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Dr. Claudio Palomo Nicolau con N.I.F. 37655199J como Director de la Tesis Doctoral: "Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions: Divergent Access to α -Quaternary Δ^4 - and Δ^5 -Dehydroprolines" realizada en el Programa de Doctorado Química Sintética e Industrial por el Doctorando Doña. Amaiur Odriozola Nuin, autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia a 05 de Noviembre de 2018

EL DIRECTOR DE LA TESIS

Fdo.: Claudio Palomo Nicolau



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Dr. Juan Miguel Oyarbide Garmendia con N.I.F. 15968197X como Director de la Tesis Doctoral: "Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions: Divergent Access to α -Quaternary Δ^4 - and Δ^5 -Dehydroprolines" realizada en el Programa de Doctorado Química Sintética e Industrial por el Doctorando Doña. Amaiur Odriozola Nuin, autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia a 05 de Noviembre de 2018

EL DIRECTOR DE LA TESIS

Fdo.: Juan Miguel Oyarbide Garmendia

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AUTORIZACIÓN DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO

La Comisión Académica del Programa de Doctorado en Química Sintética e Industrial en la reunión celebrada el día 5 de Noviembre de 2018, ha acordado dar la conformidad a la presentación de la Tesis Doctoral titulada: Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions: Divergent Access to α -Quaternary Δ^4 - and Δ^5 -Dehydroprolines dirigida por los Dres. Claudio Palomo Nicolau y Juan Miguel Oyarbide Garmendia y presentada por Dña. Amaiur Odriozola Nuin adscrita al Departamento de Química Orgánica I.

En Leioa, a 5 de Noviembre de 2018

LA RESPONSABLE DEL PROGRAMA DE DOCTORADO

Fdo.: Esther Lete





NAZIOARTEKO BIKAINTASUN CAMPUSA CAMPUS DE EXCELENCIA INTERNACIONAL

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El Consejo del Departamento de Química Orgánica I en reunión celebrada el día 7 de Noviembre de 2018 ha acordado dar la conformidad a la admisión a trámite de presentación de la Tesis Doctoral titulada: "Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions: Divergent Access to α -Quaternary Δ^4 - and Δ^5 -Dehydroprolines" dirigida por los Dres. Claudio Palomo Nicolau y Juan Miguel Oyarbide Garmendia y presentada por Doña. Amaiur Odriozola Nuin ante este Departamento.

En Gasteiz a 7 de Noviembre de 2018

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ACTA DE GRADO DE DOCTOR O DOCTORA ACTA DE DEFENSA DE TESIS DOCTORAL

DOCTORANDA DÑA. Amaiur Odriozola Nuin TITULO DE LA TESIS: Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions: Divergent Access to α-Quaternary Δ⁴- and Δ⁵-Dehydroprolines El Tribunal designado por la Comisión de Postgrado de la UPV/EHU para calificar la Tesis Doctoral arriba indicada y reunido en el día de la fecha, una vez efectuada la defensa por el/la doctorando/a y contestadas las objeciones y/o sugerencias que se le han formulado, ha _la calificación de: unanimidad ó mayoría SOBRESALIENTE / NOTABLE / APROBADO / NO APTO Idioma/s de defensa (en caso de más de un idioma, especificar porcentaje defendido en cada idioma): Castellano Euskera ____ Otros Idiomas (especificar cuál/cuales y porcentaje) _____ En ______a ____de _____de _____ EL/LA PRESIDENTE/A, EL/LA SECRETARIO/A, Fdo.: Fdo.: Dr/a: _____ Dr/a: _____ VOCAL 1°, VOCAL 2°, VOCAL 3°, Fdo.: Fdo.: Fdo.:

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Fdo.: _____



Isocyano(thio)acetates in Asymmetric Organocatalytic Reactions:

Divergent Access to α -Quaternary Δ^4 and Δ^5 - Dehydroprolines

DOCTORAL THESIS

Amaiur Odriozola Nuin Donostia 2018



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 (Figure 1). 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. 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 adducts serve as a common intermediate for the synthesis of various types of proline derivatives. In addition, the corresponding cycloaddition reaction reported previously had provided unsatisfactory stereochemical results in the resulting prolines.

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^4 -dehydroprolines, which formally derive from [3 + 2] cycloadditions, and α -quaternary Δ^5 -dehydroprolines (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.

$$R = Aryl$$

$$R = Ary$$

$$R = Aryl$$

$$R = Ary$$

$$R = Aryl$$

$$R = Ary$$

$$R = Aryl$$

$$R = Aryl$$

$$R = Aryl$$

$$R$$

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 oxoesters 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.

$$\begin{array}{c|c}
NC & NC \\
Alk \longrightarrow & Alk \longrightarrow \\
CO_2R & COSR \\
\hline
increased acidity
\end{array}$$

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 isocyanothioacetates.

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*-Nosyl) 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.

Alk
$$\stackrel{R^2}{\longrightarrow}$$
 $\stackrel{R^2}{\longrightarrow}$ $\stackrel{R^2}{\longrightarrow}$

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

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 (Figura 1). Estos métodos además han requerido dipolarófilos muy reactivos y salvo alguna excepción, la presencia de metal para promover la reacción. 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, cuyos aductos sirven como intermedio común para la síntesis de varios tipos de derivados de prolina. Además, la reacción de cicloadición correspondiente informada previamente había proporcionado resultados estereoquímicos insatisfactorios en las prolinas resultantes.

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 la actividad del catalizador. 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.

$$R = Aril$$

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 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-Nosyl) 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.

Alk
$$R^2$$
 $RSOC$ $RSOC$

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 Acetyl group Ac Alk Alkyl group Ar Aryl group BA Brønsted acid BB Brønsted base **BINOL** 1,1'-Bi-naphtol Bn Benzyl group

Boc tert-Butyloxycarbonyl group

iBu Isobutyl (group)
 nBu n-Butyl (group)
 tBu tert-Butyl (group)
 Cat.* Chiral catalyst
 calculated

Cbz Benzyloxycarbonyl group

CoA Coenzyme A

m-CPBA *Meta*-Chloroperbenzoic acid

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)

HPLC Highperformance liquid chromatography

HOBt 1-hydroxybenzotriazole

L Ligand

LA Lewis acid

LDA Lithium diisopropylamide

M Metal m- meta-

MAHT Malonic acid half thioester

MBH Morita-Baylis-Hillman

Me Methyl (group)

MeIm 1-Methylimidazole

Mes Mesityl (2,4,6-Me $_3$ -C $_6$ H $_2$ -) MOM Methoxymethyl (CH $_3$ OCH $_2$ -)

m.p. Melting point

MS Molecular sieves

Ms Mesyl (MeSO₂-)

MTBE Methyl *tert*-butyl ether
MTM Mono thiomalonate

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- orthop- para-

PG Protecting group
Ph Phenyl group

PMP para-Methoxyphenyl (4-MeO-C₆H₄-)

*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

pTol para-Tolyl (4-Me-C₆H₄-) Ts Tosyl (4-Me-C₆H₄-SO₂-)

pTSA para-Toluenesulfonic acid

* Chiral

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Chapter 1

Introduction

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1. Introduction

1.1. Asymmetric (Organo) Catalysis

Chirality¹ 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 proposed⁴ 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).

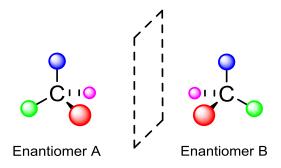


Figure 1. Both enantiomers of a chiral molecule containing a stereogenic carbon.

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

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.

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.

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.

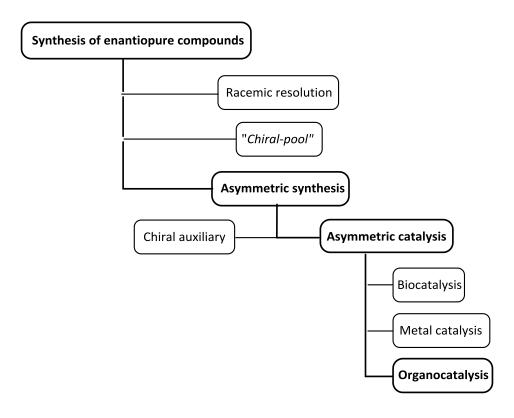


Figure 2. The strategies for obtaining enantiopure compounds.

Today, the most used strategy in the pharmaceutical industry⁸ to obtain enantiopure compounds is the resolution of racemates.⁹ The enantiopure compound is separated

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, 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. 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, carbohydrates, hydroxyacids, terpenes and alkaloids, their abundance may be another limitation for use in industrial processes.

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

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. d) Verho, O.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2015**, *137*, 3996–4009.

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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

substrate to control the stereochemical outcome of the reaction and thus the 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 catalysis¹⁸ 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.

Biocatalysis¹⁹ is mainly based on high regio-, chemo- and stereoselective enzymatic processes which are commonly limited to certain substrates and reaction categories. Organometallic catalysis²⁰ and organocatalysis²¹ 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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²¹ a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748. b) Movassaghi, M.; Jacobsen, E. N. *Science*, **2002**, *298*, 1904–1905. c) Berkessel, A.; Groger, H.; *Metal-Free Organic Catalysis in Asymmetric Synthesis* (Wiley-VCH, Weinheim) 2004. d) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. e) List, B. *Science*, **2006**, *313*, 1584–1586. f) Dalko, P. I.; *Enantioselective Organocatalysis* (Wiley-VCH, Weinheim) 2007. g) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. h) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20618–20619. i) List, B. *Science of Synthesis;* Vol. I (Georg Thieme Verlag KG, New York) 2012. j) Maruoka, K. *Science of Synthesis;* Vol. II (Georg Thieme Verlag KG, New York) 2012. k) Quin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* **2017**, *117*, 9433–9520.

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).

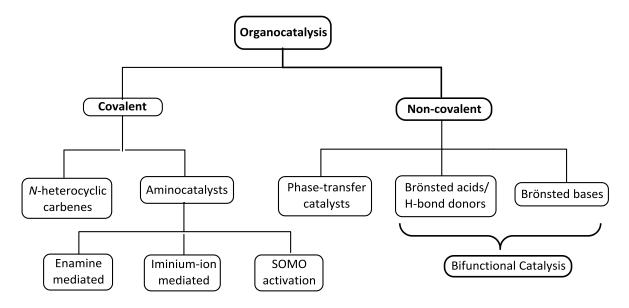


Figure 3. Activation modes in organocatalysis.

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 dienanime²⁵ and trienamine²⁶ intermediate or through SOMO

46, 1080–1102.

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.

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. i) Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K. A. *Chem. Soc. Rev.* **2017**,

activation.²⁷ Other types of catalysts, such as *N*-heterocyclic carbenes²⁸ or less frequently used tertiary amines,²⁹ alkyl pyridines³⁰ and trialkylphosphines³¹ are also employed in covalent organocatalysis. These activation modes enable the stereoselective functionalization of unmodified carbonyl compounds at the *ipso*, α and θ 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).

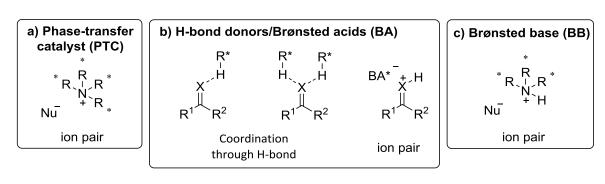


Figure 4. Substrate activation in non-covalent catalysis.

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.

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.

²⁷ Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585.

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²⁹ a) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaws, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, 107, 5841–5883. b) Gaunt, M. J.; Johanson, C. C. C. *Chem. Rev.* **2007**, 107, 5596–5605.

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

³¹ a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614–4628. b) Krishna, P. R.; Sachwani, R.; Reddy, P. S. *Synlett*, **2008**, 2897–2912. c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48.

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 catalysts³³ (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).

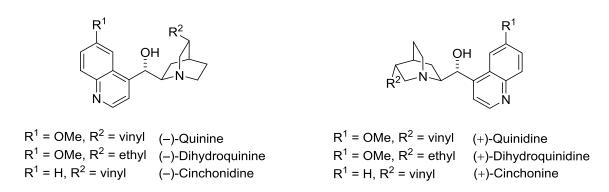


Figure 5. Alkaloids from the cinchona family.

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. d) Rahman, A.; Lin, X. *Org. Biomol. Chem.* **2018**, *16*, 4753–4777.

³⁴ a) Taylor, M. S.; Jakobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543. b) Doyle, A. G; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. c) Akiyama, Y. *Chem. Rev.* **2007**, *107*, 5744–5758. d) Yu, X.; Wang, W. *Chem. Asian. J.* **2008**, *3*, 516–532. e) Zhang, Z.; Scheriner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. f) Pihko, P. M.; *Hydrogen Bonding in Organic Synthesis* (Wiley-VCH, Weinheim) 2009. g) Sohtome, Y.; Nagasawa, K. *Synlett*, **2010**, 1–22. h) Nishikawa, Y. *Tetrahedron Lett.* **2018**, *59*, 216–223.

³⁵ For general reviews, see: a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985–3012. b) Wurz, R. P.; *Chem. Rev.* **2007**, *107*, 5570–5595. c) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638. d) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. e) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysis*; (Wiley, New York) 2009. f) Tiang, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145–200. g) Teng, B.; Lim, W. C.; Tan, C.-H. *Synlett*, **2017**, *28*, 1272–1277. For reviews in chiral guanidines, see: h) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553–557. i) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752. j) Leow, D.; Tan, C.-H. *Chem. Asian. J* **2009**, *4*, 488–507. k) Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555–1564. l) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210–8222. m) Selig, P. *Synthesis* **2013**, *45*, 703–718. For reviews in chiral iminophosphoranes, see: n) Krawcyk, H.; Dzigielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, L. *Chem. Eur. J.* **2015**, *21*, 10268–10277.

Introduction

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 (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.

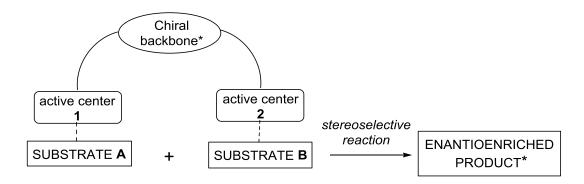


Figure 6. Bifunctional catalysis.

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,

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.

³⁷ a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057–4060. b) Hermann, K.; Wynberg, H. *J. Org.* Chem. 1979, 44, 2238-2244.

³⁸ For mechanistic studies on bifunctional catalysis promoted by cinchona alkaloids, see: Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. Chem. Commun 2009, 15, 7913-7921.

³⁹ Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

demonstrating their effectiveness in many transformations.⁴⁰ More recently, since in 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.

Rawal, 2008

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.; 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.

Introduction

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.

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.

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).

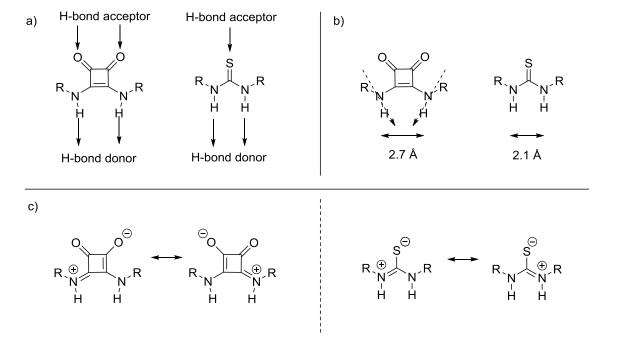


Figure 8. Structural differences between squaramide and thiourea skeletons.

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

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 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. The diverse functionalities of peptides are conditioned by physical and chemical properties of specific side chain of the amino acid

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.

residues and their three-dimensional structures (secondary structures). However, oligopeptides composed by natural L- α -amino acids often form unstable or unordered 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. In addition, α -amino acids are employed as chiral source in chemical catalysis and synthesis.

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 helixinducing potencial (Scheme 1). These effects have been attributed to the loss of conformational freedom due to the steric constraint, which restricts the secondary structure of peptides.

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.

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

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}

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

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.

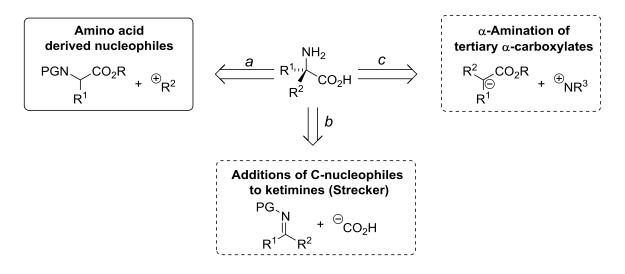
⁵³ a) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, *117*, 10597–10598. b) Yano, H.; Nakanishi, S.; Ikuina, Y.; Ando, K.; Yoshida, M.; Saitoh, Y.; Matsuda, Y. *J. Antibiot. (Tokyo)*. **1997**, *50*, 992–997. c) Becker, D.; Kiess, M.; Brückner, H. *Liebigs Ann.* **1997**, *1997*,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

⁵⁵ For general reviews on the asymmetric synthesis of quaternary α-amino acids, see: a) Cativiela, C.; Díazde-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 an example of the

those based on the stoichiometric of a chiral source, either an auxiliary or a molecule from the chiral pool, from the catalytic methods. As we mentioned before, 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.



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

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

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

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.

imines has also been carried out, a very useful reaction commonly used for the synthesis of α -quaternary α , β -diamino acids (Scheme 3).

Color of proline derivatives
$$R^2$$
 R^2 R^2 R^3 R^3 R^2 R^3 R^2 R^3 R^2 R^3 R^2 R^3 R^3 R^3 R^2 R^3 R^3

Scheme 3.

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 acids⁵⁸ 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

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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 <i>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

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

Acyclic
$$\alpha$$
-quaternary

AAs in peptides

ACYCLIC ACCOUNTY

AAS in peptides

ACYCLIC ACCOUNTY

AAS in peptides

AAS in peptides

ACYCLIC ACCOUNTY

ACYCLIC A

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

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 a) Enantioselective Organocatalysis; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007. b) See ref. 22, page 9. 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-

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.

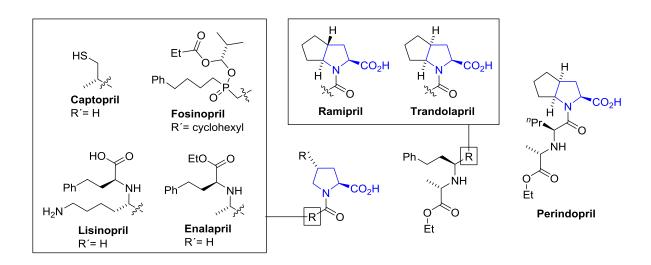


Figure 12. Pharmaceuticals containing proline core.

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. 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 and posterior clyclization. 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.

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.

Introduction

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 4). Then, the diastereoselective alkylation at the C α followed by aminal hydrolysis provides α -quaternary prolines with retention of the configuration. The strategy has been further developed, to broaden the scope of the reaction, modulate the diastereoselectivity and explore new variations.⁶⁹

Scheme 4. Seebach's self-regenation of stereocenters strategy

Alternatively, the diastereoselective $C\alpha$ alkylation of substituted L-proline esters can be achieve if the initial proline contains a second stereocenter with the set configuration. 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 $C\alpha$ arylation of L-proline derivatives have also been achieved by Claiden employing KHMDS as base (strong base) (Scheme 5).

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.

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.

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.

Scheme 5. Diastereoselective $C\alpha$ 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 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 6).

Scheme 6. Phase-transfer-catalyzed alkylation of racemic 3-oxo proline analogue.

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

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 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, in addition to which α -iminoesters (azomethine ylide precursors) with an additional activating group at α -

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.

⁷² See ref. 67, page 21.

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.

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.

position are usually required to increase the acidity of this $C\alpha$, 77 most commonly two ester groups. 78 In contrast, organocatalytic [3+2] cycloadditions involving α -aryl or α -alkyl substituted amino acid derivatives for the synthesis of α - quaternary proline have been less developed (Figure 15).

Figure 15. Most developed organocatlytic [3+2] cycloadditions for the proline derivatives synthesis.

Below are collected the main studies carried out in the synthesis of α -quaternary prolines with α -aryl or α -alkyl substituted amino acid derivatives, namely: 1) azomethyne ylide precursors (commonly α -imino esters), 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 [3+2] cycloaddition involving azomethine ylides and electron-deficient olefins. 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

Г.

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.

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.

prolines (entry 2).⁸¹ Acrylates,^{82,} fumarates/maleates,⁸³ maleimides,⁸⁴ nitroalkenes⁸⁵ and enones⁸⁶ have been the most used dipolarophiles in these reactions. To a lesser extent, allenoates,⁸⁷ alkylidene malonates,⁸⁸ methyleneindolinones^{83d,89} and vinyl sulfones⁹⁰ have also been studied.

For [3+2] cycloadditions involving az

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.

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.; 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.

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, 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.

Table 1.

Entry	Ylide precursors	Dipolarophiles
1	$Ar \nearrow N \nearrow R$ CO_2R'	acrylates, fumarates/maleates, maleimides, allenoates, alkylidene malonates, methyleneindolinones, nitroalkenes, vinyl sulfones, enones
2	Ar N R O (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 of azomethine ylides and bis-sulfonyl ethylene reported by Carretero and co-workers in 2008. The reductive elimination of both sulfonyl groups resulted in Δ^3 -dehydroprolines, and hence, bis-sulfonyl ethylene acted as masked acetylene, unreactive dipolarophile in this reaction (Scheme 7).

Scheme 7. The synthesis of α -quaternary 3-pyrrolidines through the [3+2] cycloaddition between azomethine ylides and bis-sulfonyl ethylene.

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.

⁹¹ See ref. 90c. page 27.

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 8). 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.

Ar
$$N = CO_2Alk$$
 $+ CO_2Alk$ $+ CO_2Alk$

Scheme 8. 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 9. 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}

⁹² See ref. 86g, page 26.

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

Scheme 9. 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. 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 10). The key for success is the intramolecular activation of the azomethine ylide precursor via hydrogen bond.

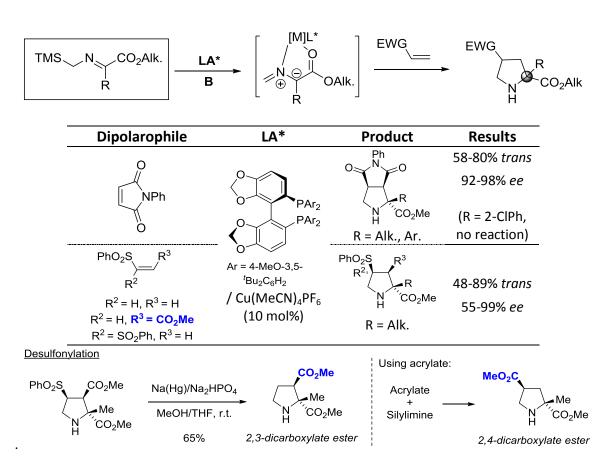
$$\begin{array}{c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

Scheme 10. 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 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 co-workers 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.



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 11).

 ⁹⁴ Hernández-Toribio, J.; Padilla, S.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 8854–8858.
 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 11. 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.
MeN O N Ar	Et₃N (20 mol%)	Ar N N N N N N N N N N N N N N N N N N N	45-90% endo 89-99% ee	97a
Alk .Ar N CO₂Alk²	Et ₃ N (20 mol%)/ CF ₃ CF ₃ CF ₃ CF ₃ (20 mol%)	HO— R Ar N CO ₂ Alk ² OH 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 12.

$$\begin{array}{c} \text{Ar} & \text{N} & \text{R}^1 \\ \text{CO}_2 \text{Alk} & + & \text{R}^2 \end{array} \xrightarrow{\begin{array}{c} \text{Michael Addition} \\ \text{R}^1 & \text{N} \end{array}} \begin{array}{c} \text{AlkO}_2 \text{C} & \text{Amine} \\ \text{R}^1 & \text{N} & \text{R}^2 \end{array} \xrightarrow{\begin{array}{c} \text{Amine} \\ \text{liberation} \end{array}} \\ \begin{array}{c} \text{AlkO}_2 \text{C} & \text{Amine} \\ \text{R}^1 & \text{N} & \text{R}^2 \end{array} \xrightarrow{\begin{array}{c} \text{Amine} \\ \text{R}^2 & \text{R}^1 \\ \text{R}^2 & \text{R}^2 \end{array}} \end{array}$$

Scheme 12. 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 13). In this case, the conventional [3+2] cycloaddition was avoided thanks to the elimination step that occurred after the Michael addition.

Scheme 13. 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 14). The products of the reaction could be transformed diastereoselectively into α -quaternary proline derivatives via hemiaminal formation. ⁹⁹

$$R^1 = Alk, Ar$$
 $R^2 = Alk, Ar$
 $R^3 = Alk, Ar$

Scheme 14.

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 25, Transformation A). Two years later, they extended the reaction to the "in situ" formation of azlactone from unprotected α -amino acids they could make a new transformation to obtain the *N*-unprotected pyroglutamic acid (Scheme 25, Transformation B). More recently, other studies have been carried out dealing with the conjugate addition of azlactones to enones, to enones, to 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.; Alemán, 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 15.

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). 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.

$$Ar \sim N \sim CO_2R \sim CO_2R \sim E^+ \sim Ar \sim N \sim CO_2R$$

Electrophile (E ⁺)	Cat.*	Product	Results	Ref.
Ar^2 R $R = Ar, Alk$	Ph ₂ P Fe Me Fe N N N Ph (5.5 mol%) AgOAc (5 mol%)/DBU (20 mol%)	Ar N CO ₂ Me	syn >50% >95:5 dr 83-99% ee	102c
Ar^2 NO_2	Ph ₂ P Fe N Me (5.5 mol%) CuOAc (5 mol%)/Py (5 mol%)	O_2N Ar^2 $CO_2M\epsilon$	74:26–92:8 syn/anti 94–99% ee (1:99 anti with AgOAc)	102b

1.3.1.2.1.3. Alkylation/allylation

In few cases, the catalytic asymmetric C-alkylation or C-allylation of azomethine ylides has also served for the formation of chiral α -quaternary proline precursors. For example, Maeda et al. developed a methodology to synthesize proline scafolls from the chiral α -allylic product obtained by Maruoka years earlier. However, 3 steps are required to get the cyclic product (Scheme 16).

¹⁰³ a) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, *7*, 1185–1187. b) Maeda, K.; Miller, R. A.; Szumigala, R. H.; Shafiee, A.; Karady, S.; Armstrong, J. D. *Tetrahedron Letters* **2005**, *46*, 1545–1549.

Scheme 16. Asymmetric allylation of azomethine ylide and transformation of chiral α -allyl functionalized compound to proline.

In a more recent study developed by Maruoka, the hydrolysis of the imine moiety in the acyclic chiral compound directly leads to an intramolecular N-alkylation providing the corresponding α -quaternary proline (Table 5). 104

Table 5. Catalytic asymmetric C-alkylation of azomethine ylides for the synthesis of chiral proline precursors.

	R ¹	R ² X	Cat.*	Acyclic chiral product	Results
1	Alk Ph	ICI	Ar Bu N⊕ Br Bu	$\begin{array}{c} Ph $	75-94% 98-99% ee (R ¹ =Ph 64% ee)
2	Alk	CICI	Ar = $3,4,5-F_3C_6H_2$ (1 mol%)/CsOH.H ₂ O (5 equiv.)	Ph N CO ₂ ^t Bu CI	44-64% 96–97% ee

¹⁰⁴ Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.-G.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900–4904.

Finally, there is one example in which the catalytic enantioselective $C\alpha$ -alkylation of azomethine ylides with preformed pyrrolidine has also allowed the synthesis of α -quaternary proline derivatives (Scheme 17). The reduction of the imine moiety even could be modulated according to the reducing agent used.

Ph
$$CO_2^t$$
Bu $\frac{\text{PTC } (2.5 \text{ mol}\%), \text{ RBr } (5 \text{ equiv.})}{\text{KOH } (5 \text{ equiv.}), \text{ tol., } -20 \,^{\circ}\text{C}}$

PTC

R = allyl, benzylic

61-98%
90-99% ee

Scheme 17. The catalytic enantioselective $C\alpha$ -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 dehydroprolines as shown in Scheme 18.

$$R^{1} \xrightarrow{\text{NO}_{2}} + \xrightarrow{\text{O}_{2}} \frac{\text{Cat}^{*}}{R^{2}} \xrightarrow{\text{AlkO}_{2}C} \xrightarrow{*} R^{2} \xrightarrow{\text{O}_{2}\text{Alk}} R^{2} \xrightarrow{\text{O}_{2}\text{Alk}} R^{2} \xrightarrow{\text{O}_{2}\text{Alk}} R^{2}$$

Scheme 18. Synthesis of α -quaternary Δ^4 -dehydroprolines 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). The cyclization step of these adducts for obtaining reduced proline scaffolds consists of an intramolecular reductive amination involving an intermediate nitrone for which optimal conditions have been found.

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

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.

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.

Introduction

Cyclization (Snider 2006)^{106c}

EtO₂C

1) 1 atm H₂, Pd/C, EtOH
2) HCl, 3.3 atm H₂

$$H_2$$
 CO_2 Et

N

CO₂Et

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 19).

F—
$$O_2$$
 O (10 mol%)
 O_2 EtO₂C
 O_2 Et
 O_2 Et
 O_3 Et
 O_4
 O_4
 O_5
 O_5
 O_6
 O_7
 O_8
 O_9
 O_9

Scheme 19. Asymmetric Michael addition between α -fluoro nitroesters and β -substituted enones.

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.

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 C₄-unsubstituted proline synthesis, what is not feasible with conventional azomethine ylides because the aryl-substitution in the iminic carbon is mandatory (Scheme 20).

$$(C4) \stackrel{\bigcirc{}}{\stackrel{}{\stackrel{}}{\stackrel{}}} N \stackrel{\bigcirc{}}{\stackrel{}{\stackrel{}}} CO_2R \xrightarrow{EWG} \xrightarrow{EWG} EWG$$

$$C4 \stackrel{\bigcirc{}}{\stackrel{}{\stackrel{}}{\stackrel{}}} CO_2R \xrightarrow{EWG} CO_2R$$

Scheme 20. 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 7, entry 1 and 3). 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 (Table 8, see entry 1, 2, 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 7, entry 7), 115 affording the corresponding proline derivatives with poor enantioselectivity, especially in case of the α -quaternary prolines (\leq 36% ee).

