Organocatalytic intramolecular *aza*-Michael reaction with enones and acid derivatives: New strategies

Cristina Mulet Chorro

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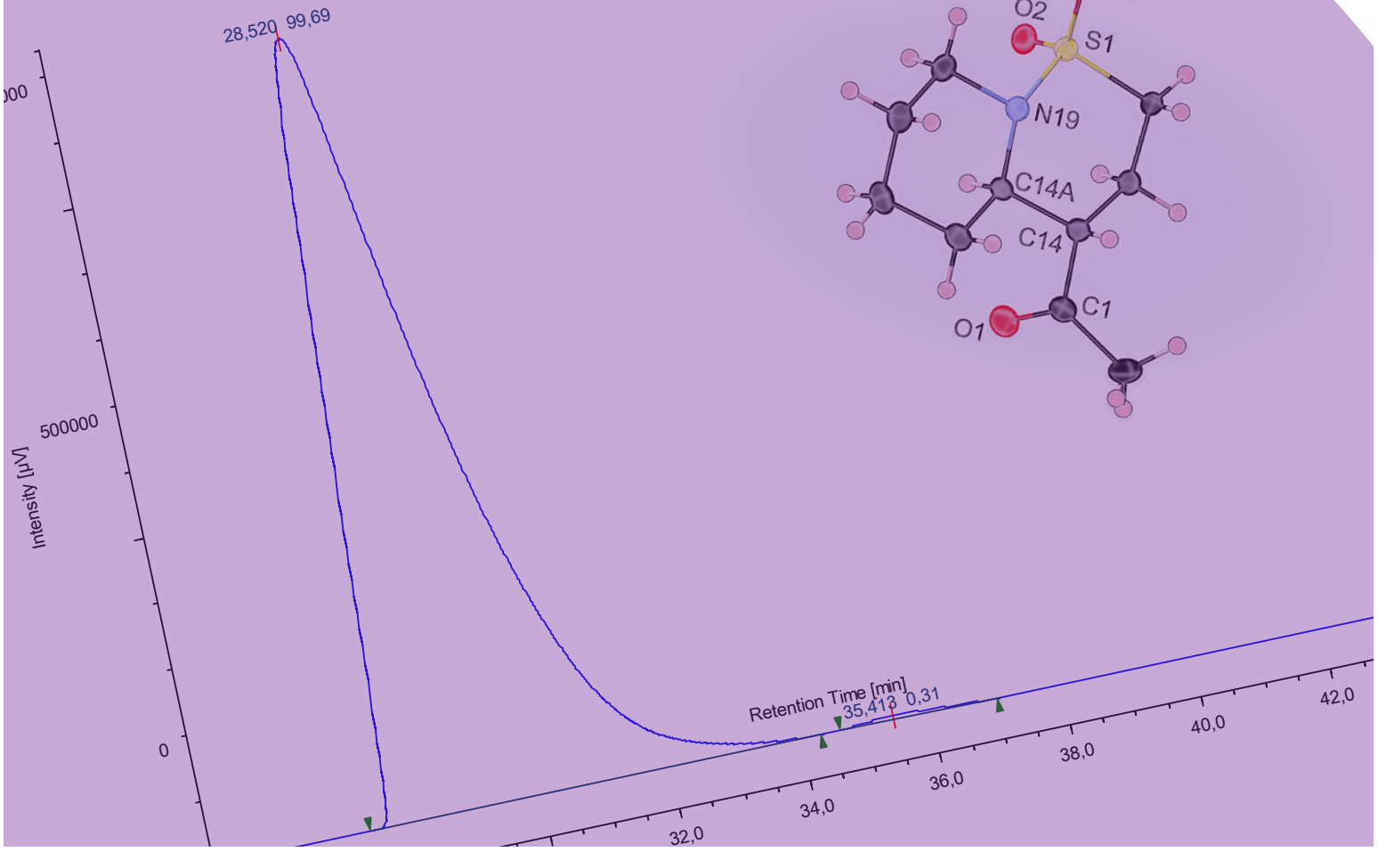

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Reacción *aza*-Michael intramolecular organocatalítica sobre enonas y derivados de ácido: Nuevas estrategias

Tesis Doctoral

Cristina Mulet Chorro

Dirigida por:

Prof. Santos Fustero Lardiés

Dr. Carlos del Pozo Losada

Valencia

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Prof. Santos Fustero Lardiés, Catedrático de Química Orgánica del Departamento de Química Orgánica de la Universidad de Valencia

Dr. Carlos del Pozo Losada, Profesor titular de Química Orgánica del Departamento de Química Orgánica de la Universidad de Valencia

CERTIFICAN:

Que la presente Tesis Doctoral, titulada "**Reacción *aza*-Michael intramolecular organocatalítica sobre enonas y derivados de ácido: Nuevas estrategias**" ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universidad deValencia, por la licenciada en Farmacia **Dña. Cristina Mulet Chorro** y autorizan su presentación para que sea calificada como Tesis Doctoral.

Valencia, Septiembre 2016

Fdo. Santos Fustero Lardiés

Fdo. Carlos del Pozo Losada

Fdo. Cristina Mulet Chorro

ABBREVIATIONS

List of Abbreviations

Å	Angstroms
aa	Amino acid
Ac	Acetyl
Ar	Aryl
BEMP	2-*Tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Bn	Benzyl
Boc	*Tert*-butyloxycarbonyl
br	Broad
BTFMBA	3,5-Bis(trifluoro-methyl)benzoic acid
Bu	Butyl
Calcd.	Calculated
Cbz	Benzyloxycarbonyl
CM	Cross metathesis
conv.	Conversion
CPME	Cyclopentyl methyl ether
CSA	(+)-10-Camphor-sulfonic acid
Cy	Cyclohexyl
d	Doblet
DBU	1,8-Diazabicycloundec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
Decomp.	Decomposition
DIC	Diisopropyl carbodiimide
DMAP	4-Dimethylamino-pyridine
DMF	*N*,*N*-Dimethyl-formamide
DMP	3,5-Dimethyl pyrazole
DNBSA	2,4-Dinitro-benzene sulfonic acid
DPP	Diphenylphospinoyl
d.r.	Diastereomeric relation
E	Electrophile
ee	Enantiomeric excess
EI	Electronic impact
equiv.	Equivalent/s
er	Enantiomeric relation
Et	Ethyl
EWG	Electro withdrawing group
FAB	Fast atom bombardment
FDA	Food and Drug Administration
G-I	Grubbs first-generation catalyst
G-II	Grubbs second-generation catalyst
h	hours
HG-II	Hoveyda-Grubbs second-generation catalyst
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass Spectrometry
Hz	Hertzs
IMAMR	Intramolecular *aza*-Michael reaction
***i*Pr**	Isopropyl
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LA	Lewis acid
LDA	Lithium diisopropylamide
LG	Leaving group
LiHMDS	Lithium hexamethyldisilazide
lit.	Literature
LUMO	Lowest unoccupied

	molecular orbital
m	Multiplet
M	Molar
mayor	Majoritary
MBH	Morita-Baylis-Hillman
Me	Methyl
Mes	Mesityl (2,4,6-trimethyl phenyl)
min	Minutes
minor	Minority
mmol	Milimols
m.p.	Melting point
Ms	Methanesulfonyl **(**mesyl)
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
MW	Microwave
NaHMDS	Sodium hexamethyldisilazide
N-Cbz-LP	*N*-Benzyloxycarbonyl-L-phenylalanine
NMR	Nuclear magnetic resonance
Ns	Nitrobenzenesulfonyl (nosyl)
Nu	Nucleophile
o-	Orto
OC	Organocatalyst
p-	Para
PC	Peptide coupling
PFPA	Pentafluoro-propionic acid
Ph	Phenyl
Pent	Pentyl
PG	Protecting group
PMP	*p*-Methoxyphenyl
***p*-NBA**	*p*-Nitrobenzoic acid
ppm	Part-per-million
Pr	Propyl
prod.	Product
py	Pyridine
q	Quadruplet
RID	Refractive index detector
r.t.	Room temperature
s	singlet
SM	Starting material
t	Triplet
t	Time
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TCE	1,1,2-Trichloroethane
TES	Triethylsilyl ether
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Toluene
Ts	*p*-Toluenesulfonyl (tosyl)
TSA	Toluene sulfonic acid
UV	Ultraviolet
UVD	Ultraviolet detector
δ	Chemical shift

ABSTRACT

RESUMEN

RESUM

Abstract

For the creation of carbon-nitrogen bonds and to access β-amino carbonylic compounds, together with the Mannich reaction, the *aza*-Michael reaction is considered one of the more appealing methodologies. It consists on the conjugate addition of a nucleophilic nitrogen source to an α,β-unsaturated system. This reaction has acquired a special relevance in its *intramolecular* version as it conducts to the formation of *nitrogen heterocycles* in a very straightforward manner. Furthermore, when the activated olefin contains prochiral centers, there are generated one or more stereogenic centers through the addition process. Thus, the *asymmetric* version of this transformation would allow the preparation of stereoselective functionalized nitrogen-containing compounds.

Whereas the conjugate addition of chiral amines to electronic deficient olefins has been the most employed strategy among the asymmetric *aza*-Michael reactions, the emergence of *catalytic* variants came late. Likewise, the *asymmetric* version of the *intramolecular* aza-*Michael* reaction has practically remained unexplored, being just organocatalyzed processes the few described examples.

The main constraint of the organocatalytic enantioselective *aza*-Micheal reaction is that the Michael acceptors are generally α,β-unsaturated aldehydes. The greater difficulty that implies the generation of the corresponding iminium ion with ketones has made the catalysis with these substrates a more compromised task. In this way, the use of primary amines, where the kinetic for the formation of the iminium intermediate is more favorable, has enabled a more efficient use of this transformation in its intermolecular version.

Similarly, the employment of α,β-unsaturated esters as Michael acceptors is not very extended and even less within the organocatalysis field. In this cases the activation process will always be through hydrogen bondings, since the ester group is not enough reactive as to form the iminium salt observed with aldehydes and ketones. Due to this poor reactivity of the conjugated esters, there have been developed a great variety of synthetic equivalents that either show an enhanced reactivity as electrophiles or they

facilitate the activation process and the formation of a more stable transition state through their hydrogen-bonding acceptors.

Taking the aforementioned into account and given the relevance of the asymmetric synthesis in organic chemistry, the objectives of the present PhD Thesis are focused on one hand, in the design of more general methodologies of organocatalytic enantioselective intramolecular *aza*-Michael reactions (IMAMR) for α,β-unsaturated ketones and esters; and on the other hand, in the application of those methodologies to the synthesis of structures of high interest, such as sultams.

The starting materials required to study the IMAMR are prepared through a cross-metathesis (CM) reaction between the α,β-unsaturated carbonylic compounds and the corresponding properly protected amines. The latter will be in turn obtained following procedures similar to those described in the literature. Once with the IMAMR substrates in hand, there will be studied the reaction conditions (solvent, temperature, catalyst, additive, …) to execute the intramolecular addition in an enantioselective fashion.

In conclusion, there have been developed several highly enantioselective protocols for the preparation of nitrogen heterocycles containing β-amino carbonylic motifs, applying chiral organocatalysts to activate α,β-unsaturated ketones and ester surrogates in the intramolecular *aza*-Michael reaction. Moreover, it has been achieved the application of one of these methodologies for the preparation of bicyclic sultams with a structural composition not described to date.

Resumen

Una de las metodologías más importantes, junto con la reacción de Mannich, para formar enlaces carbono-nitrógeno y acceder a compuestos β-amino carbonílicos, es la *reacción* aza-*Michael*, que consiste en la adición conjugada de una fuente de nitrógeno nucleófila a un sistema α,β-insaturado. Esta reacción adquiere una especial relevancia en su versión *intramolecular* ya que conduce a la formación de *heterociclos nitrogenados* de forma sencilla. Además, cuando la olefina activada contiene centros proquirales, en el proceso de adición se generan uno o más centros estereogénicos, por lo que la versión *asimétrica* de esta reacción permitiría obtener compuestos nitrogenados funcionalizados de forma estereoselectiva.

Mientras que la adición conjugada de aminas quirales a olefinas electrónicamente deficientes ha sido la estrategia más utilizada en la reacción *aza*-Michael asimétrica, la aparición de las variantes *catalíticas* ha sido mucho más tardía. De la misma forma, la versión *asimétrica* de la *reacción* aza-*Michael intramolecular* ha permanecido prácticamente inexplorada, y los ejemplos descritos hasta la fecha se basan en el empleo de organocatalizadores.

La principal limitación que presenta la reacción *aza*-Michael organocatalítica enantioselectiva es que habitualmente los aceptores de Michael son *aldehídos* α,β-insaturados. La mayor dificultad que supone generar la correspondiente sal de iminio con cetonas ha hecho que la catálisis con estos sustratos sea más comprometida. En este sentido, el empleo de aminas primarias, donde la formación de la sal de iminio tiene una cinética más favorable, ha permitido efectuar esta transformación de forma eficaz en su versión intermolecular.

Asimismo, la utilización de ésteres α,β-insaturados como aceptores de Michael no está muy extendida y aún menos en el campo de la organocatálisis. En estos casos la activación será siempre por enlaces de hidrógeno, puesto que el grupo éster es muy poco reactivo como para dar lugar a la formación del ion iminio observado con aldehídos y cetonas. Debido a esta baja reactividad de los ésteres conjugados, se han descrito muchos equivalentes sintéticos que

o bien presentan una mayor reactividad como electrófilos o bien permiten una mayor activación y fijación del estado de transición por presentar más puntos de anclaje de enlaces de hidrógeno.

Teniendo en cuenta lo expuesto anteriormente y dada la importancia de la síntesis asimétrica en química orgánica, los objetivos de la presente Tesis Doctoral se centran, por un lado, en el diseño de metodologías más generales de reacciones *aza*-Michael intramoleculares (AMIM) enantioselectivas y organocatalíticas para cetonas y ésteres α,β-insaturados; y por otra parte, en la aplicación de dichas metodologías a la síntesis de estructuras de elevado interés biológico, como por ejemplo las sultamas.

Los compuestos de partida para llevar a cabo las reacciones AMIM se prepararán a través de una reacción de metátesis cruzada (*CM*, *cross-metathesis*) entre los compuestos carbonílicos α,β-insaturados y las correspondientes aminas adecuadamente protegidas. Éstas últimas se obtendrán a su vez siguiendo procedimientos similares a los descritos en la bibliografía. Una vez preparados los sustratos para la reacción *aza*-Michael, se estudiarán las condiciones de reacción (disolvente, temperatura, catalizador, aditivo, …) que permitan efectuar esta adición intramolecular de forma enantioselectiva.

En conclusión, se han desarrollado diversos protocolos altamente enantioselectivos para la preparación de heterociclos nitrogenados con unidades β-amino carbonílicas empleando organocatalizadores quirales para la activación de la reacción *aza*-Michael intramolecular con cetonas y equivalentes de ésteres α,β-insaturados. Además, se ha conseguido aplicar una de estas metodologías para la preparación de sultamas bicíclicas con una distribución estructural no descrita hasta el momento.

Resum

Una de les metodologies més importants, junt amb la reacció de Mannich, per la formació d'enllaços carboni-nitrogen i per accedir a compostos β-amino carbonílics, és la *reacció* aza-*Michael*, que consisteix en l'addició conjugada d'una font de nitrogen nucleòfila a un sistema α,β-insaturat. Aquesta reacció adquireix una especial rellevància a la seua versió *intramolecular* ja que condueix a la formació d'*heterocicles nitrogenats* de forma senzilla. A més, quan l'olefina activada conté centres proquirals, al procés d'addició es generen un o més centres estereogènics, pel que la versió *asimètrica* d'esta reacció permetria obtenir compostos nitrogenats funcionalitats de forma estereoselectiva.

Mentre que l'addició conjugada de amines quirals a olefines electrònicament deficients ha sigut l'estratègia més utilitzada a la reacció *aza*-Michael asimètrica, l'aparició de les variants *catalítiques* ha sigut molt més tardana. De la mateixa manera, la versió *asimètrica* de la *reacció* aza-*Michael intramolecular* ha romàs pràcticament inexplorada, i els exemples descrits fins la data es basen en la utilització d'organocatalitzadors.

La principal limitació que presenta la reacció *aza*-Michael organocatalítica enantioselectiva és que habitualment els acceptors de Michael són *aldehids* α,β-insaturats. La major dificultat que suposa generar la corresponent sal d'imini amb cetones ha fet que la catàlisi amb aquests substrats estiga més compromesa. En aquest sentit, la utilització de amines primàries, on la formació de la sal d'imini té una cinètica més favorable, ha permès efectuar aquesta transformació de forma eficaç en la seua versió intermolecular.

Així mateix, la utilització d'èsters α,β-insaturats com acceptors de Michael no està molt estesa i encara menys al camp de l'organocatàlisi. En aquests casos l'activació serà sempre per enllaços d'hidrogen, posat que el grup èster és molt poc reactiu com per donar lloc a la formació de l'ió imini observat amb aldehids i cetones. Degut a aquesta baixa reactivitat dels èsters conjugats, s'han descrit molts equivalents sintètics que o bé presenten una

major reactivitat com a electròfils o bé permeten una major activació i fixació de l'estat de transició al presentar més punts d'ancoratge d'enllaços d'hidrogen.

Tenint en compte l'exposat anteriorment i donada la importància de la síntesi asimètrica en química orgànica, els objectius de la present Tesi Doctoral es centren, por una banda, en el disseny de metodologies més generales de reaccions *aza*-Michael intramoleculars (AMIM) enantioselectives i organocatalítiques per cetones y èsters α,β-insaturats; i por altra banda, en l'aplicació de dites metodologies a la síntesi d'estructures d'elevat interès biològic, com per exemple les sultames.

Els substrats de partida per realitzar les reaccions AMIM es prepararan a través d'una reacció de metàtesi creuada (*CM*, *cross-metathesis*) entre els compostos carbonílics α,β-insaturats i les corresponents amines adequadament protegides. Aquestes últimes s'obtindran a la seua vegada seguint procediments similars als descrits a la bibliografia. Una vegada preparats els substrats per la reacció *aza*-Michael, s'estudiaran les condicions de reacció (dissolvent, temperatura, catalitzador, additiu, …) què permeten efectuar aquesta addició intramolecular de forma enantioselectiva.

En conclusió, s'han desenvolupat diversos protocols altament enantioselectius per la preparació d'heterocicles nitrogenats amb unitats β-amino carboníliques utilitzant organocatalitzadors quirals per l'activació de la reacció *aza*-Michael intramolecular amb cetones i equivalents d'èsters α,β-insaturats. A més, s'ha aconseguit aplicar una d'aquestes metodologies per la preparació de sultames bicícliques amb una distribució estructural no descrita fins el moment.

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GENERAL INTRODUCTION AND OBJECTIVES

0.1. General Introduction

0.1.1. ASYMMETRIC SYNTHESIS

Among the diverse areas of influence of organic chemistry research, *design and synthesis of new drugs* occupy a prominent place, and amazing amount of resources are devoted to this endeavour due to the relevance of this task. The main goal of drug design is to prepare defined molecular structures with an expected therapeutic action. Therefore, the ***study of new synthetic methods*** that gains access to those tailor-made compounds can have a significant impact in the drug discovery process. At the same time, the need of more green and environmentally friendly processes drives current research efforts for the preparation of both new and existing drugs.

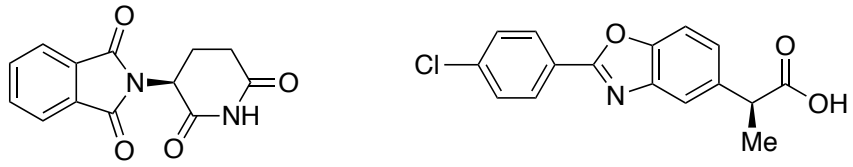
Asymmetric synthesis plays a key role in drug development, since one half of the currently marketed drugs contain at least one stereocenter, and among the top ten best selling drugs nine are composed of chiral molecules. The importance of the concept of chirality in Nature and in research it is known since long time ago, and the first to coin the term chiral (from Greek *kheir*: hand) was Lord Kelvin by the end of the nineteenth century.[1] Besides, the significance of stereoisomerism in relation to biological activity has been recognized by scientists since 1848, when Louis Pasteur discovered the optical isomerism of tartaric acid.

Nevertheless, the tools for either the resolution of racemates or for the synthesis of enantiomerically pure drugs were discovered and developed slowly. The pharmaceutical companies were already marketing demanded drugs in racemic form,[2] not being noticed the relevance of the exploration of the *in vivo* differences between enantiomers, or other chemically equivalent forms, until the early 1960's with the tragedy of thalidomide.[3] Then, in 1987, the FDA issued a set of guidelines on the submission of New Drug Applications, where the question of stereochemistry was approached directly in the guideline on the

[1] Cintas, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4016–4024.
[2] Camp, W. H. D. E. *Chirality* **1989**, *1*, 2–6.
[3] Rubey, W. W.; Morse, P. M.; Tatum, E. L. *Science.* **1962**, *137*, 497–497.

manufacturing of drug substances.[4] Such marketing regulations for synthetic drugs, coupled with recent progress in stereoselective organic synthesis, resulted in a significant increase in the proportion of single-enantiomer drugs.

In the case of thalidomide (Figure 0.1.a), the racemate (mixture of the (+)-(*R*)- and (-)-(S)-enantiomers) was introduced as a sleep-inducing agent in 1956, but it was withdrawn in 1961 for causing fetal malformations, that were lately related just to the levogyre enantiomer.[5] This is the most famous one, but not the only case of undesirable side effects caused by the different behaviour of each enantiomer of a given drug in the human body.[6] In 1982 was taken off the market a racemic preparation of benoxaprofen (Figure 0.1.b), Oraflex, once British physicians had written about its problems and after 26 patients who had taken it died of liver or kidney disorders.[7] Benoxaprofen is an anti-inflammatory compound that was at an advanced stage of clinical evaluation, when it was found that the (-)-(*R*)-enantiomer was inverted to the (+)-(*S*)-form *in vivo*, which was traduced in the accumulation of the eutomer[8] and the appearance of the overdose symptoms.[9]



(-)-(*S*)-thalidomide (+)-(*S*)-benoxaprofen

(**a**) (**b**)

Figure 0.1. Drugs with different behaviour in each enantiomer.

Until the early seventies the scientific knowledge about asymmetric synthesis and asymmetric induction wasn't very wide. Then in 1983 it was finally published a five-volume treatise [10] that included the last 10 years advances in the field of asymmetric synthesis. From this starting point, the

[4] Office of Drug Evaluation and Research (HFD-loo), F. and D. A. *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*; 5600 Fishers Lane, Rockville, MD 20857, **1987**; pp 3–4.
[5] Eriksson, T.; Björkman, S.; Roth, B.; Fyge, Å.; Höuglund, P. *Chirality* **1995**, *7*, 44–52.
[6] Simonyi, M. *Med. Res. Rev.* **1984**, *4*, 359–413.
[7] Marshall, E. *Science* **1985**, *229*, 1071–1071.
[8] Patocka, J.; Dworak, A. *J. Appl. Biomed.* **2004**, *2*, 95–100.
[9] Srinivas, N. R.; Barbhaiya, R. H.; Midha, K. K. *J. Pharm. Sci.* **2001**, *90*, 1205–1215.
[10] *Asymmetric Synthesis*, Academic P.; Morrison, J.D., Ed.: Orlando, **1983**.

literature continues to grow at such a rate that comprehensive coverage is now impossible.[11] Initially, practical access to pure enantiomers relied largely on biochemical or biological methods. However, the scope of such methods using enzymes, cell cultures, or whole microorganisms is limited because of the inherent single-handed, lock-and-key specificity of biocatalysts. On the other hand, a chemical approach constitutes a complementary method, allowing for the flexible synthesis of a wide array of enantioenriched organic substances.

The practical asymmetric synthesis features which should be fulfilled include high stereoselectivity, high rate and productivity, atom economy, cost efficiency, operational simplicity, environmental friendliness, and low-energy consumption. The decision of how to produce a molecule in enantiomerically pure form requires that the experimentalist balance the pros and cons of the available methods.[12] One of the easiest ways would be to purchase the chiral compound, as this is a very convenient and fast method; however, the availability of some specific molecules is limited and moreover the cost, in many cases, is too high, especially for academic research labs, or they are just affordable in small quantities. Apart from that, the most important and widely used methods for this purpose are commented below:

- **Chiral pool:** The convenience and time saving that implies the use of a commercially available chiral substrate makes it rarely cost effective to prepare it oneself, if the molecule is reachable at a reasonable price. However, it may not be so easy to find an appropriate compound to be purchased, for three main reasons, either the desired substructure does not yet exist, the price is beyond a laboratory's means, or it is only affordable in small quantities.
- **Classical resolution:** It can be a practical and scalable method with a great reproducibility, generally. But at the same time, it can be tedious either finding the right conditions for a successful resolution in certain cases, or the scale-up of the process. Besides, it is considered by many chemists as an inelegant method that generates to much waste since the unwanted enantiomer is discarded.

[11] Gawley, R. E.; Aubé, J. In *Principles of Asymmetric Synthesis*; **2012**; Vol. 1, pp 1–62.
[12] Gawley, R. E.; Aubé, J. In *Principles of Asymmetric Synthesis*; **2012**; Vol. 2, pp 63–95.

- **Chromatographic separation:** It is an effective method on a small scale that affords both enantiomers directly. This could be useful when studying effect of chirality on a molecule's biological activity. The drawback is that it is tiresome to validate and perform all the process with the inherent limitation of scalability, as large scale chromatographic separations are very expensive.
- **Kinetic resolution:** This could be a robust synthetic method suitable for large scale preparations, as long as the separation of the product from the unreacted starting material is feasible. But here come along also the disadvantages of the classical resolution indicated above.
- **Chiral auxiliaries:** They constitute a general tool for the synthesis of enantiomerically pure compounds, given the great amount of highly selective reactions mediated by them. The use of chiral auxiliaries in the total synthesis of natural products and biologically relevant molecules is widespread in the literature. Their cost and the inefficiency of having two additional steps are the main handicaps in this case.
- **Asymmetric catalysis:** Performing a truly effective asymmetric catalyst is hard to beat, it would be the most elegant and efficient method. However, it can be hard to find the appropriate catalyst, if time is of the essence, the need to screen various catalysts for a new reaction can be a bottleneck.

The choice of the last one as the best option was reinforced by the fact that in 2001, William S. Knowles, Ryoji Noyori and K. Barry Sharpless were awarded the Nobel Prize in Chemistry by the Royal Swedish Academy of Sciencies, for their great contribution in the development of asymmetric catalysis.[13] Since then the field of asymmetric catalysis has evolved and grown exponentially. The novel asymmetric catalysis methodologies developed were effectively applied for preparing important structural motifs found in biologically active molecules. However, the difficulties in preparing substances enriched in a particular enantiomer persist because the number of catalytic enantioselective transformations available still remain limited. Therefore, the development of new

[13] a) Knowles, W. S. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1999–2007. b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022. c) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.

methodologies of asymmetric catalysis is invariably of high interest. Taking into account that the symbiotic relationship between total synthesis and method development can continue to expand the understanding of catalysis on both fundamental and practical levels.[14]

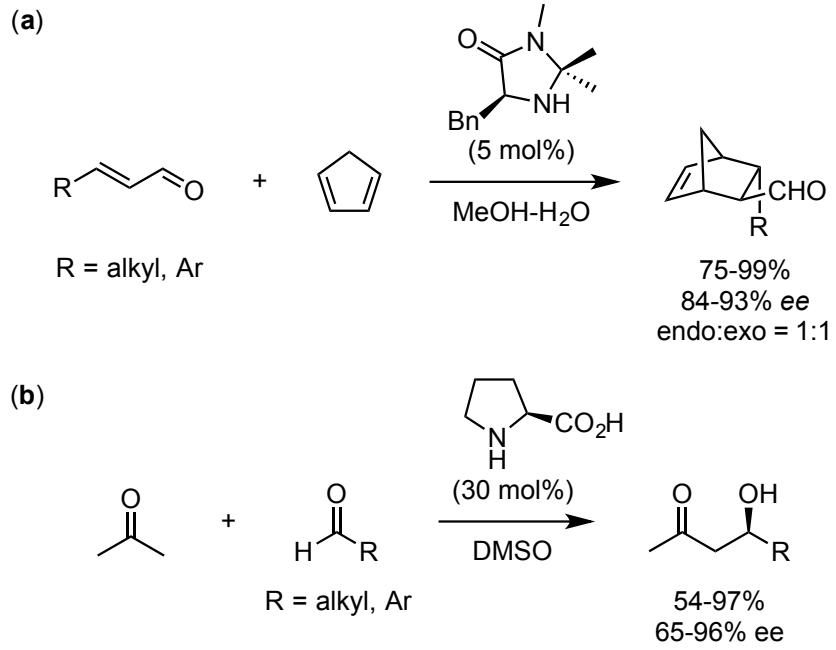
0.1.2. ORGANOCATALYSIS

Traditionally, the two pillars where asymmetric catalysis was sustained had been the use of enzymes and transition metal complexes bearing chiral ligands. The use of organic molecules as catalysts has only been documented sporadically over the past century, and those chemical studies were viewed more as unique chemical reactions than as integral parts of a larger, interconnected field.[15] Finally in the late 1990s, things began to change when it was demonstrated that the use of small organic molecules as catalysts could be used to solve important problems in chemical synthesis. This trend was initiated by the use of enantiomerically pure ketones as catalysts for the asymmetric epoxydation of simple alkenes;[16] an briefly afterwards when the Strecker reaction was performed by hydrogen-bonding catalysis with organic compounds rather than with organometallic complexes.[17]

Eventually, the term organocatalysis was introduced to the chemical literature in 2000 by MacMillan and co-workers[18] when they described a general activation strategy of iminium catalysis providing a more advantageous alternative for LUMO activation (Scheme 0.1.a). Simultaneously, it was published a complementary organocatalytic study by Barbas, Lerner and List[19] on enamine catalysis (Scheme 0.1.b). They described that proline can perform as a novel amine-based asymmetric class I aldolase mimics showing that this simple α-amino acid catalysed the direct aldol reaction with comparable

[14] Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.
[15] a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. b) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **1971**, *10*, 496-497.
[16] a) Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807. b) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491–492. c) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288–8289.
[17] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902. b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157–160.
[18] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[19] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

efficiency to the best organometallic catalyst,[20] using similar mechanisms than enzymes to accomplish the HOMO activation.



Scheme 0.1. First organocatalytic reactions

Once the organocatalysis had been introduced, it emerged as a promising strategy in asymmetric catalysis. Its exponential growth in a very short period of time (Figure 0.2) converted organocatalysis in the third pillar of asymmetric synthesis, mainly due to the real advantages that this methodology offered to the scientific researchers. Among all its benefits, the main aspects are the savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste. Organic molecule catalysts are generally stable for being insensitive to oxygen and moisture in the air. A wide variety of them are often based on natural compounds, such as sugars, peptides or amino acids, which are available from biological sources as single enantiomers, so they are cheap to prepare and readily accessible in a range of quantities. Additionally, small organic molecules are typically non-toxic and environmentally friendly, unlike it happens with the most of the organometallic systems. Apart from that, organocatalysts can easily be linked to a solid support, making them useful for industrial applications. These features transformed organocatalysis into a complementary methodology to the

[20] Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178.

traditional and highly developed inorganic and biological approaches to asymmetric catalysis.[21]

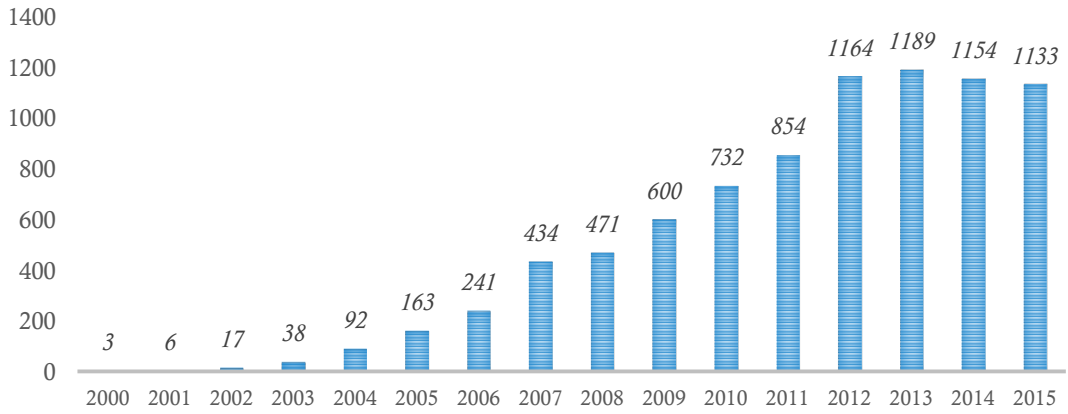


Figure 0.2. The number of publications on organocatalysis since it was coined in the literature. Data were obtained by search of Scifinder in December 2015 for the keywords organocatalysis and organocatalyst, having been substracted the entries from "Abstract of Papers" and "Chemtracts" or with "No Corporate Source data available".

Another relevant feature responsible for the success of organocatalysis was the identification of generic modes of catalyst activation, induction and reactivity. This consists of reactive species formed by the interaction of a single chiral catalyst with a principal functional group in a highly organized and predictable manner. Their value is that under this frame, it is a relatively straightforward issue to design new enantioselective reactions using these principles.

From a mechanistic perspective, organocatalytic modes of activation can be classified according to two aspects, the first the covalent or noncovalent ***character of the substrate–catalyst interaction***; and the second the ***chemical nature*** (Lewis base, Lewis acid, Brønsted base, Brønsted acid) of the organocatalyst. [22] It is important to keep in mind, however, that many organocatalysts act through both covalent and noncovalent interactions and/or display a dual acid–base character, giving way to a group known as *bifunctional catalysts*.

[21] a) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584–1586. b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308.
[22] Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724.

Among the currently operative mechanisms in asymmetric organocatalysis, the most important groups are aminocatalysis, carbene catalysis and Lewis base organocatalysis with covalent interactions; and hydrogen-bonding activation, bifunctional catalysis, phase-transfer and asymmetric counteraction-directed catalysis within the noncovalent organocatalysis modes. [23] Hereafter there will be mentioned the more established modes for their length of standing and the more related ones to the current research work.

a) Covalent organocatalysis

AMINOCATALYSIS

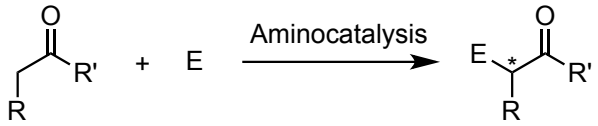
The term *aminocatalysis* has been coined [24] to designate reactions catalysed by primary and secondary amines. This field was discovered in the early 1970s[15] but it remained as a laboratory curiosity for almost thirty years.[18,19] Now, catalysis with chiral amines has become a well-established and powerful synthetic tool for the chemo- and enantioselective functionalisation of carbonyl compounds. In the last fifteen years, this field has grown at such a breathtaking pace that it is now recognized as an independent area of synthetic chemistry. [25] Among the multiple subparts this field can be classified, this memory will specifically be focused on the ones directly related with the present work.

➧ *ENAMINE CATALYSIS*

One of the two first discovered methodologies[19] in this field is the ***enamine catalysis***, that has become one of the most intensively used organocatalytic modes of activation, allowing the functionalisation of carbonyl-

[23] Moyano, A. In *Stereoselective Organocatalysis*; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2013; pp 11–80.
[24] List, B. *Synlett* **2001**, 1675–1686.
[15] a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. b) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **1971**, *10*, 496-497.
[18] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[19] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[25] a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. b) List, B. *Chem. Commun.* **2006**, 819-824.

containing compounds at the α-carbon in enantioselective manner (Scheme 0.2).[26]

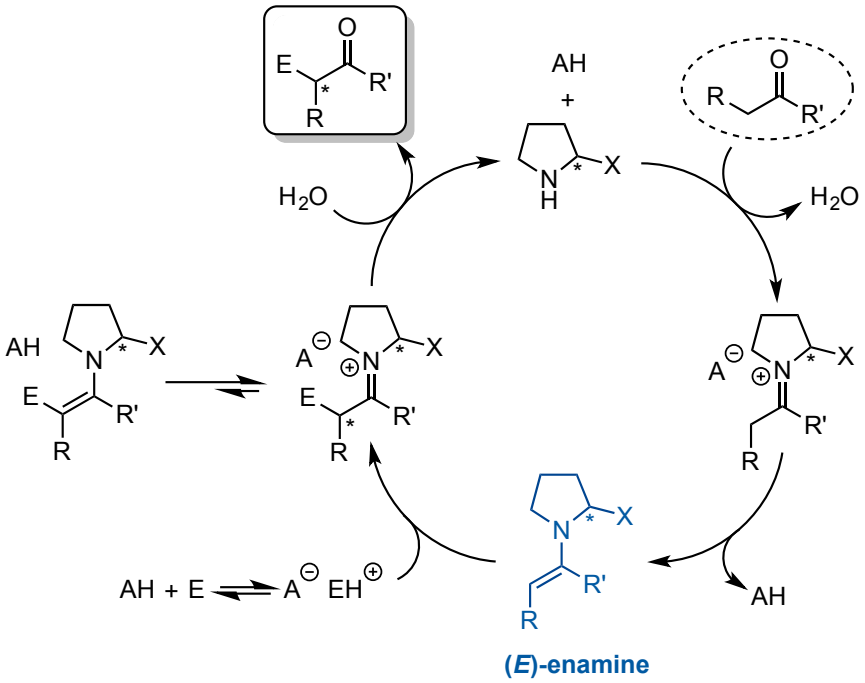


E = "C", "N", "O", "F", "S", "Cl", "Se", "Br", "I"

Scheme 0.2. Enantioselective α-functionalisation of enolizable carbonyl compounds with a huge variety of electrophiles

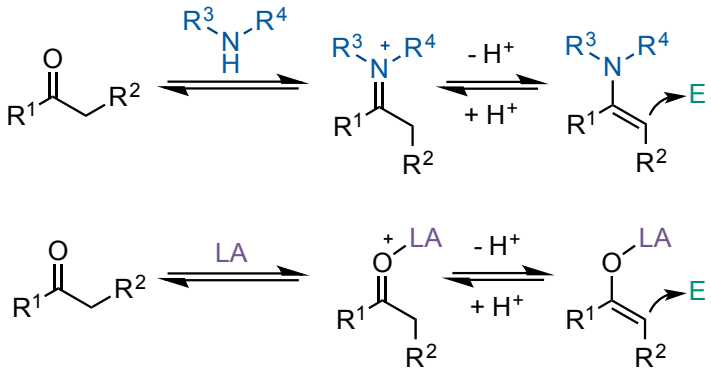
The standard catalytic cycle for a chiral amine-catalysed α-functionalisation of a carbonyl compound is depicted in Scheme 0.3. A chiral, 2-substituted pyrrolidine has been chosen as the most representative type of catalyst, acting together with an external Brønsted acid co-catalyst AH. The generalized enamine mechanism involves in the first step the acid-promoted condensation of the carbonyl with the amine to form an iminium ion. One of the α-acidic protons of the iminium ion is then removed by the conjugate base of the Brønsted acid A^-, and the key nucleophilic enamine intermediate is formed. Reaction with the electrophile (generally protonated; the protonation can take place before or during this step) generates another iminium ion, whose hydrolysis liberates the product, the acid, and the amine catalyst, which can reenter the catalytic cycle. The Brønsted acid co-catalyst can be a protic solvent or an added external acid, or it can be a functional group present in the amine catalyst.

[26] Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178-2189.



Scheme 0.3. Generalized mechanism for the enamine organocatalysis.

This reversible condensation of the chiral amine with carbonyl compounds leads to the formation of a positively charged iminium ion intermediate, mimicking the electronic situation of the π orbitals in Lewis acid catalysis (Scheme 0.4). On that intermediate, the energy of the lowest unoccupied molecular orbital (LUMO) of the system is effectively lowered, thus increasing the acidity of the α proton and consequently inducing the deprotonation at this position. Then, the enamine intermediate, considered as a nucleophilic enolate equivalent, is activated by the raising of the energy of the highest occupied molecular orbital (HOMO).



Scheme 0.4. Comparison of the activation of carbonyl compounds by a Lewis acid (LA) in enamine aminocatalysis, known as *HOMO catalysis*.

Enaminic catalysis has been successfully employed both in addition reactions and in nucleophilic substitutions, with a great variety of electrophiles. Besides the aldolic condensation (Scheme 0.1.b),[27] there were subsequently developed diverse α-functionalisation reactions of aldehydes,[28] such as Mannich reactions,[29] enantioselective α-amination reactions with azodicarboxylates,[30] hydroxylations with nitrosobenzene,[31] α-alkylations and arylations,[32] α-halogenations (Cl, Br, I, F),[33] and sulfenylations.[34] In the Scheme 0.5. are shown a summary of the α-functionalisation of aldehydes by means of enamine catalysis.

[27] a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799. b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752–1755.

[28] Revisions about organocatalytic α-heterofunctionalisation of carbonylic compounds: a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304. b) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. c) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, No. 19, 2001–2011. d) Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, *7*, 2005-2012.

[29] a) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867. b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5815. c) Verkade, J. M. M.; Hemert, L. J. C. van; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.

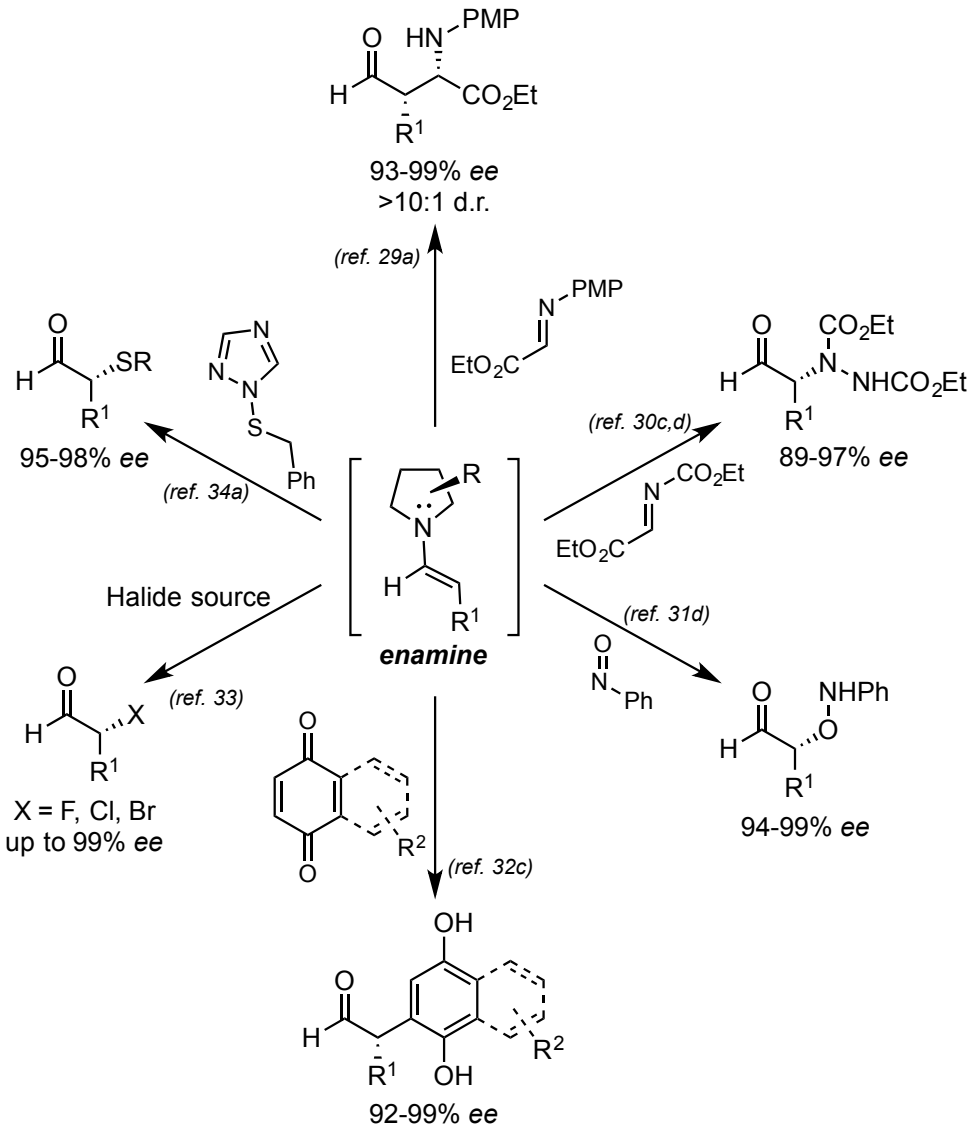
[30] a) Janey, J. M. *Angew. Chem., Int. Ed*. **2005**, *44*, 4292-4300. b) Duthaler, R. O. *Angew. Chem. Int. Ed.* **2003**, *42*, 975-978. c) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2002**, *41*, 1790-1793. d) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656-5657.

[31] a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed*. **2004**, *43*, 2995-2997. b) Palomo, P.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054-8056. c) Kuarn, S.; Oelke, A. J.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Biomol. Chem*. **2007**, *5*, 2678-2689. d) Zhong, G. *Angew. Chem. Int. Ed*. **2003**, *42*, 4247-4250.

[32] α-Alkylations of aldehydes: a) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2007**, *46*, 8707-8710. b) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450-451. α-Arylations of aldehydes: c) Aleman, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 5520-5523.

[33] α-Fluorination of aldehydes: a) Prakash, G. K. S.; Beier, P. *Angew. Chem., Int. Ed*. **2006**, *45*, 2172-2174. b) Pihko, P. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 544-547. c) Shibatomi, K.; Yamamoto, H. *Angew. Chem. Int. Ed*. **2008**, *47*, 5796-5798. d) Steiner, D. D.; Mase, N.; Barbas III, C. F. *Angew. Chem., Int. Ed*. **2005**, *44*, 3706-3710. e) Beeson, T. D. MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828. α-Chlorination of aldehydes: f) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2004**, *126*, 4108-4109. g) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2004**, *126*, 4790-4791. α-Bromination of adehydes: h) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun*. **2005**, 4821-4823.

[34] a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem. Int. Ed*. **2005**, *44*, 794-797. b) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, 959-980.



Scheme 0.5. α-Functionalisation of aldehydes via enamine activation.

Yet, at the same time, enamine catalysis has been used for conjugated additions of aldehydes to several Michael acceptors like nitroalkenes,[35] vinilketones,[36,28a] maleimides,[37] phosphonates[38] and sulfones.[39] The more

[35] a) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371. b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215. c) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721. d) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357–9367.

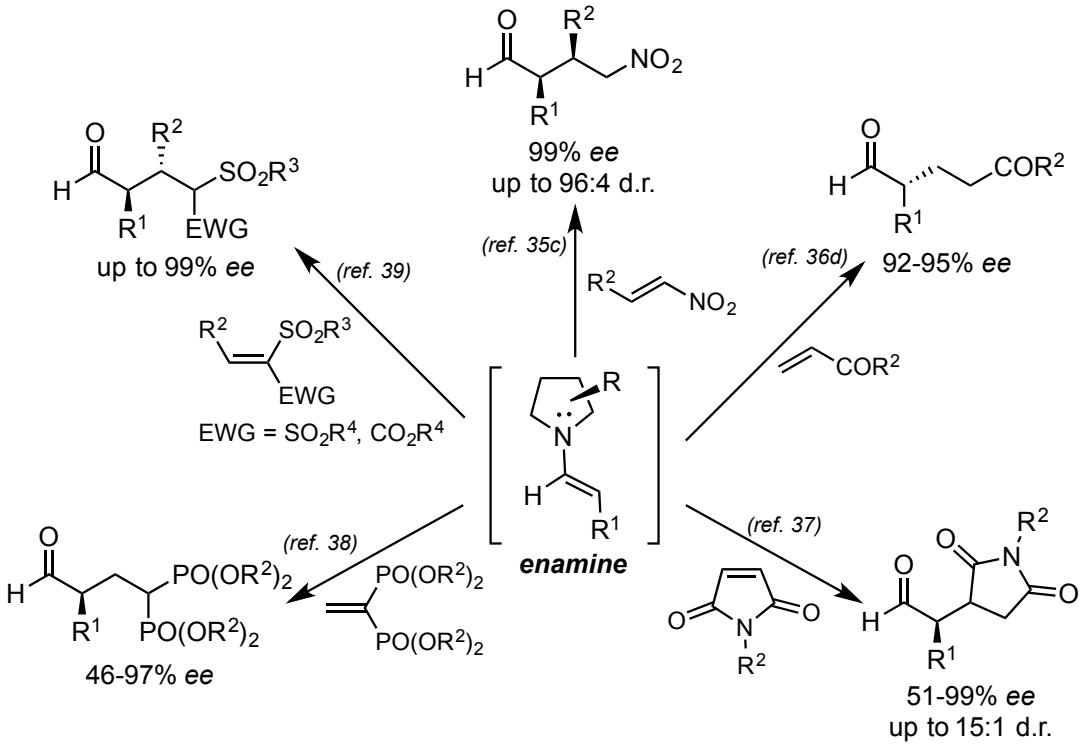
[36] a) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151–4157. b) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598–11599.

[28a] Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

[37] Zhao, G.-L.; Xu, Y.; Sunden, H.; Eriksson, L.; Sayah, M.; Cordova, A. *Chem. Commun*. **2007**, 734-735.

[38] Sulzer-Mossé, S.; Tissot, M.; Alexakis, A. *Org. Lett*. **2007**, *9*, 3749-3752.

representative examples of Michael type additions catalysed with proline or derivatives through an enamine activation are depicted in Scheme 0.6.



Scheme 0.6. Conjugated additions of aldehydes to various Michael acceptors.

IMINIUM CATALYSIS

Together with enamine catalysis, ***iminium catalysis*** is the most prominent activation mode in asymmetric aminocatalysis,[40] and the second of the first discovered methodologies. Initially, the proof of concept was done in a Diels Alder type reaction,[18] and subsequently applied to carry out 1,3-dipolar cycloadditions,[41] and afterwards extended to other reactions as Friedel-Crafts alkylations, [42] other types of cycloadditions, [43] epoxidations, [44]

[39] a) Landa, A.; Puente, A.; Santos, J. I.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2009**, 15, 11954-11962. b) Landa, A.; Maestro, M.; Masdeu, C.; Puente, A.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2009**, 15, 1562-1565. c) Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem. Eur. J.* **2009**, 15, 3204-3220.

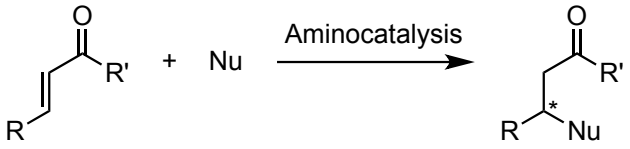
[40] a) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076. b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. c) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365. d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716.

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

[41] Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.

[42] a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371. b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895. c) Okamoto, A.; Kanatani, K.; Taiji, T.; Saito, I. *J. Am. Chem. Soc.* **2003**, *125*, 1172–1173.

cyclopropanations[45] and especially Michael additions for a large number of non-metallic nucleophilic moieties (Scheme 0.7).[26] Now it is established as a general strategy for the asymmetric conjugate addition of nucleophiles at the β–position of conjugated carbonyl compounds.



Nu = "C", "H", "N", "O", "P", "S"

Scheme 0.7. Enantioselective β-functionalisation of α,β-unsaturated carbonyl compounds with a great variety of nucleophiles

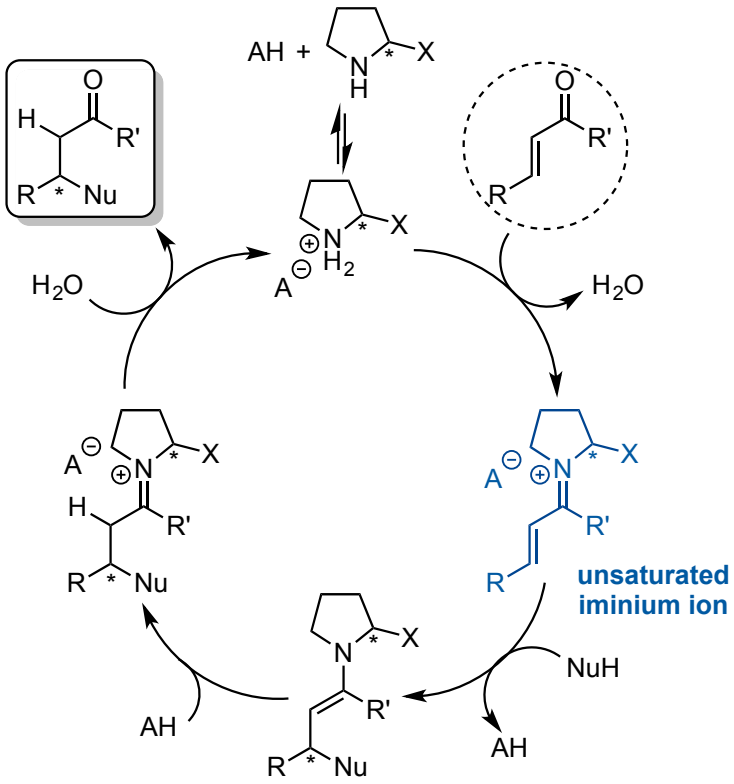
The conventional catalytic cycle for a chiral pyrrolidine-catalysed β-functionalisation of an α,β-unsaturated carbonyl compound is shown in Scheme 0.8, and it begins with the acid-promoted condensation of the carbonyl with the amine to form an unsaturated iminium ion, more electrophilic than the starting unsaturated carbonyl. This reactive intermediate suffers then the addition of the nucleophile at the β-position, leading to α,β-functionalised enamine in tautomeric equilibrium with an iminium ion. Hydrolysis of this intermediate releases both the product and the chiral ammonium salt, which can reenter the catalytic cycle.

[43] a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460. b) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059. c) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616–11617.

[44] a) Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, 62, 11413-11424. b) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, 127, 6964-6965.

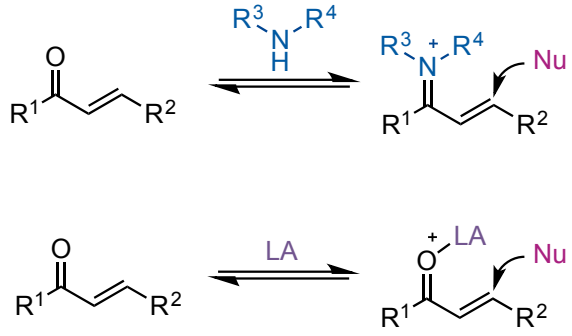
[45] Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, 127, 3240-3241.

[26] Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178-2189.



Scheme 0.8. Generalized mechanism for the chiral amine-catalysed β–functionalisation of α,β-unsaturated carbonyls.

In this case, the reversible condensation of a chiral amine with carbonyl conjugated systems leads to the formation of an iminium cation intermediate. Here the electronic redistribution facilitates nucleophilic additions, which might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis (Scheme 0.9). In this way, it is said that there is a LUMO activation due to its lowering at the iminium salts, making them more electrophilic than the corresponding carbonyl compounds and more reactive toward nucleophilic attacks.



Scheme 0.9. Comparison of the activation of conjugated carbonyl compounds by a Lewis acid (LA) in iminium aminocatalysis, known as *LUMO catalysis*.

Employing this activation via the iminium ion, there have been developed a great variety of conjugate addition reactions with diverse chiral catalysts bearing a secondary amine.[40] This organocatalytic methodology has a really wide scope (Scheme 0.10), it has been applied, for example, in additions of malonates [46] or nitroalkanes [47] to conjugated aldehydes and ketones, enantioselective reductions of β,β-disubstituted α,β-unsaturated aldehydes,[48] or 1,4-additions of sulfur-,[49] nitrogen-[50] and oxygen-derivatives.[51]

[46] For additions to enones: a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661–665. b) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, *44*, 66–68. For additions to aldehydes: c) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309.

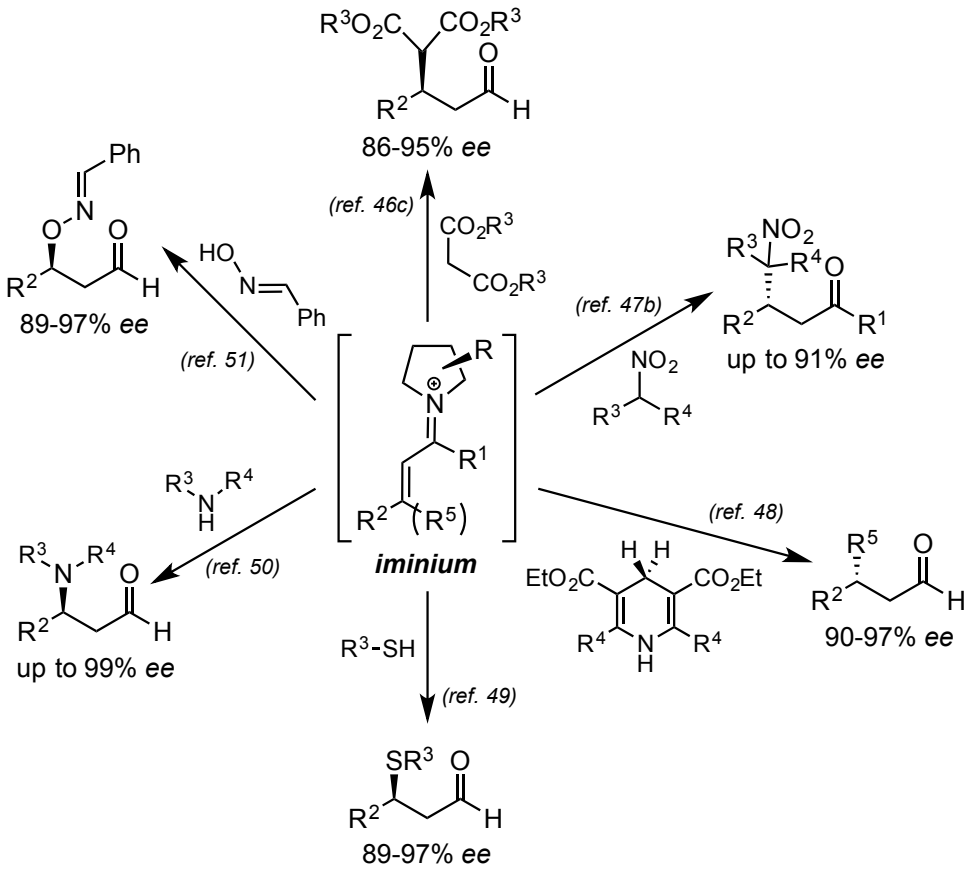
[47] a) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897–3900. b) Mitchell, C. E. T.; Brenner, S. E.; García-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 2039–2049.

[48] a) Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem. Int. Ed*. **2005**, *44*, 108-110. b) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2005**, *127*, 32-33.

[49] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 15710-15711.

[50] a) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329. b) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983–1987. c) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509–2511. d) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999–2002.

[51] Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536–1537.



Scheme 0.10. Selection of β-functionalisation of conjugated carbonylic compounds.

In most cases of organocatalysis based on iminium-activation, involving the most generalized secondary-amine catalysts, the Michael acceptor is an α,β-unsaturated aldehyde, since the generation of the iminium intermediate is more efficient with enals than with α,β-unsaturated ketones. That is due to the greater steric hindrance of ketones in both sides of the carbonylic group, leading to a poorer geometric control of the iminium intermediate (lower enantioselectivities) or even preventing the possibility of its formation (Figure 0.3.a). To avoid this problem, there have been developed primary-amine organocatalysts,[52] which allow a facile condensation between the enone and the aminocatalyst and also a better geometrical regulation given the bigger difference between the coplanar substituents of the double bound C=N of the iminium ion (Figure 0.3.b).

[52] a) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759–1772. b) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. c) Peng, F.; Shao, Z. *J. Mol. Catal. A Chem.* **2008**, *285*, 1–13. d) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807-1821. e) Jiang, L.; Chen, Y.-C. *Catal. Sci. Technol.* **2011**, *1*, 354-365.

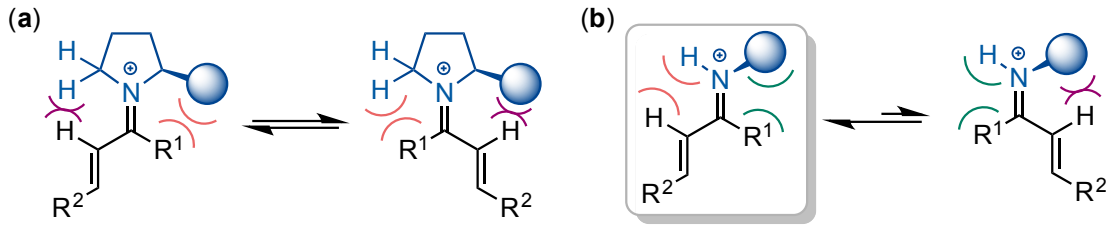


Figure 0.3. Geometric control in the iminium intermediates of secondary and primary-amine organocatalysts with α,β-unsaturated ketones.

Some other relevant mechanisms of covalent organocatalysis that won't be discussed here, for not being so prevalent or related with the current research work, are the dienamine catalysis, the SOMO catalysis or photoredox methodologies among others.

b) Noncovalent organocatalysis

As noncovalent organocatalysts, there will be included those which will activate the reaction substrate through some weaker interactions different than the covalent ones, *inter alia*, hydrogen-bonding, direct electrostatic activation and π interactions.[53] While, in some cases, this activation will occur directly between the catalyst and the substrate, in others, the organocatalyst may react previously with the starting material or with a co-catalyst (for instance, through acid-base reactions), to give rise to an intermediate that will be the responsible for the asymmetric induction of the reaction. Apart from that, it should be noted that these noncovalent interactions can take place by their own or together with some covalent activation, and in the latter case the reactivity and the enantioselectivity of the organic reaction would probably be improved.[54]

Thus, depending on the degree of proton transfer in the transition state, one may distinguish between hydrogen-bonding catalysis (when the hydrogen is still covalently bonded to the catalyst) and Brønsted acid catalysis (complete

[53] a) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136. b) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035. c) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160. d) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631–5639. e) Holland, M. C.; Metternich, J. B.; Daniliuc, C.; Schweizer, W. B.; Gilmour, R. *Chem. Eur. J.* **2015**, *21*, 10031–10038. f) Wang, L.; Chen, J.; Huang, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 15414–15418. For analysis of noncovalent interactions in organocatalysis: g) Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. *Chem. Eur. J.* **2011**, *17*, 10470–10477. h) Holland, M. C.; Berden, G.; Oomens, J.; Meijer, A. J. H. M.; Schäfer, M.; Gilmour, R. *Eur. J. Org. Chem.* **2014**, 5675–5680.

[54] Mathew, S. P.; Klussmann, M.; Iwamura, H.; Wells, Jr., D. H.; Armstrong, A.; Blackmond, D. G. *Chem. Commun.* **2006**, 4291-4293.

proton transfer from the catalyst to the substrate), but logically several intermediate situations are possible (Figure 0.4).[55] However, the term hydrogen-bonding activation is generally used to represent both hydrogen-bonding catalysis and Brønsted acid catalysis.

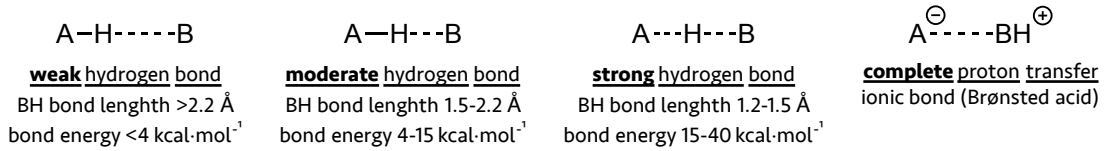
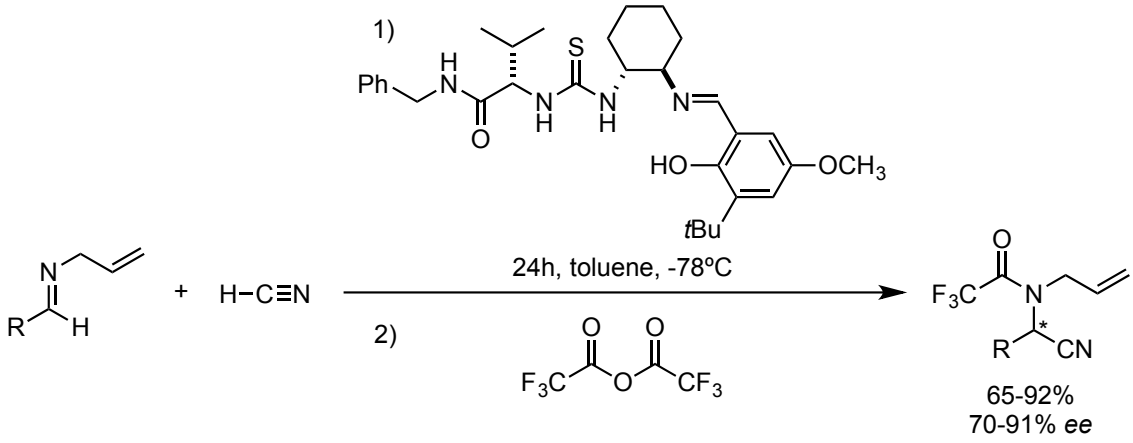


Figure 0.4. Hydrogen-bonding/Brønsted acid continuum. A = acid; B = base.

HYDROGEN-BONDING ORGANOCATALYSIS

Hydrogen-bonding catalysis can be defined as a LUMO-lowering activation by sharing of a hydrogen atom between the substrate (hydrogen bond acceptor) and the catalyst (hydrogen bond donor). The ability of hydrogen-bond donors to accelerate organic reactions was first recognized in 1942, when Wassermann reported his crucial results on the catalysis of Diels–Alder reactions by phenol or carboxylic acids.[56] Still, the full potential of hydrogen-bonding catalysis in asymmetric synthesis was not appreciated until 1998, when Sigman and Jacobsen described the use of peptide–thiourea catalysts in the enantioselective Strecker reaction (Scheme 0.11).[17a]



Scheme 0.11. Asymmetric Strecker reaction with organocatalytic thiourea.

The most widely used catalysts of this type are chiral ureas and thioureas, chiral amidinium or guanidinium ions, chiral squaramides, and chiral

[55] a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. b) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407-3417.
[56] Wassermann, A. *J. Chem. Soc.* **1942**, *128*, 621-623.
[17a] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.

diols (Figure 0.5). Among the variety of chemical transformations with hydrogen-bond donor catalysis are included the activation of carbonyls,[57] imines,[17a] and epoxides[58] toward nucleophilic attack and also the stabilization of transition states in Diels–Alder and hetero-Diels–Alder cycloadditions,[59] 1,3-dipolar cycloadditions,[60] Claisen rearrangements,[61] and aldol, Michael[62] or Mannich reactions.[63]

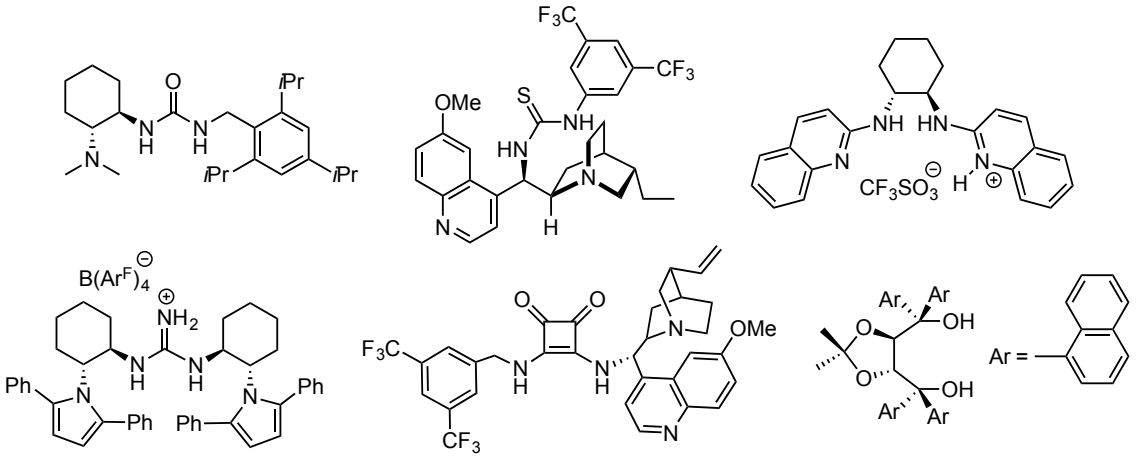
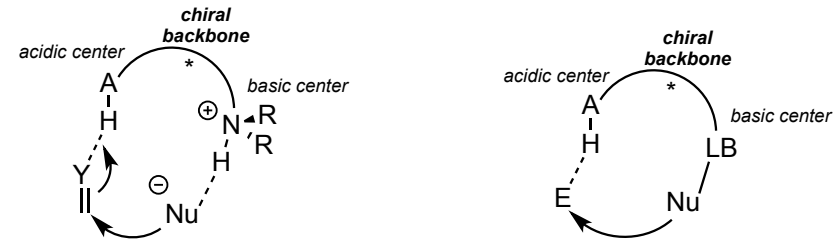


Figure 0.5. Representative chiral hydrogen-bond donor catalysts.

BIFUNCTIONAL CATALYSIS

As their name suggests, these organocatalysts interact with the reagents in, at least, two different ways throughout separated chemical units. This concept of multifunctional asymmetric catalysis has received considerable attention in the past years. Concretely, the most usual combinations of dual activations are the association of a Brønsted acid either with a Brønsted base (Figure 0.6.a) or with a Lewis base (Figure 0.6.b).

[57] Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648.
[58] a) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2000**, *65*, 2464–2471. b) Fleming, E. M.; Quigley, C.; Rozas, I.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 948–956.
[59] Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.
[60] Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 9873–9877.
[61] Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062–5075.
[62] Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097-2099.
[63] Žabka, M.; Šebesta, R. *Molecules* **2015**, *20*, 15500–15524.



Hydrogen-bond donor/
Brønsted base organocatalyst

(**a**)

Hydrogen-bond donor/
Lewis base organocatalyst

(**b**)

Figure 0.6. Dual activation of electrophile and nucleophile by a bifunctional catalyst. Nu = Nucleophile; E = Electrophile.

The synergistic activation of the reactants by acidic and basic sites in the catalyst was introduced by Shibasaki and co-workers [64] by means of organometallic entities. Simultaneously, asymmetric organocatalysis by bifunctional species containing a hydrogen-bond donor in addition to a Brønsted basic moiety was foreshadowed by Riant and Kagan,[65] first developed by Hatakeyama's and Takemoto's groups[66] and finally converted into a general and reliable strategy that has been shown to be useful in a variety of processes.[67]

On the other hand, the most symbolic catalysts with a Lewis base moiety are α-amino acids, and proline is the highest representative, albeit any chiral organic compound having a Lewis base (usually a primary or a secondary amine) and a hydrogen bond donor can be included in this category.

Thus, in ***proline catalysis*** (Scheme 0.12) has been demonstrated that both the secondary amine and the carboxylic acid moieties of the molecule are essential for its organocatalytic reactions;[15a] the first to form the enamine intermediate when condensing with carbonyl groups, and the latter to simultaneously engage with an electrophilic reaction partner through either

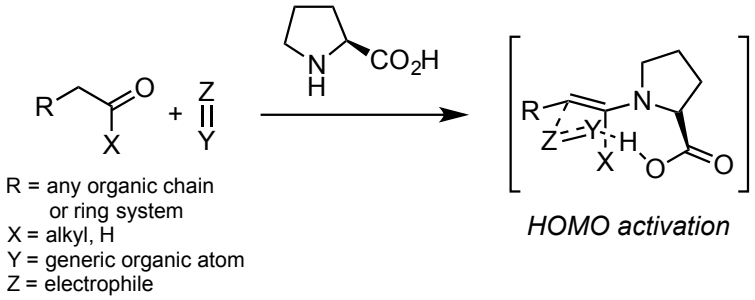
[64] a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 1236–1256. b) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2210.

[65] Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403–7406.

[66] a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220. b) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, *7*, 2030–2031. c) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[67] a) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364–6365. b) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422–2423. c) Chen, Y.-C. *Synlett* **2008**, 1919–1930. d) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298-1310.

hydrogen bonding or electrostatic attraction. It is amazing how such a simple natural amino acid efficiently imitates the concept of enzymatic catalysis. This ability has been developed extensively and with such impressive results that proline has ultimately come to be seen as the simplest "enzyme" in nature.[68]



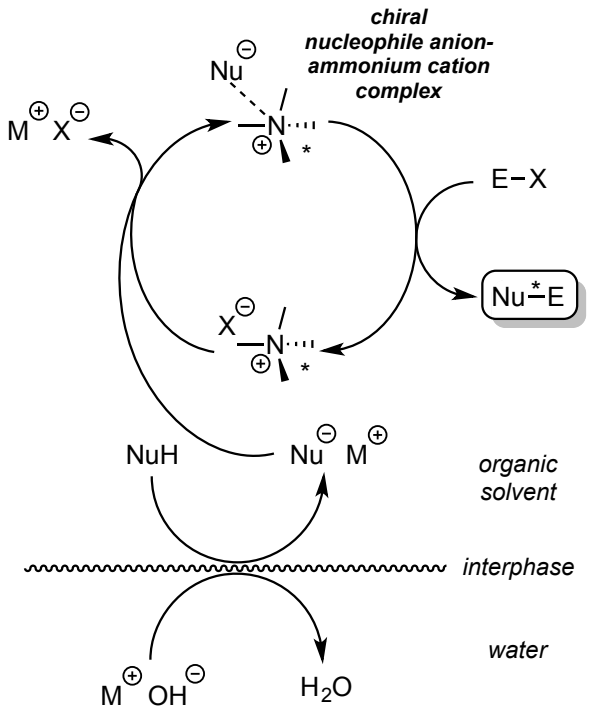
Scheme 0.12. Bifunctional Brønsted acid-enamine catalysis with proline

PHASE-TRANSFER CATALYSIS

After the first successful application of Cinchona alkaloid-based quaternary ammonium salts as chiral phase-transfer catalysts in 1984,[69] the use of chiral quaternary ammonium salts in asymmetric catalysis has experienced a notable growth [70] and it has been widely applied for the enantioselective preparation of α-amino acids.[71]

The generally accepted mechanism for asymmetric phase-transfer catalysis, depicted in Scheme 0.13, assumes that the quaternary ammonium cation forms a tight ionic complex with the nucleophile anion, generated by deprotonation of the neutral pronucleophile at the interphase of the organic and aqueous phases by an alkaline hydroxide. This ionic complex reacts with the electrophile, liberating the product and the quaternary ammonium salt, which returns to the interface for catalyst recycling.

[68] Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904–1905.
[69] Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447.
[70] a) Jew, S.; Park, H. *Chem. Commun.* **2009**, *46*, 7090-7108. b) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *8*, 1229–1279.
[71] a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355. b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598. c) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229. d) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671.



Scheme 0.13. Interphase mechanism for phase-transfer catalysis by a chiral quaternary ammonium salt.

0.1.3. β-AMINO CARBONYL COMPOUNDS: AZA-MICHAEL REACTION

One of the main goals in organic synthesis is the preparation of nitrogen containing structures, as they can be found for instance in natural products, bioactive compounds and agrochemicals. Within this general group, β-amino carbonyl compounds, beyond themselves show sometimes interesting pharmacological properties, they have a recognized relevance as versatile intermediates in organic synthesis. Even though their main representatives, β-amino acids, might be regarded as the building blocks that nature overlooked due their seldom occurrence. Although less abundant than their α-analogues, they are also present in peptides and in other natural products, such as alkaloids or terpenoids and more concretely in the well-known antineoplasic drug Paclitaxel or Taxol (Figure 0.7).

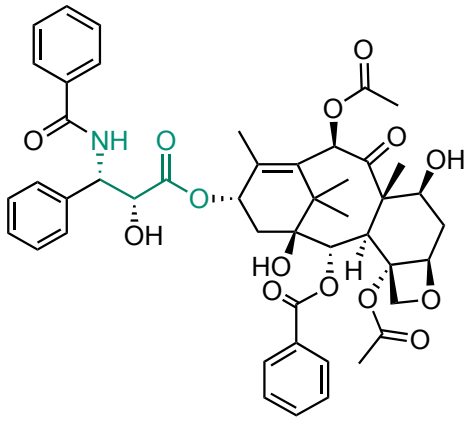


Figure 0.7. Structure of the natural alkaloid Taxol and the traded drug Paclitaxel.

Besides, it has been determined that the incorporations of β-amino acids into peptides instead of α-amino acids increases their stability against degradation by mammalian peptidases. Therefore, they are considered as an important tool in the development of drugs capable of withstanding hydrolytic degradation for prolonged periods of time. Hence, the field of β-amino acids has given rise to a considerable interest in the recent decades, including a multitude of synthetic procedures to access these residues and a large number of reviews.[72] These β-amino units can be classified according to the nomenclature suggested by Seebach,[73] depending upon the position of the side chains (Figure 0.8).

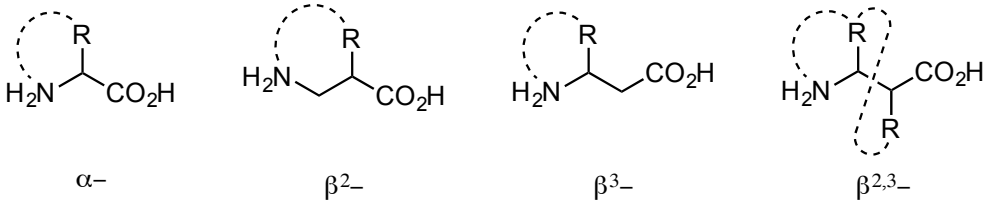


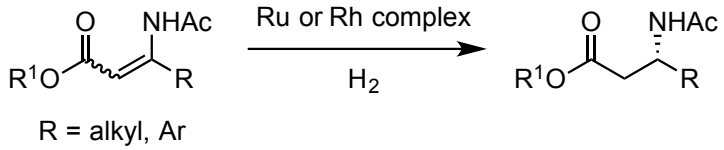
Figure 0.8. Differential denomination of the β-amino acid skeletons.

There are four main approaches to obtain optically active amino acids, namely biotechnological methods, chemical synthesis using compounds from

[72] a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. c) Schreiber, J. V; Frackenpohl, J.; Moser, F.; Fleischmann, T.; Kohler, H.-P. E.; Seebach, D. *ChemBioChem* **2002**, *3*, 424. d) Ma, J.-A. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 4290–4299. e) Sewald, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5794–5795. f) Spiteller, P.; von Nussbaum, F. In *Enantioselective Synthesis of β-Amino Acids*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2005**; pp 19–91. g) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. h) Sleebs, B.; Van Nguyen, T. T.; Hughes, A. *Org. Prep. Proced. Int.* **2009**, *41*, 429–478. i) Weiner, B.; Szymański, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656. j) Sorochinsky, A.; Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J.; Soloshonok, V. *Synthesis* **2011**, 3045–3079.

[73] Lelais, G.; Seebach, D. *Biopolymers (Peptide Science)* **2004**, *76*, 206–243.

the chiral pool, resolution of a racemic mixture, and asymmetric synthesis. Traditional diastereoselective synthesis of β-amino acids has been achieved by using stoichiometric chiral reagents or auxiliaries; however, the number of catalytic asymmetric methods is relatively small in comparison. Even so, in the recent years several research groups have described many efficient catalytic asymmetric procedures for synthesis of β-amino acids [74] In this context, the main approaches for stereoselective synthesis of these structures are the formation of a carbon-carbon bond (Mannich-type reactions), the generation of a carbon-nitrogen bond (for instance, *aza*-Michael reaction, α-amination of α-ketoesters, C-H activation of *N*-protected methyl amines) and the hydrogenation of β-aminoacrylic acid derivatives (Scheme 0.14).[75] Within this procedures, one of the simplest mechanisms is the conjugated addition of nitrogen nucleophiles to α,β-unsaturated acid derivatives, i. e. the *aza-Michael reaction*.[72d]



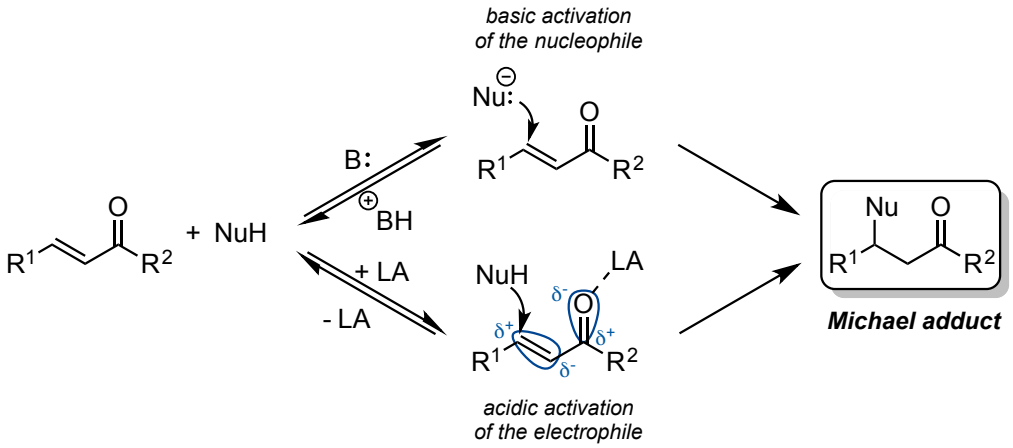
Scheme 0.14. Asymmetric hydrogenation of β-aryl-substituted β-(acyl amino)acrylates.

The ***aza-Michael reaction*** (AMR) is the most direct way to generate carbon-nitrogen bonds, which exhibits also a great simplicity, versatility and atom economy. A wide variety of nitrogen nucleophiles (amines, amides, oximes, carbamates, sulfonamides, hydrazines, azides or nitrogen-containing heterocycles) and Michael acceptors (conjugated aldehydes, ketones, esters, amides or nitriles, nitro olefins, vinyl sulfones or vinyl phosphonates) can be found as partners of this transformation. Furthermore, the process can be

[74] a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154. b) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616. c) Xu, J.; Chen, X.; Wang, M.; Zheng, P.; Song, B.-A.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 5161–5165. d) He, J.; Shigenari, T.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 6545–6549. e) Kaasik, M.; Noole, A.; Reitel, K.; Järving, I.; Kanger, T. *Eur. J. Org. Chem.* **2015**, 1745–1753. f) Xu, F.; Wu, Q.; Chen, X.; Lin, X.; Wu, Q. *Eur. J. Org. Chem.* **2015**, 1–10. g) Cheng, J.; Qi, X.; Li, M.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2015**, *137*, 2480–2483. h) Aparici, I.; Guerola, M.; Dialer, C.; Simón-Fuentes, A.; Sánchez-Roselló, M.; del Pozo, C.; Fustero, S. *Org. Lett.* **2015**, *17*, 5412–5415. i) Dai, J.; Ren, W.; Wang, H.; Shi, Y. *Org. Biomol. Chem.* **2015**, *13*, 8429–8432. j) Cheng, J.; Qi, X.; Li, M.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2015**, *137*, 2480–2483. k) Mathew, S.; Jeong, S.-S.; Chung, T.; Lee, S.-H.; Yun, H. *Biotechnol. J.* **2016**, *11*, 185–190.

[75] a) Y.-G. Zhou,W. Tang,W.-B.Wang,W. Li, X. Zhang, *J. Am. Chem. Soc*. **2002**, *124*, 4952–4953. b) S.-g. Lee, Y. J. Zhang, *Org. Lett*. **2002**, *4*, 2429–2431. c) W. Tang, X. Zhang, *Org. Lett*. **2002**, *4*, 4159–4161.

performed under basic or acidic conditions (Scheme 0.15) and even sometimes it is a spontaneous reaction, when the donor is very nucleophilic and the acceptor is not hindered or deactivated.



Scheme 0.15. AMR under basic or acidic conditions, for the activation of the electron donor or the Michael acceptor respectively. Nu = nitrogen-centered nucleophile; B = base; LA = Lewis acid.

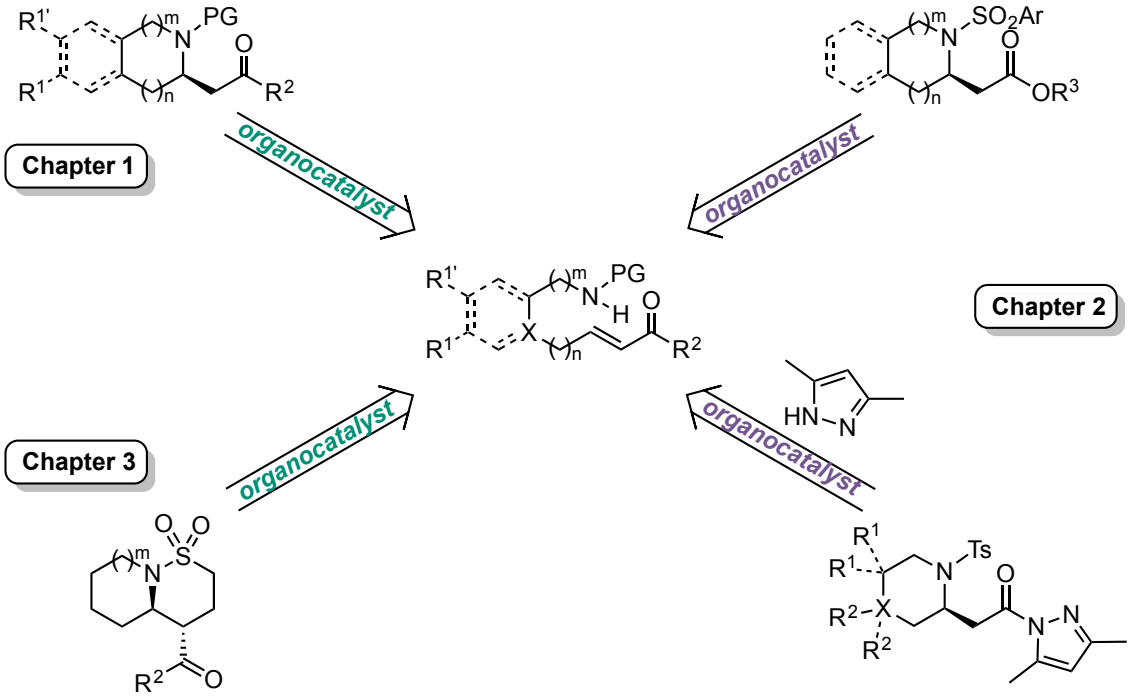
Additionally, at the Michael adduct it is generated a new stereogenic centre, creating the possibility of developing an asymmetric version, which has been less studied with nitrogen nucleophiles than with the carbon classical ones. Likewise, the employment of chiral catalysts for this aim hasn't been so developed as the use of chiral nucleophiles or Michael acceptors coordinated to chiral auxiliaries.[76] A more detailed explanation of the evolution of the *aza*-Michael reaction will be elaborated further in the first chapter of this Memory.

The methodologies described in the present Doctoral Thesis comprise a simple way to access different types of enantioenriched nitrogen-containing heterocycles by means of organocatalysis.

[76] a) Xu, L. W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, 633–639. b) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891. c) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513–538. d) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657–9672. e) Sánchez-Roselló, M.; Aceña, J. L.; Simón-Fuentes, A.; del Pozo, C. *Chem. Soc. Rev.* **2014**, *43*, 7430–7453.

0.2. General Objectives

Considering the previous information and given the importance of the asymmetric synthesis in organic chemistry, the objectives of the present Doctoral Thesis are focused on one hand, in the design of more general methodologies of organocatalytic enantioselective intramolecular *aza*-Michael reactions for α,β-unsaturated ketones and esters (chapters 1-2); and on the other hand, in the application of those methodologies to the synthesis of structures of high interest, such as sultams (chapter 3) (Scheme 0.16).



Scheme 0.16. Agreed targets for the present Doctoral Thesis.

In this way, the current PhD memory will be structured in three chapters as it is shown hereafter:

- **Chapter 1:** *Organocatalytic enantioselective intramolecular* aza-*Michael reaction with conjugated ketones.*

  Here it will be studied the addition of carbamates to α,β-unsaturated ketones by means of a primary amine organocatalyst derived from the cinchone alkaloids.

- **Chapter 2:** *Organocatalytic enantioselective intramolecular* aza-*Michael reaction with conjugated ester surrogates.*

For the complete extension of the IMAMR to all kind of α,β-unsaturated carbonylic compounds, it was performed the reaction between sulfonamides and conjugated *N*-acyl pyrazoles and catalysed by a squaramide derivatized with a cinchone alkaloid.

Moreover, it was implemented an analogous methodology, with the same aim, consisting on a tandem peptide-coupling/IMAMR.

- **Chapter 3:** *Organocatalytic synthesis of enantioenriched bicyclic sultams.*

The application of a developed methodology to the synthesis of sultams by an enantioselective IMAMR followed by a diastereoselective intramolecular Michael reaction is presented.

CHAPTER 1:

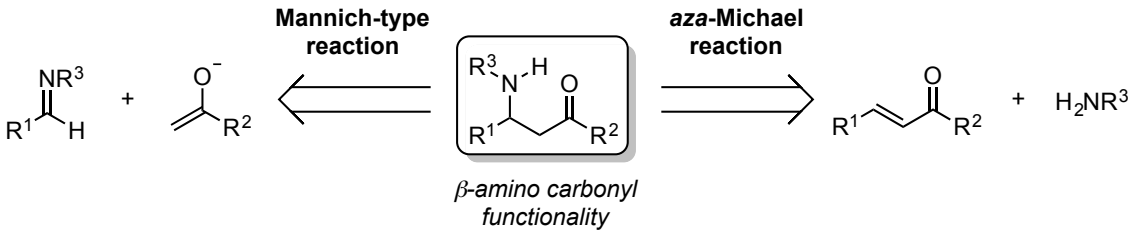
Organocatalytic enantioselective intramolecular *aza*-Michael reaction with conjugated ketones

1.1. Background

1.1.1. *AZA*-MICHAEL REACTION

Herein will be given a detailed description of the *aza*-Michael reaction (AMR), to supplement the previous general introduction. There will be considered different general approaches, but mainly centred in the enantioselective and intramolecular cases.

In a general description, there are two main ways to access β-amino carbonylic compounds. On one hand, carbon-carbon bond formation between imines and enolates (Mannich-type reaction) is one of the methods for the construction of this functionality.[77] On the other hand, carbon-nitrogen bond formation between α,β-unsaturated carbonyl compounds and nitrogen nucleophiles provides an alternative route for the same purpose (Scheme 1.1).[78] However, in the latter case, unlike Michael additions with carbon nucleophiles, the asymmetric *aza*-Michael reaction has been explored to a lesser extent, despite being a powerful tool for the synthesis of these valuable scaffolds.[50a,76a-c,79]



Scheme 1.1. Construction of β-amino carbonyl functionality

[77] a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186. b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. L. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, 37, 29-41. c) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem*. **2007**, 5797-5875.

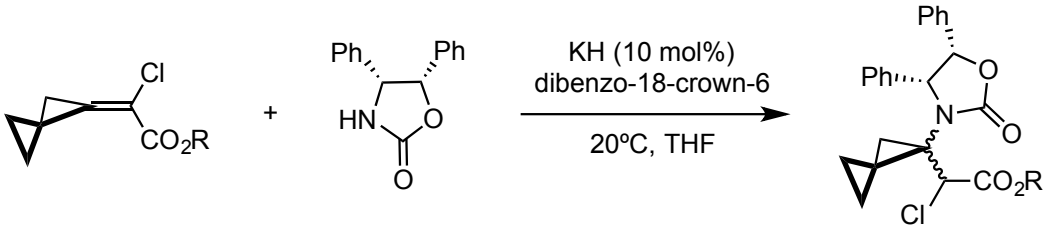
[78] Juaristi, E.; Soloshonok, V. A. In *Enantioselective Synthesis of β-Amino Acids*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2005**

[79] a) P. Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061. b) Vicario, J.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092.

[50a] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.

[76] a) Xu, L. W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, No. 4, 633–639. c) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513–538.

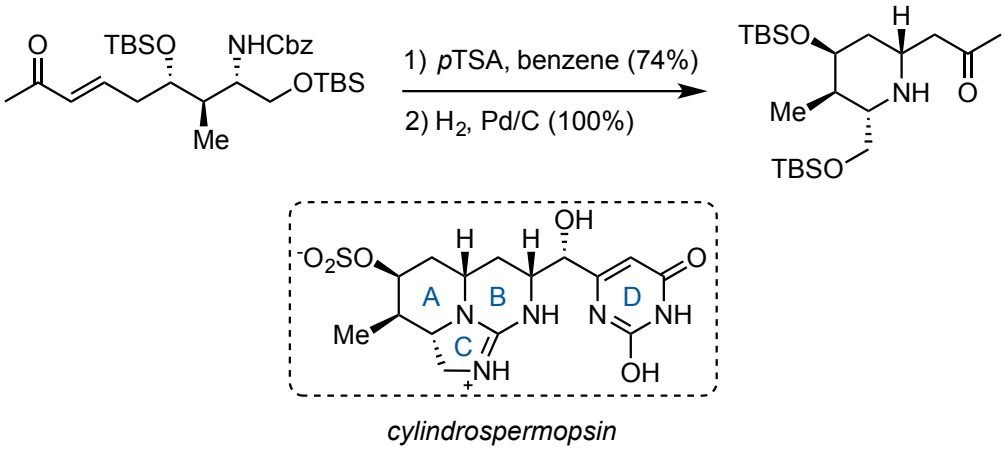
No catalyst is generally required in *aza*-Michael reactions with amines[80] or lithium amides[81] as nucleophiles. Meanwhile, for less reactive nitrogen nucleophiles there have been commonly employed base, acid or transition metal catalysts to perform the conjugated addition. For instance, Meijere's group described the use of a sub-stoichiometric amount of potassium hydride to generate a fraction of the potassium salt of an oxazolidinone, which had a sufficient nucleophilicity to undergo the *aza*-Michael reaction (Scheme 1.2).[82]



R= Me, Bn 72-91%

Scheme 1.2. basic catalysed *aza*-Michael reaction.

As regards acid catalysis, it was reported by Armstrong a synthesis of the A-ring of cylindrospermopsin, using an intramolecular conjugate addition as the key step to forming the piperidine ring (Scheme 1.3).[83]



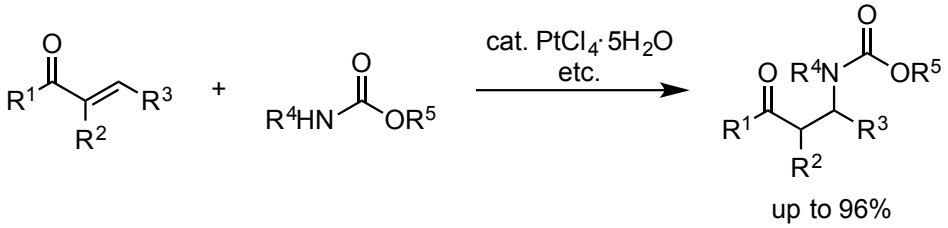
cylindrospermopsin

Scheme 1.3. Intramolecular *aza*-Michael reaction by means of an acid catalysis.

Later, it was developed the use of transition metals to catalyse this kind of transformations. Initially by means of Palladium complexes[84] but soon after

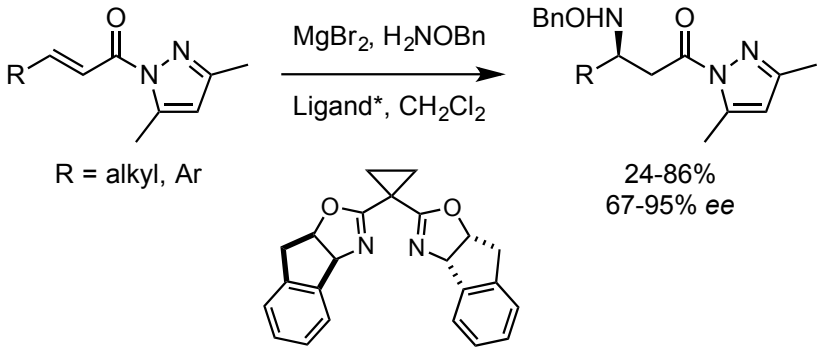
[80] a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117–128. b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582.
[81] Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274–6282.
[82] de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, 3105–3115.
[83] McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849–1853.

Kobayashi extended it to other transition metals,[85] catalysing *aza*-Michael reactions of enones with carbamates (Scheme 1.4). Thus, demonstrating that some of them were as effective as palladium, but that the conventional oxophilic Lewis acids, i. e. $BF_3{\cdot}OEt_2$, $AlCl_3$, $SnCl_4$, $Sc(OTf)_3$, and $TiCl_4$, showed lower yields.



Scheme 1.4. *Aza*-Michael reactions efficiently catalysed by several transition metal salts.

The first approaches to perform asymmetric *aza*-Michael reactions took advantage of the use of chiral auxiliaries; there were employed either chiral nitrogen nucleophiles or α,β-unsaturated substrates bearing a chiral ester.[86] Enantioselective approaches lagged behind, and in the late nineties the group of Sibi described the first highly enantioselective[87] Lewis acid-catalysed addition of amines.[74b] It consisted on the conjugated addition of *O*-benzylhydroxyl amine to unsaturated pyrazolamides (Scheme 1.5) using chiral Lewis acids as catalysts.



Scheme 1.5. First highly enantioselective catalysed *aza*-Michael reaction.

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[84] Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001**, *3*, 25–28.

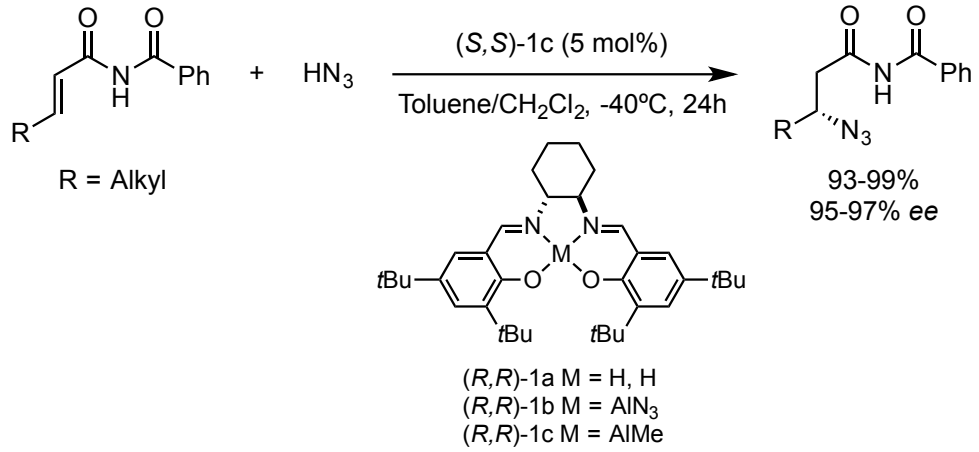
[85] Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319–1322.

[86] a) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem. Int. Ed.* **1995**, *34*, 455–457. b) Dumas, F.; Mezrhab, B.; D'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293–2304.

[74b] Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616.

[87] The first report of an *aza*-Michael addition with a chiral catalyst dates from two year earlier but they just achieve a maximum enantioselectivity of 42%. Falborg, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, *53*, 2823–2826.

Since then, more examples of enantioselective conjugated additions of hydroxyl amines to amides or enones appeared in the literature, highlighting some other reports of Sibi [88] or Shibasaki,[89] using chiral ligands derived from bis(oxazoline) and heterobimetallic chiral complexes, respectively. There have also been reported some examples employing aromatic amines as nucleophiles in this kind of reactions.[90] Finally it should be also underlined, the utilization of Al-salen complexes developed by Jacobsen to perform the 1,4-addition of hydrazoic acid and *N*-heterocycles to imides and enones with excellent enantioselectivities (Scheme 1.6).[91]



Scheme 1.6. Conjugate addition of HN_3 to α,β-unsaturated imides employing the shelf-stable (salen) Al(III)Me complex as precatalyst.

Excluding the organocatalytic methodologies, only one report of an enantioselective *aza*-Michael reaction with a less nucleophilic nitrogen, has been published by Palomo and co-workers.[92] They described in 2004 the

[88] a) Sibi, M. P.; Liu, M. Org. Lett. **2000**, 2, 3393-3396. b) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, 3, 4181-4184. c) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, 125, 11796-11797. Conjugate addition of hydrazines: d) Sibi, M. P.; Soeta, T. *J. Am. Chem. Soc.* **2007**, 129, 4522-4523.

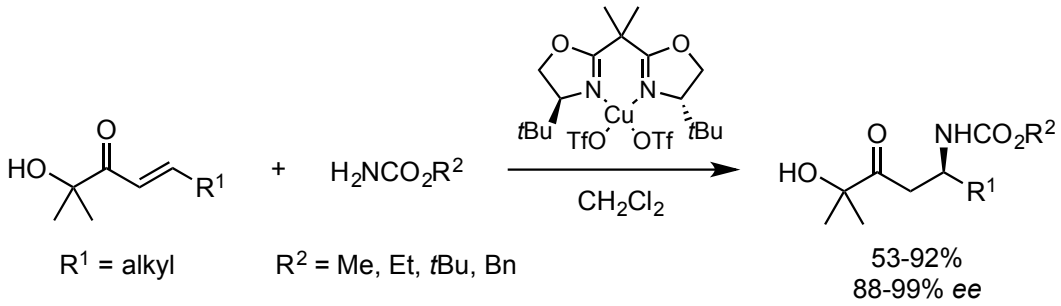
[89] a) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, 125, 16178-16179. b) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419–13427.

[90] a) Zhuang, W.; Hazell. R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240-1241. b) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, 6, 1861-1864. c) Phua, P. H.; White, A. J. P.; deVries, J. G.; Hii, K. K. *Adv. Synth. Catal.* **2006**, 348, 587-592. d) Li, K.; Hii, K. K. *Chem. Commun*. **2003**, 1132-1133.

[91] For hydrazoic acid additions: a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960. b) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, 127, 1313-1317. For *N*-heterocylces additions: c) Gandelman, M.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, 44, 2393-2397.

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

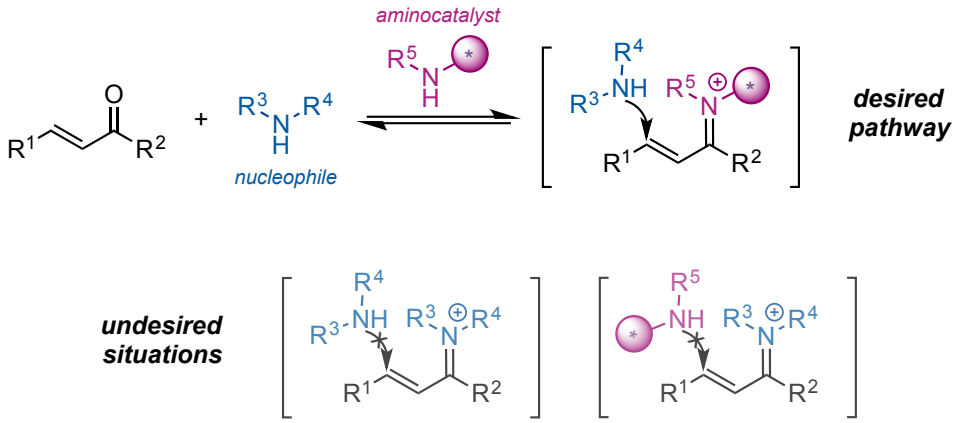
addition of carbamates (H_2N-Cbz and H_2N-Boc) to different α'-hydroxyenones by means of a chiral Cu(II)-bis(oxazoline) complex as catalyst (Scheme 1.7). Likewise, examples of the intramolecular version of the *aza*-Michael reaction remain elusive and can thus be considered as a challenging task.



Scheme 1.7. Addition of less nucleophilic carbamates to α'-hydroxyenones

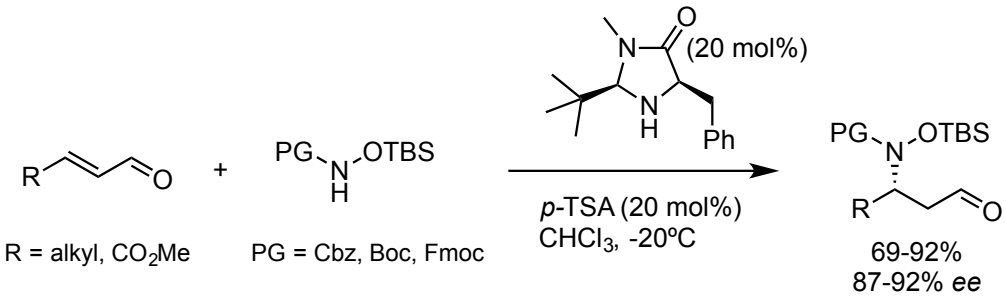
Notwithstanding, the remarkable success of organocatalysis has also reached the AMR, and a burgeoning number of publications of this protocol employing chiral organocatalysts have been reported in the last decade.[40c,50a,79b,93] Most examples described in the literature take place through an iminium activation of the Michael acceptor. In this regard, the main challenge for this transformation is to control the differential nucleophilicity between the donor nitrogen and the aminocatalyst, since both species are nitrogen-centered nucleophiles. Thus, it is essential an appropriate choice of both the organocatalyst and the nitrogenated nucleophile in order to avoid the competition for the activation and the addition, respectively, to be able to achieve high enantioselectivities (Scheme 1.8).

[40c] Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
[50a] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.
[79b] Vicario, J.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092.
[93] a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716. b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076.



Scheme 1.8. Nucleophilicity competition in aminocatalysis.

The first aminocatalytic AMR was described by MacMillan in 2006.[50a] He reported the enantioselective addition of *N*-silyloxycarbamates to α,β-unsaturated aldehydes, by virtue of a chiral imidazolidinone developed in his own group (Scheme 1.9). The achievement of a highly enantioselective reaction with good yields, is due to the elevated nucleophilicity of the nitrogen atom by the α-effect[94] of the trialkylsilyloxy group. Furthermore, the use of the carbamate protecting group avoids the reaction reversibility that could lead to a background AMR with the subsequent epimerization of the product.



