H), 1.87 – 1.73 (m, 1H), 1.05 (dd, *J* = 12.5, 6.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 163.2, 134.6, 130.1, 129.5, 125.7, 61.8, 42.0, 24.9, 22.8, 20.9. UPLC-DAD-QTOF: $C_{13}H_{16}NOS$ $[M+H]^+$ calcd.: 234.0953, found: 234.0953.

S-Phenyl 2-isocyano-3-methylbutanethioate (27D)



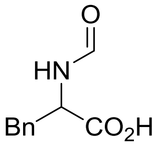
The isocyanothioate **4D** was obtained following the general procedure. Colourless oil. Yield (last step): 71 % (311 mg, 1.42 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.39 (m, 5H), 4.31 (d, *J* = 4.1 Hz, 1H), 2.55 – 2.37 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 163.2, 134.2, 129.7, 129.1, 125.4, 68.9, 31.4, 19.0, 15.8. UPLC-DAD-QTOF: $C_{12}H_{14}NOS$ $[M+H]^+$ calcd.: 220.0796, found: 220.0800.

*5.4.1.2. Synthesis of isocyano(thio)acetates **28-35, 62** and **73***



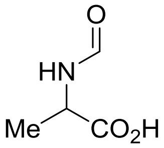
1st step:[267] A mixture of formic acid (0.96 mL, 26 mmol, 1.7 equiv.), N,N-dimethylformamide (5 mL) and the corresponding amino acid (10 mmol, 1 equiv.) was heated to reflux with good stirring. The starting amino acids got slowly dissolved as the reaction progress (about 1 h). Evaporation of the solvent gave the expected formamide.

N-Formylphenyl alanine



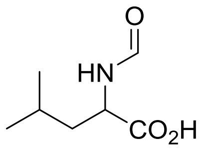
Yield: 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.34 – 7.10 (m, 5H), 4.52 (td, *J* = 8.8, 4.9 Hz, 1H), 3.08 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.87 (dd, *J* = 13.9, 9.2 Hz, 1H).

N-Formyl alanine



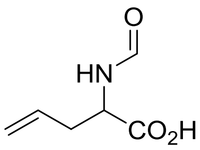
Yield: 96%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (d, *J* = 7.6 Hz, 1H), 8.01 – 7.98 (m, 1H), 4.26 (td, *J* = 7.4, 0.9 Hz, 1H), 1.26 (d, *J* = 7.3 Hz, 3H).

N-Formyl leucine



Yield: 85%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, *J* = 8.1 Hz, 1H), 8.04 – 8.01 (m, 1H), 4.34 – 4.21 (m, 1H), 1.69 – 1.55 (m, 1H), 1.53 – 1.46 (m, 2H), 0.87 (dd, *J* = 12.0, 6.4 Hz, 6H).

2-Formamidopent-4-enoic acid



Yield: 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 5.81 – 5.63 (m, 1H), 5.17 – 4.95 (m, 2H), 4.29 (td, *J* = 8.0, 5.1 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.39 – 2.26 (m, 1H).

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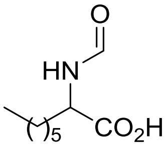
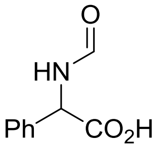
[267] Aizpurua, J. M.; Palomo, C. *Synth. Commun.*, **1983**, *13,* 745-752.

2-Formamidooctanoic acid



Yield: 88%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, *J* = 7.9 Hz, 1H), 8.02 (s, 1H), 4.23 (td, *J* = 8.3, 4.9 Hz, 1H), 1.79 – 1.47 (m, 2H), 1.34 – 1.16 (m, 8H), 0.91 – 0.79 (m, 3H).

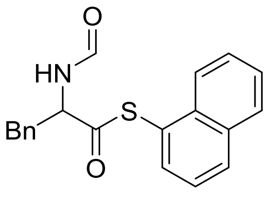
2-Formamido-2-phenylacetic acid



Yield: 95%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, *J* = 7.6 Hz, 1H), 8.12 – 8.03 (m, 1H), 7.47 – 7.27 (m, 5H), 5.44 – 5.33 (m, 1H).

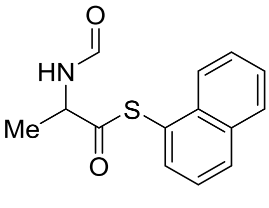
2nd step:[268] To a solution of N-formyl amino acid (5 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at 0 °C was added the corresponding thiol (1.1 equiv.) followed by DMAP (122 mg, 1 mmol, 0.2 equiv.) and DCC (1.23 g, 6 mmol, 1.2 equiv.). The reaction mixture was allowed to reach room temperature and was stirred overnight. The precipitate is filtered off and the filtrate is concentrated under reduced pressure to an oil. The residue was purified by flash column chromatography on silica gel.

S-(Naphthalen-1-yl) 2-formamido-3-phenylpropanethioate



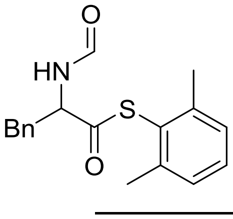
Yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.03 – 7.96 (m, 2H), 7.96 – 7.88 (m, 1H), 7.65 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.63 – 7.50 (m, 3H), 7.44 – 7.33 (m, 3H), 7.28 – 7.23 (m, 2H), 6.07 (d, *J* = 8.8 Hz, 1H), 5.40 – 5.25 (m, 1H), 3.35 – 3.22 (m, 2H).

S-(Naphth-1-yl) 2-formamidopropanethioate



Yield: 65%.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.18 – 8.08 (m, 1H), 8.04 – 7.96 (m, 1H), 7.91 (dd, *J* = 6.9, 2.6 Hz, 1H), 7.71 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.63 – 7.47 (m, 3H), 6.32 (d, *J* = 7.7 Hz, 1H), 5.06 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H).

S-(2,6-Dimethylphenyl) 2-formamido-3-phenylpropanethioate



Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.40 – 7.22 (m, 6H), 7.18 (d, *J* = 7.6 Hz, 2H), 6.11 (d, *J* = 8.3 Hz, 1H), 5.25 (dt, *J* = 8.6, 6.6 Hz, 1H), 3.32 – 3.15 (m, 2H), 2.31 (s, 6H).

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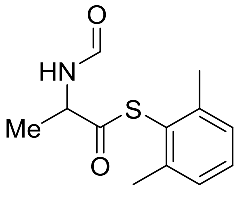
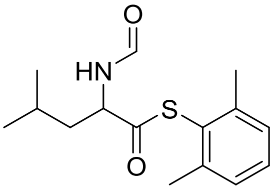
[268] Adapted from: Claraz, A.; Sahoo, G.; Berta, D.; Madarász, A.; Pápai, I.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 669-673.

S-(2,6-Dimethylphenyl) 2-formamidopropanethioate



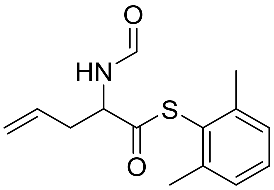
Yield: 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.32 – 7.23 (m, 1H), 7.23 – 7.14 (m, 1H), 6.34 – 6.07 (m, 1H), 5.09 – 4.89 (m, 1H), 2.36 (s, 6H), 1.57 (d, *J* = 7.2 Hz, 3H).

S-(2,6-Dimethylphenyl) 2-formamido-4-methylpentanethioate



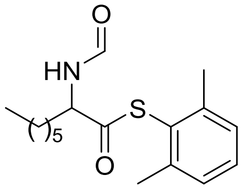
Yield: 91%.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 1H), 7.26 – 7.20 (m, 1H), 7.20 – 7.11 (m, 2H), 5.97 (d, *J* = 8.8 Hz, 1H), 5.05 – 4.90 (m, 1H), 2.33 (s, 6H), 1.84 – 1.71 (m, 2H), 1.61 – 1.55 (m, 1H), 1.00 (dd, *J* = 6.2, 2.9 Hz, 6H).

S-(2,6-Dimethylphenyl) 2-formamidopent-4-enethioate



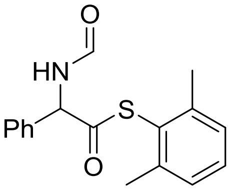
Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.35 – 7.10 (m, 3H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.87 – 5.65 (m, 1H), 5.28 – 5.13 (m, 2H), 5.05 – 4.90 (m, 1H), 2.81 – 2.52 (m, 2H), 2.33 (s, 6H).

S-(2,6-Dimethylphenyl) 2-formamidooctanethioate



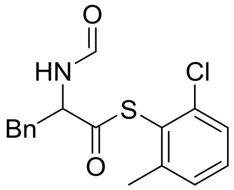
Yield: 71%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 – 8.25 (m, 1H), 7.28 – 7.24 (m, 1H), 7.22 – 7.16 (m, 2H), 6.09 (d, *J* = 8.4 Hz, 1H), 5.05 – 4.91 (m, 1H), 2.36 (s, 6H), 2.11 – 1.95 (m, 1H), 1.78 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.52 – 1.21 (m, 8H), 0.98 – 0.85 (m, 3H).

S-(2,6-Dimethylphenyl) 2-formamido-2-phenylethanethioate



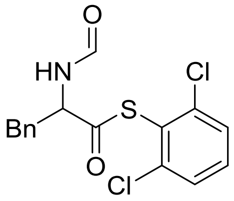
Yield: 85%.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 7.44 – 7.36 (m, 5H), 7.24 – 7.19 (m, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.64 (d, *J* = 5.8 Hz, 1H), 5.91 (dd, *J* = 7.3, 0.9 Hz, 1H), 2.18 (bs, 6H).

S-(2-Chloro-6-methylphenyl) 2-formamido-3-phenylpropanethioate



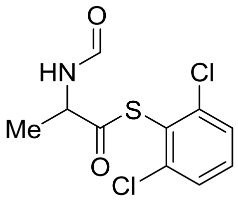
Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.45 – 7.15 (m, 8H), 6.11 (d, *J* = 8.5 Hz, 1H), 5.24 (dt, *J* = 8.6, 6.5 Hz, 1H), 3.31 – 3.21 (m, 2H), 2.36 (s, 3H).

S-(2,6-Dichlorophenyl) 2-formamido-3-phenylpropanethioate



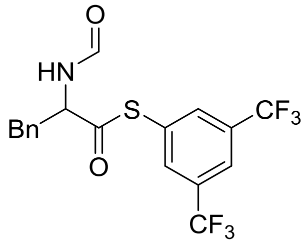
Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.43 – 7.20 (m, 6H), 6.02 (d, *J* = 8.8 Hz, 1H), 5.35 – 5.25 (m, 1H), 3.36 – 3.23 (m, 2H).

S-(2,6-Dichlorophenyl) 2-formamidopropanethioate



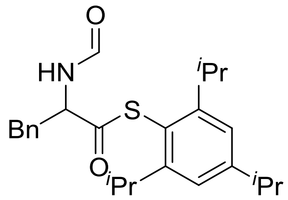
Yield: 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 1H), 7.51 – 7.42 (m, 2H), 7.32 (dd, *J* = 8.9, 7.2 Hz, 1H), 6.13 (s, 1H), 5.09 – 4.95 (m, 1H), 1.57 (d, *J* = 7.1 Hz, 3H).

S-(3,5-bis(Trifluoromethyl)phenyl) 2-formamido-3-phenylpropanethioate



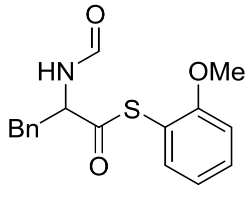
Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 – 8.24 (m, 1H), 7.95 – 7.92 (m, 1H), 7.80 (dd, *J* = 1.7, 0.9 Hz, 2H), 7.45 – 7.29 (m, 3H), 7.26 – 7.18 (m, 2H), 6.35 (s, 1H), 5.28 – 5.11 (m, 1H), 3.30 – 3.15 (m, 2H).

S-(2,4,6-Triisopropylphenyl) 2-formamido-3-phenylpropanethioate



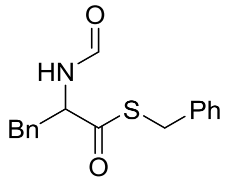
Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.22 (m, 1H), 7.42 – 7.21 (m, 7H), 6.08 (d, *J* = 8.7 Hz, 1H), 5.37 – 5.23 (m, 1H), 3.31 – 3.16 (m, 4H), 2.93 (m, *J* = 6.9 Hz, 1H), 1.34 – 1.25 (m, 6H), 1.16 (d, *J* = 7.5 Hz, 12H).

S-(2-Methoxyphenyl) 2-formamido-3-phenylpropanethioate



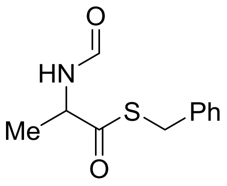
Yield: 72%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.40 – 7.22 (m, 6H), 7.18 (d, *J* = 7.6 Hz, 3H), 6.11 (d, *J* = 8.3 Hz, 1H), 4.96 (dt, *J* = 8.6, 6.6 Hz, 1H), 3.79 (s, 3H), 3.36 – 3.22 (m, 2H).

S-Benzyl 2-formamido-3-phenylpropanethioate



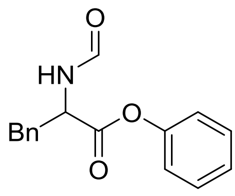
Yield: 80%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.16 (s, 1H), 7.39 – 7.17 (m, 8H), 7.15 – 7.04 (m, 2H), 6.21 – 6.06 (m, 1H), 5.11 (dt, *J* = 8.6, 6.2 Hz, 1H), 4.15 (d, *J* = 2.2 Hz, 2H), 3.16 (dd, *J* = 6.2, 4.2 Hz, 2H).

S-Benzyl 2-formamidopropanethioate



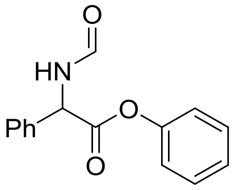
Yield: 56%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (s, 1H), 7.41 – 7.22 (m, 3H), 6.35 (d, *J* = 35.0 Hz, 1H), 4.95 – 4.78 (m, 1H), 4.17 (s, 2H), 1.46 (dd, *J* = 7.3, 2.4 Hz, 2H).

Phenyl formylphenylalaninate



Yield: 54%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.27 (s, 1H), 7.50 – 7.20 (m, 8H), 7.04 (dt, *J* = 8.0, 1.0 Hz, 2H), 6.14 (d, *J* = 6.0 Hz, 1H), 5.24 (dtd, *J* = 7.8, 5.9, 0.7 Hz, 1H), 3.35 (dd, *J* = 5.9, 1.6 Hz, 2H).

Phenyl 2-formamido-2-phenylacetate



Yield: Quantit. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.29 (t, *J* = 1.2 Hz, 1H), 7.54 – 7.31 (m, 7H), 7.26 – 7.19 (m, 1H), 7.03 – 6.97 (m, 2H), 6.69 (d, *J* = 7.2 Hz, 1H), 5.91 (d, *J* = 7.4 Hz, 1H).

3rd step:[269] To the corresponding *N*-formyl thioester (2 mmol, 1 equiv.) in CH$_2$Cl$_2$ (20 mL) was added N-methylmorpholine (0.44 mL, 4 mmol, 2 equiv.) and the mixture was cooled

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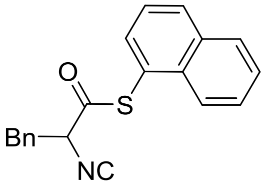
[269] See ref. 266, page 212.

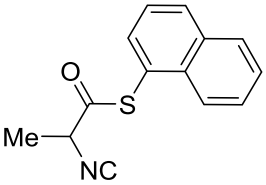
to –78 °C. Triphosgene (207 mg, 0.7 mmol, 0.35 equiv.) was added in one portion and the reaction mixture was stirred at –78 °C with TLC monitoring. The reaction was quenched by slow addition of water, quickly extracted with CH_2Cl_2 (2 × 20 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure (Keep bath temp below 23 °C). The reaction crude was purified by flash column chromatography on silica gel. The product exhibited the characteristic isonitrile NC band at IR: 2135-2137 cm^{-1}.

S-(Naphthalen-1-yl) 2-isocyano-3-phenylpropanethioate (28A)



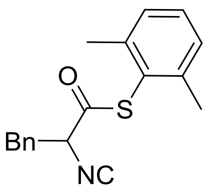
The isocyanothioester **28A** was obtained following the general procedure. Yellow oil. Yield (last step): 62 % (393 mg, 1.24 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.02 (m, 1H), 8.00 – 7.92 (m, 2H), 7.71 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.58 – 7.54 (m, 1H), 7.46 (ddd, *J* = 4.8, 2.0, 0.9 Hz, 3H), 7.40 – 7.32 (m, 2H), 4.69 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.34 (qd, *J* = 13.9, 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 164.7, 154.1, 135.8, 134.8, 134.5, 132.2, 130.2, 129.4, 129.3, 128.5, 128.1, 127.3, 127.1, 126.2, 125.4, 64.8, 40.0. UPLC-DAD-QTOF: $C_{20}H_{16}NOS$ [M+H]$^+$ calcd.: 318.0897, found: 318.0901.

S-(Naphth-1-yl) 2-isocyanopropanethioate (28B)



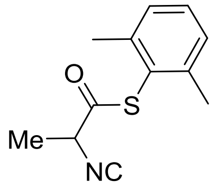
The isocyanothioester **28B** was obtained following the general procedure. Orange foam. Yield (last step): 60 % (290 mg, 1.2 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.11 (m, 1H), 8.07 – 7.99 (m, 1H), 7.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.75 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.68 – 7.49 (m, 3H), 4.55 (q, *J* = 7.1 Hz, 1H), 1.78 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 163.8, 136.4, 135.3, 135.0, 132.9, 129.9, 128.6, 127.7, 126.7, 125.7, 123.9, 59.3, 21.1. UPLC-DAD-QTOF: $C_{14}H_{12}NOS$ [M+H]$^+$ calcd.: 242.0640, found: 242.0649.

S-(2,6-Dimethylphenyl) 2-isocyano-3-phenylpropanethioate (29A)



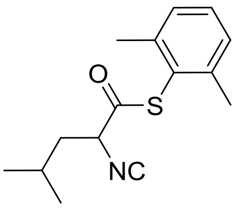
The isocyanothioester **29A** was obtained following the general procedure. Yellow oil. Yield (last step): 80 % (473 mg, 1.6 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 6H), 7.17 (d, *J* = 7.6 Hz, 2H), 4.58 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.32 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.20 (dd, *J* = 13.9, 8.4 Hz, 1H), 2.29 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 164.3, 143.5, 134.7, 131.5, 130.2, 129.5, 129.2, 128.5, 125.6, 64.9, 40.0, 22.1. UPLC-DAD-QTOF: $C_{18}H_{18}NOS$ [M+H]$^+$ calcd.: 296.1109, found: 296.1117.

S-(2,6-Dimethylphenyl) 2-isocyanopropanethioate (29B)



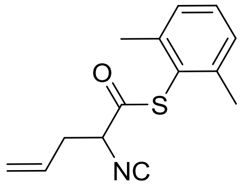
The isocyanothioester **29B** was obtained following the general procedure. Colourless oil. Yield (last step): 66 % (289 mg, 1.32 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 7.25 – 7.17 (m, 2H), 4.49 (q, *J* = 7.1 Hz, 1H), 2.38 (s, 6H), 1.75 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 162.1, 142.7, 130.3, 128.4, 124.9, 58.1, 21.4, 20.0. UPLC-DAD-QTOF: $C_{12}H_{14}NOS$ $[M+H]^+$ calcd.: 220.0796, found: 220.0803.

S-(2,6-Dimethylphenyl) 2-isocyano-4-methylpentanethioate (29C)



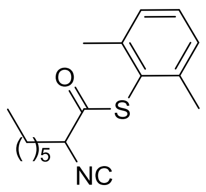
The isocyanothioester **29C** was obtained following the general procedure. Yellow oil. Yield (last step): 55 % (288 mg, 1.1 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 7.24 – 7.17 (m, 2H), 4.43 (dd, *J* = 10.0, 4.6 Hz, 1H), 2.38 (s, 6H), 2.06 – 1.90 (m, 2H), 1.85 – 1.71 (m, 1H), 1.04 (dd, *J* = 12.2, 6.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 163.4, 143.5, 131.1, 129.2, 125.7, 62.4, 42.6, 25.5, 23.4, 22.1, 21.5. UPLC-DAD-QTOF: $C_{15}H_{20}NOS$ $[M+H]^+$ calcd.: 262.1266, found: 262.1273.

S-(2,6-Dimethylphenyl) 2-isocyanopent-4-enethioate (29E)



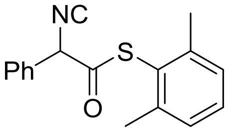
The isocyanothioester **29E** was obtained following the general procedure. Orange oil. Yield (last step): 62 % (304 mg, 1.24 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 5.98 – 5.78 (m, 1H), 5.41 – 5.27 (m, 2H), 4.46 (t, *J* = 6.3 Hz, 1H), 2.84 – 2.71 (m, 2H), 2.37 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 163.7, 143.4, 131.1, 130.6, 129.1, 125.6, 121.5, 63.2, 38.3, 22.2. UPLC-DAD-QTOF: $C_{12}H_{14}NOS$ $[M+H]^+$ calcd.: 246.0953, found: 246.0959.

S-(2,6-Dimethylphenyl) 2-isocyanooctanethioate (29F)



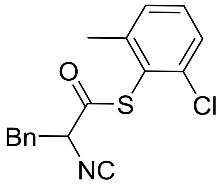
The isocyanothioester **29F** was obtained following the general procedure. Orange oil. Yield (last step): 73 % (420 mg, 1.45 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.5, 6.4 Hz, 1H), 7.25 – 7.18 (m, 2H), 4.43 (t, *J* = 6.5 Hz, 1H), 2.40 (s, 6H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.70 – 1.52 (m, 2H), 1.49 – 1.27 (m, 6H), 1.02 – 0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 163.3, 143.4, 131.0, 129.1, 125.7, 63.8, 34.1, 32.0, 28.9, 25.6, 23.0, 22.1, 14.6. UPLC-DAD-QTOF: $C_{17}H_{24}NOS$ $[M+H]^+$ calcd.: 290.1679, found: 290.1589.

S-(2,6-Dimethylphenyl) 2-isocyano-2-phenylethanethioate (29G)



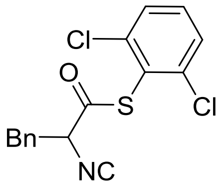
The isocyanothiester **29G** was obtained following the general procedure. Brown oil. Yield (last step): 54 % (303 mg, 1.08 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 – 7.52 (m, 1H), 7.47 – 7.45 (m, 2H), 7.16 – 7.07 (m, 5H), 5.49 (s, 1H), 2.18 (s, 6H). UPLC-DAD-QTOF: $C_{17}H_{16}NOS$ $[M-H]^-$ calcd.: 282.0960, found: 282.0967.

S-(2-Chloro-6-methylphenyl) 2-isocyano-3-phenylpropanethioate (30A)



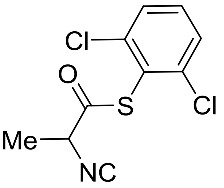
The isocyanothioester **30A** was obtained following the general procedure. Yellow foam. Yield (last step): 60 % (378 mg, 1.2 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 – 7.22 (m, 8H), 4.63 (dd, *J* = 8.5, 4.7 Hz, 1H), 3.38 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.24 (dd, *J* = 13.9, 8.6 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 189.7, 164.4, 145.3, 139.9, 134.2, 131.7, 129.7, 129.4, 129.0, 128.2, 128.0, 125.1, 64.6, 39.5, 22.2. UPLC-DAD-QTOF: $C_{17}H_{15}NOSCl$ $[M+H]^+$ calcd.: 316.0563, found: 316.0574.

S-(2,6-Dichlorophenyl) 2-isocyano-3-phenylpropanethioate (31A)



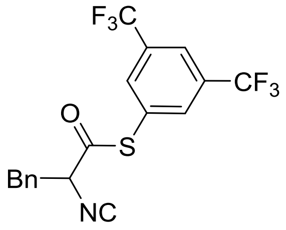
The isocyanothioester **31A** was obtained following the general procedure. Yellow oil. Yield (last step): 18 % (121 mg, 0.36 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.49 (m, 2H), 7.46 – 7.31 (m, 6H), 4.63 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.38 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.24 (dd, *J* = 14.0, 8.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 188.6, 164.8, 141.0, 133.9, 132.3, 129.6, 128.9, 128.0, 64.5, 39.4. UPLC-DAD-QTOF: $C_{16}H_{12}NOSCl_2$ $[M+H]^+$ calcd.: 337.9908, found: 337.9915.

S-(2,6-Dichlorophenyl) 2-isocyanopropanethioate (31B)



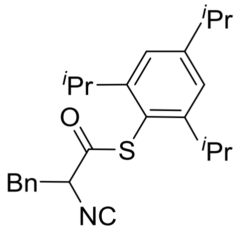
The isocyanothioester **31B** was obtained following the general procedure. Yellow oil. Yield (last step): 36 % (187 mg, 0.72 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.54 – 7.43 (m, 2H), 7.42 – 7.32 (m, 1H), 4.50 (q, *J* = 7.1 Hz, 1H), 1.75 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 189.0, 163.0, 140.6, 131.9, 128.5, 128.5, 57.9, 19.7. UPLC-DAD-QTOF: $C_{10}H_8NOSCl_2$ $[M+H]^+$ calcd.: 259.9611, found: 259.6904.

S-(3,5-bis(Trifluoromethyl)phenyl) 2-isocyano-3-phenylpropanethioate (32A)



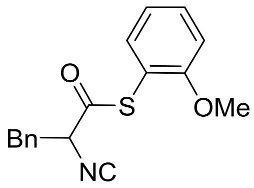
The isocyanothioester **32A** was obtained following the general procedure. Brown oil. Yield (last step): 54 % (435 mg, 1.1 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (s, 1H), 7.80 (s, 2H), 7.40 (d, *J* = 7.2 Hz, 3H), 7.35 – 7.25 (m, 2H), 4.65 (dd, *J* = 7.9, 4.7 Hz, 1H), 3.35 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.24 (dd, *J* = 13.9, 7.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 191.7, 166.6, 135.8, 135.8, 134.5, 134.1, 133.6, 130.7, 130.1, 130.0, 129.3, 125.1 (q), 65.4, 40.6. UPLC-DAD-QTOF: $C_{18}H_{12}NOSF_6$ [M+H]$^+$ calcd.: 404.0544, found: 404.0551.

S-(2,4,6-Triisopropylphenyl) 2-isocyano-3-phenylpropanethioate (33A)



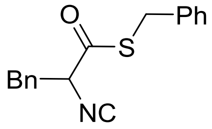
The isocyanothioester **33A** was obtained following the general procedure. White foam. Yield (last step): 64 % (503 mg, 1.28 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.45 – 7.30 (m, 5H), 7.12 (s, 2H), 3.35 (dd, *J* = 13.9, 5.2 Hz, 1H), 3.30 – 3.16 (m, 3H), 3.03 – 2.86 (m, 1H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 191.9, 163.6, 152.6, 151.9, 134.2, 129.5, 128.8, 127.8, 122.4, 119.5, 64.2, 39.3, 34.4, 32.0, 24.4, 23.9, 23.6. UPLC-DAD-QTOF: $C_{25}H_{32}NOS$ [M+H]$^+$ calcd.: 394.2205, found: 394.2213.

S-(2-Methoxyphenyl) 2-isocyano-3-phenylpropanethioate (34A)



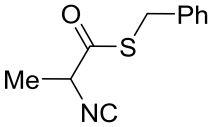
The isocyanothioester **34A** was obtained following the general procedure. Orange oil. Yield (last step): 74 % (440 mg, 1.48 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50 – 7.22 (m, 8H), 4.63 (dd, *J* = 8.5, 4.7 Hz, 1H), 3.38 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.24 (dd, *J* = 13.9, 8.6 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 189.7, 164.4, 145.3, 139.9, 134.2, 131.7, 129.7, 129.4, 129.0, 128.2, 128.0, 125.1, 64.6, 39.5, 22.2. UPLC-DAD-QTOF: $C_{17}H_{16}NO_2S$ [M+H]$^+$ calcd.: 298.0902, found: 298.0916.

S-Benzyl 2-isocyano-3-phenylpropanethioate (35A)



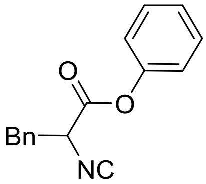
The isocyanothioester **35A** was obtained following the general procedure. Colourless oil. Yield (last step): 60 % (337 mg, 1.2 mmol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.27 (m, 7H), 7.27 – 7.20 (m, 3H), 4.50 (dd, *J* = 8.5, 4.6 Hz, 1H), 4.20 (s, 2H), 3.30 (dd, *J* = 13.9, 4.6 Hz, 1H), 3.14 (dd, *J* = 13.9, 8.5 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 193.5, 164.4, 136.7, 134.6, 130.0, 129.6, 129.4, 129.4, 128.4, 128.3, 65.1, 40.1, 34.5. UPLC-DAD-QTOF: $C_{17}H_{16}NOS$ $[M+H]^+$ calcd.: 282.0934, found: 382.0929.

S-Benzyl 2-isocyanopropanethioate (35B)



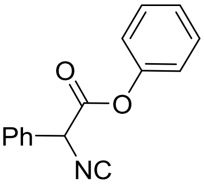
The isocyanothiester **35B** was obtained following the general procedure. Yellow oil. Yield (last step): 82 % (337 mg, 1.64 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 3H), 4.38 (q, *J* = 7.2 Hz, 1H), 4.21 (s, 2H), 1.66 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 162.1, 136.1, 128.9, 128.7, 127.7, 58.3, 33.7, 20.0. UPLC-DAD-QTOF: $C_{11}H_{12}NOS$ $[M+H]^+$ calcd.: 206.0640, found: 206.0646.

Phenyl 2-isocyano-3-phenylpropanoate (62)



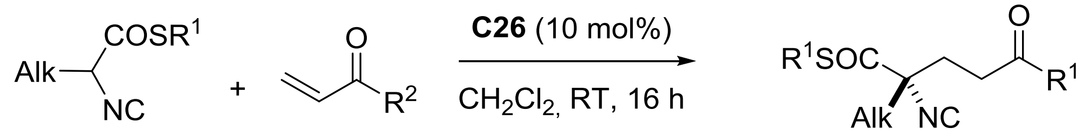
The isocyanothioester **62** was obtained following the general procedure. Yellow oil. Yield (last step): 40 % (201 mg, 0.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.22 (m, 8H), 7.10 – 6.97 (m, 2H), 4.72 (dd, *J* = 7.7, 5.4 Hz, 1H), 3.38 (qd, *J* = 13.9, 6.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 162.4, 150.6, 134.6, 130.3, 130.1, 129.6, 128.7, 127.3, 121.6, 58.6, 39.6. UPLC-DAD-QTOF: $C_{16}H_{12}NO_2$ $[M-H]^-$ calcd.: 250.0868, found: 250.0875.

Phenyl 2-isocyano-2-phenylacetate (73)



The isocyanothioester **73** was obtained following the general procedure. Yellow oil. Yield (last step): 56 % (265 mg, 1.12 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.54 – 7.47 (m, 3H), 7.42 – 7.36 (m, 2H), 7.31 – 7.27 (m, 1H), 7.09 – 7.03 (m, 2H), 5.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 163.0, 151.1, 130.8, 130.6, 130.4, 127.8, 127.6, 121.8, 116.3, 61.3. UPLC-DAD-QTOF: $C_{15}H_{12}NO_2$ $[M-H]^-$ calcd.: 238.0840, found: 238.0833.

5.4.2. General Procedure for the conjugate addition of isocyanothioacetates 27, 29 and 35 to vinyl ketones 2 and 6a.



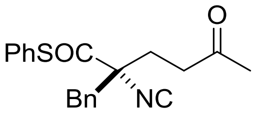
27 R^1: Ph
29 R^1: 2,6-$Me_2C_6H_3$
35 R^1: Bn

2 R^2: **a** Me **b** Et **c** Ph **d** 4-MeC_6H_4 **e** 4-ClC_6H_4 **f** 4-$MeOC_6H_4$
6a R^2: -$C(CH_3)_2OH$

36 R^1: Ph
45 R^1: 2,6-$Me_2C_6H_3$
46 R^1: Bn
49 R^1: 2,6-$Me_2C_6H_3$
R^2: -$C(CH_3)_2OH$

Catalyst **C26** (15 mg, 10 mol%) was added to a solution of the corresponding α-alkyl isocyanothioacetate (0.1 mmol, 1 equiv.) and vinyl ketone (1–2 equiv.) in CH_2Cl_2 (0.2 mL) at room temperature and the resulting mixture was stirred at the same temperature until the reaction was completed (monitored by TLC). The solvent was removed under reduced pressure and the product was purified by column chromatography.

S-Phenyl (R)-2-benzyl-2-isocyano-5-oxohexanethioate (36Aa)

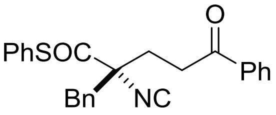


Prepared according to the general procedure starting from isocyanothioacetate **27A** (27 mg, 0.1 mmol) and vinyl ketone **2a** (14 mg, 0.2 mmol) using catalyst **C5** (7 mg, 10 mol%) instead. The title compound was obtained as a 84:16 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colorless oil. Yield: 30% (10 mg). $[\alpha]_D{}^{22}$= +14.04° (*c*=1.3, 68% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.42 (m, 3H), 7.42 – 7.35 (m, 3H), 7.34 – 7.24 (m, 4H), 3.31 (d, *J* = 13.5 Hz, 1H), 3.06 (d, *J* = 13.6 Hz, 1H), 2.81 (ddd, *J* = 17.9, 10.8, 4.8 Hz, 1H), 2.61 (ddd, *J* = 17.9, 11.0, 5.0 Hz, 1H), 2.40 (ddd, *J* = 15.4, 10.7, 4.8 Hz, 1H), 2.22 (s, 3H), 2.20 – 2.12 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 196.0, 165.3, 134.7, 132.9, 130.7, 130.3, 129.6, 128.6, 128.2, 126.3, 77.4, 45.6, 38.1, 33.0, 30.2. UPLC-DAD-QTOF: $C_{20}H_{20}NO_2S$ $[M+H]^+$ calcd.: 338.1215, found: 338.1218.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: 9.5 min (major), 11.9 min (minor)).

S-Phenyl (R)-2-benzyl-2-isocyano-5-oxo-5-phenylpentanethioate (36Ac)

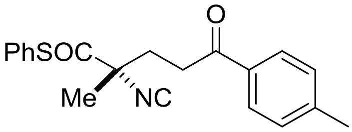


Prepared according to the general procedure starting from isocyanothioacetate **27A** (27 mg, 0.1 mmol) and vinyl ketone **2c** (26 mg, 0.2 mmol). The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colorless oil. Yield: 40% (16 mg). $[\alpha]_D{}^{22}$= +5.72° (*c*=0.60, 90% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.91 (m, 2H), 7.67 – 7.55 (m, 1H), 7.55 – 7.22 (m, 13H), 3.44 – 3.23 (m, 2H), 3.22 – 3.04 (m, 2H), 2.67 – 2.51 (m, 1H), 2.35 (ddd, *J* = 14.4, 11.1, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 196.0, 165.3, 136.5, 134.7, 133.6, 133.0, 130.8, 130.3, 129.6, 128.9, 128.7, 128.2, 128.2, 126.3, 74.6, 45.6, 33.6, 33.3. UPLC-DAD-QTOF: $C_{25}H_{22}NO_2S$ $[M+H]^+$ calcd.: 400.1371, found: 400.1364.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 22.1 min (major), 24.8 min (minor)).

S-Phenyl (S)-2-isocyano-2-methyl-5-oxo-5-(p-tolyl)pentanethioate (36Bd)

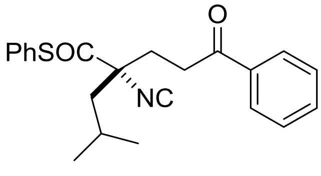


Prepared according to the general procedure starting from isocyanothioacetate **27B** (19 mg, 0.1 mmol) and vinyl ketone **2d** (44 mg, 0.3 mmol). The title compound was obtained as a 96.5:3.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colorless oil. Yield: 41% (14 mg). $[\alpha]_D{}^{22}$= –50.49° (*c*=0.55, 93% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.81 (m, 2H), 7.51 – 7.38 (m, 5H), 7.34 – 7.23 (m, 2H), 3.26 (ddd, *J* = 17.4, 10.6, 5.1 Hz, 1H), 3.11 (ddd, *J* = 17.4, 10.7, 5.1 Hz, 1H), 2.50 (ddd, *J* = 15.9, 10.8, 5.4 Hz, 1H), 2.42 (s, 3H), 2.31 (ddd, *J* = 14.4, 10.8, 5.1 Hz, 1H), 1.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 195.9, 163.4, 144.5, 134.8, 134.0, 130.2, 129.6, 129.5, 128.3, 126.2, 69.7, 34.3, 33.3, 27.2, 21.8. UPLC-DAD-QTOF: $C_{20}H_{20}NO_2S$ $[M+H]^+$ calcd.: 338.1128, found: 338.1121.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 21.2 min (minor), 23.1 min (major)).

S-Phenyl (R)-2-isobutyl-2-isocyano-5-oxo-5-phenylpentanethioate (36Cc)

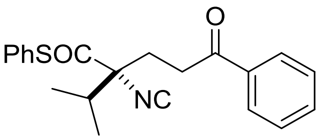


Prepared according to the general procedure starting from isocyanothioacetate **27C** (23 mg, 0.1 mmol) and vinyl ketone **2c** (26 mg, 0.2 mmol). The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 52% (19 mg). $[\alpha]_D{}^{22}$= – 36.07° (*c*=1.11, 96% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 2H), 7.68 – 7.59 (m, 1H), 7.58 – 7.37 (m, 7H), 3.36 (ddd, *J* = 17.4, 10.8, 4.9 Hz, 1H), 3.16 (ddd, *J* = 17.4, 11.0, 5.1 Hz, 1H), 2.49 (ddd, *J* = 15.5, 10.7, 5.1 Hz, 1H), 2.35 (ddd, *J* = 14.3, 11.0, 4.9 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.86 (q, *J* = 8.2 Hz, 1H), 1.13 (d, *J* = 6.2 Hz, 3H), 1.04 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 196.1, 164.6, 136.5, 134.7, 133.6, 130.2, 129.7, 128.9, 128.2, 126.4, 73.3, 47.7, 35.2, 33.1, 25.2, 24.0, 23.3. UPLC-DAD-QTOF: $C_{22}H_{24}NO_2S$ $[M+H]^+$ calcd.: 366.1528, found: 366.1528.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 12.2 min (minor), 19.4 min (major)).

S-Phenyl (R)-2-isocyano-2-isopropyl-5-oxo-5-phenylpentanethioate (36Dc)

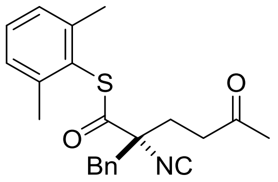


Prepared according to the general procedure starting from isocyanothioacetate **27D** (22 mg, 0.1 mmol) and vinyl ketone **2c** (26 mg, 0.2 mmol). The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colourless oil. Yield: 74% (26 mg). $[\alpha]_D{}^{22}$= –31.09° (*c*=1, 98% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.95 (m, 2H), 7.69 – 7.58 (m, 1H), 7.59 – 7.38 (m, 7H), 3.37 (ddd, *J* = 17.4, 10.7, 4.9 Hz, 1H), 3.10 (ddd, *J* = 17.3, 10.8, 5.5 Hz, 1H), 2.56 – 2.29 (m, 3H), 1.18 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 196.9, 164.7, 137.0, 135.1, 134.0, 130.7, 130.1, 129.3, 128.6, 126.9, 78.8, 36.8, 33.8, 32.3, 18.3, 17.2. UPLC-DAD-QTOF: $C_{22}H_{24}NO_2S$ $[M+H]^+$ calcd.: 366.1528, found: 366.1526.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 13.7 min (minor), 18.5 min (major)).

S-(2,6-Dimethylphenyl) (R)-2-benzyl-2-isocyano-5-oxohexanethioate (45Aa)

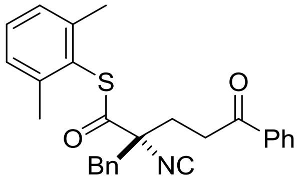


Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol) and vinyl ketone **2a** (14 mg, 0.2 mmol). The title compound was obtained as a 96:4 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a white foam. Yield: 74% (27 mg). $[\alpha]_D{}^{22}$= +24.94° (*c*=1.4, 92% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 2.85 (ddd, *J* = 17.8, 10.9, 4.9 Hz, 1H), 2.65 (ddd, *J* = 17.8, 11.2, 4.8 Hz, 1H), 2.47 – 2.28 (m, 4H), 2.22 (s, 3H), 2.21 – 2.14 (m, 1H), 2.14 – 1.97 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 194.9, 165.5, 143.4, 133.5, 131.2, 131.0, 129.1, 129.0, 128.5, 126.0, 74.6, 45.3, 38.4, 33.6, 30.6, 22.0. UPLC-DAD-QTOF: $C_{22}H_{24}NO_2S$ $[M+H]^+$ calcd.: 366.1528, found: 366.1528.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:ethanol, 95:5; flux= 1 mL/min; retention times: 9.5 min (major), 10.8 min (minor)).

S-(2,6-Dimethylphenyl) (R)-2-benzyl-2-isocyano-5-oxo-5-phenylpentanethioate (45Ac)

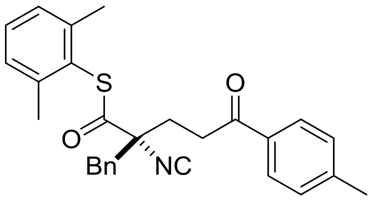


Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol) and vinyl ketone **2c** (26 mg, 0.2 mmol). The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colorless oil. Yield: 77% (33 mg). $[\alpha]_D{}^{22}$= –9.14° (*c*=1.35, 94% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.67 – 7.57 (m, 1H), 7.56 – 7.47 (m, 2H), 7.43 – 7.33 (m, 5H), 7.28 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 3.47 – 3.33 (m, 2H), 3.28 – 3.16 (m, 1H), 3.13 (d, *J* = 13.7 Hz, 1H), 2.65 – 2.50 (m, 1H), 2.47 – 2.28 (m, 4H), 2.09 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 194.6, 165.2, 136.5, 133.6, 133.1, 130.9, 130.6, 128.9, 128.8, 128.7, 128.7, 128.1, 128.1, 125.6, 74.4, 45.1, 33.9, 33.3, 21.6. UPLC-DAD-QTOF: $C_{27}H_{26}NO_2S$ $[M+H]^+$ calcd.: 428.1684, found: 428.1684.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 11.4 min (major), 13.2 min (minor)).

S-(2,6-Dimethylphenyl) (R)-2-benzyl-2-isocyano-5-oxo-5-(p-tolyl)pentanethioate (45Ad)

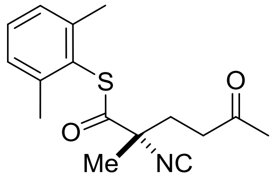


Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol) and vinyl ketone **2d** (44 mg, 0.3 mmol). The title compound was obtained as a 96:4 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 60% (26 mg). $[\alpha]_D{}^{22}$= –8.42° (*c*=1.90, 92% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.8, 2.3 Hz, 2H), 7.42 – 7.34 (m, 5H), 7.34 – 7.23 (m, 3H), 7.17 (d, *J* = 7.6 Hz, 2H), 3.46 – 3.29 (m, 2H), 3.28 – 3.07 (m, 2H), 2.65 – 2.50 (m, 1H), 2.45 (s, 3H), 2.43 – 2.28 (m, 4H), 2.10 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 194.6, 165.1, 144.5, 134.0, 133.1, 130.8, 130.5, 129.6, 129.0, 128.7, 128.7, 128.2, 128.1, 128.0, 125.6, 74.5, 45.1, 34.0, 33.1, 21.8, 21.6. UPLC-DAD-QTOF: $C_{28}H_{28}NO_2S$ $[M+H]^+$ calcd.: 442.1845, found: 442.1841.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:ethanol, 95:5; flux= 1 mL/min; retention times: 10.4 min (major), 12.4 min (minor)).

S-(2,6-Dimethylphenyl) (S)-2-isocyano-2-methyl-5-oxohexanethioate (45Ba)

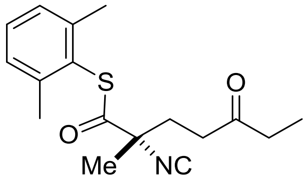


Prepared according to the general procedure starting from isocyanothioacetate **29B** (22 mg, 0.1 mmol) and vinyl ketone **2a** (14 mg, 0.2 mmol). The title compound was obtained as a 95.5:4.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 90% (26 mg). $[\alpha]_D{}^{22}$= –13.90° (*c*=0.80, 91% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 1H), 7.23 – 7.15 (m, 2H), 2.76 (ddd, *J* = 17.8, 10.8, 5.0 Hz, 1H), 2.57 (ddd, *J* = 17.8, 10.9, 4.9 Hz, 1H), 2.35 (s, 6H), 2.32 – 2.24 (m, 1H), 2.20 (s, 3H), 2.19 – 2.08 (m, 1H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3, 195.2, 163.7, 143.4, 131.1, 129.3, 126.0, 69.9, 38.7, 34.0, 30.7, 27.6, 22.2. UPLC-DAD-QTOF: $C_{16}H_{20}NO_2S$ $[M+H]^+$ calcd.: 290.1215, found: 290.1232.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min; retention times: 29.4 min (minor), 31.5 min (major)).

S-(2,6-Dimethylphenyl) (S)-2-isocyano-2-methyl-5-oxoheptanethioate (45Bb)

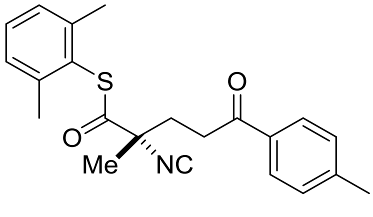


Prepared according to the general procedure starting from isocyanothioacetate **29B** (22 mg, 0.1 mmol) and vinyl ketone **2b** (17 mg, 0.2 mmol). The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a orange oil. Yield: 82% (25 mg). $[\alpha]_D^{22}$= –20.63° (*c*=1.15, 96% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 1H), 7.24 – 7.16 (m, 2H), 2.76 (ddd, *J* = 17.5, 10.8, 5.1 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.52 – 2.44 (m, 2H), 2.37 (s, 6H), 2.31 (dd, *J* = 10.7, 5.0 Hz, 1H), 2.18 (ddd, *J* = 14.3, 10.9, 5.1 Hz, 1H), 1.73 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 195.6, 164.1, 143.8, 131.5, 129.7, 126.5, 70.4, 37.8, 37.2, 34.5, 28.0, 22.6, 8.9. UPLC-DAD-QTOF: $C_{17}H_{22}NO_2S$ $[M+H]^+$ calcd.: 304.1371, found: 304.1370.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 98:2; flux= 0.5 mL/min; retention times: 23.2 min (minor), 25.2 min (major)).

S-(2,6-Dimethylphenyl) (S)-2-isocyano-2-methyl-5-oxo-5-(p-tolyl)pentanethioate (45Bd)

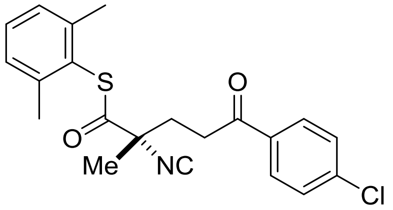


Prepared according to the general procedure starting from isocyanothioacetate **29B** (22 mg, 0.1 mmol) and vinyl ketone **2d** (44 mg, 0.3 mmol). The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 68% (25 mg). $[\alpha]_D^{22}$= –45.49° (*c*=1.15, 94% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.84 (m, 2H), 7.36 – 7.25 (m, 3H), 7.20 (d, *J* = 7.5 Hz, 2H), 3.31 (ddd, *J* = 17.3, 10.9, 4.9 Hz, 1H), 3.13 (ddd, *J* = 17.3, 11.1, 4.9 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.45 (s, 3H), 2.39 (s, 6H), 2.36 – 2.30 (m, 1H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 194.7, 163.2, 144.4, 142.9, 134.0, 130.6, 129.5, 128.7, 128.2, 125.5, 69.7, 34.2, 33.3, 27.1, 21.8, 21.77. UPLC-DAD-QTOF: $C_{22}H_{24}NO_2S$ $[M+H]^+$ calcd.: 366.1528, found: 366.1522.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 16.4 min (minor), 17.7 min (major)).

S-(2,6-Dimethylphenyl) (S)-5-(4-chlorophenyl)-2-isocyano-2-methyl-5-oxopentanethioate (45Be)

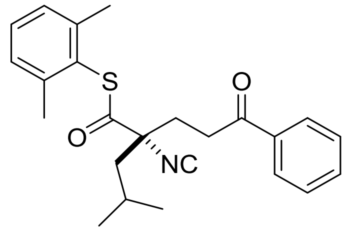


Prepared according to the general procedure starting from isocyanothioacetate **29B** (22 mg, 0.1 mmol) and vinyl ketone **2e** (33 mg, 0.2 mmol). The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a orange oil. Yield: 88% (34 mg). $[\alpha]_D^{22}$= –52.09° (*c*=1.40, 90% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.86 (m, 2H), 7.57 – 7.40 (m, 2H), 7.35 – 7.25 (m, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 3.29 (ddd, *J* = 17.5, 10.8, 4.9 Hz, 1H), 3.11 (ddd, *J* = 17.5, 10.9, 4.9 Hz, 1H), 2.51 (ddd, *J* = 15.4, 10.9, 4.9 Hz, 1H), 2.38 (s, 6H), 2.35 – 2.27 (m, 1H), 1.80 (s, 3H^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 195.1, 163.8, 143.3, 140.5, 135.2, 131.0, 129.9, 129.6, 129.2, 125.8, 69.9, 34.4, 33.8, 27.6, 22.1. UPLC-DAD-QTOF: $C_{21}H_{21}NO_2SCl$ $[M+H]^+$ calcd.: 386.0982, found: 386.0984.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane:ethanol, 99:1; flux= 1 mL/min; retention times: 10.5 min (minor), 11.2 min (major)).

S-(2,6-Dimethylphenyl) (R)-2-isobutyl-2-isocyano-5-oxo-5-phenylpentanethioate (45Cc)

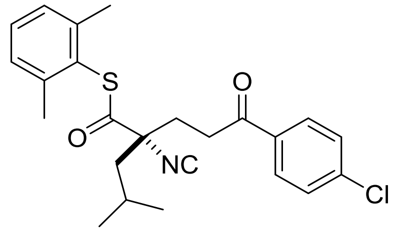


Prepared according to the general procedure starting from isocyanothioacetate **29C** (26 mg, 0.1 mmol) and vinyl ketone **2c** (26 mg, 0.2 mmol). The title compound was obtained as a 99.5:0.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 70% (28 mg). $[\alpha]_D^{22}$= –40.04° (*c*=1.45, 99% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.94 (m, 2H), 7.67 – 7.57 (m, 1H), 7.56 – 7.46 (m, 2H), 7.36 – 7.25 (m, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 3.37 (ddd, *J* = 17.4, 10.7, 5.1 Hz, 1H), 3.18 (ddd, *J* = 17.4, 10.9, 5.2 Hz, 1H), 2.55 – 2.43 (m, 1H), 2.40 (s, 6H), 2.39 – 2.32 (m, 1H), 2.16 – 1.97 (m, 2H), 1.90 – 1.74 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 195.8, 165.5, 143.9, 137.5, 134.6, 131.5, 129.8, 129.7, 129.0, 126.7, 74.2, 48.2, 36.0, 34.2, 26.3, 24.8, 24.7, 22.7. UPLC-DAD-QTOF: $C_{24}H_{28}NO_2S$ $[M+H]^+$ calcd.: 394.4841, found: 394.4839.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane:ethanol, 98:2; flux= 0.5 mL/min; retention times: 14.1 min (major), 19.3 min (minor)).

S-(2,6-Dimethylphenyl)(R)-5-(4-chlorophenyl)-2-isobutyl-2-isocyano-5-oxopentanethioate (45Ce)



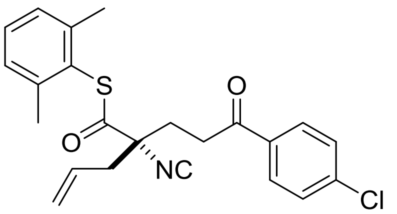
Prepared according to the general procedure starting from isocyanothioacetate **29C** (26 mg, 0.1 mmol) and vinyl ketone **2e** (34 mg, 0.2 mmol). The title compound was obtained as a 98.5:1.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 86% (36 mg). $[\alpha]_D^{22}$= –47.69° (*c*=1.25, 97% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.87 (m, 2H), 7.53 – 7.43 (m, 2H), 7.35 – 7.25 (m, 1H), 7.24 – 7.15 (m, 2H), 3.32 (ddd, *J* = 17.5, 10.6, 5.1 Hz, 1H), 3.13 (ddd, *J* = 17.5, 10.9, 5.1 Hz, 1H), 2.52 – 2.41 (m, 1H), 2.39 (s, 6H), 2.37 – 2.29 (m, 1H), 2.14 – 1.96 (m, 2H), 1.89 – 1.74 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75

MHz, $CDCl_3$) δ 196.3, 194.8, 164.6, 142.9, 140.1, 134.8, 130.6, 129.5, 129.2, 128.8, 125.7, 73.2, 47.3, 34.9, 33.2, 25.3, 23.8, 23.7, 21.8. UPLC-DAD-QTOF: $C_{24}H_{27}NO_2SCl$ $[M+H]^+$ calcd.: 428.1451, found: 428.1448.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 0.5 mL/min; retention times: 13.7 min (minor), 16.6 min (major)).

S-(2,6-Dimethylphenyl)(R)-2-(3-(4-chlorophenyl)-3-oxopropyl)-2-isocyanopent-4-enethioate (45Ee)

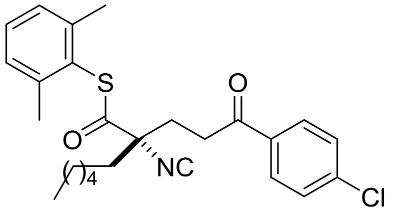


Prepared according to the general procedure starting from isocyanothioacetate **29E** (25 mg, 0.1 mmol) and vinyl ketone **2e** (34 mg, 0.2 mmol). The title compound was obtained as a 98.5:1.5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colourless oil. Yield: 63% (26 mg). $[\alpha]_D{}^{22} = -53.24°$ (*c*=0.75, 97% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.85 (m, 2H), 7.55 – 7.41 (m, 2H), 7.36 – 7.25 (m, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 6.05 – 5.85 (m, 1H), 5.42 – 5.26 (m, 2H), 3.33 (ddd, *J* = 17.4, 10.8, 5.0 Hz, 1H), 3.11 (ddd, *J* = 17.4, 11.1, 5.0 Hz, 1H), 2.83 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.70 – 2.58 (m, 1H), 2.55 – 2.43 (m, 1H), 2.38 (s, 6H), 2.35 – 2.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 195.3, 165.3, 143.8, 141.1, 135.7, 131.6, 130.4, 130.3, 130.2, 129.7, 126.5, 123.0, 74.3, 44.9, 34.2, 34.1, 22.8. UPLC-DAD-QTOF: $C_{23}H_{23}ClNO_2S$ $[M+H]^+$ calcd.: 412.1138, found: 412.1140.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 0.5 mL/min; retention times: 23.2 min (minor), 26.4 min (major)).

S-(2,6-Dimethylphenyl)(S)-2-(3-(4-chlorophenyl)-3-oxopropyl)-2-isocyanooctanethioate (45Fe)



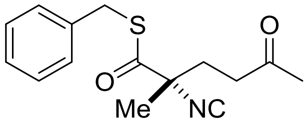
Prepared according to the general procedure starting from isocyanothioacetate **29F** (29 mg, 0.1 mmol) and vinyl ketone **2e** (34 mg, 0.2 mmol). The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colourless oil. Yield: 86% (39 mg). $[\alpha]_D^{22}$= –34.09° (*c*=1.20, 98% *ee*, CH_2Cl_2).

The reaction carried out at 3 mmol scale, using isocyanothioacetate **4F** (870 mg, 3 mmol), vinyl ketone **2e** (666 mg, 4 mmol) and catalyst **C6** (464 mg, 0.3 mmol) provided the title compound as a 99:1 mixture of enantiomers. Yield: 96% (1.313 g).

^1H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.87 (m, 2H), 7.53 – 7.44 (m, 2H), 7.35 – 7.24 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 3.32 (ddd, *J* = 17.4, 10.8, 4.9 Hz, 1H), 3.10 (ddd, *J* = 17.4, 11.1, 4.9 Hz, 1H), 2.45 (dd, *J* = 12.7, 7.9 Hz, 1H), 2.39 (s, 6H), 2.37 – 2.28 (m, 1H), 2.19 – 2.01 (m, 1H), 1.96 – 1.81 (m, 1H), 1.80 – 1.63 (m, 1H), 1.58 – 1.45 (m, 1H), 1.44 – 1.26 (m, 6H), 0.97 – 0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 195.3, 164.3, 140.6, 135.3, 130.8, 130.0, 129.7, 129.6, 129.3, 126.2, 74.5, 40.4, 34.2, 33.8, 32.1, 29.5, 24.6, 23.1, 22.3, 14.7. UPLC-DAD-QTOF: $C_{26}H_{31}ClNO_2S$ $[M+H]^+$ calcd.: 456.1765, found: 456.1759.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 8.8 min (major), 12.7 min (minor)).

S-Benzyl (S)-2-isocyano-2-methyl-5-oxohexanethioate (46Ba)

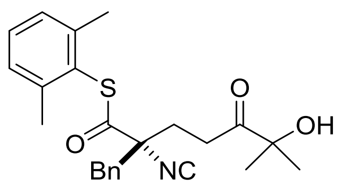


Prepared according to the general procedure starting from the corresponding isocyanothioacetate **35B** (21 mg, 0.1 mmol) and vinyl ketone **2a** (14 mg, 0.2 mmol). The title compound was obtained as a 94:6 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colourless oil. Yield: 62% (19 mg). $[\alpha]_D^{22}$= –0.56° (*c*=1.40, 88% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 3H), 4.17 (s, 2H), 2.65 (ddd, *J* = 17.9, 10.7, 5.0 Hz, 1H), 2.43 (ddd, *J* = 18.0, 10.8, 4.9 Hz, 1H), 2.33 – 2.18 (m, 1H), 2.15 (s, 3H), 2.13 – 2.03 (m, 1H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 197.7, 163.8, 137.2, 130.0, 129.8, 128.8, 70.3, 39.0, 35.3, 34.7, 31.1, 27.9. UPLC-DAD-QTOF: $C_{15}H_{18}NO_2S$ $[M+H]^+$ calcd.: 276.1058, found: 276.1072.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min; retention times: 30.5 min (major), 32.4 min (minor)).

S-(2,6-Dimethylphenyl) (R)-2-benzyl-6-hydroxy-2-isocyano-6-methyl-5-oxoheptanethioate (49Aa)



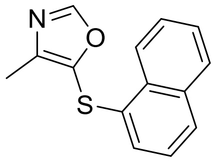
Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol) and vinyl ketone **6a** (23 mg, 0.2 mmol). The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a yellow oil. Yield: 73% (30 mg). $[\alpha]_D{}^{22}$= +41.03° (*c*=1.35, 96% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 3.43 (s, 1H), 3.34 (d, *J* = 13.6 Hz, 1H), 3.08 (d, *J* = 13.6 Hz, 1H), 2.98 (ddd, *J* = 18.0, 10.9, 4.9 Hz, 1H), 2.79 (ddd, *J* = 18.0, 11.2, 4.8 Hz, 1H), 2.49 – 2.30 (m, 4H), 2.24 (ddd, *J* = 14.3, 11.2, 4.9 Hz, 1H), 2.17 – 1.97 (m, 3H), 1.42 (d, *J* = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 194.5, 165.3, 142.9, 132.9, 130.8, 130.6, 128.7, 128.2, 125.5, 76.5, 74.2, 45.1, 33.5, 30.6, 26.9, 26.7, 21.6. UPLC-DAD-QTOF: $C_{22}H_{24}NO_3S$ [M+H]$^+$ calcd.: 382.1477, found: 382.1469.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 0.5 mL/min; retention times: 15.3 min (minor), 19.4 min (major)).

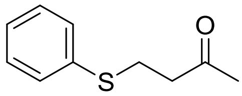
Selected isolated by-products

4-Methyl-5-(naphth-1-ylthio)oxazole (47B)



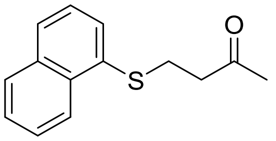
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 9.0 Hz, 1H), 7.96 (s, 1H), 7.84 (dd, *J* = 30.5, 8.0 Hz, 2H), 7.70 – 7.51 (m, 1H), 7.43 – 7.29 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 144.5, 138.8, 135.1, 133.0, 132.6, 129.7, 129.2, 128.9, 127.9, 127.6, 126.8, 125.5, 13.3. UPLC-DAD-QTOF: $C_{14}H_{12}NOS$ [M+H]$^+$ calcd.: 242.0640, found: 242.0652.

4-(Phenylthio)butan-2-one (38)



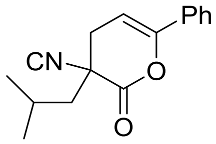
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.16 (m, 5H), 3.14 (t, *J* = 7.3 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 136.7, 130.4, 130.0, 127.2, 44.0, 31.1, 28.4. UPLC-DAD-QTOF: $C_{10}H_{12}OS$ [M+H]$^+$ calcd.: 181.2712, found: 181.2706.

4-(Naphthalen-1-ylthio)butan-2-one (48)



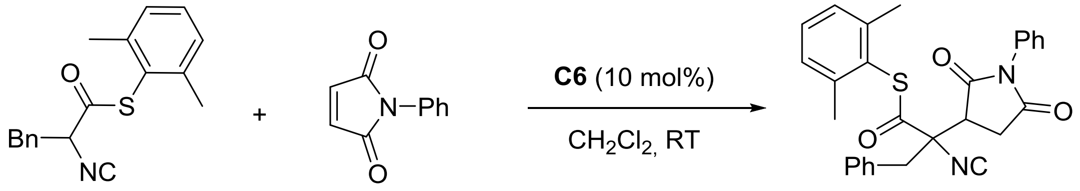
^{1}H NMR (300 MHz, CDCl$_3$) δ 8.46 – 8.38 (m, 1H), 7.93 – 7.84 (m, 1H), 7.79 (d, *J* = 8.1, 1.1 Hz, 1H), 7.65 – 7.51 (m, 3H), 7.44 (dd, *J* = 8.2, 7.2 Hz, 1H), 3.21 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 207.3, 134.7, 133.9, 133.4, 129.6, 129.3, 128.4, 127.2, 127.0, 126.2, 125.8, 43.8, 30.8, 28.8. UPLC-DAD-QTOF: $C_{14}H_{15}OS$ [M+H]$^+$ calcd.: 231.0844, found: 231.0844.

3-Isobutyl-3-isocyano-6-phenyl-3,4-dihydro-2H-pyran-2-one (39Cc)



^{1}H NMR (300 MHz, CDCl$_3$) δ 7.63 – 7.54 (m, 2H), 7.47 – 7.36 (m, 3H), 3.08 (dd, *J* = 17.5, 3.1 Hz, 1H), 2.81 (dd, *J* = 17.5, 6.3 Hz, 1H), 2.10 – 1.90 (m, 2H), 1.86 – 1.70 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.0, 162.2, 151.8, 132.0, 130.8, 129.8, 125.6, 97.5, 61.6, 45.4, 35.2, 25.8, 25.1, 24.3. UPLC-DAD-QTOF: $C_{16}H_{21}N_2O_2$ [M+NH$_4$]$^+$ calcd.: 273.1603, found: 273.1602. Isonitrile NC band at IR: 2139 cm^{-1}.

5.4.3. Reaction of 29A with *N*-phenyl maleimide



29A **75**

Catalyst **C26** (15 mg, 10 mol%) was added to a solution of the α-alkyl isocyanothioacetate **29A** (59 mg, 0.2 mmol, 1 equiv.) and *N*-phenyl maleimide (105 mg, 0.4 mmol, 2 equiv.) in CH$_2$Cl$_2$ (0.4 mL) at room temperature and the resulting mixture was stirred at the same temperature until the reaction was completed (36 h). The solvent was removed under reduced pressure and the product was purified by column chromatography on silica (hexane/EtOAc 85/15). The title compound was obtained as 70:30 mixture of diastereomers and 68% *ee* for the major diastereomer (minor diast.: 80% *ee*). Yield (mixture of diastereoisomers): 70% (66.6 mg, 0.14 mmol). $[\alpha]_D^{22}$ (major diastereomer)= –38.03° (*c*=1.1, 68% *ee*, CH$_2$Cl$_2$).

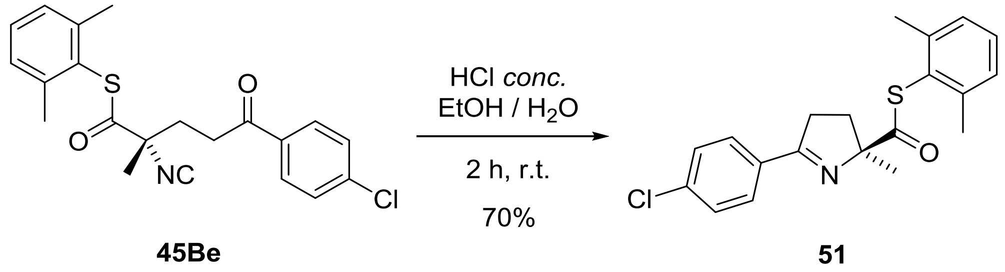
Data of major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 – 7.43 (m, 3H), 7.40 – 7.29 (m, 7H), 7.28 – 7.24 (m, 1H), 7.21 – 7.08 (m, 2H), 4.08 (d, *J* = 14.0 Hz, 1H), 3.64

(dd, *J* = 9.0, 5.3 Hz, 1H), 3.48 (d, *J* = 14.0 Hz, 1H), 3.24 – 2.99 (m, 2H), 2.31 (br s, 3H), 1.94 (br s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 174.1, 173.6, 168.4, 143.4, 134.9, 133.3, 131.5, 131.4, 129.9, 129.4, 129.3, 128.7, 127.4, 126.7, 75.7, 47.2, 43.5, 32.0, 22.3. UPLC-DAD-QTOF: calcd for $C_{28}H_{25}N_2O_3S$ $[M+H]^+$, 469.1556; found, 468.1550.

The diastereomeric and enantiomeric purity were determined on crude material by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 0.5 mL/min; retention times: diast. A (minor enantiomer) 19.9 min, diast. A (major enantiomer) 22.14 min, diast. B. 24.9 min, diast. B 35.0 min).

5.4.4. Elaboration of adduct 45B

5.4.4.1. *Synthesis of Δ^5-dehydroproline thioester **51***[270]



Concentrated HCl solution (0.5 mL) was dropwise added to a solution of **45Be** (386 mg, 1.0 mmol) in ethanol (10 mL). The mixture was stirred for 2 hour at room temperature. Then, the solvent was removed under reduced pressure. Water (10 mL) was added and the mixture was basified with NH_4OH (pH 9-10). The aqueous phase was extracted with DCM (3 × 15 mL) and the combined organic layer was washed with water and sat. brine. The organic phase was dried over $MgSO_4$ and the solvent was evaporated to give Δ^5-dehydroprolines **51** which was purified by flash column chromatography on silica (hexane/EtOAc 90/10). The pure compound **51** was isolated as colourless foam. Yield: 70% (250 mg, 0.7 mmol). $[\alpha]_D{}^{22}$= –160.41° (*c*=1, 90% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 2H), 7.50 – 7.40 (m, 2H), 7.28 – 7.17 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 3.20 – 2.96 (m, 2H), 2.52 – 2.42 (m, 1H), 2.42 – 2.18 (m, 6H), 2.07 (ddd, *J* = 13.4, 9.2, 6.4 Hz, 1H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 174.8, 143.4, 138.0, 133.2, 130.2, 130.1, 129.5, 128.9, 128.2, 87.0, 35.7, 34.7, 26.3, 22.3. UPLC-DAD-QTOF: calcd for $C_{20}H_{21}ClNOS$ $[M+H]^+$, 358.1032; found, 358.1057.

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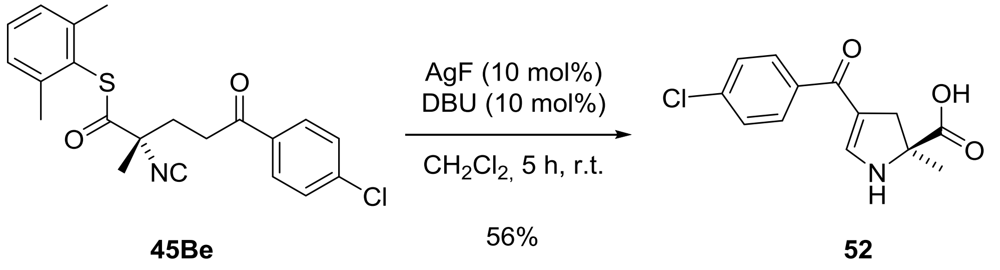
[270] Adapted from: Zhao, M; Zhu, H.; Dai, T.; Shi, M. *J. Org. Chem* **2015**, *80*, 11330-11338.

5.4.4.2. *Synthesis of Δ⁴-dehydroproline **52***

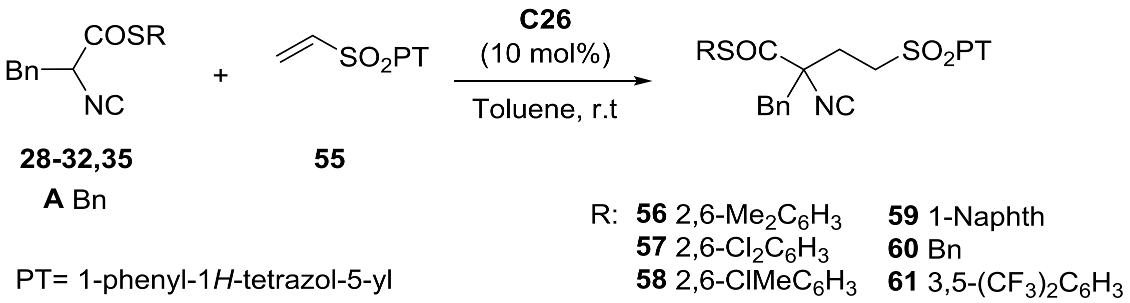


The corresponding adduct **45Be** (71.2 mg, 0.2 mmol) was dissolved in dichloromethane (0.4 ml), and AgF (2.5 mg, 0.1 equiv.) and DBU (3 mg, 0.1 equiv.) was added. The reaction mixture was stirred for 5 h at room temperature. Then, the reaction mixture was diluted with dichloromethane (2 mL), washed with HCl 1M and saturated NH_4Cl and the organic layer was dried with $MgSO_4$. The solvent was remove under reduced pressure to give compound **52** as essentially pure compound. Yield: 56% (29.8 mg, 0.11 mmol). $[\alpha]_D^{22}$= –67.68° (*c*=0.22, 90% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.6, 2.1 Hz, 2H), 7.56 – 7.39 (m, 3H), 3.50 (dd, *J* = 16.8, 2.4 Hz, 1H), 3.06 (dd, *J* = 16.9, 1.1 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 166.8, 139.1, 137.0, 136.5, 129.9, 129.2, 124.5, 68.0, 42.5, 26.5. UPLC-DAD-QTOF: calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$, 266.0523; found, 266.0522.

5.4.5. General Procedure for the conjugate addition of isocyanothioacetates to vinyl sulfone 55

Vinyl sulfone **55** was prepared following the procedure described in the literature[271] and the Michael reaction with isocyanothioacetates was performed according to the following procedure:



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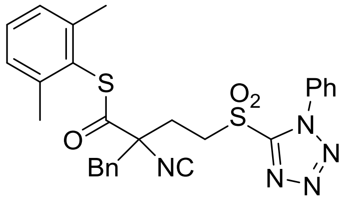
[271] See ref. 211, Chapter 3, page 120.

Catalyst **C26** (10 mol%, 15mg) was added to a solution of the corresponding isocyanothioacetate (0.1 mmol, 1 equiv.) and vinyl sulfone **55** (2 equiv., 47.2 mg, 0.2 mmol) in toluene (0.2 mL) at room temperature and the resulting mixture was stirred at the same temperature until the reaction was completed (monitored by TLC). The crude was directly purified by column chromatography.

S-(2,6-dimethylphenyl)2-benzyl-2-isocyano-4-((1-phenyl-1H-tetrazol-5-yl) sulfonyl)butanethioate (56)

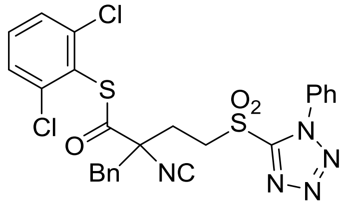


Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol). The title compound was obtained as a 72:28 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as a colorless oil. Yield: 47% (25 mg). $[\alpha]_D{}^{22}$= +38.82° (*c*=0.85, 44% *ee*, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.58 (m, 5H), 7.44 – 7.25 (m, 6H), 7.18 (d, *J* = 7.6 Hz, 2H), 4.16 – 3.86 (m, 2H), 3.40 (d, *J* = 13.7 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 2.79 (ddd, *J* = 13.8, 12.0, 4.7 Hz, 1H), 2.58 (ddd, *J* = 13.7, 12.1, 4.4 Hz, 1H), 2.37 (brs, 3H), 2.08 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 168.1, 154.1, 143.9, 133.9, 133.2, 132.7, 131.7, 130.9, 129.9, 129.7, 129.4, 126.0, 125.9, 73.8, 52.7, 45.7, 32.9, 22.7, 22.4. UPLC-DAD-QTOF: $C_{27}H_{26}N_5O_3S_2$ $[M+H]^+$ calcd.: 532.1477, found: 532.1484.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: 22.4 min (minor), 42.4 min (major)).

S-(2,6-Dichlorophenyl) 2-benzyl-2-isocyano-4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl) butanethioate (57)

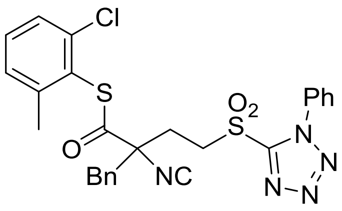


Prepared according to the general procedure starting from isocyanothioacetate **31A** (33.6 mg, 0.1 mmol). The title compound was obtained as a 81:19 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as a yellow oil. Yield: 90% (51.5 mg). $[\alpha]_D{}^{22}$= +70.82° (*c*=1.2, 62% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.58 (m, 4H), 7.55 – 7.45 (m, 2H), 7.45 – 7.35 (m, 4H), 7.35 – 7.26 (m, 3H), 4.13 – 3.97 (m, 2H), 3.45 (d, *J* = 13.7 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 2.90 – 2.72 (m, 1H), 2.69 – 2.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 168.0, 153.3, 141.2, 133.0, 132.7, 131.9, 131.9, 130.9, 130.1, 129.2, 129.1, 128.6, 125.2, 73.1, 51.8, 45.0, 32.2. UPLC-DAD-QTOF: $C_{25}H_{20}N_5O_3S_2Cl_2$ $[M+H]^+$ calcd.: 572.0385, found: 572.0385.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 80:20; flux= 0.5 mL/min; retention times: 32.3 min (minor), 43.3 min (major)).

S-(2-Chloro-6-methylphenyl)2-benzyl-2-isocyano-4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)butanethioate (58)

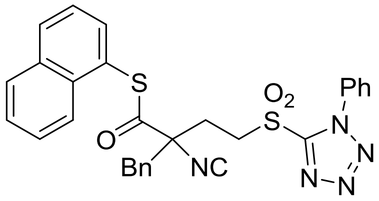


Prepared according to the general procedure starting from isocyanothioacetate **30A** (31.5 mg, 0.1 mmol) using catalyst **C27** (15 mg, 10 mol%) instead. The title compound was obtained as a 87:13 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as white foam. Yield: 64% (33.1 mg). $[\alpha]_D^{22}$= +46.33° (*c*=1.5, 74% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.52 (m, 4H), 7.44 – 7.14 (m, 8H), 4.17 – 3.78 (m, 2H), 3.37 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 2.89 – 2.70 (m, 1H), 2.70 – 2.48 (m, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 168.1, 153.8, 145.7, 140.3, 133.5, 132.8, 132.3, 131.3, 130.5, 130.0, 129.5, 129.0, 128.8, 125.7, 73.3, 52.3, 45.4, 33.1, 22.5. UPLC-DAD-QTOF: $C_{26}H_{23}N_5O_3S_2Cl$ $[M+H]^+$ calcd.: 552.0931, found: 552.0924.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: 27.2 min (minor), 44.5 min (major)).

S-(Naphthalen-1-yl)2-benzyl-2-isocyano-4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl) butanethioate

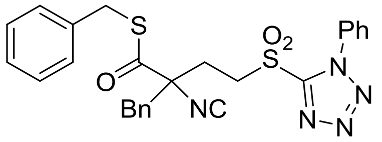


Prepared according to the general procedure starting from isocyanothioacetate **28A** (31.7 mg, 0.1 mmol). The title compound was obtained as a 70:30 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as yellow oil. Yield: 61% (33.8 mg). $[\alpha]_D{}^{22}$= +27.22° (c=1, 40% *ee*, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.4 Hz, 1H), 7.91 (dd, *J* = 6.2, 3.2 Hz, 1H), 7.85 – 7.75 (m, 1H), 7.74 – 7.51 (m, 9H), 7.51 – 7.39 (m, 3H), 7.39 – 7.28 (m, 2H), 4.09 (td, *J* = 11.9, 5.4 Hz, 1H), 3.95 (dd, *J* = 13.2, 3.5 Hz, 1H), 3.39 (d, *J* = 13.5 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 2.78 (td, *J* = 13.0, 12.5, 4.7 Hz, 1H), 2.60 (td, *J* = 13.5, 13.0, 4.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 168.0, 153.8, 135.9, 135.2, 134.9, 134.6, 132.7, 132.5, 132.3, 131.4, 130.5, 129.5, 129.4, 129.1, 128.4, 127.4, 126.4, 125.8, 125.6, 125.4, 123.5, 73.7, 52.3, 45.6, 32.6. UPLC-DAD-QTOF: $C_{29}H_{24}N_5O_3S_2$ $[M+H]^+$ calcd.: 554.1321, found: 554.1310.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: 36.9 min (minor), 54.6 min (major)).

S-Benzyl 2-benzyl-2-isocyano-4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)butanethioate (60)

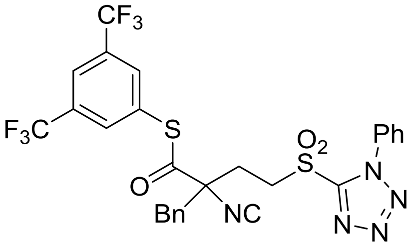


Prepared according to the general procedure starting from isocyanothioacetate **35A** (28.1 mg, 0.1 mmol). The title compound was obtained as a 64:36 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as yellow oil. Yield: 43% (22.3 mg). $[\alpha]_D{}^{22}$= −81.50° (c=0.6, 28% *ee*, CH_2Cl_2)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.58 (m, 4H), 7.39 – 7.21 (m, 8H), 7.15 (dq, *J* = 6.6, 2.3, 1.8 Hz, 3H), 4.25 – 4.07 (m, 2H), 3.90 (ddd, *J* = 14.5, 12.1, 4.3 Hz, 1H), 3.72 (ddd, *J* = 14.5, 12.2, 4.5 Hz, 1H), 3.34 (d, *J* = 13.6 Hz, 1H), 3.05 (d, *J* = 13.6 Hz, 1H), 2.77 (ddd, *J* = 13.7, 12.1, 4.5 Hz, 1H), 2.51 (ddd, *J* = 13.7, 12.2, 4.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 167.3, 153.7, 136.3, 133.5, 132.5, 132.3, 131.0, 130.5, 129.7, 129.4, 129.3, 128.9, 128.5, 125.7, 73.4, 52.2, 45.7, 35.3, 32.2. UPLC-DAD-QTOF: $C_{26}H_{24}N_5O_3S_2$ $[M+H]^+$ calcd.: 518.1321, found: 518.1309.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 80:20; flux= 0.5 mL/min; retention times: 40.5 min (minor), 53.5 min (major)).

S-(3,5-bis(Trifluoromethyl)phenyl) 2-benzyl-2-isocyano-4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)butanethioate (61)



Prepared according to the general procedure starting from isocyanothioacetate **32A** (40.3 mg, 0.1 mmol). The title compound was obtained as a 50:50 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as brown oil. Yield: 50% (32.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.95 (m, 1H), 7.75 – 7.59 (m, 6H), 7.50 – 7.37 (m, 3H), 7.35 – 7.24 (m, 3H), 4.07 (ddd, *J* = 14.4, 11.6, 4.6 Hz, 1H), 3.90 (ddd, *J* = 14.5, 11.8, 4.8 Hz, 1H), 3.35 (d, *J* = 13.6 Hz, 1H), 3.20 (d, *J* = 13.6 Hz, 1H), 2.85 (ddd, *J* = 13.9, 11.6, 4.8 Hz, 1H), 2.67 (ddd, *J* = 13.9, 11.7, 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 169.0, 153.6, 135.4, 133.8, 133.4, 133.3, 132.3, 132.2, 131.2, 130.5, 129.5, 129.4, 125.6, 124.9 (q), 73.8, 52.1, 46.0, 32.3. UPLC-DAD-QTOF: $C_{27}H_{20}N_5O_3S_2F_6$ $[M+H]^+$ calcd.: 640.0912, found: 640.0907.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: 16.0 min, 19.3 min).

5.4.6. General Procedure for the Mannich reaction of isocyanothioacetates with *N*-nosyl aldimine 64

N-nosyl aldimine **64** was prepared following the procedure described in the literature[272] and the Mannich reaction with isocyanothioacetates was performed according to the following procedure:

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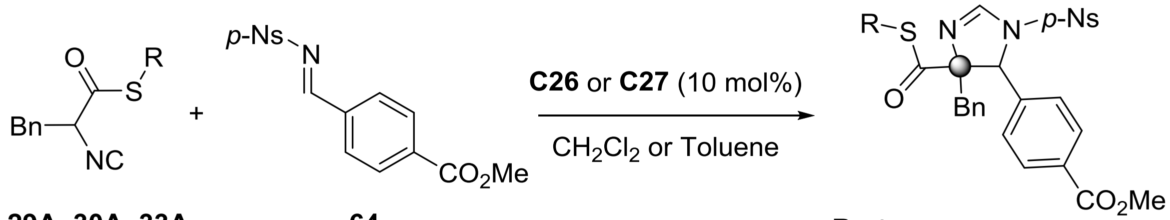
[272] Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 629–633.

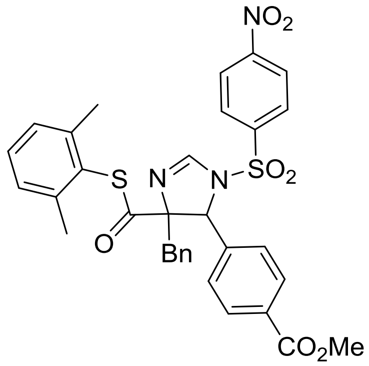


29A, **30A**, **33A** **64**

R: **65** 2,6-$Me_2C_6H_3$
66 2,4,6-$^iPr_3C_6H_2$
67 2,6-$ClMeC_6H_3$

Catalyst **C26** or **C27** (10 mol%, 15mg) was added to a solution of the corresponding isocyanothioacetate (0.1 mmol, 1 equiv.), *N*-nosyl imine **64** (52 mg, 0.15 mmol, 1.5 equiv.) and molecular sieves 4 Å (20 mg) in dried dichloromethane or toluene (0.2 mL) at room temperature and the resulting mixture was stirred at the same temperature until the reaction was completed (monitored by ^{1}H-NMR). The crude was directly purified by column chromatography.

Methyl 4-(4-benzyl-4-(((2,6-dimethylphenyl)thio)carbonyl)-1-((4-nitrophenyl) sulfonyl)-4,5-dihydro-1H-imidazol-5-yl)benzoate (65)

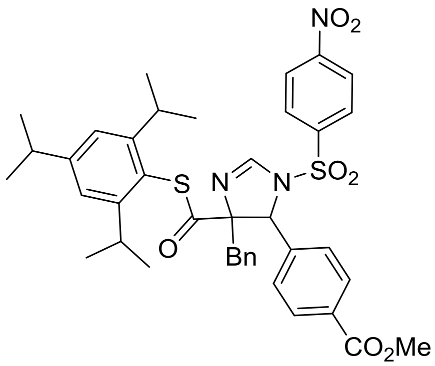


Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol). The reaction was catalyzed by **C26** (10 mol%) in dichloromethane. The title compound was obtained as a 90:10 mixture of diastereomers (36% *ee* for the major diast.). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as white foam. Yield: 47% (30 mg). $[\alpha]_D^{22}$= +8.25° (*c*=0.8, 36% *ee*, CH_2Cl_2).

Data of major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.24 (m, 2H), 8.01 (s, 1H), 7.93 – 7.85 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.16 (m, 4H), 7.16 – 7.03 (m, 5H), 5.08 (s, 1H), 3.94 (s, 3H), 2.45 (d, J = 5.9 Hz, 2H), 1.91 (brs, 3H), 1.73 (brs, 3H). 13C NMR (75 MHz, CDCl3) δ 200.8, 166.2, 150.9, 149.7, 142.4, 138.2, 134.4, 131.1, 131.0, 130.9, 130.2, 129.4, 129.2, 129.1, 128.4, 128.2, 127.2, 124.7, 124.3, 89.2, 68.4, 52.5, 42.8, 21.1. UPLC-DAD-QTOF: $C_{33}H_{30}N_3O_7S_2$ $[M+H]^+$ calcd.: 664.1525, found: 644.1533.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: diast. A (minor enantiomer) 17.7 min, diast. B 22.1 min, diast. B 23.5 min, diast. A (major enantiomer) 31.9 min).

Methyl-4-(4-benzyl-1-((4-nitrophenyl)sulfonyl)-4-(((2,4,6-triisopropylphenyl)thio) carbonyl)-4,5-dihydro-1H-imidazol-5-yl)benzoate (66)

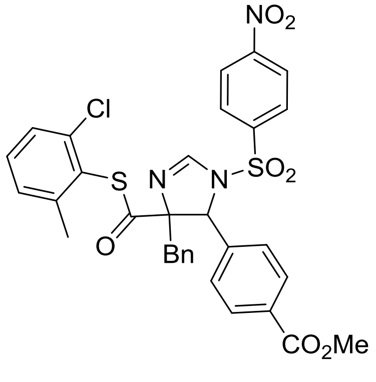


Prepared according to the general procedure starting from isocyanothioacetate **33A** (41 mg, 0.1 mmol). The reaction was catalyzed by **C26** (10 mol%) in dichloromethane. The title compound was obtained as a 70:30 mixture of diastereomers (10% *ee* for the major diast.). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as brown foam. Yield: 82% (61 mg). $[\alpha]_D{}^{22}$= +2.54° (*c*=1, 10% *ee*, CH_2Cl_2).

Data of major diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.12 (m, 2H), 8.01 (d, *J* = 4.5 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.23 (dp, *J* = 7.8, 2.7, 2.1 Hz, 3H), 7.14 (tt, *J* = 4.6, 2.3 Hz, 2H), 7.05 (d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 1.9 Hz, 1H), 6.85 (d, *J* = 12.0 Hz, 1H), 5.24 (s, 1H), 3.90 (s, 3H), 3.15 (dp, *J* = 15.6, 7.1, 5.5 Hz, 1H), 2.99 – 2.80 (m, 1H), 2.51 – 2.36 (m, 2H), 1.24 (dd, *J* = 7.0, 2.2 Hz, 6H), 1.17 (dd, *J* = 6.9, 1.3 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.07 – 0.94 (m, 3H), 0.82 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 166.1, 152.9, 152.0, 151.4, 150.7, 149.5, 143.2, 137.7, 134.6, 131.1, 130.7, 129.6, 129.0, 128.6, 128.2, 127.0, 124.4, 122.3, 89.3, 69.0, 52.5, 42.3, 34.4, 32.1, 31.5, 24.9, 24.2, 23.9, 23.7, 23.3. UPLC-DAD-QTOF: $C_{40}H_{44}N_3O_7S_2$ $[M+H]^+$ calcd.: 742.2621, found: 742.2623.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 98:2; flux= 1 mL/min; retention times: diast. A (major enantiomer) 29.7 min, diast. B 32.9 min, diast. B 37.7 min, diast. A (minor enantiomer) 78.6 min).

Methyl-4-(4-benzyl-4-(((2-chloro-6-methylphenyl)thio)carbonyl)-1-((4-nitrophenyl) sulfonyl)-4,5-dihydro-1H-imidazol-5-yl)benzoate (67)



Prepared according to the general procedure starting from isocyanothioacetate **30A** (32 mg, 0.1 mmol). The reaction was catalyzed by **C27** (10 mol%) in toluene. The title compound was obtained as a 97:3 mixture of diastereomers (74 % *ee* for the major diast.). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 9/1 to 8/2) to give the title compound as a yellow oil. Yield: 75% (50 mg). $[\alpha]_D{}^{22}$= +17.90° (*c*=0.8, 74% *ee*, CH_2Cl_2).

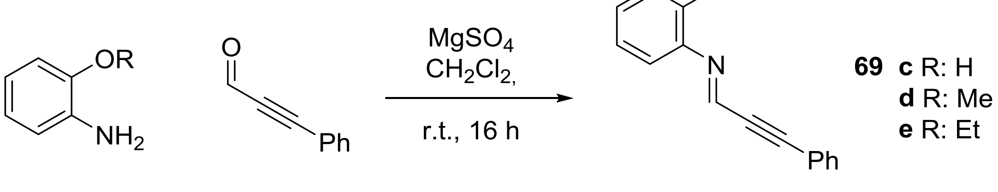
Data of major diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.2 Hz, 2H), 8.05 (s, 1H), 8.00 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.50 – 7.31 (m, 2H), 7.30 – 7.13 (m, 6H), 7.06 (t, *J* = 8.6 Hz, 3H), 5.02 (s, 1H), 3.92 (s, 3H), 2.41 (s, 2H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 166.9, 151.5, 151.0, 145.6, 142.4, 139.7, 138.9, 134.9, 131.7, 131.5, 131.4, 130.7, 130.0, 129.7, 129.1, 128.7, 128.2, 127.9, 127.7, 126.6, 125.4, 124.8, 89.6, 68.6, 53.0, 43.3, 22.2. UPLC-DAD-QTOF: $C_{32}H_{27}N_3O_7S_2Cl$ $[M+H]^+$ calcd.: 664,0979 found: 664.0974.

The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: diast. A (minor enantiomer) 23.1 min, diast. B 27.3 min, diast. B 29.0 min, diast. A (major enantiomer) 41.2 min).

5.4.7. Mannich reaction of isocyano(thio)acetates with *N*-aryl aldimines

5.4.7.1. Preparation of the N-aryl aldimines[273]

N-aryl aldimines **69c-e** were prepared according to the following procedure:



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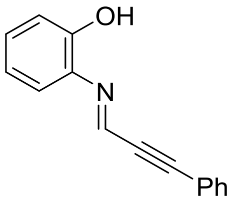
[273] Adapted from: Gómez-Bengoa, E.; Jiménez, J.; Lapuerta, I.; Mielgo, A.; Oiarbide, M.; Otazo, I.; Velilla, I.; Vera, S.; Palomo, C. *Chem. Sci.* **2012**, *3*, 2949–2957.

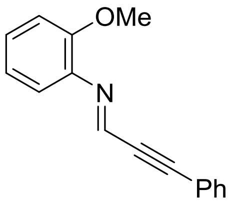
A mixture of the corresponding aldehyde (5 mmol), amine (5 mmol), and $MgSO_4$ (2g, 400 mg/mmol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature for 16 h. The mixture was filtered through celite and concentrated under reduced pressure. The resulting solid was disgregated with Et_2O and filtered to give the corresponding imines.

(E)-2-((3-Phenylprop-2-yn-1-ylidene)amino)phenol (69c)



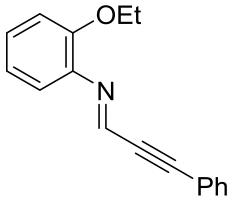
Yield: 55% (608 mg, 2.75 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.65 – 7.53 (m, 2H), 7.51 – 7.35 (m, 3H), 7.33 – 7.16 (m, 2H), 7.11 – 7.01 (m, 1H), 6.98 – 6.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 140.2, 135.5, 132.5, 130.4, 130.1, 128.7, 121.3, 120.2, 115.8, 115.6, 96.2, 88.0.

(E)-N-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-imine (69d)



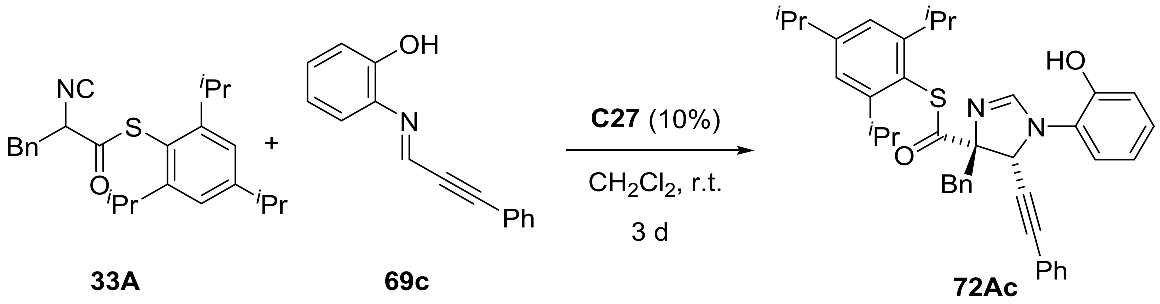
Yield: 75% (881 mg, 3.75 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.66 – 7.52 (m, 2H), 7.47 – 7.12 (m, 4H), 7.09 – 6.88 (m, 3H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 144.4, 142.9, 132.5, 129.8, 128.6, 128.1, 126.7, 121.0, 120.3, 111.6, 94.8, 88.1, 55.9.

(E)-N-(2-Ethoxyphenyl)-3-phenylprop-2-yn-1-imine (69e)



Yield: 62% (772 mg, 3.1 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.58 – 7.48 (m, 2H), 7.33 – 7.22 (m, 3H), 7.15 – 7.05 (m, 1H), 6.98 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.91 – 6.81 (m, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.11, 144.06, 142.31, 139.97, 131.81, 131.75, 129.20, 128.01, 127.95, 127.37, 121.03, 120.37, 112.42, 93.95, 87.76, 63.69, 14.27.

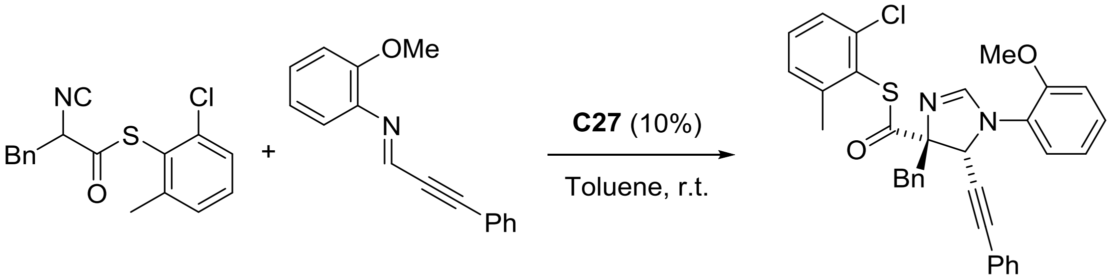
*5.4.7.2. Reaction of isocyanothioacetate **33A** with **69c***



Catalyst **C27** (10 mol%, 15mg) was added to a solution of isocyanothioacetate **33A** (39 mg, 0.1 mmol, 1 equiv.) and *N*-aryl imine **69c** (33 mg, 0.15 mmol, 1.5 equiv.) in dichloromethane (0.2 mL) at room temperature and the resulting mixture was stirred at the same temperature until the consumption of the starting material (monitored by ^{1}H-NMR). Only traces of product were observed. The crude was directly purified by flash column chromatography on silica gel (hexane/EtOAc 70/30). Yield: 5% (3.1 mg, 0.005 mmol). Due to the low yield the enantiopurity of compound **72Ac** was not determined.

Data of major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.43 – 7.29 (m, 8H), 7.25 – 7.18 (m, 2H), 7.07 (s, 2H), 7.02 – 6.94 (m, 2H), 5.16 (s, 1H), 3.59 (d, *J* = 1.8 Hz, 2H), 3.45 – 3.30 (m, 1H), 3.02 – 2.82 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.18 (dd, *J* = 6.9, 2.6 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 156.4, 152.9, 152.1, 152.0, 151.0, 135.9, 131.7, 131.0, 128.9, 128.8, 128.3, 128.0, 126.8, 126.1, 125.8, 122.1, 122.0, 120.9, 116.6, 90.5, 86.3, 82.5, 62.5, 41.7, 34.3, 32.0, 31.5, 31.0, 24.7, 24.2, 23.9, 23.6, 23.4. UPLC-DAD-QTOF: $C_{40}H_{43}N_2O_2S$ $[M+H]^+$ calcd.: 615.3045, found: 615.3046.

*5.4.7.3. Reaction of isocyanothioacetate **30A** with **69d***

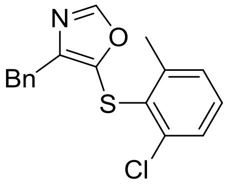


Catalyst **C27** (10 mol%, 15mg) was added to a solution of isocyanothioacetate **30A** (63 mg, 0.2 mmol, 2 equiv.) and *N*-aryl imine **69d** (23 mg, 0.1 mmol, 1 equiv.) in toluene (0.2 mL) at room temperature and the resulting mixture was stirred at the same temperature until the consumption of the imine (monitored by ^{1}H-NMR). The crude was directly purified by flash column chromatography on silica (hexane/EtOAc 80/20). The compound **70Ad** was obtained as 82:18 mixture of diastereomers (80% *ee* for the major diast.). Yield: 58% (32 mg, 0.056 mmol).

Data of major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.4 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.07 (m, 13H), 7.07 – 6.92 (m, 2H), 5.50 (s, 1H), 3.88 (s, 3H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.40 (d, *J* = 13.5 Hz, 1H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 157.3, 156.9, 154.5, 146.2, 140.8, 137.3, 132.7, 132.2, 131.5, 129.8, 129.7, 129.3, 129.1, 128.9, 128.6, 128.4, 128.0, 127.6, 125.6, 123.3, 122.0, 113.1, 90.6, 86.6, 83.9, 61.9, 56.9, 43.4, 22.8. UPLC-DAD-QTOF: $C_{33}H_{28}N_2O_2SCl$ $[M+H]^+$ calcd.: 551.1560, found: 551.1564.

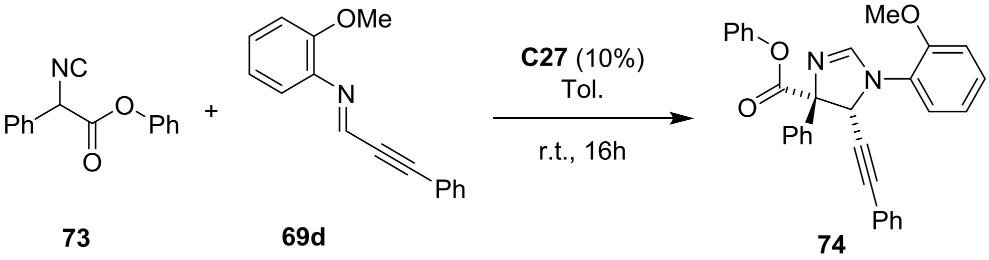
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min; retention times: diast. A (minor enantiomer) 19.9 min, diast. A (major enantiomer) 24.0 min, diast. B 33.6 min, diast. B 36.5 min).

Selected isolated by-product (71)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.43 – 7.13 (m, 8H), 4.05 (s, 2H), 2.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 145.6, 143.7, 140.1, 139.5, 139.0, 130.8, 130.0, 129.6, 129.4, 129.2, 128.8, 127.1, 33.2, 23.3. UPLC-DAD-QTOF: $C_{17}H_{15}NOSCl$ $[M+H]^+$ calcd.: 316.0563, found: 316.0570.

5.4.7.4. Reaction of isocyanoacetate ***73*** *with* ***69d***



Catalyst **C27** (10 mol%, 15mg) was added to a solution of isocyanoacetate **73** (24 mg, 0.1 mmol, 1 equiv.) and *N*-aryl imine **69d** (35 mg, 0.15 mmol, 1.5 equiv.) in toluene

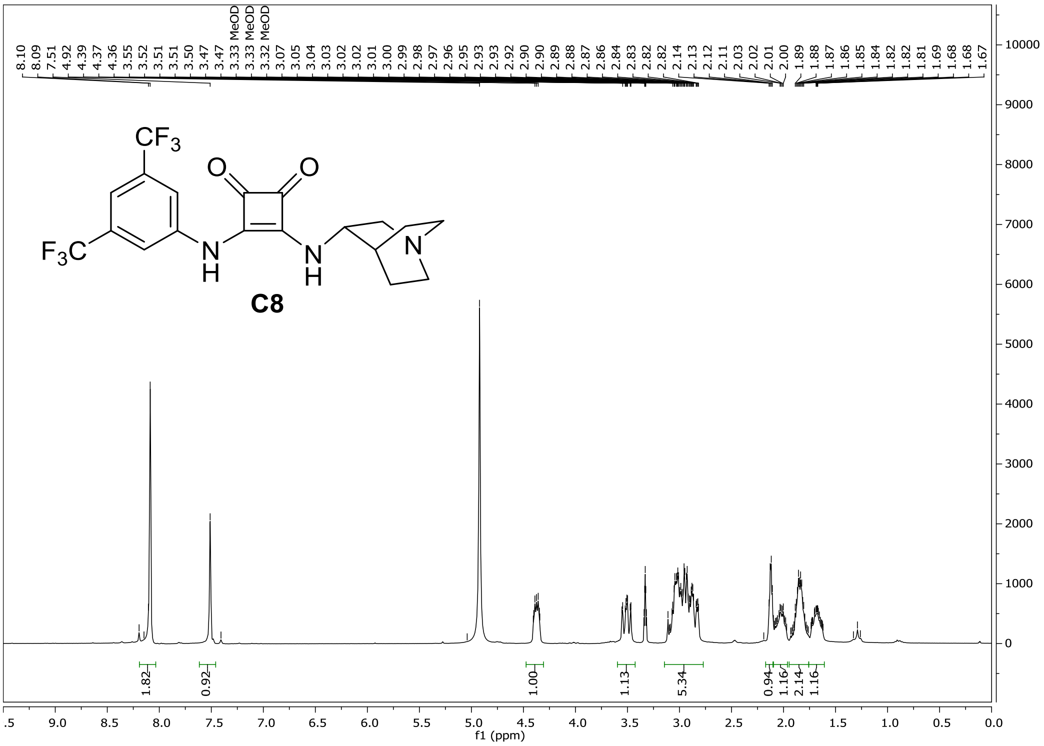
(0.2 mL) at room temperature and the resulting mixture was stirred at the same temperature until the reaction was completed (monitored by ^{1}H-NMR). The compound **74** was obtained as 40:60 mixture of diastereomers (determined by ^{1}H-NMR) and 56 % ee for the major diastereomer. The crude was directly purified by flash column chromatography on silica gel (hexane/EtOAc 80/20). Yield: 51% (24 mg, 0.051 mmol).

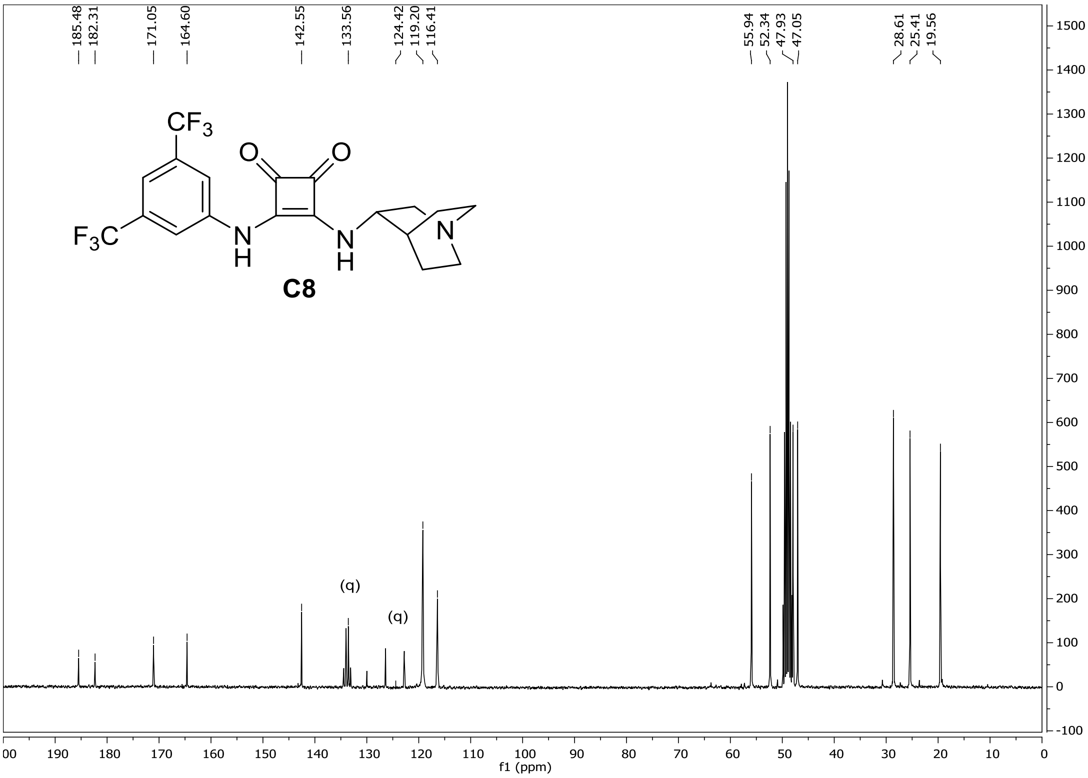
Data of major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 2H), 7.70 (s, 1H), 7.52 – 7.35 (m, 3H), 7.35 – 7.21 (m, 8H), 7.22 – 7.07 (m, 3H), 7.06 – 6.95 (m, 2H), 5.71 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 155.1, 153.8, 151.6, 141.9, 132.5, 129.8, 129.4, 129.1, 128.9, 128.9, 128.8, 127.4, 126.4, 124.7, 122.6, 122.2, 121.7, 112.7, 89.5, 84.7, 84.5, 62.8, 56.5. UPLC-DAD-QTOF: $C_{31}H_{25}N_2O_3$ $[M+H]^+$ calcd.: 473.1865, found: 473.1876.

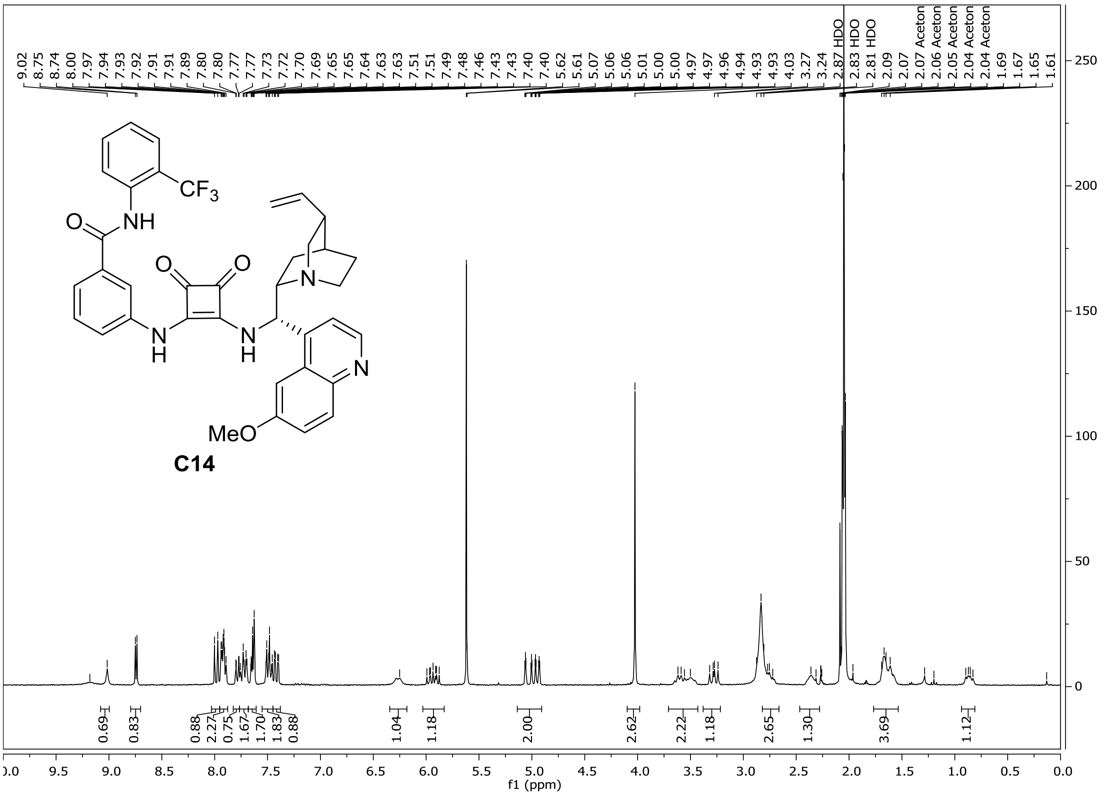
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: diast. B 9.0 min, diast. A (minor enantiomer) 13.4 min, diast. A (major enantiomer) 19.7 min, diast. B 44.2 min).

