Universidad Autónoma de Madrid | Facultad de Ciencias
Departamento de Química Orgánica

ARYLACETIC ACID DERIVATIVES AS NUCLEOPHILES IN IMINIUM ION ACTIVATION CATALYSIS.

SYNTHETIC APPLICATIONS AND MECHANISTIC INSIGHTS.

Madrid, 2013

Sara Duce Igeño

Esta Tesis Doctoral ha sido realizada en el Departamento de química orgánica de la Facultad de Ciencias de la Universidad Autónoma de Madrid bajo la dirección de la Dra. M. Belén Cid de la Plata y el Dr. José Luis García Ruano, Profesora Titular y Catedrático de dicha universidad respectivamente.

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La bibliografía de la memoria es independiente para cada uno de los capítulos en los que se divide. Algunas de las referencias se encuentran repetidas en los capítulos por distintos motivos. Las citas bibliográficas se podrán encontrar al pie de página y recopiladas al final de cada capítulo. La numeración de las tablas y los esquemas es independiente en cada capítulo. La numeración de los compuestos es consecutiva durante toda la tesis.

The references are independent for each chapter. Some of the literature references are duplicated in the different chapters for different purposes. The references are also given at the end of each chapter. The numbers of figures and schemes are particular of each chapter. The numbers of compounds are sequential throughout the chapters.

Abbreviations, acronyms and symbols

Å	Angstrom
ACIE	Angewandte Chemie International Edition
AcOH	Acetic acid
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
ASC	Advanced Synthesis and Catalysis
n-Bu	n-Butyl
BzOH	Benzoic acid
°C	Degree Celsius
CC	Chemical Communications
Cat.	Catalyst
CAJ	Chemistry. An Asian Journal
CEJ	Chemistry. A European Journal
Conv.	Conversion
δ	Chemical shift
d	Doublet
dd	Double of doublets
ΔG	Change in Gibbs free energy

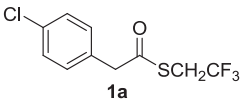
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
de	diastereomeric excess
ee	Enantiomeric excess
e.g.	Exempli gratia (for example)
EI	Electron impact
ent.	Enantiomer
equiv	Equivalents
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl acetate
et al.	*Et alii* (and others)
EWG	Electronwithdrawing group
h	Hours
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i.e.	*Id est* (that is)
IR	Infrared

iPr	Isopropyl
JACS	Journal of the American Chemical Society
JOC	Journal of Organic Chemistry
LiOAc	Lithium acetate
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet
M	Molar concentration
m.p.	Melting point
m/z	Mass to charge ratio
MS	Mass spectroscopy
Me	Methyl
min.	Minutes
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
OL	Organic Letters
ppm	Parts per million
Pr	Propyl
Ph	Phenyl
rt	Room temperature
s	Singlet
Sat.	Saturated
Solv.	Solvent

t ()	Time
T	Tetrahedron
TBAB	Tetrabutylammonium bromide
TBDPS	Tertbutyldiphenylsilyl
tBu	Tert-butyl
t	Triplet
Temp	Temperature
TES	Triethylsilyl
THF	Tetrahydrofurane
TL	Tetrahedron Letters
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state
p-TSOH	*para*-Toluenesulfonic acid
vs.	versus

Nucleophiles, catalysts and aldehydes most used in this thesis

Nucleophiles



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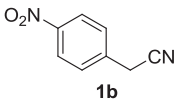

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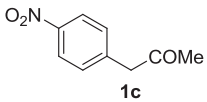

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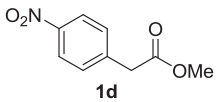

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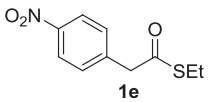

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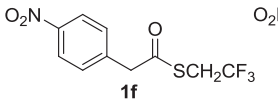

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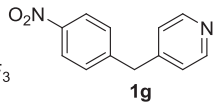

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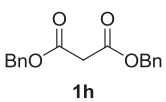

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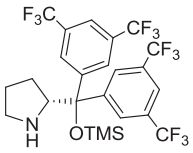
Catalyst



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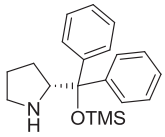

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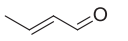

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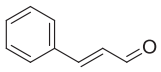

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Chapter I

Introduction and Objectives

Prologue: General aspects of asymmetric catalysis

Chirality is a universal property present in every level of life. This subject generated speculations and interpretations long time ago,[1] much before the concept itself was incorporated into the scientific community. Nowadays the idea of chirality is widespread in chemistry and related disciplines. The 'left-handed' or 'right-handed' property of objects that are mirror images of each other is everywhere in the observable world -shoes, conch shells and umbilical cords, for instance. This property extends to objects in the molecular level;[2] nearly all biomolecules in nature (such as amino acids, sugars, alkaloids and terpenes) and millions of synthetic compounds are chiral. Chirality is fundamental to the structure, properties and function of molecules. How such molecules interact with each other in recognition, binding and chemical reactions is significantly dependent on their chirality. For chemists who wish to prepare target compounds with specific properties (*e.g*. medicinal, mechanical or physical) the ability to synthesize molecules with the appropriate chirality is crucial.

Consciousness of the importance of stereoselectivity in drug action has intensified since the thalidomide[3] tragedies of the 1960s, as the difference in the pharmacology and pharmacokinetics of enantiomers has become better understood. Demand of enantiomerically pure compounds is in growth within the pharmaceutical and agrochemical industries and also in the research of new materials.

The development of truly efficient methods to obtain chiral substances in enantioenriched form is still a significant challenge for synthetic chemists. The classical resolution of racemates was the primary method used to achieve optically active compounds. Other methods involve transformation or derivatization of readily

[1] P. Cintas, *Angew. Chem. Int. Ed.* **2007**, *46*, 4016.
[2] Origins of molecular chirality: A. Guijarro, M. Yus, *The Origin of Chirality in the Molecules of Life: A revision from Awareness to the Current Theories and Perspectives of this Unsolved Problem*, RCS Publishing, **2008**.
[3] T. Stephens, R. Brynner, *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*, Cambridge, MA, Perseus, **2001**.

available natural chiral compounds (synthesis form *chiral pool*). The use of chiral auxiliaries, introduced by Corey,[4] has been a very versatile strategy incorporated in many synthetic routes.[5] For the synthesis of enantiomerically pure compounds starting from prochiral precursors, enzymes and synthetic metal complexes were considered for decades the only two accepted classes of efficient asymmetric catalysts. Biological methods, which use enzymes, cell cultures or whole microorganisms, are powerful for the preparation of chiral substances; however, the scope of such reactions is generally limited because many biological systems exhibit very high specificity. Additionally, reactions catalyzed by enzymes often need to be carried out in aqueous buffered media, which usually is problematic for the low solubility of organic compounds in these media.

The other class of accepted and efficient chiral catalysts, metal complexes, is based on organometallic chemistry. Since the late 1960s, advances in the development of metal-based chiral catalysts have provided a wealth of enantioselective transformations, culminating to the Nobel Prize awarded to Knowles, Noyori, and Sharpless in 2001. Despite the great utility, transition metal catalysts have the disadvantage of leaving possibly toxic traces of heavy metals in the final products.

In contrast, the use of organic molecules as catalysts (**organocatalysis**) has only gained attention since the late 1990s. During the last decade, organocatalysis has grown extraordinarily according to the large number of researchers and breakthroughs that continue to advance this successful area. Moreover, this field has grown from a small collection of chemically unique reactions to a successful area of general concepts, reactivity and widely applicable transformations.

Nowadays, organocatalysis is considered the third pillar of asymmetric catalysis (Figure 1.1), together with the mentioned metal catalysis and enzymatic catalysis

[4] H. E. Ensley, C. A. Parnell, E. J. Corey, *J. Org. Chem.* **1978**, *43*, 1610.
[5] F. Glorius, Y. Gnas, *Synthesis* **2006**, *12*, 1899.

(biocatalysis), and it is widely used in the synthesis of chiral molecules. In addition to enriching chemistry with another useful strategy for catalysis, this approach has some important advantages. Small organic molecule catalysts are generally stable to oxygen and moisture and fairly easy to design and synthesize. A large variety of organic catalysts are also available as single enantiomers from natural sources. They are often based on nontoxic compounds such as sugars, peptides, or even amino acids, and can be linked to a solid support, making them useful for industrial applications. In light of these facts, organocatalysis has become a field of major importance to organic chemists and has turned into a major research area on a global scale.

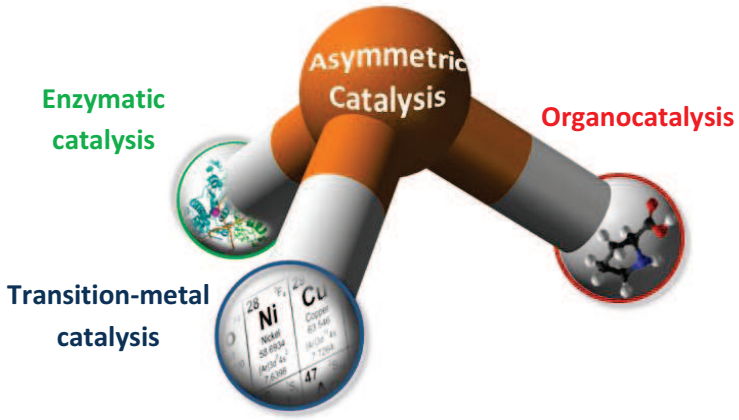


Figure 1.1. Methods in asymmetric catalysis

In spite of its many advantages, organocatalysis is still a comparatively recent research area with several aspects which can be improved. The amounts of catalyst required for organocatalytic processes are relatively high in comparison with the typical catalyst loadings employed in metal or enzymatic catalysis. One of the solutions proposed for this issue is the catalyst recycling. However, whereas this might be important for those cases where the catalysts are expensive, it is not the case for many organic catalysts, since the recovery process would result in similar cost to that of their initial purchase/synthesis. Moreover, reaction times are sometimes long, the reactions requiring several days to achieve completion. Another important

drawback to be considered in organocatalysis is that the catalytic activity is generally restricted to the presence of specific activating groups on the substrates (mostly carbonyl or similar moieties). There exist only a few types of activation in comparison with the metal catalysis. It would be interesting to design catalysts that could be applied to a broad diversity of substrates and reaction types. For these reasons, intensive efforts are underway in both academia and industry to further remove barriers for an effective scale-up by improving issues such as catalyst loading, product inhibition, and substrate scope through rational catalyst design.

A literature examination of articles that focus on the use of organocatalytic concepts indicates that this area began an exponential growth in 2000, year in which MacMillan defined the concept *'organocatalysis'* as an area itself.[6] The interest in this field has continued rapidly expanding yearly (Figure 1.2). This graphic was obtained searching by topic in the database *Web of Science* using the term "*organocataly**", which includes the terms "*organocatalyst, organocatalysis* and *organocatalytic*".[7]

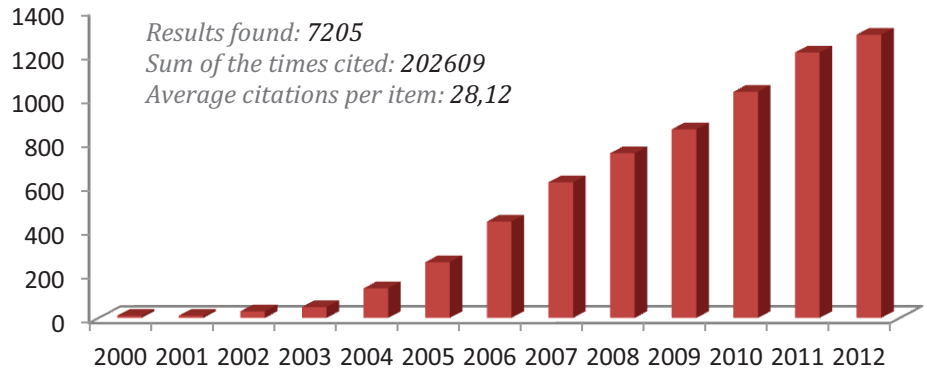


Figure 1.2. Publications with the term organocataly*(Source: web of knowledge)

[6] D. W. C. MacMillan, *Nature*, **2008**, *455*, 304.
[7] Data of the analysis: 1st September 2013.

As illustrated by the statistics, it is obvious that organocatalysis has grown quite dramatically in recent years. However, several areas are yet not fully explored, and new concepts will surely arise within the more established ones. There are already a number of organocatalytic reactions being used in the industry.[8] Even if the area is not as widespread in industry as it already is in the academic level, asymmetric organocatalysis is being increasingly utilized by the pharmaceutical industry for the enantioselective synthesis of chiral target molecules at all stages from drug discovery to product development.[9]

In the next parts of this introductory chapter, iminium ion catalysis, the subject of the Thesis, will be placed in the context of organocatalysis in general and afterwards in the development of aminocatalysis in particular. Finally, a section describing the details of iminium ion catalyzed reactions is provided. Therefore, the chapter is divided in three different sections:

1. Asymmetric organocatalysis (pages 8-25):
- **1.1** Historical background
- **1.2** Activation modes

2. Aminocatalysis: (pages 25-50)
- **2.1** History and origins of aminocatalysis.
- **2.2** Enamine catalysis
- **2.3** Iminium ion catalysis
  - **2.3.1** Most important catalysts
  - **2.3.2** General remarks of iminium ion catalysis

Finally, the objectives and the organization of the present thesis are introduced (section **3**).

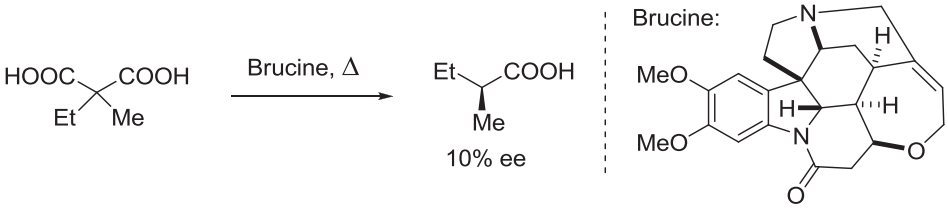
[8] Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis (Eds.: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim, **2005**, Chapter 14.
[9] P. G. Bulger, *Comprehensive Chirality*, Elsevier, 2012, Vol. 9, Chapter 9.10.

1. Asymmetric organocatalysis.

1.1. Historical background

Pioneering contributions that have set the foundations for this field will be introduced. Emphasis is placed on the discoveries that outlined for the first time new organocatalytic activation concepts.[10] These early works were milestones especially for the innovative transformations; in many cases the mechanistic implications of such transformations were not studied until many years later and hence those transformations were not included into a generic field of research. A summary of these milestones is presented in Figure 1.3, next page.

The development of the first asymmetric catalytic reactions was strongly influenced by the discovery of enzymes and enzyme functions. Indeed, the first asymmetric reaction was a decarboxylative kinetic resolution discovered by Pasteur[11], who observed that the organism *Penicillium glauca* destroyed more rapidly one of the enantiomers of a racemic solution of ammonium tartrate. As a consequence, the first example of asymmetric organocatalytic transformation was the decarboxylation of malonic acid derivative in the presence of Brucine, attributed to Marckwald in 1904 (Scheme 1.1). The resulted 2-methylbutiric acid was obtained with low enantiomeric induction (10% ee).



Scheme 1.1. Decarboxylation of a malonic acid (Marckvald), 1904.

[10] To make this chart we have followed: G. Lelais, D. W. C. MacMillan, *History and Perspective of Chiral Organic Catalysis* (Chapter 11) in *New frontiers in organic synthesis*, K. Mikami, M. Lautens, (Eds.) John Wiley & Sons, Inc., Hoboken, New Jersey, **2007**.
[11] L. C. Pasteur, *R. Hebd. Seance Acad. Sci. Paris*, **1858**, *46*, 615.

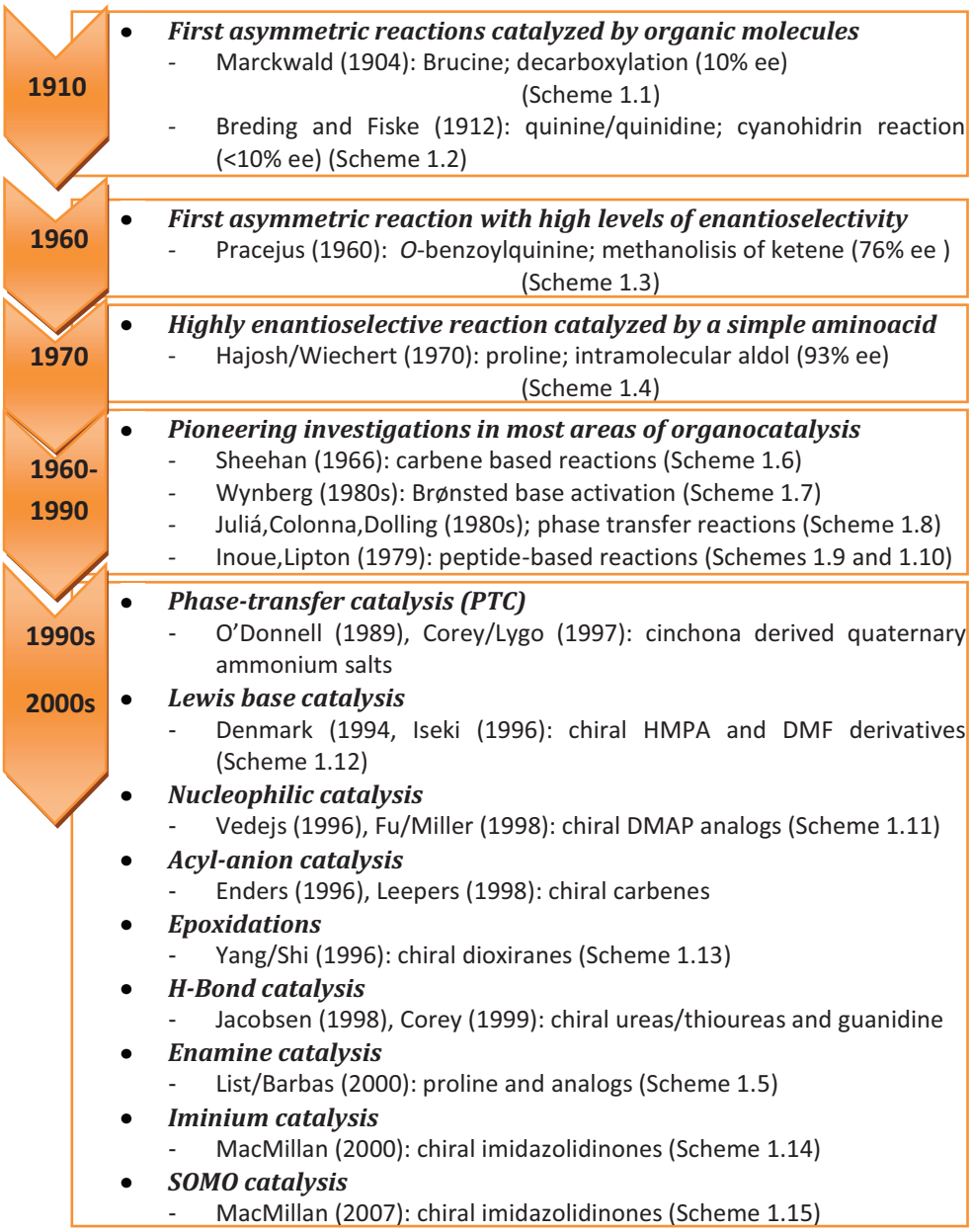
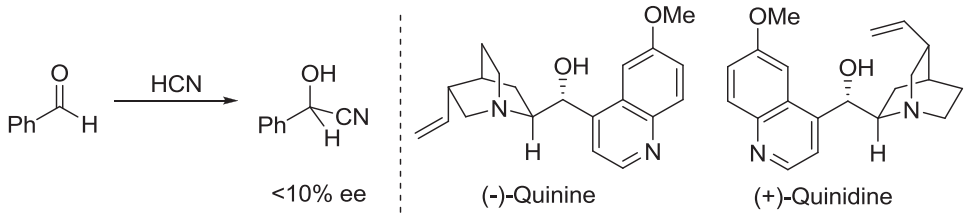


Figure 1.3. Summary of the pioneering works in organocatalysis.

Asymmetric decarboxylation reactions were re-examined under non-enzymatic conditions by Georg Bredig during the early 1900s. In his early experiments he observed enantiomerical enrichment in the thermal decarboxylation of optically active camphorcarboxylic acid in D and L limonenes, respectively.[12] As an extension of this work he studied the decarboxylation reaction in the presence of chiral alkaloids, such as nicotine or quinidine..[13] The first asymmetric C-C bond forming reaction is attributed also to him. Bredig and Fiske in 1912[14] performed the addition of hydrogen cyanide to benzaldehyde in the presence of Cinchona alkaloids as catalysts (Scheme 1.2). Also in these cases the corresponding optically active cyanohydrin was obtained with low enantiomeric excess (<10%).



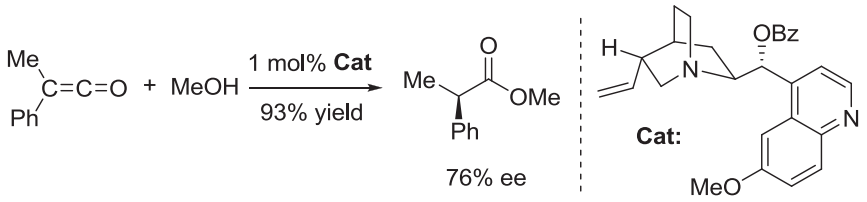
Scheme 1.2. Addition of hydrogen cyanide to benzaldehyde (Bredig, Fiske), 1912.

Although catalytic transformations gained increasing importance after the First World War, asymmetric reactions were considered at that time to be an academic curiosity. Moreover, the determination of enantioselectivity was hampered by a lack of methods to achieve not only efficient purification but also reliable analyses. Hence, the presence of a chiral impurity – which often arose from the catalyst – prevented the accurate determination of the correct optical rotation-based ee values.

It took almost 50 years before the pioneering work of Pracejus described the use of *O*-benzoylquinine as an organocatalyst to enable the enantioselective methanolysis

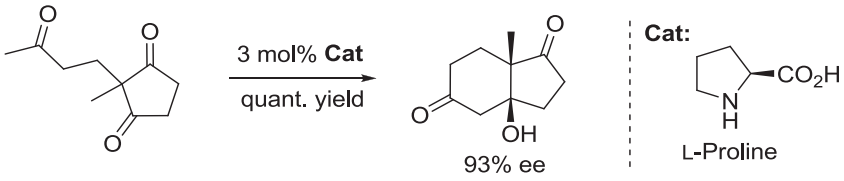
[12] G. Bredig, R.W. Balcom, *Ber. Deutsch. Chem. Ger*. **1908**, *41*, 740.
[13] G. Bredig, K. Fajans, *Ber. Deutsch. Chem. Ger.* **1908**, *41*, 752.
[14] G. Bredig, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7.

of phenylmethylketene, providing the first example of an organocatalytic transformation with, at the time, notable levels of enantioselectivity (up to 76% ee)[15] (Scheme 1.3).



Scheme 1.3. Addition of methanol to a ketene (Pracejus), 1960.

In the late 1960s and early 1970s, the groups of Hajos and Weichert reported the now-famous proline catalyzed intramolecular aldol condensation of prochiral triketones[16] (nowadays commonly named as the Hajos-Parrish reaction) (Scheme 1.4). This desymmetrizing aldol reaction provided enantioenriched bicyclic adducts in <93% ee, which were used in the total synthesis of steroids and other natural products.

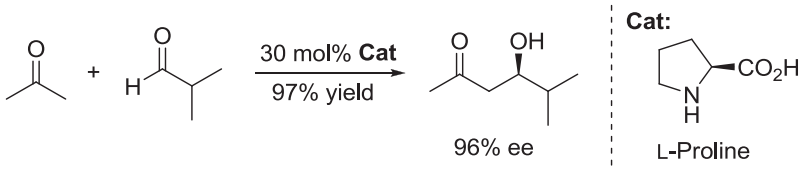


Scheme 1.4. Intramolecular aldol reaction (Hajos, Wiechert), 1971.

It is remarkable that this reaction and the underlying catalytic principle lay dormant for almost 25 years, before the pioneering work of List, Lerner and Barbas[17] established the first intermolecular variant of this aldol protocol in 2000 (Scheme 1.5).

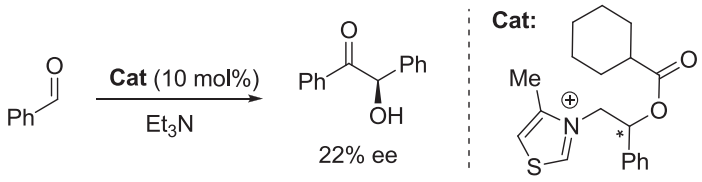
[15] H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.
[16] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615. b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.
[17] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

This enabled the rebirth and growth of an extremely important subfield of organocatalysis, which became subsequently known as enamine catalysis.



Scheme 1.5. Intermolecular aldol reaction (Barbas III, List), 2000.

Going back to the historical facts that marked the development of organocatalysis, Sheehan *et al.*, in the middle 1960s, performed the asymmetric benzoin condensation of benzaldehyde catalyzed by a chiral carbene derivative (Scheme 1.6). Although the enantiomeric excess was low (<25%),[18] this work established the first example of the subfield later known as acyl-anion catalysis, mediated by chiral carbenes,[19] which was reintroduced with extensive studies in the 1990s by Enders[20] and Leeper.[21]

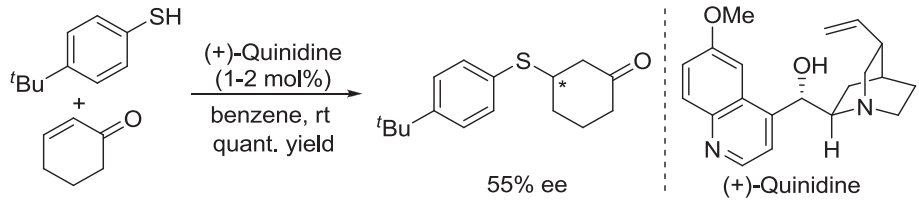


Scheme 1.6. Benzoin condensation (Sheehan), 1966.

In the 1970s and 1980s, many groups reported the use of cinchona alkaloids as chiral catalysts, providing further evidence to their status as privileged structures. The catalysts were applied in several reactions such as hetero-[2+2] cycloadditions, phase-

[18] J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc*. **1966**, *88*, 3666.
[19] a) D. Enders, D. O. Niemeier, A. Henseler, *Chem. Rev*. **2007**, *107*, 5606. b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed*. **2007**, *46*, 2988.
[20] D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217.
[21] R. L. Knight, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3611.

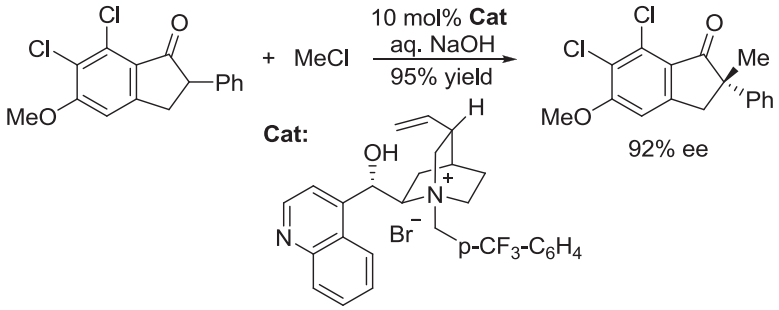
transfer catalyzed epoxidations[22] and conjugated additions. A significant example of the use of the natural alkaloid quinidine is the 1,4-addition of a thiophenol to an α,β-unstaturated ketone reported by Wynberg in the 1980s (Scheme 1.7).[23]



Scheme 1.7. Michael addition catalyzed by quinidine (Wynberg), 1981.

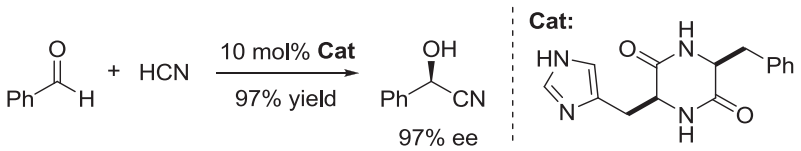
Phase-transfer catalysts derived from the same alkaloids were used also in alkylation[24] reactions. Among the possible examples, perhaps the most powerful transformation by that time is the alkaloid derived ammonium salt catalyzed methylation of indanone derivatives (Scheme 1.8),[24b] as developed by the process research group at Merck, Rahway, NJ. This strategy was dramatically implemented some years later by O'Donnell,[25] Corey[26] and Lygo[27], setting the foundation for the subfield of phase-transfer catalysis.

[22] a) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg, *Tetrahedron Lett*. **1976**, *1*, 1831. b) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem. Int. Ed*. **1980**, *19*, 929.
[23] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc*. **1981**, *103*, 417.
[24] a) S. Juliá, A. Ginebreda, J. Guixer, J. Masana, A. Tomás, S. J. Colonna, *J. Chem. Soc. Perkin Trans. 1* **1981**, 574. b) U. –H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc*. **1984**, *106*, 446. c) A. Battacharya, U. –H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem. Int. Ed.* **1986**, *25*, 476.
[25] M. J. O'Donnell, W. D. Bennett, S. D. Wu, *J. Am. Chem. Soc*. **1989**, *111*, 2353.
[26] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414.
[27] B. Lygo, J. Crosby, T. R. Lowdon, P. G. Wainwright, *Tetrahedron Lett*. **1997**, *38*, 2343.



Scheme 1.8. Phase-transfer catalyzed methylation (Dolling), 1984.

The next milestone in the area of enantioselective organocatalysis was reached by Inoue and co-workers,[28] who elegantly modernized the cyanohydrin reaction, first outlined by Bredig and Fiske in 1912 (Scheme 1.2). In these studies, a cyclic histidine-containing dipeptide catalyzed the HCN addition to aromatic aldehydes with high enantioselectivities (Scheme 1.9). This result settled effectively the way for the field of peptide-catalyzed reactions.[29]

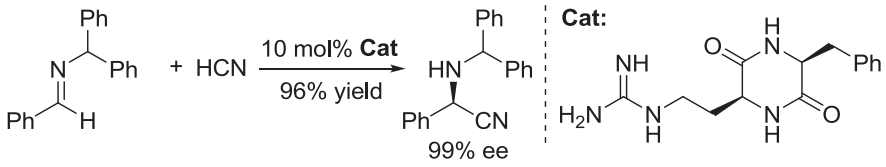


Scheme 1.9. Addition of hydrogen cyanide to nenzaldehyde (Inoue), 1979.

Indeed, some time after Inoue's studies, the first reports of enantioenriched *α*-amino acid synthesis *via* enantioselective Strecker reaction appeared in the literature (Scheme 1.10).[30] Further development by Corey and Jacobsen[31] outlined the use of a

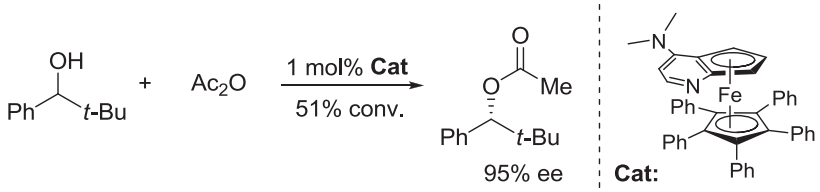
[28] a) J. Oku, N. Ito, S. Inoue, S. *Makromol. Chem*. **1979**, *180*, 1089; b) J. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.* **1981**, 229; c) K. Tanaka, A. Mori, S. Inoue, *J. Org. Chem.* **1990**, *55*, 181.
[29] For a discussion of the mechanisms in peptide-catalyzed reactions see: Y. Shvo, M. Gal, Y. Becker, A. Elgavi, *Tetrahedron:Asymmetry* **1996**, *7*, 911.
[30] M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996,** *118,* 4910.

guanidine or acyclic peptide-based catalysts, respectively, to mediate this transformation.



Scheme 1.10. Strecker reaction (Lipton), 1996.

In the 1990s, short peptides, and other nucleophiles were used as organocatalysts for a wide number of enantioselective acyl transfer processes; transformations that set the bases for the more recent research area in asymmetric nucleophilic catalysis. One of the most appealing approaches to enantioselective acyl transfer was outlined by Fu using an azaferrocene catalyst (Scheme 1.11)[32]. While these pyridyl systems are not organic catalysts in the strict sense, these azaferrocene compounds act as chiral dimethylaminopyridine equivalents for a broad range of acyl transfer processes.



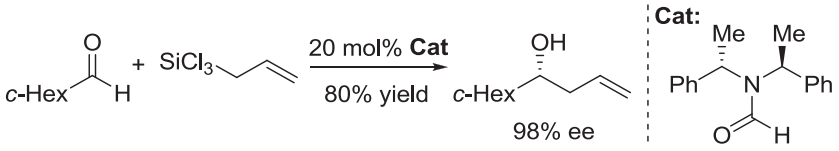
Scheme 1.11. Acyl transfer with a chiral azaferrocene (Fu), 1996.

An important area of organocatalysis that was also initiated in the early 1990s has been the area of Lewis base catalysis applied to organosilane activation. On the

[31] a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed*. **2006**, *45*, 1520. b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev*. **2007**, *107*, 5713. c) T. Akiyama, *Chem. Rev*. **2007,** *107*, 5744.

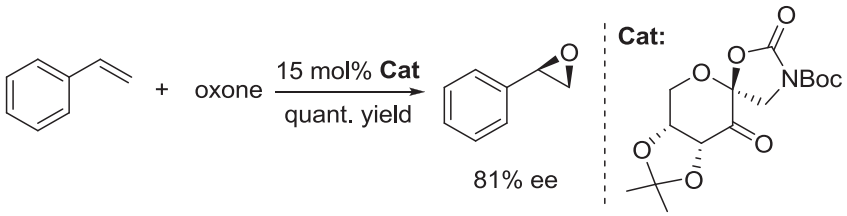
[32] a) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc*. **1997**, *119*, 1492. b) G. C. Fu, *Acc. Chem. Res*. **2000**, *33*, 412.

basis of the nonintuitive activation principle of silicon re-hybridization,[33] Denmark[34] and Iseki[35] introduced chiral HMPA and DMF variants as effective catalysts for enantioselective allylation and aldol reactions of aldehydes (Scheme 1.12).



Scheme 1.12. Allylation reaction with organosilanes (Iseki), 1994.

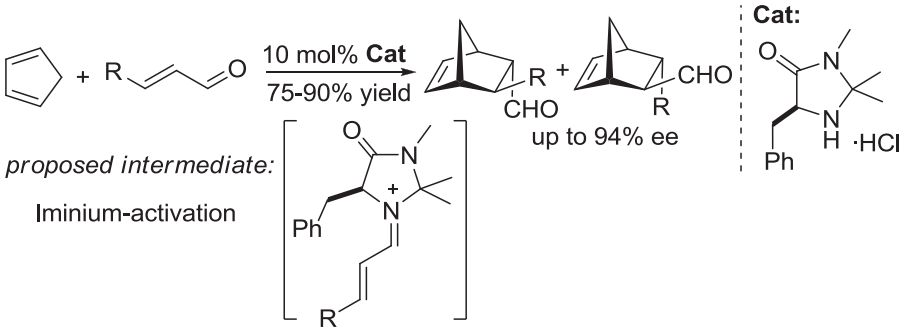
Among the most widely recognized areas of organic catalysis in the modern era it is worth mentioning the seminal studies of Yang, Shi and Denmark towards the development of non-metal enantioselective epoxidation reactions (Scheme 1.13).[36] As outlined with the Shi protocol, these reactions employ chiral ketone catalysts to mediate the asymmetric transfer of oxygen from oxone to a wide range of unfunctionalized olefins with excellent levels of enantiocontrol.



Scheme 1.13. Epoxidation reaction mediated by a ketone (Shi), 1996.

[33] S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res*. **2000**, *33*, 432.
[34] a) S. E. Denmark, D. M. Coe, N. E. Pratt, B. D. Griedel, *J. Org. Chem*. **1994**, *59*, 6161. b) S. E. Denmark, S. B. D. Winter, X. Su, K. -T. Wong, *J. Am. Chem. Soc*. **1996**, *118*, 7404.
[35] K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron Lett*. **1998**, *39*, 2767.
[36] a) D. Yang, Y. -C. Yip, M. -W. Tang, M. -K. Wong, J. -H. Zheng, K. -K. Cheiung, *J. Am. Chem. Soc*. **1996**, *118*, 491. b) Y. Tu, Z. -X. Wang, Y. Shi, *J. Am. Chem. Soc*. **1996**, *118*, 9806. c) S. E. Denmark, Z. Wu, C. M. Crudden, H. Matsuhashi, *J. Org. Chem*. **1997**, *62*, 8288.

Already in the 2000s, MacMillan[37] developed the concept of iminum ion catalysis, which will be explained in detail later on in this chapter. Even if there are previous examples using iminium catalysis as it will be shown later, it can be attributed to MacMillan the introduction of this concept as a generic mode of activation. The authors described the use of chiral secondary amine·HCl salts for the development of the asymmetric Diels-Alder reaction (Scheme 1.14).

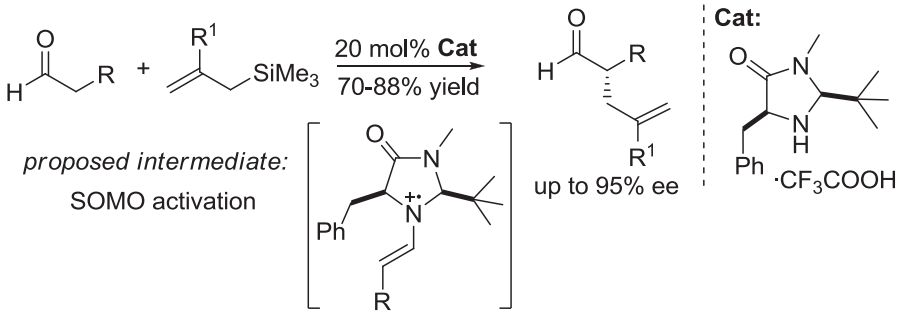


Scheme 1.14. Iminium ion catalyzed Diels-Alder reaction (MacMillan), 2000.

This publication, together with the results obtained by List and Barbas III, triggered a considerable growth to the field of organocatalysis in general and to the asymmetric catalysis mediated by secondary amines in particular: **aminocatalysis**.

Some years later the concept of SOMO catalysis was also introduced by MacMillan.[38] The concept is based on the oxidation of an electron rich enamine which generates a reactive radical cation with three π-electrons. The electrophilicity of the singly occupied molecular orbital (SOMO) of this intermediate allows it to react with a variety of weakly nucleophilic carbon-based 'SOMOphiles' at the α-carbon of the enamine, resulting for example in formal alkylation products (Scheme 1.15).

[37] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[38] T. D. Beeson, A. Mastracchio, J. Hong, K. Ashton, D. W. C. MacMillan, *Science*, **2007**, *316*, 582.



Scheme 1.15. α-Allylation *via* SOMO catalysis (MacMillan), 2007.

Having analyzed the early publications shown in the historical background, it must be explained that the emphasis was placed in the Individual transformations achieved, not in the organocatalysis as a field itself; hence a general visualization of the concept was not possible. The most crucial fact for the development of organocatalysis in the past decade was probably the identification of generic modes of activation.

1.2. Organocatalytic activation modes. Classification

The identification of the activation modes is important not only for the explanation of the stereoinduction obtained in the known reactions, but also for the expansion of the scope of enantioselective transformations. The use of a family of catalysts can be generalized only if their mechanism of action is known.

Despite the efforts made in the development and application of new catalysts, the knowledge of detailed mechanistic implications for many organocatalytic reactions is still scarce.

The first problem found when trying to classify the organocatalysts and the organocatalytic processes in which they are involved is the relative difficulty of finding the proper criteria to define reaction pathways for transformations which mechanism sometimes is still unknown. Moreover, it can also happen that one catalyst is involved in more than one activation type (bi-functional catalysts).[39]

One of the major utilized criteria for a broad classification of the organocatalysts is the nature of the interaction between the substrate and the catalyst. There are two main categories: processes where the catalyst and the substrates interact by a **non-covalent** bond; and processes where the activation occurs by a **covalent** interaction between the catalyst and the substrate (Figure 1.4).

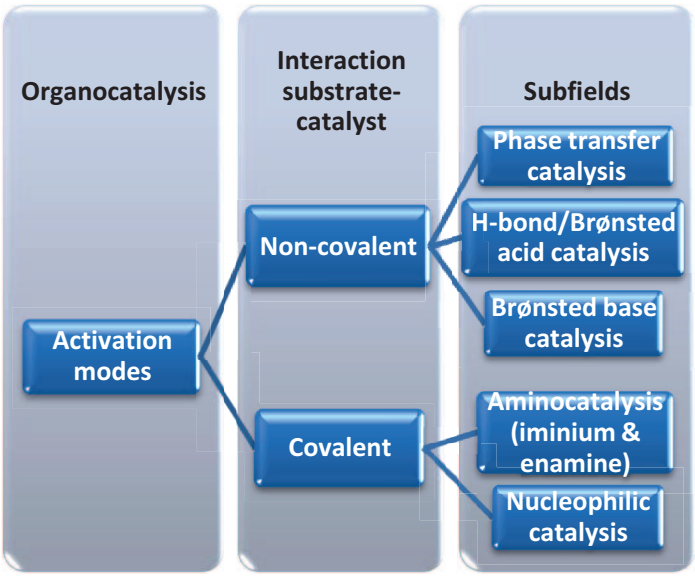


Figure 1.4. Classification of the principal activation modes in organocatalysis.

[39] Bi-functional organocatalysis, see: a) P. S. Bhadury, B. A. Song, S. Yang, D. Y. Hu, W. Xue, *Curr. Org. Synth.* **2009**, *6,* 380. b) S. J. Connon, *Chem. Commun.* **2008**, 2499.

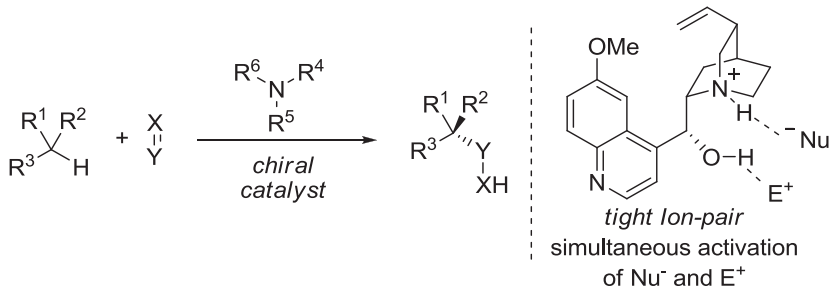
1.3. Non-covalent organocatalysis

There are a growing number of asymmetric reactions which are accelerated by weak interactions (hydrogen bonds, electrostatics, van der Waals forces, etc) with an organic catalyst. Generally, non-covalent catalysis requires lower catalyst loading and reaction times than covalent catalysis. However, the weaker nature of the catalyst-substrate interaction provides intermediates with higher conformational freedom, thus making inherently more difficult for the catalyst to provide high levels of stereoinduction and to rationalize the observed stereoselectivity.

Brønsted base catalysis

As mentioned before (see Scheme 1.2), asymmetric organocatalysis promoted by Brønsted bases represented one of the first examples of the use of organic molecules as catalysts.[13,14]

This type of catalysis is mostly based on the use of chiral amines to deprotonate a pronucleophilic substrate, featuring an appropiate acidity (usually 1,3-dicarbonyl compounds: malonates, β-ketoesters, etc). After the deprotonation occurs, a tight ion-pair is formed between the protonated catalyst and the deprotonated substrate. This interaction generates a chiral enviroment around the anion which may confer enantioselectivity to the corresponding reaction (Scheme 1.16). The intrinsic non-directional character of the electrostatic interactions of the ion-pairs makes difficult the prediction of the stereonduction.



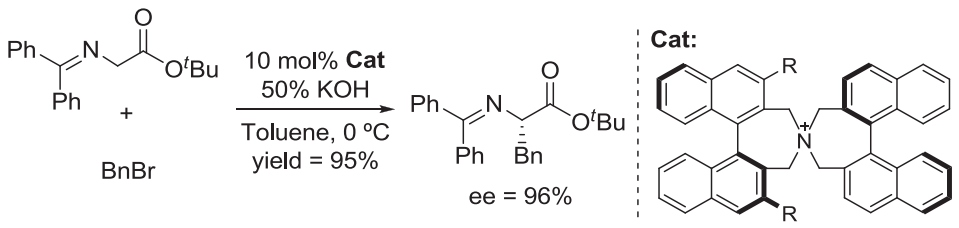
Scheme 1.16. Brønsted base catalysis concept.

The cinchona alkaloids are the most used structures for these processes. The key of the success is due to their privileged chiral architecture, which creates a chiral pocket around the deprotonated substrate. Moreover, additional groups in their structure, such as the 9-hydroxy group represented in Scheme 1.16, may coordinate the electrophile, rigidifying the resulting transition state and overall increasing the stereoinduction of the catalyst.

Phase transfer catalysis (PTC)

Asymmetric phase transfer catalysis (PTC) represents one of the most powerful modes of substrate activation within the area of organocatalysis. Phase transfer activation is founded on the use of biphasic reaction systems with catalysts (typically lipophilic ammonium salts derived from cinchona alkaloids) that can accelerate the rate of ion transfer from one phase (solid or aqueous solution) to a second phase (organic media) *via* the formation of catalyst-substrate ion-pair. The effectiveness of this ion-pair is responsible of the transmission of the chirality to the product. PTC has several preparative advantages such as simple reaction procedures, mild conditions and environmentally benign reagents, which have resulted in its broad use, including industrial applications.

Enantioselective PTC has been applied to a large number of chemical transformations; such as conjugated additions, aldol reactions, oxidations, reductions, and C-X bond formations, however, the enantioselective alkylation of methylene carbons represents one of the most thoroughly investigated reaction. In this sense, perhaps the most impressive catalysts prepared to date have been the chiral quaternary ammonium salts disclosed by Maruoka and coworkers (Scheme 1.17).[40]



Scheme 1.17. Alkylation of glycine imines (Maruoka), 2003.

Brønsted acid catalysis: Hydrogen-bond activation

The area of Brønsted acid catalysis or H-bonding catalysis is being growing since 1998 (see Schemes 1.9 and 1.10).[31] Even if there are two distinct modes of activation, both subfields are intimately related because both involve substrate LUMO-lowering activation *via* proton transfer or hydrogen association.

H-bond catalysis is defined as LUMO-lowering activation by the simultaneous sharing of the hydrogen atom by the substrate and the catalyst. The catalytic efficiency relies on the formation of strictly oriented hydrogen bonds via the bi- or multi-dentate nature of catalyst-substrate binding. Catalysts are usually alcohols, amidines, guanidines, urea and thiourea derivatives (Figure 1.5, a).

[40] K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013.

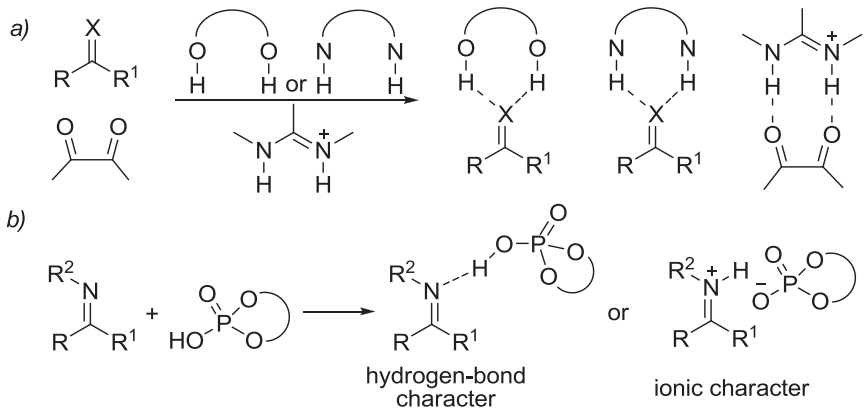
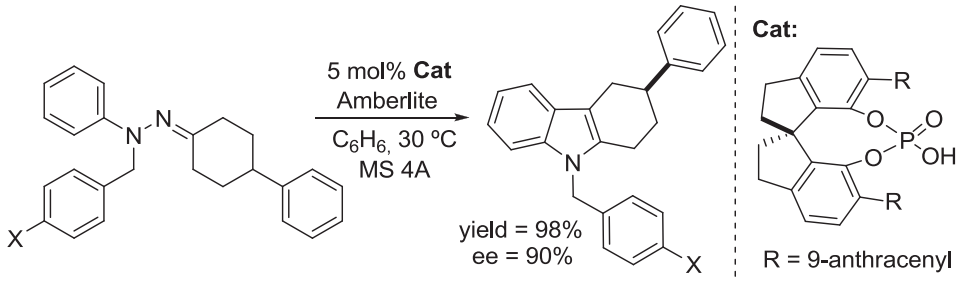


Figure 1.5. H-bond and Brønsted acid complexation modes.

Brønsted acid activation (Figure 1.5, b) implies instead substrate protonation with subsequent tight ion-pair formation between the activated substrate (cation) and the resulting catalyst conjugated base (anion). Chiral BINOL-derived phosphoric acids are the most popular catalysts. A recent and impressive example is the catalytic asymmetric Fischer indolization reported by List[41] (Scheme 1.18).



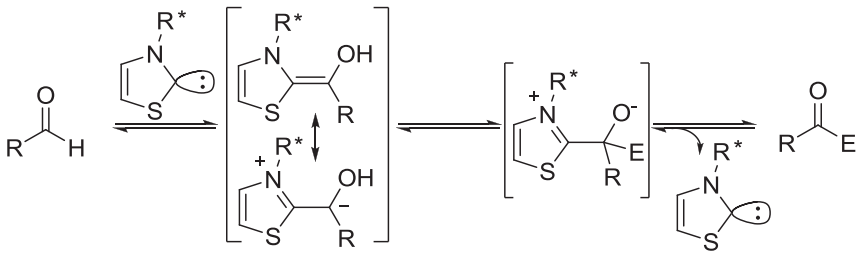
Scheme 1.18. Chiral phosphoric acid catalyzed Fisher indolization (List), 2011.

[41] S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc*. **2011**, *133*, 18534.

1.3. Covalent organocatalysis

Concurrently, a large number of organocatalytic reactions proceeds *via* covalent formation of a catalyst–substrate adduct to generate an activated complex. Representative examples of this type of catalysis are: i) amine-based reactions (*i.e*. aminocatalysis), in which amino acids, peptides, alkaloids and synthetic nitrogen-containing molecules are used as chiral catalysts, which be described in detail in subchapter 3; and ii) catalysis mediated by *N*-heterocyclic carbenes (NHCs).

In the latter case, after forming a covalent bond with an NHC, an aldehyde generates a nucleophilic intermediate (Scheme 1.19) which is able to attack an electrophilic species. The unique activation mode revealed by NHCs has created a growing interest within the area of organocatalysis due to their capacity to invert the classic reactivity of aldehydes, from being typically electrophilic to act as nucleophiles (*umpolung*).



Scheme 1.19. Nucleophilic catalysis mediated by NHCs.

2. Aminocatalysis.

The use of chiral amines as catalysts is a very relevant area within organocatalysis. The reversible formation of the activated intermediates, allows the possibility of using catalytic amounts of the amine. Moreover, the presence of covalent binding between the catalyst and the substrate usually provides high levels of stereoinduction.

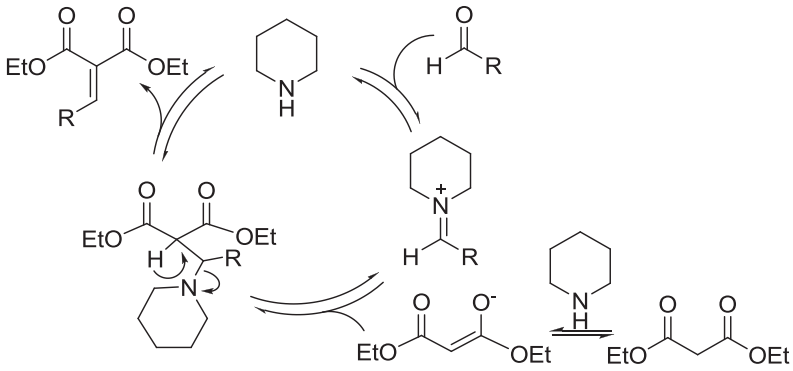
The development and the advances achieved in the area of aminocatalysis,[42] which comprises reactions catalyzed by secondary and primary amines predominantly *via* enamine and iminium ion intermediates (see Schemes 1.5 and 1.14) are presented in detail in this part. Enamine and iminium ion catalysis are two different reaction modes in organocatalysis. However, both are interconnected and based on the same origin. Enamine catalysis proceeds *via* iminium ion formation and almost always results in iminium ion formation. In an opposite but complementary way, iminium ion catalysis typically proceeds forming an enamine intermediate. The two catalytic intermediates are opposites, yet interdependent, and they consume and support each other, like the two fundamental principles ("Yin and Yang") of asymmetric aminocatalysis.[43]

2.1 History and origins of aminocatalysis.

Probably the first example of amine catalysis is the reaction of aldehydes or ketones with active methylene compounds in the presence of piperidine, known as the Knoevenagel condensation (Scheme 1.20).

Knoevenagel found that primary and secondary amines, as well as their salts, catalyze the aldol condensation of β-ketoesters or malonates with aldehydes or ketones,[44] realizing that the amines were truly catalytic.

[42] B. List, *Synlett* **2001**, 1675.
[43] B. List, *Chem. Commun*. **2006**, 819.
[44] a) E. Knoevenagel, Ber. Dtsch. Chem. Ges. **1896**, *29*, 172; b) E. Knoevenagel, Ber. Dtsch. Chem. Ges. **1898**, *31*, 738; c) E. Knoevenagel, Ber. Dtsch. Chem. Ges. **1898**, *31*, 2585; d) E. Knoevenagel, Ber. Dtsch. Chem. Ges. **1898**, *31*, 2596; for an excellent review, see e) L. F. Tietze, U. Beifuss in Comprehensive Organic Synthesis (Ed.: B. M. Trost), Pergamon, Oxford, 1991.



Scheme 1.20. Knoevenagel condensation, 1896.

In addition to inspiring bioorganic chemists, Knoevenagel's seminal discovery and mechanistic interpretation of his reaction over 100 years ago laid the historical foundation for the development of modern aminocatalysis. There is a direct connection between the seminal work of Knoevenagel and the studies of MacMillan and co-workers in 2000[45] and probably also those of Barbas III and List on amine catalysis.[46]

A long time passed between the discovery of the Knoevenagel reaction and the development of modern aminocatalysis. However, Knoevenagel's chemistry had a strong influence on other researchers. For example, in 1910 Dakin found that primary amino acids catalyze the Knoevenagel condensation.[47] Twenty years later, Kuhn and Hoffer made the important observation that secondary amines not only catalyze the Knoevenagel condensation but also the self- and cross-aldol condensations of aldehydes,[48] reactions which are still used on an industrial scale. In 1936, Kuhn et al. also found that carboxylic acid salts of amines catalyze the aldol condensation of

[45] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem.Soc*. **2000**, 122, 4243.
[46] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc*. **2000**, *122*, 2395; see also: b) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573.
[47] H. D. Dakin, *J. Biol. Chem.* **1910**, *7*, 49.
[48] R. Kuhn, M. Hoffer, *Ber. Dtsch. Chem. Ges*. **1930**, *63*, 2164.

aldehydes more effectively, and introduced piperidinium acetate as a particularly active catalyst for this reaction.[49] Interestingly, piperidinium acetate was shortly after also used by Langenbeck in the studies on the catalytic hydration of crotonaldehyde (as it will be shown later).[50] Langenbeck suggested a Knoevenagel-type covalent catalysis mechanism, and was probably the first chemist who dedicated an entire research program to study organocatalysts,[51] their mechanisms, and their relationship to enzyme action. He also introduced secondary amino acids, most notably sarcosine, as catalysts for aldolizations.[52]

Kuhn and Langenbeck did not formulate modern catalytic cycles yet; but how Knoevenagel, Kuhn, and Langenbeck were already aware of mechanistic details of their catalytic reactions, and how they used the iminium ion and the enamine activation modes is still very remarkable.

These studies likely encouraged Wieland and Miescher as well as Woodward *et al.* to investigate intramolecular aldol reactions of diketones and dialdehydes catalyzed by piperidinium acetate.[5354] These experiments were made in the context of the total syntheses of steroids and delivered methods that continue to be used today. In line with the ideas of Knoevenagel, Kuhn and Langenbeck, Woodward, Wieland, and Miescher believed that their aldolizations would proceed *via* enamine intermediates, which has subsequently been confirmed by the mechanistic studies carried out by Spencer *et al*. in 1965.[55]

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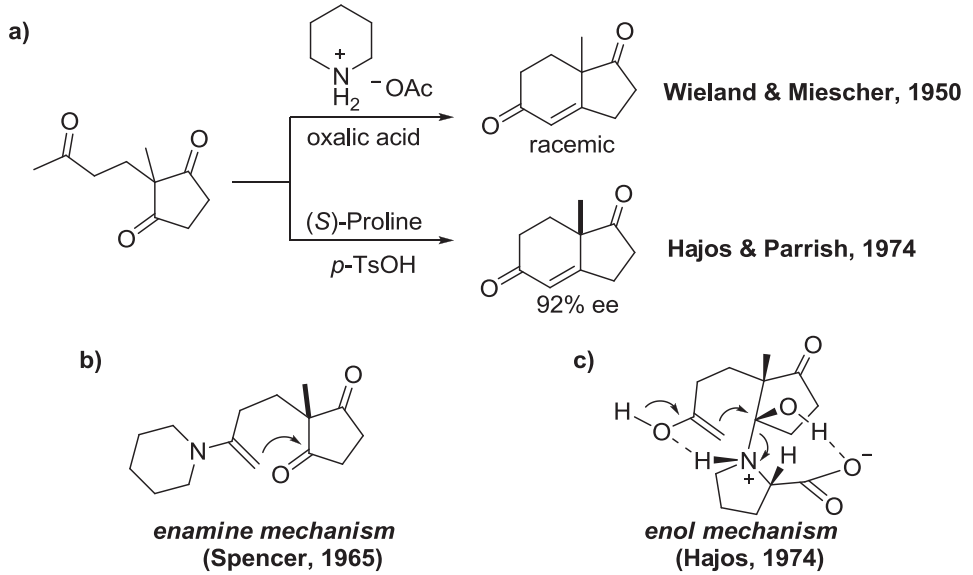
[49] R. Kuhn,W. Badst_bner, C. Grundmann, *Ber. Dtsch. Chem. Ges.***1936**, *69*, 98.
[50] W. Langenbeck, R. Sauerbier, *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 1540
[51] W. Langenbeck, *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten*, Springer, Berlin, **1935**.
[52] W. Langenbeck, G. Borth, *Ber. Dtsch. Chem. Ges*. **1942**, *75*, 951.
[53] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. M. MacLamore, *J. Am. Chem. Soc.* **1952**, *74*, 4223.
[54] P. Wieland, K. Miescher, *Helv. Chim. Acta* **1950**, *33*, 2215.
[55] T. A. Spencer, H. S. Neel, T. W. Flechtner, R. A. Zayle, *Tetrahedron Lett*. **1965**, *6*, 3889.

2.2 Enamine catalysis

This background set the stage for the discovery of the first asymmetric amine-catalyzed aldolization—the proline-catalyzed intramolecular aldol reaction—by Hajos and Parrish and by Eder, Sauer, and Wiechert in the 1970s (Scheme 1.21, a).



Scheme 1.21. Intramolecular aldol reaction and proposed mechanisms.

The finding of the catalyst is clear: while piperidinium and pyrrolidinium salts were established as achiral catalysts for inter- and intramolecular aldolizations, such as those described by Wieland and Miescher,[54] and amino acids had already shown their potential,[47,52] proline was an obvious choice as an abundantly available and chiral secondary amino acid catalyst. It was the discovery of the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[16]

There are two remarkable features to be mentioned about this discovery. First, the Wiechert research group at Schering, in contrast to Knoevenagel more than 70 years earlier, neither discussed any mechanism nor realized or at least mentioned

that their process was an early example of asymmetric catalysis. Second, and more perplexing, is the rejection of an enamine mechanism by Hajos. Instead, a mechanism involving the reaction of a weakly nucleophilic enol with a weakly electrophilic and sterically hindered hemiaminal was proposed (Scheme 1.21, c). This is at least quite surprising considering the mechanistic studies mentioned above, particularly the piperidine-catalyzed enamine mechanism proposed by Spencer *et al.*[55] for the same reaction (Scheme 1.21, b).

It is worth mentioning that the study of the enol pathway in enamine catalysis was reopened recently in the mechanistic revision of the conjugated addition of aldehydes to nitroolefines catalyzed by tripeptides derivatives.[56] The ESI-MS screening of the reaction ruled out the enol mechanism.

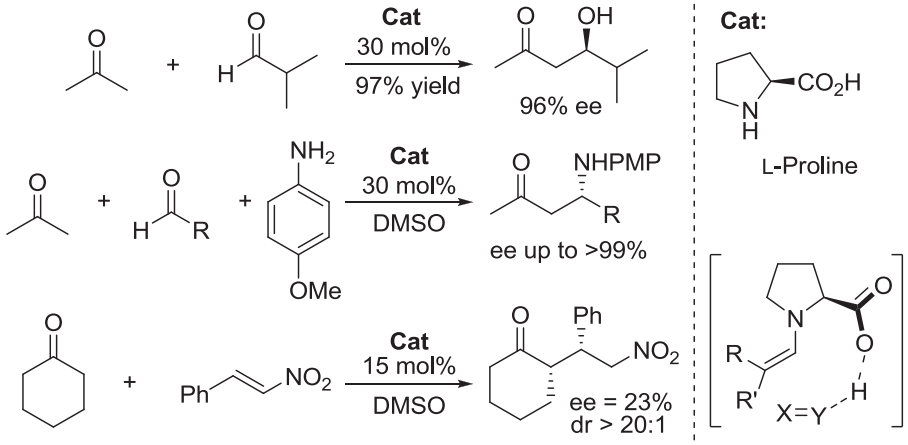
Real progress towards the generalization of aminocatalysis and a more complete mechanistic understanding of proline catalysis was not made during those years. Some possible reasons why proline catalysis and its underlying reactivity principles were not further explored are: first, the reaction was developed in industrial scenery, where the principles of a discovery are rarely fully explored; second, the suggested mechanism by Hajos was counterintuitive and could not easily be generalized such that new reactions and catalysts could be designed. Finally, the pioneering studies by Noyori, Knowles, and Sharpless as well as others on asymmetric transition-metal catalysis moved the attention of the organic chemists to this fascinating area of research for a few decades.

The studies on proline catalysis were reopened in 2000 by Barbas and List, stimulated by the disclosure of the aldolase catalytic antibodies by Lerner and Barbas. Realizing possible similarities between these aldolases and proline, it was Danishefsky who encouraged the successful exploration of the Hajos–Parrish–Eder–Sauer–

[56] F. Bächle, J. Duschmalé, C. Ebner, A. Pfaltz, H. Wennemers, *Angew. Chem. Int. Ed*. **2013**, *52*, 12619.

Wiechert reaction with antibody 38C2.[57] Later research by Barbas and Lerner also aimed at highlighting the power and scope of antibody catalysis in natural product synthesis.[58,59] These experiments also revealed certain limitations, however, which encouraged the researchers to investigate the use of small organic molecules as catalysts.

Lessons learnt from the aldolase antibodies, the Hajos-Parrish reaction and the discovery of metal complex catalyzed direct asymmetric aldol reactions,[60] led to the development of the first proline-catalyzed direct enantioselective intermolecular aldol reaction.[17] Moreover, List investigated the reactions of in situ generated imines and nitroolefins which led to the first proline-catalyzed asymmetric intermolecular Mannich and Michael reactions (Scheme 1.22).[61,62]

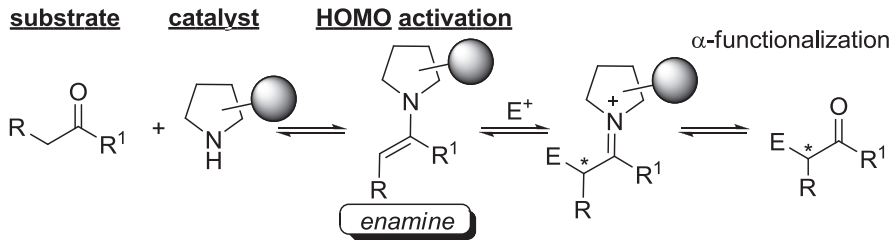


Scheme 1.19. Mannich and Michael reactions (List), 2000-2001.

[57] G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F.Barbas III, *J. Am. Chem. Soc*. **1997**, *119*, 8131.
[58] B. List, D. Shabat, C. F. Barbas III, R. A. Lerner, *Chem. Eur. J.* **1998**, *4*, 881.
[59] J. Turner, T. Bui, R. A. Lerner, C. F. Barbas III, B. List, *Chem. Eur. J*. **2000**, *6*, 2772.
[60] Y. M. Y. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1871.
[61] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336.
[62] B. List, P. Pojarliev, H. J. Martin, *Org. Lett*. **2001**, *3*, 2423.

Probably these experiments were the ones that encouraged the research community to explore and deeply study the enormous possibilities of the catalysis principle called "enamine catalysis". This concept has inspired several dozens of different reactions and literally hundreds of variations over the last decade, including C-C bond-forming reactions and α-functionalizations.[63]

The underlying activation concept of enamine catalysis is based on the reversible condensation of an amine catalyst with a simple aldehyde or ketone to form an iminium intermediate that on tautomerization generates a nucleophilic enamine species that can be subsequently trapped by an appropriate electrophile (Scheme 1.23).

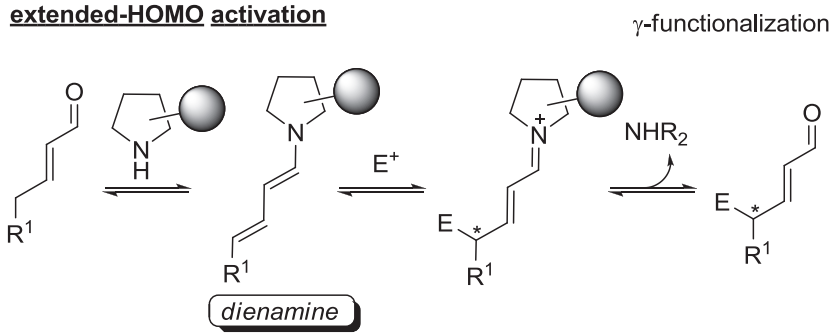


Scheme 1.23. Enamine activation concept.

Enamine catalysis involves the highest occupied molecular orbital (HOMO)-raising activation of carbons adjacent to a carbonyl moiety *via* formation of electron-rich amine-substituted olefins, which have enough π-electron density to participate in nucleophilic additions to a variety of carbon-, nitrogen-, oxygen-, sulphur-, and halogen-centred electrophiles. The chiral information present on the catalyst is responsible for the differentiation of the two faces of the enamine nucleophile, allowing the synthesis of enantioenriched compounds.

[63] a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; see also b) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev*. **2009**, *38*, 2178.

The enamine activation can be extended to its vinylogous version, as it was reported by Jørgensen and co-workers during the mechanistic studies of the *β*-functionalization of *α,β*-unsaturated aldehydes.[64] The formation of the dienamine occurs by deprotonation of the iminium ion at the *γ*-position (Scheme 1.24). This electron-rich dienamine intermediate possesses a nucleophilic character and thus is able to react with electrophiles. This concept can also be applied to more extended systems, as demonstrated by the reactions proceeding through trienamine intermediates.[65]



Scheme 1.24. Dienamine catalytic concept.

Another variant of the enamine activation is the SOMO catalysis, as presented previously. The radical species are generated by oxidation of the corresponding enamine intermediates, giving a dramatic change of their electronic properties, and enabling the attack of a somophile at the *α*-position.

Enamine catalysis has grown dramatically in the last years, allowing the synthesis of a variety of valuable chiral compounds, usually not accessible through other methodologies based on preformed enamines or enolates, illustrating the

[64] S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jørgensen, *J. Am. Chem. Soc*. **2006**, *128*, 12973.
[65] 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.

complementary nature of organocatalysis and metal based catalysis. Nowadays it finds widespread applications in a number of name reactions, including aldol, Mannich, Michael, and Diels-Alder reactions, as well as in a number of unprecedented processes that involve enantioselective α-carbonyl functionalization, such as selective α-alkylation of carbonyls,[66] a holy grail throughout the field of aminocatalysis.

2.3 Iminium ion catalysis

Iminium ion catalysis has his origin in Knoevenagel's chemistry, although the catalytic concept was not fully explored until the last decade. The idea that the reaction might proceed *via* iminium catalysis emerged slowly. Knoevenagel himself suggested a possible role for the aldehyde-derived imines or aminals in this reaction.[67] However, it is also known that the Knoevenagel-type reactions can be catalyzed by tertiary amines. Iminium mechanism was therefore one of the mechanistic possibilities. In 1931, Blanchard suggested that positive ions were involved in the catalysis of the Knoevenagel reaction with secondary amines.[68] Nowadays, the contribution of iminium catalysis to the Knoevenagel reaction is generally recognized.

The first reaction where iminium ions were postulated as active intermediates was the decarboxylation of β-ketocarboxylic acids. In 1907, Pollak reported that different proteins such as albumin as well as different amino acids and ammonium salts catalyzed these reactions (Scheme 1.25).[69]

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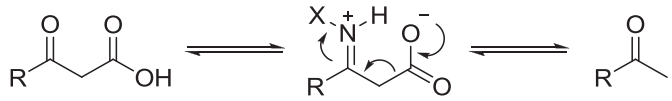
[66] For a recent example of α-alkylation, see: B. List, I. Coric, O. O. Grygorenko, P. S. J. Kaib, I.Komarov, A. Lee, M. Leutzsch, S. C. Pan, A. V. Tymtsunik, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2013**, doi: http://dx.doi.org/10.1002/anie.201306037

[67] Although Knoevenagel did not suggest specifically iminium intermediates, he nevertheless recognized that the condensation products between aldehydes and the amine catalysts might play a role in these reactions.

[68] K. C. Blanchard, D. L. Klein, J. MacDonald, *J. Am. Chem. Soc.* **1931**, *53*, 2809.

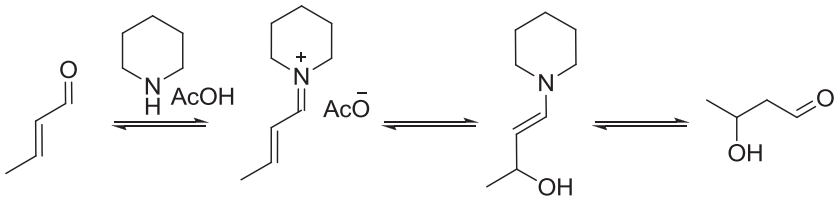
[69] E. Pollak, *Beitr. Chem. Physiol. Pathol. ("Hofmeisters Beitra¨ge"*) **1907**, *10*, 232.



Scheme 1.25. Iminium catalyzed β-decarboxylation (Pollak), 1907.

In 1934, Pedersen suggested that the amine-catalyzed decarboxylation of β-ketoacids takes place *via* a mechanism that involves iminium activation.[70]

The first iminium catalyzed conjugate addition was discovered by Langebeck in 1937 (Scheme 1.26). A 1,4-addition of water to crotonaldehyde was catalyzed by piperidinium acetate and proceeded via iminium intermediate.



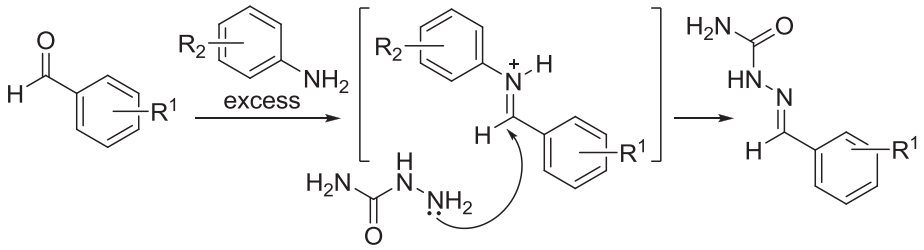
Scheme 1.26. Piperidine-catalyzed Michael addition (Langebeck), 1937.

Langenbeck noted that the aldol product is in equilibrium with the starting material. He also made a cautious suggestion that the reaction might proceed via enamine intermediates.

The discovery of the iminium-promoted transimination reaction by Cordes and Jencks in 1962 represents another important point in the history of iminium catalysis.[71] They described the aniline promoted semicarbazone (imine) formation from benzaldehyde that proceeds *via* transamination of the iminium ion formed between the starting material and the aniline[72] as illustrated in Scheme 1.27. They

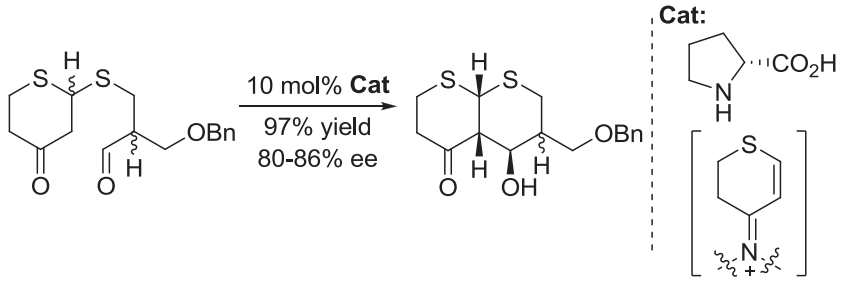
[70] K. J. Pedersen, *J. Phys. Chem.* **1934**, *38*, 559.
[71] E. H. Cordes, W. P. Jencks, *J. Am. Chem. Soc.* **1962**, *84*, 826.
[72] It is a non-catalytic process that requires high concentration of aniline in a strong acidic media

performed exhaustive kinetic experiments to confirm the existence of the iminium intermediate.



Scheme 1.27. Aniline catalysis of semicarbazone formation (Jencks), 1962.

In 1981, Woodward and co-workers[73] reported a D-proline-catalyzed retro-Michael reaction of erythromycin core, which was followed by an enantioselective Michael re-addition and subsequent aldol reaction, thus resulting in deracemization of the structure (Scheme 1.28). The authors proposed an iminium intermediate as a possible pathway for obtaining the enantioenriched compound.



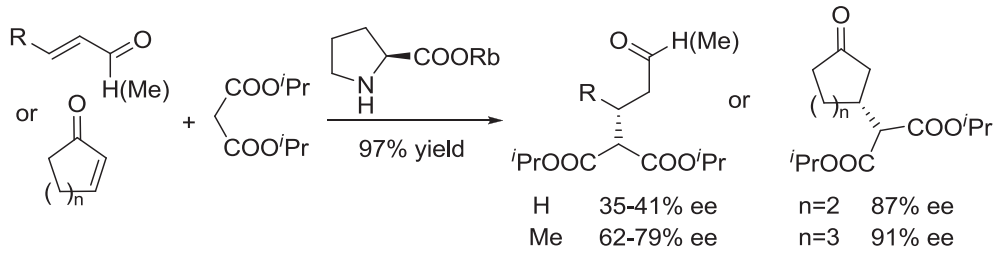
Scheme 1.28. D-Proline-catalyzed deracemization (Woodward), 1981.

The first asymmetric secondary amine-catalyzed Michael addition of malonates to α,β-unsaturated aldehydes was reported by Yamaguchi and co-workers[74]. In 1991

[73] R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3210.

[74] a) M. Yamaguchi, N. Yokota, T. Minami, *J. Chem. Soc., Chem. Commun.* **1991**, 1088.; b) M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem. Int. Ed.* **1993**, *32*, 1176.

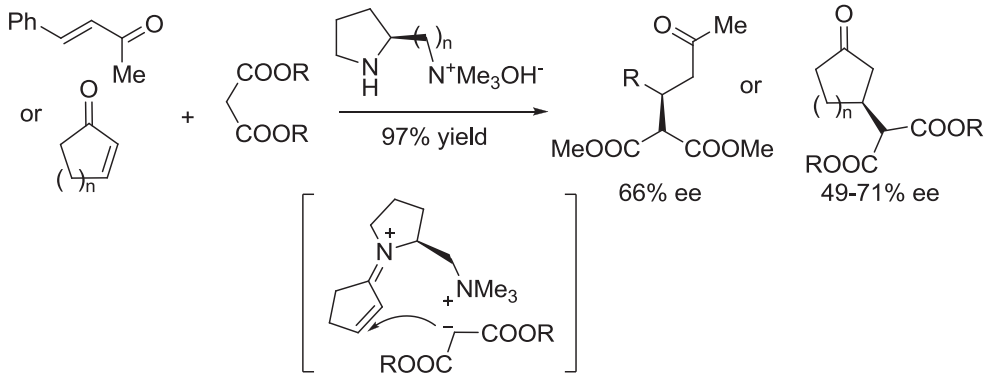
they found that lithium prolinate could effectively catalyze the reaction of dimethyl malonate and enals, but no enantioselectivities were reported. They proposed an activation model where the catalyst activates both the Michael donor and acceptor. In their later studies, rubidium prolinate was used as a more efficient catalyst for the addition of diisopropyl malonate to diverse cyclic and acyclic unsaturated ketones and aldehydes (Scheme 1.29).



Scheme 1.29. Asymmetric Michael addition of malonates to α,β-unsaturated carbonyl compounds (Yamaguchi), 1991-1993.

Literally, the first catalyst without any metal for the asymmetric Michael addition to α,β-unsaturated compounds was published by Kawara and Taguchi (Scheme 1.30)[75]. Depending on the structures of electrophiles and nucleophiles, low to moderate enantiomeric excesses were obtained. Interestingly, the opposite enantioselectivity was observed than that obtained by Yamaguchi. The authors attributed the observed stereochemistry to an interaction between the approaching nucleophile and the quaternary ammonium salt of the catalyst.

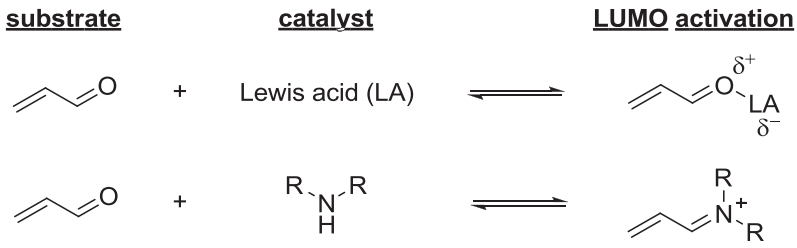
[75] A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805.



Scheme 1.30. Michael addition of malonates to α,β-unsaturated ketones (Taguchi), 1994.

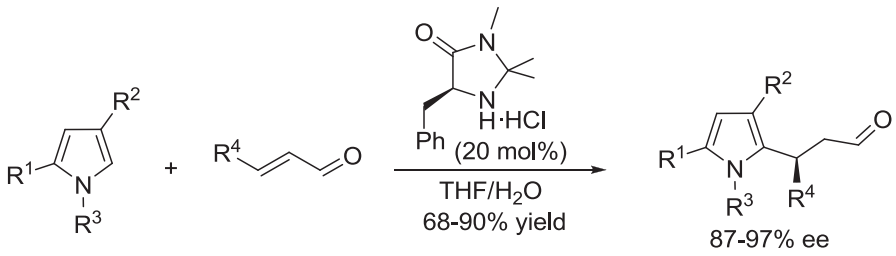
It is important to note that these researchers already suggested iminium ion activation as the catalytic principle. An inspiration from the proline-catalyzed aldolization can be envisioned in their work. Moreover, it also reflects an early interest on the underlying catalytic concepts and the connection between enamine and iminium catalysis.

Nevertheless, the rational development and application of this concept should be undoubtedly attributed to MacMillan; starting from his seminal publication on amine-catalyzed enantioselective Diels-Alder reaction reported in 2000 (see Scheme 1.14).[37] In this initial work MacMillan and co-workers propose a mechanistic postulate in which the reversible formation of iminium ions from α,β-unsaturated aldehydes and amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis (*i.e*. lowest unoccupied molecular orbital LUMO-lowering activation) (Scheme 1.31).



Scheme 1.31. Iminium ion activation concept.

Besides the Diels-Alder reaction, this mode of activation has been successfully applied to many other asymmetric transformations, such Michael additions, Friedel-Crafts alkylations[76] (Scheme 1.32), transfer hydrogenations and epoxidations.



Scheme 1.32. Organocatalytic Friedel-Crafts reaction (MacMillan), 2001.

As for enamine catalysis, this strategy has emerged as a very useful tool for the construction of C-C bonds in an enantioselective fashion, with the catalyst having the ability of providing high stereoselectivity to the process.

Since 2000 the field of iminium catalysis has expanded and now, numerous highly selective organocatalysts based on iminium activation are known and used in a wide range of interesting transformations. The reaction scope has also been expanded to include a range of different nucleophiles (C-, N-, O-, S-, P-). Furthermore, these reactions are often a part of cascade reactions, which lead to complex products in a one-pot sequence.

[76] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370.

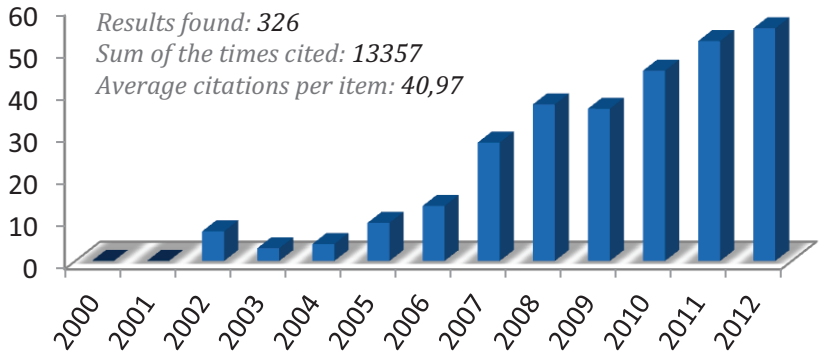
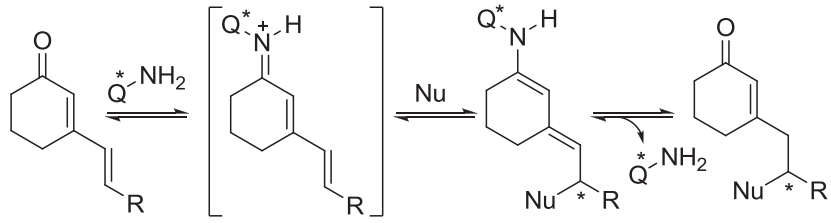


Figure 1.6. Evolution of publications on iminium ion organocatalysis.[77]

Nowadays, iminium ion catalysis is recognized as an efficient and reliable strategy for the stereoselective preparation of valuable chiral compounds. A large number of publications appear each year using this catalytic concept (Figure 1.6).

As in the case of enamine catalysis, the LUMO lowering concept can be extended to the vinylogous version. The condensation of a primary amine catalyst with a 2,4-dienone conjugated π-system allowed the first example of asymmetric aminocatalytic 1,6-addition, which afforded the desired products with high levels of stereocontrol and selectivity (Scheme 1.33).[78]



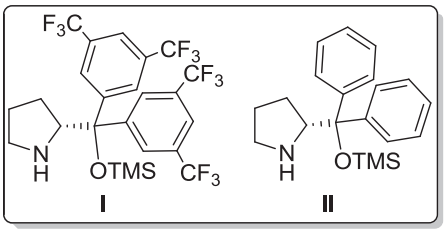
Scheme 1.33. Vinylogous iminium ion activation.

[77] Searching by topic in the database *Web of Science* using the term "iminium" and "*organocataly**". Data of the analysis: 1st September 2013.
[78] X. Xian, Y. Liu, P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 6439.

2.3.1 Most important catalysts and transformations in aminocatalysis.

After the historical overview about iminium ion catalysis, pointing out the most crucial facts which contributed to the development of this important field, something needs to be said about the organocatalysts and the transformations in which they were developed.

The most popular catalysts used nowadays in iminium and enamine catalysis are probably the diarylprolinol silyl ethers **I** and **II**. The evolution of the catalysts is detailed below and summarized in Figure 1.12, page 48.



However, in iminium ion catalysis the most general catalysts used at the early times were MacMillan's imidazolidinone-based catalysts.[79] Although they were applicable to a range of reactions, ultimate fine-tuning of the substituents was often required to reach high stereoselectivities. These catalysts were later also applied in SOMO catalysis and enamine catalysis, yet they had been designed mostly for iminium ion catalysis. Second and third-generation catalyst were also developed for the addition of indoles to enals and for the enantioselective transfer hydrogenation of enals respectively (Figure 1.7). Nowadays, these catalysts are still being widely used.

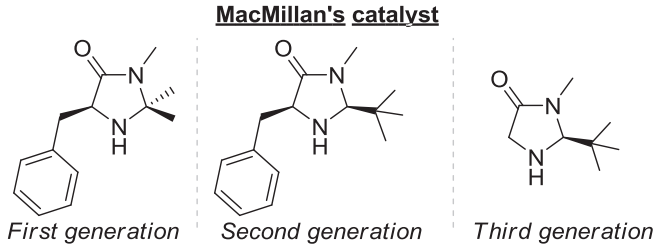


Figure 1.7. MacMillan imidazolidinone's catalysts.

[79] G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79.

The stereodiscrimination produced by the catalyst might be caused by two possible reasons. First, an stereodirecting substituent might be introduced to the catalyst, and in this case it assists the approach of the nucleophile to the same face by non-covalent interactions (Figure 1.8, a). Alternatively, the catalyst may possess a strategically introduced large substituent, disfavouring the approach of the nucleophile to one of the faces (Figure 1.8, b).

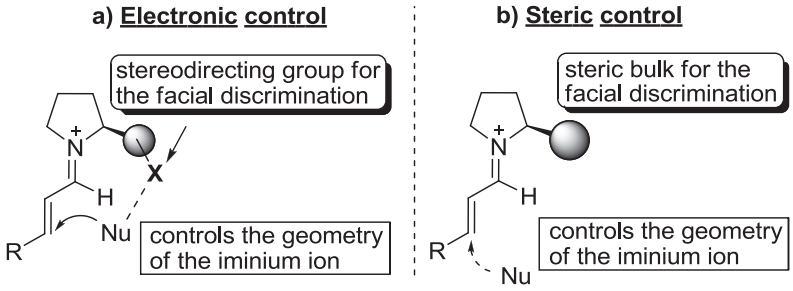


Figure 1.8. Stereo-directing paths

The design and evolution of the catalysts for iminium ion activation is intimately connected to enamine catalysis, as they are different facets of the same concept. The use of proline in enamine catalysis has been developed so extensively and with such impressive results that proline has been considered the "simplest enzyme" in nature.[80] Undoubtedly, the rational application of proline as catalyst contributed enormously to the development of aminocatalysis. However, to enlarge the scope of enamine activation it was necessary to design new families of chiral amine catalysts.

[80] M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904.

The success of proline in enamine catalysis is correlated with the hydrogen-bond-acceptor ability of the approaching electrophile. Other proline derived catalysts such as L-prolinamide, pyrrolidine sulfonamides[81] and pyrrolidine tetrazoles[82] with the same ability of H-bond interaction, were developed (Figure 1.9).

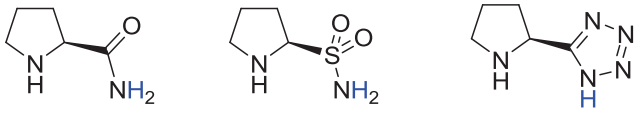


Figure 1.9. Catalysts with electrodirecting groups.

These catalysts presented some problems, such as poor stereoselectivity with substrates with low aptitude to form H-bonding interactions or low solubility. To overcome these issues and in order to find a general catalyst for enamine/iminium activation, the researchers began to focus on exploring different catalytic patterns that did not require a specific hydrogen-bonding interaction to confer high stereocontrol. In particular, chiral cyclic amines with bulky substituents were proposed for controlling the stereoselectivity by using the steric hindrance of the chiral architecture. This new tactic opened up new opportunities for the transformation of substrates which had not been suitable for proline catalysis.

[81] W. Wang, J. Wang, H. Li, *Org. Lett.*, **2004**, 6, 2817 and references cited therein.
[82] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, *3*, 558.