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

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

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

$$\begin{array}{c} NC \\ R^1 CO_2Alk \end{array} + \begin{array}{c} EWG \\ \hline Cat^* \\ \hline \end{array} \begin{array}{c} EWG \\ \hline \\ N \end{array} \begin{array}{c} R^1 \\ CO_2Alk \end{array}$$

	Electrophile Cat.*		Product	Results	Ref.
1	$R^2 \longrightarrow NO_2$ $R^2 = Alk, Ar$	(20 mol%)	O_2N R^2 CO_2Alk $R^1 = Ar, $ only Bn	51-99% 4:1->20:1 dr 90-99% ee	108
2	NR^2 $R^2 = Ar, Alk$	(5 mol%)/AgSbF ₆ (10 mol%)	$O = NR^{2} O$ R^{1} $R^{2} = Ar, Pr, Bn,$ 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	AlkO ₂ C X O O O O O O O O O	F ₃ C N N N N N N N N N N N N N N N N N N N	PGN CO_2Alk R^1 CO_2Alk R^2 R^3	41-65% 1.9:1-8:1 dr 90–99% <i>ee</i>	111a
4	R = Ar, vinyl	(20 mol%)/ Ag ₂ O (10 mol%)	AlkO ₂ C R^{1} R^{1} R^{2} R^{1} R^{2} R^{3} R^{4} R^{5} R^{6} R^{1} R^{6} R^{7} R^{1} R^{1} R^{1} R^{1} R^{2} R^{1} R^{2} R^{1} R^{2} R^{3} R^{4} R^{1} R^{2} R^{3} R^{4} R^{5} R^{6} R^{7} R^{1} R^{1} R^{2} R^{2} R^{3} R^{4} R^{5} R^{5} R^{6} R^{7} $R^{$	58-90% 4:1-11:1 dr 82-96% ee	112
5	R^2S CO_2Alk $R^2 = Alk, Ar, Ts$	(20 mol%)/ Ag ₂ O (10 mol%)	MeO ₂ C R^2S^{11} N CO_2Me $R^1 = Alk, Ar$	86-99% 52:48-75:25 dr 92-98% <i>ee</i>	114b

	Electrophile Cat.*		Product	Results	Ref.
6	$ \begin{array}{c} O \\ R^2 \\ R^3 \end{array} $ $ R^2 = Alk $ $ R^3 = Bn, Ar $	(10 mol%)/ AgNO ₃ (10 mol%)	$R^2 R^3$ R^1 R^1 CO_2Me $R^1 = Ar, only Pr$	63-91% >84:16 dr 80-98% ee	113
	0		O R ²	(R ¹ = H) 20-59% 52-89% <i>ee</i>	
7	$R^2 = Me$, Et	HON	R^1 CO_2Me $R^1 = H, Bn$	(R ¹ = Bn) 68-85% 16-36% <i>ee</i>	 115
	(10 mol%)/ AgNO₃ (5 mol%)		10-30% 66		

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 peptides¹¹⁶ and the α -helix propensity is decreased. Besides the application in peptide chemistry, nonproteinogenic α , β -diaminoacids or small peptidomimetics constitute a key structural frangments in many natural and biologically active compounds (Figure 16).

6

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.

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.;

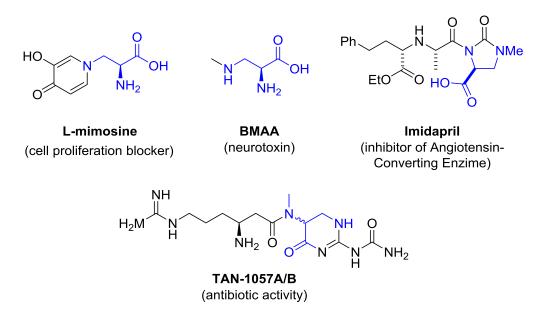


Figure 16. Biologically active compounds containing α,β -diaminoacid frangments.

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 21). The first approach consists in the addition of nucleophilic synthetic equivalent of carboxyl group to electrophilic C α (pathway a), commonly by Strecker reaction (cyanation of imines). 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 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.

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.

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 $C\alpha$, the studies carried out with α -subtituted amino acids still show important limitation; in special when α -alkyl nucleophiles and organocatalysts are used.

Scheme 21. 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.

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 1859¹²⁵ and hundred years later its synthesis became available from primary amines by dehydration of formamides. 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 heterocycles¹²⁷ 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

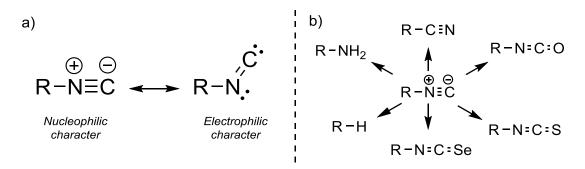


Figure 17. General resonance structure of an organo isocyanide and its possible transformations.

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

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

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

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

 $^{^{128}}$ 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.

 $C\alpha$ 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

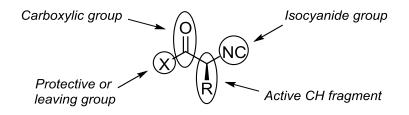


Figure 18. Reactivity centers of α -isocyanoacetate derivatives.

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 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, introgen

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

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

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.

heterocycles¹³⁴ 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. 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 22).

¹³⁴ See ref 127, page 44.

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 22. 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 $C\alpha$ acidity. 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).

4.

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 7, page 40), and equally, precedents regarding to the Mannich addition that are analyzed later (Section 3.5, page 125) 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 (Section 1.3.1.2.1.1, page 25-37). In this context, α -substituted isocyanoacetates have been seldom employed owing to the low acidity of $C\alpha$, 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 23).

$$R^{1} = Alk, Ar$$

$$R^{1} = Alk, Ar$$

$$R^{2} \times COXR^{2}$$

$$R^{1} \times R^{3}$$

$$R^{2} \times COXR^{2}$$

$$R^{3} \times R^{2} \times COXR^{2}$$

$$R^{3} \times R^{4} \times COXR^{2}$$

$$R^{1} = Alk, Ar$$

$$R^{1} = Alk, Ar$$

$$R^{2} \times COXR^{2}$$

$$R^{2} \times COXR^{2}$$

$$R^{3} \times COXR^{2}$$

$$R^{4} \times COXR^{2}$$

$$R^{5} \times COXR^{2}$$

Scheme 23. 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 24. 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 $\alpha\text{-aryl}$ isocyanoacetates to vinyl ketones: divergent synthesis of $\Delta^4\text{-}$ and $\Delta^5\text{-}dehydroprolines$

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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. 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 25). Thus, the control of enantio- and diastereoselectivity in the processes is of considerable significance.

Scheme 25. General scheme of the Michael addition reaction.

¹³⁸ For general 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. For reviews on 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. For reviews on organocatalyzed asymmetric conjugate 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.

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 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 1887¹⁴¹ 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 and organocatalysis. 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.¹⁴² In this sense, different approaches have been studied for the asymmetric Michael addition (Figure 20).

1

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). ¹⁴⁰ For reviews on aza-Michael reactions, see: a) Xu, L.-W.; Xla, 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 Marcus, Y:; Hefter, G. *Chem Rev.* **2006**, *103*, 4585–4621.

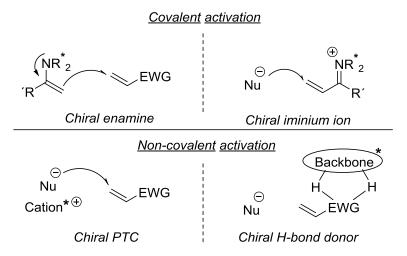


Figure 20. Organocatalytic activations in asymmetric Michael additions.

With respect to covalent activation, chiral aminocatalysts in Michael addition can operate through two mechanisms, namely: enamine activation (Nu reagent activated)¹⁴³ and iminium activation (E reagent activated).¹⁴⁴ Regarding to non-covalent activations, chiral phase-transfer catalysis (PTC)¹⁴⁵ 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.)¹⁴⁶ 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, ¹⁴⁷ 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 on the development of more effective bifunctional Brønsted base catalysts or new pronucleophilic templates suitable for soft enolization.

a) Sulzer-Mossé, S.; Alexakis, A. Chem. Commun. 2007, 3123–3135. b) See Chapter 1, ref. 24, page 10.
 See Chapter 1, ref. 23, page 9.

¹⁴⁵ a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. b) Maruoka, K. *Organic Process Research & Development* **2008**, *12*, 679–697.

¹⁴⁶ a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543. b) Nishikawa, Y. *Tetrahedron Letters* **2018**, *59*, 216–223.

¹⁴⁷ See Chapter1, ref. 35, page 11.

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 26).¹⁴⁸

CO₂Et
$$R^2$$
 CO_2 Et R^2 CO_2 Et R^2 CO_2 Et R^2 R^2

Scheme 26. 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 27). 149 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 $C\alpha$ stereocenter.

¹⁴⁸ Schöllkopf, U.; Hantke, K. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 896–897.

¹⁴⁹ 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.

A)
$$RO_{2}C \longrightarrow EWG \qquad heat (or [Me]) \qquad RO_{2}C \longrightarrow EWG \qquad heat (or [Me]) \qquad R^{2}N \qquad R^{1} \qquad R^{2}N \qquad R^{2}$$

Scheme 27. 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 28). The electron-withdrawing group stabilizes the negative charge in the $C\alpha$ 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.

$$R^{1} \xrightarrow{CO_{2}R^{2}} EWG$$

$$R^{1} \xrightarrow{R^{1}} EWG$$

$$R^{1} \xrightarrow{R^{1}} NC \text{ insertion}$$

$$Stabilized carbanion$$

$$EWG$$

$$N^{*} CO_{2}R^{2}$$

$$Stabilized carbanion$$

$$[3+2] cycloaddition product$$

Scheme 28. 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 8).¹⁵⁰

In these works, only very specific Michael acceptor have been employed and mainly with α -aryl isocyanoacetates. Shi and collaborators extended the addition to Naryl maleimides employing squaramide bifunctional bronsted bases, ^{150c} 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 8, 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 R² postition.

¹⁵⁰ 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.

Table 8. Reported asymmetric Michael additions of α -substituted isocyanoacetates that stop at the acyclic adduct.

$$R^{1} \xrightarrow{CO_{2}Alk} + \underbrace{EWG} \xrightarrow{Cat^{*}} \left[AlkO_{2}C \xrightarrow{EWG} \right] \xrightarrow{Protonation} AlkO_{2}C \xrightarrow{EWG}$$

	Electrophile	Cat.*	Product	Results	Ref
1	NR^2 $R^2 = Ar, Alk$	CF ₃ S N N N N N N N N N N N N N N N N N N	AlkO ₂ C NR^2 R^1 NC O 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	 150a
2	SeO₂Ph	"Buo N HO N (10 mol%)	MeO_2C SeO_2Ph R^1 NC R^1 = only Ar	62-96% 75-96% ee	150b
3	F_3C R^2 $R^2 = Ar$, $-CH_2CH_2Ph$	(20 mol %)	AlkO ₂ C R^1 NC R^2 R^1 = Ar, Bn	$R^{1}/R^{2} = Ar/Ar$ $45-97\%$ $>21:1 dr$ $79-99\% ee$ $R^{1} = Bn, 2 MeC_{6}H_{4}$ No reaction $R^{2} = -CH_{2}CH_{2}Ph$ No reaction	. 150d

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 44).

Significally, a brief review of the precedents reported related to the possible transformations with this type of compounds (Scheme 26 and Scheme 27, 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 29). 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 $C\alpha$ to this isocyano, giving rise Δ^4 -dehydroprolines by means of a two-step cycloaddition.

Scheme 29. 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 30, right). In addition, a sole example was known related to the [3+2] cycloaddition variant of these substrate partners affording the corresponding Δ^4 -

dehydroproline products with moderate (52-74% ee, R^1 = H) or poor (16-36% ee, R^1 = Bn) enantioselectivity (Scheme 30, left). ¹⁵¹

Scheme 30. State of the art.

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 8) and vinyl selenones (entry 2, Table 8). 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 (See, Scheme 29).

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 9). While **C1-C4** catalysts (DHQ₂Pyr, (–)-Quinine, thiourea and

¹⁵¹ See ref. 115, Chapter 1, page 39.

ureidopeptide) gave essentially no stereocontrol, the squaramide **C5** provided the product with good enantiopurity (86% *ee*).

Table 9. Screening of H-bond donors.

[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 1H -RMN spectroscopy and the ee values by chiral HPLC on the reaction crude. [b] Reaction carried out at 0 $^{\circ}$ 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). 152

¹⁵² 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.

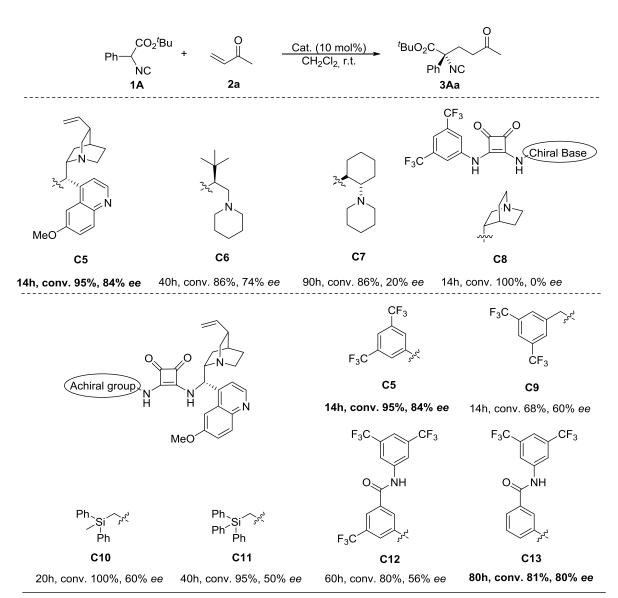
Figure 21. Activation model proposed by Zhong and Schreiner.

From the results using squaramide bases **C5-C8**, the first one was the most appropriate given product **3Aa** with 84% *ee* (Table 10, 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. 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. 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.

¹⁵³ Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138*, 3282–3285.

¹⁵⁴ 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 10. Screening of the chiral Brønsted base and the achiral motif.



[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 1H -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.¹⁵⁵ 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.¹⁵⁶

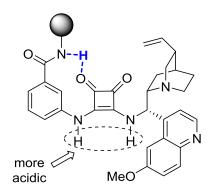


Figure 22. Internal H- bond interaction.

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 31). 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.

¹⁵⁶ 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.

¹⁵⁵ 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.

Scheme 31. Synthesis of *ortho*-substitued amide catalysts **C14-C19**.

Results with the newly prepared catalysts **C14-C19** are collected in Table 11. 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% *ee* 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 11. Screening of *ortho*-substitued amide catalysts.

[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 1H -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 12), it was discovered that for a successful addition of the Grignard reagent to the ester group, the amine had to be acetylated previously.

Table 12. 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 32. 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 loading 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 32. General procedure for synthesis of new catalysts.

As shown in the Table 13 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 13. Screening of catalysts containing tertiary alkoxy groups.

[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 1H -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.

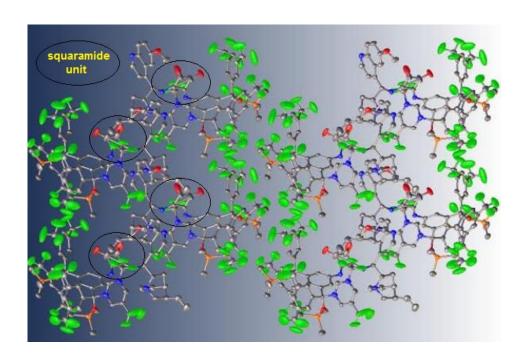
A comparison of the reaction progress using 2 mol% of catalysts **C5**, **C24** and **C26** demonstrated that both **C26** and **C24** were a little more active than **C5** (Figure 24). Although the reaction catalyzed by **C24** was faster, 2 mol% of catalyst **C26** was enough to obtain 90% of conversion 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 1H -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).¹⁵⁷ 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.



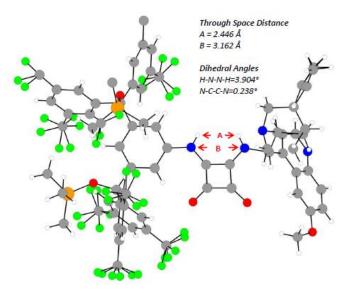


Figure 25. X-ray structure and extracted datas of the catalyst C26.

 $^{^{\}rm 157}$ 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

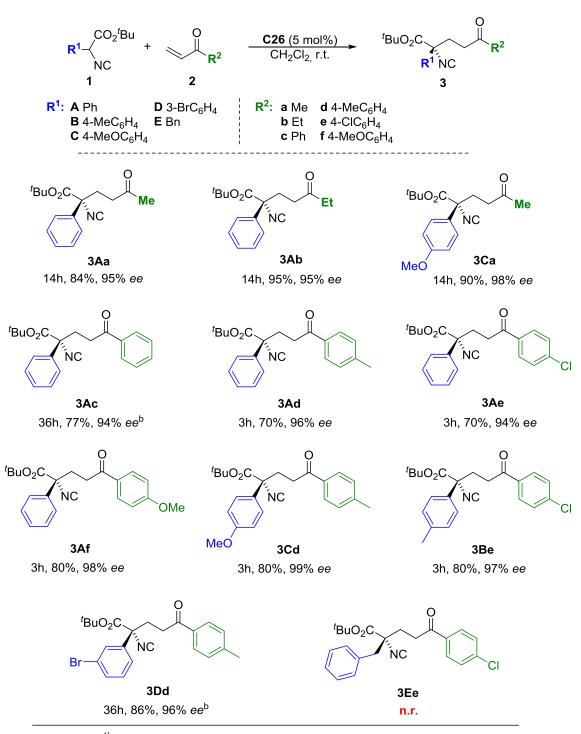
2.4.1. Vinyl ketones as Michael acceptors

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 14).

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. this reaction also did not tolerate α -alkyl substitution pattern in the nucleophiles (**3Ee**).

¹⁵⁸ See ref. 150d, page 60.

Table 14. Scope of the Michael addition involving vinyl ketones as Michael acceptor.



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 15). 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. 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 15. Michael addition to different α,β -unsaturated carbonyl compounds.

Entry	Acceptor	t (h)	Product	Conversion (%)	Yield (%)	ee (%)
1	O OMe	40	7	15	n.d.	n.d.
2	0 5	2	8	85	n.d.	34
3	O OH 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 1H -RMN spectroscopy and the ee values by chiral HPLC on the reaction crude.

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.¹⁶⁰ However, to

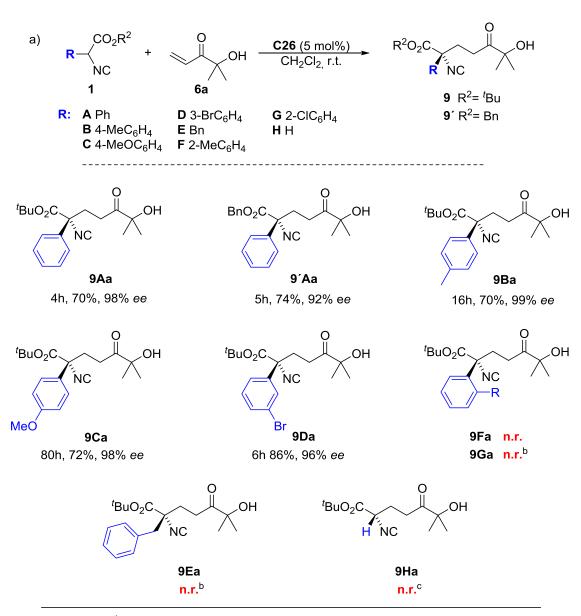
¹⁵⁹ Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garía, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.
 ¹⁶⁰ a) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189. b) Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*,

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 16 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.

^{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 16. Scope of the Michael addition involving α' -hydroxyeones as Michael acceptor.



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 17). 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 14, compound **3Ee**).

Table 17. Attempts of the Michael reaction with α - and β -substituted α' -hydroxyeones.

Ph
$$CO_2^{t}Bu$$
 R^1 O CH_2CI_2 , $60 \, ^{\circ}C$ Ph NC R^2 OH R^2

[a] Reaction conduced on a 0.2 mmol scale in 0.4 mL CH₂Cl₂ (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 8, entry 3, page 61).

2.4.3. Stereochemical course of the reaction

The mechanism of this catalytic reaction remains to be clarified. However, here we present a brief discussion about some plausible reaction stereomodels, based on the configuration of the resulting products (16, page 83 and 26, page 88) and also taking into account the transition-state models previously proposed for similar reactions involving isocyanoesters.

Figure 26 shows three pertinent TS proposals for metal-(a), 161 bifunctional BB/H-bonding (b), 162 and hybrid catalyst-(c) 163 mediated processes, respectively. In these models nucleophilic enolate gets activated through H-bonding to the protonated quinuclidine (b, c) while the isonitrile group coordinates to the metal (Ag $^{+}$) or a suitable H-bonding donor site. In its turn, the Michael acceptor is activated via metal coordination or H-bond.

¹⁶² See ref. 150b, page 60.

¹⁶¹ See ref. 113, page 39.

¹⁶³ See ref. 110a, page 39.

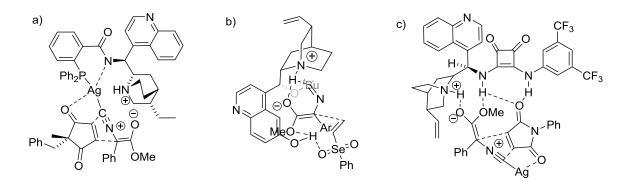


Figure 26. TS models previously proposed for similar reactions involving isocyanoesters.

By a similar taken, in our case two main stereomodels (A and B, Figure 27) could be considered, where the enolate is coordinated through the enol group and the isocyanide group. In one of the plausible transition-state model (A) the electrophile is H-bonded to the squaramide and the nucleophile coordinates to the tertiary amine, in a similar manner to Takemoto model. In model B the nucleophilic and eletrophilic reactants interchange their coordination positions relative to A, with the enolate H-bonded to squaramide group and the enone H-bonded to the protonated quinuclidine, in concordance to Pápai and Soós model. In both cases, a *Si*-face attack of the *Z* enolate to vinyl ketone would deliver the Michael adduct with an absolute *R* configuration.

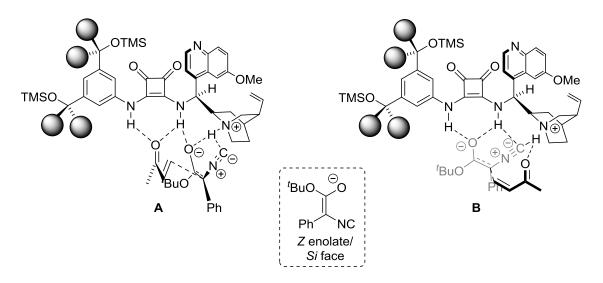


Figure 27. Possible transition-state models for the catalytic Michael addition.

¹⁶⁵ Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631–5639.

¹⁶⁴ Okino, T.; Hoashi, Y.; Takemoto, Y. J. Am. Chem. Soc. **2005**, 127, 119–125.

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.

2.5.1. Synthesis of α -quaternary Δ^5 -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 33). Thus treatment of adducts with concentrated hydrochloride acid, led in all cases tested, the corresponding product **10-13** in good yields.

Scheme 33. 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. 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 18, entry 1). Instead, exposure of **10** to H₂ over Pd on charcoal gave product **14** with an excellent diastereomeric ratio and good yield (Table 18, 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 28). 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 18, 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 18. Reduction of dehydroprolines **10-11** to α -quaternary prolines **14-15**.

Reductor, solvent, T (°C) 16 h

10 R: Me 11 R: Et 15 R: Et
$$trans$$

Entry	R	Reductor	Solvent	Temp. (°C)	cis:trans	Product	Yield (%)
1	N4-	L-Selectride	THF	–78→r.t.	1:1	1.4	
2	Me	Pd/C, H ₂	EtOH	r.t.	>20:1	14	80
3	Et	Pd/C, H ₂	EtOH	r.t.	>20:1	15	75

Figure 28. 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 34. Reduction of α -quaternary Δ^5 -dehydroprolines.

2.5.2. Synthesis of α -quaternary Δ^4 -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 35).

a) Previous work: Ito, 1991

Scheme 35. 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 19) owing to the success of these reagents on other cycloadditions reactions. 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 AgNO₃ 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 Et₃N and DIPEA the reaction was incompleted after 5 h, in DBU and P₄^tBu 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.

¹⁶⁸ See Table 7, Chapter 1, page 40.

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¹⁶⁷ See ref. 149f, page 58.

Table 19. Screening of reaction conditions for the synthesis of Δ^4 -dehydroproline scaffold.

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	35
3	Agi	DIPLA	24	95
			5	25
6	AgF	Et_3N	24	50
			100	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 20). 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 20. Scope of the transformation of adducts into α -quaternary Δ^4 -dehydroprolines.

CO₂tBu CO₂^tBu CO2^tBu 19 20 21 92% 85% 85% HQ CO2^tBu CO2^tBu CO2^tBu OMe 22 23 24 88% 78% 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

Pyroglutamates¹⁶⁹ bearing α -quaternary stereocenter serve as the core structures in many natural alkaloids and bioactive molecules, as for example Oxazolomycin A¹⁷⁰ or previously mentioned Salinosporamide A¹⁷¹ 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 17.

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. 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 36).

Scheme 36. 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 $NalO_4$ 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 15, 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 37).

87

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 32. g) See ref. 99, Chapter 1, page 33.

¹⁷⁴ a) ref. 159, page 77. b) ref. 160, page 77.

Scheme 37. 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 28, 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

 $\begin{array}{c} \text{Catalytic addition reactions of } \alpha\text{-alkyl} \\ \text{isocyanothioacetates: enantioselective synthesis of} \\ \alpha\text{-quaternary dehydroprolines and imidazolines} \end{array}$

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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 38). 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 38. The basic pathway of fatty acid and polyketide biosynthesis.

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 units¹⁷⁶. In addition, thioesters are also rather reactive acyl-transfer agents¹⁷⁷, 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 29).

Figure 29. 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.

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

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

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 39, 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 39, b).

a) Condensation in polyketide biosynthesis

b) Asymmetric catalytic approach

$$\begin{array}{c|c}
 & O & O \\
 & R'S & O' & \\
\hline
 & R'S & R$$

Scheme 39. Decarboxylative Claisen condensation with malonic acid half thioesters and its implementation into asymmetric C-C bond technologies.

Based on this approach catalytic asymmetric aldol (Table 21, entry 1-2), ¹⁷⁸ Michael (Table 21, entry 3), 179 and Mannich (Table 21, entry 4-5) 180 reactions involving addition of MAHTs, including organocatalytic methods, have been developed. 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 21. Representative catalytic asymmetric addition of MAHTs.

$$R^2S$$
 OH + Electrophile Cat^* R^2S R^2S R^2S R^2S R^2S

	Electrophile	Cat.*	Product	Results	Ref.
1		O N N Ph (13 mol%) Cu(OTf) ₂ (10 mol%)	PhS $\stackrel{\overset{\circ}{=}}{\underset{\overset{\circ}{=}}{\stackrel{\circ}{=}}} R^3$ $\stackrel{\circ}{=}$ Ar, Alk	59-83% 2.2:1-36:1 dr 89-96% <i>ee</i>	178b
2	Q R ³ H	O S N N N	PhS \mathbb{R}^3 \mathbb{R}^1 \mathbb{R}^3 \mathbb{R}^4 \mathbb{R}^3 = Ar, Alk, Allyl	$\frac{R^{1}=H/R^{3}=Ar}{61-96\%}$ $89-96\% \ ee$ $\frac{R^{1}=}{Me/R^{3}=Ar}$ 31%, 5:1 dr $97\% \ ee$	178c
		(30 mol%)	IX - AI, AII, AIIYI	$\frac{R^3 \neq Ar}{16-32\%}$ 73-91% ee	
3	R^3 NO $_2$	CF ₃ O N N N N N N N N N N N N N N N N N N	O R^3 NO_2 $R^1 = H$ $R^2 = p\text{-OMeC}_6H_4$ $R^3 = Ar, Alk$	23-93% 61-90% ee	179
4		N N HO (20 mol%)	O HN Ts R^2S R^3 R^3 $R^4 = H$ $R^2 = p\text{-OMeC}_6H_4$, $p\text{-CIC}_6H_4$ $R^3 = Ar, Ph(CH_2)_2$	47-84% 51-79% ee (R ³ =o- BrC ₆ H ₄ : 21-38% ee)	180a
5	Ts N R ³	tBu N N tBu H (10 or 20 mol%)	O HN Ts t_{BuS} R^1 R^1 R^3 R^3 R^3 R^3	$\frac{R^{1} = H}{43-85\%}$ >20:1 dr $85-97\% \ ee$ $\frac{R^{1} \neq H}{37-70\%}$ 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, Wennemers and co-workers have employed MTMs in catalytic asymmetric Michael (Table 22, entries 1-2)¹⁸¹ and Mannich (Table 22, entries 3-4)¹⁸² reactions giving rise products containing a α -quaternary stereocenter in several instances.

Table 22. Representative catalytic asymmetric addition of MTMs.

$$R^2S$$
 R^1 + Electrophile R^2S R^2S R^1

	Electrophile	Cat.*	Product	Results	Ref.
1	> NO	CF ₃ S N N	after decarboxylation: O R^3 PMPS NO ₂ R ³ = Ar, Alk	82-98% 91-99% <i>ee</i>	181a
2	R ³ NO ₂	(<5 mol%) (R ³ = Alk: 20 mol%)	PMPS NO_2 PMBO O $R^3 = Ar$	70-87% 3:1-10:1 dr 92-99% <i>ee</i>	181c
	Cbz _N		after decarboxylation: O HN Cbz PMPS Ar R ¹ = H	62-93% 90-99% ee	
3	N Ar	F ₃ C N N N N N N N N N N N N N N N N N N N	PMPS Ar PMBO O R ¹ = Alk	51-99% 6:1->20:1 dr 90-99% <i>ee</i>	182a
4	$X \stackrel{\text{N-Cbz}}{=} O$	MeO (<5 mol%)	O SPMP Cbz NH Alk CO ₂ PMB NR ³ R ³ = H, Me, Ac, Allyl, Boc	42-96% 4:1->20:1 dr 73-99% ee	182b

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.* **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 23). These reagents could be applied as donors in asymmetric Michael additions involving α,β -unsaturated aldehydes¹⁸³ and in Mannich additions involving sulphonyl imines¹⁸⁴. 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. 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 23. Representative catalytic asymmetric addition of arylacetic thioesters.

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

2

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	OSiMe ₃	Ar ¹ Ar ² = 4-OMeC ₆ H ₄ Ar ² = 4-OMe-3,5-(Me) ₂ C ₆ H ₂ (20 mol%)/ 4-nitrobenzoic acid (20 mol%)	^t BuS Alk CHO	60-76% 88-96% ee	183d
4	PhS Ar ¹	Nap-1 0 N Ar N Ar H H H H H H H H H H H H H H H H H H	O HN Ts PhS = Ar ² Ār ¹	82-97% 19:9-98:2 dr 90-98% <i>ee</i>	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 40). 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 40. Reaction pathways of β , γ -unsaturated carboxylic acid derivative nucleophiles additions.

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 two works, one developed by Alemán¹⁸⁶ and the other by our group,¹⁸⁷ where in Brønsted base catalyzed α -functionalization of β , γ -unsaturated carbonyl compounds with three potentially reactive sites (α , γ and α) has proceeded in a stereocontrolled manner. 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 41). In the study previously carried out by Tan and collaborators, the asymmetric addition of β , γ -unsaturated thioester to azodicarboxylate compounds was γ -selective. ¹⁸⁸

PhX
Ph
Ph
NO₂
Cat*
(10 mol%)
CH₂Cl₂
Ph
Ph
NO₂
A-product
$$\alpha / \gamma$$
 α -product
 α / γ
 α -product
 α -p

Scheme 41. 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 42). 189

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¹⁸⁶ Frias, M.; Mas-Ballesté, R.; Arias, S.; Alvarado, C.; Alemán, J. *J. Am. Chem. Soc.* **2017**, *139*, 672–679.

¹⁸⁷ Iriarte, I.; Olaizola, O.; Vera, S.; Gamboa, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864.

¹⁸⁸ Wang, J.; Chen, J.; Kee, C. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 2382–2386.

¹⁸⁹ Rotstein, B. H.; Winternheimer, D. J.; Yin, L. M.; Deber, C. M.; Yudin, A. K. *Chem. Commun.* **2012**, *48*, 3775–3777.