5.5. Representative NMR spectra

5.5.1. Catalysts



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4.96
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3.24
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2.83 HDO
2.81 HDO
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2.07
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2.06 Aceton
2.05 Aceton
2.04 Aceton
2.04 Aceton
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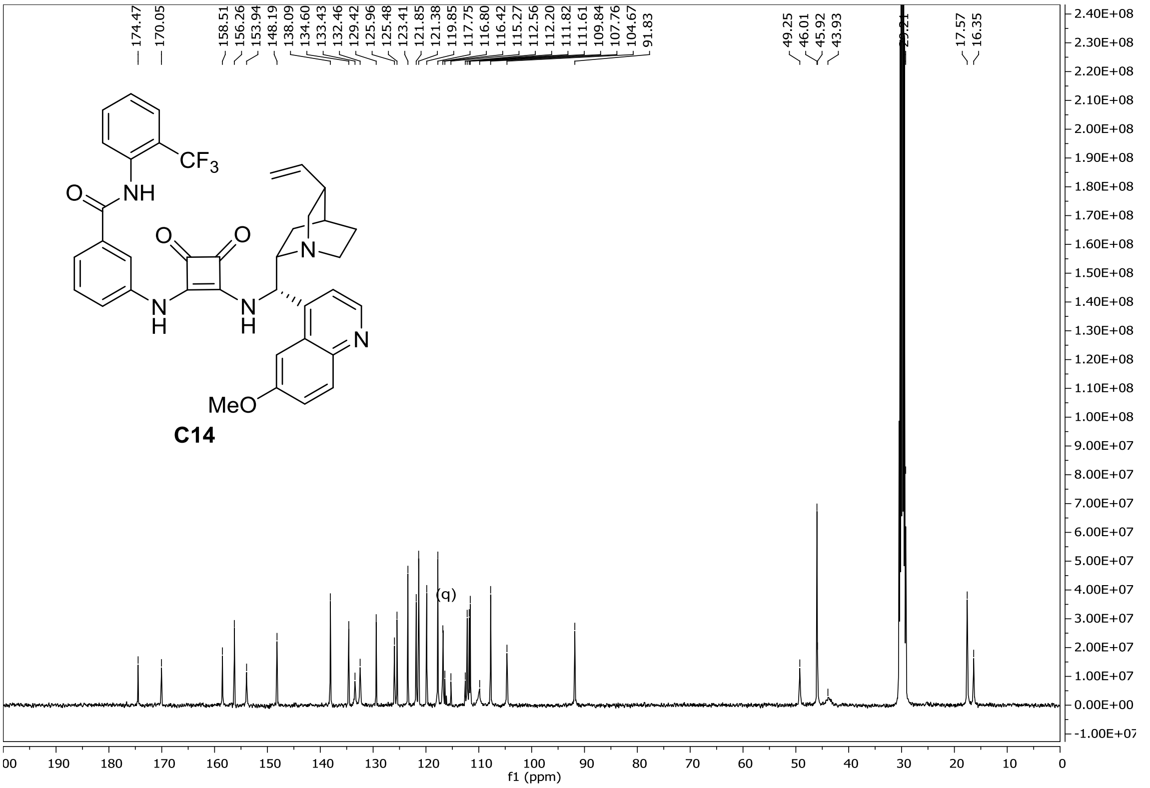
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MeO
C14
(q)
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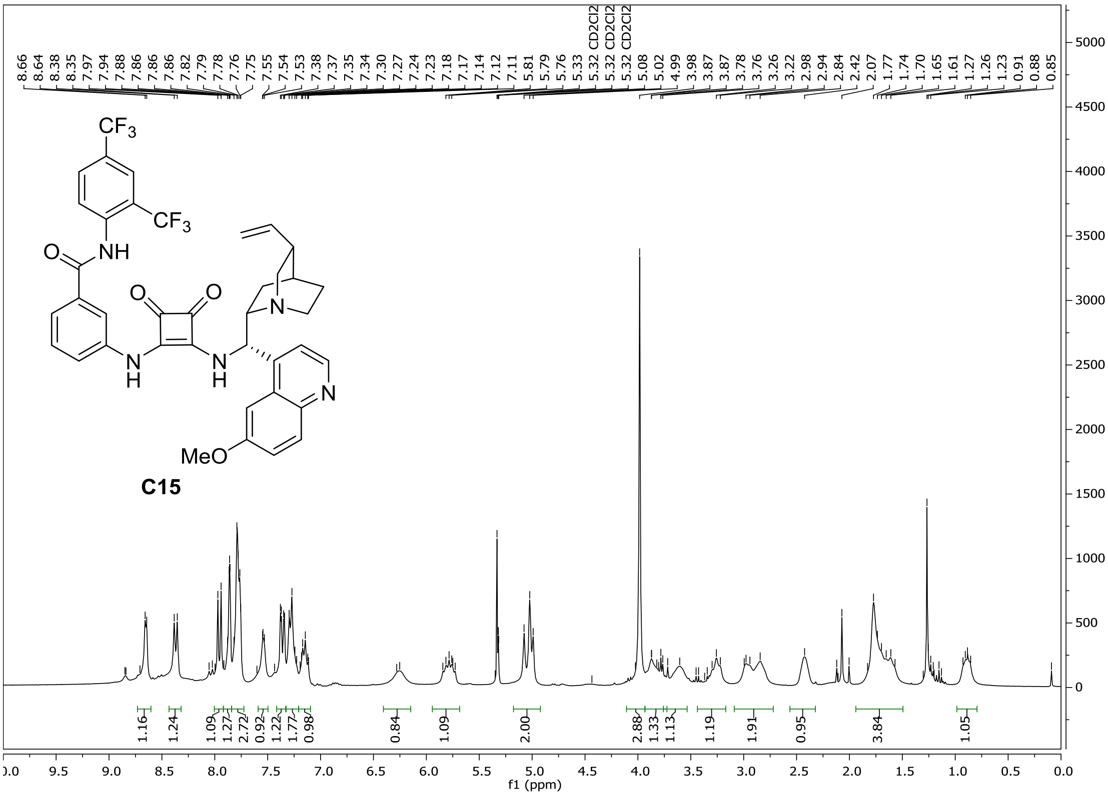
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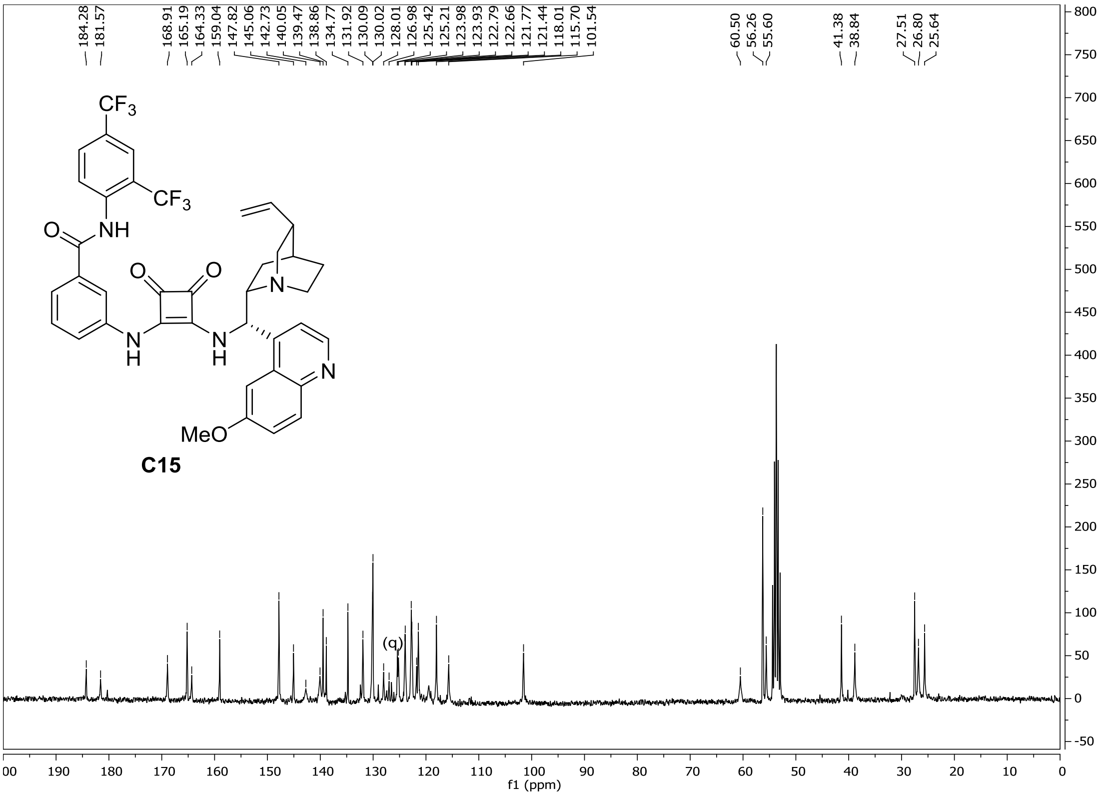
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(q)
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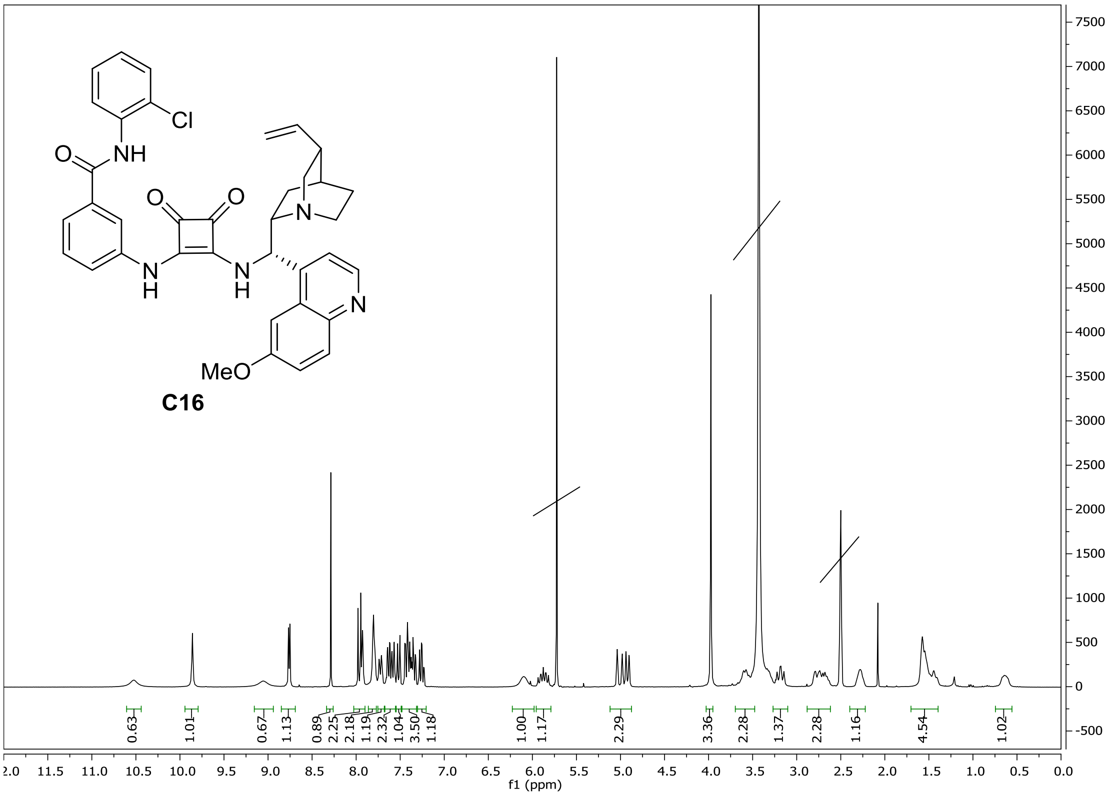
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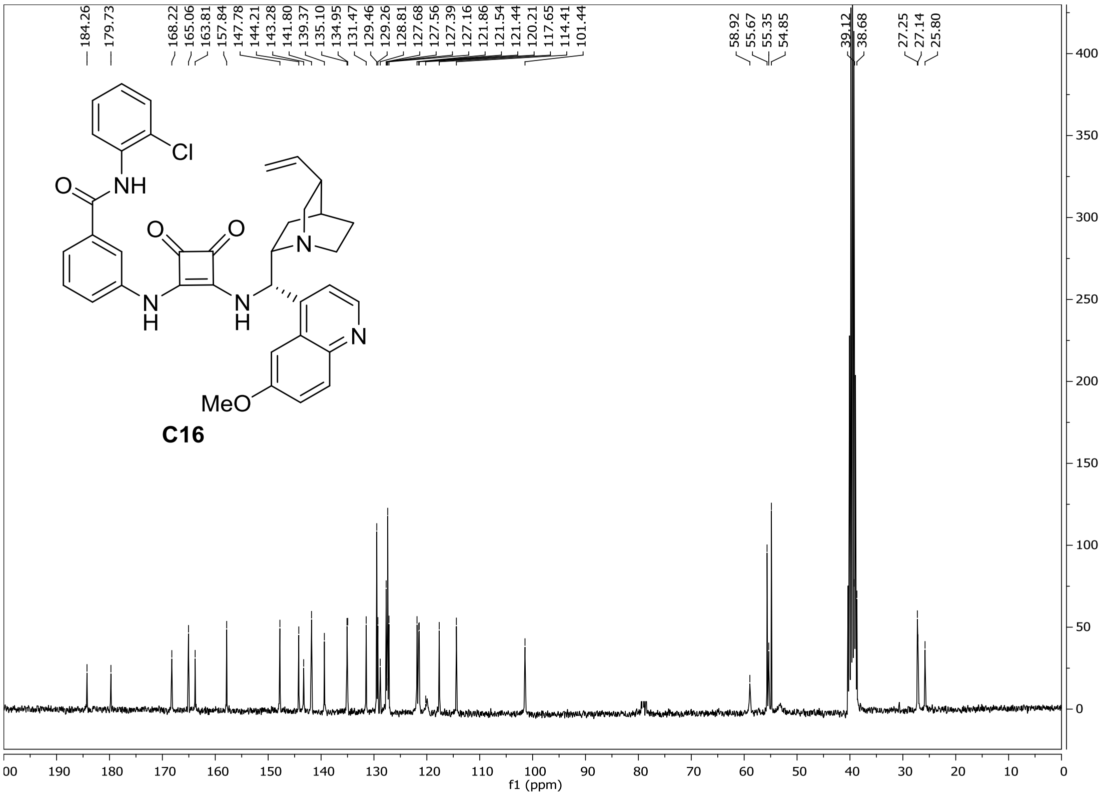
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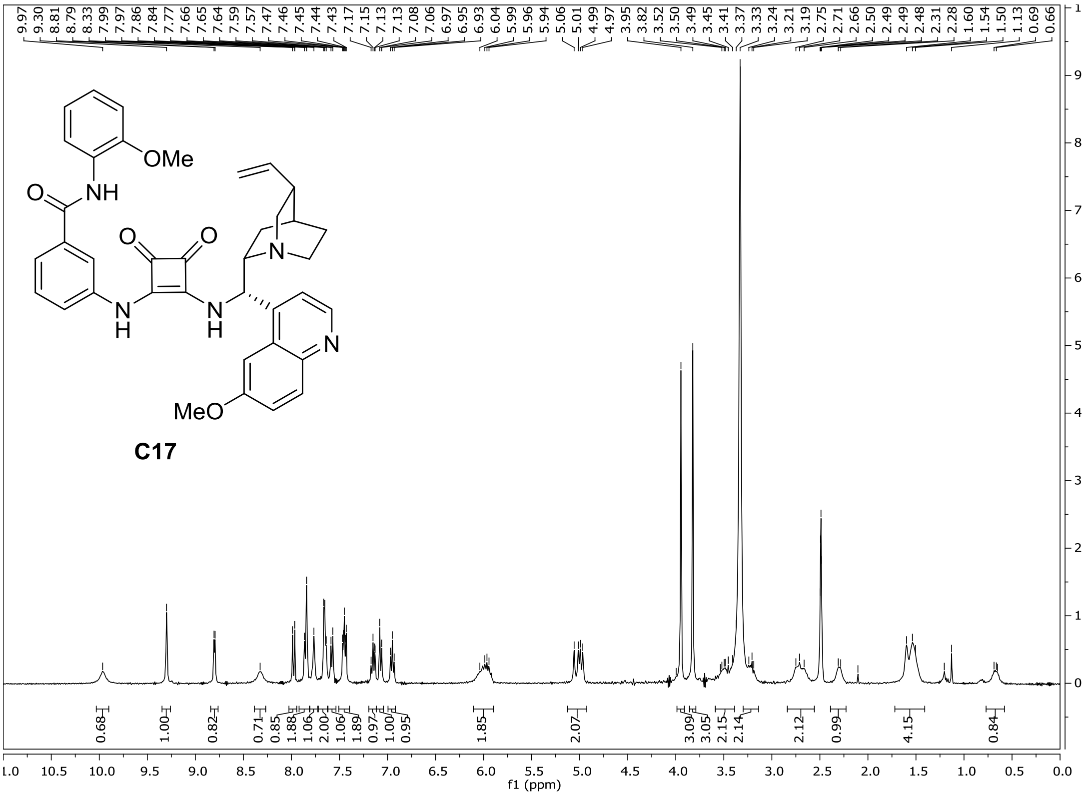
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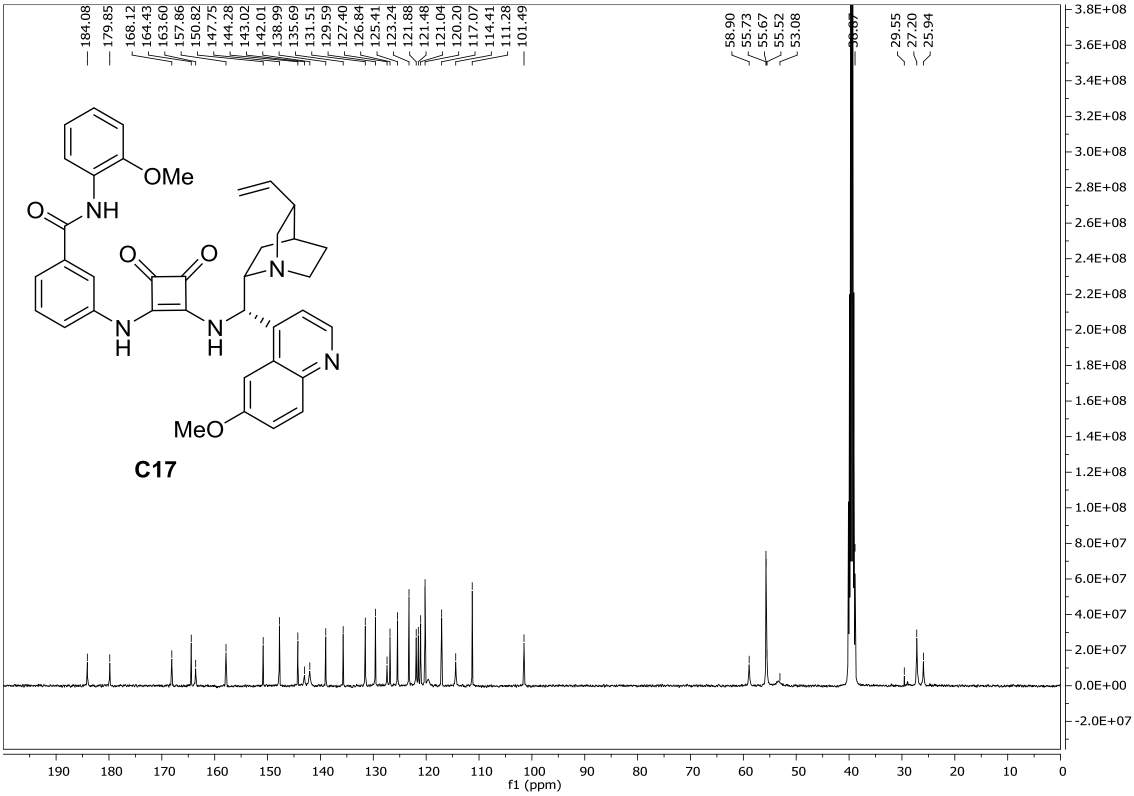
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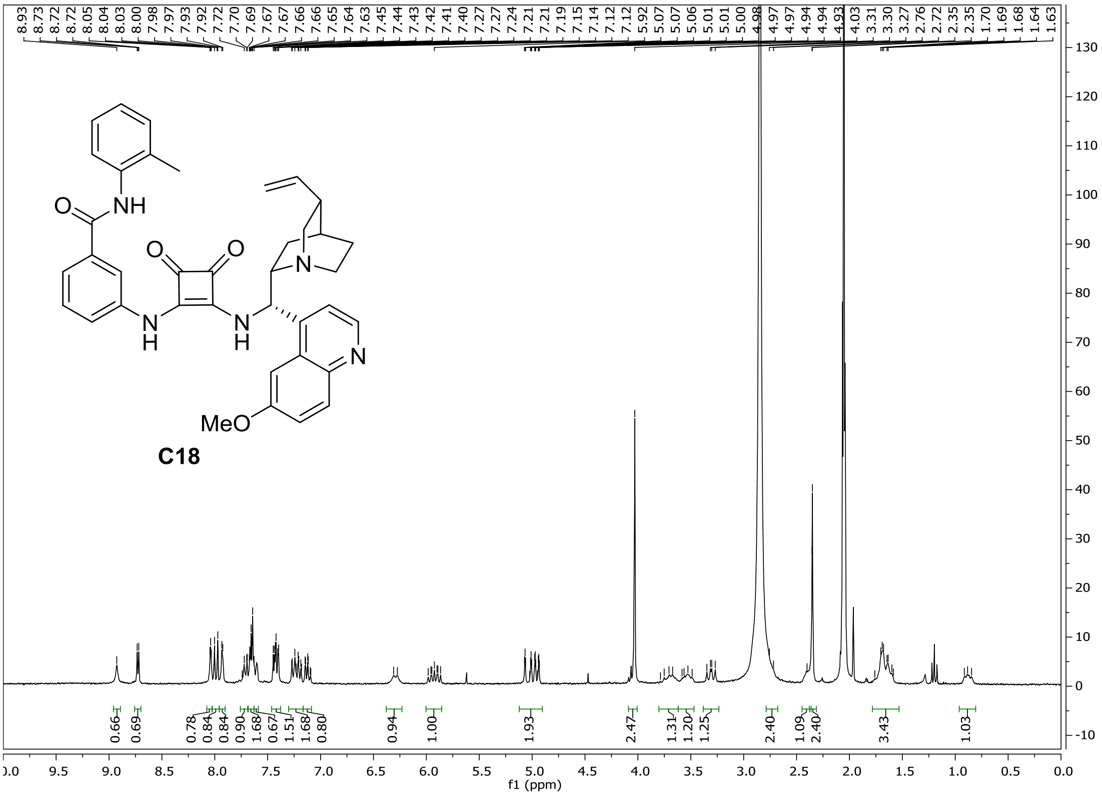
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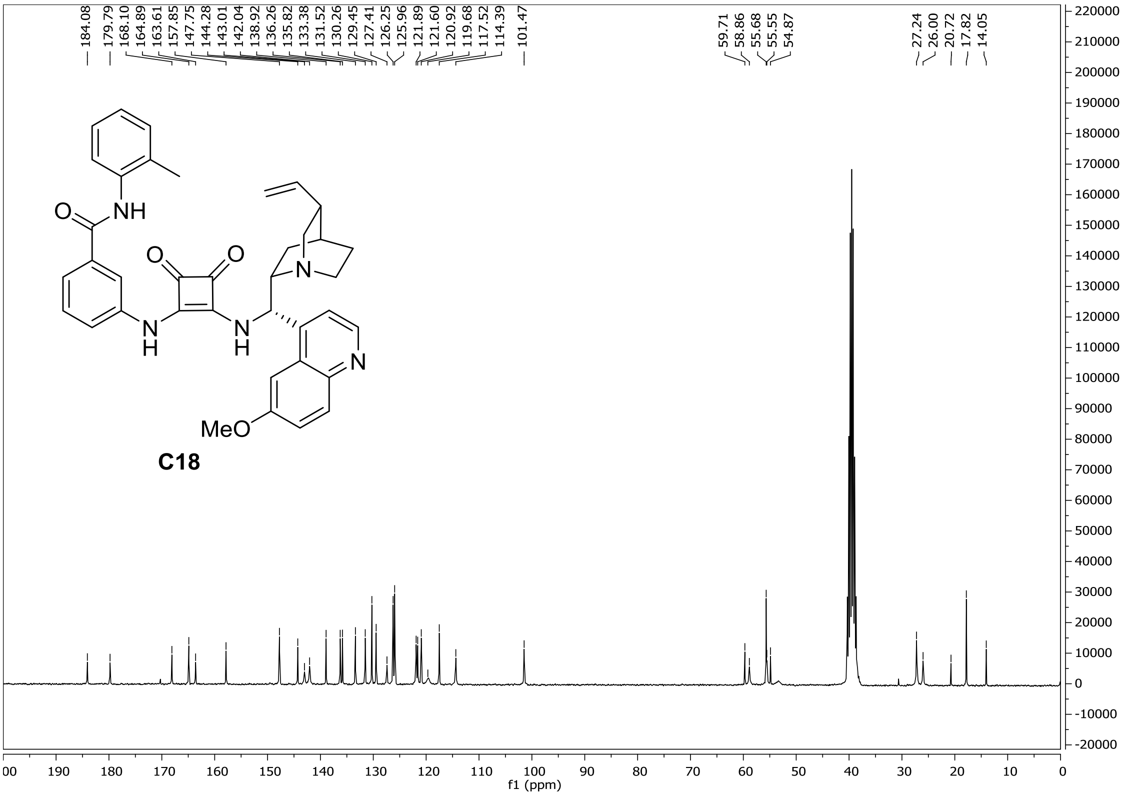
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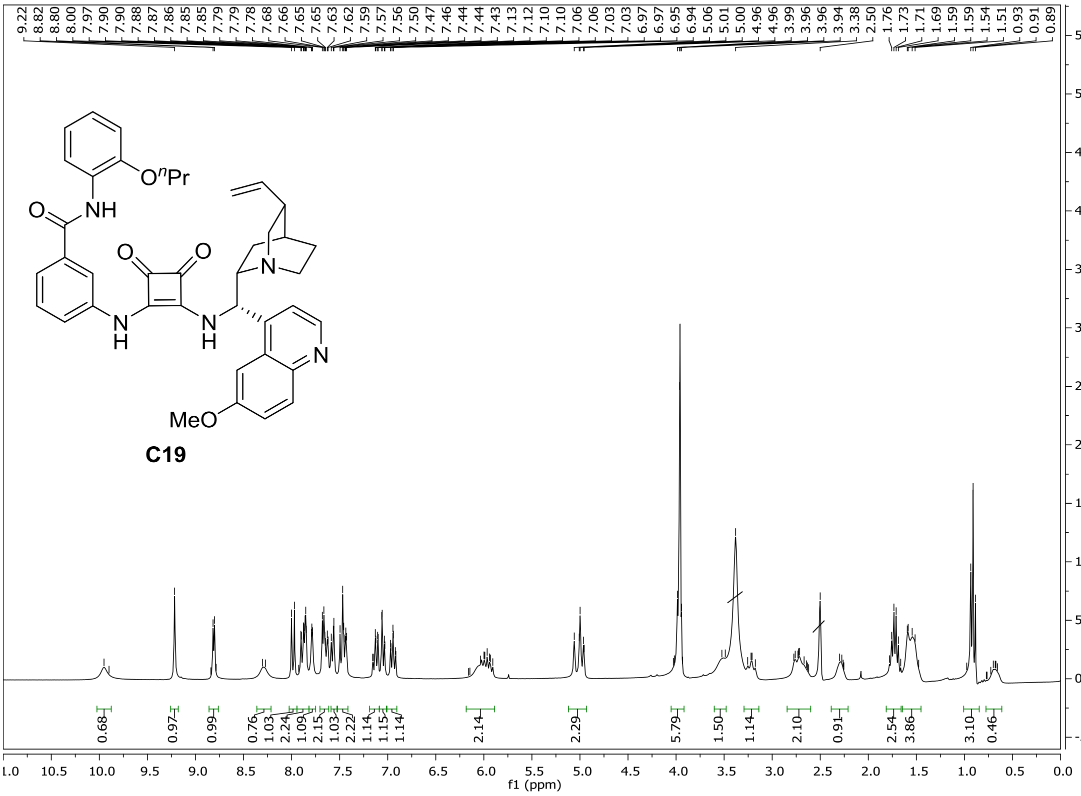
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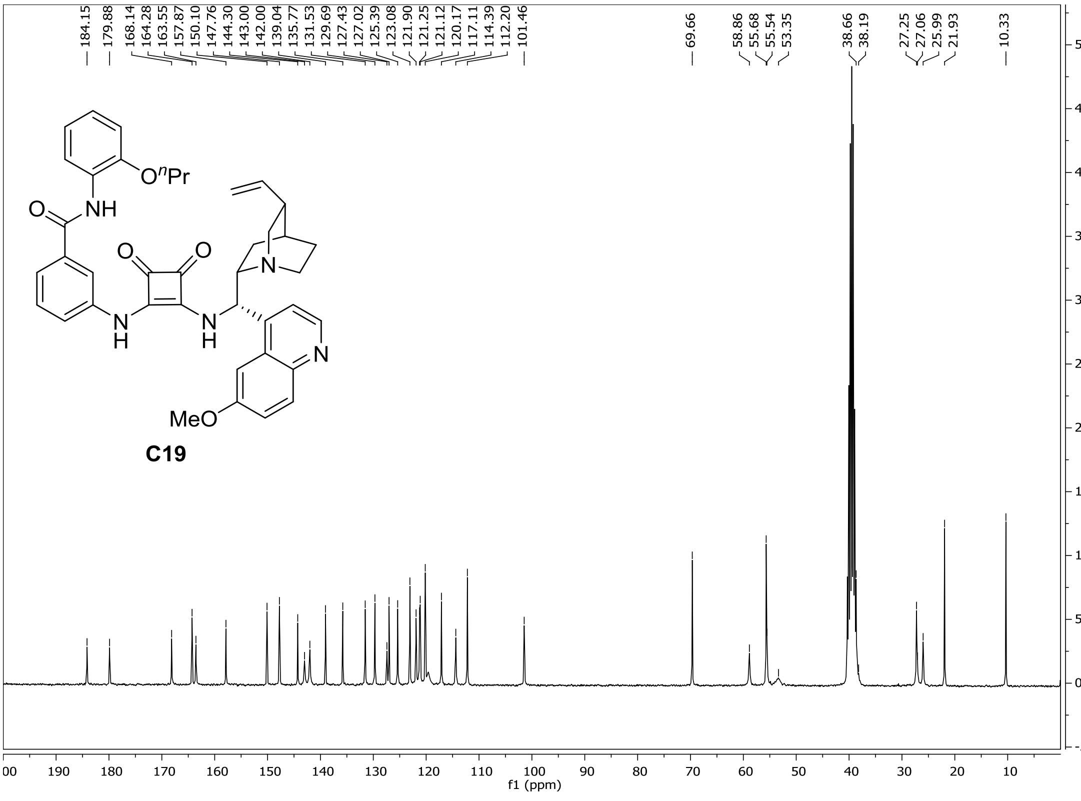
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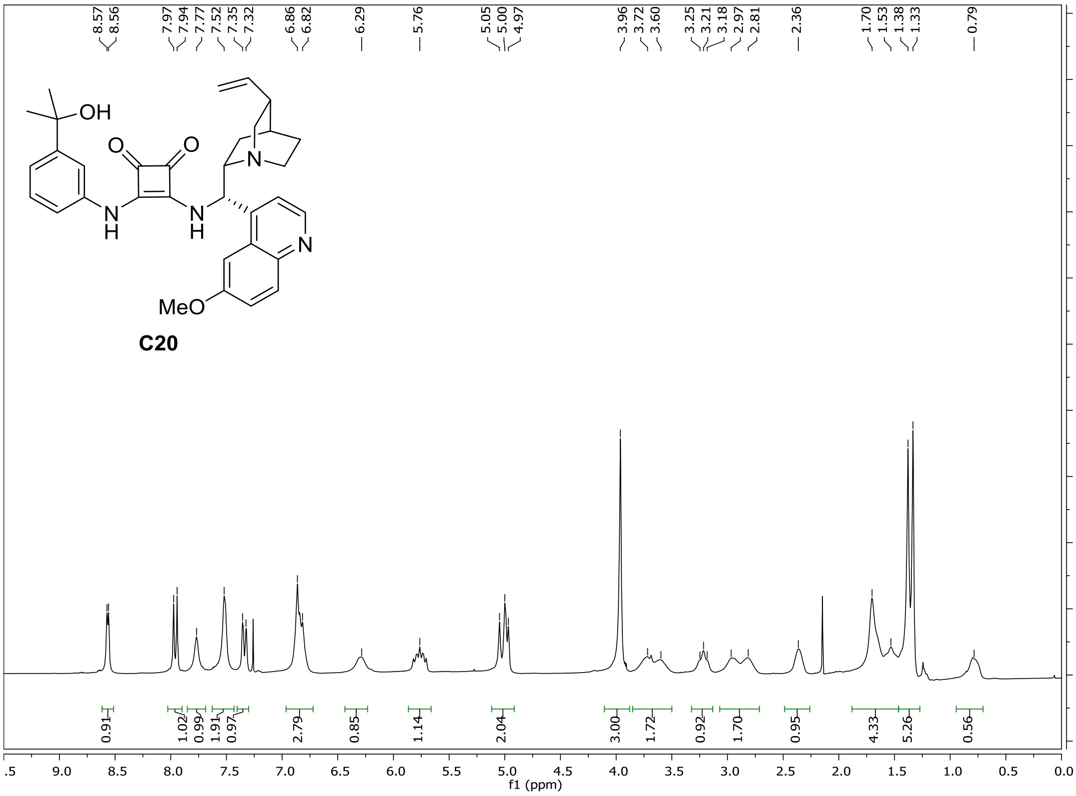
C19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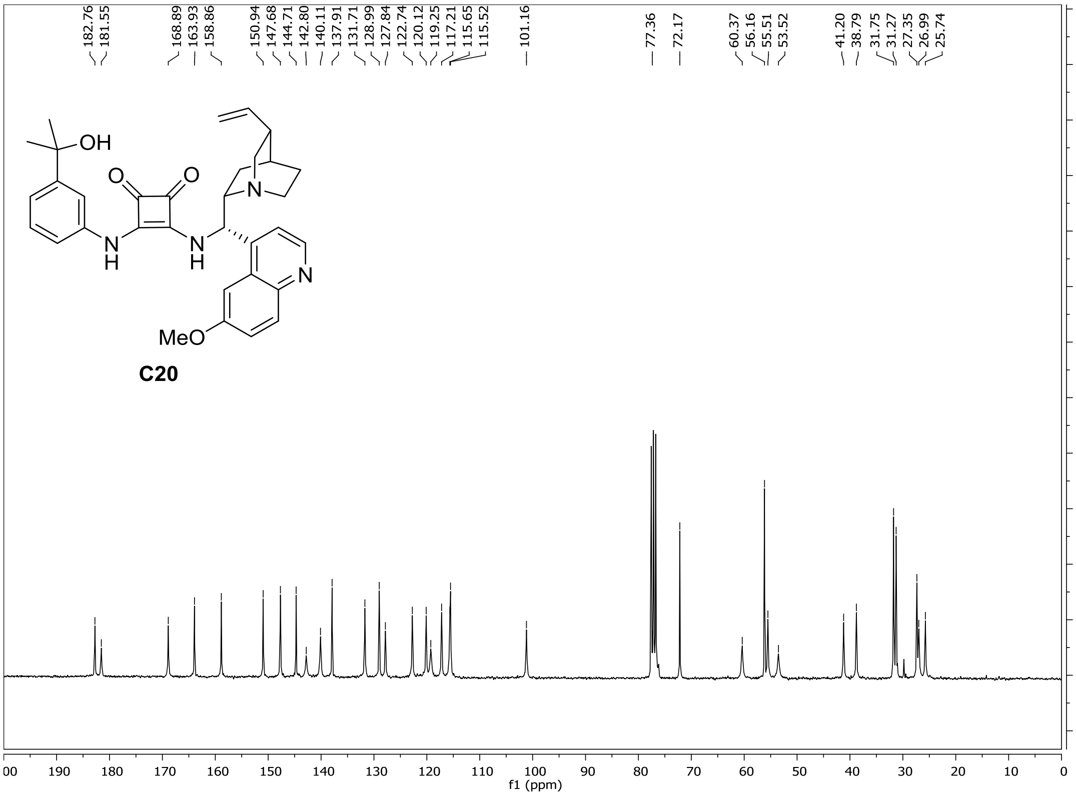
3.60
3.25
3.21
3.18
2.97
2.81
2.36
1.70
1.53
1.38
1.33
0.79
OH
O
O
N
N
H
N
H
N
MeO
C20
0.91
1.02
0.99
1.91
0.97
2.79
0.85
1.14
2.04
3.00
1.72
0.92
1.70
0.95
4.33
5.26
0.56
f1 (ppm)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181.55
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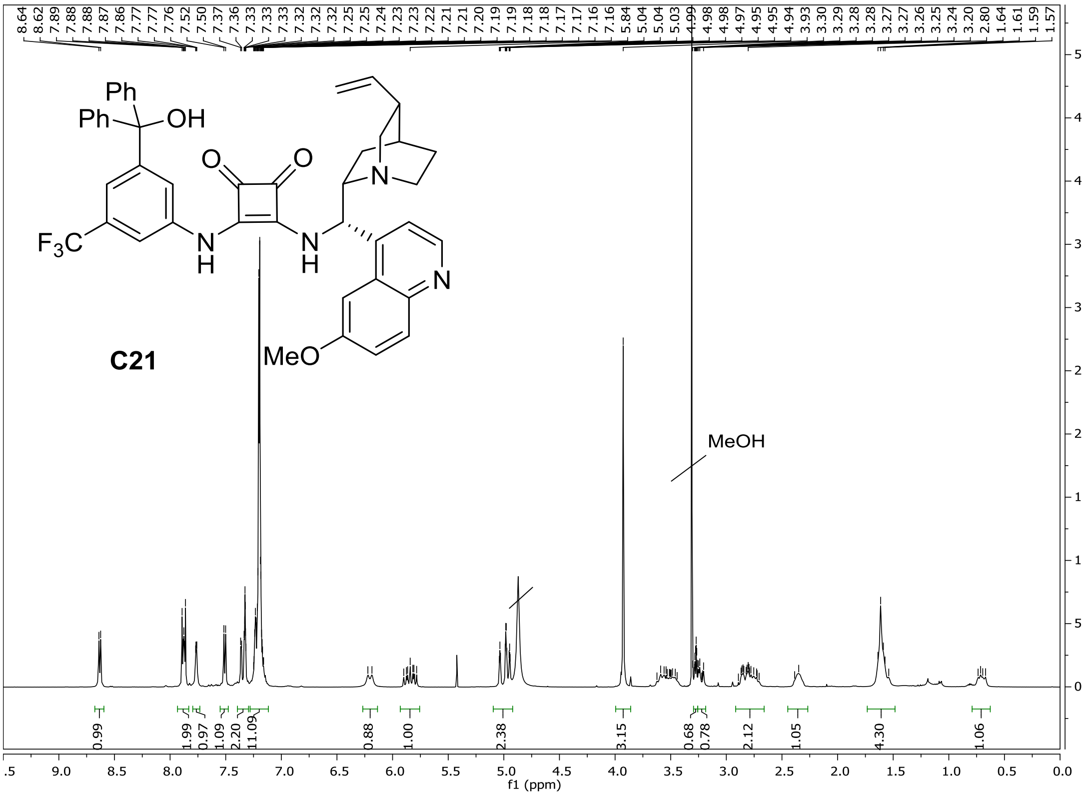
158.86
150.94
147.68
144.71
142.80
140.11
137.91
131.71
128.99
127.84
122.74
120.12
119.25
117.21
115.65
115.52
101.16
77.36
72.17
60.37
56.16
55.51
53.52
41.20
38.79
31.75
31.27
27.35
26.99
25.74
OH
O
O
N
N
H
N
H
N
MeO
C20
f1 (ppm)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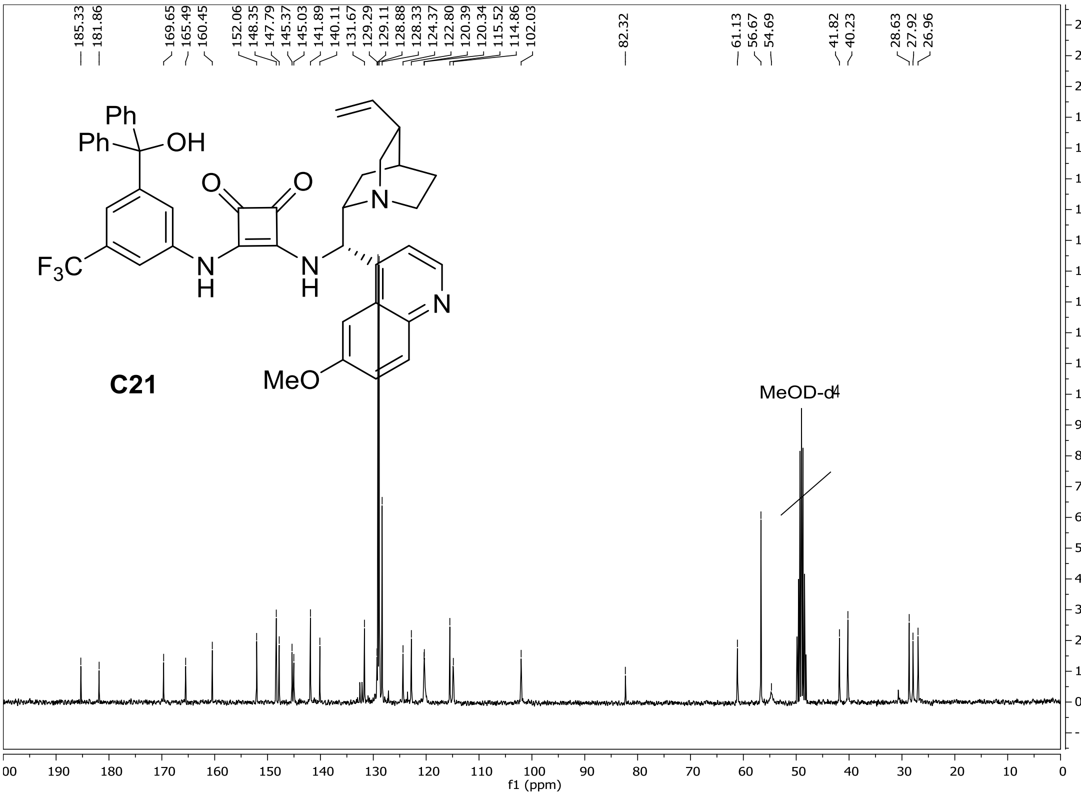
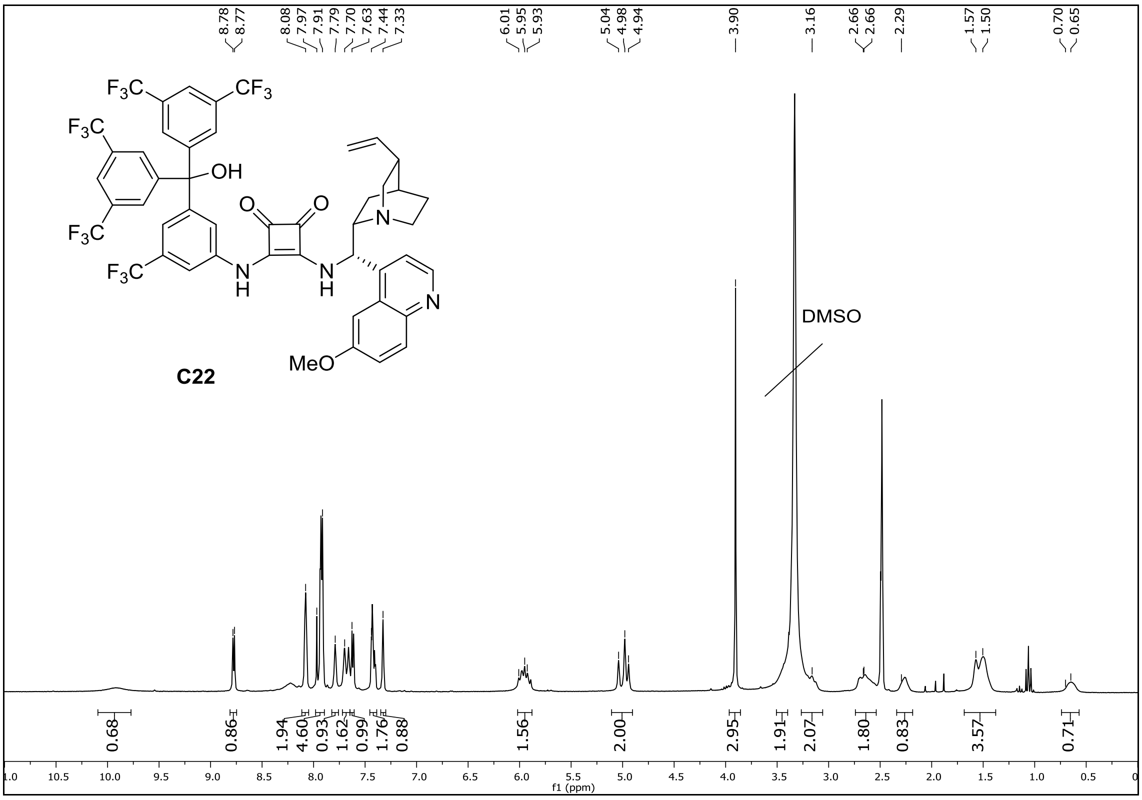
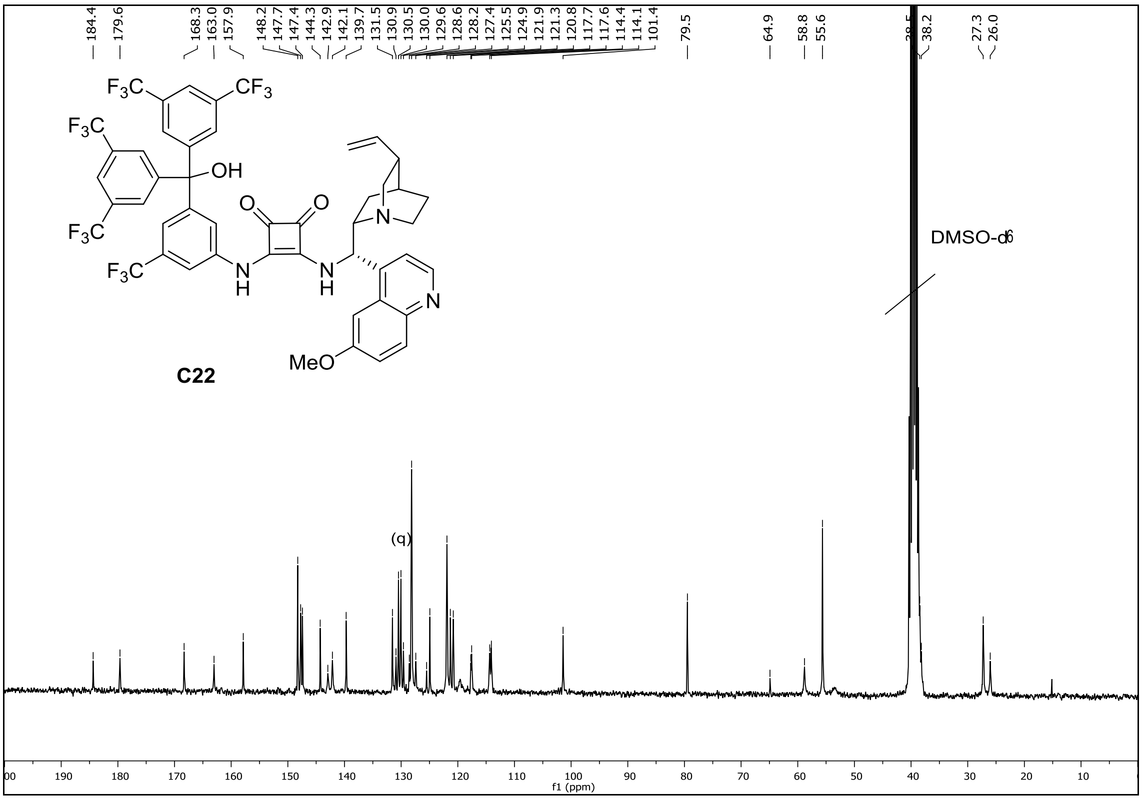
8.62
7.89
7.88
7.87
7.86
7.77
7.77
7.76
7.52
7.50
7.37
7.36
7.33
7.33
7.33
7.32
7.32
7.32
7.25
7.25
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.19
7.19
7.18
7.18
7.17
7.17
7.16
5.84
5.04
5.04
5.03
4.99
4.98
4.98
4.97
4.95
4.95
4.94
3.93
3.30
3.29
3.28
3.28
3.27
3.27
3.26
3.25
3.24
3.20
2.80
1.64
1.61
1.59
1.57
Ph
Ph
OH
O
O
N
F3C
N
H
N
H
N
N
MeO
C21
MeOH
0.99
1.99
0.97
1.09
2.20
11.09
0.88
1.00
2.38
3.15
0.68
0.78
2.12
1.05
4.30
1.06
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
.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)


185.33
181.86
169.65
165.49
160.45
152.06
148.35
147.79
145.37
145.03
141.89
140.11
131.67
129.29
129.11
128.88
128.33
124.37
122.80
120.39
120.34
115.52
114.86
102.03
82.32
61.13
56.67
54.69
41.82
40.23
28.63
27.92
26.96
Ph
Ph
OH
O
O
N
F3C
N
H
N
H
N
N
MeO
C21
MeOD-d4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.78
8.77
8.08
7.97
7.91
7.79
7.70
7.63
7.44
7.33
6.01
5.95
5.93
5.04
4.98
4.94
3.90
3.16
2.66
2.66
2.29
1.57
1.50
0.70
0.65
F3C
CF3
F3C
OH
O
O
N
F3C
F3C
N
H
N
H
N
MeO
C22
DMSO
0.68
0.86
1.94
4.60
0.93
1.62
0.99
1.76
0.88
1.56
2.00
2.95
1.91
2.07
1.80
0.83
3.57
0.71
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
f1 (ppm)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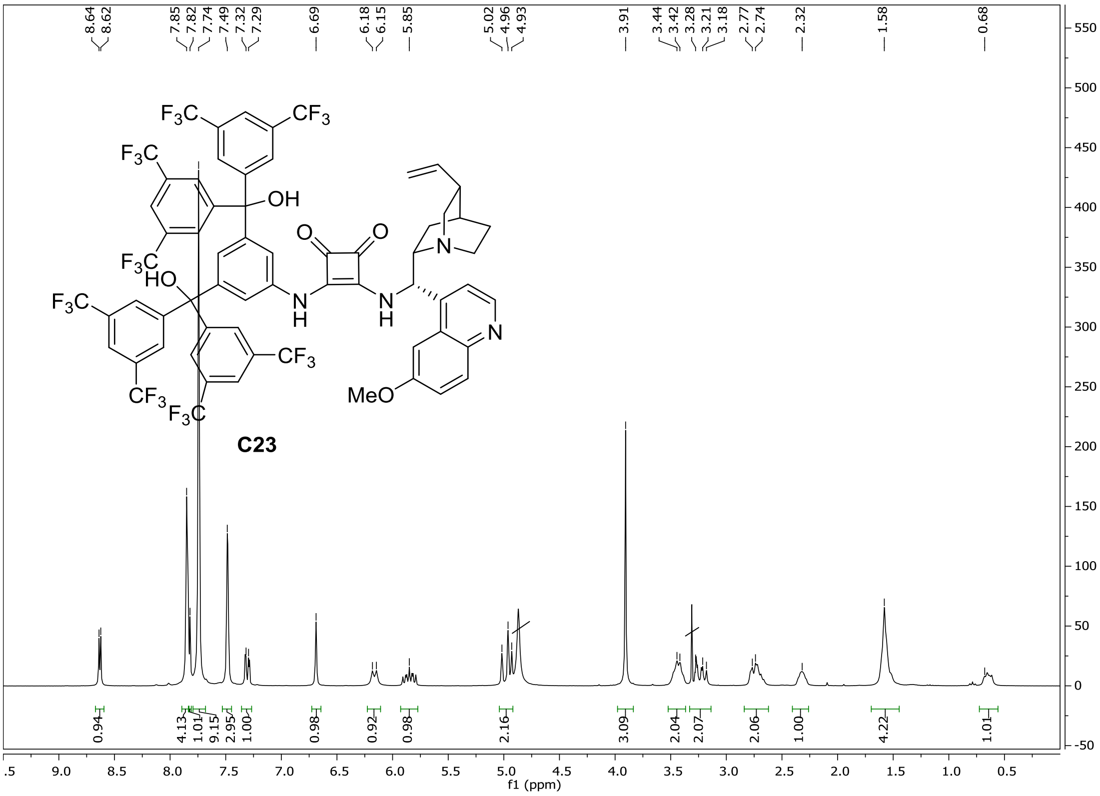
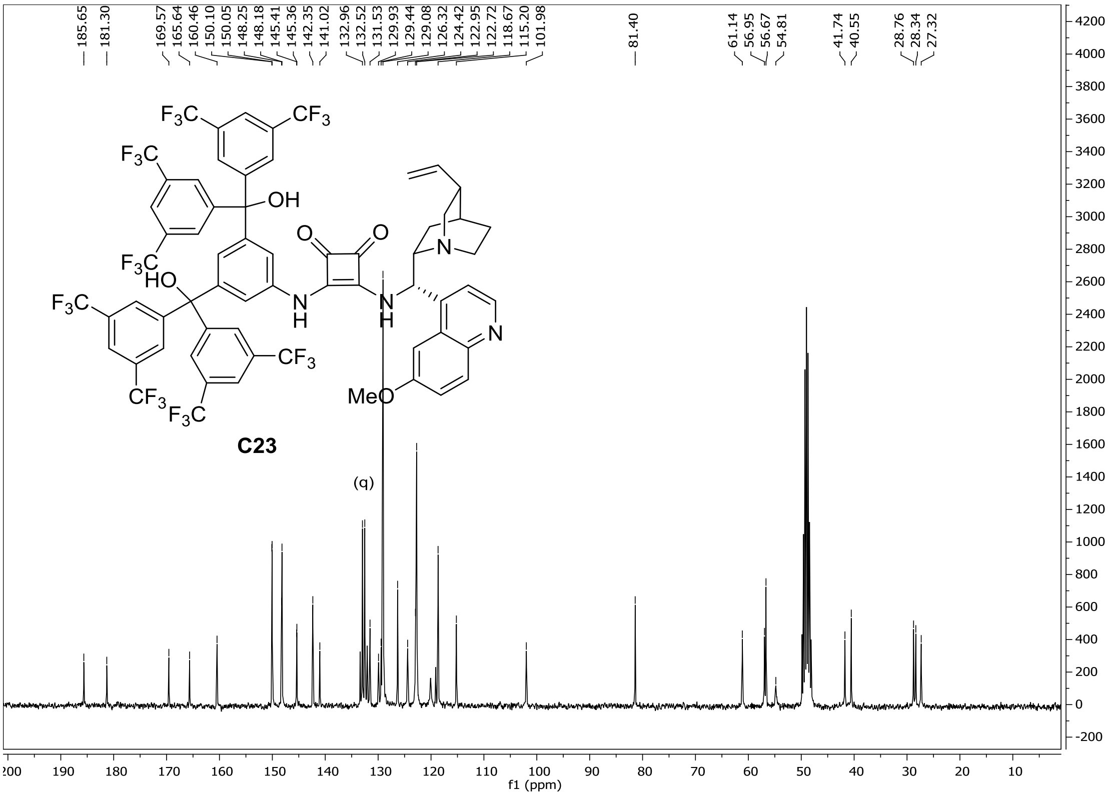
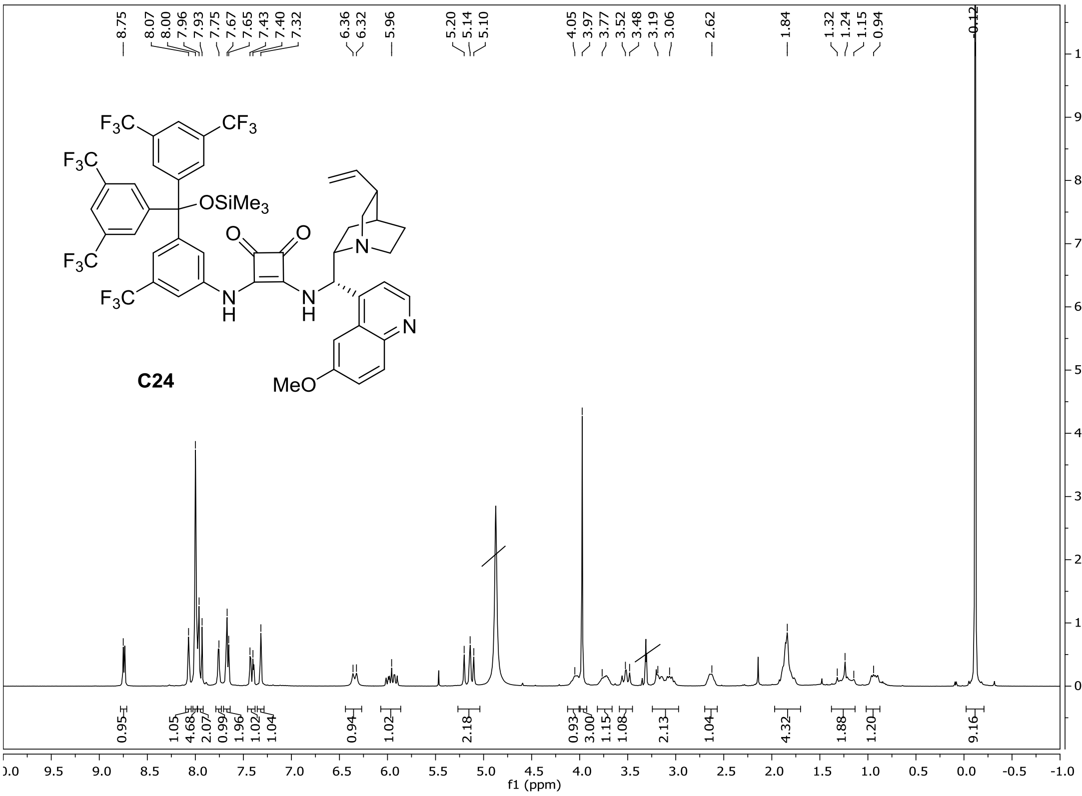
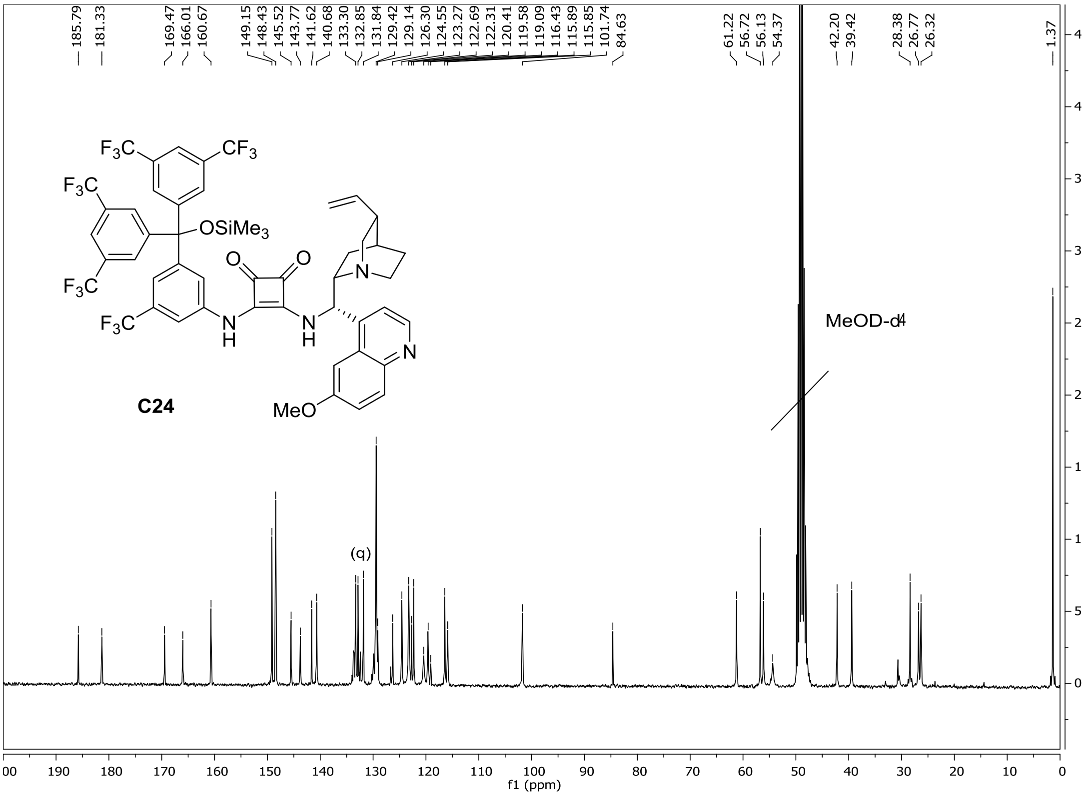
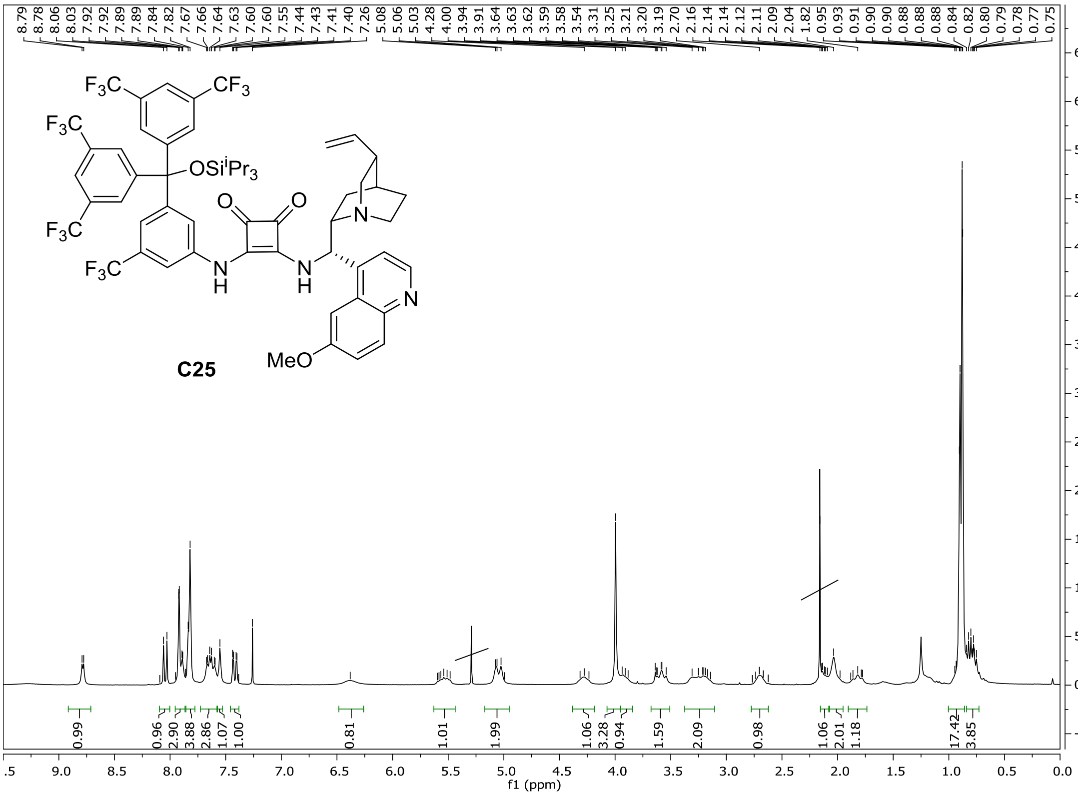
179.6
168.3
163.0
157.9
148.2
147.7
147.4
144.3
142.9
142.1
139.7
131.5
130.9
130.5
130.0
129.6
128.6
128.2
127.4
125.5
124.9
121.9
121.3
120.8
117.7
117.6
114.4
114.1
101.4
79.5
64.9
58.8
55.6
38.2
27.3
26.0
F3C
CF3
F3C
OH
O
O
N
F3C
F3C
N
H
N
H
N
MeO
C22
DMSO-d6
(q)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

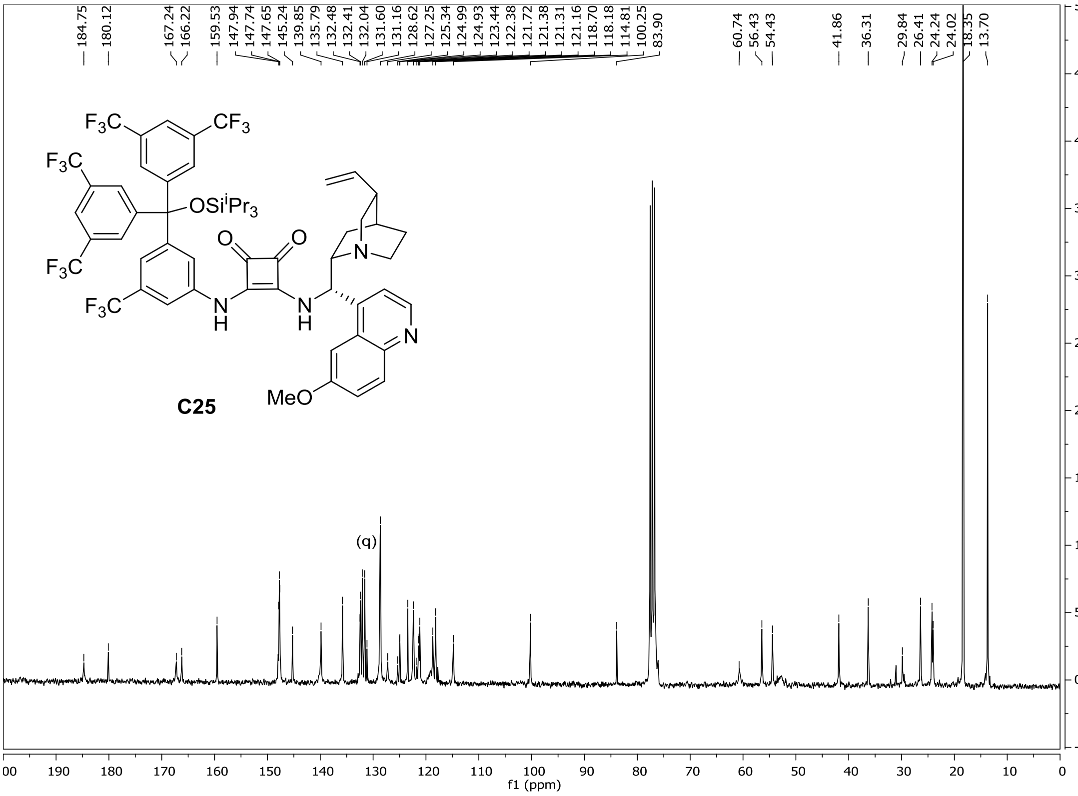

8.64
8.62
7.85
7.82
7.74
7.49
7.32
7.29
6.69
6.18
6.15
5.85
5.02
4.96
4.93
3.91
3.44
3.42
3.28
3.21
3.18
2.77
2.74
2.32
1.58
0.68
0.94
4.13
1.01
9.15
2.95
1.00
0.98
0.92
0.98
2.16
3.09
2.04
2.07
2.06
1.00
4.22
1.01
C23
f1 (ppm)

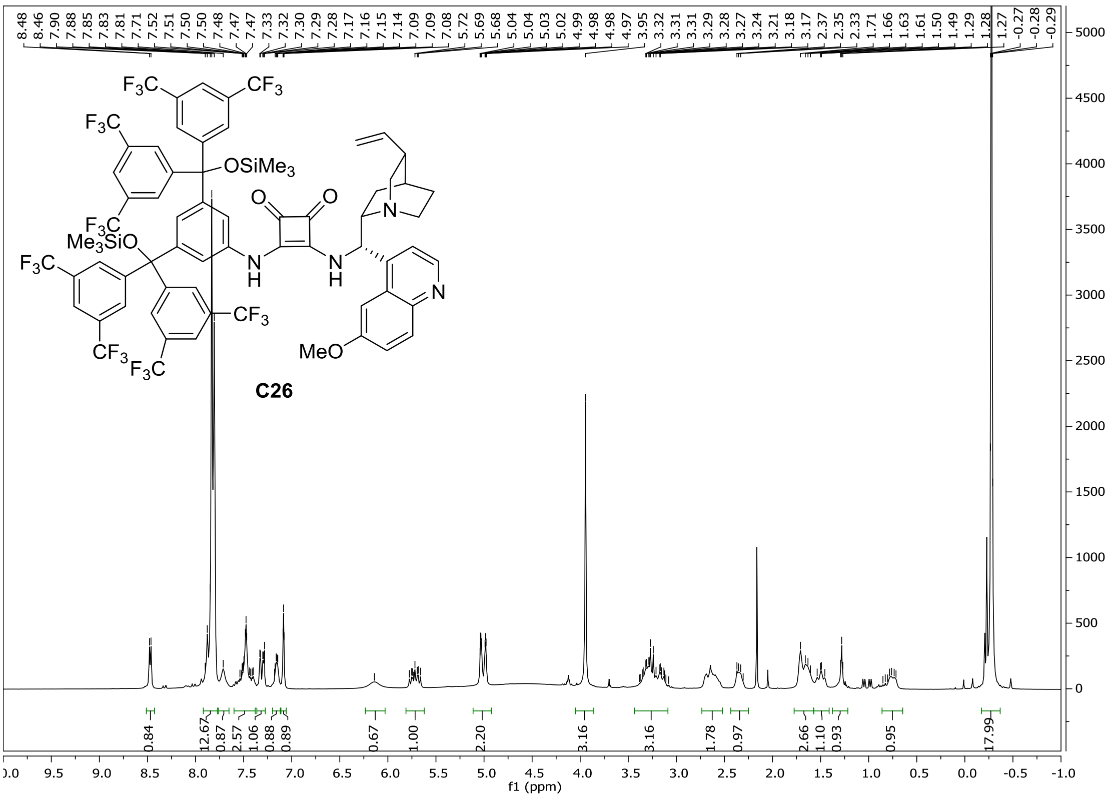

185.65
181.30
169.57
165.64
160.46
150.10
150.05
148.25
148.18
145.41
145.36
142.35
141.02
132.96
132.52
131.53
129.93
129.44
129.08
126.32
124.42
122.95
122.72
118.67
115.20
101.98
81.40
61.14
56.95
56.67
54.81
41.74
40.55
28.76
28.34
27.32
C23
(q)
f1 (ppm)


8.75
8.07
8.00
7.96
7.93
7.75
7.67
7.65
7.43
7.40
7.32
6.36
6.32
5.96
5.20
5.14
5.10
4.05
3.97
3.77
3.52
3.48
3.19
3.06
2.62
1.84
1.32
1.24
1.15
0.94
0.12
F3C
CF3
F3C
OSiMe3
O
O
N
F3C
F3C
N
H
N
H
N
MeO
C24
0.95
1.05
4.68
2.07
0.99
1.96
1.02
1.04
0.94
1.02
2.18
0.93
3.00
1.15
1.08
2.13
1.04
4.32
1.88
1.20
9.16
1000
900
800
700
600
500
400
300
200
100
0
.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
-0.5
-1.0
f1 (ppm)


185.79
181.33
169.47
166.01
160.67
149.15
148.43
145.52
143.77
141.62
140.68
133.30
132.85
131.84
129.42
129.14
126.30
124.55
123.27
122.69
122.31
120.41
119.58
119.09
116.43
115.89
115.85
101.74
84.63
61.22
56.72
56.13
54.37
42.20
39.42
28.38
26.77
26.32
1.37
F3C
CF3
F3C
OSiMe3
O
O
N
F3C
F3C
N
H
N
H
N
MeO
C24
MeOD-d4
(q)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.79 8.78 8.06 8.03 7.92 7.92 7.89 7.89 7.84 7.82 7.67 7.66 7.64 7.63 7.60 7.60 7.55 7.44 7.43 7.41 7.40 7.26 5.08 5.06 5.03 4.28 4.00 3.94 3.91 3.64 3.63 3.62 3.59 3.58 3.54 3.31 3.25 3.21 3.20 3.19 2.70 2.16 2.14 2.14 2.12 2.11 2.09 2.04 1.82 0.95 0.93 0.91 0.90 0.90 0.88 0.88 0.88 0.84 0.82 0.80 0.79 0.78 0.77 0.75
F3C
CF3
OSiiPr3
O
N
H
MeO
C25
0.99 0.96 2.90 3.88 2.86 1.07 1.00 0.81 1.01 1.99 1.06 3.28 0.94 1.59 2.09 0.98 1.06 2.01 1.18 17.42 3.85
f1 (ppm)
650 600 550 500 450 400 350 300 250 200 150 100 50 0 -50


184.75 180.12 167.24 166.22 159.53 147.94 147.74 147.65 145.24 139.85 135.79 132.48 132.41 132.04 131.60 131.16 128.62 127.25 125.34 124.99 124.93 123.44 122.38 121.72 121.38 121.31 121.16 118.70 118.18 114.81 100.25 83.90 60.74 56.43 54.43 41.86 36.31 29.84 26.41 24.24 24.02 18.35 13.70
F3C
CF3
OSiiPr3
O
N
H
MeO
C25
(q)
f1 (ppm)
50000 45000 40000 35000 30000 25000 20000 15000 10000 5000 0 -5000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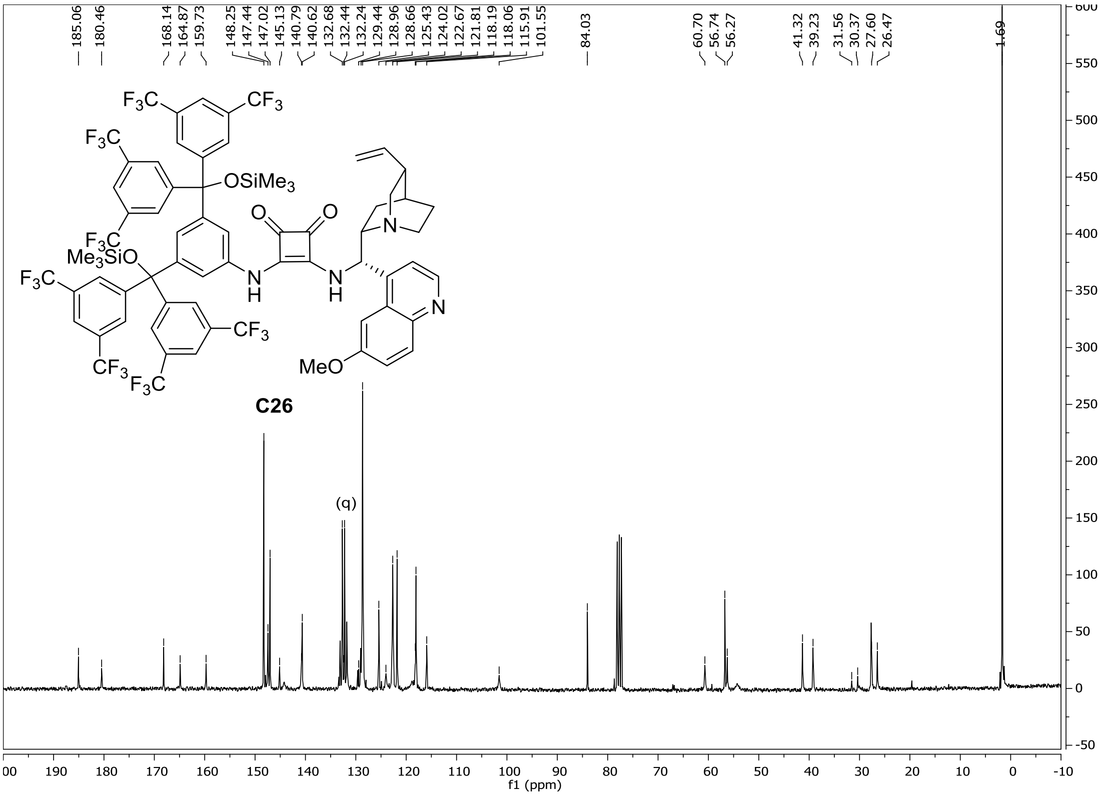
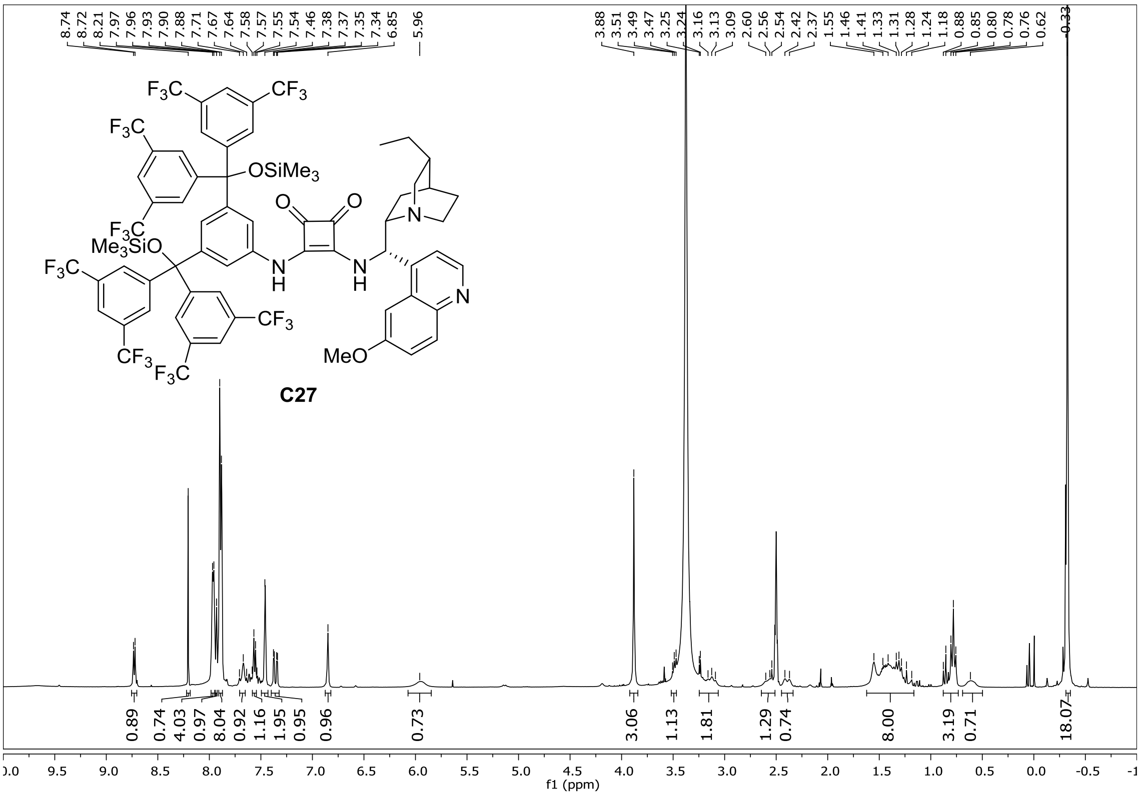
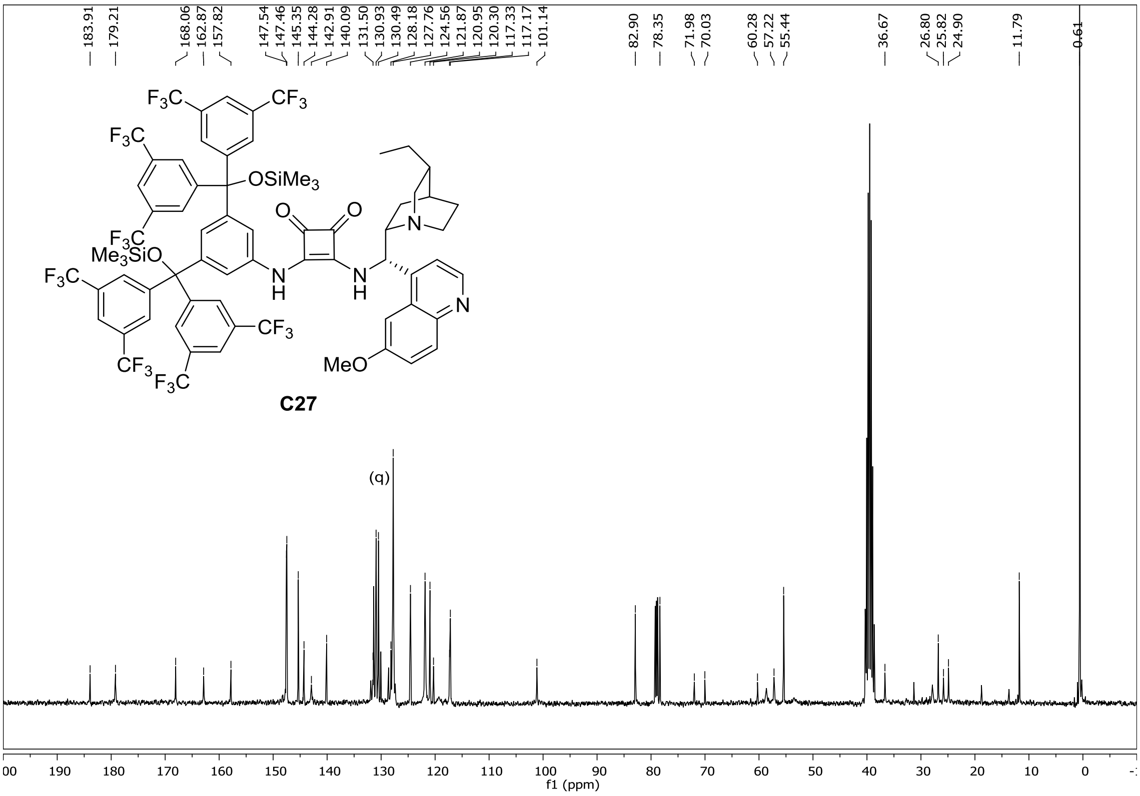
8.46
7.90
7.88
7.85
7.83
7.81
7.71
7.52
7.51
7.50
7.50
7.48
7.47
7.47
7.33
7.32
7.30
7.29
7.28
7.17
7.16
7.15
7.14
7.09
7.09
7.08
5.72
5.69
5.68
5.04
5.04
5.03
5.02
4.99
4.98
4.98
4.97
3.95
3.32
3.31
3.31
3.29
3.28
3.27
3.24
3.21
3.18
3.17
2.37
2.35
2.33
1.71
1.66
1.63
1.61
1.50
1.49
1.29
1.28
1.27
-0.27
-0.28
-0.29
F3C
CF3
F3C
OSiMe3
O
O
N
F3C
Me3SiO
N
H
N
H
F3C
N
CF3
CF3
F3C
MeO
C26
0.84
12.67
0.87
2.57
1.06
0.88
0.89
0.67
1.00
2.20
3.16
3.16
1.78
0.97
2.66
1.10
0.93
0.95
17.99
f1 (ppm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0

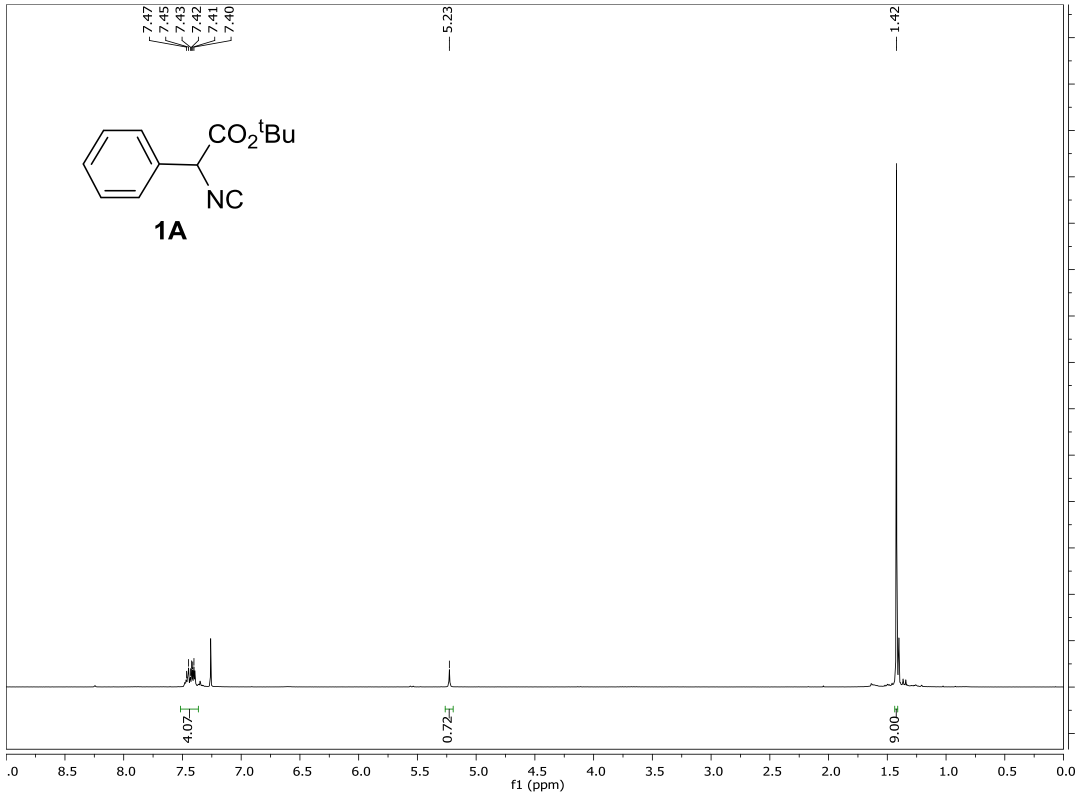

185.06
180.46
168.14
164.87
159.73
148.25
147.44
147.02
145.13
140.79
140.62
132.68
132.44
132.24
129.44
128.96
128.66
125.43
124.02
122.67
121.81
118.19
118.06
115.91
101.55
84.03
60.70
56.74
56.27
41.32
39.23
31.56
30.37
27.60
26.47
1.69
F3C
CF3
F3C
OSiMe3
O
O
N
F3C
Me3SiO
N
H
N
H
F3C
N
CF3
CF3
F3C
MeO
C26
(q)
f1 (ppm)
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

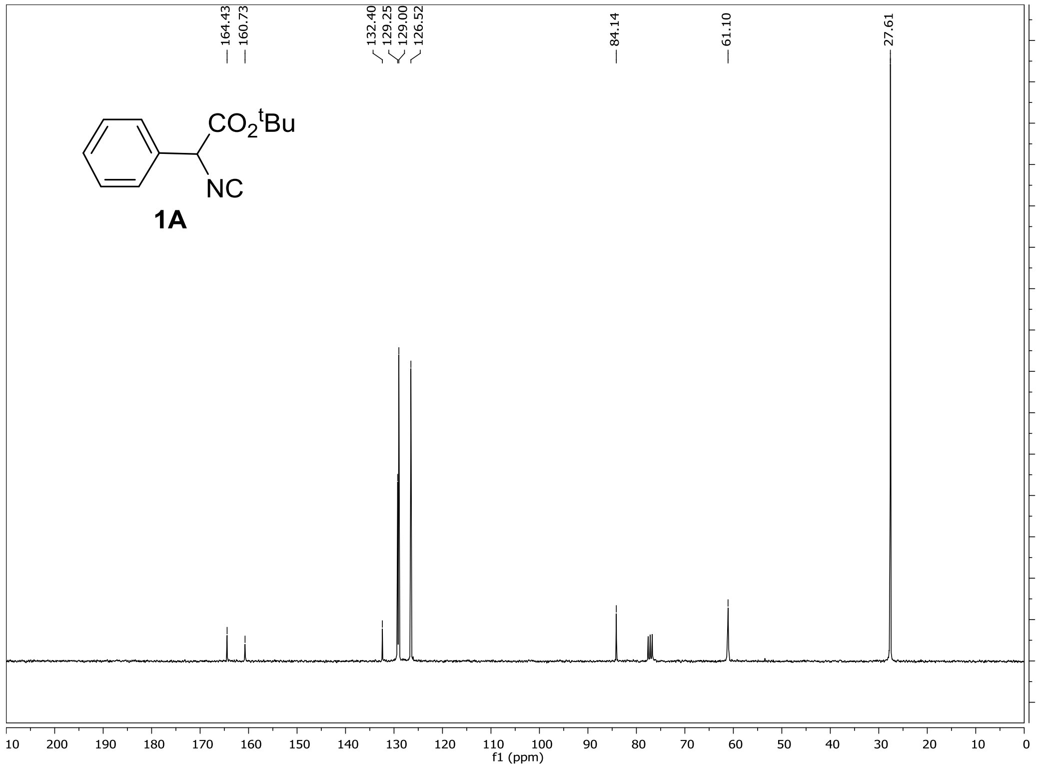

8.74
8.72
8.21
7.97
7.96
7.93
7.90
7.88
7.71
7.67
7.64
7.58
7.57
7.55
7.54
7.46
7.38
7.37
7.35
7.34
6.85
5.96
3.88
3.51
3.49
3.47
3.25
3.24
3.16
3.13
3.09
2.60
2.56
2.54
2.42
2.37
1.55
1.46
1.41
1.33
1.31
1.28
1.24
1.18
0.88
0.85
0.80
0.78
0.76
0.62
-0.33
F3C
CF3
F3C
OSiMe3
F3C
Me3SiO
F3C
O
O
N
N
H
N
H
N
CF3
MeO
CF3
F3C
C27
0.89
0.74
4.03
0.97
8.04
0.92
1.16
1.95
0.95
0.96
0.73
3.06
1.13
1.81
1.29
0.74
8.00
3.19
0.71
18.07
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
-0.5
f1 (ppm)

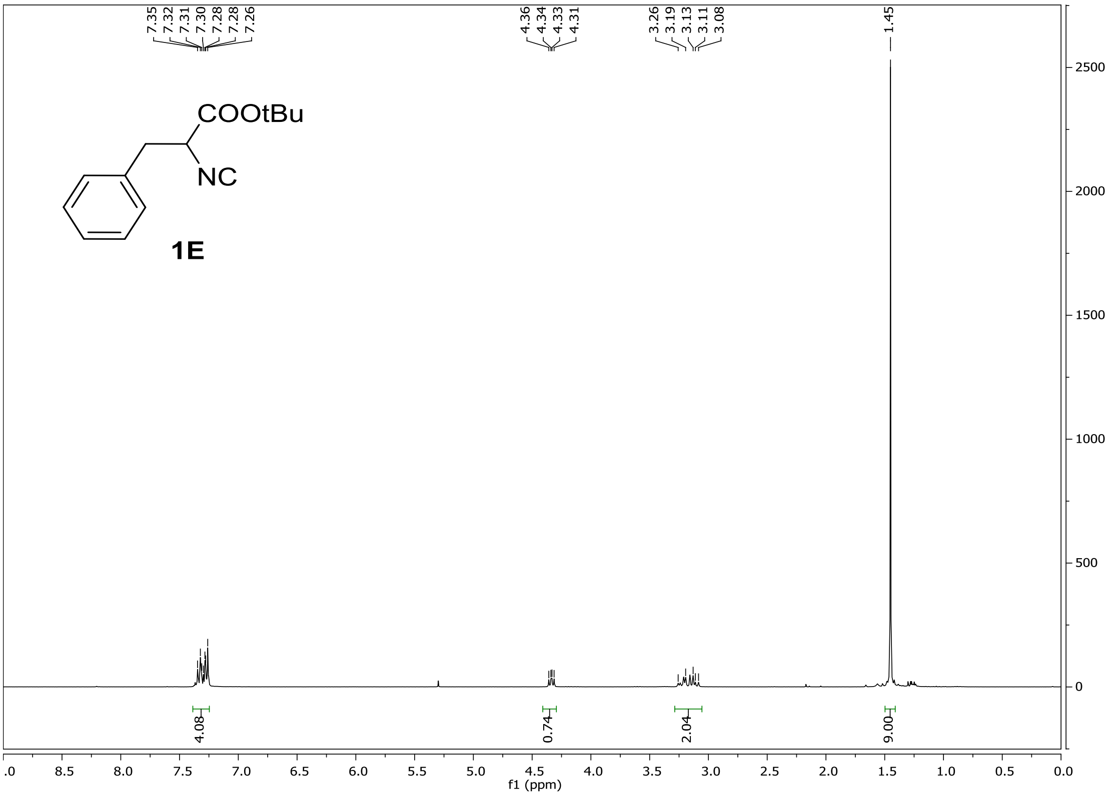

183.91
179.21
168.06
162.87
157.82
147.54
147.46
145.35
144.28
142.91
140.09
131.50
130.93
130.49
128.18
127.76
124.56
121.87
120.95
120.30
117.33
117.17
101.14
82.90
78.35
71.98
70.03
60.28
57.22
55.44
36.67
26.80
25.82
24.90
11.79
0.61
F3C
CF3
F3C
OSiMe3
F3C
Me3SiO
F3C
O
O
N
N
H
N
H
N
CF3
MeO
CF3
F3C
C27
(q)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

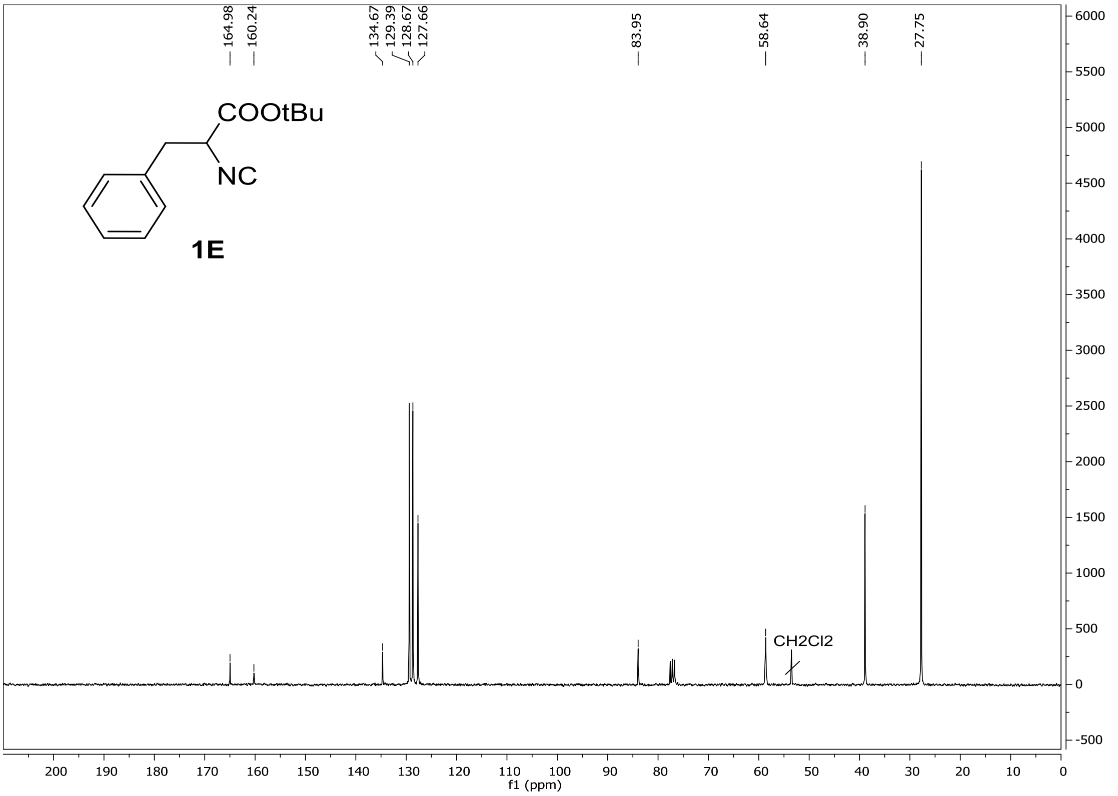
5.5.2. Chapter 2

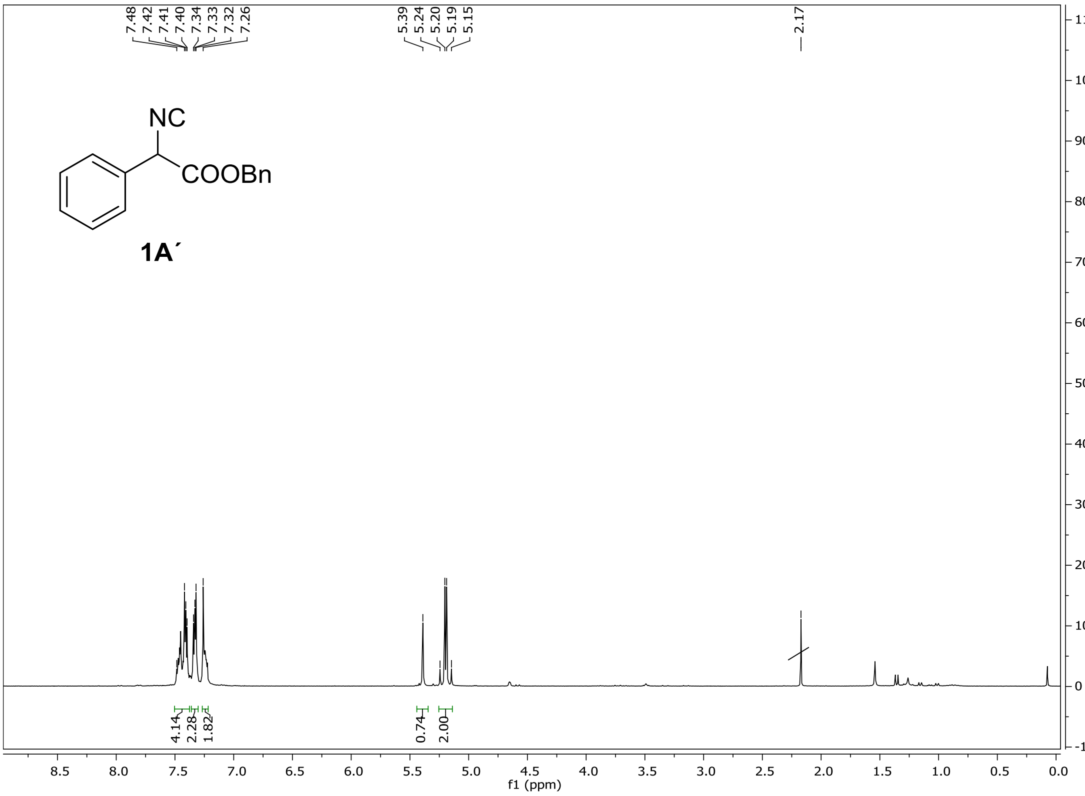
*5.5.2.1. Isocyanoacetates **1***

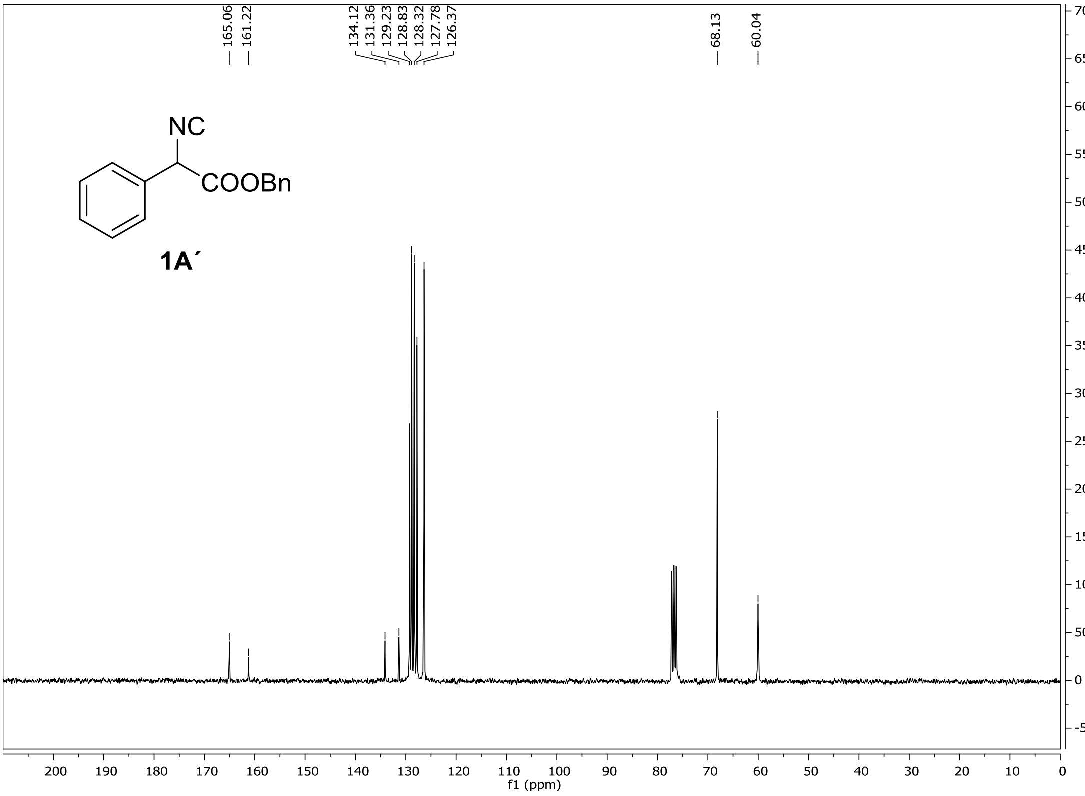


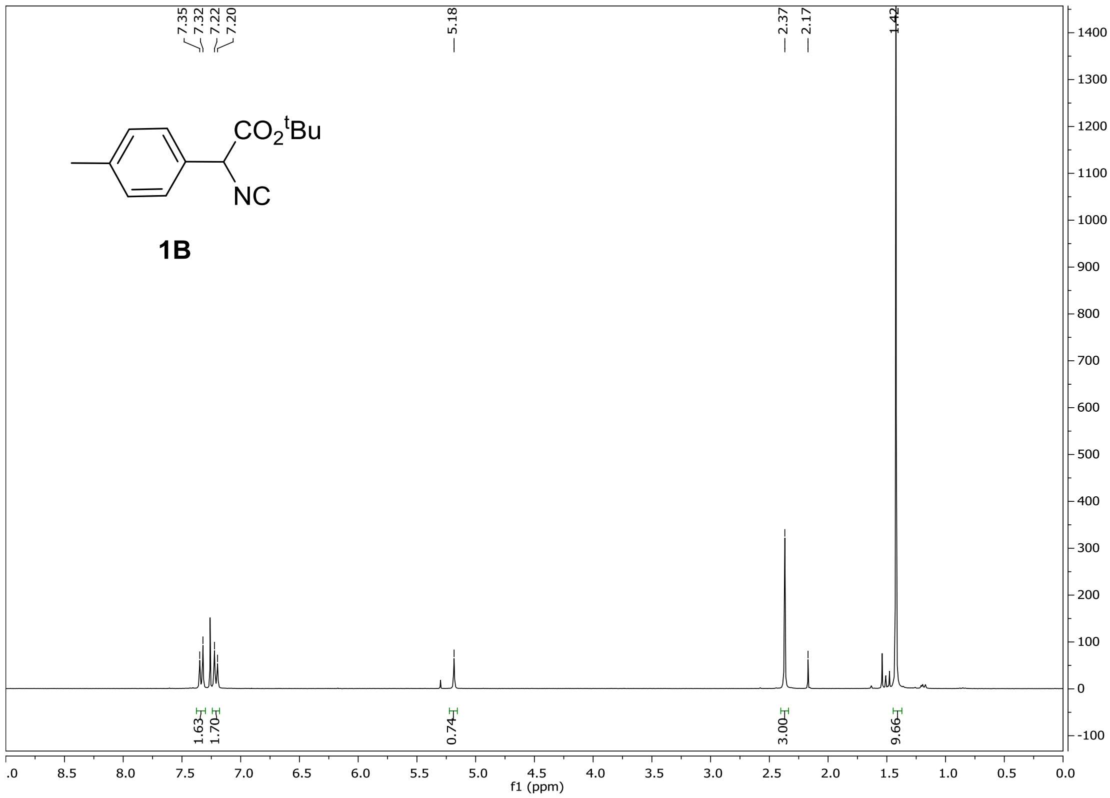


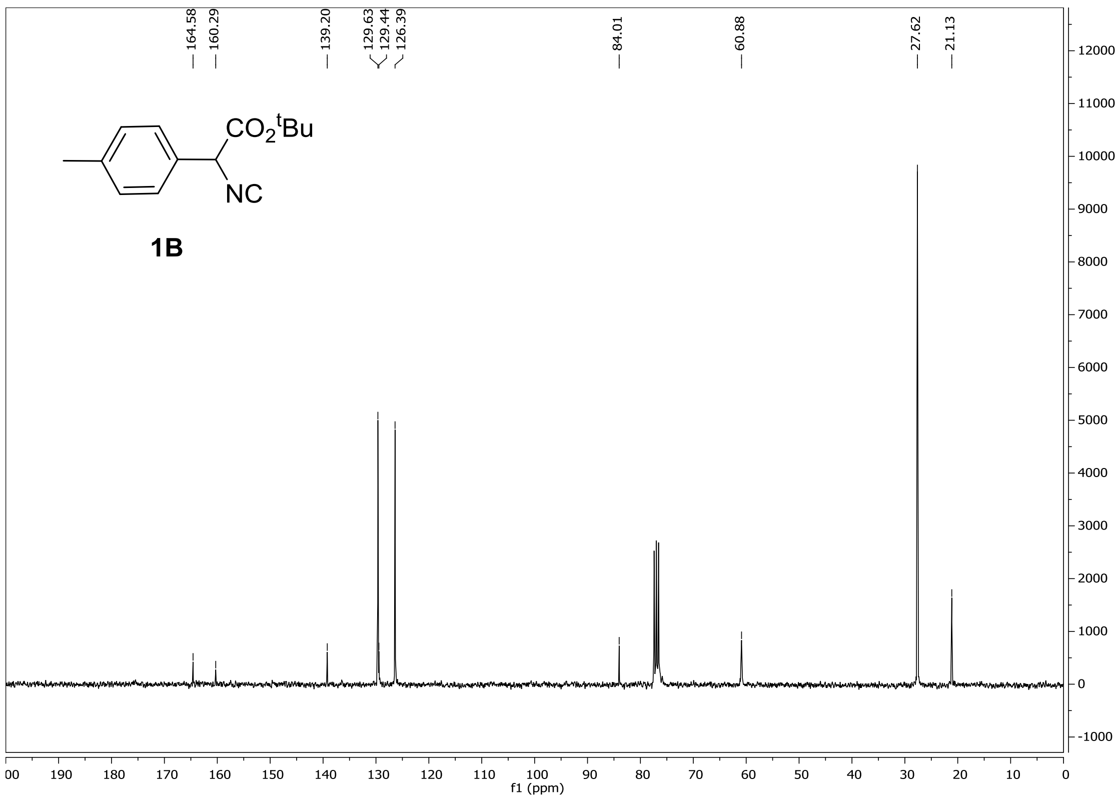

7.35
7.32
7.31
7.30
7.28
7.28
7.26
4.36
4.34
4.33
4.31
3.26
3.19
3.13
3.11
3.08
1.45
COOtBu
NC
1E
4.08
0.74
2.04
9.00
2500
2000
1500
1000
500
0
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

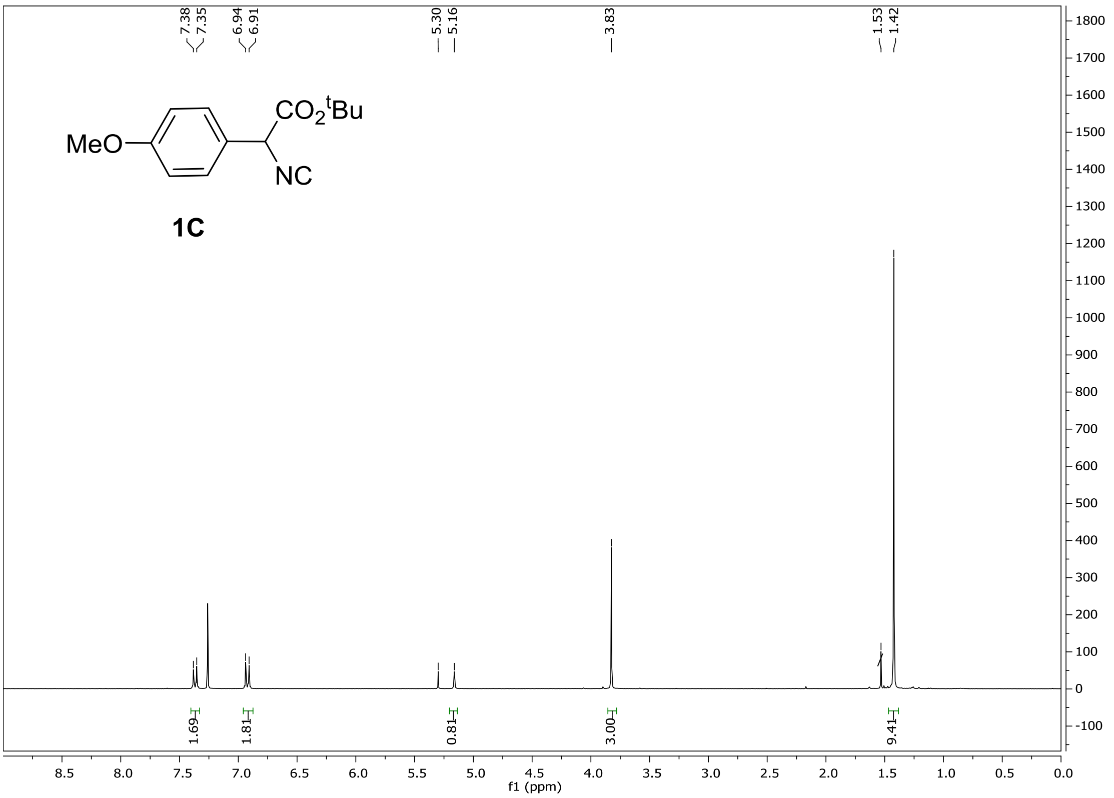

164.98
160.24
134.67
129.39
128.67
127.66
83.95
58.64
38.90
27.75
COOtBu
NC
1E
CH2Cl2
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

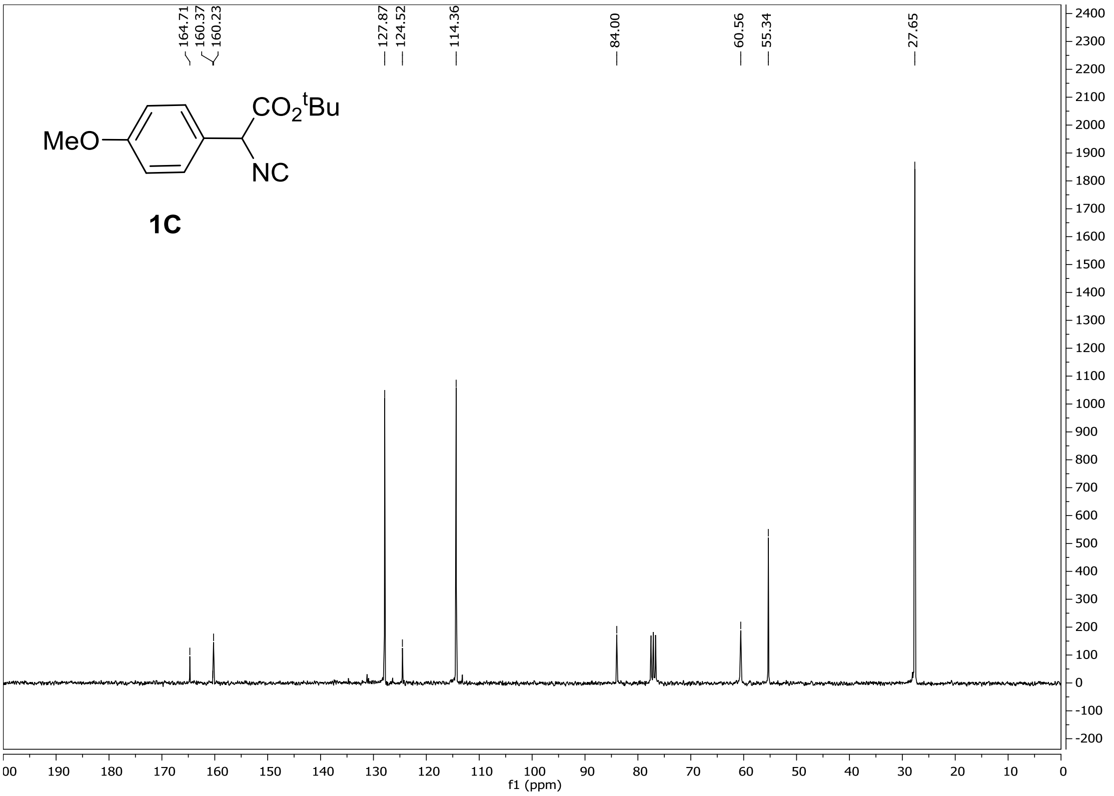

7.48
7.42
7.41
7.40
7.34
7.33
7.32
7.26
5.39
5.24
5.20
5.19
5.15
2.17
NC
COOBn
1A´
4.14
2.28
1.82
0.74
2.00
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

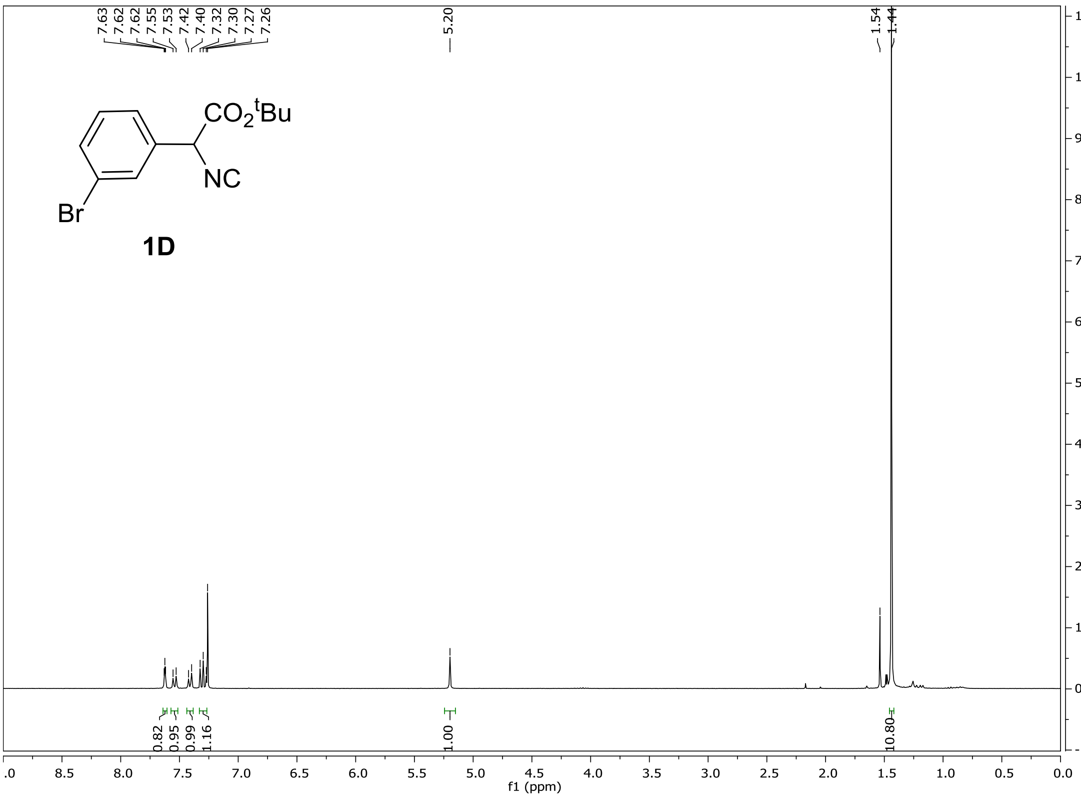

165.06
161.22
134.12
131.36
129.23
128.83
128.32
127.78
126.37
68.13
60.04
NC
COOBn
1A´
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

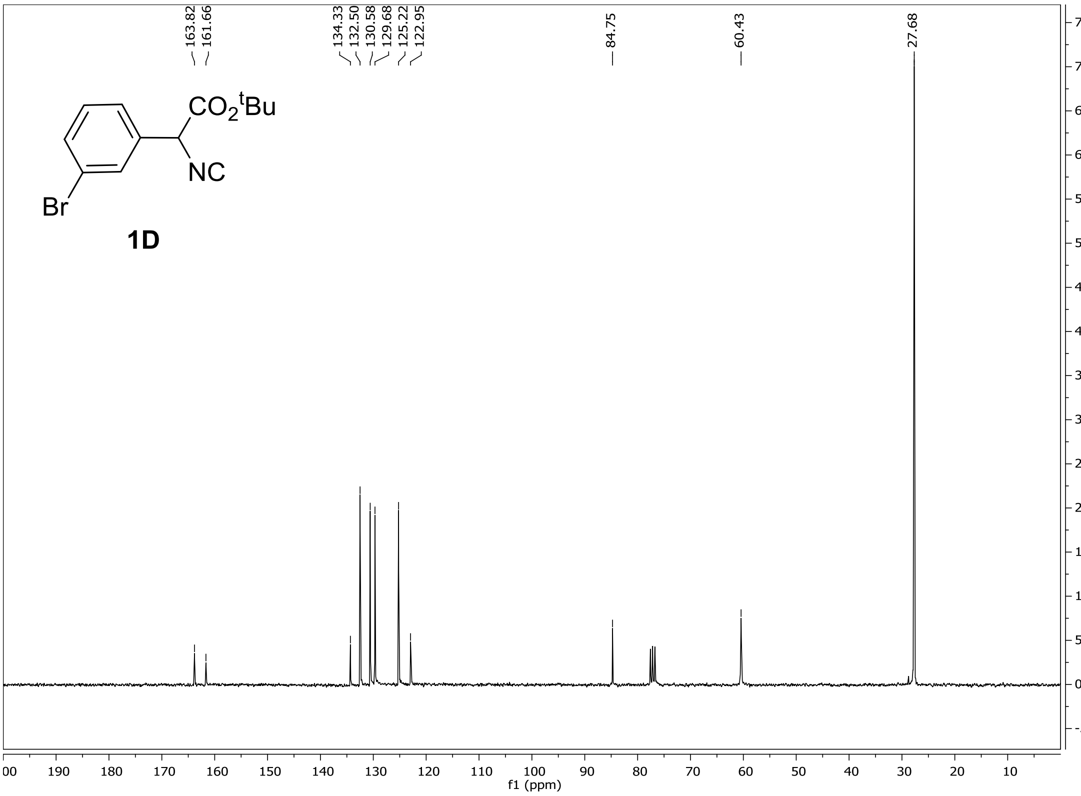

7.35
7.32
7.22
7.20
5.18
2.37
2.17
1.42
CO$_2$^{t}Bu
NC
1B
1.63
1.70
0.74
3.00
9.66
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

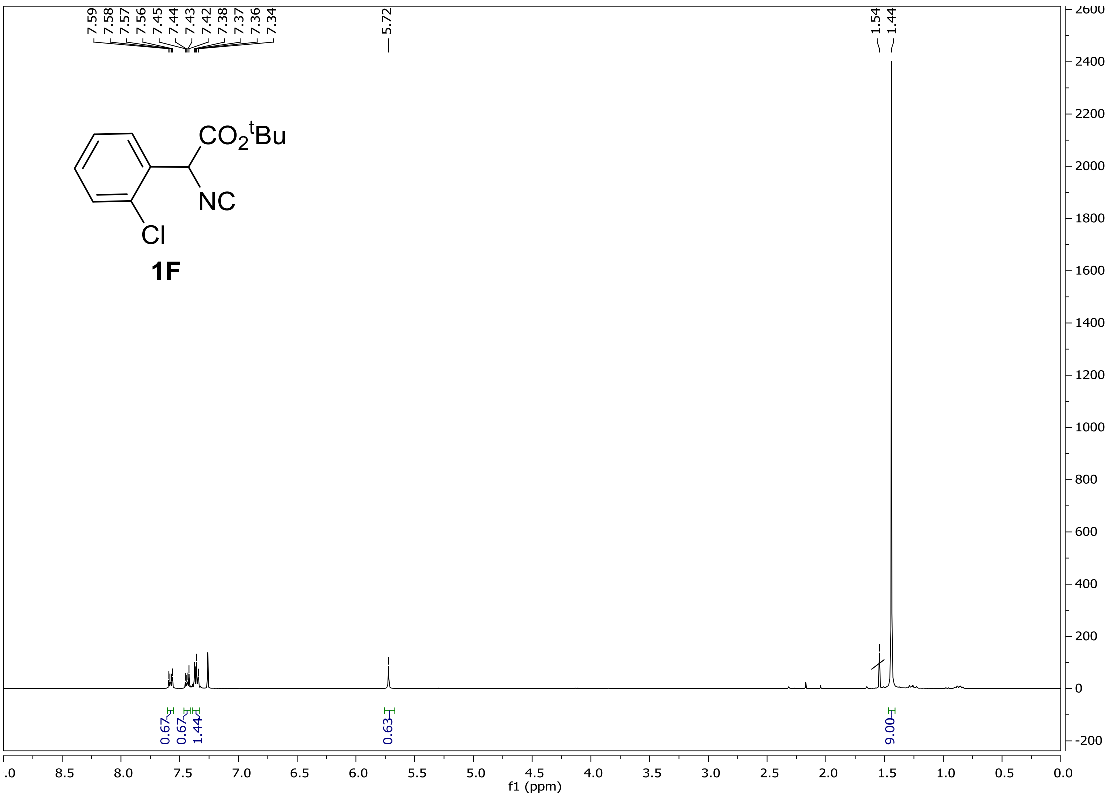

164.58
160.29
139.20
129.63
129.44
126.39
84.01
60.88
27.62
21.13
CO$_2$^{t}Bu
NC
1B
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

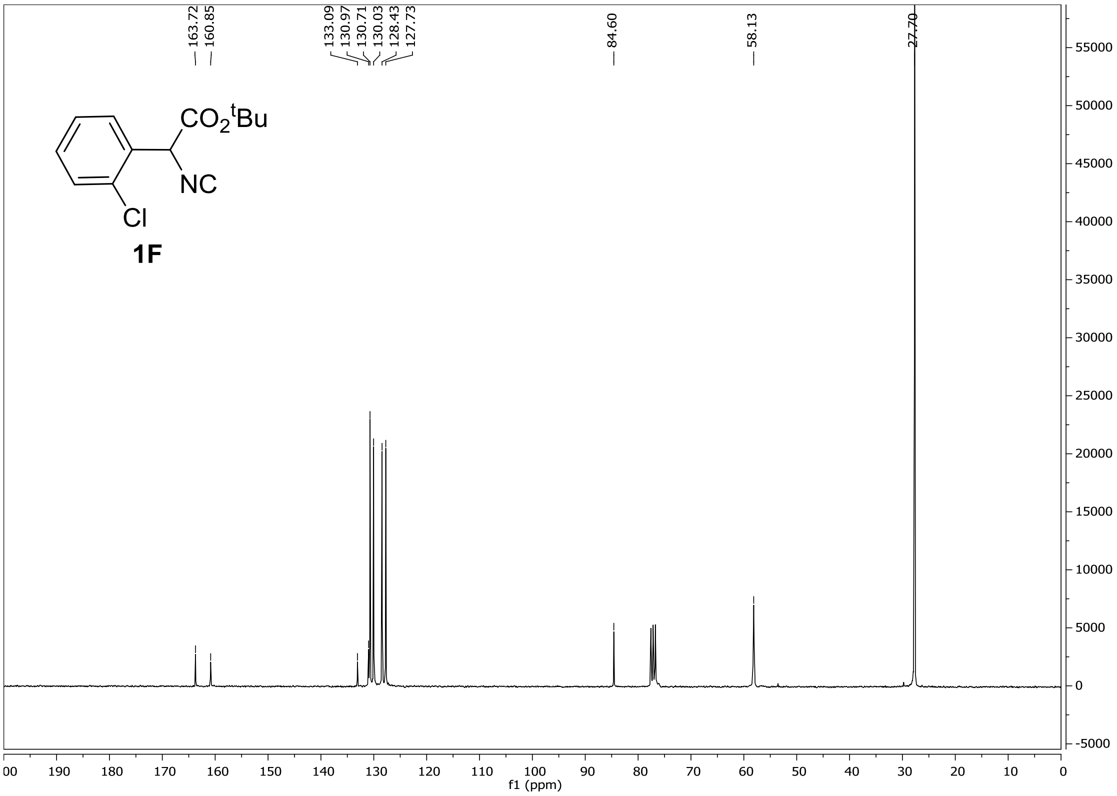

7.38
7.35
6.94
6.91
5.30
5.16
3.83
1.53
1.42
CO2tBu
MeO
NC
1C
1.69
1.81
0.81
3.00
9.41
f1 (ppm)


164.71
160.37
160.23
127.87
124.52
114.36
84.00
60.56
55.34
27.65
CO2tBu
MeO
NC
1C
f1 (ppm)

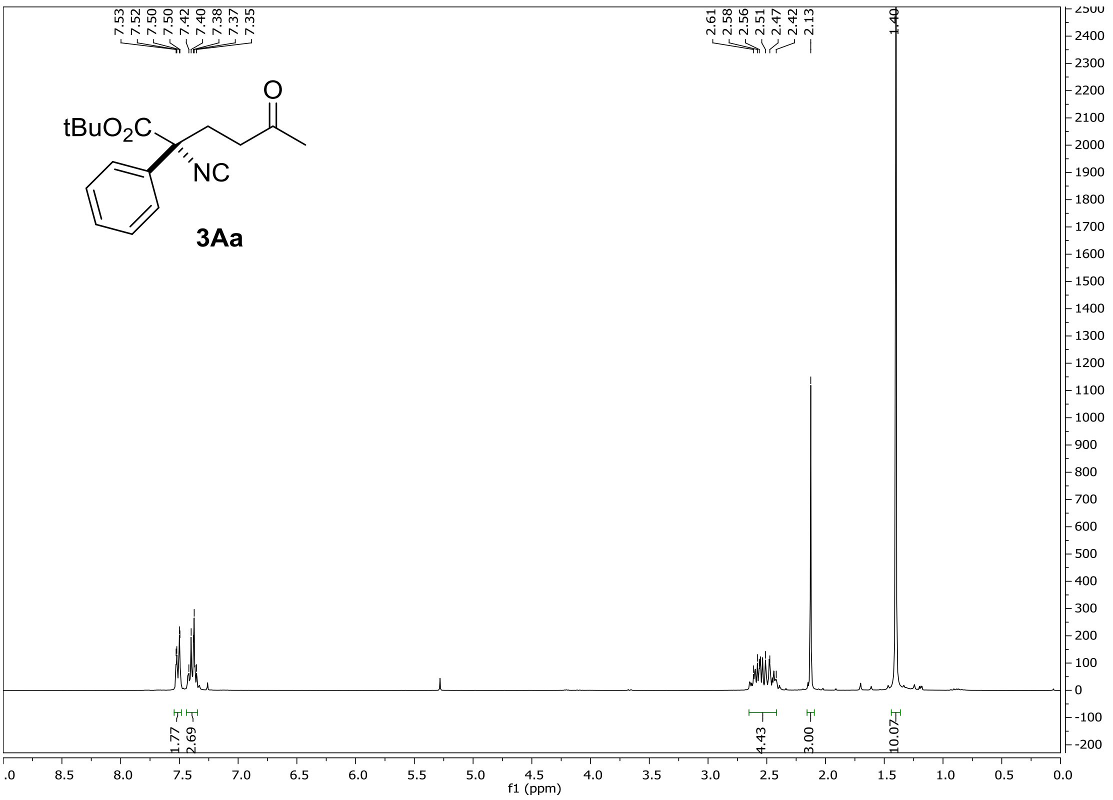

7.63
7.62
7.62
7.55
7.53
7.42
7.40
7.32
7.30
7.27
7.26
5.20
1.54
1.44
CO2tBu
NC
Br
1D
0.82
0.95
0.99
1.16
1.00
10.80
f1 (ppm)