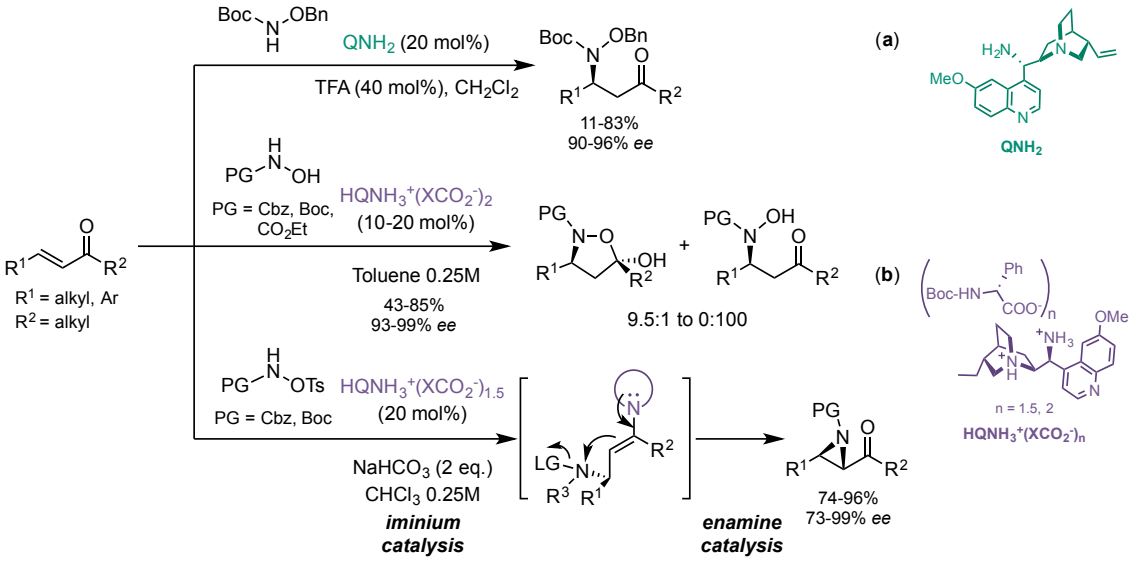
Scheme 1.9. First aminocatalytic AMR performed in MacMillan's group. PG = protecting group.

Henceforward, several research groups expanded upon this transformation with different kinds of nucleophiles and with conjugated aldehydes as Michael acceptors.[95] The application of this methodology to

[94] Heaton, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 2004–2008.

[95] Carbamate nucleophiles: a) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965–968. b) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Chem. Commun.* **2007**, *48*, 849–851. c) Sundén, H.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827–832. d) Vesely, J.; Ibrahem, I.; Rios, R.; Zhao, G.-L.; Xu, Y.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2193–2198. e) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 778–781. f)

enones remained virtually unexplored[96] until 2008, when Deng *et al* published an AMR with α,β-unsaturated ketones catalysed by a quinine derivative functionalised with a primary amine (Scheme 1.10.a).[97] Almost at the same time, the group of Melchiorre unrolled both a domino Michael addition-intramolecular aldol sequence and a domino conjugate-cyclisation azidirination sequence with conjugated ketones by means of an iminium or iminium/enamine organocatalytic activation with a primary amine derived from hydroquinidine (Scheme 1.10.b).[98]



Scheme 1.10. First aminocatalytic AMR with conjugated ketones as Michael acceptors.

In this context, also worthy of mention are the conjugate additions of *N*-heterocycles to α,β-unsaturated ketones published in 2009 by Wang and Zhao. The first one exposes the *aza*-Michael reaction between 1H-benzotriazole and 5-phenyl-1H-tetrazole and various enones catalysed by a chiral cinchona

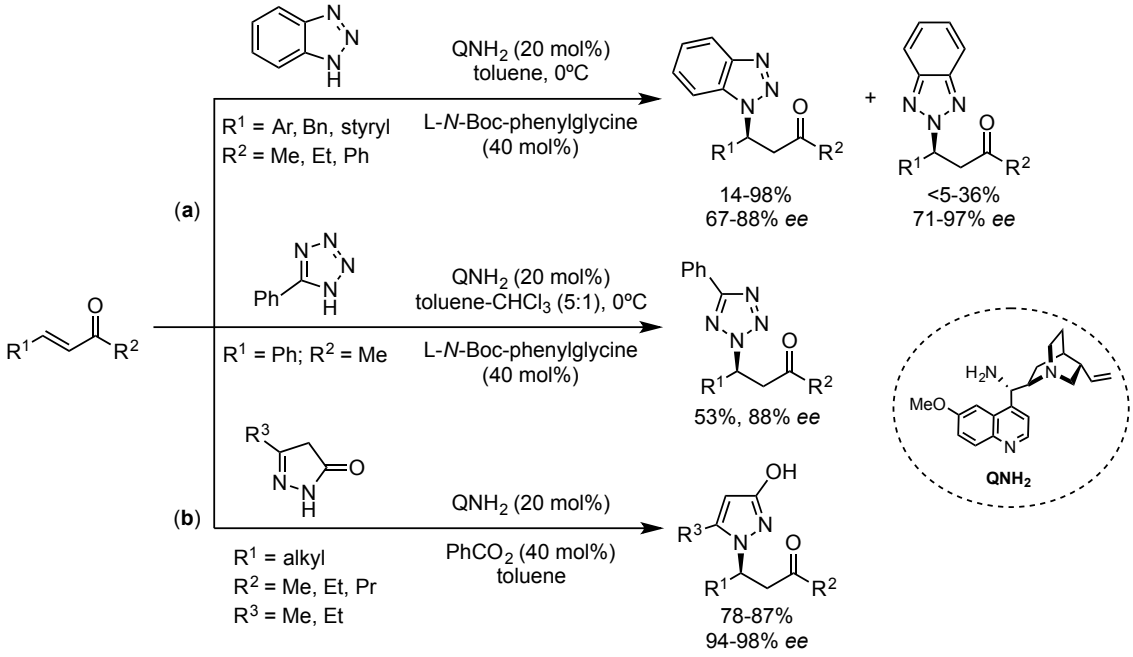
Chen, L.-Y.; He, H.; Pei, B.-J.; Chan, W.-H.; Lee, A. *Synthesis* **2009**, 1573–1577. *N*-heterocycles nucleophiles (ref. 50b-d): g) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983–1987. h) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509–2511. i) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999–2002.

[96] The first example with enones participating in an aminocatalysed AMR was in an enantioselective aza-Diels-Alder reaction catalysed with proline, where the hypothesized pathway proceeds through a tandem Mannich/intramolecular aza-Michael sequence. Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 4877–4880.

[97] Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 7710–7713.

[98] Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8703–8706.

alkaloid derived primary amine (Scheme 1.11.a).[99] And the second one describes the enantioselective addition of 2-pyrazolin-5-ones to aliphatic conjugated ketones, employing the same primary amine organocatalyst derived from quinine (Scheme 1.11.b).[100]



Scheme 1.11. Asymmetric organocatalytic conjugate addition of *N*-heterocycles to α,β-unsaturated ketones.

As we have seen, the primary amines have revealed to be very efficient as organocatalysts to activate enones in 1,4-additions, since they avoid the problematic in the formation of the iminium intermediate between ketones (or other Michael acceptors with steric hindrance) and the usually employed secondary-amine organocatalysts (Figure 0.3). In addition, the particular family of cinchona alkaloid derivatives (Schemes 1.10 and 1.11) have been widely deployed given its bifunctionality. These aminocatalysts activate both the electrophile through the formation of the iminium ion, and the nucleophile thanks to the deprotonation promoted by the tertiary amine of the quinuclidine. Thus, there can be obtained a well-organized transition state that will lead to an excellent stereocontrol.

Although most of the published examples about the organocatalytic *aza*-Michael reaction are based on an iminium catalysis, there also exist some

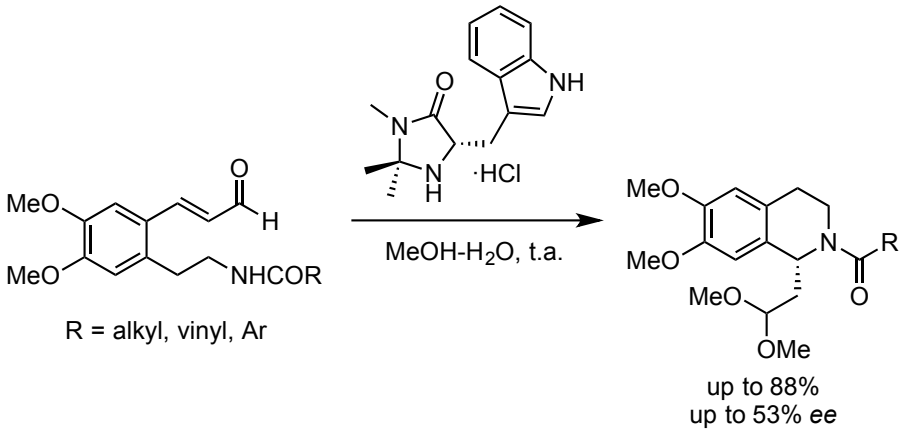
[99] Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Synthesis* **2009**, 1564–1572.
[100] Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249–2252.

reports of other activation methodologies. In this way, a catalytic peptide containing histidine has been employed for the conjugate addition of $TMSN_3$ to α,β-unsaturated oxazolidinones.[53a, 101] Furthermore, cinchone alkaloids derivatives have been also used as chiral bases to perform the 1,4-addition of *N*-heterocycles,[102] and azides[103] to nitroalkenes. Additionally, they have been employed for the conjugate addition of hydrazones to cyclic enones,[104] as well as for the addition of aniline to diverse chalcones in neat conditions.[105] Finally, chiral thioureas and its derivatives have been used as organocatalysts for the *aza*-Michael reactions between hydroxyl amines and enoates,[106] the same way that between O-benzylhydroxyl amine to chalcones.[107]

ORGANOCATALYTIC INTRAMOLECUAR *AZA*-MICHAEL REACTION

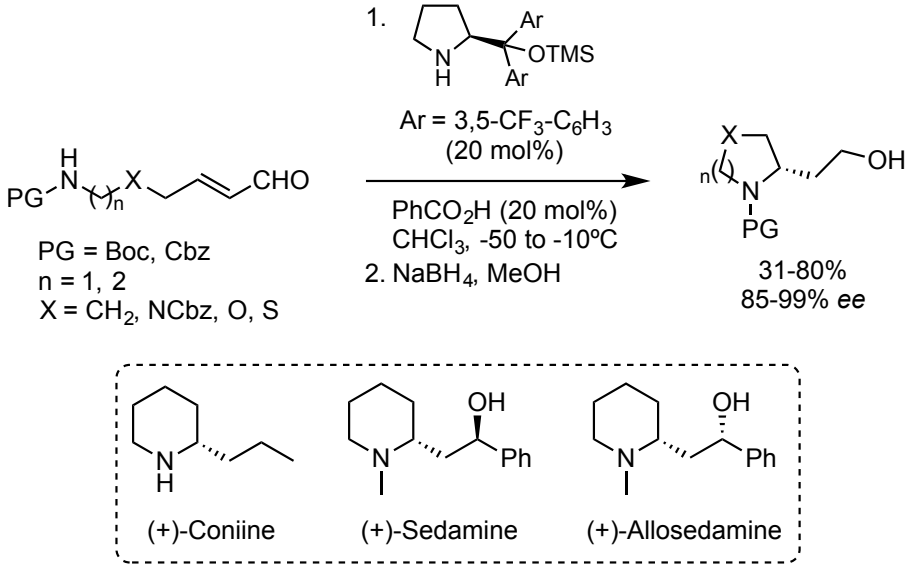
It should be considered that the intramolecular *aza*-Michael reaction (IMAMR) implies a simply direct way to procure nitrogen-containing heterocycles, privileged structures for their presence in biologically active compounds and for their versatility as synthetic intermediates. However, this version has been explored to a lesser extend despite its great synthetic potential, especially in an enantioselective manner. The first example dates from 2003 with the report of an intramolecular addition of amides to α,β-unsaturated aldehydes using an imidazolidinone type catalyst and achieving tetrahydroisoquinolines with moderate enantioselectivity (Scheme 1.12).[108]

[53a] Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136.
[101] Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem.* **2000**, *112*, 3781–3784. *Angew. Chem. Int. Ed.* **2000**, *39*, 3635-3638.
[102] Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett*. **2006**, 8, 1391-1394.
[103] Nielsen, M.; Zhuang, W.; Jørgensen, K. A. *Tetrahedron* **2007**, 63, 5849-5854.
[104] Jørgensen, K. A.; Perdicchia, D. *J. Org. Chem*. **2007**, 72, 3565-3568.
[105] Scettri, A.; Massa, A.; Palombi, L.; Villano, R.; Acocella, M. R. *Tetrahedron: Asymmetry* **2008**, 19, 2149-2152.
[106] Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc*. **2007**, 129, 8064-8065
[107] Pettersen, D.; Piana, P.; Bernardi, L.; Fini, F.; Fochi, M.; Sgarzani, V.; Ricci, A. *Tetrahedron Lett*. **2007**, 48, 7805-7808.
[108] Ihara, M.; Takasu, K.; Maiti, S. *Heterocycles* **2003**, *59*, 51-55.



Scheme 1.12. First aminocatalytic intramolecular *aza*-Michael reaction.

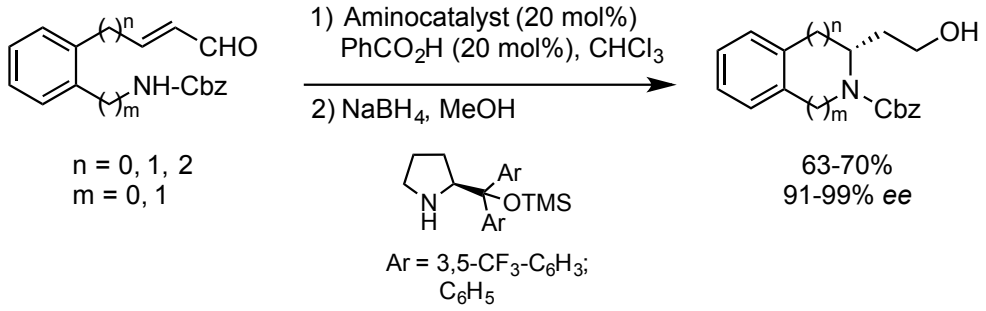
The next relevant example was developed in our research group and it comprises the organocatalytic and enantioselective intramolecular conjugated addition of carbamates to enals.[109] The substrates have both functional groups separated the appropriate distance to obtain different 5 and 6-membered heterocycles, in the presence of the fluorinated Jorgensen-Hayashi diaryl prolinol as catalyst. After reducing *in situ* the formyl group, there was prepared a family of amino alcohols with good yields and excellent enantioselectivities (Scheme 1.13). Moreover, this methodology was applied for the enantioselective synthesis of three natural piperidine alkaloids: (+)-Coniine, (+)-Sedamine and (+)-Allosedamine.



Scheme 1.13. Highly enantioselective IMAMR between carbamates and α,β-unsaturated aldehydes.

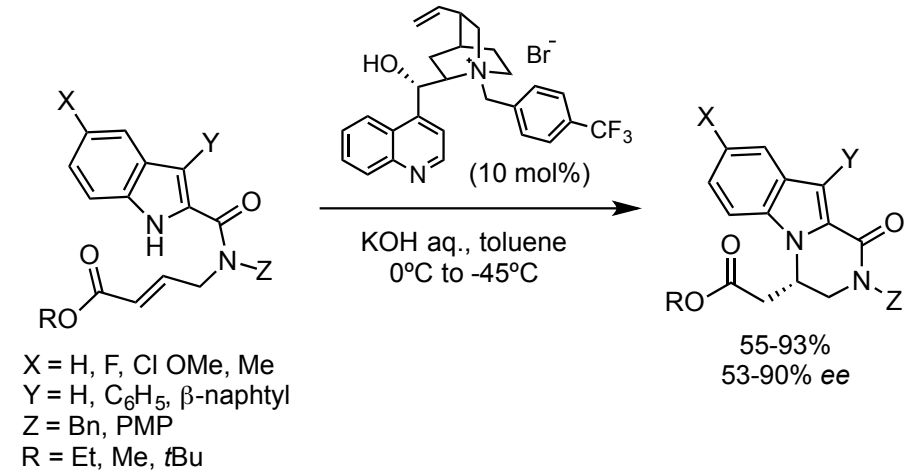
[109] Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286.

In the same way, our research group extended this IMAMR methodology to *o*-substituted anilines and benzyl amines bearing a remote α,β-unsaturated aldehyde. [110] Thus, a concise way to prepare enantiomerically enriched tetrahydroquinolines, tetrahydroisoquinolines, indolines and isoindolines in a very simple manner was described (Scheme 1.14).



Scheme 1.14. Enantioselective IMAMR for the preparation of benzofused *N*-heterocycles.

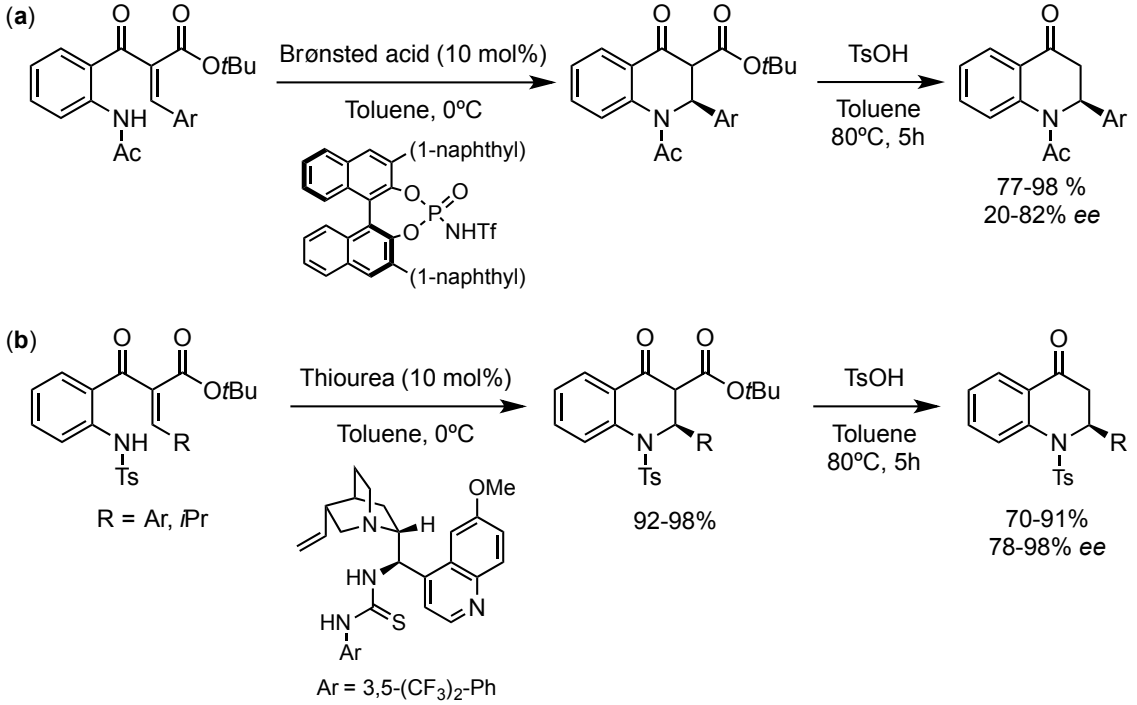
Shortly after, the application of the IMAMR was expanded to other activation modes, nitrogen nucleophiles and Michael acceptors. The first example was published by Umani-Ronchi and Bandini's group [111] and it consisted on a conjugated addition of the indole nitrogen to α,β-unsaturated esters to obtain the corresponding tricycles with variable yields and enantioselectivities by means of phase transfer catalysis with a chiral ammonium salt of cinchonidine derivative (Scheme 1.15).



Scheme 1.15. Extension of the organocatalytic IMAMR to conjugated esters.

[110] Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872.
[111] Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3238–3241.

Then, in 2010, You and co-workers reported the first example of an IMAMR with ketones as Michael acceptors.[112] They employed an acetamide as nitrogen source, a conjugated β-keto-ester as the Michael acceptor and a chiral *N*-trifyl binolphosphoramide as the catalyst (Scheme 1.16.a). The authors envisioned that the presence of the β-keto-ester moiety would enhance the electrophilicity of the Michael acceptor. In the same year, this methodology was improved by Lu,[113] when they envisioned that a sulfonyl substituted aniline could be used as the nucleophilic component, and by means of a tertiary amine-thiourea organic catalyst, they synthesized highly enantioselective dihydroquinolones in very good yields(Scheme 1.16.b).

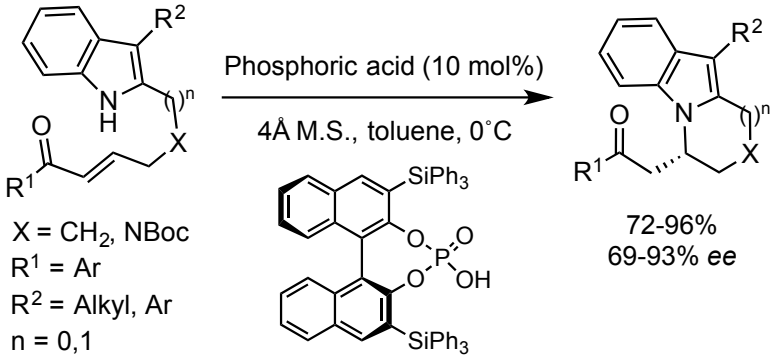


Scheme 1.16. IMAMR of alkyliden β-keto-esters bearing a sulfonamide by means of a bifunctional tertiary amine-thiourea organocatalyst.

Almost at the same time, the nucleophilic addition of an indolic nitrogen to aromatic ketones, catalysed by a chiral Brønsted acid, was reported.[114]. Here, indole derivatives bearing a remote chalcone functionality in the position 2 underwent the IMAMR in the presence of the BINOL-phosphoric acid and

[112] Z. Feng, Q.-L. Xu, L.-X. Dai and S.-L. You, *Heterocycles*, **2010**, 80, 765-771.
[113] Liu, X.; Lu, Y. *Org. Lett.* **2010**, *12*, 5592–5595.
[114] Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2010**, *49*, 8666–8669.

molecular sieves. Tricyclic indoles were obtained in good yields and excellent levels of enantioselection (Scheme 1.17).



Scheme 1.17. IMAMR between indoles and chalcones.

1.1.2. ENANTIOSELECTIVE SYNTHESIS OF BENZOFUSED HETEROCYLCIC SYSTEMS

Benzofused heterocycles have been the subject of several asymmetric syntheses, due to their ubiquitous presence in natural products and to the inherent biological activity that this substructure impart in many of these compounds.[115] In this section it will be shortly reviewed the most prominent and recent asymmetric syntheses of indolines, isoindolines, tetrahydroquinolines and tetrahydroisoquinoines (Figure 1.1), for being the ones studied in the present chapter of this Doctoral Thesis.

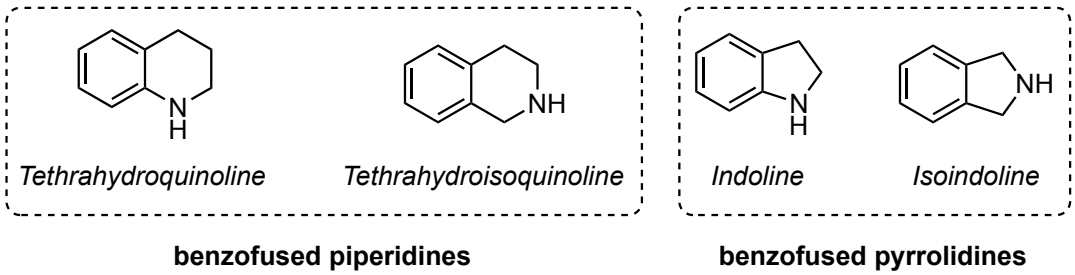
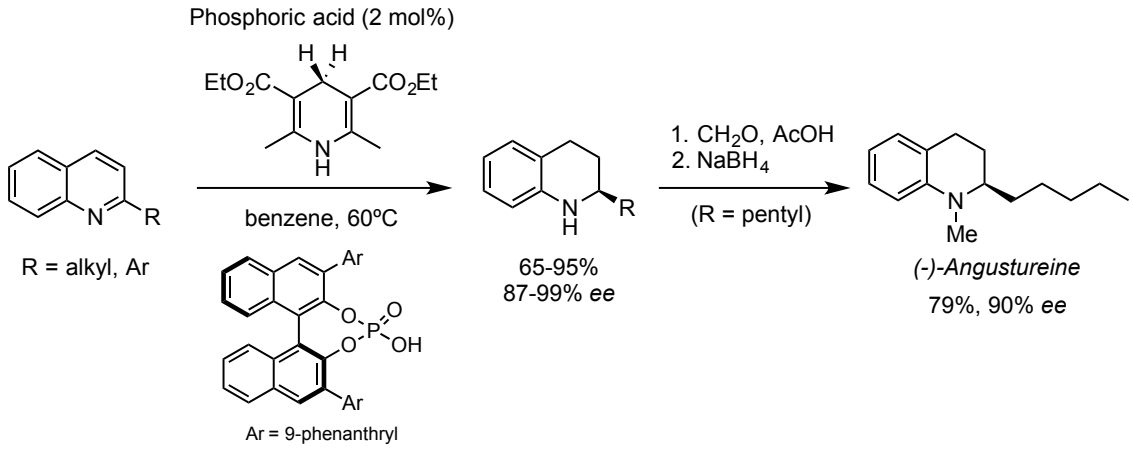


Figure 1.1. Reviewed benzofused substructures

[115] a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031-15070. b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787-828. c) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730. d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930. e) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341-3370. f) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151-161.

a) Enantioselective synthesis of tetrahydroquinolines

Within piperidines family, for the catalytic enantioselective synthesis of tetrahydroquinolines there can be considered two different strategies.[116] The first involves the asymmetric hydrogenation of the corresponding aromatic quinolines by means of metallic chiral catalysts[117] or, more recently, with chiral Brønsted acids.[118] For instance, Rueping's group developed an efficient methodology to perform the cascade asymmetric hydrogenation (1,4 hydride addition/ isomerization/ 1,2 addition) of quinolines employing BINOL-phosphoric acid derivatives, as chiral Brønsted acids catalysts (Scheme 1.18).[118a] This methodology gives access to enantiomerically enriched 2-substituted tetrahydroquinolines, and its utility was later exemplified in the preparation of the natural product Angustureine.



Scheme 1.18. Synthesis of Angustureine by means of a chiral BINOL-phosphoric acid catalyst.

The second main approach for the enantioselective preparation of tetrahydroquinolines is the *aza*-Diels-Alder reaction.[119] Concretely, it is a

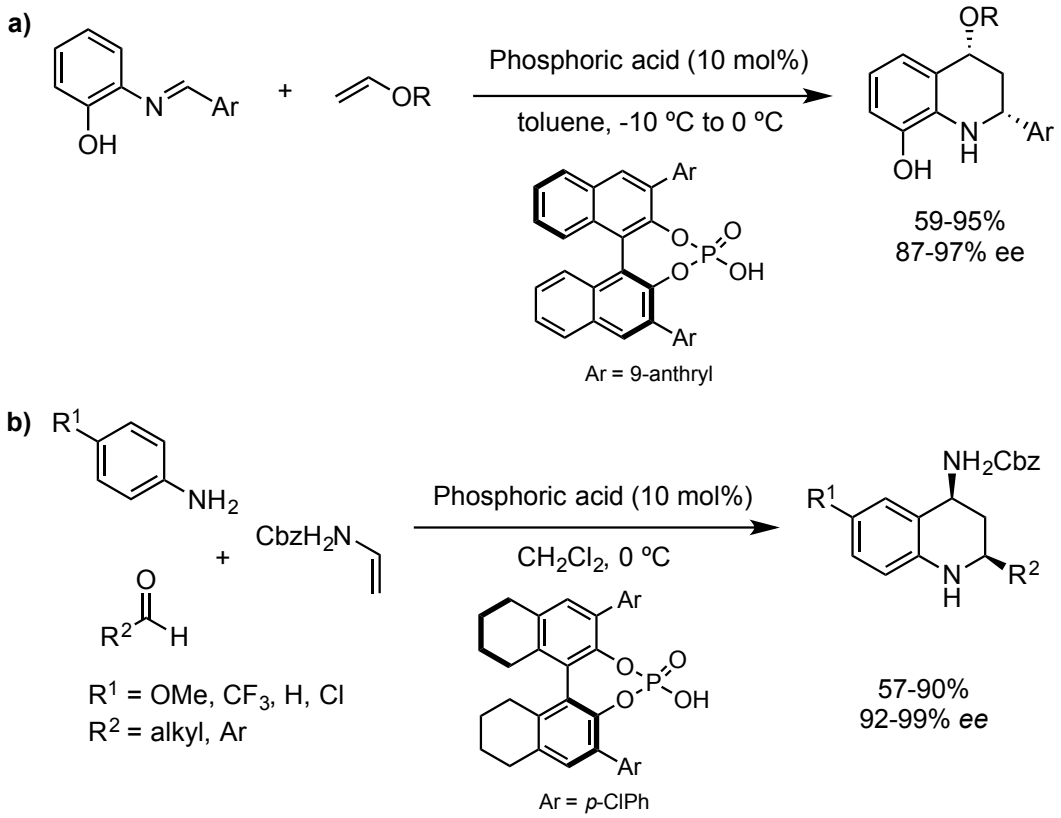
[116] a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev*. **2011**, *40*, 3445-3454. b) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci*. **2011**, *13*, 65-71.

[117] a) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2006**, *25*, 2260-2263. b) Wang, Z.-J.; Deng, G.-J.; Li, Y.; He, Y.-M.; Tang, W.-J.; Fan, Q.-H. *Org. Lett.* **2007**, *9*, 1243-1246. c) Wang, C.; Li, C. Q.; Wu, X. F.; Pettman, A.; Xiao, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524-6528. d) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc*., **2009**, *131*, 9182- 9183. e) Tang, W.; Sun, Y.; Xu, L.; Wang, T.; Fan, Q.; Lam, K.-H.; Chan, A. S. C. *Org. Biomol. Chem*. **2010**, *8*, 3464-3471.

[118] a) Rueping, M.; Antonchick, A. P.; Theismann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683-3686. b) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759-762. c) Rueping, M.; Stoeckel, M.; Sugiono, E.; Theissmann, T. *Tetrahedron* **2010**, *66*, 6565-6568.

[119] a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett*. **1996**, *37*, 7357-7360. b) Akiyama, T. T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc*. **2006**, *128*, 13070-13071. c) Xie, M. S.; Chen, X. H.;

Povarov reaction, comprising an inverse electron demand *aza*-Diels-Alder reaction mechanism to obtain tetrahydroquinolines with good yields, and very good enantiomeric and diastereoisomeric excesses favouring the *cis* isomer. This organocatalytic approach can be developed as a regular intermolecular transformation between aldimines and enolic ethers (Scheme 1.19.a) or as a three component reaction starting from aliphatic aldehydes, anilines and *N*-vinyl benzyl carbamates (Scheme 1.19.b).



Scheme 1.19. Asymmetric organocatalytc Povarov reactions.

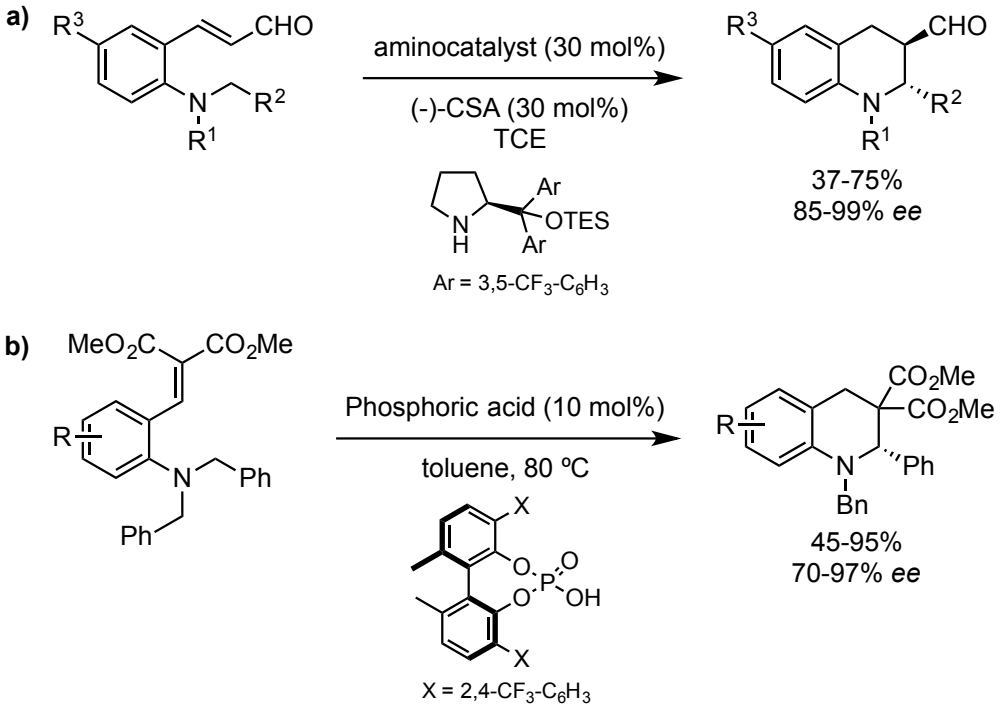
Beside these general procedures, there have been described other ways to synthesize enantioenriched tetrahydroquinolines,[120] several of them also employing organocatalysts. For instance, the intramolecular *aza*-Michael reaction described in our research group, with carbamates as nucleophiles and α,β-unsaturated aldehydes as Michael acceptors and employing a chiral diaryl

Zhu, Y.; Gao, B.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem. Int. Ed*. **2010**, *49*, 3799-3802. d) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc*. **2009**, *131*, 4598-4599.

[120] a) Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Org. Lett*. **2009**, *11*, 1237-1240. b) Murarka, S.; Deb, I.; Seidel, D. *J. Am. Chem. Soc*. **2009**, 131, 13226-13227. c) Kang, Y. K.; Kim, S M.; Kim, D. Y. *J. Am. Chem. Soc*. **2010**, *132*, 11847-11849. d) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc*. **2011**, *133*, 6166-6169. e) Jia, Z.X.; Luo, Y.C.; Xu, P.F. *Org. Lett*. **2011**, *13*, 832-835.

prolinol catalyst (Scheme 1.14), that, among other final products, it allowed the access to tetrahydroquinolines with very good yields and enantioselectivities.[110]

It has also been described an alternative methodology based on a C-H activation,[121] which is employed in these two organocatalytic synthesis of tetrahydroquinolines based on an enantioselective C-H functionalisation through a sequence of 1-5 hydride transference followed by a ring closure (intern redox process). In one of them the organocatalyst employed is a secondary amine derived from diaryl prolinol (Scheme 1.20.a),[120c] while in the second example they use a chiral phosphoric acid as catalyst (Scheme 1.20.b).[120d] In both cases the corresponding tetrahydroquinolines where obtaining with moderate to good yields and very good enantiomeric excesses.



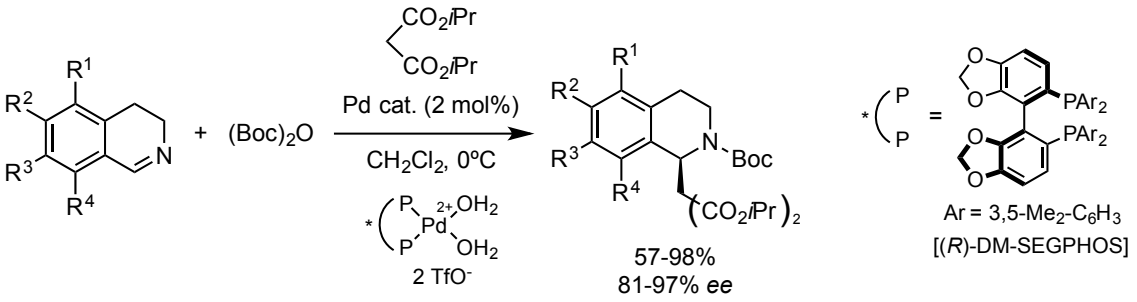
Scheme 1.20. Organocatalytic asymmetric C-H functionalisation.

b) Enantioselective synthesis of tetrahydroisoquinolines

One of the most common approaches to access enantioenriched tetrahydroisoquinolines consists on the asymmetric hydrogenation of the isoquinoline and dihydroisoquinoline scaffolds, generally in the presence of

[110] Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872.
[121] Yadav, A. K.; Yadav, L. D. S. *Tetrahedron Lett.* **2016**, *57*, 1489–1491.

metals.[122] However, presumably the most popular methodology to obtain this type of benzofused structures is based on the nucleophilic addition to the C=N bond of dihydroisoquinolines.[123] A representative example is the publication of Sodeoka and co-workers about the asymmetric addition of malonates catalysed by Pd(II) chiral complexes (Scheme 1.21). It involves an asymmetric Mannich type reaction of malonates with the dihydroisoquinoline iminium ions formed *in situ*.[123e]



Scheme 1.21. Mannich type reaction between malonates and dihydroisoquinolines catalysed by a Pd(II) chiral complex.

Some procedures that have also been used with the same purpose are the Pictet-Spengler synthesis, [124] allylic amination reactions, [125] or cycloisomerizations.[126] Among them, an interesting example reported by Enders expose the organocatalytic synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines, based on a tandem process reductive amination/ intramolecular *aza*-Michael reaction (Scheme 1.22). [127] Throughout the optimised conditions, several methyl ketones bearing Michael acceptors (α,β

[122] a) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227- 4230. b) Tietze, L. F.; Rackelmann, N.; Sekar, G. *Angew. Chem. Int. Ed*. **2003**, *42*, 4254-4257. c) Wang, Z.-J.; Deng, G.-J.; Li, Y.; He, Y.-M.; Tang, W.-J.; Fan, Q.-H. *Org. Lett*. **2007**, *9*, 1243-1246. d) Evanno, L.; Ormala, J.; Pihko, P. M. *Chem. Eur. J*. **2009**, *15*, 12963-12967. e) Yan, P.-C.; Xie, J.-H.; Hou, G.-H.; Wang, L.-X.; Zhou, Q.L. *Adv. Synth. Catal*. **2009**, *351*, 3243-3250.

[123] a) Jensen, K. B.; Roberson, M.; Jorgensen, K. A. *J. Org. Chem*. **2000**, *65*, 9080- 9084. b) Funabashi, F.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 10784-10785. c) Wang, S.; Seto, C. T. *Org. Lett*. **2006**, *8*, 3979-3982. d) Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T. *Synlett* **2006**, 1595-1597. e) Dubs, C.; Hamashima, Y.; Sasamoto, M.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem*. **2008**, *73*, 5859-5871. f) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc*. **2010**, *132*, 4076-4077.

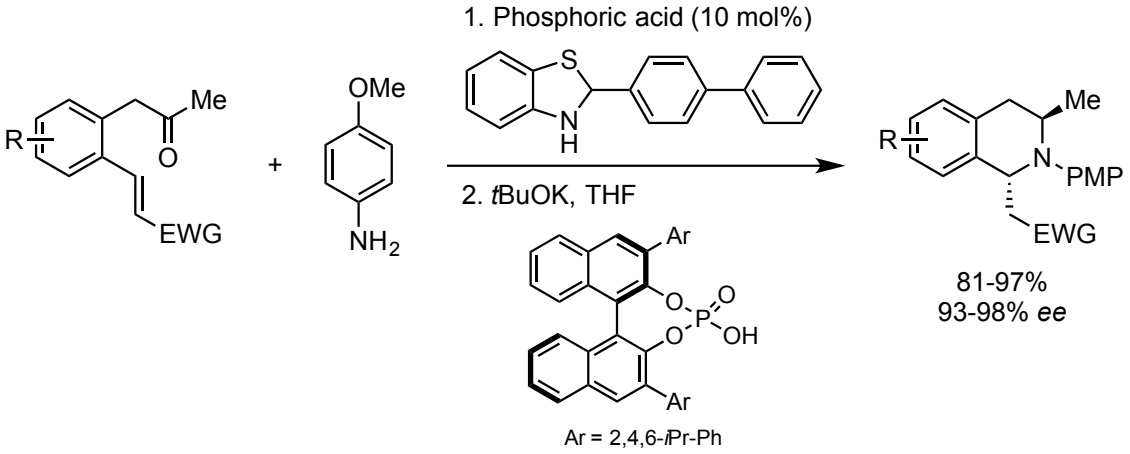
[124] a) Nuhant, P.; Raikar, S. B.; Wypych, J. C.; Delpech, B.; Marazano, C. *J. Org. Chem*. **2009**, *74*, 9413-9421. b) Pesnot, T.; Gershater, M. C.; Ward, J. M.; Hailes, H. C. *Chem. Commun*., **2011**, *47*, 3242-3244.

[125] a) Teichert, J. F.; Fañanás-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 688-691. b) Kawai, N.; Abe, R.; Matsuda, M.; Uenishi, J. *J. Org. Chem*. **2011**, *76*, 2102-2114.

[126] Hashmi, A. S. K.; Ata, F.; Haufe, P.; Rominger, F. *Tetrahedron* **2009**, *65*, 1919-1927.

[127] Enders, D.; Liebich, J. X.; Raabe, G. *Chem. Eur. J.* **2010**, *16*, 9763-9766.

unsaturated esters and amides) reacted with *p*-anisidine in the presence of benzothiazoline as reducing agent. The intermediate amine cyclised with *t*BuOK, affording exclusively the corresponding *trans* isomers of the tetrahydroisoquinolines with excellent yields and enantioselectivities.



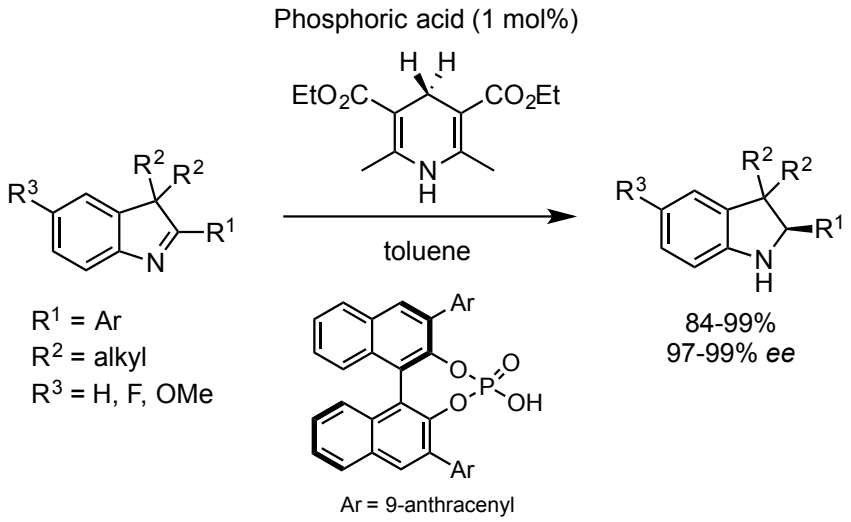
Scheme 1.22. Synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines.

c) Enantioselective synthesis of indolines

Regarding pyrrolidines family (Figure 1.1), indoline skeleton is the most important substructure and, still nowadays, its synthesis is object of study of a large number of research groups.[128] In fact, in recent years there have appeared a large number of enantioselective synthesis, and again many of them are based on the asymmetric hydrogenation of the indol system.[129] A representative example of this methodology is the synthesis described by Rueping and co-workers,[129b] where a enantioselective reduction of 3H-indoles is catalysed by a Brønsted acid in the presence of a derivative of the Hantzsch dihydropyridine as hydrogen source (Scheme 1.23).

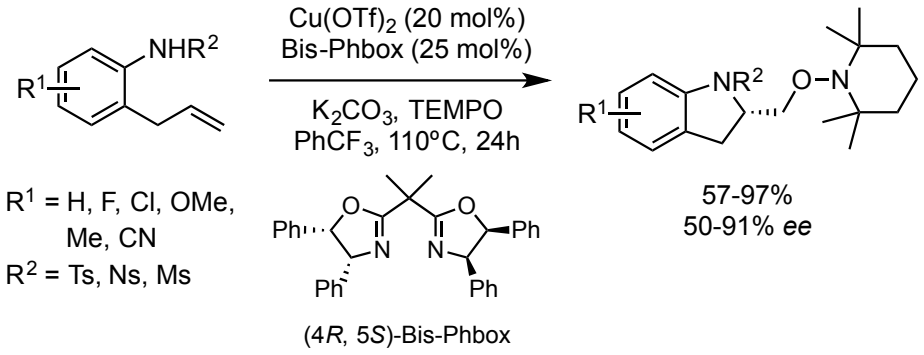
[128] a) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240–2245. b) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304–5305. c) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009–1011. d) Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193-2199. e) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944–2947. f) Turnpenny, B. W.; Hyman, K. L.; Chemler, S. R. *Organometallics* **2012**, *31*, 7819–7822. g) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658–3661. h) Tasker, S. Z.; Jamison, T. F. *J. Am. Chem. Soc.* **2015**, *137*, 9531–9534.i) Daniels, B. E.; Ni, J.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 3398–3402. j) Zhao, F.; Li, J.; Chen, Y.; Tian, Y.; Wu, C.; Xie, Y.; Zhou, Y.; Wang, J.; Xie, X.; Liu, H. *J. Med. Chem.* **2016**, *59*, 3826–3839.

[129] a) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213–2215. b) Baeza, A.; Pfaltz, A. *Chem. Eur. J.* **2010**, *16*, 2036–2039. c) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911. d) Rueping, M.; Brinkmann, C.; Antonchick, A. P.; Atodiresei, I. *Org. Lett.* **2010**, *12*, 4604–4607. e) Duan, Y.; Chen, M.-W.; Ye, Z.-S.; Wang, D.-S.; Chen, Q.-A.; Zhou, Y.-G. *Chem. Eur. J.* **2011**, *17*, 7193–7197.



Scheme 1.23. Asymmetric synthesis of indolines by hydrogenation of 3H-indoles.

Notwithstanding the foregoing, there are also different organometallic approaches to synthesize enantioenriched indolines, such as the tandem oxidative cyclisation employing a palladium catalyst and (-)-sparteine, described by Yang in 2006,[130] the intramolecular aminooxygenation of alkenes catalysed by a Cu-bisoxazoline (Scheme 1.24),[131] and the one-pot synthesis of tricyclic indolines developed by Buchwald and co-workers consistent on a Pd-catalysed γ–arylation of β,γ-unsaturated ketones.[132]

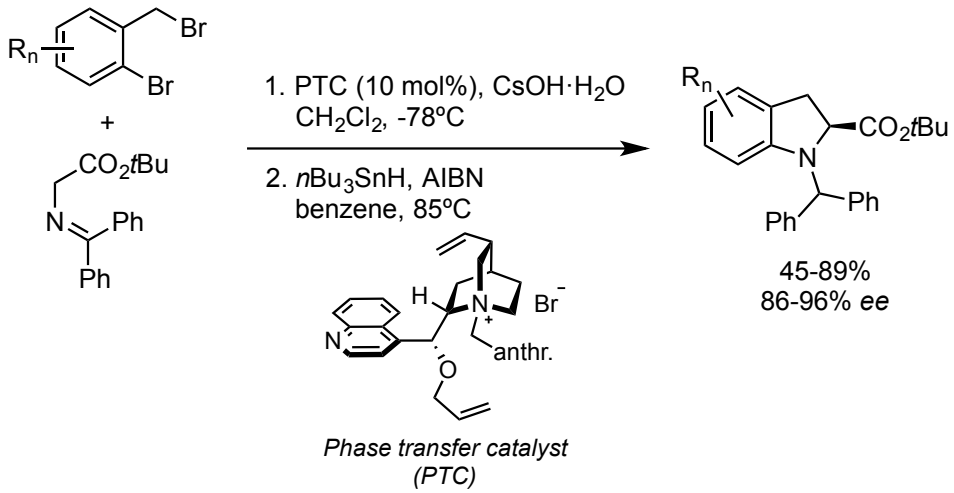


Scheme 1.24. Asymmetric synthesis of indolines via aminooxygenation of alkenes.

As well as many and various organocatalytic procedures to prepare indolines distinct than hydrogenation have been devised. For instance, in 2004 Johnston's group published a phase transfer-catalysed enantioselective alkylation of glycinyl imines followed by a free radical-mediated aryl amination,

[130] Yip, K.; Yang, M.; Law, K.; Zhu, N.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131.
[131] Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639.
[132] Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177–180.

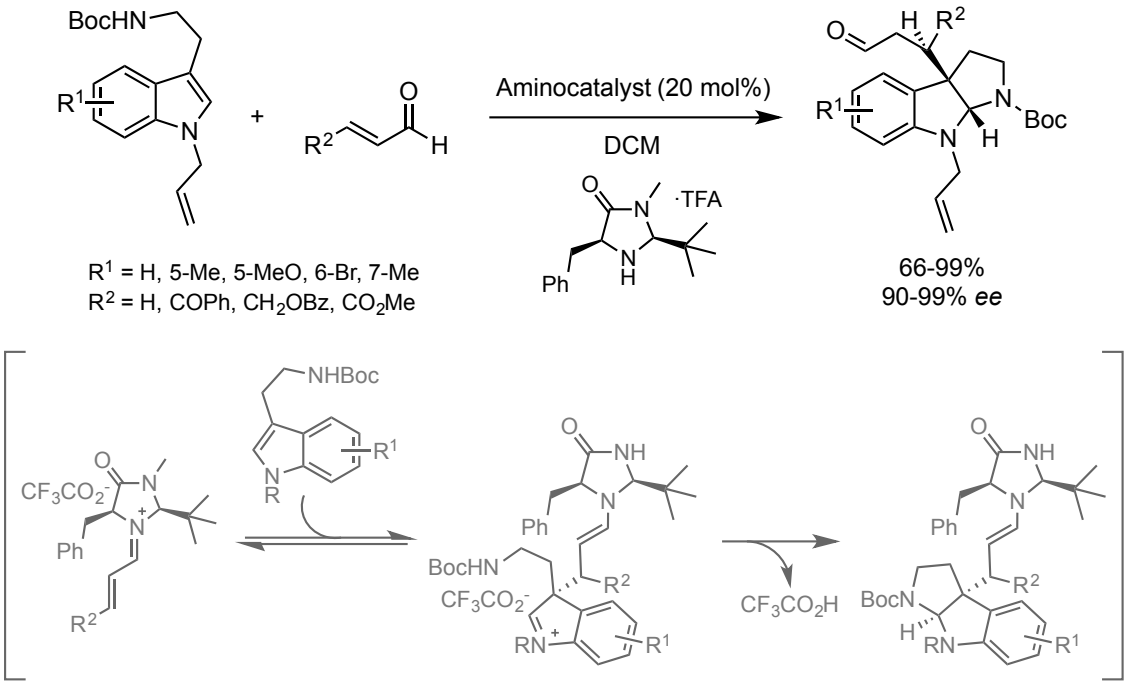
to provide indoline α–amino acids with high enantioselectivites (Scheme 1.25).[133]



Scheme 1.25. Enantioselective synthesis of indoline α-amino acids.

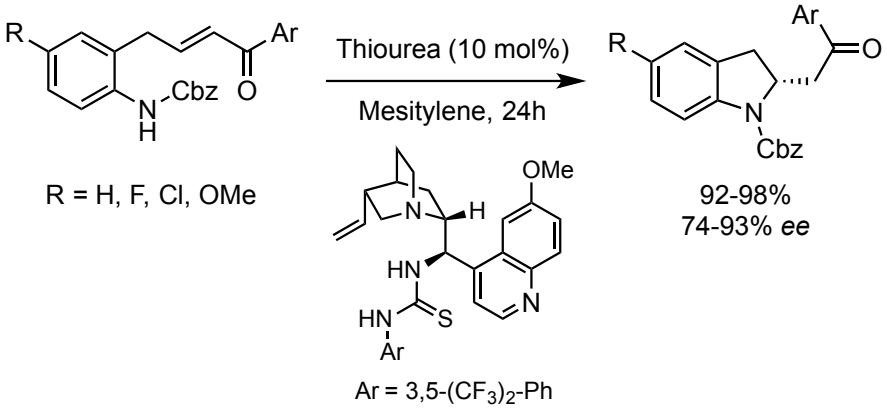
It is also worth mentioning the study of MacMillan and co-workers, they designed a cascade process for the preparation of enantioenriched tricyclic pyrrolindolines, a subclass of alkaloid structural motifs.[134] The addition-cyclisation of tryptamines with α,β-unsaturated aldehydes in the presence of imidazolidinone catalysts provides the desired products in high yield and excellent enantioselectivities. Making use of the iminium catalysis, it is created a quaternary stereocenter on the C3 of the indolium intermediate, that cannot undergo rearomatization by means of proton loss in contrast to the analogous 3-H indole addition pathway. As a result, it takes place a 5-*exo*-heterocyclisation of the pendant ethyl amine, thereby generating the sought tricyclic system (Scheme 1.26).

[133] Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163–168.
[134] Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482–5487.



Scheme 1.26. Aminocatalysed synthesis of pyrrolindolines.

And one of the last examples published is from Matsubara and Asano,[128g] who described the synthesis of indolines using a non-covalent type catalyst to cyclise substituted *N*-benzyloxycarbonyl anilines with aromatic conjugated ketones as the best Michael acceptors (Scheme 1.27). In this way there were obtained the corresponding indolines with excellent yields and enantioselectivities using a quinine-derived bifunctional thiourea.[135]

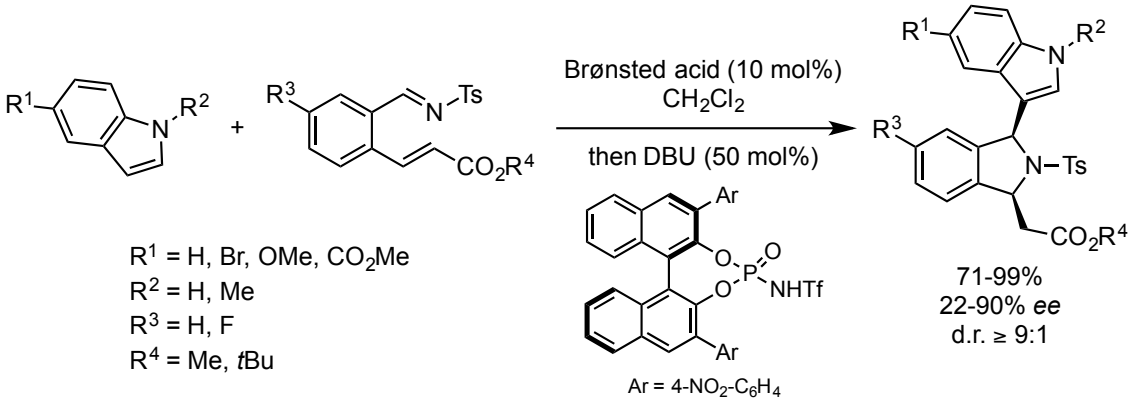


Scheme 1.27. Synthesis of 2-substituted indolines through an IMAMR with conjugated ketones as acceptors.

[128g] Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658–3661.

d) Enantioselective synthesis of isoindolines

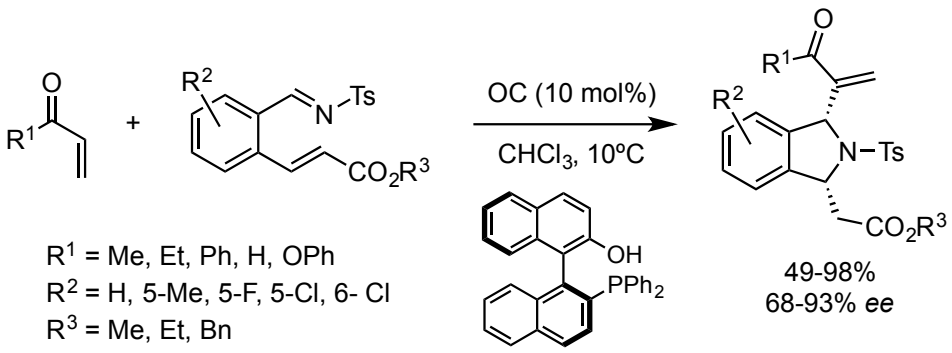
Lastly, the asymmetric synthesis of compounds with a isoindoline substructure has been studied to a lesser extent and most examples are based on the use of chiral substrates or chiral auxiliaries, being very few enantioselective. In this context, in 2008 Enders and co-workers published the first catalytic asymmetric synthesis of 1,3-disubstituted isoindolines (Scheme 1.28).[136] Which consists on a metal-free one-pot Brønsted acid catalysed Friedel-Crafts/base-catalysed *aza*-Michael addition reaction of bifunctional ε-iminoenoates and indoles. By using a chiral BINOL-derived *N*-triflyl phosphoramide organocatalyst in the first step, there were obtained the isoindoline products in high yields and good diastereo-and enantiomeric ratios.



Scheme 1.28. Asymmetric Brønsted acid catalysed isoindoline synthesis.

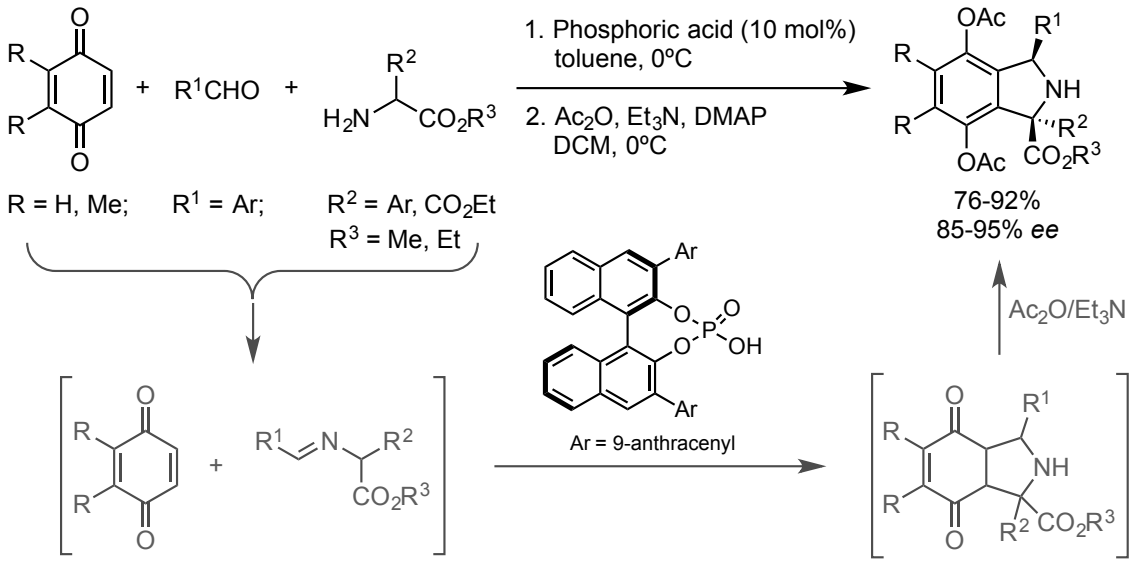
The same type of ε-iminoenoates were employed to prepare another family of 1,3-disubstituted isoindolines with slightly better enantioselectivities (Scheme 1.29).[137] The depicted procedure consists on a domino *aza*-Morita-Baylis-Hillman/intramolecular *aza*-Michael reaction of electron-deficient alkenes and *N*-tosylimines promoted by a chiral acid-base organocatalyst, that is, a Lewis base joined to a Brønsted acid through a chiral backbone.

[136] Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5661–5665.
[137] Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9725–9729.



Scheme 1.29. Organocatalysed domino process based on the *aza*-MBH reaction for an enantioselective synthesis of isoindollines.

Another example with a different kind of starting material is the asymmetric organocatalytic formal double-arylation of azomethines reported in 2010 (Scheme 1.30).[138] By means of a Brønsted acid-catalysed 1,3-dipolar addition and a subsequent organic base-mediated isomerization, starting from an aldehyde, an aminomalonate and quinone derivatives, there are accessed a variety of chiral isoindoline derivatives with high enantiomeric excesses.

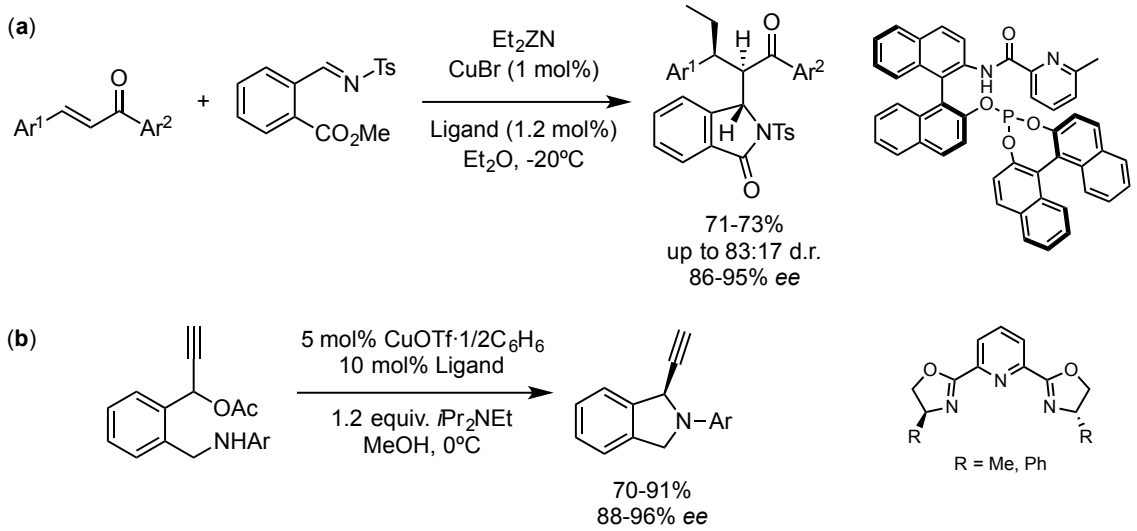


Scheme 1.30. Synthesis of highly enantiomerically enriched isioindolines by organocatalytic formal double arylation of azomethines.

Finally, it can be cited two more reports of enantioselective synthesis of isoindolines employing organometallic catalysts. One consists on a diastereo- and enantioselective catalytic domino Michael addition/Mannich reaction of organozinc reagents and acyclic conjugated ketones in the presence of imines, to access to chiral isoindolinones with multiple stereocenters, among other β-

[138] Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275-1277.

aminocarbonyl derivatives (Scheme 1.31.a).[139] And the last example to date of an asymmetric catalysis, reports an enantioselective intramolecular propargylic amination using chiral copper-pybox complexes as catalysts to give enantioenriched 1-ethynyl-isoindolines (Scheme 1.31.b).[140]

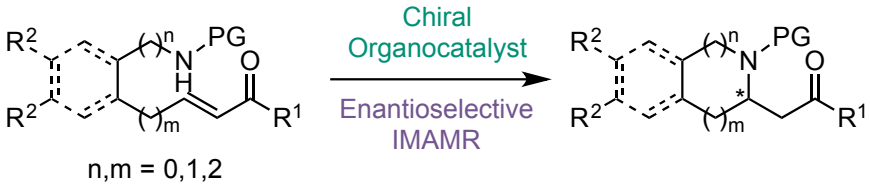


Scheme 1.31. Organometallic approaches to enantioenriched isoindolines.

[139] Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 2728–2731.
[140] Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2014**, *50*, 7874-7877.

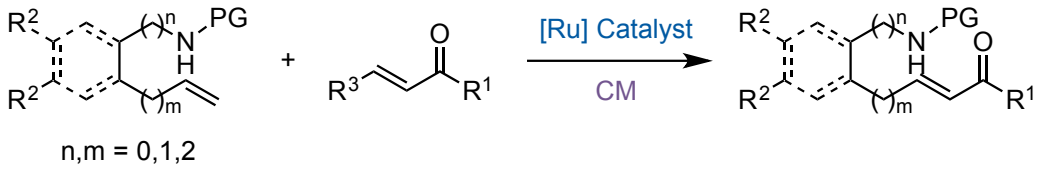
1.2. Objectives

Given the importance of the *aza*-Michael reaction for the creation of C-N bonds and because of scarcity of related published literature regarding its enantioselective and intramolecular version, the present research work intends to develop a general methodology to perform an asymmetric intramolecular *aza*-Michael reaction (IMAMR) employing α,β-unsaturated ketones as Michael acceptors and carbamates as nucleophiles (Scheme 1.32) and by means of an organocatalyst. Thus, this is aimed at synthesizing a small library of diverse enantiomerically enriched cyclic β-amino carbonylic compounds. Depending on the chain length of the acyclic or benzofused precursors and on the position of the nitrogen atom in them, there will be obtained pyrrolidine-, piperidine-, indoline-, isoindoline-, tetrahydroquinoline- or tetrahydroisoquinoline derivatives.



Scheme 1.32. General objectives of the present chapter.

First, it needs to be synthesized the specific starting materials where the IMAMR will be evaluated. To this end, a cross-metathesis reaction (CM) will be implemented between vinyl ketones and assorted olefins carriers of protected amines (Scheme 1.33). These amines will be in turn prepared starting from distinct acyclic and aromatic compounds commercially available and following some procedures described in the literature.



Scheme 1.33. Synthesis of the starting materials through a CM.

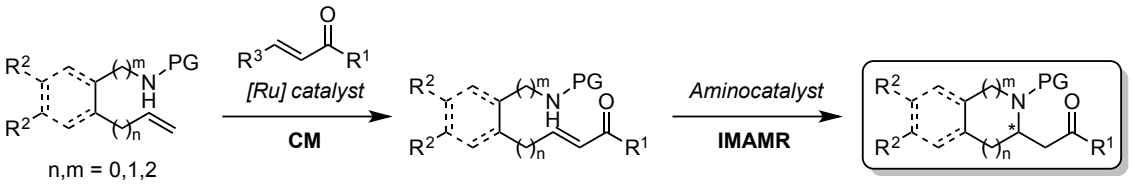
Once achieved the desired enones, there will be studied the conditions for the IMAMR throughout the application of various chiral aminocatalysts,

nitrogen protecting groups, solvents, temperatures, etc. with the purpose of optimising a setting to accomplish both a good stereocontrol of the process and a good yield. It thereupon was examined the scope of the reaction with the goal of generalizing the method for the enantioselective synthesis of nitrogenated heterocycles indicated above.

1.3. Results and Discussion

Considering the objectives set out and the previously introduced topics of aminocatalysis and the *aza*-Michael reaction, in this section there will be described the more relevant results achieved during the study of the asymmetric intramolecular *aza*-Michael reaction (IMAMR) involving α,β-unsaturated ketones and carbamates.

The synthetic strategy adopted for the preparation of this final products consists on a two-step sequence cross-metathesis (CM) between protected unsaturated amines and vinyl ketones by means of a ruthenium catalyst, followed by an IMAMR of the nitrogen nucleophile to the previously generated conjugated ketone (Scheme 1.34).



Scheme 1.34. General synthetic strategy for the study of the asymmetric IMAMR with α,β-unsaturated ketones as Michael acceptors.

1.3.1. PREPARATION OF THE STARTING MATERIALS

The acyclic and aromatic protected amines carrying a terminal olefin used as substrates for the cross-metathesis (Figure 1.2) are not commercially available. Therefore, they have to be synthesized in the laboratory as it is described below.

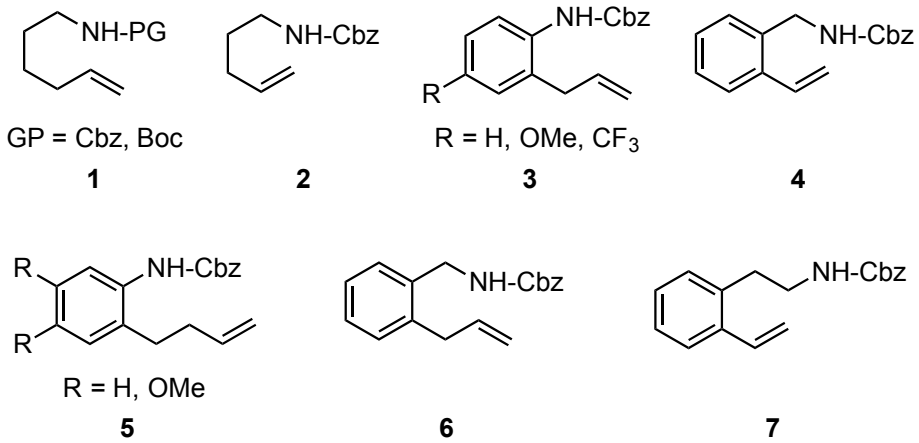
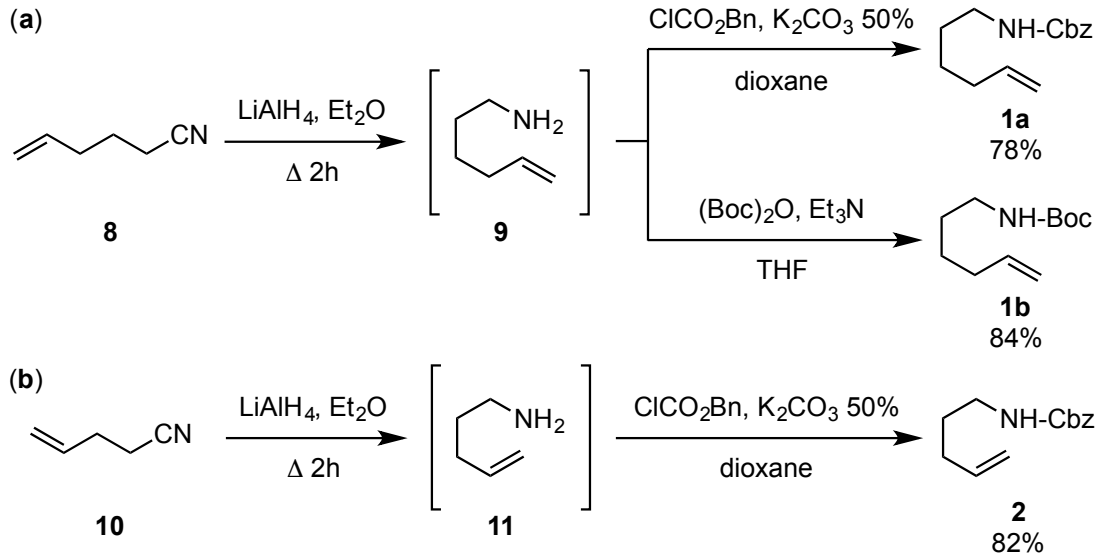


Figure 1.2. Starting protected amines bearing a remote terminal olefin.

1.3.1.1. Synthesis of the N-protected amino-olefins 1 and 2

Synthesis of protected amines **1** was assembled from commercially available 5-hexenenitrile **8**, which was reduced to the corresponding volatile amine with lithium aluminium hydride. The title amine was protected *in situ* without further purification either as bencyloxycarbonyl amine (*N*-Cbz) **1a** or as *tert*-butyloxycarbonyl amine (*N*-Boc) **1b** (Scheme 1.35.a). Likewise, the amino-olefin **2** was prepared starting from 4-pentenitrile **10** and following an analogous synthetic sequence (Scheme 1.35.b).[141]



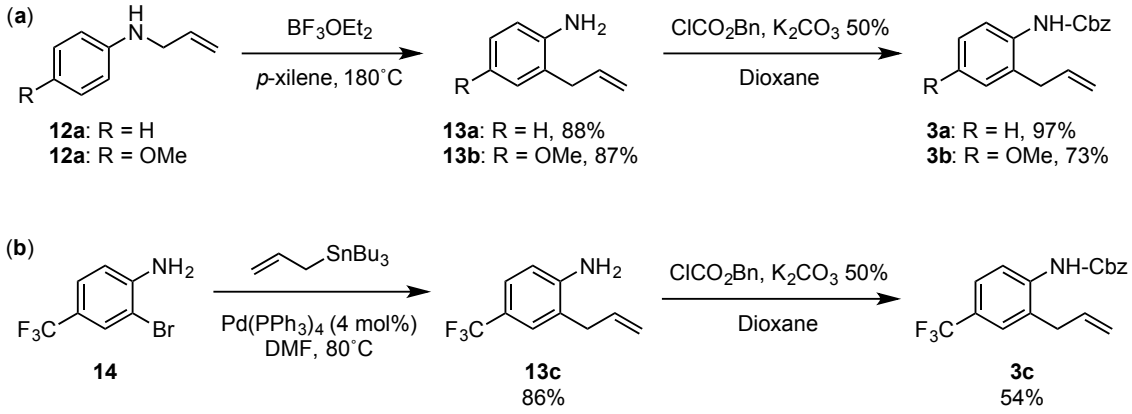
Scheme 1.35. Synthesis of the protected amino-olefins **8** and **9**.

1.3.1.2. Synthesis of the N-Cbz protected o-allyl anilines 3

o-Allyl anilines **3a-c** were prepared following two different pathways depending on the commercial availability of the starting materials. On one hand, *N*-allyl aniline **12a** and *p*-methoxy-*N*-allyl aniline **12b** were subjected to an *aza*-Claisen rearrangement and the corresponding free amines **13a** and **13b** were protected with benzyl chloroformate to obtain the *N*-Cbz protected *o*-allyanilines **3a** and **3b** (Scheme 1.36.a).[142] On the other hand, the synthesis of the trifluoromethylated compound **3c** started from the *o*-bromo-*p*-trifluoromethyl-

[141] a) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc*. **2007**, *129*, 6700- 6701. b) Chandler, B. D.; Roland, J. T.; Li, Y.; Sorensen, *E. J. Org. Lett*. **2010**, *12*, 2746-2749.
[142] Organ, M. G.; Xu, J., N'Zemba, B. M. *Tetrahedron Lett*. **2002**, *43*, 8177-8180.

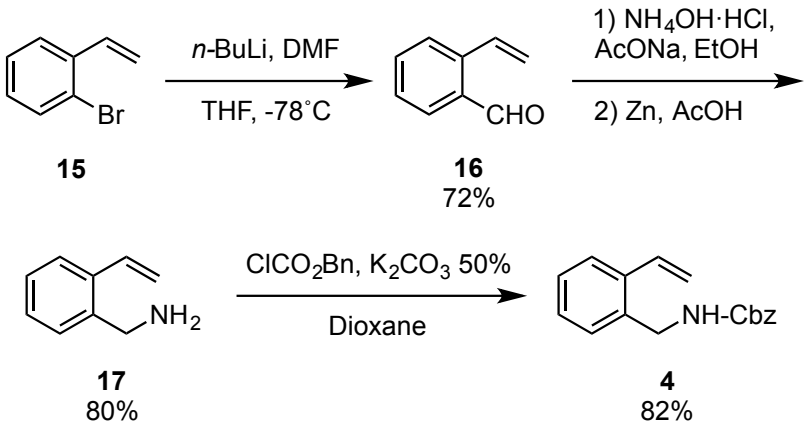
aniline **14** with an initial a Stille cross-coupling followed by the protection with Cbz-chloride of the free aniline **13c** (Scheme 1.36.b).[143]



Scheme 1.36. Synthesis of *o*-allyanilines 3.

1.3.1.3. Synthesis of the N-Cbz protected o-vinyl benzyl amine 4

In order to prepare compound **4** there was developed a four-step synthesis starting from the commercially available *o*-bromostyrene **15** (Scheme 1.37). First of all, it was carried out on the aromatic ring a formylation reaction, through a bromine-lithium exchange employing *n*-BuLi, to obtain the *o*-vinylbenzaldehyde **16**.[144] Consecutively, the aldehyde was condensed with hydroxyl amine in the presence of sodium acetate to form the intermediate oxime, which was reduced, with zinc in acetic acid, to obtain the primary *o*-vinylbenzyl amine **17**.[145] Finally, it was protected with benzyl chloroformate to achieve the desired product.

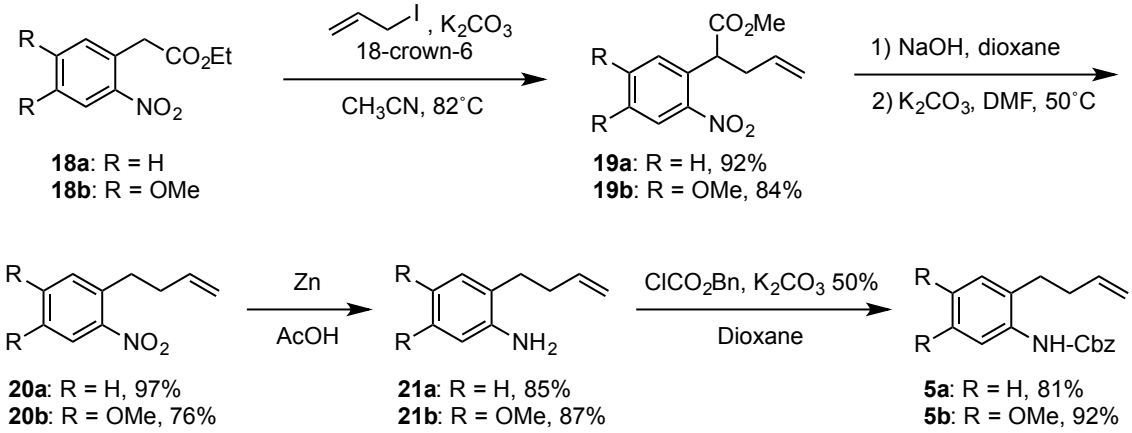


Scheme 1.37. Synthesis of *o*-vinyl benzyl amine **4**.

[143] Hoyt, S. B.; London, C.; Park, M. *Tetrahedron Lett.* **2009**, *50*, 1911-1913.
[144] Dieltiens, N.; Stevens, C. V. *Synlett* **2006**, *17*, 2771-2776.
[145] Bennasar, M.-L.; Roca, T.; Monerris, M.; Garcia-Diaz, D. *J. Org. Chem*. **2006**, *71*, 7028-7034.

1.3.1.4. Synthesis of the N-Cbz protected o-homoallyl anilines 5

Protected amines **5** were elaborated through an initial allylation of the benzylic carbon [146] of the commercial starting materials **18** to form the *o*-nitrophehyl methylacetate **19a** and the 4,5-dimethoxy analogue **19b**. [147] Subsequent ester hydrolysis and decarboxylation in basic media afforded intermediates **20**;[141b, 148] and finally the reduction of the nitro group to the corresponding free amines **21** and their protection with Cbz-chloride rendered final products **5** (Scheme 1.38).



18a: R = H
18b: R = OMe

19a: R = H, 92%
19b: R = OMe, 84%

20a: R = H, 97%
20b: R = OMe, 76%

21a: R = H, 85%
21b: R = OMe, 87%

5a: R = H, 81%
5b: R = OMe, 92%

Scheme 1.38. Preparation of *o*-homoallyl anilines **5**.

1.3.1.5. Synthesis of the N-Cbz protected o-allyl benzyl amine 6

For the preparation of starting protected amine **6** it was taken the commercially available *o*-bromobenzyl bromide **22** to perform a copper-mediated cross-coupling with vinyl magnesium bromide to obtain compound **23** bearing a vinyl group at the benzylic position.[149] Then, it was formylated with magnesium and DMF to give the corresponding aldehyde **24**. Afterwards it was undertaken a reductive amination followed by a reduction of the oxime with zinc to form the primary amine **25**, that was subsequently Cbz-protected (Scheme 1.39).

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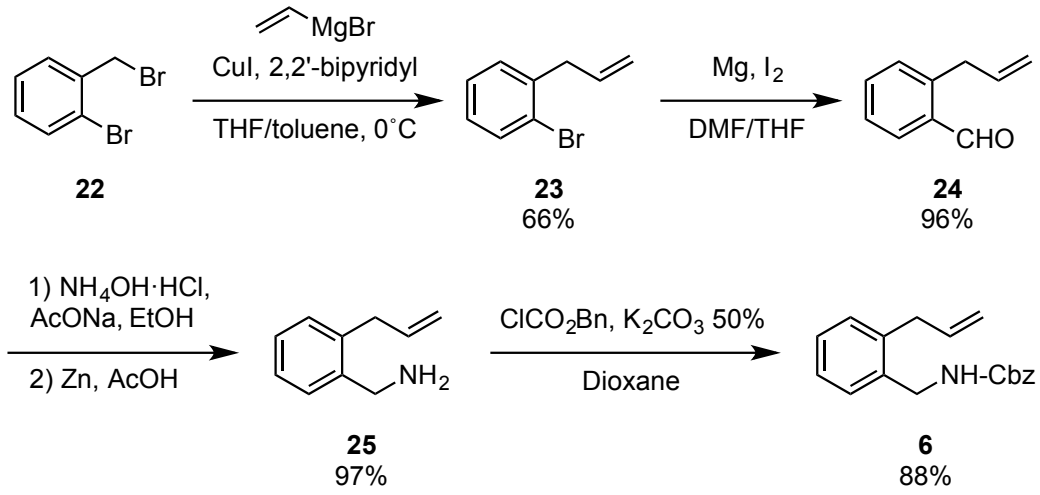
[146] Makosza, M.; Tyrala, A. *Synth. Commun.* **1986**, *16*, 419-423.

[147] The corresponding acid was esterificated by means of EtOH/Dowex. a) Furniss, B. S.; Hannaford, A. J; Smith, P. W. G.; Tatchell, A. R. *Vogel´s Textbook of Practical Organic Chemistry*, 5th ed.; Longman: New York, **1989**: p 701. b) Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem*. **2000**, *65*, 2847-2850.

[141b] Chandler, B. D.; Roland, J. T.; Li, Y.; Sorensen, *Eur. J. Org. Lett*. **2010**, *12*, 2746-2749.

[148] Bull, D. J.; Fray, M. J.; Mackenny, M. C.; Malloy, K. A. *Synlett* **1996**, 647-648.

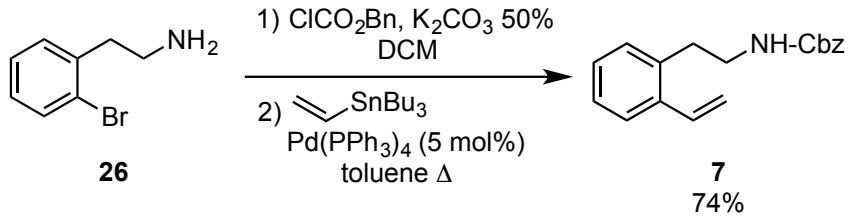
[149] Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin. Trans. 1* **1989**, 979-984.



Scheme 1.39. Elaboration of the *o*-allyl benzyl amine **6**.

1.3.1.6. Synthesis of the N-Cbz protected o-vinyl phenethyl amine 7

The synthesis of the protected amine **7** was a simple two-step sequence, consisting first of all on the protection of the amine and then the introduction of the vinyl group through a Stille cross-coupling (Scheme 1.40).



Scheme 1.40. Synthesis of *o*-vinyl phenethyl amine **7**.

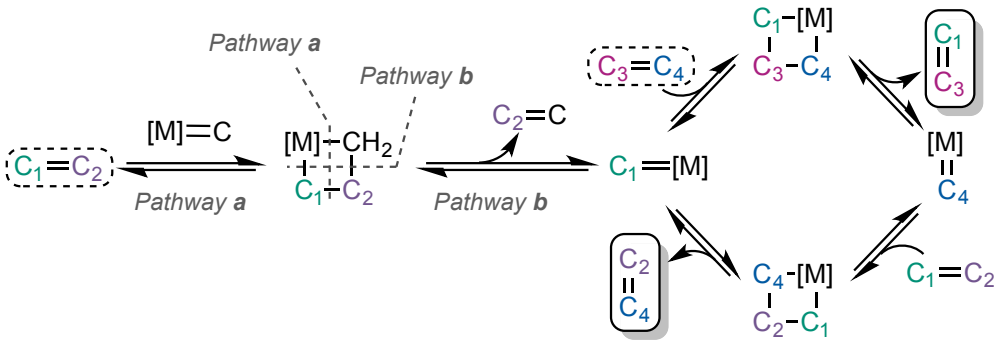
1.3.2. CROSS-METATHESIS REACTION

Once prepared the olefin-carbamates **1-7** exposed above, they were subjected to a cross-metathesis reaction with various vinyl ketones with the aim of obtaining the corresponding α,β-unsaturated substrates for the subsequent IMAMR (Scheme 1.34). But before detailing the results obtained for these procedures, there will be introduced some relevant concepts about this cross-metathesis transformation.

The ***olefin metathesis*** consists on a redistribution of double bonds between two alkenes through their cleavage and formation of new ones by means of a metallic carbene catalyst (Scheme 1.41).[150] In the last decades, due

[150] a) J. L. Hérisson, Y. Chauvin, *Makromol. Chem.* **1970**, 141, 161–176. b) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. English* **1997**, *36*, 2036–2056.

to the great development on the design of new catalysts able to combine a high catalytic activity together with a good tolerance to diverse functional groups, this procedure has become one of the most efficient methodologies to create new carbon-carbon double bonds.[151]



Scheme 1.41. Mechanism of olefin metathesiss according to the Chauvin model.

Some examples of alkene and alkyne metathesis reactions are: cross-, ring-closing-, enyne-, alkyne- and ring-closing-alkyne-metathesis or ring-opening-, acyclic-diene and alkyne metathesis polymerizations. Simplified schemes of the three more classical ones are depicted in Figure 1.3. Among them, the cross-metathesis (CM) is the one that will be developed further below. As shown in Scheme 1.35 and Figure 1.3, with an appropriate catalyst, C_1=C_2 and C_3=C_4 can be transposed into C_1=C_3 and C_2=C_4. It is perhaps difficult to see, at first glance, why one set of olefins would be favoured; this is a key issue, as all olefin metathesis reactions are in principle reversible. The possibility that products might be re-converted to the starting materials dictates that chemists must design reactions that avoid back-tracking.[152] To the progress in the use of this methodology have contributed on the one hand the new developments in more active catalysts, and on the other hand a better understanding of the structural characteristics of the olefins to avoid the homodimers formation.[153]

[151] Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH Verlag: Weinheim, **2003**, Vols. 1-3.

[152] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[153] a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751-1753. b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784. c) Choi, T. L.; Lee, C. W.; Chatterjee, A.K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417-10418. d) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277-1279. e) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939-1942.

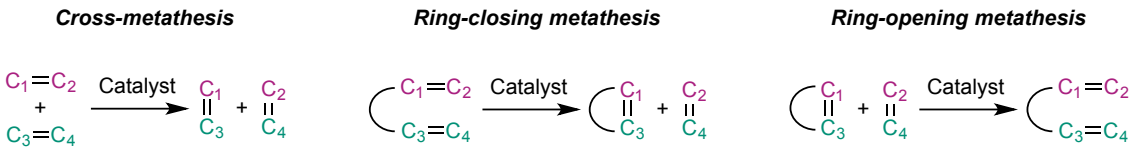


Figure 1.3. Different types of olefin metathesis.

Regarding the advances in the development of new homogeneous catalysts, it could be highlighted the ruthenium carbenes, mainly designed by Grubbs and co-workers. And amongst them, the first widely employed ruthenium catalyst was the *Grubbs first-generation* (**G-I**) complex[154] (Figure 1.4.a). Later, the arrival of the so-called "second-generation" catalysts clearly contributed to a greater growth of the cross-metathesis as an efficient synthetic methodology. These 2nd-generation catalysts are structurally distinguished for the presence of a *N*-heterocyclic carbene ligand, and there can be highlighted the *Grubbs second-generation* (**G-II**) catalyst[155] (Figure 1.4.b) and the more recent one *Hoveyda-Grubbs second-generation* (**HG-II**) catalyst[156] (Figure 1.4.c).

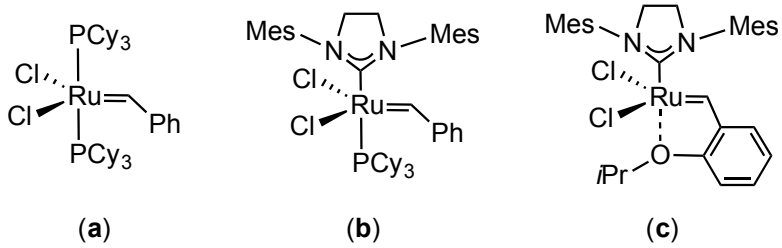


Figure 1.4. Ruthenium carbene catalysts.

In particular, for the CM reactions performed in the present thesis, it is specially suitable the HG-II catalyst since, besides being the most stable and functional-group tolerant, it works much better with electron deficient olefins.[157] Taking this into account, the synthesis of the starting materials **27** and **28** was performed by reaction of protected amines **1** and **2** with conjugated ketones

[154] a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975. b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039-2041. c) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.

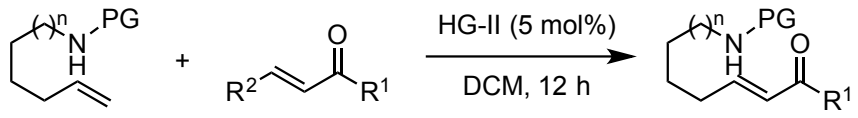
[155] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

[156] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

[157] a) Randa, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430-432. b) Hoveyda, A. H.; Gillingham, D. G.; van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Garrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8-23. c) Carreras, J.; Avenoza, A.; Busto, J. H.; Peregrina, J. M. *Org. Lett.* **2007**, *9*, 1235-1238.

34a-d in the presence of HG-II. After 12 hours at room temperature there were obtained the corresponding α,β-unsaturated ketones **27-28** with good yields (Table 1.1).

Table 1.1. Synthesis of the acyclic α,β-unsaturated substrates **27** and **28**.



1, **2** **34** **27**, **28**

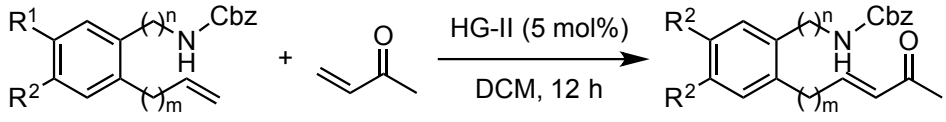
Entry	*n*	*R¹*	*R²*	*PG*	*Product*	*Yield (%)*[a]
1	1	Me	H	Cbz	**27a**	90
2	1	Me	H	Boc	**27b**	95
3	1	Pr	H	Cbz	**27c**	94
4	1	Pent	H	Cbz	**27d**	88
5	1	Ph	Me	Cbz	**27e**	71
6	0	Me	H	Cbz	**28**	76

[a] Isolated yields after flash chromatography purification.

The preparation of the aliphatic products **27a-d** proceeded with good yields (Table 1.1, entries 1-4). However, aromatic ketone **27a** was obtained in lower yield (Table 1.1, entries 5). This is probably due to the presence in the starting ketone **34** of a methyl group in the β position, since metathesis reactions are in general very sensitive to steric hindrance, which also explains the presence of some *Z*-isomer.[152] Alternatively, compound **28** (Table 1.1, entry 6) was also achieved in a lower yield due to the partial *in situ* cyclisation of **28** to the corresponding 5-membered ring (10% yield, easily separable).

Those conditions were further extended to benzofused derivatives. Substrates **3-7** underwent CM with conjugated ketone **34a** efficiently, rendering compounds **29-33** in good yields. Obtained results are depicted in Table 1.2

Table 1.2. Synthesis of the aromatic α,β-unsaturated substrates **29-33**.



3-7 **34** **29-33**

[152] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Entry	*m*	*n*	R^1	R^2	*Product*	*Yield (%)*[a]
1	1	0	H	H	**29a**	91
2	1	0	H	MeO	**29b**	79
3	1	0	H	CF_3	**29c**	69
4	0	1	H	H	**30**	92
5	2	0	H	H	**31a**	89
6	2	0	MeO	MeO	**31b**	83
7	1	1	H	H	**32**	83
8	0	2	H	H	**33**	77

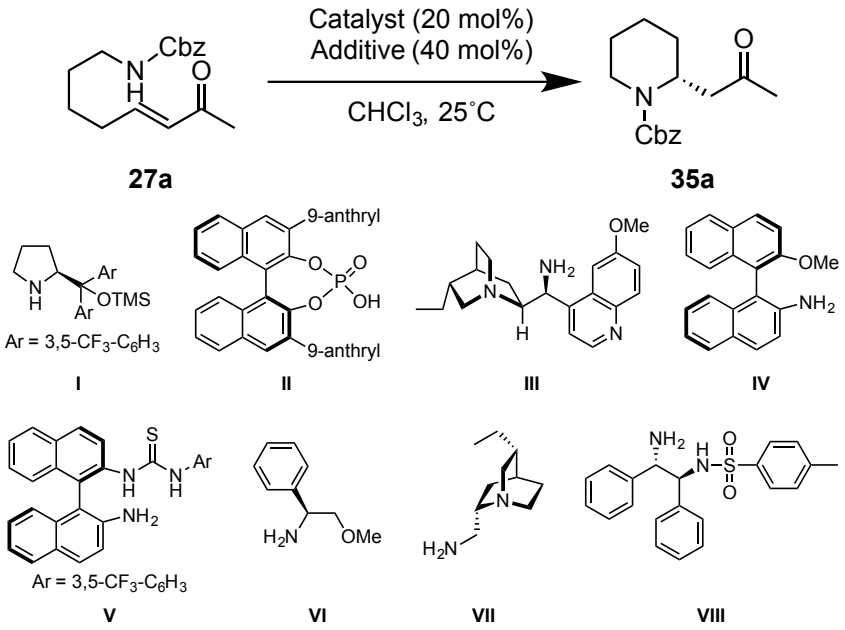
[a] Isolated yields after flash chromatography purification.

1.3.3. OPTIMISATION OF THE INTRAMOLECULAR *AZA*-MICHAEL REACTION CONDITIONS

With starting α,β-unsaturated ketones **27-33** in hand, next step of our study was directed to the optimisation of the reaction conditions to perform the IMAMR. To this end, several organocatalysts, solvents, temperatures and additives were evaluated in order to find the best combination of yield and enantioselectivity.

Initial attempts were performed with a battery of eight different organocatalysts, either commercially available or previously prepared in the laboratory. The conjugate addition of the acyclic Cbz-protected amine **27a** was used as a model reaction. The obtained results in the preparation of the corresponding piperidine **35a** are detailed in Table 1.3.

Table 1.3. Results for the organocatalyst analysis in the IMAMR with enone **27a**.



Entry	*Catalyst*	*Additive*	*Time (h)*	*Yield (%)*[a]	*ee (%)*[b]
1	**I**	$PhCO_2H$	96	-	-
2	**II**	-	20	92	20
3	**III**	TFA	15	88	91
4	**IV**	TFA	20	81	8
5	**V**	TFA	20	65	13
6	**VI**	TFA	20	84	14
7	**VI**	N-Cbz-LP[c]	96	73	22
8	**VII**	TFA	20	84	40
9	**VII**	N-Cbz-LP[c]	20	73	51
10	**VIII**	TFA	72	62	13

[a] Isolated yields after flash chromatography purification.
[b] Determined by chiral stationary phase HPLC.
[c] *N*-bencyloxycarbonyl-L-phenylalanine.

Initially, it was checked the catalytic activity of the diaryl prolinol derivative **I**, which had given rise to excellent results in analogous reactions with α,β-unsaturated aldehydes. However, as it was expected, it was unreactive due to the steric hindrance between the ketone and the secondary amine, which avoids the formation of the intermediate iminium ion (Table 1.3, entry 1) (Figure 0.3).

[114] Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2010**, *49*, 8666–8669.

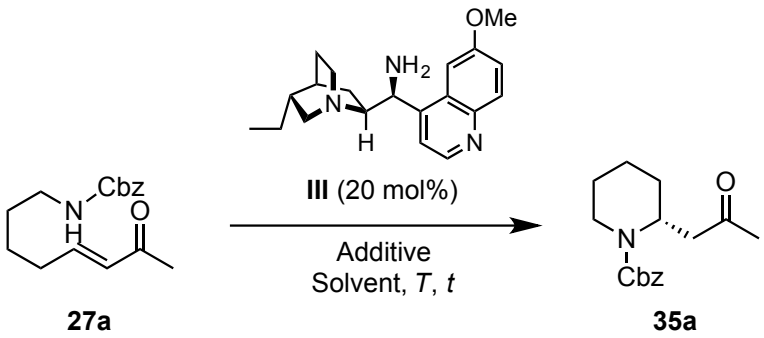
Since the only previous example of an IMAMR involving conjugated ketones was achieved employing a chiral phosphoric acid as catalyst,[114] next attempt of our study was performed with organocatalyst **II** (Table 1.3, entry 2). Nevertheless, despite it seems to be a good activator for the cyclisation, the enantioselectivity was poor.

Hereafter, all the efforts were centred on the use of primary amines as catalysts, since presumably, they will be able to form an iminium intermediate to activate the Michael acceptor and to induce an enantioselective addition. Then, there was carried out the IMAMR in substrate **27a** in the presence of an aminocatalyst derived from hydroquinine, concretely the 9-amino-9-deoxi-*epi*-hydroquinidine **III** (Table 1.3, entry 3), and trifluoroacetic acid (TFA) as the additive. The reaction was completed with high enantioselectivity (91% *ee*) and good yield (88%) after 15 hours at room temperature.

The rest of the primary amine-derived chiral organocatalysts, with different structural characteristics, in combination with acidic additives did not provide the desired product with good enantioselectivities although they occurred with reasonable yields. Thus, binaphthyl derived amines **IV** and **V** (Table 1.3, entries 4-5) produced piperidine **1a** with 8 and 13% *ee*, respectively. The 14% of *ee* achieved with the phenyl glycinol derivative **VI** (Table 1.3, entry 6) was slightly improved (until a 22% *ee*) by changing the TFA as additive for the chiral amino acid *N*-bencyloxycarbonyl-L-phenylalanine (N-Cbz-LP) (Table 1.3, entry 7). The same effect was observed with the quinuclidine derivative **VII**, despite the higher enantioselectivity reached was only 51% (Table 1.3, entries 8-9). Chiral sulfonamide **VII** provided also a less efficient result (Table 1.3, entry 10).

Therefore, it seems clear that the cinchone-alkaloid derived primary amine **III** is the ideal organocatalyst to perform the desired transformation. The next step was to optimise the rest of the reaction conditions, i. e. additive, solvent, temperature and time. Using the same model reaction, the obtained results are depicted below (Table 1.4).

Table 1.4. Optimisation of the IMAMR of **26a** with the OC **III**.



27a **35a**

Entry	*Additive (mol%)*	*Solvent*	*T (ºC)*	*t (h)*	*Yield (%)*[a]	*ee (%)*[b]
1	TFA (40)	$CHCl_3$	25	15	88	91
2	TFA (20)	$CHCl_3$	25	15	91	95
3	TFA (10)	$CHCl_3$	25	15	48	91
4	-	$CHCl_3$	25	96	-	-
5	TFA (20)	$CHCl_3$	10	24	80	97
6	TFA (20)	$CHCl_3$	4	24	71	95
7	TFA (20)	$CHCl_3$	-10	24	60	75
8	TFA (20)	THF	25	15	78	97
9	TFA (20)	Et_2O	25	8	72	97
10	TFA (20)	DCM	25	15	88	93
11	TFA (20)	Toluene	25	15	91	84
12	TFA (20)	*i*PrOH	25	24	90	47
13	NLFA (20)	$CHCl_3$	25	72	48	87
14	CSA (20)	$CHCl_3$	25	24	60	69
15	BTFMBA (20)	$CHCl_3$	25	48	85	85
16	*p*NBA (20)	$CHCl_3$	25	15	76	80
17	DNBSA (20)	$CHCl_3$	25	72	64	52
18	PFPA (20)	$CHCl_3$	25	15	93	96
19	TFA (20)	$CHCl_3$	80[c]	0.5	91	90
20	TFA (20)	$CHCl_3$	60[c]	1	93	95
21	PFPA (20)	$CHCl_3$	60[c]	1	94	95
22	TFA (20)	THF	60[c]	1	60	90

[a] Isolated yields after flash chromatography purification.
[b] Determined by chiral stationary phase HPLC.
[c] Microwave irradiation.

First of all, the optimal loading of the additive was examined with TFA. We realized that the best results were obtained with a 1:1 ratio catalyst/ additive (Table 1.4, entry 2), instead of the originally expected 1:2 ratio (Table 1.4, entry 1) or the lately checked 2:1 ratio by using just a 10 mol% of TFA (Table 1.3, entry 3). Moreover, it was confirmed the need of the acidic additive; when the reaction was performed in the absence of it no reaction was observed after 4 days (Table 1.3, entry 4).

Secondly, it was tested the temperature at which the best combination of yield and enantioselectivity was obtained. When diminishing the temperature to 4ºC and 10ºC (Table 1.3, entries 5-6) the *ee* increased slightly but in clear detriment of the yield. When the temperature was settled at -10ºC, both the yield and the enantioselectivity decreased (Table 1.3, entry 7).

Concerning the solvent, there were checked some non-polar (toluene, Et_2O), aprotic polar (DCM, THF) and protic polar (*i*PrOH) solvents. It was observed that there was an excellent asymmetric induction when employing THF, Et_2O or DCM (Table 1.3, entries 8-10) as solvents, whereas the use of toluene or *i*PrOH led to a significant drop of the *ee* values (Table 1.3, entries 11-12). Anyway, the achieved yields were lower than the ones reached with chloroform as solvent (Table 1.3, entry 2).

Regarding the additive, once determined the loading needed, a screening of various acids was performed in order to improve the results by finding a better interaction with the catalyst. Initially, two different chiral acids, the amino acid *N*-benzyloxycarbonyl-L-phenylalanine (*N*-Cbz-LP) and the (+)-10-camphorsulfonic acid (CSA) were tested (Table 1.3, entries 13-14), but both proved to act as a mismatch pairs with the catalyst by lowering both yield and enantiomeric excess. On the other hand, substituted benzoic acids such as the 3,5-bis(trifluoromethyl)benzoic acid (BTFMBA) or the *p*-nitrobenzoic acid (*p*-NBA) (Table 1.3, entries 15-16) gave reasonable yields and enantioselectivities but still worse than those obtained with TFA. Finally, 52% *ee* was obtained with 2,4-dinitrobenzenesulfonic acid (DNBSA) and 96% *ee* and 93% yield with pentafluoropropionic acid (PFPA) (Table 1.3, entries 17-18).

The last part of our study was directed to determine the influence of microwave (MW) irradiation in the process. It has been demonstrated its ability

to activate several asymmetric organocatalytic reactions in order to shorten reaction time and catalyst loading.[160] In our case it was observed that the MW irradiation had a positive effect in the reaction time, maintaining comparable results of yield and enantioselectivity. Thus, when the IMAMR was performed at 80ºC, it was obtained a 90% *ee* and a 91% yield in just 30 minutes (Table 1.3, entry 19). By lowering the temperature to 60ºC during 1 hour the enantiomeric excess rose to 95%, using either TFA or PFPA as additive (Table 1.3, entry 20-21). However, when using THF as solvent worse results were achieved than those obtained with the same solvent at room temperature (Table 1.3, entry 22 *vs.* 8).

Therefore, piperidine **35a** was obtained with 93% yield and a 96% enantiomeric excess with the optimised conditions, that is, when performing the IMAMR at 25ºC, during 15 hours and employing $CHCl_3$ as solvent, the hydroquinidine derivative **III** as catalyst and PFPA as additive, the two latter ones with a 20 mol% loading (Table 1.4, entry 18). There were also optimised the conditions to carry out the transformation under MW irradiation, at 60ºC and during 1 hour, maintaining the other reaction conditions in the same way than at room temperature, thereby obtaining piperidine **35a** with 94% yield and 95% *ee* (Table 1.4, entry 21).

1.3.4. ENANTIOSELECTIVE SYNTHESIS OF MONOCYCLIC *N*-HETEROCYCLES: PIPERIDINES *35* AND PYRROLIDINE *36*

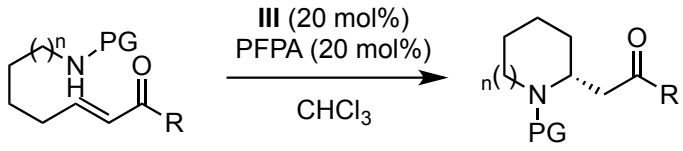
Once determined the optimum reaction conditions to perform the IMAMR, they were extended to the rest of starting materials **27-28**. The obtained results are summarized in Table 1.5. The type of carbamate did not affect significantly the process and both *N*-Cbz-piperidine **35a** and *N*-Boc-piperidine **35b** were obtained with excellent yields and enantioselectivities (Table 1.5, entries 1, 2).

[160] a) de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178. b) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417–1424. c) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629–639. d) Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517–2519. e) Procopio, A.; De Nino, A.; Nardi, M.; Oliverio, M.; Paonessa, R.; Pasceri, R. *Synlett* **2010**, 1849–1853. f) Enders, D.; Krüll, R.; Bettray, W. *Synthesis* **2010**, 567–572. g) Massolo, E.; Benaglia, M.; Parravicini, D.; Brenna, D.; Annunziata, R. *Tetrahedron Lett.* **2014**, *55*, 6639–6642.

Likewise, the IMAMR was highly efficient for the preparation of the propyl- and pentyl-substituted piperidines **35c** and **35d** with yields over 90% and the enantiomeric excesses up to 98% (Table 1.5, entries 3, 4). Nevertheless, for the transformation with the aromatic ketone **27e** it was needed a higher reaction time (240 hours) and the corresponding piperidine **35e** was obtained in excellent *ee* but just with a moderate yield (Table 1.5, entry 5). On the other hand, the synthesis of pyrrolidine **36** proceeded with slightly lower yield and enantioselectivity, 80% and 82% respectively (Table 1.5, entry 6).

Finally, when the same piperidines **35b-e** (Table 1.5, entries 7-10) and pyrrolidine **36** (Table 1.5, entry 11) were prepared under the MW irradiation-optimised conditions, there were obtained with comparable results of both yield and enantiomeric excess to those achieved at room temperature.

Table 1.5. Extension of the scope of the IMAMR for the enantioselective synthesis of piperidines **35** and pyrrolidine **36**, both at room temperature and under MW irradiation.