HN
$$\stackrel{\text{OH}}{=}$$
 $\stackrel{\text{OH}}{=}$ $\stackrel{\text{OH}}{=}$

Scheme 42. 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 43). ¹⁹⁰ 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 43. 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.

¹⁹⁰ 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 45). 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 $C\alpha$, 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 C α 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 44). Finally, to demonstrate thioester isocyanides generality and synthetic utility, several electrophiles, such as vinyl sulphones and imines with different reactivity would be studied.

Alk NC
$$R^1$$
 O R^1 O R^2 O R^2

Scheme 44. 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. Hence, we started with the preparation of thiophenylester-isocyanides following the reactions sequence shown in Scheme 45 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.

¹⁹¹ 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.

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Scheme 45. 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 24, 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 24. Conditions for the formylation step.

Entry	R	Formylation conditions	Yield of formyl products (%)	Byproduct	
1	Me	1. NaHCO₃ sat.	16%	Yes	
1	ivie	2. HCO₂Et, 6 h ,reflux	10%	res	
2	Me	1. NaHCO ₃ sat.	Mossy	Yes	
2	ivie	2. HCO_2H , I_2 , 6 h ,reflux ¹⁹²	Messy	163	
3	Me	HCO₂H, Si(OEt)₄, Et₃N CH₃CN, r.t. ¹⁹³	Messy	Yes	
	Me		85	No	
4	Bn	1. HCO ₂ H/EDCI, CH ₂ Cl ₂ 2. NMM, 5 °C, 16 h ¹⁹⁴	94	No	
	ⁱ Bu	2. INIVIIVI, 3 C, 10 II	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 25, entry 1). Similar results were obtained with SO₂Cl/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**.

¹⁹² Kim, J.-G.; Jang, D. O. *Synlett* **2010**, *14*, 2093–2096.

¹⁹³ Nishikawa, Y.; Nakamura, H.; Ukai, N.; Adachi, W.; Hara, O. *Tetrahedron Lett.* **2017**, *58*, 860–863.

¹⁹⁴ Chem, F. M. F.; Benoitton, N. L. *Synthesis* **1979**, *9*, 709–710.

Table 25. Conditions for the dehydration step.

Entry	Alk	Conditions	Product	Yield (%)
1	POCl ₃ , DIPA		27A	Messy
1	ווט	CH ₂ Cl ₂ , –30 °C, 2 h ¹⁹⁵	2/8	iviessy
2	Bn	SO₂CI, DMAP	27A	Messy
2	ы	CH ₂ Cl ₂ , –30 °C, 2 h ¹⁹⁶	2/A	iviessy
	Bn		27A	60
3	Me	Triphosgene/NMM	27B	62
3	ⁱ Bu	–78 °C, 2 h ¹⁹⁷	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 30).

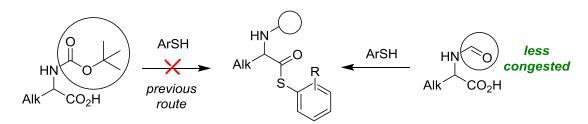


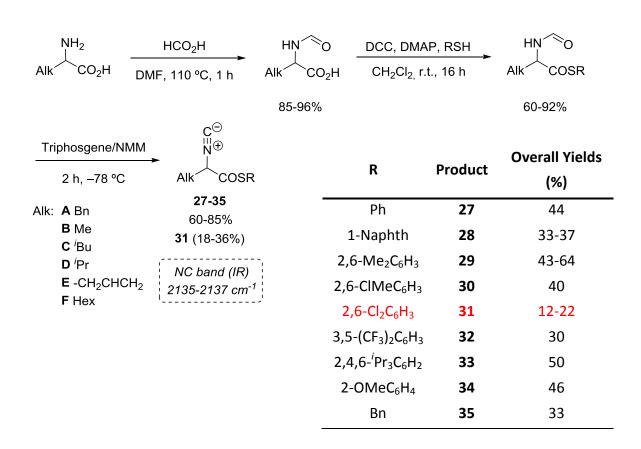
Figure 30. Strategy for the formation of the thioester group.

¹⁹⁵ Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.

¹⁹⁶ Arrieta, A.; García, T.; Palomo, C. *Synth. Commun.* **1982**, *12*, 1139–1146.

¹⁹⁷ Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.*, **2009**, *50*, 577–579.

Following the reactions sequence shown in Scheme 46 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 198, 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. 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.



Scheme 46. Synthetic route for α -substituted aryl isocyano thioacetates.

Eventually it was found that this route was also applicable to α-benzyl phenylthioesterisocyanide (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

¹⁹⁸ Aizpurua, J. M.; Palomo, C. Synth. Commun. **1983**, *13*, 745–752.

¹⁹⁹ 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 7, page 40). 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 47). 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.

Pyroglutamate esters

OH

$$OH$$
 OH
 OH

Scheme 47. 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 48). 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 8, page 61, 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, isocyanothioacetates would be applied in the conjugate addition to vinylsulfones, an unexplored reaction to date.

Alk NC BB* Alk NC
$$R^2$$
 Acid R^2 $Acid$ $Acid$

Scheme 48. 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.

COXR
$$Ar/Alk$$
 Ar/Alk Ar/Al

Figure 31. 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 49). 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 49. 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 49. 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 50). In these instances by products analogs to **37A** and **38** were not observed. Instead, a new byproduct **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%).

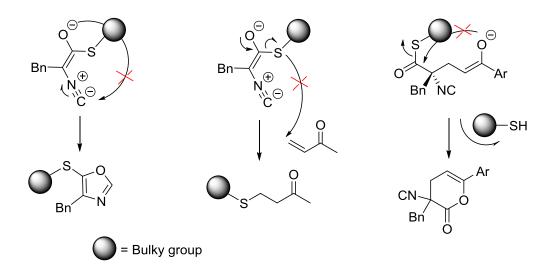
Scheme 50. Catalytic asymmetric Michael addition of **27A** to aryl vinyl ketones **2c-d**.

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 51).

Scheme 51. 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 52).



Scheme 52. Strategy to avoid the formation of by-products.

For that purpose, α -akylisocyanothioacetates with more sterically demanding thiols, namely 1-naphthyl, 2,6-Me₂C₆H₃ and Bn groups, were prepared and evaluated (Table 26). 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 26. Substrate optimization for the Michael addition to methyl vinyl ketone **2a**. ^a

	Isocyanothioa R ²	cetate	Products Products ratio		Yield (%) ^b	ee (%)
1	274	27A	36Aa:37A:38	38:24:38	30	68 ^b
2		28B	44Ba:47B:48	0:57:43		- -
3	Zri,	35B	46Ba	100:0:0	62	88
4	22	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 27) 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 27. Substrate optimization for the Michael addition to aryl vinyl ketones 2c-d. ^a

R1: **A** Bn **B** Me **C** Bu **D** Pr

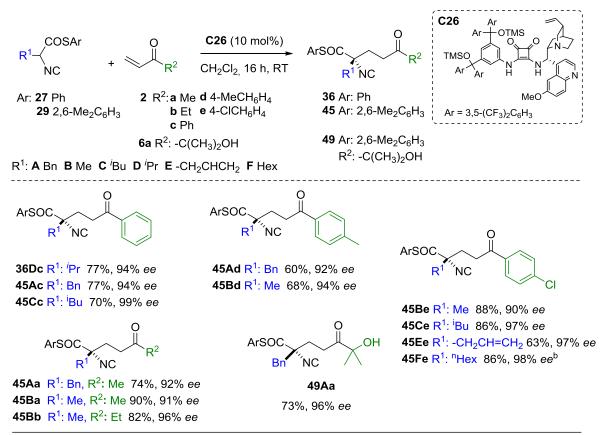
	Isocyanothioacetate R ²		Vinyl	Products	Products	Yield	ee
			ketone	Products	ratio	(%) ^b	(%)
1		27A	2c	36Ac:39Ac	75:25	40	90
2		27A	2d	36Ad:39Ad	85:15	60	94
3		27B	2d	36Bd:39Bd	75:25	41	93
4	>	27C	2c	36Cc:39Cc	80:20	52	96
5		27D	2 c	36Dc:39Dc	90:10	74	98
6	32%	29A	2 c	45Ac	100:0	77	94
7		29A	2d	45Ad	100:0	70	92 ^c

[a] Reaction conduced on a 0.1 mmol scale in 0.4 mL CH₂Cl₂ (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 28). 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 28. Reaction scope of α -alkyl isocyanothioacetates asymmetric Michael addition to vinyl ketone. ^a



[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 16, page 79, compounds **9Fa** and **9Ga**). However, as shown in Scheme 53, 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 53.

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. 200

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 82-113).

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 54).

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 8, entry 1, page 61), 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 54. 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 55. 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, 201 including asymmetric versions. 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 56). As alternative routes to enantiopure α,α -dialkyl amino acids, the

²⁰¹ 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.

²⁰² 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)²⁰³ and the Strecker reaction involving ketimines²⁰⁴ are the most commonly employed.

PGN
$$CO_2R^2$$
 + SO_2R^3 PGN CO_2R^2 Alk SO_2R^3 Elimination PGN CO_2R^2 Alk α -Alkyl AA Alk α -Dialkyl AA A

Scheme 56. 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. 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 57). 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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²⁰³ a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *8*, 3013–3028. b) see Chapter 1, ref 103b, page 35.

²⁰⁴ 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.
²⁰⁵ See Chapter 1, ref. 90, page 27.

²⁰⁶ 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 57. 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 bissulfones²⁰⁷ 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.

 $\textbf{Scheme 58.} \ \ \text{Enantioselective catalytic conjugate addition of } \alpha\text{-alkyl azlactones to vinyl sulfones}.$

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

²⁰⁷ Alba, A.-N. R.; Compayó, X.; Valero, G.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2010**, *16*, 5354–5361.

Chapter 2, Table 8, page 61), 208 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 29). Phenylsulfonylethylene was initially selected as model acceptor, ²⁰⁹ but it displayed very low reactivity (entry 1). Then the comparatively more reactive geminal bis-sulfone group was tested, ²¹⁰ 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. ²¹¹ Specifically, it has been demonstrated that sulfones with a phenyltetrazole ring at the sulfur atom are more reactive and show interesting sythetic possibilities, ²¹² 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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See: a) ref 150b, 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.

²⁰⁹ See ref. 201, page 117.

²¹⁰ 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. 206b, page 118. g) see ref. 207, page 118.

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.

²¹² 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 29. Screening of vinyl sulfones.^a

PT= 1-Phenyl-1 H-tetrazol-5-yl

Entry	Vinyl sulfone	Conditions	Product	Results
1	SO ₂ Ph 53	r.t., 16 h	56	No reaction
2	SO_2Ph SO_2Ph 54	−20 °C, 2 h	57	Messy crude
3	O=S N-N N-N S S N-N	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 30, 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 30, reaction b), so the thioester group at the nucleophile resulted essential.

Table 30. Screening of the (thio)ester group. ^a

a)
$$\begin{array}{c} \text{COSR} \\ \text{Bn} & \text{COSR} \\ \text{NC} \\ & \text{28-32,35} \\ \text{A Bn} \\ & \text{PT= 1-phenyl-1} \\ \text{H-tetrazol-5-yl} \end{array} \begin{array}{c} \text{C26} \\ \text{(10 mol\%)} \\ \hline \text{Toluene} \\ \text{r.t, t (h)} \\ \hline \text{RSOC} \\ \hline \text{Bn NC} \\ \hline \text{Bn NC} \\ \\ \text{TMSO} \\ \\ \text{Ar = 3,5-(CF_3)_2C_6H_3} \\ \text{MeO} \\ \\ \text{Ar = 3,5-(CF_3)_2C_6H_3} \\ \\ \text{SR : 2,6-ClleC}_{6}H_{3} \\ \\ \text{SR$$

Entry	Nucleophile	R	t (h)	Product	Yield (%)	ee (%)
1	29A	72	48	56	47 (70) ^b	44
2	31A	CI Z ₂ CI	16	57	90	62
3	30A	CI	16	58	60	65
4	28A	7.7	16	59	61	40
5	35A	35	48	60	43	28
6	32A	CF ₃	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 31). 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 31. Screening of catalysts.

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

$$F_3$$
C F_3 F_3 C F

[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. Along the process, imines work as electrophilic reagents and β -amino carbonyl compound with up to two new stereogenic centers can be generated (Figure 32).

Figure 32. General Mannich reaction.

Many approaches have been developed to afford asymmetric Mannich reactions. Some of them are based on the use of chiral auxiliaries, ²¹⁴ but in the last decades catalytic asymmetric Mannich methodologies have been developed based on the use of metal catalysts ²¹⁵ or organocatalysts, particularly enamine mediated methods using aldehydes and ketones as donor carbonyl components. ^{216,217}

²¹³ 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.

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.

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.

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, important structural motifs that are contained in many biologically active compounds (see Chapter 1, section 1.4, page 41). 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 59). Several α -AA surrogates (particularly α -carboxy azomethine ylides, and introesters, and isothiocyanates being underdeveloped 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.

²¹⁷ 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. ²¹⁸ See Chapter 1, ref. 124, page 44.

²¹⁹ 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.

²²⁰ 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.

²²¹ 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.

²²² 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.

Ar
$$CO_2R'$$
 R^1 CO_2R' PG N NCS $Cat.* R^2 R^3 RO_2C $NHPG$ R^1 NCS R^2 R^3 RO_2C $NHPG$ R^1 NCS R^2 R^3 RO_2C R^2 R^3 RO_2C R^2 R^3 RO_2C R^2 R^3 RO_2C R^3 RO_2C R^4 $R^4$$

Scheme 59. 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. ²²³ 2-Imidazolines may be formed by catalytic asymmetric Mannich addition/cyclization reactions between isocyanoacetates and imines (Scheme 60).

Scheme 60. 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 compounds²²⁴ and they are useful for the synthesis of cyclopalladated complexes, chiral catalysts and chiral solvating agents as well.²²⁵ Due to these practical interests, chemists

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.

²²³ 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.

²²⁵ 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. In 1996 Hayashi et al. reported the Au(I)-catalyzed *cis*-diastereoselective Mannich reaction of isocyanoacetates with *N*-sulfonylimines and the following studies showed that the diastereoselectivity depends closely on the catalyst used. 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 32. ²²⁹ In 1999, Lin et al. found that the reaction between ethyl isocyanoacetate and *N*-Tosyl aldimines can be catalyzed by Me₂SAuCl 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.

²²⁶ Meyer, R.; Schöllkoptf, U.; Bohme, P. *Justus Liebigs Ann. Chem.* **1977**, 1183–1193.

²²⁷ Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969–4972.

²²⁸ 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.

²²⁹ 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 32. Asymmetric Mannich reactions of isocyanoacetates with imines promoted by metal catalysts.

$$R^{1}$$
 $CO_{2}R$
 R^{2}
 R^{3}
 EWG
 $RO_{2}C$
 R^{3}
 R^{1}
 R^{2}
 R^{3}

	Electrophile	Cat.*	Product	Results	Ref
1	.,_Ts	Me Me Me PPh ₂ Me PPh ₂ N (0.5 mol%)/ Me ₂ SAuCl (0.5 mol%)	N∕N∕Ts EtO ₂ C Ár	79-91% 85:15-96:4 dr 46-88% ee	229a
2	Ar Ts	(1 mol%)	$N \sim N$ MeO ₂ C Ar Ar = Ph	98% 1:4 dr 75% ee	229c
3	$R = \begin{cases} X \\ 0 \\ 0 \end{cases}$	PPh ₂ N MeO (20 mol%)/ Ag ₂ O (10 mol%)	MeO ₂ C O	84-92% 20:1 dr 93-91% <i>ee</i>	229e
4	N P(O)Ph ₂	(20 mol%)/ Ag ₂ O (5 mol%)	$P(O)Ph_2$ $N P(O)Ph_2$ $MeO_2C R$ $R = Ar$	70-98% 73:27-99:1 dr 90-99% ee	229d

	Electrophile	Cat.*	Product	Results	Ref
		F ₃ C N H	N P(O)Ph ₂	R: Ar (syn) 44-68% 81:19-92:8 dr 91-99% ee	_
5		(10 mol%)/ Cu(OTf) ₂ (10 mol%)/ Cs ₂ CO ₃ (20 mol%)	MeO₂C Alk syn	R: Alk (anti) 54-78% 40:60-28:72 dr 93-95% ee	229f
6	N P(O)Ph ₂	(10 mol%)/ NiCl ₂ (10 mol%)/ Cs ₂ CO ₃ (20 mol%)	AlkO ₂ C'') Alk R R= Alk, Ar	68-99% 85:15-99:1 dr 8092% ee	229g
7		N H PPh ₂ MeO (10 mol%)/ AgOAc (5 mol%)	N-P(O)Ph ₂ *BuO ₂ C'') Alk R R= Ar, -CH ₂ CH ₂ Ph	48-90% 98:2 dr 87-95% <i>ee</i>	229h

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 33 are known, 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

²³⁰ 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 33. Asymmetric Mannich reactions of isocyanoacetates with imines promoted by organocatalysts.

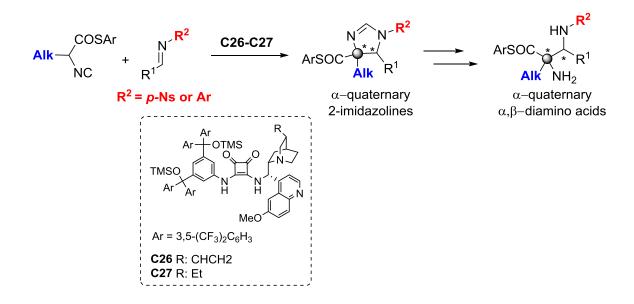
	Electrophile	Cat.*	Product	Results	Ref.
1	N Ts Ar	0 N N (10 mol%)	MeO ₂ C Ar	34-79% 91:9-99:1 dr 5-70% ee	230a
2	O O			<u>R= Ar</u> 71-99% 81:19-99:1 dr 74-96% <i>ee</i>	230b
	Ar	CF ₃ S N	MesO ₂ C' $\stackrel{\checkmark}{R}$ Ar Mes: 2,4,6-Me ₃ C ₆ H ₂ R= Alk, Ar	R= Alk 73:27-99:1 dr 78-88 % <i>ee</i> (R= 'Pr: no reaction)	
3	Boc N N N R	(10 mol%)	AlkO ₂ C N R^{1} N-Boc $X = 0$	55-90% 20:1 dr 69-98% <i>ee</i>	230c
			N R' R ¹ = Ar	R ¹ = Bn, 2- BrC ₆ H ₄ : no reaction	
4	N Boc Ar	1) Mannich reaction: CF3 PPh2 (0.5 mol%)/ Methyl acrylate (0.5 mol%) 2) Cyclization: AgOAc (10 mol%)/ PPh2Me (20 mol%)	AlkO ₂ C $\stackrel{\text{N}}{\longrightarrow}$ Ar R = Ar	85-98% 1.1:1-9:1 dr 50-93% ee	230d

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 61).



Scheme 61. 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 34). 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 34. Substrate optimization for the Mannich reaction with *N-p*-Nosyl aldimines.^a

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.		
2		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_2CI_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 35). The Mannich reaction with catalyst **C26** in toluene as solvent (97:3 dr and 70% ee) 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 35. Study of reaction conditions for the addition of 30A to 64.

[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.

98

80:20

16

29

Toluene

r.t.

6

Unfortunately, the bulkier α^{-1} Pr isocyanothioacetate **27D** resulted inactive under the present catalytic conditions (Scheme 62), even heating at 50 °C.

32

Scheme 62.

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 33), 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 32, page 129 and Table 33, page 131).

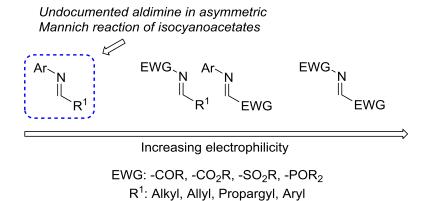


Figure 33. Classification of aldimines according to their electrophilicity/reactivity.

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,²³¹ or alternatively can be partially or totally

²³¹ 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). ^{231b} 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. ²³² These features make the resulting propargylamine adducts potentially versatile building-blocks in the synthesis of natural products, ²³³ drugs²³⁴ and pesticides, ²³⁵ as well as a number of bioactive compounds. ²³⁶

Enamine-mediated Mannich methodology involving propargylic imines has been previously developed in our laboratory using a new type of α,α -dialkylprolinol catalysts (Scheme 63). ^{231d}

Scheme 63. 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 64).

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

²³² 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.

²³³ 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.

²³⁴ 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. ²³⁵ Swithenbank, C.; McNulty, P. J.; Viste, K. L. *Agric. Food. Chem.* **1971**, *19*, 417–423.

²³⁶ 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.

Alk NC
$$R^2$$
 C (BB^*) R^1 R^2 C (BB^*) R^1 R^2 R^2 R^2 R^3 R^4 R

Scheme 64. 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 36). 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 49, page 110), derived from the intramolecular hydroalkoxylation of the isonitrile group.

Table 36. Screenig of propargylic *N*-aryl imines.^a

45:55

4/3

[5]

69e

20

messy

[[]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 CH₂Cl₂, 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 34, 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 34). It should be noted that this imine was soluble in CH₂Cl₂ 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.

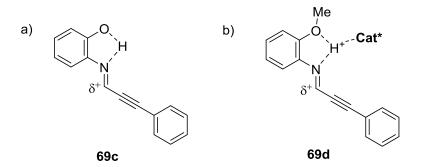


Figure 34. Speculative models to justify the increase of reactivity in 69c and 69d imines.

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 37 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 37. Screenig of the thioester group.

Entry	Isocyano thioacetate	Imine	С	t (h)	70:71	Yield of 70 (%)	dr	ee (%)
1	CI	69c	27	16	60:40	20	40:60	20/20
2	30A	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	Zrr ¹		27	16	Messy +			
6	MeO 34A	69c	5	16	71 traces Messy + 71 traces			
7	29A	69d	27	16	Messy + 71 traces			
8	Zer's	69c	5	72	Messy + 72Ac traces			
9	33A	69d	27	72	Messy + 72Ad traces			

[[]a] Reaction conduced on a 0.1 mmol scale in 0.2 mL CH_2CI_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 38). Surprisingly, we could observe by ¹H-NMR that changing the solvent from CH₂Cl₂ 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 38. Study of reaction conditions for the addition of 30A to 69d.

Entry	30A	69d	Solvent	t	70Ad:71	Yied of	dr	ee (%)
Entry	equiv.	equiv.	(mL/mmoL)	(h)	70Au.71	70Ad (%)	ui	CC (70)
1	1	1.5	CH ₂ Cl 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 35). According to this observation, we believe that the low chemical stability of adducts may be one of the causes of the unsatisfactory yields.

Figure 35.

Then, the reaction was extended to the corresponding α -aryl isocyanoacetates (Table 39). 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 39. 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 36) and that for the remaining adducts including those derived from α -akyl isocyanothioacetates (**70** and **72**) was assumed based on a uniform mechanism.

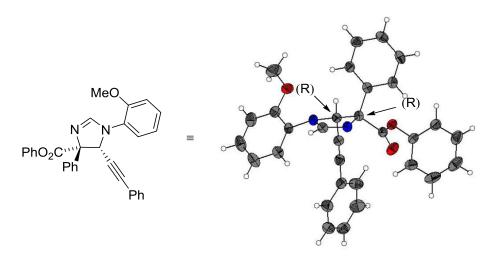


Figure 36. ORTEP diagram of compound 74.

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 oxoester.

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.²³⁷ Dichloromethane was dried over CaH₂, 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 $_2$ SO $_4$ 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.

155

²³⁷ 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 μ m 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) ([α]_D) are reported in 10⁻¹ deg.cm².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 CDCl₃, 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, ²³⁸ C4, ²³⁹ C5, ²⁴⁰ C6, ²⁴¹ C7, ²⁴² C9, ²⁴³ C10, ²⁴⁴ C11, ²⁴⁴ C12, and C13, 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

²³⁸ Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

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.

²⁴⁰ Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

²⁴¹ Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.

²⁴² Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241–1246.

²⁴³ See ref. 41, Chapter 1, page 13.

²⁴⁴ a) See ref. 153, 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.

²⁴⁵ a) See ref. 154a, 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)epiquinine²⁴⁶

1st step:²⁴⁷ 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 MgSO₄, 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:²⁴⁸ 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 NaN₃ (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 MgSO₄, filtered and evaporated under reduced pressure to obtain the

²⁴⁶ Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

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

²⁴⁸ 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.

 3^{rd} step:²⁴⁸ The azide derived crude product was dissolved in THF (250 mL) and PPh₃ (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 H₂O (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 MgSO₄ 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. ¹H NMR (300 MHz, CDCl₃), 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)epihydroquinine²⁴⁹

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. ¹H NMR (300 MHz, CD₃OD), 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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²⁴⁹ 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:

$$F_{3}C$$

$$NH_{2}$$

$$NH_{3}$$

$$NH_{4}$$

$$NH_{4}$$

$$NH_{4}$$

$$NH_{4}$$

$$NH_{4}$$

$$NH_{4}$$

$$NH_{5}$$

$$N$$

 1^{st} step:²⁵⁰ 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. ¹H 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 CH₂Cl₂ (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, CH₂Cl₂ (15 mL) was added and the mixture was washed with water (3 x 10 mL), dried with anhydrous MgSO₄ and the solvent was evaporated under reduced pressure. The product was submitted to purification by silica gel column chromatography (CH₂Cl₂/MeOH, 95:5), affording the catalyst **C8** as white solid (936 mg, 2.16 mmol, 72%). ¹H 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). ¹³C 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.

²⁵⁰ 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**.²⁵¹

 1^{st} step: METHOD A: 252 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 MgSO₄. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the title product.

²⁵¹ See ref. 245, page 157.

²⁵² 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 HCI (1 M) (2 × 30 mL) and brine (30 mL), dried over MgSO₄ and the solvent was eliminated under reduced pressure affording the desired amide.

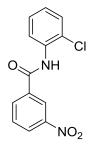
N-(2-(Trifluoromethyl)phenyl)-3-nitrobenzamide

Yield: 56% (method A). 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). H NMR (300 MHz, CDCl₃) 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

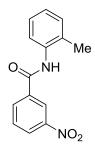


Yield: Quantit (method B). 1 H NMR (300 MHz, CDCl₃) δ 8.78 (t, J = 2.0 Hz, 1H), 8.54 – 8.49 (m, 1H), 8.48 – 8.42 (m, 2H), 8.26 (dt, J = 7.8, 1.3 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.0, 1.5 Hz, 1H), 7.38 (td, J = 8.4, 7.9, 1.5 Hz, 1H), 7.15 (td, J = 7.8, 1.6 Hz, 1H).

N-(2-Methoxyphenyl)-3-nitrobenzamide

Yield: 70% (method A). ¹H NMR (300 MHz, CDCl₃) 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). ¹H NMR (300 MHz, CDCl₃) 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), 7.80 – 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_2CO_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 \times 5 mL), dried over MgSO₄ and the solvent was eliminated under reduced pressure affording the desired

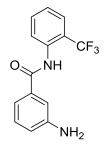
product. Yield: 84%. ¹H NMR (300 MHz, DMSO- d_6) δ 9.98 (s, 1H), 8.76 (t, J = 2.1 Hz, 1H), 8.49 - 8.33 (m, 2H), 7.84 (t, J = 8.0 Hz, 1H), 7.64 (dd, J = 7.8, 1.7 Hz, 1H), 7.22 (ddd, J = 8.7, 7.4, 1.7 Hz, 1H), 7.11 (dd, J = 8.2, 1.4 Hz, 1H), 6.99 (td, J = 7.6, 1.4 Hz, 1H), 6.14 - 5.97 (m, 1H), 5.42 (dd, 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 H₂ 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

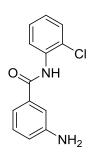


Yield: 75% (method A). 1 H NMR (300 MHz, CDCl₃) δ 8.43 (d, J = 8.3 Hz, 1H), 8.19 (s, 1H), 7.74 – 7.54 (m, 2H), 7.32 – 7.26 (m, 2H), 7.24 – 7.20 (m, 1H), 7.16 (ddt, J = 7.6, 1.5, 0.8 Hz, 1H), 6.87 (ddt, J = 7.9, 2.4, 0.8 Hz, 1H), 3.88 (brs, 2H).

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

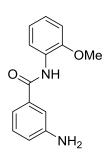
Yield: 56% (method A). H NMR (300 MHz, CDCl₃) δ 8.75 (d, J = 8.7 Hz, 1H), 8.36 (s, 1H), 7.93 – 7.81 (m, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.21 (t, J = 2.1 Hz, 1H), 7.15 (ddd, J = 7.7, 1.8, 0.9 Hz, 1H), 6.90 (ddd, J = 8.0, 2.4, 0.9 Hz, 1H), 3.90 (brs, 2H).

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



Yield: 88% (method B). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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). ¹H NMR (300 MHz, CDCl₃) 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%. ¹H 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).

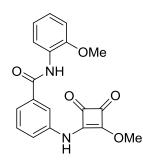
N-(2,4-bis(Trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino) benzamide

Yield: 82%. ¹H 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%. ¹H 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%. ¹H 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%. ¹H 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%. ¹H 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:

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, CD₂Cl₂) 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,

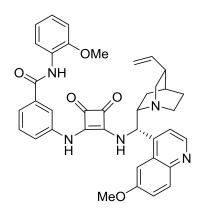
CD₂Cl2) δ 184.3, 181.6, 168.9, 165.2, 164.3, 159.0, 147.8, 145.1, 142.7, 140.1, 139.5, 138.9, 134.8, 131.9, 130.1, 130.0, 128.0, 126.7 (q), 125.4, 125.2, 124.0, 123.9, 122.8, 122.7, 121.8, 121.4, 118.0, 115.7, 101.5, 60.5, 56.3, 55.60, 4.38, 38.8, 27.5, 26.8, 25.6. UPLC-DAD-QTOF: $C_{39}H_{34}N_5O_4F_6$ [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 ¹H 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,

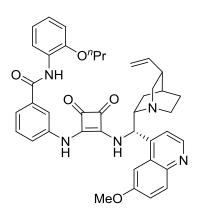
3H), 3.55 (s, 2H), 3.60 - 3.39 (m, 2H), 3.29 - 3.11 (m, 1H), 2.83 - 2.60 (m, 3H), 2.30 (d, J = 10.4 Hz, 1H), 1.70 - 1.40 (m, 4H), 0.75 - 0.59 (m, 1H). ¹³C NMR (101 MHz, DMSO- d_6) δ 184.1, 179.9, 168.1, 164.4, 163.6, 157.9, 150.8, 147.8, 144.3, 143.0, 142.0, 139.0, 135.7, 131.5, 129.6, 127.4, 126.8, 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). ¹³C 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). ¹³C 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**

1st **step:** To a solution 3-aminobenzoic acid (1.37 g, 10 mmol, 1.0 equiv.) in MeOH (10 mL) was added concentrated H₂SO₄ (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 %). ¹H NMR (400 MHz, CDCl₃) 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).

 2^{nd} step:²⁵³ To a solution of the obtained aniline (1.51 g, 10 mmol) and Et₃N (1.40 mL, 10 mmol) in CH₂Cl₂ (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 MgSO₄ 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. ¹H-

²⁵³ Adapted from: Yang, H.; Zhou, L.; Wang, P. *Photochem. Photobiol. Sci.***2012**, *11*, 514–517.