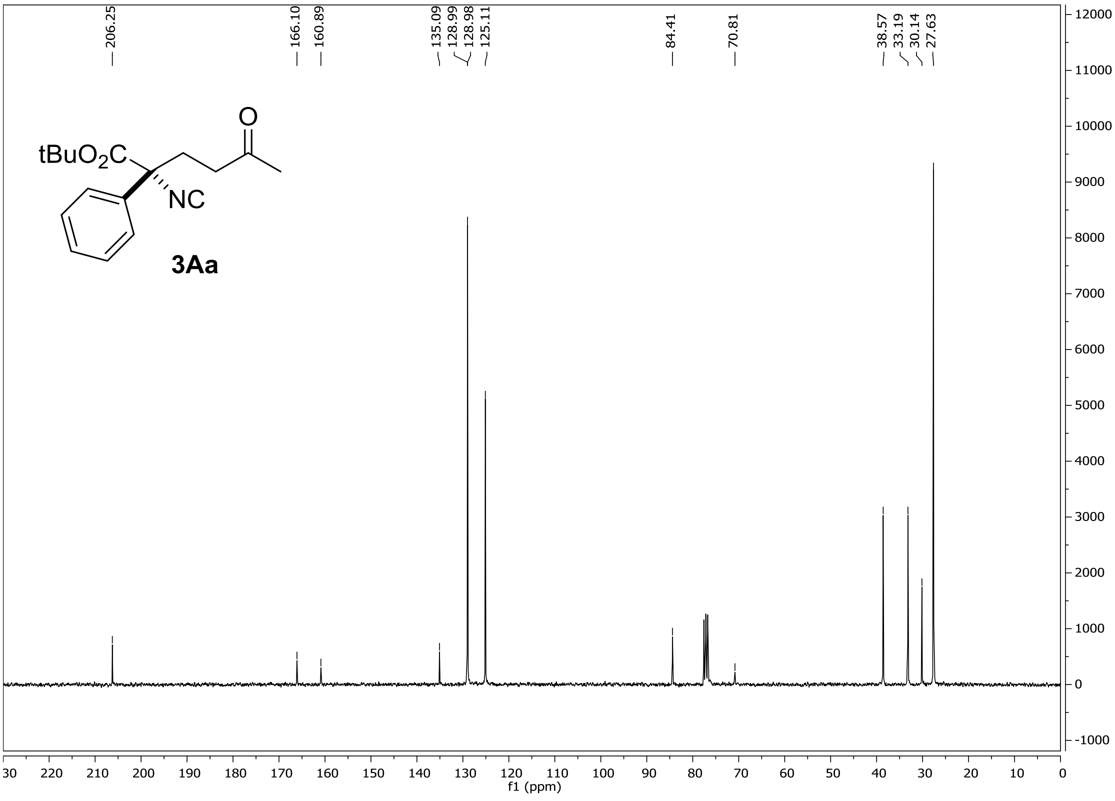

163.82
161.66
134.33
132.50
130.58
129.68
125.22
122.95
84.75
60.43
27.68
CO2tBu
NC
Br
1D
f1 (ppm)

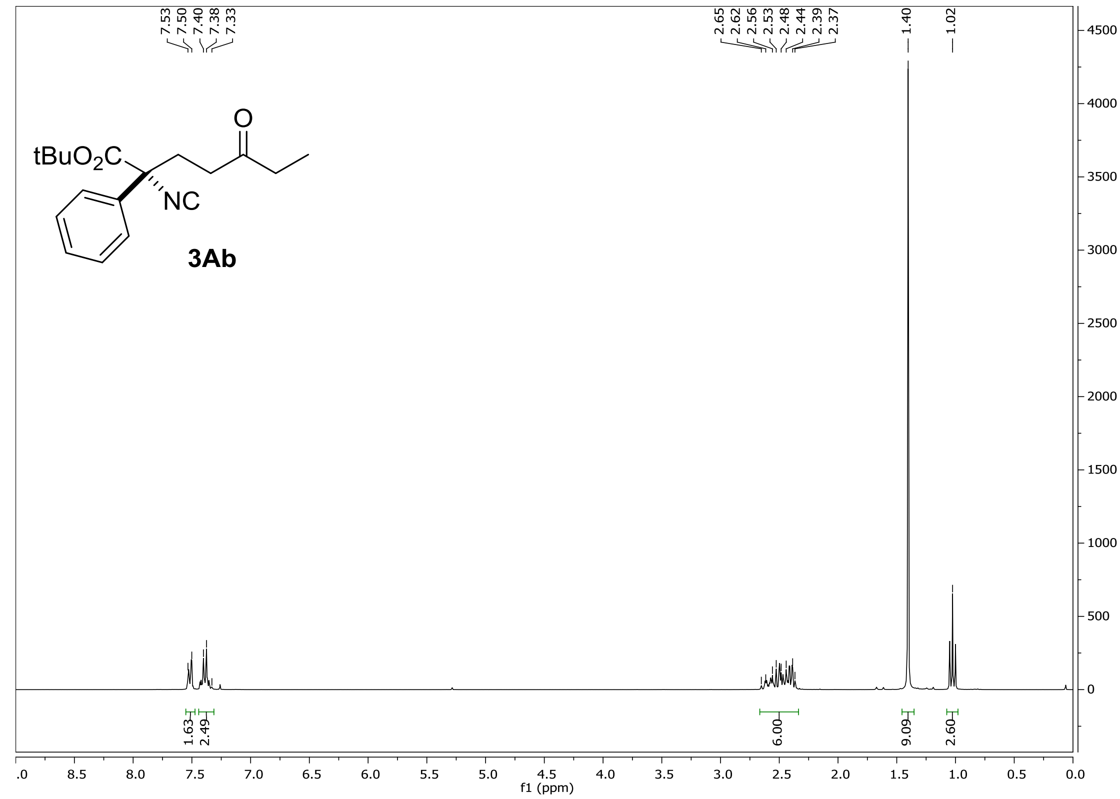

7.59
7.58
7.57
7.56
7.45
7.44
7.43
7.42
7.38
7.37
7.36
7.34
5.72
1.54
1.44
$CO_2{}^tBu$
NC
Cl
1F
0.67
0.67
1.44
0.63
9.00
f1 (ppm)
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

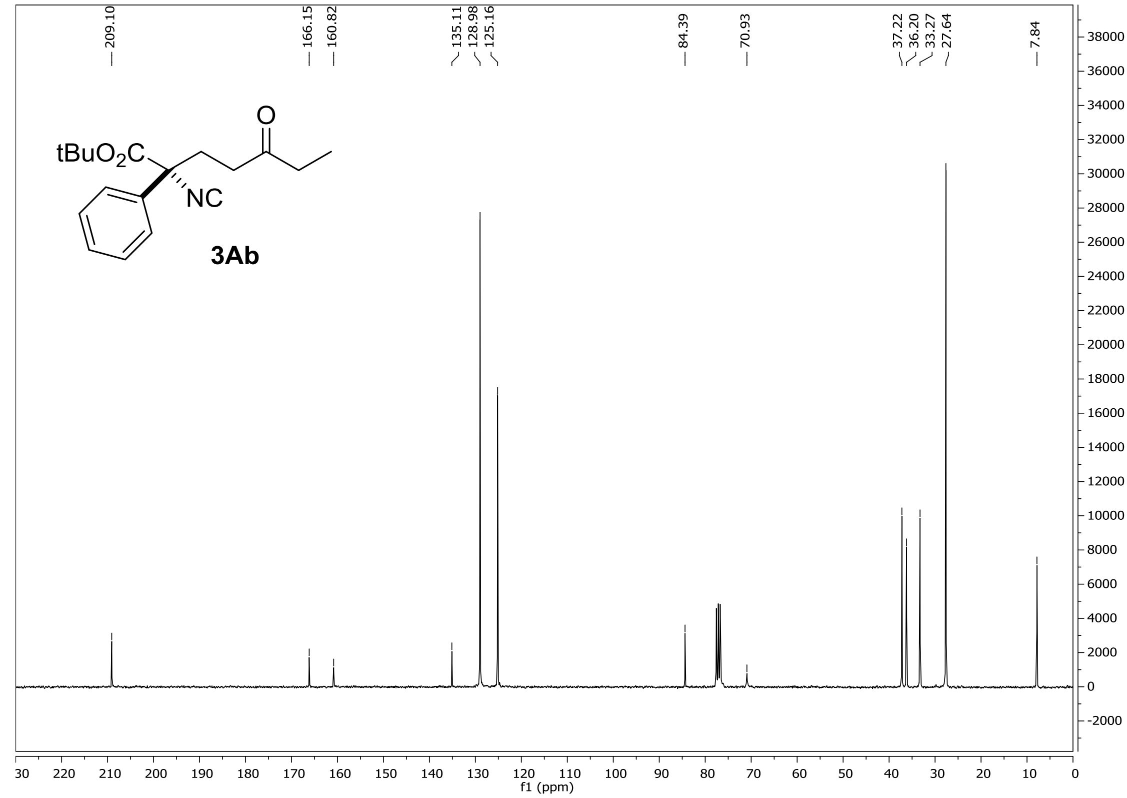

163.72
160.85
133.09
130.97
130.71
130.03
128.43
127.73
84.60
58.13
27.70
$CO_2{}^tBu$
NC
Cl
1F
f1 (ppm)
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000

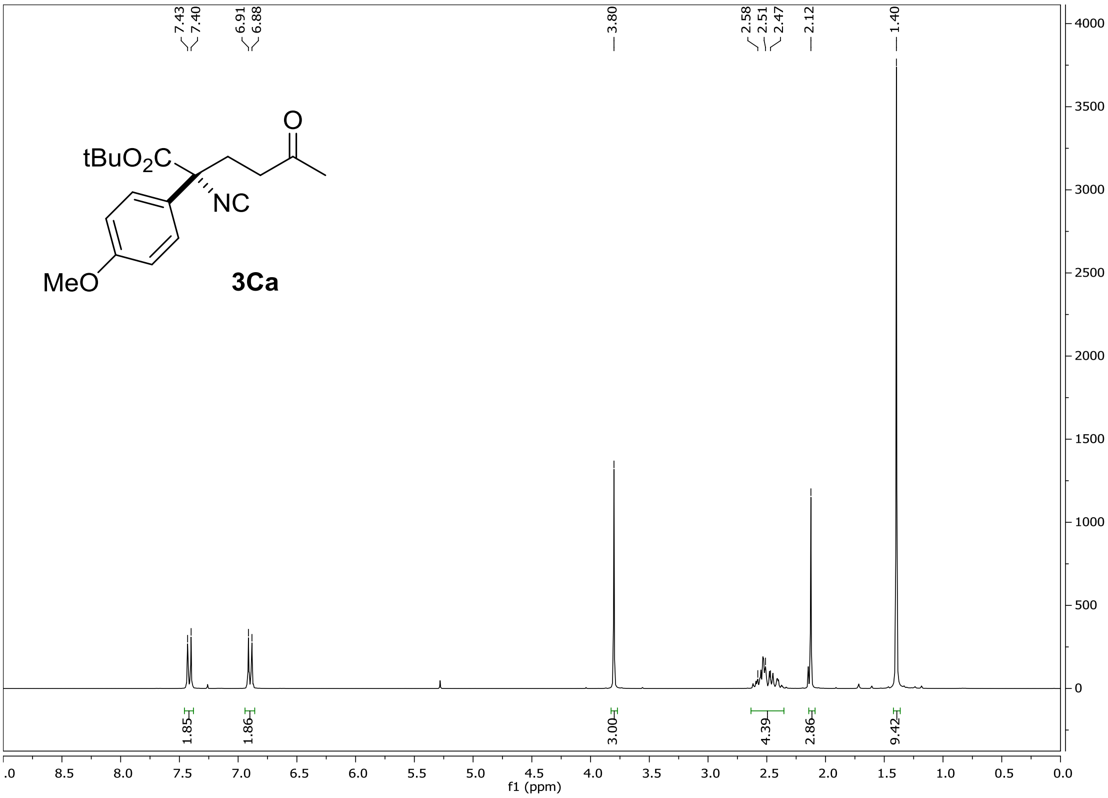
*5.5.2.2. Michael adducts **3***

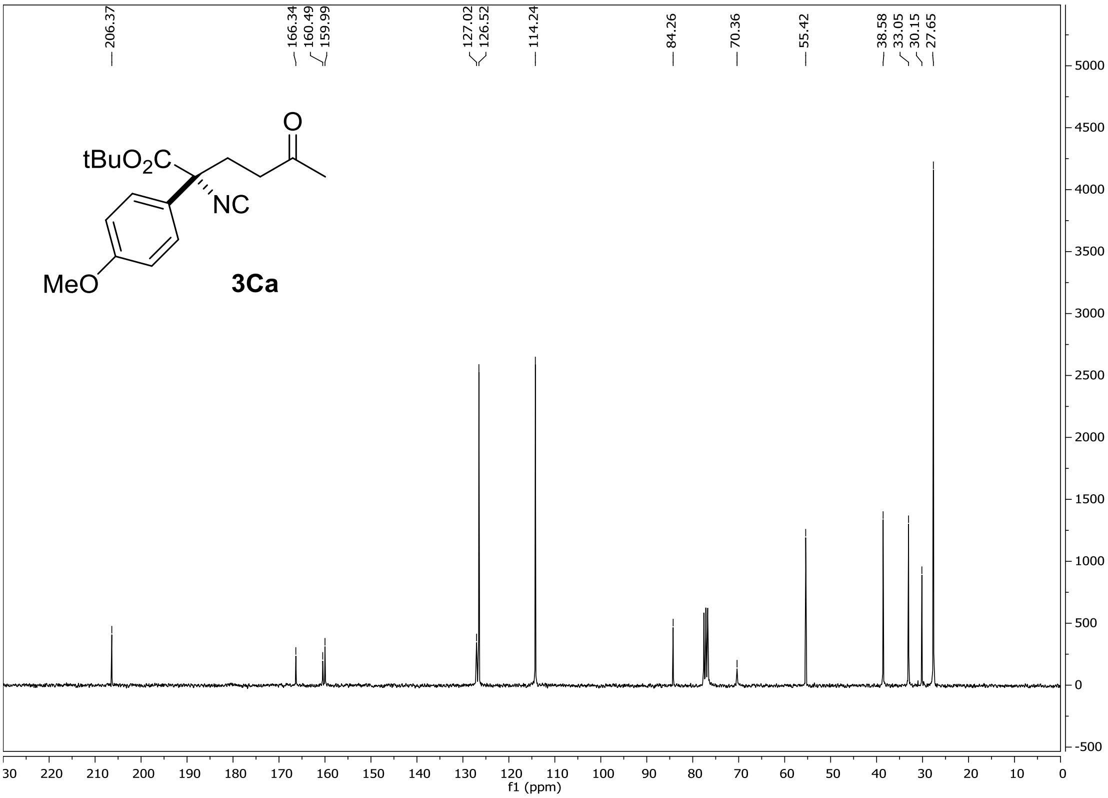


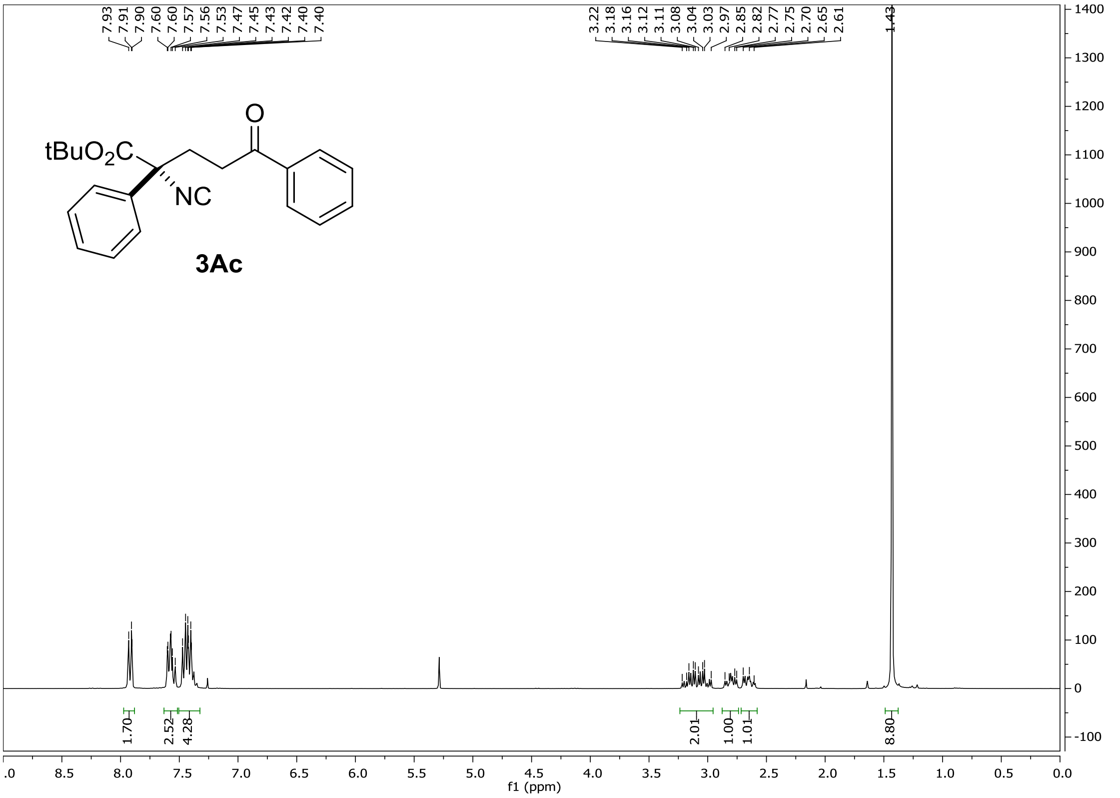


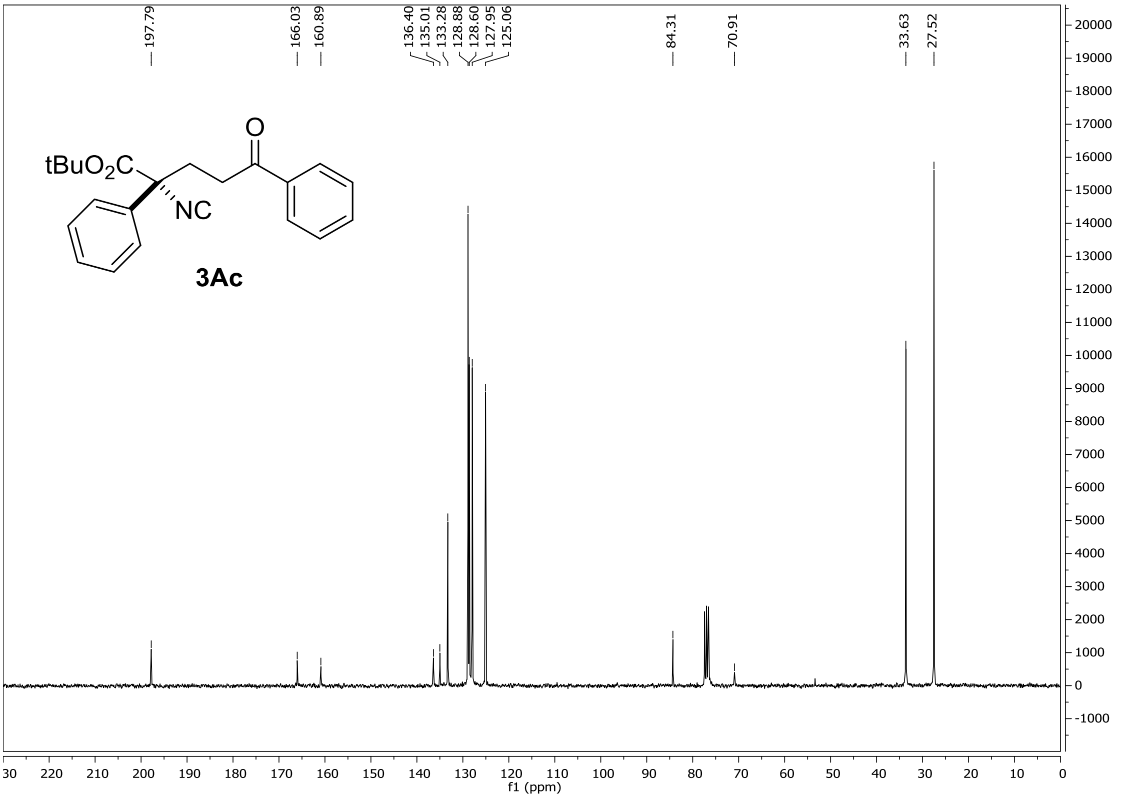

7.53
7.50
7.40
7.38
7.33
2.65
2.62
2.56
2.53
2.48
2.44
2.39
2.37
1.40
1.02
tBuO$_2$C
O
NC
3Ab
1.63
2.49
6.00
9.09
2.60
f1 (ppm)
4500
4000
3500
3000
2500
2000
1500
1000
500
0

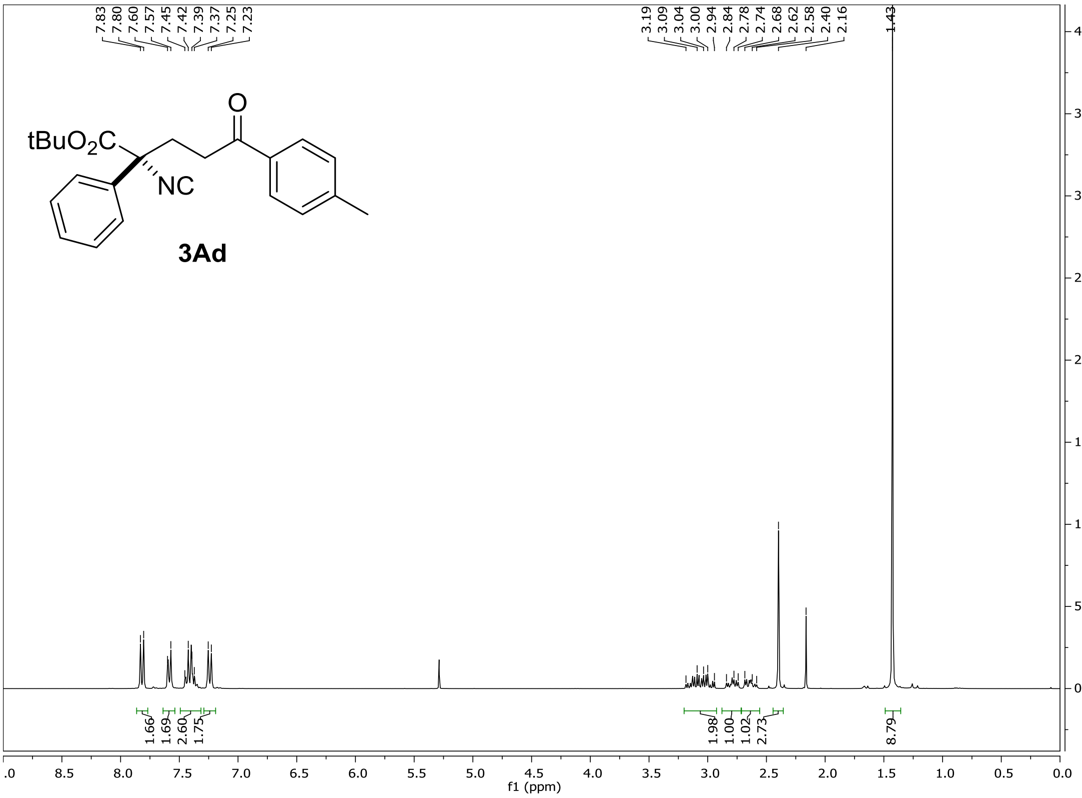

209.10
166.15
160.82
135.11
128.98
125.16
84.39
70.93
37.22
36.20
33.27
27.64
7.84
tBuO$_2$C
O
NC
3Ab
f1 (ppm)
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

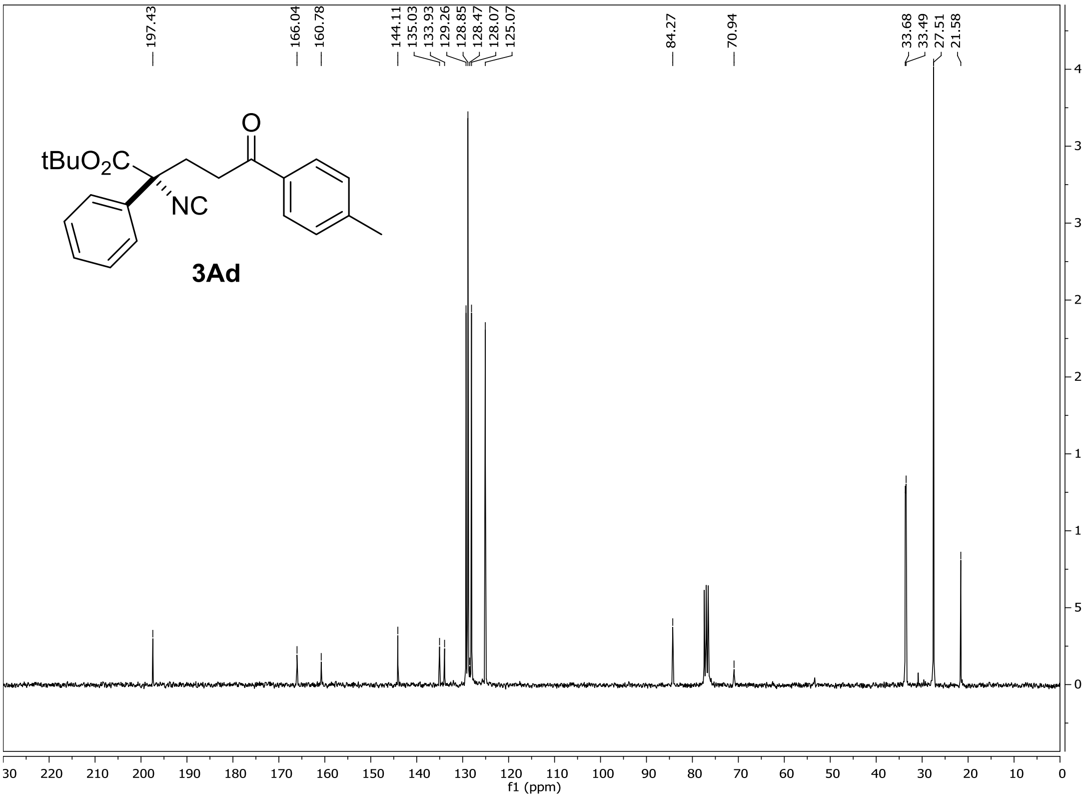

7.43
7.40
6.91
6.88
3.80
2.58
2.51
2.47
2.12
1.40
tBuO$_2$C
O
NC
MeO
3Ca
1.85
1.86
3.00
4.39
2.86
9.42
f1 (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0

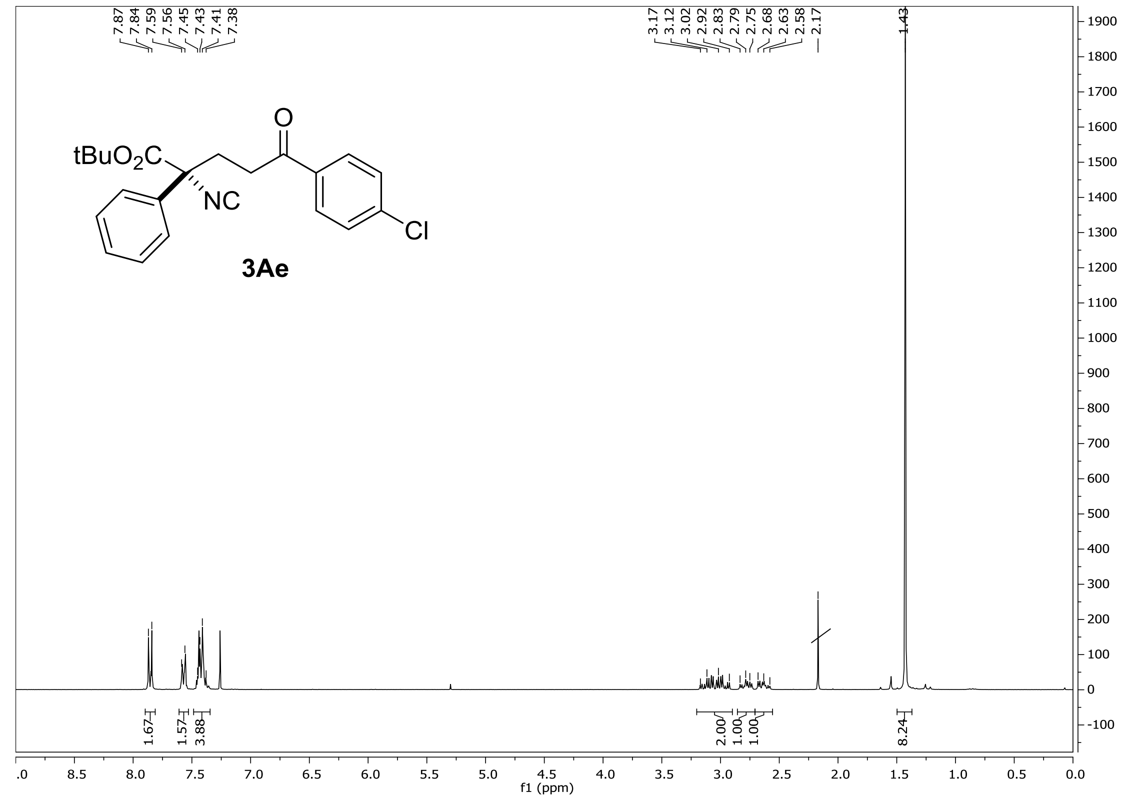

206.37
166.34
160.49
159.99
127.02
126.52
114.24
84.26
70.36
55.42
38.58
33.05
30.15
27.65
tBuO$_2$C
O
NC
MeO
3Ca
f1 (ppm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

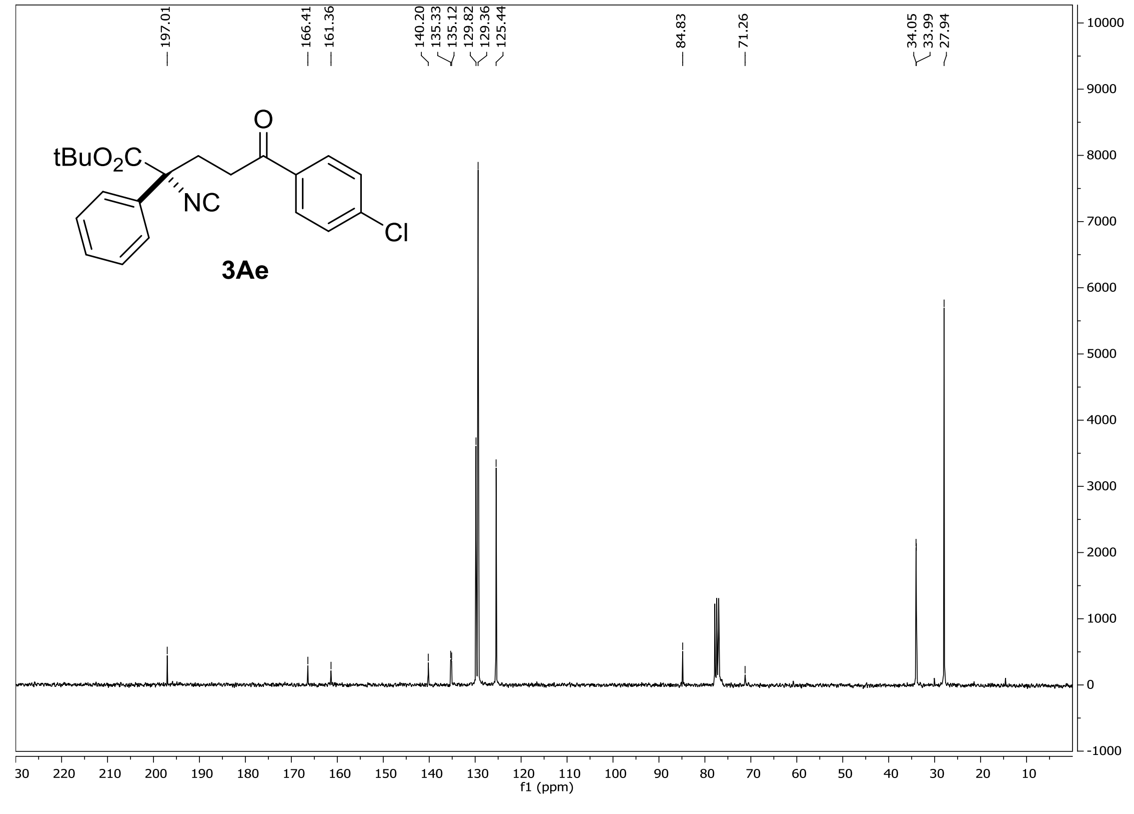

7.93
7.91
7.90
7.60
7.60
7.57
7.56
7.53
7.47
7.45
7.43
7.42
7.40
7.40
3.22
3.18
3.16
3.12
3.11
3.08
3.04
3.03
2.97
2.85
2.82
2.77
2.75
2.70
2.65
2.61
1.43
tBuO2C
O
NC
3Ac
1.70
2.52
4.28
2.01
1.00
1.01
8.80
f1 (ppm)

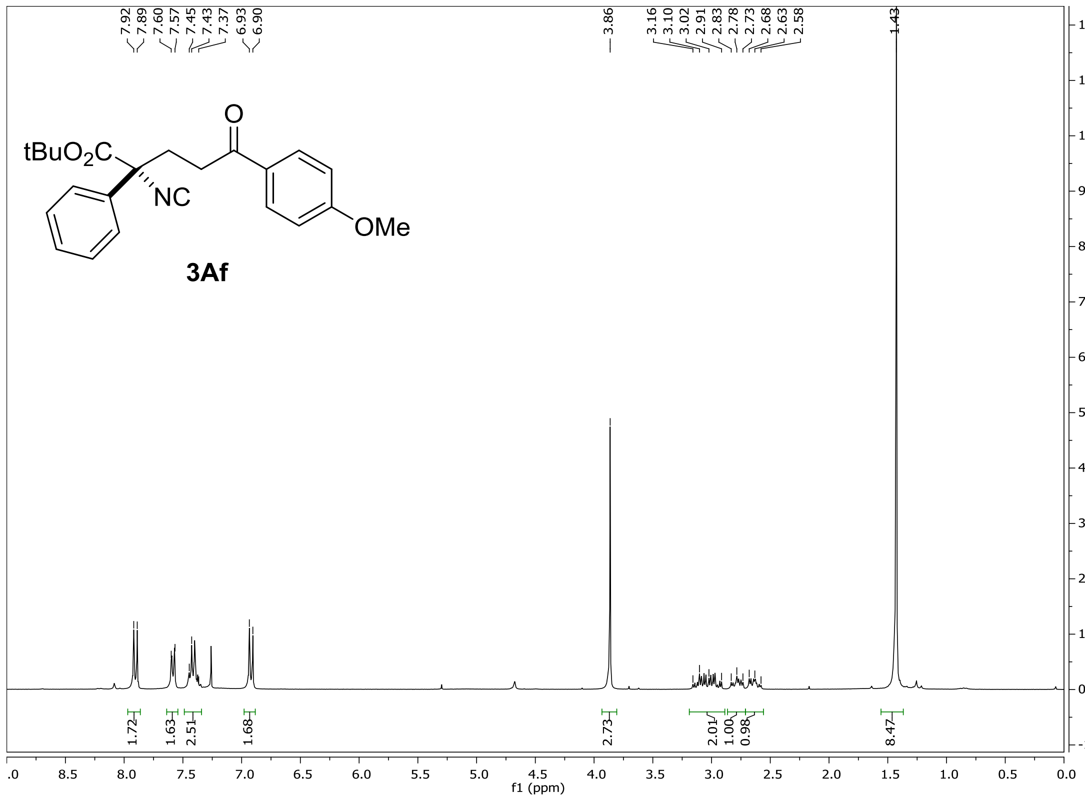

197.79
166.03
160.89
136.40
135.01
133.28
128.88
128.60
127.95
125.06
84.31
70.91
33.63
27.52
tBuO2C
O
NC
3Ac
f1 (ppm)

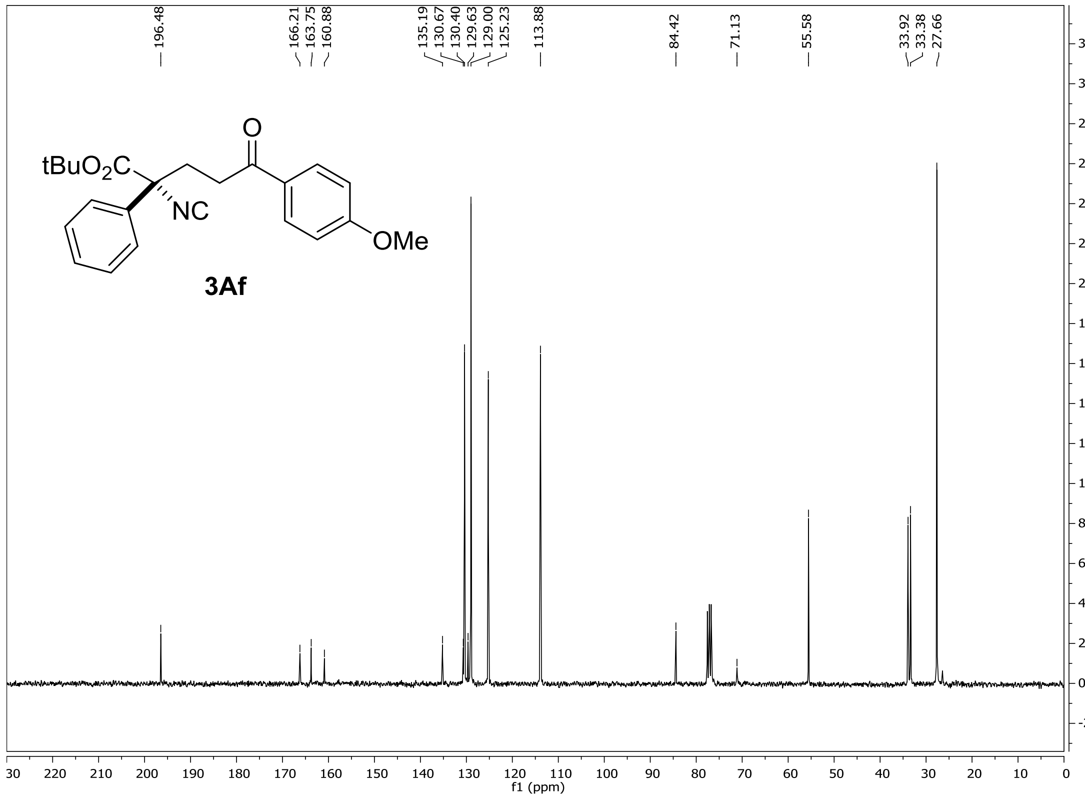

7.83
7.80
7.60
7.57
7.45
7.42
7.39
7.37
7.25
7.23
3.19
3.09
3.04
3.00
2.94
2.84
2.78
2.74
2.68
2.62
2.58
2.40
2.16
1.43
tBuO2C
NC
O
3Ad
1.66
1.69
2.60
1.75
1.98
1.00
1.02
2.73
8.79
4000
3500
3000
2500
2000
1500
1000
500
0
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

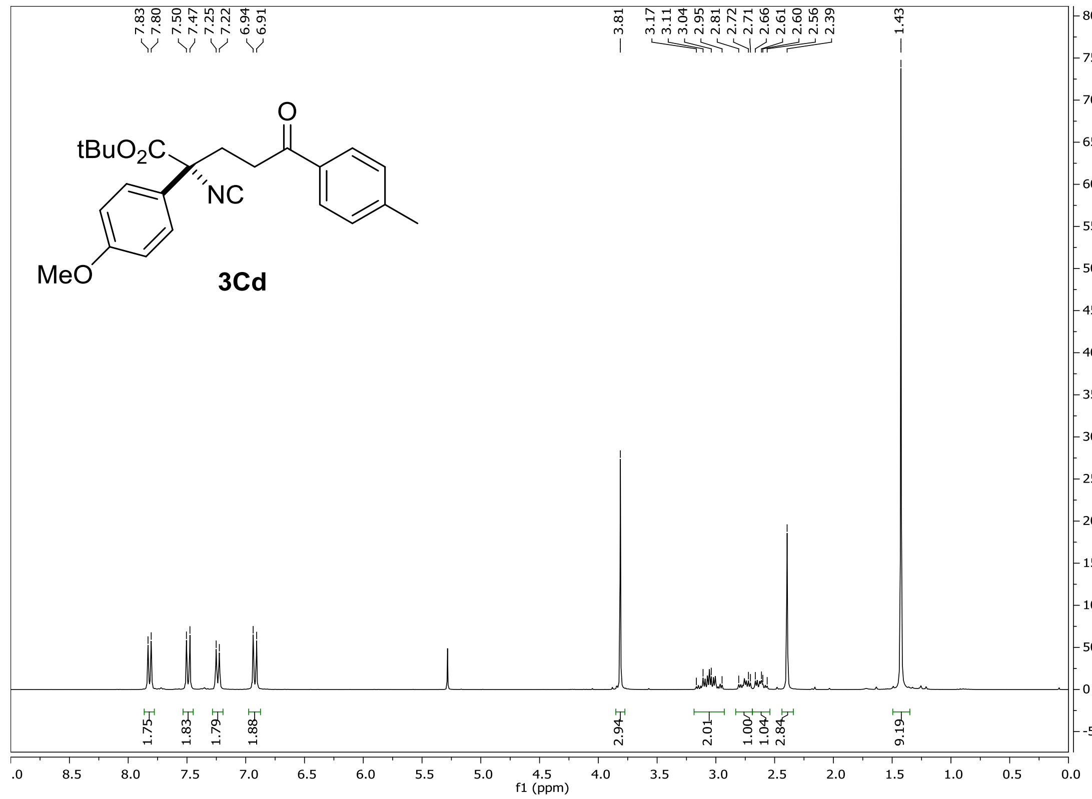

197.43
166.04
160.78
144.11
135.03
133.93
129.26
128.85
128.47
128.07
125.07
84.27
70.94
33.68
33.49
27.51
21.58
tBuO2C
NC
O
3Ad
4000
3500
3000
2500
2000
1500
1000
500
0
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

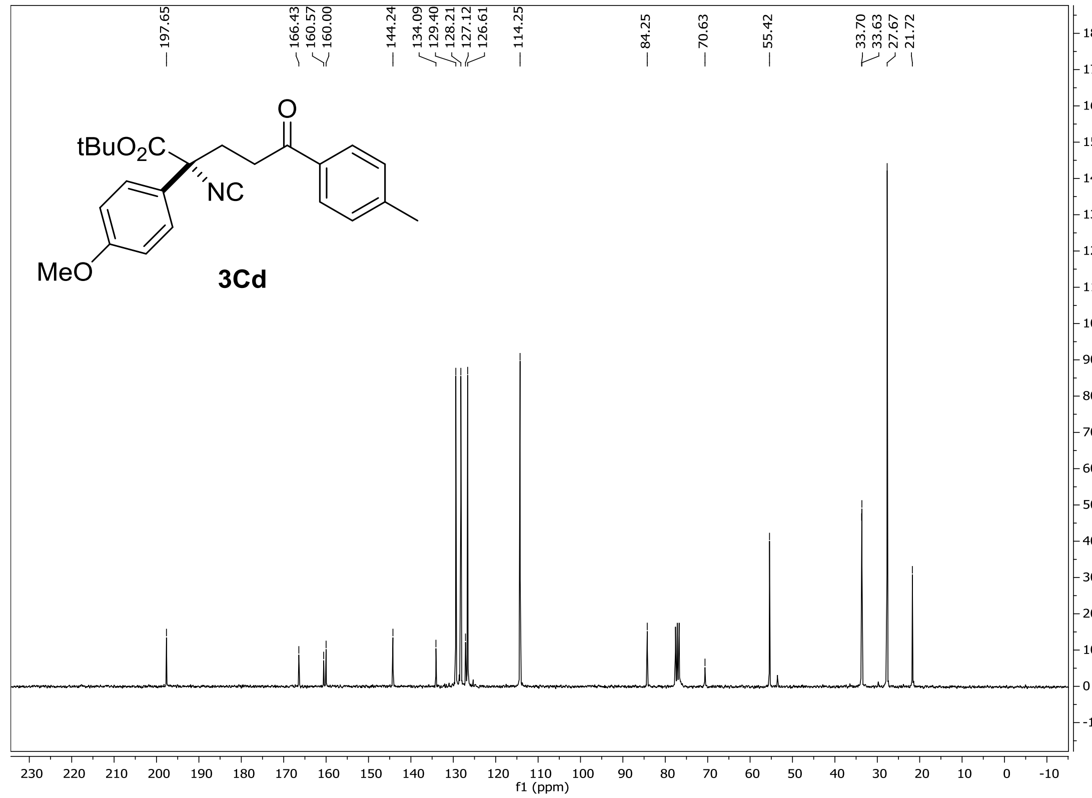

7.87
7.84
7.59
7.56
7.45
7.43
7.41
7.38
3.17
3.12
3.02
2.92
2.83
2.79
2.75
2.68
2.63
2.58
2.17
1.43
tBuO2C
NC
O
Cl
3Ae
1.67
1.57
3.88
2.00
1.00
1.00
8.24
f1 (ppm)

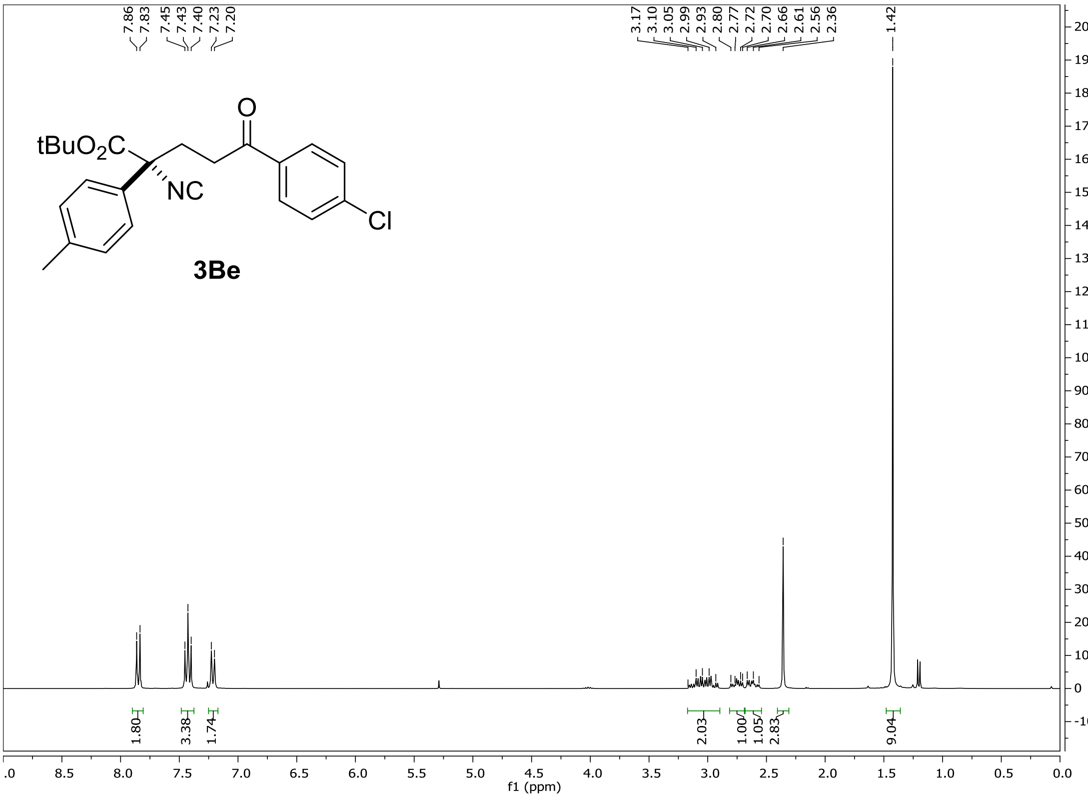

197.01
166.41
161.36
140.20
135.33
135.12
129.82
129.36
125.44
84.83
71.26
34.05
33.99
27.94
tBuO2C
NC
O
Cl
3Ae
f1 (ppm)

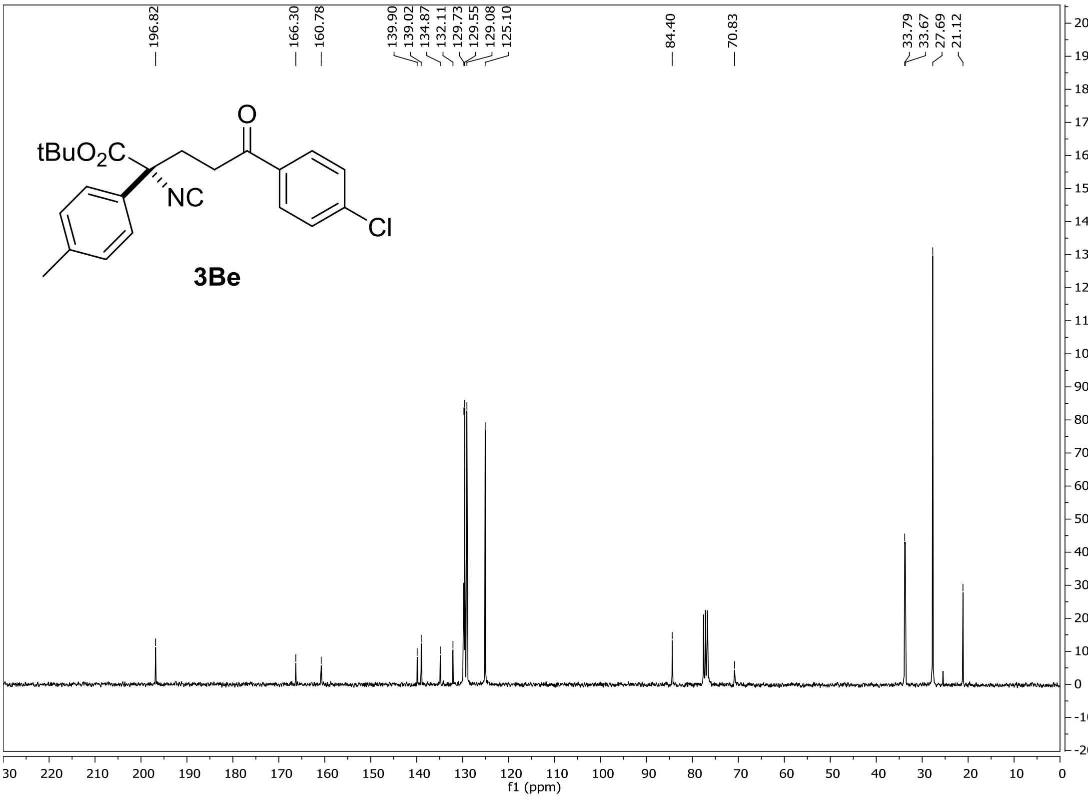

7.92
7.89
7.60
7.57
7.45
7.43
7.37
6.93
6.90
3.86
3.16
3.10
3.02
2.91
2.83
2.78
2.73
2.68
2.63
2.58
1.43
tBuO$_2$C
NC
O
OMe
3Af
1.72
1.63
2.51
1.68
2.73
2.01
1.00
0.98
8.47
f1 (ppm)

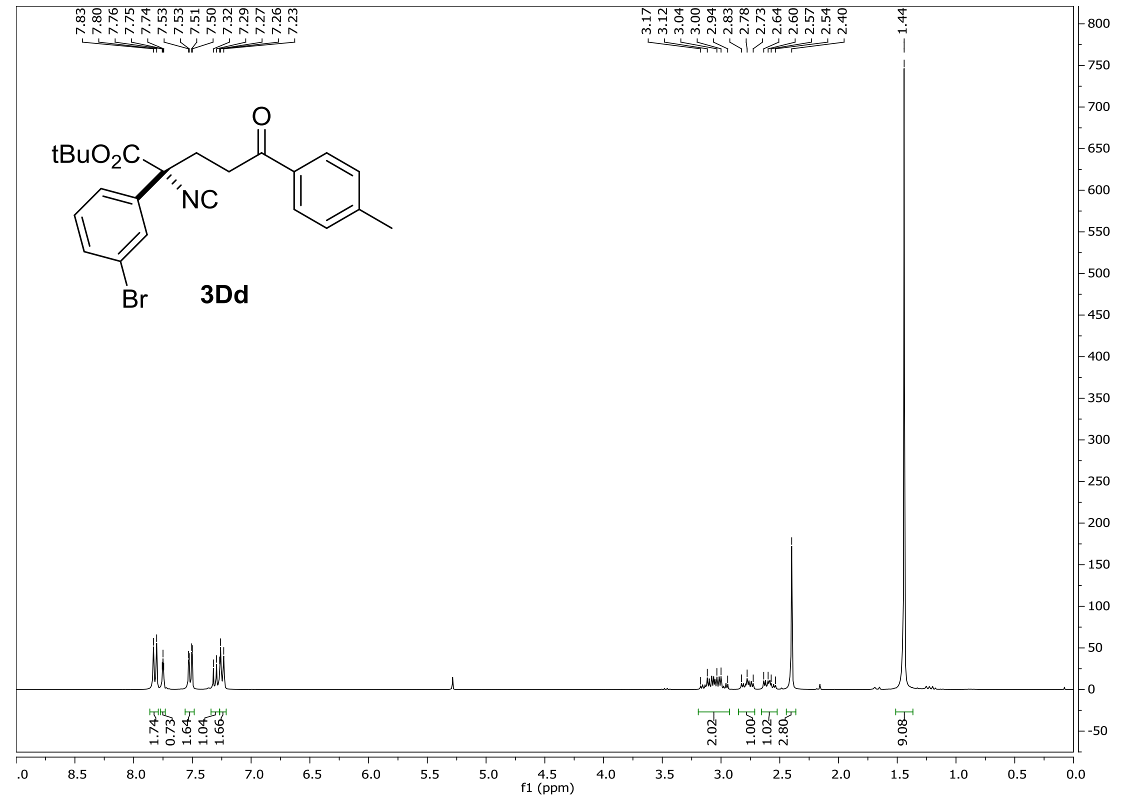

196.48
166.21
163.75
160.88
135.19
130.67
130.40
129.63
129.00
125.23
113.88
84.42
71.13
55.58
33.92
33.38
27.66
tBuO$_2$C
NC
O
OMe
3Af
f1 (ppm)

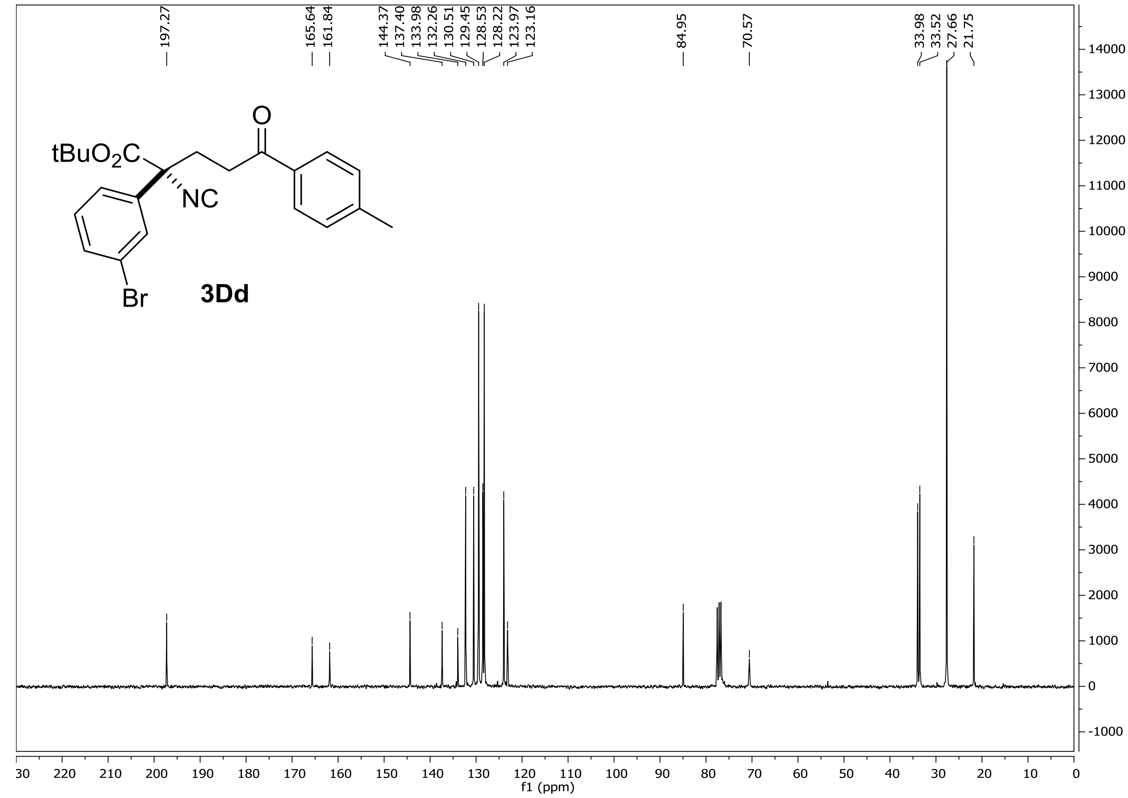

7.83
7.80
7.50
7.47
7.25
7.22
6.94
6.91
3.81
3.17
3.11
3.04
2.95
2.81
2.72
2.71
2.66
2.61
2.60
2.56
2.39
1.43
tBuO2C
O
NC
MeO
3Cd
1.75
1.83
1.79
1.88
2.94
2.01
1.00
1.04
2.84
9.19
f1 (ppm)


197.65
166.43
160.57
160.00
144.24
134.09
129.40
128.21
127.12
126.61
114.25
84.25
70.63
55.42
33.70
33.63
27.67
21.72
tBuO2C
O
NC
MeO
3Cd
f1 (ppm)

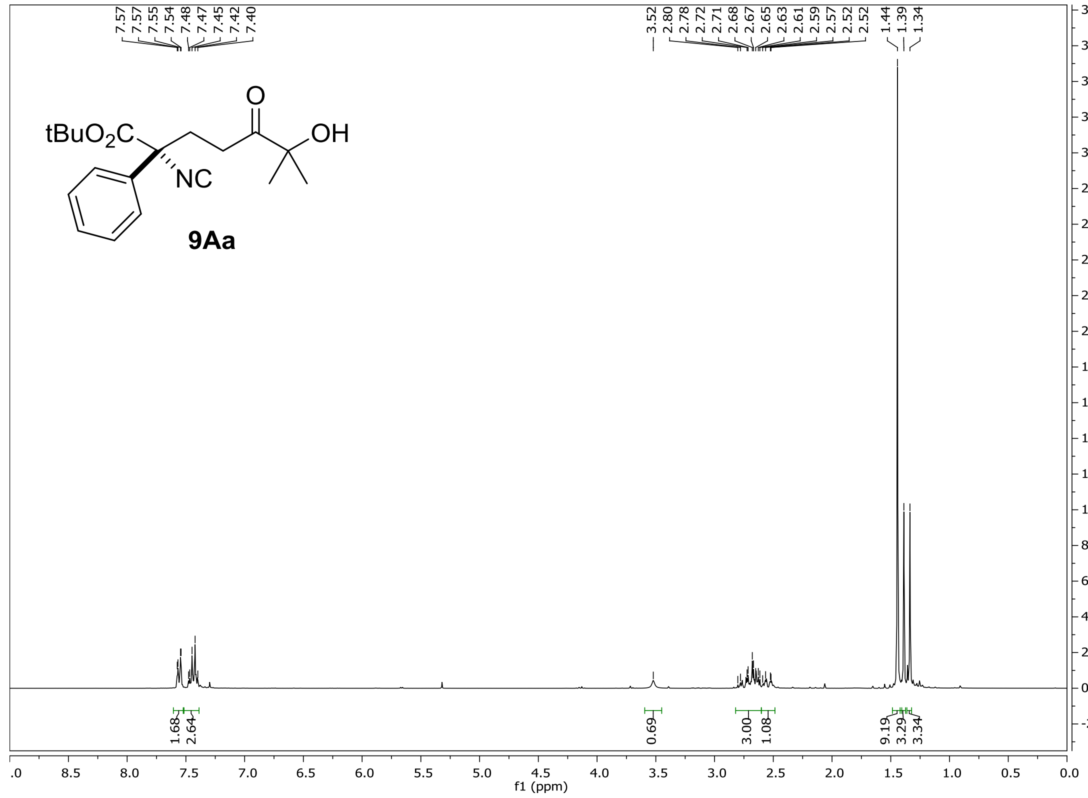

7.86
7.83
7.45
7.43
7.40
7.23
7.20
3.17
3.10
3.05
2.99
2.93
2.80
2.77
2.72
2.70
2.66
2.61
2.56
2.36
1.42
tBuO$_2$C
O
NC
Cl
3Be
1.80
3.38
1.74
2.03
1.00
1.05
2.83
9.04
f1 (ppm)

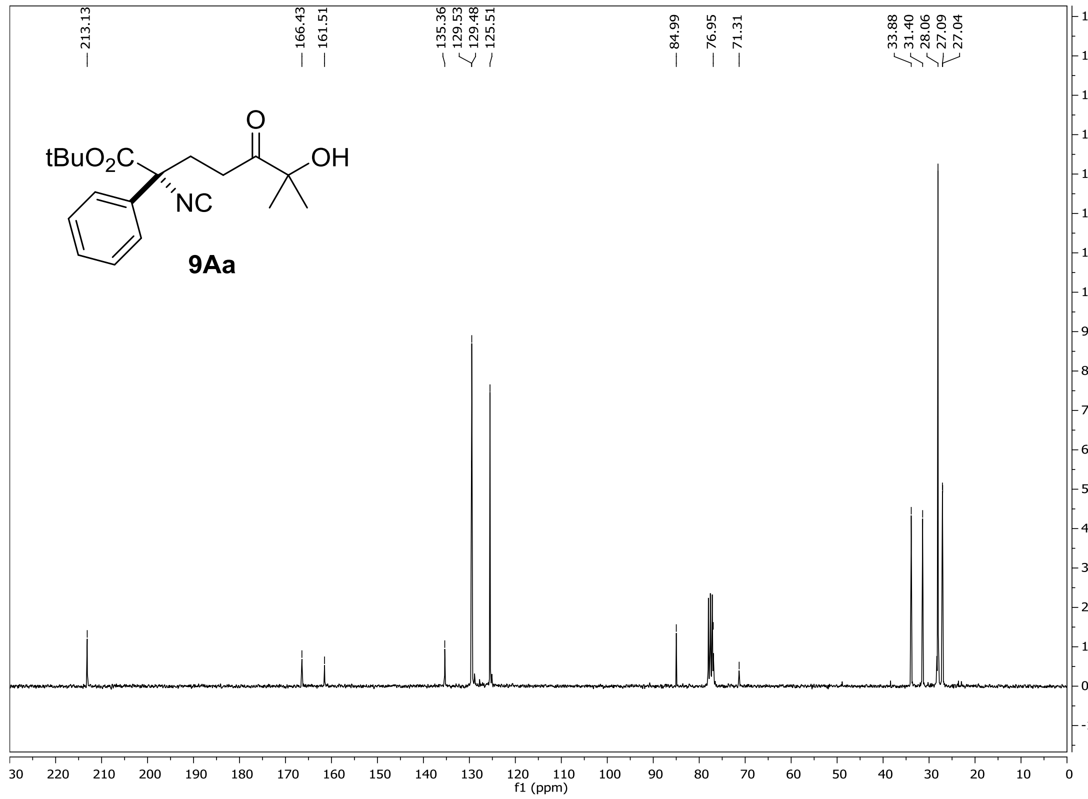

196.82
166.30
160.78
139.90
139.02
134.87
132.11
129.73
129.55
129.08
125.10
84.40
70.83
33.79
33.67
27.69
21.12
tBuO$_2$C
O
NC
Cl
3Be
f1 (ppm)

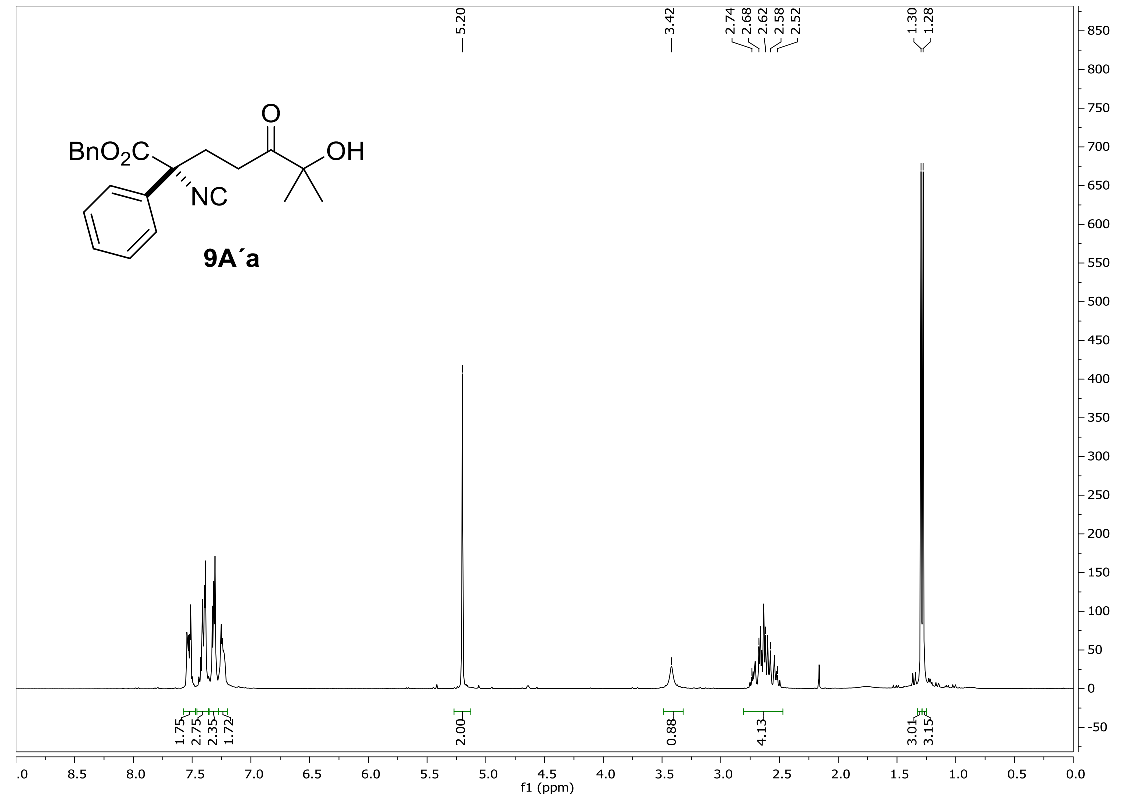

7.83
7.80
7.76
7.75
7.74
7.53
7.53
7.51
7.50
7.32
7.29
7.27
7.26
7.23
3.17
3.12
3.04
3.00
2.94
2.83
2.78
2.73
2.64
2.60
2.57
2.54
2.40
1.44
tBuO2C
NC
O
Br
3Dd
1.74
0.73
1.64
1.04
1.66
2.02
1.00
1.02
2.80
9.08
f1 (ppm)

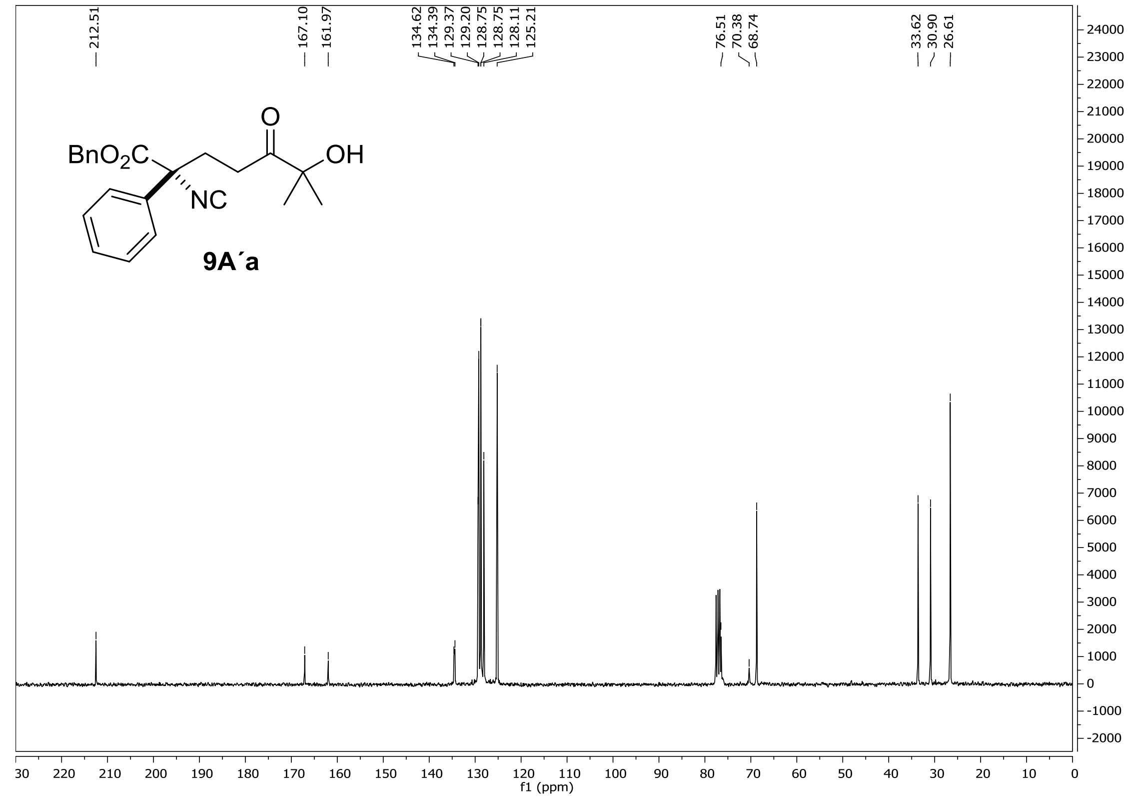

197.27
165.64
161.84
144.37
137.40
133.98
132.26
130.51
129.45
128.53
128.22
123.97
123.16
84.95
70.57
33.98
33.52
27.66
21.75
tBuO2C
NC
O
Br
3Dd
f1 (ppm)

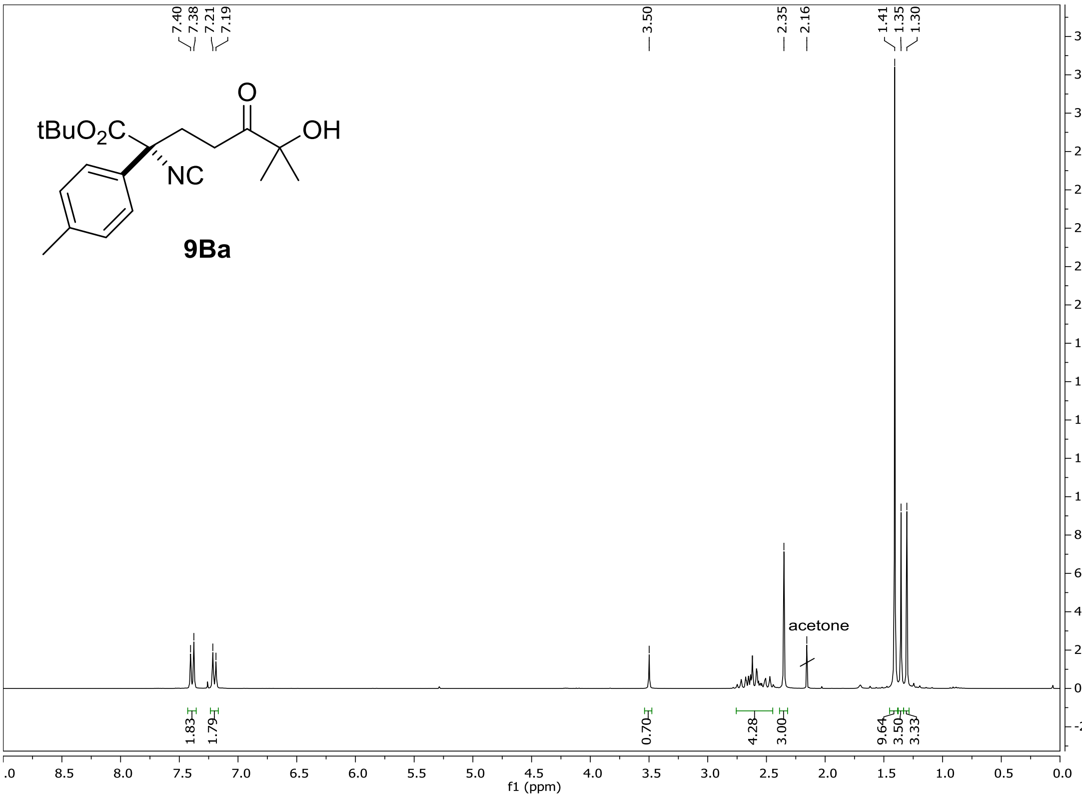
*5.5.2.3. Michael adducts **9***

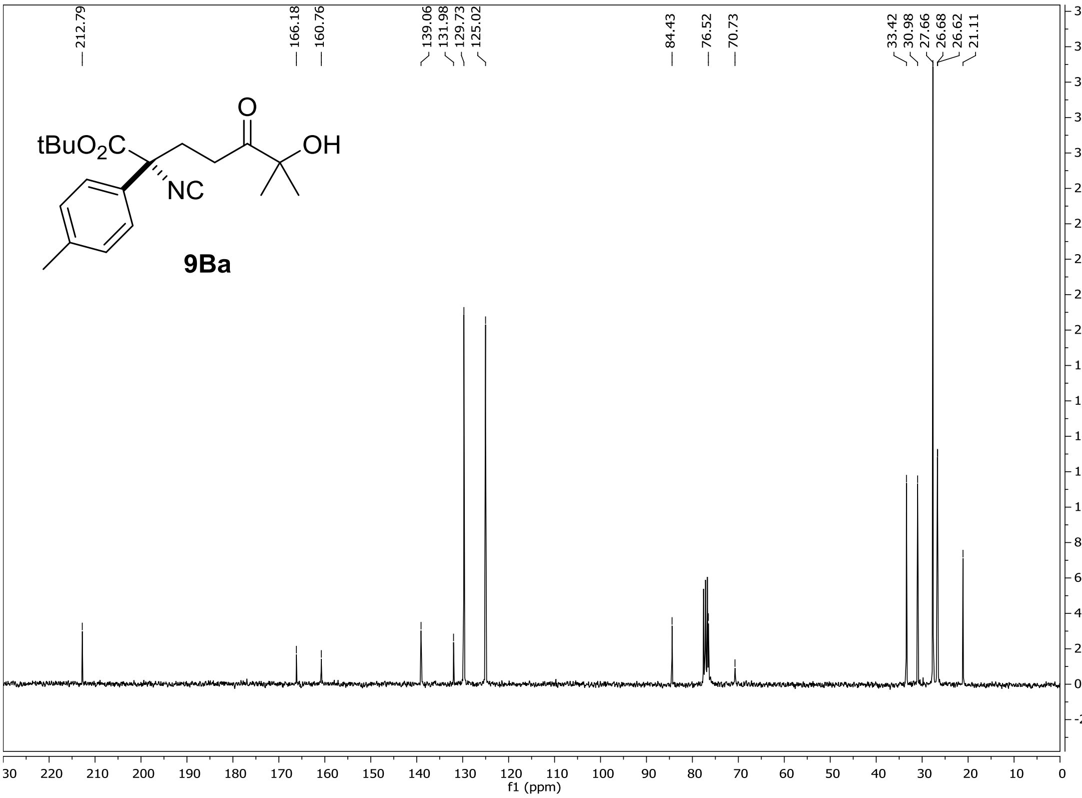


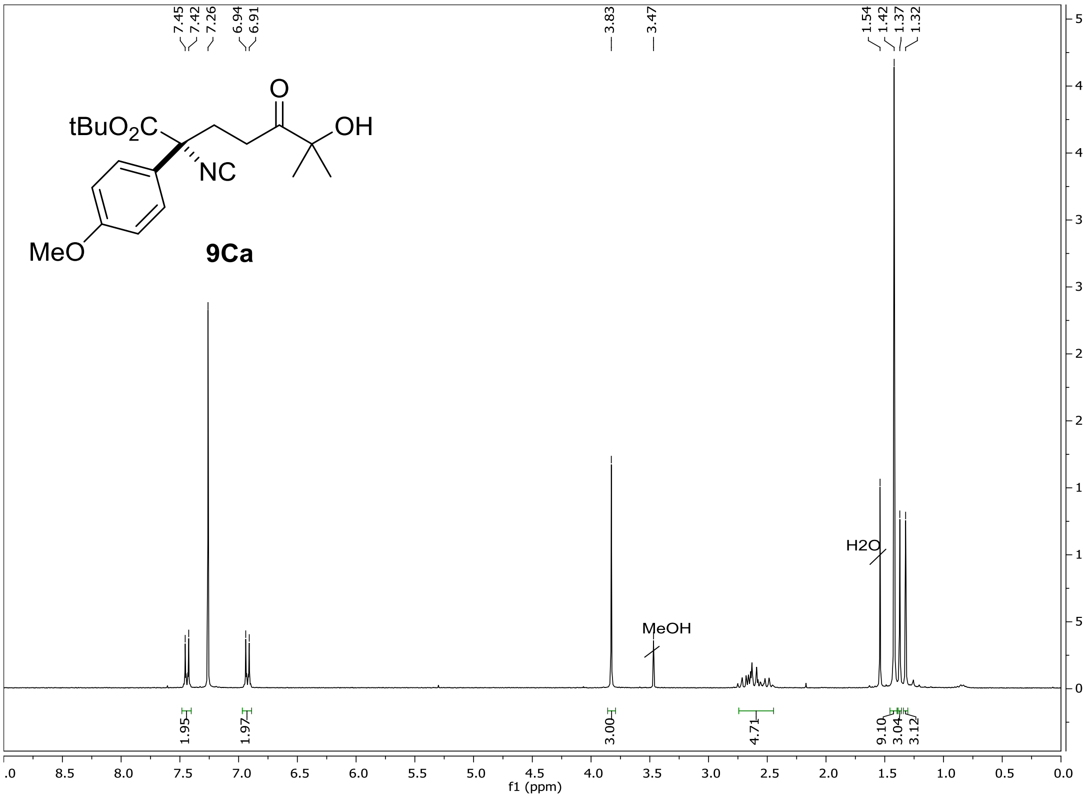


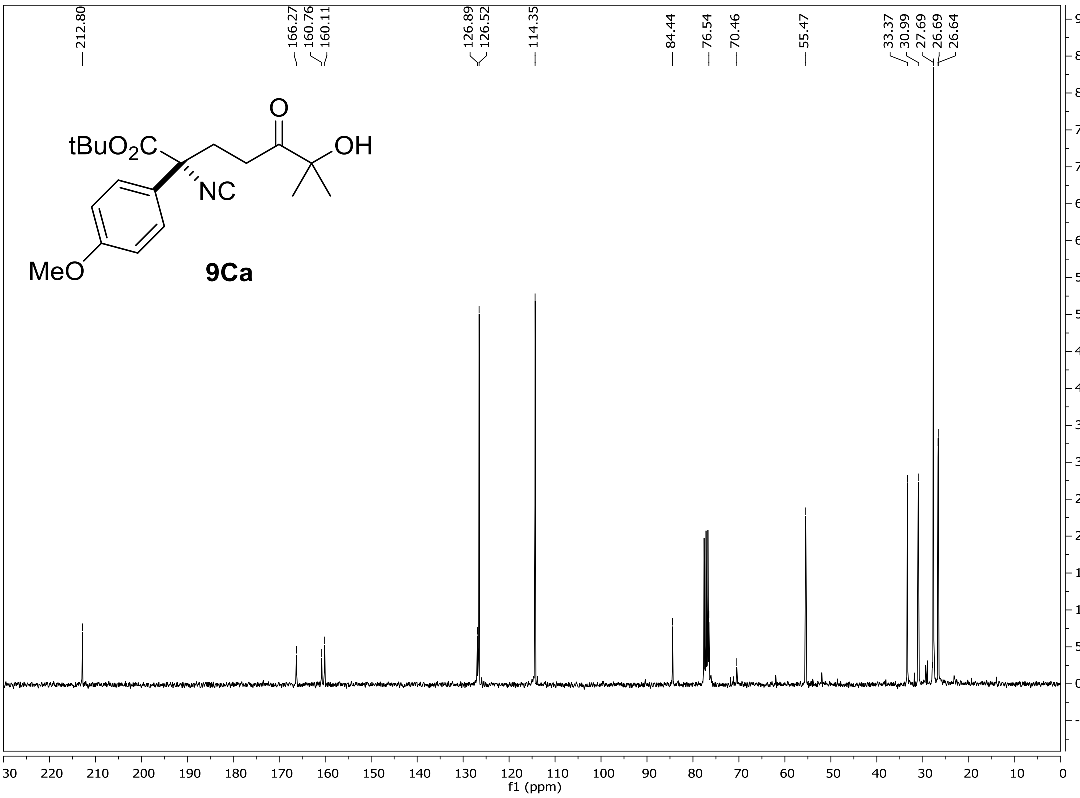

5.20
3.42
2.74
2.68
2.62
2.58
2.52
1.30
1.28
BnO2C
O
OH
NC
9A´a
1.75
2.75
2.35
1.72
2.00
0.88
4.13
3.01
3.15
f1 (ppm)

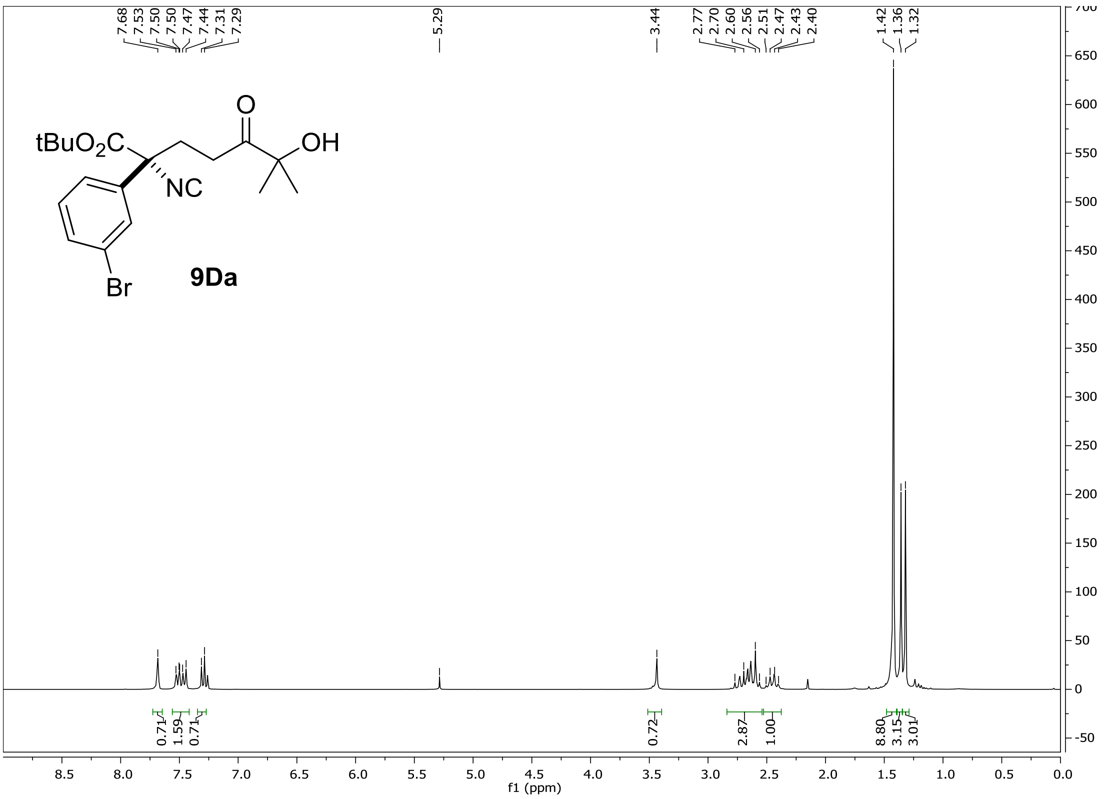

212.51
167.10
161.97
134.62
134.39
129.37
129.20
128.75
128.75
128.11
125.21
76.51
70.38
68.74
33.62
30.90
26.61
BnO2C
O
OH
NC
9A´a
f1 (ppm)

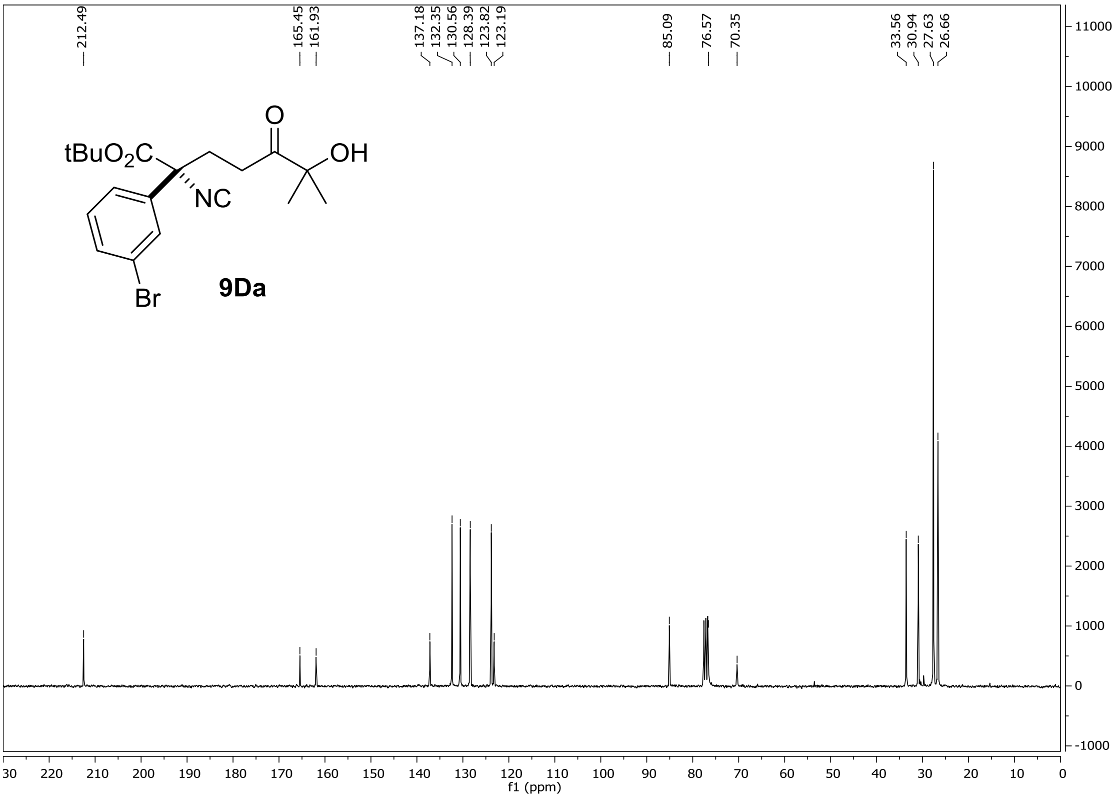

7.40
7.38
7.21
7.19
3.50
2.35
2.16
1.41
1.35
1.30
tBuO2C
O
OH
NC
9Ba
acetone
1.83
1.79
0.70
4.28
3.00
9.64
3.50
3.33
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


212.79
166.18
160.76
139.06
131.98
129.73
125.02
84.43
76.52
70.73
33.42
30.98
27.66
26.68
26.62
21.11
tBuO2C
O
OH
NC
9Ba
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
30
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)

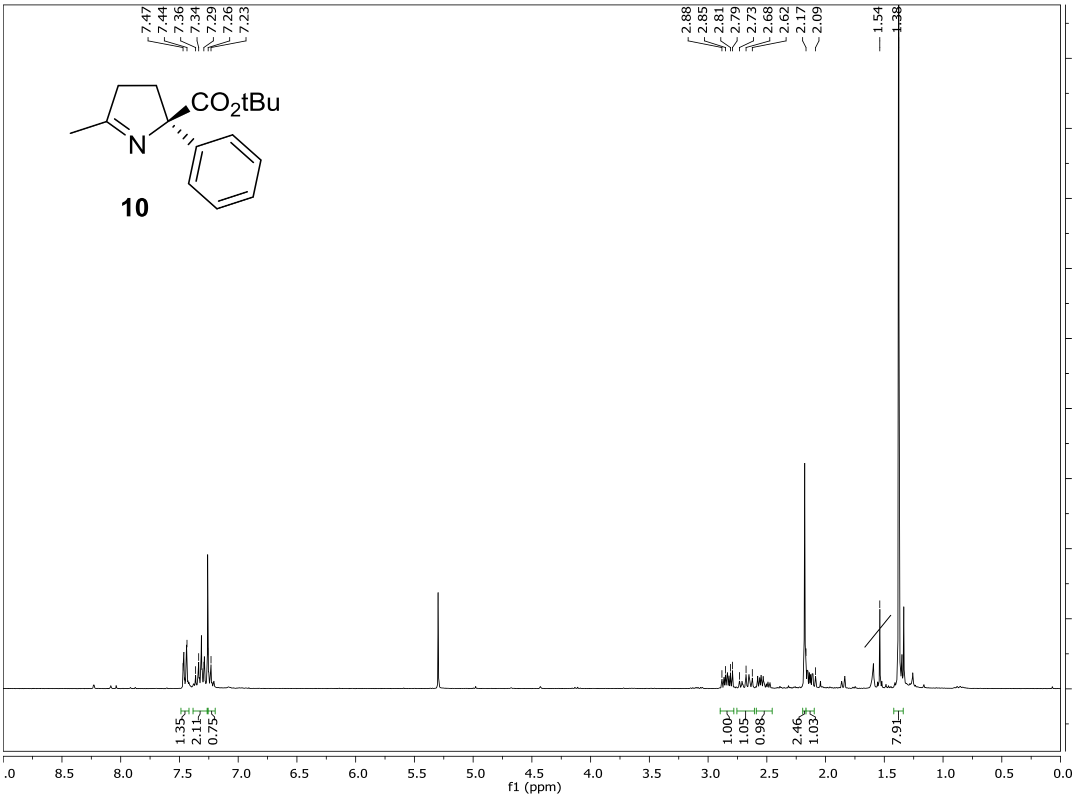

7.45
7.42
7.26
6.94
6.91
3.83
3.47
1.54
1.42
1.37
1.32
tBuO2C
NC
O
OH
MeO
9Ca
MeOH
H2O
1.95
1.97
3.00
4.71
9.10
3.04
3.12
f1 (ppm)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
500 450 400 350 300 250 200 150 100 50 0


212.80
166.27
160.76
160.11
126.89
126.52
114.35
84.44
76.54
70.46
55.47
33.37
30.99
27.69
26.69
26.64
tBuO2C
NC
O
OH
MeO
9Ca
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
9000 8500 8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

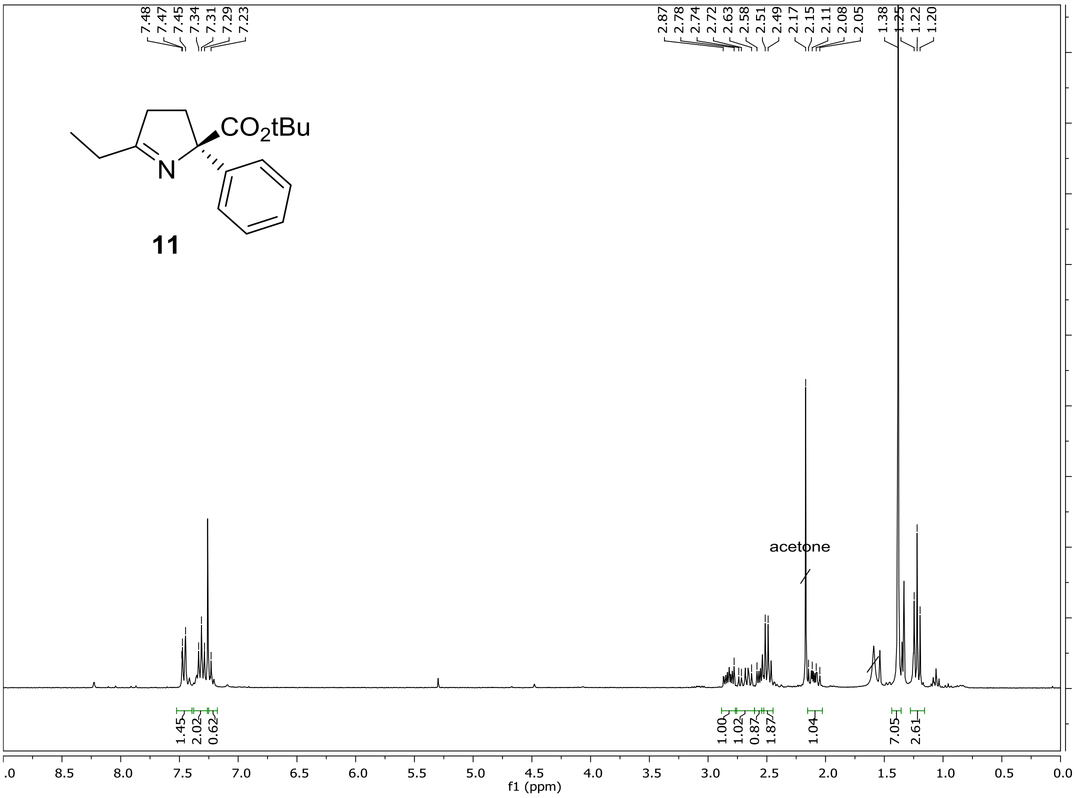

7.68
7.53
7.50
7.50
7.47
7.44
7.31
7.29
5.29
3.44
2.77
2.70
2.60
2.56
2.51
2.47
2.43
2.40
1.42
1.36
1.32
tBuO2C
O
OH
NC
Br
9Da
0.71
1.59
0.71
0.72
2.87
1.00
8.80
3.15
3.01
f1 (ppm)


212.49
165.45
161.93
137.18
132.35
130.56
128.39
123.82
123.19
85.09
76.57
70.35
33.56
30.94
27.63
26.66
tBuO2C
O
OH
NC
Br
9Da
f1 (ppm)

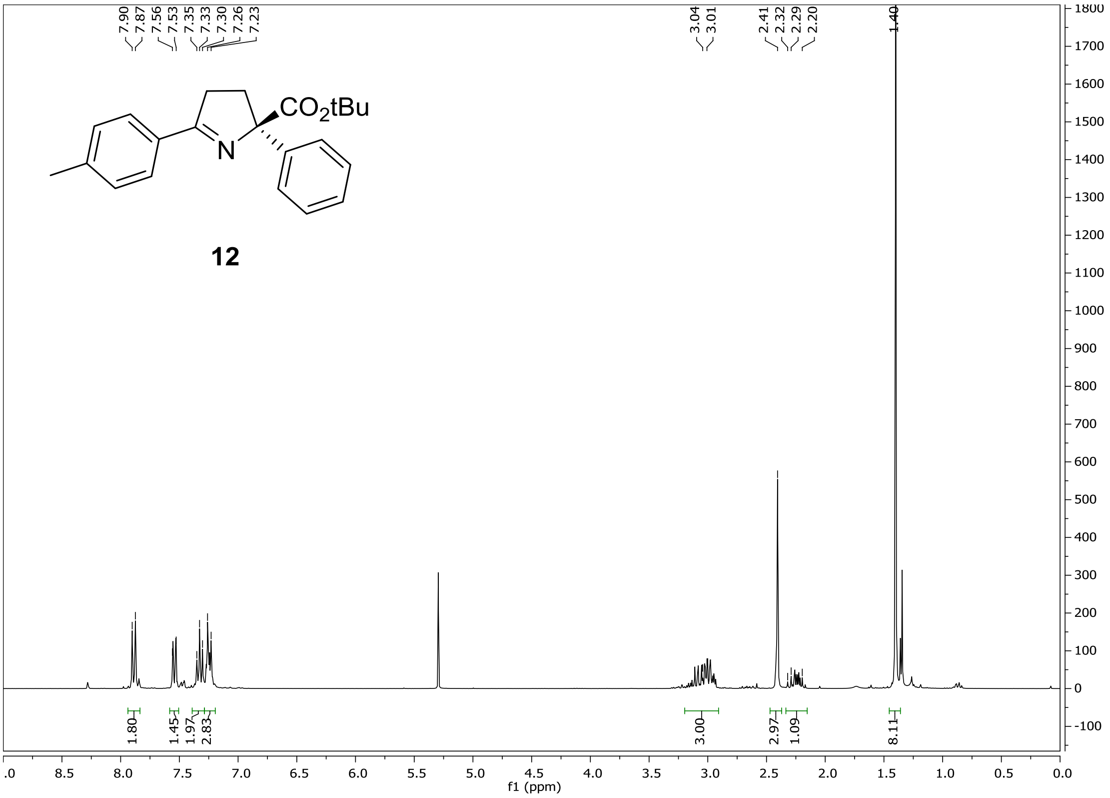
5.5.2.4. Elaboration of adducts

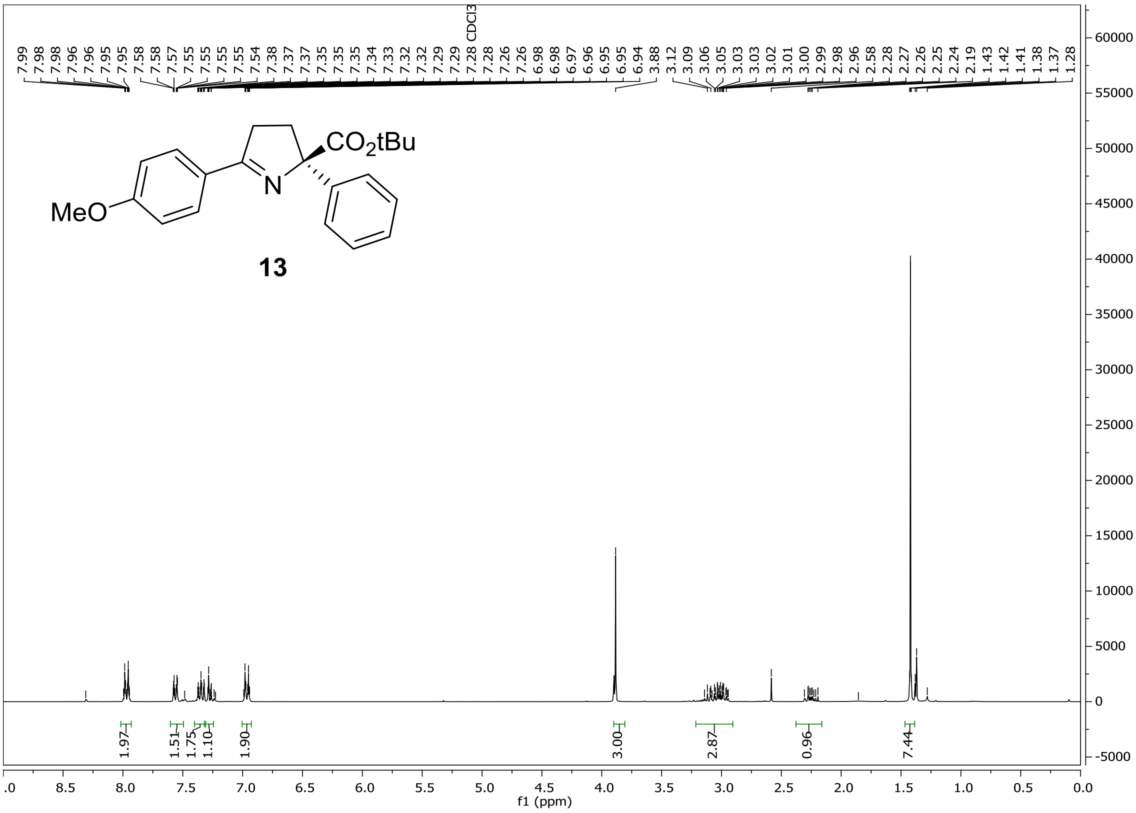


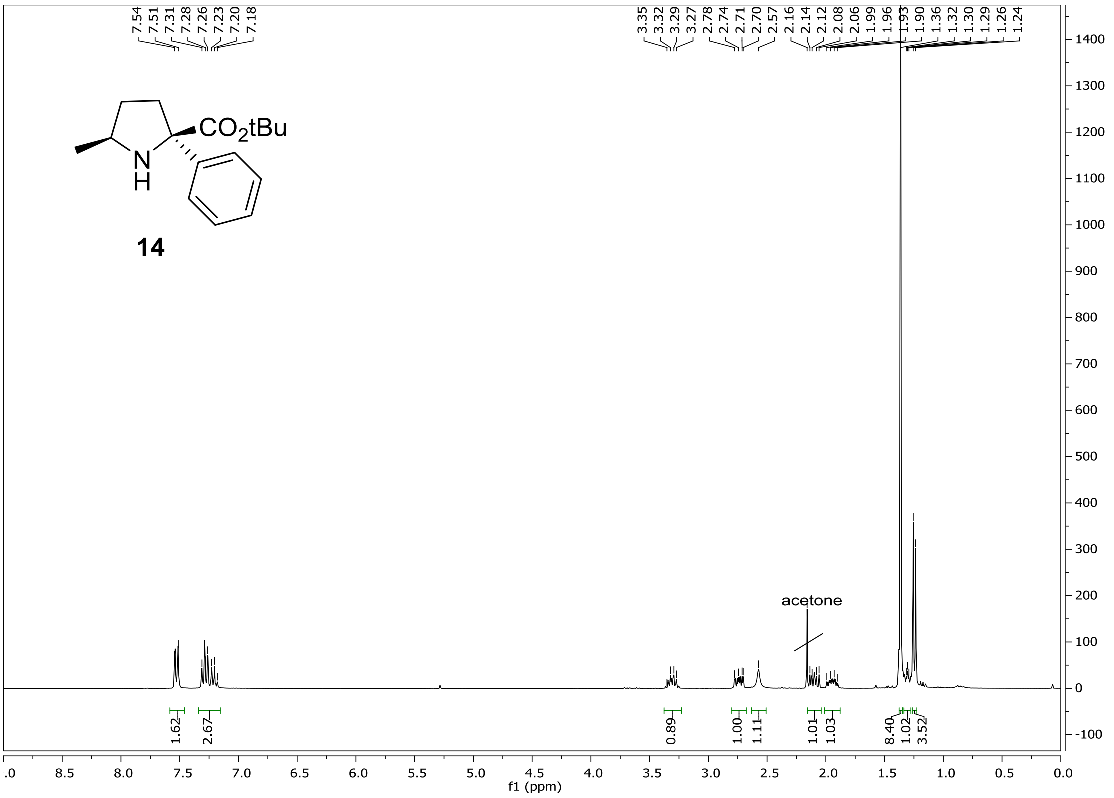
10

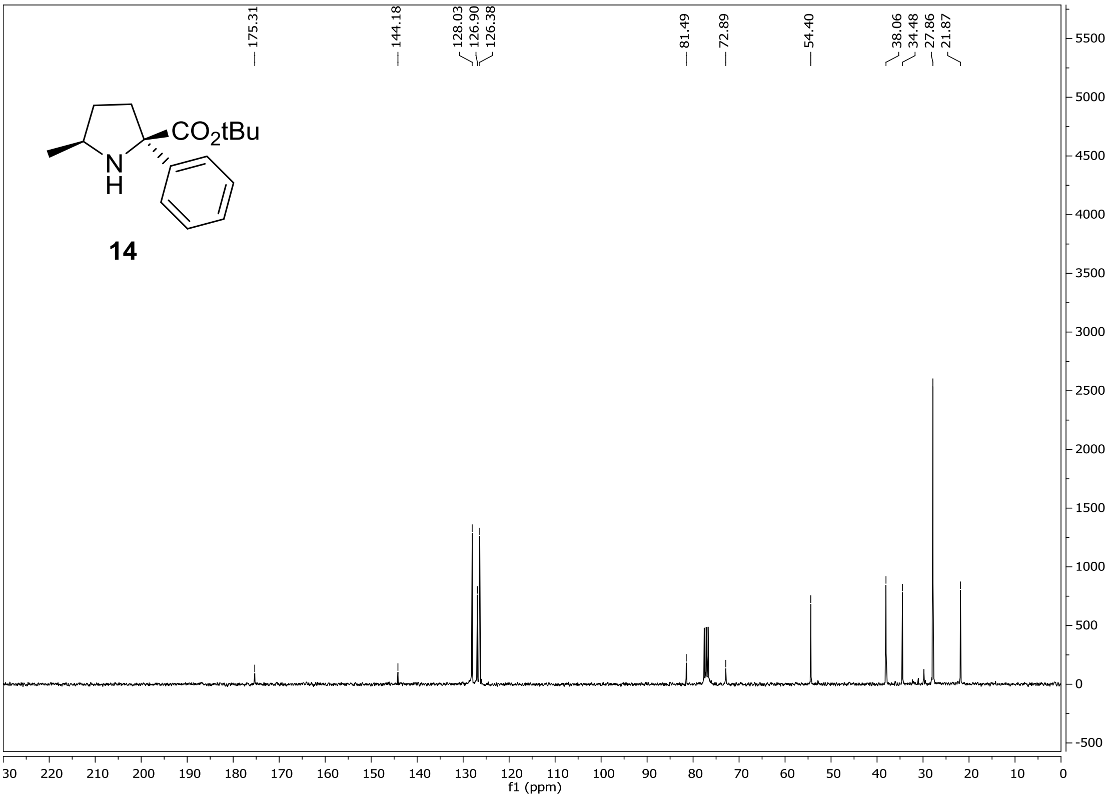


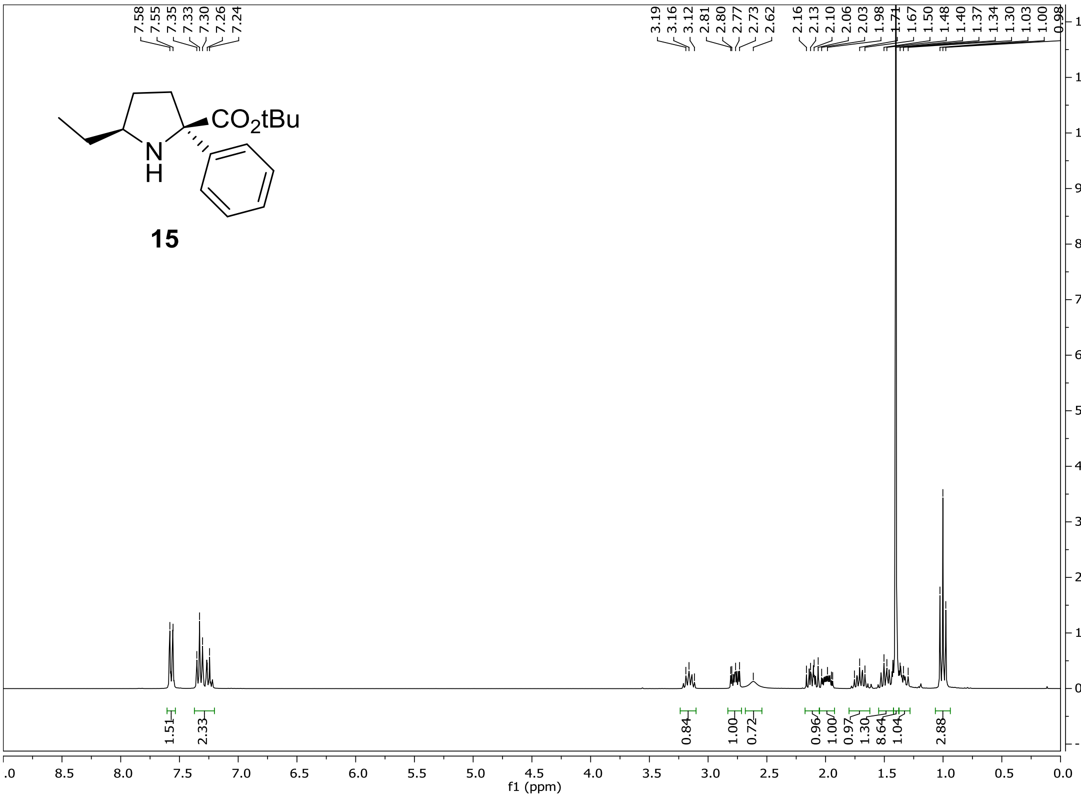
11

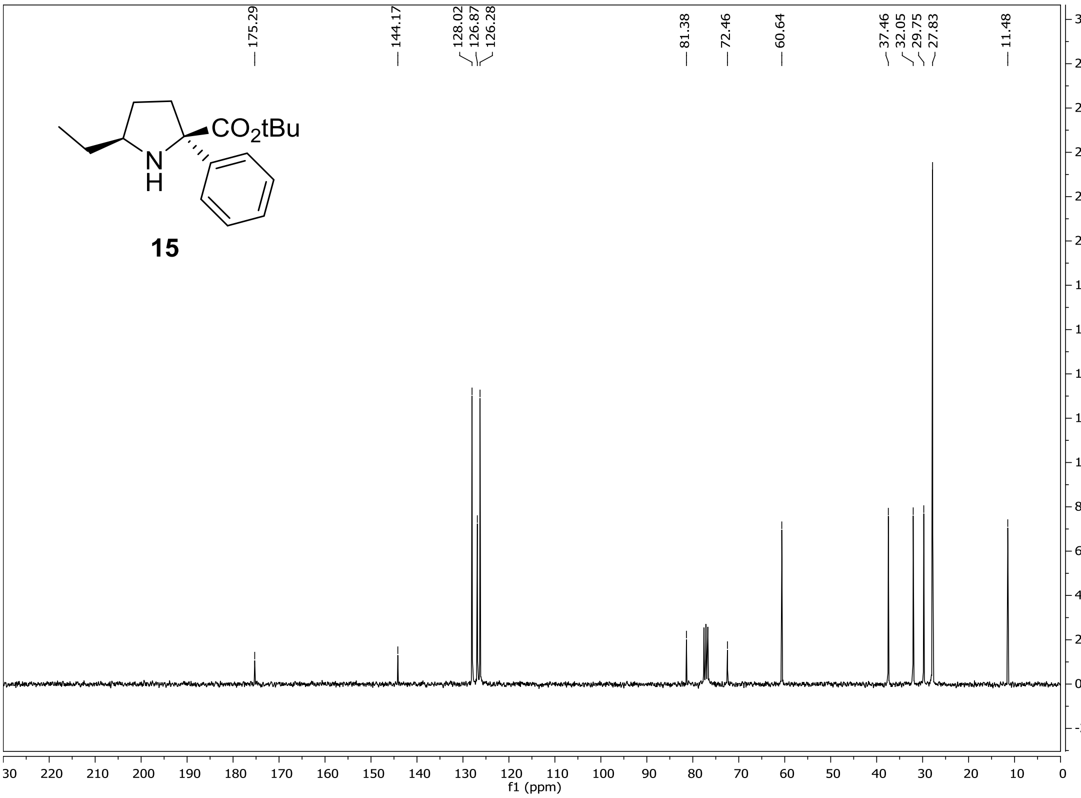

7.90
7.87
7.56
7.53
7.35
7.33
7.30
7.26
7.23
3.04
3.01
2.41
2.32
2.29
2.20
1.40
CO2tBu
N
12
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
1.80
1.45
1.97
2.83
3.00
2.97
1.09
8.11
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

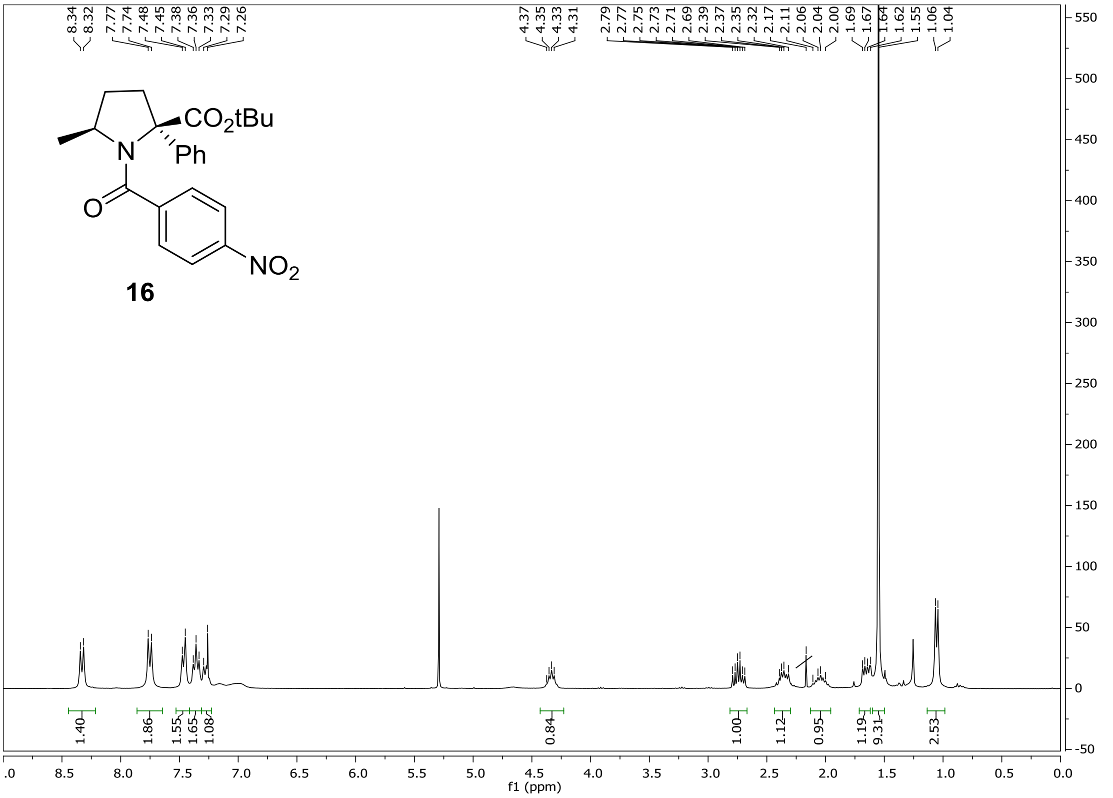

7.99
7.98
7.98
7.96
7.96
7.95
7.95
7.58
7.57
7.55
7.55
7.55
7.55
7.54
7.38
7.37
7.37
7.35
7.35
7.35
7.34
7.33
7.32
7.32
7.29
7.29
CDCl3
7.28
7.28
7.26
7.26
6.98
6.98
6.97
6.96
6.95
6.95
6.94
3.88
3.12
3.09
3.06
3.05
3.03
3.02
3.01
3.00
2.99
2.98
2.96
2.58
2.28
2.27
2.26
2.25
2.24
2.19
1.43
1.42
1.41
1.38
1.37
1.28
CO2tBu
MeO
N
13
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
1.97
1.51
1.75
1.10
1.90
3.00
2.87
0.96
7.44
.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)

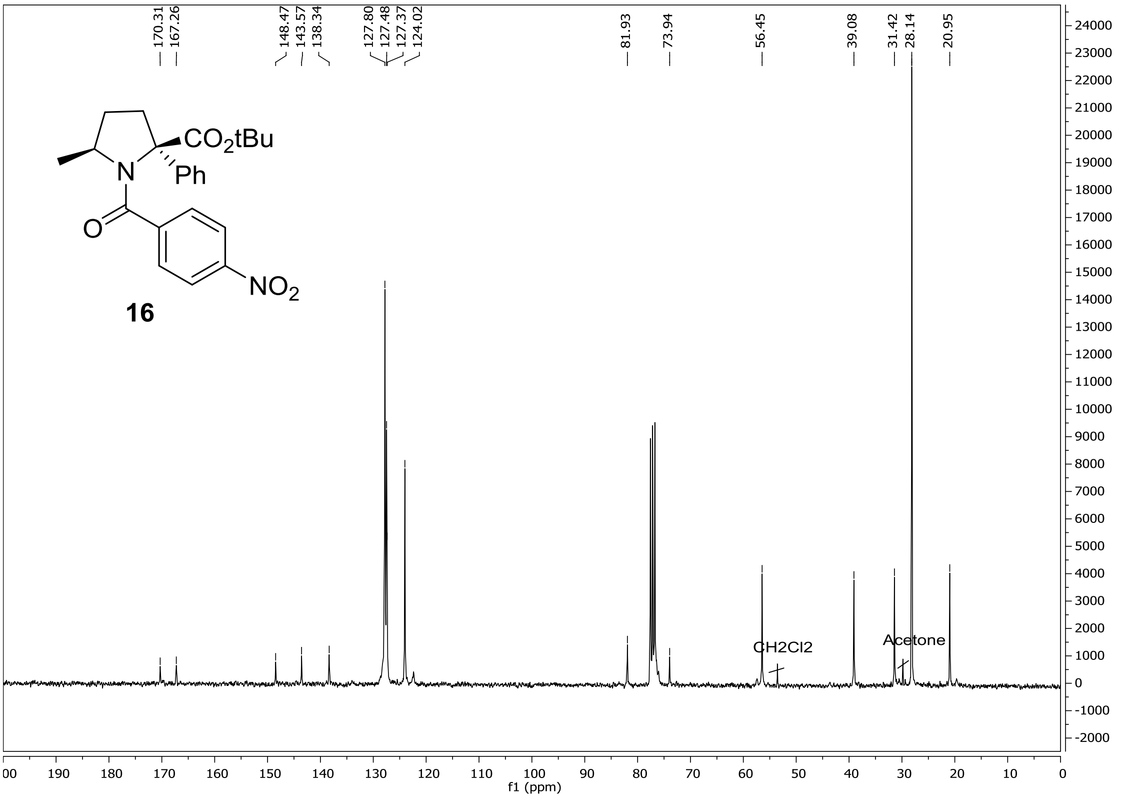

7.54
7.51
7.31
7.28
7.26
7.23
7.20
7.18
3.35
3.32
3.29
3.27
2.78
2.74
2.71
2.70
2.57
2.16
2.14
2.12
2.08
2.06
1.99
1.96
1.93
1.90
1.36
1.32
1.30
1.29
1.26
1.24
CO2tBu
N
H
14
acetone
1.62
2.67
0.89
1.00
1.11
1.01
1.03
8.40
1.02
3.52
f1 (ppm)

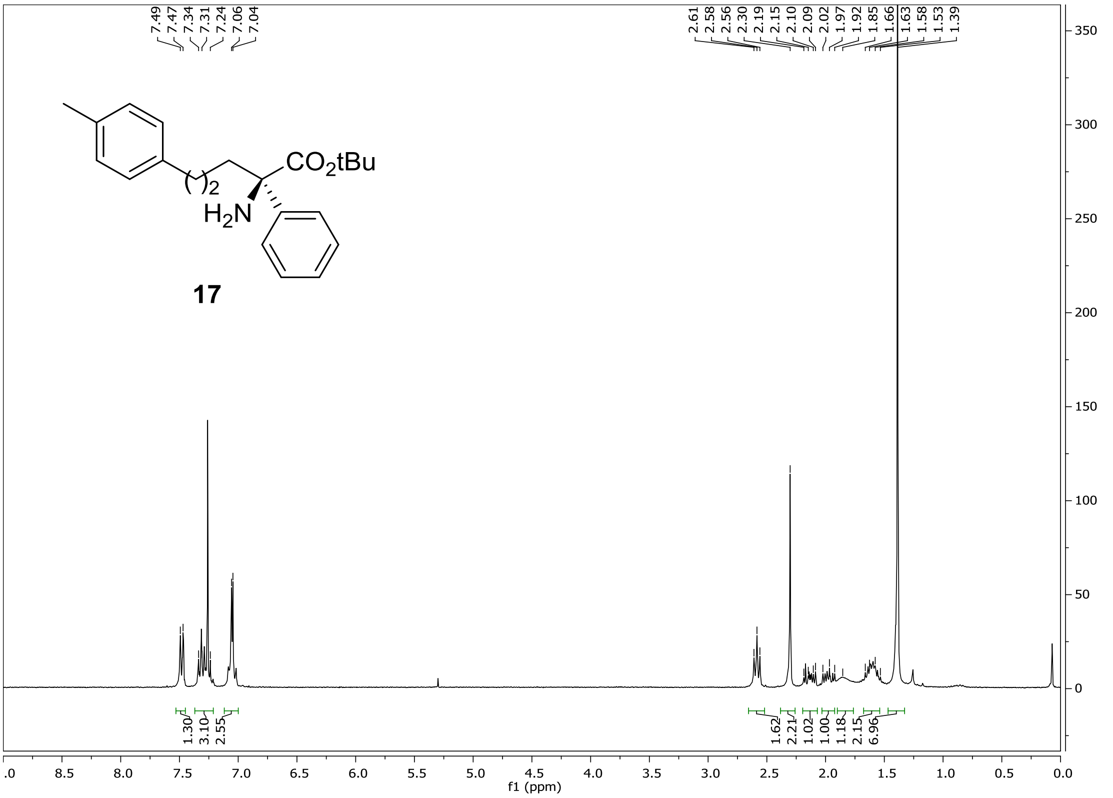

175.31
144.18
128.03
126.90
126.38
81.49
72.89
54.40
38.06
34.48
27.86
21.87
CO2tBu
N
H
14
f1 (ppm)


