UNIVERSITÀ DEGLI STUDI DI SALERNO

FACOLTÀ DI SCIENZE MATEMATICHE, FISICHE E NATURALI

PhD course in "Scienza e Tecnologie per l'industria chimica, farmaceutica e alimentare"_ Curriculum in chimica

(XI Cycle)

2009-2012

STEREOSELECTIVE CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION MEDIATED BY BIFUNCTIONAL ORGANOCATALYSTS

Supervisor:
Prof. A. Lattanzi

Co-supervisors:
Prof. A. Spinella
Dr. M. Bella

Doctorate Student:
Claudia De Fusco

PhD Coordinator
Prof. G. Guerra

TABLE OF CONTENT

ABSTRACT

This PhD work describes the development of different Michael and Michael type processes employing different bifunctional organocatalysts. All the processes studied involved a non-covalent activation of the substrates provided by the organic promoters.

An asymmetric epoxidation of electron-poor trisubstituted olefins has been developed by employing the commercially available diphenyl prolinol which afforded the epoxides in high yield, complete diastereocontrol and good enantioselectivity. Diaryl prolinols were found to promote a Michael addition of β-ketoesters to nitroalkenes. An unexpected high efficiency and stereocontrol was observed with hexafluorobenzene as unconventional solvent, but also employed as an additive. A convenient tandem double Michael addition process was developed to access symmetrically and unsymmetrically 3,5-diaryl substituted cyclohexanones by using quinine as catalyst. An aziridination reaction of terminal electron-poor olefins has been disclosed by using a commercially available aminothiourea catalyst. The desired aziridines, bearing a quaternary stereocenter, were isolated in good yield and enantiocontrol. These compounds, were regioselectively ring-opened to access valuable α,α-disubstituted α-amino ester derivatives. Finally, an asymmetric Fischer indolization to produce helical molecules was investigated employing a chiral phosphoric acid as promoter and an ion-exchange polymer as ammonia scavenger.

LIST OF ABBREVIATION

Ac	acetyl
ACDC	Asymmetric Counteranion-Directed Catalysis
Ar	aryl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
calcd.	calculated
cat.	catalyst(s)
Cbz	carbobenzyloxy
CG50	amberlite CG50
CHP	cumene hydroperoxide
CD	cinchonidine
CN	cinchonine
Conc.	Concentration
Cy	cyclohexyl
d	days
d	doublet
dd	double doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPP	diphenyl phosphoric acid
dr	diastereoisomeric ratio
e	*epi*
ee	enantiomeric excess
EI	electron impact

El	electrophile
eq.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
h	hour(s)
HOMO	Higher Occupied Molecular Orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Herz
i	iso
L	ligand
LDA	lithium diisopropylamide
LG	leaving group
LUMO	Lower Unoccupied Molecular Orbital
M	molar (concentration)
M	major diastereoisomer
m	minor diastereoisomer
m	*meta*
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
MIRC	Michael Initiated Ring Closure
m.p.	melting point
MS	mass spectrometry
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	atomic mass units per charge
Nap	naphthyl
n.d.	not determined
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
o	*ortho*
p	*para*
Ph	phenyl

PG	protecting group
PIB	*p*-iodo benzyl
PLA	poly-(L)-alanine
PLL	poly-(L)- leucine
Pr	propyl
PTC	Phase Transfer Catalysis
*p*TSA	*para*-toluenesulfonic acid
QN	quinine
QD	quinidine
rt	room temperature
s	singlet
S_N	nucleophile substitution
SOMO	Singly Occupied Molecular Orbital
SPINOL	1,1'-spirobiindane-7,7'-diol
t	*tert*
t	time
t	triplet
T	Temperature
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyl dimethylsilyl
THF	tetrahydrofuran
TMS	tetramethylsilyl
^{t}BuOK	potassium *tert*-butoxide
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
t_R	retention time
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	*para*-toluenesulfonyl
VANOL	3,3′-Diphenyl-2,2′-bi-1-naphthalol
VAPOL	2,2'-diphenyl-(4-biphenanthrol)

1. INTRODUCTION

1.1 Why Chirality?

Chirality, which concerns a rigid object not superimposable to its mirror image (Figure 1.1), is at the basis of the life.

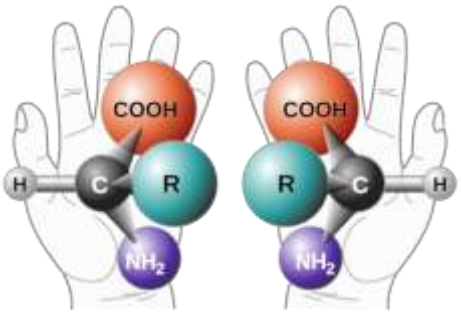


Figure 1.1 Human hands and amino acids are classical examples of chiral objects.

Most of the biological systems interacts recognizing an enantiomer better than the other (molecules with a chemically identical structure) and are able to synthesize optically active compounds in an enantiopure form. Amino acids, sugars, nucleotides are all small chiral components whose chiral information can affect an entire macroscopic environment. Effects in the macroscopic world can have their origin at the molecular level, such as the common phenomena of perception of odours and tastes by human brain. Signals interpreted as a perception of sense come from the interaction and the specific fitting of a molecule, for example an odorant, in its complementary chiral receptor or ensemble of receptors, giving different responses in dependence on its absolute configuration. As an example, amino acids belonging to different stereochemical series (Figure 1.1) taste different: D-aminoacids tend to have a sweet taste, while those belonging to the L-series are generally tasteless. D-carvone and L-carvone,

shown in Figure 1.2, have a different odour since they interact with different ensembles of receptors assigned to the sense of smell. The D-carvone is responsible for the odour of caraway while its enantiomer smells like spearmint. [1]

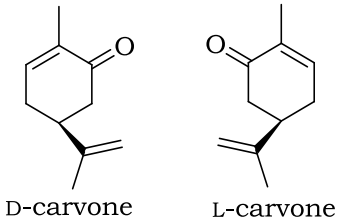


Figure 1.2 D and L-carvone.

In 2003 a review on flagrances and flavours reported that 285 couples of enantiomers exhibited different odour qualities and intensities.[2]

Even more important is the role of chirality in regulating enantiomerically specific bioactivity in drugs, agrochemicals or the way the nature communicates, such as the power of a signal depending on the stereoisomer of a given pheromone.

The concept of chirality was introduced after the middle of the 19th century by Pasteur, vant'Hoff and LeBel describing for the first time a carbon with four different substituents as a chiral unit.[3] Nevertheless until the end of the 20th century synthetic drugs were produced almost exclusively in racemic form although enantiomerically pure natural compounds have been employed as drugs since ancient times.[4]

[1] T. J. Leitereg, D. G. Guadagni, J. Harris, T. R. Mon, R. Teranishi, *J. Agric. Food. Chem.* **1971**, *19*, 785.
[2] E. Brenna, C. Fuganti, S. Serra, *Tetrahedron: Asymmetry* **2003**, *14*, 1.
[3] a) L. Pasteur, *Compt. Rend. Acad. Sci.* **1848**, *34*, 535; b) J. H. van't Hoff, *Arch. Neerl. Sci. Exactes Nat.* **1874**, *9*, 445; c) J. A. Le Bel, *Bull. Soc. Chim. France* **1874**, *22*, 331.
[4] J. Gal, in *Chirality in Drug Research*, E. Francotte, W. Lindner (Eds.), Wiley-VCH: Weinheim, **2006**.

It is dramatically known the effect of the "wrong" enantiomer of the thalidomide, a drug introduced to treat morning sickness and to aid sleep although soon one of the two enantiomers was proved to be teratogen. Since then a particular effort has been invested by pharmaceutical companies and research groups to obtain enantiopure active compounds or at least to study the effects of the separate stereoisomers. From this and similar episodes and a growing awareness of the different activity of some enantiomer pairs, in the 90s FDA (Food and Drug Administration) and other international regulatory agencies fixed some guidelines in the synthesis and in the tests of optically active drugs.[5]

Given the appeal of enantiopure compounds, the traditional methods such as resolution or diastereoselective chemical synthesis soon revealed to be insufficient to meet the demand. Therefore both stoichiometric and catalytic asymmetric synthesis was increasingly exploited. In asymmetric catalysis, a small amount of enantiopure catalyst can transfer the asymmetric information to many optically active molecules of product from a chiral or a non-chiral precursor, by being continuously regenerated during the process.[6] In the past, metal and enzymatic catalysis were the most widespread strategies in asymmetric catalysis. In recent years a third pillar has joined this fundamental field, organocatalysis, the acceleration of chemical reactions with chiral organic molecules employed in a substoichiometric amount to obtain enantioenriched products. [7]

A number of advantages can be recognised in the absence of transition-metals and the feasible lack of toxic wastes. Moreover these catalysts are generally easily accessible and reactions can be run under air and without restrictive precautions since they usually are not air and moisture-sensitive compounds. As a substantially different approach, this third

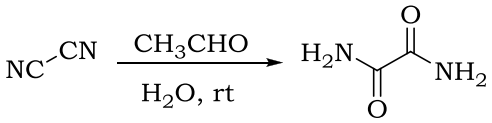
[5] FDA's Policy Statement for the Development of New Stereoisomeric Drugs, *Chirality* **1992**, *4*, 338.
[6] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods*, Wiley-VCH, Weinheim, **1996**.
[7] D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

pillar provides a complement to the other two in order to achieve asymmetric induction in catalytic reactions. Indeed, some processes, not compatible with metal- or biocatalysis have been successfully addressed by organocatalysis and vice versa.[8]

In the field of natural products and drug synthesis the organocatalysis is becoming more represented, as witnessed by the several reviews concerning this argument.[9]

1.2 Historical Development

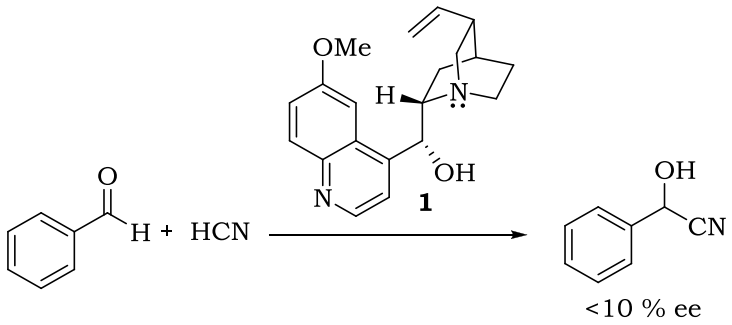
The first "traces" of reactions promoted by organic molecules can be dated back to the 1800s when pioneering studies of van Liebig showed that the cyanogen in the presence of acetaldehyde furnished the oxalamide (Scheme 1.1).[10]



Scheme 1.1 Oxamide synthesis by Liebig.

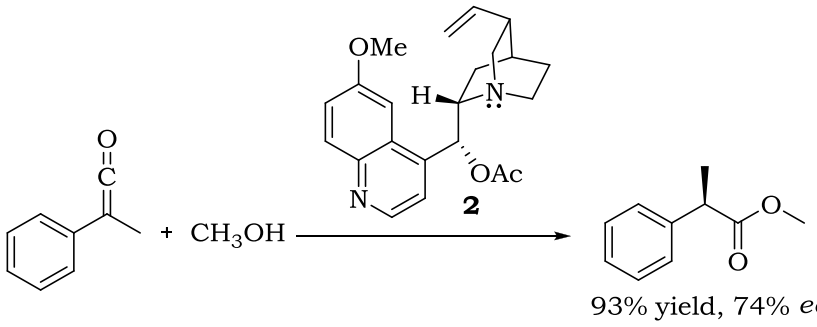
Afterwards, an investigation on the catalytic activity of cinchona alkaloids was conducted by Bredig, who reported in 1912 the addition of hydrogen cyanide to benzaldehyde promoted by quinine **1** (Scheme 1.2).[11]

[8] B. List, *Adv. Synth. Catal.* **2004**, *346*, 1021.
[9] For reviews on the organocatalytic synthesis of drugs and of bioactive natural products, see: a) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575; b) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167; c) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138.
[10] J. von Liebig, *Annalen der Chemie und Pharmacie* **1860**, *113*, 246.
[11] G. Breding, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7.



Scheme 1.2 Addition of hydrogen cyanide to benzaldehyde promoted by quinine **1**.

Although the enantiocontrol of the reaction was low, it is important to consider this process as an ancestor of asymmetric organocatalytic reactions despite at that time it was not further investigated. In the 60s another example of process promoted by the cinchona alkaloid derivative **2** was reported by Pracejus: the addition of methanol to ketenes furnished the corresponding ester with good enantiocontrol (Scheme 1.3).[12]

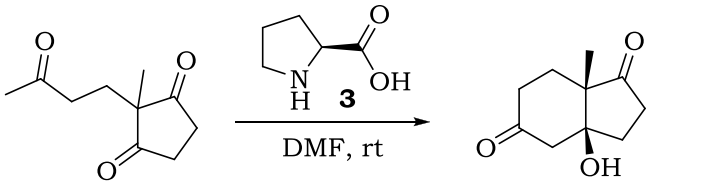


Scheme 1.3 Addition of methanol to a ketene catalysed by the cinchona alkaloid derivative **2**.

Enantiocontrol above 90% was achieved in the asymmetric version of the Robinson annulation, developed at the end of the 70s by Hajos and Parrish[13] and Eder, Sauer, Wiechert.[14] They disclosed that a catalytic

[12] H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.
[13] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1973**, *38*, 3239; *J. Org. Chem.* **1974**, *39*, 1615.
[14] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

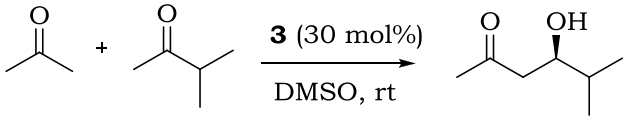
amount of the amino acid proline (**3**) could promote the formation of a bicyclic product with 93% *ee* (Scheme 1.4).



>99% yield, 93% *ee*

Scheme 1.4 Asymmetric Robinson annulation.

Despite these promising few examples of reactions catalysed by small organic molecules, only at the beginning of the new century the full potential of organocatalysis was realised with the discovery of List and Barbas that proline **3** could catalyse the direct intermolecular aldol reaction with good enantiocontrol (Scheme 1.5).[15]

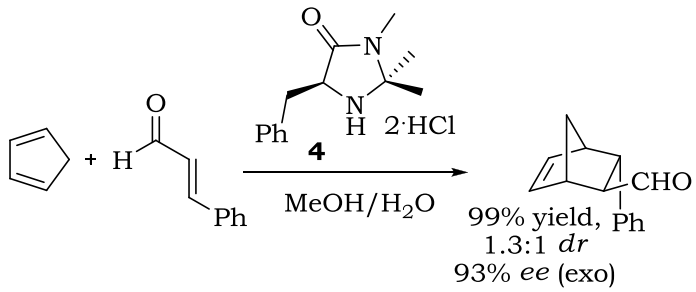


97% yield, 96% *ee*

Scheme 1.5 Direct aldol reaction promoted by L-proline.

At the same time an enantioselective Diels-Alder reaction was developed by MacMillan and co-workers exploiting the imidazolinone salt **4** to activate the reagents (Scheme 1.6).[16]

[15] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[16] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.



Scheme 1.6 Enantioselective Diels-Alder.

Both the publications reported mechanistic insights and the generality of this activation mode could give a reason for the rapid growth of the field in the last 12 years. The increasing annual number of publications found in a research on scifinder database with "organocatalysis" as key word is shown in the diagram in figure 1.3.[17]

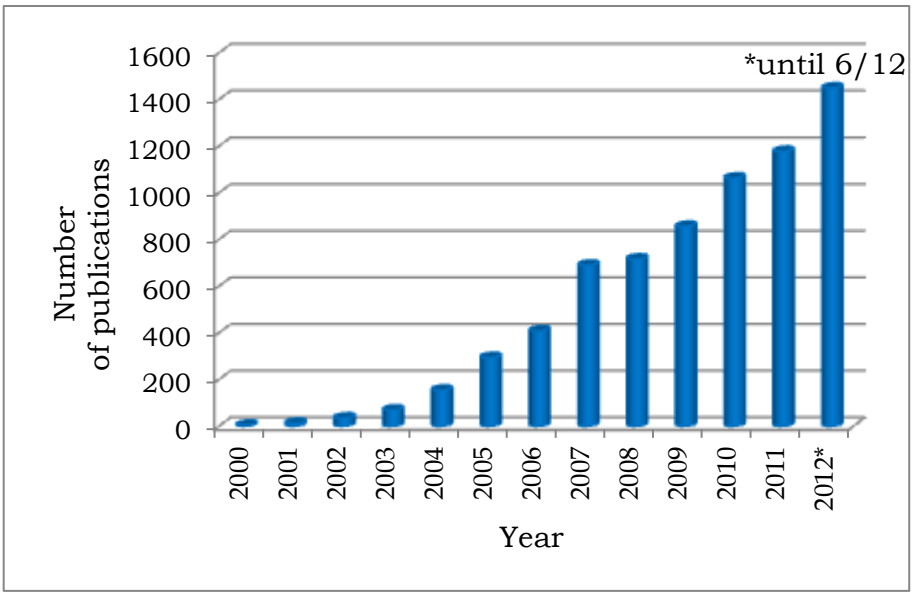
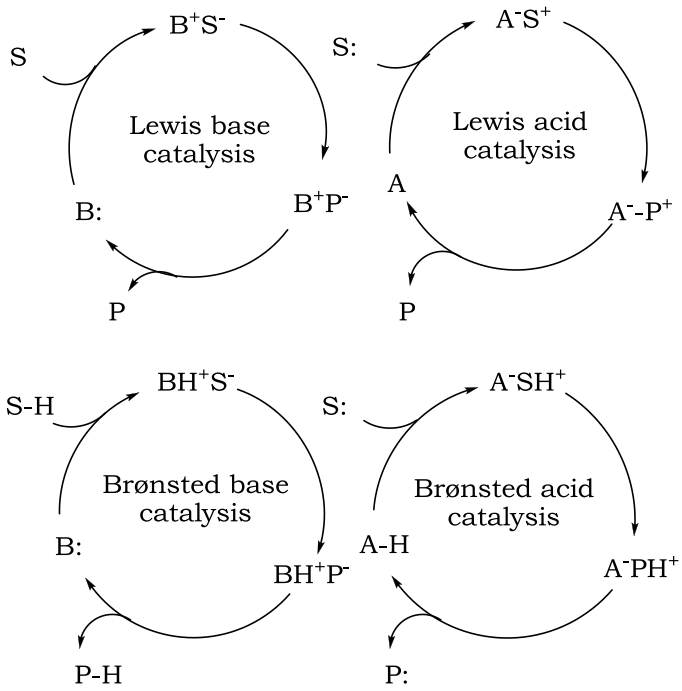


Figure 1.3 Number of publications per year with the key concept "organocatalysis".

[17] The research on Scifinder database was performed on the 6th December 2012.

1.3 Different Activation Modes

The exponential growth of reports in the field of the organocatalysis has been likely due to the individuation of generic activation modes that could be broadly applied to different systems. In the wide spectrum of organocatalysed reactions several kinds of classifications can help in their rationalization. Most of the reactions can be divided into four classes depending on the activation strategy of the substrates by the catalyst and on its chemical nature: Lewis base, Lewis acid, Brønsted base and Brønsted acid.[18] The general simplified mechanisms for the four classes of catalysts are shown in Scheme 1.7.



Scheme 1.7 Simplified mechanism for the four classes of organocatalytic activation (S = substrate, P = product, B = base, A = acid).

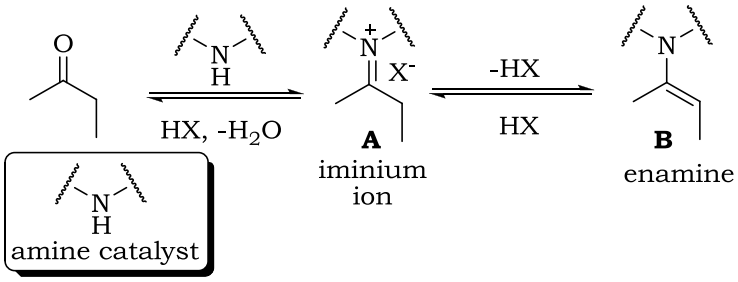
[18] J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719.

According to the traditional definition of Lewis base and acid this catalysis is based on the donation of an electron pair from the catalyst to the substrate or vice versa. Covalent intermediates, i.e. Lewis adducts, are formed and afterwards break yielding the product and regenerating the catalyst. The Brønsted activation exploits complete or partial transfer of protons, although there is not a sharp border between the above mentioned regimes since there could be synergistic effects. As an example, in order for the reaction to proceed, Lewis base catalysts often require a Brønsted acid co-catalyst. The possibility to form covalent intermediates or non-covalent interactions is another interesting and broader classification in the organocatalytic activation.[19] The formation of covalent intermediates usually involves bond energies exceeding 15 kcal/mol, while H-bonding, ion pairs, van der Waals forces, π-stacking are the most exploited non-covalent interactions characterized by an energy that usually does not overcome 4 Kcal/mol.

1.3.1 Covalent Activation Mode

Amino-acids, peptides, alkaloids and synthetic nitrogen-containing compounds received particular attention as catalysts in the covalent strategy. It involves a reaction between an amine-catalyst with carbonyl compounds to give enamines and/or iminium ions which are more reactive towards respectively electrophiles and nucleophiles.[20] Scheme 1.8 displays how these species are correlated to each other.

[19] A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH: Weinheim, **2005**.
[20] For reviews about iminium-enamine catalysis, see: a) B. List, *Chem. Commun.* **2006**, 819; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; c) A. Erikkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107,* 5416.



Scheme 1.8 Equilibrium between iminium ion and enamine generated from a carbonyl compound and an amine catalyst.

A carbonyl compound with a secondary amine can form an iminium ion (intermediate **A**), thereby decreasing the energy of the LUMO (Lower Unoccupied Molecular Orbital) of the substrate, which results in an increase in electrophilicity and in the acidity of the α-position (Figure 1.4, a). The α–deprotonation of the intermediate **A** leads to the enamine **B**, whose HOMO (Highest Occupied Molecular Orbital) is raised in energy, gaining a more nucleophilic character (Figure 1.4, b).

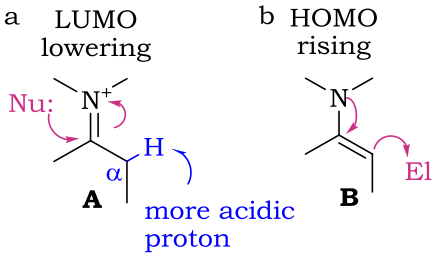


Figure 1.4 Activation of a carbonyl compound as iminium ion (a) or as enamine (b).

The classical paradigm iminium/enamine has been recently extended to α,β and to α,β,γ,δ unsaturated carbonyl compound to form dienamine (**C**) and trienamine (**D**) (Figure 1.5).[21]

[21] a) S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973; b) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem. Int. Ed.* **2010**,

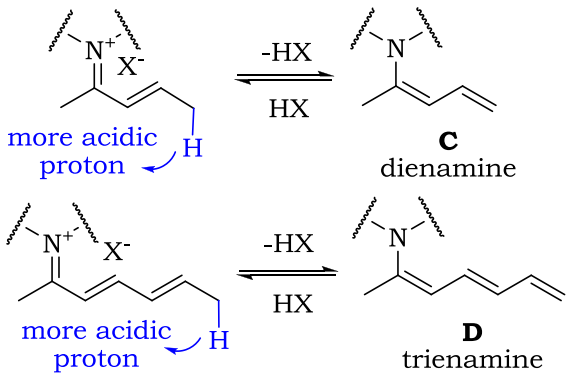


Figure 1.5 Dienamine and trienamine intermediates.

Another novelty in terms of the covalent activation mode has been introduced by MacMillan in 2006. He exploited the concept that an electron-rich enamine can undergo one-electron oxidation generating a reactive radical cation (**E**, Figure 1.6) characterized by a SOMO (Singly Occupied Molecular Orbital). The generated intermediate is able to interact with weakly nucleophilic and previously difficult to combine species, such as radicals, halides and π-nucleophiles.[7, 22]

49, 9685; c) J. Stiller, E. Marques-Lopez, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70; d) Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 2543; e) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053; f) Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212; g) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen *J. Am. Chem. Soc.* **2012**, *134*, 12943.

[22] For selected examples on SOMO-based catalysis, see: a) T. D. Beeson, A. Mastracchio, J. B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) K. C. Nicolaou, R. Reingruber, D. Sarlah, S. Brase, *J. Am. Chem. Soc.* **2009**, *131*, 2086; c) R. Sebastian, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027; d) R. Beel, S. Kobialka, M. L. Schmidt, M. Engeser, *Chem. Commun.* **2011**, *47*, 3293.

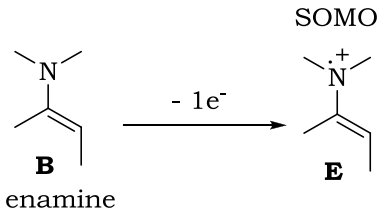


Figure 1.6 Radical cation which reacts with its SOMO.

The wide applicability of these activation modes is witnessed by the high number of possible reactions performable exploiting enamine (aldol reaction with a wide range of reactants, Michael and Mannich reactions and α-functionalization of carbonyl compounds),[20b] or iminium catalysis (nucleophilic 1,2 and 1,4-addition, cycloaddition, *trans*-amination, Diels-Alder reactions).[20c]

The enantioselectivity is addressed through the controlled approach of the other reactant to the covalent intermediate formed between the catalyst and the substrate. Mainly one face of the pro-chiral reactive site is accessible. The steric hindrance offered by the catalyst itself or another active site of the catalyst interact and guide the second partner of the reaction.

Primary amines as catalysts have late entered in the literature because of their lower reactivity due to the unfavourable iminium/enamine equilibrium (Figure 1.7).

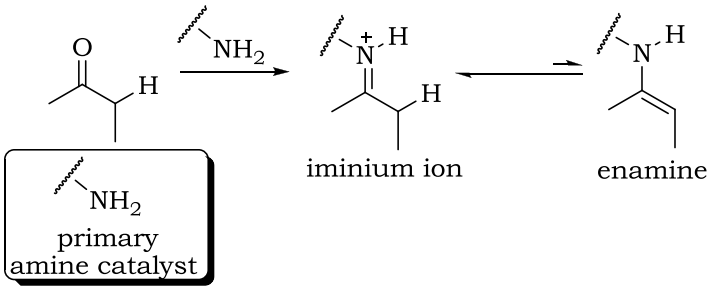


Figure 1.7 Unfavourable equilibrium iminium/enamine for primary amine catalyst

Recently primary amine catalysis has been rediscovered in the activation of particularly hindered and more challenging substrates which are not able to form covalent intermediates with secondary amine.[23]

9-Amine-9-deoxy derivatives of the cinchona alkaloids **5**, diamines with different chiral scaffolds, such as compound **6**, thioureas derivatives, such as species **7**, amino-acids **8** are only few examples of the primary amine catalysts exploited in the last years (Figure 1.8).

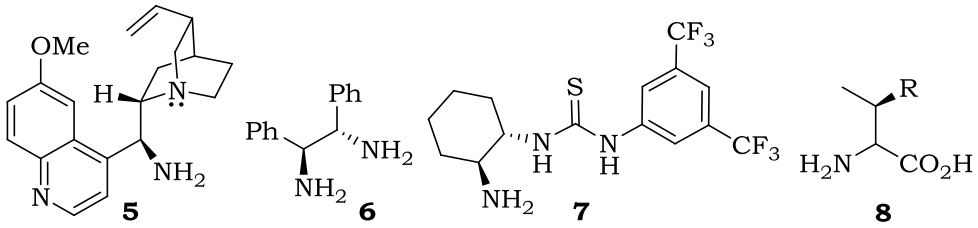


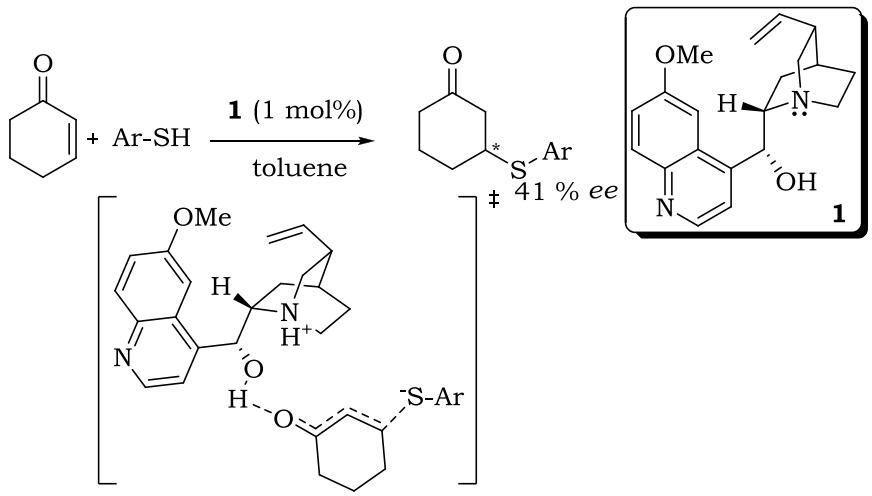
Figure 1.8 Examples of primary amine catalysts.

[23] For some reviews on primary amine catalysts, see: a) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 12, 1579; b) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; c) L. W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807.

1.3.2 Non-covalent Activation Mode

Organic molecules with a framework able to establish non-covalent interactions can be responsible of a different type of activation mode of the substrates. H-bonding are particularly important but also ion pair formation, π- π stacking, cation- π interaction, van der Waals forces. The synergistic effect of weak interactions among the catalyst and the reactants leads the reaction to proceed with some extent of enantiocontrol. The cooperation among the active sites of a catalyst reminds the action of the enzymes. Indeed, some specific portions of the enzyme activate the substrate through attractive non-covalent interactions stabilizing the transition state.[24]

In the 80s cinchona alkaloids mediated reactions were found to proceed through a non-covalent complex involving a well-defined network of hydrogen bonding and ion pair, as demonstrated by Wynberg and Hiemstra for the addition of thiols to cyclic enones (Scheme 1.9).[25]

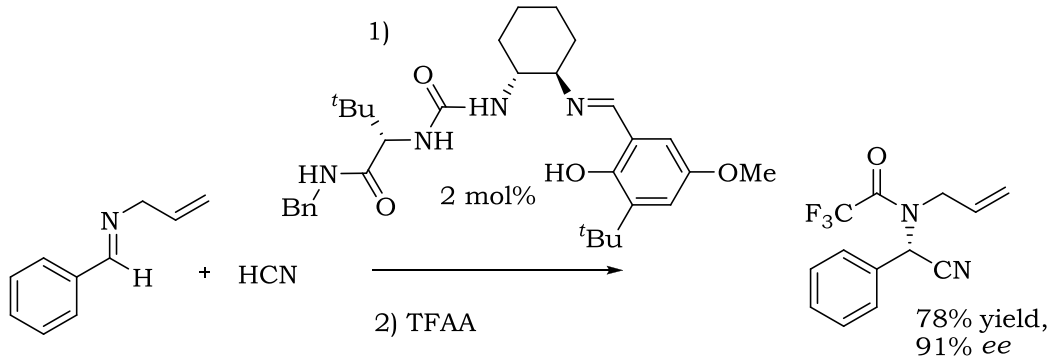


Scheme 1.9 Asymmetric addition of phenyl thiols to cyclohexanone promoted by quinine.

[24] R. R. Knowles, E. N. Jacobsen, *Proc Natl Acad Sci USA*, **2010**, *107*, 20678.
[25] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417.

Cinchona alkaloids are today widely exploited both in their natural form and as their chemical derivatives. For example their salts are often implicated in PTC (Phase Transfer Catalysis), which involves not only the activation of the substrates but also their transfer from a phase to another. Ureas and thioureas, and other derivatives modified on the skeleton are other representatives of the class.[26]

Chiral urea and thioureas were subsequently developed as double hydrogen bonding donors, first employed by Sigman and Jacobsen in the asymmetric Strecker reaction of HCN to aldimines (Scheme 1.10). [27]



Scheme 1.10 Strecker reaction promoted by a urea catalyst.

Thioureas became more popular than the corresponding ureas because of the weaker intermolecular hydrogen bonds that play an important role on the solubility and the NH acidity. For this reason thioureas seem to be more suitable in catalysis because of their higher reactivity and solubility

[26] a) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961; b) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem., Int. Ed.* **2006**, *45*, 7496; c) S. J. Connon, *Chem. Commun.* **2008**, 2499; d) C. E. Song, *Cinchona alkaloids in synthesis and catalysis*, Wiley-VCH, Weinheim, **2009**; e) S. S. Jew, H. G. Park, *Chem. Commun.* **2009**, 7090; f) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229.

[27] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.

(in non-polar solvents ureas often form aggregates which render difficult the catalysis).[28]

Thioureas are known to be able to form cooperative hydrogen bonds not only with carbonyl compounds, but also with nitro groups and dicarbonyl compounds (Figure 1.9) and for this reason they have been employed in a variety of reactions. [26c, 29]

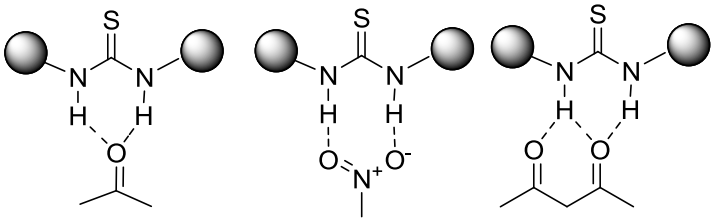
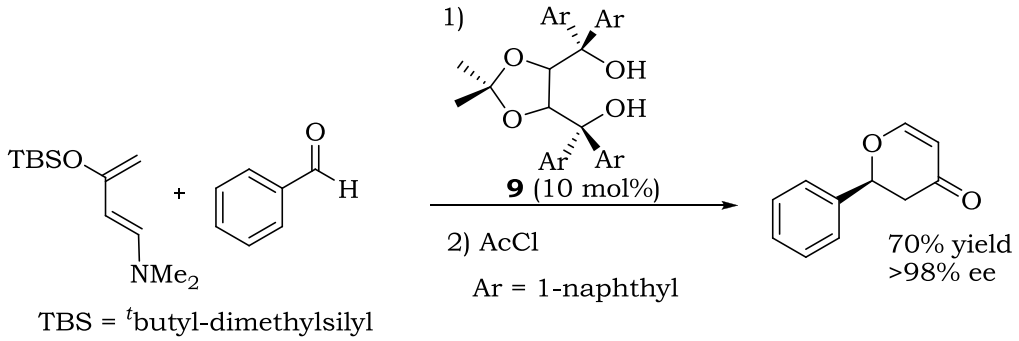


Figure 1.9 Different hydrogen bond patterns with different substrates.

Based on the observation that hetero Diels-Alder reactions were accelerated in alcoholic solvents, Rawal's group investigated the use of the TADDOL derivative **9** as promoter for the asymmetric version of the hetero Diels-Alder reaction (Scheme 1.11).[30]



Scheme 1.11 Hetero Diels-Alder catalysed by the diol **9**.

[28] A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem., Int. Ed.* **2005**, *44*, 807.
[29] a) S. J. Connon, *Chem. Eur. J.* **2006**, 12, 5418; b) M. Kotke, P.R. Schreiner, (Thio)urea organocatalysts in *Hydrogen bonding in organic synthesis*, Wiley-VCH, Weinheim, **2009**.
[30] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.

Different catalysts are able to activate the substrates *via* hydrogen bonding and many research groups have given their contributions exploiting chiral squaramides, thioureas derivatives, guanidinium, amidinium and many others.[31]

Catalysts mentioned until now mainly work under general Brønsted acid catalysis, but when the catalyst pK_a (in DMSO) decreases to <4 it is more appropriate to refer to specific Brønsted acid catalysis.

Strong acidic catalysts have been recently developed and widely employed in the field of organocatalyzed reactions. In 2004, the groups of Akiyama and Terada independently disclosed that the BINOL derivative of phosphoric acid (**10a**) could promote a Mannich addition in quantitative yield and excellent enantioselectivity.[32] Afterwards many different phosphoric acid derivatives have been designed, with BINOL, TADDOL (**11**),[33] VAPOL (**12**),[34] and recently SPINOL (**13**) skeletons[35] (Figure 1.10).

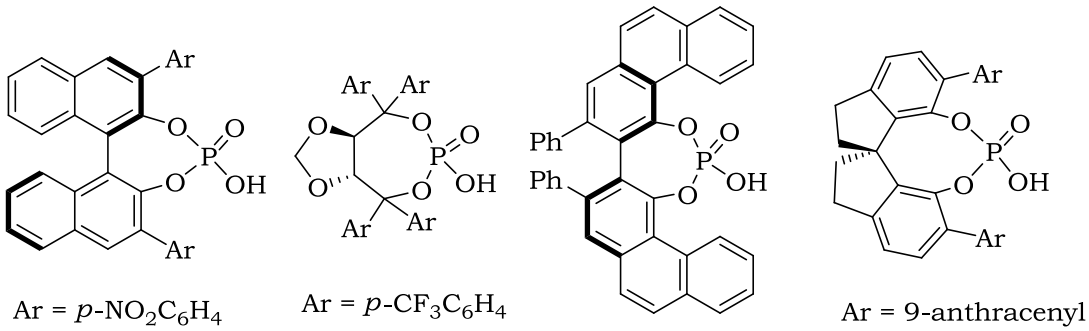


Figure 1.10 Different phosphoric acid-based catalysts.

[31] For some reviews, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Cat.* **2006**, *348*, 999; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; c) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890.
[32] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem., Int Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.
[33] T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523.
[34] G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696.
[35] S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534.

These are only few examples of the wide class of strong Brønsted acid catalysts which include also phosphorodiamidic acids, phosphoramides, dicarboxylic acids.[36] This class emerged as versatile ensemble of catalysts whose acidity can be finely modulated by choosing the active moieties and modifying substituents on the aromatic rings. They can promote several different asymmetric processes, among the others Mannich, Friedel Craft, cycloaddition, oxidation, Pictet-Spengler and reductive amination reactions.[37]

1.4 Bifunctional organocatalysts

Most of the reported organocatalysts incorporates two complementary functionalities able to synergistically activate the electrophile and the nucleophile.

The formation of new bonds and the creation of new stereocenter(s) are fundamental issues to address in a asymmetric synthetic process. The simultaneous activation of both the partners positioned in an opportune geometry is necessary to achieve a certain degree of stereocontrol.[38] Both covalent and non covalent interactions can be responsible for the activation and the achievement of the optimized transition state. In the contest of the "non-covalent catalysis", diaryl prolinols, cinchona alkaloids and their derivatives, such as thioureas, represent clear examples of bifunctionality (Figure 1.11).

[36] For selected examples, see: a) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, 133; b) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626; c) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054.
[37] For reviews on strong chiral Brønsted acid catalysis, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; b) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2009**, *291*, 395; c) M. Terada, *Synthesis* **2010**, 1929.
[38] L. Lu, X. L. An, J. R. Chen, W. J. Xiao, *Synlett* **2012**, 490.

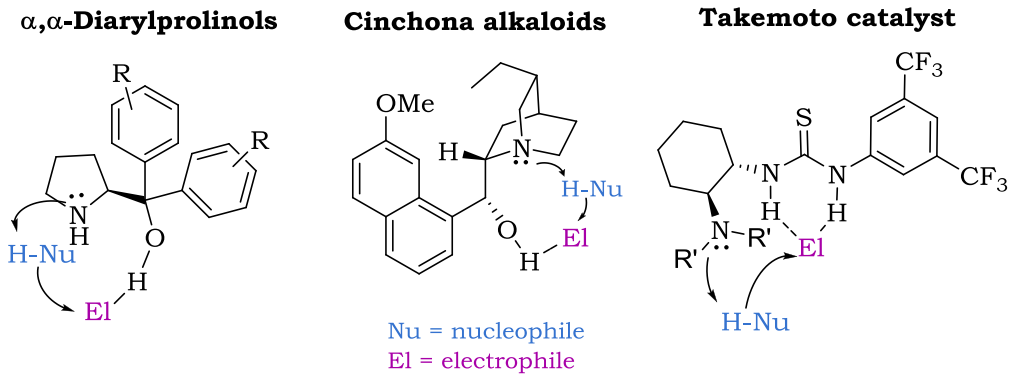


Figure 1.11 Concurrent activation of electrophile and nucleophile

The amine moiety (secondary for the prolinols, tertiary for the cinchona alkaloids and the Takemoto catalyst) activates the nucleophile through (partial) deprotonation and possibly forming an ion pair while the hydrogen bond donor activates the electrophile. This double activation provides a ternary complex where the approach between the two reactants occurs in a highly preferential manner.[24, 39]

1.5 Tandem Reactions

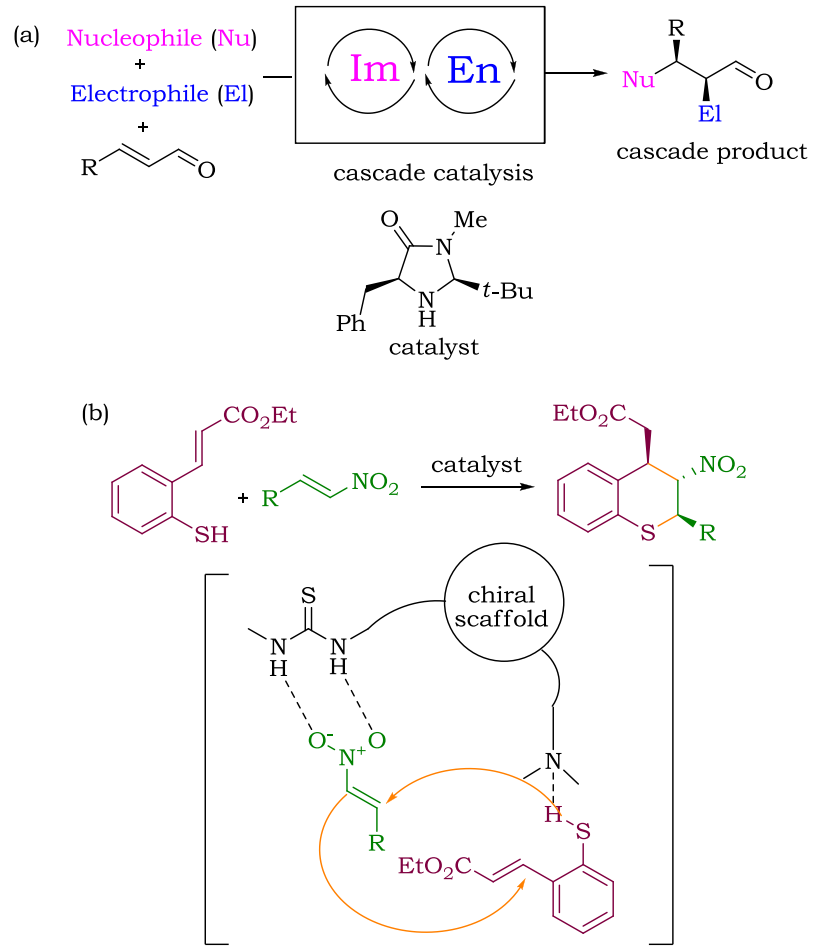
Organocatalysts have been recently employed in tandem or domino reaction, a new field which allows to perform subsequent transformations in a single pot.[40] The possibility to create in the reactants functionalities that in the same reaction environment can undergo to further modifications can be addressed to build complex molecular structures with a simple experimental procedure. Thus, multiple C-C and C-

[39] a) E. Marqués-López, R. P. Herrera, *Current Organic Chemistry* **2011**, *15*, 2311; b) A. Lattanzi, *Chem. Commun.* **2009**, 1452; c) J.L. Zhu, Y. Zhang, C. Liu, A. Zheng, W. Wang, *J. Org. Chem.* **2012**, *21*, 9813; d) C. S. Cucinotta, M. Kosa, P. Melchiorre, A. Cavalli, F. L. Gervasio, *Chem. Eur. J.* **2009**, *15*, 7913.
[40] For some reviews, see: a) H. Guo, J. Ma, *Angew. Chem., Int. Ed.* **2006**, *45*, 354; b) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638.

heteroatom bonds can be consecutively formed to give multifunctionalized products, often with several stereogenic centers. The new bonds can be formed in a single mechanistic cycle or can derive from different and independent catalytic cycles. Moreover the catalyst can be involved in the first transformation or can participate in all the reactions that occur in the pot. In this case, the complexity and the stereochemistry of the final product is dependent on each step where the catalyst operates.[41] Combinig more synthetic steps, while avoiding intermediate purifications and separations is a highly appealing strategy. The atom economy, the high efficiency, the reduced times and costs of cascade processes render them very advantageous also in the synthesis of natural products. Towards this direction stereocontrolled construction of carbon- or heterocycles with one or more fused rings has being developed.[42]

In the young area of organocatalyzed cascade processes, covalent catalysis, based on enamine/iminium ion formation from primary or secondary amines as catalysts, is widely represented (Scheme 1.12, a).[43] In contrast, just few examples of non-covalent activation mode can be found, mostly involving chiral phosphoric acid,[44] cinchona-based and Takemoto thioureas[45] (Scheme 1.12, b).

[41] For a clear review on the different types of one-pot reaction, see: N. Shindoh, Y. Takemoto, K. Takasu, *Chem. Eur. J.* **2009**, *15*, 12168.
[42] For a review on organocatalyzed cyclization reaction see: A. Moyano, R. Rios *Chem.Rev.* **2011**, *111*, 4703.
[43] For selected examples, see: a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; b) T. Urushima, D. Sakamoto, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 4588; c) X. Wu, L. Nie, H. Fang, J. Chen, W. Cao, G. Zhao, *Eur. J. Org. Chem.* **2011**, *33*, 6755.
[44] For selected examples, see: a) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem., Int. Ed.* **2006**, *45*, 3683; b) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336; c) M. Rueping, A. P. Antonchick, *Angew. Chem., Int. Ed.* **2008**, *47*, 5836.
[45] For selected examples, see: a) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873; b) C. Yu, Y. Zhang, A. Song, Y. Ji, W. Wang, *Chem. Eur. J.* **2011**, *17*, 770.



Scheme 1.12 Examples of covalent (a) and non-covalent (b) cascade organocatalyzed reactions.

1.6 Research Objectives

Chiral bifunctional organocatalysts have a huge potential to promote, via non-covalent activation, a plethora of organic reactions for the construction of carbon-carbon and carbon-heteroatom bonds in a stereocontrolled fashion. Over the last years, we have assisted to an increasing number of novel transformations catalysed by these promoters coupled with the design of new chiral organocatalysts bearing more effective acid and basic groups.

Among the different reactions available to study, the Michael addition reaction occupies a special place. It offers a great variety of combinations between Michael donors and acceptors to produce highly functionalised chiral molecules. Moreover, tandem processes can be exploited as in Michael initiated ring closure reactions (MIRC) to prepare important chiral cyclic compounds of different nature and sizes such as epoxides, cyclopropanes, aziridines and more.

The main target of this present doctoral work is to develop novel stereoselective methodologies in the area of Michael type reactions and in MIRC approaches by using easily available bifunctional organocatalysts. First of all, commercially available promoters based on classical scaffolds such as L-proline, cinchona alkaloids, amino thioureas will be checked in some selected processes. The synthesis of modified bifunctional organocatalysts is also envisaged by tuning the stereoelectronic features or modifying the chiral backbone and eventually the basic and acidic sites involved in the catalysis. Another goal of the study is working on further derivatization of the chiral products obtained in the asymmetric processes to demonstrate their potential synthetic applications. Finally, being relatively few the reports on the detailed mechanism of the organocatalytic reactions, efforts into clarification of the pathway will be carried out by the

aid of spectroscopic detection or characterization of intermediates and by means of computational methods.

2. ASYMMETRIC EPOXIDATION OF α-CYANOCHALCONES

2.1 Background

The asymmetric synthesis of epoxides is an important goal, gaining attention by many scientists in the last decades.[46] The asymmetric epoxidation reaction has been intensively investigated due to the importance of epoxides as compounds of biological and pharmaceutical interest. Moreover they are desirable targets in organic chemistry because of their high synthetic potential as intermediates and precursors of a wide range of chiral compounds. The asymmetric epoxidation and the further epoxide manipulation frequently constitute the key steps of natural products total synthesis such as (+)-scuteflorin and polyrhacitide A, a polyol obtained through iterative epoxidation, or more recently in the synthesis of heronapyrrole C.[47]

Optically active epoxides can be accessed through a variety of reactions such as the epoxidation of olefins, alkylidenation of carbonyl compounds by ylides, Darzens condensation and they can also be regio- and stereoselectively opened with different carbon and heteroatom based nucleophiles to furnish a great variety of functionalised derivatives.[48]

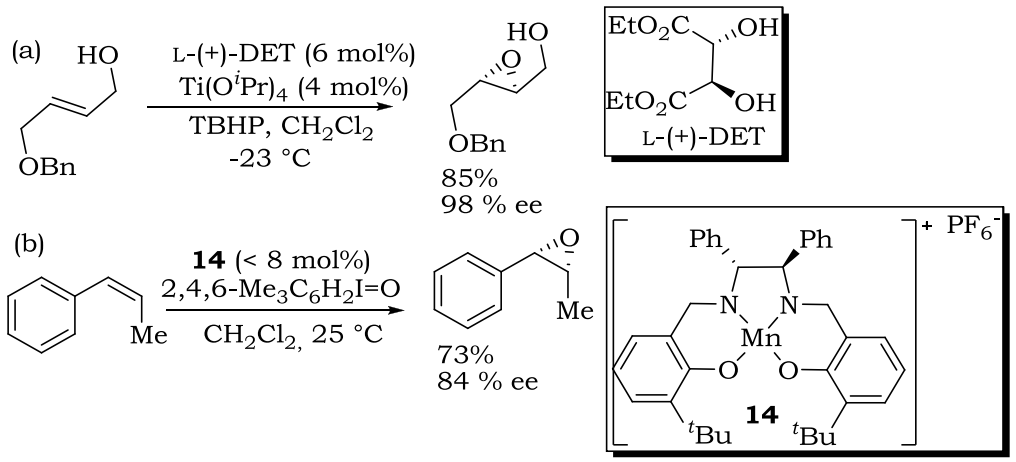
The importance of the epoxidation reaction is demonstrated by the Nobel prize awarded to Sharpless for his contribution in this area, with the asymmetric epoxidation of allylic alcohols mediated by titanium/tartrate

[46] For some reviews on the asymmetric epoxidation, see: a) J. E. Bäckvall, *Modern Oxidation Methods*, Wiley-VCH, Weinheim, **2004**; b) Q.H. Xia, H.Q. Ge, C.P. Ye, Z.M. Liu, K.X. Su, *Chem. Rev.* **2005**, *105*, 1603; c) O. A. Wong, Y. Shi *Chem. Rev.* **2008,** *108,* 3958; d) K. M. Weiß, S. B. Tsogoeva, *The Chemical Record* **2011**, *11*, 18.

[47] a) C. J. Bartlett, D. P. Day, Y. Chan, S. M. Allin, M. J. McKenzie, A. M. Z. Slawin, P.C. B. Page *J. Org. Chem* **2012**, *77*, 772; b) G. Kumaraswamy, A. N. Murthy, K. Sadaiah *Tetrahedron* **2012**, *68*, 3179; c) J. Schmidt, C. B. W. Stark *Org. Lett.* **2012**, *14*, 4042.

[48] *Aziridines and Epoxides in Organic Synthesis*; A. K. Yudin, Ed. Wiley-VCH, Weinheim, **2006**.

system and with *tert*-butyl hydroperoxide (TBHP) as the oxygen source (Scheme 2.1 a).[49] Several metal-based asymmetric epoxidation reactions have been successively developed, the Jacobsen and Katsuki's epoxidation of unfunctionalized alkenes with Mn-Salen complexes represents just one of the most relevant examples (Scheme 2.1 b).[50]



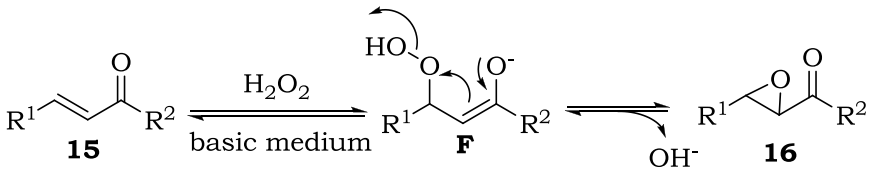
Scheme 2.1 Early stages of the metal-based asymmetric epoxidation of alkenes.

Among the structurally different accessible epoxides, epoxy carbonyl derivatives are an important class of versatile compounds, due to the possible transformations of the epoxide and carbonyl moieties. Indeed, carbonyl compounds and the epoxide ring can be selectively manipulated leading to a wide variety of optically active compounds possibly containing polyoxygenated groups, such as allylic epoxy alcohols, α- or β- hydroxyl ketones, α,β-epoxy esters.[51]

[49] a) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765; b) K. B. Sharpless, *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.
[50] a) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801; b) R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345; c) R. Irie, K. Noda, Y. Ito, T. Katsuki, *Tetrahedron Lett.* **1991**, *32*, 1055.
[51] C. Lauret, *Tetrahedron: Asymmetry* **2001**, *12*, 2359.

2.1.1 *Weitz-Scheffer* Metal-Catalysed Epoxidation

The epoxidation of α,β-unsaturated carbonyl compounds and more generally the epoxidation of electron-poor olefins follows the mechanism proposed by Weitz and Scheffer in 1921 for the epoxidation of the α,β-unsaturated ketone **15** with basic hydrogen peroxide under basic conditions (Scheme 2.2).[52]



Scheme 2.2 Proposed mechanism for the Weitz-Scheffer epoxidation

It involves a conjugate addition of the hydroperoxide anion to substrate **15** forming the β-peroxyenolate intermediate **F**. The following intramolecular ring closure with the elimination of the hydroxyl group allows the epoxy ketone **16** to be formed. This mechanism is different from the concerted addition of a peracid, such as *m*-CPBA, to simple olefins since, in contrast with the concerted addition, the *Weitz-Scheffer* reaction is not stereospecific. Indeed a *trans*/*cis* mixture of isomers can be found, proving the existence of intermediate **F** where rotation around the C_α-C_β bond, before the ring-closure, can occur.

Although its lack of stereospecificity, this reaction has been exploited in several asymmetric variants, where both the diastereo- and the enantioselectivity issues were addressed, relying on the activation of the substrate and/or the peroxide reagent by the catalyst.

The metal-catalysed asymmetric epoxidation of electron-poor alkenes has been widely investigated and a number of methodologies have been

[52] E. Weitz, A. Scheffer, *Chem Ber.* **1921**, *54*, 2327.

developed from the 90s up to now. The most relevant based on Lewis acid-chiral ligand systems are summarized in Figure 2.1.[53]

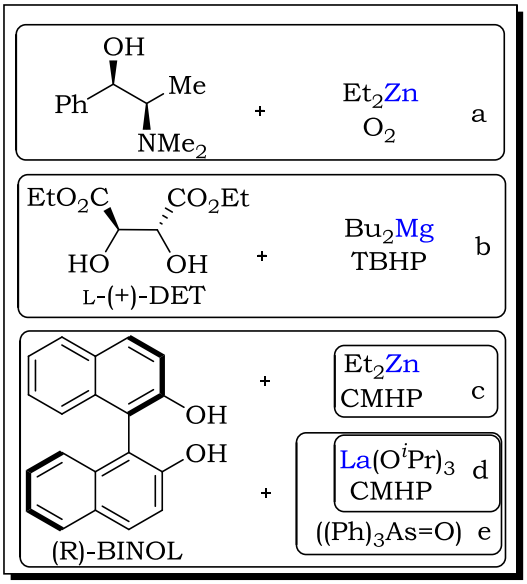


Figure 2.1 Typical Lewis acids with chiral ligands employed in the *Weitz-Scheffer* epoxidation.

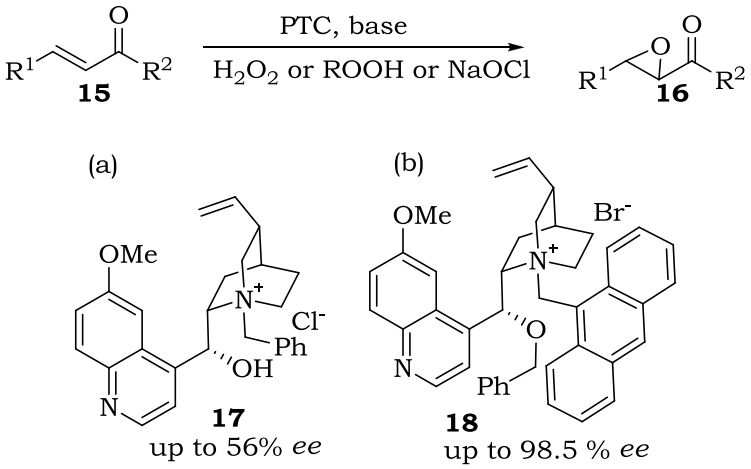
They include zinc-aminoalcohol complexes with molecular oxygen as the oxidant firstly reported by Enders (a), magnesium-L-diethyl tartrate complexes investigated by Jackson (b), 1,1'-bi-naphthol (BINOL) used as ligand both for zinc (c), as investigated by Dötz, and lanthanum systems developed by Shibasaki (d, e). Another variant as the gallium-BINOL system was reported, while the supported-BINOL ligands are employed with ytterbium and lanthanum complexes.[54] Challenging epoxidation reactions of poorly electrophilic α,β-unsaturated amides and esters has

[53] a) D. Enders, J. Zhu, G. Raabe, *Angew. Chem., Int. Ed.* **1996**, *35*, 1725; b) C. L. Elston, R. F. W. Jackson, S. J. F. MacDonald, P. J. Murray, *Angew. Chem., Int. Ed.* **1997**, *36*, 410; c) A. Minatti, K. H. Dötz, *Synlett* **2004**, 1634; d) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329; e) T. Nemoto, H. Kakei, V. Ganadesikan, S.-Y. Tosaki, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2725.
[54] a) R. Chen, C. Qian, J. G. de Vries, *Tetrahedron* **2001**, *57*, 9837; b) D. Jayaprakash, Y. Kobayashi, T. Arai, Q.-S. Hu, X.-F. Zheng, L. Pu, H. Sasai, *J. Mol. Cat. A. Chem.* **2003**, *196*, 145.

been developed by using modified BINOL-samarium or other yttrium complexes.[55]

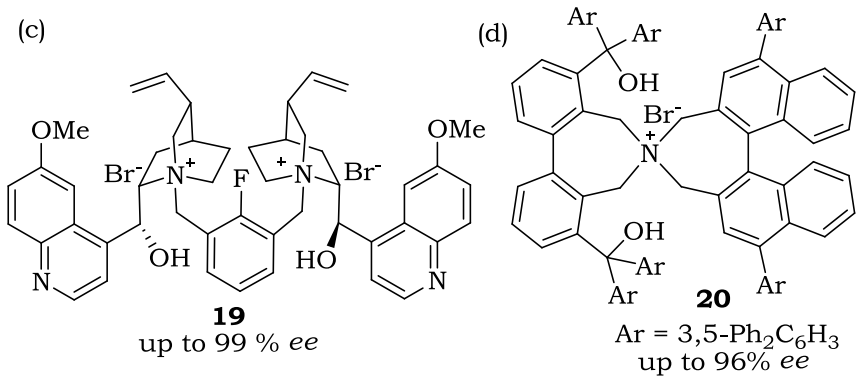
2.1.2 Organocatalyzed Epoxidation of α,β-Unsaturated Carbonyl Compounds

Among the first examples of metal-free methods, the epoxidation of unsaturated carbonyl compounds under phase transfer catalysis (PTC) was introduced by Wynberg in the 70s and afterwards widely investigated. The most representative results obtained with PTC are summarized in Scheme 2.3. Wynberg pioneered the use of quaternary ammonium salt **17** derived from cinchona alkaloids using hydrogen peroxide, alkyl hydroperoxides or sodium hypochloride in biphasic medium.[56]



[55] a) T. Nemoto, H. Kakei, V. Gnanadesikan, S. Tosaki, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14544; b) H. Kakei, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 8962.

[56] a) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering H. Wynberg, *Tetrahedron Lett.* **1976**, *17*, 1831; b) H. Wynberg, B. Greijdanus, *J. Chem. Soc. Chem Commun.* **1978**, 427; c) H. Wynberg, B. Marsman, *J. Org. Chem.* **1980**, *45*, 158; d) H. Plium, H. Wynberg, *J. Org. Chem.* **1980**, *45*, 2498.



Scheme 2.3 PTC in the asymmetric epoxidation of α,β-unsaturated carbonyl compounds.

Highly effective catalysts were developed during the last years including hindered derivatives of quaternized cinchona alkaloids (e.g. the anthracenyl derivative **18**),[57] the dimeric species **19**,[58] and the recently investigated axially chiral quaternary spiro ammonium salt **20** reported by Maruoka.[59]

Chiral crown ethers and guanidinium/urea systems, such as derivative **21** (figure 2.2, a) and C_2-symmetric guanidinium salt **22** (figure 2.2, b),[60] have been investigated as efficient PTC promoters in the asymmetric epoxidation of α,β-unsaturated carbonyl compounds.[61]

[57] a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599; b) E. J. Corey, F.-Y. Zhang, *Org. Lett.* **1999**, *1*, 1287.
[58] S. Jew, J.H. Lee, B.S. Jeong, M.S. Yoo, M.J. Kim, Y.J. Lee, J. Lee, S.H. Choi, K. Lee, M.S. Lah, H.G. Park, *Angew. Chem. Int. Ed.* **2005**, *44*, 1383.
[59] T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844.
[60] M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* **2003**, *44*, 8677.
[61] a) P. Bakó, T. Bakó, A. Mészáros, G. Keglevich, À. Szöllösy, S. Bodor, A. Makó, L. Töke, *Synlett* **2004**, 643; b) K. Hori, M. Tamura, K. Tani, N. Nishiwaki, M. Ariga Y. Tohda, *Tetrahedron Letters* **2006**, *47*, 3115; c) S. Tanaka, K. Nagasawa, *Synlett* **2009**, 667.