RMN (300 MHz, CDCl₃) 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:** ²⁵³ 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 NH₄Cl saturated solution and the solvent was evaporated under reduced pressure. The mixture was extracted with dichloromethane (3 × 10 mL), dried over MgSO₄ and concentrated under reduced pressure. After recrystallization from petroleum ether and CH₂Cl₂ the trityl alcohol was obtained as a brown solid (754 mg, 3.9 mmol, 78%). ¹H NMR (300 MHz, CDCl₃) 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 MgSO₄ 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, CDCl₃) 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, CDCl₃) 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 CH₂Cl₂ (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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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)

$$F_{3}C \xrightarrow{\text{CO}_{2}\text{H}} \xrightarrow{\text{HNO}_{3}} \xrightarrow{\text{H}_{2}\text{SO}_{4}} \xrightarrow{\text{H}_{2}\text{SO}_{4}} \xrightarrow{\text{RO}_{2}\text{H}} \xrightarrow{\text{HO}_{2}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{2}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}\text{HO}_{4}} \xrightarrow{\text{HO}_{4}\text{$$

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 $^{\circ}$ C over 15 min. The mixture was stirred at 35 $^{\circ}$ 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, CDCl₃) 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%). ¹H NMR (CDCl₃, 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 H₂SO₄ (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, CDCl₃) 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 Et₃N (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 MgSO₄ 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. ¹H-RMN (300 MHz, CDCl₃) 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

 1^{st} 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 NH₄Cl saturated solution, the solvent was evaporated under reduced pressure and diluted with water (20 mL). The mixture was extracted with CH₂Cl₂

(3 × 10 mL), the combined organic layers was dried over MgSO₄ 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, CDCl₃) 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 CH₂Cl₂ (3 × 10 mL), the combined organic layers were dried over MgSO₄ 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, CDCl₃) 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, CDCl₃) 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: $C_{25}H_{19}NO_{4}F_{3}$ [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 CH₂Cl₂ (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. ¹H 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). ¹³C 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

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 NH₄Cl saturated solution, the solvent was evaporated under reduced pressure and diluted wit water (20 mL). The mixture was extracted with CH₂Cl₂ (3 × 10 mL), the combined organic layers was dried over MgSO₄ 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). ¹³C 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: C₂₆H₁₅NO₂F₁₅ [M+H]⁺ calcd.: 658.0863, found: 658.0859.

 2^{nd} 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 CH₂Cl₂ (3 × 10 mL), the combined organic layers were dried over MgSO₄

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%). 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%). H NMR (300 MHz, CDCl₃) 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 CH₂Cl₂ (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 **C22** catalyst as a yellow solid (346 mg, 0.34 mmol, 68%). M.p.= 175-183 °C. ¹H 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). ¹³C 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: C₄₈H₃₆N₄O₄F₁₅ [M+H]⁺ calcd.: 1017.2497, found: 1017.2518.

Preparation of catalyst C24

$$F_3C$$
 F_3C
 F_3C

To a suspension of catalyst C22 (102 mg, 0.1 mmol, 1 equiv.) and DMAP (20 mg, 0.15 mmol, 1.5 equiv.) in CH₂Cl₂ (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, CH₂Cl₂ (2 mL) was added and the organic layer was washed twice with water and HCl 1M, dried over MgSO₄ 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. ¹H 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 = 9.3, 2.5 Hz11.4 Hz, 1H), 5.96 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.04 (d, J = 10.3Hz, 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). ¹³C NMR $(75 \text{ MHz}, \text{MeOD}) \delta 185.8, 181.3, 169.5, 166.0, 160.7, 149.1, 148.4, 145.5, 143.8, 141.6,$ 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

$$F_3C$$
 F_3C
 F_3C

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 MgSO₄ 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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

 1^{st} step: To a solution 5-aminoisophthalic acid (1.81 g, 10 mmol, 1.0 equiv.) in MeOH (20 mL) was added concentrated H₂SO₄ (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 MgSO₄, 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, CDCl₃) 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 Et₃N (1.0 mL, 6.84 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (2 × 10 mL) to provide the title compound as white solid (1.55 g, 6.16 mmol, 90%) which was used without further purification. ¹H 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 NH₄Cl saturated solution and solvent evaporated under reduced pressure. The resulting residue was extracted with CH₂Cl₂ (3 × 5.0 mL), and the combined organic layers were dried over MgSO₄ 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. ¹H NMR (300 MHz, CDCl₃) 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: C₄₂H₂₂NO₃F₂₄ [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 MgSO₄, filtered and the solvent was evaporated under reduced pressure to give the title compound as a brown solid (431 mg, 0.43 mmol, 85%). ¹H NMR (300 MHz, CDCl₃) 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

 1^{st} step: To a solution of the squaric ester monoamide prepared above (218 mg, 0.20 mmol) in CH_2Cl_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_2Cl_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_2Cl_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_2Cl_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 ($CH_2Cl_2/MeOH$ 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). ¹³C 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.= $160-168 \, ^{\circ}\text{C}$. ^{1}H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C27)

Ar OTMS

O O N

TMSO

Ar Ar

$$F_3C$$
 CF_3

MeO

 CF_3

Yellow solid. Yield after 2 steps: 65% (202 mg, 0.13 mmol). M.p.= 155–160 $^{\circ}$ C. 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). ¹³C 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**

NH₂ r.t. 12 h NH₂
$$\rightarrow$$
 R CO₂^tBu \rightarrow NH₂ \rightarrow HCO₂Et \rightarrow NH₂ \rightarrow HN H \rightarrow CO₂^tBu \rightarrow So °C, 2 h \rightarrow R: Ph R: Bn \rightarrow POCl₃, $^{t}\text{Pr}_{2}\text{NH}$ \rightarrow CO₂^tBu \rightarrow 1A R: Ph \rightarrow CO₂^tBu \rightarrow 1.5 h

 1^{st} step:²⁵⁴ To a solution of the aminoacid (30 mmol, 1 equiv.) in tert-butyl acetate (70 mL) at 0 °C, was added slowly HClO₄ (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 H₂O (100 mL) and hydrochloric acid 1M (50 mL). The resulting combined aqueous solution was adjusted to pH 9 by addition of sat. K₂CO₃ solution, and then extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were dried with anhydrous MgSO₄, 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

NH₂ Yield: 81%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 7.43 – 7.27 (m, 5H), 4.48 (s, COOtBu 1H), 1.84 (brs, 2H), 1.39 (s, 9H).

tert-Butyl 2-isocyano-3-phenylpropanoate

NH₂ Yield: 93%. ¹H NMR (300 MHz, CDCl₃) 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.

 3^{rd} step:²⁵⁵ To a solution of previously obtained formamide (10 mmol, 1 equiv.) in CH₂Cl₂ (30 mL) was added DIPA (5.19 mL, 37 mmol, 3.7 equiv.) and the mixture was cooled to -30 °C. POCl₃ (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 Na₂CO₃ (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), HCl 1M (2 × 20 mL), dried over MgSO₄ 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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²⁵⁴ Chen, H.; Feng, Y.; Xu, Z.; Ye, T. *Tetrahedron* **2005**, *61*, 1113-–11140.

²⁵⁵ Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.

tert-Butyl 2-isocyano-2-phenylacetate (1A)

CO₂tBu 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, CDCl₃) δ 7.54 – 7.35 (m, 5H), 5.23 (s, 1H), 1.42 (s, 9H). 13 C NMR (75 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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**:²⁵⁶ 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%. ¹H 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).

²⁵⁶ 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 70°C 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:²⁵⁷ To a solution of previously obtained formamide (10 mmol, 1 equiv.) in CH₂Cl₂ (30 mL) was added DIPA (5.19 mL, 37 mmol, 3.7 equiv.) and the mixture was cooled to -30 °C. POCl₃ (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 Na₂CO₃ (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), HCl 1M (2 × 20 mL), dried over MgSO₄ 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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₁₄NO₂ [M+H]⁺, 252.0913; found, 222.0918.

5.3.1.3. Synthesis of isocyanoacetates **1B-D** and **1F-G**

$$R = \frac{1}{70 \text{ °C, overnight}} = \frac{1}{R} = \frac{1}{1} = \frac$$

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.

2

²⁵⁷ Adapted form: see ref. 255, page 185.

 2^{nd} step:²⁵⁸ To a solution of previously obtained formamide (10 mmol, 1 equiv.) in CH₂Cl₂ (30 mL) was added DIPA (5.19 mL, 37 mmol, 3.7 equiv.) and the mixture was cooled to -30 °C. POCl₃ (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 Na₂CO₃ (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), HCl 1M (2 × 20 mL), dried over MgSO₄ 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

Vield (2 steps): 80%.
1
H NMR (300 MHz, CDCl₃) δ 7.27 – 7.18 (m, 4H), 4.60 (s, 2H), 2.37 (s, 3H).

1-(Isocyanomethyl)-4-methoxybenzene

MeO Yield (2 steps): 89%.
1
H NMR (300 MHz, CDCl₃) δ 7.29 – 7.24 (m, NC 2H), 6.95 – 6.89 (m, 2H), 4.57 (s, 2H), 3.82 (s, 3H).

1-Bromo-3-(isocyanomethyl)benzene

Yield (2 steps): 83%.
1
H NMR (300 MHz, CDCl₃) δ 7.56 – 7.44 (m, 2H), NC 7.33 – 7.23 (m, 2H), 4.63 (s, 2H).

1-(Isocyanomethyl)-2-methylbenzene

Yield (2 steps): 66%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 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%.
1
H NMR (300 MHz, CDCl₃) δ 7.59 – 7.54 (m, 1H), 7.43 – 7.29 (m, 3H), 4.75 (s, 2H).

²⁵⁸ Adapted from: see ref. 255, page 185.

3rd step:²⁵⁹ 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 NH₄Cl (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 MgSO₄. 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)

CO₂tBu 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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₄H₁₈NO₂ [M+H]⁺, 232.1338; found, 232.1332.

tert-Butyl 2-isocyano-2-(4-methoxyphenyl)acetate (1C)

CO2tBu The isocyanoacetate 1C was obtained following the general procedure. White solid. Yield (last step): 65 % (1.61 g, 6.5 mmol). H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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 C₁₄H₁₈NO₃ [M+H]⁺, 248.1287; found, 248.1282.

tert-Butyl 2-(3-bromophenyl)-2-isocyanoacetate (1D)

The isocyanoacetate 1D was obtained following the general Br. procedure. Yellow oil. Yield (last step): 80 % (2.37 g, 8.0 mmol). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz,

²⁵⁹ 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.

CDCl₃) 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 C₁₃H₁₅NO₂Br [M+H]⁺, 296.0286; found, 296.0287.

tert-Butyl 2-isocyano-2-(o-tolyl)acetate (1F)

CO₂tBu The isocyanoacetate **1F** was obtained following the general procedure. Yellow oil. Yield (last step): 85 % (1.97 g, 8.5 mmol). 1 H NMR (300 MHz, CDCl₃) 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)

CO₂tBu The isocyanoacetate **1G** was obtained following the general procedure. Yellow oil. Yield (last step): 87 % (2.19 g, 8.7 mmol). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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 $2c-f^{260}$

To a solution of the corresponding acetophenone (10 mmol) and paraformaldehyde (600 mg, 20 mmol, 2 equiv.) in dry THF (10 mL) were successively added disopropylammonium 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

²⁶⁰ 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 $\rm Et_2O$ and washed with HCl 1M, NaOH 1M and brine. The resulting organic solution was dried over MgSO₄ 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. 261

1-Phenylprop-2-en-1-one (2c)

1-(p-Tolyl)prop-2-en-1-one (2d)

Colorless oil. Yield: 78%. ¹H NMR (CDCl₃, 300 MHz)
$$\delta$$
 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)

1-(4-Methoxyphenyl)prop-2-en-1-one (2f)

Colorless oil. Yield: 75%. 1 H NMR (CDCl₃, 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).

Guo S.H. Ying S.7. Mao S. Gao V.R. Chen W. I. Wang V.O. *Tetrah*

²⁶¹ 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**. 262

To a solution of methoxypropadiene (3.50 g, 50 mmol, 1 equiv.) in dry Et_2O (100 mL) at -40 °C, nBuLi (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 (CDCl₃) 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). ¹³C NMR (CDCl₃) 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.

²⁶² 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). $[\alpha]_D^{22} = -7.22^\circ$ (c=1, 95% ee, CH_2Cl_2).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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).
$$[\alpha]_D^{22} = -6.43^\circ$$
 (c =0.85, 98% ee , CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₃NO₄Na [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 , CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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). $[\alpha]_D^{22} = -8.44^{\circ}$ (c=1.5, 96% ee, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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). [α]_D 22 = - 5.27° (c=1.45, 94% ee, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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).
$$[\alpha]_D^{22} = -18.48^\circ$$
 (c =0.6, 98% ee , CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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).
$$[\alpha]_D^{22} = -1.79^\circ$$
 ($c=3$, 99% ee , CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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). $[\alpha]_D^{22} = -6.89^\circ$ (c=2.05, 97% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₃H₂₅NO₃Cl [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). $[\alpha]_D^{22} = -3.00^{\circ}$ (c=2.55, 96% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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).
$$[\alpha]_D^{22} = -3.54^\circ$$
 ($c = 1, 98\%$ ee , CH_2CI_2).

 1 H NMR (300 MHz, CDCl₃) δ 7.56 (dd, J = 8.2, 1.6 Hz, 2H), 7.49 – 7.39 (m, 3H), 3.52 (brs, 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, CDCl₃) 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)

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, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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 (brs, 1H), 2.81 – 2.47 (m, 4H), 1.30 (s, 3H), 1.28 (s, 3H). 13 C NMR (75 MHz, CDCl₃) 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)

$$\begin{array}{c} \text{tBuO}_2\text{C} \\ \text{NC} \end{array} \begin{array}{c} \text{O} \\ \text{NC} \end{array}$$

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). $[\alpha]_D^{22} = -2.88^\circ$ (c = 1.65, 99% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 3.50 (brs, 1H), 2.78 – 2.43 (m, 4H), 2.35 (s, 3H), 1.41 (s, 9H), 1.35 (s, 3H), 1.30 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) 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). $[\alpha]_D^{22} = -4.84^{\circ}$ (c=2.65, 98% ee, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) δ 7.47 – 7.41 (m, 2H), 6.96 – 6.88 (m, 2H), 3.81 (s, 3H), 3.49 (brs, 1H), 2.77 – 2.43 (m, 4H), 1.41 (s, 9H), 1.36 (s, 3H), 1.31 (s, 3H). 13 C NMR (75 MHz, CDCl₃) 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). $[\alpha]_D^{22} = -4.63^{\circ}$ (c=3.15, 96% ee, CH_2CI_2).

 1 H NMR (300 MHz, CDCl₃) 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 (brs, 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, CDCl₃) 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 Δ^5 -dehydroprolines **10-13** and corresponding derivatives **14-18**

 $\Delta^{5}\text{-Dehydroprolines}$ 10-13 were prepared according to the following procedure: 263

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 NH₄OH (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 MgSO₄ 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). 1 H NMR (300 MHz, CDCl₃) 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). H NMR (300 MHz,

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²⁶³ Adapted from: Zhao, M.; Zhu, H.; Dai, T.; Shi, M. J. Org. Chem **2015**, 80, 11330-11338.

CDCl₃) δ 7.50 – 7.40 (m, 2H), 7.37 – 7.20 (m, 3H), 2.88 – 2.76 (m, 1H), 2.75 – 2.61 (m, 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, CDCl₃) 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, CDCl₃) 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

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)

Me $\stackrel{\text{CO}_2\text{tBu}}{\text{H}}$ 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). $[\alpha]_D^{22} = -5.6^\circ$ (c=0.55, 98% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₂₄NO₂ [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). $[\alpha]_D^{22} = -6.23^\circ$ (c=1, 94% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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

Me
$$\begin{array}{c} O \\ N \\ Ph \\ O_2N \end{array}$$
 $\begin{array}{c} O \\ CI \\ \hline \\ CI \\ \hline \\ CI \\ \hline \\ CO_2tBu \\ \hline \\ 2h, rt \\ \hline \\ O_2N \\ \\ O_2N \\ \hline \\ O_2N \\ \\ O_2N \\ \hline \\ O_2N \\ \\$

To a solution of pyrrolidine **14** (52 mg, 0.2 mmoL, 1 equiv.) and Et_3N (42 μ L, 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 MgSO₄, 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). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) δ 170.3, 167.3, 148.5, 143.6, 138.3, 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

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.=
$$45^{\circ}$$
C. Yield: 82% (139.2 mg, 0.41 mmol). [α]_D 22 = $-$ 22.46° (c =0.65, 96% ee , CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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)

MeO
$$CO_2$$
tBu H_2 N

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). $[\alpha]_D^{22} = -10.34^{\circ}$ (c=1.65, 96% ee, CH_2Cl_2).

 1 H NMR (300 MHz, CDCl₃) 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 Δ^4 -dehydroprolines **19-23**

 Δ^4 -Dehydroprolines **19-23** were prepared according to the following procedure:

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 NH₄Cl and the organic layer was dried with MgSO₄. 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).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₃H₂₅NO₃Br [M+H]⁺, 442.0101; found, 442.0105.

tert-Butyl (R) 4-(4-methylbenzoyl)-2-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate (20)

O CO₂tBu H 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).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₃H₂₆NO₃ [M+H]⁺, 364.1913; found, 364.1913.

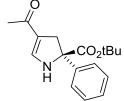
tert-Butyl (R) 4-acetyl-2-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (21)

O CO₂tBu H

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).

¹H NMR (300 MHz, CDCl₃) δ 7.34 – 7.25 (m, 2H), 7.26 (d, J OMe = 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₄NO₄ [M+H]⁺, 318.1705; found, 318.1711.

tert-Butyl (R) 4-acetyl-2-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate (22)

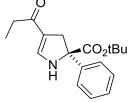


Prepared according to the general procedure starting from **3Aa** (57.5 mg, 0.2 mmol). The title compound was isolated as a yellow foam. Yield: 85% (48.9 mg, 0.17 mmol).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: ²⁶⁴ A suspension of sodium periodate NaIO₄ (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 Et₂O (3 × 7 mL) and washed with water. The organic phase was dried over MgSO₄, 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, CDCl₃) 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). 1 H NMR (300 MHz, CDCl₃) 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 NH₄OH (pH 9-10). The aqueous phase was extracted with CH₂Cl₂ (3 × 3 mL) and the combined organic layer was washed with water and sat. brine. The organic phase was dried over MgSO₄, 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, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₀NO₃ [M+H]⁺, 262.1443; found, 262.1445.

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

 1^{st} 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, Boc₂O (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 KHSO₄ 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 MgSO₄ and was concentrated under reduced pressure. The crude material was used in the next step without purification.

(tert-Butoxycarbonyl)phenylalanine

NHBoc Yield: Quantit.
1
H NMR (300 MHz, CDCl₃) δ 7.36 – 7.23 (m, 3H), Ph CO_{2} H 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

NHBoc Yield: 93%.
1
H NMR (300 MHz, CDCl₃) δ 5.06 (s, 1H), 4.48 – 4.30 Me 1 CO₂H (m, 1H), 1.55 – 1.45 (m, 12H).

(tert-Butoxycarbonyl)leucine

NHBoc Yield: Quantit. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 4.95 – 4.77 (m, 1H), CO_2H 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:**²⁶⁵ 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

NHBoc Yield: 82%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 7.53 – 7.19 (m, 10H),
Ph COSPh 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

NHBoc Yield: 89%. ¹H NMR (300 MHz, CDCl₃) δ 7.41 (s, 5H), 5.06 – 4.95 Me COSPh (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

NHBoc Yield: 74%. ¹H NMR (300 MHz, CDCl₃) δ 7.51 – 7.35 (m, 5H), COSPh 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

NHBoc Yield: 97%. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (d, J = 1.3 Hz, 5H), COSPh 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).

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.

 3^{rd} 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 Et₂O and filtered. The title compound was obtained as a white solid.

S-Phenyl 2-aminopropanethioate hydrochloride

NH₂.HCl Yield: Quantit. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 8.65 (s, 3H), 7.53 – Me COSPh 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

NH₂.HCl Yield: 88%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 8.85 (s, 3H), 7.49 – COSPh 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

NH₂HCl Yield: Quantit. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 8.90 (s, 3H), 7.53 – COSPh 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).

 4^{th} step: METHOD A: The amine hydrochloride (5 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with saturated NaHCO₃ (3 × 20 mL), dried over MgSO₄ 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 B²⁶⁶: 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 NaHCO₃ (20 mL). The solution was dried with anhydrous MgSO₄, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel giving the formamide compound.

²⁶⁶ 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, CDCl₃) δ 8.26 (s, HN 2 1H), 7.53 – 7.16 (m, 10H), 6.01 (d, J = 8.6 Hz, 1H), 5.31 – 5.19 (m, 1H), Ph 2 COSPh 2 3.25 (d, J = 6.3 Hz, 2H).

S-Phenyl 2-formamidopropanethioate

Yield: 85% (method B).
1
H NMR (300 MHz, CDCl₃) 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 = 1 Me COSPh 7.1 Hz, 3H).

S-Phenyl 2-formamido-4-methylpentanethioate

Yield: 94% (method B).
1
H NMR (300 MHz, CDCl₃) 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). ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 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, COSPh 1H), 2.50 – 2.32 (m, 1H), 1.10 (dd, J = 6.8, 1.9 Hz, 3H), 1.00 (m, 3H).

5th **step:**²⁶⁷ To the corresponding *N*-formyl thioester (2 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added N-methylmorpholine NMM (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 MgSO₄ 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.

²⁶⁷ Adapted from: Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.*, **2009**, *50*, 577-579.

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 NMR (300 MHz, CDCl₃) 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, CDCl₃) 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)

COSPh The isocyanothioate **4A** was obtained following the general Me Procedure. Yellow oil. Yield (last step): 62 % (237 mg, 1.24 mmol). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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**

$$R \xrightarrow{NH_{2}} \xrightarrow{HCO_{2}H} \xrightarrow{DMF, 110 \ ^{\circ}C} \xrightarrow{R} \xrightarrow{DCC, DMAP, ArXH} \xrightarrow{DCO_{2}H} \xrightarrow{DCM, r.t., overnight} \xrightarrow{X= S \text{ or } O}$$

$$R \xrightarrow{HN} \xrightarrow{Triphosgene/NMM} \xrightarrow{R} \xrightarrow{NC} \xrightarrow{COXAr} \xrightarrow{2 \text{ h, } -78 \ ^{\circ}C} \xrightarrow{COXAr}$$

1st step:²⁶⁸ 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%. ¹H 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), Bn CO_2H 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%. ¹H NMR (300 MHz, DMSO-
$$d_6$$
) δ 8.34 (d, J = 7.6 Hz, 1H), HN 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%. ¹H 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%. ¹H 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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²⁶⁸ Aizpurua, J. M.; Palomo, C. *Synth. Commun.*, **1983**, *13*, 745-752.

2-Formamidooctanoic acid

Yield: 88%. ¹H 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%. ¹H 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).

 2^{nd} step:²⁶⁹ To a solution of N-formyl amino acid (5 mmol, 1 equiv.) in CH₂Cl₂ (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.

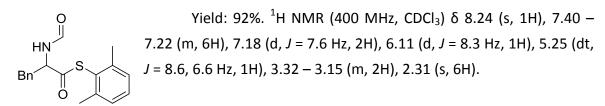
S-(Naphthalen-1-yl) 2-formamido-3-phenylpropanethioate

Yield:
$$62\%$$
. ¹H NMR (300 MHz, CDCl₃) 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:
$$65\%$$
. ¹H NMR (300 MHz, CDCl₃) 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

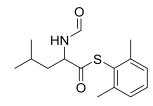


²⁶⁹ Adapted from: Claraz, A.; Sahoo, G.; Berta, D.; Madarász, A.; Pápai, I.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 669-673.

S-(2,6-Dimethylphenyl) 2-formamidopropanethioate

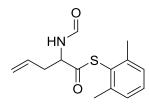
Yield: 84%. ¹H NMR (300 MHz, CDCl₃) δ 8.26 (s, 1H), 7.32 – 7.23 (m, 1H), 7.23 – 7.14 (m, 1H), 6.34 – 6.07 (m, 1H), 5.09 – 4.89 (m, 1H), 2.36 (s, 6H), 1.57 (d, J = 7.2 Hz, 3H).

S-(2,6-Dimethylphenyl) 2-formamido-4-methylpentanethioate



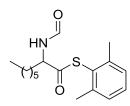
Yield: 91%. H NMR (300 MHz, CDCl₃) δ 8.32 – 8.23 (m, 1H), 7.26 – 7.20 (m, 1H), 7.20 – 7.11 (m, 2H), 5.97 (d, J = 8.8 Hz, 1H), 5.05 – 4.90 (m, 1H), 2.33 (s, 6H), 1.84 – 1.71 (m, 2H), 1.61 – 1.55 (m, 1H), 1.00 (dd, J = 6.2, 2.9 Hz, 6H).

S-(2,6-Dimethylphenyl) 2-formamidopent-4-enethioate



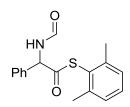
Yield: 60%. 1 H NMR (300 MHz, CDCl₃) δ 8.23 (s, 1H), 7.35 – 7.10 (m, 3H), 6.71 (d, J = 8.2 Hz, 1H), 5.87 – 5.65 (m, 1H), 5.28 – 5.13 (m, 2H), 5.05 – 4.90 (m, 1H), 2.81 – 2.52 (m, 2H), 2.33 (s, 6H).

S-(2,6-Dimethylphenyl) 2-formamidooctanethioate



Yield: 71%. 1 H NMR (300 MHz, CDCl₃) 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%.¹H NMR (300 MHz, CDCl₃) 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, CDCl₃) δ 8.25 (s, 1H), 7.45 – HN $^{\circ}$ CI 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, CDCl₃) δ 8.28 (s, 1H), 7.49 (d, J HN CI = 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, CDCl₃) 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%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 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%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 8.28 – 8.22 (m, HN ⁱPr 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%. ¹H NMR (400 MHz, CDCl₃)
$$\delta$$
 8.24 (s, 1H), 7.40 – OMe 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%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 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, $J = Bn$) 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%. ¹H NMR (400 MHz, CDCl₃)
$$\delta$$
 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, Me \rightarrow Ph 2H), 1.46 (dd, J = 7.3, 2.4 Hz, 2H).

Phenyl formylphenylalaninate

Yield: 54%. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 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. ¹H NMR (300 MHz, CDCl₃)
$$\delta$$
 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).

 3^{rd} step: ²⁷⁰ 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

²⁷⁰ See ref. 267, 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 MgSO₄ 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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).

¹H NMR (300 MHz, CDCl₃) 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).

¹³C NMR (75 MHz, CDCl₃) δ 191.1, 162.1, 142.7, 130.3, 128.4, 124.9, 58.1, 21.4, 20.0. UPLC-DAD-QTOF: C₁₂H₁₄NOS [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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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} H₁₅NOSCl [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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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, CDCl₃) 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 91.9, 163.6, 152.6, 151.9, 134.2, 129.5, 128.8, 127.8, 122.4, 119.5,

(75 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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: $C_{17}H_{16}NO_{2}S$ [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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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.

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 CH₂Cl₂ (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)

PhSOC 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). $[\alpha]_D^{22} = +14.04^\circ$ (c=1.3, 68% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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)

Phsoc 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 , CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: C₂₅H₂₂NO₂S [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)

PhSOC 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).
$$[\alpha]_D^{22} = -50.49^\circ$$
 (c =0.55, 93% ee , CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: C₂₀H₂₀NO₂S [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)

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). $[\alpha]_D^{22} = -36.07^{\circ}$ (c=1.11, 96% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: C₂₂H₂₄NO₂S [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)

Phsoc 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). $[\alpha]_D^{22} = -31.09^\circ$ (c=1, 98% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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). $[\alpha]_D^{22} = -9.14^{\circ}$ (c=1.35, 94% ee, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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: C₂₇H₂₆NO₂S [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) (45Ad)

(R)-2-benzyl-2-isocyano-5-oxo-5-(p-tolyl)pentanethioate

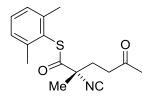
Prepared according to the general procedure starting from isocyanothioacetate **29A** (30 mg, 0.1 mmol) and vinyl ketone **2d** (44 mg, 0.3 mmol). The title compound was obtained as a 96:4 mixture of enantiomers. The crude material was purified by flash

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). $[\alpha]_D^{22} = -8.42^{\circ}$ (c=1.90, 92% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: C₂₈H₂₈NO₂S [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, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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

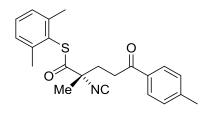
¹H NMR (300 MHz, CDCl₃) δ 7.34 – 7.24 (m, 1H), 7.24 – 7.16 (m, 2H), 2.76 (ddd, J = 17.5, 10.8, 5.1 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.52 – 2.44 (m, 2H), 2.37 (s, 6H), 2.31 (dd, J = 10.7, 5.0 Hz, 1H), 2.18 (ddd, J = 14.3, 10.9, 5.1 Hz, 1H), 1.73 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 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) (45Bd)

²²= –20.63° (*c*=1.15, 96% *ee*, CH₂Cl₂).

(S)-2-isocyano-2-methyl-5-oxo-5-(p-tolyl)pentanethioate



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). $[\alpha]_D^{22} = -45.49^\circ$ (c=1.15, 94% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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) oxopentanethioate (45Be)

(S)-5-(4-chlorophenyl)-2-isocyano-2-methyl-5-

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). $[\alpha]_D^{22} = -52.09^\circ$ (c=1.40, 90% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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, 3H¹³C NMR (75 MHz, CDCl₃) 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: C₂₁H₂₁NO₂SCl [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)

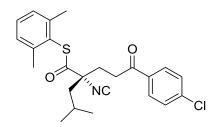
Prepared according to the general procedure starting from isocyanothioacetate **29C** (26 mg, 0.1 mmol) and vinyl ketone **2c** (26 mg, 0.2 mmol). The title compound was obtained as a 99.5:0.5 mixture of enantiomers. The crude material was purified by flash column

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). $[\alpha]_D^{22} = -40.04^\circ$ (c=1.45, 99% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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). $[\alpha]_D^{22} = -47.69^\circ$ (c=1.25, 97% ee, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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). $[\alpha]_D^{22} = -53.24^\circ$ (c=0.75, 97% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: $C_{23}H_{23}CINO_2S$ [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). $[\alpha]_D^{22} = -34.09^\circ$ (c=1.20, 98% ee, CH₂Cl₂).

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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: $C_{26}H_{31}CINO_2S$ [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)

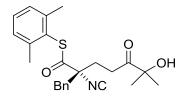
Prepared according to the general procedure starting from the corresponding isocyanothioacetate **35B** (21 mg, 0.1 mmol) and vinyl ketone **2a** (14 mg, 0.2 mmol). The title compound was obtained as a 94:6 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 98/2 to 95/5) to give the title compound as a colourless oil. Yield: 62% (19 mg).
$$[\alpha]_D^{22} = -0.56^{\circ}$$
 (c =1.40, 88% ee , CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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) oxoheptanethioate (49Aa)

(R)-2-benzyl-6-hydroxy-2-isocyano-6-methyl-5-



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 sh column chromatography on silica gel (eluting with hexane/

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, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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)

N O S

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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: C₁₄H₁₂NOS [M+H]⁺ calcd.: 242.0640, found: 242.0652.

4-(Phenylthio)butan-2-one (38)

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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)

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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)

Ph
1
H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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+NH₄] $^+$ calcd.: 273.1603, found: 273.1602. Isonitrile NC band at IR: 2139 cm $^{-1}$.