7.58
7.55
7.35
7.33
7.30
7.26
7.24
3.19
3.16
3.12
2.81
2.80
2.77
2.73
2.62
2.16
2.13
2.10
2.06
2.03
1.98
1.71
1.67
1.50
1.48
1.40
1.37
1.34
1.30
1.03
1.00
0.98
CO2tBu
N
H
15
1.51
2.33
0.84
1.00
0.72
0.96
1.00
0.97
1.30
8.64
1.04
2.88
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
.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)

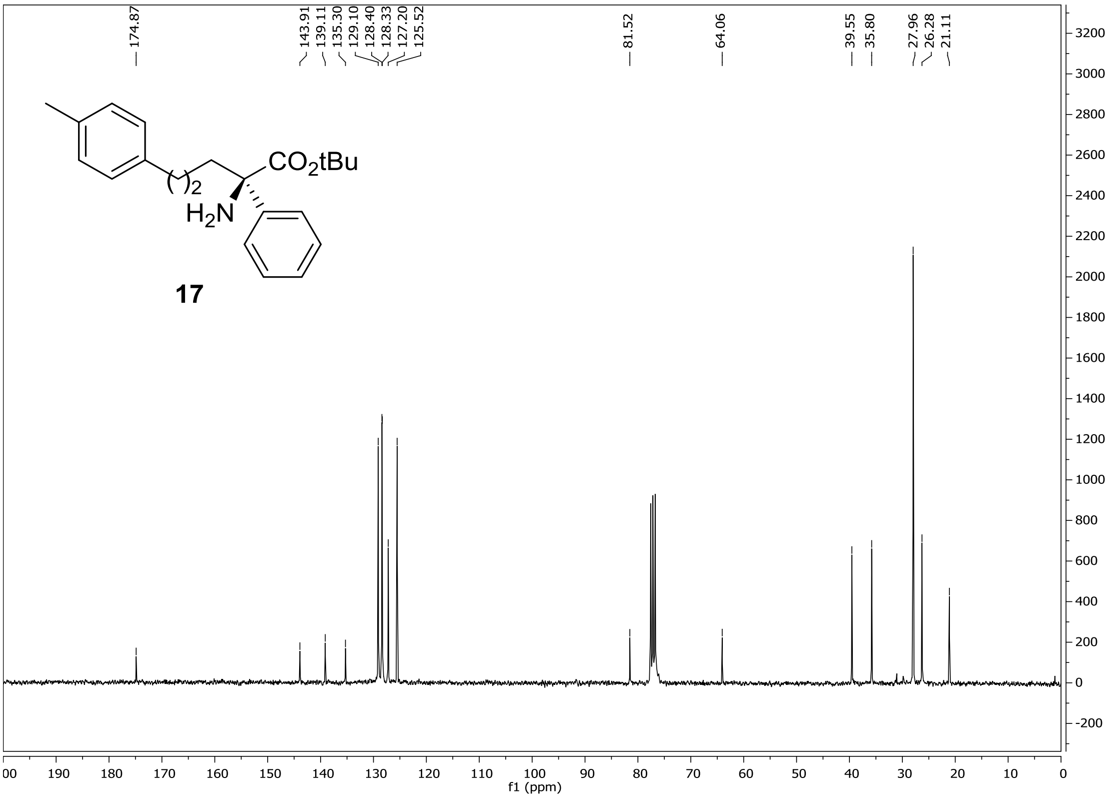

175.29
144.17
128.02
126.87
126.28
81.38
72.46
60.64
37.46
32.05
29.75
27.83
11.48
CO2tBu
N
H
15
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.34
8.32
7.77
7.74
7.48
7.45
7.38
7.36
7.33
7.29
7.26
4.37
4.35
4.33
4.31
2.79
2.77
2.75
2.73
2.71
2.69
2.39
2.37
2.35
2.32
2.17
2.11
2.06
2.04
2.00
1.69
1.67
1.64
1.62
1.55
1.06
1.04
CO_2tBu
N
Ph
O
NO_2
16
1.40
1.86
1.55
1.65
1.08
0.84
1.00
1.12
0.95
1.19
9.31
2.53
f1 (ppm)

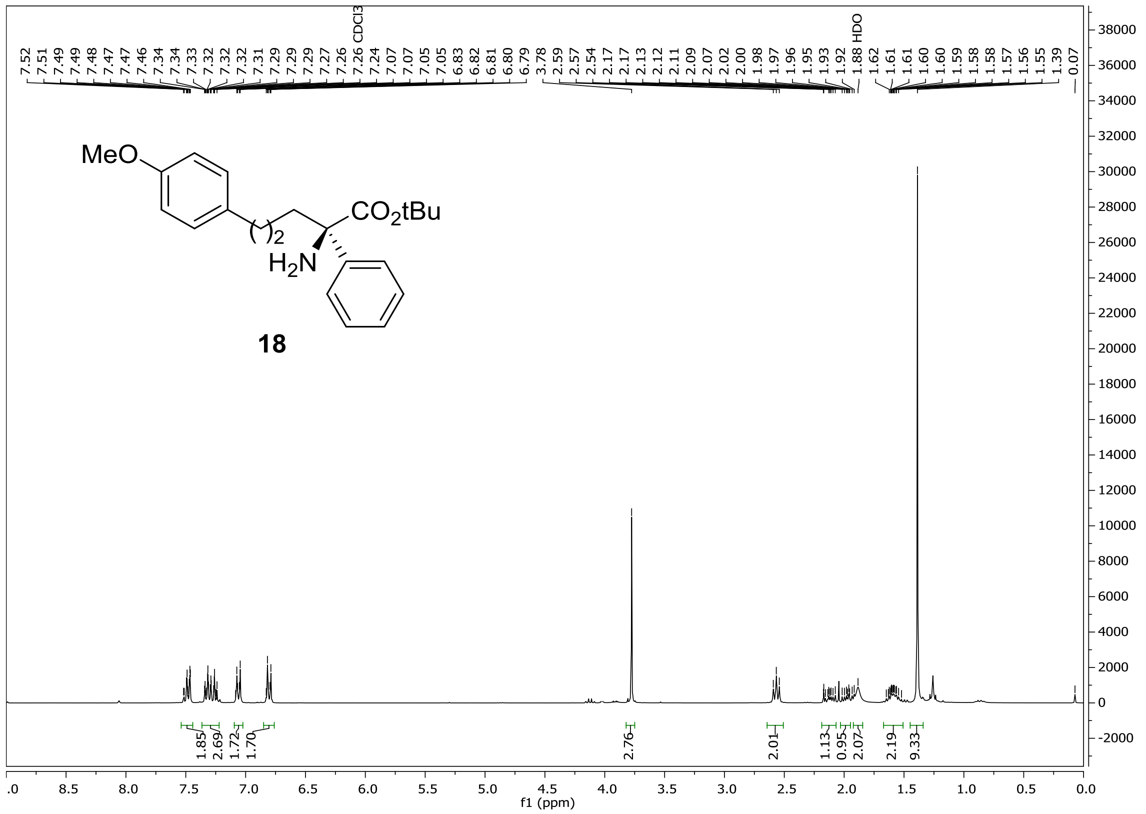

170.31
167.26
148.47
143.57
138.34
127.80
127.48
127.37
124.02
81.93
73.94
56.45
39.08
31.42
28.14
20.95
CO_2tBu
N
Ph
O
NO_2
16
CH2Cl2
Acetone
f1 (ppm)

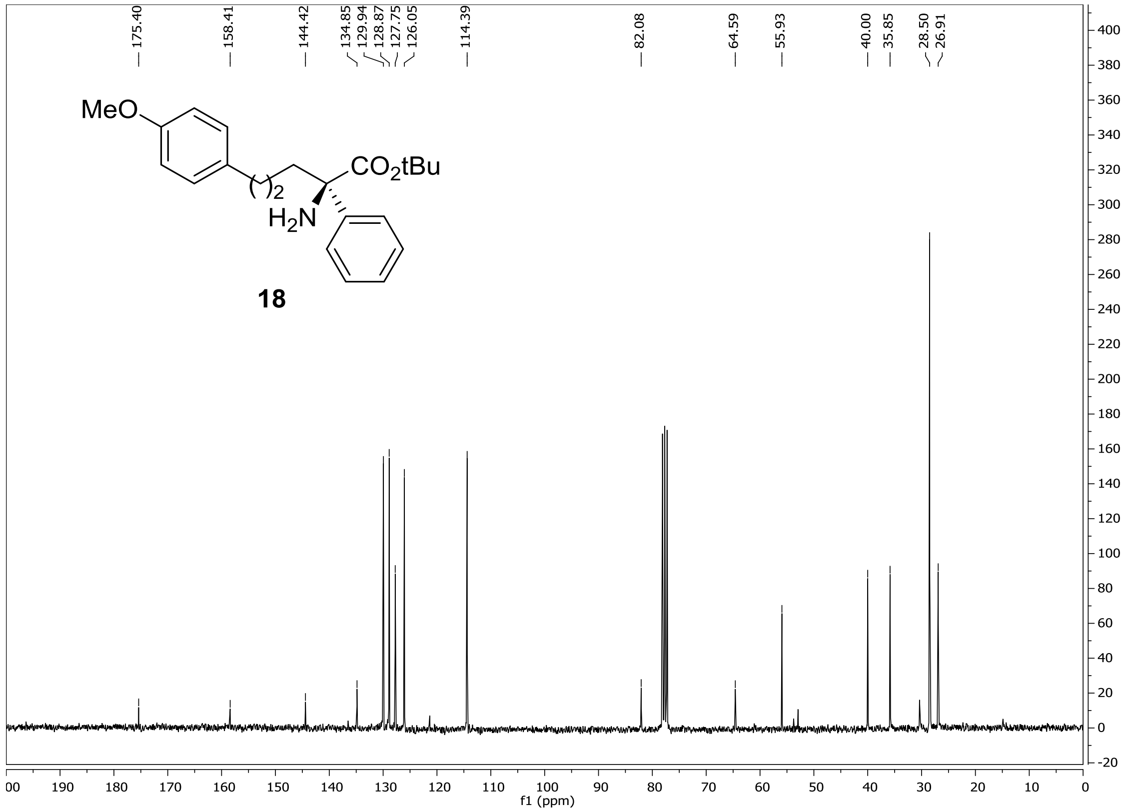

7.49
7.47
7.34
7.31
7.24
7.06
7.04
2.61
2.58
2.56
2.30
2.19
2.15
2.10
2.09
2.02
1.97
1.92
1.85
1.66
1.63
1.58
1.53
1.39
CO2tBu
H2N
2
1.30
3.10
2.55
1.62
2.21
1.02
1.00
1.18
2.15
6.96
f1 (ppm)
350
300
250
200
150
100
50
0

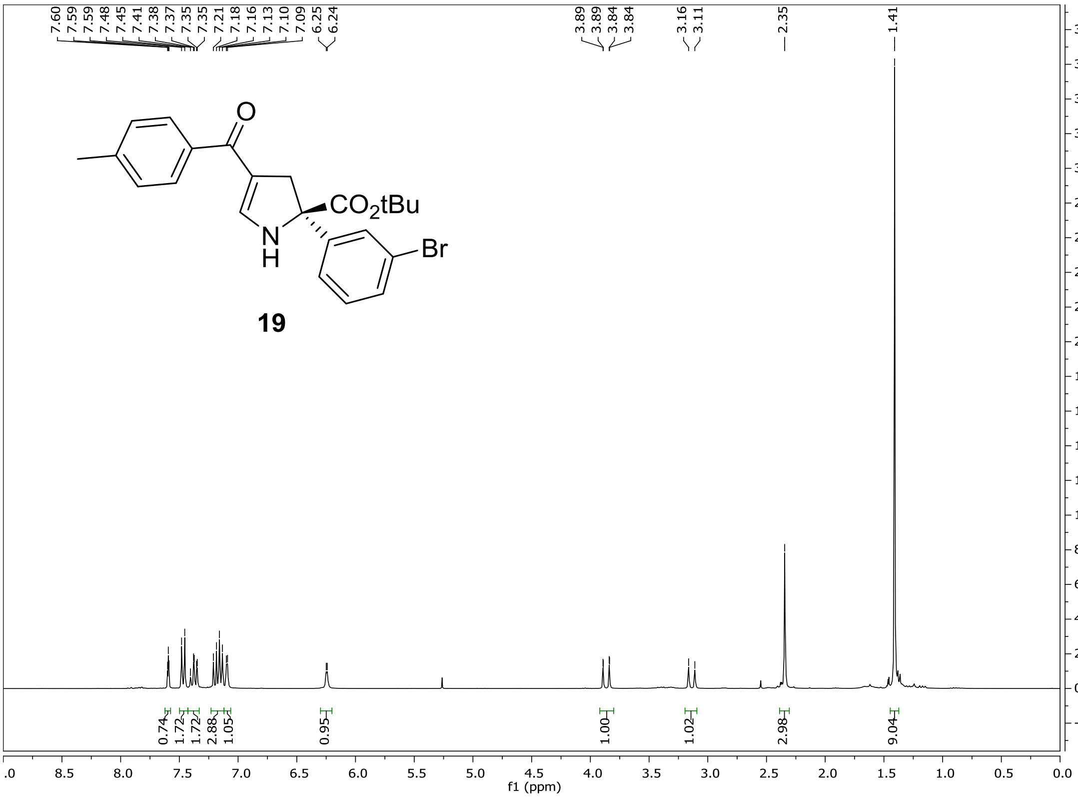
17

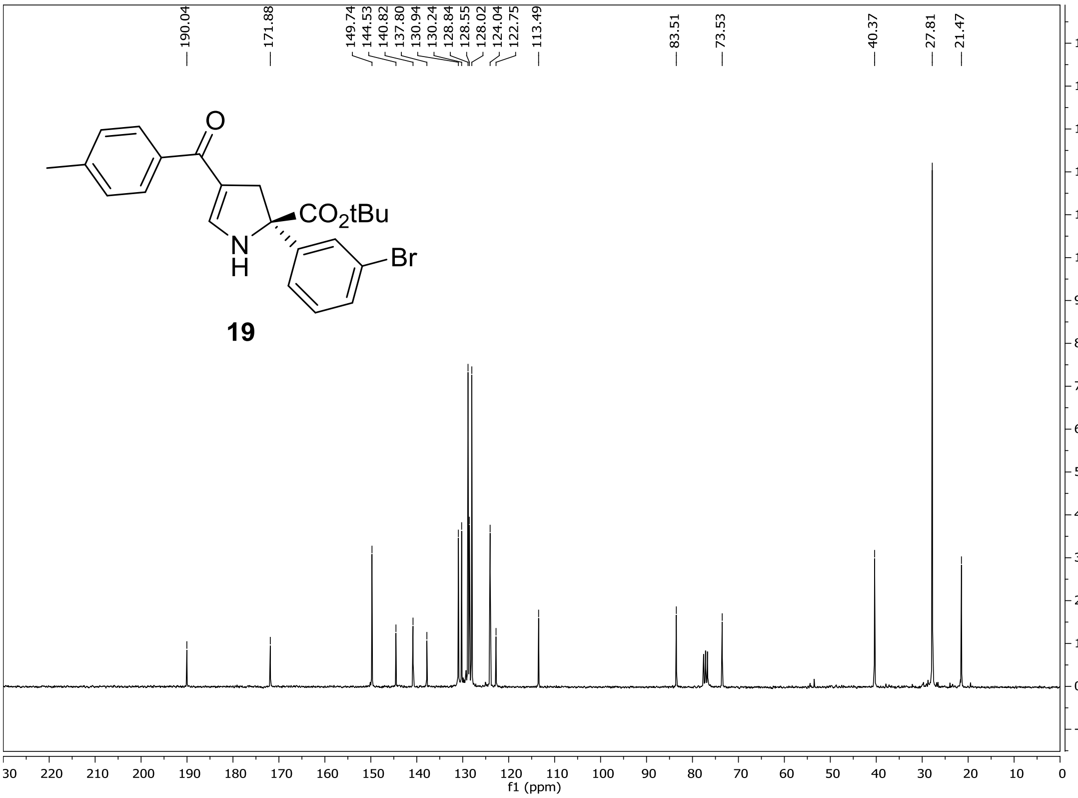

174.87
143.91
139.11
135.30
129.10
128.40
128.33
127.20
125.52
81.52
64.06
39.55
35.80
27.96
26.28
21.11
CO2tBu
H2N
2
f1 (ppm)
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

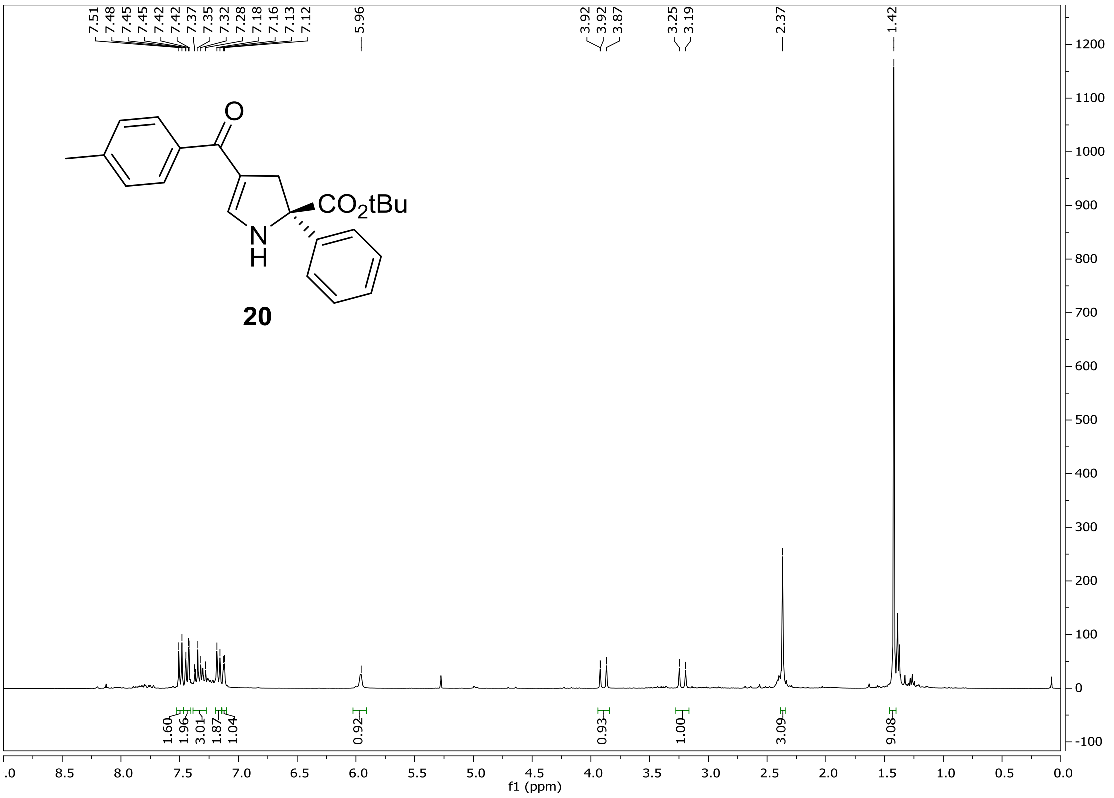
17

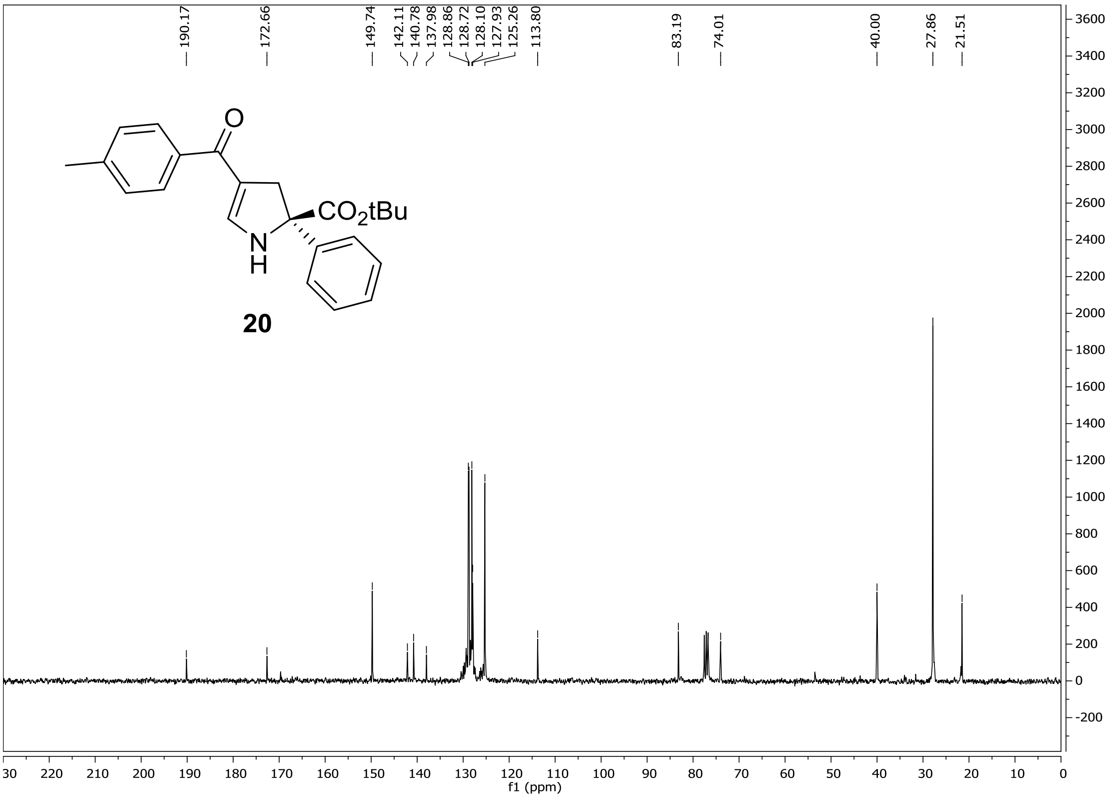

7.52
7.51
7.49
7.49
7.48
7.47
7.47
7.46
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.29
7.29
7.29
7.27
7.26 CDCl3
7.24
7.07
7.07
7.05
7.05
6.83
6.82
6.81
6.80
6.79
3.78
2.59
2.57
2.54
2.17
2.17
2.13
2.12
2.11
2.09
2.07
2.02
2.00
1.98
1.97
1.96
1.95
1.93
1.92
1.88 HDO
1.62
1.61
1.61
1.60
1.60
1.59
1.58
1.58
1.57
1.56
1.55
1.39
0.07
MeO
CO2tBu
2
H2N
18
1.85
2.69
1.72
1.70
2.76
2.01
1.13
0.95
2.07
2.19
9.33
f1 (ppm)

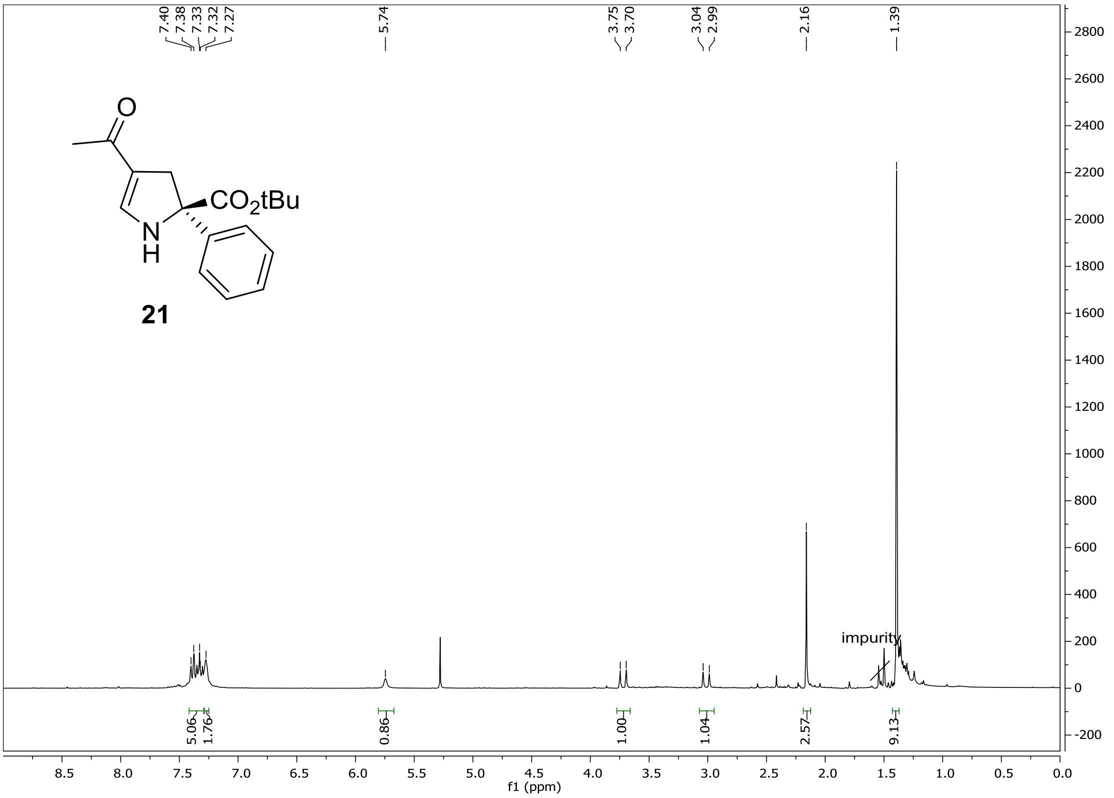

175.40
158.41
144.42
134.85
129.94
128.87
127.75
126.05
114.39
82.08
64.59
55.93
40.00
35.85
28.50
26.91
MeO
CO2tBu
2
H2N
18
f1 (ppm)

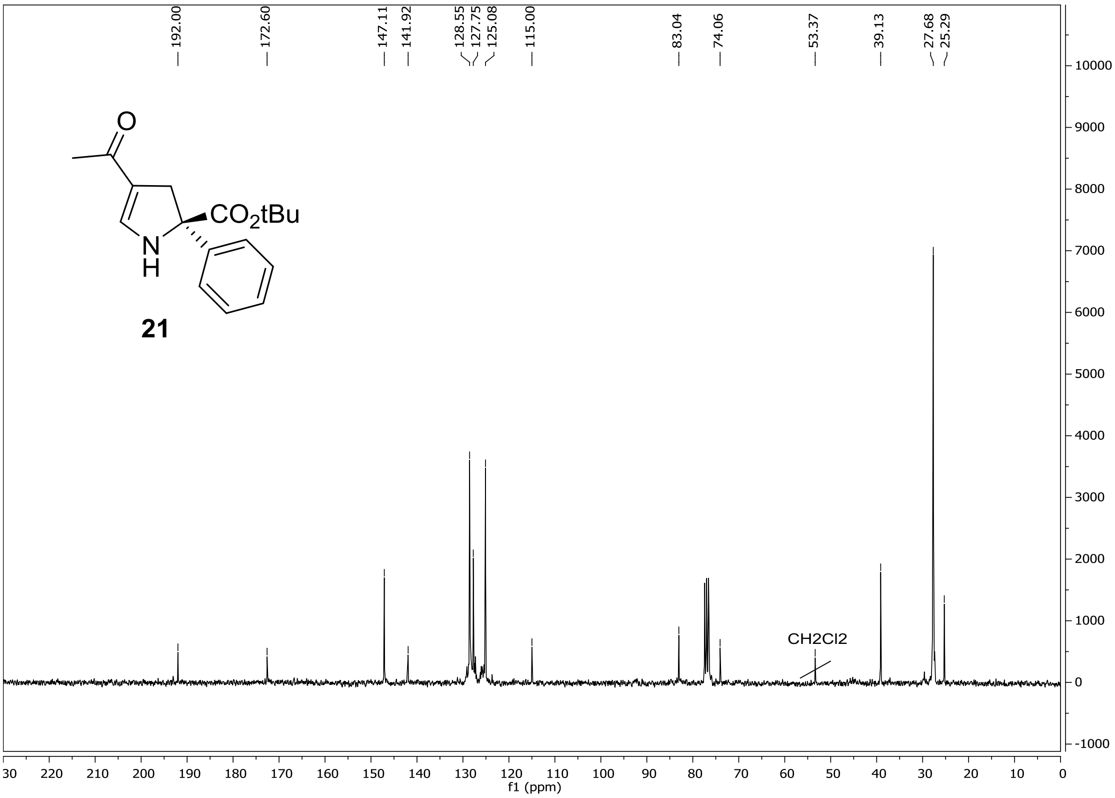

7.60
7.59
7.59
7.48
7.45
7.41
7.38
7.37
7.35
7.35
7.21
7.18
7.16
7.13
7.10
7.09
6.25
6.24
3.89
3.89
3.84
3.84
3.16
3.11
2.35
1.41
O
CO2tBu
N
H
Br
19
0.74
1.72
1.72
2.88
1.05
0.95
1.00
1.02
2.98
9.04
f1 (ppm)

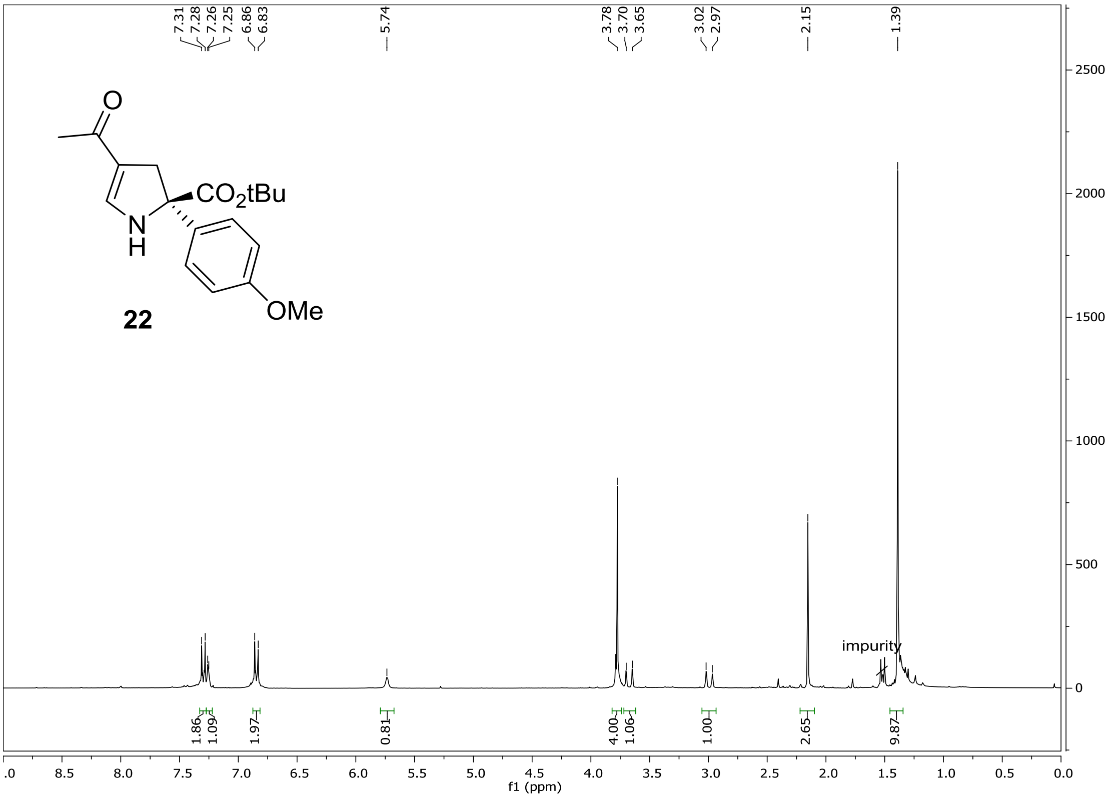

190.04
171.88
149.74
144.53
140.82
137.80
130.94
130.24
128.84
128.55
128.02
124.04
122.75
113.49
83.51
73.53
40.37
27.81
21.47
O
CO2tBu
N
H
Br
19
f1 (ppm)

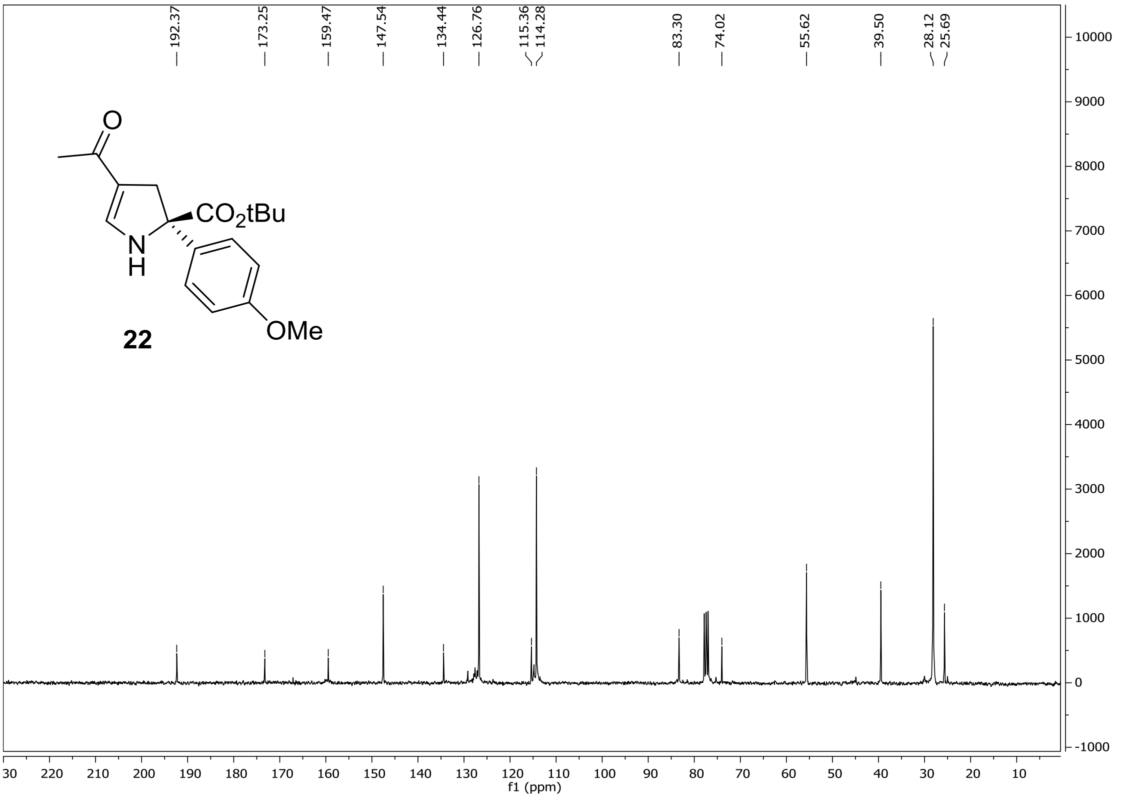

7.51
7.48
7.45
7.45
7.42
7.42
7.37
7.35
7.32
7.28
7.18
7.16
7.13
7.12
5.96
3.92
3.92
3.87
3.25
3.19
2.37
1.42
O
CO$_2$tBu
N
H
20
1.60
1.96
3.01
1.87
1.04
0.92
0.93
1.00
3.09
9.08
f1 (ppm)

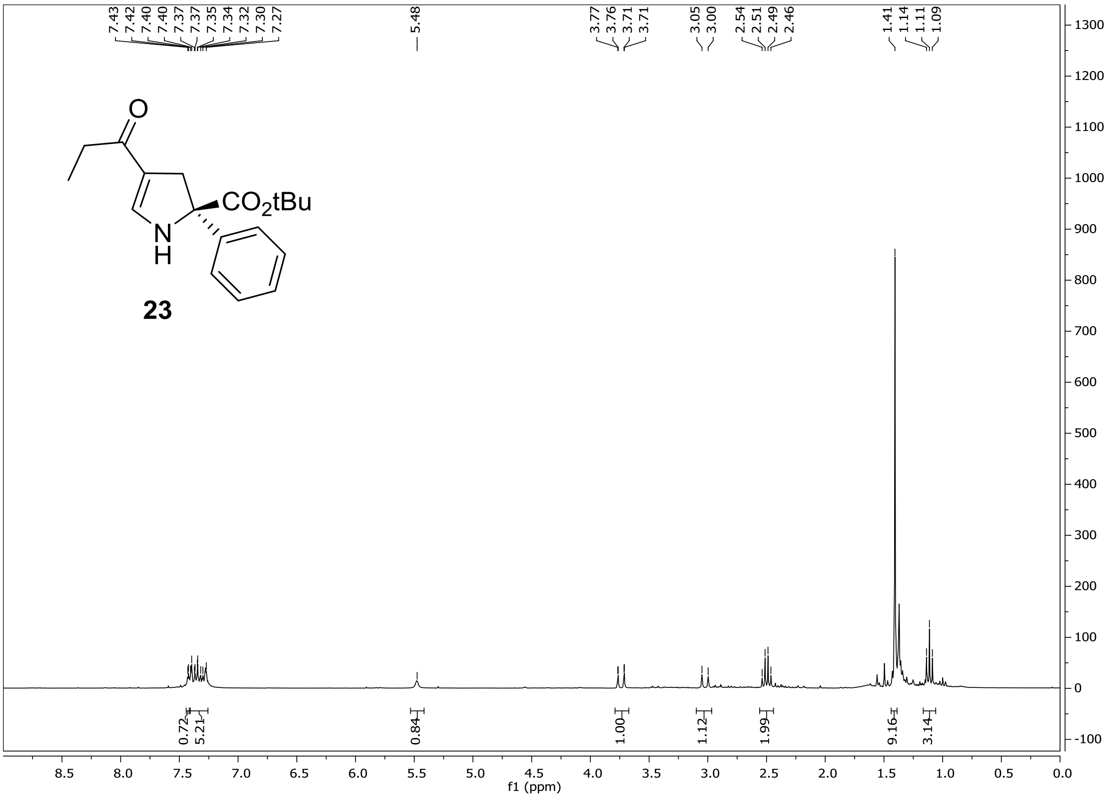

190.17
172.66
149.74
142.11
140.78
137.98
128.86
128.72
128.10
127.93
125.26
113.80
83.19
74.01
40.00
27.86
21.51
O
CO$_2$tBu
N
H
20
f1 (ppm)

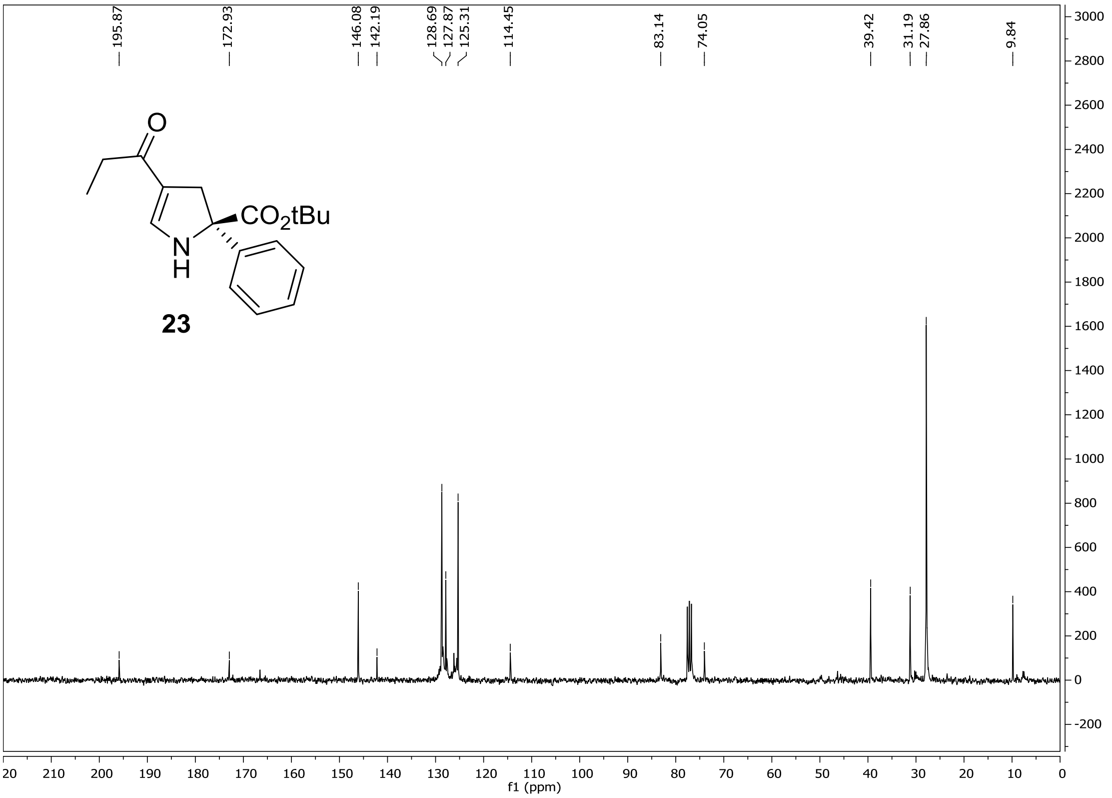

7.40
7.38
7.33
7.32
7.27
5.74
3.75
3.70
3.04
2.99
2.16
1.39
O
CO2tBu
N
H
21
impurity
5.06
1.76
0.86
1.00
1.04
2.57
9.13
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

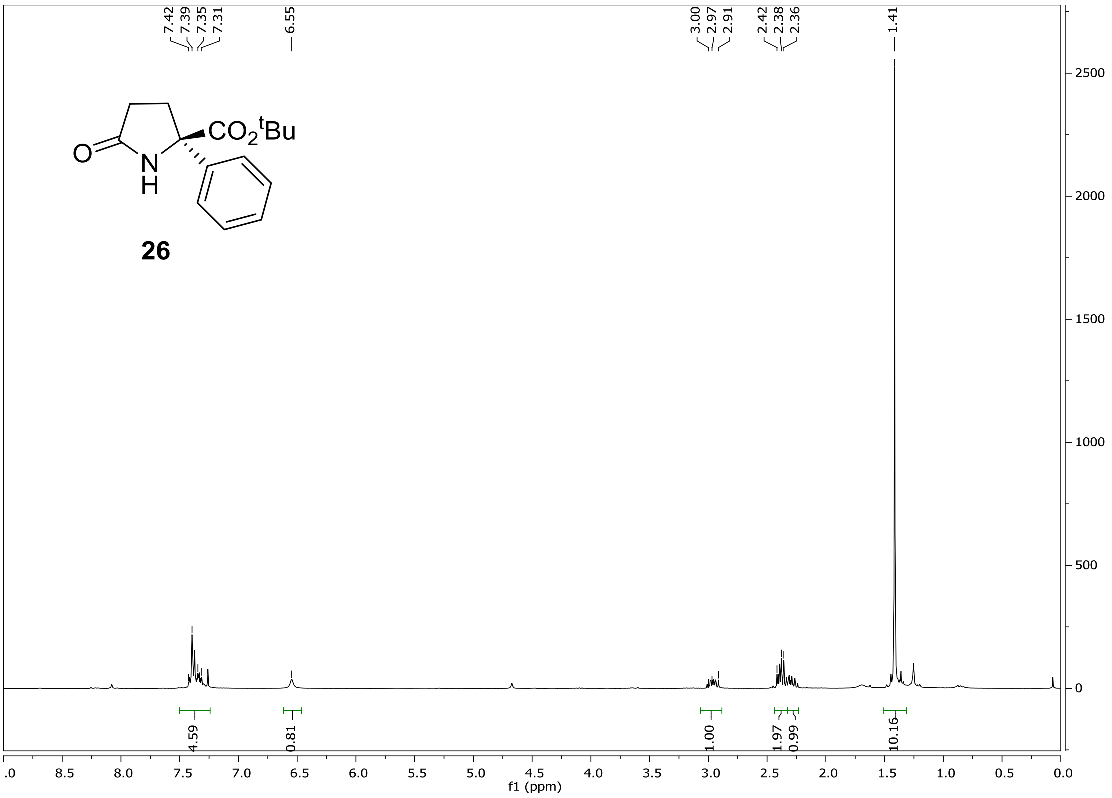

192.00
172.60
147.11
141.92
128.55
127.75
125.08
115.00
83.04
74.06
53.37
39.13
27.68
25.29
O
CO2tBu
N
H
21
CH2Cl2
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

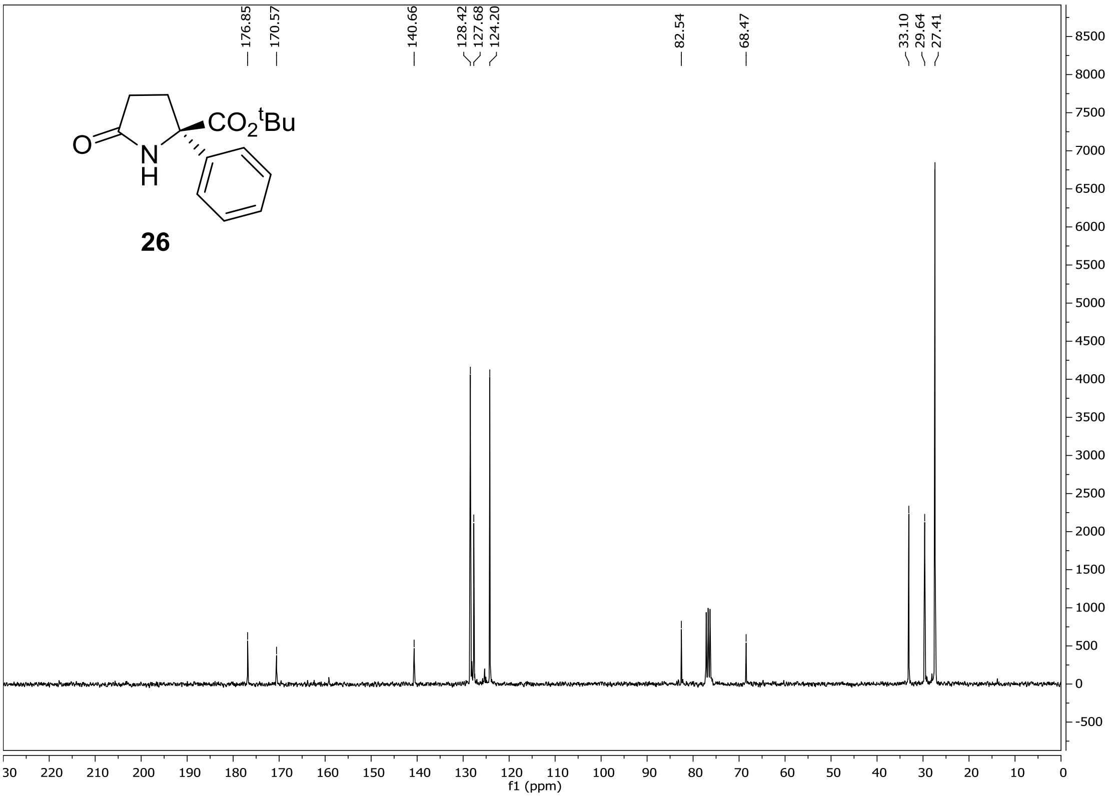

7.31
7.28
7.26
7.25
6.86
6.83
5.74
3.78
3.70
3.65
3.02
2.97
2.15
1.39
CO$_2$tBu
N
H
O
OMe
22
impurity
1.86
1.09
1.97
0.81
4.00
1.06
1.00
2.65
9.87
f1 (ppm)
2500
2000
1500
1000
500
0


192.37
173.25
159.47
147.54
134.44
126.76
115.36
114.28
83.30
74.02
55.62
39.50
28.12
25.69
CO$_2$tBu
N
H
O
OMe
22
f1 (ppm)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


7.43
7.42
7.40
7.37
7.37
7.35
7.34
7.32
7.30
7.27
5.48
3.77
3.76
3.71
3.71
3.05
3.00
2.54
2.51
2.49
2.46
1.41
1.14
1.11
1.09
O
CO2tBu
N
H
23
0.72
5.21
0.84
1.00
1.12
1.99
9.16
3.14
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)

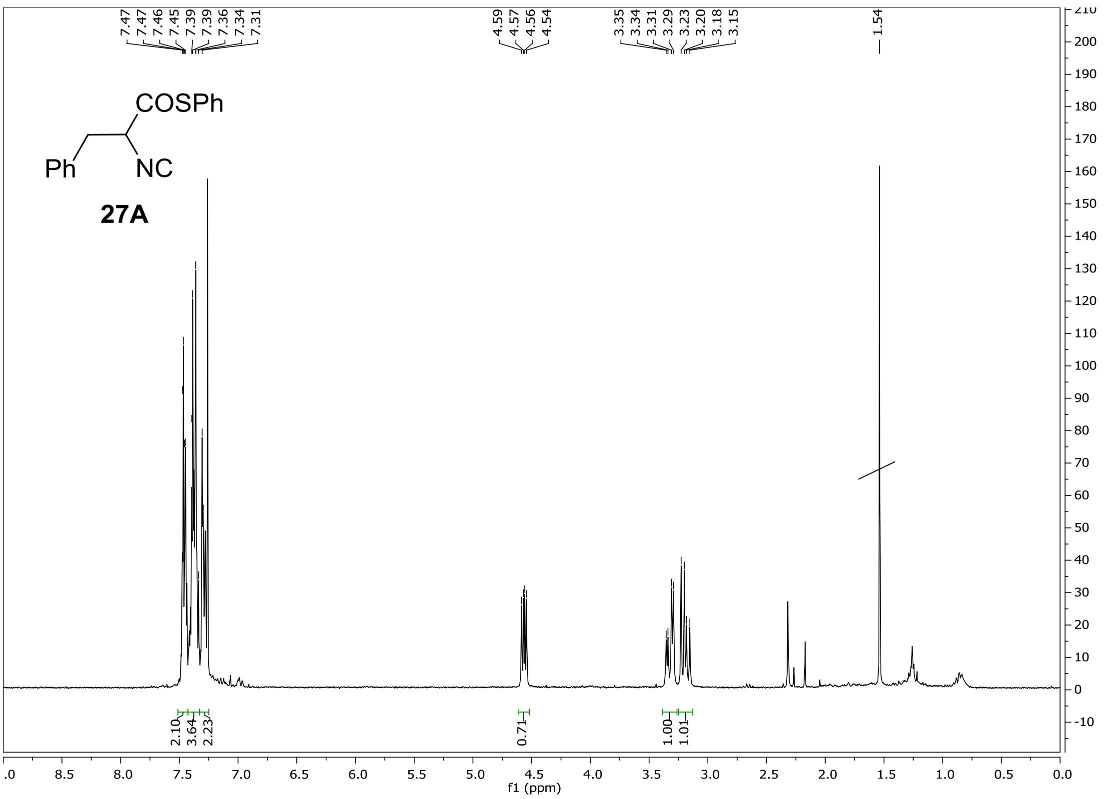

195.87
172.93
146.08
142.19
128.69
127.87
125.31
114.45
83.14
74.05
39.42
31.19
27.86
9.84
O
CO2tBu
N
H
23
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

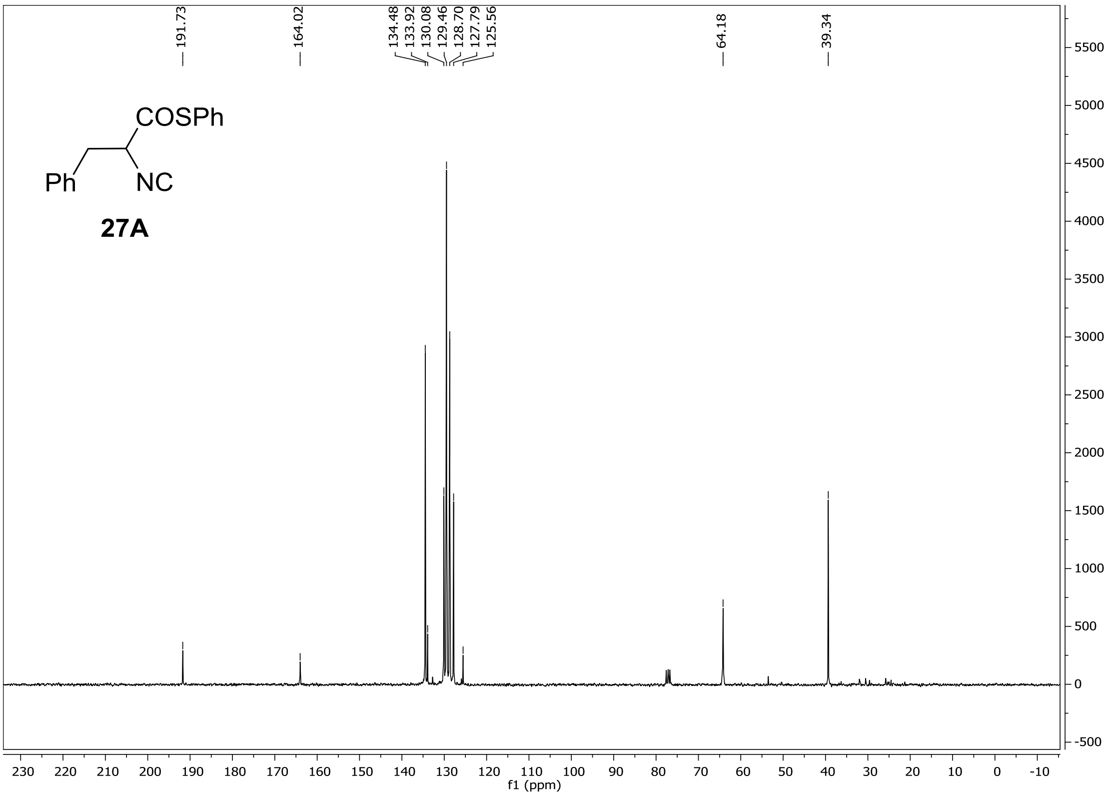

7.42
7.39
7.35
7.31
6.55
3.00
2.97
2.91
2.42
2.38
2.36
1.41
CO2tBu
O
N
H
26
4.59
0.81
1.00
1.97
0.99
10.16
2500
2000
1500
1000
500
0
f1 (ppm)

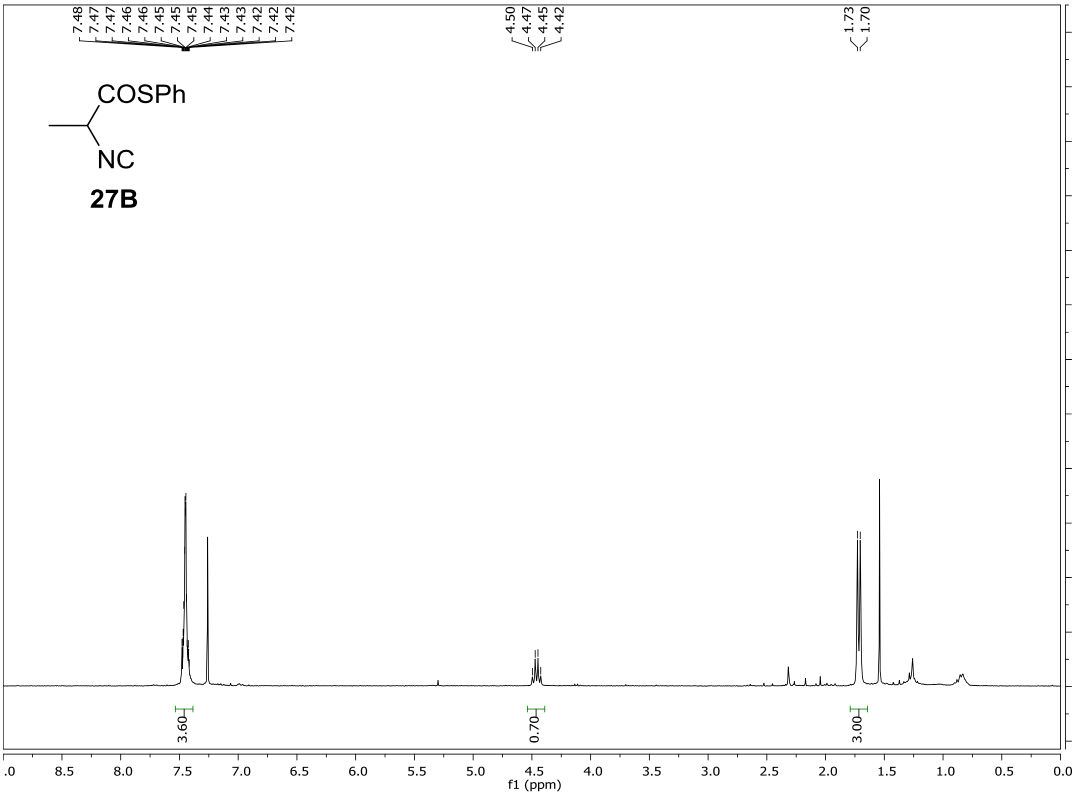

176.85
170.57
140.66
128.42
127.68
124.20
82.54
68.47
33.10
29.64
27.41
CO2tBu
O
N
H
26
f1 (ppm)

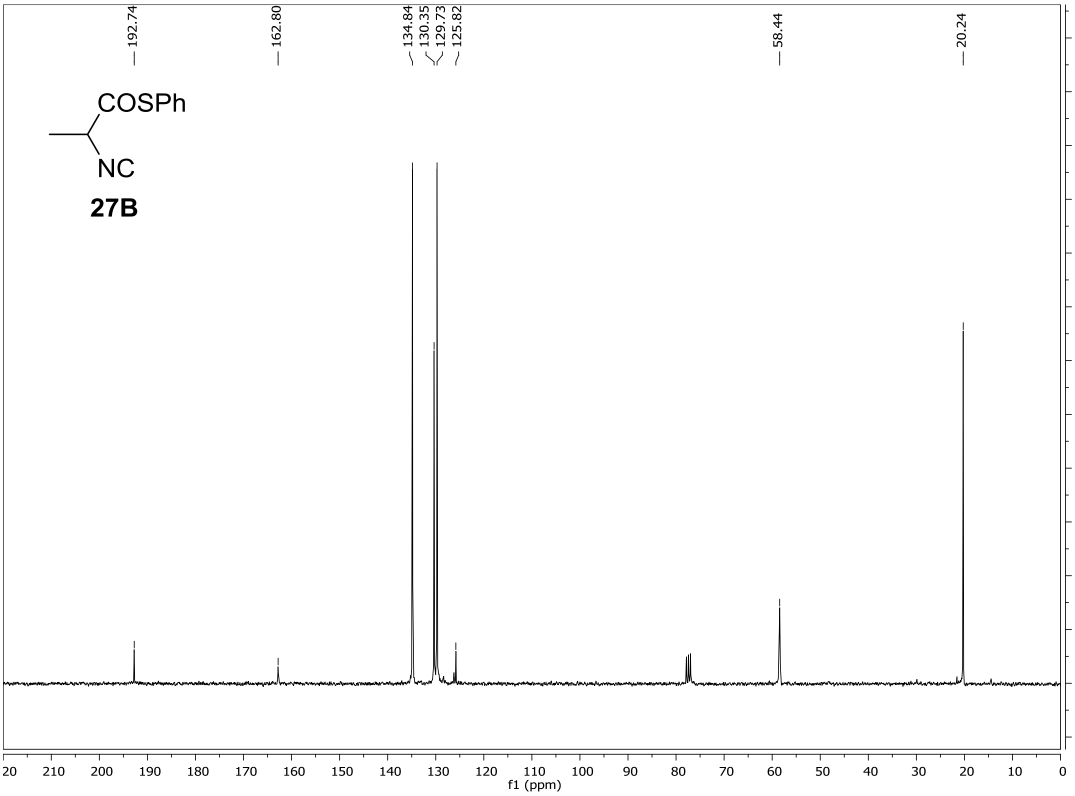
5.5.3. Chapter 3

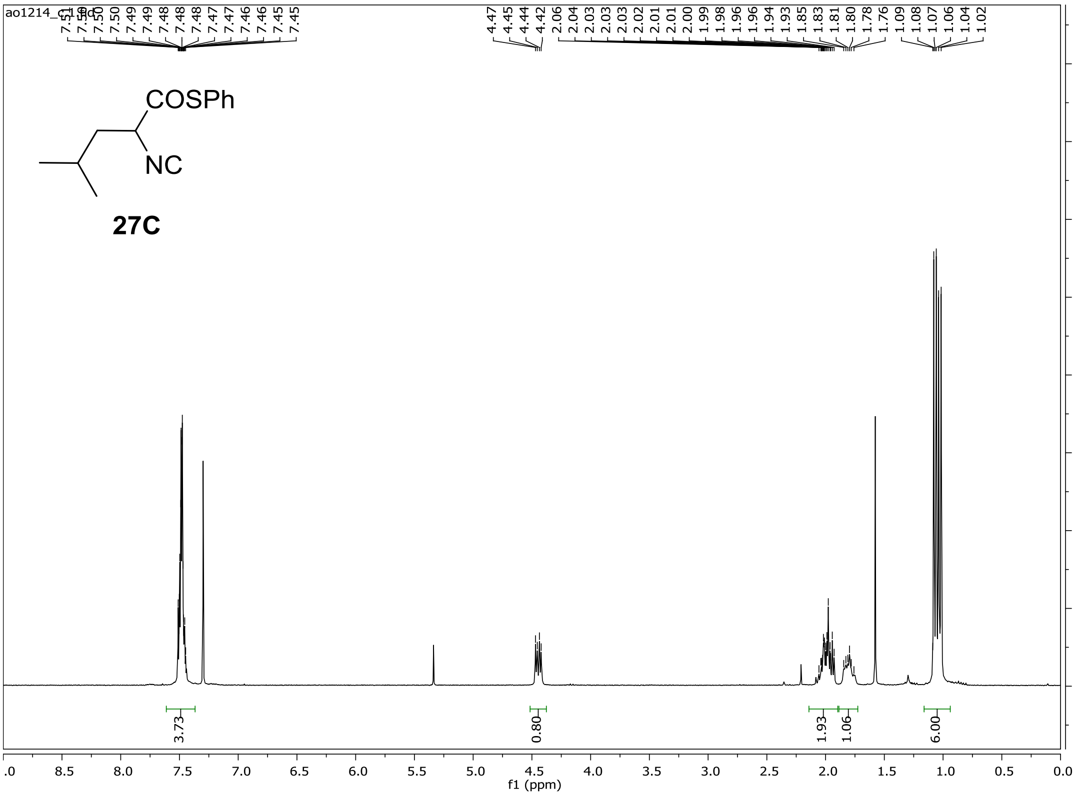
*5.5.3.1. Isocyano(thio)acetates **27-35, 62 and 73***

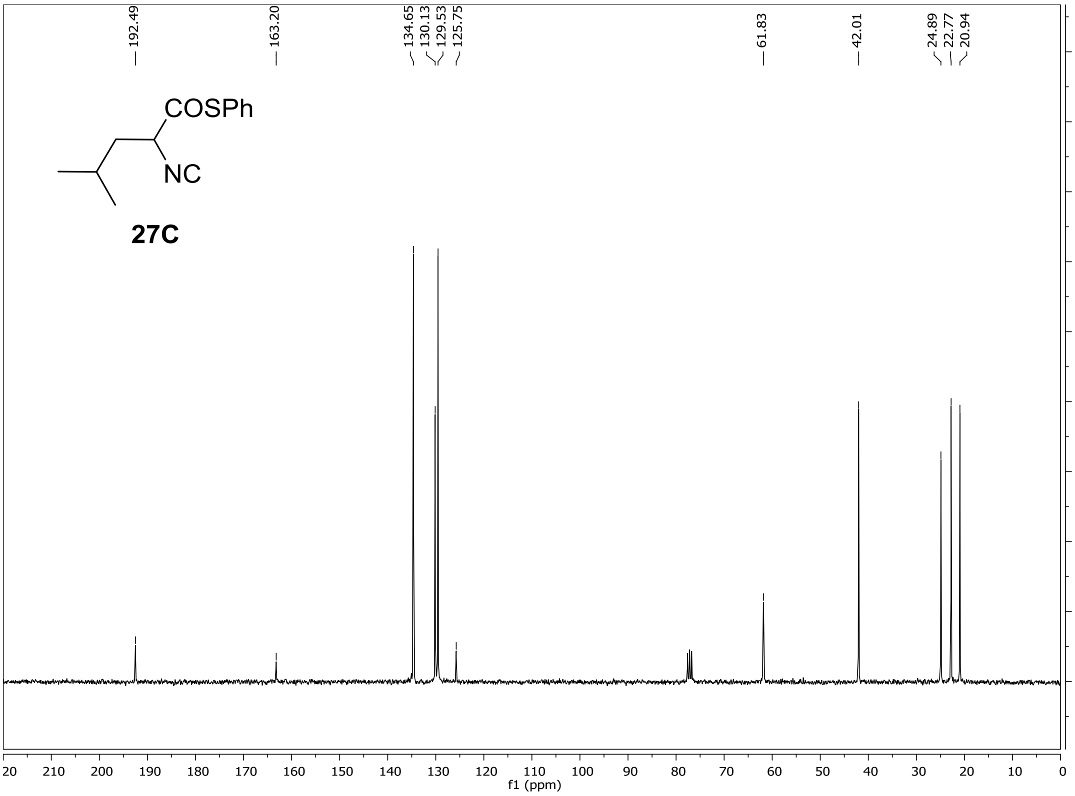


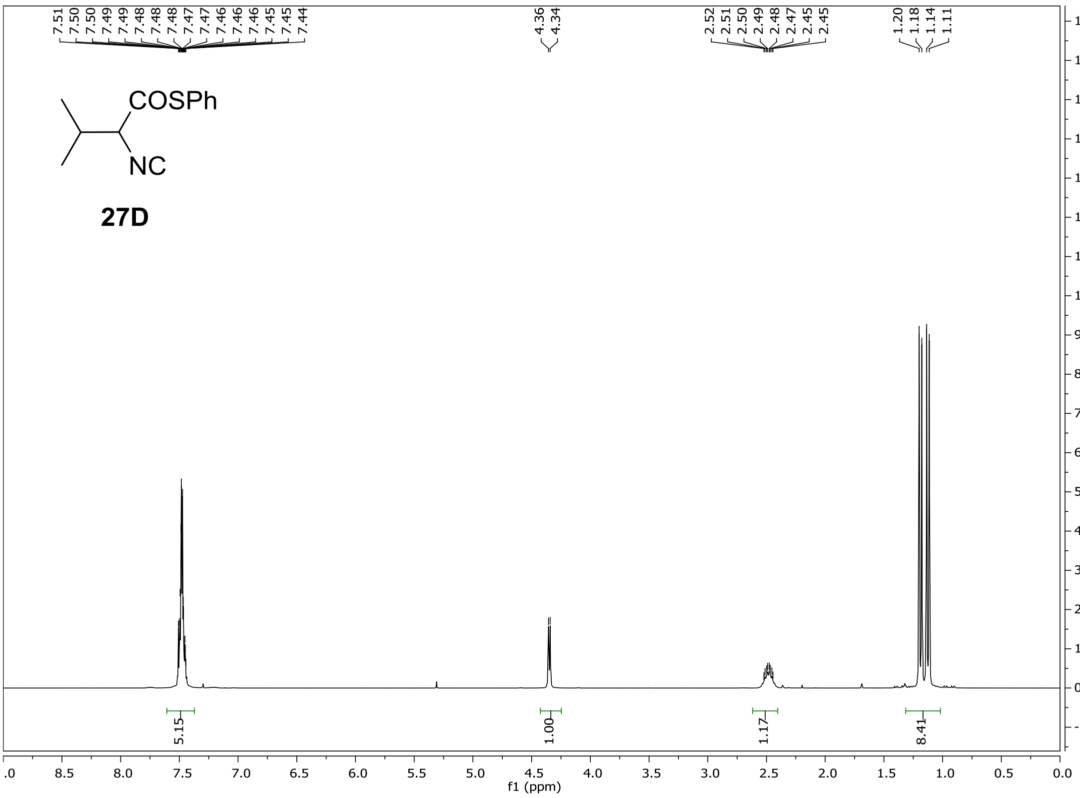


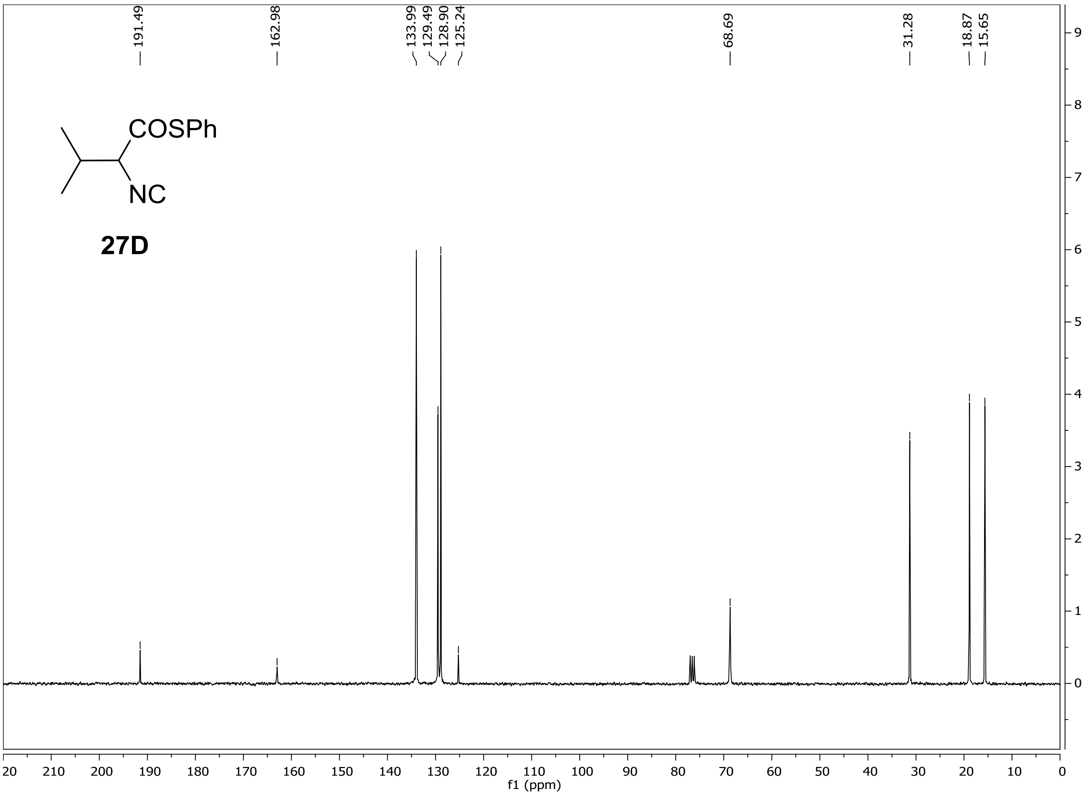

7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.44
7.43
7.43
7.42
7.42
7.42
4.50
4.47
4.45
4.42
1.73
1.70
COSPh
NC
27B
3.60
0.70
3.00
f1 (ppm)

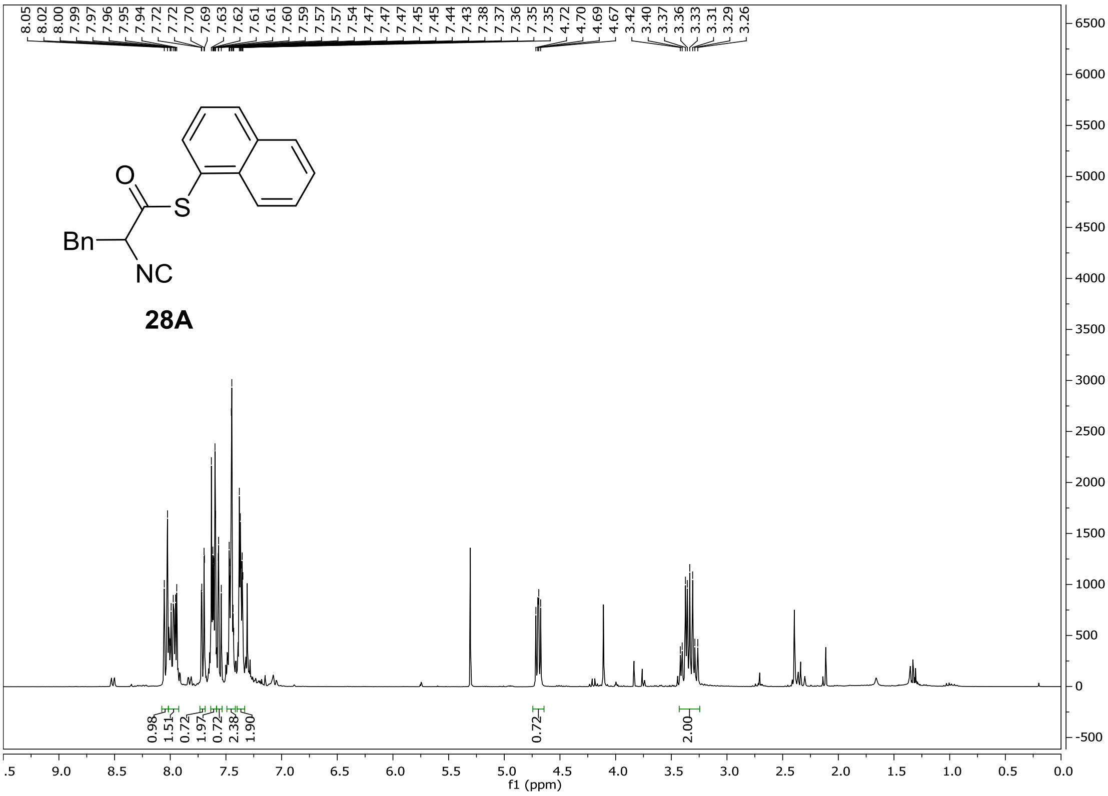

192.74
162.80
134.84
130.35
129.73
125.82
58.44
20.24
COSPh
NC
27B
f1 (ppm)

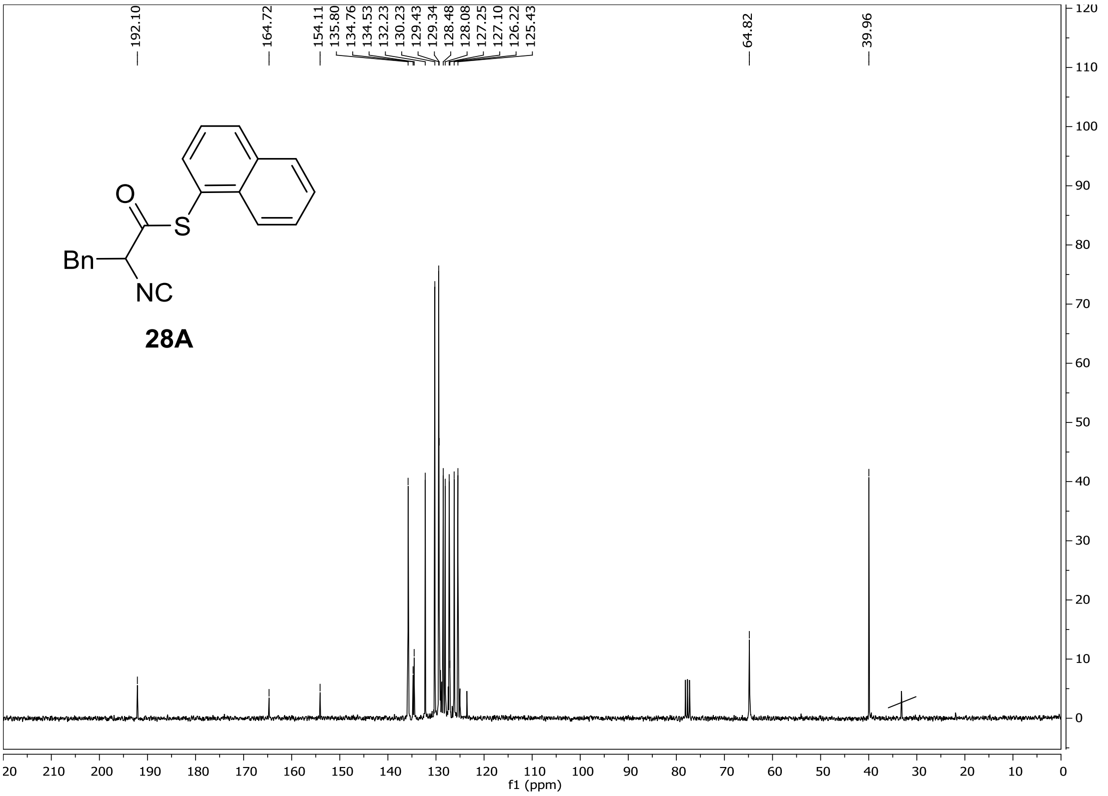

7.51
7.50
7.50
7.50
7.49
7.49
7.48
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.45
4.47
4.45
4.44
4.42
2.06
2.04
2.03
2.03
2.03
2.02
2.01
2.01
2.00
1.99
1.98
1.96
1.96
1.94
1.93
1.85
1.83
1.81
1.80
1.78
1.76
1.09
1.08
1.07
1.06
1.04
1.02
COSPh
NC
27C
400
350
300
250
200
150
100
50
0
3.73
0.80
1.93
1.06
6.00
.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)

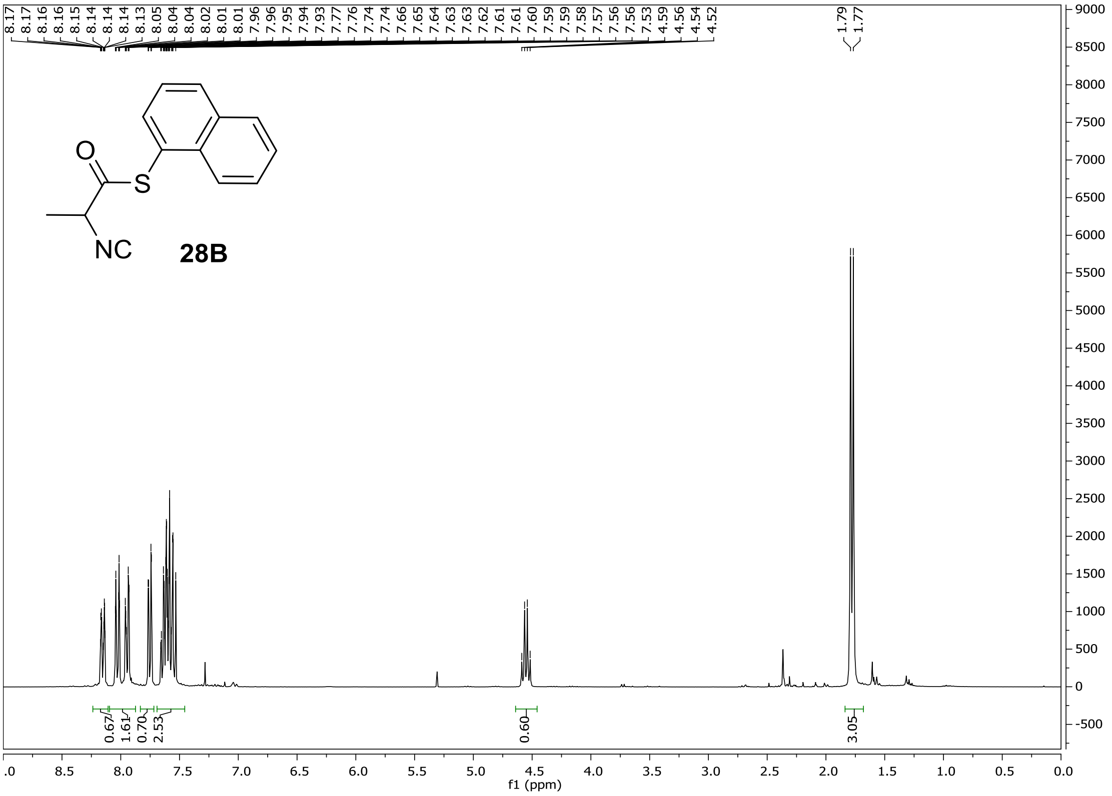

192.49
163.20
134.65
130.13
129.53
125.75
61.83
42.01
24.89
22.77
20.94
COSPh
NC
27C
4500
4000
3500
3000
2500
2000
1500
1000
500
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

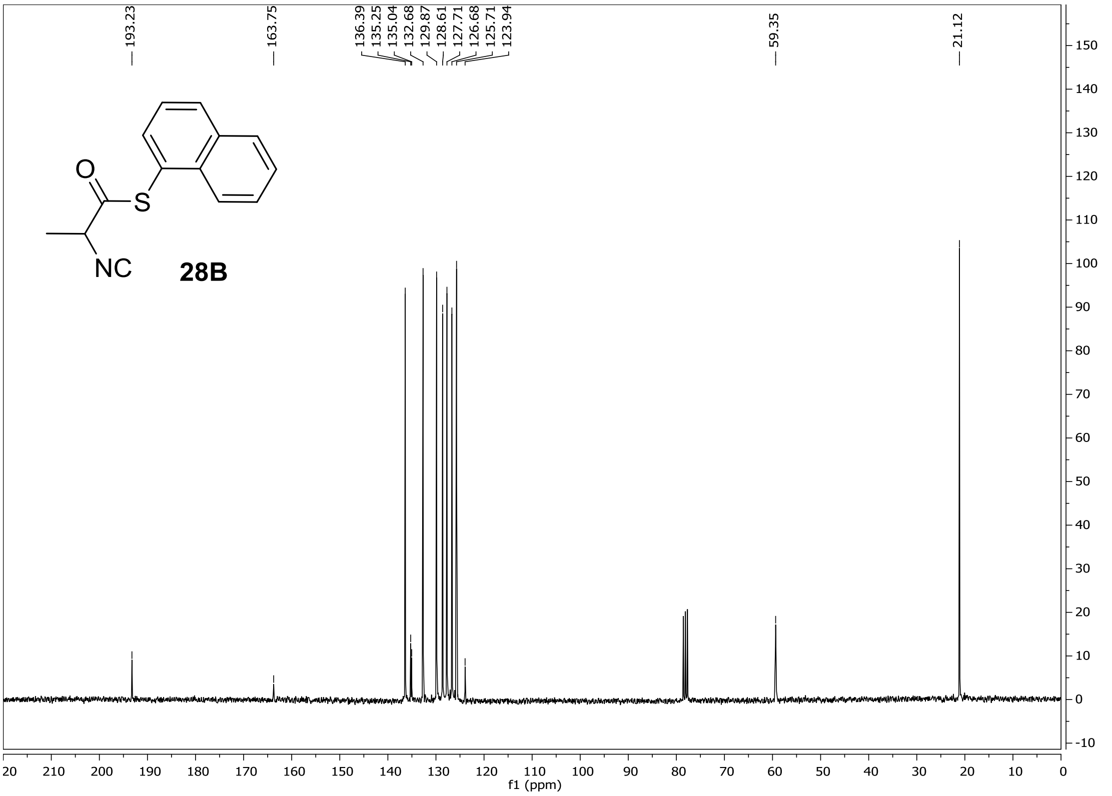

7.51
7.50
7.50
7.49
7.49
7.48
7.48
7.48
7.47
7.47
7.46
7.46
7.46
7.45
7.45
7.44
4.36
4.34
2.52
2.51
2.50
2.49
2.48
2.47
2.45
2.45
1.20
1.18
1.14
1.11
COSPh
NC
27D
5.15
1.00
1.17
8.41
f1 (ppm)

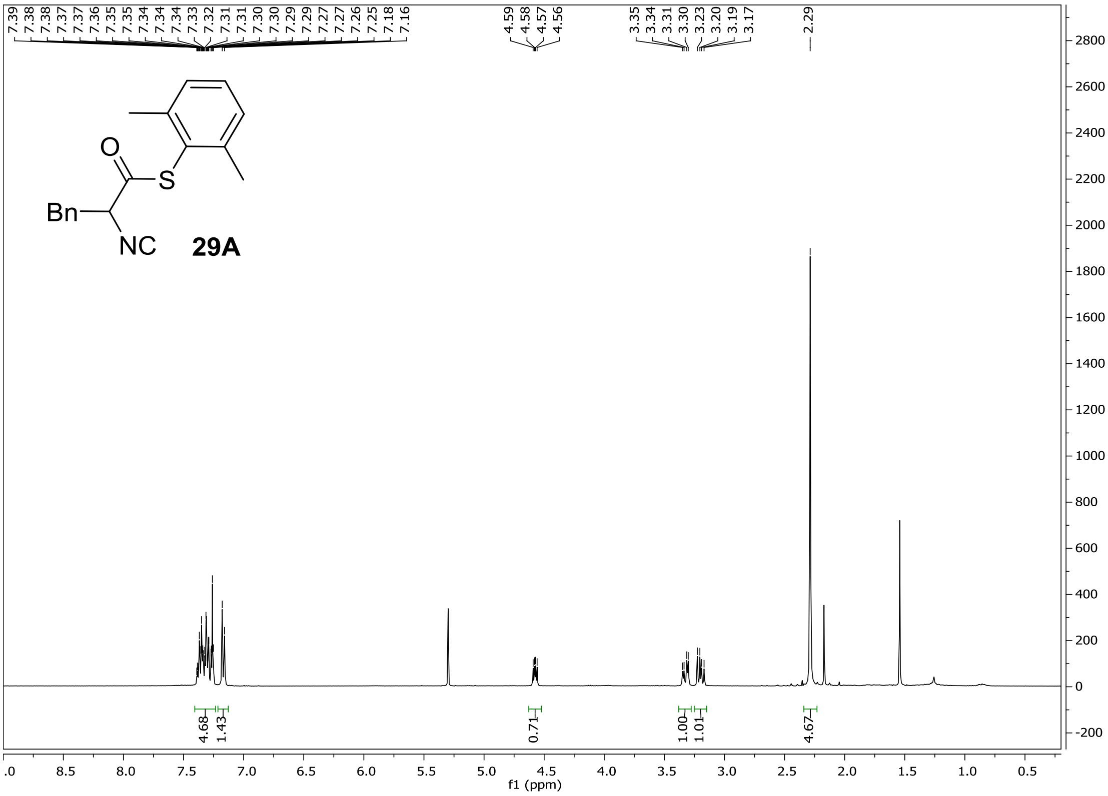

191.49
162.98
133.99
129.49
128.90
125.24
68.69
31.28
18.87
15.65
COSPh
NC
27D
f1 (ppm)

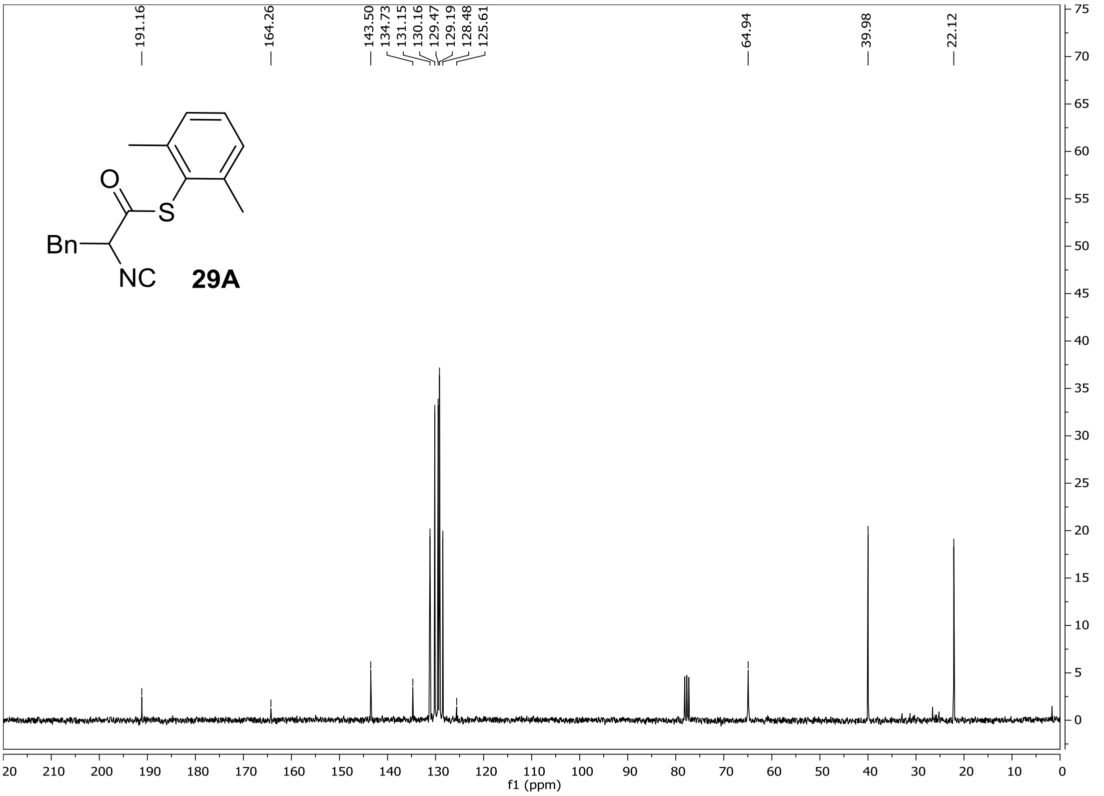

8.05 8.02 8.00 7.99 7.97 7.96 7.95 7.94 7.72 7.72 7.70 7.69 7.63 7.62 7.61 7.61 7.60 7.59 7.57 7.57 7.54 7.47 7.47 7.47 7.45 7.45 7.44 7.43 7.38 7.37 7.36 7.35 7.35 4.72 4.70 4.69 4.67 3.42 3.40 3.37 3.36 3.33 3.31 3.29 3.26
O
S
Bn
NC
28A
0.98 1.51 0.72 1.97 0.72 2.38 1.90
0.72
2.00
f1 (ppm)

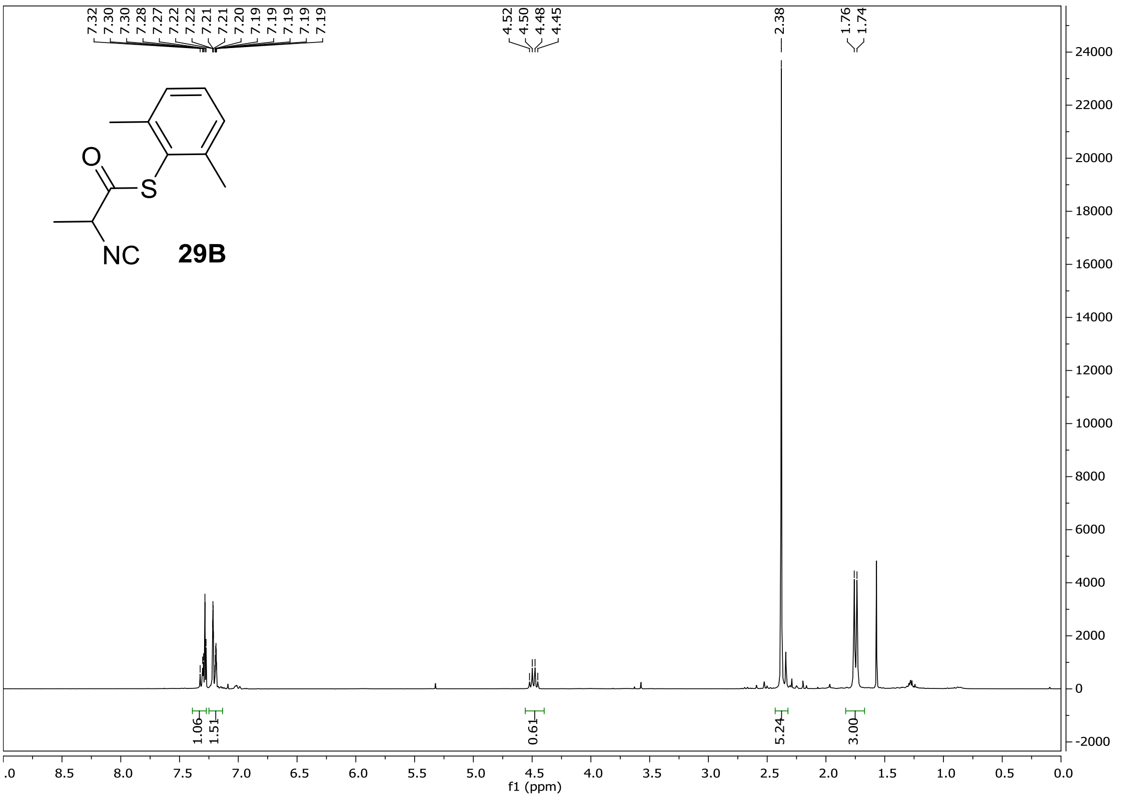

192.10
164.72
154.11 135.80 134.76 134.53 132.23 130.23 129.43 129.34 128.48 128.08 127.25 127.10 126.22 125.43
64.82
39.96
O
S
Bn
NC
28A
f1 (ppm)

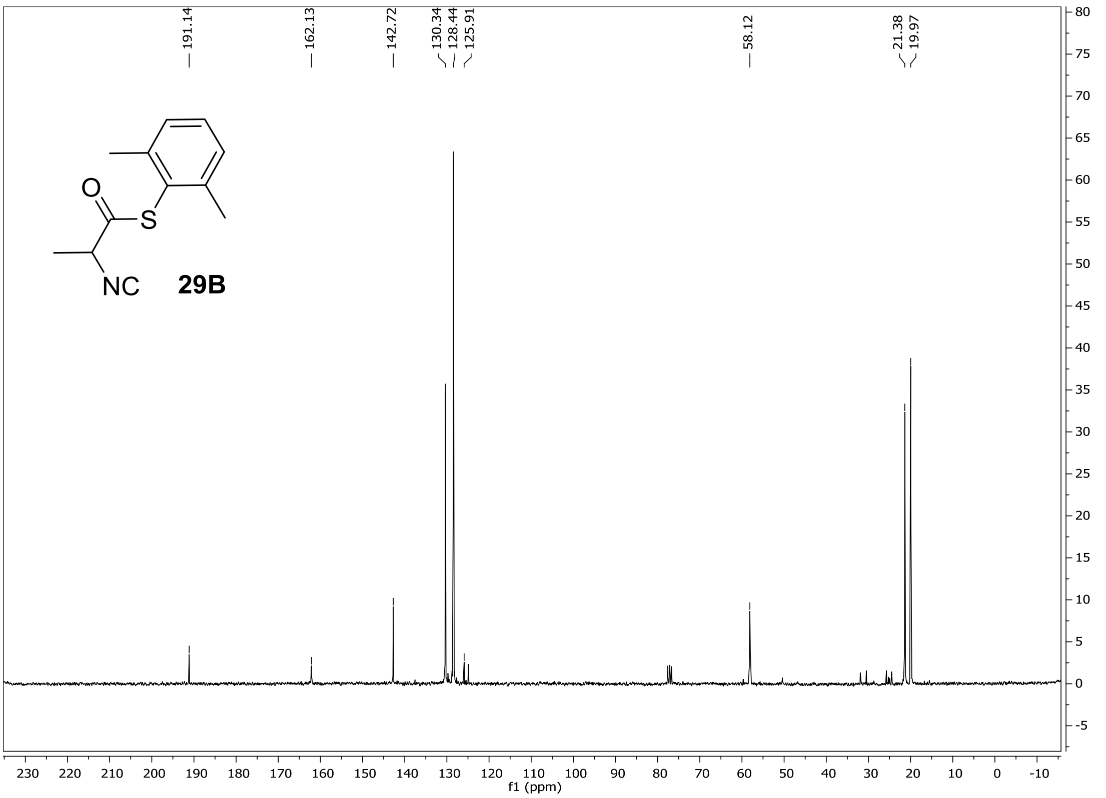

8.17
8.17
8.16
8.15
8.14
8.14
8.14
8.13
8.05
8.04
8.04
8.02
8.01
8.01
7.96
7.96
7.95
7.94
7.93
7.77
7.76
7.74
7.74
7.66
7.65
7.64
7.63
7.63
7.62
7.61
7.61
7.60
7.59
7.59
7.58
7.57
7.56
7.56
7.53
4.59
4.56
4.54
4.52
1.79
1.77
O
S
NC
28B
0.67
1.61
0.70
2.53
0.60
3.05
f1 (ppm)

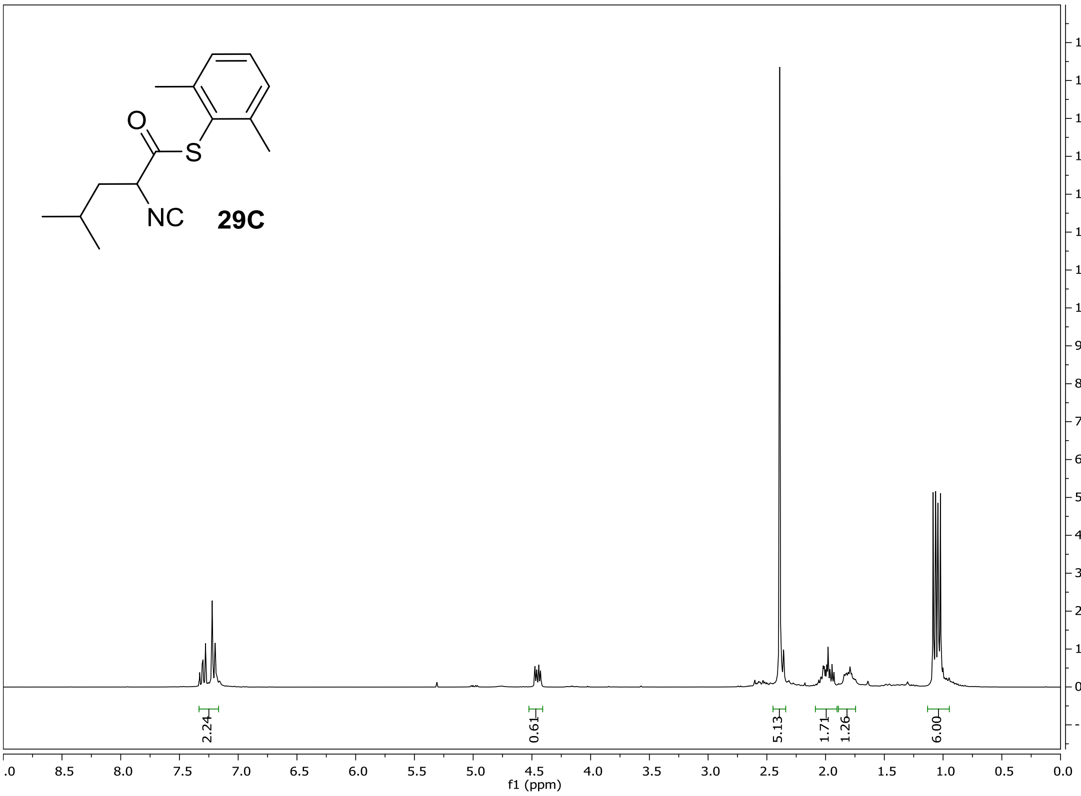

193.23
163.75
136.39
135.25
135.04
132.68
129.87
128.61
127.71
126.68
125.71
123.94
59.35
21.12
O
S
NC
28B
f1 (ppm)


7.39
7.38
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.27
7.27
7.26
7.25
7.18
7.16
4.59
4.58
4.57
4.56
3.35
3.34
3.31
3.30
3.23
3.20
3.19
3.17
2.29
O
S
Bn
NC
29A
4.68
1.43
0.71
1.00
1.01
4.67
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
.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
f1 (ppm)

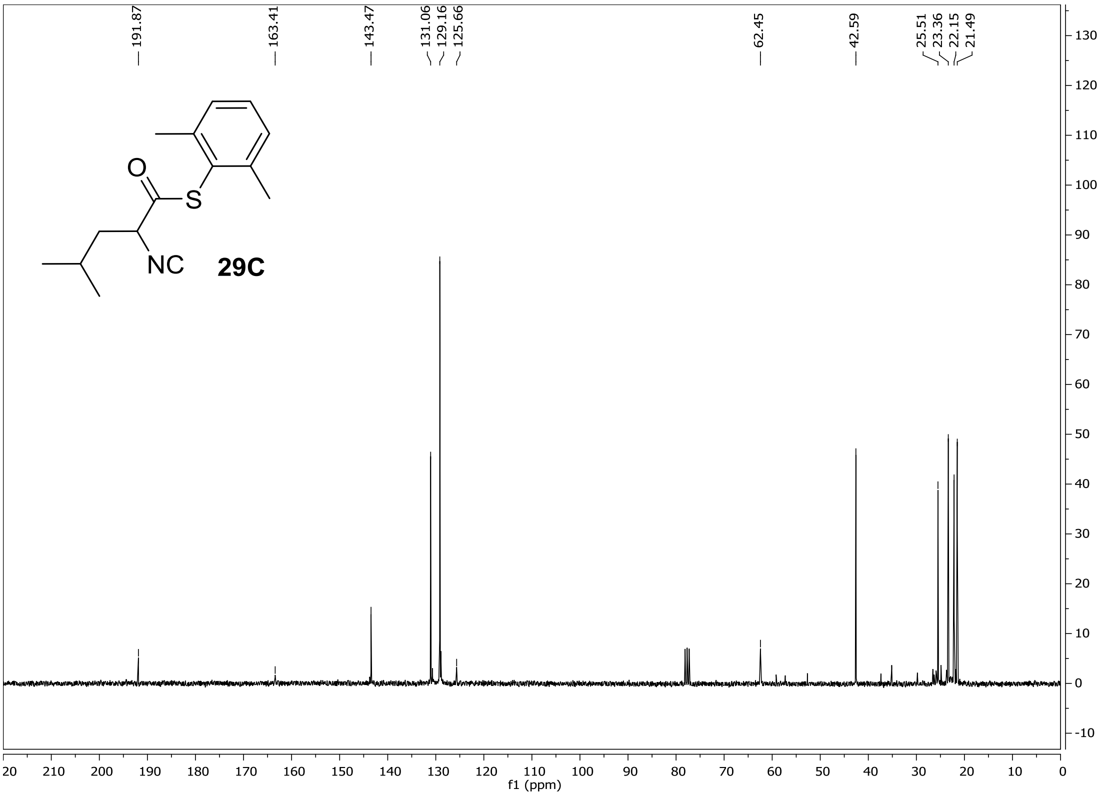

191.16
164.26
143.50
134.73
131.15
130.16
129.47
129.19
128.48
125.61
64.94
39.98
22.12
O
S
Bn
NC
29A
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.32
7.30
7.30
7.28
7.27
7.22
7.22
7.21
7.21
7.20
7.19
7.19
7.19
7.19
7.19
4.52
4.50
4.48
4.45
2.38
1.76
1.74
O
S
NC
29B
1.06
1.51
0.61
5.24
3.00
f1 (ppm)
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

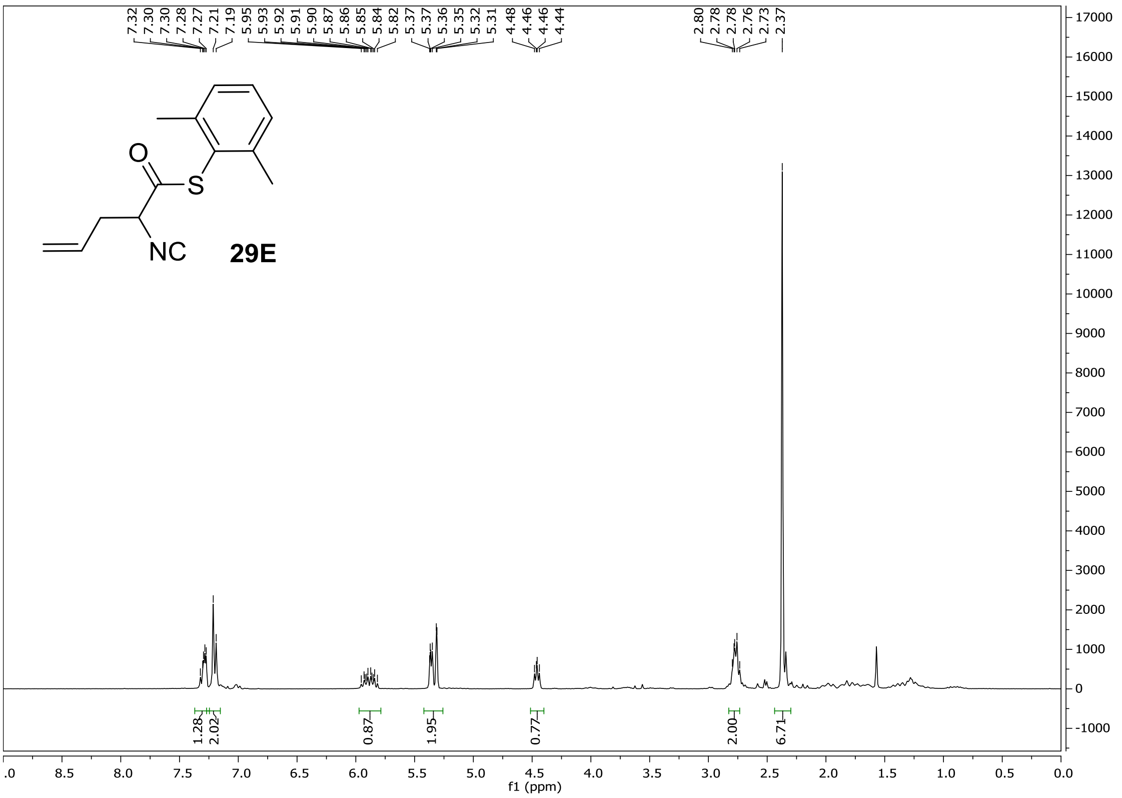

191.14
162.13
142.72
130.34
128.44
125.91
58.12
21.38
19.97
O
S
NC
29B
f1 (ppm)
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5

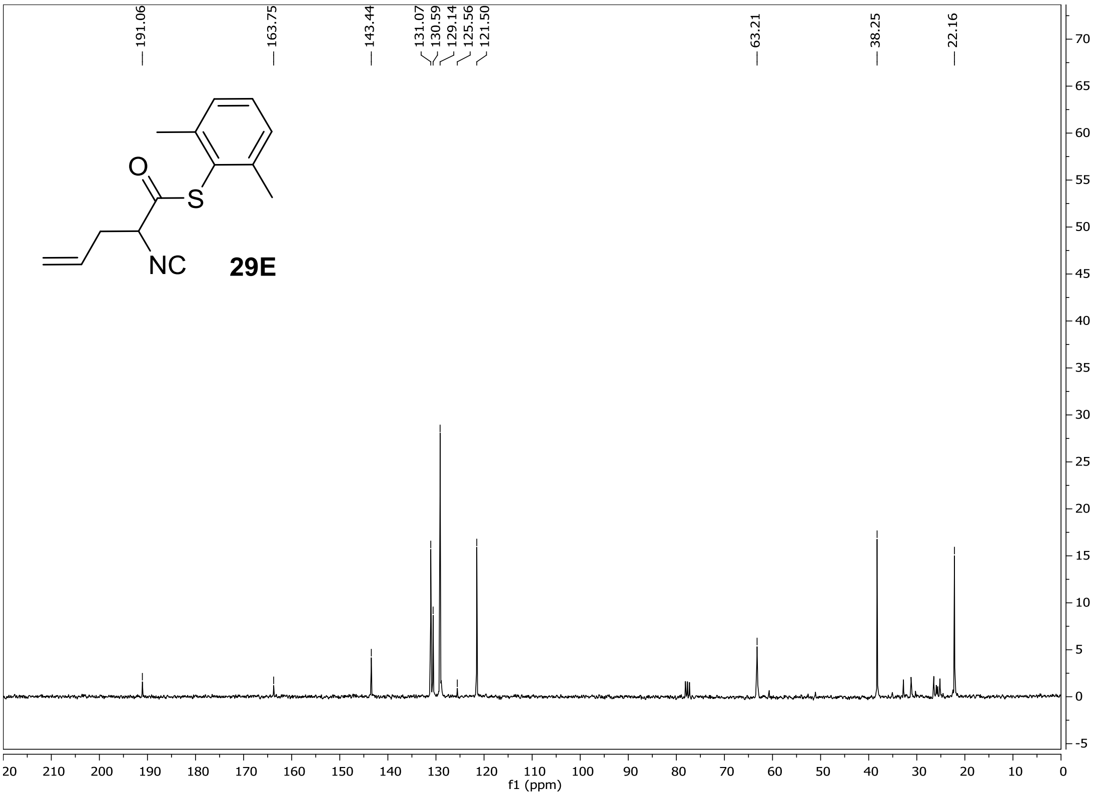


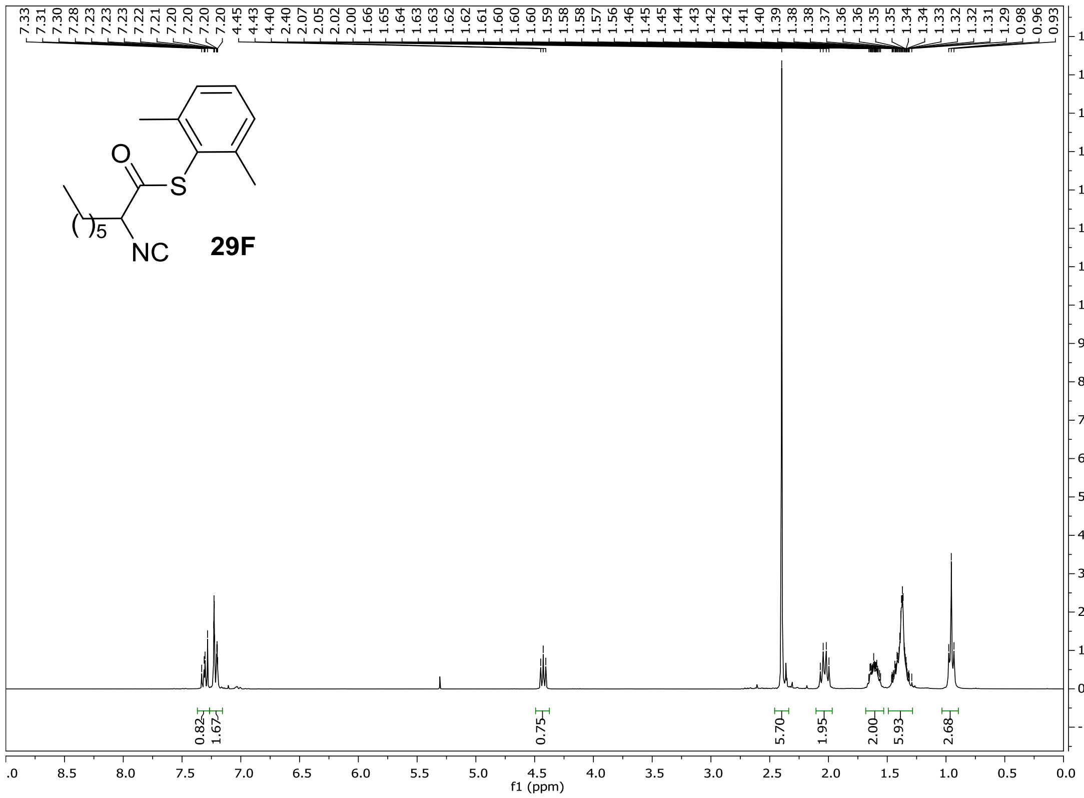
O
S
NC
29C
2.24
0.61
5.13
1.71
1.26
6.00
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

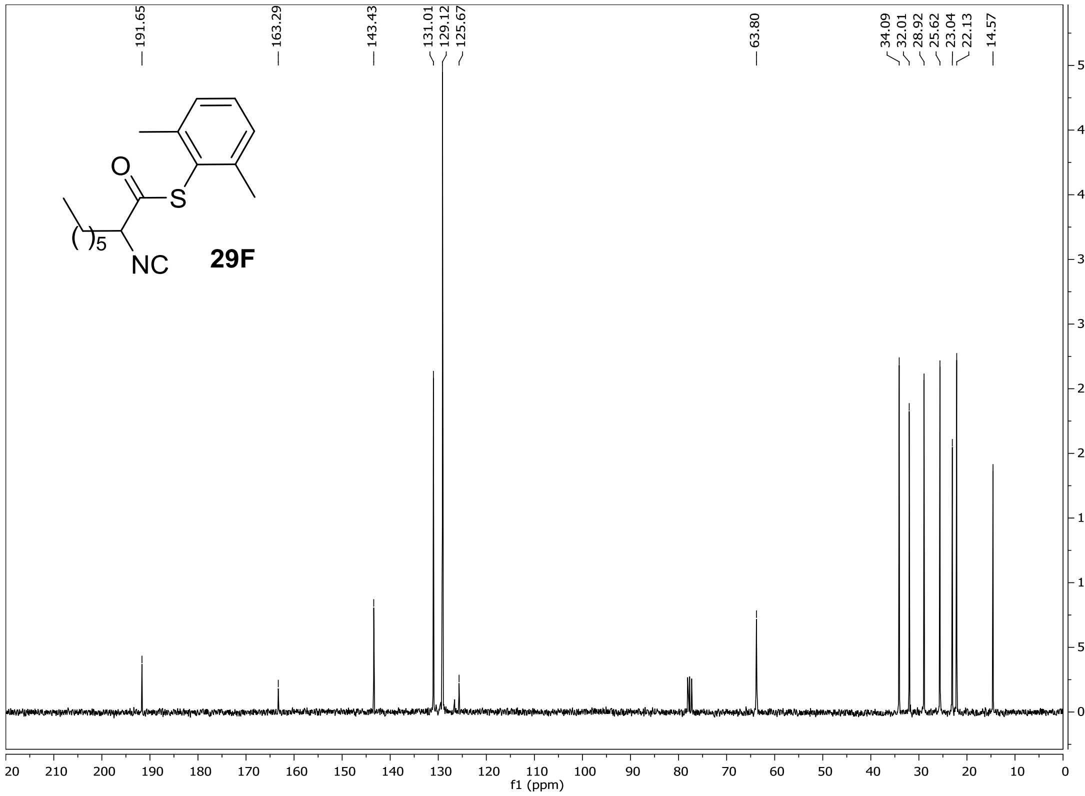


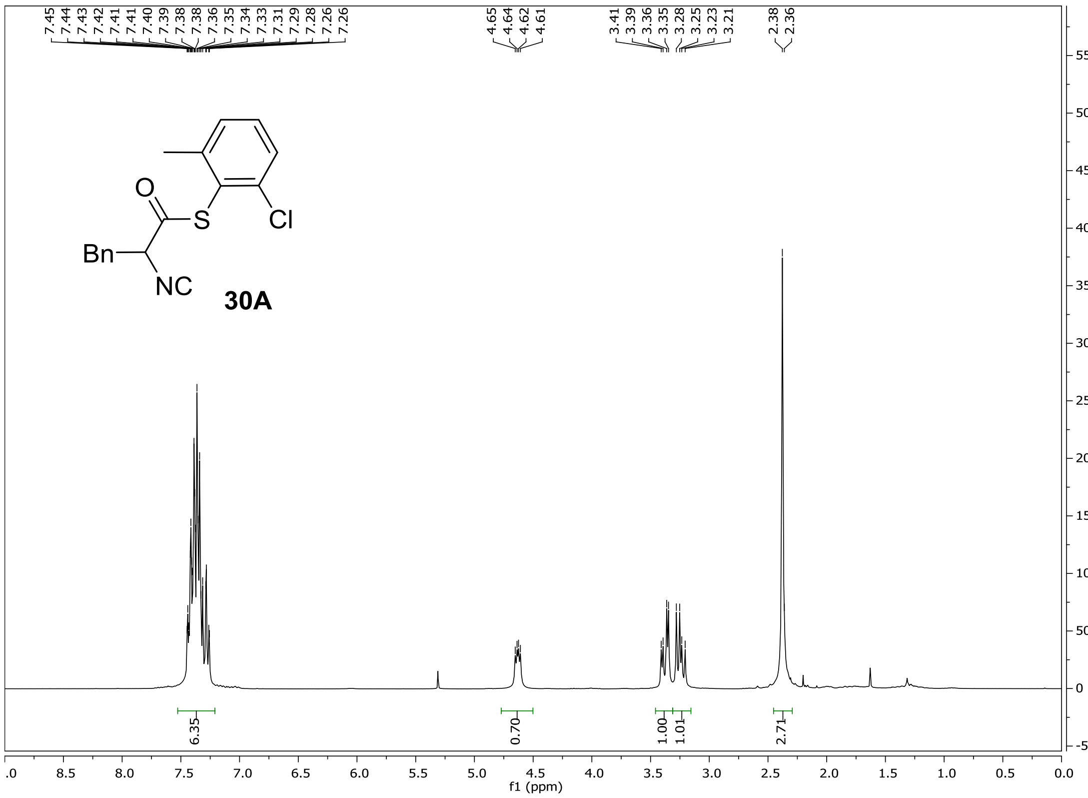
191.87
163.41
143.47
131.06
129.16
125.66
62.45
42.59
25.51
23.36
22.15
21.49
O
S
NC
29C
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

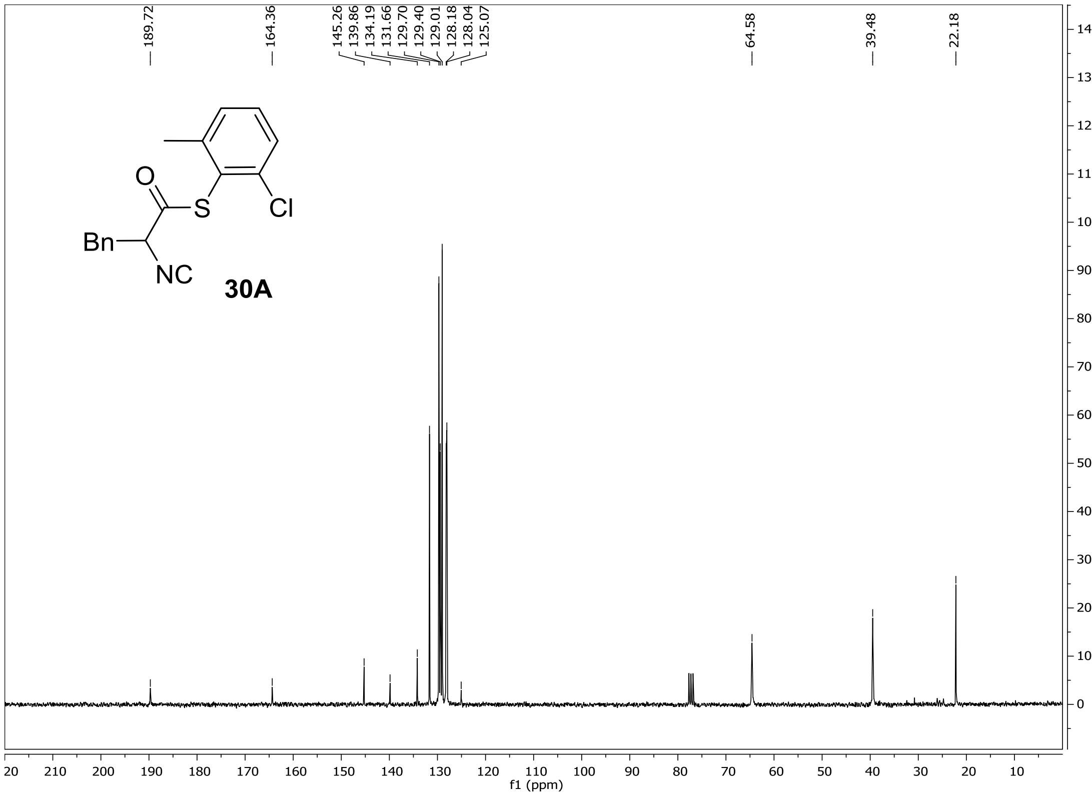

7.32
7.30
7.30
7.28
7.27
7.21
7.19
5.95
5.93
5.92
5.91
5.90
5.87
5.86
5.85
5.84
5.82
5.37
5.37
5.36
5.35
5.32
5.31
4.48
4.46
4.46
4.44
2.80
2.78
2.78
2.76
2.73
2.37
O
S
NC
29E
1.28
2.02
0.87
1.95
0.77
2.00
6.71
f1 (ppm)