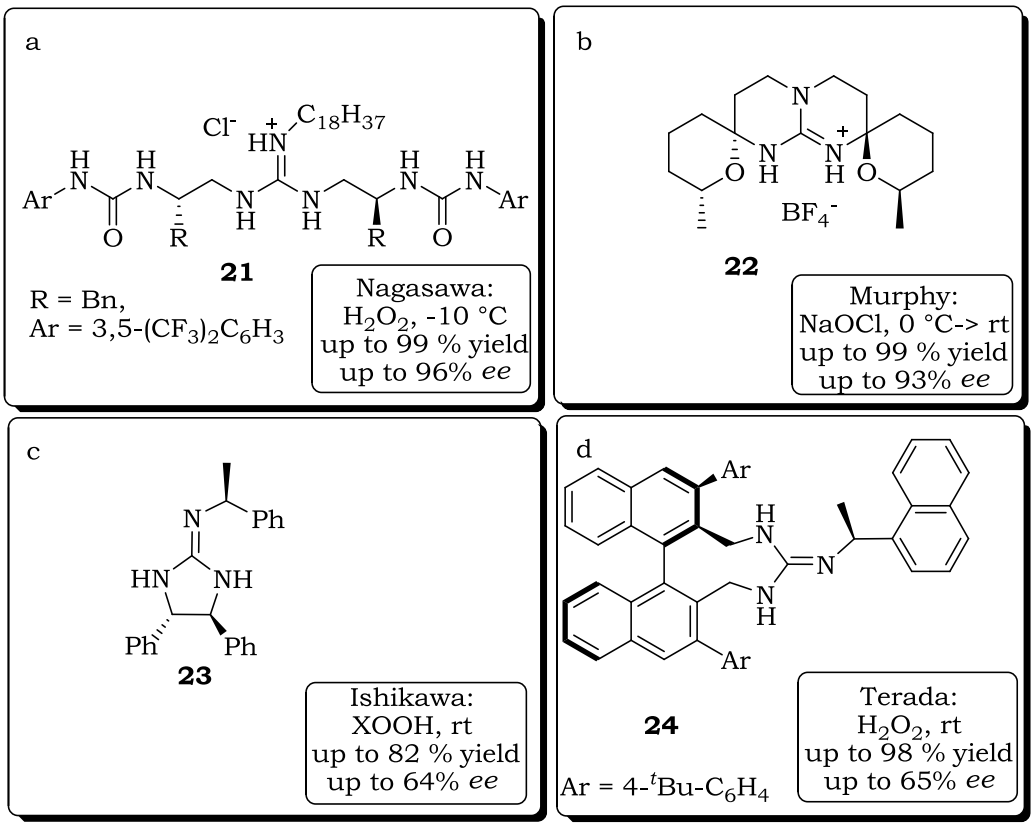
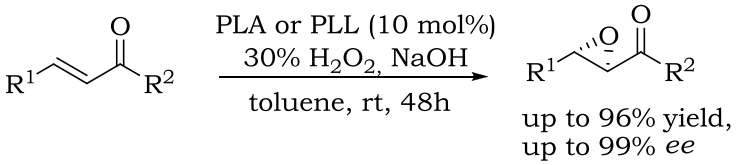


Figure 2.2 Different guanidine catalysts employed in the asymmetric epoxidation of unsaturated ketones.

Strong bases such as guanidine containing compounds have been also applied in the asymmetric epoxidation of α,β-unsaturated ketones with different hydroperoxides as the oxygen source, although inferior level of enantiocontrol was achieved. Compound **23** (figure 2.2, c)[62] and the binaphthyl derivative **24** (figure 2.2, d)[63] are the most representative examples.

[62] T. Ishikawa, T. Isobe, *Chem. Eur. J.* **2002**, *8*, 552.
[63] M. Terada, M. Nakano, *Heterocycles* **2008**, *76*, 1049.

In the 80s Juliá and Colonna disclosed polyamino acids as catalysts for the asymmetric epoxidation of enones.[64] Poly-L-Alanine (PLA) and Poly-L-Leucine (PLL) provided good level of asymmetric induction when used in basic aqueous medium and with hydrogen peroxide as oxidant at room temperature (Scheme 2.4). The optimum efficiency was achieved with the optimized number of 30 amino acids in the chain. Subsequently modified versions of this system and the mechanism of the reaction have been investigated.[46d, 65]



Scheme 2.4 Asymmetric epoxidation of enones promoted by poly amino acids.

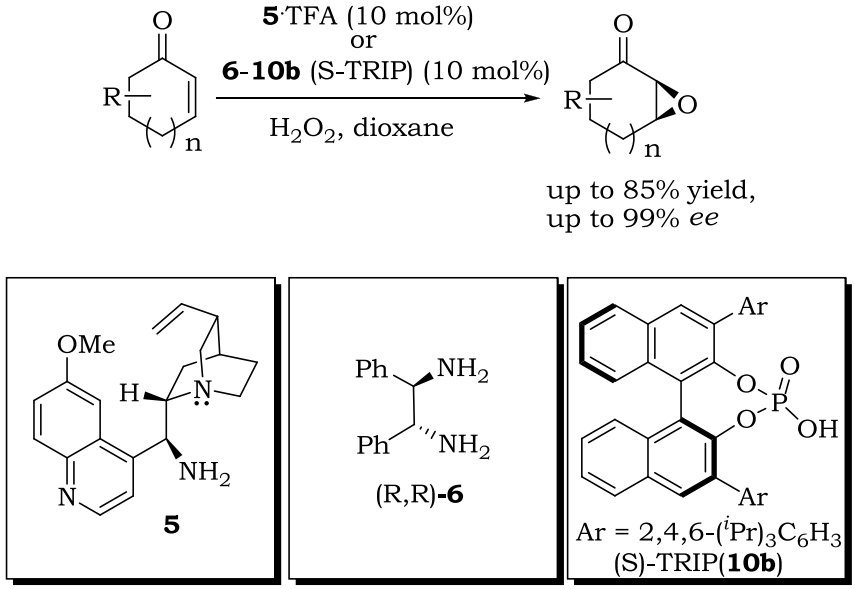
Recently rather challenging aliphatic enones and enals were converted into the corresponding epoxides by chincona derived primary amine catalysts exploiting a covalent regime.

Cyclic enones were successfully epoxidized with the primary amine **5** or exploiting the ACDC tool (Asymmetric Counteranion Directed Catalysis) by means of the salt formed by diamine **6** and chiral phosphoric acid TRIP **10b** (Scheme 2.5).[66]

[64] a) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem., Int. Ed.* **1980**, *19*, 929; b) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317.

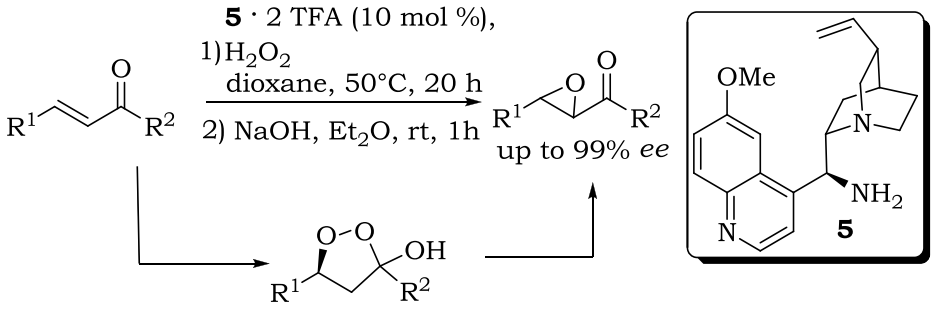
[65] a) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem., Int. Ed.* **1980**, *19*, 929; b) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317.

[66] a) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.,* **2008**, *130*, 6070; b) A. Lee, C. M. Reisinger, B. List, *Adv. Synth. Catal.* **2012**, *354*, 1701.



Scheme 2.5 Asymmetric epoxidation of cyclic enones

Moreover, List and co-workers developed a method based on **5**/TFA/H_2O_2 system which converted aliphatic acyclic ketones into peroxyhemiketals (Scheme 2.6).[67] A basic treatment furnished the corresponding epoxides up to 99% *ee*.

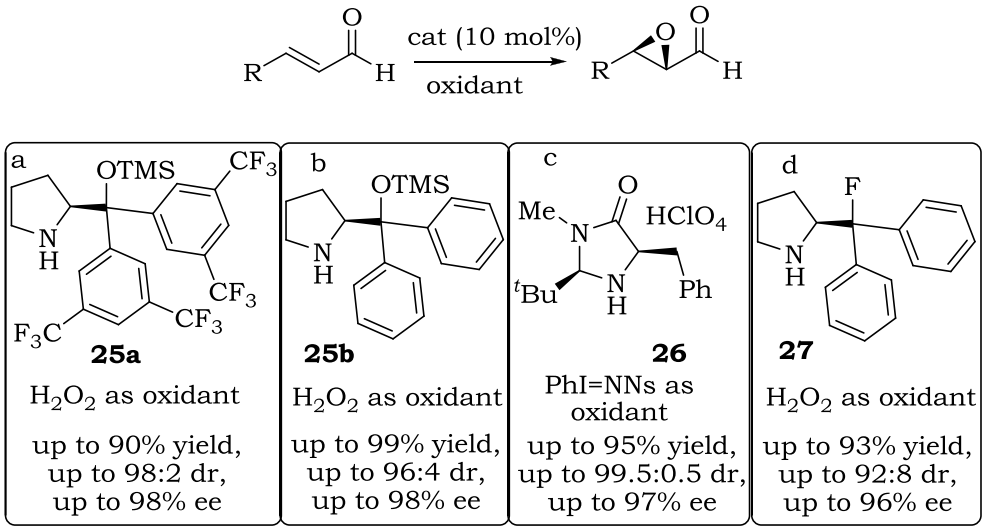


Scheme 2.6 Covalent catalysis in the asymmetric epoxidation of aliphatic enones.

The issue concerning the organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes was faced only recently by Jørgensen and

[67] C. M. Reisinger, X. Wang, B. List, *Angew. Chem., Int. Ed.,* **2008**, *47*, 8112.

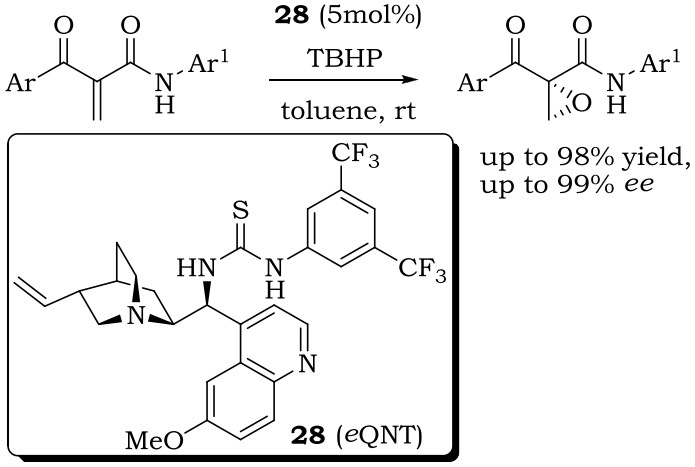
coworkers. In 2005 they demonstrated that the O-TMS protected diaryl pyrrolidinemethanol derivative **25a** furnished the corresponding epoxy aldehydes in good diastereoseletivity and high enantiocontrol using H_2O_2 in dichloromethane at room temperature (Scheme 2.7, a).[68] Córdova and co-workers exploited a similar approach using the O-silylated diphenyl prolinol **25b** (Scheme 2.7, b).[69] Instead MacMillan's group performed the reaction with the imidazolidinone salt **26** and iodosobenzene as oxidant generated *in situ* from the reaction between [(N-Nosylimino)iodo]benzene (PhI=NNs) and acetic acid (Scheme 2.7, c).[70] The fluoro derivative **27** reported by Gilmour and co-workers proved to be an effective catalyst in the epoxidation of α,β-unsaturated aldehyde with H_2O_2 as the oxidant (Scheme 2.7, d).[71]



Scheme 2.7 Asymmetric epoxidation of enals by catalysts **25a**, **25b**, **26** and **27**.

[68] M. Marigo, G. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964.
[69] (a) H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99; (b) G. L. Zhao, I. Ibrahem, H. Sundén, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1210.
[70] S. Lee, D. W. C. MacMillan, *Tetrahedron* **2006**, *62*, 11413.
[71] C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem., Int. Ed.* **2009**, *48*, 3065.

Recently, the asymmetric epoxidation of disactivated terminal olefins to terminal epoxides has been developed by using for the first time cinchona alkaloid based thioureas as promoters with TBHP as the oxidant. The corresponding synthetically useful epoxides, bearing a quaternary stereocenter, were obtained with excellent yield and enantioselectivity (Scheme 2.8).[72]



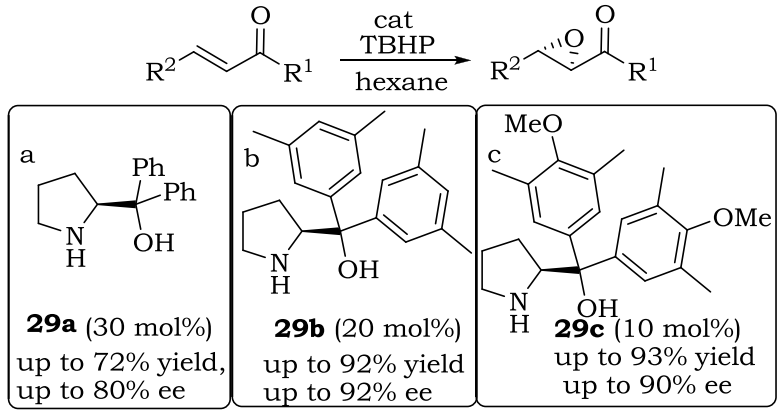
Scheme 2.8 Asymmetric epoxidation of disubstituted terminal olefins promoted by cinchona alkaloid thioureas.

2.1.3 Diaryl Prolinol Catalysed Epoxidation

In 2005, Lattanzi disclosed that easily accessible diaryl prolinols could catalyse the asymmetric epoxidation of α,β-unsaturated carbonyl compounds at 30 mol% loading with TBHP as oxidant in hexane as solvent.[73] The commercially available diphenyl pyrrolidinemethanol **29a** furnished the corresponding epoxy ketones with up to 80% *ee* (Scheme 2.9, a). Further studies demonstrated that electron-donating groups in the aromatic ring of promoters **29b** and **29c** were beneficial for the catalyst activity as attested by the higher yield and enantioselectivity of the

[72] A. Russo, G. Galdi, G. Croce, A. Lattanzi, *Chem. Eur. J.* **2012**, *18*, 6152.
[73] A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579.

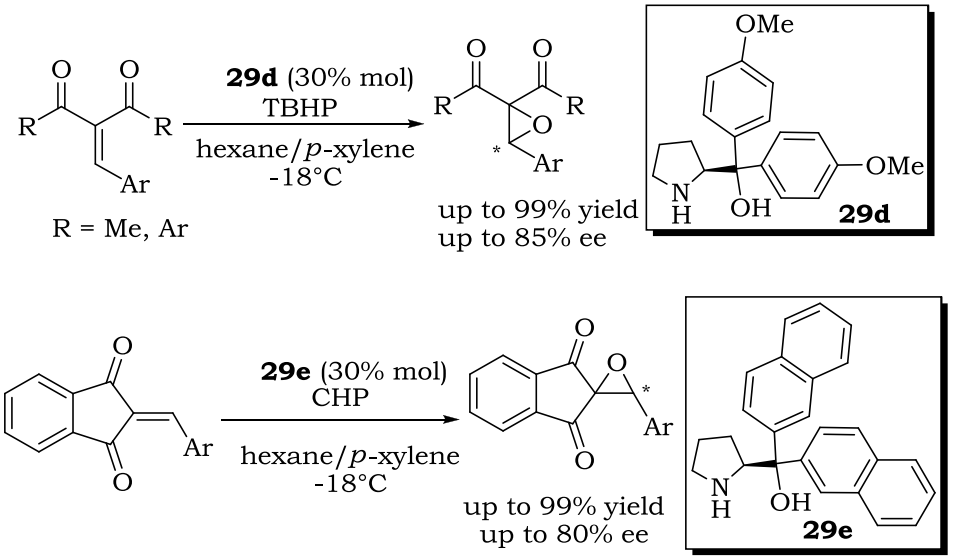
epoxides achieved when working with reduced catalyst loading (Scheme 2.9, b and c).[74]



Scheme 2.9 Asymmetric epoxidation of enones by diarylprolinols.

Trisubstituted electron-poor olefins were also investigated as substrates for the epoxidation reaction mediated by diarylprolinols, such as the acyclic and cyclic 2-arylidene-1,3-diketones, obtaining the epoxides with excellent yields and up to 85% ee (Scheme 2.10).[75]

[74] a) A. Lattanzi, *Adv. Synth. Catal.* **2006**, *348*, 339; b) A. Lattanzi, A. Russo, *Tetrahedron* **2006**, *62*, 12264.
[75] Russo, A.; Lattanzi, A. *Org. Biomol. Chem.*, **2010**, 8, 2633.



Scheme 2.10 Asymmetric epoxidation of some trisubstituted electron-poor olefins.

The mechanism of the nucleophilic epoxidation of simple enones was recently investigated by DFT calculations. From an experimental point of view, the catalytic activity dramatically decreased when passing from hexane to polar and protic solvents. Furthermore, the presence of acidic co-catalysts, which are known to increase the reaction rate when iminium or enamine intermediates are formed, prevented the reaction to occur. A non-covalent mechanism, where the catalyst activates the reagents under general acid and base catalysis was then suggested. Two energetically similar pathways (red and blue in figure 2.3) were calculated with L-diphenyl prolinol **29a** and a *trans*-enone. They show similar features and energetics only differing in the hydrogen bonding coordination pattern of the reagents with the organocatalyst.

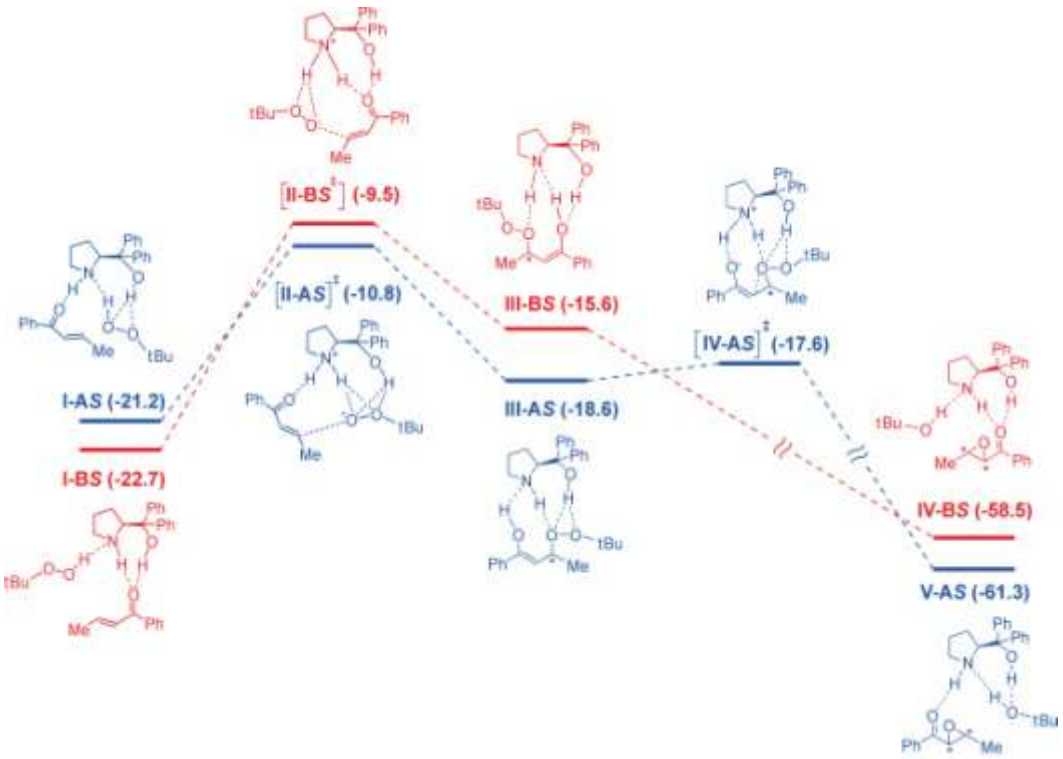


Figure 2.3 Two possible pathways for the asymmetric epoxidation of enones by diphenyl prolinol **29a**.

The ternary complexes evolve via an oxa-Michael addition into the adduct. This process was found to be the rate- and stereoselectivity determining-step. Ring closure of the peroxy adduct was calculated to proceed almost without energetic barrier. This fast ring closure is in agreement with complete control of the diastereoselectivity, as experimentally observed. The most energetically affordable transition state for the oxa-Michael addition would lead, after ring-closure, to the 2*R*,3*S*-configured epoxide as the preferentially formed epoxide, in line with the experimental data.

The feasibility of the non-covalent pathway would be also supported by calculations on the binary hydrogen-bonded complex **G** and the first

intermediate along the covalent pathway such as the hemiaminal **H**, which was found to be 14 kcal/mol higher in energy (Figure 2.4).[76]

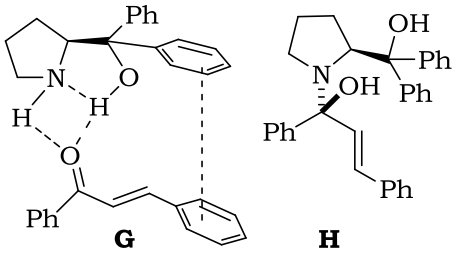
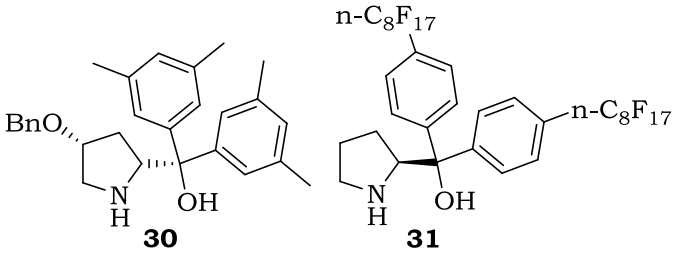


Figure 2.4 Non-covalent binary complex vs hemiaminal.

Other groups reported modified diaryl pyrrolidinemethanol derivatives, such as the 4-*O*-benzyl derivative **30** and catalyst **31** with an alkyl fluorinated chain as substituent on the aromatic ring. They were used in the asymmetric epoxidation of enones furnishing the epoxides in some examples with slightly improved enantioselectivity (Scheme 2.11).[77]



Scheme 2.11 Two structurally similar catalysts for the asymmetric epoxidation of enones.

[76] A. Capobianco, A. Russo, A. Lattanzi, A. Peluso, *Adv. Synth. Cat* **2012**, *354*, 2789.
[77] a) Y. Li, X. Liu, Y. Yang, G. Zhao, *J. Org. Chem.* **2007**, *72*, 288; b) H. Cui, Y. Li, C. Zheng, G. Zhao, S. Zhu, *J. Fluor. Chem.* **2008**, *129*, 45.

2.2 Results and Discussion[78]

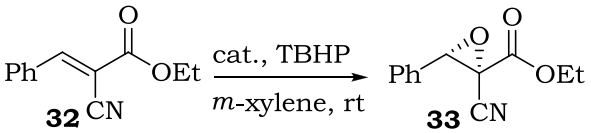
Although the asymmetric epoxidation is a very well-studied reaction, organocatalytic epoxidation of trisubstituted electron-poor olefins has been poorly explored. The introduction of a cyano group as a substituent on the alkene seemed to us particularly appealing owing to the possibility of obtaining diversely functionalized epoxides containing groups amenable to further transformations. Moreover, an ever-increasing number of nitrile-containing compounds can be found in natural products and pharmaceutically active species.[79]

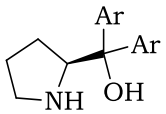
Ethyl α-cyanophenylacrylate **32** was initially chosen as model substrate for the optimization of the epoxidation reaction with diarylprolinols as catalysts (Table 2.1). In the previously optimized conditions, catalysts **29b** and **29e** and TBHP as oxidant, the reaction proceeded smoothly with complete control of the diastereoselectivity, although epoxide **33** was isolated with only 23 and 16 % *ee* (entries 1 and 2). The use of more sterically demanding cumene hydroperoxide (CHP) as oxygen source drastically suppressed the conversion to the product (entry 3).

[78] The results presented in this chapter are partially reported in the paper: C. De Fusco, C. Tedesco, A. Lattanzi, *J. Org. Chem.* **2011**, *76*, 676,

[79] a) T. Nagasawa, H. Yamada, *Pure Appl. Chem.* **1990**, *62,* 1441; b) F.F. Fleming, *Nat. Prod. Rep.* **1999**, 597; c) V. J. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta,* **2005**, *358*, 1; d) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.*, **2010**, *53*, 7902.

Table 2.1 Initial screening of the reaction conditions using model compound **32**.[a]





Ar = 3,5-$(CH_3)_2C_6H_3$ **29b**
Ar = 2-naphthyl **29e**

Entry	Cat.	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	**29b**	19	99	23
2	**29e**	45	99	16
3[d]	**29b**	68	12	37

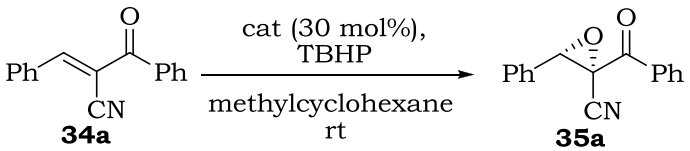
[a] Unless otherwise noted, reactions were carried with **32** (0.1 mmol), TBHP (1.2 equiv), **29** (30 mol%) in 0.5 mL of solvent. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] CHP as the oxidant.

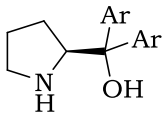
Since compound **32** was found not to be a promising substrate for the reaction, 2-benzoyl-3-phenyl-acrylonitrile **34a** was then tested.

Differently substituted diarylprolinols were screened as catalysts in the epoxidation reaction of 2-benzoyl-3-phenyl-acrylonitrile **34a** with TBHP as the oxygen source in methylcyclohexane at room temperature. As summarized in Table 2.2, all catalysts could smoothly promote the reaction to give product **35a** as a single diastereoisomer, as judged by the ^{1}H-NMR of the crude mixture, in quantitative yield in most of the cases. As expected, the enantioselectivity was strongly influenced by the substituents on the aromatic rings of the catalysts. The α,α-diphenyl prolinol **29a** afforded the product with poor *ee* value (entry 1). The

dimethyl substituted diaryl prolinol **29b** was confirmed to be the best catalyst in terms of reactivity and asymmetric induction, furnishing the product in 56 % *ee* (entry 2).

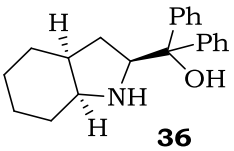
Table 2.2. Screening of the catalysts in the asymmetric epoxidation of the model substrate **34a**.[a]



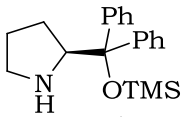


29

29a Ar = Ph
29b Ar = 3,5-$(CH_3)_2C_6H_3$
29d Ar = 4-$MeOC_6H_4$
29e Ar = 2-naphthyl
29f Ar = 4-^{t}BuC_6H_4



36



25b

Entry	cat	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	**29a**	3	99	21
2	**29b**	3	94	56
3	**29d**	6	88	43
4	**29e**	3	97	48
5	**29f**	3	99	36
6	**36**	4	99	2
7	**25b**	4	99	rac

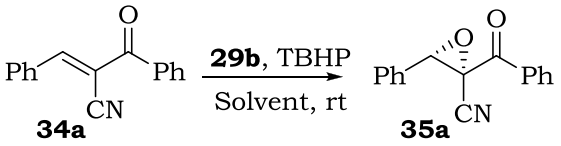
[a] Unless otherwise noted, reactions were carried with **34a** (0.1 mmol), TBHP (1.2 equiv), cat (30 mol%) in 0.5 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

The *para*-substituted derivatives **29d** and **29f** and the naphthyl derivative **29e** furnished the product in moderate enantioselectivity (entries 3-5),

whereas the bicyclic derivative **36** proved to be completely unselective (entry 6). In order to prove that the hydroxyl group of the catalyst was fundamental for the reaction to proceed in a stereocontrolled fashion, the Hayashi-Jørgensen catalyst **25b** was tested and the epoxide was isolated in quantitative yield although in racemic form (entry 7).

A solvent screening was then performed with catalyst **29b** (Table 2.3).

Table 2.3 Solvent screening.[a]



34a **35a**

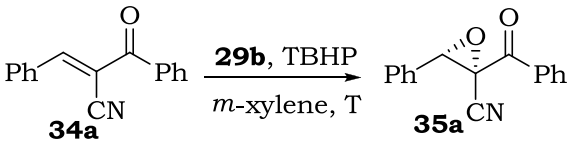
entry	Solvent	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	Hexane	3	99	54
2	$CHCl_3$	6	96	48
3	Toluene	3	99	57
4	ClC_6H_5	3	99	60
5	$CF_3C_6H_5$	3	99	58
6	*p*-xylene	3	97	63
7	*m*-xylene	3	99	64

[a]Unless otherwise noted, reactions were carried with **34a** (0.1 mmol), TBHP (1.2 equiv), **29b** (30 mol%) in 0.5 mL of solvent. [b]Isolated yield. [c]Determined by HPLC analysis.

The epoxide was always isolated in quantitative yield and, as expected for a non-covalent activation mode, non-polar solvents guaranteed higher enantioselectivity. Xylenes were found to be the best media (entries 6 and 7) and *m*-xylene was chosen for further optimization studies.

Other parameters were examined to optimise the reaction conditions as shown in Table 2.4.

Table 2.4 Optimization of reaction parameters.[a]



entry	T	Conc. (M)	29b (mol %)	*t* (h)	yield (%)[b]	*ee* (%)[c]
1[d]	rt	0.2	30	17	69	47
2	rt	0.1	30	5	99	63
3	-20 °C	0.1	10	20	90	77
4	-20 °C	0.05	10	18	99	78
5	-20 °C	0.05	5	18	88	71
6	-25 °C	0.05	10	24	99	76
7	-30 °C	0.2	20	48	99	74
8[e]	-60 °C	0.2	10	60	99	73

[a]Unless otherwise noted, reactions were carried with **34a** (0.1 mmol), TBHP (1.2 equiv), **29b** (30 mol%) solvent (0.5 mL). [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis on a chiral stationary phase. [d]CHP employed as the oxidant. [e]The reaction medium was a mixture of toluene/*m*-xylene 1/3.

Cumene hydroperoxide (CHP) proved to be a poor alternative to TBHP in terms of yield and enantioselectivity (entry 1). The reaction carried out under more diluted conditions did not improve the performance of the catalyst at room temperature (entry 2) but, pleasingly, the reaction performed at -20°C with reduced catalyst loading (10 mol%) and at 0.1 or 0.05 M concentration, led to the formation of epoxide **35a** in excellent yield and up to 78% ee (entries 3 and 4). Decreasing the catalyst amount to 5 mol% under similar conditions slightly affected the efficiency of the process (entry 5).

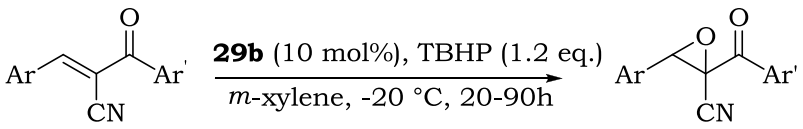
A small drop in the enantioselectivity was observed when working at -25° and -30°C, even increasing the catalyst loading and the concentration (entries 6-7). An experiment performed at -60 °C with a mixture of toluene and *m*-xylene allowed to obtain the product in quantitative yield but only in 73% *ee* (entry 8).

Under the optimized conditions, the scope of the reaction of *trans*-α-carbonyl-β-substituted acrylonitriles, easily synthesized via Knoevenagel condensation,[80] was investigated. In all the examples, the *trans*-epoxide was formed exclusively in high to excellent yield and good enantiocontrol with both electron-rich and electron-poor phenyl substituted derivatives (Table 2.5).

The *ortho*-substitution had a detrimental effect on the stereoselectivity (entry 3), while the introduction of a naphthyl ring led to the product **35f** with 77% *ee* (entry 6). The heteroaromatic and *trans*-cinnamyl alkenes **34g** and **34h** afforded the products in 81 and 84 % *ee*, respectively (entries 7 and 8). Alkenes bearing a β-alkyl group such as compound **34l** were epoxidized with lower enantiocontrol (entry 12). Interestingly, the α-acetyl derivative, **34m**, afforded the epoxide with good enantioselectivity (entry 13).

[80] J. S. Yadav, B.V. Subba Reddy, A. K. Basak, B. Visali, A.V. Narsaiah, K. Nagaiah, *Eur. J. Org. Chem.* **2004**, 546.

Table 2.5 Substrate scope of the epoxidation of *trans*-α-carbonyl-β-substituted acrylonitriles.



34 **35**

Entry	Ar	Ar'	35	Yield(%)[b]	*ee* (%)[c]
1	Ph	Ph	**a**	99 (70)	78 (94)
2	Ph	4-^{t}BuC$_6$H$_4$	**b**	92	73
3	Ph	2-CH$_3$C$_6$H$_4$	**c**	77	57
4	Ph	4-BrC$_6$H$_4$	**d**	99 (67)	76 (99)
5	Ph	4-CNC$_6$H$_4$	**e**	99	70
6	Ph	2-naphthyl	**f**	96	77
7	Ph	3-furyl	**g**	99	81
8	Ph	*trans*-cinnamyl	**h**	78	84
9	3-ClC$_6$H$_4$	Ph	**i**	99	73
10	4-CH$_3$OC$_6$H$_4$	Ph	**j**	99 (60)	79 (>99)
11	4-CH$_3$OC$_6$H$_4$	4-BrC$_6$H$_4$	**k**	99	79
12	Ph	Cyclohexyl	**l**	95	48
13	Me	Ph	**m**	90	83

[a] Conditions: **34** (0.2 mmol), TBHP (1.2 equiv), **29b** (10 mol%) *m*-xylene (4 mL). [b] Isolated yield after flash chromatography; in parenthesis yield after crystallization. [c] Determined by HPLC analysis on a chiral stationary phase; in parenthesis *ee* after crystallization.

A single crystallization performed by using hexane/isopropanol mixture allowed to obtain epoxides up to 99% *ee*. X-ray analysis performed on a single crystal of the bromo-derivative **35d** led to the determination of the

absolute configuration as 2*R*,3*S* (Figure 2.5). The absolute configuration for all other compounds **35** was assigned by analogy.

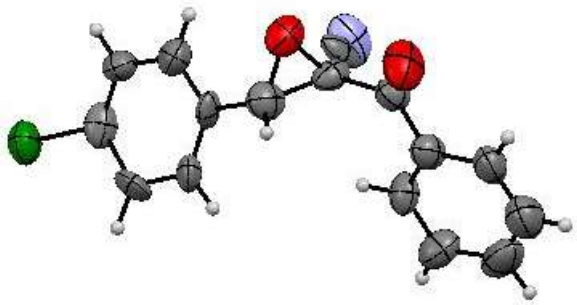


Figure 2.5 Crystallographic structure of the bromo derivative **35d** determined by X-ray analysis.

The stereochemical outcome of the reaction is consistent with that previously observed in the epoxidation of *trans*-disubstituted-α,β-enones mediated by the same system and supported by DFT calculations. [74,76] The proposed transition state for the oxa- Michael addition step of TBHP to *trans*-α-benzoyl-β-aryl-acrylonitriles promoted by the diaryl prolinol **29b** is depicted in Figure 2.6.

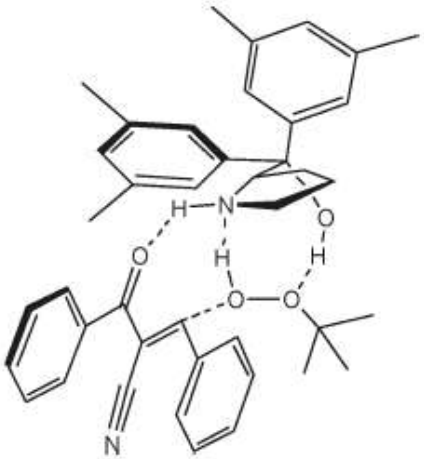
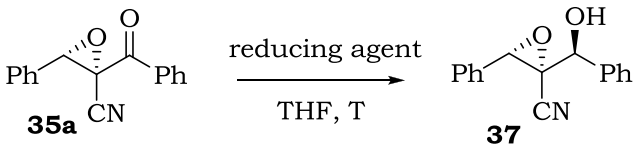


Figure 2.6 Proposed transition state for the oxa-Michael addition step of the epoxidation of *trans*-α-benzoyl-β-aryl-acrylonitriles.

To demonstrate the synthetic utility of epoxides **35**, reduction of the carbonyl moiety of epoxide **35a** was studied in order to obtain the corresponding α,β-epoxy alcohol **37**. This is a challenging product, not easily accessible by using the alternative approach based on the asymmetric Sharpless epoxidation of the corresponding electron-poor allylic alcohol. Indeed, few examples are reported in which cyano allylic alcohols have been epoxidized employing the system $Ti(O^iPr)_4$/(L)-DET/TBHP under stoichiometric conditions.[81]

Different reducing agents afforded the product with variable level of diastereoselectivity (Table 2.6).

Table 2.6 Screening of the reducing agents.[a]



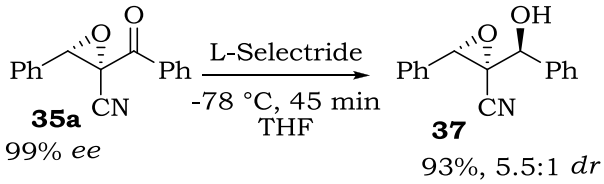
entry	reducing agent	T (°C)	*t* (min)	*dr*[b]
1[c]	$NaBH_4$	0	40	1.5:1
2	K-selectride	-30	90	2.5:1
3	K-selectride	-78	90	4.5:1
4	L-selectride	-78	60	5.5:1
5	DIBAL	-78	24 h	3.5:1[d]

[a] Unless otherwise noted, reactions were performed with **35a** (0.1mmol) and the reducing agent (0.1 mmol) in dry THF (0.05M) at -78 °C. The data are given for full conversion monitored by TLC. [b] determined via ^{1}H-NMR analysis on the crude mixture. [c] reaction performed in Et_2O/MeOH 1:3 as solvent mixture. [d] low conversion.

As expected less sterically demanding $NaBH_4$ provided the product in low diastereocontrol (entry 1). A slight improvement of the diastereoisomeric

[81] M. Aiai, A. Robert, M. Baudy-Floc'h, P. Le Grel, *Tetrahedron: Asymmetry* **1995**, *6*, 2249.

ratio was achieved using K-selectride at -30 °C (entry 2). Decreasing the temperature to -78°C led to the product as a 4.5:1 isomeric mixture (entry 3). Changing the counterion of the reducing agent from K^+ to Li^+ the product was isolated in 5.5/1 dr (entry 4). The reduction proceeded slugghishly when employing DIBAL (entry 5). The final reduction reaction was carried out with L-selectride in THF at -78 °C and the desired epoxyalcohol **37**, containing three contiguous stereocentres, was obtained with 93% yield and good diastereoisomeric ratio (Scheme 2.12).



Scheme 2.12 Diastereoseletive reduction of compound **35a**.

Both diastereoisomers were determined to have 99% *ee*. The *anti*-isomer was supposed to be preferentially obtained *via* a chelated cyclic transition state according to the Cram chelation model as previously reported in the reduction of differently substituted α,β-epoxy ketones with hydrides.[51]

2.3 Conclusion

The first stereoselective method for the epoxidation of *trans*-α-carbonyl-β-substituted acrylonitriles has been developed by using the easily available diaryl prolinol/TBHP system. The functionalised epoxides, bearing two contiguous stereocentres, one being quaternary, were obtained in excellent yields, as a single diastereoisomer and up to 84% ee. Enantioselectivity up to 99% could be achieved by a single crystallization and the absolute configuration of epoxides was assigned by X-ray analysis. Reduction of the carbonyl group led to the desirable epoxy

alcohol, bearing three contiguous stereocenters, with high yield and good diastereoselectivity.

3. AN ASYMMETRIC NITRO MICHAEL ADDITION: A PECULIAR SOLVENT EFFECT

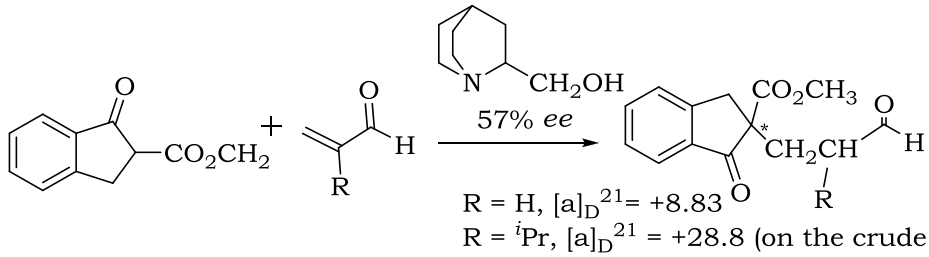
3.1 Introduction

The Michael-type reaction is the conjugate addition of carbon or heteroatom based nucleophiles to electron-deficient olefins and it represents one of the most powerful strategies to form C-C and C-heteroatom bonds. The impact of this reaction is evident by the huge number of examples in which it has been applied as strategic key-step in total synthesis.[82] Asymmetric Michael and hetero-Michael reactions, promoted by a variety of organocatalysts, have been extensively exploit in one-step or multi-step reactions, creating stereogenic centres in compounds then possibly subjected to other transformations.[83] Some carbon nucleophiles include β-ketoesters, malonates, and β-cyanoesters giving rise to products containing a highly useful 1,5-dioxygenated pattern, when using α,β-unsaturated carbonyl compounds as the Michael acceptors. The first example of an organocatalytic Michael addition was performed by Långström and Bergson by using enantioenriched (57% *ee*) 2-(hydroxymethyl)-quinuclidine which catalysed the reaction between β-

[82] For selected examples, see: a) O. Andrey, A. Vidonne, A. Alexakis, *Tetrahedron Letters* **2003**, *44*, 7901; b) P. Jakubec, D. M. Cockfield, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 16632; c) H. Mitsunuma, M. Shibasaki, M. Kanai, S. Matsunaga, *Angew. Chem., Int. Ed.* **2012**, 51, 5217; d) K. L. Jensen, C. F. Weise, G. Dickmeiss, F. Morana, R. L. Davis, K. A. Jørgensen, *Chem. Eur. J.* **2012**, *18*, 11913; d) W. Zi, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2012**, *134*, 9126.

[83] For some general reviews on the asymmetric Michael reaction, see: a) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; b) N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171. For some reviews on organocatalyzed Michael addition, see: a) N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; b) J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; c) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, *14*, 2065; d) Catalytic Asymmetric Conjugate Reactions, ed. A. Córdova, Wiley-VCH, Weinheim, **2010**.

ketoesters and α-substituted acrolein furnishing an optically active compound (Scheme 3.1).[84]



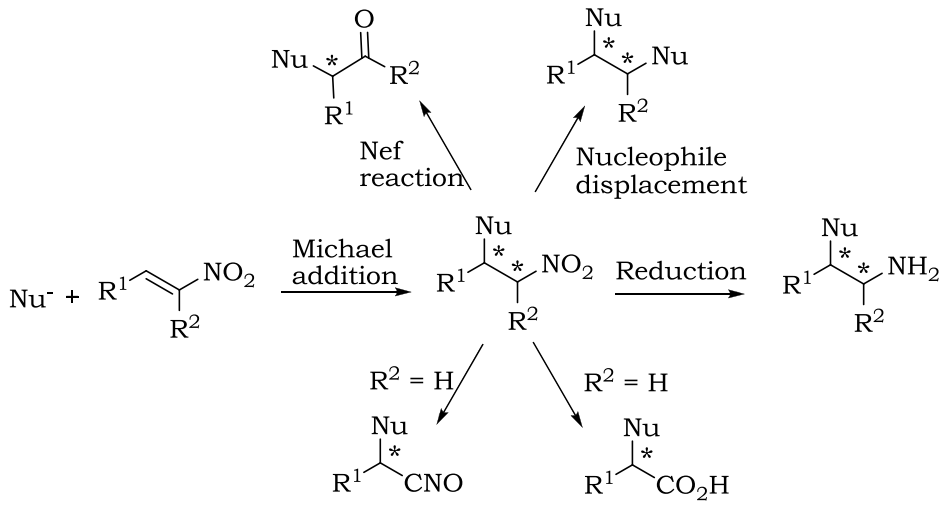
Scheme 3.1 First Michael addition, reported by Långström and Bergson.

Given the large number of organocatalytic asymmetric Michael addition reactions reported, only some classes will afterwards be cited.

3.1.1 Nitro-Michael Reaction

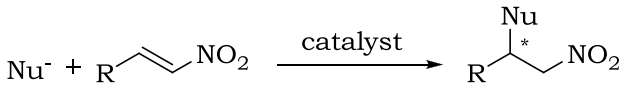
One of the most studied Michael reactions is the addition of easily enolizable carbonyl compounds to nitroolefins, due to the high versatility of the nitro group in organic synthesis and the possibility to obtain enantioenriched, densely functionalized products (Scheme 3.2).[85]

[84] B. Långström, G. Bergson, *Acta Chem. Scand.* **1973**, *27*, 3118.
[85] For general reviews on transformations of nitro functionality, see: a) A. G. M. Barrett, G. G. Graboski, *Chem. Rev.* **1986**, *86*, 751; b) R. Ballini, A. Palmieri, P. Righi, *Tetrahedron* **2007**, *63*, 12099; c) I. N. Ono, *The Nitro Group in Organic Synthesis*; Wiley-VCH, Weinheim, **2001**.



Scheme 3.2 Some examples of the transformations that the nitro group can undergo.

A variety of nucleophiles was added to nitroolefins employing different organocatalysts, thus affording differently substituted nitroalkanes, as exemplified in Scheme 3.3.[86]



Scheme 3.3 Generic scheme for the Michael addition to nitroalkenes

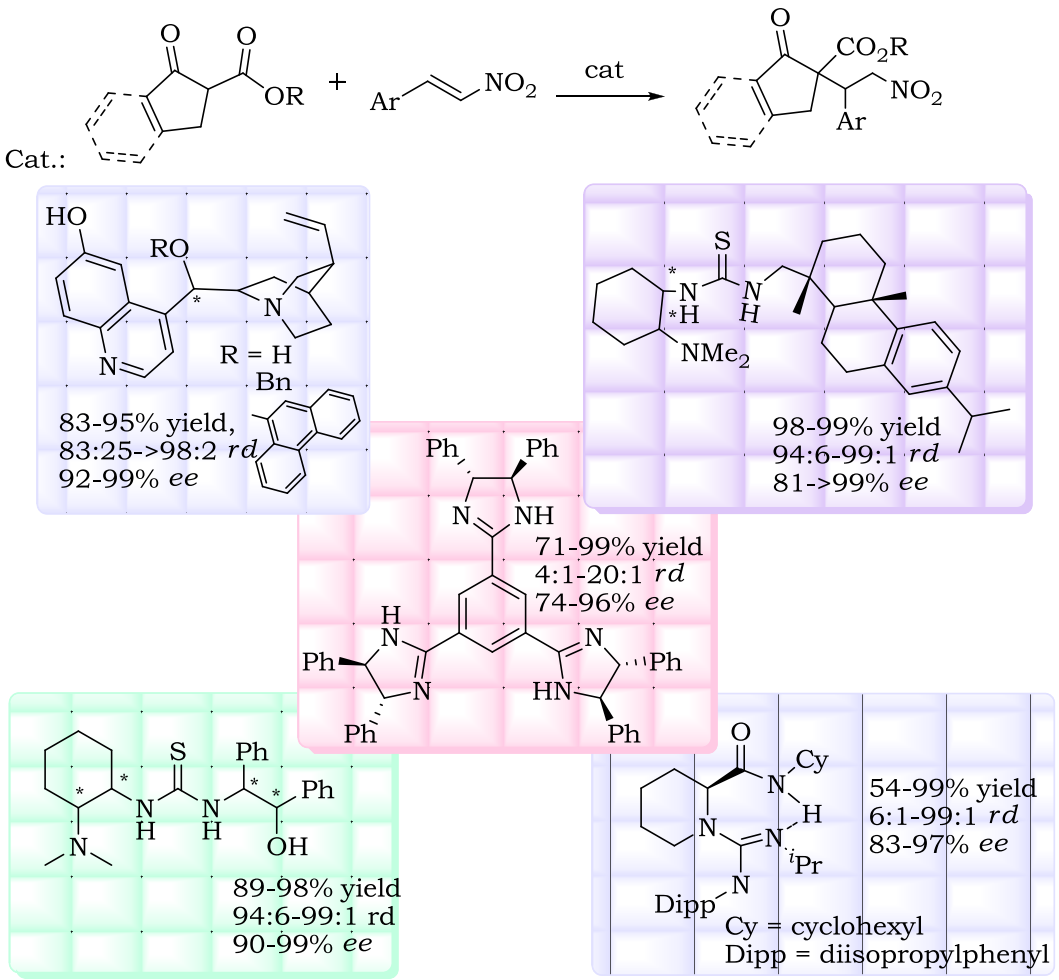
Primary amine catalysts were employed in the nitro-Michael addition of ketones by Córdova and co-workers,[87] and several pyrrolidine-derivatives, such as morpholinomethyl-pyrrolidine,[88] pyrrolidine-pyridine[89] or bipyrrolidine were also developed.[90] Examples of amino thiourea

[86] For some reviews on nitro-Michael addition, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, *11*, 1701; c) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561.
[87] Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460.
[88] J. M. Betancort, C. F. Barbas, *Org. Lett.,* **2001**, *3*, 3737.
[89] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558.
[90] O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147.

derivatives can be found in the literature, installed on a BINOL scaffold,[91] on a cinchona alkaloid[92] or on a cyclohexandiamine also known as Takemoto catalyst.[93] Structural developments on the catalyst and reaction parameters for this process were intensively investigated. Barbas and co-workers explored the possibility to perform the reaction in brine[94] or chiral ionic-liquids were reported as effective organocatalysts.[95] TMS-protected diphenyl prolinol **25b** was employed by Hayashi and co-workers in the addition of acetaldehyde to different nitrostyrenes affording the products with good yield and high enantioselectivity.[96]

In the past five years, many research groups studied the addition of cyclic β-keto esters to nitroolefins using catalysts, such as amino thioureas, cinchona alkaloids and cinchona-based thioureas, imidazole derivatives and guanidines (Scheme 3.4).[97]

[91] J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.*, **2005**, *7*, 4713.
[92] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.*, **2005**, 4481.
[93] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.,* **2003**, *125*, 12672.
[94] N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, *J. Am. Chem. Soc*, **2006**, *128*, 4966.
[95] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng*, Angew. Chem., Int. Ed.* **2006**, *45*, 3093.
[96] Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem., Int. Ed.*, **2008**, *47*, 4722.
[97] a) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105; b) Z. Zhang, X. Dong, D. Chen, C. Wang, *Chem. Eur. J.* **2008**, *14*, 8780; c) X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.* **2009**, *74*, 5562; d) K. Murai, S. Fukushima, S. Hayashi, Y. Takahara, H. Fujioka, *Org. Lett.* **2010**, *12*, 964; e) Z. Yu, X. Liu, L. Zhou, L. Lin, X. Feng, *Angew. Chem., Int. Ed.* **2009**, *48*, 5195.

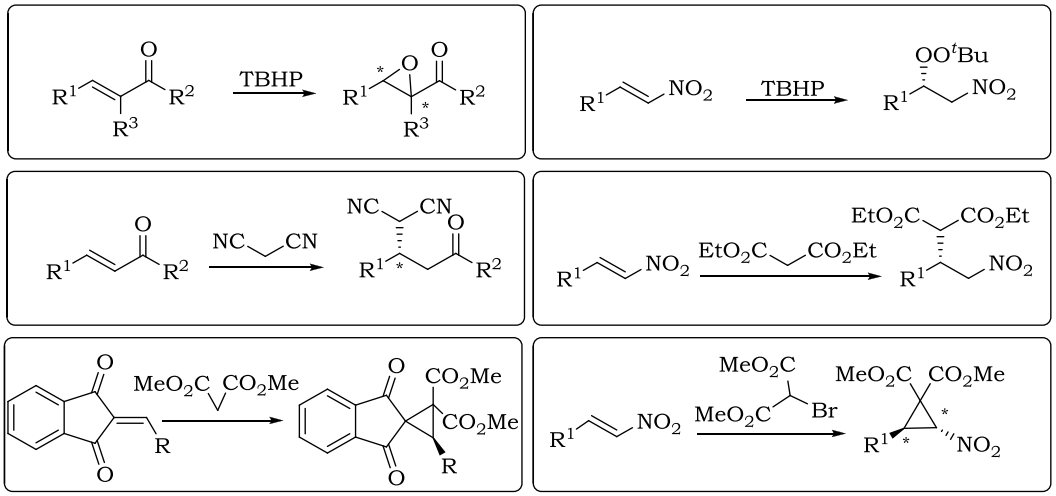


Scheme 3.4 Addition of β-ketoesters to nitroolefines promoted by different catalysts.

In this contest, we became interested in studying the same reaction by using easily accessible or commercially available diaryl prolinols as catalysts. These bifunctional organocatalysts were found to be suitable catalyst for different Michael type and MIRC (Michael Initiated Ring Closure) reactions.[98] According to the different carbon or oxygen-based nucleophiles and the Michael acceptor, epoxides, acyclic peroxides,

[98] For a review on diaryl prolinols see: 39b

cyclopropanes, nitroalkanes and β-substituted carbonyl compounds could be isolated with moderate to good enantiocontrol (Scheme 3.5).[99]



Scheme 3.5 Michael addition reactions catalysed by diaryl prolinols.

The authors suggested a non-covalent activation of the reagents provided by the secondary amine and the hydroxyl group of the diarylprolinol as general acid and base catalysis, which was in some examples[99f] supported by DFT calculations.

The efficiency of a catalytic system is strongly dependent on the reaction medium, in particular when a non-covalent activation mode of the reagents is involved. Solvents able to preserve the network of non-covalent interactions established among the catalyst and the reagents (ion pairs and hydrogen bonding) are essential for the formation of conformationally rigid and more effective systems. Finding a systematic solvent effect or the individuation of a universal efficient solvent is unrealistic. Nevertheless, discovering and giving a rationale for solvent dependent enhancements on

[99] a) A. Lattanzi, *Tetrahedron: Asymmetry* **2006**, *17*, 837; b) A. Russo, A. Lattanzi, *Adv. Synth Cat.* **2008**, *350*, 1991; c) A. Russo, A. Lattanzi, *Synthesis* **2009**, *9,* 1551; d) A. Russo, A. Lattanzi, *Tetrahedron: Asymmetry* **2010,** 211155; e) A. Russo, S. Meninno, C. Tedesco, A. Lattanzi, *Eur. J. Org. Chem.* **2011**, 5096; f) A. Russo, A. Capobianco, A. Perfetto, A. Lattanzi, A. Peluso, *Eur. J. Org. Chem.* **2011**, 1922.

the reaction efficiency and stereoselectivity is a particularly important issue. Recently, some aromatic fluorinated solvents showed to positively affect the Ru-catalysed olefin metathesis in terms of rate enhancement and regiocontrol. In just one example the enantioselectivity was positively affected by the employment of the hexafluorobenzene.[100] The origin of these effects was ascribed to π-π interactions between the solvent and the catalyst or direct fluorine-ruthenium interactions.

3.2 Results and Discussion[101]

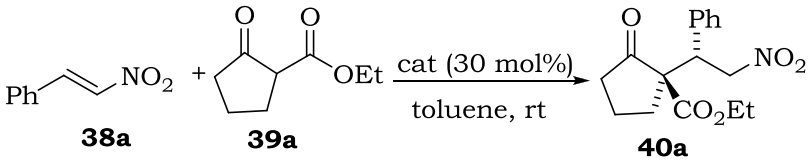
A preliminary screening of commercially or easily available diaryl prolinols and derivatives as catalysts was carried out in the Michael addition of model β-ketoester **39a** to nitrostyrene **38a** (Table 3.1).

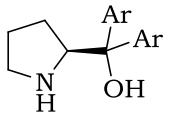
High yields, but only low to moderate diastereoselectivity and enantioselectivity for the major diastereoisomer were generally observed in toluene as solvent.

[100] a) C. Samojlowicz, M. Bieniek, A. Zarecki, R. Kadyrov, K. Grela, *Chem. Commun.*, **2008**, 6282; b) D. Rost, M. Porta, S. Gessler, S. Blechert, *Tetrahedron Lett.* **2008**, *49*, 5968; c) C. Samojlowicz, M. Bieniek, A. Pazio, A. Makal, K. Woźniak, A. Poater, L. Cavallo, J. Wójcik, K. Zdanowski, K. Grela, *Chem. Eur. J.* **2011**, 17, 12981; d) C. Samojlowicz, E. Borré, M. Mauduit, K. Grela, *Adv. Synth. Catal.* **2011**, *353*, 1993; e) A. Grandbois, S. K. Collins, *Chem. Eur. J.* **2008**, *14*, 9323.

[101] The results presented in this chapter are partially reported in the paper: A. Lattanzi, C. De Fusco, A. Russo, A. Poater, L. Cavallo *Chem. Commun.* **2012**, *48*, 1650.

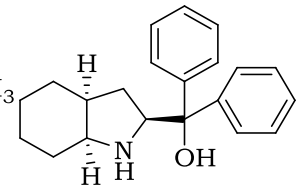
Table 3.1 Catalyst screening in the addition of model ketoester **39a** to nitrostyrene **38a**.[a]



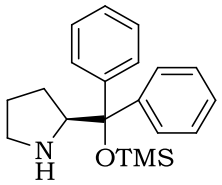


29

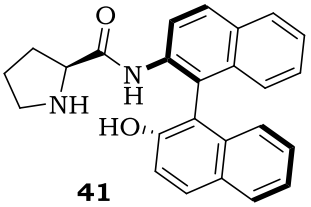
29a Ar = Ph
29b Ar = 3,5-$(CH_3)_2C_6H_3$
29d Ar = 4-$MeOC_6H_4$
29e Ar = 2-naphthyl
29f Ar = 4-^{t}BuC_6H_4



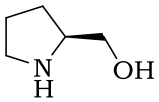
36



25b



41



42

Entry	cat.	t (h)	yield (%)[b]	*dr*[c]	*ee* (M)[d]	*ee* (m)[d]
1	**29a**	18	91	3:1	28	54
2	**29b**	16	80	4:1	12	50
3	**29d**	32	95	5:1	6	38
4	**29e**	17	>99	4.5:1	16	50
5	**29f**	17	98	4:1	50	40
6	**36**	55	87	3.5:1	60	42
7	**41**	40	94	4.5:1	32	26
8	**42**	3	99	4:1	4	14
9	**25b**	36	-	-	-	-

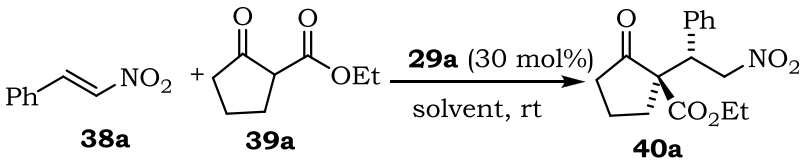
[a] All reactions were performed at C 0.5 M in toluene at 0.2 mmol scale of **38a** and **39a**. [b] Yield of isolated product. [c] The diastereoisomeric ratio was determined by ^{1}H NMR analysis on the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase.

When employing the commercially available catalysts **29a**, **29b** and **29e** the yields were good, but the enantioselectivity was only up to 30% *ee* for the major diastereoisomer (entries 1, 2 and 4). Lower stereoselectivity was observed with catalyst **29d** (entry 3), whereas the product was obtained with promising 50% and 60 % *ee*, when using more hindered catalysts **29f** and bicyclic derivative **36** (entries 5 and 6). NOBIN-prolinamide **41** could smoothly promote the reaction but without any improvement in the enantioselectivity (entry 7). Simple pyrrolidine methanol **42** led to a severe loss of stereoselectivity although the reactivity was preserved (entry 8). Interestingly, the Jørgensen-Hayashi catalyst **25b** showed to be completely inactive, possibly due to the sterically hindered structure and the absence of the free OH group (entry 9).

In order to improve the level of stereocontrol, a solvent screening using diphenyl prolinol **29a** was then carried out (Table 3.2).