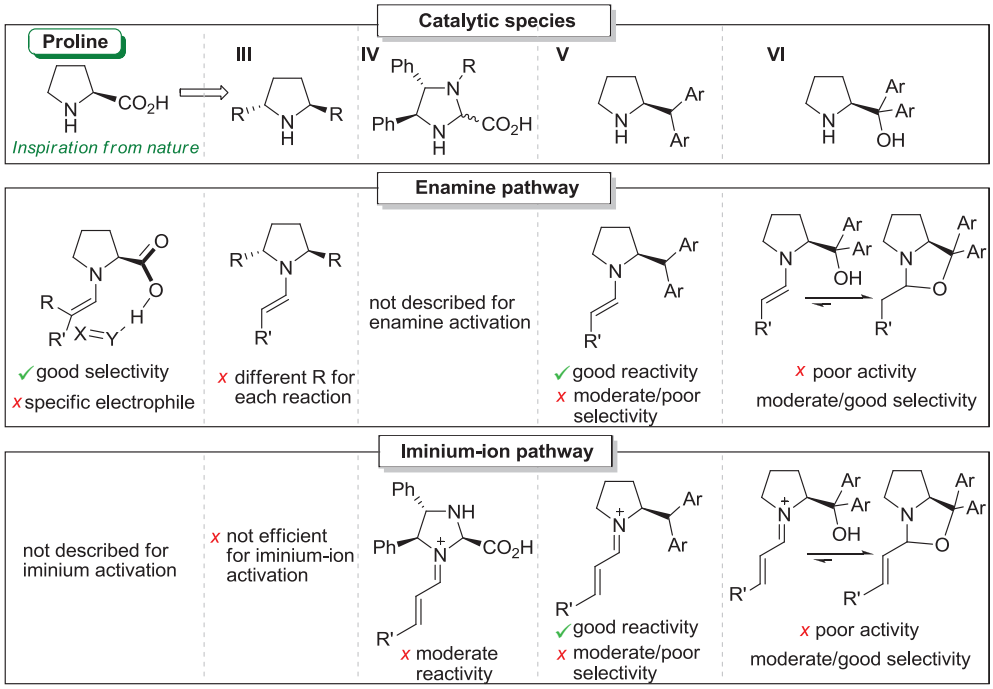


Figure 1.10. Secondary amines as catalyst

A new class of C_2-symmetric pyrrolidines **III** was developed (Figure 1.10).[83] The main disadvantage was the necessity of fine-tuning the R-substituent (R = Alkyl, aryl) for each individual reaction. Moreover, the facial differentiation in iminium-ion-mediated pathways was not very efficient. Diamine catalysts **IV** displayed good activity and some generality for enone substrates; however, prolonged reaction times sometimes were needed.[84]

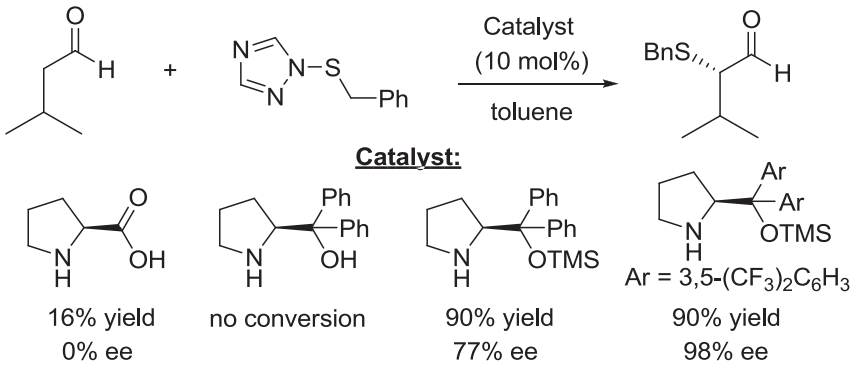
At that time, Jørgensen and co-workers started the search for a general organocatalyst, with the capacity to promote both enamine- and iminium-ion-

[83] N. Halland, A. Braunton, S. Bechmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790.
[84] N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 4955.

mediated reactions with good stereoselectivities. The lead structures were diarylmethylpyrrolidine **V** and diarylprolinol **VI**, which previously had been shown to exhibit catalytic acitivity.[85] The level of steric shielding provided by diarylmethylpyrrolidines was usually insufficient and provided only in rare cases high enantioselectivities, although good reactivity was observed for a range of different transformations.[86] Contrarily, the prolinol system often promoted good stereocontrol while lacking the ability to achieve sufficient catalyst turnover. The formation of a "parasitic" oxazolidine species was rationalized as the main reason of catalyst inhibition.[87] In order to circumvent this inhibitory pathway, a silyl-protected version of the diarylprolinol catalyst was designed and synthesized (see figure 1.11).[88] Gratifyingly, this turned out to be the final adjustment required to furnish a sterically demanding, yet highly active and general organocatalyst.[89]

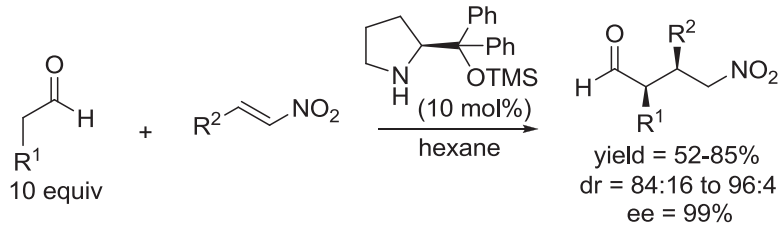
The TMS-protected prolinol catalyst **I** was initially developed for the asymmetric α-sulfenylation of aldehydes *via* enamine activation (Scheme 1.34).[88] In the model reaction, L-Proline and other secondary amine catalysts proved to be unreactive and/or nonselective. With catalyst **II** (developed independently by Hayashi and Jorgensen's groups), a significant increase in both reactivity and selectivity was observed (90% yield, 77% ee). Further catalyst modification to the more bulky aryl-groups of **I** afforded a remarkable increase in selectivity (90% yield, 98% ee).

[85] a) T. Bui, C. F. Barbas III, *Tetrahedron Lett*. **2000**, *41*, 6951; b) B. Jiang, Y. Feng, J. Zheng, *Tetrahedron Lett*. **2000**, *41*, 10281.
[86] K. Juhl, K. A. Jørgensen, *Angew. Chem., Int. Ed*. **2003**, *42*, 1498.
[87] J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.
[88] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
[89] For general reviews on the use of silyldiarylprolinol ethers as catalysts see: a) A. Mielgo and C. Palomo, *Chem.–Asian J.* **2008**, *3*, 922; b) L.-W. Xu, L. Li and Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352*, 243.



Scheme 1.34. α-sulfenylation of aldehydes (Jørgensen), 2005.

Almost simultaneously, the first α-C-C-bond forming reaction implementing the diphenylprolinol ether system was demonstrated by Hayashi *et al.* in the Michael addition of aldehydes to nitroalkenes (Scheme 1.35).[90] With various aliphatic aldehydes, the reaction was demonstrated for a series of nitroolefins with excellent stereocontrol both in terms of enantio- and diastereoselectivity.



Scheme 1.35. Michael addition to nitroalkenes (Hayashi), 2005.

Excellent face-differentiation and enantiocontrol (Figure 1.11, right) are provided by the bulky side-chain of the catalyst, forcing the reacting electrophile / nucleophile to approach from the least sterically hindered side of the catalyst-bound intermediate (enamine / iminium ion). At the same time the enamine or iminium ion geometry is fixed as consequence of the non bonding interaction between the bulky substituent

[90] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

on the pyrrolidine ring and the reactive carbon (E-*anti* geometry of the enamine or iminium ion, Figure 1.11, middle). From a library of synthesized diarylprolinol silyl ethers (TMS = trimethylsilyl), two of them, **I** (Ar =3,5-$(CF_3)_2C_6H_3$) and **II** (Ar = Ph), proved to be the most successful catalysts (Figure 1.11, left).[91]

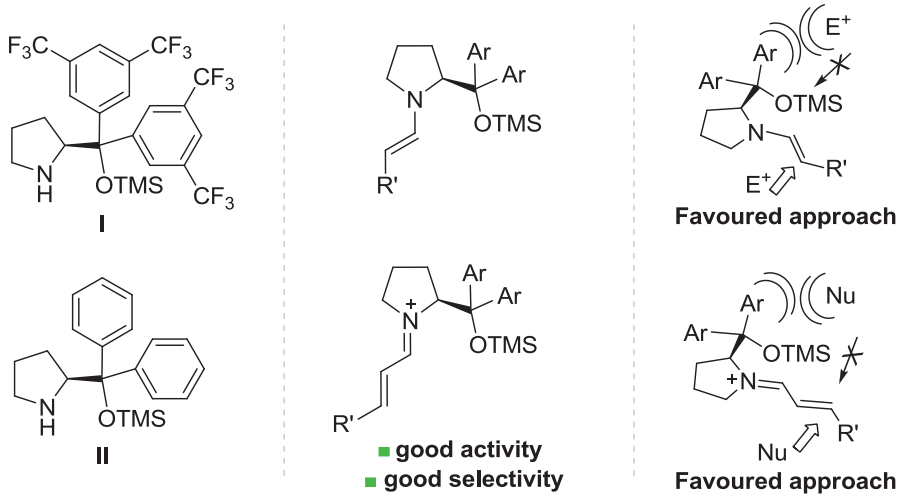


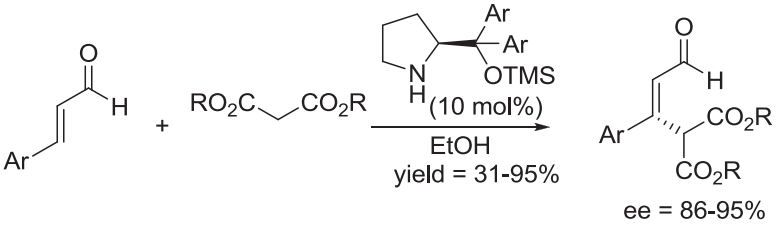
Figure 1.11. Silyl prolinol ether catalysts and modes for stereoinduction.

Another remarkable feature of these catalytic species is their ability to direct the addition in the conjugated position. A main challenge often encountered in conjugate additions to α,β-unsaturated aldehydes is in fact related to the possibility of 1,2-addition to the carbonyl group of the starting enal, which is especially pronounced in the case of hard nucleophiles. Among the multitude of aminocatalysts capable of iminium ion formation, the diarylprolinol silyl ethers possess a great ability of enabling chemoselective 1,4-additions even when hard nucleophiles are employed. Furthermore, high enantioselectivities arising from the abovementioned shielding effect of catalyst **I** and **II** are observed in most of the cases. As a result, the number of

[91] K. L. Jensen, G. V. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248.

publications in this field describing the use of catalysts **I** and **II** has increased dramatically within the last years.

The first application of diarylprolinol silyl ethers as catalysts in iminium ion activation was made in the context of the Michael addition of heteronucleophiles[92] to α,β-unsaturated aldehydes and afterwards was extended to carbon centered nucleophiles (Scheme 1.36).[93]



Scheme 1.36. Michael addition to enals (Jørgensen), 2006.

In Figure 1.12 is represented the evolution of the catalyst used in aminocatalysis, from the amino acid proline until the modified silyl prolinol derived catalysts. In the figure are also depicted the transformations and the years in which these catalysts were employed for the first time.

[92] a) M. Marigo, J. FranzLn, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; b) W. Zhuang, M. Marigo, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 3883.
[93] S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2006**, *45*, 4305.

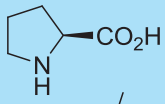
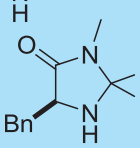
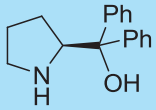
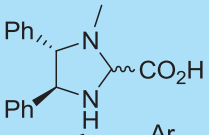
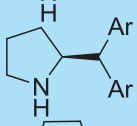
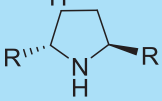
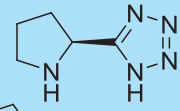
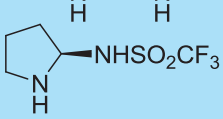
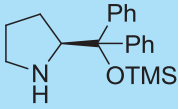
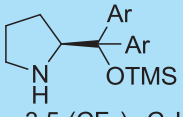
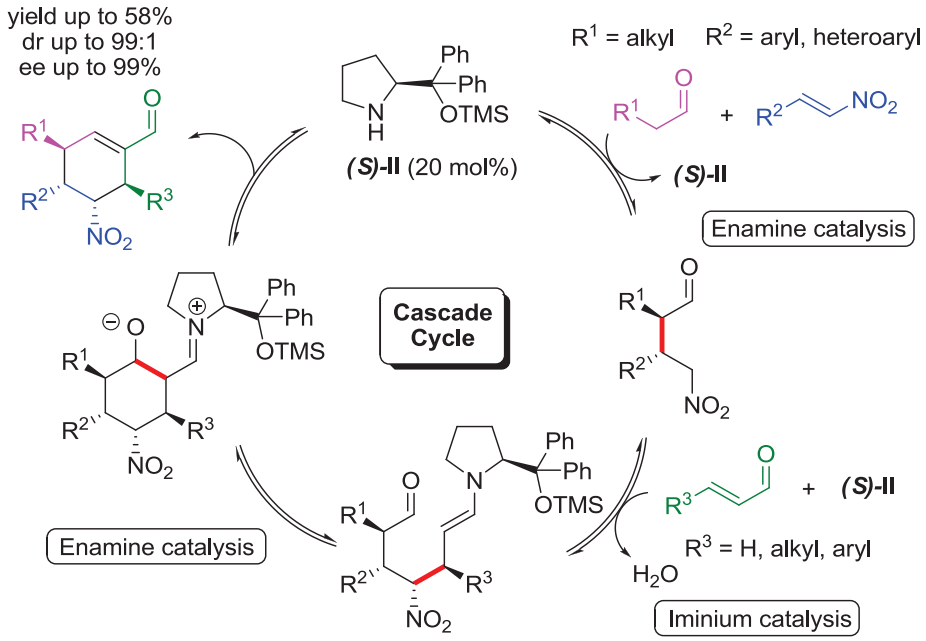
Year	Catalyst	Activation mode	Author	Reaction
2000		Enamine	List, Barbas III	Aldol
2000		Iminium ion	MacMillan	Diels-Alder
2000		Enamine	Barbas III	Robinson annulation
2003		Iminium ion	Jørgensen	Conjugated addition
2003		Enamine	Jørgensen	Michael addition
2004		Enamine	Jørgensen	α-Chlorination
2004		Enamine	Ley	Michael
2004		Enamine	Wang	Aminoxilation
2005		Enamine	Jørgensen-Hayashi	α-Functionalization/ Michael addition
2005		Enamine	Jørgensen	α-Sulfenylation
2005	Ar = 3,5-$(CF_3)_2$-C_6H_4	Iminium ion	Jørgensen	Epoxidation

Figure 1.12. Evolution of the catalysts used in iminium/enamine catalysis

As commented in the introduction of aminocatalysis, enamine and iminium ion concepts are interconnected. Combining the two catalytic principles is obviously an attractive goal, for the generation of molecular complexity in a simple one flask operation. The versatility of the diarylprolinol silyl ethers has been also demonstrated in this type of multicomponent or tandem/ domino processe[94] in which enamine and iminium ion activation are combined to form several C-C or C-heteroatom bonds to obtain highly functionalized compounds. In this sense, Scheme 1.37 represents the first triple cascade process published,[95]a brilliant example of formation of a cyclohexene with four stereocentres in a one-pot process.[96]

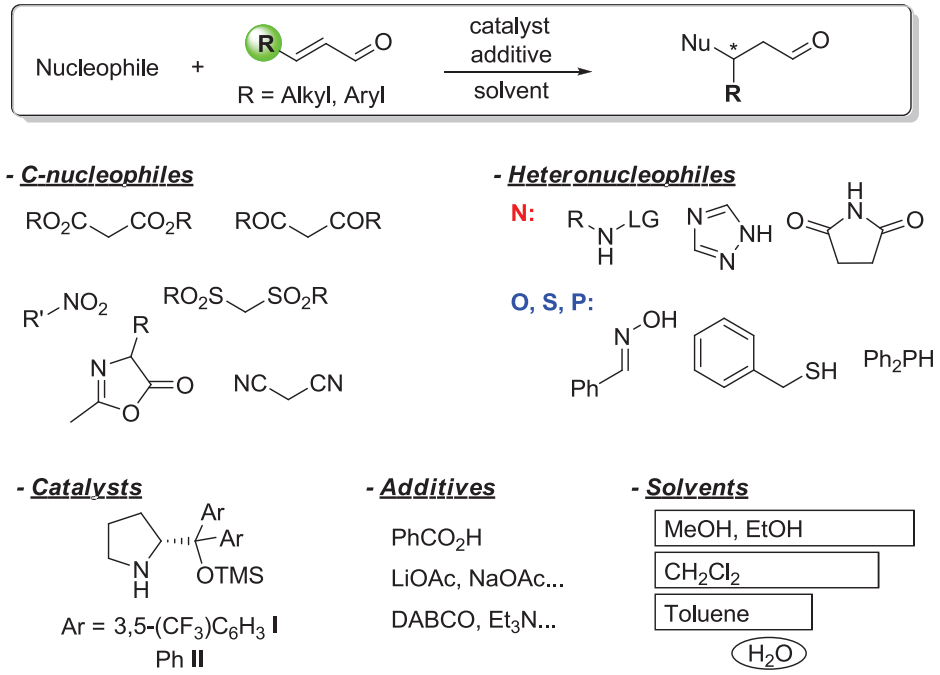


Scheme 1.37. Triple organocascade enamine / iminium / enamine.

[94]L.F. Tietze, G. Brasche. K. M. Gerike, *Domino Reactions in Organic Synthesis*, Wiley-VCH, 2**006**.
[95] D. E. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature*, **2006**, *441*, 861.
[96] a) D. E. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed*. **2007**, *46*, 1570. b) A. Dondoni, A. Massi, *Ang. Chem. Int. Ed*. **2008**, *47*, 4638. c) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Ang. Chem. Int. Ed*. **2008**, *47*, 6138.

2.3.2. General remarks on iminium catalyzed Michael additions

To be activated as an iminium ion for organocatalytic Michael additions, the electrophilic partner must be an α,β-unsaturated carbonyl compound (aldehyde or ketone). The nucleophile can be centred at a carbon atom or heteroatom (H, N, O, S, Si, Se, P). The great potential of this reaction has been demonstrated in a large number of publications.



Scheme 1.38. General scheme for iminium catalyzed Michael additions.

A variety of carbon and hetero-nucleophiles has been studied in the amine catalyzed conjugate addition to α,β-unsaturated aldehydes, some of them are represented in Scheme 1.38.[97] For the carbon centred nucleophiles, with exception of

[97] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007,** *107*, 5416.

the nitro derivatives, a common feature in the structure is the presence of two EWG groups directly bonded to the reactive centre, to ensure sufficient acidity. It was postulated that there is a pKa barrier of 16-17 for the pro-nucleophiles to intervene in the iminium ion catalyzed Michael additions.[98] This requirement limits the range of nucleophiles which can be employed in organocatalytic Michael additions.

The catalysts and reaction conditions can be roughly summarized as follows:

i) Although MacMillan's imidazolidinones were the only catalysts of choice for iminium catalysis in the beginning, silyl prolinol ether derivatives have gained increasing attention in these reactions. In particular, derivatives **I** and **II** are the most widespread catalysts[99] followed by other derivatives with bulkier silyl groups (TES; TBS) and/ or with different substitution at the aromatic rings.

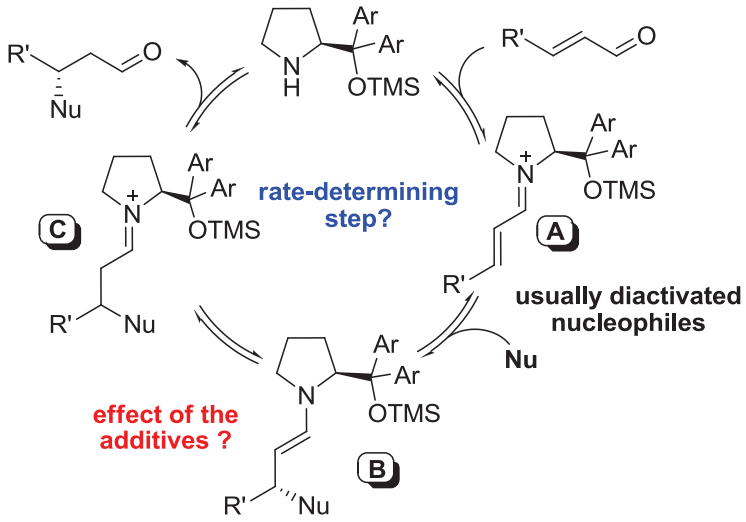
ii) Even if acidic additives have often been used, presumably to promote the formation of the reactive iminium ion, in the last few years there appeared in the literature a number of publications describing the use of bases as additive. The role of these additives is still not well established.

iii) The most common solvents are MeOH and EtOH followed by CH_2Cl_2 and toluene (H_2O is used in many cases as a co-solvent).

Despite many publications dealing with iminium ion catalyzed Michael additions, the real mechanism of these transformations has not been studied in detail. The generally accepted catalytic cycle starts with the formation of the iminium ion intermediate **A** from aldehyde and catalyst (Scheme 1.39). The reactivity of the iminium ion intermediates can be explained by a lower energy of the LUMO when compared to the corresponding unsaturated carbonyl compound. Iminium ions are ambident electrophiles, but, in analogy to the carbonyl compound, the largest coefficient of the LUMO is at the 4-position, which is then attacked by the

[98] D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem., Int. Ed*. **2008**, *47*, 4588.
[99] Shearched in Scifinder.

nucleophile. The enamine intermediate **B** is protonated before being hydrolyzed to the final product with concomitant regeneration of the catalyst.



Scheme 1.39. Catalytic cycle of Michael additions *via* iminium activation.

However, there are not systematic studies in the literature regarding the effect of the parameters (additive, solvent, etc…) on the reactivity and enantioselectivity thus making difficult the rationalization of their role. A literature examination is not enough to elucidate the best conditions that will succeed in each case.

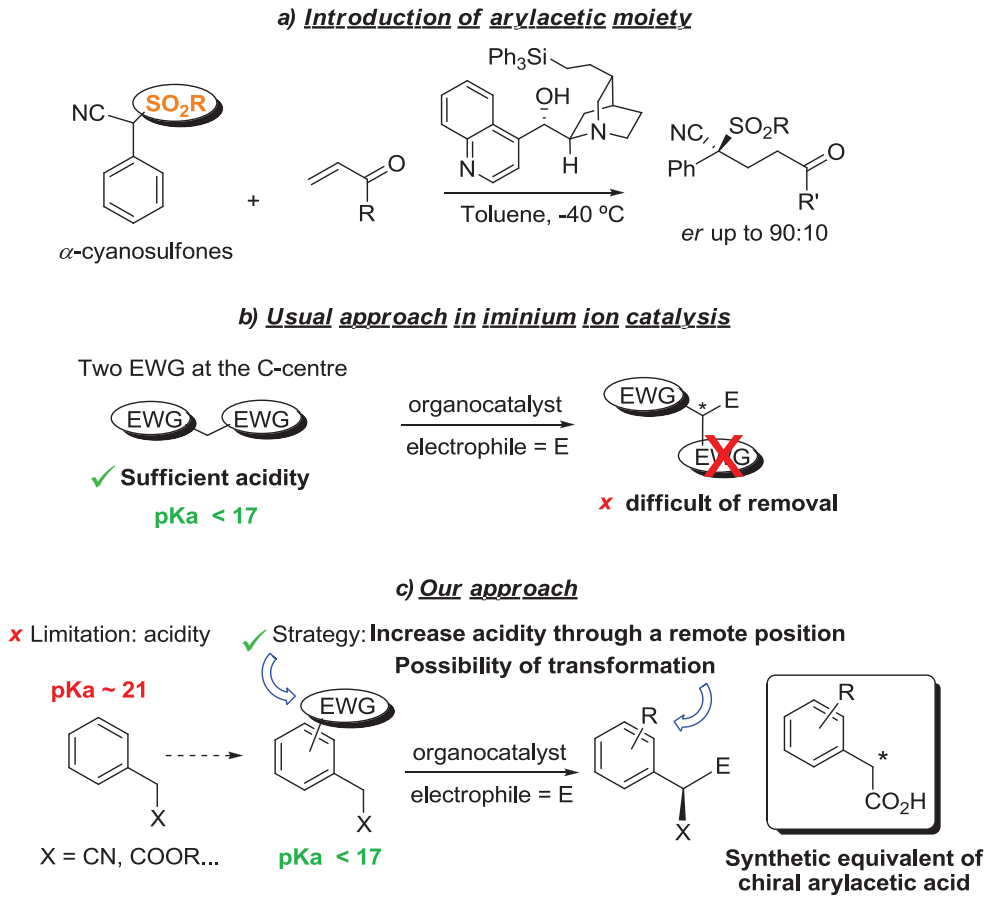
3. Research objectives and Thesis organization

In spite of the great potential of the iminium ion catalyzed Michael addition, highlighted in a large number of publications, as shown previously (see figure 1.7), there is still a considerable limitation regarding the structure of the pro-nucleophiles that can be successfully employed.

In the context of the study of new type of pro-nucleophiles for the iminium ion catalyzed Michael addition, and with the aim of expanding the scope of carbon nucleophiles, we focused our interest on the use of α-aryl acetic derivatives nucleophiles, as they are very attractive substructures. The arylacetic substructure is an important core in organic synthesis for the construction of biologically and synthetically interesting intermediates. The use of the arylacetic surrogate in organocatalytic 1,4-additions is a challenge due to the low acidity of the benzylic protons (pKa ~ 21-23).

The arylacetic moiety can be effectively introduced as nucleophile with the presence of an electron-withdrawing group (EWG) at the α-position. In particular is well known that the sulfonyl moiety can be successfully used as an activating group, increasing the acidity of the protons at its α-position and thus making possible the participation of these derivatives in organocatalytic processes. Moreover, the sulfonyl group is interesting in medicinal chemistry since it is considered as mimic of the carbonyl moiety in the transition state. In this context our research group showed that α-aryl cyano-sulfones can behave as competent nucleophiles in organocatalytic processes mediated by a chiral base (Scheme 1.40, a).[100] However, in that case the elimination of the sulfonyl group would have led to product racemisation.

[100] M. B. Cid, J. López-Cantarero, S. Duce, J. L. García Ruano, *J. Org. Chem.* **2009***, 74,* 431.



Scheme 1.40. Development of equivalents of chiral aryl acetic acids.

As in that case, with the exception of nitro derivatives, the carbon-centred pro-nucleophilic species require in fact the presence of two geminal electron-withdrawing groups, as in malonates for instance, to be sufficiently acidic for being able to react in the organocatalytic process.[101,102] As the second group is usually not desired in the

[101] F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1991**, *56*, 4218.

final product, it should be removed once it has exerted its activating function. Besides complicating the whole process, this produces epimerization, making very challenging the stereoselective formation of compounds bearing stereogenic centres at the nucleophilic carbon (Scheme 1.40, b).

Inspired by the antecedent of our group, we envisioned that the corresponding substrates with the sulfonyl or other activating group in a remote position, 'arylogous' of the α-cyano sulfones, could be applied in asymmetric organocatalytic transformations. In the previous case the pro-nucleophiles were used in conjugated additions using Brønsted base catalysis, while in our case we have focused in iminium ion catalysis, although other activation pathways can be employed as well.

Our strategy consists of the incorporation of a EWG group at the aromatic ring, which confers enough acidity to the benzylic protons to intervene in the organocatalytic process. We reasoned that the incorporation of an appropriate electron-withdrawing group to an aromatic ring could increase the acidity of the benzylic protons, allowing the use of any arylacetic acid derivative in organocatalytic processes (Scheme 1.40, c). This stands in contrast with the usual approach which requires the presence of two EWG directly bonded to the reactive centre. Among all the possible EWG groups we considered, like sulfonyl, cyano or trifluoromethyl groups, the one presenting more advantages was certainly the nitro group. Many nitrophenyl acetic acid derivatives are cheap and commercially available (Figure 1.13). Moreover, the nitro group can be transformed into a broad range of different functionalities *via* diazonium salts after reduction to the amine.

[102] For examples of non prochiral monofunctionalyzed enolates see: a) A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. Pérez Herrera, V. Sgarzani, *Adv. Synth. Catal.* **2007**, *349*, 1037. b) J. Lubkoll, H. Wennemers, *Angew. Chem., Int. Ed*. **2007**, *46*, 6841.

With this aim we established the general objectives of the present work. The thesis will be divided in two different parts:

➢ ***Chapter II*** will be focused on the synthetic aspects of the methodology. We have study the behaviour of functional group of different nature at the benzylic position, being the main studied nucleophiles: 1) nitrophenylacetonitriles, 2) nitrophenylacetone and 3) nitrophenyl esters and thioesters. In each case we have analyzed the viability of the reaction and demonstrated the versatility of the methodology by synthesizing different optically pure molecules.

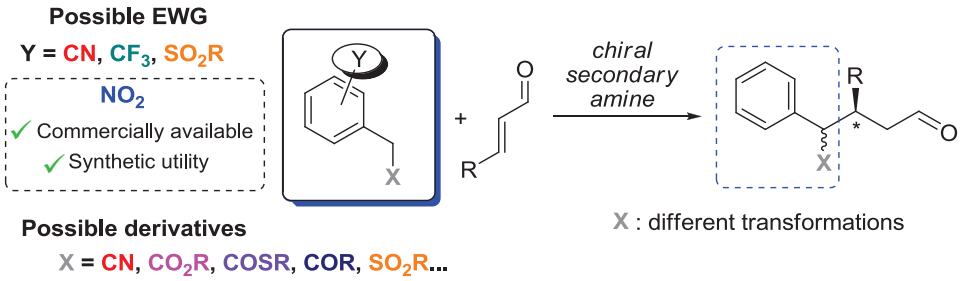


Figure 1.13. Structures of the possible nucleophiles

➢ During the research carried out in chapter II we have paid special attention to some unknown mechanistic aspects. Analysis of the effect of additives, the solvent, catalysts, acidity of the nucleophile on the reactivity and enantioselectivity of the process; as well as the study of the different behaviour of aromatic and aliphatic enals, and some kinetic and theoretical studies are collected in ***Chapter III***.

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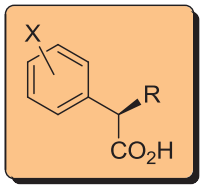
Chapter II

Arylacetic acid derivatives: a new type of nucleophile in iminium ion catalyzed Michael additions

1. Introduction



α-Arylated carbonyl compounds are commonly occurring motifs in biologically relevant molecules and therefore, they are of high interest to the pharmaceutical industry. In particular, enantioenriched α-aryl carboxilic acids that bear a tertiary α stereocenter, including arylpropionic acids, serve as important therapeutics[1] as well as useful intermediates in organic synthesis. For example, this structural feature is present in the non steroidal anti-inflammatory drugs, such as ibuprofen.

Metal catalyzed α-arylation of enolates has a broad application in organic synthesis as an efficient strategy to form C-C bonds.[2] However, the development of enantioselective methods for the formation of tertiary α-aryl carbonyl compounds is still a challenge, presumably due to the problems of product racemization under the necessary basic conditions. There are alternative solutions described in the literature to circumvent this problem. For example the metal catalyzed cross coupling of α-halo carbonyls with aryl-organometallic reagents to afford the α-aryl carbonyls in high enantioselectivity,[3] developed by Fu and co-workers. Another efficient and elegant strategy is the α-arylation of *N*-acyloxazolidinones with diaryliodonium salts published by Gaunt (Scheme 2.1).[4]

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[1] D. Lednicer, L. A. Mitscher, The Organic Chemistry of Drug Synthesis; John Wiley: New York 980, vol. 2, pp 63-84.

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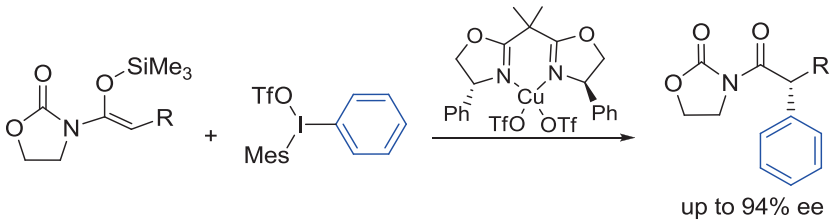
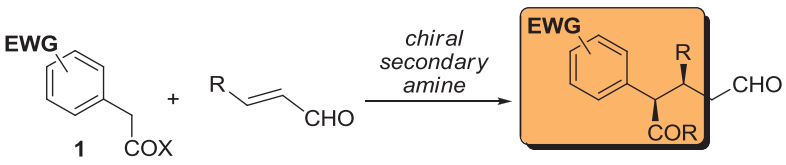


Scheme 2.1. α-arylation of *N*-acyloxazolidinones with diaryliodonium salts.

As enantioselective organocatalysis involving iminium ion activation[5] provides an excellent strategy for the incorporation of nucleophiles at the β position of α,β-unsaturated aldehydes, we planned to exploit this catalytic manifold in combination with synthetic equivalents of 2-phenylacetic acids as nucleophiles (**1**) for the preparation of enantiomerically enriched highly functionalized 2-phenylacetic acids (Scheme 2.2). The direct use of these derivatives is a challenge due to their low acidity. As described in the previous chapter, we envisioned that the introduction of the nitro as an activating group at the aromatic ring, based in our antecedents using the α-cyanosulfones, could overcome this issue.

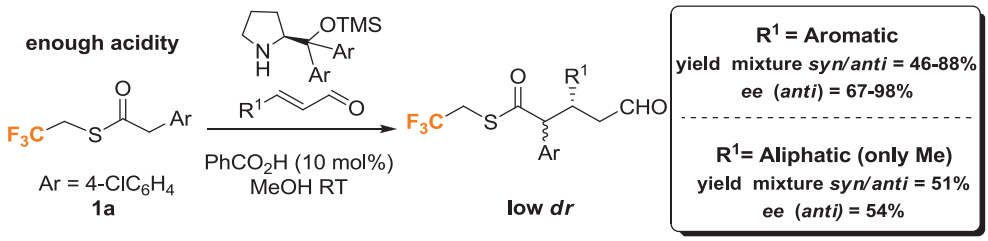


Scheme 2.2. Enantioselective Michael addition *via* imminium activation. An approach to substituted arylacetic derivatives.

Before going to the description of our work, it must be mentioned that while our studies were already in progress, appeared in the literature one example of the use of a pro-chiral arylacetic derivative as nucleophile in iminum ion catalyzed Michael addition, developed by Barbas III and co-workers. This work dealt with the reaction of

[5]For a recent review on organocatalytic asymmetric conjugate reactions see: J. L. Vicario, E. Reyes, D. Badia and L. Carrillo, in Catalytic asymmetric conjugate reactions, ed. A. Cordova, Wiley-VCH, Weinheim, Germany, **2010**, ch. 6, pp. 219-293.

trifluoroethyl thioesters derived from arylacetic acids with α,β-unsaturated aldehydes *via* iminium ion activation [6] (Scheme 2.3).



Scheme 2.3. Organocatalytic Michael addition of trifluoroethyl thioesters acting as monofunctionalyzed nucleophiles.

The electron-withdrawing nature of the trifluoroethyl substituent present in their derivatives conferred enough acidity to the benzylic protons to allow their reactions with aromatic α,β-unsaturated aldehydes. Among the aryl derivatives tested, the one affording better results was the Cl at *para* position **1a**.

Trans-cinammaldehyde and related aromatic enals presented high reactivity towards the desired products with excellent enantioselectivities. However, for the only aliphatic enal used, crotonaldehyde, the reactivity and enantioselectivity decreased dramatically. In both cases, a low diastereoselectivity was observed and the enantiomeric excess was determined only for one of the two diastereomers of each pair.

As a drawback from this methodology we can mention the necessity of the preparation of each derivative **1**, being the precursor trifluoroethyl thiol extremely expensive. Even if is not strictly a precedent in the sense that we did not based our research on this work it must be mentioned now as it was published before our results.

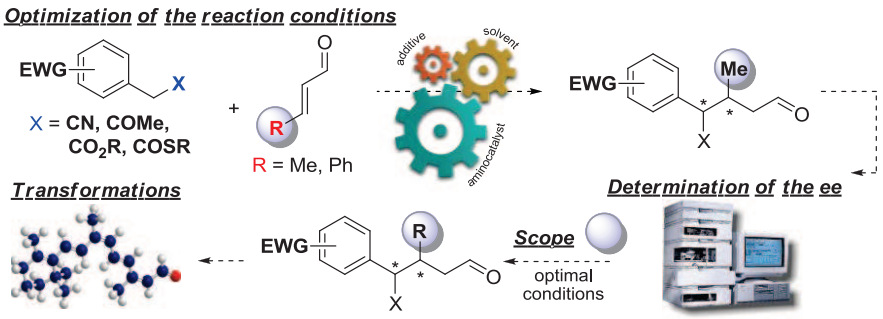
[6] D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem., Int. Ed*. **2008**, *47*, 4588.

2. Results and discussion

Having established the main objectives and commented the antecedents and their limitation, we will follow with the presentation and the discussion of the most relevant results obtained in our research. In this chapter we will consider the synthetic achievements of our methodology. Besides the application in the construction of interesting molecules, the use of arylacetic derivatives will reveal many unsolved questions in the iminium ion catalyzed Michael additions that will be briefly introduced here and discussed in detail in the next chapter.

We have studied mainly four nucleophiles (**X = CN, COMe, CO_2R, COSR**) that will be treated separately (Scheme 2.4) following the plan showed below:

- ❖ Study of the viability of the reaction.
- ❖ Establishment of a good method to determine the enantiomeric excesses of the products.
- ❖ Optimization of the reaction conditions analyzing the effect of the different parameters (catalyst, additive, solvent).
- ❖ Extension of the optimized reaction conditions to a series of α,β-unsaturated aldehydes to evaluate the scope of the reaction.
- ❖ Determination of the absolute configuration
- ❖ Development of some useful transformations to demonstrate the synthetic versatility of the methodology.



Scheme 2.4.Working plan

2.1 Arylacetonitriles as nucleophiles in organocatalytic 1,4-additions:

The nitro group at *para* (compound **1b**) and *ortho* (compound **1b'**) position has been chosen as EWG group, in order to achieve the highest efficiency of its activating influence. Compund **1b''** with the nitro group in *meta* position was also tested.[7] The reported nucleophilicity of compound **1b** is similar to those of cyanoesters,[8] which have been widely used in organocatalysis.[9] Moreover, compounds **1b**, **1b'** and **1b''** are cheap and commercially available and have demonstrated a high synthetic usefulness in other type of non-asymmetric processes.[10]

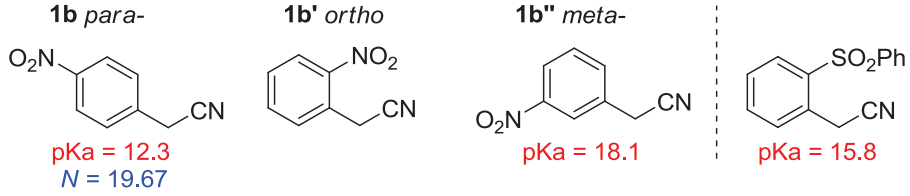


Figure 2.1. Aryl acetontriles tested.

It is worth mentioning that in a first approximation we started the study of the derivatives with the phenyl sulfonyl at the *ortho* position (Figure 2.1, right). However, our preliminary results were not satisfactory with this pro-nucleophile. This fact and the necessity of synthesizing the derivative were crucial to move our attention to the nitro derivatives.

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[7] For the pKa values of arylacetonitrile in DMSO, see: F. G. Bordwell, J. -P. Cheng, M. J. Bausch, J. E. Bares, *J. Phys. Org. Chem.* **1988**, *1*, 209.

[8] O. Kaumanns, R. Appel, T. Lemek, F. Seeliger, H. Mayr, *J. Org. Chem.* **2009**, *74*, 75.

[9] a) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc*. **2004**, *126*, 8120; b) J. López-Cantarero, M. B. Cid, T. B. Poulsen, M. Bella, J. L. García Ruano, K. A. Jørgensen, *J. Org. Chem*. **2007**, *72*, 7062.

[10] a) A. Gaudemer, K. Nguyen-Van-Duong, N. Shahkarami, S. S. Achi, M. Frostin-Rio, D. Pujol, *Tetrahedron* **1985**, *41*, 4095. b) J. E. Sheppeck II, J. L. Gilmore, A. Tebben, C. -B. Xue, R. -Q. Liu, C. P. Decicco, J. J. -W. Duan, *Bioorg. Med. Chem. Lett.* **2007,** *17,* 2769.

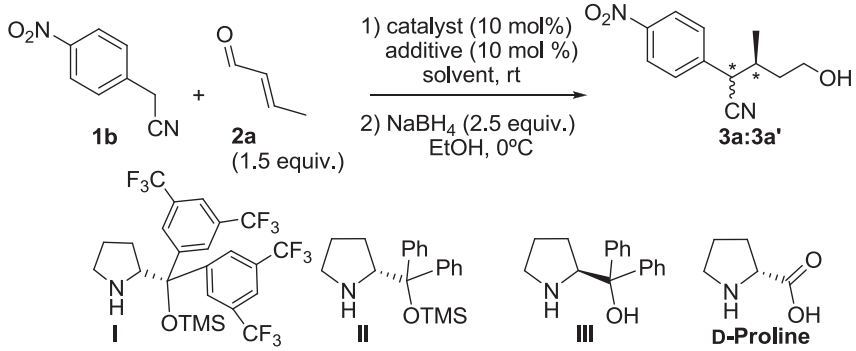
2.1.1 Model reaction. Optimization of the reaction conditions

We began the study of the viability of the method using crotonaldehyde (**2a**) as starting aldehyde for optimizing reactions with compound **1b** (Table 2.1), employing common reaction conditions that are, Jørgensen prolinol **I** as catalyst[11] at 10 mol% loading and benzoic acid as additive. Fortunately, even these initial conditions led to the formation of the desired adduct with very good conversion, and a 59:41 diastereomeric ratio (entry 1), using THF/H_2O mixture as solvent. As anticipated, prior to the screening of the optimal conditions it was necessary to establish a method to determine accurately the enantiomeric excesses obtained in the reactions. Even if the aldehyde products could be readily purified and the two diastereoisomers separated by flash chromatography, these adducts apparently decompose during HPLC analysis, thus preventing the direct determination of their enantiomeric excess. It was thus necessary to reduce these aldehydes to the corresponding alcohols (**3a** and **3a'**) before determining their optical purity. $NaBH_4$ reduction in EtOH of the reaction crude of the Michael addition,[12] once the solvent (THF and H_2O) was eliminated under vacuum, worked well for this purpose and allowed us to determine by HPLC an enantiomeric excess close to 90% for both alcohols **3** (entry 1). As the reductions proceeded in almost quantitative yield, the yields indicated in this and in the following Tables correspond to the Michael step. Having a reliable method to determine the yield and the enantioselectivity of the organocatalytic Michael addition step, different catalysts and additives were tested and the results are collected in Table 2.1.

[11] *a*) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew.Chem., Int. Ed.*, **2005**, *44*, 794; *b*) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem., Int. Ed.*, **2005**, *44*, 4212. For a review of chiral diarylprolinol ether catalysis, see: C. Palomo, A. Mielgo, *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

[12] $NaBH_4$ reduction of the diastereomerically pure aldehydes produce epimerization into their thermodinamic mixture.

Table 2.1. Details of the screening of different catalysts, solvents and additives for the addition of *p*-nitrophenylacetonitrile **1b** to crotonaldehyde **2a**.



Entry	Cat	Additive	Solvent	t (h)	yield[a] (%)	de[b] 3a:3a'	ee (%)[c] 3a	ee (%)[c] 3a'
1	**I**	$PhCO_2H$	THF/H_2O	40	90	59:41	90	89
2	**I**	LiOAc	THF/H_2O	20	95	63:37	90	89
3	**I**	NaOAc	THF/H_2O	24	63	60:40	84	88
4	**I**	DABCO	THF/H_2O	24	65	63:37	84	88
5	**I**[d]	LiOAc	THF/H_2O	40	93	63:37	91	90
6	**II**	LiOAc	THF/H_2O	24	84	60:40	86	70
7	**III**	LiOAc	THF/H_2O	24	82[e]	60:40	-50[f]	-62[f]
8	**D-Pro**	LiOAc	THF/H_2O	24	54[e]	61:39	15	16
9	**I**	$PhCO_2H$	MeOH	24	95[e]	nd	80	70
10	**I**	LiOAc	MeOH	15	87[e]	60:40	88	87
11	**I**	LiOAc	EtOH	15	85[e]	64:36	86	87
12	**I**	LiOAc	CH_2Cl_2	48	30[e]	nd	nd	nd
13	**I**	LiOAc	Et_2O	48	nr	-	-	-
14	**I**	LiOAc	Toluene	48	nr	-	-	-

[a] Isolated yield after flash chromatography
[b] Determined by NMR analysis of the crude.
[c] Determined by HPLC in the alcohols **3**.
[d] Reaction at 0°C.
[e] Conversion.
[f] The other enantiomer was obtained with catalyst **III**.

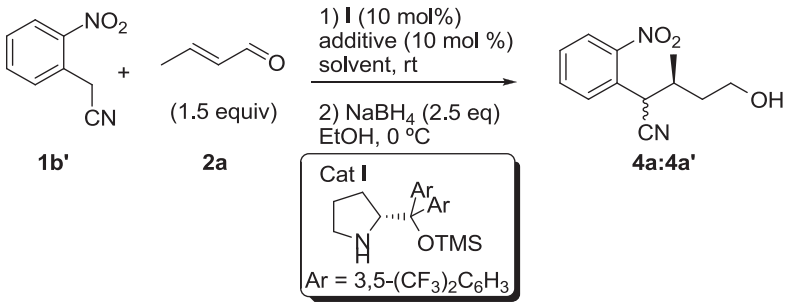
The use of non acidic additives reduced the reaction times (entries 2-4), with LiOAc providing the best results (entry 2).[13] A decrease in the temperature did not produce any significant improvement in the enantioselectivity (entry 5). The use of other catalysts like **II**, **III** and D-Proline provided lower yields and enantiomeric excesses (entries 6-8).

We next studied the effect of different solvents on the reaction using catalyst **I** (entries 9-14). The use of alcoholic solvents in combination with LiOAc decreased the reaction times but did not have any positive influence on the enantioselectivity (entries 10 and 11). When CH_2Cl_2 was used as solvent very low conversion was observed after 2 days (entry 12). Other low polar solvents like diethyl ether and toluene, did not even afford the desired product (entries 13 and 14). According to these results, conditions of entry 2 of table 2.1 (catalyst **I**, LiOAc and THF/H_2O, RT) were chosen as the optimal for the Michael step.

We then investigated the reaction of the *ortho*-derivative **1b'**. In principle, this derivative should present similar acidity and reactivity of **1b**. In fact, the use of the best conditions determined for nucleophile **1b** afforded the desired adducts **4a** and **4a'** in good yield (table 2.2, entry 2). The reactivity of this derivative **1b'** was slightly lower than derivative **1b**, probably due to the steric hindrance of the nitro group in *ortho* position. In this case we had the same problem to determine the enantiomeric excess of the Michael adducts due to the decomposition of the aldehydes in the HPLC columns, which was again solved by *in situ* reduction to the alcohols **4**.

[13] For other examples were LiOAc have been used see: a) Y. Wang, P. Li, X. Liang, Y. Zhang, J. Ye, *Chem. Commun*. **2008**, 1232. b) J. L. García Ruano, V. Marcos, J. J. Alemán, *Chem. Commun*. **2009**, 4435.

Table 2.2. Effects of solvent and additive on the Michael addition of **1b'** to crotonaldehyde **2a** catalyzed by **I.**



Entry	Solvent	Additive	t (h)	yield (%)	de[a] 4a:4a'	ee [b](%) 4a
1	THF/H_2O	$PhCO_2H$	72	85	59:41	80
2	THF/H_2O	LiOAc	24	84	62:38	84
3	THF/H_2O	DABCO	48	-	58:42	82
4	THF/H_2O	CsF	48	-	60:40	58
5	MeOH	LiOAc	20	-	59:41	76
6	MeOH	DABCO	48	-	58:42	84

[a] Determined by ^1H NMR analysis of the crude of the Michael addition.
[b] Determined by chiral phase HPLC analysis of the corresponding alcohols **4**.
Conditions to determine the ee of compound **4a'** could not be found.

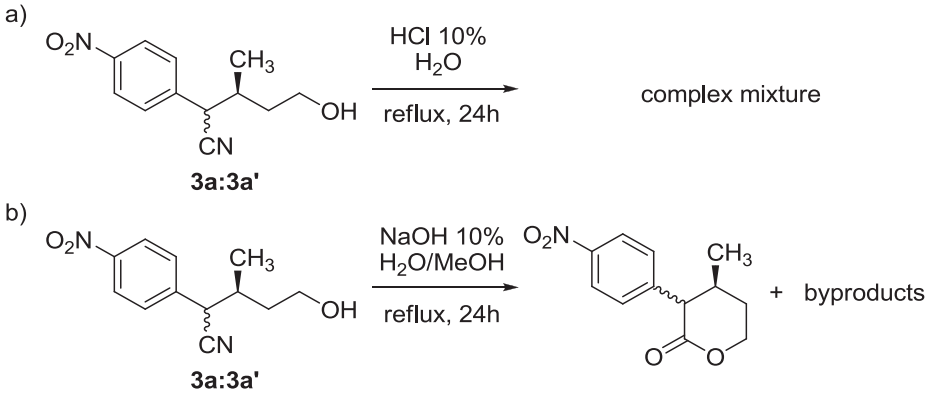
Moreover, even after reduction, in this case we only could find conditions for an efficient separation of the peaks for one of the two diastereomers (**4a**). In table 2.2 are summarized the most relevant results for the optimization of the conditions for nucleophile **1b'**. The results obtained with nucleophile **1b'** were slightly poorer in terms of enantioselectivity than those obtained for nucleophile **1b**.

It is important to note that even after chromatographic separation of the diastereomers resulting from the Michael addition; the mixture turned into the epimeric mixture after reduction with $NaBH_4$, due to the configurational instability of

the benzylic carbon, in the case of both **1b** and **1b'**. It can be assumed that the diastereomeric ratios (*ca* 60:40) observed in the reactions of both pro-nucleophile **1b** and **1b'** correspond to the thermodynamic ratios of the two aldehyde diastereoisomers, as the acidity of this chiral centre should be quite similar both in the starting pronucleophile and the product.

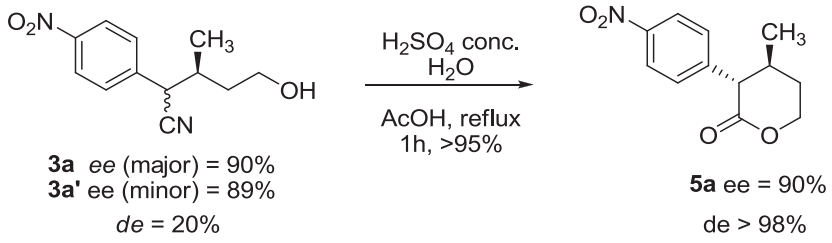
In order to control the configuration at this benzylic carbon, we took advantage of its intrinsic acidity to epimerize it to the most stable isomer in a cyclic substrate. This strategy has been used previously by our and other research groups. [14] The most obvious approach would be the formation of the corresponding lactone. In a first attempt (Scheme 2.5, a), we tried the hydrolysis of the cyano group of the derivatives **3a:3a'** to the corresponding carboxylic acid under mild acidic conditions, expecting a subsequent cyclization. The reaction did not afford the desired products, but a complex reaction mixture. We next tried the same lactonization reaction but using a basic aqueous solution, in order to promote a basic hydrolysis of the cyano group and the successive attack of the alkoxide (Scheme 2.5, b). Again, the reaction afforded a complex mixture, but in this case it was possible to observe the desired lactone in the ^{1}H NMR spectrum of the crude. However, other attempts of performing the reaction under different basic conditions resulted unsuccessful. A possible reason could be the formation of the benzylic anion which could evolve following other undesired pathways.

[14] a) J. L. García Ruano, T. de Haro, R. Singh, M. B. Cid, *J. Org. Chem.* **2008**, *73*, 1150. For another example: b) S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2006,** *45*, 4305.



Scheme 2.5. First attempts of cyclization

Finally, resorting to drastically different acidic promoters, as reported in the literature for related substructures, allowed us to find suitable conditions for the hydrolysis and subsequent lactonization.[15] To our delight, when the diastereomeric mixture of alcohols **3a** and **3a'** was treated with H_2SO_4 in AcOH, diastereomerically pure lactone **5a** was obtained in quantitative yield, without erosion of the enantiomeric purity (90% ee, Scheme 2.6) after 1h of reaction.

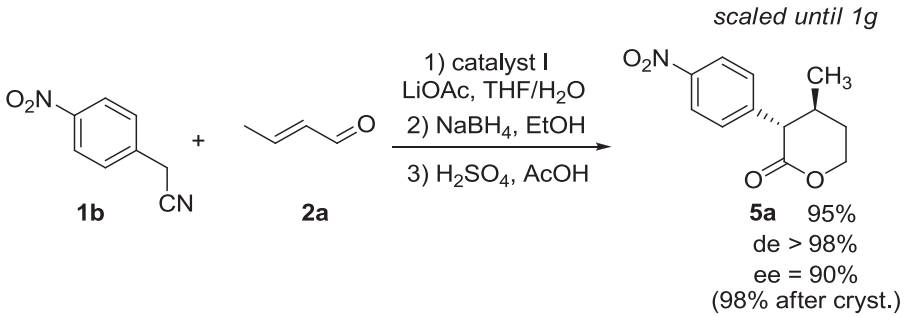


Scheme 2.6. Formation of diastereomerically pure lactone **6a**

In principle, the most stable *trans* disposition of the substituents at the C-3 and C-4 positions should be obtained, and this assumption was confirmed by the coupling constant J_{H3-H4} (>11 Hz), characteristic for a *trans* diaxial arrangement.

[15] J. E. T. Corrie, V. R. N. Munasinghe, *J. Labelled Compd. Radiopharm*. **2005**, *48*, 231.

With the three steps optimized and affording excellent yields we then searched for a sequential Michael addition / reduction / lactonization procedure, which allowed the direct synthesis of lactone **5a** from compounds **1b** and **2a** without isolation of the intermediates. It required the elimination under vacuum of the solvents after the first step and the filtration through a short pad of silica gel of the reduction crude. Using this protocol, **5a** was obtained as single diastereoisomer (de > 98%) in 95% yield and 90% *ee* (entry 1, Table 4). The enantiomeric excess was increased until 98 % ee by simple crystallization and the reaction could be scaled up until 1 g of product (Scheme 2.7).



Scheme 2.7. Three step protocol on a gram scale.

2.1.2 Scope of the reaction

This sequential procedure (Table 2.4) was applied to different enals **3**, which reacted with similar efficiency for synthesizing the more stable *trans*-lactones **5**. The Michael additions of derivative **1b** proceeded with excellent conversions. Reductions of the aldehydes to the corresponding alcohols evolved in very high conversions in all cases. Lactones **5a-5e** with R = alkyl (entries 1-5) were finally obtained with very good enantioselectivities and complete diastereoselectivities. In these cases the enantiomeric excesses of the Michael addition step was determined directly in the final lactones at the end of the sequence. Bulkier groups at the β-position required longer reaction times for the Michael addition and in the case of *i*Pr (entry 5) the time

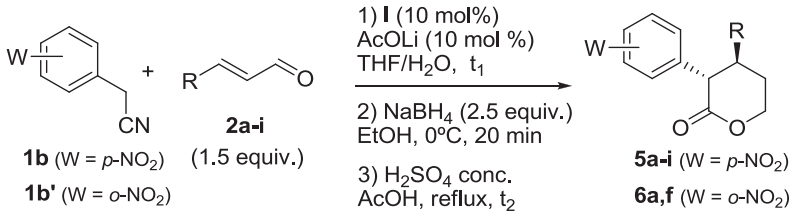
for the cyclization was also longer. With cinnamaldehyde derivatives (R = aromatic, entries 6-9), diastereoselectivity remained complete but the enantioselectivities were lower than in the case of aliphatic enals. In particular, it seemed that electron donating groups, like *p*-OMe, seriously reduced the ee (entry 7), whereas it was slightly improved by electron withdrawing groups as *p*-NO_2 (entry 8). The reaction times for the aromatic derivatives were also found to be longer, not only in the Michael step but also during the lactonization process (entries 6-9). The reactions were followed by TLC and at all times starting nucleophile **1** could be detected, thus the reaction times were considered longer.

ortho-Nitrophenylacetonitrile **1b'** also reacted with aldehydes **2a** (R = Me) and **2f** (R = Ph), under the same sequential procedure used for **1b** (entries 10 and 11) affording **6a** and **6f** respectively. The conversions of the Michael addition were slightly lower than in the case of derivative **1b**. Reaction times for cyclization (t_2) were longer than those required for **1b** (compare entries 1 and 10 or 6 and 11), probably due to the steric hindrance of the *ortho* substituent. Furthermore, in line with the results obtained with **1b**, the enantiomeric excess was significantly lower in the case of the cinnamaldehyde **2f** (entry 11).

The different behaviour of aromatic and aliphatic enals under the same reaction conditions is a common fact described in the literature, however not general explanation has been given for this particular detail. It will be encountered in cases throughout this thesis and will be discussed in detail in Chapter III.

It is also remarkable that *m*-nitrophenylacetonitrile **1b''** did not react under the same conditions. As the pKa for this compound is 18.1 in DMSO, this lack of reactivity might be related to a low acidity of the methylenic protons. Nevertheless, we have observed that this barrier can be overcome under different reaction conditions (see next chapter).

Table 2.4. Scope for the addition of *p*-nitrophenylacetonitriles **1b** and **1b'**.[a]



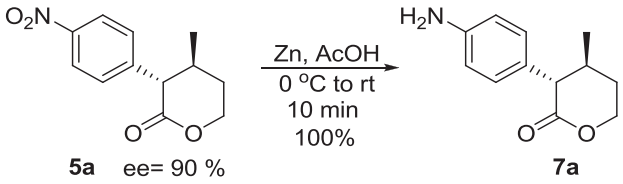
1b (W = *p*-NO_2) **1b'** (W = *o*-NO_2) **2a-i** (1.5 equiv.) **5a-i** (W = *p*-NO_2) **6a,f** (W = *o*-NO_2)

Entry	donor	R	t_1[b] (h)	t_2[c] (h)	Product	Overall yield (%)	*ee* [d] (%)
1	**1b**	**2a** Me	20	1	**5a**	95	90
2	**1b**	**2b** Et	24	1	**5b**	89	92
3	**1b**	**2c** *n*Pr	48	1	**5c**	92	92
4	**1b**	**2d** *n*Bu	48	1	**5d**	89	90
5	**1b**	**2e** *i*Pr	120	3	**5e**	90	96
6	**1b**	**2f** (Ph)	48	8	**5f**	79	80
7	**1b**	**2g**(*p*-OMe-C_6H_4)	72	30	**5g**	82	30
8	**1b**	**2h**(*p*-NO_2-C_6H_4)	48	48	**5h**	86	85[e]
9	**1b**	**2i** (*p*-Br-C_6H_4)	72	3.5	**5i**	84	70
10	**1b'**	**2a** (Me)	24	8	**6a**	78	84
11	**1b'**	**2f** (Ph)	40	25	**6f**	76	50

[a] Reactions performed on 1mmol scale
[b] For the Michael addition.
[c] For the cyclization process.
[d] Determined by HPLC.
[e] Estimated from the ee of the mixture of alcohols.

2.1.3 Transformations of the adducts

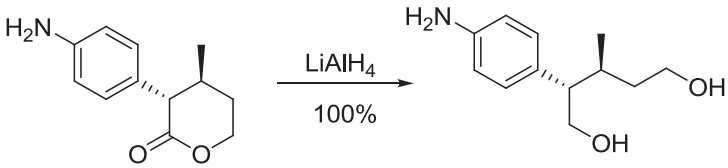
In order to illustrate the versatility of these nucleophiles several transformations have been carried out in the resulting lactones. The reduction of the nitro group into the corresponding amine moiety opens the gate to the broad scope of synthetic transformation *via* diazonium salts. Moreover, this transformation is fundamental for decreasing the acidity of the benzylic position, thus minimizing its tendency to epimerize. After a carefully search of the methods described in the literature this reduction could be easily performed in quantitative yield by treatment of **5a** with Zn/AcOH[16] (Scheme 2.8).



5a ee= 90 % **7a**

Scheme 2.8. Reduction of the nitro group in **5a**.

The aniline **7a** was transformed into the acyclic diol **8a** without epimerization at C-4 after treatment with $LiAlH_4$ (Scheme 2.9).

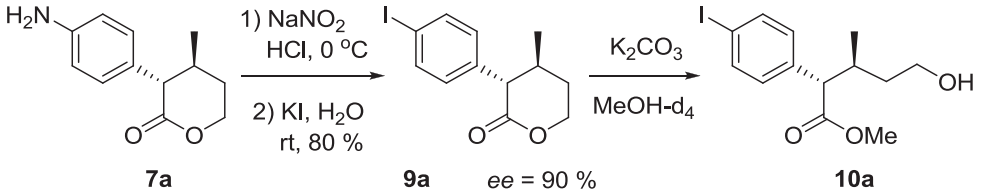


7a **8a** *ee* = 90 %

Scheme 2.9. Synthesis of the acyclic diol **8a**.

[16] K. Higuchi, Y. Sato, M. Tsuchimochi, K. Sugiura, M. Hatori, T. Kawasaki, *Org. Lett.* **2009**, *11,* 197.

It was also possible to obtain the corresponding iodide derivative **9a** in good yield obtained from **7a** after the corresponding coupling with the diazonium salt.[17] This compound can act in principle as a useful starting material for metal catalyzed cross coupling reactions. The derivative **9a** could also be ring opened to the ester **10a** under basic conditions in a reaction followed by ^{1}H NMR analysis (Scheme 2.10).



7a **9a** *ee* = 90 % **10a**

Scheme 2.10. Transformations of **7a**

[17] I. Peretto, S. Radaelli, C. Parini, M. Zandi, L. F. Raveglia, G. Dondio, L. Fontanella, P. Misiano, C. Bigogno, A. Rizzi, B. Riccardi, M. Biscaioli, M. Marcello, S. Marchetti, P. Puccini, S. Catinella, I. Rondelli, V. Cenacchi, P. T. Bolzoni, P. Caruso, G. Villetti, F. Facchinetti, E. Del Giudice, N. Moretto, B. P. Imbimbo, *J. Med. Chem.* **2005**, *48*, 5705.

2.1.4 Determination of the absolute configuration

The absolute configuration of the lactone **9a** was unequivocally established as **(3*S*, 4*S*)** by X-ray diffraction studies (Figure 2.2).

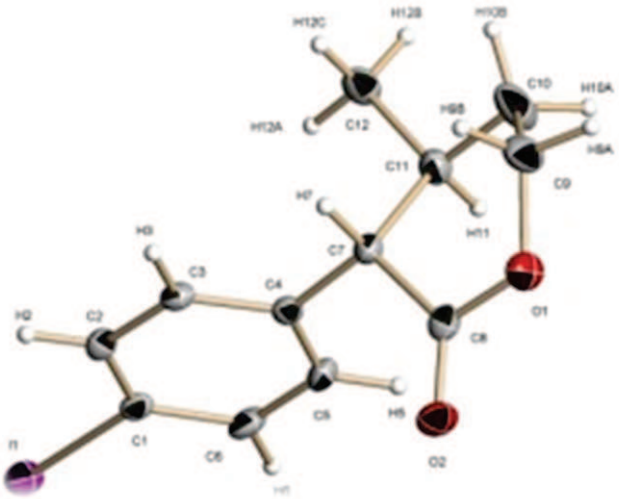
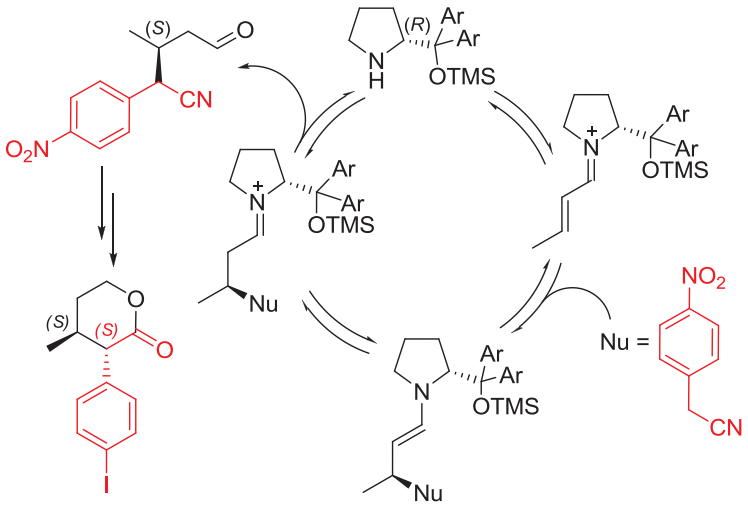


Figure 2.2. X-Ray structure of **9a**.

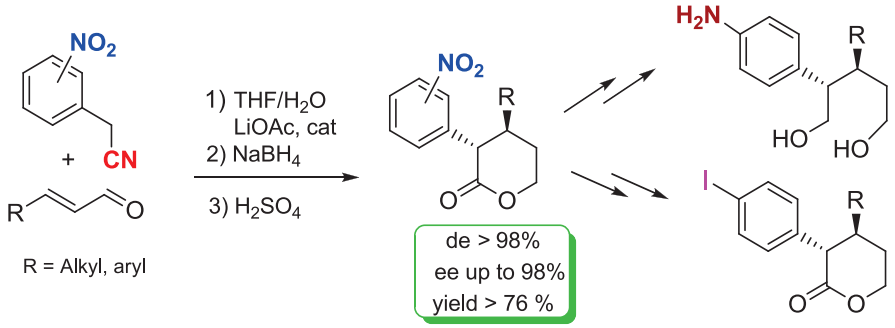
The same relative and absolute configuration was assumed for the other lactones **7a**, **5** and **6**, and is in line with the generally accepted model employed to justify the observed stereoselectivity of prolinol **I** catalyzed Michael additions to enals.[18] This model involves the formation of an iminium ion forced in the conformation shown by the large diaryl-trimethylsilyl group. This same group effectively shields the *Re* bottom face thus allowing the attack of the nucleophile only at the *Si* face of the olefin (Scheme 2.11). On these grounds, the same configuration was assigned by analogy to all other compounds.

[18] a) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta,* **2008**, *91*, 1999; b) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend; S. Bertelsen, K. A. Jørgensen, *Chem. Commun.*, **2011**, *47*, 632.



Scheme 2.11. Stereochemical model

In conclusion, these nucleophiles allowed us the development of a formal diastereoselective α-arylation of lactones (Scheme 2.12). As cyclic and acyclic optically enriched acyclic compounds were obtained, we can consider the strategy presented in this chapter as an indirect approach for getting such transformation.



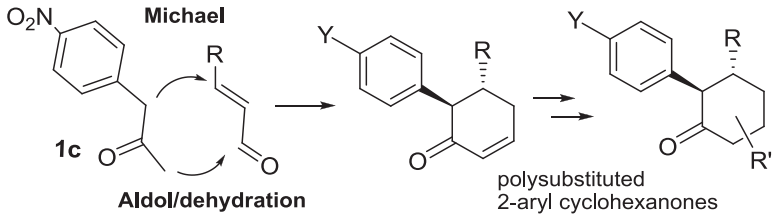
Scheme 2.12. Arylacetonitriles as nucleophiles

Encouraged by the good results we decided to extend the methodology to other versatile pro-nucleophiles.

2.2 *p*-Nitrophenylacetone as nucleophile in organocatalytic 1,4-additions

We next investigated the derivative **1c** with a ketone group at the benzylic position. Even if this is not strictly a carboxylic acid derivative, we considered that the possibilities offered by this functionality would be of high synthetic importance justifying its employment.

With the sequential procedure previously developed for the nitrophenylacetonitriles in mind, we envisioned that α,β-disubstituted cyclohexenones could be obtained after the organocatalytic Michael addition of the commercially available ketone **1c** to α,β-unsaturated aldehydes,[19] followed by intramolecular aldol condensation reaction (Scheme 2.13).



Scheme 2.13. Proposal for the synthesis of α-aryl cyclohexanones

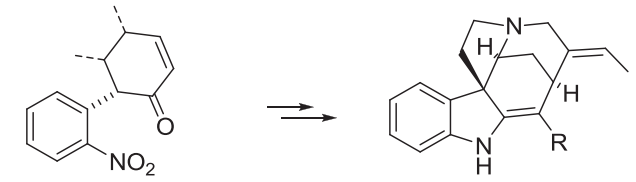
Optically active cyclohexenones are especially attractive compounds that have found widespread applications in syntheses of target molecules,[20] mainly due to their chemical versatility that allows them to participate in various interesting

[19] For some examples on one-pot strategies using α,β-unsuturated aldehydes that afford complex structures, see: a) B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem., Int. Ed*. **2009**, *48*, 4349; b) Ł. Albrecht, L. K. Ransborg, B. Gschwend, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 17886; c) K. L. Jensen, P. T. Franke, C. Arróniz, S. Kobbelgaard, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 1750 and references cited therein. For an impresive example see: d) M. Reiter, S. Torssell, S. Lee, D. W. C. MacMillan, *Chem. Sci.,* **2010***, 1*, 37.

[20] For some examples, see: a) A. R. Angeles, D.C. Dorn, C. A. Kou, M. A. S. Moore, S. J. Danishefsky, *Angew. Chem., Int. Ed.* **2007**, *46*, 1451; b) W. Zhao, J. Zhang, *Org. Lett.* **2011,** *13,* 688; c) H. Haning, C. Giro-Manas, V. L. Paddock, C. G. Bochet, A. J. P. White, G. Bernardinelli, I. Mann, W. Oppolzer, A. G. Spivey, *Org. Biom. Chem.* **2011**, *9*, 2809.

transformations.[21] Most of the reported procedures for synthesizing these compounds use classical approaches starting from the *chiral pool*, usually terpenes;[22] but there are also some methods based on asymmetric synthesis,[23] including enantioselective organocatalysis.[24]

The particular case of α-aryl cyclohexenones is interesting as they have been used for the preparation of a wide range of natural products, but only in racemic version (see for example Scheme 2.14)[25] possibly due to the difficulty of the obtainment of these compounds in enantiomerically pure form.



α-aryl cyclohexenones *Strychnos* alkaloids

Scheme 2.14. α,β-Disubstituted cyclohexenones as precursor of natural products.[25d]

As none of the strategies mentioned above provides a general method for their preparation in optically pure form, the search for new strategies leading to a broad

[21] a) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070; b) E. Zang, C-A. Fan, Y-Q. Tu, F. M. Zhang, Y-L. Song, *J. Am. Chem. Soc.* **2009**, *131*, 14626; c) H. Jiang, N. Holub, K. A. Jørgensen, *Proc. Natl. Acad. Sci.* **2010**, *107*, 20630.

[22] a) Y. Chen, T. Ju, *Org. Lett.* 2011, **13**, 86; b) G. Mehta, S. K. Chattopadhyay, J. D. Umarye, *Tetrahedron Lett.* **1999**, *40*, 4881.

[23] See for example: G. Franck, K. Bördner, G. Helmchen, *Org. Lett*. **2010**, *12*, 3886.

[24] a) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun*. **2006**, 4928; b) P. Bolze, G. Dickmeiss, K. A. Jørgensen, *Org. Lett*. **2008**, *10*, 3753; c) L-L. Wang, L. Peng, J-F. Bai, Q-C. Huang, X-Y. Xu, L-X. Wang, *Chem. Commun*. **2010**, *46*, 8064.

[25] For some examples as intermediates to prepare natural products: a) A. Biechy, S. Hachisu, B. Quiclet-Sire, L. Ricard, S. Z. Zard, *Angew. Chem. Int. Ed.* **2008**, *47*, 1436; b) N. Yamamoto, H. Fujii, S. Imaide, S. Hirayama, T Nemoto, J. Inokoshi, H Tomoda, H. Nagase, *J. Org. Chem*. **2011**, *76*, 2257; c) D. Sole, J. Bonjoch, J. Bosch, *J. Org. Chem*. **1996**, *61*, 4194; d) D. Sole, S. García-Rubio, L. Vallverdu, J. Bonjoch, *J. Org. Chem.* **2001**, *66*, 5266.

range of substitutions in 2-aryl cyclohexenones is of high interest.[26] As it was commented in the introduction, the preparation of α-arylated[4] is nontrivial[27] and usually requires *umpolung* strategies of or long reaction sequences.[28] As shown in the previous section, we have demonstrated that the presence of the nitro group can be used for introducing other substituents at the aromatic ring of the products. Considering also the chemical versatility of the cyclohexenone moiety, the adducts resulting from our proposed organocatalytic Michael-aldol condensation sequence (Scheme 2.13) can be considered as powerful intermediates for synthesizing a variety of enantiomerically enriched polysubstituted 2-aryl cyclohexanones.

2.2.1 Model reaction. Optimization of the reaction conditions

As a model reaction we studied the addition of ketone **1c** to crotonaldehyde (**2a**), searching for the optimal conditions for the Michael addition. Following the same strategy described in the previous section, we commenced our studies by using various proline derived catalysts, with or without additives in different solvents.

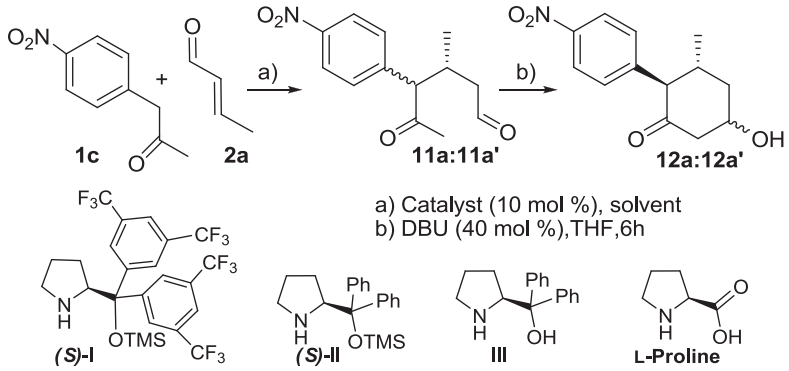
As shown in Table 2.5, the reaction took place in CH_2Cl_2 with the screened pyrrolidine-based catalysts affording a mixture of epimers at the benzylic carbon **11a** and **11a'** (Table 2.5, entries 1-4). However, it was not possible to determine the enantiomeric excesses in the Michael adducts, due to the decomposition of the aldehydes during HPLC analysis.

As in the case of the nitrile derivatives, we thought about a sequential procedure to determine the enantiomeric excess at the end of the process. In this case, instead

[26] We have not found any method to prepare 6-aryl-5-substituted cyclohexenones in enantiomerically pure form. For the synthesis of a related compound in racemic version see H. E. Zimmerman, D. Lynch, *J. Am. Chem. Soc.* **1985**, *56*, 7745.
[27] See: a) V. K. Aggarwal, B. Olofsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 5516 and references cited therein; b) A. Yanagisawa, T. Touge, T. Arai, *Angew. Chem. Int. Ed.* **2005**, *44*, 1546; c) For a recent racemic example see: X. Huang, N. Maulide, *J. Am. Chem. Soc.* **2011**, *133*, 8510.
[28] D. L. J. Clive, P. L. Wickens, G. V. J. da Silva, *J. Org. Chem.* **1995**, *60*, 5532.

of reducing the aldehyde moiety, we thought it would be more convenient to determine the enantiomeric excess in compounds **12a** and **12a'**, the cyclic products obtained after treatment with DBU, which were successfully obtained after a short optimization as explained below. We could establish that **I** and **II**[29] were the most promising catalysts (entries 1 and 2)[11]. Prolinol catalyst **III** and L-proline afforded high conversions (calculated for the Michael addition step) but very low enantioselectivities (entries 3 and 4). For catalysts **I**, higher conversion and similar enantioselectivity was obtained using EtOH as solvent instead of CH_2Cl_2 (compare entries 1 and 5).

Table 2.5. Catalyst and solvent screening of the sequence Michael / cyclization. [a]



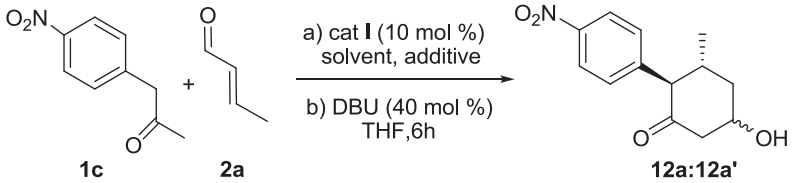
Entry	Catalyst	Additive	solvent	t (h)	Conv step a[b] (%)	*ee* (%) [c] 12a:12a'
1	**I**	-	CH_2Cl_2	24	40	90:90
2	**II**	-	CH_2Cl_2	24	95	73:70
3	**III**	-	CH_2Cl_2	24	75	<5%
4	**L-Pro**	-	CH_2Cl_2	24	95	10:16
5	**I**	-	EtOH	24	90	84:88
6	**II**	-	EtOH	24	90	69:70

[a] The reactions were carried out on a 0.2 mmol scale with **2a** (1.5 equiv) and $[\mathbf{1c}]_0$ = 1 M
[b] Determined by ^{1}H NMR of the crude of the Michael addition.
[c] Determined by HPLC analysis of the alcohols **12a** and **12a'**.

[29] The *(S)* enantiomers of both catalysts **I** and **II** were used due to the availability at the lab.

As catalyst **I** afforded the best result in terms of enantioselectivity, we next investigated the influence of several additives and different solvents on the reaction time and enantioselectivity of the process with this catalyst (Table 2.6). The use of acidic additives of different strength did not provide any beneficial effect in either reactivity or enantioselectivity (entries 1-5). The combination of protic solvents with basic additives decreased instead the reaction times (entries 6-10), the most convenient combination being EtOH as solvent and LiOAc as additive (entry 10). Unfortunately, the enantiomeric excess was not improved by decreasing the temperature (entry 11), and even decreased upon dilution (entry 12), or when a polar non-protic solvent such as DMF was employed (entry 13). The use of CH_2Cl_2 as solvent provided the best results in terms of enantioselectivity but at the expense of the product yield (entry 14). Finally, an attempt to perform the reaction in water did not succeed (entry 15). Thus we decided to keep the conditions reported in Table 2.6, entry 10 (EtOH as solvent, LiOAc as additive) as the optimal for the organocatalytic step of this reaction.

Table 2.6. Screening of different solvents and additives with catalyst **I**. [a]

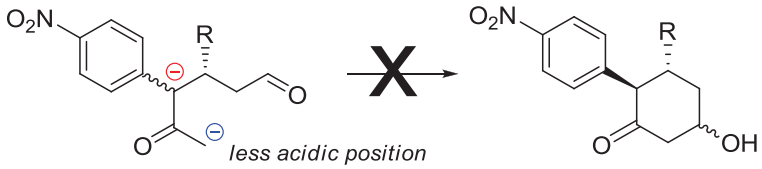


1c **2a** **12a:12a'**

Entry	Additive	Solvent	t[b] (h)	Conv step a (%)	*ee*[c](%)
1	$PhCO_2H$	THF/H_2O	48	85	70; 80
2	$PhCO_2H$	MeOH	24	90	77; 81
3	$PhCO_2H$	EtOH	20	95	78; 80
4	*m*-Cl-C_6H_4-CO_2H	MeOH	30	90	74; 75
5	*p*-NO_2-C_6H_4-CO_2H	MeOH	30	85	72; 77
6	LiOAc	THF/H_2O	24	90	80; 85
7	LiOAc	MeOH	15	95	88; 90
8	CsOAc	EtOH	20	95	80; 78
9	DABCO	EtOH	20	95	80; 84
10	LiOAc	EtOH	12	95	90;90
11	LiOAc	EtOH[d]	24	95	90;90
12	LiOAc	EtOH[e]	72	90	61;62
13	LiOAc	DMF	10	95	65;66
14	LiOAc	DCM	24	60	93;90
15	LiOAc	H_2O	96	no reaction	-

[a] Reactions conditions: **2a** (0.3 mmol), proline derived catalyst (10 mol%), **1c** 0.2 mmol, $[\mathbf{1c}]_0$= 1M) and additive (10 mol%) at room temperature.
[b] Reaction time of the Michael addition.
[c] The *ee* values were determined by HPLC on a chiral stationary phase.
[d] Reaction performed at 0°C.
[e] $[\mathbf{1c}]_0$=0.1 M

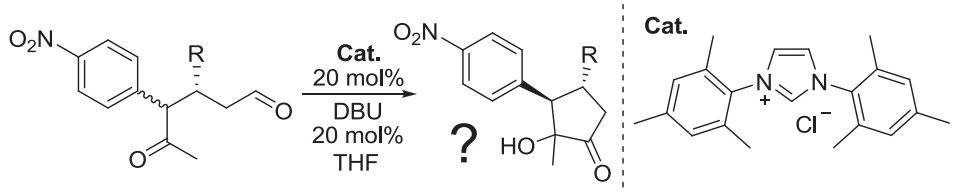
Going back to the short optimization which turned out to be necessary to carry on the Michael products **11** to the aldol adduct **12**, it must be first first mentioned that a search in the literature for an intramolecular aldol reaction in substructures related to **11** did not give any result. Hypothesising that the lack of literature precedents was due to the presence of the highly acidic benzylic proton in compounds **11a**, which might override deprotonation and ensuing cyclization at the desired position (Scheme 2.15), we were highly concerned about the feasibility of this transformation.



Scheme 2.15.

However, after few unsuccessful attempts, searching for an intramolecular crossed benzoin reaction, we serendipitously found that the treatment of the Michael adducts with DBU[30] afforded cleanly an equimolecular mixture of 3-hydroxycyclohexanones, **12a** and **12a'**, epimers at the hydroxylic center in very good yields (see table 2.5). The diastereomeric mixture **11a:11a'** was treated with an *N*-heterocyclic carbene in the presence of DBU expecting the corresponding five member ring (see Scheme 2.16). cyclization. Therefore the use of the carbene catalyst was not necessary for the cyclization and we optimized the aldol reaction using 40 mol% of DBU.

[30] In a first attempt, we envisioned that an intramolecular crossed benzoin reaction mediated by *N*-heterocyclic carbene catalysis may succeed in our structure, see: D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1463-1467.



Scheme 2.16. Attempt of benzoin reaction.

However, the analysis of the crude spectrum of the reaction showed that the major product was in fact the corresponding aldol adduct obtained after deprotonation at the α-position of the ketone and subsequent Thus, despite the considerable acidity of the benzylic proton, there seems to be enough terminal enolic form to promote the cyclization reaction. As described for the lactone **5a**, the epimerization at the benzylic center towards the presumably most stable *trans* 2,3-substituted diastereoisomer had also taken place, due to the high acidity of the benzylic proton. To our delight, it was possible to determine the enantiomeric excesses of **12a** and **12a'** by chiral HPLC.

2.2.2 Configurational assignment of alcohols 12a and 12'a

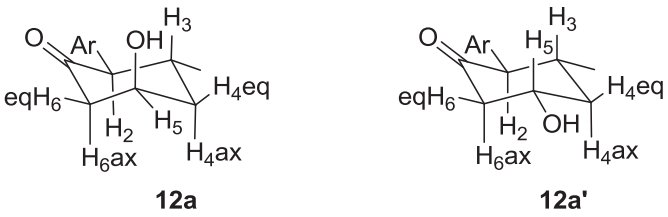


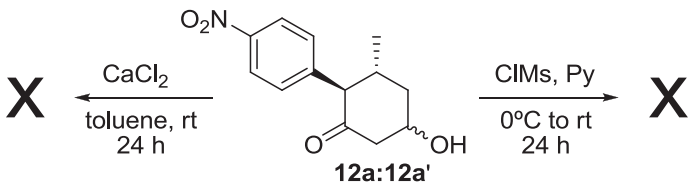
Figure 2.3. Structures of the isomers **12a** and **12a'**

The relative configuration of **12a** and **12a'** was assigned according to the following bases:

a) The high values of the coupling constants between H_2-H_3 (J = 11.7 Hz for both isomers) agree with an axial disposition of these hydrogen atoms in both diastereomers.

b) Coupling constants of H_{6ax} and H_{4ax} with H_5 (equatorial in compound **12a** and axial in compound **12a'**) determine the assignment of the configuration at the hydroxylic center (C_5) of each diastereoisomer. The higher coupling constants in diastereomer **12a'** than in **12a** agree with the represented configuration.

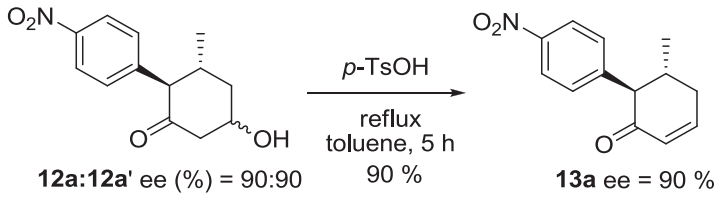
With the optimal conditions for the Michael addition (entry 8, table 2.5) and the aldol reaction established above, the next step was then investigated. We tried classical dehydrating agents and elimination sequences[31], but the desired cyclohexenone was not obtained (Scheme 2.16).



Scheme 2.16. Attemps of dehydration and elimination

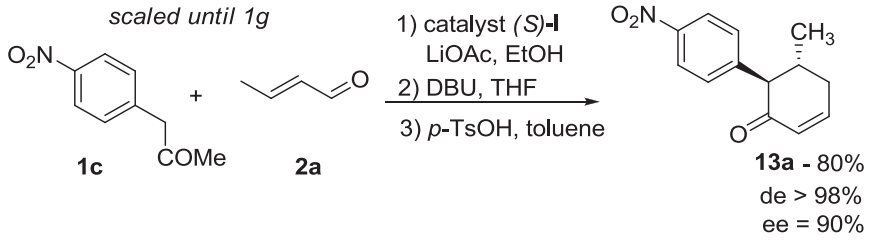
However, diastereomerically pure cyclohexenone **13a** was cleanly obtained in high yield, without erosion of the enantioselectivity, after treatment of the mixture **12a:12a'** with *p*-TsOH. (Scheme 2.17).

[31] Y. Liu, W. W. McWhorter, Jr., *J. Am. Chem. Soc.*, **2003**, *125*, 4240.



Scheme 2.17. Dehydration of aldols **12a**:**12a'**

Fortunately, reaction conditions used in the elimination step could be applied to the crude mixture **12** resulting after aldol reaction and thus, the sequential procedure (Michael addition / aldol reaction / dehydration) could be performed requiring only a filtration through a short pad of silica gel after the first two steps, and a final chromatographic purification affording **13a** in 80 % yield (overall yield for the three steps) (Table 2.7, entry 1). This sequence was scaled up starting from 1 g of substrate **1c** with the same result (Scheme 2.18).



Scheme 2.18. Three step protocol on a gram scale.

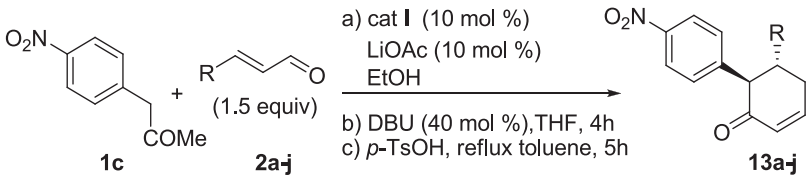
2.2.3 Scope of the reaction

Having the best conditions optimized for the sequential procedure Michael addition / aldol reaction / dehydration, a series of α,β-unsaturated aldehydes were tested in order to explore the scope of this protocol (Table 2.7).

This simple sequence was successfully applied to a range of β-alkyl substituted α,β-unsaturated aldehydes (entries 1-6). In all these cases, very high ee values were obtained (up to 96%). The length of the chain had a small influence on the

enantioselectivity, being the most bulky derivative the one that required longer reaction times while giving lower ee (entry 5).