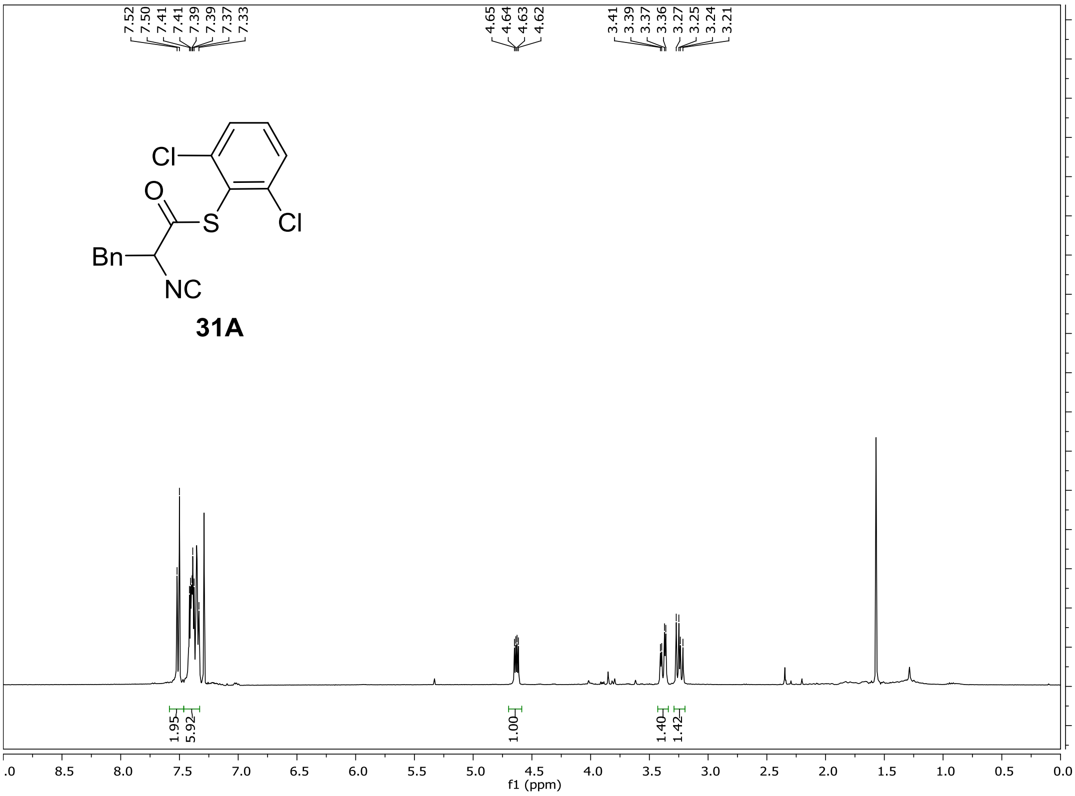

191.06
163.75
143.44
131.07
130.59
129.14
125.56
121.50
63.21
38.25
22.16
O
S
NC
29E
f1 (ppm)

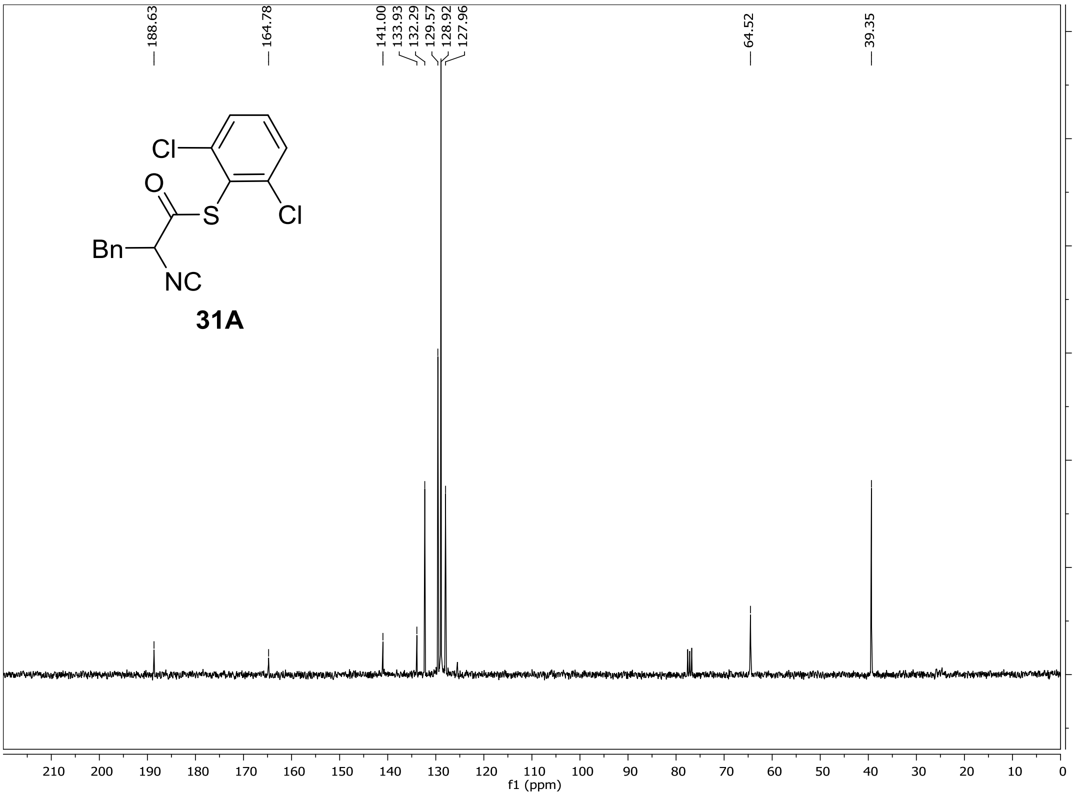

29F
NC
O
S
( )5
7.33 7.31 7.30 7.28 7.23 7.23 7.23 7.22 7.21 7.20 7.20 7.20 7.20 4.45 4.43 4.40 2.40 2.07 2.05 2.02 2.00 1.66 1.65 1.64 1.63 1.63 1.62 1.62 1.61 1.60 1.60 1.59 1.58 1.58 1.57 1.56 1.46 1.45 1.45 1.44 1.43 1.42 1.42 1.41 1.40 1.39 1.38 1.38 1.37 1.36 1.36 1.35 1.35 1.34 1.34 1.33 1.32 1.32 1.31 1.29 0.98 0.96 0.93
0.82 1.67 0.75 5.70 1.95 2.00 5.93 2.68
f1 (ppm)

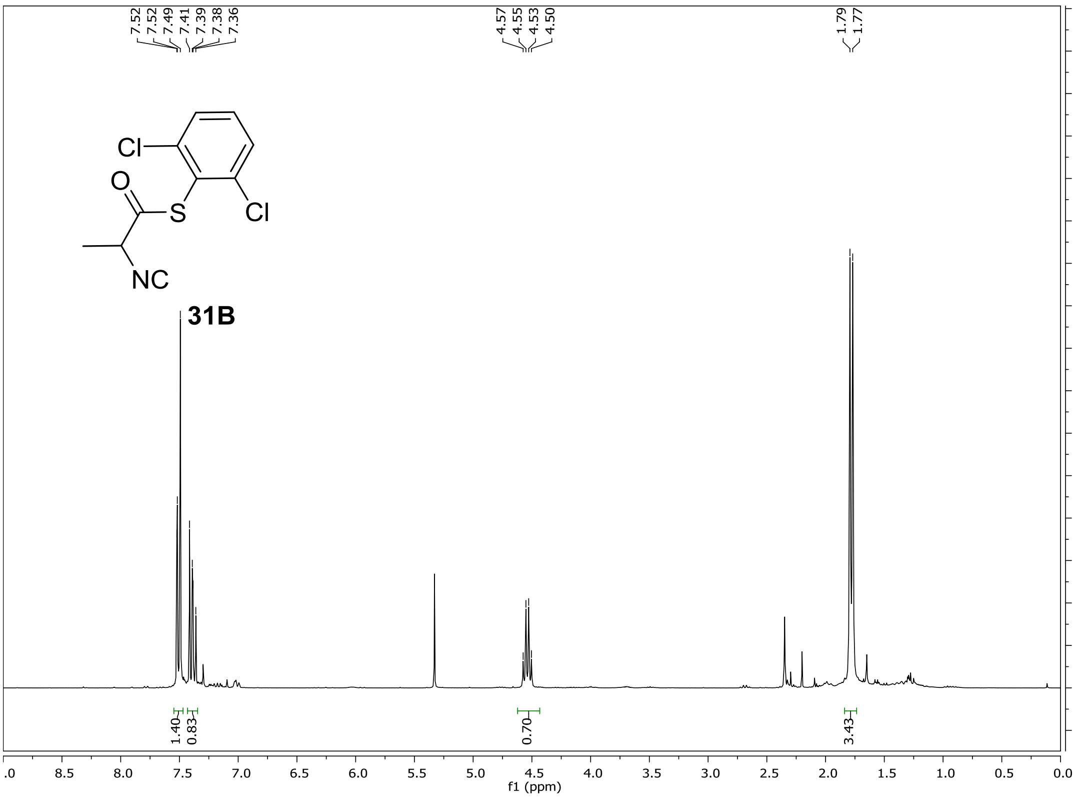

29F
NC
O
S
( )5
191.65
163.29
143.43
131.01 129.12 125.67
63.80
34.09 32.01 28.92 25.62 23.04 22.13
14.57
f1 (ppm)

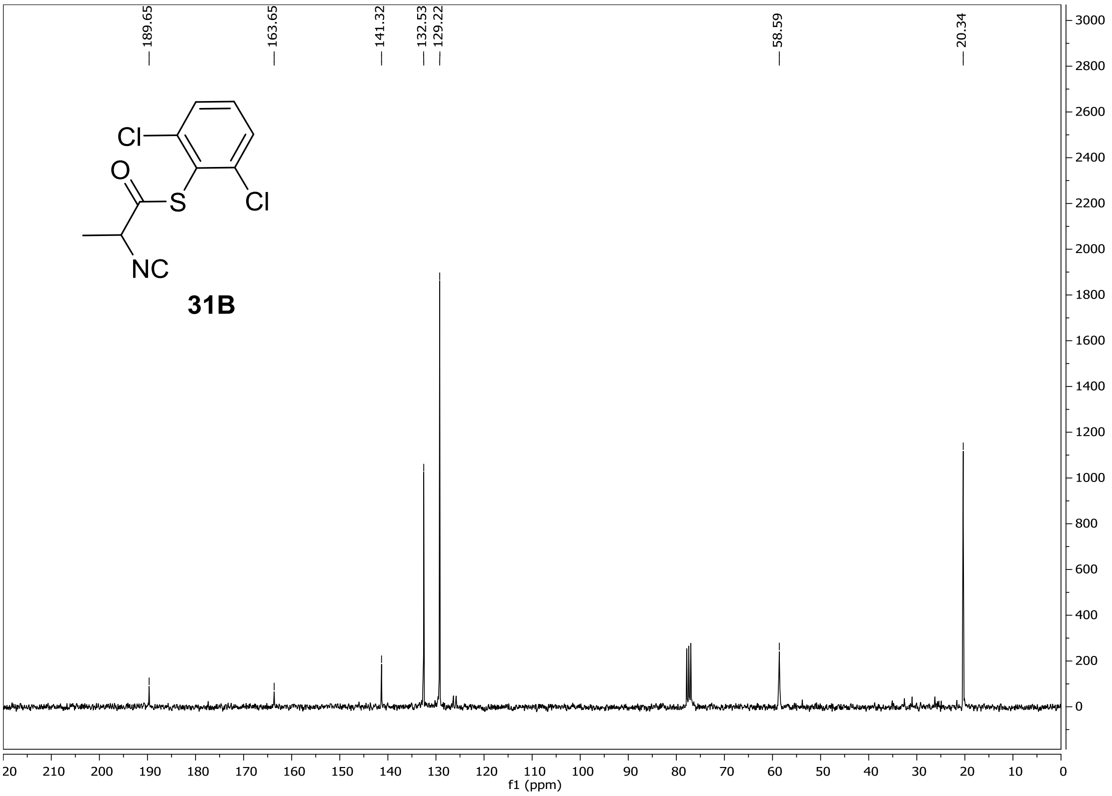

7.45
7.44
7.43
7.42
7.41
7.41
7.40
7.39
7.38
7.38
7.36
7.35
7.34
7.33
7.31
7.29
7.28
7.26
7.26
4.65
4.64
4.62
4.61
3.41
3.39
3.36
3.35
3.28
3.25
3.23
3.21
2.38
2.36
O
S
Cl
Bn
NC
30A
6.35
0.70
1.00
1.01
2.71
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

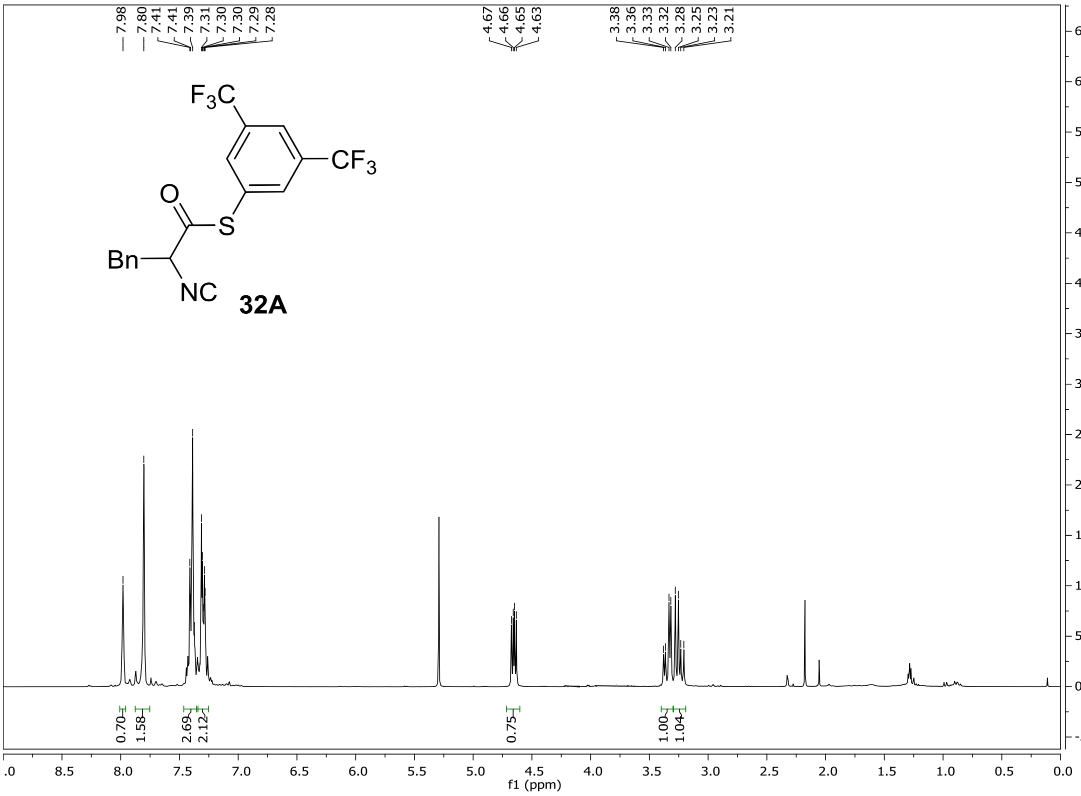

189.72
164.36
145.26
139.86
134.19
131.66
129.70
129.40
129.01
128.18
128.04
125.07
64.58
39.48
22.18
O
S
Cl
Bn
NC
30A
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.52
7.50
7.41
7.41
7.39
7.39
7.37
7.33
4.65
4.64
4.63
4.62
3.41
3.39
3.37
3.36
3.27
3.25
3.24
3.21
Cl
O
S
Cl
Bn
NC
31A
1.95
5.92
1.00
1.40
1.42
f1 (ppm)

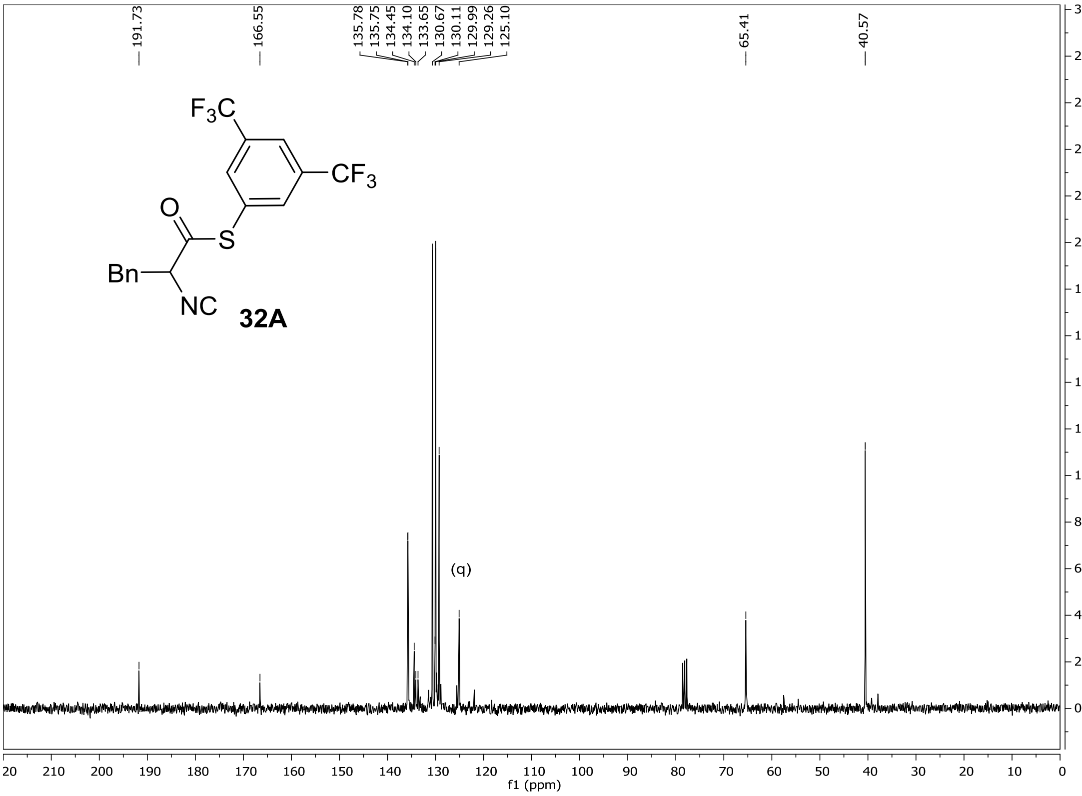

188.63
164.78
141.00
133.93
132.29
129.57
128.92
127.96
64.52
39.35
Cl
O
S
Cl
Bn
NC
31A
f1 (ppm)


7.52
7.52
7.49
7.41
7.39
7.38
7.36
4.57
4.55
4.53
4.50
1.79
1.77
Cl
O
S
Cl
NC
31B
1.40
0.83
0.70
3.43
f1 (ppm)

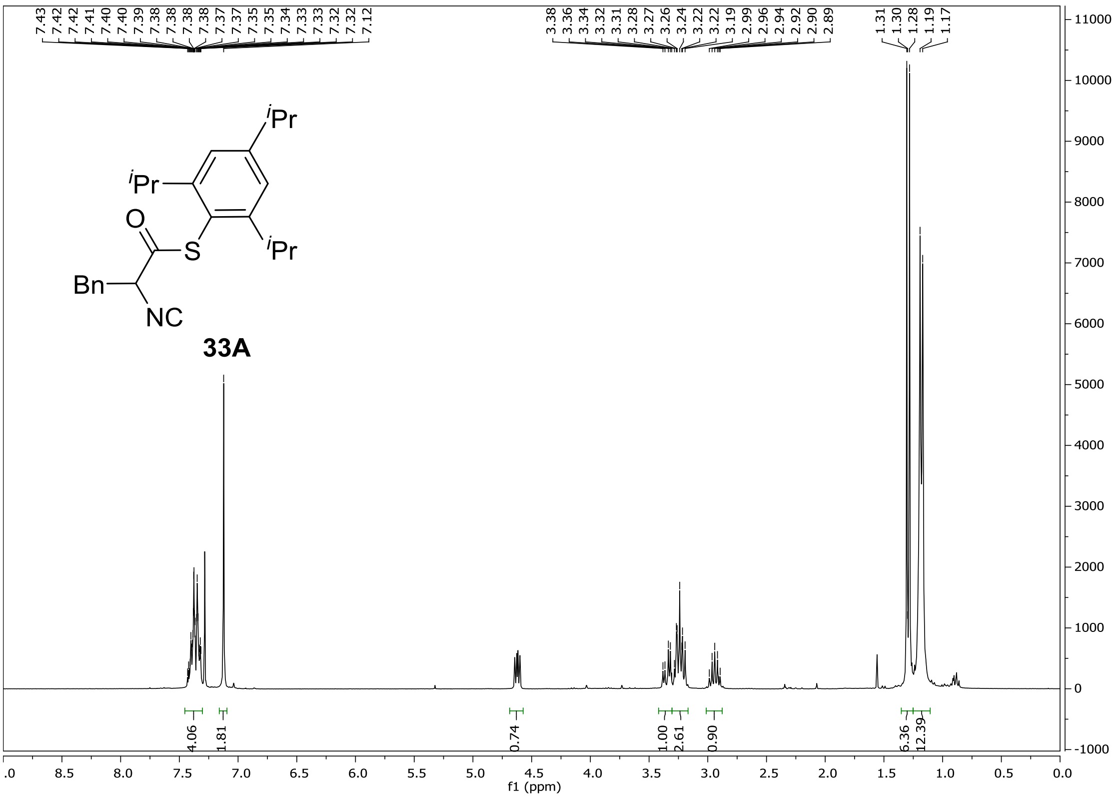

189.65
163.65
141.32
132.53
129.22
58.59
20.34
Cl
O
S
Cl
NC
31B
f1 (ppm)

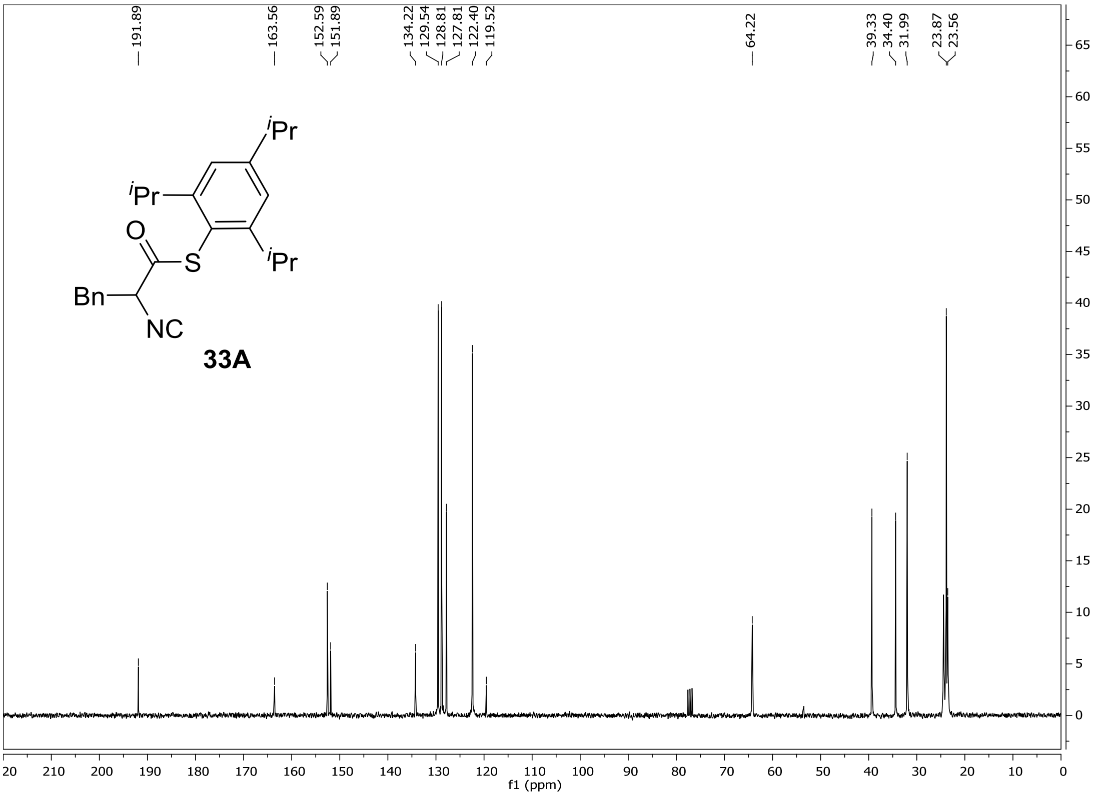

7.98
7.80
7.41
7.41
7.39
7.31
7.30
7.30
7.29
7.28
4.67
4.66
4.65
4.63
3.38
3.36
3.33
3.32
3.28
3.25
3.23
3.21
F3C
CF3
O
S
Bn
NC
0.70
1.58
2.69
2.12
0.75
1.00
1.04
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

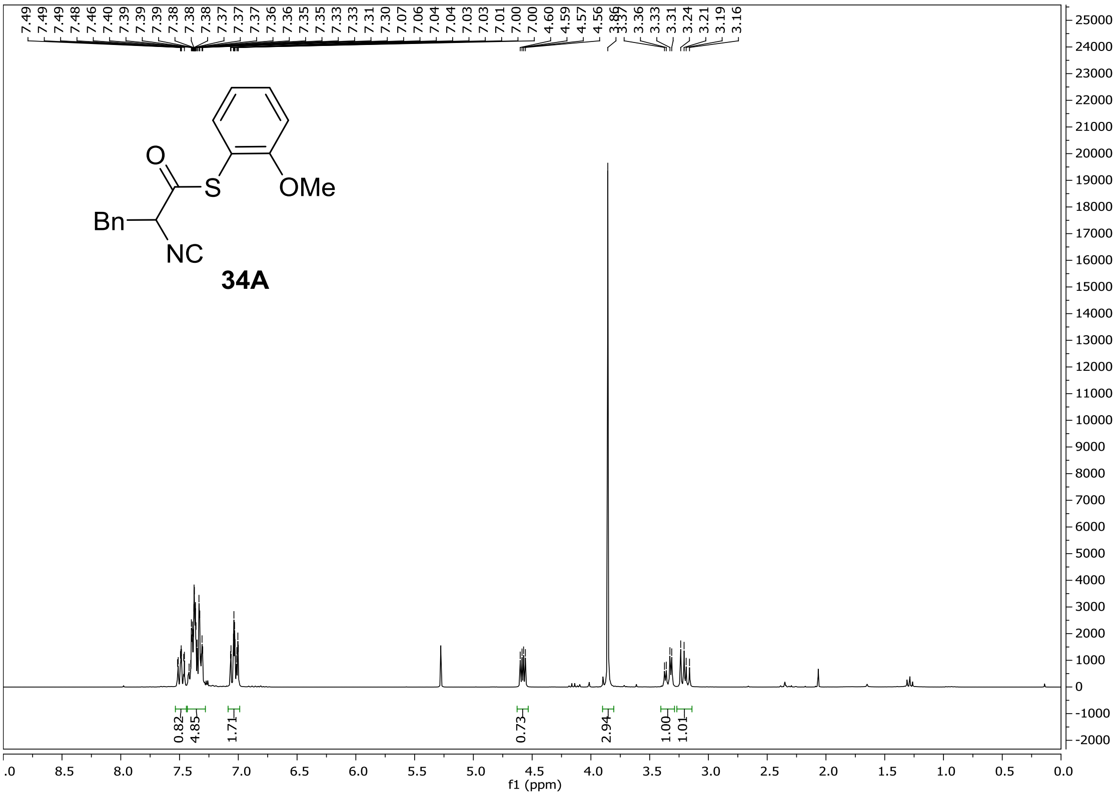
32A

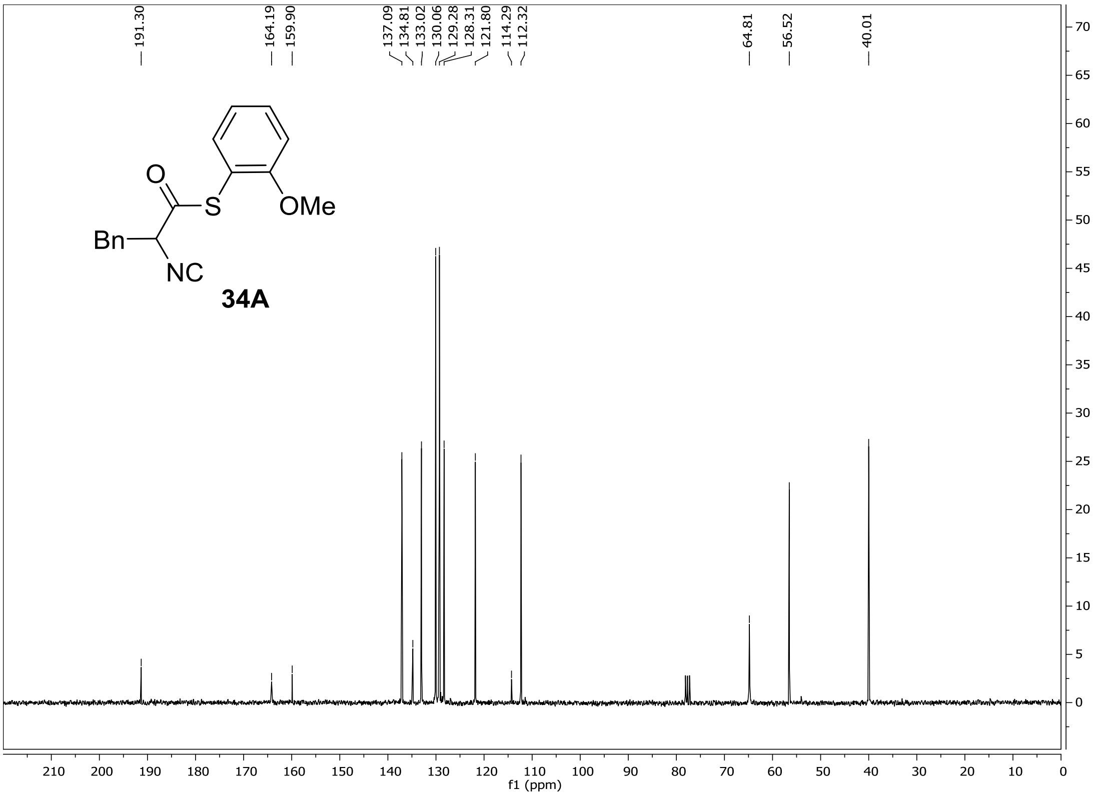

191.73
166.55
135.78
135.75
134.45
134.10
133.65
130.67
130.11
129.99
129.26
125.10
65.41
40.57
F3C
CF3
O
S
Bn
NC
(q)
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

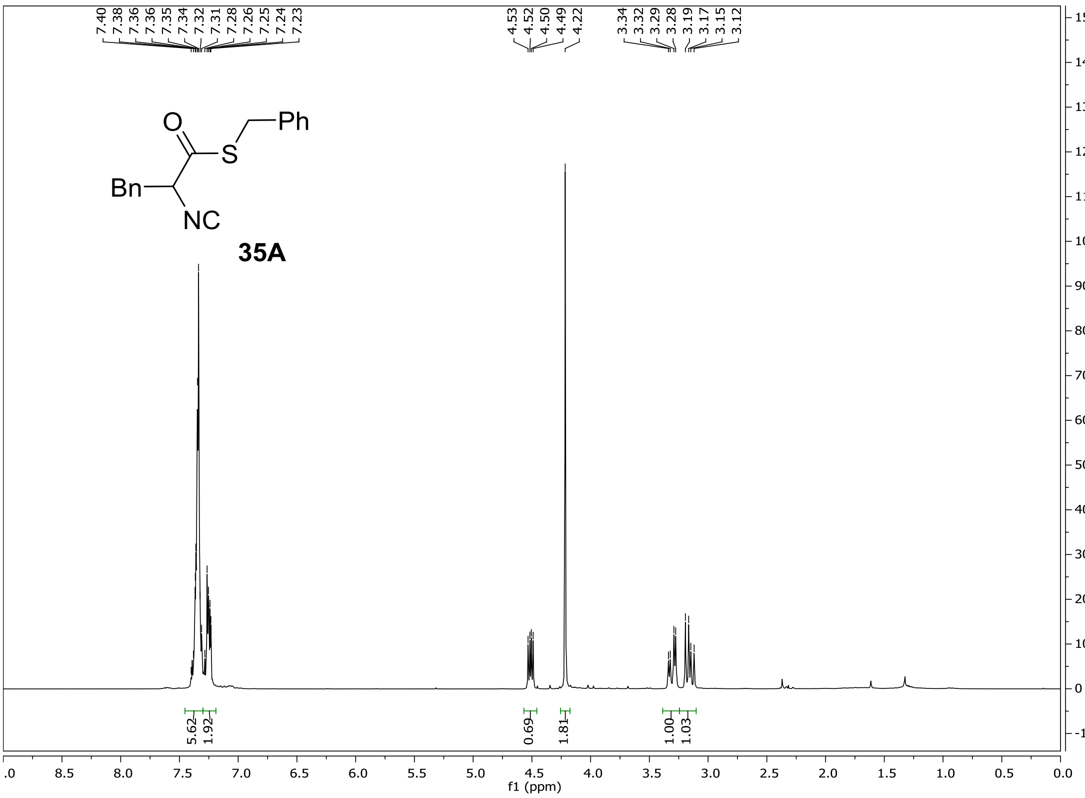
32A

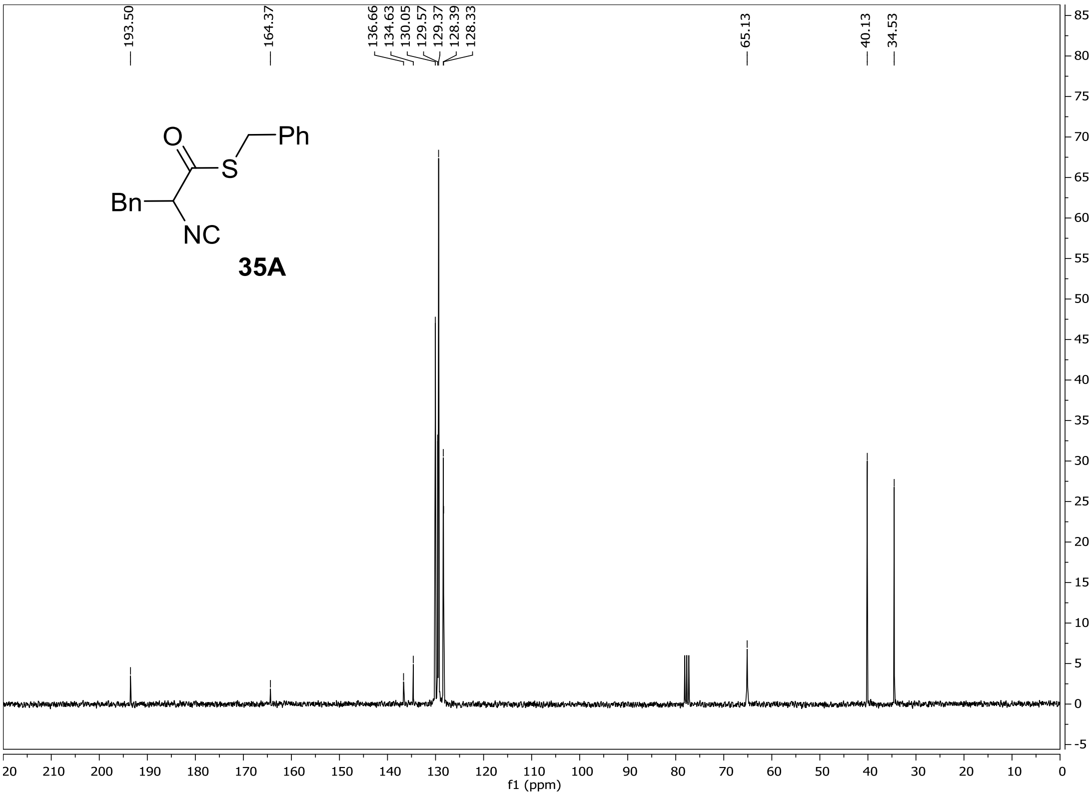

7.43
7.42
7.42
7.41
7.40
7.39
7.38
7.38
7.38
7.38
7.37
7.37
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.12
3.38
3.36
3.34
3.32
3.31
3.28
3.27
3.26
3.24
3.22
3.22
3.19
2.99
2.96
2.94
2.92
2.90
2.89
1.31
1.30
1.28
1.19
1.17
iPr
iPr
iPr
O
S
Bn
NC
33A
4.06
1.81
0.74
1.00
2.61
0.90
6.36
12.39
f1 (ppm)

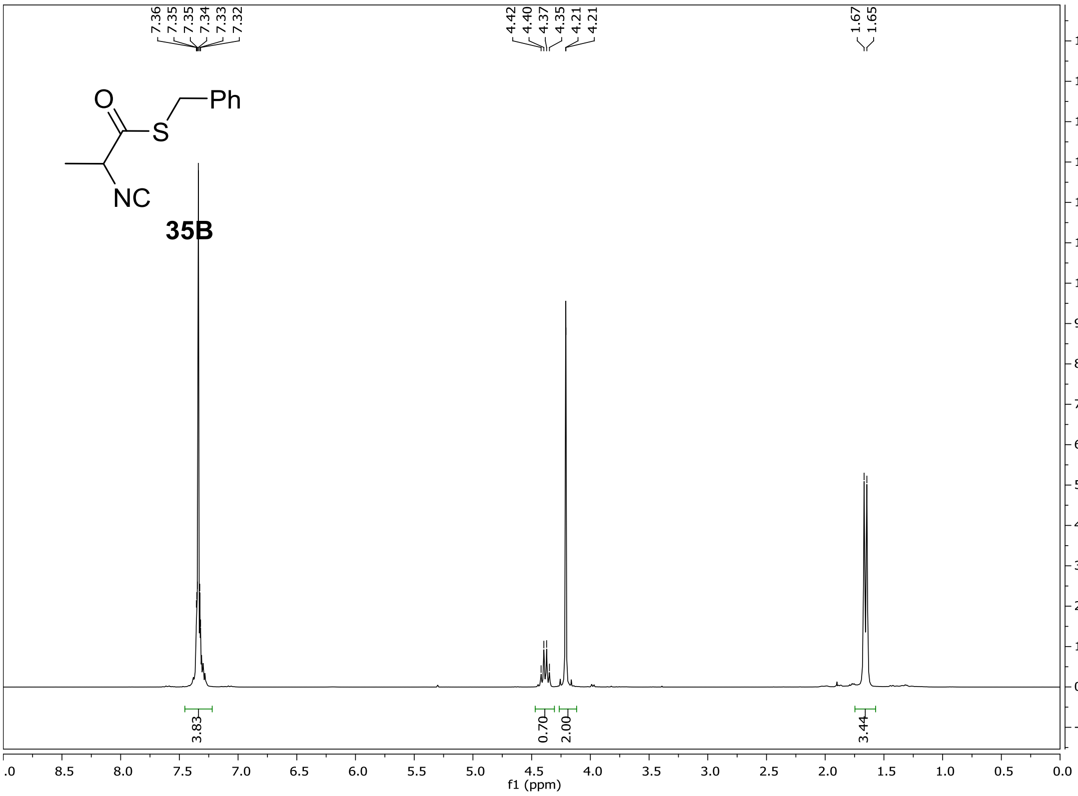

191.89
163.56
152.59
151.89
134.22
129.54
128.81
127.81
122.40
119.52
64.22
39.33
34.40
31.99
23.87
23.56
iPr
iPr
iPr
O
S
Bn
NC
33A
f1 (ppm)

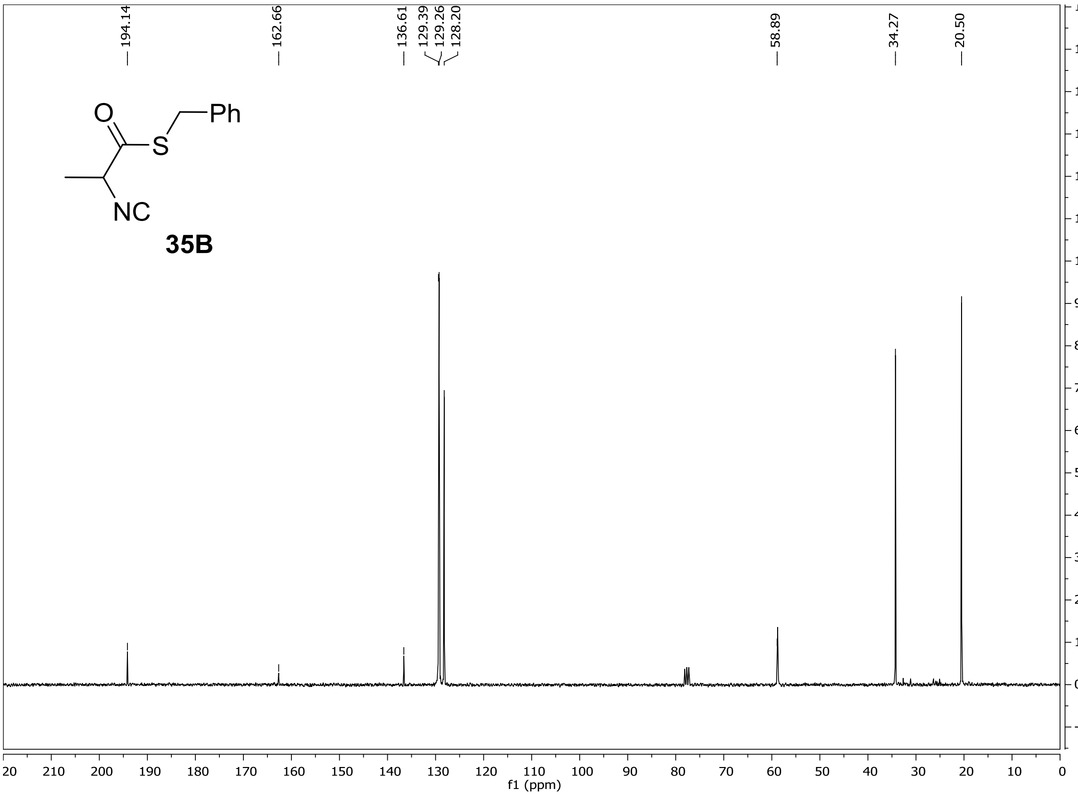

7.49
7.49
7.49
7.48
7.46
7.40
7.39
7.39
7.39
7.38
7.38
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.33
7.33
7.31
7.30
7.07
7.06
7.04
7.04
7.03
7.03
7.01
7.00
7.00
4.60
4.59
4.57
4.56
3.86
3.37
3.36
3.33
3.31
3.24
3.21
3.19
3.16
O
S
OMe
Bn
NC
34A
0.82
4.85
1.71
0.73
2.94
1.00
1.01
f1 (ppm)
.0
8.5
8.0
7.5
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
25000
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000

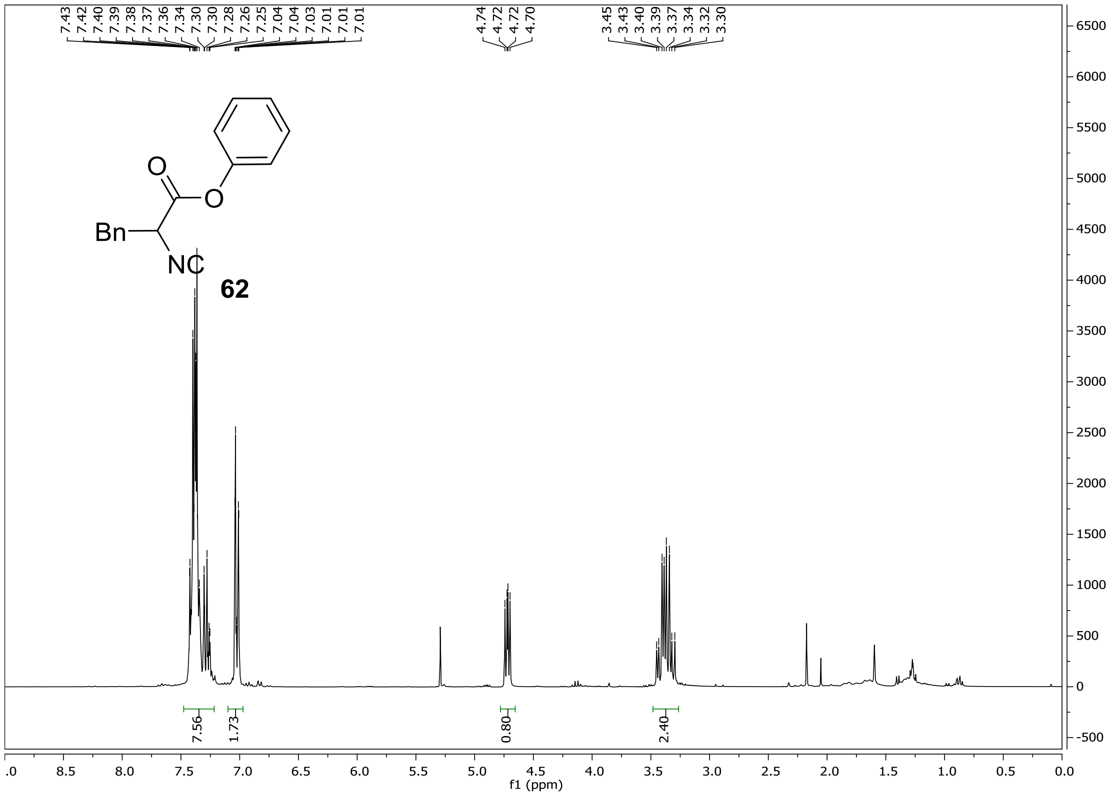

191.30
164.19
159.90
137.09
134.81
133.02
130.06
129.28
128.31
121.80
114.29
112.32
64.81
56.52
40.01
O
S
OMe
Bn
NC
34A
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

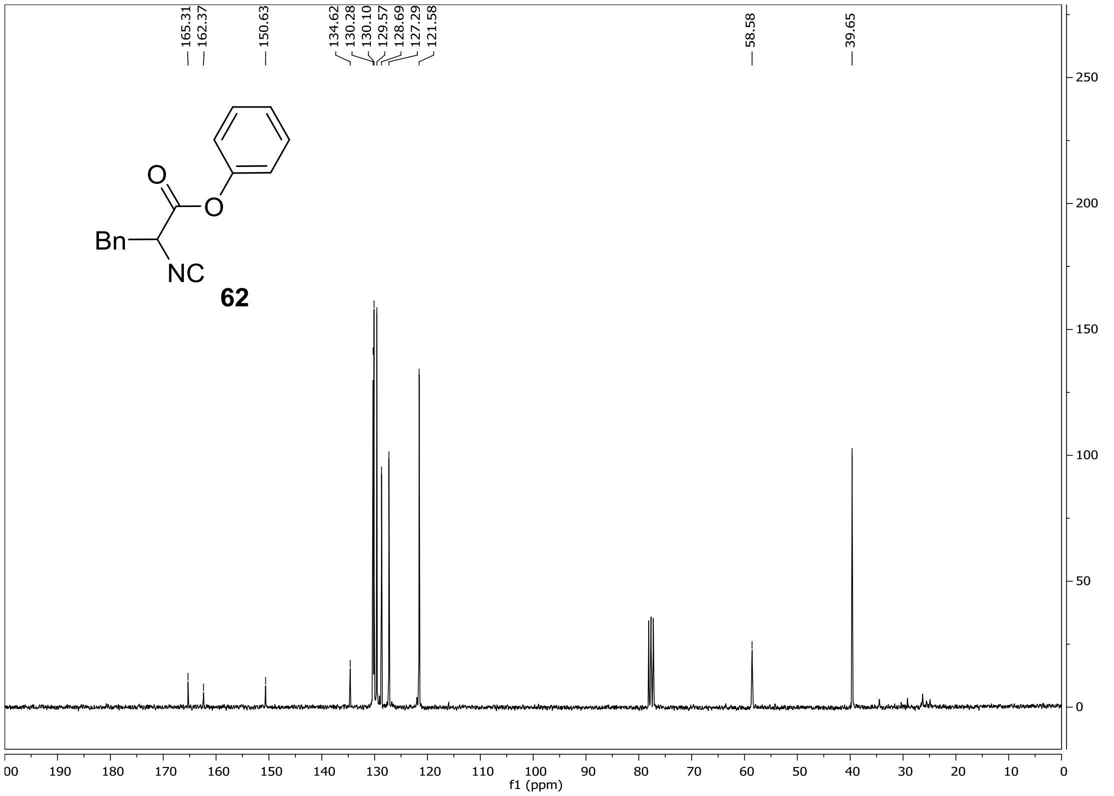

7.40
7.38
7.36
7.36
7.35
7.34
7.32
7.31
7.28
7.26
7.25
7.24
7.23
4.53
4.52
4.50
4.49
4.22
3.34
3.32
3.29
3.28
3.19
3.17
3.15
3.12
O
Ph
S
Bn
NC
35A
5.62
1.92
0.69
1.81
1.00
1.03
f1 (ppm)

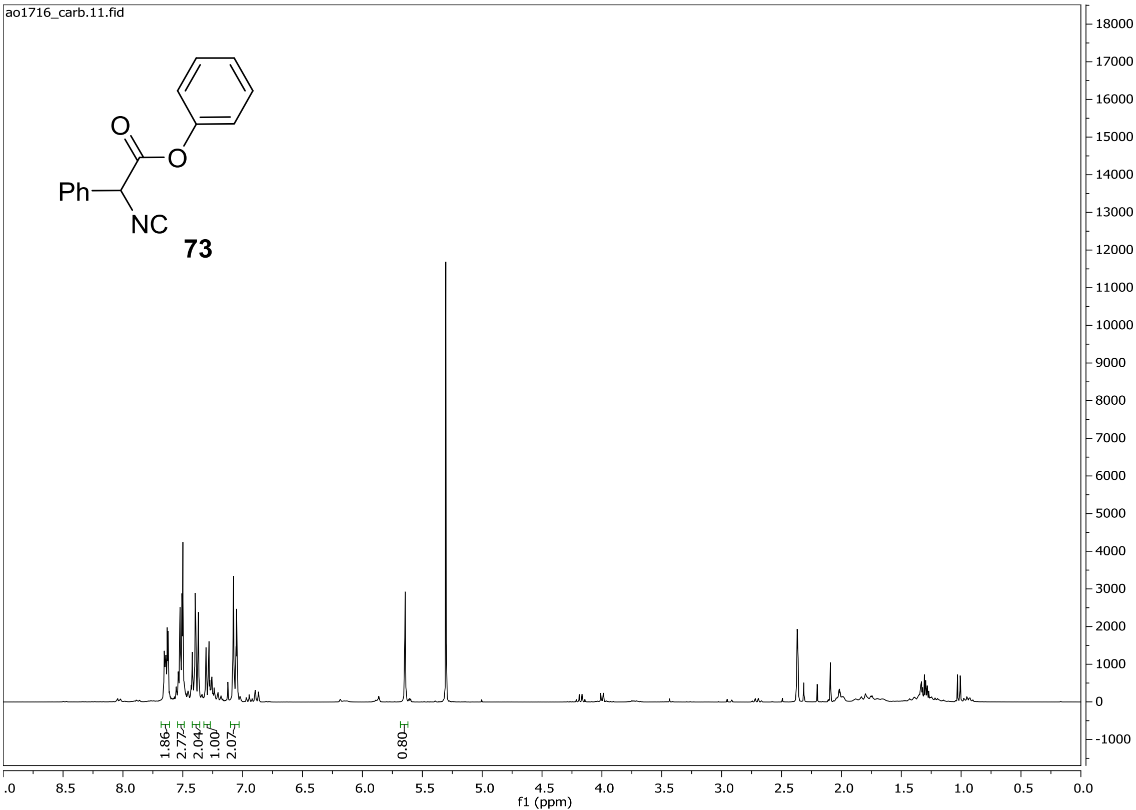

193.50
164.37
136.66
134.63
130.05
129.57
129.37
128.39
128.33
65.13
40.13
34.53
O
Ph
S
Bn
NC
35A
f1 (ppm)

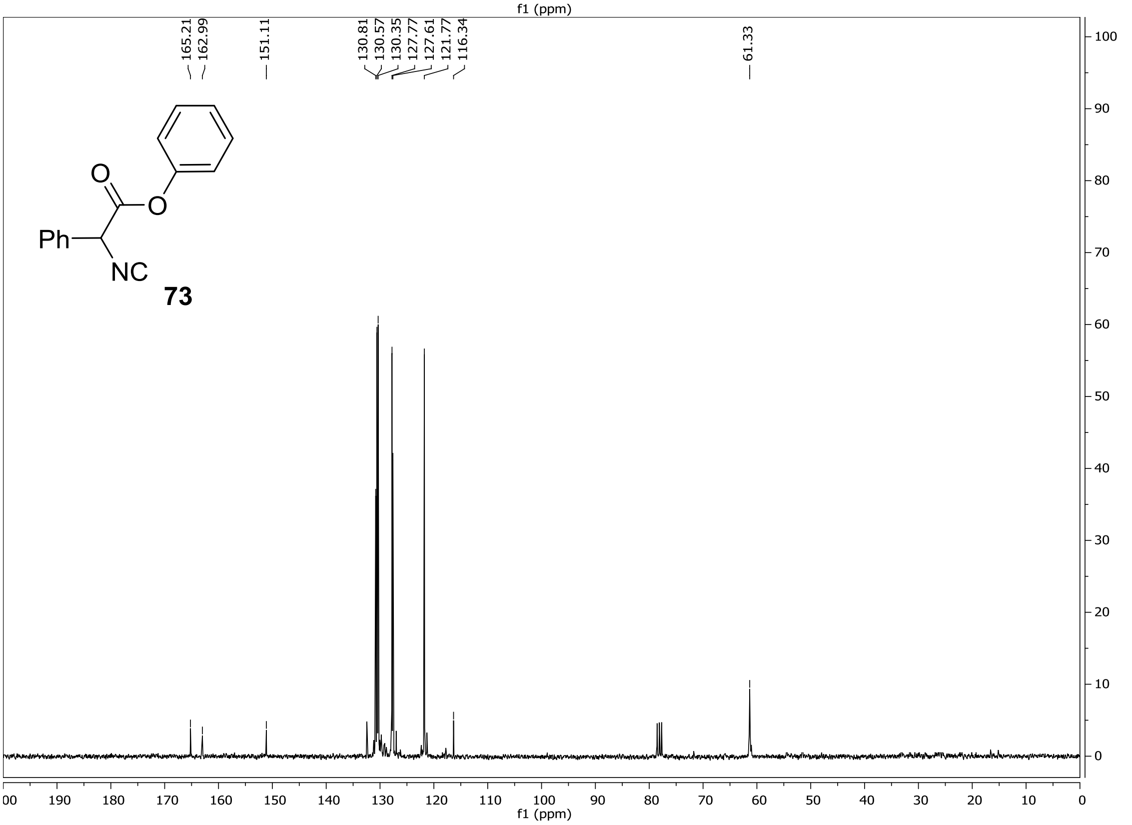

7.36
7.35
7.35
7.34
7.33
7.32
4.42
4.40
4.37
4.35
4.21
4.21
1.67
1.65
O
S
Ph
NC
35B
3.83
0.70
2.00
3.44
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


194.14
162.66
136.61
129.39
129.26
128.20
58.89
34.27
20.50
O
S
Ph
NC
35B
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

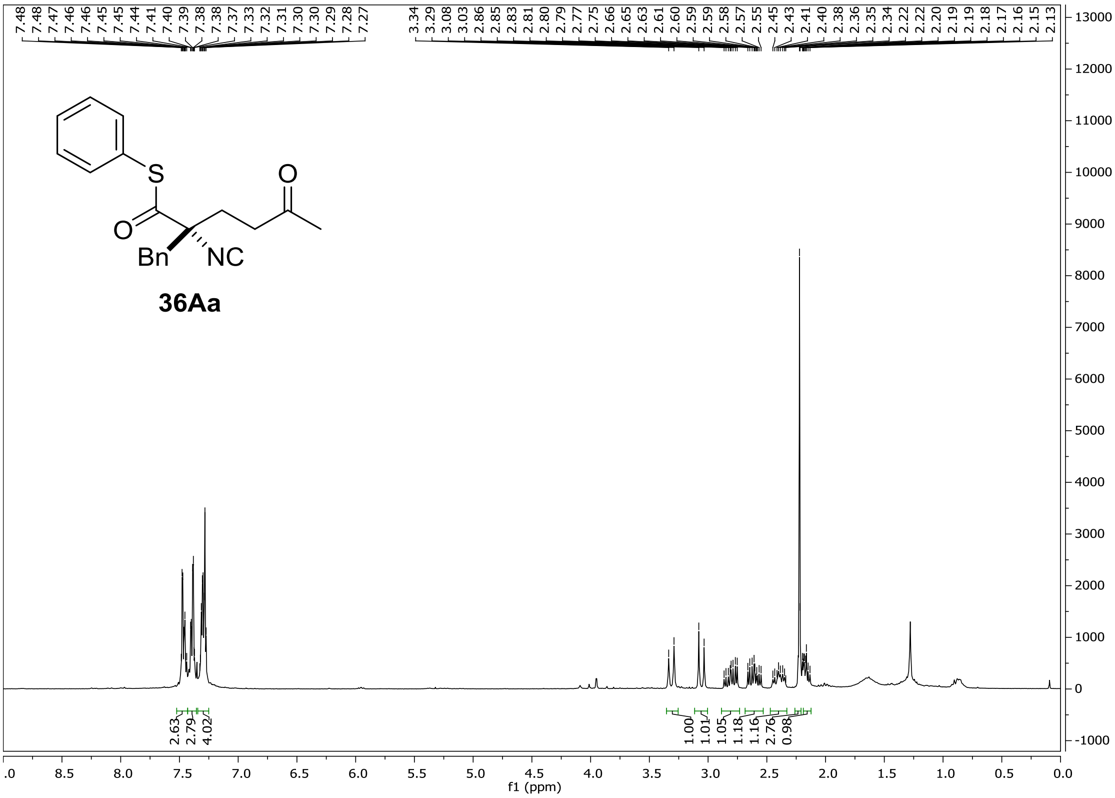

7.43
7.42
7.40
7.39
7.38
7.37
7.36
7.34
7.30
7.30
7.28
7.26
7.25
7.04
7.04
7.03
7.01
7.01
7.01
4.74
4.72
4.72
4.70
3.45
3.43
3.40
3.39
3.37
3.34
3.32
3.30
O
O
Bn
NC
62
7.56
1.73
0.80
2.40
f1 (ppm)

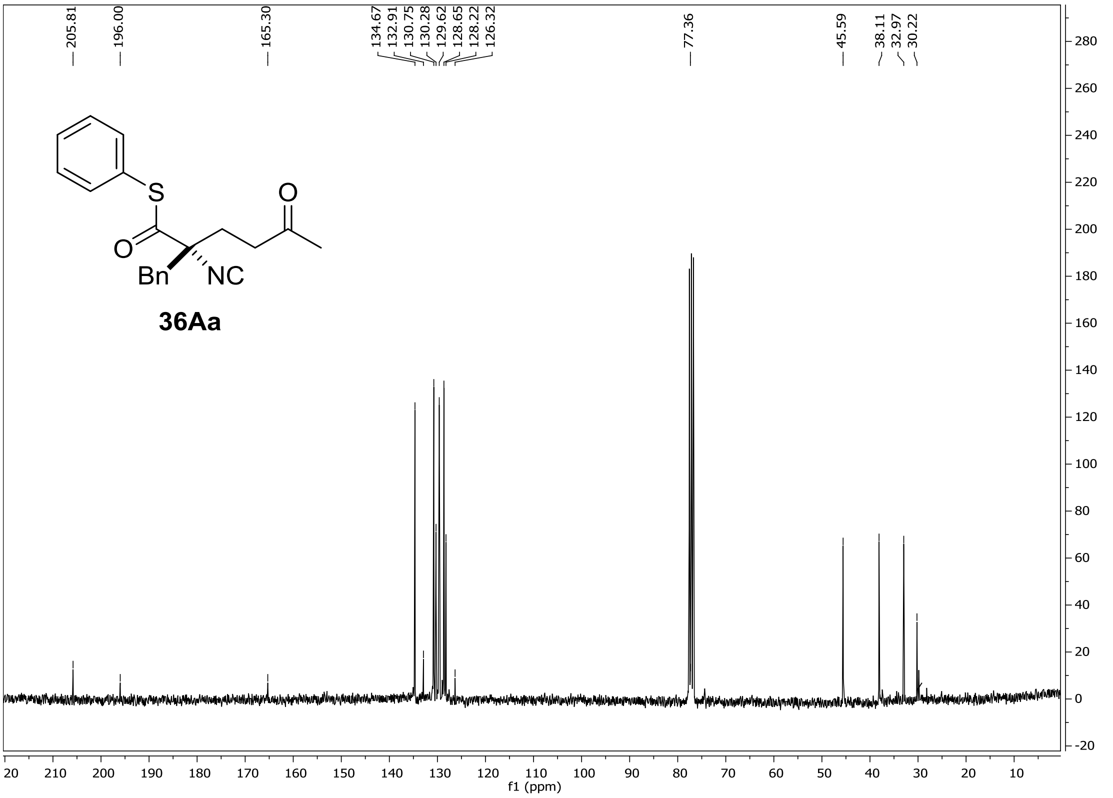

165.31
162.37
150.63
134.62
130.28
130.10
129.57
128.69
127.29
121.58
58.58
39.65
O
O
Bn
NC
62
f1 (ppm)

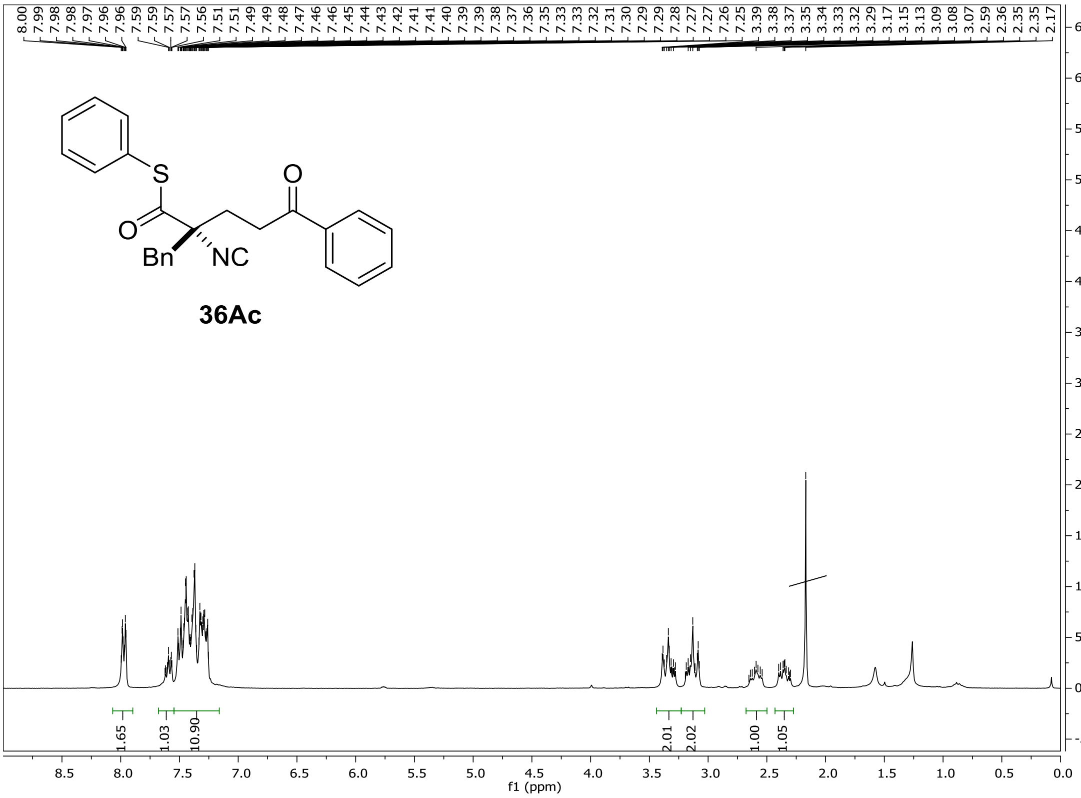

ao1716_carb.11.fid
O
O
Ph
NC
73
1.86
2.77
2.04
1.00
2.07
0.80
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

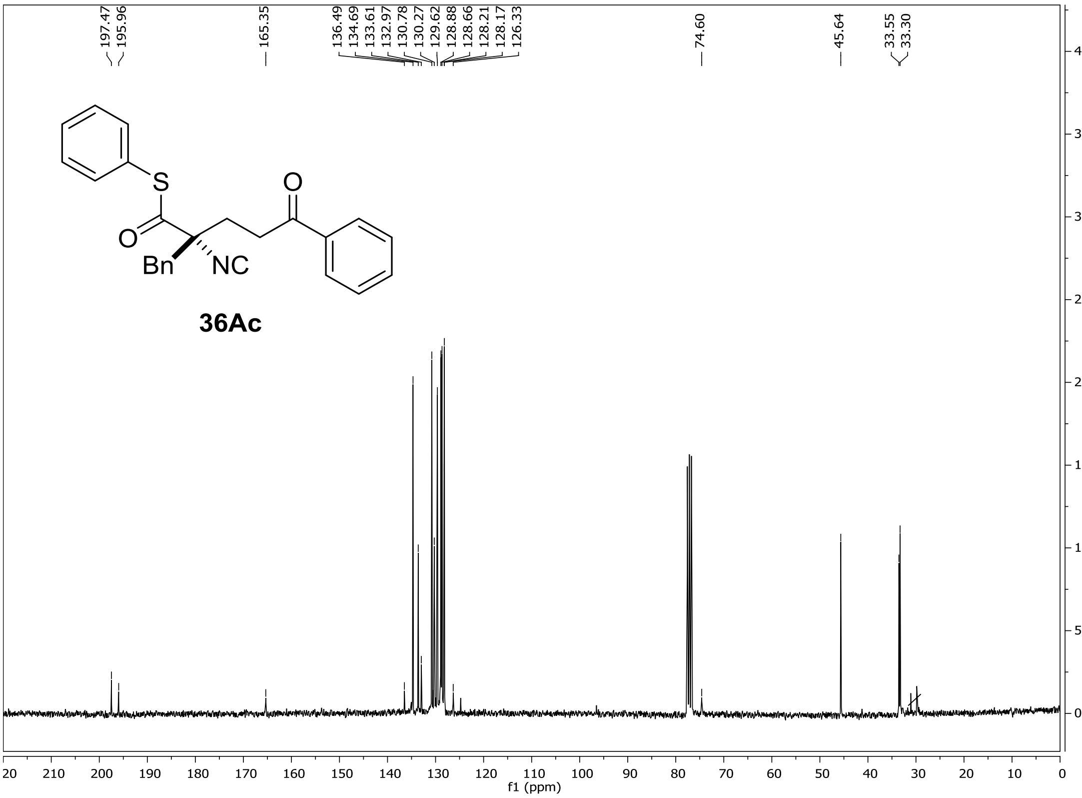

165.21
162.99
151.11
130.81
130.57
130.35
127.77
127.61
121.77
116.34
61.33
O
O
Ph
NC
73
100
90
80
70
60
50
40
30
20
10
0
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

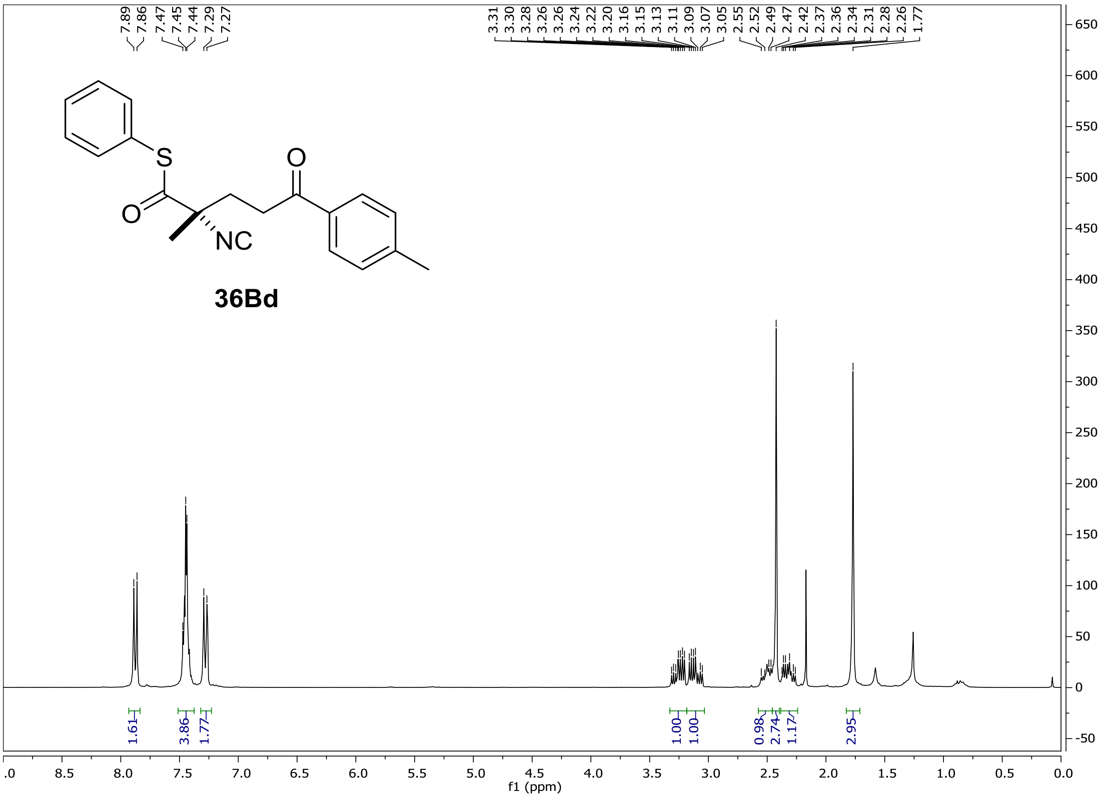
5.5.3.2. Adducts of the Michael addition to vinyl ketones

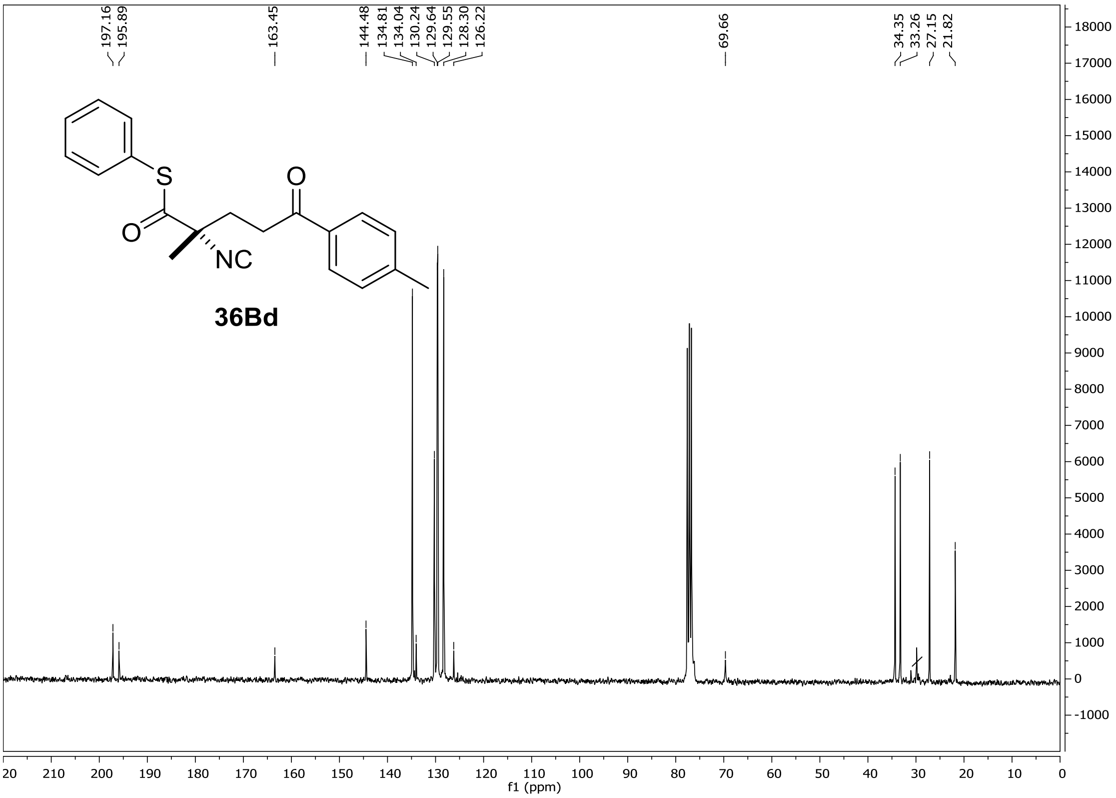


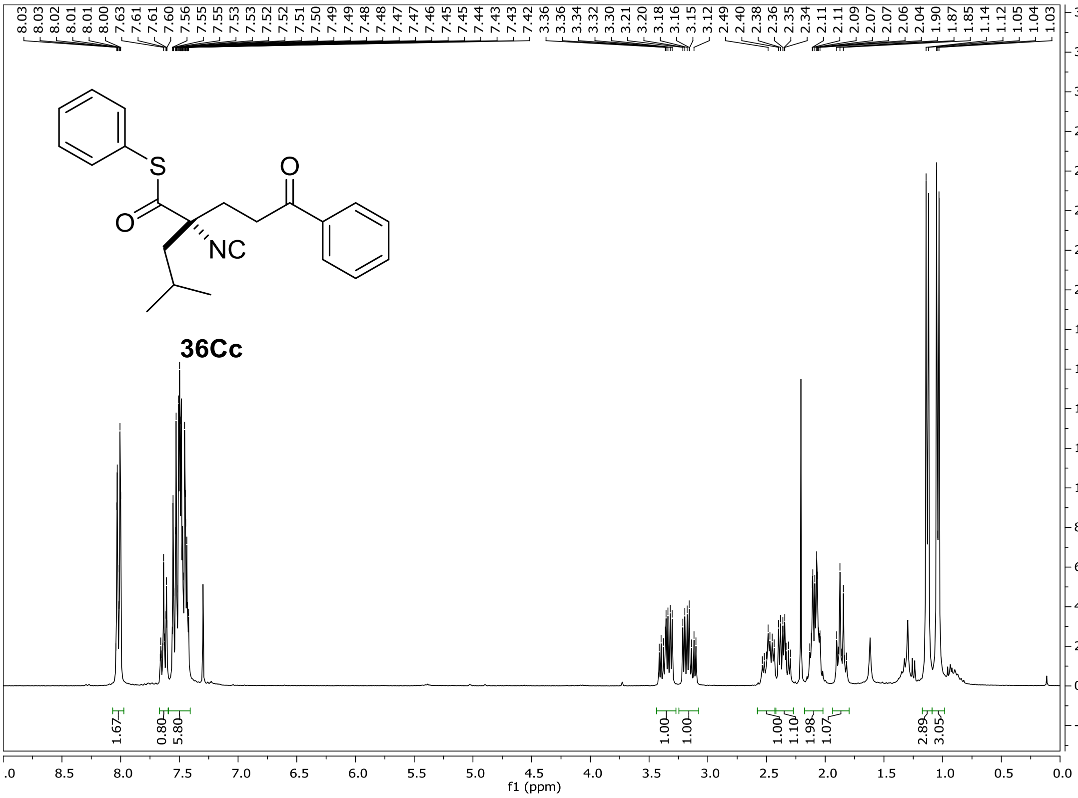


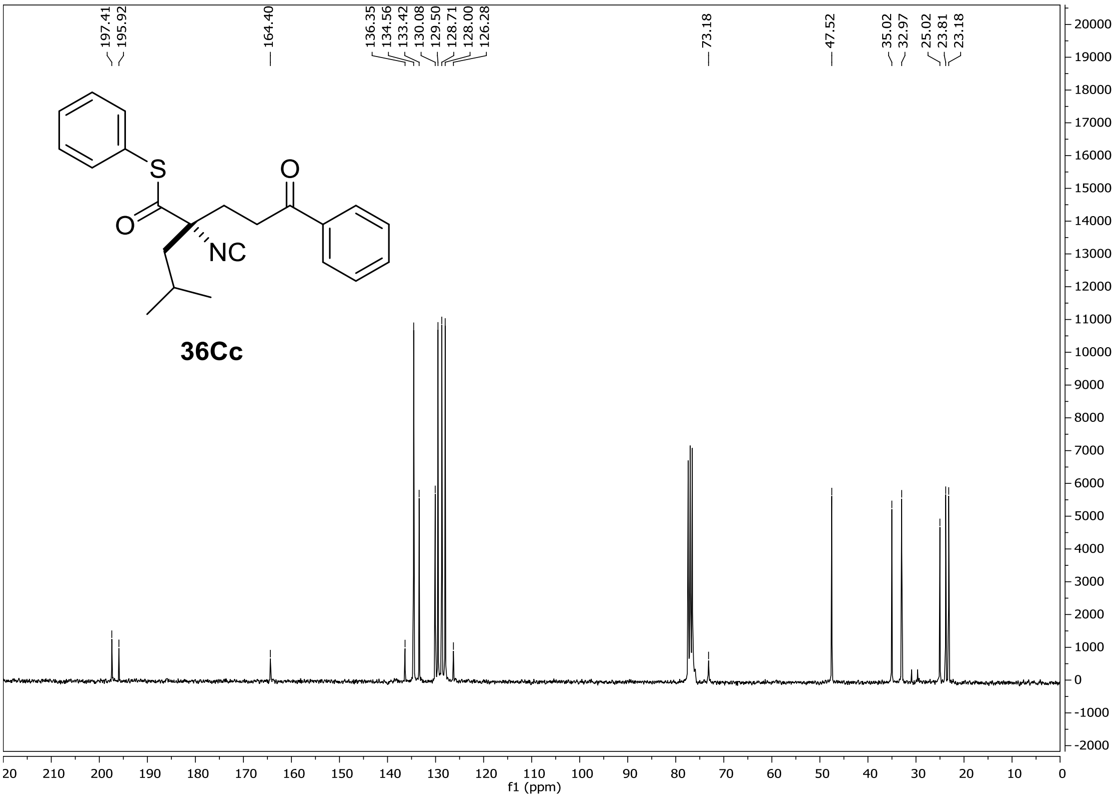

8.00
7.99
7.98
7.98
7.97
7.96
7.96
7.59
7.59
7.57
7.57
7.56
7.51
7.51
7.49
7.49
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.36
7.35
7.33
7.33
7.32
7.31
7.30
7.29
7.29
7.28
7.27
7.27
7.26
7.25
3.39
3.38
3.37
3.35
3.34
3.33
3.32
3.29
3.17
3.15
3.13
3.09
3.08
3.07
2.59
2.36
2.35
2.35
2.17
S
O
O
Bn
NC
36Ac
1.65
1.03
10.90
2.01
2.02
1.00
1.05
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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)

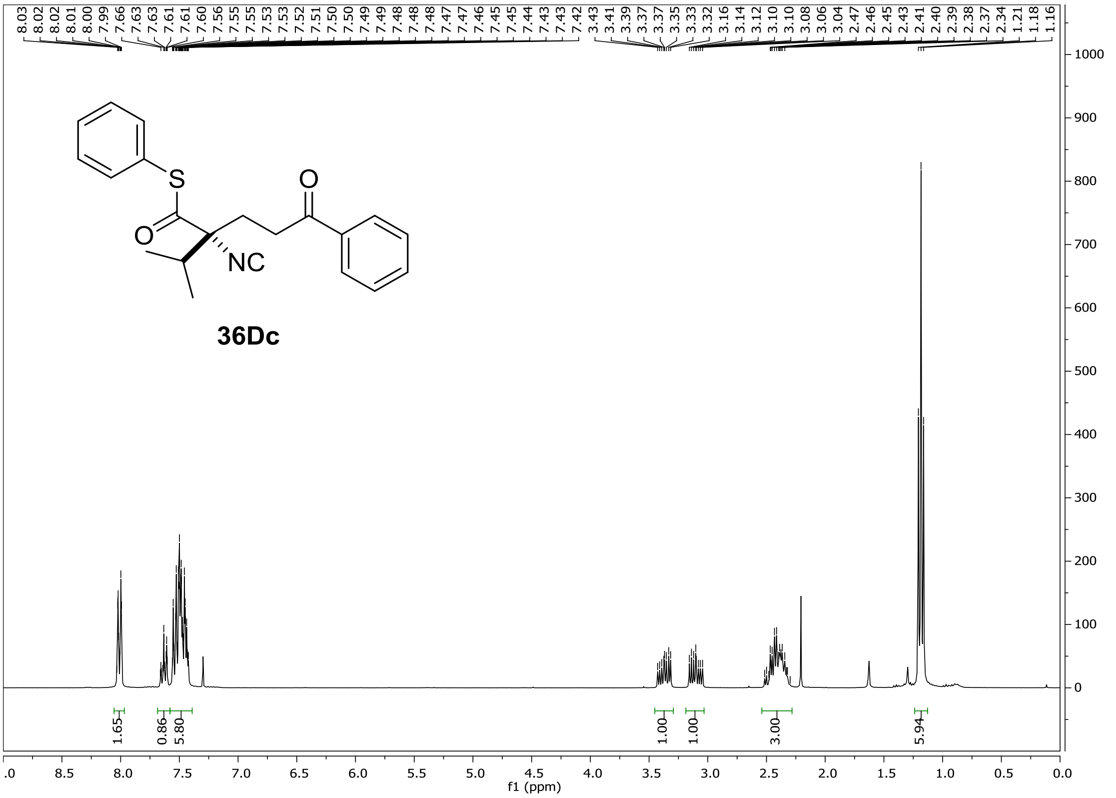

197.47
195.96
165.35
136.49
134.69
133.61
132.97
130.78
130.27
129.62
128.88
128.66
128.21
128.17
126.33
74.60
45.64
33.55
33.30
S
O
O
Bn
NC
36Ac
400
350
300
250
200
150
100
50
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


36Bd
7.89
7.86
7.47
7.45
7.44
7.29
7.27
3.31
3.30
3.28
3.26
3.26
3.24
3.22
3.20
3.16
3.15
3.13
3.11
3.09
3.07
3.05
2.55
2.52
2.49
2.47
2.42
2.37
2.36
2.34
2.31
2.28
2.26
1.77
S
O
O
NC
1.61
3.86
1.77
1.00
1.00
0.98
2.74
1.17
2.95
f1 (ppm)


36Bd
197.16
195.89
163.45
144.48
134.81
134.04
130.24
129.64
129.55
128.30
126.22
69.66
34.35
33.26
27.15
21.82
S
O
O
NC
f1 (ppm)


36Cc
S
O
O
NC
8.03
8.03
8.02
8.01
8.01
8.00
7.63
7.61
7.61
7.60
7.56
7.55
7.55
7.53
7.53
7.52
7.52
7.51
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.43
7.43
7.42
3.36
3.36
3.34
3.32
3.30
3.21
3.20
3.18
3.16
3.15
3.12
2.49
2.40
2.38
2.36
2.35
2.34
2.11
2.11
2.09
2.07
2.07
2.06
2.04
1.90
1.87
1.85
1.14
1.12
1.05
1.04
1.03
1.67
0.80
5.80
1.00
1.00
1.00
1.10
1.98
1.07
2.89
3.05
f1 (ppm)


36Cc
S
O
O
NC
197.41
195.92
164.40
136.35
134.56
133.42
130.08
129.50
128.71
128.00
126.28
73.18
47.52
35.02
32.97
25.02
23.81
23.18
f1 (ppm)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7.99
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7.55
7.55
7.53
7.53
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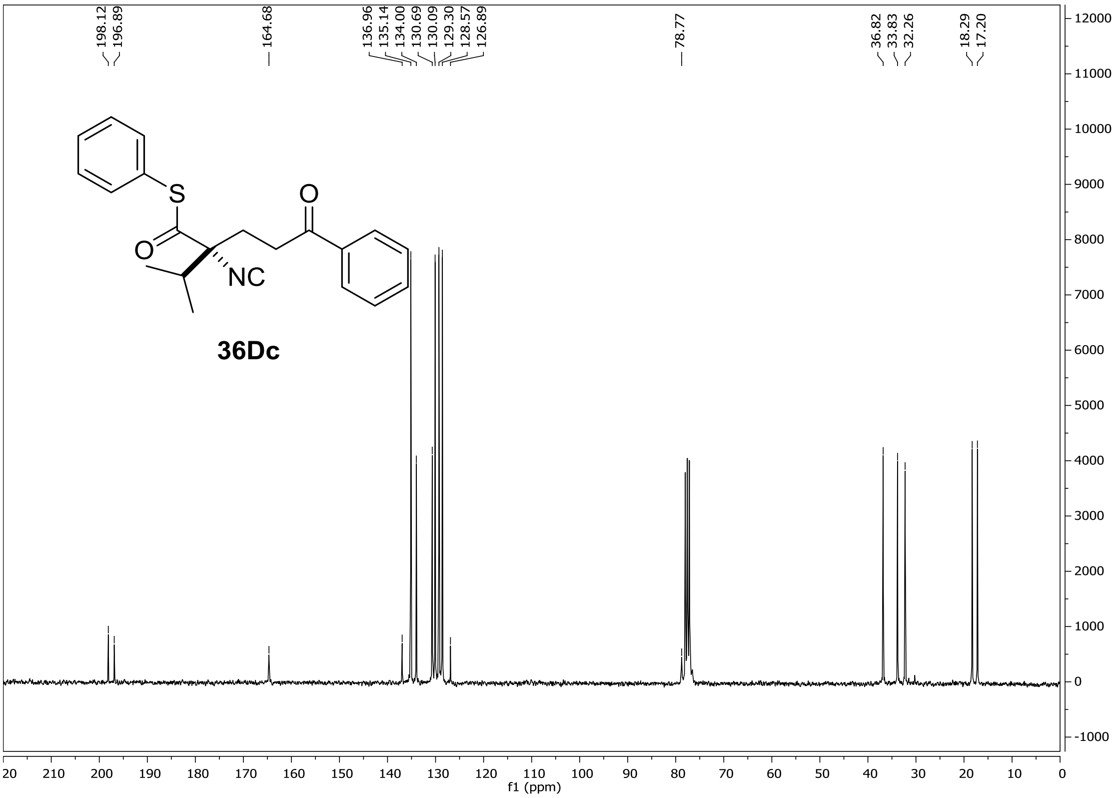
7.51
7.50
7.50
7.49
7.49
7.48
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.43
7.43
7.42
3.43
3.41
3.39
3.37
3.37
3.35
3.33
3.32
3.16
3.14
3.12
3.10
3.10
3.08
3.06
3.04
2.47
2.46
2.45
2.43
2.41
2.40
2.39
2.38
2.37
2.34
1.21
1.18
1.16
S
O
O
NC
36Dc
1.65
0.86
5.80
1.00
1.00
3.00
5.94
1000
900
800
700
600
500
400
300
200
100
0
.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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78.77
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33.83
32.26
18.29
17.20
S
O
O
NC
36Dc
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
20
210
200
190
180
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120
110
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90
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50
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30
20
10
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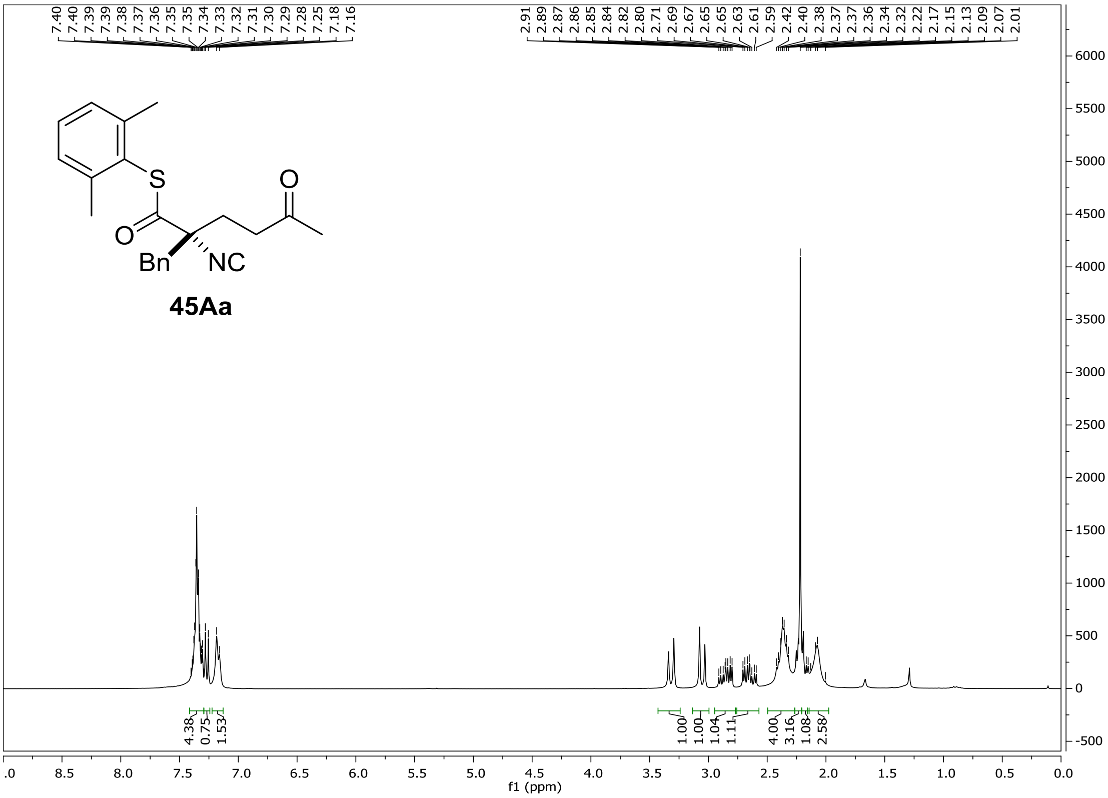
f1 (ppm)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7.29
7.28
7.25
7.18
7.16
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2.89
2.87
2.86
2.85
2.84
2.82
2.80
2.71
2.69
2.67
2.65
2.65
2.63
2.61
2.59
2.42
2.40
2.38
2.37
2.37
2.36
2.34
2.32
2.22
2.17
2.15
2.13
2.09
2.07
2.01
S
O
O
Bn
NC
45Aa
4.38
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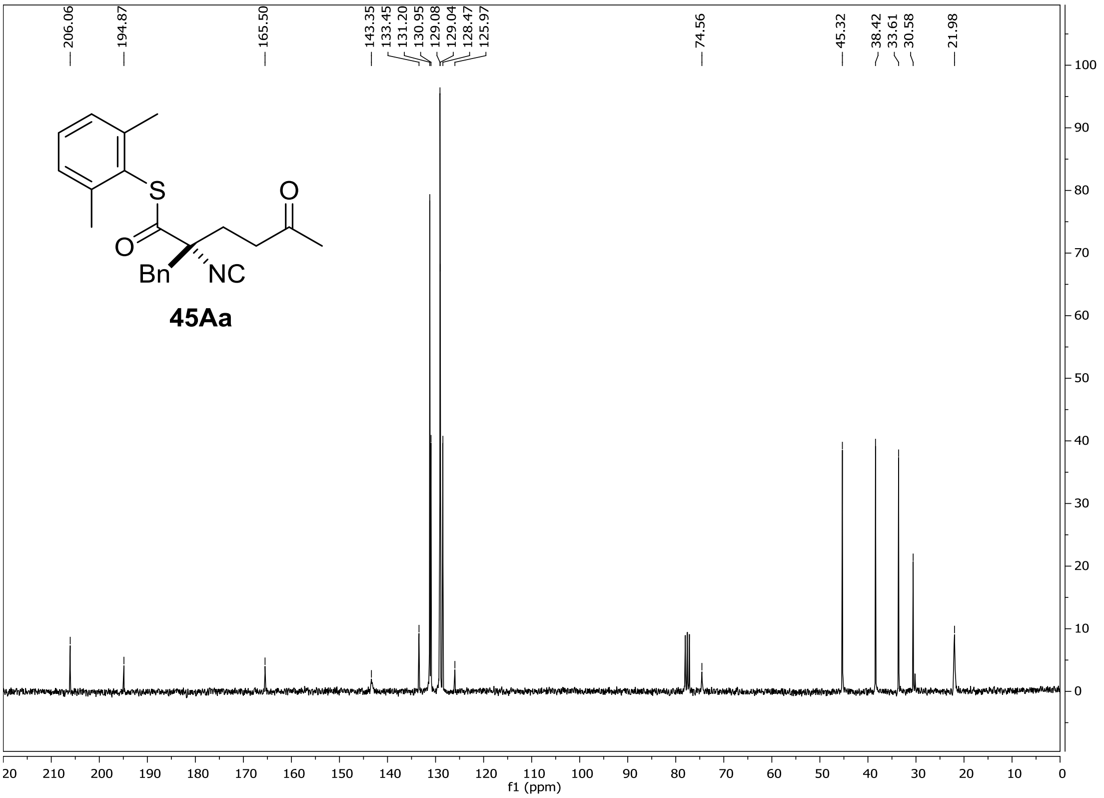
1.53
1.00
1.00
1.04
1.11
4.00
3.16
1.08
2.58
f1 (ppm)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133.45
131.20
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129.08
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128.47
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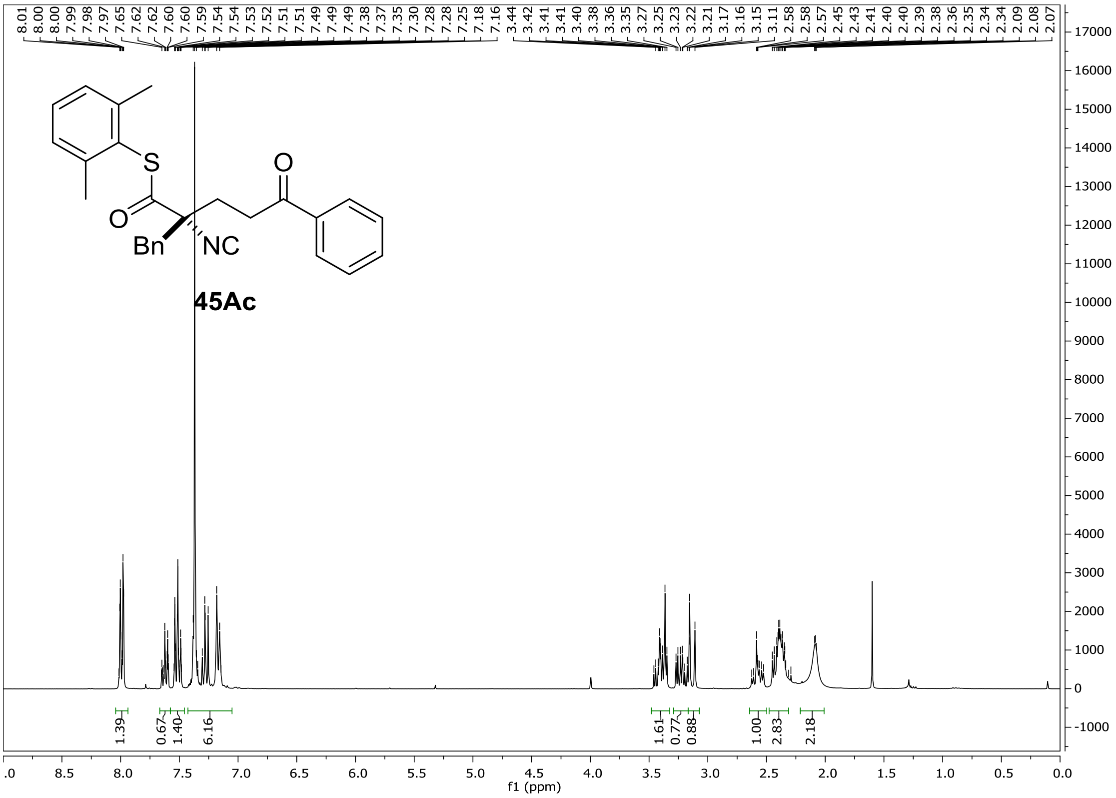
38.42
33.61
30.58
21.98
S
O
O
Bn
NC
45Aa
f1 (ppm)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7.54
7.54
7.53
7.52
7.51
7.51
7.49
7.49
7.49
7.38
7.37
7.35
7.30
7.28
7.28
7.25
7.18
7.16
3.44
3.42
3.41
3.41
3.40
3.38
3.36
3.35
3.27
3.25
3.23
3.22
3.21
3.17
3.16
3.15
3.11
2.58
2.58
2.57
2.45
2.43
2.41
2.40
2.40
2.39
2.38
2.36
2.35
2.34
2.34
2.09
2.08
2.07
S
O
O
Bn
NC
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1.61
0.77
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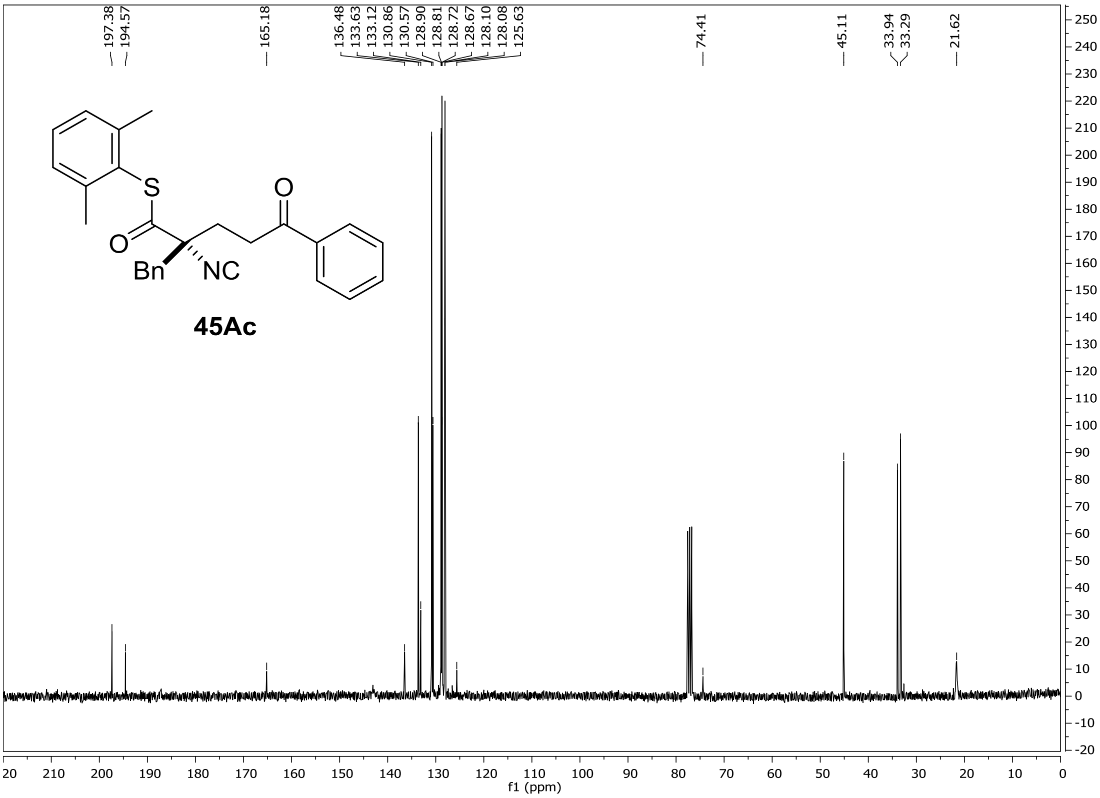
2.18
f1 (ppm)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133.63
133.12
130.86
130.57
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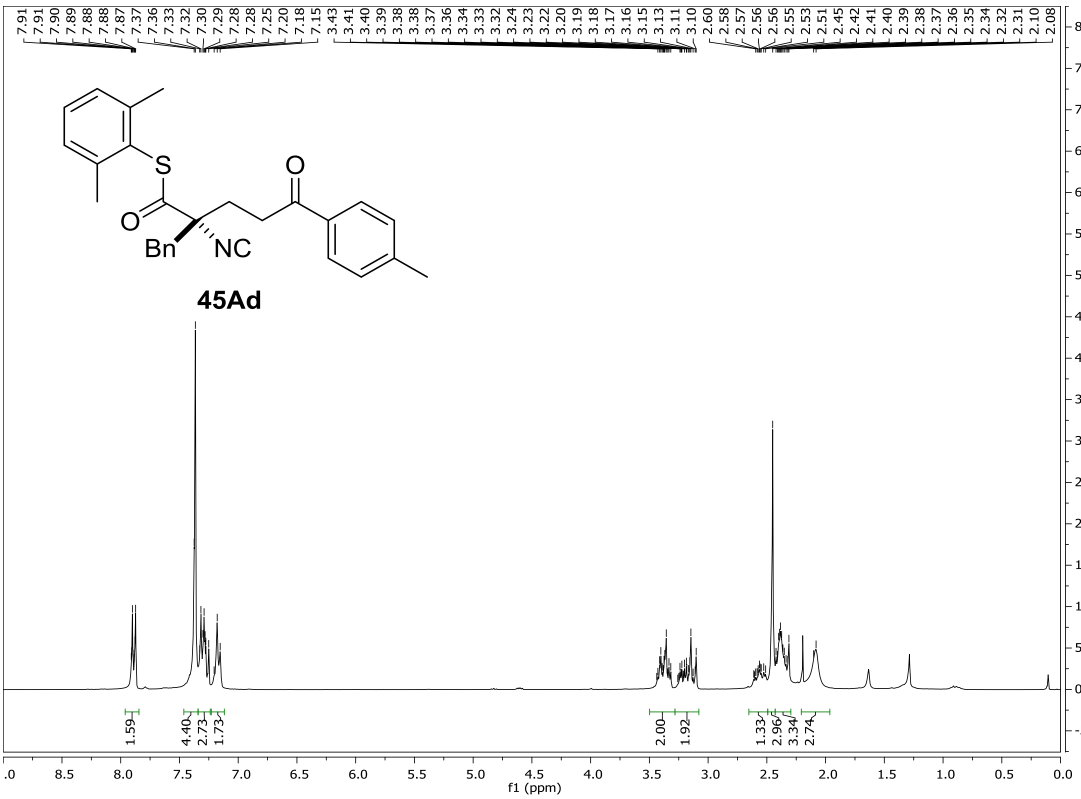
128.81
128.72
128.67
128.10
128.08
125.63
74.41
45.11
33.94
33.29
21.62
S
O
O
Bn
NC
45Ac
f1 (ppm)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7.89
7.88
7.88
7.87
7.37
7.36
7.33
7.32
7.30
7.29
7.28
7.28
7.25
7.20
7.18
7.15
3.43
3.41
3.40
3.39
3.38
3.38
3.37
3.36
3.34
3.33
3.32
3.24
3.23
3.22
3.20
3.19
3.18
3.17
3.16
3.15
3.13
3.11
3.10
2.60
2.58
2.57
2.56
2.56
2.55
2.53
2.51
2.45
2.42
2.41
2.40
2.39
2.38
2.37
2.36
2.35
2.34
2.32
2.31
2.10
2.08
S
O
O
Bn
NC
45Ad
1.59
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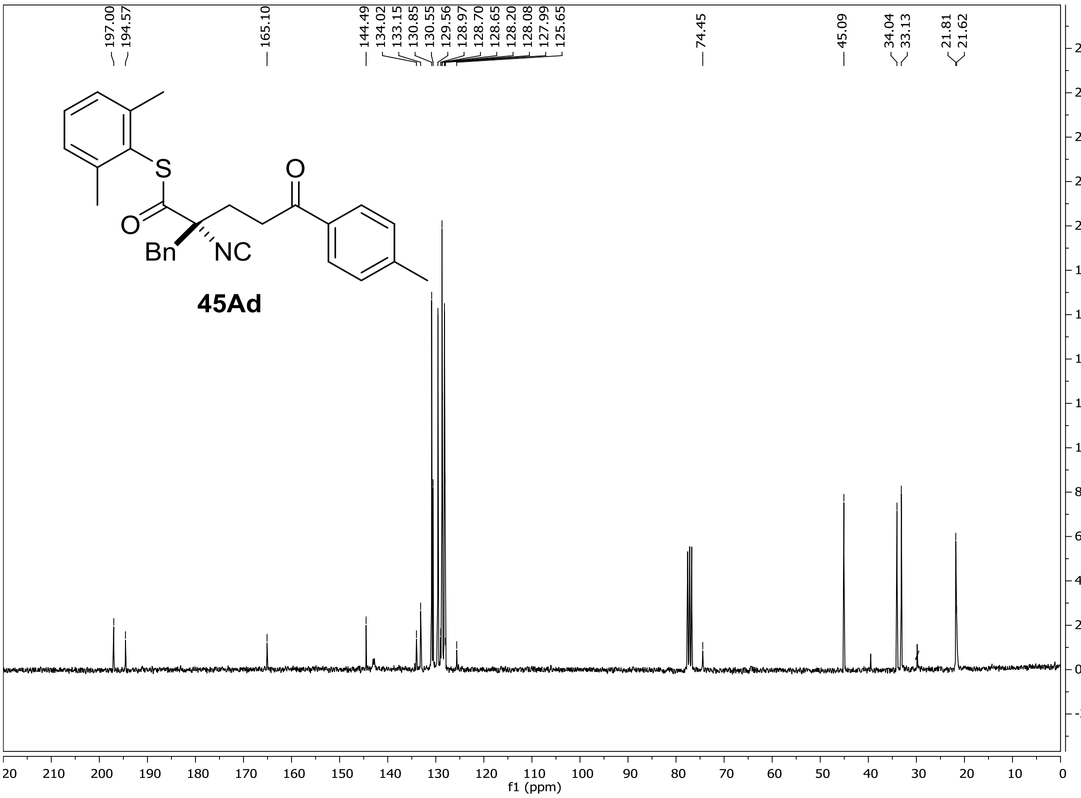
2.73
1.73
2.00
1.92
1.33
2.96
3.34
2.74
f1 (ppm)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130.55
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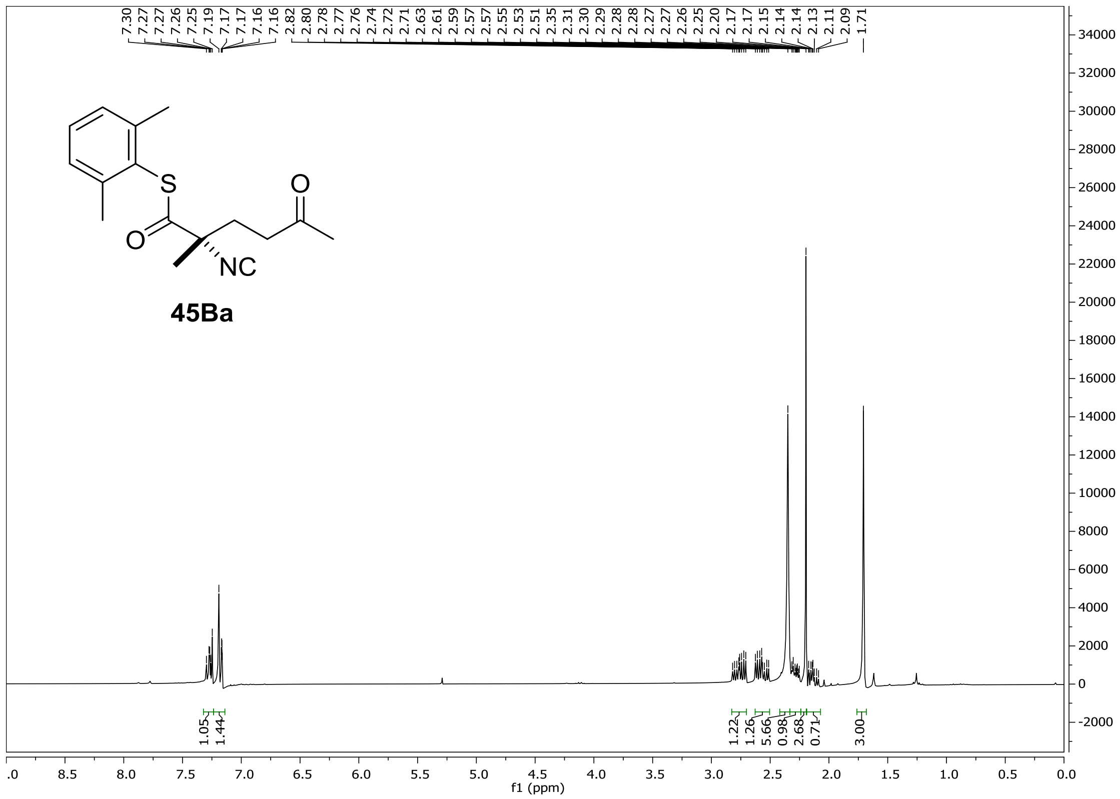
128.97
128.70
128.65
128.20
128.08
127.99
125.65
74.45
45.09
34.04
33.13
21.81
21.62
S
O
O
Bn
NC
45Ad
f1 (ppm)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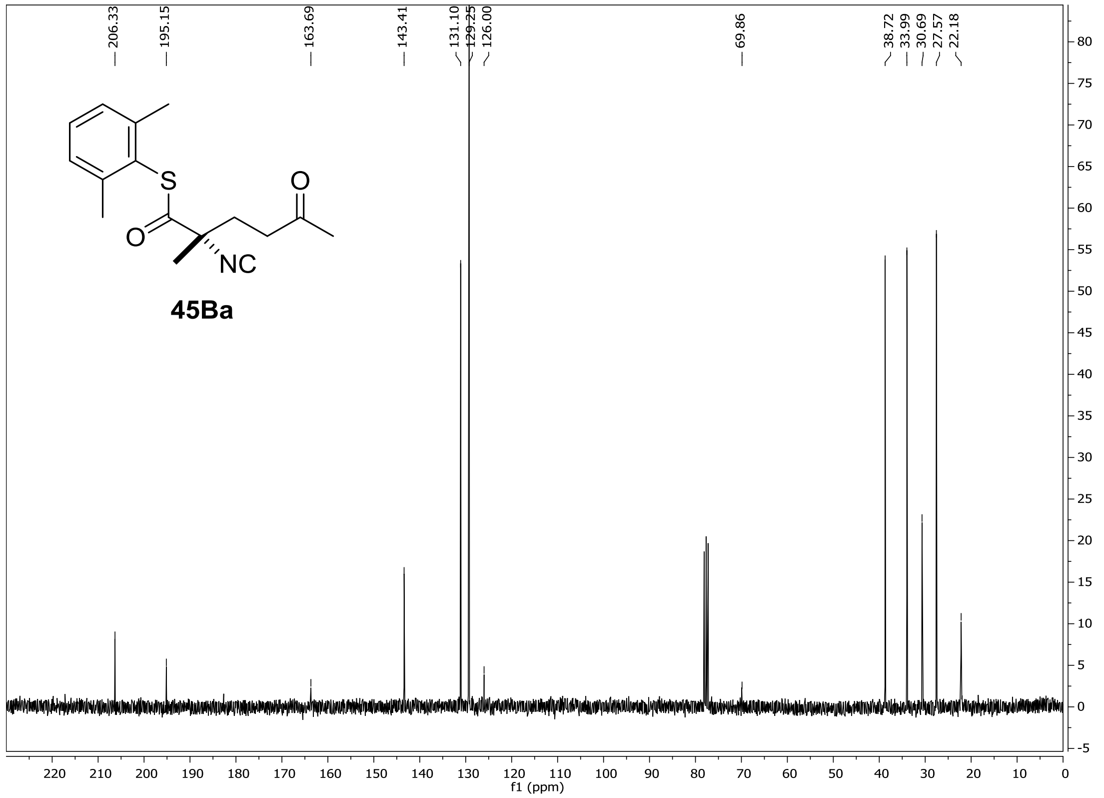
7.25
7.19
7.17
7.17
7.16
7.16
2.82
2.80
2.78
2.77
2.76
2.74
2.72
2.71
2.63
2.61
2.59
2.57
2.57
2.55
2.53
2.51
2.35
2.31
2.30
2.29
2.28
2.28
2.27
2.27
2.26
2.25
2.20
2.17
2.17
2.15
2.14
2.14
2.13
2.11
2.09
1.71
S
O
O
NC
45Ba
1.05
1.44
1.22
1.26
5.66
0.98
2.68
0.71
3.00
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
.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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163.69
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131.10
129.25
126.00
69.86
38.72
33.99
30.69
27.57
22.18
S
O
O
NC
45Ba
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
220
210
200
190
180
170
160
150
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130
120
110
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90
80
70
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40
30
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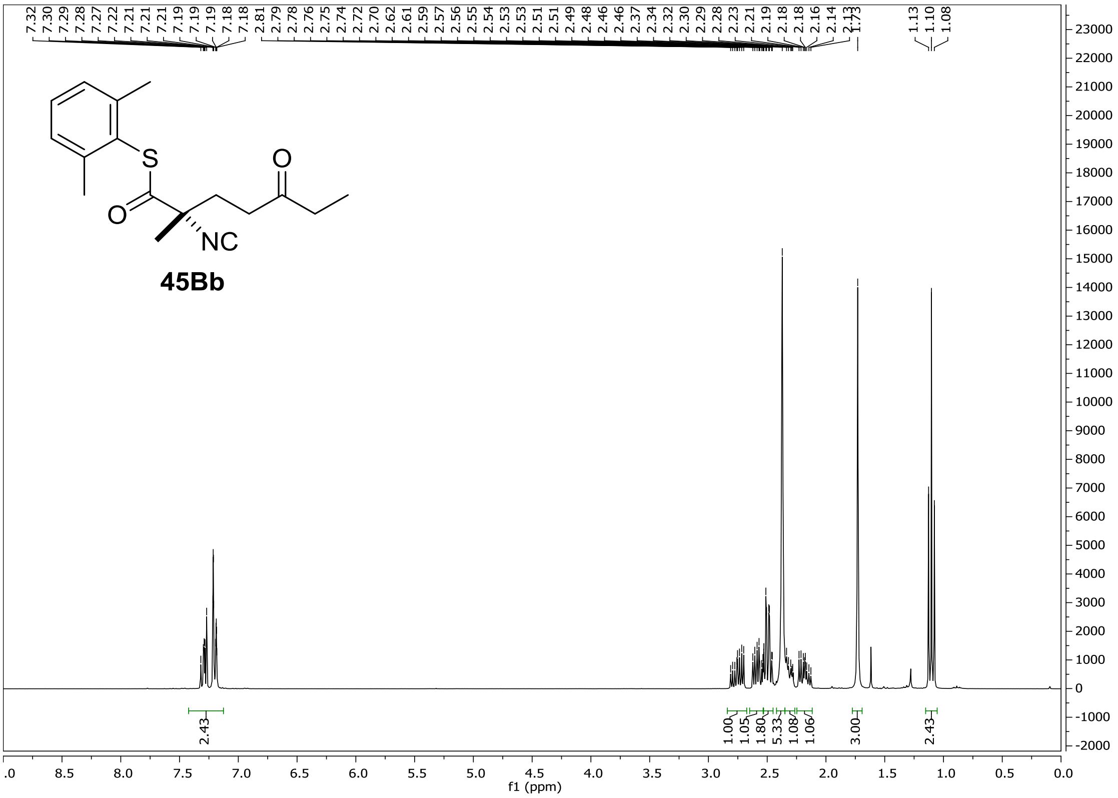
0
f1 (ppm)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7.21
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7.19
7.19
7.18
2.81
2.79
2.78
2.76
2.75
2.74
2.72
2.70
2.62
2.61
2.59
2.57
2.56
2.55
2.54
2.53
2.53
2.51
2.51
2.49
2.48
2.46
2.46
2.37
2.34
2.32
2.30
2.29
2.28
2.23
2.21
2.19
2.18
2.18
2.16
2.14
2.13
1.73
1.13
1.10
1.08
S
O
O
NC
45Bb
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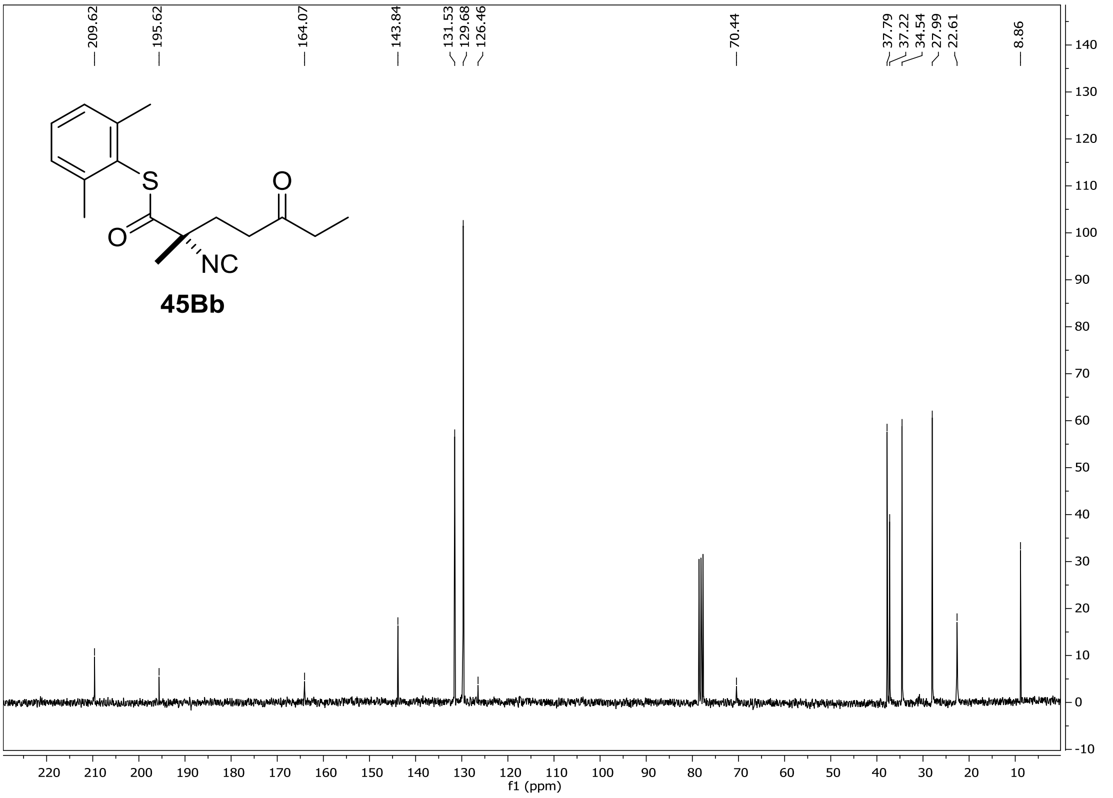
1.00
1.05
1.80
5.33
1.08
1.06
3.00
2.43
f1 (ppm)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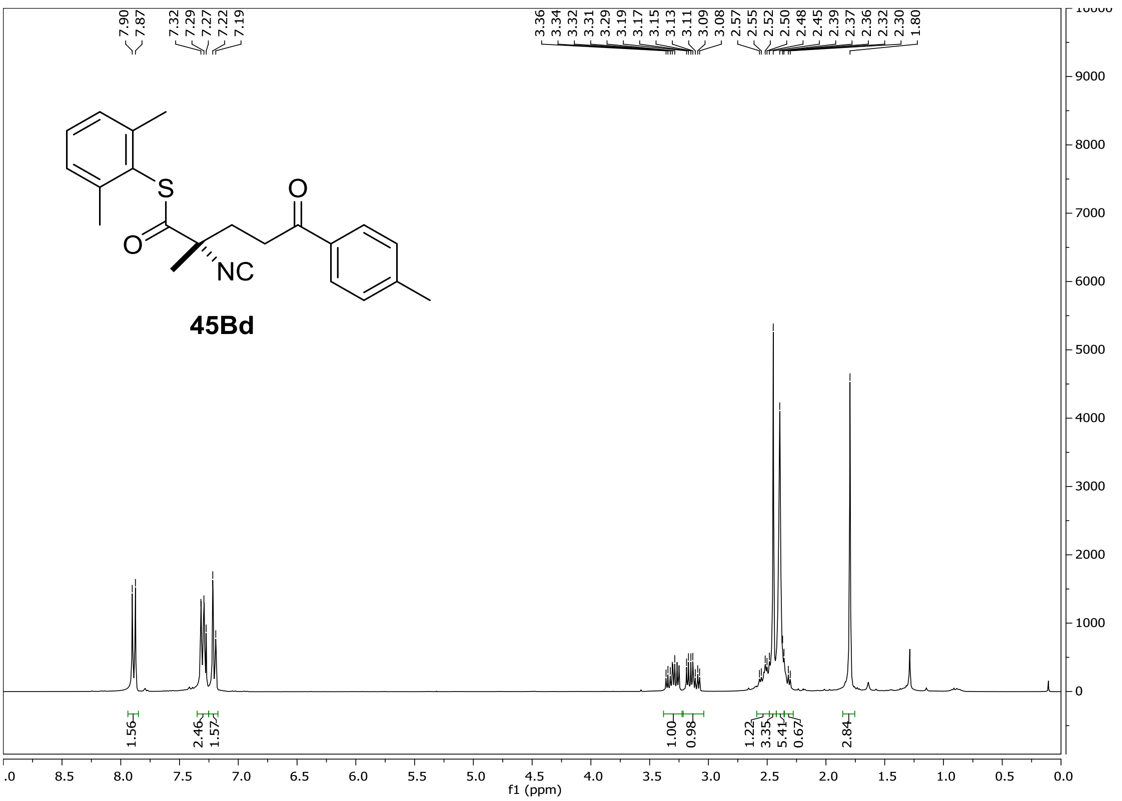
37.22
34.54
27.99
22.61
8.86
S
O
O
NC
45Bb
f1 (ppm)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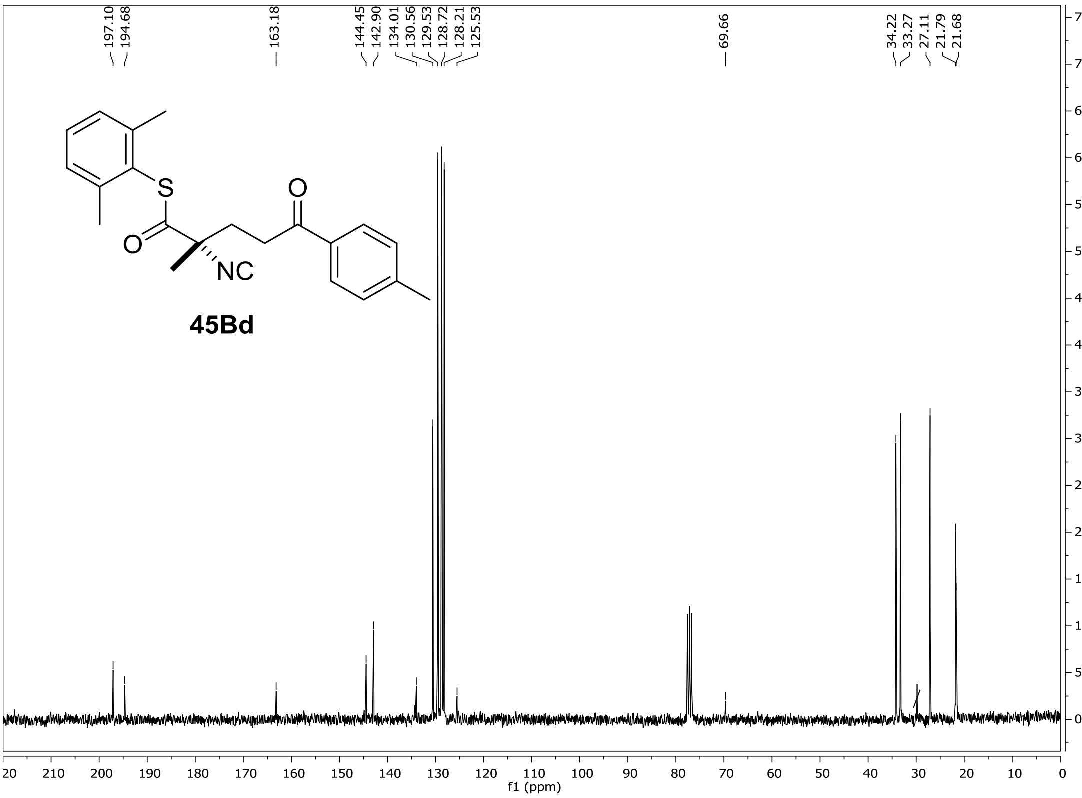
3.36
3.34
3.32
3.31
3.29
3.19
3.17
3.15
3.13
3.11
3.09
3.08
2.57
2.55
2.52
2.50
2.48
2.45
2.39
2.37
2.36
2.32
2.30
1.80
S
O
O
NC
45Bd
1.56
2.46
1.57
1.00
0.98
1.22
3.35
5.41
0.67
2.84
f1 (ppm)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0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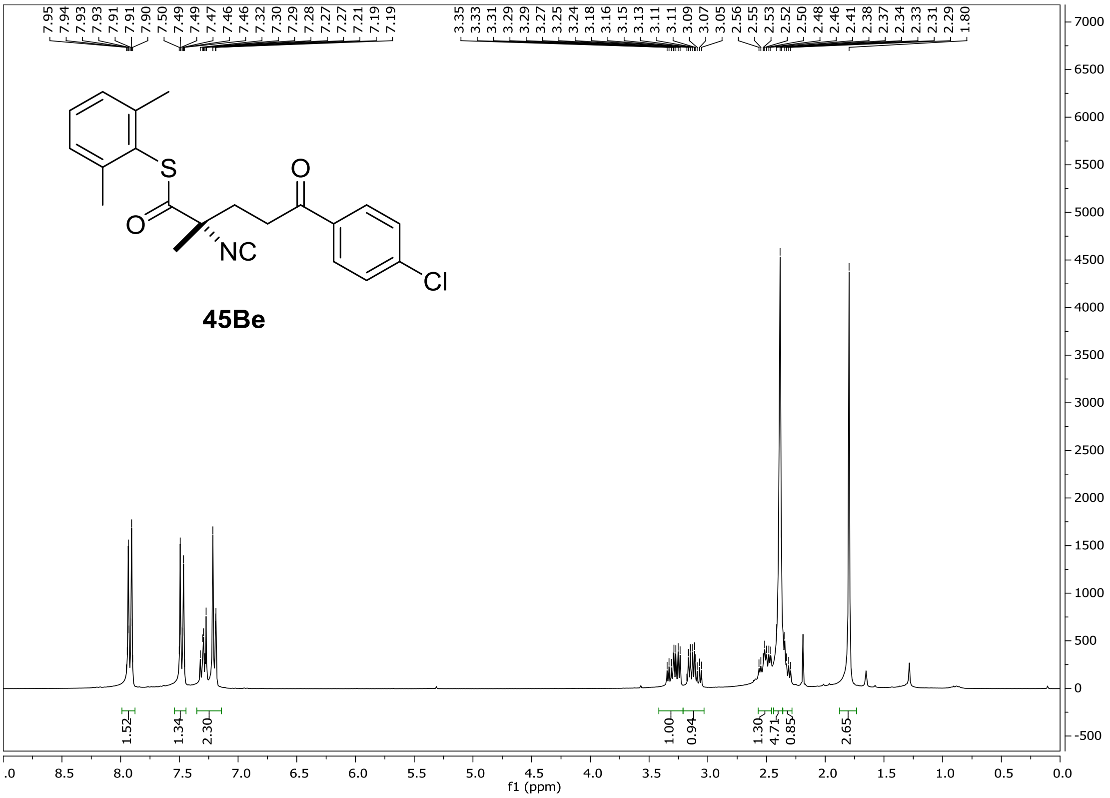
163.18
144.45
142.90
134.01
130.56
129.53
128.72
128.21
125.53
69.66
34.22
33.27
27.11
21.79
21.68
S
O
O
NC
45Bd
f1 (ppm)
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0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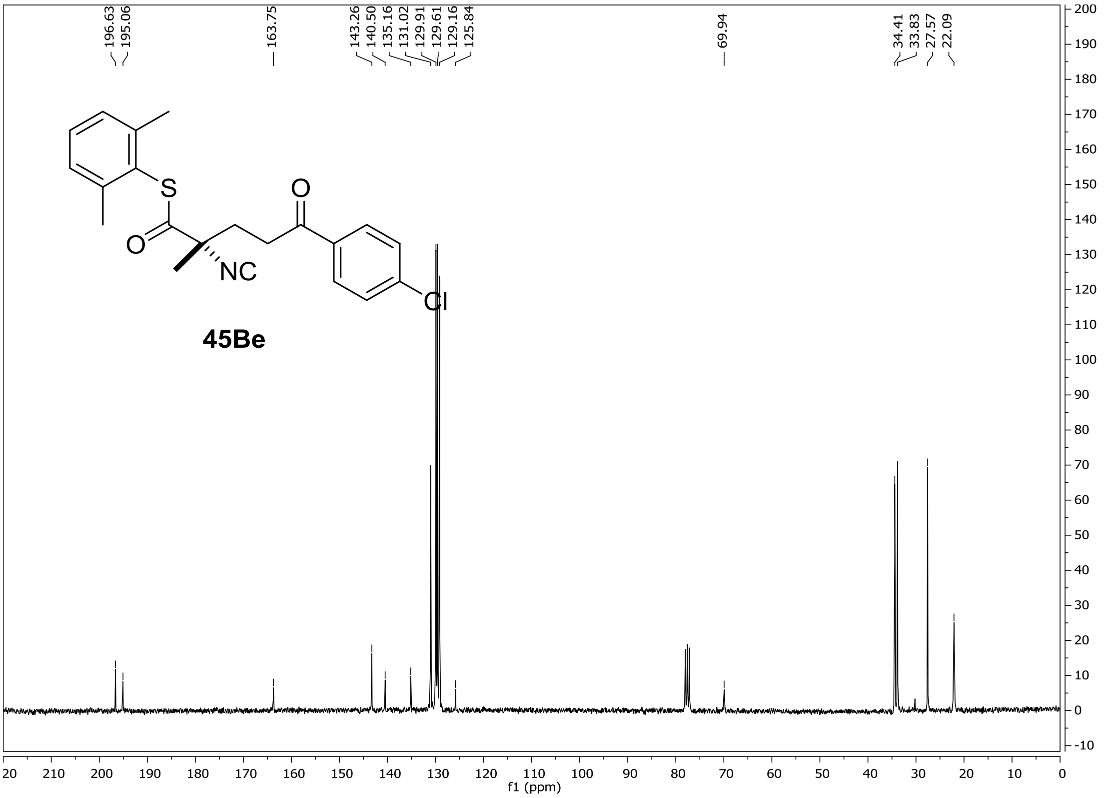
3.35 3.33 3.31 3.29 3.29 3.27 3.25 3.24 3.18 3.16 3.15 3.13 3.11 3.11 3.09 3.07 3.05 2.56 2.55 2.53 2.52 2.50 2.48 2.46 2.41 2.38 2.37 2.34 2.33 2.31 2.29 1.80
S
O
O
NC
Cl
45Be
1.52
1.34
2.30
1.00
0.94
1.30
4.71
0.85
2.65
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.0 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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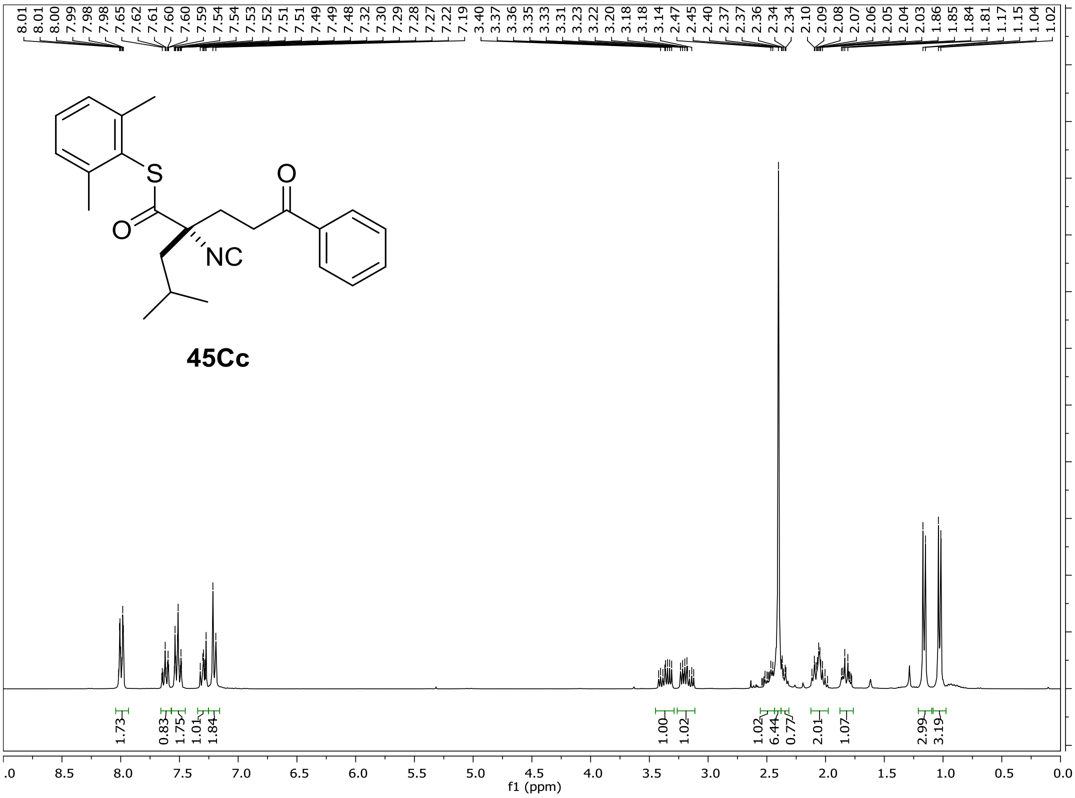
143.26 140.50 135.16 131.02 129.91 129.61 129.16 125.84
69.94
34.41 33.83 27.57 22.09
S
O
O
NC
Cl
45Be
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.54
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7.52
7.51
7.51
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7.49
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7.19
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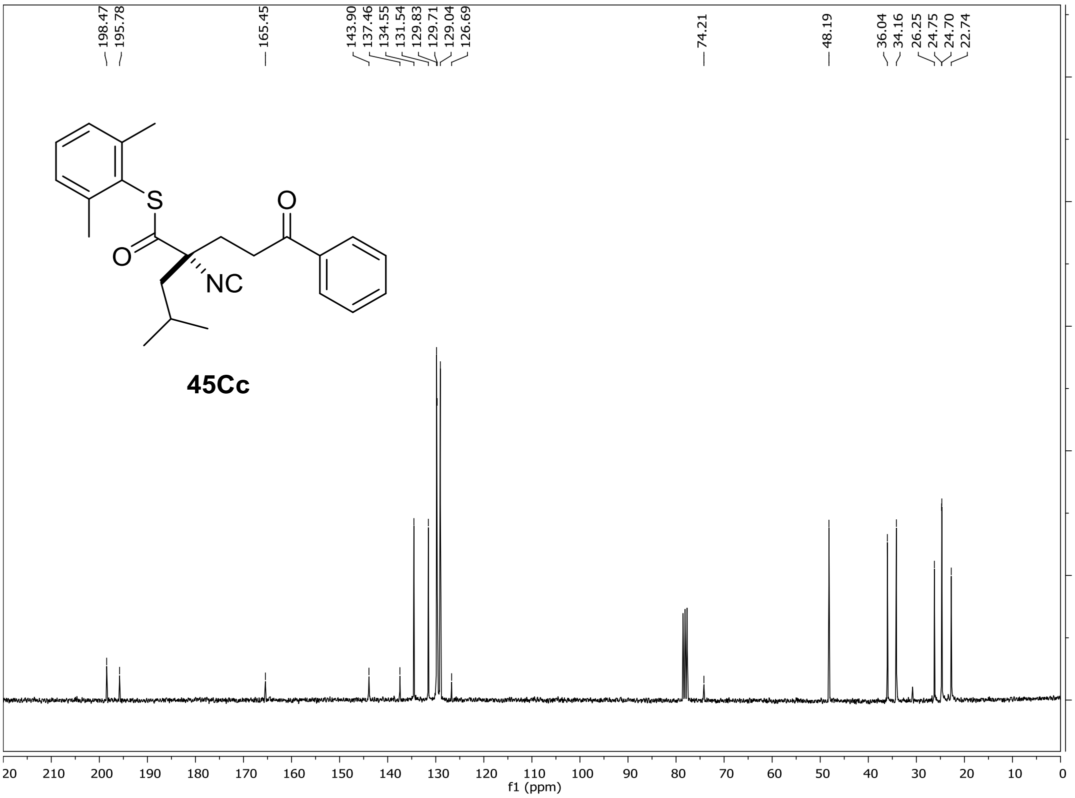
3.37
3.36
3.35
3.33
3.31
3.23
3.22
3.20
3.18
3.18
3.14
2.47
2.45
2.40
2.37
2.37
2.36
2.34
2.34
2.10
2.09
2.08
2.07
2.06
2.05
2.04
2.03
1.86
1.85
1.84
1.81
1.17
1.15
1.04
1.02
S
O
O
NC
1.73
0.83
1.75
1.01
1.84
1.00
1.02
1.02
6.44
0.77
2.01
1.07
2.99
3.19
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.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)