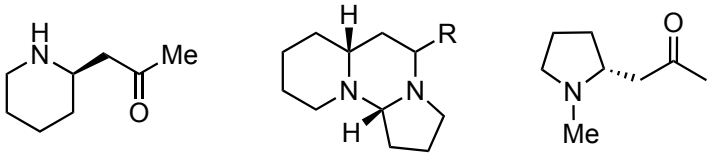


27, **28** **35, 36**

Entry	*n*	*SM*	*PG*	*R*	*T (ºC)*	*t (h)*	*Prod.*	*Yield (%)*[a]	*ee (%)*[b]
1	1	**27a**	Cbz	Me	25	15	**35a**	93	96
2	1	**27b**	Boc	Me	25	15	**35b**	92	93
3	1	**27c**	Cbz	Pr	25	15	**35c**	95	98
4	1	**27d**	Cbz	Pent	25	15	**35d**	92	98
5	1	**27e**	Cbz	Ph	25	240	**35e**	58	93
6	0	**28**	Cbz	Me	25	24	**36**	80	82
7	1	**27b**	Boc	Me	60[c]	1	**35b**	97	90
8	1	**27c**	Cbz	Pr	60[c]	1	**35c**	94	96
9	1	**27d**	Cbz	Pent	60[c]	1	**35d**	89	97
10	1	**27e**	Cbz	Ph	60[c]	4	**35e**	75	84
11	0	**28**	Cbz	Me	60[c]	1	**36**	85	79

[a] Isolated yields after flash chromatography purification.
[b] Determined by chiral stationary phase HPLC.
[c] Microwave irradiation.

The absolute configuration of the newly created stereocenter was determined to be *R* by comparing the optical rotation values of compounds **35a-d** and **36** with those published in the literature.[161] Moreover, it is worth mentioning that the synthesis of piperidines **35a** and **35b** constitute a formal synthesis of the alkaloid *pelletierine,*[108,110,162] only remaining the removal of the nitrogen protecting group. Likewise, starting from compounds **35c** and **35d**, there could be easily prepared various members of the *tetraponerine* family.[161e,f;163] Additionally, the reduction of the Cbz group in **2f** would lead to the skeleton of the pyrrolidine alkaloid *hygrine* (Figure 1.5).[164]



Pelletierine *Tetraponerine* *Hygrine*

Figure 1.5. Natural alkaloids possibly derived from the synthesized chiral products.

1.3.5. ENANTIOSELECTIVE SYNTHESIS OF BENZOFUSED *N*-HETEROCYCLES: INDOLINES *37*, ISOINDOLINES *38*, TETRAHYDROQUINOLINES *39* AND TETRAHYDROISOQUINOLINES *40-41*.

The extension of this protocol to the synthesis of several benzofused heterocycles was examined next. The optimal conditions for the IMAMR were applied to conveniently functionalised aniline, benzyl amine and phenethyl amine substrates **3-7** (Figure 1.2) to obtain enantiomerically enriched indolines,

[161] For **1a**: a) Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047–3054. b) See ref. 109: Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. For **1b**: c) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192–10213. d) Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, *75*, 4069–4077. For **1c** and **1d**: e) Macours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415–1428. f) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, J.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670–8673. For **2**: g) Majik, M. S.; Tilve, S. G. *Tetrahedron Lett.* **2010**, *51*, 2900–2902.

[108] Ihara, M.; Takasu, K.; Maiti, S. *Heterocycles* **2003**, *59*, 51-55.

[110] Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872.

[162] a) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158. b) Galinovsky, F.; Bianchetti, G.; Vogl, O. *Monatshefte für Chemie* **1953**, *84*, 1221–1227.

[163] Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591.

[164] Lee, J.-H.; Jeong, B.-S.; Ku, J.-M.; Jew, S.; Park, H. *J. Org. Chem.* **2006**, *71*, 6690–6692.

isoindolines, tetrahydroquinolines, and tetrahydroisoquinolines **37-49** (Table 1.6).

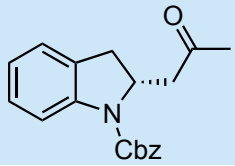
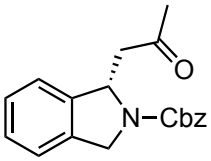
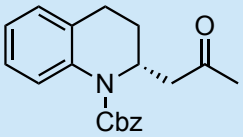
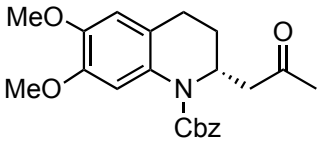
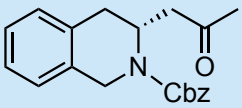
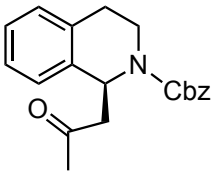
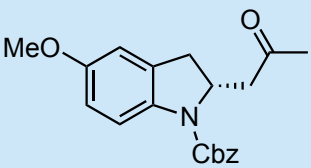
Pyrrolidine benzofused products **37a** and **38** were obtained in excellent yields and *ee* values either at room temperature or under microwave heating at 60ºC (Table 1.6, entries 1, 2). Even better results were achieved in the preparation of the two tetrahydroisoquinolines **40** and **41** (Table 1.6, entries 5, 6). The synthesis of the tetrahydroquinoline derivative **39a** proceeded with lower enantioselectivity, concretely 88% and 86% of *ee* at room temperature and 60ºC, respectively (Table 1.6, entry 3). However, this *ee* value, as well as the yield of the *aza*-Michael product, improved when two methoxy groups were attached to the aromatic ring (Table 1.6, entry 4). This is probably due to the enhanced nitrogen nucleophilicity of the starting material **31b**, making the conjugate addition faster, thus avoiding alternative reaction pathways promoted by protons liberated during the process (Brønsted acid catalysis).

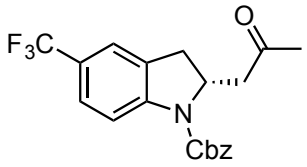
This non-selective process, on account of the released protons, would compete with the iminium activation by the organocatalyst and decrease the enantioselectivity of the overall reaction. This effect was proved by comparing the results achieved in the synthesis of indolines **37b** and **37c**, with an electron-donating (MeO-) and an electron-withdrawing group (F_3C-), respectively. Whereas **37b** was obtained in good yield and enantioselectivity (Table 1.6, entry 7), the *aza*-Michael addition on compound **29c** bearing a trifluoromethyl moiety was less efficient (Table 1.6, entry 8). Both at room temperature and under MW irradiation, these reactions proceeded in lower yield, and significantly diminished *ee*.

It can be seen that due to electronic issues related to the nitrogen nucleophilicity, there are slight differences, especially referring to yields, between aniline-, benzyl amine- and phenethyl amine-substrates. In the cases where it is an aniline-nitrogen, the delocalization of the lonely electron pair decreases its nucleophilicity, making it less accessible for the conjugated addition and, therefore, the obtained results are not so good.

Table 1.6. Extension of the scope of the IMAMR for the enantioselective synthesis of benzofused *N*-heterocycles **37-41**, both at room temperature and under MW irradiation.

29-33 **37-41**

	Product		*Yield (%)[a,c]*	*ee (%)[b,c]*	*Yield (%)[a,d]*	*ee (%)[b,d]*
1		**37a**	90	93	83	91
2		**38**	96	93	91	92
3		**39a**	80	88	93	86
4		**39b**	95	91	92	87
5		**40**	97	97	95	97
6		**41**	94	98	91	96
7		**37b**	85	92	81	90

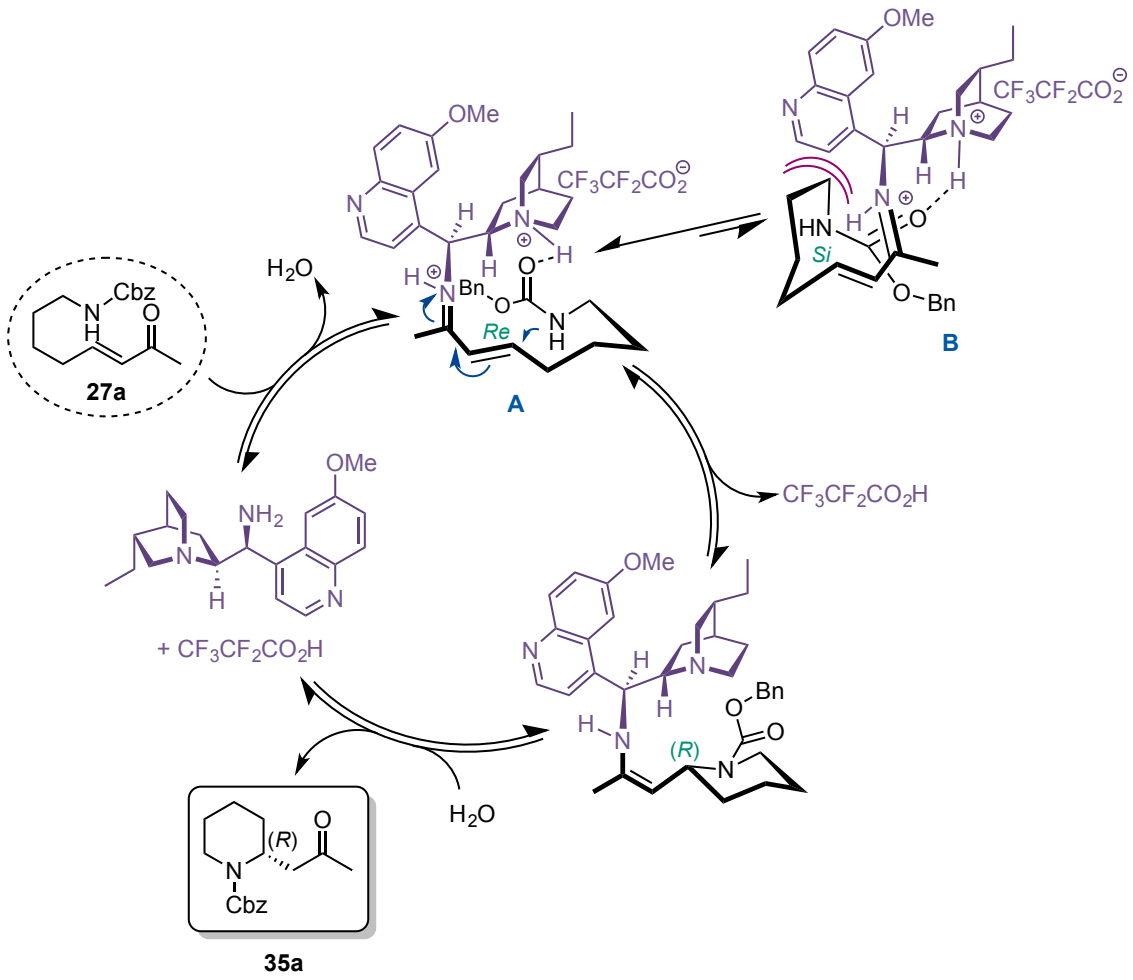
8	 **37c**	71	68	68	63

[a] Isolated yields after flash chromatography purification.
[b] Determined by chiral stationary phase HPLC.
[c] Stirring at 25ºC during 20 hours.
[d] Microwave heating at 60ºC during 1 hour.

1.3.6. MECHANISTIC PROPOSAL FOR THE INTRAMOLECULAR *AZA*-MICHAEL REACTION BETWEEN CARBAMATES AND α,β-UNSATURATED KETONES

The mechanism commonly invoked to rationalize the organocatalytic conjugate additions of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds involves activation of the Michael acceptor by the catalyst through the formation of an iminium ion, thereby facilitating the intramolecular addition of the nucleophile to the β-carbon. It is thus proposed a possible mechanism that accounts for the *R* stereochemical assignment mentioned above.

First, the primary amine catalyst would react with the enone (**27a** in Scheme 1.42) to form an iminium intermediate under the acid conditions. Simultaneously, the quinuclidine nitrogen would be protonated and a hydrogen-bond interaction would be established with the carbamate carbonyl oxygen. In this conformation, the attack of the nitrogen nucleophile would take place onto the *Re* face of the less sterically constrained (*E*)-iminium transition state **A** to furnish the *aza*-Michael product [(*R*)-**35a** in Scheme 1.42] after hydrolysis.

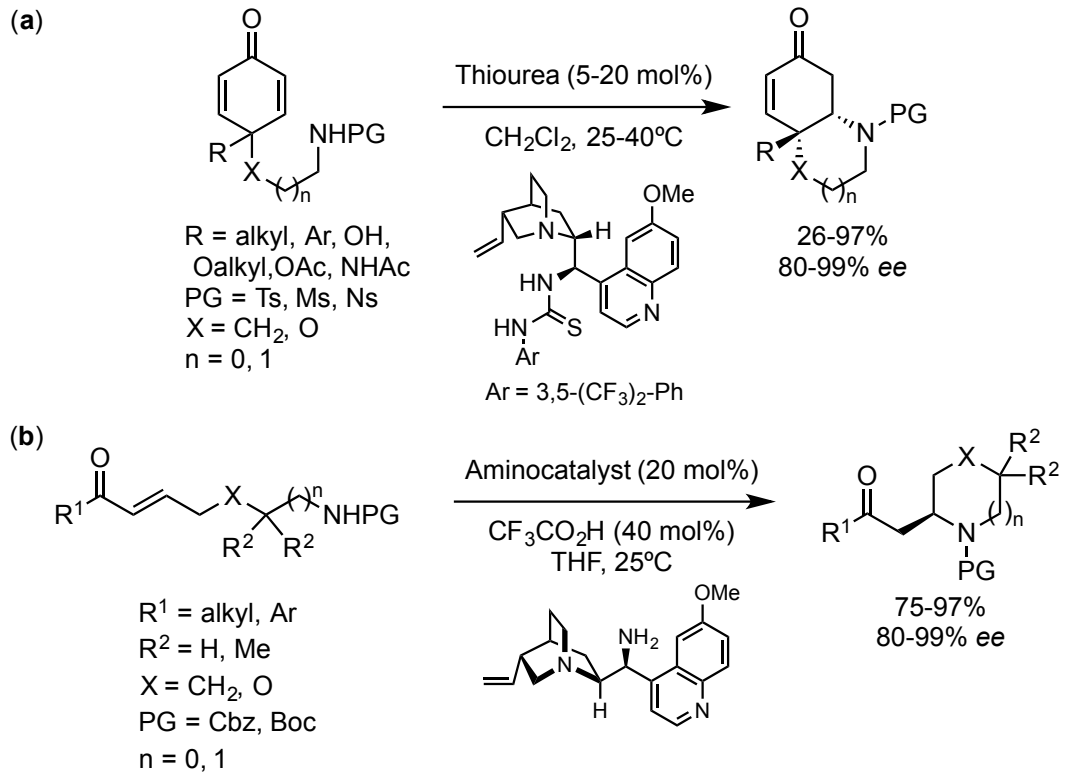


Scheme 1.42. Plausible mechanistic pathway and transition state of the IMAMR.

1.4. Recent contributions to the IMAMR with enones

Together with this study developed in our research group, the same year there appeared two other publications related to the IMAMR with α,β-unsaturated ketones as Michael acceptors. In one case they developed a cinchonine-derived thiourea catalysed desymmetrization of cyclohexandienones, affording a series of highly enantioenriched pyrrolidine and morpholine derivatives in excellent yields (Scheme 1.43.a).[165] In the second case, they obtained 2-substitued six- and five-membered heterocycles enantioselectively, using the catalytic combination of a chiral primary-tertiary diamine and a simple achiral Brønsted acid (Scheme 1.43.b).[166]

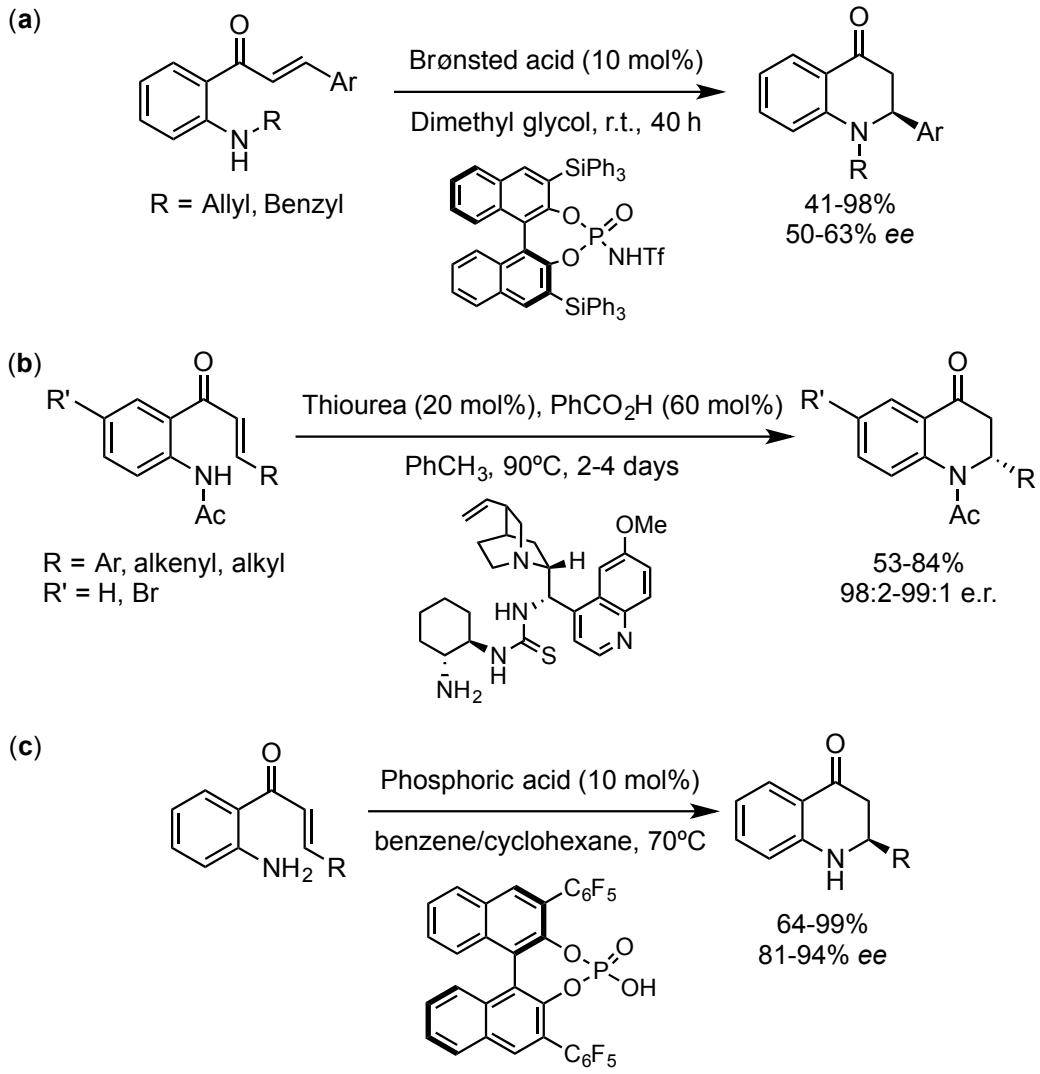
[165] Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519.
[166] Liu, J. D.; Chen, Y. C.; Zhang, G. B.; Li, Z. Q.; Chen, P.; Du, J. Y.; Tu, Y. Q.; Fan, C. A. *Adv. Synth. Catal.* **2011**, *353*, 2721–2730.



Scheme 1.43. IMAMR reported the same year of our publication.

Later, there were published some methodologies to prepare enantioenriched *aza*-flavanones using an organocatalytic 6-*endo aza*-Michael addition catalysed either by a chiral *N*-trifyl binolphosphoramide,[167] a cinchone-derived thiourea[168] or a chiral phosphoric acid.[169] In the first case, starting from *N*-allyl or *N*-benzyl anilines substituted with a chalcone moiety in the *ortho* position, the IMAMR afforded dihydroquinolones in good yields and with moderate enantioselectivies (Scheme 1.44.a). Using the second procedure, there were prepared in good yields and excellent enantioselectivities a variety of 2-aryl-, 2-vinyl and 2-methyl-*aza*-flavanones (Scheme 1.44.b). And in the last example, the desired products were synthesized based on a chiral phosphoric acid catalysed intramolecular *aza*-Michael addition using *N*-unprotected 2-aminophenyl vinyl ketones as substrates in good yields and high enantioselectivities (Scheme 1.44.c).

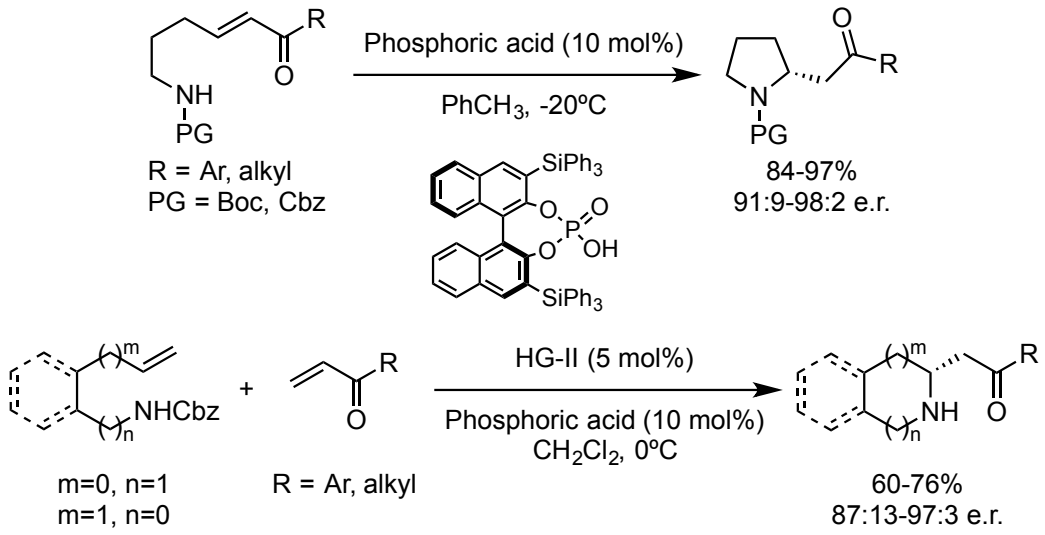
[167] Rueping, M., Moreth, S. A., Bolte, M. Z. Z. *Naturforsch. B* **2012**, 67, 1021-1029.
[168] Cheng, S.; Zhao, L.; Yu, S. *Adv. Synth. Catal.* **2014**, *356*, 982–986.
[169] Saito, K.; Moriya, Y.; Akiyama, T. *Org. Lett.* **2015**, *17*, 3202–3205.



Scheme 1.44. Enantioselective synthesis of *aza*-flavanones.

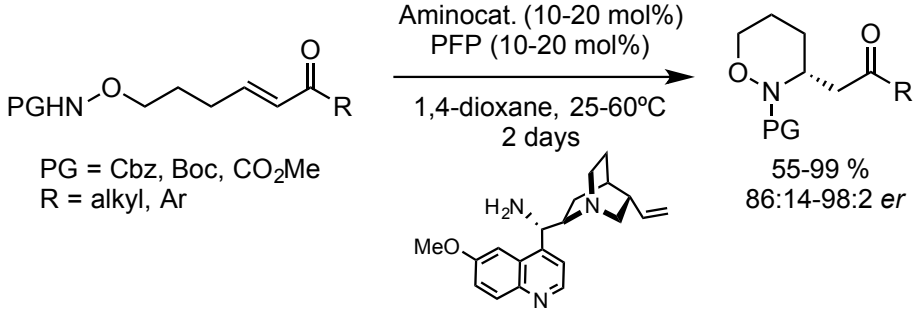
In 2013, Yu *et al* described the preparation of enantioenriched 2-substituted pyrrolidines and benzopyrrolidines, either through an intramolecular *aza*-Michael addition catalysed by a phosphoric acid or *via* domino cross-metathesis/ intramolecular *aza*-Michael reaction promoted by the cooperation of the Hoveyda-Grubbs II catalyst and the same chiral phosphoric acid (Scheme 1.45).[170]

[170] Liu, H.; Zeng, C.; Guo, J.; Zhang, M.; Yu, S. *RSC Adv.* **2013**, *3*, 1666–1668.



Scheme 1.45. Synthesis of enantioenriched 2-subtituted pyrrolidines.

This last example, exposes an enantioselective synthesis of 3-substituted 1,2-oxazines via an organocatalytic intramolecular *aza*-Michael addition.[171] Thus, by means of a quinine-derived primary-tertiary diamine catalyst and pentafluoropropionic acid as co-catalyst, there was performed the 6-*exo-trig* conjugate addition to obtain the corresponding products in high yields and good enantioselectivities (Scheme 1.46).



Scheme 1.46. Organocatalytic synthesis of chiral oxazines through an IMAMR.

[171] Cheng, S.; Yu, S. *Org. Biomol. Chem.* **2014**, *12*, 8607–8610.

1.5. Conclusions

In this research work, a general protocol for a highly enantioselective organocatalytic intramolecular *aza*-Michael reaction has been developed, employing carbamates as nitrogen nucleophiles and α,β-unsaturated ketones as Michael acceptors.[172]

Through this procedure it was possible to obtain a small library of fourteen compounds with excellent yields and enantioselectivities. Concretely, 2-substituted *piperidines* (**35**) and *pyrrolidine* (**36**), and differently substituted *indolines* (**37**), *isoindolines* (**38**), *tetrahydroquinolines* (**39**) and *tetrahydroisoquinolines* (**40** and **41**) have been prepared (Figure 1.6). These nitrogenated heterocycles have a great interest due to their presence in many natural products with biological activity.

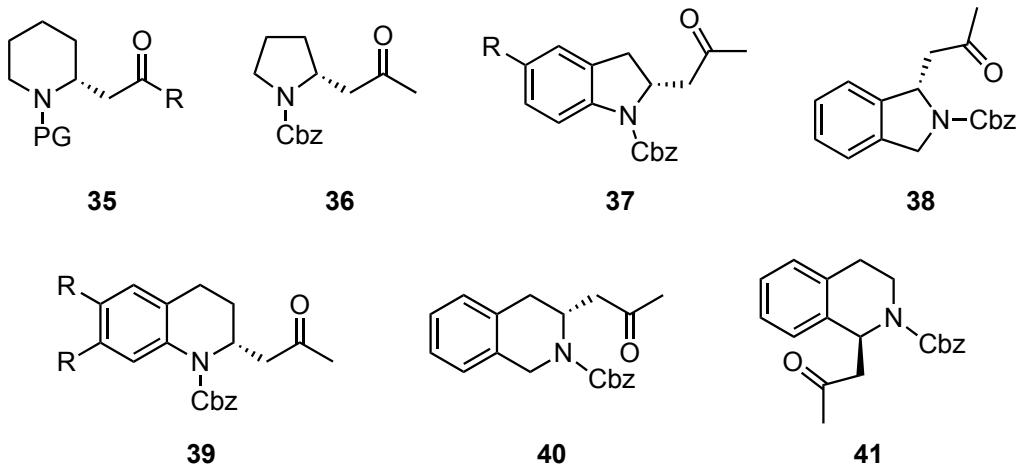


Figure 1.6. Substructures of the final products.

The combination of 9-amino-9-deoxy-*epi*-hydroquinidine and pentafluoro-propionic acid has been demonstrated as an efficient catalytic system for this conjugate addition.

Interestingly, the cyclisation step under microwave irradiation led to comparable results in terms of yield and *ee* to those obtained at room temperature. This is, as far as we know, the first report of a microwave accelerating effect in a Michael-type reaction catalysed by a cinchona alkaloid derivative.

[172] Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sánchez-Roselló, M. *Chem. Eur. J.* **2011**, *17*, 14267–14272.

1.6. Experimental Section

1.6.1. GENERAL METHODS

1.6.1.1. Spectroscopical and physical technics

NMR SPECTROSCOPY (^{1}H, ^{13}C, ^{19}F)

NMR spectra were recorded on a Bruker 300 MHz spectrometer, running at 300 MHz for ^{1}H, ^{13}C and ^{19}F using deuterated chloroform ($CDCl_3$) or methanol (CD_3OD) as solvent. Chemical shifts (δ) are given in ppm relative to the residual solvent signals of non-deuterated chloroform (7.26 ppm), methanol (3.31 ppm) and acetone (2.05 ppm) for ^{1}H NMR; deuterated chloroform (77.0 ppm), deuterated methanol (49.0 ppm) and deuterated acetone (29.84 ppm) for ^{13}C NMR; the internal reference of trichlorofluoromethane (0.0 ppm) for ^{19}F NMR. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. The letters br indicate that the signal is broad.

MASS SPECTROSCOPY

Mass spectra were recorded on a VG AUTOESPEC (micromass) spectrometer, employing the electronic impact (EI) technic performed at 70 eV, whereas the acceleration speed of the ions beam Cs^{+} at the fast atom bombardment (FAB) spectra was 30,000 V. The listed values for each compounds of the memory are expressed in units of *m/z*.

IR ANALYSIS

Infrared spectra were taken with a FT-IR apparatus.

DETERMINATION OF THE ENANTIOMERIC RATIO

The enantiomeric ratios were generally determined with the aid of high-performance liquid chromatography (HPLC) analysis (Jasco PU-2089 *Plus* pump and a Jasco MD-2010 detector) of the corresponding solutions of the compounds in mixtures of hexane: *i*propanol as eluents.

The chiral columns employed are:

- Chiracel OD-H column (25 cm x 0.46 cm)

- Chiralpack AD column (25 cm x 0.46 cm)

DETERMINATION OF THE OPTICAL ROTATION

Optical rotations were measured on either a Perkin-Elmer 241 polarimeter or a Jasco P-1020 polarimeter, employing a sodium lamp as radiation source and spectroscopic grade chloroform to prepare the solutions in a 10 cm long cell.

DETERMINATION OF THE MELTING POINT

Melting points have been determined either with a *Cambridge Instrusments* or with a *Büchi melting point P-450* apparatus.

1.6.1.2. Cromatographic technics

THIN-LAYER CROMATOGRAPHY

Reactions and purifications were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated Merck silica gel plates actives in UV light (Kiesegel 60 F_{254} on aluminium). Visualization was carried out with 254nm UV light and employing the appropriate stain, such as aqueous ceric ammonium molybdate solution, potassium permanganate and *p*-anisaldehyde.

FLASH CROMATOGRAPHY

Flash column chromatography purifications was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm).

1.6.1.3. Solvents drying

The employed solvents were either distilled and dried under nitrogen atmosphere prior to use:[173] THF and toluene were distilled from sodium, CH_2Cl_2 from calcium hydride; or anhydrous category solvents proceeding from commercial sources, being used without any previous purification.

1.6.1.4. Reagents and reaction conditions

The employed reagents were obtained of the best possible grade from commercial sources and were directly used. Air-sensitive reagents were

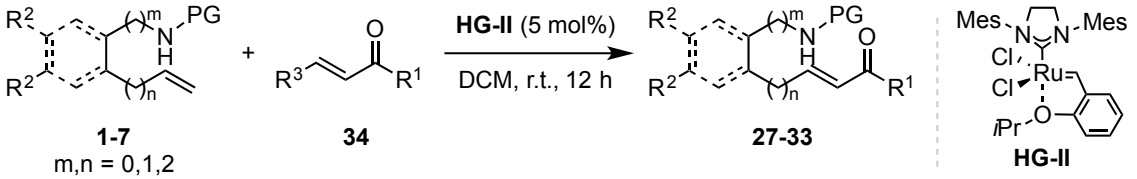
[173] *Purification of Laboratory Chemicals* 2nd edition; Perrin, D. D.; Ed. Pergamon Press; England, **1988**.

employed under nitrogen atmosphere. Reactions were carried out under nitrogen atmosphere unless otherwise indicated.

MICROWAVE IRRADIATION

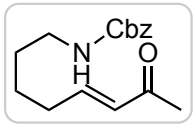
Microwave reactions were carried out at 0.1M solution in a 0.5-2 mL vial with an Initiator™ 2.0 (Biotage). The solutions were pre-stirred before the irradiation was started. The absorbance of the solvent was set as "normal" and 4-5 bars at 100ºC were reached. The reaction time was initiated as soon the system reached the input temperature, although approximately two minutes were needed to reach it.

1.6.2. SYNTHESIS OF THE *N*-PROTECTED α,β-UNSATURATED KETOAMINES 27-33



To a solution of *N*-protected amine **1-7** (1.0 equiv.) in CH_2Cl_2 (0.1 M) under nitrogen atmosphere, the corresponding conjugated ketone **34** (3.0 equiv.) and Hoveyda-Grubbs 2nd generation catalyst (5 mol%) were added. The resulting solution was stirred for 12 h at room temperature and then, solvents were removed and the crude mixture purified by flash chromatography with hexanes: ethyl acetate as eluents. Amines **27b**[141b] and **28**[141a] had been previously described. [174]

(*E*)-8-Benzyloxycarbonyl amino-3-octen-2-one (27a)



Physical state:	Pale yellow oil
Empiric Formula:	$C_{16}H_{21}NO_3$
Molecular weight (g/mol):	275.35
Yield (%):	90
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm):	1.48-1.53 (m, 4H), 2.15-2.26 (m, 2H), 2.21 (s, 3H), 3.15-3.21 (m, 2H), 4.94 (br s, 1H), 5.07

[141] a) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, 129, 6700-6701. b) Chandler, B. D.; Roland, J. T.; Li, Y.; Sorensen, *E. J. Org. Lett.* **2010**, 12, 2746-2749.

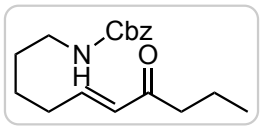
(s, 2H), 6.04 (d, *J* = 16.2 Hz, 1H), 6.70-6.80 (m, 1H), 7.28-7.35 (m, 5H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 25.0 (CH_2), 26.8 (CH_3), 29.4 (CH_2), 31.9 (CH_2), 40.6 (CH_2), 66.5 (CH_2), 128.0 (CH), 128.2 (CH), 128.4 (CH), 131.4 (CH) 136.5 (C), 147.6 (CH), 156.3 (C), 198.6 (C)

HRMS (EI$^+$): Calcd. for $C_{16}H_{21}NO_3$ [M^+]: 275.1521, found: 275.1519

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **27a** (212 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-5-hexenamine.

(*E*)-10-Benzyloxycarbonyl amino-5-decen-4-one (27c)



Physical state: Pale brown solid

Empiric Formula: $C_{18}H_{25}NO_3$

Molecular weight (g/mol): 303.40

Yield (%): 94

Melting point (ºC): 45-47

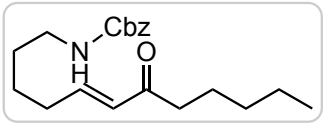
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 0.93 (t, *J* = 7.4 Hz, 3H), 1.50-1.57 (m, 2H), 1.59-1.69 (m, 4H), 2.19-2.26 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 3.17-3.24 (m, 2H), 4.77 (br s, 1H), 5.09 (s, 2H), 6.08 (d, *J* = 15.1 Hz, 1H), 6.73-6.83 (m, 1H), 7.32-7.36 (m, 5H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 13.8 (CH_3), 17.6 (CH_2), 25.2 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 40.7 (CH_2), 42.0 (CH_2), 66.6 (CH_2), 128.1 (CH), 128.5 (CH), 130.6 (2CH), 136.5 (C), 146.3 (CH), 156.4 (C), 200.7 (C)

HRMS (EI$^+$): Calcd. for $C_{18}H_{25}NO_3$ [M^+]: 303.1834, found: 303.1842

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- **27c** (244 mg) was obtained from propyl vinyl ketone and *N*-benzyloxycarbonyl-5-hexenamine

(*E*)-12-Benzyloxycarbonyl amino-7-dodecen-6-one (27d)



Physical state: Pale brown solid

Empiric Formula: $C_{16}H_{21}NO_3$

Molecular weight (g/mol): 331.46

Yield (%): 88

Melting point (ºC): 44-46

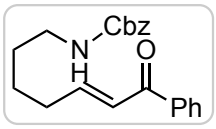
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 0.89 (t, *J* = 6.9 Hz, 3H), 1.25-1.33 (m, 4H), 1.48-1.68 (m, 6H), 2.19-2.26 (m, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 3.17-3.24 (m, 2H), 4.77 (br s, 1H), 5.09 (m, 2H), 6.08 (d, *J* = 16.0 Hz, 1H), 6.73-6.83 (m, 1H), 7.33-7.36 (m, 5H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 13.9 (CH_3), 22.5 (CH_2), 23.9 (CH_2), 25.2 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 31.9 (CH_2), 40.2 (CH_2), 40.7 (CH_2), 66.6 (CH_2), 128.1 (2CH), 128.5 (CH), 130.6 (CH), 136.5 (C), 146.2 (CH), 156.4 (C), 200.8 (C)

HRMS (EI$^+$): Calcd. for $C_{20}H_{29}NO_3$ [M^+]: 331.2159, found: 331.2147

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- **27d** (250 mg) was obtained from pentyl vinyl ketone and *N*-benzyloxycarbonyl-5-hexenamine.

(*E*)-7-Benzyloxycarbonyl amino-1-phenyl-2-hepten-1-one (27e)



Physical state: Pale brown solid

Empiric Formula: $C_{21}H_{23}NO_3$

Molecular weight (g/mol): 337.42

Yield (%): 71

Melting point (ºC): 40-42

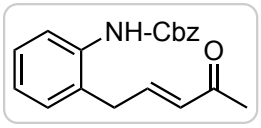
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 1.54-1.57 (m, 4H), 2.31-2.34 (m, 2H), 3.18-3.23 (m, 2H), 4.87 (br s, 1H), 5.09 (s, 2H), 6.87 (d, *J* = 15.4 Hz, 1H), 6.98-7.07 (m, 1H), 7.30-7.35 (m, 5H), 7.43-7.57 (m, 3H), 7.90-7.93 (m, 2H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 25.2 (CH_2), 29.6 (CH_2), 32.3 (CH_2), 40.7 (CH_2), 66.6 (CH_2), 126.2 (CH), 128.1 (CH), 128.5 (2CH), 132.6 (CH), 136.5 (C), 137.8 (C), 149.0 (CH), 156.4 (C), 190.7 (C)

HRMS (EI$^+$): Calcd. for $C_{21}H_{23}NO_3$ [*M*+1]: 338.1756, found: 338.1763

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **27e** (206 mg) was obtained from (*E*)-1-phenyl-2-buten-1-one and *N*-benzyloxycarbonyl-5-hexenamine.

(*E*)-5-(2-Benzyloxycarbonyl amino)phenyl-3-penten-2-one (29a)



Physical state: Pale brown solid

Empiric Formula: $C_{19}H_{19}NO_3$

Molecular weight (g/mol): 309.37

Yield (%): 91

Melting point (ºC): 47-49

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.07 (s, 3H), 3.40 (d, *J* = 6.3 Hz, 2H), 5.07 (s, 2H), 5.88 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.55 (br s, 1H), 6.71-6.81 (m, 1H), 7.03 (d, *J* = 4.1 Hz, 2H), 7.15-7.28 (m, 6H), 7.56 (d, *J* = 7.7 Hz, 1H)

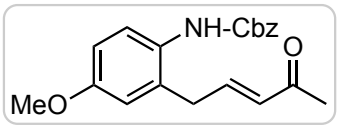
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 27.0 (CH_3), 34.4 (CH_2), 67.0 (CH_2), 125.4 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 130.1 (CH), 131.9 (CH), 135.4 (C), 135.9 (C), 136.5 (C), 144.6 (CH), 154.0 (C), 198.0 (C)

HRMS (EI$^+$): Calcd. for $C_{19}H_{19}NO_3$ [M^+]: 309.1365, found: 309.1363

Remarks:

- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **29a** (210 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-2-allyl aniline.[110]

(*E*)-Benzyl 4-methoxy-2-(4-oxopent-2-enyl)phenylcarbamate (29b)



Physical state: Pale brown solid

Empiric Formula: $C_{20}H_{22}NO_4$

Molecular weight (g/mol): 339.39

Yield (%): 79

Melting point (ºC): 62-64

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.20 (s, 3H), 3.47 (dd, *J* = 6.3, 1.6 Hz, 2H), 3.78 (s, 3H) 5.98 (dd, *J* = 15.9, 1.6 Hz, 1H), 6.21 (br s, 1H), 6.70 (d, *J* = 3.0 Hz, 1H), 6.79-6.90 (m, 2H), 7.34-7.37 (m, 6H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 27.1 (CH_3), 34.8 (CH_2), 55.4 (CH_3), 67.2 (CH_2), 112.8 (CH), 115.7 (CH), 128.1 (C), 128.3 (CH), 128.6 (CH), 132.1 (CH), 136.1

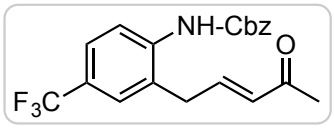
[110] Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872.

(C), 144.7 (CH), 154.7 (C), 156.2 (C), 171.1 (C), 198.8 (C)

HRMS (EI$^+$): Calcd. for $C_{20}H_{22}NO_4$ [*M*+H$^+$]: 340.1553, found: 340.1543

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- **29b** (178 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-4-methoxy-2-allyl aniline.

(*E*)-5-(2-benzyloxycarbonyl amino-4-trifluoromethyl)phenyl-3-penten-2-one (29c)



Physical state: Pale brown solid

Empiric Formula: $C_{20}H_{19}NO_3F_3$

Molecular weight (g/mol): 377.36

Yield (%): 69

Melting point (ºC): 90-92

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.22 (s, 3H), 3.55 (dd, *J* = 6.2, 1.7 Hz, 2H), 5.20 (s, 2H), 5.99 (dt, *J* = 16.0, 1.7 Hz, 1H), 6.55 (br s, 1H), 6.84 (dt, *J* = 16.0, 6.0 Hz, 1H), 7.37-7.41 (m, 6H), 7.56 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H)

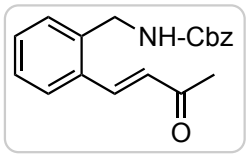
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 27.4 (CH_2), 34.4 (CH_3), 67.6 (CH_3), 121.9 (CH), 123.9 (q, *J* = 271.5 Hz, CF_3), 125.4 (q, *J* = 3.9 Hz, CH), 126.5 (q, *J* = 33.0 Hz, C), 127.2 (q, *J* = 3.9 Hz, CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 132.5 (CH), 135.5 (C), 139.0 (C), 142.7 (CH), 153.3 (C), 197.6 (C)

^{19}F NMR (CDCl3, 282.4 MHz) δ (ppm): -72.6 (s, 3F)

HRMS (EI$^+$): Calcd. for $C_{20}H_{19}NO_3F_3$ [*M*+H$^+$]: 378.1313, found: 378.1312

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- **29c** (155 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-4-trifluoromethyl-2-allyl aniline.

(*E*)-4-(2-Benzyloxycarbonyl aminomethyl)phenyl-3-buten-2-one (30)



Physical state: Pale yellow oil

Empiric Formula: $C_{19}H_{19}NO_3$

Molecular weight (g/mol): 309.37

Yield (%): 92

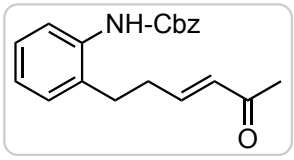
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.34 (s, 3H), 4.54 (d, *J* = 5.9 Hz, 2H), 5.06 (br s, 1H), 5.12 (s, 2H), 6.60 (d, *J* = 16.1 Hz, 1H), 7.29-7.37 (m, 8H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 16.1 Hz, 1H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 27.0 (CH_3), 43.0 (CH_2), 66.9 (CH_2), 127.0 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.6 (CH), 129.8 (CH), 130.3 (CH), 133.5 (C), 136.5 (C), 137.3 (C), 140.0 (CH), 155.9 (C), 198.8 (C)

HRMS (EI$^+$): Calcd. for $C_{19}H_{19}NO_3$ [*M*+1]: 310.1443, found: 310.1446

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **30** (213 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-2-vinylbenzyl amine.[110]

(*E*)-6-(2-Benzyloxycarbonyl amino)phenyl-3-hexen-2-one (31a)



Physical state: Pale yellow oil

Empiric Formula: $C_{20}H_{21}NO_3$

Molecular weight (g/mol): 323.39

Yield (%): 89

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.20 (s, 3H), 2.46-2.53 (m, 2H), 2.70-2.75 (m, 2H), 5.20 (s, 2H), 6.07 (dt, *J* = 16.0 and 1.5 Hz, 1H), 6.54 (br s, 1H), 6.72-6.82 (m, 1H), 7.08-7.17 (m, 2H), 7-21-7.24 (m, 1H), 7.33-7.41 (m, 5H), 7.68 (d, *J* = 7.5 Hz, 1H)

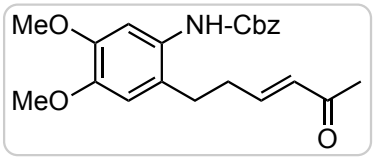
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 26.9 (CH_3), 29.7 (CH_2), 32.2 (CH_2), 67.1 (CH_2), 123.5 (CH), 125.2 (CH), 127.3 (CH), 128.3 (CH), 128.6 (CH), 129.2 (CH), 131.8 (CH), 135.0 (C), 136.0 (C), 137.8 (C), 146.3 (CH), 154.1 (C), 198.4 (C)

HRMS (EI$^+$): Calcd. for $C_{20}H_{21}NO_3$ [M^+]: 323.1521, found: 323.1525

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.

- **31a** (205 mg) was obtained from methyl vinyl ketone and *N*-Benzyloxycarbonyl-2-homoallyl aniline.[110]

(*E*)-6-(2-Benzyloxycarbonyl amino-4,5-dimethoxy)phenyl-3-hexen-2-one (31b)



Physical state:	Pale yellow oil
Empiric Formula:	$C_{22}H_{25}NO_5$
Molecular weight (g/mol):	383.44
Yield (%):	83

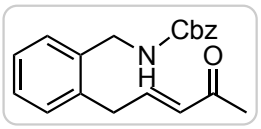
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.21 (s, 3H), 2.42-2.50 (m, 2H), 2.64-2.70 (m, 2H), 3.84 (s, 6H), 5.19 (m, 2H), 6.07 (d, *J* = 16.0 Hz, 1H), 6.32 (br s, 1H), 6.72 (s, 1H), 6.74-6.81 (m, 1H), 7.18 (s, 1H), 7.35-7.39 (m, 5H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 27.0 (CH_3), 29.6 (CH_2), 32.9 (CH_2), 55.9 (CH_3), 56.1 (CH_3), 67.2 (CH_2), 108.4 (CH), 112.1 (CH), 127.6 (C), 128.3 (CH), 128.4 (CH), 128.6 (2CH), 131.8 (C), 136.0 (C), 146.4 (CH), 146.7 (C), 147.7 (C), 154.5 (C), 198.4 (C)

HRMS (EI$^+$): Calcd. for $C_{22}H_{25}NO_5$ [M^+]: 383.1733, found: 383.1729

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **31b** (186 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-4,5-dimethoxy-2-homoallyl aniline.[108]

(*E*)-5-(2-Benzyloxycarbonyl aminomethyl)phenyl-3-penten-2-one (32)



Physical state:	Pale yellow oil
Empiric Formula:	$C_{20}H_{21}NO_3$
Molecular weight (g/mol):	323.39
Yield (%):	83

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.18 (s, 3H), 3.58 (d, *J* = 6.0 Hz, 2H), 4.35 (d, *J* = 5.9 Hz, 2H), 4.93 (br s, 1H), 5.10 (s, 2H), 5.94 (d, *J* = 15.6 Hz, 1H), 6-85-6.94 (m, 1H), 7.12-7.33 (m, 9H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 26.0 (CH_3), 35.4 (CH_2), 42.8 (CH_2), 66.9

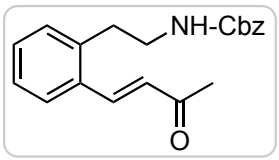
[108] Ihara, M.; Takasu, K.; Maiti, S. *Heterocycles* **2003**, *59*, 51-55.

(CH_2), 127.4 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.1 (CH), 130.4 (CH), 132.0 (CH), 135.9 (C), 136.1 (C), 136.3 (C), 145.9 (CH), 156.0 (C), 198.3 (C)

HRMS (EI^+): Calcd. for $C_{20}H_{21}NO_3$ [M^+]: 323.1521, found: 323.1522

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **32** (192 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-2-allylbenzyl amine.[110,177]

(*E*)-4-(2-Benzyloxycarbonyl aminoethyl)phenyl-3-buten-2-one (33)



Physical state: Pale yellow oil

Empiric Formula: $C_{20}H_{21}NO_3$

Molecular weight (g/mol): 323.39

Yield (%): 77

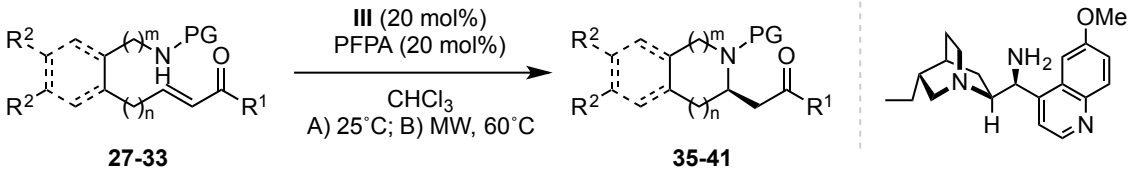
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.42 (s, 3H), 3.00 (t, *J* = 7.30 Hz, 2H), 3.35-3.42 (m, 2H), 4.89 (br s, 1H), 5.09 (s, 2H), 6.64 (d, *J* = 16.1 Hz, 1H), 7.19-7.36 (m, 8H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.91 (d, *J* = 16.1 Hz, 1H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 27.5 (CH_3), 33.6 (CH_2), 42.2 (CH_2), 66.7 (CH_2), 126.8 (CH), 127.3 (CH), 128.1 (CH), 128.1 (CH), 128.5 (CH), 129.0 (CH), 130.4 (CH), 130.5 (CH), 133.5 (C), 136.4 (C), 138.5 (CH), 140.3 (CH), 156.3 (C), 198.6 (C)

HRMS (EI^+): Calcd. for $C_{20}H_{21}NO_3$ [M^+]: 323.1521, found: 323.1522

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- **33** (177 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-2-vinylphenethyl amine.[110]

1.6.3. MICHAEL ADDUCTS SYNTHESIS: PREPARATION OF 2-SUBSTITUTED NITROGEN HETEROCYCLES 35-41



27-33 **35-41**

[177] O. Okitsu, R. Suzuki, S. Kobayashi, *J. Org. Chem.* **2001**, *66*, 809-823.

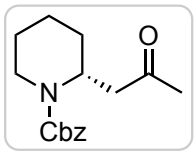
Methodology A

In a 10 mL round bottomed flask, α,β-unsaturated ketones **27**-**33** (1.0 equiv.) were dissolved in chloroform (0.1 M). A mixture of catalyst **III** (20 mol%) and pentafluoropropionic acid (PFPA) (20 mol%, added from a freshly prepared stock solution in chloroform) was added and the resulting solution was stirred at room temperature. After 12-96 hours, the crude reaction mixture was subjected to flash chromatography on silica gel using mixtures of hexanes: ethyl acetate 3:1-5:1 as eluents to afford the corresponding heterocycles **35-41**. The enantiomeric ratios were determined by means of HPLC analysis with a Chiracel OD-H column (25 cm x 0.46 cm).

Methodology B

The corresponding α,β-unsaturated ketones (**27-33**) (1.0 equiv.) were dissolved in chloroform (0.1M) in a microwave vial and then, catalyst **III** (20 mol%) and PFPA (20 mol%, added from a freshly prepared stock solution in $CHCl_3$) were successively added. The vial was sealed and the corresponding solution was heated under microwave irradiation at 60 ºC for 1-4h. After this time, the crude reaction mixture was purified by means of flash chromatography on silica gel using the appropriate eluent (hexanes: ethyl acetate 3:1-5:1) to afford the corresponding heterocycles **35-41**. The enantiomeric ratios were determined by means of HPLC analysis with a Chiracel OD-H column (25 cm x 0.46 cm).

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)piperidine (35a)[161a]



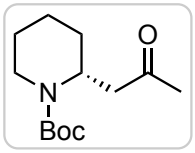
Physical state:	Colorless oil
Empiric Formula:	$C_{16}H_{21}NO_3$
Molecular weight (g/mol):	275.35
Optical rotation $[\alpha]_D^{25}$:	+11.6 (*c* 1.0, $CHCl_3$) [lit. +10.2 (*c* 2.5, $CHCl_3$)][161a]

Remarks: ‣ **35a** (38 mg) was obtained from **27a** in 93% yield and 96% *ee* at room temperature [94% yield (39 mg) and 95% *ee* at 60ºC under microwave irradiation].

[161a] Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047–3054.

- Spectroscopic data in agreement with those previously reported in the literature.[161a]
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}= 14.1 min, t_{minor}=14.8 min.

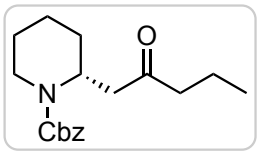
(2*R*)-*N*-*t*-Butoxycarbonyl-2-(2-oxopropyl)piperidine (35b)[161c]



Physical state:	Colorless oil
Empiric Formula:	$C_{13}H_{23}NO_3$
Molecular weight (g/mol):	241.33
Optical rotation $[\alpha]_D^{25}$:	+4.1 (*c* 1.0, $CHCl_3$). [lit. +8.2 (*c* 2.0, $CHCl_3$)][161c]

Remarks:
- **35b** (33 mg) was obtained from **27b** in 92% yield and 93% *ee* at room temperature [97% yield (35 mg) and 90% *ee* at 60°C under microwave irradiation].
- Spectroscopic data in agreement with those previously reported in the literature.[161c]
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 98:2); flow rate = 1.0 mL/min, t_{major}=7.3 min, t_{minor}=8.5 min.

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopentyl)piperidine (35c)[161e]



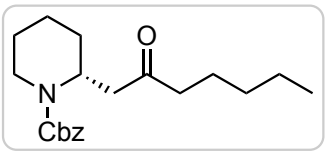
Physical state:	Colorless oil
Empiric Formula:	$C_{18}H_{25}NO_3$
Molecular weight (g/mol):	303.18
Optical rotation $[\alpha]_D^{25}$:	+4.6 (*c* 1.0, $CHCl_3$) [lit. +4.4 (*c* 1.54, $CHCl_3$)][161e]

Remarks:
- **35c** (43 mg) was obtained from **27c** in 95% yield and 98% *ee* at room temperature [94% yield (42 mg) and 96% *ee* at 60°C under microwave irradiation].
- Spectroscopic data in agreement with those previously reported in the literature.[161e]
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H

[161c] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192–10213.
[161e] Macours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415–1428.

column (hexane:isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}=10.5 min, t_{minor}=9.0 min.

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxoheptyl)piperidine (35d)[161a]



Physical state: Colorless oil

Empiric Formula: $C_{20}H_{29}NO_3$

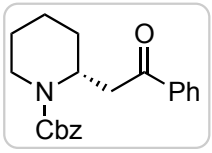
Molecular weight (g/mol): 331.46

Optical rotation $[\alpha]_D^{25}$: +3.2 (*c* 1.0, $CHCl_3$) [lit. +9.5 (*c* 0.64, $CHCl_3$)].[161a]

Remarks:

- **35d** (46 mg) was obtained from **27d** in 92% yield and 98% *ee* at room temperature [89% yield (44 mg) and 97% *ee* at 60°C under microwave irradiation].
- Spectroscopic data in agreement with those previously reported in the literature.[161a]
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}=8.4 min, t_{minor}=7.1 min.

(2*R*)-*N*-Benzyloxycarbonyl -2-(2-oxo-2-phenylethyl)piperidine (35e)[180]



Physical state: Colorless oil

Empiric Formula: $C_{21}H_{23}NO_3$

Molecular weight (g/mol): 337.42

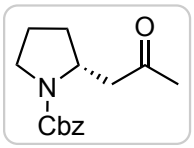
Optical rotation $[\alpha]_D^{25}$: -16.6 (*c* 1.0, $CHCl_3$)

Remarks:

- **35e** (29 mg) was obtained from **27e** in 58% yield and 93% *ee* at room temperature [75% yield (38 mg) and 84% *ee* at 60°C under microwave irradiation].
- Spectroscopic data in agreement with those previously reported in the literature.[177,180]
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}=17.0 min, t_{minor}=15.9 min.

[177] O. Okitsu, R. Suzuki, S. Kobayashi, *J. Org. Chem.* **2001**, *66*, 809-823.
[180] Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989-990.
[161g] Majik, M. S.; Tilve, S. G. *Tetrahedron Lett.* **2010**, *51*, 2900–2902.

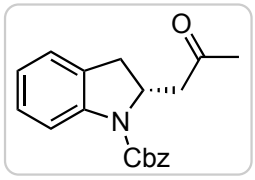
(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxoheptyl)pyrrolidine (36)[161g]



Physical state:	Colorless oil
Empiric Formula:	$C_{15}H_{19}NO_3$
Molecular weight (g/mol):	261.32
Optical rotation $[\alpha]_D^{25}$:	+35.8 (*c* 1.0, $CHCl_3$) [lit. -37.5 (*c* 0.72, $CHCl_3$) for the opposite enantiomer].[161g]

Remarks:
- **36** (31 mg) was obtained from **28** in 80% yield and 82% *ee* at room temperature [85% yield (33 mg) and 79% *ee* at 60°C under microwave irradiation].
- Spectroscopic data in agreement with those previously reported in the literature.[161g]
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}=20.3 min, t_{minor}=16.5 min.

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)indoline (37a)



Physical state:	Colorless oil
Empiric Formula:	$C_{19}H_{19}NO_3$
Molecular weight (g/mol):	309.37
Optical rotation $[\alpha]_D^{25}$:	+82.5 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.10 (s, 3H), 2.61-2.73 (m, 2H), 3.00-3.04 (m, 1H), 3.45 (dd, *J* = 16.6 and 9.6 Hz, 1H), 4.83-4.89 (m, 1H), 5.29 (s, 2H), 6.94-6.99 (m, 1H), 7.12-7.17 (m, 2H), 7.33-7.41 (m, 5H), 7.70-7.81 (m, 1H)

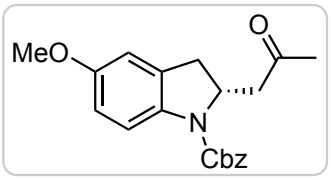
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 30.4 (CH_3), 34.5 (CH_2), 48.2 (CH_2), 55.6 (CH) 67.3 (CH_2), 115.4 (CH), 123.1 (CH), 125.1 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.7 (C), 136.1 (C), 136.7 (C), 161.0 (C), 206.7 (C)

IR (film spectroscopy) ν (cm^{-1}): 3489, 2884, 1707, 1600, 1482, 1402, 1128, 751

HRMS (EI$^+$): Calcd. for $C_{19}H_{19}NO_3$ [M^+]: 309.1365, found: 309.1369

Remarks:
- **37a** (42 mg) was obtained from **29a** in 90% yield and 93% *ee* at room temperature [83% yield (38 mg) and 91% *ee* at 60°C under microwave irradiation].
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}=19.4 min, t_{minor}=15.8 min.

(2*R*)-*N*-Benzyloxycarbonyl-5-methoxy-2-(2-oxopropyl)indoline (37b)



Physical state: White solid

Empiric Formula: $C_{20}H_{22}NO_4$

Molecular weight (g/mol): 339.39

Melting point (ºC): 85-87

Optical rotation $[\alpha]_D^{25}$: +82.5 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.04-2.12 (m, 3H), 2.61-2.70 (m, 2H), 2.90-3.18 (m, 1H), 3.43 (dd, *J* = 15.0, 9.0 Hz, 1H), 3.76 (s, 3H), 4.84 (tt, *J* = 16.7, 9.6 Hz, 1H), 5.27 (s, 2H), 6.71 (m, 2H), 7.32-7.45 (m, 5H), 7.72 (br s, 1H)

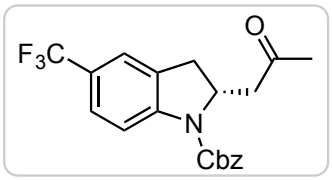
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 30.4 (CH_3), 34.7 (CH_2), 48.3 (CH_2), 55.6 (CH_3), 60.4 (CH), 67.1 (CH_2), 111.3 (CH), 112.3 (CH), 112.9 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 128.8 (C), 131.2 (C), 134.8 (C), 136.2 (C), 156.0 (C), 206.8 (C)

IR (film spectroscopy) ν (cm^{-1}): 3543, 3402, 2819, 1692, 1494, 1398, 1265, 1120, 743

HRMS (EI^+): Calcd. for $C_{20}H_{22}NO_4$ [*M*+H^+]: 340.1543, found: 340.1542

Remarks:
- **37b** (46 mg) was obtained from **29b** in 85% yield and 92% *ee* at room temperature [81% yield (41 mg) and 90% *ee* at 60°C under microwave irradiation].
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=22.8 min, t_{minor}=17.8 min.

(2*R*)-*N*-Benzyloxycarbonyl-5-trifluoromethyl-2-(2-oxopropyl)indoline (37c)



Physical state: White solid

Empiric Formula: $C_{20}H_{19}NO_3F_3$

Molecular weight (g/mol): 377.36

Melting point (ºC): 120-122

Optical rotation $[\alpha]_D^{25}$: +35.7 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.11 (s, 3H), 2.62-2.78 (m, 2H), 3.04 (br s, 1H), 3.49 (dd, *J* = 16.9, 9.6 Hz, 1H), 4.90 (tt, *J* = 10.0, 2.7 Hz, 1H), 5.30 (dd, *J* = 14.8, 12.3 Hz, 2H), 7.20-7.45 (m, 7H), 7.76 (br s, 1H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 30.4 (CH_3), 34.3 (CH_2), 47.9 (CH_2), 56.1 (CH), 67.8 (CH_2), 115.1 (CH), 122.2 (q, *J* = 3.8 Hz, CH), 124.7 (q, *J* = 271.7 Hz, CF_3), 125.2 (q, *J* = 33.4 Hz, C), 125.4 (q, *J* = 3.8 Hz, CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 130.6 (C), 135.7 (C), 152.5 (C), 206.3 (C)

^{19}F NMR (CDCl3, 282.4 MHz) δ (ppm): -72.1 (s, 3F)

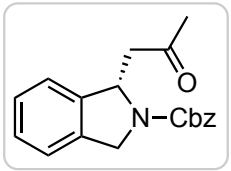
IR (film spectroscopy) ν (cm^{-1}): 3611, 3562, 3055, 2880, 1741, 1707, 1364, 1219, 823

HRMS (EI^+): Calcd. for $C_{20}H_{19}NO_3F_3$ [*M*+H^+]: 378.1313, found: 378.1304

Remarks:

- **37c** (36 mg) was obtained from **29c** in 71% yield and 68% *ee* at room temperature [68% yield (34 mg) and 63% *ee* at 60ºC under microwave irradiation].
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=10.0 min, t_{minor}=13.6 min.

(1*R*)-*N*-Benzyloxycarbonyl-1-(2-oxopropyl)isoindoline (38)



Physical state: Colorless oil

Empiric Formula: $C_{19}H_{19}NO_3$

Molecular weight (g/mol): 309.37

Optical rotation $[\alpha]_D^{25}$: +90.6 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.00 (s, 1H), 2.14 (s, 2H), 2.77-2.97 (m, 1H), 3.11 (dd, *J* = 16.8, 3.3 Hz, 0.5H), 3.32 (dd, *J* = 17.1, 3.5 Hz, 0.5H), 4.65-4.85 (m, 2H), 5.14-5.27 (m, 2H), 5.49-5.52 (m, 1H), 7.22-

7.40 (m, 9H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 30.6 (CH_3), 48.5 (CH_2), 50.0 (CH_2), 51.8 (CH_2), 52.2 (CH_2), 58.9 (CH), 59.7 (CH), 66.9 (CH_2), 67.1 (CH_2), 122.4 (CH), 122.6 (CH), 122.9 (CH), 123.0 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.1 (CH), 128.5 (CH), 135.9 (C), 136.2 (C), 136.4 (C), 136.6 (C), 140.2 (C), 140.7 (C), 154.5 (C), 206.2 (C), 206.4 (C)

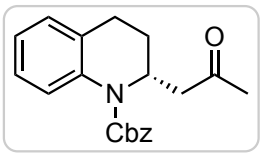
IR (film spectroscopy) ν (cm^{-1}): 3487, 3334, 1692, 1646, 1204, 1101, 759

HRMS (EI^+): Calcd. for $C_{19}H_{19}NO_3$ [M^+]: 309.1365, found: 309.1369

Remarks:

- **38** (45 mg) was obtained from **30** in 96% yield and 93% *ee* at room temperature [91% yield (42 mg) and 92% *ee* at 60°C under microwave irradiation].
- ^{1}H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 3:2 ratio.
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=21.2 min, t_{minor}=15.9 min.

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)tetrahydroquinoline (39a)



Physical state: Colorless oil

Empiric Formula: $C_{20}H_{21}NO_3$

Molecular weight (g/mol): 323.39

Optical rotation $[\alpha]_D^{25}$: +76.3 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 1.54-1.65 (m, 1H), 2.09 (s, 3H), 2.30-2.41 (m, 1H), 2.48 (dd, *J* = 16.1 and 8.1 Hz, 1H), 2.65-2.7 (m, 2H), 2.80 (dd, *J* = 16.1 and 5.6 Hz, 1H), 4.94-5.03 (m, 1H), 5.22 (dd, *J* = 33.5 and 12.5 Hz, 2H), 7.02-7.17 (m, 3H), 7.30-7.37 (m, 5H), 7.50 (d, *J* = 8.1 Hz, 1H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 24.7 (CH_2), 29.1 (CH_2), 30.3 (CH_3), 47.5 (CH_2), 49.9 (CH), 67.6 (CH_2), 124.5 (CH), 125.6 (CH), 126.2 (CH), 127.9 (CH), 128.1 (CH), 128.5 (2CH), 131.5 (C), 136.2 (C), 136.3 (C), 154.5 (C), 206.5 (C)

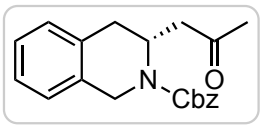
IR (film spectroscopy) ν (cm^{-1}): 3749, 3498, 3055, 2872, 1699, 1414, 1349, 1109, 881, 763

HRMS (EI^+): Calcd. for $C_{20}H_{21}NO_3$ [M^+]: 323.1521, found: 323.1512

Remarks:

- **39a** (39 mg) was obtained from **31a** in 80% yield and 88% *ee* at room temperature [93% yield (45 mg) and 86% *ee* at 60°C under microwave irradiation].
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 95:5); flow rate = 1.0 mL/min, t_{major}=20.6 min, t_{minor}=19.3 min.

(3*R*)-*N*-Benzyloxycarbonyl-3-(2-oxopropyl)tetrahydroisoquinoline (40)



Physical state: Colorless oil

Empiric Formula: $C_{20}H_{21}NO_3$

Molecular weight (g/mol): 323.39

Optical rotation $[\alpha]_D^{25}$: -34.4 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.01 (s, 1.5H), 2.13 (s, 1.5H), 2.41-2.49 (m, 1H), 2.53-2.80 (m, 2H), 3.08-3.14 (m, 1H), 4.38 (d, *J* = 17.0 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.85-5.02 (m, 1H), 5.18 (s, 2H), 7.10-7.38 (m, 9H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 30.2 (CH_3), 30.3 (CH_3), 32.9 (CH_2), 33.1 (CH_2), 43.3 (CH_2), 43.4 (CH_2), 45.8 (CH_2), 46.1 (CH_2), 46.5 (CH), 67.3 (CH_2), 126.1 (CH), 126.2 (CH), 126.5 (CH), 126.9 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 129.1 (CH), 129.3 (CH), 132.3 (C), 132.4 (C), 132.6 (C), 136.5 (C), 155.2 (C), 155.3 (C), 206.4 (C), 206.6 (C)

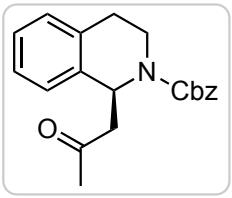
IR (film spectroscopy) ν (cm^{-1}): 3745, 3619, 3494, 3024, 2793, 1715, 1421, 1357, 1216, 872

HRMS (EI^+): Calcd. for $C_{22}H_{25}NO_5$ [M^+]: 383.1733, found: 383.1738

Remarks:

- **40** (47 mg) was obtained from **32** in 97% yield and 97% *ee* at room temperature [95% yield (46 mg) and 97% *ee* at 60°C under microwave irradiation].
- ^{1}H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 1:1 ratio.
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=16.4 min, t_{minor}=12.3 min.

(1*S*)-*N*-Benzyloxycarbonyl-1-(2-oxopropyl)tetrahydroisoquinoline (41)



Physical state: Colorless oil

Empiric Formula: $C_{20}H_{21}NO_3$

Molecular weight (g/mol): 323.39

Optical rotation $[\alpha]_D^{25}$: +78.2 (*c* 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 2.04 (s, 1.5H), 2.25 (s, 1.5H), 2.74-2.89 (m, 4H), 3.32-3.50 (m, 1H), 3.97-4.03 (m, 0.5H), 4.14-4.19 (m, 0.5H), 5.10-5.22 (m, 2H), 5.67-5.73 (m, 1H), 7.13-7.37 (m, 9H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 28.2 (CH_2), 28.4 (CH_2), 30.1 (CH_3), 30.5 (CH_3), 38.5 (CH_2), 38.8 (CH_2), 51.1 (CH), 51.4 (CH_2), 51.6 (CH_2), 67.3 (CH_2), 67.4 (CH_2), 126.5 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH) 128.5 (CH), 128.9 (CH), 129.0 (CH), 134.0 (C), 134.1 (C), 136.5 (C), 136.6 (C), 155.0 (C), 155.4 (C), 205.7 (C), 206.1 (C)

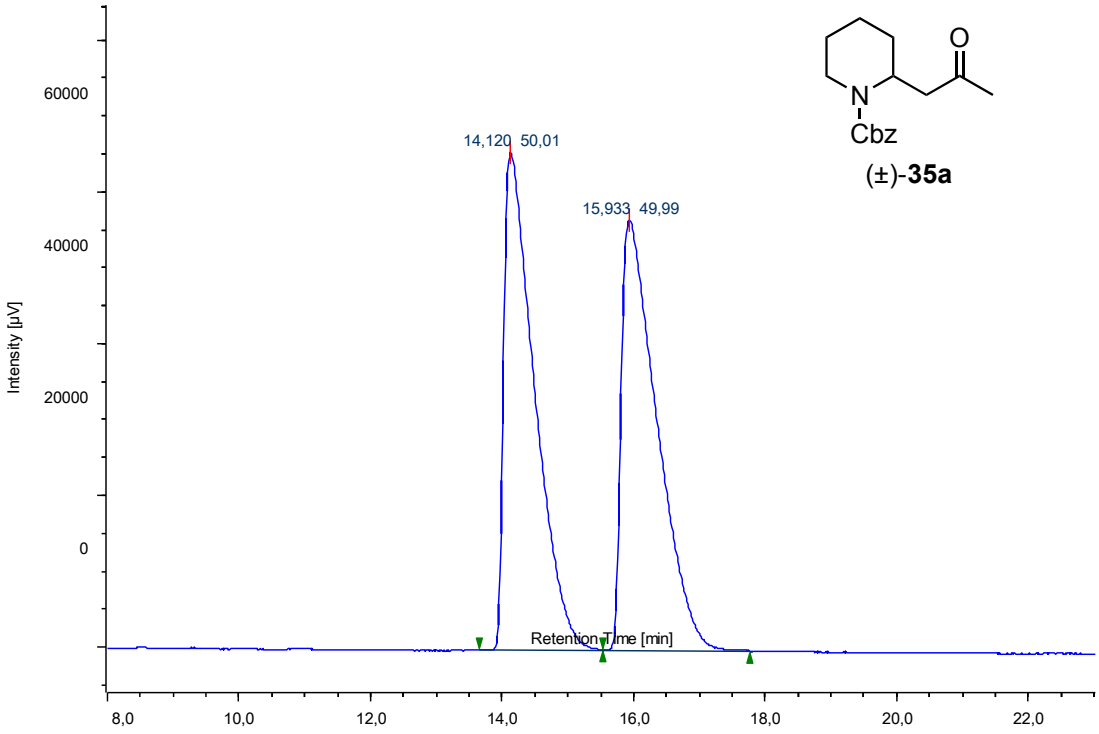
IR (film spectroscopy) ν (cm^{-1}): 3745, 3611, 2886, 1688, 1534, 1421, 1094, 879

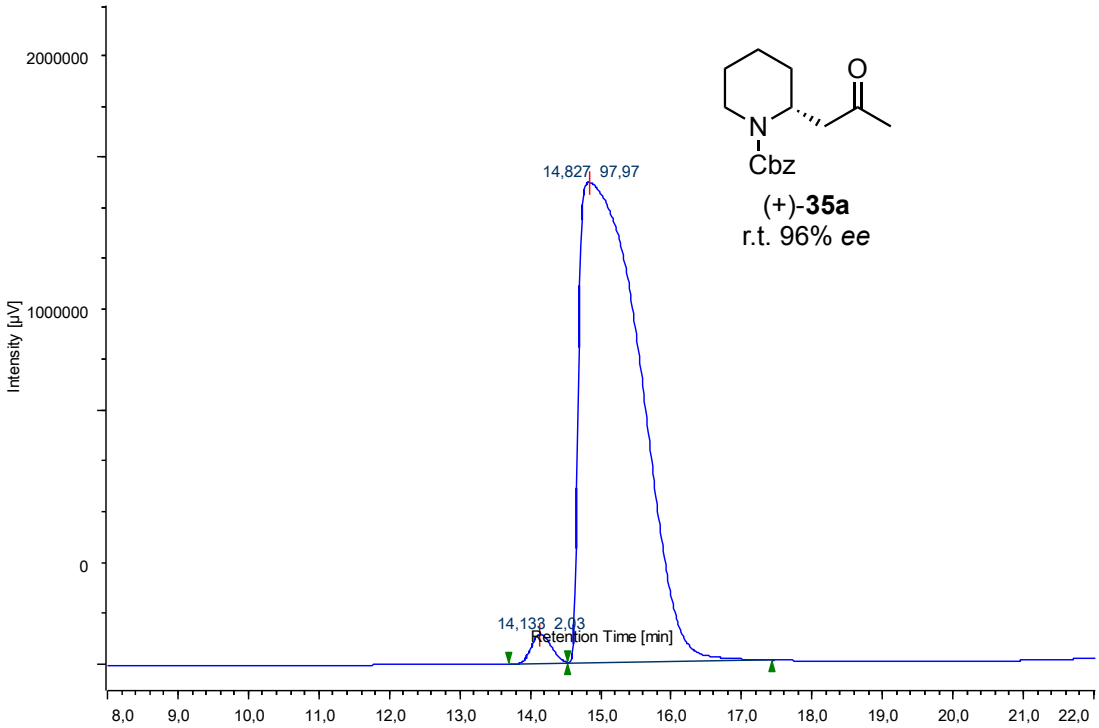
HRMS (EI^+): Calcd. for $C_{20}H_{21}NO_3$ [M^+]: 323.1521, found: 323.1519

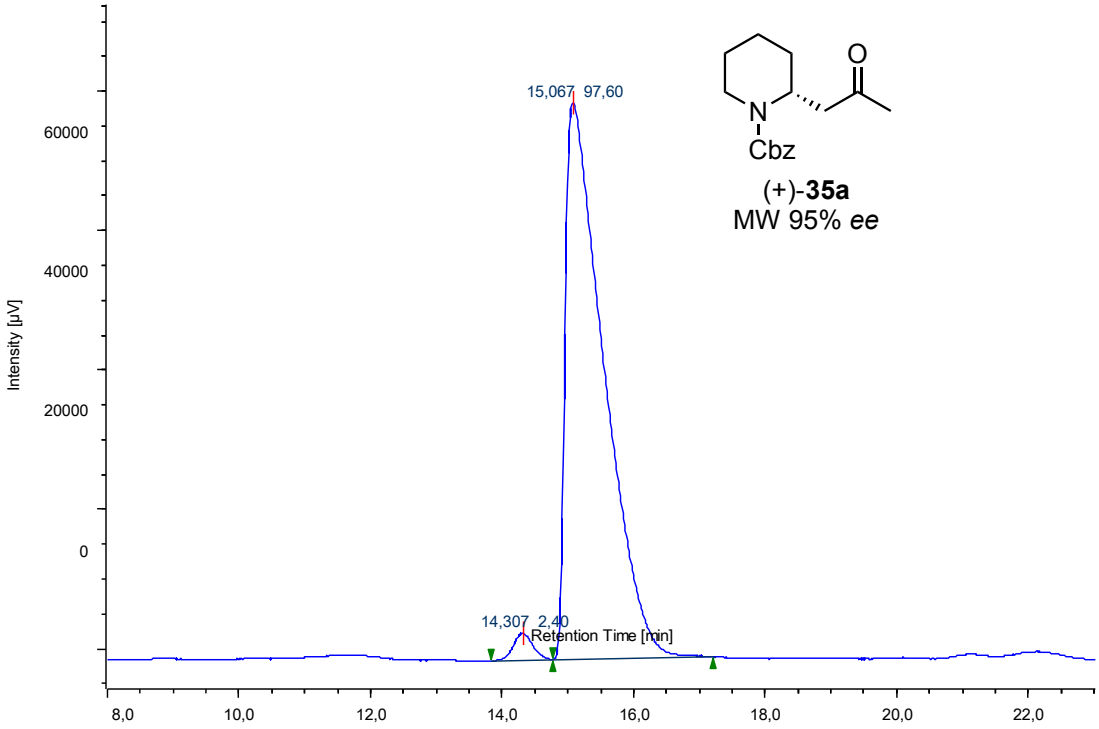
Remarks:

- **41** (46 mg) was obtained from **33** in 94% yield and 98% *ee* at room temperature [91% yield (44 mg) and 97% *ee* at 60°C under microwave irradiation].
- ^{1}H and ^{13}C NMR show the presence of rotamers about the carbamate bond in ca. 1:1 ratio.
- The *ee* values were determined by HPLC analysis using a Chiracel OD-H column (hexane:isopropanol 85:15); flow rate = 1.0 mL/min, t_{major}=14.5 min, t_{minor}=13.9 min.

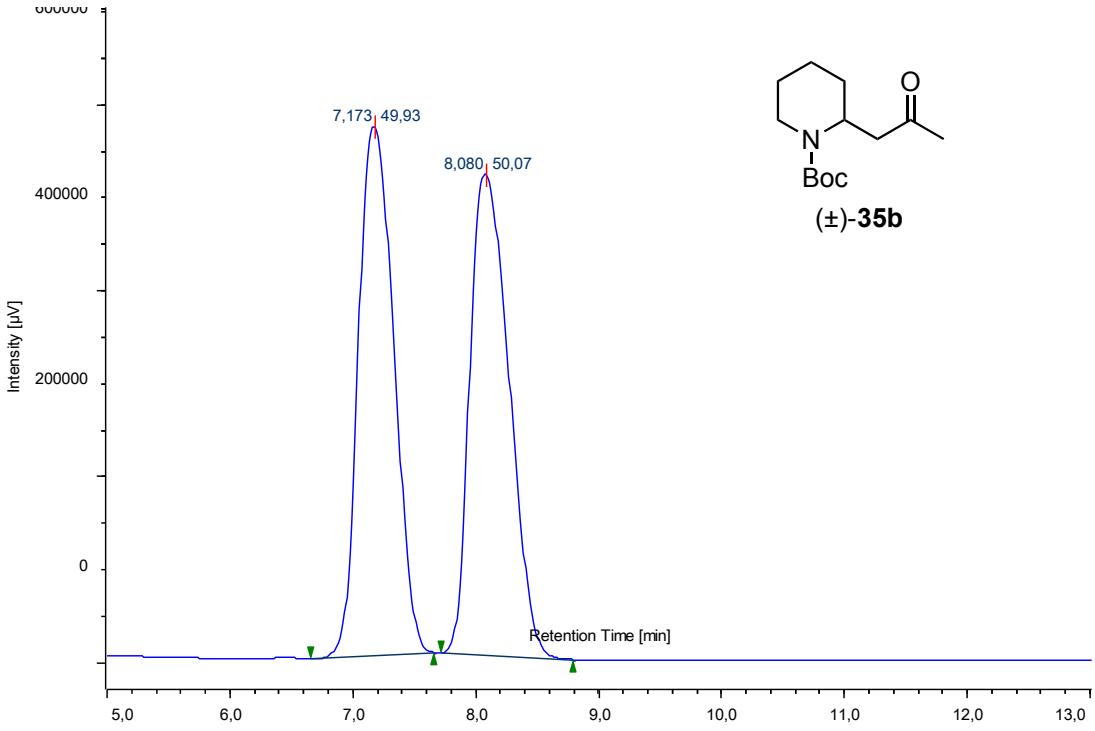
1.6.4. HPLC TRACES OF ENANTIOENRICHED COMPOUNDS 35-41



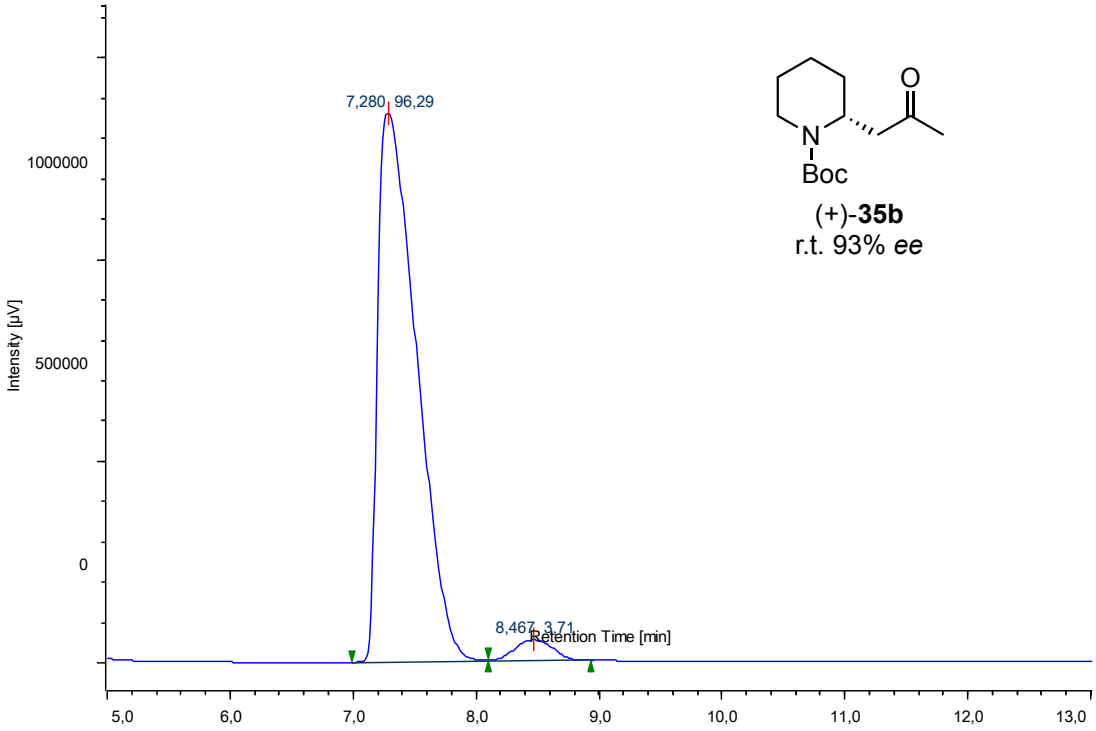




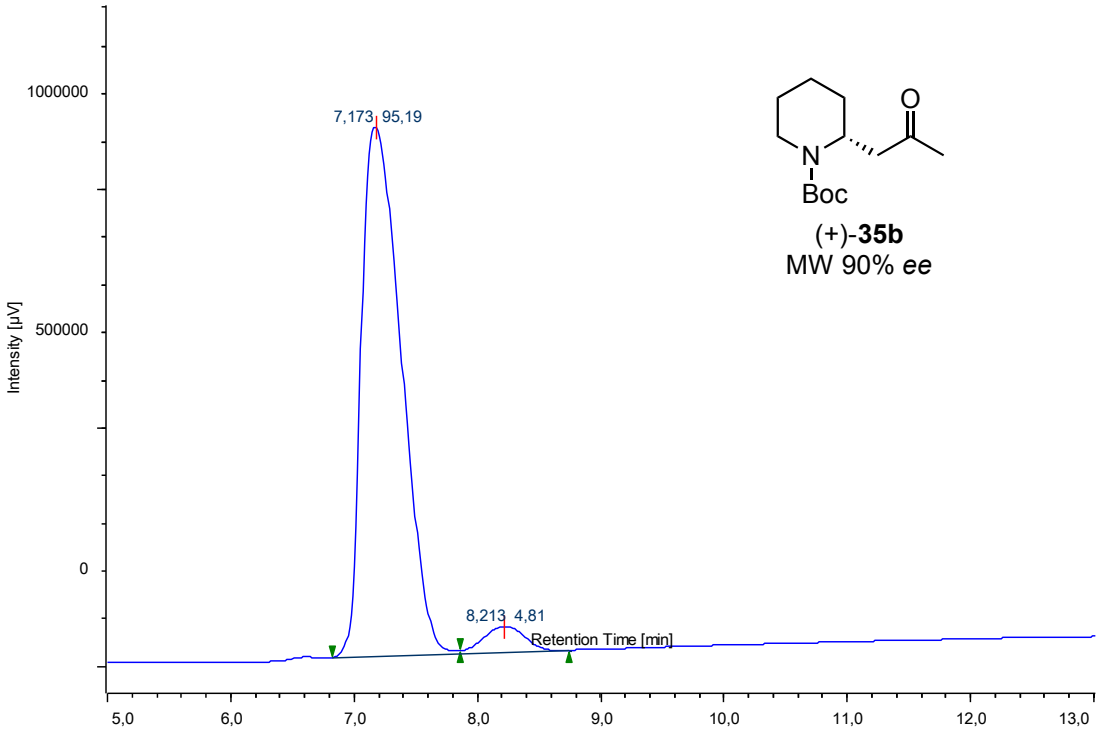
(+)-**35a**
MW 95% *ee*



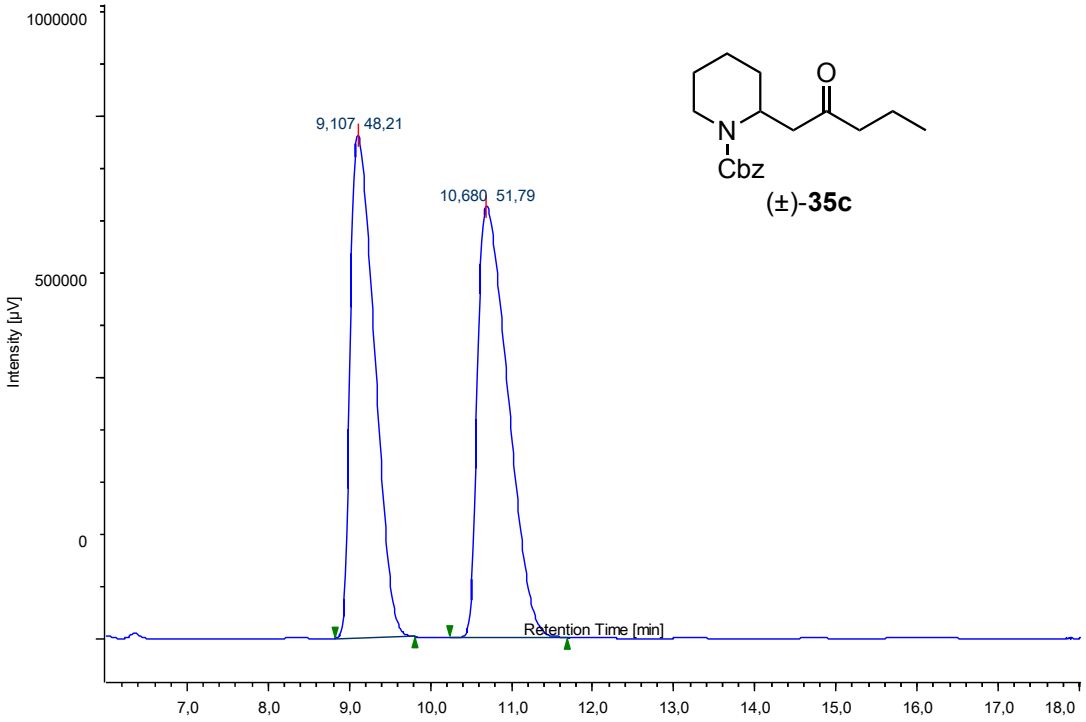
(±)-**35b**



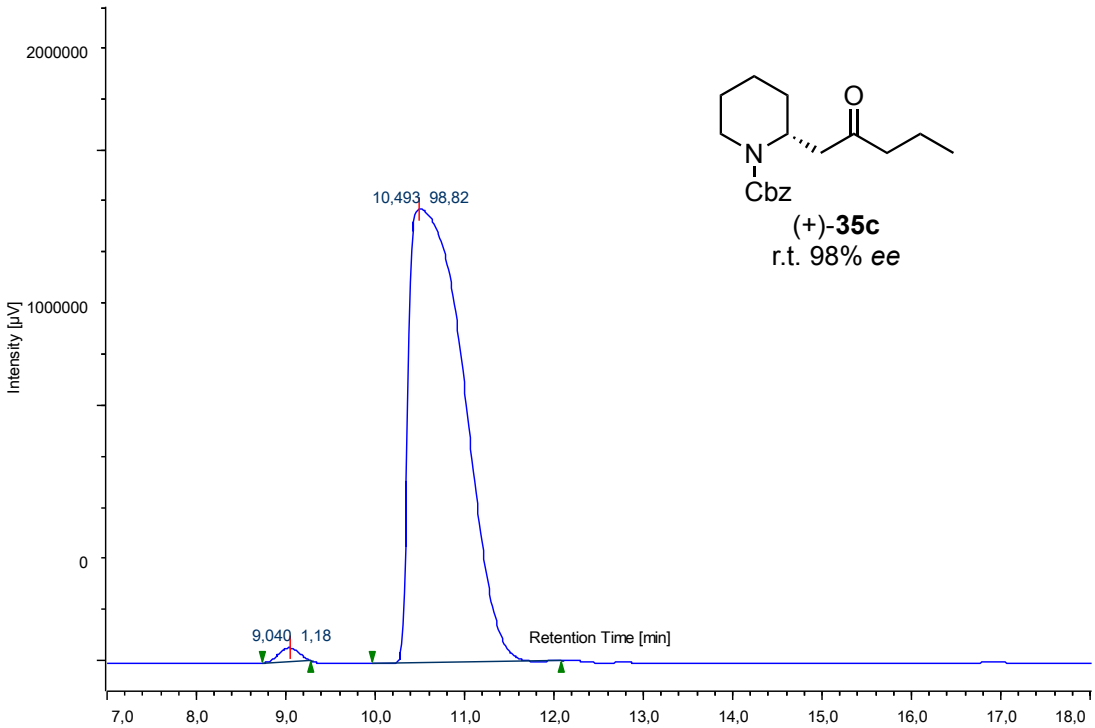
(+)-**35b**
r.t. 93% *ee*



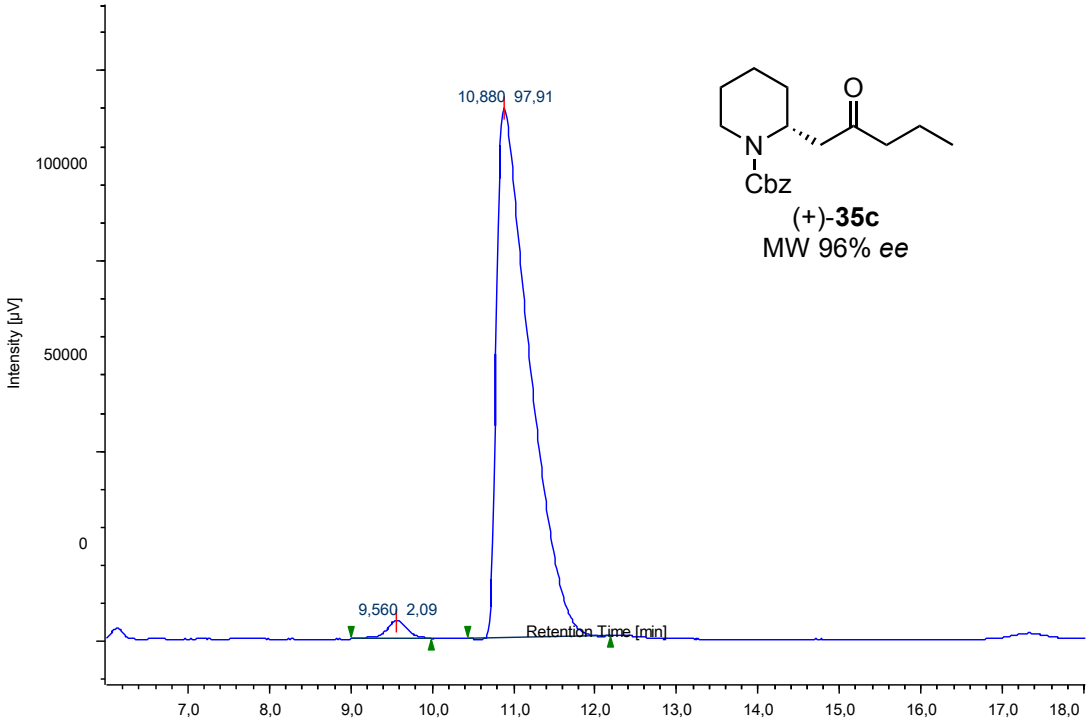
(+)-**35b**
MW 90% *ee*



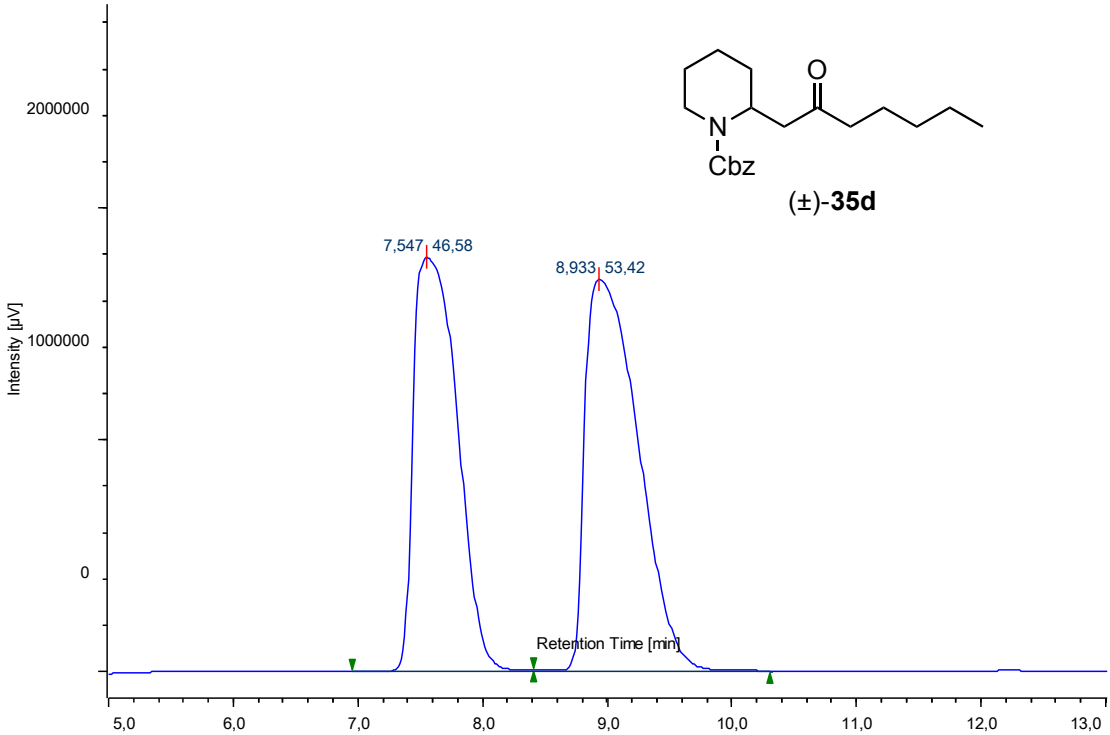
(±)-**35c**



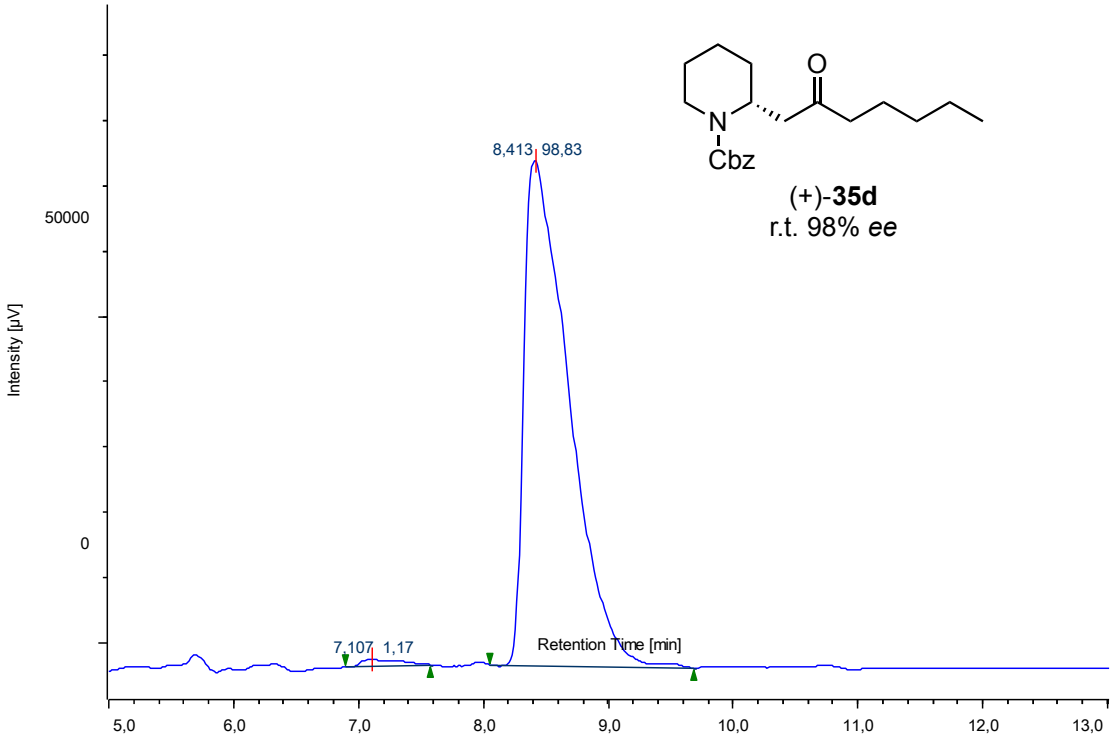
(+)-**35c**
r.t. 98% *ee*

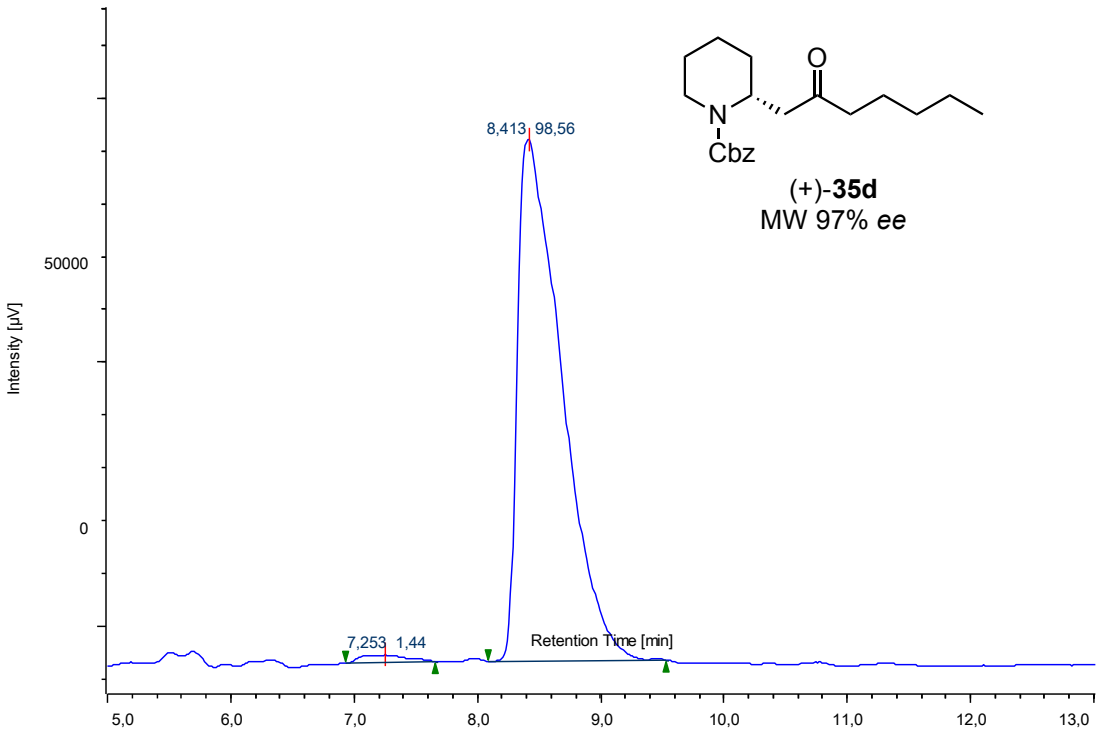


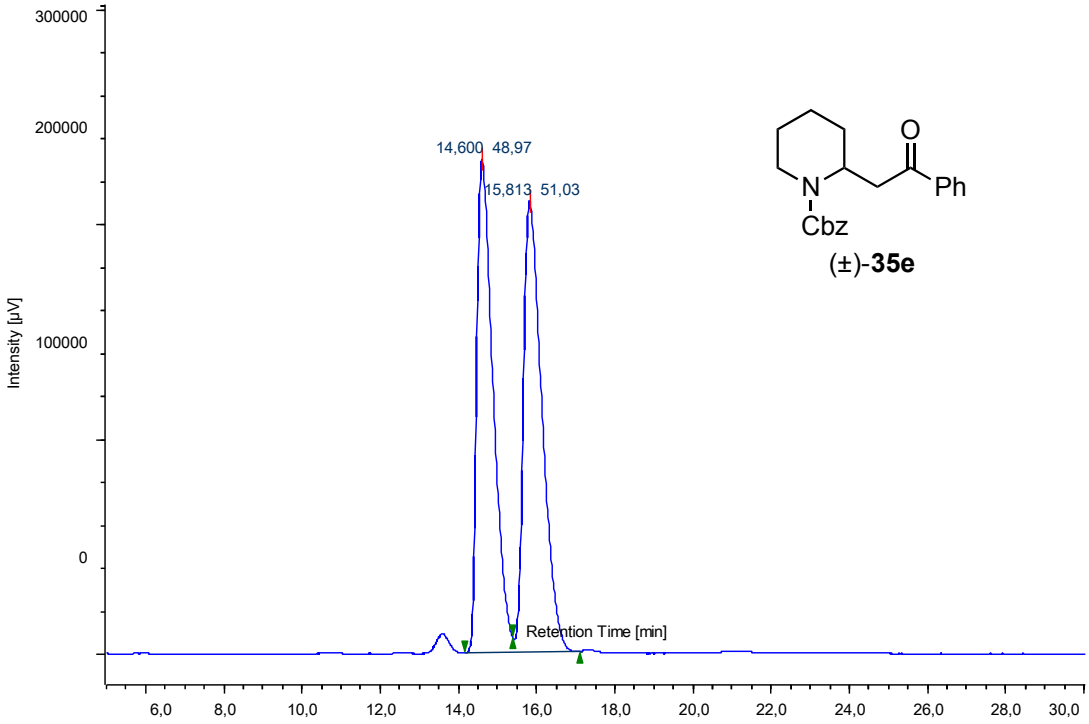
(+)-**35c**
MW 96% *ee*



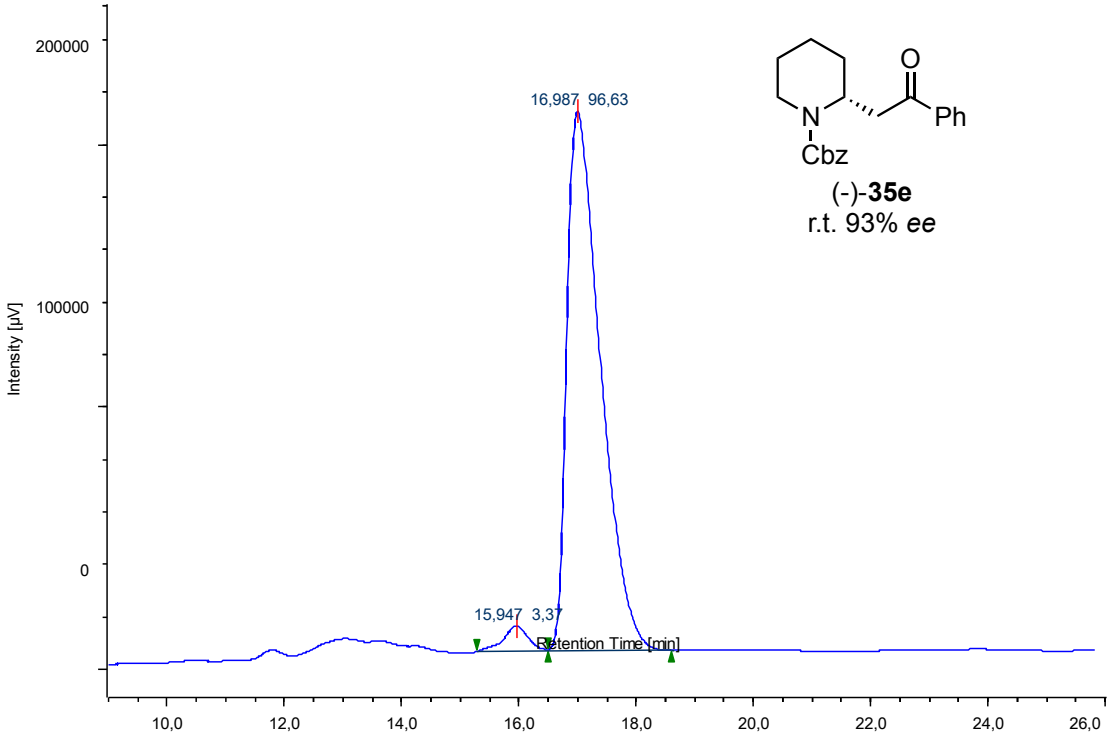
(±)-**35d**


8,413 98,83
50000
0
Intensity [µV]
7,107 1,17
Retention Time [min]
5,0
6,0
7,0
8,0
9,0
10,0
11,0
12,0
13,0
O
N
Cbz
(+)-35d
r.t. 98% ee