Table 2.7. Aldehyde scope of the reaction sequence Michael addition / aldol reaction / dehydration. [a]



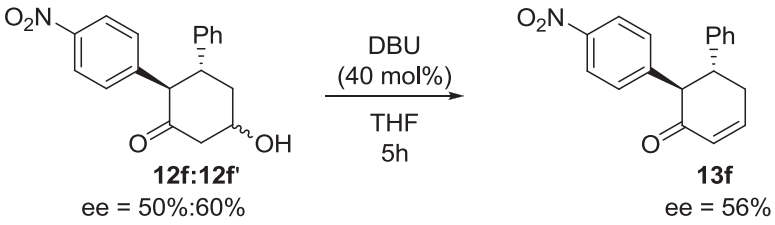
Entry	R	Additive	step a t (h)	Product	Overall Yield (%)	*ee* 13[b] (%)
1	**2a** (Me)	LiOAc	12	**14a**	80	90
2	**2b** (Et)	LiOAc	15	**14b**	76	91
3	**2c** (*n*-Pr)	LiOAc	26	**14c**	78	96
4	**2d** (*n*-Bu)	LiOAc	48	**14d**	70	92
5	**2e** (^{i}Pr)	LiOAc	50	**14e**	74	80
6	**2j** -$(CH_2)_2CH{=}CH(CH_2CH_3)$	LiOAc	30	**14f**	56	94
7	**2f** (Ph)	LiOAc	48	**14g**	100[c]	46
8	**2f** (Ph)	LiOAc	2	**14g**	100[c]	66
9	**2g** (*p*-OMe-C_6H_4)	LiOAc	24	**14h**	100[c]	0
10	**2g** (*p*-OMe-C_6H_4)	$PhCO_2H$	16	**14h**	100[c]	75[d]
11	**2h** (*p*-NO_2-C_6H_4)	LiOAc	24	**14i**	75	58
12	**2h** (*p*-NO_2-C_6H_4)	-	48	**14i**	100	76[e]

[a] Reactions performed on 0.4 mmol scale.
[b] Determined by HPLC analysis on the final product **13**.
[c] Conversion.

By contrast, reactions of enals bearing aromatic substituents (entries 7-12) also evolved rapidly and with complete diastereoselectivity, but lower ee values were obtained. Additionally, the ee values for ketones **13g** and **13h** were changing with

time and conditions. For example, reaction of cinammadehyde afforded the desired product in 46% ee after 48h, while the same reaction stopped after 2h afforded the compound in 66% ee (compare entries 7 and 8). Compund **13g** resulted from *p*-OMe-cinnamaldehyde was even obtained as racemic form after 24 h of reaction (entry 9), while in the presence of benzoic acid as additive the ee was increased until 75% (entry 10). Finally, reaction of **2h** resulted to be more enantioselective in the absence of additives (compare entries 11 and 12).

In order to discard that DBU promoted retro aldol / retro Michael racemization of compounds **13** derived from cinnamaldehydes leading to the observed low enantioselectivity occurred, a sample of alcohols **13f**:**13f'** derived from the Michael addition / aldol reaction of cinnamaldehyde, of known enantiomeric purity, was treated with DBU during 5h. No change was observed in neither reaction composition or ee, thus discarding a DBU promoted racemization as the reason for the low enantiomeric excess of this adduct (Scheme 2.19).

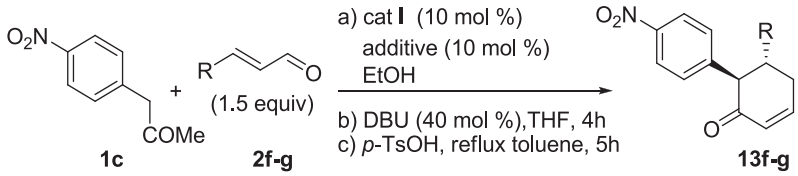


Scheme 2.19

To obtain some insights about the factors determining the low enantiomeric excesses obtained with aromatic enals, several other reaction conditions were tested. A summary of these conditions is depicted in Table 2.8.

In all cases the enantiomeric excesses were low and more importantly they were changing with time.

Table 2.8. Representative results from the screening of different conditions with catalyst **I**.[a]



Entry	R	additive	T (°C)	t(h)	Conv. (%)	*ee* (%)
1	Ph	-	rt	1	100	40/50[c]
2	Ph	-	rt	48	100	35/45[c]
3	Ph	-	0	2	100	53/60[c]
4	Ph	$PhCO_2H$[d]	rt	8	100	56[b]
5	Ph	LiOAc	rt	2	100	66[b]
6	Ph	LiOAc	rt	48	100	46[b]
7	*p*-MeOPh	-	rt	1	100	42/58[c]
8	*p*-MeOPh	-	rt	48	100	10/15[c]
9	*p*-MeOPh	-	0	2	100	55/65[c]
10	*p*-MeOPh	$PhCO_2H$[d]	rt	16	100	75[b]
11	*p*-MeOPh	LiOAc	rt	1	100	40[b]
12	*p*-MeOPh	LiOAc	rt	24	100	rac[b]

[a] Reactions conditions: **3** (0.3 mmol), proline derived catalyst (10 mol %), **1** (0.2 mmol, $[\mathbf{1c}]_0$ = 1.0M).
[b] The *ee* values were determined in the final cyclohexenone **13**.
[c] The *ee* values were determined in the aldol **12**.
[d] 30 mol % of additive was used.

The enantiomeric excess of the reaction of cinnamaldehyde **2f** decreased slowly with time in the absence of additives (compare entries 1 and 2). A decrease in the temperature of the Michael addition slightly increased the ee value (entry 3). The best conditions found in terms of enantioselectvity were the use of LiOAc after 2h of reaction (entry 5). For the reactions of aldehyde **2g** in the absence of additive (entries

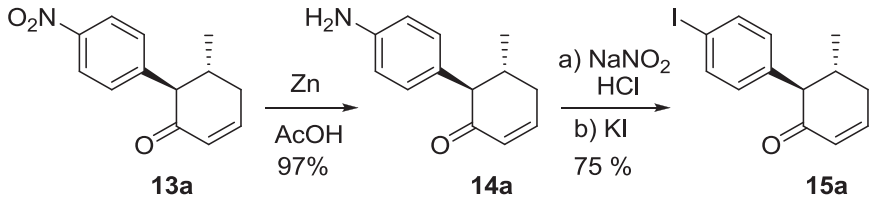
7-9) a decrease in the enantioselectivity with time was observed. As in the case of 2f, a decrease in the temperature did not afford a notable increase in the ee (entry 9). It can be speculated that the variation of the enantioselectivity observed with time might be a consequence of the reversibility of the Michael addition.[32] Thus, equilibration destroys the kinetic asymmetric control, allowing a thermodynamic equilibration that affords in some cases even racemic products (entry 12).[33] It is worth stressing that the same behaviour had been already observed with arylacetonitriles and that it was not found to be an issue for any of the aliphatic enals employed. The issue regarding the reversibility of the Michael addition as well as the role of the different additives is discussed thoroughly in the next chapter.

2.2.4 Synthetic elaborations and configurational assignment of the adducts

Cyclohexenones **13** resulting in these reactions have many synthetic possibilities that we have illustrated by studying the behaviour of **13a** under different reaction conditions.

First, the presence of the NO_2 group opens the gate to introduce different substituents at the aromatic ring taking advantage of the diazonium salt's chemistry. Thus, chemoselective Zn/AcOH reduction of the NO_2 group in the presence of the enone moiety afforded amine **14a**, which was easily transformed into the aryliodide **15a**, using the same conditions optimized for the lactone **5a** in the previous section (Scheme 2.19).

[32] This fenomena has been pointed out several times in the bibliography: A. Quintard, A. Alexakis, *Chem. Commun*. **2011**, *47*, 7212 and references cited therein.
[33] Y. K. Chen, M. Yoshida, D. W. C. MacMillan *J. Am. Chem. Soc.* **2006**, *128*, 9328.



Scheme 2.19. Transformation of the nitro group in **13a**.

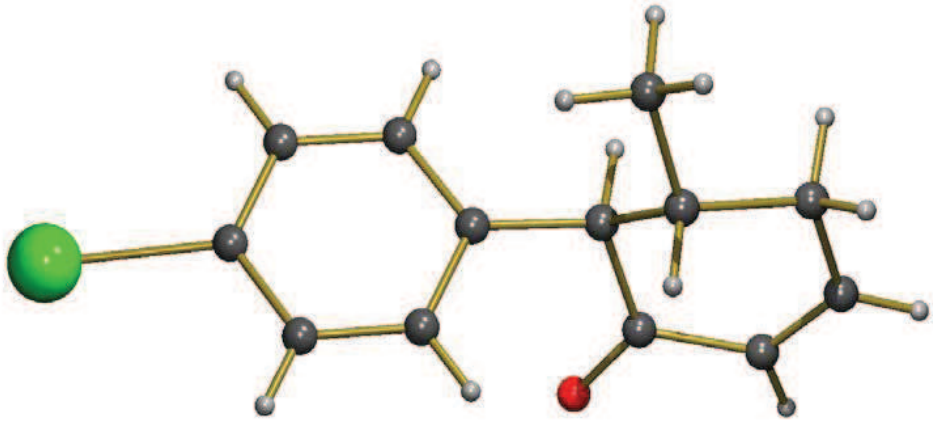
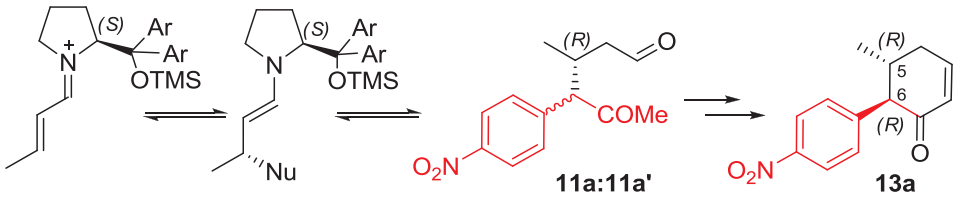


Figure 2.4. X-Ray structure of **15a**

Thanks to the presence of the heavy atom, compound **15a**, that can be employed as starting material in different coupling reactions, was used for unequivocally establishing the absolute configuration of the stereogenic carbons of **13a** (and presumably those of the rest of the cyclohexenones **13** of Table 2.6) as **(5*R*, 6*R*)** by X-ray diffraction studies. As already highlighted in the previous section describing arylacetonitriles,[34] the (*R*) configuration assigned to C-5 agrees with the predicted one

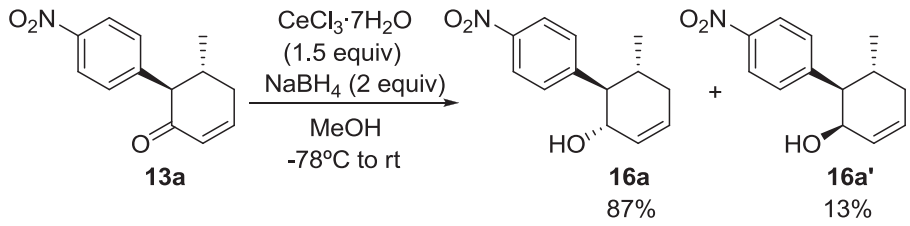
[34] In this case the other configuration is obtained as the other enantiomer of catalyst **I** was used.

by the models used for explaining the stereochemical course of the organocatalytic Michael additions to β-substituted α,β-unsaturated aldehydes involving iminium ion intermediates (see Scheme 2.11).[18] The (*R*) configuration assigned to C-6 agrees with the expected one by assuming the thermodynamic equilibration of the carbanion generated at C-6 (Scheme 2.20).



Scheme 2.20. Stereochemical model

Chemoselective transformations of the C=O and C=C bonds at compounds **13** can also be easily performed. The selective reduction of the carbonyl group of cyclohexenones is a very interesting transformation because of the high synthetic versatility of the allylic alcohols.[35] Under Luche conditions,[36] **13a** was transformed into **16a** with good stereo induction (87:13 *dr*, Scheme 2.21).[37]



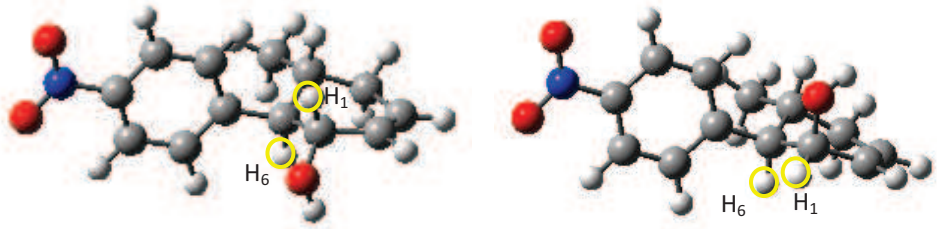
Scheme 2.21. Chemoselective reaction on C=O of **13a.**

[35] a) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307; b) J. K. Cha, N-S. Kim, *Chem. Rev.* **1995**, *95*, 1761; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.

[36] a) A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.*, **1981,** *103*, 5454; b) B. Bradshaw, G. Etxebarria-Jard, J. Bonjoch, *J. Am. Chem. Soc.* **2010,** *132*, 5966.

[37] Similar stereoselectivities but lower yields were obtained using DIBAL-H (with this reagent, a significant amount of 1,4-reduction was observed).

The relative stereochemistry of the newly created stereogenic center was assigned by comparing the different coupling constants between H1 and H6 of both diastereoisomers. The torsional angle H1-C1-C6-H6, determined in the optimized structures **16a** and **16a'** by computational studies at the DFT (B3LYP) level, is indicated in Figure 2.5 and is consistent with the observed coupling constant, which suggests an axial-axial relationship in compound **16a** (J = 11.6 Hz) and an axial-equatorial one in **16a'** (J = 3.4 Hz).



16a
J_{H1-H6} = 11.6 Hz
axial-axial relationship
torsion angle H1-C1-C6-H6 = -167.5°

16a'
J_{H1-H6} = 3.4 Hz
axial-equatorial relationship
torsion angle H1-C1-C6-H6 = -56.3°

Figure 2.5.

Thus, there seems to be a small preference for hydride insertion to give the more stable stereoisomer **16a** with the hydroxyl group in equatorial position. Most of the stereoselectivities that have been reported in the reduction of biased cyclohexanones can be explained taking into account torsional or steric effects.

In order to get some insight about the subtle reasons for the observed selectivity in our specific case, which involves a particular cyclohexanone featuring two substituents and a double bond, we decided to carry out some theoretical

calculations, which were performed at the DFT (B3LYP) level,[38,39] of the most stable conformer of the starting ketone **13a**.

The calculations gave structural parameters for **13a** fully comparable with those found in the X-ray structure of **15a**, with a torsion angle O-C_1-C_6-C_{ipso} = 17.8° and short distances (Å) both in the upper face between C_1 and H_5 (2.77) and H_{ortho} (2.93) and also in the lower face with H_6 (2.12).

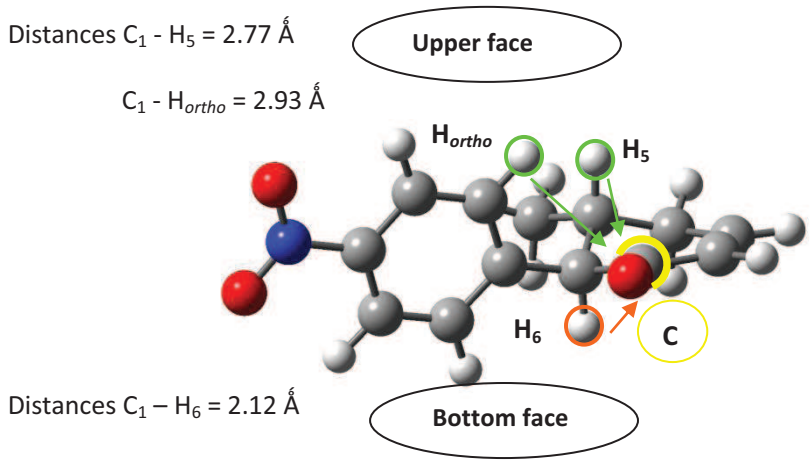
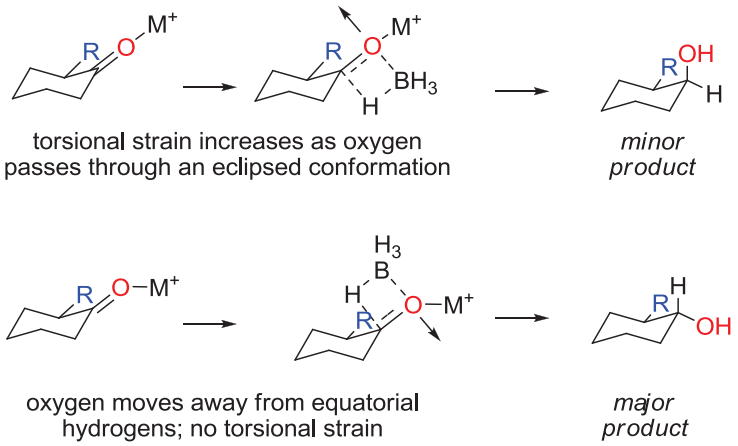


Figure 2.6. Calculated structural parameters of **13a**.

Thus, these studies revealed the scarce steric differentiation of the two prochiral carbonyl faces, suggesting that the observed stereoselectivity must be attributed to the different torsional effects that take place during the hydride attack to each face.[40] Thus, the major factor in the preference for the equatorial isomer is probably the

[38] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B,* **1988**, *37*, 785; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372.
[39] Gaussian 09, Revision B.01, M. J. Frisch, *et al*., Gaussian, Inc., Wallingford CT, **2010**.
[40] a) W. T. Wipke, P. Gund, *J. Am. Chem. Soc.* **1976**, *98,* 8107; b) J. C. Perlberger, P. Mueller, *J. Am. Chem. Soc.* **1977**, *99*, 6316; c) D. Mukherjee, Y. D. Wu, F. R. Fronczek, K. N. Houk, *J. Am. Chem. Soc.* **1988**, *110*, 3328.

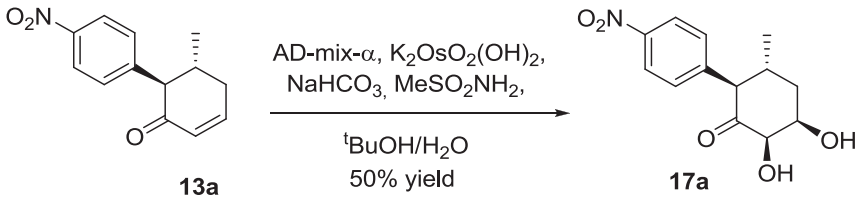
torsional strain, with the bulky 6-aryl group, that develops in the formation of the axial alcohol. This is in line with the generally accepted models for hydride additions to substituted cyclohexanones, wherein the less bulky hydride tends to go into the axial and the more bulky hydroxyl into the equatorial position of the resulting alcohol (Scheme 2.22).[41]



Scheme 2.22. Hydride addition to substituted cyclohexanones.

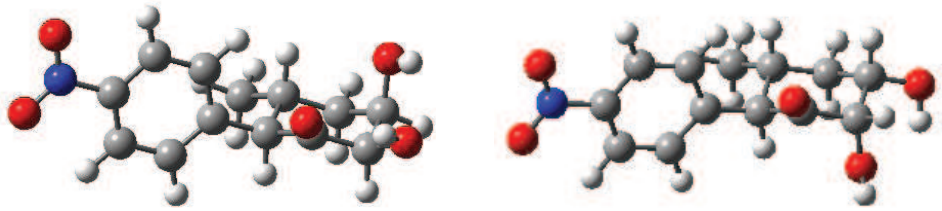
Then, we decided to perform some transformations on the double bond of the adducts **13**. In particular, dihydroxilation and epoxidation reactions of the double bond of **13a** afforded carbocyclic sugar analogues in a highly stereoselective manner (Schemes 2.23 and 2.24).[42] Compound **17a** was obtained *via* asymmetric Sharpless dihydroxylation,[43] adapting the original procedure to this less electron-rich charcter of the olefin, thus using an excess of osmium salt. Sodium bicarbonate was used in order to avoid the epimerization of the acidic α-carbonyl position.

[41] T. Ohwada, *Chem. Rev.* **1999**, *99*, 1337.
[42] The synthesis of similar compounds has been reported. See: J. Clayden, S. Parris, Cabedo, A. H. Payne, *Angew. Chem. Int. Ed.* **2008**, *47*, 5060.
[43] a) P. J. Walsh, K. B. Sharpless, *Synlett,* **1993**, 605; b) M. B. Cid, G. Pattenden, *Synlett,* **1998**, 540.



Scheme 2.23. Dihydroxilation reaction of compound **13a**

Compound **17a** was obtained as a single diastereomer in agreement with the selectivity expected under the conditions used in the asymmetric Sharpless dihydroxylation with AD-mix-α. Its stereochemistry and relative configuration were further confirmed via a combination of experimental and computational approach, as outlined below.



Upper face **17a** Bottom face **17a'**

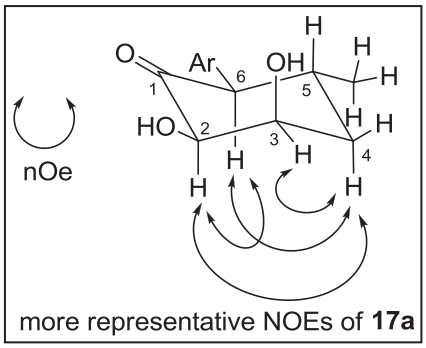
Figure 2.7. Most stable conformers of **17a** and **17a'**.

In particular, the most stable conformations of compound **17a** and its isomer **17a'** were determined by theoretical calculations (Figure 1.7). Then, the experimental ^{1}H NMR spectra were compared to these structures, trying to find the best match:

1) The high value (J = 11.8 Hz) of the coupling constant between H_5-H_6 indicates that the configuration at carbons C_5 and C_6 has not changed during the dihydroxilation reaction.

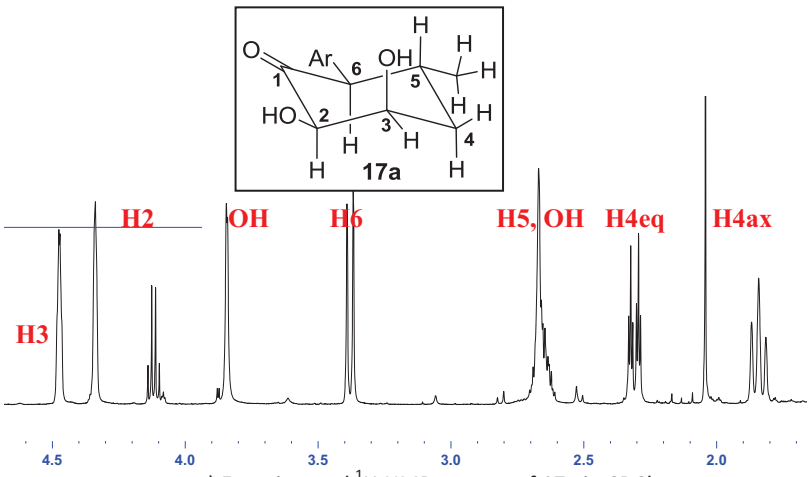
2) The value (J = 3.5 Hz) of the coupling constants between H_2-H_3 is in agreement with a *syn* disposition of these hydrogen atoms, as in **17a**.

3) The NOE observed between H_2 and H_6 and the absence of NOE between H_3 and H_5 is in agreement with the proposed structure of **17a**.

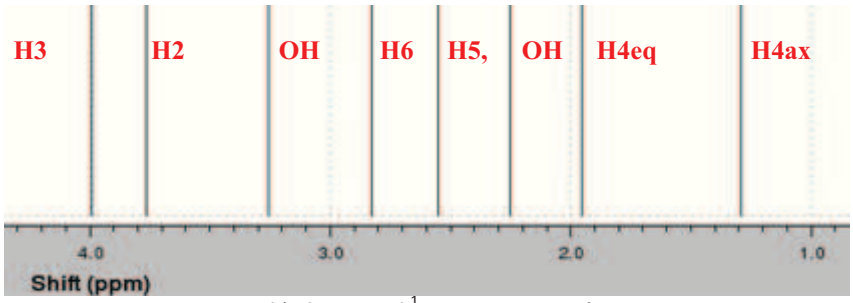


4) Finally, the stereochemical assignment was further confirmed by comparing the chemical shifts of experimental (Figure 2.8, a) and theoretical (Figure 2.8, b) ^{1}H NMR spectra of **17a**, when the OH groups are located in the upper face. The chemical shifts of the experimental spectrum match with the theoretical values obtained for **17a**. If the OH groups were located in the bottom face as in **17a'**, these groups would produce a strong deshielding of the H6 signal whereas the opposite effect would be observed for H5 signal (see below Figure 2.8, c).

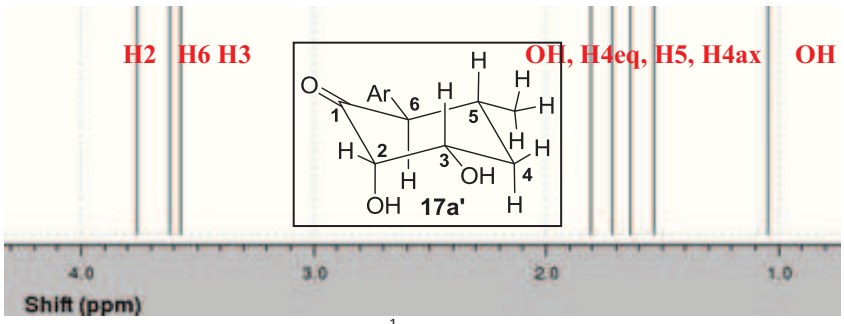
Thus, all together, we can safely assign the stereochemistry of the newly formed chiral centres in **17a** as shown above.



a) Experimental ^{1}H NMR spectra of **17a** in $CDCl_3$.



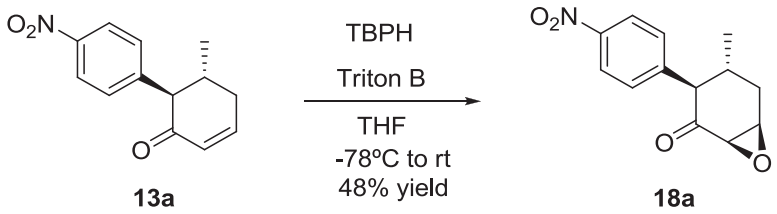
b) Theoretical ^{1}H NMR spectra of **17a**



c) Theoretical ^{1}H NMR spectra of diol-down **17a'**

Figure 2.8. Comparison of the a) experimental spectra and theoretical spectra of b) **17a** and c) **17a'**.

Epoxidation of **13a** with TBHP[44] yielded diastereomerically pure epoxide **18a** in moderate yield (Scheme 2.24).



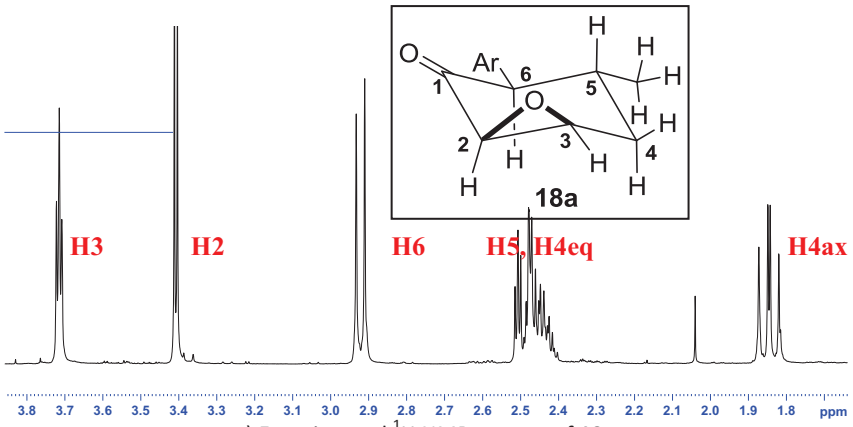
13a **18a**

Scheme 2.24. Epoxidation reaction of compound **13a.**

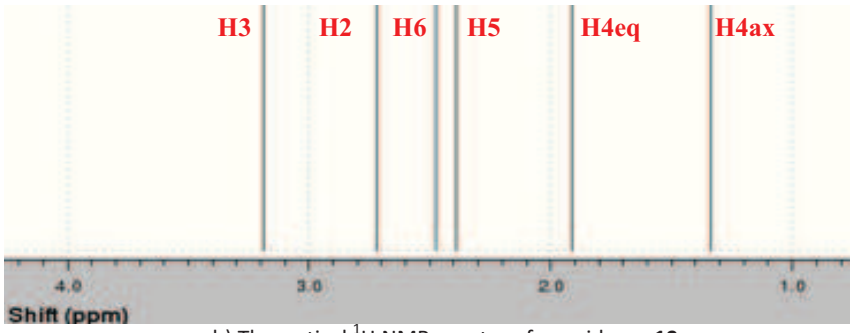
Since NOESY experiments did not allow to unequivocally establish the configuration of the only detected epoxide **18a**, we performed again calculations at the DFT (B3LYP) level, of the chemical shift values in the ^{1}H NMR spectra corresponding to the two possible stereoisomeric epoxides **18a** and **18a'**. Their comparison with the experimentally obtained spectra (Figure 2.9, a) supports the assignment indicated in Scheme 2.24.[45] The chemical shifts obtained theoretically for isomer **18a** (Figure 2.9, b), even if the exact values are not the same, are in agreement with the experimental values. However, according to the calculations, if epoxide oxygen were located in the bottom face as in **18a'** (epoxide down) it would produce a strong deshielding of the H6 signal whereas the opposite effect would be observed for H5 signal (Figure 2.9, c).

Presumably, torsional effects are again responsible for the observed stereoselectivity. Axial approach of the reagent to C3 is favored as equatorial approach would afford an enolate with a near eclipsing interaction of C3 and C4.

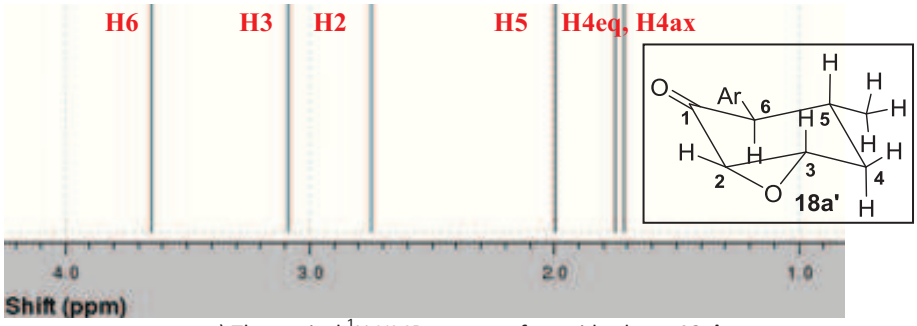
[44] E. Merino, R. P. A. Melo, M. Ortega-Guerra, M. Ribagorda, M. C. Carreño, *J. Org. Chem.* **2009**, *74*, 2824.
[45] C. F. Christian, T. Takeya, M. J. Szymanski, D. A. Singleton, *J. Org. Chem.* **2007**, *72*, 6183.



a) Experimental ^{1}H NMR spectra of **19a**



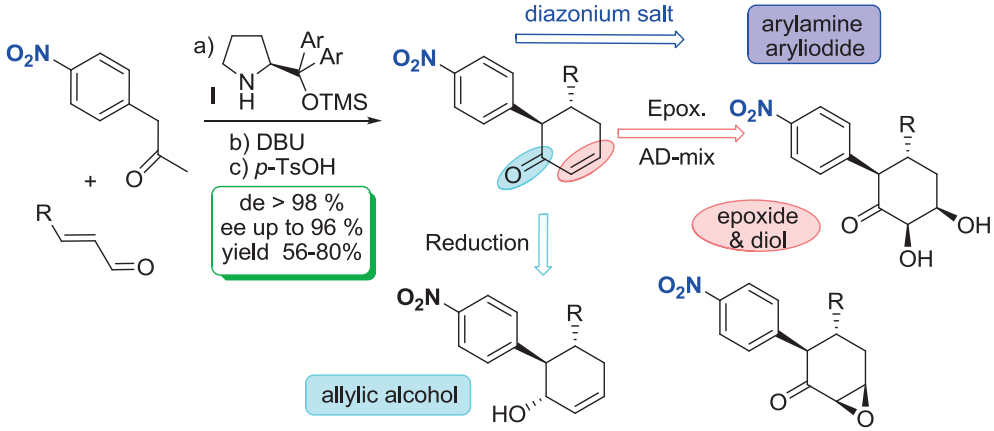
b) Theoretical ^{1}H NMR spectra of epoxide-up **19a**



c) Theoretical ^{1}H NMR spectra of epoxide-down **19a'**

Figure 2.9. Comparison of the a) experimental spectra and theoretical spectra of b) **18a** and c) **18a'**.

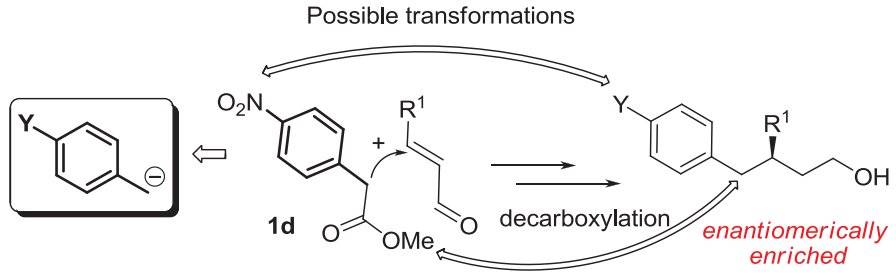
Therefore, we can summarize that *p*-nitrophenylacetone reacted with a variety of β-substituted α,β-unsaturated aldehydes to afford β-substituted α-aryl-cyclohexenones **13** *via* Michael addition / aldol reaction / dehydration protocol in a highly enantio- and diastereoselctive manner. Catalyst **I** was especially successful for aldehydes with alkyl substituents (ee up to 96%). The α-aryl-cyclohexenones can be easily functionalized not only on the aromatic ring but also on the enone moiety in an effective way. Thus, this sequence can be considered as a general, efficient and simple procedure for the synthesis of poly-substituted α-aryl cyclohexenones and cyclohexanones (Scheme 2.25).



Scheme 2.25. Arylacetone as nucelophile

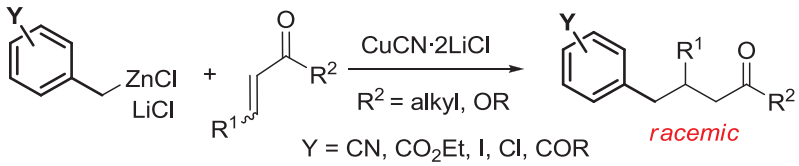
2.3 *p*-Nitrophenyl methyl acetate as nucleophile in organocatalytic 1,4-additions. Indirect β-benzylation of α,β-unsaturated aldehydes

We next applied the strategy of the nitro as a temporary activating group to the ester derivative **1d**. On the basis of previous results described in the preceding sections, we envisioned that the ester derivative could act as a masked functionalized benzylating reagent of α,β-unsaturated aldehydes (Scheme 2.26). The desired products would be obtained by subsequent decarboxylation of the resulting Michael adducts. Additionally, further derivatization of the nitro group would provide compounds not easily accessible by other routes.



Scheme 2.26. Formal benzylation of enals (*via* Michael addition / decarboxylation)

The introduction of benzyl-functionalized fragments to unsaturated carbonyl compounds is still a challenge in enantioselective catalysis. Indeed, only one method has been reported[46] to solve the problem efficiently in a racemic version of the reaction (Scheme 2.27). In this example the authors described the addition of aryl zincates to enones and acrilates.

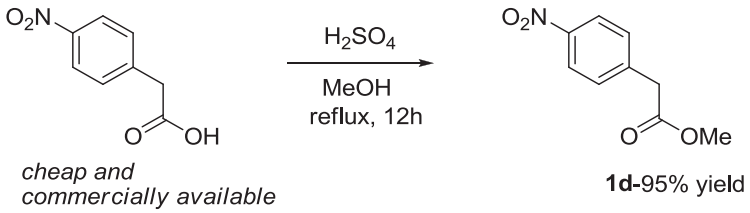


Scheme 2.27. Reactions with functionalyzed benzylic zincates

[46]. a) A. Metzger, M. A. Schade, P. Knochel *Org. Lett*. **2008**, *10*, 1107; b) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678 and references cited therein.

2.3.1 Model reaction. Optimization of the reaction conditions

Our investigations began with the synthesis of the ester nucleophile **1d**, carried out by simple Fischer esterification of the corresponding carboxylic acid under acidic catalysis (Scheme 2.28).



Scheme 2.28. Synthesis of derivative **1d**

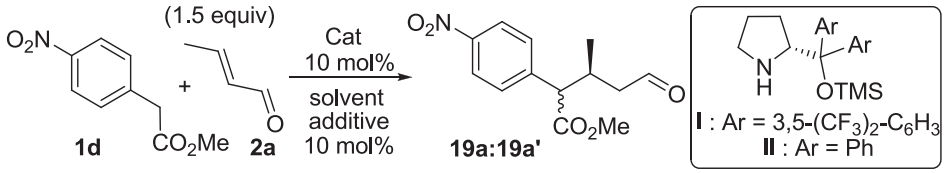
With the nucleophile in hand, following our usual strategy we started evaluating the viability of the reaction. As a model reaction we studied the addition of **1d** to crotonaldehyde (**2a**) looking for the optimal conditions of the Michael addition (Table 2.9). No reaction was observed with catalyst **I**[11] in the absence of additives (entry 1) or in the presence of the acidic additive $PhCO_2H$ (entry 2), whereas the addition of LiOAc yielded the expected compound **19** with moderate conversion and 80% ee (entry 3).

Preliminary experiments showed a problem for the determination of the enantiomeric excesses of the corresponding adducts. As expected from the experiences with the nitrile and ketone derivatives, the aldehydes products 20a and 20a' decomposed during HPLC analysis. In this casewe had to determine the ee after reduction of the Michael adducts and subsequent lactonization (see below).

With the method for the determination of the enantioselectivity of the reaction established, we continued with the screening of conditions. A similar result, but with better conversion and ee, was obtained using the less bulky silyl prolinol **II** as the catalyst. With this catalyst, we were able to establish that the use of basic additives led to good conversions and enantiomeric excesses (entry 8), whereas the addition of acidic additives had a negative effect on the reactivity with an inverse relationship

between the degree of conversion and the acidity of the additive (entries 4-7). By contrast, the influence of the additive on the *ee* value was not significant (compare entries 6 and 8). As the use of LiOAc as an additive has limitations derived from its low solubility in aprotic solvents (we found low reproducibility of reactions in CH_2Cl_2), we also decided to study the influence of tetrabutylammonium bromide (TBAB) as a neutral additive. The use of this additive was inspired by its known effect in the activation of sulfinil imines towards the aza-Henry reaction.[47]

Table 2.9. Optimization of the Michael addition of **1d** to **2a**.



Entry	Cat.	Solvent	Additive	Time (h)	Conv[a] (%)	*ee*[b] (%)
1	**I**	EtOH	-	48	0	-
2	**I**	EtOH	$PhCO_2H$	24	0	-
3	**I**	EtOH	LiOAc	48	65	80
4	**II**	EtOH	*p*-NO_2-C_6H_4-CO_2H	16	15	-
5	**II**	EtOH	$PhCO_2H$	16	23	-
6	**II**	EtOH	AcOH	16	47	88
7	**II**	EtOH	-	16	53	-
8	**II**	EtOH	LiOAc	16	87	89
9	**II**	EtOH	TBAB[c][d]	24	80	87
10	**II**	CH_2Cl_2	TBAB[c]	24	90	90

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture.
[b] Determined by HPLC after reduction and lactonization. See below
[c] 1 equiv was used.
[d] With 20 mol% of TBAB 70 % conversion was observed after 24 h

[47] J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, M. Belén Cid, *Org. Lett.* **2005**, *7*, 4407.

The addition of TBAB to reactions of **1d** and **2a** catalyzed by **II** in both aprotic (CH_2Cl_2) and protic (EtOH) solvents provided similar results to that obtained with LiOAc (compare entries 9 and 10 with entry 8).[48] It is worth noting that the reaction also worked with a catalytic amount of TBAB (see footnote d, table 2.9). Even if TBAB is soluble in different media, and has been used as counterion to solubilise proline in the activation of aldehydes, it had never been used before as an additive in iminium ion catalysis.[49] Thus we decided to investigate in detail the effect of this salt with a combined experimental and computational approach, as described later in the next chapter.

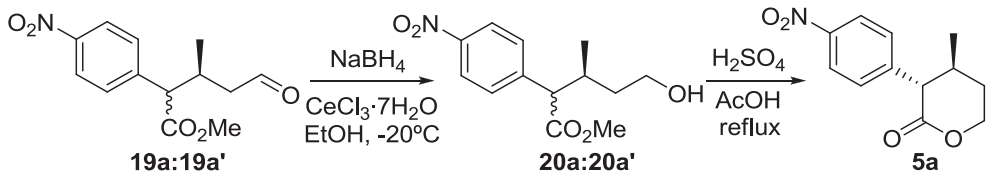
2.3.2 Transformation of the adducts

Before going to the scope of the reaction, we first need to mention the synthetic elaborations performed on the Michael adducts. As commented before, the aldehydes **19** decomposed during HPLC analysis. We first tried the reduction of these aldehydes to the corresponding alcohols **20** and **20a'** with $NaBH_4$ as a possibility to determine the enantiomeric excess. However, in this case the resolution of the peaks in the HPLC chromatograms was almost impossible. A possible reason for this fact may be the transesterification or lactonization processes occurring during the injection of such compounds in the HPLC columns. Thus, in order to determine the enantiomeric excesses in the most straightforward way, we transformed the Michael adducts into the corresponding known lactone **5a** after the reduction[50] (Scheme 2.29).

[48] a) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem., Int. Ed*. **2008**, *47*, 10187. b) J. E. Hein, J. Burés, Y.-H. Lam, M. Hughes, K. N. Houk, A. Armstrong, D. G. Blackmond *Org. Lett.* **2011**, *13*, 5644.

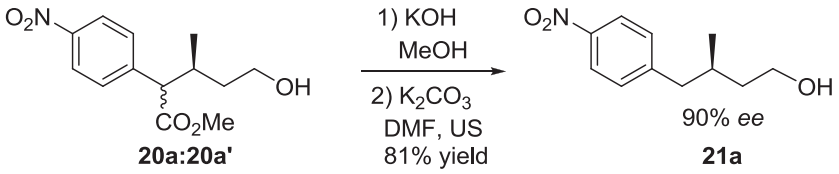
[49] a) E. J. Corey, F. Y. Zhang, *Angew. Chem. Int. Ed*. **1999**, *38*, 1931; b) H. Zhao, B. Qin, Z. Liu, Z. Feng *Tetrahedron,* **2007**, *63*, 6822. For the use of TBAB in imine activation, see: J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, M. B. Cid *Org. Lett.* **2005**, *7*, 4407.

[50] D. Caine, S.D. Venkataramu, A. Kois, *J. Org. Chem.* **1992**, *57*, 2960.



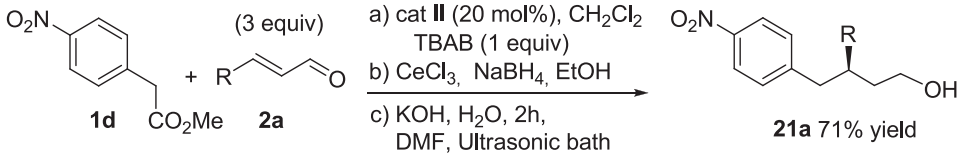
Scheme 2.29. Transformation for the determination of the ee.

As our objective was the decarboxylation, it was necessary to remove the ester group without affecting the enantiomeric excess of the Michael adducts to establish the validity of nucleophile **1d** as a synthetic equivalent of a benzylic anion. Thus, the corresponding alcohols **20** were subjected to hydrolysis of the ester group under basic conditions and subsequent decarboxylation by ultrasound treatment[51] to afford **21a** in high yield and 90% ee (Scheme 2.30).



Scheme 2.30. Hydrolysis and decarboxylation of **20a:20a'**.

As for the previous nucleophiles, it was possible to apply a sequential procedure Michael addition / reduction / decarboxylation without isolation of the intermediates and just one chromatographic purification at the end of the process, with an overall yield of 71% for **21a** from **1d** (Scheme 2.31).



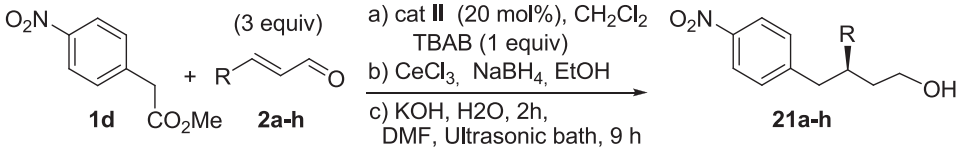
Scheme 2.31. Three steps protocol

[51] For other example of decarboxylation of nitrophenyl esters: J.M. Kim, S. H. Kim, H. S. Lee, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 5322.

2.3.3 Scope of the reaction

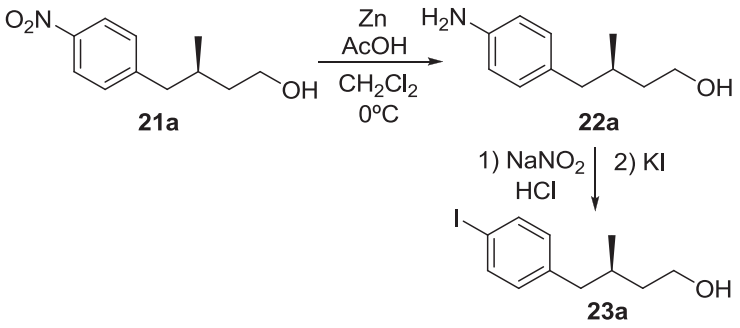
With the optimized sequential procedure in hand, the overall process for the conversion of **2a** to **21a** was then applied to other aldehydes **2** (Table 2.10). Alcohols **21** with linear (entries 1-4) and branched aliphatic residues (entry 5) were obtained in moderate overall yields and excellent *ee's.* The reaction of the phenyl-substituted aldehyde **2f** (entry 6) was also successful within a shorter reaction time. However, when the reaction was stopped after 24h, the racemic compound was obtained. I is worth recalling that this behaviour was also observed in the case of ketone **1c** (even at shorter times). The influence of the reaction conditions in the decrease of the *ee* with the time will be discussed in the next chapter. In order to obtain better enantioselectivities with aromatic enals **2g-2h** catalyst **I** was used (entries 7 and 8). With this catalyst, the derivative with an electron withdrawing group was obtained with only moderate *ee* (entry 8).

Table 2.10. Scope of the Michael /reduction/decarboxylation sequence.



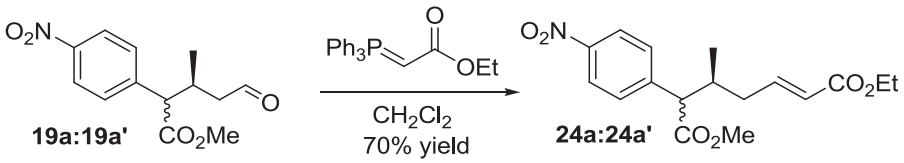
Entry	2 (R)	Michael addition Conv[a] (%)	time (h)	Overall Yield (%)	*ee*[b] (%)
1	**a** (Me)	100	24	71	90
2	**b** (Et)	100	24	61	90
3	**c** (*n*-Pr)	75	66	52	91
4	**d** (*n*-Bu)	80	96	55	96
5	**e** (*i*-Pr)	80	66	59	94
6	**f** (Ph)	100	2	66	86
7[c]	**g** (*p*-OMe-C_6H_4)	100	48	68	90
8[c]	**h** (*p*-NO_2-C_6H_4)	80	48	55	64

As in the case of the previous derivatives, we carried out a synthetic transformation converting the nitro group on a versatile (considering possible cross-coupling reactions) iodo substituent (Scheme 2.32).



Scheme 2.32. Transformations of the nitro group

Next to this, we have also performed the Wittig olefination on aldehydes **19** (Scheme 2.33).

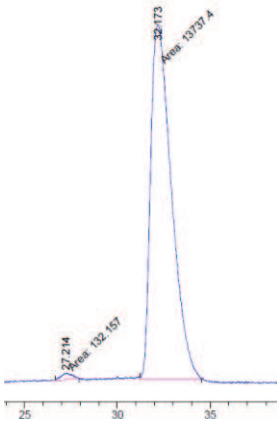


Scheme 2.33. Wittig reaction

2.3.4 Stereochemical Assignment

The absolute configuration at C-3 was determined after transformation of the Michael adducts **19a** and 19**20a'** into the known lactone **5a** by reduction and cyclization (Scheme 2.30). The sign of the optical rotation value as well as the HPLC chromatogram (Figure 2.10) were in agreement with an *(S)*-configuration. The configuration of the remaining compounds was assigned assuming a stereochemically homogeneous behaviour in the Michael addition, according to the general accepted model for this type of iminium ion catalyzed reactions (see Scheme 2.11).

98% ee, derived from nucleophile nitrile **1b**



90% ee, derived from nucleophile ester **1d**

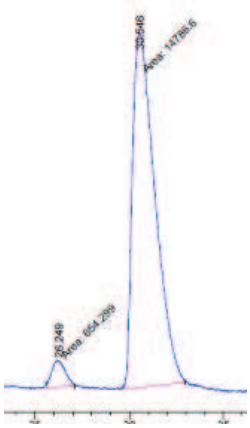


Figure 2.10. Comparison of HPLC chromatograms

Therefore, *para*-nitrophenyl acetate was found to be an efficient nucleophile in iminium ion catalyzed Michael additions to enals. Whereas alcohol reduction and cyclization gave the same lactone products **5** obtainable from the arylacetonitrile nucleophile **1b**, decarboxylation provided an unprecedented and highly valuable formal asymmetric benzylation of enals. The initial low reactivity showed by derivative **1d** could be solved using TBAB as additive in the Michael addition. The possible role of this additive was investigated and some conclusions are discussed in the next chapter.

However, even if the catalytic asymmetric reaction worked very well with aliphatic enals, cinnamaldehydes were more problematic, giving usually moderate and time dependant enantioselectivities. Thus, looking for synthetic alternatives potentially useful also for cinnamaldehydes, we turned our attention towards the corresponding thioesters.

2.4 *p*-Nitrophenyl ethyl thioester as nucleophile in organocatalytic 1,4-additions

Until this moment, we have described a series of nucleophiles which react successfully in organocatalytic Michael additions *via* iminium ion activation. Moreover, we have demonstrated their synthetic utility through a number of transformations. However, at this point we had still unsolved the question of finding a general nucleophile that performs well in terms of reactivity and enantioselectivity with both types of enals (aliphatic and aromatic).

Summarizing the results obtained until now, β-alkyl enals exhibited very good reactivity and enantiomeric excess with the nitrile **1b-1b'** and the ketone **1c**, whereas the ester **1d** had some problems of reactivity. On the other hand, β-aryl enals afforded lower enantioselectivities with all these nucleophiles (in some cases even racemic products were obtained). In contrast, the trifluoroethyl thioester **1a** described by Barbas (see reference 6) provided good yields and enantiomeric excess with β-aryl enals but showed problems of reactivity and lower enantioselectivity with β-alkyl enals (Figure 2.11). However, no general explanations for these observations were found or general conditions for each type of enal and nucleophile were established. This aspect will be discussed in detail in the following chapter.

According to these results, we hypothesized that this different behaviour could be due to the structural differences in the nucleophile but also to the experimental conditions. Optimization studies for our nucleophiles **1b, 1c** and **1d** were performed on the *trans*-crotonaldehyde, whereas trans-cinnamaldehyde was used with **1a**. As the optimal conditions established in each case are different, we hypothesized that this indiscriminate optimization could be a possible cause of the failures of yield and enantioselectivity for arylacetic pro-nucleophiles with either aromatic or aliphatic enals. This suggests that an independent optimization of both types of electrophiles could improve the results for every nucleophile.

With the aim of synthesizing a general aryl acetic pro-nucleophile derivative we envisioned a hybrid structure with both synthetic features: nitro group and thioester

moiety. With this nucleophile we expected to achieve good results as well as understand better the behaviour of this type of pro-nucleophiles in the Michael reaction.

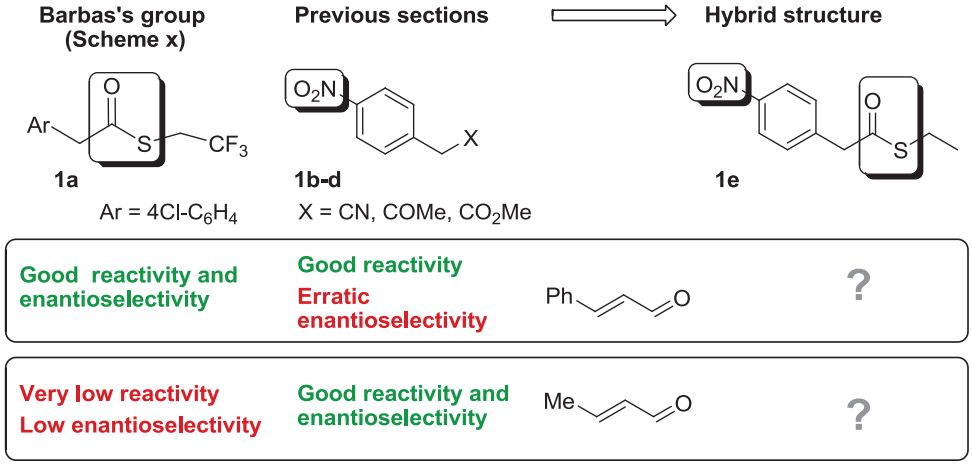
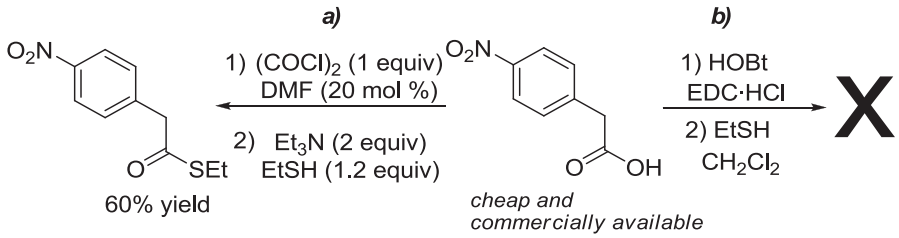


Figure 2.11. Proposal of a hybrid nucleophile

2.4.1 Synthesis of the thioester derivative

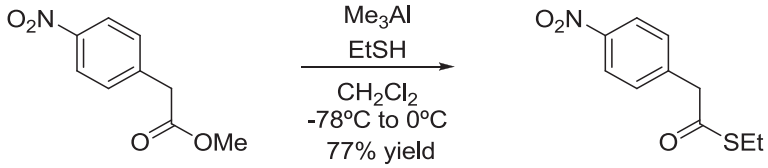
We first tried the synthesis of thioester **1e** with the most conventional methods described in the literature[52] *via* formation of the acid chloride (Scheme 2.34, a). The desired compound was obtained only with moderate yield and hence we decided to apply the same procedure described by Barbas for the synthesis of their derivatives[6] (Scheme 2.34, b). Unfortunately, this method did not afford the compound **1e**.

[52] T. Miyazaki, Y. Han-ya, H. Tokuyama, T. Fukuyama, *Synlett* **2004**, *3*, 470-480.



Scheme 2.34.

In order to find an appropriate method to provide the desired pro-nucleophile in good yields and with minimal lab manipulations, we performed an extensive optimization after a carefully search in the literature. Finally **1e** could be synthesized from the corresponding ester derivative using a procedure described for a similar structure[53] (Scheme 2.35).



Scheme 2.35. Synthesis of **1e**

2.4.2 Model reaction. Optimization of the reaction conditions

Once we had a method to synthesize **1e**, we began the optimization of the Michael addition. As commented above, we thought that an independent optimization of β-aromatic and β-aliphatic substituted enals could allow us to find optimal conditions to achieve good results with both type of enals.

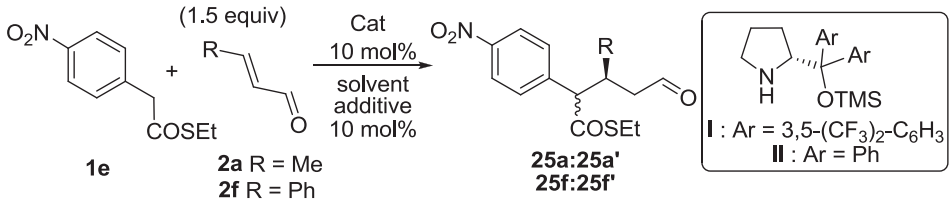
In all the cases, Michael reactions afforded mixtures of two diastereomers (**25** and **25'**, epimers at C-2), with *dr* values ranging between 1:1 and 2.3:1. It is important to note that as in the case of the previous derivatives described, it was not possible to

[53] D. Swinnen, D. Hilvert, *Org. Lett*. **2000**, *2*, 2439.

determine the enantiomeric excesses directly in the aldehydes resulting from the Michael addition. In this case we determined the enantioselectivity of the reaction performing the reduction over the aldehydes. This procedure is described in detail in the next section.

The results from the independent optimization are depicted in Table 2.11.

Table 2.11. Optimization of the Michael addition of **1e** to **2a** and **2f**.[a]



Entry	R^1	Cat	Solvent	Additive	t (h)	Conv (%)[b]	*ee* (%)[c]
1	Ph	**I**	CH_2Cl_2	-	6	5	-
2	Ph	**II**	CH_2Cl_2	-	6	90	10
3	Ph	**I**	EtOH	-	0.25	50	87
4	Ph	**II**	EtOH	-	0.25	91	60
5	Ph	**I**	EtOH	-	3.5	95	87
6	Ph	**II**	EtOH	-	3.5	95	<5
7	Ph	**I**	EtOH	TBAB[d]	3.5	>95	74
8	Ph	**I**	EtOH	LiOAc	3.5	>95	86
9	Ph	**I**	EtOH	$PhCO_2H$	3.5	95	90
10[e]	**Ph**	**I**	**EtOH**	**$PhCO_2H$**	**36**	**95**	**94**
11	Me	**I**	CH_2Cl_2	-	6	<5	-
12	Me	**II**	CH_2Cl_2	-	6	70	-
13	Me	**I**	EtOH	-	6	36	75
14	Me	**II**	EtOH	-	6	61	75
15	Me	**II**	EtOH	-	48	85	75
16	**Me**	**II**	**EtOH**	**TBAB[d]**	**3**	**>95**	**80**
17	Me	**II**	EtOH	LiOAc	6	95	68
18	Me	**II**	EtOH	$PhCO_2H$	6	35	74

[a] The reactions were carried out at rt on a 0.2 mmol scale with 2 (1.5 equiv) and $[\mathbf{1e}]_0$ = 0.5 M.
[b] Determined by ^{1}H NMR analysis of the crude of the Michael addition.
[c] Determined by chiral phase HPLC analysis of the alcohol **26** resulting in the reduction of the major *syn*-**25** diastereoisomer.
[d] 1 equiv was used.
[e] Performed at -20°C.

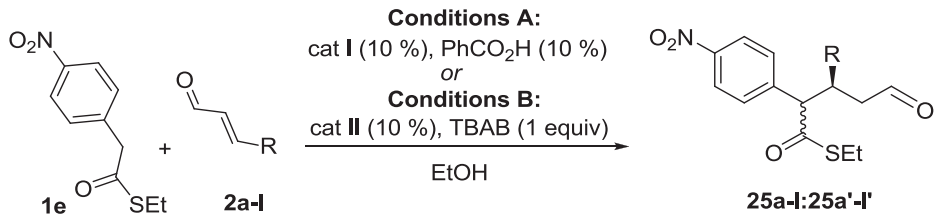
Concerning the optimization reactions with cinnamaldehyde **2f**, we can clearly deduce that EtOH is more efficient as solvent than CH_2Cl_2 and the reactions with catalyst **II** are faster than reactions with catalyst **I** (compare entries 1 and 2 with 3 and 4). However, the influence of the catalyst on the enantioselectivity is very remarkable. In the case of catalyst **I** the enantioselectivity is higher and remains almost constant for longer reaction times (compare entries 3 and 5); whereas *ee* is lower with catalyst **II** and significantly decreases with time (compare entries 4 and 6). This behaviour suggests that the decrease of the *ee* could be due to the reversivility of the process in reactions catalyzed by **II**. Therefore catalyst **I**, although it is less effective in terms of reactivity, should be chosen for these reactions because it is less prone to reversibility. Finally, we have studied the effect of some additives in these reactions, with the $PhCO_2H$ providing better *ee* than TBAB and LiOAc (compare entries 7, 8 and 9). This analysis suggests that the best conditions to perform the reactions of **1e** with β-aryl enals would be those involving the use of catalyst **I** in the presence of $PhCO_2H$ as additive. Finally, an improvement of the *ee* was achieved by decreasing the temperature (entry 10).

Reactions carried out with crotonaldehyde **2a** (entries 11-18) are slower than those with cinnamaldehyde **2f** under similar conditions. The influence of the catalyst and the solvent on the reaction rate is less significant in the case of **2a**, although reactions catalyzed by **II** are still slightly faster (entries 11-14).

Nevertheless, the main difference regarding aromatic enals is the lack of-influence of the reaction time on the ee obtained with catalyst **II** (entries 14 and 15), which suggests that reactions with crotonaldehyde **2a** are less prone to reversibility than those with cinnamaldehyde **2f**. As a consequence, catalyst **II** was chosen to continue the optimization process. To compare the influence of additives with the aromatic enals (entries 7-10), we performed the reactions in EtOH. We observed that reaction times decreased with TBAB and LiOAc (entries 16 and 17) and increased with $PhCO_2H$ (entry 18). The best reactivity / enantioselective balance for aliphatic enals was achieved using catalyst **II** in the presence of TBAB (entry 16).

2.4.3 Scope of the reaction

Table 2.12. Scope of the Michael addition.[a]



Entry	Enal	Conditions	Prod	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	**2f**(Ph)	**A**	**25f**	-20	36	93	94
2	**2g** (*p*-OMe-C_6H_4)	**A**	**25g**	-20	60	70	87
3	**2k** (*o*-OMe-C_6H_4)	**A**	**25k**	15	36	90	88
4	**2h** (*p*-NO_2-C_6H_4)	**A**	**25h**	15	84	75	86
5	**2l** (2-Furyl)	**A**	**25l**	rt	48	60	70
6	**2a** (Me)	**B**	**25b**	rt	6	85	80
7	**2e** (^{i}Pr)	**B**	**25e**	rt	48	80	80
8	**2f** (Ph)	**B**	**25f**	rt	15'	50	44
9	**2f** (Ph)	**B**	**25f**	rt	3	85	<5
10	**2a** (Me)	**A**	**25a**	rt	96	80	83
11	**2e** (^{i}Pr)	**A**	**25e**	rt	48	50	92

[a] Reactions were carried out on a 0.4 mmol scale with 3 equiv of the corresponding aldehyde and $[\mathbf{1e}]_0$ = 0.5 M.
[b] Isolated yield of **25**.
[c] Determined by chiral phase HPLC analysis of the corresponding alcohol **26** resulting in the reduction of the major *syn*-**25** diastereoisomer.

Once established the conditions at the entries 10 (conditions A: catalyst **I** and $PhCO_2H$ as additive) and 16 (conditions B: catalyst **II** and TBAB as additive) as the best ones for β-aryl and β-alkyl enals respectively, we studied the scope of the reactions of **1e** with different conjugated aldehydes **2**. Results are collected in Table 2.12.

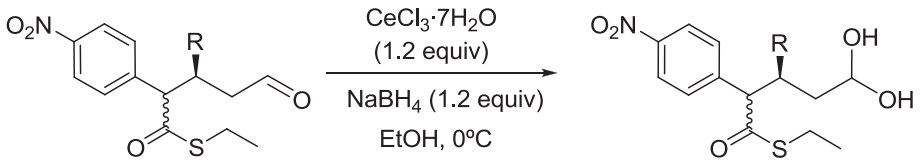
Aryl derivative **2f** and the aryl substituted enals **2g**, **2h** and **2k**, reacted with a similar enantioselectivities (>86%) under conditions A, regardless of the electron character of the substituents at the aryl ring. Even the heteroaryl substituted enal **2l** evolves in a similar way but with a slightly lower stereoselectivity (entry 5). Concerning β-alkyl enals, an increase in the size of the substituent did not have a significant influence on the stereoselectivity but, obviously, decreases the reactivity (compare entries 5 and 6).

In order to confirm our hypothesis on the importance of the careful tuning of the reaction conditions depending on the nature of the enal we employed the optimized conditions for aromatic enals with the aliphatic ones and vice versa. Entries 8-11 clearly show that the reaction conditions are not interchangeable. When we used catalyst **II** and TBAB as additive (conditions B, optimized for aliphatic enals) with cinnamaldehyde we observed a fast reaction but a very low *ee* (entry 8), evolving to the racemic compound after 3 h of reaction (entry 9). When conditions A (optimized for aromatic enals) were employed with the aliphatic ones **1e** the corresponding adducts were obtained with good enantioselectivity but reaction times were remarkably longer than when TBAB was used (compare entries 6 - 10 and 7 - 11).

We suspect that this behavior is not restricted to the thioester nucleophile **1e**, as it was even more evident with the less reactive ester **1d**, which did not afford the desired products when catalyst **I** and acidic additives were used with aliphatic enals. Thioester **1e** in contrast reacted with catalyst **I** and benzoic acid as additive (conditions A) with aliphatic enals, requiring longer reactions times. However, these set of conditions was not valid for the thioester **1a**, indicating that the structural features of the pro-nucleophiles are also very important, as it will be discussed later.

2.4.4 Reduction of the Michael adducts

As described for the other arylacetic derivatives, it was not possible to determine the enantiomeric excesses of the Michael addition directly on the aldehydes. Thus, we performed the reduction of the aldehydes **25:25'** to the corresponding alcohols as a first attempt. However, the reduction with $NaBH_4$ in MeOH at 0°C[54] afforded a complex reaction mixture with the thioester group partially reduced. To avoid the thioester reduction (as in the case of the ester derivative **1d**), we performed the reduction in the presence of $CeCl_3 \cdot 7H_2O$; however, the reaction was sluggish and afforded the desired alcohols in very low yields. Under Luche conditions, aldehydes undergo rapid acetalization (or hydration), which can prevent their reduction (Scheme 2.36). This may be the reason for the little amount of alcohol obtained after the reaction. It is worth nothing that we did no observe the same phenomenon in the reduction of the Michael adducts of ester **1d**.



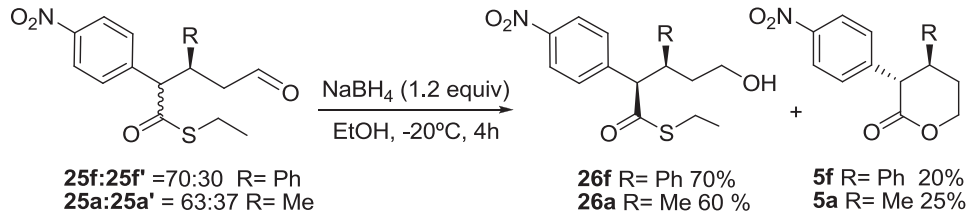
Scheme 2.36. Possible acetalization

We then tried to optimize the reduction of the Michael adducts only with $NaBH_4$, using low temperatures to avoid thioester reduction. The reaction afforded surprisingly diastereomerically pure alcohols **26**[55] in moderate yields. In order to understand this result, we performed some DFT calculations into the thermodynamic stability of both alcohols (*syn* and *anti* diastereomers). However, both alcohols had almost the same energy (see below).

[54] Conditions used by Barbas, see ref 6.

[55] With the other derivatives we always obtained almost 1:1 diastereomeric mixtures after reduction.

A carefully analysis of the crude ^{1}H NMR spectra of the reaction mixture obtained from **25a:25a'** allowed us to understand what was happening during the reduction process. The reductions of the mixture of the two diastereomeric aldehydes (epimers at C-2) provided in fact a new mixture, formed by the diastereomerically pure alcohol **26a** and the corresponding lactone **5a** (Scheme 2.37). Alcohol **26a** resulted from the reduction of the major aldehyde **26a**, whereas lactone **5a** was obtained by spontaneous cyclization of the alcohol **26a'**[56] derived from the corresponding minor diastereomers **25a'**.[57] This reaction was general for the rest of aldehydes studied (Table 2.12). The major diastereomer **26** was obtained in quantitative yield from the major aldehyde **25** and the minor aldehydes **25'** afforded the corresponding lactones **5** (see below). The appropriate separation of the corresponding alcohols **26a-g** by HPLC, allowed us to determine the enantiomeric excesses indicated in Tables 2.11 and 2.12.



25f:25f' =70:30 R= Ph
25a:25a' = 63:37 R= Me

26f R= Ph 70%
26a R= Me 60 %

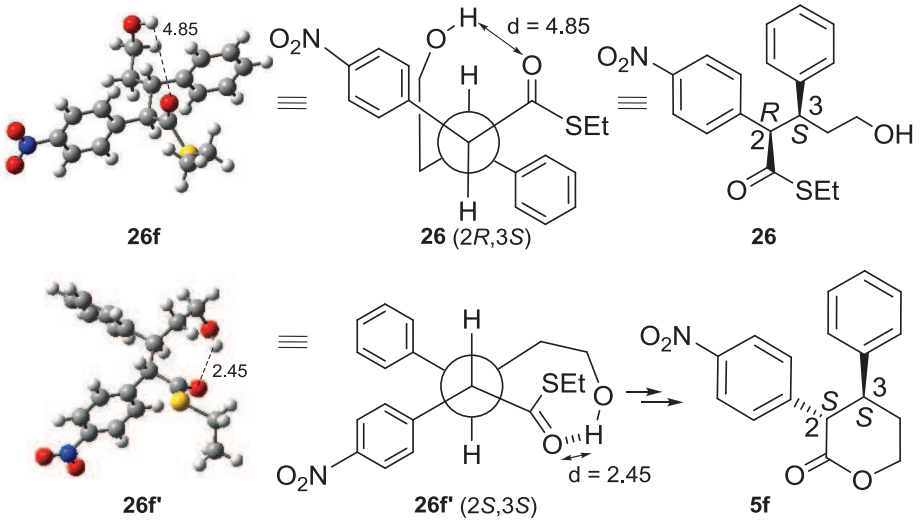
5f R= Ph 20%
5a R= Me 25%

Scheme 2.37. Reduction of Michael the adducts **25**

The relative configuration of alcohols **26f** and **26f'** was determined by comparison of their chemical shifts on the^{1}H-NMR spectra with those obtained by theoretical calculations at the DFT (B3LYP)[58] level by using Gaussian 09.[59] Molecular structures of the most stable conformer of each diastereomer are shown in Scheme

[56] Traces of these alcohols were detected when the reactions were performed in large scale.
[57] We have confirmed that diastereomerically pure aldehyde **28** afforded **29** quantitatively under the reduction conditions with no epimerization.
[58] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B,* 1988, **37**, 785. b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372.
[59] Gaussian 09, Revision B.01, M. J. Frisch *et al*., Gaussian, Inc., Wallingford CT, 2010.

2.42. Interestingly, a hydrogen bond between the hydroxyl group and the thioester group is only observed in the minor diastereoisomer **26'**, which could explain the easy formation of lactone **5** preventing the isolation of **26'** (Scheme 2.38). In fact, **26f'** was only detectable when the reaction was performed on a large scale.

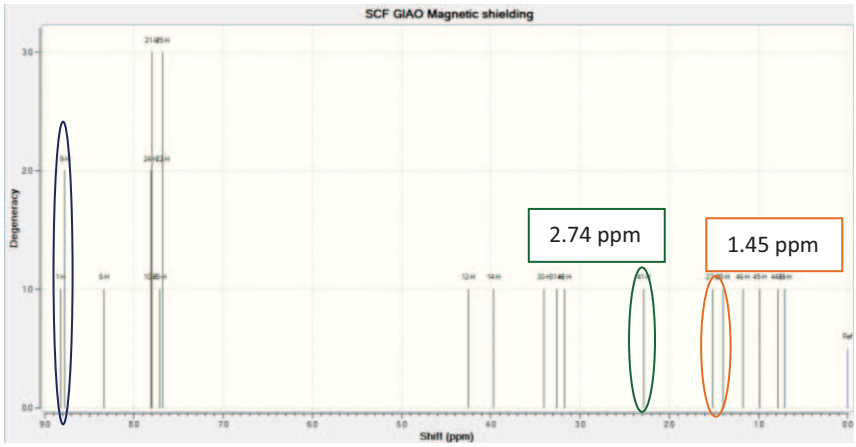


Scheme 2.38. Molecular structures of alcohols 4A and 4A'. Representative distances (Å) H-O are indicated.

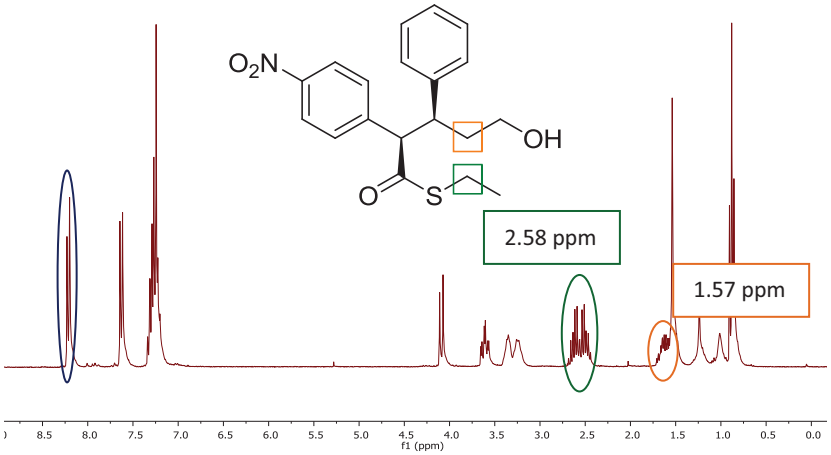
2.4.5 Assignment of the relative configuration of alcohols 26f:26f'

The relative configurations of **26f** and **26f'** were deduced by comparison of theoretical ^{1}H-NMR spectral results, provided by Dr Inés Alonso, with the ^{1}H-NMR experimental spectra of both diastereoisomers.

Major diastereomer 29f:



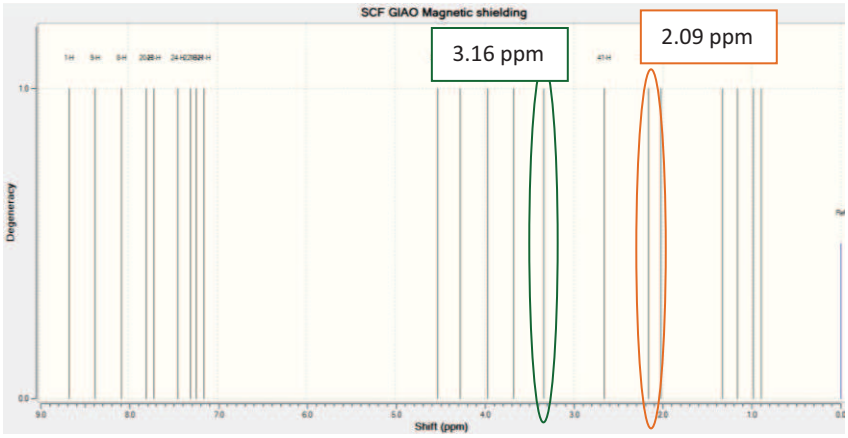
a) Theoretical spectrum of **26f**



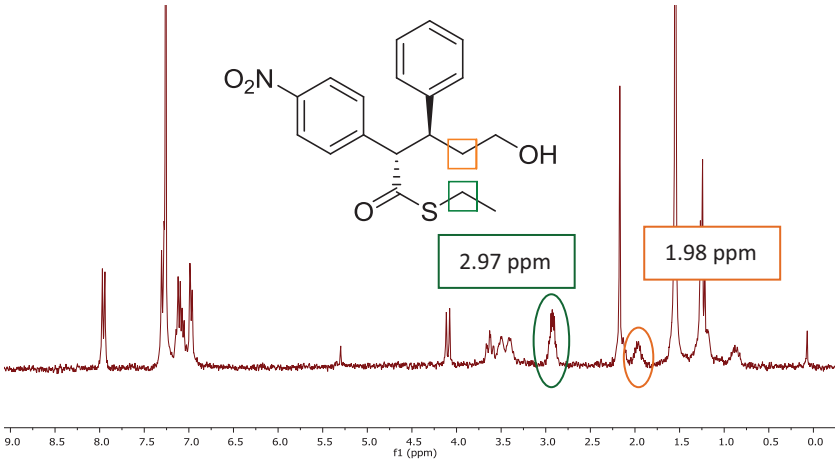
b) Experimental spectrum of **26f**

Figure 2.12. Comparison of the a) experimental and b) theoretical spectra of **26f**.

Minor diastereomer 26f'



a) Theoretical spectrum **26f'**



b) Experimental spectrum **26f'**

Figure 2.13. Comparison of the a) experimental and b) theoretical spectra of **26f'**.

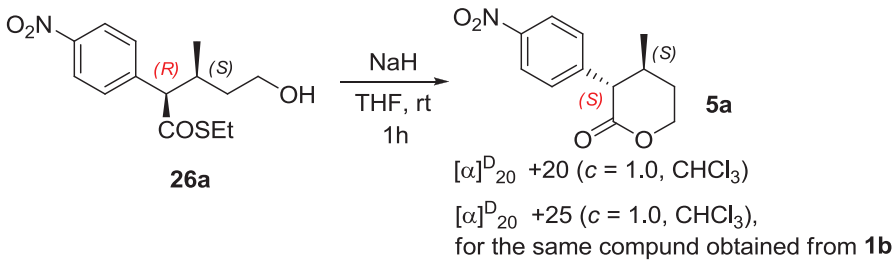
Even if the experimental spectra of both diastereomers are very similar, we can observe small differences. The aromatic protons for the major diastereomer **26f** are de-shielded to lower field, whereas in the minor diastereomer **26f'** these protons appear below the chloroform signal. Moreover, the α-protons to the thioester and

hydroxyl groups are more shielded than the corresponding protons in the minor diastereomer. This pattern is in agreement with the theoretical spectra. Thereby we could assign the relative configuration of C-2 and C-3 as *syn* disposition (see Figures 2.12 and 2.13).

2.5.6 Transformations of the Michael adducts

To illustrate the versatility of thioester group, several transformations have been carried out. Formation of lactones **5** and the decarboxylation reaction had been previously optimized in the Michael adducts obtained from aldehydes with aliphatic substituents and the nitrile and ester nucleophiles **1b** and **1d** respectively. As these nucleophiles did not afford high enantioselectivities with aromatic enals, we optimized the reactions of lactonization and decarboxylation from alcohol **26f**, featuring the thioester moiety, in order to obtain these compounds in high enantioselectivities.

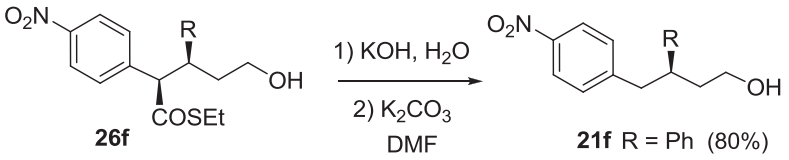
Diastereomerically pure lactones were formed by treatment of the corresponding alcohols **26a-f** with NaH, indicating that reactions took place with complete epimerization at C-2 (Scheme 2.39). These transformations allowed us to unequivocally determine the absolute configuration of adducts resulted from the Michael addition by chemical correlation with lactone **5a** previously synthesized (see previous sections).



Scheme 2.39. Lactonization and comparison of optical rotation values.

The sign of the optical rotation value as well as the HPLC chromatogram were in agreement for an *(S)*-configuration. The configuration of the rest of the compounds was assigned assuming a stereochemically homogeneous behaviour in the Michael addition (see Scheme 2.11).

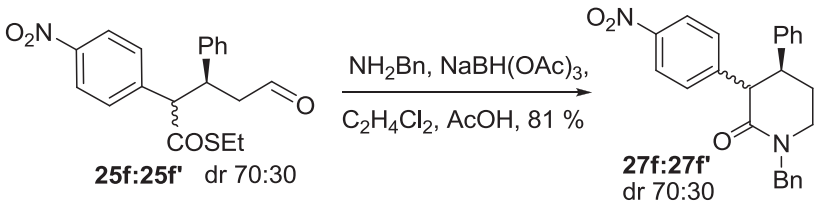
Decarboxylation of the alcohol **26f** to give compound **21f** also converts the thioester derivative **1e** in masked reagent for the enantioselective β-benzylation of enals, which is significant because as mentioned above, the introduction of functionalized benzylic substituents is not an easy task, even in racemic version.[46] Compound **21f** was prepared by hydrolysis of the thioester group to the acid under basic conditions followed by decarboxylation (Scheme 2.40).



Scheme 2.40. Decarboxylation of the alcohol **26**

Piperidone pharmacophore is a privileged structure, widely found in natural products, which displays a broad-spectrum of biological actions. The reductive amination of the aldehydes mixture **25f:25f'** and its subsequent cyclization[60] led us to obtain the lactams **27f**:**27f'** as a (70:30) diastereomeric mixture in 81 % yield. Interestingly, whereas lactone **5f** was obtained diastereomerically pure (Scheme 2.39), the afforded lactam **27f** kept the ratio of diastereisomers of the starting material (70:30) (Scheme 2.41).

[60] K. E. Murphy, A. H. Hoveyda, *Org. Lett.* **2005**, *7*, 1255.

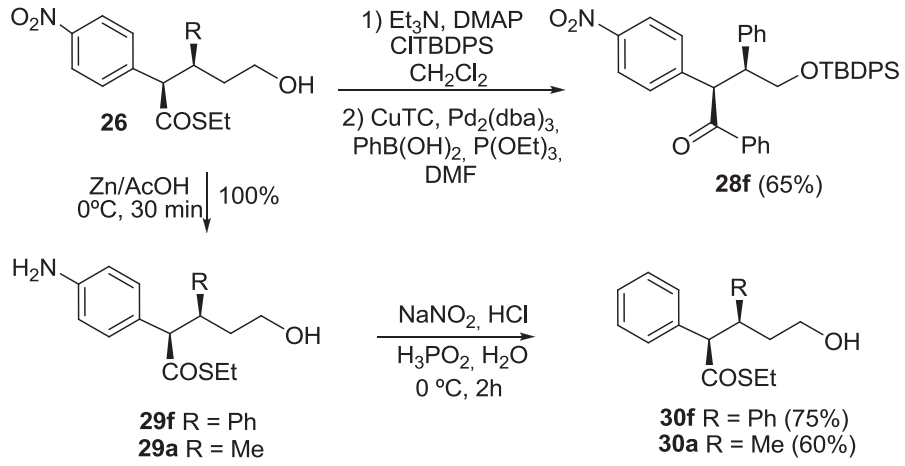


Scheme 2.41. Reductive amination of **25f** to prepare lactam **27f**.

Moreover, we also performed the cross coupling reaction[61] of the protected alcohol with phenyl boronic acid, yielding the ketone **28** in 65% yield (Scheme 2.42). The synthesis of compound **28** shows that it is possible to prepare enantio and diastereomerically pure α-aryl ketones. As mentioned earlier, the alternative method of α-arylation of ketones is not a standard transformation.[3,4]

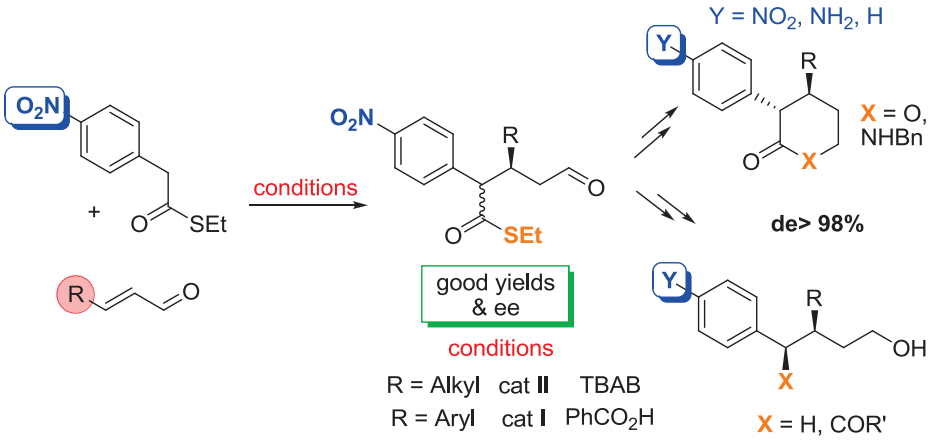
In this case we also exploited the versatility of the nitro group through the corresponding diazonium salt. Besides the formation of the corresponding iodide derivative, we performed the elimination or substitution by a hydrogen atom[62] to afford compounds **30**.

[61] L. S. Liebeskind, E. C. Garnier-Amblard, D. C. Liotta, WO 2010/085547.
[62] K. Asakawa, N. Noguchi, S. Takashima, M. Nakada, *Tetrahedron: Asymmetry* **2008**, *19*, 2304.



Scheme 2.42. Transformation of thioester and nitro groups of **29**.

To summarize this section, *p*-nitrophenylethyl thioester reacted with a variety of β-substituted α,β-unsaturated aldehydes. The independent optimization of the reaction conditions allowed obtaining high yields and enantioselectivities for both aliphatic and aromatic enals. The corresponding adducts have been proven to be very versatile substrates (Scheme 2.43).

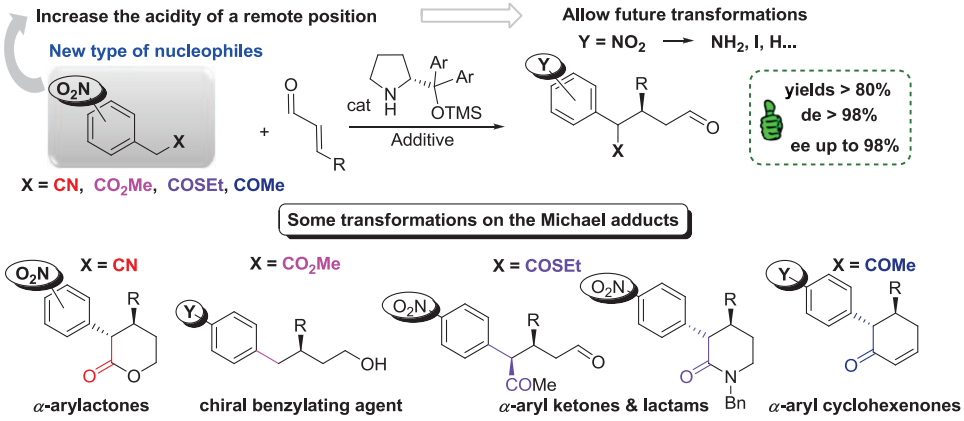


Scheme 2.43. Arylthioester as nucleophile

3. Summary and general conclusions of this part of the work

The nitro group acted as an efficient activating group, providing the necessary acidity to the arylacetic pro-nucleophiles to successfully react in organocatalytic Michael additions *via* iminium activation. The nitro group could be transformed or eliminated in all cases through easy procedures (Scheme 2.44, top).

Four different nucleophiles with different possibilities of transformation were developed (X = CN, COMe, CO_2Me, COSEt). In each case we designed simple and reliable sequential procedures for the synthesis of diastereo- and enantiomerically pure interesting molecules. The low diastereoselectivity of the Michael addition was solved with transformation to cyclic products or elimination of the group at the benzylic position. Cyclic and acyclic diastereomerically pure compounds were obtained. These compounds are attractive building blocks for the construction of more complex molecules (Scheme 2.44, bottom).



Scheme 2.44. Synthetic applications of arylacetic acid in catalysis *via* iminium activation.

The conjugated addition takes place efficiently in the presence of O-TMS protected diaryl prolinol **I** and **II** as catalysts. In our examples was observed that each nucleophile, although with similar structure, required slightly different reaction conditions (catalyst, solvent, additive).