45Cc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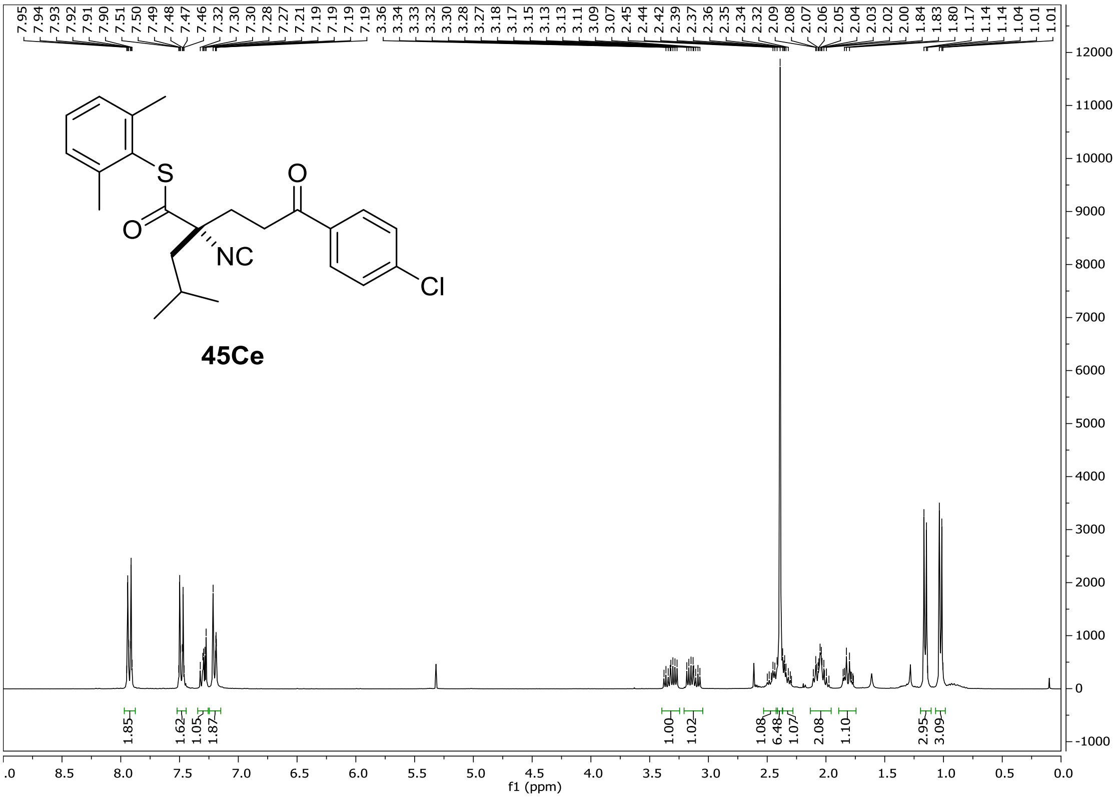
129.83
129.71
129.04
126.69
74.21
48.19
36.04
34.16
26.25
24.75
24.70
22.74
S
O
O
NC
250
200
150
100
50
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

45Cc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7.46
7.32
7.30
7.30
7.28
7.27
7.21
7.19
7.19
7.19
7.19
3.36
3.34
3.33
3.32
3.30
3.28
3.27
3.18
3.17
3.15
3.13
3.13
3.11
3.09
3.07
2.45
2.44
2.42
2.39
2.37
2.36
2.35
2.34
2.32
2.09
2.08
2.07
2.06
2.05
2.04
2.03
2.02
2.00
1.84
1.83
1.80
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1.14
1.14
1.04
1.01
1.01
S
O
O
NC
Cl
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6.48
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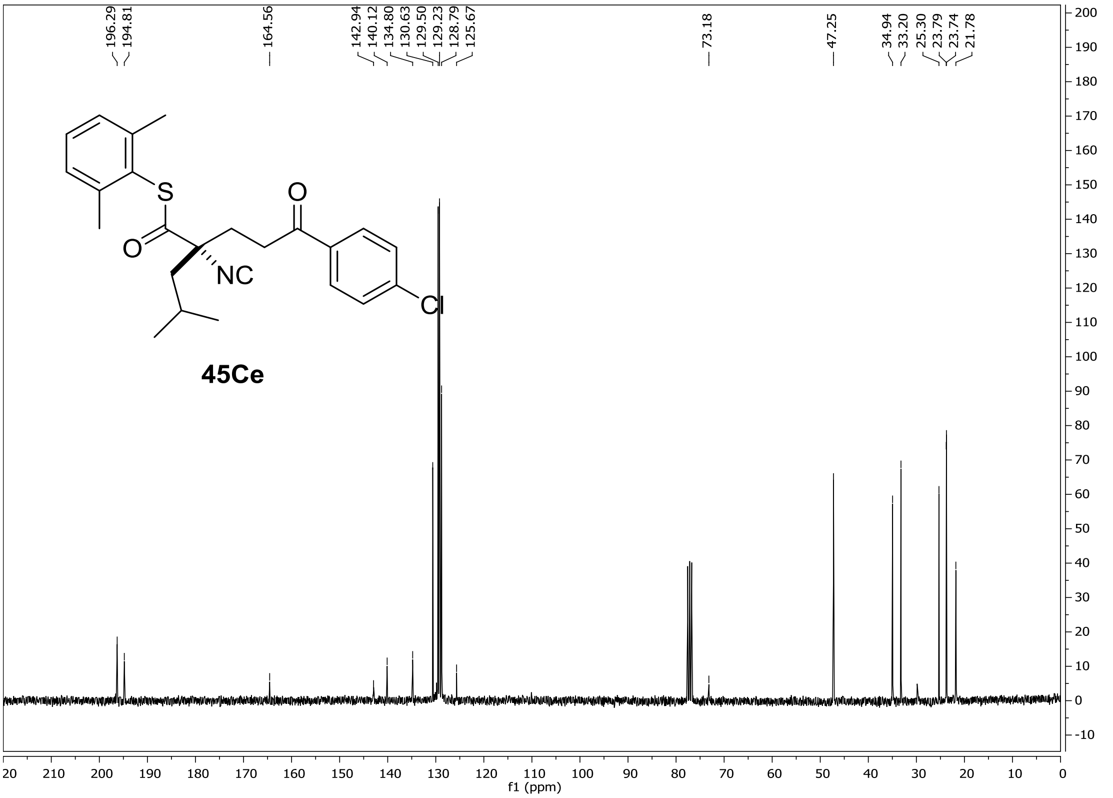
1.10
2.95
3.09
f1 (ppm)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128.79
125.67
73.18
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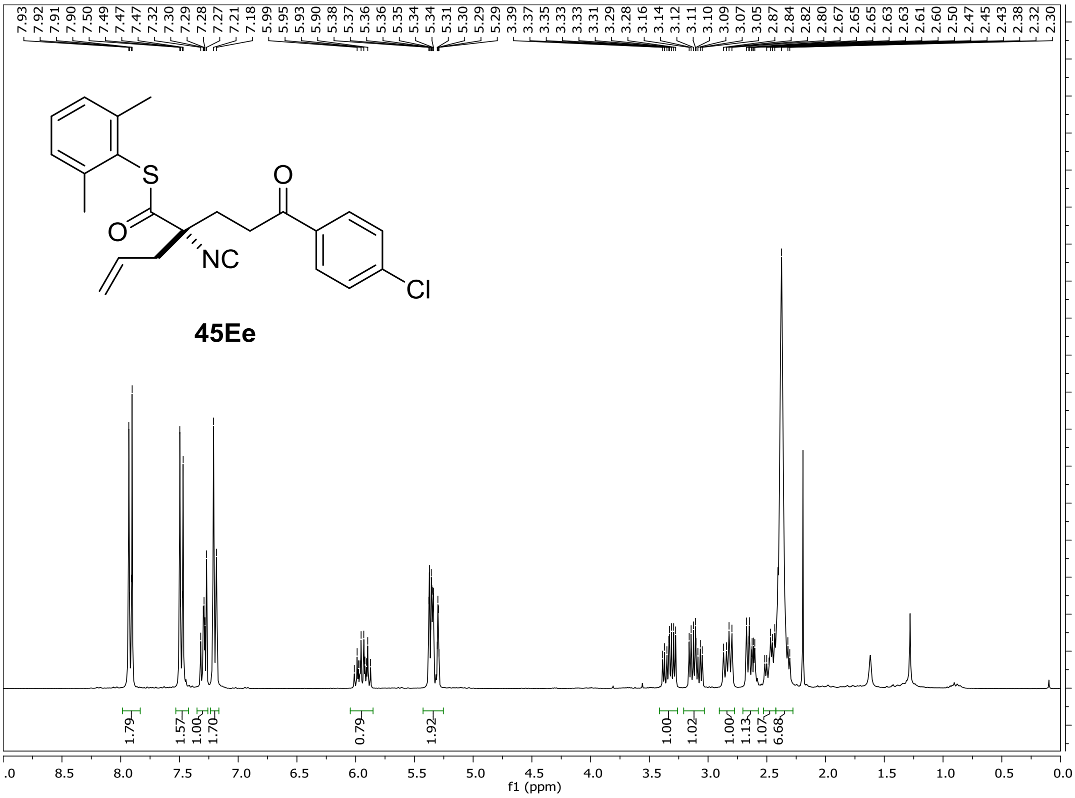
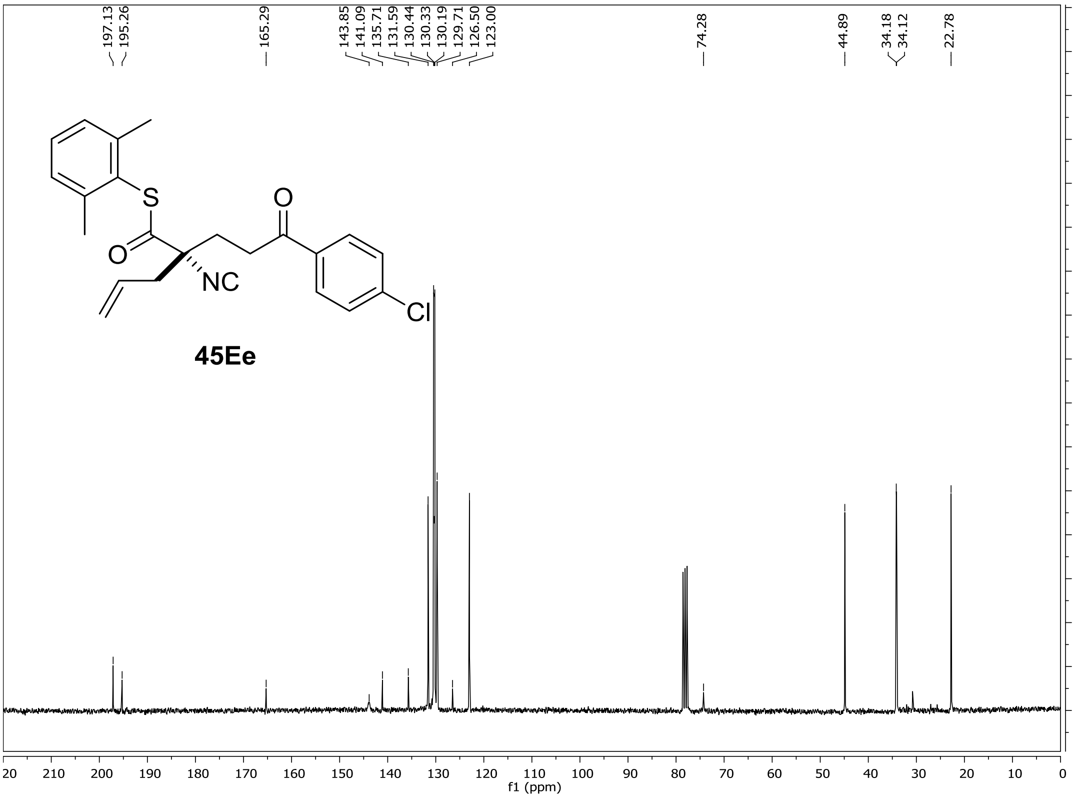
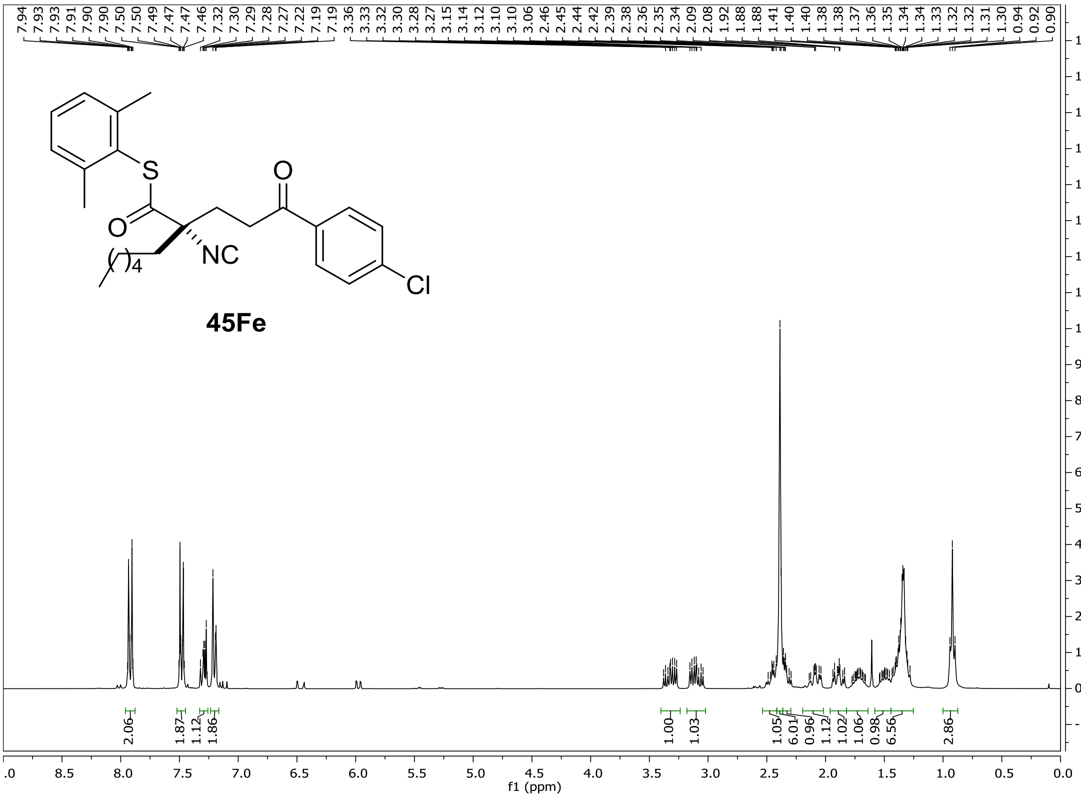
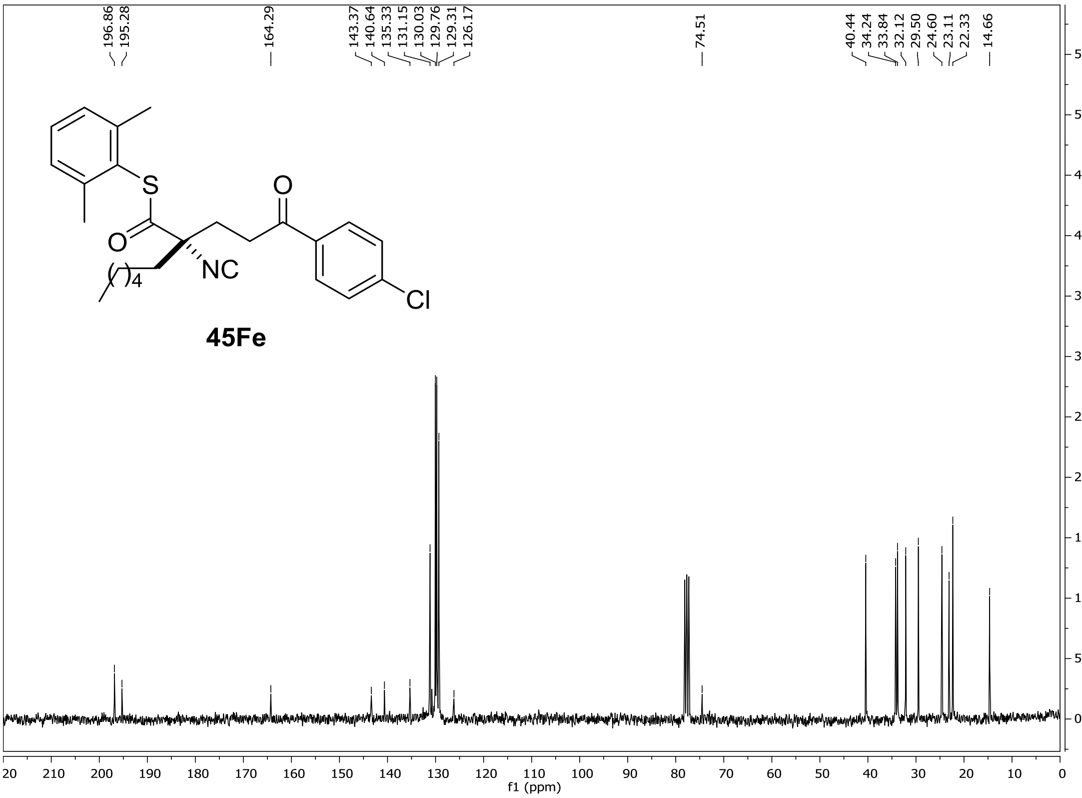
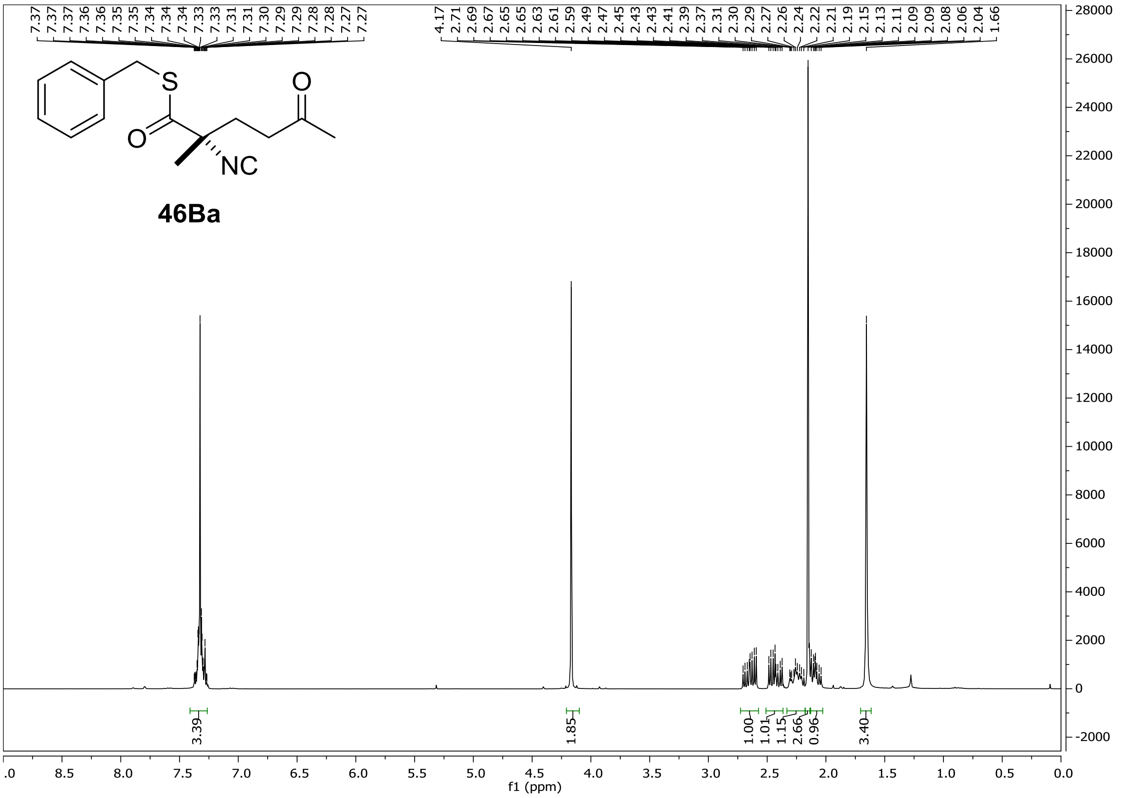
34.94
33.20
25.30
23.79
23.74
21.78
S
O
O
NC
Cl
45Ce
f1 (ppm)


7.93 7.92 7.91 7.90 7.50 7.49 7.47 7.47 7.32 7.30 7.29 7.28 7.27 7.21 7.18 5.99 5.95 5.93 5.90 5.38 5.37 5.36 5.35 5.34 5.34 5.31 5.30 5.29 5.29 3.39 3.37 3.35 3.33 3.33 3.31 3.29 3.28 3.16 3.14 3.12 3.11 3.10 3.09 3.07 3.05 2.87 2.84 2.82 2.80 2.67 2.65 2.65 2.63 2.63 2.61 2.60 2.50 2.47 2.45 2.43 2.38 2.32 2.30
1.79 1.57 1.00 1.70 0.79 1.92 1.00 1.02 1.00 1.13 1.07 6.68
45Ee
S
O
O
NC
Cl
f1 (ppm)


197.13 195.26 165.29 143.85 141.09 135.71 131.59 130.44 130.33 130.19 129.71 126.50 123.00 74.28 44.89 34.18 34.12 22.78
45Ee
S
O
O
NC
Cl
f1 (ppm)

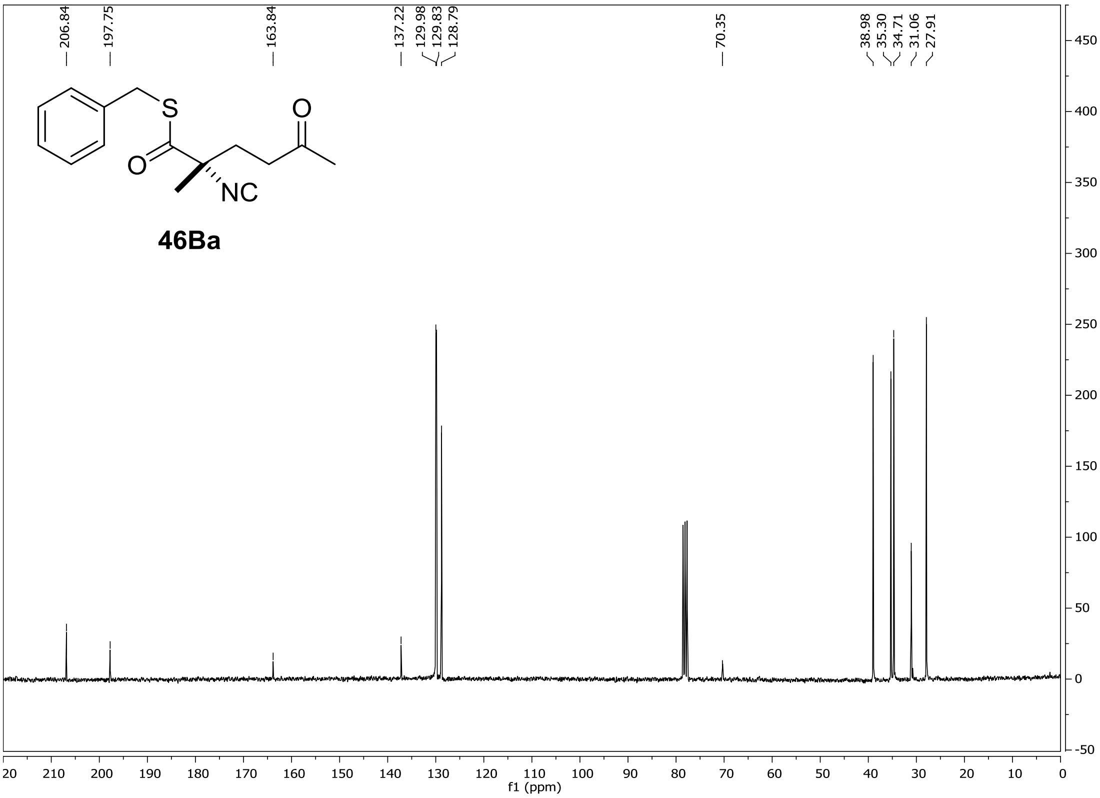

7.94
7.93
7.93
7.91
7.90
7.90
7.50
7.50
7.49
7.47
7.47
7.46
7.32
7.30
7.29
7.28
7.27
7.22
7.19
7.19
3.36
3.33
3.32
3.30
3.28
3.27
3.15
3.14
3.12
3.10
3.10
3.06
2.46
2.45
2.44
2.42
2.39
2.38
2.36
2.35
2.34
2.09
2.08
1.92
1.88
1.88
1.41
1.40
1.40
1.38
1.38
1.37
1.36
1.35
1.34
1.34
1.33
1.32
1.32
1.31
1.30
0.94
0.92
0.90
S
O
O
NC
Cl
4
45Fe
2.06
1.87
1.12
1.86
1.00
1.03
1.05
6.01
0.96
1.12
1.02
1.06
0.98
6.56
2.86
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.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)


196.86
195.28
164.29
143.37
140.64
135.33
131.15
130.03
129.76
129.31
126.17
74.51
40.44
34.24
33.84
32.12
29.50
24.60
23.11
22.33
14.66
S
O
O
NC
Cl
4
45Fe
55
50
45
40
35
30
25
20
15
10
5
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



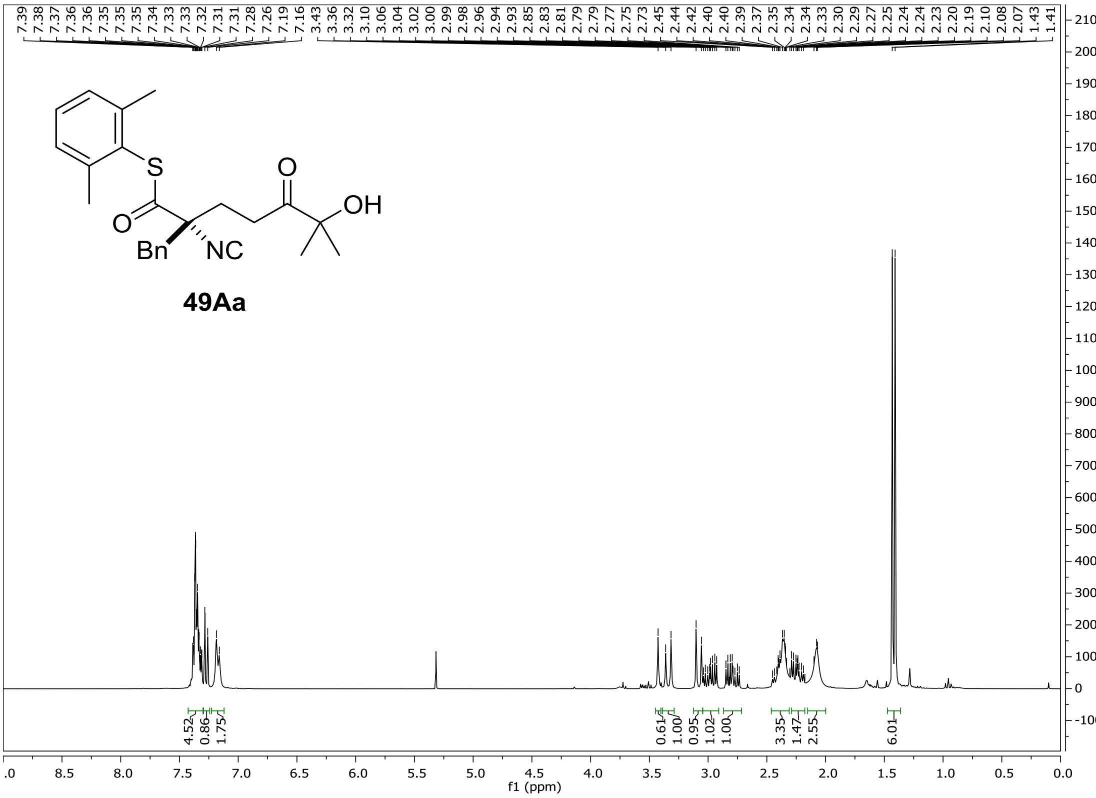
46Ba

7.37 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.31 7.31 7.30 7.29 7.29 7.28 7.28 7.27 7.27
4.17 2.71 2.69 2.67 2.65 2.65 2.63 2.61 2.59 2.49 2.47 2.45 2.43 2.43 2.41 2.39 2.37 2.31 2.30 2.29 2.27 2.26 2.24 2.22 2.21 2.19 2.15 2.13 2.11 2.09 2.09 2.08 2.06 2.04 1.66
S
O
O
NC
3.39
1.85
1.00
1.01
1.15
2.66
0.96
3.40
f1 (ppm)
.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
28000 26000 24000 22000 20000 18000 16000 14000 12000 10000 8000 6000 4000 2000 0 -2000

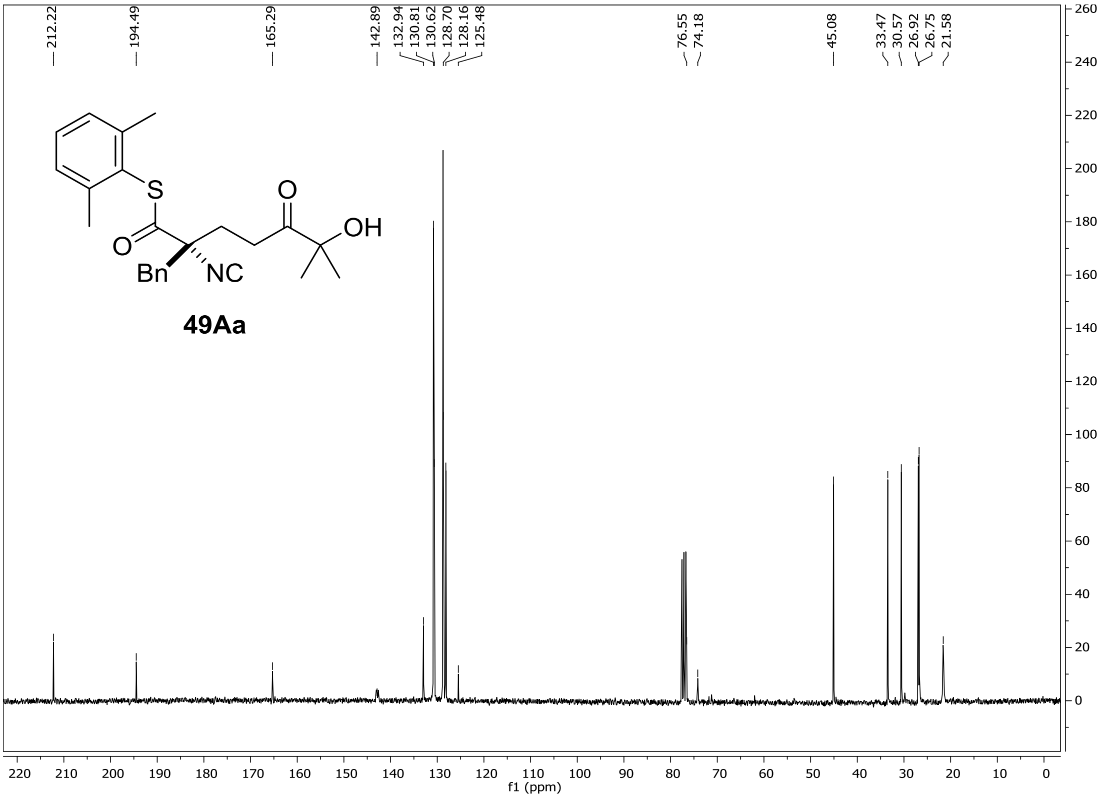


46Ba

206.84
197.75
163.84
137.22 129.98 129.83 128.79
70.35
38.98 35.30 34.71 31.06 27.91
S
O
O
NC
f1 (ppm)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
450 400 350 300 250 200 150 100 50 0 -50

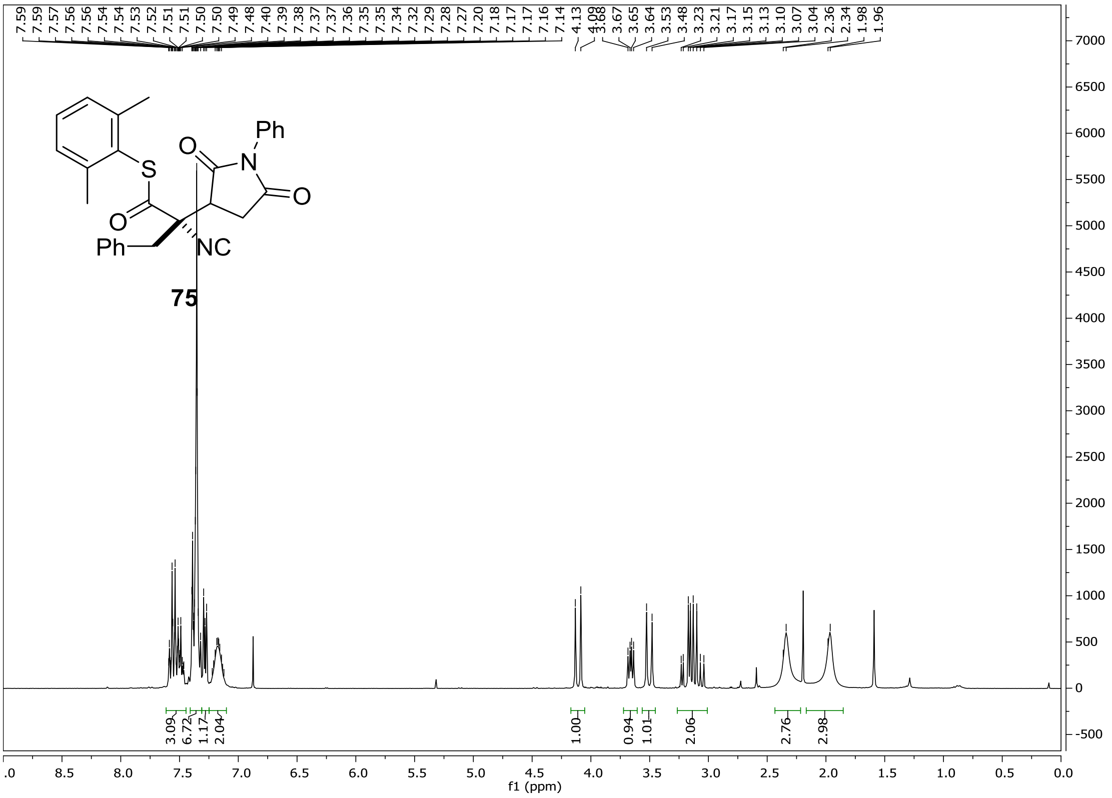

7.39
7.38
7.37
7.36
7.36
7.35
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.28
7.26
7.19
7.16
3.43
3.36
3.32
3.10
3.06
3.04
3.02
3.00
2.99
2.98
2.96
2.94
2.93
2.85
2.83
2.81
2.79
2.79
2.77
2.75
2.73
2.45
2.44
2.42
2.40
2.40
2.39
2.37
2.35
2.34
2.34
2.33
2.30
2.29
2.27
2.25
2.24
2.24
2.23
2.20
2.19
2.10
2.08
2.07
1.43
1.41
S
O
OH
O
Bn
NC
4.52
0.86
1.75
0.61
1.00
0.95
1.02
1.00
3.35
1.47
2.55
6.01
f1 (ppm)

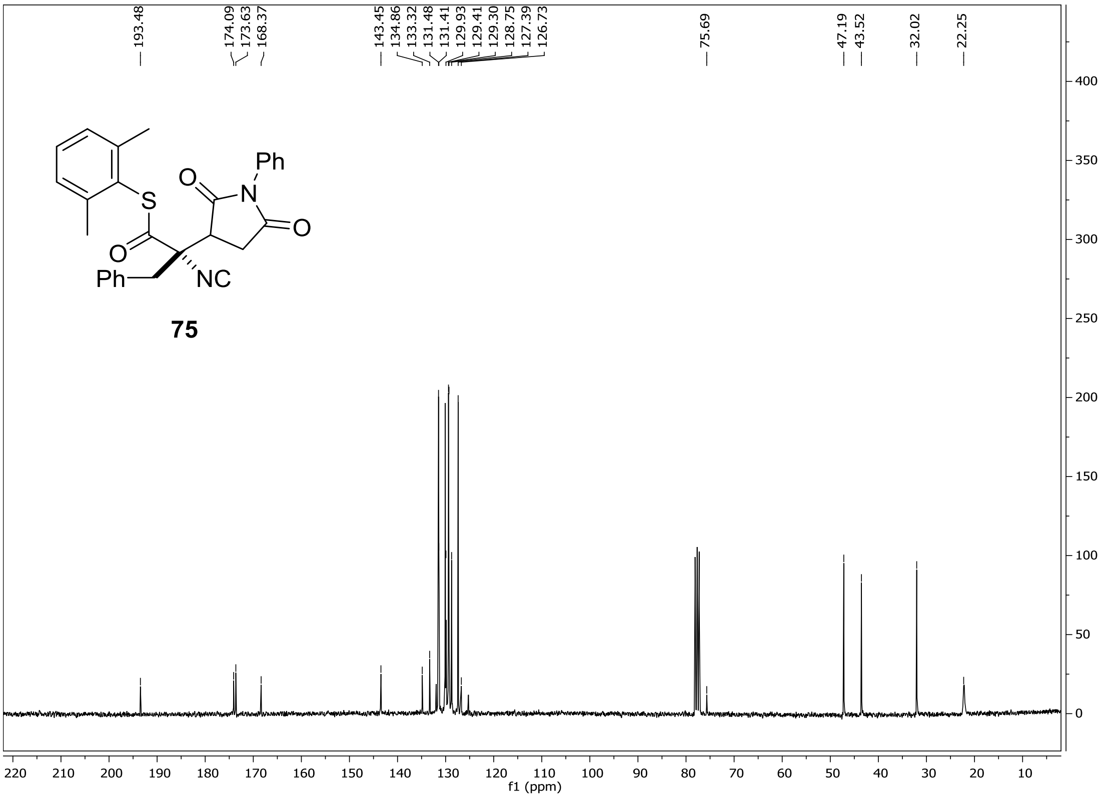
49Aa


212.22
194.49
165.29
142.89
132.94
130.81
130.62
128.70
128.16
125.48
76.55
74.18
45.08
33.47
30.57
26.92
26.75
21.58
S
O
OH
O
Bn
NC
f1 (ppm)

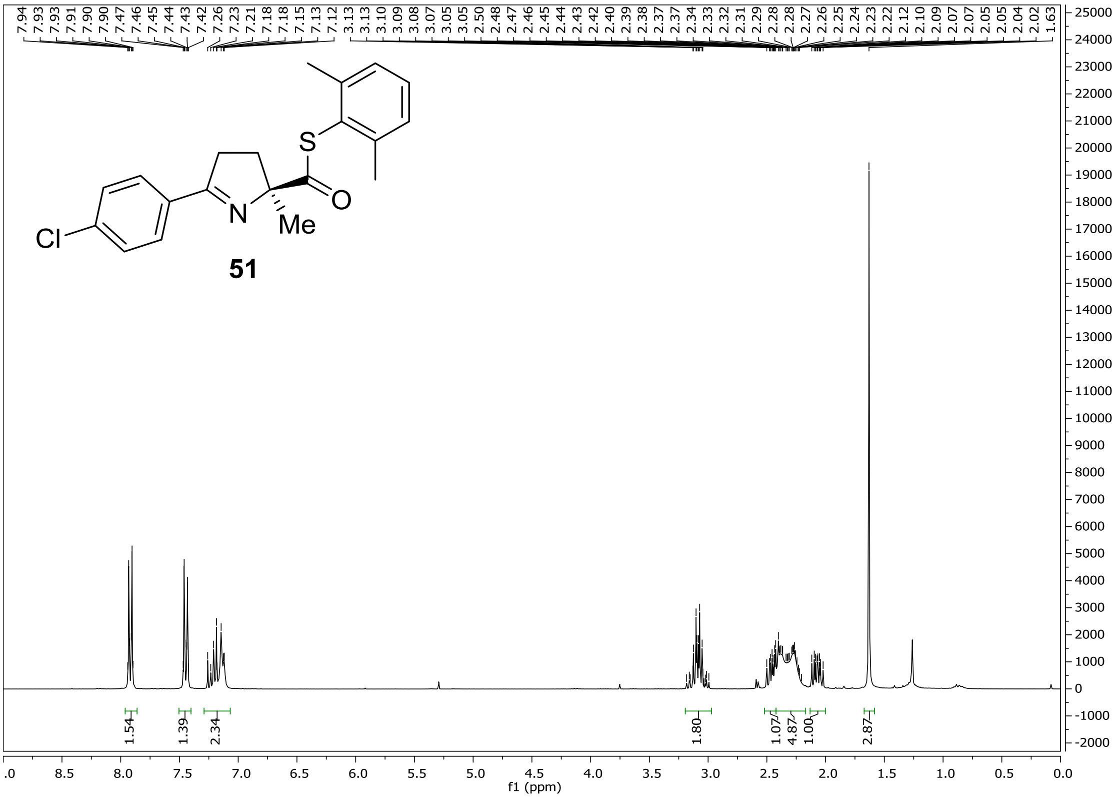
49Aa

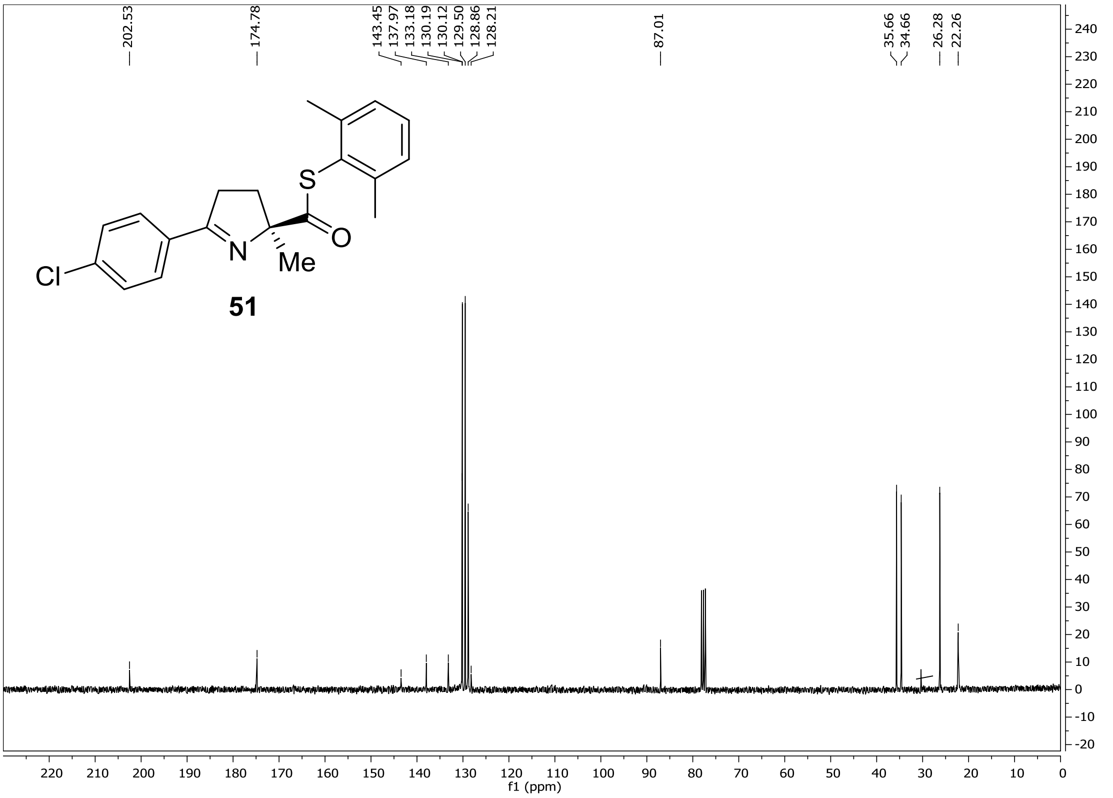
*5.5.3.3. Reaction of **29A** with N-phenyl maleimide*

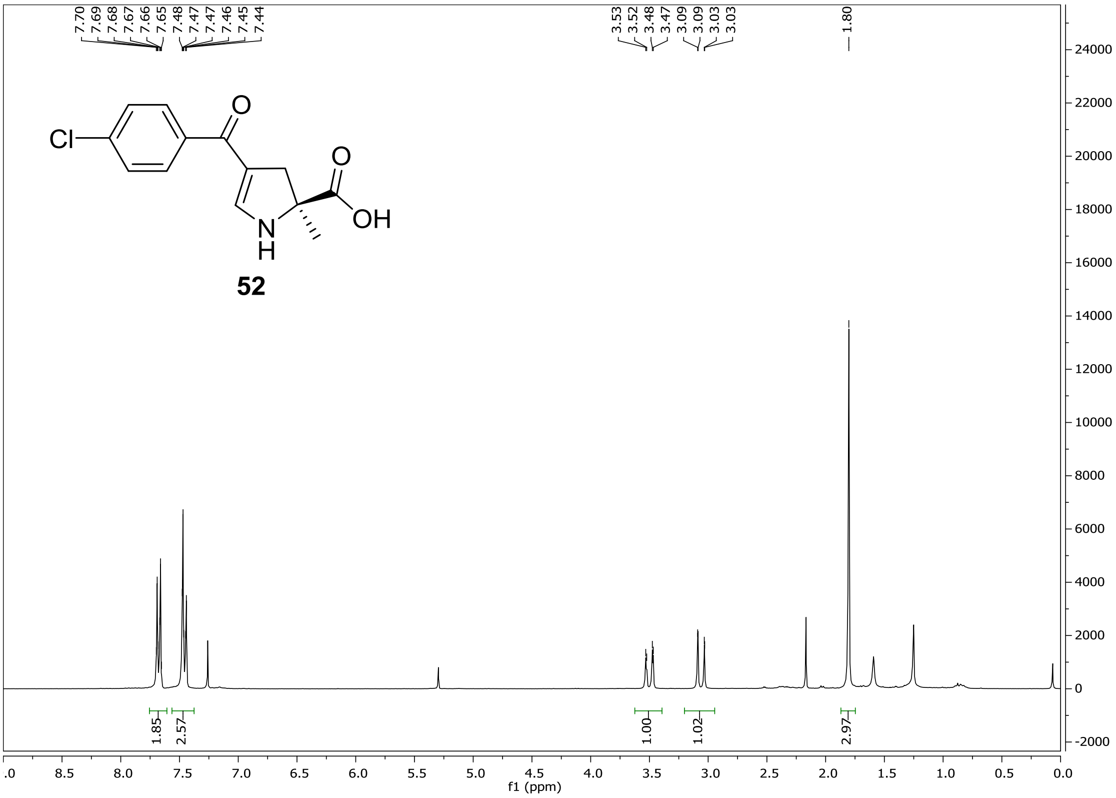


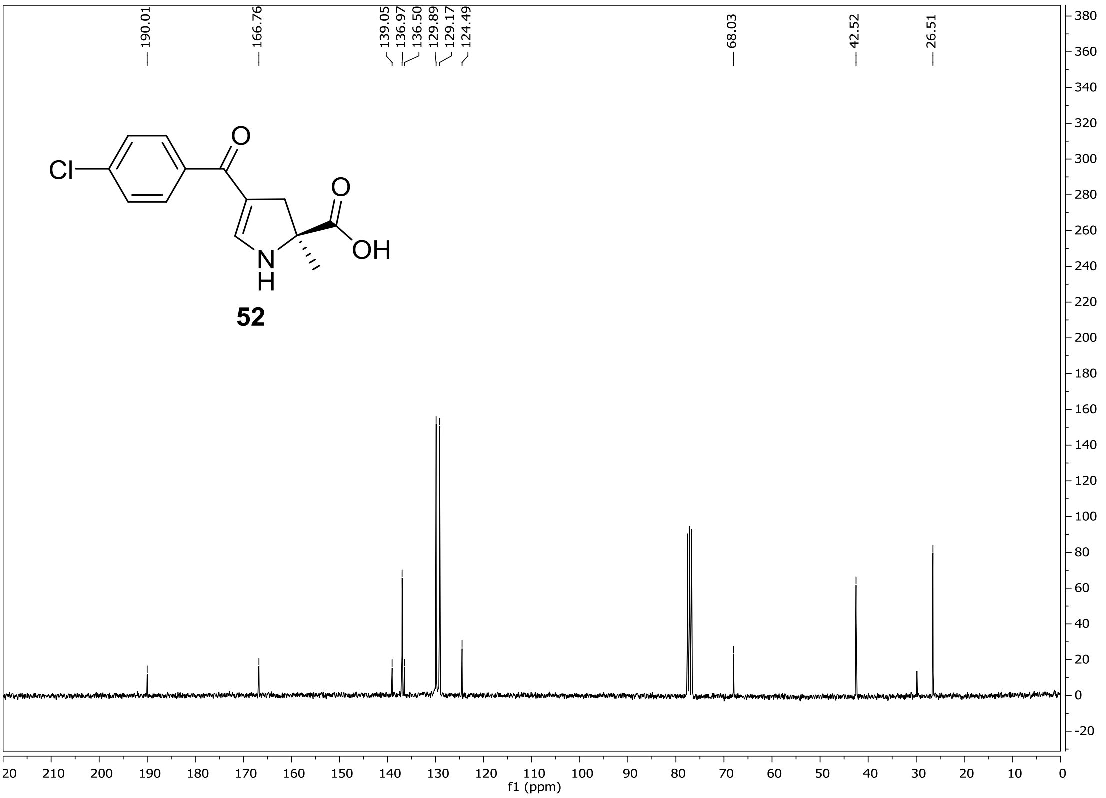


*5.5.3.4. Elaboration of adduct **45Be***

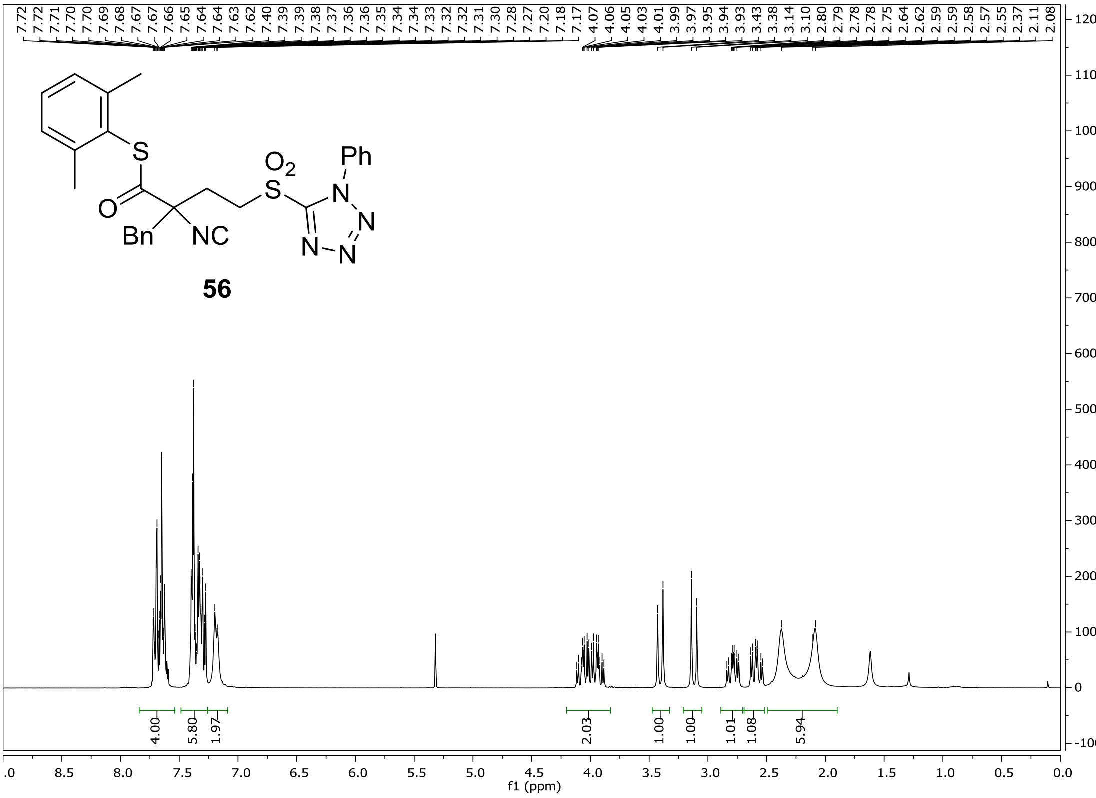


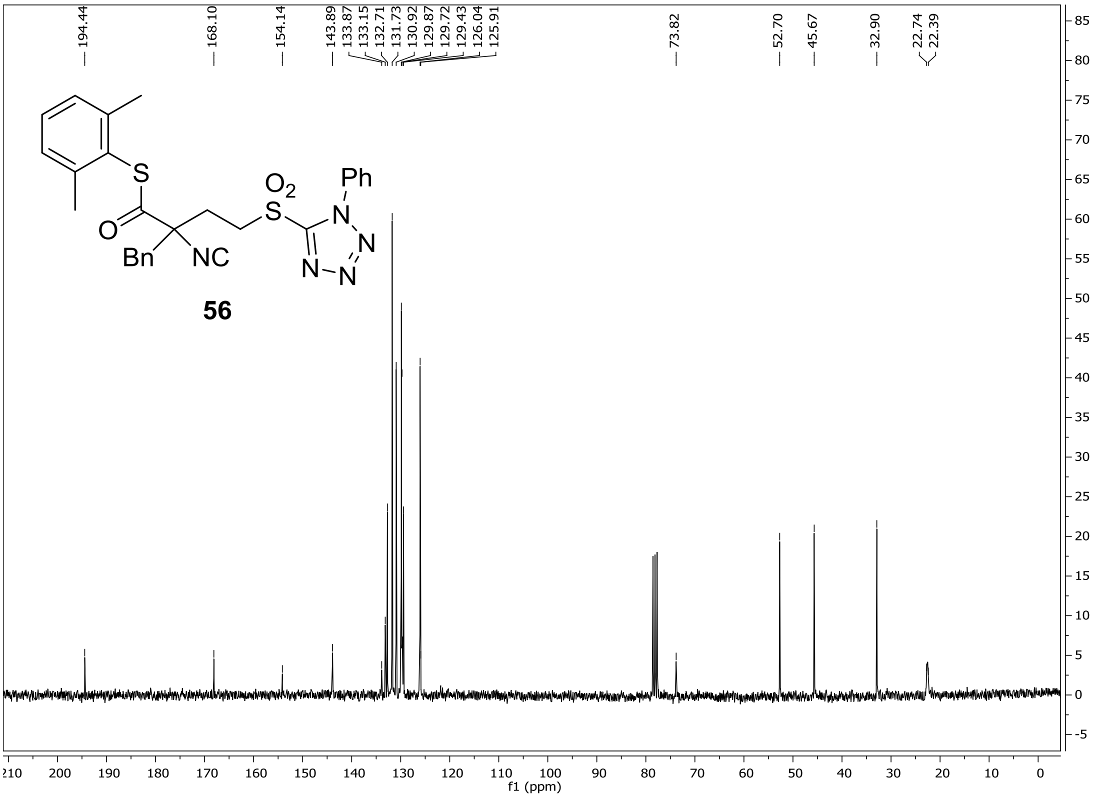


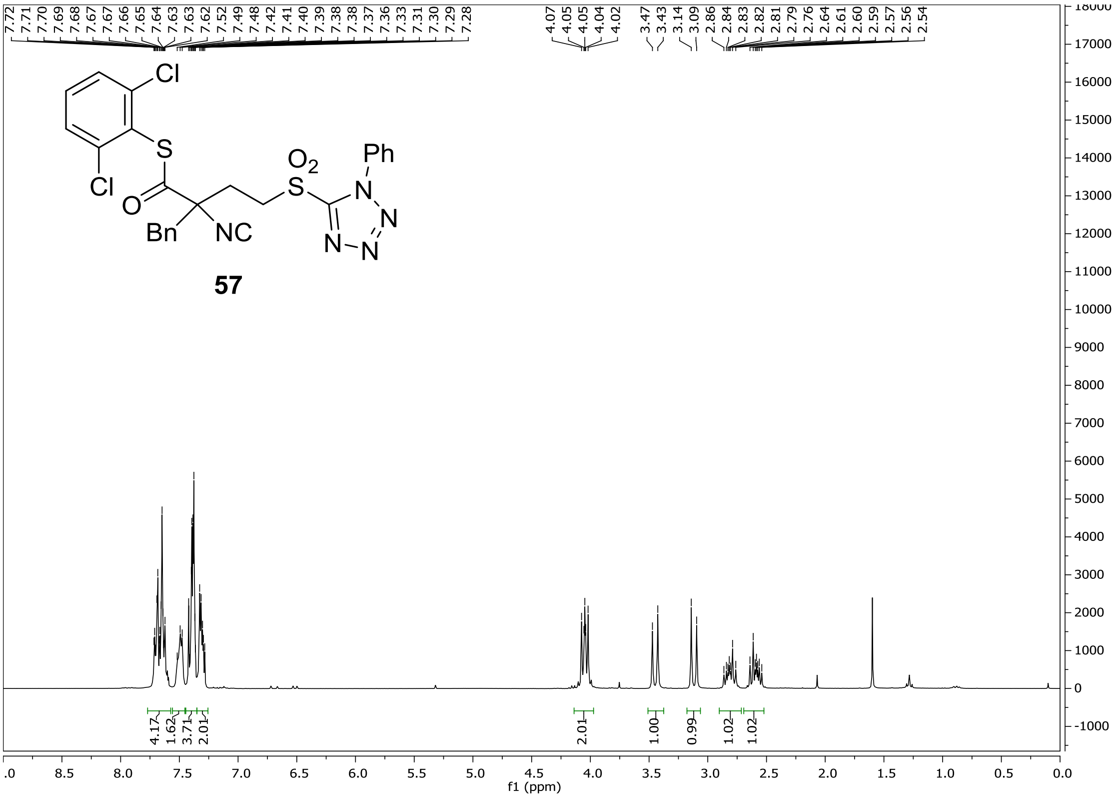

7.70
7.69
7.68
7.67
7.66
7.65
7.48
7.47
7.47
7.46
7.45
7.44
3.53
3.52
3.48
3.47
3.09
3.09
3.03
3.03
1.80
Cl
O
O
OH
N
H
52
1.85
2.57
1.00
1.02
2.97
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

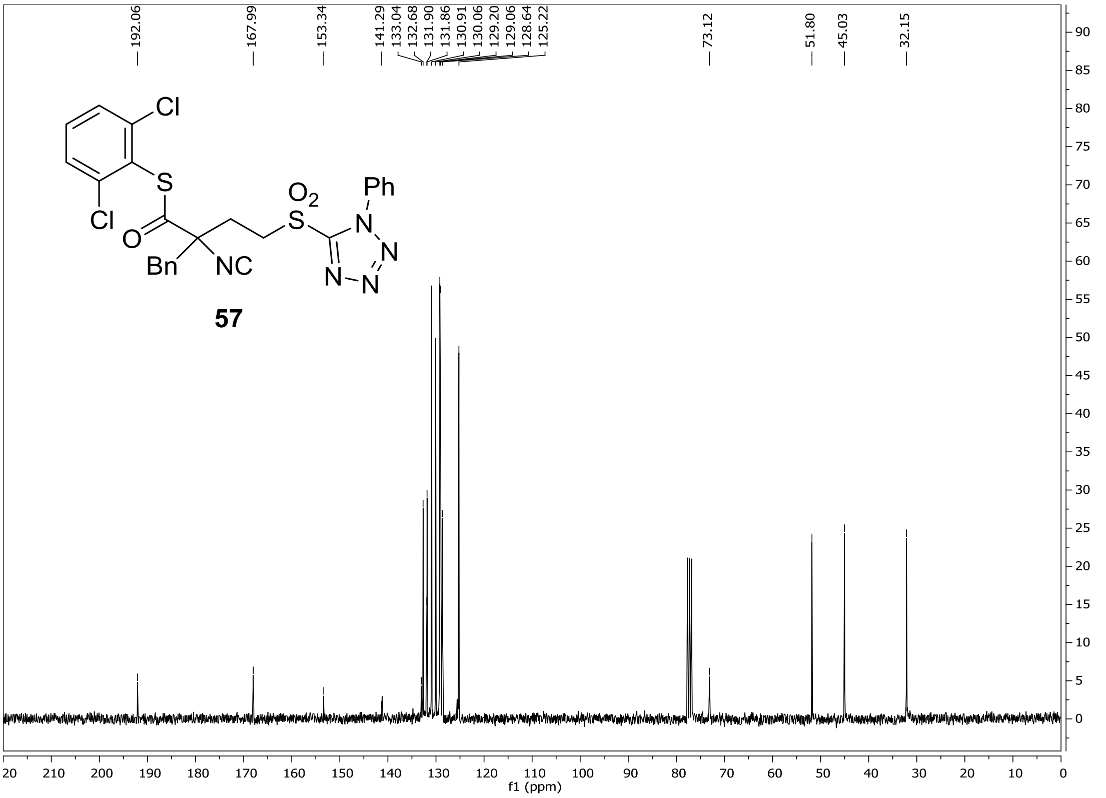

190.01
166.76
139.05
136.97
136.50
129.89
129.17
124.49
68.03
42.52
26.51
Cl
O
O
OH
N
H
52
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

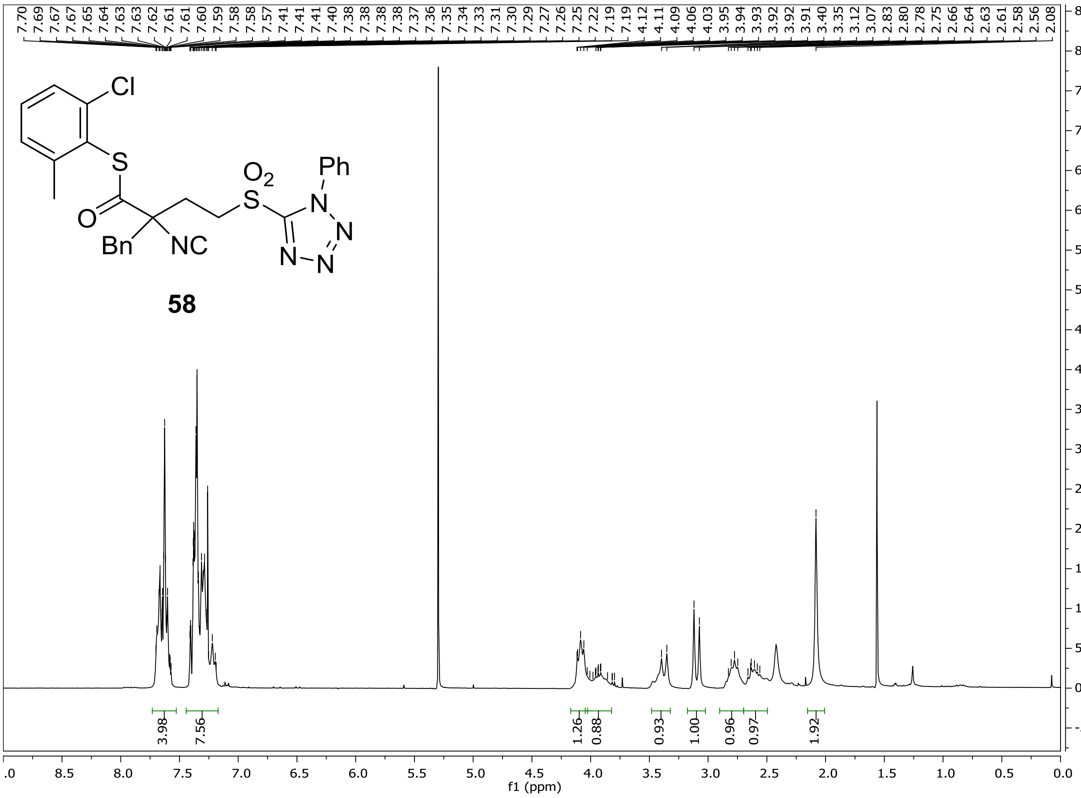
*5.5.3.5. Adducts of the Michael addition to vinyl sulfone **55***

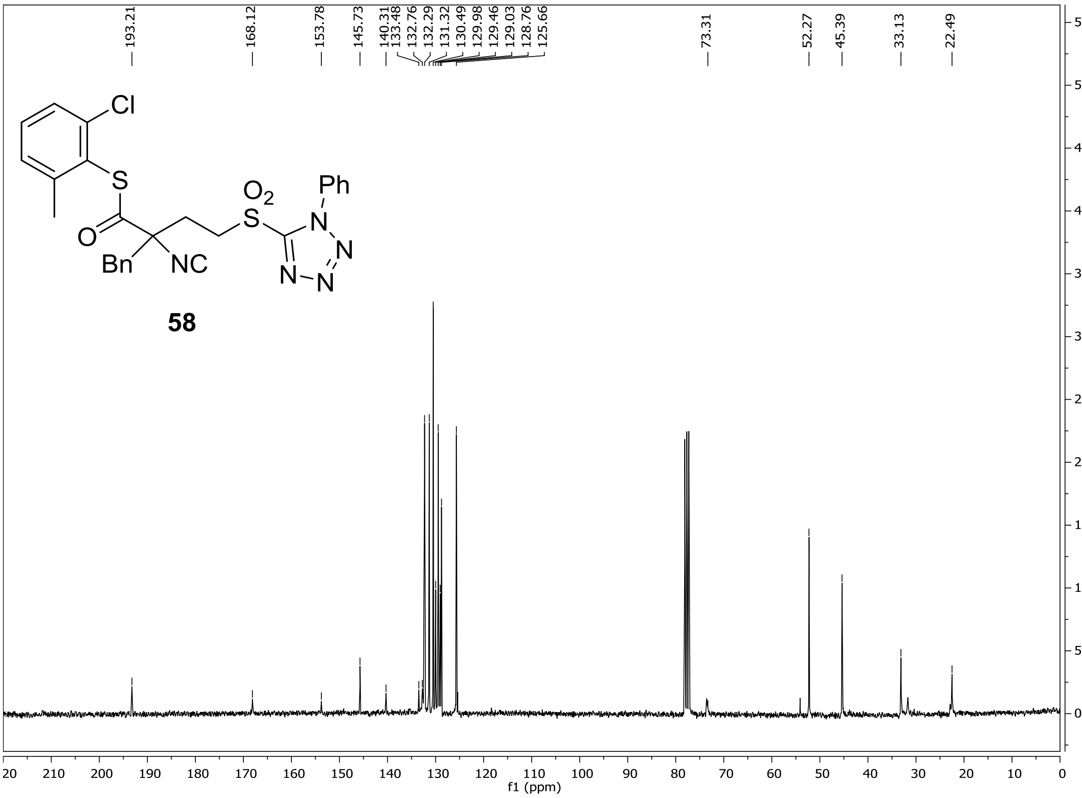


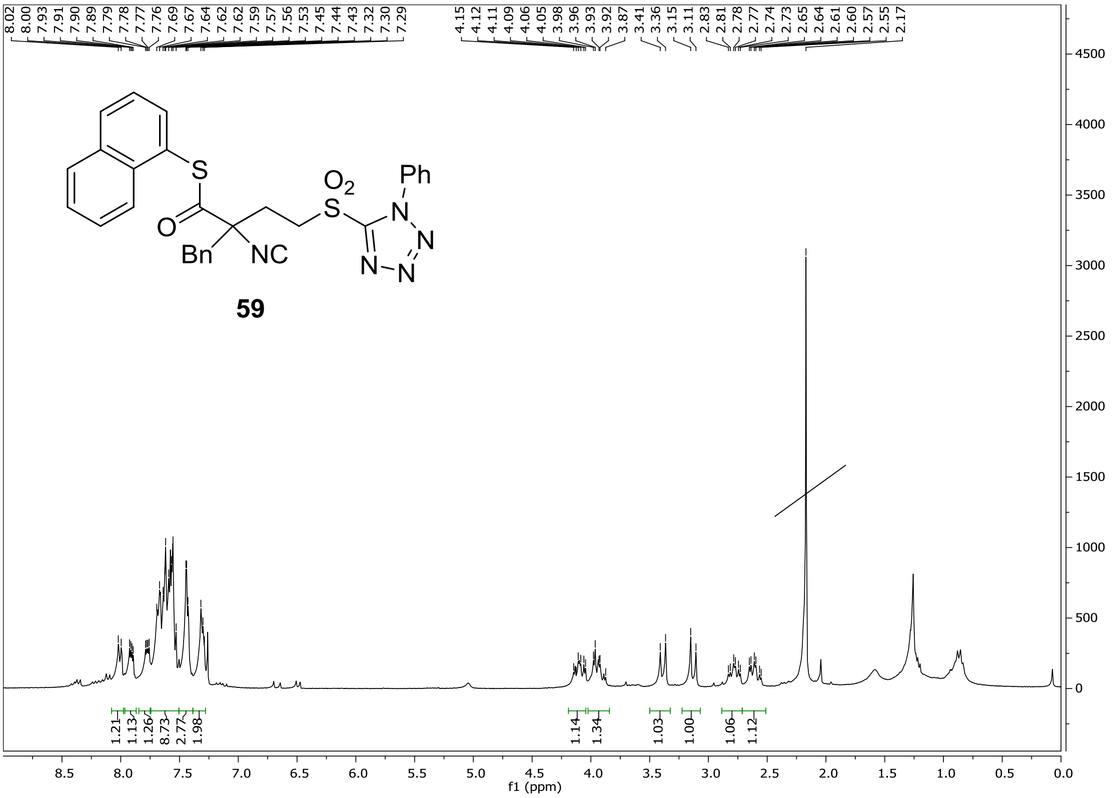



7.72
7.71
7.70
7.69
7.68
7.67
7.67
7.66
7.65
7.64
7.63
7.63
7.62
7.52
7.49
7.48
7.42
7.41
7.40
7.39
7.38
7.38
7.37
7.36
7.33
7.31
7.30
7.29
7.28
4.07
4.05
4.05
4.04
4.02
3.47
3.43
3.14
3.09
2.86
2.84
2.83
2.82
2.81
2.79
2.76
2.64
2.61
2.60
2.59
2.57
2.56
2.54
Cl
S
Cl
O
Bn
NC
O2
S
Ph
N
N
N
N
57
4.17
1.62
3.71
2.01
2.01
1.00
0.99
1.02
1.02
f1 (ppm)

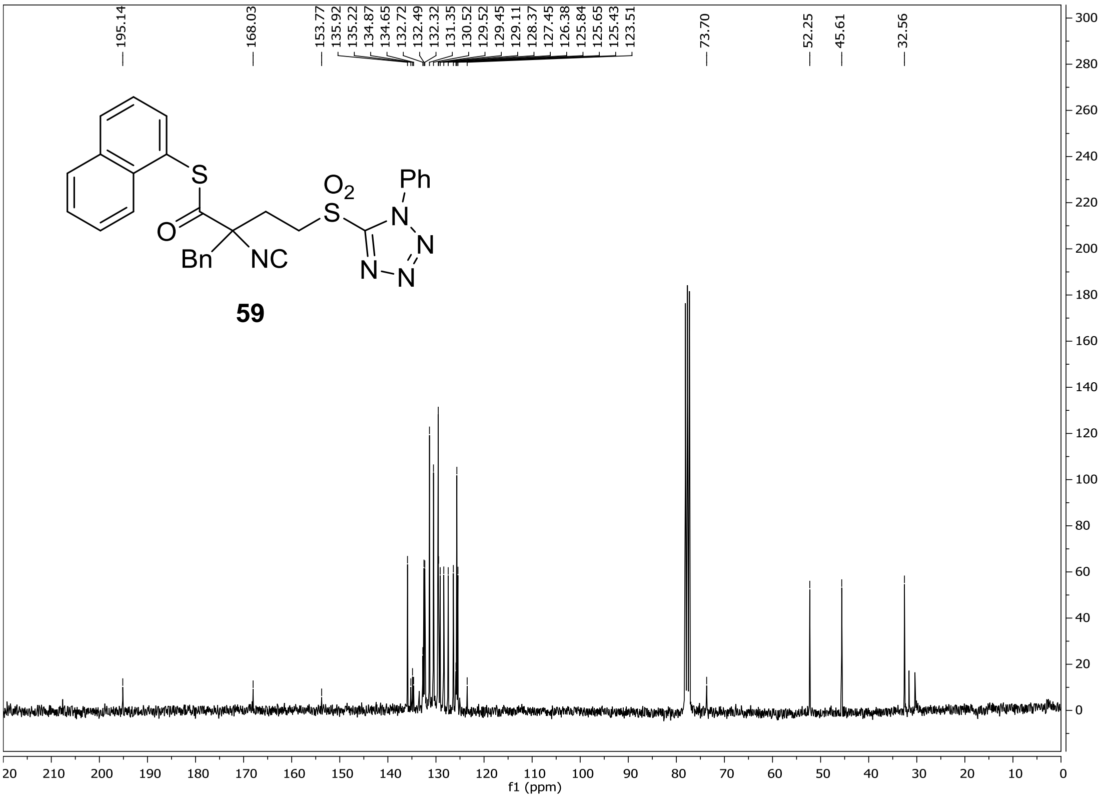

192.06
167.99
153.34
141.29
133.04
132.68
131.90
131.86
130.91
130.06
129.20
129.06
128.64
125.22
73.12
51.80
45.03
32.15
Cl
S
Cl
O
Bn
NC
O2
S
Ph
N
N
N
N
57
f1 (ppm)


7.70
7.69
7.67
7.67
7.65
7.64
7.63
7.63
7.62
7.61
7.61
7.60
7.59
7.58
7.58
7.57
7.41
7.41
7.41
7.40
7.38
7.38
7.38
7.38
7.37
7.36
7.35
7.34
7.33
7.31
7.30
7.29
7.27
7.26
7.25
7.22
7.19
7.19
4.12
4.11
4.09
4.06
4.03
3.95
3.94
3.93
3.92
3.92
3.91
3.40
3.35
3.12
3.07
2.83
2.80
2.78
2.75
2.66
2.64
2.63
2.61
2.58
2.56
2.08
Cl
S
O
O2
S
Ph
N
N
N
N
Bn
NC
58
3.98
7.56
1.26
0.88
0.93
1.00
0.96
0.97
1.92
f1 (ppm)

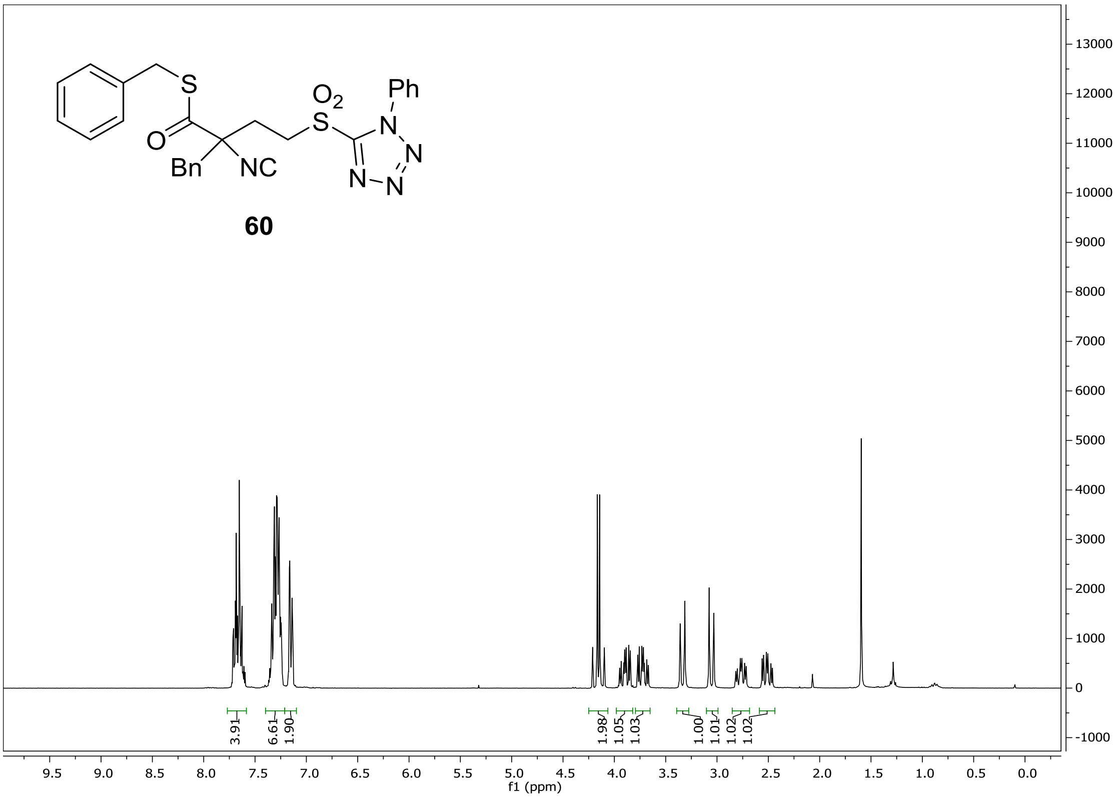

193.21
168.12
153.78
145.73
140.31
133.48
132.76
132.29
131.32
130.49
129.98
129.46
129.03
128.76
125.66
73.31
52.27
45.39
33.13
22.49
Cl
S
O
O2
S
Ph
N
N
N
N
Bn
NC
58
f1 (ppm)

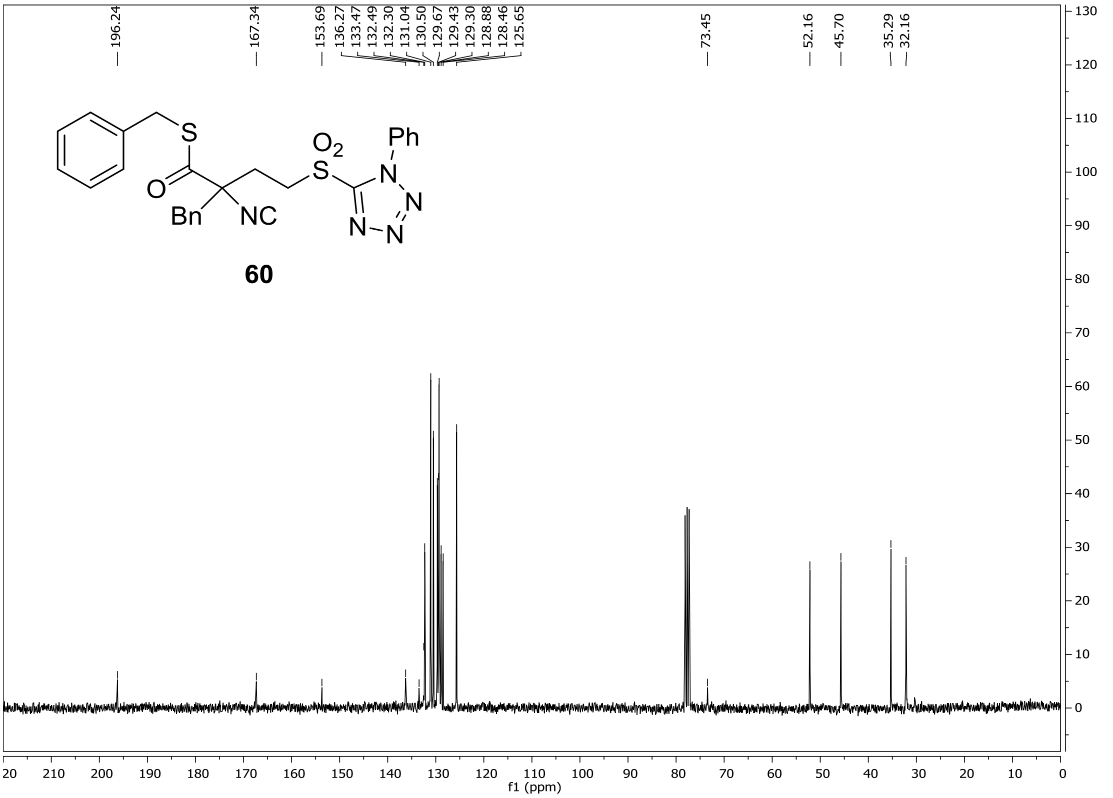

8.02
8.00
7.93
7.91
7.90
7.89
7.79
7.78
7.77
7.76
7.69
7.67
7.64
7.62
7.59
7.57
7.56
7.53
7.45
7.44
7.43
7.32
7.30
7.29
4.15
4.12
4.11
4.09
4.06
4.05
3.98
3.96
3.93
3.92
3.87
3.41
3.36
3.15
3.11
2.83
2.81
2.78
2.77
2.74
2.73
2.65
2.64
2.61
2.60
2.57
2.55
2.17
S
O2
Ph
S
N
N
N
N
N
O
Bn
NC
1.21
1.13
1.26
8.73
2.77
1.98
1.14
1.34
1.03
1.00
1.06
1.12
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)
4500
4000
3500
3000
2500
2000
1500
1000
500
0

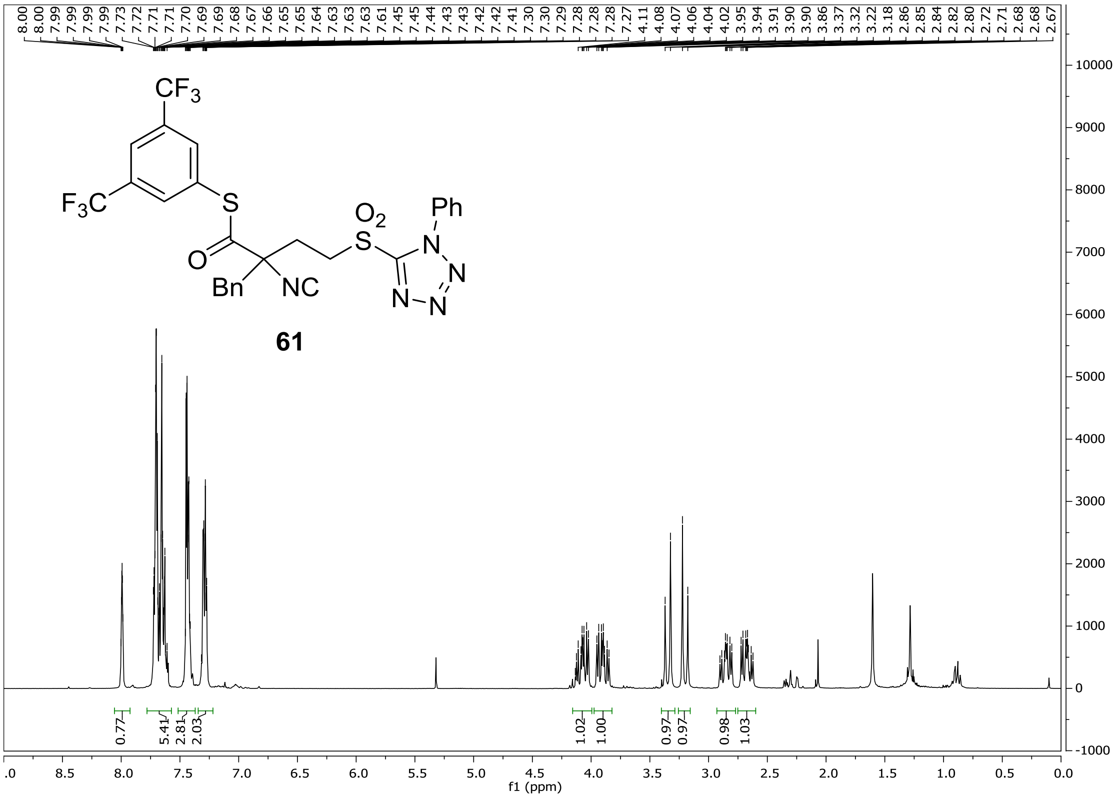
59

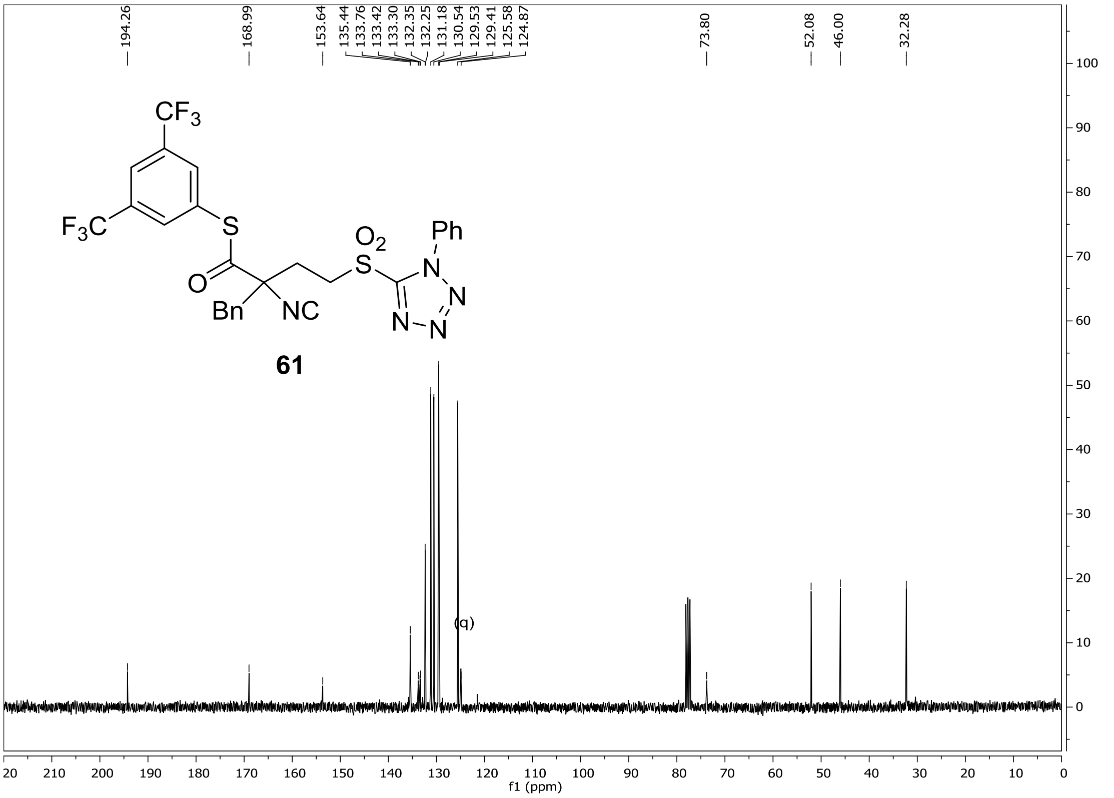

195.14
168.03
153.77
135.92
135.22
134.87
134.65
132.72
132.49
132.32
131.35
130.52
129.52
129.45
129.11
128.37
127.45
126.38
125.84
125.65
125.43
123.51
73.70
52.25
45.61
32.56
S
O2
Ph
S
N
N
N
N
N
O
Bn
NC
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0

59

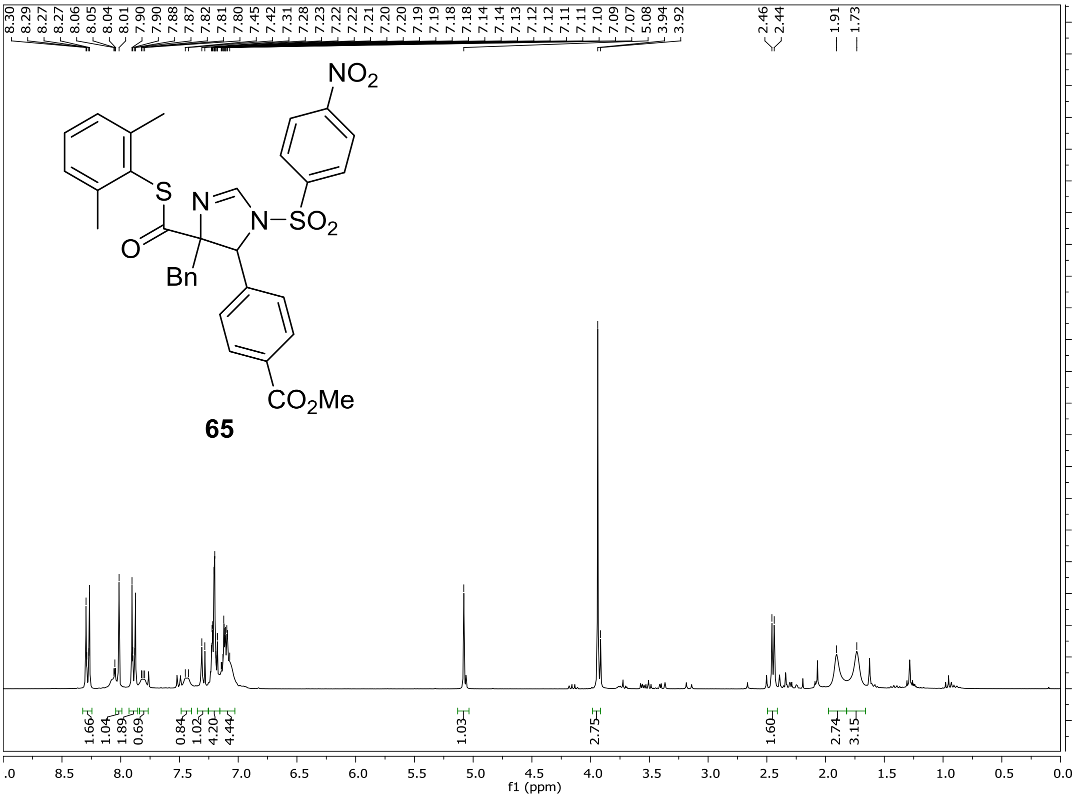

S
O
Bn
NC
O2
S
Ph
N
N
N
N
60
3.91
6.61
1.90
1.98
1.05
1.03
1.00
1.01
1.02
1.02
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

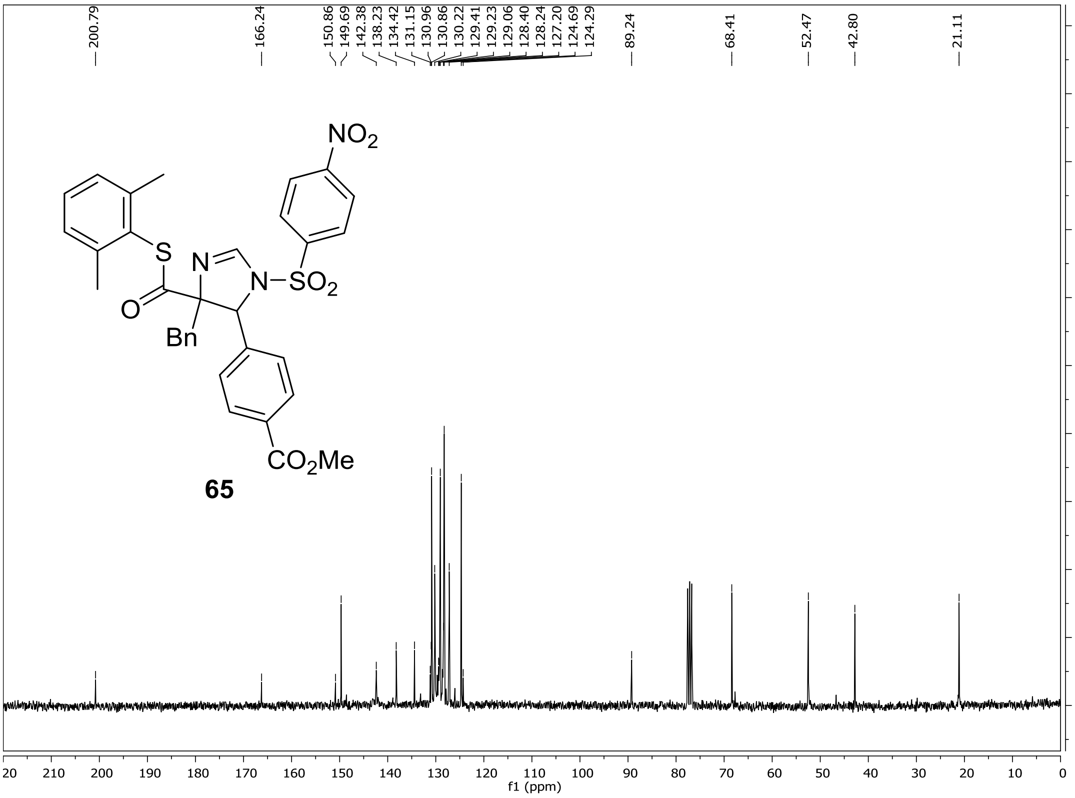

196.24
167.34
153.69
136.27
133.47
132.49
132.30
131.04
130.50
129.67
129.43
129.30
128.88
128.46
125.65
73.45
52.16
45.70
35.29
32.16
S
O
Bn
NC
O2
S
Ph
N
N
N
N
60
130
120
110
100
90
80
70
60
50
40
30
20
10
0
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

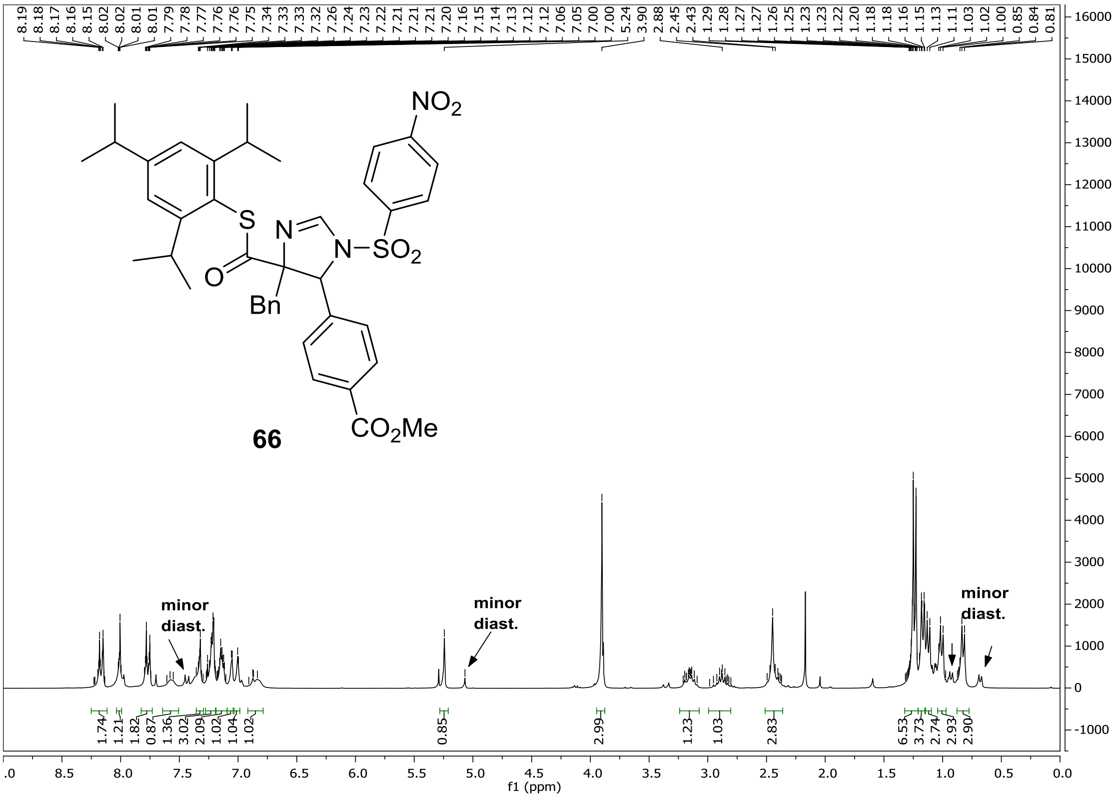

8.00
8.00
7.99
7.99
7.99
7.99
7.73
7.72
7.71
7.71
7.70
7.69
7.69
7.68
7.67
7.66
7.65
7.65
7.64
7.63
7.63
7.63
7.61
7.45
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.30
7.30
7.29
7.28
7.28
7.28
7.27
4.11
4.08
4.07
4.06
4.04
4.02
3.95
3.94
3.91
3.90
3.90
3.86
3.37
3.32
3.22
3.18
2.86
2.85
2.84
2.82
2.80
2.72
2.71
2.68
2.68
2.67
CF3
F3C
S
O
O2
S
Ph
N
N
N
N
Bn
NC
61
0.77
5.41
2.81
2.03
1.02
1.00
0.97
0.97
0.98
1.03
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.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)

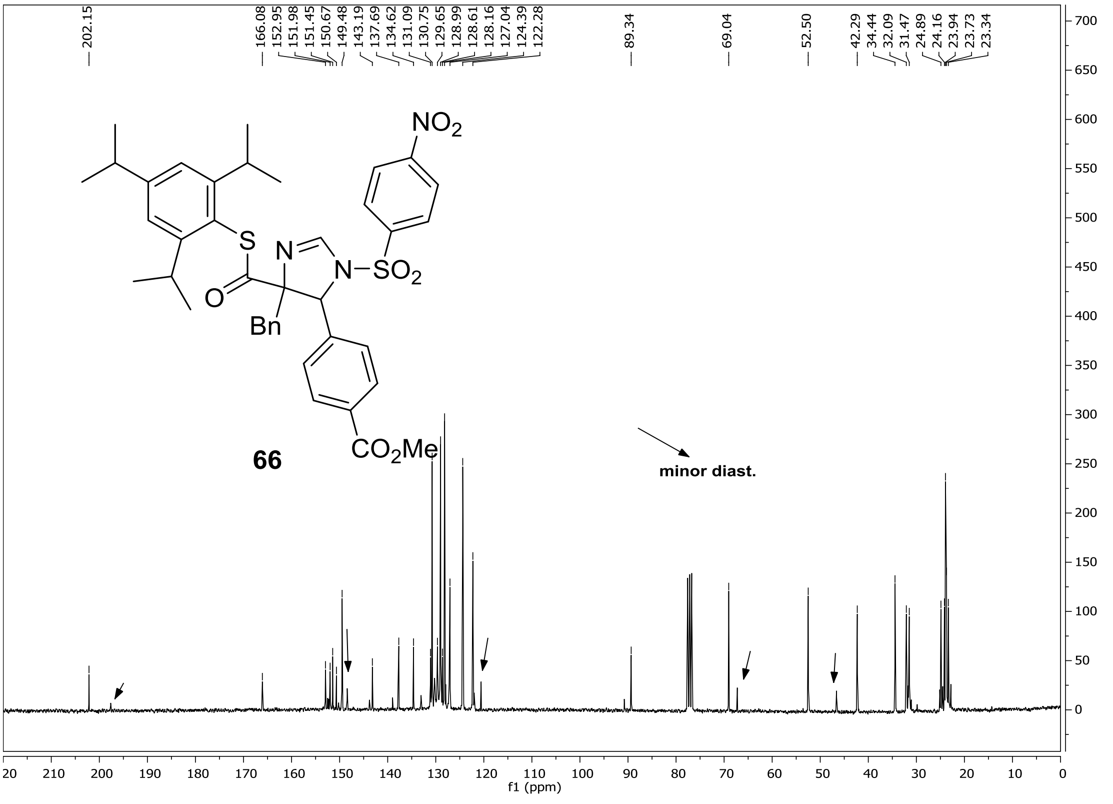

194.26
168.99
153.64
135.44
133.76
133.42
133.30
132.35
132.25
131.18
130.54
129.53
129.41
125.58
124.87
73.80
52.08
46.00
32.28
CF3
F3C
S
O
O2
S
Ph
N
N
N
N
Bn
NC
61
(q)
100
90
80
70
60
50
40
30
20
10
0
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

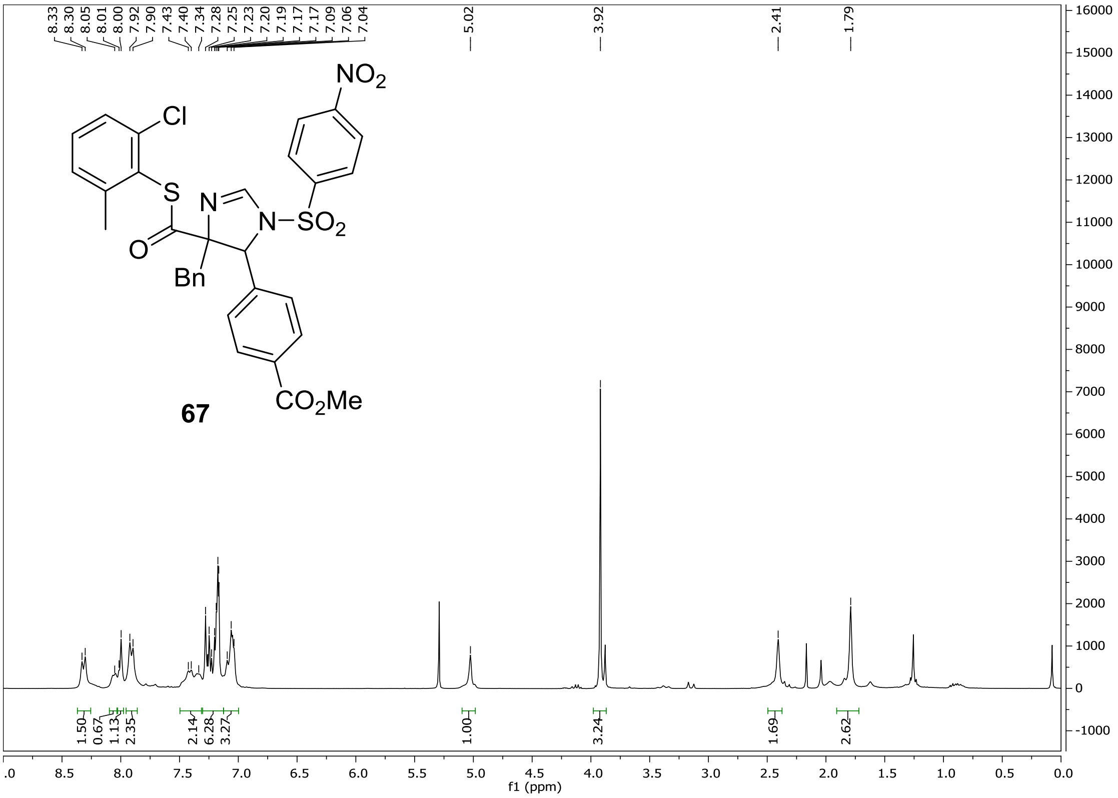
*5.5.3.6. Adducts of the Mannich reaction with N-nosyl aldimine **64***