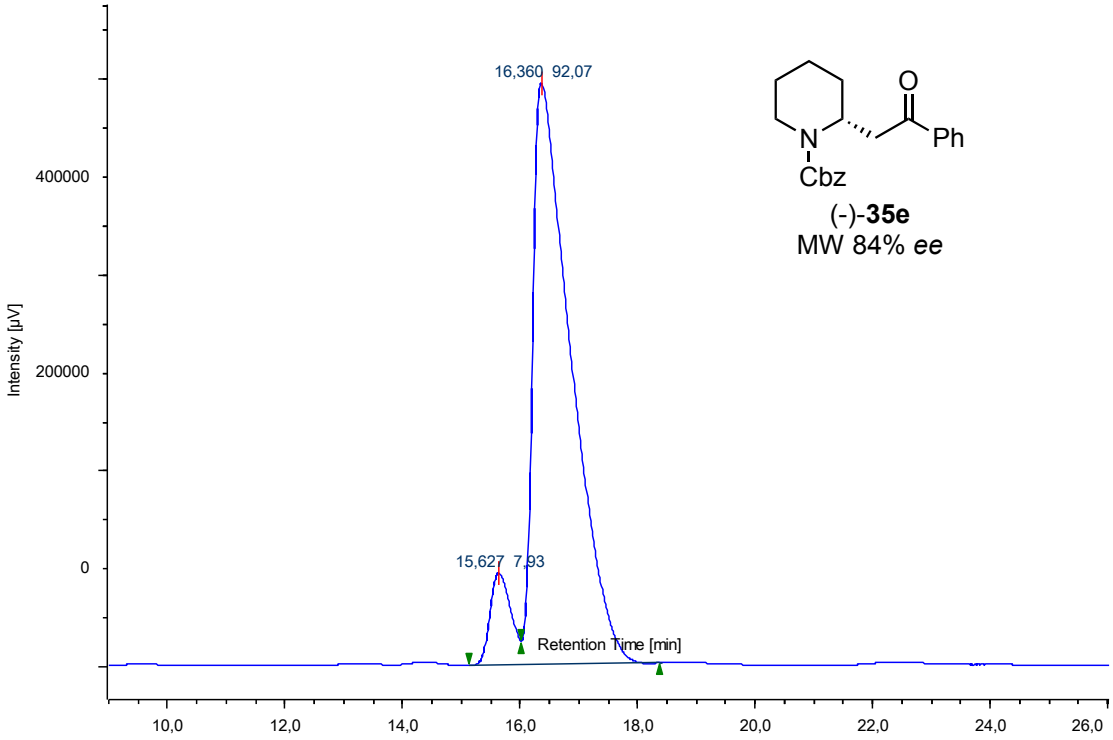

8,413 98,56
50000
0
Intensity [µV]
7,253 1,44
Retention Time [min]
5,0
6,0
7,0
8,0
9,0
10,0
11,0
12,0
13,0
O
N
Cbz
(+)-35d
MW 97% ee



(±)-**35e**



(-)-**35e**
r.t. 93% *ee*



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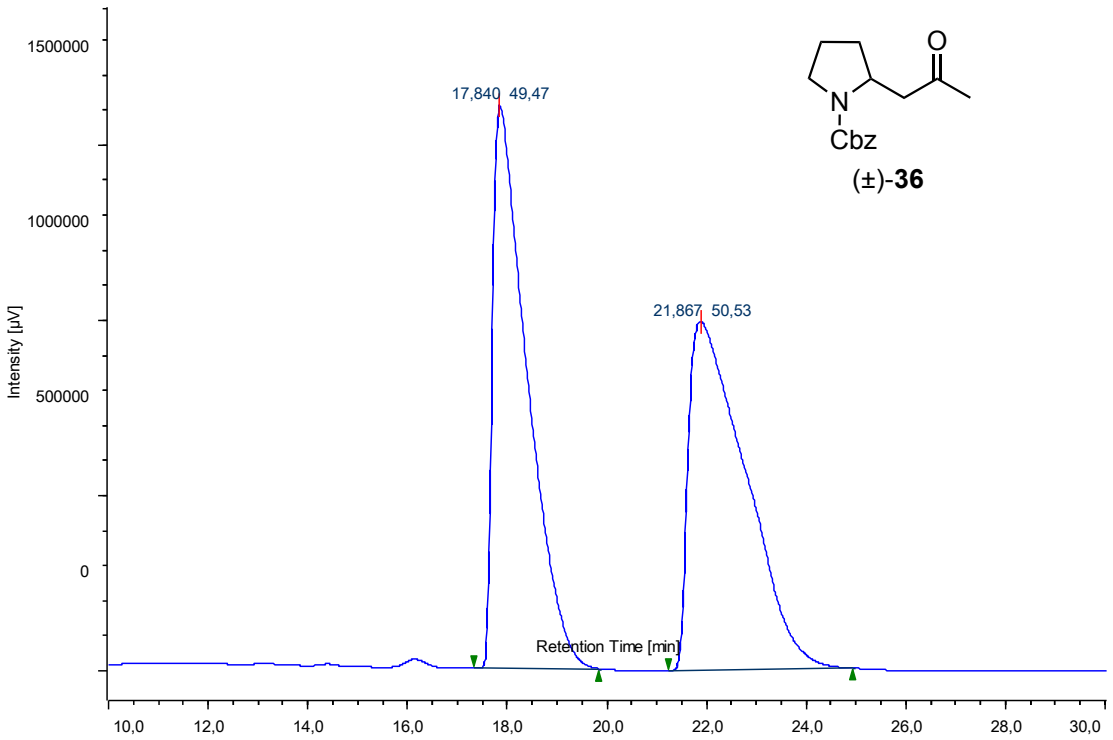
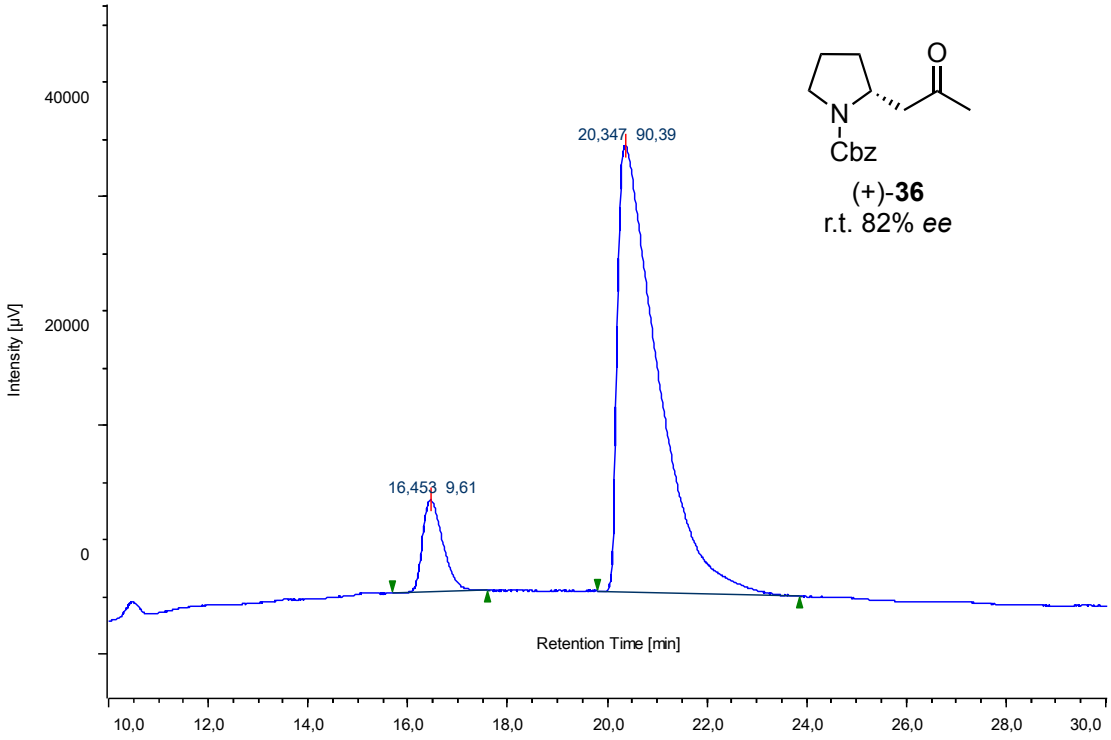
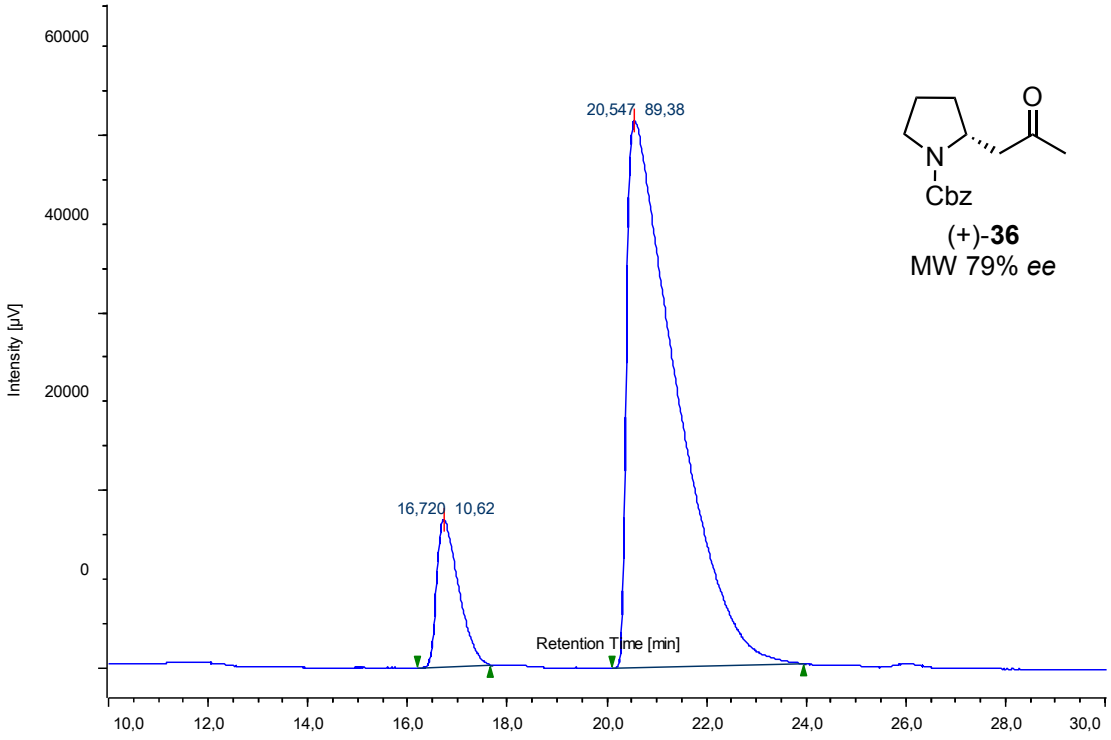


(±)-**36**



(+)-**36**
r.t. 82% *ee*



(+)-**36**
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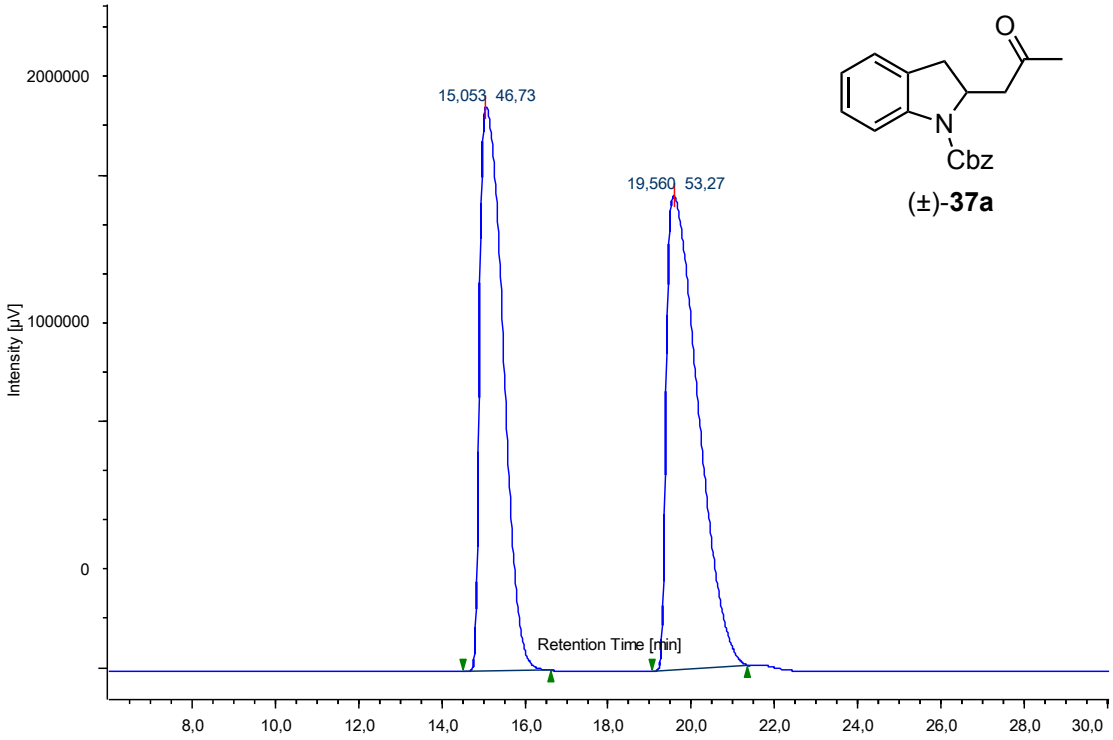
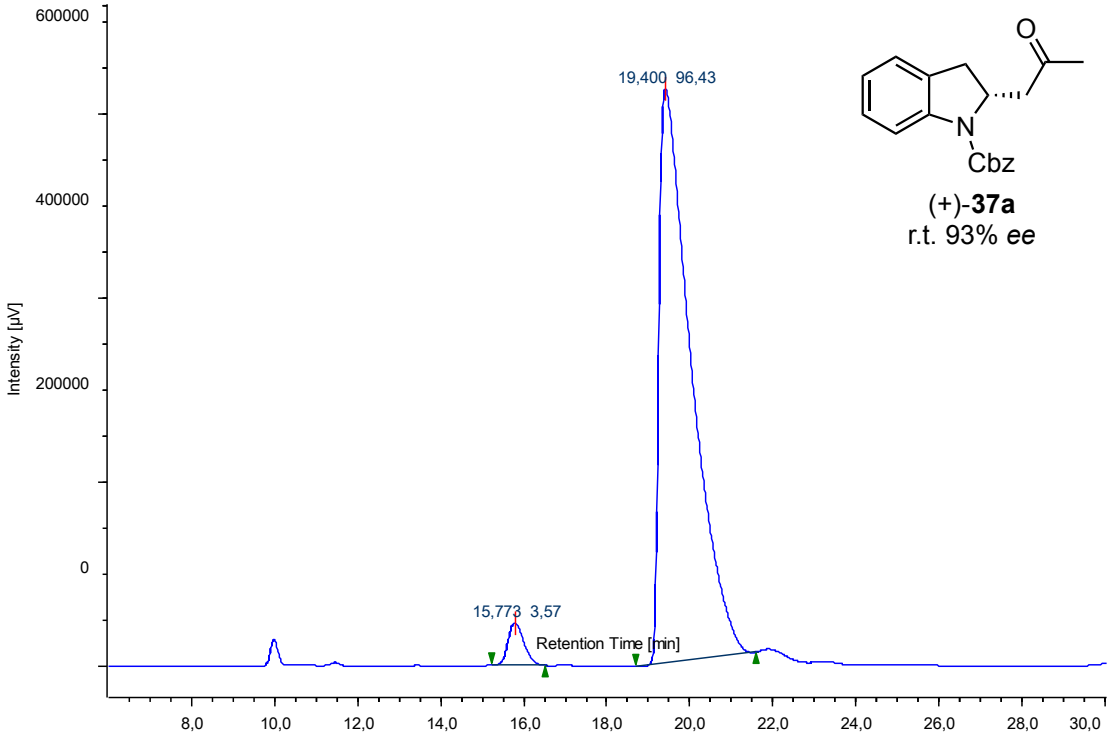


(±)-**37a**



(+)-**37a**
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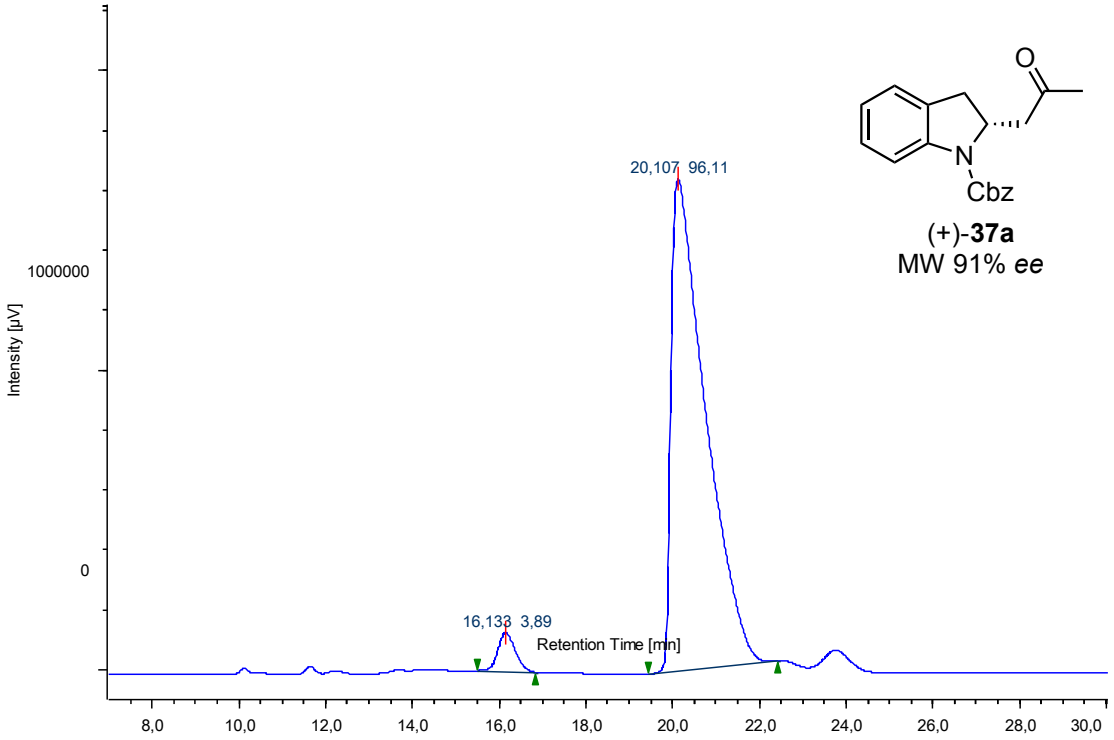
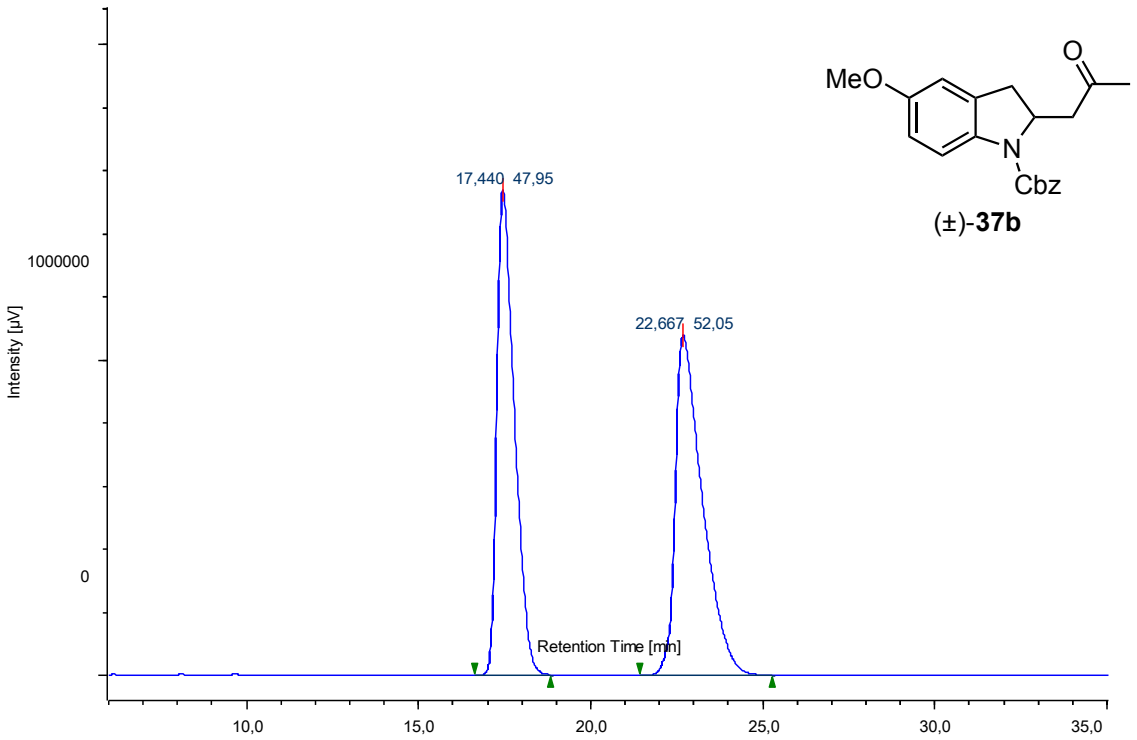
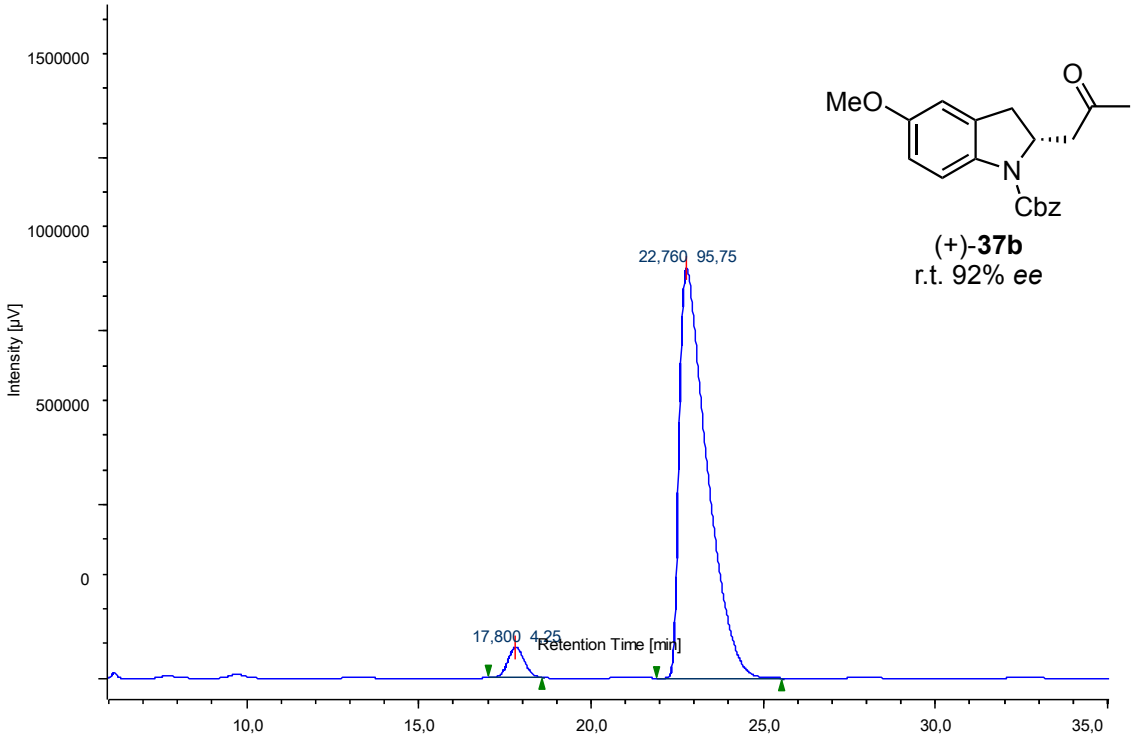


(+)-**37a**
MW 91% *ee*



(±)-**37b**



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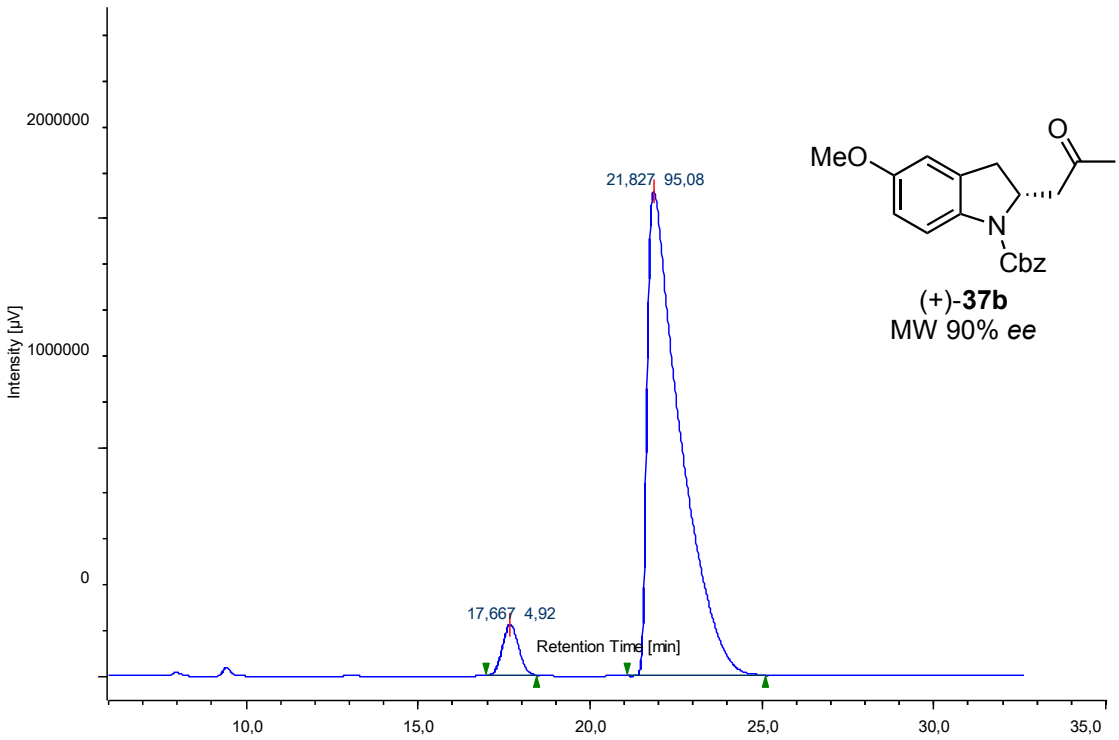

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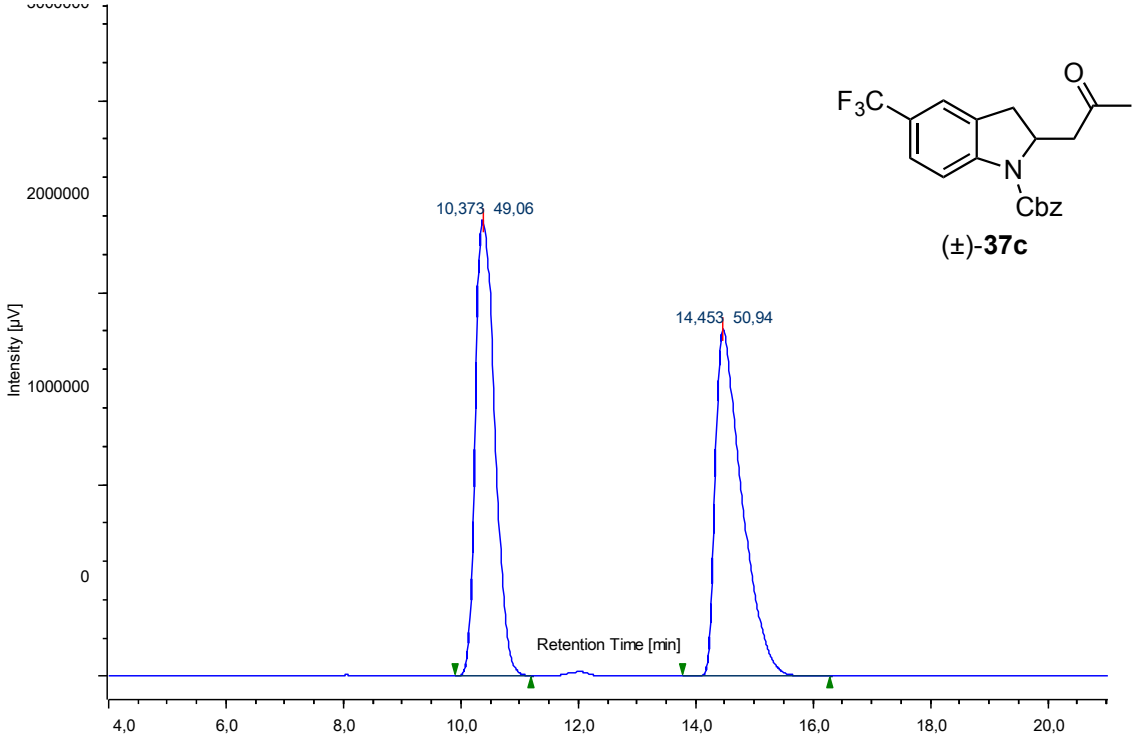
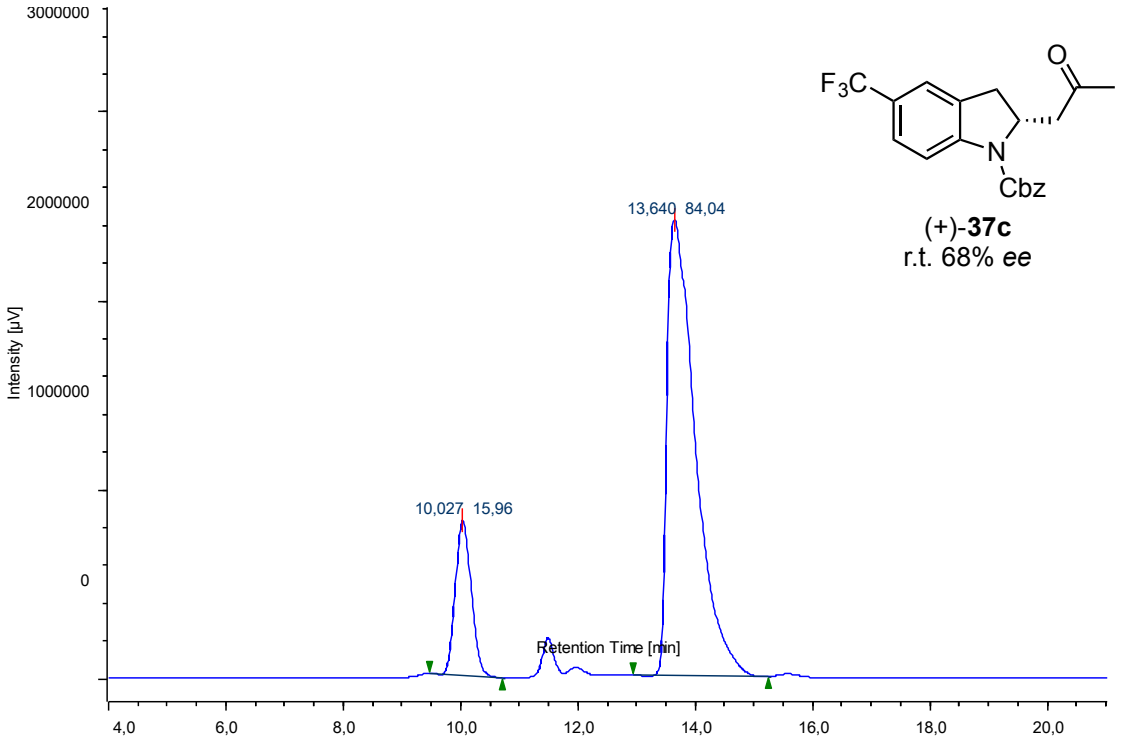
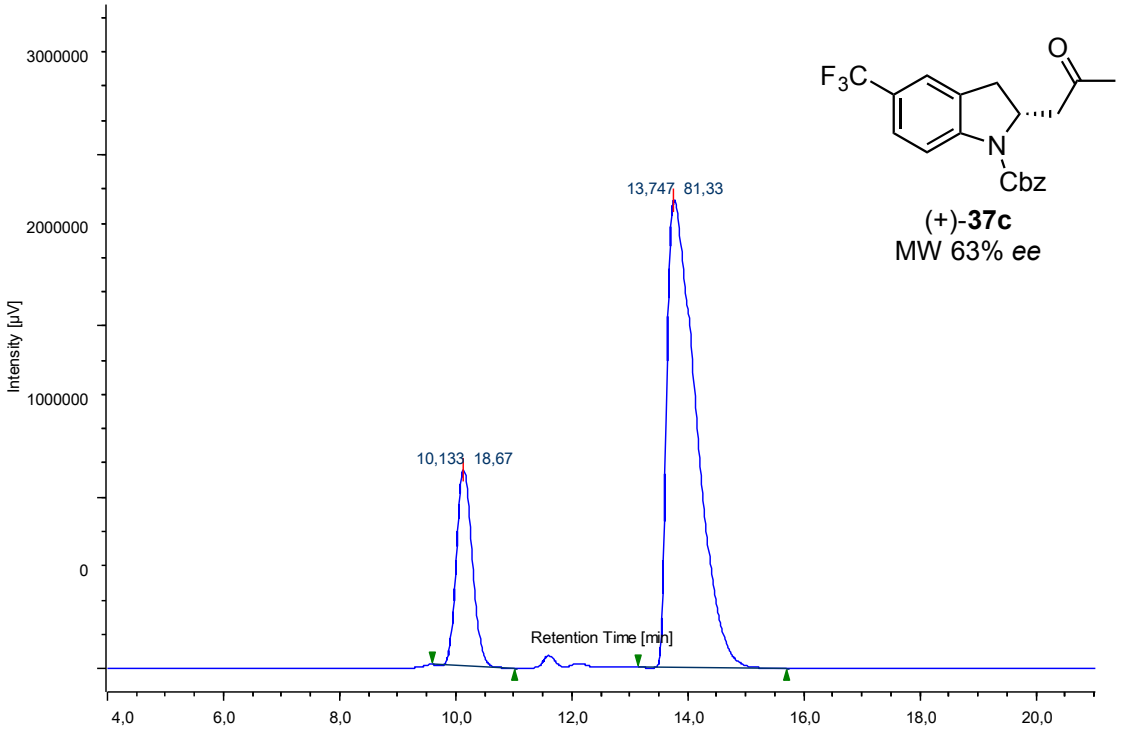


(±)-**37c**



(+)-**37c**
r.t. 68% *ee*



(+)-**37c**
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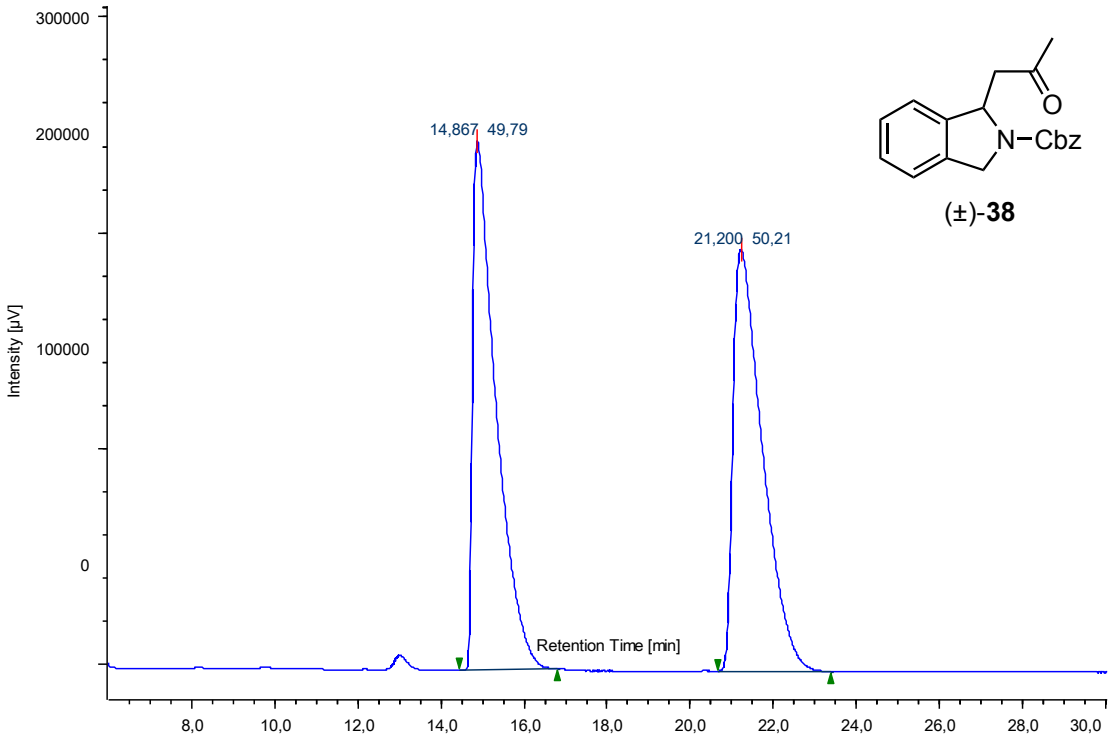
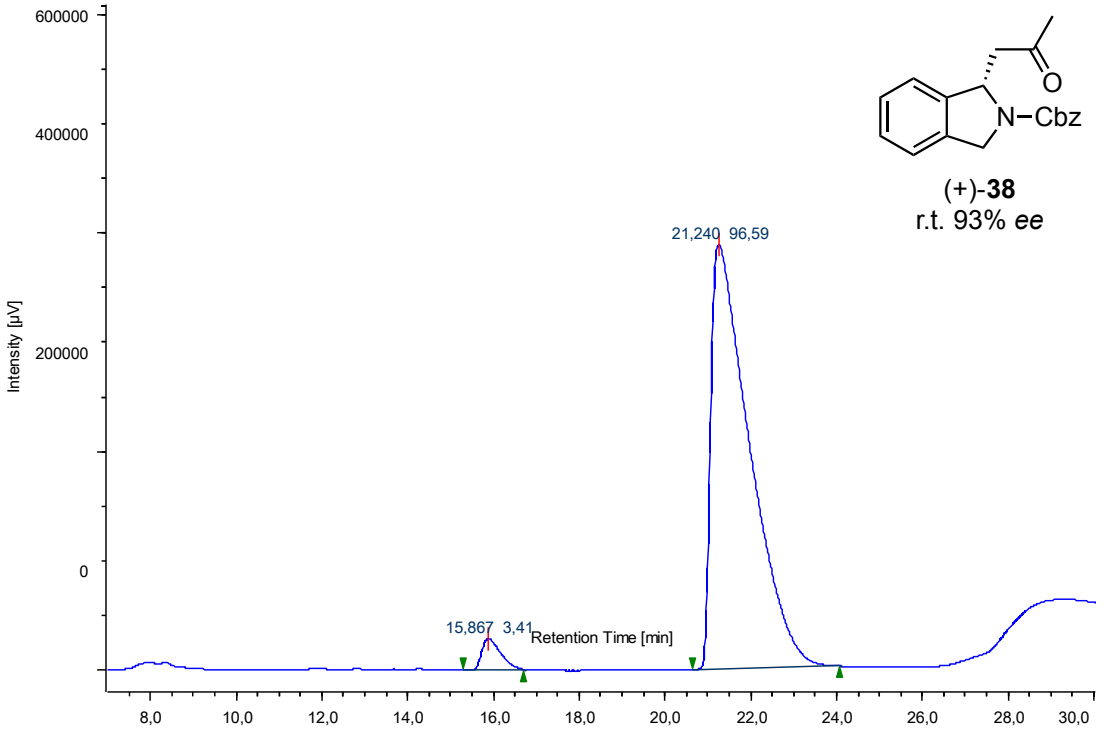


(±)-**38**



(+)-**38**
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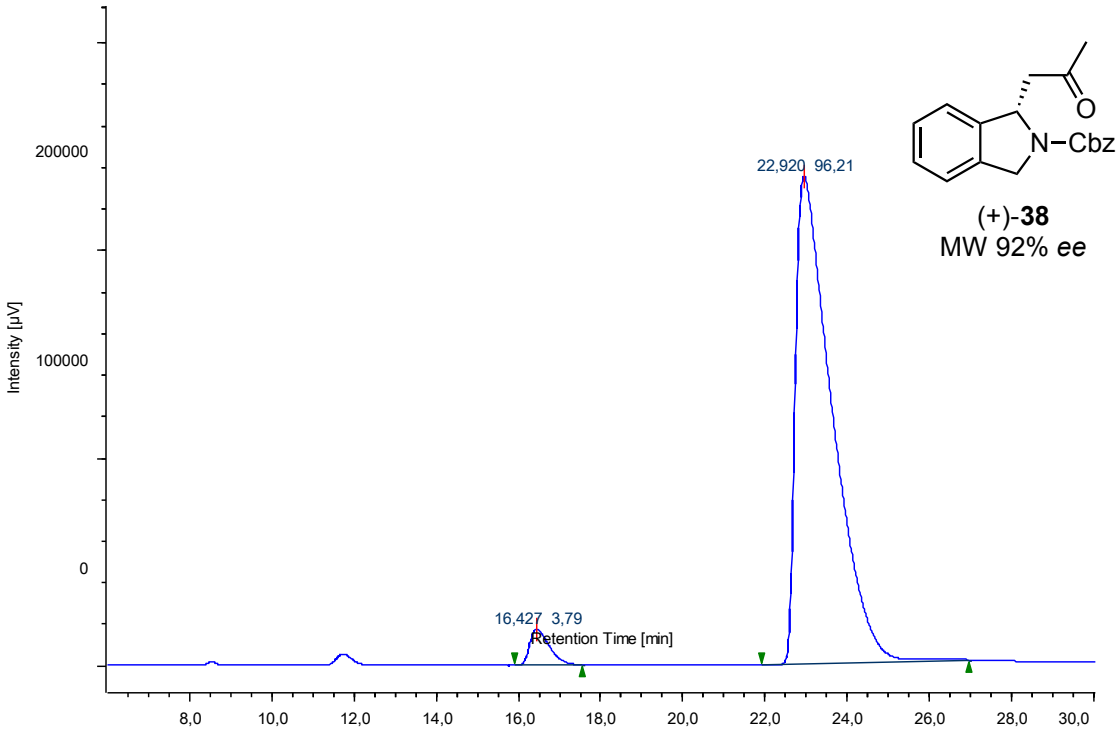
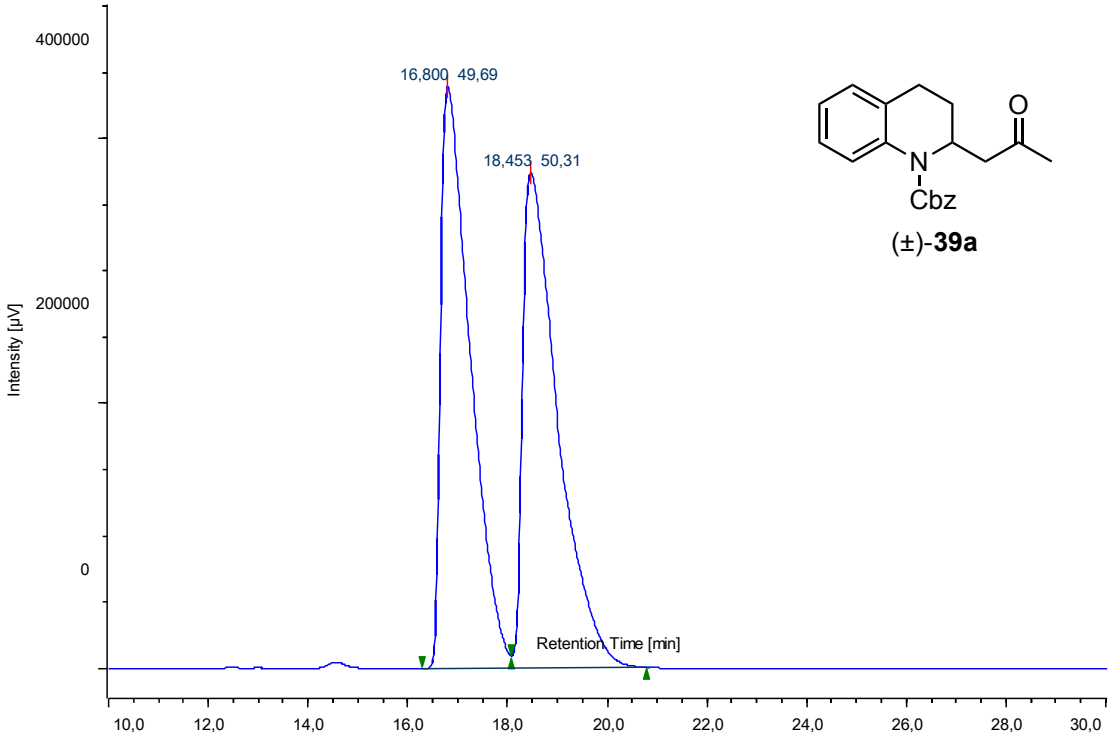
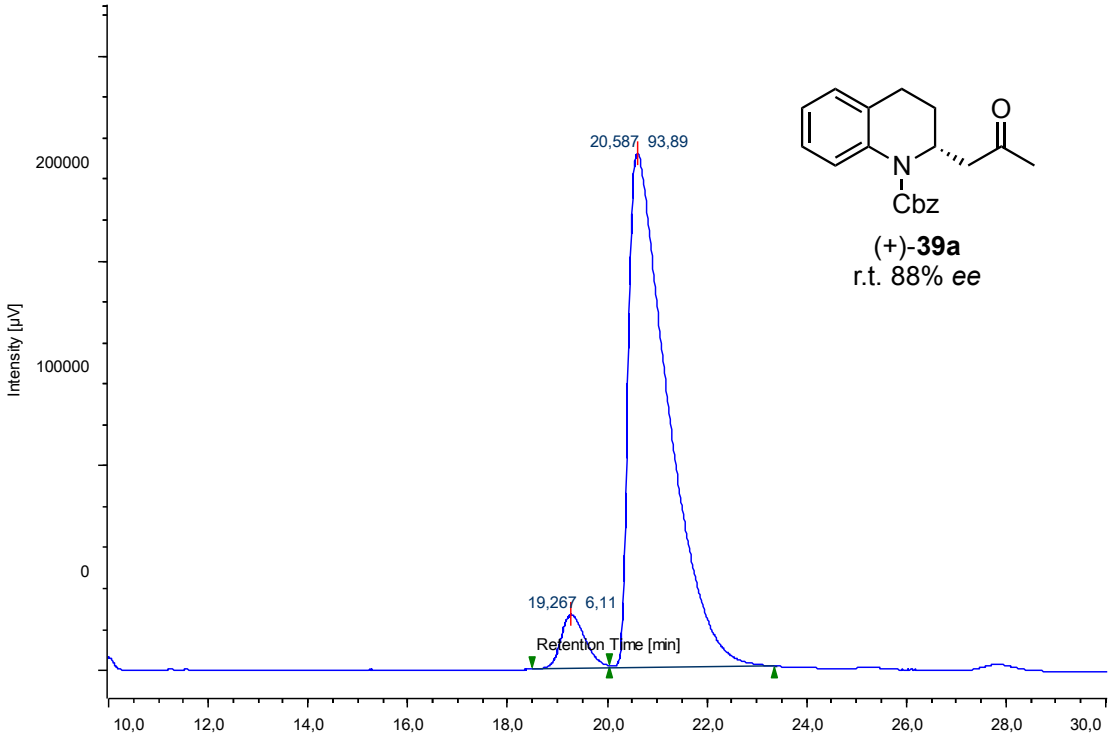


(+)-**38**
MW 92% *ee*



(±)-**39a**



(+)-**39a**
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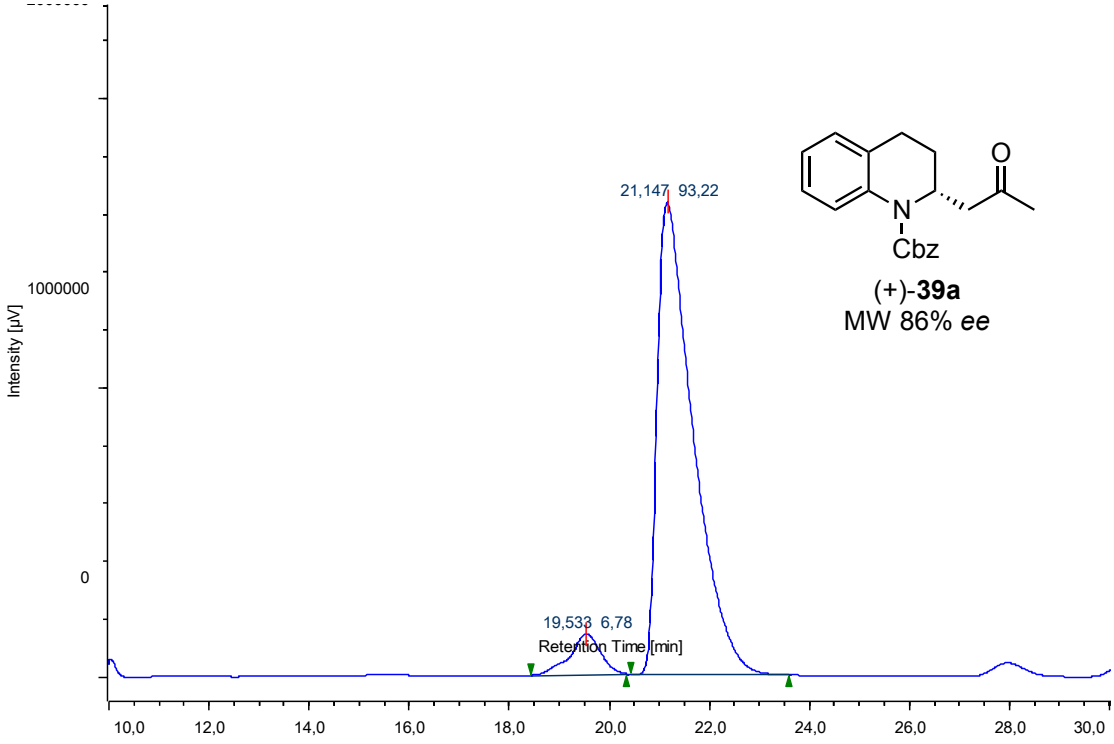
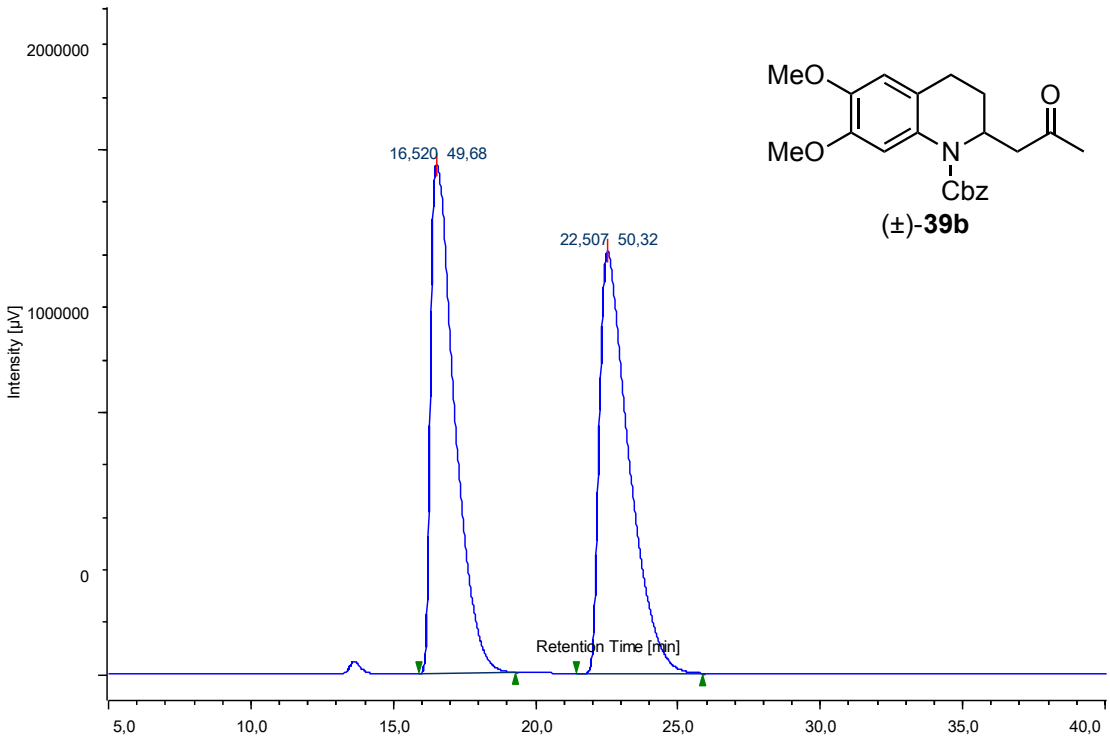


(+)-**39a**
MW 86% *ee*



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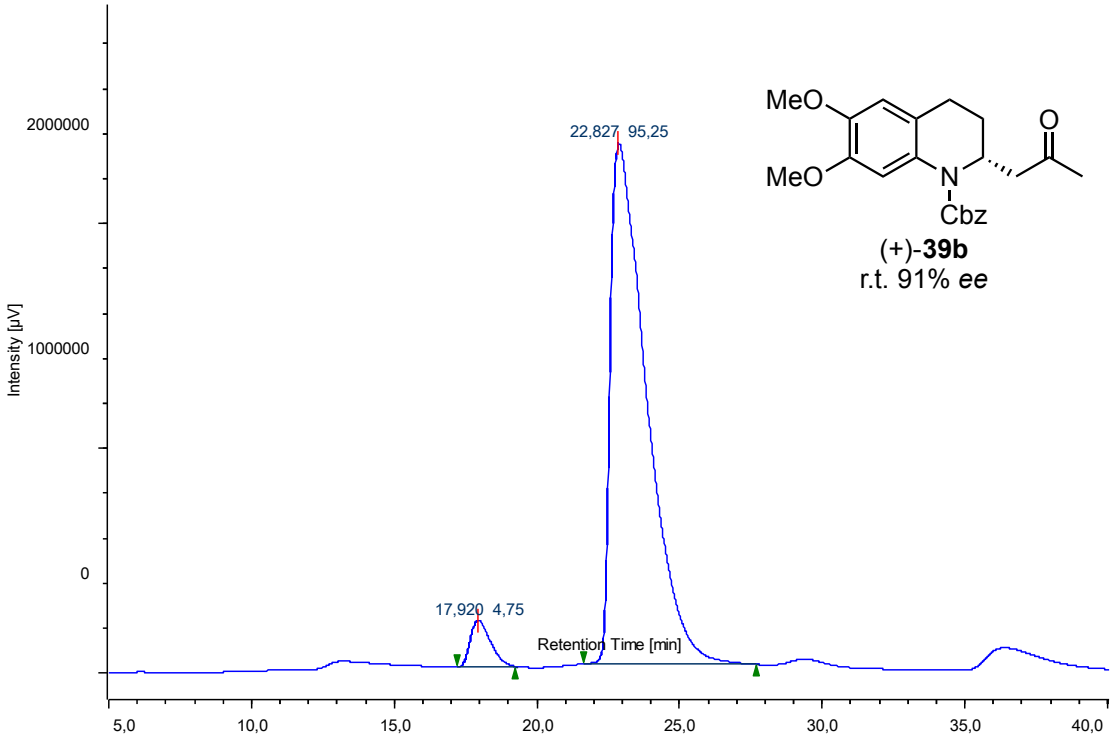
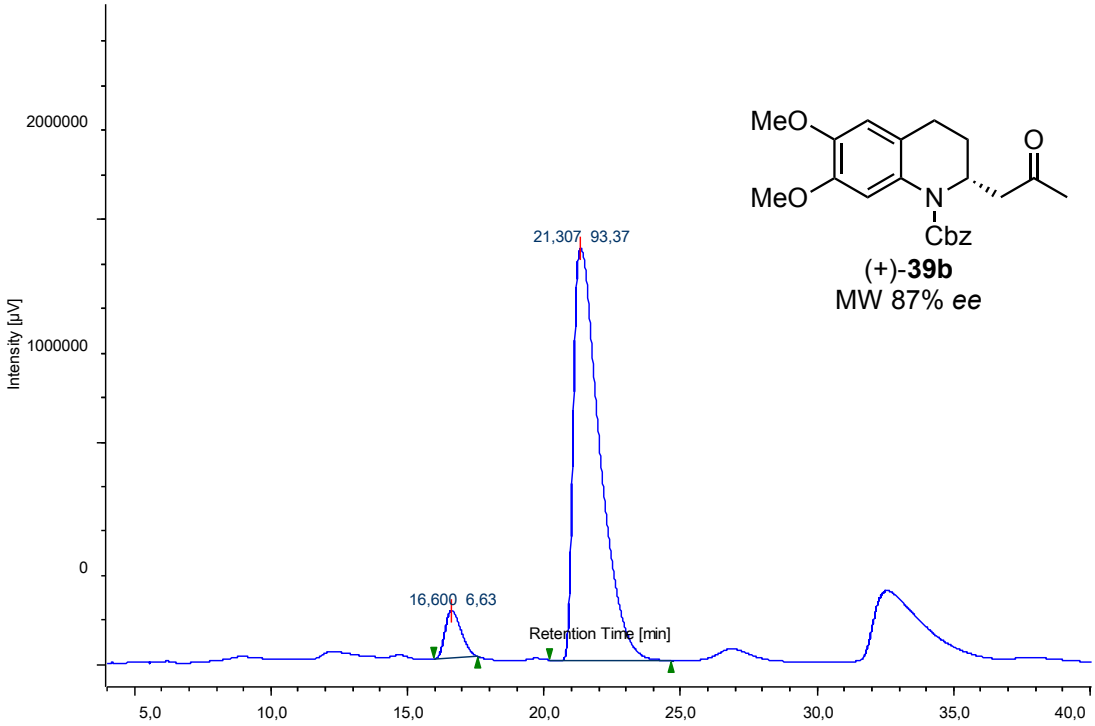
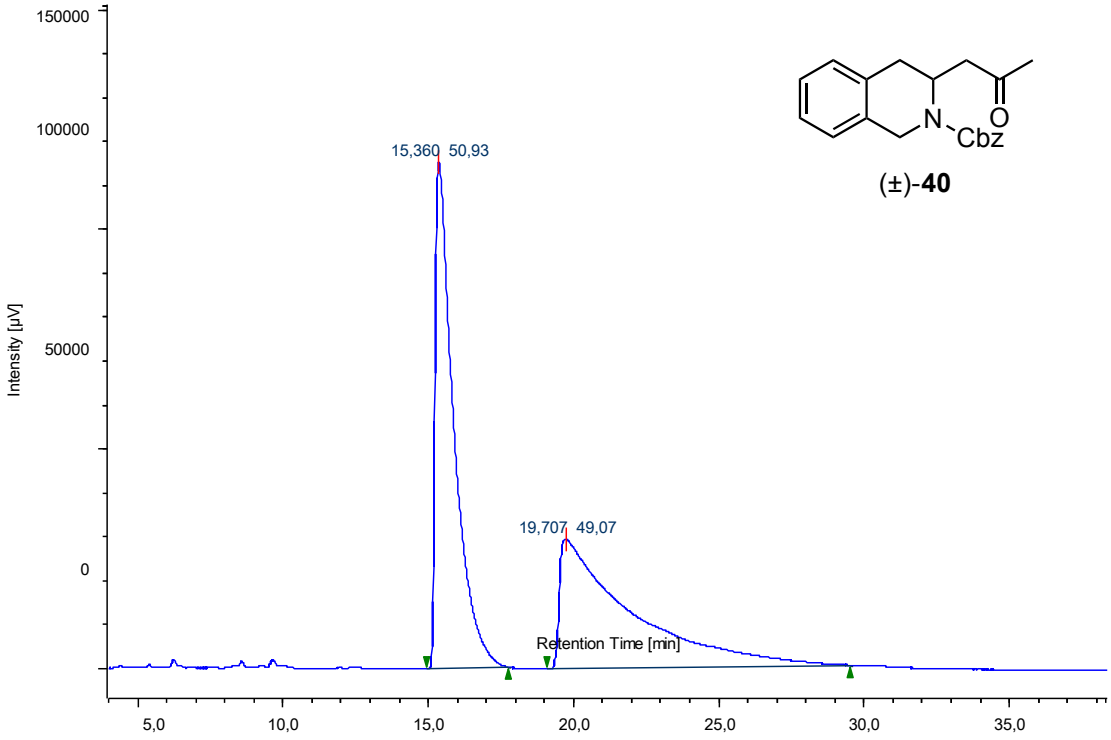


(+)-**39b**
r.t. 91% *ee*



(+)-**39b**
MW 87% *ee*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100000
50000
0
Intensity [µV]
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19,707 49,07
Retention Time [min]
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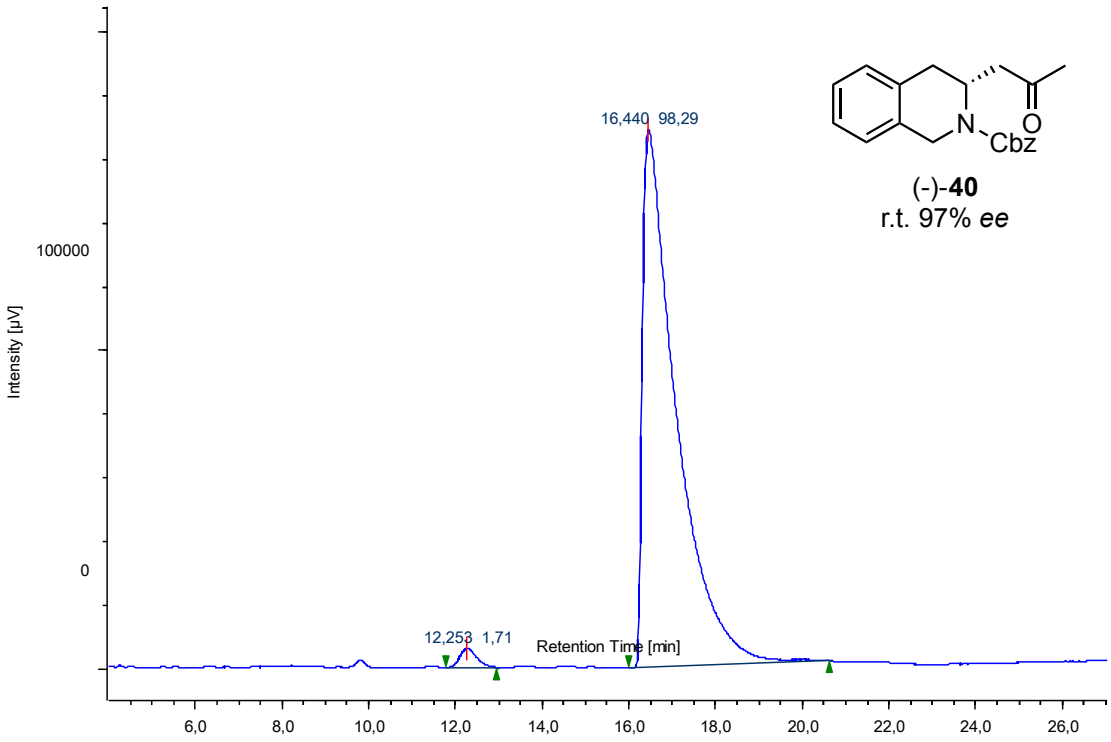
15,0
20,0
25,0
30,0
35,0
N
O
Cbz

(±)-**40**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12,0
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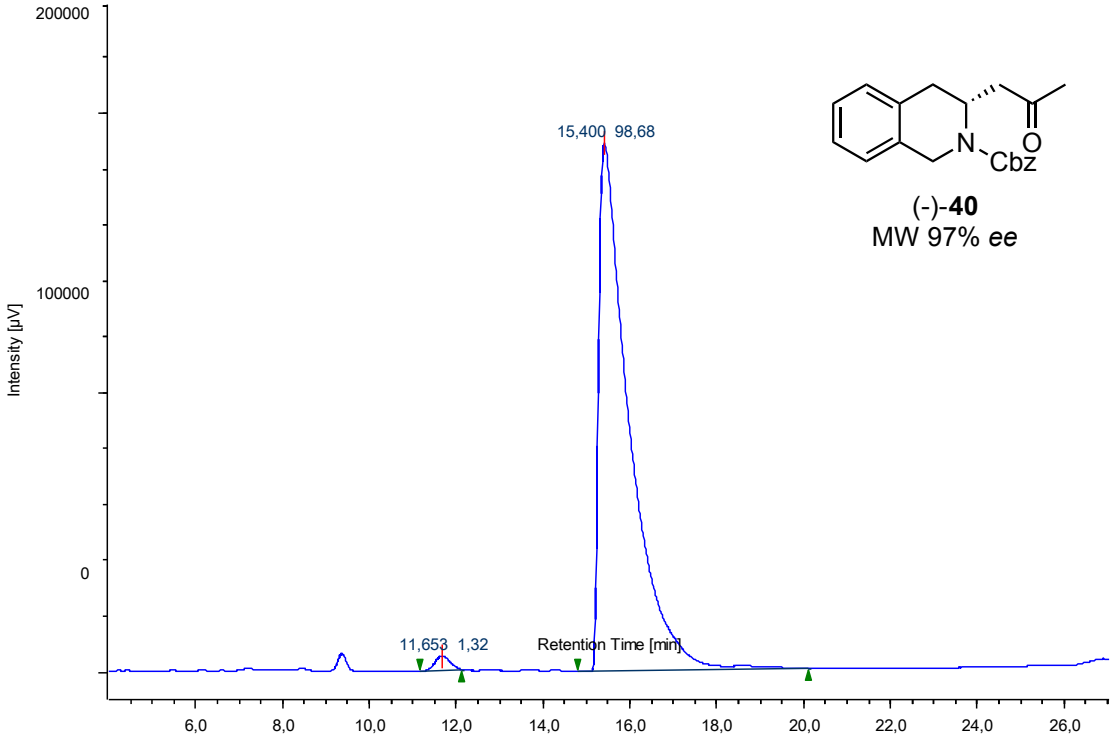
16,0
18,0
20,0
22,0
24,0
26,0
N
O
Cbz

(-)-**40**
r.t. 97% *ee*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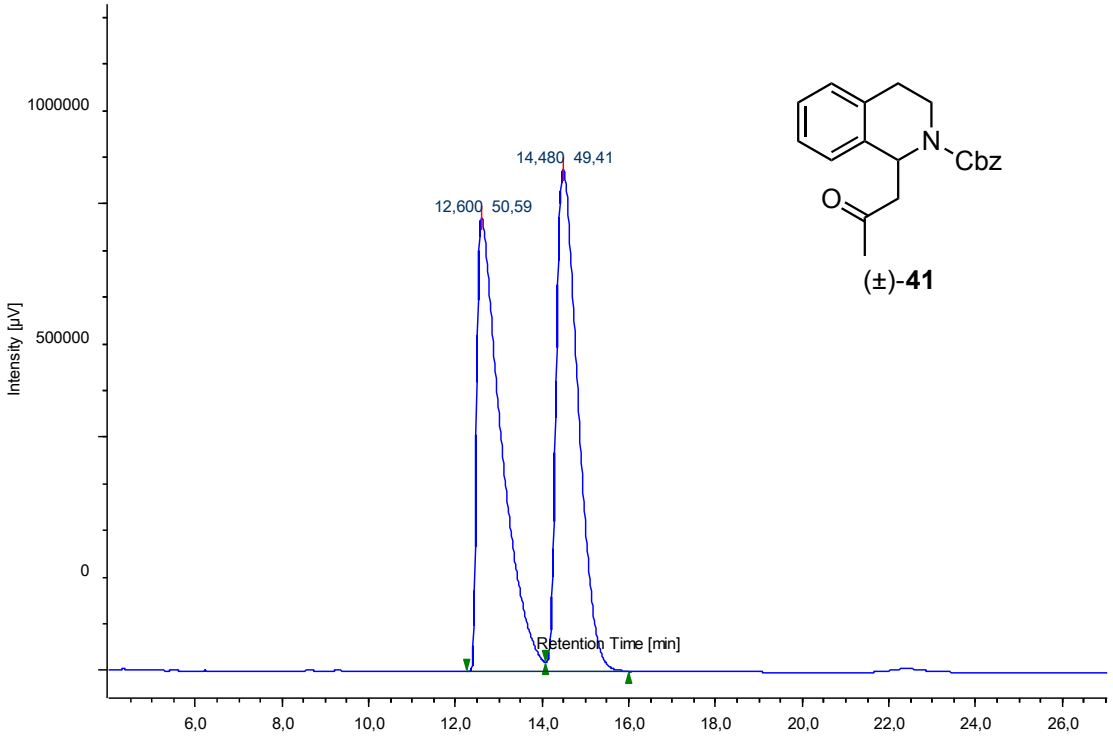
26,0
N
Cbz
O

(-)-**40**
MW 97% *ee*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500000
0
Intensity [µV]
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12,600 50,59
Retention Time [min]
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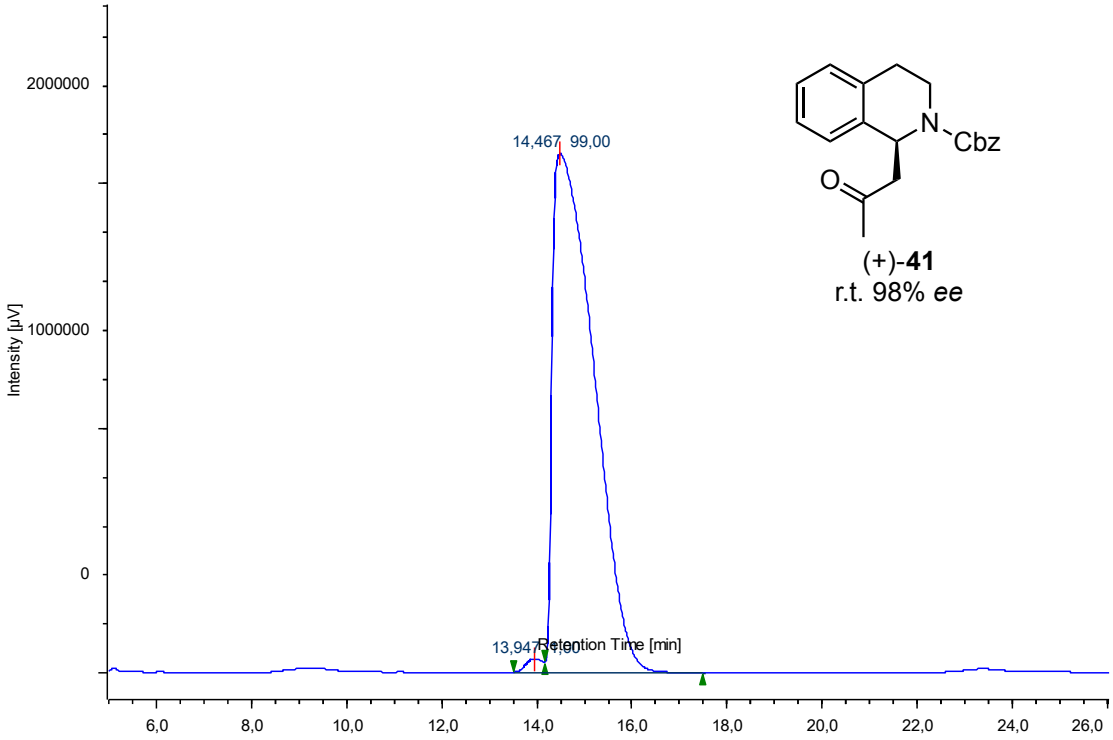
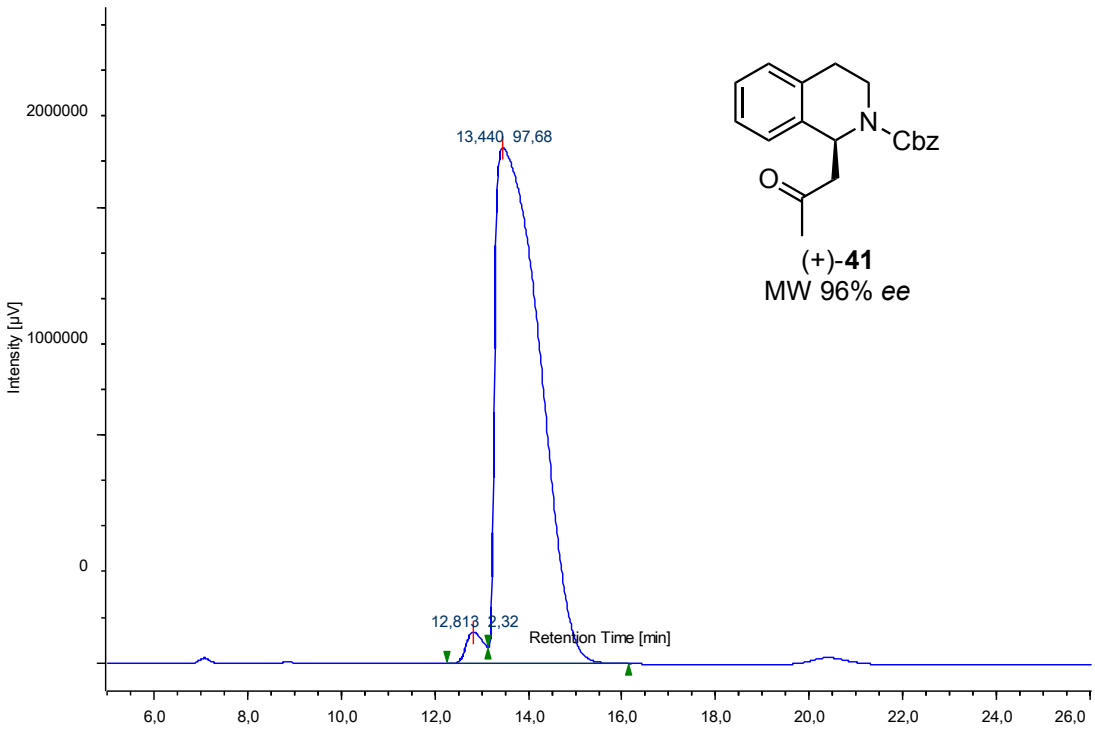
20,0
22,0
24,0
26,0
N
Cbz
O

(±)-**41**



(+)-**41**
r.t. 98% *ee*



(+)-**41**
MW 96% *ee*

CHAPTER 2:

Organocatalytic enantioselective intramolecular *aza*-Michael reaction with conjugated ester surrogates

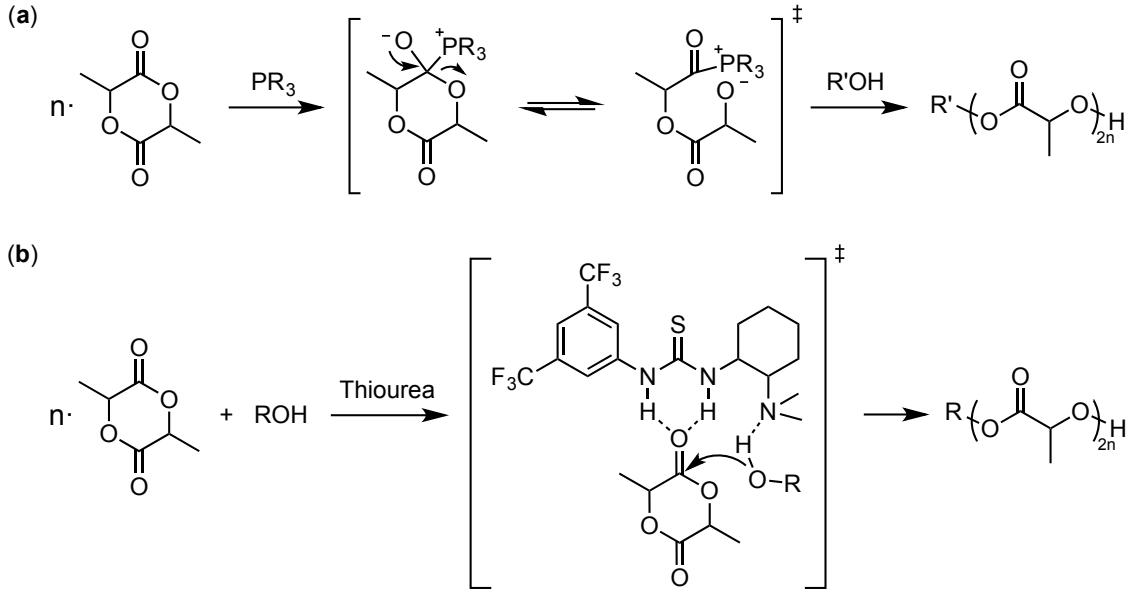
2.1. Background

2.1.1. ORGANOCATALYTIC ACTIVATION OF ESTERS AND ESTER SURROGATES

Ester functionality plays a central role in biological and synthetic organic transformations. However, its use in the area of organocatalysis is still quite limited because the most commonly employed organocatalytic activation modes, the iminium and enamine pathways, cannot be applied to esters unlike their ketone and aldehyde counterparts. Therefore, other activation mechanisms are required to make esters and acid derivatives more reactive.

In 2001 it was described the first organocatalytic approach to the living ring-opening polymerization (ROP) of lactide through a transesterification reaction.[180] This new approximation implied a highly desirable alternative to traditional organometallic approaches for the development of biodegradable polymers. Since then, organic catalysis for this kind of controlled polymerizations has been extended employing assorted organocatalysts such as *N*-heterocyclic carbenes[181] guanidines,[182] phosphines[183] or pyridine derived bases[180] which involved a nucleophilic mechanism (Scheme 2.1.a), or thioureas[184] and protonated phosphazenes[185] working through a hydrogen-bonding activation (Scheme 2.1.b).

[180] Nederberg, F.; Connor, E. F.; Möller, M.; Glauser, T.; Hedrick, J. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 2712–2715.
[181] Connor, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914–915.
[182] a) Lohmeijer, B. G. G.; Pratt, R. C.; Leibfarth, F.; Logan, J. W.; Long, D. A.; Dove, A. P.; Nederberg, F.; Choi, J.; Wade, C.; Waymouth, R. M.; Hedrick, J. L. *Macromolecules* **2006**, *39*, 8574–8583. b) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556–4557.
[183] Myers, M.; Connor, E. F.; Glauser, T.; Möck, A.; Nyce, G.; Hedrick, J. L. *J. Polym. Sci. Part A Polym. Chem.* **2002**, *40*, 844–851.
[184] Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 13798–13799.
[185] Jardel, D.; Davies, C.; Peruch, F.; Massip, S.; Bibal, B. *Adv. Synth. Catal.* **2016**, *358*, 1110–1118.



Scheme 2.1. ROP of a lactide by (a) phosphines or (b) thioureas.

On the other hand, regarding the activation of ***conjugated esters in asymmetric organocatalysis***, these and other organic catalysts have also been used in different chemical transformations. Among them, *N*-heterocyclic carbenes (NHC) are probably the most widely used family of catalysts for this purpose.[186] Initially they were employed to catalyse transesterification reactions activating the ester moiety.[187] Recently, they have been used for the HOMO activation of saturated α-aryl acetic esters to generate enolate intermediates for enantioselective reactions; [188] and in formal LUMO activations of α,β-unsaturated esters for highly enantioselective reactions, generally with enamides.[189] In the latter, the key step involves the addition of the NHC catalyst to the conjugated ester to form an α,β-unsaturated acyl azolium intermediate, which has an increased electrophilicity at the β-carbon. However, the formal

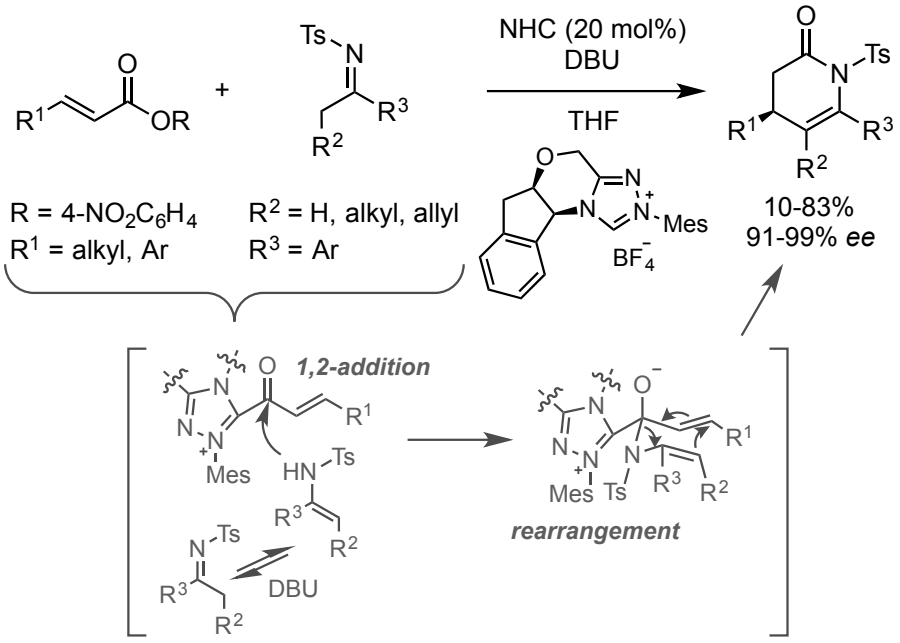
[186] a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000. b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

[187] a) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. **2002**, 2–5. b) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587–3590. c) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177. d) Candish, L.; Lupton, D. W. *Org. Biomol. Chem.* **2011**, *9*, 8182–8189. e) Candish, L.; Lupton, D. W. *Chem. Sci.* **2012**, *3*, 380–383. f) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906–4917.

[188] Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154–2157.

[189] a) Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8592–8596. b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956–4959. c) Chauhan, P.; Enders, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 1485–1487.

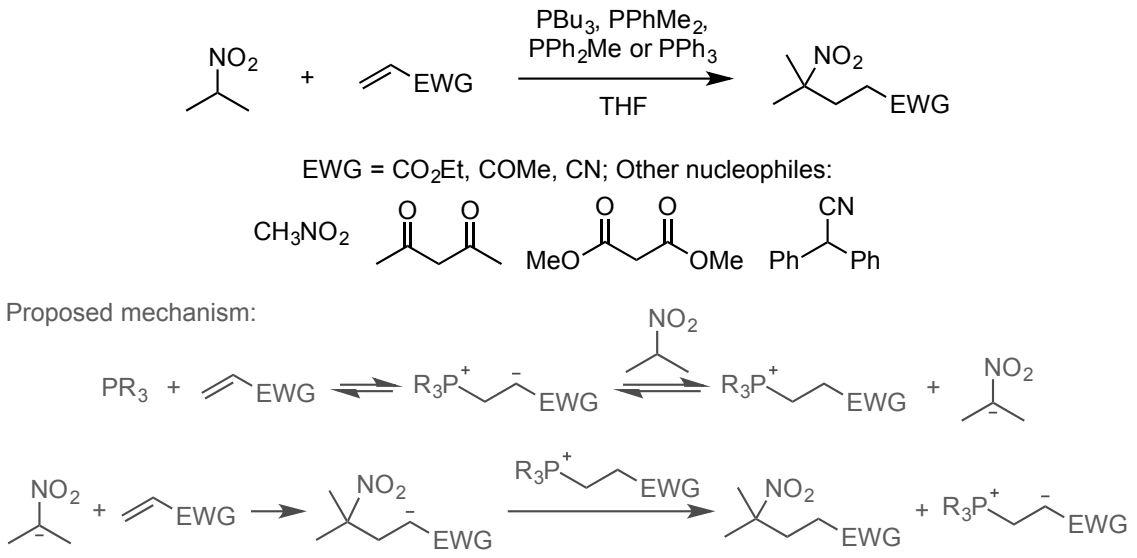
1,4-addition is postulated to be achieved through a 1,2-addition followed by an *aza*-Claisen type rearrangement (Scheme 2.2).



Scheme 2.2. Activation of conjugated esters for a domino addition/lactamization.

The use of nucleophilic phosphine organocatalysts to activate unsaturated carbonyl compounds was published by Roush in 2004.[190] It was described the activation of conjugated esters by phosphines in several transformations, such as the Rauhut-Currier, the Morita-Baylis-Hillman and the Michael addition reactions among others. Concretely, for the latter the proposed mechanism involves the formation of a zwitterionic phosphine-alkene adduct intermediate, that behaves as the general base of the reaction deprotonating the carbon acid of the nucleophile, which then undergoes Michael addition to another α,β-unsaturated carbonylic compound (Scheme 2.3).

[190] Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.



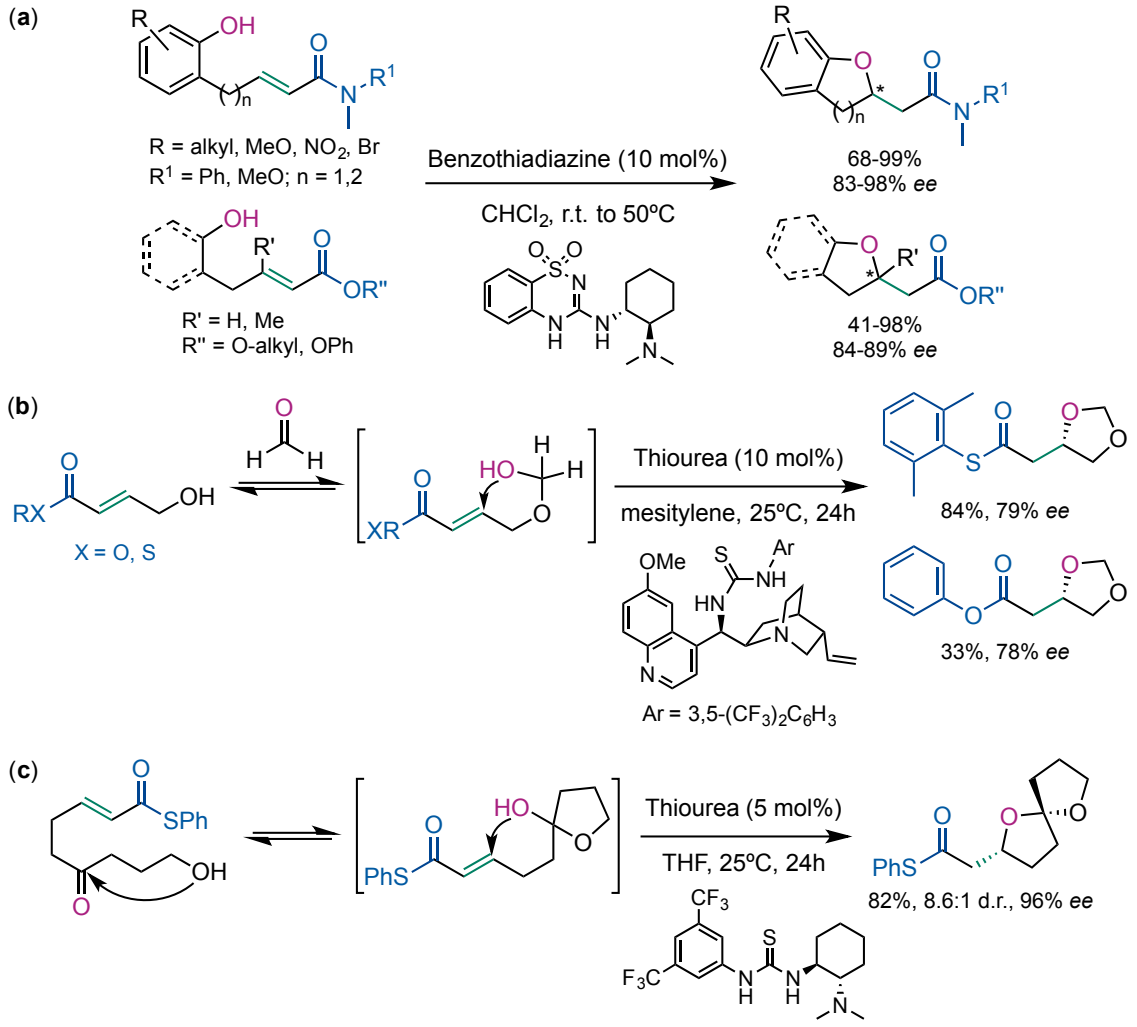
Scheme 2.3. Phosphine-catalysed Michael addition of carbon acids.

Regarding hydrogen bonding organocatalysts, there have been described a great variety of examples and a selection of the more representatives will be outlined below. They are classified according to the type of the transformation, *oxa*-, *sulfa*- and classic Michael reactions, and in some cases also depending on the nature of the catalyst employed.

Takemoto[191] and later Matsubara,[192] recently published enantioselective intramolecular *oxa*-Michael reactions of α,β-unsaturated amides, thioesters and esters. On the one hand, Takemoto's report employs a chiral benzothiadiazine to activate conjugated amides and esters as electrophiles and facilitate the production of a variety of *O*-heterocycles with very good yields and enantioselectivities (Scheme 2.4.a). On the other hand, Matsubara introduced isolated examples of conjugated thioesters or esters as Michael acceptors. First in the preparation of cyclic acetals, employing formaldehyde as nucleophile in an asymmetric oxa-Michael addition to γ-hydroxy-α,β-unsaturated carbonyl compounds using a quinine-derived thiourea organocatalyst through hemiacetal intermediates (Scheme 2.4.b). After, in the asymmetric synthesis of spiroketal structures through the relay formation of contiguous oxacycles, in which the

[191] Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 11114–11118.
[192] a) Yoneda, N.; Hotta, A.; Asano, K.; Matsubara, S. *Org. Lett.* **2014**, *16*, 6264–6266. b) Yoneda, N.; Fukata, Y.; Asano, K.; Matsubara, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 15497–15500. c) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Biomol. Chem.* **2014**, *12*, 119–122.

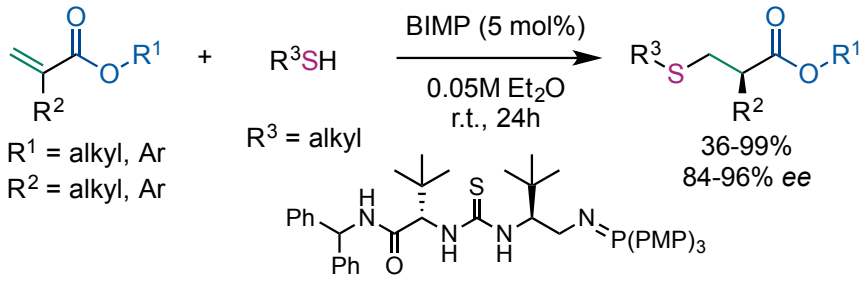
bifunctional aminothiourea organocatalyst imparts high enantioselectivity (Scheme 2.4.c).



Scheme 2.4. Asymmetric intramolecular *oxa*-Michael reactions

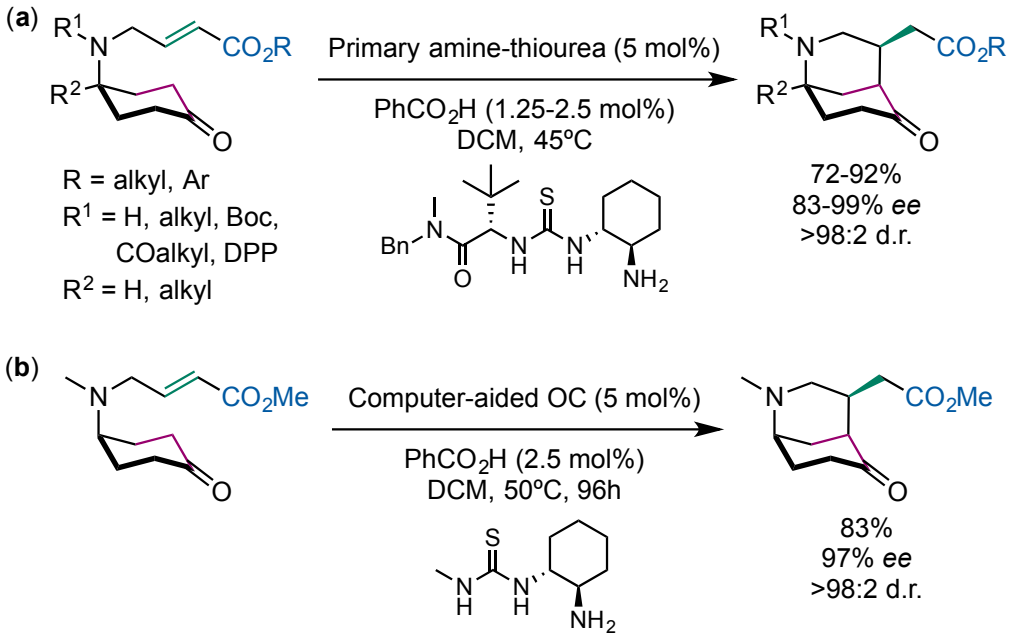
Recently, it has been described by Dixon the enantioselective *sulfa*-Michael addition to unactivated α-substituted acrylate esters using a second generation bifunctional iminophosphorane (BIMP) superbase organocatalyst.[193] Here they overcome the low inherent conjugated ester electrophilicity by raisin the Brønsted basicity of the catalyst. In this way, there were achieved good levels of reactivity and excellent enantioselectivities across a diverse range of alkyl thiols and acrylate esters (Scheme 2.5).

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



Scheme 2.5. *Sulfa*-Michael addition of thiol pro-nucleophiles to conjugated esters.

The same year, Dixon's group also published the employment of simple aminocatalysts for the enantioselective desymmetrization of prochiral cyclohexanones through intramolecular Michael addition to α,β-unsaturated esters.[194] They developed a primary amine catalysed Michael addition of a ketone to unactivated conjugated esters, providing access to the morphan scaffold in high enantio- and diastereoselectivity (Scheme 2.6.a). Computational studies to probe the origins of the high enantiocontrol were performed, and the results of the calculations identified a new low-molecular-weight catalyst that can impart the same level of enantioselectivity (Scheme 2.6.b).

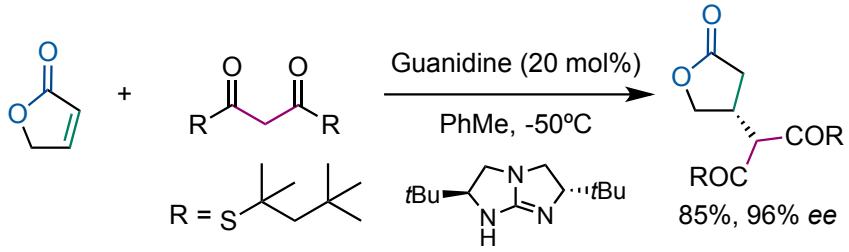


Scheme 2.6. Desymmetrization by intramolecular Michael reaction to conjugated esters.

There have also been reported several guanidine-catalysed enantioselective 1,4-additions of carbon-centred nucleophiles to α,β-

[194] Gammack Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 4899–4903.

unsaturated esters, thioesters and amides.[195] For instance, an unsaturated lactone underwent Michael addition with a 1,3-dithiomalonate to give the desired product with good yield and excellent enantioselectivity in the presence of a catalytic amount of a chiral bicyclic guanidine (Scheme 2.7.).

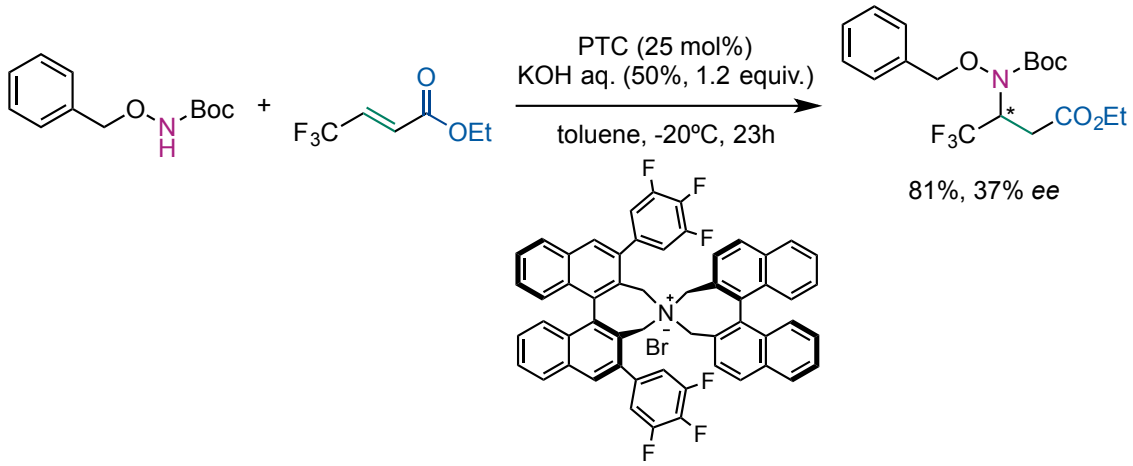


Scheme 2.7. Asymmetric Michael addition to an unsaturated furanone.

2.1.2. *AZA*-MICHAEL REACTIONS WITH ESTER DERIVATIVES AS MICHAEL ACCEPTORS

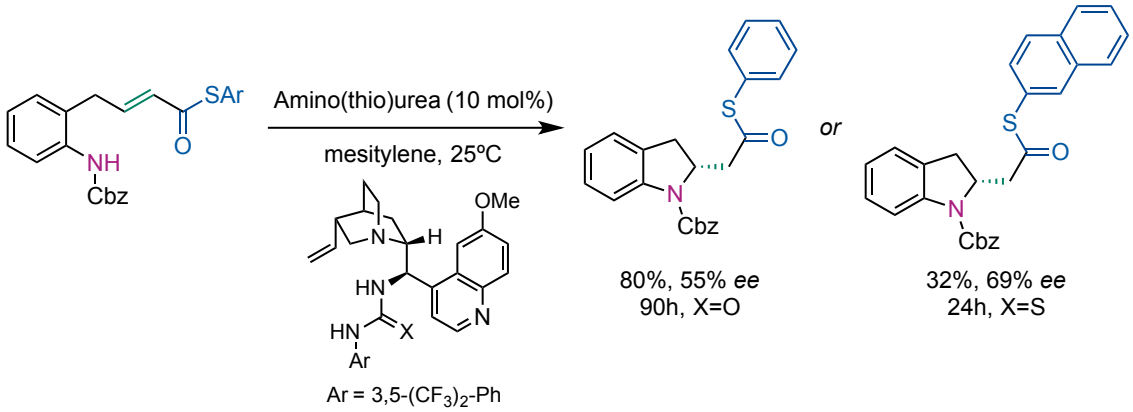
Finally, regarding *aza*-Michael reactions there are really few examples with α,β-unsaturated esters or thioesters. On the one hand, Weiß *et al* reported in 2012 a proof of concept for the asymmetric *aza*-Michael addition with readily available alkyl enoate as substrate in the presence of a chiral phase-transfer catalyst (PTC), leading to the enantioenriched adduct. However, the asymmetric induction remained limited to enantiomeric excesses of up to 37% (Scheme 2.8).[196] The electrophilicity of the Michael acceptor is enhanced by adding a CF_3-substituent at the β-position, whereas the *N*-nucleophile is activated by the α-effect of the alkoxy group.[94] Furthermore, it is necessary the addition of a stoichiometric amount of a basic solution to the reaction mixture.

[195] *Chiral Guanidines in Michael Reactions*, Nájera, C.; Yus, M. Springer Berlin Heidelberg: Berlin, Heidelberg, **2015**; pp. 1–34 and references therein.
[196] Weiß, M.; Borchert, S.; Rémond, E.; Jugé, S.; Gröger, H. *Heteroat. Chem.* **2012**, *23*, 202–209.
[94] Heaton, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 2004–2008.



Scheme 2.8. *Aza*-Michael addition to conjugated esters with an alkoxy carbamate.

Matsubara and Asano reported also two isolated examples of intramolecular *aza*-Michael additions of aniline carbamates to conjugated thioesters by means of bifunctional quinine-derived amino(thio)urea catalysts.[128g] The corresponding 2-substituted indolines were prepared with moderate yields and enantioselectivities (Scheme 2.9).



Scheme 2.9. Asymmetric IMAMR with α,β-unsaturated thioesters to synthesize indolines.

On the other hand, Bandini and Umani-Ronchi published in 2008[111,197] the first and only direct protocol until the moment[198] for *aza*-Michael additions to α,β-unsaturated esters. As it consists on an intramolecular *aza*-Michael

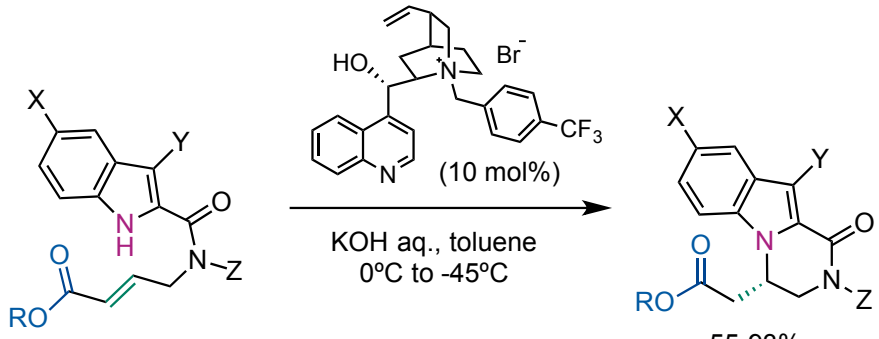
[128g] Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658–3661.

[197] For theoretical studies: Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. Pietro; Stenta, M. *Chem. Eur. J.* **2010**, *16*, 12462–12473.

[111] Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3238–3241.

[198] There have been also used β-keto-esters for IMAMR, but in those cases the enone was the Michael acceptor, activated by the ester at the β-position, which was subsequently removed (Scheme 1.16). a) See ref. 112: Z. Feng, Q.-L. Xu, L.-X. Dai and S.-L. You, *Heterocycles*, **2010**, 80, 765. b) See ref. 113: Liu, X.; Lu, Y. *Org. Lett.* **2010**, *12*, 5592–5595. c) Xiao, X.; Liu, X.; Dong, S.; Cai, Y.; Lin, L.; Feng, X. *Chem. Eur. J.* **2012**, *18*, 15922–15926.

reaction, it has already been mentioned in the corresponding section in Chapter 1. However, given the relevance in this conjugate esters branch, it has been newly referred. Here the indole nitrogen is added to α,β-unsaturated esters affording tricycles with good yields and enantioselectivities by means of phase transfer catalysis with a chiral ammonium salt of cinchonidine derivative (Scheme 2.9).

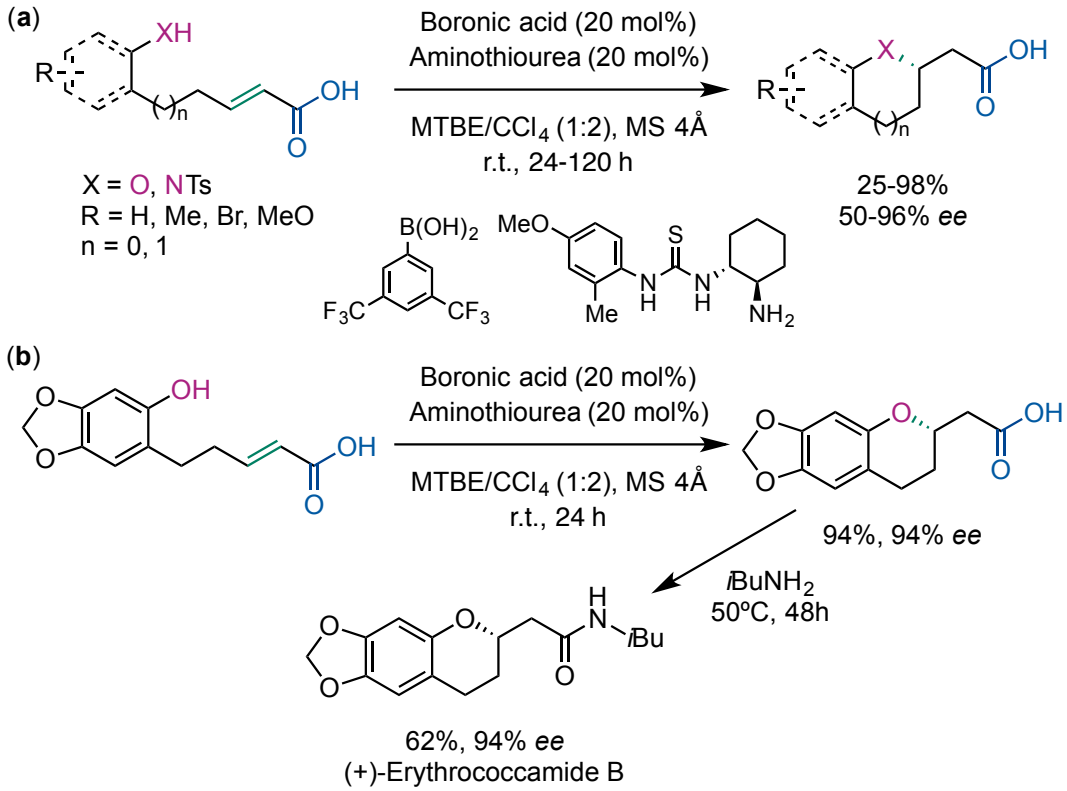


X = H, F, Cl OMe, Me
Y = H, C_6H_5, β-naphtyl
Z = Bn, PMP
R = Et, Me, *t*Bu

Scheme 2.9. *Aza*-Michael addition to conjugated esters with an indolic nitrogen.

In addition, Takemoto's group described, for the first time, the use of aminoboronic acids as efficient catalysts for the direct intramolecular hetero-Michael addition of α,β-unsaturated carboxylic acids.[199] Furthermore, they developed an asymmetric version of this protocol using a dual catalytic system composed of an aminothiourea and an arylboronic acid allowing the successfully synthesis of the desired heterocycles in high yields and *ee*'s (Scheme 2.1.a). The overall utility of this protocol was demonstrated by a one-pot enantioselective synthesis of (+)-Erythrococcamide B, which proceeded via sequential Michael and amidation reactions (Scheme 2.1.b).