A positive influence was found using TBAB as additive in the Michael reactions, especially for the less reactive nucleophiles. This effect will be analyzeded in detail in the next chapter. A different behaviour between aliphatic and aromatic substituted enals was observed, requiring in some cases a tailored optimization for the two enal classes in order to obtain satisfactory results. Nitrile **1b** and ketone **1c** derivatives afforded the highest conversions, while ester **1d** had some problems of reactivity. These problems were solved using the thioester derivative **1e**, which showed to be general for both aliphatic and aromatic enals under adequate conditions.

Inspired by our work, appeared in the literature other examples of arylacetic derivatives or related structures (Figure 2.14). The importance of the acidity of the pro-nucleophile is evident in all these cases, where the choice of the activating group was crucial to provide an effective increase in the acidity of the methylenic moiety without introducing any additional activating group.

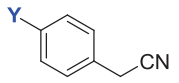
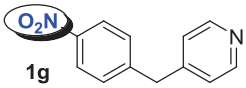
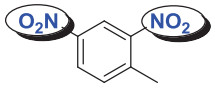
Y-arylacetonitriles	***NO_2-arylpyridine***	***2,4-$(NO_2)_2$-toluene***
Y = CN, CO_2Me  Y = NO_2, X = CO_2Me **1d** *TL* **2012**, 2809, Kim	✓ transformation or elimination of the nitro  **1g** *Synlett* **2011**, 489, Melchiorre	✓ transformation or elimination of the nitro  *CEJ* **2013**, 9147, Wang *EJOC* **2013**, 5262, Jørgensen

Figure 2.14. Examples of nucleophiles

Kim and co-workers described the use of other activating groups in similar molecules, as cyano or ester group at the *para* position of the aromatic ring. Moreover, in the same work, the authors also described the employment of **1d** as pro-nucloophiles for the iminium ion catalyzed Michael addition with aromatic enals.

4-(4-nitrobenzyl)-pyridine **1g** developed by Melchiorre acted as an efficient nucleophile in the Michael addition to aromatic enals. In this case the authors specifically mentioned the lack of reactivity of the aliphatic enals. Some transformations were also performed on the nitro group.

It is worth mentioning the example of the 2,4-dinitrotoluene, published independently by Wang and Jørgensen. This derivative is also precursor of the corresponding benzylated adducts obtained with **1d** or **1e**. Although in this case there is not electron-withdrawing group at the benzylic position, this group needs to be introduced as a second activating group at the aromatic ring to gain enough acidity.

From a synthetic point of view, all these examples show the necessity of a fine manipulation of the activating groups in order to get the appropriate acidity to react in these processes. The different results obtained with these nucleophiles from the mechanistic perspective are discussed in the next chapter.

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31. Y. Liu, W. W. McWhorter, Jr., *J. Am. Chem. Soc.*, **2003**, *125*, 4240.

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33. Y. K. Chen, M. Yoshida, D. W. C. MacMillan *J. Am. Chem. Soc.* **2006**, *128*, 9328.

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37. Similar stereoselectivities but lower yields were obtained using DIBAL-H (with this reagent, a significant amount of 1,4-reduction was observed).

38. a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B,* **1988**, *37*, 785; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372.

39. Gaussian 09, Revision B.01, M. J. Frisch, *et al*., Gaussian, Inc., Wallingford CT, **2010**.

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41. T. Ohwada, *Chem. Rev.* **1999**, *99*, 1337.

42. The synthesis of similar compounds has been reported. See: J. Clayden, S. Parris, Cabedo, A. H. Payne, *Angew. Chem. Int. Ed.* **2008**, *47*, 5060.

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45. C. F. Christian, T. Takeya, M. J. Szymanski, D. A. Singleton, *J. Org. Chem.* **2007**, *72*, 6183.

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49. a) E. J. Corey, F. Y. Zhang, *Angew. Chem. Int. Ed*. **1999**, *38*, 1931; b) H. Zhao, B. Qin, Z. Liu, Z. Feng *Tetrahedron,* **2007**, *63*, 6822. For the use of TBAB in imine activation, see: J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, M. B. Cid *Org. Lett.* **2005**, *7*, 4407.

50. D. Caine, S.D. Venkataramu, A. Kois, *J. Org. Chem.* **1992**, *57*, 2960.

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52. T. Miyazaki, Y. Han-ya, H. Tokuyama, T. Fukuyama, *Synlett* **2004**, *3*, 470-480.

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54. Conditions used by Barbas, see ref 6.

55. With the other derivatives we always obtained almost 1:1 diastereomeric mixtures after reduction.

56. Traces of these alcohols were detected when the reactions were performed in large scale.

57. We have confirmed that diastereomerically pure aldehyde **28** afforded **29** quantitatively under the reduction conditions with no epimerization.

58. a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B,* 1988, **37**, 785. b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372.

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Chapter III

Mechanistic studies on iminium ion catalyzed reactions

1. Introduction

In spite of the impressive recent advances in the area of asymmetric organocatalysis, detailed understanding of the mechanism followed by many organocatalytic reactions remains elusive. Consequently, the proposed catalytic cycles tend to remain largely speculative. The percentage of publications including mechanistic studies (in blue) is minimal in comparison with the total number of publications (in red, Figure 3.1).

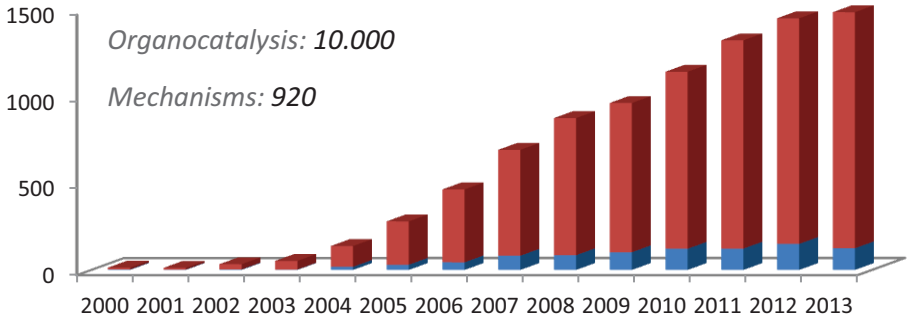


Figure 3.1. Comparison of the number of publications in organocatalysis (red), with publications including mechanistic studies (blue).[1]

The field of iminium ion catalysis is not an exception within the area of asymmetric organocatalysis, where mechanistic studies are scarce compared to new synthetic applications. There are not studies concerning for example: i) the relation of the structure of the nucleophiles with the reaction outcome, ii) the relation between catalyst structure and enantioselectivity, iii) the effect of the additives on the catalytic cycle or iv) the rate-determining step of the reaction. These are key points considering that a better understanding of these factors would allow the design of more-efficient processes.

[1] This graphic was obtained searching by topic in the database *Web of Science* using the term *"organocataly*"*, for the red bars and *"organocataly*"* and refining with *"mechanis*"* for the blue bars. Data of the analysis : 22nd November, 2013.

Aminocatalysis seems to follow relatively few basic mechanistic principles, most of which are based on old organic concepts, as shown in the introductory chapter. However, trying to unfold the factors influencing the organocatalytic functionalizations of α,β-unsaturated aldehydes shows that the reaction mechanisms often are more complex than anticipated and new aspects of the reaction courses are revealed.

In iminium ion catalysis it is relatively common to find reactions that involve substrates with similar chemical structures which require in contrast very different reaction conditions. Clear examples were pointed out during our investigations on the reaction of the aryl acetic derivatives showed in the previous chapter. The lack of a detailed mechanistic study or mechanistic understanding makes the optimization processes of these reactions purely empirical, which mostly consist of testing all the catalysts, additives and solvents available without further rationalization.

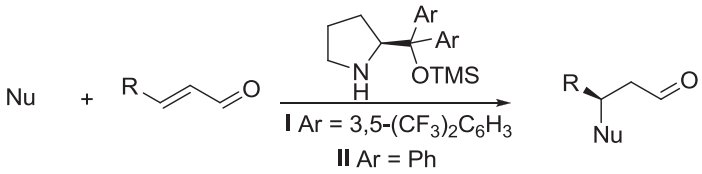
Nowadays the study of the mechanisms is undergoing a great advance due to powerful tools such as theoretical calculations or spectroscopic analyses. The detection and characterization of intermediates in catalytic organic reactions is crucial for the understanding of mechanisms and the rational optimization of reaction parameters. However, the usual approaches are based on preformed species rather than *in situ* detection of the intermediates in the catalytic reactions.[2] Moreover, in iminium ion catalysis this study is even more complicated considering that the proposed reactive intermediates are not detectable by NMR analysis of the course of the reaction. Although iminium ions are isolable intermediates under particular conditions (with specific counteranions), usually these are not the conditions used in the catalytic Michael additions. This fact probably contributes to the scarce mechanistic studies of these reactions.

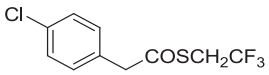
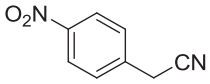
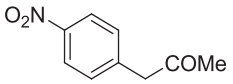
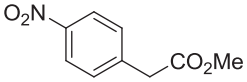
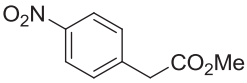
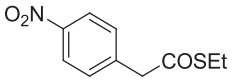
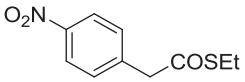
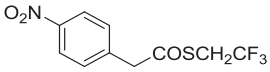
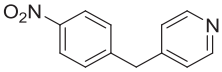
[2] For the first ^{1}H NMR studies on the detection and structural characterization of *in situ* formed enamine intermediates in proline-catalyzed aldol reactions, see: M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem., Int. Ed.* **2010**, *49*, 4997.

During the development of our investigations on the applicability of aryl acetic derivatives as nucleophiles in iminium ion catalysis we realized that with the existing information some aspects did not present a reasonable and straightforward explanation. Table 3.1 summarizes the general results obtained with the nucleophiles described in the previous chapter. We have also included two nucleophiles developed by Barbas III (entries 1 and 8)[3] as well as the example of Melchiorre[4] (entry 9) that appeared in the literature during the realization of the present research and after the publication of our first work. It is also worth mentioning the example published by Kim[5] (entry 5) concerning the same nucleophile **1d** described by us. This set of nucleophiles represents a series of similar structures that showed very different behaviour in the Michael addition of β-aromatic and β-aliphatic enals *via* iminium ion activation, therefore offers an interesting opportunity for systematic studies addressed to understand this apparently inconsistent behaviour. As shown in entry 1, Barbas described the reaction of nucleophile **1a**, cinnamaldehyde derivatives and an acidic additive to obtain the corresponding Michael adducts with high enantioselectivities. However, this set of conditions afforded the corresponding adducts with crotonaldehyde in low yield and optical purity. This is in sharp contrast with the results obtained by our research group with nucleophiles **1b-c** using LiOAc and TBAB as additives (entries 2-3),[6] which showed very high enantioselectivity for aliphatic α,β-unsaturated aldehydes (R = aliphatic) and only low and/or variable enantiomeric excesses in the case of β-aromatics ones (R = aromatic).

[3] D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem., Int. Ed*. **2008**, *47*, 4588.
[4] Vera, S.; Liu, Y.; Marigo, M.; Escudero-Adán, E. C.; Melchiorre, P. *Synlett* **2011**, 489.
[5] Seo, S. W.; Kim, S.-G. *Tetrahedron Lett*. **2012**, *53*, 2809.
[6] For pioneering examples using basic additives, see: a) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2006**, *128*, 14986-14991. b) H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.*, **2007**, *13*, 9068-9075. For other examples where LiOAc has been used see: c) Y. Wang, P. Li, X. Liang, T. Y. Zhang, Ye, J. *Chem. Commun.* **2008**, *44*, 1232-1234. d) J. L. García Ruano, V. Marcos, J. Alemán, *Chem. Commun*. **2009**, 4435-4437.

Table 3.1.Reported tendencies in enantioselectity and reactivity observed for the reaction between nucleophiles **1a-g** and *β*-aromatic or *β*-aliphatic enals.[7]



Entry	Nu		Ref	Catalyst and additive		R = Aryl	R = Alkyl
1		**1a**	3	**I**	BzOH	High ee	Low reactivity and ee
2		**1b**	our work	**I**	LiOAc	Erratic ee	High yield and ee
3		**1c**	our work	**I**	LiOAc	Erratic ee	High yield and ee
4		**1d**	our work	**II**	TBAB	Erratic ee	High yield and ee
5		**1d**	5	**I**	BzOH	High ee	No reaction
6		**1e**	our work	**II**	TBAB	Erratic ee	High yield and ee
7		**1e**	our work	**I**	BzOH	High ee	Low reactivity
8		**1f**	3	**I**	BzOH	Erratic ee	-
9		**1g**	4	**II**	DABCO	High ee	No reaction

[7] Catalyst **I** or **II** were used, independently of their configuration.

The results indicated in Table 3.1 suggest two main possibilities detailing the different behavior of these nucleophiles in the reactions with aromatic or aliphatic enals. The first aspect is that a slight modification in the structure of the nucleophile might heavily influence the reaction outcome, even when reacting under the same conditions. This is observed in entries 1 and 8, where nucleophiles **1a** and **1f** only differing in the nature of the group at the *para* position, presented a contradictory result even under the same reaction conditions. Whereas **1a** afforded high enantioselectivity in the reaction with cinnamaldehyde, nucleophile **1f** afforded lower enantiomeric excesses and more important, variable with time. The higher acidity of nucleophile **1f**, due to the presence of the strong activating nitro group, suggests a possible reason for this apparent inconsistent behavior.

The second aspect is that the successful evolution of aromatic and aliphatic enals seems to require different reaction conditions with the same nucleophile. Entries 4 and 5 show the contradictory results reported by our group and Kim for nucleophile **1d**; under our reaction conditions (catalyst **II** and TBAB as additive) excellent reactivity and enantioselectivities for aliphatic enals were observed but lower enantioselectivities for aromatic ones were obtained instead. In contrast, Kim employed a combination of catalyst **I** and BzOH as additive to obtain high enantiomeric excess values with β-aromatic enals, but the reaction for the aliphatic enals was not described. Nucleophile **1e** proved to be the most general affording high enantioselectivities with both types of aldehydes (entries 6 and 7). However, this nucleophile showed a similar trend as nucleophile **1d**: β-aromatic enals afforded better enantiomeric excesses with acidic additives and catalyst **I**, whereas TBAB and catalyst **II** were more effective for the aliphatic enals (compare entries 6 and 7 with 4 and 5). These results corroborate that independent optimization processes for β-alkyl and β-aryl enals may be an important point to achieve high yields and enantioselectivities for both types of enals.

Although the reaction conditions are very different, the completely opposite behavior observed for nucleophile **1f** studied by Barbas (entry 8) and 4-pyridyl 4-nitrophenyl methylene **1g** developed by Melchiorre (entry 9), probably the most and less acidic nucleophiles of the series, also corroborates the importance of the acidity of the nucleophile. Whereas the enantioselectivities observed for the presumably more acidic nucleophile **1f** with β-aryl enals were dependent on time (as **1b** and **1c**), nucleophile **1g** did not even react with β-alkyl enals.

The obtaining of erratic ee values, *i.e.* variable with time, is attributed to the reversibility of the Michael addition, which would end in the racemization of the final product to the thermodynamic mixture of both enantiomers. With the results observed with nucleophiles **1f** and **1g**, we hypothesized that both reactivity and reversibility are controlled by the acidity of the nucleophile.

The importance of the acidity of the nucleophile had already been analyzed by Barbas, who proposed that the required pK_a of a nucleophile must be lower than in the range of 16-17 to react in this type of processes.[3]

We decided to investigate if this particular behaviour was also shared by other nucleophile types under iminium ion catalysis with prolinol derived catalysts. Thus, a careful analysis of the nucleophiles described in the literature was carried out, with the results summarized in Figures 3.2-3.4. It is important to note that we have selected representative examples related to our study in order to clearly explain the problem under analysis. For example, cyclopentadiene and some nucleophiles involved in Friedel-Crafts type reactions have been excluded as the mechanism is expected to be different.

In Figures 3.2, 3.3 and 3.4 are collected the nucleophiles which only reacts in good yields and enantioselectivities with β-alkyl enals (Figure 3.2), β-aryl enals (Figure 3.3) and both type of enals (Figure 3.4).

The references are ordered chronologically and below each nucleophile are specified the main reaction conditions. The references are given using a special short reference system, indicating the journal code, the year and the pages.[8]

It is important to note that in most of the original references no rationalization is attempted on the different reactivity observed between aliphatic and aromatic α,β-unsaturated aldehydes with the same nucleophiles. In some cases, the authors attributed this difference to the minor reactivity of one or another type of enal, being the information available contradictory in many cases.

Looking at the collected data, it is difficult to rationalize if the different behaviour is only a consequence of the structure of the nucleophile or is also dependent on the reaction conditions.

As it can be observed in the figures, each nucleophile reacted under very different conditions. This is due to the fact that the reaction of each nucleophile was optimized usually with the purpose of obtaining the final product in high yield and enantioselectivity. Thus, is very difficult to draw some conclusions about the influence of the parameters (catalyst, additives, solvent) on the enantioselectivity and reactivity of the process. The lack of comparative systematic optimization procedures avoids a general rationalization about the mechanistic aspects of these reactions. Moreover, in many cases the nucleophiles are involved in cascade reactions and the real behaviour of the organocatalytic Michael addition get masked into the overall process. For an easier interpretation the nucleophiles involved in cascade or tandem processes are marked as ©.

[8] This special system has been used in order to facilitate the reading. For the abbreviations of the journals we have used: *A Manual Prepared for Intending Authors by the Editor - Alan R. Katritzky.* url: *http://www.ark.chem.ufl.edu/Books_and_Series/InstructionsforAuthors.pdf*. See also the abbreviations section of the thesis.

In figure 3.2 are summarized a wide variety nucleophiles which reacted in high yields and enantioselectivities only with β-alkyl enals. As can be seen in the figure, these nucleophiles are mostly heteronucleophiles. It was not until 2008 when Jørgensen and co-workers reported the use of 1,3-diketones as the first example of a C-centred nucleophile that reacted in high yields and enantioselectivities with this type of enal. After these results Alemán and Ruano presented in 2009 and 2010 the bisulfones and β-keto sulfones respectively as useful C-centred nucleophiles.

Additionally, in the figure are also included our nucleophiles-(CN **1b**, COMe **1c** and CO_2Me **1d**), that although presented an excellent reactivity with aromatic enals, they did not afford satisfactory results regarding enantioselectivity.

Although the authors of these reports ascribed in some cases the low conversions obtained with β-aromatic enals to their low reactivity, the absence of satisfactory results might instead attributed to the reversibility of the reactions, as anticipated in our case for **1c** as shown in the previous chapter.

The use of additives seems to be arbitrary in these examples, being more used acidic additives for heteronucleophiles and basic additives for the C-centred nucleophiles. It is important to remark that in our experiments we always observed better results with basic or neutral additives rather than the usual acidic ones. In these examples the most common solvents are CH_2Cl_2 and $CHCl_3$.

Diaryl prolinol catalyst **I** and **II** are the most widely used, being more used the first one.

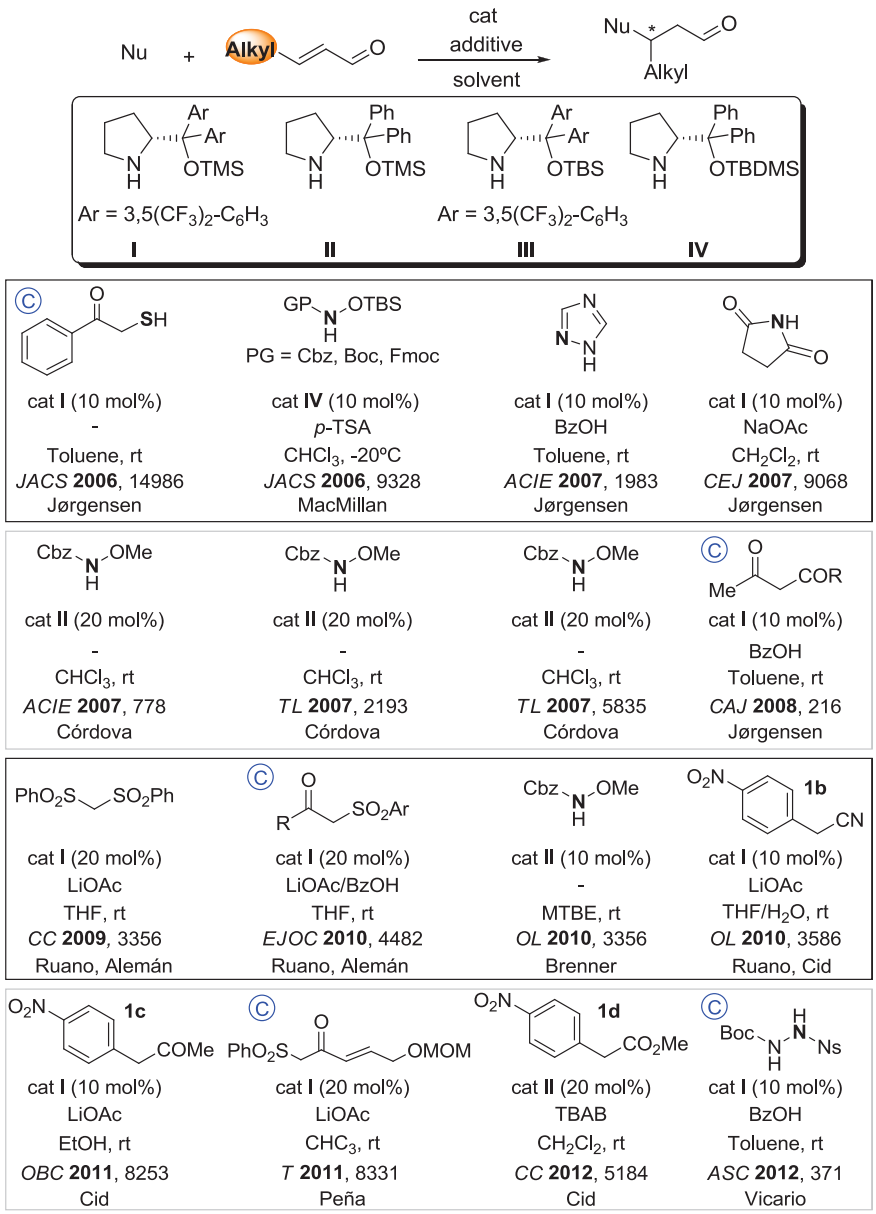


Figure 3.2. Nucleophiles which are only succesful with β-alkyl enals

The nucleophiles that react with β-aryl enals but do not react with β-alkyl enals (Figure 3.3) are almost exclusively carbon centred nucleophiles. Mostly with two electron-withdrawing groups (like malonates, β-ketoesters, etc.) directly bonded to the reactive C-centre, but also other type of nucleophiles with attracting groups of other nature, as the ones developed by Barbas (**1a**), Melchiorre (**1g**) and Kim (**1d**). In this sense, nucleophile **1d** is present in both figures as mentioned above; while Kim and co-workers described the reaction of this nucleophile with aromatic enals we found a better reactivity and enantioselectivity with aliphatic enals under different conditions (Figure 3.2).

The additives used are either of acidic or basic nature and the solvents tend to present a polar protic nature, predominantly alcohols, however, no explanation is given for the choice of these conditions in the original references.

In this case, catalyst **II** followed by catalyst **I** are the most used.

In most cases the authors attributed the lack of reactivity of the β-aliphatic enals to the intrinsic lower reactivity nature of these aldehydes. It is noteworthy that while the derivatives that only react successfully with aliphatic enals are mostly of heteronucleophilic nature (see Figure 3.2); the C-centred nucleophiles seem to prefer the reaction with aromatic enals. As mentioned early, according to our experience with nucleophile **1c**, aromatic enals are more likely to reversibility than aliphatic enals. Moreover, the Michael adducts formed in the reactions of heteronuclophiles might be more prone to reversibility than the Michael adducts derived from C-nucleophiles. We may speculate that the absence of examples of β-aromatic with heteronucleophiles may be a consequence of the high tendency to reversibility of the Michael products rather than a lack of reactivity.

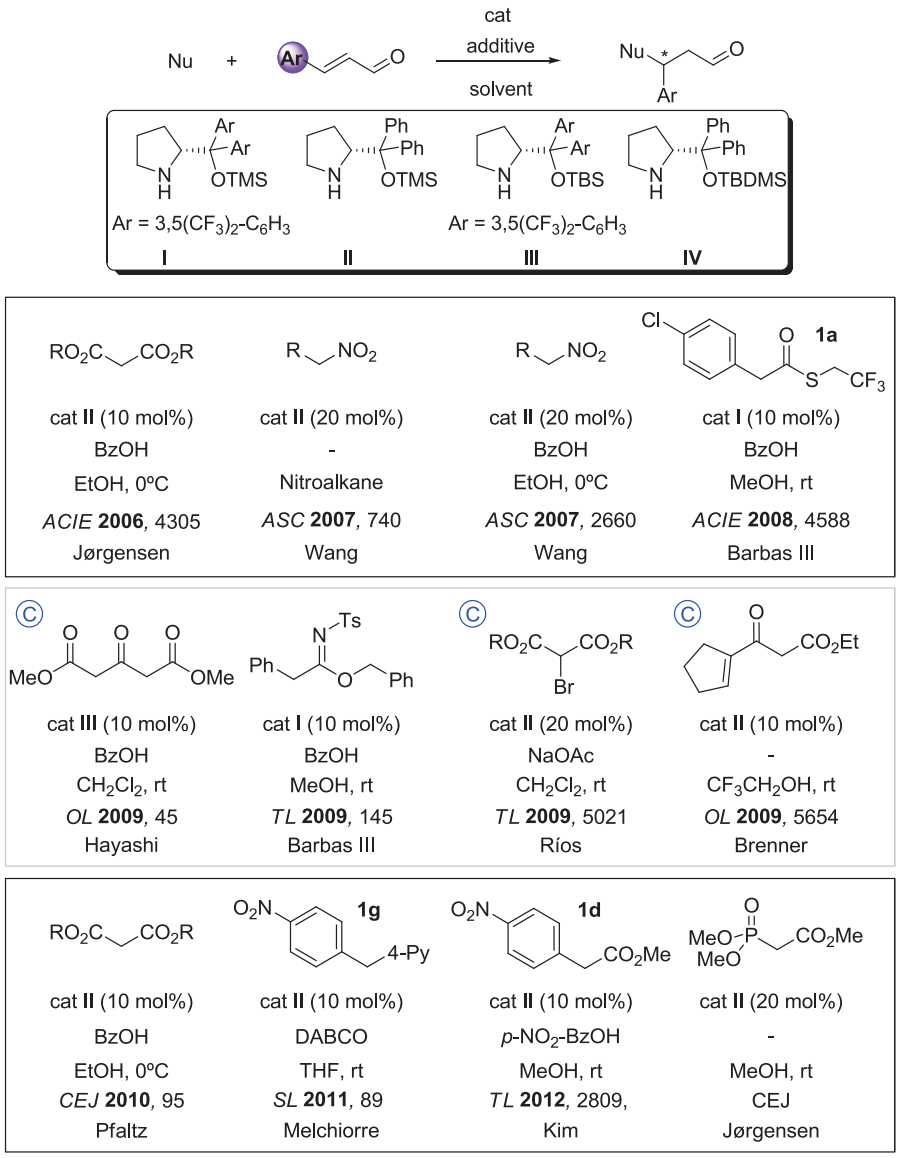


Figure 3.2. Nucleophiles which only react with β-aryl enals

In fact, when the heteronucleophiles are involved in cascade processes, they react with both types of enals (Figure 3.4). The first example of heteronucleophile reacting with both aryl and alkyl enals is the thiol developed by Wang, which is involved in a Michael/Aldol sequence. The phosphorous-centred nucleophile developed by Melchiorre is the only heteronucleophile not involved in a cascade process. However, the nucleophiles in figure 3.4 are mostly carbon nucleophiles.

The reaction conditions are sometimes different depending on the aldehyde nature. In some cases they use basic additives with carbon-nucleophiles and aliphatic aldehydes, while the use of these additives is less extended for the hetero-nucleophiles.

It is curious the case of the nitroalkanes, which were described in 2007 for the reaction with aromatic enals in the presence of benzoic acid as additive (see Figure 3.3). Shortly after the reaction of nitromethane could be extended to both type of enals (Figure 3.4), however it is important to note that the authors specify the use of benzoic acid as additive for the reactions with β-aryl enals (as in Figure 3.3) but not for the reactions with β-alkyl enals.

Cyclic bisulfone developed by Palomo and co-workers reacted with both type of enals, in contrast with the result obtained with the acyclic one described the same year by Alemán and Ruano that only reacted with aliphatic enals (see Figure 3.2).

After having analyzed the literature in detail, it can be appreciated that the different behaviour showed by β-aliphatic and β-aromatic enals is a common issue; however a general explanation for this fact is not clearly given. Although we can speculate, it is difficult to rationalize the results as each reaction was performed under different conditions and as commented before the nucleophiles are often involved in cascade processes.

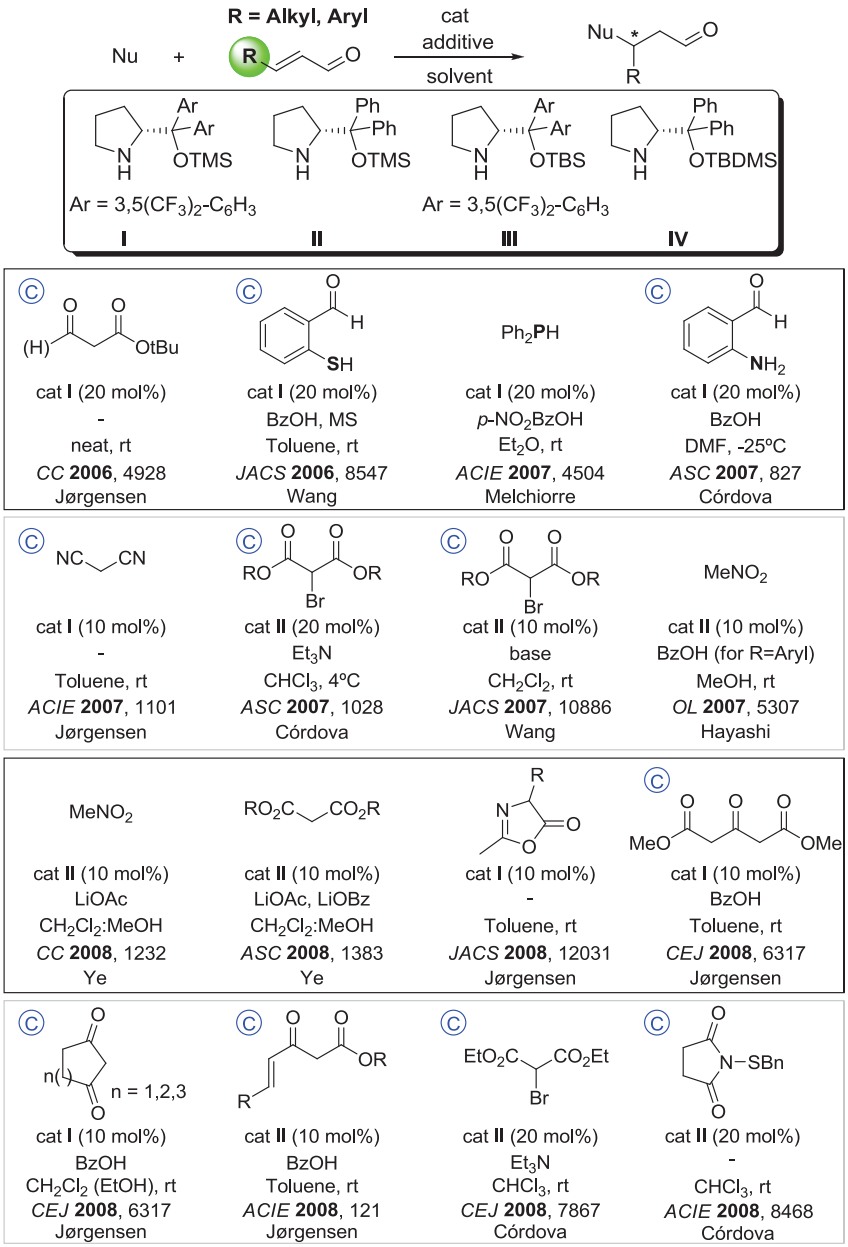


Figure 3.4. Nucleophiles which react with both type of enals

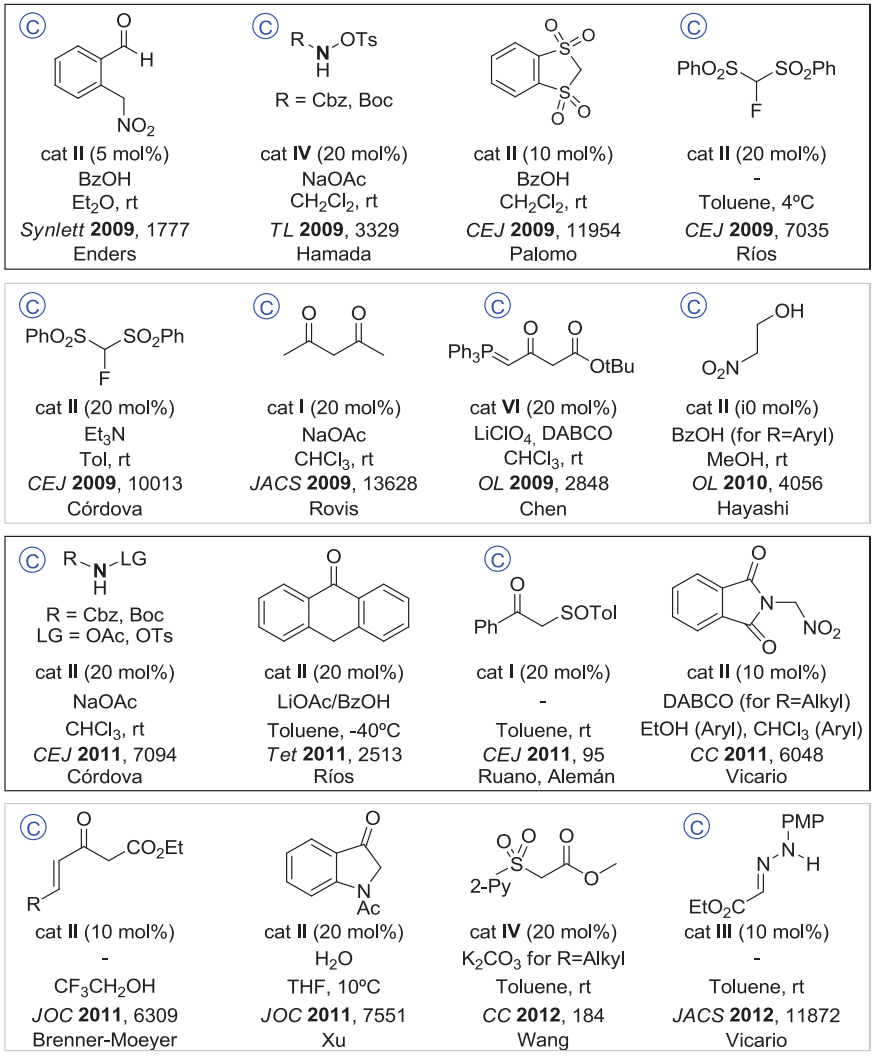
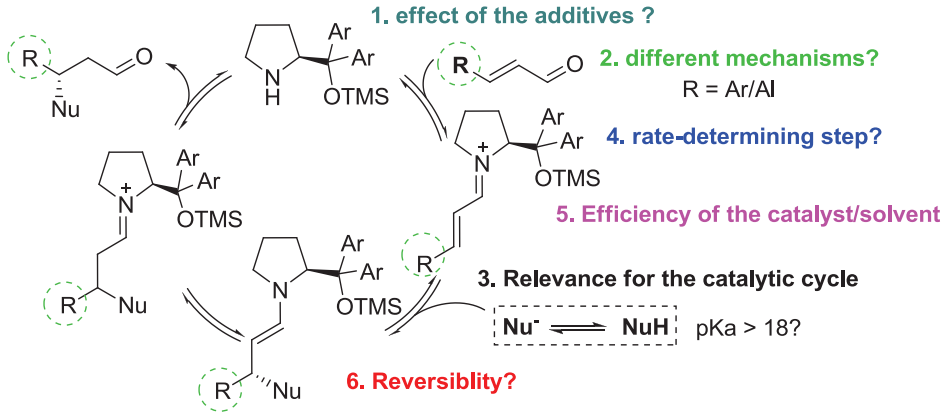


Figure 3.4 *Cont.* Nucleophiles which react with both types of enals

2. Unknown aspects of the mechanism

The careful examination of the literature and the results described in the previous chapter highlights that this variety of conditions and the lack of explanations is a consequence of the several general mechanistic aspects that remain unsolved in the iminium ion catalyzed reactions. Below are identified some of them (Scheme 3.1):

1. What is the actual role of the additives?
2. What are the reasons of the different behaviour showed by aliphatic and aromatic enals? It is possible to find conditions for successful reaction of both aldehydes with the same nucleophile? Are there different mechanisms operating for the different type of enals?
3. What is the importance of the acidity of the nucleophile for the outcome of the reaction?
4. Which is the rate determining step?
5. It is possible to predict which catalysts and solvents are more efficient for a particular reaction?
6. What are the reasons of the erosion of the enantioselectivity in the reaction of aromatic enals with some nucleophiles?



Scheme 3.1. Unknown factors

3. Working hypotheses

In light of these facts and in accordance with our investigations, we postulate the following hypotheses:

- The acidity of the nucleophile is very important for the outcome of the process, implicated in both the reactivity and the reversibility observed. This acidity could be related to the rate determining step of the reaction.
- The reaction conditions are also crucial for the success of the reaction, modulating the intrinsic reactivity of the nucleophiles.
- Due to the different behaviour showed by aliphatic and aromatic enals and the fact that some nucleophiles only react with one type of enal, it can be speculated that the reactions with these aldehydes could follow distinct mechanistic pathways.

4. Working plan and organization of the chapter.

In the absence of comparatives studies addressed to understand the effect of the reaction parameters it is difficult to rationalize the results obtained during the course of our investigations. With the aim of clarifying some mechanistic aspects we appealed to different tools available for the study of mechanisms and reaction pathways, such as theoretical calculations, kinetic studies and NMR experiments. In each case a brief introduction of the concepts as well as the techniques used will be made.

Nevertheless, it is important to note that this part of the work is still ongoing. Due to the complexity of the possible interpretations about the large amount of collected data, obtaining truly conclusions is a hard issue, and some of the results are still difficult to rationalize.

As introduced in the previous chapter, the role of the additives that act along with the catalysts in the organocatalytic reactions is sometimes highly important in order to achieve good conversions and enantioselectivities. In this sense, TBAB proved to be very efficient as additive.

In the first section we will present the studies about the possible roles of TBAB in the Michael reaction of ester pro-nucleophile **1d**. Nevertheless, other implication of using TBAB as additive will be discussed throughout the chapter.

This chapter shows our advances in the effort of understanding the mechanistic implications of iminium ion catalyzed reactions. Therefore the chapter is divided in different subchapters that represent the different approaches to the problem followed during our research.

4.1. Study of the possible role of the n-tetrabutyl ammonium bromide (TBAB) as additive in the organocatalytic Michael addition, as it was not exploited before in the literature (see previous chapter).

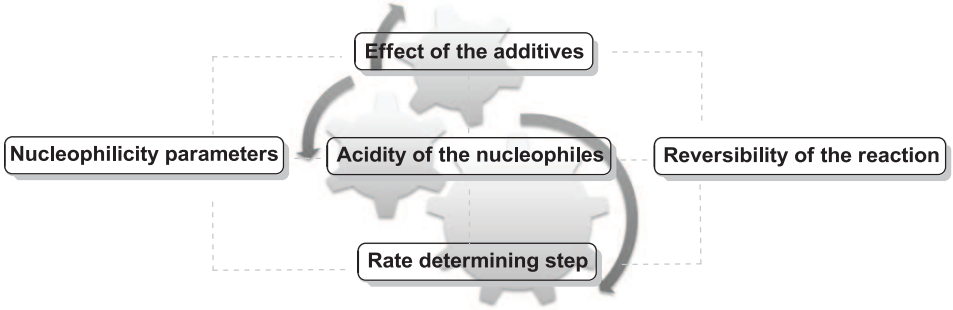
4.2. Study of the relative acidity of the nucleophiles and investigation of the relation of this acidity with the outcome of the reaction.

4.3. Systematic study of the reaction conditions employing the carbon centred nucleophiles described until now. ^{1}H NMR analysis of the Michael reactions.

4.4. Investigation of the effect of the different catalyst (**I** or **II**), solvent and additives used on the reversibility of the process.

4.5. Comparison nucleophilicity *vs*. acidity of the nucleophile.

4.6. Identification of the rate determining step of the reaction.

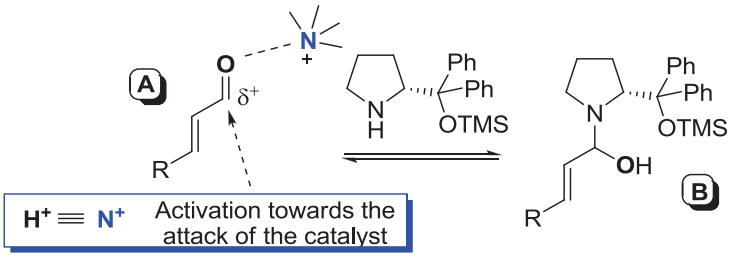


Scheme 3.2. Working plan.

4.1. Studies on the effect of the *n*-tetrabutylammonium bromide (TBAB)

A positive effect of TBAB on the reaction rate was found during our investigations with ester **1d** as nucleophile; in fact was the poor reactivity showed by this nucleophile what encouraged us to find reagents not used previously as additives for a more efficiency of the reactions for this type of nucleophiles. With the satisfactory results presented in the previous section, we decided to investigate the possible roles of the TBAB in the different steps of the catalytic cycle and therefore, to try to explain the positive influence on the reaction rate. The possible effect in the activation of the electrophile and/or nucleophile respectively will be considered.

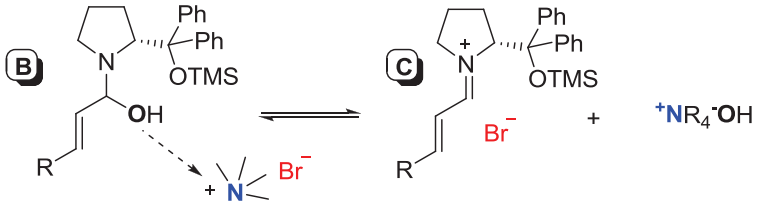
It has been described that ammonium salts may activate carbonyl compounds towards the attack of nucleophiles.[9] In a first step the NR_4^+ ion could act as a Lewis acid to activate the aldehyde to form the corresponding hemiaminal intermediate B (Scheme 3.3). In this way, the NR_4^+ ion may act like a proton, but do not cause deactivation of the nucleophile or a decrease in the concentration of the amine through protonation.



Scheme 3.3. Possible activation of the aldehyde

[9] a) E. J. Corey, F. Y. Zhang, *Angew. Chem. Int. Ed.*, **1999**, *38*, 1931. For the use of TBAB in imine activation, see: b) J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, M. B. Cid *Org. Lett.* **2005**, *7*, 4407. c) H. Zhao, B. Qin, Z. Liu, Z. Feng *Tetrahedron,* **2007**, *63*, 6822.

The formation of the iminium ion would imply the loss of the $^{-}$OH group. Theoretical studies have suggested that the elimination of $^{-}$OH needs to be assisted.[10] In fact, despite repeated attempts of optimization, the iminium hydroxide could not be obtained. Instead, the $^{-}$OH always collapsed to form the hemiaminal **B**. Thus after aldehyde activation, we may propose the assistance of the NR_4^+ ion in the elimination of $^{-}$OH from the hemiaminal intermediate **B** and stabilization of the iminium **C** by Br^- (Scheme 3.4).[11]



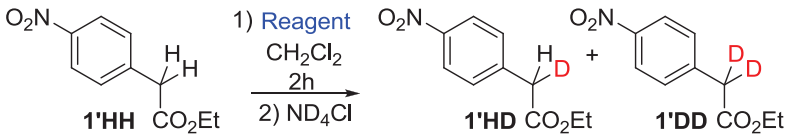
Scheme 3.4. Possible iminium ion stabilization

We wondered about the possible role of the tetrabutylammonium hydroxide (TBAOH) generated. We may speculate that it could act as a base deprotonating the nucleophile. Therefore, we performed several deuteration experiments. Nucleophile 1d' dissolved in CH_2Cl_2 was treated with 1 equivalent of different additives and quenched with ND_4Cl after 2h. A high level of deuteration was observed when the same protocol was carried out using Bu_4NOH, nevertheless, in the presence of TBAB or LiOAc and no deuterium exchange was observed. (see Table 3.2 and Figure 3.5).

[10] P. P. Mahendra, R. B. Sunoj, *Chem. Asian J.,* **2009**, *4*, 714.

[11] The counteranion of a given additive plays a pivotal role in acting as the counteranion of the iminium **C**, thus changing its properties: a) H. Mayr, A. R. Ofial, E.-U. Würthwein, N. C. Aust, *J. Am. Chem. Soc*., **1997**, *119*, 12727. b) S. Lakhdar, H. Mayr *Chem. Commun.,* **2011**, *47*, 1866. c) D. Marcoux, P. Bindschädler, A. W. H. Speed, A. Chiu, J. E. Pero, G. A. Borg, D. A. Evans, *Org. Lett.,* **2011**, *7*, 3758.

Table 3.2. Deuteration experiments of nucleophile **1d'**.



TBAOH (1 equiv)	10	20	70
TBAB (1 equiv)	100	0	0
LiOAc (1 equiv)	100	0	0

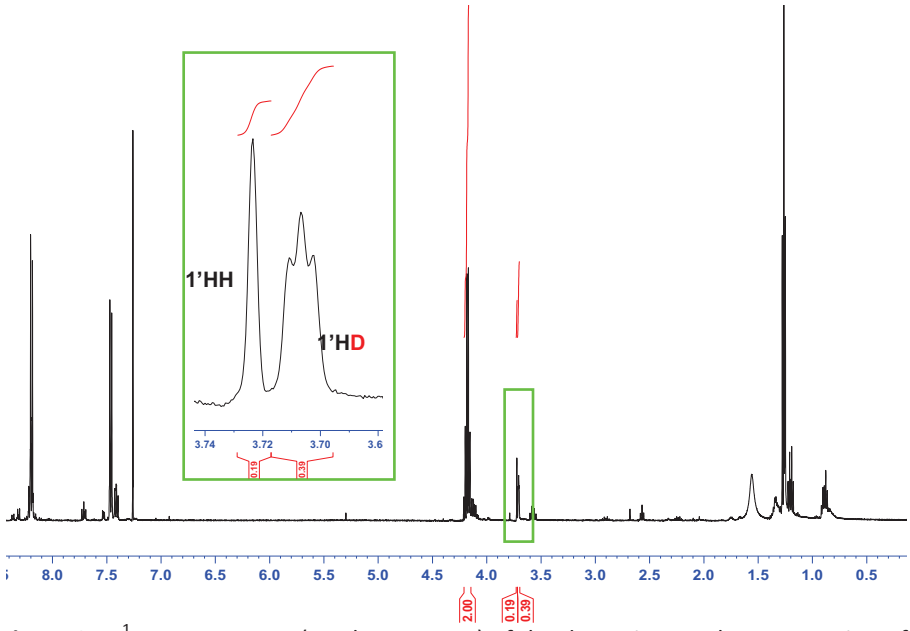


Figure 3.5. ^{1}H NMR spectra ($CDCl_3$, 300 MHz) of the deuterium exchange reaction of *p*-nitrophenyl ethyl acetate **1d'** with TBAOH after 2h.

Deuteration experiments were carried out using commercially available *p*-nitrophenyl ethyl acetate **1d'** instead of the corresponding methyl ester **1d** for the more clear separation of the ^{1}H NMR signals.

The deprotonation of the nucleophile by the resulting Bu_4NOH was also supported by theoretical calculations. According to the calculations, the deprotonation step with the hydroxide generated after iminium ion formation seems to be quite favourable. The profile of the deprotonation step shows an stabilization free energy of -27.7 kcal computed at the $CPCM_{(DCM)}$/B3LYP/6-311G(d,p)//6-31G(d) level of theory (Figure 3.6). Me_4N^+ ion has been used as a simplified model for the corresponding nBu_4N^+ one in all the calculations.

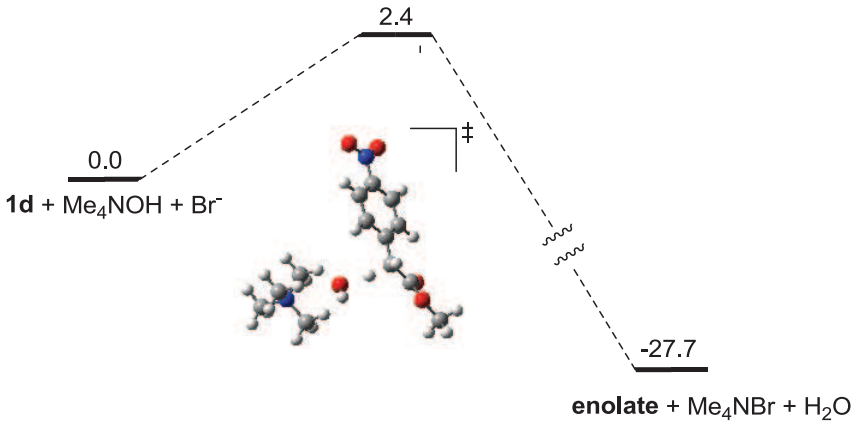
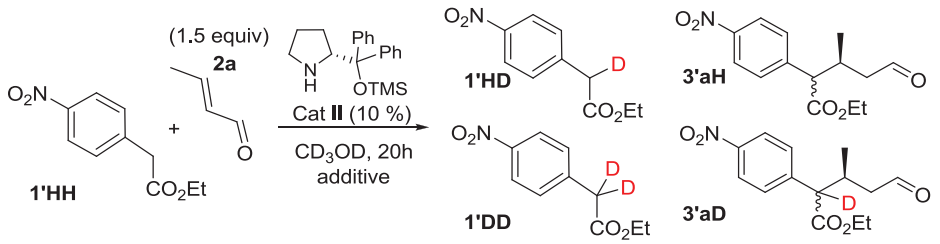


Figure 3.6. Deprotonation profile using the Gibbs free energies ΔG (kcal·mol^{-1})

We also carried out some deuteration experiments under the Michael reaction conditions using CD_3OD as a continuous source of deuterium. We may propose that the deuteration values give a qualitative idea of the amount of anion formed in each case (Table 3.3). Using TBAB or specially LiOAc as additives a detectable degree of deuteration in both starting materials and reaction products was observed, however, following the same procedure we did not observe deuteration in the presence of benzoic acid or without additive (see also figure 3.7 in next page).

Table 3.3. Deuteration experiments of nucleophile **1d'**



Entry	Additive	1'HH (%)	1'HD (%)	1'DD (%)	3'aH (%)	3'aD (%)	Deut (%)	Conv (%)
1	$PhCO_2H$ (10%)	>95	traces	-	<5	-	-	<5
2	-	>95		-	<5	-	-	<5
3	TBAB (1 equiv)	66	14	4	12	4	**22**	**16**
4	LiOAc (10%)	32	24	12	24	8	**44**	**32**

The ethyl ester **1d'** is less reactive than the corresponding methyl ester **1**. Therefore the conversions obtained were lower than those obtained for the nucleophile **1d**. Only when TBAB and LiOAc were used as additives significant deuteration of nucleophile **1d'** as well as conversion were observed.

We may postulate the generation of a base during the reaction course with TBAB or LiOAc in order to explain the different results obtained with these additives, comparing to the absence of additive or the use of benzoic acid.

The spectra of the different reactions after 20h are represented in the next page.

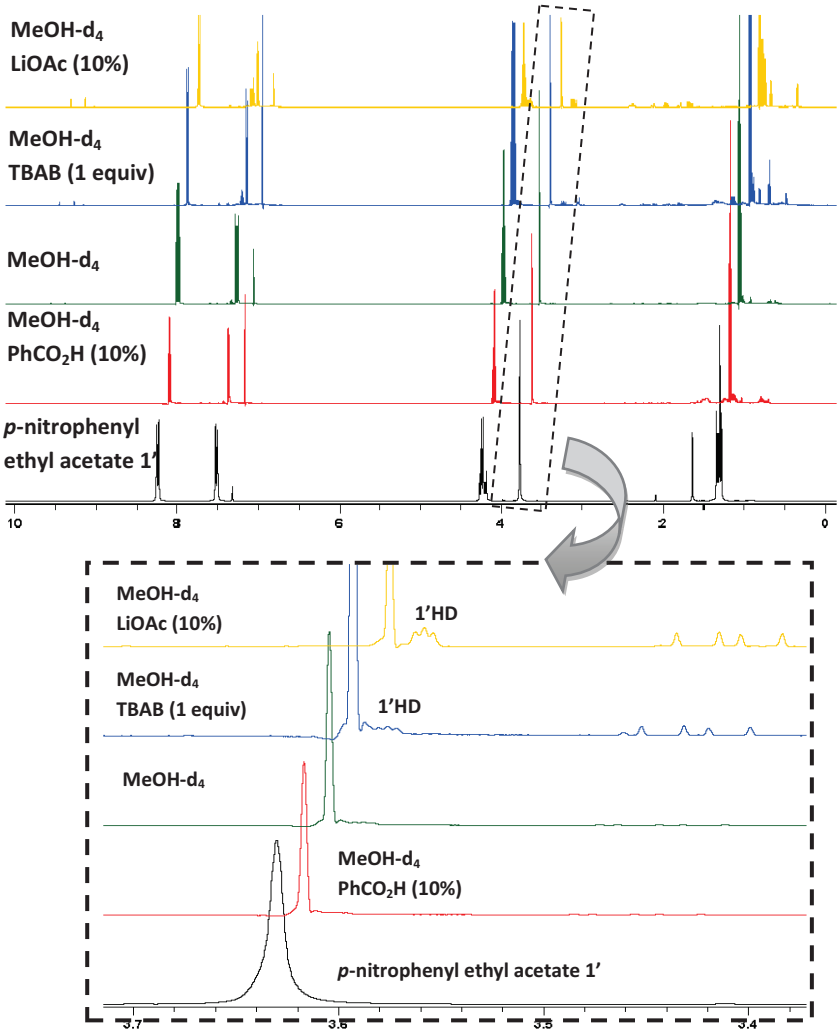


Figure 3.7. ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of the deuterium exchange of *p*-nitrophenyl ethyl acetate **1d'** with different additives after 20h.

However, other explanations for the higher amount of deuteration found with this additives may be possible, as the different properties conferred to the reaction media. The addition of ammonium salts, in particular TBAB, to solvents with low or medium premitivitty, increases the dielectric constant of the solvent as the concentration of the salt increases as well.[12]

We next postulated the enolate as the attacking specie and not the corresponding enolic form. To investigate this hypothesis, we calculated the geometries and stabilities of the possible transition states of the Michael reactions of the enol and enolate forms of **1d** with the iminium ion derived from **2a** (Figure 3.8) at the $CPCM_{(DCM)}$/B3LYP/6-311G(d,p)//6-31G(d) level of theory.

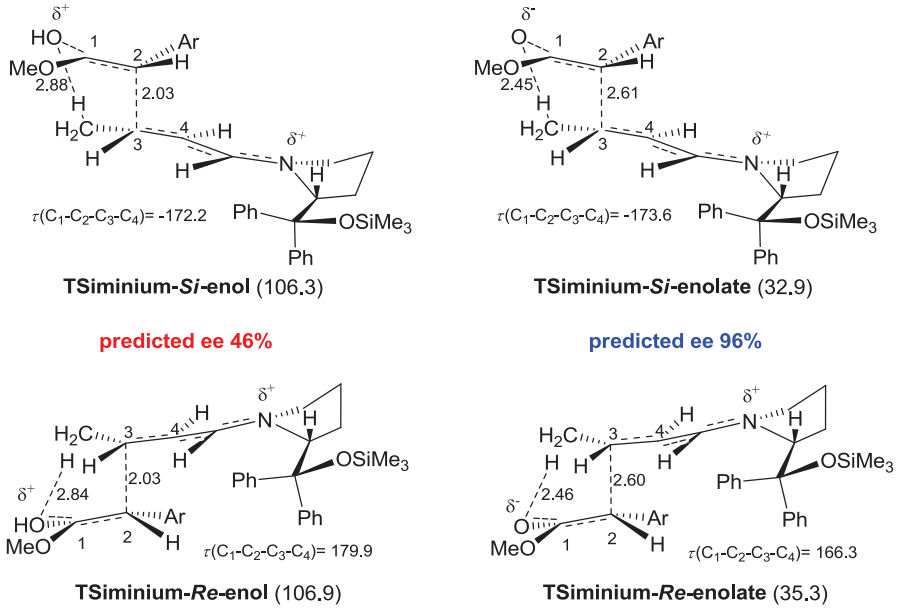


Figure 3.8. $\Delta G^{\ddagger}$ (kcalmol^{-1}) values (with respect to the separate reactants), significant distances (Å), and torsion angles (°) calculated for the transition states of the addition of the enol and enolate derived from **1d** to the *Re* and *Si* faces of the iminium intermediate derived from **2a**.

[12] P. Wang, A. Anderko, *Fluid Phase Equilibria* **2001**, *186*, 103.

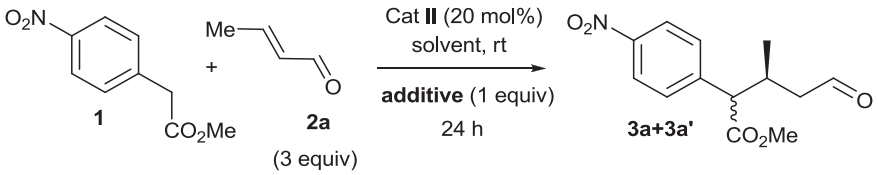
The activation barriers were significantly higher for the attack of the enol than for the attack of the enolate form of the nucleophile, in which case the transition states (TSs) are earlier (longer C---C distance). Steric interactions that ensure that the nucleophile can approach the *Si* face of the iminium ion more easily than the *Re* face are higher in the case of enolate making difficult the preferred *anti* approach (compare torsion angle). Thus, stability difference of the two TSs obtained for the enolate (ΔG = 2.4 kcal mol^{-1}, equivalent to 96% *ee*) is compatible with the experimentally obtained results (>90% *ee*, see chapter 2 pages xx), which is not the case for attack of the enol (ΔG = 0.6 kcal·mol^{-1} would only predict 46% *ee*).

We also studied the effect of other ammonium salts in the reaction, in both dichloromethane and ethanol as solvents (Table 3.4). The presence of ^{-}OH affords low ee values in both solvents, presumably due to the background reaction (entry 1). TBAOAc forms the anion in dichloromethane favouring the background reaction too, but not in ethanol (entry 3).

The use of ammonium salts with different counteranions afforded similar results (compare entries 4, 5 and 6).

A positive effect was also found using phosphonium salts (Bu_4PBr, entry 8). The influence of these additives might be also interesting and worthy of further study.

Table 3.4. Study of the influence of the counteranion in the reactivity and enantioselectivity of the Michael addition.



Entry[a]	Additive	CH_2Cl_2		EtOH	
		Conv (%)	*ee*[a](%)	Conv (%)	*ee*[a](%)
1	Et_4NOH	56	10	63	10
2	Bu_4NOH	51	nd	76	nd
3	Bu_4NOAc	73	2	85	78
4	Bu_4NCl	85	86	91	86
5	Bu_4N Br	90	90	78	88
6	Bu_4NI	75	86	89	86
7	Me_4NBr	10[13]	85	77	88
8	Bu_4P Br	90	90		

.[a] Determined by HPLC analysis in lactone **5a**. [d] not determined

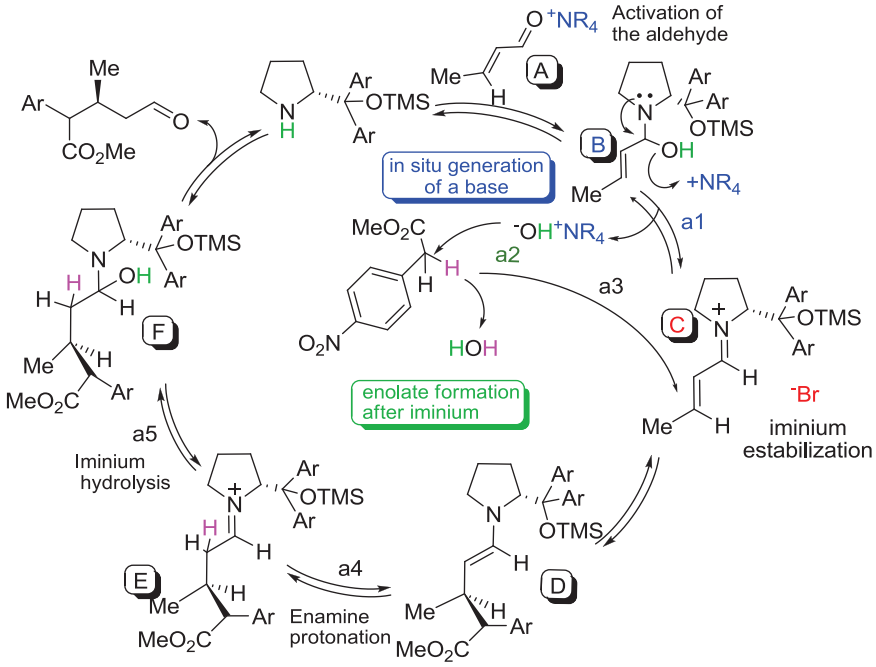
To summarize this study we may suggest some possibilities about the role of TBAB in the iminium ion catalyzed Michael additions (Scheme 3.5). In a first step, the ammonium salt could activate the aldehyde towards the attack of the catalyst, forming the iminium ion which could be stabilized by the Br^- ion. The ammonium cation may also assist the elimination of the ^-OH group form the hemiaminal to the iminium ion (step a1). Deuteration in both starting material and reaction products was observed when the reaction of **1d'** and crotonaldehyde **2a** was performed in the presence of TBAB or LiOAc as additives; however no deuteration was observed performing the same experiment in the presence of benzoic acid or in the absence of additive. Thus we may propose that a base is generated during the catalytic cycle using these additives (step a2). Nevertheless, other important roles may also be

[13] A high amount of water was present.

displayed, as the different properties of the reaction media using these additives. The in situ generated base may be responsible of the deprotonation of the nucleophile to form the corresponding enolate, which is attacking the iminium ion (step a3).

The attack of the enolate and not the enol form is supported by theoretical calculations.

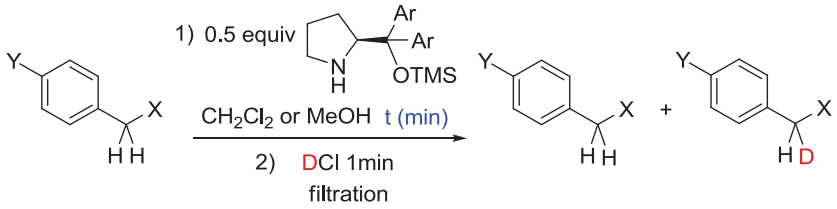
Nevertheless, other possible roles of TBAB in the catalytic cycle are being currently studied and some of them will be analyzed later in the chapter.



Scheme 3.5. Possible roles of TBAB.

4.2. Relative acidity of the nucleophiles

The pK_a value is the ideal parameter to assess the facility of deprotonation of a given nucleophile. However, it is typically determined in water or DMSO, whereas organocatalyzed Michael additions are usually carried out in dichloromethane or alcoholic solvents. Moreover, there are many potential nucleophiles for which precise pK_a values are not known, which include some of the nucleophiles studied in this thesis. Therefore, we have designed an experiment to evaluate the relative degree of deprotonation of a given nucleophile, employing the catalysts and the solvents more used in these reactions. The facility of deuteration of the α-position of nucleophiles **1a-g** (depicted in table 3.1) was determined by stirring each nucleophile in CH_2Cl_2 with either catalyst **I** or **II** (0.5 equiv), and subsequent treatment with 0.5 equiv of deuterated hydrochloric acid (DCl) at different times (Scheme 3.6). DCl was chosen as deuterium source for a quantitative and fast protonation of the anion formed until the time of the reaction was stopped. [14] Moreover, we proved that the treatment of the nucleophile with DCl in a short time, without the presence of the catalyst, did not produce any deuteration. Thus we can conclude that the deuteration degree observed is a consequence of the previously formed anion with the catalyst.



Scheme 3.6. Deuterium experiments of nucleophiles **1a-1g.**

The deuteration degree of each nucleophile is represented in the next figures. In figure 3.9 are shown the results obtained in dichloromethane after 4h of stirring each

[14] The treatment of the nucleophile with ND_4Cl did not produce a quantitative deuteration and thus we used DCl instead.

nucleophile with the corresponding catalyst. We can observe that the deuteration degree in all the cases is much higher with catalyst **II** than with catalyst **I**. As the level of deuteratium exchange with catalyst I was not detectable for almost all the nucleophiles after 4h, we have also performed the same experiments stopping the reactions after 48h.

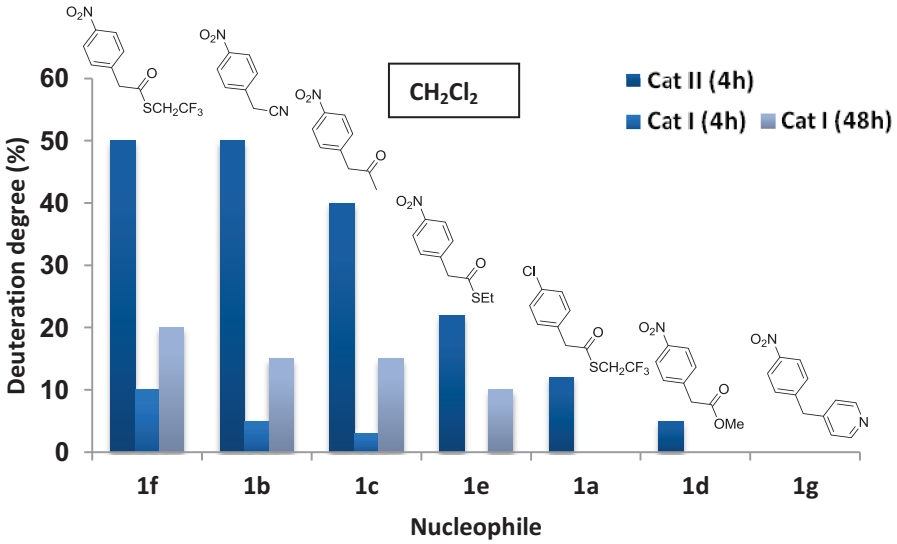


Figure 3.9. Deuterium exchange in CH_2Cl_2.

Some conclusions can be drawn from the experiments depicted in Figure 3.9: first, the degree of deuteration seems to be directly related to the reported reactivity of these nucleophiles. Specifically, those less prone to deuteration (**1a, 1d** and **1g**, right side of the graphic) have problems to react with aliphatic enals (see Table 3.1). Secondly, it seems that the variable ee values obtained in the Michael addition with aromatic enals (see also Table 3.1) is characteristic of the more acidic nucleophiles (**1b, 1c** and **1f**, left side of the graphic) react. Nucleophile **1e**, for which the most consistent behavior has been observed in reactions with both types of enals, appears in the intermediate region of the figure. Finally, the deuteration degree observed in

these reactions, which for catalyst **II** is higher than for catalyst **I** in all pairs of experiments**,** seems to be related to the basicity of the catalyst, which is higher for catalyst **II**.

The same experiments were conducted in MeOH-d_4 as solvent (Figure 3.10). It is important to note that this experiment is different to the previously described. While in the first one (Figure 3.9) the anion formed during the reaction with the catalyst is quantitative quenched, in methanol-d_4 deprotonation and deuteration are continuous during the reaction as the deuterium source is present in the reaction media.

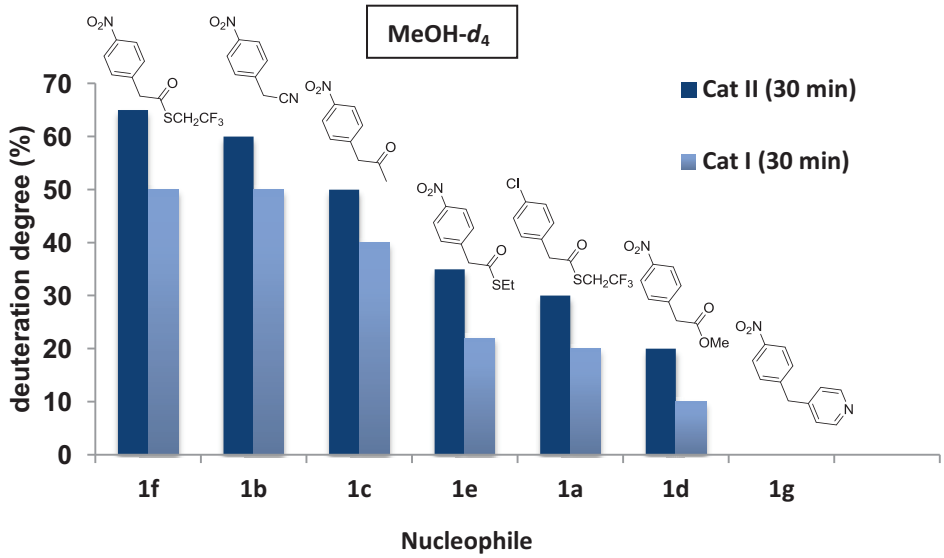


Figure 3.10 Deuterium exchange in MeOH-d_4.

The first difference is that in all cases higher degree of deuteration was observed and also in shorter reaction times. The reaction was stopped after 30 minutes because for longer reaction times the differences between the nucleophiles were not observable. A similar trend in the basicity of catalysts **I** and **II** (*i.e*. **I** less basic than **II**) was observed. However, the differences observed between both catalysts were less significant than in dichloromethane.

We compared the deuteration values obtained experimentally with the thermodynamic acidity of the nucleophiles calculated theoretically[15] by Dr. Inés Alonso and Dr. Al Mokhtar Lamsabhi using M06-2X/6-311G++G(3df,2p)//M06-2X/6-311G** (Figure 3.11).

We have used the expression pKa = ΔG/2.303RT to calculate the theoretical pKa values, where ΔG is the free energy of the deprotonation reaction showed in the figure.

The trends obtained are in agreement with the experimental observations. Catalyst **II** is more effective than catalyst **I** to deprotonate the nucleophiles. As a consequence, the pKa values obtained with catalyst **II** as base are lower than the corresponding ones obtained using catalyst **I**. The calculated pK_a values in EtOH are significantly lower than in CH_2Cl_2 for both catalysts, showing that the deprotonation is more favourable. In both solvents, the values of thioester **1e** are out of the tendency observed experimentally.

From this study the higher basicity of catalyst **II** comparing to catalyst **I** was also demonstrated. The implications of this difference will be commented later.

[15] N. Derbel, I. Clarot, M. Mourer, J.-B. Regnouf-de-Vains, M. F. Ruiz-López, *J. Phys. Chem. A*, **2012**, 116, 9404.

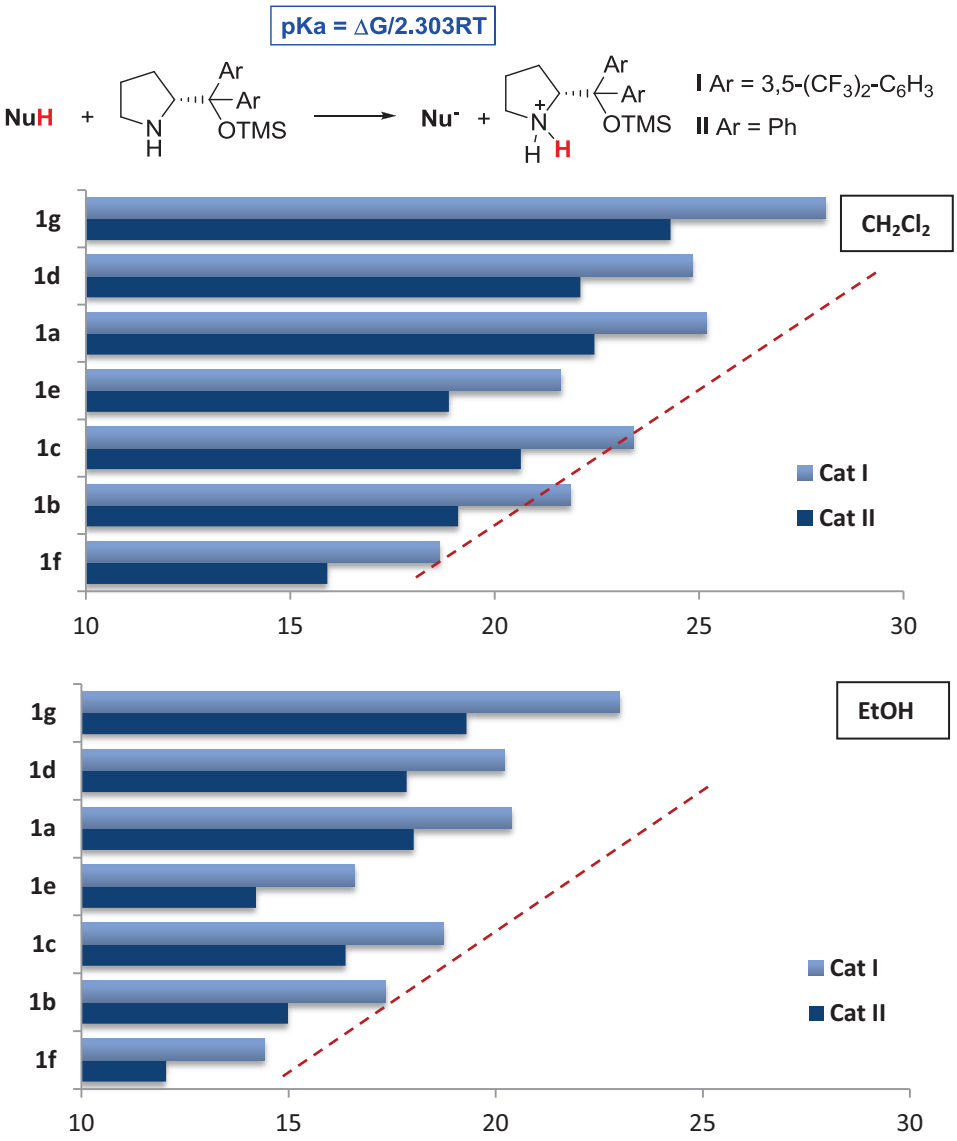


Figure 3.11. Theoretical **pK$_a$** values of nucleophiles **1a-g** in CH_2Cl_2 and EtOH.

A possible relation between the acidity and the reactivity of the corresponding nucleophile in the Michael addition was found, taking into account the results obtained in the deuteration and deprotonation studies and the results depicted in Table 3.1.

However, as commented in the introduction, each nucleophile reacted under very different conditions, and thus the order of reactivity cannot be clearly displayed. In order to relate unequivocally the acidity of the nucleophiles with its reactivity, the reaction of nucleophiles **1b-e** in dichloromethane was stopped at the same time. We compared the effect of catalyst **I** and **II** on the reactions with the four nucleophiles **1b-e** and crotonaldehyde **2a** (Figure 3.12).

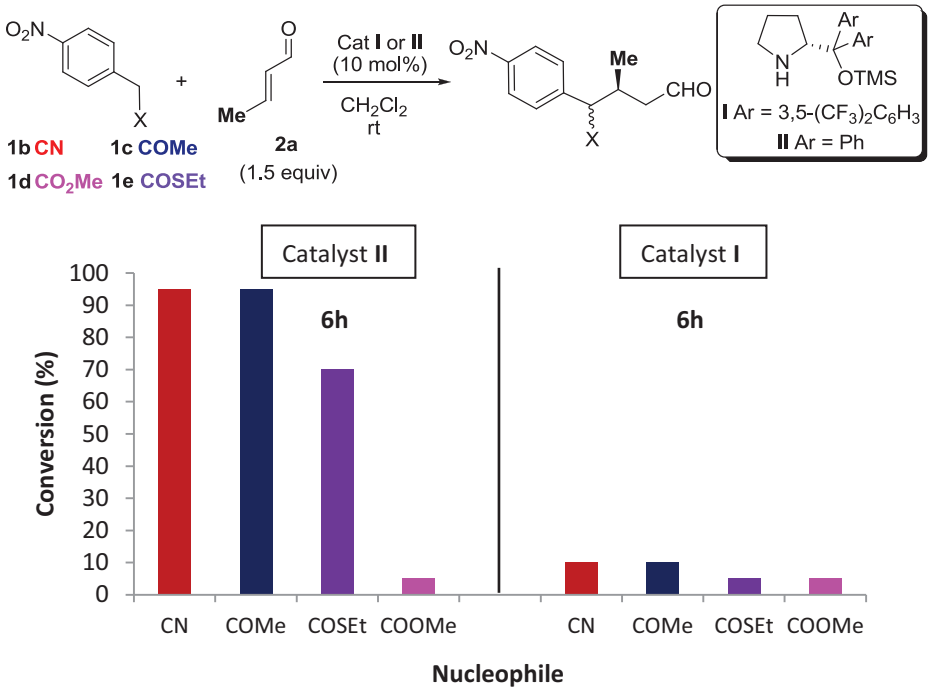


Figure 3.12. Comparison of reactivity between catalyst **I** and **II**.

Keeping the same catalyst loading and using CH_2Cl_2 as solvent in the absence of additive, we clearly observed that the conversions were higher when using catalyst **II**. After 6h reactions, catalyst **I** afforded very low conversions, time in which the catalyst **II** achieved almost completion for some nucleophiles (Figure 3.12). The same trend was observed with cinnamaldehyde but the difference in the reactivity was more acute for the reactions with crotonaldehyde.

It might be postulated that the more acidic nucleophiles (**1f**, **1b** and **1c**) showed high reactivity but found in some cases problems of reversibility. In contrast, the less acidic nucleophiles (**1a**, **1d** and **1g**) afforded more consistent enantiomeric excess values but had some problems of reactivity, especially with the aliphatic aldehydes (see also Table 3.1). The thioester derivative **1e** with an intermediate acidity afforded the best balance between reactivity and enantioselectivity (Figure 3.13).

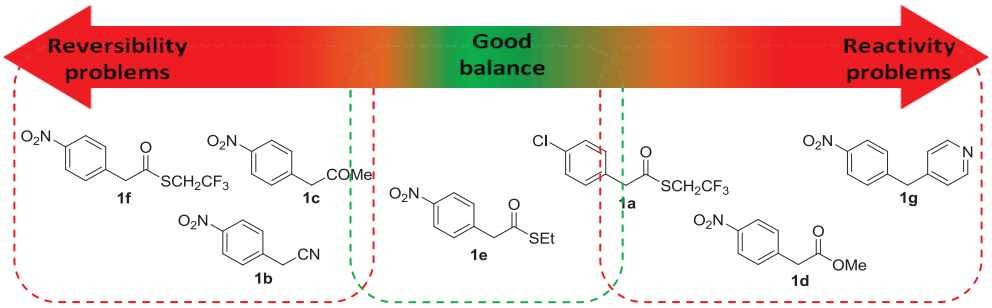


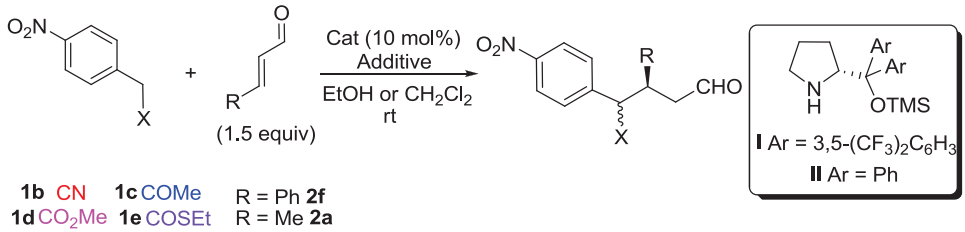
Figure 3.13. Reactivity tendencies of nucleophiles **1a-g**.

Therefore we have confirmed that the order of reactivity observed in the absence of additives is in agreement with the order of acidity previously obtained. Moreover, the reversibility showed by some nucleophiles in the Michael additions seems to be also related to the acidity.

4.3. Systematic study of the reaction conditions

As postulated in the introduction, not only the acidity but also the conditions may modulate the behaviour of the different nucleophiles. The reactions of the nucleophiles studied in the previous chapter (**1b-e**), as well as the nucleophiles described in the literature (**1a**, **1f**, **1g**, and **1h**), were carried out in very different conditions. In order to evaluate the results at the same times and under the same conditions we performed a comparative systematic study on the reactions of our nucleophiles **1b-e**.

Different additives ($PhCO_2H$, LiOAc, TBAB and no additive) and solvents (CH_2Cl_2, EtOH) were tested for each nucleophile (X = CN **1b**, COMe **1c**, CO2Me **1d** and COSEt **1e**; Scheme 3.7). The two main silyl prolinol catalysts used in these reactions (i.e. catalyst **I** and catalyst **II**) were tested.



Scheme 3.7. Systematic study of the reaction conditions

This study was performed not only to find the best conditions in terms of reactivity for each nucleophile but also to understand if the requirement of very different reaction conditions for the different nucleophiles and the different enals could be related to a change in the mechanism. As it was shown in the introduction, the data available in the literature are not sufficient to rationalize the effect of these parameters.

The tables collecting the results obtained are reported in the experimental part. Among all the possible comparisons between the results obtained, we decided to summarize the most representative in the next figures.

The nucleophiles are placed in the order of acidity obtained in the previous study. Catalyst **I** was chosen for the comparison of the other parameters as this catalyst afforded more remarkable differences.

Although it may seem obvious, the order of reactivity of aromatic and aliphatic enals was not totally clear, neither to us nor in the literature. As commented in chapter II, the fact that we always observed remaining starting nucleophile by TLC and NMR of the crude for the reactions of aromatic enals was attributed initially to unfinished slow reactions. The information available in the literature is also confusing in this point. However, when we stopped the reactions at very short times, reactions of aromatic enals were clearly faster than reactions of aliphatic enals (Figure 3.14). Choosing catalyst **I** and CH_2Cl_2 as solvent in the absence of additives and stopping the reactions after 15 minutes we could clearly observe high conversions with cinnamaldehyde **2f**. Nevertheless, using the same conditions, very low conversions were achieved with crotonaldehyde **2a** even after 6h.

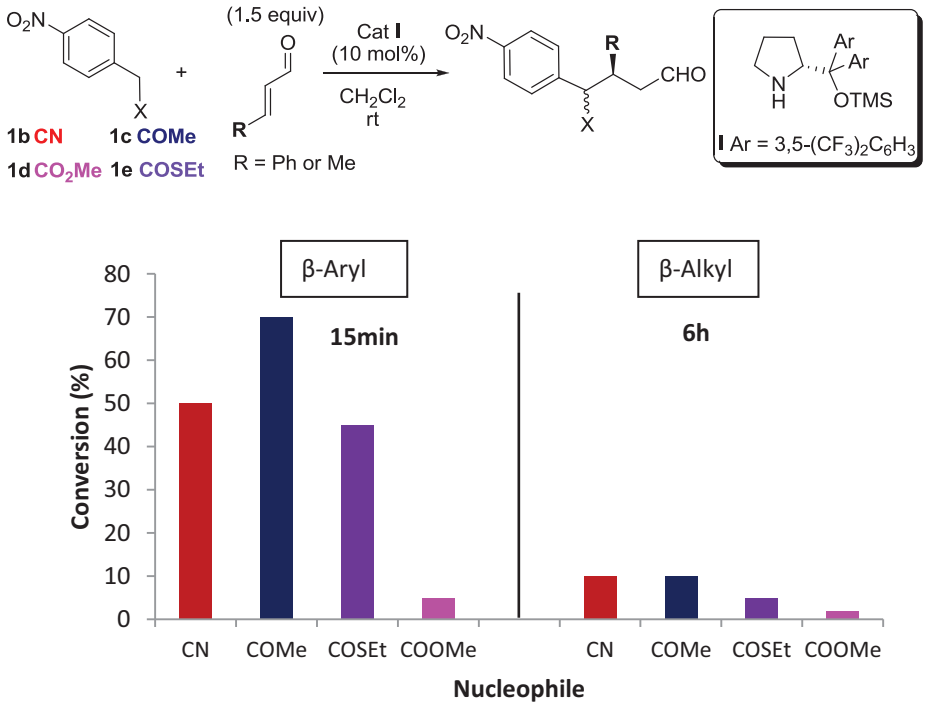


Figure 3.14. Comparison between cinnamaldehyde (left) and crotonaldehyde (right).

Using catalyst **I** in the absence of additives we analyzed the effect of the solvent in the reaction of the less reactive β-alkyl enals (Figure 3.15). We observed that EtOH seemed to accelerate the reactions of the nucleophiles with crotonaldehyde **2a**. [16] Although reactions with cinnamaldehyde **2f** seemed to follow the same trend, the differences were less notable than the observed for the reactions of crotonaldehyde **2a** (see tables in experimental part).

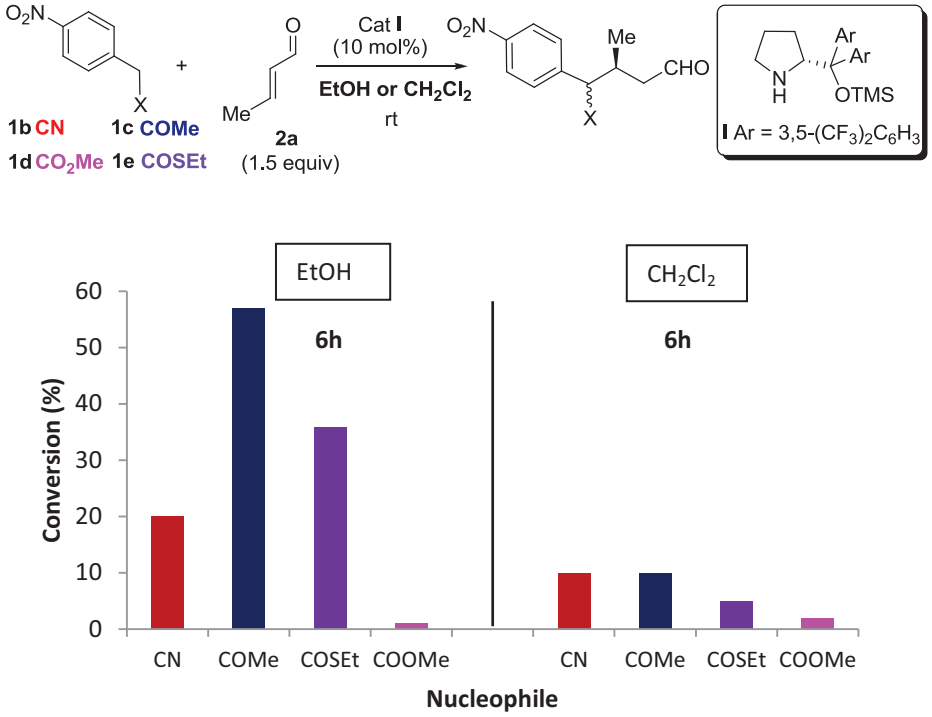


Figure 3.15. Comparison between EtOH (left) and CH_2Cl_2 (right).

[16] The low reactivity of nucleophile **1b** may be atributted to its low solubility in EtOH.

Finally we analyzed the effect of the additives with β-alkyl and β-aryl enals (Figure 3.16 and Figure 3.18). Using catalyst **I** and crotonaldehyde **2a** in EtOH as solvent we could observe that the effect of the additive depended on the nucleophile (Figure 3.16). When using acidic or no additives the reactions of ester **1d** and thioester **1e** derivatives were longer than the reactions of the ciano **1b** and ketone **1c** derivatives. However, the use of TBAB or LiOAc as additives was more favourable for the reactions of **1e** and **1d**, almost inverting the order of reactivity. The low reactivity of **1b** might be attributed again to its low solubility in EtOH.

We also tried to analyze the effect of the additives on the reactions with catalyst **II**. Nevertheless, reactions with ciano **1b** and ketone **1c** derivatives were so fast that was difficult to draw any conclusion from the study.