All the solvents afforded the product in almost quantitative yield. Aromatic and/or apolar solvents such as benzene, chlorobenzene, *m*-xylene and *n*-hexane were found to be similar to toluene in terms of stereocontrol (entries 1-5). Chloroform and acetonitrile proved to be unsuccessful (entries 6 and 7), whereas moving to ethereal solvents (THF, diethyl and di-*n*-butyl ether) a remarkable effect was noted since an improved enantioselectivity was found (entries 8-10). A surprising enhancement of diastereo- and enantioselectivity was observed when employing hexafluorobenzene as medium (entry 11).

Table 3.2 Solvent Optimization Study.[a]

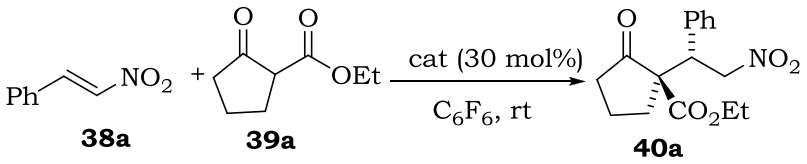


Entry	Solvent	t (h)	yield (%)[b]	*dr*[c]	*ee* (M)[d]	*ee* (m)[d]
1	Toluene	18	91	3:1	28	54
2	Benzene	16	85	3:1	32	50
3	*m*-xylene	24	95	4:1	24	54
4	Cl-C_6H_5	25	92	4:1	28	51
5	*n*-hexane	7	>99	4:1	32	26
6	$CHCl_3$	18	99	3:1	20	52
7	CH_3CN	16	98	5:1	14	10
8	THF	23	85	5:1	54	30
9	Et_2O	16	97	4.5:1	58	40
10	$^nBu_2O$	16	89	5:1	64	34
11	C_6F_6	19	98	7:1	62	26
12	$CF_3C_6H_5$	16	98	5:1	52	28

[a] All reactions were performed at C 0.5 M at 0.2 mmol scale of **38a** and **39a** and 30% mol of **29a**. [b] Yield of isolated product. [c] The diastereoisomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. (M = major diastereoisomer, m = minor diastereoisomer)

Since non-polar solvents are the most suitable to use in non-covalent catalysis, the hexafluorobenzene (ε = 2.05) appeared to us a promising solvent for further investigation. Some of the already investigated catalysts were then screened in hexafluorobenzene (Table 3.3).

Table 3.3 Catalysts screen in hexafluorobenzene as solvent.[a]



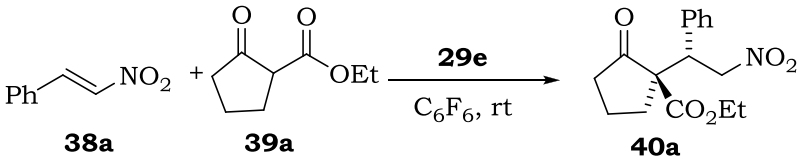
Entry	cat.	t (h)	yield (%)[b]	*dr*[c]	*ee* (M)[d]	*ee* (m)[d]
1	**29a**	19	98	7:1	62	26
2	**29b**	19	94	8:1	70	26
3	**29e**	19	99	13:1	83	1
4	**35**	64	64	5:1	54	26
5	**41**	16	10	5:1	14	n.d.[e]
6	**42**	5	98	6:1	4	20

[a]All reactions were performed at C 0.5 M in hexafluorobenzene at 0.2 mmol scale of **38a** and **39a**. [b]Yield of isolated product. [c]The diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase. (M = major diastereoisomer, m = minor diastereoisomer) [e]Not determined.

Interestingly, commercially available catalysts **29a**, **29b** and **29e** in hexafluorobenzene afforded the product with higher stereocontrol than in toluene, with up to 83% *ee* obtained when using the naphthyl based-prolinol **29e** (entries 1-3). More or less sterically demanding catalysts **41** and **42** showed poorer selectivity (entries 5 and 6).

Fine tuning of the reaction conditions by modifying the reaction concentration and the amount of the catalyst **29e** are reported in Table 3.4. The reaction performed in benzene and diethyl ether with the same catalyst resulted in a significantly poorer stereocontrol when compared to the results obtained in C_6F_6 (entries 2 and 3 vs 1).

Table 3.4 Study of the reaction concentration and the amount of the catalyst **29e** in the model Michael reaction.[a]



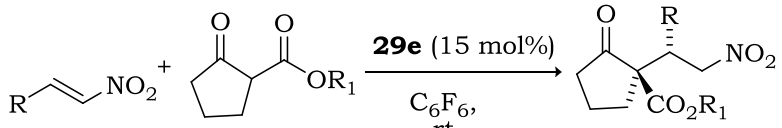
Entry	29e (% mol)	Conc. (M)	t (h)	yield (%)[b]	*dr*[c]	*ee* (M)[d]	*ee* (m)[d]
1	30%	0.5	20	99	13:1	83	1
2[e]	30%	0.5	7	97	5:1	45	42
3[f]	30%	0.5	16	98	6:1	30	21
4	15%	0.5	6	93	19:1	84	4
5	10%	0.5	21	94	19:1	85	7
6	15%	0.4	7	98	19:1	90	12
7	15%	0.2	24	85	16:1	81	2
8[g]	15%	0.2	48	98	16:1	71	8
9	15%	0.8	3	97	16:1	82	60
10	15%	Neat	6	94	5:1	35	19

[a]All reactions were performed in C_6F_6 at 0.2 mmol scale of **38a** and **39a**. [b]Yield of isolated product. [c]The diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase. (M = major diastereoisomer, m = minor diastereoisomer) [e] Reaction conducted in benzene [f] Reaction performed in Et_2O. [g] reaction performed at 0°C.

Pleasingly, the reaction carried out with 15 mol% loading of catalyst proceeded in a similar manner (entry 4), whereas further decrease of the catalyst loading resulted in slower reaction rate (entry 5). To our delight, under slightly more diluted conditions, product **40a** was isolated after 7 hours in excellent yield, almost as a single diastereoisomer with 90% *ee*

(entry 6). No further improvements were achieved under more diluted conditions or at lower temperature (entries 7 and 8). Under more concentrated or neat conditions, the product was isolated with reduced stereoselectivity (entries 9 and 10). All these findings showed that solvent effects governed the stereocontrol of the process. With the optimized conditions in hand, we examined the scope of the asymmetric Michael addition in C_6F_6 as medium (Table 3.5).

Table 3.5 Scope of the asymmetric Michael addition of cyclic β-ketoesters to nitroalkenes[a]



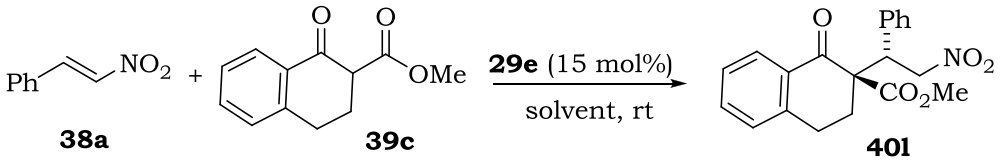
38 **39** **40**

Entry	R (38)	R^1 (39)	Yield (%)[b] (40)	dr[c]	ee[d] (M)
1	Ph (**38a**)	Et (**39a**)	98 (**40a**)	24:1	90
2	2-naphthyl (**38b**)	Et (**39a**)	98 (**40b**)	19:1	88
3	3-BrC_6H_4 (**38c**)	Et (**39a**)	94 (**40c**)	19:1	90
4	4-FC_6H_4 (**38d**)	Et (**39a**)	98 (**40d**)	19:1	88
5	2-ClC_6H_4 (**38e**)	Et (**39a**)	92 (**40e**)	32:1	90
6	2-furyl (**38f**)	Et (**39a**)	89 (**40f**)	10:1	72
7	2-thienyl (**38g**)	Me (**39b**)	98 (**40g**)	16:1	84
8	Ph (**38a**)	Me (**39b**)	97 (**40h**)	16:1	88
9	4-MeC_6H_4 (**38h**)	Me (**39b**)	98 (**40i**)	13:1	66
10	4-$MeOC_6H_4$ (**38i**)	Me (**39b**)	95 (**40j**)	9:1	58
11	Cyclohexyl (**38j**)	Me (**39b**)	52 (**40k**)	24:1	62

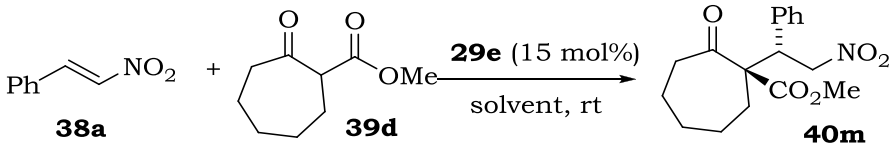
[a]All reactions were performed in C_6F_6 with 0.2 mmol of **38** and **39**. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase.

Almost quantitative yields and high diastereo- and enantio- selectivity were observed when the reaction was performed using ethyl β-ketoester as Michael donor and differently substituted aryl nitroalkenes (entries 1-5). Heteroaromatic rings were tolerated in the Michael acceptor (**38f**-**g**) also when using methyl ketoester **39b** as Michael donor (entries 6-7). Reactions performed on nitroalkenes bearing electron-donating groups on the phenyl ring furnished the product with slightly reduced enantiocontrol (entries 9 and 10). More challenging and less reactive aliphatic nitroalkene **38j** provided the product with satisfactory level of stereocontrol (entry 11).

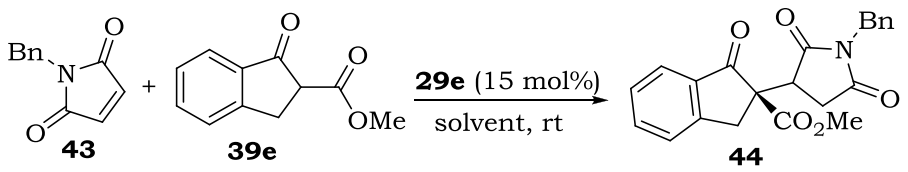
Other Michael donors and acceptors were investigated performing the reaction both in toluene and C_6F_6 for comparative purpose (Scheme 3.6).



solvent	t (h)	yield (%)	dr	*ee* (M)	*ee* (m)
toluene	120	30	5:1	32	62
C_6F_6	120	61	2:1	26	88



solvent	t (h)	yield (%)	dr	*ee* (M)	*ee* (m)
toluene	79	24	1:1	44	62
C_6F_6	72	28	2:1	62	36



Solvent	t (h)	yield (%)	dr	*ee* (M)	*ee* (m)
Toluene	18	90	1:1	8	10
C_6F_6	7	98	1.5:1	22	44

Scheme 3.6 Investigation of other Michael donors and acceptors.

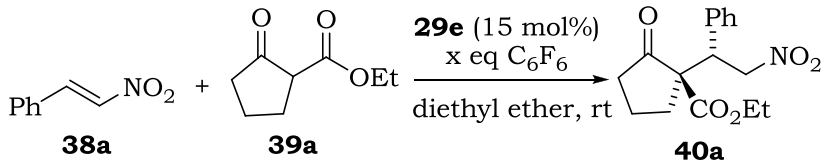
Michael donor **39c** reacted sluggishly with model nitroolefin **38a**, although in hexafluorobenzene the product was recovered in much better yield than in toluene. The minor diastereoisomer of the desired product **40l** showed a higher enantiomeric excess in C_6F_6. When using the 7-membered ring **39d** as nucleophile, the conversion was low in both solvent, although the stereocontrol was improved in C_6F_6. When the *N*-benzylmaleimide **43** was employed as Michael acceptor, both the reactivity and the stereocontrol were better in C_6F_6. The data suggested that the positive effect displayed by C_6F_6 as solvent might turn out to be more general, at least in Michael type addition reactions.

The use of C_6F_6 as additive rather than as a solvent was also investigated in the model reaction (Table 3.6).

When *trans*-β-nitrostyrene **38a** was reacted in Et_2O the major diastereoisomer of the compound **40a** was isolated with 60 % *ee* (entry 1). Notably, the addition of 10 or 5 equivalents of C_6F_6 (entries 2 and 3) to the reaction mixture was sufficient to achieve the enantiocontrol found in the case of the reaction conducted in pure C_6F_6 (entry 1, Table 3.5). Interestingly, further reduction to only 3 equivalents of C_6F_6 afforded an acceptable result (entry 4), while decreasing the temperature caused a drop in the stereocontrol (entry 5). As previously observed, the

concentration significantly affected the process, indeed both under more concentrated or diluted conditions using different amounts of C_6F_6, the product was recovered with lower enantioselectivity (up to 76 % *ee*) (entries 6-9). The reaction performed with *n*-butyl ether as solvent with C_6F_6 as additive (5 eq.) led to the product with a satisfying enantioselectivity (entry10).

Table 3.6 Investigation of the optimized conditions for the use of C_6F_6 as additive for the model reaction.[a]

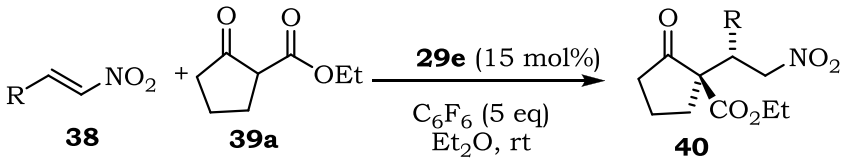


Entry	C (M)	C_6F_6 (eq)	Yield (%)[b]	dr[c]	*ee* (M)[d]
1	0.4	-	64	11:1	60
2	0.25	10	74	19:1	89
3	0.25	5	90	16:1	90
4	0.25	3	98	24:1	86
5[e]	0.25	3	99	32:1	77
6	0.5	5	98	19:1	75
7[f]	0.5	3	99	19:1	76
8[f]	0.5	1	99	16:1	74
9	0.1	3	96	16:1	68
10[g]	0.25	5	98	16:1	83

[a] All reactions were performed in Et_2O at 0.2 mmol scale of **38a** and **39a**. [b] Yield of isolated product. [c] The diastereoisomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. (M = major diastereoisomer) [e] reaction performed at -20 °C. [f] 30 mol% of catalyst was employed. [g] reaction conducted in di-*n*-butyl ether as solvent.

The optimized conditions reported in entry 3 proved not to be of general applicability to all the substrates, but reaction conditions need to be finely optimized for each different nitroalkene derivative. Reactions of representative nitroalkenes **38a**, **38b**, **38d** carried out with the ethyl β-ketoester **39a** in Et_2O using 5 equivalents of C_6F_6 are illustrated in Table 3.7.

Table 3.7 Catalytic asymmetric Michael addition in Et_2O with C_6F_6 as additive.[a]



Entry	R	yield (%)[b]	*dr*[c]	*ee* (M)[d]
1	Ph (**38a**)	90 (**40a**)	16:1	90
2[e]	2-naphthyl (**38b**)	98 (**40b**)	24:1	75
3	4-FC_6H_4 (**38d**)	98 (**40d**)	12:1	77
4[f]	4-FC_6H_4 (**38d**)	98 (**40d**)	16:1	86

[a] All reactions were performed at C=0.25 M in Et_2O, using 5 equivalents of C_6F_6 at 0.2 mmol scale of **38** and **39a**. [b] Yield of isolated product. [c] The diastereoisomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. (M = major diastereoisomer) [e] Reaction performed at C=0.4 M in Et_2O. [f] reaction performed at C=0.5 M in Et_2O.

In order to shed some light on the role of hexafluorobenzene, ^1H-NMR experiments were conducted on dinaphthyl prolinol **29e** in $CDCl_3$ adding different amounts of hexafluorobenzene (Figure 3.1). Coalescence of the **CH_2**NH proton resonances was observed when increasing the equivalents of C_6F_6. A plausible polar interaction of hexafluorobenzene with its

partially positively charged ring centre and the lone pair of nitrogen atom of pyrrolidine might account for the observed coalescence.

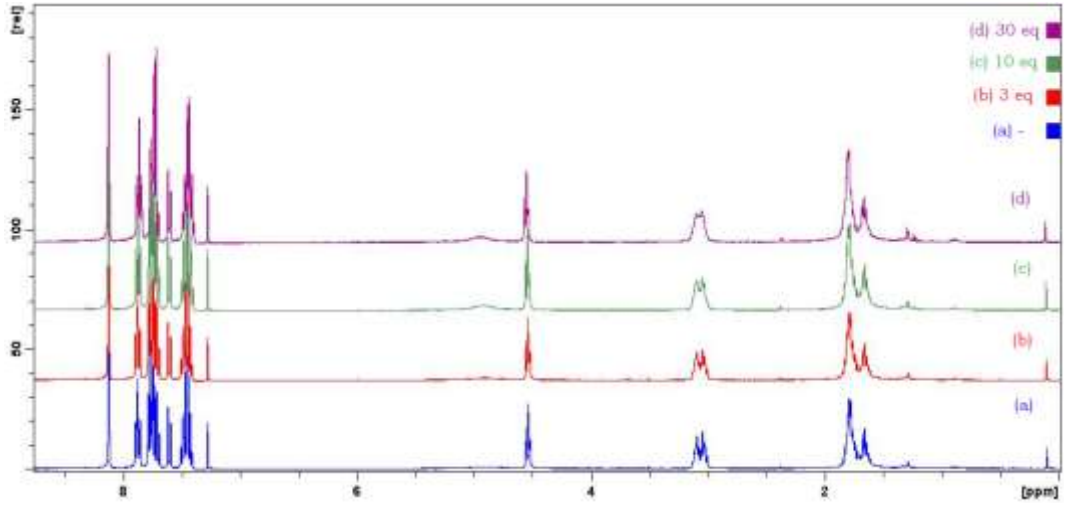


Figure 3.1 ^{1}H-NMR spectra of the dinaphthyl prolinol **29e** with different amounts of hexafluorobenzene.

3.3 Computational Study

In order to clarify the stereochemical outcome of the reaction in hexafluorobenzene, DFT calculations were performed by the group of Cavallo.[102]

The originally proposed general acid-base catalysis provided by diaryl prolinols in Michael type reactions of acyclic β-ketoesters with nitroalkenes[99a] was recently supported by Zhu and co-workers who demonstrated the unfeasibility of enamine intermediate formation between hindered diaryl prolinol and the carbonyl group of the substrate in the

[102] Geometries were optimized at the BP86 level using the SVP basis set. The reported free energies correspond to in solvent M06/TZVP//BP86/SVP energies. BP86/SVP thermal corrections at 300 K are included. For more details, see the experimental part.

asymmetric α-sulfenylation of β-ketoesters catalysed by diaryl prolinols.[103] Indeed, the authors showed, through NMR NOE studies, the establishment of hydrogen bonding interactions between the catalyst and the enol form of the β-ketoester.

Being the C-C bond formation the rate limiting step, the transition state energies of this process were calculated for each of the four possible stereoisomers. The calculations indicated the (*pro-R,S*)[104] transition state as the most energetically affordable, in agreement with the experimental data since the configuration of the major product was determined to be 2*R*,3*S* by comparison with literature data.[105]

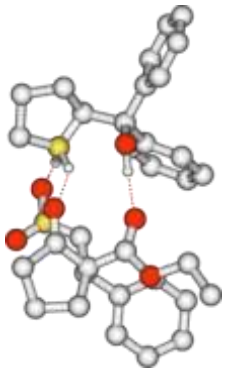
Figure 3.2 shows the calculated transition states leading to the enantiomers of the major diastereoisomer in the absence and in the presence of one molecule of hexafluorobenzene. The (*pro-R,S*) transition state was favored by a higher number of H-bonds between the catalyst and the reagents.

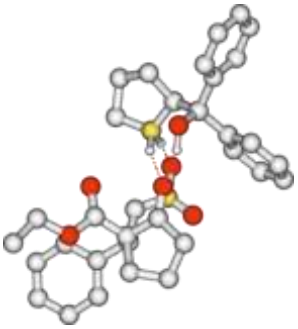
Similar results were obtained inserting two or three molecules of hexafluorobenzene in the calculation. Concerning the beneficial effect of hexafluorobenzene, it appeared that the C_6F_6 ring was found stacked over the enolate group. This can be explained considering that C_6F_6 is characterized by a quadrupole moment with the positive lobes above the aromatic ring, which optimizes electrostatic interaction with the electron density delocalized on the enolate π-orbitals. The energy difference between the transition states was higher when hexafluorobenzene was included in the calculation (1.3 Kcal/mol with respect to 0.4 Kcal/mol calculated in toluene as solvent), in agreement with the experimental data.

[103] L. Fang, A. Lin, H. Hu, C. Zhu, *Chem. Eur. J.* **2009**, *15*, 7039.
[104] Pro-R,S and pro-S,R indicate the configuration at the C2 and C3 atoms of the forming product.
[105] D. Almaşi, D. Alonso, E. Gómez-Bengoa, C. Nájera, *J. Org. Chem.* **2009**, *74*, 6163.

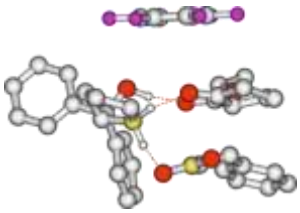
Pro-*R*,*S*: **Pro-S,R:**

(a) (b)





(c) (d)



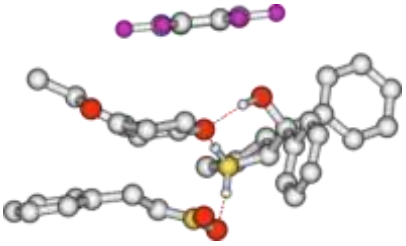


Figure 3.2 Comparison of transition states pro-R,S and pro-S,R, (a) and (b), respectively and the same TS in the presence of one molecule of hexafluorobenzene, (c) and (d).

3.4 Conclusion

These results showed for the first time that hexafluorobenzene, a non-polar solvent (ε = 2.05), could positively affect the reactivity and the stereocontrol of organocatalytic asymmetric Michael additions proceeding via non-covalent activation mode. Indeed, the conjugate addition of β-ketoesters to nitroolefins, conveniently catalyzed by a commercially available prolinol, was turned from scarcely to highly enantioselective process.

Moreover, the dramatic amplification of the stereoselectivity can be more conveniently observed when using hexafluorobenzene simply as additive. DFT calculations helped to suggest a reason for the stereoselectivity enhancement observed.

4. AN ASYMMETRIC DOUBLE MICHAEL ADDITION

4.1 Introduction

The Michael reaction, already discussed in chapter 3, is a 1,4-addition of a carbon nucleophile to α,β-unsaturated carbonyl compounds. Its potential to form C-C bonds can be exploited in domino and multi step reactions (described in the paragraph 1.5) to construct cyclic skeletons through different cascade routes.

Cyclic and polycyclic compounds are extremely important, since the majority of natural products and biologically and pharmaceutically active compounds contains complex skeletons characterized by one or more rings of different size. Michael-aldol, Michael-Mannich and Michael-Michael are only some of the sequences exploited in the literature to construct complex molecules through tandem reactions,[106, 43c] and several are the organocatalysts able to promote them.[107]

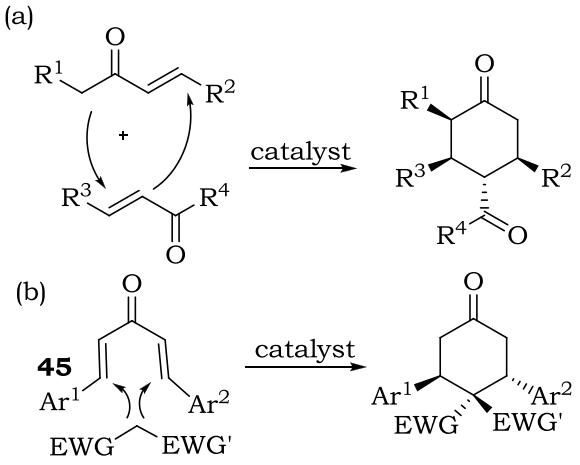
The synthesis of products featuring a cyclohexane unit has been an important research topic for a long time. Among the other reasons, they are precursors of carbasugars or fundamental component in the skeleton of many natural products.[108] Different synthetic pathways can be designed. A nucleophile bearing a Michael acceptor unit, reacting with enones, can be involved in a domino conjugate addition to afford highly

[106] For selected examples, see; a) C. Schneider, O. Reese, *Angew. Chem., Int. Ed.* **2000**, *39*, 2948; b) C. Schneider, O. Reese, *Chem.–Eur. J.* **2002**, *8*, 2585; c) D. Heber, E. V. Stoyanov, *Synthesis* **2003**, 227; d) D. B. Ramachary, Y. V. Reddy, B. V. Prakash, *Org. Biomol. Chem.* **2008**, *6*, 719.

[107] For a review, see: D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

[108] For selected examples, see: a) E. Maudru, G. Singh, R. H. Wightman, *Chem. Comm.* **1998**, 1505; b) S. L. Boulet, L. A. Paquette, *Synthesis* **2002**, 895.

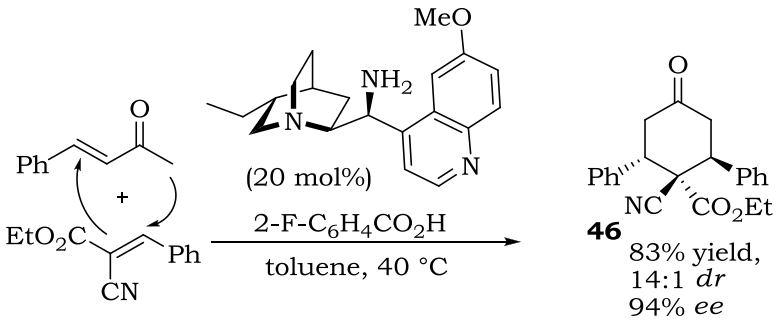
functionalized cyclohexanones (pathway a, Scheme 4.1).[109] Similar products can be obtained reacting active methylene compounds and divinylketones **45**, although this route has been less explored. The reaction consists of a double conjugated addition providing cyclohexanones bearing a quaternary stereogenic center (pathway b, Scheme 4.1).[110]



Scheme 4.1 Construction of highly functionalized cyclohexanones through organocatalytic asymmetric conjugate addition.

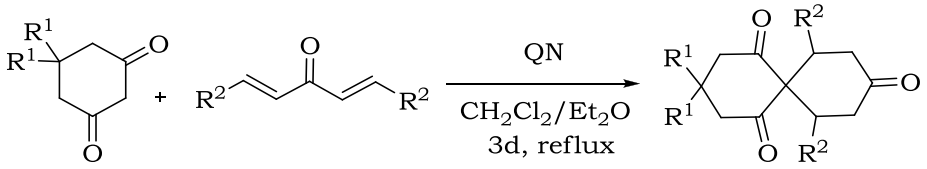
Melchiorre *et al.* reported, for example, the synthesis of **46** with the first double Michael approach promoted by the amino-deoxy-*epi*-hydroquinine and an acid co-catalyst, as shown in Scheme 4.2.[111]

[109] For selected examples, see: a) H. Li, L. S. Zu, H. X. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833; b) A. Q. Ma, D. W. Ma, *Org. Lett.* **2010**, *12*, 3634.
[110] For a racemic process, see: D. Zhang, X. Xu, J. Tan, Q. Liu, *Synlett* **2010**, *6*, 917.
[111] L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7196.



Scheme 4.2 Synthesis of derivative **46** reported by Melchiorre.

Pioneering studies on double conjugated addition of cyclic 1,3-dicarbonyl compounds to divinylketones to access spirocyclohexanones promoted by quinine were conducted by Wynberg. The spiro-product was obtained in moderate yield (< 50%), as a mixture of *trans*/*cis* isomers (*trans*/*cis* ≥ 2:1) with an optical yield of 30 % in one specific case (Scheme 4.3).[112]



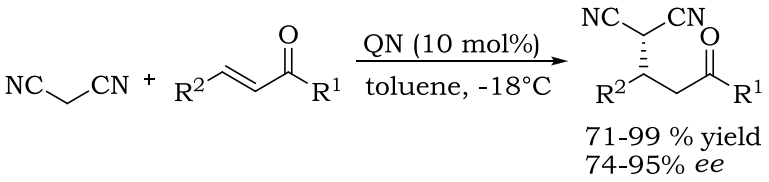
Scheme 4.3 Double Michael addition to divinylketones pioneered by Wynberg.

In the context of the Michael addition reaction to enals, enones, nitroalkenes, which represent the most common Michael acceptors, different donors were exploited, such as malonates, nitroalkanes and 1,3-

[112] W. ten Hoeve, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 1508.

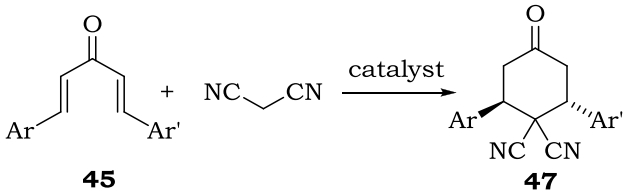
dicarbonyl compounds.[113,86b] Instead, only few example concerning the use of malononitrile addition appeared in the literature.[114]

Recently, Lattanzi and co-workers reported a highly enantioselective Michael addition of malononitrile to α,β-enones using quinine as a general acid base catalyst (Scheme 4.4).[115] The same process was demonstrated to be promoted by diarylprolinols, although achieving lower enantiocontrol.[99f]



Scheme 4.4 Addition of malononitrile to chalcones catalysed by quinine.

With this background in mind and looking for the development of a simple stereoselective approach to cyclohexanone derivatives, the tandem Michael-Michael addition of commercially available malononitrile to easily available diaryl dienones **45** was investigated (Scheme 4.5).



45 **47**

Scheme 4.5 Double Michael addition of malononitrile to dienones.

[113] For reviews, see: a) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123; c) A. Córdova (Ed.), *Catalytic Asymmetric Conjugate Reactions*, Wiley-VCH, Weinheim, **2010**, 9419. For selected examples, see: a) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652; b) C. G. Oliva, A. M. S. Silva, F. A. A. Paz, J. A. S. Cavaleiro, *Synlett* **2010**, 7, 1123.

[114] For selected examples, see: a) T. Inokuma, Y. Hoashi, Y. J. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413; b) X.-F. Li, L.-F. Cun, C.-X. Lian, L. Zhong, Y.-C. Chen, J. Liao, J. Zhu, J.-G. Deng, *Org. Biomol. Chem.* **2008**, *6*, 349; c) Ren, Y.-J. Gao, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13594.

[115] a) A. Russo, A. Perfetto, A. Lattanzi, *Adv. Synth. Catal.*, **2009**, *351*, 3067.

At the same time, a stereoselective access to cyclohexanones from dienones and malononitrile using 9-amino-9-deoxyepiquinine **5** and TFA as co-catalyst was developed by Yan and co-workers. In this example, the formation of an iminium-ion intermediate between the catalyst and the dienone was suggested to be involved.[116]

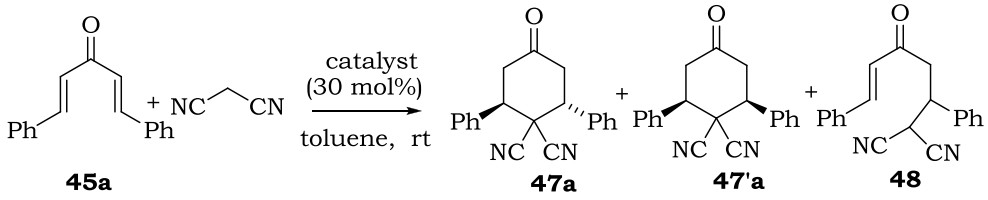
4.2 Results and discussion[117]

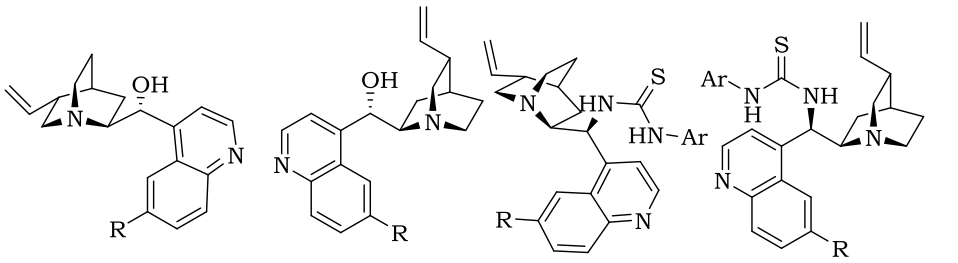
Malononitrile and model *trans*, *trans*-dibenzylideneacetone **45a** were reacted in toluene with different cinchona based organocatalysts, to give 2,5-diphenyl-1,1-dicyanocyclohexanone **47a**/**47'a** in good to high diastereocontrol, together with the mono-adduct **48** in generally minor amount (Table 4.1).

The reaction catalysed by quinine gave the product in 44% of yield with a good *trans*/*cis* ratio and 65% *ee* (entry 1). The starting material was almost completely consumed but the presence of a coloured solid was observed, which could be the oligomerization by-products. The process was found to be strongly dependent on the concentration. This was supported by higher yield and improved enantiocontrol (79% *ee*) obtained when performing the reaction under more diluted conditions (C = 0.04 M) (entry 4). Under these conditions a variety of catalysts were tested. Quinidine allowed to obtain the opposite enantiomer of diastereoisomer **47a** with 51 % *ee* (entry 5). Cinchonidine provided an effective stereocontrol but a poor reactivity, indeed the product was recovered in only 17% yield and the mono-adduct **48** was isolated in 46% yield and 52% *ee* (entry 6).

[116] X.-M. Li, B. Wang, J.-M. Zhang, M. Yan, *Org. Lett.* **2011**, *13*, 374.
[117] The results presented in this chapter are partially reported in the paper: C. De Fusco, A. Lattanzi, *Eur. J. Org. Chem.* ***2011****, 3728.*

Table 4.1 Screen of reaction conditions and catalysts in the double conjugate addition of malononitrile to dibenzylideneacetone **45a**.[a]





QN, R = OMe (**1**) QD, R = OMe (**50**) eQNT, R = OMe (**28**) eQDT, R = OMe (**52**)
CD, R = H (**49**) CPD, R =OH (**51**) Ar = 3,5-$(CF_3)_2C_6H_3$ Ar = 3,5-$(CF_3)_2C_6H_3$

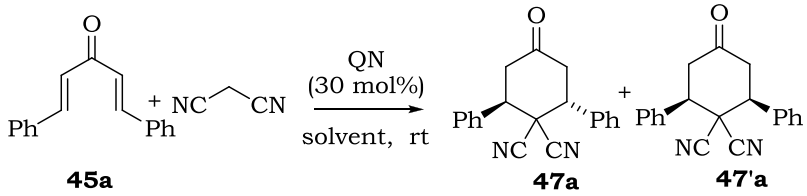
Entry	Cat.	C [M]	*t* [h]	47a/ 47'a[b]	Yield[c] 47a [48]	*ee*[d] 47a [48]
1	QN	0.2	87	9/1	44	65
2[e]	QN	0.1	42	2/1	43	72
3[f]	QN	0.1	48	5/1	48	77
4[g]	QN	0.04	66	10/1	70	79
5[h]	QD	0.04	52	24/1	61	-51
6	CD	0.04	54	30/1	17 [46]	80 [52]
7	CPD	0.04	71	n.d.[i]	- [37]	- [45]
8	eQNT	0.04	66	n.d.	<5 [76]	n.d. [86]
9	eQDT	0.04	66	>30/1	15 [57]	-86 [-76]

[a] Reaction conditions: **45a** (0.1 mmol)/malononitrile (0.12 mmol)/quinine (0.03 mmol). [b] Determined via ^{1}H-NMR analysis on the crude mixture. [c] Yield of isolated product; yield of **48** in parenthesis. [d] Determined by HPLC analysis on a chiral stationary phase; *ee* of **48** in parenthesis. [e] 1 equivalent of quinine was used. [f] 0.05 mmol of malononitrile was used. [g] 0.1 mmol of malononitrile was used. [h] Negative *ee* is indicative of the formation of the opposite enantiomer. [i] Not determined.

Cupreidine was poorly active, indeed only the mono-adduct **48** was obtained in modest enantioselectivity (entry 7). Thioureas derivatives of the cinchona alkaloids demonstrated to be less reactive than their natural precursors affording the mono-adduct **48** as the most abundant product (entries 8 and 9).

A screen of solvents was then carried out (Table 4.2).

Table 4.2. Solvent effect and optimization study for the double conjugate addition of malononitrile to compound **45a** with quinine.[a]



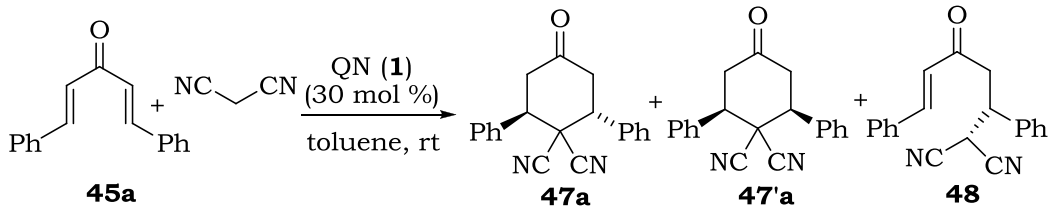
45a **47a** **47'a**

Entry	Solvent	*t* [h]	47a/ 47'a[b]	yield (%)[c]	*ee* (%)[d]
1	ClC_6H_5	36	14/1	66	72
2[e]	ClC_6H_5	47	>30/1	61	76
3	*m*-xylene	70	20/1	66	80
4	$CHCl_3$	67	18/1	50	62
5	THF	67	n.d.[f]	< 5	n.d.
6[g]	toluene	91	>30/1	54	83
7[h]	toluene	74	>30/1	56	80
8[i]	toluene	103	>50/1	55	86

[a] Reaction conditions: **45a** (0.1 mmol)/malononitrile (0.1 mmol)/quinine (0.03 mmol) in 2.5 mL of solvent. [b] Determined via ^{1}H-NMR analysis on the crude mixture. [c] Yield of isolated product. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction performed at -18 °C. [f] not determined. [g] Reaction performed at 4 °C. [h] 20 mol% of catalyst was used. [i] C = 0.02 M

Reaction performed in chlorobenzene gave the product with moderate yield but satisfactory enantiomeric excess (entry 1) and performing the reaction at lower temperature slightly improved the stereocontrol (entry 2). *m*-Xylene was comparable with toluene (entry 3), while halogenated and ethereal solvents had a detrimental effect (entries 4 and 5). The reaction carried out in toluene at lower temperature or with a smaller amount of catalyst led to satisfactory level of stereoselectivity (entries 6 and 7). The product was obtained in excellent diastereoselectivity and 86% *ee* altought with longer reaction time, when working under more diluted conditions (entry 8).

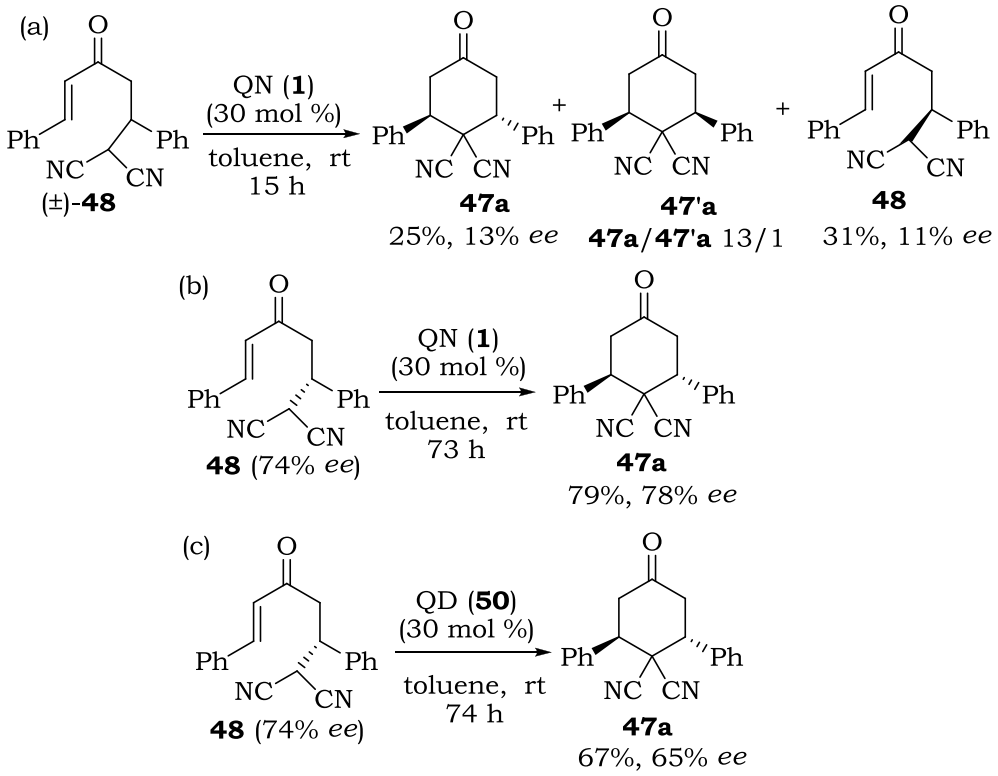
In order to better understand the stereochemical outcome of the entire process, the reaction of **45a** and malononitrile with quinine was quenched at different times (Scheme 4.6).



Scheme 4.6 Monitoring of the double Michael addition over time.

After 28 hours, the product **47a** was isolated in moderate yield, high enantiomeric excess (84% *ee*) and high diastereoisomeric ratio, whereas compound **48** was recovered in 30% yield and 69% *ee*. After 48 hours, the yield of the product **47a** slightly increased but lower enantio- and diastereoselectivity were observed, whereas only traces of the reaction intermediate were detected. In both cases, starting compound **45a** was not totally consumed. On the basis of the data illustrated in Scheme 4.6, it can be suggested that the second Michael addition step is influenced by

the chiral non racemic adduct **48**. If the opposite were true, according to Horeau's principle,[118] compound **47a** would be expected to achieve 92% *ee* and *cis*-**47'a** product formed in around 25% yield at full conversion. In order to shed light on the second step some experiments were performed on racemic and enantioenriched adduct **48** (Scheme 4.7).



Scheme 4.7 Stereochemical outcome of the second Michael addition step

The racemic Michael adduct **48** was reacted with QN in toluene and after 15 hours the unreacted **48** was recovered with 11% *ee*, whereas the cyclized product **47a**/**47'a** was isolated in 25% yield, 13/1

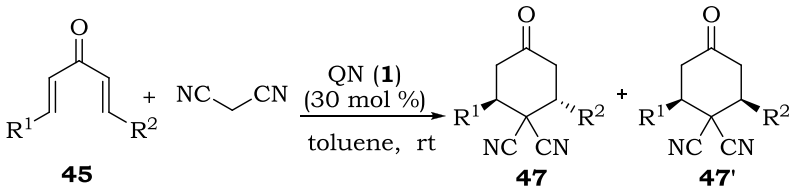
[118] a) J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973**, *29*, 1055; b) K. Soai, H. Hori, M. Kawahara, *J. Chem. Soc. Chem. Commun.* **1992**, 106; c) S. E. Baba, K. Sartor, J.-C. Poulin, H. B. Kagan, *Bull. Chim. Soc. Fr.* **1994**, *131*, 525.

diastereoisomeric ratio and 13% *ee* (Scheme 4.7, a). To evaluate matching and mismatching effects, the enantioenriched intermediate (74% ee) was reacted either with quinine **1** and with its pseudoenantiomer quinidine **50** (Scheme 4.7, b and c). With the quinine, results were comparable to those obtained in the model reaction (case b vs entry 4, Table 4.1). When using quinidine as the catalyst, a lower enantiomeric excess of compound **47a** was observed along with a lower yield, showing a mismatching effect. These experiments indicate that the organocatalyst predominantly controls the stereochemical outcome of the process, although a minor substrate control is active in the second step.

The procedure for the double asymmetric Michael addition with malononitrile was investigated using different substituted dienones, synthetized according to a known procedure (Table 4.3).[119] Symmetrically substituted diaryl dienones **45a-c** furnished the cyclized product in satisfactory yields, high diastereoselectivity and up to 86 % *ee* (entries 1-3). Unsymmetrically disubstituted dienones **45d-f** were also suitable substrates for the process (entries 4-6). The heteroaromatic derivative allowed to isolate the *trans*-product **47g** in excellent diastereoisomeric ratio, 86% *ee* although with a modest yield (entry 7). A better yield of the product could be obtained quenching the reaction after a longer time (entry 8). Reactions carried out with methyl malonate and nitromethane as donors did not furnish any product.

[119] W. Tully, L. Main, B. K. Nicholson, *Journal of Organometallic Chemistry* **2001**, *633*, 162.

Table 4.3 Scope of the double Michael addition of malononitrile to dienones **45**.[a]



Entry	R^1	R^2	t (h)	47/47'[b]	Yield 47 [%][c]	*ee* 47 [%][d]
1	Ph	Ph **a**	103	>50/1	55	86
2	*p*MeC$_6$H$_4$	*p*MeC$_6$H$_4$ **b**	96	>50/1	54	85
3	*p*CF$_3$C$_6$H$_4$	*p*CF$_3$C$_6$H$_4$ **c**	118	19/1	62	83
4	*p*MeC$_6$H$_4$	Ph **d**	95	>30/1	68	82
5	*p*MeOC$_6$H$_4$	Ph **e**	97	>40/1	48	85
6	*p*ClC$_6$H$_4$	Ph **f**	118	>40/1	53	80
7	2-thienyl	Ph **g**	99	>40/1	32	86
8	2-thienyl	Ph **g**	150	16/1	47	80

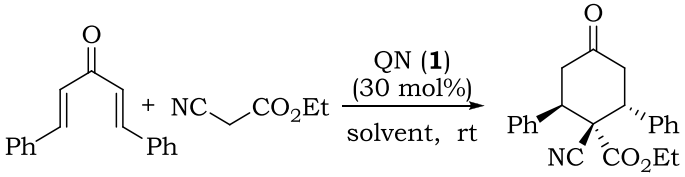
[a] Reaction conditions: **45a** (0.1 mmol)/malononitrile (0.1 mmol)/quinine (0.03 mmol) in 5 mL of solvent. [b] Determined via ^{1}H-NMR analysis. [c] Yield of isolated product. [d] Determined by HPLC analysis on a chiral stationary phase.

The absolute configuration of the major enantiomer of the *trans*-product **47a** was supposed to be (2*R*, 6*R*), assuming product **48** to be *S*-configured as reported in the previous report on addition of malononitrile to chalcones.[115a] To confirm this hypothesis compound **45a** was reacted with ethyl cyano malonate affording previously reported cyclic compound **46**.

A brief optimization study was conducted between dienone **45a** and ethyl cyanoacetate as the nucleophile (Table 4.4).

Different solvents were evaluated as medium for the reaction, but as expected non polar, aromatic solvents proved to be the most effective (entries 1 and 3).

Table 4.4 Optimization study for the addition of ethyl cyano malonate to dienone **45a**. [a]



45a **46**

Entry	Solvent	t (h)	yield (%)[b]	dr[c]	*ee*[d]
1	Toluene	93	92	>40: 1	60
2	ClC_6H_5	64	95	>40: 1	47
3	*m*-xylene	64	76	>40: 1	60
4	$CHCl_3$	72	74	>40: 1	44
5	EtOAc	72	65	>40: 1	52
6	Et_2O	96	71	>40: 1	50

[a] Reaction conditions: **45a** (0.1 mmol), ethyl cyano malonate (0.1 mmol), 0.3 M in toluene. [b] Yield of isolated product. [c] Determined via ^{1}H-NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

The absolute configuration of compound **46** was determined to be (2*R*, 6*R*) by comparing HPLC retention times and optical rotation with those previously reported.[111] This result confirmed that the stereochemical outcome of the first conjugate addition on compounds **45a**, to give adduct **48**, was consistent with our previous findings.

4.3 Conclusion

In conclusion, a tandem Michael-Michael reaction to highly substituted cyclohexanones with high levels of diastereoselectivity and good enantiocontrol was developed using a low cost catalyst and easily available starting materials. It has been demonstrated that this non covalent organocatalytic approach can be considered an efficient alternative strategy to enamine-iminium cascade processes to stereoselectively obtain cyclohexane based scaffolds.

5. AN ASYMMETRIC AZIRIDINATION REACTION

5.1 Introduction

Aziridines are strained three-membered nitrogen-containing heterocycles. These small units are often contained in natural compounds showing biological and pharmaceutical activities. Moreover, they have also been object of attention for their potential use to access valuable nitrogen-containing compounds such as lactams, amino acids, amino alcohols, after selective ring-opening.[48]

Among the most important classes of aziridine-containing natural compounds, mitomycins, porfiromycins and azinomycins have to be remembered for being potent antitumor and antibiotic agents (Figure 5.1).[120] Their activity has been attributed to the aziridine ring, involved in the DNA alkylation process and in the *cross-linking* between the bases.

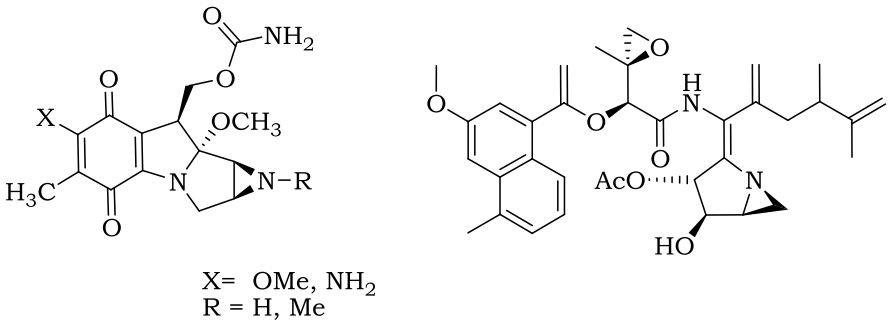


Figure 5.1 Examples of aziridine-containing natural products.

Aziridine containing compounds have mostly anticancer, antileukemic or antibiotic activities. These compounds, usually structurally different, only

[120] a) M. Kasai, M. Kono, *Synlett* **1992**, 778; b) Y. Na, S. Wang, H. Kohn, *J. Am. Chem. Soc.* **2002**, *124*, 4666; c) T. J. Hodgkinson, M. Shipman, *Tetrahedron* **2001**, *57*, 4467.

share the aziridine moiety which is responsible for the activity (Figure 5.2).[121]

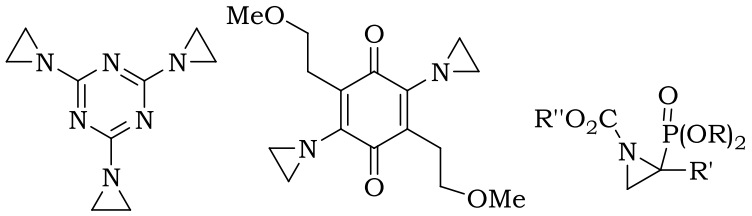
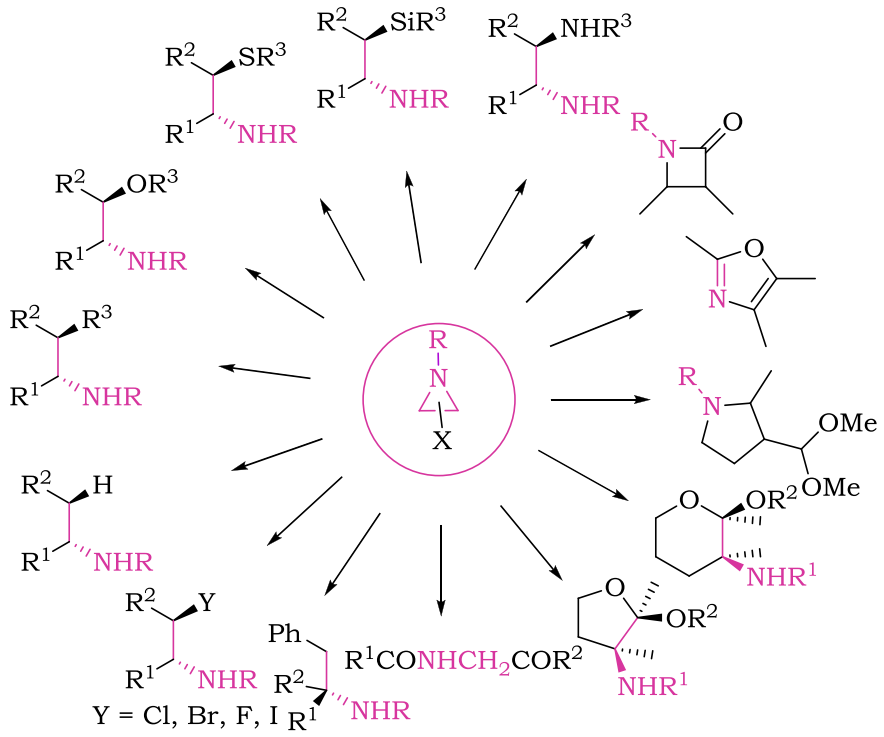


Figure 5.2 Compounds with pharmaceutical activities due to the aziridine ring.

Chiral aziridines have also been employed as ligands in asymmetric metal catalysis. Tanner and co-workers used a ligand containing two aziridine rings, among the other, for the copper-mediated asymmetric hydroxylation of olefins, cyclopropanation and aziridination.[122] Enantiopure aziridines bearing 2-carbinol moiety have been employed as ligands for boron and zinc in a number of asymmetric reaction.[123]

Even though aziridines are less reactive than epoxides, due to the minor electronegativity of the nitrogen with respect to the oxygen, aziridine ring opening have also been deeply investigated. Optically active aziridines treated with different carbon or heteroatom based nucleophiles allowed to access a variety of enantioenriched nitrogen containing compounds, such as amino alcohols, amino thiols, diamines.[124] Furthermore, electrophilic ring opening, ring expansion, rearrangements are only few of the possible transformations, as shown in Scheme 5.1.

[121] G. S. Singh, M. D'Hooghe, N. De Kimpe, *Chem. Rev.* **2007**, *107*, 2080.
[122] D. Tanner, A. Harden, F. Johansson, P. Wyatt, P.G. Andersson, *Acta Chem. Scand.* **1996**, *50*, 361.
[123] M. McCoull, F. A. Davis, *Synthesis* **2000**, 1347.
[124] For a recent review on aziridine ring-opening, see: P. Lu, *Tetrahedron* **2010**, *66*, 2549.



Scheme 5.1 Overview of important transformations of aziridines

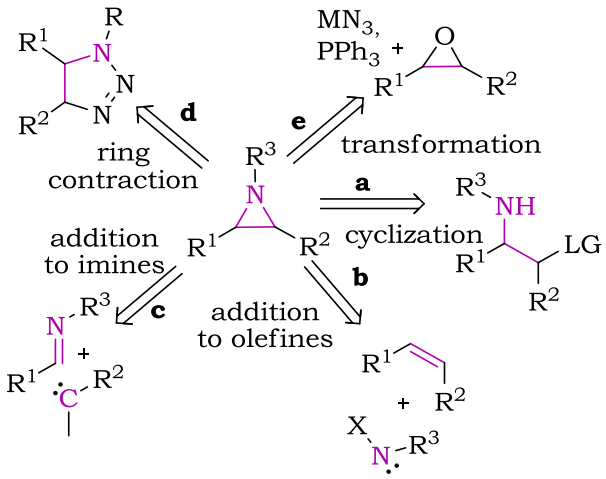
The fate of the aziridine, the stereoselectivity of the resulting products are strongly influenced by steric and electronic features of the substituents on the aziridine ring, for example a nucleophile usually attacks the less substituted carbon but electronic effects can invert the regioselectivity.[121,125]

For all these reasons, intensive investigations towards the development of asymmetric methodologies for the synthesis of aziridines have been developed in recent years.

[125] For some reviews on transformations of aziridines, see: a) D. Tunner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; b) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701.

5.1.1 Synthesis of Chiral Aziridines

Different strategies to obtain aziridines can be employed: (a) cyclization reactions, (b) transfer of nitrogen to olefins or (c) carbenes to imines, (d) ring contraction, (e) transformation of functional groups (Scheme 5.2).[126]



Scheme 5.2 General approaches to aziridines

Diastereo- and enantiomerically enriched aziridines can be prepared either via chiral auxiliary approach or by using chiral ligands-metal based catalysis and by organocatalysis.[127]

Concerning the chiral auxiliary approach, it is worth mentioning the employment of *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide with iodosylbenzene to afford the aziridinating agent *in situ* for a variety of alkenes with Cu-catalysis.[128] The Aza-Darzens reaction, via generation of

[126] For selected examples, see: a) W. Lwowsky, *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 897; b) L. Casarrubios, J. A. Perez, M. Brookhart, J. L. Templeton, *J. Org. Chem.* **1996**, *61*, 8358; c) F. Palacios, A. M. Ochoa de Retana, E. Martinez de Marigorta, J. Manuel de los Santos, *Eur. J. Org. Chem.* **2001**, *66*, 2401; d) D. K. Wang, L. X. Dai, X. L. Hou, *Chem. Commun.* **1997**, 1231; e) T. Satoh, T. Sato, T. Oahara, K. Yamakawa, *J. Org. Chem.* **1989**, *54*, 3973; f) B. Olofsson, R. Wijtmans, P. Somfai, *Tetrahedron* **2002**, *58*, 5979; g) H. Pellisier, *Tetrahedron* **2010**, *66*, 1509.

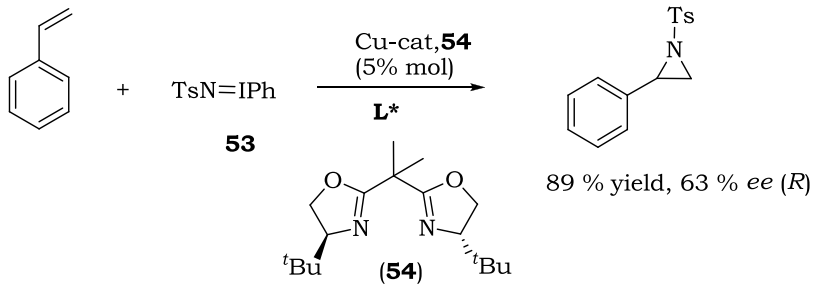
[127] For some reviews, see: a) R. S. Atkinson, *Tetrahedron* **1999**, *55*, 1519; b) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905.

[128] P. H. Di Chenna, F. Robert-Peillard, P. Dauban, R. H. Dodd, *Org. Lett.* **2004**, *6*, 4503.

chiral α-halo or α-sulfonio anions, has been exploited to access the aziridines in diastereoselective manner.[129]

5.1.1.1 Metal-Catalyzed Enantioselective Methods

In 1993, the group of Evans[130] developed a Cu-catalysed method for the asymmetric aziridination of alkenes using [N-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) as the nitrene source (Scheme 5.3).

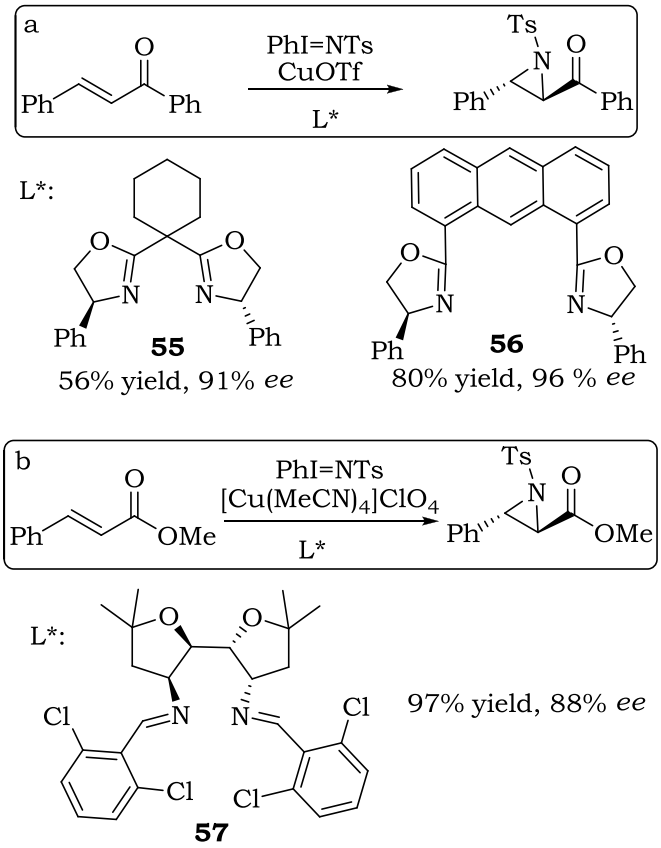


Scheme 5.3 Aziridination of styrene trough metal catalysis.

Bisoxazoline **54** was found the most effective ligand, subsequently employed by Che,[131] who introduced $PhI(OAc)_2$ in the presence of sulphonamides to generate the nitrene precursor. Dauban[132] and other groups improved this system and extended the scope of the aziridination. Other oxazoline-based ligands, such as cyclohexane or anthracene derivatives **55** and **56**, were investigated in the Cu-catalysed aziridination

[129] J. Sweeney, *Eur. J. Org. Chem.* **2009**, 4911.
[130] D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328.
[131] H. L. Kwong, D. Liu, K.-Y. Chan, C.-S. Lee, K.-H. Huang, C.-M. Che, *Tetrahedron Lett.* **2004**, *45*, 3965.
[132] A. Esteoule, F. Duran, P. Retailleau, R. H. Dodd, P. Dauban, *Synthesis* **2007**, 8, 1251.

of chalcones (Scheme 5.4, a). Instead the C_2-symmetric diimine **57** was employed in the aziridination of α,β-unsaturated esters (Scheme 5.4, b).[133]



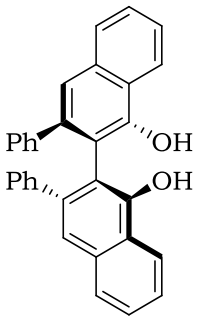
Scheme 5.4 Aziridination of α,β-unsaturated ketones and esters with Cu-catalysis.