[199] Azuma, T.; Murata, A.; Kobayashi, Y.; Inokuma, T.; Takemoto, Y. *Org. Lett.* **2014**, *16*, 4256–4259.



Scheme 2.10. Construction of asymmetric heterocyclic compounds with intramolecular hetero-Michael reactions with α,β-unsaturated carboxylic acids as electrophiles.

2.1.3. ORGANOCATALYTIC INTRAMOLECULAR AZA-MICHAEL REACTIONS IN DOMINO PROCESSES

The ability to create complex molecules in only a few steps has long been the dream of chemists. Now, with the development of domino reactions, the dream has become almost true for the laboratory chemist, at least partly. In addition, this kind of transformations are frequently used not only in basic research but also in applied chemistry.[200]

Nowadays, the main issue is the efficiency of a synthesis, which can be defined as the increase of complexity per transformation. Notably, modern syntheses must obey the needs of our environment, which includes the preservation of resources and the avoidance of toxic reagents as well as toxic

[200] a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. c) Tietze, L. F.; Brasche, G.; Gericke, K. M. In *Domino Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2006**. d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.

solvents.[201] Such an approach has advantages not only for Nature but also in terms of economics, as it allows reductions to be mad in production time as well as in the amounts of waste products.

For a long time, the general procedure for the synthesis of organic compounds has been a stepwise formation of individual bonds in the target molecules, with work-up stages after each transformation. In contrast, the denominated ***domino reactions***[202] would comprise transformations of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former-bond constructing reactions.

Inside classification of domino processes, the anionic domino reactions are the most often encountered in the chemical literature, being included in this group those where the primary step in the process is the attack of either an anion or a *pseudo* anion, as an uncharged nucleophile, onto an electrophilic center. Therefore, transformations such as Michael addition, aldol reactions or peptide couplings can be included in this category.

Concretely, organocatalytic intramolecular *aza*-Michael reactions (IMAMR) have been involved in several domino processes, such as the sequences IMAMR/ alkylation, [203] *aza*-Morita-Baylis-Hillman/ IMAMR,[135] Mannich/ IMAMR,[204] aminoxylation/ IMAMR,[205] or hydroxylation/ IMAMR.[206] As

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[201] a) Sheldon, R. a. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. b) Sheldon, R. a. *Green Chem.* **2005**, *7*, 267-278.

[202] The word *tandem* is often used to describe this type of process, but it is less appropriate as the encyclopedia defines tandem as "locally, two after each other", as on a tandem bicycle. Thus, the term *tandem* does not fit so well with the time-resolved aspects of the domino reaction type. For a proper example of a tandem reaction, where individual transformations of independent functionalities take place under the same reaction conditions, see: Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419.

[135] Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9725–9729.

[203] Guo, J.; Yu, S. *Org. Biomol. Chem.* **2015**, *13*, 1179–1186.

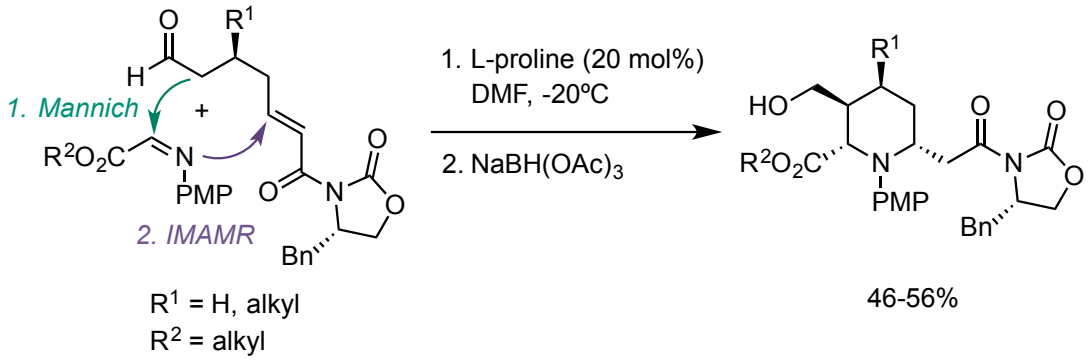
[204] a) Enders, D.; Goddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal*. **2010**, 352, 2863-2868. b) Yang, H.; Carter, R. G. *J. Org. Chem*. **2009**, 74, 5151-5156. c) Rueping, M.; Azap, C. *Angew. Chem. Int. Ed*. **2006**, 45, 7832-7835. d) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301–4304. e) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533–1535. f) Khaliel, S.; Nandakumar, M. V.; Krautscheid, H.; Schneider, C. *Synlett*. **2008**, 2705-2707. g) See Ref. 96: Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 4877–4880.

[205] a) Lu, M.; Zhu, D.; Lu, Y. P.; Hou, Y. X.; Tan, B.; Zhong, G. F. *Angew. Chem. Int. Ed*. **2008**, *47*, 10187-10191. b) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. *Org. Lett*. **2008**, *10*, 4585-4588.

[206] Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963.

noted, most of the cases have the IMAMR as the second step of the sequence, what makes especially sense when α,β-unsaturated esters are the Michael acceptors, because the previous reaction will be generating a more nucleophilic intermediate able to react with those less electrophilic moieties.

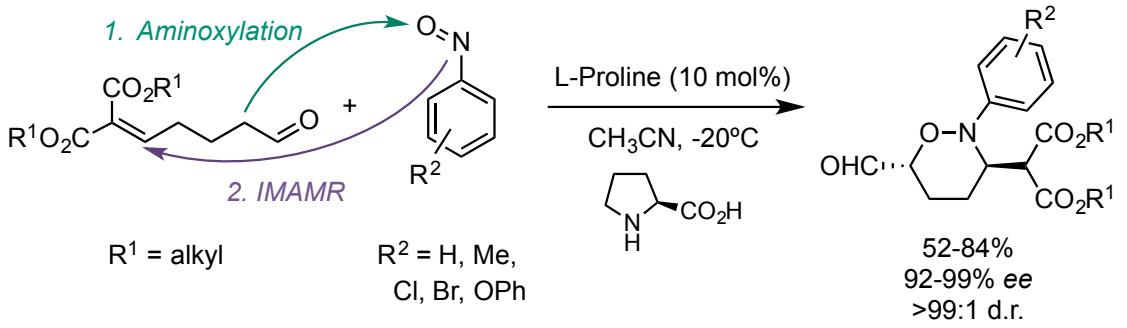
Activated ester equivalents have been involved in two examples of organocatalytic domino sequences with IMAMR. On the one hand, Schneider's group reported in 2008[204f] a proline-catalysed domino Mannich/ *aza*-Michael reaction of chiral 7-oxo-2-enimides containing an aldehyde moiety tethered to an α,β-unsaturated oxazolidinone with glyoxyl imines to furnish highly substituted pipecolic esters in moderate yields and excellent stereocontrol (Scheme 2.11). Throughout this process two new σ bonds and three new stereogenic centers are formed as a single stereoisomer as it was already demonstrated by Barbas and co-workers for similar Mannich reactions.[29]



Scheme 2.11. Domino Mannich/ IMAMR to an activated ester surrogate

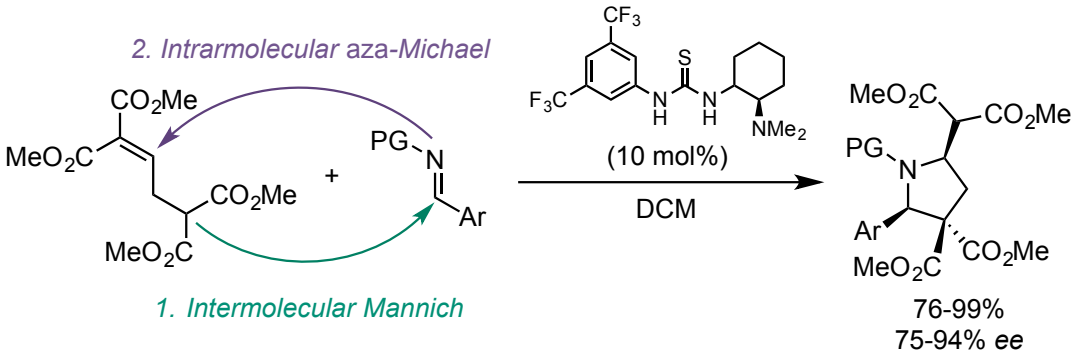
On the other hand, α,β-unsaturated diesters where involved in an asymmetric organocatalytic domino aminoxylation/ *aza*-Michael reaction for the synthesis of multifunctionalised tetrahydro-1,2-oxazines.[207] The C-O/ C-N bond formations are achieved in moderate to good yields with excellent diastereo- (<99:1 d.r.) and enantioselectivities (92% to >99% *ee*) by means of L-proline catalyst (Scheme 2.12).

[207] Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585–4588.



Scheme 2.12. Asymmetric domino aminoxylation/ IMAMR which conjugated diesters.

In addition, Enders and co-workers reported an efficient domino Mannich/*aza*-Michael reaction[204a] between *N*-protected aryl aldimines and γ-malonate-substituted α,β-unsaturated methyl esters promoted by a bifunctional thiourea catalyst. This methodology furnishes 2,5-*cis*-configured polyfunctionalised pyrrolidines in good to excellent yields, enantioselectivities and excellent diastereoselectivities (Scheme 2.13). They initially intended to perform the same protocol with simple conjugated esters but that Michael acceptor nature was not sufficiently electrophilic to enable a direct subsequent *aza*-Michael addition with the generated secondary amine.

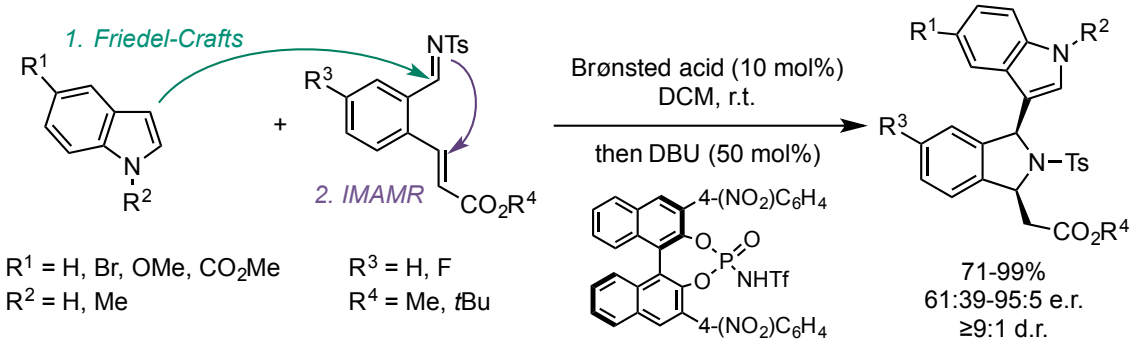


Scheme 2.13. Asymmetric synthesis of pyrrolidines through a domino Mannich/ IMAMR with conjugated diesters.

Apart from that, there have been also described some IMAMR to conjugated esters in organocatalysed domino processes, generally for the preparation of benzofused scaffolds.[208] Enders published in 2008 the first catalytic asymmetric synthesis of 1,3-disubstituted isoindolines, based on a metal-free one-pot Brønsted acid catalysed Friedel-Crafts/ base-catalysed *aza*-

[208] The following transformations described in Schemes 2.14-16 have already been partially discussed in the benzofused heterocycles Section 1.1.2., at Schemes 1.22, 28-29 in tetrahydroisoquinolines and isoindolines subsections, respectively.

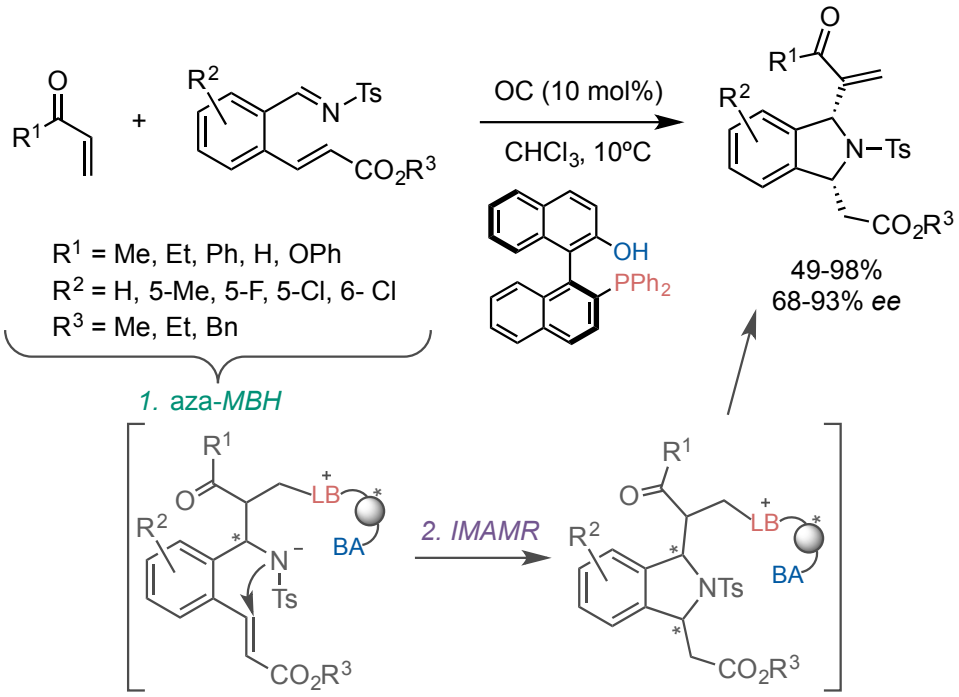
Michael addition reaction of bifunctional ε-iminoenoates and indoles.[136] Chiral BINOL-derived *N*-triflyl phosphoramides catalysed the initial Friedel-Crafts reaction and the isoindoline products were obtained in high yields and excellent diastereo- and enantiomeric ratios (Scheme 2.14).



Scheme 2.14. One-pot Friedel-Crafts/ IMAMR with ε-iminoenoates.

Sasai and co-workers[137] described the enantioselective synthesis of insoindolines, through an organocatalysed *aza*-Morita-Baylis-Hillman/intramolecular *aza*-Michael reaction of α,β-unsaturated esters and *N*-tosylimines promoted by the chiral acid-base catalyst (*S*)-2-diphenylphosphanyl-[1,1']binaphtalenyl-2-ol. This procedure easily accessed to afford 1,3-disbustitued isoindolines in good yields with excellent diastereo- and enantioselectivities (Scheme 2.15).

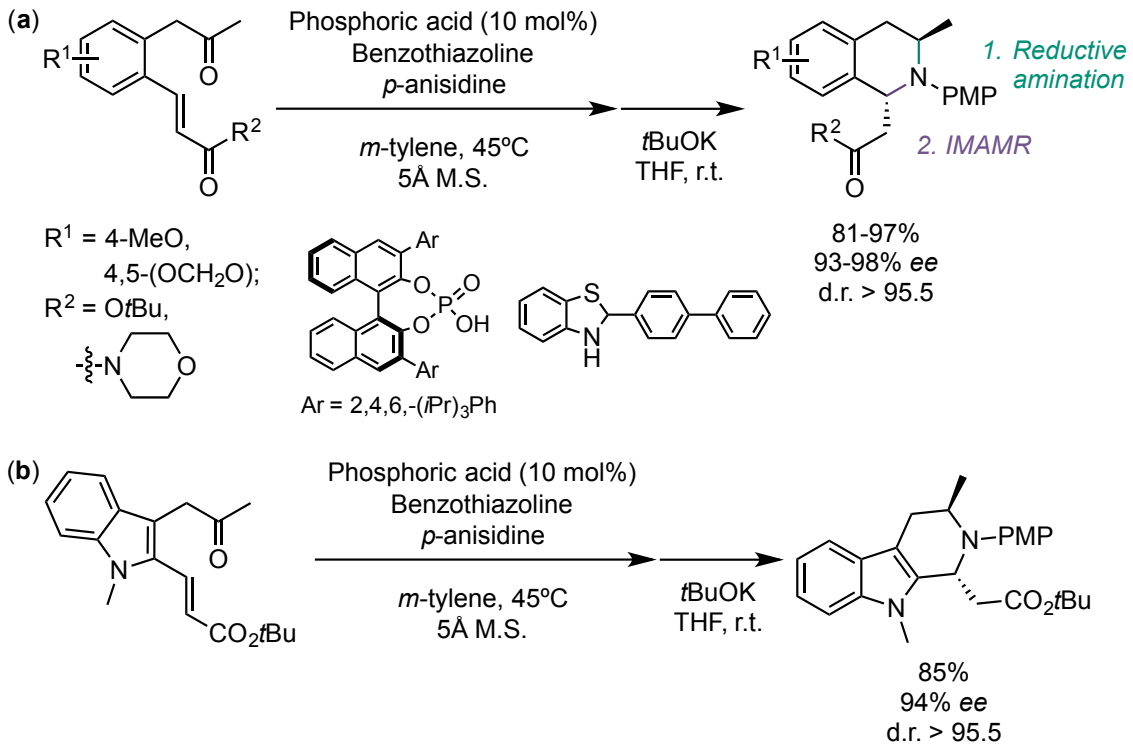
[136] Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5661–5665.
[137] Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9725–9729.



Scheme 2.15. *aza*-MBH/intramolecular *aza*-Michael addition domino reaction.

A domino strategy consisting of a reductive amination/ *aza*-Michael addition sequence was successfully applied by Enders *et al.* for the asymmetric synthesis of trans-1,3-disubstituted tetrahydroisoquinolines.[127] Using a chiral phosphoric acid as an organocatalyst and a biphenyl-substituted benzothiazoline as hydride source, they reacted *p*-anisidine with keto enoates to yield the reductive amination intermediates, that would suffer the IMAMR to reach the final products (Scheme 2.16.a). Notably, an indole-derived *trans*-disubstituted β-carboline was also obtained with this three-component sequence in excellent yield and stereoselectivity (Scheme 2.16.b).

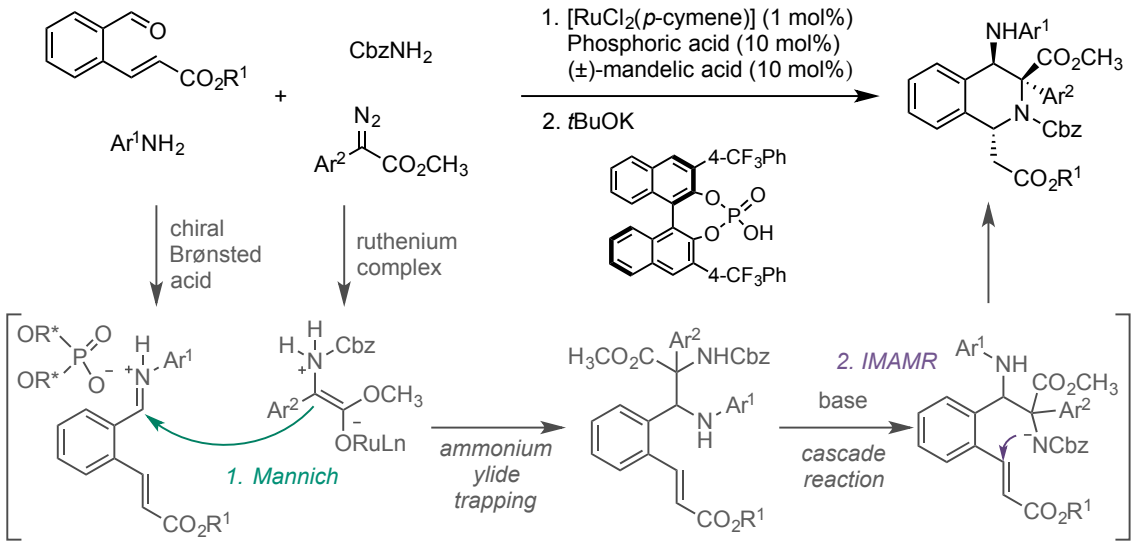
[127] Enders, D.; Liebich, J. X.; Raabe, G. *Chem. Eur. J.* **2010**, *16*, 9763–9766.



Scheme 2.16. Reductive amination/ IMAMR with α,β-unsaturated esters.

Finally, in 2014 has been published an elegant synergistic catalytic system comprising a ruthenium complex with a chiral Brønsted acid for an enantioselective four-component Mannich/cascade *aza*-Michael reaction.[211] The ruthenium-associated ammonium ylides successfully trapped with in situ generated imines indicates a septwise process of proton transfer in the ruthenium catalysed carbenoid N-H insertion reaction. This transformation features a mild, rapid, and efficient method to synthesize 1,3,4-tetrasubstitued tetrahydroisoquinolines bearing a quaternary stereogenic carbon center from simple starting precursors in moderate yields with high diastereo- and enantioselectivity (Scheme 2.17).

[211] Jiang, J.; Ma, X.; Ji, C.; Guo, Z.; Shi, T.; Liu, S.; Hu, W. *Chem. Eur. J.* **2014**, *20*, 1505–1509.



Scheme 2.17. Asymmetric Mannich/ IMAMR cascade with α,β-unsaturated-esters.

2.1.4. CONJUGATED ESTER SURROGATES AS ACCEPTORS IN MICHAEL-TYPE REACTIONS

As it has been seen, α,β-unsaturated esters are poor Michael acceptors and their application in organocatalysed conjugated additions is compromised by their low reactivity. This problem can be overcome by using activated ***ester surrogates***, which facilitate the activation of the electrophilic moiety. In the literature there can be found several functional groups acting as ester equivalents, such as fluorinated derivatives (**a**),[212] acyl oxazolidinones (**b**),[213] pyrrolidinone (**c**),[213] imides (**d**),[214] phosphonates (**e**),[215] pyrroles (**f**),[216] pyrazoles

[212] Fang, X.; Dong, X.-Q.; Liu, Y.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2013**, *54*, 4509–4511.

[213] For oxazolidinones: a) Evans, D. a; Scheidt, K. a; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491. b) Hird, A. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1276–1279. c) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240–1241. d) Kanemasa, S. *J. Synth. Org. Chem. Japan* **2003**, *61*, 1073–1080. e) See Ref. 204f: Khaliel, S.; Nandakumar, M.; Krautscheid, H.; Schneider, C. *Synlett* **2008**, 2705–2707. For pyrrolidinones: f) See Ref 53b: Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035. For both of them: g) See Ref. 53a: Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136. h) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263–3296. i) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 10069–10073.

[214] a) Goodman, S. N.; Jacobsen, E. N. *Adv. Synth. Catal.* **2002**, *344*, 953–956. b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443. c) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796–11797. d) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960. e) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205. f) Sallio, R.; Lebrun, S.; Schifano-Faux, N.; Goossens, J. F.; Agbossou-Niedercorn, F.; Deniau, E.; Michon, C. *Synlett* **2013**, *24*, 1785–1790.

(**g**)[213d,217] and pyrazolidinones (**h**).[218] In addition, there have been also added extra functionalities to enhance the conjugated ester's electrophilicity, such as an extra ester group at the geminal carbon[219] (**i**) or an α-keto residue[220] (**j**) (Figure 2.1).

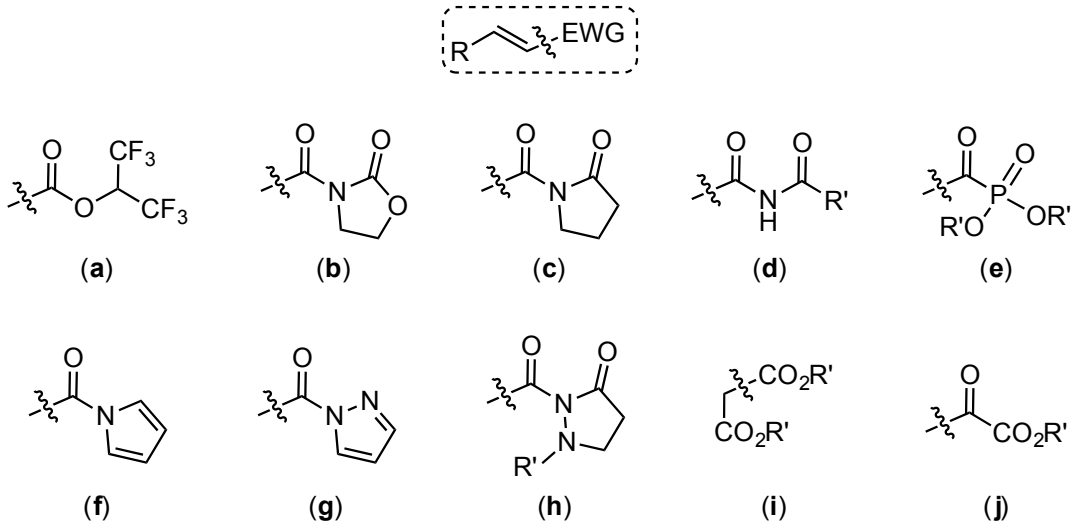


Figure 2.1. Ester equivalents used to activate the Michael acceptor.

Given the relevance in the present memory, there will pointed out some examples containing α,β-unsaturated *N*-acyl pyrazole as electrophiles in conjugate additions. Sibi described in 2007[217b] an efficient conjugate hydroxyl amine addition to enoates that proceed with high levels of enantioselectivity using a bifunctional organocatalyst. Overall, it was achieved good substrate scope for the addition of amines to pyrazole derived enoates using a thiourea

[215] a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780–10781. b) Bachu, P.; Akiyama, T. *Chem. Commun.* **2010**, *46*, 4112-4114. c) Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775–2783.

[216] a) Lee, S. D.; Brook, M. A.; Chan, T. H. *Tetrahedron Lett.* **1983**, *24*, 1569–1572. b) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559–7570. c) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368. d) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3188–3191.

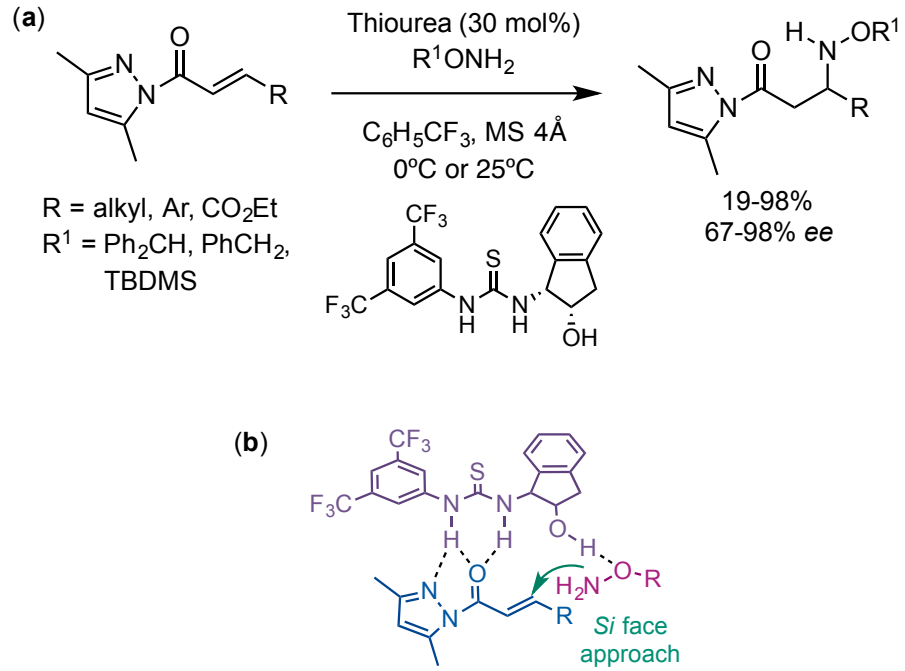
[217] a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394–13395. b) See Ref. 106: Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc*. **2007**, 129, 8064-8065. c) See Ref. 74b: Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616. d) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Adv. Synth. Catal.* **2012**, *354*, 1141–1147. e) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2012**, *48*, 7238-7240.

[218] Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181–4184.

[219] Enders, D.; Göddertz, D. P.; Beceño, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863–2868.

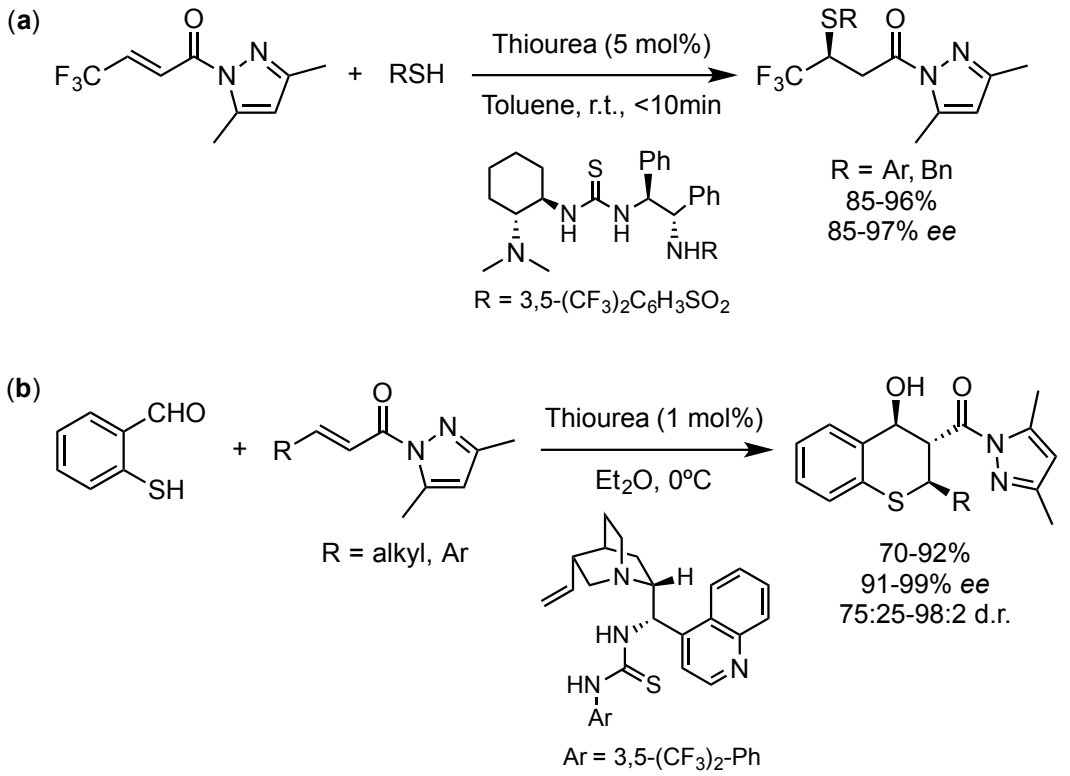
[220] Xu, D.-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, *16*, 4177–4180.

catalyst, providing access to a variety of enantioenriched β-amino acid derivatives (Scheme 2.17.a). Their results also indicate that the pyrazole template plays a crucial role in providing H-bond acceptor sites for better organization and hence higher levels of selectivity in these organocatalytic reactions (Scheme 2.17.b).



Scheme 2.17. Thiourea catalysed asymmetric intermolecular *aza*-Michael reaction.

In 2012 Wang published two complementary procedures involving organocatalytic asymmetric *sulfa*-Michael additions to *N*-acyl pyrazoles. In the first one,[217d] a variety of thiols reacted with the easily available *trans*-4,4,4-trifluorocrotonamide in excellent yields and good to excellent enantioselectivities (Scheme 2.18.a). They also evaluated the role of the pyrazole motif and the electron-withdrawing CF_3 group, revealing the importance of both of them especially for a higher stereocontrol. In the second,[217e] they developed a direct construction of highly substitutes and biologically active thiochromanes *via* a *sulfa*-Michael-aldol reaction of 2-mercaptobenzaldehyde with various α,β-unsaturated *N*-acyl pyrazoles, obtaining excellent diastereoselectivities and enantioselectivities for both β-aryl and β-alkyl conjugated substrates (Scheme 2.18.b).



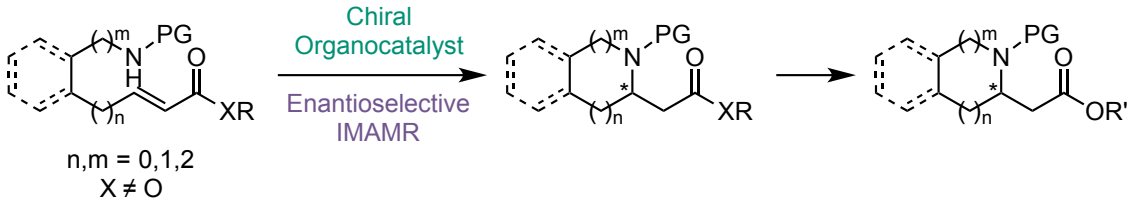
Scheme 2.18. Organocatalytic asymmetric *sulfa*-Michael additions to *N*-acyl pyrazoles.

2.2. Objectives

Because of the relevance of nitrogen-containing heterocycles and its synthesis in a straightforward manner with the intramolecular *aza*-Michael reaction (IMAMR), it seemed an appealing matter to complete the project, started several years ago in our research group, aimed at the development of convenient methodologies to carry out the IMAMR in an asymmetric organocatalytic fashion. The objective was to extend this procedure to conjugated esters as Michael acceptors,[221] since it had been already successfully applied to α,β-unsaturated aldehydes and ketones.[222]

It was a real challenge, the use of the ester functionality in this setting, because the most commonly employed organocatalytic activation modes, that is, the iminium and enamine pathways, cannot be applied to esters, unlike their ketone and aldehyde counterparts. Therefore, other types of activation, such as hydrogen bonding are required for the activations of esters and derivatives.

Initially, it was needed to find the appropriate combination of nitrogen nucleophile and organocatalyst to perform the enantioselective IMAMR with conjugated esters. However, at the end also the Michael acceptor required to be changed to an ester surrogate, able to be activated and later to be easily transformed into the equivalent ester (Scheme 2.18).



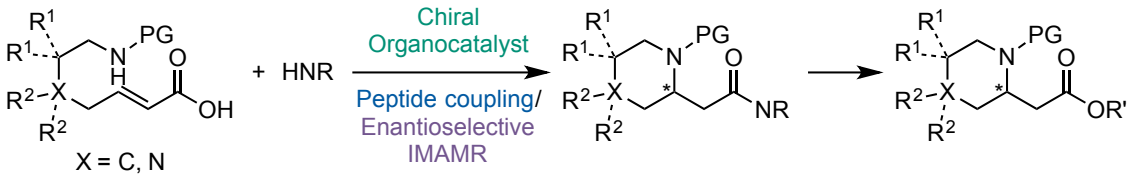
Scheme 2.18. Initial objective of the present chapter.

Finally, it was our desire to develop a domino process to prepare some other *N*-heterocycles combining a peptide coupling with the enantioselective

[221] Only one example of an organocatalytic direct IMAMR involving conjugated esters as Michael acceptors has been reported to date: (Ref. 111) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3238–3241.

[222] For enals: a)[109] Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. b)[110] Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872. c)[172] Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sánchez-Roselló, M. *Chem. Eur. J.* **2011**, *17*, 14267–14272.

IMAMR, starting from the corresponding conjugated carboxylic acids (Scheme 2.19).



Scheme 2.19. Desired domino peptide coupling-IMAMR

2.3. Results and discussion

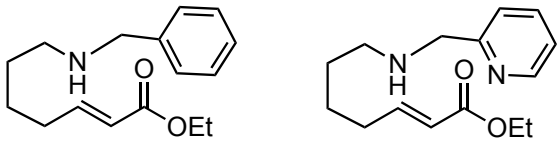
In light of the low reactivity of the α,β-unsaturated esters, it was envisioned that a more nucleophilic nitrogen would be necessary to develop the sought intramolecular *aza*-Michael reaction (IMAMR). Moreover, given the inability of esters to be activated through an iminium covalent activation, the introduction of additional hydrogen bonding anchorage points at the substrates would also be interesting for both the activation and the chiral induction.

2.3.1. SEARCH OF SUITABLE STARTING MATERIALS

2.3.1.1. Study of alkyl amine conjugated esters 42 and 43

SYNTHESIS OF BENZYL AMINE 42

In a first attempt, a secondary amine seemed to be a good partner for the IMAMR, since the more nucleophilic amine (when compared with the usual carbamates employed in those processes) would compensate the lower reactivity of conjugated esters. To this end, benzyl amine **42** and the pyridylmethyl amine **43** bearing an α,β-unsaturated ethyl ester were synthesized (Figure 2.2).

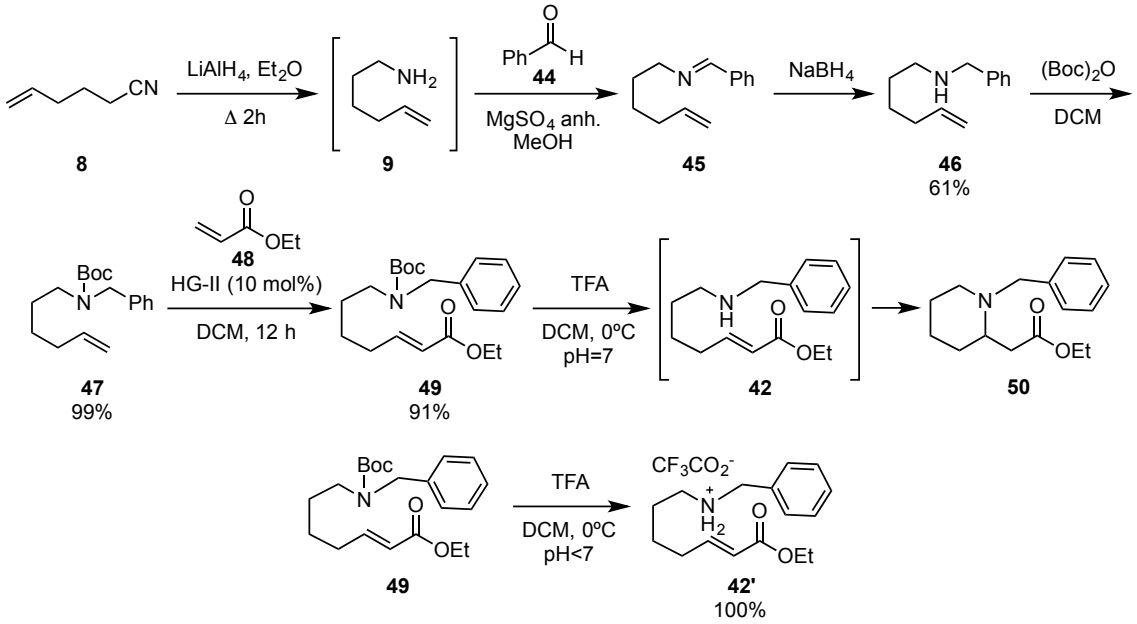


42 **43**

Figure 2.2. Desired starting materials **42** and **43**.

Starting from the commercial available 5-hexenenitrile **8**, it was reduced to the corresponding primary amine with lithium aluminium hydride and condensed *in situ* with benzaldehyde to give imine **45**, that was reduced to the benzyl amine by means of sodium borohydride. The next step of the sequence was a cross-metathesis (CM) with the ruthenium catalyst Hoveyda-Grubbs second-generation (HG-II). Since the catalyst could be poisoned by a secondary amine, **46** should be previously protected; the optimised approximation was to use di-*tert*-butyl dicarbonate to generate the Boc carbamate **47**, that underwent the CM with ethyl acrylate with good yield.

Finally, the secondary amine was deprotected with trifluoroacetic acid. However, when the free amine was released at neutral pH the desired compound **42** was never isolated, since it suffered a spontaneous racemic cyclisation. To avoid this undesired situation, it was isolated as the corresponding ammonium trifuoroacetate salt **42'** maintaining acid pH (Scheme 2.20).



Scheme 2.20. Approximation to the synthesis of benzyl amine **42**.

INTRAMOLECULAR *AZA*-MICHAEL REACTIONS OF ALKYL AMMONIUM SALT 42'

Benzyl ammonium **42'** was used as starting material to perform the desired IMAMR with a battery of 14 different organocatalysts (Figure 2.3) in the presence of base. Unfortunately, only in some cases the desired product was obtained and always in racemic form, indicating that the base-mediated cyclisation is faster that the organocatalysed process.

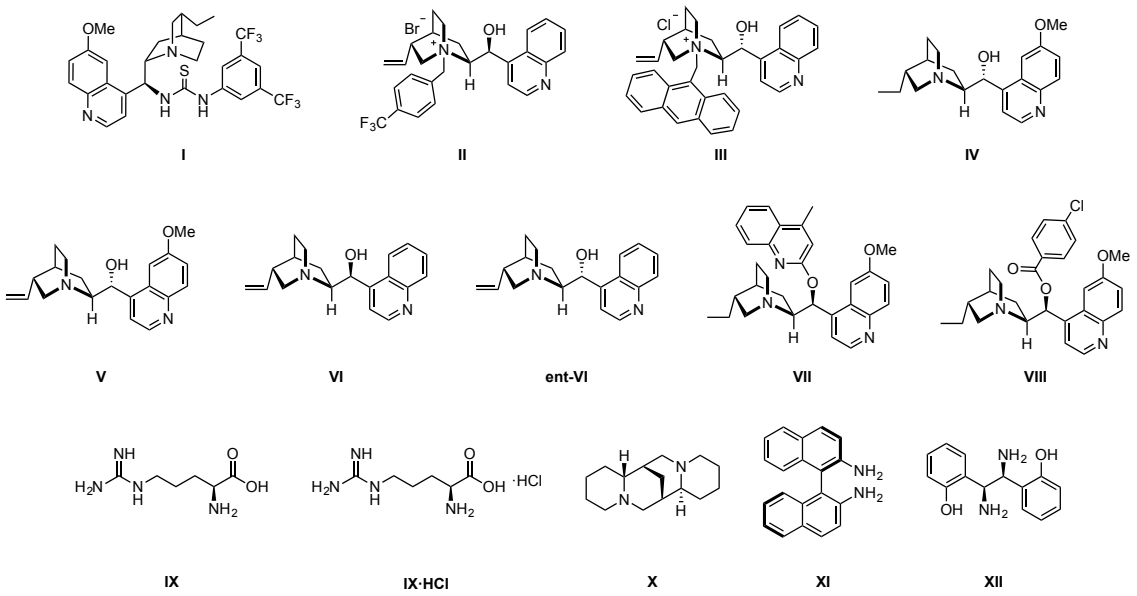


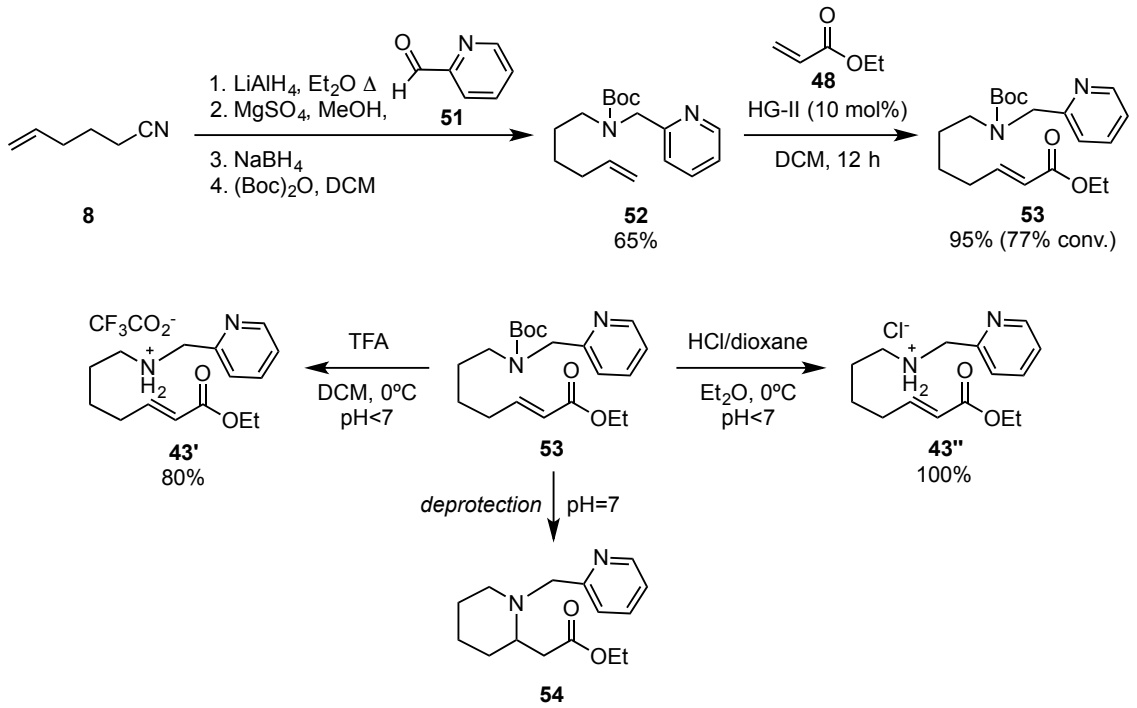
Figure 2.3. First batch of tested organocatalysts.

Thiourea **I**, in combination with triethyl amine, gave 33% of racemic product **50** after one week at room temperature. The phase-transfer catalyst (PTC) **II** together with aqueous KOH produced after 3 days the racemic adduct with 40% yield. PTC **III** produced the racemic product with 62% yield in the presence of K_2CO_3. Hydroquinine **IV** combined with *t*BuOK did not yield the Michael adduct, whereas quinine **V** with K_2CO_3 provided the cyclic product **50** with 86% yield but also racemic. When cinchonidine **VI** was used with *t*BuOK no reaction was observed. Hydroquinidine derived ethers **VII** and **VIII** gave racemic compound **50** with 65% and 50% yield, respectively. L-arginine **IX** either naked or as hydrochloride was not able to induce the Michael reaction. Sparteine **X**, with a catalytic amount of K_2CO_3, produced racemic Michael adduct **50**. However, binaphtyl diamine **XI** did not give rise to the desired product with catalytic K_2CO_3. Finally, with hydroxyphenyl diamine **XII** in the presence of catalytic K_2CO_3 provided 79% of racemic product **50**.

SYNTHESIS OF PYRIDYL AMINE 43

Conjugated ester **43'** bearing the pyridyl unit in the ammonium salt was prepared next, since the heterocycle would provide an extra hydrogen bond acceptor point, and a better coordination with the organocatalyst would be expected. The synthetic sequence applied was analogous to the one used for compound **42'**. However, in this case the final Boc-deprotection could not be completed, remaining always unprotected **53** unreacted. Thus, to avoid this

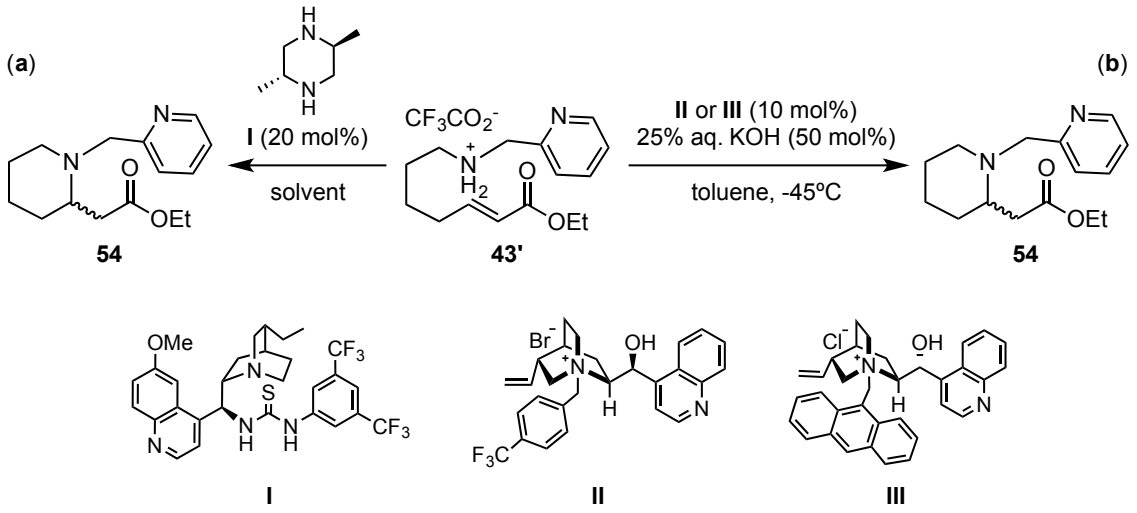
problem the ammonium chloride compound **43''** was prepared, showing now a complete conversion from **53** with a solution of hydrochloric acid in dioxane. Again, after release of the amine functionality at pH=7 the spontaneous cyclisation occurred, giving rise to the racemic Michael adduct **54** (Scheme 2.21).



Scheme 2.21. Approximation to the synthesis of pyridyl amine **43**.

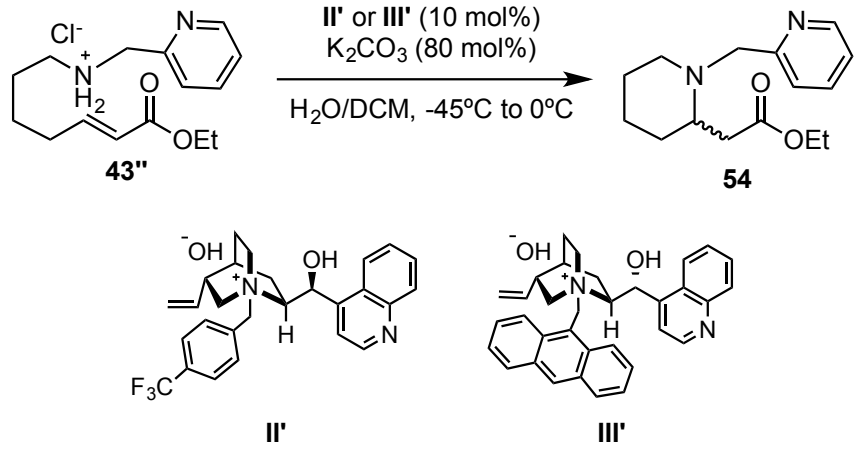
INTRAMOLECULAR *AZA*-MICHAEL REACTIONS OF ALKYL AMMONIUM SALT 43''

With the substrate in hand, the first attempt was performed using a hydrogen bond activation, with the hydroquinidine thiourea **I** as catalyst. However, as no reaction was observed it was added a prochiral base, *trans*-2,5-dimethylpiperazine. The desired compound **54** was finally obtained but, either employing acetonitrile, chloroform, tetrahydrofurane or toluene as solvent, was isolated as a racemic product. In order to favour the thiourea activation of the starting material, microwave irradiation was tested in absence of base, however it did not' succeed (Scheme 2.22.a). Likewise, the trifluoroacetate salt **43'** gave the racemic Michael adduct by means of PTC **II** and **III** in the presence of a substoichiometric charge of aqueous KOH at -45ºC (Scheme 2.22.b).



Scheme 2.22. Cyclisation of the trifluoroacetate salt **43'**.

When chlorhydrate **43''** was used as starting material instead of trifluoroacetate **43'**, piperidine **54** was not obtained with thiourea **I** as catalyst. When employing PTC **II** the reaction temperature needed to be risen to room temperature and an extra charge of 50 mol% of aqueous potassium hydroxide was added to allow the *aza*-Michael reaction to takes place, although without asymmetric induction. The difference of reactivity between ammonium salts **43'** and **43''** could be explained on the basis of the basicity of the trifluoroacetate anion of the starting material. Therefore, it was performed an anionic exchange with bromide and chloride PTC **II** and **III** by means of Amberlyst A26 resin to prepare the analogous hydroxide PTC **II'** and **III'**.[223] However, the desired IMAMR just took place by adding 0.8 equivalents of K_2CO_3 and rising temperature to 0ºC, obtaining again the racemic Michael adduct (Scheme 2.23).



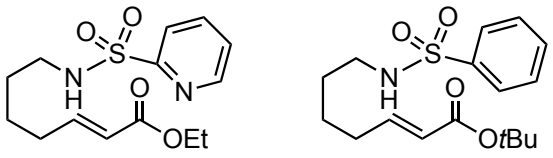
Scheme 2.23. Cyclisation of the chlorhydrate salt **43''**.

[223] Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557-10559.

2.3.1.2. Study of sulfonamide conjugated esters 55 and 56

SYNTHESIS OF SUBSTRATS 55 AND 56

Since alkyl amines were too nucleophilic and the classically used carbamates were not reactive enough, it was sought a nitrogen source with an intermediate nucleophilicity. In this way, sulfonamides reach those requirements, showing also higher acidity of the amine hydrogen and offering both oxygens to possible additional anchorage points for a hydrogen bond activation. Thus, there were synthesized pyridine-2-sulfonamide ester **55** and benzenesulfonamide ester **56** (Figure 2.4).

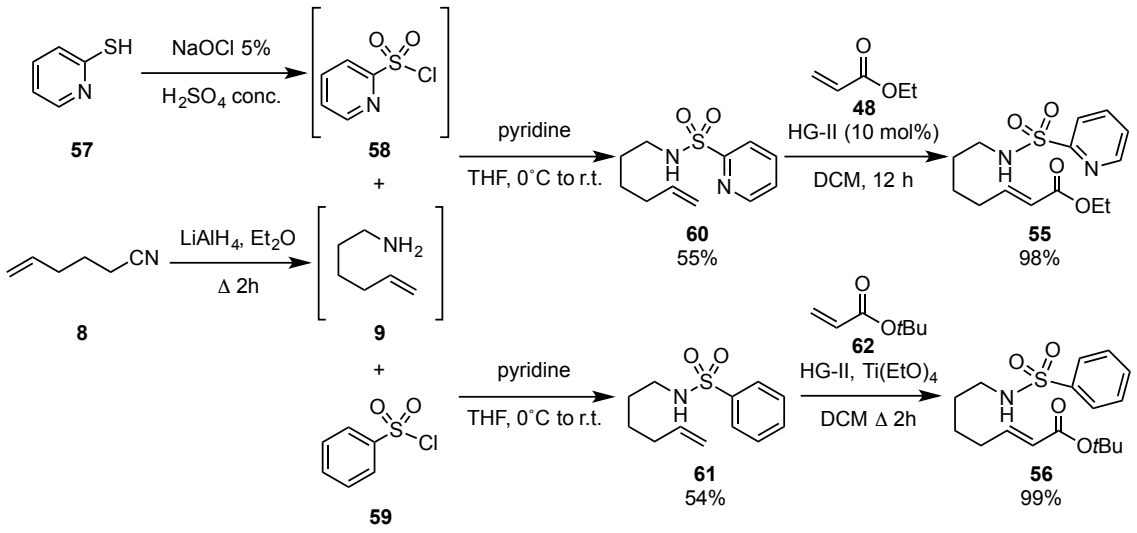


55 **56**

Figure 2.4. Starting sulfonamide α,β-unsaturated esters **55** and **56**.

These starting materials were prepared following the synthetic sequence shown hereunder (Scheme 2.24). Starting from hexenenitrile **8**, after reduction with lithium aluminium hydride, it was obtained the primary amine **9**, which was *in situ* added to sulfonyl chlorides **58** and **59** in the presence of pyridine to give sulfonamide olefins **60** and **61** [224] respectively in moderate yields. Benzenesulfonyl chloride **59** was commercially available, whereas pyridine-2-sulfonyl chloride **58** needed to be prepared *in situ* by oxidation of pyridine-2-thiol **57** to react with **9** without isolation.[225] Terminal olefins **60** and **61** gave upon cross-metathesis with catalyst Hoveyda-Grubbs second generation (HG-II) with the corresponding acrylates the desired compounds **55** and **56** with very good yields.[226]

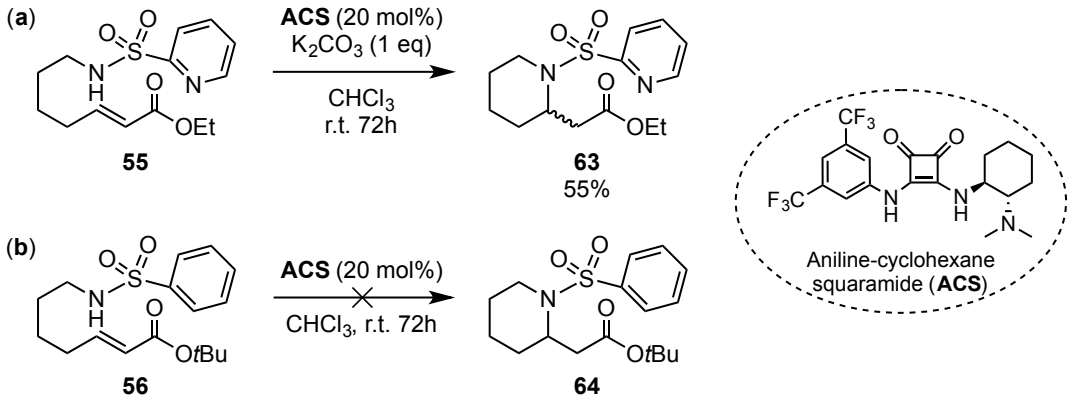
[224] Luo, S.-P.; Guo, L.-D.; Gao, L.-H.; Li, S.; Huang, P.-Q. *Chem. Eur. J.* **2013**, *19*, 87–91.
[225] García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem.* **2011**, *123*, 11119–11123. *Angew. Chem. Int. Ed.* **2011**, *50*, 10927–10931.
[226] Fustero, S.; Monteagudo, S.; Sánchez-Roselló, M.; Flores, S.; Barrio, P.; del Pozo, C. *Chem. Eur. J.* **2010**, *16*, 9835–9845.



Scheme 2.24. Preparation of sulfonamide esters **55** and **56**.

INTRAMOLECULAR *AZA*-MICHAEL REACTIONS OF SULFONAMIDES 55 AND 56

The cyclisation of conjugated ester **55** was firstly attempted with the classical combination[172] of primary-amine hydroquinidine with trifluoroacetic acid in chloroform used for enones, however it did not react. Then it was tested as hydrogen-bonding organocatalyst the hydroquinidine-thiourea **I**, but it did not succeed promoting the desired IMAMR either alone or in the presence of bases like the *trans*-2,5-dimethylpiperazine or K_2CO_3 in racemic manner. Notwithstanding, the use of squaramide **ACS** in the presence of K_2CO_3 gave rise to the Michael adduct **63** but still as a racemic mixture (Scheme 2.25.a). Then, it was confirmed the necessity of a base to undergo the conjugate addition when substrate **56** could not be transformed into the corresponding piperidine **64** just in the presence of the squaramide (Scheme 2.25.b).



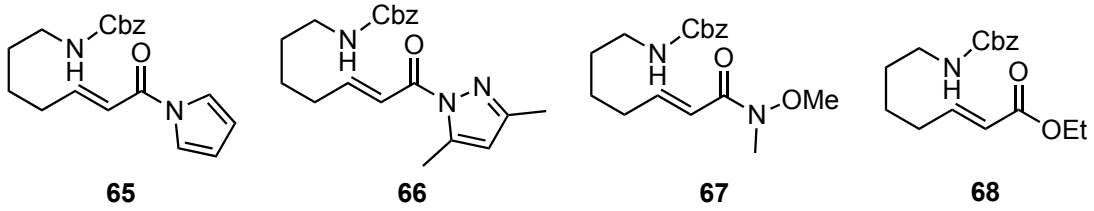
Scheme 2.25. Cyclisation of the sulfonamide α,β-unsaturated esters **55** and **56**.

[172] Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sánchez-Roselló, M. *Chem. Eur. J.* **2011**, *17*, 14267–14272.

2.3.1.3. Study of N-Cbz-protected amine conjugated ester and surrogates 65-68

SYNTHESIS OF SUBSTRATES 65-68

Once proved the difficulty to activate α,β-unsaturated esters as Michael acceptors for the desired enantioselective IMAMR, there were prepared several ester surrogates expected to act both as ester equivalents and as better electrophiles. They were combined initially with benzyloxycarbonyl (Cbz) protected amines, since this kind of carbamate moiety is easily accessible. Thus, there were synthesized the conjugated *N*-acyl pyrrol **65**, *N*-acyl pyrazole **66** and Weinreb amide **67**. It was also prepared the analogous compound **68** with an ethyl ester group to experimentally compare its reactivity also with the previously mentioned surrogates **65-67**.



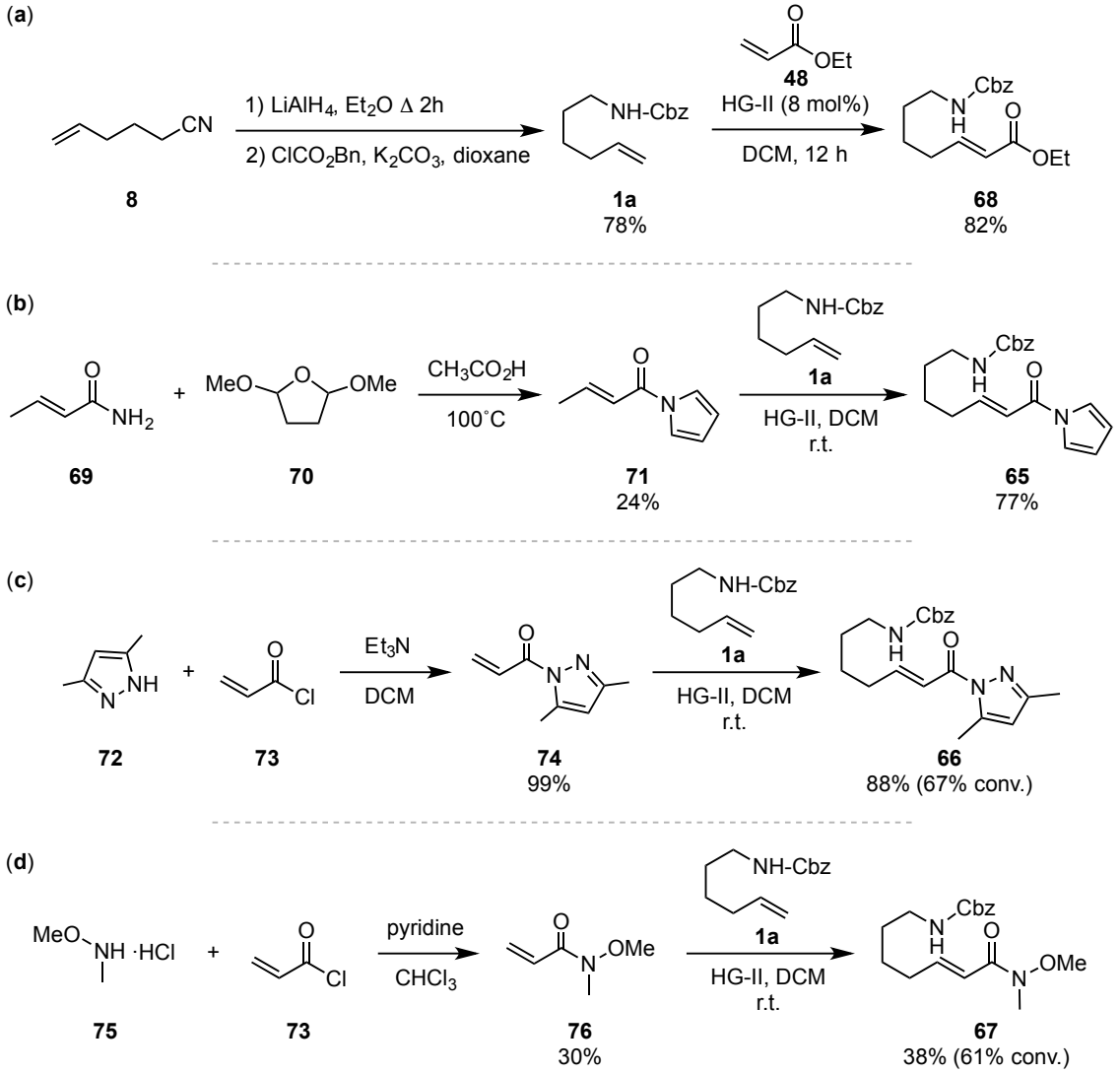
65 **66** **67** **68**

Figure 2.5. Starting carbamates functionalised with α,β-unsaturated ester and surrogates.

The conjugated ester **68** was simply prepared in good yield by CM reaction of carbamate **1a** with ethyl acrylate **48** (Scheme 2.26.a). The synthetic sequence for the ester surrogates consisted on the preparation of the corresponding α,β-unsaturated CM counterparts, that were combined with the terminal olefin **1a** following the CM reaction conditions. On the one hand, conjugated *N*-acyl pyrrol **71** was prepared by the nucleophilic substitution of methyl acryl amide **69** to 2,5-dimethoxytetrahydrofuran **70** in the presence of acetic acid.[228] Then, after CM reaction with olefin **1a** (previously described in Chapter 1) it was obtained the desired product **65** with good yield (Scheme 2.26.b). On the other hand, given the commercial availability of pyrazole **72**, it was reacted with acryloyl chloride **73** to give adduct **74** with excellent yield. Although the subsequent CM reaction could not arrive to completion (67% conversion), final product **66** was obtained with good yield (Scheme 2.26.c). Likewise, Weinreb amine hydrochloride **75** combined with acryloyl chloride **73**

[228] Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3188–3191.

gave conjugate amide **76** with moderate yield.[229] And the following CM reaction to obtain compound **67** proceed also with low yield and incomplete conversion (Scheme 2.26.d).



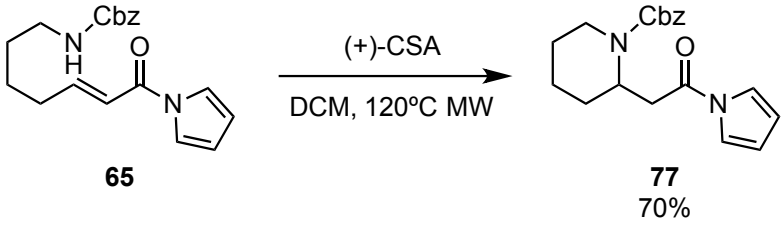
Scheme 2.26. Synthesis of conjugated ester **68** and ester surrogates **65-67**.

INTRAMOLECULAR *AZA*-MICHAEL REACTIONS OF CARBAMATES 65-68

With the sought starting materials on hand, the cyclisation conditions were studied. α,β-Unsaturated ester **68** remained unaltered after 60 h in the presence of **ACS** catalyst, either at room temperature or in $CHCl_3$ under reflux. Regarding pyrrolamide **65**, it decomposed with tetrabutyl ammonium fluoride (TBAF) and produced cyclic piperidine **77** in only 15% yield in presence of *t*BuOK. When acidic conditions were used, it did not react employing

[229] Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735–1738.

trifluoroacetic acid (TFA), but with (1*S*)-(+)-camphorsulfonic acid (CSA) it gave Michael adduct **77** in 45% yield, which could be improved to a 70% by microwave irradiation at 120ºC (Scheme 2.27). Then, it was combined primary-amine hydroquinidine with CSA expecting some chiral induction, however just the racemic piperidine **77** was obtained in all cases. Nevertheless, compounds **66** and **67** did not cyclise neither with *t*BuOK nor with the hydrogen-bonding organocatalysts like squaramides or thioureas.



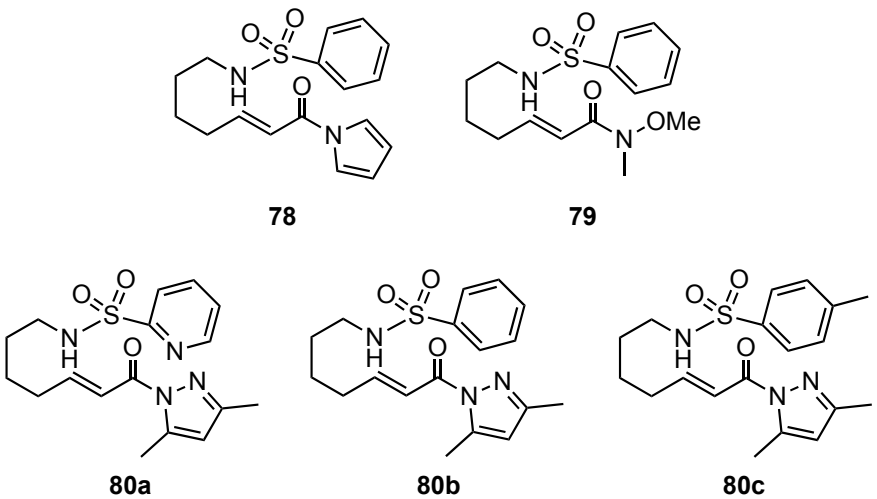
65 **77** 70%

Scheme 2.27. Best result obtained for cyclisation of starting material **65**.

2.3.1.4. Study of sulfonamide conjugated ester surrogates 78-82

SYNTHESIS OF SUBSTRATE CANDIDATES 78-80

After this tough trial/error-based development process, it was designed a family of starting materials for the IMAMR that possessed both a sulfonamide as nitrogen nucleophile, and an ester surrogate as Michael acceptor. Thus, sulfonamide would provide a more acidic hydrogen and more anchoring points for catalysis, and the ester surrogate would show a higher electrophilicity and again more hydrogen-bond acceptors positions for enhance catalysis (Figure 2.6).

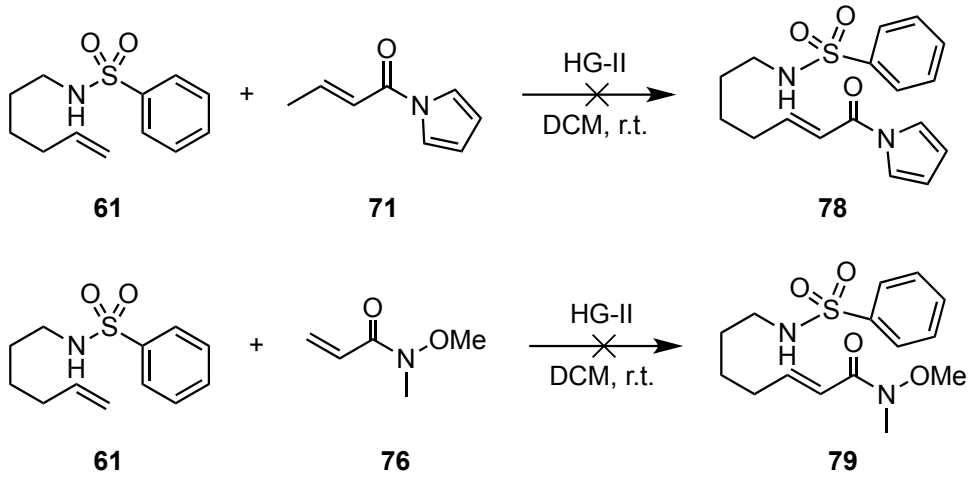


78 **79**

80a **80b** **80c**

Figure 2.6. Starting sulfonamides functionalised with α,β-unsaturated ester surrogates **78-80**.

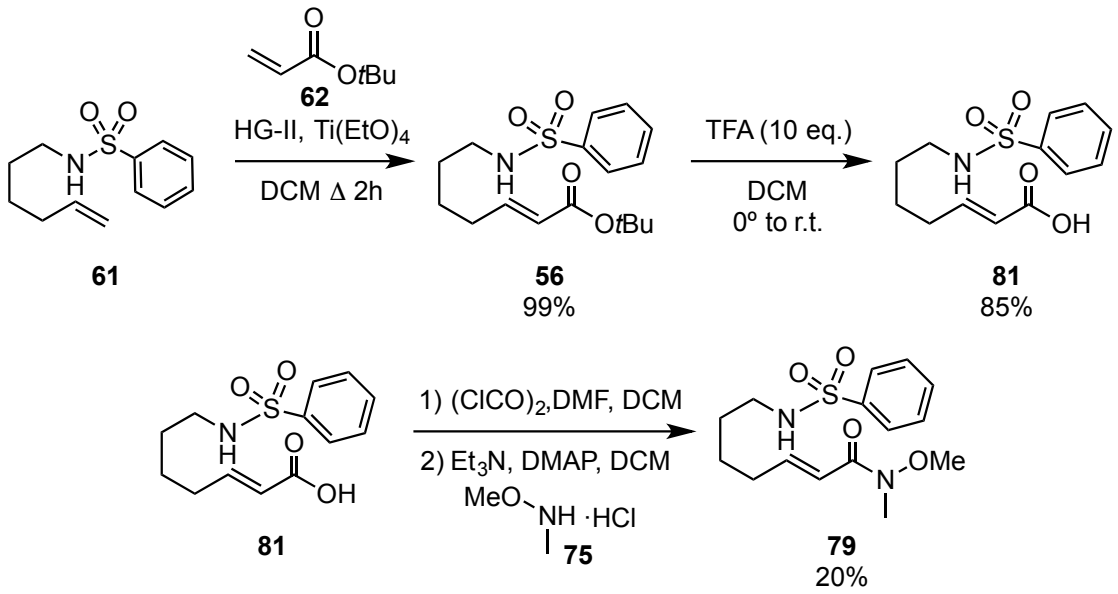
The initial approximation for the synthesis of compounds **78** and **79** was following the aforementioned preparation of the protected amines with the terminal olefin; in this case the CM reaction of sulfonamide **61** with the previously prepared *N*-acyl pyrrol **71** and *N*-methoxy-*N*-methyl amide **76** respectively. However, after several attempts these transformations did not proceed (Scheme 2.28).



Scheme 2.28. Unsuccessful CM reactions for the synthesis of **78** and **79**.

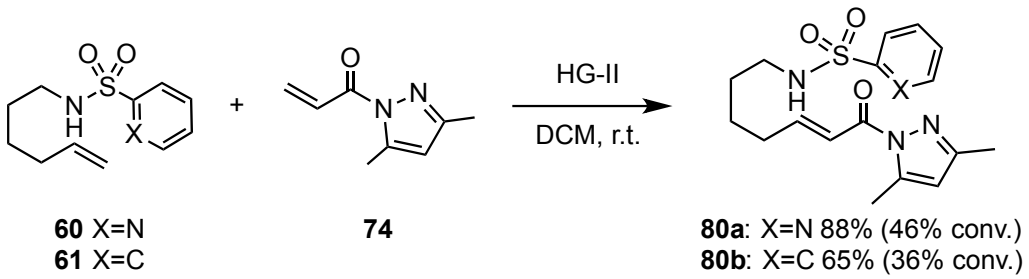
For the preparation of the Weinreb amide derivative **79** it was found an alternative route[230] that comprised a CM reaction of **61** with *tert*-butyl acrylate **62**, followed by the ester hydrolysis in acidic media of **56** with 10 equivalents of TFA to give the corresponding acid **81**. Then, this compound was converted into an acyl chloride that would react with Weinreb amine hydrochloride **75** in the presence of triethyl amine and 4-dimethyl aminopyridine, to finally give rise to the desired product **79** but with a low yield (Scheme 2.29). It was tried an alternative peptide coupling for this last step but it did not produce the desired amide.

[230] Fustero, S.; Báez, C.; Sánchez-Roselló, M.; Asensio, A.; Miro, J.; del Pozo, C. *Synthesis* **2012**, *44*, 1863–1873.



Scheme 2.29. Preparation of Weinreb-amide derivative **79**.

Initially, *N*-acyl pyrazoles **80a** and **80b** were prepared following the stablished sequence of separately preparing sulfonamides **60** and **61** and pyrazole amide **74** to make them react afterwards in a CM reaction producing the starting-material candidates **80a** and **80b** for the IMAMR. However, conversion in both cases was poor and the yield of the converted part just moderate (Scheme 2.30; Table 2.1. entries 1-2).

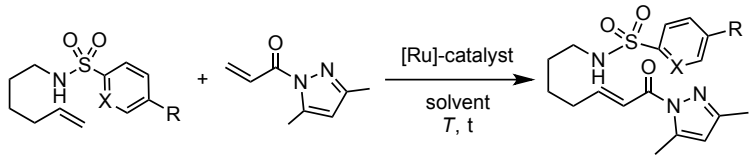


Scheme 2.30. Preparation of *N*-acyl pyrazoles **80a** and **80b**.

Given the importance of this substrates, that will be commented later, there was developed a thorough optimisation of this CM reaction conditions (Table 2.1). When the transformation was undergone in reflux of dichloromethane conversion diminished although the yield improved (Table 2.1. entries 3-4). Additives did not help either; $Ti(EtO)_4$ avoided formation of the desired product (Table 2.1. entry 5) and *p*-TSA led to the racemic cyclisation of the formed compound **80b** (Table 2.1. entry 6). Heating the crude to 60ºC under microwave irradiation (MW) improved the yield but not the conversion (Table

2.1. entry 7). The employment of toluene or dichloroethane as solvents gave worse results in terms of yield (Table 2.1. entries 8-9). A second addition of the catalyst enhanced the yield of the converted starting material comparing to the same conditions with just one loading of HG-II (Table 2.1. entries 10 *vs*. 2). The addition of the 20 mol% loading of HG-II in four times employing *p*-toluenesulfonamide **82** as substrate lead to higher conversion and yield after 24 hours at room temperature (Table 2.1. entry 11). However, the same conditions utilizing the ruthenium catalyst Grubbs second generation (G-II) could not give any better result (Table 2.1. entry 12). Given the yield enhancement achieved with MW irradiation, it was studied its combination with the 4-step catalyst addition together with a higher concentration of the crude (Table 2.1. entry 13), obtaining a better conversion with good yield after heating at 100ºC during 5 minutes after each load of HG-II. A higher concentration of 1 M respect to the usually employed 0.1 M seemed to respond favourably, although when it was performed in neat conditions (Table 2.1. entry 14) results weren't better. An extra ruthenium catalyst with an indene functionalization was tried out, not giving better results at either at 0.1M or 1M concentration (Table 2.1. entries 15-16). Finally, the cross-metathesis reaction of sufonamide **83** with the optimised conditions of 20 mol% HG-II added in four steps while heating at 100ºC under MW during a total of 20 minutes gave rise to a good conversion and an excellent yield (Table 2.1. entry 17).

Table 2.1. Optimisation of the cross-metathesis reaction to prepare *N*-acyl pyrazole sulfonamides **80a-b**.



60 X=N, R=H
61 X=C, R=H
83 X=C, R=Me

74

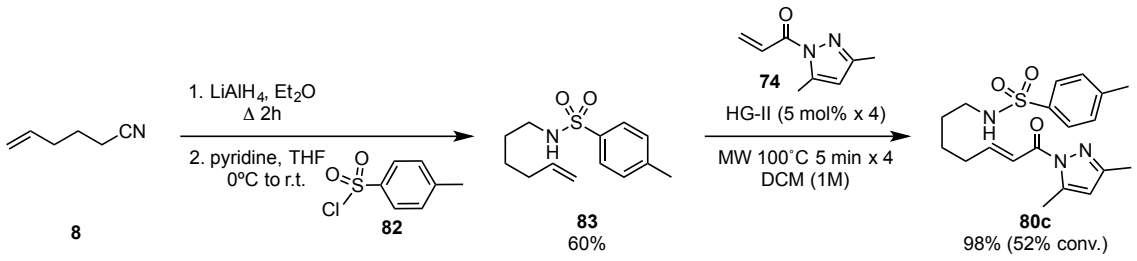
80a X=N, R=H
80b X=C, R=H
80c X=C, R=Me

Entry	*Prod.*	*[Ru] (mol%)*	*Solvent*	*T (ºC)*	*t (h)*	*Yield (%)*[a]	*Conv. (%)*
1	**80**	HG-II (20)	DCM	25	24	88	46
2	**81**	HG-II (10)	DCM	25	16	65	36
3	**81**	HG-II (10)	DCM	25-45	24	70	35
4	**81**	HG-II (10)	DCM	45	48	96	26
5	**81**	HG-II (10)[b]	DCM	45	24	0	33

6	**81**	HG-II (10)[c]	DCM	25-45	2	29[d]	91
7	**80**	HG-II (10)	DCM	60[e]	2	83	24
8	**81**	HG-II (10)	toluene	100[e]	2	44	50
9	**81**	HG-II (15)	DCE	80	24	22	64
10	**81**	HG-II (10+10)	DCM	25	24	82	33
11	**82**	HG-II (5x4)	DCM	25	24	94	53
12	**82**	G-II (5x4)	DCM	25	24	71	48
13	**81**	HG-II (5x4)	DCM[f]	100[e]	0.33[g]	70	78
14	**81**	HG-II (5x4)	-	100[e]	0.33[g]	63	60
15	**81**	indene (5x4)	DCM	100[e]	0.33[g]	26	30
16	**81**	indene (5x4)	DCM[f]	100[e]	0.33[g]	40	28
17	**82**	HG-II (5x4)	DCM[f]	100[e]	0.33[g]	94	53

[a] Isolated yields after flash chromatography purification of the converted SM.
[b] 10 mol% $Ti(EtO)_4$ added
[c] 2 eq. *p*TSA[231] added
[d] Desired product partially cyclised to the racemic Michael adduct
[e] Microwave irradiation
[f] 1 Molar (usually 0.1M)
[g] 20 minutes

Thus, the optimised synthesis of a sulfonamide with an α,β-unsaturated *N*-acyl pyrazole consisted in the preparation of tosyl amide **83**[232] starting from hexenenitrile **8** and tosyl chloride **82** following the stablished conditions of nitrile reduction with $LiAlH_4$ and amine protection with pyridine. Then it was performed the CM reaction with the previously prepared counterpart **74** in DCM (1M) and 20 mol% HG-II catalyst added in 4 times followed by 5 minutes of MW irradiation at 100ºC, to give rise to the desired product **80c** in excellent yield and moderate conversion (Scheme 2.31).



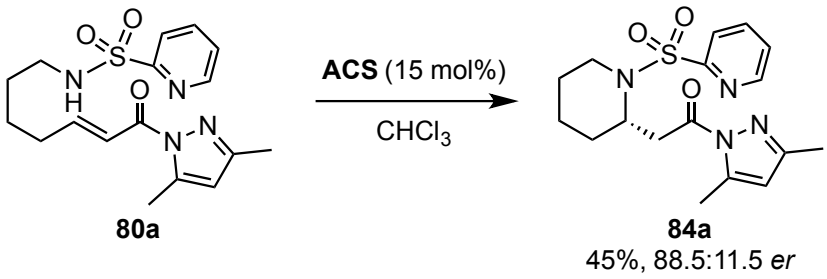
Scheme 2.31. Synthesis of tosyl amide **82**.

[231] Cuñat, A. C.; Flores, S.; Oliver, J.; Fustero, S. *Eur. J. Org. Chem.* **2011**, *2011*, 7317–7323.
[232] Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444–2451.

INTRAMOLECULAR *AZA*-MICHAEL REACTIONS OF SULFONAMIDES 79, 80A-C

Sulfonamide **79** functionalised with a conjugated Weinreb amide as ester surrogate was cyclised with *t*BuOK to prepare the racemic Michael adduct and try to separate its enantiomers with a chiral column in the HPLC. However, this separation could not be achieved and this substrate was dismissed.

The very first attempt of an asymmetric IMAMR performed with the family of *N*-acyl pyrazole substrates was with sulfonamide **80a** in the presence of squaramide **ACS** in $CHCl_3$ as solvent at room temperature (Scheme 2.32). After 88h the reaction hadn't finished, however it was finally accomplished the desired chiral induction and Michael adduct **84a** was obtained with 88.5:11.5 *er* and moderate yield.

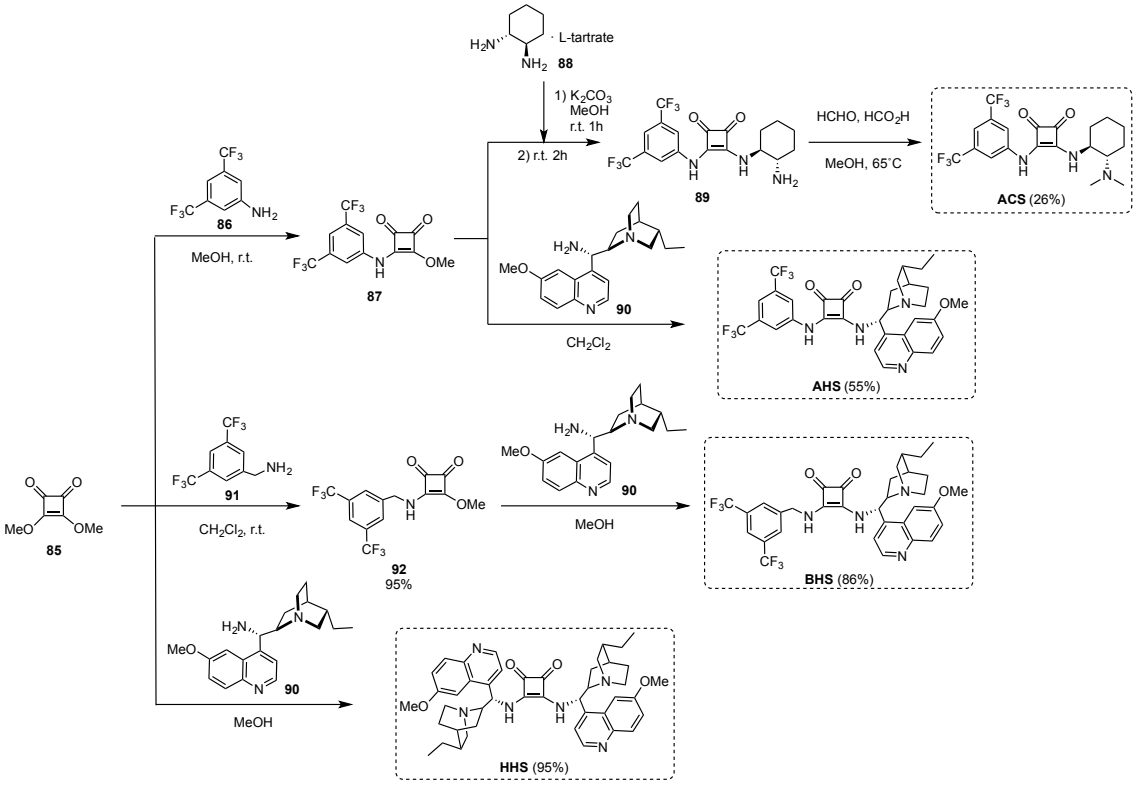


Scheme 2.32. First accomplished asymmetric IMAMR with conjugated *N*-acyl pyrazole **80a**.

Hence, some other squaramide analogues were prepared in order to find the best match pair of catalyst-substrate (Scheme 2.33). Starting from cyclobutenedione **85** it was initially performed the nucleophilic substitution with aniline **86** to give the one-side functionalised squaramide **87**. This crude could be added to the previously deprotonated diamine **88** to give rise to squaramide **91**, that was then methylated with formaldehyde and formic acid in methanol to give the tertiary-amine functionalised aniline-cyclohexane squaramide (**ACS**). The crude of **87** was subjected, in parallel, to a nucleophilic substitution with the primary-amine hydroquinidine **90** to produce aniline-hydroquinidine squaramide (**AHS**).[233] On the other hand, when compound **85** was combined with benzyl amine **91** yielded intermediate **92**, which after the nucleophilic addition of amine **90** originated benzyl amine-hydroquinidine squaramide (**BHS**).[234] Finally, the

[233] Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028–2031.
[234] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

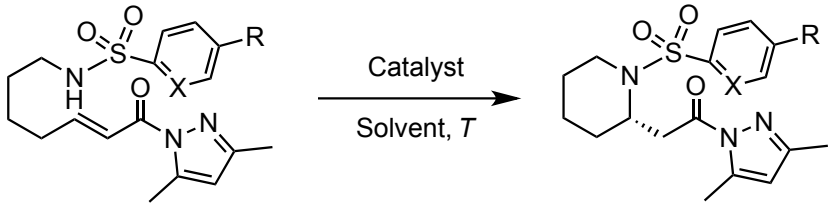
doubly substituted with hydroquinidine-hydroquinidine squaramide (**HHS**) was obtained with excellent yield from **85**.[235]



Scheme 2.33. Synthesis of squaramide organocatalysts.

With this family of squaramides in hand, the IMAMR was evaluated in order to find out the optimal conditions by modifying the aromatic ring of the sulfonamide, the catalyst and its loading, the solvent and the temperature as it is shown in Table 2.2.

Table 2.2. Optimisation of the IMAMR with *N*-acyl pyrazole sulfonamides **80a-c** to obtain piperidines **84a-c**.



80a X=N, R=H
80b X=C, R=H
80c X=C, R=Me

84a X=N, R=H
84b X=C, R=H
84c X=C, R=Me

[235] Woong Lee, J.; Hi Ryu, T.; Suk Oh, J.; Yong Bae, H.; Bin Jang, H.; Eui Song, C. *Chem. Commun.* **2009**, 7224-7226.

Entry	SM	Catalyst (mol%)	Solvent	T (ºC)	Yield (%)[a]	er[b]
1	**80a**	ACS (15)	$CHCl_3$	25	45	88.5:11.5
2	**80a**	ACS (15)	THF	25	-	-
3	**80a**	ACS (15)	CH_3CN	25	-	-
4	**80a**	ACS (15)	Toluene	25	47	85:15
5	**80b**	ACS (15)	$CHCl_3$	25	95	93:7
6	**80b**	I	$CHCl_3$	25	48	90:10
7	**80b**	ACS (15)	Toluene	0	10	92:8
8	**80b**	ACS (10)	DCE	85	58	89:11
9	**80b**	ACS (10)	DCE	60[c]	60	92.5:7.5
10	**80a**	BHS (15)	$CHCl_3$	25	72	89.5:10.5
11	**80b**	BHS (10)	$CHCl_3$	25	52	96:4
12	**80b**	AHS (10)	$CHCl_3$	25	55	98:2
13	**80b**	AHS (10)	$CHCl_3$	60[c]	55	96.5:3.5
14	**80b**	AHS (15)	$CHCl_3$	60[c]	53	96.5:3.5
15	**80b**	AHS (5)	$CHCl_3$	60[c]	30	96.5:3.5
16	**80b**	AHS (10)	DCE	60[c]	45	97:3
17	**80b**	AHS (10)	Et_2O	60[c]	50	97.5:2.5
18	**80b**	AHS (10)	Acetone	60[c]	20	96.5:3.5
19	**80b**	AHS (10)	$MeNO_2$	60[c]	51	96.5:3.5
20	**80a**	BHS (10)	$CHCl_3$[d]	60[c]	48	92.5:7.5
21	**80a**	BHS (10)	$CHCl_3$[e]	60[c]	42	92:8
22	**80a**	BHS (10)	$CHCl_3/Et_2O$	60[c]	30	91.5:8.5
23	**80a**	BHS (10)	$CHCl_3/MeNO_2$	60[c]	10	80.5:19.5
24	**80a**	AHS (10)	$CHCl_3$	60-100[c]	66	90.5:9.5
25	**80a**	AHS (10)	$CHCl_3$	100[c]	86	87.5:12.5
26	**80b**	AHS (10)	$CHCl_3$	60-100[c]	91	95.5:4.5
27	**80b**	AHS (10)	$CHCl_3$	100[c]	89	93:7
28	**80b**	AHS (10)	CPME[f]	90[c]	92	96.5:3.5
29	**80c**	AHS (10)	CPME[f]	60-100[c]	82	97:3
30	**80c**	AHS (10)	$CHCl_3$	25	-	-
31	**80c**	AHS (10)	CPME[f]	25	8	97.5:2.5
32	**80c**	AHS (10)	CPME[f]	90[c]	91	96:4
33	**80c**	AHS (10)	CPME[f]	110	92	95:5

34	**80c**	HHS (10)	CPME[f]	90[c]	25	92:8

[a] Isolated yields after flash chromatography purification.
[b] Determined by chiral stationary phase HPLC
[c] Microwave irradiation
[d] 0.2 Molar (usually 0.1M)
[e] 0.05 Molar
[f] Cyclopentyl methyl ether

After screening a number of solvents it was initially thought that chloroform was the optimum one (Table 2.2. entries 2-4, 7-9, 16-19, 22-23) in terms of both yield and stereoselectivity (Table 2.2. entry 26). However, after some extra bibliographic research,[236] it was finally identified cyclopentyl methyl ether (CPME) as the most suitable solvent both for the obtained results and its chemical properties (e.g. boiling point and solubility). Among the five tested organocatalysts, squaramides **ACS**, **BHS**, **AHS** and **HHS** and thiourea **I**, the aniline-hydroquinidine squaramide (**AHS**) was found to give the better chiral induction (Table 2.2, entries 12 *vs*. 5, 11; entries 32 *vs*. 34) with the optimal loading of 10 mol% (Table 2.2, entries 13 *vs*. 14, 15). Regarding thermal conditions, the studied IMAMR was monitored at room temperature, at 0ºC, at solvent reflux and with microwave irradiation, being finally determined 90ºC with microwave irradiation as the optimal conditions for the synthesis of piperidines **84** (Table 2.2. entries 28, 32).

Besides all the variations included in Table 2.2. it was also checked out that the employment of additives such as benzoic acid, TFA or tetrabutyl ammonium iodide, just led to a worse progress of the reaction.

2.3.2. ENANTIOSELECTIVE SYNTHESIS OF PIPERIDINES, PYRROLIDINES, ISOINDOLINE AND TETRAHYDROISOQUINOLINES *84 AND 93-96*

The optimised intramolecular *aza*-Michael reaction (IMAMR), employing aromatic sulfonamides as nucleophiles and an α,β-unsaturated 3,5-dimethyl pyrazole (DMP) as Michael acceptor, was applied to the synthesis of differently functionalised piperidines (**84**), pyrrolidines (**93**), isolindoline (**94**) and

[236] a) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251–258. b) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711–16713. c) Okamura, T.; Asano, K.; Matsubara, S. *Chem. Commun.* **2012**, *48*, 5076-5078.

tetrahydroisoquinolines (**95-96**) (Figure 2.7) with excellent yields and good to very good enantioselectivities (Table 2.3).

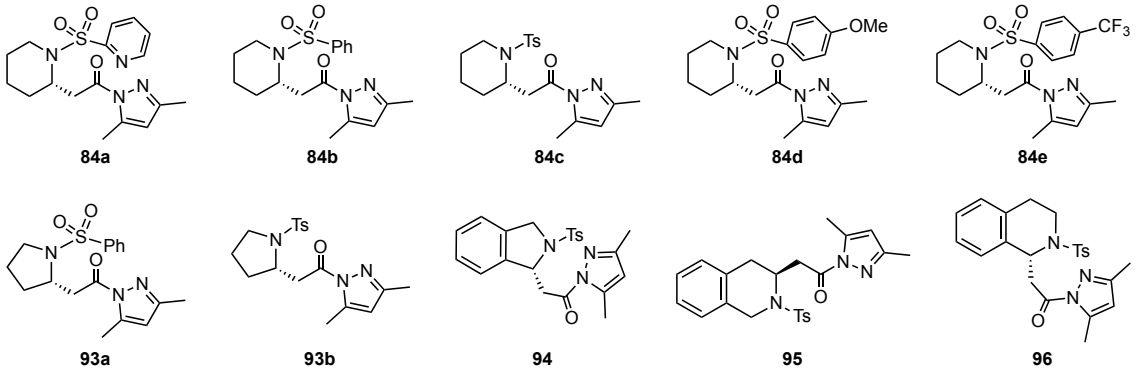
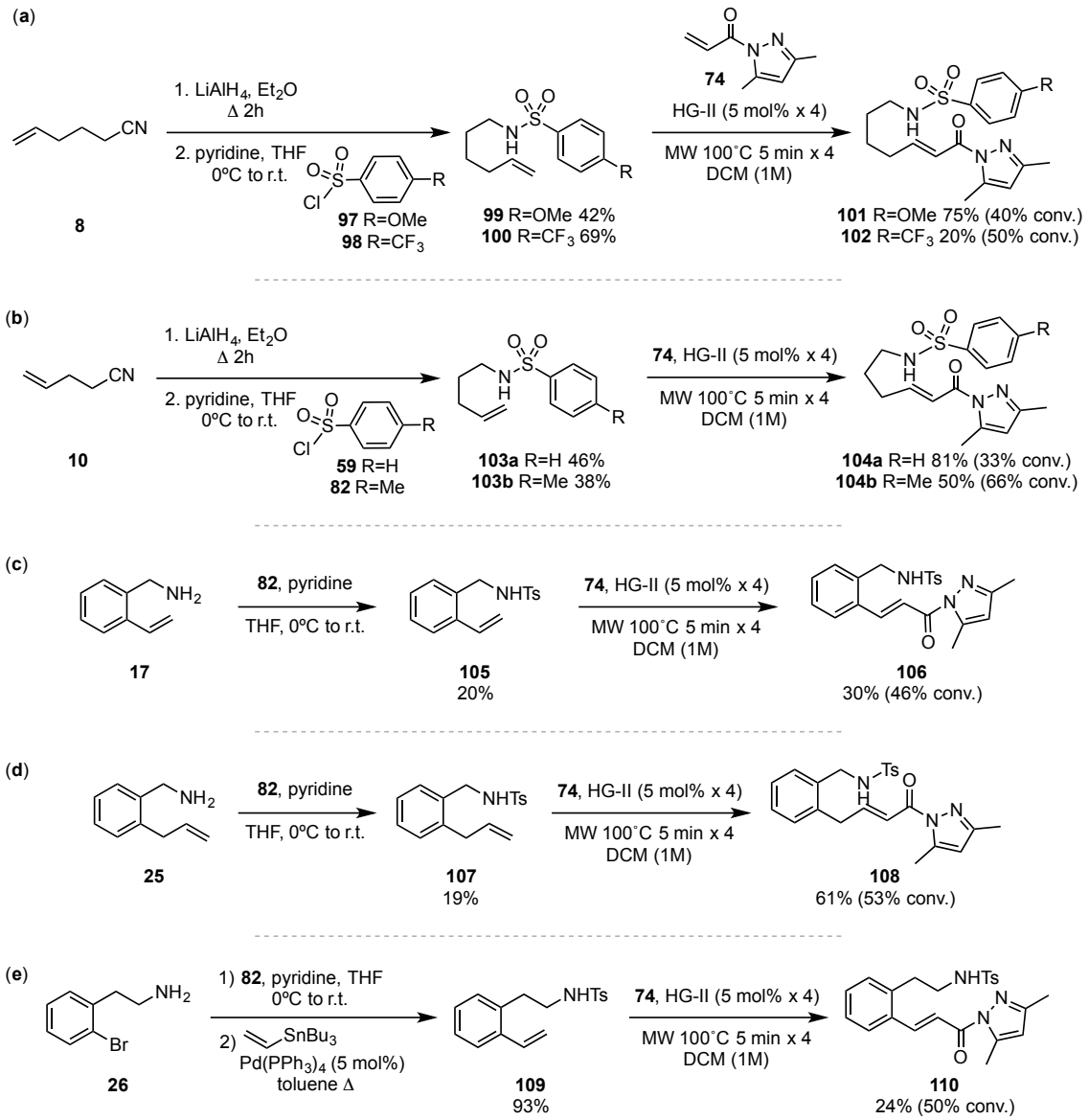


Figure 2.7. Scope of the optimised IMAMR with ester surrogates.

Substrates for the synthesis of products **84d-e** and **94-96** were prepared following analogous procedures to those described previously in this Memory for the protection of the free amines and the CM reactions with pyrazole amide **74**. Compound **101** was obtained in good yield, whereas preparation of **102** had lower yield (Scheme 2.34.a). Synthesis of **104a** and **104b** starting from 4-pentenenitrile **10** proceed with moderate yields for both in the construction of sulfonamides **103a** [237] and **103b**[224] and in the subsequent CM reactions (Scheme 2.34.b). Amine **17** (Scheme 1.37) was protected with tosyl chloride **82** giving compound **105**[238] with low yield, as well as it happened with the following CM reaction with conjugated DMP **74** (Scheme 2.34.c). Likewise, amine **25** (Scheme 1.39) gave rise to tosyl amide **107**[239] with poor yield, although CM reaction to obtain compound **108** proceeded with good yield (Scheme 2.34.d). Finally, starting from commercial phenethyl amine **26** it was synthesized protected amine **109**[240] with very good yield, to then prepare compound **110** through CM reaction with low yield (Scheme 2.34.d).

[237] Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949.
[224] Luo, S.-P.; Guo, L.-D.; Gao, L.-H.; Li, S.; Huang, P.-Q. *Chem. Eur. J.* **2013**, *19*, 87–91.
[238] Bennasar, M. L.; Roca, T.; Monerris, M.; García-Díaz, D. *J. Org. Chem.* **2006**, *71*, 7028–7034.
[239] Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807.
[240] Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905.



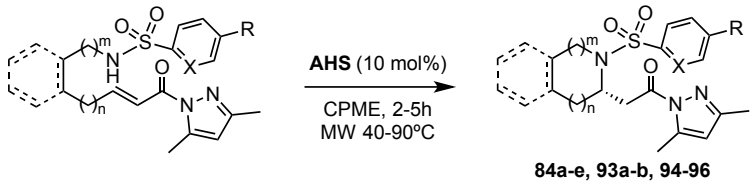
Scheme 2.34. Synthesis of conjugated-DMP substrates for IMAMR.

In order to prove the influence of the electronic requirements of the aromatic sulfonamide in the process, substrates containing both electron-donating and electron-withdrawing substituents were synthesized. In all cases, piperidine derivatives **84a-e** were obtained in very good yields (70-92%) and enantioselectivities (up to 96.5:3.5 *er*. Table 2.3, entries 1-5). However, the formation of the pyrrolidine counterparts took place with decreased enantioselectivity, giving rise to compounds **93a-b** with 90:10 and 88:12 *er*, respectively (Table 2.3, entries 6-7).[241] This protocol was next extended to

[241] The formation of five-membered rings by intramolecular organocatalytic reactions was found to be less effective than the corresponding six-membered rings: a) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016–16017. b) See Ref.

benzofused derivatives **106**, **108** and **110**. Thus, isoindoline **94** and tetrahydroisoquinoline **95** were obtained in good yield (93 and 84% respectively) and enantioselectivity (90:10 and 93.5:6.5 *er*, respectively. Table 2.3, entries 8-9). 1-Substituted tetrahydroisoquinoline **96** was also efficiently synthesized, although enantioselection was in this case lower (85:15 *er*. Table 2.3, entry 10).

Table 2.3. Extension of the scope of the IMAMR for the enantioselective synthesis of monocyclic **84** and **93** and benzofused **94-96** *N*-heterocycles.



84a-e, 93a-b, 94-96

Entry	*m*	*n*	*SM*	*X*	*R*	*T (ºC)*	*t (h)*	*Prod.*	*Yield (%)*[a]	*er*[b]
1	1	1	**80a**	N	H	25[c]	120	**84a**	71	92.5:7.5
2	1	1	**80b**	C	H	90	4	**84b**	92	96.5:3.5
3	1	1	**80c**	C	Me	90	4	**84c**	91	96:4
4	1	1	**101**	C	MeO	90	5	**84d**	70	96.5:3.5
5	1	1	**102**	C	CF_3	90	5	**84e**	91	95:5
6	1	0	**104a**	C	H	60	2	**93a**	98	90:10
7	1	0	**104b**	C	Me	40	5	**93b**	84	88:12
8	1	0	**106**	C	Me	60	4	**94**	93	90:10
9	1	1	**108**	C	Me	60	4	**95**	84	93.5:6.5
10	2	0	**110**	C	Me	60	4	**96**	88	85:15

[a] Isolated yields after flash chromatography purification.
[b] Determined by chiral stationary phase HPLC
[c] Without microwave irradiation

2.3.3. ENANTIOSELECTIVE SYNTHESIS OF 6-MEMBERED RING *N*-HETEROCYCLES THROUGH A DOMINO PROCESS

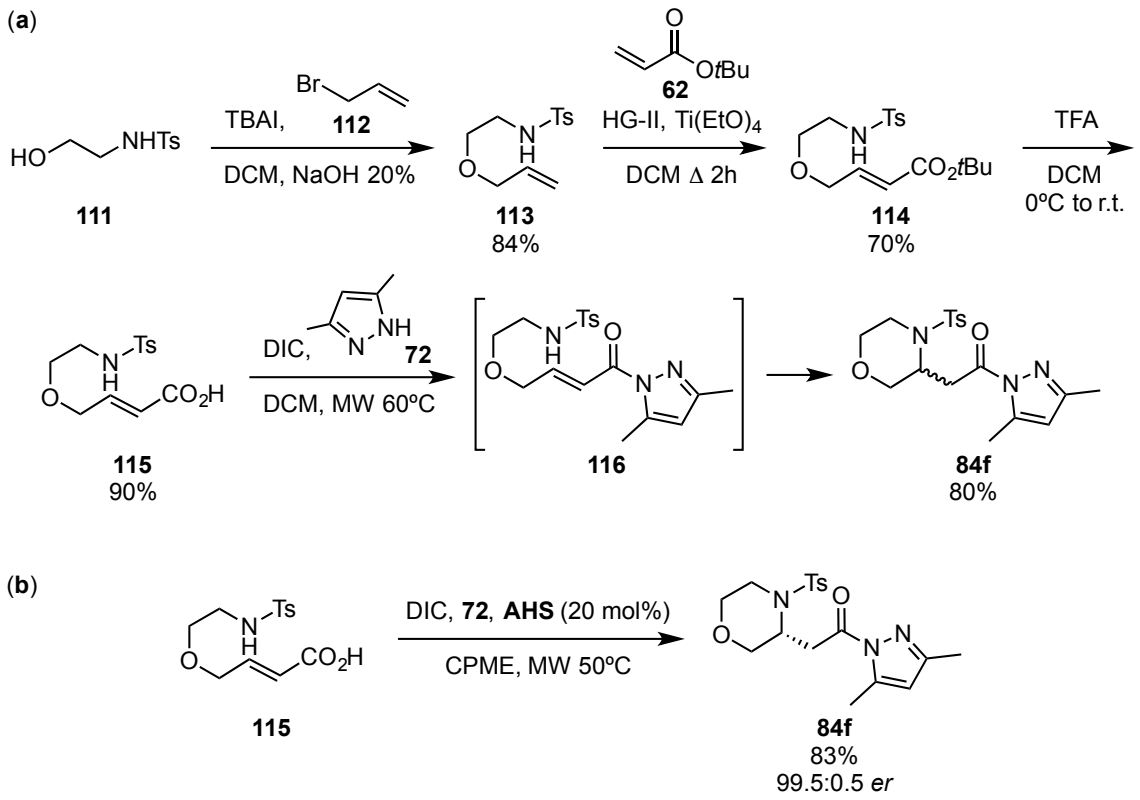
The results presented in Table 2.3 show that this IMAMR is especially efficient in the formation of piperidine derivatives and therefore, it was decided to evaluate the synthesis of different 6-membered ring heterocycles by means of this methodology. To this end, it was first considered the possibility of

172: Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sánchez-Roselló, M. *Chem. Eur. J.* **2011**, *17*, 14267–14272.

synthesize a morpholine derivative. The corresponding conjugated pyrazolamide substrate for the IMAMR should be obtained through a CM reaction between **113** and 3,5-dimethylpyrazol acryl amide **74** in the presence of ruthenium catalyst Hoveyda-Grubbs second generation (HG-II) in a similar way than other substrates had been previously prepared. However, this CM reaction on compound **113** did not proceed even when the reaction mixture was heated under reflux in the presence of a Lewis acid [$Ti(EtO)_4$] or a Brønsted acid (*p*-TSA).