5.4.3. Reaction of 29A with *N*-phenyl maleimide

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 CH₂Cl₂ (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). [α]_D ²² (major diastereomer)= -38.03° (c=1.1, 68% *ee*, CH₂Cl₂).

Data of major diastereomer: 1 H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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**²⁷¹

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 NH₄OH (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 MgSO₄ 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). [α]_D ²²= -160.41° (c=1, 90% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₀H₂₁CINOS [M+H]⁺, 358.1032; found, 358.1057.

²⁷¹ Adapted from: Zhao, M; Zhu, H.; Dai, T.; Shi, M. J. Org. Chem **2015**, 80, 11330-11338.

5.4.4.2. Synthesis of Δ^4 -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 NH₄Cl and the organic layer was dried with MgSO₄. The solvent was remove under reduced pressure to give compound **52** as essentially pure compound. Yield: 56% (29.8 mg, 0.11 mmol). [α]_D ²²= -67.68° (c=0.22, 90% ee, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₃H₁₃ClNO₃ [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 literature²⁷² and the Michael reaction with isocyanothioacetates was performed according to the following procedure:

²⁷² See ref. 212, 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).
$$[\alpha]_D^{22} = +38.82^\circ$$
 (c =0.85, 44% ee , CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 S O O Ph 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).
$$[\alpha]_D^{22} = +70.82^\circ$$
 ($c=1.2$, 62% ee , CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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). [α]_D 22 = +46.33° (c=1.5, 74% ee, CH₂Cl₂).

 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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). $[\alpha]_D^{22} = +27.22^{\circ}$ (c=1, 40% ee, CH_2Cl_2).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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).
$$[\alpha]_D^{22} = -81.50^\circ$$
 (c =0.6, 28% ee , CH_2Cl_2)

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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).

¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 literature²⁷³ and the Mannich reaction with isocyanothioacetates was performed according to the following procedure:

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²⁷³ Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 629–633.

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 ¹H-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)

$$NO_2$$
 NO_2
 NO_2

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, CH₂Cl₂).

Data of major diastereomer: 1 H NMR (300 MHz, CDCl₃) 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). $[\alpha]_D^{22} = +2.54^{\circ}$ (c=1, 10% ee, CH_2Cl_2).

Data of major diastereomer: 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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)

$$NO_2$$
 $N - SO_2$
 $O Bn$
 CO_2Me

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_2CI_2).

Data of major diastereomer: 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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 aldimines²⁷⁴

N-aryl aldimines **69c-e** were prepared according to the following procedure:

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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 MgSO₄ (2g, 400 mg/mmol) in dry CH₂Cl₂ (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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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). H NMR (300 MHz, CDCl₃) 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). S NMR (75 MHz, CDCl₃) 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 ¹H-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, CDCl₃) 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, CDCl₃) 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 ¹H-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, CDCl₃) 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, CDCl₃) 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: $C_{33}H_{28}N_2O_2SCI~[M+H]^+$ 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)

¹H NMR (300 MHz, CDCl₃) δ 7.82 (s, 1H), 7.43 – 7.13 (m, 8H), 4.05 (s, 2H), 2.65 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) 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 ¹H-NMR). The compound **74** was obtained as 40:60 mixture of diastereomers (determined by ¹H-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).

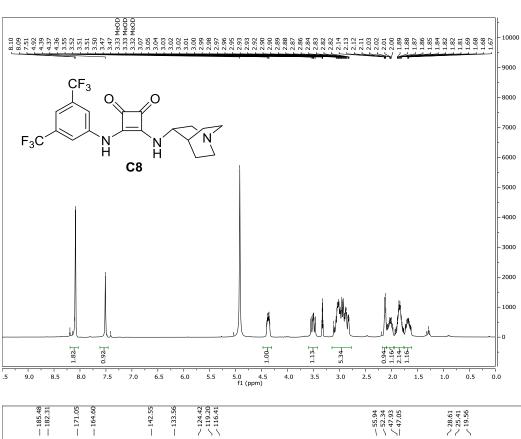
Data of major diastereomer: 1 H NMR (300 MHz, CDCl $_{3}$) δ 7.92 – 7.84 (m, 2H), 7.70 (s, 1H), 7.52 – 7.35 (m, 3H), 7.35 – 7.21 (m, 8H), 7.22 – 7.07 (m, 3H), 7.06 – 6.95 (m, 2H), 5.71 (s, 1H), 3.87 (s, 3H). 13 C NMR (75 MHz, CDCl $_{3}$) δ 169.2, 155.1, 153.8, 151.6, 141.9, 132.5, 129.8, 129.4, 129.1, 128.9, 128.9, 128.8, 127.4, 126.4, 124.7, 122.6, 122.2, 121.7,

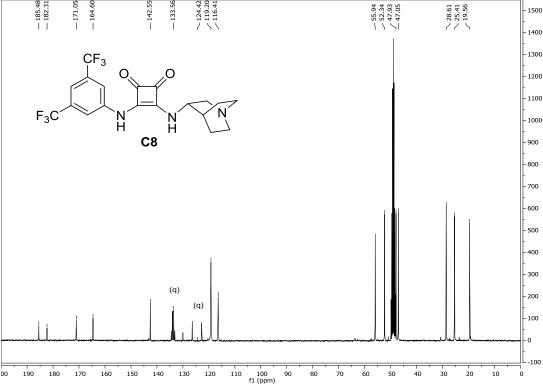
112.7, 89.5, 84.7, 84.5, 62.8, 56.5. UPLC-DAD-QTOF: $C_{31}H_{25}N_2O_3\left[M+H\right]^+$ calcd.: 473.1865, found: 473.1876.

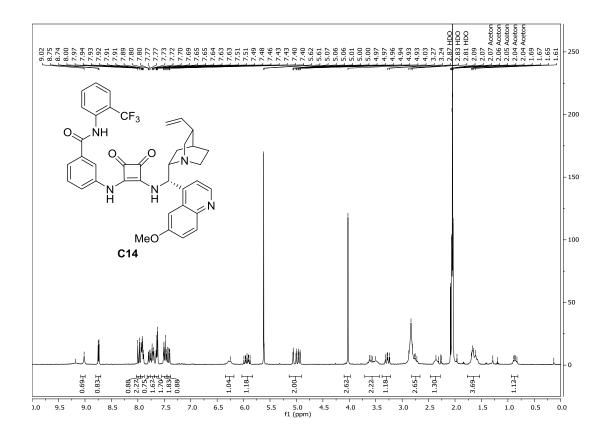
The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane:ethanol, 90:10; flux= 1 mL/min; retention times: diast. B 9.0 min, diast. A (minor enantiomer) 13.4 min, diast. A (major enantiomer) 19.7 min, diast. B 44.2 min).