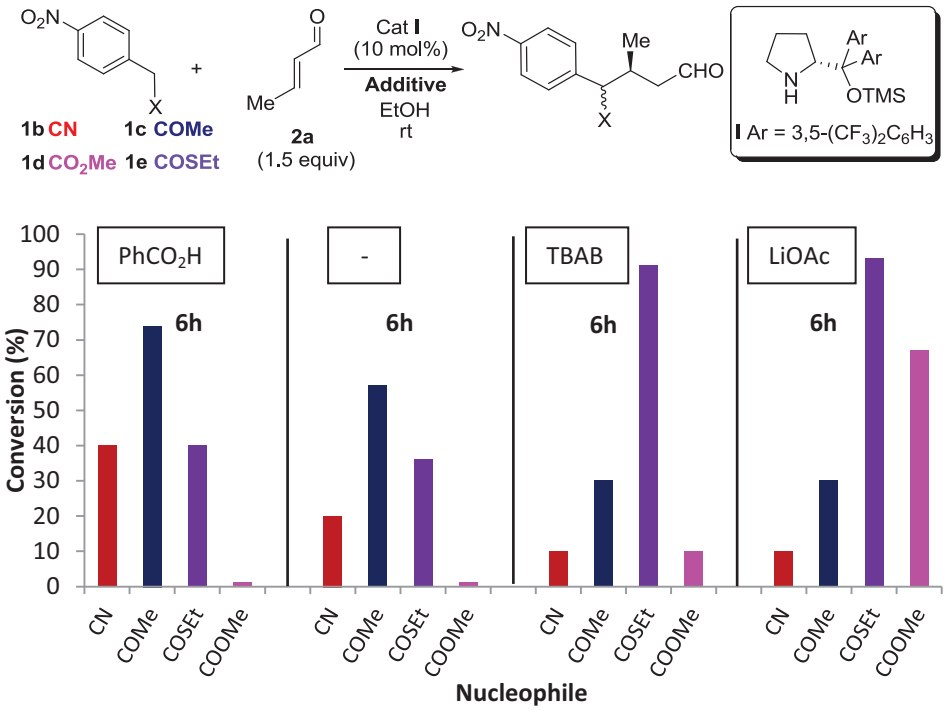


Figure 3.16. Comparison between the different additives with crotonaldehyde.

This study suggests that different conditions are appropriated regarding the nature of the nucleophile, as anticipated in the previous chapter, pointing out the following tendencies (Figure 3.17):

1. Crotonaldehyde **2a** and in extension aliphatic enals are less reactive than cinnamldehyde **2f** and aromatic enals.
2. Reactions catalyzed by **I** are slower than reactions catalyzed by **II**.
3. EtOH seems to accelerate the reactions.
4. The effect of the additives on the reaction clearly depends on the nature of the nucleophile. It seems that the reaction of the more acidic nucleophiles worked better with acidic additives whereas less acidic nucleophiles reacted faster with LiOAc or TBAB.

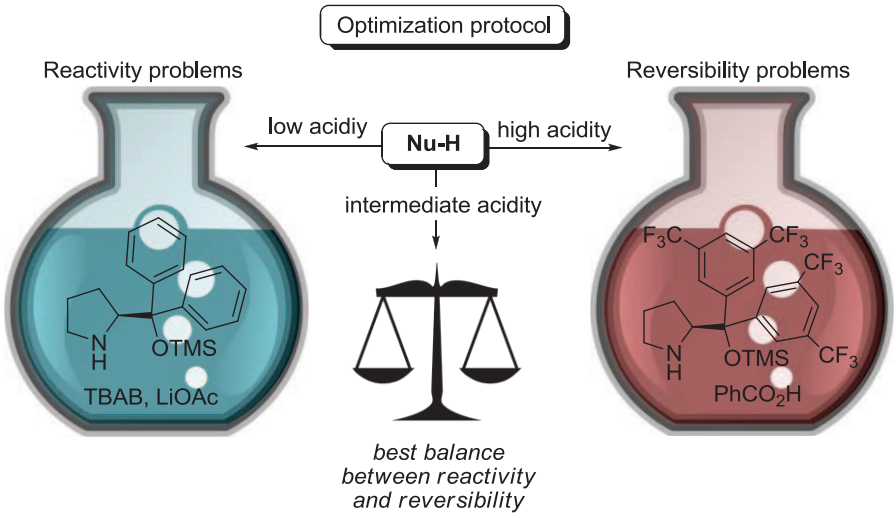
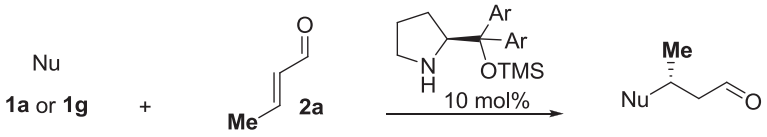
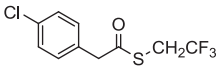
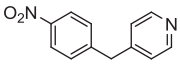


Figure 3.17.

Thus, to demonstrate that the conditions that showed to be successful in terms of reactivity for our nucleophiles were general for other nucleophiles that presented problems of reactivity with aliphatic enals, we tested this protocol with nucleophiles **1a**[3] and **1g**[4]. We were glad to observe that these nucleophiles afforded higher conversions and ee in the case of **1a** with crotonaldehyde **2a**, and reaction was also observed for **1g**.[17] Therefore, from a synthetic point of view, we could solve the problem of these nucleophiles (Scheme 3.8).



Nu	conditions	additive	results
1a *ACIE*, **2008**, 4588	cat **I**, DMF, 36h	$PhCO_2H$	51% yield 54% *ee*
	cat **II**, CH_2Cl_2, 36h	TBAB	80 % yield 80 % *ee*
	cat **II**, EtOH, 36h	LiOAc	75% yield 70% *ee*
1g *Synlett*, **2011**, 489	cat **II**, THF	DABCO	no reaction
	cat **II**, EtOH, 48h	TBAB	75 % yield *ee* nd

Scheme 3.8.

The effect of the additives was also studied in the reaction of cinnamaldehyde **2f** with catalyst **I**. From the next figure it can only be suggested that the order of reactivity with cinnamaldehyde **2f** was mainly controlled by the acidity of the nucleophile and that the reaction conditions did not have a significant influence. Nucleophile **1c** afforded very high conversions even after 5 minutes, while nucleophiles **1d** and **1e** showed very low reactivity (Figure 3.18).

[17] We could not find conditions for HPLC analysis.

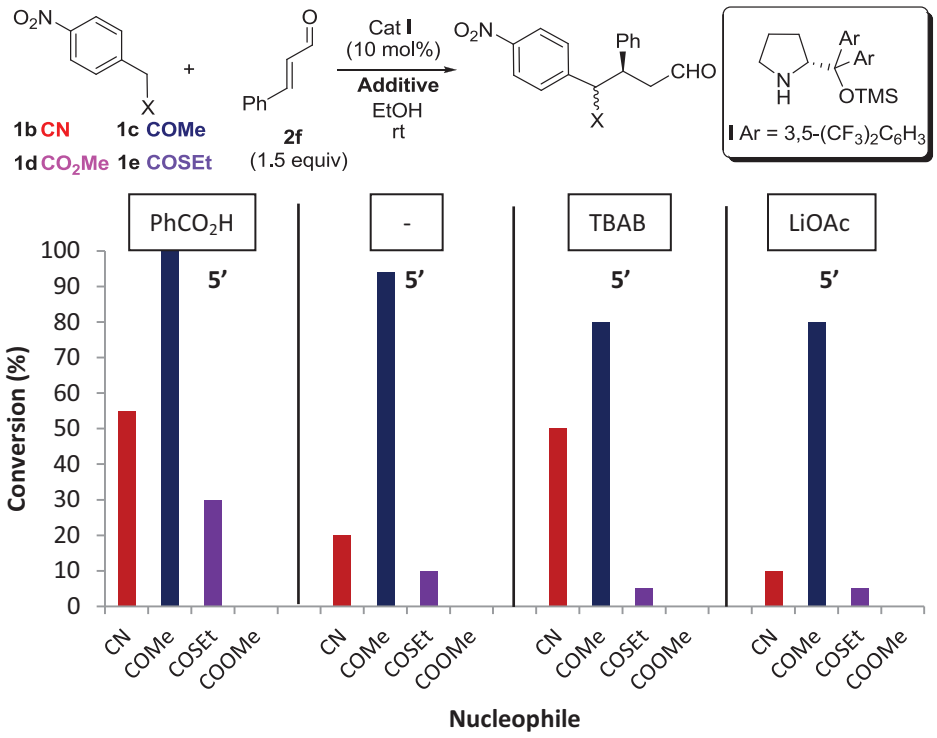


Figure 3.18. Comparison between the different additives with cinnamaldehyde.

However, it is important to note that at this point we started to be confused as different batches of aldehydes afforded not reproducible reactions. The high conversions reached at short reaction times in some reactions were also quite confuse considering the reaction times found previously. This fact made us to suspect that the traces of acid present in the aldehydes could have an important influence on the reactivity of a given nucleophile.

Thus, the conclusions from this study presented above represent a qualitative tendency that, however, must be cautiously interpreted. Nevertheless, the application of this protocol allowed us to overcome some reactivity problems using commercial aldehydes.

In order to get more reliable conclusions and more accurate understanding further experiments on the effect of the additives on the reactions were carried out using freshly distilled aldehydes.

Derivatives **1c** and **1d**, with apparent different behaviour, were chosen as representative examples of nucleophiles to study in detail the effect of the additives on the reaction rate and in order to draw the reaction profile. Other examples of the literature were also studied.

In contrast to the previous study, we did not quench the reactions to determine the conversions, which were followed instead by ^{1}H NMR analysis. Therefore, some intermediates could be detected.

The reaction of the ketone derivative **1c** with cinnamaldehyde **2f** in the presence of catalyst **II** was firstly investigated. Surprisingly, we found that the reaction was very slow in the absence of additives, not even starting after 2h, which was in principle confusing considering the results obtained in the previous study (Figure 3.19). All the subsequent reactions were carried out with catalyst **II** because reactions with catalyst **I** showed to be very low for NMR analysis.

As represented in the graphic, the reaction experienced a great acceleration in the presence of benzoic acid as additive, while the use of tetrabutylammonium bromide[18] slightly improved the conversion compared to the absence of additive. Moreover, the use of an organic base as additive (Et_3N) dramatically inhibited the reaction of this derivative.

The conversion values obtained were in sharp contrast with the values obtained in our previous systematic study (see previous pages and experimental part). These previous values are represented as single dots (after 15 minutes of reaction) at the left side of the graphic.

[18] 1 equivalent of TBAB was used.

The effect of the additives on the reactivity when the aldehyde was distilled is in almost inverse order to the order obtained in the previous study with not distilled aldehyde. This fact highlights the important influence of the acid to the reaction rate. Indeed, the addition of benzoic acid strongly affected the reaction rate.

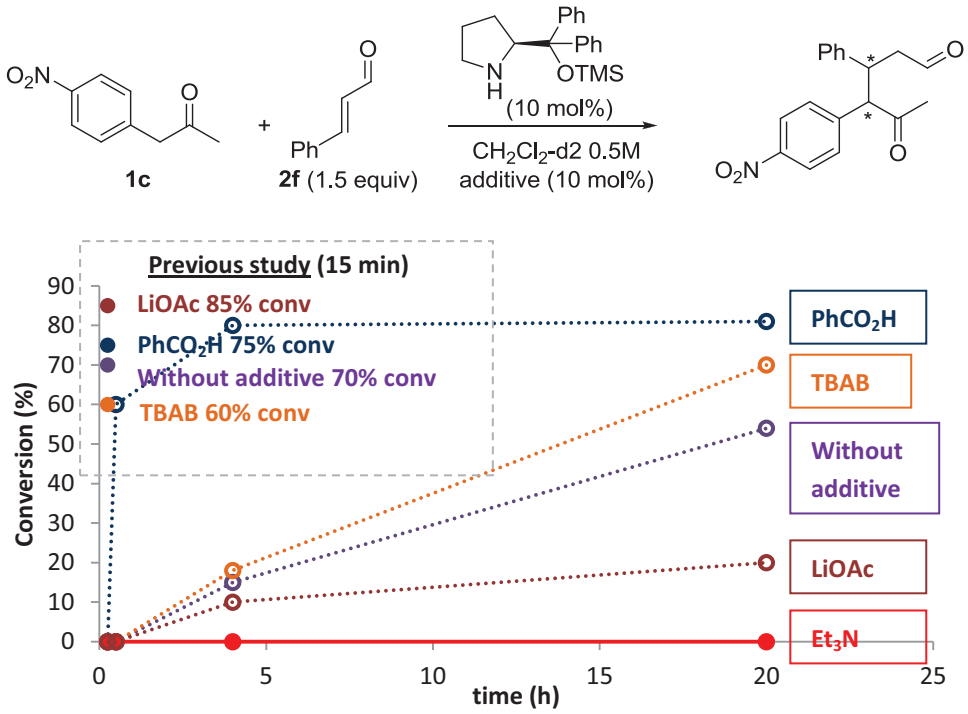


Figure 3.19. NMR conversions of the reaction of **1c** with **2f** and different additives

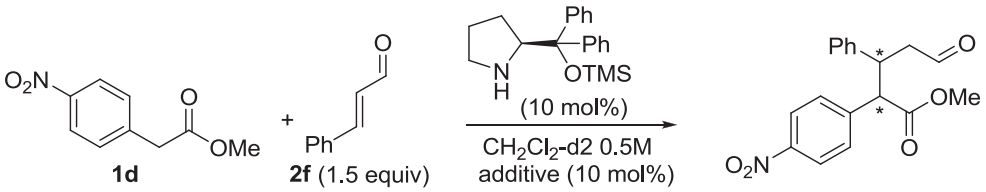
It is also remarkable that the reaction profiles were very different. The reaction in the presence of benzoic acid was very fast at the beginning and reached the equilibrium in short time, while in the presence of TBAB or in the absence of additive the reactions were getting accelerated with time, possibly due to the generation of an acid by aldehyde oxidation. This acid generation was observed during the reaction course.

The addition of a basic additive inhibited the reaction of this nucleophile with cinnamaldehyde **2f**. However, the reaction took place very slowly in the absence of additive.

We next investigated the reaction of the ester derivative **1d** with cinnamaldehyde **2f**. This derivative, as shown in the previous chapter, was presenting favourable behaviour to the addition of a basic additive. Moreover, it was the lack of reactivity of this derivative which motivated us to find additives that promoted efficiently these reactions.

In Figure 3.20, an acceleration of the reaction using either benzoic acid or tetrabutyl ammonium bromide can be observed. The evolution observed is again in contrast with the previous values obtained (left side of the graphic). Concerning the reactions of nucleophile **1d** we can say that these reactions were slower than with derivative **1c**, in agreement with the previous study. The acceleration in the presence of benzoic acid was also observed. However, the effect was not as marked as for **1c**. The addition of TBAB had also a beneficial effect. In fact, the reaction after 24h did not take place in the absence of additive, in contrast with the reaction of **1c**. The addition of a base also had a detrimental effect on the reaction; however the reaction started slowly after some hours, probably due to the generation of acid by aldehyde oxidation again.

We also attributed the great difference in the reactivity showed by **1d** with the previous values to the acid present in the commercial aldehydes. Indeed, the reaction was strongly accelerated using an equimolecular mixture of benzoic acid and TBAB, being the most effective combination found for this reaction. Moreover, a mixture of NEt_3 and benzoic acid also accelerated the reaction.



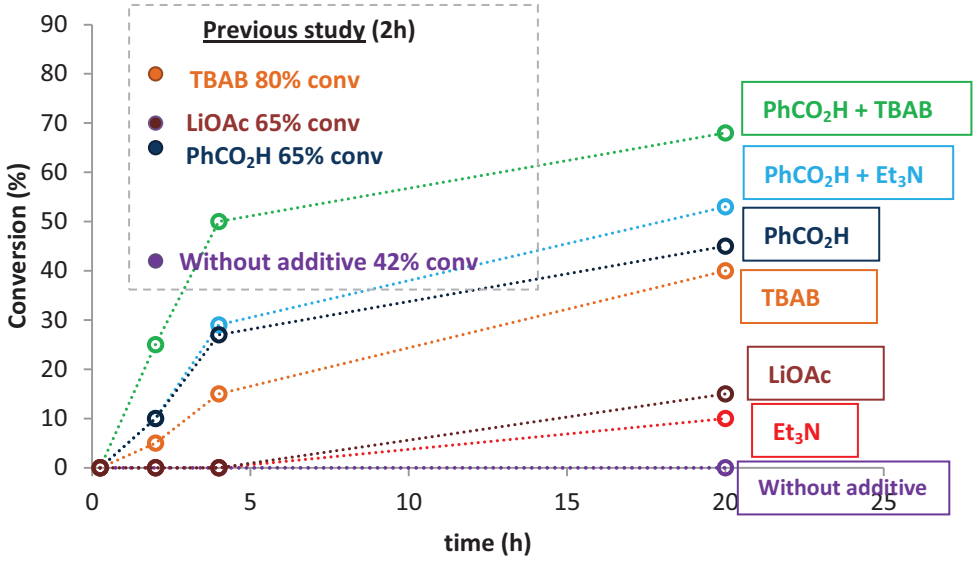
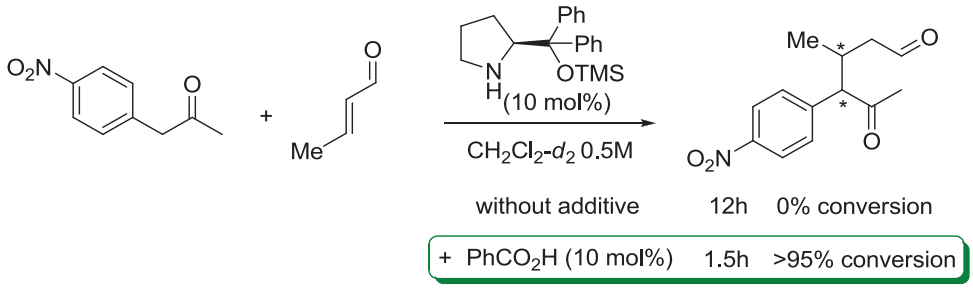


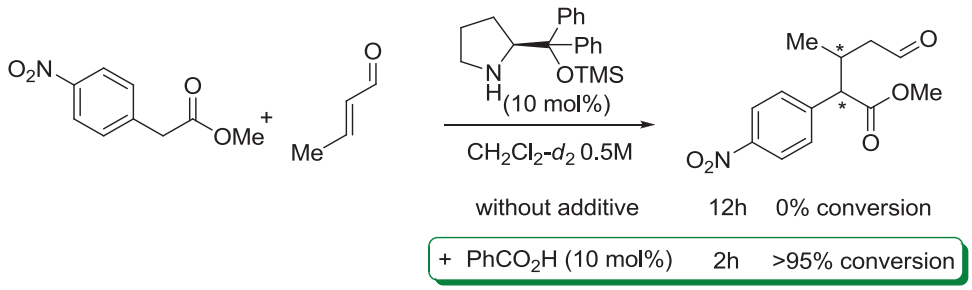
Figure 3.20. NMR conversions of the reaction of **1d** with **2f** and different additives

The effect of the acid on the reaction was even more notable in the case of crotonaldehyde **2a**, where the reaction did not take place without the addition of an external acidic additive. The reaction of ketone **1c** with crotonaldehyde **2a** in dichloromethane-d_2 did not show evolution to the Michael adduct after 12 h of reaction. In contrast the dienamine formed between the catalyst and the aldehydes was observed. However, the reaction reached almost full conversion in less than 2 h with the addition of benzoic acid (Scheme 3.9).



Scheme 3.9. Reaction of **1c** with crotonaldehyde **2a**.

In the reaction of nucleophile **1d** with crotonaldehyde **2a** we found the same trend than for **1c**. The reaction did not take place without the addition of an acidic additive (Scheme 3.10).



Scheme 3.10. Reaction of **1d** with crotonaldehyde **2a**.

The use of additives in the iminium ion catalyzed reactions is controversial, as was demonstrated in the introduction. The use of basic additives is reported in the literature, especially for the less acidic C-centred nucleophiles.[4, 19] In our studies, the use of a base was detrimental for the outcome of the reactions of nucleophiles **1c** and **1d** with cinnamaldehyde **2f** in dichloromethane. However, we were intrigued about the role of the basic additives in other examples described in the literature. We performed similar studies with some other nucleophiles described in the literature using basic additives, in order to obtain more insights about the role of the basic or acidic additives (Figure 3.21). Interestingly, nucleophile **1i** was described independently by Wang and Jørgensen, using benzoic acid and triethylamine as additives respectively. Some interesting results were obtained.

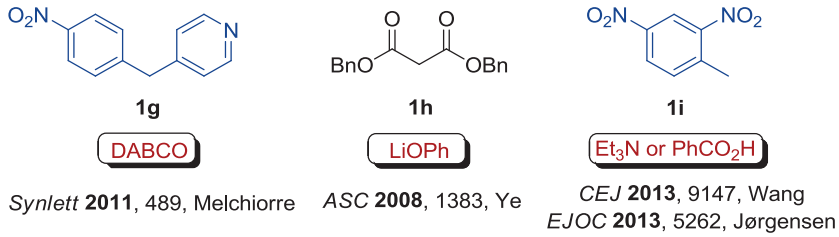


Figure 3.21. Use of basic additives with different nucleophiles.

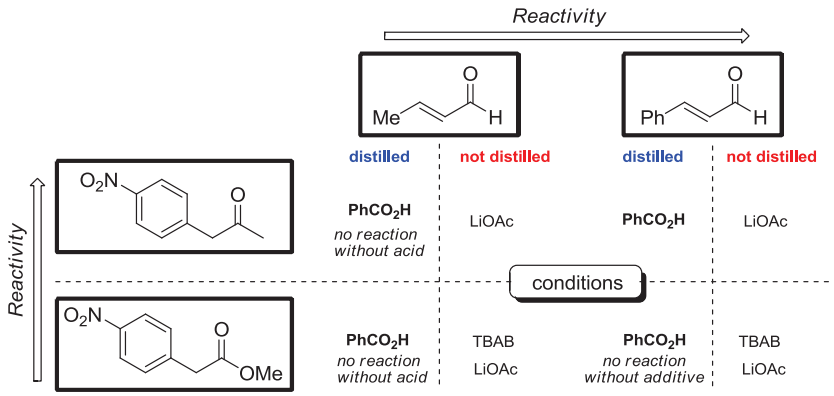
The reaction of nucleophiles **1g** and **1h** were described in the presence of basic additives; however, when we studied the reactions of these nucelophiles, reactions of both **1g** and **1h** with cinnamaldehyde **2f** were accelerated in the presence of benzoic acid, while in the absence of additive the reactions were very slow or even they did not take place. Moreover, the reaction in the presence of basic additives evolved very slowly, which might be attributed to the generation of acid by aldehydes oxidation, as in the case of ketone **1c** and ester **1d**.

[19] a) Y. Wang, P. Li, X. Liang, J. Ye, *Adv. Synth. Catal*. **2008**, *350*, 1383; b) Y. Wang, P. Li, X. Liang, T. Y. Zhang, J. Ye , *Chem. Commun.* **2008**, 1232; c) B. Alonso, E. Reyes, L. Carrillo, J. L. Vicario, D. Badía, *Chem. Eur. J.* **2011**, *17*, 6048; d) L. Dell'Amico, X. Companyó, T. Naicker, T. M. Bräuer, K. A. Jørgensen, *Eur. J. Org. Chem.* **2013**, 5262.

The case of nucleophile **1h** was even more curious. The reaction in dichloromethane is accelerated by the addition of triethylamine while in dimethylsulfoxide as solvent the reaction does not need the addition of a base. This observation may indicate that in dichloromethane the deprotonation step is more important for the outcome of the reaction. A similar positive effect was observed adding a mixture of benzoic acid and triethylamine as in the reaction of **1d**.

From this study it can be concluded that the outcome of the Michael reactions highly depends on the acid amount of the starting aldehyde. In this study we also appreciated a higher reactivity for nucleophile **1c**. With this nucleophile, the reaction was strongly accelerated by the addition of benzoic acid; however, the reaction was also working in the absence of additives. The addition of a base decelerated or even inhibited the reaction. The reaction profiles obtained were in sharp contrast with the values previously obtained. For the reactions of nucleophile **1d**, we also appreciated acceleration in the presence of benzoic acid or TBAB. In this case, the reaction did not take place in the absence of additive.

The use of a base decreased the reaction rate in both cases, thus the deprotonation of the nucleophile can be discarded as rate determining step for the reactions studied, as the use of a base would help this particular step. However, in this study the positive effect of the addition of an acidic additive to the reaction was demonstrated in either less or more acidic pro-nucleophiles **1d** and **1c** respectively. The positive influence of the added acid on the reaction was observed in both cinnamaldehyde **2f** and crotonaldehyde **2a**, being more evident in the latter case, where the reaction did not take place in the absence of an external acidic additive (Scheme 3.11).



Scheme 3.11. Reactivity tendencies.

As the reactions were followed by NMR analysis, we could identify some intermediates during the reaction course. In the absence of additives the reaction of both nucleophiles **1c** and **1d** with cinammaldehyde **2f** was very slow, or even did not take place after 24h as in the case of **1d**.

Next figure represents the spectrum of the reaction of **1d** with cinnamaldehyde **2f** in the presence of catalyst **II** (10 mol%) after 4h. The signals of the starting aldehyde and nucleophile are clearly identified (Figure 3.22).

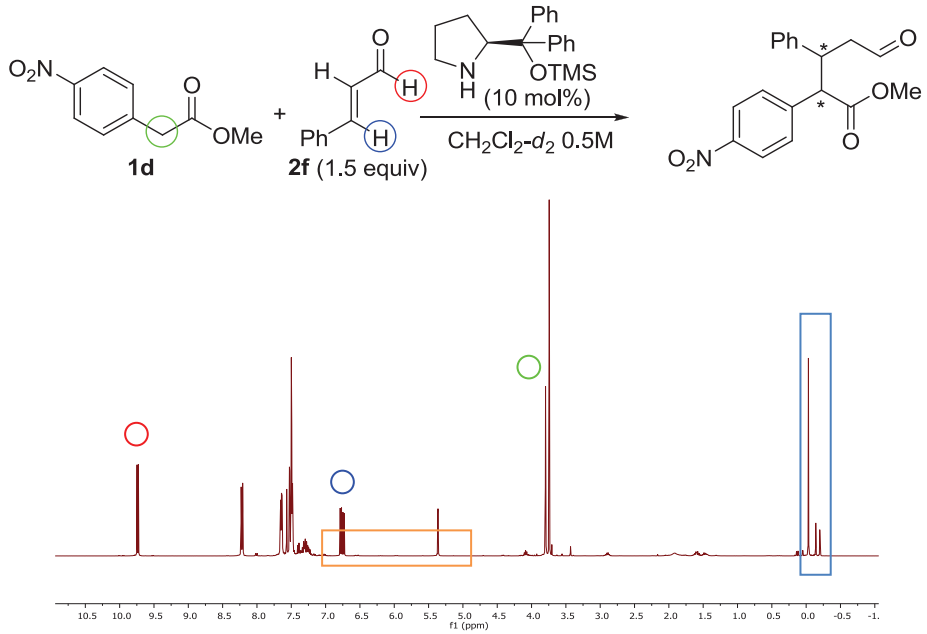


Figure 3.22. Spectrum of the reaction of **1d** with cinnamaldehyde **2f** after 4h.

However, in a more detailed observation of the spectrum the signals of the product enamines were also identified. Even when the reaction did not take place, we could observe the product enamines, showing that the attack of the nucleophile had taken place (see catalytic cycle in Scheme 3.12). The more deshielded protons of the enamine system and the two different trimethyl groups of protons next to the silyl atom were clearly identified. It is important to note that there are two set of signals because the presence of the nucleophile in the enamine adds an extra stereogenic center (Figure 3.23).

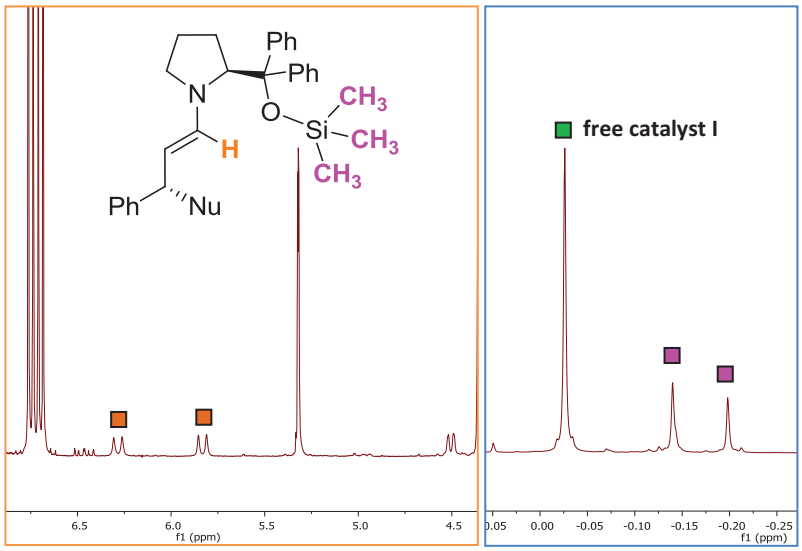


Figure 3.23. Sections of the spectrum showed in Figure 3.22

For the reaction of nucleophile **1c** with cinnamaldehyde **2f** in the presence of catalyst **II** the same observation was made. However, in that case, the ratio free catalyst to product enamines was almost totally shifted towards the product enamines.

When benzoic acid (10 mol%) was added, the product enamines were also identified, although in fewer ratios, and small amounts of Michael adducts were detected even at short times. Moreover, a new signal appeared in the area of the trimethyls groups that was assigned to the corresponding protons of the protonated catalyst (Figure 3.24).

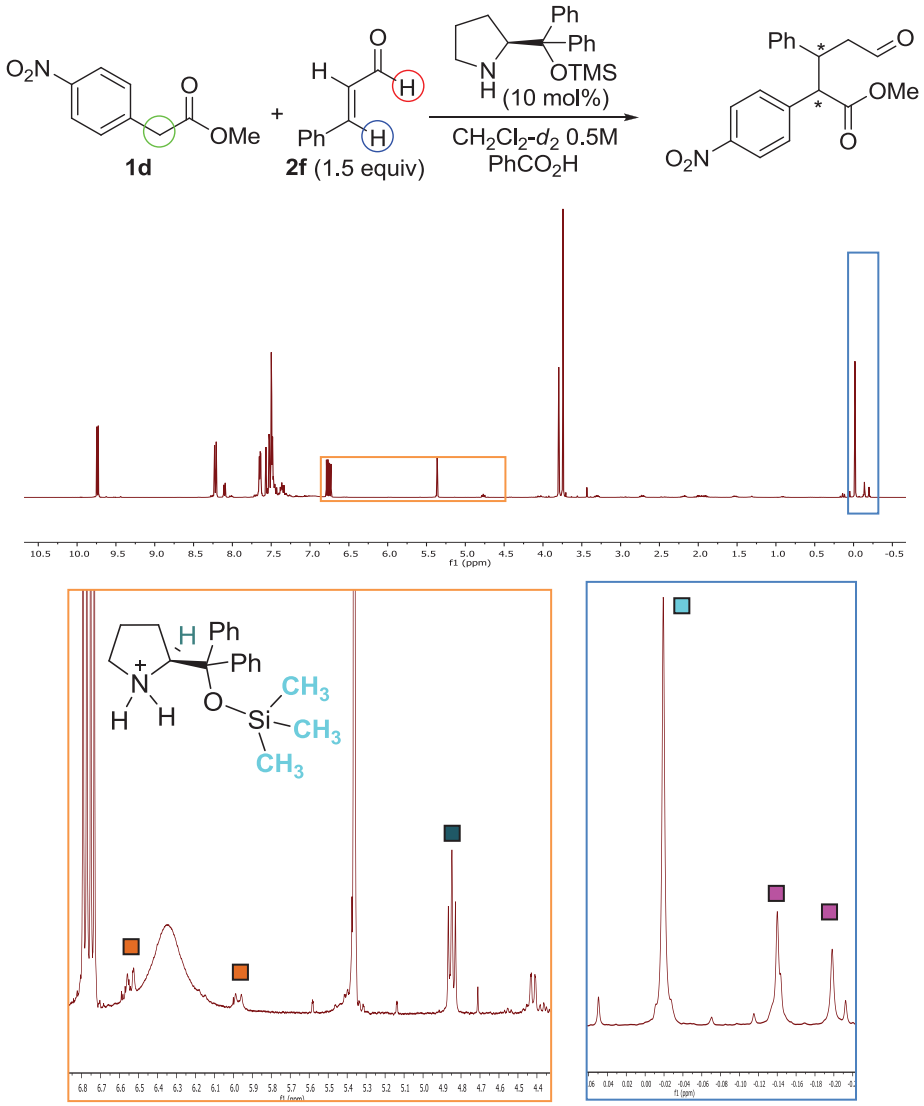
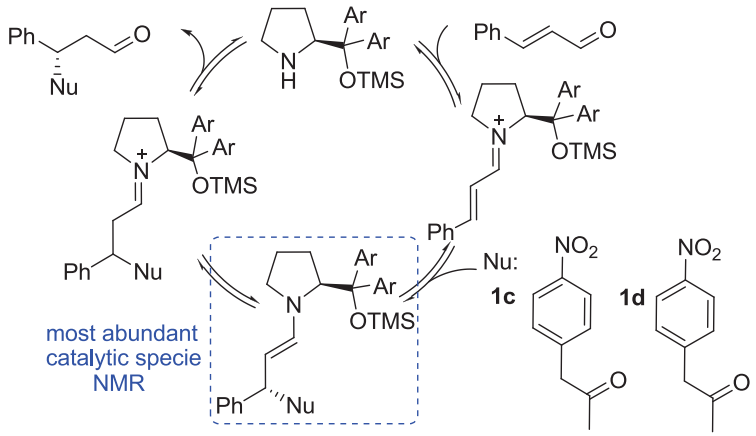


Figure 3.24. Spectrum of the reaction of **1d** with cinnamaldehyde **2f** after 2h with $PhCO_2H$.

The same course was observed for the reaction of nucelophile **1c**, where the addition of benzoic acid rapidly produced the formation of the Michael adducts.

Interestingly, the addition of TBAB to the reaction of nucleophile **1d** with cinammaldehyde **2f** increased the ratio between the free catalyst and the product enamines towards the enamines. However, the same effect was not observed for the reaction of nucleophile **1c**. It is important to recall that the use of TBAB notably accelerated the reaction of derivative **1d** (see Figure 3.20) compared to the absence of additive, where the reaction did not take place.

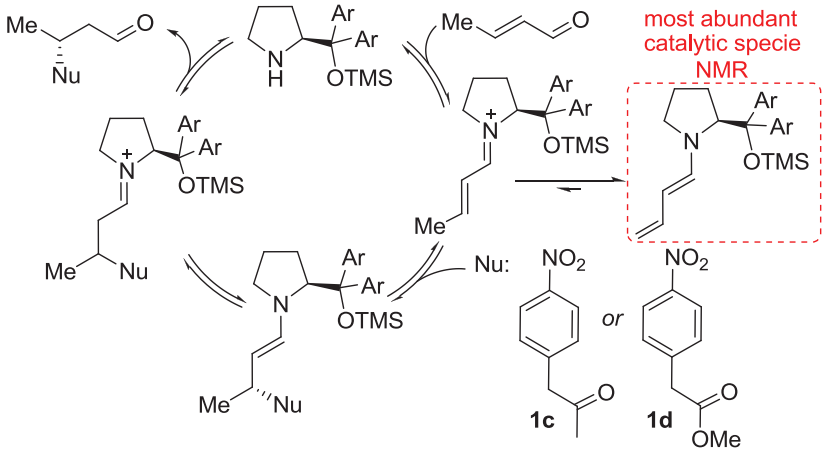
In this study the product enamines were identified as the most abundant catalytic species in the absence of additives for the reaction of cinnamaldehyde **2f** with both nucleophiles **1c** and **1d** (Scheme 3.12).



Scheme 3.12. Catalytic cycle for the reaction with cinnamaldehyde

The analysis of the reactions with crotonaldehyde **2a** was more complicated. The first important difference between aliphatic and aromatic enals is the ability of the former ones to form dienamine species with secondary amines. NMR studies revealed that in the absence of additives the dienamine was the most abundant catalytic specie in the reaction of catalyst **II** with crotonaldehyde **2a** and both nucleophiles **1c** and **1d**.

Moreover, in the absence of additives the reaction did not take place with either **1c** or **1d**. The catalyst was occupied forming the dienamine, formed between the catalyst and the aldehyde and thus out of the catalytic cycle (Scheme 3.13).



Scheme 3.13. Catalytic cycle for the reaction with crotonaldehyde

The most characteristic signals of the dienamine were identify by ^{1}H NMR, according to the chemical shifts and coupling constants (see Figure 3.25).[20]

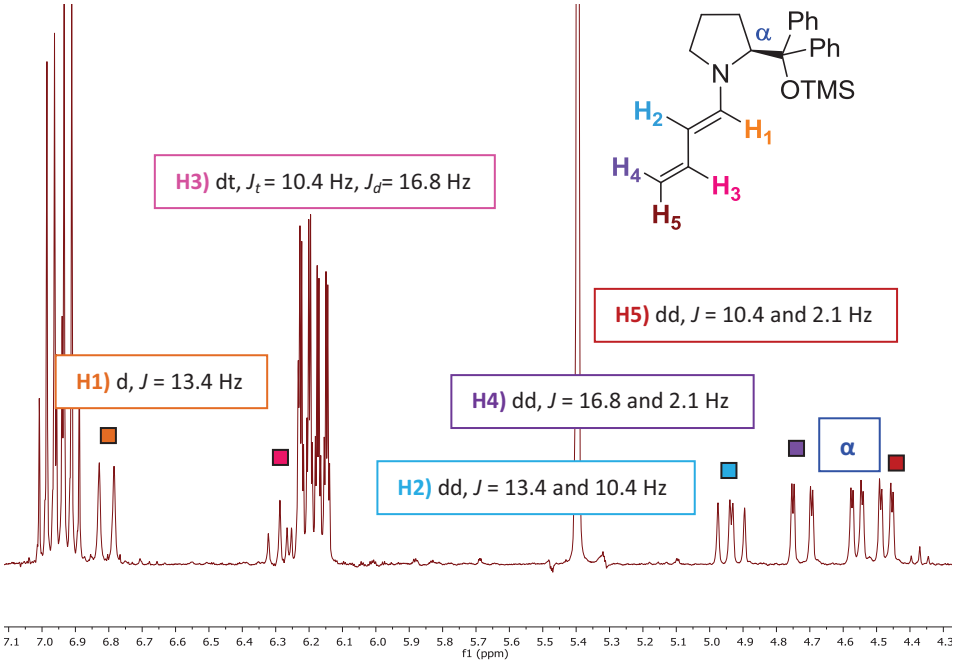


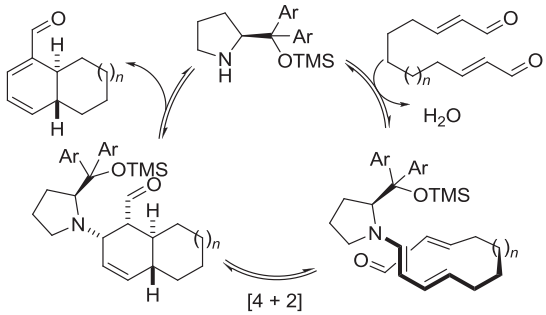
Figure 3.25. Most characteristic signals of the dienamine.

[20] The reaction was performed with 20 mol% of catalyst **II** in order to asigne the signals.

When an acidic additive (in our case benzoic acid) was added and the reaction started, a possible side reaction started as well. Moreover, we could not detect the product enamines during the reaction course, as were detected for the case of reactions with cinnamaldehyde **2f**; but other intermediates were formed instead. This intermediate is present during the entire reaction course. If this intermediate contains the catalyst in its structure it would be sequestering part of the catalyst out of the catalytic cycle of the desired reaction. However, in the case of nucleophiles **1c** and **1d**, the Michael addition took place in the presence of benzoic acid reaching almost full conversion. Nevertheless, it cannot be discarded that this side reaction becomes more important for other nucleophiles with less ability to shift the equilibrium to the Michael products and might be the reason of the lack of reactivity of β-alkyl enals with some nucleophiles.

In 2008 Christmann and co-workers described the amine-catalyzed cyclization of tethered α,β-unsaturated aldehydes.[21] In this paper the authors proposed an intramolecular Diels-Alder reaction for the synthesis of bycyclic scaffolds (Scheme 3.14). This reaction takes place in the presence of prolinol derivatives **I** and **II** and is strongly accelerated with acidic additives. Indeed, the reaction reaches completion to the bicyclic products in only 1h in the presence of catalyst **II** and benzoic acid in dichloromethane.

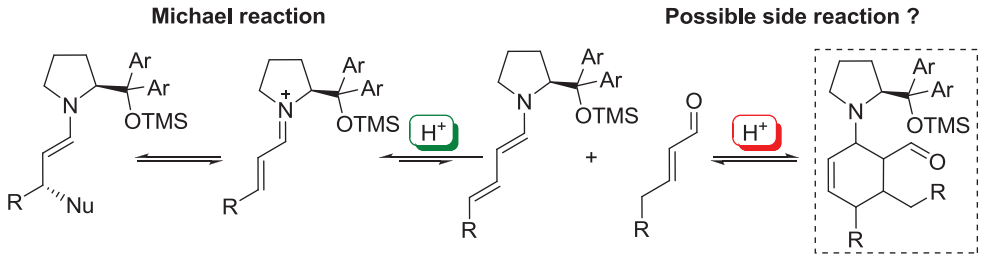
Catalyst	Additive	Solvent	t (h)
I	BzOH	Toluene	3
II	BzOH	Toluene	3
II	-	Toluene	144
II	AcOH	Toluene	12
II	BzOH	CH_2Cl_2	1
II	BzOH	THF	96



Scheme 3.14. Proposed catalytic cycle for the cyclization of unsaturated dialdehydes

[21] R. M. Figuereido, R. Frölich, M. Christmann, *Angew. Chem. Int. Ed*. **2008**, *47*, 1450.

We may propose a similar catalytic cycle for the reaction of crotonaldehyde **2a** and other aliphatic enals (Scheme 3.11). Even if the intermolecular reaction must be less favourable than the corresponding intramolecular, is difficult to exclude this process considering the results obtained by Christmann.



Scheme 3.15.

From this experiment we may conclude that in the absence of additives the protonation of the dienamine to form the iminium ion and thus start the reaction usually occurs due to the presence of acidic traces in the aldehydes. Therefore, the excess of acid in these aldehydes presumably helps their reaction in the iminium ion catalyzed reactions. However, a large excess of acid can be also detrimental if the possible secondary reaction is also catalyzed in the presence of acids. Thus, the reason for the lower reactivity showed for the aliphatic enals in some cases and ascribed to the intrinsic low reactivity of these aldehydes, might be instead a consequence of the low catalyst loading that is truly acting in the catalytic cycle.

4.4. Analysis of the factors that may affect the reversibility of the process.

The erosion of the enantioselectivity observed in some cases was attributed to the reversibility of the process. The effect of the different parameters (aldehyde, nucleophile, catalyst, additive and solvent) on the reversibility of the Michael reaction was studied.

Effect of the aldehyde

The reaction profile of the Michael addition of nucleophile **1c** with cinnamaldehyde **2f** in dichloromthane (obtained by ^{1}H NMR analysis) showed that the reaction is faster at the beginning and becomes slower as it approaches to the equilibrium. Moreover, the equilibrium is reached at *ca*. 80% conversion (Figure 3.26) and thus is not totally shifted to the final product.

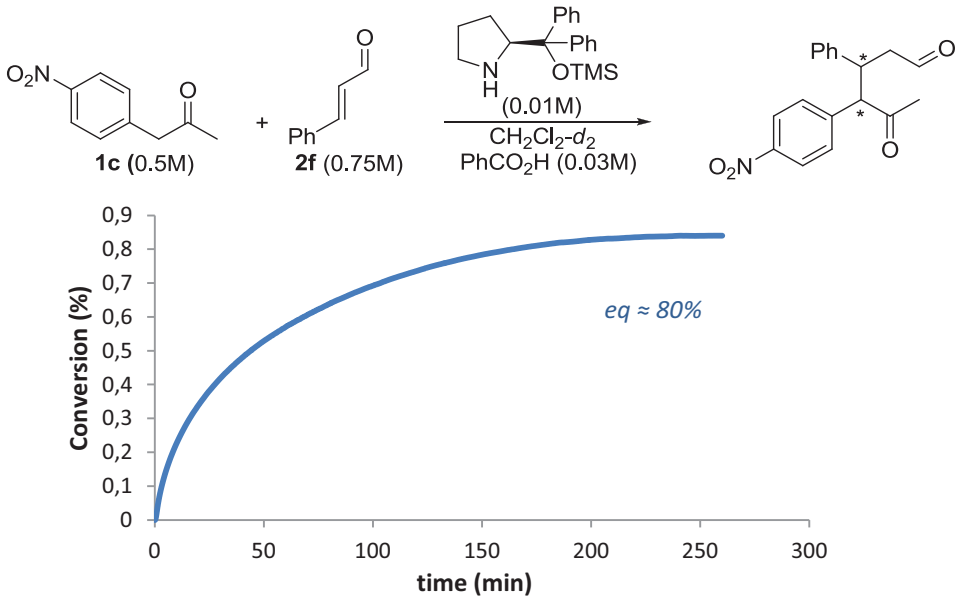


Figure 3.26. Reaction profile of the reaction of **1c** with cinnamaldehyde **2f** and catalyst **II**.

The reaction of the same nucleophile with crotonaldehyde **2a** was slower, as showed in the previous section, and thus required more catalyst to achieve similar conversions in the same time. The reaction profile for the reaction with crotonaldehyde was also analyzed. In this case, the equilibrium is instead totally shifted to the Michael product (Figure 3.27). This fact might explain the higher degree of reversibility observed for the Michael addition of nucleophiles to aromatic enals compared with the reactions with aliphatic enals.

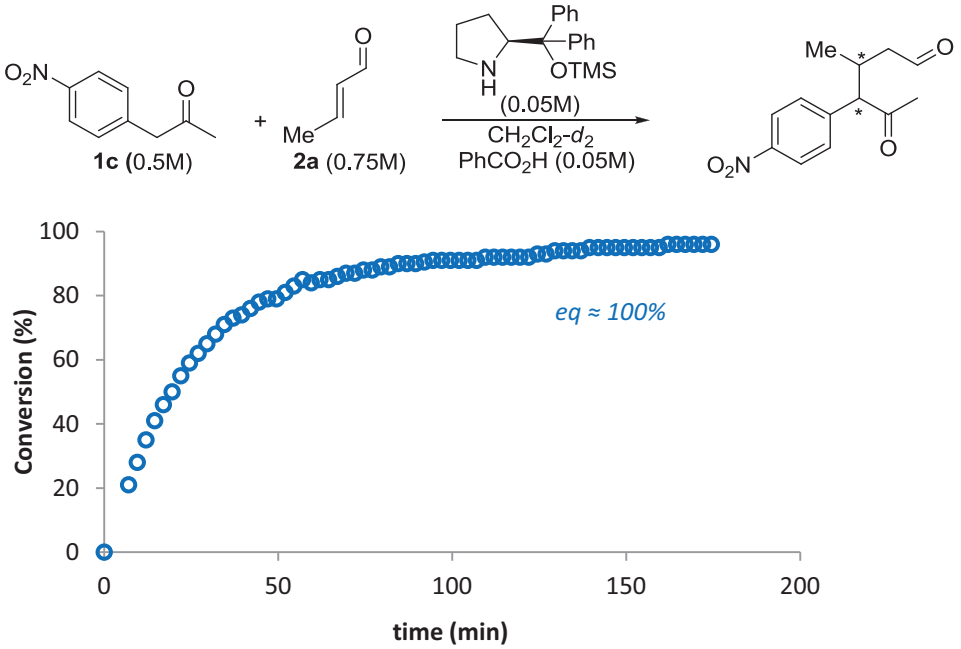


Figure 3.27. Reaction profile of the reaction of **1c** with crotonaldehyde **2a** and catalyst **II**.

As the global reversibility of a reaction depends on how much favoured is this reaction and this is controlled by the Gibbs free energy, we next calculated the ΔG values of the Michael reaction of our set of nucleophiles **1a-g**.

The ΔG values for the global reaction of nucleophiles **1a-1g** with crotonaldehyde **2a** and cinnamaldehyde **2f** were calculated theoretically by Dr. Inés Alonso and Dr. Al Mokhtar Lamsabhi at the M06-2X/6-311G++G(3df,2p)//M06-2X/6-311G** level of theory.

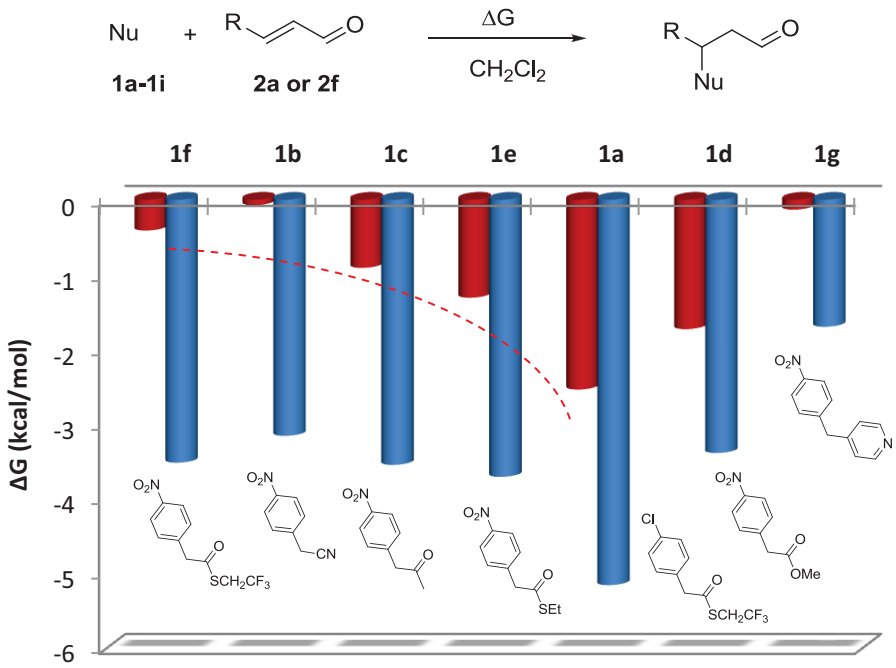
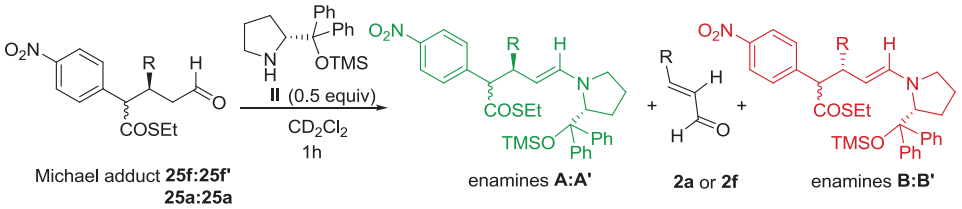


Figure 3.28. ΔG values of the Michael reaction of nucleophiles **1a-g** with cinnamaldehyde (red) and crotonaldehyde (blue).

The ΔG values obtained for the Michael reaction with crotonaldehyde **2a** (in blue) were much higher (in absolute values) in all cases than the corresponding theoretical values calculated for the reactions of cinnamaldehyde **2f** (in red). Thus, we may conclude from the NMR profiles and the theoretical calculations that the reactions of aliphatic enals are more favoured. This fact may explain the lower tendency to the reversibility of the final products to the starting materials.

A relation between the acidity of the nucleophiles and the reversibility in the reaction with aromatic enals may be envisioned for the most acidic nucleophiles (left side of the graphic). For the most acidic nucleophiles **1f**, **1b, 1c** and **1e**, a relation between the acidity and the stability of the final products is found.

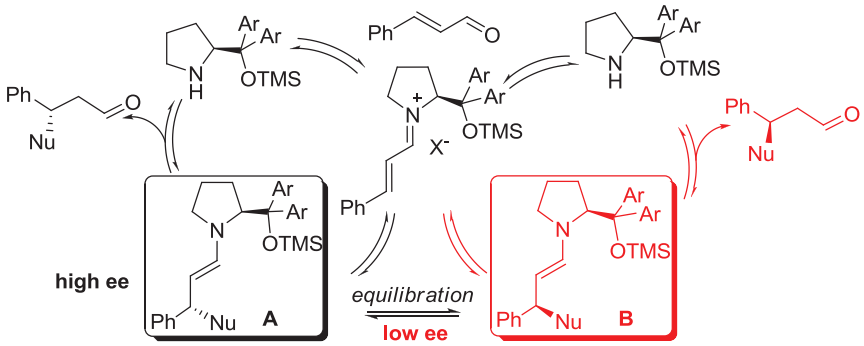
The reversibility tendencies were also studied in the retro-Michael reaction of adducts **25f:25f'** and **25a:25a'** derived from the reaction of thioester **1e** with cinnamaldehyde **2f** and crotonaldehyde **2a** respectively. The reaction of these adducts in the presence of 0.5 equivalents of catalyst **II** in dichloromethane-d_2 was followed by NMR analysis (Scheme 3.16). The reactions were performed with 0.5 equivalents of catalyst in order to identify the species. However, as these are not the conditions used in the reactions, the results are taken as qualitative tendencies.



a)	37	**R = Ph**	16	29	18
b)	60	**R = Me**	40	-	-
c)	100 + **2a**	**R = Me**	-	-	-

Scheme 3.16. Retro-Michael reaction of adducts **25**.

After 1h of reaction with adducts **25f** we observed a high proportion of the product enamines A and the starting aldehyde **2f** (Scheme 3.16, a). Moreover, another set of enamines were also observed. These enamines B are presumably formed by equilibration with enamines A (Scheme 3.17).



Scheme 3.17. Enamines equilibration

The adduct **25a** also formed the product enamines A in the presence of catalyst **II**. However, the starting aldehyde **2a** and the other enamines B were not observed (Scheme 3.16, b). This experiment showed that both adducts prented tendency to form the enamines in the presence of an excess of the catalyst. However, in the case of the Michael adducts from **1e** and cinnamaldehyde **2f** we even observed the starting enal and more important, the equilibration with the other enamines. This observation was not found in the case of the retro-Michael reaction of adducts derived form crotonaldehyde **2a**. Moreover, when the same experiment was performed in the presence of an excess of crotonaldehyde **2a** (0.5 equiv to 1.5 equiv), not even the enamines were detected, showing again that other interactions are present in the reaction of silyl prolinol catalysts **I** or **II** with β-aliphatic enals. In addition, the extra added crotonaldehyde **2a** disappeared totally after 2h (Scheme 3.16, c).

It is important to remind that the dienamine may play a significant role in the absence of reversibility found in the Michael reactions of aliphatic enals. As shown in the previous section, this species is formed in the reactions of all the nucelophiles studied. The catalyst is involved in other pathways thus reducing the amount of free catalyst available not only for the forward reaction but also for the retro-Michael reaction.

Effect of the catayst

The reaction of nucleophile **1c** with cinnamaldehyde **2f** with both catalysts **I** and **II** in the absence of additive was followed by NMR analysis (Figure 3.29).

At the beginning of the reaction with catalyst **II** the nucleophile presumably attacks to the iminium ion to form the corresponding product enamines (A). Two diastereomeric product enamines are formed as the nucleophile adds another stereogenic centre to the molecule. The signal of the free catalyst rapidly disappears to form the corresponding product enamines.

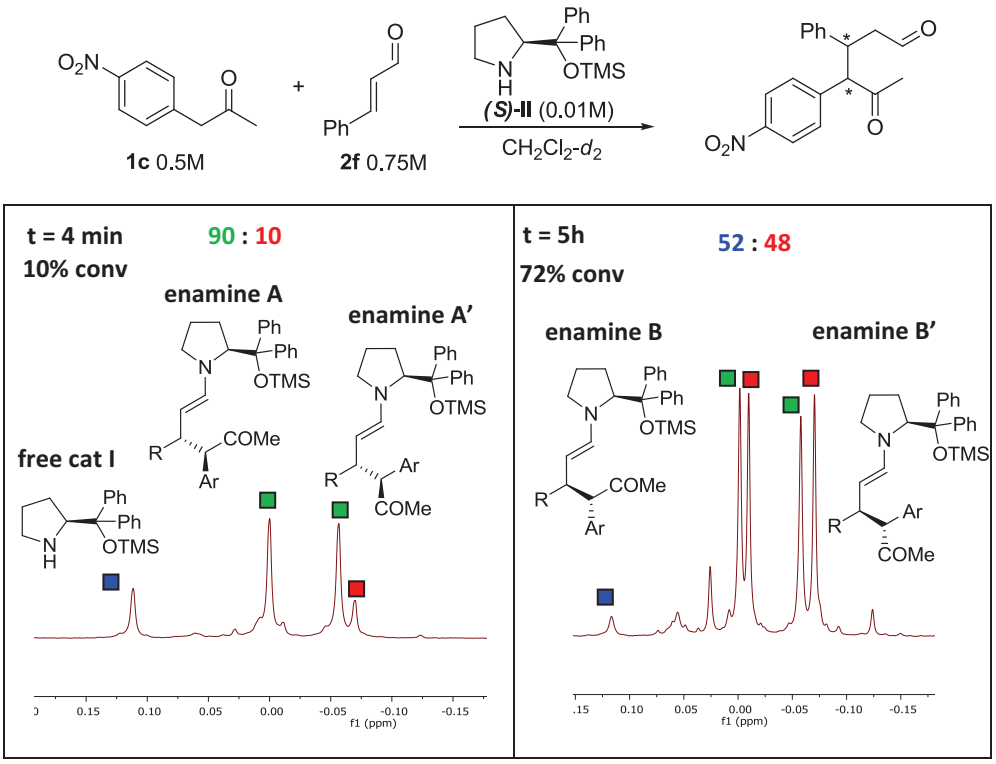


Figure 3.29. Evolution of the species in the reaction of **1c** and **2f** catalyzed by **II**.

A second pair of enamines (B) is formed in minutes, probably due to product equilibration (see Scheme 3.17). When the reaction almost reaches the equilibrium (after 5h, conversion 72% conversion), the ratio between the product enamines A and B is almost 50:50. Moreover, the total ratio between the enamines and the free catalyst is kept nearly constant during the reaction course. The equilibration of these enamines would result in a racemization of the final adduct.

Thus it may be proposed that the problem of the low enantioselectivity found in some reactions with catalyst **II** and cinnamaldehyde **2f** is not a consequence of the low facial differentiation in the attack of the nucleophile provided by this catalyst. The poor selectivity may be attributed instead to the equilibration of the product enamines during the course of the reaction. As this equilibration is faster than the completion of the reaction, it is impossible to obtain high enantioselectivities for high conversion levels (Scheme 3.17).

The same experiment was performed using catalyst **I** (Figure 3.30). The first difference observed was the fewer amounts of intermediates formed and the slow reaction observed, which forced us to increase the catalyst concentration. The free catalyst was disappearing more slowly to form the corresponding enamines. A pair of signals is observed; however, in this case we did not observe the other pair formed with catalyst **II**. Even after 18h, when the conversion reached 70%, only two set of signals corresponding to the diastereomeric enamines were observed.

It can be concluded that for the reactions of catalyst **I** the equilibration of the corresponding product enamines occurs later and in some cases is not observed after reaction completion.

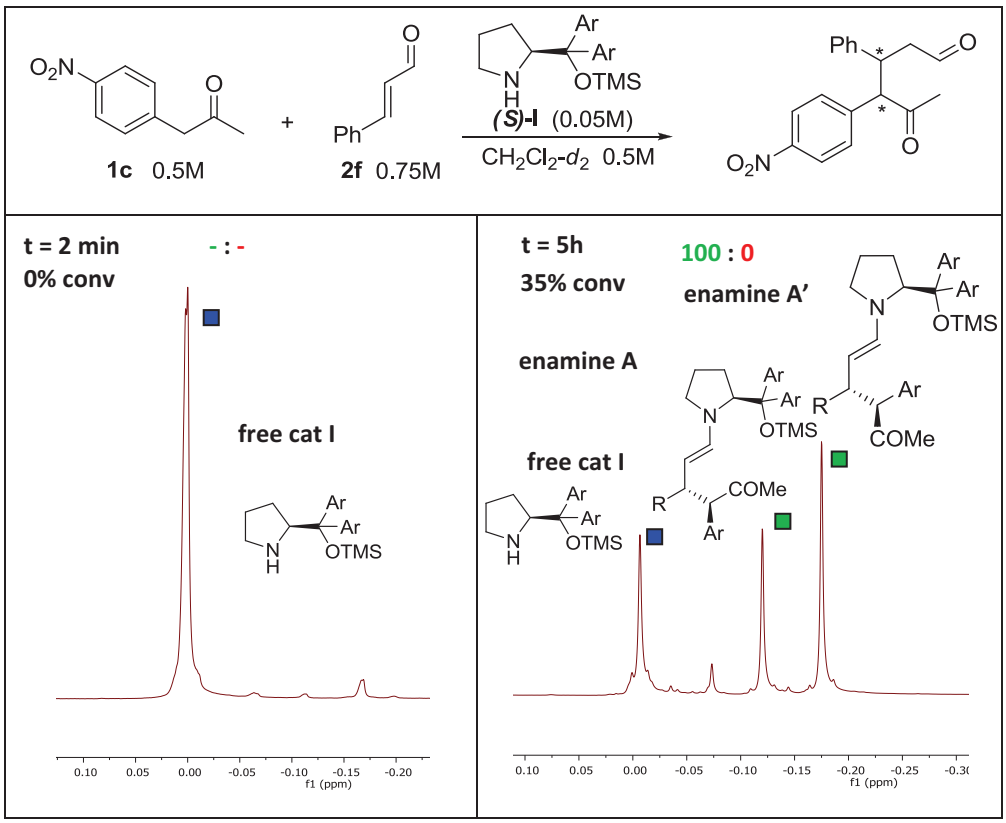


Figure 3.30. Evolution of the species in the reaction of **1c** and **2f** catalyzed by **I**.

As commented previously, we clearly observed the lower tendency of catalyst **I** to form the product enamines compared to catalyst II in the reaction of nucleophile **1c** with cinnamaldehyde **2f**. The reaction with both catalysts was performed in the absence of additives. With the same concentration of catalyst, the ratio of free catalyst **II** to product enamines after ten minutes is much smaller in comparison with the same experiment performed with catalyst **I** (Figure 3.31).

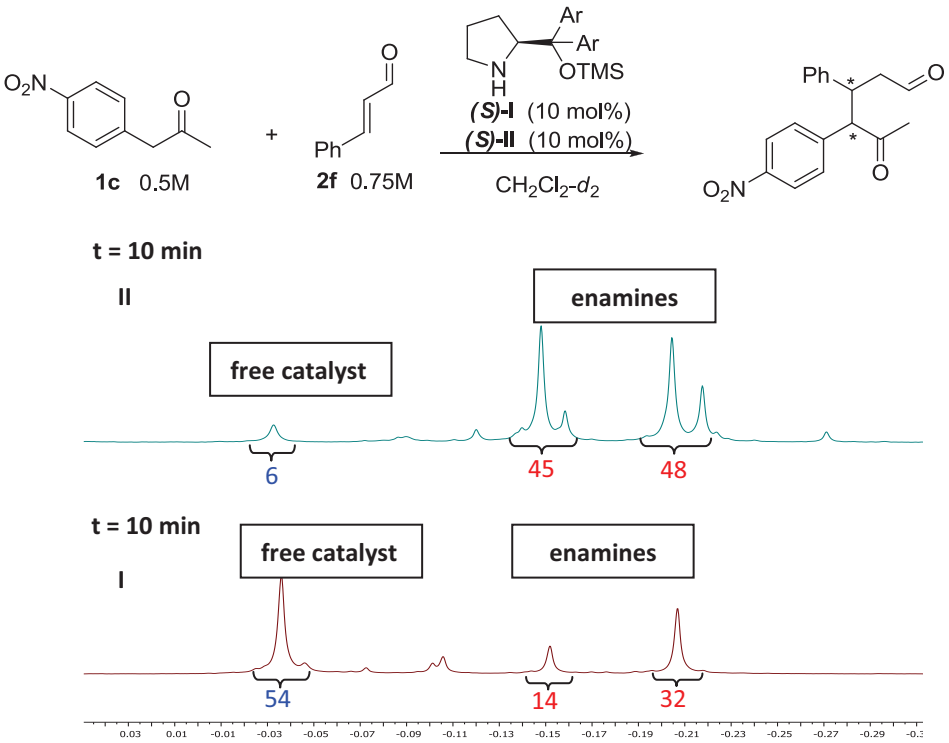
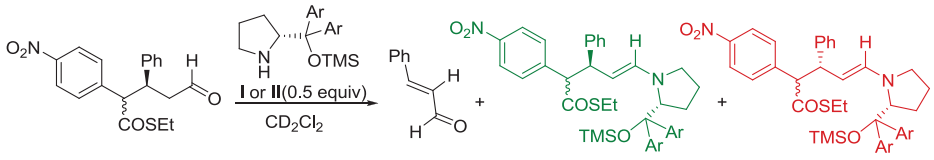


Figure 3.31. Enamines/free catalyst ratio

We also performed NMR studies on the retro-Michael reaction of the Michael adducts **25f** derived from the addition of nucleophile **1e** to cinnamaldehyde **2f**. The experiments were carried out with 0.5 equivalents of catalyst **I** or **II** (Scheme 3.18). The tendencies observed were in agreement with the previous study. The reactions with catalyst **I** presented less tendency to form the product enamines, and moreover, they did not show enamine equilibration even after 72h.



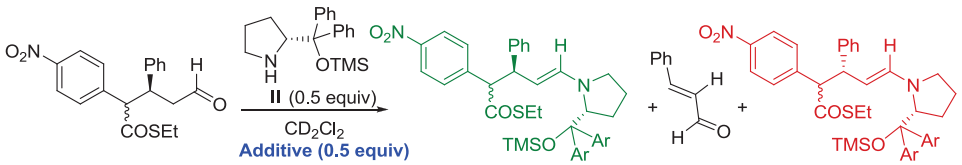
Michael adduct **25f:25f'** cinnamaldehyde **2f** enamines **A:A'** enamines **B:B''**

37	cat **II**	29	16	18
72	cat **I**	-	28	-

Scheme 3.18.

Effect of the additive

The retro-Michael reaction over the Michael adducts of thioester **1e** with cinnamaldehyde **2f** in the presence of catalyst **II** and different additives (Scheme 3.19). Again the results cannot be compared to the reaction under the usual conditions as was performed using 0.5 equivalents of catalyst and additive. However, some interesting tendencies were observed. The presence of TBAB seemed to increase the tendency to the retro-reaction, increasing the amounts of cinnamaldehyde and enamines observed. The addition of acidic additives decreased the ratio of both enamines and cinnamaldehyde; however, this fact is not excluding their formation in the reaction, they can be formed but being protonated and hydrolyzed so fast avoiding their detection.



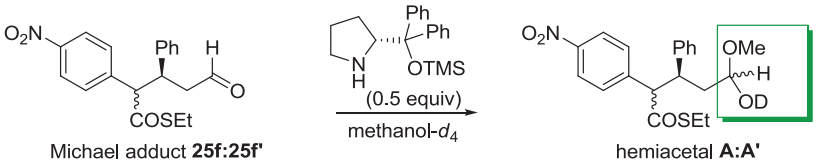
Michael adduct **XXf:xxf'** | enamines **4a:4a'** | **2f** | enamines **5a:5a''**

37	-	16	29	18
23	TBAB	16	38	23
53	BZOH	8	29	10
68	*p*-NO_2-BzOH	-	32	-

Scheme 3.19

Effect of the solvent

Interestingly, the Michael adducts **25f** of thioester **1e** and cinnamaldehyde **2f** in the presence of an excess catalyst **I** or **II** in methanol-d_4 spontaneously formed the hemiacetal form.



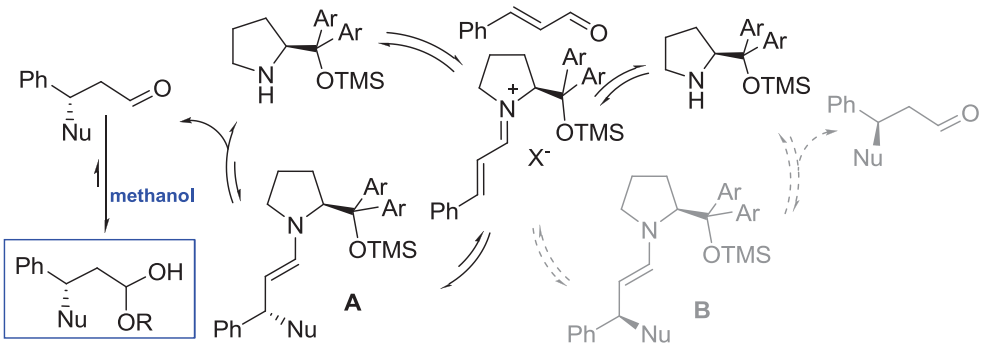
Scheme 3.20. Hemiacetalization

The addition of different additives did not produce any change to this result obtained with catalyst **II** or catalyst **I** in methanol-d_4.

We tried to follow the catalytic reactions of **1c** with cinnamaldehyde **2f** or crotonaldehyde **2a** by NMR analysis but the large amount of different species makes very difficult this analysis.

The starting aldehydes **2a** or **2f** do not show this hemiacetalization process under the reaction conditions, at least in noticeable amounts; however, the Michael adducts cannot be almost identified as they form rapidly these species in the reactions performed in methanol-d_4.

If the erosion of the enantioselectivity of the Michael adducts with time is a consequence of the reversibility, the employment of methanol as solvent might decrease this process, shifting the equilibrium to the hemiacetalic species (Scheme 3.21). The aldehydes would be less available to get into the catalytic cycle again, minimizing the retro-reaction.



Scheme 3.21. Catalytic cycle in methanol

However, as the equilibrium between the hemiacetal and the aldehydes species is present, the reversibility process would not be totally avoided.

More investigations need to be done in this interesting point in order to get more reliable conclusions.

4.5. Nucleophilicity *vs*. acidity of the nucleophile.

The comparison of the nucleophilicities and electrophilicities of different classes of compounds is of considerable importance for the understanding and prediction of organic reactivity.

During the last yeasrs Mayr's scales have become very popular in order to predict the relative reactivity of electrophilic and nucleophilic compounds. Based on kinetic studies of the Michael addition, performed with large amounts of nucelophile or electrophile and comparing the reactivities against reference compounds,[22] they described reactivity scales. All these parameters are compiled in a database, which allow calculating the rate constants for combination reactions of electrophiles with nucleophiles by Equation (1):

$$\textbf{(1)} \quad \log k = s_N (N+E)$$

E = electrophilicity parameter
N = nucleophilicity parameter
s_N = nucleophile-specific sensitivity parameter

In the context of iminium ion catalysis, Mayr and co-workers investigated electrophilic reactivities of α,β-unsaturated iminium ions.[23] They could isolate triflate salts of iminium ions derived from MacMillan's imidazolidinones catalyst and derived from silyl prolinol **II**. The electrophilicity parameters of iminium ions were determined. Among the tested iminium ions, the ones formed from cinnamaldehyde with imidazolidinone and prolinol derived catalyst were the most electrophilic (Figure 3.28, left).

[22] a) H.Mayr, B.Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66; b) H. Mayr, A. R. Ofial, *Carbocation Chemistry*; G. A. Olah, G. K. S. Prakash, Eds.; Wiley: Hoboken, NJ, 2004; pp 331-358. c) A. R. Ofial, H. Mayr, *Macromol. Symp.* **2004**, *215*, 353; d) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807. e) H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584.
[23] S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem. Int. Ed.* **2008**, *47*, 8723.

The nucleophilicity parameters of some hetero and carbon-nucleophiles used in iminum ion catalysis were also calculated. Moreover, some nucleophiles studied by us[24] are included in these scales (Figure 3.28, right).

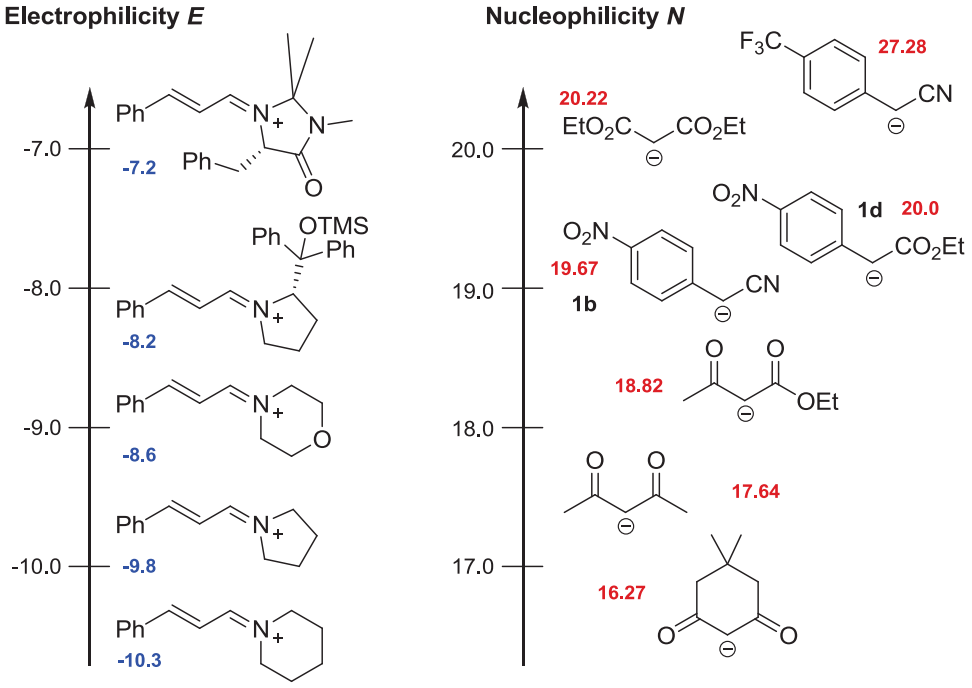


Figure 3.28. Reactivity scales

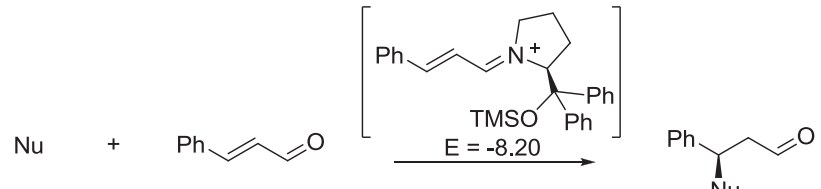
Therefore we tried to understand some reactivity problems that we found using Mayr's reactivity scales. Nevertheless, we found some discrepancies in these reactivity scales that should be commented.

Enantioselective additions are only possible with nucleophiles which react readily with the iminium ions but not with the corresponding unsaturated carbonyl compounds (background reaction). According to Mayr only nucleophiles with

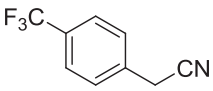
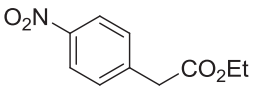
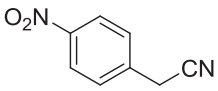
[24] Kaumanns, O.; Appel, R.; Lemek, T.; Seeliger, F.; Mayr, H.; *J. Org. Chem.* **2009**, *74*, 75.

nucleophilic parameters between 3 and 12 would be appropriated for that purpose: *"nucleophiles which are strong enough to react with iminium ions but weak enough not to react with the precursor carbonyl compounds were found to have nucleophilicity parameters 3<N<12".*[22d] Nevertheless, many successful nucleophiles are out of this range. Moreover, we never observed background reaction with nucleophiles **1b** or **1d** with nucleophilicities much higher than 12.

The second inconsistency was found in the order of reactivity predicted by these scales for our nucleophiles. Taking into account the E parameter obtained for the iminium ion derived from catalyst **II**, and the nucleophilicity parameters of nucleophiles **1b-j**, the corresponding reactivity scale should be as follows: **1j >1d >1b**.



Nu:

1j	**1d**	**1b**
		
N = 27.28 S_N = 0.50	N = 20 S_N = 0.71	N = 19.67 S_N = 0.68
$k_{calc} = 10^{9.54}$	$k_{calc} = 10^{8.38}$	$k_{calc} = 10^{7.79}$
pKa 18	pKa 16	pKa 12

However, when the reaction of these derivatives with cinnamaldehyde **2f** and catalyst **II** in dichloromethane-d_2 was followed by ^{1}H NMR analysis, the order of reactivity observed was the opposite form the expected from equation 1 (Figure 3.29):

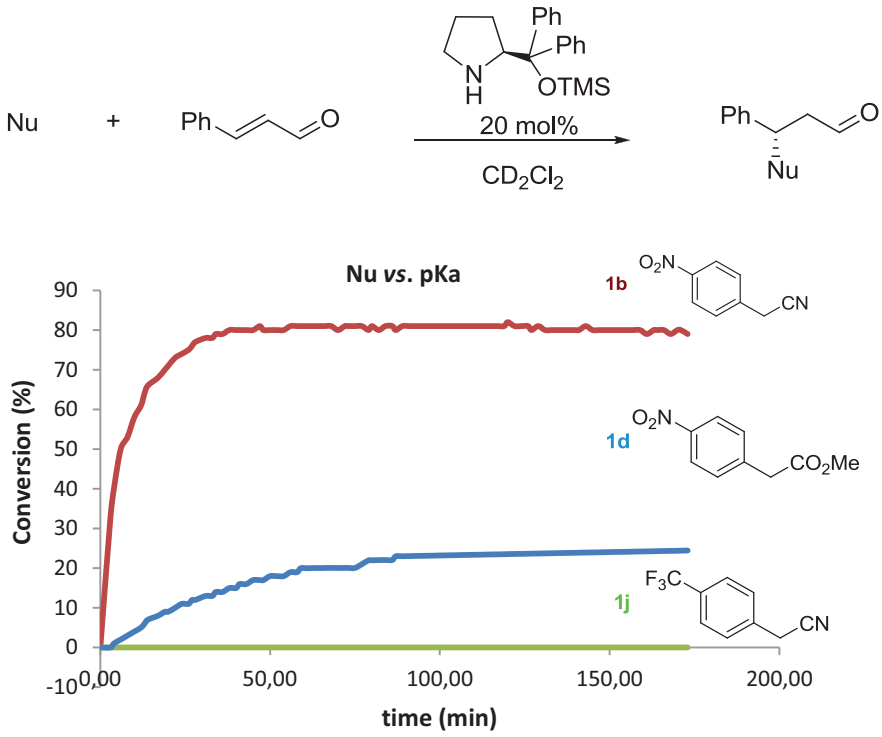
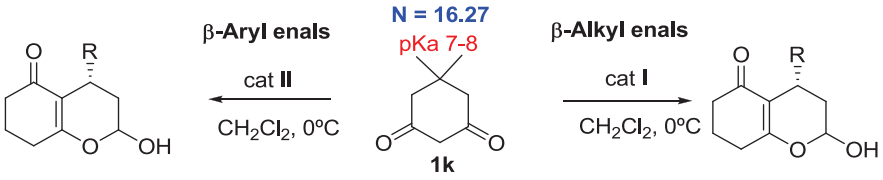


Figure 3.29. ^{1}H NMR evolution of the reaction of **1b-1j** with cinnamaldehyde.

Nucleophile **1j**, with the highest k_{calc}, was unreactive under the reaction conditions, whereas **1b**, with the lowest k_{calc}, was the most reactive nucleophile of the series. However, it is interesting to note that in the reaction of **1j**, although no conversion to the final products was observed after 4h, the NMR analysis of the reaction indicated the presence of the product enamines, showing that the attack of the nucleophile had taken place.

In the literature similar cases can be also observed, for example nucleophile **1k** reacted very fast with both aromatic and aliphatic enals, but presented a relative low nucleophilicity comparing with nucleophile **1j**. In contrast, the acidity of the methylenic protons in **1k** is much higher than the in the nucleophiles **1b-i** (Scheme 3.18).



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Scheme 3.18.

We reckon that these orders could be applicable if both quantitative anion and iminium ion were reacting, because this equation does not count the formation of these species. In the catalytic cycle, the enolate and the iminium ion need to be formed, and thus the concentration of these species may also be important for the success of the reaction. It seems that the acidity of the nucleophile is more important in predicting the reactivity orders than the corresponding nucleophilicity parameters.

Even if the quantitative anion were formed, the catalytic cycle for the iminium ion catalyzed Michael additions includes more steps, and if the determining step is not the formation of the C-C bond, the equation cannot be used for predicting the reactivity expected in these reactions.

It may be deduced that in organocatalytic processes, not only the reactivities of the iminium ions and the carbanions control the rates of the overall processes, but also the rates of their formation as well as their equilibrium concentrations, which have to be considered for optimizing the catalytic cycles.

We performed kinetics studies in order to identify the rate determining step of the reaction.

4.6. Identification the rate determining step of the reaction

Introduction: The role of kinetics in the study of mechanisms

The study of the kinetics of a reaction is a useful tool for understanding reaction mechanisms, for future catalyst designing as well as in the research and development of industrial processes. Therefore, the use of kinetic analysis is growing in the research areas which involve the study of complex organic catalytic reactions.

The determination of the true kinetics of a reaction, at the beginning of a mechanistic study, can provide a wealth of information, helping in the formulation of a mechanistic proposal and quickly discarding incorrect mechanisms. When two different mechanistic proposals have been made, kinetics can help in choosing the correct one. Information about catalyst deactivation and the rate limiting step can be quickly obtained.

The technique of Reaction Progress Kinetic Analysis (RPKA) has been developed in recent years by Blackmond[25] to derive a precise kinetic picture of a reaction while carrying out a small, carefully designed, set of experiments. Reaction progress kinetic analysis is defined as "*the analysis of experimental data acquired over the course of a reaction under synthetically relevant (non-pseudo zero order) substrate concentrations*".[26] It enables the extraction of significant kinetic information from a small number of experiments. It relies on two important concepts: (**1**) the concept of "excess" and (**2**) the concept of graphical rate equations.

Two different types of experiments can be run: (1) '**same excess**' experiments or (2) '**different excess**' experiments. The "same excess" experiment gives information on catalyst stability, *i.e.* catalyst activation/deactivation or product induction/inhibition. The "different excess" experiment gives information on reaction orders. The reactions are monitored using *in-situ* tools, under conditions similar to

[25] D. G. Blackmond *Angew. Chem. Int. Ed*. **2005**, *44*, 4302–4320.
[26] Classical kinetics methods such as initial rate do not consider the whole reaction.

those typically employed for synthesis or in chemical processes, i.e. the concentrations of the substrates are not distorted as in traditional methods which make use of initial rate measurements based on pseudo zero order conditions in one substrate.

In the case of a general chemical transformation A + B → C; the concentrations of **A** and **B** are related during the course of the reaction through the parameter "excess". **Excess** is defined for a constant volume reaction as the difference in the initial concentration of the two reactive substrates, as in the following expressions:

$$e = [A]_0 - [B]_0 \rightarrow [A] - [B] = [A]_0 - [B]_0 = e \rightarrow [B] = [A] + e$$

Excess can be zero, a positive or a negative number. It is a constant value for a given set of reaction conditions. Excess has the same concentration units as [A] and [B] (typically M or mM), and is not identical to the number of equivalents or to a percentage excess, both of which vary during the reaction.

The second important point is the concept of developing **graphical rate equations**. The curves generated during experiments are usually manipulated in an Excel worksheet and plotted as a function of reaction rate *vs*. concentration of one of the substrates. The key is to find what function generates graphical overlay of the plots of reactions carried out under different defined conditions; once this function is obtained, valuable information about the reaction can be extracted.

The data to manipulate is obtained by monitoring the reaction with *in situ* techniques, such as reaction calorimetry, FTIR, NMR, etc. Data collection may be carried out by using any method that provides an adequate and accurate response (both in signal strength and in time resolution) that is related in a known way to reaction turnover.[27]

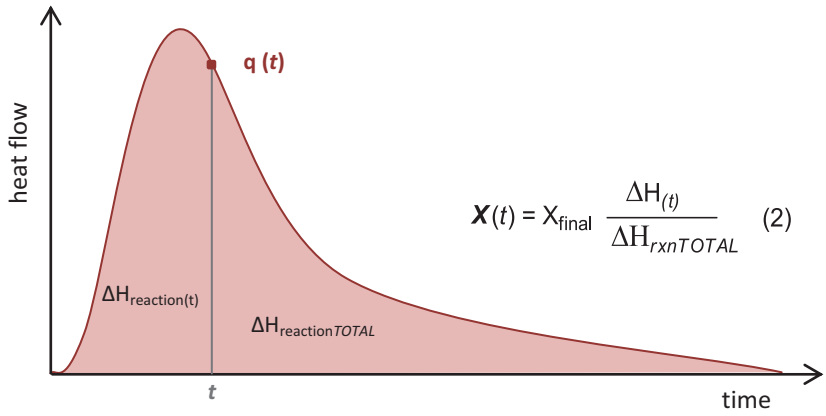
[27] For a discussion of the possible techniques and the differences between them see the experimental section.

Some of the reactions studied in this thesis have been monitored using reaction calorimetry, which is a very powerful technique because it provides a direct and precise measure of the reaction rate vs. time. Moreover, a large number of data points can be collected in one simple experiment. As the rate values are obtained directly, the mathematical treatment of the data conversion *vs*. time is not necessary, avoiding the ensuing mistake derived from the process.

The energy balance around the calorimetric vial, which is kept at a constant temperature when the reactions occur, has the following expression (1):

$$\boldsymbol{q}(t) = V\ \Delta H_{(t)}\ (\boldsymbol{rate}) \qquad (1)$$

Where *V* is the total volume of the reactive solution (which is considered invariant), $\Delta H_{(t)}$ is the heat of the reaction at a *t* time. The heat of the reaction can be obtained from integration under the curve of the heat flow versus time.



From the function of heat *vs*. time, we can also obtain an expression for the conversion X*(t)* (2). The numerator represents the area under the heat flow at any time point t and the denominator represents the total area under the heat flow curve ($\Delta H_{rxnTOTAL}$). The final conversion (X_{final}) can be verified independently with other techniques, such as NMR or HPLC.

The conversion curve calculated from the calorimetric data needs to be compared with a conversion plot calculated through another technique (for example NMR analysis); to assure that the calorimeter actually monitors the real heat produced by the reaction under study. Another condition that has to be verified in order for the calorimetric experiment to be valid is that the volume of the reactive solution does not change over time.

Experimental setup: The reaction calorimeter used in this thesis was an Omnical Insight. This calorimeter has an incorporated magnetic stirrer and can monitor up to ten reactions at the same time. A measurement of the heat flow can be taken up to every two seconds. The temperature is kept constant by an external PC-controlled circulating bath. The vials have a 16 ml volume and are equipped with a septum cap. In a typical experiment, the vials are placed in the calorimeter holes and thermally equilibrated under stirring at the reaction temperature; equilibration usually takes 40-60 minutes and is completed when the monitored heat flow is constant. A plastic syringe, containing a catalyst solution (and other additives if necessary) is placed in the compartment on top of the calorimeter vial and it is thermally equilibrated, so that the temperature of the solution in the vial and in the syringe is the same. The content of the syringe is then injected and the reaction begins.