At this point, it was decided to employ an alternative synthetic approach to access the desired IMAMR substrate **116**, analogous in the first steps to that employed for the preparation of the Weinreb amide derivative **79** (Scheme 2.29). Once synthesized **113**[242] through a controlled alkylation of ethanolamine **111** with allyl bromide **112** by means of tetrabutyl ammonium iodide and sodium hydroxide, the route designed involved the CM between **113** and *tert*-butyl acrylate **62**, followed by ester deprotection on compound **114** and peptide coupling (PC) of α,β-unsaturated acid **115** with 3,5-dimethyl pyrazole (DMP) **72**. Unfortunately, under the conditions employed to effect the PC, racemic morpholine derivative **84f,** arising from the IMAMR of intermediate **116**, was directly obtained (Scheme 2.35.a). Despite this unexpected result, it was envisioned the potential of developing a domino enantioselective process in the presence of chiral squaramide **AHS**. To our delight, treatment of acid **115** with **AHS**, diisopropyl carbodiimide (DIC), and DMP **72** in CPME at 50ºC under microwave irradiation, led to the formation of the morpholine derivative **84f** in 83% yield and 99.5:0.5 *er* (Scheme 2.35.b).

[242] Lu, Z.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1234–1237.



Scheme 2.35. Development of an organocatalytic domino PC-IMAMR.

This domino protocol was next extended to substrates depicted in Figure 2.8. Besides morpholine derivative **84f**, this methodology was efficient in the formation of other 6-membered rings such as geminal-substituted piperidines **84g** and **84h** or keto piperazine **84i**, which were obtained in moderate yields and good enantioselectivities. Compound **84c** was also obtained through this domino procedure with similar results in terms of enantioselectivity when compared to the stepwise process, although in lower yield (Table 2.3, entry 3). In the formation of pyrrolidine **93b** some erosion of enantioselectivity also occurred (Table 2.3, entry 7).

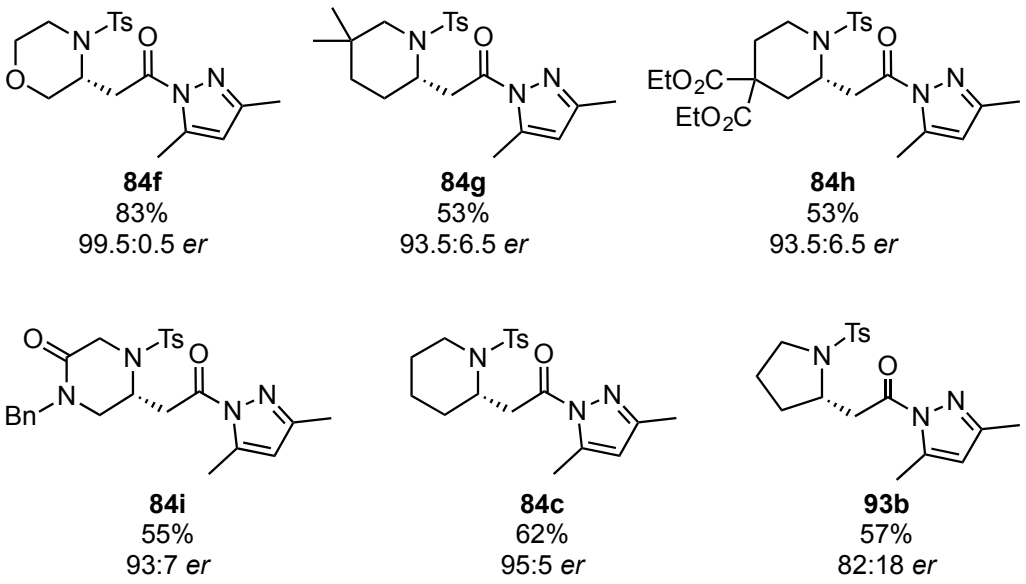
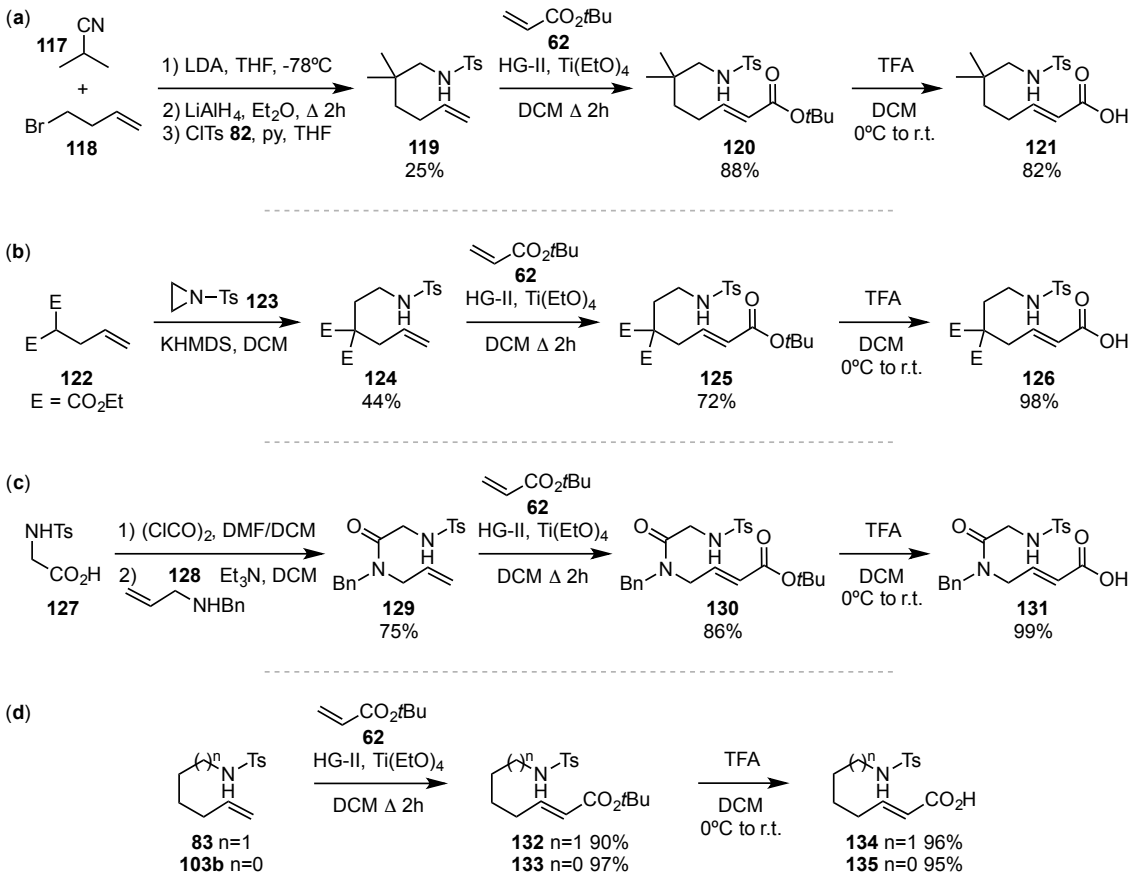


Figure 2.8. Products obtained through the organocatalytic domino PC-IMAMR.

Preparation of the rest of conjugated acid substrates for the domino PC-IMAMR are described in Scheme 2.36. Addition of LDA-deprotonated isobutyronitrile **117** to 4-bromobutene **118**,[243] followed by the stablished nitrile reduction and amine protection gave sulfonamide **119** with three-step moderate yield. The subsequent CM reaction with *tert*-butyl acrylate and ester hydrolysis proceed with good yields to obtain compound **121** (Scheme 2.36.a). Synthesis of product **126** followed an analogous sequence of CM reaction and TFA ester hydrolysis, but in this case the first step was the addition of diethyl 2-allylmalonate to *N*-tosyl aziridine in presence of potassium bis(trimethyl)amide (KHMDS) giving rise to substrate for CM reaction **124** with moderate yield (Scheme 2.36.b). Preparation of substrate for the preparation of piperazinone substructure **131** proceeded with very good yields in the four steps of the sequence (Scheme 2.36.c), which started with the formation of acyl chloride derivative of *N*-tosyl glycine by means of oxalyl chloride and the subsequent nucleophilic substitution of benzylallyl amine in presence of triethyl amine to obtain **129**. Finally, compounds **134** and **135** were obtained with excellent yields starting from the previously described tosyl amides **83** and **103b** (Scheme 2.36.d).

[243] Gribkov, D. V; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748–3759.



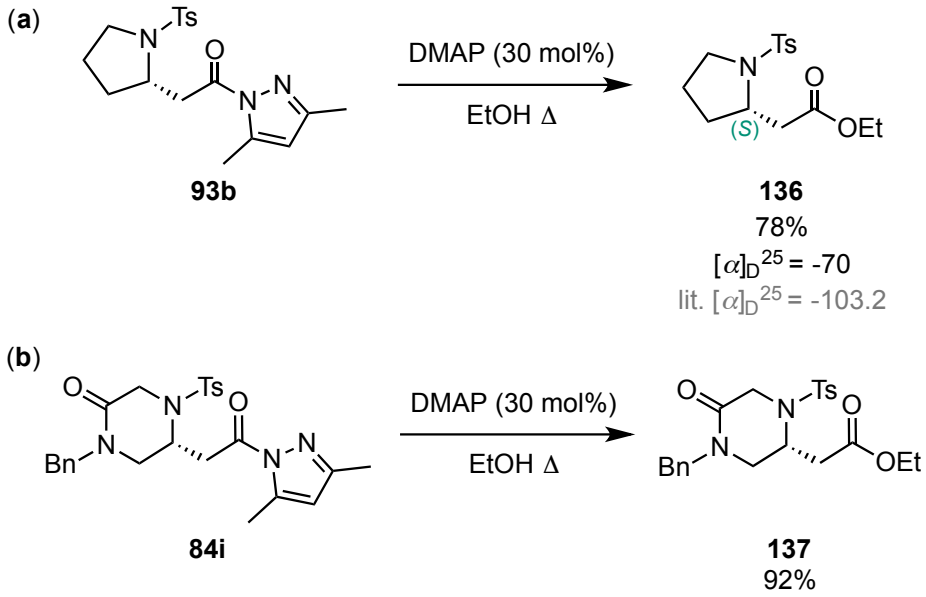
Scheme 2.36. Preparation of substrates for the domino PC-IMAMR.

2.3.4. TRANSFORMATION OF SURROGATES INTO THE CORRESPONDING ENANTIOENRICHED ESTERS

The transformation of the pyrazole moiety of pyrrolidine **93b** into the ethyl ester derivative **136** was successfully achieved by treatment with 4-dimethyl aminopyridine (DMAP) in ethanol under reflux conditions (Scheme 2.37.a). Comparison of the optical rotation ($[\alpha]_D$) value of **136** with that reported in the literature led to the conclusion that the newly created stereocenter holds the *S* absolute configuration.[244] The same stereochemical outcome was assumed for all other compounds of the IMAMR. Additionally, DMP substituent of piperazinone **84i** was also converted into an ethyl ester, obtaining product **137** with excellent yield (Scheme 2.37.b). Preparation of **137** was necessary to determine the *er* ratio of **84i** because it was impossible to separate its enantiomers with the HPLC. Likewise, **137** could not be separated with any

[244] Joselice e Silva, M.; Cottier, L.; Srivastava, R. M.; Sinou, D.; Thozet, A. *Carbohydr. Res.* **2005**, *340*, 309–314.

chiral column using HPLC analysis. However, the enantiomeric relation was finally obtained by means of a NMR study of the diastereoisomers formed in a solution of **137** (0.8 mL, 10 mg/mL) after the progressive addition of portions of a solution of europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] in $CDCl_3$ (0.225 mL, 20 mg/mL). After the addition of three portions, the separation of one of the NMR signals was satisfactory.



Scheme 2.37. Transformation of pyrazole amides into the corresponding esters.

2.3.5. MECHANISTIC PROPOSAL FOR THE INTRAMOLECULAR *AZA*-MICHAEL REACTION BETWEEN SULFONAMIDES AND α,β-UNSATURATED *N*-ACYL PYRAZOLES

Eventually, a possible mechanism that accounts for the *S* stereochemical assignment mentioned above[244] has been postulated (Figure 2.9). The preferred approach would result from a combination of an acid-base reaction and multiple hydrogen bonding interactions. Sulfonamide group [245] in the substrate would be deprotonated by the quinuclidine moiety in the squaramide catalyst. At the same time, squaramide-amine hydrogens would establish two hydrogen bonds each one with sulfonamide oxygens and with the carbonyl oxygen or the DMP nitrogen. This would fix the transition state, thereby promoting the attack of the nitrogen nucleophile on the *Si* face of the double bond.

[245] Sulfonamides are more acidic than carbamates.

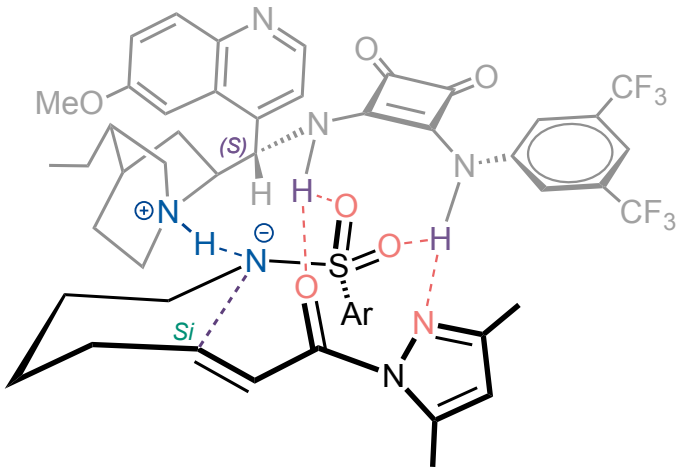


Figure 2.9. Elected transition state of the IMAMR.

However, this is just a presumption of a plausible transition state and many others could be designed. For instance, two years ago when the results of this study where published, the defended mechanism consisted on a π-stacking with an aromatic sandwich of the two rings of the substrate and one of the squaramide, combined with multiple hydrogen bonding interactions. Here again, the sulfonamide group would be deprotonated by the quinuclidine moiety, and two hydrogen bonds would be established between the oxygen atoms in the substrate and the N-H bonds in the catalyst. This approach would promote also the attack on the *Si* face of the double bond (Figure 2.10). Nevertheless, it does not actively involve any dimethyl pyrazole nitrogen, which has been considered pivotal for this transformation. Therefore, despite this was the first postulation, it has been chosen preferably the former transition state (Figure 2.9) to explain the chirality induction in the IMAMR.

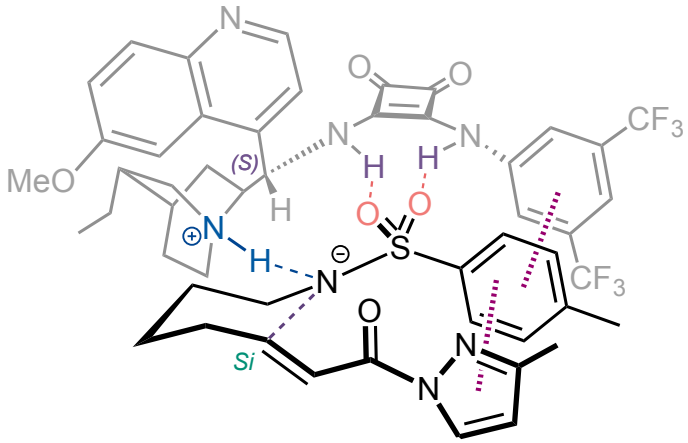


Figure 2.10. Plausible transition state of the IMAMR.

2.4. Conclusions

The described research work, has led to the development of an organocatalytic enantioselective intramolecular *aza*-Michael reaction (IMAMR) of sulfonamides bearing a remote α,β-unsaturated pyrazole amide.[246]

Aniline-hydroquinidine squaramide (**AHS**) was found to be the best catalyst to activate the sophisticated-designed starting materials throughout several hydrogen bond interactions. The role of **AHS** for this transformation, could be performed both in a step wise and in a domino fashion combined with a peptide coupling reaction. Allowing the access to a diverse range of enantioenriched heterocyclic β-amino esters, since it has been demonstrated the facility of conversion of the dimethyl pyrazole into a ester moiety.

Therefore, the use of pyrazole amides as ester synthetic equivalents is a very convenient strategy to perform this transformation with conjugated esters as Michael acceptors, a process that has remained elusive to date.

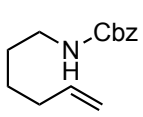
[246] Sánchez-Roselló, M.; Mulet, C.; Guerola, M.; del Pozo, C.; Fustero, S. *Chem. Eur. J.* **2014**, *20*, 15697–15701.

2.5. Experimental Section

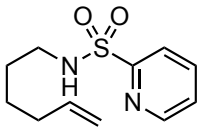
DETERMINATION OF THE ENANTIOMERIC RATIO

In the specific case of compound **86i** it was sought an alternative procedure using the Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] complex to form diastereoisomers that could be separately detected with ^{1}H NMR.

2.5.1. PREPARATION OF THE TERMINAL-OLEFIN *N*-PROTECTED AMINES



1a



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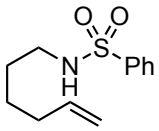
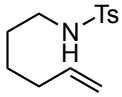


61



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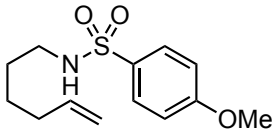

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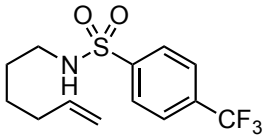

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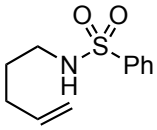
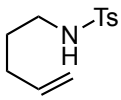
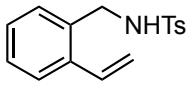


103a



103b



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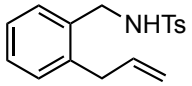

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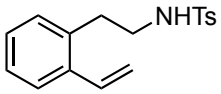

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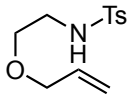
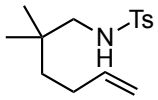


113



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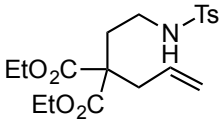
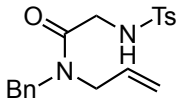


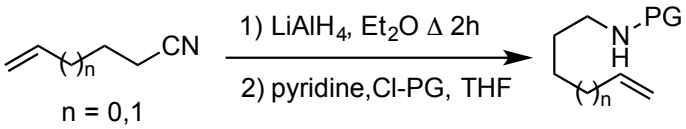
124



129

Amines **1a**,[172] **61**,[224] **83**,[232] **103a**,[237] **103b**,[224] **105**,[238] **107**,[239] **109**,[240] **113**[242] and **119**[243] had been previously described.

2.5.1.1. General procedure for the preparation of N-protected amines, including 99, 100

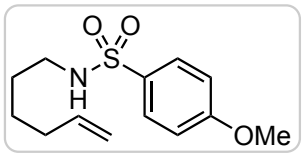


To a suspension of $LiAlH_4$ (6 mmol) in diethyl ether (10 mL) was added dropwise 5- hexenenitrile (2,0 mmol) at room temperature. After heating for 2h at reflux, the suspension was allowed to reach room temperature and $Na_2SO_4 \cdot 10H_2O$ was added with vigorous stirring until aluminium salts turned white. The suspension was filtered through a short pad of Celite® washing with

small portions of diethyl ether. The filtrate was concentrated under vacuum obtaining a yellow oil that used without further purification.

The crude amine was dissolved in THF (10 mL) and pyridine (2.4 equiv.) was added at 0 ºC followed by sulfonyl chloride (1.5 equiv.). The reaction mixture was allowed to reach room temperature overnight and then it was hydrolised with NH_4Cl saturated, extracted with ethyl acetate and dried over Na_2SO_4 anhydrous. Finally, solvents were removed and the crude mixture purified by flash chromatography with hexanes: ethyl acetate as eluents.

N-(5-Hexenyl)-4-methoxybenzenesulfonamide (99)



Physical state: Pale yellow oil

Empiric Formula: $C_{13}H_{19}NO_3S$

Molecular weight (g/mol): 269.36

Yield (%): 42

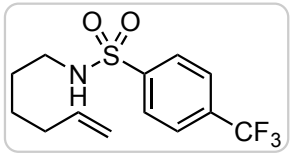
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.70 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.66 – 5.49 (m, 1H), 5.40 (br s, 1H), 4.89 – 4.71 (m, 2H), 3.72 (s, 3H), 2.77 (q, *J* = 6.5 Hz, 2H), 1.84 (q, *J* = 6.5 Hz, 2H), 1.41 – 1.17 (m, 4H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 163.1, 138.4, 131.8, 129.3, 114.7, 114.2, 55.2, 42.5, 32.6, 28.3, 25.2

HRMS (EI^+): Calcd. for $C_{13}H_{19}NO_3S$ [*M*+]: 270.1158, found: 270.1160

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

N-(5-Hexenyl)-4-(trifluoromethyl)benzenesulfonamide (100)



Physical state: White solid

Empiric Formula: $C_{13}H_{16}F_3NO_2S$

Molecular weight (g/mol): 307.33

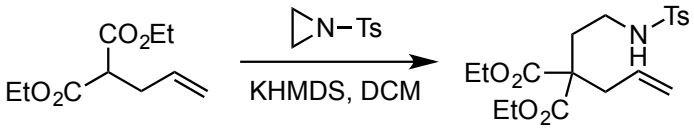
Yield (%): 69

Melting point (ºC): 77-79

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.00 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 5.69 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (br t, *J* = 5.8 Hz, 1H), 4.97 – 4.87 (m, 2H), 2.97 (dt, *J* = 6.7, 6.7 Hz, 2H), 2.02 –

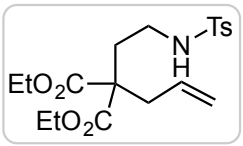
	1.92 (m, 2H), 1.54 – 1.42 (m, 2H), 1.41 – 1.29 (m, 2H)
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm):	143.81, 138.03, 134.44 (q, $^{2}J_{CF}$ = 33 Hz), 127.67, 126.39 (q, $^{3}J_{CF}$ = 4 Hz), 123.36 (q, $^{1}J_{CF}$ = 272 Hz), 43.26, 33.11, 29.08, 25.73
^{19}F NMR (CDCl3, 282.4 MHz) δ (ppm):	−63.6 (s, 3F)
HRMS (EI$^+$):	Calcd. for $C_{13}H_{16}F_3NO_2$ [*M*+]: 308.0927, found: 308.0923
Remarks:	‣ Purification by flash chromatography with hexanes: ethyl acetate 8:1 as eluent.

2.5.1.2. Synthesis of diethyl 2-allyl-2-{2-[(4-methylphenyl)sulfonamido] ethyl}malonate 124



KHMDS (2.4 ml, 0.5M solution in toluene) was added to a solution of diethyl 2-allylmalonate (200 mg, 1.0 mmol) in THF (5 mL) at 0 ºC. The mixture was stirred for 20 min and then another solution of *N*-tosyl aziridine (216 mg, 1.1 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 5 additional hours, hydrolysed with saturated ammonium chloride (10 mL), extracted with EtOAc (3 x 5 mL) and dried over anhydrous Na_2SO_4.

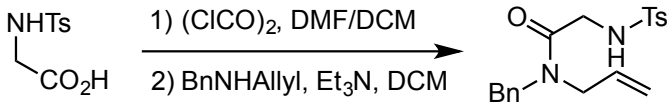
Diethyl 2-allyl-2-{2-[(4-methylphenyl)sulfonamido] ethyl}malonate (124)



Physical state:	Colorless oil
Empiric Formula:	$C_{19}H_{27}NO_6S$
Molecular weight (g/mol):	397.49
Yield (%):	44
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm):	7.71 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 5.63–5.46 (m, 1H), 5.10–4.98 (m, 2H), 4.63 (t, J = 6.2 Hz, 1H), 4.16 (q, J = 7.1 Hz, 4H), 3.03–2.91 (m, 2H), 2.59 (d, J = 7.4 Hz, 2H), 2.42 (s, 3H), 2.08–1.99 (m, 2H), 1.22 (t, J = 7.1 Hz, 6H)
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm):	170.83, 143.46, 136.94, 131.93, 129.76, 127.19, 119.60, 61.81, 56.18, 39.29, 37.96, 32.91, 21.70, 14.21
HRMS (EI$^+$):	Calcd. for $C_{19}H_{27}NO_6S$ [M^+]: 398.1632, found: 398.1623

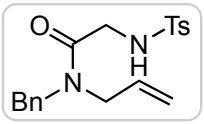
Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.

2.5.1.3. Synthesis of N-Allyl-N-benzyl-2-[(4-methylphenyl)sulfonamido] acetamide 129



Oxalyl chloride (1.2 mmol, 2.0M solution in DCM) and two drops of DMF were successively added to a solution of N-tosyl glycine (1.0 mmol) in DCM (5 mL) under nitrogen at 0 ºC, and the resulting mixture stirred at this temperature for 1 h. Then, a solution of benzyl allyl amine (1.2 mmol) and triethyl amine (3 mmol) in DCM (5 mL) was added dropwise. The reaction was stirred overnight, hydrolysed with saturated ammonium chloride (10 mL), extracted with DCM (3 x 5 mL) and dried over anhydrous Na_2SO_4.

_N_-Allyl-_N_-benzyl-2-[(4-methylphenyl)sulfonamido]acetamide (129)



Physical state:	Colorless oil
Empiric Formula:	$C_{19}H_{22}N_2O_3S$
Molecular weight (g/mol):	358.46
Yield (%):	75

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.71 (d, J = 7.6 Hz, 1.27H), 7.65 (d, J = 7.6 Hz, 0.73H), 7.32–7.22 (m, 5H), 7.17–6.93 (m, 2H), 5.80–5.67 (m, 1H), 5.35–5.27 (m, 1H), 5.24–5.14 (m, 1H), 4.72 (s, 1.28H), 4.56 (s, 0.72H), 4.22–3.91 (m, 4H), 2.81 (s, 3H)

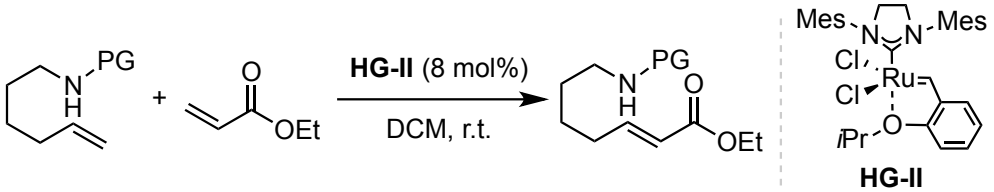
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 167.4, 167.1, 143.5, 136.3, 136.1, 135.9, 135.2, 131.9, 131.3, 129.7, 129.1, 128.7, 128.2, 127.9, 127.7, 127.3, 126.3, 118.3, 117.5, 49.1, 48.6, 48.1, 43.8, 43.6, 21.6

HRMS (EI$^+$): Calcd. for $C_{19}H_{22}N_2O_3S$ [M^+]: 359.1385, found: 359.1382

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.
- ^{1}H and ^{13}C NMR show the presence of rotamers about the amide bond in ca. 1.3:0.7 ratio.

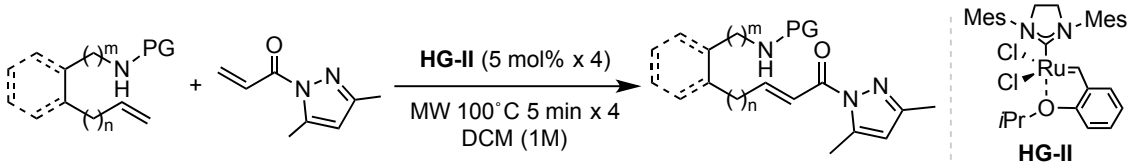
2.5.2. PREPARATION OF THE α,β-UNSATURATED *N*-PROTECTED AMINES CANDIDATES FOR IMAMR SUBSTRATES

Method A: Cross-metathesis reaction with ethyl acrylate



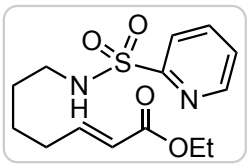
To a solution of N-protected amine (1.0 equiv.) in CH_2Cl_2 (0.1 M) under nitrogen atmosphere, ethyl acrylate (3.0 equiv.) and Hoveyda-Grubbs 2nd generation catalyst (8 mol%) were added. The resulting solution was stirred for 12 h at room temperature and then, solvents were removed and the crude mixture purified by flash chromatography with hexanes: ethyl acetate as eluents.

Method B: Cross-metathesis reaction with 3,5-dimethylpyrazol acryl amide



To a solution of N-protected amine (1.0 equiv.) in CH_2Cl_2 (0.1 M) under nitrogen atmosphere in a microwave vial, and 3,5-dimethylpyrazol acryl amide (3.0 equiv.) and an initial 5 mol% charge of Hoveyda-Grubbs 2nd generation catalyst were added. The mixture was heated under microwave irradiation at 100 ºC for 5 minutes. Three more portions of catalyst (20 mol% total) were successively added while heating each time at the same temperature and time. Finally, solvents were removed and the crude reaction mixture purified by flash chromatography with hexanes: ethyl acetate as eluents.

Ethyl (*E*)-7-(2-Pyridinesulfonamido)-2-heptenoate (55)



Physical state: Brown thick oil

Empiric Formula: $C_{17}H_{23}NO_4$

Molecular weight (g/mol): 312.38

Yield (%): 98

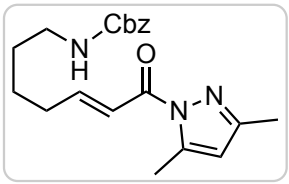
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.70 (dd, *J* = 4.6, 1.3, 1H), 8.01 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.92 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.50 (ddd, *J* = 7.7, 4.6, 1.3 Hz, 1H), 6.87 (dt, *J* = 14.1, 6.8 Hz, 1H), 5.77 (dt, *J* = 14.1, 1.3 Hz, 1H), 5.02 (br t, *J* = 6.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.09 – 3.03 (m, 2H), 2.20 – 2.13 (m, 2H), 1.58 – 1.43 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 166.66, 157.64, 150.19, 148.26, 138.20, 126.79, 122.33, 122.00, 60.36, 43.52, 31.58, 29.38, 24.97, 14.40

HRMS (EI$^+$): Calcd. for $C_{14}H_{20}N_2O_4S$ [M^+]: 313.1177, found: 313.1162

Remarks:
- By means of the procedure described as Method A.
- Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.

Benzyl (*E*)-[7-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-oxo-5-heptenyl]carbamate (66)



Physical state: Pale brown oil

Empiric Formula: $C_{20}H_{25}N_3O_3$

Molecular weight (g/mol): 355.44

Yield (%): 88 (67% conv.)

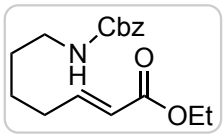
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.27 – 7.18 (m, 6H), 7.13 – 7.01 (m, 1H), 5.89 (s, 1H), 5.01 (br s, 2H), 4.72 (br s, 1H), 3.19 – 2.99 (m, 2H), 2.48 (s, 3H), 2.38 – 2.23 (m, 2H), 2.17 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.24, 156.52, 151.96, 150.74, 144.53, 136.72, 128.62, 128.20, 128.20, 121.70, 111.43, 66.75, 40.89, 32.36, 29.70, 25.36, 14.74, 13.93

HRMS (EI$^+$): Calcd. for $C_{20}H_{25}N_3O_3$ [M^+]: 356.1929, found: 356.1930

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

Ethyl (*E*)-7-(Benzyloxycarbonyl amino)-2-heptenoate (68)



Physical state: Colorless oil

Empiric Formula: $C_{17}H_{23}NO_4$

Molecular weight (g/mol): 305.37

Yield (%): 82

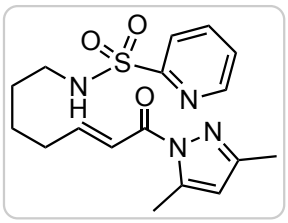
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.21 – 7.02 (m, 5H), 6.71 (dt, *J* = 15.5, 6.9 Hz, 1H), 5.60 (dt, *J* = 15.5, 1.3 Hz, 1H), 4.88 (s, 2H), 4.73 (br s, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.06 – 2.88 (m, 2H), 2.08 – 1.90 (m, 2H), 1.38 – 1.15 (m, 4H), 1.07 (t, *J* = 7.1 Hz, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 166.65, 156.51, 148.54, 136.69, 128.54, 128.11, 128.11, 121.75, 66.63, 60.23, 40.77, 31.72, 29.53, 25.16, 14.30

HRMS (EI^+): Calcd. for $C_{17}H_{23}NO_4$ [M^+]: 306.1840, found: 306.1835

Remarks:
- By means of the procedure described as Method A.
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

(*E*)-*N*-[7-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-oxo-5-heptenyl]-2-pyridine sulfonamide (80a)



Physical state: Colorless oil

Empiric Formula: $C_{17}H_{22}N_4O_3S$

Molecular weight (g/mol): 362.45

Yield (%): 89% (46% conv.)

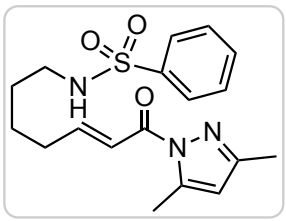
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.67 (dd, *J* = 4.8, 1.1 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.1, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.1, 4.8 Hz, 1H), 7.19 (d, *J* = 15.6 Hz, 1H), 7.04 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.94 (s, 1H), 5.82 (br t, *J* = 5.4 Hz, 1H), 3.09 – 2.94 (m, 2H), 2.51 (s, 3H), 2.26

	– 2.16 (m, 5H), 1.54 – 1.42 (m, 4H)
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm):	165.54, 157.87, 152.29, 150.91, 150.41, 144.72, 138.52, 126.99, 122.57, 121.76, 111.54, 43.01, 31.69, 28.93, 24.56, 14.20, 13.37

HRMS (EI^+): Calcd. for $C_{17}H_{22}N_4O_3S$ [M^+]: 363.1485, found: 363.1487

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.

(*E*)-*N*-[7-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-oxo-5-heptenyl]benzene sulfonamide (80b)



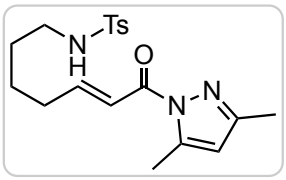
Physical state:	Brown oil
Empiric Formula:	$C_{18}H_{23}N_3O_3S$
Molecular weight (g/mol):	361.46
Yield (%):	71% (35% conv.)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm):	8.67 (dd, *J* = 4.8, 1.1 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.1, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.1, 4.8 Hz, 1H), 7.19 (d, *J* = 15.6 Hz, 1H), 7.04 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.94 (s, 1H), 5.82 (br t, *J* = 5.4 Hz, 1H), 3.09 – 2.94 (m, 2H), 2.51 (s, 3H), 2.26 – 2.16 (m, 5H), 1.54 – 1.42 (m, 4H)
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm):	165.07, 164.92, 151.94, 151.90, 150.39, 149.37, 144.40, 140.01, 132.61, 129.13, 127.03, 122.04, 121.63, 111.40, 42.92, 42.60, 32.00, 29.61, 29.10, 28.20, 25.00, 14.60, 13.80

HRMS (EI^+): Calcd. for $C_{18}H_{23}N_3O_3S$ [M^+]: 362.1533, found: 362.1531

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 4:1 as eluent.
- ^{1}H and ^{13}C NMR show the presence of rotamers in ca. 1:1 ratio

(*E*)-*N*-[7-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-oxo-5-heptenyl]-4-methyl benzenesulfonamide (80c)



Physical state: Brown oil

Empiric Formula: $C_{19}H_{25}N_3O_3S$

Molecular weight (g/mol): 375.49

Yield (%): 94% (53% conv.)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.71 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 15.6 Hz, 1H), 7.04 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.94 (s, 1H), 5.20 (br t, *J* = 5.1 Hz, 1H), 2.99 – 2.80 (m, 2H), 2.51 (s, 3H), 2.36 (s, 3H), 2.27 – 2.14 (m, 5H), 1.56 – 1.37 (m, 4H)

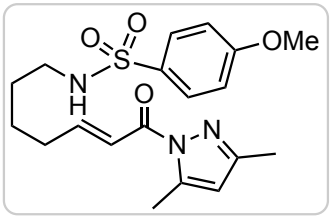
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.54, 152.28, 150.98, 144.70, 143.69, 137.19, 129.97, 127.33, 121.69, 111.54, 42.57, 31.69, 28.65, 24.62, 21.08, 14.20, 13.37

HRMS (EI^+): Calcd. for $C_{19}H_{25}N_3O_3S$ [M^+]: 376.1689, found: 376.1690

Remarks:

- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 8:1 as eluent.

(*E*)-*N*-[7-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-oxo-5-heptenyl]-4-methoxy benzenesulfonamide (101)



Physical state: Brown oil

Empiric Formula: $C_{19}H_{25}N_3O_4S$

Molecular weight (g/mol): 391.49

Yield (%): 75% (40% conv.)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.77 (d, *J* = 8.4 Hz, 2H), 7.21 (dd, *J* = 15.7, 0.7 Hz, 1H), 7.12 – 6.99 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.94 (s, 1H), 5.05 (br s, 1H), 3.81 (s, 3H), 2.97 – 2.82 (m, 2H), 2.52 (s, 3H), 2.24 – 2.17 (m, 5H), 1.58 – 1.37 (m, 4H)

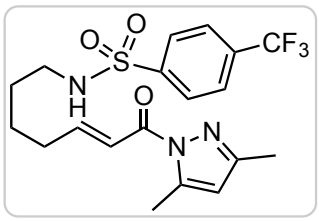
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.56, 163.31, 152.28, 150.86, 144.74, 131.88, 129.49, 121.82, 114.43, 111.53, 55.43, 42.60, 31.71, 28.73, 24.70, 14.17,

13.36

HRMS (EI$^+$): Calcd. for $C_{19}H_{25}N_3O_4S$ [M^+]: 392.1639, found: 392.1633

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 3:1 as eluent.

(*E*)-*N*-[7-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-oxo-5-heptenyl]-4-(trifluoromethyl)benzenesulfonamide (102)



Physical state: Pale pink solid

Empiric Formula: $C_{19}H_{22}F_3N_3O_3S$

Molecular weight (g/mol): 391.49

Yield (%): 20% (50% conv.)

Melting point (ºC): 79-81

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.93 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.14 (m, 1H), 7.03 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.91 (s, 1H), 4.96 (br s, 1H), 2.97 – 2.89 (m, 2H), 2.49 (s, 3H), 2.30 – 2.21 (m, 2H), 2.18 (s, 3H), 1.51 – 1.39 (m, 4H)

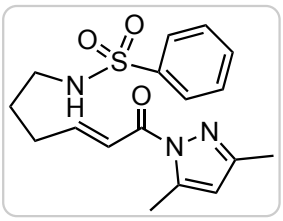
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.04, 152.01, 150.09, 147.64, 144.51, 143.75, 127.65, 126.39, 121.87, 111.48, 43.21, 32.11, 29.39, 25.16, 14.80, 14.00

^{19}F NMR (CDCl3, 282.4 MHz) δ (ppm): -63.31 (s, 3F)

HRMS (EI$^+$): Calcd. for $C_{19}H_{22}F_3N_3O_3S$ [M^+]: 430.1407, found: 430.1403

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 6:1 as eluent.

(*E*)-*N*-[6-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-oxo-4-hexenyl]benzene sulfonamide (104a)



Physical state: Pale brown foam

Empiric Formula: $C_{17}H_{21}N_3O_3S$

Molecular weight (g/mol): 347.43

Yield (%): 81% (33% conv.)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.85 – 7.79 (m, 2H), 7.58 – 7.43 (m, 3H), 7.29 – 7.20 (m, 1H), 7.06 (dt, *J* = 14.3, 6.3 Hz, 1H), 6.07 (s, 1H), 5.03 (br s, 1H), 3.35 (dt, *J* = 6.3, 6.2 Hz, 2H), 2.93 (s, 3H), 2.77 – 2.68 (m, 2H), 2.65 (s, 3H), 2.21 – 2.10 (m, 2H)

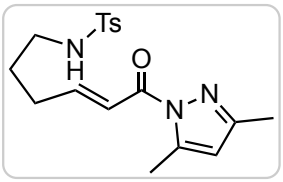
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 164.91, 151.97, 149.18, 144.45, 140.01, 132.71, 129.20, 127.07, 122.19, 111.48, 42.77, 29.75, 28.40, 14.78, 13.99

HRMS (EI^+): Calcd. for $C_{17}H_{21}N_3O_3S$ [M^+]: 348.1376, found: 348.1373

Remarks:

- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 6:1 as eluent.

(*E*)-*N*-[6-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-oxo-4-hexenyl]-4-methyl benzenesulfonamide (104b)



Physical state: Brown oil

Empiric Formula: $C_{18}H_{23}N_3O_3S$

Molecular weight (g/mol): 361.46

Yield (%): 50% (66% conv.)

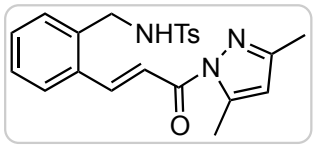
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.74 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.04 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.97 (s, 1H), 4.93 (br s, 1H), 2.97 (dt, *J* = 6.7, 6.9 Hz, 2H), 2.54 (s, 3H), 2.39 (s, 3H), 2.31 (dd, *J* = 6.7, 6.8 Hz, 2H), 2.24 (s, 3H), 1.73 – 1.63 (m, 2H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.55, 152.49, 149.83, 144.91, 143.96, 137.40, 130.17, 127.49, 122.42, 111.71, 42.47, 29.42, 27.98, 21.25, 14.32, 13.52

HRMS (EI^+): Calcd. for $C_{18}H_{23}N_3O_3S$ [M^+]: 362.1533, found: 362.1532

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 8:1 as eluent.

(*E*)-*N*-{2-[3-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-oxo-1-propenyl]benzyl}-4-methylbenzenesulfonamide (106)



Physical state: Brown solid

Empiric Formula: $C_{22}H_{23}N_3O_3S$

Molecular weight (g/mol): 409.50

Yield (%): 30% (46% conv.)

Melting point (ºC): 121-123

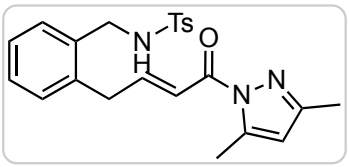
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.75 – 7.65 (m, 3H), 7.64 – 7.59 (m, 1H), 7.28 – 7.17 (m, 5H), 5.97 (s, 1H), 5.09 (br t, *J* = 6.0 Hz, 1H), 4.24 (d, *J* = 6.0 Hz, 2H), 2.55 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 164.44, 151.55, 143.82, 142.81, 141.11, 136.12, 134.88, 132.94, 129.72, 129.10, 129.02, 127.70, 126.71, 126.44, 119.98, 110.75, 43.46, 20.15, 13.20, 12.40

HRMS (EI$^+$): Calcd. for $C_{22}H_{23}N_3O_3S$ [M^+]: 410.1533, found: 410.1532

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 4:1 as eluent.

(*E*)-*N*-{2-[4-(3,5-Dimethyl-1H-pyrazol-1-yl)-4-oxo-2-butenyl]benzyl}-4-methylbenzenesulfonamide (108)



Physical state: Brown oil

Empiric Formula: $C_{23}H_{25}N_3O_3S$

Molecular weight (g/mol): 423.53

Yield (%): 61% (53% conv.)

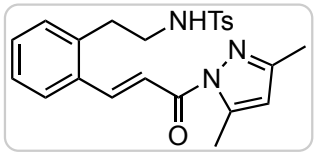
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.66 – 7.60 (m, 2H), 7.42 – 7.38 (m, 1H), 7.29 – 7.28 (m, 2H), 7.27 (s, 2H), 7.15 (dd, *J* = 5.4, 3.4 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.98 – 6.91 (m, 1H), 6.02 (s, 1H), 5.14 (t, *J* = 5.8 Hz, 1H), 4.10 – 4.06 (m, 2H), 3.61 –

	3.53 (m, 2H), 2.59 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H)
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm):	164.73, 152.52, 147.83, 144.31, 143.46, 136.49, 135.94, 134.35, 130.41, 130.24, 129.63, 128.68, 127.61, 127.03, 122.79, 111.51, 44.87, 35.81, 21.51, 14.47, 13.85

HRMS (EI$^+$): Calcd. for $C_{23}H_{25}N_3O_3S$ [M^+]: 424.1689, found: 424.1686

Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 6:1 as eluent.

(*E*)-*N*-{2-[3-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-oxo-1-propenyl]phenethyl}-4-methylbenzenesulfonamide (110)



Physical state:	Brown oil
Empiric Formula:	$C_{23}H_{25}N_3O_3S$
Molecular weight (g/mol):	423.53
Yield (%):	24% (50% conv.)

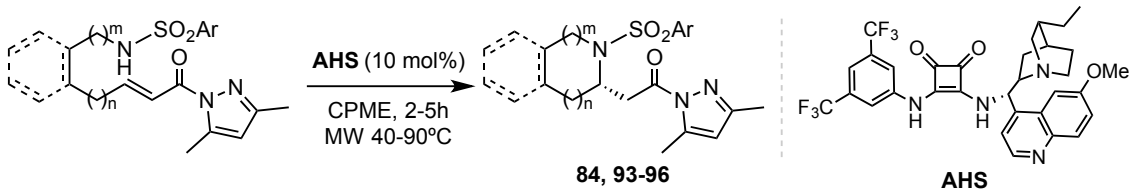
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.03 (d, *J* = 15.8 Hz, 1H), 7.79 (d, *J* = 15.8 Hz, 1H), 7.73 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.36 – 7.28 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.20 – 7.15 (m, 2H), 6.03 (s, 1H), 4.48 (br t, *J* = 6.2 Hz, 1H), 3.18 (td, *J* = 7.1, 6.2 Hz, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 2.38 (s, 3H), 2.29 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.29, 152.27, 144.59, 143.54, 142.49, 137.75, 136.99, 133.72, 130.91, 130.70, 129.88, 127.89, 127.62, 127.22, 120.18, 111.74, 44.05, 33.73, 21.60, 14.80, 13.99

HRMS (EI$^+$): Calcd. for $C_{23}H_{25}N_3O_3S$ [M^+]: 424.1689, found: 424.1685

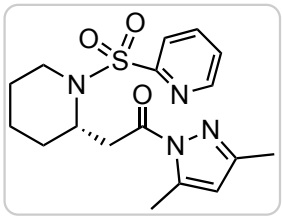
Remarks:
- By means of the procedure described as Method B.
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

2.5.3. MICHAEL ADDUCTS SYNTHESIS: PREPARATION OF 2-SUBSTITUTED NITROGEN HETEROCYCLES 84A-E AND 93-96



The corresponding α,β-unsaturated *N*-acyl pyrazole 1 or 3 (1.0 equiv.) was dissolved in cyclopentyl methyl ether (CPME) (0.1M) in a microwave vial and then catalyst **AHS** (10 mol%) was added. The vial was sealed and the corresponding solution was heated under microwave irradiation at 40-90 ºC for 2-5h. After this time, the crude reaction mixture was purified by means of flash chromatography on silica gel using the appropriate eluent.

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-[1-(2-pyridylsulfonyl)piperidin-2-yl]-1-ethanone (84a)



Physical state:	Colorless oil
Empiric Formula:	$C_{17}H_{22}N_4O_3S$
Molecular weight (g/mol):	362.45
Yield (%):	48%
Enantiomeric relation:	92.5:7.5
Optical rotation $[\alpha]_D^{25}$:	-17.7 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.60 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 7.99 – 7.92 (m, 1H), 7.88 – 7.77 (m, 1H), 7.39 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 5.93 (s, 1H), 4.81 (br s, 1H), 3.99 (dd, *J* = 13.8, 3.2 Hz, 1H), 3.41 (d, *J* = 7.1 Hz, 2H), 3.33 – 3.19 (m, 1H), 2.45 (s, 3H), 2.22 (s, 3H), 1.72 – 1.58 (m, 6H)

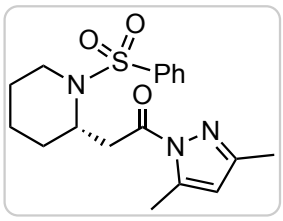
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.95, 159.39, 152.54, 150.46, 144.59, 138.21, 126.57, 122.68, 111.59, 50.16, 42.01, 35.98, 28.36, 24.84, 18.37, 14.18, 13.55

HRMS (EI$^+$): Calcd. for $C_{17}H_{22}N_4O_3S$ [M^+]: 363.1485, found: 363.1492

Remarks:
- Reaction performed at 60ºC for 4 hours, employing $CHCl_3$ as solvent and BHS as catalyst in this case.

- Purification by flash chromatography with hexanes: ethyl acetate 7:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-[1-(phenylsulfonyl)piperidin-2-yl]-1-ethanone (84b)



Physical state: Colorless oil

Empiric Formula: $C_{18}H_{23}N_3O_3S$

Molecular weight (g/mol): 361.46

Yield (%): 92%

Enantiomeric relation: 96.5:3.5

Optical rotation $[\alpha]_D^{25}$: -5.8 (*c* 1.0 $CHCl_3$)

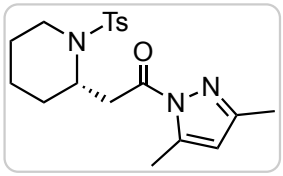
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.84 – 7.79 (m, 2H), 7.54 – 7.41 (m, 3H), 5.93 (s, 1H), 4.80 – 4.69 (m, 1H), 3.86 (dd, *J* = 14.0, 3.8 Hz, 1H), 3.42 (dd, *J* = 15.5, 8.4 Hz, 1H), 3.25 (dd, *J* = 15.5, 6.1 Hz, 1H), 3.20 – 3.08 (m, 1H), 2.48 (s, 3H), 2.22 (s, 3H), 1.46 – 1.30 (m, 2H), 0.92 – 0.78 (m, 1H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 209.88, 171.94, 152.66, 144.62, 141.86, 132.66, 129.40, 127.39, 111.69, 49.83, 41.16, 35.80, 28.02, 24.62, 18.30, 14.22, 13.55

HRMS (EI$^+$): Calcd. for $C_{18}H_{23}N_3O_3S$ [M^+]: 362.1533, found: 362.1531

Remarks:
- Reaction performed at 90ºC for 4 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 10:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(1-tosylpiperidin-2-yl)-1-ethanone (84c)



Physical state: Brown oil

Empiric Formula: $C_{19}H_{25}N_3O_3S$

Molecular weight (g/mol): 375.49

Yield (%): 91%

Enantiomeric relation: 96:4

Optical rotation $[\alpha]_D^{25}$: -16.2 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.69 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.93 (s, 1H), 4.72 (br s, 1H), 3.85 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.40 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.23 (dd, *J* = 15.6, 6.1 Hz, 1H), 3.17 – 3.05 (m, 1H), 2.48 (s, 3H), 2.38 (s, 3H), 2.22 (s, 3H), 1.64 – 1.50 (m, 6H)

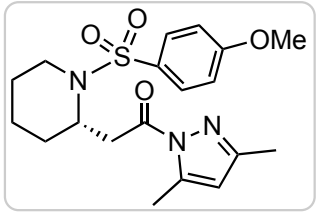
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.39, 152.15, 144.17, 142.97, 138.40, 129.68, 127.13, 111.41, 49.88, 41.29, 35.96, 28.28, 24.92, 21.63, 18.67, 14.62, 13.95

HRMS (EI^+): Calcd. for $C_{19}H_{25}N_3O_3S$ [M^+]: 376.1689, found: 376.1678

Remarks:

- Reaction performed at 90ºC for 4 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 6:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min.

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-{1-[(4-methoxyphenyl)sulfonyl] piperidin-2-yl}-1-ethanone (84d)



Physical state: Brown oil

Empiric Formula: $C_{19}H_{25}N_3O_4S$

Molecular weight (g/mol): 391.49

Yield (%): 70%

Enantiomeric relation: 96.5:3.5

Optical rotation $[\alpha]_D^{25}$: -18.9 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.74 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.93 (s, 1H), 4.74 – 4.67 (m, 1H), 3.86

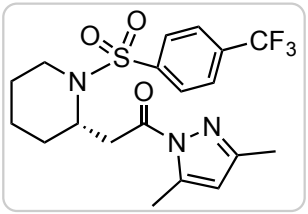
– 3.81 (m, 4H), 3.40 (dd, *J* = 15.5, 8.3 Hz, 1H), 3.25 (dd, *J* = 15.5, 6.1 Hz, 1H), 3.15 – 3.08 (m, 1H), 2.49 (s, 3H), 2.22 (s, 3H), 1.64 – 1.57 (m, 6H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 172.03, 163.22, 152.55, 144.58, 133.57, 129.58, 114.44, 111.63, 55.52, 49.77, 41.05, 35.82, 28.13, 24.72, 18.42, 14.16, 13.51

HRMS (EI$^+$): Calcd. for $C_{19}H_{25}N_3O_4S$ [M^+]: 392.1639, found: 392.1632

Remarks:
- Reaction performed at 90ºC for 5 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 4:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-{1-[(4-trifluoromethylphenyl) sulfonyl]piperidin-2-yl}-1-ethanone (84e)



Physical state: Pale pink solid

Empiric Formula: $C_{19}H_{22}F_3N_3O_3S$

Molecular weight (g/mol): 429.46

Yield (%): 91%

Melting point (ºC): 96-98

Enantiomeric relation: 95.5:4.5

Optical rotation [α]$_D^{25}$: -6.7 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.91 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 5.92 (s, 1H), 4.77 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.89 (dd, *J* = 13.8, 4.3 Hz, 1H), 3.32 (dd, *J* = 7.1, 5.3 Hz, 2H), 3.24 – 3.14 (m, 1H), 2.43 (s, 3H), 2.21 (s, 3H), 1.67 – 1.63 (m, 6H)

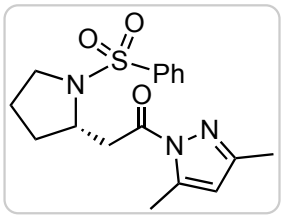
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.69, 152.77, 145.59, 144.59, 134.35 (q, $^2J_{CF}$ = 33 Hz), 127.84, 126.45, 123,76 (q, $^1J_{CF}$ = 272 Hz), 111.83, 50.33, 41.39, 36.02, 28.58, 24.97, 18.36, 14.09, 13.47

^{19}F NMR (CDCl3, 282.4 MHz) δ (ppm): -63.54 (s, 3F)

HRMS (EI$^+$): Calcd. for $C_{19}H_{22}F_3N_3O_3S$ [M^+]: 430.1407, found: 430.1409

Remarks:
- Reaction performed at 90ºC for 5 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-[1-(phenylsulfonyl)pyrrolidin-2-yl]-1-ethanone (93a)



Physical state: Brown oil

Empiric Formula: $C_{17}H_{21}N_3O_3S$

Molecular weight (g/mol): 347.43

Yield (%): 98%

Enantiomeric relation: 90:10

Optical rotation $[\alpha]_D^{25}$: -18.8 (*c* 1.0 $CHCl_3$)

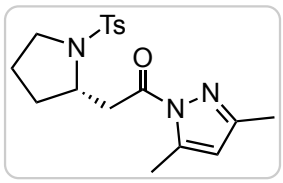
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.91 – 7.84 (m, 2H), 7.63 – 7.48 (m, 3H), 5.96 (s, 1H), 4.20 (ddt, *J* = 11.0, 7.3, 3.8 Hz, 1H), 3.73 (dd, *J* = 17.4, 3.8 Hz, 1H), 3.56 – 3.47 (m, 1H), 3.42 (dd, *J* = 17.4, 10.0 Hz, 1H), 3.20 – 3.08 (m, 1H), 2.53 (s, 3H), 2.24 (s, 3H), 1.85 – 1.53 (m, 4H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 172.50, 152.79, 144.50, 137.60, 133.16, 129.53, 128.03, 111.56, 56.39, 49.09, 42.53, 31.70, 23.58, 14.21, 13.57

HRMS (EI^+): Calcd. for $C_{17}H_{21}N_3O_3S$ [M^+]: 348.1376, found: 348.1373

Remarks:
- Reaction performed at 60ºC for 2 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 4:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(1-tosylpyrrolidin-2-yl)-1-ethanone (93b)



Physical state:	Pale pink solid
Empiric Formula:	$C_{18}H_{23}N_3O_3S$
Molecular weight (g/mol):	361.46
Yield (%):	84%
Melting point (ºC):	127-129
Enantiomeric relation:	88:12
Optical rotation $[\alpha]_D^{25}$:	-84.5 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.75 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.95 (s, 1H), 4.18 (ddd, *J* = 13.2, 7.5, 3.6 Hz, 1H), 3.72 (dd, *J* = 17.3, 3.6 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.40 (dd, *J* = 17.3, 10.0 Hz, 1H), 3.12 (dt, *J* = 10.3, 7.5 Hz, 1H), 2.52 (s, 3H), 2.42 (s, 3H), 2.24 (s, 3H), 1.90 – 1.81 (m, 1H), 1.80 – 1.73 (m, 1H), 1.69 – 1.62 (m, 1H), 1.59 – 1.52 (m, 1H)

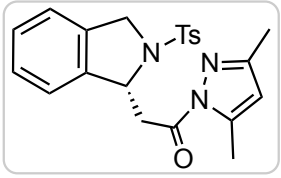
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 170.15, 150.35, 142.09, 141.56, 132.34, 127.75, 125.71, 109.14, 54.00, 46.71, 40.19, 29.34, 21.23, 18.95, 11.81, 11.19

HRMS (EI$^+$): Calcd. for $C_{18}H_{23}N_3O_3S$ [M^+]: 362.1533, found: 362.1533

Remarks:

- Reaction performed at 40ºC for 5 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*R*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(2-tosylisoindolin-1-yl)-1-ethanone (94)



Physical state:	Pale pink solid
Empiric Formula:	$C_{22}H_{23}N_3O_3S$
Molecular weight (g/mol):	409.50
Yield (%):	93%
Melting point (ºC):	128-130
Enantiomeric relation:	93:7

Optical rotation $[\alpha]_D^{25}$: -125.3 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.76 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.22 – 7.11 (m, 4H), 5.96 (s, 1H), 5.60 – 5.50 (m, 1H), 4.80 (dd, *J* = 14.0, 2.5 Hz, 1H), 4.60 (d, *J* = 14.0 Hz, 1H), 4.01 (dd, *J* = 17.7, 4.1 Hz, 1H), 3.75 (dd, *J* = 17.7, 7.6 Hz, 1H), 2.57 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H)

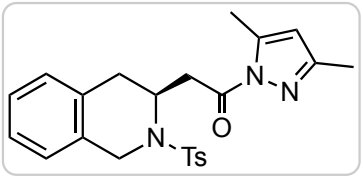
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.51, 152.49, 144.41, 144.00, 140.45, 136.05, 134.72, 130.17, 128.38, 128.24, 127.98, 123.27, 122.74, 111.55, 62.11, 54.28, 44.67, 21.87, 14.87, 14.19

HRMS (EI$^+$): Calcd. for $C_{22}H_{23}N_3O_3S$ [M^+]: 410.1533, found: 410.1535

Remarks:

- Reaction performed at 60ºC for 4 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 8:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-1-ethanone (95)



Physical state: Orange solid

Empiric Formula: $C_{23}H_{25}N_3O_3S$

Molecular weight (g/mol): 423.53

Yield (%): 84%

Melting point (ºC): 125-127

Enantiomeric relation: 93.5:6.5

Optical rotation $[\alpha]_D^{25}$: -125.3 (*c* 1.0 $CHCl_3$)

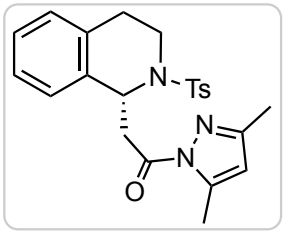
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.58 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.18 – 7.02 (m, 4H), 7.02 – 6.89 (m, 1H), 5.94 (s, 1H), 5.78 – 5.64 (m, 1H), 3.87 (ddd, *J* = 14.1, 5.6, 3.3 Hz, 1H), 3.73 – 3.57 (m, 1H), 3.56 – 3.45 (m, 2H), 2.88 – 2.62 (m, 2H), 2.51 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.01, 152.60, 144.74, 143.54, 137.91, 136.37, 133.58, 129.77, 129.46, 127.54, 127.54, 127.22, 126.87, 111.46, 53.27, 44.15, 39.40, 26.81, 21.20, 14.15, 13.59

HRMS (EI$^+$): Calcd. for $C_{23}H_{25}N_3O_3S$ [M^+]: 424.1689, found: 424.1685

Remarks:
- Reaction performed at 60ºC for 4 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 8:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 99:1); flow rate = 2.5 mL/min

(*R*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-ethanone (96)



Physical state: Colorless oil

Empiric Formula: $C_{23}H_{25}N_3O_3S$

Molecular weight (g/mol): 423.53

Yield (%): 88%

Enantiomeric relation: 85:15

Optical rotation $[\alpha]_D^{25}$: -70.3 (*c* 1.0 $CHCl_3$)

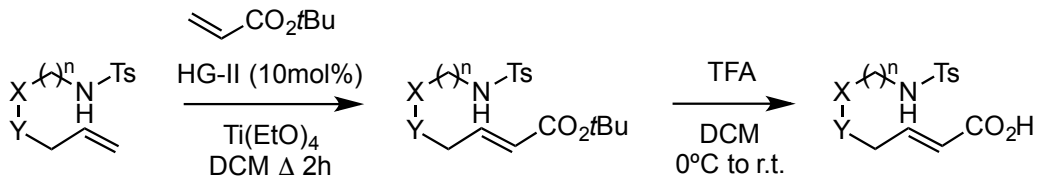
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.68 (d, *J* = 8.3 Hz, 2H), 7.23 – 6.95 (m, 6H), 5.92 (s, 1H), 4.95 – 4.80 (m, 1H), 4.73 (d, *J* = 16.4 Hz, 1H), 4.44 (d, *J* = 16.4 Hz, 1H), 3.31 – 3.09 (m, 2H), 2.99 (dd, *J* = 16.2, 5.7 Hz, 1H), 2.72 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.50 (s, 3H), 2.35 (s, 3H), 2.17 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.29, 152.22, 144.17, 143.38, 136.86, 131.93, 131.78, 129.72, 129.00, 127.33, 127.15, 126.62, 126.24, 111.39, 48.91, 43.77, 38.48, 29.85, 21.60, 14.56, 13.86

HRMS (EI^+): Calcd. for $C_{23}H_{25}N_3O_3S$ [M^+]: 424.1689, found: 424.1685

Remarks:
- Reaction performed at 60ºC for 4 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 10:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 20 minutes gradient 92:8 to 99:1); flow rate = 1.0 mL/min

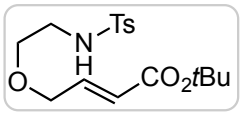
2.5.4. MICHAEL ADDUCTS SYNTHESIS: PREPARATION OF SULFONAMIDO ESTERS AND SULFONAMIDO ACIDS



To a solution of terminal-olefin *N*-protected amine (1.0 equiv.) in CH_2Cl_2 (0.1 M) under nitrogen atmosphere, titanium tetraethoxide (10 mol%), *tert*-butyl acrylate (5.0 equiv.) and Hoveyda-Grubbs 2nd generation catalyst [HG-II] (10 mol%) were sequentially added. The resulting solution was refluxed for 2-4 hours and, after cooling to room temperature, solvents were removed and the crude mixture purified by flash chromatography with hexanes: ethyl acetate as eluents.

The *tert*-butyl α,β-unsaturated ester was dissolved in CH_2Cl_2 (0.1 M) and trifluoroacetic acid (10.0 equiv.) was added at 0 ºC. The resulting solution was allowed to warm to room temperature and stirred for 4-12 hours. Solvents were then removed to give the corresponding conjugated acids that were employed without further purification.

tert-Butyl (*E*)-4-[2-(4-Methylphenyl)sulfonamidoethoxy]-2-butenoate (114)



Physical state:	Pale yellow oil
Empiric Formula:	$C_{17}H_{25}NO_5S$
Molecular weight (g/mol):	355.45
Yield (%):	70%

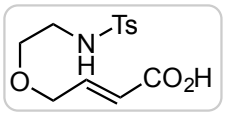
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.62 (d, *J* = 7.4 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 6.60 (dt, *J* = 14.3, 5.4 Hz, 1H), 5.89 (d, *J* = 14.3 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 2H), 3.96 (br s, 2H), 3.55 (t, *J* = 4.6 Hz, 2H), 3.12 (s, 1H), 2.76 (s, 3H), 1.87 (s, 9H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 164.81, 143.64, 140.96, 136.21, 129.78, 127.14, 125.76, 80.73, 60.90, 50.16, 49.78, 28.07, 21.54

HRMS (EI^+): Calcd. for $C_{17}H_{25}NO_5S$ [M^+]: 356.1587, found: 356.1584

Remarks: ‣ Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.

tert-Butyl (*E*)-4-[2-(4-Methylphenyl)sulfonamidoethoxy]-2-butenoate (115)



Physical state: Grey foam

Empiric Formula: $C_{13}H_{17}NO_5S$

Molecular weight (g/mol): 299.34

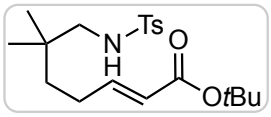
Yield (%): 90%

^{1}H-RMN (Acetone, 300 MHz) δ (ppm): 7.30 (d, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.41 (dt, *J* = 14.4, 5.3 Hz, 1H), 5.67 (d, *J* = 14.4 Hz, 1H), 3.91 (dd, *J* = 5.3, 1.3 Hz, 2H), 3.54 (t, *J* = 5.6 Hz, 2H), 3.19 (t, *J* = 5.6 Hz, 2H), 2.39 (s, 3H)

^{13}C-RMN (Acetone, 75.5 MHz) δ (ppm): 167.1, 144.4, 144.1, 137.7, 130.4, 127.9, 124.2, 61.2, 51.2, 50.4, 21.3

HRMS (EI$^+$): Calcd. for $C_{13}H_{17}NO_5S$ [M^+]: 300.0900, found: 300.0902

tert-Butyl (*E*)-6,6-Dimethyl-7-[(4-methylphenyl)sulfonamide}-2-heptenoate (120)



Physical state: Brown oil

Empiric Formula: $C_{20}H_{31}NO_4S$

Molecular weight (g/mol): 381.53

Yield (%): 88%

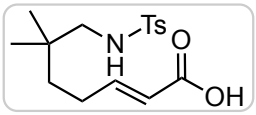
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.70 (d, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 6.81 (dt, *J* = 14.3, 6.2 Hz, 1H), 5.80 (dt, *J* = 14.3, 1.4 Hz, 1H), 4.98 (br t, *J* = 6.3 Hz, 1H), 3.04 (d, *J* = 6.3 Hz, 2H), 2.81 (s, 3H), 2.51 – 2.40 (m, 2H), 1.93 (s, 9H), 1.83 – 1.75 (m, 2H), 1.36 (s, 6H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 166.0, 147.7, 143.4, 137.0, 129.8, 127.1, 123.1, 80.2, 52.9, 37.7, 34.0, 28.3, 26.6, 25.0, 21.7

HRMS (EI$^+$): Calcd. for $C_{20}H_{31}NO_4S$ [M^+]: 382.2040, found: 382.2040

Remarks: ‣ Purification by flash chromatography with hexanes: ethyl acetate 10:1 as eluent.

(*E*)-6,6-Dimethyl-7-[(4-methylphenyl)sulfonamide}-2-heptenoic acid (121)



Physical state: Brown foam

Empiric Formula: $C_{16}H_{23}NO_4S$

Molecular weight (g/mol): 325.42

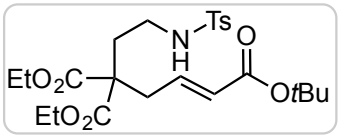
Yield (%): 82%

^{1}H-RMN (CD_3OD , 300 MHz) δ (ppm): 8.93 (d, *J* = 7.4 Hz, 2H), 8.59 (d, *J* = 7.4 Hz, 2H), 8.18 (dt, *J* = 14.4, 6.2 Hz, 1H), 7.13 (dt, *J* = 14.4, 1.4 Hz, 1H), 4.23 (s, 2H), 4.05 (s, 3H), 3.86 – 3.69 (m, 2H), 3.14 – 2.97 (m, 2H), 2.62 (s, 6H)

^{13}C-RMN (CD_3OD, 75.5 MHz) δ (ppm): 170.0, 151.5, 144.4, 139.1, 130.6, 127.9, 122.1, 53.7, 38.6, 34.9, 27.8, 25.3, 21.5

HRMS (EI$^+$): Calcd. for $C_{16}H_{23}NO_4S$ [M^+]: 326.1421, found: 326.1413

1-(*tert*-Butyl) 4,4-Diethyl (*E*)-6-[(4-methylphenyl)sulfonamide]-1-hexene-1,4,4-tricarboxylate (125)



Physical state: Yellow oil

Empiric Formula: $C_{24}H_{35}NO_8S$

Molecular weight (g/mol): 497.60

Yield (%): 72%

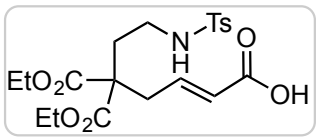
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.67 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 6.64 (dt, *J* = 14.2, 7.0 Hz, 1H), 5.86 (dt, *J* = 14.2, 1.2 Hz, 1H), 4.90 (br t, *J* = 5.9 Hz, 1H), 4.43 (q, *J* = 6.6 Hz, 4H), 3.37 – 3.28 (m, 2H), 3.07 (dd, *J* = 7.0, 1.2 Hz, 2H), 2.81 (s, 3H), 2.47 (t, *J* = 6.2 Hz, 2H), 1.93 (s, 9H), 1.72 (t, *J* = 6.6 Hz, 6H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 170.4, 165.1, 143.5, 140.6, 136.8, 129.8, 127.1, 127.1, 80.7, 62.1, 56.0, 39.3, 36.2, 33.3, 28.3, 21.7, 14.2

HRMS (EI$^+$): Calcd. for $C_{24}H_{35}NO_8S$ [M^+]: 498.3117, found: 498.3111

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

(*E*)-5,5-Bis(ethoxycarbonyl)-7-[(4-methylphenyl)sulfonamide]-2-heptenoic acid (126)



Physical state: White foam

Empiric Formula: $C_{20}H_{27}NO_8S$

Molecular weight (g/mol): 441.50

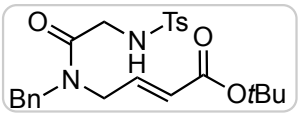
Yield (%): 98%

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.65 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.81 (dt, *J* = 14.2, 7.0 Hz, 1H), 5.93 (d, *J* = 14.2 Hz, 1H), 5.4 (br s, 1H), 4.41 (q, *J* = 6.5 Hz, 4H), 3.29 (br t, *J* = 6.6 Hz, 2H), 3.10 (d, *J* = 7.0 Hz, 2H), 2.78 (s, 3H), 2.47 (br t, *J* = 6.6 Hz, 2H), 1.69 (t, *J* = 6.5 Hz, 6H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.1, 170.8, 144.7, 144.1, 137.2, 130.3, 128.7, 127.6, 62.7, 56.4, 39.6, 36.6, 33.6, 22.2, 14.7

HRMS (EI$^+$): Calcd. for $C_{20}H_{27}NO_8S$ [M^+]: 442.1530, found: 442.1517

tert-Butyl (*E*)-7-[(4-Methylphenyl)sulfonamide]-2-heptenoate (130)



Physical state: Colorless oil

Empiric Formula: $C_{24}H_{30}N_2O_5S$

Molecular weight (g/mol): 458.57

Yield (%): 86%

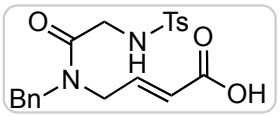
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.60 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.11 (m, 5H), 7.02 – 6.95 (m, 1H), 6.93 – 6.87 (m, 1H), 6.61 – 6.46 (m, 1H), 5.81 – 5.62 (m, 2H), 4.62 (s, 1H), 4.47 (s, 1H), 4.23 – 4.14 (m, 1H), 4.01 (d, *J* = 4.2 Hz, 1H), 3.97 (dd, *J* = 4.6, 2.9 Hz, 2H), 2.71 (s, 3H), 1.85 (s, 4.5H), 1.82 (s, 4.5H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 167.3, 167.2, 164.8, 164.4, 143.7, 140.0, 139.5, 136.0, 135.9, 135.9, 134.7, 129.8, 129.2, 128.8, 128.2, 128.2, 128.0, 127.3, 127.3, 126.3, 125.2, 124.9, 81.3, 80.9, 49.8, 49.4, 46.7, 46.4, 43.9, 43.7, 28.2, 21.7, 21.7

HRMS (EI$^+$): Calcd. for $C_{24}H_{30}N_2O_5S$ [M^+]: 459.2109, found: 459.2107

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 4:1 as eluent.
- ^{1}H and ^{13}C NMR show the presence of rotamers in ca. 1:1 ratio.

(*E*)-4-{*N*-Benzyl-2-[(4-methylphenyl)sulfonamido]acetamido}-2-butenoic acid (131)



Physical state: Dark brown foam

Empiric Formula: $C_{20}H_{22}N_2O_5S$

Molecular weight (g/mol): 402.47

Yield (%): 99%

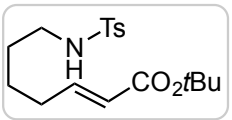
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 10.88 (br s, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.23 (m, 5H), 7.13 – 7.06 (m, 1H), 7.06 – 6.97 (m, 1H), 6.89 – 6.82 (m, 1H), 6.82 – 6.75 (m, 1H), 6.14 (br s, 1H), 5.93 – 5.86 (m, 1H), 5.86 – 5.79 (m, 1H), 4.72 (s, 1H), 4.62 (s, 1H), 4.39 – 4.06 (m, 4H), 2.78 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 170.4, 169.9, 168.5, 144.3, 144.0, 143.9, 143.6, 135.8, 135.4, 134.3, 130.1, 129.8, 129.3, 128.9, 128.4, 128.2, 128.2, 127.2, 126.5, 122.3, 50.6, 49.8, 47.2, 46.8, 44.0, 21.7

HRMS (EI^+): Calcd. for $C_{20}H_{22}N_2O_5S$ [M^+]: 403.2350, found: 403.2347

Remarks:
- ^{1}H and ^{13}C NMR show the presence of rotamers in ca. 1:1 ratio.

tert-Butyl (*E*)-7-[(4-Methylphenyl)sulfonamide]-2-heptenoate (132)



Physical state: Pale yellow oil

Empiric Formula: $C_{18}H_{27}NO_4S$

Molecular weight (g/mol): 353.48

Yield (%): 90%

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.58 (d, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 2H), 6.77 – 6.56 (m, 1H), 5.68 (dt, *J* = 14.3, 1.3 Hz, 1H), 5.17 (br s, 1H), 3.14 (dt, *J* = 6.2, 6.5 Hz, 2H), 2.68 (s, 3H), 2.38 (tdd, *J* = 6.5, 6.4, 1.3 Hz, 2H), 1.84 – 1.75 (m, 13H)

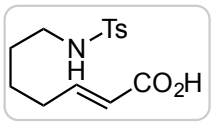
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.91, 147.02, 143.27, 136.96, 129.66, 127.04, 123.36, 80.13, 42.93, 31.42, 29.06,

28.24, 25.05, 21.60

HRMS (EI$^+$): Calcd. for $C_{18}H_{27}NO_4S$ [M^+]: 354.1694, found: 354.1689

Remarks: ‣ Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

(*E*)-7-[(4-Methylphenyl)sulfonamido]-2-heptenoic acid (134)



Physical state: Brown solid

Empiric Formula: $C_{14}H_{19}NO_4S$

Molecular weight (g/mol): 297.43

Yield (%): 96%

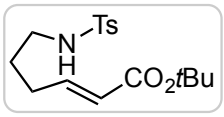
Melting point (ºC): 92-94

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.98 (dt, *J* = 15.6 and 6.9 Hz, 1H), 5.77 (dt, *J* = 15.6 and 1.4 Hz, 1H), 5.25 (t, *J* = 6.1 Hz, 1H), 2.96–2.90 (m, 2H), 2.42 (s, 3H), 2.20-2.13 (m, 2H), 1.48–1.44 (m, 4H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.4, 151.3, 143.3, 136.7, 129.6, 126.9, 120.9, 42.6, 31.4, 28.8, 24.6, 21.4

HRMS (EI$^+$): Calcd. for $C_{14}H_{19}NO_4S$ [M^+]: 298.1068, found: 298.1063

tert-Butyl (*E*)-6-[(4-Methylphenyl)sulfonamide]-2-hexenoate (133)



Physical state: Yellow oil

Empiric Formula: $C_{17}H_{25}NO_4S$

Molecular weight (g/mol): 339.45

Yield (%): 97%

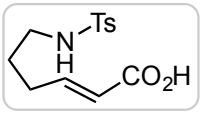
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.70 (d, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 6.85 – 6.69 (m, 1H), 5.80 (d, *J* = 14.3 Hz, 1H), 4.87 (br s, 1H), 3.30 (dt, *J* = 6.2, 6.3 Hz, 2H), 2.81 (s, 3H), 2.57 (dt, *J* = 6.4, 6.5 Hz, 2H), 2.17 – 2.00 (m, 2H), 1.93 (s, 9H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 165.80, 145.97, 143.54, 136.98, 129.82, 127.15, 123.99, 80.38, 42.73, 42.73, 29.07, 28.33, 21.72

HRMS (EI$^+$): Calcd. for $C_{17}H_{25}NO_4S$ [M^+]: 340.1538, found: 340.1535

Remarks: ‣ Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

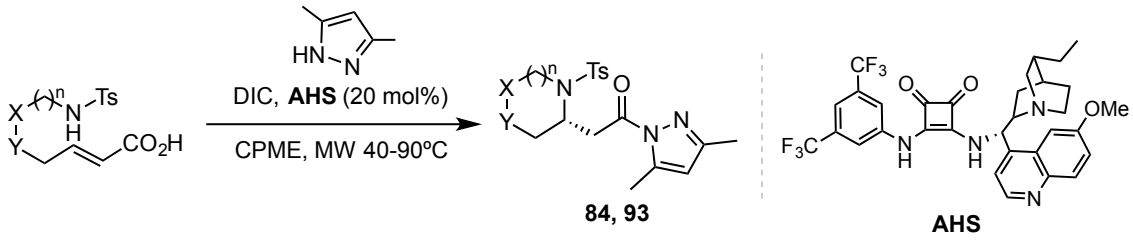
(*E*)-6-[(4-Methylphenyl)sulfonamido]-2-hexenoic acid (135)



Physical state:	White foam
Empiric Formula:	$C_{13}H_{17}NO_4S$
Molecular weight (g/mol):	283.34
Yield (%):	95%
^{1}H-RMN (Acetone, 300 MHz) δ (ppm):	7.33 – 7.23 (m, 2H), 7.01 – 6.91 (m, 2H), 6.48 (dt, *J* = 14.3, 6.4 Hz, 1H), 6.06 (br t, *J* = 5.4 Hz, 1H), 5.48 (dt, *J* = 14.3, 1.4 Hz, 1H), 2.86 (dt, *J* = 5.4, 5.9 Hz, 2H), 2.38 (s, 3H), 2.28 – 2.19 (m, 2H), 1.74 – 1.63 (m, 2H)
^{13}C-RMN (Acetone, 75.5 MHz) δ (ppm):	167.26, 149.00, 143.60, 138.93, 130.27, 127.61, 122.51, 43.15, 29.33, 28.78, 21.36

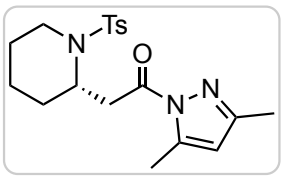
HRMS (EI$^+$): Calcd. for $C_{13}H_{17}NO_4S$ [M^+]: 284.0951, found: 284.0951

2.5.5. GENERAL PROCEDURE FOR THE DOMINO PC-IMAMR: PREPARATION OF 2-SUBSTITUTED NITROGEN HETEROCYCLES 84C,F-I AND 93B.



The corresponding α,β-unsaturated acid (1.0 equiv.) was dissolved in cyclopentyl methyl ether (CPME) (0.1M) in a microwave vial and then, diisopropyl carbodiimide (DIC) (1.5 equiv.), 3,5-dimetylpyrazol (1.2 equiv.) and catalyst **AHS** (20 mol%) were added sequentially. The vial was sealed and the solution was heated under microwave irradiation at 50-90 ºC for <1-7 hours. After this time, the crude reaction mixture was purified by means of flash chromatography on silica gel using the appropriate eluent.

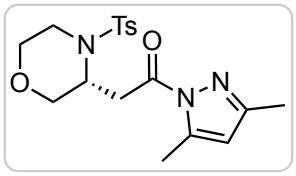
(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(1-tosylpiperidin-2-yl)-1-ethanone (84c)



Physical state:	Brown oil
Empiric Formula:	$C_{19}H_{25}N_3O_3S$
Molecular weight (g/mol):	375.49
Yield (%):	62
Enantiomeric relation:	95:5
Optical rotation $[\alpha]_D^{25}$:	-16.2 (*c* 1.0, $CHCl_3$)

Remarks:
- Reaction performed at 90ºC for 6 hours.
- The spectroscopic data are in agreement with those previously reported.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min.

(*R*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(4-tosylmorpholin-3-yl)-1-ethanone (84f)



Physical state:	Pale yellow solid
Empiric Formula:	$C_{18}H_{23}N_3O_4S$
Molecular weight (g/mol):	377.46
Yield (%):	83%
Melting point (ºC):	117-119
Enantiomeric relation:	99.7:0.3
Optical rotation $[\alpha]_D^{25}$:	-16.2 (*c* 1.0 $CHCl_3$)

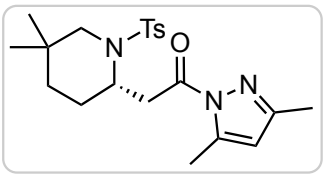
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.60 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 6.05 (d, *J* = 0.7 Hz, 1H), 4.50 – 4.37 (m, 1H), 4.17 (ddd, *J* = 10.7, 3.1, 1.6 Hz, 1H), 4.06 – 3.90 (m, 2H), 3.85 – 3.75 (m, 1H), 3.66 (dd, *J* = 15.0, 7.5 Hz, 1H), 3.42 (dd, *J* = 15.0, 4.1 Hz, 1H), 2.90 (d, *J* = 0.9 Hz, 3H), 2.87 – 2.78 (m, 4H), 2.66 (dd, *J* = 10.4, 9.3 Hz, 1H), 2.61 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 130.3, 128.4, 112.0, 72.0, 66.4, 50.4, 45.9, 39.6, 22.1, 15.0, 14.4

HRMS (EI^+): Calcd. for $C_{18}H_{23}N_3O_4S$ [M^+]: 378.1482, found: 378.1475

Remarks:
- Reaction performed at 50ºC for 1 hour.
- Purification by flash chromatography with hexanes: ethyl acetate 4:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 95:5); flow rate = 1.0 mL/min

(*S*)-2-(5,5-Dimethyl-1-tosylpiperidin-2-yl)-1-(3,5-dimethyl-1H-pyrazol-1-yl)-1-ethanone (84g)



Physical state: Colorless oil

Empiric Formula: $C_{21}H_{29}N_3O_3S$

Molecular weight (g/mol): 403.54

Yield (%): 53%

Enantiomeric relation: 94:6

Optical rotation $[\alpha]_D^{25}$: +3.4 (*c* 1.0 $CHCl_3$)

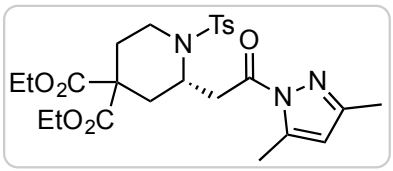
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.65 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 6.03 (s, 1H), 4.97 – 4.85 (m, 1H), 3.74 (dd, *J* = 12.0, 1.0 Hz, 1H), 3.67 (dd, *J* = 14.5, 8.7 Hz, 1H), 3.31 (ddd, *J* = 14.5, 4.1, 1.0 Hz, 1H), 3.16 (d, *J* = 12.0 Hz, 1H), 2.85 (s, 3H), 2.76 (s, 3H), 2.62 (s, 3H), 2.36 – 2.27 (m, 1H), 1.97 – 1.93 (m, 1H), 1.93 – 1.87 (m, 1H), 1.81 – 1.76 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.4, 152.0, 144.0, 142.8, 138.2, 129.5, 127.1, 111.4, 51.7, 49.2, 34.8, 32.2, 30.7, 29.1, 25.3, 23.7, 21.7, 14.7, 14.0

HRMS (EI$^+$): Calcd. for $C_{21}H_{29}N_3O_3S$ [M^+]: 404.2002, found: 404.2000

Remarks:
- Reaction performed at 40ºC for 3 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 6:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 98:2); flow rate = 1.5 mL/min

Diethyl (*S*)-2-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethyl]-1-tosylpiperidine-4,4-dicarboxylate (84h)



Physical state: Colorless oil

Empiric Formula: $C_{25}H_{33}N_3O_7S$

Molecular weight (g/mol): 519.61

Yield (%): 53%

Enantiomeric relation: 94:6

Optical rotation $[\alpha]_D^{25}$: -1.1 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.64 (d, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 2H), 6.02 (s, 1H), 5.00 – 4.89 (m, 1H), 4.48 – 4.23 (m, 4H), 4.15 – 4.05 (m, 1H), 3.81 – 3.69 (m, 1H), 3.62 (dd, *J* = 15.6, 7.8 Hz, 1H), 3.50 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.90 – 2.82 (m, 4H), 2.78 (s, 3H), 2.76 – 2.69 (m, 1H), 2.66 – 2.55 (m, 4H), 2.17 – 2.08 (m, 1H), 1.69 – 1.58 (m, 6H)

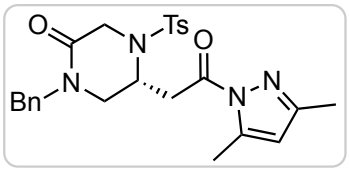
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.1, 170.8, 170.6, 151.9, 143.9, 143.2, 137.9, 129.7, 127.1, 111.2, 62.1, 62.0, 50.9, 48.5, 38.7, 37.3, 32.0, 29.8, 21.7, 14.8, 14.1, 14.0, 13.8

HRMS (EI^+): Calcd. for $C_{25}H_{33}N_3O_7S$ [M^+]: 520.2112, found: 520.2108

Remarks:

- Reaction performed at 50ºC for 7 hours, adding 40 mol% of AHS.
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiracel AD column (hexane: isopropanol 80:20); flow rate = 1.0 mL/min.

(*R*)-1-Benzyl-5-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)-4-tosylpiperazin-2-one (84i)



Physical state: Colorless oil

Empiric Formula: $C_{25}H_{28}N_4O_4S$

Molecular weight (g/mol): 480.58

Yield (%): 53%

Enantiomeric relation: 93:7

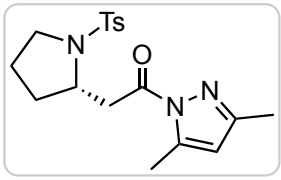
Optical rotation $[\alpha]_D^{25}$: -9.6 (*c* 1.0 $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm):	7.64 (d, *J* = 7.7 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.16 – 7.06 (m, 5H), 6.04 (s, 1H), 4.97 (d, *J* = 13.3 Hz, 1H), 4.89 – 4.76 (m, 1H), 4.55 (d, *J* = 16.3 Hz, 1H), 4.44 (d, *J* = 13.3 Hz, 1H), 4.24 (d, *J* = 16.3 Hz, 1H), 3.69 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.60 (dd, *J* = 15.6, 8.6 Hz, 1H), 3.52 – 3.43 (m, 2H), 2.80 (s, 3H), 2.77 (s, 3H), 2.62 (s, 3H)
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm):	171.2, 170.1, 164.3, 152.4, 144.1, 144.0, 135.8, 135.7, 130.0, 128.6, 128.5, 127.7, 127.3, 111.6, 67.2, 60.5, 53.6, 49.8, 48.3, 48.3, 45.4, 35.9, 31.8, 22.9, 21.8, 21.2, 14.4, 14.3, 13.9

HRMS (EI^+): Calcd. for $C_{25}H_{28}N_4O_4S$ [M^+]: 481.1904, found: 481.1897

Remarks:
- Reaction performed at 40ºC for 5 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 10:1 as eluent.
- The *er* value was determined by complexation with a europium salt.
- ^{1}H and ^{13}C NMR show the presence of rotamers

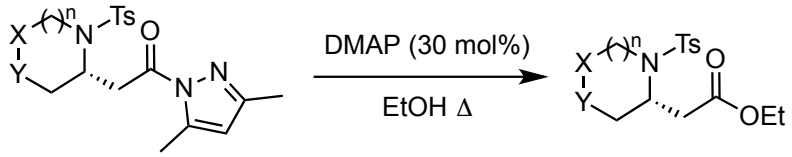
(*S*)-1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(1-tosylpyrrolidin-2-yl)-1-ethanone (93b)



Physical state:	Pale pink solid
Empiric Formula:	$C_{18}H_{23}N_3O_3S$
Molecular weight (g/mol):	361.46
Yield (%):	57
Melting point (ºC):	127-129
Enantiomeric relation:	82:18
Optical rotation $[\alpha]_D^{25}$:	-84.5 (*c* 1.0, $CHCl_3$)

Remarks:
- Reaction performed at 50ºC for 2 hours.
- The spectroscopic data are in agreement with those previously reported.
- The *er* value was determined by HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 92:8); flow rate = 1.0 mL/min

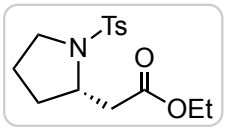
2.5.6. GENERAL PROCEDURE FOR THE TRANSFORMATION OF PYRAZOLAMIDES 84 AND 93 INTO ESTERS 136 AND 137



84, 93 **136, 137**

To a solution of heterocycle **86** or **95** (1.0 equiv.) in EtOH (0.1 M), 4-(dimethyl amino)pyridine (DMAP) (30 mol%) was added. The resulting solution was refluxed for 4 hours and, after cooling to room temperature, solvents were removed and the crude mixture was purified by flash chromatography with hexanes: ethyl acetate as eluents.