The group of Jacobsen found that a Cu-catalyst with a diimine ligand could promote the asymmetric aziridination of *cis*-olefines and imines.[134]

In the field of the ruthenium catalysis, good results (up to 99% *ee*) were obtained in the aziridination of a wide range of monosubstituted alkenes with different azides. For example, Katsuki reported the enantioselective

[133] a) L. Ma, D.-M. Du, J. Xu, *J. Org. Chem.* **2005**, *70*, 10155; b) J. Xu, L. Ma, P. Jiao, *Chem. Comm.,* **2004**, 1616; c) X. Wang, K. Ding, *Chem. Eur. J.* **2006**, *12*, 4568.
[134] a) Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889; b) K. B. Hansen, N. S. Finney, N. Jacobsen, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676.

catalytic aziridination of terminal alkenes promoted by Ru-(Salen)(CO) complexes.[135] Intramolecular rhodium-catalysis was often exploited by using an internal nucleophile, although the stereoselectivity was generally inferior to that obtained in the case of Cu-catalysis.[136] Aggarwal and coworkers reported a Rh-catalysed aziridination reaction using catalytic quantities of a chiral sulphide and tosylhydrazone salt as the nitrogen source achieving up to 98% *ee*.[137] Wulff and co-workers disclosed a catalytic enantioselective aziridination process reacting imines and diazoacetates with catalytic loadings of the chiral VANOL-borate complex (figure 5.3).[138]



(S)-VANOL
58

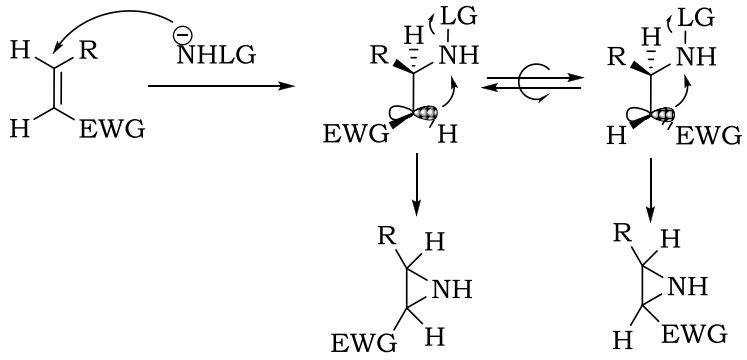
Figure 5.3 VANOL ligand for boron complexes.

5.1.1.1 Aza-MIRC Approach and Organocatalyzed Aziridination

The Aza-MIRC (Michael Initiated Ring Closure) reaction is a two-step reaction: a nitrogen-based nucleophile attacks the substrate usually forming an anionic intermediate that trough intramolecular nucleophilic

[135] a) K. Omura, T. Uchida, R. Irie, T. Katsuki, *Chem. Commun.* **2004**, 2060; b) H. Kawabata, K. Omura, T. Uchida, T. Katsuki, *Chem. Asian. J.*, **2007**, 2, 248.
[136] a) J.-L. Liang, S.-X. Yuan, P. W. Hong Chan, C.-M. Che, *Tetrahedron Lett.* **2003**, *44*, 5917; b) C. J. Hayes, P. W. Beavis, L. A. Humphries, *Chem. Commun.* **2006**, 4501; c) M. Yamawaki, M. Tanaka, T. Abe, M. Anada, S. Hashimoto, *Heterocycles* **2007**, 72, 709.
[137] V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni *Angew. Chem. Int. Ed.* **2001**, *40*, 1433.
[138] J. C. Antilla, W. D. Wulff, *J. Am. Chem. Soc.* **1999**, *121*, 5099.

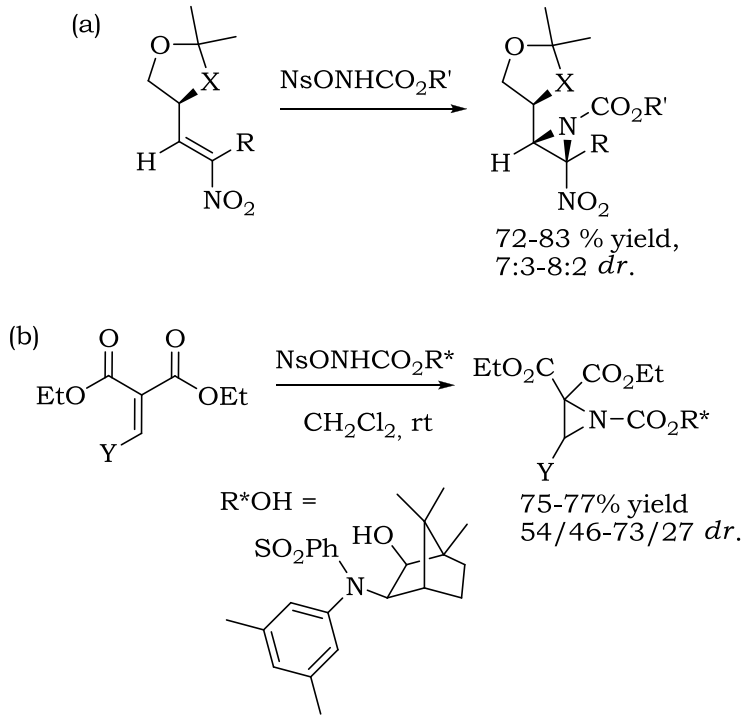
substitution furnishes the aziridine. The stereoselectivity of the reaction is strongly dependent on the relative rate of the second step with respect to the speed of rotation around the C-C bond (Scheme 5.5).



Scheme 5.5 Aza-MIRC aziridination mechanism.

Diastereoselective aza-MIRC reactions to optically active aziridines have been performed, exploiting preformed chirality placed on nucleophile or substrate. Pellacani and coworkers developed both the strategies. Optically pure nitro alkenes were reacted with an alkyl nosyloxycarbamate under basic conditions to give the corresponding nitro aziridines in high yields and good diastereoselectivity (Scheme 5.6, a). Alternatively, a chiral nosyloxycarbamate was employed with electron-poor alkenes (Scheme 5.6, b).[139] The diastereocontrol of the reactions was strongly influenced by the chiral residue used, more than by reaction conditions.

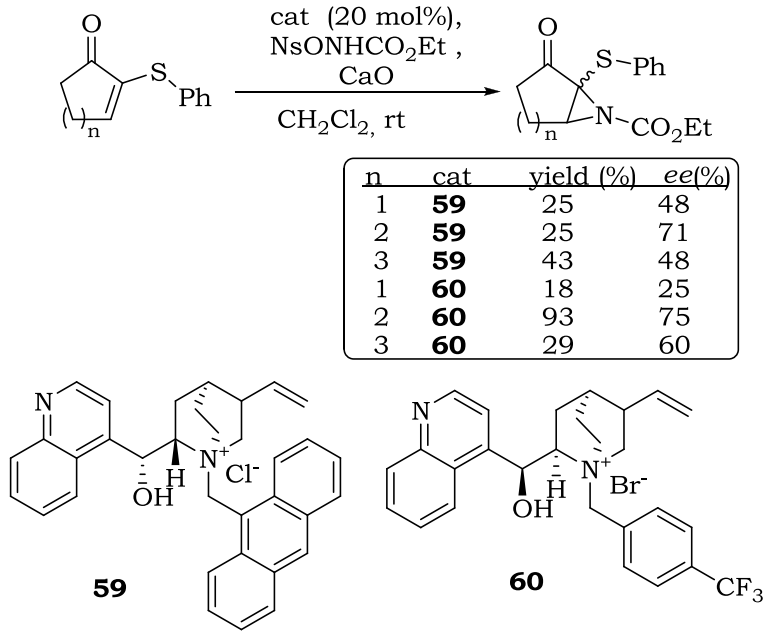
[139] a) S. Fioravanti, F. Marchetti, L. Pellacani, L. Ranieri, P. Tardella *Tetrahedron: Asymmetry* **2008**, *19*, 231; b) S. Fioravanti, L. Pellacani, P. A. Tardella, *Eur. J. Org. Chem.* **2003**, 4549.



Scheme 5.6 Diastereoselective synthesis of aziridines by Pellacani.

The same group developed an organocatalytic method based on the use of cinchona alkaloids derived quaternary salts in the aziridination of 2-(phenyl-sulfanyl)-2-cycloalkenones (Scheme 5.7).[140] This phase-transfer catalysed process provided the aziridines in satisfactory yields and moderate enantioselectivity strongly dependent on the nature of the substrates.

[140] S. Fioravanti, M. Guni. Mascia, L. Pellacani, P. A. Tardella, *Tetrahedron* **2004**, *60*, 8073.



n	cat	yield (%)	*ee*(%)
1	**59**	25	48
2	**59**	25	71
3	**59**	43	48
1	**60**	18	25
2	**60**	93	75
3	**60**	29	60

Scheme 5.7 Aziridination of 2-(phenylsulfanyl)-2-cycloalkenones mediated by cinchona alkaloids based quaternary salts.

Different cinchona alkaloids were developed for phase-transfer catalysis in the asymmetric aziridination of electron-poor olefins. Murugan and Siva reported a methodology in which tosyl derivatives of cinchona alkaloids (catalyst **61a** and **b**, Figure 5.4, a) were employed with *N*-acyl-*N*-aryl hydroxamic acids to furnish the corresponding aziridines with up to 95 % *ee*.[141] Minakata *et al.* employed *N*-chloro-*N*-sodio carbamate with catalysts **62a** and **b**, respectively cinchonidine and cinchonine derivatives, achieving 87% *ee* (Figure 5.4, b).[142]

[141] E. Murugan, A. Siva, *Synthesis* **2005**, *12*, 2022.
[142] S. Minakata, Y. Murakami, R. Tsuruoka, S. Kitanaka, *Chem. Commun.* **2008**, 6363.

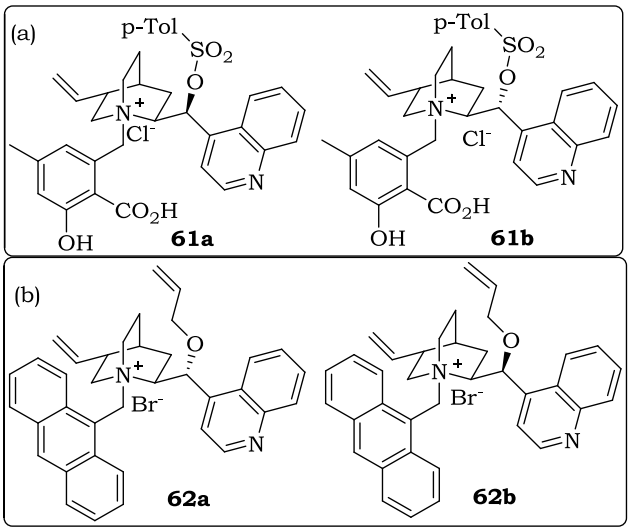
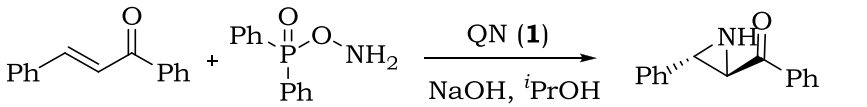


Figure 5.4 Some cinchona alkaloid derivatives employed in phase-transfer catalysis for aziridination of electron-poor olefins.

Armstrong and co-workers investigated the asymmetric aziridination of *trans*-chalcone with an aminimide generated *in situ* from O-(diphenylphosphinyl)hydroxylamine with a tertiary amine, such as the quinine.[143] A promising level of enantioselectivity was achieved using quinine (Scheme 5.8).

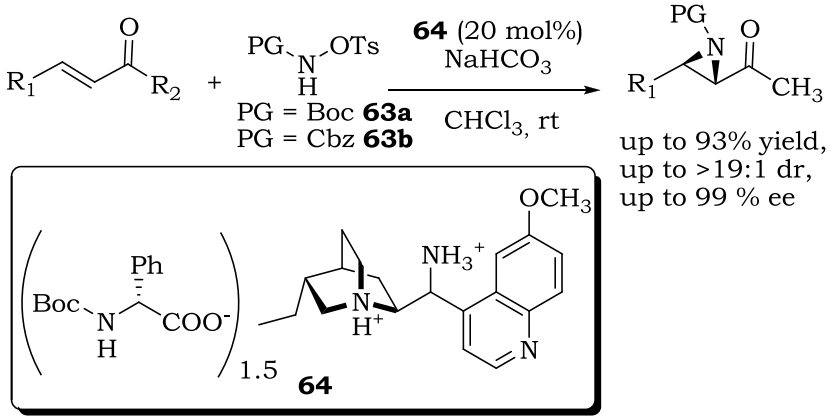


Scheme 5.8 Aziridination of *trans*-chalcone promoted by quinine.

A highly efficient methodology for asymmetric aziridination of α,β-unsaturated ketones with *N*-protected hydroxylamine bearing a potential leaving group (**63a**, **b**) was introduced by the group of Melchiorre (Scheme

[143] A. Armstrong, C. A. Baxter, S. G. Lamont, A.R. Pape, R. Wincewicz, *Org. Lett.* **2007**, *9*, 351.

5.9).[144] The employed catalyst was the primary amine salt **64** obtained by combining easily available 9-amino(9-deoxy)*epi*-hydroquinine with D-*N*-Boc Phenylglycine.

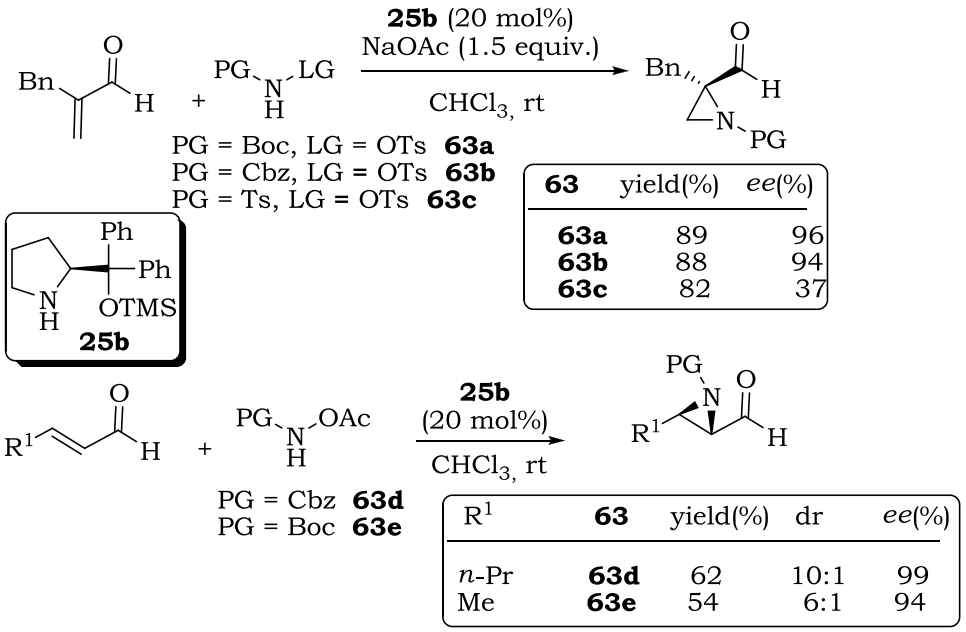


Scheme 5.9 Asymmetric aziridination of enones mediated by catalyst **64**.

A highly efficient organocatalytic aziridination of α,β-unsaturated aldehydes was disclosed by Córdova and co-workers to be promoted by the simple chiral pyrrolidine derivative **25b** (Scheme 5.10). Both branched terminal and linear 1,2-disubstituted olefins were suitable substrates for this reaction furnishing the corresponding aziridines with quaternary or tertiary stereocentres with high enantioselectivity.[145] The mechanism proposed by the authors involved the formation of an iminium ion intermediate between the aldehyde and the catalyst.

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

[145] a) J. Vasely, I. Ibrahem, G. L. Zhao, R. Rios, A. Còrdova *Angew. Chem. Int. Ed.* **2007**, *46*, 778; b) L. Deiana, G. L. Zhao, S. Lin, P. Dziedzic, Q. Zhang, H. Leijonmarck, A. Còrdova, *Adv. Synth. Catal.* **2010**, *352*, 3201; d) A. Desmarchelier, D. Peirera de Sant'Ana, V. Terrasson, J. M. Campagne, X. Moreau, C. Greck, R. M. de Figueiredo, *Eur. J. Org. Chem.* **2011**, 4046.



63	yield(%)	*ee*(%)
63a	89	96
63b	88	94
63c	82	37

R^1	63	yield(%)	dr	*ee*(%)
n-Pr	**63d**	62	10:1	99
Me	**63e**	54	6:1	94

Scheme 5.10 Enantioselective aziridination promoted by catalyst **27**.

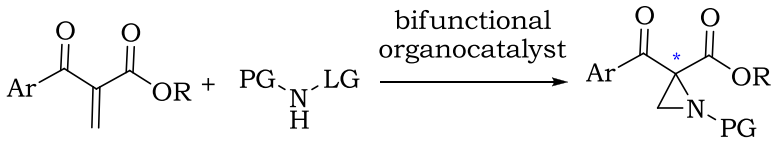
Terminal aziridines are prone to regioselective opening with a variety of nucleophiles. In substrats bearing a quaternary stereocenter, important α-substituted amino acid derivatives can be obtained.[146] Indeed quaternary α-amino-acids are gaining more importance because of their biological and chemical properties, activity and applicability in biochemical and drug discovery research.

5.2 Results and Discussion[147]

With this background in mind and taking into account the few methods available for the asymmetric synthesis of terminal aziridines bearing a

[146] For some reviews, see: a) H. Vogdt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406; b) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569.
[147] The results presented in this chapter are partially reported in the paper: C. De Fusco, T. Fuoco, G. Croce, A. Lattanzi, *Org. Lett.* **2012**, *14*, 4078.

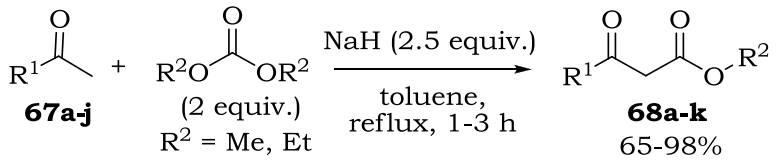
quaternary stereocenter, the aziridination reaction of a new class of electron-poor terminal olefins was investigated. Olefins **65** with *N*-protected hydroxylamine derivatives as pro-nucleophile gave the terminal *N*-protected aziridines **66** (Scheme 5.11). We envisioned that bifunctional organocatalysts could promote the aza-MIRC reaction under general acid-base catalysis. Indeed when hydrogen bonded to the catalyst, the thus-generated prochiral aza-Michael adduct could close in a preferential manner to afford enantioenriched aziridine.



Scheme 5.11 General scheme for the synthesis of aziridines **66**.

5.2.1 Synthesis of Starting Materials

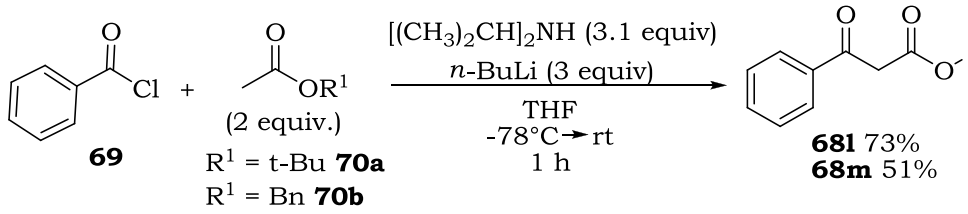
The required methylene β-ketoesters were prepared from the corresponding β-ketoesters, which could be synthetized through two different strategies. Following a literature procedure[148] methyl ketones **67** were reacted with the proper carbonate (methyl or ethyl) with NaH as base, to give the condensation products **68** with good to excellent yields (Scheme 5.12).



Scheme 5.12 Synthesis of β-ketoesters from ketones and carbonate.

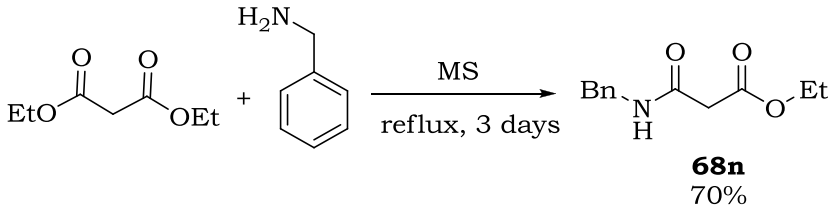
[148] Y. Jiang, X. Chen, Y. Zheng, Z. Xuel, C. Shu, W. Yuan, X. Zhang, *Angew. Chem., Int. Ed.* **2011**, *50*, 7304.

This procedure could not be extended to *t*ert-butyl and benzyl ketoesters to obtain the desired products **68l** and **68m** and a different approach was employed. Acyl halide **69** was added to a solution of the corresponding ester **70** with LDA to give the products in satisfactory yield (Scheme 5.13).



Scheme 5.13 Synthesis of *t*Bu and Bn β-ketoesters.

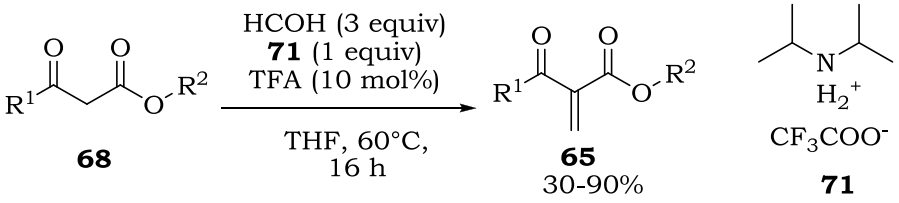
The β-carbamoylester **68n** was also synthetized via condensation between diethyl malonate and benzylamine in the presence of molecular sieves (Scheme 5.14).



Scheme 5.14 Synthesis of the β-carbamoylester **68n**.

The dicarbonyl compounds were subjected to a methylenation reaction, according a procedure reported in the literature,[149] in which formaldehyde and diisopropylammonium trifluoroacetate **71** were employed (Scheme 5.15).

[149] A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun.* **2010**, *46*, 1715.



Scheme 5.15 Synthesis of terminal olefins **65**.

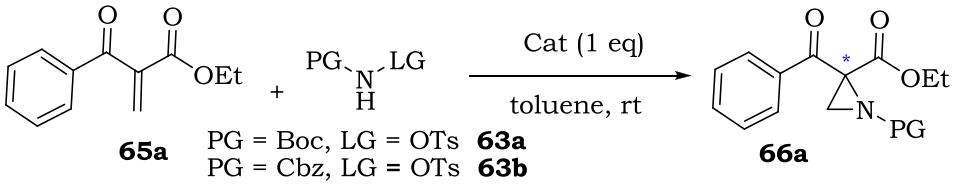
Acrylates **65** were prone to polymerization reaction, so they have to be used freshly prepared.

5.2.2 Asymmetric Aziridination Reaction

First experiments were directed to select a good class of promoters for the aziridination reaction of model ethyl benzoyl acrylate **65a** with Boc or Cbz *N*-protected *O*-tosyl hydroxylamines **63a** and **b**, as summarized in Table 5.1. For the first screening a stoichiometric amount of structurally different bifunctional organocatalysts was employed because in the process *p*-toluene sulfonic acid is released in the reaction mixture and could poison the organocatalyst.

Quinine **1** furnished the aziridine **66a** in high yield but almost as a racemate (entry 1), whereas with cinchona derived thioureas **72** a significant improvement of the enantioselectivity could be observed (entry 2). Reagent **63b** gave slightly inferior results in terms of stereocontrol with catalysts **72** and **28** (entries 3 and 4). Pleasingly, performing the reaction with the Takemoto thiourea **73a** led to the product with 72% and 69% *ee* respectively for compound **63a** and **63b** (entry 5 and 6). Structurally similar thioureas **7** and **73b** were tested, but the primary amine derivative **7** gave a racemic product, whereas **73b**, bearing longer alkyl chains at the nitrogen atom, afforded the product with 56 % *ee* (entries 7 and 8).

Table 5.1 Screening of the catalysts for the aziridination reaction between nitrogen nucleophiles **63** and acrylate **65a**.[a]

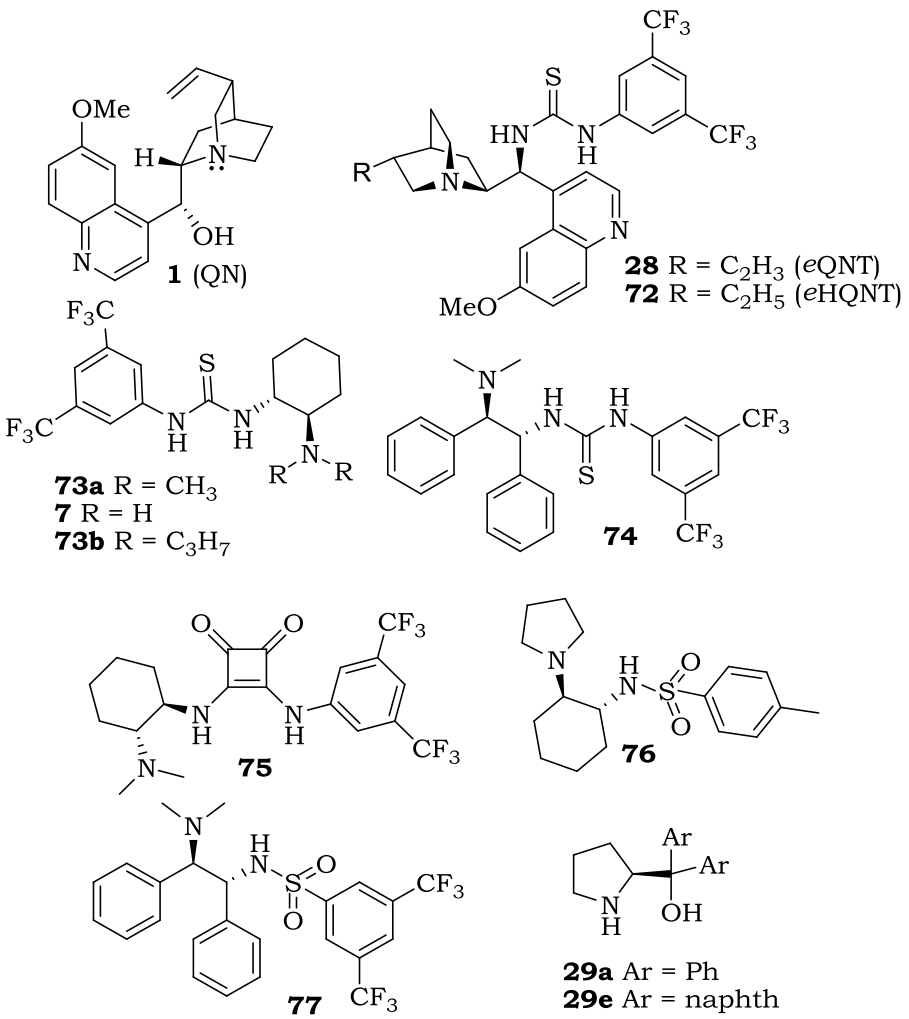


65a PG = Boc, LG = OTs **63a**
PG = Cbz, LG = OTs **63b**

66a

Entry	63	Promoter	t (h)	yield %[b]	ee %[c]
1[d]	**63a**	**1**	2	90	9
2	**63a**	**72**	6	92	-51
3	**63b**	**72**	6	40	-47
4	**63b**	**28**	4	77	-45
5	**63a**	**73a**	7	76	72
6	**63b**	**73a**	5	59	69
7	**63a**	**7**	5	42	Rac
8	**63a**	**73b**	2	99	56
9	**63a**	**74**	2	50	36
10[e]	**63a**	**75**	2	43	14
11	**63a**	**76**	24	96	10
12	**63a**	**77**	21	71	-10
13[d]	**63a**	**29a**	6	93	39
14	**63b**	**29a**	6	75	46
15	**63a**	**29e**	5	72	38
16	**63b**	**29e**	15	84	48

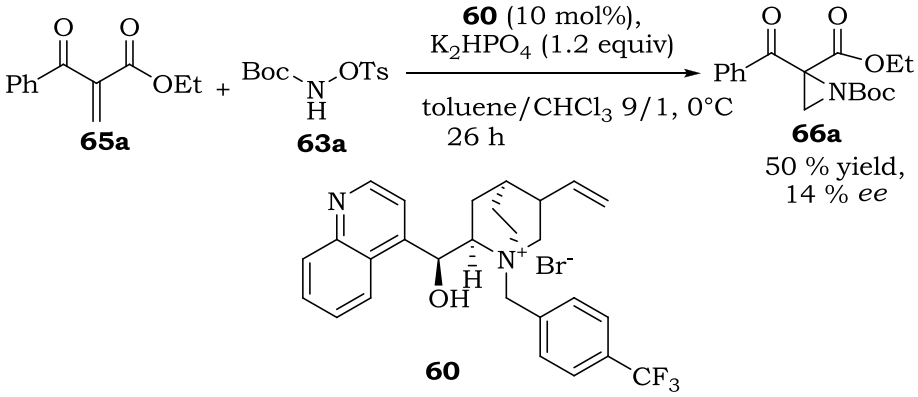
[a] Unless otherwise noted, reactions were carried out with **65a** (0.1 mmol), **63**(0.1 mmol), catalyst (0.1 mmol) in toluene (2 mL). [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis.[d] Reaction performed at C = 0.1 M [e] Reaction performed with 5 mol% of catalyst **75** with K_2CO_3 (0.1 mmol).



The diphenyl dimethyldiamine based thiourea **74** was less efficient than Takemoto catalyst **73a** (entry 9). Squaramide **75**, employed at catalytic loading due to its low solubility, revealed to be moderately active but less selective that the corresponding thiourea **73a** (entry 10). Catalysts bearing a sulfonamide unit **76** and **77** proved to be active although poorly enantioselective compounds (entries 11 and 12). Finally, diaryl prolinols **29a**, **e** gave good conversion to the product, although a moderate level of enantiocontrol was observed (entries 13-16) These findings showed that catalyst being able to provide double hydrogen bonding interactions, such

as thiourea derivatives, proved to be the most efficient catalysts for this reaction.

Phase transfer catalyst **60** was also tested, although it proved to be a poorly effective promoter (scheme 5.16).

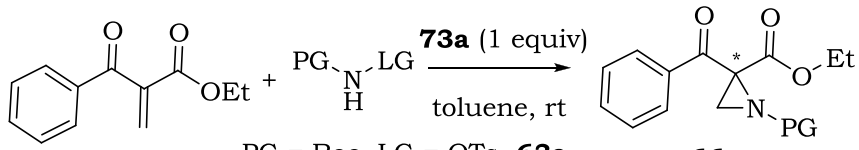


Scheme 5.16 Aziridination of alkene **65a** with phase transfer catalysis.

Different ambiphilic nitrogen sources were then investigated in the presence of the catalyst **73a**,[150] showing that the nature of *N*-protecting (PG) and leaving groups (LG) had a strong effect on the reactivity and the selectivity of the reaction (Table 5. 2). The Boc protected tosyl hydroxylamine **63a** was confirmed to be the most effective nucleophile although the Cbz-protected **63b** gave similar results (entries 1 and 2). The tosyl protecting group had a detrimental effect on the stereocontrol (entry 3), as previously noted for the analogous reaction on the aldehyde.[145a] The acetate derivative did not react and only starting material was recovered (entry 4). The phosphinate protected compound **63f** afforded a modest result in terms of enantiocontrol (entry 5).

[150] For the synthesis of the protected amine, see: a) Ł. Albrecht, H. Jiang, G. Dickmeiss, B. Gschwend, S. G. Hansen, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2010**, *132*, 9188; b) L. Deiana, P. Dziedzic, G.-L. Zhao, J. Vesely, I. Ibrahem, R. Rios, J. Sun, A. Córdova, *Chem. Eur. J.* **2011**, *17,* 7904.

Table 5.2 Screen of protecting and leaving groups on the nitrogen source.[a]



65a

PG = Boc, LG = OTs **63a**
PG = Cbz, LG = OTs **63b**
PG = Ts, LG = OTs **63c**
PG = Boc, LG = OAc **63e**
PG = Boc, LG = $PO(Ph)_2$ **63f**

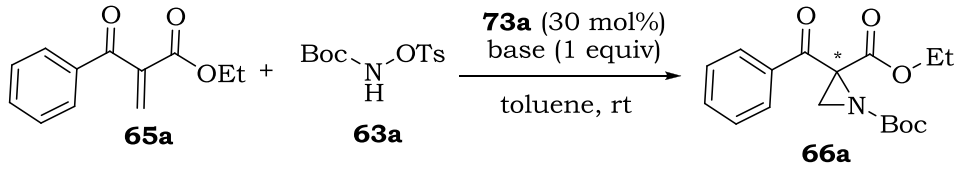
66

Entry	63	t (h)	66a	yield (%)[b]	ee (%)[c]
1	**63a**	7	**66aa**	76	72
2	**63b**	4.5	**66ab**	59	69
3	**63c**	21	**66ac**	61	36
4	**63e**	3	**66aa**	/	/
5	**63f**	1	**66aa**	39	34

[a] Unless otherwise noted, reactions were carried with **65a** (0.1 mmol), **63** (0.1 mmol), catalyst (0.1 mmol) in toluene (2 mL). [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

In order to develop a catalytic aziridination reaction a variety of basic additives were tested as scavengers of *p*-toluene sulfonic acid. Organic and inorganic bases, at stoichiometric loading, were added under previously optimized conditions (Table 5.3). Organic bases appeared to compete with the organocatalyst, leading to loss of enantioselectivity (entries 1-2). Inorganic bases were more effective as illustrated when using $NaHCO_3$, AcONa, $PhCO_2Na$, Na_2CO_3 and K_2CO_3 which provided the product with good level of enantioselectivity (entries 3-7).

Table 5.3 screening of the basic additive in the catalytic aziridination reaction. [a]



65a **63a** **66a**

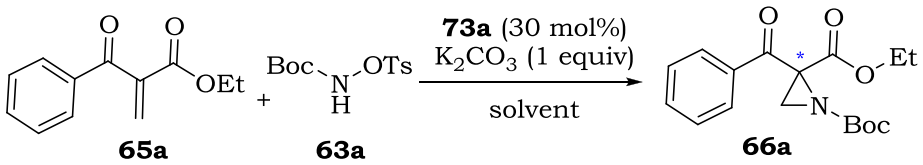
Entry	Base	t(h)	yield %[b]	ee%[c]
1	Et_3N	0.5	40	46
2	Proton-sponge	0.5	58	58
3	$NaHCO_3$	2	70	65
4	AcONa	2	69	78
5	$PhCO_2Na$	1.5	48	78
6	Na_2CO_3	3	68	76
7	K_2CO_3	2	72	78
8	K_2CO_3[d]	2	67	66
9	K_2CO_3[e]	2	30	0

[a] Reaction conditions: **65a** (0.1 mmol), **63a** (0.1 mmol), and **73a** (0.03 mmol) in 2mL of toluene. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 3 eq of K_2CO_3 were employed. [e] Background reaction, performed in the absence of the catalyst.

K_2CO_3 revealed to be the most suitable base furnishing the product with 72% yield and 78% *ee* (entry 7). An excess of the base resulted in a drop of reactivity and enantiocontrol (entry 8). To check the relevance of background aziridination provided by K_2CO_3, the reaction was carried out without the organocatalyst (entry 9). The racemic route to aziridine was not found to be a negligible process.

Other reaction parameters were screened in the asymmetric catalytic aziridination (Table 5.4).

Table 5.4 Optimization of reaction parameters.[a]



65a **63a** **66a**

Entry	Solvent	T(°C)	t(h)	yield %[b]	*ee* %[c]
1	*m*-xylene	rt	2	63	72
2	Diethyl ether	rt	2.5	83	68
3	Cl-benzene	rt	2	39	58
4	chloroform	rt	2	69	54
5	C_6F_6	rt	2	44	50
6	toluene	0	2	98	74
7 [d]	toluene	0	3.5	95	78
8[d]	toluene	-20	24	91	66

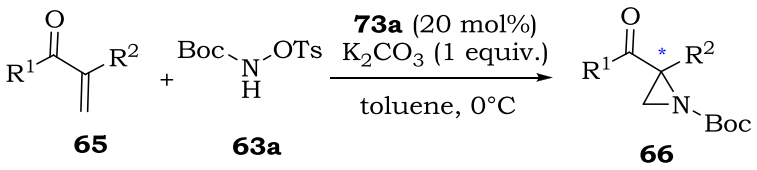
[a] Unless otherwise noted, reactions were carried with **65a** (0.1 mmol), **63a**(0.1 mmol), catalyst (0.03 mmol) in toluene (2 mL). [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis on a chiral stationary phase. [d] 20 mol% of **73a**.

m-Xylene furnished the product in moderate yield and 72% *ee* (entry 1) and diethyl ether improved the conversion maintaining the level of enantioselectivity (entry 2). Halogenated solvents had a detrimental effect on the reactivity and the stereocontrol of the reaction (entries 3-5). Lowering the temperature helped to significantly improve the conversion to the product although without observing any enhancement of the

enantioselectivity (entry 6 and 8). Reduced catalyst loading to 20 mol%, when working at 0°C, enabled to achieve a satisfactory result (entry 7).

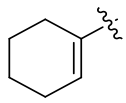
With the optimised conditions in hands, we examined the scope of the aziridination reaction (Table 5.5).

Table 5.5 Scope of the aziridination reaction.[a]



65 **63a** **66**

Entry	R^1	R^2	t (h)	66	Yield (%)[b]	ee (%)[c]
1	Ph	CO_2Et	3.5	**66a**	95	78
2	4-MeC_6H_4	CO_2Et	8	**66b**	84	78
3	3-MeC_6H_4	CO_2Et	18	**66c**	80	82
4	2-MeC_6H_4	CO_2Et	8	**66d**	91	50
5	4-$MeOC_6H_4$	CO_2Et	29	**66e**	93	80
6	4-ClC_6H_4	CO_2Et	20	**66f**	98	78
7	3-BrC_6H_4	CO_2Et	16	**66g**	87	70
8	2-naphthyl	CO_2Et	15	**66h**	93	74
9	2-furyl	CO_2Et	19	**66i**	86	74

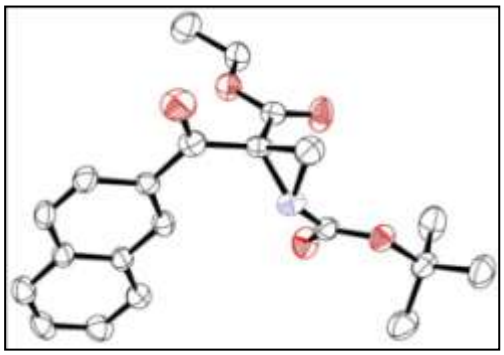
10		CO_2Et	24	**66j**	67	74
11	Ph	CO_2Me	6	**66k**	79	78
12	Ph	$CO_2{}^tBu$	5	**66l**	83	76
13	Ph	CO_2Bn	4	**66m**	79	72
14	Ph	$PO(OEt)_2$	15	**66n**	72	50
15	NHBn	CO_2Et	18	**66o**	82	72

[a] Reaction conditions: **65** (0.1 mmol), **63a** (0.1 mmol), **73a** (0.02 mmol), K_2CO_3 (0.1 mmol) in 2 mL of toluene. [b] Yield of isolated product.[c] Determined by HPLC analysis on a chiral stationary phase.

Electron withdrawing and electron donating substituents on the aromatic ring were well tolerated at the *para* and *meta* positions, while the *ortho* methyl derivative **65d** led to the corresponding aziridine in good yield but lower *ee* values (entries 2-7). The naphthyl and heteroaromatic derivatives **65h**, **65i** afforded the corresponding aziridines in high yield and 74% *ee* (entries 8-9). The cyclohexenyl acrylate **65j** was slightly less reactive but the reaction was regioselective and the product was obtained with 74% *ee* (entry 10). The bulkiness and the nature of the ester group in the acrylate **65** slightly influenced the outcome of the reaction (entries 11-13). Different functionalities, such as phosphonate and amide groups were tolerated on the starting alkene, leading to the aziridines with slightly lower enantioselectivity (entries 14-15).

5.2.3 Determination of the Absolute Configuration

The absolute configuration of the quaternary sterocenter of the aziridines **66** was determined to be R by X-ray analysis on a single crystal of the naphthyl derivative **66h** (Figure 5.5).



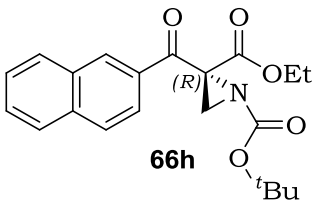


Figure 5.5 Crystal structure of aziridine **66h**.

With the knowledge of the absolute configuration and reminding the transition state proposed by Takemoto in the Michael addition to imides with the catalyst **73a**,[114a] we speculated on the origin of the enantiocontrol that occurred in the second step. The prochiral enolate, formed by attack of the nucleophile to the olefin, is involved in a hydrogen bonding network with the catalyst, so that the intramolecular S_N2 displacement is assisted by the ammonium portion of the catalyst. Preferential *Re*-face closure would lead to the R enantiomer (Figure 5.6).

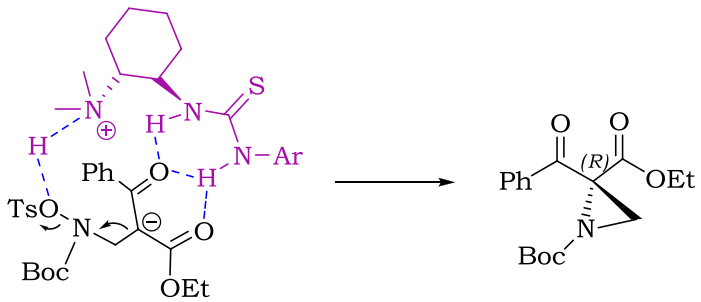
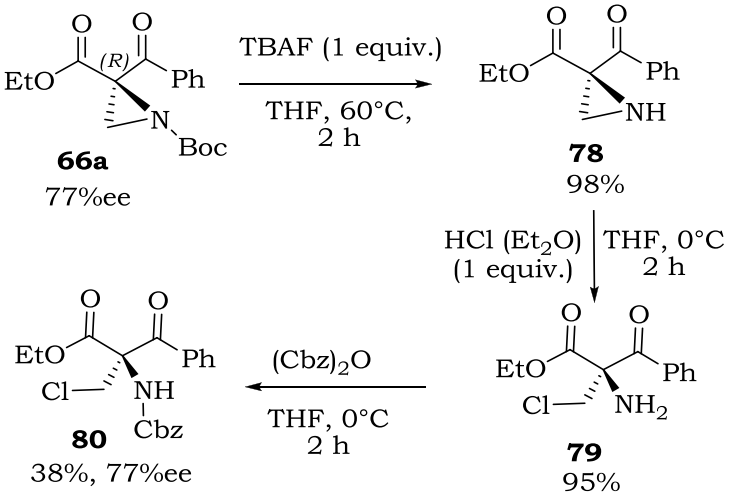


Figure 5.6 Transition state proposal for the ring closure step.

5.2.4 Regioselective Opening of the Aziridine 66a

Enantiomerically enriched terminal aziridines are interesting intermediates for the synthesis of highly desirable amino acid derivatives. A preliminary investigation demonstrated the synthetic potential of aziridine **66a** to obtain α,α-disubstituted α-amino acid esters with a quaternary center (Scheme 5.17).



Scheme 5.17 Access to α,α-disubstituted α-amino acid esters from aziridine **66a**.

Enantioenriched aziridine **66a** was deprotected with tetrabutyl ammonium fluoride (TBAF) to furnish the aziridine **78** in excellent yield. Ring opening of the aziridine with an ethereal solution of HCl was found to give regioselectively the expected α-aminoacid ester **79** with 95% yield. No racemization occurred as proved by HPLC analysis conducted on the Cbz-protected product **80**.

5.3 Conclusion

In conclusion an asymmetric aza-MIRC process for the synthesis of highly functionalised terminal aziridines bearing a quaternary stereogenic center employing the commercially available thiourea **73a**/K_2CO_3 system was developed. By reacting easily available α-acyl acrylates with tosyloxy carbamates, the aziridines were obtained in high yield and good enantioselectivity, up to 82% *ee*. The aziridines represent valuable intermediates to access highly desirable α,α-disubstituted α-amino acid esters.

Mülheim an der Ruhr

(Germany)

Under the supervision of Prof. B. List

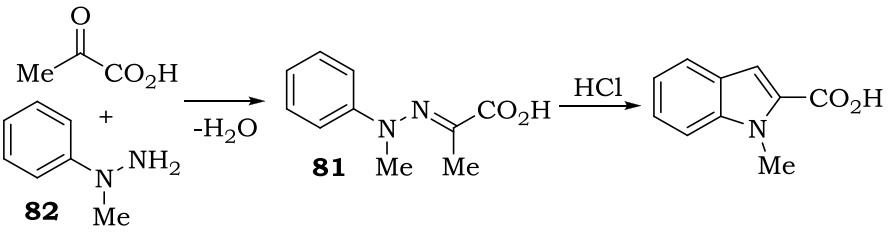
6. AN ORGANOCATALYTIC SYNTHESIS OF HELICENES

(the reported results were obtained in collaborative effort with Dr. M. J. Webber)

6.1 Introduction

6.1.1 The Fischer indolization

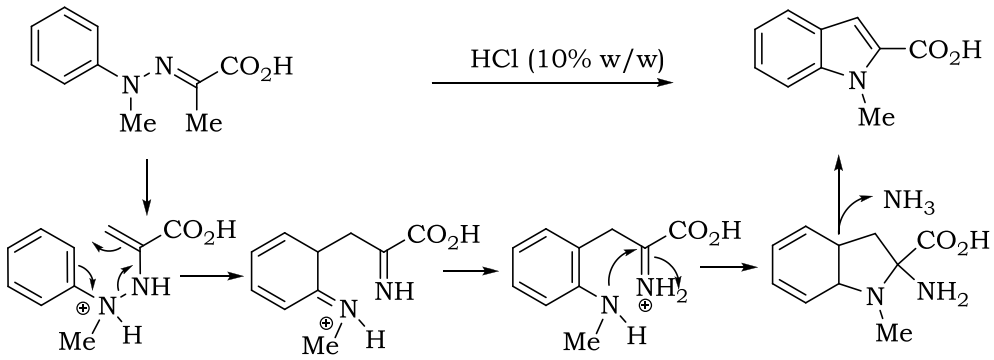
The Fischer indolization is still one of the main routes to synthesize indoles. It was discovered more than 120 years ago that heating the hydrazone **81** (derived from *N*-methyl phenyl hydrazine **82** and piruvic acid) in hydrochloric acid a new compound was obtained with loss of ammonia (Scheme 6.1).[151]



Scheme 6.1 Fischer indolization route to access indoles.

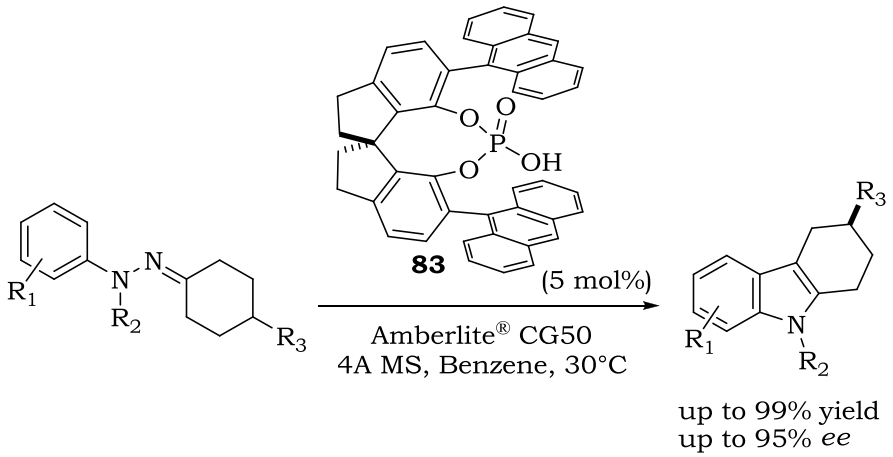
Initially proposed mechanisms eventually were shown to be wrong and only in 1924 Robinson and Robinson proposed the mechanism that is still accepted today (Scheme 6.2). It involvs a [3,3]-sigmatropic rearrangement and the generated imine undergoes intramolecular attack. By loss of ammonia the energetically favoured indole ring is formed.[152]

[151] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559.
[152] G. M. Robinson, R. Robinson, *J. Chem. Soc., Trans.* **1924**, *125*, 827.



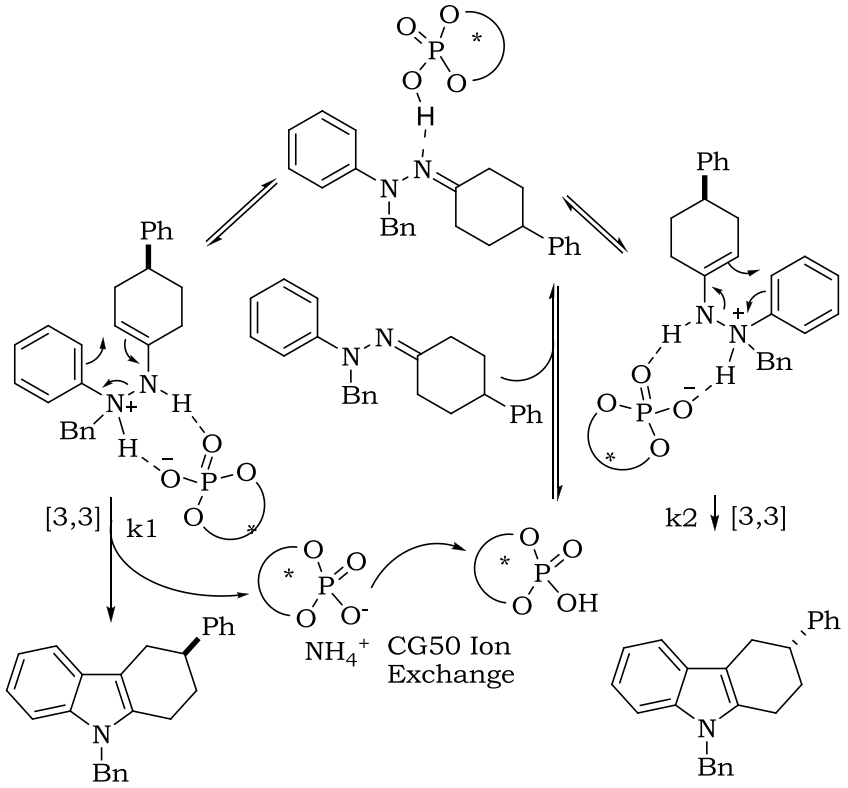
Scheme 6.2 Accepted mechanism for the Fischer indolization.

The Fischer indolization usually requires rather harsh conditions and a stoichiometric amount of acid to efficiently promote the reaction since ammonia is developed as by-product that can potentially quench the acid. Indole is a flat, achiral molecule but it is also possible to generate chiral products by means of Fischer indolization: enantioenriched indolenines and tetrahydrocarbazoles are only two of the possible examples. Recently, the List group reported the first catalytic asymmetric version of the Fischer indolization on 4-substituted cyclohexanone-derived phenylhydrazones. It was promoted by 5 mol % of a novel spirocyclic chiral phosphoric acid **83**, with a weakly acidic cation-exchange polymer as ammonia scavenger (Amberlite® CG50) (Scheme 6.3).[35]



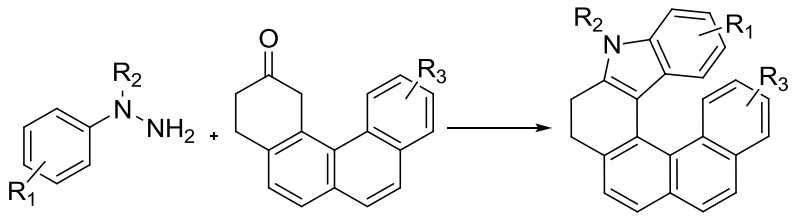
Scheme 6.3 The first asymmetric catalytic Fischer indolization.

The mechanism proposed by the authors involves a dynamic kinetic resolution in which one of the two possible diastereoisomeric ion pairs hydrazone-catalyst undergoes the [3,3] sigmatropic rearrangement to give the product at a higher rate (Scheme 6.4). The two complexes hydrazone-substrate are reversibly formed via protonation of the substrate by the chiral catalyst, followed by the irreversible pericyclic process thus leading to a quantitative yield of the highly enantioenriched product.



Scheme 6.4 Proposed mechanism based on a kinetic dynamic resolution.

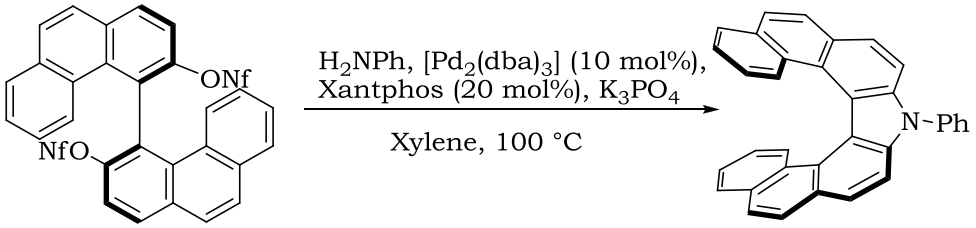
Another possible application of the asymmetric Fisher indolization could involve the synthesis of helical chiral molecules containing an indole moiety (Scheme 6.5).



Scheme 6.5 Synthesis of helicenes starting from hydrazine and polycyclic ketone.

6.1.2 Helicenes

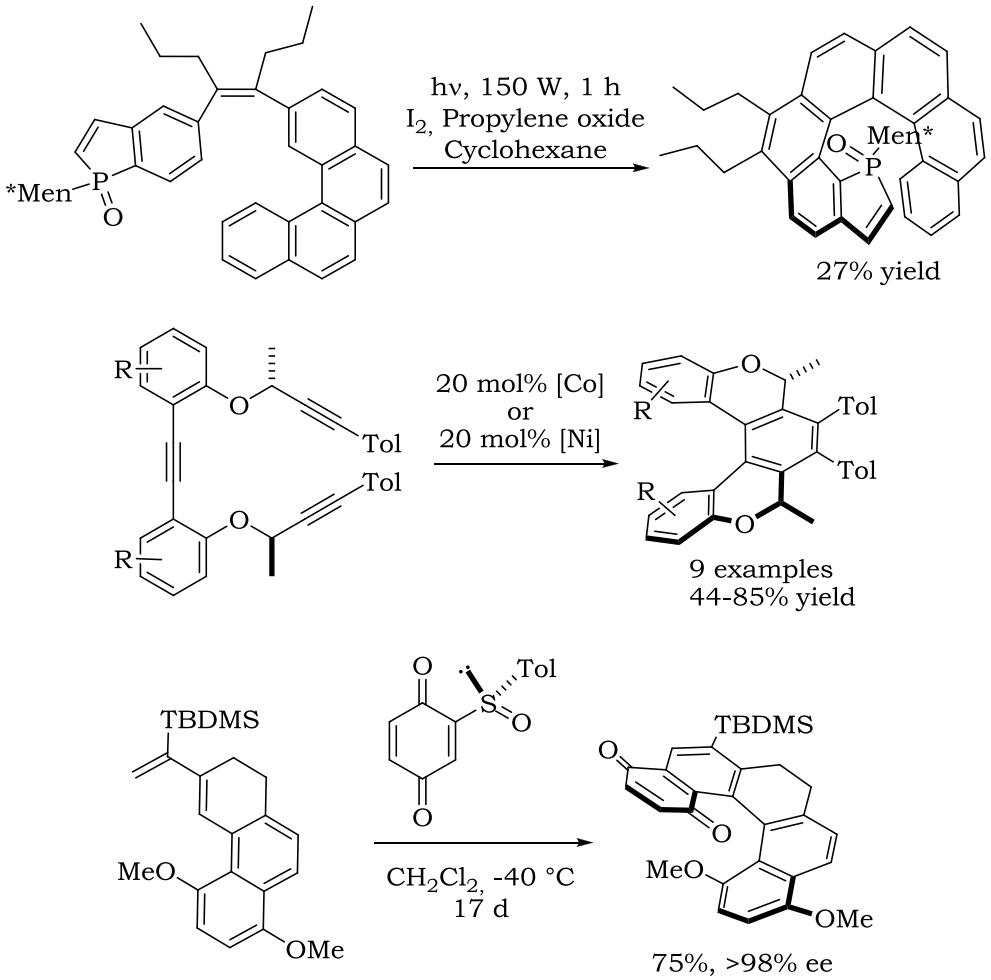
"Helicenes are polycyclic aromatic compounds with nonplanar screw-shaped skeletons formed by ortho-fused benzene or other aromatic rings."[153] They are known to have interesting optical and electronic properties exploited in some applications (as ligands, chiral auxiliaries or catalysts, but also as molecular machines and dye material). The bottle neck to their wide diffusion still concerns their synthesis and/or resolution; the main strategies developed until now to obtain enantioenriched and functional helicenes involve the use of chiral starting materials[154] or chiral auxiliaries[155] (Scheme 6.6).



>99% ee

94% yield, >99% ee

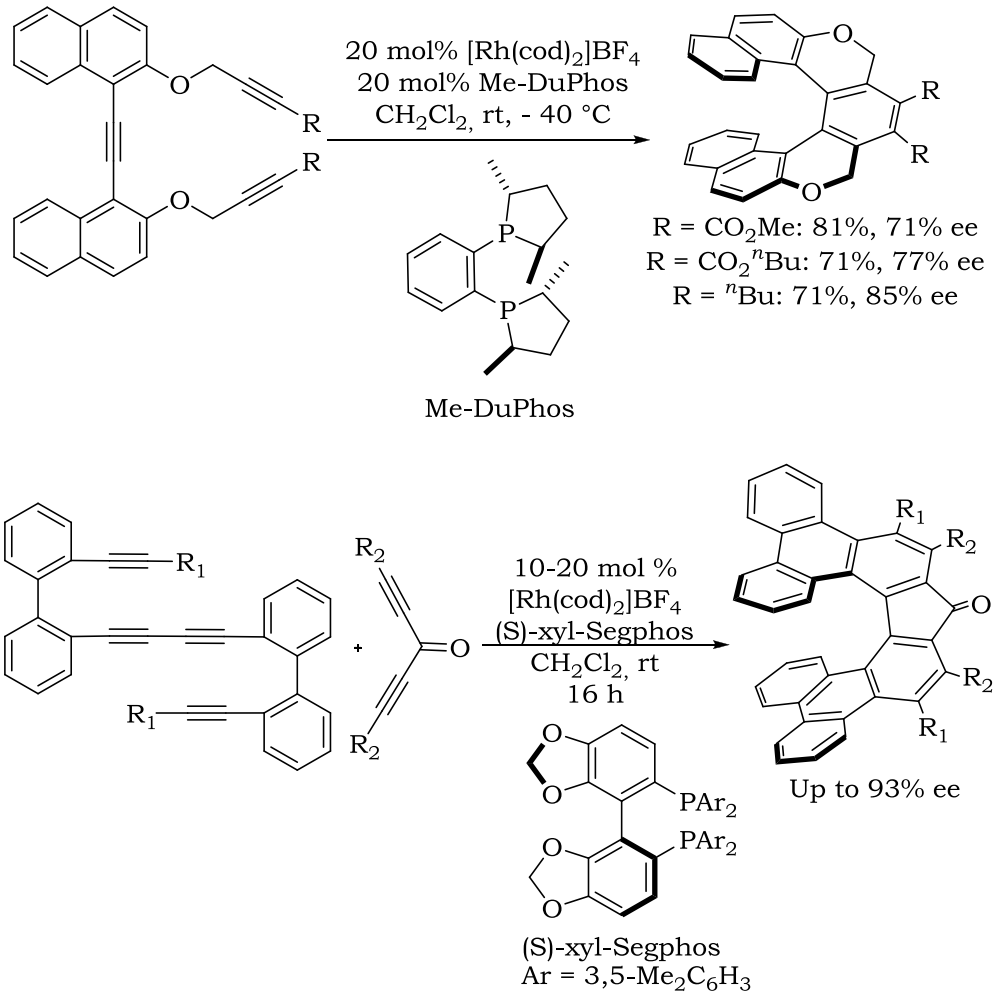
[153] For a review see: Y. Shen, C. F. Chen, *Chem. Rev.* **2012**, *112*, 1463.
[154] a) K. Nakano, Y. Hidehira, K. Takahashi, T. Hiyama, K. Nozaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 7136; b) K. Yavari, S. Moussa, B. Ben Hassine, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem., Int. Ed.* **2012**, *51*, 6748; c) J. Žádný, A. Jančařík, A. Andronova, M. Šámal, J. Chocholoušová, J. Vacek, R. Pohl, D. Šaman, I. Císařová, I. Stará, I. Starý, *Angew. Chem., Int. Ed.* **2012**, *51*, 5959.
[155] M.C. Carreño, S. García-Cerrada, A. Urbano, *J. Am. Chem. Soc.* **2001**, *123*, 7929.



Scheme 6.6 Synthesis of optically active and functional helicenes.

Only few examples of asymmetric catalytic synthesis of helicenes can be found in the literature, based on starting materials requiring multi-step synthesis and suffering from lack of a wide substrate scope. Tanaka in 2007 and in 2012 proposed two Rh-catalyzed reactions to access helicenes and hetero-helicenes (Scheme 6.7).[156]

[156] a) K. Tanaka, A. Kamisawa, T. Suda, K. Noguchi, M. Hirano, *J. Am. Chem. Soc.* **2007**, 129, 12078; b) Y. Sawada, S. Furumi, A. Takai, M. Takeuchi, K. Noguchi, K. Tanaka, *J. Am. Chem. Soc.* **2012**, *134*, 4080.