Picture 1. Omnical Insight 10-port reaction calorimeter

The Michael reaction of nuclophile **1c** and cinnamaldehyde **2f** with catalyst **II** in the absence of additives was monitored by reaction calorimetry (Figure 3.30). The rate of the reaction is directly proportional to the heat released or absorbed: ***q = rate·V·ΔH$_{reaction}$***

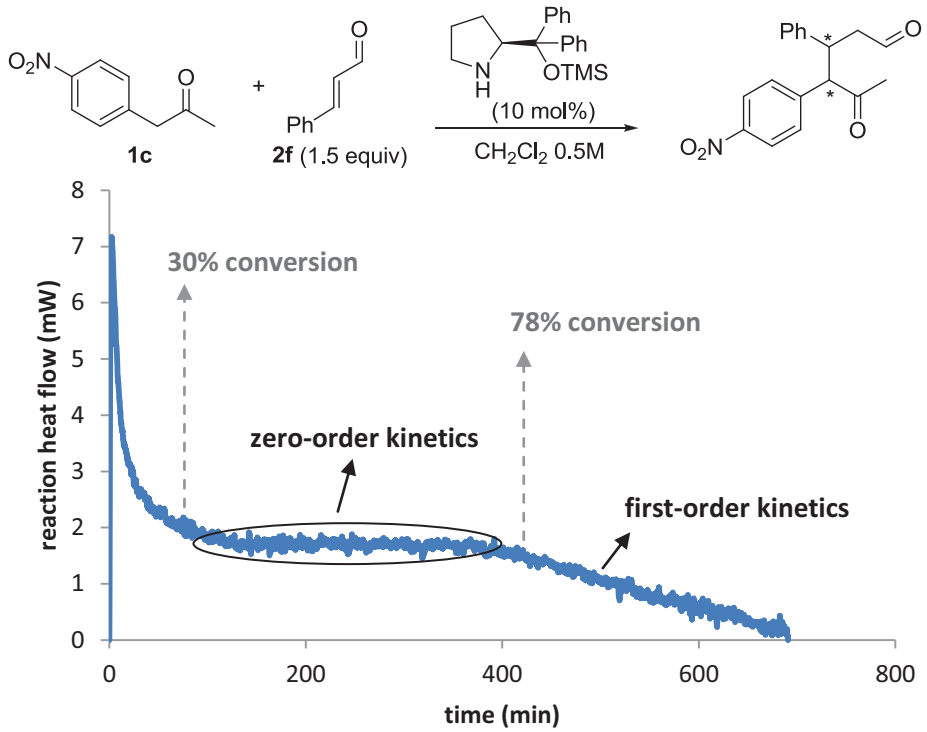
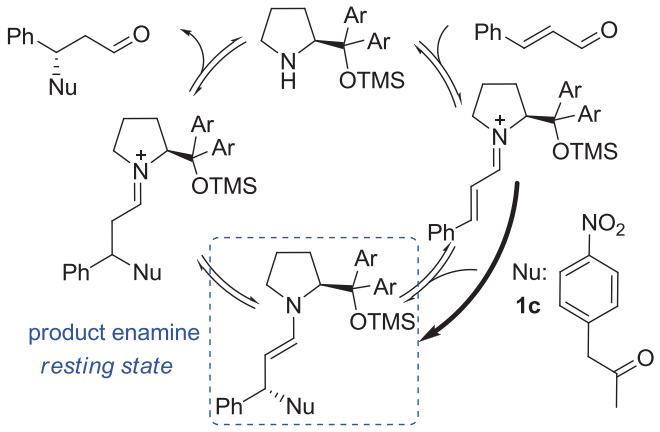


Figure 3.30. Temporal reaction rate in the reaction in Scheme 2 with initial concentrations **[1c]$_0$**= 0.5 M, **[2f]$_0$**= 0.75 M, and **[II]**= 0.01M monitored by reaction calorimetry, showing an initial spike in rate (left inset) and the subsequent flat (middle) and decreasing rate profile (right).

The reaction starts with an initial spike (Figure 3.30, left) corresponding presumably to the first catalytic turnover. Then the profile turns flat, indicating that the rate is constant while the concentration of **1c** and **2f** is changing. At this point (40

min), the conversion is 30%. When the curve is flat, the heat released in each cycle and therefore the rate is constant, while the concentrations of nucleophile and aldehyde are decreasing. This behaviour is characteristic for zero-order kinetics in both **1c** and **2f**, where the rate does not depend on the concentrations of the reactants. At the beginning of the reaction the concentration of nucleophile and aldehyde are high enough to shift the equilibrium to the enamine (saturation). Thus, in each cycle one product enamine is protonated and hydrolyzed and the rate of this reaction does not depend on the amount of nucleophile or aldehyde. Therefore, the heat released remains constant in each cycle.



Scheme 3.19.

At the end of the reaction, after 400 min, the rate is decreasing as the concentration of the reactants is decreasing with almost a lineal dependence (Figure 3.30, right). Thus, in each cycle the reaction is releasing less heat. After 400 min in the absence of additive, the conversion for this reaction in dichloromethane was 78%. Therefore, the reaction had reached almost the equilibrium at this point. When the concentration of **1c** and/or **2f** is very low and/or the reaction is very close to the equilibrium, then the influence on the concentrations of the reactants **1c** and **2f** is

more important on the reaction rate. Therefore, the order of the reactants would be changing during the reaction, from zero to one.

From a qualitative point of view, we can say that at the beginning of the reaction, only the forward reaction is important. As the concentration of Michael products is increasing and the starting materials decreasing, the backward reaction becomes more important (Figure 3.31).

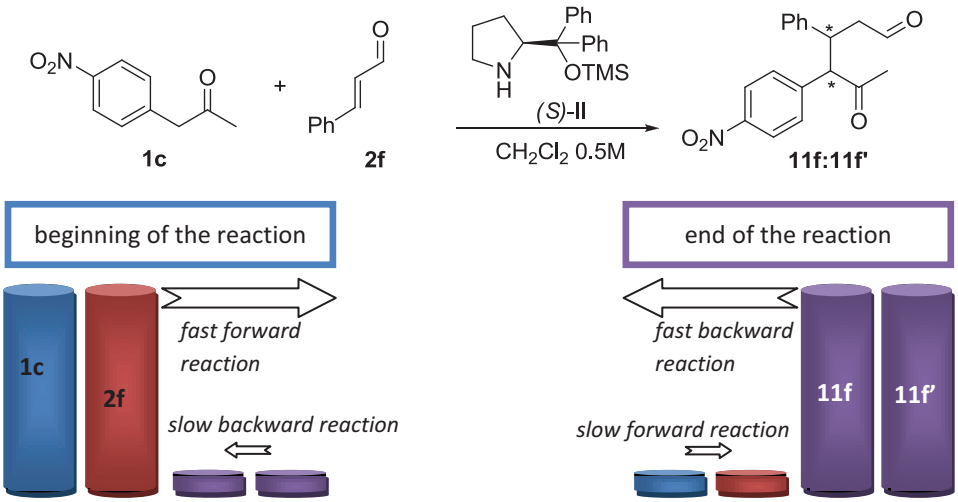
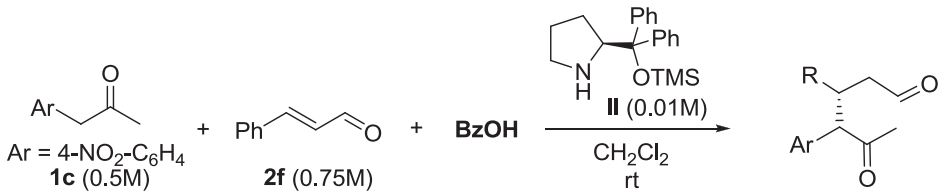


Figure 3.31

We may suggest that this observation of apparent zero-order kinetics in both **1c** and **2f** implies that the rate-determining step for this reaction occurs in the cycle after addition of both substrates and that the resting state of the catalyst contains both substrates. As we always observed the product enamines in the reaction of cinnamaldehyde we may assign this species as the resting state of the catalyst; however, other possibilities cannot be discarded. Moreover, these observations would be in agreement with enamine protonation as rate-determining step and would rule out the iminum ion formation or the nucleophile attack as rate determining steps for these transformations.

We next studied the reaction of nucleophile **1c** and cinnamaldehyde **2d** with catalyst **II** in the presence of different concentrations of benzoic acid. The reaction rate profiles obtained by reaction calorimetry are represented in Figure 3.32.



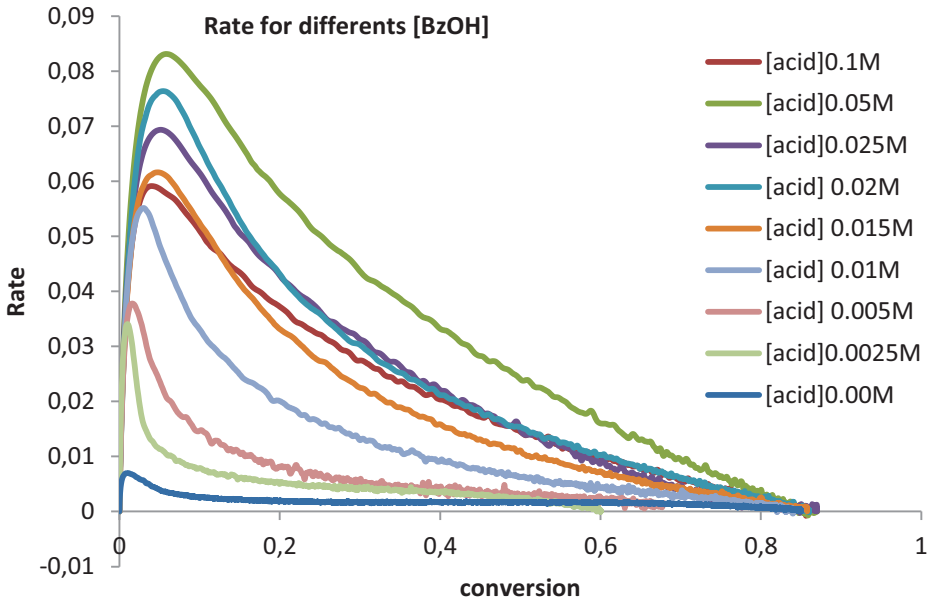


Figure 3.32. Reaction rate vs reaction conversion or the reaction in scheme 4.

[1f]$_0$ = 0.5 M, **[2f]$_0$** = 0.75 M, and **[II]** = 0.01M.

As is shown in Figure 3.32 the initial spike of the curve is larger for a larger concentration of benzoic acid until it starts to decay.

For a clearer analysis of the effect of the acid concentration on the reaction rate, we represented the rate at 20% conversion *vs*. acid concentration (Figure 3.33).

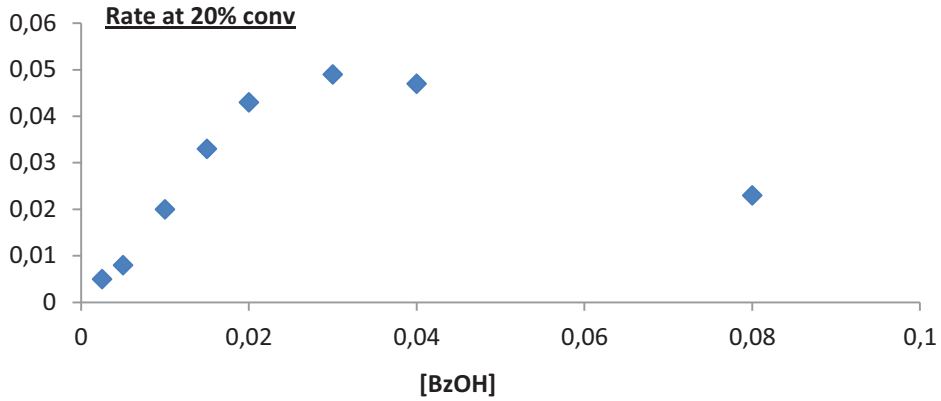


Figure 3.33. Reaction rate vs. acid concentration at 20% conversion (data obtained from figure 3.32). $[\mathbf{1c}]_0$= 0.5 M, $[\mathbf{2f}]_0$= 0.75 M, and **[II]**= 0.01M.

The reaction seems to be first order dependent with acid concentration until a saturation level is reached. In fact, the rate plot fits with a linear polynomial fit until the saturation level is reached (Figure 3.34).

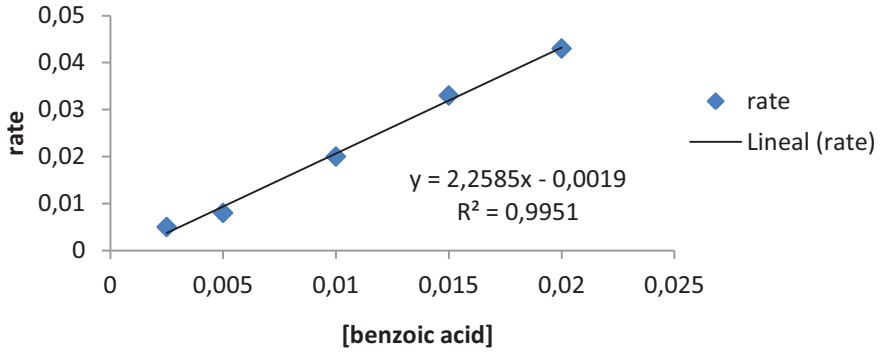
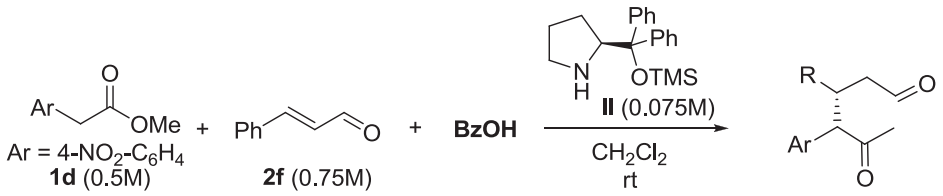


Figure 3.34. Lineal dependence of the rate with acid concentration

Reaction calorimetry was also performed for the ester derivative **1d** (Scheme 3.20). However, the saturation level was reached at much lower acid concentration. Moreover, the reaction, although very slowly took place in the presence of small concentration triethylamine (Figure 3.35).[28]



Scheme 3.20.

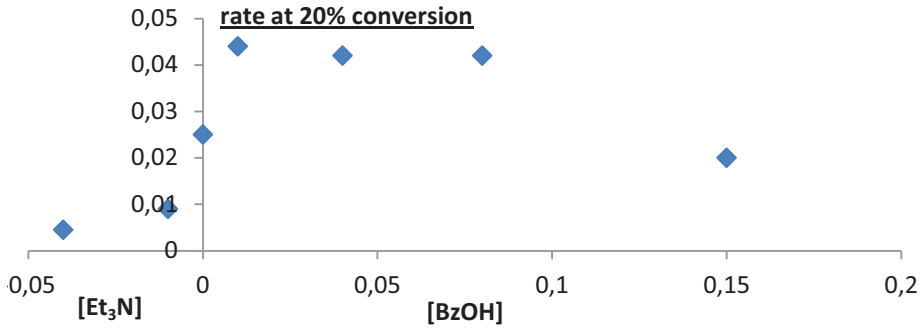
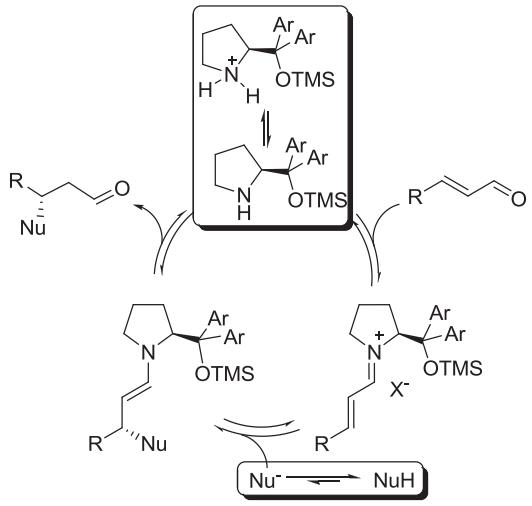


Figure 3.35

[28] Reactions were performed with 15 mol% of catalyst **II** and 15 mol% of TBAB to be suitable for calorimetry analysis.

This observation is in agreement with the enamine protonation as rate determining step for the Michael addition. At some point the reaction reaches a saturation level for acid concentration. After that moment, the rate remains almost constant with the increment of acid concentration until it starts to decrease, presumably because all the catalyst is protonated and therefore out of the catalytic cycle. The saturation level for acid does not correspond with a 1:1 stoichiometry with catalyst concentration. This fact leads to an interesting feature. Maybe the saturation in acid concentration is reached not only because the catalyst is protonated and hence not able to participate in the cycle, but also because a specific acidity of the reaction media is not compatible with the generation of the reactive anion of the corresponding nucleophile. Even if the rate determining step is the enamine protonation, some reaction conditions could be not compatible with the existence of the enolate of the nucleophile. This explanation is in agreement with the observation of different saturation levels for different nucleophiles.



The reaction needs to pass these two steps, the deprotonation of the nucleophile and the enamine protonation. The conditions that are favourable for one step might be not favourable for the other. Thus, the success of a reaction depends on a fine modulation of the reaction conditions.

For a very high acid concentration the catalyst exists as protonated catalyst (demonstrated by NMR analysis). This fact may be especially important for the less acidic nucleophiles where a specific acid concentration, favourable for the enamine protonation, may not be compatible with the prevalence of the anion nucleophile.

Relevance of the acidity of the nucleophile in the catalytic cycle.

The results obtained for the ketone **1c** and the ester **1d** nucleophiles suggested that the maximum acid concentration value tolerated in the reaction is related to the intrinsic acidity of the nucleophile. The reaction is much slower with the ester **1d** than with the ketone **1c**, and the saturation level for acid concentration is also lower.

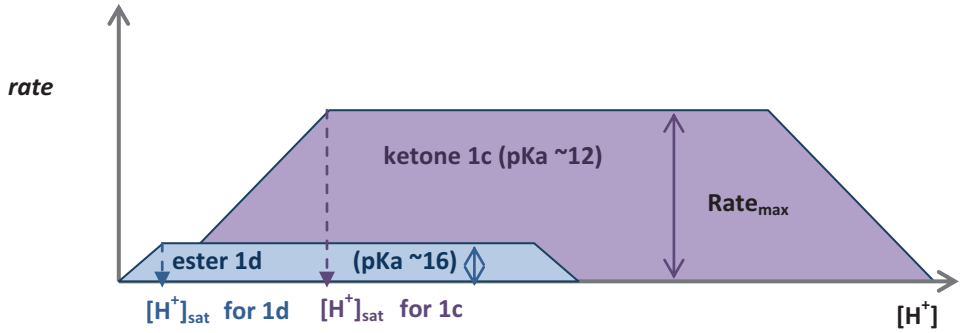


Figure 3.36. Cualitative representation of the relative rates of 1c and 1d.

The maximum rate for the more acidic nucleophile is higher than for the less acidic one. The higher reactivity showed by ketone **1c** was also observed in the NMR analysis of the reaction. The saturation level for acid concentration is also higher for the more acidic nucleophile, showing that the acidity tolerated in the reaction media for the more successful reaction is different regarding the corresponding acidity of the nucleophile.

Taking into account the high acidity of derivative **1c** and the fact that the reaction of **1c** worked in the absence of additives, we may postulate that the acidity conferred by this derivative to the reaction media is enough to protonate the product enamine resulting in the attack to the iminium ion. The addition of an external acid is accelerating the reaction rate for this nucleophile, reaching a saturation level when all the catalyst is pushed out of the catalytic cycle. The possible pathways for this protonation are currently being investigated in our group.

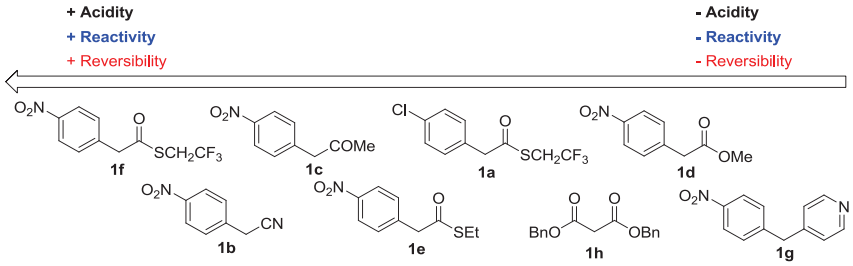
The reaction of ester **1d** is also accelerated in the presence of benzoic acid. However, the reaction of this derivative in the absence of additives did not take place, probably, maybe because the acidity of the reaction is not appropriate to protonate the enamine of the product. This observation is supported by the low acidity found and calculated for this nucleophile comparing to other nucleophiles and by the observation of the product enamine but not the final product in the reaction of this derivative with cinnamaldehyde in the absence of additives followed by ^{1}H NMR.

5. Summary and conclusions from this part of the work

During our investigations on the applicability of aryl acetic derivatives in iminium ion catalysis we found some aspects that did not have a straightforward explanation. Despite the great advance experienced in the area of iminium ion catalysis, the Information available was not enough to understand some of the contradictory results obtained. Due to the complexity of the issue, we appealed to the different techniques available, as well as the literature examination of similar reactions.

In order to explain the order of reactivity obtained in our set of nucleophiles we used the reactivity scales developed by Mayr. However, the predicted reactivity was in almost inverse order that the one experimentally obtained. Thus, it may be suggested that in organocatalytic reactions the rate of the overall process depends not only on the reactivities of the reactive intermediates, but also on their formation as well as their equilibrium concentrations, which might be crucial for the outcome of the reaction.

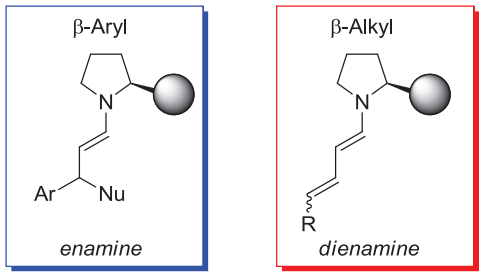
The study of the relative acidity of the nucleophiles allowed us to establish that the order of reactivity observed was agreement with the order of acidity obtained and theoretically calculated. Moreover, the reversibility showed by some nucleophiles in the Michael additions seemed to be also related to the acidity.



We performed a comparative systematic study on the reactions of nucleophiles **1**, which allowed us to find suitable conditions using commercial aldehydes for the reaction of derivatives that showed problems of reactivity.

In a deeper study of the effect of the additives we realized of the important role of the acid factor in the Michael reactions. However, different optimal acid concentration for different pKa range of the nucleophile was found.

The NMR analysis of the reactions allowed us to detect some of the intermediates formed. For the reaction of different nucleophiles **1** with cinnamaldehyde **2f** and silyl prolinol catalysts, the product enamines were identify as the most abundant catalytic species. However, the same reactions performed with crotonaldehyde 2a showed that in the absence of additives the catalyst formed the dienamine with the aldehydes and the reaction did not take place without the addition of an external acid. This important difference between β-alkyl and β-aryl enals might explain the reactivity displayed by these electrophiles in the Michael additions.



Theoretically calculated ΔG values showed that reactions of nucleophiles **1** with β-aliphatic enals are more favoured than the reactions with β-aromatic enals; and thus less prone to reversibility.

The influence of the catalyst (**I** or **II**), the aldehyde and nucleophile used (ΔG), additives and solvent on the reversibility of the reaction was studied. The enamines equilibration observed was suggested as a cause of variation of enantioselectivity observed in some cases.

The positive influence of the acidic addives, the observation of the enamines and the kinetic studies performed on the reaction suggested the protonation of the product enamine as possible rate determining step.

Further studies on the mechanism of the iminium ion catalyzed Michael reactions are currently ongoing in our group.

6. References

1. This graphic was obtained searching by topic in the database *Web of Science* using the term *"organocataly*"*, for the red bars and *"organocataly*"* and refining with *"mechanis*"* for the blue bars. Data of the analysis: 22nd November, 2013.

2. For the first ^{1}H NMR studies on the detection and structural characterization of *in situ* formed enamine intermediates in proline-catalyzed aldol reactions, see: M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem., Int. Ed.* **2010**, *49*, 4997.

3. D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem., Int. Ed*. **2008**, *47*, 4588.

4. Vera, S.; Liu, Y.; Marigo, M.; Escudero-Adán, E. C.; Melchiorre, P. *Synlett* **2011**, 489.

5.Seo, S. W.; Kim, S.-G. *Tetrahedron Lett*. **2012**, *53*, 2809.

6. For pioneering examples using basic additives, see: a) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2006**, *128*, 14986-14991. b) H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.*, **2007**, *13*, 9068-9075. For other examples where LiOAc has been used see: c) Y. Wang, P. Li, X. Liang, T. Y. Zhang, Ye, J. *Chem. Commun.* **2008**, *44*, 1232-1234. d) J. L. García Ruano, V. Marcos, J. Alemán, *Chem. Commun*. **2009**, 4435-4437.

7. Catalyst **I** or **II** were used, independently of their configuration.

8. This special system has been used in order to facilitate the reading. For the abbreviations of the journals we have used: *A Manual Prepared for Intending Authors by the Editor - Alan R. Katritzky.* url: *http://www.ark.chem.ufl.edu/Books_and_Series/InstructionsforAuthors.pdf*. See also the abbreviations section of the thesis.

9. a) E. J. Corey, F. Y. Zhang, *Angew. Chem. Int. Ed*., **1999**, *38*, 1931. For the use of TBAB in imine activation, see: b) J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, M. B. Cid *Org. Lett.* **2005**, *7*, 4407. c) H. Zhao, B. Qin, Z. Liu, Z. Feng *Tetrahedron,* **2007**, *63*, 6822.

10. P. P. Mahendra, R. B. Sunoj, *Chem. Asian J.,* **2009**, *4*, 714.

11. The counteranion of a given additive plays a pivotal role in acting as the counteranion of the iminium **C**, thus changing its properties: a) H. Mayr, A. R. Ofial, E.-U. Würthwein, N. C. Aust, *J. Am. Chem. Soc*., **1997**, *119*, 12727. b) S. Lakhdar, H. Mayr *Chem. Commun.,* **2011**, *47*, 1866. c) D. Marcoux, P. Bindschädler, A. W. H. Speed, A. Chiu, J. E. Pero, G. A. Borg, D. A. Evans, *Org. Lett.,* **2011**, *7*, 3758.

12. P. Wang, A. Anderko, *Fluid Phase Equilibria* **2001**, *186*, 103.

13. A high amount of water was present.

14. The treatment of the nucleophile with ND_4Cl did not produce a quantitative deuteration and thus we used DCl instead.

15. N. Derbel, I. Clarot, M. Mourer, J.-B. Regnouf-de-Vains, M. F. Ruiz-López, *J. Phys. Chem. A*, **2012**, 116, 9404.

16. The low reactivity of nucleophile **1b** may be atributted to its low solubility in EtOH.

17. We could not find conditions for HPLC analysis.

18. 1 equivalent of TBAB was used.

19. a) Y. Wang, P. Li, X. Liang, J. Ye, *Adv. Synth. Catal*. **2008**, *350*, 1383; b) Y. Wang, P. Li, X. Liang, T. Y. Zhang, J. Ye , *Chem. Commun.* **2008**, 1232; c) B. Alonso, E. Reyes, L. Carrillo, J. L. Vicario, D. Badía, *Chem. Eur. J.* **2011**, *17*, 6048; d) L. Dell'Amico, X. Companyó, T. Naicker, T. M. Bräuer, K. A. Jørgensen, *Eur. J. Org. Chem.* **2013**, 5262.

20. The reaction was performed with 20 mol% of catalyst **II** in order to asigne the signals.

21. R. M. Figuereido, R. Frölich, M. Christmann, *Angew. Chem. Int. Ed*. **2008**, *47*, 1450.

22. a) H.Mayr, B.Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66; b) H. Mayr, A. R. Ofial, *Carbocation Chemistry*; G. A. Olah, G. K. S. Prakash, Eds.; Wiley: Hoboken, NJ, 2004; pp 331-358. c) A. R. Ofial, H. Mayr, *Macromol. Symp.* **2004**, *215*, 353; d) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807. e) H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584.

23. S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem. Int. Ed.* **2008**, *47*, 8723.

24. Kaumanns, O.; Appel, R.; Lemek, T.; Seeliger, F.; Mayr, H.; *J. Org. Chem.* **2009**, *74*, 75.

25. D. G. Blackmond *Angew. Chem. Int. Ed*. **2005**, *44*, 4302–4320.

26. Classical kinetics methods such as initial rate do not consider the whole reaction.

27. For a discussion of the possible techniques and the differences between them see the experimental section.

28. Reactions were performed with 15 mol% of catalyst **II** and 15 mol% of TBAB to be suitable for calorimetry analysis.

Chapter IV

Experimental Part

1. General methods and materials

Nuclear Magnetic Resonance (NMR)

Monodimensional and/or bidimensional NMR spectra were acquired at 25°C on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, and 77.0 ppm for ^{13}C NMR) and coupling constants (J) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. 13C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective NOESY, TOCSY and HSQC experiments were acquired to confirm precise molecular conformations.

Melting points

Melting points were measured using a *Büchi B-540* and/or *Gallenkamp* apparatus in open capillary tubes.

Optical rotation

Optical rotation was recorded in cells with 10 cm path length on a Perkin- Elmer 241 MC polarimeter. Concentration (mg/mL) and solvent are indicated in each case.

Enantiomeric excesses (ee) were determined by chiral-phase HPLC using an Agilent-1100 instrument in the indicated column and conditions in each case.

Mass spectrometry

Mass spectra (MS) and High-resolution mass spectra (HRMS) were recorded on a Hewlett-Packard HP-5985 under ESI, EI or FAB conditions.

Infrared spectra

Infrared spectra (IR) were measured in a Perkin Elmer 1600 apparatus, in the interval between 400 and 400 cm-1. Only characteristic bands are given in each case.

Chromatography

For thin layer chromatography (TLC), silica gel plates *Supelco* (Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (12 g), in EtOH (250 mL) followed by heating or treatment with a solution of $KMnO_4$ (1.5 g), K_2CO_3 (10g), and 10% NaOH (1.25 mL) in H_2O (200 mL). For flash column chromatography (FCC) Merck 60, 230-400 mesh silica gel was used.

High performance liquid chromatography (HPLC) on a chiral stationary phase was performed in an Agilent 1100 intrument . Daicel Chiralpack AD, AS, IA, IB, IC, ID and Chiralcel OD columns (0.46 cm x 25 com) were used; specific conditions are indicated in each case.

X-Ray

Crystallographic data of compound **15a** were collected on a Bruker Smart 1000 CCD diffractometer at CACTI (Universidade de Vigo) at 20 °C using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å), and were corrected for Lorentz and polarisation effects. The structure (Figure 1) was solved by direct methods using the program SHELXS97.

Miscellaneous

Commercial grade reagents and solvents were used without further purification unless specified.

Hexane, EtOAc, dichloromethane and EtOH were supplied by *Sharlau* and used without any previous treatment. Starting materials **1b, 1b'** and **1c** were purchased in *Aldrich* and *Alfa Aesar* respectively.

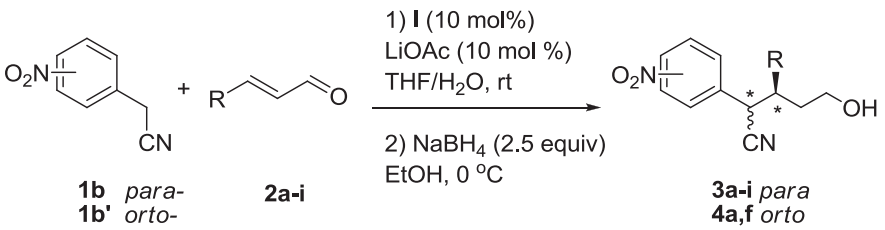
Sonications were performed in a Transsionic 460H (*Elma*) apparatus.

NMR spectra, HPLC chromatograms, crystallographic details and theoretical calculations are included in the CD.

Experimental Part of Chapter II

2. Michael addition of 4- and 2-Nitrophenylacetonitriles

2.1 General procedure for the catalytic Michael addition of 4-nitrophenylacetonitrile 1b and 2-nitrophenylacetonitrile 1b' to α,β-unsaturated aldehydes (2a-i) and corresponding reduction.



To a solution of (*R*)-α-α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**I**) (10 mol%, 0.1 mmol) in THF/H_2O (1 mL) was added the corresponding α,β-unsaturated aldehyde (**2a-i**) (1.5 equiv, 1.5 mmol). After the resulting mixture was stirred at room temperature for 10 min, the corresponding nitrophenylacetonitrile **1b** or **1b'** (1 mmol, 162 mg) and LiOAc (10 mol%, 0.1mmol) were sequentially added. The reactions were followed by TLC (until the disappearance of the nitrophenylacetonitrile derivative, see Table 4.1 for reaction times). Then, the procedure for aliphatic and aromatic aldehydes is slightly different:

a) Aliphatic aldehydes: the excess of aldehyde was removed under vacuum.

b) Aromatic aldehydes: the crude was filtered through a short pad of silica gel using first hexane as eluent to remove the excess of aldehyde **2** and then EtOAc to recover the corresponding Michael adduct.

To a cooled solution (0 °C) of $NaBH_4$ (2.5 equiv, 2.5 mmol) in EtOH (20 mL) a solution of the reaction mixture redissolved in EtOH (5 mL) was added dropwise. The reaction was stirred at 0 °C for 20 min and afterwards quenched with H_2O (20 mL) and

extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was finally evaporated and the crude compound was purified by a short pad of silica gel using *n*-hexane: EtOAc (1:2) as eluent. These products were obtained as a mixture of diastereomers (see table 4.1) and were used in the next step without further purification. Yields, as well as enantiomeric excesses and diastereomeric ratios are indicated in each case and summarized in Table 4.1.

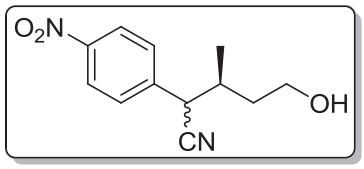
The racemic compounds were obtained following the same procedure described above for the Michael addition by using a mixture of (*R*) and (*S*)-α-α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (5mol% *(R)* and 5mol% *(S)*) as catalyst and LiOAc (10 mol%) as additive.

Table 4.1. Reaction details for the Michael addition of nitrophenylacetonitrile **1b** and **1b'** to α,β-unsaturated aldehydes **2**.

Entry	Aldehyde (R)	Nu	t (h)	Product	yield (%)	*dr*	*ee* (%) *maj.*	*ee* (%) *min.*
1	**2a** (Me)	**1b**	20	**3a:3a'**	95	63:37	90	89
2	**2b** (Et)	**1b**	24	**3b:3b'**	94	56:44	90	94
3	**2c** (Pr)	**1b**	48	**3c:3c'**	95	58:42	90	94
4	**2d** (Bu)	**1b**	48	**3d:3d'**	90	59:41	a	94
5	**2e** (*i*-Pr)	**1b**	120	**3e:3e'**	90	56:44	94	98
5	**2f** (Ph)	**1b**	48	**3f:3f'**	85	68:32	80	79
6	**2g** (*p*-$OMeC_6H_4$)	**1b**	72	**3g:3g'**	85	62:38	[a]	[a]
7	**2h** (*p*-$NO_2C_6H_4$)	**1b**	48	**3h:3h'**	90	67:33	96	68
8	**2i**(*p*-BrC_6H_4)	**1b**	72	**3i:3i'**	90	61:39	[a]	[a]
9	**2a** (Me)	**1b'**	24	**4a:4a'**	84	62:38	84	[a]
10	**2f** (Ph)	**1b'**	40	**4f:4f'**	80	61:39	54	[a]

[a]Conditions to determine the ee of this compound could not be found

(2*R*, 3*S* and 2*S*, 3*S*)-5-Hydroxy-3-methyl-2-(4-nitrophenyl) pentanenitrile (3a and 3a')



The title compound was obtained as a yellow oil according to the general procedure as a 67:37 mixture of diastereomers (95% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.23 (d, J = 8.3 Hz, $2H_{major}$, $2H_{minor}$), 7.53 (d, J = 8.3 Hz, $2H_{major}$, $2H_{minor}$), 4.20 (d, J = 4.7 Hz, $1H_{major}$), 3.97 (d, J = 5.7 Hz, $1H_{minor}$), 3.86-3.70 (m, $2H_{major}$, $2H_{minor}$), 2.30-2.22 (m, $1H_{major}$, $1H_{minor}$), 1.87-1.40 (m, $3H_{major}$, $3H_{minor}$), 1.09 (d, J = 6.6 Hz, $3H_{minor}$), 0.96 (d, J = 6.6 Hz, $3H_{major}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.8 (C), 147.7 (C), 142.2 (C), 141.3 (C), 129.2 (2CH), 128.9 (2CH), 124.2 (4CH), 118.9 (CN), 118.3 (CN), 60.0 (CH_2), 59.9 (CH_2), 43.9 (CH), 43.0 (CH), 37.3 (CH_2), 35.7 (CH), 35.3 (CH), 35.0 (CH_2), 17.5 (CH_3), 15.4 (CH_3).

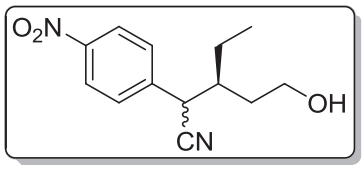
MS (ESI) *m/z* 235 (M+1, 100), 171 (37), 156 (34), 129 (21).

HRMS (ESI) Calcd. for $C_{12}H_{15}N_2O_3$ $[M+H]^+$: 235.1078; found, 235.1077.

The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min:

- major diastereomer, 90% *ee*: τ_{major} = 12.4 min, τ_{minor} = 11.4 min
- minor diastereomer , 89% *ee*: τ_{major} = 15.0 min, τ_{minor} = 14.2 min.

(2*R*, 3*S* and 2*S*, 3*S*)-3-Ethyl-5-hydroxy-2-(4-nitrophenyl) pentanenitrile (3b and 3b')



The title compound was obtained as a yellow oil according to the general procedure as a 56:44 mixture of diastereomers (94% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.24 (d, J = 9 Hz, $2H_{major}$, $2H_{minor}$), 7.54 (d, J = 9 Hz, $2H_{major}$, $2H_{minor}$), 4.35 (d, J = 6 Hz, $1H_{major}$), 4.20 (d, J = 6 Hz, $1H_{minor}$), 3.89-3.78 (m, $2H_{major}$), 3.67-3.58 (m, $2H_{minor}$), 1.89-1.79 (m, $1H_{major}$, $1H_{minor}$), 1.72-1.38 (m, $5H_{major}$, $5H_{minor}$), 1.03 (t, J = 6.6 Hz, $3H_{minor}$), 0.86 (t, J = 7.6 Hz, $3H_{major}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.6 (C), 147.5 (C), 142.4 (C), 142.0 (C), 129.0 (2CH), 128.9 (2CH), 124.1 (2CH), 124.0 (2CH), 118.7 (CN), 118.6 (CN), 60.0 (CH_2), 59.8 (CH_2), 42.1 (CH), 41.8 (CH), 41.1 (CH), 40.7 (CH), 33.2 (CH_2), 32.6 (CH_2), 24.3 (CH_2), 22.8 (CH_2), 11.2 (CH_3), 11.1 (CH_3).

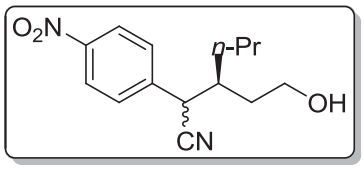
MS (ESI) *m/z* 249 (M+1, 100), 231 (60), 149 (40).

HRMS (ESI) Calcd. for $C_{13}H_{17}N_2O_3$ $[M+H]^+$: 249.1242; found, 249.1233.

The enantiomeric excess was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min:

- major diastereomer: 90% *ee*, τ_{major} = 32.3 min, τ_{minor} = 28.9 min
- minor diastereomer: 94% *ee*, τ_{major} = 57.6 min, τ_{minor} = 60.9 min.

(2*R*, 3*S* and 2*S*, 3*S*)-3-(2-Hydroxyethyl)-2-(4-nitrophenyl) hexanenitrile (3c and 3c')



The title compound was obtained as a yellow oil according to the general procedure as a 58:42 mixture of diastereomers (95% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.21 (d, J = 9 Hz, $2H_{major}$, $2H_{minor}$), 7.53 (d, J = 8.7 Hz, $2H_{major}$, $2H_{minor}$), 4.36 (d, J = 6 Hz, $1H_{major}$), 4.18 (d, J = 6 Hz, $1H_{minor}$) 3.89-3.74 (m, $2H_{major}$), 3.65-3.50 (m, $2H_{minor}$), 2.15-2.07 (m, $1H_{major}$, $1H_{minor}$), 1.87-1.75 (m, $1H_{major}$, $1H_{minor}$), 1.63-1.50 (m, $1H_{major}$, $1H_{minor}$), 1.50-1.31 (m, $4H_{major}$, $4H_{minor}$), 0.91 (t, J = 6.6 Hz, $3H_{minor}$), 0.75 (t, J = 7.6 Hz, $3H_{major}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.7 (C), 147.6 (C), 142.3 (C), 142.0 (C), 129.0 (2CH), 128.9 (2CH), 124.1 (2CH), 124.0 (2CH) 118.6 (C), 118.5 (C), 60.4 (CH_2), 60.0 (CH_2), 41.3 (CH), 41.2 (CH), 40.4 (CH), 40.0 (CH), 33.8 (CH_2),32.8 (CH_2), 32.2 (CH_2), 29.7 (CH_2), 20.1 (CH_2), 19.9 (CH_2)14.0 (CH_3), 13.9 (CH_3).

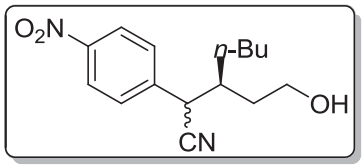
MS (ESI) *m/z* 263 (M+1, 100), 245 (57), 149 (21).

HRMS (ESI) Calcd. for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1390; found, 63.1404.

The enantiomeric excess was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min:

- major diastereomer: 90% *ee*,τ_{major} = 24.1 min, τ_{minor} = 22.3 min
- minor diastereomer: 94% *ee,* τ_{major} = 45.3 min, τ_{minor} = 48.3 min.

(2*R*, 3*S* and 2*S*, 3*S*)-3-(2-Hydroxyethyl)-2-(4-nitrophenyl) heptanenitrile (3d and 3d')



The title compound was obtained as a brown oil according to the general procedure as a (59:41) mixture of diastereomers (90% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.23 (d, J = 8.8 Hz, $2H_{major}$, $2H_{minor}$), 7.55 (d, J = 8.8 Hz, $2H_{major}$, $2H_{minor}$), 4.37 (d, J = 5.7 Hz, $1H_{major}$), 4.21 (d, J = 5.8 Hz, $1H_{minor}$), 3.88-3.76 (m, $2H_{major}$), 3.67-3.54 (m, $2H_{minor}$), 2.16-1.94 (m, $1H_{major}$, $1H_{minor}$), 1.86-1.77 (m, $1H_{major}$, $1H_{minor}$), 1.37-1.10 (m, $6H_{major}$, $6H_{minor}$), 0.91 (t, J = 7 Hz, $3H_{minor}$), 0.78 (t, J = 7 Hz, $3H_{major}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.7 (C), 147.6 (C), 142.4 (C), 142.0 (C), 129.0 (2CH), 128.9 (2CH), 124.1 (2CH), 124.0 (2CH), 118.6 (CN), 118.5 (CN), 60.4 (CH_2), 60.0 (CH_2), 41.3 (CH), 41.2 (CH), 40.6 (CH), 40.2 (CH), 33.8 (CH_2), 32.8 (CH_2), 31.3 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 13.9 (CH_3), 13.8 (CH_3).

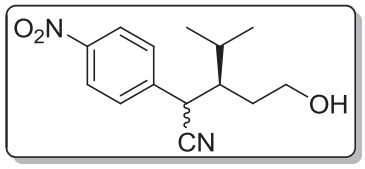
MS (ESI) *m/z* 277 (M+1, 15), 149 (40), 61 (100).

HRMS (ESI) Calcd. for $C_{15}H_{21}N_2O_3$ $[M+H]^+$: 277.1548; found: 277.1546.

The enantiomeric excess was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min:

- the enantiomeric excess of the major diastereoisomer could not be determined
- minor diastereomer: 94% *ee,* τ_{major} = 19.4 min, τ_{minor} = 17.9 min.

(2*R*, 3*R* and 2*S*, 3*R*)-3-(2-Hydroxyethyl)-4-methyl-2-(4-nitrophenyl)pentanenitrile (3e and 3e')



The title compound was obtained as a yellow oil according to the general procedure as a 56:44 mixture of diastereomers (90% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.25 (d, *J* = 8.8 Hz, $2H_{major}$, $2H_{minor}$), 7.58 (d, *J* = 8.4 Hz, $2H_{minor}$), 7.56 (d, *J* = 8.8 Hz, $2H_{major}$), 4.27 (d, *J* = 6.5 Hz, $1H_{minor}$), 4.13 (d, *J* = 4.6 Hz, $1H_{major}$), 3.64 (m, $2H_{minor}$), 3.52 (m, $2H_{major}$), 2.07 (m, $1H_{major}$, $1H_{minor}$), 1.89 (m, $1H_{major}$, $1H_{minor}$), 1.81 (m, $1H_{major}$, $1H_{minor}$), 1.66 (m, $1H_{major}$, $1H_{minor}$) 1.06 (m, $6H_{minor}$), 0.99 (d, *J* = 6.6 Hz, $3H_{major}$), 0.87 (d, *J* = 7.1 Hz, $3H_{major}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.6 (C), 147.5 (C), 143.0 (C), 142.6 (C), 129.0 (2CH), 128.8 (2CH), 124.2 (2CHx2), 119.2 (C), 119.0 (C), 61.1 (CH_2), 60.7 (CH_2), 46.3 (CH), 45.3 (CH), 40.2 (CH), 39.0 (CH), 31.3 (CH), 29.9 (CH),29.6 (CH_2), 28.3 (CH_2), 22.1 (CH_3), 19.9 (CH_3), 19.4 (CH_3), 16.8 (CH3).

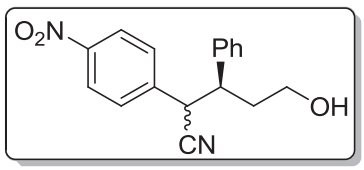
MS (ESI) *m/z* 263 (M+1, 52), 149 (20), 61 (100).

HRMS (ESI) Calcd. for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1399; found: 263.1390.

The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min:

- major diastereomer: 94% *ee*,τ_{major} = 19.1 min, τ_{minor} = 16.6 min
- minor diastereomer: 98% *ee,* τ_{major} = 24.5 min, τ_{minor} = 25.4 min.

(2*R*, 3*S* and 2*S*, 3*S*)-5-Hydroxy-2-(4-nitrophenyl)-3-phenylpentanenitrile (3f and 3f')



The title compound was obtained as a yellow oil according to the general procedure as (68:32) a mixture of diastereomers (85% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (major diastereomer): δ 8.11 (d, J = 8.7 Hz, $2H_{major}$, $2H_{minor}$), 7.29 (d, J = 8.7 Hz, $2H_{minor}$), 7.22 (d, J = 8.9 Hz, $2H_{major}$), 7.11-7.02 (m, $5H_{major}$, $5H_{minor}$), 4.35 (d, J = 6 Hz, $1H_{major}$), 4.11 (d, J = 7.8 Hz, $1H_{minor}$), 4.00 (m, $1H_{major}$),3.85-3.78 (m, $1H_{minor}$), 3.76-3.30 (m, $2H_{major}$, $2H_{minor}$), 2.32-2-12 (m, $2H_{major}$, $2H_{minor}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 148.7 (C), 148.5 (C), 144.7 (C), 144.4 (C), 129.2 (2CH), 129.1 (2CH), 128.8 (2CH), 128.7 (2CH), 128.4 (2CH), 128.3 (2CH), 127.8 (CH), 127.5 (CH), 126.4 (C), 125.9 (C), 123.9 (2CH), 123.8 (2CH), 122.7 (CN), 122.6 (CN), 59.9 (CH_2), 59.8 (CH_2), 48.1 (CH), 47.0 (CH), 44.4 (CH), 43.8 (CH), 37.4 (CH_2), 35.7 (CH_2).

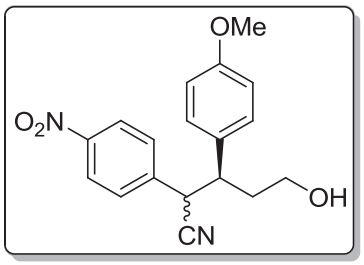
MS (ESI) *m/z* 263 (M+1, 52), 149 (20), 61 (100).

HRMS (ESI) Calcd. for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1399; found: 263.1390.

The enantiomeric excess was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min:

- major diastereomer: 80% *ee*,τ_{major} = 11.5 min, τ_{minor} = 14.6 min
- minor diastereomer: 79% *ee*,τ_{major} = 30.3 min, τ_{minor} = 25.7 min

(2*R*, 3*S* and 2*S*, 3*S*) -5-Hydroxy-3-(4-methoxyphenyl)-2-(4-nitrophenyl) pentanenitrile (3g and 3g')



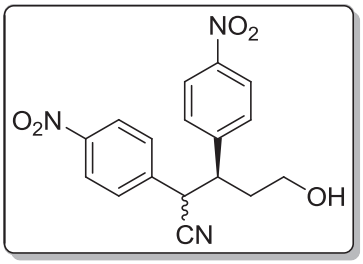
The title compound was obtained as a yellow oil according to the general procedure as a 62:38 mixture of diastereomers (85% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.12 (d, J = 8.5 Hz, $2H_{major}$, $2H_{minor}$), 7.29 (d, J = 8.5 Hz, $2H_{minor}$), 7.22 (d, J = 8.5 Hz, $2H_{major}$), 6.98 (d, J = 8.5 Hz, $2H_{minor}$), 6.94 (d, J = 8.7 Hz, $2H_{major}$), 6.80 (d, J = 8.5 Hz, $2H_{minor}$), 6.78 (d, J = 8.7 Hz, $2H_{major}$), 4.31 (d, J = 5.6 Hz, $1H_{major}$), 4.07 (d, J = 7.7 Hz, $1H_{minor}$), 3.78 (s, $3H_{major}$), 3.68 (s, $3H_{minor}$), 3.54 (m, $2H_{major}$, $2H_{minor}$), 3.29 (m, $1H_{major}$, $1H_{minor}$), 2.17 (m, $2H_{major}$, $2H_{minor}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.9 (C), 147.8 (C), 147.6 (C), 147.5 (C), 130.5 (C), 130.2 (C), 129.5 (2CH), 129.4 (2CH), 129.1 (2CH), 129.0 (2CH), 123.8 (2CH), 123.7 (2CH), 122.5 (C), 122.4 (C), 120.3 (CN), 120.2 (CN), 114.1 (2CH), 114.0 (2CH), 60.0 (CH_2), 59.9 (CH_2), 55.8 (CH_3), 55.7 (CH_3), 44.2 (CH), 44.1 (CH), 38.0 (CH), 37.9 (CH), 33.9 (CH_2), 33.7 (CH_2).

The enantiomeric excess was determined in the corresponding lactone **6g**.

(2*R*, 3*S* and 2*S*, 3*S*)-5-Hydroxy-2,3-bis(4-nitrophenyl) pentanenitrile (3h and 3h')



The title compound was obtained as a yellow oil according to the general procedure as a mixture 67:33 of diastereomers (90% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

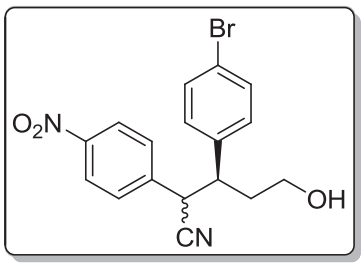
^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.15 (m, $4H_{major}$, $4H_{minor}$), 7.27 (m, $4H_{major}$, $4H_{minor}$), 4.48 (d, J = 6 Hz, $1H_{major}$), 4.21 (d, J = 7.5 Hz, $1H_{minor}$3.84-3.77 (m, $2H_{minor}$), 3.72-3.65 (m, $1H_{minor}$), 3.57-3.50 (m, $2H_{major}$), 3.37-3.30 (m, $1H_{major}$), 2.29-2.18 (m, $2H_{major}$, $2H_{minor}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.9 (C), 147.8 (C), 147.7 (C), 147.6 (C), 145.7 (C), 145.0 (C), 140.6 (C), 140.4 (C), 129.4 (2CH), 129.1 (2CH), 128.8 (2CH), 128.2 (2CH), 124.1 (2CH), 124.0 (2CH), 123.9 (2CH), 123.8 (2CH), 118.3 (C), 117.7 (C), 59.4 (CH_2), 59.2 (CH_2), 46.8 (CH), 46.7 (CH), 43.6 (CH), 43.0 (CH), 35.4 (CH_2),34.3 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min:

- major diastereomer: 96% *ee*, τ_{major} = 27.6 min, τ_{minor} = 23.0 min
- minor diastereomer: 68% *ee,* τ_{major} = 20.0 min, τ_{minor} = 18.0 min

(2*R*, 3*S* and 2*S*, 3*S*)-3-(4-Bromophenyl)-5-hydroxy-2-(4-nitrophenyl) pentanenitrile (3i and 3i')



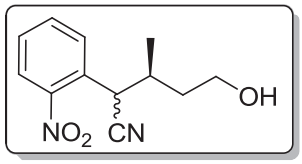
The title compound was obtained as a yellow oil according to the general procedure as a 61:39 mixture of diastereomers (90% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.15 (d, J = 8.9 Hz, $2H_{major}$), 8.14 (d, J = 8.6 Hz, $2H_{minor}$), 7.36 (m, $4H_{major}$, $4H_{minor}$), 7.23 (m, $2H_{major}$, $2H_{minor}$), 6.96 (d, J = 8.4 Hz, $2H_{minor}$), 6.91 (d, J = 8.0 Hz, $2H_{major}$), 4.36 (d, J = 5.8 Hz, $1H_{major}$), 4.10 (d, J = 7.8 Hz, $1H_{minor}$), 3.76 (m, $2H_{major}$, $2H_{minor}$), 3.64 (m, $1H_{minor}$), 3.51 (m, $1H_{major}$), 3.34 (m, $1H_{major}$, $1H_{minor}$), 3.21 (m, $2H_{major}$, $2H_{minor}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.8 (C), 147.7 (C), 141.2 (C), 141.0 (C), 137.2 (C), 136.3 (C), 132.2 (2CH), 131.9 (2CH), 130.1 (2CH), 129.8 (2CH), 129.2 (2CH), 129.0 (2CH),124.0 (2CH), 123.9 (2CH), 122.2 (C), 122.1 (C), 118.7 (CN), 118.2 (CN), 59.7 (CH_2), 59.5 (CH_2), 46.7 (CH), 46.5 (CH), 44.1 (CH), 43.5 (CH), 35.6 (CH_2), 35.5 (CH_2).

The enantiomeric excess was determined in the corresponding lactone **6i**.

(2*R*, 3*S* and 2*S*, 3*S*)-5-Hydroxy-3-methyl-2-(4-nitrophenyl) pentanenitrile (4a and 4a')



The title compound was obtained as a yellow oil according to the general procedure as a (62:38) mixture of diastereomers (84% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.06 (d, *J* = 8.0 Hz, $1H_{major}$, $1H_{minor}$), 7.77 (d, *J* = 7.8 Hz, $1H_{major}$, $1H_{minor}$), 7.70 (d, *J* = 8.0 Hz, $1H_{major}$, $1H_{minor}$), 7.53 (d, *J* = 7.8 Hz, $1H_{major}$, $1H_{minor}$), 5.05 (d, *J* = 4.0 Hz, $1H_{major}$), 4.83 (d, *J* = 5.2 Hz, $1H_{minor}$), 3.86-3.70 (m, $2H_{major}$, $2H_{minor}$), 2.30-2.22 (m, $1H_{major}$, $1H_{minor}$), 1.87-1.60 (m, $2H_{major}$, $2H_{minor}$), 1.20 (d, *J* = 6.3 Hz, $3H_{major}$), 1.00 (d, *J* = 7.5 Hz, $3H_{minor}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 149.6 (C), 149.5 (C), 133.8 (CH), 133.7 (CH), 131.2 (CH), 130.9 (CH), 130.1 (C), 130.0 (C), 129.5 (CH), 129.4 (CH), 126.0 (CH), 125.9 (CH), 118.9 (CN), 118.4 (CN), 60.1 (CH_2), 60.0 (CH_2), 40.0 (CH), 39.4 (CH), 38.0 (CH_2), 34.7 (CH), 34.6 (CH_2), 18.0 (CH_3), 15.6 (CH_3).

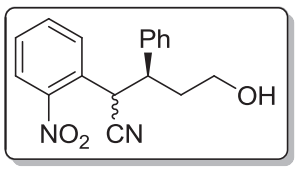
MS (ESI) *m/z* 235 (M+1, 100), 171 (37), 156 (34), 129 (21).

HRMS (ESI) Calcd. for $C_{12}H_{15}N_2O_3$ $[M+H]^+$: 235.1078; found, 235.1077.

The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min:

- major diastereomer: 84% *ee*, τ_{major} = 12.4 min, τ_{minor} = 11.4 min
- the enantiomeric excess of the minor diastereoisomer could not be determined.

(2*R*, 3*S* and 2*S*, 3*S*)-5-Hydroxy-2-(2-nitrophenyl)-3-phenylpentanenitrile (4f and 4f')



The title compound was obtained as a brown oil according to the general procedure as a (61:39) mixture of diastereomers (80% yield). The diastereomeric ratio (*dr*) was determined by HPLC analysis.

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.06 (dd, J = 1.6, 7.9 Hz, $1H_{major}$), 7.92 (dd, J = 1.2, 8.0 Hz, $1H_{minor}$), 7.79 (dd, J = 1.3, 7.8 Hz, $1H_{minor}$), 7.68 (dt, J = 1.2, 7.5 Hz, $1H_{major}$), 7.60 (d, J = 8.3 Hz, $1H_{minor}$), 7.50-7.36 (m, $4H_{major}$, $3H_{minor}$),7.19 (m, $1H_{major}$, $1H_{minor}$), 7.04 (m, $2H_{major}$, $2H_{minor}$), 5.26 (d, J = 5.6 Hz, $1H_{major}$), 5.11 (d, J = 6.8 Hz, $1H_{minor}$), 3.78-3.70 (m, $1H_{minor}$), 3.62-3.64 (m, $1H_{major}$), 3.42-3.32 (m, $2H_{major}$, $2H_{minor}$), 2.29-2.19 (m, $2H_{major}$, $2H_{minor}$).

^{13}C NMR (75 MHz) (mixture of diastereomers): δ 147.9 (C), 147.7 (C), 138.3 (C), 137.6 (C), 133.6 (CH), 133.3 (CH), 131.3 (CH), 131.0 (CH), 129.8 (C), 129.6 (CH), 129.4 (C), 129.3 (CH),129.2 (CH), 129.0 (CH), 128.6 (2CH), 128.5 (2CH),127.9 (2CH), 127.8 (2CH), 125.6 (CH), 125.3 (CH), 119.0 (CN), 118.7 (CN), 60.1 (CH_2), 59.8 (CH_2), 46.3 (CH), 46.1 (CH), 40.4 (CH), 39.8 (CH), 34.0 (CH_2), 33.7 (CH_2).

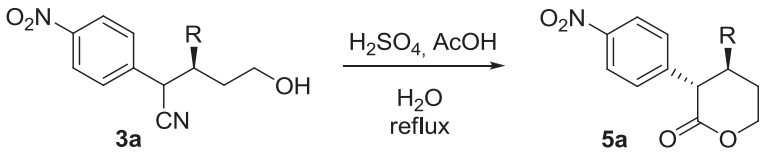
MS (ESI) *m/z* 235 (M+1, 100), 171 (37), 156 (34), 129 (21).

HRMS (ESI) Calcd. for $C_{12}H_{15}N_2O_3$ $[M+H]^+$: 235.1078; found, 235.1077.

The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min:

- major diastereomer: 54% *ee*, τ_{major} = 10.6 min, τ_{minor} = 8.9 min
- minor diastereomer, ee could not be determined

2.2 Optimized procedure for the lactonization.



The cyanoalcohol **3a:3a'** (obtained as described previously) (100 mg) was mixed with water (100 µL), concentrated H_2SO_4 (100 µL) and acetic acid (100 µL) and refluxed for 1h. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 15 mL). The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the corresponding lactone **5a** as a single diastereomer. The product was purified by flas column chromatography using *n*-hexane:EtOAc (2:1) as eluent (99% yield). The racemic compound was obtained following the same procedure with the corresponding racemic cyanolcohol **3a**.

(3*S*, 4*S*)-4-Methyl-3-(4-nitrophenyl)-tetrahydropyran-2-one (5a)

m.p. 106-110 °C.

^{1}H NMR (300 MHz): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.7, 2H), 4.58-4.42 (m, 2H), 3.38 (d, *J* = 11 Hz, 1H), 2.33-2.22 (m, 1H), 2.20-2.07 (m, 1H), 1.74-0.98 (m, 1H), 0.95 (d, *J* = 6 Hz, 3H). **^{13}C NMR** (75 MHz): δ 171.0 (CO), 147.3 (C), 145.2 (C), 130.0 (2CH), 123.9 (2CH), 68.2 (CH_2), 55.6 (CH), 34.3 (CH), 30.9 (CH_2), 20.3 (CH_3).

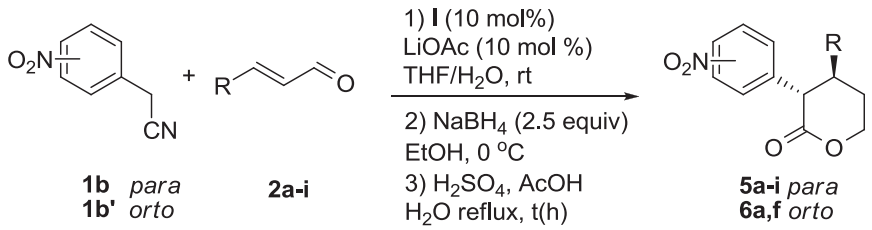
MS (FAB) *m/z* 236 (M+1, 100), 219 (13), 107 (35), 71 (44), 57 (58), 55 (85).

HRMS (FAB) Calcd. for $C_{12}H_{13}NO_4$ $[M+H]^+$: 236.0917; found: 236.0923.

The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 30.3 min, τ_{minor} = 26.4min (98% *ee,* after crystallization). **$[\alpha]_D^{20}$** +25 (*c* = 1.0, $CHCl_3$).

IR (film) 2964, 1723, 1526, 1347 cm^{-1}.

2.3 Sequential procedure of the three reactions: Michael/ reduction / lactonization.



To a solution of **I** (10 mol%, 0.1 mmol) in THF/H_2O (1 mL) the corresponding α,β-unsaturated aldehyde (**2a-i**) (1.5 equiv, 1.5 mmol) was added. After the resulting mixture was stirred at room temperature for 10 min, 4-nitrophenylacetonitrile **1b** or **1b'** (1 mmol, 162 mg) and LiOAc (10 mol%, 0.1mmol) were sequentially added. The reactions were followed by TLC (until the disappearance of the 4-nitrophenylacetonitile), whereupon the solvent was evaporated under vacuum. The residue was redisolved in EtOH (5 mL) and added dropwise to o a cooled solution (-0 °C) of $NaBH_4$ (2.5 eq., 2.5 mmol) in EtOH (20 mL). The reaction was stirred at 0 °C for 20 min, quenched with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the crude mixture was filtered through a short pad of silica gel using sequentially hexane and EtOAc as eluents. Acetic acid (400 µL), water (100 µL) and concentrated H_2SO_4 (100 µL) were sequentially added to the corresponding cyanoalcohols **3a-i**:**3a'-3i'** (100 mg) and the reaction refluxed for the indicated time in Table 4.2. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 15 mL). The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The reactions were purified by flash chromatography using *n*-hexane:EtOAc (2:1) as eluent to give the corresponding lactones **5a-i** and **6a,f** in the yields indicated in Table 4.2.

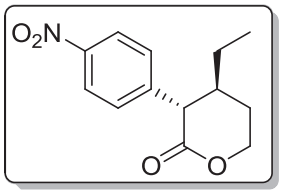
Table 4.2. Reaction details for the compounds **5a-i** and **6a,f**.

Entry	alcohol (R)	t (h)	Product	yield (%)	*ee* (%)
1	**3a and 3a'** (Me)	1	**5a**	>99	90
2	**3b and 3b'** (Et)	1	**5b**	95	92
3	**3c and 3'c'**(Pr)	1	**5c**	97	92
4	**3d and 3d'** (Bu)	1.5	**5d**	99	90
5	**3e and 3e'** (i-Pr)	3	**5e**	>99	96
6	**3f and 3f'** (Ph)	8	**5f**	93	80
7	**3g and 3g'** (*p*-$OMeC_6H_4$)	30	**5g**	97	30
8	**3h and 3h'** (*p*-$NO_2C_6H_4$)	48	**5h**	95	85[a]
9	**3i and 3i'** (*p*-BrC_6H_4)	3.5	**5i**	93	70
10	**4a and 4a'** (Me)	8	**6a**	93	84
11	**4f and 4f'** (Ph)	25	**6f**[b]	95	50

[a] Estimated from the *ee* of the mixture of alcohols.

[b] *dr*= 94:6

(3*S*, 4*S*)-4-Ethyl-3-(4-nitrophenyl)-tetrahydropyran-2-one (5b)



According to the procedure described above, the title compound was obtained as a single diastereomer (>95% yield).

m.p. 138-140 °C.

^{1}H NMR (300 MHz): δ 8.22 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5, 2H), 4.57-4.41 (m, 2H), 3.50 (d, *J* = 11.6 Hz, 1H), 2.22-2.03 (m, 1H), 1.83-1.71 (m, 1H), 1.43-1.32 (m, 1H), 1.25-1.14 (m, 2H), 0.87 (t, *J* = 6 Hz, 3H).

^{13}C NMR (75 MHz): δ 169.0 (CO), 146.5 (C), 145.0 (C), 129.7 (2CH), 120.9 (2CH), 69.2 (CH_2), 55.3 (CH), 34.3 (CH), 37.9 (CH_2), 20.3 (CH_2), 11.5 (CH_3).

MS (ESI) *m/z* 250 (M+1, 10), 149 (100).

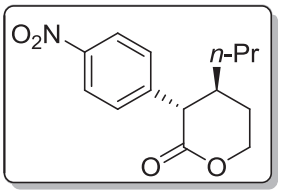
HRMS (ESI) Calcd. for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1073; found: 250.1071.

The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 30.3 min, τ_{minor} = 26.4min (92% *ee*).

$[\alpha]_D^{20}$ +13.6 (*c* = 0.8, $CHCl_3$).

IR (film) 3020, 1647, 1524, 1350, 1044 cm^{-1}.

(3*S*, 4*S*)-3-(4-Nitrophenyl)-4-propyl-tetrahydropyran-2-one (5c)



According to the procedure described above, the title compound was obtained as a single diastereomer (97% yield). **m.p.** 125-127 °C.

^{1}H NMR (300 MHz): δ 8.22 (d, J = 9 Hz, 2H), 7.37 (d, J = 9, 2H), 4.55-4.40 (m, 2H), 3.48 (d, J = 11 Hz, 1H), 2.22-2.11 (m, 1H), 1.82-1.71 (m, 1H), 1.44-1.36 (m, 1H), 1.29-1.15 (m, 4H), 0.81 (t, J = 6 Hz, 3H).

^{13}C NMR (75 MHz): δ 171.2 (CO), 146.5 (C), 145.0 (C), 130.2 (2CH), 124.2 (2CH), 68.2 (CH_2), 53.9 (CH), 38.6 (CH), 36.2 (CH_2), 28.1 (CH_2), 19.7 (CH_2), 14.0 (CH_3).

MS (FAB) *m/z* 264 (M+1, 13), 69 (66), 55 (100).

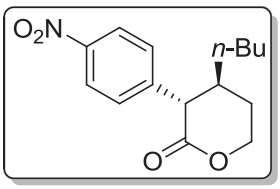
HRMS (FAB) Calcd. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1236; found: 264.1237.

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 20.1 min, τ_{minor} = 23.5 min (92% *ee*).

$[\alpha]_D^{20}$ +19.3 (c = 0.7, $CHCl_3$).

IR (film) 3020, 2962, 2930, 1732, 1524, 1349, 756, 669 cm^{-1}.

(3*S*, 4*S*)-4-Butyl-3-(4-nitrophenyl)tetrahydro-2H-pyran-2-one (5d)



According to the procedure described above, the title compound was obtained as a single diastereomer (99% yield).

m.p. 121-125 °C.

^{1}H NMR (300 MHz): δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7, 2H), 4.49 (m, 2H), 3.48 (d, *J* = 10.5 Hz, 1H), 2.16 (m, 2H), 1.76 (m, 1H), 1.20-1.14 (m, 6H), 0.81 (t, *J* = 7 Hz, 3H).

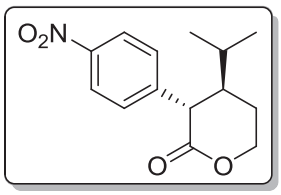
^{13}C NMR (75 MHz): δ 171.3 (CO), 145.5 (C), 145.0 (C), 130.0 (2CH), 123.9 (2CH), 68.1 (CH_2), 53.9 (CH), 38.8 (CH), 33.6 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 30.3 min, τ_{minor} = 26.4min (90% *ee*).

$[\alpha]_D^{20}$ +4.1 (*c* = 0.5, $CHCl_3$).

IR (film) 3009, 2932, 1680, 1521, 1371 cm^{-1}

(3*S*, 4*R*)-4-*iso*-Propyl-3-(4-nitrophenyl)-tetrahydropyran-2-one (5e)



According to the procedure described above, the title compound was obtained as a single diastereomer (>99% yield). **m.p**. 118-120 °C.

^{1}H NMR (300 MHz): δ 8.22 (d, *J* = 9 Hz, 2H), 7.37 (d, *J* = 9, 2H), 4.55-4.40 (m, 2H), 3.48 (d, *J* = 11 Hz, 1H), 2.22-2.11 (m, 1H), 1.82-1.71 (m, 1H), 1.44-1.36 (m, 1H), 1.29-1.15 (m, 4H), 0.81 (t, *J* = 6 Hz, 3H).

^{13}C NMR (75 MHz): δ 171.2 (CO), 146.5 (C), 145.0 (C), 130.2 (2CH), 124.2 (2CH), 68.2 (CH_2), 53.9 (CH), 38.6 (CH), 36.2 (CH_2), 28.1 (CH_2), 19.7 (CH_2), 14.0 (CH_3).

MS (FAB) *m/z* 264 (M+1, 80), 108 (78), 70 (63).

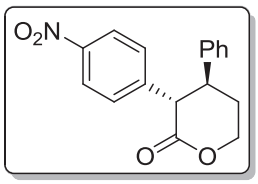
HRMS (FAB) Calcd. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1236; found: 264.1232. Anal. calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32; found, C, 63.75; H, 6.52; N, 5.38.

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 43.2 min, τ_{minor} = 37.9min (96% *ee*).

$[\alpha]_D^{20}$ +21.7 (*c* = 1, $CHCl_3$).

IR (film) 2962, 2932, 1736, 1521, 1371, 842, 747 cm^{-1}.

(3*S*, 4*S*)-3-(4-Nitrophenyl)-4-phenyltetrahydro-2H-pyran-2-one (5f)



According to the procedure described above, the title compound was obtained as a single diastereomer (93% yield).

m.p. 220-223 °C.

^{1}H NMR (300 MHz): δ 8.11 (d, *J* = 9 Hz, 2H), 7.30 (d, *J* = 8.2, 2H), 7.19 (m, 3H), 7.04 (d, *J* = 7.8, 2H), 4.71 (m, 2H), 4.02 (d, *J* = 11.8 Hz, 1H), 3.32 (m, 1H), 2.39 (m, 2H).

^{13}C NMR (75 MHz): δ 169.6 (CO), 141.2 (C), 133.4 (C), 133.3 (C), 128.8 (2CH), 128.6 (2CH), 127.5 (2CH), 127.2 (2CH), 126.0 (CH), 68.8 (CH), 46.1 (CH), 45.3 (CH), 35.5 (CH_2).

MS (FAB) *m/z* 298 (M+1, 100), 154 (27), 136 (30), 55 (100).

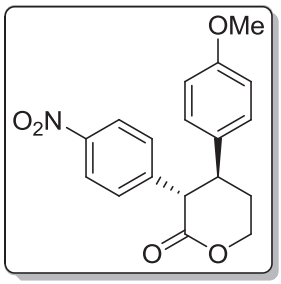
HRMS (FAB) Calcd. for $C_{17}H_{16}NO_4$ $[M+H]^+$: 298.1079; found: 298.1072.

The enantiomeric excess was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 18.2, τ_{minor} = 17.2min (80% *ee*).

$[\alpha]_D^{20}$ +57.0 (*c* = 1, $CHCl_3$).

IR (film) 2926, 1736, 1522, 1367, 1280, 758 cm^{-1}.

(3S, 4*S*)-4-(4-Methoxyphenyl)-3-(4-nitrophenyl)tetrahydro-2H-pyran-2-one (5g)



According to the procedure described above, the title compound was obtained as a single diastereomer (97% yield).

m.p. 234-236 °C.

^{1}H NMR (300 MHz): *δ* 8.06 (d, *J* = 9.6 Hz, 2H), 7.14 (d, *J* = 9.6, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.74 (d, *J* = 8.2, 2H), 4.64 (m, 2H), 3.90 (d, *J* = 11.5 Hz, 1H), 3.24 (m, 1H), 2.30 (m, 2H).

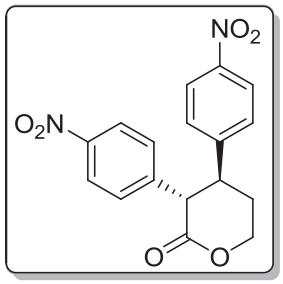
^{13}C NMR (75 MHz): *δ* 170.8 (CO), 158.9 (C), 147.1 (C), 145.1 (C), 132.8 (C), 130.0 (2CH), 128.0 (2CH), 123.6 (2CH), 114.4 (2CH), 68.8 (CH_2), 55.4 (CH), 55.2 (CH), 45.7 (CH_3), 31.0 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 33.4 min, τ_{minor} = 39.9min (30% *ee*).

$[\alpha]_D^{20}$ +19.4 (*c* = 0.5, $CHCl_3$).

IR (film): 2920, 1719, 1515, 1347, 1259, 1087 cm^{-1}.

(3*S*, 4*S*)-3,4-bis(4-Nitrophenyl)tetrahydro-2H-pyran-2-one (5h)



According to the procedure described above, the title compound was obtained as a single diastereomer (95% yield).

m.p. 250-253 °C.

^{1}H NMR (300 MHz): δ 8.04 (d, *J* = 8.3 Hz, 2H), 9.02 (d, *J* = 8.4, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.4, 2H), 4.69-4.55 (m, 2H), 3.90 (d, *J* = 11.8 Hz, 1H), 3.73 (m, 1H), 2.35-2.25 (m, 2H).

^{13}C NMR (75 MHz): δ 169.6 (CO), 147.9 (C), 147.5 (C), 143.8 (C), 141.8 (C), 129.9 (2CH), 127.9 (2CH), 124.3 (2CH), 123.9 (2CH), 68.5 (CH_2), 54.6 (CH), 46.9 (CH), 46.2 (CH_3), 30.6 (CH_2).

MS (FAB) *m/z* 343 (M+1, 100), 149 (30), 55 (100).

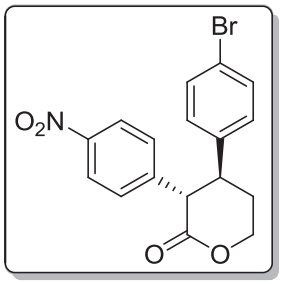
HRMS (FAB) Calcd. for $C_{17}H_{15}N_2O_6$ $[M+H]^+$: 343.0852; found: 343.0862.

It has not been possible to determine the *ee* of **6h** using several HPLC columns under different conditions. It has been proven that the mixtures of alcohols **4a-e** and **4a'-e'** evolve into one lactone in an *ee* value average of the values of the *ee* of the corresponding alcohols. Assuming that the 67/33 mixture of alcohols **4h** (*ee* = 96 %) and **4h'** (*ee* = 68 %) had a similar behaviour to that observed for other alcohols, the ee of **6h** could be tentatively deduced as approximately 85 %.

$[\alpha]_D^{20}$ -4.3 (*c* = 0.5, $CHCl_3$).

IR (film) 2921, 2851, 1736, 1520, 1307 cm^{-1}.

(3*S*, 4*S*)-4-(4-Bromophenyl)-3-(4-nitrophenyl)tetrahydro-2H-pyran-2-one (5i)



According to the procedure described above, the title compound was obtained as a single diastereomer (93% yield).

m.p. 149-151 °C.

^{1}H NMR (300 MHz): *δ* 8.08 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6, 2H), 4.64 (m, 2H), 3.90 (d, *J* = 12.1 Hz, 1H), 3.27 (m, 1H), 2.30 (m, 2H).

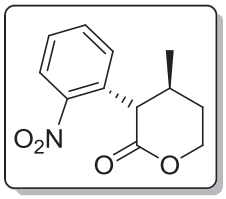
^{13}C NMR (75 MHz): *δ* 170.3 (CO), 147.3 (C), 144.6 (C), 139.8 (C), 132.3 (2CH), 130.0 (2CH), 128.7 (2CH), 123.8 (2CH), 121.6 (C), 68.7 (CH_2), 55.0 (CH), 45.9 (CH), 30.7 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 50.8 min, τ_{minor} = 41.3min (70% *ee*).

$[\alpha]_D^{20}$ +17.8 (*c* = 0.5, $CHCl_3$).

IR (film) 2921, 2851, 1720, 1520, 1260 cm^{-1}.

(3*S*, 4*S*)-4-Methyl-3-(2-nitrophenyl)-tetrahydropyran-2-one (6a)



According to the procedure described above, the title compound was obtained as a single diastereomer (93% yield).

m.p. 109-111 °C.

^{1}H NMR (300 MHz): δ 8.20 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.62 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.50 (dt, *J* = 1.5, 8.2 Hz, 1H), 7.35 (dd, *J* = 1.3, 7.6 Hz), 4.62 (dt, *J* = 3.2, 11.6 Hz, 1H), 4.51 (ddd, *J* = 2.8, 4.6, 11.2 Hz, 1H), 3.50 (d, *J* = 11.1, 1H), 2.38 (m, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 0.97 (d, *J* = 7 Hz, 3H).

^{13}C NMR (75 MHz): δ 170.1 (C), 134.7 (C), 133.8 (C), 133.7 (2CH), 128.9 (CH), 126.3 (CH), 68.5 (CH_2), 33.2 (CH), 31.6 (CH_2), 20.7 (CH), 15.2 (CH_3).

MS (FAB) *m/z* 236 (M+1, 38), 81 (57), 69 (85), 55 (100).

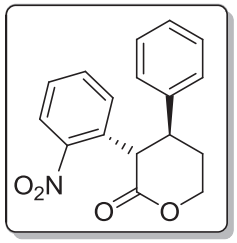
HRMS (FAB) Calcd. for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0923; found: 236.0918.

The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 20.1 min, τ_{minor} = 14.6 min (84% *ee*).

$[\alpha]_D^{20}$ +20.6 (*c* = 0.5, $CHCl_3$).

IR (film) 2964, 1723, 1526, 1347, 821, 747 cm^{-1}.

(3S, 4S)-3-(2-Nitrophenyl)-4-phenyl-tetrahydropyran-2-one (6f)



According to the procedure described above, the title compound was obtained as a (94:6) mixture of diastereomers (95% yield).

m.p. 122-124 ºC.

^{1}H NMR (300 MHz) (Data obtain from the major diastereomer): δ 8.14 (d, J = 8.1 Hz, 1H), 7.6 (dt, J = 1.6, 7.6 Hz, 1H), 7.29 (dd, J = 1.6, 7.6 Hz, 1H), 7.21 (m, 3H); 6.97 (m, 2H), 6.68 (d, J = 7 Hz, 1H), 4.78 (dt, J = 3.8, 12.2 Hz, 1H), 4.66 (ddd, J = 2.6, 4.7, 11.2 Hz, 1H), 3.99 (d, J = 11 Hz, 1H), 3.52 (dt, J = 4.6, 11.7 Hz, 1H), 2.43 (m, 1H), 2.20 (m, 1H).

^{13}C NMR (75 MHz): δ 170.0(C), 147.4 (C), 141.3 (C), 134.6 (C), 133.4 (CH), 133.3 (CH), 128.9 (2CH), 128.7 (CH), 127.5 (CH), 127.2 (2CH), 126.0 (CH), 68.8 (CH_2), 46.2 (CH), 45.3 (CH), 30.6 (CH_2).

MS (FAB) *m/z* 298 (M+1, 100), 154 (27), 136 (30), 55 (100).

HRMS (FAB) Calcd. for $C_{17}H_{16}NO_4$ $[M+H]^+$: 298.1079; found: 298.1068.

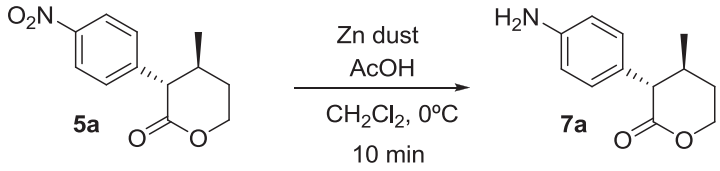
The enantiomeric excess was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 42.8 min, τ_{minor} = 31.4 min (50% *ee*).

$[\alpha]_D^{20}$ +0.9 (*c* = 0.85, $CHCl_3$).

IR (film) 1731, 1525, 1345, 789, 758, 701 cm^{-1}.

2.4 Transformations of the nitro group

(3S, 4S)-3-(4-Aminophenyl)-4-methyl-tetrahydropyran-2-one (7a)



To a solution of (3*S*,4*S*)-4-methyl-3-(4-nitrophenyl)-tetrahydropyran-2-one **5a** (0.17 mmol, 40 mg) in CH_2Cl_2 (2mL) was added sequentially Zn dust (2.38 mmol, 155 mg) and AcOH (28 mmol, 285 µL) at 0 °C. After stirring at room temperature for 10 minutes, the reaction mixture was filtered through Celita and the filtrate was neutralized with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the pure product in quantitative yield.

m.p. 127-129 °C.

^{1}H NMR (300 MHz): δ 6.99 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5, 2H), 4.52-4.36 (m, 2H), 3.15 (d, *J* = 11 Hz, 1H), 2.23-2.12 (m, 1H), 2.10-2.00 (m, 1H), 1.72 (m, 1H), 0.95 (d, *J* = 6 Hz, 3H).

^{13}C-RMN (75 MHz): δ 172.8 (CO), 145.6 (C), 129.9 (C), 129.7 (2CH), 116.3 (2CH), 68.0 (CH_2), 55.1 (CH), 34.3 (CH), 31.0 (CH_2), 20.5 (CH_3).

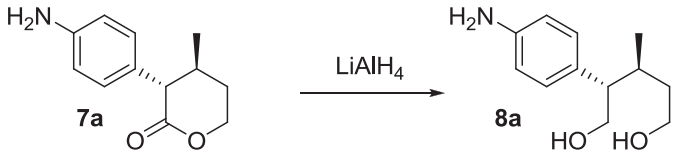
MS (FAB) *m/z* 206 (M+1, 82), 149 (100).

HRMS (FAB) Calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1175; found: 206.1181.

$[\alpha]_D^{20}$ +9.4 (*c* = 0.5, $CHCl_3$).

IR (film): 3361, 2924, 2854, 1725, 1551, 1418, 1261 cm^{-1}.

(2*S*, 3*S*)-2-(4-Aminophenyl)-3-methylpentane-1,5-diol (8a)



To a solution of lactone **7a** (0.049 mmol, 10 mg), in THF (5 mL), cooled at 0 ºC and under magnetic stirring was added $LiAlH_4$ (0.39 mmol, 15 mg) portionwise. The suspension was stirred at rt for 10 minutes, cooled to 0 ºC and water, 15% aq. NaOH solution and water were added successively. Excess anhydrous $MgSO_4$ was added and the mixture was vigorously stirred. After filtration, the solide residue was washed with ethyl acetate and the combined organic phases were evaporated at reduced pressure to give yellow oil in quantitative yield.

^{1}H NMR (300 MHz): δ 6.96 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 8.3, 2H), 3.85-3.67 (m, 6H), 2.61-2.54 (m, 1H), 1.97-1.87 (m, 1H), 1.78-1.68 (m, 1H), 1.38-1.25 (m, 1H), 0.75 (d, *J* = 6.7 Hz, 3H).

^{13}C-RMN (75 MHz): δ 145.0 (C), 130.4 (C), 129.7 (2CH), 115.3 (2CH), 64.9 (CH_2), 61.0 (CH_2), 52.9 (CH), 37.6 (CH), 31.5 (CH_2), 17.0 (CH_3).

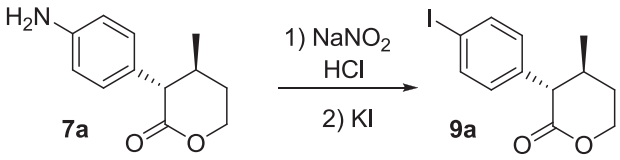
MS (ESI) *m/z* 210 (M+1, 10), 192 (54), 149 (40), 106 (100).

HRMS (FAB) Calcd. for $C_{12}H_{20}NO_2$ $[M+H]^+$: 210.1475; found: 210.1481.

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/EtOH/DEA = 80:20:0.1]; flow rate 1.0 mL/min; τ_{major} = 14.2 min, τ_{minor} = 17.6 min (90% *ee*). $[\alpha]_D^{20}$ +3.1 (*c* = 0.7, $CHCl_3$).

IR (film): 3348, 2960, 2922, 1623, 1520, 1264 cm^{-1}.

(3*S*,4*S*)-3-(4-Iodophenyl)-4-methyl-tetrahydropyran-2-one (9a)



To a solution of **7a** (0.11 mmol, 26 mg) in HCl 6N (0.18 mL) cooled to 0 °C, a solution of $NaNO_2$ (73 mg) in water (0.5 mL) was added dropwise. The resulting solution was added dropwise to a solution of KI (730 mg) in water (1 mL), keeping the bath temperature at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, then extracted with ethyl acetate. The combined organic layers were washed in sequence with 10% $Na_2S_2O_3$ and brine, then dried over $MgSO_4$ and concentrated under vacuum to give **9a** in 80% yield.

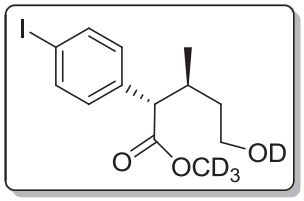
^{1}H NMR (300 MHz): δ 7.67 (d, *J* = 9 Hz, 2H), 6.93 (d, *J* = 9, 2H), 4.52-4.37 (m, 2H), 3.18 (d, *J* = 11.6 Hz, 1H), 2.23-2.14 (m, 1H), 2.11-2.03 (m, 1H), 1.81-1.67 (m, 1H), 0.94 (d, *J* = 7 Hz, 3H).

^{13}C NMR (75 MHz): δ 171.8 (CO), 146.7 (C), 138.0 (2CH), 131.1 (2CH), 93.1 (C), 68.3 (CH_2), 55.7 (CH), 34.4 (CH), 29.6 (CH_2), 20.6 (CH_3).

The enantiomeric excess was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 30.6 min, τ_{minor} = 28.2 min (90% *ee*).

$[\alpha]_D^{20}$ +4.8 (*c* = 0.5, $CHCl_3$).

d_4-(2*S*,3*S*)-Methyl 5-hydroxy-2-(4-iodophenyl)-3-methylpentanoate (10a)

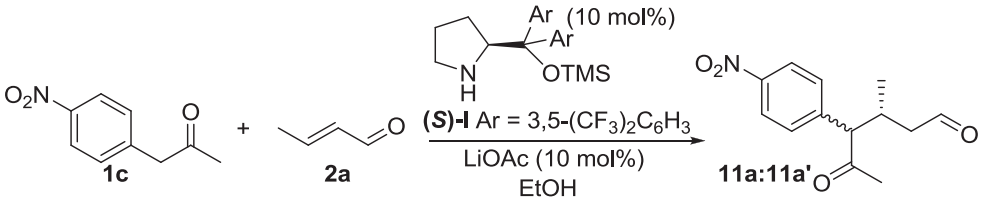


Lactone **9a** (0.06 mmol, 20 mg) was dissolved in MeOH (0.5 mL), K_2CO_3 (0.16 mmol, 22 mg) was added to the solution and the reaction mixture stirred at room temperature. After 24h the transformation of the starting material in a new product was detected by TLC. Nevertheless, once K_2CO_3 was eliminated by filtration and the solvent evaporated, lactone **9a** was the only observed product. The formation of the ester **10a** as only one diastereomer was demonstrated by carrying out the reaction under the same conditions indicated above but using d_4-MeOH and following the reaction by **^{1}H NMR**: δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.2, 2H), 3.63-3.48 (m, 2H), 2.94 (d, *J* = 11.0 Hz, 1H), 2.18-2.06 (m, 1H), 1.85-1.75 (m, 1H), 1.35-1.25 (m, 2H), 0.94 (d, *J* = 7 Hz, 3H).