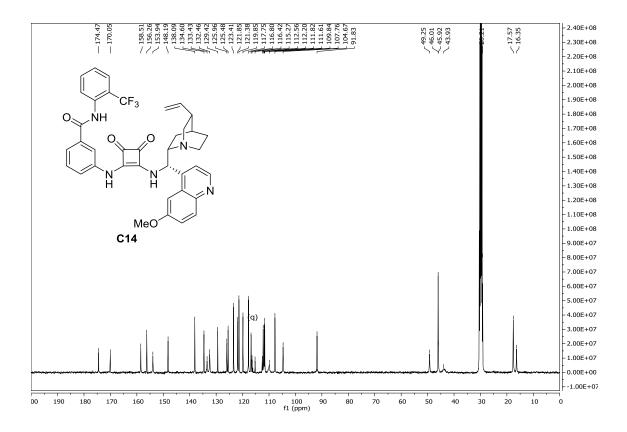
5.5. Representative NMR spectra

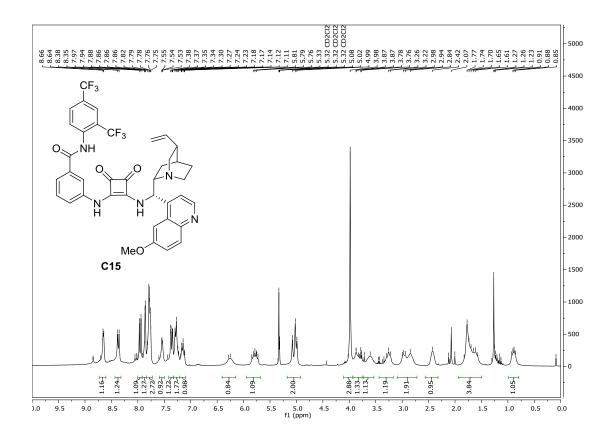
5.5.1. Catalysts

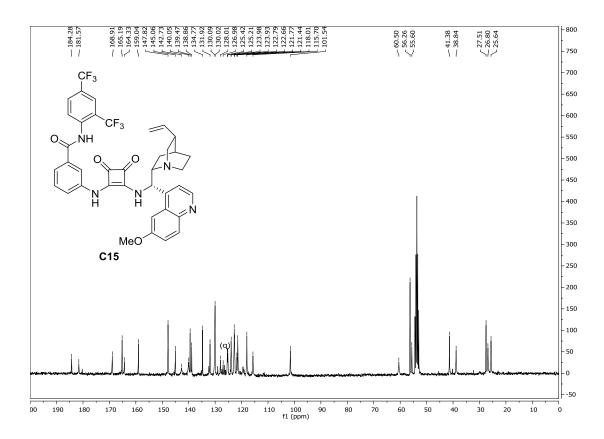


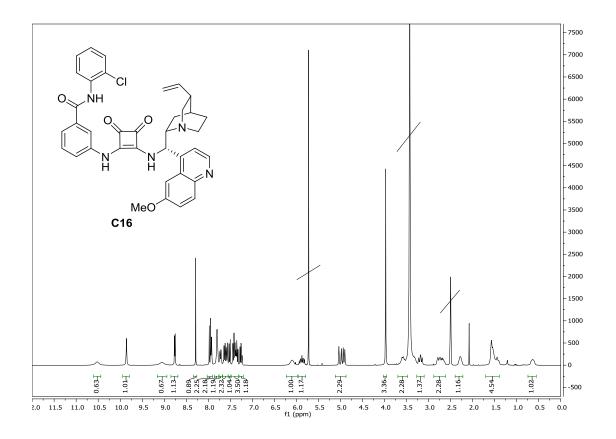


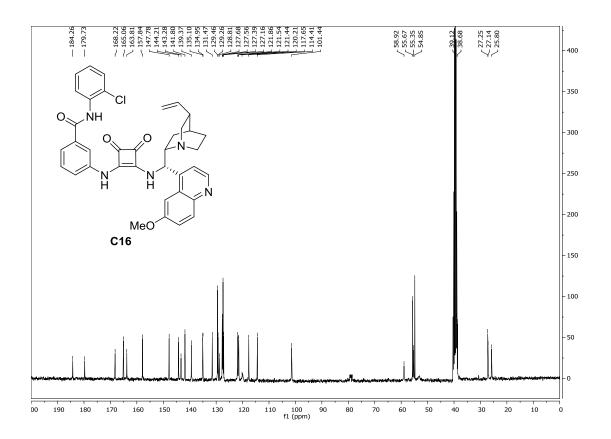


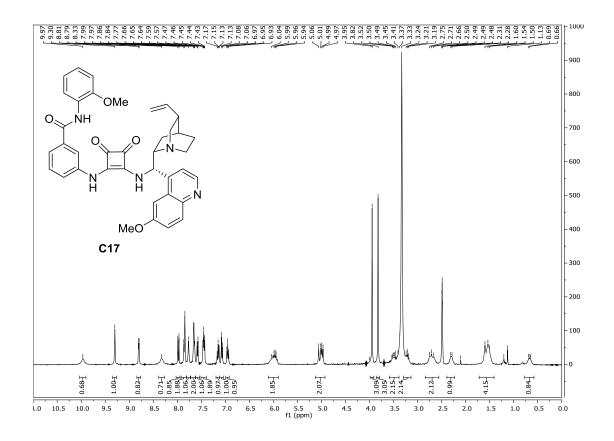


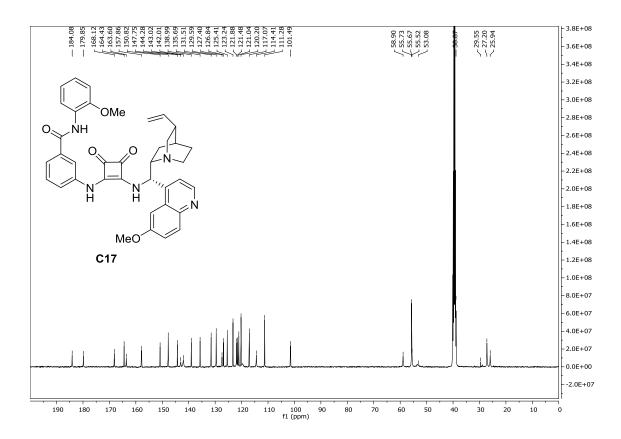


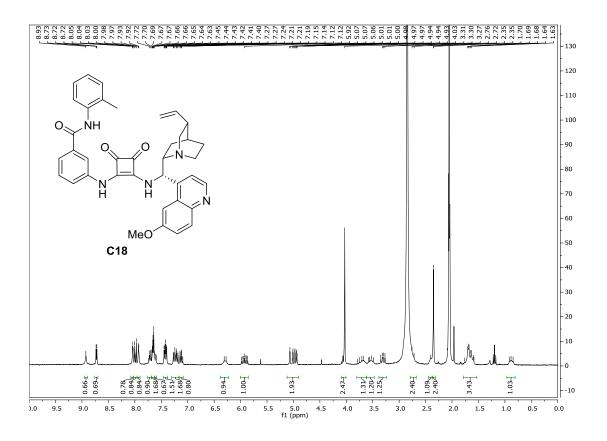


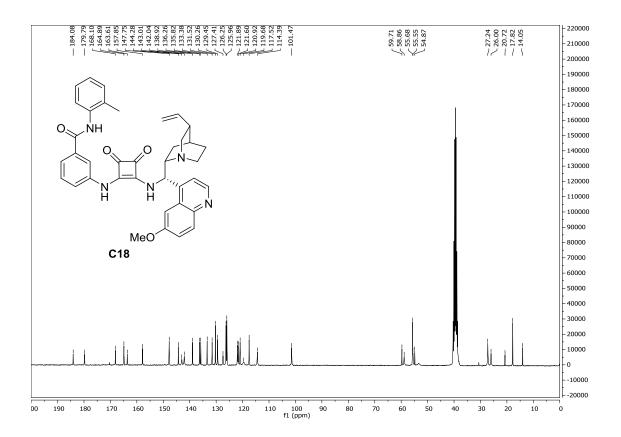


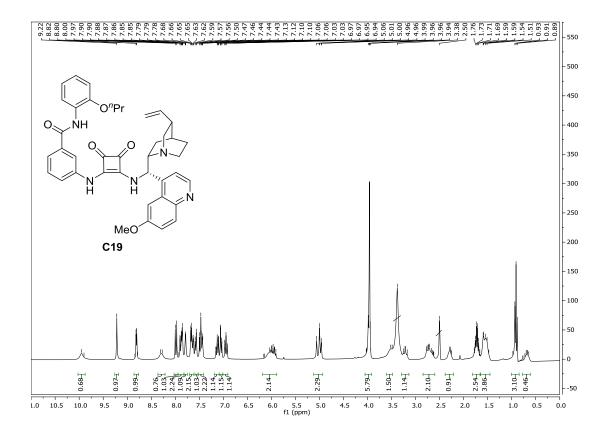


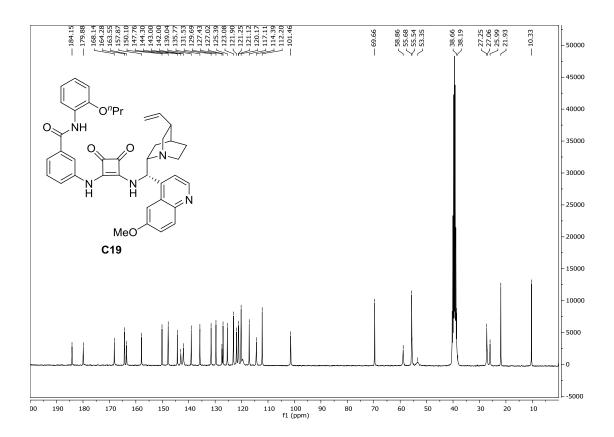


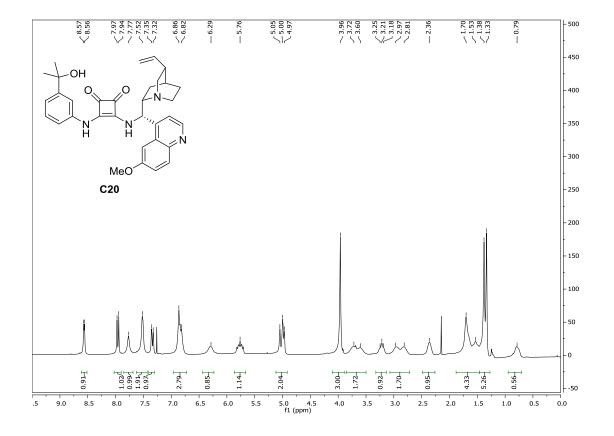


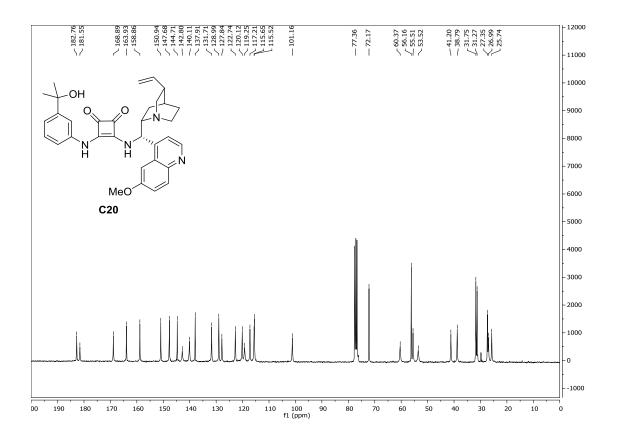


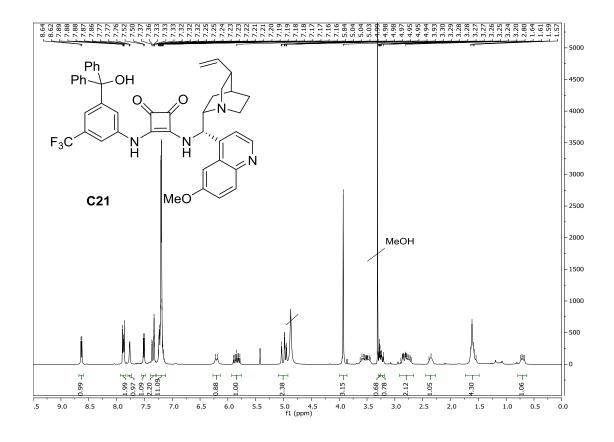


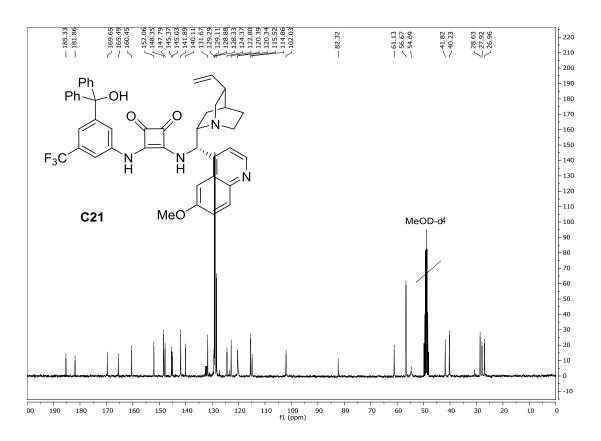


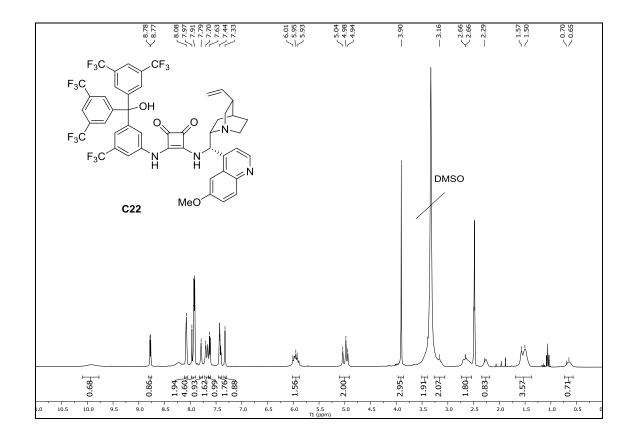


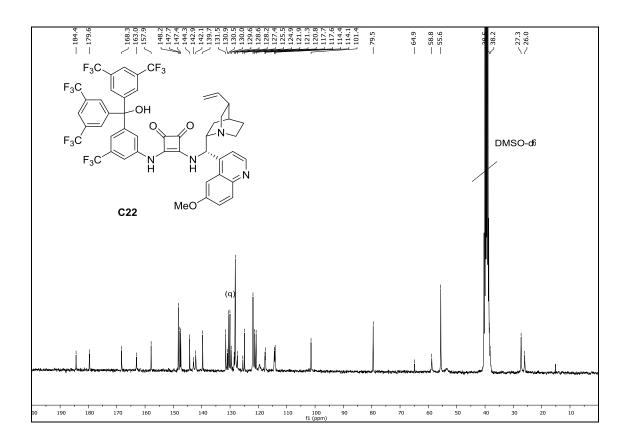


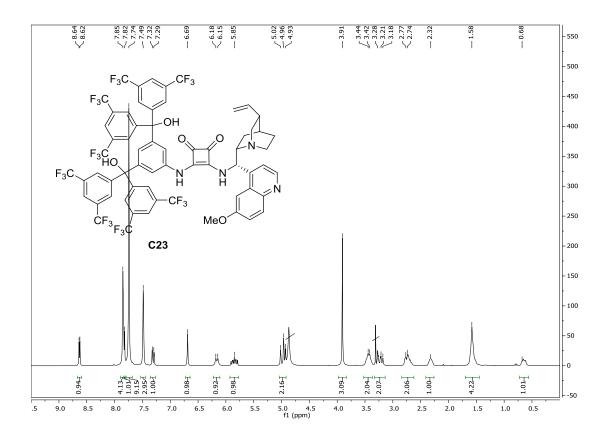


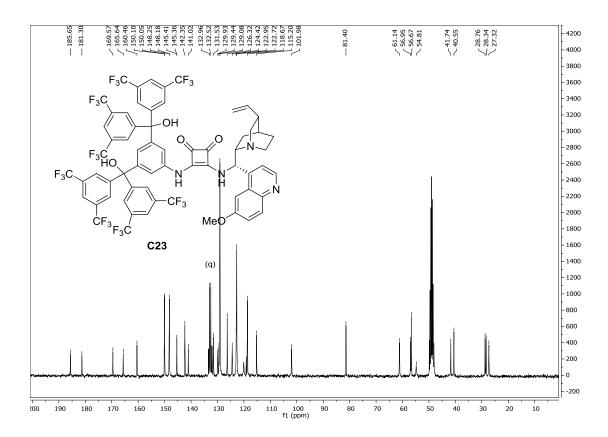


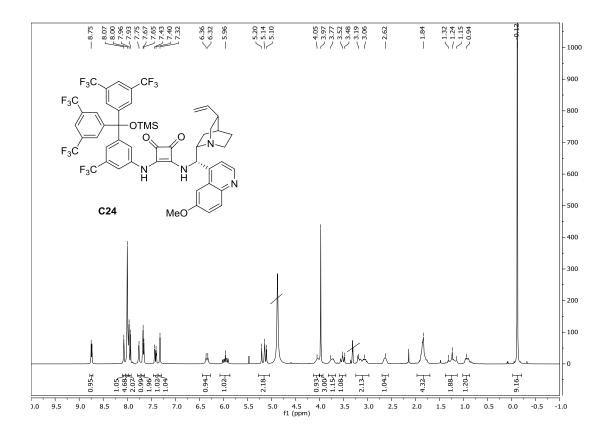


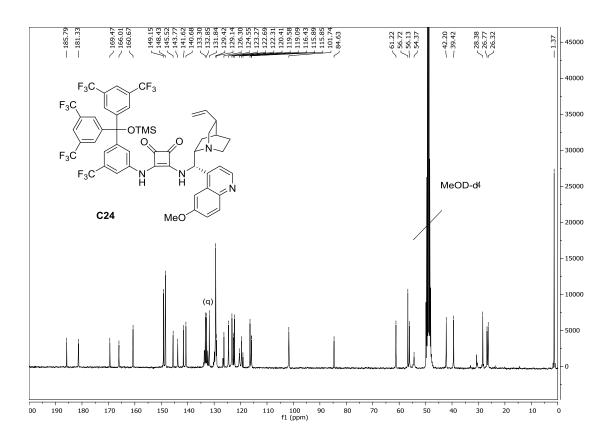


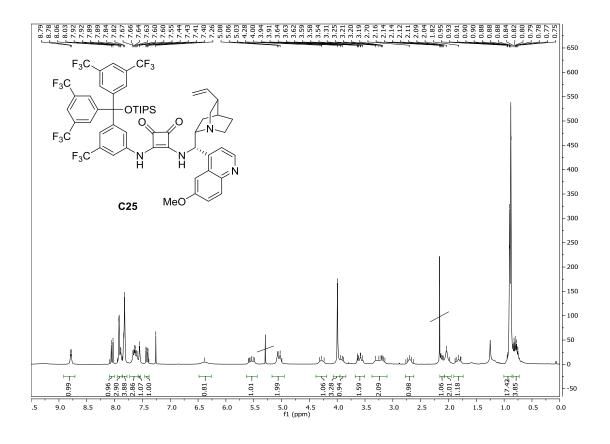


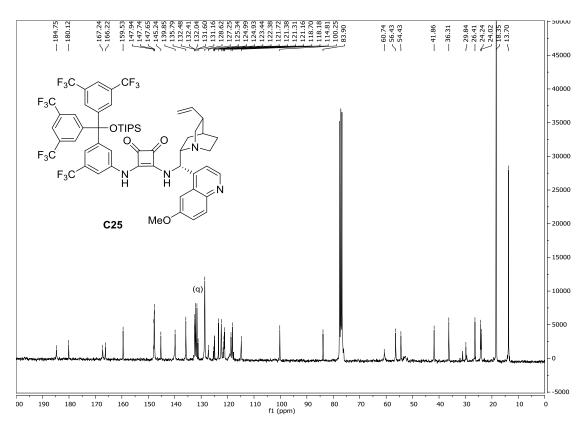


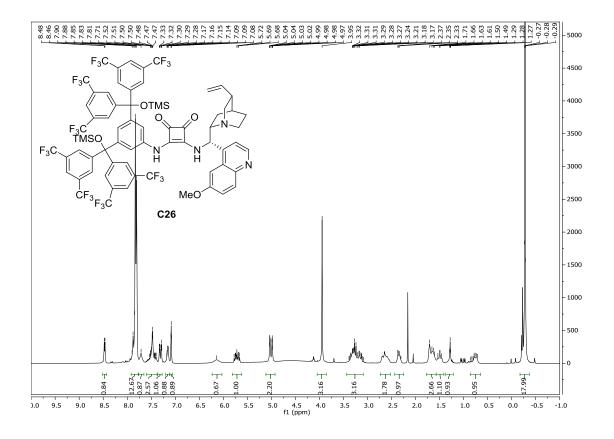


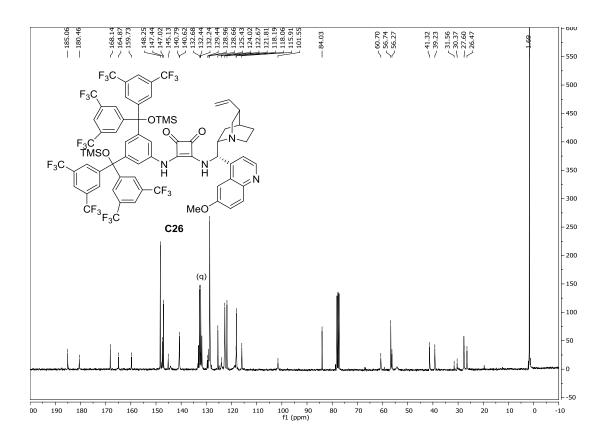


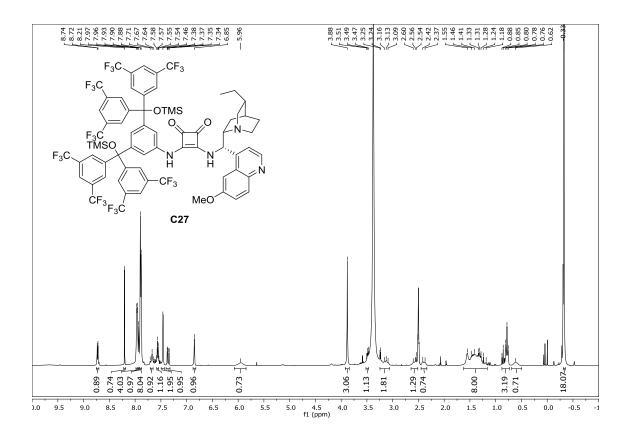


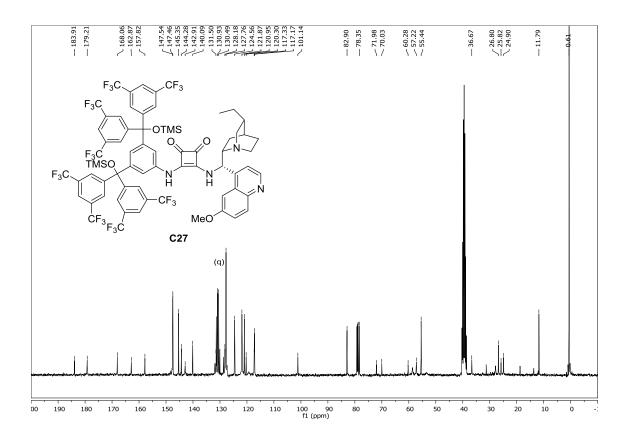






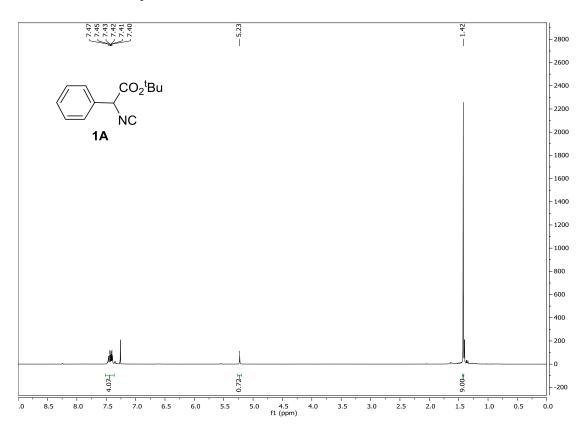


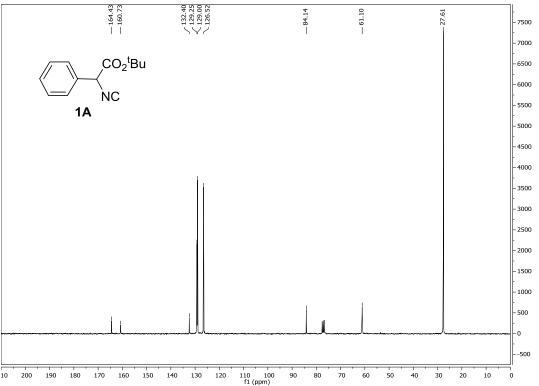


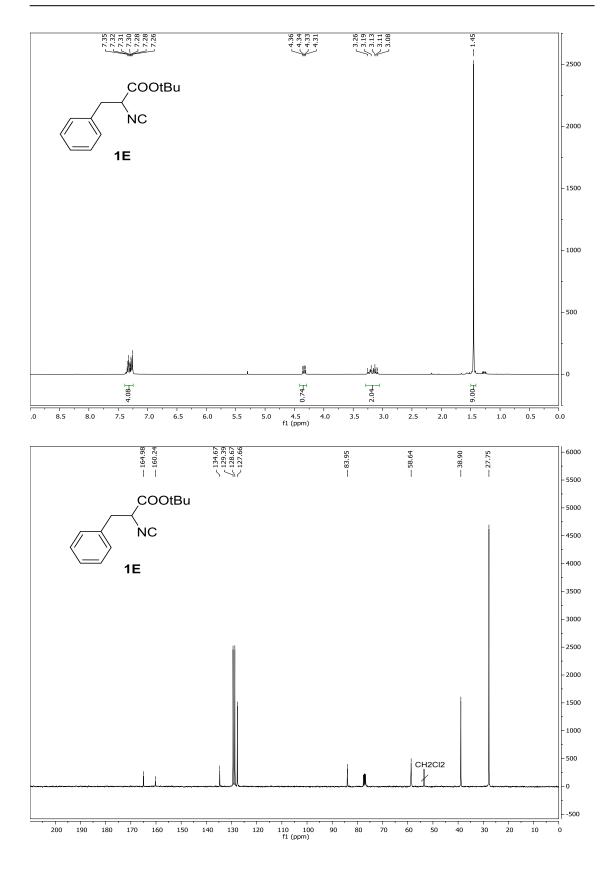


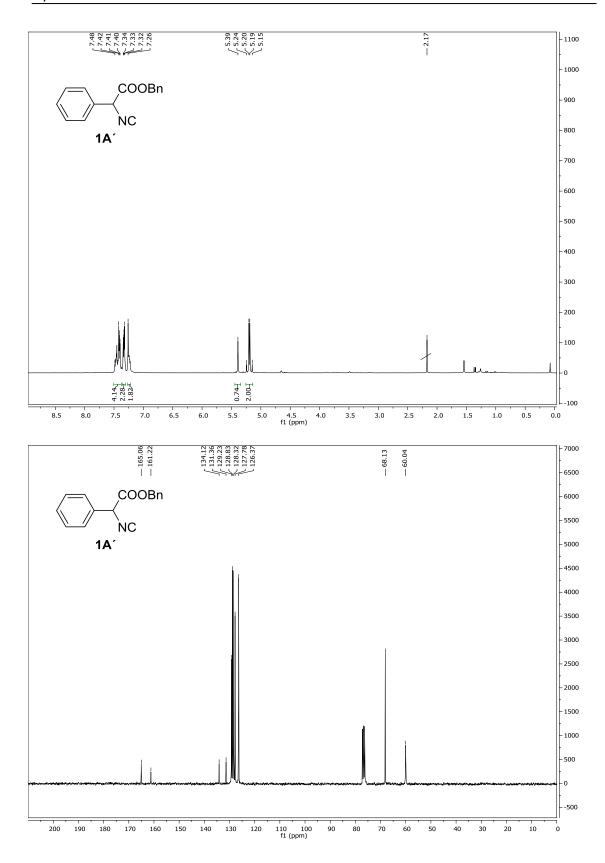
5.5.2. Chapter 2

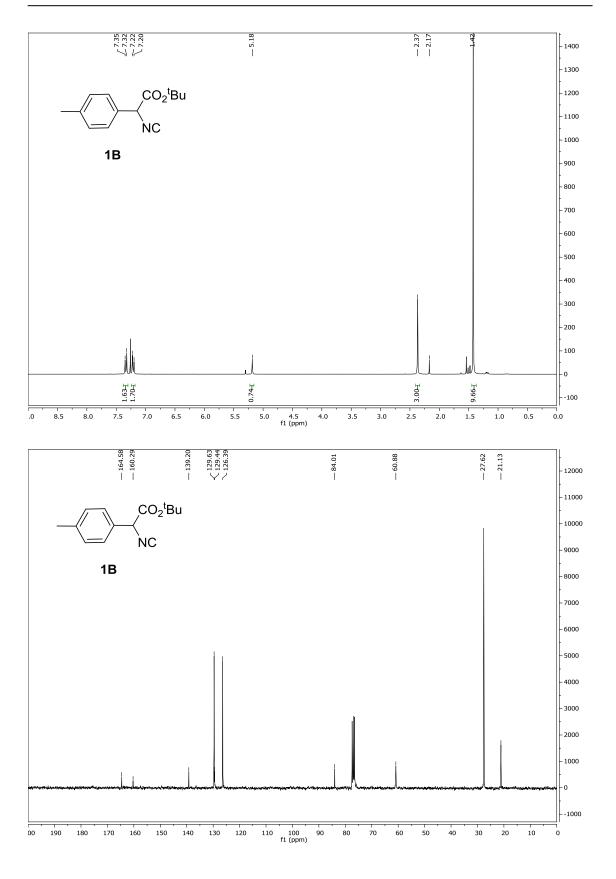
5.5.2.1. Isocyanoacetates 1

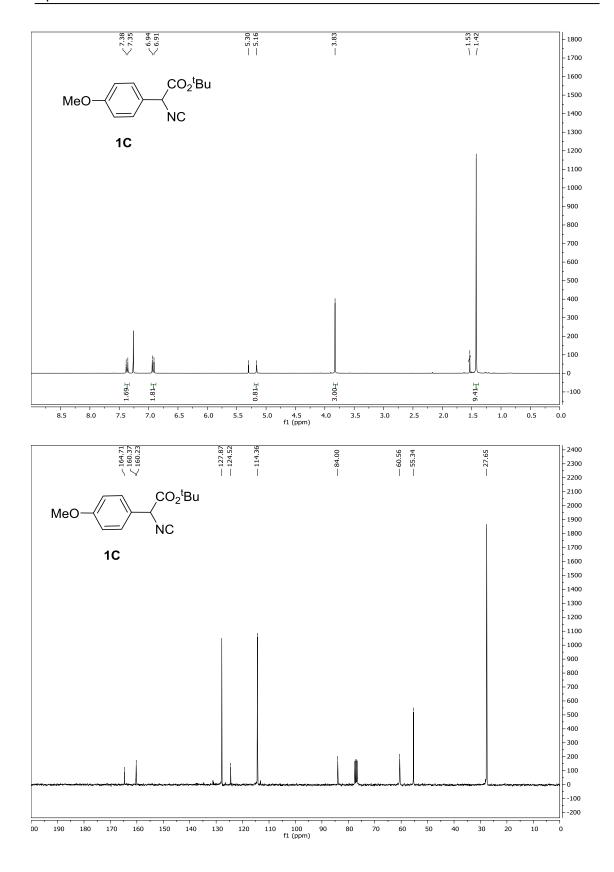


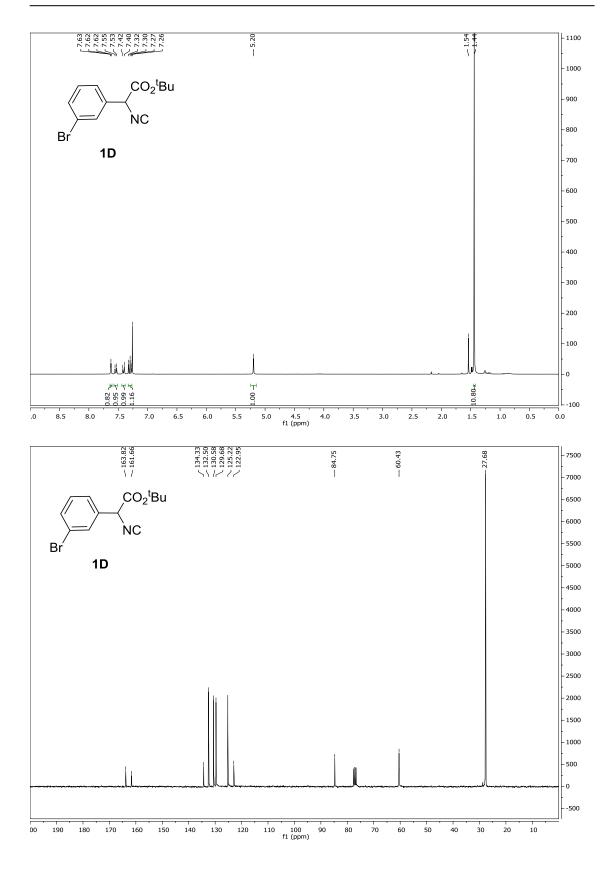


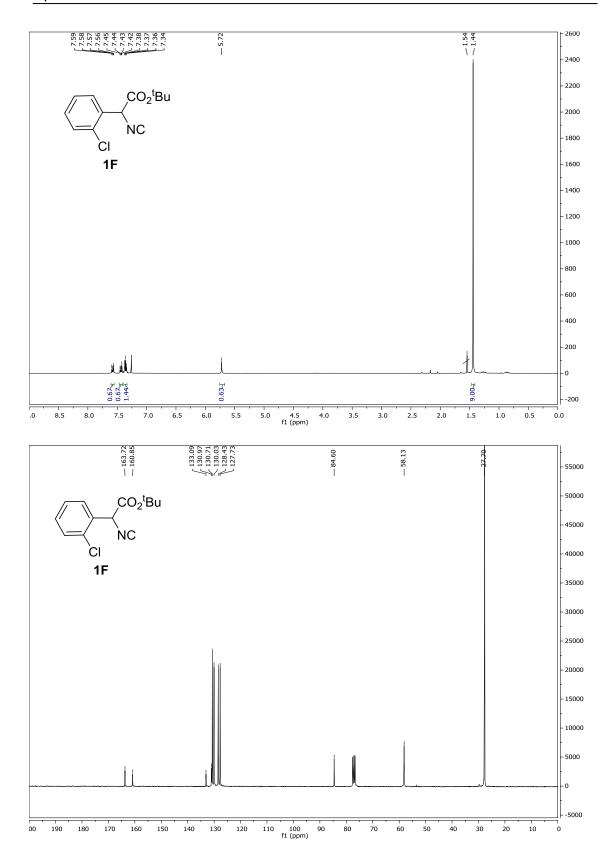




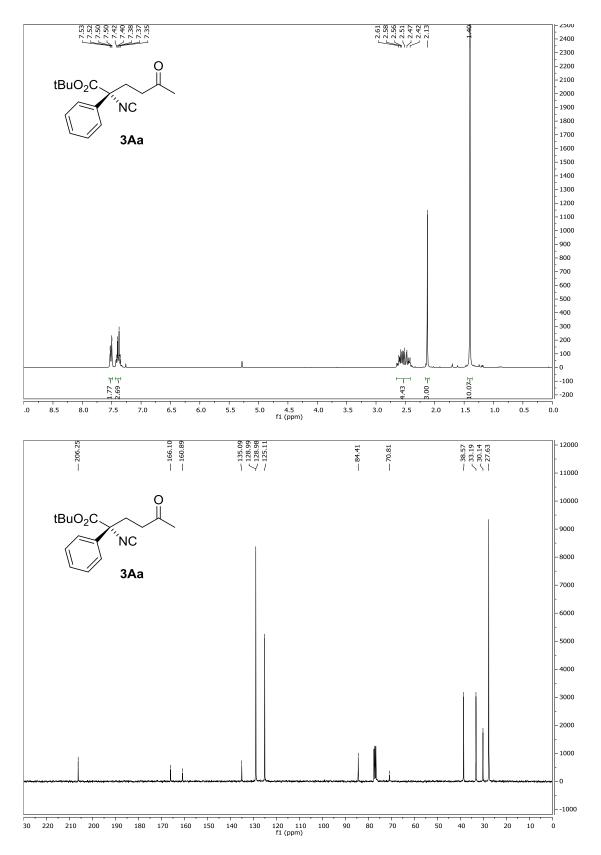