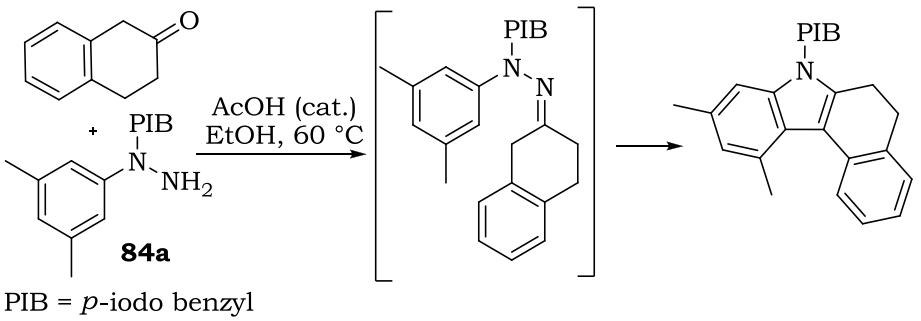


Scheme 6.7 Asymmetric Rh-catalyzed synthesis of helicenes.

6.2 Results and Discussion

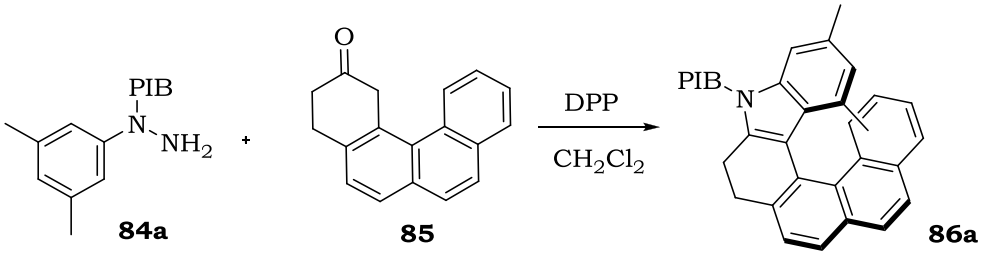
6.2.1 Preliminary Studies

On the basis of previous results obtained in the List group,[35] mixing the hydrazine **84** and 2-tetralone in EtOH with a catalytic amount of acetic acid at 60 °C the hydrazone was expected to form. Instead, the only isolated compound was the Fisher indolization product (Scheme 6.8).



Scheme 6.8 Indole formation by reaction of hydrazine and tetralone.

Performing the reaction with the polycyclic aromatic ketone **85** and stoichiometric amount of the diphenyl phosphoric acid (DPP), the dihydrohelicene **86a** was obtained after few hours at room temperature (Scheme 6.9).



Scheme 6.9 Synthesis of the dihydrohelicene **86a** by means of Fischer indolization.

The influence of Amberlite CG50 and MS on the rate of the process was investigated in the racemic reaction between dimethyl *N*-PIB protected hydrazine **84a** and the polycyclic ketone **85** (Figure 6.1).

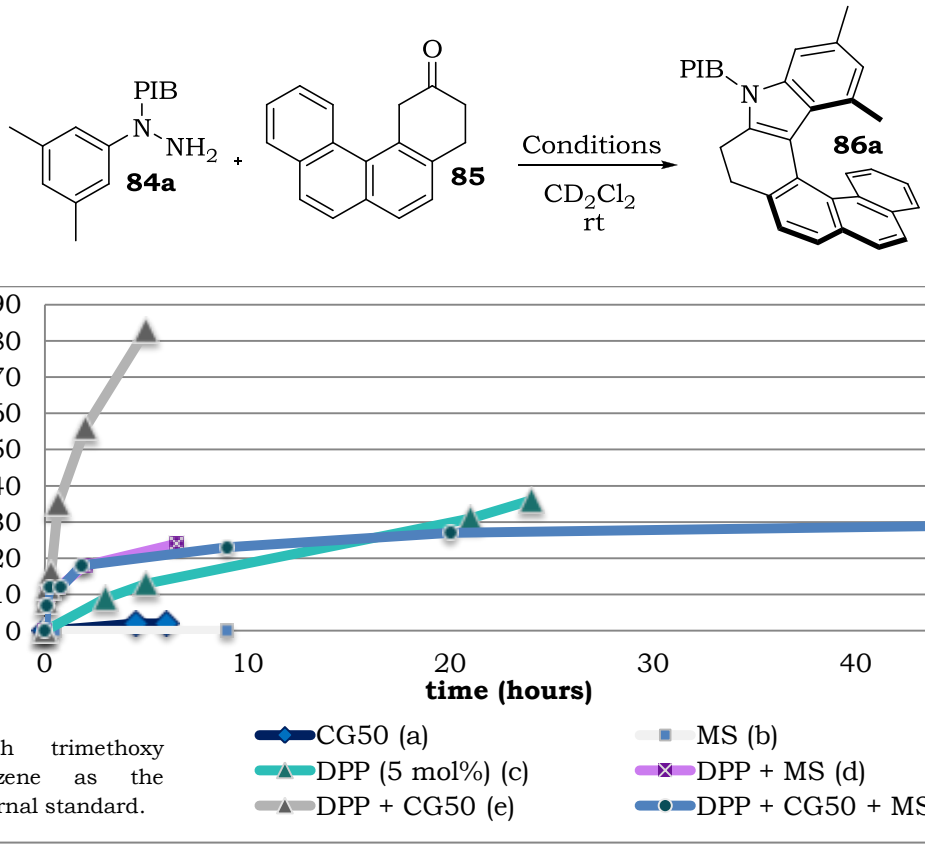
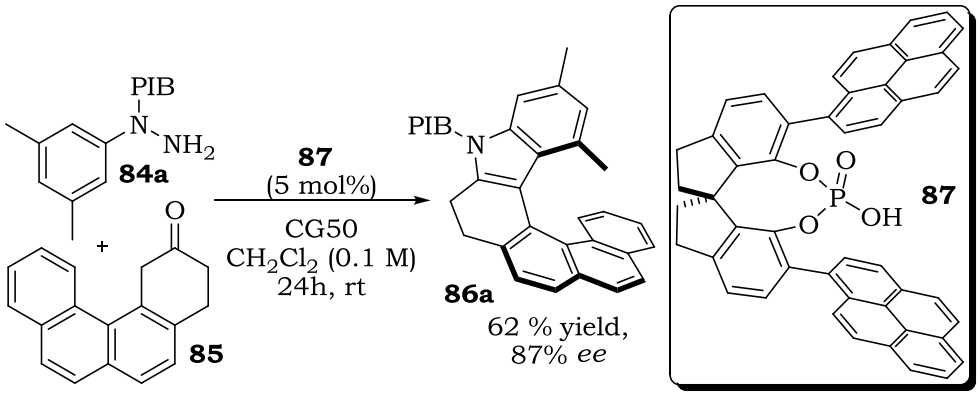


Figure 6.1 Influence of the CG50 and the molecular sieves on the rate of the process.

Background reactions in the absence of the catalyst were not observed using either CG50 alone or molecular sieves alone (lines a and b). In the presence of 5 mol% of the diphenyl phosphoric acid (DPP) the reaction proceeded slowly, but seemed to have a certain extent of turnover, indeed after 24 hours the NMR yield was 34% (line c). The presence of molecular sieves did not improve the reactivity of the system (line d), while the reaction rate substantially increased with the addition of the weakly acidic polymer Amberlite CG50 (the NMR yield was more than 80 % in 5 hours) (line e). The presence of both molecular sieves and CG50 was detrimental for the NMR yield of the process (line f), even if it is important to consider the occurrence of by-products over time.

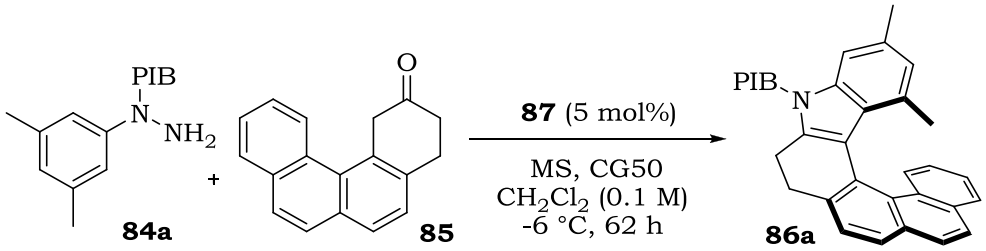
Among different BINOL and SPINOL-based phosphoric acids, the SPINOL-pyrene derivative **87** proved to be the best catalyst and dichloromethane the best solvent to achieve the highest enantioselectivity (Scheme 6.10).



Scheme 6.10 Catalyst **87** as the best promoter for the Fischer indolization reaction.

Reaction conditions were optimized performing the reaction with 5 mol% of catalyst **87** at -6°C (Table 6.1). The amount of CG50 did not seem to affect the enantioselectivity up to 1g/mmol ratio of CG50 to substrate (entries 1-3) but with a ratio of 2g/mmol, the enantioselectivity dropped (entry 4). Decreasing the ratio of molecular sieves to substrate from 2 to 0 g/mmol facilitated a slight increase in enantiocontrol up to 91% *ee* (entries 5-7). The selectivity of the reaction did not significantly improve when working at different concentration (entries 8-9).

Table 6.1 Investigation of some condition parameters.[a]

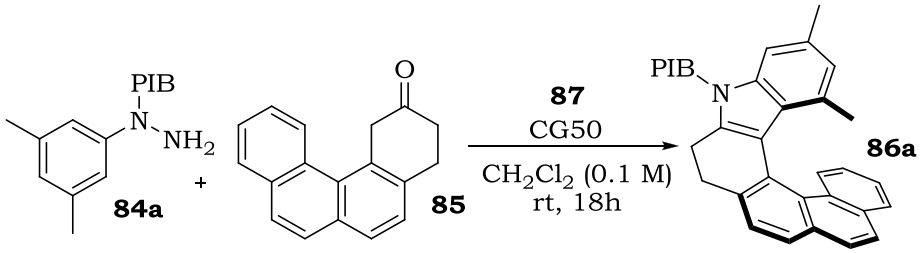


Entry	CG50 (g/mmol)	MS (g/mmol)	C (M)	*ee*[b]
1	0.1	0.5	0.1	88
2	0.5	0.5	0.1	90
3	1	0.5	0.1	88
4	2	0.5	0.1	81
5	0.5	2	0.1	81
6	0.5	1	0.1	88
7	0.5	/	0.1	91
8	0.5	/	0.05	84
9[c]	0.5	/	0.2	87

[a] reaction conditions: **84a** (0.025 mmol) and **85** (0.025 mmol) in CH_2Cl_2 with **87** ($1.25*10^{-3}$ mmol) and CG50 and/or MS. [b] determined by HPLC analysis on a chiral stationary phase. [c] 20 h

A brief screen of catalyst loading was then performed at room temperature (Table 6.2). The model reaction carried out at room temperature with 5 mol% of catalyst afforded the product with 80% *ee* after 18h (entry 1). Decreasing or increasing the amount of the phosphoric acid **87** reduced and improved the yield, respectively, without affecting the enantiocontrol (entries 2 and 3).

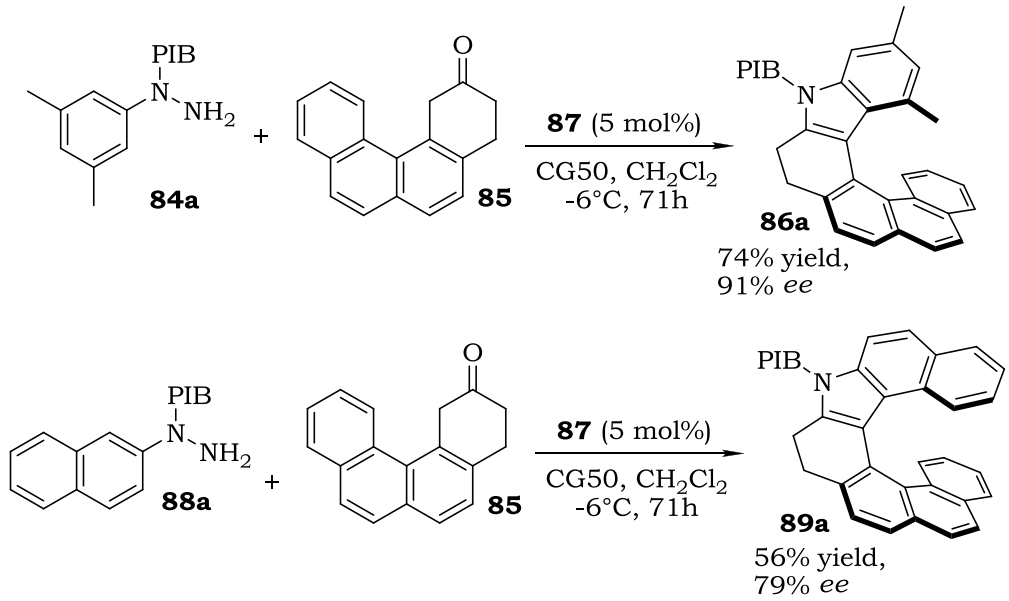
Table 6.2 Catalyst loading study.[a]



Entry	87 (mol%)	NMR yield[b]	*ee*[c]
1	5	39	80
2	2	27	79
3	10	51	80

[a] Reaction conditions: **84a** (0.025 mmol) and **85** (0.025 mmol) in CH_2Cl_2 in 250 μL with **87** ($1.25*10^{-3}$ mmol) and CG50 and/or MS. [b] Determined using trimethoxy benzene as the internal standard; [c] Determined by HPLC analysis on a chiral stationary phase.

The reaction carried out with hydrazine **84a** and ketone **85**, under the optimized conditions, furnished the product **86a** with 74% yield and 91% *ee*. The employment of the naphthyl hydrazine **88a** with the same ketone led to the expected product **89a** in 56% yield and 79% *ee* (Scheme 6.11).



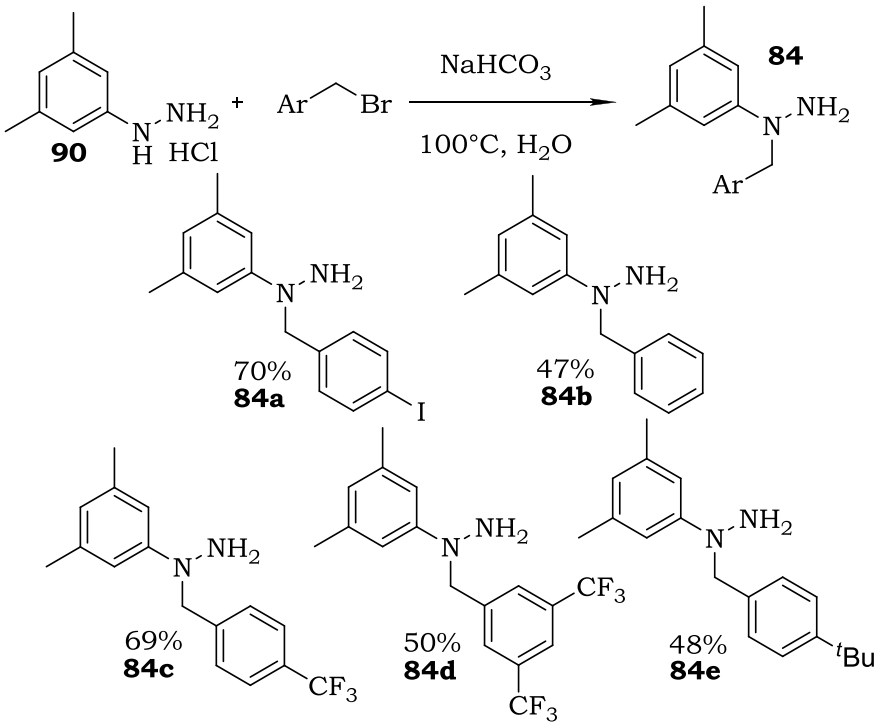
Scheme 6.11 Synthesis of the helicenes **86a** and **89a**.

6.2.2 Synthesis of the Starting Materials.

6.2.2.1 Synthesis of the Hydrazines

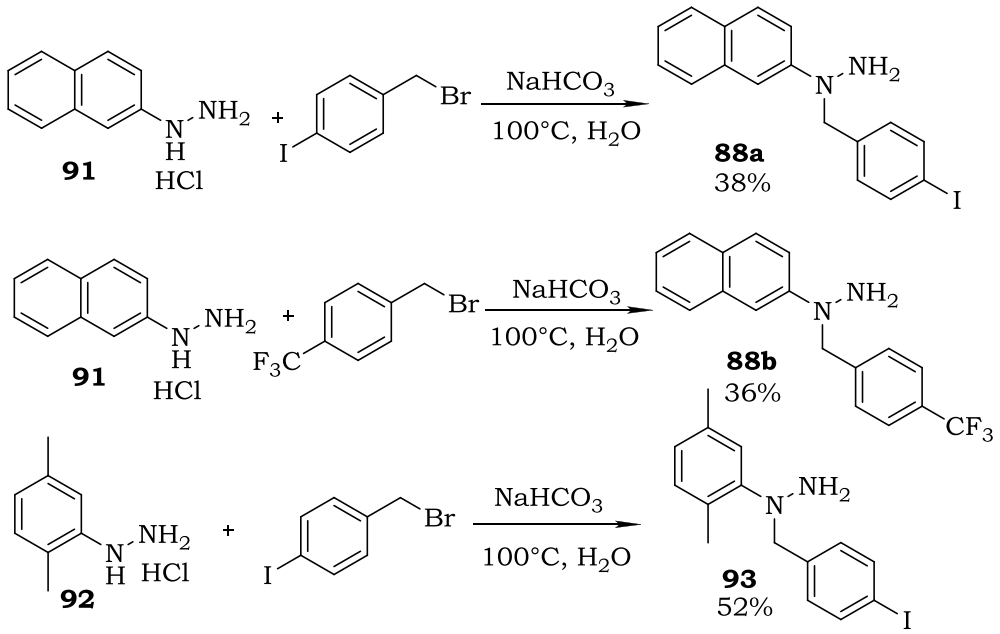
N-Protected hydrazines were synthesized following a literature procedure.[157] The hydrazine hydrochloride salt was treated with $NaHCO_3$ and the appropriate benzyl bromide in H_2O at 100°C to give the substitution product. Differently *N*-protected 3,5-dimethyl-phenyl hydrazine **84a-e** were obtained reacting 3,5-dimethyl-hydrazine hydrochloride salt **90** with differently substituted benzyl bromides (Scheme 6.12).

[157] R. B. Perni, G. W. Gribble, *Org. Prep. Proced. Int.* **1982**, *14*, 343.



Scheme 6.12 Differently *N*-protected 3,5-dimethyl-phenyl hydrazines **84a-e**.

Following the same procedure, naphthyl hydrazine hydrochloride salt **91** and 2,5-dimethyl hydrochloride salt **92** were employed to synthesize the *p*-iodo and *p*-trifluoromethyl benzyl naphthylhydrazines **88a** and **88b** and the *p*-iodo benzyl 2,5-dimethyl-phenyl hydrazine **93**, although the latter compound showed to be particularly unstable (Scheme 6.13). Yields of the desired products were only moderate because the reaction led to a mixture of the regioisomer compounds alkylated on the two different nitrogen atoms.

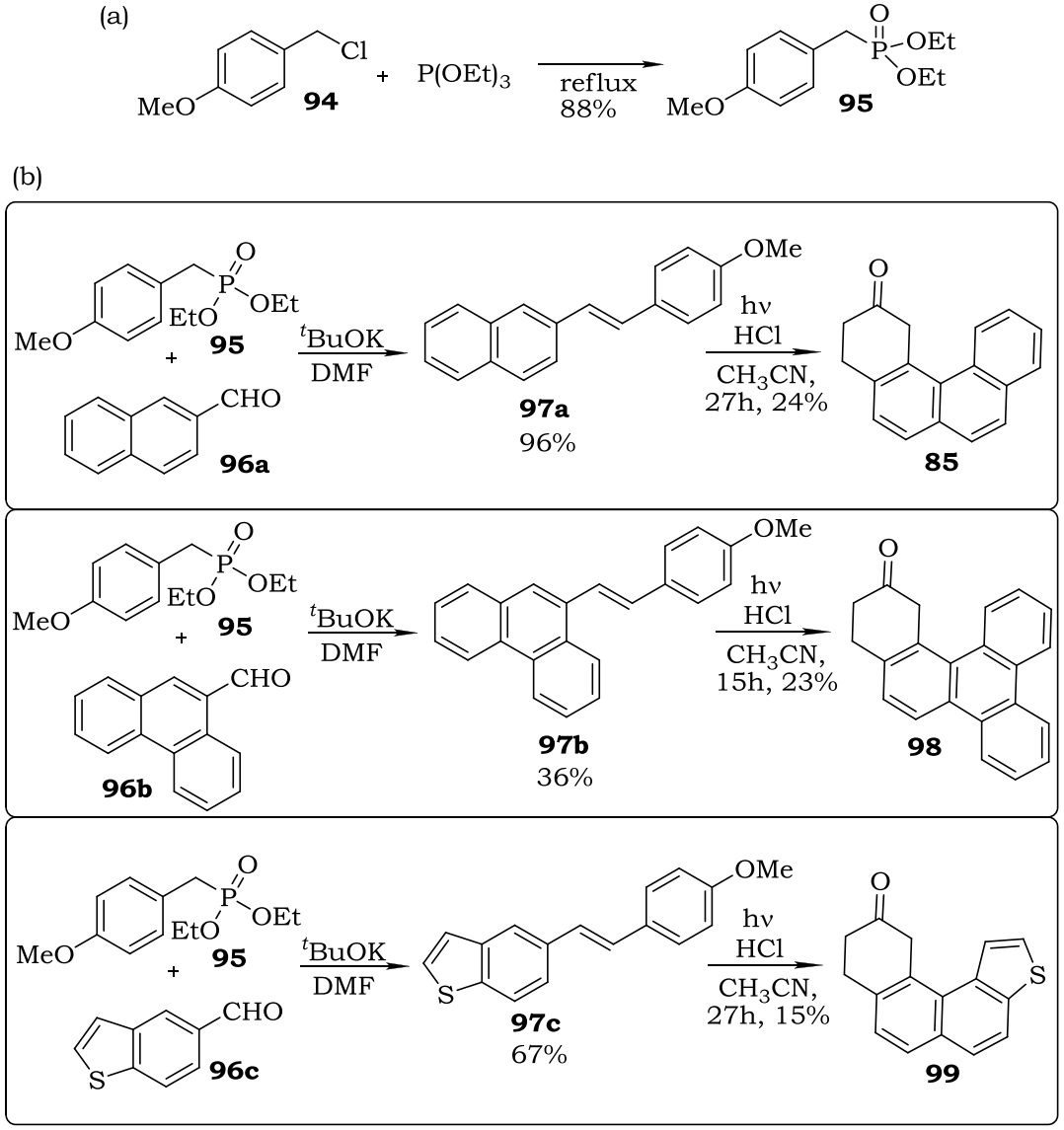


Scheme 6.13 Synthesis of hydrazines **88a**, **b** and **93**.

6.2.2.2 Synthesis of Ketones

The ketones were synthesized following procedures reported in the literature.[158] Refluxing methoxybenzylchloride **94** and triethylphosphite led to the methoxy benzylphosphonate **95** (Scheme 6.14 a). **95** was reacted with the aldehydes **96a-c** in DMF and with ^{t}BuOK as the base to furnish the corresponding stilbenes **97a-c**. Compounds **97a-c** were then subjected to a photochemical rearrangement with a Rayonet apparatus at 300 nm under acid conditions in CH_3CN to afford the ketones in low yield (Scheme 6.14 b).

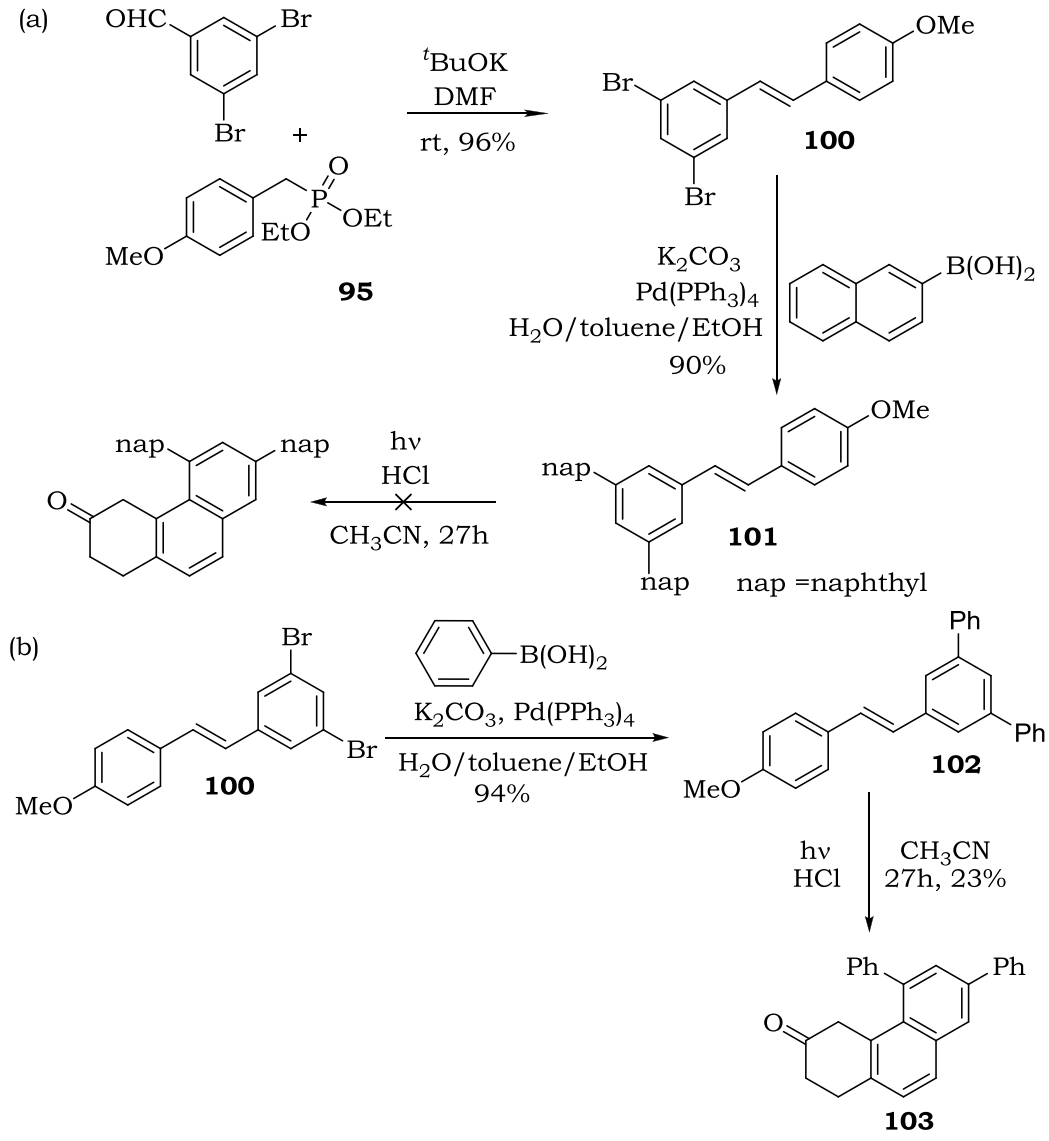
[158] a) J.-H. Ho, T.-I. Ho, R. S. Liu, *Org. Lett.* **2001**, *3*, 409; b) A. S. Khartulyari, M. Kapur, M. E. Maier, *Org. Lett.* **2006**, *8*, 5834.



Scheme 6.14 Synthetic route to ketones **85**, **98** and **99**.

The dibromo stilbene derivative **100**, obtained from dibromobenzaldehyde and phosphonate **95**, was subjected to the Suzuki coupling with naphthyl and phenyl boronic acids to give the corresponding products **101** and **102** in high yield. Unfortunately, the naphthyl derivative **101** was not a suitable substrate for the cyclization reaction (Scheme 6.15 a), whereas

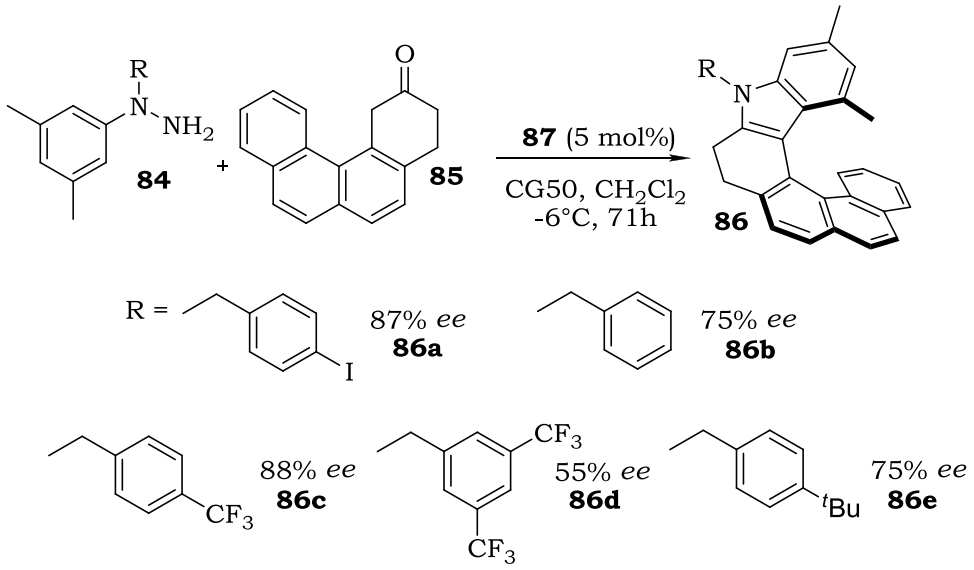
the diphenyl substituted stilbene **102** was successfully subjected to the cyclization reaction to give the polycyclic compound **103** (Scheme 6.15 b).



Scheme 6.15 Synthetic route to other ketones.

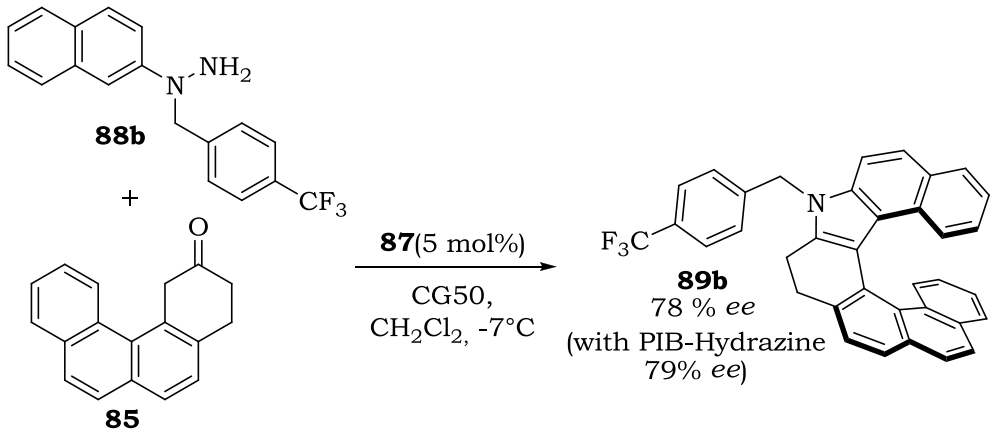
6.2.3 Study of the *N*-protecting Group

Replacement of the *p*-iodo benzyl group with the simple benzyl group (hydrazine **84b**) or the *p-tert*-butyl benzyl (hydrazine **84c**) or the *m,m*-trifluoromethylbenzyl (hydrazine **84d**) significantly decreased the enantiocontrol. The *p*-trifluoromethyl benzyl hydrazine **84e** furnished the product with a comparable level of enantioselectivity to the PIB protected compound (Scheme 6.16).



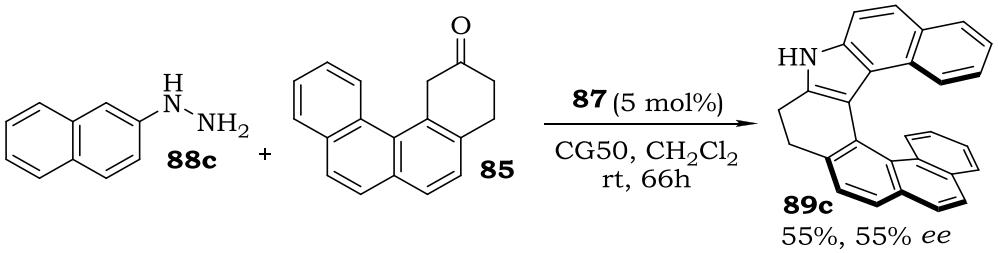
Scheme 6.16 Screen of different *N*-protecting groups.

The *p*-trifluoromethyl benzyl protecting group was tested on the naphthyl hydrazine (**88b**) leading to a result comparable to the reaction conducted on the PIB protected derivative (Scheme 6.17).



Scheme 6.17 Use of naphthyl hydrazine **88b** in the reaction.

The *N*-unprotected naphthyl hydrazine gave the desired product with only modest enantiocontrol (Scheme 6.18).

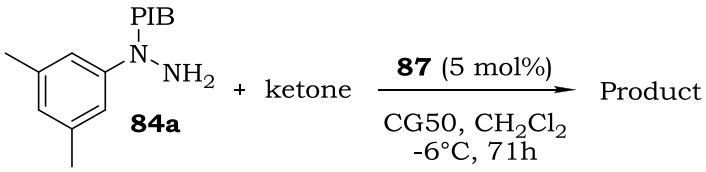


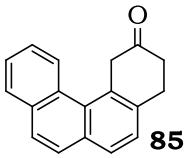
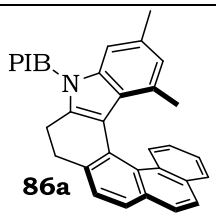
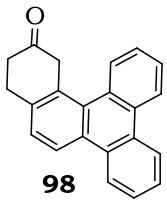
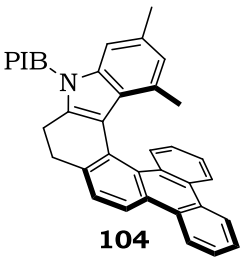
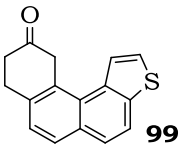
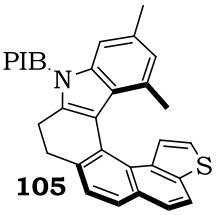
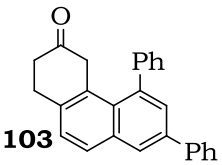
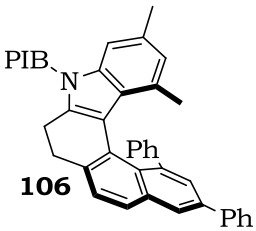
Scheme 6.18 Fischer indolization with unprotected naphthyl hydrazine **88c**.

6.2.4 Substrate Scope and Limitation of the Reaction

The dimethyl phenyl hydrazine **84a** (Table 6.3) and the naphthyl hydrazine **88a** (Table 6.4) were reacted with different ketones under the optimized conditions. When reacting dimethyl phenyl hydrazine **84a** with the phenanthrene containing ketone **98** and the thiophene derivative **99**, respectively products **104** and **105** were obtained in good yield and high enantioselectivity.

Table 6.3 Scope of the reaction with the hydrazine **84a**.

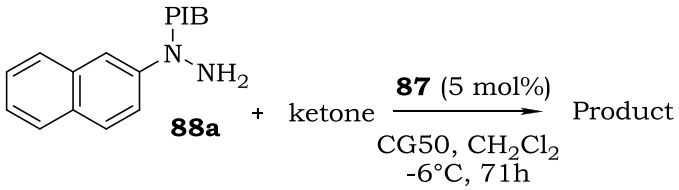


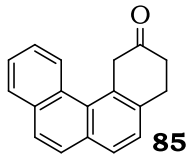
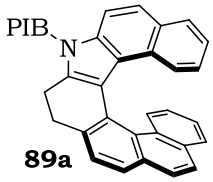
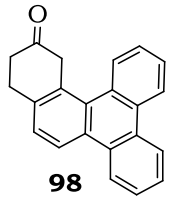
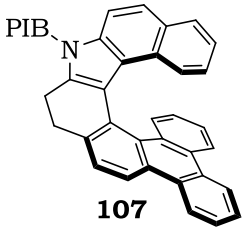
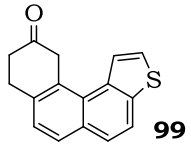
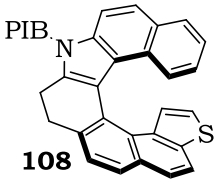
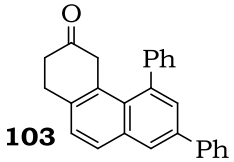
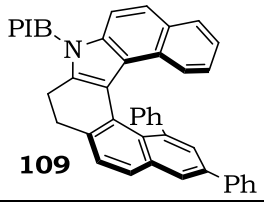
Entry	Ketone	Product	yield (%)[b]	*ee* (%)[c]
1	 **85**	 **86a**	74	91
2	 **98**	 **104**	98	92
3	 **99**	 **105**	66	93
4	 **103**	 **106**	91	67[d]

[a] Reaction conditions: **84a** (0.05 mmol) and the ketone (0.05 mmol) in CH_2Cl_2 (250 μL) with **87** ($1.25*10^{-3}$ mmol) and CG50 (500 mg/mmol). [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Racemization observed, in 5 hours the isolated product was found as a racemate.

Ketone **103** furnished a product whose enantiomeric excess decreased over time (from 67% *ee* to racemate in 5 hours).

Table 6.4 scope of the reaction with the hydrazine **88a**.



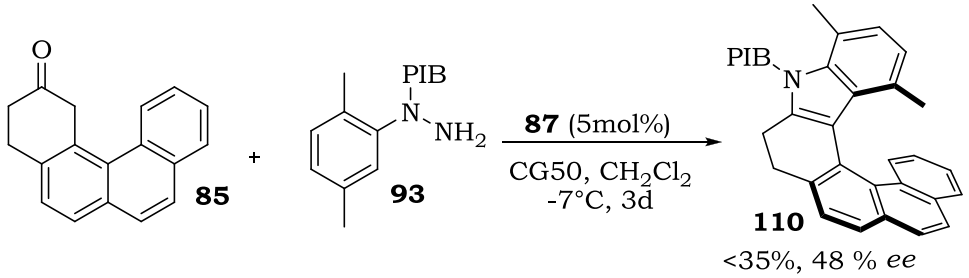
entry	ketone	Product	yield (%)[b]	*ee* (%)[c]
1	 **85**	 **89a**	56	79
2[d]	 **98**	 **107**	61	84
3	 **99**	 **108**	54	75
4	 **103**	 **109**	75	76

[a] reaction conditions: **88a** (0.05 mmol) and the ketone (0.05 mmol) in CH_2Cl_2 (250 μL) with **87** ($1.25*10^{-3}$ mmol) and CG50 (500 mg/mmol). [b] isolated yield after flash chromatography. [c] determined by HPLC analysis on a chiral stationary phase. [d] reaction performed at -2°C.

Naphthyl hydrazine **88a**, reacted with ketones **85**, **98**, **99** and **103**, afforded the products with up to 84% ee, showing a lower enantiocontrol with respect to the results presented in Table 6.3.

Interestingly, diphenylketone **103** provided the product with 76% *ee*, which was found stable towards time-dependent racemization.

Finally, the 2,5-dimethyl hydrazine **93** gave a poor result in terms of yield and enantioselectivity possibly due to its instability (Scheme 6.19).



Scheme 6.19 Reaction performed starting from the 2,5-dimethylhydrazine **93**.

6.2.5 Configuration of the Helicenes and their Reactivity

A general correlation between the optical activity and stereochemistry (helicity) of helicenes has been established.[159] The synthesized compounds were levorotatory ($[\alpha]_D < 0$) so it was possible to assign the M configuration, and this was also proved by X-ray crystallographic analysis of the compound **86a** (Figure 6.2).

[159] R. H. Martin, *Angew. Chem., Int. Ed.* **1974**, *13*, 649.

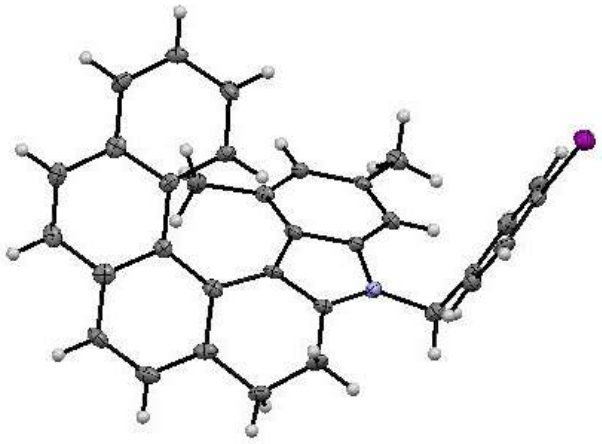
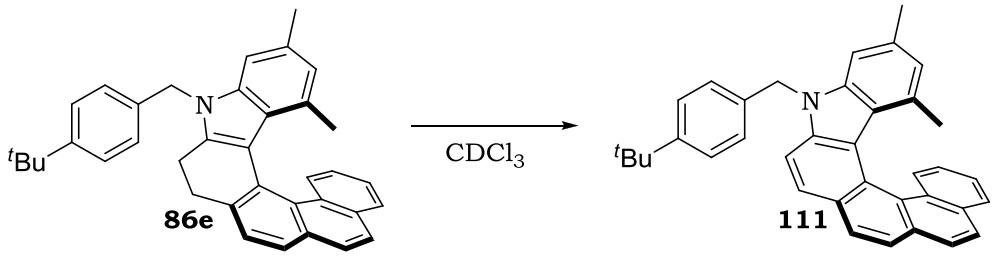


Figure 6.2 Crystallographic structure of the compound **86a**

The dihydrohelicenes are prone to oxidation to the aromatic derivatives, as it was observed in the case of compound **86e**. The ^{1}H-NMR analysis of a $CDCl_3$ solution of compound **86e** showed the formation, over time, of a by-product corresponding to the oxidized compound **111** (Scheme 6.20).

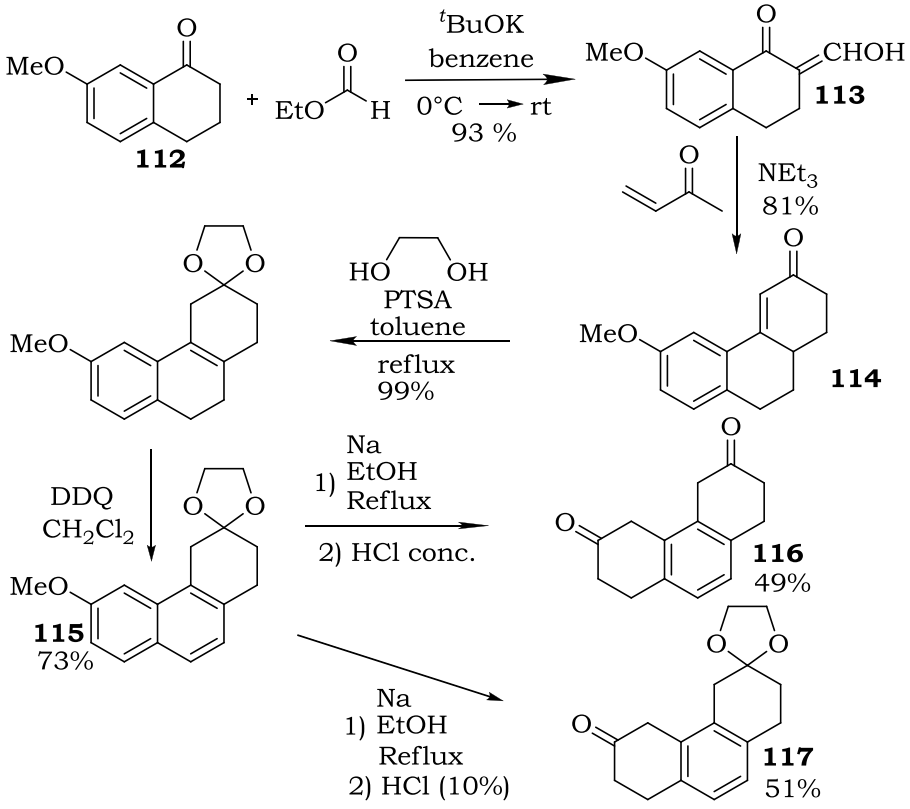


Scheme 6.20 Aromatic helicene found as by-product of **86e**.

This transformation will be the subject of further investigations.

6.2.6 Preliminary Studies on the Double Indolization Process

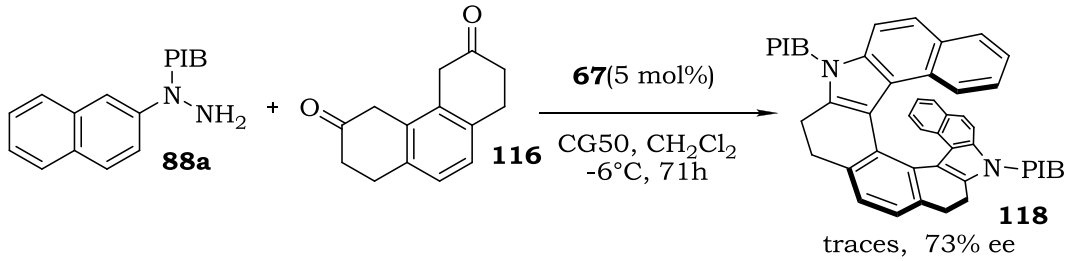
A diketone was then targeted in order to perform a double indolization on each of the ketone moieties leading longer helicene structures. Tetralone **112** was first reacted with ethyl formate to give the 2-hydroxymethylene derivative **113**, which was then reacted with methyl vinyl ketone to give the tricyclic compound **114**. The ketone was protected with glycol as a ketal and the isomerization of the double bond concurrently occurred. The intermediate was then oxidized with DDQ to give compound **115**. Dearomatization with Na in EtOH, followed by a strongly acidic work up furnished the desired product **116**. On the contrary, ketal **117** was obtained under weakly acidic work up (Scheme 6.21).[160]



Scheme 6.21 Synthesis of compound **116** and **117**.

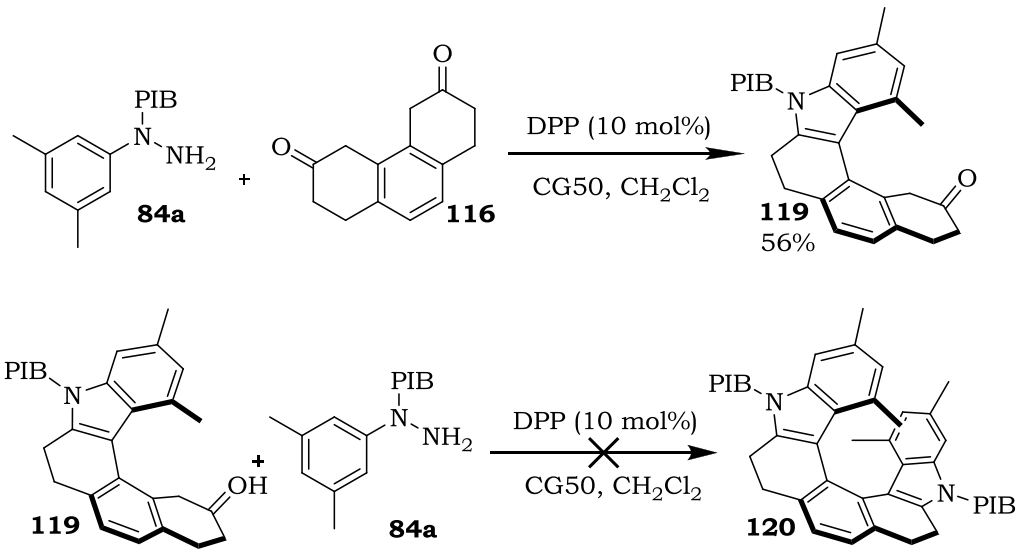
[160] a) R. B. Turner, D. E. Nettleton, R. Ferebee, *J. Am. Chem. Soc.* **1956**, *78,* 22, 5923; b) M. C. Carreño, M. González-López, A. Urbano, *Chem. Commun.* **2005**, 611.

Unfortunately, the reaction between naphthyl hydrazine **88a** and diketone **116** afforded only traces of the desired product **118** with 73% *ee* (Scheme 6.22).



Scheme 6.22 Synthetic attempt to a double Fischer indolization process.

Reacting 1 equivalent of dimethyl phenylhydrazine **84a** with diketone **116**, the product of single Fisher indolization could be detected and isolated. This compound was then reacted with another equivalent of hydrazine **84a** but the reaction did not proceed to the desired product **120** and only unidentified by-products were formed (Scheme 6.23).



Scheme 6.23 Synthetic attempt to a stepwise double Fischer indolization.

The double Fisher indolization between hydrazines **84a** and **88a** and bis-ketone **116** to access structurally more extended helicenes will be subject of future work.

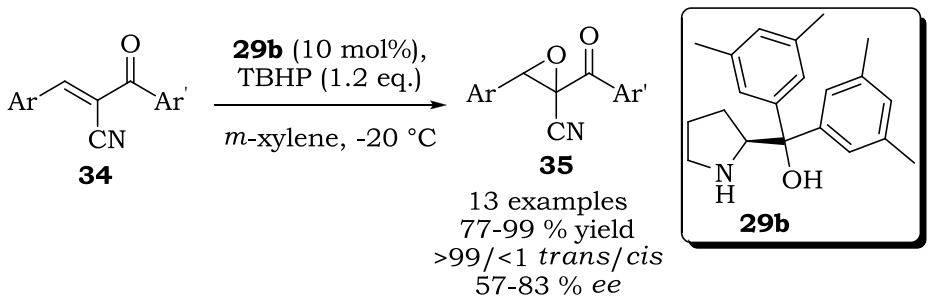
6.3 Conclusion

In conclusion, preliminary interesting results have been achieved on the Fischer indolization between hydrazines and polycyclic ketones catalysed by SPINOL-based phosphoric acids. The challenging helical products were obtained in good yield and good to high enantiocontrol. An approach to extended helicenes via double indolization has been also designed.

7. SUMMARY

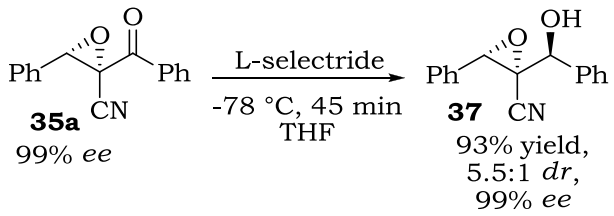
Chirality, often found in many natural products and in molecules of interest for pharmaceutical applications and for biological studies, is targeted in many synthetic strategies. In this PhD work, several methodologies were developed aimed to form C-C and C-heteroatom bonds in a stereoselective fashion, by employing easily accessible small organic molecules as promoters. The investigations focused on Michael type and MIRC (Michael Initiated Ring Closure) reactions by employing different Michael acceptors and donors, and testing several bifunctional organocatalysts. Our interest was directed towards those catalytic processes where the substrates were activated through a non-covalent activation mode by the organocatalyst.

Since heteroatom-containing three-membered rings are among the most useful and important synthetic targets in organic chemistry, a significant part of the PhD work was spent to develop new methodologies to produce enantioenriched epoxides and aziridines. A new class of functionalised epoxides was synthesized via a diastereo- and enantioselective nucleophilic epoxidation of trisubstituted electron-poor olefins bearing a cyano group (Scheme 7.1).



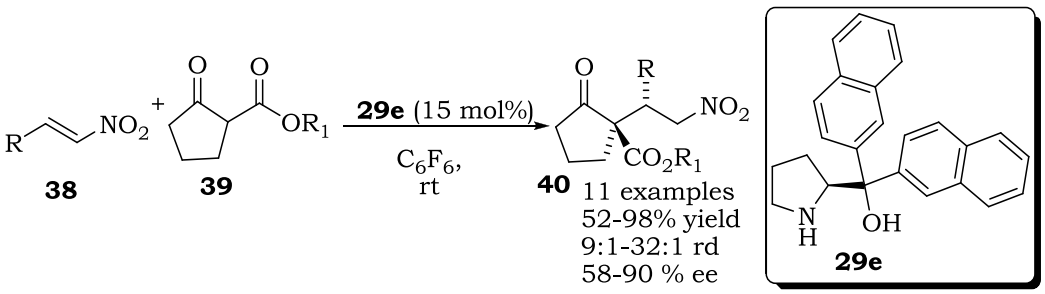
Scheme 7.1 Stereoselective epoxidation of α–cyano-α,β-unsaturated ketones.

A commercially available diaryl prolinol was employed and the desired epoxides were obtained in high yield, complete diastereoselectivity and good enantioselectivity. As an example of the synthetic utility of these compounds, reduction of the carbonyl compound was performed on model epoxide to generate the corresponding synthetically challenging electron-poor epoxy alcohol with good diastereocontrol (Scheme 7.2).



Scheme 7.2 Reduction of the carbonyl moiety to obtain the epoxy alcohol **37**.

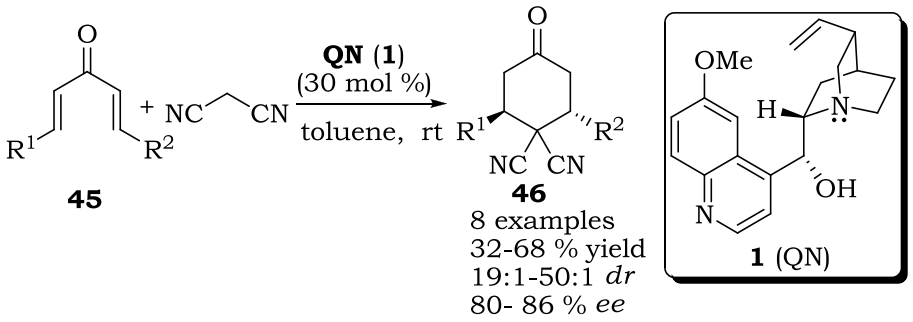
Diaryl prolinols were also found to be efficient catalysts in the asymmetric Michael addition of cyclic β-ketoesters to nitroolefines. An unusual and impressive effect of hexafluorobenzene as solvent was disclosed, able to turn the process from scarcely to highly stereoselective. The desired products were obtained in excellent yield, almost as a single diastereoisomer and high enantioselectivity (Scheme 7.3).



Scheme 7.3 Addition of cyclic β-ketoesters to nitroolefins in hexafluorobenzene.

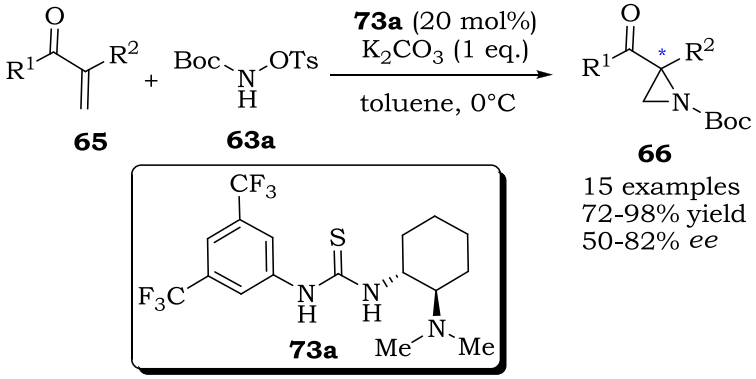
A plausible explanation for reaction rate and stereoselectivity enhancement, was provided by DFT calculations. The development of stabilizing interactions, between hexafluorobenzene with the negatively charged reactive enolate were responsible for the observed selectivity.

A double Michael type sequence was exploited to construct densely functionalized 6-membered rings starting from the easily available divinylketones **45** and malononitrile as the nucleophile. The process, promoted by low cost quinine, allowed to obtain compounds **46** in satisfactory overall yield, high diastereoselectivity and good enantiocontrol (Scheme 7.4).



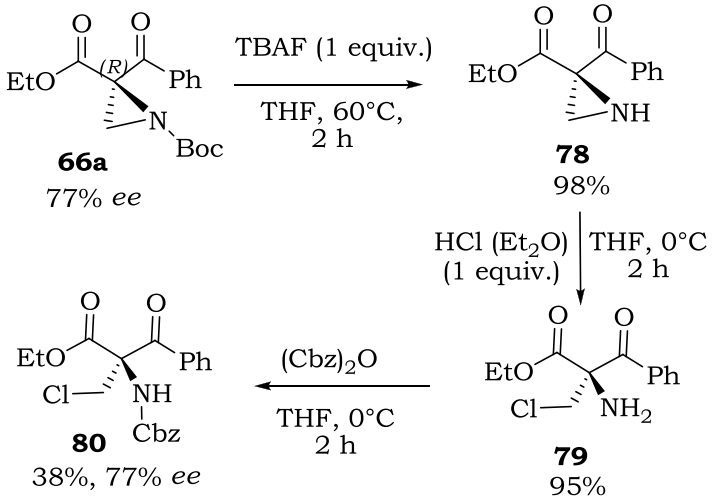
Scheme 7.4 Tandem double Michael reaction for the construction of cycloehexanones.

An enantioselective aza-MIRC (Michael Initiated Ring Closure) reaction has been developed to access difficult targets such as terminal aziridines bearing a quaternary stereocenter. Electron-poor acrylates **65** were reacted with the ambiphilic reagent **63a** in the presence of a substoichiometric amount of commercially available catalyst **73a** and K_2CO_3 to furnish the desired aziridines **66** in high yield and good enantioselectivity (Scheme 7.5)



Scheme 7.5 Aziridination of acrylates **65** mediated by Takemoto catalyst **73a**.

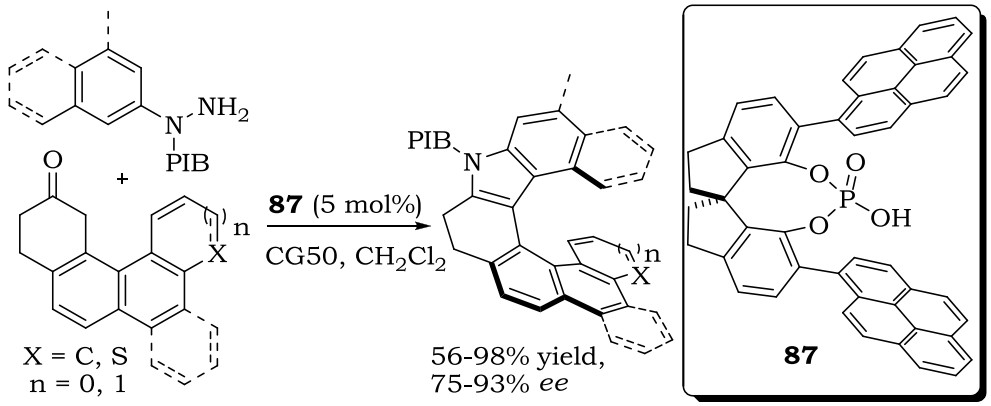
The synthetic potential of this class of aziridines has been demonstrated in the regioselective ring-opening of model aziridine **66a** to obtain highly useful enantiomerically enriched α,α-disubstituted α-amino acid esters (Scheme 7.6).



Scheme 7.6 Deprotection and regioselective ring-opening of the aziridine **66a** to obtain an α-amino acid ester derivative.

During the period spent at the Max Planck Institute für Kohlenforschung, an asymmetric version of the Fischer indolization for the synthesis of

helical molecules was developed. Phosphoric acid **87** was found to catalyse the process in the presence of an ammonia scavenger, the Amberlite CG50, providing the compounds in good yield and good to high stereocontrol (Scheme 7.7).



Scheme 7.7 Asymmetric Fischer indolization catalysed by phosphoric acid **87**

These preliminary results will be subject of future investigation.

8. EXPERIMENTAL SECTION

8.1 General experimental conditions

General methods and materials

All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of nitrogen. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualised by UV light and/or different stain reagents: phosphomolybdic acid/ethanol spray test or I_2 vapors. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 or 500 MHz spectrometers at room temperature in $CDCl_3$ or CD_2Cl_2 as solvent. Chemical shifts for protons are reported in ppm (δ) relative to tetramethylsilane with the solvent resonance employed as the internal standard (CD_2Cl_2 δ 5.32 ppm; $CDCl_3$ δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, dd = double doublet, sept = septet, m = multiplet, br = broad), coupling constants (Hz) and integration). ^{13}C chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard (CD_2Cl_2, δ 53.8 ppm; $CDCl_3$, δ 77.0 ppm).

Optical rotations were determined with Jasco Dip-1000 digital polarimeter or Autopol IV polarimeter (Rudolph Research Analytical) at 582 nm (sodium D-line) using a 3.5 mm x 100 mm cell. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (c in g/100 mL), and solvent.

FTIR spectra were recorded as thin films on KBr plates using Bruker Vertex 70 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}).

ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source.

High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). All masses are given in atomic units/elementary charge (*m*/*z*) and reported in percentage relative to the basic peak.

Melting points (uncorrected) were measured on a digital Electrothermal 9100 apparatus.