See ^{1}H-NMR of **9a** and **10a** in d_4-MeOH in the spectra section (CD).

3. Michael addition of 4- nitrophenyl acetone 1c.

3.1 Optimized procedure for the Michael addition of nitrophenylacetone 1c to crotonaldehyde 2a.



To a solution of (*S*)-α,α-bis [3,5-bis (trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **(*S*)-I** (10 mol %, 0.04 mmol) in ethanol (0.4 mL) was added *crotonaldehyde* (**2a**) (1.5 equiv, 0.6 mmol). After the resulting mixture was stirred at room temperature for 15 min nitrophenylacetone **1** (0.4 mmol, 72 mg) and LiOAc (10 mol %, 0.04mmol) were sequentially added. After 12 h the reaction mixture was filtered through a short pad of silica gel and the solvent was evaporated under vacuum to give a mixture of **11a:11a'** = 2:1 in 95% yield. The two diastereomers could be separated by flash chromatography (4:1 *n*-hexane: EtOAc).

(3*R*, 4*R* and 3*R*, 4*S*)-3-Methyl-4-(4-nitrophenyl)-5-oxohexanal (11a and 11a')

Data of the major diastereomer **11a:**

^{1}H NMR (300 MHz): *δ* 9.55 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 3.82 (d, *J* = 10.3 Hz, 1H), 2.95-2.80 (m, 1H),2.22 (dd, J = 17.2, 3.8 Hz, 1H), 2.13 (s, 3H), 2.04 (ddd, J = 17.2, 10.4, 1.9 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H).

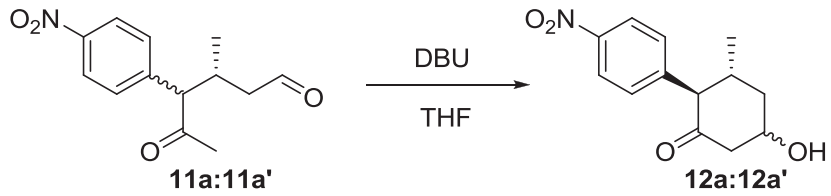
^{13}C NMR (75 MHz): *δ* 206.4 (CO), 200.8 (CHO), 147.5 (C), 144.1 (C), 129.6 (2CH), 124.1 (2CH), 64.1 (CH), 47.5 (CH_2), 31.2 (CH_3), 30.8 (CH), 18.8 (CH_3).

MS (ESI) *m/z* 304 (M+Na^{+}MeOH, 100), 250 (M+1, 3), 232 (10).

HRMS (ESI) Calcd. for $C_{13}H_{16}NO_4$ $[M+H]^{+}$: 250.1073; found, 250.1076.

$[\alpha]_D^{20}$ +98.0 (*c* = 1.0, $CHCl_3$).

3.2 Optimized cyclization process



11a:11a' **12a:12a'**

The mixture of diastereomers **11a:11a'** was placed in a vial with a stirring bar and dissolved in THF (0.5 mL). DBU was added (0.4 equiv, 0.16 mmol), the reaction was stirred at room temperature for 6h and then filtered through a plug of silica gel. The solvent was eliminated under vacuum to give the aldol **12a:12a'** as a mixture of diastereomers (95%).

(2*R*, 3*R*, 5*R* and 2*R*, 3*R*, 5*S*)-5-Hydroxy-3-methyl-2-(4-nitrophenyl) cyclohexanone (12a and 12a')

^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 8.12 (d, J = 8.7 Hz, $2H_{major}$, $2H_{minor}$), 7.21 (d, J = 8.7 Hz, $2H_{major}$), 7.14 (d, J = 8.7 Hz, $2H_{minor}$) 4.50 (quint, J = 3.0 Hz, $1H_{major}$), 4.02 (m, $1H_{minor}$), 3.32 (d, J = 11.7 Hz, $1H_{major}$), 3.28 (d, J = 11.7 Hz, $1H_{minor}$), 2.95-2.88 (m, $1H_{minor}$), 2.78-2.51 (m, 4H), 2.40-2.30 (m, $1H_{minor}$), 2.23-2.13 (m, $1H_{major}$), 2.09-1.97 (m, $1H_{minor}$), 1.94-1.67 (m, 2H), 0.86 (d, J = 6.6 Hz, $3H_{minor}$), 0.83 (d, J = 6.6 Hz, $3H_{major}$).

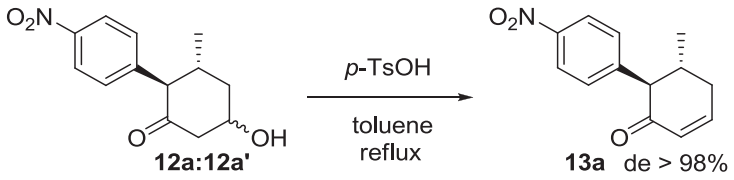
^{13}C NMR (75 MHz) (mixture of diastereomers): δ 207.1(C), 205.6 (C), 147.1 (C), 147.0 (C), 145.1 (C), 144.7 (C), 130.4 (2CH), 130.3 (2CH), 123.5 (2CH), 123.4 (2CH), 68.5 (CH), 68.4 (CH), 64.8 (CH), 63.5 (CH), 50.9 (CH_2), 48.9 (CH_2), 43.3 (CH_2), 40.3 (CH_2), 34.6 (CH), 34.5 (CH), 20.6 (CH_3), 20.5 (CH_3).

MS (EI) *m/z* 231 (M^+, 18), 163 (70), 133 (100), 115 (48).

HRMS (EI) Calcd. for $C_{13}H_{13}NO_3$ $[M]^+$: 231.0895; found, 231.0903.

3.3 Optimized elimination process

(5*R*, 6*R*)-5-Methyl-6-(4-nitrophenyl) cyclohex-2-enone (13a)



A sealed tube equipped with a magnetic stirring bar was charged with the aldols **12a:12a'** (0.40 mmol), *p*-toluenesulphonic acid (20 mol %) and toluene (2 mL). The sealed tube was capped, placed in a sand bath at 120 °C and the mixture was then vigorously stirred at the same temperature for 5h. The product can be purified by flash chromatography (4:1 to 2:1 *n*-hexane: AcOEt) to provide cyclohexenone **13a** as a single diastereomer (white solid, 90% yield). **m.p.** 103-105 °C.

^{1}H NMR (300 MHz): δ 8.20 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5, 2H), 7.06 (ddd, J= 10.0, 5.7, 2.4 Hz, 1H), 6.17 (ddd, J = 10.0, 2.8, 0.9 Hz, 1H), 3.37 (d, J = 12.2 Hz, 1H), 2.60 (dt, J_t = 5.7 Hz, J_d = 18.4 Hz, 1H), 2.52-2.40 (m, 1H), 2.30 (ddt, J_t = 2.4 Hz, J_d = 18.4, 10.0 Hz, 1H), 0.86 (d, J =6.4 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.1 (C), 149.5 (CH), 147.0 (C), 146.1 (C), 130.1 (2CH), 129.6 (CH), 123.7 (2CH), 61.6 (CH), 36.3 (CH_2), 34.6 (CH), 20.1 (CH_3).

MS (ESI) *m/z* 232 (M+1, 100), 150 (16), 149 (59).

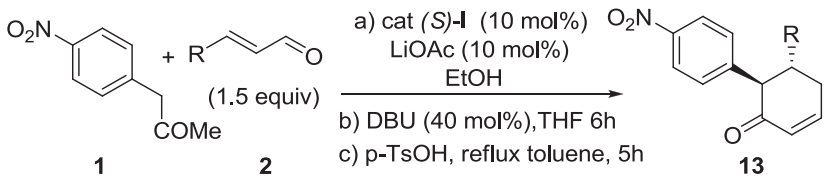
HRMS (ESI) Calcd. for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0968; found: 232.0967.

The enantiomeric excess was determined by HPLC using a Chirapack AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 19.1 min, τ_{minor} = 28.5 min (90% *ee*).

$[\alpha]_D^{20}$ -49.8 (c = 1.0, $CHCl_3$).

IR (KBr) 1674, 1514, 1342, 742, 706 cm^{-1}.

3.4 Sequential procedure for the Michael / aldol / dehydration reactions

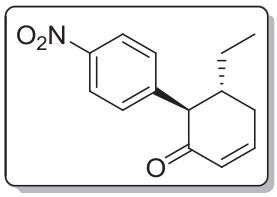


To a solution of (*S*)-α-α-bis [3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether ***(S)*-I** (10 mol %, 0.04 mmol) in ethanol (0.4 mL) the corresponding *α,β*-unsaturated aldehyde (**2a-j**) (1.5 equiv, 0.6 mmol) was added. After the resulting mixture was stirred at room temperature for 15 min, 4-nitrophenylacetone **1c** (0.4 mmol, 72 mg) and LiOAc (10 mol %, 0.04mmol) were sequentially added. The reactions were followed by TLC (until the disappearance of the 4-nitrophenylacetone **1c**), whereupon the solvent was evaporated under vacuum. The residue was dissolved in THF (0.5 mL) and DBU was added (0.4 equiv, 0.16 mmol). The reaction was stirred at room temperature during 6 h, and then filtered through a plug of silica gel. The solvent was evaporated and the crude was placed in a sealed tube and dissolved in toluene. *p*-toluenesulphonic acid (20 mol %) was added and the reaction mixture was stirred and heated under reflux during 5 h. The residue was directly purified by flash chromatography (6:1 to 4:1 *n*-hexane: EtOAc) to give the corresponding cyclohexenones **13a-j** in the yields summarized in table 4.3.

Table 4.3. Reaction details for sequence Michael addition/ aldol reaction/ dehydration of nitrophenylacetone **1c** and α,β-unsaturated aldehydes **2**

Entry	R	t (h) step a	Product	Overall Yield (%)	*ee* 13 (%)
1	**2a** (Me)	12	**13a**	80	90
2	**2b** (Et)	15	**13b**	76	91
3	**2c** (*n*-Pr)	26	**13c**	78	96
4	**2d** (*n*-Bu)	48	**13d**	70	92
5	**2e** (^{i}Pr)	50	**13e**	74	80
6	**2j** 	30	**13j**	56	94
7	**2f** (Ph)	2.5	**13f**	69	66
8	**2g** (*p*-OMe-C_6H_4)[b]	16	**13g**	71	75
9	**2h** (*p*-NO_2-C_6H_4)[c]	24	**13hi**	75	76

(5*R*, 6*R*)-5-Ethyl-6-(4-nitrophenyl) cyclohex-2-enone (13b)



The title compound was obtained as a single diastereomer according to the sequential procedure described above (76% yield).

m.p. 110-112 °C.

^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.6, 2H), 7.09 (ddd, *J*= 10.0, 6.2, 2.3 Hz, 1H), 6.18 (ddd, *J* = 10.0, 2.7, 1.3 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 2.71-2.60 (m, 1H), 2.43-2.21 (m, 2H), 1.34-1.08 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.3 (C), 149.4 (CH), 147.1 (C), 146.2 (C), 130.1 (2CH), 129.6 (CH), 123.6 (2CH), 59.7 (CH), 42.0 (CH), 30.8 (CH_2), 26.4 (CH_2), 10.3 (CH_3).

MS (ESI) *m/z* 246 (M+1, 100), 150 (11), 149 (49).

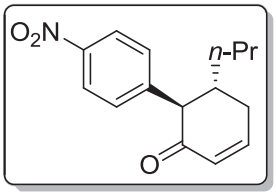
HRMS (ESI) Calcd. for $C_{14}H_{16}NO_3$ [M+1]: 246.1124; found: 246.1130.

The enantiomeric excess was determined by HPLC using a Chirapack AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 17.4 min, τ_{minor} = 24.5 min (92% *ee*).

$[\alpha]_D^{20}$ -21.4 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1685, 1515, 1342, 742, 704 cm^{-1}.

(5*R*, 6*R*)-6-(4-Nitrophenyl)-5-propylcyclohex-2-enone (13c)



The title compound was obtained as a single diastereomer according to the sequential procedure described above (78% yield).

m.p. 125-127. °C.

^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7, 2H), 7.11-7.04 (m, 1H), 6.18 (dd, *J* = 10.1, 2.6 Hz, 1H), 3.46 (d, *J* = 10.1 Hz, 1H), 2.66 (dt, J_t = 4.7 Hz, J_d = 18.1 Hz, 1H), 2.42-2.33 (m, 1H), 2.32-2.20 (m 1H), 1.35 (m 1H), 1.14-1.30 (m 1H), 1.25 (t, *J* = 6.6Hz, 1H), 1,14 (m 2H), 0.78 (t, *J* =6.6 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.3 (C), 149.4 (CH), 147.2 (C), 146.3 (C), 130.2 (2CH), 129.6 (CH), 123.7 (2CH), 60.1 (CH), 40.5 (CH_2), 36.0 (CH_2), 31.4 (CH),19.2 (CH_2), 13.9 (CH_3).

MS (ESI) 282 (M+22, 929), *m/z* 260 (M+1, 100), 149 (92), 59 (19).

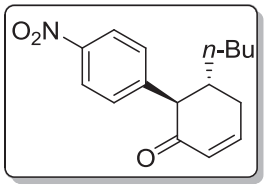
HRMS (ESI) Calcd. for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1281; found: 260.1287.

The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 13.9 min, τ_{minor} = 20.5 min (96% *ee*).

$[\alpha]_D^{20}$ -37.6 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1670, 1514, 860, 742, 705 cm^{-1}.

(5*R*, 6*R*)-5-Butyl-6-(4-nitrophenyl)cyclohex-2-enone (13d)



The title compound was obtained as a single diastereomer according to the sequential procedure described above (70% yield).

m.p. 130-133 °C.

^{1}H NMR (300 MHz): δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6, 2H), 7.08 (ddd, *J* = 10.0, 5.9, 2.6 Hz, 1H), 6.18 (d, *J* = 10.0 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 2. 67 (dt, J_t = 5.2 Hz, J_d = 18.4 Hz, 1H), 2.45-2.19 (m, 2H), 1.40-1.05 (m, 6H), 0.79 (d, *J* = 6.8Hz, 3H).

^{13}C NMR (75 MHz) δ 198.8 (C), 149.9 (CH), 147.0 (C), 146.2 (C), 130.1 (2CH), 129.6 (CH), 123.7 (2CH), 60.1 (CH), 40.6 (CH), 33.4 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 13.8 (CH_3).

MS (ESI) *m/z* 274 (M+1, 100), 149 (69).

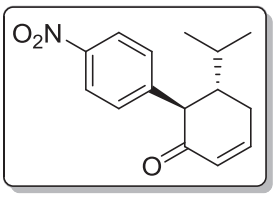
HRMS (ESI) Calcd. for $C_{16}H_{19}NO_3$ $[M+H]^+$: 274.1437; found: 274.1440.

The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 12.8 min, τ_{minor} = 19.2 min (92% *ee*).

$[\alpha]_D^{20}$ -46.1 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1669, 1517, 1347 cm^{-1}.

(5*S*, 6*R*)-5-*iso*-Propyl-6-(4-nitrophenyl) cyclohex-2-enone (13e)



The title compound was obtained as a single diastereomer according to the sequential procedure described above (74% yield).

m.p. 106-108 °C.

^{1}H NMR (300 MHz): δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8, 2H), 7.16-7.09 (m, 1H), 6.16 (dd, *J* = 10.0, 2.6Hz, 1H), 3.61 (d, *J* = 12.1 Hz, 1H), 2.54-2.29 (m, 3H), 1.39 (dsept, J_d = 2.4, J_{sept} = 6.8 Hz, 1H), 0.90 (d, *J* = 6.8Hz, 3H), 0.79 (d, *J* =6.8 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.8 (C), 149.9 (CH), 147.1 (C), 146.2 (C), 130.3 (2CH), 129.5 (CH), 123.8 (2CH), 58.1 (CH), 46.0 (CH), 27.8 (CH), 25.1 (CH_2), 20.7 (CH_3), 15.3 (CH_3).

MS (EI) *m/z* 259 (M^+, 60), 243 (100).

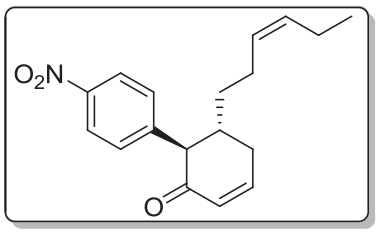
HRMS (EI) Calcd. for $C_{15}H_{17}NO_3$ $[M]^+$: 259.1208; found: 259.1208.

The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 15.8 min, τ_{minor} = 20.1 min (80% *ee*).

$[\alpha]_D^{20}$ -37.6 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1677, 1514, 1343, 842 cm^{-1}.

(5*R*, 6*R*)-5-((Z)-hex-3-enyl)-6-(4-Nitrophenyl) cyclohex-2-enone (13j)



The title compound was obtained as a single diastereomer according to the sequential procedure described above (56% yield).

m.p. 110-112 °C.

^{1}H NMR (300 MHz): δ 8.20 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8, 2H), 7.08 (ddd, J = 10.0, 5.8, 2.4 Hz, 1H), 6.18 (d, J = 10.0 Hz, 1H), 5.39-5.28 (m, 1H), 5.15-5.05 (m, 1H), 3.48 (d, J = 11.9 Hz, 1H), 2. 69 (dt, J_t = 4.6 Hz, J_d = 18.4 Hz, 1H), 2.50-2.35 (m, 1H), 2.28 (ddt, J_t = 2.4 Hz, J_d = 18.4, 10.0 Hz, 1H), 2.10-1.88 (m, 4H), 1.23 (q, J = 7.5 Hz, 2H), 0.79 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.1 (C), 149.2 (CH), 147.0 (C), 146.1 (C), 132.7 (CH), 130.1 (2CH), 129.6 (CH), 127.4 (CH), 123.7 (2CH), 60.1 (CH), 40.1 (CH), 33.7 (CH_2), 31.3 (CH_2), 23.6 (CH_2), 20.5 (CH_2), 14.2 (CH_3).

MS (EI) *m/z* 299 (M^+, 5), 229 (46), 216 (27), 141 (26), 116(67), 115 (77), 68 (100).

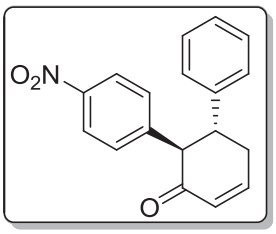
HRMS (EI) Calcd. for $C_{16}H_{21}NO_3$ $[M]^+$: 299.1521; found: 299.1525.

The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 11.2 min, τ_{minor} = 17.2 min (94% *ee*). .

$[\alpha]_D^{20}$ -23.3 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1675, 1521, 1346 cm^{-1}.

(5*R*, 6*R*)-6-(4-Nitrophenyl)-5-phenylcyclohex-2-enone (13f)



The title compound was obtained as a single diastereomer according to the sequential procedure described above (69% yield).

m.p. 149-152 °C.

^{1}H NMR (300 MHz): δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.11 (m, 8H), 6.27 (ddd, *J*= 10.1, 2.4, 1.4 Hz, 1H), 4.00 (d, *J* = 12.8 Hz, 1H), 3.63-3.53 (m, 1H), 2.90-2.70 (m, 2H).

^{13}C NMR (75 MHz) δ 197.4 (C), 149.0 (CH), 145.5 (2C), 141.0 (C), 130.4 (2CH), 129.8 (CH), 128.7 (2CH), 127.4 (2CH), 127.2 (CH), 123.4 (2CH), 59.9 (CH), 48.3 (CH), 34.9 (CH_2).

MS (EI) 282 (M+), *m/z* 293 (M+, 6), 225 (100), 195 (23), 178 (46).

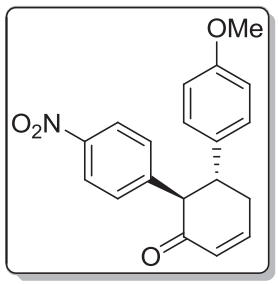
HRMS (EI) Calcd. for $C_{18}H_{15}NO_3$ $[M]^+$: 293.1052; found: 293.1046.

The enantiomeric excess was determined by HPLC using a Chiralpack IA column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 28.2 min, τ_{minor} = 36.0 min (66% *ee*).

$[\alpha]_D^{20}$ -45.6 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1674, 1514, 1342, 860, 742, 705 cm^{-1}.

(5*R*, 6*R*)-5-(4-Methoxyphenyl)-6-(4-nitrophenyl) cyclohex-2-enone (13g)



The title compound was obtained as a single diastereomer using 30 mol % of $PhCO_2H$ as additive instead of LiOAc in the Michael addition (71% yield).

m.p. 196-198 °C.

^{1}H NMR (300 MHz): δ 8.87 (d, J = 8.8 Hz, 2H), 7.16-7.12 (m, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H),), 6.70 (d, J = 8.6 Hz, 2H), 6.30-6.23 (m, 1H), 3.96 (d, J = 13.2 Hz, 1H), 3.59-3.48 (m, 1H), 2.81-2.73 (m, 2H).

^{13}C NMR (75 MHz) δ 197.6 (C), 158.5 (C), 149.1 (C), 145.7 (C), 133.0 (CH), 130.3 (2CH), 129.8 (CH), 128.3 (2CH), 123.3 (2CH), 114.0 (2CH), 60.4 (CH_3), 55.2 (CH), 47.5 (CH), 35.1 (CH_2).

MS (ESI) *m/z* 324 (M+1, 100), 282 (14), 149 (59), 121 (30).

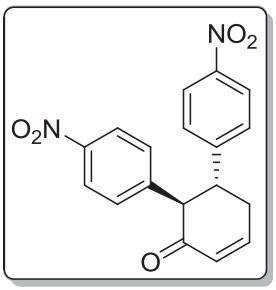
HRMS (ESI) Calcd. for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1229; found: 324.1230.

The enantiomeric excess was determined by HPLC using a Chiralpack AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 22.9 min, τ_{minor} = 28.5 min (75% *ee*).

$[\alpha]_D^{20}$ -42.2 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1675, 1517, 1349cm^{-1}.

(5*R*, 6*R*)-5-(4-Nitrophenyl)-6-(4-nitrophenyl)-cyclohex-2-enone (13h)



The title compound was obtained as a single diastereomer according to the sequential procedure described above without using any additive in the Michael addition step (75% yield).

m.p. 168-170 °C.

^{1}H NMR (300 MHz): δ 8.06 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.15 (m,1H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.32 (bd, *J* = 10.4 Hz, 1H), 4.03 (d, *J* = 13.4 Hz, 1H), 3.80-3.71 (m, 1H), 2.85-2.79 (m, 2H).

^{13}C NMR (75 MHz) δ 196.2 (C), 148.1 (C), 148.0 (CH), 147.0 (C), 146.9 (C), 144.4 (C), 130.2 (2CH), 130.0 (CH), 128.3 (2CH), 124.1 (2CH), 123.6 (2CH), 59.1 (CH), 47.9 (CH), 34.4 (CH_2).

MS (EI) *m/z* 338 (M^+, 1), 270 (100), 165 (35), 68 (97).

HRMS (EI) Calcd. for $C_{18}H_{14}N_2O_5$ $[M]^+$: 338.0903; found: 338.0899.

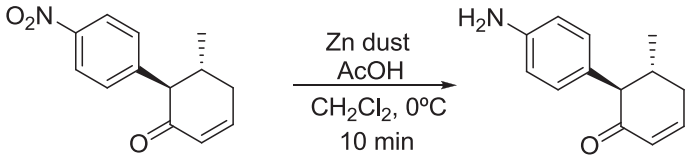
The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 47.0 min, τ_{minor} = 44.1 min (76% *ee*).

$[\alpha]_D^{20}$ -40.8 (*c* = 1.0, $CHCl_3$).

IR (KBr) 1674, 1514, 1347 cm^{-1}.

3.5 Transformations of the nitro group.

(5*R*, 6*R*)-6-(4-aminophenyl)-5-methylcyclohex-2-enone (14a)



13a **14a**

To a solution of (5*R*, 6*R*)-6-(4-nitrophenyl)-5-methylcyclohex-2-enone **13a** (0.20 mmol, 40 mg) in CH_2Cl_2 (2mL) was added sequentially Zn dust (2.80 mmol, 177 mg) and AcOH (5.6 mmol, 340 µL) at 0 ^{o}C. After stirring at room temperature for 10 minutes, the reaction mixture was filtered through Celita. The filtrate was neutralized with a saturated solution of $NaHCO_3$, the aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the pure product in quantitative yield.

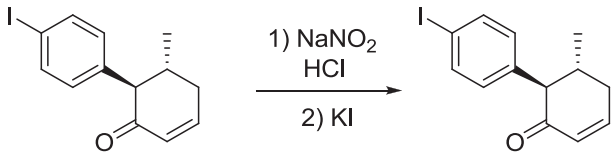
^{1}H NMR (300 MHz): δ 6.96 (ddd, *J*= 2.6, 5.4, 10.1 Hz, 1H),6.85 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.13 (ddd, *J* = 10.0, 2.7, 1.1 Hz, 1H), 3.6 (bs, 2H, NH_2), 3.10 (d, *J* = 11.6 Hz, 1H), 2.51 (dt, J_t = 5.4 Hz, J_d = 18.3 Hz, 1H), 2.43-2.27 (m, 1H), 2.30 (ddt, J_t = 2.6 Hz, J_d = 18.3, 9.8Hz, 1H), 0.86 (d, *J* =6.5 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.3 (C), 148.6 (CH), 145.3 (C), 130.1 (CH), 129.8 (2CH), 128.3 (C), 115.3 (2CH), 60.9 (CH), 36.5 (CH), 34.4 (CH_2), 20.3 (CH_3).

MS (EI) *m/z* 201, 133 (100), 132 (23).

HRMS (EI) Calcd. for $C_{13}H_{15}NO$ $[M]^+$: 201.1154; found: 201.1151.

(5*R*, 6*R*)-6-(4-Iodophenyl)-5-methylcyclohex-2-enone (15a)



14a **15a**

To a solution of **14a** (0.2 mmol, 26 mg) in HCl 6N (0.3 mL) cooled to 0 °C, a solution of $NaNO_2$ (1 equiv, 13.8 mg) in water (1 mL) was added dropwise. The resulting solution was added dropwise to a solution of KI (4 equiv, 133 mg) in water (1.5 mL), keeping the bath temperature at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight, then extracted with ethyl acetate. The combined organic layers were washed in sequence with 10% $Na_2S_2O_3$ and brine, then dried over $MgSO_4$ and concentrated under vacuum to give **15a** with 75% yield.

^{1}H NMR (300 MHz): δ 7.66 (d, J = 8.5 Hz, 2H), 7.01 (ddd, J= 2.5, 5.9, 10.0 Hz, 1H), 6.83 (d, J = 8.5, 2H), 6.15 (ddd, J = 0.9, 2.6, 10.0 Hz, 1H), 3.17 (d, J = 11.9 Hz, 1H), 2.55 (dt, J_t = 5.7 Hz, J_d = 18.4 Hz, 1H), 2.46-2.33 (m, 1H), 2.24 (ddt, J_t = 2.5 Hz, J_d = 10.0, 18.4 Hz, 1H), 0.86 (d, J =6.4 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.0 (C), 149.1 (CH), 138.0 (C), 137.6 (2CH), 131.2 (2CH), 129.9 (CH), 92.5 (C), 61.34 (CH), 36.3 (CH_2), 34.6 (CH), 20.3 (CH_3).

MS (EI) *m/z* 312 (M^+, 60), 243 (100), 117 (20), 115 (27).

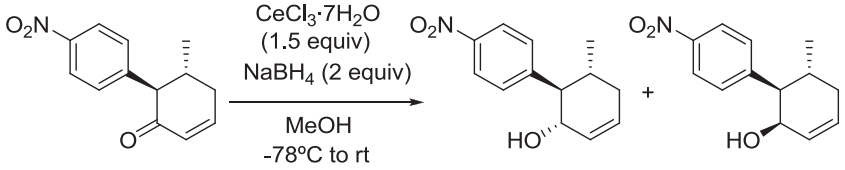
HRMS (EI) Calcd. for $C_{13}H_{13}IO$ $[M]^+$: 312.0011; found: 312.0013.

$[\alpha]_D^{20}$ -14.1 (c = 0.3, $CHCl_3$).

IR (KBr) 1674, 1386, 1262, 1098, 802, 549 cm^{-1}.

3.6 Transformations of the cyclohexene ring

3.6.1 Reduction of ketone 13a



13a **16a** 87% **16a'** 13%

(1*S*, 5*R*, 6*R*)-5-Methyl-6-(4-nitrophenyl) cyclohex-2-enol (8a)

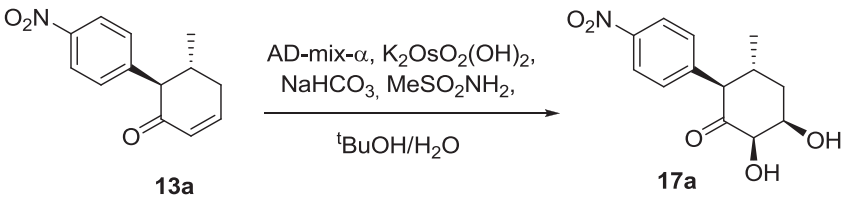
To a solution of enone **5a** (50 mg, 0.21 mmol), and $CeCl_3 \cdot 7H_2O$ (117 mg, 0.31 mmol) in MeOH (5 mL) at -78 °C $NaBH_4$ (16 mg, 0.42 mmol) was added in one portion. The resulting mixture was stirred for 1 h at -78 ºC and slowly warmed up to room temperature during 4 h. The reaction was quenched by addition of 1 mL of acetone and then 1 mL of H_2O. The solvent was evaporated and the residue partitioned between Et_2O (10 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (6:1 *n*-hexane: EtOAc) gave **16a** as a white solid (68% yield). **m.p.** 108-110 °C. $[\alpha]_D^{20}$ -4.1 (*c* = 3.0, $CHCl_3$).

^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6, 2H), 5.89-5.82 (m, 1H), 5.75 (d, *J* = 10.1 Hz, 1H), 4.42-4.30 (m, 1H), 2.46 (dd, *J* = 11.4, 11.6 Hz, 1H), 2.28 (dt, J_t = 2.5 Hz, J_d = 17.9 Hz, 1H), 2.14-2.01 (m, 1H), 1.98-1.84 (m, 1H), 1.44 (d, J = 5.6 Hz, OH), 0.69 (d, *J* =6.5 Hz, 3H). **^{13}C NMR** (75 MHz) δ 150.6 (C), 146.9 (C), 130.0 (CH), 129.2 (2CH), 128.7 (CH), 123.8 (2CH), 73.3 (CH), 57.1 (CH), 34.6 (CH_2), 32.8 (CH), 19.6 (CH_3).

IR (KBr) 3512, 1530, 1348, 751, 700 cm^{-1}.

Representative ^{1}H NMR data of **16a'**: δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6, 2H), 4.08 (m, 1H), 2.69 (dd, *J* = 11.6, 3.4 Hz, 1H, H_6), 0.79 (d, *J* =6.3 Hz, 3H).

3.6.2 Dihydroxylation of ketone 13a



(2*R*, 3*R*, 5*R*, 6*R*)-2,3-dihydroxy-5-Methyl-6-(4-nitrophenyl)cyclohexanone (17a)

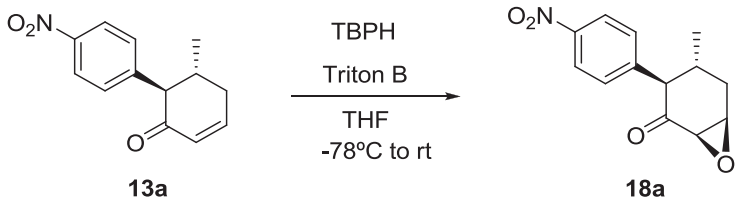
A 5 mL round-bottomed flask was charged with 40 mg of α,β-unsaturated ketone **13a** (1 equiv, 0.158 mmol) and dissolved in 800 µl of *t*-BuOH. Then, 300 mg of AD-mix-α, 40 mg of $NaHCO_3$ (3 equiv, 0.474 mmol), 15 mg of methylsulfonamide (1 equiv, 0.158 mmol), 10 mg of $K_2OsO_2(OH)_2$ (0.16 equiv, 0.027 mmol) and 800 µl of H_2O were subsequently added and the mixture was vigorously stirred at room temperature for 4 days. Whereupon the mixture was transferred to a 25 ml Erlenmeyer flask, diluted with 10 ml of EtOAc and stirred for 1 h with 10 ml of a 40% solution of $NaHSO_3$. The aqueous layer was extracted with EtOAc (15 ml x 4), the combined organic layers were sequentially washed with a 10 % solution of NaOH and brine, dried over $MgSO_4$ and the solvent evaporated under vacuum. The crude was purified by flash chromatography (2:1 to 1:1 *n*-hexane: EtOAc) to afford 23 mg of diastereomerically pure **17a** (50% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 4.47 (dd, J = 5.5, 3.5 Hz, 1H), 4.34 (bs, 1H), 3.80 (d, J = 2.0 Hz, OH), 3.38 (d, J = 11.8 Hz,), 2.67 (bs, OH), 2.65 (m, 1H), 2.31 (dt, J_d = 14.7 Hz, J_t = 3.8 Hz, 1H), 1.84 (t, J = 14.3 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H).

^{13}C NMR (75 MHz) (benzene-d6): δ 206.8(C), 147.6 (C), 143.3 (C), 130.4 (2CH), 123.5 (2CH), 77.1 (CH), 71.8 (CH), 61.6 (CH), 36.8 (CH_2), 34.7 (CH), 19.9 (CH_3).

$[\alpha]_D^{20}$ +32.1 (c = 1.0, $CHCl_3$).

3.6.3 Epoxidation of ketone 135a



13a **18a**

(1*R*, 3*R*, 4*R*, 6*R*)-4-Methyl-3-(4-nitrophenyl)-7-oxabicyclo [4.1.0] heptan-2-one (18a)

To a solution of **13a** (50 mg, 0.21 mmol, 1 equiv) in THF (1 mL) at -78 ºC, a solution of *tert*-butylhydroperoxide (TBPH) (5-6 M in decane, 3 equiv) and 4 drops of benzyl trimethylammonium hydroxide (Triton B) (40% in MeOH) were sequentially added. The mixture was stirred at room temperature overnight and then treated with saturated aqueous solution of Na_2SO_3 and extracted with AcOEt. The residue was purified by flash chromatography (n-hexane/AcOEt 5:1), to give **18a** as colourless oil (48% yield).

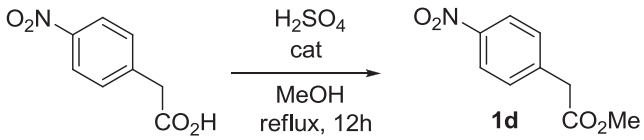
^{1}H NMR (500 MHz)(benzene-d6): δ 7.77 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8, 2H), 3.00 (d, J = 4.0 Hz, 1H), 2.82 (t, J = 3.8 Hz, 1H), 2.15 (d,J = 11.8 Hz, 1H), 2.02-1.92 (m, 1H), 1.66 (dt, J_t = 3.8 Hz, J_d = 15.0 Hz, 1H), 0.87 (dd, J = 15.0, 12.0 Hz, 1H), 0.26 (d, J =6.5 Hz, 3H).

^{13}C NMR (75 MHz) δ 204.1 (CO), 147.2 (C), 146.1 (C), 130.1 (2CH), 123.9 (2CH), 61.6 (CH), 54.6 (CH), 54.4 (CH), 31.5 (CH_2), 28.7 (CH), 19.5 (CH_3).

$[\alpha]_D^{20}$ -9.1 (c = 0.7, $CHCl_3$).

4. Michael addition of 4-Nitropheny methyl acetate.

4.1 Synthesis of *p*-nitrophenyl methyl acetate 1d.



To a solution of *p*-nitrophenyl acetic acid (3.5 g, 19.3 mmol) in MeOH (75 mL) 3.5 mL of H_2SO_4 were added. The reaction mixture was heated under reflux for 12 hours. After evaporation of the solvent, 25 mL of EtOAc were added and the organic phase was washed with a saturated solution of $NaHCO_3$ (3 x 15 mL), brine (3 x 15 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to afford 3.5 g of *p*-nitrophenyl methyl acetate **1d** (yield 95%) as a white crystalline solid.

m.p. 46-48ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 3.67 (s, 2H), 3.62 (s, 3H).

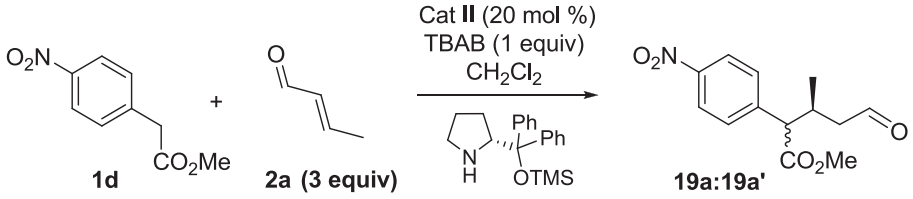
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (CO), 147.3 (C), 141.2 (C), 130.3 (2 CH), 123.8 (2 CH), 52.4 (CH_3), 40.8 (CH_2).

MS (ESI): m/z 195 (M+1, 28), 106 (100), 89 (57), 78 (41).

HRMS (ESI) Calcd. for $C_9H_{10}NO_4$ $[M+H]^+$: 195.0532; found: 195.0536.

IR (film): 3112, 3079, 2961, 2844, 1725 (CO), 1601, 1513, 1340, 1255, 1015, 881, 856, 757 cm^{-1}.

4.2 Optimized procedure for the conjugate addition of *p*-nitrophenyl methyl acetate 1d to crotonaldehyde 2a.



To a solution of (*R*)-α-α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**II**) (20 mol %, 0.02 mmol) in CH_2Cl_2 (150 µL) crotonaldehyde **2a** (0.3 mmol, 3.0 equiv) was added. After stirring for 10 minutes, *p*-nitrophenyl methyl acetate **1** (19.5 mg, 0.1 mmol) and TBAB (32.2 mg, 0.1 mmol) were sequentially added. The reaction was stirred until completion (TLC) (Hexane / EtOAc = 2:1). The solvent was evaporated under vacuum and the product was filtered through a short pad of silica gel. The solvent was removed under reduced pressure, and the crude was used in the next step without further purification.

(2*S*, 3*S* and 2*R*, 3*S*)- Methyl 3-methyl-2-(4-nitrophenyl)-5-oxopentanoate (19a and 19a')

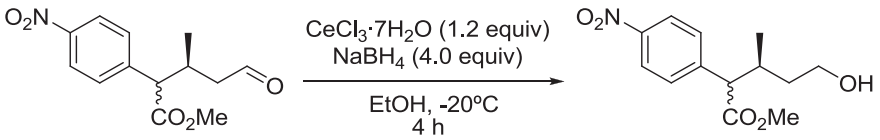
^{1}H NMR (300 MHz, $CDCl_3$): (mixture of diastereomers 1:1) δ 9.76 (s, 1H), 9.59 (s, 1H), 8.21 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.61 (d, *J* = 10.2 Hz, 1H), 3.58 (d, *J* = 9.9 Hz, 1H), 2.92 – 2.76 (m, 2H), 2.43 – 1.99 (m, 4H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): (mixture of diastereomers 1:1) δ 200.4 (CHO), 200.3 (CHO), 172.1 (CO), 172.0 (CO), 147.1 (2 C), 144.2 (2 C), 129.4 (2 CH), 129.3 (2 CH), 123.5 (2 CH), 123.4 (2 CH), 56.5 (CH), 56.4 (CH), 52.0 (CH_3), 51.9 (CH_3), 48.3 (CH_2), 47.1 (CH_2), 31.7 (CH), 31.2 (CH), 18.1 (CH_3), 17.2 (CH_3).

MS (ESI): m/z 266 (M+1, 40), 233 (151), 193 (138), 188 (115), 149 (152).

HRMS (ESI) Calculated for $C_{13}H_{16}NO_5$ $[M+H]^+$: 266.1022; found: 266.1034.

4.3 Optimized procedure for the reduction reaction.



19a:19a' **20a:20a'**

The mixture of diastereomers **19a**:**19a'** (0.1 mmol) was dissolved in EtOH (1.0 mL), and $CeCl_3 \cdot 7H_2O$ (0.12 mmol) was added[1]. The mixture was introduced in a cooling bath at -20°C and was stirred for 5 minutes whereupon a suspension of $NaBH_4$ (0.4 mmol) in EtOH (1.0 mL) was added dropwise. The reaction was stirred at -20 °C for 4 hours and quenched with sat. aq. $NaHCO_3$ solution (5 mL), concentrated under reduced pressure and filtered through a short pad of Celite® and washed with EtOAc. The filtrate was washed with water (5 x 10 mL), brine (3 x 10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to afford the mixture **20a:20a'**, which was used in the next step without further purification.

(2*S*, 3*S* and 2*R*, 3*S*)-Methyl 5-hydroxy-3-methyl-2-(4-nitrophenyl) (20a and 20a')

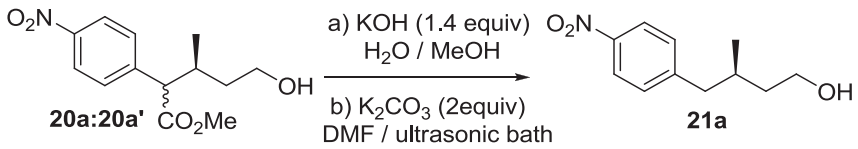
^{1}H NMR (300 MHz, $CDCl_3$): (mixture of diastereomers 1:1) δ 8.19 (d, *J* = 8.6 Hz, 4H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 3.8-3.5 (m, 4H), 3.68 (s, 6H), 3.48 (d, *J* = 10.3 Hz, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 2.50-2.35 (m, 2H), 1.54-1.34 (m, 2H), 1.29-1.13 (m, 2H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): (mixture of diastereomers 1:1) δ 173.3 (CO), 173.0 (CO), 147.4 (2 C), 145.2 (2 C), 129.7 (2 CH), 129.6 (2 CH), 123.8 (2 CH), 123.7 (2 CH), 60.4 (CH_2), 60.2 (CH_2), 58.4 (CH), 58.3 (CH), 52.3 (CH), 52.2 (CH), 38.0 (CH_2), 36.2 (CH_2), 33.8 (CH_3), 33.6 (CH_3), 17.8 (CH_3), 17.0 (CH_3).

MS (ESI): m/z 290 (M+Na, 15), 236 (48), 110 (40).

HRMS (ESI): Calcd. for $C_{13}H_{17}NO_5Na$ $[M+Na]^+$: 290.0998; found: 290.1010.

[1] When this reaction was carried out using only $NaBH_4$ in dry EtOH the partial reduction of the ester was also observed, even controling the amount of the reducing agent and temperature.

4.4 Optimized procedure for the decarboxylation reaction.



The mixture of diasteromeric alcohols **20a** and **20a'** (0.1 mmol) was dissolved in MeOH (1 mL) and a solution of KOH (0.133 mmol) in water (0.5 mL) was added. The mixture was stirred for 2 hours, whereupon MeOH was removed under reduced pressure. The crude was redissolved in DMF (0.5 mL) and K_2CO_3 (2 equiv, 0.2 mmol) was added. The reaction was placed in an ultrasonic bath for 8 hours. The reaction was quenched with sat. NH_4Cl and the organic phase was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to afford the decarboxylated product **5a** in 81% yield (71% overall yield for the 3 steps).

(*R*)-3-Methyl-4-(4-nitrophenyl) butan-1-ol (21a)

Yellowish oil. **Yield:** 81% (71% overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 3.70 (m, 2H), 2.76 (dd, *J* = 6.4, 13.4 Hz, 1H), 2.52 (dd, *J* = 8.2, 13.4 Hz, 1H),1.97 (m, 1H), 1.62 (m, 1H), 1.55 (m, 1H), 1.43 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1 (C), 146.4 (C), 129.9 (2 CH), 123.5 (2 CH), 60.7 (CH_2), 43.6 (CH_2), 39.3 (CH_2), 31.6 (CH), 19.3 (CH_3).

MS (ESI): m/z 210 (M+1, 4), 192 (24), 149 (34), 146 (22), 79 (100), 64 (25).

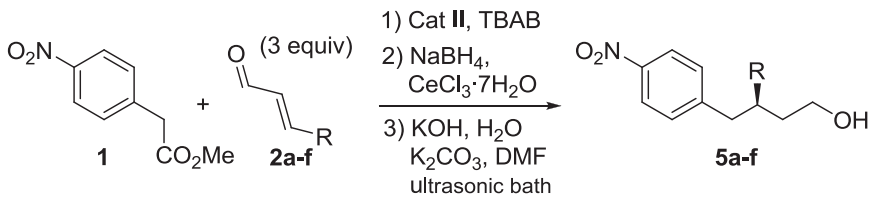
HRMS (ESI): Calcd. $C_{11}H_{16}NO_3$ $[M+H]^+$: 210.1124; found: 210.1124.

The procedure to obtain this product has been scaled up until 500 mg (2.6 mmol) of ester **1d**. Yield = 75% (3 steps).

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH = 95:5]; flow rate 1.0 mL/min; ee = 89%, τ_{minor} = 22.3 min, τ_{major} = 23.4 min.

$[\alpha]_D^{20}$ +1,8 (*c* = 2.1, $CHCl_3$).

4.5 General procedure for the synthesis of alcohols 5a-5f: Sequence Michael / reduction / decarboxylation



To a solution of (*R*)-α-α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**II**) (20 mol %, 0.04 mmol) in CH_2Cl_2 (400 µL) the corresponding aldehyde **2a-h** (0.6 mmol, 3.0 equiv) was added. After stirring for 10 minutes, *p*-nitrophenyl methyl acetate **1d** (40 mg, 0.2 mmol) and TBAB (64 mg, 0.2 mmol) were sequentially added. The reaction was stirred during the time indicated in each case in table 2 in the manuscript. The solvent was evaporated under vacuum and the product was filtered through a short pad of silica gel.

The crude was dissolved in EtOH (2.0 mL), and $CeCl_3 \cdot 7H_2O$ (0.24 mmol) was added. The mixture was introduced in a cooling bath at -20°C and a suspension of $NaBH_4$ (0.8 mmol) in EtOH (2.0 mL) was added dropwise. The reaction was stirred at -20 °C for 4 hours whereupon the reaction was quenched with sat. aq. $NaHCO_3$ solution (5 mL), concentrated under reduced pressure and filtrated through a short pad of Celite® and washed with EtOAc. The filtrate was washed with water (5 x 10 mL), brine (3 x 10 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. This crude was dissolved in MeOH (1 mL) and a solution of KOH (0.26 mmol) in water (1 mL) was added. The mixture was stirred for 2 hours, whereupon the solvent was removed under reduced pressure.

The crude was redissolved in DMF (1 mL) and was introduced in an ultrasonic bath for 8 hours. The reaction was quenched with NH_4Cl sat and the organic phase was extracted with diethyl ether (3 x 10 mL). The combined organic layers were

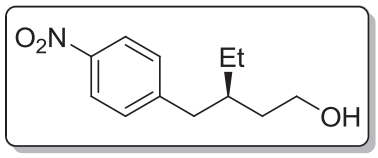
washed with water (3 x 10 mL), brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure.

The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to afford the corresponding decarboxylated product **21** in the yields indicated in each case and table 4.4.

Table 4.4. Reaction details for sequence Michael addition/ reduction/ decarboxilation of *p*-nitrophenylacetate **1c** and α,β-unsaturated aldehydes **2**

Entry	R	t (h) Michael addition	Product	Overall Yield (%)	ee 21 (%)
1	**2a** (Me)	24	**21a**	75	90
2	**2b** (Et)	24	**21b**	61	90
3	**2c** (*n*-Pr)	66	**21c**	52	91
4	**2d** (*n*-Bu)	96	**21d**	50	94
5	**2e** (^{i}Pr)	66	**21e**	59	96
6	**2f** (Ph)	2	**21f**	66	86
7	**2g** (*p*-OMe-C_6H_4)[b]	48	**21g**	66	90
8	**2h** (*p*-NO_2-C_6H_4)[c]	48	**215h**	66	64

(*R*)-3-(4-Nitrobenzyl) pentan-1-ol (21b)



The title compound was obtained following the general procedure described above. Yellowish oil. Yield: 61% (overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 3.68 (m, 2H), 2.69 (m, 2H), 1.82 (sept, 1H), 1.55 (m, 2H), 1.34 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 146.4 (C), 129.9 (2 CH), 123.5 (2 CH), 60.8 (CH_2), 40.1 (CH_2), 37.8 (CH), 35.8 (CH_2), 25.7 (CH_2), 10.6 (CH_3).

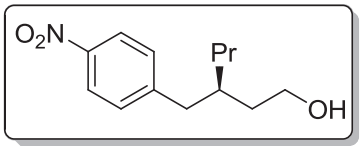
MS (ESI): m/z 224 (M+1, 7), 206 (17), 149 (35), 79 (64), 74 (44), 64 (11).

HRMS (ESI): Calcd. $C_{12}H_{18}NO_3$ $[M+H]^+$: 224.1275; found: 224.1281.

The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH = 98:2]; flow rate 0.9 mL/min; ee = 90%, τ_{minor} = 55.2 min, τ_{major} = 58.9 min.

$[\alpha]_D^{20}$ +3.7 (*c* = 2.7, $CHCl_3$).

(*R*)-3-(4-Nitrobenzyl) hexan-1-ol (21c)



The title compound was obtained following the general procedure described above. Yellowish oil. Yield: 52% (overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 3.67 (m, 2H), 2.68 (m, 2H), 1.87 (m, 1H), 1.54 (m, 2H), 1.30 (m, 4H), 0.87 (t, *J* = 6.4 Hz, 3H).

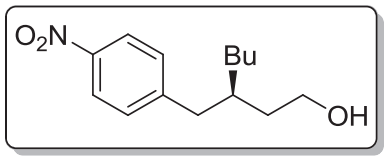
^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 146.4 (C), 129.9 (2 CH), 123.5 (2 CH), 60.8 (CH_2), 40.6 (CH_2), 36.3 (CH_2), 36.2 (CH), 35.6 (CH_2), 19.6 (CH_2), 14.3 (CH_3).

MS (ESI): m/z 238 (M+1, 3), 220 (19), 174 (14), 163 (13), 149 (82), 131 (22), 79 (72), 64 (100).

HRMS (ESI) calculated $C_{13}H_{20}NO_3$ $[M+H]^+$: 238.1439; found: 238.1437.

The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH = 98:2]; flow rate 1.0 mL/min; ee = 91%, τ_{minor} = 44.5 min, τ_{major} = 48.2 min.

(*R*)-3-(4-Nitrobenzyl) heptan-1-ol (21d)



The title compound was obtained following the general procedure described above. Yellowish oil. Yield**:** 50% (overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 3.68 (m, 2H), 2.69 (m, 2H), 1.86 (m, 1H), 1.54 (m, 4H), 1.28 (m, 4H), 0.88 (t, *J* = 6.6 Hz, 3H).

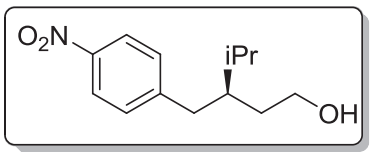
^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 146.4 (C), 129.9 (2 CH), 123.5 (2 CH), 60.8 (CH_2), 40.6 (CH_2), 36.4 (CH), 36.3 (CH_2), 33.0 (CH_2), 28.6 (CH_2), 22.9 (CH), 14.0 (CH_3).

MS (ESI): m/z 252 (M+1, 2), 234 (20), 163 (25), 149 (17), 79 (100), 64 (24).

HRMS (ESI): Calcd. $C_{14}H_{22}NO_3$ $[M+H]^+$: 252.1594; found: 252.1594.

The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH = 95:5]; flow rate 0.9 mL/min; ee = 94%, τ_{major} = 32.2 min, τ_{minor} = 31.3 min. **$[\alpha]_D^{20}$** +10.4 (*c* = 1.0, $CHCl_3$).

(*R*)-4-Methyl-3-(4-nitrobenzyl) pentan-1-ol (21e)



The title compound was obtained following the general procedure described above. Yellowish oil. Yield**:** 59% (overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 3.60 (m 2H), 2.74 (dd, *J* = 6.3, 13.7 Hz, 1H), 2.57 (dd, *J* = 7.6, 13.6 Hz, 1H), 1.65 (m, 2H), 1.41 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0 (C), 146.4 (C), 129.8 (2 CH), 123.6 (2 CH), 61.4 (CH_2), 42.4 (CH), 37.3 (CH_2), 33.0 (CH_2), 29.0 (CH), 18.9 (CH_3), 18.6 (CH_3).

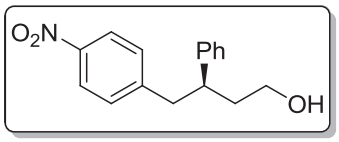
MS (ESI): m/z 260 (M+23^{+}, 20), 220 (11), 163 (21), 149 (15), 79 (100), 64 (23).

HRMS (ESI): Calcd. $C_{13}H_{19}NO_3Na$ $[M+Na]^{+}$: 260.1261; found: 260.1257.

The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH = 98:2]; flow rate 0.9 mL/min; ee = 96%, τ_{minor} = 48.2 min, τ_{major} = 56.6 min.

$[\alpha]_D^{20}$ +2.3 (*c* = 1.6, $CHCl_3$).

(*R*)-4-(4-Nitrophenyl)-3-phenylbutan-1-ol (21f)



The title compound was obtained following the general procedure described above. Colourless oil. Yield**:** 66% (overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.7 Hz, 2H), 7.21 (m, 3H), 7.08 (m, 4H), 3.56 (m, 1H), 3.44 (m, 1H), 3.03 (m, 3H), 1.95 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2 (C), 146.4 (C), 142.9 (C), 129.9 (2 CH), 128.6 (2 CH), 127.7 (2 CH), 126.8 (CH), 123.3 (2 CH), 60.7 (CH_2), 44.2 (CH), 43.5 (CH_2), 38.5 (CH_2).

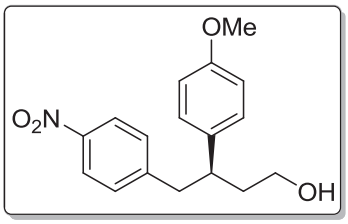
MS (ESI): m/z 272 (M+1), 149 (21), 79 (100), 64 (22).

HRMS (ESI): Calcd. C16H18NO3 $[M+1]^+$: 272.1281; found: 272.1290.

The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH = 95:5]; flow rate 1.0 mL/min; ee = 86%, τ_{major} = 38.0 min, τ_{minor} = 44.7 min.

$[\alpha]_D^{20}$ +36.1 (*c* = 1.0, $CHCl_3$).

(*R*)-3-(4-methoxyphenyl)-4-(4-nitrophenyl) butan-1-ol (21g)



The title compound was obtained following the general procedure described above using (*R*)-α-α-bis [3,5-bis (trifluoromethyl) phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**I**) as catalyst[2]. Yellow oil. Yield: 66% (overall yield for the 3 steps).

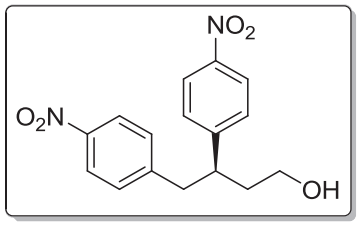
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.75 (s, 3H), 3.53 (m, 1H), 3.43 (m, 1H), 3.06-2.86 (m, 3H), 1.99-1.80 (m, 2H).

[2] Catalyst **I** usually gives better results in terms of enantioselectivity but could not be used in the case of aliphatic aldehydes due to their lower reactivies.

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4 (C), 148.5 (C), 146.4 (C), 134.9 (C), 130.0 (2 CH), 128.6 (2 CH), 123.3 (2 CH), 114.1 (2 CH), 60.7 (CH_2), 55.2 (CH), 43.6 (CH_2), 43.4 (CH_3), 38.7 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak ID column [hexane/*i*-PrOH = 90:10]; flow rate 1.0 mL/min; ee = 90%, τ_{major} = 18.1 min, τ_{minor} = 29.5 min. $[\alpha]_D^{20}$ +98.7 (*c* = 1.0, $CHCl_3$).

(*R*)-3,4-bis(4-nitrophenyl)butan-1-ol (21h)



The title compound was obtained following the general procedure described above using (*R*)-α-α-bis [3,5-bis (trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**I**) as catalyst. Yellow oil. Yield: 66% (overall yield for the 3 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.54 (m, 1H), 3.35 (m, 1H), 3.23 (m, 1H), 3.09 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.90 (dd, *J* = 13.4, 9.1 Hz, 1H), 1.99 (m, 1H), 1.87 (m, 1H).

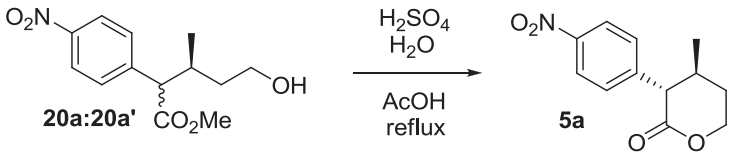
^{13}C NMR (75 MHz, $CDCl_3$): δ 151.1 (C), 147.1 (C), 146.8 (C), 146.6 (C), 129.8 (2 CH), 128.6 (2 CH), 123.9 (2 CH), 123.6 (2 CH), 59.9 (CH_2), 43.9 (CH), 42.8 (CH_2), 38.2 (CH_2).

The enantiomeric excess was determined by HPLC using a Chiralpak ID column [hexane/*i*-PrOH = 90:10]; flow rate 1.0 mL/min; ee = 64%, τ_{major} = 35.2 min, τ_{minor} = 40.2 min.

$[\alpha]_D^{20}$ +61.1 (*c* = 1.0, $CHCl_3$).

4.6 Lactonization process

(3*S*, 4*S*)-4-Methyl-3-(4-nitrophenyl)-tetrahydro-2H-pyran-2-one (6a)



This lactone has already been described by us (see page xx) and has been prepared in order to establish the stereochemistry of the new stereogenic centre created in the Michael addition and to determine the *ee* of the Michael adducts during the optimization process.

The alcohol **20a:20a'** (obtained as described previously) (26 mg, 0.1 mmol) was dissolved in acetic acid (100 µL). Water (50 µL) and concentrated H_2SO_4 (50 µL) were added and the reaction was refluxed overnight. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 15 mL). The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the lactone **5a** (80% yield). Yellow solid.

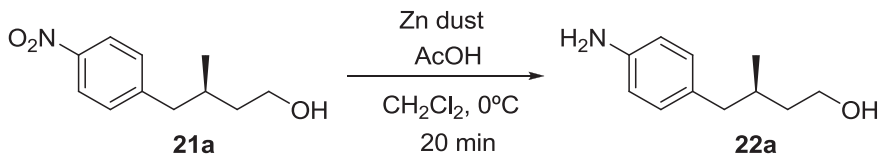
The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH = 80:20]; flow rate 1.0 mL/min; *ee* = 90%, τ_{major} = 30.5 min, τ_{minor} = 26.2 min.

$[\alpha]_D^{20}$ +5.7 (*c* = 0.5, $CHCl_3$).

$[\alpha]_D^{20}$ + 25 (c = 1.0, $CHCl_3$) for the same compound synthesized from **1b** (98% ee).

4.7 Transformations of the nitro group

(*R*)-4-(4-Aminophenyl)-3-methylbutan-1-ol (22a)



21a **22a**

To a solution of (*R*)-3-methyl-4-(4-nitrophenyl) butan-1-ol **21a** (0.11 mmol, 23 mg) in CH_2Cl_2 (1130 µL) was added sequentially Zn dust (1.51 mmol, 99 mg) and AcOH (15.82 mmol, 161 µL) at 0°C. After stirring at the same temperature for 20 minutes, the reaction mixture was filtered through Celite® and the filtrate was neutralized with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the pure product in quantitative yield. Brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.2, 2H), 3.68 (m, 2H), 3.00 (s, 2H), 2.51 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.33 (dd, *J* = 13.5, 7.7 Hz, 1H), 1.81 (m, 1H), 1.64 (m, 1H), 1.38 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H).

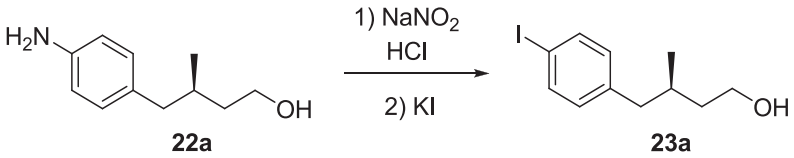
^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1 (C), 131.2 (C), 130.0 (2CH), 115.2 (2CH), 61.2 (CH_2), 43.0 (CH_2), 39.4 (CH_2), 31.8 (CH), 19.4 (CH_3).

MS (ESI): *m/z* 180 (M+1, 8), 162 (100).

HRMS (ESI): Calculated for $C_{11}H_{18}NO$ [M+1]: 180.1390; found: 180.1382.

$[\alpha]_D^{20}$ +4.0 (*c* = 0.6, $CHCl_3$).

(*R*)-4-(4-Iodophenyl)-3-methylbutan-1-ol (23a)



22a **23a**

To a suspension of **22a** (0.081 mmol, 14.6 mg) in HCl 6N (0.1 mL) at 0 °C, a solution of $NaNO_2$ (1 equiv, 5.5 mg) in water (1 mL) was added dropwise. The resulting mixture was added dropwise to a solution of KI (4 equiv, 53.8 mg) in water (0.6 mL), keeping the bath temperature at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight, then extracted with ethyl acetate. The combined organic layers were washed in sequence with 10% $Na_2S_2O_3$ and brine, then dried over $MgSO_4$ and concentrated under vacuum to give **23a** in 90% yield. Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.1, 2H), 3.69 (m, 2H), 2.58 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.37 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.87 (m, 1H), 1.63 (m, 1H), 1.40 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7 (C), 137.2 (2CH), 131.3 (2CH), 90.9 (C), 61.0 (CH_2), 43.2 (CH_2), 39.4 (CH_2), 31.6 (CH), 19.4 (CH_3).

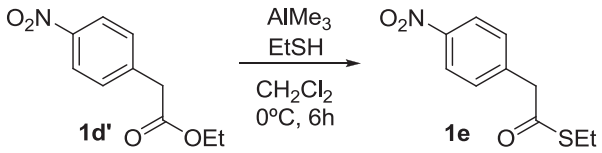
MS (ESI): m/z 291 (M+1, 13), 165 (45), 81 (60), 55 (100).

HRMS (ESI): Calculated for $C_{11}H_{15}OINa$ $[M+Na]^+$: 313.0047; found: 313.0049.

$[\alpha]_D^{20}$ +3.7 (*c* = 1.0, $CHCl_3$).

5. Michael addition of 4-Nitrophenyethyl thioester 1e

5.1 Synthesis of *S*-ethyl 2-(4-nitrophenyl) ethanethioate 1e



Thioester **1e** was prepared following a procedure described in the literature for the synthesis of a benzilic thioester[3]. A solution of trimethylaluminum (2M in hexane, 10.0 mL, 20.0 mmol) is diluted with 50 mL of dry dichloromethane followed by 4.5 mL of ethane thiol (60 mmol)at -78 °C. Methane evolution occurs and the solution is allowed to warm to ambient temperature to give a solution of Me_2AlSEt. The *p*-nitrophenyl ethyl acetate (2.1 g, 10 mmol) is dissolved in dichlromethane (20 mL), cooled to -78 °C and treated with the aluminum thiolate. The reaction is allowed to warm to 0°C and stirring is continued for 6 hours. The reaction is recooled and quenched with saturated aqueous sodium potassium tartrate (30 mL) and stirred vigorously for 1 hour. The resulting solution transferred to a separatory funnel. The aqueous fraction extracted with 3 portions of CH_2Cl_2 (30 mL each). The combined organics are dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography (20:1 n-hexane/EtOAc) to yield the title compound as a yellow oil (1.5 g, 75%).

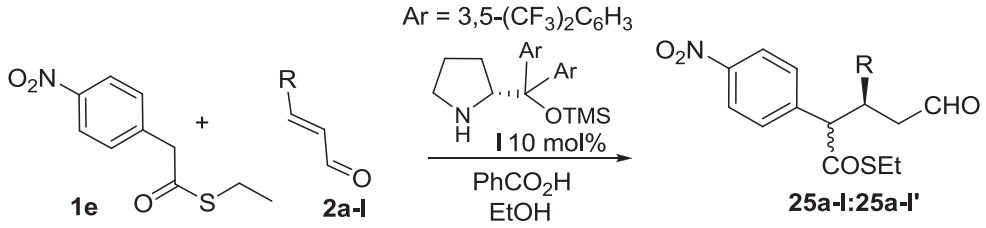
^{1}H NMR (300 MHz): δ 8.20 (d, J = 10.1 Hz, 2H), 7.47 (d, J = 10.1 Hz, 2H), 3.92 (s, 2H), 2.92 (q, J = 6.9 Hz, 2H), 1.25 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz) δ 196.0 (CO), 147.4 (C), 141.3 (C), 130.6 (2CH), 124.0 (2CH), 50.1 (CH_2), 24.0 (CH_2), 14.6 (CH_3).

MS (FAB) *m/z* 226 ($M+1^+$, 100).

HRMS (ESI) Calcd. for $C_{10}H_{12}NO_3S$ [M+1]: 226.0538; found, 226.0535.

[3] D. Swinnen, D. Hilvert, *Org. Lett*. **2000**, *2*, 2439-2442.

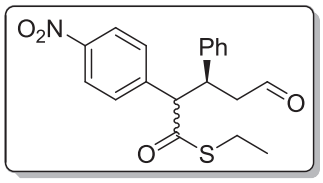
5.2 General procedure for the Michael addition of thioester 1e to α,β-unsaturated aldehydes 2.



To a solution of (*R*)-α-α-bis-[3,5-bis(trifluoromethyl)-phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **I** (0.1 equiv, 0.03 mmol) in EtOH (0.5M) the corresponding *α,β*-unsaturated aldehyde **2a-l** (1.5 equiv, 0.45 mmol) and benzoic acid (0.1 equiv, 0.03 mmol) were sequentially added. After the resulting mixture was stirred at room temperature for 10 min, thioester **1e** (67 mg, 0.3 mmol) was added. The reactions were followed by TLC until the disappearance of the starting thioester **1e**. The resulting Michael adducts were purified by flash column chromatography (10:1 *n*-hexane/EtOAc for aliphatic aldehydes and 8:1 for aromatic) to give the corresponding aldehydes **25a-l:25a'-l'** as mixture of diastereomers in the yields and dr's indicated in Table 4.5.

The enantiomeric excesses were determined in all cases in the corresponding alcohols after the reduction with $NaBH_4$.

(2*R*, 3*S* and 2*S*, 3*S*)- S-Ethyl 2-(4-nitrophenyl)-5-oxo-3-phenylpentanethioate (25f and 25f')



The title compound was obtained as a (70:30) mixture of diastereomers according to the general procedure (Michael addition, 93% yield).

m.p. 121-123 ºC.

Data obtained from the major diastereomer:

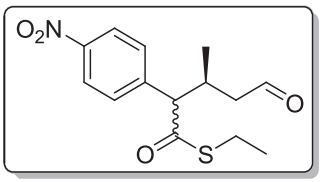
^{1}H NMR (300 MHz): δ 9.41 (s, 1H), 8.23 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.38-7.20 (m, 5H), 4.20 (d, J = 11.1 Hz, 1H), 4.07 (td, J_t = 11.1 Hz, J_d = 4.0, 1H), 2.75-2.48 (m, 3H), 2.41 (dd, J = 17.1, 4.1 Hz, 1H), 0.94 (t, J = 6.8 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.6 (CHO), 197.5 (C), 147.8 (C), 143.4 (C), 139.7 (C), 129.6 (2CH), 128.8 (2CH), 128.3 (2CH), 127.6 (CH), 124.2 (2CH), 65.5 (CH), 47.1 (CH_2), 43.6 (CH), 23.81 (CH_2), 14.3 (CH_3).

MS (ESI) *m/z* 358 ($M+1^+$, 4), 279 (95), 149 (56).

HRMS (ESI) Calcd. for $C_{19}H_{20}NO_4S$ [M+1]: 358.1107; found, 358.1101.

(2*R*, 3*S* and 2*S*, 3*S*)-S-Ethyl 3-methyl-2-(4-nitrophenyl)-5-oxopentanethioate (25a and 25a')



The title compound was obtained as a (62:38) mixture of diastereomers according to the general procedure (72% yield). Data obtained from the mixture of diastereomers.

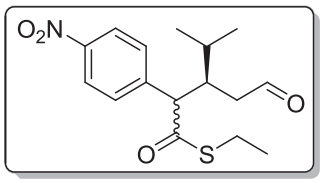
^{1}H NMR δ 9.75 (s, 1H$_{minor}$), 9.57 (s, 1H$_{major}$), 8.19 (d, *J* = 8.8 Hz, 2H$_{minor}$), 8.17 (d, *J* = 8.7 Hz, 2H$_{major}$), 7.51 (d, *J* = 8.8 Hz, 2H$_{major}$, 2H$_{minor}$), 3.78 (d, *J* = 10.5 Hz, 1H$_{major}$), 3.74 (d, *J* = 10.2 Hz, 1H$_{minor}$), 3.00-2.73 (m, 3H$_{major}$, 3H$_{minor}$), 2.58 (dd, J_d = 17.3, 3.6 Hz, 1H$_{minor}$), 2.35 (ddd, *J* = 16.6, 8.6, 2.2 Hz, 1H$_{minor}$), 2.18 (dd, *J* = 17.3, 3.6 Hz, 1H$_{major}$), 2.05 (ddd, *J* = 17.4, 8.6, 2.2 Hz, 1H$_{minor}$), 1.14 (t, *J* = 7.5 Hz, 3H$_{major}$), 1.13 (t, *J* = 7.4 Hz, 3H$_{minor}$), 1.07 (d, *J* = 6.6 Hz, 3H$_{major}$), 0.73 (d, *J* = 6.6 Hz, 3H$_{minor}$).

^{13}C NMR (75 MHz) δ 200. 5 (CHO), 200.4 (CHO), 198.7 (C), 198.5 (C), 147.6 (C), 147.5 (C), 144.2 (2CH), 129.5 (2CH), 124.0 (2CH), 124.0 (2CH), 65.4 (CH), 65.3 (CH), 48.4 (CH), 47.7 (CH), 32.4 (CH_2), 31.9 (CH_2), 18.5 (CH_3), 17.9.3 (CH_3), 14.4 (CH_3), 14.3 (CH_3).

MS (IE) *m/z* 295 (M^+, 1), 206 (100), 160 (5), 142 (40), 118 (25), 115 (40), 89 (28).

HRMS (IE) Calcd. for $C_{14}H_{17}NO_4S$ [M^+]: 295.0878; found, 295.0891.

(2*R*, 3*S* and 2*S*, 3*S*)- S-Ethyl 2-(4-nitrophenyl)-5-oxo-3-isopropylpentanethioate (25e and 25e')



The title compound was obtained as a (68:32) mixture of diastereomers according to the general procedure (50% yield). Data obtained from the mixture of diastereomers.

^{1}H NMR δ 9.63 (s, 1H$_{minor}$), 9.24 (s, 1H$_{major}$), 8.13 (d, *J* = 8.8 Hz, 2H$_{minor}$), 8.09 (d, *J* = 8.8 Hz, 2H$_{major}$), 7.47 (d, *J* = 8.8 Hz, 2H$_{major}$, 2H$_{minor}$), 3.83 (d, *J* = 11.1 Hz, 1H$_{major}$), 3.80 (d, *J* = 10.7 Hz, 1H$_{minor}$), 3.04-2.96 (m, 1H$_{major}$), 2.88-2.68 (m, 5H), 2.47-2.3958 (m, 1H$_{minor}$), 2.32-2.18 (m, 2H), 1.97-1.87 (m, 2H), 1.37 (dsept, J_d = 3.2 Hz, J_{sept} = 6.8 Hz, 1H$_{major}$), 0.87 (t, *J* = 5.8 Hz, 6H), 0.78 (d, *J* = 6.8 Hz, 3H$_{major}$), 0.65 (d, *J* = 6.8 Hz, 3H$_{minor}$).

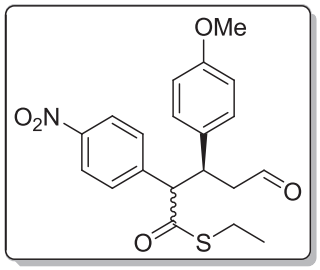
^{13}C NMR (75 MHz) δ 200.9 (CHO), 199.9 (CHO), 198.8 (C), 198.6 (C), 147.6 (2C), 144.4 (C), 144.0 (CH), 129.8 (2CH), 129.4 (2CH), 124.1 (2CH), 124.0 (2CH), 63.5 (CH), 63.1

(CH), 42.1 (CH), 41.8 (CH), 41.6 (CH), 41.4 (CH), 29.1(CH_2), 27.8 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 21.6 (CH_3), 21.2 (CH_3), 16.6 (CH_3), 15.8 (CH_3), 14.3 (CH_3), 14.2 (CH_3).

MS (ESI) *m/z* 324 ($M+1^+$, 20), 262 (24), 216 (20), 79 (3).

HRMS (ESI) Calcd. for $C_{16}H_{22}NO_4S$ [$M+1^+$]: 324.1264; found, 324.1273.

(2*R*, 3*S* and 2*S*, 3*S*)-S-Ethyl -3-(4-methoxyphenyl)-2-(4-nitrophenyl)-5-oxopentanethioate (25g and 25g')



The title compound was obtained as a (64:36) mixture of diastereomers according to the general procedure (Michael addition, 70% yield). Data obtained from the mixture of diastereomers.

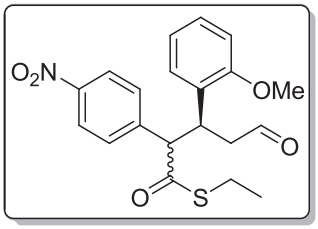
^{1}H NMR (300 MHz): δ 9.55 (s, 1H), 9.40 (s, 1H), 8.22 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 4.14 (d, *J* = 11.1 Hz, 1H), 4.08 (d, *J* = 11.4 Hz, 1H), 4.00 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 2.94-2.84 (m, 3H), 2.74-2.53 (m, 4H), 2.37 (dd, *J* = 17.1, 4.1 Hz, 1H), 1.22 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.9 (CHO), 199.8 (CHO), 198.4 (C), 197.6 (C), 158.9 (C), 158.5 (C), 147.8 (C), 147.2 (C), 143.7 (C), 143.5 (C), 131.6 (C), 131.1 (C), 129.6 (2CH), 129.4 (2CH), 129.3 (2CH), 128.9 (2CH), 124.2 (2CH), 123.5 (2CH), 114.2 (2CH), 114.1 (2CH), 65.7 (CH), 65.6 (CH), 55.2 (CH_3), 55.1 (CH_3), 48.0 (CH_2), 47.2 (CH_2), 43.1 (CH), 42.9 (CH), 24.1 (CH_2), 23.8 (CH_2), 14.4 (CH_3), 14.2 (CH_3).

MS (ESI) *m/z* 388 ($M+1^+$, 4), 149 (56).

HRMS (ESI) Calcd. for $C_{20}H_{22}NO_5S$ [$M+1^+$]: 388.1213; found, 388.1216.

(2*S*, 3*S* and 2*R*, 3*S*)-S-Ethyl 3-(2-methoxyphenyl)-2-(4-nitrophenyl)-5-oxopentanethioate (25k and 25k')



The title compound was obtained as a (64:36) mixture of diastereomers according to the general procedure (Michael addition, 90% yield). Data obtained from the mixture of diastereomers.

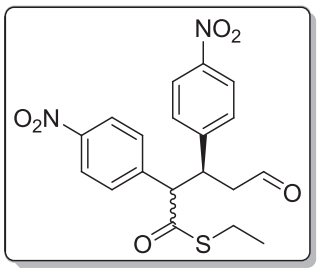
^{1}H NMR (300 MHz): δ 9.54 (s, 1H), 9.38 (s, 1H), 8.20 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.19 (m, 2H), 7.03 (m, 1H), 6.95-6.85 (m, 3H), 6.72-6.64 (m, 2H), 4.57 (d, J = 11.4 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.35 (td, J_t = 11.1 Hz, J_d = 4.2, 1H), 4.22 (td, J_t = 11.1 Hz, J_d = 4.4, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.04-3.74 (m, 5H), 2.72-2.47 (m, 2H), 2.35 (ddd, J = 17.1, 4.4, 1.5 Hz, 1H), 1.21 (t, J = 7.6 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.6 (CHO), 200.5 (CHO), 198.7 (C), 197.8 (C), 157.4 (C), 156.8 (C), 147.7 (C), 147.1 (C), 144.1 (C), 143.8 (C), 130.7 (CH), 129.9 (CH), 129.8 (2CH), 129.2 (2CH), 128.8 (CH), 128.6 (CH), 127.1 (C), 126.9 (C), 123.9 (2CH), 123.2 (2CH), 120.8 (CH), 120.7 (CH), 111.1 (CH), 110.8 (CH), 63.3 (CH), 62.3 (CH), 55.4 (CH_3), 55.2 (CH_3), 46.6 (CH_2), 45.3 (CH_2), 40.8 (CH), 39.4 (CH), 24.0 (CH_2), 23.5 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

MS (ESI) *m/z* 388 (M+1^{+}, 4), 326 (8), 163 (6).

HRMS (ESI) Calcd. for $C_{20}H_{22}NO_5S$ [M+1^{+}]: 388.1213; found, 388.1232.

(2*S*, 3*S* and 2*R*, 3*S*)-S-Ethyl-2,3-bis(4-nitrophenyl)-5-oxopentanethioate (25h and 25h')



The title compound was obtained as a (70:30) mixture of diastereomers according to the general procedure (Michael addition, 75% yield). Data obtained from the major diastereomer.

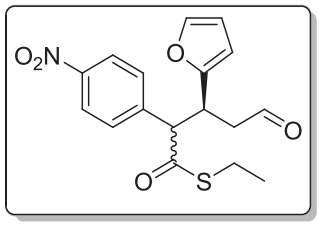
^{1}H NMR (300 MHz): δ 9.41 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 8.50 (d, *J* = 8.8 Hz, 2H), 4.21 (m, 2H), 2.71 (m, 1H), 2.61 (m, 2H), 2.53 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.2 (CHO), 197.0 (C), 148.0 (C), 147.8 (C), 147.2 (C), 142.6 (CH), 129.5 (2CH), 129.4 (2CH), 124.3 (2CH), 123.8 (2CH), 64.5 (CH), 47.0 (CH_2), 42.9 (CH), 23.9 (CH_2), 14.5 (CH_3).

MS (ESI) *m/z* 358 ($M+1^+$, 4), 279 (95), 149 (56).

HRMS (ESI) Calcd. for $C_{19}H_{20}NO_4S$ $[M+H]^+$: 358.1107; found, 358.1101.

(2*S*, 3*S* and 2*R*, 3*S*)-S-Ethyl 3-(furan-2-yl)-2-(4-nitrophenyl)-5-oxopentanethioate (25l and 25l')



The title compound was obtained as a (70:30) mixture of diastereomers according to the general procedure (Michael addition, 60% yield). Data obtained from the mixture of diastereomers (unpurified with **2l**).

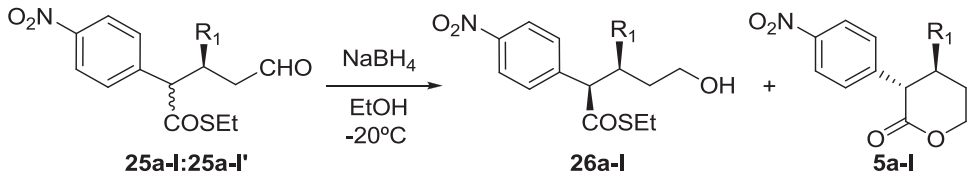
^{1}H NMR (300 MHz): δ 9.60 (s, 1H), 9.50 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 4H), 7.37-7.32 (m, 2H), 6.28 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.14 (d, *J* = 3.3 Hz, 1H), 6.05 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.49 (d, *J* = 3.3 Hz, 1H), 4.29 (d, *J* = 10.3 Hz, 1H), 4.25-4.08 (m, 2H), 4.23 (d, *J* = 10.8 Hz, 1H), 2.99-2.60 (m, 7H), 2.41 (dd, *J* = 17.4, 3.9 Hz, 1H), 1.22 (t, *J* = 7.5 Hz, 3H) 1.09 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz) δ 199.2 (C), 199.1 (CHO), 197.6 (C), 192.9 (CHO), 152.4 (Cx2), 145.9 (Cx2), 142.8 (Cx2), 142.0 (CH), 141.9 (CH), 129.6 (2CH), 129.2 (2CH), 124.1 (2CH), 123.6 (2CH), 110.4 (CH), 110.2 (CH), 108.3 (CH), 108.1 (CH), 63.0 (CH), 62.7 (CH), 45.4 (CH_2), 44.4 (CH_2), 37.3 (CH), 36.7 (CH), 24.1 (CH_2), 23.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

MS (ESI) *m/z* 370 ($M+Na^+$, 4), 360 (12), 149 (4).

HRMS (ESI) Calcd. for $C_{17}H_{17}NO_5SNa$ [$M+Na^+$]: 370.0719; found, 370.0724.

5.3 General procedure for the reduction of the Michael adducts 25.



25a-l:25a-l' **26a-l** **5a-l**

To a cooled solution (-20°C) of the corresponding aldehyde **25a-l**:**25a'-l'** (0.3 mmol) in EtOH (0.05 M), $NaBH_4$ (1.2 equiv) was added. The reaction mixture was stirred at -20°C for 4 hours and quenched at the reaction temperature with water (10 mL). The product was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was finally evaporated and the crude compounds were purified by flash column chromatography using the eluent indicated in each case to afford the corresponding alcohols in quantitative yields. The minor diasteromers were obtained as lactones **5** by in situ cyclization after

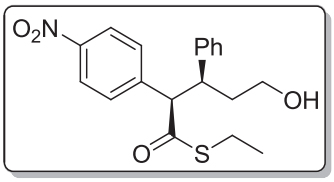
reduction. The enantiomeric excesses of the Michael addition were determined in the mayor diastereomers alcohols **26a-g** by chiral HPLC analysis. The enantiomeric excesses are summarized in table 4.5.

Table 4.5. Reaction details for the Michael addition of S-ethyl 2-(4-nitrophenyl) ethanethioate **1e** to α,β-unsaturated aldehydes **2** and the subsequent reduction.

Entry	R	Product	Temp (°C)	t (h) [a]	Yield (%) [b]	*dr* [c] (%)	*ee* [d] (%)
1	**2f** Ph[f]	**26a**	-20	36	93	70:30	94
2	**2a** Me	**26b**	rt	96	72	63:37	83
3	**2e** ^{i}Pr	**26c**	rt	96	40	68:32	92
4	**2g** *p*-OMe-C_6H_4	**26d**	-20	60	68	63:37	87
5	**2k** (*o*-OMe-C_6H_4	**26e**	15	36	80	xx	88
6	**2h** (*p*-NO_2-C_6H_4	**26f**	15	84	70	70:30	86
7	**2l** 2-Furyl[g]	**26g**	rt	48	52	50:50	70

a Of the Michael addition
b Isolated yield for the Michael addition.
c Determined by ^{1}H NMR analysis.
d Determined by HPLC analysis of the corresponding alcohol

(*2R*, *3S*)-S-Ethyl 5-hydroxy-2-(4-nitrophenyl)-3-phenylpentanethioate (26f)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (4:1 *n*-hexane/EtOAc).

m.p. 134-135 ºC.

^{1}H NMR (300 MHz): δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.35-7.18 (m, 5H), 4.09 (d *J* = 11.4 Hz, 1H), 3.61 (td, J_t = 11.4 Hz, J_d = 3.0 Hz, 1H), 3.43-3.31 (m, 1H), 3.30-3.18 (m, 1H), 2.71-2.42 (m, 2H), 1.73-1.54 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz) δ 197.8 (C), 147.5 (C), 144.3 (C), 140.4 (C), 129.6 (2CH), 128.6 (2CH), 128.4 (2CH), 127.2 (CH), 124.0 (2CH), 66.5 (CH_2), 60.2 (CH), 46.0 (CH_2), 35.8 (CH), 23.7 (CH_2), 14.2 (CH_3).

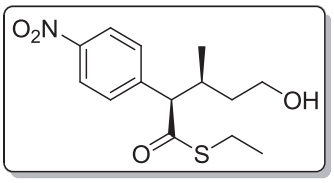
MS (FAB) *m/z* 361 (M+1$^+$, 5), 360 (28), 298 (100).

HRMS (ESI) Calcd. for $C_{19}H_{22}NO_4S$ $[M+H]^+$: 360.1264; found, 360.1277.

The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 19.1 min, τ_{minor} = 15.4 min (94 % *ee*).

$[\alpha]^{20}_D$ +10.6 (*c* = 0.5, $CHCl_3$) (For (*2S*, *3R*) enantiomer).

(*2R*, *3S*)-S-Ethyl 5-hydroxy-3-methyl-2-(4-nitrophenyl) pentanethioate (26a)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (4:1 *n*-hexane/EtOAc).

^{1}H NMR (300 MHz): δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 3.62 (d, *J* = 9.1 Hz, 1H), 3.67-3.49 (m, 2H), 2.94-2,74 (m, 2H), 2.56-2.44 (m, 2H), 1.63-1.45 (m, 1H), 1.42-1.29 (m, 1H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.9 (CO), 147.3 (C), 144.8 (C), 129.6 (2CH), 124.0 (2CH), 66.9 (CH_2), 60.0 (CH), 36.4 (CH), 34.0 (CH_2), 23.8 (CH_2), 17.4 (CH_3), 14.5 (CH_3).

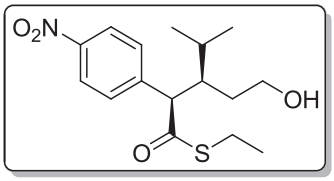
MS (ESI) *m/z* 326 ($M+1^+$, 12), 236 (100), 79 (47).

HRMS (ESI) Calcd. For $C_{14}H_{20}NO_4S$ $[M+H]^+$: 298.1107; found, 298.1035.

The enantiomeric excess was determined by HPLC using a Chiralcel IA column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 16.7 min, τ_{minor} = 14.1 min (83 % *ee*).

$[\alpha]^{20}_D$ -66.9 (*c* = 2.0, $CHCl_3$).

(2*R*,3*R*)-S-Ethyl 5-hydroxy-3-isopropyl-2-(4-nitrophenyl)pentanethioate (26e)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (4:1 *n*-hexane/EtOAc).

m.p. 86-87 ºC.

^{1}H NMR (300 MHz): δ 8.17 (d, *J* = 8.5 Hz, 2H), 8.18 (d, *J* = 8.5 Hz, 2H), 3.82 (d, *J* = 11.3 Hz, 1H), 3.24-3.12 (m, 1H), 3.11-2.98 (m, 1H), 2.96-2.72 (m, 2H), 2.41-2.24 (m, 1H), 1.94 (dsept, J_{sept} = 7.1 Hz, J_d = 2.8 Hz, 1H), 1.67-1.42 (m, 2H), 1.18 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NRM (75 MHz) δ 199.3 (CO), 147.7 (C), 144.9 (C), 130.4 (2CH), 123.7 (2CH), 64.2 (CH_2), 62.2 (CH), 43.7 (CH), 30.6 (CH_2), 29.6 (CH), 23.9 (CH_2), 21.2 (CH_3), 16.8 (CH_3), 14.2 (CH_3).

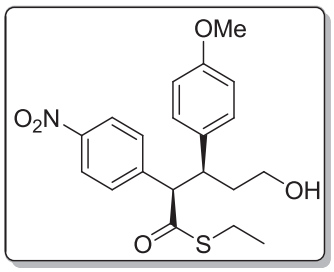
MS (ESI) *m/z* 326 ($M+1^+$, 25), 264 (100).

HRMS (ESI) Calcd. for $C_{16}H_{24}NO_4S$ $[M+H]^+$: 326.1420; found, 326.1418.

The enantiomeric excess was determined by HPLC using a Chiralcel AD column [hexane/*i*PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 8.8 min, τ_{minor} = 5.8 min (92 % *ee*).