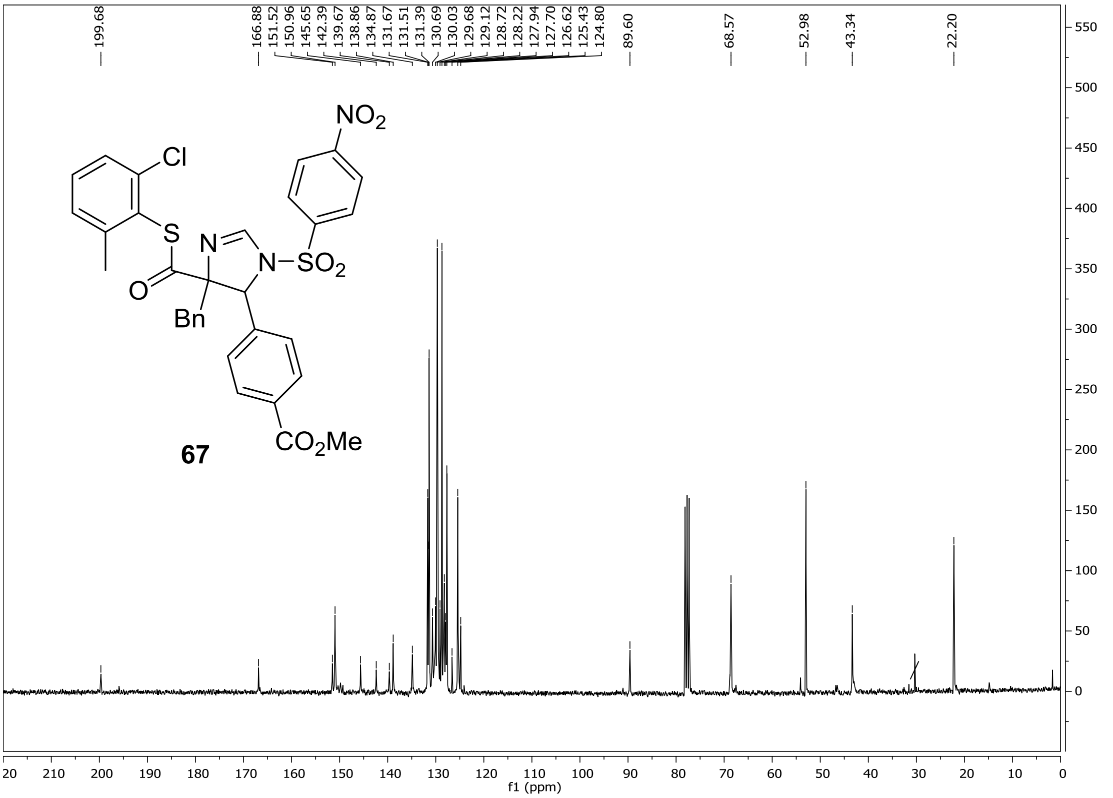




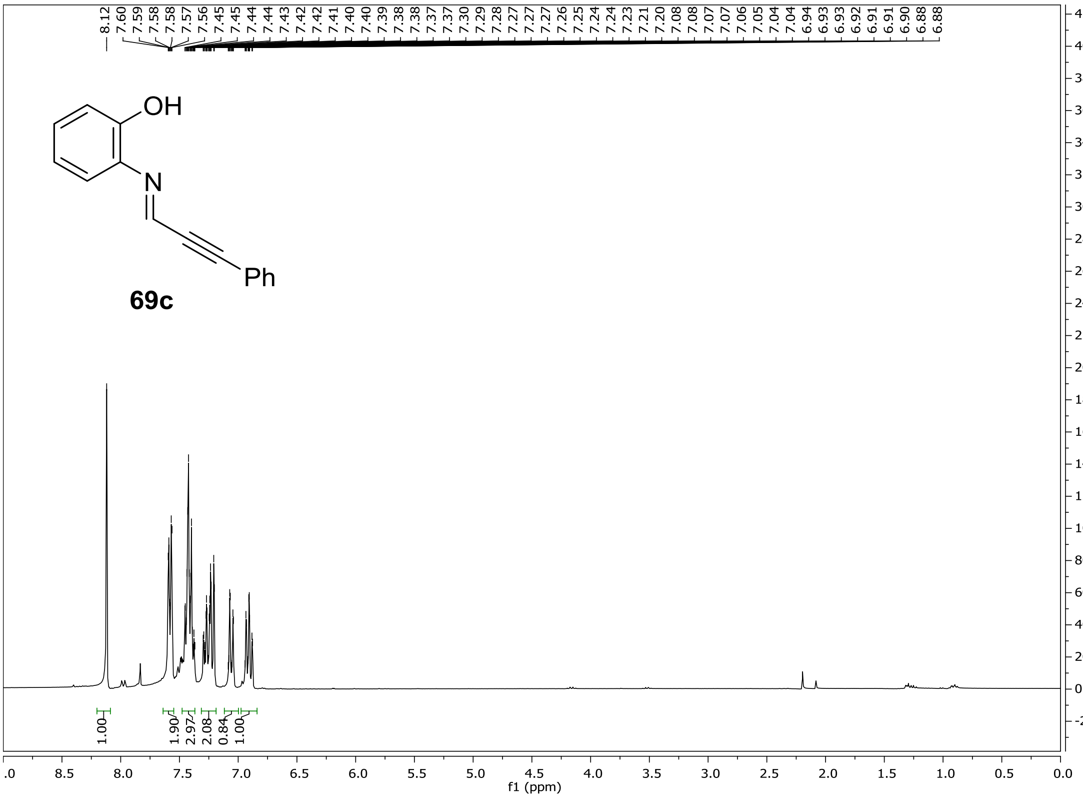

8.19
8.18
8.17
8.16
8.15
8.02
8.02
8.01
7.79
7.78
7.77
7.76
7.76
7.75
7.34
7.33
7.33
7.32
7.26
7.24
7.23
7.22
7.21
7.21
7.21
7.20
7.16
7.15
7.14
7.13
7.12
7.12
7.06
7.05
7.00
7.00
5.24
3.90
2.88
2.45
2.43
1.29
1.28
1.27
1.27
1.26
1.25
1.23
1.23
1.22
1.20
1.18
1.18
1.16
1.15
1.13
1.11
1.03
1.02
1.00
0.85
0.84
0.81
NO2
S
N
N–SO2
O
Bn
CO2Me
66
minor diast.
minor diast.
minor diast.
1.74
1.21
1.82
0.87
1.36
3.02
2.09
1.02
1.04
1.02
0.85
2.99
1.23
1.03
2.83
6.53
3.73
2.74
2.93
2.90
f1 (ppm)

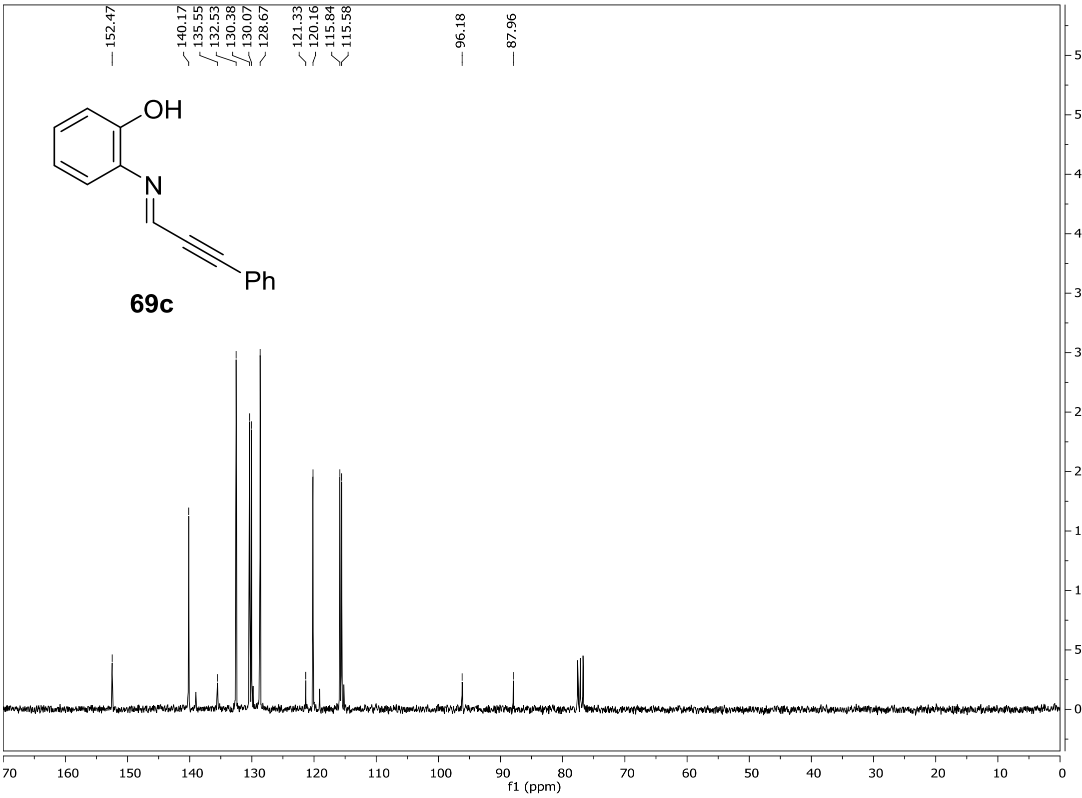

202.15
166.08
152.95
151.98
151.45
150.67
149.48
143.19
137.69
134.62
131.09
130.75
129.65
128.99
128.61
128.16
127.04
124.39
122.28
89.34
69.04
52.50
42.29
34.44
32.09
31.47
24.89
24.16
23.94
23.73
23.34
NO2
S
N
N–SO2
O
Bn
CO2Me
66
minor diast.
f1 (ppm)

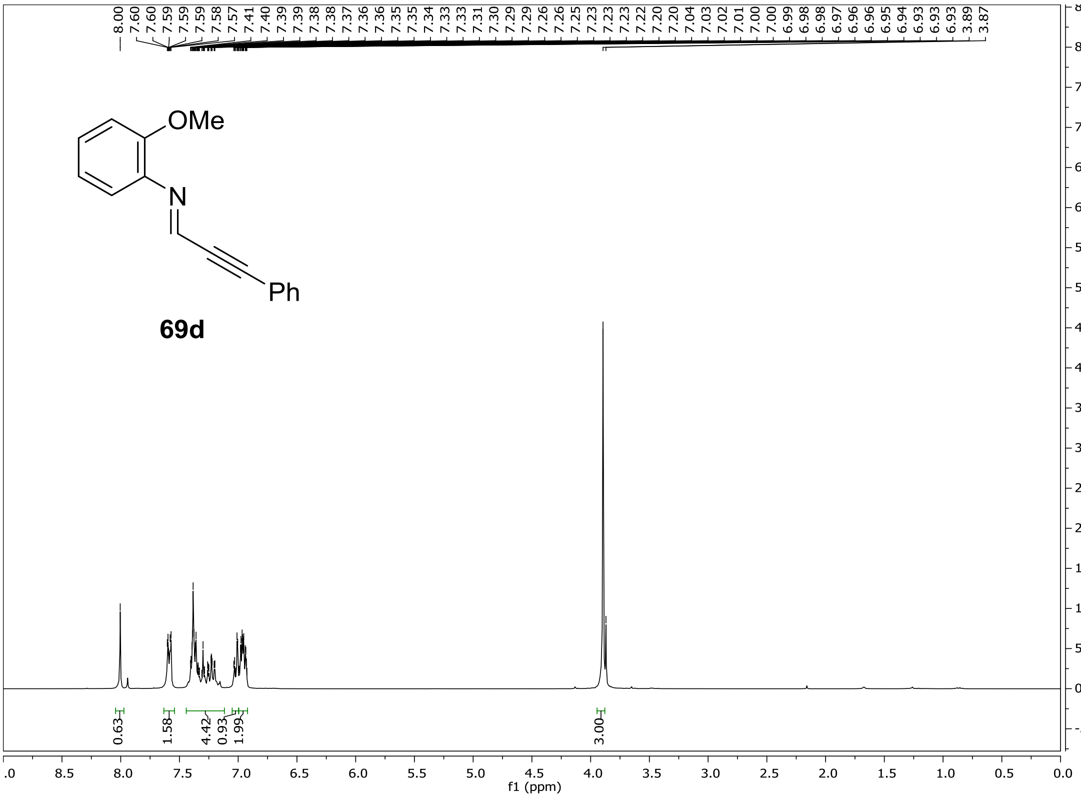

8.33
8.30
8.05
8.01
8.00
7.92
7.90
7.43
7.40
7.34
7.28
7.25
7.23
7.20
7.19
7.17
7.17
7.09
7.06
7.04
5.02
3.92
2.41
1.79
NO2
Cl
S
N
N–SO2
O
Bn
CO2Me
67
1.50
0.67
1.13
2.35
2.14
6.28
3.27
1.00
3.24
1.69
2.62
f1 (ppm)

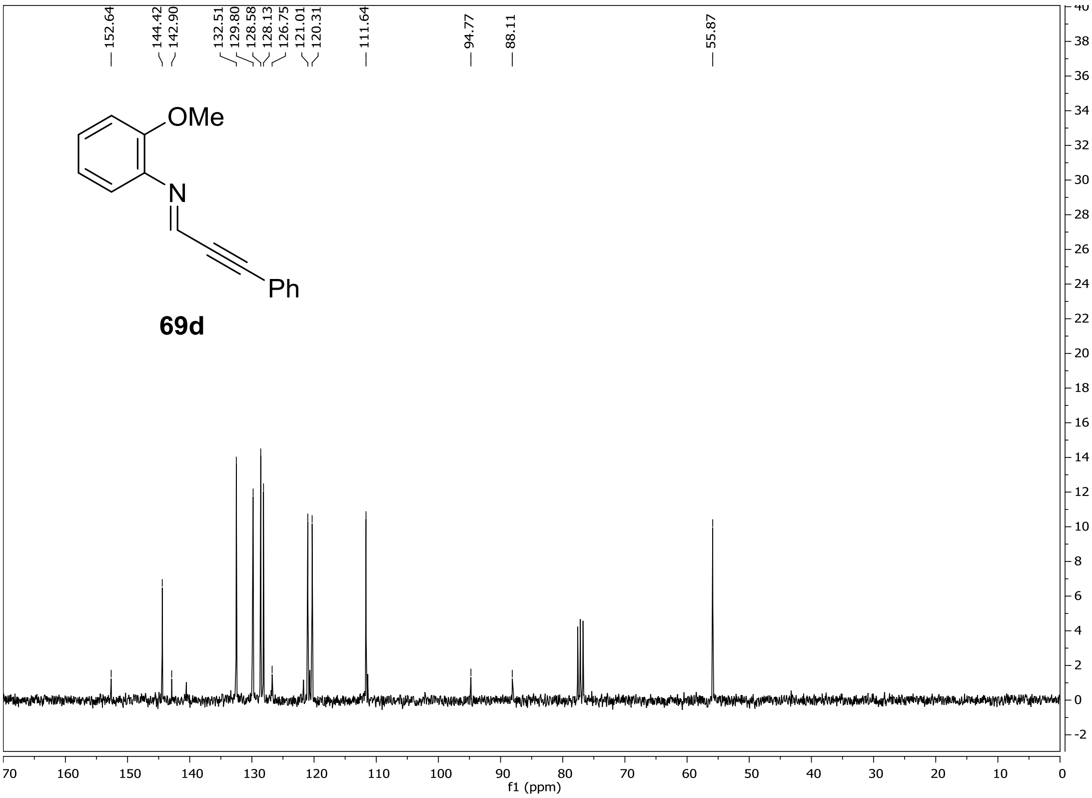

199.68
166.88
151.52
150.96
145.65
142.39
139.67
138.86
134.87
131.67
131.51
131.39
130.69
130.03
129.68
129.12
128.72
128.22
127.94
127.70
126.62
125.43
124.80
89.60
68.57
52.98
43.34
22.20
NO2
Cl
S
N
N–SO2
O
Bn
CO2Me
67
f1 (ppm)

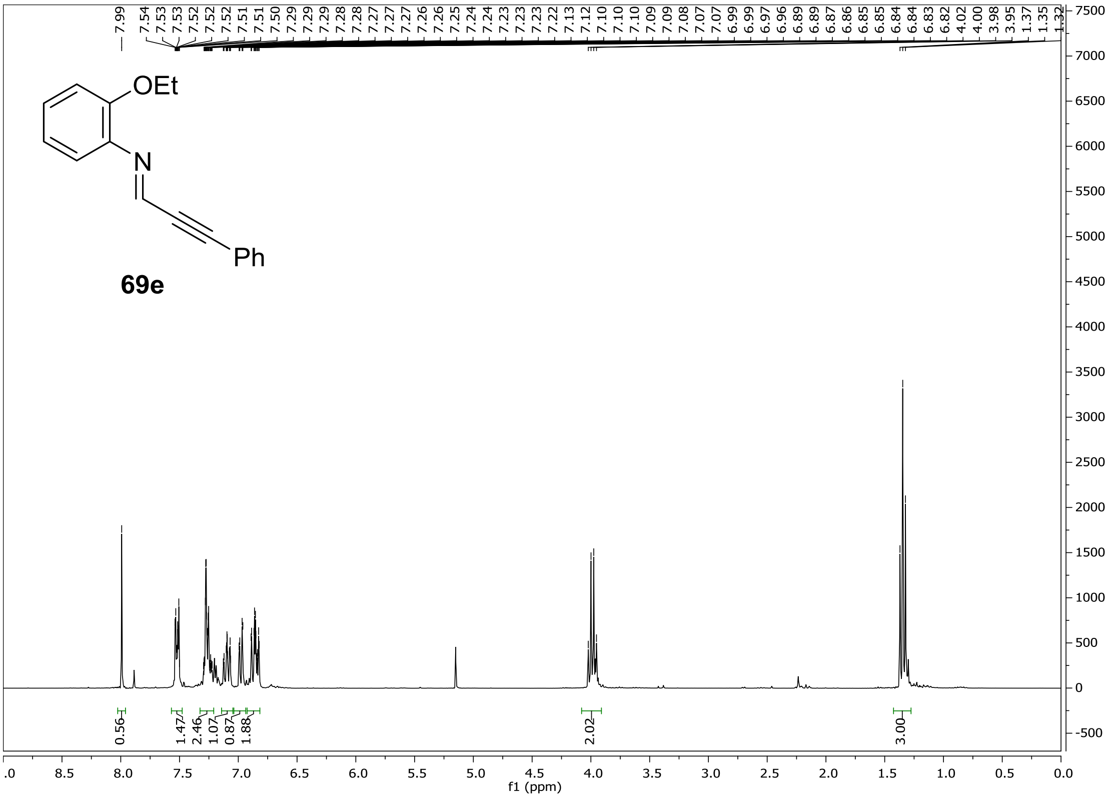
*5.5.3.7. N-Aryl propargylic aldimines **69c-e***

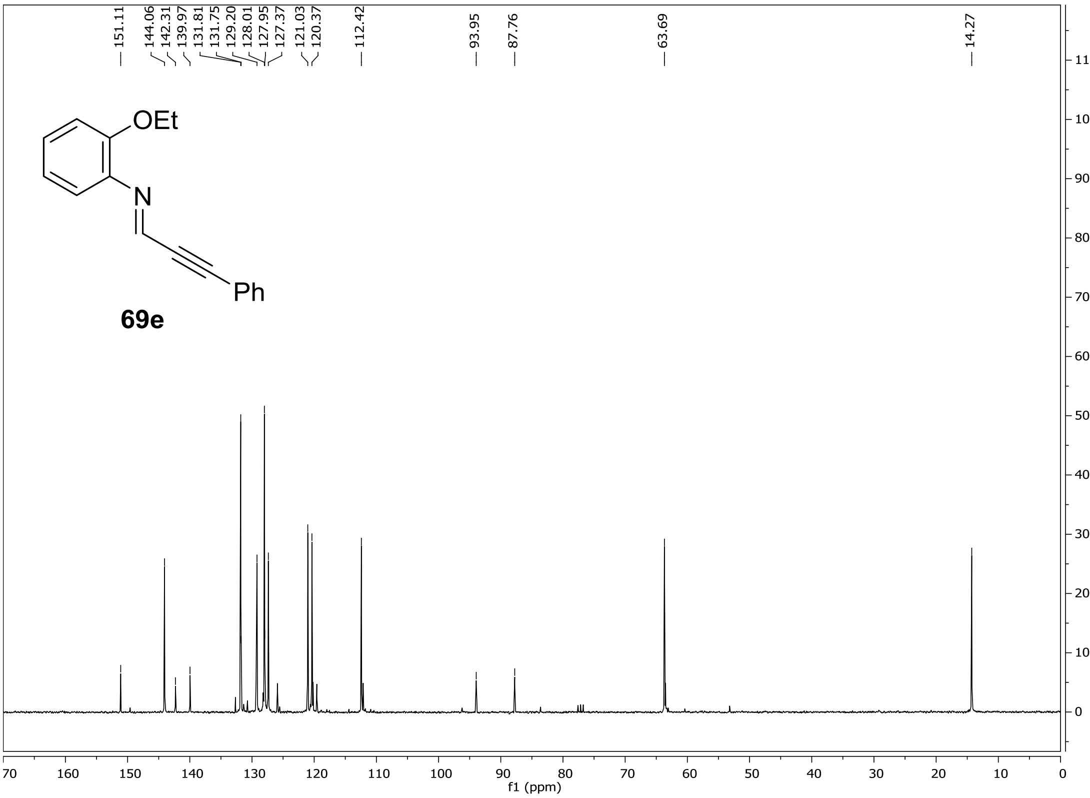




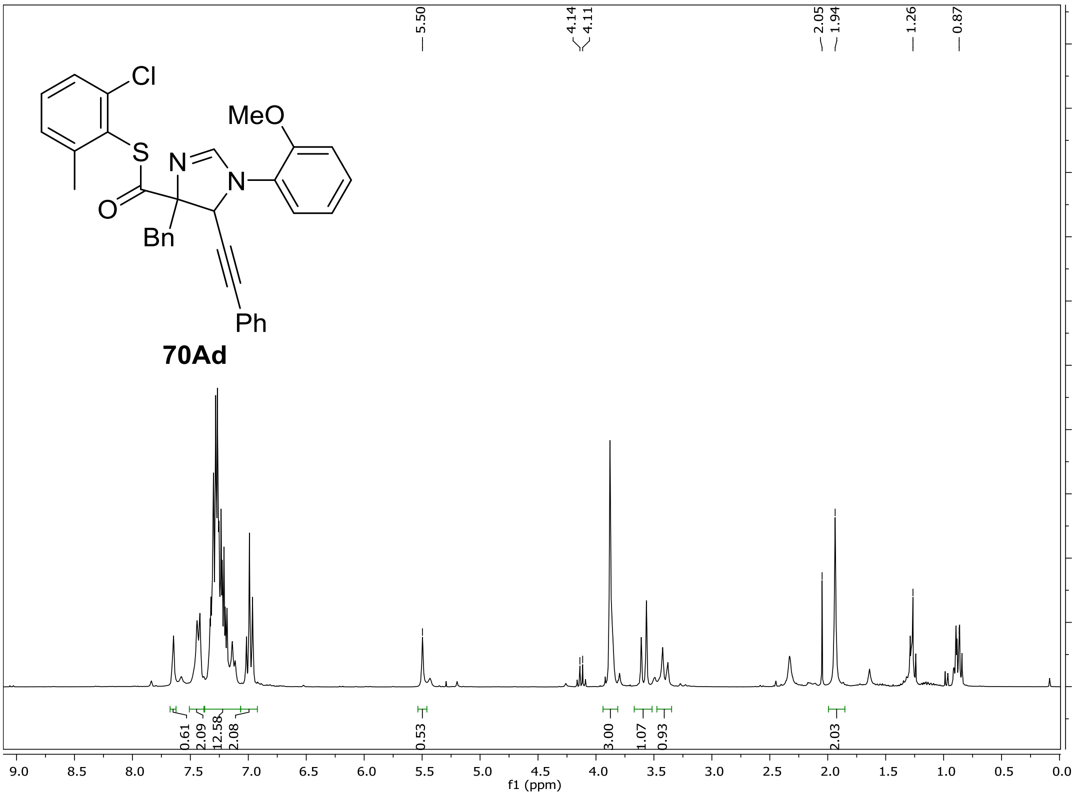

8.00
7.60
7.60
7.59
7.59
7.59
7.58
7.57
7.41
7.40
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.31
7.30
7.29
7.29
7.26
7.25
7.23
7.23
7.23
7.22
7.20
7.20
7.04
7.03
7.02
7.01
7.00
6.99
6.98
6.98
6.97
6.96
6.96
6.95
6.94
6.93
6.93
6.93
3.89
3.87
OMe
N
Ph
69d
0.63
1.58
4.42
0.93
1.99
3.00
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.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)

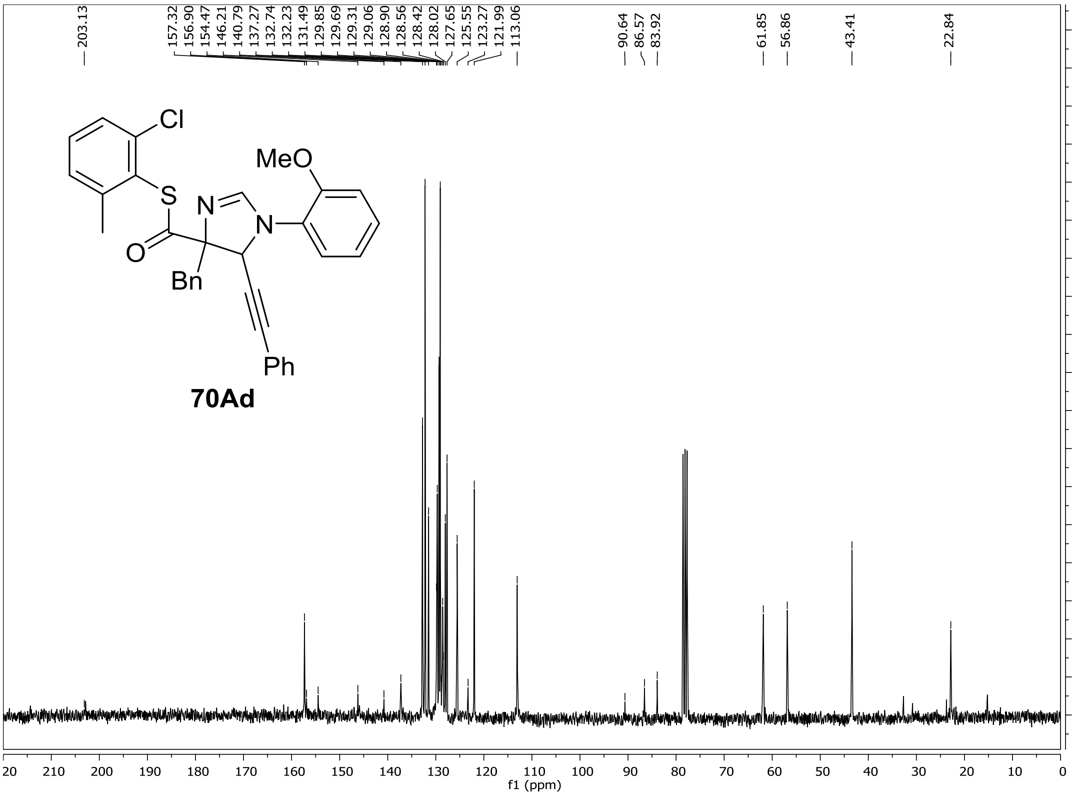

152.64
144.42
142.90
132.51
129.80
128.58
128.13
126.75
121.01
120.31
111.64
94.77
88.11
55.87
OMe
N
Ph
69d
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

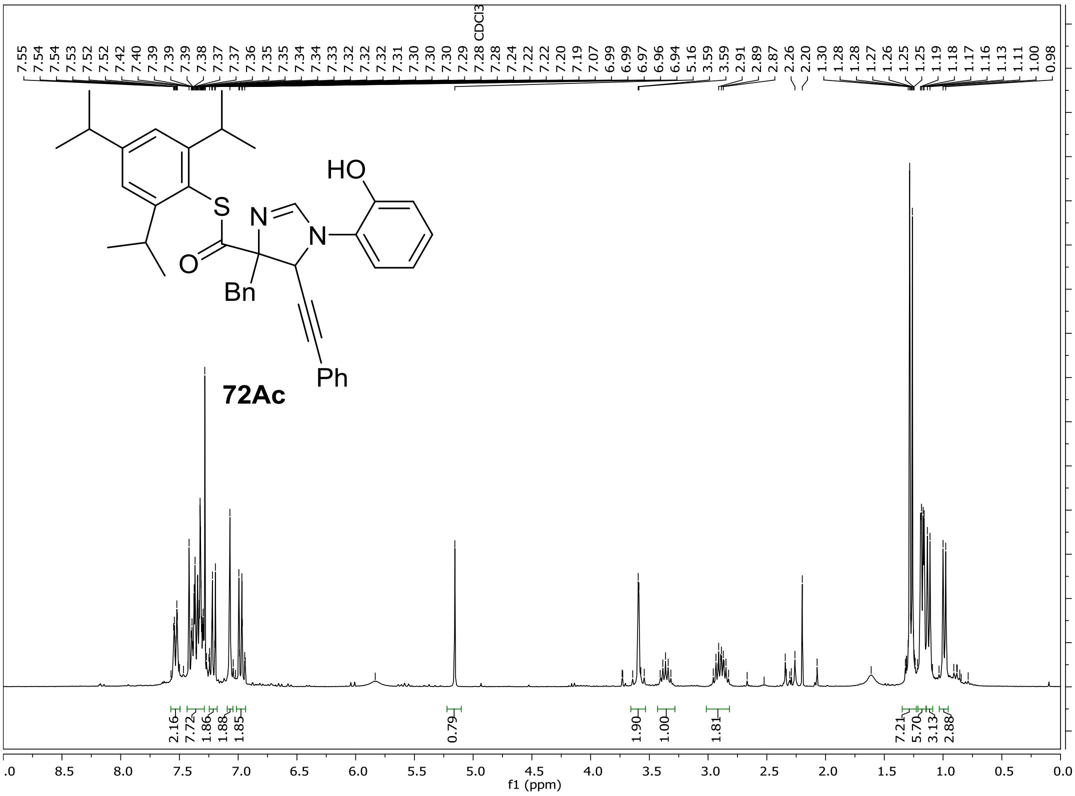

OEt
N
Ph
69e
7.99
7.54
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.23
7.22
7.13
7.12
7.10
7.10
7.10
7.09
7.09
7.08
7.07
7.07
6.99
6.99
6.97
6.96
6.89
6.89
6.87
6.86
6.85
6.85
6.85
6.84
6.84
6.83
6.82
4.02
4.00
3.98
3.95
1.37
1.35
1.32
0.56
1.47
2.46
1.07
0.87
1.88
2.02
3.00
f1 (ppm)

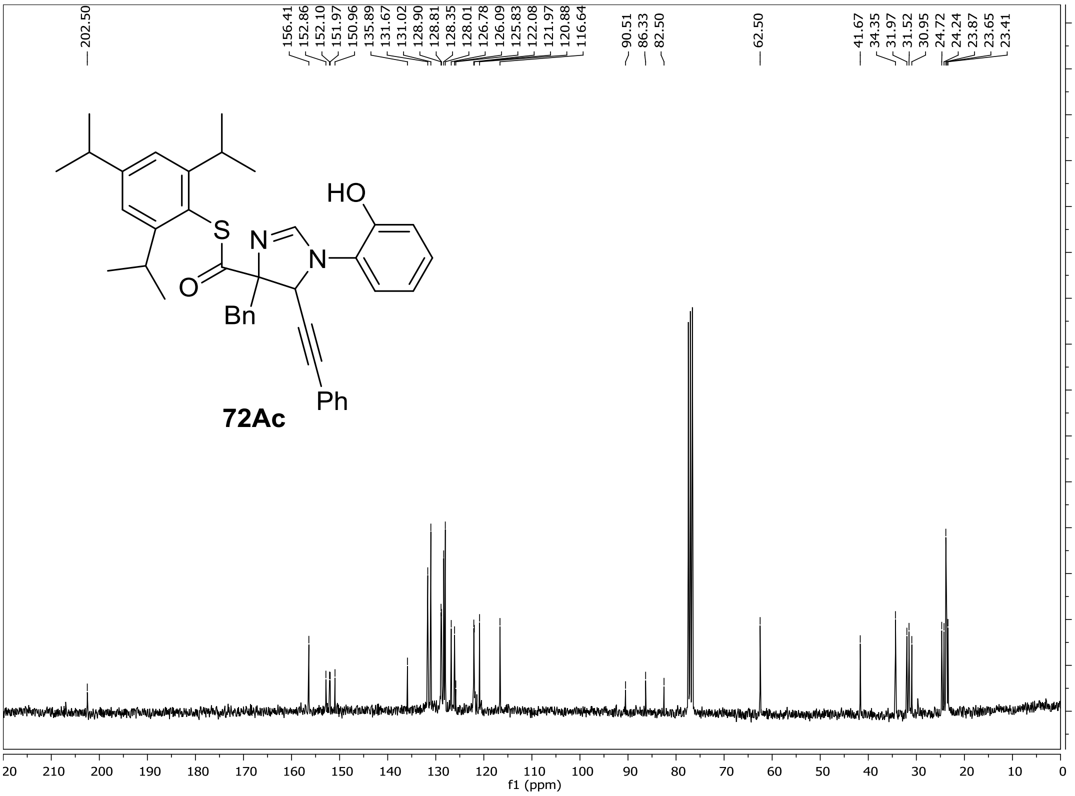

OEt
N
Ph
69e
151.11
144.06
142.31
139.97
131.81
131.75
129.20
128.01
127.95
127.37
121.03
120.37
112.42
93.95
87.76
63.69
14.27
f1 (ppm)

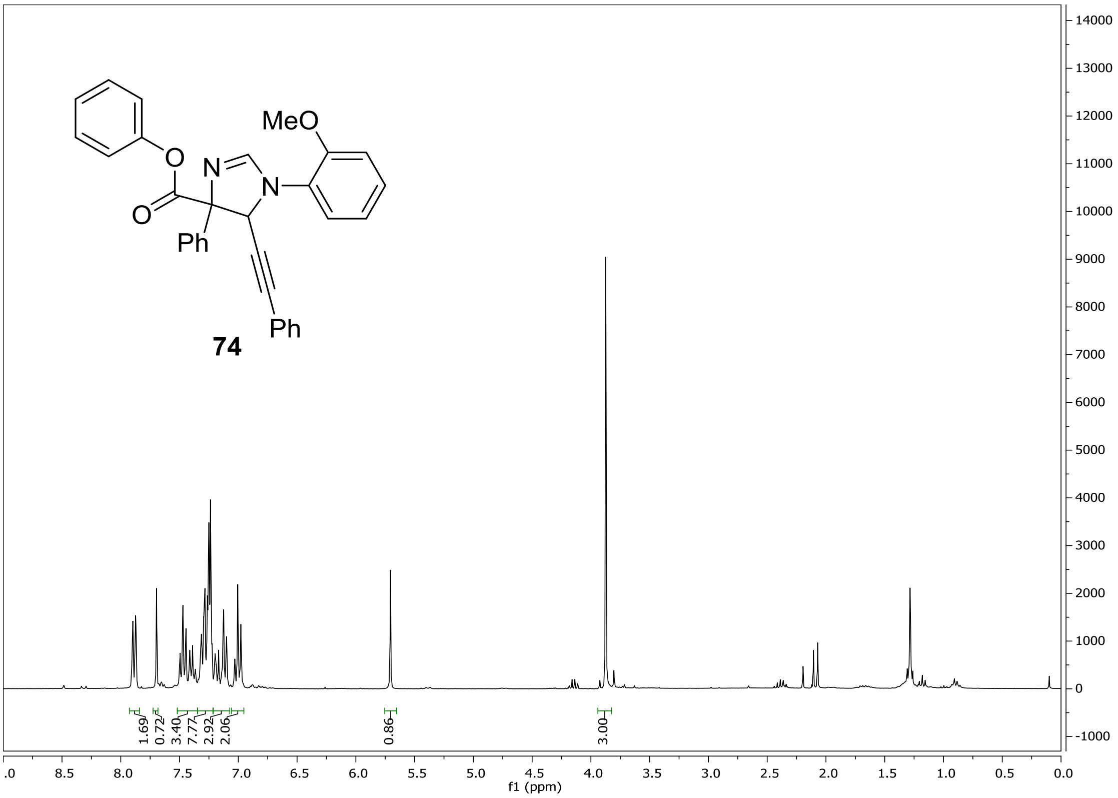
5.5.3.8. Adducts of the Mannich reaction with N-aryl aldimines

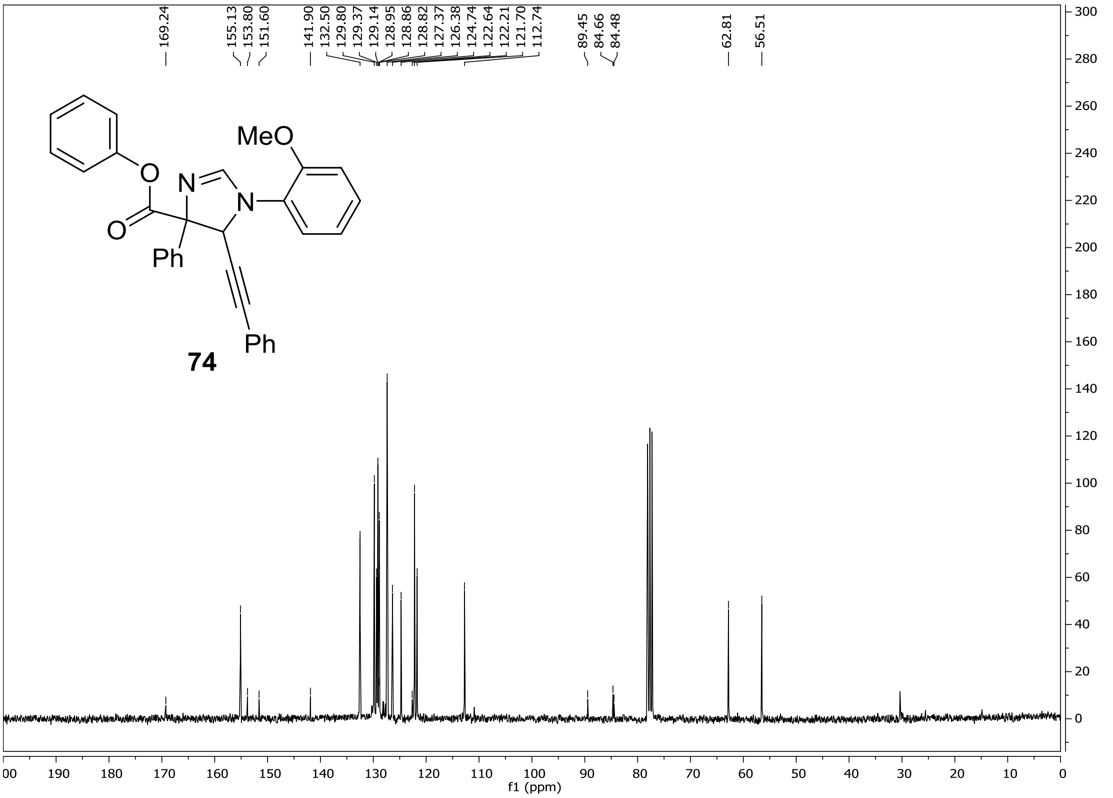




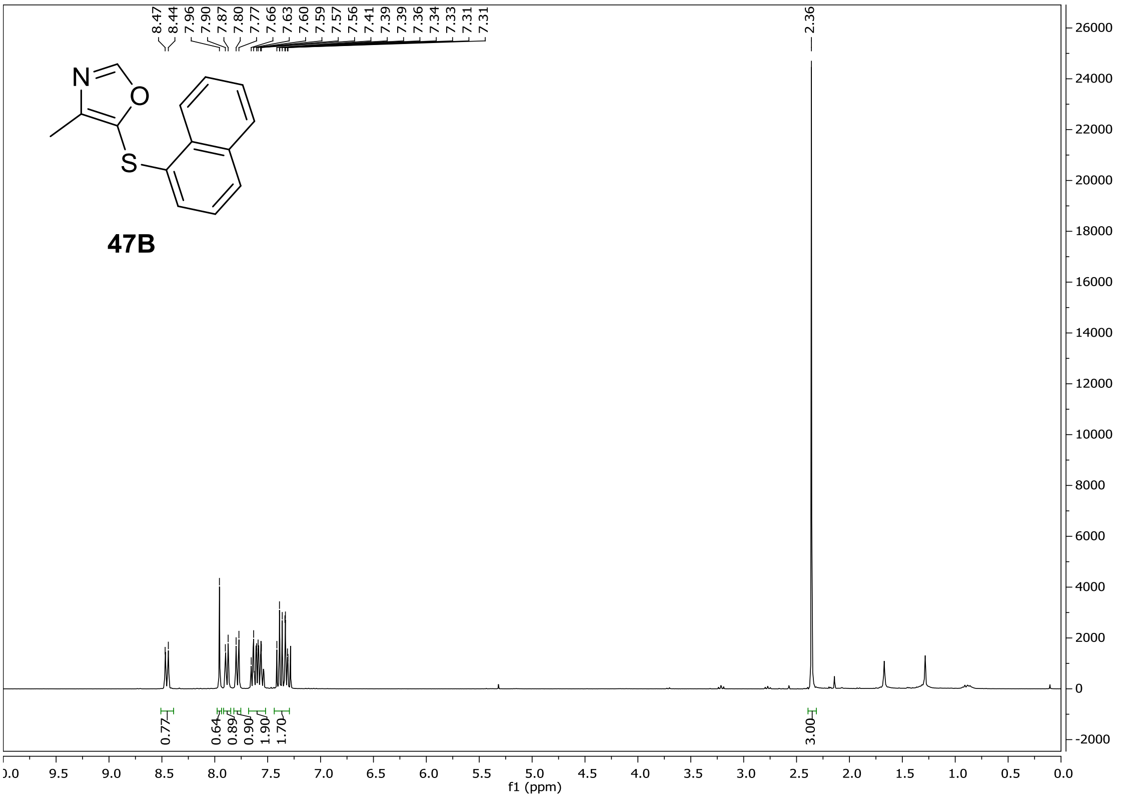

7.55 7.54 7.54 7.53 7.52 7.52 7.42 7.40 7.39 7.39 7.39 7.38 7.37 7.37 7.36 7.35 7.35 7.34 7.34 7.33 7.32 7.32 7.32 7.31 7.30 7.30 7.30 7.29 7.28 CDCl3 7.28 7.24 7.22 7.22 7.20 7.19 7.07 6.99 6.99 6.97 6.96 6.94 5.16 3.59 3.59 2.91 2.89 2.87 2.26 2.20 1.30 1.28 1.28 1.27 1.26 1.25 1.25 1.19 1.18 1.17 1.16 1.13 1.11 1.00 0.98
2.16
7.72
1.86
1.88
1.85
0.79
1.90
1.00
1.81
7.21
5.70
3.13
2.88
HO
S
N
N
O
Bn
Ph
72Ac
f1 (ppm)
.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
7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

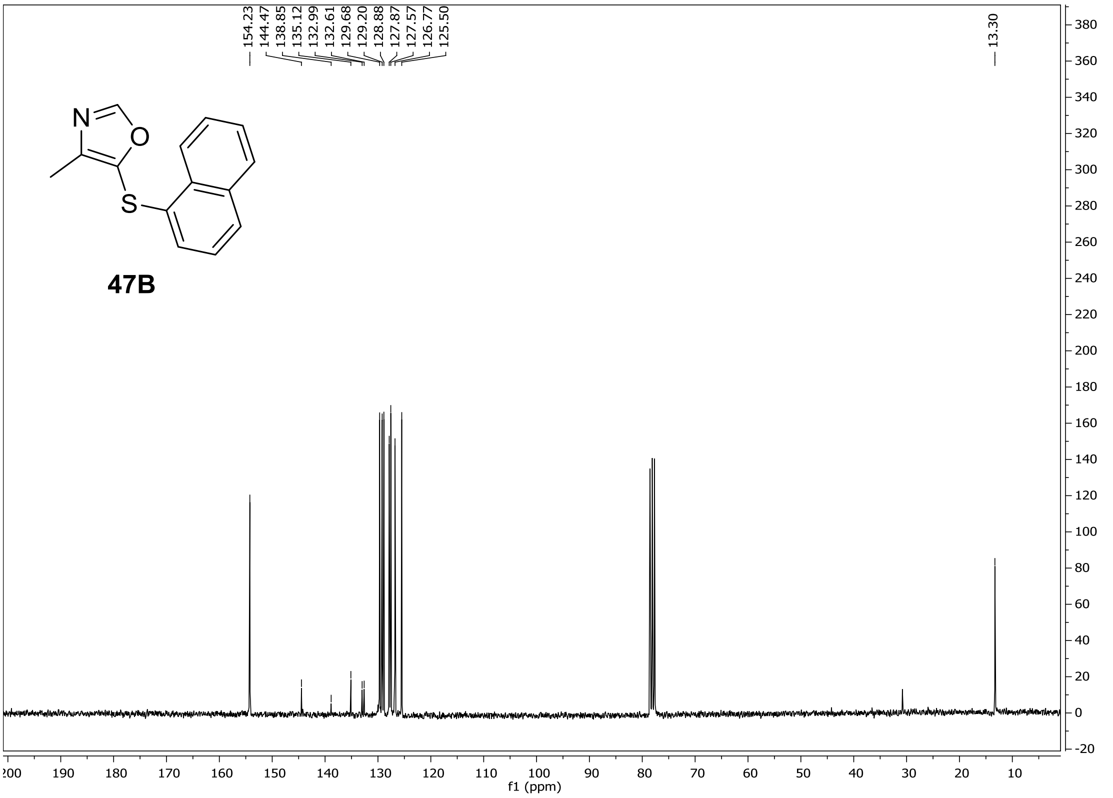

202.50
156.41 152.86 152.10 151.97 150.96 135.89 131.67 131.02 128.90 128.81 128.35 128.01 126.78 126.09 125.83 122.08 121.97 120.88 116.64
90.51 86.33 82.50
62.50
41.67 34.35 31.97 31.52 30.95 24.72 24.24 23.87 23.65 23.41
HO
S
N
N
O
Bn
Ph
72Ac
f1 (ppm)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0

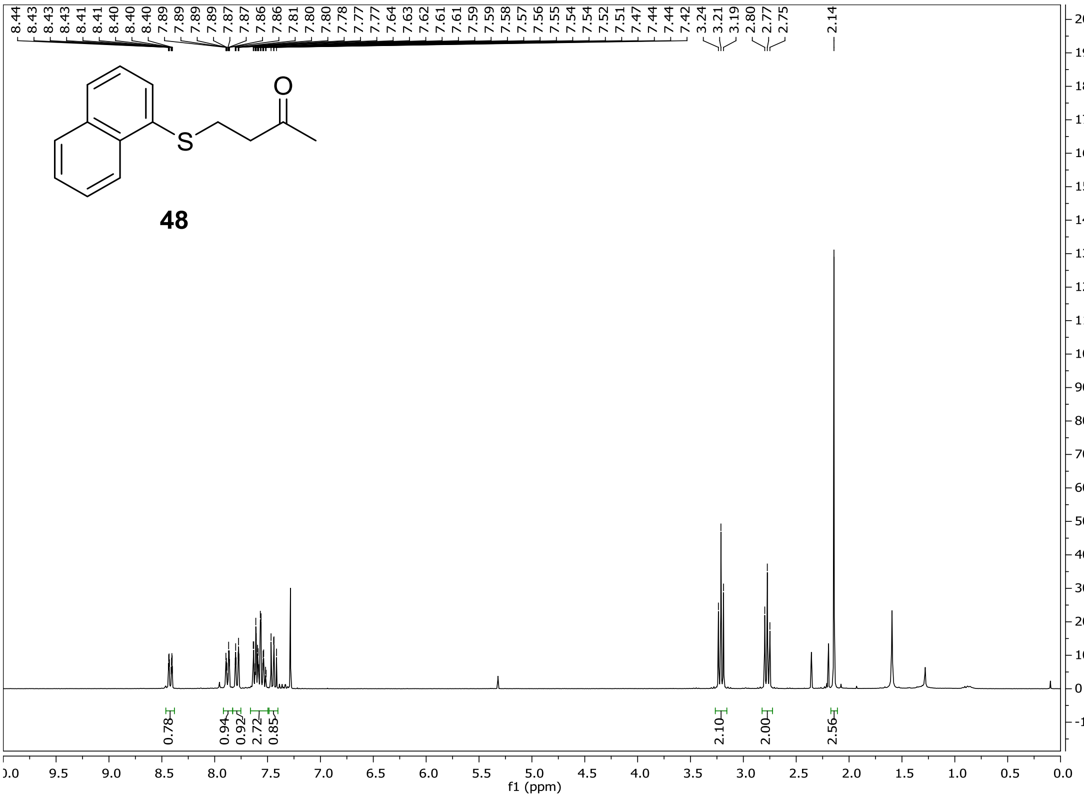

MeO
O
N
N
O
Ph
Ph
74
1.69
0.72
3.40
7.77
2.92
2.06
0.86
3.00
f1 (ppm)
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000

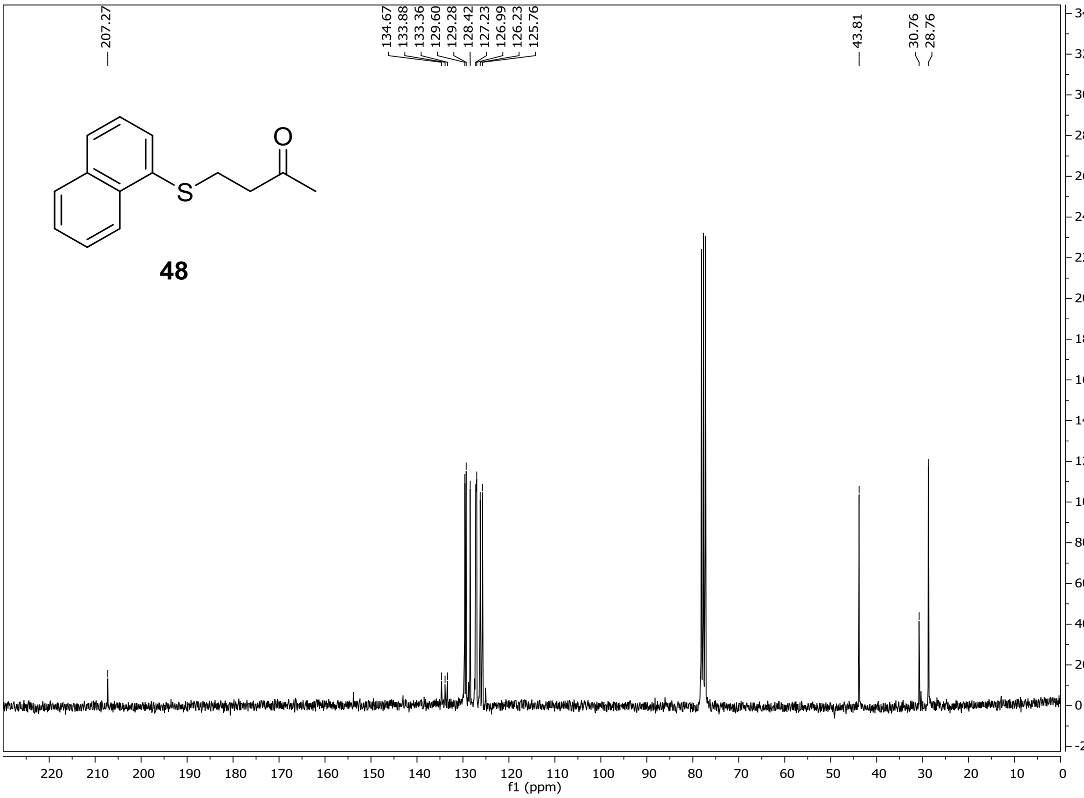

169.24
155.13
153.80
151.60
141.90
132.50
129.80
129.37
129.14
128.95
128.86
128.82
127.37
126.38
124.74
122.64
122.21
121.70
112.74
89.45
84.66
84.48
62.81
56.51
MeO
O
N
N
O
Ph
Ph
74
f1 (ppm)
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0

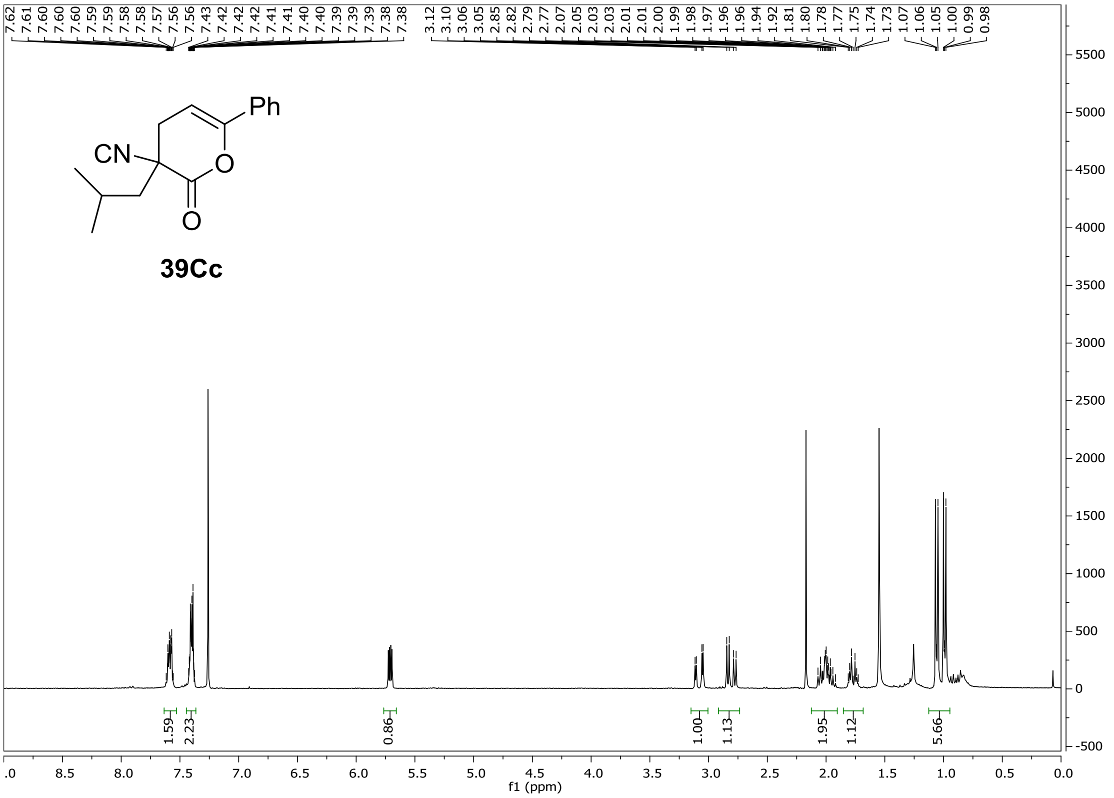
5.5.3.9. Isolated by-products

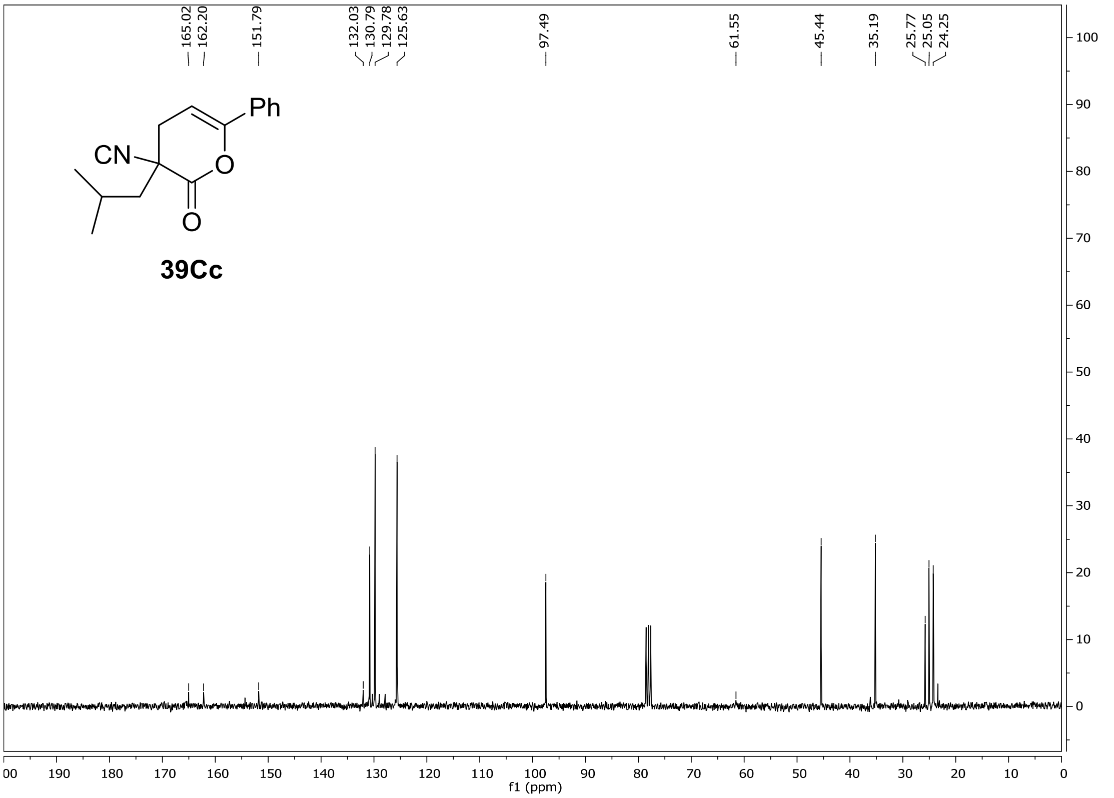


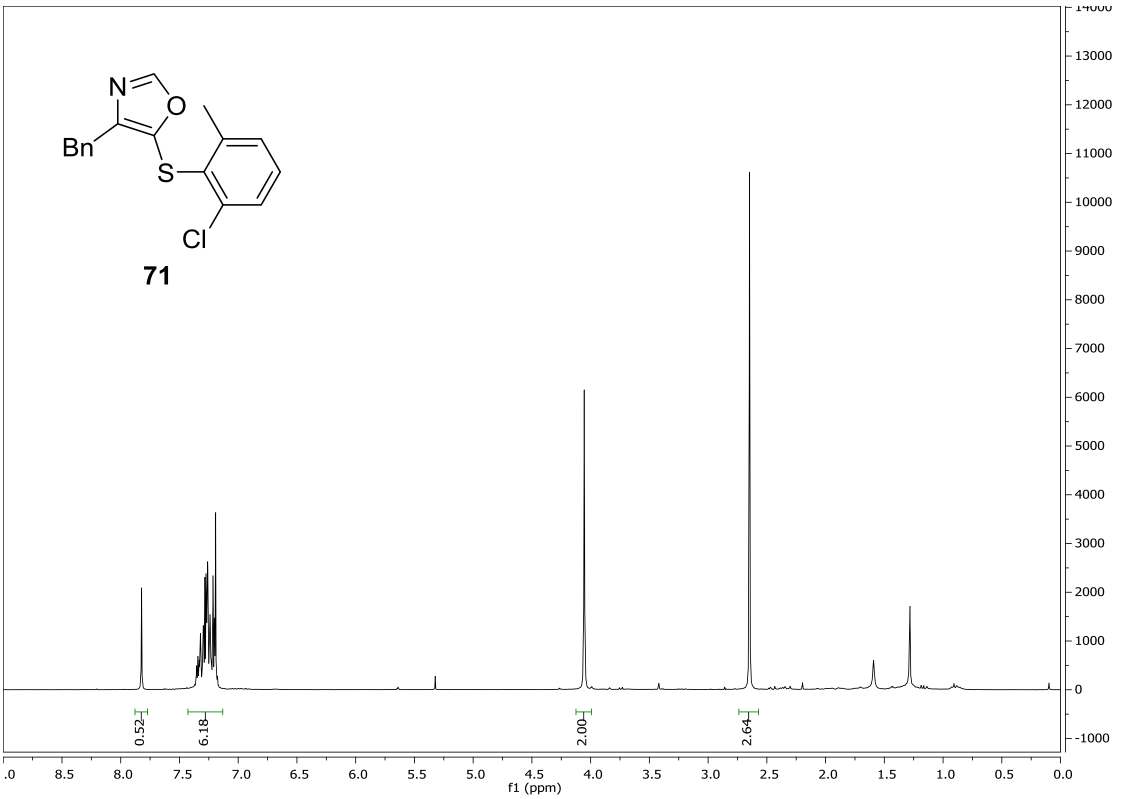


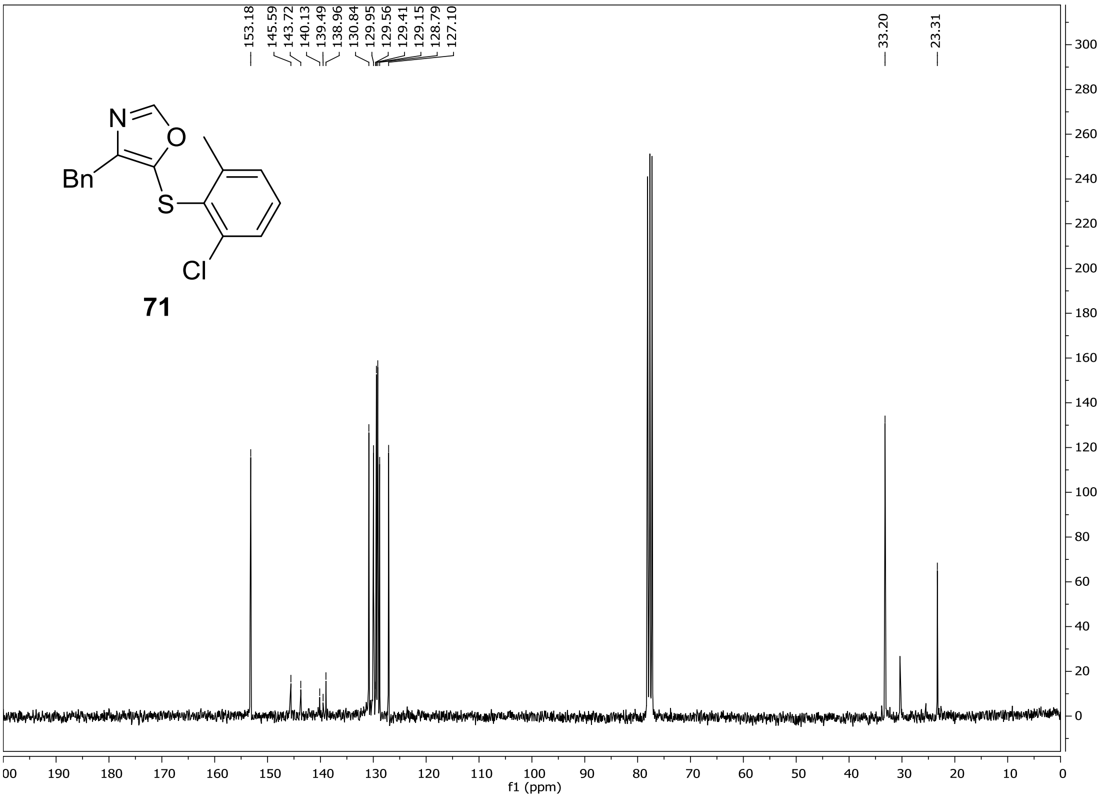

8.44 8.43 8.43 8.43 8.41 8.40 8.40 8.40 7.89 7.89 7.89 7.87 7.87 7.86 7.86 7.81 7.80 7.78 7.77 7.77 7.64 7.63 7.62 7.61 7.61 7.59 7.59 7.58 7.57 7.56 7.55 7.54 7.54 7.52 7.51 7.47 7.44 7.44 7.42 3.24 3.21 3.19 2.80 2.77 2.75 2.14
O
S
48
0.78
0.94
0.92
2.72
0.85
2.10
2.00
2.56
f1 (ppm)
20000 19000 18000 17000 16000 15000 14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000


207.27
134.67 133.88 133.36 129.60 129.28 128.42 127.23 126.99 126.23 125.76
43.81
30.76 28.76
O
S
48
f1 (ppm)
340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20


7.62
7.61
7.60
7.60
7.59
7.59
7.58
7.58
7.57
7.56
7.56
7.43
7.42
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.39
7.38
7.38
3.12
3.10
3.06
3.05
2.85
2.82
2.79
2.77
2.07
2.05
2.03
2.03
2.01
2.01
2.00
1.99
1.98
1.97
1.96
1.96
1.94
1.92
1.81
1.80
1.78
1.77
1.75
1.74
1.73
1.07
1.06
1.05
1.00
0.99
0.98
Ph
CN
O
O
39Cc
1.59
2.23
0.86
1.00
1.13
1.95
1.12
5.66
f1 (ppm)

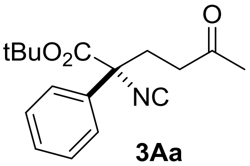

165.02
162.20
151.79
132.03
130.79
129.78
125.63
97.49
61.55
45.44
35.19
25.77
25.05
24.25
Ph
CN
O
O
39Cc
f1 (ppm)


N
O
Bn
S
Cl
71
0.52
6.18
2.00
2.64
f1 (ppm)
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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


153.18
145.59
143.72
140.13
139.49
138.96
130.84
129.95
129.56
129.41
129.15
128.79
127.10
33.20
23.31
N
O
Bn
S
Cl
71
f1 (ppm)
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

5.6. HPLC chromatograms of representative compounds

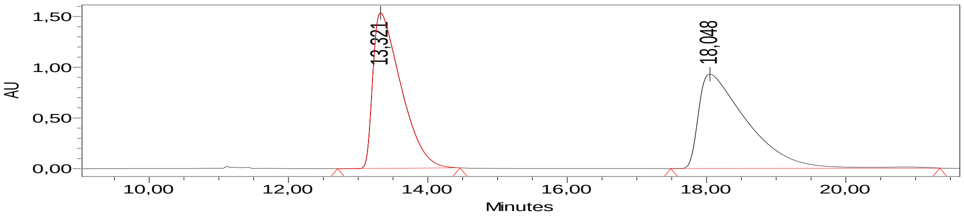
5.6.1. Chapter 2



3Aa

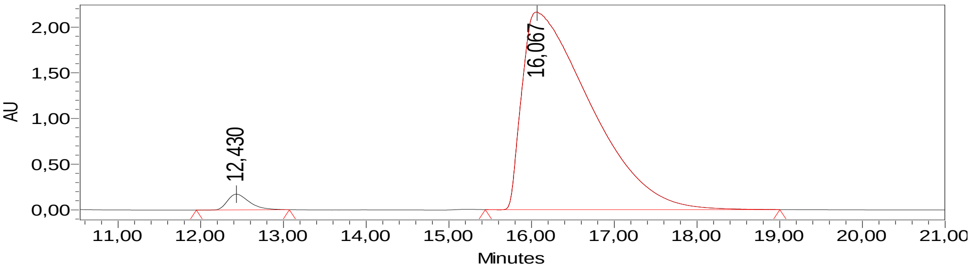
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 99:1; flux= 1 mL/min).

Rac-**3Aa**



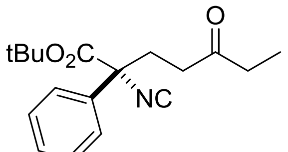
Retention Time	% Area
13,321	48,83
18,048	51,17

Scalemic-**3Aa**



Retention Time	% Area
12,430	2,47
16,067	97,53

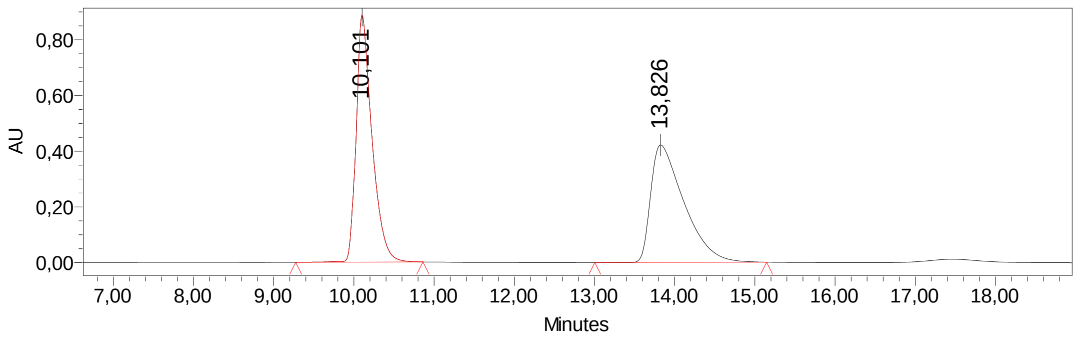
95% *ee*



3Ab

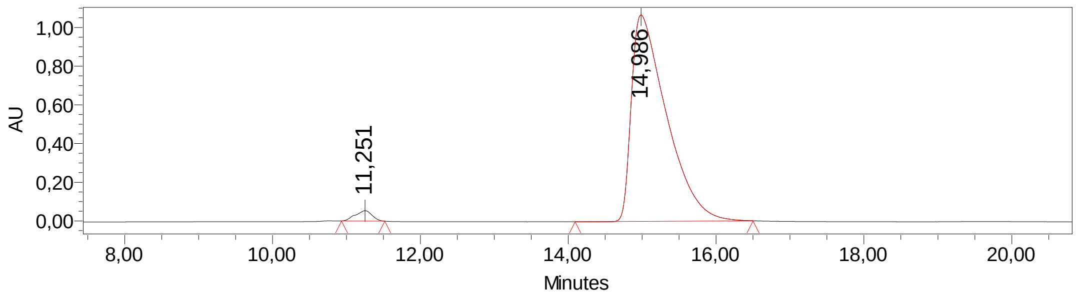
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 99:1; flux= 1 mL/min).

Rac-**3Ab**



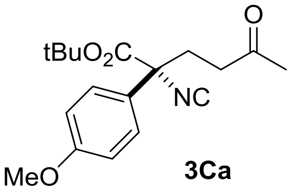
Retention Time	% Area
10,101	50,16
13,826	49,84

Scalemic-**3Ab**



Retention Time	% Area
11,251	2,33
14,986	97,67

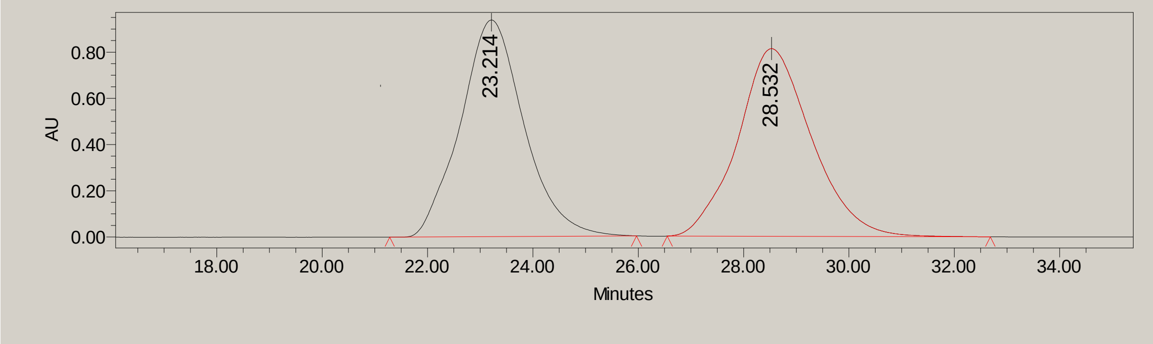
95% *ee*



3Ca

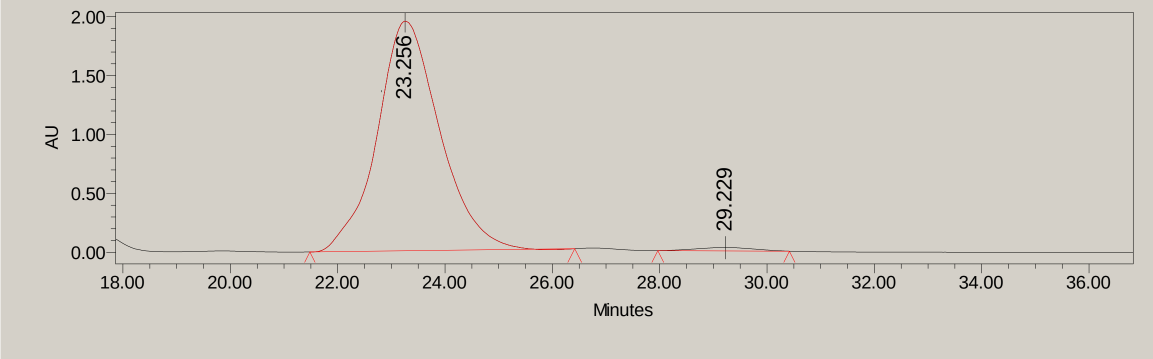
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:isopropanol, 99:1; flux= 0.5 mL/min).

Rac-**3Ca**



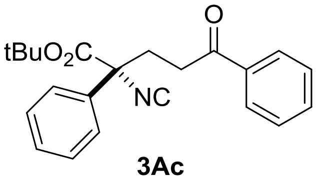
Retention Time	% Area
23.214	49.82
28.532	50.18

Scalemic-**3Ca**



Retention Time	% Area
23.256	98.70
29.229	1.30

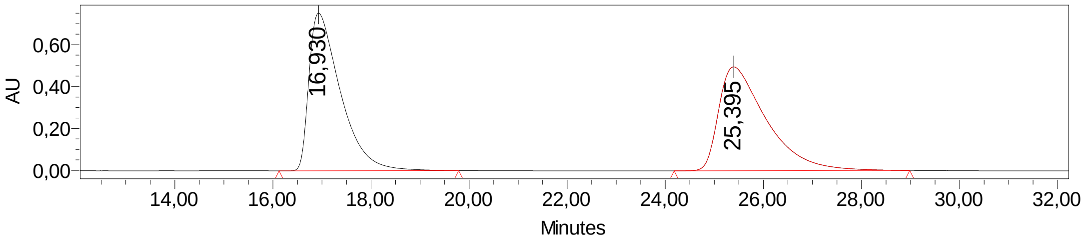
98% ee



3Ac

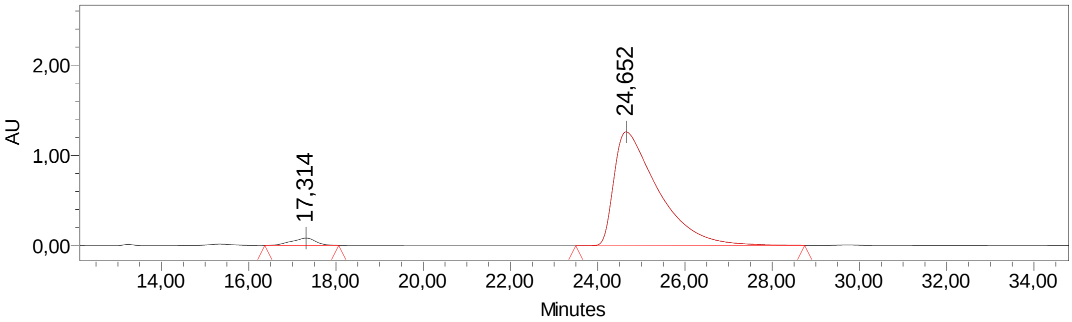
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 99:1; flux= 1 mL/min).

Rac-**3Ac**



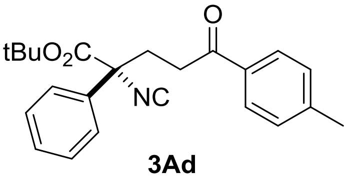
Retention Time	% Area
16,930	50,07
25,395	49,93

Scalemic-**3Ac**



Retention Time	% Area
17,314	3,40
24,652	96,60

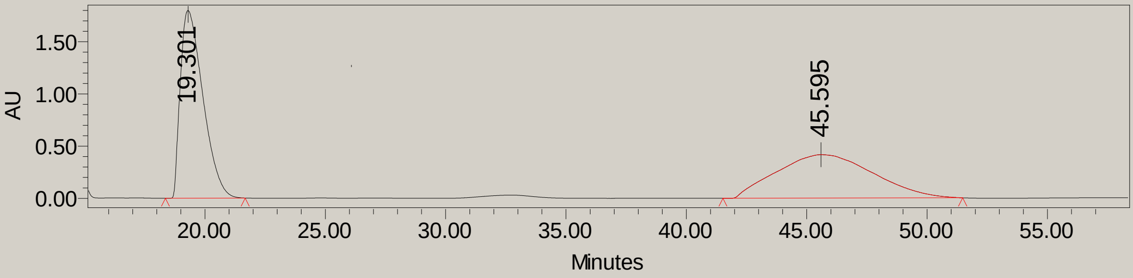
94% *ee*



3Ad

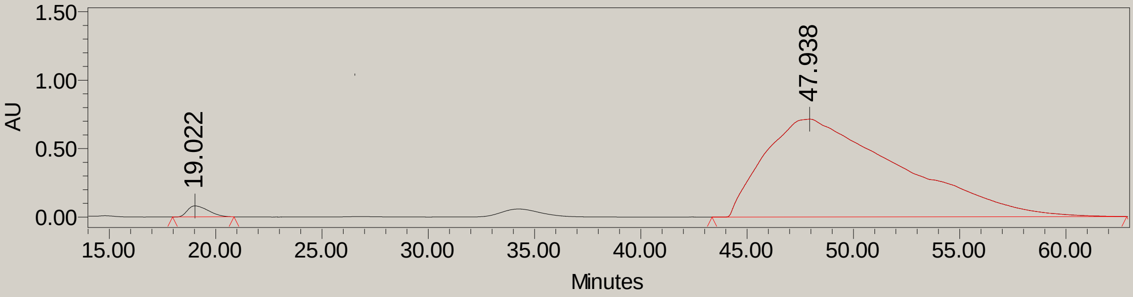
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane:ethanol, 99:1; flux= 1 mL/min).

Rac-**3Ad**



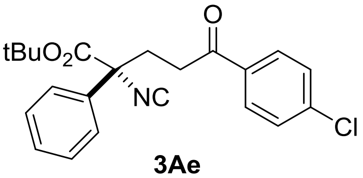
	Retention Time	% Area
	19.301	50.13
	45.595	49.87

Scalemic-**3Ad**



	Retention Time	% Area
	19.022	1.72
	47.938	98.28

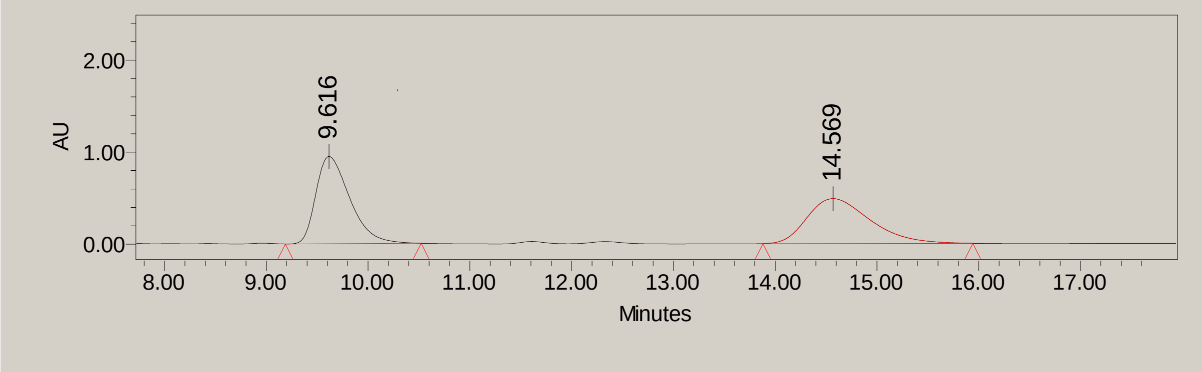
96% ee



3Ae

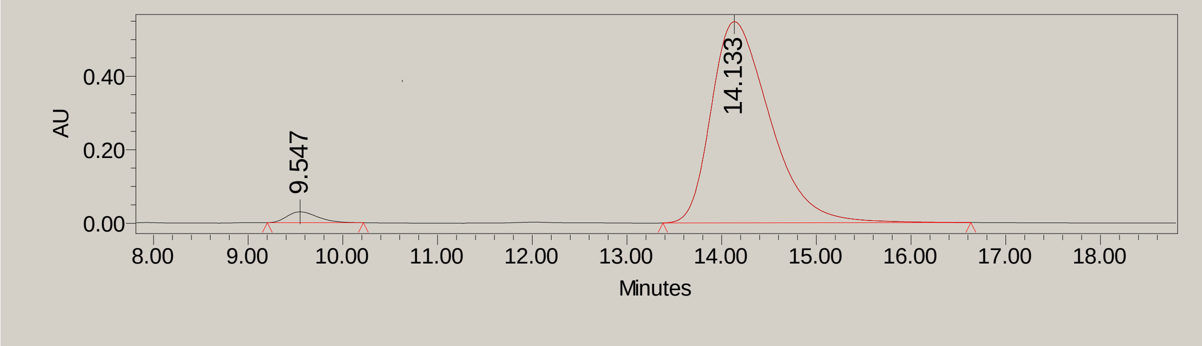
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 97:3; flux= 1 mL/min).

Rac-**3Ae**



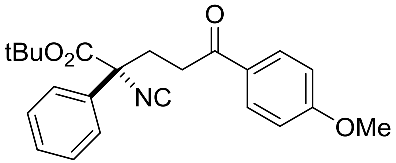
	Retention Time	% Area
	9.616	51.15
	14.569	48.85

Scalemic-**3Ae**



	Retention Time	% Area
	9.547	2.74
	14.133	97.26

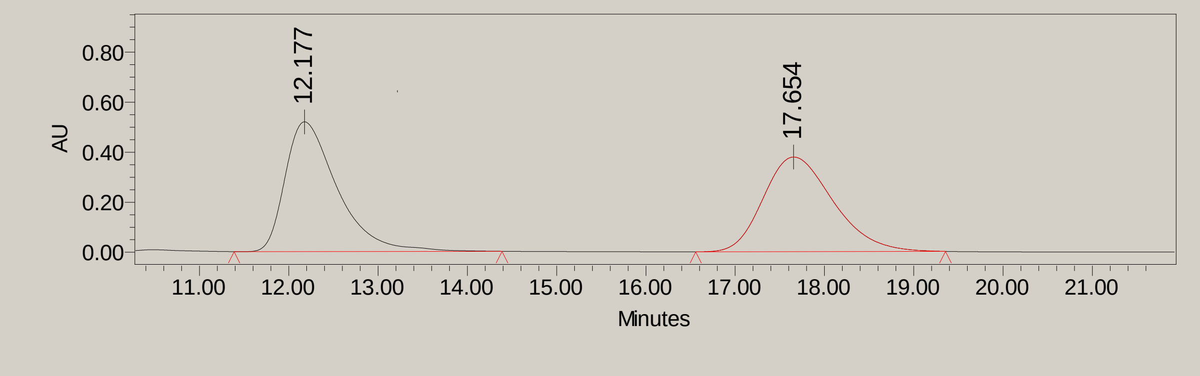
94% ee



3Af

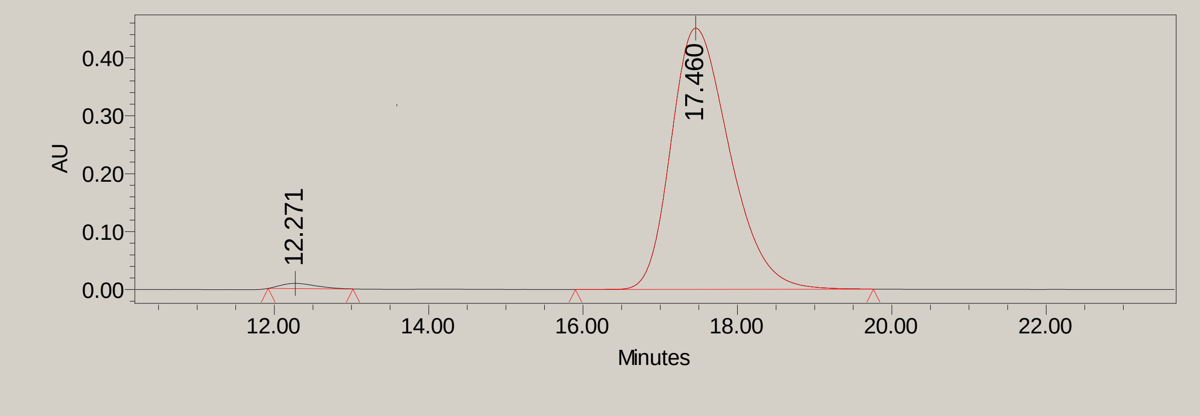
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**3Af**



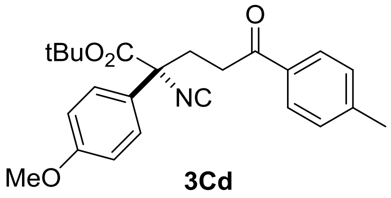
	Retention Time	% Area
	12.177	50.52
	17.654	49.48

Scalemic-**3Af**



	Retention Time	% Area
	12.271	1.17
	17.460	98.83

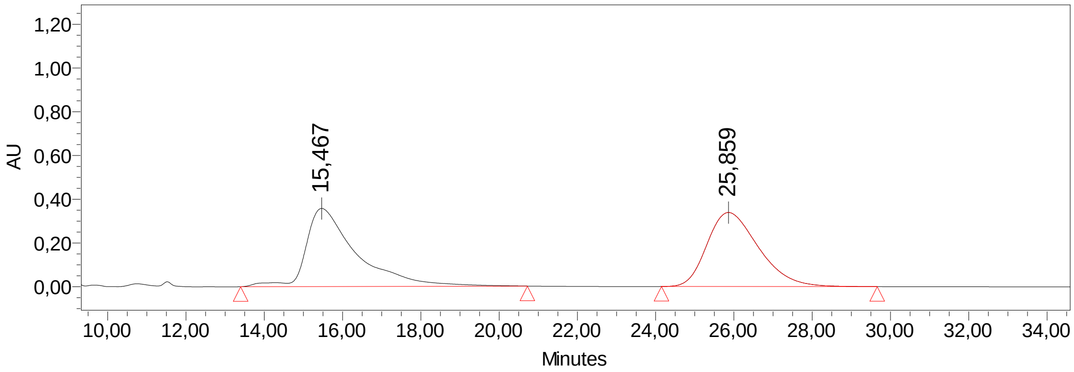
98% ee



3Cd

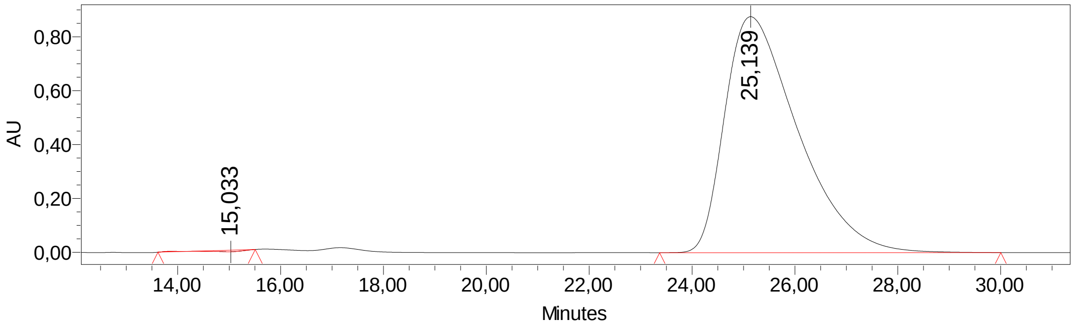
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 1 mL/min).

Rac-**3Cd**



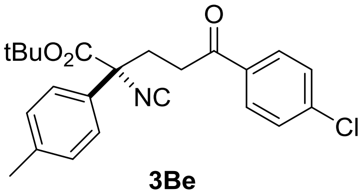
Retention Time	% Area
15,467	50,83
25,859	49,17

Scalemic-**3Cd**



Retention Time	% Area
15,033	0,31
25,139	99,69

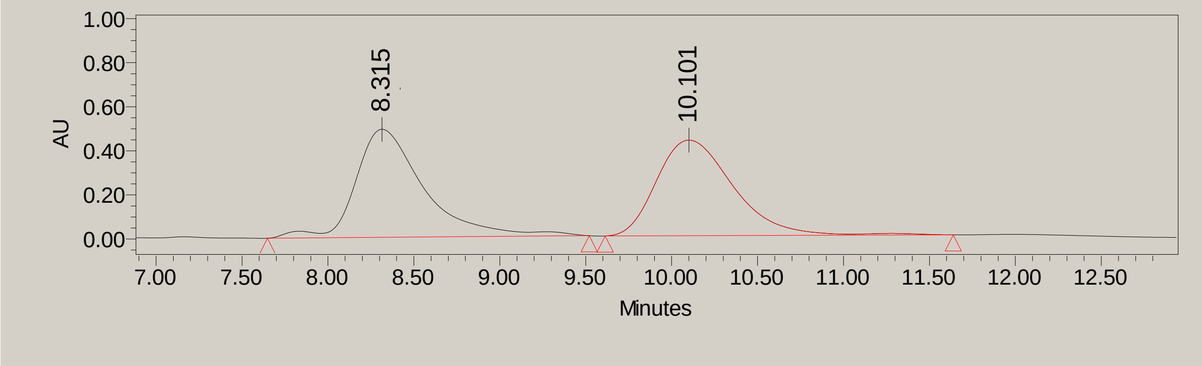
99% *ee*



3Be

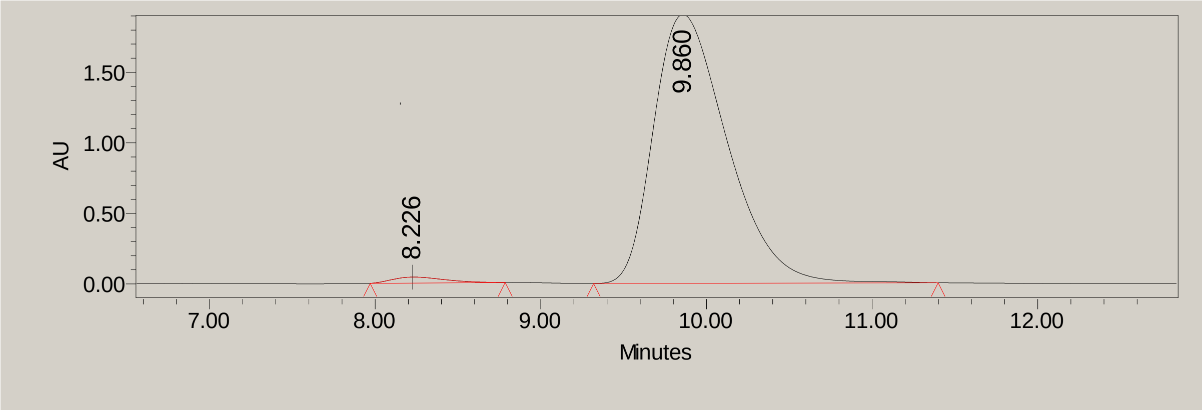
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 1 mL/min).

Rac-**3Be**



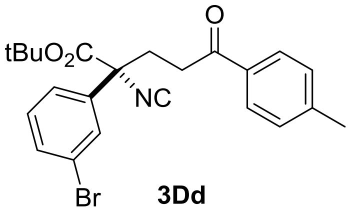
	Retention Time	% Area
	8.315	50.30
	10.101	49.70

Scalemic-**3Be**



	Retention Time	% Area
	8.226	1.56
	9.860	98.44

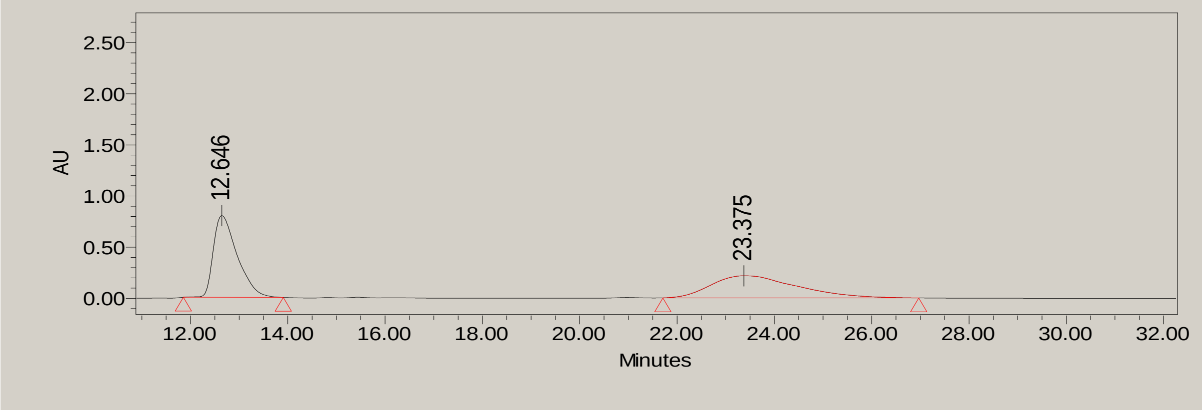
97% *ee*



3Dd

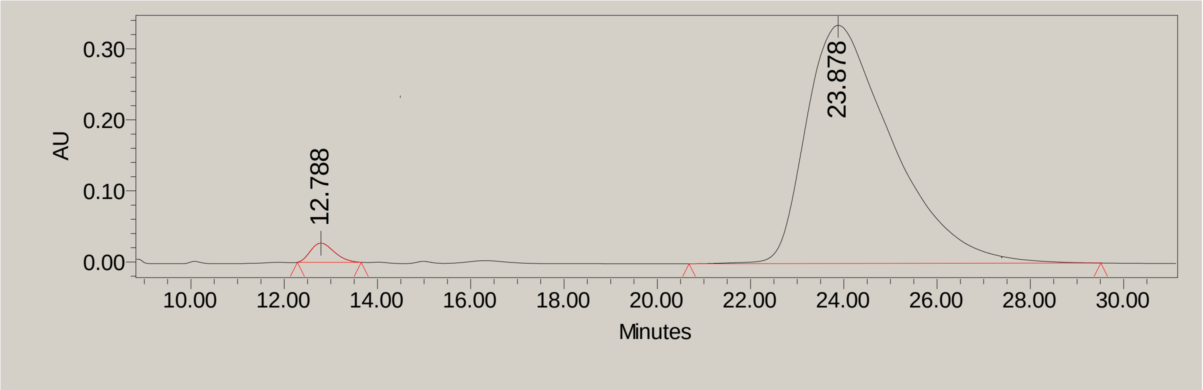
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**3Dd**



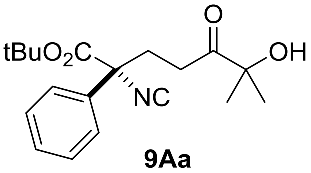
	Retention Time	% Area
	12.646	50.85
	23.375	49.15

Scalemic-**3Dd**



	Retention Time	% Area
	12.788	2.16
	23.878	97.84

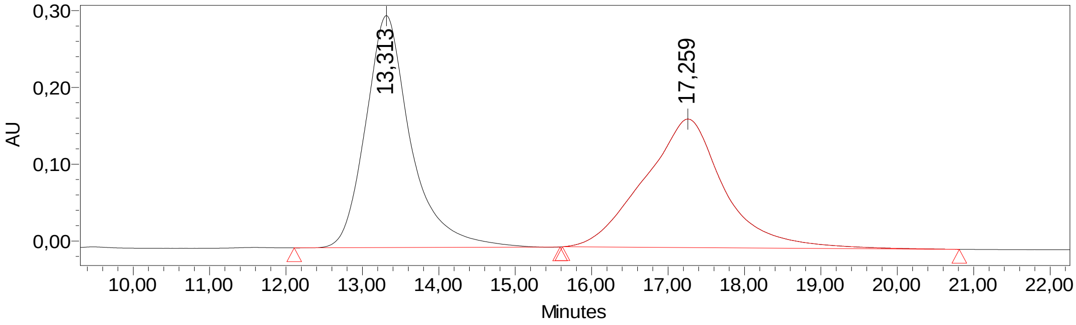
96% ee



9Aa

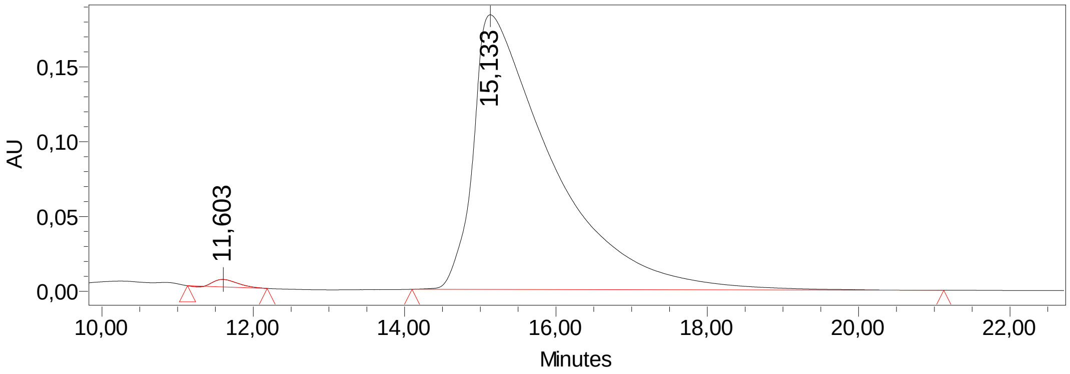
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**9Aa**



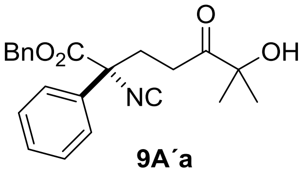
Retention Time	% Area
13,313	50,47
17,259	49,53

Scalemic-**9Aa**



Retention Time	% Area
11,603	0,88
15,133	99,12

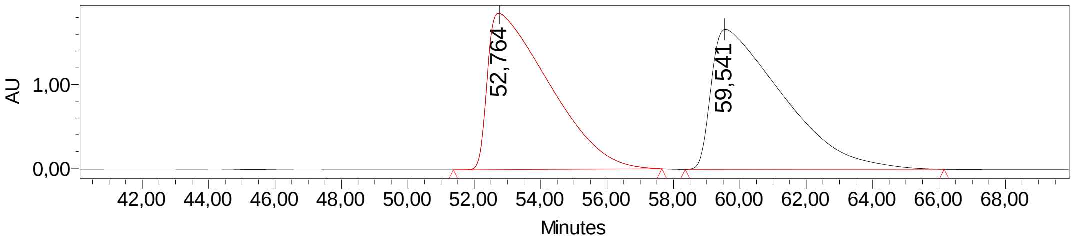
98% ee



9A´a

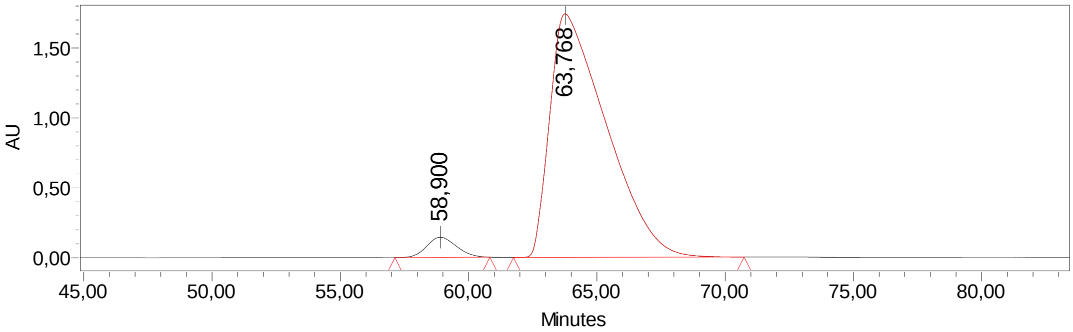
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**9A´a**



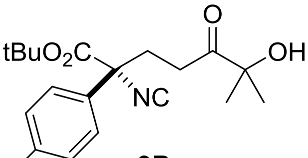
Retention Time	% Area
52,764	49,05
59,541	50,95

Scalemic-**9A´a**



Retention Time	% Area
58,900	4,18
63,768	95,82

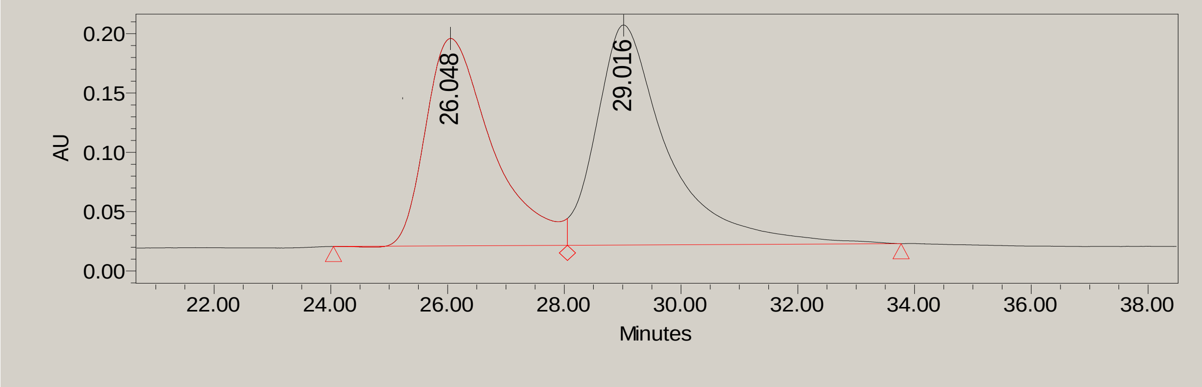
92% ee



9Ba

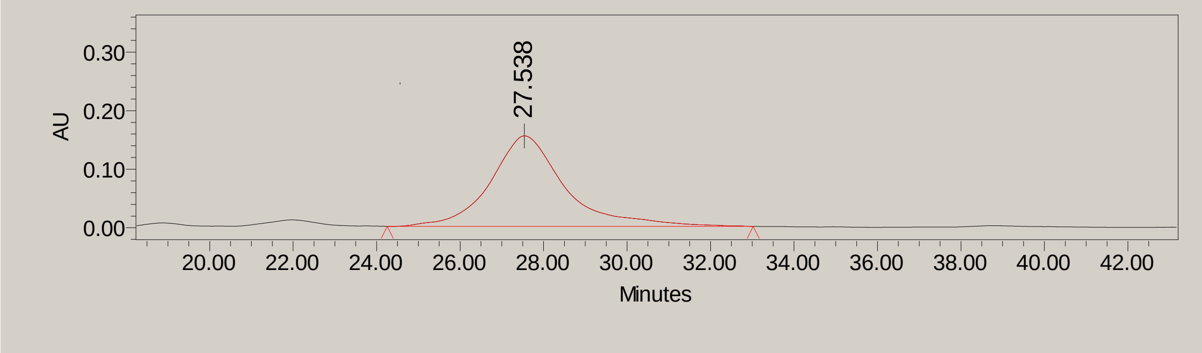
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**9Ba**



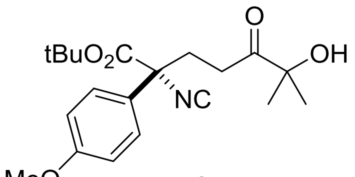
	Retention Time	% Area
	26.048	49.47
	29.016	50.53

Scalemic-**9Ba**



	Retention Time	% Area
	27.538	100.00

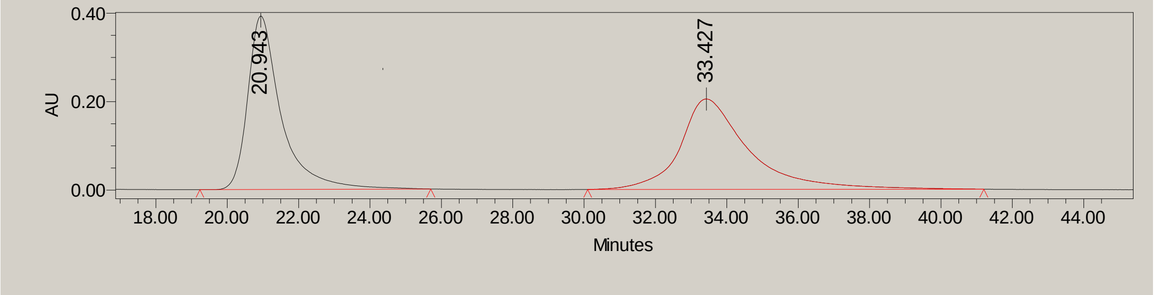
99% *ee*



9Ca

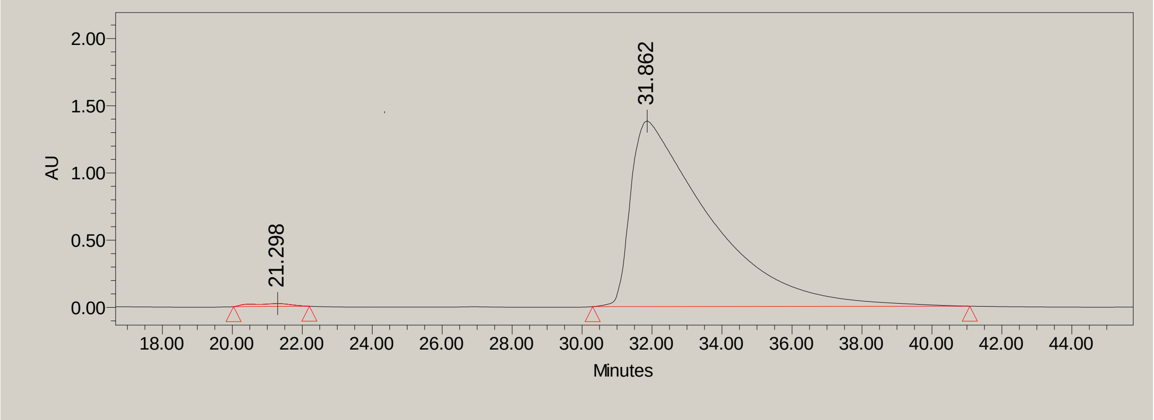
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**9Ca**



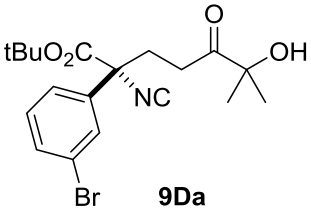
Retention Time	% Area
20.943	48.30
33.427	51.70

Scalemic-**9Ca**



Retention Time	% Area
21.298	0.80
31.862	99.20

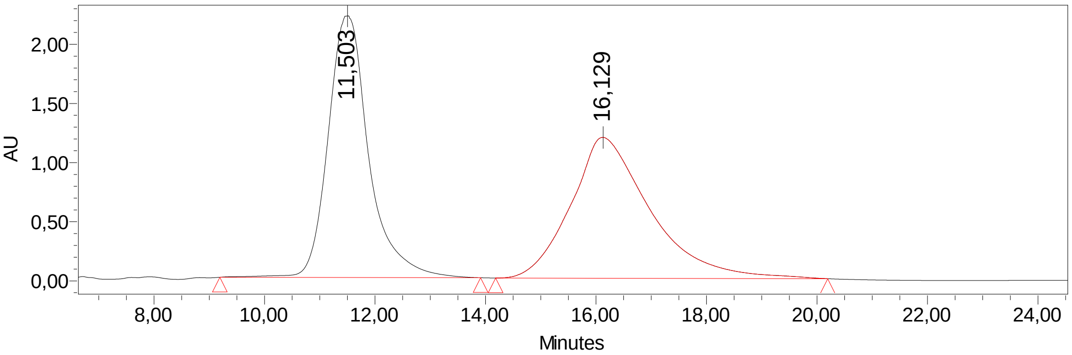
98% ee



9Da

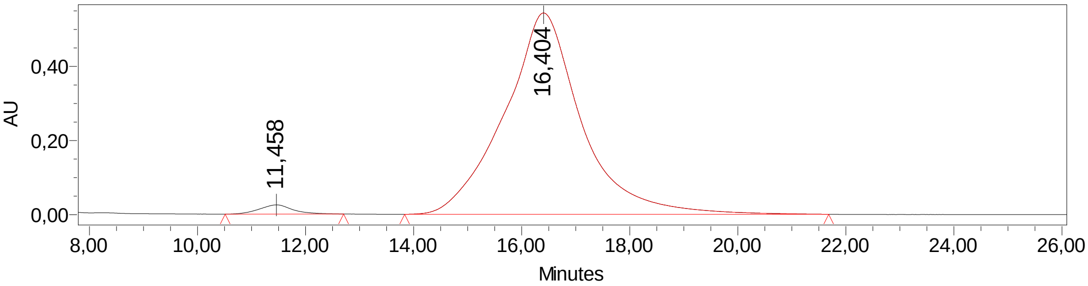
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**9Da**



Retention Time	% Area
11,503	48,80
16,129	51,20

Scalemic-**9Da**

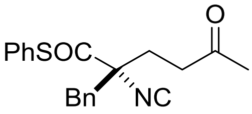


Retention Time	% Area
11,458	1,96
16,404	98,04

96% ee

5.6.2. Chapter 3

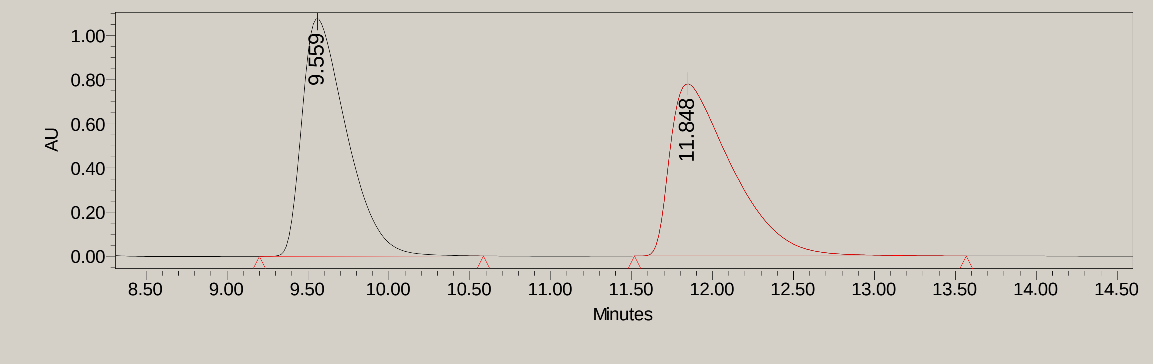
5.6.2.1. Adducts of the Michael additions to vinyl ketones



36Aa

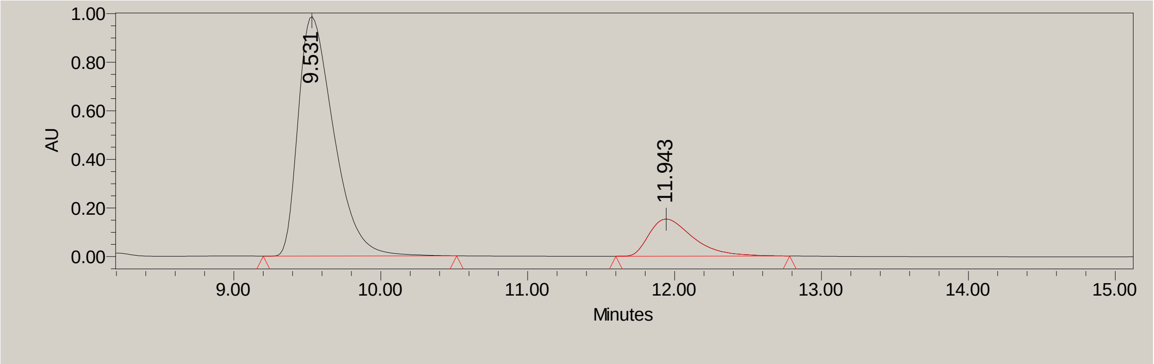
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**36Aa**



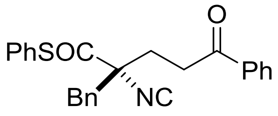
	Retention Time	% Area
1	9.559	49.86
2	11.848	50.14

Scalemic-**36Aa**



	Retention Time	% Area
1	9.531	83.95
2	11.943	16.05

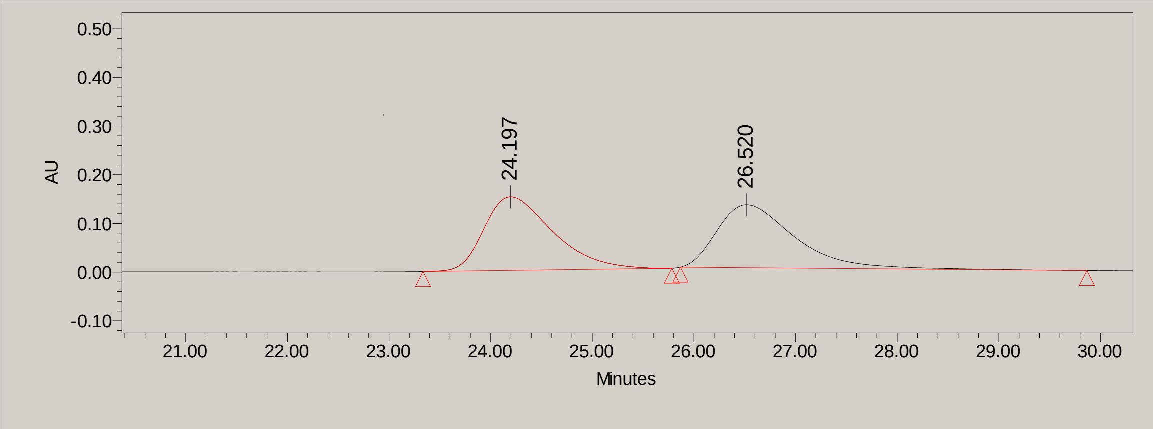
68% *ee*



36Ac

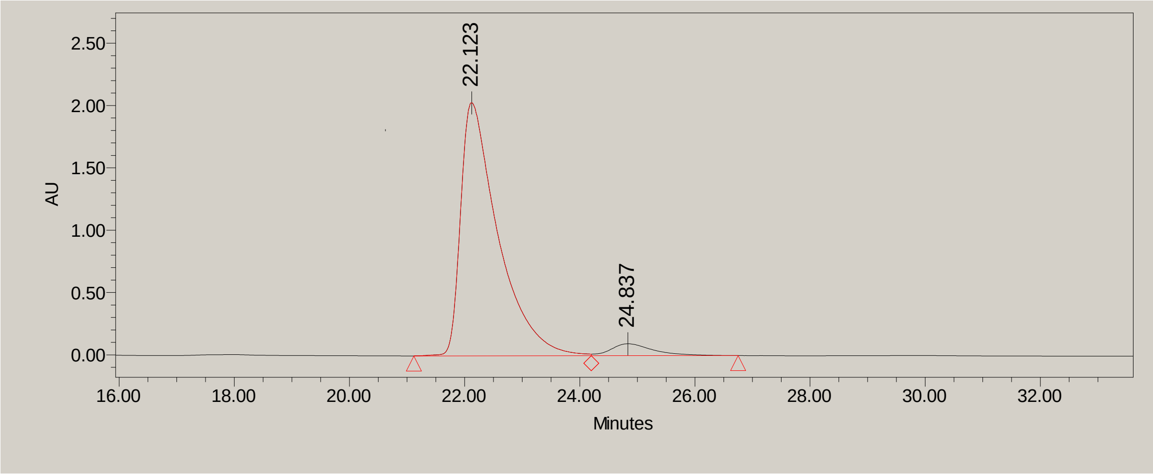
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**36Ac**



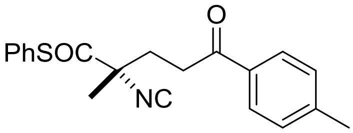
	Retention Time	% Area
1	24.197	50.38
2	26.520	49.62

Scalemic-**36Ac**



	Retention Time	% Area
1	22.123	94.95
2	24.837	5.05

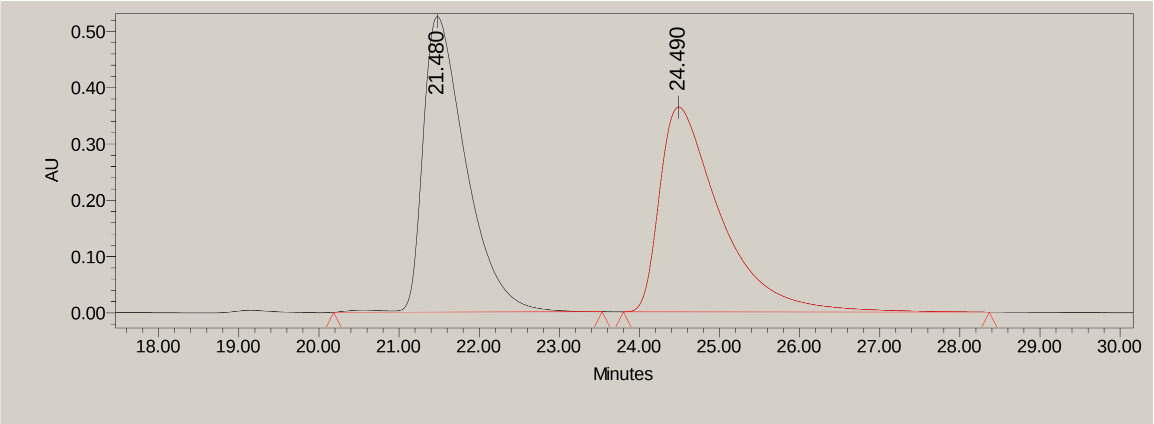
90% *ee*



36Bd

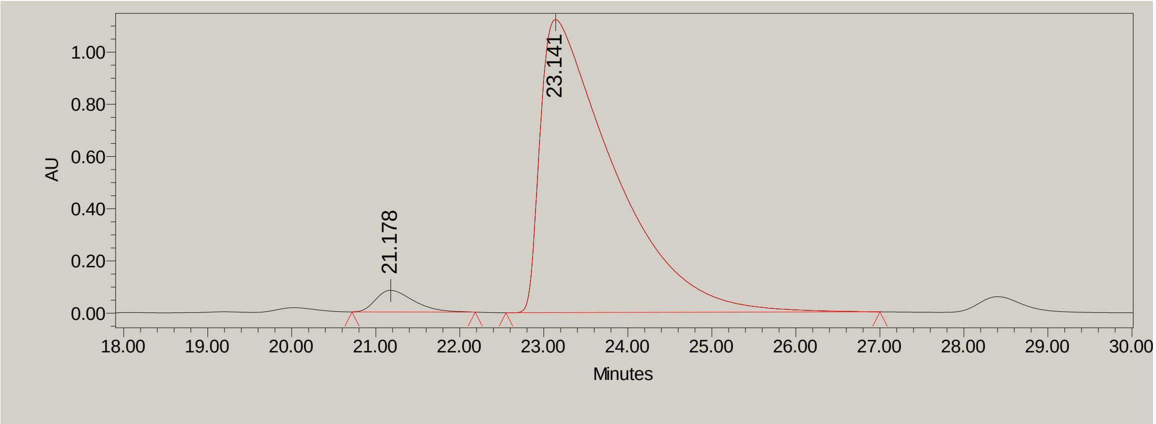
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**36Bd**



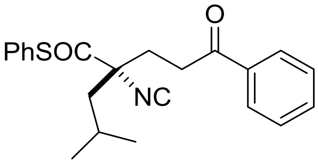
	Retention Time	% Area
1	21.480	50.35
2	24.490	49.65

Scalemic-**36Bd**



	Retention Time	% Area
1	21.178	3.66
2	23.141	96.34

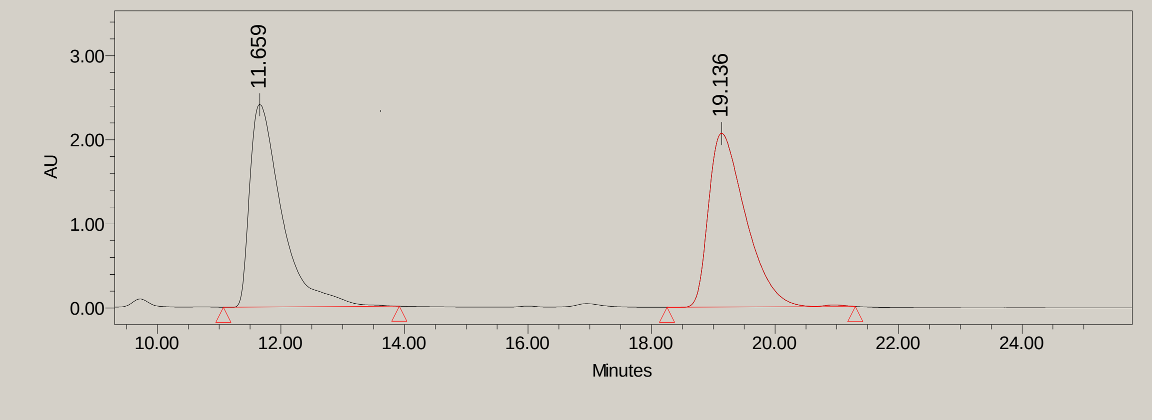
93% ee



36Cc

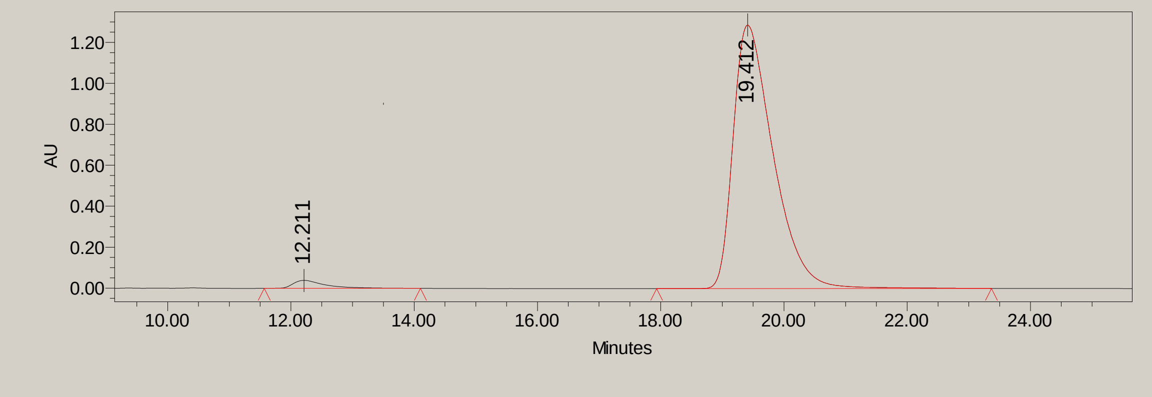
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**36Cc**



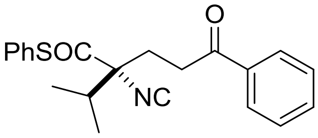
	Retention Time	% Area
1	11.659	50.11
2	19.136	49.89

Scalemic-**36Cc**



	Retention Time	% Area
1	12.211	2.36
2	19.412	97.64

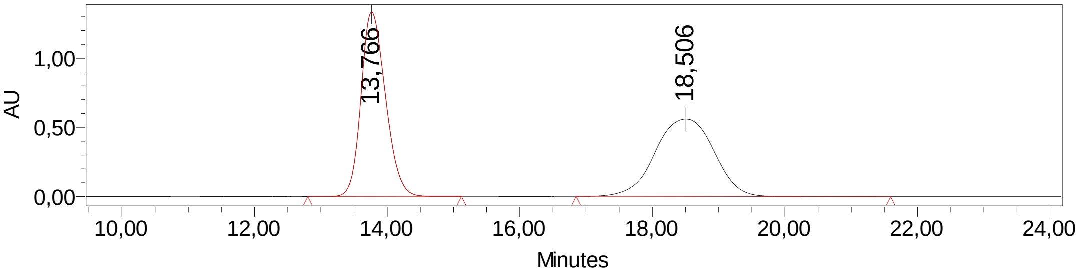
96% *ee*



36Dc

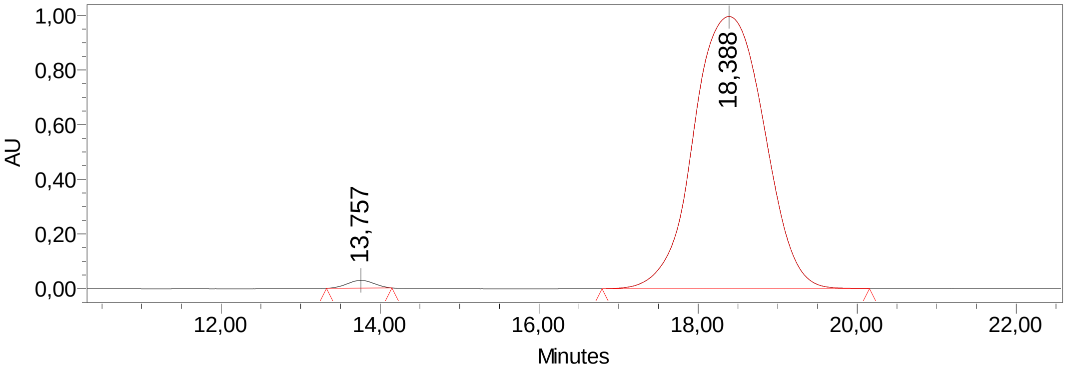
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**36Dc**



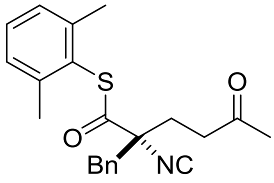
	Retention Time	% Area
1	13,766	49,74
2	18,506	50,26

Scalemic-**36Dc**



	Retention Time	% Area
1	13,757	1,07
2	18,388	98,93

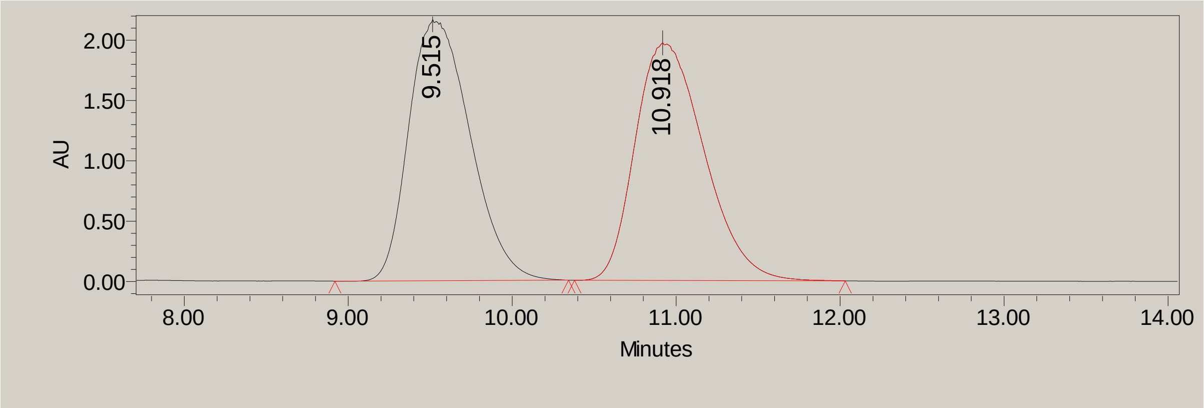
98% *ee*



45Aa

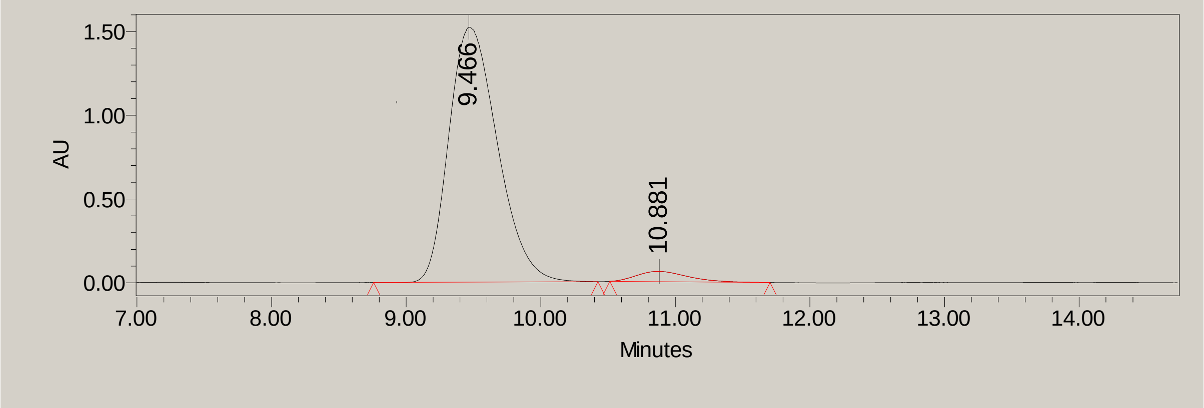
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:ethanol, 95:5; flux= 1 mL/min).