HPLC analyses were performed on a Waters-Breeze 2487 system, equipped with a dual absorbance detector and a 1525 Binary HPLC Pump or on a Shimadzu LC-2010C system equipped with a spectrophotometric detector. The chiral stationary phase of the columns is specified in each experiment.

The solvents were purified and dried by standard procedures prior to use. Anhydrous toluene and all starting materials (unless otherwise noted) were purchased from different commercial suppliers and used without further purification. Petroleum ether refers to light petroleum ether (boiling point 40-60°C).

Catalysts

Diaryl prolinol derivative catalysts not commercially available were synthetized according to a procedure reported by Mathre *at al.*[161] Peryhydroindolyl methanol derivative **36** was obtained following a procedure reported in the literature,[162] and NOBIN-prolinamide **41** synthesis was performed according a procedure by Lattanzi *et al.*[163] Cinchona alkaloid thioureas were synthetized according the procedure introduced by Soós and co-workers,[164] and CPD **51** following a procedure by Deng.[165] Thioureas **7** and **73b** and the diphenylethane diamine

[161] D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum, E. J. J. Grabowski, *J. Org. Chem.*, **1991**, *56*, 751.
[162] a) R. S. Luo, J. Weng, H. B. Ai, G. Lu, A.S.C. Chan, *Adv. Synth. Catal.* **2009**, *351*, 2449; b) K. M. B. Gross, Y. M. Jun, P. Beak, *J. Org. Chem.* **1997**, *62*, 7679.
[163] A. Russo, G. Botta, A. Lattanzi, *Synlett* **2007**, *5*, 795.
[164] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967.
[165] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.

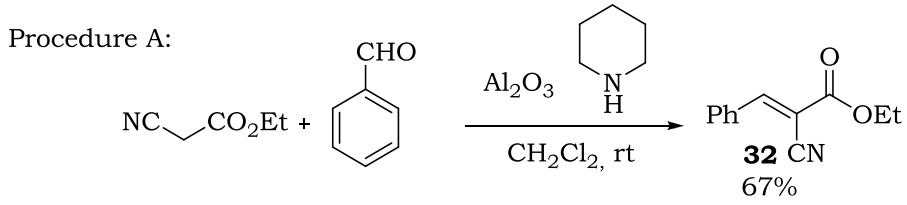
derivative **74** were prepared following general procedures.[166] The squaramide **75** was synthesized following the procedure of Rawal *et al.*[167] Sulfonimides **76** and **77** were obtained following a procedure reported by Liang, Ye and co-workers.[168] For the synthesis of catalyst **87** a recently reported procedure was adapted.[35]

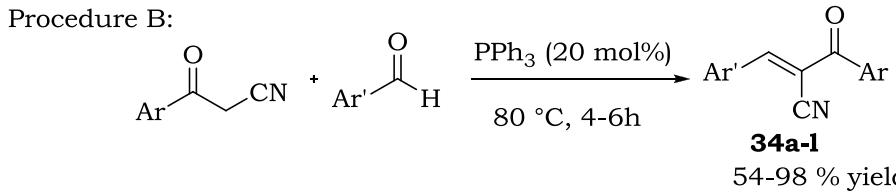
[166] a) J. M. Mitchell, N. S. Finney, *Tetrahedron Lett.* **2000**, *41*, 8431; b) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.*, **2005**, *127* , 8964; c) L. N. Jia, J. Huang, L. Peng, L. L. Wang, J. F. Bai, F. Tian, G. Y. He, X. Y. Xu, L. X. Wang, *Org. Biomol. Chem.* **2012**, *10*, 236.
[167] H. Konishi, T. Y. Lam, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2010**, *12*, 2028.
[168] F. Yu, X. Sun, Z. Jin, S. Wen, X. Liang, J. Ye, *Chem. Commun.* **2010**, *46*, 4589.

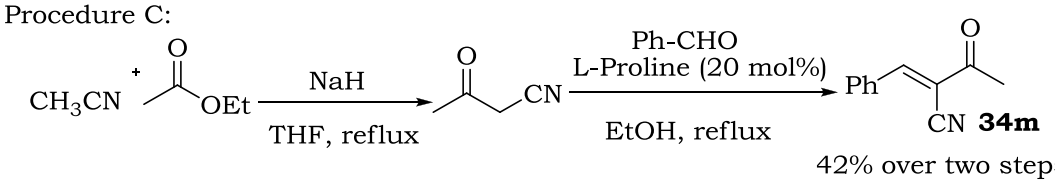
8.2 Asymmetric Epoxidation

8.2.1 Starting Materials

Compounds **32** and **34a-m** were prepared using general procedures reported in the literature. [80,169]







Procedure A: to a solution of ethyl 2-cyanoacetate (9 mmol) and benzaldehyde (9 mmol) in 30 mL of dry CH_2Cl_2, Al_2O_3 (4.5 mmol) and 5 drops of piperidine were added. The mixture is stirred at room temperature until completion, monitored by TLC (eluent: petroleum ether/EtOAc 8:2). A solid was formed and the precipitate was filtered and purified by flash chromatography (petroleum ether/EtOAc 9:1 as eluent) to give the product in 67% yield.

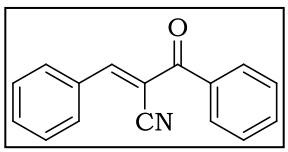
---

[169] For the characterization of the compounds, see also: a) S. Fioravanti, A. Morreale, L. Pellacani, P. A. Tardella, *Synlett* **2004**, 1083; b) P. K. Amancha, Y.-C. Lai, I-C. Chen, H.-J. Liu, J.-L. Zhu, *Tetrahedron* **2010**, *66*, 871; c) S. J. Deshpande, P. R. Leger, S. R. Sieck *Tetrahedron Letters,* **2012**, *53*, 1772.

Procedure B: in a round bottom flask equipped with a condenser to the opportune 3-oxo propanenitrile (3 mmol) and aryl aldehyde (3.9 mmol), PPh_3 (0.6 mmol) was added and the mixture was heated to 80 °C. After completion, monitored by TLC (eluent: petroleum ether/Et_2O 8:2) the mixture was allowed to cool at room temperature, diluted in EtOAc and washed with water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was isolated by flash chromatography (eluent: petroleum ether/Et_2O 9:1) in 54-98% yield.
Procedure C: to a suspension of NaH (12 mmol) in dry THF (20 mL) under a positive pressure of nitrogen acetonitrile (4 mmol) is added. After 30 minutes under reflux, EtOAC (16 mmol) is added quickly. After 18 h the mixture is allowed to cool to room temperature, the solvent was evaporated and the mixture was neutralized with HCl 1N and extracted with CH_2Cl_2. The unified organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude was dissolved in ethanol, benzaldehyde (4 mmol), a drop of piperidine, and L-Proline (0.8 mmol) were added and the mixture was heated to reflux. The solution was stirred until completion, monitored by TLC (petroleum ether/EtOAc 9:1 as eluent), concentrated under reduced pressure and directly subjected to flash chromatography (eluent: mixtures of petroleum ether/Et_2O 95:5 to petroleum ether /EtOAc 9:1) in 42% yield.

For some selected examples, ^1H and ^{13}C-NMR characterization are reported:

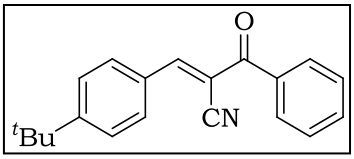
(*E*)-2-benzoyl-3-phenylacrylonitrile (34a)



^1H NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.94-7.86 (m, 2H), 7.65-7.62 (m, 1H), 7.61-7.39 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ

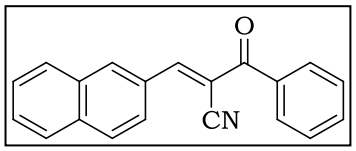
188.9, 155.6, 135.8, 133.43, 133.39, 131.8, 131.1, 129.3, 128.7, 116.8, 110.1.

(*E*)-2-benzoyl-3-(4-*tert*-butylphenyl)acrylonitrile (34b)



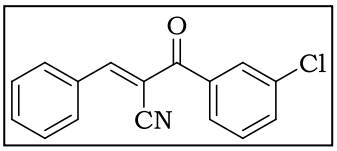
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.90-7.86 (m, 2H), 7.67-7.60 (m, 1H), 7.56-7.49 (m, 4H), 1.36 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 189.2, 157.8, 155.6, 136.0, 133.3, 131.2, 129.3, 129.2, 128.6, 126.4, 117.2, 109.0, 35.4, 31.0.

(*E*)-2-benzoyl-3-(naphthalen-2-yl)acrylonitrile (34f)



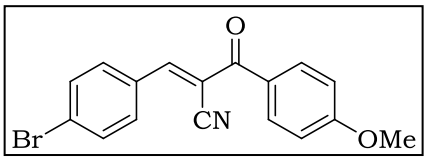
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.27-8.21 (m, 2H), 7.94-7.87 (m, 5H), 7.68-7.62 (m, 2H), 7.62-7.52 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 189.1, 155.6, 135.9, 135.5, 134.3, 133.4, 132.9, 129.44, 129.40, 129.34, 129.26, 129.20, 128.7, 127.9, 127.3, 125.3, 117.2, 109.9.

(*E*)-2-(3-chlorobenzoyl)-3-phenylacrylonitrile (34i)



^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (s, 1H), 8.04 (d, *J* = 7.52 Hz, 2H), 7.85 (apparent t, *J* = 1.8 Hz, 1H), 7.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.63-7.57 (m, 2H), 7.55-7.51 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 187.6, 156.1, 137.3, 135.1, 133.7, 133.4, 131.6, 131.3, 129.9, 129.4, 129.2, 127.3, 116.6, 109.6.

(*E*)-3-(4-bromophenyl)-2-(4-methoxybenzoyl)acrylonitrile (34k)



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (s, 1H), 7.94 (d, *J* = 6.8 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 6.9 Hz, 2H), 3.90 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 186.6, 164.1, 153.3, 132.6, 132.1, 132.0, 130.8, 128.1, 128.0, 117.1, 114.0, 110.7, 55.6.

8.2.2 Experimental Procedures and Compounds Characterization

General procedure for the synthesis of racemic epoxides

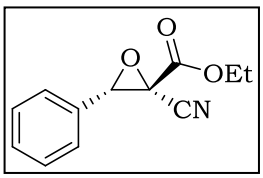
A sample vial was charged with the opportune alkene **34** (0.20 mmol), 2-piperidinemethanol (9.2 mg, 0.080 mmol) and toluene (1 mL). TBHP (5-6 M decane solution, 44 μL, 0.24 mmol) was added to the solution at room temperature. Stirring was maintained until the alkene was consumed as monitored by TLC. The crude reaction mixture was directly purified by flash chromatography on silica gel (eluent: petroleum ether/Et_2O 80:20) affording the racemic epoxides in 51-99% yield.

General procedure for the asymmetric epoxidation of *trans*-4-carbonyl-β-substituted acrylonitrile 32 and 34a-m.

A sample vial was charged with alkene (0.20 mmol), catalyst **29b** (6.2 mg, 0.020 mmol) and *m*-xylene (4.0 mL). TBHP (5-6 M decane solution, 44 μL, 0.24 mmol) was then added to the stirred solution at -20°C. The reaction was monitored by TLC (petroleum ether/diethyl ether 80:20 as eluent). The solvent was removed under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of petroleum ether/Et_2O 80:20 to

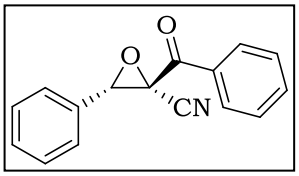
provide the epoxide. Crystallization using *n*-hexane/^{i}PrOH mixtures performed at room temperature gave prismatic crystals in an enantioenriched form.

(2R,3S)-ethyl 2-cyano-3-phenyloxirane-2-carboxylate (33)



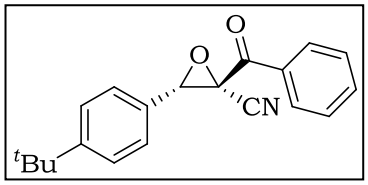
White solid, m.p. 34.2-35.6; $[\alpha]_D^{24}$ = -40.5 (*c* 0.58, $CHCl_3$), 23% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 1758, 1719, 1271, 1053, 750, 724; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.41 (m, 5H), 4.52 (s, 1H), 4.46-4.35 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 162.7, 130.4, 129.8, 128.8, 126.8, 112.9, 64.2, 64.0, 53.3, 14.0; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 10.4 min, major enantiomer t_R = 11.2 min.

(2*R*,3*S*)-2-benzoyl-3-phenyloxirane-2-carbonitrile (35a)



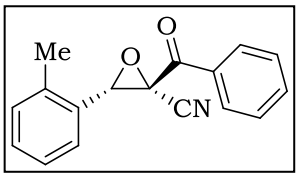
White solid, m.p. 93-95°C; $[\alpha]_D^{21}$ = -163.4 (*c* 0.50, $CHCl_3$), 94% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3065, 1699, 1449, 1256, 1156, 760, 696; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.71-7.68 (m, 1H), 7.57-7.51 (m, 7H), 4.41 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 186.8, 135.0, 132.8, 130.5, 130.0, 129.3, 129.1, 129.0, 126.7, 114.1, 64.2, 58.6; Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62; Found: C, 76.28; H, 4.46; N, 5.21; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 18.4 min, major enantiomer t_R = 14.0 min.

(2*R*,3*S*)-2-benzoyl-3-(4-*tert*-butylphenyl)oxirane-2-carbonitrile (35b)



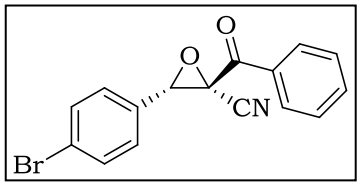
White solid, m.p. 75-76°C; $[\alpha]_D^{23}$ = -93.3 (*c* 0.42, $CHCl_3$), 73% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 2923, 1701, 1256, 764, 696. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 (dd, *J* = 7.8, 1.3 Hz, 2H) , 7.71-7.67 (m, 1H), 7.56-7.50 (m, 4H), 7.45-7.43 (m, 2H), 4.37 (s, 1H), 1.36 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 186.8, 153.7, 134.9, 132.8, 129.2, 129.0, 126.9, 126.5, 125.9, 114.2, 64.4, 58.6, 34.8, 31.2; Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59; Found: C, 77.88; H, 6.02; N, 4.85; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/*i*PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 11.4 min, major enantiomer t_R = 8.1 min.

(2*R*,3*S*)-2-benzoyl-3-*o*-tolyloxirane-2-carbonitrile (35c)



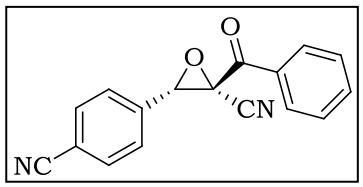
White solid, m.p. 96-98°C; $[\alpha]_D^{21}$ = -9.2 (*c* 0.49, $CHCl_3$), 57% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3064, 1700, 1449, 1257, 758, 696; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.12 (dd, *J* = 8.4, 1.1 Hz, 2H) , 7.73-7.68 (m, 1H), 7.58-7.54 (m, 2H), 7.45-7.43 (m, 1H), 7.40-7.31 (m, 2 H) , 7.28-7.26 (m, 1H), 4.52 (s, 1H), 2.42 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 187.0, 136.5, 135.0, 132.7, 130.4, 129.9, 129.3, 129.1, 128.8, 126.4, 125.3, 114.1, 62.8, 58.1, 18.8; Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32; Found: C, 76.23; H, 5.08; N, 5.10; **HPLC** analysis with Chiralpak AS-H column, 98:2 *n*-hexane/*i*PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 26.0 min, major enantiomer t_R = 22.6 min.

(2*R*,3*S*)-2-benzoyl-3-(4-bromophenyl)oxirane-2-carbonitrile (35d)



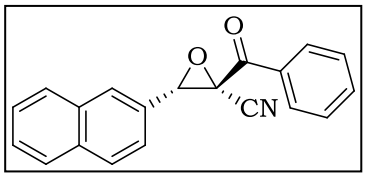
White solid, m.p. 132-134°C; $[\alpha]_D^{25}$ = -156.1 (*c* 0.55, $CHCl_3$), 99% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3064, 2359, 1699, 1596, 1257, 1071, 1012, 898, 703; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.04 (dd, *J* = 8.2, 1.4 Hz, 2H) , 7.72-7.68 (m, 1H), 7.64 (dd, *J* = 6.7, 1.8 Hz, 2H) , 7.57-7.53 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.38 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 186.4, 135.0, 132.6, 132.2, 129.2, 129.1, 128.2, 124.8, 113.8, 63.5, 58.4; Anal. Calcd. for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.27; Found: C, 56.90; H, 3.79; N, 4.89; **HPLC** analysis with Chiralpak AS-H column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 18.7 min, major enantiomer t_R = 12.1 min.

(2*R*,3*S*)-2-benzoyl-3-(4-cyanophenyl)oxirane-2-carbonitrile (35e)



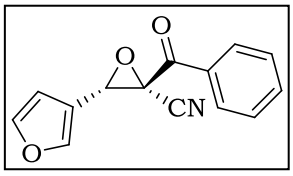
Yellow solid, m.p. 166-167°C; $[\alpha]_D^{22}$ = -80.1 (*c* 0.53, $CHCl_3$), 70% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 2924, 2231, 1703, 1597, 1449, 1256, 1156, 900, 696; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* 7.5 Hz, 2H) , 7.80 (d, *J* = 8.2 Hz, 2H), 7.73-7.70 (m, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.58-7.54 (m, 2H), 4.49 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 185.9, 135.3, 132.7, 132.4, 129.3, 129.2, 127.9, 127.4, 117.9, 114.4, 113.5, 62.8, 58.3; Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.67; N, 10.21; Found: C, 73. 78; H, 4.03; N, 9.35; **HPLC** analysis with Chiralpak OD-H column, 70:30 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 14.7 min, major enantiomer t_R = 17.7 min.

(2*R*,3*S*)-2-benzoyl-3-(naphthalen-2-yl)oxirane-2-carbonitrile (35f)



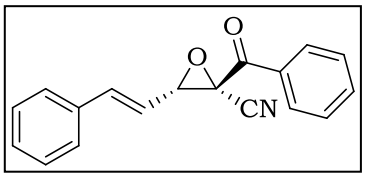
White solid, m.p. 113-115°C; $[\alpha]_D^{19}$ = -116.0 (*c* 0.58, $CHCl_3$), 77% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3069, 1685, 1457, 1245, 764, 696; **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.09-8.07 (m, 2H) , 8.01-7.97 (m, 2H), 7.93-7.91 (m, 2H), 7.72.7.68 (m, 1H) , 7.60-7.54 (m, 5H), 4.57 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 186.7, 135.0, 134.1, 132.8, 129.2, 129.1, 129.0, 128.2, 127.9, 127.4, 127.3, 127.1, 126.9, 114.1, 64.5, 58.8. Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68; Found: C, 73.93; H, 3.81; N, 4.03; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 27.2 min, major enantiomer t_R = 21.3 min.

(2*R*,3*S*)-2-benzoyl-3-(furan-3-yl)oxirane-2-carbonitrile (35g)



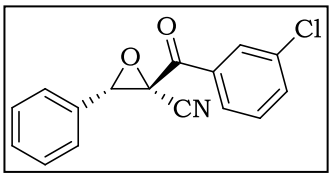
Yellow solid, m.p. 56-58°C; $[\alpha]_D^{25}$ = -89.8 (*c* 0.68, $CHCl_3$), 81% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3139, 1701, 1598, 1268, 1166, 1024, 876, 699; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 (dd, J = 8.3, 1.2 Hz, 2H) , 7.76 (s, 1H), 7.72-7.68 (m, 1H), 7.56-7.53 (m, 3H), 6.64-6.62 (m, 1H), 4.32 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 186.8, 144.2, 143.6, 135.0, 132.7, 129.2, 129.1, 117.1, 114.5, 108.4, 58.7, 57.9. Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86; Found: C, 70.60; H, 3.82; N, 5.46; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 27.6 min, major enantiomer t_R = 17.9 min.

(2*R*,3*S*)-2-benzoyl-3E-styryloxirane-2-carbonitrile (35h)



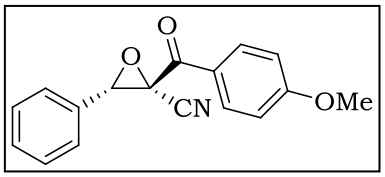
Yellow oil; $[\alpha]_D^{23}$ = -121.9 (*c* 0.81, $CHCl_3$), 84% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3065, 1703, 1245, 1010, 760, 699; **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.05 (dd, *J* = 7.82, 1.24 Hz, 2H) , 7.71-7.67 (m, 1H), 7.56-7.47 (m, 4H) , 7.42-7.36 (m, 3H) , 7.07 (d, *J* = 15.9, 1H), 6.20 (dd, *J* = 15.9, 8.2 Hz, 1H), 4.01 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 187.1, 141.2, 134.9, 134.6, 132.8, 129.6, 129.2, 129.1, 128.9, 127.2, 118.9, 114.5, 64.2, 57.2. Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4. 76; N, 5.09; Found: C, 77.40; H, 3.71; N, 5.78; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 22.1 min, major enantiomer t_R = 15.2 min.

(2*R*,3*S*)-2-(3-chlorobenzoyl)-3-phenyloxirane-2-carbonitrile (35i)



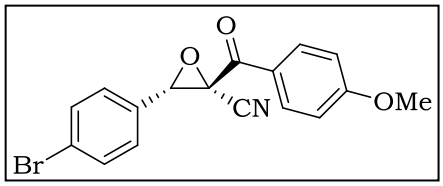
Yellow solid, m.p. 86-90°C; $[\alpha]_D^{27}$ = -97.3 (*c* 0.68, $CHCl_3$), 73% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3068, 1685, 1245, 1157, 1078, 900, 860, 696; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.04 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.68-7.65 (m, 1H) , 7.50-7.47 (m, 6H), 4.42 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 186.0, 135.5, 134.8, 134.1, 130.6, 130.3, 129.7, 129.1, 128.9, 127.3, 126.6, 113.6, 64.2, 58.9; Anal. Calcd. for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94; Found: C, 66.22; H, 3.61; N, 4.60; **HPLC** analysis with Chiralpak AS-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 12.0 min, major enantiomer t_R = 10.1 min.

(2*R*,3*S*)-2-(4-methoxybenzoyl)-3-phenyloxirane-2-carbonitrile (35j)



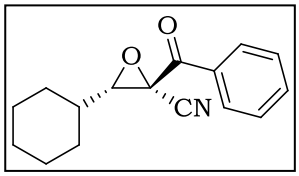
White solid, m.p. 102-104°C; $[\alpha]_D^{24}$ = -138.6 (*c* 0.65, $CHCl_3$), >99% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 2845, 1661, 1600, 1261, 1154, 1025, 764, 699; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (dd, *J* = 8.5, 0.48 Hz, 2H) , 7.50 (bs, 5H), 7.00 (d, *J* = 8.5 Hz, 2H) , 4.39 (s, 1H), 3.90 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 184.7, 165.0, 131.8, 130.3, 130.2, 128.8, 126.6, 125.5, 114.4, 63.9, 58.5, 55.6; Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02; Found: C, 71.38; H, 4.66; N, 4.85; **HPLC** analysis with Chiralpak AS-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 30.2 min, major enantiomer t_R = 20.5 min.

(2*R*,3*S*)-3-(4-bromophenyl)-2-(4-methoxybenzoyl)oxirane-2-carbonitrile (35k)



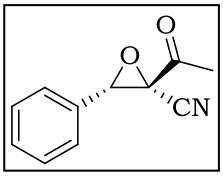
White solid, m.p. 98-101°C; $[\alpha]_D^{28}$ = -81.6 (*c* 0.58, $CHCl_3$), 79% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3020, 1683, 1257, 764, 703; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 4.36 (s, 1H), 3.97 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 184.3, 165.1, 132.1, 131.8, 129.3, 128.2, 125.4, 124.7, 114.4, 114.2, 63.3, 58.3, 55.7; Anal. Calcd. for $C_{17}H_{12}BrNO_3$: C, 57.00; H, 3.38; N, 3.91; Found: C, 55.78; H, 3.09; N, 4.60; **HPLC** analysis with Chiralpak OD-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 19.2 min, major enantiomer t_R = 16.5 min.

(2*R*,3*S*)-2-benzoyl-3-cyclohexyloxirane-2-carbonitrile (35l)



Colorless oil; $[\alpha]_D^{28}$ = -15.2 (*c* 0.53, $CHCl_3$), 48% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3020, 1635, 1450, 1216, 750, 669; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 7.7 Hz, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H) , 3.09 (d, *J* = 8.9 Hz, 1H), 1.98 (dd, *J* = 25.0, 12.4 Hz, 2H), 1.75-1.66 (m, 2H) , 1.63-1.54 (m, 2H), 1.56-1.13 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 187.7, 134.7, 132.9, 129.1, 128.9, 114.8, 67.9, 55.5, 39.2, 29.8, 28.2, 25.7, 24.9; Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; Found: C, 73.58; H, 7.34; N, 4.78; **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 7.9 min, major enantiomer t_R = 6.7 min.

(2R,3S)-2-acetyl-3-phenyloxirane-2-carbonitrile (35m)



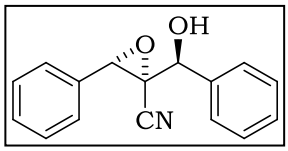
Pale yellow solid, m.p. 77.3-78.9°C; $[\alpha]_D^{24}$ = -188.9 (*c* 0.628, $CHCl_3$), 83% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3025, 2360, 1457,1127, 864, 813, 606; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.41 (m, 5H), 4.42 (s, 1H), 2.38 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 195.5, 130.4, 129.8, 128.8, 126.6, 113.4, 64.1, 59.0, 25.0; Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48; Found: C, 71.36; H, 4.98; N, 7.63; **HPLC** analysis with Chiralpak AS-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 20.6 min, major enantiomer t_R = 14.1 min.

Procedure for the reduction of 35a to epoxy alcohol 37

L-selectride (200 μL, 0.2 mmol, 1.0 M in THF) was added to a stirred solution of **35a** (50 mg, 0.2 mmol) in anhydrous THF (4 mL) at -78°C. After the consumption of the reagent, monitored by TLC (petroleum ether/Et_2O 70:30 as eluent) the mixture was diluted with water and

extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was analysed via ^{1}H-NMR to determine the diastereoisomeric ratio (*dr* 5.5/1) then purified by flash chromatography on silica gel (petroleum ether/Et_2O 70:30 as eluent) providing the mixture of the two diasteroisomers in 93% yield. Further flash chromatography on silica gel (petroleum ether/Et_2O 90:10 as eluent) allowed to separate the two diasteroisomers.

(2S,3S)-2-((S)-hydroxy(phenyl)methyl)-3-phenyloxirane-2-carbonitrile (37)



Colorless oil; $[\alpha]_D^{28}$ = -225.8 (*c* 0.67, $CHCl_3$), 99% *ee*; **FTIR** ν_{max} (KBr)/cm^{-1} 3066, 3035, 1498, 1455, 760, 698; major diastereoisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40-7.54 (m, 10 H), 4.92 (s, 1H), 4.40 (s, 1H), 2.68 (bs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 136.9, 131.2, 129.6, 129.4, 129.0, 128.6, 126.6, 126.3, 114.8, 74.0, 61.4, 61.1; Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; found: C, 74.27, H, 6.40; N, 4.08; **HPLC** analysis with Chiralpak AS-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor diasteroisomer: minor enantiomer t_R = 27.7 min, major enantiomer t_R = 16.1 min; major diasteroisomer: minor enantiomer t_R = 17.6 min, major enantiomer t_R = 21.0 min.

8.3 Asymmetric Michael Addition to Nitrostyrene

Trans-nitrostyrene **38a**, maleimide **43** and the cyclic β-ketoesters **39a**-**e** were commercially available and employed without further purification. *Trans*-nitroalkenes **38b**-**j** were prepared using general procedures reported in the literature.[170] All Michael adducts **40a**-**m** and **44** are known compounds. [97,171]

General procedure for the synthesis of racemic Michael adducts 40b, d, e, i, k.

In a sample vial, β-ketoester **39** (0.2 mmol) was added to a solution of the appropriate *trans*-nitroolefin (0.2 mmol) and the piperidinemethanol (11.5 mg, 0.1 mmol) in toluene (200 μL) at room temperature. The mixture was stirred until completion (monitored by TLC, petroleum ether/Et_2O 8:2 as eluent), then it was directly loaded onto silica gel and purified by flash chromatography, eluting with petroleum ether/Et_2O (8:2 to 7:3) to give racemic adducts (yields from 76 to 97 %).

General procedure for the asymmetric conjugate addition

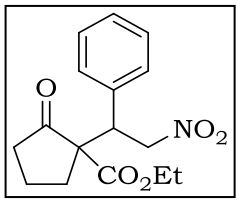
In a sample vial β-ketoester **39** (0.2 mmol) was added to a solution of appropriate *trans*-nitroolefin (0.2 mmol) and catalyst **29e** (10.6 mg, 0.03 mmol) in hexafluorobenzene (500 μL) at room temperature. The mixture was stirred until completion (monitored by TLC, petroleum ether/Et_2O 8:2

[170] a) O. Andrey, A. Alexakis, G. Belardinelli, *Org. Lett.* **2003**, *5*, 2559; b) A. Côté, V. N. G. Lindsay, A. B. Charette *Org. Lett.* **2007**, *9*, 85.

[171] a) For data of compound **40a**, **40l** and **40m**, see: R. Manzano, J. M. Andrés, M. Muruzábal, R. Pedrosa, R. *Adv. Synth. Cat.* **2010**, 352, 3364; b) For data of compounds **40b-f**, see: 97c; c) For data of compounds **40g-h**, see: 97d; d) For data of compounds **40i-l**, see: 97b; e) For data of compound **40m**, see: T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto *J. Am. Chem. Soc.* **2005**, *127*, 119 ; f) For data of compound **44**, see: G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre *Angew. Chem. Int. Ed.* **2006**, *45*, 4966.

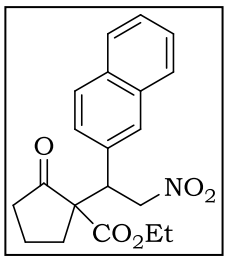
as eluent), then it was directly loaded onto silica gel and purified by flash chromatography, eluting with petroleum ether/Et_2O (8:2 to 7:3) to give the pure adducts **40a-m** and **44**.

(2*R*, 3*S*)-Ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentane carboxylate (40a)



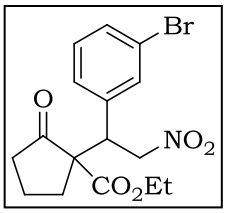
Pale yellow oil; $[\alpha]_D^{20}$ = -68.1 (*c* 0.63, $CHCl_3$), 90% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33-7.24 (m, 5H), 5.18 (dd, *J* = 13.6, 4.0 Hz, 1H), 5.01 (dd, *J* = 13.6, 10.8 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.08 (dd, *J* = 10.8, 4.0 Hz, 1H), 2.41-2.31 (m, 2H), 2.08-1.79 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.4, 169.3, 135.3, 129.3, 128.8, 128.3, 76.5, 62.4, 62.2, 46.2, 37.9, 31.2, 19.4, 14.0; **HPLC** analysis with Chiralcel OD-H column, 90:10 *n*-hexane/^{i}PrOH, 0.5 mL/min, detection at 210 nm; minor enantiomer t_R = 26.1 min, major enantiomer t_R = 36.7 min.

(2*R*, 3*S*)-Ethyl 1-(1-(naphthalen-2-yl)-2-nitroethyl)-2-oxocyclopentane carboxylate (40b)



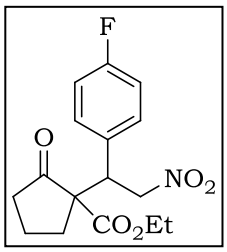
Yellow oil; $[\alpha]_D^{18}$ = -32.8 (*c* 1.01, $CHCl_3$), 88% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81-7.78 (m, 3H), 7.73-7.72 (m, 1H), 7.49-7.38 (m, 3H), 5.26 (dd, *J* = 13.6, 3.8 Hz, 1H), 5.15 (dd, *J* = 13.6, 10.9 Hz, 1H), 4.27-4.19 (m, 3H), 2.42-2.31 (m, 2H), 2.08-1.96 (m, 2H), 1.94-1.77 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.3, 169.4, 133.1, 132.91, 132.87, 128.9, 128.7, 128.0, 127.6, 126.7, 126.5, 126.4, 76.6, 62.5, 62.3, 46.3, 37.9, 31.4, 19.4, 14.0; **HPLC** analysis with Chiralpak IC column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 23.8 min, major enantiomer t_R = 31.6 min.

(2*R*, 3*S*)-Ethyl 1-(1-(3-bromophenyl)-2-nitroethyl)-2-oxocyclopentane carboxylate (40c)



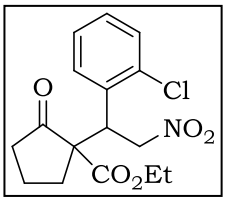
Pale yellow oil; $[\alpha]_D^{18}$ = -15.9 (*c* 1.03, $CHCl_3$), 90% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-7.42 (m, 2H), 7.28-7.17 (m, 2H), 5.20 (dd, *J* = 13.6, 3.6 Hz, 1H), 5.00 (dd, *J* = 14.0, 11.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.97 (dd, *J* = 10.8, 3.2 Hz, 1H), 2.46-2.32 (m, 2H), 2.17-2.09 (m, 1H), 1.97-1.67 (m, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.1, 169.1, 138.0, 132.3, 131.5, 130.3, 128.1, 122.8, 76.2, 62.3, 62.2, 45.8, 37.8, 31.8, 19.3, 14.0; **HPLC** analysis with Chiralcel OD-H column, 90:10 *n*-hexane/*i*PrOH, 0.7 mL/min, detection at 210 nm; minor enantiomer t_R = 22.9 min, major enantiomer t_R = 28.6 min.

(2*R*, 3*S*)-Ethyl 1-(1-(4-fluorophenyl)-2-nitroethyl)-2-oxocyclopentane carboxylate (40d)



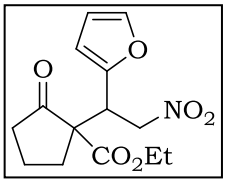
Pale yellow oil; $[\alpha]_D^{19}$ = -18.6 (*c* 1.02, $CHCl_3$), 88% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29-7.27 (m, 2H), 7.03-6.98 (m, 2H), 5.15 (dd, *J* = 13.5, 3.8 Hz, 1H), 4.97 (dd, *J* = 13.5, 11.1 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.05 (dd , *J* = 11.1, 3.6 Hz, 1H), 2.43–2.32 (m, 2H), 2.08-1.82 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.3, 169.3, 162.4 (d, *J* = 46.5 Hz), 131.1 (d, *J* = 10 Hz), 115.9, 115.7, 76.5, 62.4, 62.3, 45.5, 37.9, 31.4, 19.4, 14.0; **HPLC** analysis with Chiralpak IC column, 80:20 *n*-hexane/*i*PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 10.2 min, major enantiomer t_R = 13.1 min.

(2*R*, 3*S*)-Ethyl 1-(1-(2-chlorophenyl)-2-nitroethyl)-2-oxocyclopentane carboxylate (40e)



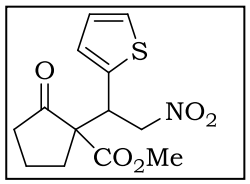
Yellow oil; $[\alpha]_D^{23}$ = 17.8 (*c* 0.92, $CHCl_3$), 90% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.58-7.55 (m, 1H), 7.40-7.37 (m, 1H), 7.26-7.22 (m, 2H), 5.48 (dd, *J* = 14.1, 3.6 Hz, 1H), 5.10 (dd, *J* = 13.8, 10.5 Hz, 1H), 4.52 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.27-1.88 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.6, 169.3, 135.5, 134.7, 130.1, 129.3, 129.0, 127.6, 76.8, 62.1, 37.8, 33.0, 29.7, 19.3, 14.0; **HPLC** analysis with Chiralpak IC column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 19.3 min, major enantiomer t_R = 24.5 min.

(2*R*, 3*S*)-Ethyl 1-(1-furan-2-yl)-2-nitroethyl)-2-oxocyclopentane carboxylate (40f)



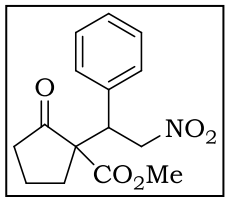
Pale yellow oil; $[\alpha]_D^{23}$ = -31.4 (*c* 0.58, $CHCl_3$), 72% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33 (d, *J* = 1.2 Hz, 1H), 6.30 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 4.95-4.91 (m, 2H), 4.44 (dd, *J* = 9.8, 4.6 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.51-2.30 (m, 2H), 2.15-1.95 (m, 3H), 1.80-1.72 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.1, 168.9, 149.1, 142.7, 110.8, 110.1, 74.5, 62.3, 61.9, 40.4, 37.9, 30.2, 19.5, 14.0; **HPLC** analysis with Chiralcel OD-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 10.3 min, major enantiomer t_R = 14.9 min.

(2*R*, 3*S*)-Methyl 1-(2-nitro-1-(2-thienyl)ethyl)-2-oxocyclopentane carboxylate (40g)



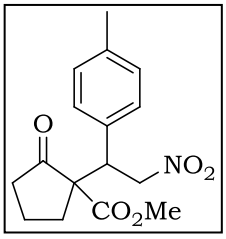
Yellow wax; $[\alpha]_D^{24}$ = -32.3 (*c* 0.88, $CHCl_3$), 84% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.24-7.23 (m, 1H), 6.96-6.92 (m, 2H), 5.12 (dd, *J* = 13.8, 3.7 Hz, 1H), 4.92 (dd, *J* = 13.8, 10.1 Hz, 1H), 4.41 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.77 (s, 3H), 2.45-2.37 (m, 2H), 2.16-1.91 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.3, 169.8, 137.4, 128.6, 126.8, 126.1, 77.5, 62.4, 53.1, 42.1, 38.0, 31.5, 19.4; **HPLC** analysis with Chiralcel OD-H column, 88:12 *n*-hexane:EtOH, 0.5 mL/min, detection at 233 nm; minor enantiomer t_R = 24.9 min, major enantiomer t_R = 42.1 min.

(2*R*, 3*S*)-Methyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentane carboxylate (40h)



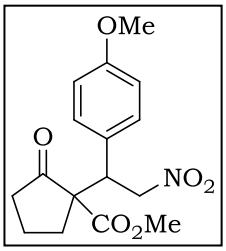
White wax; $[\alpha]_D^{20}$ = -24.3 (*c* 1.00, $CHCl_3$), 88% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32-7.22 (m, 5H), 5.20-5.14 (dd, *J* = 13.8, 4.2 Hz, 1H), 5.07-4.98 (dd, *J* = 13.5, 10.8 Hz, 1H), 4.08 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.76 (s, 3H), 2.30–2.43 (m, 2H), 1.77–2.09 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.2, 169.8, 135.2, 129.3, 128.8, 128.3, 76.4, 62.4, 53.1, 46.2, 37.9, 31.1, 19.3; **HPLC** analysis with Chiralcel OD-H column, 90:10 *n*-hexane: /^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 17.0 min, major enantiomer t_R = 25.2 min.

(2*R*, 3*S*)-Methyl 1-(2-nitro-1-*p*-tolyethyl)-2-oxocyclopentane carboxylate (40i)



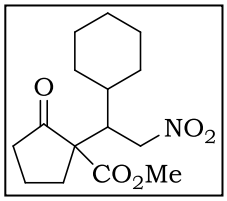
Pale yellow oil; $[\alpha]_D^{24}$ = -24.2 (*c* 0.97, $CHCl_3$), 66% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.14-7.08 (m, 4H) , 5.13 (dd, *J* = 13.2, 4.5 Hz, 1H), 4.99 (dd, *J* = 13.2, 11.1 Hz, 1H), 4.07 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.76 (s, 3H), 2.52-2.34 (m, 2H), 2.30 (s, 3H), 2.07-1.77 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.64, 170.07, 138.36, 132.20, 129.78, 129.35, 76.7, 62.7, 53.3, 46.0, 38.3, 31.2, 21.3, 19.6; **HPLC** analysis with Chiralpak IC column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 22.5 min, major enantiomer t_R = 33.6 min.

(2*R*, 3*S*)-Methyl 1-(1-(4-methoxyphenyl)-2-nitroethyl)-2-oxo cyclopentanecarboxylate (40j)



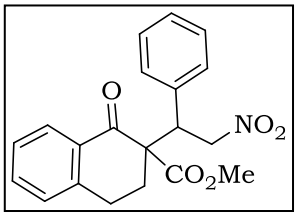
Pale yellow oil; 58% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.18-7.15 (m, 2H), 6.84-6.82 (m, 2H), 5.11 (dd, *J* = 13.3, 4.1 Hz, 1H), 5.01-4.89 (dd, *J* = 13.3, 11 Hz, 1H), 4.04 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.78 (s, 3H), 3.75(s, 3H), 2.44-2.30 (m, 2H), 2.06-1.80 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 212.3, 169.8, 159.3, 130.4, 126.9, 114.1, 76.5, 62.6, 55.1, 53.0, 45.4, 37.9, 30.9, 19.3; **HPLC** analysis with Chiralpak ASH column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 31.5 min, major enantiomer t_R = 24.8 min.

(2*R*, 3*S*)-Methyl 1-(1-cyclohexyl-2-nitroethyl)-2-oxocyclopentane carboxylate (40k)



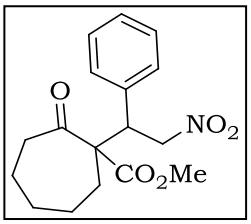
Pale yellow oil; $[\alpha]_D^{24}$ = -34.1 (*c* 0.33, $CHCl_3$), 62% *ee*; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.06 (dd, *J* = 15.6, 3.9 Hz, 1H) , 4.53 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.66 (s, 3H), 2.73-2.64 (m, 2H) , 2.42-2.37 (m, 2H), 2.01-2.00 (m, 3H), 1.70-1.47 (m, 5H), 1.20-0.98 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 213.2, 170.2, 74.0, 62.3, 53.0, 45.3, 39.5, 38.1, 33.0, 32.4, 28.8, 27.0, 26.7, 26.1, 19.5; **HPLC** analysis with Chiralpak IC column, 97:3 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 38.9 min, major enantiomer t_R = 47.8 min.

Methyl 2-(2-nitro-1-phenylethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene -2-carboxylate (40l)



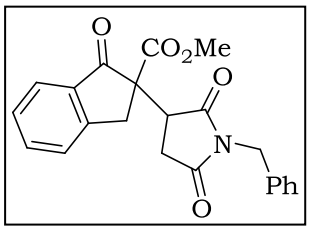
White solid; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.38-7.28 (m, 6H), 7.20 (d, *J* = 7.5 Hz, 1H), 5.16 (dd, *J* = 13.8, 4.5 Hz, 1H), 5.06 (dd, *J* = 13.2, 10.2 Hz, 1H), 4.21 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.65 (s, 3H), 2.99-2.95 (m, 2H), 2.46-2.32 (m, 1H), 2.08-1.99 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.4, 170.5, 142.7, 136.1, 134.3, 130.1, 129.6, 129.0, 128.9, 128.7, 128.5, 127.3, 78.1, 60.0, 53.0, 47.4, 31.0, 25.8; **HPLC** analysis with Chiralcel OD column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; major diastereoisomer t_R = 35.6 min (minor enantiomer), t_R = 19.4 min (major enantiomer); minor diastereosiomer t_R = 24.5 min (minor enantiomer), t_R = 51.0 min (major enantiomer).

(2R, 3S)- Methyl 1-(2-nitro-1-phenylethyl)-2-oxocycloheptane carboxylate (40m)



Colorless oil; major diastereoisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35-7.25 (m, 3H), 7.21-7.10 (m, 2H), 5.00-4.89 (m, 2H), 4.07 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.78 (s, 3H), 2.66-2.49 (m, 2H), 2.53 (ddd, *J* = 12.7, 8.9, 4.3 Hz, 1H), 1.94-1.40 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 208.3, 171.3, 135.5, 129.4, 128.7, 128.3, 77.8, 65.4, 52.4, 48.4, 41.3, 32.8, 28.9, 25.0, 24.4; **HPLC** analysis with Chiralcel OD-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; major diastereoisomer: t_R = 14.3 min (minor enantiomer), t_R = 31.3 min (major enantiomer), minor diastereosiomer t_R = 13.1 min (minor enantiomer), t_R = 27.2 min (major enantiomer).

Methyl 2-(3-benzyl-2,4-dioxocyclopentyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (44)

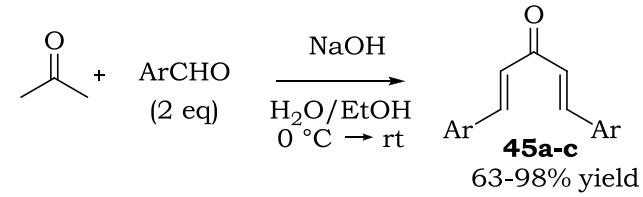


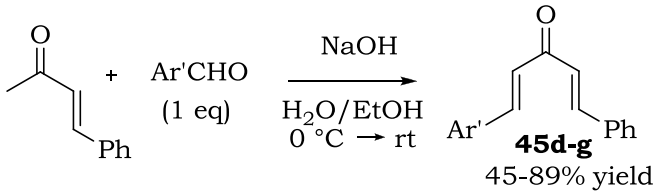
White solid; the diastereoisomers (1:1) could not be separated. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.72-7.69 (m, 1H), 7.66-7.61 (m, 1.85H), 7.50-7.32 (m, 3.7H), 7.30-7.25 (m, 9.3H), 4.60 (m, 3.8H), 4.06 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.05-3.95 (m, 0.9H), 3.75 (s, 2.5H), 3.28-3.02 (m, 1.85H), 3.0-2.78 (m, 1.9H), 2.38 (dd, *J* = 18.4, 6.0 Hz, 1H), 2.35-2.19 (m, 0.85H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 200.2, 199.5, 176.9, 176.6, 175.6, 174.9, 170.2, 169.2, 152.8, 152.4, 136.1, 135.8, 135.4, 134.7, 134.6, 128.7, 128.6, 128.5, 128.2, 127.9, 127.8, 126.4, 124.9, 60.7, 60.5, 53.4, 53.0, 43.9, 43.1, 42.5, 37.1, 34.0, 32.3, 31.4, 26.3; **HPLC** analysis with Chiralpak AD-H column, 75:25 *n*-hexane/^{i}PrOH, 0.75 mL/min, detection at 254 nm; major diastereoisomer t_R = 27.0 min (minor enantiomer), t_R = 34.8 min (major enantiomer), minor

diastereosiomer t_R = 36.4 min (minor enantiomer), t_R = 22.4 min (major enantiomer).

8.4 Asymmetric Double Michael Addition

Malononitrile and ethyl cyano acetate were commercially available reagents and employed as purchased without further purification. Dienones **45a-g** were prepared using general procedures reported in the literature.[172,119]





In a round-bottom flask 18 mmol of NaOH were dissolved in H_2O (5.5 mL), 3 mmol of the opportune ketone and 6 mmol of the correct aldehyde (3 mmol for the synthesis of the asymmetric dienones) were dissolved in EtOH (3.7 mL) and the solution was added dropwise at 0 °C. The mixture was stirred at room temperature until full conversion of the starting materials monitored by TLC eluent petroleum ether/Et_2O 7:3). The formed yellow solid is filtered and washed with H_2O until neutrality, dissolved in CH_2Cl_2, dried over Na_2SO_4 and the solvent was removed under reduced pressure.

[172] a) W. M. Weber, L. A. Hunsaker, S. F. Abcouwer, L. M. Deck, D. L. Vander Jagt, *Bioorg. Med. Chem.* **2005**, *13*, 3811; b) N. G. Rule, M. R. Detty, J. E. Kaeding, J. A. Sinicropi, *J. Org. Chem.* **1995**, *60*, 1665.

General procedure for the synthesis of racemic diaryl cyclohexanones

A solution of **45** (0.2 mmol), malononitrile (13.2 mg, 0.2 mmol) and 2-piperidinemethanol (23.0 mg, 0.2 mmol) in toluene (5 mL) was stirred at room temperature until the dienone was consumed as monitored by TLC (petroleum ether/Et_2O 6:4 as eluent). The crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of petroleum ether/Et_2O (9:1 to 7:3) affording cyclohexanones in 30-50% yield.

General procedure for the asymmetric synthesis of *trans*-4-oxo-2,6-diaryl-cyclohexane-1,1-dicarbonitriles 47a-g.

A solution of the opportune divinylketone **45** (0.2 mmol), malononitrile (13.2 mg, 0.2 mmol) and quinine (19.4 mg, 0.06 mmol) in toluene (10 mL) was stirred at room temperature until the starting materials were consumed as monitored by TLC (petroleum ether/Et_2O 6:4 as eluent). The crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of petroleum ether/Et_2O (9:1 to 7:3) affording the pure cyclohexanones.

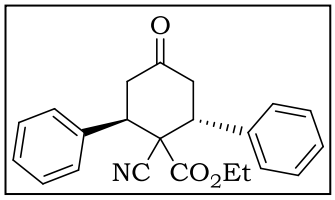
Procedure for the asymmetric synthesis of 46

Ethyl 2-cyanoacetate (22 μL, 0.2 mmol) was added to a solution of **45a** (56.2 mg, 0.24 mmol) and quinine (19.4 mg, 0.06 mmol) in toluene (666 μL) at room temperature. Stirring was maintained until **45a** was consumed as monitored by TLC (petroleum ether/Et_2O 6:4 as eluent). The crude reaction mixture was directly purified by flash chromatography on silica gel eluting with mixtures of petroleum ether/Et_2O (9:1 to 7:3) affording **46** in 85% yield.

Procedure for the kinetic resolution of 48

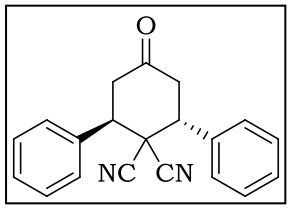
A solution of **48** (60.1 mg, 0.2 mmol) and quinine (19.5 mg, 0.06 mmol) in toluene (5 mL) was stirred for 15 h at room temperature. The compound **48a** and the cyclized product **47a** were recovered by flash chromatography on silica gel (eluent: petroleum ether/ Et_2O 9:1 to 6:4).

(2R,6R)-ethyl 1-cyano-4-oxo-2,6-diphenyl cyclohexane carboxylate (46)[111]



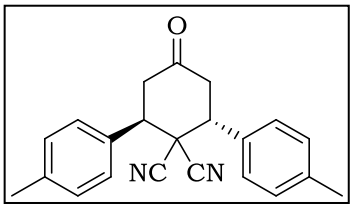
white solid, $[\alpha]_D^{20}$ = 34.7 (*c* 0.70, $CHCl_3$), *ee* 60%; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41-7.27 (m, 8H), 7.22-7.14 (m, 2H), 4.02-3.93 (m, 2H), 3.86-3.74 (m, 2H), 3.23-3.12 (m, 2H), 3.04 (dd, *J* = 16.6, 5.5 Hz, 1H), 2.81 (ddd, *J* = 16.7, 3.9, 1.0 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 207.2, 166.2, 137.3, 136.7, 128.7, 128.6, 128.5, 128.4, 128.3, 118.4, 62.7, 55.7, 48.0, 42.9, 42.4, 41.6, 13.3. **HPLC** analysis with Chiralpak AD-H column, 90:10 *n*-hexane/^{i}PrOH, 0.75 mL/min, detection at 220 nm; minor enantiomer t_R = 25.4 min, major enantiomer t_R = 20.0 min.

(2R,6R)-4-oxo-2,6-diphenylcyclohexane-1,1-dicabonitrile (47a)



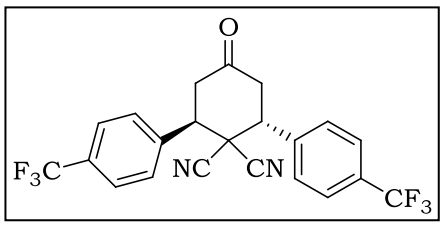
White solid, mp 68-70 °C; $[\alpha]_D^{23}$ = -2.71 (*c* 1.14, $CHCl_3$), *ee* 86%; **FTIR** ν_{max} (KBr)/cm^{-1} 3034, 2252, 1720, 1500, 1219, 700; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44-7.41 (m, 6H) , 7.33–7.29 (m, 4H), 3.82 (dd, *J* = 7.3, 6.1 Hz, 2H), 3.18-3.05 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 204.5, 135.0, 129.6, 129.2, 128.9, 113.8, 45.6, 45.0, 42.4; **MS** (ESI) *m/z* 299.33 [(M-H)$^-$]. **HPLC** analysis with Chiralpak OD-H column, 70:30 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 34.1 min, major enantiomer t_R = 56.1 min.

(2R,6R)-4-oxo-2,6-di-*p*-tolylcyclohexane-1,1-dicabonitrile (47b)



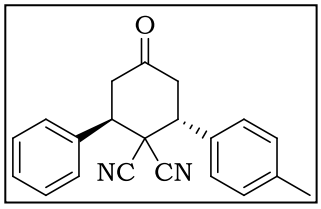
Yellow solid, mp 168-170 °C; $[\alpha]_D^{17}$ = 22.2 (*c* 0.43, $CHCl_3$), *ee* 85%; **FTIR** ν_{max} (KBr)/cm^{-1} 3024, 2256, 1719, 1516, 1216, 758; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.22-7.16 (m, 8H) , 3.80-3.76 (m, 2H), 3.14-3.01 (m, 4H), 2.37 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 204.9, 139.5, 132.0, 129.8, 128.7, 114.0, 45.2, 42.4, 21.1; **MS** (ESI^-) *m/z* 327.54 [$(M-H)^-$]. **HPLC** analysis with Chiralpak AD-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 10.8 min, major enantiomer t_R = 17.1 min.

(2R,6R)-4-oxo-2,6-bis(4-(trifluoromethyl)phenyl)cyclohexane-1,1-dicarbonitrile (47c)



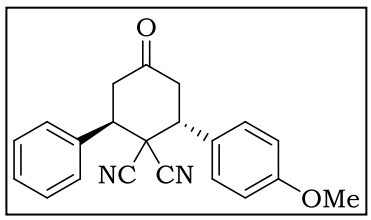
White solid, mp 159-160 °C; $[\alpha]_D^{18}$ = 4.70 (*c* 0.85, $CHCl_3$), *ee* 83%; **FTIR** ν_{max} (KBr)/cm^{-1} 2925, 2249, 1728, 1424, 1327, 759; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.72-7.70 (m, 2H), 7.48-7.44 (m, 2H), 3.89-3.84 (m, 2H), 3.21-3.09 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 203.2, 138.4, 132.0 (q, *J* = 33.0 Hz) , 129.4, 126.3 (q, *J* = 3.6 Hz), 123.5 (q, *J* = 272.3 Hz), 113.1, 45.4, 44.3, 42.0; **MS** (ESI^-) *m/z* 435.45 [$(M-H)^-$]. **HPLC** analysis with Chiralpak AD-H column, 75:25 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 8.5 min, major enantiomer t_R = 7.3 min.

(2R,6R)-4-oxo-2-phenyl-6-*p*-tolylcyclohexane-1,1-dicabonitrile (47d)



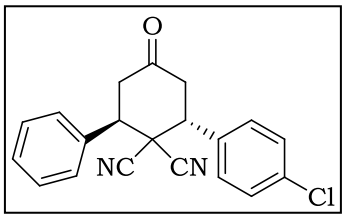
White solid, mp 56-58 °C; $[\alpha]_D^{16}$ = 4.8 (*c* 0.46, $CHCl_3$), *ee* 82%; **FTIR** ν_{max} (KBr)/cm^{-1} 3031, 2923, 2253,1721, 1516, 1218, 762, 701; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.43-7.41 (m, 3H), 7.32-7.29 (m, 2H), 7.23-7.17 (m, 4H), 3.83-3.79 (m, 2H), 3.17-3.03 (m, 4H), 2.37 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 204.8, 139.6, 135.0, 131.9, 129.8, 129.5, 129.1, 128.9, 128.8, 113.9, 113.8, 45.41, 45.36, 45.1, 42.4, 21.1; **MS** (ESI) *m/z* 313.61 [(M-H)$^-$]. **HPLC** analysis with Chiralpak AD-H column,95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 16.7 min, major enantiomer t_R = 18.5 min.

(2*R*,6*R*)-2-(4-methoxyphenyl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile (47e)



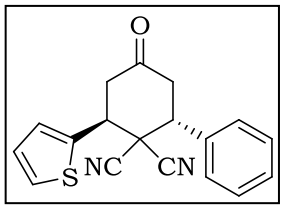
Pale yellow solid, mp 55-57 °C; $[\alpha]_D^{22}$ = 14.7 (*c* 0.28, $CHCl_3$), *ee* 85%; **FTIR** ν_{max} (KBr)/cm^{-1} 2965, 2226, 1722, 1516, 1258, 756; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44-7.40 (m, 3H), 7.32-7.28 (m, 2H), 7.25-7.20 (m, 2H) , 6.95-6.90 (m, 2H), 3.84-3.76 (m, 5H), 3.17-3.01 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 204.8, 160.3, 135.0, 130.1, 129.5, 129.2, 128.8, 126.8, 114.4, 113.92, 113.87, 55.3, 45.3, 45.1, 42.5, 42.4, 29.7; **MS** (ESI$^-$) *m/z* 329.52 [(M-H)$^-$]. **HPLC** analysis with Chiralpak AD-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 19.0 min, major enantiomer t_R = 26.1 min.

(2*R*,6*R*)-2-(4-chlorophenyl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile (47f)



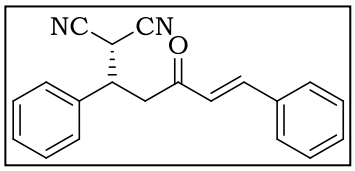
White solid, mp 92-94 °C; $[\alpha]_D^{19}$ = 14.0 (*c* 0.90, $CHCl_3$), *ee* 80%; **FTIR** ν_{max} (KBr)/cm^{-1} 2925, 2252, 1722, 1495, 1218, 762; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.40 (m, 5H) 7.34-7.27 (m, 4H), 3.86–3.82 (m, 1H), 3.80 (dd, *J* = 8.2, 5.8 Hz, 1H), 3.19-3.04 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 204.2, 135.8, 134.8, 133.4, 130.2, 129.7, 129.4, 129.2, 128.9, 113.6, 113.5, 45.8, 44.84, 44.78, 42.3, 42.2; **MS** (ESI$^-$) *m/z* 333.45 [(M-H)$^-$]. **HPLC** analysis with Chiralpak OD column, 50:50 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 26.4 min, major enantiomer t_R = 52.9 min.

(2*R*,6*S*)-4-oxo-2-phenyl-6-(tiophen-2-yl)cyclohexane-1,1-dicarbonitrile (47g)



Yellow solid, mp 117-119 °C; $[\alpha]_D^{22}$ = -2.17 (*c* 0.69, $CHCl_3$), *ee* 86%; **FTIR** ν_{max} (KBr)/cm^{-1} 2973, 2227, 1722, 1634, 1216, 701; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44-7.39 (m, 4H) , 7.34-7.31 (m, 2H), 7.14-7.12 (m, 1H) , 7.09-7.06 (m, 1H), 4.23-4.19 (m, 1H) , 3.84 (dd, *J* = 9.3, 5.2 Hz, 1H), 3.25-2.98 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 203.4, 137.0, 134.8, 129.6, 129.2, 128.8, 128.7, 127.5, 127.0, 113.6, 45.4, 43.8, 43.6, 42.4, 42.3; **MS** (ESI) *m/z* 305.49 [(M-H)$^-$]. **HPLC** analysis with Chiralpak AD-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 19.3 min, major enantiomer t_R = 18.0 min.

(S, *E*)-2-(3-oxo-1,5-diphenylpent-4-enyl)malononitrile (48)

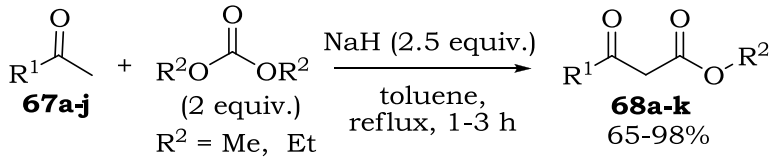


White wax, $[\alpha]_D^{19}$ = 2.2 (*c* 1.21, $CHCl_3$), *ee* 69%; **FTIR** ν_{max} (KBr)/cm^{-1} 3032, 2256, 1688, 1610, 1180, 701; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 16.2 Hz, 1H) , 7.58-7.37 (m, 10H), 6.76 (d, *J* = 16.2 Hz, 1H) , 4.63 (d, *J* = 5.1 Hz, 1H), 3.90-3.85 (m, 1H), 3.47-3.30 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.3, 144.6, 136.4, 133.7, 131.2, 129.3, 129.13, 129.08, 128.5, 127.9, 125.0, 111.8, 111.7, 42.0, 41.1, 28.7; **MS** (ESI) *m/z* 299.52 [$(M-H)^-$]. **HPLC** analysis with Chiralpak AD-H column, 70:30 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 11.1 min, major enantiomer t_R = 19.8 min.