$[\alpha]^{20}_D$ -20.0 (*c* = 1.0, $CHCl_3$).

(2*R*, 3*S*)-S-Ethyl 5-hydroxy-3-(4-methoxyphenyl)-2-(4-nitrophenyl) pentanethioate (26g)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (6:1 *n*-hexane/EtOAc).

m.p. 115-116 ºC.

^{1}H NMR (300 MHz): δ 8.22 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.58 (td, J_t = 11.2 Hz, J_d = 3.6 Hz, 1H), 3.44-3.33 (m, 1H), 3.32-3.21 (m, 1H), 2.72-2.47 (m, 2H), 1.69-1.50 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.0 (CO), 158.7 (C), 147.7 (C), 144.5 (C), 132.2 (C), 129.6 (2CH), 129.3 (2CH), 124.0 (2CH), 114.1 (2CH), 66.9 (CH), 60.2 (CH_2), 55.3 (CH_3), 45.2 (CH_2), 35.9 (CH), 23.7 (CH_2), 14.4 (CH_3).

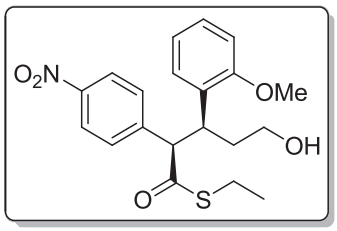
MS (ESI) *m/z* 390 (M+1$^+$, 32), 328 (100), 135 (45).

HRMS (ESI) Calcd. For $C_{20}H_{24}NO_5S$ $[M+H]^+$: 390.1369; found, 390.1373.

The enantiomeric excess was determined by HPLC using a Chiralcel IA column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 23.5 min, τ_{minor} = 18.7 min (87 % *ee*).

$[\alpha]^{20}_D$ -1.97 (*c* = 1.0, $CHCl_3$).

(2*R*, 3*S*)-S-Ethyl 5-hydroxy-3-(2-methoxyphenyl)-2-(4-nitrophenyl) pentanethioate (26k)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (6:1 *n*-hexane/EtOAc).

^{1}H NMR (500 MHz)($C_2D_2Cl_4$): δ 8.13 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.17 (td, J_t = 8.2 Hz, J_d = 1.7, 1H), 7.11 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.86 (m, 2H), 4.42 (d, *J* = 10.6 Hz, 1H), 3.32-3.27 (m, 1H), 3.23-3.19 (m, 1H), 2.65-2.58 (m, 1H), 2.54-2.46 (m, 1H), 1.78-1.71 (m 1H), 1.54-1.48 (m 1H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz) δ 198.0 (C), 158.1 (C), 148.0 (C), 144.9 (C), 129.9 (2CH), 128.6 (C), 128.3 (CH), 123.8 (2CH), 121.1 (CH), 111.9 (CH), 64.2 (CH), 60.6 (CH_2), 55.9 (CH_3), 34.9 (CH_2), 29.6 (CH), 23.6 (CH_2), 14.2 (CH_3).

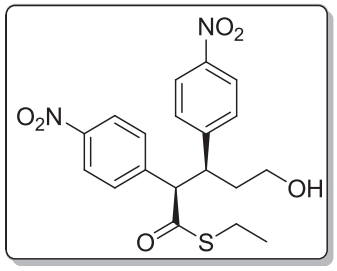
MS (ESI) *m/z* 390 ($M+1^+$, 14), 328 (100), 149 (49), 135 (54), 64 (56).

HRMS (ESI) Calcd. for $C_{20}H_{24}NO_5S$ $[M+H]^+$: 390.1369; found, 390.1371.

The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 13.8 min, τ_{minor} = 18.9 min (88 % *ee*).

$[\alpha]^{20}_D$ -12.4 (*c* = 1.0, $CHCl_3$).

(2*R*, 3*S*)-S-Ethyl 5-hydroxy-2,3-bis(4-nitrophenyl) pentanethioate (26h)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (6:1 *n*-hexane/EtOAc).

m.p. 157-158 ºC.

^{1}H NMR (300 MHz): δ 8.23 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7,48 (d, *J* = 8.19 Hz, 2H), 4.12 (d, *J* = 9.8, 1H), 3.82 (td, J_t = 9.8 Hz, J_d = 5.1 Hz, 1H), 3.44-3.33 (m, 1H), 3.24-3.12 (m, 1H), 2.69-2.47 (m, 2H), 1.71-1.54 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz) δ 197.4 (CO), 148.5 (C), 147.8 (C), 147.1 (C), 143.5 (C), 129.6 (2CH), 129.5 (2CH), 124.2 (2CH), 123.8 (2CH), 65.6 (CH_2), 59.4 (CH), 45.5 (CH_2), 35.6 (CH), 23.8 (CH_2), 14.2 (CH_3).

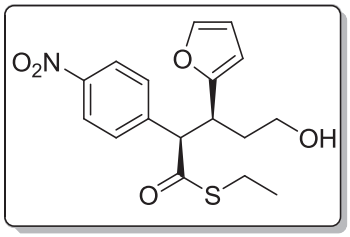
MS (ESI) *m/z* 405 ($M+1^+$, 13), 343 (88), 282 (100), 225 (44), 149 (90), 79 (42), 64 (77).

HRMS (ESI) Calcd. for $C_{19}H_{21}NO_6S$ $[M+H]^+$: 405.1138; found, 405.1114.

The enantiomeric excess was determined by HPLC using a Chiralcel IC column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 56.9 min, τ_{minor} = 43.6 min (86 % *ee*).

[α]$^{20}_{D}$ -14.5 (*c* = 0.7, $CHCl_3$).

(2*S*, 3*S* and 2*R*, 3*S*) *S*-ethyl 3-(furan-2-yl)-5-hydroxy-2-(4-nitrophenyl) pentanethioate (26l)



The title compound was obtained following the general procedure. The crude was purified by flash chromatography (4:1 *n*-hexane/EtOAc).

^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.24 (dd, J_d = 0.61 Hz, J_d = 1.71, 1H), 6.29 (dd, J_d = 1.71 Hz, J_d = 3.20, 1H), 6.17 (dd, J_d = 0.61 Hz, *J*d = 3.20, 1H), 4.21 (d, *J* = 10.7, 1H), 3.79 (td, J_t = 10.7 Hz, J_d = 4.1 Hz, 1H), 3.50-3.27 (m, 2H), 2.81-2.58 (m, 2H), 1.77-1.66 (m 1H), 1.54-1.42 (m 1H), 1.05 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.0 (CO), 153.3 (C), 147.5 (C), 143.7 (C), 142.0 (CH), 129.7 (2CH), 124.0 (2CH), 110.2 (CH), 108.1 (CH), 64.1 (CH), 60.2 (CH_2), 39.3 (CH_2), 34.0 (CH_2), 23.7 (CH), 14.2 (CH_3).

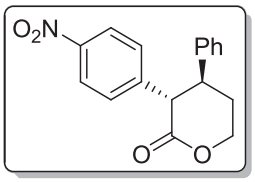
MS (FAB) *m/z* 350 (M+1, 22), 327 (67), 283 (100).

HRMS (FAB) Calcd. for $C_{17}H_{20}NO_5$ [M+1]: 350.1062; found: 350.1058.

The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 13.8 min, τ_{minor} = 18.9 min (70 % *ee*). **[α]$^{20}_{D}$** -10.8 (*c* = 2.0, $CHCl_3$).

5.4 Transformations of the thioester moiety

(3*S*,4*S*)-3-(4-Nitrophenyl)-4-phenyltetrahydro-2H-pyran-2-one (5f)



To a solution of the alcohol **4a** (0.2 mmol) in dry THF (0.03 M) NaH (1.1 equiv) was added. After stirring the resulting mixture at room temperature for 1h, the reaction was quenched by addition of a saturated dissolution of NH_4Cl (10 mL) and extracted with EtOAc (2 x 15 mL). The organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was finally evaporated and the crude was purified by flash chromatography (4:1 *n*-hexane/EtOAc) to afford the desired product in 50% yield.

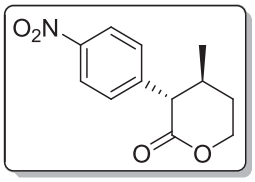
^{1}H NMR (300 MHz): δ 8.11 (d, *J* = 9 Hz, 2H), 7.30 (d, *J* = 8.2, 2H), 7.19 (m, 3H), 7.04 (d, *J* = 7.8, 2H), 4.71 (m, 2H), 4.02 (d, *J* = 11.8 Hz, 1H), 3.32 (m, 1H), 2.39 (m, 2H).

^{13}C NMR (75 MHz): δ 169.6 (CO), 141.2 (C), 133.4 (C), 133.3 (C), 128.8 (2CH), 128.6 (2CH), 127.5 (2CH), 127.2 (2CH), 126.0 (CH), 68.8 (CH), 46.1 (CH), 45.3 (CH), 35.5 (CH_2).

MS (FAB) *m/z* 298 (M+1, 100), 154 (27), 136 (30), 55 (100).

HRMS (FAB) Calcd. for $C_{17}H_{16}NO_4$ [M+1]: 298.1079; found: 298.1072.

(3*S*,4*S*)-4-Methyl-3-(4-nitrophenyl)-tetrahydropyran-2-one (5a)



Following the same procedure described for **4a** but starting from alcohol **4b**, the lactone **5b** was obtained as a single diastereomer (85% yield).

^{1}H NMR (300 MHz): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 4.58-4.42 (m, 2H), 3.38 (d, *J* = 11 Hz, 1H), 2.33-2.22 (m, 1H), 2.20-2.07 (m, 1H), 1.74-0.98 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (75 MHz): δ 171.0 (CO), 147.3 (C), 145.2 (C), 130.0 (2CH), 123.9 (2CH), 68.2 (CH_2), 55.6 (CH), 34.3 (CH), 30.9 (CH_2), 20.3 (CH_3).

MS (FAB) *m/z* 236 (M+1, 100), 219 (13), 107 (35), 71 (44), 57 (58), 55 (85).

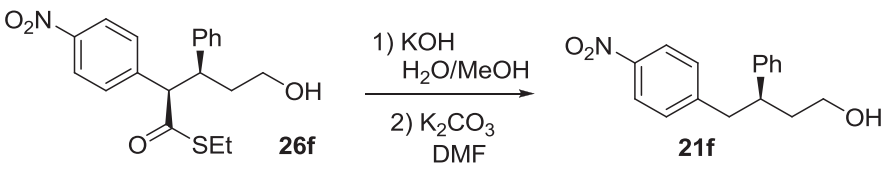
HRMS (FAB) Calcd. for $C_{12}H_{13}NO_4$ [M+1]: 236.0917; found: 236.0923.

The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH = 90:10]; flow rate 1.0 mL/min; τ_{major} = 30.3 min, τ_{minor} = 26.4min (83 % *ee*).

$[\alpha]_D^{20}$ +20 (*c* =1.0, $CHCl_3$).comentar correlacion

IR (film) 2964, 1723, 1526, 1347 cm^{-1}.

(*R*)-4-(4-Nitrophenyl)-3-phenylbutan-1-ol (21f)



To a solution of the alcohol **26f** (36 mg, 0.1 mmol) in MeOH (0.5 mL) were added KOH (1.2 equiv) and water (2 mL). The reaction was stirred for 2 hours until the disappearance of the starting material. After this time, the solvent was evaporated and K_2CO_3 (2.0 equiv) and DMF (5 mL) were added. The reaction was performed in an ultrasonic bath during 6 h at room temperature. Afterward water was added to the reaction mixture and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was finally evaporated and the crude compound was purified by flash chromatography (4:1 *n*-hexane/EtOAc). (80% yield).

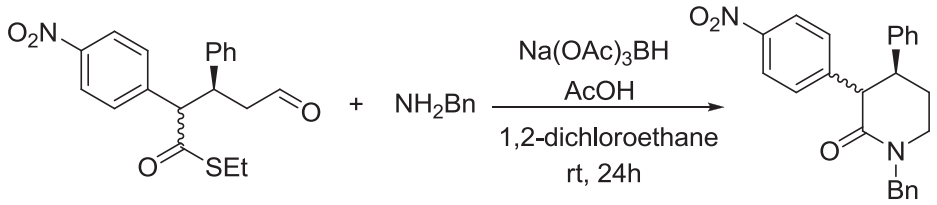
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J = 8.7 Hz, 2H), 7.21 (m, 3H), 7.08 (m, 4H), 3.56 (m, 1H), 3.44 (m, 1H), 3.03 (m, 3H), 1.95 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2 (C), 146.4 (C), 142.9 (C), 129.9 (2 CH), 128.6 (2 CH), 127.7 (2 CH), 126.8 (CH), 123.3 (2 CH), 60.7 (CH_2), 44.2 (CH), 43.5 (CH_2), 38.5 (CH_2). MS (ESI): m/z 272 (M+1), 149 (21), 79 (100), 64 (22).

HRMS (ESI): Calcd. C16H18NO3 (M+1): 272.1281; found: 272.1290.

The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH = 95:5]; flow rate 1.0 mL/min; τ_{major} = 20.1 min, τ_{minor} = 17.9 min (90 % *ee*).

(3*S*, 4*S* and 3*R*, 4*S*)-1-Benzyl-3-(4-nitrophenyl)-4-phenylpiperidin-2-one (27a:27a')



To a solution of **25f:25f'** (72 mg, 0.2 mmol) in 1,2-dichloroethane (166 mL) at 0ºC, benzylamine (3 equiv, 0.6 mmol), acetic acid (12 µl, 0.2 mmol) and sodium triacetoxyborohydride (5 equiv) were added. The resulting mixture was stirred at rt for 24 h. After this time, the reaction mixture was quenched by adding 10 mL of an aqueous solution of $NaHCO_3$ and the product was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$.The solvent was evaporated in vacuum to give the crude product, which was purified by flash chromatography (4:1 *n*-hexane/EtOAc) to afford the lactam 2**7f:27f'** as a (70:30) mixture of diastereomers (81% yield).

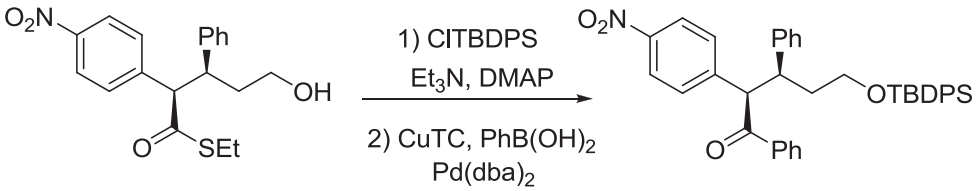
^{1}H NMR (300 MHz): δ 8.05 (d, J = 8.7 Hz, 2H$_{major}$), 7.90 (d, J = 8.5 Hz, 2H$_{minor}$), 7.45-7.31 (m, 6H$_{major}$, 5H$_{minor}$), 7.22-7.15 (m, 2H$_{major}$, 3H$_{minor}$), 7.12 (d, J = 9.0 Hz, 2H$_{major}$), 6.98-6.93 (m, 2H$_{major}$), 6.81 (d, J = 8.7 Hz, 2H$_{minor}$), 6.77-6.73 (m, 2H$_{minor}$), 5.03 (d, J = 14.3 Hz, 1H$_{minor}$), 4.75 (d, J = 14.1 Hz, 1H$_{major}$), 4.56 (d, J = 14.5 Hz, 1H$_{major}$), 4.52 (d, J = 13.1 Hz, 1H$_{minor}$), 4.21 (d, J = 5.7 Hz, 1H$_{minor}$), 3.93 (d, J = 11.3 Hz, 1H$_{major}$), 3.49-3.64 (m, 2H$_{major}$), 3.48-3.38 (m, 3H$_{minor}$), 3.15 (td, J_t = 11.4 Hz, J_d = 4.1 Hz, 1H$_{major}$), 2.37-2.08 (m, 2H$_{major}$, 2H$_{minor}$).

^{13}C NMR (75 MHz): δ 169.3 (CO), 169.1 (CO), 147.9 (C), 147.2 (C), 146.7 (C), 145.0 (C), 141.6 (C), 139.7 (C), 137.0 (C), 136.9 (C), 130.7 (2CH), 129.9 (2CH), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.5 (2CH), 128.4 (2CH), 127.9 (2CH), 127.8 (2CH), 127.4 (2CH), 127.2 (2CH), 126.9 (2CH), 123.4 (2CH), 122.6 (2CH), 56.4 (CH_2), 54.5 (CH), 50.9 (CH_2), 50.7 (CH), 47.8 (CH_2), 46.7 (CH_2), 46.5 (CH), 43.2 (CH), 29.6 (CH_2), 22.3 (CH_2).

MS (EI) *m/z* 386 (M^+, 46), 91 (100).

HRMS (EI) Calcd. for $C_{24}H_{22}NO_3$ [M^+]: 386.1630; found, 386.1647.

(2*R*, 3*S*)-4-(tert-Butyldiphenylsilyloxy)-2-(4-nitrophenyl)-1,3-diphenyl butan-1-one (28f)



A solution of the alcohol **26f** (36 mg, 0.10 mmol), tert-butyl(choro)diphenylsilane (1.2 equiv, 0.12 mmol), triethylamine (2.0 equiv, 0.20 mmol) and DMAP (6 mg, 0.05 mmol) dichloromethane (2 mL) was stirred overnight at room temperature. The

resulting mixture was filtered on a short pad of silica gel using CH_2Cl_2 as eluent to obtain the protected alcohol as a single diastereomer in quantitative yield.

The protected alcohol (63 mg, 0.10 mmol), cooper (I) thiophene-2-carboxylate (32 mg, 0.17 mmol), phenylboronic acid (13 mg, 0.11 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.2 mg, 0.025 mmol), and triethylphosphite (3.3 mg, 0.2 mmol) were placed in a sealed tube previously flushed with argon. DMF (300 µl) was added and the mixture was stirred for 3 days at 100ºC. Et_2O (10 mL) was added and the suspension was washed with water (3 x 15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The resulting solid was purified by column chromatography (12:1 *n*-hexane/EtOAc) to afford **28f** as a single diastereomer in 65% yield.

^{1}H NMR (300 MHz): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.60 (dd, *J* = 8.6, 6.5 Hz, 3H), 7.44 (t, *J* = 7.05 Hz, 6H), 4.05 (d, *J* = 11.9 Hz, 1H), 3.80-3.68 (m, 1H), 3.40-3.20 (m, 2H), 2.68-2.41 (m, 2H), 0.99 (s, 9H).

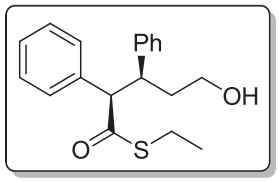
^{13}C NMR (75 MHz): δ 211.9 (CO), 152.4 (C), 151.9 (C), 147.2 (C), 145.3 (Ch), 141.6 (CH), 137.0 (CH), 133.6 (C), 133.2 (2CH), 129.9 (2CH), 129.6 (2CH), 129.5 (2CH), 128.5 (2CH), 128.4 (2CH), 128.3 (2CH), 128.1 (2CH), 127.5 (2CH), 127.4 (2CH), 124.1 (2CH), 60.9 (CH), 59.5 (CH), 45.4 (CH_2), 36.1 (CH), 26.7 ($3CH_3$).

MS (ESI): m/z 614 (M+1), 242 (100), 149 (72).

HRMS (ESI): Calcd. $C_{39}H_{40}NO_4Si$ (M+1): 614.2721; found: 614.26.

5.5 Transformations of the nitro group

(2*R*, 3*S*)-S-Ethyl 5-hydroxy-2,3-diphenylpentanethioate 30f.



To a solution of **26f** (0.30 mmol, 110 mg) in CH_2Cl_2 (4mL) was added sequentially Zn dust (14 equiv, 270 mg) and AcOH (28 equiv, 490 µL) at 0 °C. After stirring at room temperature for 30 minutes, the reaction mixture was filtered through Celita and the filtrate was neutralized with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the pure amine **29f** in quantitative yield. The crude was treated with aqueous 50% H_3PO_2 (2.5 mL) and $NaNO_2$ (2.6 equiv, 54 mg) was added at 0 °C. After 2 h, K_2CO_3 was added to the reaction mixture. The aqueous layer was extracted with Et_2O (15 mL x 3). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 6:1) to afford **30f** (75% yield).

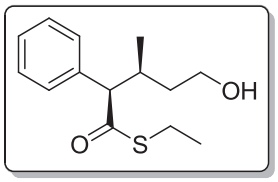
^{1}H NMR (300 MHz): δ 7.46-7.27 (m, 10H), 3.98 (d J = 11.3 Hz, 1H), 3.58 (dt, J_d = 11.3 Hz, J_t = 7.7 Hz, 1H), 3.40-3.22 (m, 2H), 2.69-2.44 (m, 2H), 1.67-1.60 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz) δ 198.9 (C), 141.4 (C), 137.1 (C), 128.8 (2CH), 128.6 (2CH), 128.5 (2CH), 128.4 (2CH), 127.8 (CH), 126.9 (CH), 66.9 (CH), 60.7 (CH_2), 45.8 (CH), 36.2 (CH_2), 23.4 (CH_2), 14.3 (CH_3).

MS (ESI) *m/z* 315 ($M+1^+$, 19), 297 (45), 253 (100).

HRMS (ESI) Calcd. for $C_{19}H_{23}O_2S$ [M+1]: 314.1346; found, 314.1356.

(2*R*, 3*S*)-5-oxo-2,3-diphenylpentanoic acid 30a.



Following the same procedure described above for **30f**, **30a** was obtained in 60% yield from **26a**.

^{1}H NMR (300 MHz): δ 7.34-7.29 (m, 5H), 3.65-3.48 (m, 2H), 3.48 (d *J* = 10.6 Hz, 1H), 2.93-2.73 (m, 2H), 2.56-2.42 (m, 1H), 1.50-1.39 (m, 2H), 1.19 (t, *J* = 7.4 Hz, 3H), 1.07 (d, J = 6.6 Hz, 1H).

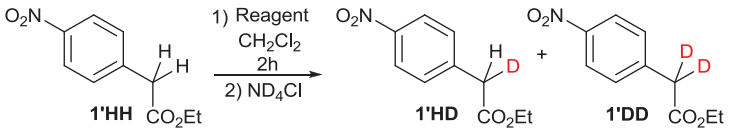
^{13}C NMR (75 MHz) δ 200.2 (C), 137.5 (C), 128.7 (2CH), 128.6 (2CH), 127.5 (CH), 67.4 (CH), 60.6 (CH_2), 36.8 (CH_2), 33.5 (CH), 23.6 (CH_2), 18.0 (CH_3), 14.5 (CH_3).

MS (ESI) *m/z* 253 ($M+1^+$, 22), 235 (43), 191 (100).

HRMS (ESI) Calcd. for $C_{14}H_{21}O_2S$ [M+1]: 253.1256; found, 253.1266.

6. ^{1}H NMR studies of the effect of TBAB in the Michael addition

6.1 Deuteration experiments of the deprotonation reaction.



	1'HH	1'HD	1'DD
A: **TBAB** (1 equiv)	100	0	0
B: **LiOAc** (1 equiv)	100	0	0
C: **TBAOH** (1 equiv)	10	20	70
D: **TBAOH** (1 equiv)	15	25	60

p-Nitrophenyl ethyl acetate **1d'** was dissolved in CH_2Cl_2 and the corresponding additive was added. The reaction was quenched with ND_4Cl as deuterium source after 2h of stirring. The solution was filtered through a short pad of silica gel and the spectra were registered in a Bruker 500 instrument.

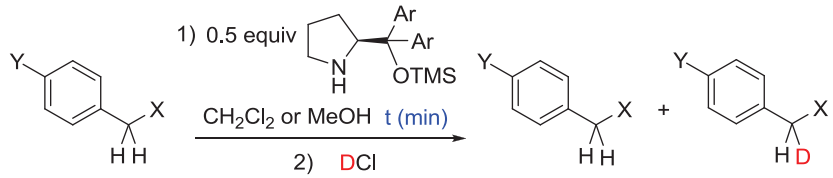
6.2 Procedure for the deuteration experiments under the reaction conditions:

To a solution of catalyst (*R*)-**II**, 10 mol %, 0.02 mmol) in CD_3OD (200µL) crotonaldehyde **2a** (1.5 equiv, 0.3 mmol) was added. After the resulting mixture was stirred at room temperature for 15 min *p*-nitrophenyl ethyl acetate 1' (0.2 mmol, 42 mg) and the corresponding additive (10 mol%, 0.02mmol) were sequentially added. After 20 h the reactions were filtered through a plug of silica gel and the solvent evaporated under vacuum. The fraction of deuterated products and conversion were determined by ^{1}H NMR integration of the crude mixture in $CDCl_3$.

We carried out the deuteration experiment under the Michael reaction conditions using CD_3OD as a continuous source of deuterium. However, it is worth to note that CD_3OD has a similar pKa value to the nucleophile and therefore it cannot quantitatively deuterate the anion. Therefore, the deuteration values give a qualitative idea of the amount of anion formed in each case.

Experimental Part of Chapter III

7. ^{1}H NMR studies for the determination of the relative acidity of the nucleophiles



A solution of the corresponding catalyst **I** or **II** (0.5 equiv) and the corresponding nucleophile **1a-g** (0.5M) in dichloromethane-d_2 was stirred during the indicated time in each case (4h for catalyst **II** or 48h for catalyst **I**). The reaction was quenched with a solution of DCl (10% in D2O) and filtered through a short pad of silica gel. All the ^{1}H NMR spectra were performed in a *Bruker 500* instrument. The deuteration values were calculated comparing with the signals of the non-deuterated starting material.

The same procedure was performed in methanol-d_4 for all nucleophiles. It is worth noting that in this case the deuterium source is continuous during the experiments and therefore the deuteration degrees can be higher than 50% .

8. Systematic study of Michael addition with the different nucleophiles

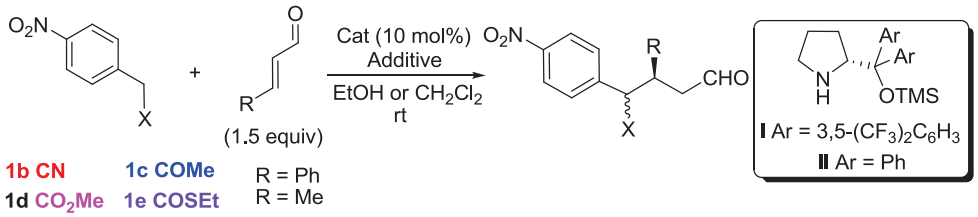
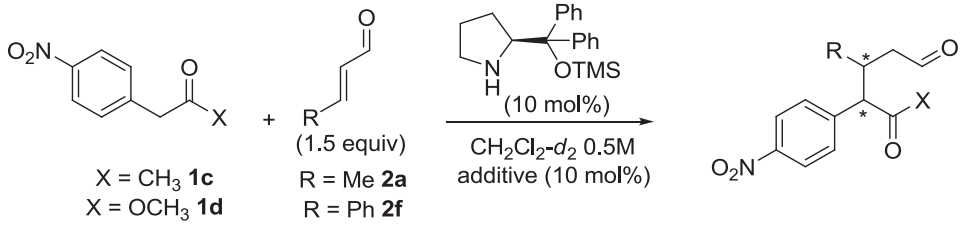


Table 4.6. Conversion values obtained in the study.

cat I		1b		1c		1e		1d	
		EtOH	CH_2Cl_2	EtOH	CH_2Cl_2	EtOH	CH_2Cl_2	EtOH	CH_2Cl_2
R'	Additive	5'	15'	5'	15'	5'	15'	48h	48h
Ph	$PhCO_2H$ (10 mol%)	55	60	100	80	25	46	50	<5
	---	20	50	94	70	5	45	56	<5
	TBAB (1 equiv)	60	45	82	60	10	65	80	20
	LiOAc (10 mol%)	<10	-	80	-	5	-	90	-
		6h	6h	6h	6h	6h	6h	48h	48h
Me	$PhCO_2H$ (10 mol%)	30	<10	74	<10	40	<5	nr	<5
	---	20	<10	57	<10	36	<5	nr	<5
	TBAB (1 equiv)	<10	40	30	50	91	20	10	20
	LiOAc (10 mol%)	<10	-	30	-	93	-	67	-
cat II									
R'	Additive	5'	15'	5'	15'	5'	15'	2h	2h
Ph	$PhCO_2H$ (10 mol%)	90	75	93	75	94	75	73	65
	---	75	70	86	70	67	45	46	42
	TBAB (1 equiv)	85	50	76	60	20	55	64	80
	LiOAc (10 mol%)	95	-	86	-	92	-	70	-
		6h	6h	6h	6h	6h	6h	16h	16h
Me	$PhCO_2H$ (10 mol%)	>95	50	100	52	35	20	23	<5
	---	>95	95	71	95	61	70	42	<5
	TBAB (1 equiv)	>95	40	54	50	80	50	80	65
	LiOAc (10 mol%)	>95	-	100	-	95	-	87	-

9. NMR studies of the Michael addition of 1c and 1d with cinnamaldehyde 2f and crotonaldehyde 2a.

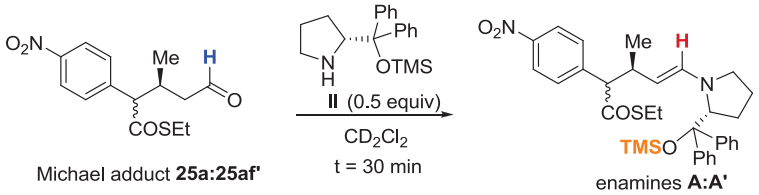


The reaction were performed in dichloromethane-d2 as solvent, in the presence of catalyst ***(S)*-II** (10 mol%) and different additives. Freshly distilled aldehydes 2a and 2f were used. NMR spectra were acquired at 25°C on a Bruker 400 spectrometer. The conversions were calculated comparing the signals of the starting nucleophiles with the corresponding Michael adducts.

10. NMR studies of the retro-Michael reaction of 25f and 25a with catalyst I and II and different additives.

General procedure for the NMR experiments:

The experiments were carried out in dichloromethane-d_2 and methanol-d_4. 0.5 mL of a stock solution of Michael adducts **25f:25f'** or **25a:25a'** in CD_2Cl_2 or MeOD was placed in an NMR tube (0.5 M). 100 µL of a stock solution of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**II**) or (*R*)-α-α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**I**) (and the corresponding additive in each case) was added to the NMR tube, the solution was shaken and this time was taken as time zero of the reaction.



To identify and characterize the product enamines xx the retro-reaction of the Michael adducts xx was performed in the presence 0.5 equivalents of catalyst **II**. The spectrum was acquired after 30 minutes in a Bruker 500 spectrometer (Figure 4.1).

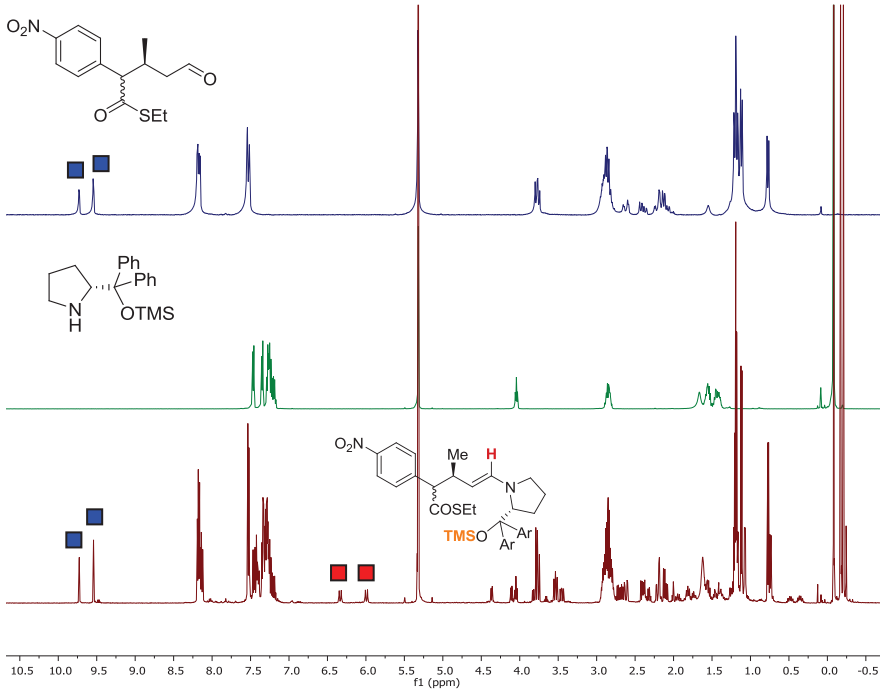


Figure 4.1

The most characteristic signals of the enamine were clearly identify (Figure 4.2).

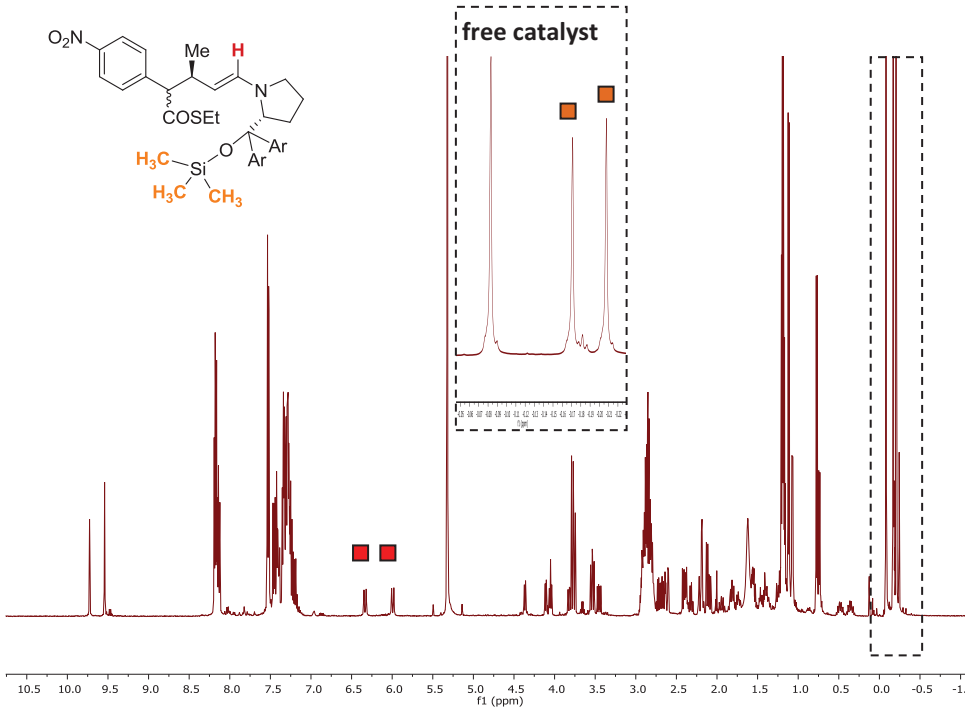


Figure xx. 1H NMR of the crude spectrum of 4.2

The rest of the signal of the corresponding diastereomeric enamines were identified by ^{1}H NMR and TOCSY experiments. The TOCSY (Total Correlation Spectroscopy) experiment is similar to COSY, in that it maps out which hydrogens are coupled to each other, but in a TOCSY spectrum, correlations are seen between all hydrogens in the same spin system, not just those directly coupled to each other. For example, we could identify the hydrogens form the enamine system and the hydrogens from the pyrrolidine system. Finally a NOE difference spectrum was carried out to correlate the enamine spin system with the corresponding pyrrolidine system.

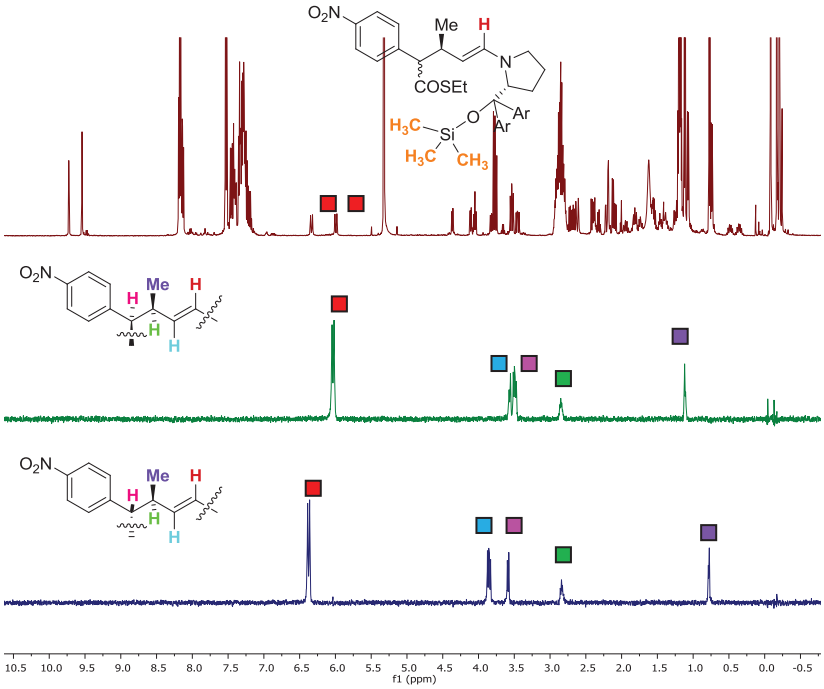


Figure xx. Spin system of the enamine.

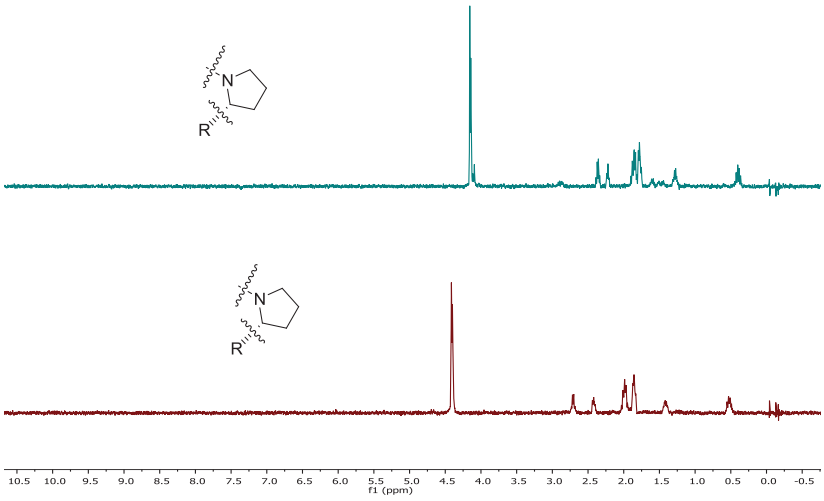


Figure 4.3. Spin system of the pyrrolidine.

Correlation between the enamine and the pyrrolidine systems:

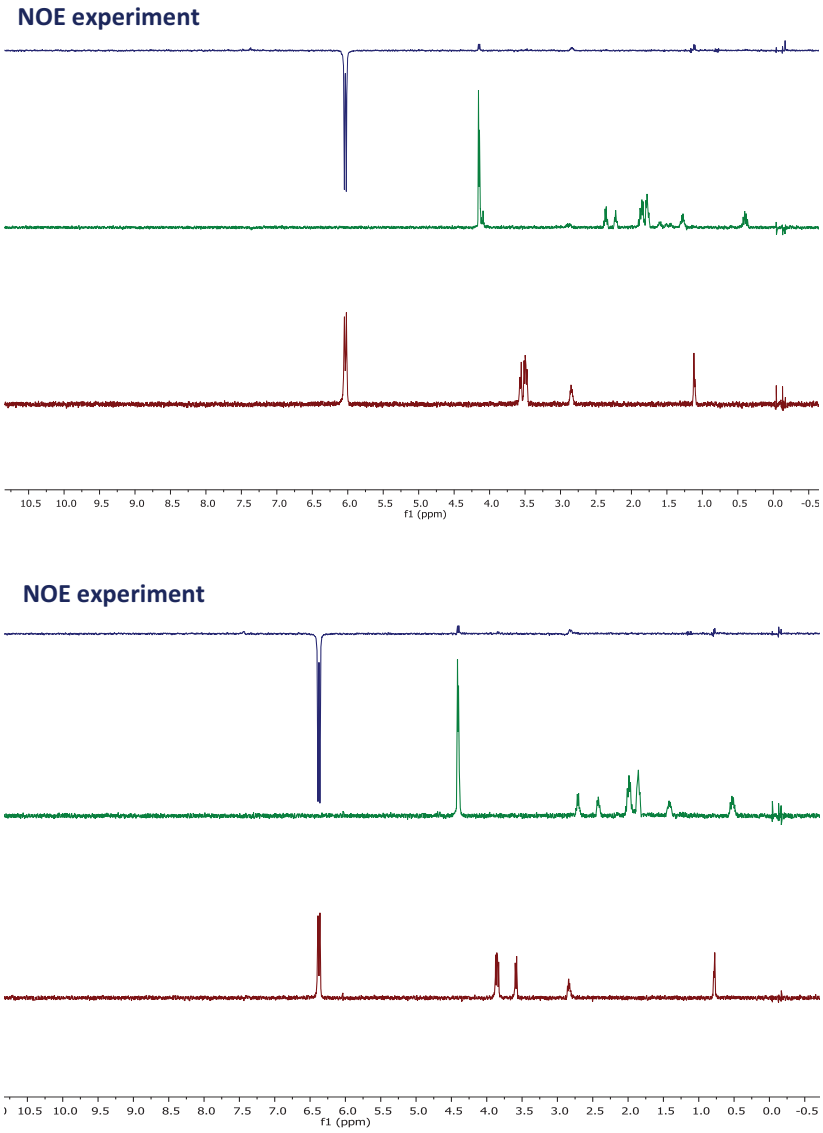
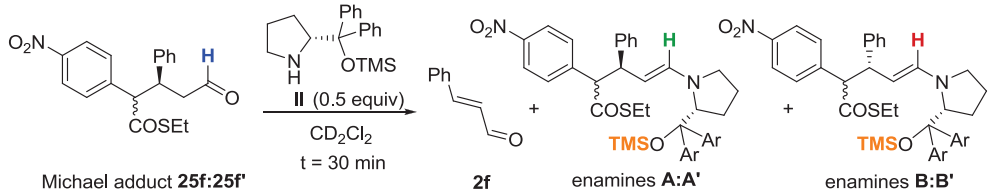


Figure 4.5. Correlation between the systems



For the retro-reaction of the Michael adducts xx with 0.5 equivalents of catalyst ***(S)*-II** four set of signals were observed, due to equilibration of the product enamines. Moreover, in the crude spectrum of the retro-reaction, cinnamaldehyde **2f** was also observed (Figure 4.6).

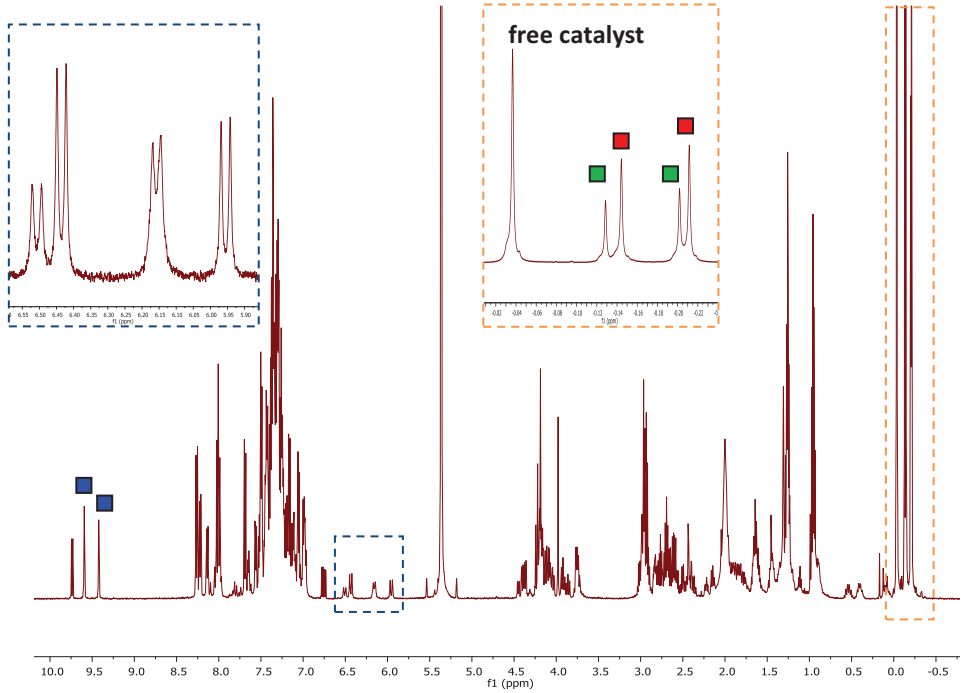


Figure 4.6.

The effect of the additives in the retro reaction of **25f** with catalyst **II** was also studied (Figure 4.7).

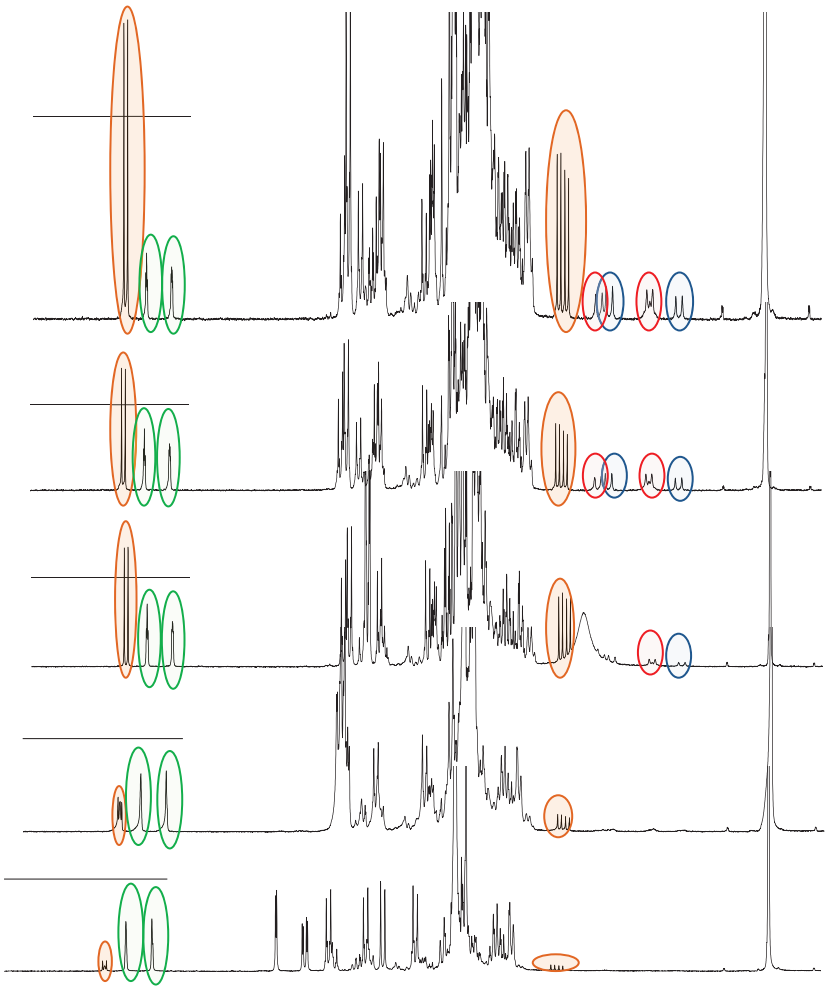


Figure 4.7. Sections of the ^{1}H NMR spectra of the retro-Michael reaction of **xx** in the presence of catalyst **II** (0.5 equiv) and different additives (0.5 equiv) at 60 minutes in CD_2Cl_2 at 300 K. a) Without additive b) TBAB (1 equiv) c) $PhCO_2H$ d) p-NO_2BZOH e) 2,4-$(NO_2)_2$BzOH.

11. Introduction to RPKA

Reaction progress kinetic analysis (RPKA) is defined as "the analysis of experimental data acquired over the course of a reaction under synthetically relevant (non-pseudo zero order) substrate concentrations.[4] It enables the extraction of significant kinetic information from a small number of experiments. It relies on two important concepts: (1) the concept of excess and (2) the concept of graphical rate equations.

In the case of a general chemical transformation A + B → C; the concentrations of **A** and **B** are related during the course of the reaction through the parameter "excess". **Excess** is defined for a constant volume reaction as the difference in the initial concentration of the two reactive substrates, as in the following expressions:

$$e = [A]_0 - [B]_0 \rightarrow [A] - [B] = [A]_0 - [B]_0 = e \rightarrow [B] = [A] + e$$

Excess can be zero, a positive or a negative number. It is a constant value for a given set of reaction conditions. Excess has the same concentration units as [A] and [B] (typically M or mM), and is not identical to the number of equivalents or to a percentage excess, both of which vary during the reaction.

The second important point is the concept of developing **graphical rate equations**. The curves generated during experiments are usually manipulated in an Excel worksheet and plotted as a function of reaction rate vs. concentration of one of the substrates. The key is to find what function generates graphical overlay of the plots of reactions carried out under different defined conditions; once this function is obtained, valuable information about the reaction can be extracted. In the next sections we show how to interpret graphical overlay.

Two different types of experiments can be run: (1) '**same excess**' experiments or (2) '**different excess**' experiments. The "same excess" experiment gives information

[4] Classical kinetics methods such as initial rate do not consider the whole reaction.

on catalyst stability, *i.e.* catalyst activation/deactivation or product induction/inhibition. The "different excess" experiment gives information on reaction orders. The reactions are monitored using *in-situ* tools, under conditions similar to those typically employed for synthesis or in chemical processes, i.e. the concentrations of the substrates are not distorted as in traditional methods which make use of initial rate measurements based on pseudo zero order conditions in one substrate.

Possible *in situ* tools include reaction calorimetry, FTIR spectroscopy, NMR spectroscopy, etc. *In situ* tools can be divided into two categories: (1) Differential methods, which offer a direct measure of the reaction rate over time, and (2) integral methods which offer a direct measure of the substrate or product concentration over time.

Table 4.7. Integral vs. differential measurements in reaction progress.

NMR spectroscopy as an example of an integral measurement	**Reaction calorimetry as an example of a differential measurement**
signal α conversion	q = ΔHreaction x rate x volume
rate= $\frac{dc}{dt}$	conversion = $\int_{t=0}^{t=t} q(t)\,dt \,/ \int_{t=0}^{t=t(end)} q(t)\,dt$
measured parameter: conversion	measured parameter: reaction rate
processed parameter: reaction rate	processed parameter: conversion

Kinetic methods that rely on a relationship between the measurable parameter and species concentration are called integral measurements because concentration is proportional to the integral of the reaction rate. For example, NMR spectroscopic analysis relates the signal intensity to temporal reactant or product concentrations (Table 4.7, left column). The reaction rate is obtained by differentiating the

experimental concentration versus time data. Thus, with integral methods, rate is termed a "processed" parameter to the "primary" parameter of concentration or conversion of the substrate. Typically, some method of smoothing the concentration data is applied before calculating the rate to minimize the error inherent in the derivative process.[5]

Methods that measure reaction rate directly are termed differential or derivative measurements (Table 4.7, right column). These methods include reaction calorimetry, which measures the instantaneous heat flow of the reaction. The reaction rate is related to the heat flow ***q*** through the thermodynamic heat of reaction (ΔHreaction). In this case the rate is the primary measured parameter, while concentration or conversion (the processed parameters) is proportional to the integral of the rate versus the time.

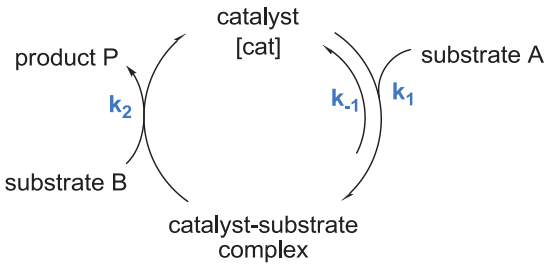
As the operation of integration smoothes random noise while derivation amplifies the noise, methods offering a direct measure of the rate generally provide higher quality data sets. The choice of the *in situ* method has to be made on a case-by-case basis depending on the characteristics of the reaction under study. For example, if the reaction does not produce a sufficient amount of heat, reaction calorimetry cannot be used; if the substrates or products do not show distinguishable peaks in the NMR spectra, this method cannot be used.

Once the real time behaviour of the reaction has been established, the data are manipulated on an Excel worksheet and different types of graphical rate equations may be developed and plotted. Let us examine in detail "same and different excess" experiments.

[5] Rate may be calculated from (concentration, time) data sets by fitting the data to an arbitrary function (e.g., a 9th order polynomial) and then differentiating this function to obtain (rate, time) data. Care must be taken to insure that the fit is accurate to obtain an accurate rate profile.

Same excess experiments

Two different reactions are monitored; these reactions have different starting concentrations but the value of the parameter excess is identical in each reaction. Let us consider the simplest two-substrate reaction presented in Scheme 4.1, where the first substrate **A** binds to the catalyst, forming a catalyst-substrate complex which then reacts with the second substrate **B** to form the product and regenerate the catalyst (**cat**).



Scheme 4.1. Catalytic reaction scheme involving two substrates

The reaction rate for the Scheme 4.1 can be easily derived and has the following expression:

$$\boldsymbol{rate} = \frac{k_1 k_2\,[A][B][cat]_{TOTAL}}{k_{-1} + k_1\,[A] + k_2[B]}$$

The complexity of this equation is that, during the course of a reaction, both substrates concentrations vary at the same time. But if we substitute with excess **[*e*]**, we obtain the next expression:

$$\boldsymbol{rate} = \frac{a'\,[A][e] + [A]^2}{1 + b'\,[A]}\,[cat]_{TOTAL} \quad ; \qquad a' = \frac{k_1 k_2}{k_{-1} + k_2\,[e]} \qquad b' = \frac{k_1 + k_2}{k_{-1} + k_2\,[e]}$$

In second equation, the reaction rate only depends on the concentration of the substrate **A**; the rest of the expression is made of constants. During a "same excess" experiment, where the excess is the same, it is clear that if equation x truly describes the system, the reaction rate of two different reactions having different initial concentrations must be the same for any given value of the concentration of substrate **A**: two graphs of reaction rate vs [A] necessarily present graphical overlay. If this is not true it means that equation, where it was postulated that the total catalyst concentration remains constant over time, does not represent well the system. This is the case for example during catalyst deactivation, where the catalyst concentration ($[cat]_{TOTAL}$) decreases over time; during induction periods, where the catalyst concentration ($[cat]_{TOTAL}$) increases over time; during product inhibition or product activation, where a term describing the dependence of the rate on the concentration of the product has to be added to the expression.

Let us examine in detail how to proceed in practice once the data of both reactions has been collected. We need to construct a graph, with the reaction rate on the *y*-axis and the concentration of one of the two substrates on the *x*-axis. The two curves, plotted on the same graph, either overlay or do not overlay (Figure 4.8); if they overlay this confirms that the two reactions exhibit the same rate at the same substrate concentrations. Let us consider Figure x, left: the vertical black line highlights the value of the reaction rate, for both reactions, at the same value of concentration of **A** (the value of the *x*-axis); this point also corresponds to the value of the rate at the same value of concentration of **B** (as the excess is the same: [B]=[A]+e); the only difference between the two runs, considering the same concentration of **A**, is that one of the reactions has been running for longer, *i.e.* the catalyst has undergone more turnovers, and the product concentration is higher; if the reaction rate is the same, i.e. there is graphical overlay, it is clear that the fact that the catalyst has undergone more turnovers and the higher product concentration does not have any effect on the reaction rate. The conclusion is that there is not catalyst

activation/deactivation nor product inhibition; if on the contrary the reaction rate is different (curves do not overlay, Figure 4.8 right), then it is clear that something other than the concentration of **A** and **B** is affecting the rate, either caused by a different concentration of the active catalyst or of the product. If the curve referring to the reaction with the higher substrate initial concentration (which has been running for longer) shows higher rate, it means that the catalyst was activated over time; on the contrary, when this curve shows smaller rate, it means that either the catalyst was deactivated over time or that there is product inhibition. In order to distinguish between these two possibilities, two experiments can be run under the same exact conditions and initial concentrations, with the product added to one of the vials.

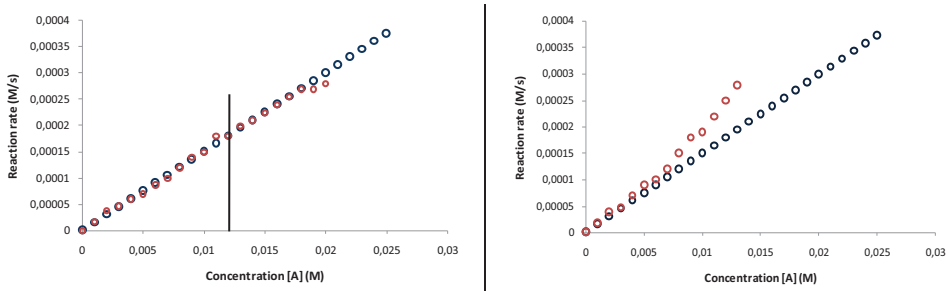


Figure 4.8

Finally, we wish to underline the importance of the "same excess" experiment for any kinetic investigation devoted to finding a reaction rate law and reaction orders. If catalyst deactivation occurs, higher reactions orders may be observed, and thus true reaction orders in substrate concentrations can only be established when it has been previously verified the absence of catalyst activation/deactivation: the same excess experiment can provide a powerful tool.

Different excess experiments

During the "different excess" experiment at least two reactions are monitored; these reactions have different starting concentrations and the excess is also different ($e = [A]_0 - [B]_0$).

This experiment is useful for determining the exact rate law of a reaction involving two substrates. The goal is to produce a plot of a straight line $y = mx$. The function we plot on the *y*-axis will be related to rate and one concentration. The function we plot on the *x*-axis will be related to a concentration. Plotting the results of multiple reactions in which we achieve a straight line in which the data from different reactions overlay provides mechanistic information as described below. For a general two substrates reaction, or in a catalytic reaction presenting a clear rate limiting step, the reaction rate often may be approximated by a power law equation. Let us consider for example the following reaction: A + B → C

A simple rate law that we can propose for this reaction is:

$$\boldsymbol{rate} = k\,[A]^{\alpha}[B]^{\beta}$$

A common goal is to determine the order of reaction in both substrates, *i.e.* the value of the exponents α and β. We proceed by normalizing the reaction rate by the function of one of the two substrates; for example, if we normalize in the substrate **A**, we obtain an expression:

$$\frac{\boldsymbol{rate}}{[A]^{\alpha}} = f(B) = [B]^{\beta}$$

This function *f(B)* only depends on the concentration of substrate **B**; that is, we have removed all dependence on [A] from the right hand side (the *x*-axis) of the equation. As a consequence the graphical rate equation of the normalized rate, plotted vs. the concentration of **B**, necessarily presents graphical overlay. The standard procedure used to determine α is therefore the following:

1) A different excess experiment is carried out; two reactions are monitored in the calorimeter having different starting substrate concentrations and different excess.

2) A plot for both the reactions of the rate/ $[A]^z$ (z is a generic value) vs. the concentration of **B** is presented on the same graph.

3) z is varied until the two curves present graphical overlay: this value of z is the required order of reaction α.

Once α is determined, the dependence on the concentration of substrate **B** (β) can be inferred by the shape of the rate curve. For example, if the curve of the rate vs. [B] is a horizontal line, *i.e.* the value of **B** has no influence on the rate; the reaction is zero order in **B**. If it is a straight line that passes through the origin, *i.e.* there is a linear relationship between rate and [B], the reaction is first order in **B**.

Although the expression of the reaction rate of complex catalytic reactions may not always be approximated as a power rate law, this procedure may be useful for mechanistic investigations even in these cases; obtaining the reaction orders using this method, which provides the best approximation with a power rate law, can give important information regarding the driving forces of the reaction under study.

It is clear that an alternative approach using regression analysis to determine the values of α and β would give the same result. The graphical approach offers a visual methodology. Regarding the determination of more complex rate laws, in the previous section we introduced the simple two substrate catalytic reaction (Scheme 2.1) and the equation 2.x describing its catalytic rate. The rate equation 2.x contains two adjustable parameters a' and b'; fitting the kinetic data to this equation would allow for the determination of two parameters, and no unique solution for the three constants k_1, k_{-1}, k_2 involved in the mechanism. The different excess experiment provides an additional independent set of data that can be fitted in the equation for a unique determination of the three constants.

12. Reaction calorimetry

Some of the reactions studied in this thesis have been monitored using reaction calorimetry, which is a very powerful technique because it provides a direct and precise measure of the reaction rate vs. time. As the rate values are obtained directly, the mathematical treatment of the data conversion vs. time is not necessary, avoiding the ensuing mistake derived from the process. The most important equations regulating reaction calorimetry are introduced. It is possible to model the vial in the calorimeter as a batch reactor, with substrates neither added nor removed over time; the energy balance around the calorimetric vial, which is kept at a constant temperature when the reactions occur, has the following expression:

$$\boldsymbol{q}(t) = V \sum_i \Delta H_i \left(\frac{dC_i}{dt} \right)$$

Where V is the total volume of the reactive solution (which is considered invariant), ΔH_i is the heat of reaction of the i^{th} reaction, (dC_i/dt) is the rate of the i^{th} reaction. In case of a single reaction (i=1), as it is the often the case, the expression can be simplified as follows:

$$\boldsymbol{q}(t) = V \ \Delta H_{reaction} \ (\boldsymbol{rate})$$

From the function of heat vs. time, we can obtain an expression for the conversion; by considering the fraction of time $t + dt$, we can assume that the fraction of heat generated in this time $t + dt$ is equal to the fraction of conversion achieved in the same time, as in the following equation:

$$\frac{X(t)}{X_{final}} = \frac{\int_0^t q(t)dt}{\int_0^{t(final)} q(t)dt} \qquad \Rightarrow \qquad X(t) = X_{final} \frac{\int_0^t q(t)dt}{\int_0^{t(final)} q(t)dt}$$

The final conversion (X_{final}) can be verified independently with other techniques, such as NMR or HPLC.

The following equation represents an expression of the conversion vs. time; we need to calculate the total heat generated by the reaction, which corresponds to the total area under the heat curve:

$$\boldsymbol{X}(t) = X_{final} \frac{\Delta H_{(t)}}{\Delta H_{reaction}}$$

By dividing the total heat by the total moles of product produced, a value for the heat of reaction can be obtained. This value is a thermodynamic measure of the actual energy required to break and form chemical bonds. Every time that the same reaction is monitored, the same heat of reaction should be obtained. This value therefore provides an independent check on the validity of the measurement.

Once an expression for the conversion vs. time is obtained, it is straightforward to derive an expression for the concentration of substrates and product versus time, as the following equations (referred to the limiting substrate):

$$[substrate]_t = [substrate]_0 (1-X_t)$$
$$[product]_t = [substrate]_0 (X_t)$$

A sampling experiment, in which the conversion curve calculated from the calorimetric data is compared to a conversion plot calculated through another technique, has to be carried out for every new system. This is to assure that the calorimeter actually monitors the real heat produced by the reaction under study; in mathematical terms, this is to verify that equation is valid. If the system under study is not a single reaction but presents several parallel reactions, the methodology would become more complex and different monitoring techniques would need to be used; nevertheless, reaction calorimetry can be employed with success even in these cases.

Another condition that has to be verified in order for the calorimetric experiment to be valid is that the volume of the reactive solution does not change over time.

12.1 Experimental procedures for calorimetry kinetics

Measurements were performed using an Omnical Insight CPR-220 reaction calorimeter, which allows continuous monitoring of the instantaneous heat absorbed or released by a chemical reaction occurring in the vessel. The sample vessel is a 16 mL septum-cap vial equipped with a magnetic stirring bar. The system operates as a differential scanning calorimeter (DSC) by comparing the heat released or consumed in a sample vessel with that from a reference compartment at intervals of 2-6 seconds over the course of the reaction. The temperature of the DSC was held constant at 25°C, ensuring that the reaction would proceed under isothermal conditions.

In a typical calorimetry experiment, a reaction vessel containing a solution of the proper amounts of 4-nitrophenyl acetone (**1c**, Alfa-aesar) and cinnamaldehyde (**2f**, freshly distilled) in dicloromethane was placed in the calorimeter. A syringe, containing a solution of (*S*)-α-α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether ***(S)*-II,** purified by column chromatography) and benzoic acid (Sigma Aldrich) was placed in the sample injection port of the calorimeter. All the system was allowed to thermally equilibrate for at least 60 minutes. The reaction was initiated by injecting the catalyst into the reaction vessel. A raw data curve was produced by measuring the heat flow from the sample vessel every 6 seconds during the reaction. When no more heat was developed, a 100 micro-liter sample from the reaction mixture was taken and quenched by filtration over a short pad of silica gel. The mixture was subjected to ^{1}H NMR analysis to determine the final conversion.

Due to the delay between the instantaneous moment heat evolved from the reaction vessel and the time that the thermophile sensor detects the heat flow, the raw data curve must be calibrated. To accomplish this calibration, a constant amount of current was passed through a resistor in the sample chamber of the calorimeter thereby producing a known quantity of heat. This process results in a response curve,

which is then transformed into a square wave allowing for the response time of the instrument to be calculated using the Omnical Winsight software (see figure 4.9).

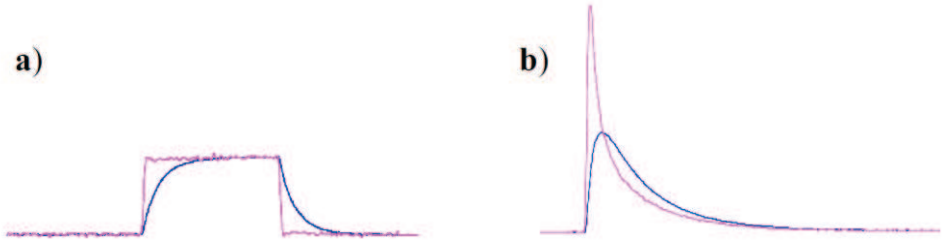


Figure 4.9. Mathematical correction of heat flow data: a) square wave; b) experimental data. Blue line: uncorrected data; pink line: corrected data.

The blue curve is the heat flow measured by the calorimeter during this calibration. It is clear that the calorimeter does not respond instantaneously to the on and off steps of the calibration signal. Through the calibration program, it is possible to find the lag time (**τ**) which is necessary to transform the blue curve into the violet curve as in Figure Xa. This same value **τ** is then applied to the calorimetric curve of the reaction, as in Figure Xb. The value of **τ** depends on the thickness of the wall of the particular vial used; for this reason, the "tau correction" has to be carried out after each experiment using a different vial.

Application of the response time to the raw data gives a "tau corrected data curve" (plot of heat flow (mJ/s) versus time). The reaction rate and the fraction conversion at any time can be obtained from the "tau corrected" heat flow (equation 1). Where Δ $_{\text{eaction}}$ is the heat of the reaction and V is the reaction volume

$$\mathbf{q = \Delta H_{reaction} \cdot V \cdot rate} \qquad (1)$$

The instantaneous concentrations of reactants/products can all be calculated from the conversion and the initial concentrations of the reactants (2).

$$conversion = \frac{\int_0^t q(t)dt}{\int_0^{tf} q(t)dt} \quad (2)$$

The numerator represents the area under the heat flow to any time point t and the denominator represents the total area under the heat flow curve.

Calibration of the method

The in-situ calorimetry technique needs to be calibrated with an independent analytical method; therefore the final conversion determined from the heat flow was compared in all cases with the one obtained by ^{1}H NMR measurements. To calibrate the method (and corroborate that the heat measured corresponds to the heat released by the reaction of interest), aliquots of the reaction mixture were taken at different times in a duplicate experiment carried out in the calorimeter at the same time that the typical procedure. The aliquots were quenched by filtration over a short pad of silica gel and the conversion was analyzed by ^{1}H NMR. The overlaying obtained in Figure 4.10, confirms that the observed heat flow represents an accurate measure of the rate of the reaction under study.

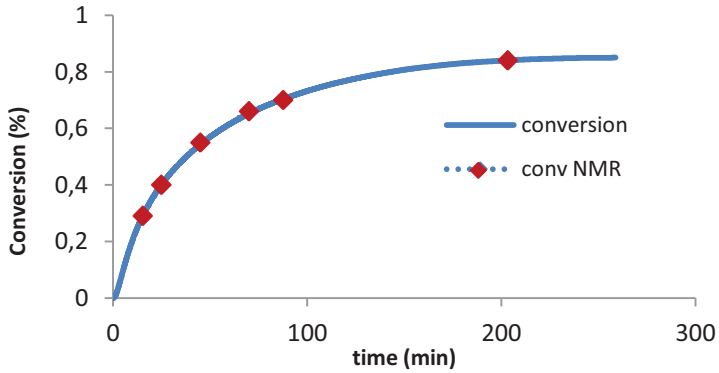


Figure 4.10. Comparison between the conversions obtained by reaction calorimetry and by ^{1}H NMR analysis.

Appendix

Resumen de la Tesis

El trabajo de investigación realizado en esta tesis doctoral está enmarcado dentro de la organocatálisis enantioselectiva, que consiste en la utilización de pequeñas moléculas orgánicas quirales como catalizadores en reacciones orgánicas. En los últimos años, el área de la organocatálisis ha experimentado un avance espectacular y se describen catalizadores cada vez más sofisticados que son capaces de efectuar transformaciones a su vez más interesantes y complejas. Hoy en día se puede decir que la *organocatálisis* se ha convertido en uno de los tres pilares la *catálisis asimétrica,* junto con la *catálisis metálica* y la *biocatálisis*.

Son muchas las reacciones que se han podido llevar a cabo de manera enantioselectiva usando organocatalizadores. Cada día son más las transformaciones y procesos sintéticos que utilizan la organocatálisis en alguna de sus etapas. Este crecimiento tan espectacular, producido en la última década, sólo es posible cuando un campo ofrece ventajas reales a los investigadores propios del área y a los que utilizan los resultados de ésta. Estas ventajas son consecuencia, a su vez, de cuatro factores de carácter conceptual y operacional: 1) La organocatálisis permite el desarrollo de nuevos modos de activación de sustratos, lo que posibilita la invención de transformaciones. 2) Los procesos organocatalíticos permiten catalizar transformaciones orgánicas conocidas, con quimio-, regio-, diastereo-, o enantioselectividades ortogonales o complementarias a las catalizadas por metales. 3) Los catalizadores orgánicos son, generalmente, estables al oxígeno y a la humedad de la atmósfera. En consecuencia, ni requieren el uso de atmósferas inertes, ni reactivos o disolventes secos, ni es necesario almacenarlos en recipientes libres de aire o humedad. 4) Una cantidad considerable de moléculas orgánicas pueden obtenerse como un único enantiómero de fuentes naturales (aminoácidos, carbohidratos, hidroxiácidos, alcaloides, etc.). Esto implica un abaratamiento de costes en su preparación, facilidad en su manipulación y la posibilidad de obtener grandes cantidades del mismo. Además, en muchos casos los organocatalizadores son

accesibles en ambas formas enantioméricas, lo que es de gran importancia en la industria farmacéutica.

Sin duda los resultados más espectaculares se han obtenido utilizando aminas secundarias a mediante la activación de grupos carbonilos a través de dos ***vías***: **iminio** (activación del LUMO) o **enamina** (activación del HOMO), pudiéndose combinar ambos procesos en una secuencia sintética dominó. En este sentido, son de destacar los catalizadores desarrollados respectivamente por MacMillan y Jørgensen-Hayashi que toman como modelo la simple prolina, que sentó las bases de la organocatálisis.

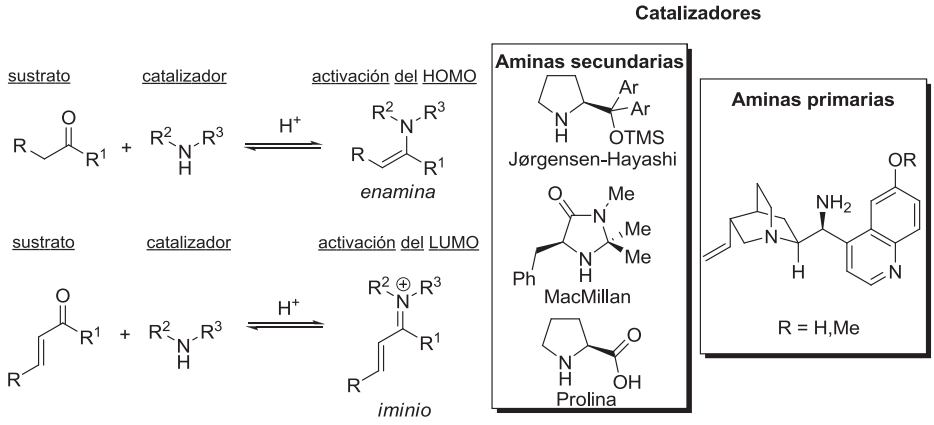
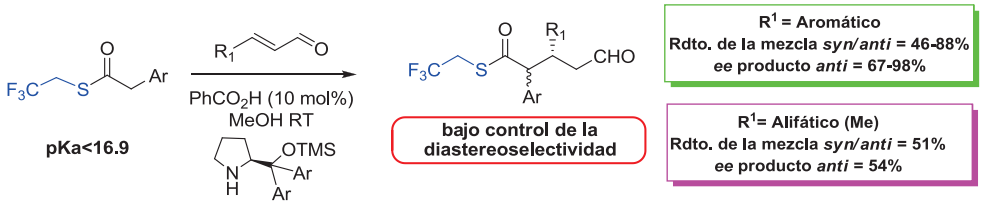


Figura R.1. Fundamento de activación *vía* iminio y *vía* enamina. Catalizadores más usuales.

Las reacciones llevadas a cabo en este trabajo se han catalizado principalmente utilizando activación *vía* ión iminio. A pesar del gran esfuerzo que se ha realizado en estos últimos años en esta área de la organocatálisis, existe un amplio abanico de reacciones y posibles funcionalizaciones de sustratos que están aún sin explorar. Una de las principales limitaciones en la activación *vía* iminio radica en las restricciones estructurales de los nucleófilos. A excepción de los nitroderivados, las especies pro-nucleofílicas normalmente requieren la presencia de dos grupos atractores de electrones en posición geminal para proporcionar a los protones metilénicos la acidez

necesaria para participar en procesos organocatalíticos. Dado que generalmente el segundo grupo atractor no está presente en la molécula final, este debe ser eliminado una vez ha desempeñado su función activante. Una de las principales limitaciones de este proceso proviene de la epimerización que normalmente se produce en la etapa de eliminación de este segundo grupo activante, lo que hace muy complicada la formación estereoselectiva de compuestos que posean centros estereogénicos en el carbono nucleófilo.

El único antecedente relativo al uso de nucleófilos pro-quirales derivados de arilacéticos con la creación simultánea de dos centros estereogénicos, es el trabajo realizado por Barbas III, que implica la reacción de derivados de trifluoroetil tioésteres con aldehídos α,β-insaturados activados *vía* ión iminio. (Esquema R.1).



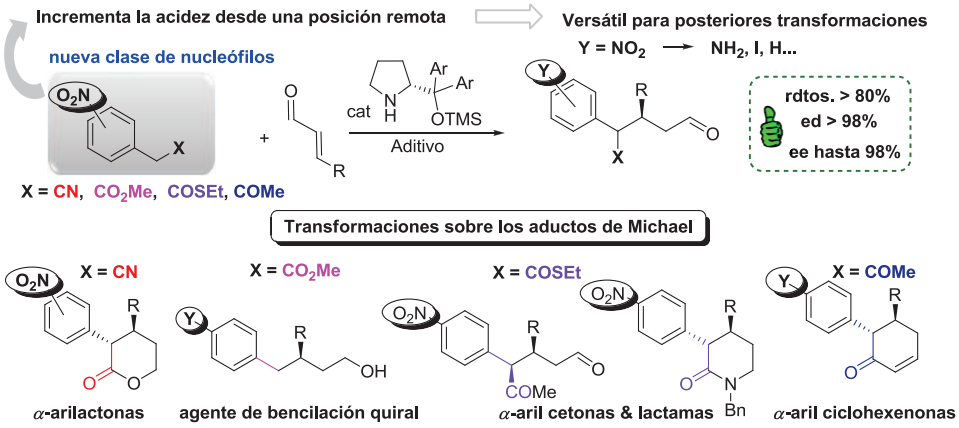
Esquema R.1. Reacción de Michael organocatalítica de trifluoroetil tioésteres actuando como nucleófilos monofuncionalizados

En este trabajo se hace un pequeño estudio sobre el límite de pK_a que deben tener los nucleófilos para su activación con una amina, encontrándose éste entre 16 y 17. El malonato de etilo, que se utiliza habitualmente en organocatálisis asimétrica con aminas quirales, tiene un pK_a de 16.4, sin embargo las cetonas con un pK_a del protón en α cercano a 18, necesitan activación *vía* enamina.

Considerando estos antecedentes, nos planteamos como objetivo el desarrollo de nuevos nucleófilos derivados de ácidos aril-acéticos y su aplicación en reacciones catalizadas *vía* iminio, con el fin de aumentar la variedad de sustratos y posibilidad de transformaciones. Para ello, nuestra estrategia ha consistido en la incorporación de un grupo atractor de electrones en el anillo aromático, confiriendo así la acidez necesaria para que estos derivados puedan participar en este tipo de reacciones.

En este sentido el grupo nitro actuó como un grupo activante muy eficiente, proporcionando la acidez necesaria a los protones metilénicos de los pro-nucleófilos, dando lugar a las reacciones en altos rendimientos. Además el grupo pudo ser eliminado o transformado en todos los casos (Esquema R.3, parte superior).

Se han desarrollado principalmente cuatro nucleófilos diferentes con distintas posibilidades de transformación (X = CN, COMe, CO_2Me, COSEt). En cada caso se diseñaron simples y eficientes procesos secuenciales para la síntesis de interesantes moléculas diastereo- y enatioméricamente puras. La baja diastereoselectividad obtenida en la adición de Michael fue superada mediante la formación de productos cíclicos o eliminación del grupo en posición bencílica. Tanto compuestos cíclicos como acíclicos diastereoméricamente puros fueron obtenidos. Estos compuestos son estructuras interesantes para la construcción de moléculas de alta complejidad sintética (Esquema R.3, parte inferior).



Esquema R.3. Aplicaciones sintéticas de derivados arilacéticos in catálisis vía iminio.

Las reacciones de estos derivados (**1**) tienen lugar en presencia de los catalizadores silil prolinol éteres **I** y **II**. En los ejemplos estudiados, aunque de estructura parecida, se requirió condiciones de reacción diferentes en cada derivado para conseguir buenos resultados (catalizador, disolvente, aditivo).

Se encontró una influencia muy positiva en el empleo de TBAB como aditivo, un compuesto no utilizado previamente en este tipo de reacciones con esta función, especialmente para los nucleófilos menos reactivos. Se observe un diferente comportamiento en las reacciones de enales alifáticos y aromáticos. Los derivados **1b** y **1c** proporcionaron las conversiones más altas, mientras que el ester **1d** presentó ciertos problemas de reactividad. Estos problemas fueron solucionados con el empleo del tioester derivado **1e**, que resultó ser general para la reacción de enales β-alquil y β-aril sustituidos en las condiciones adecuadas.

Inspirados en nuestro trabajo, han aparecido en la bibliografía otros ejemplos relativos al uso de derivados de aril-acéticos o estructuras similares (Figura R.2). La importancia de la acidez del pro-nucleófilo es evidente en todos los casos, donde la elección del grupo activante resulta ser crucial para la eficacia de la reacción.

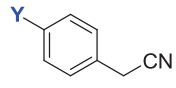
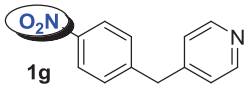
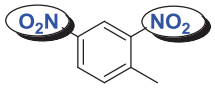
Y-arilacetonitrilos	***NO_2-arilpyridina***	***2,4-$(NO_2)_2$-tolueno***
Y = CN, CO_2Me  Y = NO_2, X = CO_2Me **1d** *TL* **2012**, 2809, Kim	✓ transformación o eliminación del grupo nitro  **1g** *Synlett* **2011**, 489, Melchiorre	✓ transformación o eliminación del grupo nitro  *CEJ* **2013**, 9147, Wang *EJOC* **2013**, 5262, Jørgensen

Figura R.2. Ejemplos de nucleófilos

Desde un punto de vista sintético, estos ejemplos y los desarrollados por nosotros muestran la necesidad de manipular adecuadamente los grupos activantes con el objetivo de conseguir la acidez apropiada para reaccionar en este tipo de

procesos. Sin embargo, los resultados a veces dispares obtenidos, revelan el desconocimiento de muchos aspectos mecanísticos de estas reacciones.

Las aplicaciones sintéticas en el área de la organocatálisis en general y de la activación *vía* iminio en particular, están yendo muy por delante del entendimiento de muchos aspectos mecanísticos. El desconocimiento de estos aspectos mecanísticos hace necesario optimizar, en cada caso concreto, catalizador, disolvente y aditivo. Sería por lo tanto interesante una racionalización de los procesos y un mejor entendimiento de los factores que influyen en la reactividad y enantioselectividad de las reacciones, con el fin de poder controlarlos y poder saber a priori que condiciones podrían ser las idóneas para una reacción en concreto.

En nuestro estudio de la aplicación de los derivados de arilacéticos (**1**) en adiciones de Michael catalizadas *vía* iminio hemos encontrado algunos resultados que no tenían una explicación sencilla y directa. Puesto que se trata de nucleófilos con estructuras relativamente similares, hemos considerado esta serie (**1b**, **1c**, **1d** y **1e**) como una buena oportunidad para realizar un estudio mecanístico más profundo. En este estudio también han sido incluidos otros nucleófilos relacionados estructuralmente con los nuestros (**1a**, **1f** y **1g**)

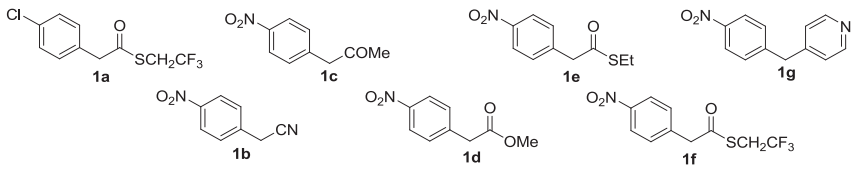


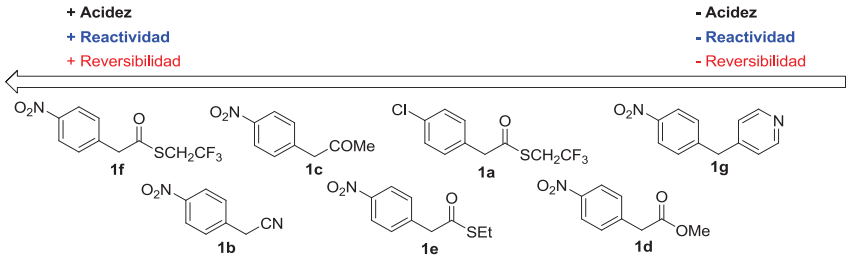
Figura R.3. Nucleófilos estudiados

Debido a la complejidad que encierra el estudio de los mecanismos de las reacciones, hemos recurrido a diferentes técnicas disponibles, así como de un análisis profundo de los datos descritos en la bibliografía.

El primer punto a estudiar fue la disparidad en la reactividad manifestada por los nucleófilos, ya que se trata de estructuras relativamente parecidas. Con el fin de

poder explicar el orden de reactividad encontrado, recurrimos a las escalas de reactividad descritas por el profesor Mayr, muy de moda últimamente. Sin embargo, el orden predicho por dichas escalas de reactividad resultó ser prácticamente el opuesto al obtenido experimentalmente. Por lo tanto, se propone que en las reacciones catalíticas la velocidad del proceso global depende no solo de las reactividades de los intermedios presentes en el ciclo, sino también de su formación y de la concentración de éstos, que puede ser crucial para el desarrollo de la reacción.

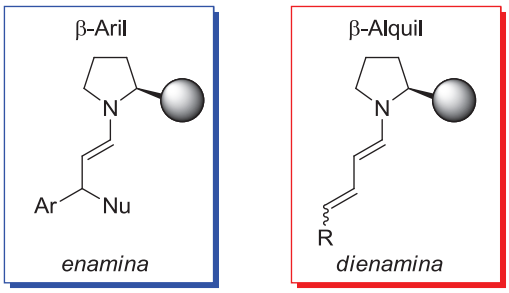
El estudio de la acidez relativa de estos nucleófilos nos permitió establecer un orden de reactividad, que resulta estar íntimamente ligado al orden de dicha acidez. Además, la reversibilidad de la reacción, a la que se atribuye el cambio en la enantioselectividad observado en algunos casos, parece estar relacionado con la acidez, siendo los nucleófilos más ácidos los que presentan una mayor tendencia a este fenómeno.



Los estudios comparativos de la reactividad de estos nucleófilos **1**, nos permitió encontrar condiciones de reacción óptimas para cada uno de ellos utilizando aldehídos comerciales.

En un estudio más profundo sobre el efecto de los aditivos en la reacción nos dimos cuenta de la gran importancia del ácido presente en las reacciones en los aldehídos comerciales. Sin este ácido, las reacciones de los derivados estudiados no tuvieron lugar sin la adición de un ácido externo. Sin embargo, la cantidad adecuada de ácido encontrada para cada uno de los nucleófilos fue distinta, y aparentemente dependiente de la acidez del propio nucleófilo.

En los estudios de ^{1}H-RMN de las reacciones algunos intermedios pudieron ser detectados. En las reacciones de los derivados **1c** y **1d** con cinamaldehído **2f** con silil-prolinol éteres **I** y **II** como catalizadores y en ausencia de aditivo, las enaminas del producto fueron identificadas como las especies más abundantes que contenían el catalizador. Sin embargo, en las mismas reacciones con crotonaldehído **2a**, mostraron que en ausencia de aditivos el catalizador se encuentra formando preferentemente la dienamina con el aldehído α,β-insaturado. Además, la reacción no tenía lugar sin la adición de un aditivo ácido. Esta importante diferencia puede explicar el diferente comportamiento observado en las reacciones de Michael con enales alifáticos o aromáticos.



Se calcularon los valores teóricos de ΔG para las reacciones netas de todos los nucleófilos 1 estudiados, tanto para enales aromáticos como alifáticos. Estos valores mostraron que las reacciones de los enales alifáticos están más favorecidas, explicando así su menor tendencia a la reversibilidad.

Se estudió asimismo la influencia del catalizador (**I** o **II**), el aldehído y nucleófilos empleados (ΔG), aditivos y disolventes en la reversibilidad de las reacciones, fenómeno al que se atribuye la erosión de la enantioselectividad observado en algunos casos.

La influencia positiva de los aditivos ácidos, la observación de las enaminas en el transcurso de la reacción así como los estudios cinéticos realizados sugieren que la etapa determinante de las reacciones estudiadas pueda ser la protonación de dicha enamina. En este momento se están realizando más estudios en nuestro grupo, tanto a nivel experimental como teórico, con el objetivo de profundizar en el mecanismo de estas reacciones.

Hasta este momento, el trabajo recogido en la presente memoria ha dado lugar a las siguientes publicaciones:

1. "*Nitrophenylacetonitriles as Versatile Nucleophiles in Enantioselective Organocatalytic Conjugate Additions"* Cid, M.B.; Duce, S; Morales, S; Rodrigo, E.; García Ruano, J.L. *Org. Lett.,* **2010***, 12,* 3586-3589*.*

2. "*An organocatalytic approach to enantiomerically enriched α-arylcyclohexenones and cyclohexanones"* Duce, S.; Jorge, M.; Alonso, I.; García Ruano, J.L.; Cid, M.B. *Org. Biomol. Chem.*, **2011**, *9*, 8253-8260.

3. "*Role of quaternary ammonium salts as new additives in the enantioselective organocatalytic β-benzylation of enals"* Duce, S.; Mateo, A.; Alonso, I.; García Ruano, J.L.; Cid, M.B. *Chem. Commun.*, **2012**, *48*, 5184-5186.

4. *"p-Nitrophenyl Ethylthioester in Enantioselective Organocatalytic Michael Additions: Different Behaviour of β-Aryl and β-Alkyl Enals".* Sara Duce, María Jorge, Inés Alonso, José Luis García Ruano, and M. Belén Cid, *Eur. J. Org. Chem.* **2013**, 7067-7075.

Papers