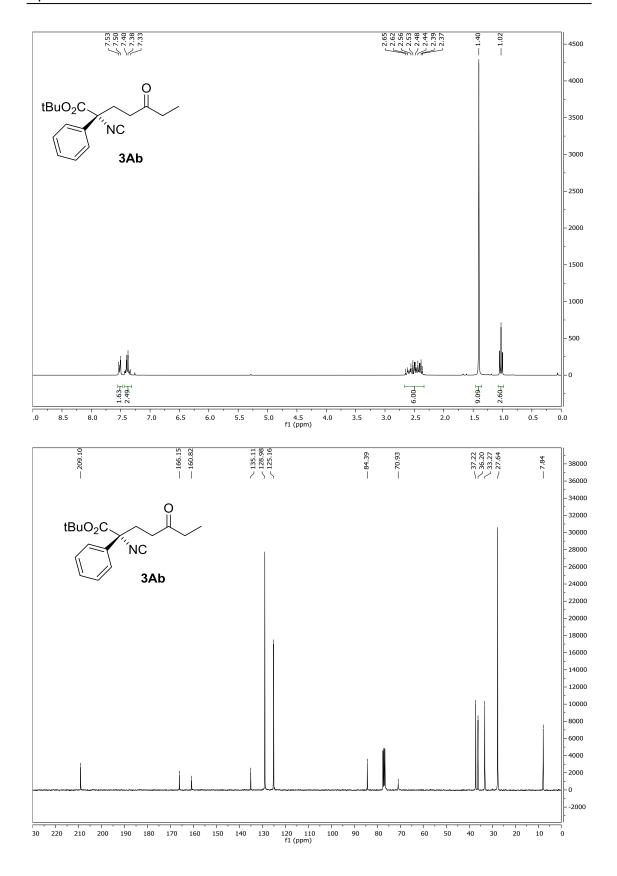


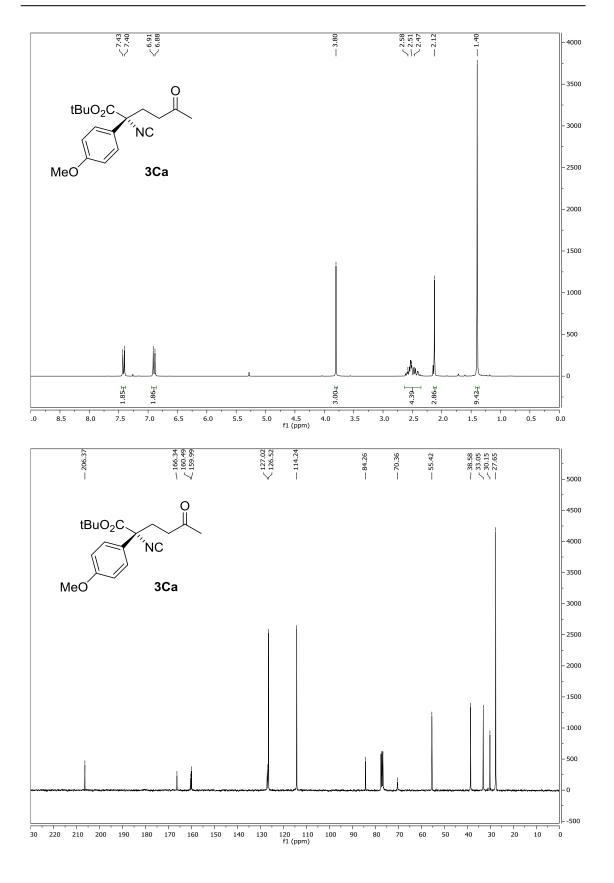


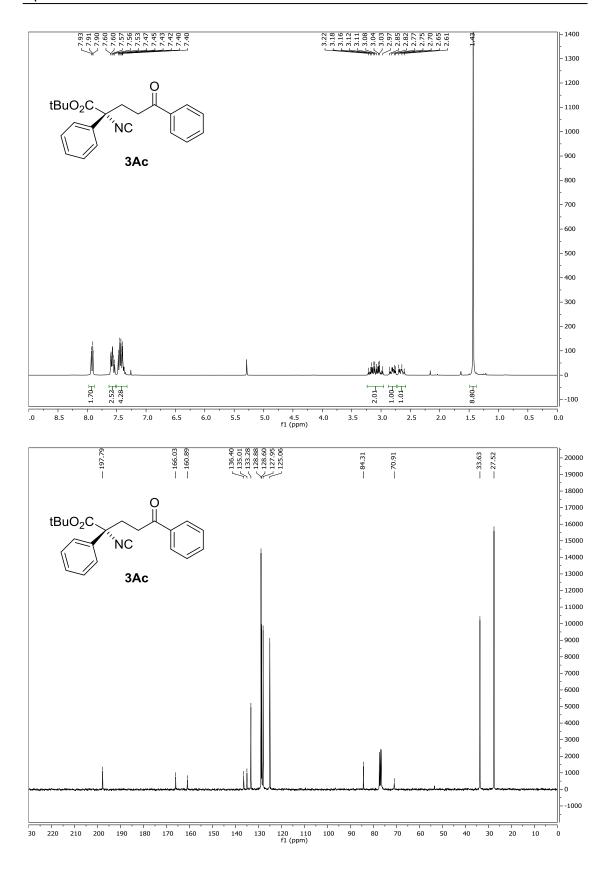


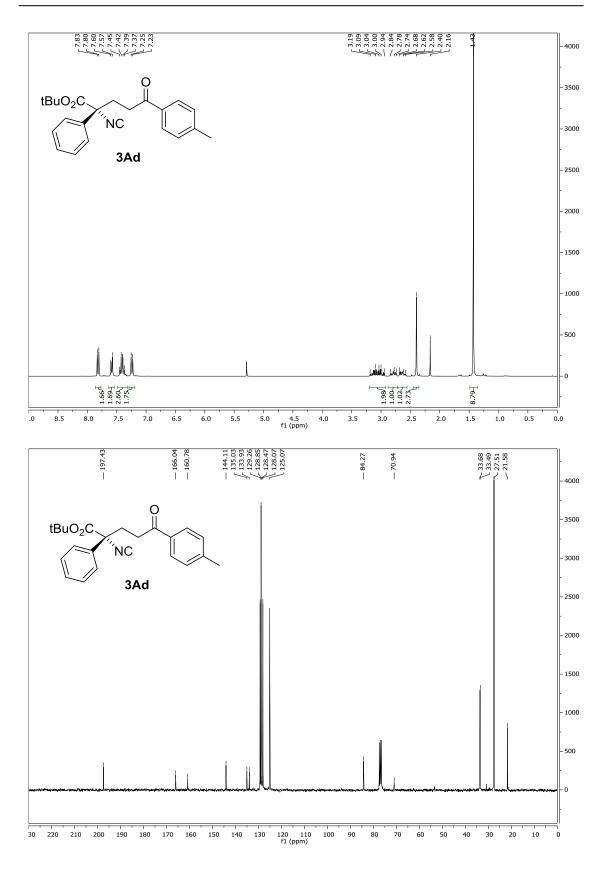
5.5.2.2. Michael adducts 3

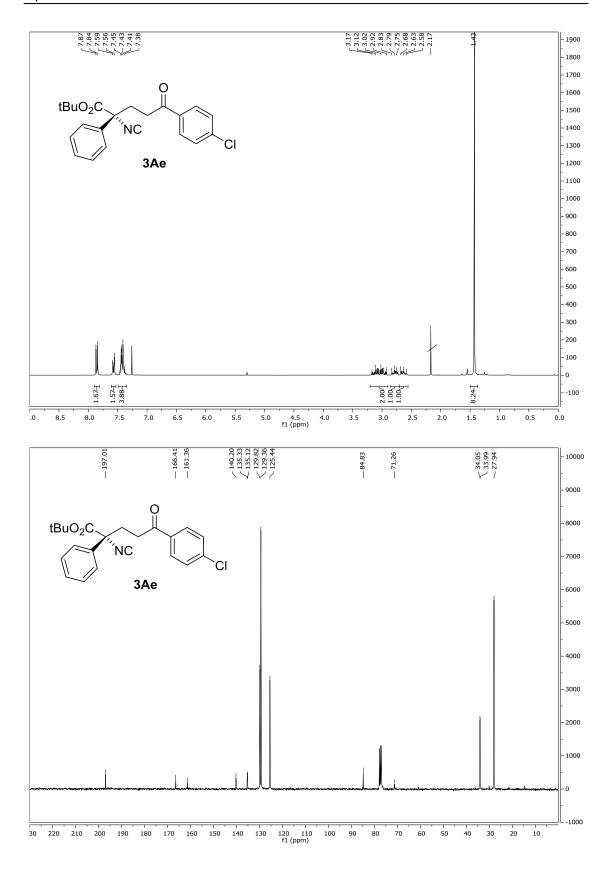


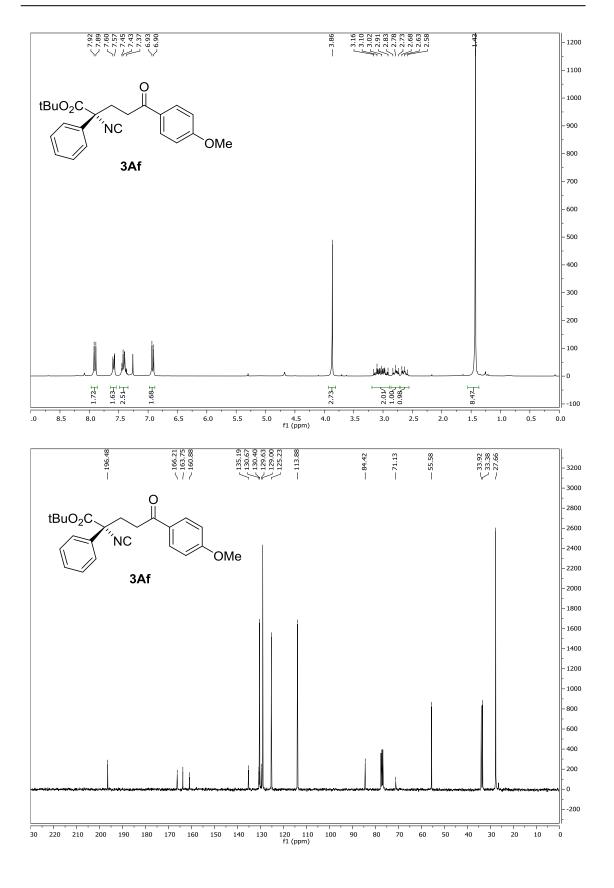


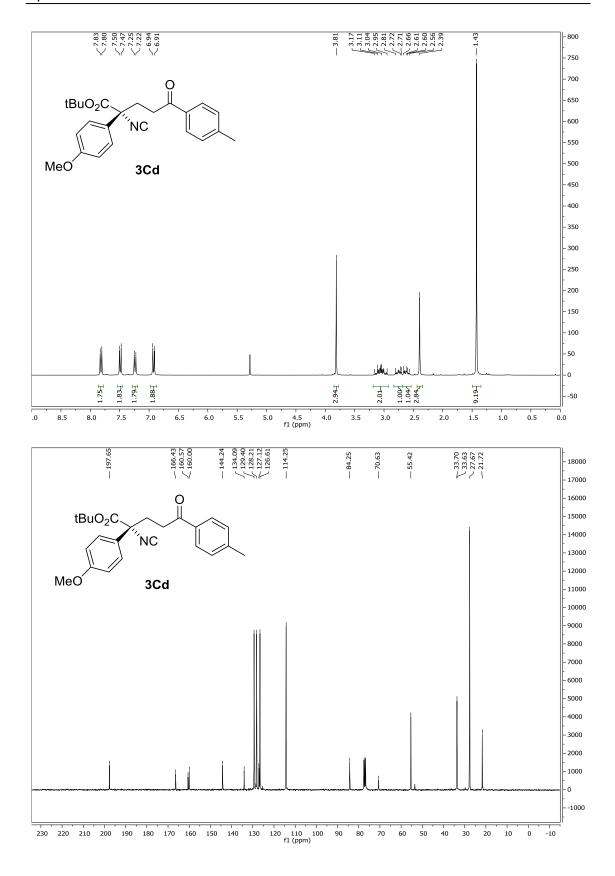


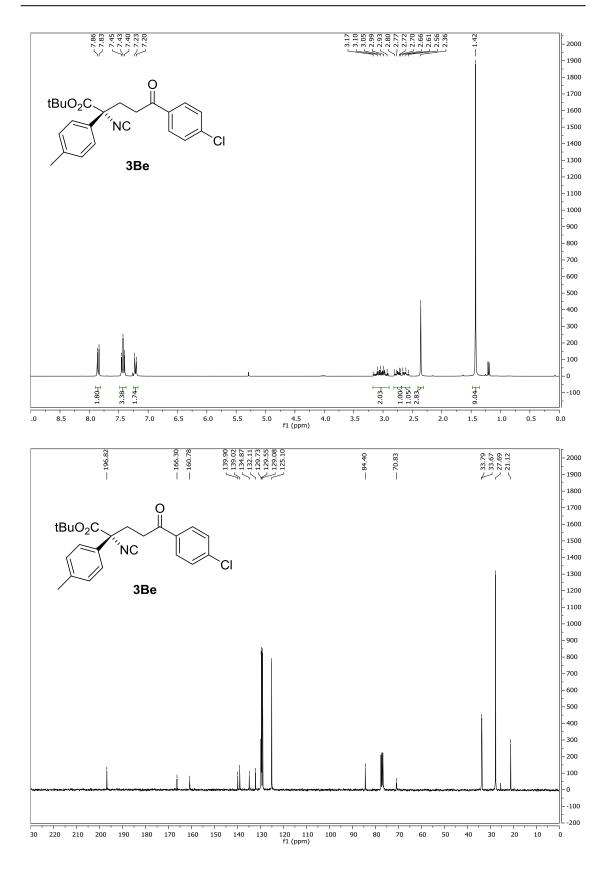


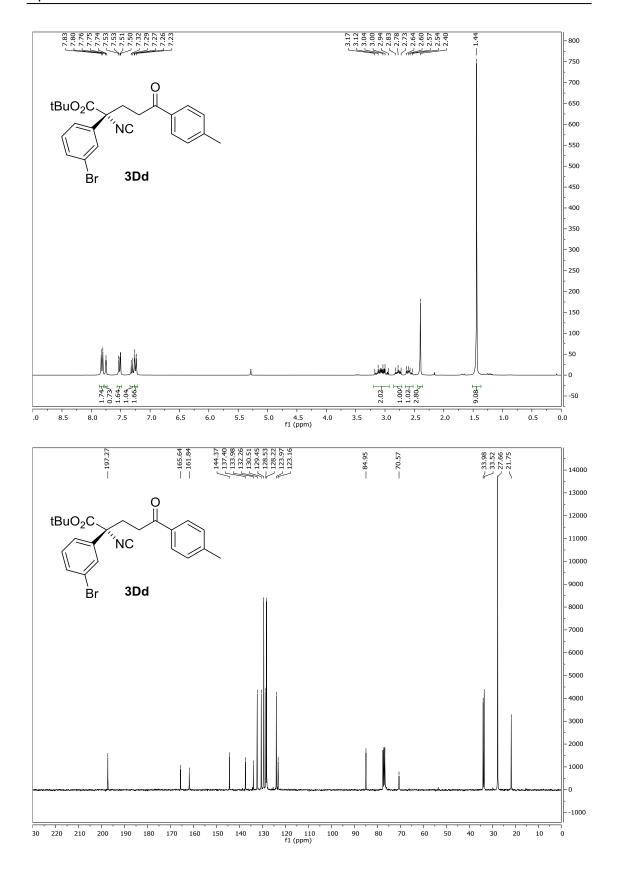




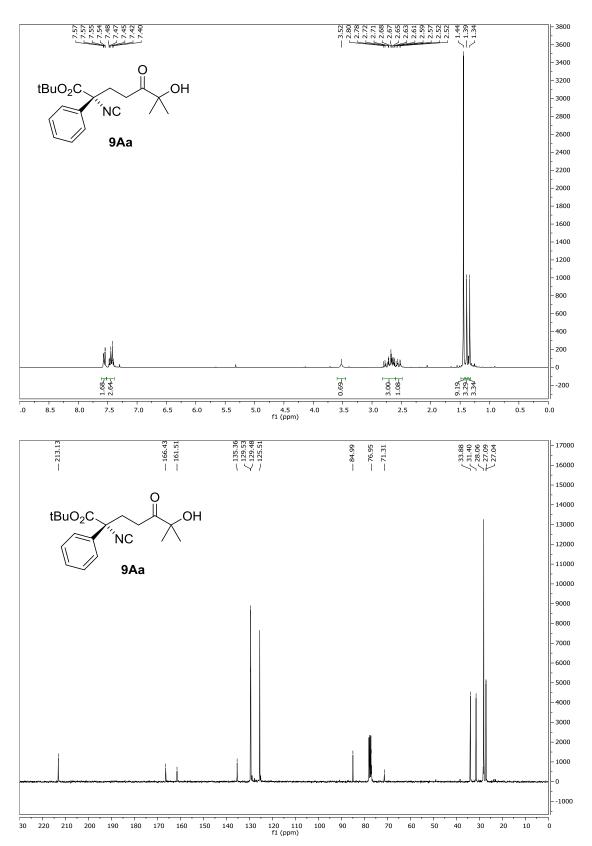


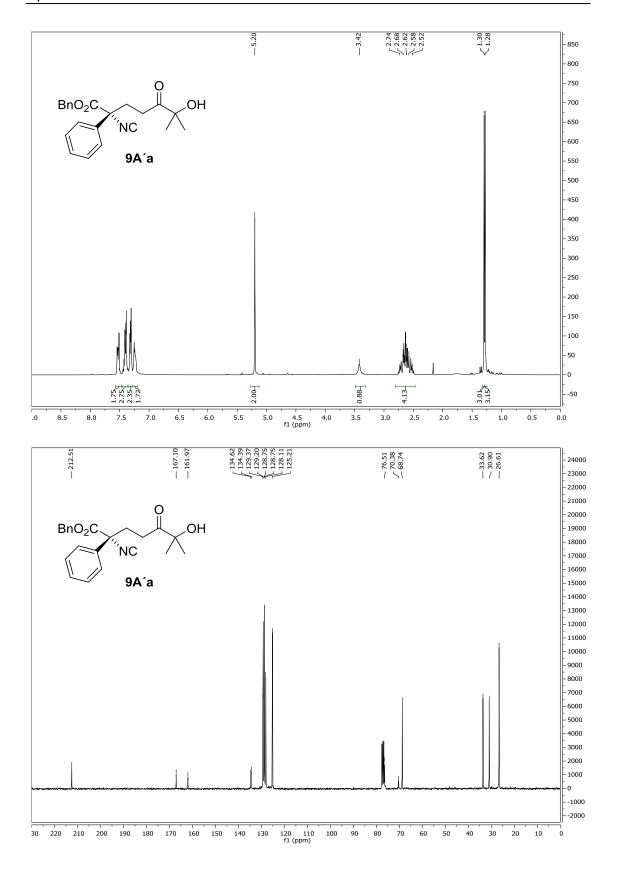


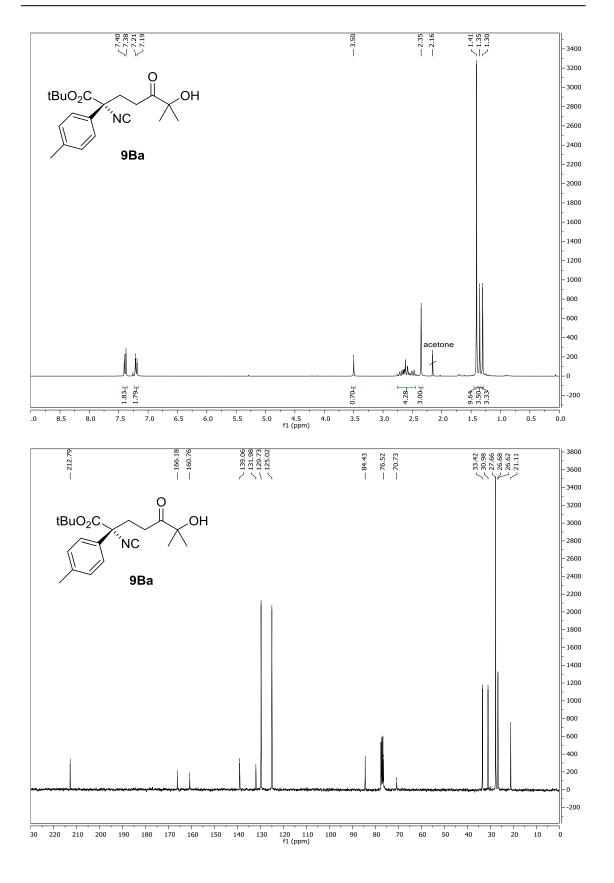


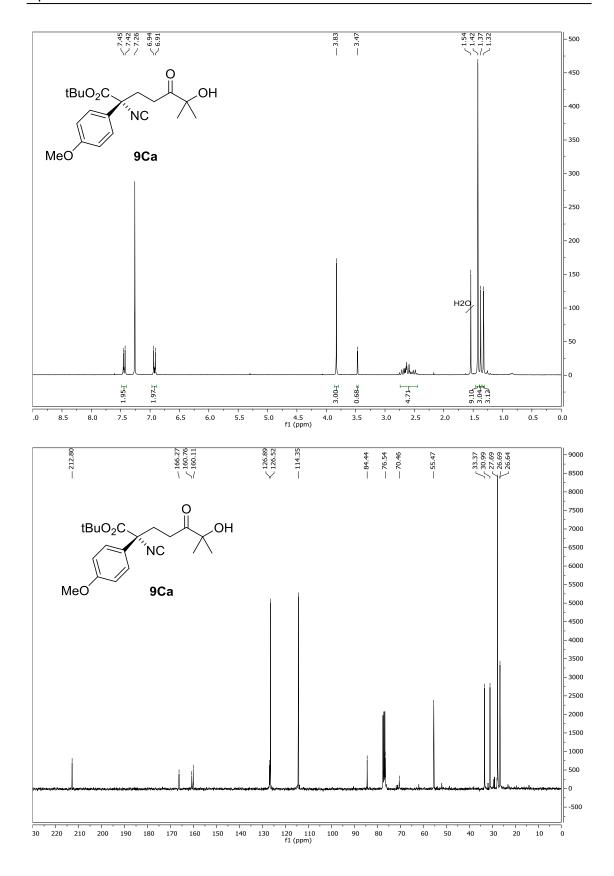


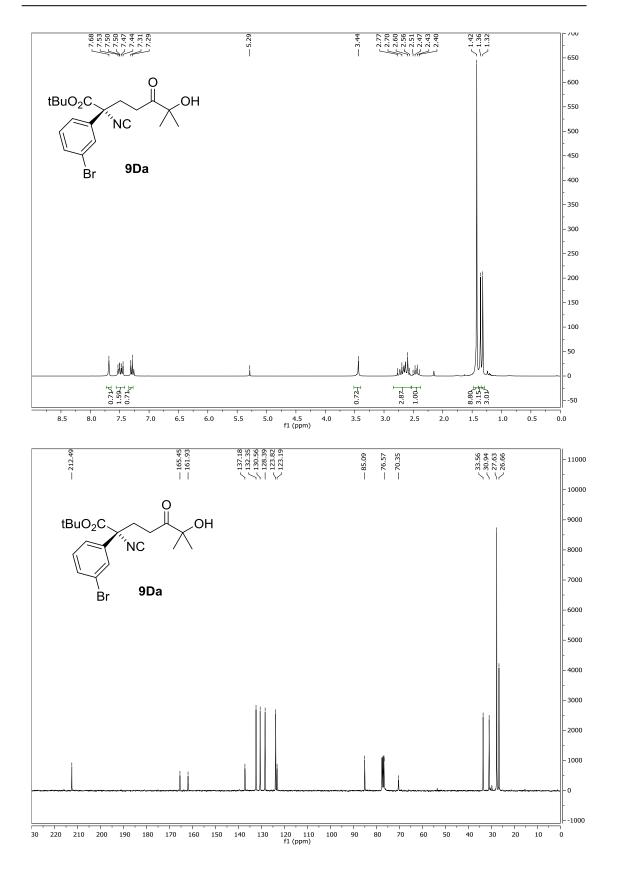
5.5.2.3. Michael adducts 9



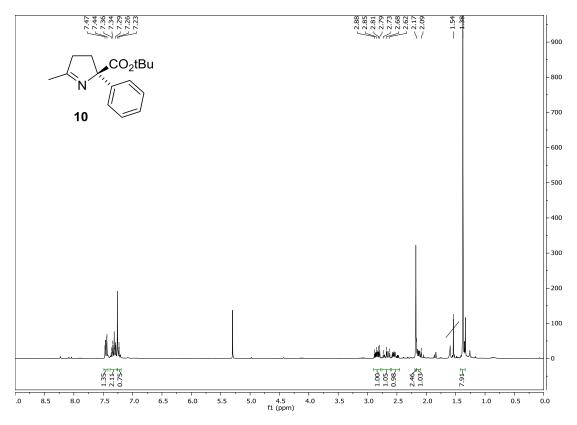


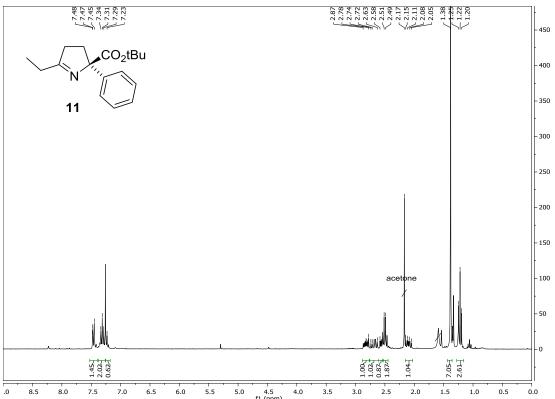


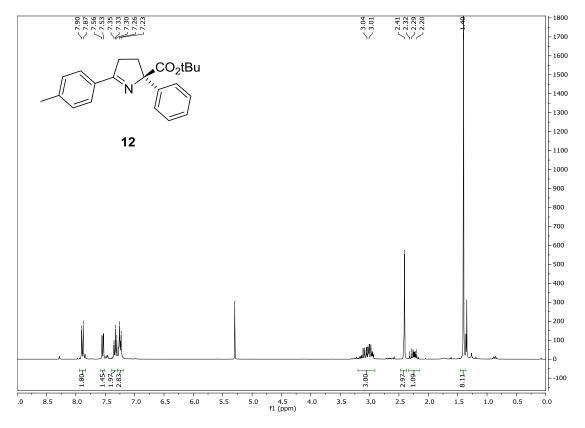


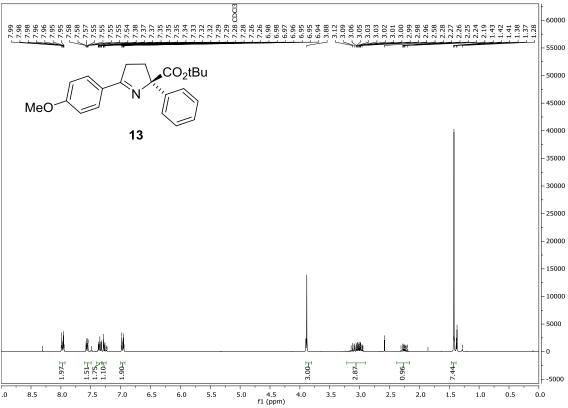


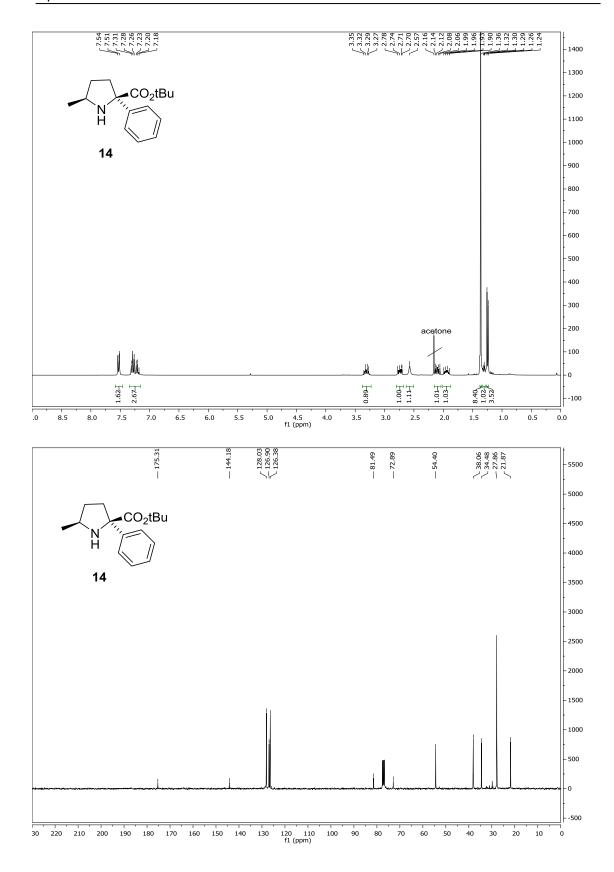
5.5.2.4. Elaboration of adducts

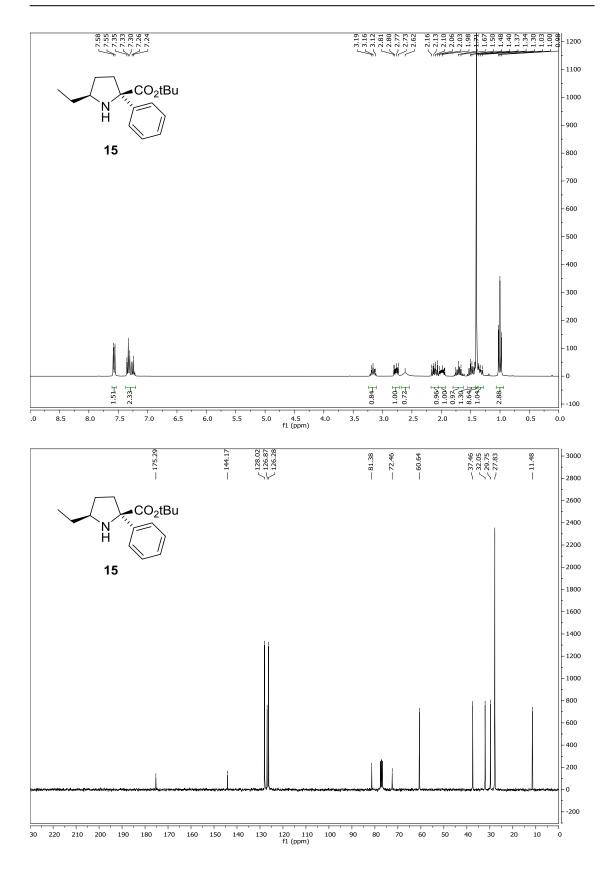


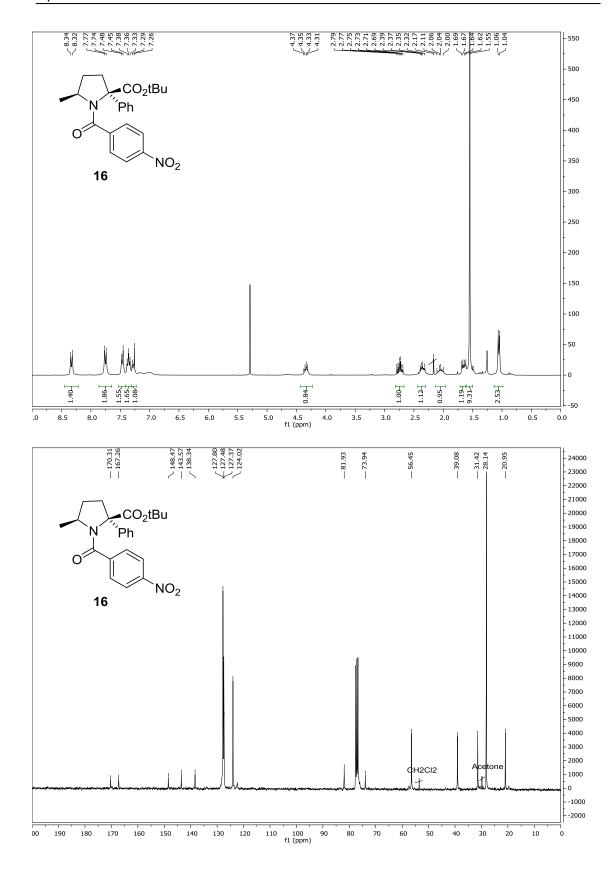


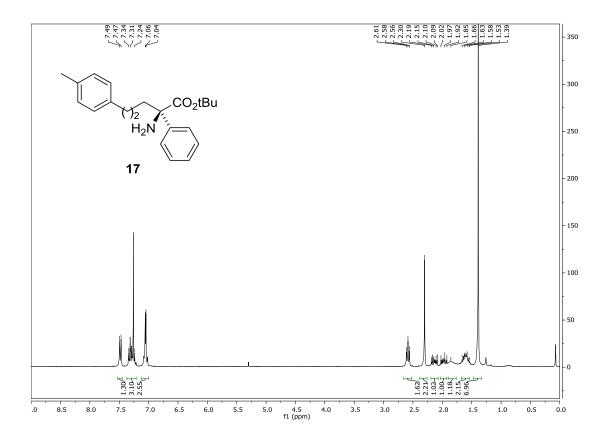


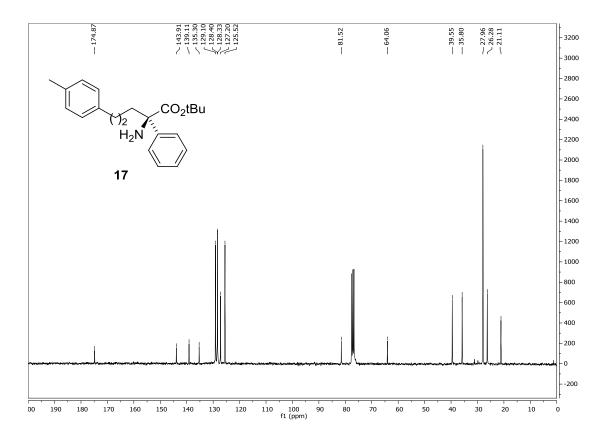


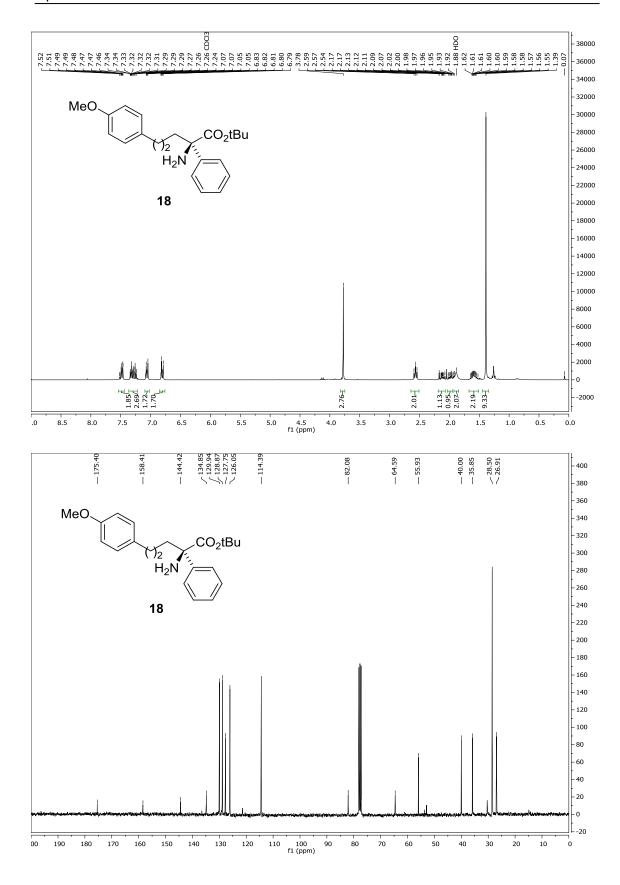


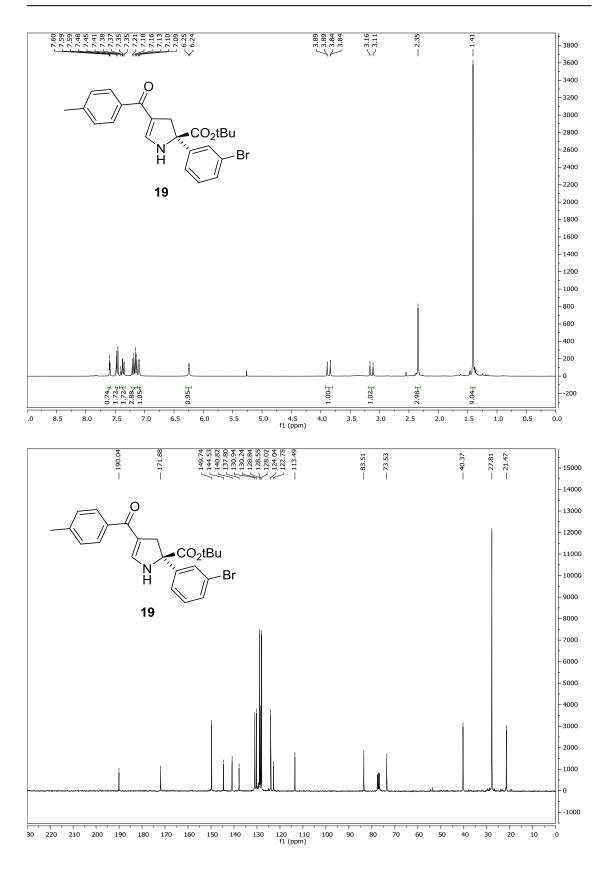


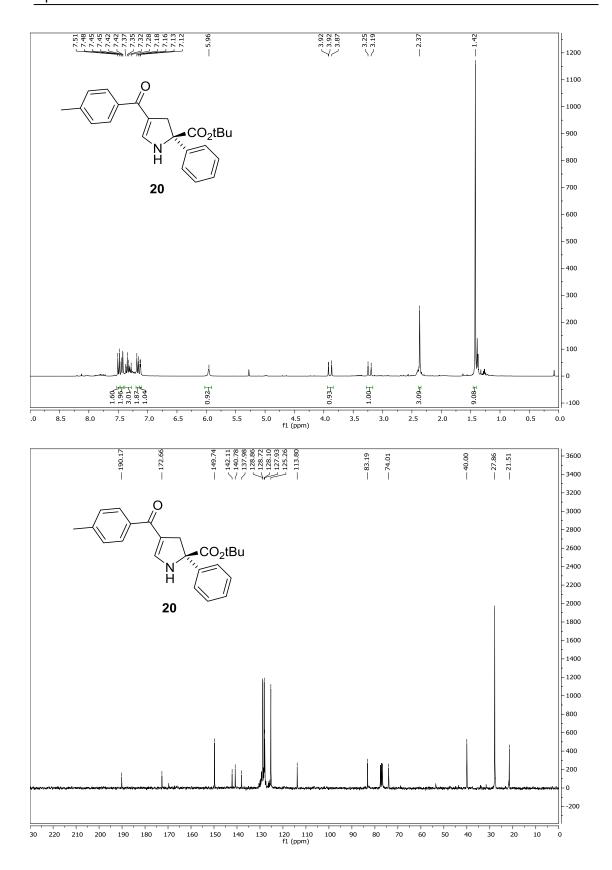


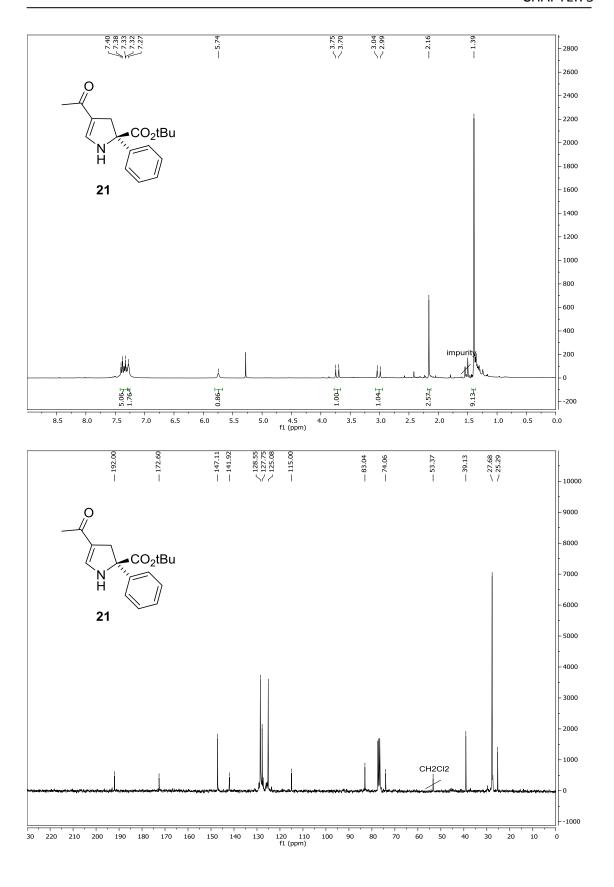


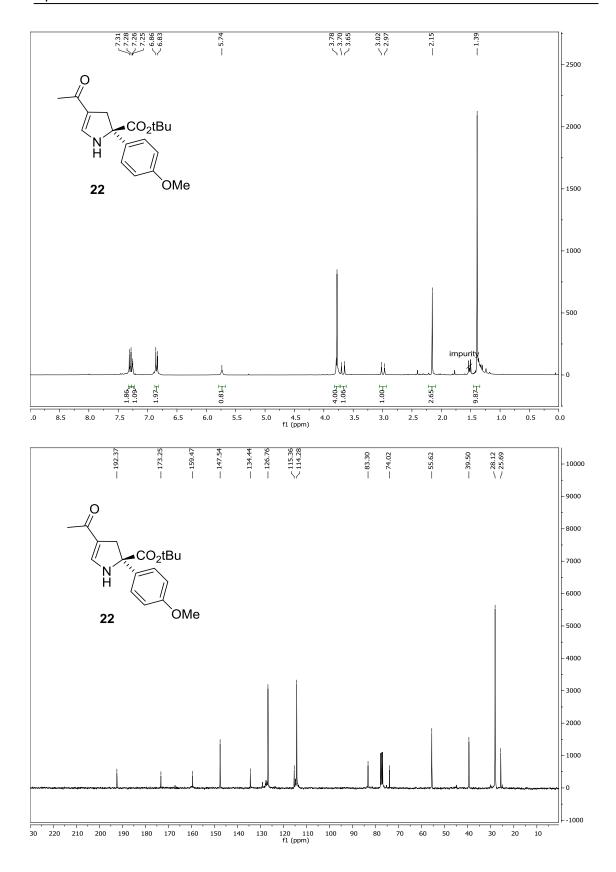


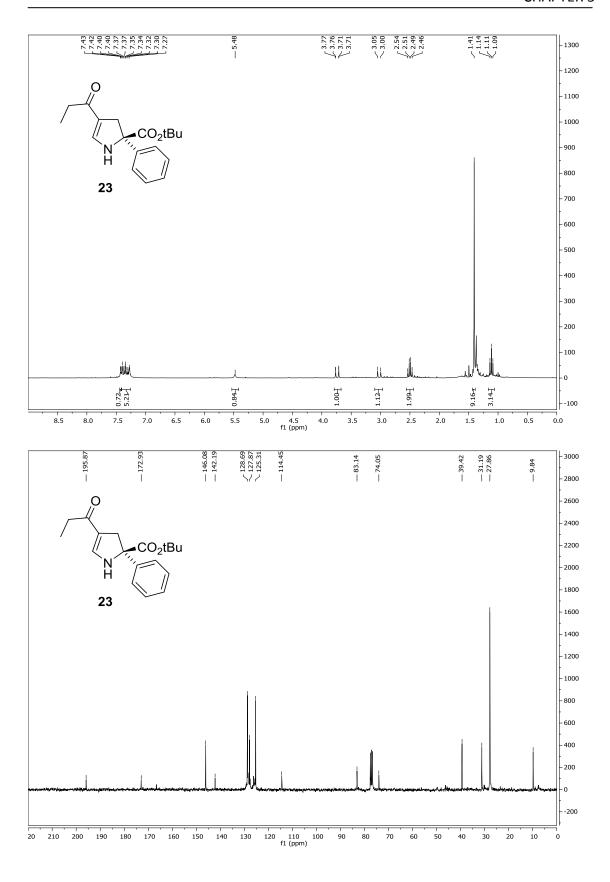


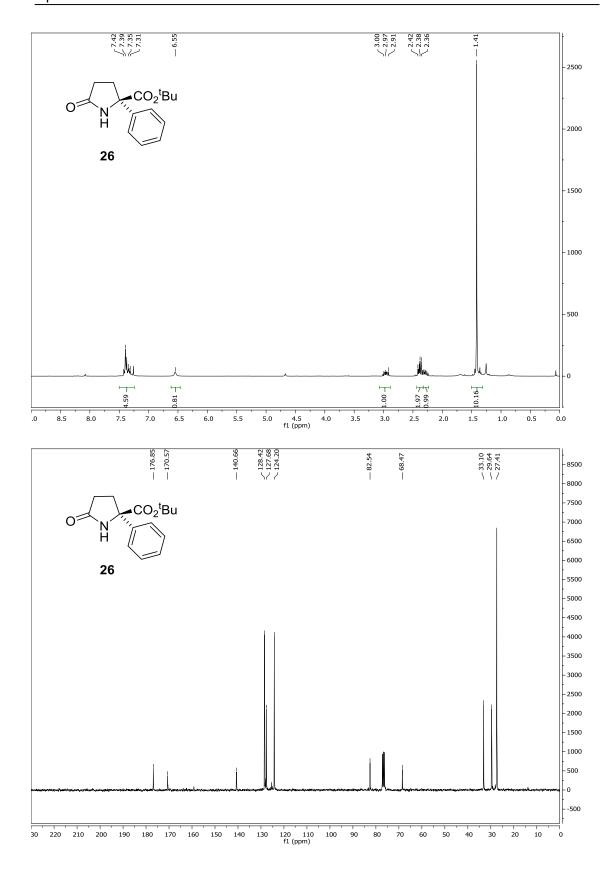






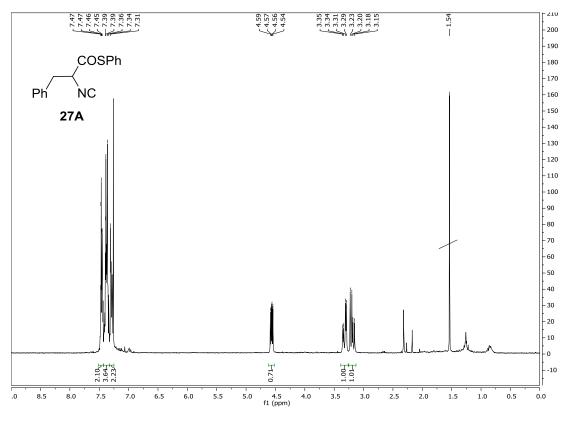


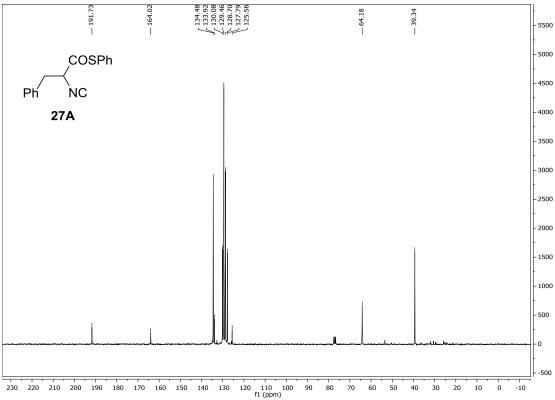


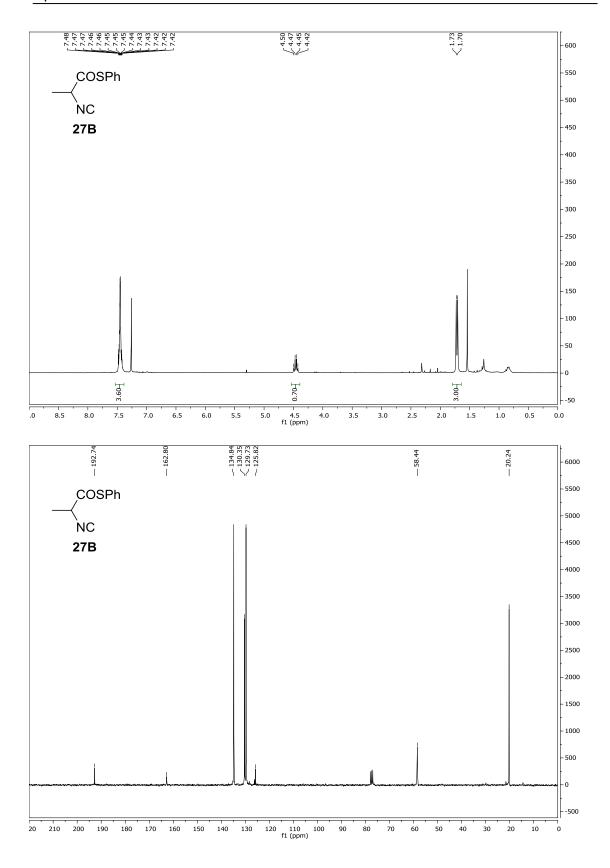


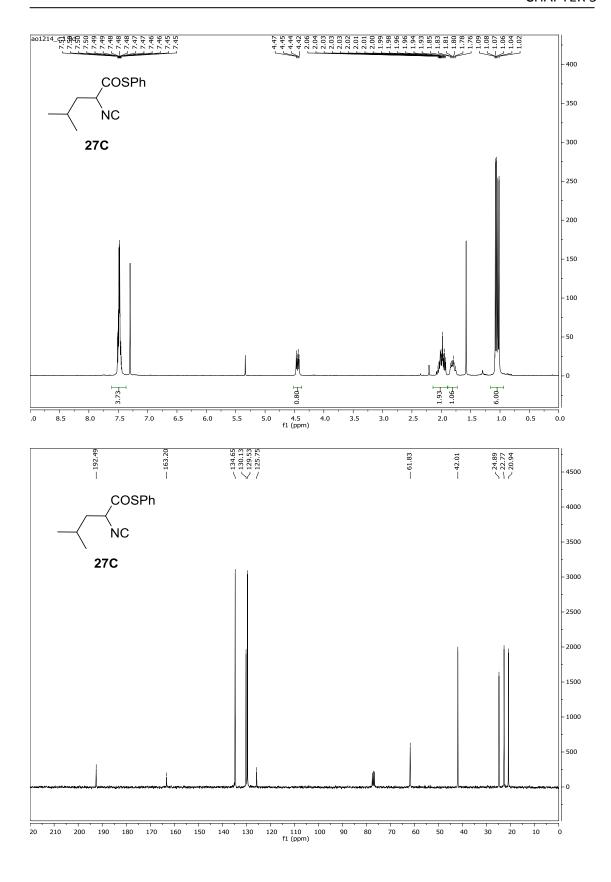
5.5.3. Chapter 3

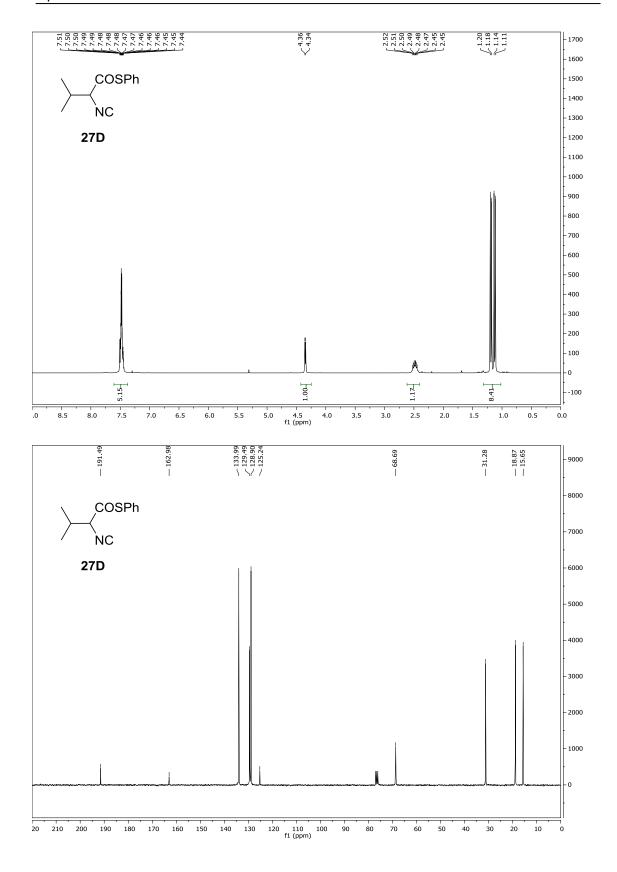
5.5.3.1. Isocyano(thio)acetates **27-35, 62 and 73**