Ethyl (*R*)-2-(1-Tosylpyrrolidin-2-yl)acetate (136)



Physical state: Colorless oil

Empiric Formula: $C_{15}H_{21}NO_4S$

Molecular weight (g/mol): 311.40

Yield (%): 78%

Optical rotation $[\alpha]_D^{25}$: -70.0 (*c* 1.0 $CHCl_3$)

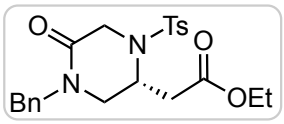
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.74 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.14 (q, *J* = 7.1, 2H), 4.03 – 3.89 (m, 1H), 3.50 – 3.38 (m, 1H), 3.18 – 3.01 (m, 2H), 2.55 – 2.45 (m, 1H), 2.43 (s, 3H), 1.82 – 1.70 (m, 2H), 1.68 – 1.62 (m, 1H), 1.58 – 1.49 (m, 1H), 1.26 (t, *J*= 7.1 Hz, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 171.5, 143.7, 134.3, 129.9, 127.8, 60.6, 56.7, 49.3, 41.6, 31.8, 23.9, 21.7, 14.3

HRMS (EI^+): Calcd. for $C_{15}H_{21}NO_4S$ [M^+]: 312.2325, found: 312.2319

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

Ethyl (*R*)-2-(4-Benzyl-5-oxo-1-tosylpiperazin-2-yl)acetate (137)



Physical state: Colorless oil

Empiric Formula: $C_{22}H_{26}N_2O_5S$

Molecular weight (g/mol): 430.52

Yield (%): 92%

Optical rotation $[\alpha]_D^{25}$: +1.2 (*c* 1.0 $CHCl_3$)

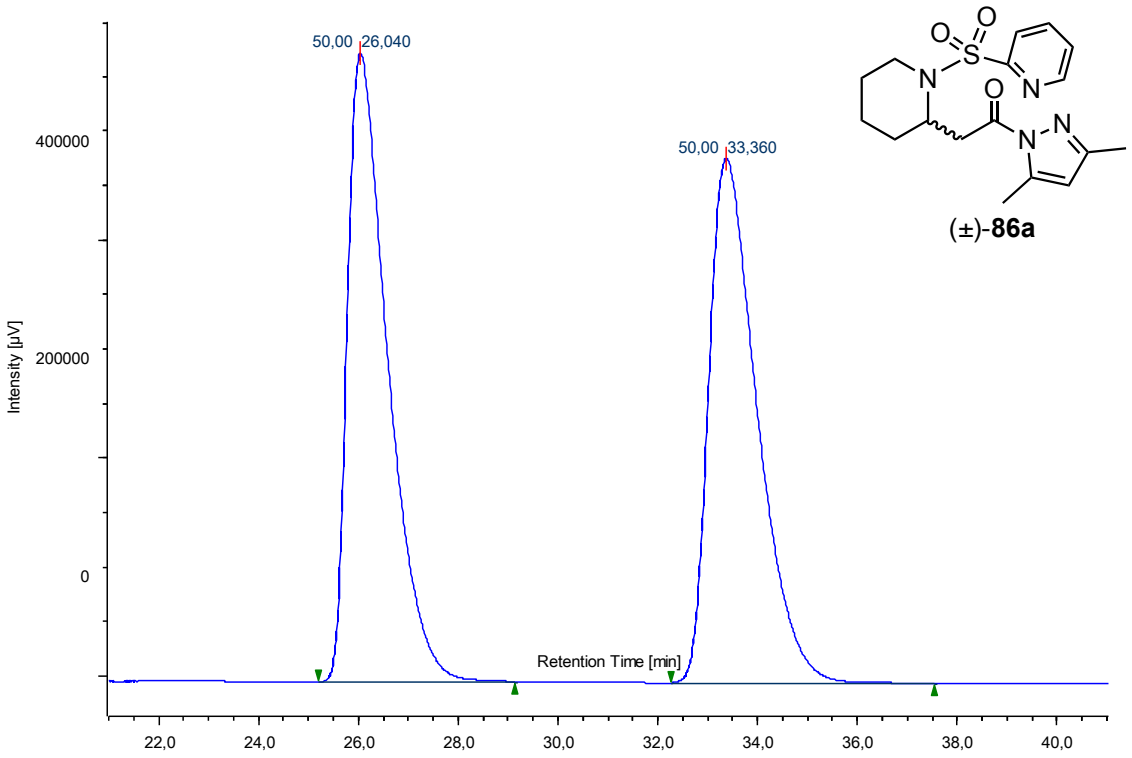
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 7.69 (d, *J* = 6.6 Hz, 2H), 7.35 – 7.26 (m, 5H), 7.09 (dd, *J* = 6.6, 2.9 Hz, 2H), 4.66 (d, *J* = 14.4 Hz, 1H), 4.46 – 4.34 (m, 1H), 4.28 (d, *J* = 3.6 Hz, 1H), 4.23 (s, 1H), 4.07 – 3.89 (m, 2H), 3.81 (d, *J* = 17.7 Hz, 1H), 3.33 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.13 (dd, *J* = 13.0, 2.7 Hz, 1H), 2.46 – 2.40 (m, 4H), 1.25 (s, 1H), 1.17 (t, *J* = 7.1 Hz, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 169.9, 164.4, 144.3, 135.7, 135.5, 130.2, 128.8, 128.5, 128.0, 127.4, 61.2, 49.9, 48.5, 48.2, 45.5, 34.9, 21.8, 14.2

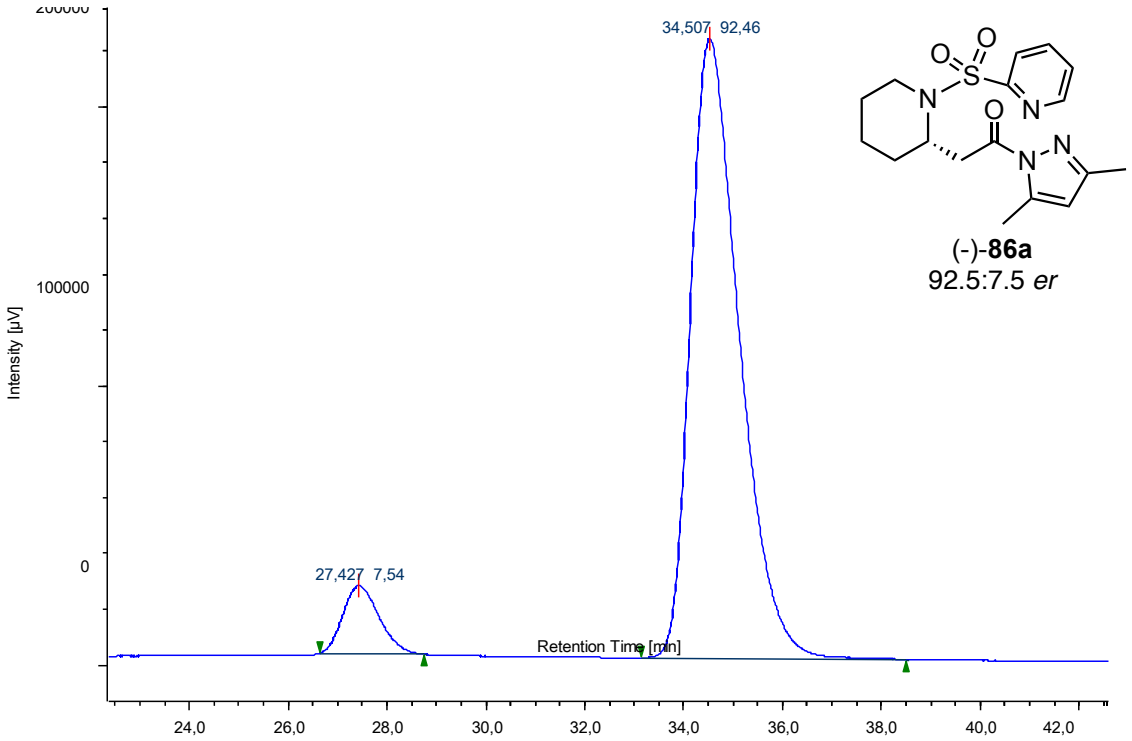
HRMS (EI$^+$): Calcd. for $C_{22}H_{26}N_2O_5S$ [M^+]: 431.1596, found: 431.1588

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

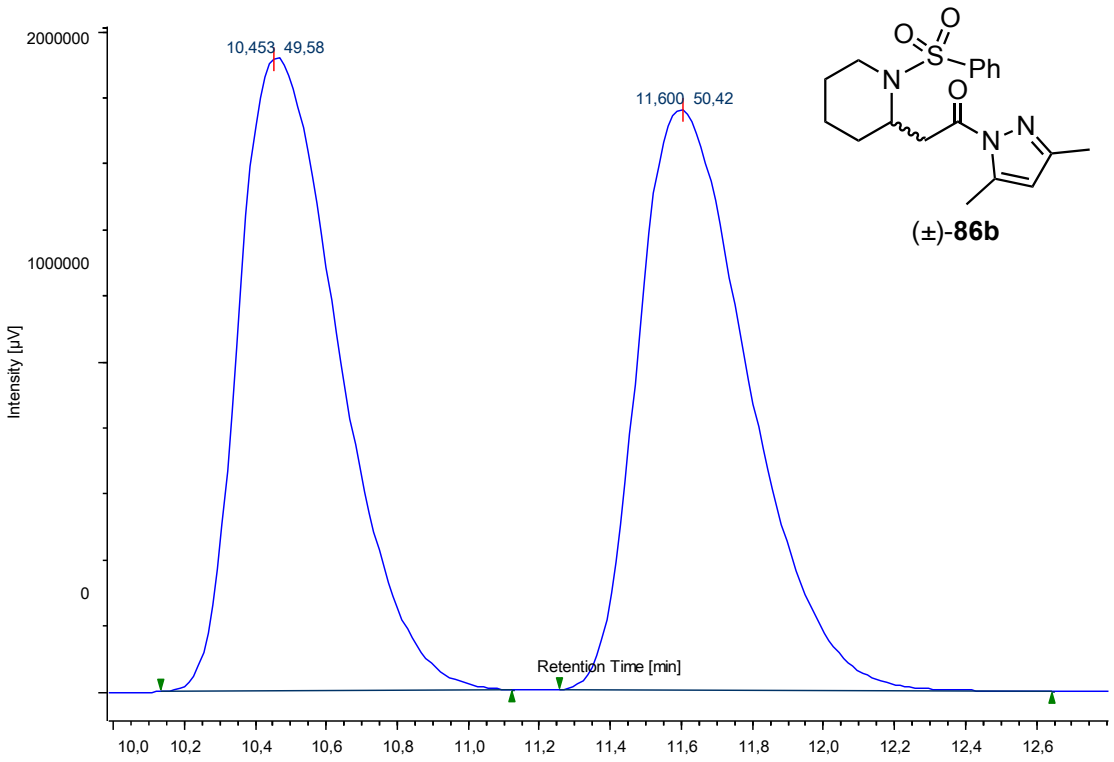
2.5.7. HPLC TRACES AND NMR *ER* DETERMINATION SPECTRA OF ENANTIOENRICHED COMPOUNDS 84 AND 93-96



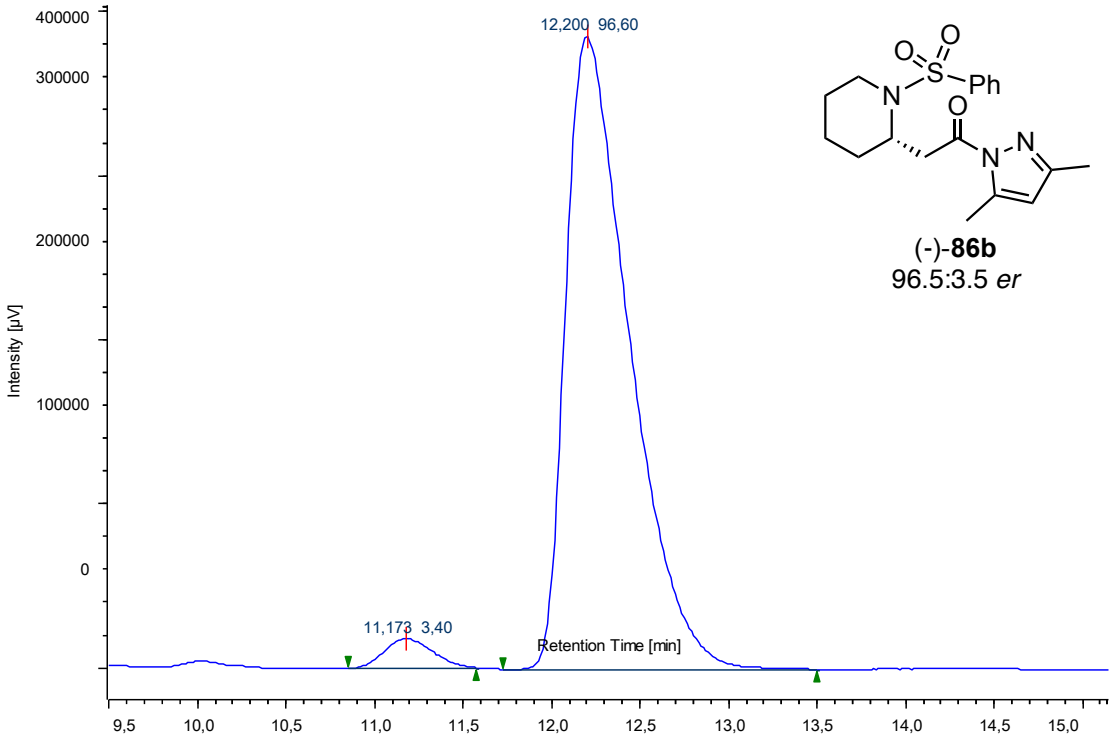
(±)-**86a**



(-)-**86a**
92.5:7.5 *er*



(±)-**86b**



(-)-**86b**
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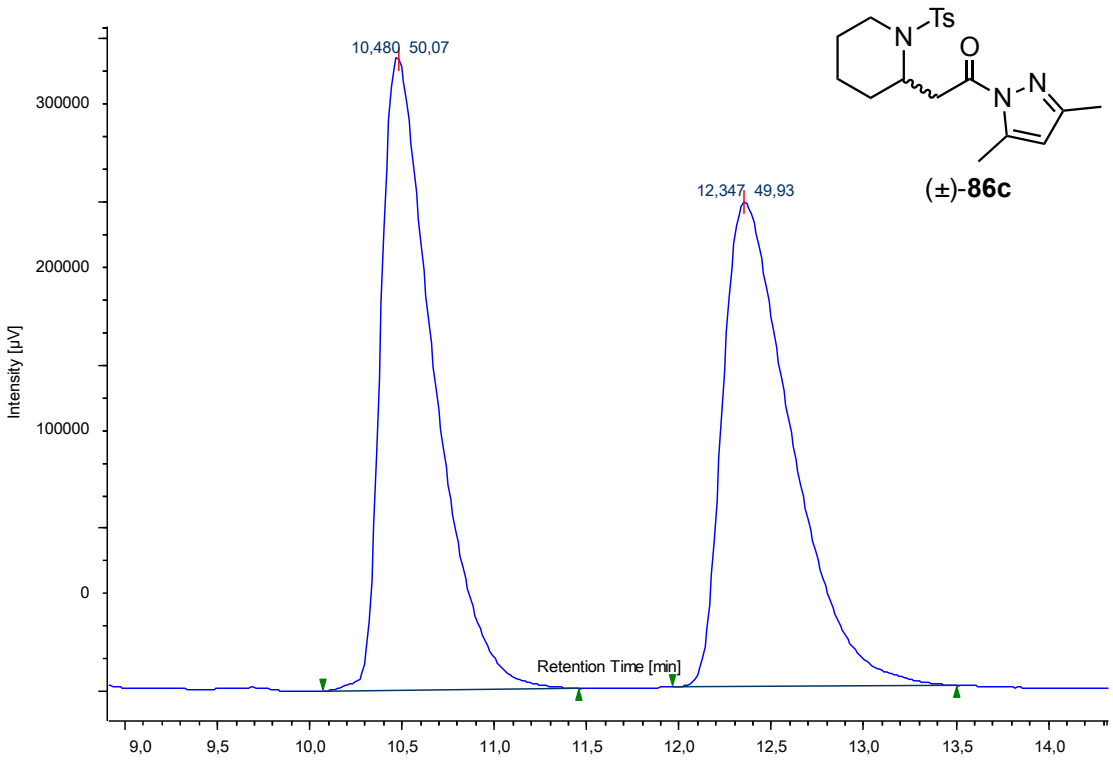
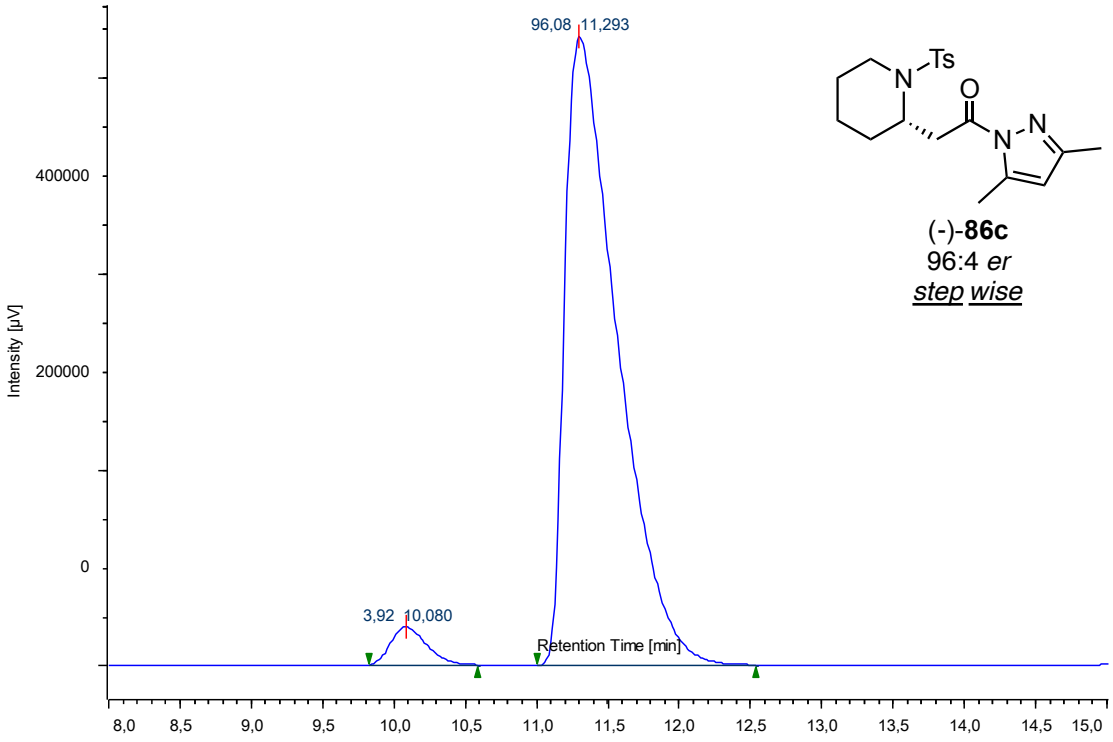
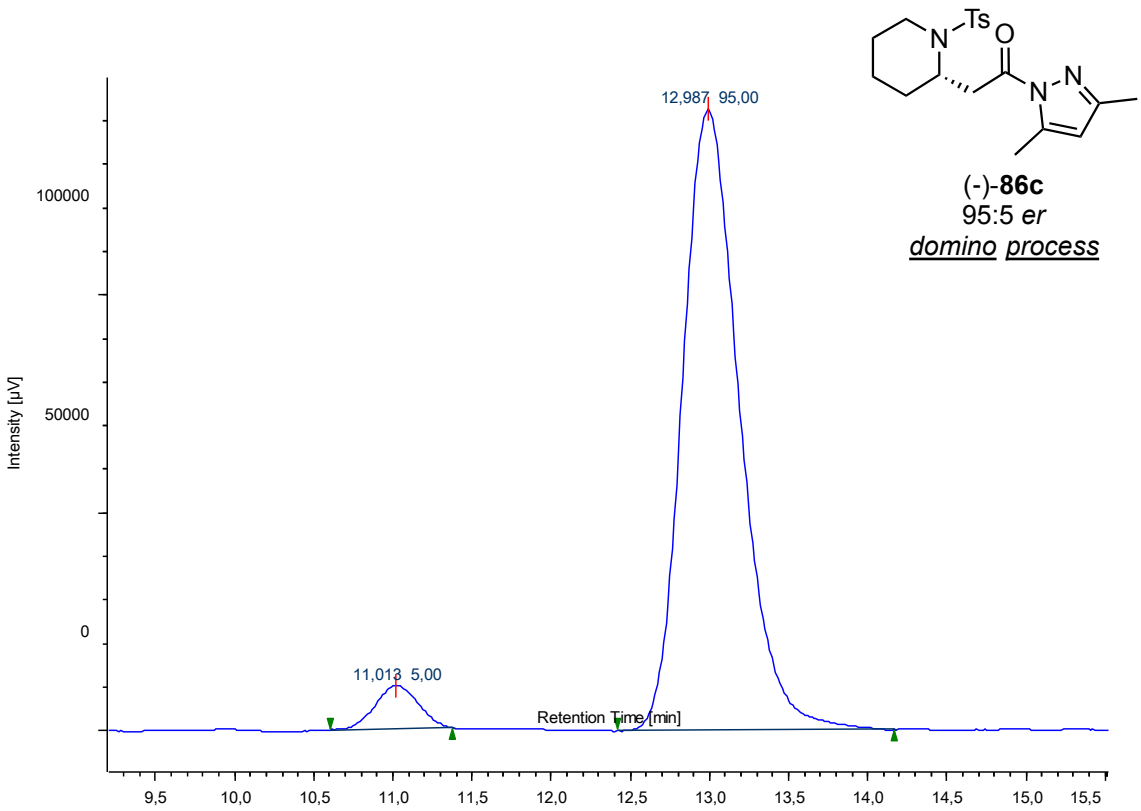


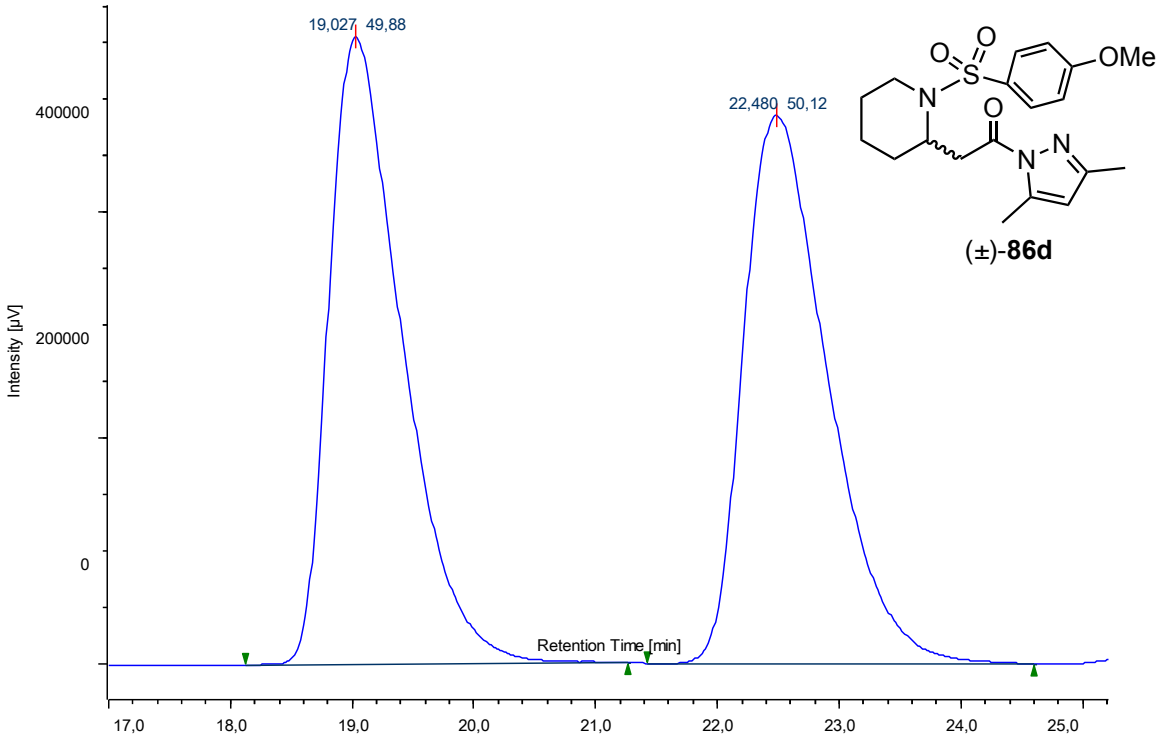
(±)-**86c**



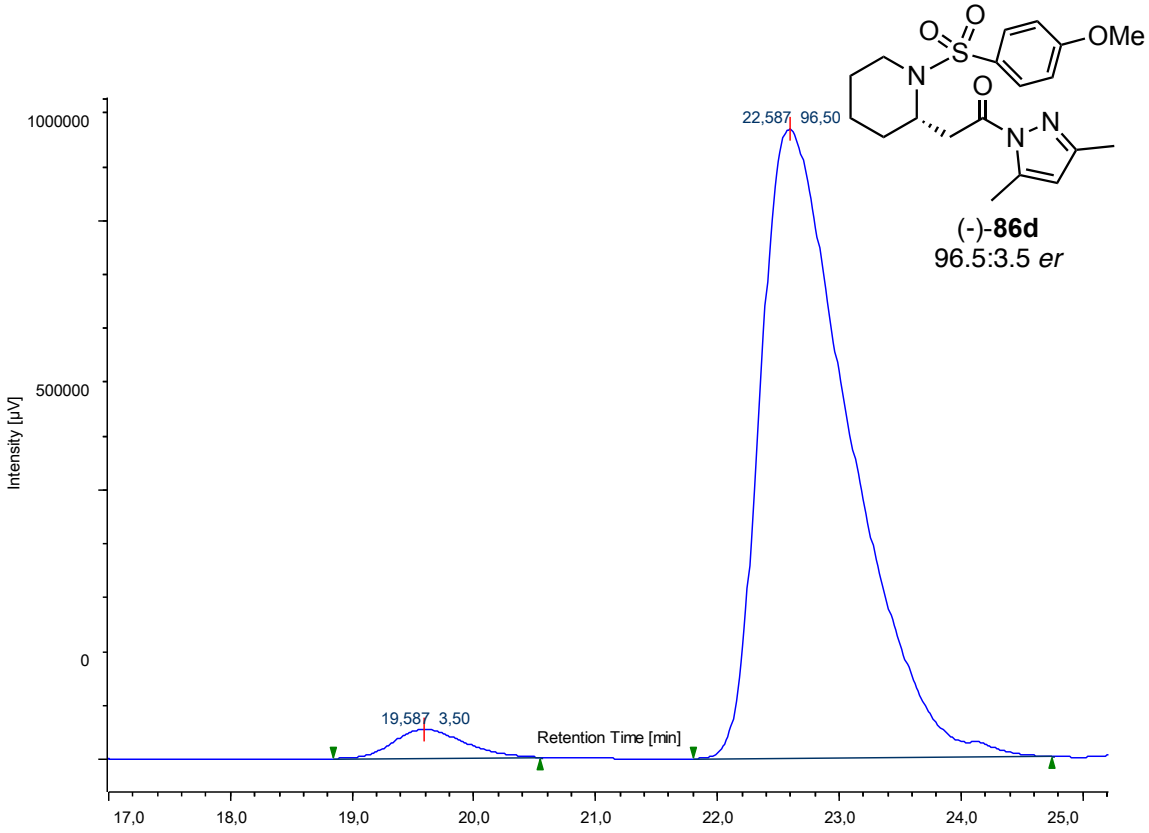
(-)-**86c**
96:4 *er*
step wise



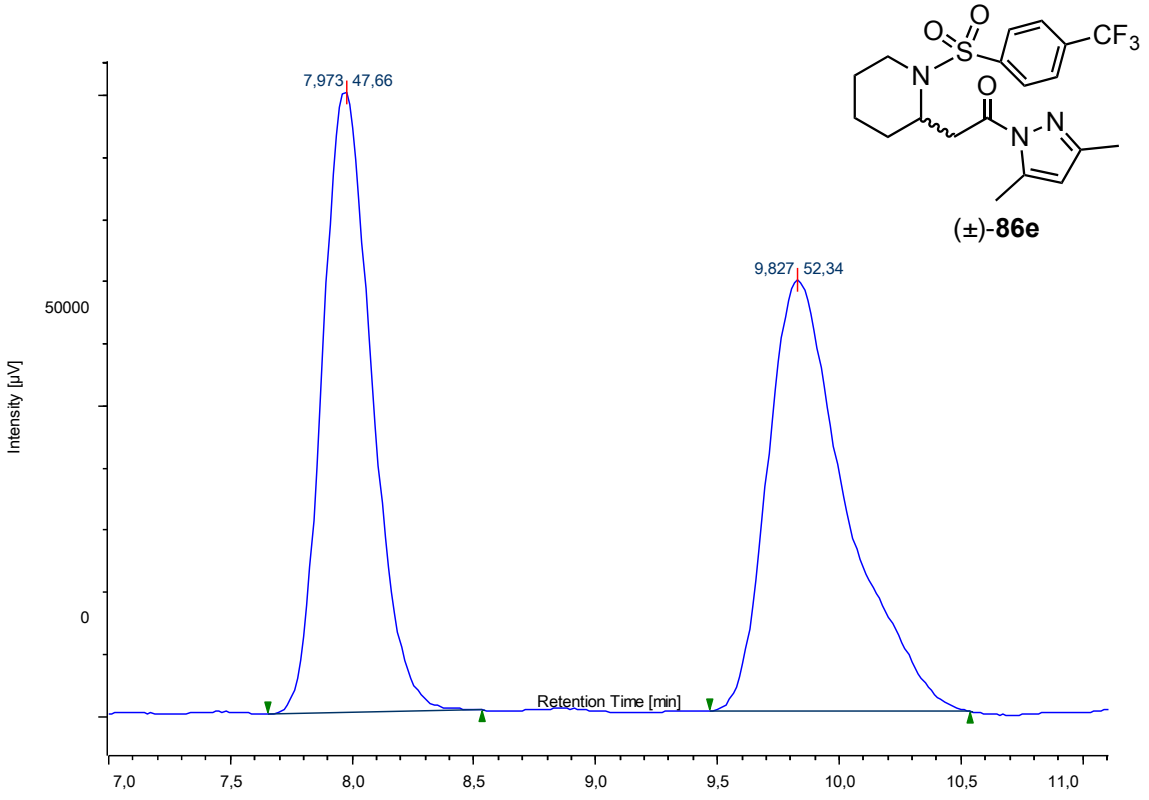
(-)-**86c**
95:5 *er*
domino process



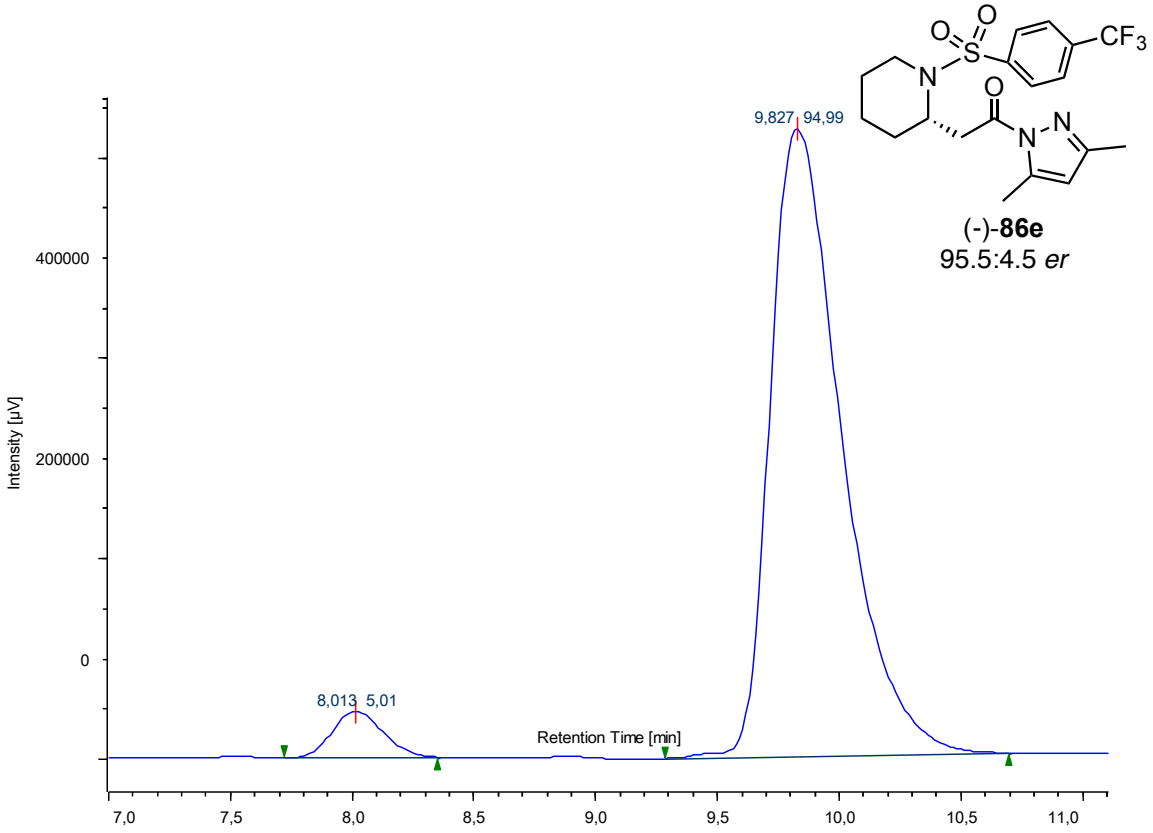
(±)-**86d**



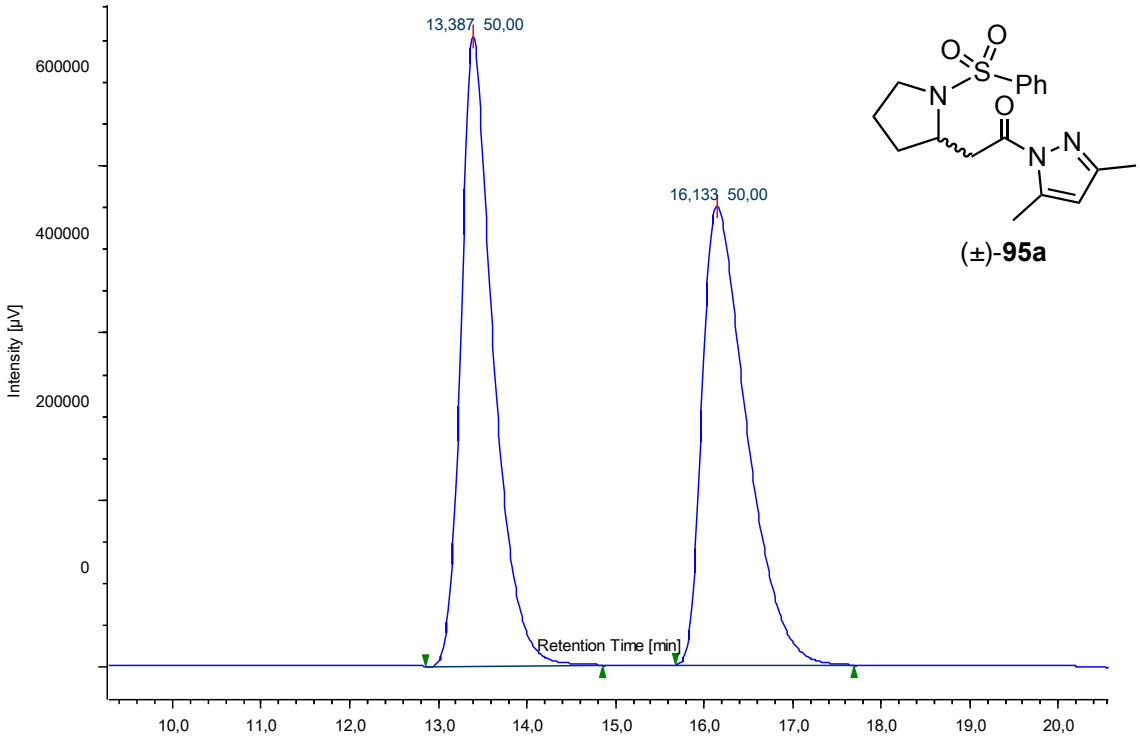
(-)-**86d**
96.5:3.5 *er*



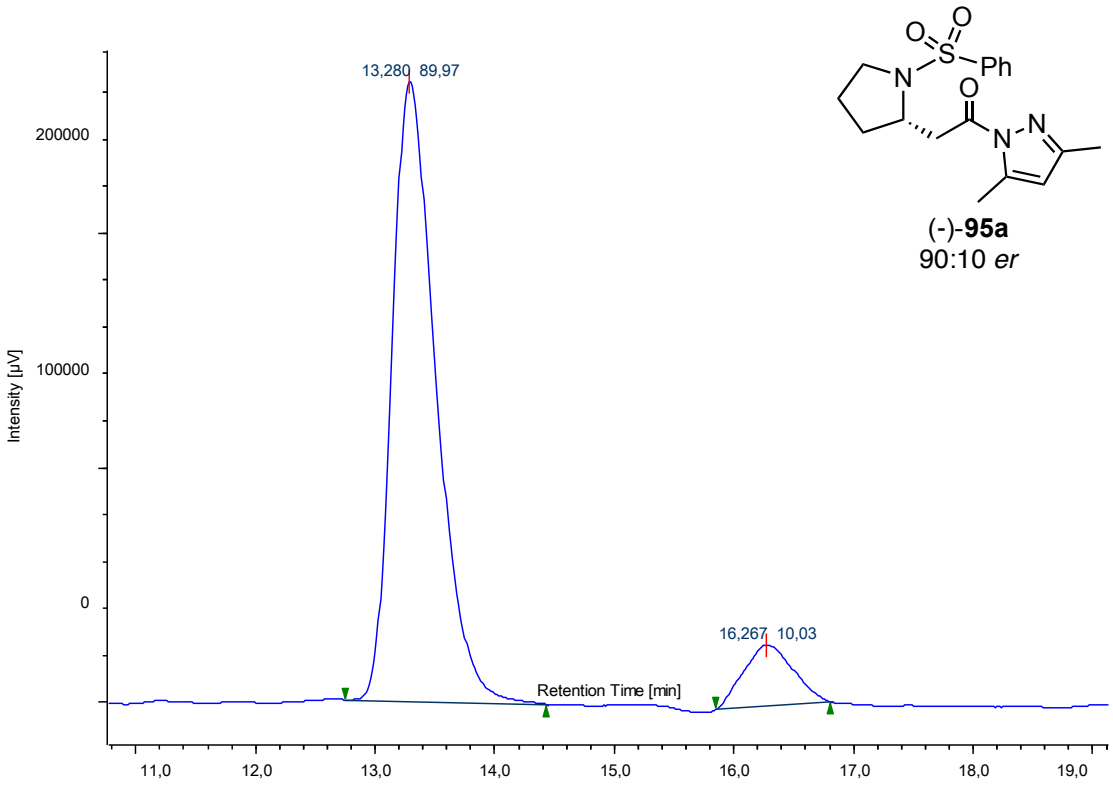
(±)-**86e**



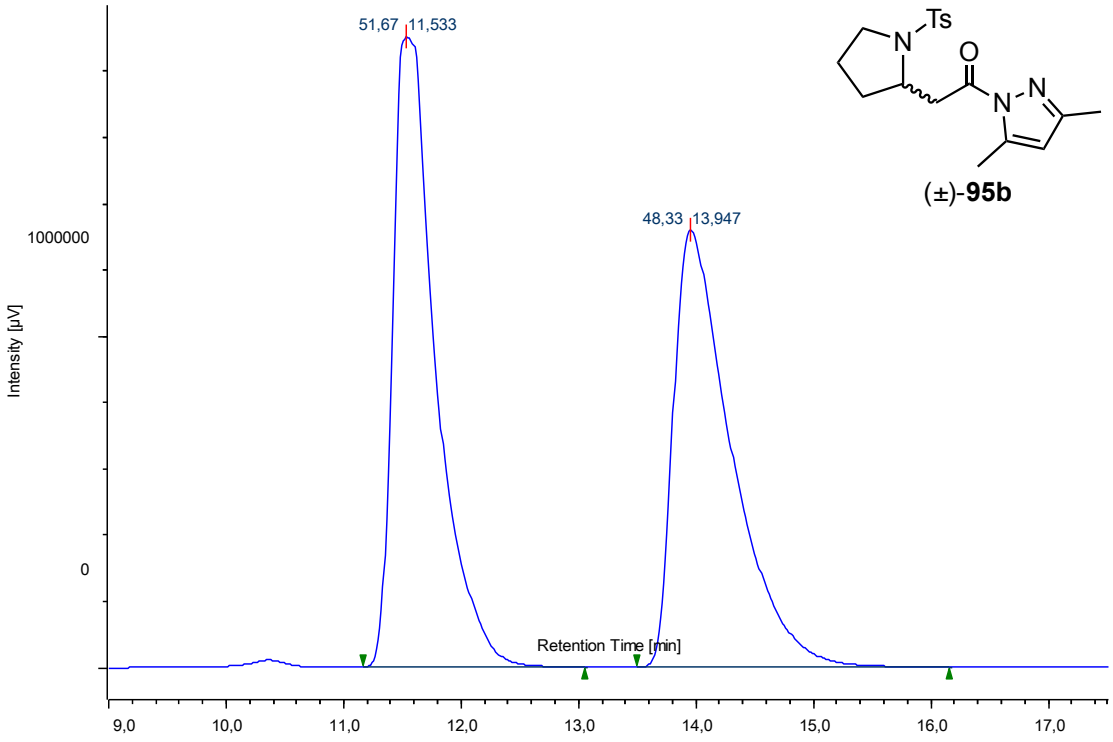
(-)-**86e**
95.5:4.5 *er*



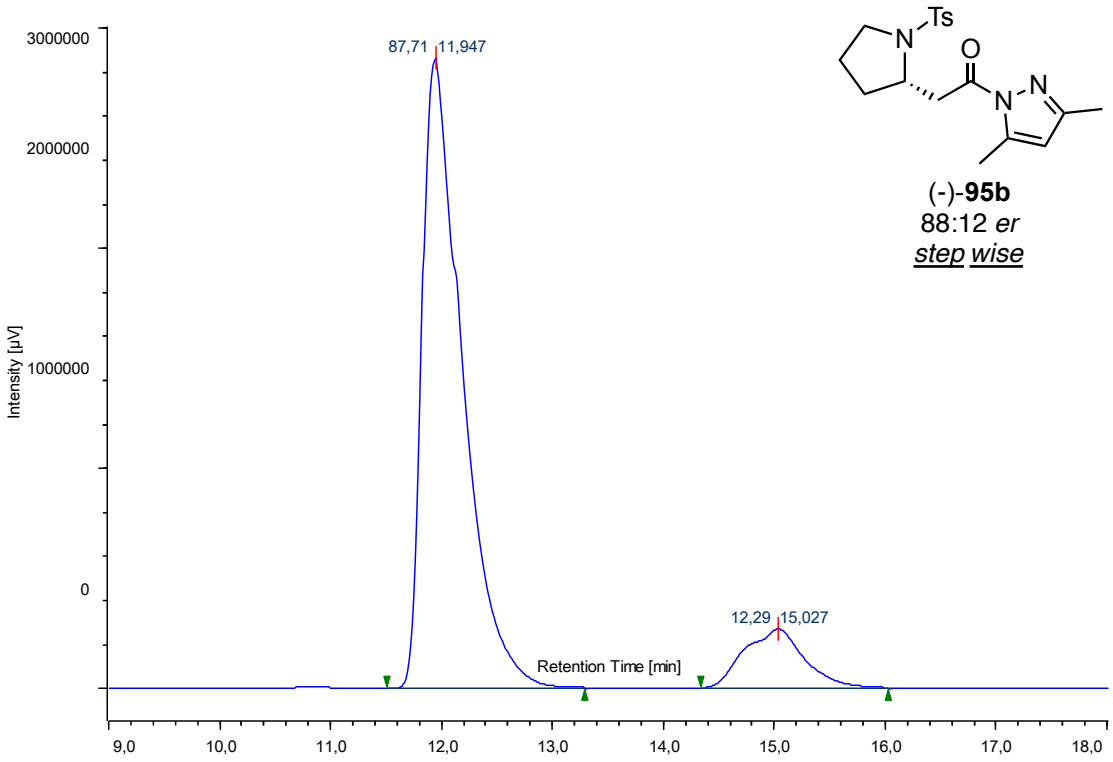
(±)-**95a**



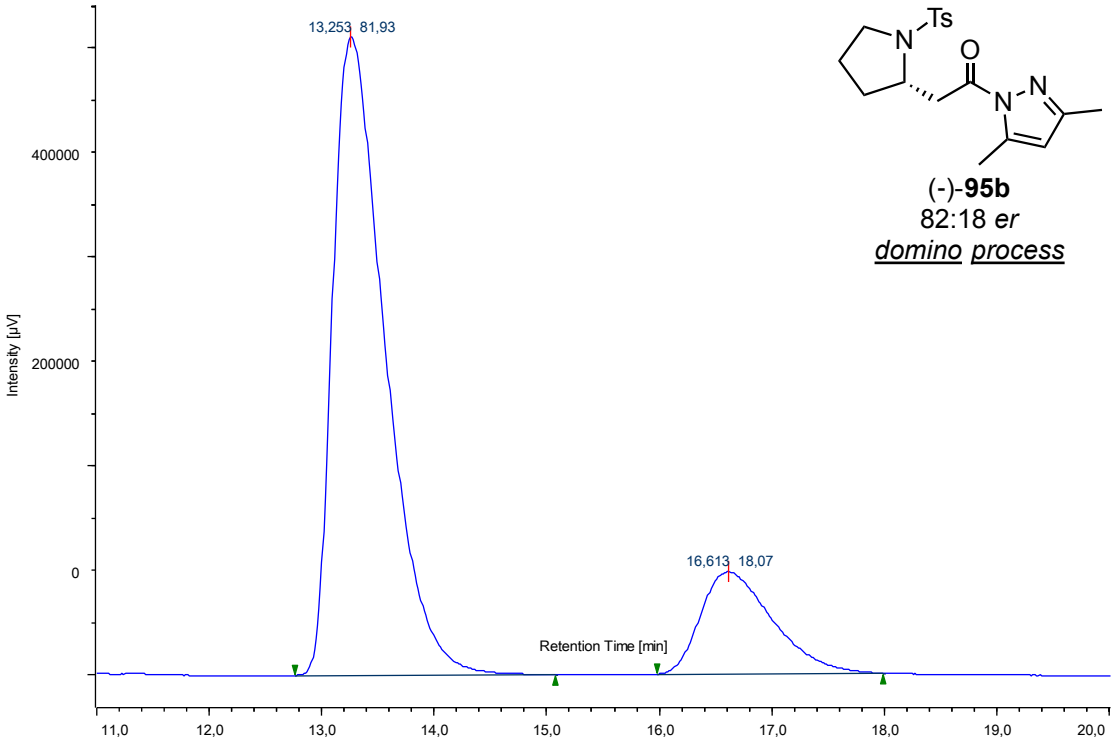
(-)-**95a**
90:10 *er*



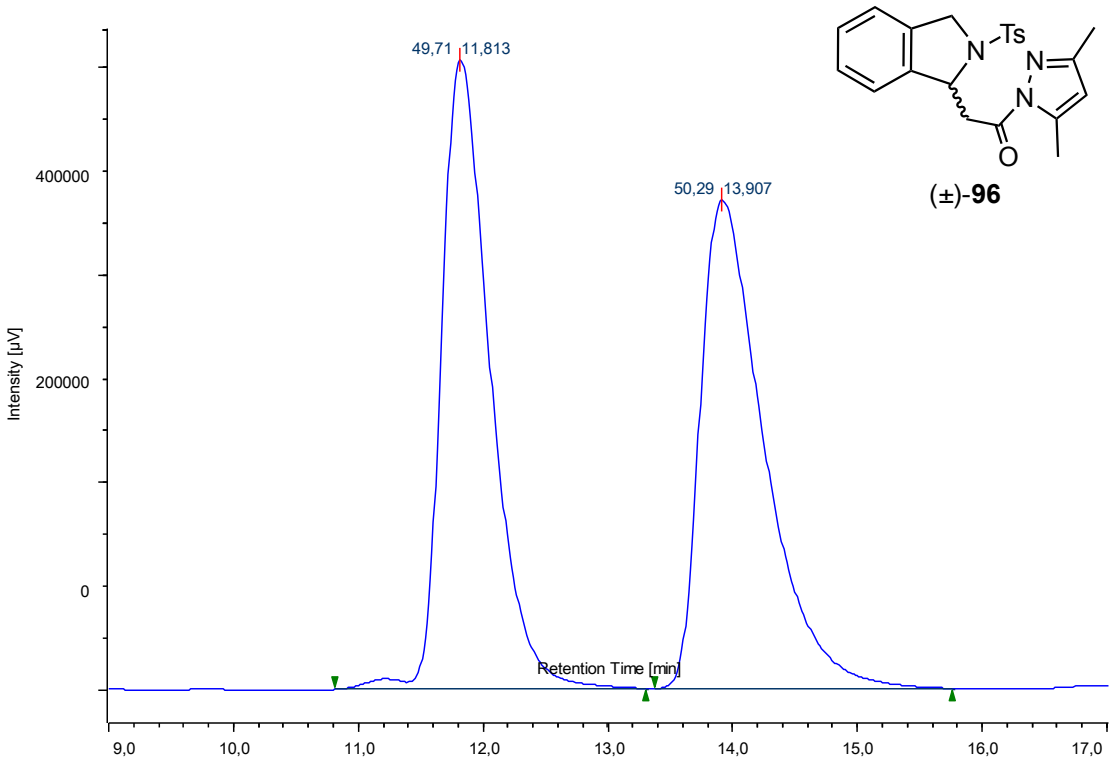
(±)-**95b**



(-)-**95b**
88:12 *er*
step wise



(-)-**95b**
82:18 *er*
domino process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50,29 13,907
400000
200000
0
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Retention Time [min]
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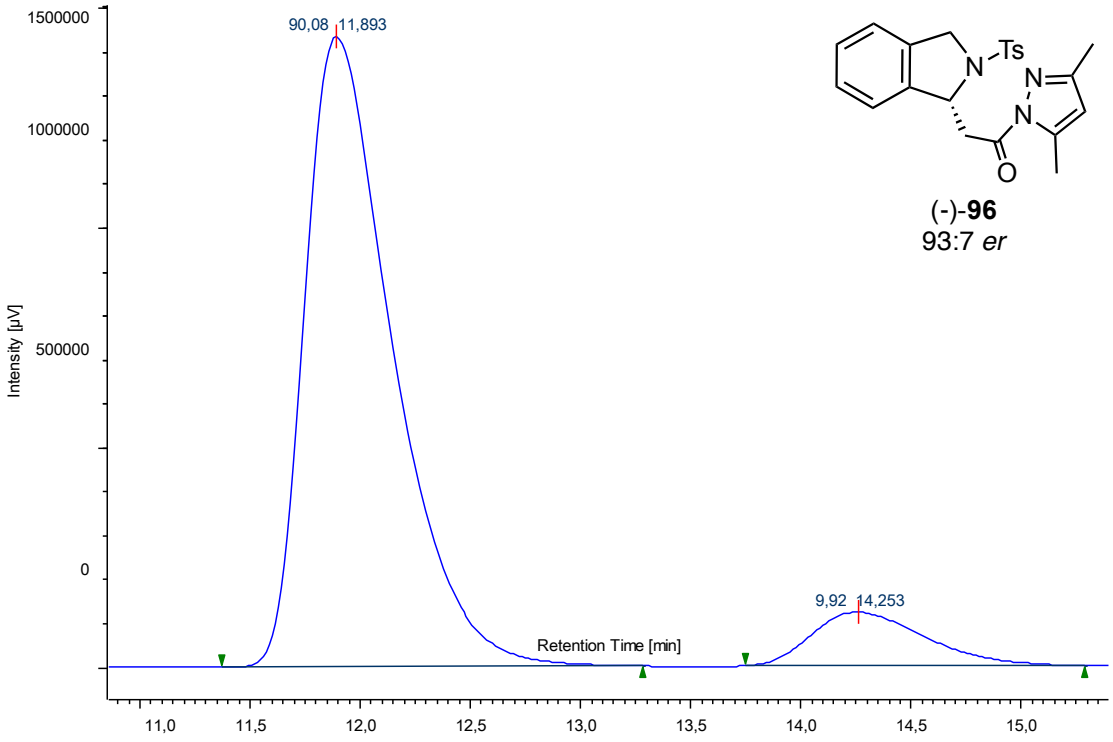
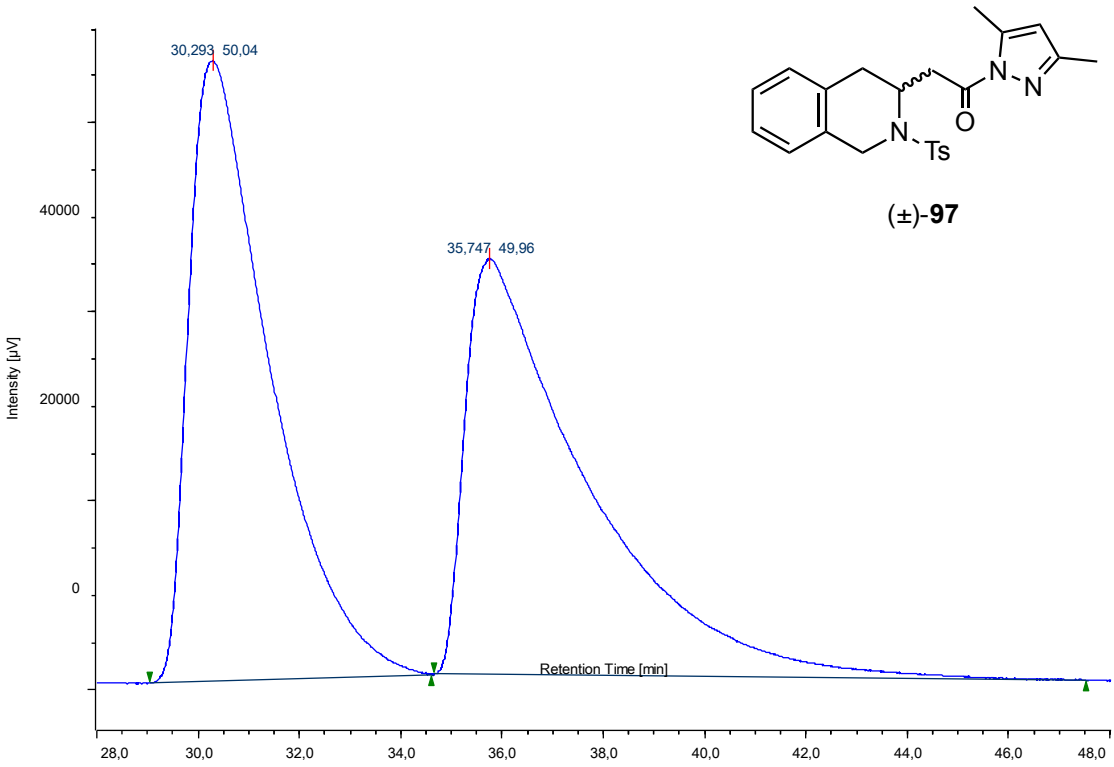
10,0
11,0
12,0
13,0
14,0
15,0
16,0
17,0
Ts
N
N
O

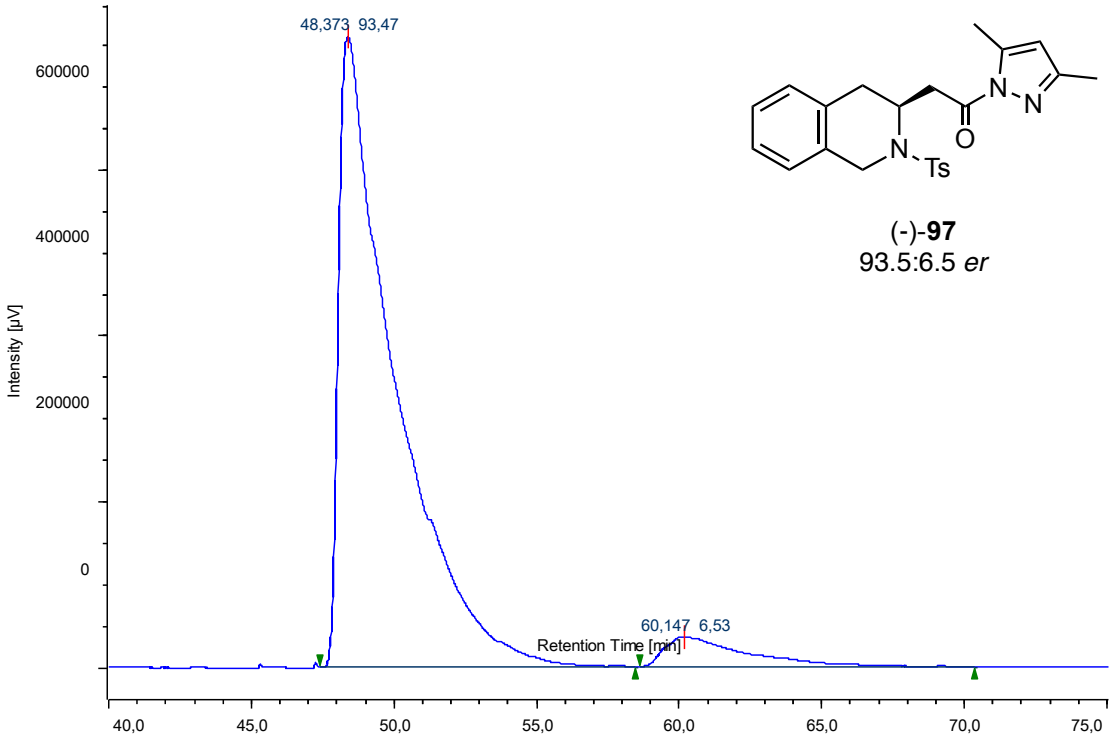
(±)-**96**


90,08 11,893
9,92 14,253
1500000
1000000
500000
0
Intensity [µV]
Retention Time [min]
11,0
11,5
12,0
12,5
13,0
13,5
14,0
14,5
15,0
Ts
N
N
O

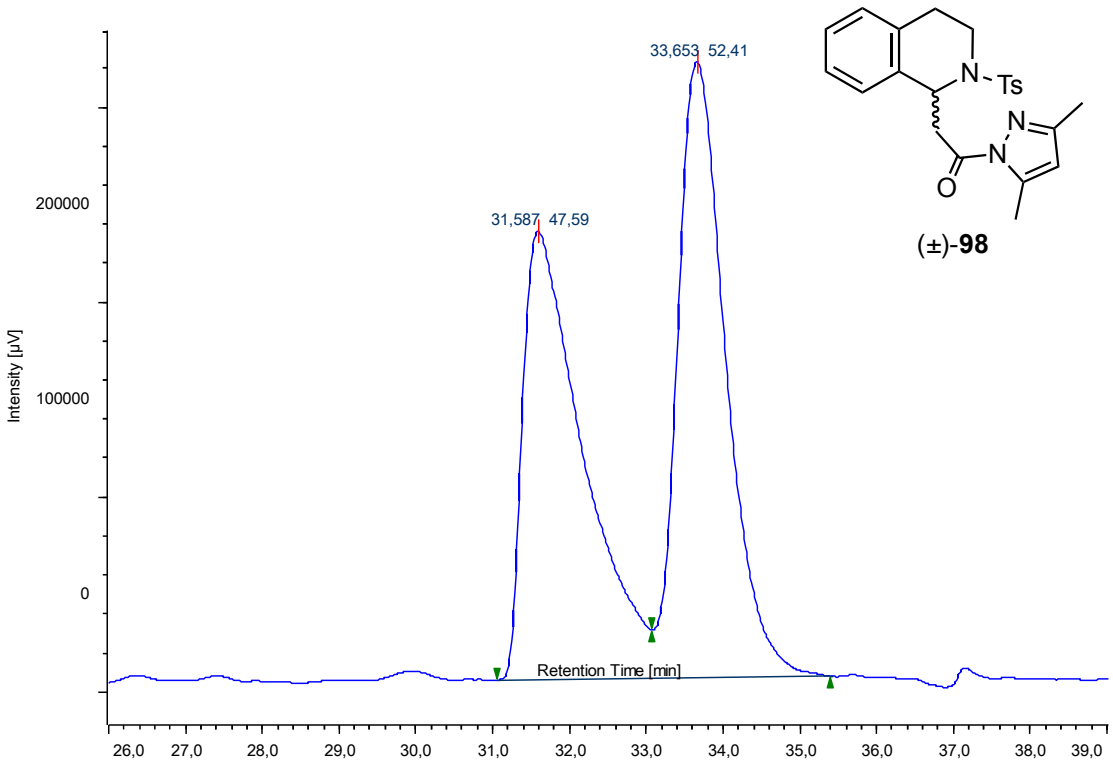
(-)-**96**
93:7 *er*



(±)-**97**



(-)-**97**
93.5:6.5 *er*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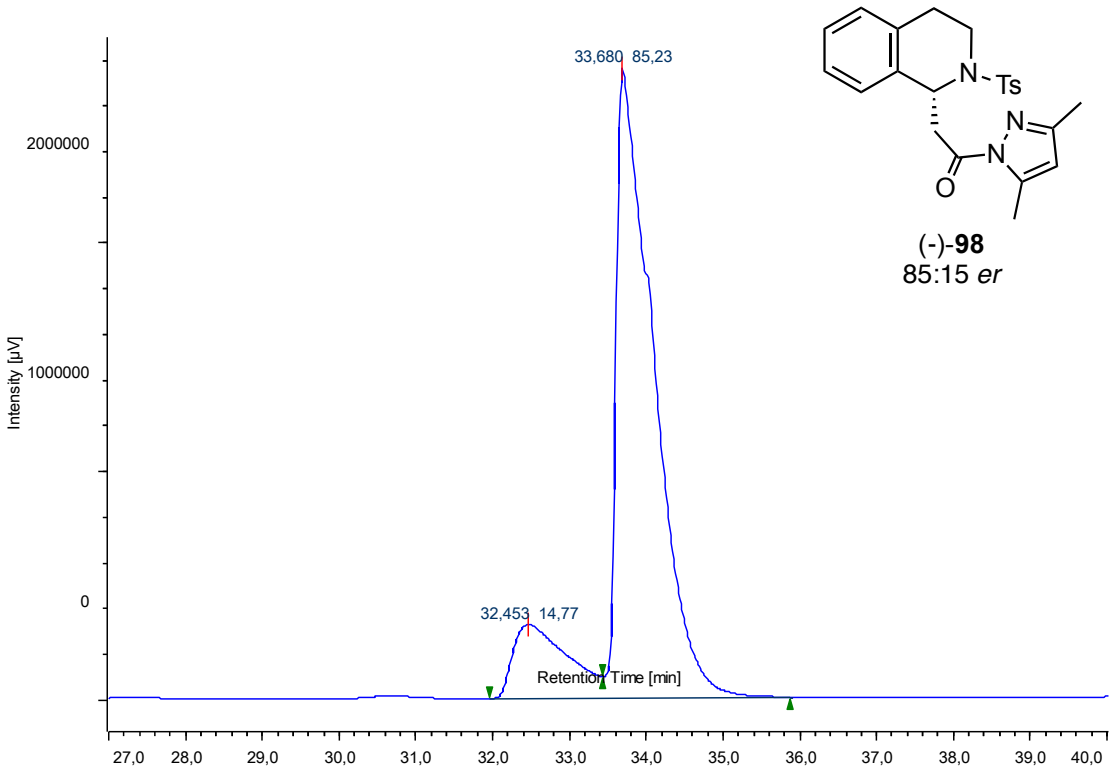
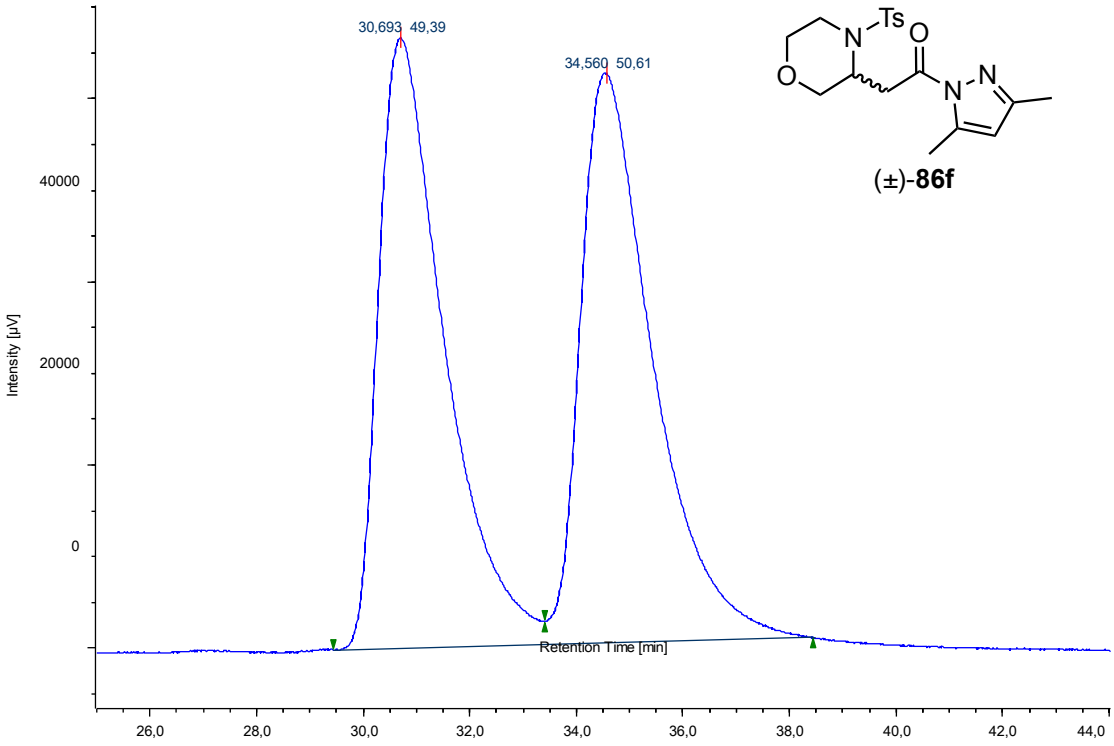
31,587 47,59
200000
100000
0
Intensity [µV]
Retention Time [min]
26,0 27,0 28,0 29,0 30,0 31,0 32,0 33,0 34,0 35,0 36,0 37,0 38,0 39,0
N
Ts
N
N
O

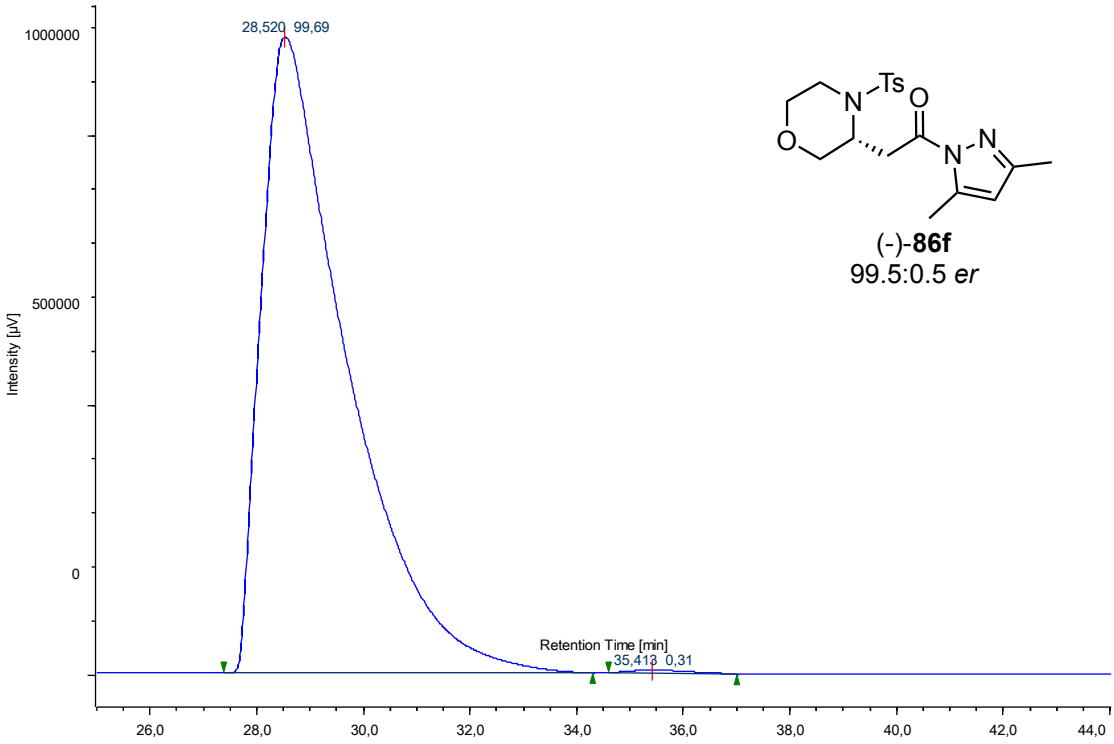
(±)-**98**


33,680 85,23
32,453 14,77
2000000
1000000
0
Intensity [µV]
Retention Time [min]
27,0 28,0 29,0 30,0 31,0 32,0 33,0 34,0 35,0 36,0 37,0 38,0 39,0 40,0
N
Ts
N
N
O

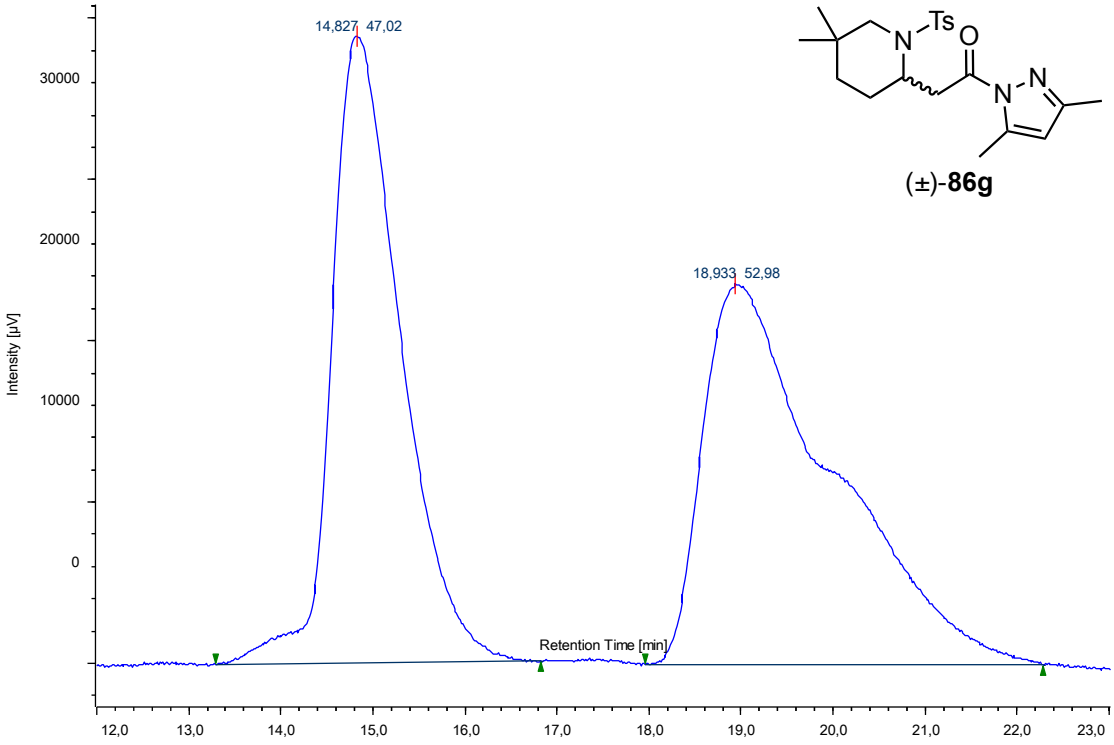
(-)-**98**
85:15 *er*



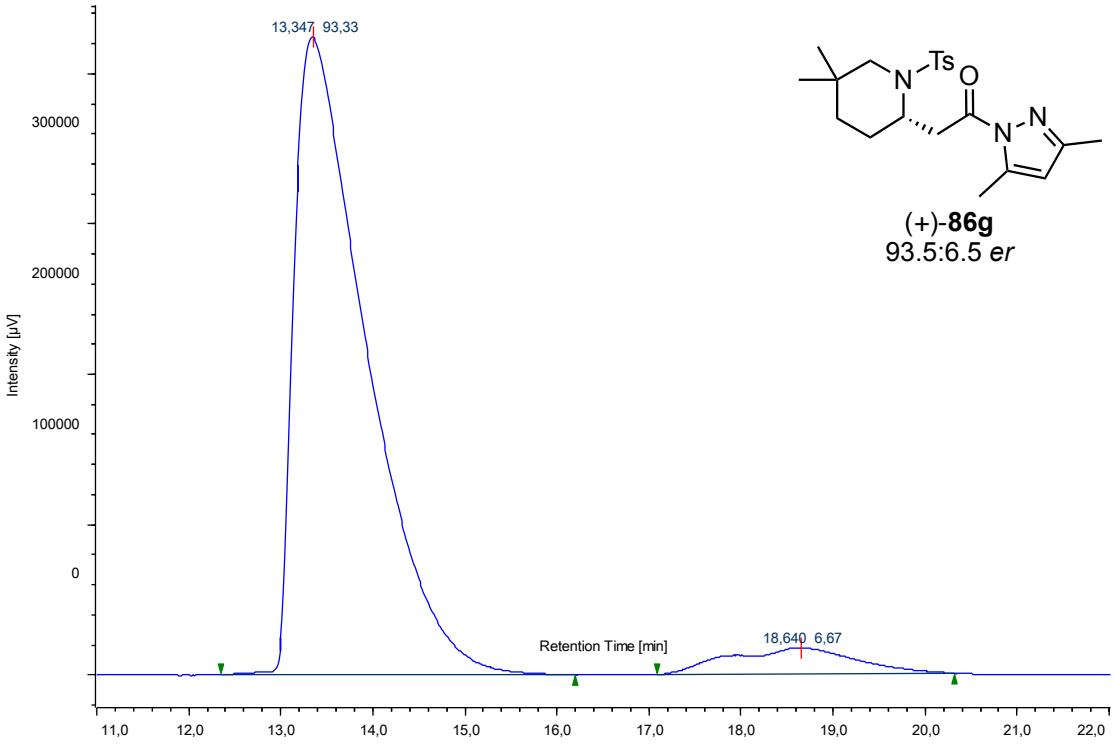
(±)-**86f**



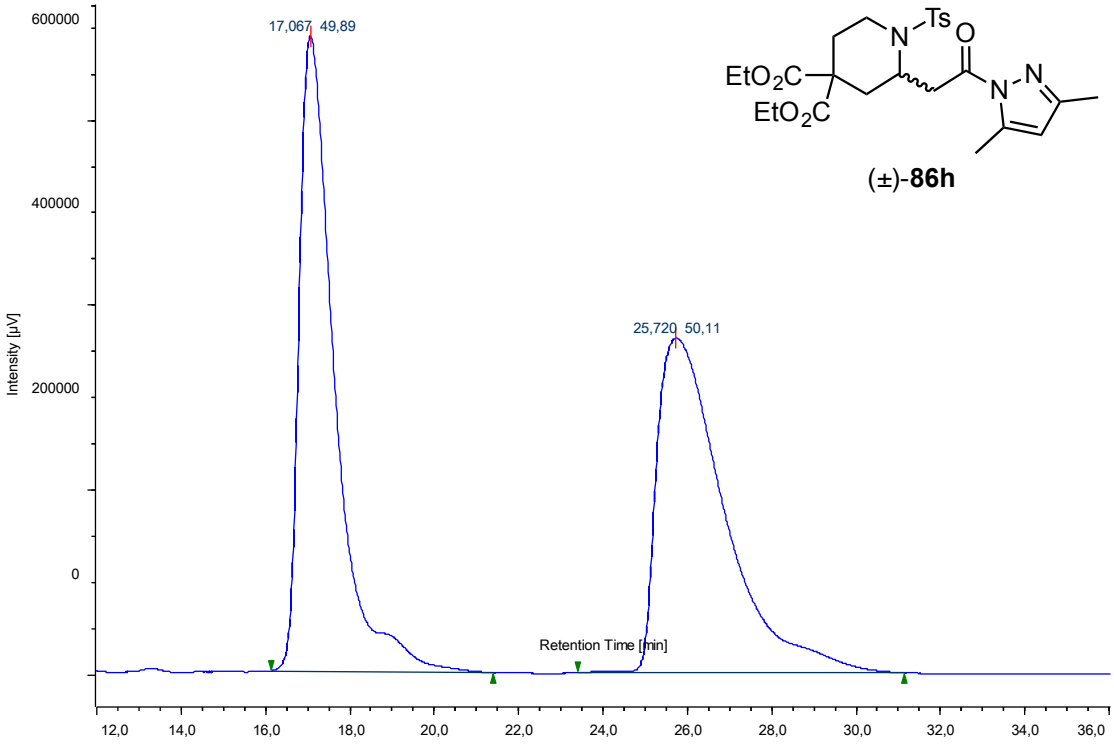
(-)-**86f**
99.5:0.5 *er*



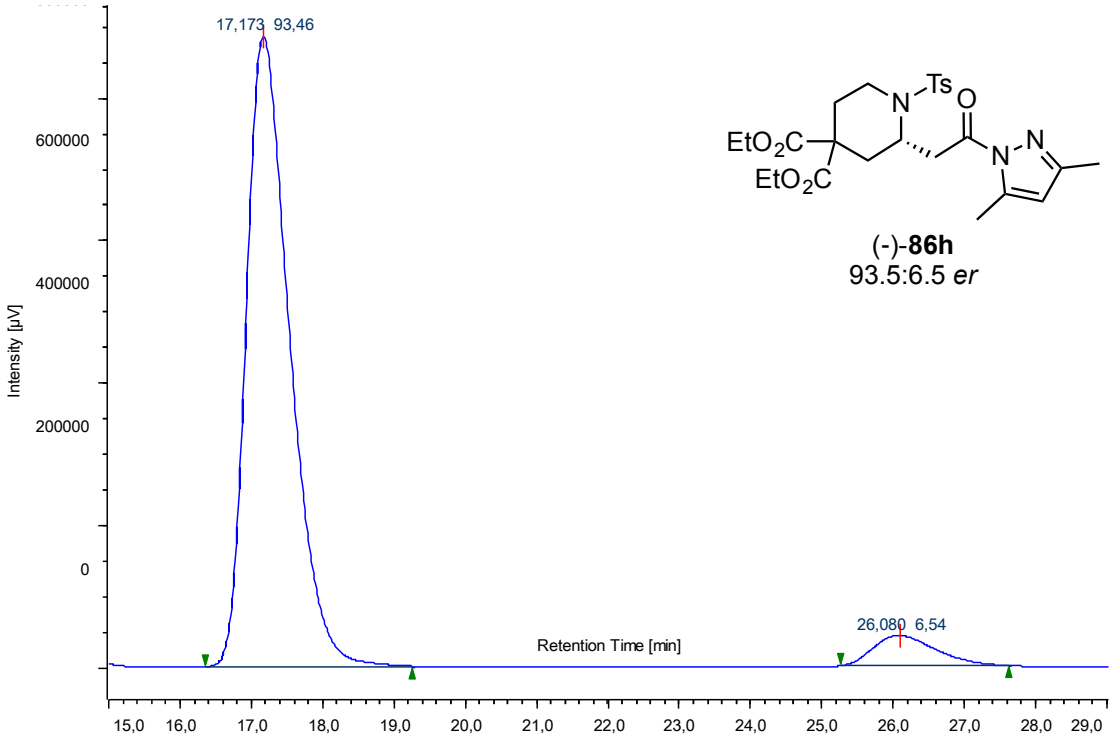
(±)-**86g**



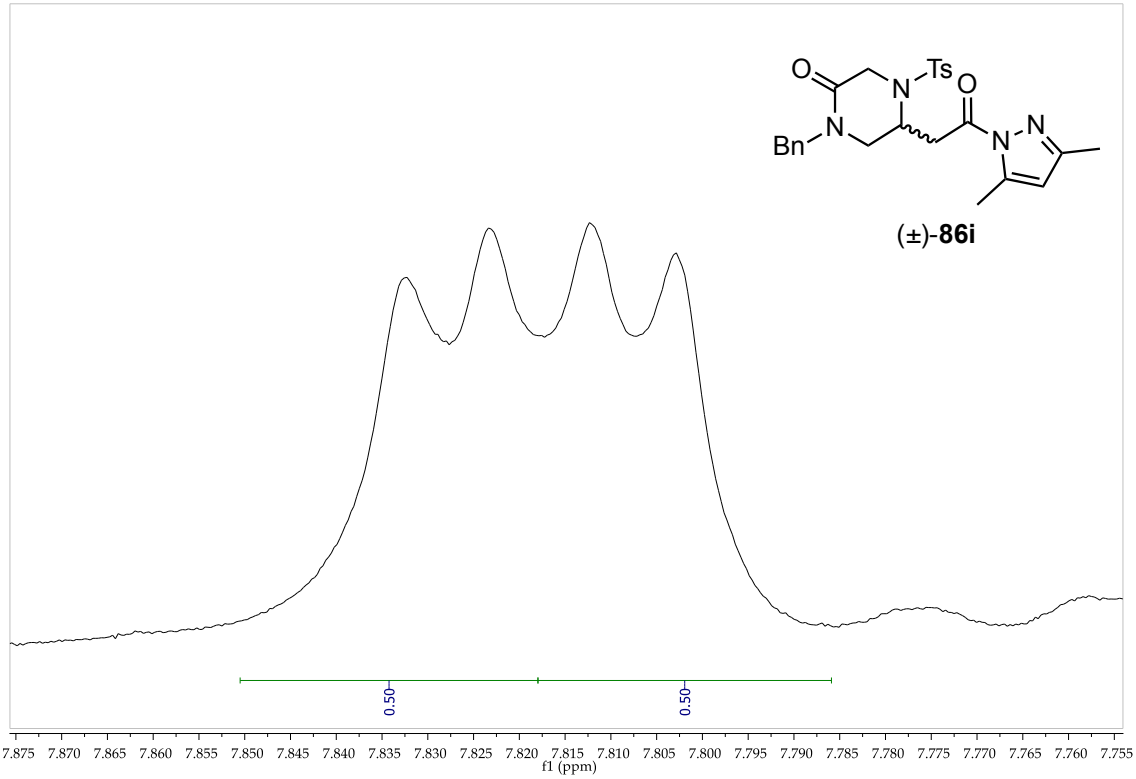
(+)-**86g**
93.5:6.5 *er*



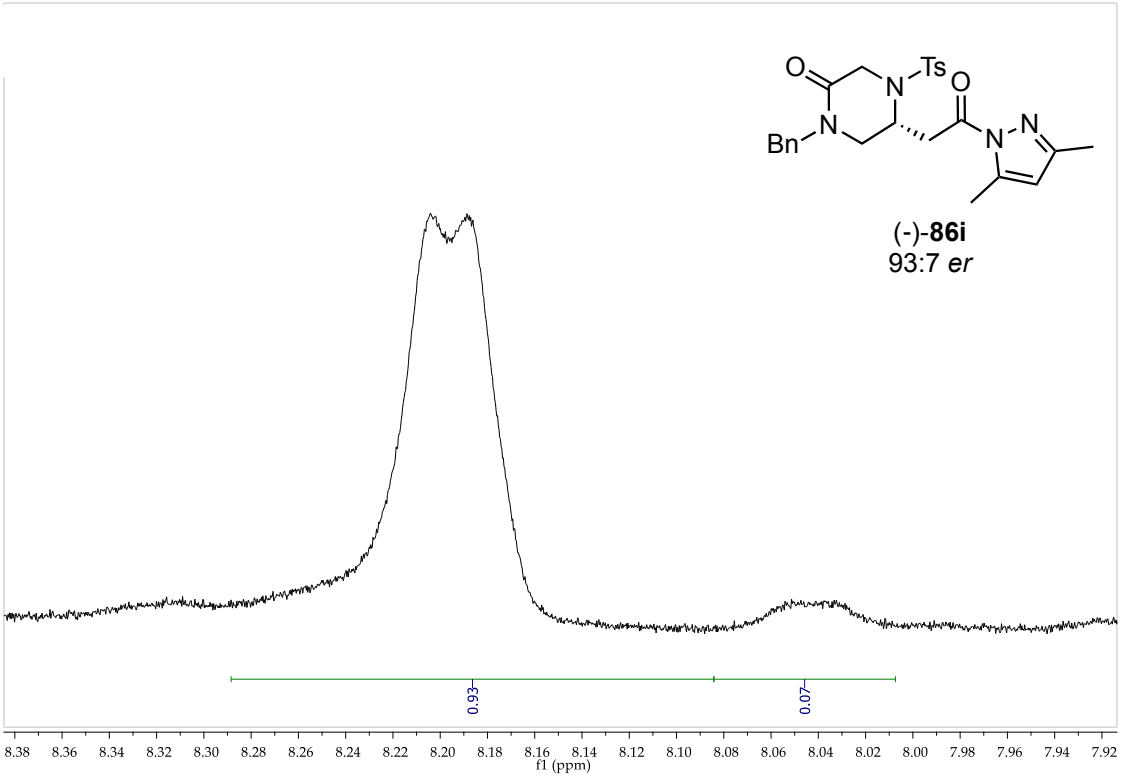
(±)-**86h**



(-)-**86h**
93.5:6.5 *er*



(±)-**86i**



(-)-**86i**
93:7 *er*

CHAPTER 3:
Organocatalytic synthesis of enantioenriched bicyclic sultams

3.1. Background

3.1.1. MICHAEL ADDITIONS TO VINYL SULFONES

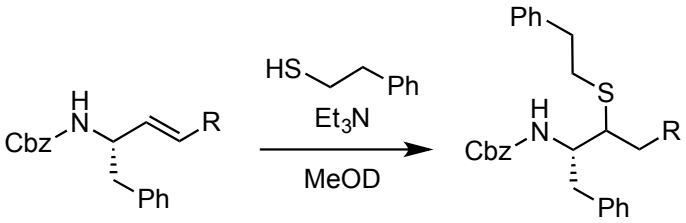
Sulfones are widely used intermediates of unique synthetic versatility in organic synthesis. Conjugated additions of carbon nucleophiles to vinyl sulfones constitute a class of synthetically valuable C-C bond forming reactions. Accordingly, considerable efforts have been devoted to the development of the asymmetric version of those types of additions. Although significant advances have been made in the use of the chiral auxiliary strategy, enantioselective catalytic Michael additions remained elusive until more or less ten years ago.[247]

First of all, two studies that highlighted the importance of the substituents in the vinyl sulfone for its role as Michael acceptor will be introduced, which could result interesting for the understanding of the results reported below in this PhD thesis.

Roush reported in 2003 [248] the dependence of the reactivity of the Michael acceptor on the nature of the sulfonyl substituent (SO_2R) (Scheme 3.1). The rates of the Michael addition of 2'-(phenethyl)thiol, in the presence of triethyl amine, vary over 3 orders of magnitude, with phenyl vinyl sulfonate esters (R = SO_2OPh) being ca. 3000-fold more reactive than *N*-benzyl vinyl sulfonamides (R = SO_2NHBn). The relative rates of Michael addition to α,β-unsaturated esters, amides, and ketones are readily understood when considering of the electrophilicity of the enoyl β-carbon. However, the situation differs for conjugate addition reactions of vinyl sulfonyl acceptors. As these compounds undergo conjugate additions, the reactive intermediate is an α-carbanion, which is stabilised by the sulfur atom of the sulfonyl unit. In contrast to enoyl Michael acceptors, electronic effects arising from the linking oxygen or nitrogen atoms of the sulfonate ester and sulfonamide groups are exclusively

[247] a) Pinheiro, S.; Guingant, A.; Desmaële, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003-1006. b) d'Angelo, J.; Revial, G. *Tetrahedron: Asymmetry* **1991**, *2*, 199-202. c) Enders, D.; Müller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem*. **2000**, 879-892. d) Sanki, A. K.; Suresh, C. G.; Falgune, U. D.; Pathak, T. *Org. Lett*. **2003**, *5*, 1285-1288. e) See Ref. 40c: Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
[248] Reddick, J. J.; Cheng, J.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1967–1970.

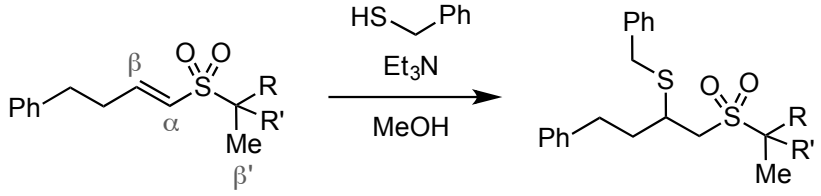
inductive. Therefore, strong σ-electron-withdrawing inductive effects would be expected to stabilize the α-carbanion formation.



R	relative *k*
SO_2OPh	3000
COMe	2700
SO_2Ph	120
SO_2OEt	90
$SO_2N(Me)OBn$	150
SO_2NHOBn	50
CO_2Me	17
$SO_2N(Me)Bn$	3
SO_2NHBn	1

Scheme 3.1. Relative pseudo-first-order rate constants in Michael additions to differently R-substituted vinyl sulfones.

Then, in 2007 Posner et al. reported the unexpected steric effects of "remote" alkyl groups on the rate of conjugate additions to alkyl α,β-ethylenic sulfones.[249] They showed that what are widely considered to be remote alkyl groups in –CH=CHS(O)$_n$–alkyl systems are actually not remote from the β-carbon of these Michael acceptors. Molecular modelling shows clearly that the alkyl groups in these conjugated systems shield the β-carbons. Competition experiments established that the relative rates of Michael addition are in the following order: Et > *i*Pr > *t*Bu.

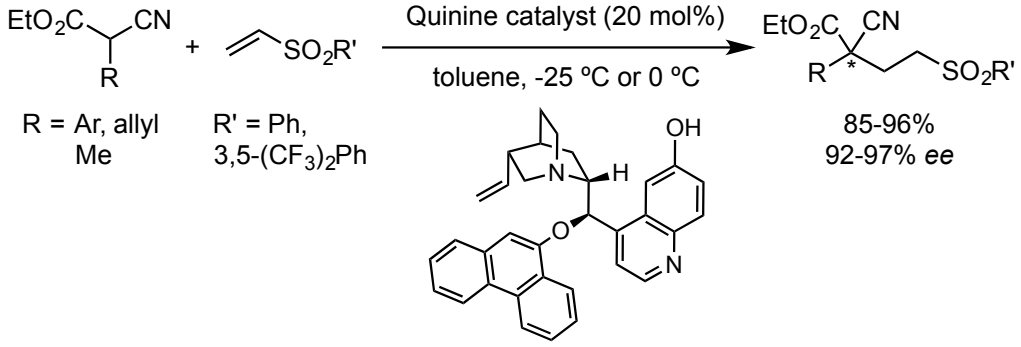


R	R'	relative *k*
H	H	10.3
CH_3	H	3
CH_3	CH_3	1

Scheme 3.2. Relative rates of formation of the Michael adduct depending on the β'-substituents.

[249] Usera, A. R.; Posner, G. H. *J. Org. Chem.* **2007**, *72*, 2329–2334.

Focusing now on the organocatalytic approaches, Deng published in 2005 the first highly enantioselective catalytic conjugate addition to vinyl sulfones.[250] α-Cyanoacetates bearing a range of alkyl or aryl groups, of varying electronic and steric properties, underwent efficient enantioselective addition to aryl vinyl sulfones, providing the Michael adduct bearing the all-carbon quaternary stereocenter in excellent enantioselectivity and good to excellent yield by means of cinchona alkaloid organocatalysts (Scheme 3.3). They also applied this procedure to develop a new catalytic approach for the asymmetric synthesis of the biologically significant α,α-disubstituted amino acids. A similar study employing α-substituted cyanoacetates and a chiral bifunctional thiourea catalyst was developed by Chen et al. shortly after.[62]



Scheme 3.3. Enantioselective Michael addition of α-cyanoacetates to vinyl sulfones.

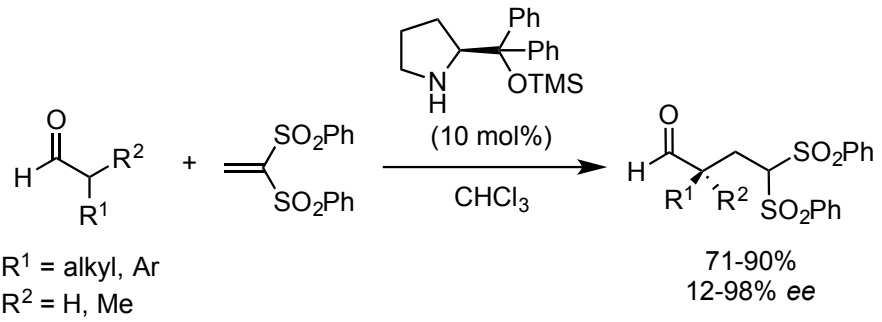
On the other hand, Alexakis has developed several studies related to conjugate additions to vinyl sulfones.[251] Although they could not accomplish the reaction with mono-activated vinyl sulfones, his research group demonstrated the principle of double activation through the presence of geminal sulfonyl groups for inducing reactivity. They disclosed the first intermolecular enantioselective organocatalytic Michael reaction of aldehydes with vinyl sulfones employing a catalytic system of chiral amine with diphenyl prolinol silyl ether (Scheme 3.4).[251a] Thus, leading to optically active γ-*gem*-sulfonyl aldehydes, with good yields and enantioselectivities, as useful tunable chiral

[250] Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949.

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

[251] a) Sulzer-Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem. Eur. J.* **2009**, *15*, 3204–3220. b) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123-3135. c) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361–4364. d) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559–2562.

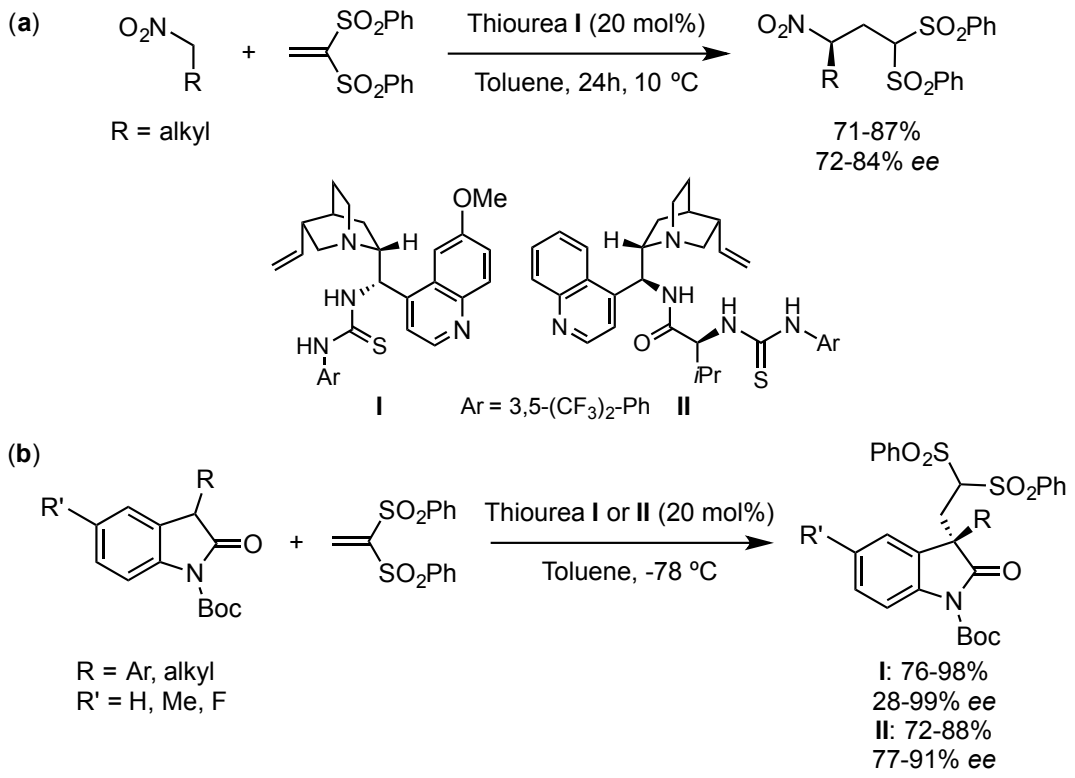
synthons. The analogous addition of ketones to conjugated sulfones has not been described yet.[40c]



Scheme 3.4. Asymmetric conjugate addition of aldehydes to vinyl bis(sulfone).

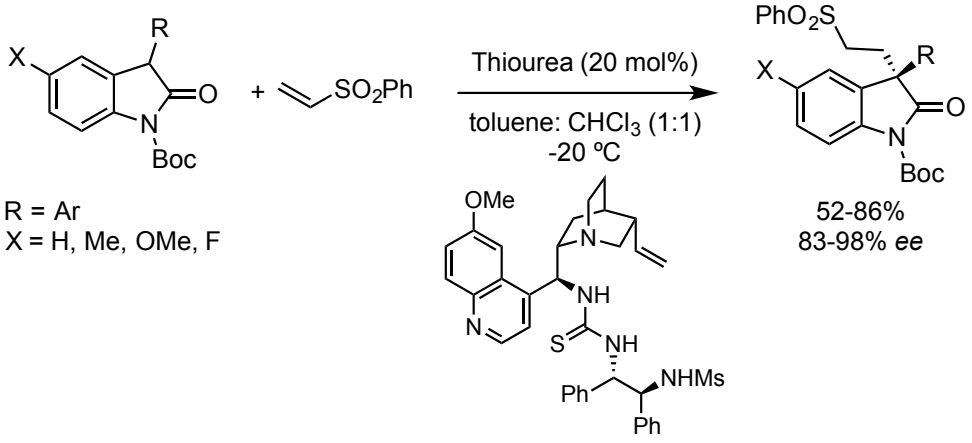
In addition, Lu's research group published the conjugate additions of nitroalkanes[252] and oxindoles[253] to vinyl bis(sulfone) molecules by means of thiourea organocatalysts. In 2009, they reported the first organocatalytic enantioselective Michael reaction between nitroalkanes and vinyl sulfone promoted by a quinidine-derived thiourea catalyst (Scheme 3.5.a). This procedure, together with facile reduction and desulfonilation, represents a novel approach to access α-branched chiral amines. Then, in 2010 they disclosed highly enantioselective Michael additions of both 3-aryl- and 3-alkyl-disubstituted oxindoles to conjugated sulfone by means of bifunctional and trifunctional thiourea catalyst containing natural amino acid residues (Scheme 3.5.b).

[40c] Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
[252] Zhu, Q.; Lu, Y. *Org. Lett.* **2009**, *11*, 1721–1724.
[253] Zhu, Q.; Lu, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756.



Scheme 3.5. Cinchona-derived thiourea catalysed Michael additions to vinyl bis(sulfone).

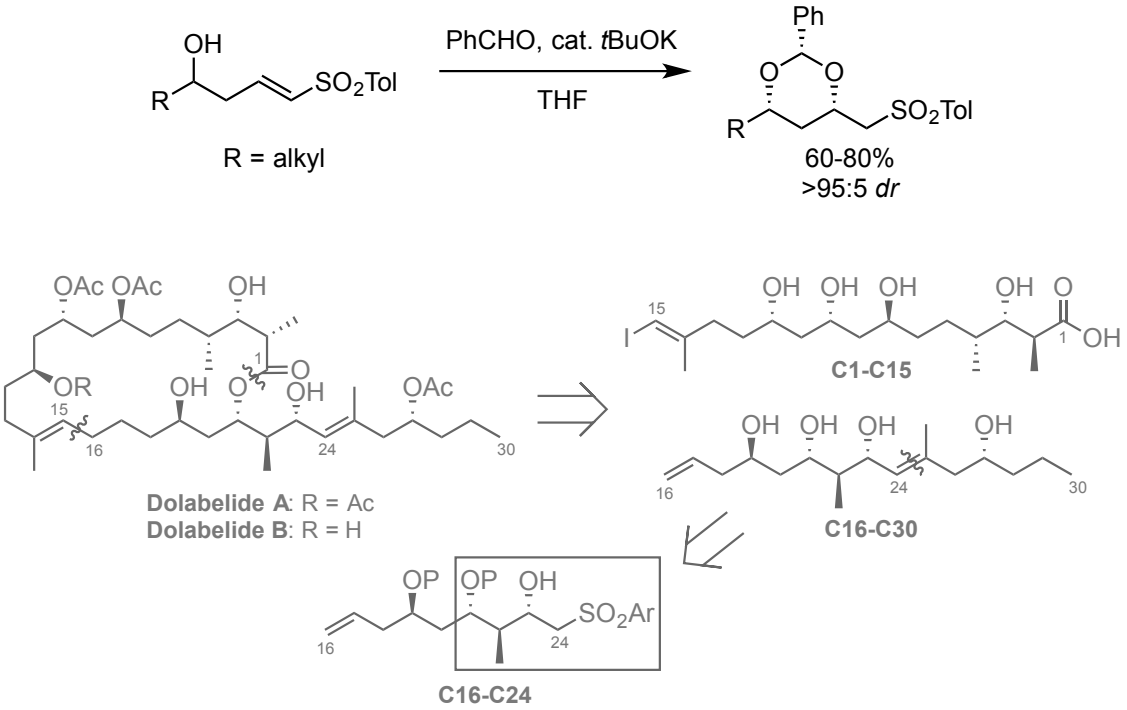
More recently, a highly enantioselective Michael addition of 3-aryl-*N*-Boc-oxindoles to the mono-activated phenyl vinyl sulfone catalysed by a quinine derived bifunctional amine-thiourea-bearing sulfonamide as multiple hydrogen-bonding donor catalyst was published.[254] The corresponding adducts, which contain a chiral quaternary carbon center at the 3-position of the oxindole, were obtained in good yields (52-86%) with very good enantioselectivities (83-98% *ee*).



Scheme 3.6. Enantioselective Michael addition of oxindoles to phenyl vinyl sulfone.

[254] Zhao, M.-X.; Tang, W.-H.; Chen, M.-X.; Wei, D.-K.; Dai, T.-L.; Shi, M. *Eur. J. Org. Chem.* **2011**, *2011*, 6078–6084.

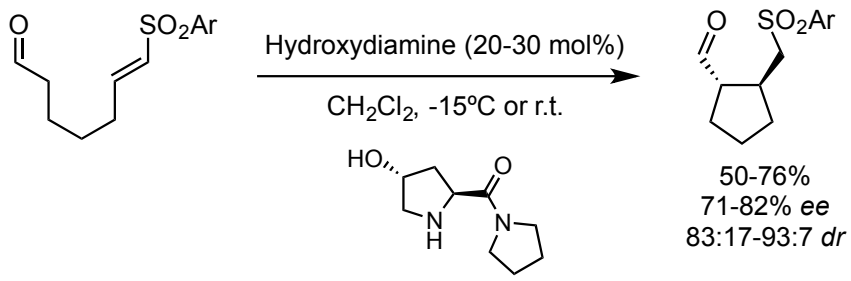
Finally, regarding intramolecular conjugate additions to vinyl sulfones there are two noteworthy examples. Prunet et al. developed in 2002 a new method to make sulfone synthons with a *syn* 1,3-diol motif, which constitute models for the C16-C24 portion of cytotoxic Dolabelides (Scheme 3.7). The intramolecular *oxa*-Michael reaction in the presence of benzaldehyde and a catalytic amount of potassium *tert*-butoxide proceeded in good yields and selectivity starting from homoallylic alcohols functionalized with a toluenesulfone.



Scheme 3.7. Stereoselective intramolecular conjugate addition in the synthesis of Dolabelides precursors.

Then, in 2010 Alexakis research group disclosed the first organocatalytic intramolecular Michael addition of aldehydes bearing various vinyl sulfones in good yields with good enantioselectivities and diastereoselectivities.[255] In the intermolecular version, no reaction occurred with mono-activated phenyl vinyl sulfone; whereas in the intramolecular version, full conversion was observed. This reaction was promoted by a readily available *trans*-4-hydrozyprolyl amide, and the catalytic reaction might involve an activation of the sulfone by a hydrogen-bonding interaction (Scheme 3.8).

[255] Bournaud, C.; Marchal, E.; Quintard, A.; Sulzer-Mossé, S.; Alexakis, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1666–1673.



Scheme 3.8. Intramolecular Michael addition to vinyl sulfones.

3.1.2. SULTAMS

Significant interest has been directed toward cyclic sulfonamides, also known as sultams. These compounds possess unique physical and chemical properties, rendering them attractive targets for probing biological systems.[256] Although not found in nature,[257] sultams are known as privileged structures in drug discovery due to their diverse biological properties.[258] The more prominent include the Ampiroxicam anti-inflammatory agent (Figure 3.1.a), [259] benzodithiazine dioxides displaying anti-HIV-1 activity (Figure 3.1.b), [260] antiepileptic agent Sulthiame (Figure 3.1.c),[261] Brinzolamide for the treatment of glaucoma (Figure 3.1.d)[262] and anti-Alzheimer compounds as BACE-1 inhibitors (Figure 3.1.e).[263]

[256] a) Asad, N.; Samarakoon, T. B.; Zang, Q.; Loh, J. K.; Javed, S.; Hanson, P. R. *Org. Lett.* **2014**, *16*, 82–85. b) Ukrainets, I. V; Petrushova, L. A.; Dzyubenko, S. P.; Sim, G. *Chem. Heterocycl. Compd.* **2014**, *50*, 103–110. c) Valente, C.; Guedes, R. C.; Moreira, R.; Iley, J.; Gut, J.; Rosenthal, P. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4115–4119. d) Fu, L.N. *Letters in Organic Chemistry*, **2014**, *11*, 13-17

[257] Cyclic sulfonamides (sultams) can be considered to be the functional analogues of the corresponding lactam structures: Hinchliffe, P. S.; Wood, J. M.; Davis, A. M.; Austin, R. P.; Beckett, R. P.; Page, M. I. *Org. Biomol. Chem.* **2003**, *1*, 67–80.

[258] a) A. Scozzafava, T. Owa, A. Mastrolorenzo and C. T. Supuran, *Curr. Med. Chem*., **2003**, *10*, 925-953; b) M. D. McReynolds, J. M. Dougherty and R. R. Hanson, *Chem. Rev*., **2004**, *104*, 2239-2258; c) Z. Liu and Y. Takeuchi, *Heterocycles*, **2009**, *78*, 1387-1412; d) K. C. Majumdar, S. Mondal, *Chem. Rev*., **2011**, *111*, 7749-7773; e) V. A. Rassadin, D. S. Grosheva, A. A. Tomashevskii, V. V. Sokolov, *Chem. Heterocycl. Compd*., **2013**, *49*, 39-65.

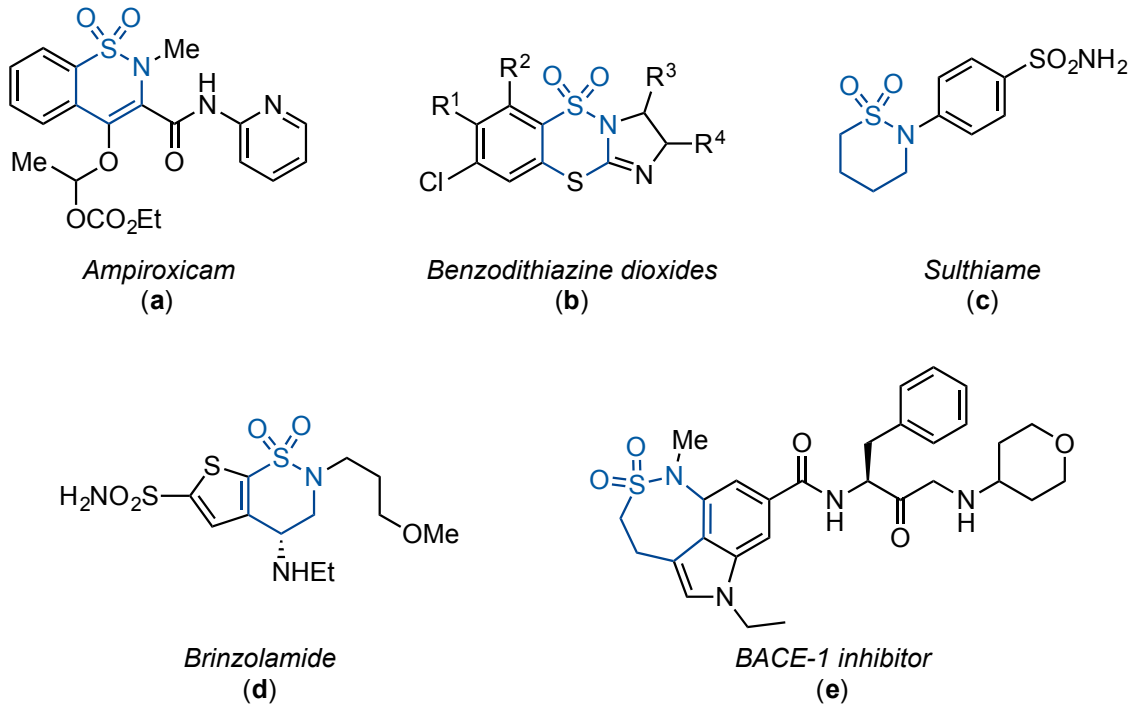
[259] Rabasseda, X.; Hopkins, S. J. *Drugs Today* **1994**, *30*, 557–563.

[260] F. Brzozowski, F. Saczewski, N. Neamati, *Bioorg. Med. Chem. Lett*., **2006**, *16*, 5298-5302.

[261] Tanimukai, H.; Inui, M.; Hariguchi, S.; Kaneko, Z. *Biochem. Pharmacol*. **1965**, *14*, 961–970.

[262] Wroblewski, T.; Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 365-369.

[263] N. Charrier, B. Clarke, L. Cutler, E. Demont, C. Dingwall, R. Duns- don, J. Hawkins, C. Howes, J. Hubbard, I. Hussain, G. Maile, R. Matico, J. Mosley, A. Naylor, A. O'Brian, S. Redshaw, P. Rowland, V. Soleil, K. J. Smith, S. Sweitzer, P. Theobald, D. Vesey, D. S. Walter, G. Wayne, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3674-3678.



Ampiroxicam (**a**) *Benzodithiazine dioxides* (**b**) *Sulthiame* (**c**)

Brinzolamide (**d**) *BACE-1 inhibitor* (**e**)

Figure 3.1. Biologically active sultams.

Furthermore, these scaffolds have been utilized as reagents to perform specific organic transformations and also, they have been used as chiral auxiliaries to carry out asymmetric synthesis. Concretely, the applications of Oppolzer camphorsultam (Figure 3.2.a), first reported in 1984,[264] have grown rapidly over the past few years and nowadays is considered to be one of the most useful and suitable chiral auxiliaries for asymmetric synthesis. Back to initial papers by Oppolzer et al.[265] and continuous reports by others[266] proved the usefulness of the sultam for controlling stereochemistry in the absence of any chelating metals. Since then, much attention has been paid to the thermal chemistry of acryloyl derivatives of Oppolzer's sultam (Figure 3.2.b). [267]

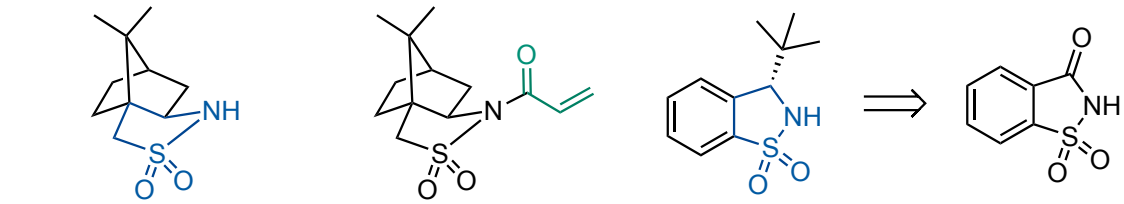
[264] Oppolzer, W.; Chauis, C.; Bernardinelli, G. *Helv. Chim. Acta*, **1984**, *67*, 1397-1401.

[265] a) Oppolzer, W. *Tetrahedron*, **1987**, *43*, 1969-2004 b) Oppolzer, W. *Pure Appl. Chem*. **1990**, *62*, 1241–1250. c) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1998**, *81*, 324–329. d) Oppolzer, W.; Poli, G.; Starkemann, C.; Bemardinelli, G. *Tetrahedron Lett*. **1988**, *29*, 3559–3562.

[266] a) Ahn, K. H.; Ham, C.; Kim, S.-K.; Cho, C.-W. *J. Org. Chem*. **1997**, *62*, 7047-7048. b) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem*., **2006**, *71*, 337-340. c) Shinada, T.; Oe, K.; Ohfune, Y. *Tetrahedron Lett.* **2012**, *53*, 3250-3253. d) Takao, K.-I.; Sakamoto, S.; Touati, M. A.; Kusakawa, Y.; Tadano, K.-I. *Molecules* **2012**, *17*, 13330–13344. e) Heravi, M. M.; Zadsirjan, V. *Tetrahedron: Asymmetry* **2014**, *25*, 1061–1090.

[267] Hyean Kim, B.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293–318.

Oppolzer's research group also described shortly after a family of chiral toluene-2,α-sultam auxiliaries derived from saccharin (Figure 3.2.c).[268]



(1*R*)-(+)-2,10-camphorsultam (**a**) | Oppolzer's sultam acryloyl derivative (**b**) | chiral benzosultam (**c**) | *Saccharin*

Figure 3.2. Sultams as chiral auxiliaries.

Consequently, a simple and convenient method for their synthesis has been required in order to access all that sultams have to offer. Currently, methods [269] that have been used to prepare sultams include Diels–Alder reactions, [270] radical cyclisations, [271] ring-closing metathesis reactions, [272] nucleophilic aromatic substitutions,[273] cyclisations of aminosulfonyl chlorides,[274] and intramolecular Heck reactions.[275] Michael reactions to access this scaffolds are not a generalized methodology but there is a remarkable example from 2008,[276] where the first examples of intramolecular *oxa*-Michael and Baylis-Hillman reactions to vinyl sulfonamides is described for the preparation of five-, six-, seven- and eight-membered ring sultams with excellent yields and good to

[268] a) Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019–5022. b) Ahn, K. H.; Kim, S.-K.; Ham, C. *Tetrahedron Lett.* **1998**, *39*, 6321–6322. c) Ahn, K. H.; Baek, H.-H.; Lee, S. J.; Cho, C.-W. *J. Org. Chem.* **2000**, *65*, 7690–7696.

[269] For recent reviews on the synthesis of sultams, see: a) Szostak, M.; Aube, J. *Chem. Rev.* **2013**, *113*, 5701–5765. b) Rassadin, V. A.; Grosheva, D. S.; Tomashevskiy, A. A.; Sokolov, V. V. *Chem. Heterocycl. Compd.* **2013**, *49*, 39–65. c) Majumdar, K. C.; Mondal, S. *Chem. Rev.* **2011**, *111*, 7749–7773.

[270] a) Greig, I. R.; Tozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369– 371. b) Rogachev, V. O.; Filimonov, V. D.; Fröhlich, R.; Kataeva, O.; Metz, P. *Heterocycles* **2006**, *67*, 589– 595.

[271] a) Paquette, L. A.; Barton, W. R. S.; Gallucci, J. C. *Org. Lett.* **2004**, *6*, 1313–1315; b) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835–3838.

[272] a) McReynolds, M. D.; Dougherty, J.M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258. b) Jiménez-Hopkins, M.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2223–2226.

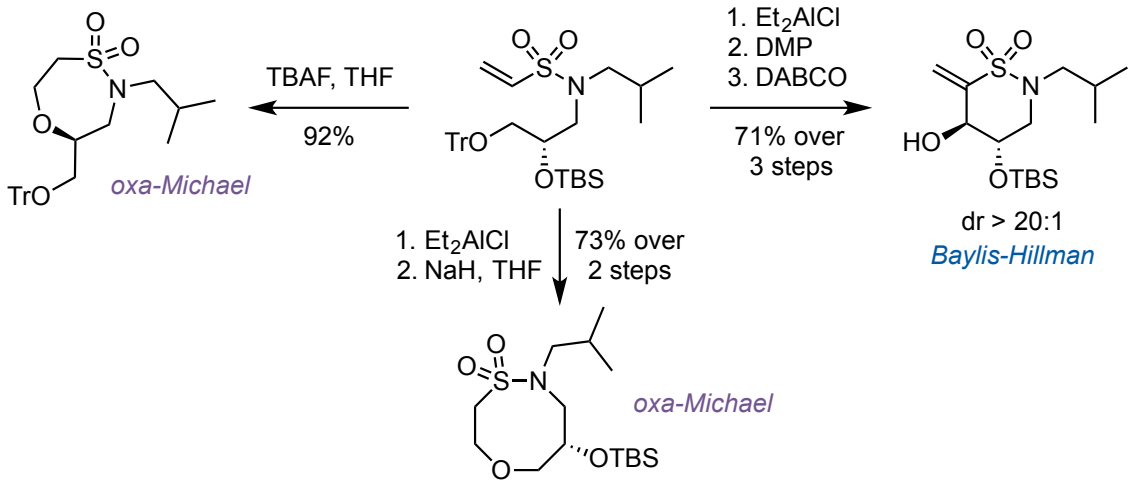
[273] Wojciechowski, K.; Kosinski, S.*Tetrahedron* **2001**, *57*, 5009– 5014

[274] Enders, D.; Moll, A.; Bats, J.W. *Eur. J. Org. Chem.* **2006**, 1271– 1284.

[275] a) Evans, P.; McCabe, T.; Morgan, B. S.; Reau, S. *Org. Lett.* **2005**, *7*, 43–46. b) Merten, S.; Fröhlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Catal.* **2005**, *347*, 754–758. c) Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255–7258.

[276] Zhou, A.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2951–2954.

excellent levels of diastereoselectivity throughout the Baylis-Hillman study (Scheme 3.9).

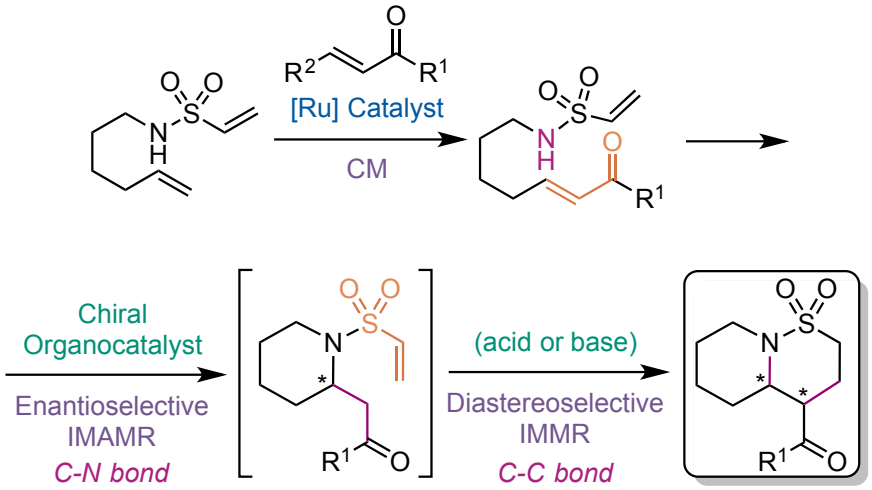


Scheme 3.9. Synthesis of enantioenriched sultams.

3.2. Objectives

Considering the aforementioned significance of sultams as privileged structures, it seemed an attractive and very appealing strategy to combine the previously studied organocatalytic intramolecular *aza*-Michael reaction (IMAMR) with a second intramolecular Michael addition, to eventually prepare a new family of bicyclic sultams. Thus, the key of this sequence rely on the use of vinyl sulfonamides as both, nitrogen nucleophiles and Michael acceptors.

The preparation of the starting materials would involve a selective cross-metathesis (CM) reaction with the terminal olefin. Next, the conditions for the enantioselective IMAMR needed to be set to create the C-N bond. Finally, the sulfonamide moiety properly functionalised to act as the Michael acceptor would allow the following diastereoselective intramolecular Michael reaction (IMMR) generating a new C-C bond and affording bicyclic sultams with two new stereocenters (Scheme 3.10). Both the step-wise and the domino approaches will be evaluated.



Scheme 3.10. Initial goal of the present chapter.

The sought molecules imply a very exclusive family of enantioenriched sultams, given the bridgehead position of the sulfonamide nitrogen, not reported to date in enantiomerically enriched manner.

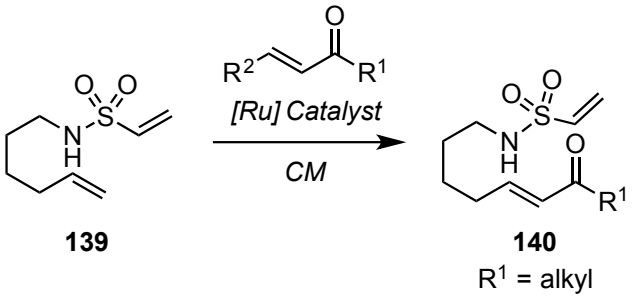
3.3. Results and Discussion

Taking into account the previously introduced objectives, the selected results show the synthetic strategy for the desired highly functionalized starting materials, followed by the optimization of the first cyclisation (IMAMR) and then the different approaches for the final preparation of the targeted bicyclic sultams.