Rac-**45Aa**



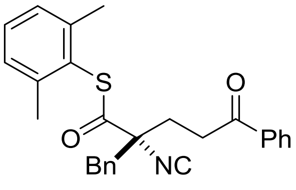
	Retention Time	% Area
1	9.515	49.52
2	10.918	50.48

Scalemic-**45Aa**



	Retention Time	% Area
1	9.466	95.92
2	10.881	4.08

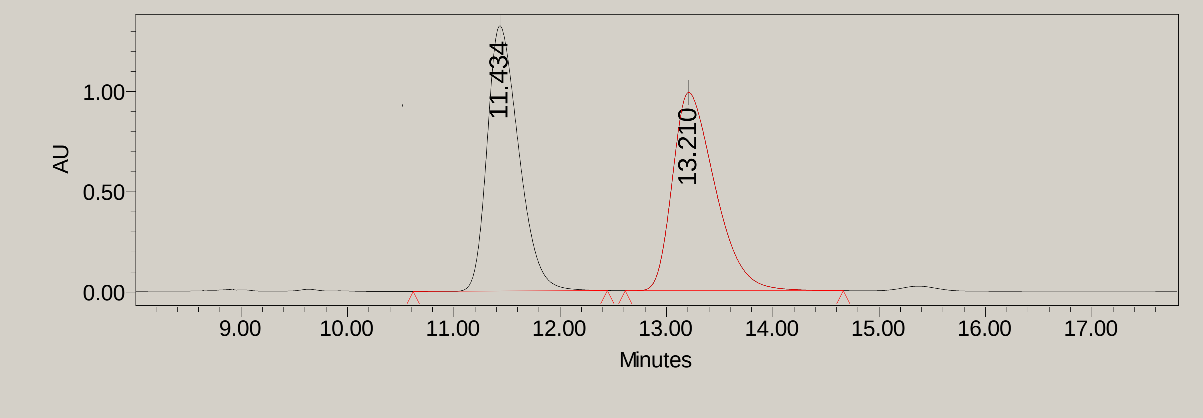
92% *ee*



45Ac

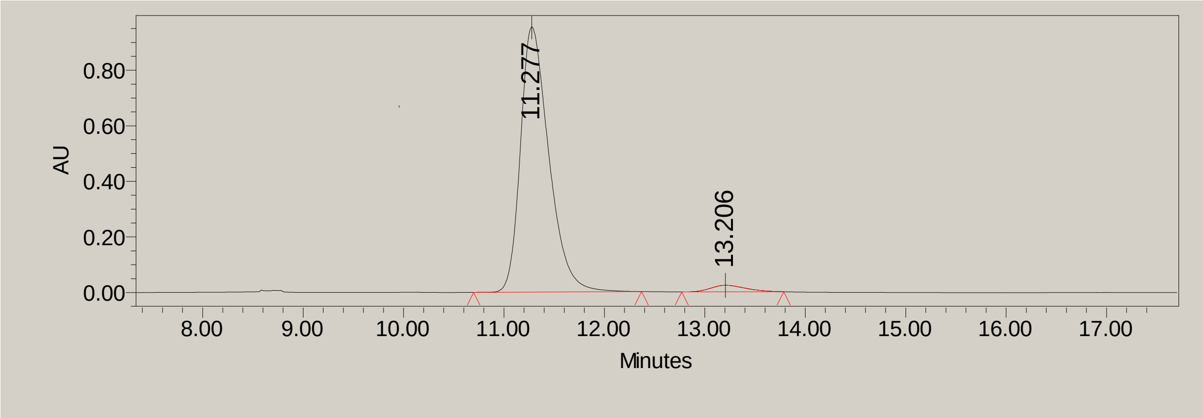
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**45Ac**



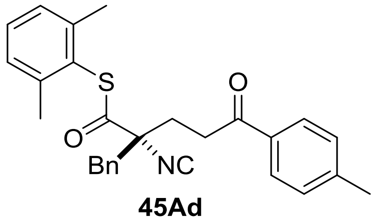
	Retention Time	% Area
1	11.434	49.81
2	13.210	50.19

Scalemic-**45Ac**



	Retention Time	% Area
1	11.277	97.05
2	13.206	2.95

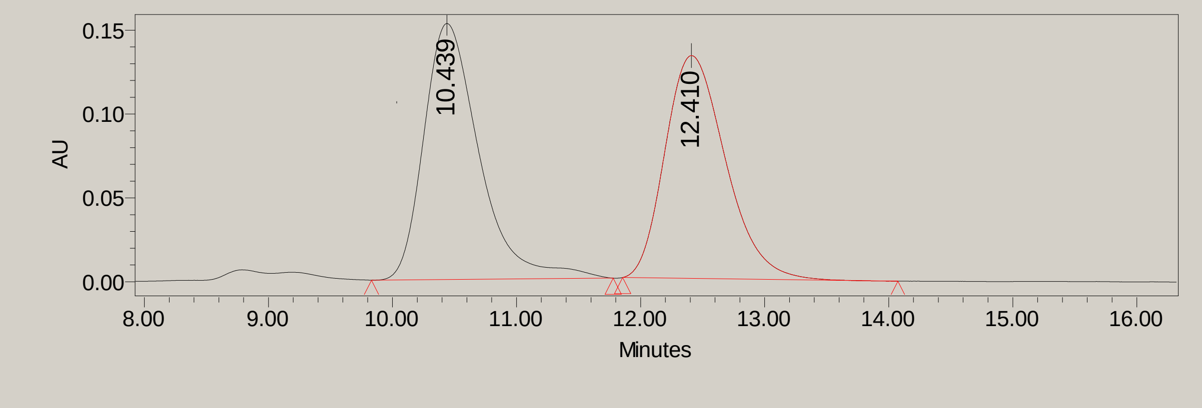
94% *ee*



45Ad

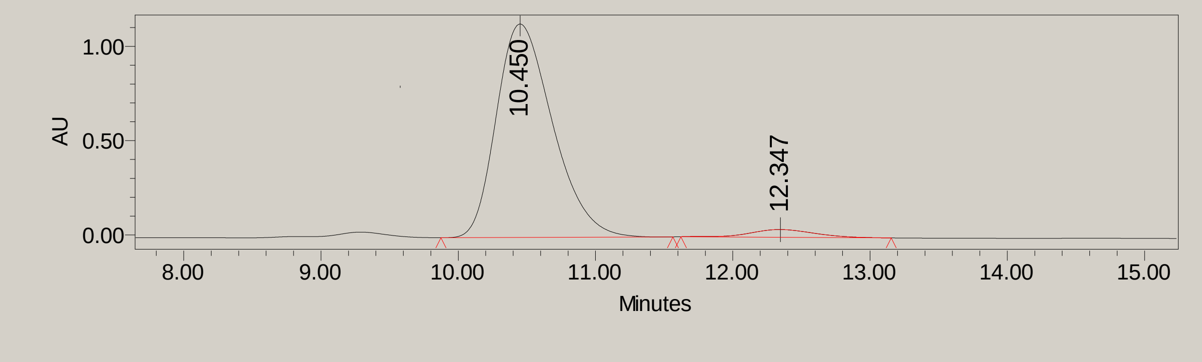
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:ethanol, 95:5; flux= 1 mL/min).

Rac-**45Ad**



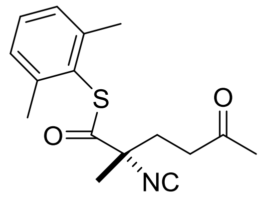
	Retention Time	% Area
1	10.439	50.88
2	12.410	49.12

Scalemic-**45Ad**



	Retention Time	% Area
1	10.450	96.06
2	12.347	3.94

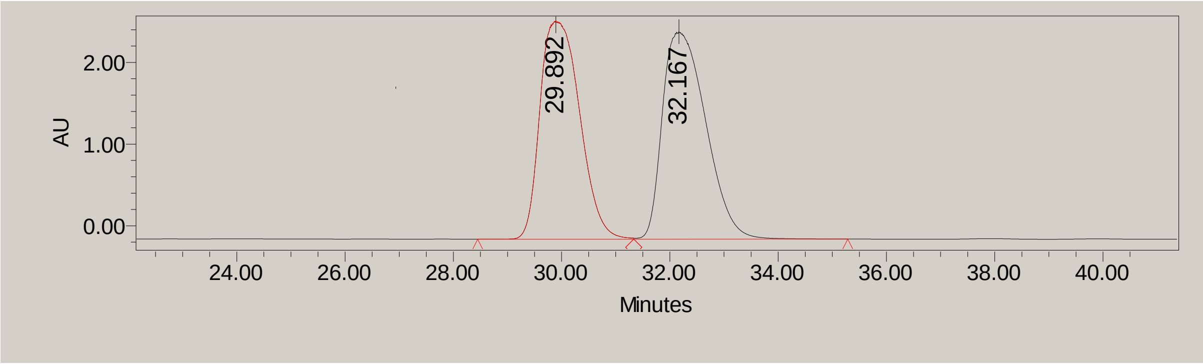
92% *ee*



45Ba

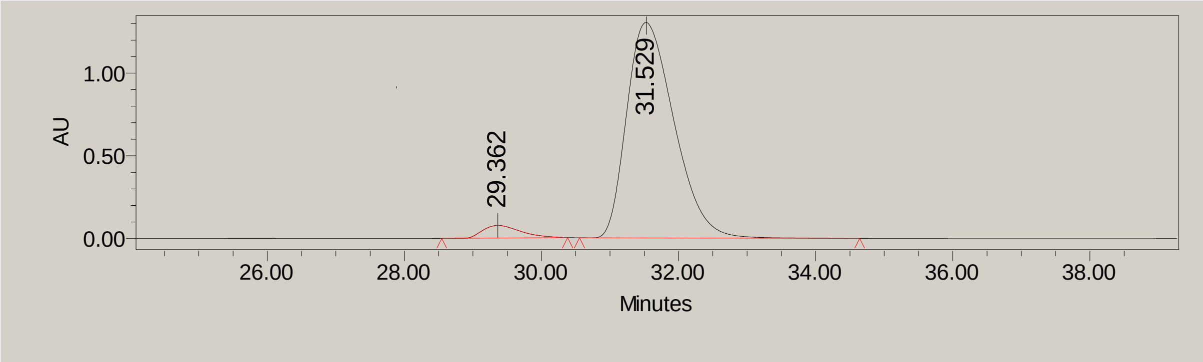
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min).

Rac-**45Ba**



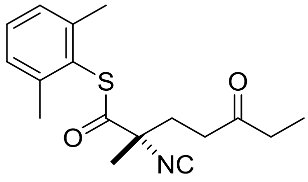
	Retention Time	% Area
1	29.892	49.07
2	32.167	50.93

Scalemic-**45Ba**



	Retention Time	% Area
1	29.362	4.42
2	31.529	95.58

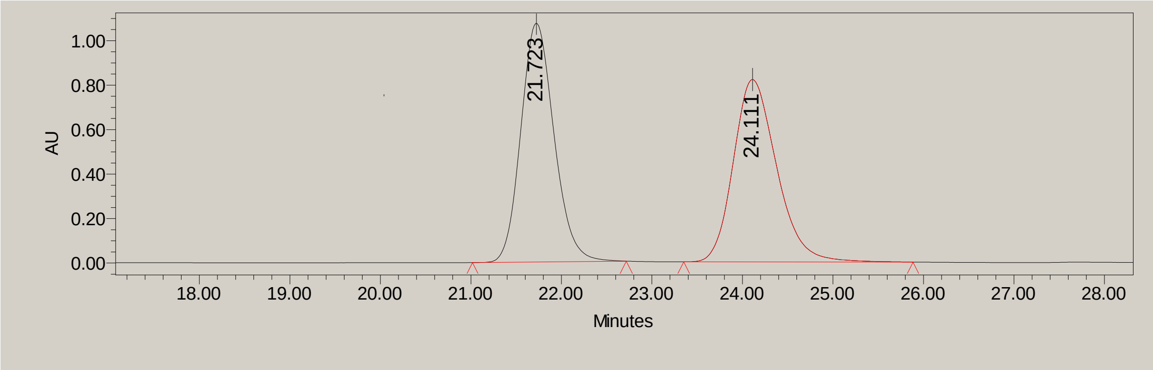
91% *ee*



45Bb

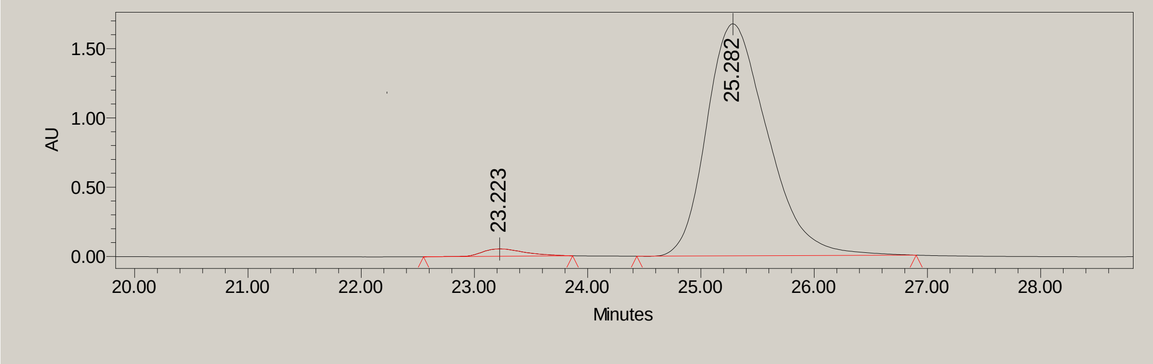
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 98:2; flux= 0.5 mL/min).

Rac-**45Bb**



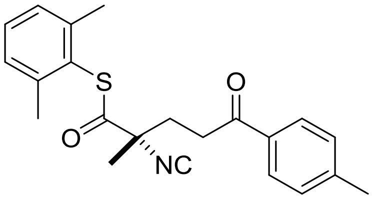
	Retention Time	% Area
1	21.723	50.11
2	24.111	49.89

Scalemic-**45Bb**



	Retention Time	% Area
1	23.223	2.13
2	25.282	97.87

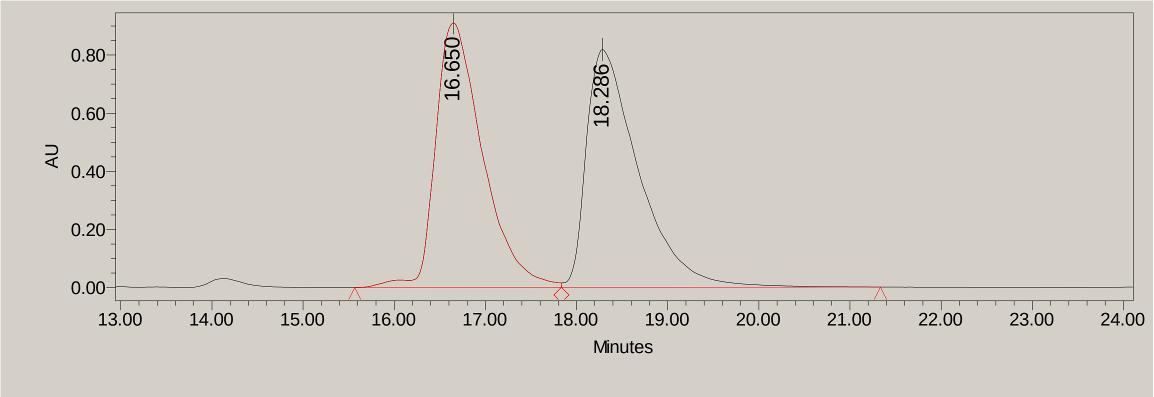
96% ee



45Bd

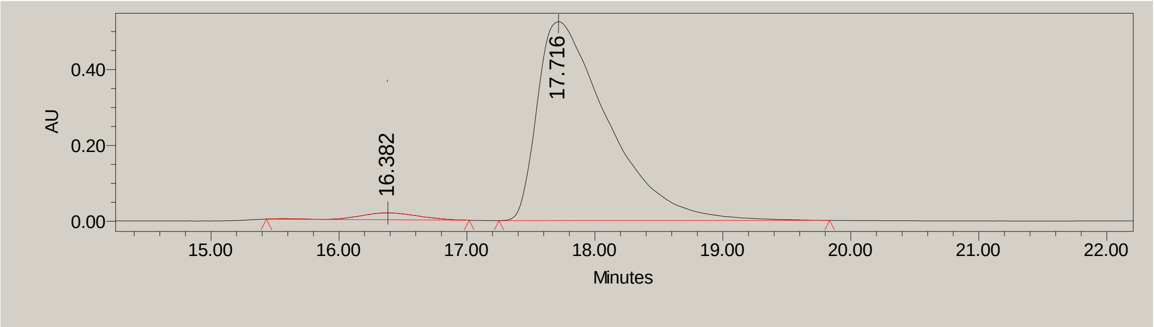
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**45Bd**



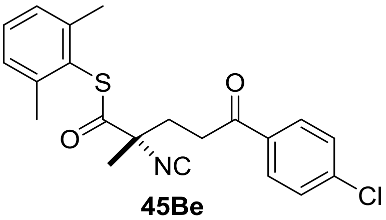
	Retention Time	% Area
1	16.650	50.04
2	18.286	49.96

Scalemic-**45Bd**



	Retention Time	% Area
1	16.382	2.82
2	17.716	97.18

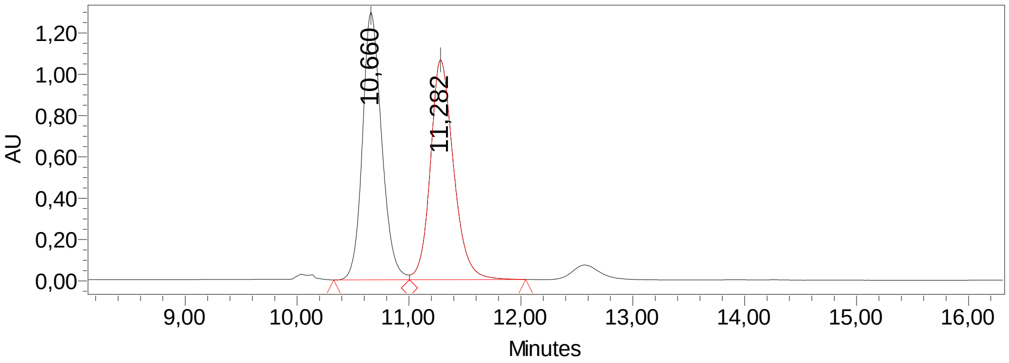
94% *ee*



45Be

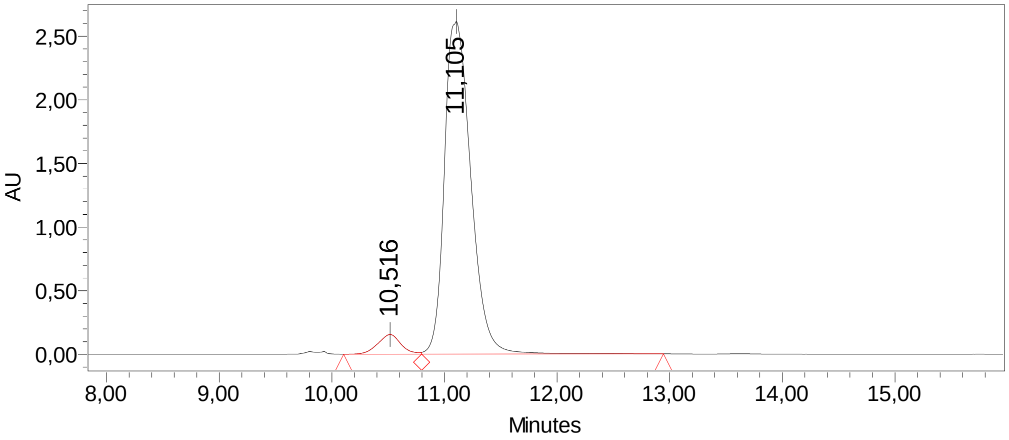
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane:ethanol, 99:1; flux= 1 mL/min; retention times).

Rac-**45Be**



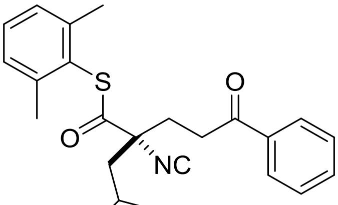
	Retention Time	% Area
1	10,660	50,40
2	11,282	49,60

Scalemic-**45Be**



	Retention Time	% Area
1	10,516	4,88
2	11,105	95,12

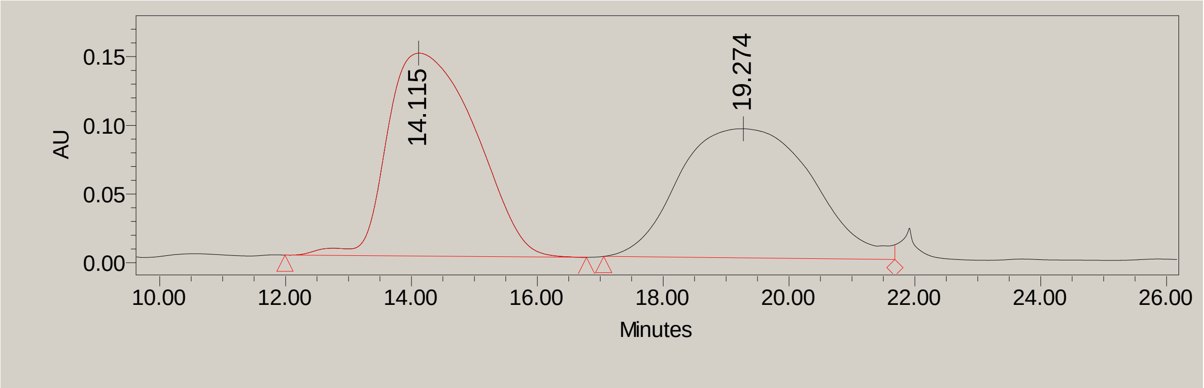
90% *ee*



45Cc

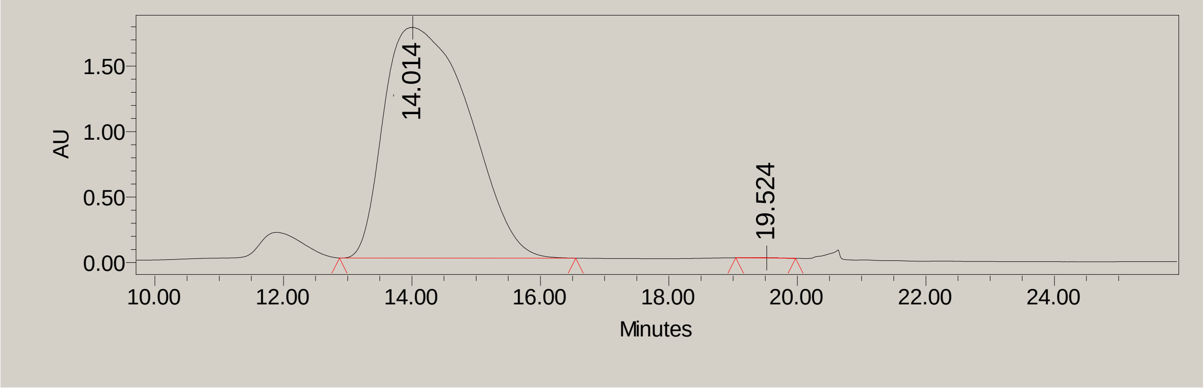
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IB, hexane:ethanol, 98:2; flux= 0.5 mL/min).

Rac-**45Cc**



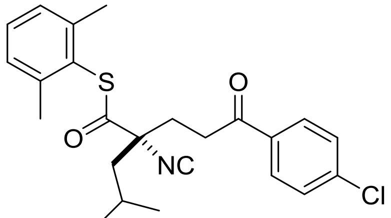
	Retention Time	% Area
1	14.115	51.03
2	19.274	48.97

Scalemic-**45Cc**



	Retention Time	% Area
1	14.014	99.95
2	19.524	0.05

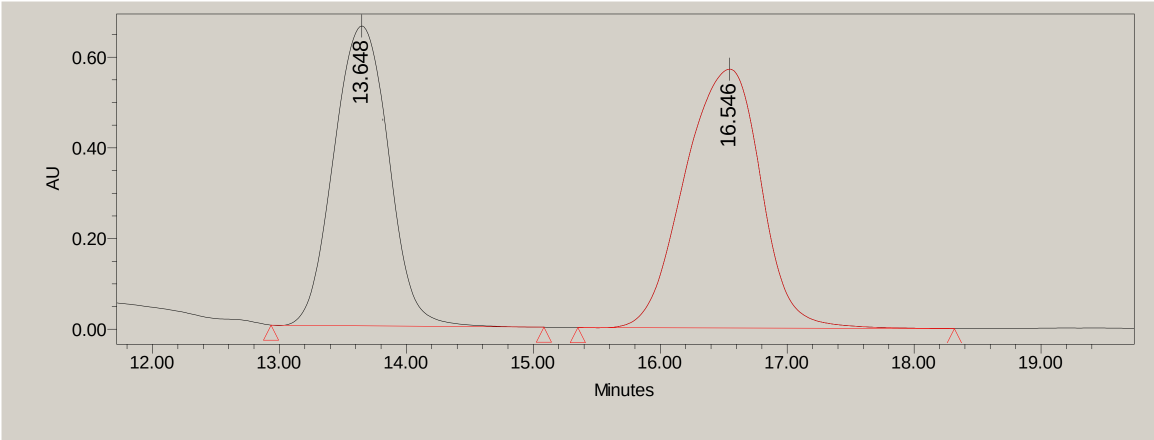
99% ee



45Ce

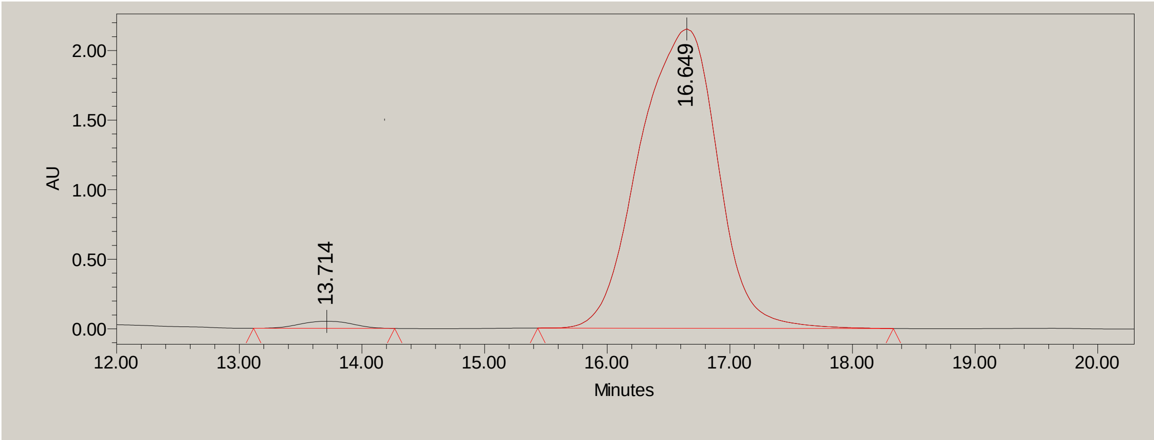
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane:ethanol, 98:2; flux= 0.5 mL/min).

Rac-**45Ce**



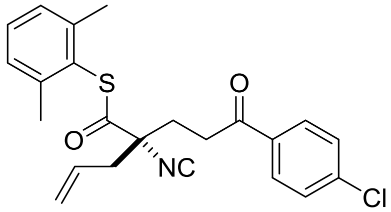
	Retention Time	% Area
1	13.648	48.46
2	16.546	51.54

Scalemic-**45Ce**



	Retention Time	% Area
1	13.714	1.59
2	16.649	98.41

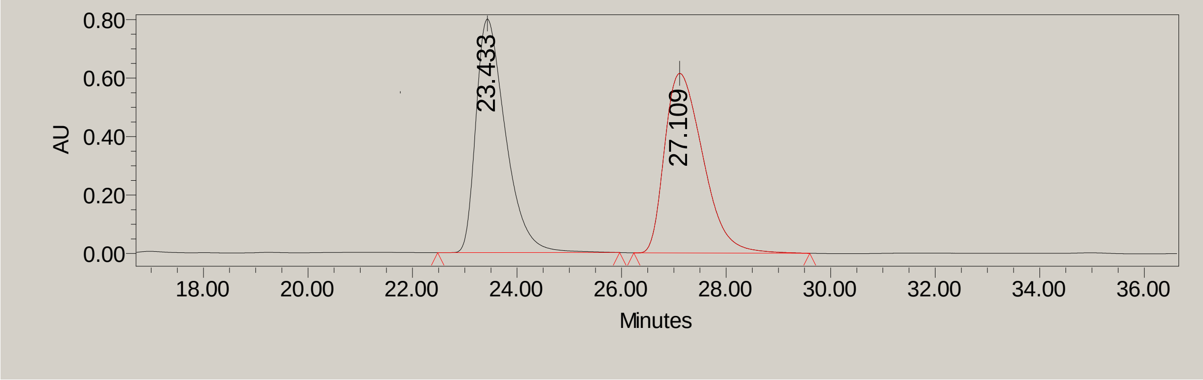
97% ee



45Ee

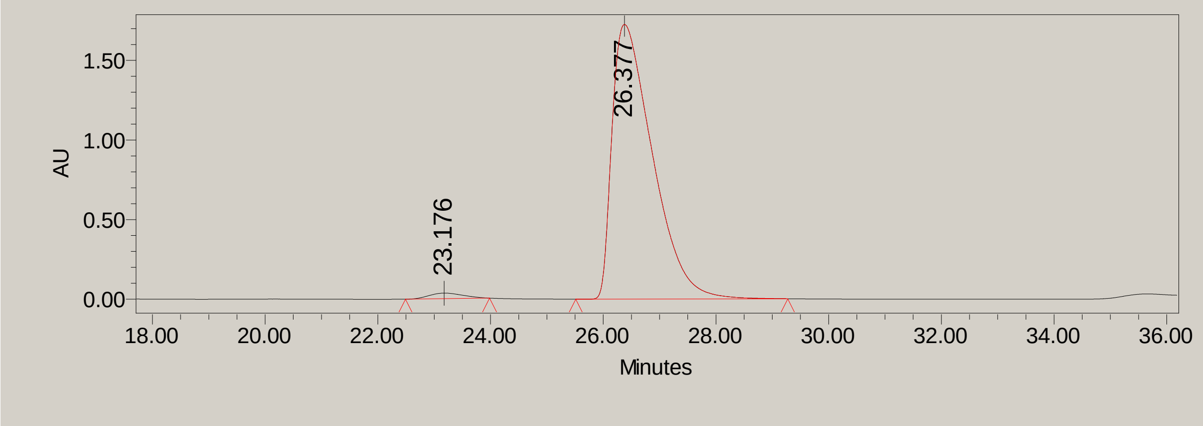
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 0.5 mL/min).

Rac-**45Ee**



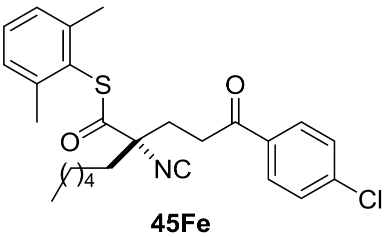
	Retention Time	% Area
1	23.433	50.17
2	27.109	49.83

Scalemic-**45Ee**



	Retention Time	% Area
1	23.176	1.68
2	26.377	98.32

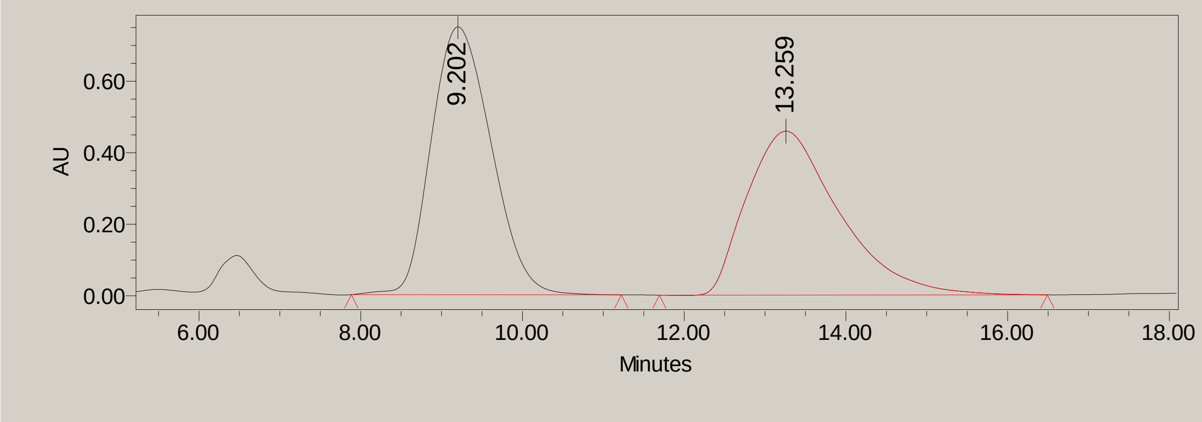
97% ee



45Fe

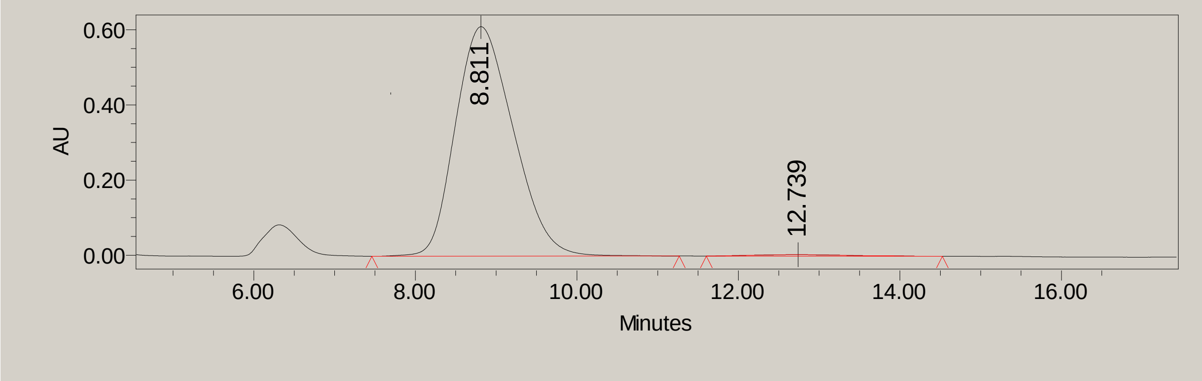
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ODH, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**45Fe**



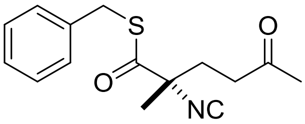
	Retention Time	% Area
1	9.202	51.55
2	13.259	48.45

Scalemic-**45Fe**



	Retention Time	% Area
1	8.811	98.98
2	12.739	1.02

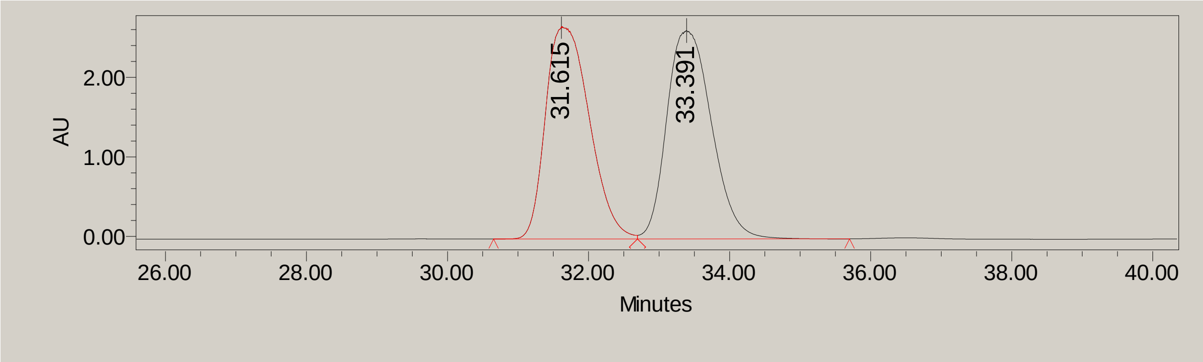
98% ee



46Ba

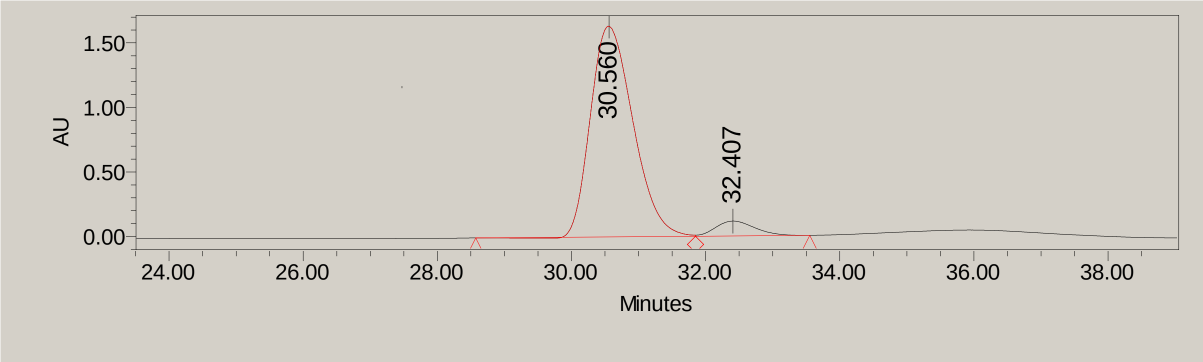
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min).

Rac-**346Ba**



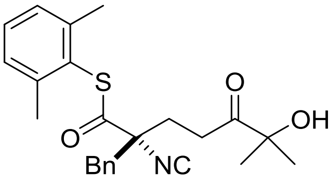
	Retention Time	% Area
1	31.615	49.93
2	33.391	50.07

Scalemic-**46Ba**



	Retention Time	% Area
1	30.560	93.95
2	32.407	6.05

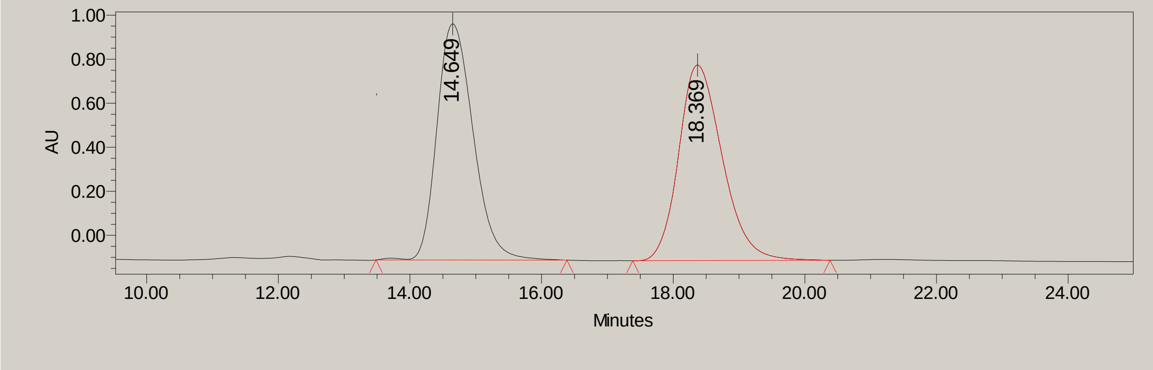
88% ee



49Aa

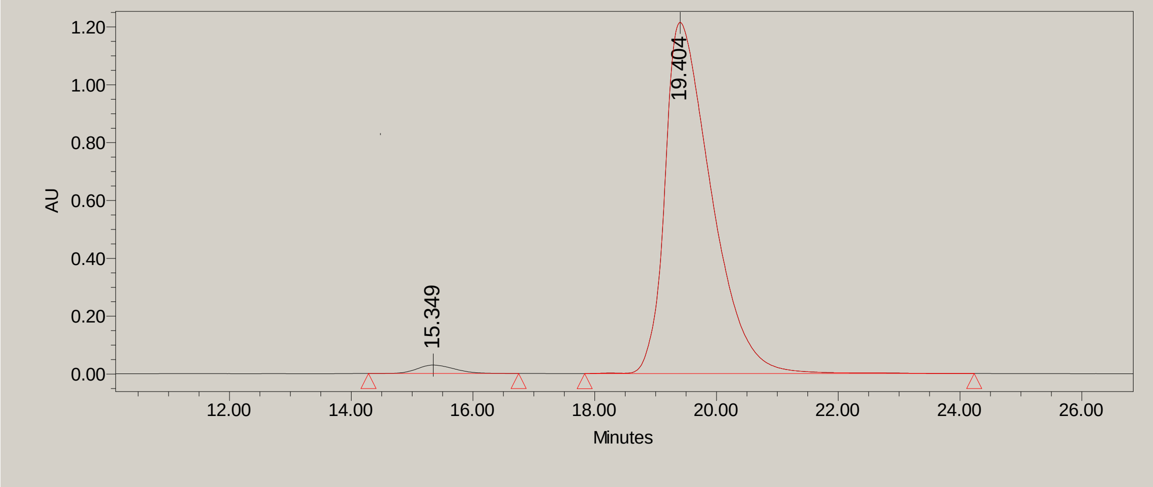
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 95:5; flux= 0.5 mL/min).

Rac-**49Aa**



	Retention Time	% Area
1	14.649	50.16
2	18.369	49.84

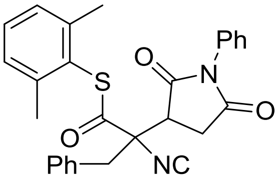
Scalemic-**49Aa**



	Retention Time	% Area
1	15.349	1.86
2	19.404	98.14

96% ee

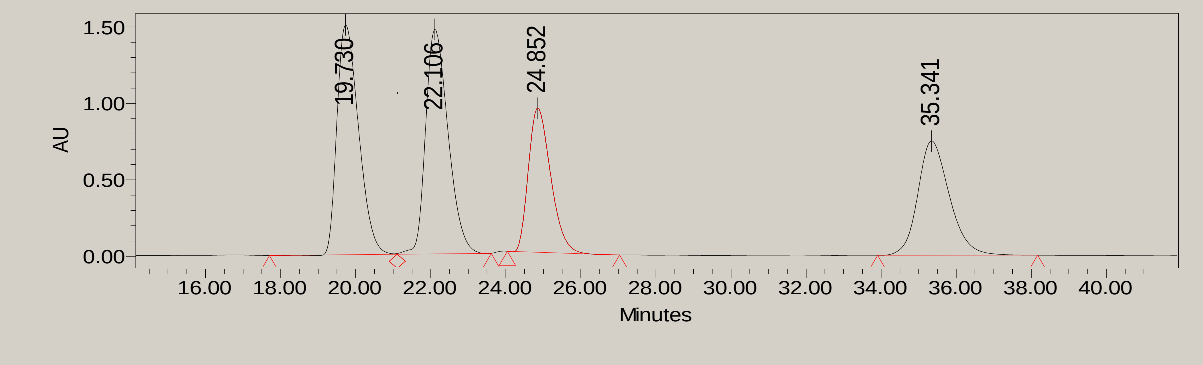
5.6.2.2. Adduct of the Michael addition to N-phenyl maleimide



75

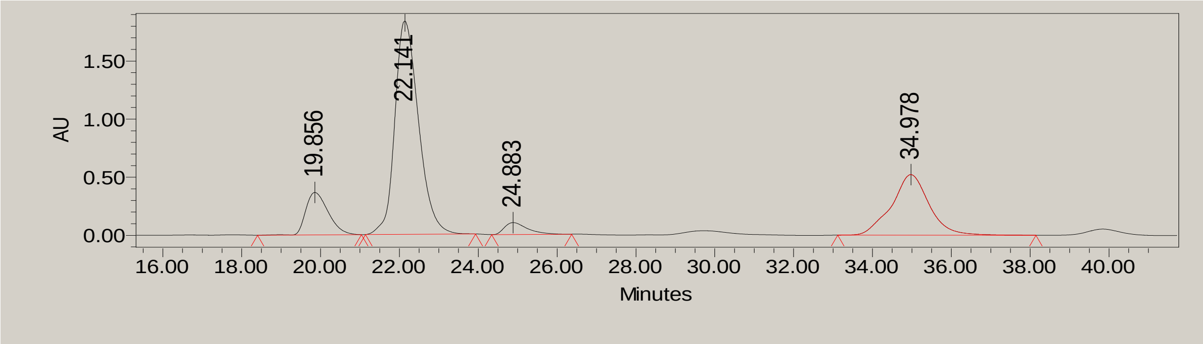
The diastereomeric and enantiomeric purity were determined on crude material by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 0.5 mL/min).

Rac-**XX**



	Retention Time	% Area
1	19.730	29.58
2	22.106	29.97
3	24.852	19.08
4	35.341	21.37

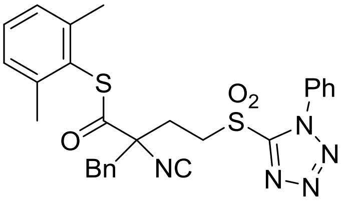
Scalemic-**XX**



	Retention Time	% Area
1	19.856	11.13
2	22.141	59.11
3	24.883	3.19
4	34.978	26.56

dr= 70:30, 68% *ee* (minor: 80% *ee*)

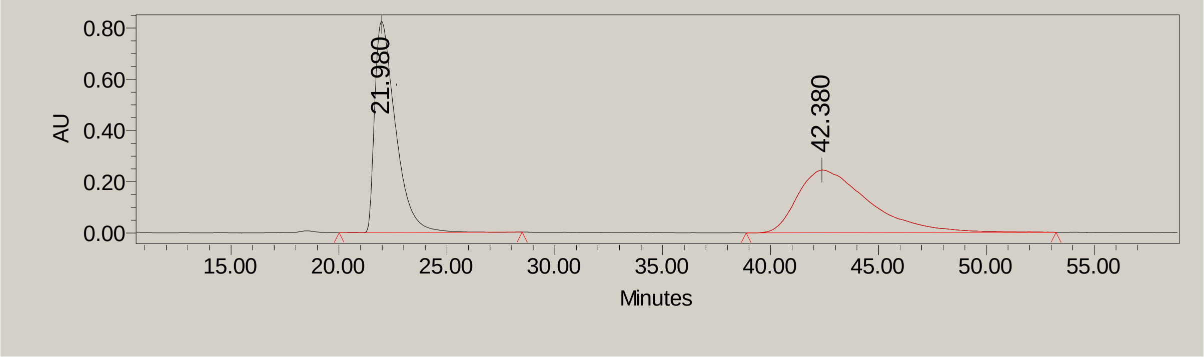
*5.6.2.3. Adducts of Michael addition to vinyl sulfone **55***



56

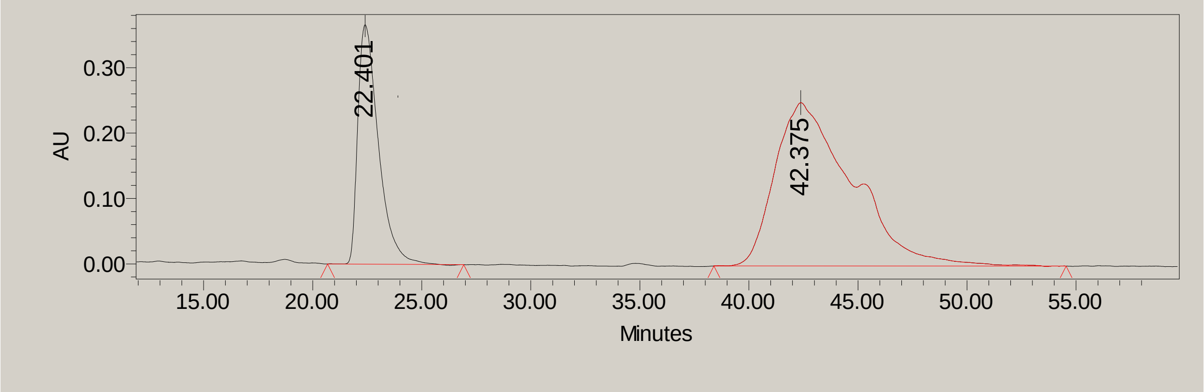
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**56**



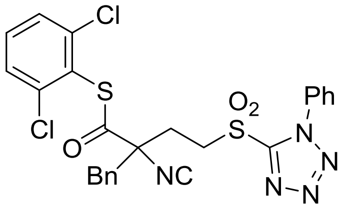
	Retention Time	% Area
1	21.980	49.53
2	42.380	50.47

Scalemic-**56**



	Retention Time	% Area
1	22.401	28.15
2	42.375	71.85

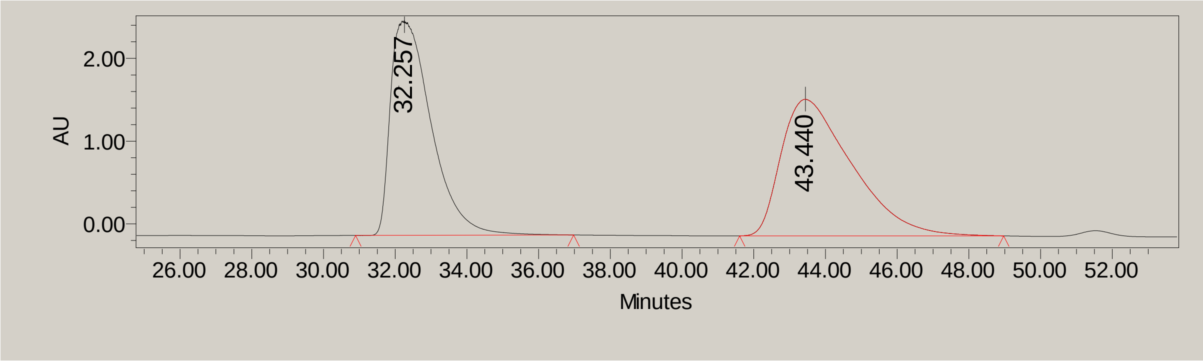
44% *ee*



57

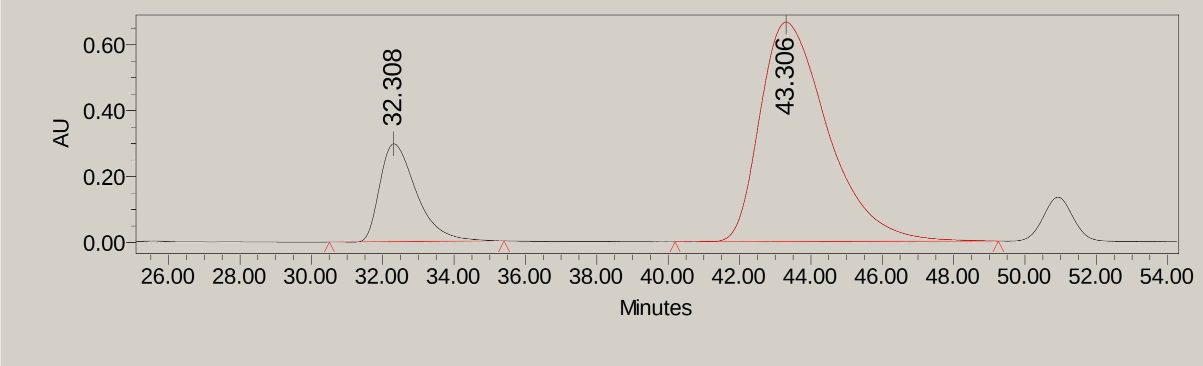
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 80:20; flux= 0.5 mL/min).

Rac-**57**



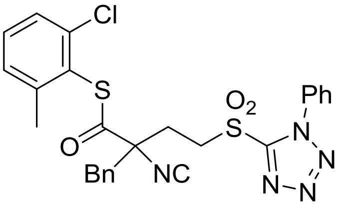
	Retention Time	% Area
1	32.257	47.61
2	43.440	52.39

Scalemic-**57**



	Retention Time	% Area
1	32.308	19.46
2	43.306	80.54

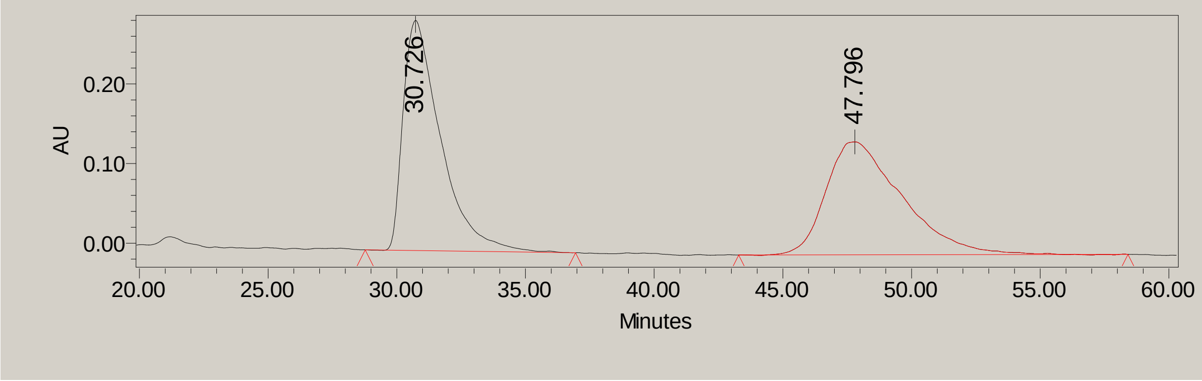
62% *ee*



58

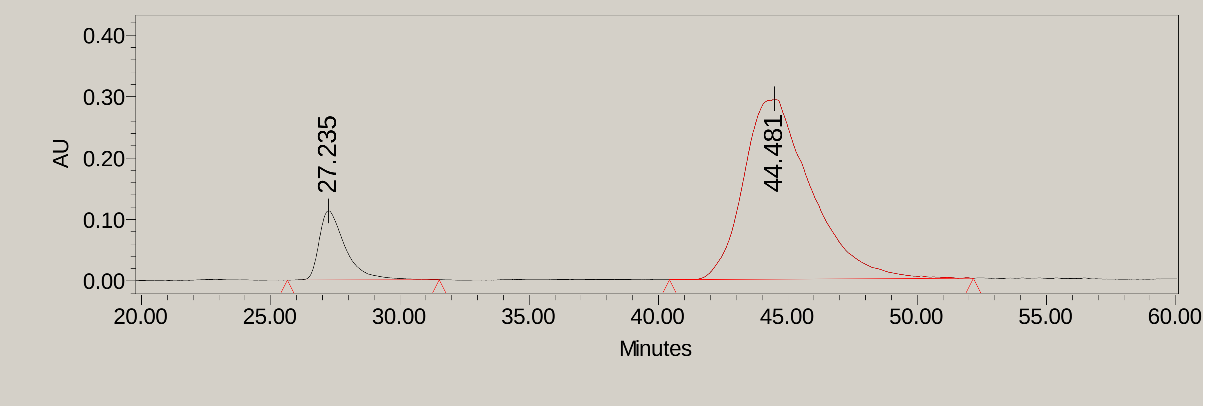
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**58**



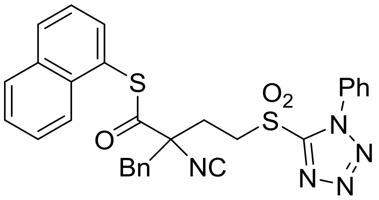
	Retention Time	% Area
1	30.726	50.20
2	47.796	49.80

Scalemic-**58**



	Retention Time	% Area
1	27.235	12.99
2	44.481	87.01

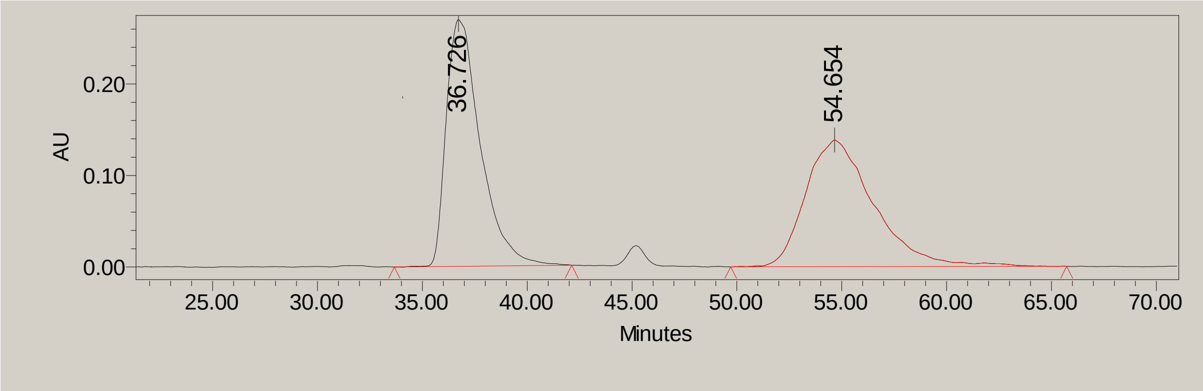
74% ee



59

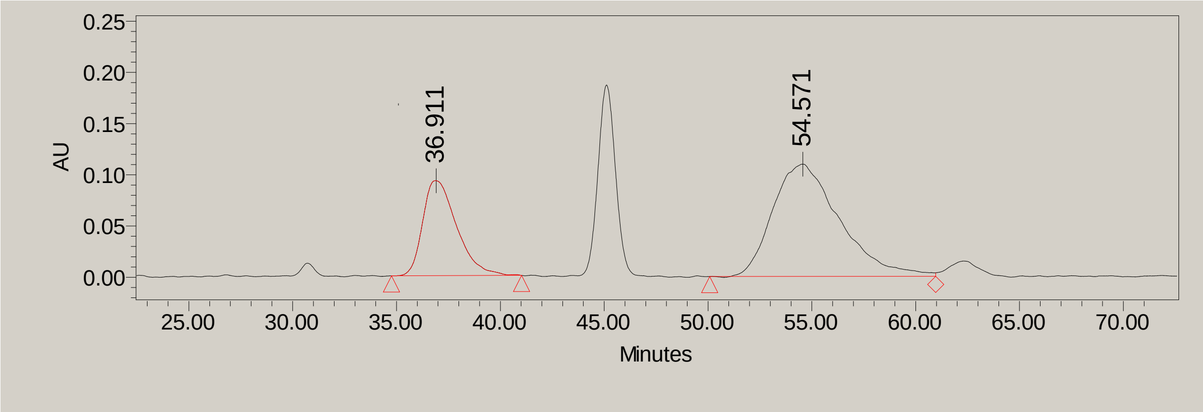
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**59**



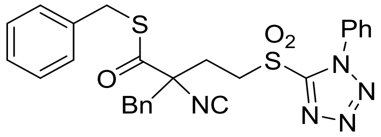
	Retention Time	% Area
1	36.726	49.42
2	54.654	50.58

Scalemic-**59**



	Retention Time	% Area
1	36.911	29.99
2	54.571	70.01

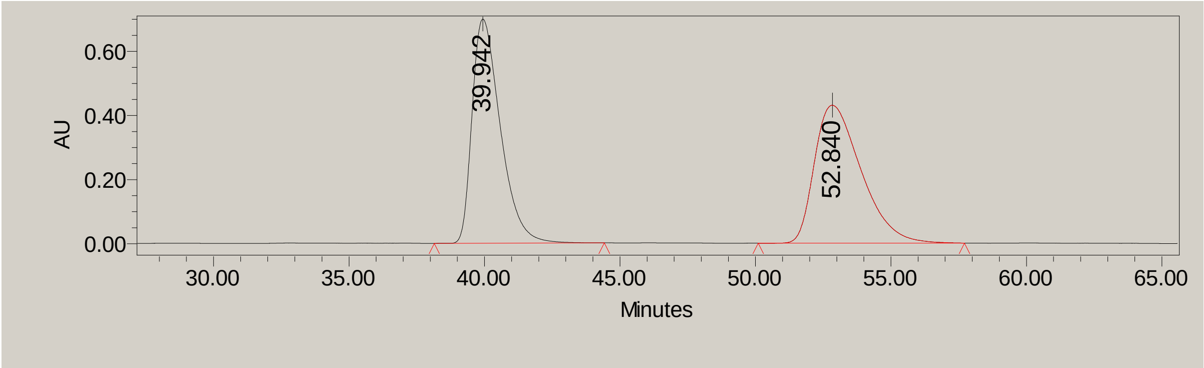
40% *ee*



60

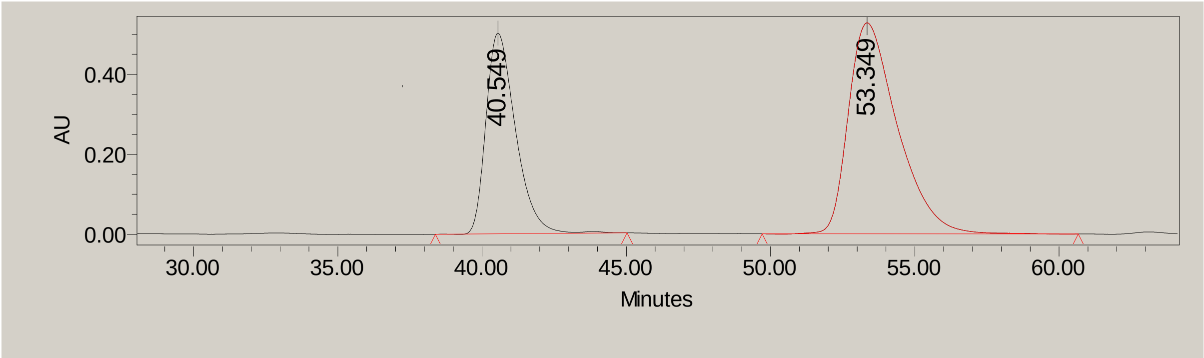
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AYH, hexane:ethanol, 80:20; flux= 0.5 mL/min).

Rac-**60**



	Retention Time	% Area
1	39.942	49.66
2	52.840	50.34

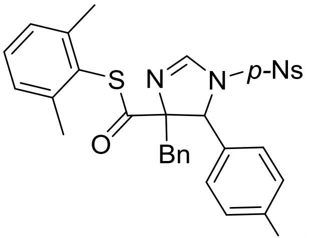
Scalemic-**60**



	Retention Time	% Area
1	40.549	36.46
2	53.349	63.54

28% ee

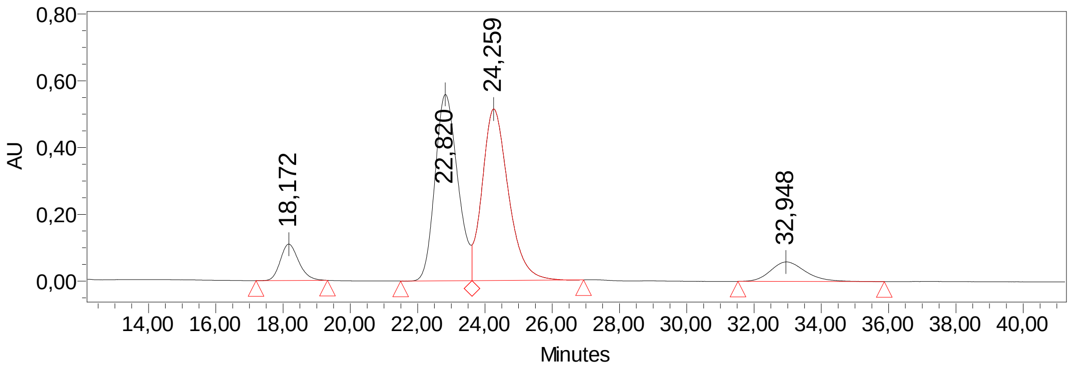
*5.6.2.4. Adducts of Mannich reaction with N-nosyl aldimine **64***



65

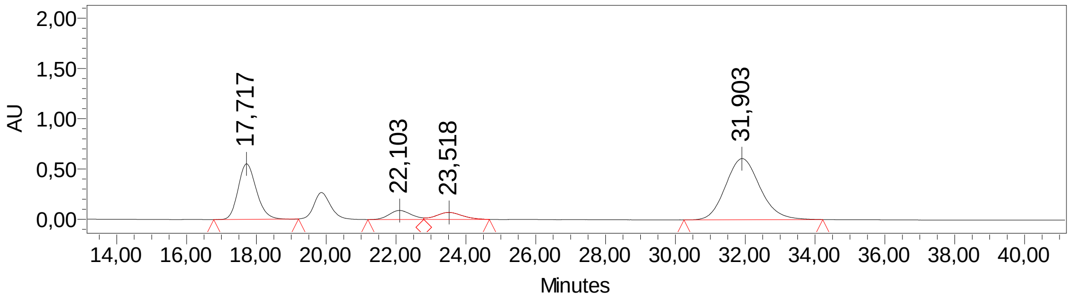
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**65**



Retention Time	% Area
18,172	6,64
22,820	42,09
24,259	44,55
32,948	6,72

Scalemic-**65**

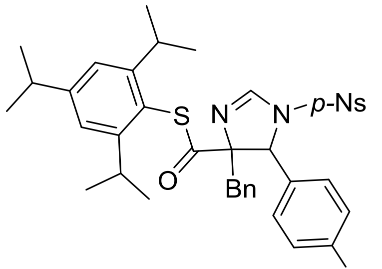


MAJOR DIASTEREOISOMER

Retention Time	% Area
17,717	28,87
22,103	5,68
23,518	5,22
31,903	60,22

Retention Time	% Area
17,717	32,41
31,903	67,59

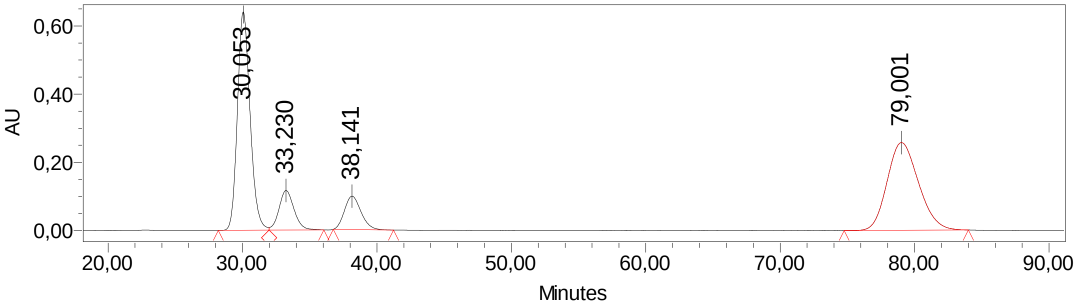
dr 90:10 36% *ee*



66

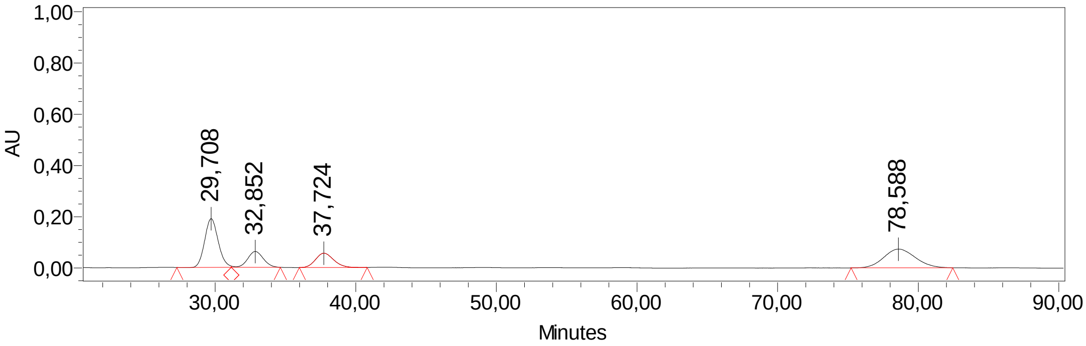
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 98:2; flux= 1 mL/min).

Rac-**66**



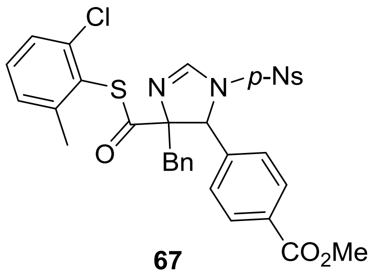
Retention Time	% Area
30,053	41,51
33,230	8,92
38,141	8,30
79,001	41,27

Scalemic-**66**



Retention Time	% Area
29,708	37,50
32,852	14,22
37,724	14,73
78,588	33,55

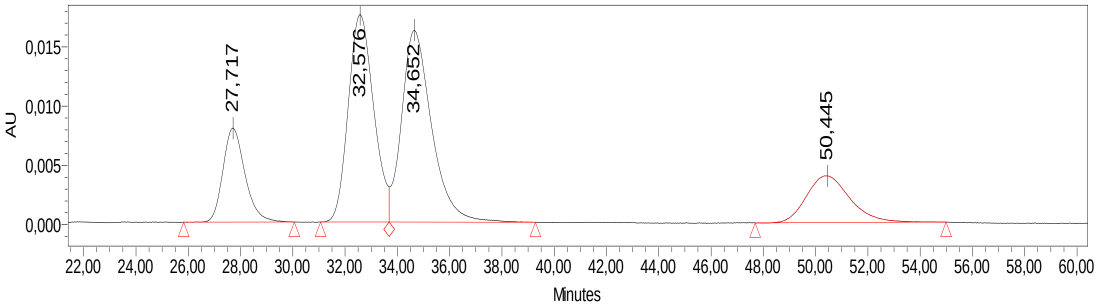
dr 70:30   10% *ee*



67

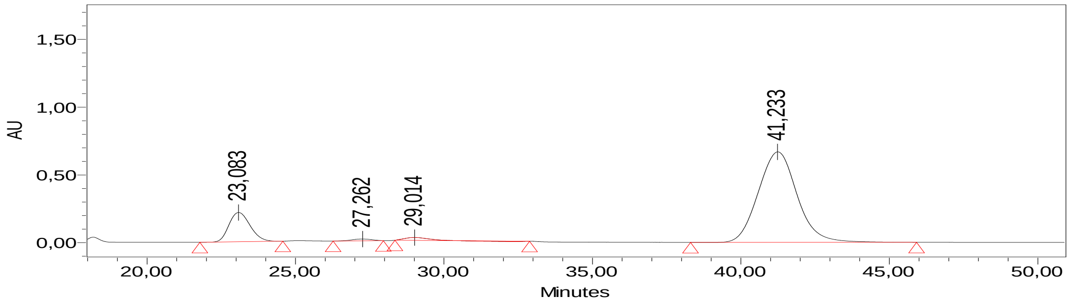
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**67**



Retention Time	% Area
27,717	13,71
32,576	34,80
34,652	38,05
50,445	13,44

Scalemic-**67**



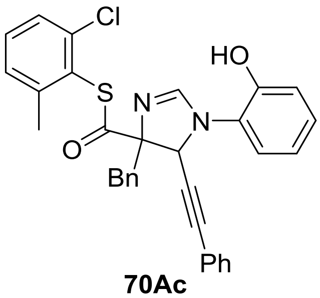
MAJOR DIASTEREOISOMER

Retention Time	% Area
23,083	12,92
27,262	1,03
29,014	2,19
41,233	83,89

Retention Time	% Area
23,083	13,10
41,233	86,90

dr 97:3 **74% *ee***

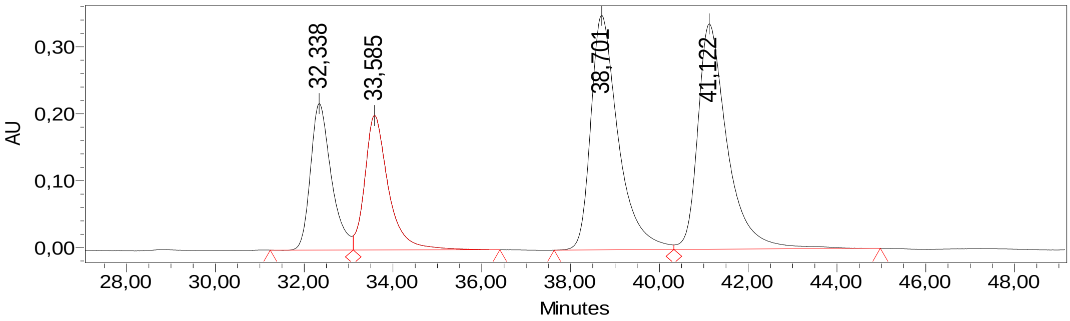
5.6.2.5. *Adducts of Mannich reaction with N-aryl aldimines*



70Ac

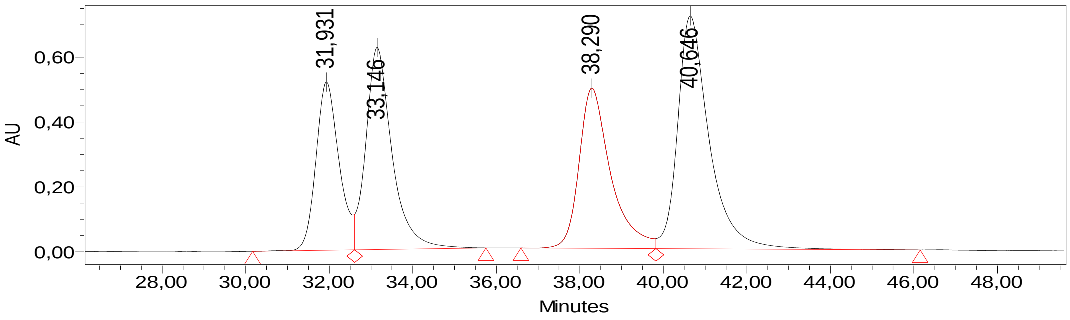
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min).

Rac-**70Ac**



	Retention Time	% Area
1	32,338	15,83
2	33,585	16,38
3	38,701	33,40
4	41,122	34,38

Scalemic-**70Ac**



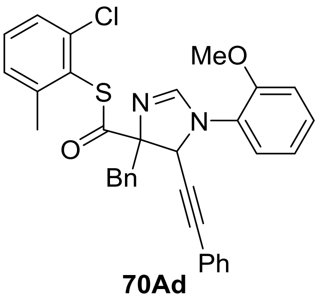
Retention Time	% Area
31,931	17,41
33,146	23,77
38,290	23,93
40,646	34,88

Retention Time	% Area
31,931	41,23
33,146	58,77

20% *ee* minor diast.

Retention Time	% Area
38,290	40,69
40,646	59,31

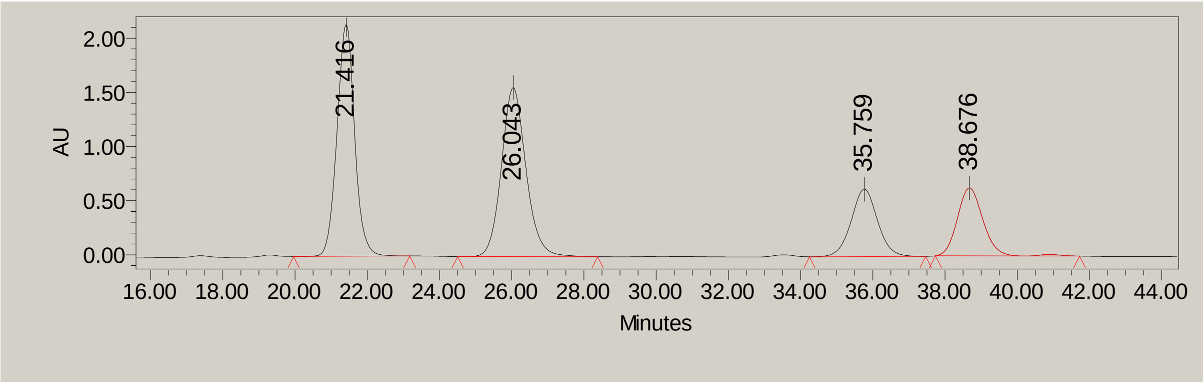
20% *ee* major diast.



70Ad

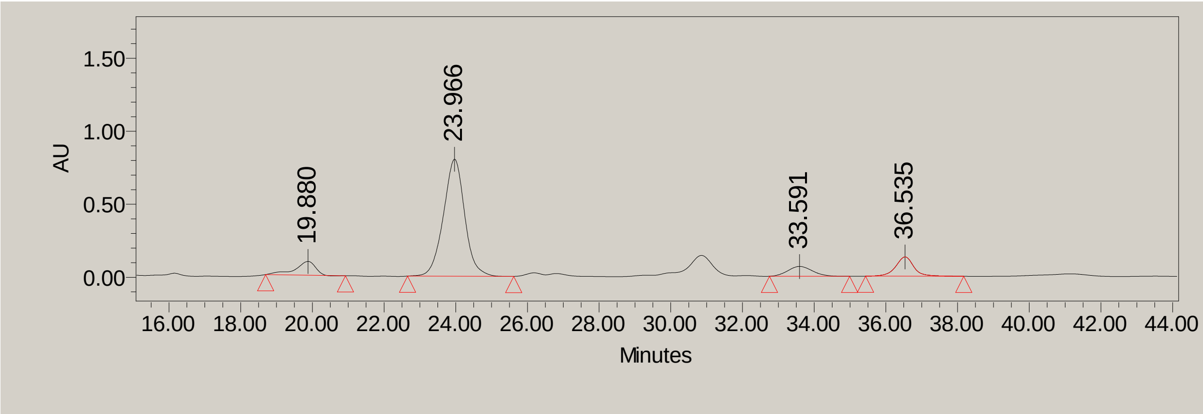
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 95:5; flux= 0.5 mL/min).

Rac-**70Ad**



Retention Time	% Area
21.416	34.81
26.043	35.22
35.759	15.12
38.676	14.85

Scalemic-**70Ad**

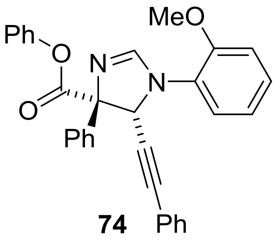


Retention Time	% Area
19.880	8.48
23.966	73.92
33.591	7.16
36.535	10.44

Major diastereomer

Retention Time	% Area
19.880	10.29
23.966	89.71

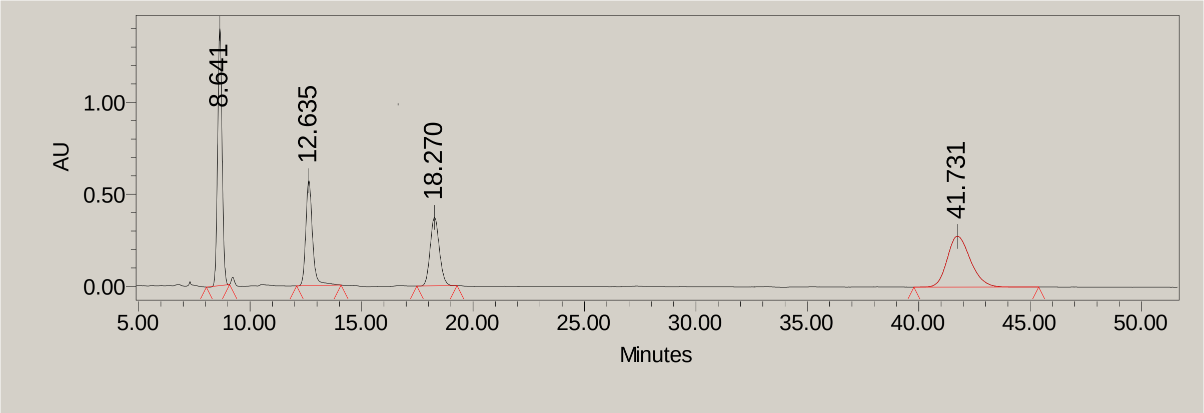
dr 82:18 80% *ee*



74

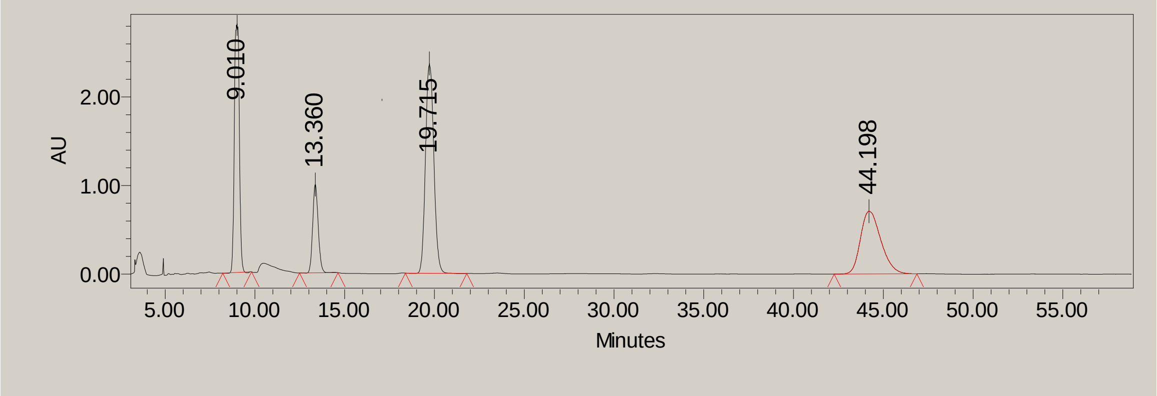
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min).

Rac-**74**



Retention Time	% Area
8.641	31.68
12.635	18.61
18.270	17.29
41.731	32.42

Scalemic-**70Ad** (purified)



Retention Time	% Area
9.010	26.25
13.360	10.19 major in the crude
19.715	36.70 major in the crude
44.198	26.86

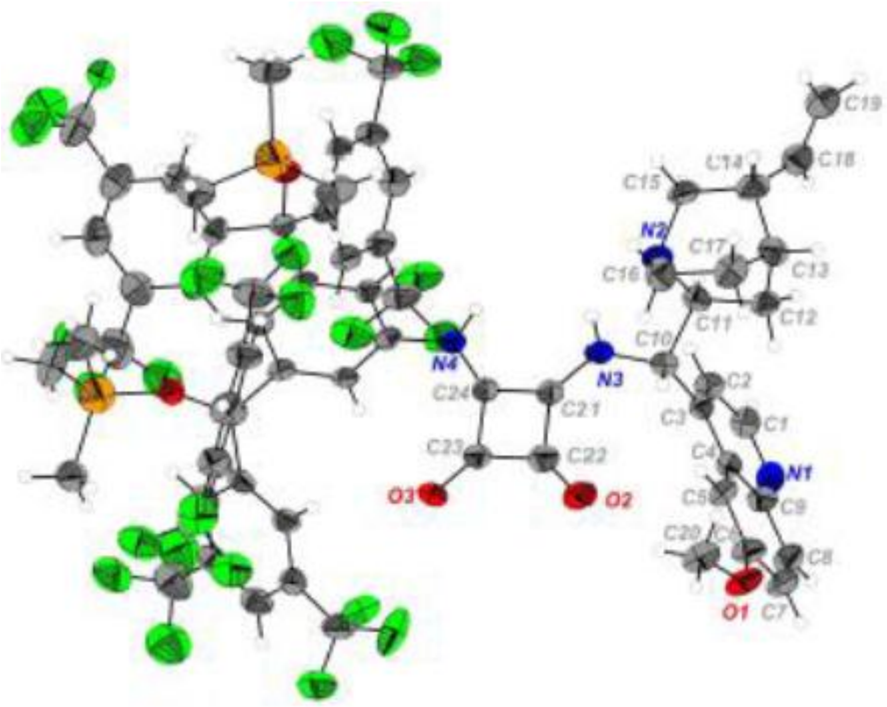
Retention Time	% Area
13.360	21.82
19.715	78.18

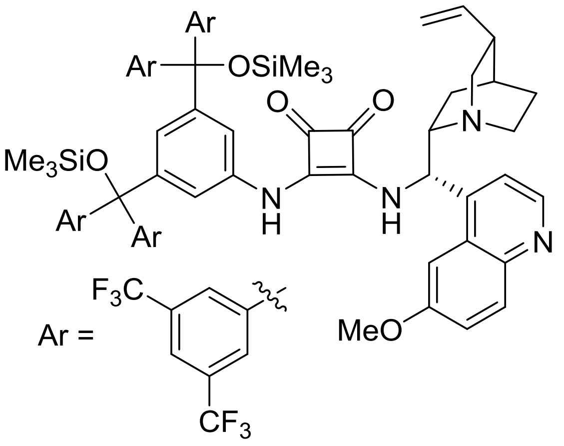
56% *ee*

5.7. X-Ray analysis

5.7.1. ORTEP diagram of catalyst C26

CCDC-1555683 contains the supplementary crystallographic data for the structural analysis of **C26**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

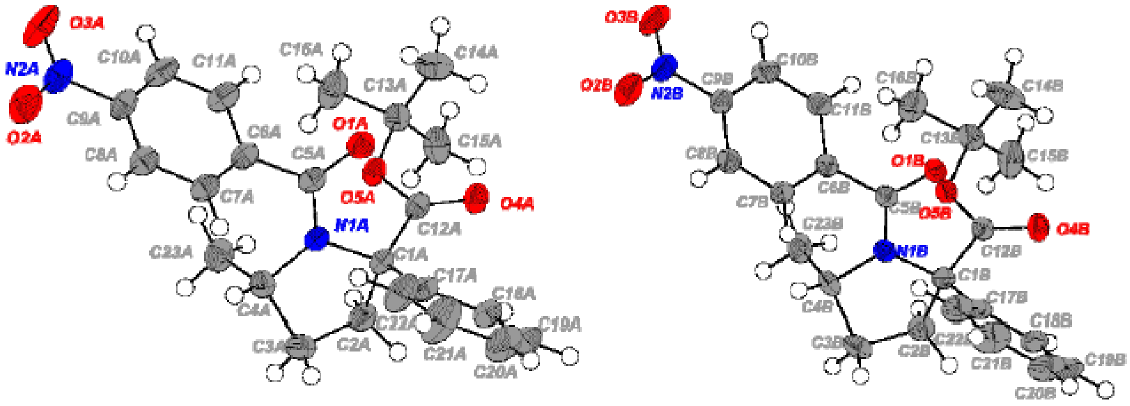




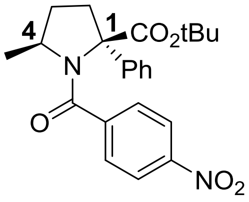
C26

5.7.2. ORTEP diagram of compound 16

CCDC-1555684 contains the supplementary crystallographic data for the structural analysis of **16**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



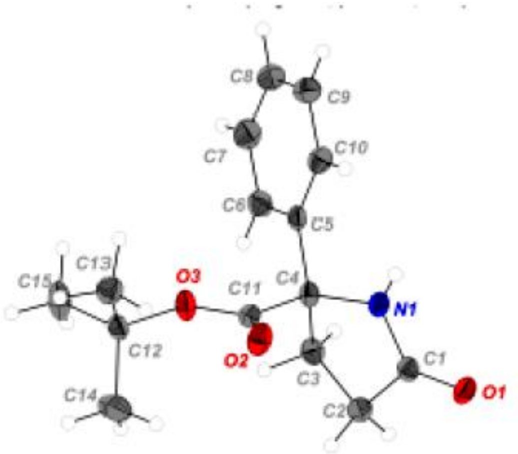
Molecule A Molecule B

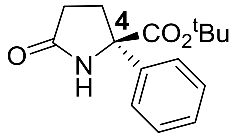


16

5.7.3. ORTEP diagram of compound 26

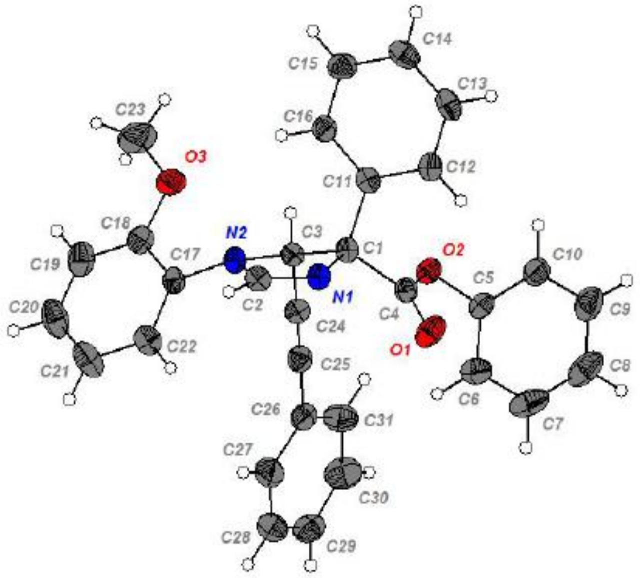
CCDC-1555682 contains the supplementary crystallographic data for the structural analysis of **26**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

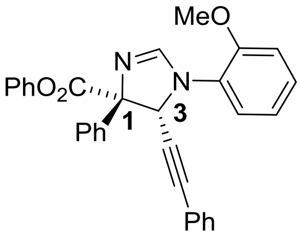




26

5.7.4. ORTEP diagram of compound 74





73

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Communication

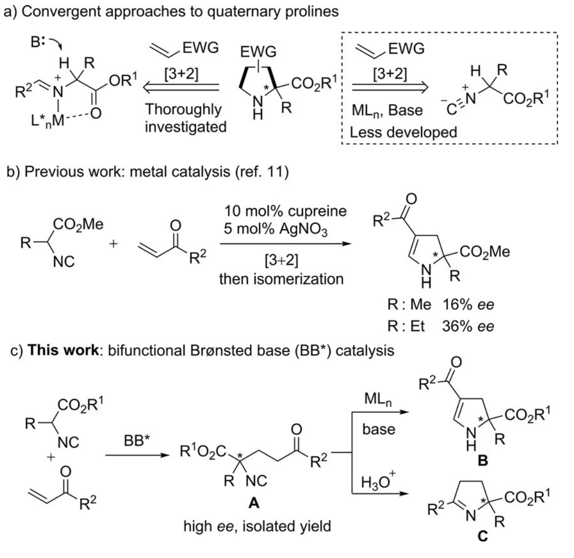
▌Cycloaddition

Enantioselective Synthesis of Quaternary Δ^4- and Δ^5-Dehydroprolines Based on a Two-Step Formal [3+2] Cycloaddition of α-Aryl and α-Alkyl Isocyano(thio)acetates with Vinyl Ketones

Amaiur Odriozola, Mikel Oiarbide, and Claudio Palomo*[a]

Abstract: A divergent synthesis of optically active quaternary Δ^4- and Δ^5-dehydro prolines is developed based on the first catalytic enantioselective conjugate addition of α-substituted isocyano(thio)acetates to vinyl ketones that is general for both α-aryl and α-alkyl isocyano(thio)acetates. The new tetrasubstituted C–N stereocenter is formed without the need of any metal salt due to a bifunctional tertiary amine/squaramide catalyst, featuring a bulky polyaryl sidearm and an unusually short squaramide diamide H···H interatomic distance in the solid state.

The α-carboxy-pyrrolidine units, generically referred to as prolines, are widespread within natural products and biologically active substances, and have attracted considerable interest in peptide chemistry.[1] In this context, α-substituted (quaternary) prolines constitute a particularly relevant subclass owing to their unique structural biases, and much attention has been paid to their stereoselective synthesis.[2] One major thoroughly investigated convergent approach to the enantioselective synthesis of these heterocyclic systems relies on the catalytic [3+2] cycloaddition reaction between azomethine ylides and electron-deficient olefins (Scheme 1 a, left).[3] In contrast, the catalyst-controlled formal [3+2] cycloaddition involving α-isocyanoacetates and olefins (Scheme 1 a, right), which also affords the pyrrolidine system through concomitant formation of the N–C_2 and C_4–C_5 bonds, has been much less developed.[4] Most studies on catalytic enantioselective cycloadditions of α-isocyanoacetates involve very reactive olefins, such as maleimides,[5] nitroalkenes,[6] β,γ-unsaturated α-keto esters,[7] methyleneindolinones[8] and allenoates,[9] and require, with a few exceptions,[6,8] combined metal/Brønsted base catalysis. Generalization of this type of cooperative catalysis is often hampered by the problem of Lewis acid/amine base self-quenching, which leads to catalyst deactivation and unfavorable reaction stereocontrol, especially during formation of quaternary stereocenters.[10] In this context, a sole example of cycloaddition involving simple vinyl ketones as the reaction partner has been reported so far, affording the corresponding dehydroproline adducts with moderate (52–74 % *ee*, R = H) or poor (≤ 36 % *ee*, R = Me, Et) enantioselectivity.[11]



Scheme 1. Convergent approaches to enantioenriched quaternary proline derivatives. EWG = electron-withdrawing group.

We were intrigued by the possibility of triggering the α-isocyanoacetate–olefin addition reaction through an alternative organocatalytic activation mode, whereby the bifunctional catalyst would activate both the donor and acceptor reaction components in a manner similar to that assumed for the metal-mediated process (model **II** vs. **I**, Figure 1). Eventually, the absence of a metal catalyst might also slow down the subsequent intramolecular cyclization step[12] (**III**) thus allowing α-protonation to occur preferentially (**IV**) leading to adduct **A**. Upon these assumptions, a divergent access to 4,5- and 1,5-de-

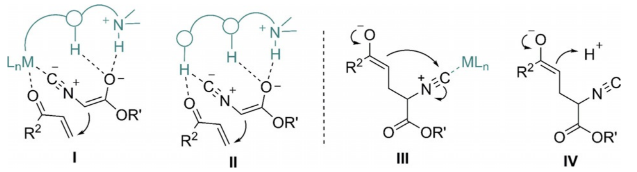


Figure 1. Idealized dual activation modes (left) and reaction pathways (right) in the presence or absence of a metal.

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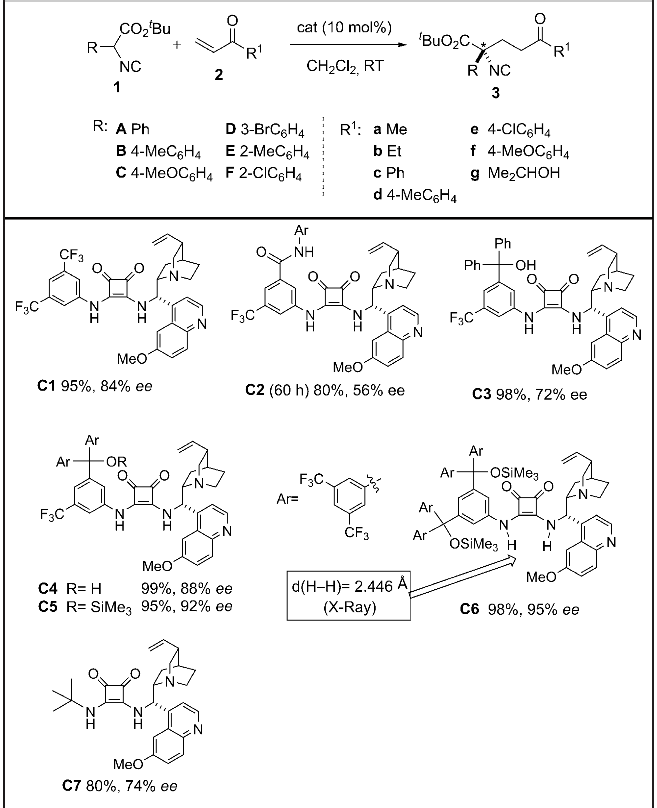
hydroprolines **B** and **C** from the common intermediate **A** would be conceivable (Scheme 1 c), resulting in a substantial enlargement of product scope. The challenge here is to perform the 1,4-addition reaction leading to **A** efficiently and with good enantiocontrol.[13] Indeed, the relatively low carbon acidity of most α-substituted isocyanoacetates means that catalytic conjugate additions have only been carried out using highly reactive acceptors,[14] and to the best of our knowledge conjugate addition to simple vinyl ketones has been undocumented so far. Another serious limitation in scope concerns the isocyanoacetate component; essentially all asymmetric organocatalytic reactions hitherto reported have dealt with α-aryl substituted isocyanoacetates.[15] Aside from these issues, another significant challenge concerns the control of stereochemistry during the generation of the quaternary carbon center.[16] Herein we report the first enantioselective conjugate addition of both α-aryl and α-alkyl isocyano(thio)acetates to vinyl ketones enabled by bifunctional Brønsted base catalysts, ultimately resulting in a new approach to enantioenriched quaternary dehydroproline products of type **B** and **C**.

Table 1. Reaction of α-cyanoacetates **1** with enones **2** and catalyst screening for the reaction of **1A** with **2a** to give **3Aa**.[a]

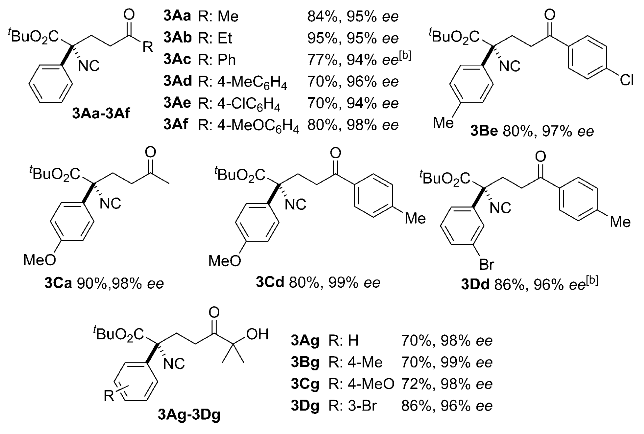


[a] Reactions conducted on a 0.1 mmol scale in 0.2 mL CH$_2$Cl$_2$ (molar ratio of **1A**/**2a**/catalyst 1:2:0.1). Data refer to reaction conversion at 14 h unless otherwise specified. *ee* determined by chiral HPLC.

The investigation was initiated by studying the reaction of α-phenyl *tert*-butyl isocyanoacetate **1A** with methyl vinyl ketone **2a** in the presence (10 mol%) of a selection of benchmark bifunctional Brønsted base organocatalysts.[17] From this initial screening,[18] the known catalyst **C1**[19] proved to be superior in terms of reaction conversion and enantioselectivity. As shown in Table 1, attempts to improve the result using catalysts **C2**, which has proven to be effective in difficult to control stereoselective reactions,[20] were unfruitful giving adduct **3Aa** in good yield but poor *ee* (56%). We then decided to explore the more sterically demanding *gem*-diaryl catalysts **C3**, **C4** and **C5**, and the *gem*,*gem*-(bis)diaryl congener **C6**, which could be easily prepared through modification of the *meta* mono- and diester group(s) of the aniline fragment through a Grignard reaction.[18] We presumed that the bulky polyaryl moiety near the squaramide framework might prevent catalyst self-aggregation, a phenomenon that affects hydrogen-bond-accepting substrate recognition.[21] Gratifyingly, each catalyst produced a clean reaction with essentially complete conversion, whereas the highest selectivities were obtained with the bulkiest catalysts **C5** and **C6** (92% and 95% *ee*, respectively). In this respect, the X-ray structure analysis data of crystallized **C6** are worthy of mention. The interatomic diamide H···H distance in **C6** is unusually short (2.446 Å) as compared with the typical values previously reported for related squaramide catalysts ($\approx$2.85 Å),[19c,21] and get closer to that found for the parent thiosquaramides.[22] On the other hand, squaramide units in the solid structure of **C6** do not self-aggregate through dual hydrogen-bonding as is generally assumed. Instead, both N–H bonds of each squaramide unit point toward the quinoline nitrogen of a contiguous molecule.[18] It is likely that these features, probably induced by the bulky polyaryl sidearm in **C6** would also prevail in solution, and impact the catalytic behavior. For comparison, catalyst **C7**[23] was also tested, resulting in lower reactivity and efficiency (14 h, 80% conversion, 74% *ee*) probably due to its lower solubility. Further experiments involving **1A** and catalyst **C6** showed that the stereochemical outcome of the reaction appears to be independent of the enone partner. As the data in Table 2 show, both alkyl- and aryl-vinyl ketones **2a–f** upon reaction with **1A** provided adducts **3Aa–f** with good isolated yields and *ee* up to 98%. The reaction also worked quite well with respect the isocyanoacetate component. Thus, each **1B**, **1C** and **1D** reacted with the corresponding vinyl enone **2** to give products **3Be**, **3Ca**, **3Cd**, and **3Dd** with yields within the 80–90% range and *ee* values greater than 96%. Nonetheless, *o*-substituted aryl isocyanoacetates **1E**/**1F** as well as α-alkyl isocyanoacetates were not competent reaction partners. On the other hand, methyl acrylate, a less-reactive Michael acceptor compared to vinyl ketones, was not effective in this reaction regardless of the catalyst employed. However, reactions of α-hydroxy enone **2g**, an acrylate surrogate recently reported within our group,[24] proceeded smoothly in a reaction with **1A–D** to give the corresponding adducts **3Ag**, **3Bg**, **3Cg**, and **3Dg** in good yields and excellent enantioselectivity. For these reactions a 5 mol% catalyst loading was systematically employed, although both selectivity and yield remained essentially the same using 2 mol% catalyst only (products **3Ac** and **3Dd**).

Next, the inability of α-alkyl isocyanoacetates to react under the above conditions was addressed by using the corresponding thioesters instead, and assuming that thioesters are gener-

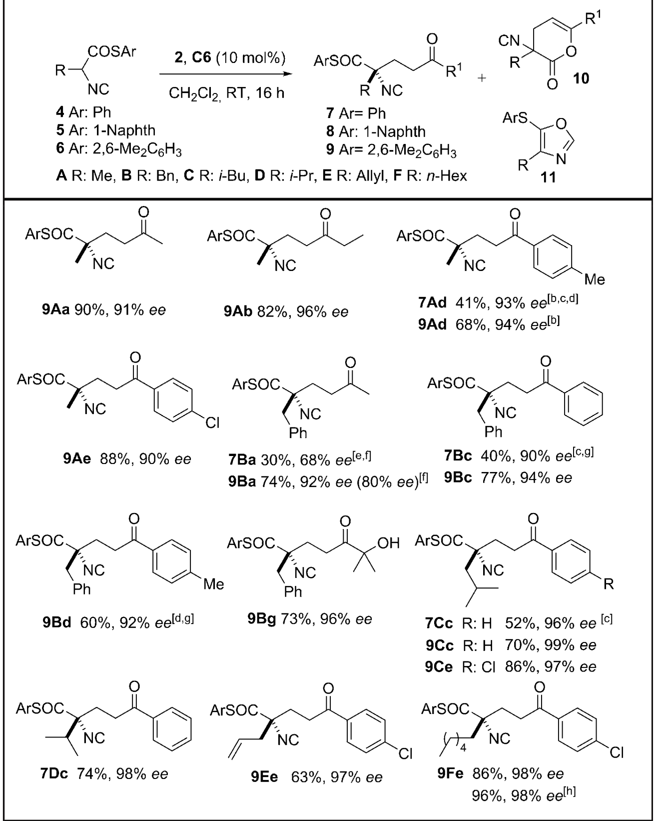
Table 2. Scope of the conjugate addition of **1** to vinyl ketones **2** catalyzed by **C6**.[a]



[a] Reactions conducted on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 (molar ratio of **1**/**2**/catalyst 1:2:0.05) at room temperature, unless otherwise stated. Yields of isolated product after column chromatography. Enantioselectivity determined by chiral HPLC. [b] 2 mol% of **C6** used (reaction run for 36 h).

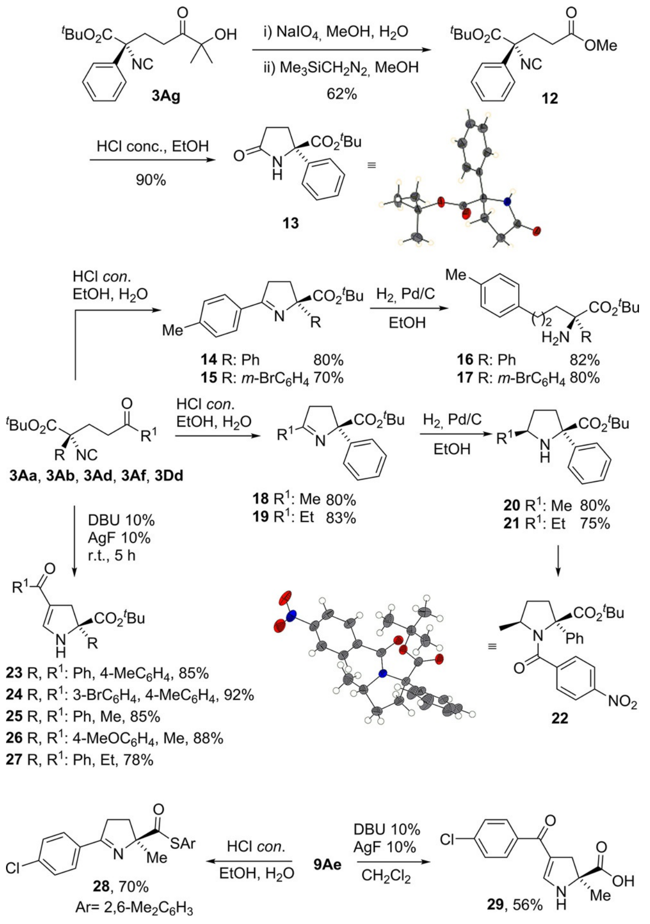
ally more acidic than oxoesters. At the outset, however, it was not clear whether α-alkyl isocyanoacetate thioesters would be effective donor substrates in this reaction. In fact, a few classes of thioesters only, with inherently acidic character, for example, arylacetic,[25] β,γ-unsaturated carboxylic acid,[26] and malonic acid thioesters,[27] have been successfully employed in catalytic asymmetric carbon–carbon bond forming reactions and, as far as we know, α-substituted isocyanoacetic thioesters have never been reported.[28] In initial attempts, we observed that the **C6**-catalyzed reactions of various α-alkyl isocyanoacetate thioesters **4** (Ar = Ph) with enones **2** provided the Michael adducts **7** in good *ee*, but with formation of considerable amounts (20%–40%) of undesired byproducts such as **10**, **11** and sulfa-Michael products.[29] In case of thioester **5** (Ar = 1-naphthyl) and methyl vinyl ketone, compound **11Aa** was the major product formed with no even traces of **8Aa** detected. In view of these complications,[30] some precursors of α-isocyanothioesters, such as α-substituted α-formamido thioesters and *N*-Boc α-amino acid thioesters, were also evaluated for the above reactions, but these substrates were completely unreactive under the above catalytic conditions. After some screening,[18] it was finally found that α-alkyl isocyanoacetate thioester **6A**, with a di-*ortho* substituted phenyl group installed (Ar = 2,6-$Me_2C_6H_3$), reacted cleanly to produce the corresponding adduct **9A** essentially as the sole reaction product. This reactivity pattern was quite general for an array of isocyanoacetates **6** bearing short, medium, and longer α-alkyl linear as well as branched chains. As the data in Table 3 show, upon reaction with enones **2** the corresponding products **9** were obtained in good to very good isolated yields and excellent enantioselectivity, without traces of accompanying by-products.[31] Furthermore, as the production of compound **9Fe** illustrates, the reaction can be run at 3 mmol scale without any detriment in yield or selectivity.

Table 3. Conjugate addition of α-alkylisocyanothioacetates **4**–**6** to vinyl ketones **2** catalyzed by **C6**.[a]



[a] Reactions conducted on a 0.1 mmol scale in 0.2 mL CH_2Cl_2 (molar ratio of thioester/**2**/catalyst 1:2:0.1). Yields of isolated product after column chromatography. Enantioselectivity determined by chiral HPLC. [b] reaction run for 3 days. [c] about 30% of product **10** formed. [d] 3 equiv. of **2d** used. [e] About 35% of product **11** formed. [f] with catalyst **C1**. [g] Reaction run for 2 days. [h] Reaction run at 3 mmol scale using 1.3 equiv. of **2e**.

The synthetic utility of the method was briefly explored as shown in Scheme 2. For example, the oxidative cleavage of the acyloin moiety in adduct **3Ag** provided, after methylation of the intermediate carboxylic acid, ester **12**. This product is difficult to obtain enantioselectively from a direct addition to methyl acrylate. Of practical interest, acetone is the only carbon by-product formed during this two-step transformation. Product **12** could be transformed into the pyroglutamate ester **13** in good yield. On the other hand, mild acid hydrolysis of adducts **3Ad** and **3Dd**, followed by spontaneous cyclisation, provided the 1,5-dehydroproline esters **14** and **15** in 80% and 70% yield, respectively. Exposure of these adducts to H_2 over Pd on charcoal proceeded with concomitant cleavage of the benzylic C–N bond to give the corresponding α,α-disubstituted α-amino esters **16** and **17**. Conversely, when 1,5-dehydroproline esters **18** and **19**, obtained from **3Aa** and **3Ab** as above, were submitted to the same hydrogenation conditions, pyrrolidines **20** and **21** were produced with almost perfect stereocontrol at the newly generated stereocenter (d.r.: > 20:1).[32] The absolute configuration of compounds **13** and **22** was determined by X-ray single crystal structure analysis[33] and that



Scheme 2. Elaboration of adducts. Ellipsoids drawn at the 50 % probability level.

of the remaining adducts by analogy assuming a uniform reaction mechanism. Finally, it was gratifying to observe that adducts **3 Aa**, **3 Ab**, **3 Af**, **3 Ca** and **3 Dd** upon treatment with 10 mol % of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and AgF led to 4,5-dehydroprolines **23–27** in very good yields through a clean cyclization and isomerization process. Other bases examined for this process, Et_3N and $i\mathrm{Pr}_2EtN$, were also effective, but longer reaction times were required for completion, whereas in the absence of silver salts the reactions did not proceed.[34] Importantly, using this approach, prolines with an α-alkyl substituent could be produced, as illustrated with compounds **28** and **29** derived from **9 Ae**.

In conclusion, we report here a new divergent synthesis of quaternary Δ^4- and Δ^5-dehydroprolines with broad substitution patterns based on a catalytic enantioselective two-step formal [3+2] cycloaddition of α-substituted isocyano(thio)acetates with vinyl ketones. For the first time, the key to the success was the development of isocyanoacetic acid thioesters as donor reagents in asymmetric synthesis, and the design of a new subtype of squaramide/tertiary amine catalyst featuring a sterically congested polyaryl side-arm. We anticipate that these two key elements will find future applications in the realm of asymmetric catalysis.

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Conflict of interest

The authors declare no conflict of interest.

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[31] This reactivity pattern appears to be independent of the acceptor. For example, although *N*-phenyl maleimide hardly reacts with α-benzyl isocyanoacetate methyl ester through Brønsted base catalysis (ref. [14c]), the reaction with isocyanothioacetate **6B** proceeded smoothly (10 mol% **C6**, RT, overnight) to produce the corresponding adduct in 70% isolated yield, albeit as a mixture of diastereomers (d.r. = 70:30, 68%/80% *ee*).

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[34] $AgNO_3$, AgOTf and AgOAc were also tested as alternative silver source, but among them only the latter was effective.

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