8.5 Asymmetric Aziridination Reaction.

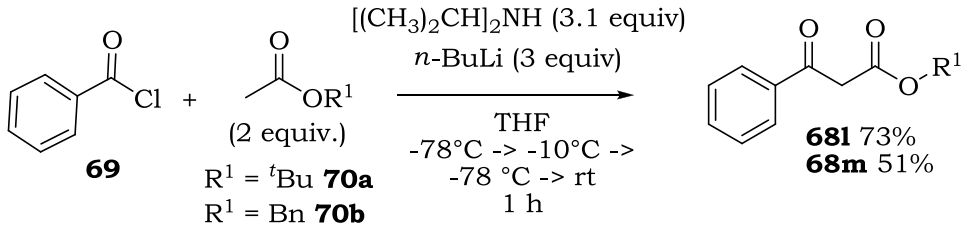
Experimental Procedures and Compounds Characterization

β-ketoesters, precursors of the required acrylate substrates, that were not commercially available, were synthetized according literature procedures.[148] Differently substituted methyl ketones **67** were reacted with the opportune carbonate (methyl or ethyl) with NaH as base, to give the condensation products **68** with good to excellent yields, up to 98%.



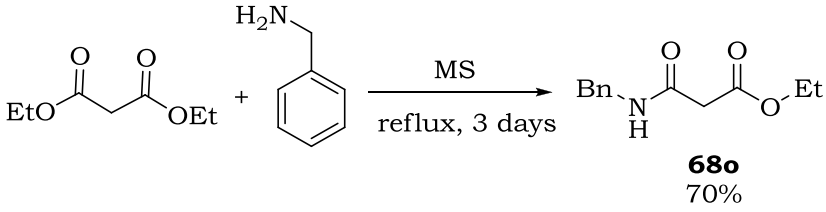
NaH (60% w/w, 856 mg, 21.4 mmol) was suspended in dry toluene (3 mL) under a positive pressure of nitrogen, the opportune carbonate was added, followed by a solution of the ketone **67** in dry toluene (3 mL). The mixture was stirred under reflux for 1-3 hours and afterwards neutralized with a saturated solution of NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography (eluent: petroleum ether/ Et_2O 95:5 to 9:1)

This procedure could not be extended to the ^{t}butyl and benzyl ketoesters to obtain the desired products **68m** and **n** so a different approach was employed: the acyl halide **69** was reacted with the corresponding ester **70** with LDA to give the corresponding prodicts in satisfactory yield.



In a two-necked round bottom flask under a positive pressure of nitrogen, dry THF (18 mL) was added to the diisopropylamine (3.9 mL, 27.9 mmol). The solution is cooled to -78°C and butyllithium was added quickly but keeping low the temperature. The system was allowed to warm to -10 °C and after 15 minutes it is again cooled to -78 °C. The opportune ester (27 mmol)) is slowly added and finally the acyl chloride (1 mL, 9 mmol) as a THF solution. The mixture is allowed to warm to room temperature until completion monitored by TLC (eluent petroleum ether/Et_2O 9:1). After 1h the reaction is quenched with a diluted HCl solution and extracted with / Et_2O three times. The unified organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash chromatography (eluent: petroleum ether/Et_2O 100:5).

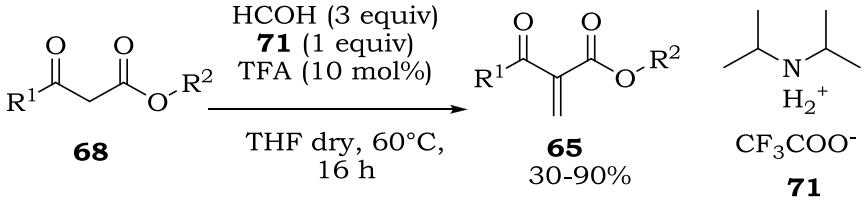
The β-amidoester was synthetized by means of a condensation between diethyl malonate and benzylamine in the presence of molecular sieves.



The ethyl diester (10 mmol) and the benzyl amine (10 mmol) in dry toluene over molecular sieves were refluxed under nitrogen for the necessary time (3-5 days monitoring by TLC, petroleum ether/EtOAc 8:2 as eluent). Then molecular sieves were filtered off, and the solution extracted with

EtOAc/HCl (1N) two times. The organic layer was collected, dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by flash chromatography, eluent petroleum ether /Et_2O 8:2 to Petroleum ether/EtOAc 6:4).

The dicarbonyl compounds were subjected to a methylenation reaction, according a procedure reported in the literature,[149] in which formaldehyde and diisopropylammonium trifluoroacetate were employed.



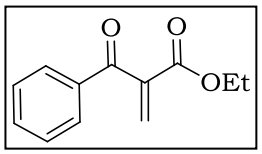
In a screw capped vial containing freshly distilled THF (40 mL), β-ketoesters (4.0 mmol), *p*-formaldehyde (360 mg, 12 mmol) and $CF_3COONH_2{}^iPr_2$ salt (861 mg, 4 mmol) were added. CF_3COOH (31 μL, 0.40 mmol) was added and the mixture was warmed to 60°C and stirred overnight. The reaction mixture was then extracted with EtOAc/water and the organic layer dried over Na_2SO_4. The solvent was then removed under vacuum. The residue was loaded onto silica gel and purified by flash chromatography (petroleum ether/EtOAc 9:1 as eluent) to obtain the alkenes.[173]

Starting amines **63a-e** were synthesized according to the literature.[150] As an example, the Boc-protected amine is prepared as follows: to a solution of the Boc-hydroxylamine (1 mmol) in dry CH_2Cl_2 (2 mL), pyridine was added (2.4 mmol). The solution was cooled at -20°C followed by a portion-wise addition of TsCl (1 mmol). The mixture is allowed to warm to room

[173] Alkenes **65a-o** need to be used freshly prepared, because they are prone to spontaneous polymerization on standing.

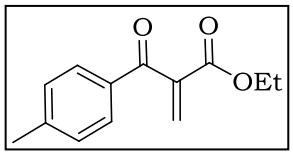
temperature and after completion, monitored by TLC (eluent petroleum ether/EtOAc 6:4), diluted with $CHCl_3$ and washed with water. The organic layers were concentrated *under vacuum* and the product was isolated by flash chromatography.

Ethyl 2-benzoylacrylate (65a)



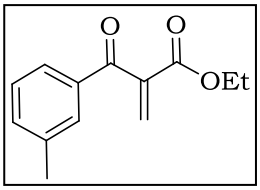
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2982, 1728, 1665, 1241, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.84-7.82 (m, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 6.66 (s, 1H), 6.04 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.0, 164.2, 141.3, 136.1, 133.5, 131.2, 129.3, 128.4, 61.4, 13.8. **MS** (ESI *m/z*) 205.10 [MH^+, 100%], 227.09 [MNa^+, 35%].

Ethyl 2-(4-methylbenzoyl)acrylate (65b)



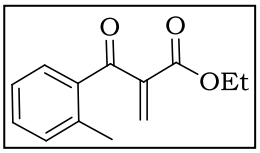
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2983, 1727, 1671, 1237, 771. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.67 (s, 1H), 6.03 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 192.9, 164.4, 144.6, 141.5, 133.7, 131.0, 129.6, 129.2, 61.5, 21.7, 14.0. **MS** (ESI *m/z*) 219.25 [MH^+, 10%], 256.39 [MK^+, 60%].

Ethyl 2-(3-methylbenzoyl)acrylate (65c)



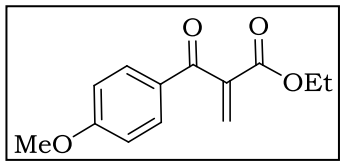
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2982, 1728, 1675, 1251, 763. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (s, 1H), 763-7.58 (m, 1H), 7.58-7.27 (m, 2H), 6.64 (s, 1H), 6.01 (s, 1H), 4.19 (q, J = 7.1 H, 2H z), 2.36 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.2, 164.2, 141.3, 138.3, 136.1, 134.3, 131.0, 129.6, 128.3, 126.6, 61.3, 21.1, 13.8. **MS** (ESI *m/z*) 219.37 [MH$^+$, 10%], 256.41 [MK$^+$, 70%].

Ethyl 2-(2-methylbenzoyl)acrylate (65d)



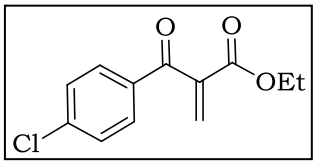
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2867, 1718, 1636, 1219, 771. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51-7.42 (m, 1H), 7.41-7.35 (m, 1H), 7.28-7.19 (m 2H), 6.63 (s, 1H), 6.12 (s, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.51 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 195.2, 164.6, 143.0, 138.6, 136.7, 132.4, 131.7, 129.8, 125.4, 61.4, 20.7, 13.9. **MS** (ESI *m/z*) 219.44 [MH$^+$, 15%], 256.39 [MK$^+$, 90%].

Ethyl 2-(4-methoxybenzoyl)acrylate (65e)



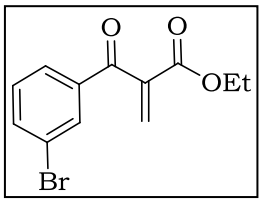
Purified by flash chromatography (petroleum ether/EtOAc 97:3 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2982, 1725, 1666, 1600, 1263, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85 (d, 2H, J = 8.8 Hz), 6.94 (d, 2H, J = 8.8 Hz), 6.66 (s, 1H), 6.00 (s, 1H), 4.23 (q, 2H, J = 7.1 Hz), 3.88 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 191.8, 164.5, 164.0, 141.5, 131.9, 130.5, 129.2, 113.8, 61.5, 55.5, 14.0. **MS** (ESI *m/z*) 235.24 [MH$^+$, 5%], 257.19 [MNa$^+$, 100%].

Ethyl 2-(4-chlorobenzoyl)acrylate (65f)



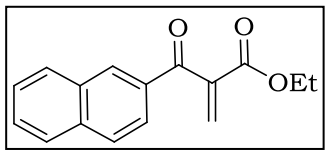
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 1732, 1683, 1588, 1220, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 6.70 (s, 1H), 6.07 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 192.0, 164.1, 141.0, 140.1, 134.6, 131.7, 130.7, 128.9, 61.6, 13.9. **MS** (ESI *m/z*) 239.34 [MH$^+$, 55%], 261.37 [MNa$^+$, 85%], 268.38 [MK$^+$, 45%].

Ethyl 2-(3-bromobenzoyl)acrylate (65g)



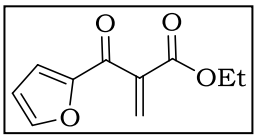
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 1733, 1687, 1565, 1233, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.77-7.53 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 6.71 (d, J = 0.7 Hz, 1H), 6.09 (d, J = 0.6 Hz, 1H), 4.26-4.18 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 191.7, 164.0, 140.8, 138.0, 136.4, 132.14, 132.09, 130.1, 127.9, 122.8, 61.6, 13.9. **MS** (ESI *m/z*) 305.19 [MNa$^+$, 100%]

Ethyl 2-(2-naphthoyl)acrylate (65h)



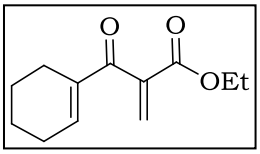
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2981, 1727, 1673, 1222, 771. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 8.01-7.89 (m, 4H), 7.65-7.53 (m, 2H), 6.77 (d, J = 0.6 Hz, 1H), 6.12 (d, J = 0.6 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H): **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.2, 164.4, 141.4, 135.8, 133.6, 132.3, 131.9, 131.4, 129.6, 128.8, 128.6, 127.8, 126.9, 124.4, 61.6, 14.0. **MS** (ESI *m/z*) 255.47 [MH$^+$, 10%], 277.37 [MNa$^+$, 100%].

Ethyl 2-(furan-2-carbonyl)acrylate (65i)



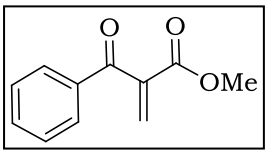
Purified by flash chromatography (petroleum ether/EtOAc 95:5 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 3134, 2984, 1726, 1661, 1465, 1255, 771. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.64-7.61 (m, 1H), 7.17-7.15 (m, 1H), 6.62 (s, 1H), 6.54 (dd, J = 3.6, 1.7 Hz, 1H), 6.17 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 179.8, 164.0, 151.8, 147.5, 140.5, 131.7, 120.1, 112.4, 61.5, 13.9. **MS** (ESI *m/z*) 195.26 [MH$^+$, 15%], 217.26 [MNa$^+$, 100%], 233.19 [MK$^+$, 10%].

Ethyl 2-(cyclohex-1-enecarbonyl)acrylate (65j)



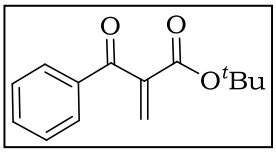
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2941, 1724, 1658, 1634, 1220, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.76 (t, J = 3.9 Hz, 1H), 6.49 (s, 1H), 5.81 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 2.35-2.19 (m, 4H), 1.70-1.56 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.6, 164.5, 145.4, 141.2, 139.2, 129.2, 61.3, 26.3, 22.8, 21.7, 21.5, 14.0. **MS** (ESI *m/z*) 231.31 [MNa*, 100%] .

Methyl 2-benzoylacrylate (65k)



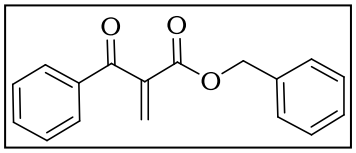
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2980, 1725, 1673, 1223, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85 (dd, 2H, J_1 = 7.1 Hz, J_2 = 1.1 Hz), 7.61-7.57 (m, 1H), 7.48-7.44 (m, 2H), 6.71 (s, 1H), 6.05 (s, 1H), 3.75 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.0, 164.7, 140.8, 136.0, 133.6, 131.5, 129.4, 128.6, 52.4. **MS** (ESI *m/z*) 191.08 [MH$^+$, 100%].

***tert*-Butyl 2-benzoylacrylate (65l)**



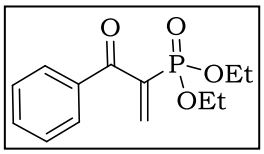
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 2979, 1725, 1678, 1248, 1148, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 7.3 Hz, 2H), 7.60-7.55 (m, 1H), 7.48-7.42 (m, 2H), 6.58 (s, 1H), 6.05 (s, 1H), 1.34 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz δ 193.7, 163.4, 143.3, 136.7, 133.3, 130.7, 129.0, 128.4, 82.3, 27.7. **MS** (ESI m/z) 234.50 [MH$^+$, 40%], 255.46 [MNa$^+$, 100%].

Benzyl 2-benzoylacrylate (65m)



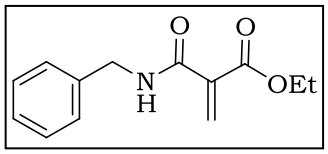
Purified by flash chromatography (petroleum ether/EtOAc 95:5 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-1} 3033, 1729, 1674, 1221, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85-7.82 (m, 2H), 7.62-7.55 (m, 1H), 7.47-7.41 (m, 2H), 7.31-7.27 (m, 3H), 7.21-7.16 (m, 2H), 6.73 (s, 1H), 6.12 (s, 1H), 5.20 (s, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 192.9, 164.1, 141.2, 136.2, 135.1, 133.5, 132.0, 129.3, 128.5, 128.4, 128.2, 127.9, 67.0. **MS** (ESI m/z) 289.42 [MNa$^+$, 100%]

Diethyl 3-oxo-3-phenylprop-1-en-2-ylphosphonate (65n)



Purified by flash chromatography (petroleum ether/EtOAc 1:1 as eluent). Colourless oil, **FTIR** ν_{max} (KBr)/cm^{-1} 2985, 1667, 1251, 1023, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85 (d, 2H, J = 7.4 Hz), 7.62-7.53 (m, 1H), 7.49-7.43 (m, 2H), 6.81 (d, 1H, J = 23.5 Hz), 6.28 (d, 1H, J = 45.0 Hz), 4.22-4.13 (m, 4H), 1.31 (t, 6H, J = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.9, 139.6, 138.3, 136.1, 133.5, 129.8, 128.5, 62.8 (d, J = 5 Hz), 16.2 (d, J = 6 Hz). **MS** (ESI m/z) 269.27 [MH$^+$, 30%], 291.24 [MNa$^+$, 100%], 307.20 [MK$^+$, 40%].

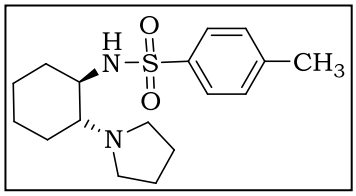
Ethyl 2-(benzylcarbamoyl)acrylate (65o)



Purified by flash chromatography (petroleum ether/EtOAc 9:1 as eluent). Pale yellow oil. **FTIR** ν_{max} (KBr)/cm^{-} 2982, 1714, 1663, 1534, 1143, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.79 (bs, 1H), 7.34-7.17 (m, 5H), 7.17 (s, 1H), 6.79 (s, 1H), 4.57 (d, J = 5.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.2, 162.1, 138.4, 137.9, 132.4, 128.6, 127.6, 127.3, 61.7, 43.6. **MS** (ESI *m/z*) 256.13 [MNa^{+}, 100%].

Catalyst **76** was synthesized according to literature procedure.[174]

4-methyl-*N*-((1*R*, 2*R*)-2-(pyrrolidin-1-yl)cyclohexyl) benzene sulfonamide (76)



Yellow oil, $[\alpha]_D^{19}$ = -64.0 (*c* 0.98, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 2933, 1219, 1164, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.69-2.58 (m, 1H), 2.51-2.34 (m, 7H), 2.19-2.05 (m, 2H), 1.80-1.72 (m, 2H), 1.64-1.52 (m, 5H), 1.28-1.04 (m, 6H), 0.93-0.79 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.1, 137.0, 129.4, 127.2, 61.4, 55.2, 46.6, 32.7, 24.9, 24.2, 23.4, 21.8, 21.5. **MS** (ESI *m/z*) 323.14 [MH^{+}, 100%].

General procedure for the synthesis of racemic aziridines 66

A sample vial was charged with compound **65** (0.20 mmol) and amine **63** (0.20 mmol) in anhydrous toluene (4.0 mL). Triethylamine (0.20 mmol) was added and the solution was stirred at room temperature until completion (1-3 hours), monitored by TLC (eluent petroleum ether/$CHCl_3$

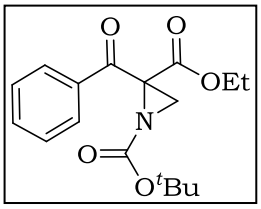
[174] F. Yu, X. Sun, Z. Jin, S. Wen, X. Liang, J. Ye, *Chem. Commun.* **2010**, *46*, 4589.

3:7) Flash chromatography (petroleum ether/Et_2O 95:5 as eluent) gave racemic aziridines **63**.

Procedure for the asymmetric aziridination of compounds 65

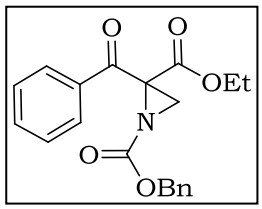
To a sample vial charged with the appropriate catalyst (0.02 mmol), K_2CO_3 (0.1 mmol) and the amine (0.1 mmol) a solution of the alkene (0.1 mmol) in anhydrous toluene (2 mL), cooled at 0°C for 10 minutes, was added and the reaction mixture stirred at 0°C. After completion, monitored by TLC (eluent petroleum ether/$CHCl_3$ 3:7), the reaction mixture was directly loaded onto silica gel and purified by flash chromatography (eluting with petroleum ether/Et_2O 95:5) to give the corresponding chiral aziridines **65a-o**.

(*R*)-1-*tert*-butyl 2-ethyl 2-benzoylaziridine-1,2-dicarboxylate (66aa)



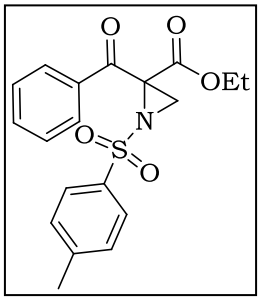
Colourless oil. $[\alpha]_D^{13}$ = -79.2 (*c* 0.88, $CHCl_3$), 78% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2981, 1747, 1733, 1688, 1369, 1249, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24 (d, *J* = 8.2 Hz, 2H), 7.63-7.58 (m, 1H), 7.52-7.43 (m, 2H), 4.31-4.20 (m, 1H), 4.19-4.11 (m, 1H), 2.95 (s, 1H), 2.70 (s, 1H), 1.52 (s, 9H), 1.11 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.7, 166.6, 158.0, 134.7, 133.7, 129.6, 128.4, 82.9, 62.8, 48.6, 36.4, 27.9, 13.9. **MS** (ESI *m/z*) 342.40 [MNa$^+$, 80%]. **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 13.3 min, major enantiomer t_R = 10.1 min.

1-Benzyl 2-ethyl 2-benzoylaziridine-1,2-dicarboxylate (66ab)



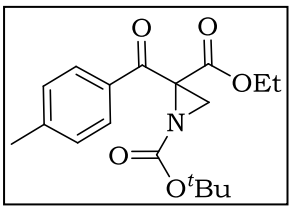
Colourless oil. $[\alpha]_D^{20}$ = -57.4 (*c* 0.70, $CHCl_3$), *ee* 70%. **FTIR** ν_{max} (KBr)/cm^{-1} 2923, 1744, 1730, 1685, 1219, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.22-8.16 (m, 2H), 7.62-7.52 (m, 2H), 7.48-7.36 (m, 6H), 5.25 (s, 2H), 4.24-4.04 (m, 2H), 3.04 (d, *J* = 1.28 Hz, 1 H), 2.77 (d, *J* = 1.28 Hz, 1 H), 1.06 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.3, 166.4, 159.4, 135.0, 134.5, 133.8, 129.5, 128.6, 128.5, 69.0, 63.0, 48.5, 36.5, 13.8. **MS** (ESI *m/z*) 376.41 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 80:20 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 13.8 min, major enantiomer t_R = 10.7 min.

Ethyl 2-benzoyl-1-tosylaziridine-2-carboxylate (66ac)



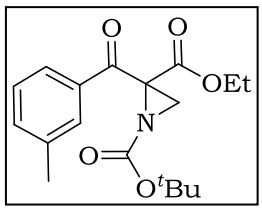
Colourless oil. $[\alpha]_D^{18}$ = 8.6 (*c* 0.92, $CHCl_3$), 36% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2977, 1751, 1733, 1691, 1220, 1166, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.10 (d, 2H, *J* = 8.2 Hz), 7.89-7.68 (m, 2H), 7.63-7.55 (m, 1H), 7.51-7.41 (m, 2H), 7.33-7.27 (m, 2H), 4.34-4.16 (m, 2H), 3.37 (s, 1H), 2.94 (s, 1H), 2.42 (s, 3H), 1.17 (t, 3H, *J* = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 188.9, 164.9, 144.8, 136.2, 134.3, 134.0, 129.7, 129.6, 128.5, 127.8, 63.2, 53.6, 37.3, 21.6, 13.6. **MS** (ESI *m/z*) 396.36 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 70:30 *n*-hexane/^{i}PrOH, 0.8 mL/min, detection at 220 nm; minor enantiomer t_R = 19.3 min, major enantiomer t_R = 14.9 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(4-methylbenzoyl)aziridine-1,2-dicarboxylate (66b)



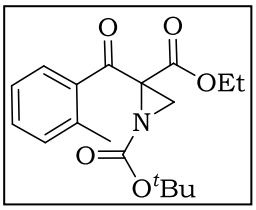
Colourless oil. $[\alpha]_D^{22}$ = -73.6 (*c* 0.48, $CHCl_3$), 78% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2979, 1746, 1685, 1249, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.14 (d, 2H, *J* = 8.1 Hz), 7.27 (d, 2H, *J* = 8.2 Hz), 4.30-4.21 (m, 1H), 4.20-4.09 (m, 1H), 2.94 (s, 1H), 2.68 (s, 1H), 2.42 (s, 3H), 1.52 (s, 9H), 1.13 (t, 3H, *J* = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.3, 166.7, 158.0, 144.8, 132.2, 129.8, 129.1, 82.8, 62.7, 48.6, 36.4, 27.9, 21.8, 13.9. **MS** (ESI *m/z*) 356.37 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column,95:5 *n*-hexane:2-propanol, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 14.0 min, major enantiomer t_R = 11.2 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(3-methylbenzoyl)aziridine-1,2-dicarboxylate (66c)



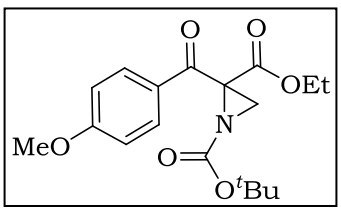
Colourless oil. $[\alpha]_D^{22}$ = -69.7 (*c* 0.47, $CHCl_3$), 82% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2981, 1747, 1732, 1686, 1250, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 7.5 Hz, 1H), 7.98 (s, 1H), 7.42-7.32 (m, 2H), 4.31-4.09 (m, 2H), 2.94 (d, *J* = 1.4 Hz, 1H), 2.68 (d, *J* = 1.4 Hz, 1H), 2.42 (s, 3H), 1.52 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 191.0, 166.6, 158.0, 138.3, 134.7, 134.6, 129.7, 128.3, 127.1, 82.8, 62.7, 48.7, 36.5, 27.9, 21.3, 13.9. **MS** (ESI *m/z*) 334.28 [MH^+, 10%], 356.43 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 12.8 min, major enantiomer t_R = 9.4 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(2-methylbenzoyl)aziridine-1,2-dicarboxylate (66d)



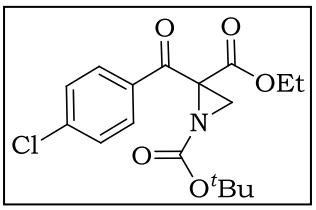
Colourless oil. $[\alpha]_D^{23}$ = -24.0 (*c* 0.60, $CHCl_3$), 50% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2979, 1746, 1688, 1248, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.19-8.11 (m, 1H), 7.45-7.38 (m, 1H), 7.29- 7.27 (m, 2H), 4.25-4.13 (m, 1H), 4.12-4.05 (m, 1H), 2.90 (d, *J* = 1.6 Hz, 1H), 2.77 (d, *J* = 1.6 Hz, 1H), 2.54 (s, 3H), 1.49 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.1, 166.7, 157.9, 139.8, 134.8, 132.2, 131.8, 130.5, 125.4, 82.8, 62.5, 49.8, 36.6, 27.9, 21.2, 13.7. **MS** (ESI *m/z*) 334.34 [MH^+, 10%], 356.45 [MNa^+, 100%]. **HPLC** analysis with Chiralpak IC column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 13.6 min, major enantiomer t_R = 12.5 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(4-methoxybenzoyl)aziridine-1,2-dicarboxylate (66e)



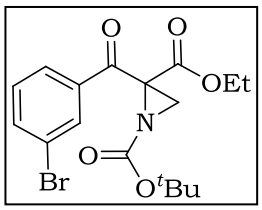
Colourless oil. $[\alpha]_D^{23}$ = -56.6 (*c* 0.82, $CHCl_3$), 80% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2982, 1746, 1678, 1251, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.29-4.25 (m, 1H), 4.24-4.11 (m, 1H), 3.88 (s, 3H), 2.93 (d, *J* = 1.0 Hz, 1H), 2.66 (d, *J* = 1.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 189.2, 166.8, 164.0, 158.1, 132.2, 127.8, 113.7, 82.8, 62.7, 55.5, 48.6, 36.5, 27.9, 13.9. **MS** (ESI *m/z*) 372.18 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 80:20 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 12.5 min, major enantiomer t_R = 10.4 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(4-chlorobenzoyl)aziridine-1,2-dicarboxylate (66f)



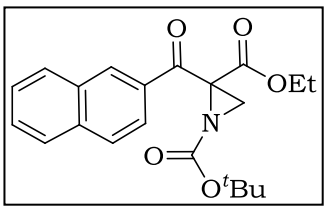
Colourless oil. $[\alpha]_D^{19}$ = -59.0 (*c* 0.61, $CHCl_3$), 78% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2981, 1749, 1735, 1690, 1250, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.22 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 4.32-4.21 (m, 1H), 4.20-4.07 (m, 1H), 2.95 (s, 1H), 2.68 (s, 1H), 1.53 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H)*;* **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 189.7, 166.3, 157.8, 140.3, 133.0, 131.0, 128.8, 83.1, 62.9, 48.4, 36.5, 27.9, 13.9. **MS** (ESI *m/z*) 376.19 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 98:2 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 13.5 min, major enantiomer t_R = 11.5 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(3-bromobenzoyl)aziridine-1,2-dicarboxylate (66g)



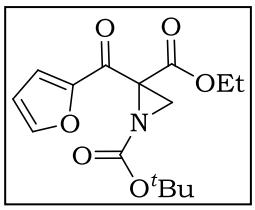
Colourless oil. $[\alpha]_D^{24}$ = -52.1 (*c* 0.62, $CHCl_3$), 70% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2978, 1749, 1733, 1693, 1567, 1370, 1248, 1155,772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.35 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 7.9, 0.84 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 4.35-4.22 (m, 1H), 4.21-4.09 (m, 1H), 2.97 (d, *J* = 0.6 Hz, 1H), 2.67 (d, *J* = 0.6 Hz, 1H), 1.54 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 189.7, 166.2, 157.8, 136.6, 136.5, 132.3, 130.0, 128.4, 122.8, 83.3, 62.9, 48.4, 36.5, 28.0, 13.9. **MS** (ESI *m/z*) 422.10 [MNa^+, 100%]. HPLC analysis HPLC with Chiralpak AS-H column, 90:10 *n*-hexane/^{i}PrOH, 0.8 mL/min, detection at 254 nm; minor enantiomer t_R = 7.5 min, major enantiomer t_R = 6.1 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(2-naphthoyl)aziridine-1,2-dicarboxylate (66h)



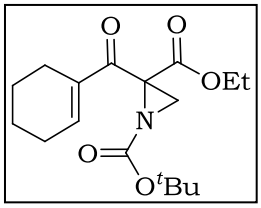
White solid. Mp 72.5-74.0 °C. $[\alpha]_D^{22}$ = -55.23 (*c* 0.67, $CHCl_3$), 74% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2980, 1746, 1733, 1683, 1250, 1156, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.90 (s, 1H), 8.23-8.18 (m, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.93-7.85 (m, 2H), 7.63-7.57 (m, 1H), 7.56-7.49 (m, 1H), 4.30-4.05 (m, 2H), 3.02 (s, 1H), 2.75 (s, 1H), 1.57 (s, 9H), 1.10 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.8, 166.7, 158.1, 135.8, 132.4, 132.2, 132.0, 129.9, 128.9, 128.2, 127.8, 126.7, 124.6, 83.0, 62.8, 48.8, 36.7, 28.0, 13.9. **MS** (ESI *m/z*) 392.16 [MNa^+, 100%], 408.11 [MK^+, 20%]. **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 15.0 min, major enantiomer t_R = 12.3 min.

(*R*)-1-*tert*-butyl 2-ethyl 2-(furan-2-carbonyl)aziridine-1,2-dicarboxylate (66i)



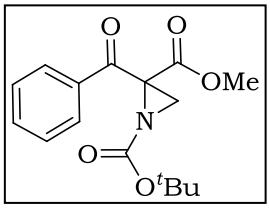
Colourless oil. $[\alpha]_D^{20}$ = -94.4 (*c* 0.56, $CHCl_3$), 74% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2983, 1748, 1733, 1678, 1252, 1219, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 3.2 Hz, 1H), 7.66 (s, 1H), 6.59-6.54, (m, 1H), 4.32-4.11 (m, 2H), 2.94 (s, 1H), 2.64 (s, 1H), 1.49 (s, 9H), 1.21-1.11 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 178.6, 166.0, 157.8, 150.6, 147.7, 121.7, 112.5, 82.9, 62.8, 48.1, 36.1, 27.9, 14.0. **MS** (ESI *m/z*) 332.18 [MNa^+, 100%], 348.14 [MK^+, 20%]. **HPLC** analysis with Chiralpak AS-H column, 90:10 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 8.9 min, major enantiomer t_R = 7.9 min.

1-*tert*-butyl 2-ethyl 2-(cyclohex-1-enecarbonyl)aziridine-1,2-dicarboxylate (66j)



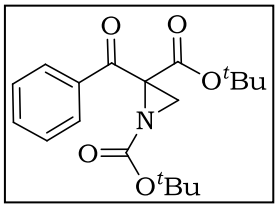
Colourless oil. $[\alpha]_D^{22}$ = -57.14 (*c* 0.42, $CHCl_3$), 72% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1}2938, 1746, 1673, 1369, 1220, 1158, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.52-7.47 (m, 1H), 4.36-4.23 (m, 1H), 4.21-4.09 (m, 1H), 2.79 (d, *J* = 1.4 Hz, 1H), 2.54 (d, *J* = 1.4 Hz, 1H), 2.38-2.12 (m, 4H), 1.73-1.58 (m, 4H), 1.49 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 191.3, 167.0, 158.1, 145.6, 137.1, 82.5, 62.5, 48.2, 36.2, 27.9, 26.3, 22.9, 21.7, 21.4, 14.0. **MS** (ESI *m/z*) 346.20 [MNa^+, 100%], 362.18 [MK^+, 25%]. **HPLC** analysis with Chiralpak AD-H column, 98:2 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 220 nm; minor enantiomer t_R = 14.9 min, major enantiomer t_R = 13.4 min.

(*R*)-1-*tert*-butyl 2-methyl 2-benzoylaziridine-1,2-dicarboxylate (66k)



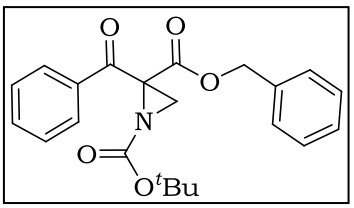
Colourless oil. $[\alpha]_D^{13}$ = -65.8 (*c* 0.90, $CHCl_3$), 78% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2979, 1751, 1733, 1688, 1370, 1251, 1156, 802. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.27-8.21 (m, 2H), 7.63-7.58 (m, 1H), 7.51-7.46 (m, 2H), 3.74 (s, 3H), 2.97 (d, *J* = 1.4 Hz, 1H), 2.70 (d, *J* = 1.4 Hz, 1H), 1.53 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.6, 167.1, 157.9, 134.5, 133.9, 129.7, 128.5, 83.0, 53.4, 48.4, 36.6, 27.9. **MS** (ESI *m/z*) 328.30 [MNa^+, 100%], 344.15 [MK^+, 5%]. **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 14.4 min, major enantiomer t_R = 10.5 min.

(*R*)-di-*tert*-butyl 2-benzoylaziridine-1,2-dicarboxylate (66l)



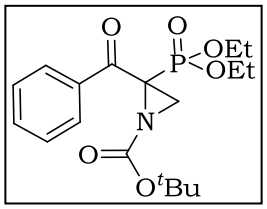
Colourless oil. $[\alpha]_D^{22}$ = -55.1 (*c* 0.56, $CHCl_3$), 76% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2979, 2933, 1725, 1678, 1248, 1148, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49-7.42 (m, 2H), 2.89 (d, *J* = 1.0 Hz, 1H), 2.68 (d, *J* = 1.0 Hz, 1H), 1.54 (s, 9H), 1.30 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 191.0, 165.3, 158.3, 135.1, 133.4, 129.4, 128.2, 84.4, 82.7, 49.3, 35.8, 27.9, 27.6 . **MS** (ESI *m/z*) 370.42 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 9.1 min, major enantiomer t_R = 8.3 min.

(*R*)-2-benzyl 1-*tert*-butyl 2-benzoylaziridine-1,2-dicarboxylate (66m)



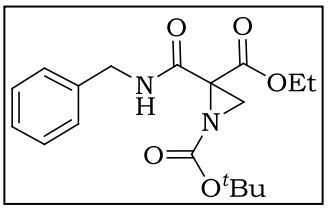
Colourless oil. $[\alpha]_D^{20}$ = -73.2 (*c* 0.45, $CHCl_3$), 72% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 3032, 2347, 1735, 1685, 1220, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.19 (d, *J* = 1.2 Hz, 2H), 7.61-7.53 (m, 1H), 7.46-7.38 (m, 2H), 7.32-7.18 (m, 3H), 7.07-7.01 (m, 2H), 5.26 (d, *J* = 12.3 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 2.96 (d, *J* = 1.5 Hz, 1H), 2.75 (d, *J* = 1.4 Hz, 1H), 1.45 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.4, 166.5, 157.9, 134.7, 134.4, 133.7, 129.6, 128.4, 128.1, 82.9, 68.1, 48.6, 36.4, 27.8. **MS** (ESI *m/z*) 404.27 [MNa^+, 100%]. **HPLC** analysis with Phenomenex Lux column, 90:10 *n*-hexane/^{i}PrOH, 1.0 mL/min, detection at 254 nm; minor enantiomer t_R = 13.8 min, major enantiomer t_R = 11.2 min.

tert-butyl 2-benzoyl-2-(diethoxyphosphoryl)aziridine-1-carboxylate (66n)



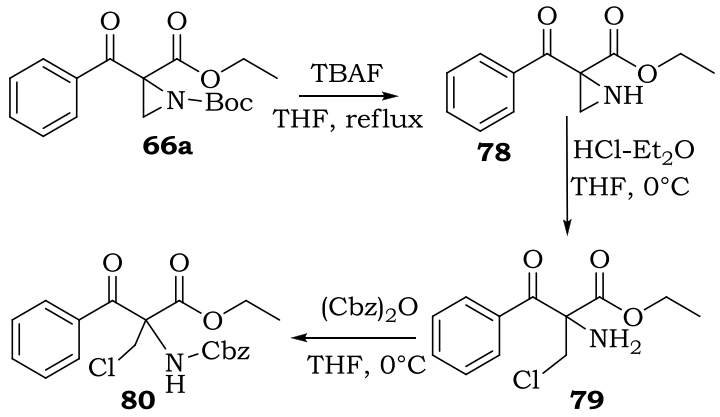
Colourless oil. $[\alpha]_D^{24}$ = 46.3 (*c* 0.48, $CHCl_3$), 50% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2982, 1729, 1679, 1271, 1159, 1023, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.41-8.34 (m, 2H), 7.62-7.54 (m, 1H), 7.49-7.42 (m, 2H), 4.28-4.10 (m, 4H), 3.02 (dd, *J* = 9.4, 0.9 Hz, 1H), 2.50 (dd, *J* = 3.9, 1.0 Hz, 1H), 1.56 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 192.4 (d, *J* = 11 Hz), 158.3 (d, *J* = 9 Hz), 134.6, 133.8, 130.5, 128.1, 82.8, 63.9 (d, *J* = 7 Hz), 63.5 (d, *J* = 6 Hz), 45.8, 44.1, 33.7, 27.9, 16.1. **MS** (ESI *m/z*) 406. 25 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AS-H column, 95:5 *n*-hexane/^{i}PrOH, 0.6 mL/min, detection at 254 nm; minor enantiomer t_R = 9.3 min, major enantiomer t_R = 12.2 min.

1-_tert_-butyl 2-ethyl 2-(benzylcarbamoyl)aziridine-1,2-dicarboxylate (66o)



Colourless oil. $[\alpha]_D^{20}$ = -20.8 (*c* 0.87, $CHCl_3$), 72% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 2981, 1734, 1676, 1531, 1370, 1249, 1157, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68 (bs, 1H), 7.40-7.19 (m, 5H), 4.51 (d, *J* = 5.8 Hz, 2H), 4.38-4.15 (m, 2H), 2.94 (d, *J* = 1.1 Hz, 1H), 2.72 (d, *J* = 1.1 Hz, 1H), 1.43 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.0, 164.0, 157.5, 137.6, 128.7, 127.6, 82.7, 62.8, 44.7, 43.5, 37.6, 27.8, 13.9. **MS** (ESI *m/z*) 371.25 [MNa^+, 100%]. **HPLC** analysis with Chiralpak AD-H column, 95:5 *n*-hexane/^{i}PrOH, 1 mL/min, detection at 220 nm; minor enantiomer t_R = 17.6 min, major enantiomer t_R = 16.2 min.

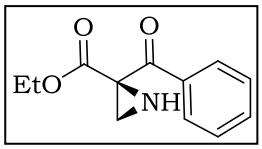
Procedure for synthesis of compound 80



Enantiomerically enriched aziridine **66a** (0.2 mmol, 77% *ee*) dissolved in dry THF (1 mL) was treated with tetrabutylammonium fluoride (0.2 mmol, 1 M solution in THF) at 60°C. After completion of reaction, monitored by TLC (eluent petroleum ether/EtOAc 6:4), the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc (3 x 50 mL). Combined organic phases were evaporated under reduced pressure. The residue was purified by flash chromatography and isolated in 98% yield.

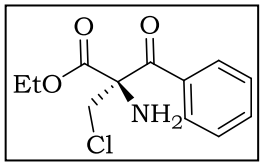
Deprotected aziridine **78** was dissolved in dry THF (4 mL) and at 0°C a solution of $HCl{\cdot}Et_2O$ (0.2 mmol) diluted in THF (0.14 M) was added dropwise. After 2 hours the reaction mixture was treated with 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 50 mL), combined organic phases were evaporated under reduced pressure. The residue was directly treated with a solution of benzyl dicarbonate (1.4 equivalents) in dry THF (800 μL) at 0°C. After 2 hours the mixture was diluted with EtOAc and washed with water. Aqueous phase was extracted with EtOAc (2 x 50 mL). Combined organic layers were evaporated and after purification by flash chromatography (eluent petroleum ether/EtOAc 98:2) compound **80** was obtained in 38% yield (77% *ee*).

(*R*)-Ethyl 2-benzoylaziridine-2-dicarboxylate (78)



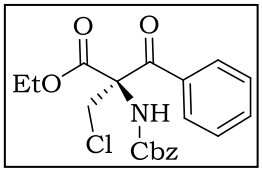
Purified by flash chromatography (petroleum ether/Et_2O 8:2 as eluent). Colourless oil. $[\alpha]_D^{20}$ = -12.3 (*c* 0.52, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^- 2924, 2854, 1733, 1688, 1220, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.58-7.52 (m, 2H), 7.50-7.32 (m, 3H), 4.30-3.98 (m, 3.6H), 2.64 (d, *J* = 9.2 Hz, 1H), 2.47 (t, *J* = 9.6 Hz, 1H), 2.39 (d, *J* = 10.9 Hz, 1H), 2.33 (d, *J* = 9.0 Hz, 1H), 2.12 (d, *J* = 10.0 Hz, 1H), 2.06 (t, *J* = 9.5 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.3, 191.9, 170.9, 168.9, 135.6, 135.3, 133.6, 133.5, 128.8, 128.6, 128.5, 128.3, 62.7, 62.0, 44.7, 43.1, 33.4, 32.7, 13.8,13.6 **MS** (ESI *m/z*) 220.45 [MH^+, 25%], 242.44 [MNa^+, 100%].

(*R*)-Ethyl 2-amino-2-(chloromethyl)-3-oxo-3-phenylpropanoate (79)



Colourless oil. $[\alpha]_D^{22}$ = +15.1 (*c* 0.50, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 2360, 1729, 1692, 1219, 772 **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.62-7.52 (m, 1H), 7.49-7.37 (m, 2H), 4.45-4.15 (m, 3H), 4.11 (d, *J* = 11.6 Hz, 1H), 1.15 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 193.4, 169.4, 134.2, 133.5, 129.0, 128.6, 69.4, 63.0, 49.2, 13.7. **MS** (ESI *m/z*) 256.24 [MH^+, 100%].

(*R*)-Ethyl 2-(benzyloxycarbonylamino)-2-(chloromethyl)-3-oxo-3-phenylpropanoate (80)



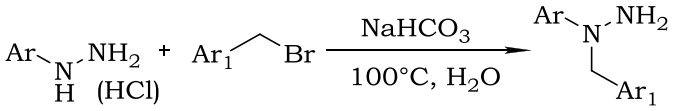
Purified by flash chromatography (petroleum ether/EtOAc 98:2 as eluent). Colourless oil. $[\alpha]_D^{22}$ = +8.8 (*c* 0.50, $CHCl_3$), 77% *ee*. **FTIR** ν_{max} (KBr)/cm^{-1} 1724, 1694, 1497, 1289, 1219, 1038, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.59-7.49 (m, 1H), 7.47-7.41

(m, 2H), 7.32-7.21 (m, 3H), 7.12-7.03 (m, 2H), 6.64 (s, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.91 (d, J = 12.4 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.38-4.18 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 190.5, 166.9, 153.9, 135.8, 134.2, 133.4, 128.5, 128.4, 128.1, 127.7, 70.5, 67.0, 63.8, 46.6, 13.8. **HPLC** analysis with Chiralpak IC column, 95:05 *n*-hexane/^{i}PrOH, 0.8 mL/min, detection at 220 nm; minor enantiomer t_R = 15.0 min, major enantiomer t_R = 15.6 min.

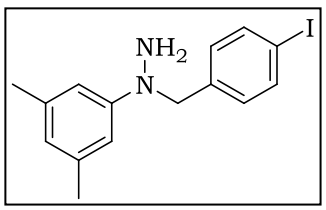
8.6 Asymmetric Synthesis of Helicenes

Synthesis and Characterization of Hydrazines

N-protected hydrazines were synthesized following a procedure reported in the literature.[157] The hydrazine or its hydrochloride salt (4.0 mmol) was treated with $NaHCO_3$ (1 equivalent for the free hydrazine, 2 for the hydrochloride salt) and the appropriate benzyl bromide in H_2O at 100°C under vigorous stirring. After 3 hours the mixture was allowed to cool to room temperature, diluted with MTBE (30 mL) and the organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2.

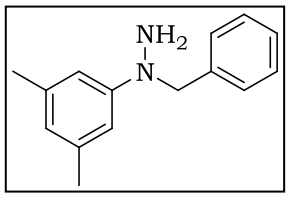


1-(3,5-dimethylphenyl)-1-(4-iodobenzyl)hydrazine (84a)



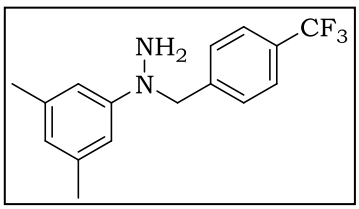
Purified by flash chromatography (pentane/MTBE 8:2), pale brown solid. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.68 (s, 2H), 6.51 (s, 1H), 4.51 (s, 2H), 3.56 (bs, 2H), 2.29 (s, 6H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 152.1, 139.1, 138.1, 138.0, 130.1, 121.2, 111.7, 92.9, 60.2, 22.0. **MS** (EI) *m/z* (%): 352 (24), 217 (9), 135 (100). **HRMS** (EI) *m/z* calculated for $C_{15}H_{17}N_2I$ ($M+Na^+$) 352.043646, found 352.043555.

1-benzyl-1-(3,5-dimethylphenyl) hydrazine (84b)



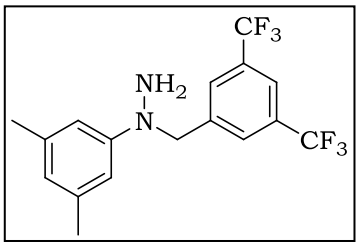
The reaction was conducted on a 2.0 mmol scale. Purified by flash chromatography (hexane/MTBE 9:1), yellow oil. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 6.77 (s, 2H), 6.52 (s, 1H), 4.58 (s, 2H), 3.53 (bs, 2H), 2.32 (s, 6H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 151.9, 138.7, 137.8, 128.6, 127.9, 127.3, 120.6, 111.5, 60.4, 21.7. **MS** (EI) *m/z* (%): 226 (37), 135 (83), 91 (100). **HRMS** (EI) *m/z* calculated for $C_{15}H_{18}N_2Na$ ($M+Na^+$) 249.136214, found 249.136000.

1-(3,5-dimethylphenyl)-1-(4-(trifluoromethyl)benzyl) hydrazine (84c)



Purified by flash chromatography (hexane/MTBE 8:2), dark yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 6.67 (s, 2H), 6.52 (s, 1H), 4.63 (s, 2H), 3.62 (s, 2H), 2.29 (s, 6H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 151.7, 142.4, 138.9, 129.5 (q, J = 32.6 Hz), 127.9, 125.5 (sept, J = 4.2 Hz), 124.2 (q, J = 272.0 Hz), 120.9, 111.2, 60.0, 21.7. **MS** (EI) *m/z* (%): 294 (30), 159 (50), 135 (100), 105 (40). **HRMS** (EI) *m/z* calculated for $C_{16}H_{18}F_3N_2$ 295.141658, found 295.141704.

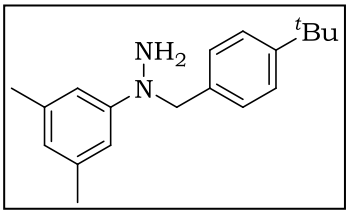
1-(3,5-bis(trifluoromethyl)benzyl)-1-(3,5-dimethylphenyl) hydrazine (84d)



Purified by flash chromatography (hexane/MTBE 8:2), dark yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (s, 3H), 6.65 (s, 2H), 6.57 (s, 1H), 4.64 (s, 2H), 3.69 (bs, 2H), 2.31 (s, 6H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 151.8, 141.6, 139.1, 131.8 (q, J = 33.0 Hz), 127,8 (d, J = 3.6 Hz), 123.3 (q, J = 271.2

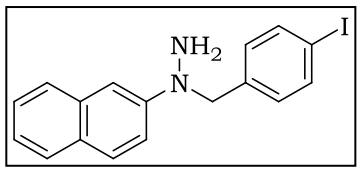
Hz), 121.6, 121.2 (sep, J = 3.7 Hz), 111.4, 60.0, 21.7. **MS** (EI) m/z (%): 362 (35), 227 (16), 135 (100). **HRMS** (EI) m/z calculated for $C_{17}H_{16}F_6N_2Na$ ($M+Na^+$) 385.110988, found 385.111507.

1-(4-(*tert*-butyl)benzyl)-1-(3,5-dimethylphenyl) hydrazine (84e)



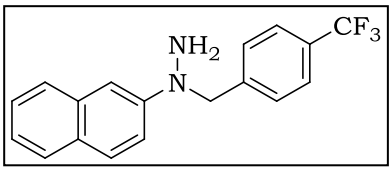
Purified by flash chromatography (hexane/MTBE 9:1), white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.25 Hz, 2H), 7.25 (d, J = 8.25 Hz, 2H), 6.76 (s, 2H), 6.50 (s, 1H), 4.53 (s, 2H), 3.50 (bs, 2H), 2.30 (s, 6H), 1.33 (s, 9H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 152.0, 150.2, 138.7, 134.6, 127.7, 125.6, 120.6, 111.6, 60.1, 34.5, 31.3, 21.7. **MS** (EI) m/z (%): 282 (35), 147 (41), 135 (100). **HRMS** (EI) m/z calculated for $C_{19}H_{27}N_2$ 283.216872, found 283.216712.

1-(4-iodobenzyl)-1-(naphthalene-2-yl)hydrazine (88a)



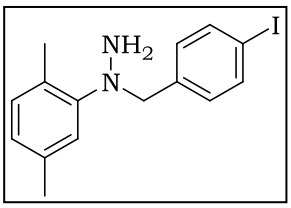
Purified by flash chromatography (pentane/MTBE 8:2), red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H), 7.68-7.64 (m, 3H), 7.44-7.37 (m, 2H), 7.30-7.25 (m, 2H), 7.08 (d, J = 8.3 Hz, 2H), 4.64 (s, 2H), 3.66 (bs, 2H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 149.2, 137.8, 137.0, 134.5, 130.0, 128.9, 128.0, 127.4, 126.6, 126.4, 123.1, 117.1, 107.8, 92.9, 59.9. **MS** (EI) m/z (%): 374 (29), 217 (8), 157 (100), 128 (51). **HRMS** (EI) m/z calculated for $C_{17}H_{15}N_2INa$ ($M+Na^+$) 397.017217, found 397.017385

1-(naphthalen-2-yl)-1-(4-trifluoromethyl)benzyl)hydrazine (88b)



The reaction was conducted on a 2.0 mmol scale. Purified by flash chromatography (hexane/MTBE 100:2), yellow solid. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.71 (t, J = 9.4 Hz, 2H), 7.64 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 7.42-7.39 (m, 1H), 7.38-7.33 (m, 1H), 7.26-7.21 (m, 2H), 4.76 (s, 2H), 3.75 (bs, 2H).

1-(2,5-dimethylphenyl)-1-(4-iodobenzyl)hydrazine (93)



The reaction was conducted on a 2.0 mmol scale. Purified by flash chromatography (pentane/MTBE 8:2), orange oil. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.66 (d, J = 7.3 Hz, 2H), 7.16 (d, J = 7.4 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.80 (d, J = 7.6 Hz, 1H), 4.01 (s, 2H), 2.31 (s, 3H), 2.27 (s, 3H).

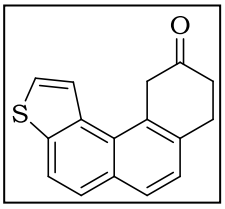
Synthesis and Characterization of Ketones

The ketones were synthesized from the corresponding stilbenes according a known literature procedure.[158a]

The stilbenes were obtained following a Wittig-Horner procedure: to a suspension of ^{t}BuOK (15 mmol) in DMF, a 0.2 M solution of the 4-methoxybenzylphosphonate (9 mmol) was added. After ten minutes a solution of the corresponding aldehyde (6 mmol) was added and the mixture is kept under vigorous stirring until completion (monitored by TLC, eluent: hexane/EtOAc 20:1). Water was added and the mixture is extracted with MTBE, the organic layers were washed three times with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product is purified by crystallization from EtOAc.

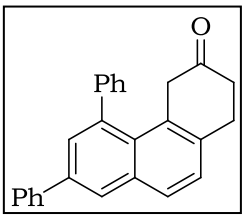
The stilbene (500 mg) is added to a 0.5 M solution of HCl in 500 mL of degassed acetonitrile. After consumption of the starting material (monitored by TLC, eluent hexane/EtOAc 7:3) the mixture is neutralized with Na_2CO_3 (aq) and the organic layer is separated, dried over $MgSO_4$ and concentrated under reduced pression. The product is purified by column chromatography on SiO_2.

8,9-dihydrophenanthro[3,4-*b*]tiophene-10(11*H*)-one (99)



Purified by flash chromatography with hexane/CH_2Cl_2 8:2 as eluent, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (d, J = 5.9 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 4.36 (s, 2H), 3.35 (t, J = 6.9 Hz, 2H), 2.77 (t, J = 6.9 Hz, 2H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 210.0, 140.2, 134.3, 133.9, 133.4, 131.3, 128.8, 128.7, 128.0, 126.1, 126.0, 124.8, 120.7, 45.3, 38.5, 30.2. **MS** (EI) *m/z* (%): 252 (100), 210 (61). **HRMS** (EI) *m/z* calculated for $C_{16}H_{12}OSNa$ ($M+Na^+$) 275.050105, found 275.050258.

5,7-diphenyl-1,2-dihydrophenanthren-3(4H)-one (103)



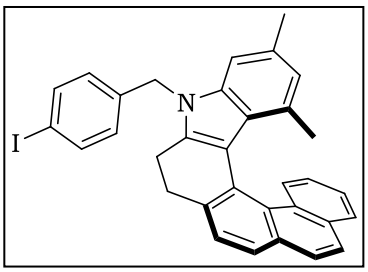
Purified by flash chromatography with hexane/EtOAc 9:1 as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.65 (s, 1H), 7.51-7.42 (m, 5H), 7.42-7.35 (m, 4H), 3.25-3.17 (m, 4H), 2.49 (t, J = 6.7 Hz, 2H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 210.5, 144.4, 140.1, 139.8, 138.7, 135.9, 134.4, 130.0, 129.42, 129.37, 129.1, 128.9, 128.4, 128.3, 127.5, 127.4, 127.2, 127.1, 126.3, 45.6, 37.4, 29.8. **MS** (EI) *m/z* (%): 348 (100), 77 (25).

General procedure for the asymmetric Fisher indolization:

A reaction vial was charged with catalyst **87** (1.79 mg, 0.0025 mmol), Amberlite® CG50 (25 mg), the corresponding hydrazine (0.05 mmol) and the opportune ketone (0.05 mmol). CH_2Cl_2 was added and the mixture was stirred for 3 days at -5°C. The crude reaction mixture was directly submitted to column chromatography.

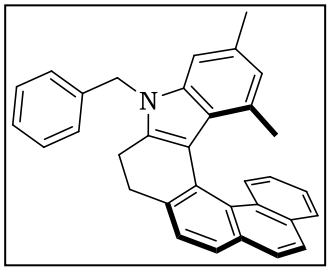
The racemates were prepared using a stoichiometric amount of diphenyl phosphate in respect to the hydrazine and the ketone. The reaction was performed at rt for 4 hours. The crude reaction mixture was directly submitted to column chromatography.

7-(4-iodobenzyl)-9,11-dimethyl-6,7-dihydro-5H-phenanthro[3,4-c]carbazole (86a)



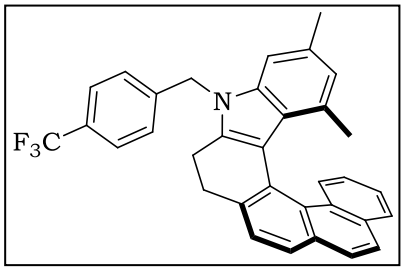
Purified by flash chromatography with hexane/MTBE 19:1 as eluent. $[\alpha]_D^{25}$ = -454.21 (C = 0.38, CH_2Cl_2, 91% *ee*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.32 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.77-7.56 (m, 5H), 7.48 (d, J = 7.6 Hz, 1H), 7.38-7.33 (m, 1H), 6.91-6.83 (m, 4H), 6.35 (s, 1H), 5.41 (d, J = 17.1 Hz, 1H), 5.36 (d, J = 17.3 Hz, 1H), 2.98-2.82 (m, 4H), 2.29 (s, 3H), 1.14 (s, 3H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 139.9, 138.0, 137.84, 137.81, 136.8, 132.6, 132.3, 131.5, 131.11, 131.06, 128.3, 128.1, 127.32, 127.30, 126.9, 126.6, 126.13, 126.11, 125.7, 124.9, 124.2, 123.81, 123.75, 114.4, 106.9, 92.5, 46.3, 31.7, 21.24, 21.17, 19.4. **MS** (EI) *m/z* (%): 561 (100), 344 (17), 217 (4). **HRMS** (EI) *m/z* calculated for $C_{33}H_{25}NINa$ ($M+Na^+$) 584.084562, found 584.084112. **HPLC** analysis with Chiralcel OD-RH column, 80:20 MeCN/H_2O, 1.0 mL/min, detection at 235 nm; minor enantiomer t_R = 17.4 min, major enantiomer t_R = 15.5 min.

7-benzyl-9,11-dimethyl-6,7-dihydro-5*H*-phenanthro[3,4-c]carbazole (86b)



Purified by flash chromatography with hexane/MTBE 19:1 as eluent. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.35 (d, J = 8.5 Hz, 1H), 7.74 (dd, J = 7.8, 1.0 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.38-7.29 (m, 3H), 7.28-7.23 (m, 1H), 7.11 (d, 7.3 Hz, 2H), 6.92-6.88 (m, 2H), 6.35 (s, 1H), 5.47 (d, J = 17.0 Hz, 1H), 5.42 (d, J = 17.0 Hz, 1H), 2.99-2.86 (m, 4H), 2.29 (s, 3H), 1.15 (s, 3H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 140.2, 138.0, 137.9, 136.9, 132.6, 132.34, 132.30, 131.6, 131.0, 130.9, 128.9, 128.3, 127.4, 127.3, 126.9, 126.6, 126.1, 126.07, 126.01, 125.6, 124.8, 124.2, 123.73, 123.67, 114.2, 107.0, 46.7, 31.7, 21.25, 21.20, 19.5. **MS** (EI) m/z (%): 437 (100), 346 (29), 91 (7). **HRMS** (EI) m/z calculated for $C_{33}H_{27}NNa$ ($M+Na^+$) 460.203570, found 460.203745. **HPLC** analysis with Chiralcel OD-3R column, 80:20 MeCN/H_2O, 1.0 mL/min, detection at 237 nm; minor enantiomer t_R = 13.0 min, major enantiomer t_R = 11.8 min.

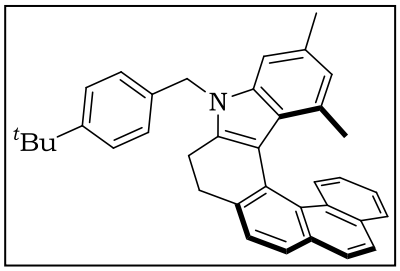
7-(4-(*tert*-butyl)benzyl)-9,11-dimethyl-6,7-dihydro-5*H*-phenanthro[3,4-c]carbazole (86c)



Reaction conducted on 0.02 mmol scale. Isolated by preparative TLC with hexane/EtOAc 7:3 as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.66-7.56 (m, 5H), 7.48 (d, J = 7.4 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 6.93-6.87 (m, 1H), 6.87 (s, 1H), 5.52 (d, J = 17.4 Hz, 1H), 5.47 (d, J = 17.4 Hz, 1H), 2.99-2.82 (m, 4H), 2.29 (s, 3H), 1.16 (s, 3H). **HPLC** analysis with Chiralcel OD-RH column, 85:15 MeCN/H_2O, 1.0

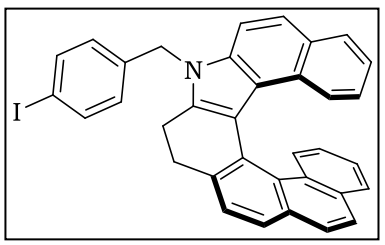
mL/min, detection at 235 nm; minor enantiomer t_R = 7.5 min, major enantiomer t_R = 6.9 min.