3.3.1. PREPARATION OF THE STARTING MATERIALS

The starting materials of choice were vinyl sulfonamides **140** bearing a conjugated ketone in a remote position, in turn prepared by means of a CM reaction of starting sulfonamides **139** containing the terminal olefin moiety.

Conjugated ketones were selected as Michael acceptors for the first cyclization step. Thus, using the methodology developed in the first chapter, the initial IMAMR will be evaluated. On the other hand, vinyl sulfonamides were the Michael acceptors of the second cyclization step, due to more simple access to those derivatives. Furthermore, the incorporation of substitution at the β-position of the starting vinyl sulfone would form an additional chiral center, increasing the complexity of the overall process. The synthesis of vinyl sulfonamides **140** is depicted below in Scheme 3.11.



139 **140**

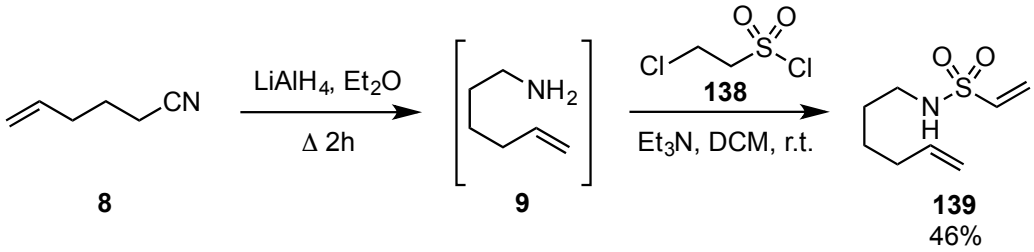
R^1 = alkyl

Scheme 3.11. Synthesis of starting material **140**.

3.3.1.1. Synthesis of the conjugated sulfonamide-olefin 139

The synthesis of **139** started with nitrile **8**. Its preparation was performed by initial reduction of the nitrile functionality to the primary amine by means of lithium aluminium hydride. Then, amine **9** was treated, without further purification, with 2-chloroethane-1-sulfonyl chloride, and the corresponding sulfonamide underwent elimination of HCl under the basic reaction conditions,

generating the vinyl sulfone. Thus, the desired conjugated sulfonamide was finally obtained in a 3-step protocol in good yield (Scheme 3.12).



Scheme 3.12. Preparation of vinyl sulfonamide **139**.

3.3.1.2. Selective cross-metathesis reaction: Synthesis of α,β-unsaturated sulfonamide-ketones 140.

Once prepared starting sulfonamide **139**, it was subjected to a cross-metathesis (CM) reaction with various vinyl ketones with the aim of obtaining the corresponding α,β-unsaturated substrates **140** for the subsequent conjugate additions (Figure 3.11).

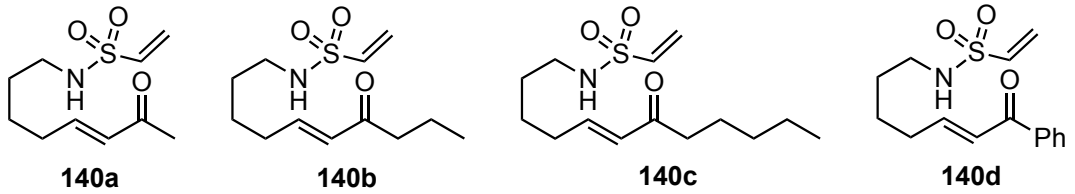


Figure 3.11. Starting materials for the synthesis of bicyclic sultams.

Given the presence of two different terminal double bonds in substrate **139**, regioselectivity problems would arise in the CM reaction. Additionally, a competitive ring closing metathesis reaction would also occur. Therefore, three possible scenarios have to be considered: the desired CM with the isolated olefin (Figure 3.12.a), a CM reaction with the vinyl sulfonamide (Figure 3.12.b) and a ring-closing-metathesis (RCM) cyclisation (Figure 3.12.c).

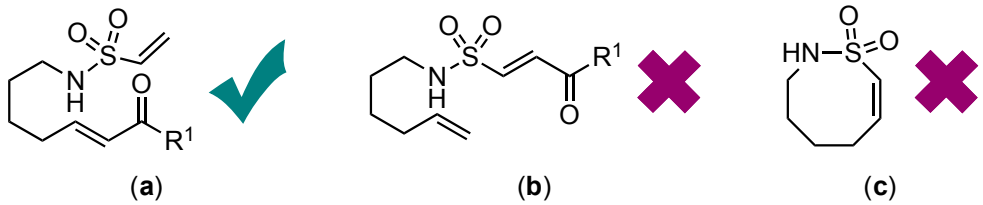


Figure 3.12. Plausible metathesis reactions with substrates **139**.

Based on electronic considerations, Grubbs [277] has developed a classification of olefins in four different types according to their ability to undergo CM reactions.[152] Using this data, is possible to make some predictions regarding the most favoured CM pair, as well as the propensity of the involved olefins to suffer homodimerization. A general trend could be extracted from this study; when the two olefins have a greater difference, which means that they belong to more separated olefin types, more favourable will be a CM reaction between them.

Preparation of compounds **140** involved a CM reaction between olefin **139** and alkyl- or aryl-vinyl ketones **34**. According to the previously mentioned classification, compound **139** contain two types of olefins; the vinyl sulfonamide is a type III olefin whereas the isolated olefin can be considered as a type I olefin. On the other hand, conjugated ketones **34a-c** are olefins of type II whereas **34d**, that bears substitution at the β-position, is a type III olefin. The most reactive olefin in CM reactions is the isolated one of compound **139**; this type I olefin would react in a more favourable manner with conjugated ketones of type II (or type III). Olefins of type I have a high homodimerization ratio, but this could be avoided by adding a big excess of the conjugated ketone (usually 3 equivalents). Vinyl sulfonamides (olefins of type III) are low reactive olefins in CM reactions, which means that in the reaction of **139** and **34** it can be achieved a regioselective process to access the desired conjugated ketones **140** (Figure 3.13).

The RCM reaction could be also a competitive reaction. Compound **139** would undergo RCM rendering an 8-membered ring sultam. Although those intramolecular processes are more favourable entropically than the intermolecular CM reaction, in this case the slow rate of formation of an 8-membered ring and the use of diluted reactions would allow us to direct the process to the CM product.

[277] Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140 and references therein.
[152] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

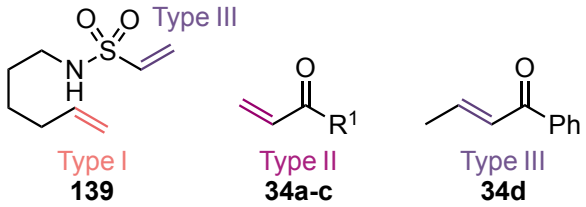
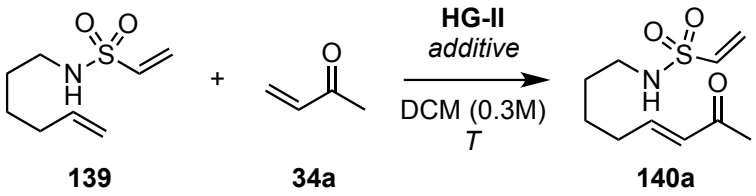


Figure 3.13. Classification of the involved olefins in **139** and **34**.

Taking into account what has been exposed in the first chapter with regard to CM catalysts, it was chosen Hoveyda-Grubbs 2nd generation catalyst in DCM as solvent to optimize the desired transformation employing substrate **139** (Table 3.1). At room temperature the reaction did not progress satisfactorily (28% yield) (Table 3.1, entry 1) and at reflux the RCM product was observed as the major product (Table 3.1, entry 2). The increase of the catalyst loading (added in two times) was traduced in a slight improvement of the desired product until 40% (Table 3.1, entry 3). This result was improved by adding a 20 mol% of a Lewis acid (titanium isopropoxide) which coordinates the ketone oxygen making the enone more reactive for the CM reaction (Table 3.1, entry 4). Finally, the best results (86% yield) were obtained with a total load of 24 mol% of HG-II and seven equivalents of the conjugated ketone distributed into three separate additions (Table 3.1, entry 5).

Table 3.1. Optimization of the regioselective CM reaction

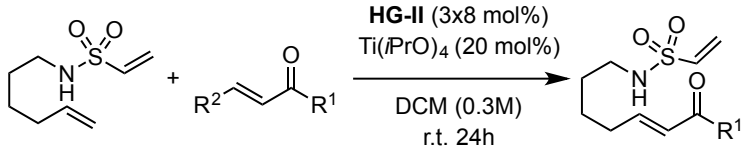


Entry	*HG-II (mol%)*	*additive*	*T (ºC)*	*Yield (%)*[a]
1	8	-	25	28
2	8	-	45	RCM[b]
3	16	-	25	40
4	16	Ti(*i*PrO)$_4$[c]	25	53
5	24	Ti(*i*PrO)$_4$[c]	25	86

[a] Isolated yields after flash chromatography purification.
[b] Ring-closing-metathesis product mainly obtained
[c] 20 mol% loading

Then the optimized reaction conditions were applied to the synthesis of the different α,β-unsaturated sulfonamide-ketones **140** (Table 3.2). Compounds **140a-c** (Table 3.2, entries 1-3) were obtained with good yields. However, synthesis of **140e** wasn't very efficient (Table 3.2, entry 4) due to the aforementioned problematic selectivity and also because of the steric sensitivity of the CM reaction, the methyl group at the R^2 position would make the transformation rate slower, occurring in this way some side reactions such as the RCM and the formation of the *Z*-isomer (10% yield).

Table 3.2. Synthesis of the conjugated sulfonamide-ketones **140**



139 **34** **140**

Entry	*ketone*	R^1	R^2	*Product*	*Yield (%)*[a]
1	**34a**	Me	H	**140a**	86
2	**34b**	Pr	H	**140b**	81
3	**34c**	Pent	H	**140c**	66
4	**34d**	Ph	Me	**140d**	31

[a] Isolated yields after flash chromatography purification

3.3.2. ENANTIOSELECTIVE INTRAMOLECULAR *AZA*-MICHAEL REACTION OF α,β-UNSATURATED SULFONAMIDE-KETONES 140 [278]

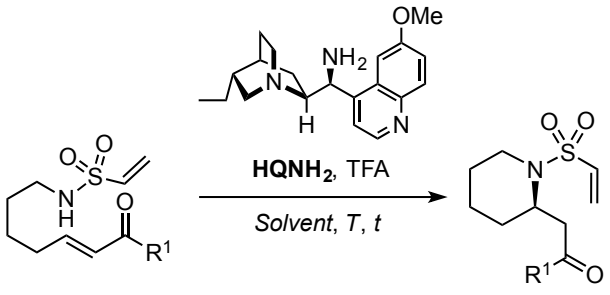
With starting α,β-unsaturated ketones **140** in hand, next step was the optimization of the IMAMR conditions, taking as starting point the study disclosed in the first chapter[172] and sulfonamide **140a** as a model substrate. Thus, hydroquinidine primary amine (**$HQNH_2$**) was chosen as organocatalyst and trifluoroacetic acid (TFA) as additive, evaluating different solvents and temperatures in order to find the best combination in terms of yield and enantioselectivity (Table 3.3).

Equimolecular amounts of both catalyst and additive (20 mol%) in $CHCl_3$ as solvent was firstly tested, yielding the Michael adduct **141a** with quite good

[172] Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sánchez-Roselló, M. *Chem. Eur. J.* **2011**, *17*, 14267–14272.

efficiency and enantiocontrol (Table 3.3, entry 1) after 24 hours of reaction at room temperature. Variation of the solvent to tetrahydrofuran gave slightly worse results, giving rise to **141a** with only 47% yield and 82:18 *er* (Table 3.3, entry 2). Diminishing the reaction temperature to 0 ºC, enantioselectivities were improved, although yields were poor and incomplete conversion was achieved even after 5 days (Table 3.3, entries 3 and 4). Likewise, when the reaction was performed under microwave heating neither the yield nor the enantioenrichment of the product were improved (Table 3.3, entry 5). The employment of a highly polar solvent like acetonitrile did not allow the reaction to happen (Table 3.3, entry 6). A modification of the catalyst: additive ratio from 1:1 to 2:1 implied a drastic drop both in the yield and the enantiomeric relation in $CHCl_3$ or THF as solvents (Table 3.3, entries 7 and 8). By decreasing the loadings, it was maintained enantioselectivity with slightly lower yield (Table 3.3, entries 9-10). The use of cyclopentyl methyl ether (CPME) as solvent, inspired by the good results obtained in the second chapter,[67] did not lead to a higher enantiocontrol but the results were also good (Table 3.3, entry 11). Finally, a serendipitous miscalculation made us realize that a 1:2 combination of catalyst: additive of 13 and 26 mol% loadings, respectively, conduct to the best enantioselection (Table 3.3, entry 12). Other catalysts such as a squaramide and a BINOL phosphoric acid were also tested without any success.[279]

Table 3.3. Optimization of the IMAMR with conjugated sulfonamide-ketone **140a**.



140a **141a**

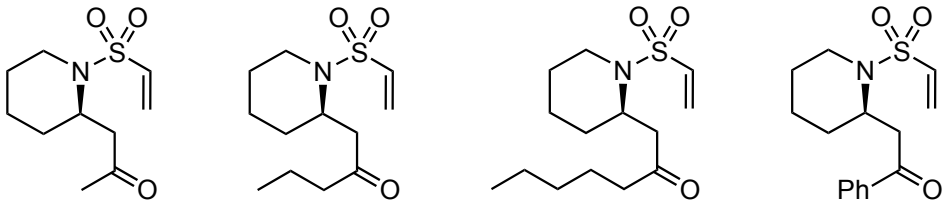
Entry	*$HQNH_2$ (mol%)*	*TFA (mol%)*	*T (ºC)*	*t (h)*	*Solvent*	*Yield (%)*	*er*
1	20	20	25	24	$CHCl_3$	57	92:8
2	20	20	25	24	THF	47	82:18
3	20	20	0	120	$CHCl_3$	22[a]	95:5

[67] Sánchez-Roselló, M.; Mulet, C.; Guerola, M.; del Pozo, C.; Fustero, S. *Chem. Eur. J.* **2014**, *20*, 15697–15701.

4	20	20	0	120	THF	50[a]	94:6
5	20	20	100[b]	10	$CHCl_3$	55	87:13
6	20	20	25	120	CH_3CN	-	-
7	20	10	25	72	$CHCl_3$	25	60:40
8	20	10	25	72	THF	13	55:45
9	15	15	25	22	$CHCl_3$	58	95.5:4.5
10	10	10	25	24	$CHCl_3$	40	96:4
11	11	11	25	13	CPME	85	96:4
12	13	26	25	17	$CHCl_3$	76	97:3

[a] Incomplete conversion after 5 days of reaction
[b] Microwave irradiation

The optimal IMAMR conditions (Table 3.3, entry 13) were extended to the rest of the prepared starting materials **140** to obtain a small library of enantioenriched *N*-heterocycles (Figure 3.3) with very good yields and excellent enantioselectivities in the synthesis of piperidines **141a-d**. The assignment of the absolute configuration of the newly created stereocenter has been determined to be *R* in consistence with the previously described methodology for the organocatalytic IMAMR of conjugated ketones with **$HQNH_2$**, which extension to the present transformation seems reasonable (Scheme 1.42). Furthermore, it was later confirmed by an X-ray analysis of a crystalline sultam (Figure 3.6).



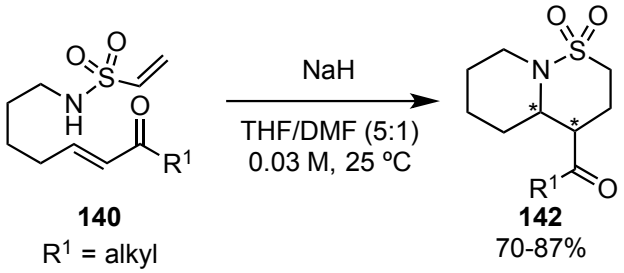
141a 76% 97:3 *er* | **141b** 71% 98.5:1.5 *er* | **141c** 90% 98:2 *er* | **141d** 85% 97.5:2.5 *er*

Figure 3.3. Scope of the IMAMR of α,β-unsaturated sulfonamide-ketones **140**.

It is important to point out here that to date, it was not possible to perform both cyclisations in a domino manner. All the attempts mentioned in Table 3 indicated that the process stop after the IMAMR. That means that the synthesis of the desired bicyclic lactams has to be performed in a step-wise fashion.

3.3.3. DIASTEREOSELECTIVE INTRAMOLECULAR MICHAEL REACTION OF *N*-HETEROCYCLIC α,β-UNSATURATED SULFONAMIDES 141

With the chiral *N*-heterocycles **141** in hand, the last step of the present study was to develop a diastereoselective IMMR to synthesize the desired enantioenriched sultams **142**. Initially, it was performed the synthesis of final products in a racemic manner. To this end, it was envisioned the possibility of performing both cyclisations in a domino fashion, under basic catalysis. To our delight, when compounds **140** were treated with NaH, the domino protocol took place in a very efficient way in only 4-6 h, giving rise to the bicyclic sultams **142** in good yields and complete diastereoselectivity (Scheme 3.13).



Scheme 3.13. Synthesis of the racemic bicyclic sultams **142**.

With this result, the next step was the preparation of sultams **142** in a enantiomerically enriched manner. Since it was not possible to perform the organocatalytic process in a tandem fashion, piperidines **141** were subjected to the intramolecular Michael addition in basic media. Again, the application of the conditions developed for the racemic synthesis was very effective, giving rise to the final sultams **142** in good yields with sodium hydride in THF/DMF (Figure 3.4).

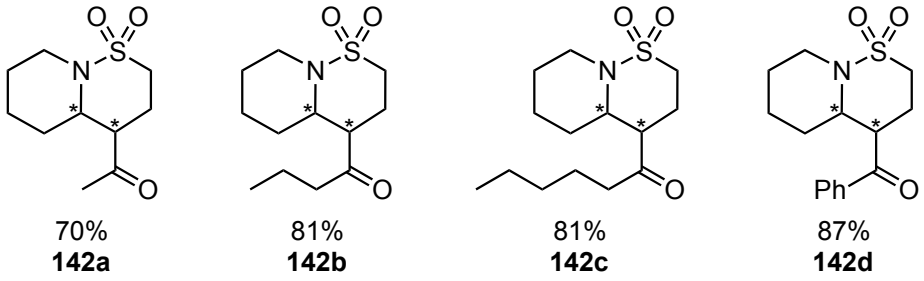
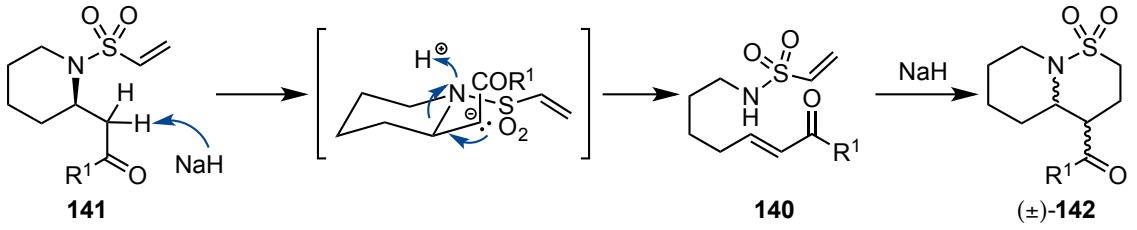


Figure 3.4. Desired bicyclic sultams **142**.

Nevertheless, the chirality of the sultams could not be determined by the HPLC used until the moment, since it has a UV-detector and any of the final

products (except sultam **145d** that contains an aromatic ring) were able to significantly absorb UV light. It was attempted the alternative procedure for the determination of the enantioselectivity used in the second chapter, consisting on the formation of diastereoisomers with a europium salt in order to unfold any of the ^{1}H-NMR signals. However, their spectra were quite complex and any of the signals reacted in the aimed way. Finally, an alternative HPLC apparatus, with a refractive index detector (RID) instead of the UV one led us to determine the final enantiomeric excesses. To our disenchantment, all of the synthesized sultams (step-wise and one-pot prepared) resulted to be racemic. Apparently, a retro-*aza*-Michael reaction was taking place with the use of NaH (Scheme 3.14), epimerizing in this way the chiral stereocenter initially created with aid of the organocatalyst.



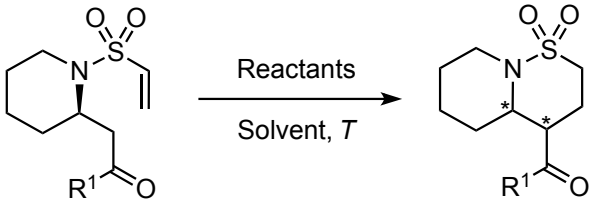
Scheme 3.14. Base-mediated retro-*aza*-Michael reaction and racemic synthesis of **142**.

With a proper methodology to examine sultams chirality in hand, it was developed a thoroughly study to discover the IMMR conditions that could avoid the undesired retro-*aza*-Michael reaction (Table 3.4). A variety of bases, acids and organocatalysts (Table 3.4, entries 1-18) were tested unsuccessfully until a slight chirality maintenance was finally achieved (22% *ee*) with the use of a Verkade's base (Table 3.4, entry 19). However, by modifying the reaction conditions it could not be accomplished a good combination of yield and enantiocontrol with any Verkade's base (Table 3.4, entries 20-23). Was the use of phosphazene base P_2-Et, included in *superbases* family,[280] which finally came up with an acceptable rate of chirality and yield of the bicyclic sultam (Table 3.4, entry 24). The change of the solvent from THF to toluene did not allowed the reaction to be completed (Table 3.4, entry 25). And by reducing the loading of the base to 10 mol% there was any further improvement in the chirality maintenance and a longer reaction time was needed for a slightly lower

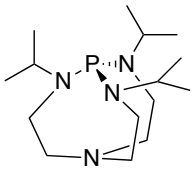
[280] Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627–1634.

yield (Table 3.4, entry 26). The employment of a bulkier phosphazene superbase, seeking a better stereocontrol, resulted to be too hindered to allow the reaction to proceed (Table 3.4, entry 27).

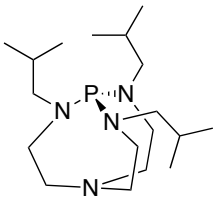
Table 3.4. Optimization of the IMMR of *N*-heterocyclic conjugated sulfonamides **144**.



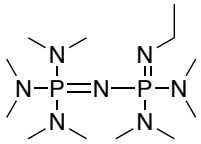
141 **142**



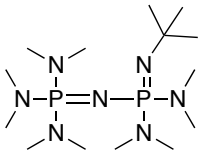
*i*Pr-Verkade's base



*i*Bu-Verkade's base



Phosphazene base P_2-Et



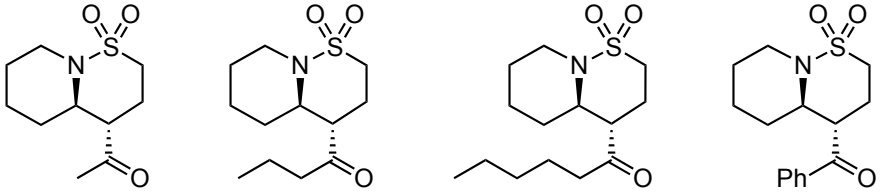
Phosphazene base P_2-*t*Bu

Entry	*Reactants*	*Solvent*	*T (ºC)*	*Results*
1	LiHMDS	THF	-78/0/25/67	SM
2	KHMDS	THF	25	Decomp.
3	*t*BuOK	THF	25[a]	Racemic prod.
4	BF_3OEt_2	THF	25	SM
5	BF_3OEt_2	DCM	60-80[b]	SM
6	TBAF	THF	25	SM
7	DBU	THF	25	SM
8	Thiourea+ L-arginine	MeOH	25	SM
9	Thiourea+*trans*-2,5-dimethylpiperazine	DCM	45	SM
10	$CF_3SO_3TMS+Et_3N$ $+BF_3OEt_2$	Et_2O	0 to 25	Side product
11	*trans*-2,5-dimethyl piperazine	MEOH	25	Side product
12	*trans*-2,5-dimethyl piperazine	DCM	45	Side product
13	Pyrrolidine	MeOH	25/65	Side product
14	L-proline	MeOH	25	Side product
15	L-proline	DMF	25	Side product
16	BEMP[c]	THF	67	Racemic prod.
17	BEMP[c]	THF	70-120[b]	Racemic prod.
18	BEMP[c]	THF	160[b]	Side product.

19	*i*Pr-Verkade's base[d]	THF	25	93%, 22% *ee*
20	*i*Pr-Verkade's base[d]	THF	-78 to -40	95%, 50% *ee*
21	*i*Pr-Verkade's base[d]	THF	-40[e]	78%, 22% *ee*
22	*i*Pr-Verkade's base[d]	THF	-78[e,f]	24%, 95% *ee*[h]
23	*i*Bu-Verkade's base[g]	THF	-78[e]	SM
24	Phosphazene base P_2-Et[i]	THF	-78[e,j]	77%, 84% *ee*[h]
25	Phosphazene base P_2-Et[i]	Toluene	-78[e]	33% (50%conv.)
26	Phosphazene base P_2-Et[i]	THF	-78[e,k]	70%, 88% *ee*[l]
27	Phosphazene base P_2-*t*Bu[m]	THF	-78[e,j]	SM

[a] 20 minutes
[b] Microwave irradiation
[c] 2-*tert*-Butylimino-2-diethyl amino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
[d] 2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane
[e] MS 4Å, vial heated with microwave irradiation at 120ºC for 10 minutes
[f] 26 hours
[g] 2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane
[h] SM: **141a** (95% *ee*)
[i] 1-Ethyl-2,2,4,4,4-pentakis(dimethyl amino)-2λ^5,4λ^5-catenadi(phosphazene)
[j] 1 equiv. base, 2 hours
[k] 0,1 equiv. base, 24 hours
[l] SM: **141b** (97% *ee*)
[m] 1-*tert*-Butyl-2,2,4,4,4-pentakis(dimethyl amino)-2λ^5,4λ^5-catenadi(phosphazene)

Then, according to entry 24, the use of 1 equivalent of the phosphazene base P_2-Et in THF during 2 hours of reaction at -78ºC chosen as the optimal condition for the IMMR, were applied for the synthesis of the five bicyclic sultams **142** (Figure 3.5). They were all obtained with good yields and moderate to good enantiomeric excesses, with a slight erosion of the chirality from that of the starting piperidines **141** (Figure 3.3). Conversely, the diastereoselectivity of the second cycloaddition was complete (>99% *d.r.*) as it could be checked in the more sensitive UVD-HPLC of the aromatic sultam **142d** as well as in the NMR spectra, where just one diastereoisomer was observed.



142a 77% 93:7 *er* | **142b** 70% 94:6 *er* | **142c** 73% 95:5 *er* | **142d** 80% 90:10 *er*

Figure 3.5. Scope of chiral bicyclic sultams **142**.

The absolute configuration of the final products was determined by X-Ray analysis of crystals of sultam **142a**, possible given the solid consistence of these sultams. Thus, it was confirmed the *anti*-configuration of the two stereocenters as ($C_{14}S$, $C_{14a}R$) according to the structure shown in Figure 3.6, as well as the expected *R* configuration of the first-created stereocenter. The same stereochemical evolution was assumed of all sultams **142**.

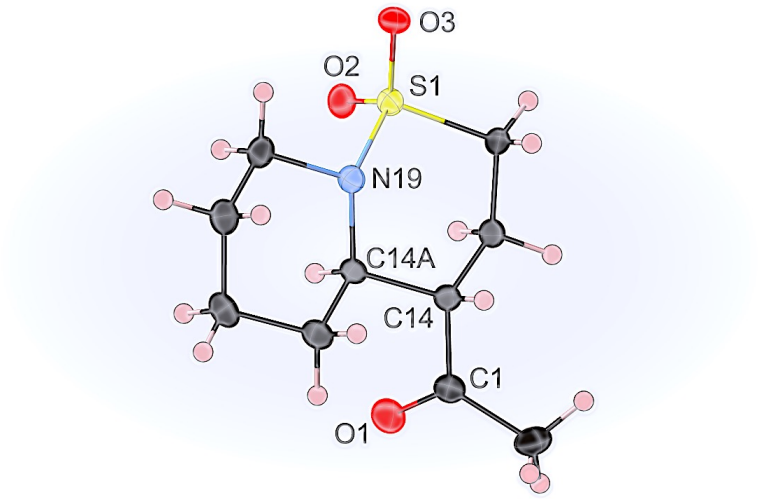
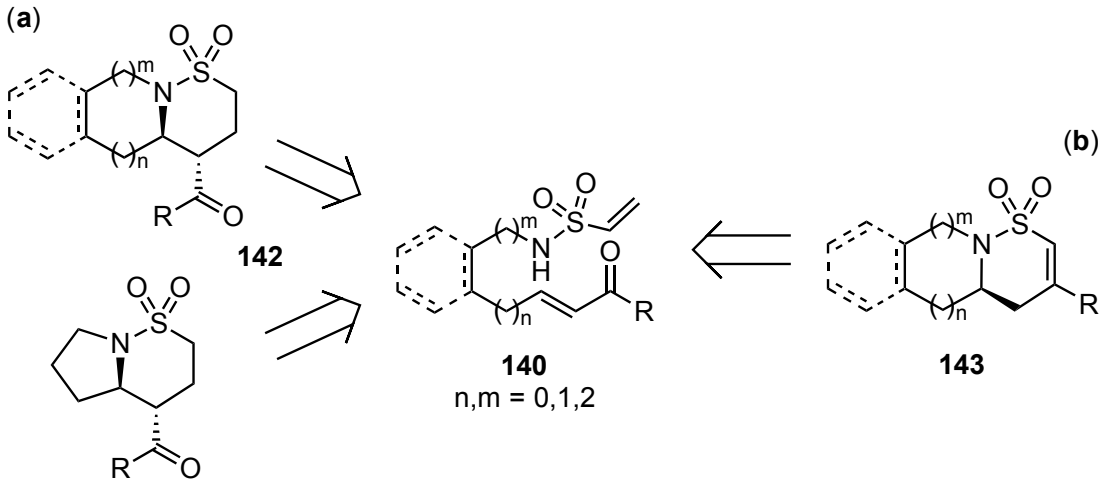


Figure 3.6. X-Ray of sultam **142a**.

3.3.4. COMPLEMENTARY ONGOING WORK

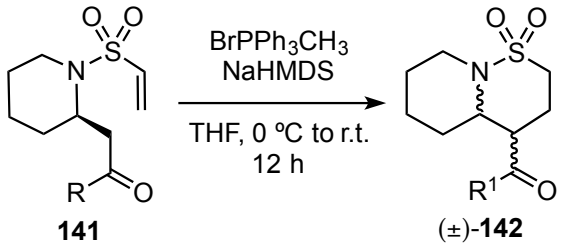
Two complementary studies related to the project showed in the present chapter have been initiated. The first one is the extension of the scope of the process to 5-membered rings and to benzofused derivatives (Scheme 3.15.a). The second one, as a consequence of the problems encountered in the second cyclization step, involve the modification of this synthetic sequence to access a different family of bicyclic sultams (Scheme 3.15.b).



Scheme 3.15. Complementary work within the sultams project.

The extension of the scope to benzofused derivatives is currently ongoing, and some problems related with the preparation of the starting materials have to be solved. Regarding the synthesis of sultams containing a five membered ring, the initial studies indicated that the IMAMR takes place with low levels of stereocontrol. Additionally, the use of the phosphazene base P_2-Et does not avoid the racemization of the final products.

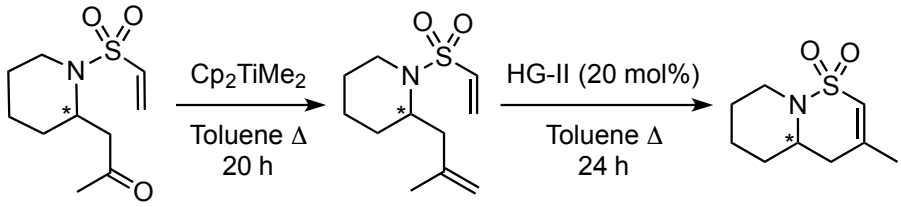
The synthesis of the second family of sultams **143**, was designed involving a Wittig reaction over the ketone moiety of substrates **141**, followed by a RCM reaction with the vinyl sulfonamide. An initial attempt was performed in substrate **141a**, which was subjected to the corresponding Wittig reagent. Unfortunately, the phosphorus ylide acted as a base and the racemization of the starting material was produced (Scheme 3.16).



Scheme 3.16. Attempt of Wittig reaction to access sultams **143**.

To overcome this problem, a methylenation reaction that avoid basic media was performed. In this context, it was described in the literature that Petasis reagent could act as an efficient methylenating agent without the need

of a base.[281] Therefore, when compound **141a** was treated with Cp_2TiMe_2 (Petasis reagent) in toluene at reflux for 20 hours, the methylenation of the ketone was produced efficiently. With the dienic compound **144** in hand, the RCM reaction was carried out with second generation Hoveyda-Grubbs catalyst (HG-II), affording the desired sultam **143** in good yield. An HPLC analysis showed that the integrity of the chiral center was maintained in this sequence, and bicyclic sultam **143a** was obtained with a small erosion of the final ee (Scheme 3.17). The extension of this methodology to the rest of starting ketones **141** is currently underway in our laboratory.



141a **144a** 75% **143a** 71% 92:8 *er*

Scheme 3.17. Alternative route from piperidines **141** for the synthesis of sultams **143**.

[281] a) Petasis N. A., Bzowej E. I., *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394. b) Tetrahedron Letters **1995**, *36*, 2393-2396. c) Adriaenssens L. V., Hartley R. C., *J. Org. Chem.* **2007**, *72*, 10287–10290.

3.4. Conclusions

A step-wise procedure for the synthesis of enantiomerically enriched bicyclic sultams has been performed. It is started with an enantioselective intramolecular *aza*-Michael reaction of a sulfonamide nucleophile to an α,β-unsaturated ketone by means of a catalytic system composed by a molecule of 9-amino-9-deoxy-*epi*-hydroquinidine organocatalyst (**HQNH$_2$**) and two molecules of trifluoroacetic acid. Followed by a *superbase*-mediated diastereoselective intramolecular Michael reaction of the α-carbonylic carbon to the conjugated sulfonamide.

This methodology is a nice combination of the two studies performed in the previous chapters and allows the access to an especial family of sultams with the nitrogen in the bridgehead position of the bicycle, structures not reported to date.

3.5. Experimental Section

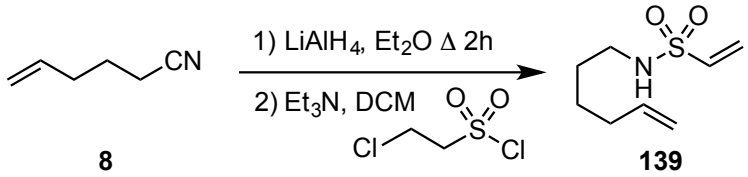
X-RAY DETERMINATION

X-ray diffraction analysis of **compound 142a** was performed with an automatic four cycles diffractometer with Kappa geometry: KappaCCD (nonius). This apparatus held an Oxford low temperature system and an informatics platform for the control, processing and resolution of the crystalline structures.

DETERMINATION OF THE ENANTIOMERIC RATIO

All the aliphatic sultams were analysed with an HPLC Agilent 1100 series equipped with a refractive index detector (RID).

3.5.1. PREPARATION OF FUNCTIONALISED SULFONAMIDES 142

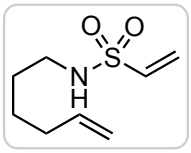


8 **139**

To a suspension of $LiAlH_4$ (6 mmol) in diethyl ether (10 mL) was added dropwise nitrile **8** (2,0 mmol) at room temperature. After heating for 2h at reflux, the suspension was allowed to reach room temperature and $Na_2SO_4 \cdot 10H_2O$ was added with vigorous stirring until aluminium salts turned white. The suspension was filtered through a short pad of Celite® washing with small portions of diethyl ether. The filtrate was concentrated under vacuum obtaining a yellow oil that used without further purification.

The crude amine was dissolved in CH_2Cl_2 (4 mL) and triethyl amine (2.0 equiv.) was added at 0 ºC followed by 2-chloroethane-1-sulfonyl chloride (1.0 equiv.). The reaction mixture was allowed to reach room temperature overnight and then it was hydrolised with HCl (3 molar), extracted with CH_2Cl_2 and dried over Na_2SO_4 anhydrous. Finally, solvents were removed and the crude mixture purified by flash chromatography with hexanes: ethyl acetate as eluents.

_N_-(5-hexenyl)ethenesulfonamide (139)



Physical state:	Pale yellow oil
Empiric Formula:	$C_8H_{15}NO_2S$
Molecular weight (g/mol):	189.27
Yield (%):	46

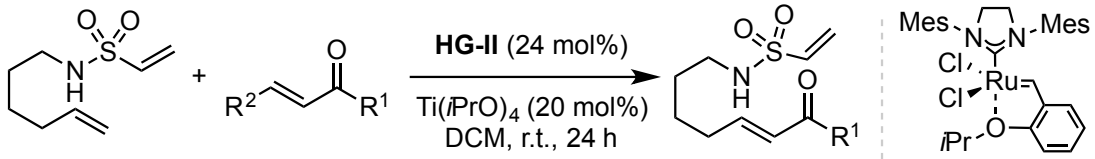
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.50 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.19 (dd, *J* = 16.6, 0.7 Hz, 1H), 5.91 (dd, *J* = 9.9, 0.4 Hz, 1H), 5.84 – 5.65 (m, 1H), 4.94 (tdd, *J* = 10.2, 1.9, 1.1 Hz, 3H), 2.97 (dd, *J* = 13.4, 6.6 Hz, 2H), 2.02 (t, *J* = 7.1 Hz, 2H), 1.60 – 1.47 (m, 2H), 1.47 – 1.34 (m, 2H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 138.6, 136.3, 126.9, 115.3, 43.3, 33.5, 29.6, 26.1

HRMS (EI^+): Calcd. for $C_8H_{15}NO_2S$ [*M*+]: 190.0896, found: 190,0890

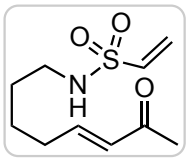
Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 5:1 as eluent.

3.5.2. SYNTHESIS OF *N*-CONJUGATED SULFONAMIDE α,β-UNSATURATED KETOAMINES 140



To a solution of *N*-protected amine **139** (1.0 equiv.) in CH_2Cl_2 (0.3 M) under nitrogen atmosphere, the corresponding conjugated ketone **34** (3.0 equiv.), titanium isopropoxide (20 mol%) and an initial 8 mol% charge of Hoveyda-Grubbs 2nd generation catalyst were added. Two more portions of catalyst (24 mol% total) were added together with 2.0 more equivalents of ketone, after 2-3 hours stirring the crude at room temperature. The resulting solution was overall stirred for 12 h at room temperature and then solvents were removed and the crude mixture purified by flash chromatography with hexanes: ethyl acetate as eluents.

(*E*)-*N*-(7-oxo-5-octenyl)ethenesulfonamide (140a)



Physical state: Brown oil

Empiric Formula: $C_{10}H_{17}NO_3S$

Molecular weight (g/mol): 231.31

Yield (%): 86

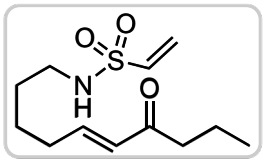
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.76 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.50 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.23 (d, *J* = 16.6 Hz, 1H), 6.07 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.94 (dd, *J* = 9.9, 3.9 Hz, 1H), 4.58 (s, 1H), 3.10 – 2.92 (m, 2H), 2.34 – 2.15 (m, 5H), 1.65 – 1.45 (m, 4H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 198.9, 147.8, 135.9, 131.5, 126.4, 42.6, 31.7, 29.2, 26.8, 24.9

HRMS (EI^+): Calcd. for $C_{10}H_{17}NO_3S$ [*M*+]: 232,1002, found: 232,1005

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.

(*E*)-*N*-(7-oxo-5-decenyl)ethenesulfonamide (140b)



Physical state: Brown oil

Empiric Formula: $C_{12}H_{21}NO_3S$

Molecular weight (g/mol): 259.36

Yield (%): 81

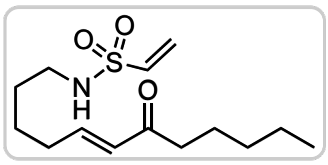
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.75 (dt, *J* = 15.9, 6.9, 1H), 6.47 (dd, *J* = 16.6, 9.9, 1H), 6.17 (d, *J* = 16.6, 1H), 6.05 (dt, *J* = 15.9, 1.5, 1H), 5.90 (d, *J* = 9.9, 1H), 4.98 (t, *J*=5.9, 1H), 2.97 (q, *J*=6.5, 2H), 2.46 (t, *J*=7.3, 2H), 2.19 (td, *J*=6.9, 5.8, 2H), 1.67 – 1.41 (m, 6H), 0.88 (t, *J*=7.4, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 201.0, 146.4, 135.9, 130.7, 126.6, 42.7, 42.1, 31.8, 29.3, 25.0, 17.7, 13.8

HRMS (EI^+): Calcd. for $C_{12}H_{21}NO_3S$ [*M*+]: 260,1315, found: 260,1308

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.

(*E*)-*N*-(7-oxo-5-dodecenyl)ethenesulfonamide (140c)



Physical state: Brown oil

Empiric Formula: $C_{14}H_{25}NO_3S$

Molecular weight (g/mol): 287.42

Yield (%): 66

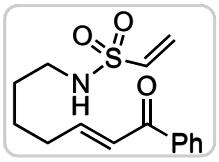
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.42 (dd, *J* = 16.5, 9.7, 1H), 6.20 (d, *J* = 16.5, 1H), 5.88 (d, *J* = 9.7, 1H), 4.50 – 4.31 (m, 1H), 3.63 (d, *J* = 12.8, 1H), 3.04 – 2.91 (m, 1H), 2.81 – 2.74 (m, 2H), 1.74 – 1.45 (m, 8H), 1.38 – 1.16 (m, 4H), 0.89 (t, *J* = 7.0, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 208.6, 136.4, 126.1, 49.0, 43.3, 41.2, 31.5, 28.7, 25.5, 25.4, 23.5, 22.6, 18.8, 14.0

HRMS (EI^+): Calcd. for $C_{14}H_{25}NO_3S$ [*M*+]: 288,4255, found: 288,1625

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.

(*E*)-*N*-(7-oxo-7-phenyl-5-heptenyl)ethenesulfonamide (140d)



Physical state: Brown oil

Empiric Formula: $C_{15}H_{19}NO_3S$

Molecular weight (g/mol): 293.38

Yield (%): 35

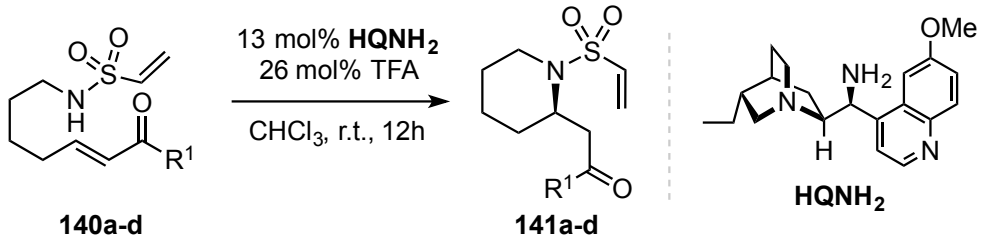
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.01 – 7.86 (m, 2H), 7.59 – 7.50 (m, 1H), 7.49 – 7.41 (m, 2H), 7.00 (dd, *J* = 14.3, 7.6, 1H), 6.88 (d, *J* = 15.4, 1H), 6.50 (dd, *J* = 16.5, 9.9, 1H), 6.22 (d, *J* = 16.5, 1H), 5.92 (d, *J* = 9.8, 1H), 4.73 (s, 1H), 3.02 (t, *J* = 6.2, 3H), 2.43 – 2.22 (m, 2H), 1.59 (dd, *J* = 8.3, 5.1, 4H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 190.9, 148.9, 137.9, 136.0, 132.9, 128.7, 128.4 126.7, 126.4, 42.8, 32.2, 29.5, 25.2

HRMS (EI^+): Calcd. for $C_{15}H_{19}NO_3S$ [*M*+]: 294,3885, found: 294,1157

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.

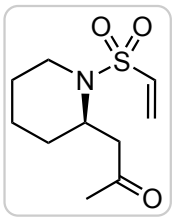
3.5.3. *AZA*-MICHAEL ADDUCT SYNTHESIS: PREPARATION OF 2-SUBSTITUTED NITROGEN HETEROCYCLES 141



140a-d **141a-d**

In a 25 mL round bottomed flask, α,β-unsaturated ketones **140a-d** (1.0 equiv.) were dissolved in chloroform (0.1 M). A mixture of catalyst **$HQNH_2$** (13 mol%) and trifluoroacetic acid (TFA) (26 mol%, added from a freshly prepared stock solution in chloroform) was added and the resulting solution was stirred at room temperature. After 24-96 hours, the crude reaction mixture was subjected to flash chromatography on silica gel using mixtures of hexanes: ethyl acetate as eluents to afford the corresponding *N*-heterocycles **141a-d**. The enantiomeric ratios were determined by means of HPLC analysis with a Chiralpack AD column (25 cm x 0.46 cm).

1-(1-(vinylsulfonyl)piperidin-2-yl)-2-propanone (141a)



Physical state:	Colorless oil
Empiric Formula:	$C_{10}H_{17}NO_3S$
Molecular weight (g/mol):	231.31
Yield (%):	76
Enantiomeric relation:	97:3
Optical rotation $[\alpha]_D^{25}$:	+20 (c 1.0, $CHCl_3$)

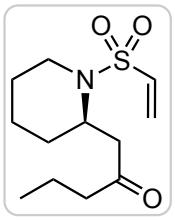
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.50 – 6.35 (m, 1H), 6.20 (dd, *J* = 16.5, 0.5, 1H), 5.89 (dd, *J* = 9.7, 0.5, 1H), 4.42 (dd, *J* = 12.8, 5.5, 1H), 3.62 (d, *J* = 12.8, 1H), 2.98 (dd, *J* = 14.5, 11.6, 1H), 2.81 (d, *J* = 7.1, 2H), 2.23 – 2.11 (m, 3H), 1.79 – 1.43 (m, 7H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 206.1, 136.3, 126.2, 49.0, 44.7, 41.3, 30.4, 28.7, 25.3, 18.8

HRMS (EI^+): Calcd. for $C_{10}H_{17}NO_3S$ [*M*+]: 232.1002, found: 232,0996

Remarks:
- Reaction stirred during 17 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiralpack AD column (hexane: isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=21.0 min, t_{minor}=18.9 min

1-(1-(vinylsulfonyl)piperidin-2-yl)-2-pentanone (141b)



Physical state: Yellow oil

Empiric Formula: $C_{12}H_{21}NO_3S$

Molecular weight (g/mol): 259.36

Yield (%): 71

Enantiomeric relation: 98.5:1.5

Optical rotation $[\alpha]_D^{25}$: -10 (c 1.0, $CHCl_3$)

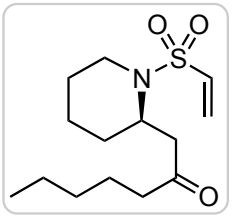
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.43 (dd, *J* = 16.5, 9.7, 1H), 6.20 (d, *J* = 16.5, 1H), 5.88 (d, *J* = 9.7, 1H), 4.42 (dd, *J* = 12.2, 5.8, 1H), 3.63 (d, *J* = 13.0, 1H), 3.03 – 2.91 (m, 1H), 2.85 – 2.70 (m, 2H), 2.42 (t, *J* = 7.3, 2H), 1.76 – 1.43 (m, 8H), 0.91 (t, *J* = 7.4, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 208.5, 136.4, 126.1, 49.0, 45.7, 43.7, 41.2, 28.7, 25.4, 18.8, 17.3, 13.8

HRMS (EI^+): Calcd. for $C_{12}H_{21}NO_3S$ [*M*+]: 260,1315, found: 260,1310

Remarks:
- Reaction stirred during 21 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiralpack AD column (hexane: isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=13.0 min, t_{minor}=9.9 min

1-(1-(vinylsulfonyl)piperidin-2-yl)-2-heptanone (141c)



Physical state: Yellow oil

Empiric Formula: $C_{14}H_{25}NO_3S$

Molecular weight (g/mol): 287.42

Yield (%): 90

Enantiomeric relation: 98.5:2.5

Optical rotation $[\alpha]_D^{25}$: +1,5 (c 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 6.42 (dd, *J* = 16.5, 9.7, 1H), 6.20 (d, *J* = 16.5, 1H), 5.88 (d, *J* = 9.7, 1H), 4.51 – 4.33 (m, 1H), 3.63 (d, *J* = 12.8, 1H), 3.05 – 2.89 (m, 1H), 2.82 – 2.74 (m, 2H), 2.47 – 2.38 (m, 2H), 1.78 – 1.45 (m, 8H), 1.39 – 1.16 (m, 4H), 0.89 (t, *J* = 7.0, 3H)

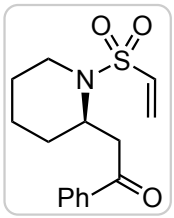
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 208.6, 136.4, 126.1, 49.0, 43.6, 43.3, 41.2, 31.5, 28.7, 25.5, 25.4, 23.5, 22.6, 18.8, 14.0

HRMS (EI^+): Calcd. for $C_{14}H_{25}NO_3S$ [*M*+]: 288,4255, found: 288,1625

Remarks:

- Reaction stirred during 18 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiralpack AD column (hexane: isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=10.9 min, t_{minor}=9.1 min

1-phenyl-2-(1-(vinylsulfonyl)piperidin-2-yl)-1-ethanone (141d)



Physical state: Colorless oil

Empiric Formula: $C_{15}H_{19}NO_3S$

Molecular weight (g/mol): 287.42

Yield (%): 85

Enantiomeric relation: 97.5:2.5

Optical rotation $[\alpha]_D^{25}$: -1,2 (c 1.0, $CHCl_3$)

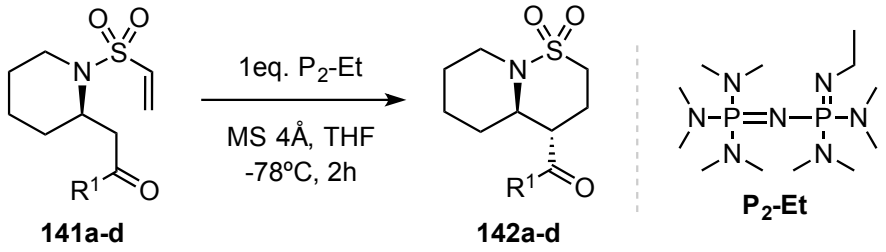
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.06 – 7.90 (m, 2H), 7.63 – 7.54 (m, 1H), 7.54 – 7.43 (m, 2H), 6.43 (dd, *J* = 16.5, 9.7, 1H), 6.20 (d, *J* = 16.5, 1H), 5.85 (d, *J* = 9.7, 1H), 4.59 (dd, *J* = 10.6, 7.2, 1H), 3.78 – 3.64 (m, 1H), 3.48 – 3.27 (m, 2H), 3.16 – 3.01 (m, 1H), 1.87 – 1.41 (m, 6H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 197.7, 136.7, 136.3, 133.6, 128.9, 128.4, 126.1, 49.6, 41.3, 39.7, 28.3, 25.5, 18.8

HRMS (EI$^+$): Calcd. for $C_{15}H_{19}NO_3S$ [*M*+]: 294,3885, found: 294,1156

Remarks:
- Reaction stirred during 144 hours.
- Purification by flash chromatography with hexanes: ethyl acetate 2:1 as eluent.
- The *er* value was determined by HPLC analysis using a Chiralpack AD column (hexane: isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}=29.7 min, t_{minor}=16.2 min

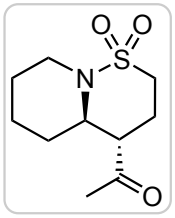
3.5.4. MICHAEL ADDUCT SYNTHESIS: PREPARATION OF SULTAMS 142



141a-d **142a-d**

A microwave oven-dried vial was filled with oven-dried MS 4Å and stirring bar and heated at 120ºC during 10 minutes under microwave irradiation. Then, piperidine **141a-d** (1.0 equiv.) was dissolved in THF (0.1 M) and introduced into the vial. After immersing it in a -78ºC acetone bath, phosphazene base P_2-Et was added and the resulting mixture was stirred at that temperature for 2 hours. Then the crude reaction mixture was hydrolysed with HCl 1M, extracted with AcOEt and dried over Na_2SO_4 anhydrous. Finally it was subjected to flash chromatography on silica gel using mixtures of hexanes: ethyl acetate as eluents to afford the corresponding bicyclic sultams **142a-e**. The enantiomeric ratios were determined by means of RID- or UVD-HPLC analysis with a Chiracel OD-H column (25 cm x 0.46 cm).

1-((4*S*,4a*R*)-1,1-dioxidooctahydropyrido[1,2-*b*][1,2]thiazin-4-yl)-1-ethanone (142a)



Physical state: White solid

Empiric Formula: $C_{10}H_{17}NO_3S$

Molecular weight (g/mol): 231.31

Yield (%): 77

Melting point (ºC) 34-36

Enantiomeric relation: 93:7

Optical rotation $[\alpha]_D^{25}$: +1,9 (c 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 3.78 (ddd, *J* = 10.5, 6.5, 4.0, 1H), 3.40 – 3.24 (m, 1H), 3.20 – 2.95 (m, 3H), 2.86 (ddd, *J* = 12.5, 10.9, 3.8, 1H), 2.44 – 2.25 (m, 1H), 2.25 – 2.10 (m, 4H), 1.83 – 1.19 (m, 9H)

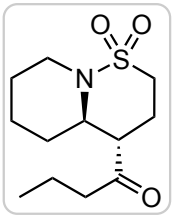
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 208.1, 58.5, 50.0, 45.2, 42.1, 29.8, 29.5, 26.1, 24.7, 21.0

HRMS (EI^+): Calcd. for $C_{10}H_{17}NO_3S$ [*M*+]: 232,1002, found: 232,0996

Remarks:

- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.
- The *er* value was determined by RID-HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 85:15); flow rate = 1.0 mL/min, t_{major}= 23.2 min, t_{minor}= 20.3 min

1-((4*S*,4a*R*)-1,1-dioxidooctahydropyrido[1,2-*b*][1,2]thiazin-4-yl)-1-butanone (142b)



Physical state: White solid

Empiric Formula: $C_{12}H_{21}NO_3S$

Molecular weight (g/mol): 259.36

Yield (%): 70

Melting point (ºC): 193-195

Enantiomeric relation: 94:6

Optical rotation $[\alpha]_D^{25}$: (c 1.0, $CHCl_3$)

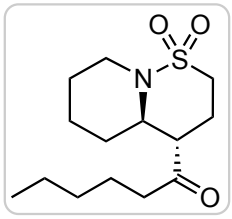
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 3.72 (ddd, *J* = 10.7, 6.7, 4.0, 1H), 3.35 – 3.21 (m, 1H), 3.12 – 2.89 (m, 3H), 2.79 (ddd, *J* = 12.5, 10.8, 3.7, 1H), 2.51 – 2.19 (m, 3H), 2.05 (dq, *J* = 14.1, 3.8, 1H), 1.75 – 1.14 (m, 8H), 0.91 – 0.77 (m, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 210.5, 58.9, 49.6, 45.6, 45.4, 42.3, 29.8, 26.5, 24.9, 21.4, 17.0, 14.1

HRMS (EI^+): Calcd. for $C_{12}H_{21}NO_3S$ [*M*+]: 260,1276 , found: 260,1312

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.
- The *er* value was determined by RID-HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 85:15); flow rate = 1.0 mL/min, t_{major}=17.4 min, t_{minor}=15.0 min

1-((4*S*,4a*R*)-1,1-dioxidooctahydropyrido[1,2-*b*][1,2]thiazin-4-yl)-1-hexanone (142c)



Physical state: White solid

Empiric Formula: $C_{12}H_{21}NO_3S$

Molecular weight (g/mol): 287.42

Yield (%): 73

Melting point (ºC): >310ºC

Enantiomeric relation: 95:5

Optical rotation $[\alpha]_D^{25}$: (c 1.0, $CHCl_3$)

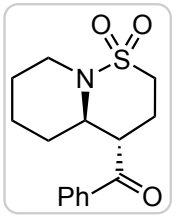
^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 3.79 (ddd, *J* = 10.6, 6.6, 3.9, 1H), 3.41 – 3.28 (m, 1H), 3.19 – 2.92 (m, 3H), 2.92 – 2.80 (m, 1H), 2.60 – 2.24 (m, 3H), 2.21 – 2.05 (m, 1H), 1.84 – 1.14 (m, 12H), 0.89 (dd, *J*=9.1, 4.8, 3H)

^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 210.7, 58.9, 49.6, 45.6, 43.5, 42.3, 31.7, 29.8, 26.5, 24.9, 23.3, 22.8, 21.4, 14.3

HRMS (EI^+): Calcd. for $C_{12}H_{21}NO_3S$ [*M*+]: 288,1519, found: 288,1632

Remarks:
- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.
- The *er* value was determined by RID-HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 85:15); flow rate = 1.0 mL/min, t_{major}=15.2 min, t_{minor}=13.3 min

1-((4*S*,4a*R*)-1,1-dioxidooctahydropyrido[1,2-*b*][1,2]thiazin-4-yl)(phenyl)methanone (142d)



Physical state: White solid

Empiric Formula: $C_{15}H_{19}NO_3S$

Molecular weight (g/mol): 293.38

Yield (%): 80

Melting point (ºC): 105-108

Enantiomeric relation: 90:10

Optical rotation $[\alpha]_D^{25}$: (c 1.0, $CHCl_3$)

^{1}H-RMN ($CDCl_3$, 300 MHz) δ (ppm): 8.00 – 7.93 (m, 2H), 7.67 – 7.60 (m, 1H), 7.56 – 7.48 (m, 2H), 3.97 (ddd, *J* = 10.7, 6.6, 3.8, 1H), 3.78 (ddd, *J* = 12.3, 10.4, 3.5, 1H), 3.54 – 3.43 (m, 1H), 3.22 – 3.12 (m, 2H), 3.13 – 3.01 (m, 1H), 2.49 (dddd, *J* = 14.2, 12.3, 10.4, 6.9, 1H), 2.28 – 2.14 (m, 1H), 1.87 – 1.44 (m, 6H)

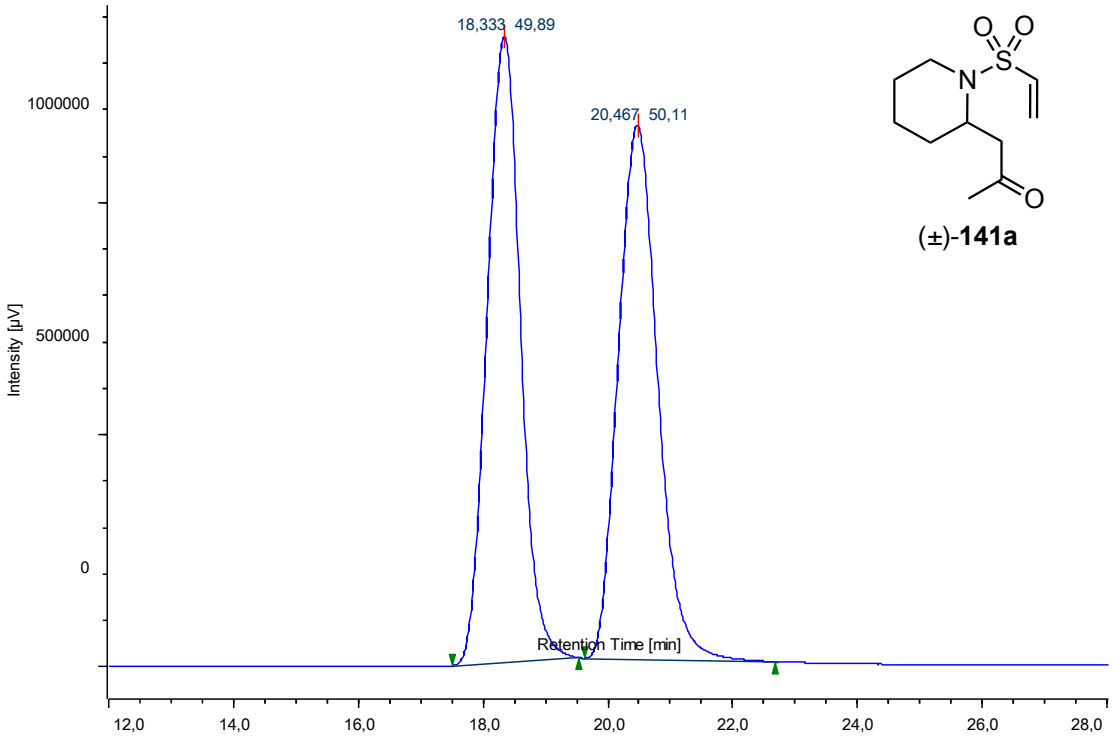
^{13}C-RMN ($CDCl_3$, 75.5 MHz) δ (ppm): 200.3, 136.4, 134.1, 129.2, 128.4, 59.7, 45.8, 44.0, 42.1, 29.8, 27.2, 24.7, 21.6

HRMS (EI^+): Calcd. for $C_{15}H_{19}NO_3S$ [*M*+]: 294,3885, found: 294,1158

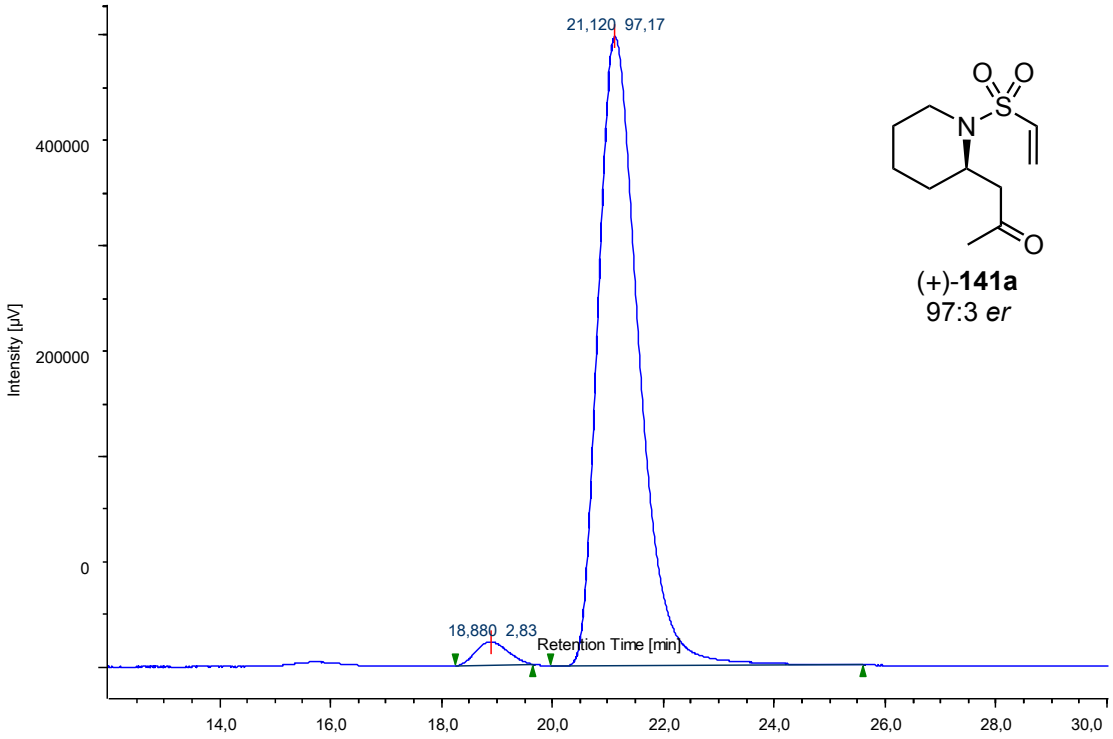
Remarks:

- Purification by flash chromatography with hexanes: ethyl acetate 1:1 as eluent.
- The *er* value was determined by UVD-HPLC analysis using a Chiracel OD-H column (hexane: isopropanol 85:15); flow rate = 1.0 mL/min, t_{major}=51.0 min, t_{minor}=43.2 min

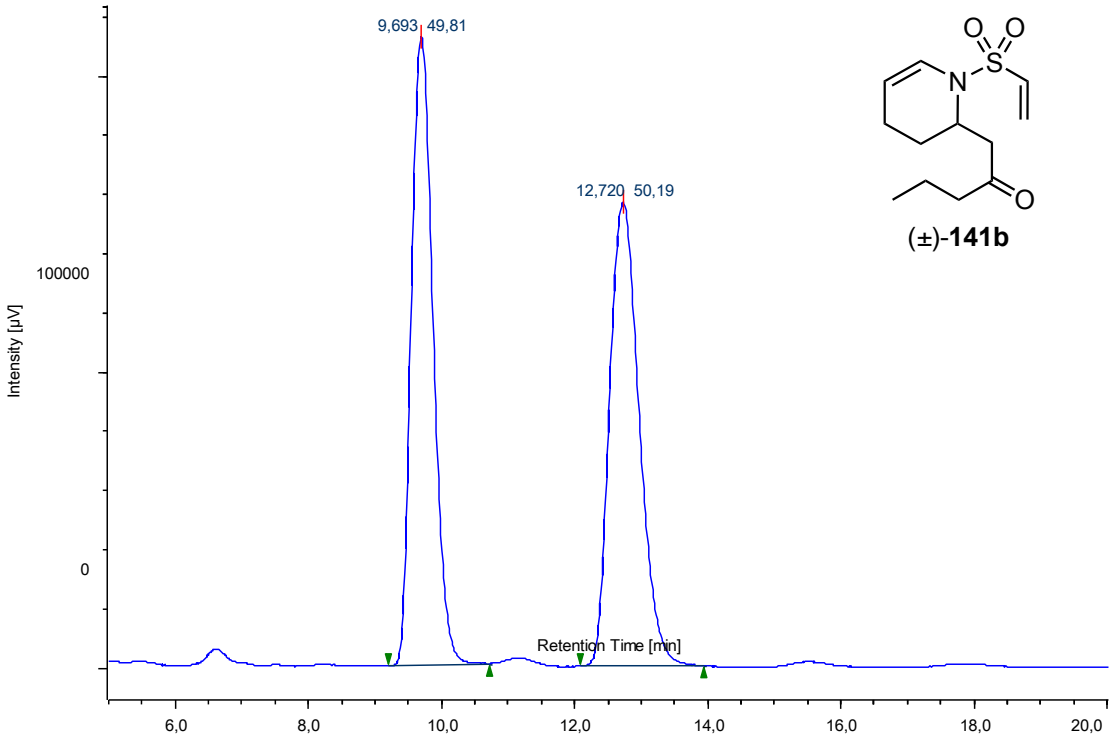
3.5.5. HPLC TRACES OF ENANTIOENRICHED COMPOUNDS 141 AND 142



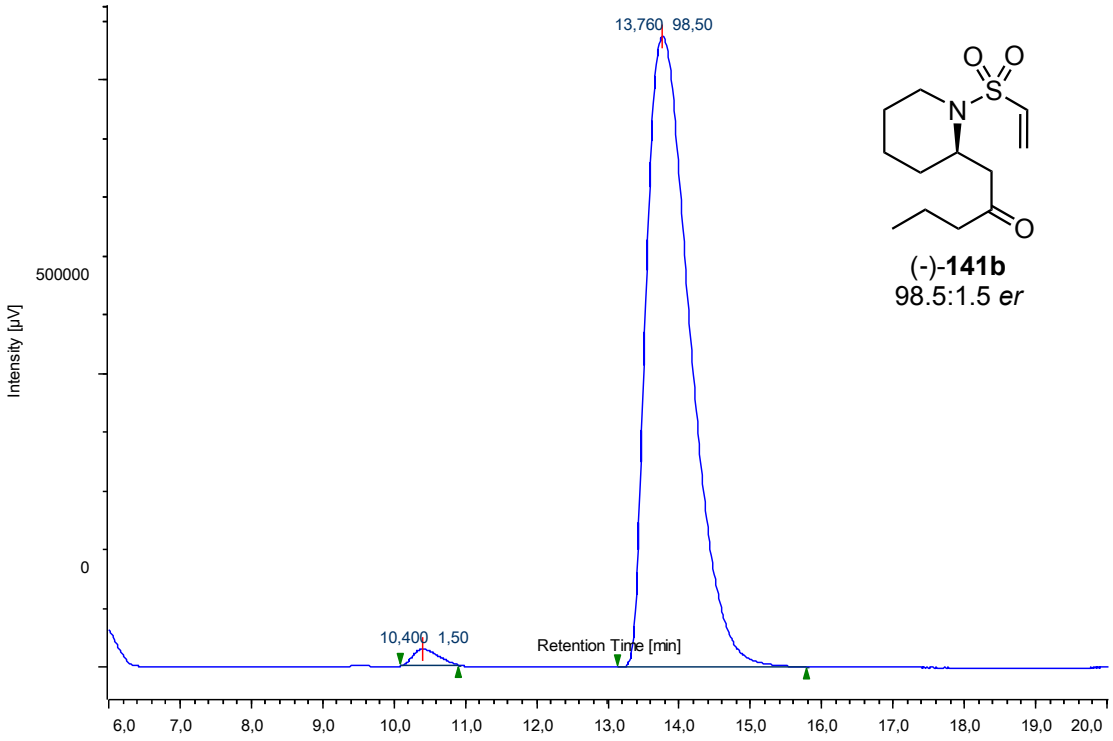
(±)-**141a**



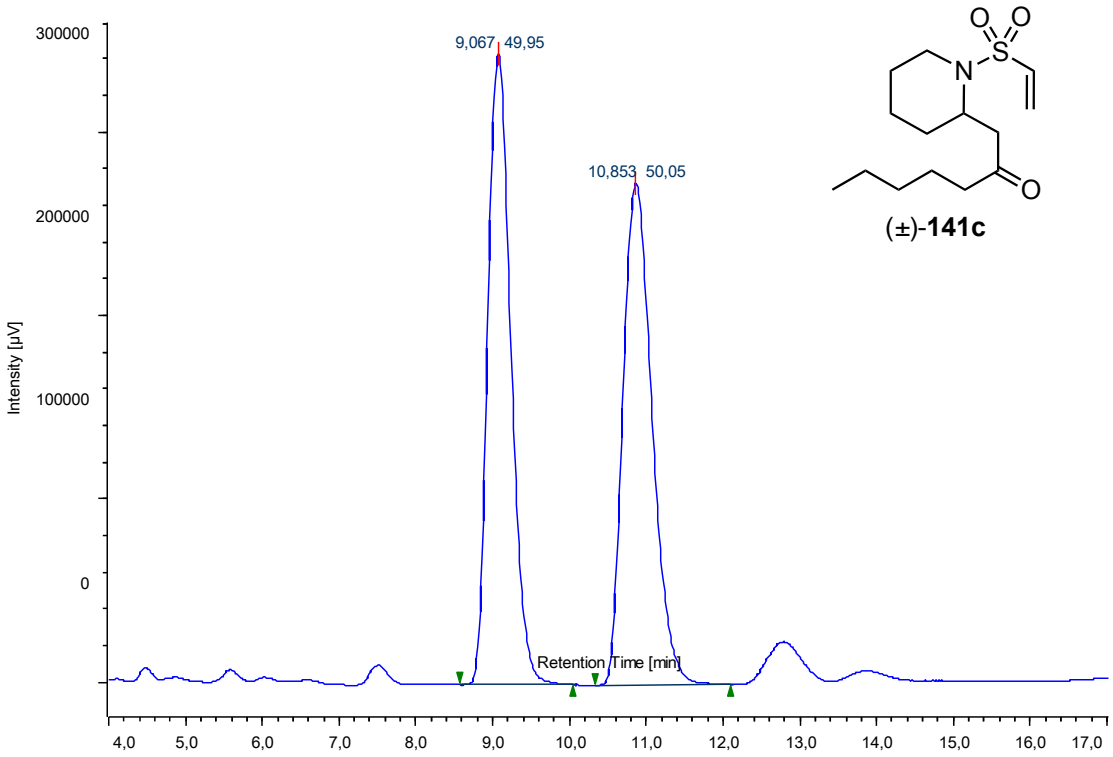
(+)-**141a**
97:3 *er*



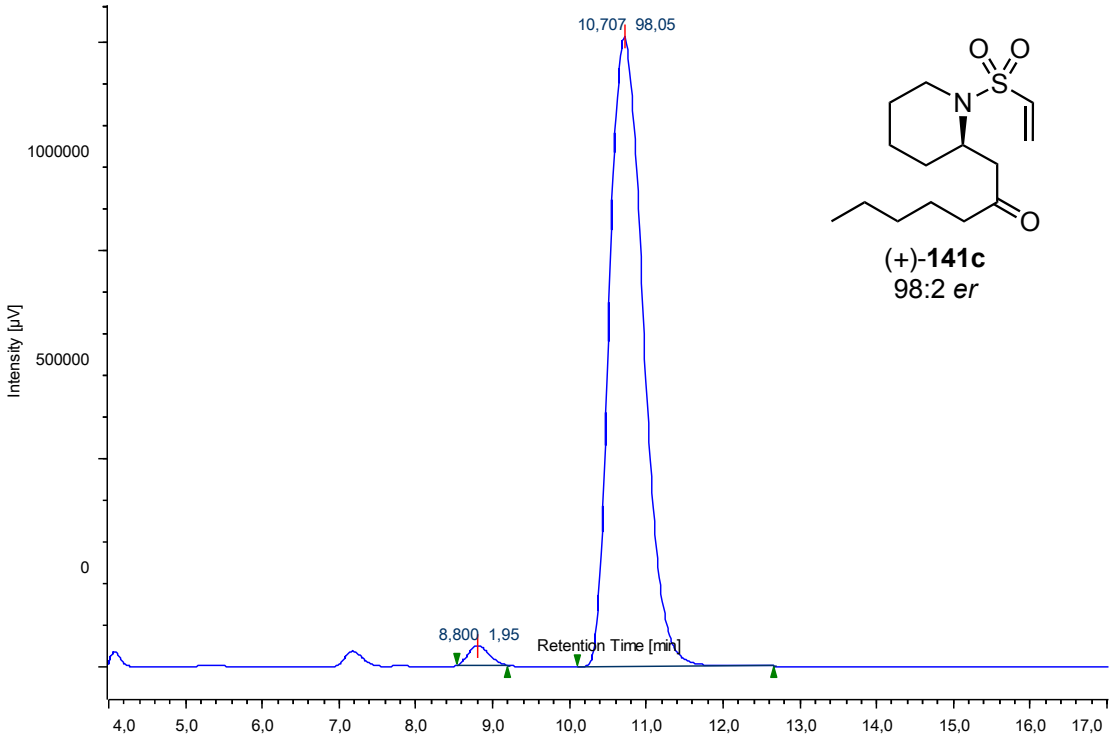
(±)-**141b**



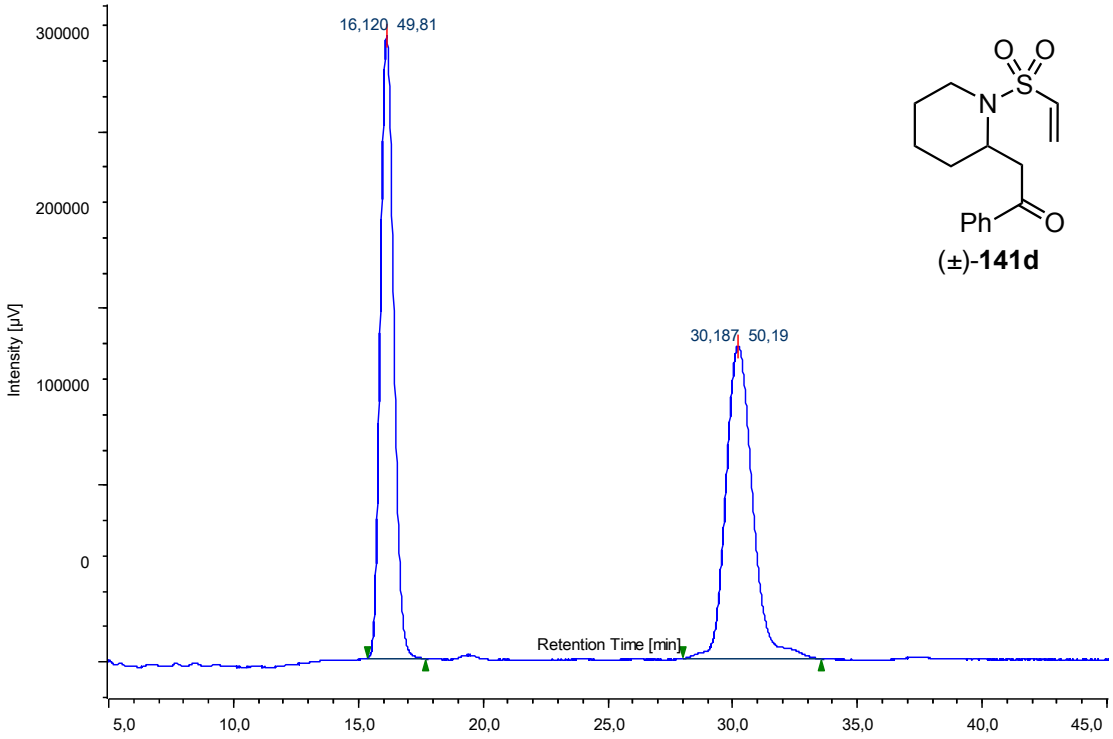
(-)-**141b**
98.5:1.5 *er*



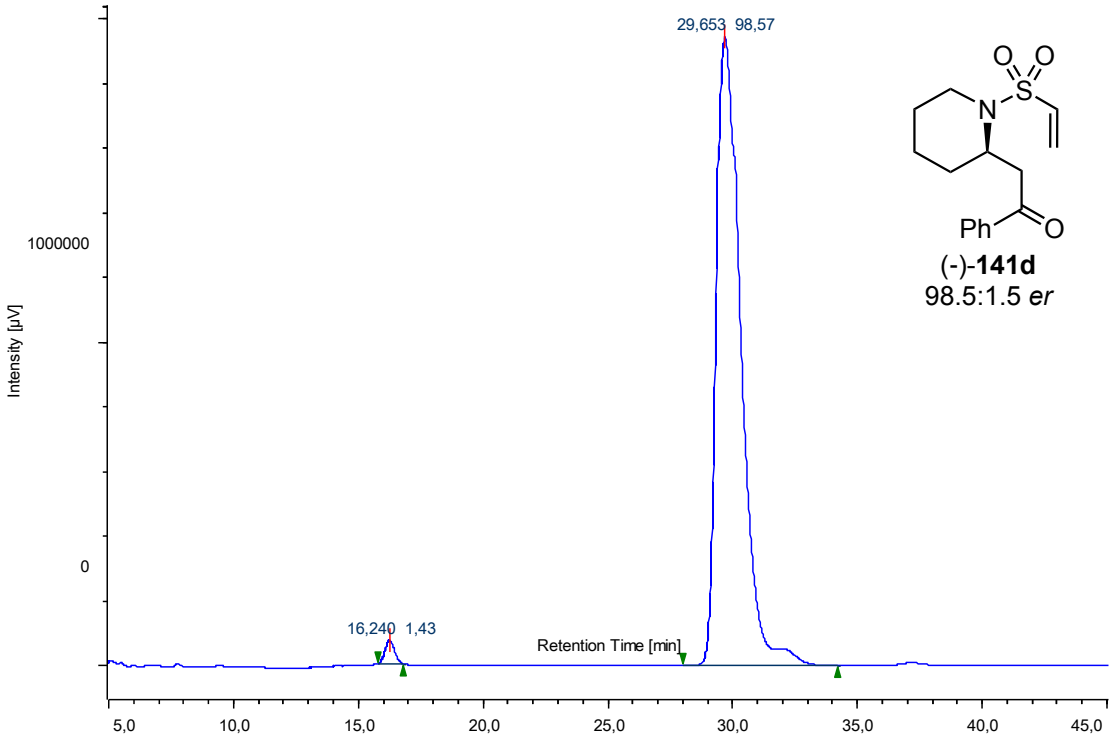
(±)-**141c**



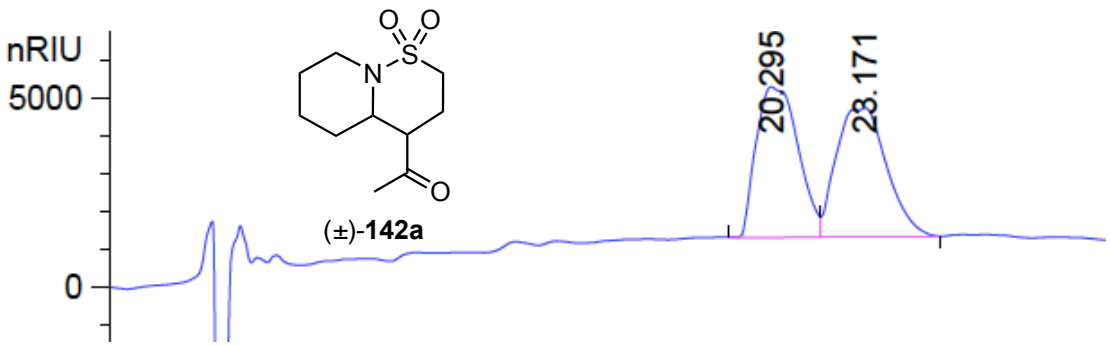
(+)-**141c**
98:2 *er*



(±)-**141d**



(-)-**141d**
98.5:1.5 *er*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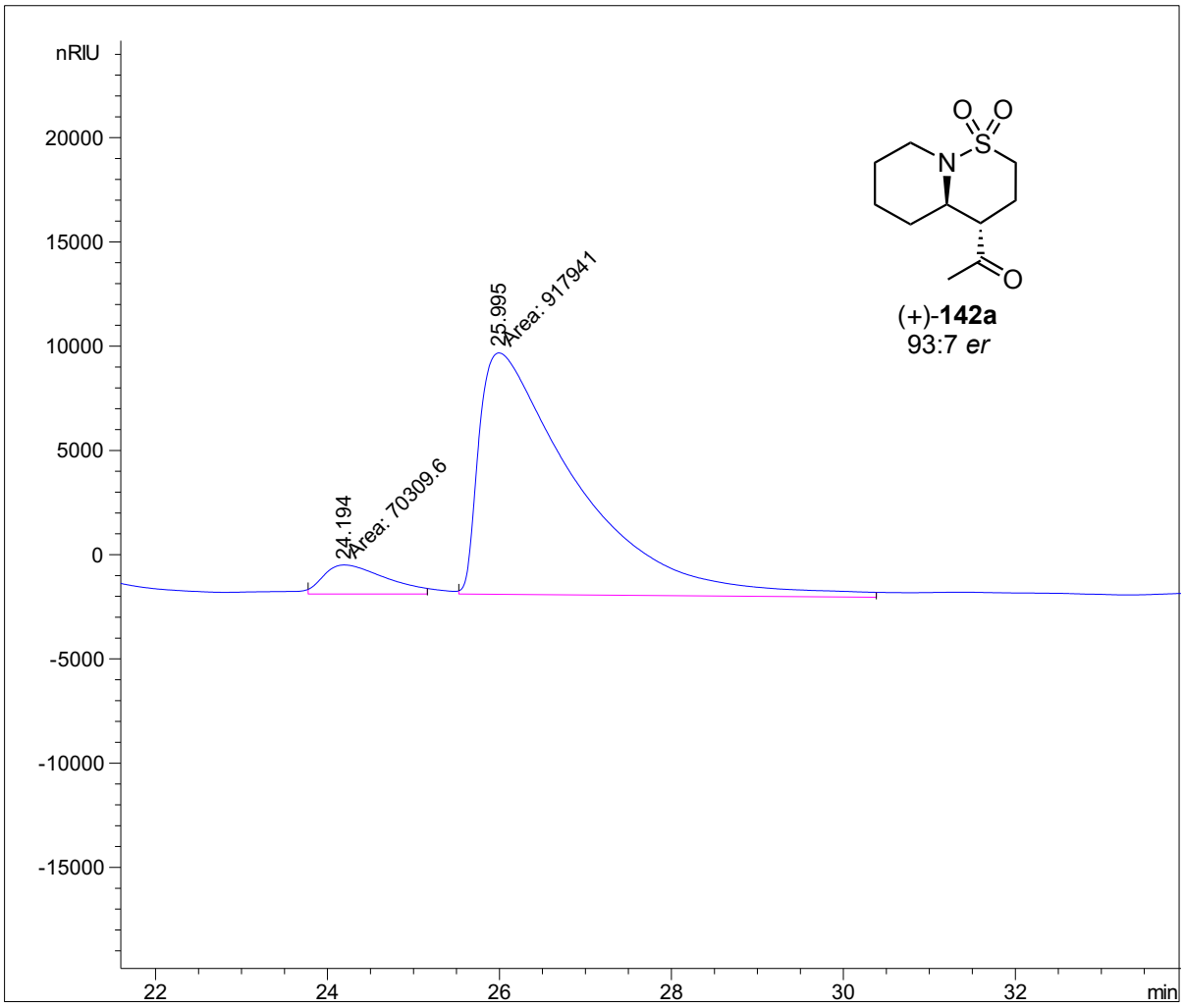
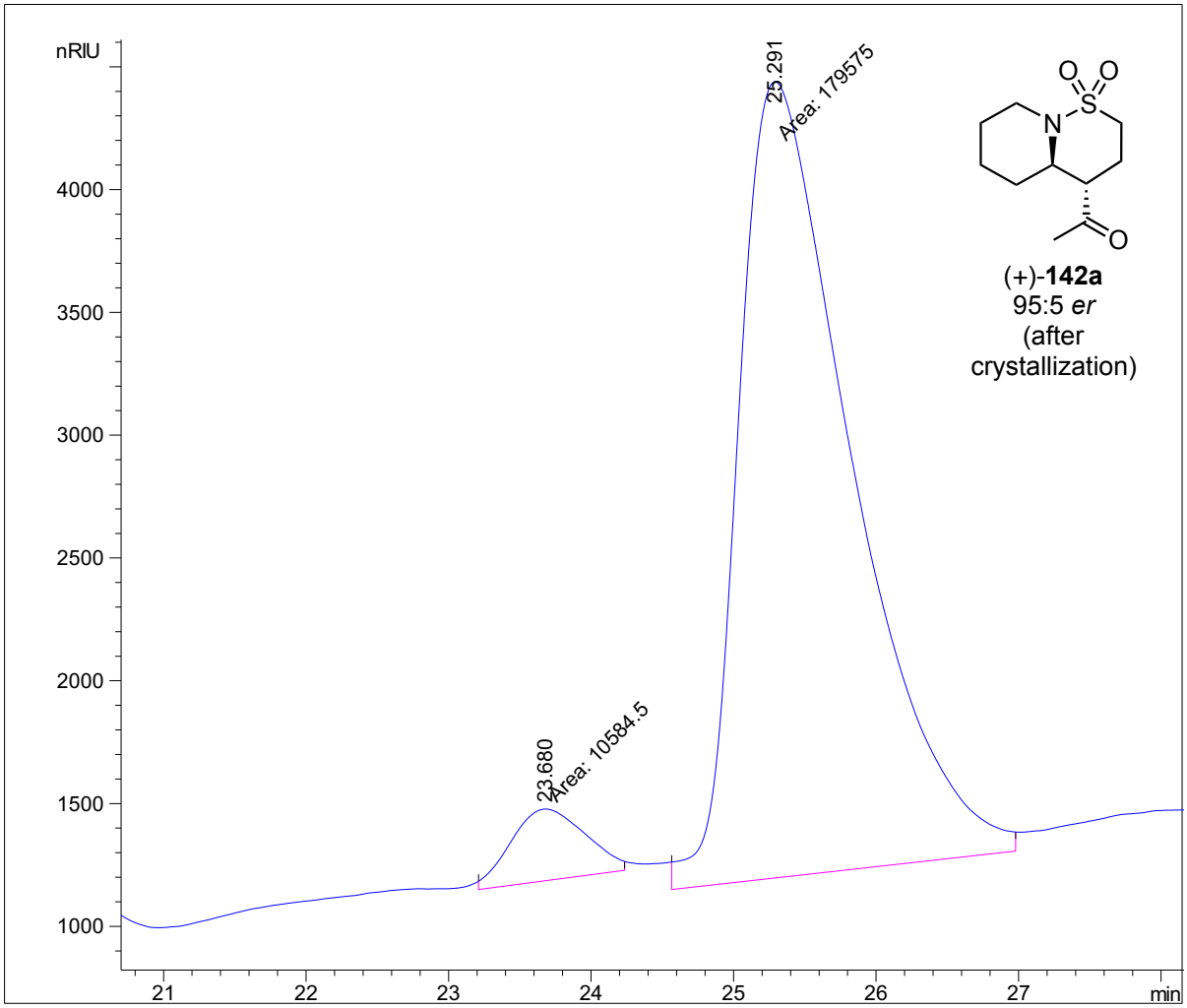
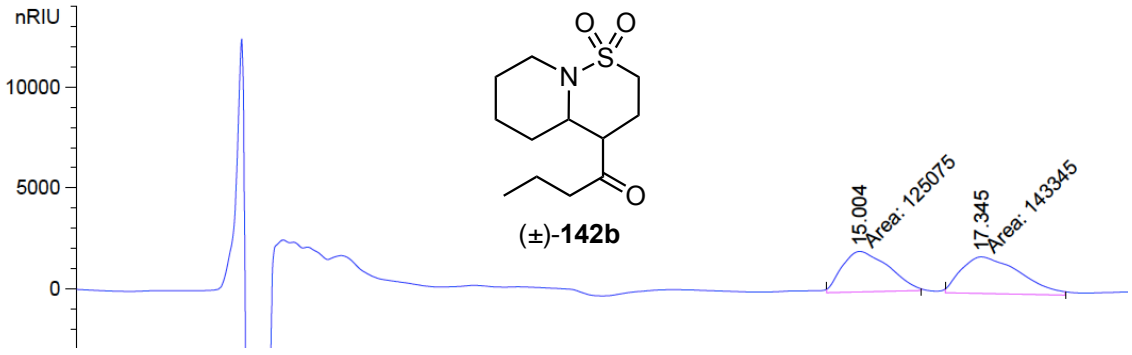
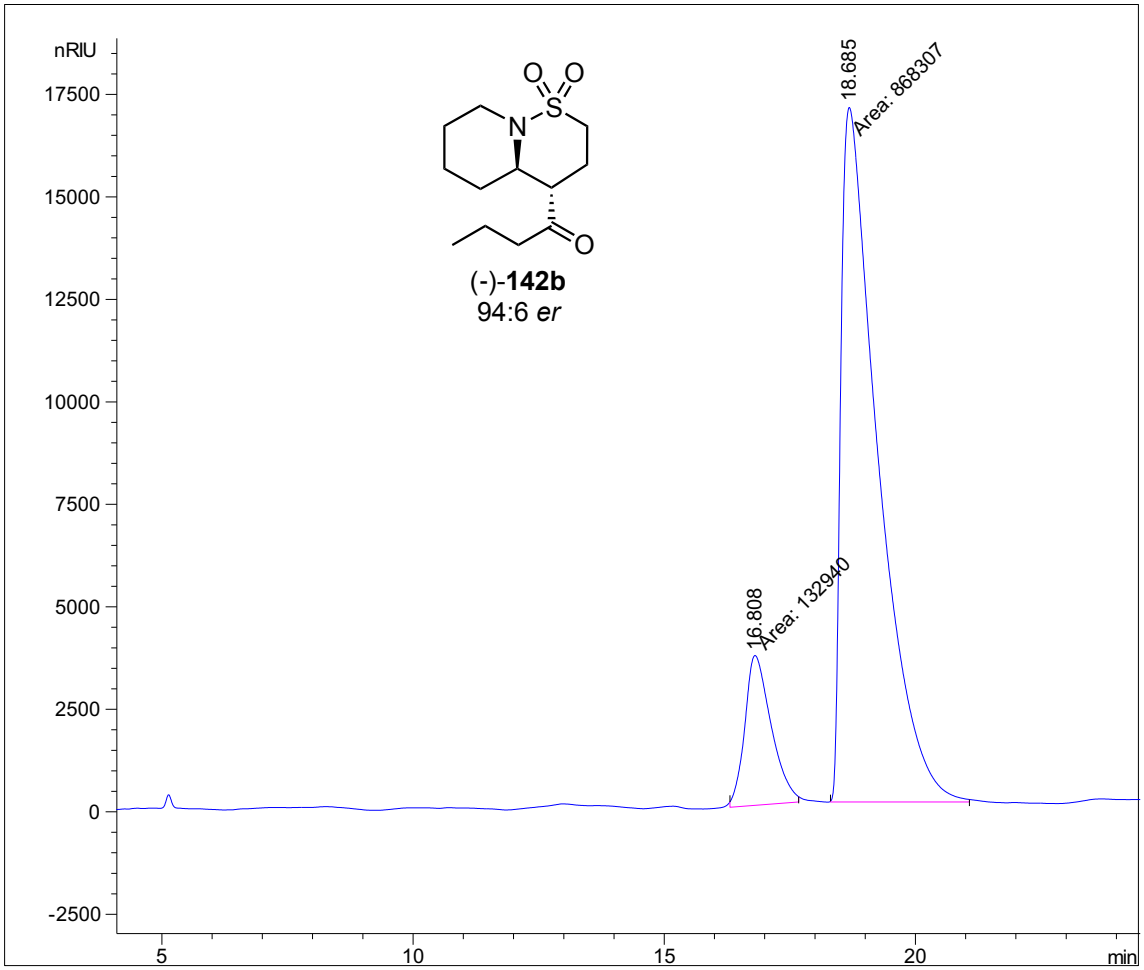
0
20.295
23.171
(±)-142a

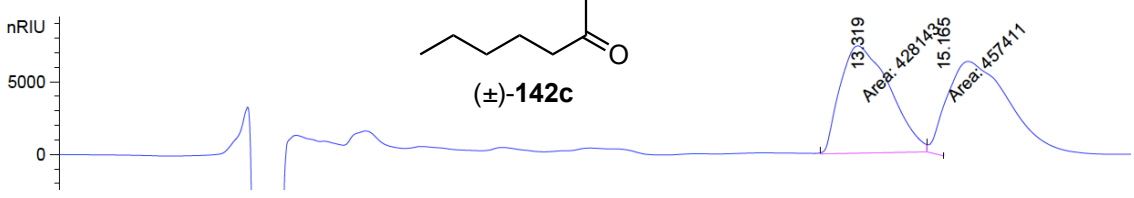

nRIU
20000
15000
10000
5000
0
-5000
-10000
-15000
22
24
26
28
30
32
min
24.194
Area: 70309.6
25.995
Area: 917941
(+)-142a
93:7 er


nRIU
4000
3500
3000
2500
2000
1500
1000
21
22
23
24
25
26
27
min
23.680
Area: 10584.5
25.291
Area: 179575
(+)-142a
95:5 er
(after
crystallization)

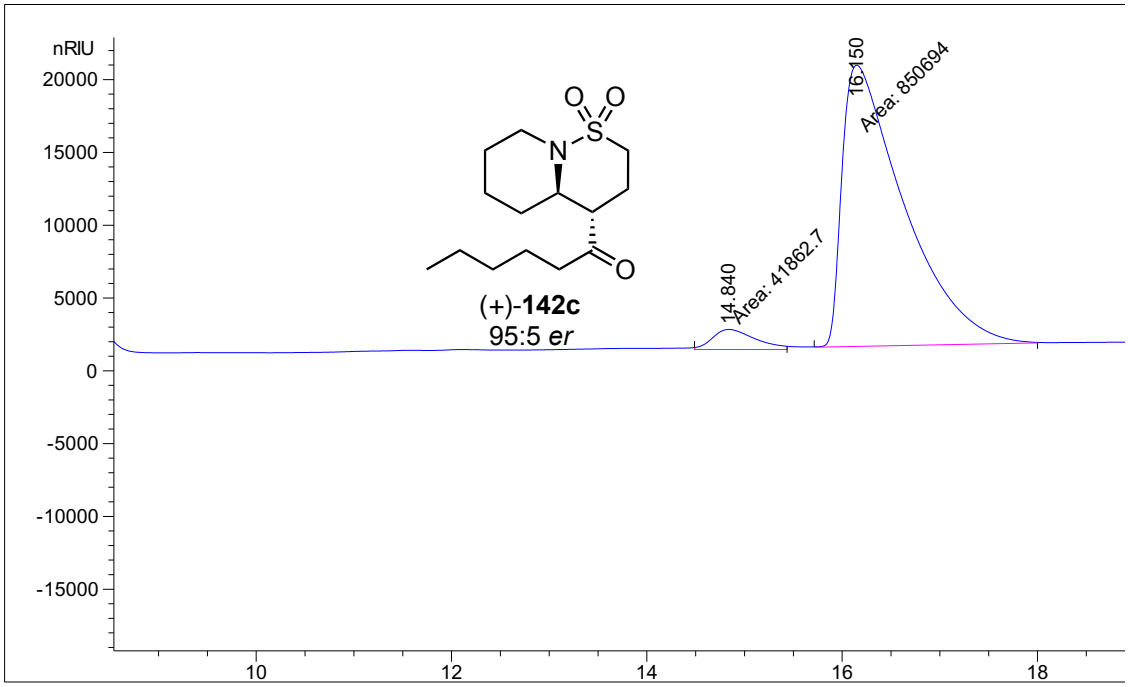

nRIU
10000
5000
0
(±)-142b
15.004
Area: 125075
17.345
Area: 143345

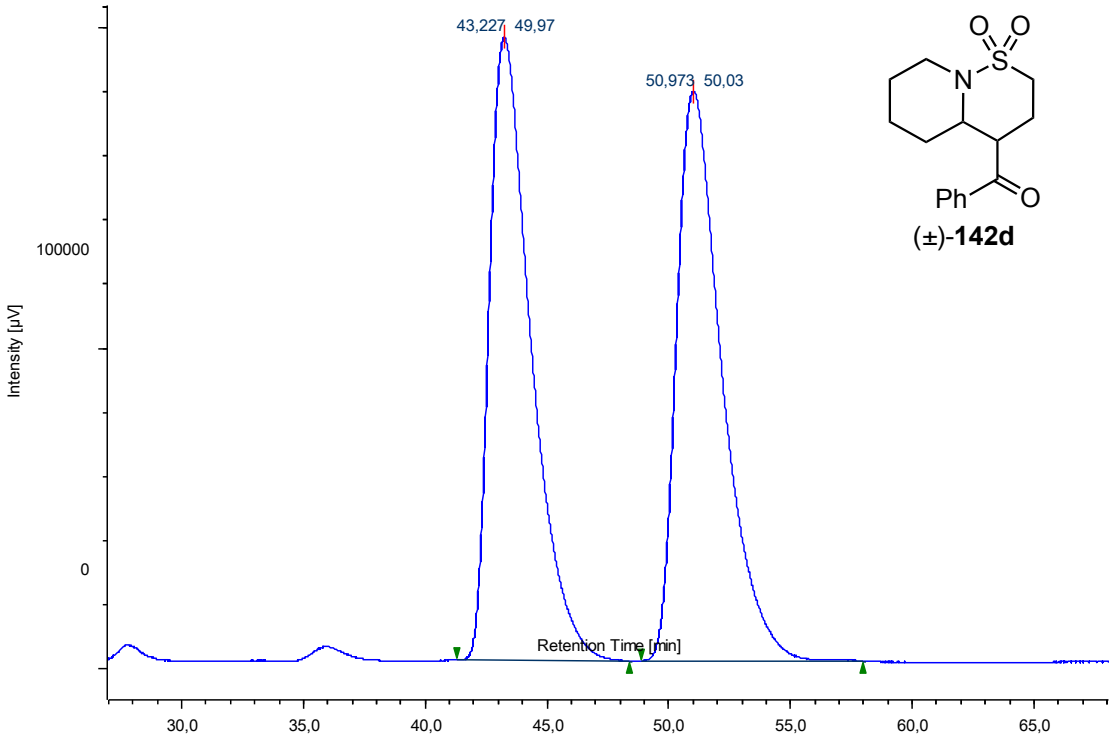


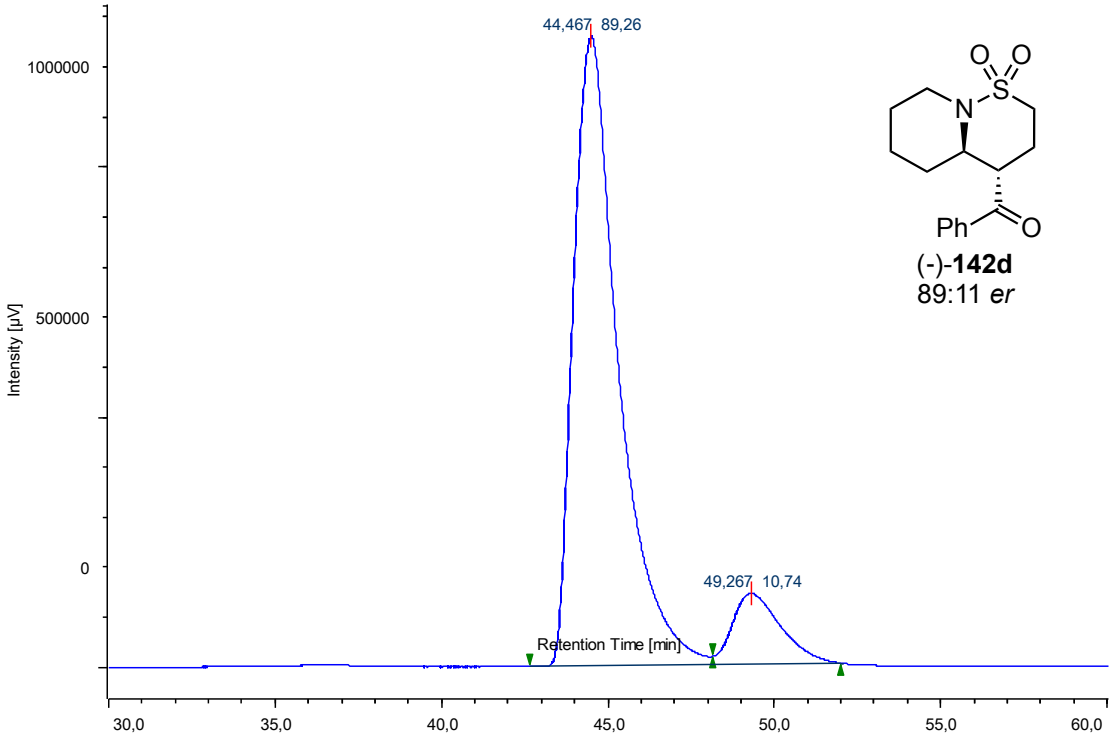
(-)-**142b**
94:6 *er*



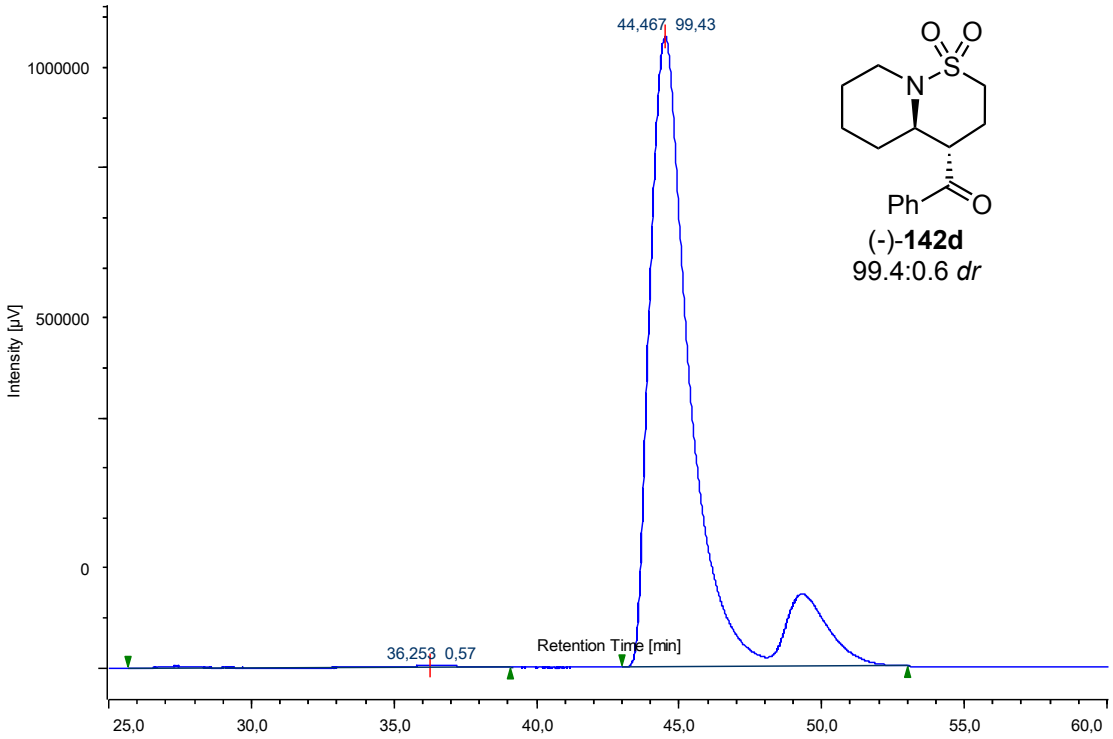
(±)-**142c**


nRIU
20000
15000
10000
5000
0
-5000
-10000
-15000
10
12
14
16
18
14.840
Area: 41862.7
16.150
Area: 850694
(+)-142c
95:5 er


43,227 49,97
50,973 50,03
100000
0
Intensity [µV]
Retention Time [min]
30,0
35,0
40,0
45,0
50,0
55,0
60,0
65,0
Ph
(±)-142d



(-)-**142d**
89:11 *er*



(-)-**142d**
99.4:0.6 *dr*