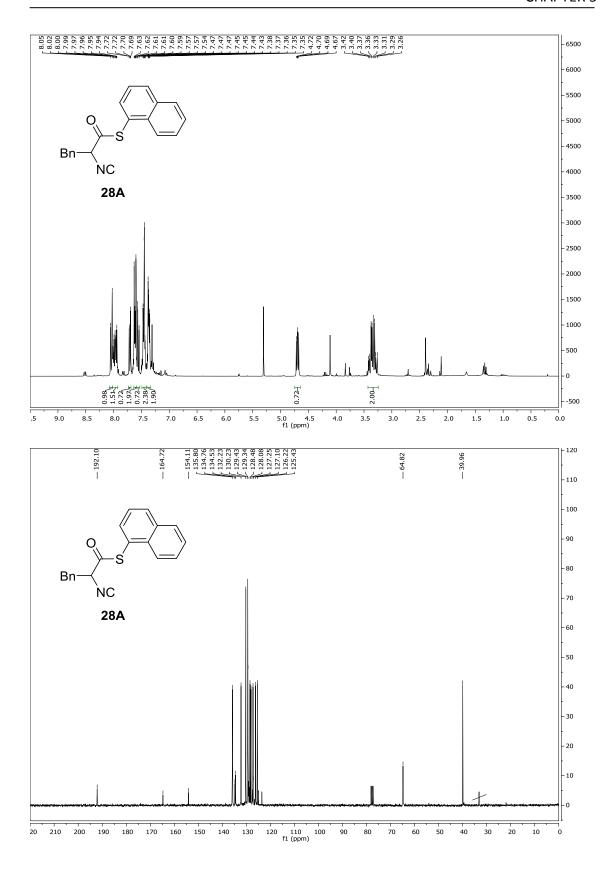


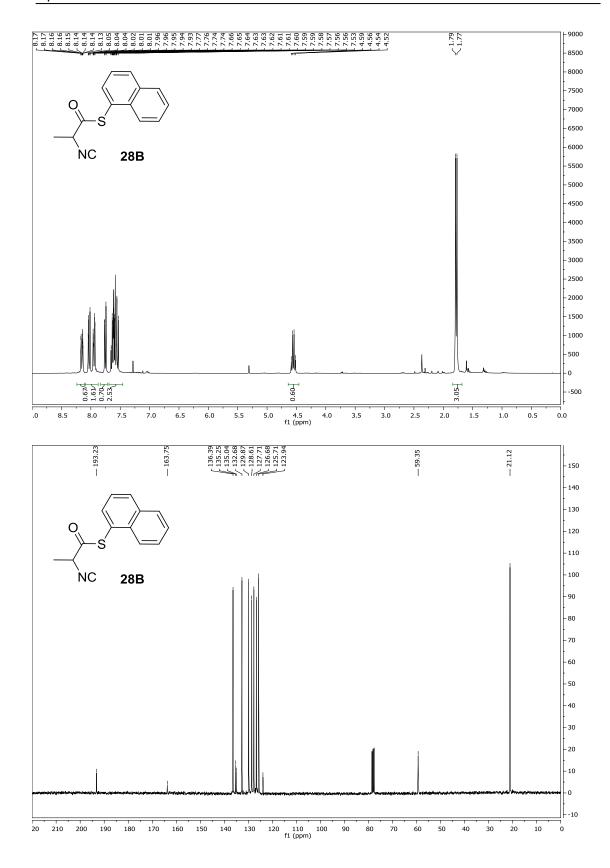


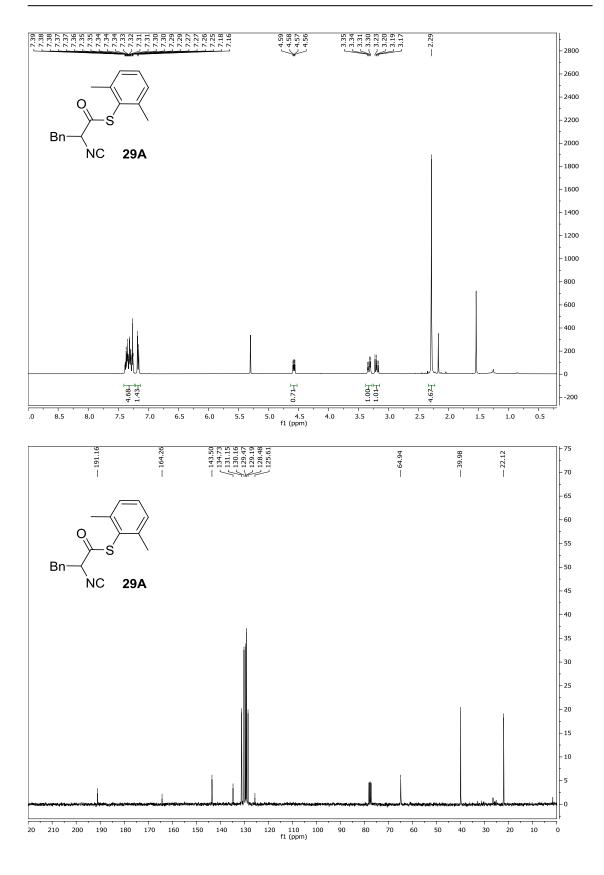


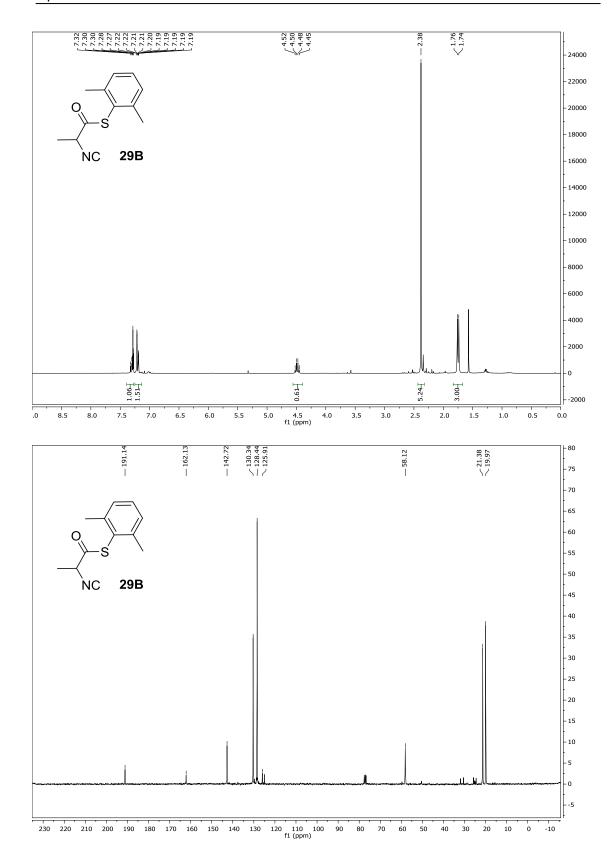


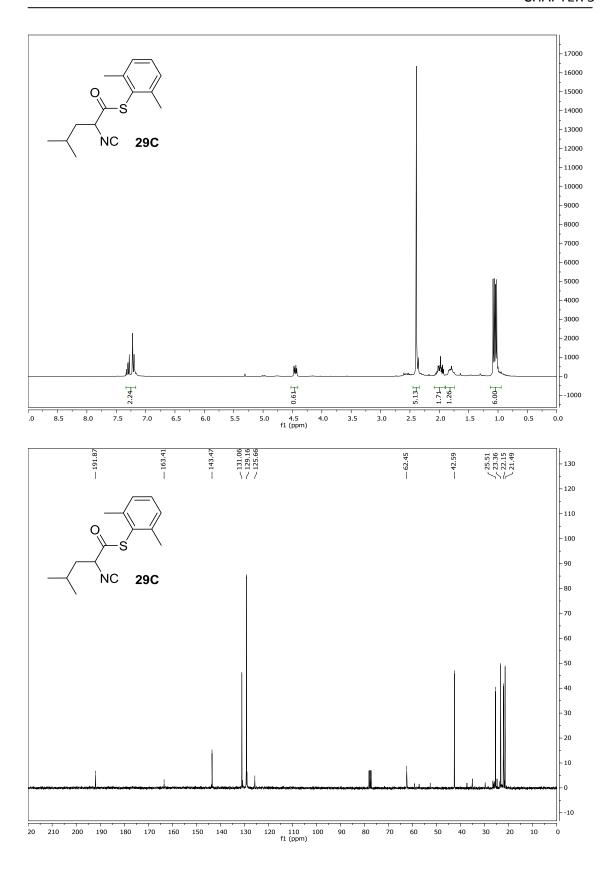


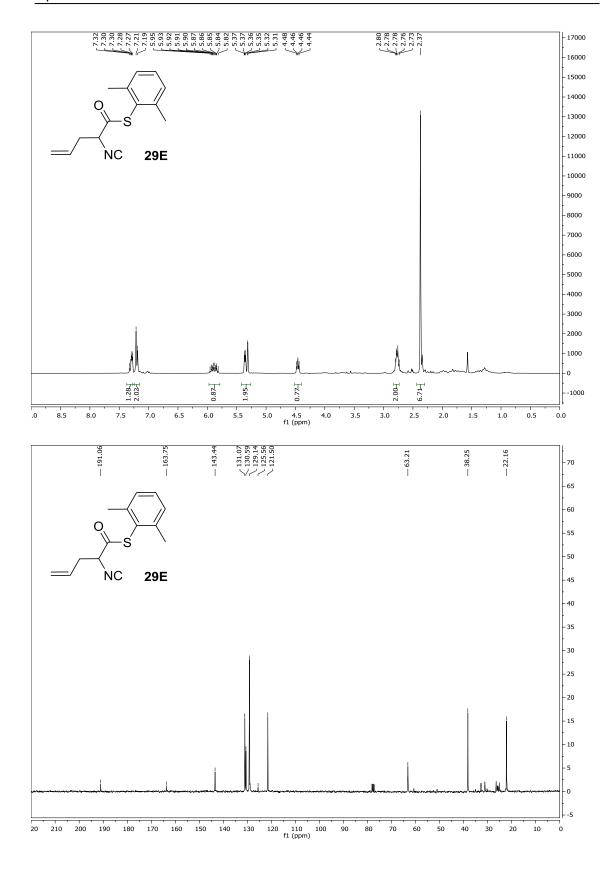


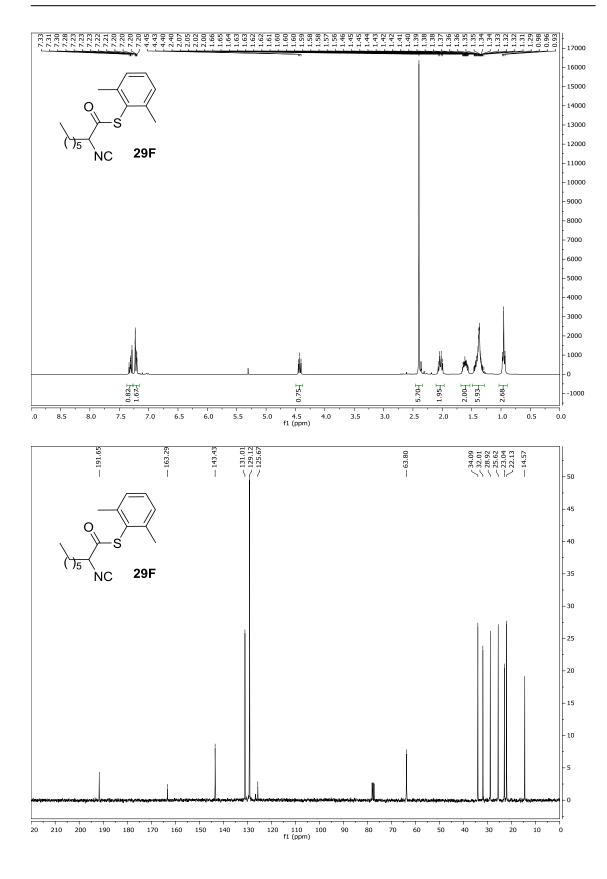


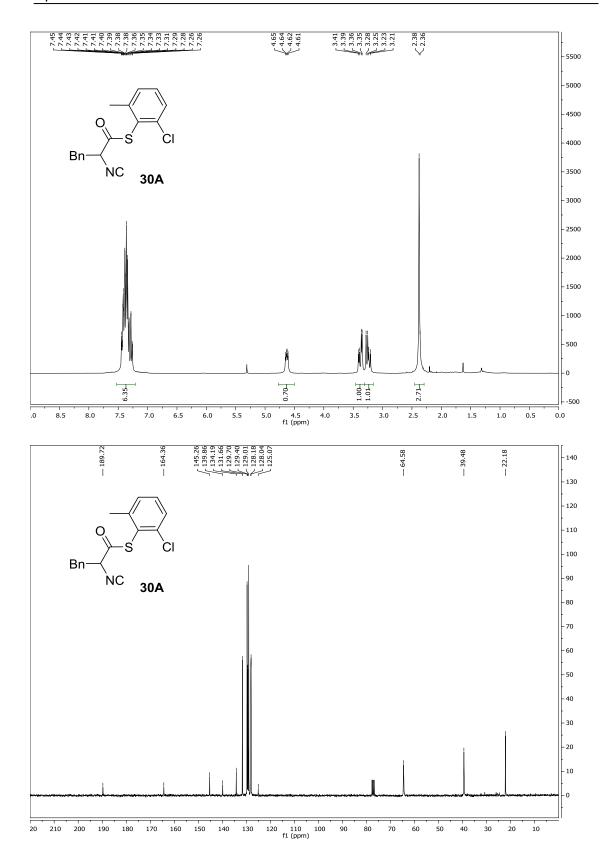


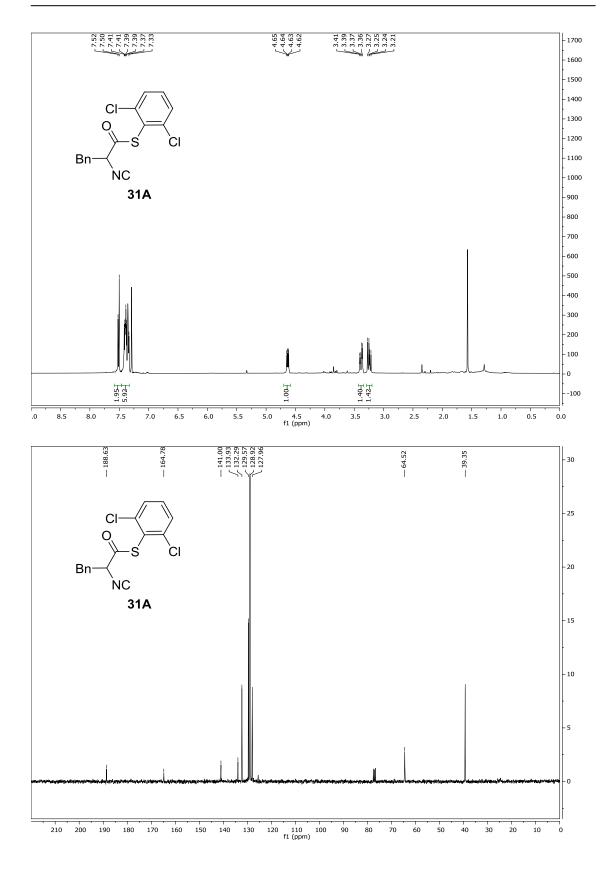


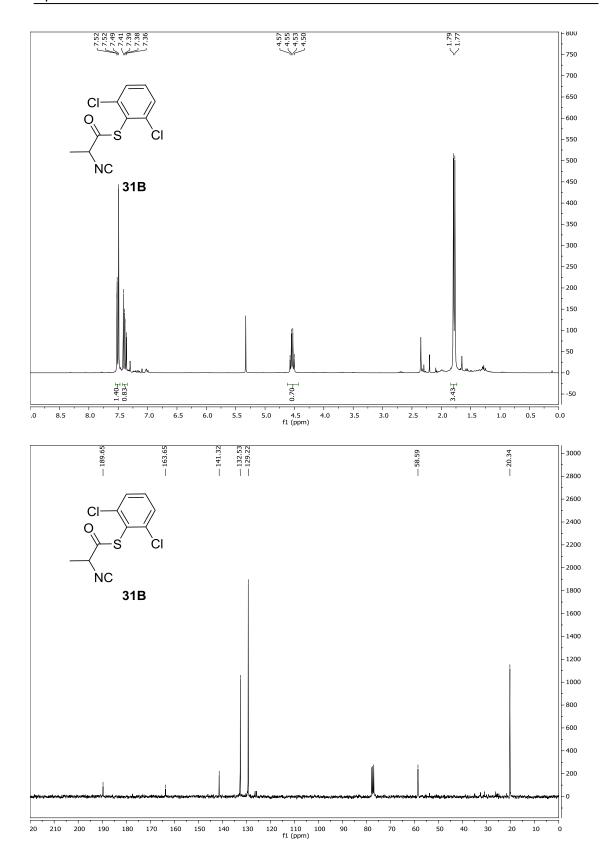


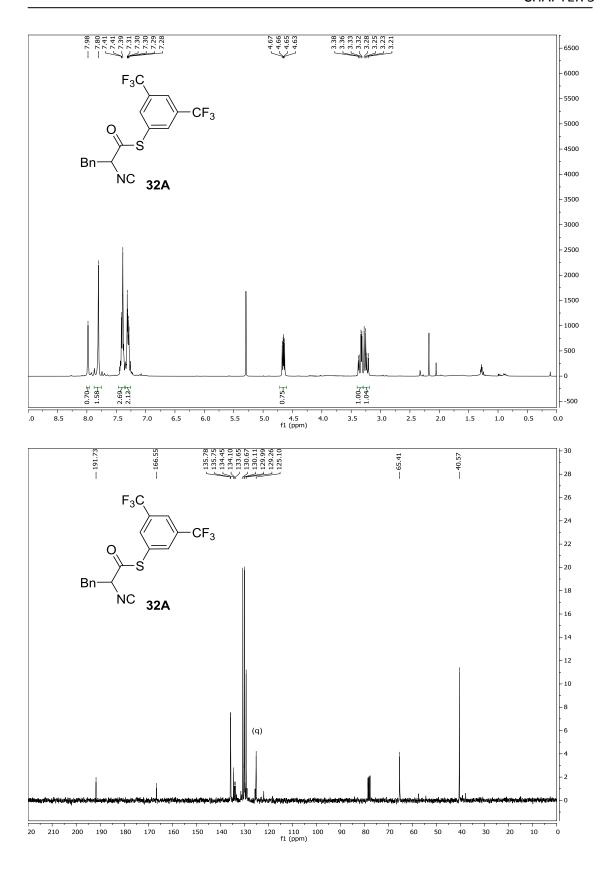


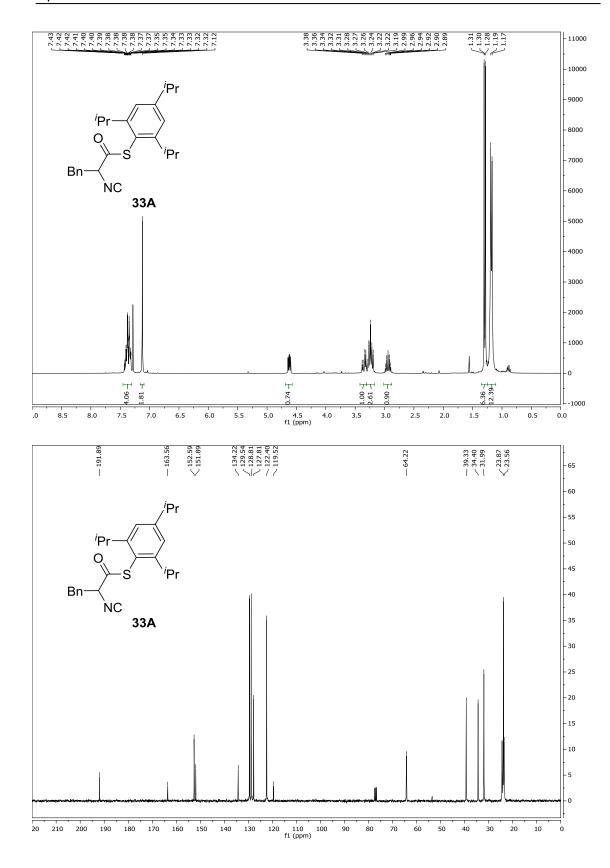


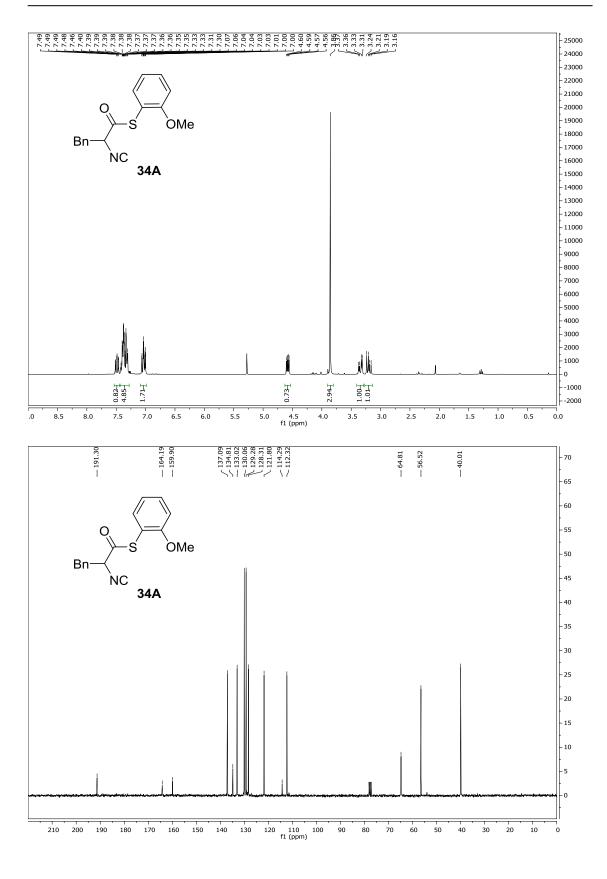


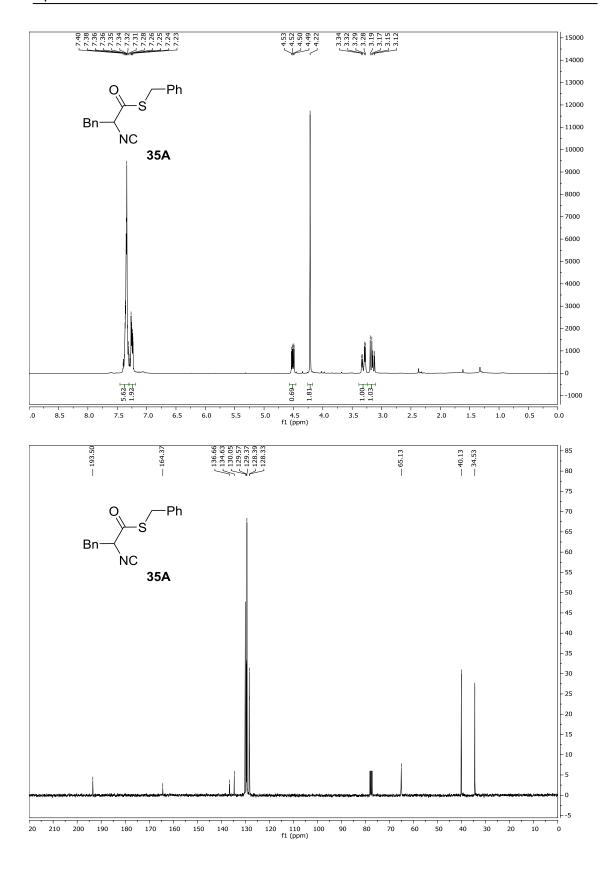


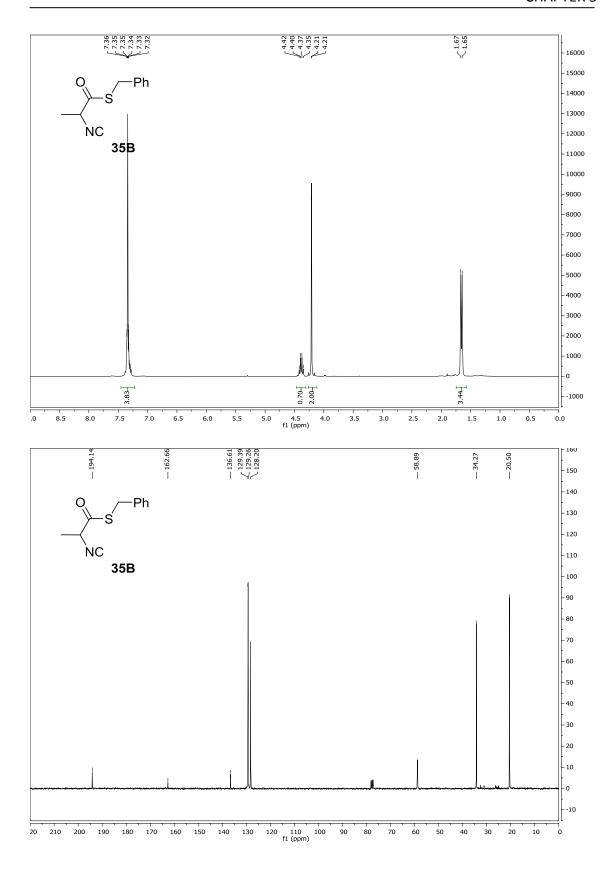


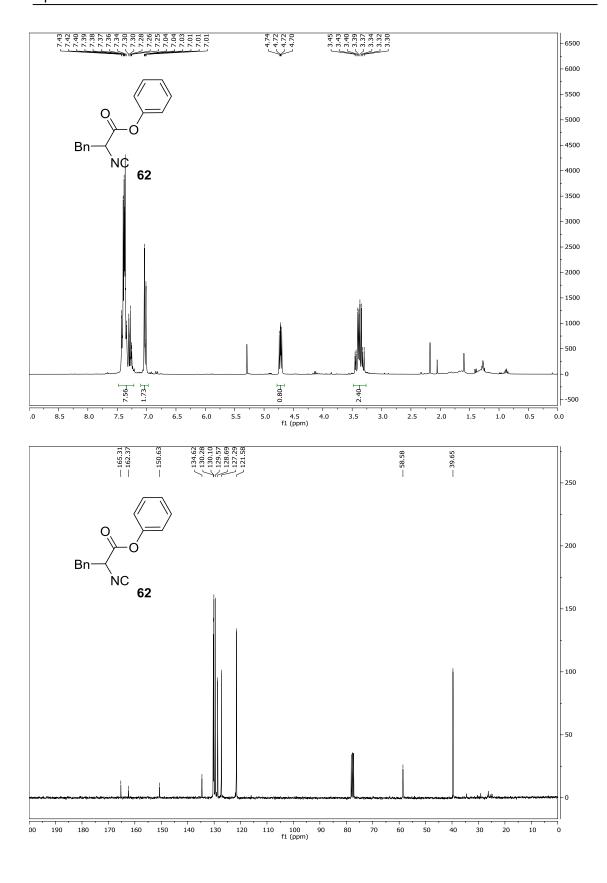


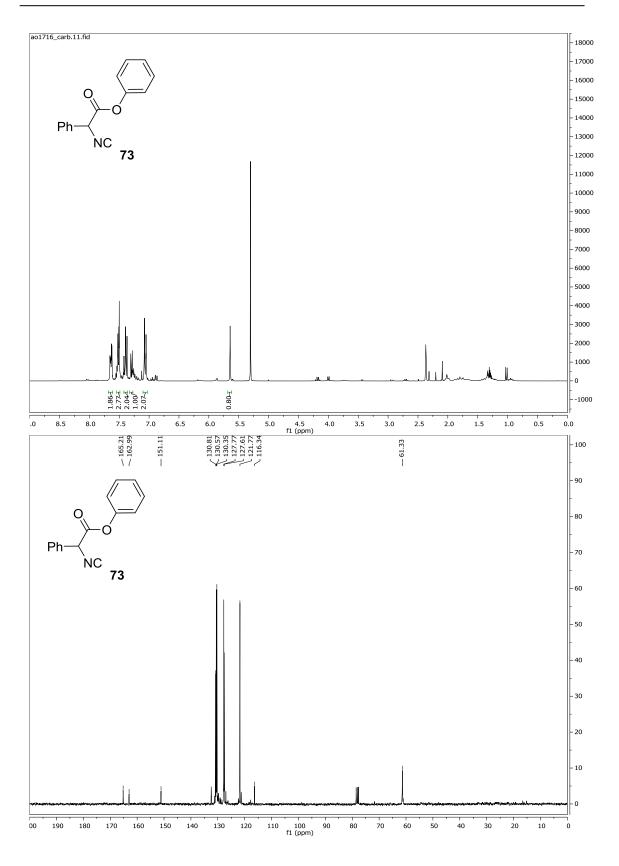












5.5.3.2. Adducts of the Michael addition to vinyl ketones