7-(4-(*tert*-butyl)benzyl)-9,11-dimethyl-6,7-dihydro-5*H*-phenanthro[3,4-c]carbazole (86e)



Reaction conducted on 0.02 mmol scale. Isolated by preparative TLC with hexane/EtOAc 7:3 as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.41 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 7.1 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.57 (d, 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.39-7.33 (m, 3H), 7.06 (d, J = 8.3 Hz, 1H), 6.99-6.84 (m, 1H), 6.93 (s, 1H), 6.39 (s, 1H), 5.45 (d, J = 17.0 Hz, 1H), 5.39 (d, J = 16.9 Hz, 1H), 2.98-2.86 (m, 4H), 2.33 (s, 3H), 1.26 (s, 9H), 1.22 (s, 3H). **HPLC** analysis with Chiralcel OD3 column, 99:1 heptane/^{i}PrOH, 1.0 mL/min, detection at 235 nm; minor enantiomer t_R = 7.6 min, t_R = 6.3 min.

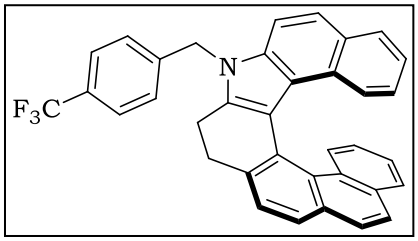
7-(4-iodobenzyl-6,7-dihydro-5*H*-benzo[c]phenanthro[4,3-g]carbazole (89a)



Purified by flash chromatography with hexane/MTBE 19:1 as eluent. $[\alpha]_D^{25}$ = -536.67 (C = 0.36, CH_2Cl_2, 79% *ee*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.27 (d, J = 8.5 Hz, 1H), 7.75-7.53 (m, 8H), 7.47 (d, J = 8.9 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 2H), 6.47-6.41 (m, 2H), 5.59-5.50 (m, 2H), 3.08-2.92 (m, 4H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 138.9, 138.0, 137.6, 137.5, 133.2, 132.6, 132.4, 131.8, 131.2, 129.4, 128.5, 128.0, 127.8, 127.4, 127.2, 127.0, 126.5, 126.4, 125.82, 125.77, 125.6, 124.4, 123.8,

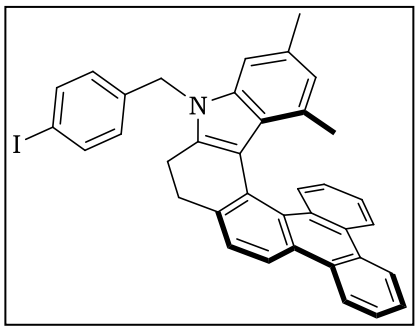
123.6, 122.65, 122.59, 119.9, 116.0, 110.9, 92.7, 46.6, 31.9, 21.2. **MS** (EI) *m/z* (%): 585 (100), 368 (63), 217 (9). **HRMS** (EI) *m/z* calculated for $C_{35}H_{24}NINa$ ($M+Na^+$) 608.084564, found 608.084892. **HPLC** analysis with Chiralcel OD-RH column, 80:20 MeCN/H_2O, 1.0 mL/min, detection at 237 nm; minor enantiomer t_R = 19.2 min, major enantiomer t_R = 16.5 min.

7-(4-trifluoromethyl)benzyl-6,7-dihydro-5*H*-benzo[c]phenanthro[4,3-g]carbazole (89b)



Isolated by preparative TLC with hexane/EtOAc 7:3 as eluent. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.28 (d, J = 8.4 Hz, 1H), 7.75-7.66 (m, 3H), 7.65 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 3H), 7.49-7.42 (m, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.47-6.42 (m, 2H), 5.73-5.63 (m, 2H), 3.1-2.9 (m, 4H). **HPLC** analysis with Chiralcel OD-RH column, 85:15 MeCN/H_2O, 1.0 mL/min, detection at 237 nm; minor enantiomer t_R = 8.0 min, major enantiomer t_R = 7.0 min.

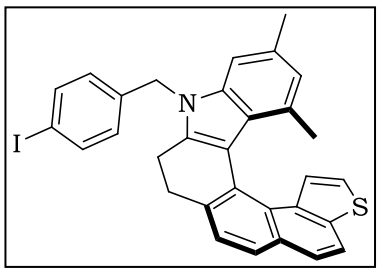
9-(4-iodobenzyl)-11,13-dimethyl-8,9-dihydro-7*H*-triphenyleno[2,1-c]carbazole (104)



Purified by flash chromatography with hexane/MTBE 19:1 as eluent. $[\alpha]_D^{25}$ = -574.40.21 (C = 0.50, CH_2Cl_2, 92% *ee*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.46 (d, J = 7.5 Hz, 1H), 8.43 (d, J = 7.8 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.07 (d, J, = 8.3 Hz, 1H), 7.57-7.49 (m, 4H), 7.42 (d, J = 7.9 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 6.79-6.71 (m, 4H), 6.25 (s, 1H), 5.30 (d, J = 17.3 Hz, 1H), 5.25 (d, J = 17.3 Hz, 1H), 2.93-2.73 (m,

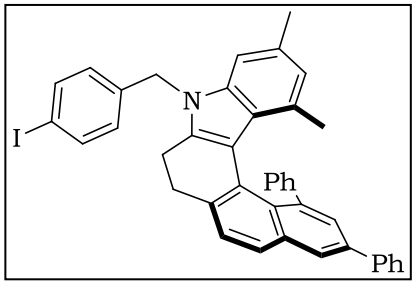
4H), 2.18 (s, 3H), 1.21 (s, 3H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 139.9, 138.0, 137.9, 137.8, 137.3, 132.2, 131.7, 131.2, 131.1, 130.5, 130.2, 130.0, 129.7, 128.0, 128.0, 127.4, 127.2, 126.8, 126.4, 126.3, 125.1, 123.8, 123.6, 123.4, 123.2, 122.8, 119.2, 114.6, 106.9, 92.6, 46.3, 31.4, 21.25, 21.19, 19.4. **MS** (EI) *m/z* (%): 613 (100), 396 (27), 217 (4). **HRMS** (EI) *m/z* calculated for $C_{37}H_{28}NINa$ (MNa^+) 636.115865, found 636.115964. **HPLC** analysis with Chiralcel OD-RH column, 95:5 MeCN:H_2O, 1.0 mL/min, detection at 235 nm; minor enantiomer t_R = 29.4 min, major enantiomer t_R = 10.1 min.

7-(4-iodobenzyl)-9,11-dimethyl-6,7-dihydro-5*H*-thieno[2´,3´:7,8] naphtho[2,1-c]carbazole (105)



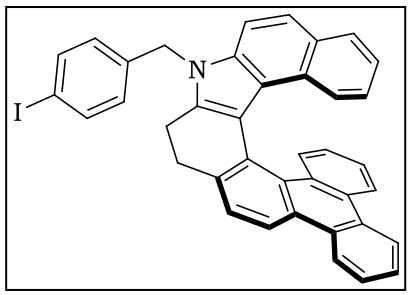
Purified by flash chromatography with hexane/CH_2Cl_2 9:1 as eluent. $[\alpha]_D^{25}$ = -528.54 (C = 0.41, CH_2Cl_2, 93% *ee*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.69-7.62 (m, 4H), 7.53 (d, *J* = 5.3 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 5.6 Hz, 1H), 6.90 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.49 (s, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 2.97-2.89 (m, 2H), 2.87-2.77 (m, 2H), 2.33 (s, 3H), 1.43 (s, 3H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 140.4, 138.0, 137.8, 137.6, 137.4, 136.5, 136.1, 131.9, 131.05, 130.94, 130.7, 128.1, 128.0, 126.1, 125.2, 125.1, 124.7, 124.1, 122.6, 119.9, 113.5, 107.0, 92.6, 46.3, 32.0, 21.3, 21.2, 19.6. **MS** (EI) *m/z* (%): 569 (100), 352 (20), 217 (6). **HRMS** (EI) *m/z* calculated for $C_{31}H_{24}NISNa$ (MNa^+) 592.056638, found 592.056951. **HPLC** analysis with Chiralpak AD3R column, 60:40 MeCN:H_2O, 1 mL/min, detection at 235 nm; minor enantiomer t_R = 49.6 min, major enantiomer t_R = 57.0 min.

9-(4-iodobenzyl)-11,13-dimethyl-1,3-diphenyl-8,9-dihydro-7*H*-naphtho[2,1-c]carbazole (106)



Purified by flash chromatography with hexane/EtOAc 19:1 as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 2H), 7.62 (s, 1H), 7.52-7.44 (m, 4H), 7.41-7.35 (m, 1H), 6.86 (d, J = 7.8 Hz, 2H), 6.78-6.71 (m, 2H), 6.62 (s, 1H), 6.49 (s, 2H), 6.42 (s, 1H), 5.17 (d, J = 17.1 Hz, 1H), 5.06 (d, J = 16.1 Hz, 1H), 2.96-2.62 (m, 4H), 2.28 (s, 3H), 1.20 (s, 3H). **MS** (EI) *m/z* (%): 665 (100), 448 (17), 217 (7). **HRMS** (EI) *m/z* calculated for $C_{41}H_{32}INNa$ (MNa^+) 688.147167, found 688.147838. **HPLC** analysis with Chiralcel OD3R column, 90:10 MeCN:H_2O, 1 mL/min, detection at 235 nm; minor enantiomer t_R = 10.8 min, major enantiomer t_R = 9.6 min.

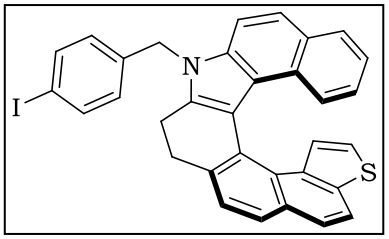
9-(4-iodobenzyl)-8,9-dihydro-7*H*-benzo[c]triphenyleno[1,2-g]carbazole (107)



Purified by flash chromatography with hexane/ CH_2Cl_2 19:1 as eluent. $[\alpha]_D^{25} = -789.89$ (C = 0.44, CH_2Cl_2, 84% *ee*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.63-8.57 (m, 2H), 8.40 (d, J = 8.1 Hz, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.13 (dd, J = 8.4, 0.9 Hz, 1H), 7.70-7.57 (m, 6H), 7.46 (d, J = 9.1 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.11-7.06 (m, 1H), 6.99-6.95 (m, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.50-6.43 (m, 2H), 5.58 (d, J = 17.4 Hz, 1H), 5.54 (d, J = 17.3 Hz, 1H), 3.13-2.96 (m, 4H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 138.8, 138.0, 137.8, 137.6, 133.4, 131.7, 131.5, 130.6, 130.3, 130.2, 129.9, 129.3, 128.4, 128.0, 127.9, 127.8, 127.3, 127.0, 126.7, 126.4, 126.2, 124.5, 124.1, 123.8,

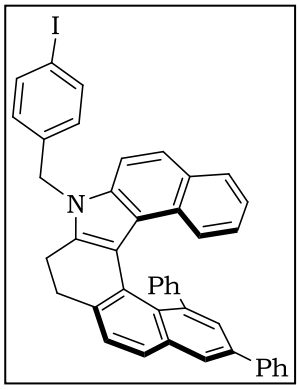
123.5, 123.3, 122.8, 122.64, 122.60, 119.6, 119.5, 116.1, 110.8, 92.7, 46.6, 31.4, 21.3. **MS** (EI) *m/z* (%): 635 (100), 418 (43), 217 (5). **HRMS** (EI) *m/z* calculated for $C_{39}H_{26}INNa$ (MNa^+) 658.100216, found 658.100460. **HPLC** analysis with Amycoat column, 80:20 MeCN/H2O, 1.0 mL/min, detection at 257 nm; minor enantiomer t_R = 9.2 min, major enantiomer t_R = 16.8 min.

7-(4-iodobenzyl)-8,9-dihydro-7*H*-benzo[c]thieno[2´,3´:7,8]naphtho[1,2-g]carbazole (108)



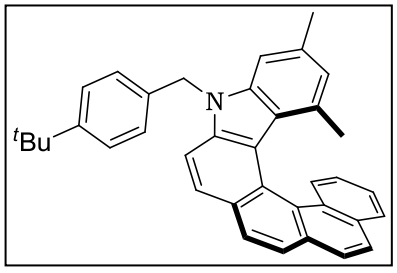
Purified by flash chromatography with hexane/CH_2Cl_2 9:1 as eluent. $[\alpha]_D^{25}$ = -546.67 (C = 0.28, CH_2Cl_2, 75% *ee*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.87 (d, *J* = 8.7 Hz, 1H), 7.81-7.76 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.64 (d, 8.3 Hz, 2H), 7.55-7.47 (m, 3H), 7.35 (d, *J* = 5.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.10-7.05 (m, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.64-6.56 (m, 2H), 5.58 (d, *J* = 17.2 Hz, 1H), 5.53 (d, *J* = 17.2 Hz, 1H), 3.06-2.99 (m, 2H), 2.99-2.87 (m, 2H). **^{13}C-NMR** (125 MHz, CD_2Cl_2) δ 139.4, 138.1, 138.0, 137.6, 136.9, 135.8, 133.0, 131.9, 130.5, 129.6, 128.6, 128.1, 127.6, 127.3, 126.2, 126.0, 125.41, 125.37, 124.5, 123.7, 122.9, 122.5, 122.1, 120.9, 120.3, 115.1, 111.0, 92.8, 46.7, 32.2, 21.2. **MS** (EI) *m/z* (%): 591 (100), 374 (56), 217 (9). **HRMS** (EI) *m/z* calculated for $C_{33}H_{22}NISNa$ (MNa^+) 614.040986, found 614.041543. **HPLC** analysis with chiralpak AD3R column, 70:30 MeCN:H_2O, 1 mL/min, detection at 235 nm; minor enantiomer t_R = 19.2 min, major enantiomer t_R = 23.3 min.

9-(4-iodobenzyl)-1,3-diphenyl-8,9-dihydro-7*H*-benzo[c]naphtho[1,2-g]carbazole (109)



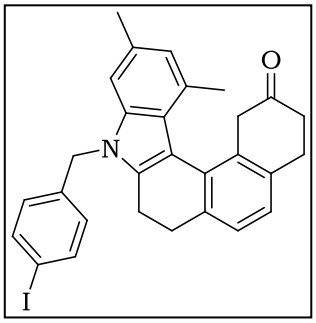
Purified by flash chromatography with hexane/EtOAc 19:1 as eluent. **^{1}H NMR** (500 MHz, CDCl3) δ 8.09 (d, J = 1.7 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 2H), 7.71 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.53-7.48 (m, 2H), 7.44 (d, J = 1.6 Hz, 1H), 7.41-7.37 (m, 1H)7.30 (d, J = 8.8 Hz, 1H), 7.28-7.22 (m, 2H), 7.04 (d, J = 9.2 Hz, 1H), 6.98-6.93 (m, 1H), 6.82 (d, J = 8.1 Hz, 2H), 6.64-6.56 (m, 2H), 6.46-6.31 (m, 2H), 6.18-6.19 (m, 1H), 5.36 (d, J = 16.8 Hz, 1H), 5.23 (d, J = 17.1 Hz, 1H), 3.1-2.7 (m, 4H). **MS** (EI) *m/z* (%): 687 (100), 470 (18), 217 (5). **HRMS** (EI) *m/z* calculated for $C_{43}H_{30}INNa$ (MNa^+) 710.131514, found 710.130804. **HPLC** analysis with Chiralcel OD3R column, 75:25 MeCN/H_2O, 1 mL/min, detection at 235 nm; minor enantiomer t_R = 70.9 min, major enantiomer t_R = 65.7 min.

7-(4-(*tert*-butyl)benzyl)-9,11-dimethyl-7*H*-phenanthro[3,4-c]carbazole (111)



Isolated by preparative TLC with hxane/EtOAc 6:4 as eluent. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.09 (d, J = 8.8 Hz, 1H), 7.98-7.92 (m, 3H), 7.80-7.75 (m, 3H), 7.55 (d, J = 8.4 Hz, 1H), 7.47-7.42 (m, 1H), 7.31 (d, J = 8.5 H, 2H), 7.14-7.10 (m, 3H), 7.01-7.66 (m, 1H), 6.48 (s, 1H), 5.70 (d, J = 17.0 Hz, 1H), 5.65 (d, J = 17.0 Hz, 1H), 2.41 (s, 3H), 1.25 (s, 9H), 1.04 (s, 3H). **MS** (EI) *m/z* (%): 491 (100), 147 (11). **HRMS** (EI) *m/z* calculated for $C_{37}H_{33}NNa$ (MNa^+) 514.251619, found 514.250948.

9-(4-iodobenzyl)-11,13-dimethyl-3,4,7,8-tetrahydro-1*H*-naphtho[2,1-c]carbazol-2(9*H*)-one (119)



Purified by flash chromatography with hexane/EtOAc 19:1 as eluent. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.62-7.57 (m, 2H), 7.14 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.87 (s, 1H), 6.80-6.75 (m, 3H), 5.28 (d, J = 17.1 Hz, 1H), 5.21 (d, J = 17.0 Hz, 1H), 3.97 (d, J = 18.9 Hz, 1H), 3.23 (d, J = 18.4 Hz, 1H), 3.15-3.08 (m, 1H), 3.01-2.93 (m, 1H), 2.81-2.75 (m, 2H), 2.73-2.64 (m, 1H), 2.53-2.40 (m, 3H), 2.37 (s, 3H), 2.32 (s, 3H).

8.7 Computational Details

The DFT geometry optimizations were performed at the GGA level with the Gaussian09 package,[175] using the BP86 functional of Becke and Perdew.[176] The electronic configuration of the molecular systems was described with the standard split-valence plus basis set with a polarization function of Ahlrichs and co-workers (SVP keyword in Gaussian09).[177] The geometry optimizations were performed without symmetry constraints, and the characterization of the located stationary points was performed by analytical frequency calculations. The energies discussed in the text have been obtained through single point energy calculations on the BP86/SVP optimized geometries using the M06 functional[178] in connection with the TZVP basis set.[179] Solvent effects including contributions of non electrostatic terms have been estimated in single point calculations on the gas phase optimized structures, based on the polarizable continuous solvation model PCM, using toluene or C_6F_6 as the solvent.[180] Zero point energy and thermal corrections were included from gas-phase vibrational analysis at the BP86 level on the SVP optimized geometries.

---

[175] **Gaussian 09**, **Revision A.1**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[176] a) A. D. Becke, *Phys. Rev. A*, **1988**, *38*, 3098; b) J. P. Perdew, *Phys. Rev. B*, **1986**, *33*, 8822; c) J. P. Perdew, *Phys. Rev. B*, **1986**, *34*, 7406.

[177] A. Schaefer, H. Horn and R. Ahlrichs, *J. Chem. Phys.*, **1992**, *97*, 2571.

[178] Y. Zhao; D. G. Truhlar, *Theor Chem Acc.*, **2008**, *120*, 215.

[179] A. Schaefer; C. Huber; R. Ahlrichs, *J. Chem. Phys.*, **1994**, *100*, 5829.

[180] V. Barone and M. Cossi, *J. Phys. Chem. A*, **1998**, *102*, 1995.

Gas-phase BP86/TZVP energy of the calculated transition states

Table 8.1. Relative free energy, in kcal/mol, of the four possible transition states for the reaction of **37a** and **38a** promoted by **29a**. Geometries have been optimized in the gas-phase with the BP86 functional and the SVP basis set. The energy of the structures in bold has been further refined through single point energy calculations in solvent with the M06 functional and the TZVP basis set.

	E (kcal/mol)
Pro-*S,R*	**0.0**
Pro-*R,S*	**0.4**
Pro-*R,R*	1.6
Pro-*S,S*	0.6
Pro-*S,R* +C_6F_6	**0.0**
Pro-*R,S* +C_6F_6	**1.3**
Pro-*S,R* +2C_6F_6	0.0
Pro-*R,S* +2C_6F_6	1.3

BP86 and M06 interaction energy between the C_6F_6 molecule and the reacting system in transition state pro-*S,R* + C_6F_6.

The interaction energy between the reacting system and the C_6F_6 molecule in transition state pro-*S,R* + C_6F_6 is calculated as follows:

$$E(\text{interaction}) = -[E(\text{pro-}S,R + C_6F_6) - E(\text{pro-}S,R) - E(C_6F_6)]$$

With this approach, E(interaction) is calculated to be 4.8 kcal/mol in the gas-phase at the BP86/SVP level, and 14.6 kcal/mol in solvent at the M06/TZVP level. Although the BP86 value can be affected by the BSSE, the strong interaction at the M06 level indicates a rather strong interaction more driven by electrostatic interaction rather than dispersion. This strong interaction is more typical of a well defined minimum on the potential energy surface, rather than of a rather floppy potential energy surface.

Steric profiles in transition states pro-*R,S* and pro-*S,R*

The closer proximity between C_6F_6 and the enolate in TS pro-*R,S* can be rationalized by visual inspection of the steric profiles of the TS, see Figure 8.1.

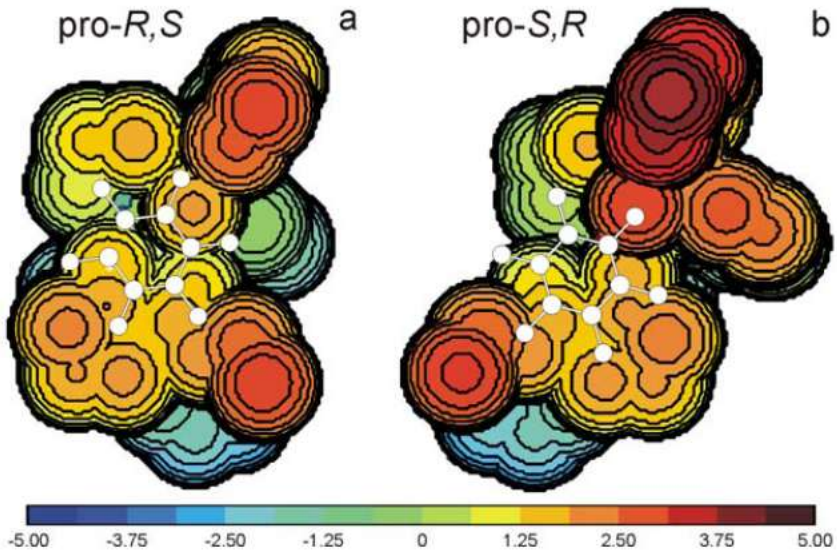


Figure 8.1 Steric profile of the pro-*R,S* and pro-*S,R* TS. The optimized geometry of C_6F_6, in white, is plotted on top of the steric profiles.

In case of TS pro-*R,S*, steric hindrance by one of the Ph rings of the catalyst and the ethoxy group of **38a** is higher on the right side, as evidenced by the red isocontour lines. On the left side, instead, the orange isocontour lines indicates reduced steric hindrance, so that C_6F_6 can be accommodated comfortably above the enolate. Differently, in TS pro-*S,R* the ethoxy group is placed on the left of the catalyst so that the ethoxy group and one of the Ph rings of the catalyst shape a narrow groove preventing optimal stacking of C_6F_6 on top of the enolate. The steric profiles of Figure 8.1 have been calculated using the geometry of transition states pro-*R,S* and pro-*S,R* in presence of a C_6F_6 molecule. The points in space defining the steric profile were located with the Samb*V*ca package developed by Cavallo's group.[181]

[181] A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, 1759.

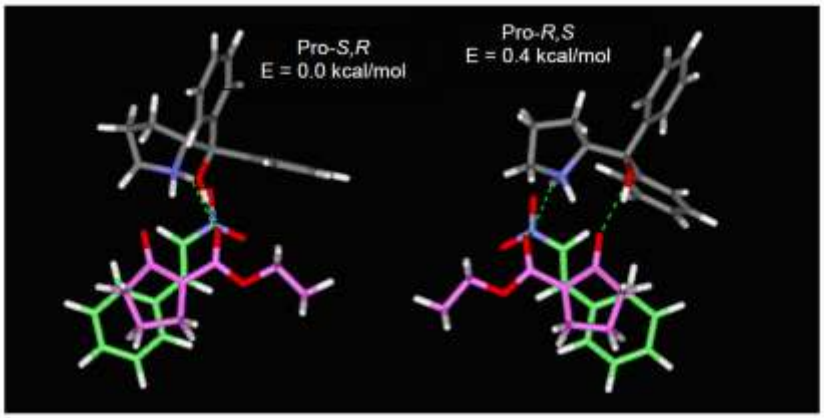


Figure 8.2. Structure of the pro-*S,S* and pro-*R,R* transition states and their relative energy with respect to the pro-S,R transition state. Structures are oriented along the forming C2-C3 bond. C atoms of **38a** and **39a** are coloured in pale green and pink, respectively.

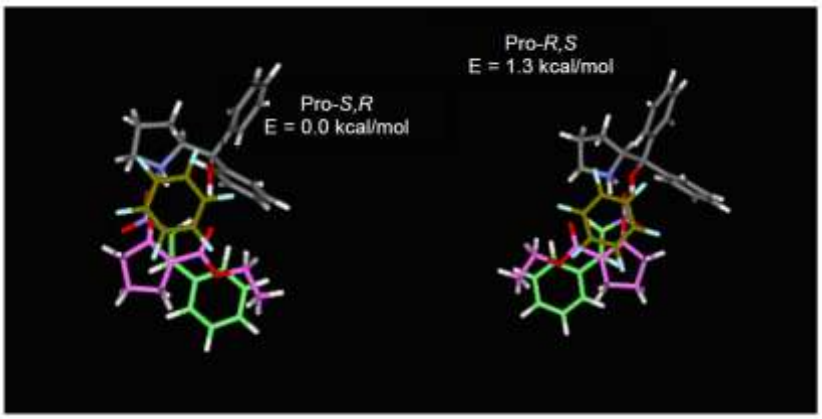


Figure 8.3. Structure of the pro-*S,R* and pro-*R,S* transition states in presence of a C_6F_6 molecule. Structures are oriented along the forming C2-C3 bond. C atoms of **38a** and **39a** are colored in pale green and pink, respectively. C and F atoms of C_6F_6 are coloured in olive green and light blue, respectively.

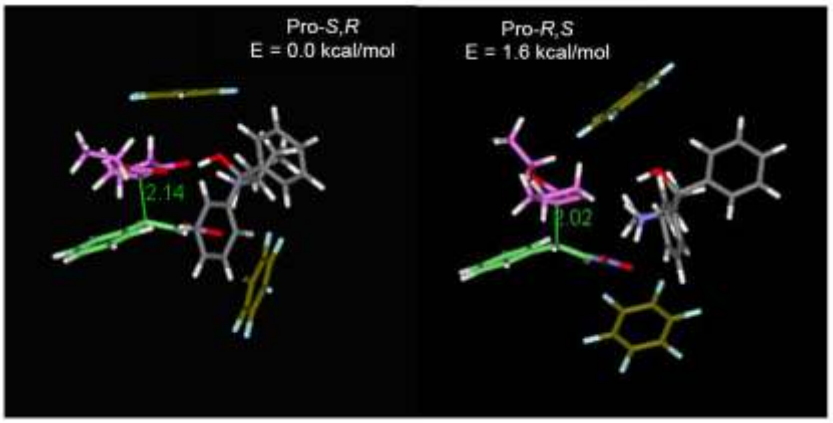
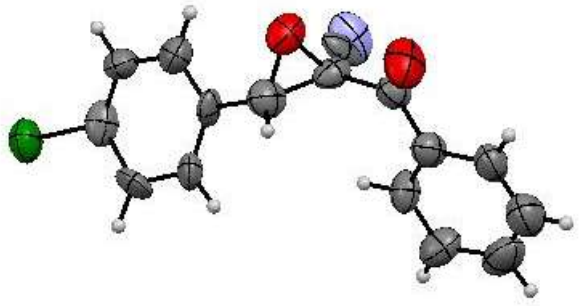


Figure 8.4. Structure of the pro-*S,R* and pro-*R,S* transition states in presence of 2 C_6F_6 molecules. Structures are oriented along the forming C2-C3 bond. C atoms of **38a** and **39a** are coloured in pale green and pink, respectively. C and F atoms of C_6F_6 are coloured in olive green and light blue, respectively.

8.8 X-Ray Crystal Structure Data

Compound 35d



X-Ray molecular structure of epoxide **35d**. Thermal ellipsoids are drawn at 20% probability level.

X-ray diffraction quality single crystals of **35d** were obtained by slow evaporation of a solution of **35d** in hexane/^{i}PrOH/$CHCl_3$.

A suitable crystal of **35d** was selected and glued on a glass fiber and measured at room temperature with a Rigaku AFC11K diffractometer equipped with a Saturn944 CCD detector using Cu$K\alpha$ radiation. Data reduction was performed with the crystallographic package CrystalClear.[182] Data have been corrected for Lorentz, polarization and absorption. The structures were solved by direct methods using the program IL MILIONE[183] and refined by means of full matrix least-squares based on F^2 using the program SHELXL97.[184]

All non-hydrogen atoms were refined anisotropically, hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined.

[182] CrystalClear, Crystal Structure Analysis Package, Rigaku-Molecular Structure Corp.
[183] Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Siliqi, D.; Spagna, R. *J. Appl. Cryst.* **2007**, *40*, 609.
[184] Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.

A total of 181 refinable parameters were finally considered, final disagreement indices are R1= 0.0638 (1211 reflections $F^2>2\sigma F^2$), $_wR2$= 0.2247 (all 1771 independent. reflections).

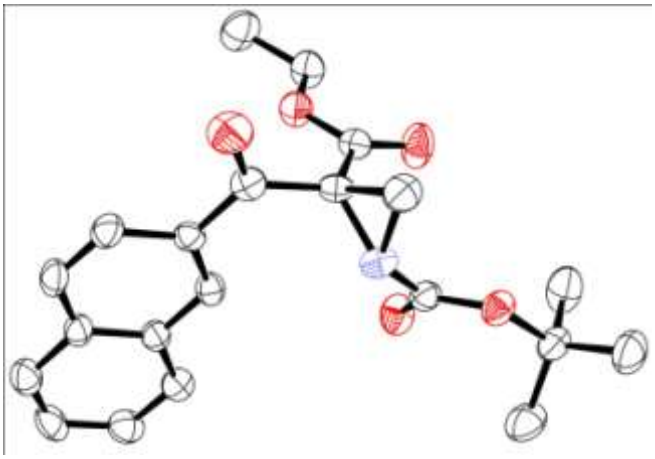
Flack parameter is -0.06(7).

ORTEP plot is obtained by means of the program ORTEP32.[185]

Crystal data: $C_{16}H_{10}BrNO_2$, monoclinic, space group *P*2, *Z*= 2, *a*= 8.132(4) Å, *b*= 8.188(4) Å, *c*=10.529(5) Å, β = 91.449(14)°, *V*=700.8(6) Å^3, D_x = 1.555 gcm^{-3}, μ_{calc} = 4.003 mm^{-1}.

[185] Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.

Compound 66h



ORTEP plot of (66h) with 30% probability ellipsoids (for seek of brevity H atoms are not shown).

Single crystal diffraction data were collected on a Oxford Xcalibur CCD area detector diffractometer, using graphite monochromatic Mo Kα (λ = 0.71069Å) radiation. Data reduction and absorption correction were performed using CrysAlisPRO 171.34.44 (Oxford Diffraction). The structure was solved by direct methods using SIR2011[186] and refined by full-matrix least squares using SHELX-97[187]. Hydrogen atoms were generated in calculated position using SHELX-97. The absolute structure of the title compound was determined on the basis of the Flack x parameter[188] and Bayesian statistics on Bijvoet differences.[189]

Details of data collections and refinements are given in table below.

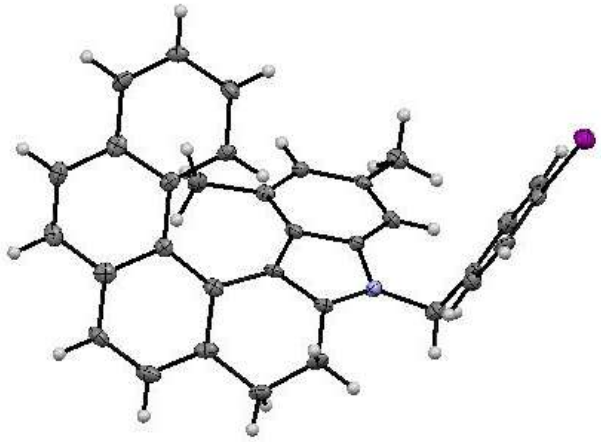
[186] M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, D. Siliqi, R. Spagna, *J. Appl. Cryst.* **2007**, *40*, 609.
[187] G. M. Sheldrick, *Acta Cryst. A* **2007**, *64*, 12.
[188] H. D. Flack, *Acta Cryst.* **1983**, *A39*, 876.
[189] R. W. W. Hooft, L. H. Straver, A. L. Spek, *J. Appl. Cryst.* **2008**, 41, 96.

Crystal data for 66h

Empirical formula	C21 N1 O5 H23	
Formula weight	369.40	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.852(5) Å	α= 90°.
	b = 11.039(5) Å	β= 96.987(5)°.
	c = 15.374(5) Å	γ = 90°.
Volume	985.8(10) $Å^3$	
Z	2	
Density (calculated)	1.245 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	392	
Crystal size	0.8 x 0.6 x 0.3 mm^3	
Theta range for data collection	4.14 to 28.20°.	
Index ranges	-7<=h<=7, -14<=k<=14, -20<=l<=20	
Reflections collected	19850	

Independent reflections	4481 [R(int) = 0.0522]
Completeness to theta = 25.00∞	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.86524
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4481 / 1 / 249
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0703, wR2 = 0.1737
R indices (all data)	R1 = 0.1207, wR2 = 0.1962
Largest diff. peak and hole	0.274 and -0.172 $e.V.^{-3}$

Compound 86a

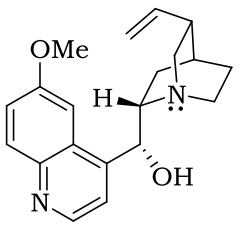


Crystal data and structure refinement.

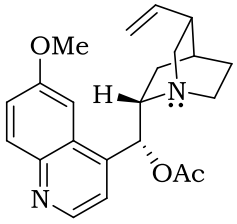
Identification code	7859sadabs	
Empirical formula	C_{33} H_{26} I N	
Color	orange	
Formula weight	563.45 g · mol^{-1}	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	MONOCLINIC	
Space group	p 21 , (no. 4)	
Unit cell dimensions	a = 11.595(3) Å	α= 90°.
	b = 8.301(2) Å	β= 104.403(6)°.
	c = 13.141(3) Å	γ = 90°.
Volume	1225.1(5) $Å^3$	
Z	2	
Density (calculated)	1.527 Mg · m^{-3}	

Absorption coefficient	10.425 mm^{-1}
F(000)	568 e
Crystal size	0.57 x 0.34 x 0.13 mm^3
θ range for data collection	3.47 to 65.08°.
Index ranges	$-12 \leq h \leq 13$, $-9 \leq k \leq 8$, $-13 \leq l \leq 15$
Reflections collected	41725
Independent reflections	3529 [R_{int} = 0.0594]
Reflections with I>2σ(I)	3527
Completeness to θ = 65.08°	94.2 %
Absorption correction	Gaussian
Max. and min. transmission	0.33497 and 0.02099
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3529 / 1 / 318
Goodness-of-fit on F^2	1.078
Final R indices [I>2σ(I)]	R_1 = 0.0318 wR^2 = 0.0827
R indices (all data)	R_1 = 0.0318 wR^2 = 0.0827
Absolute structure parameter	0.005(5)
Largest diff. peak and hole	0.473 and -1.585 e · $Å^{-3}$

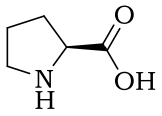
9. STRUCTURE INDEX



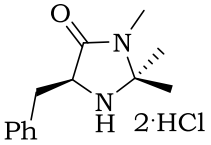
1 (QN)



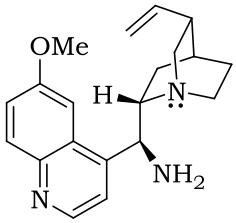
2



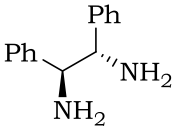
3



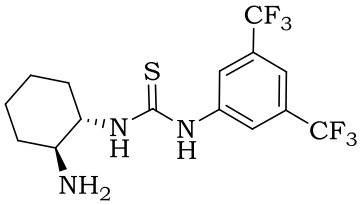
4



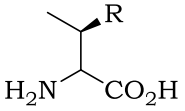
5



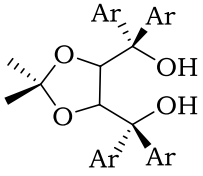
6



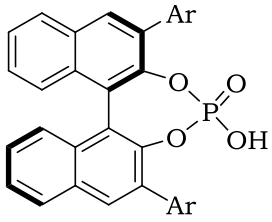
7



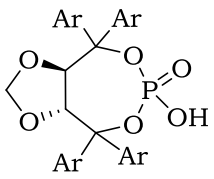
8



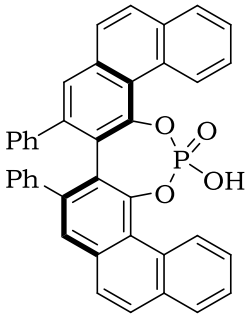
9



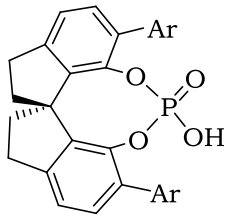
10a Ar = *p*-$NO_2C_6H_4$
10b Ar = 2,4,6-$^{i}Pr_3C_6H_2$, (S)-TRIP



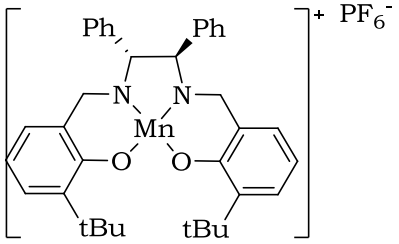
Ar = *p*-$CF_3C_6H_4$
11



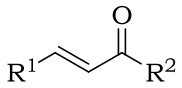
12



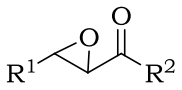
Ar = 9-anthracenyl
13



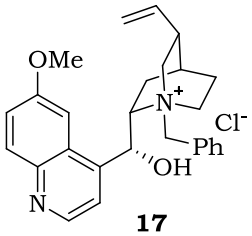
14



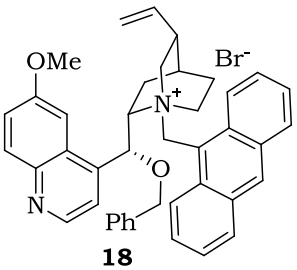
15



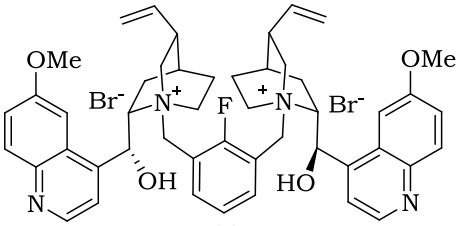
16



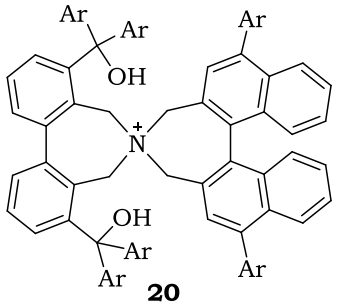
17



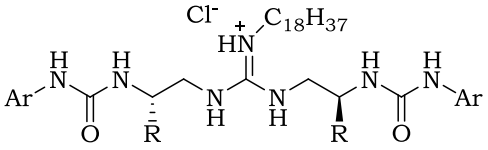
18



19

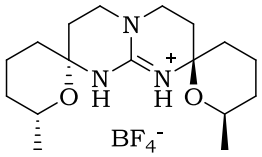


20

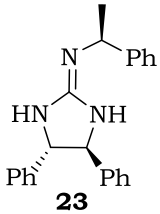


R = Bn, Ar = 3,5-$(CF_3)_2C_6H_3$

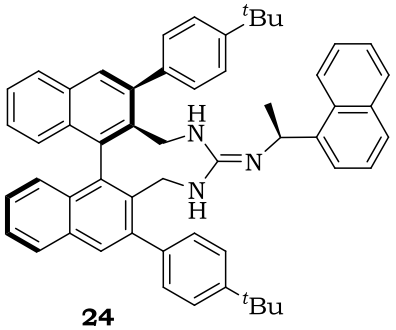
21



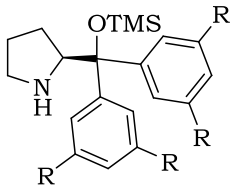
22



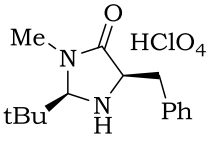
23



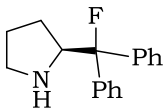
24



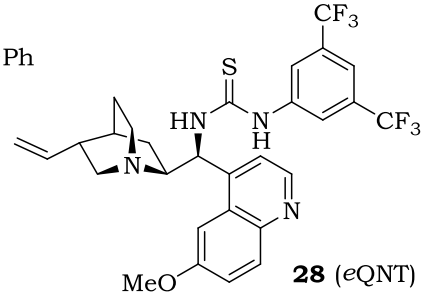
25a R = CF_3
25b R = H



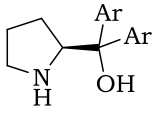
26



27

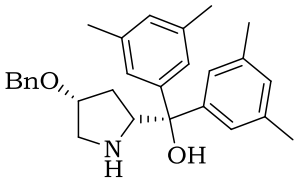


28 (*e*QNT)

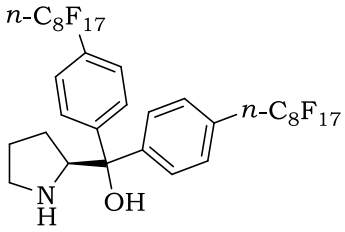


29

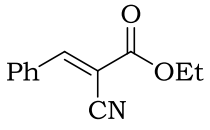
29a Ar = Ph
29b Ar = 3,5-$(CH_3)_2C_6H_3$
29c Ar = 3,5-$(CH_3)_2$-4-$MeOC_6H_2$
29d Ar = 4-$MeOC_6H_4$
29e Ar = 2-naphthyl
29f Ar = 4-^{t}BuC_6H_4



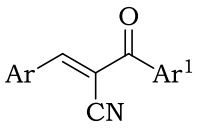
30



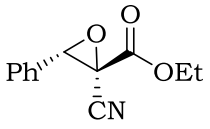
31



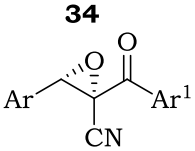
32



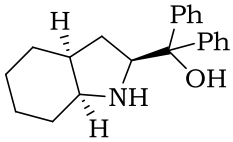
34



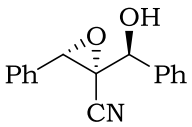
33



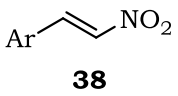
35



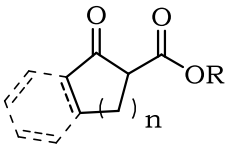
36



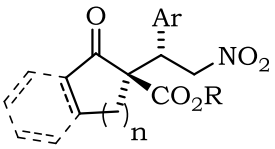
37



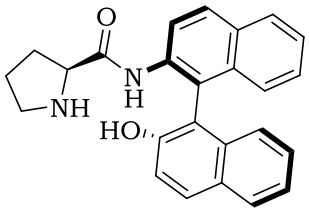
38



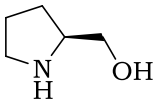
39



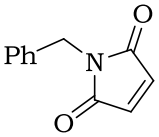
40



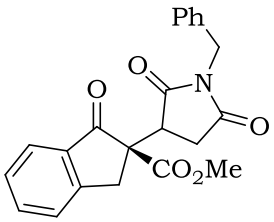
41



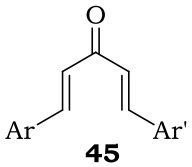
42



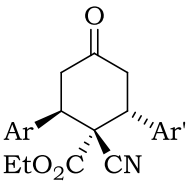
43



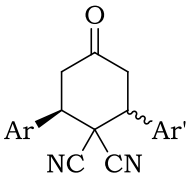
44



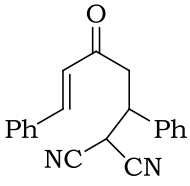
45



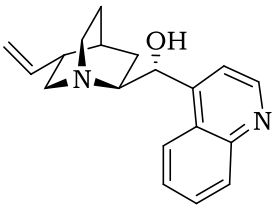
46



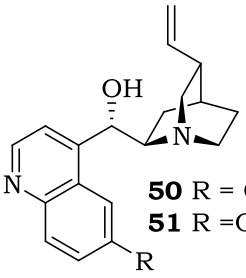
47



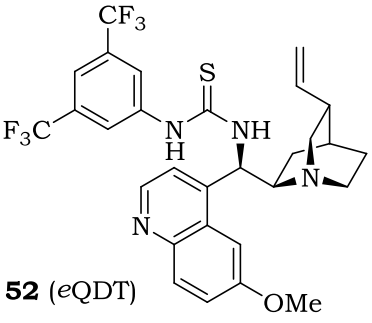
48



49 (CD)



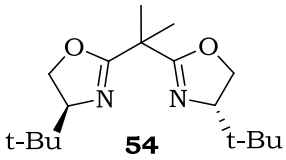
50 R = OMe (QD)
51 R =OH (CPD)



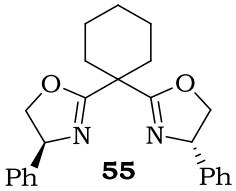
52 (*e*QDT)

TsN=IPh

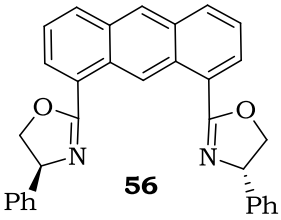
53



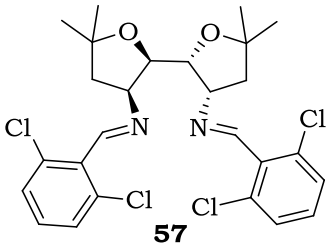
54



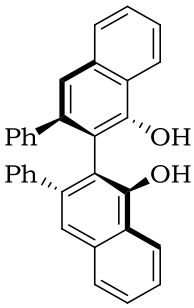
55



56

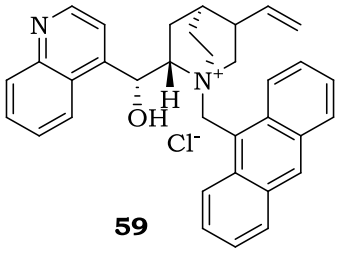


57

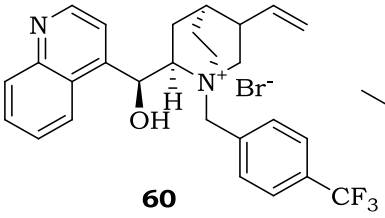


(S)-VANOL

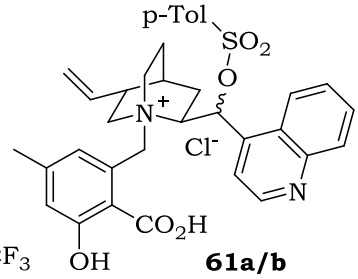
58



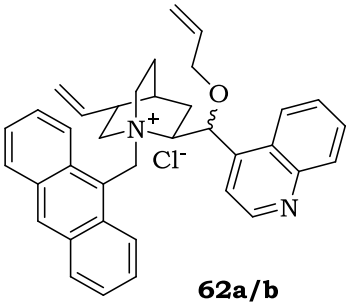
59



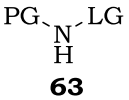
60



61a/b

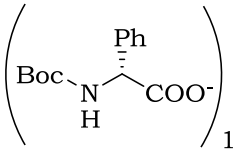


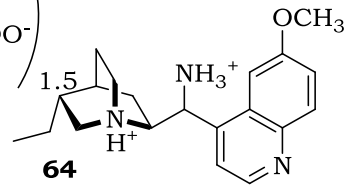
62a/b



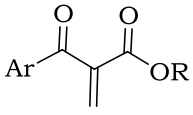
63

PG = Boc, LG = OTs **63a**
PG = CBz, LG = OTs **63b**
PG = Ts, LG = OTs **63c**
PG = CBz, LG = OAc **63d**
PG = Boc, LG = OAc **63e**
PG = Boc, LG = $PO(Ph)_2$ **63f**

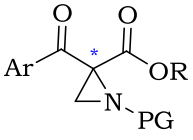




64

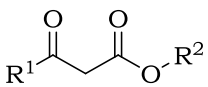


65

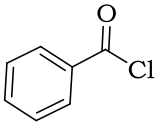


66

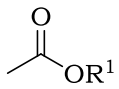
67



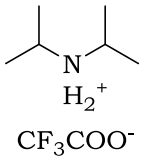
68



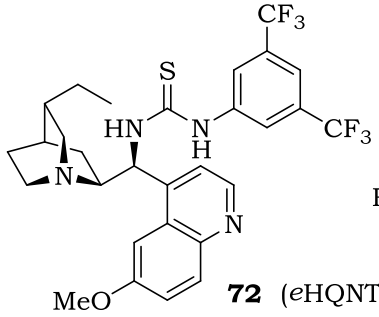
69



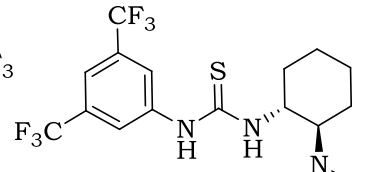
70



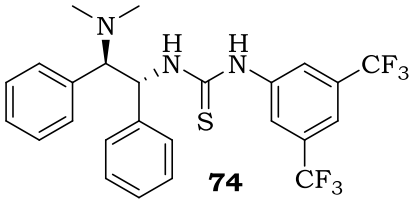
71



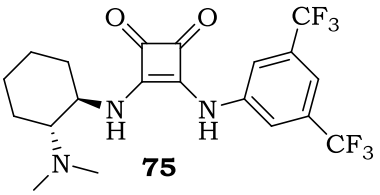
72 (*e*HQNT)



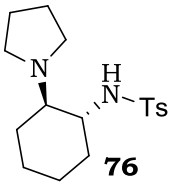
73a R = CH_3
73b R = C_3H_7



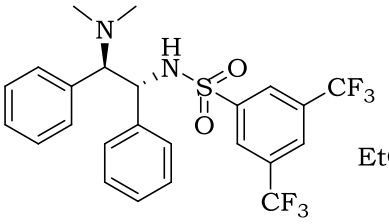
74



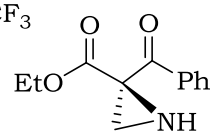
75



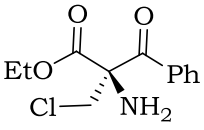
76



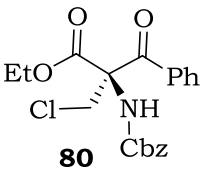
77



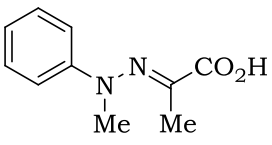
78



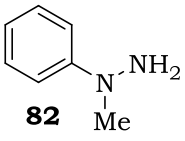
79



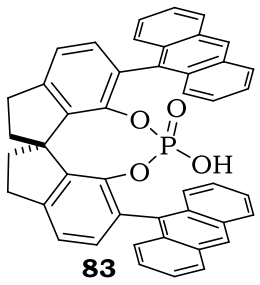
80



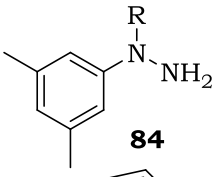
81



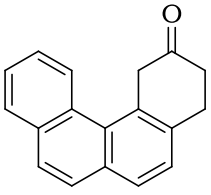
82



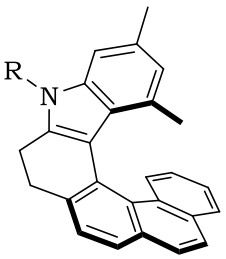
83



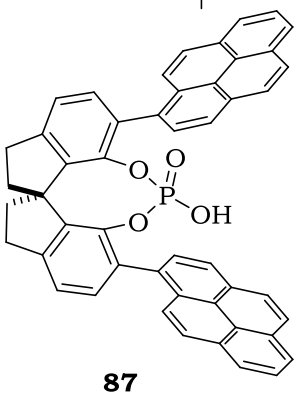
84



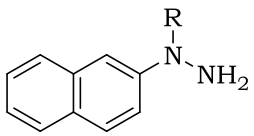
85



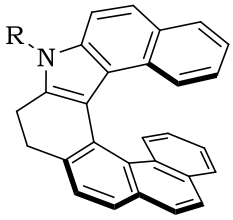
86



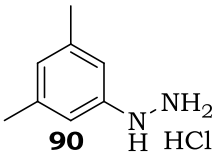
87



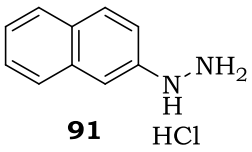
88



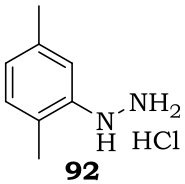
89



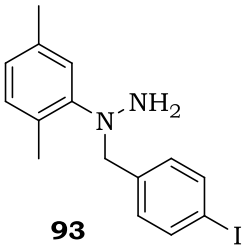
90



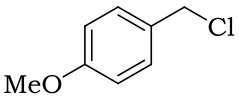
91



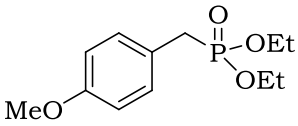
92



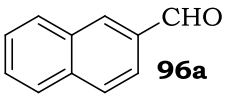
93



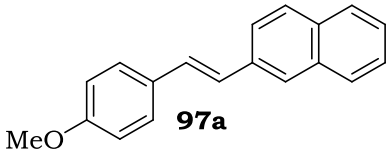
94



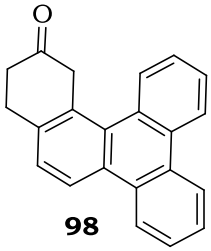
95



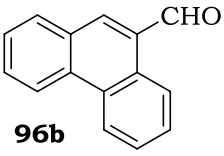
96a



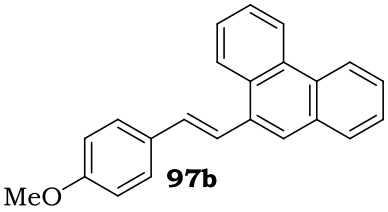
97a



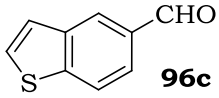
98



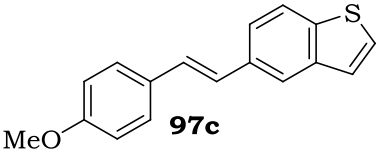
96b



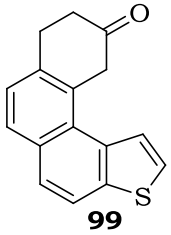
97b



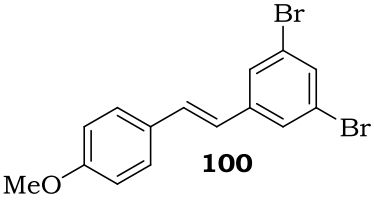
96c



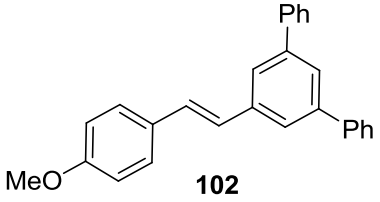
97c



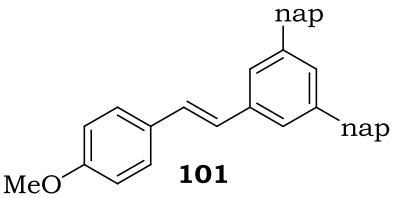
99



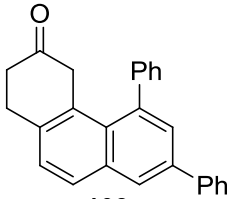
100



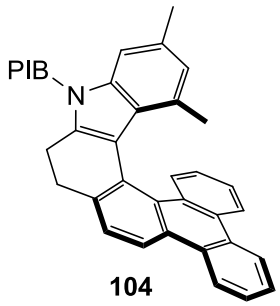
102



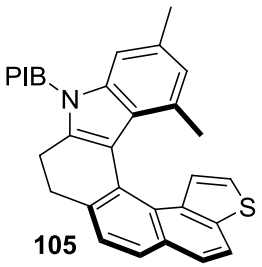
101



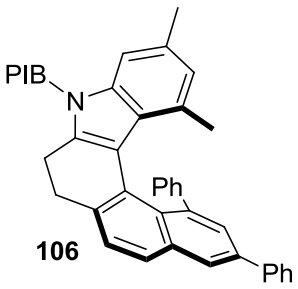
103



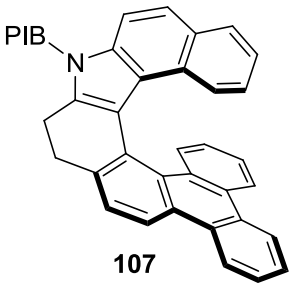
104



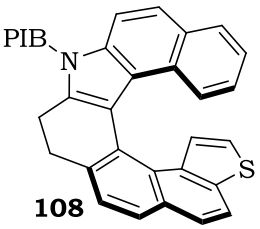
105



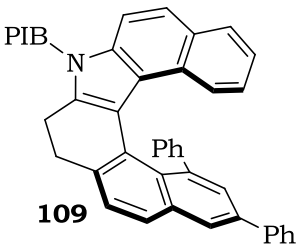
106



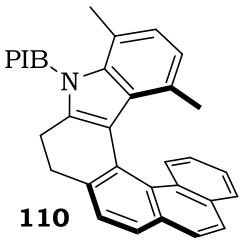
107



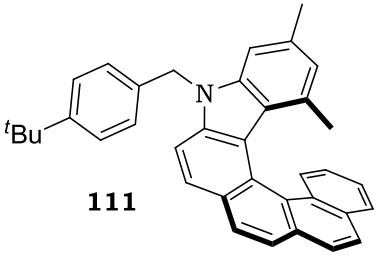
108



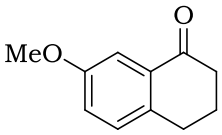
109



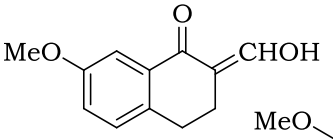
110



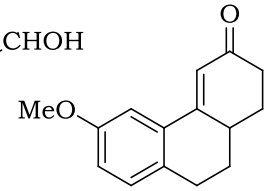
111



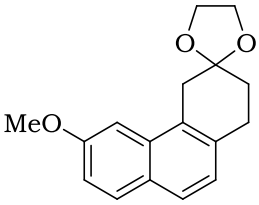
112



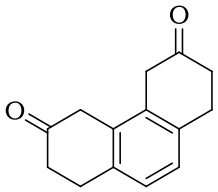
113



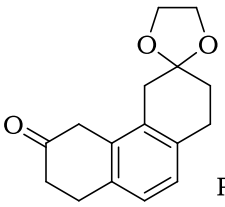
114



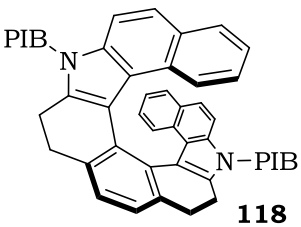
115



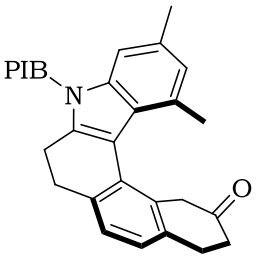
116



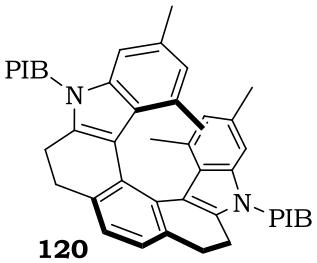
117



118



119



120

The work contained within this thesis is partially described in the following publications:

- "Organocatalytic Stereoselective Epoxidation of Trisubstituted Acrylonitriles"
  C. De Fusco, C. Tedesco, A. Lattanzi, *J. Org. Chem.* **2011**, 76, 676-679.

- "Hexafluorobenzene: a powerful solvent for a noncovalent stereoselective organocatalytic Michael addition reaction"
  A. Lattanzi, C. De Fusco, A. Russo, A. Poater, L. Cavallo, *Chem. Commun.* **2012**, 48, 1650-1652.

- "Quinine-Catalysed Double Michael Addition of Malononitrile to 1,5-Disubstituted Pentadien-3-ones: A Stereoselective Route to Cyclohexanones"
  C. De Fusco, A. Lattanzi, *Eur. J. Org. Chem.* ***2011****, 3728-3731.*

- "Noncovalent Organocatalytic Synthesis of Enantioenriched Terminal Aziridines with a Quaternary Stereogenic Center"
  C. De Fusco, T. Fuoco, G. Croce, A. Lattanzi, *Org. Lett.* **2012**, 14, 16, 4078-4081.

Moreover the following reviews on organocatalytic processes have been published:

- "Enantioselective organocatalytic α-heterofunctionalization of active methines"
  A. Russo, C. De Fusco, A. Lattanzi, *RSC Advances* **2012**, 2, 385–397.

- "Organocatalytic Asymmetric Oxidations with Hydrogen Peroxide and Molecular Oxygen"
  A. Russo, C. De Fusco, A. Lattanzi, *ChemCatChem* **2012**, 4, 901 – 916.