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Cinchona alkaloids and BINOL derivatives as privileged catalysts or ligands in asymmetric synthesis.

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Abstract

During the last fifteen years organocatalysis emerged as a powerful tool for the enantioselective functionalization of the most different organic molecules. Both C-C and C-heteroatom bonds can be formed in an enantioselective fashion using many types of catalyst and the field is always growing. Many kind of chiral catalysts have emerged as privileged, but among them Proline, cinchona alkaloids, BINOL, and their derivatives showed to be particularly useful chiral scaffolds.
This thesis, after a short presentation of many organocatalysts and activation modes, focuses mainly on cinchona alkaloid derived primary amines and BINOL derived chiral Brønsted acids, describing their properties and applications.
Then, in the experimental part these compounds are used for the catalysis of new transformations.
The enantioselective Friedel-Crafts alkylation of cyclic enones with naphthols using cinchona alkaloid derived primary amines as catalysts is presented and discussed. The results of this work were very good and this resulted also in a publication.
The same catalysts are then used to accomplish the enantioselective addition of indoles to cyclic enones. Many catalysts in combination with many acids as co-catalysts were tried and the reaction was fully studied. Selective N-alkylation was obtained in many cases, in combination with quite good to good enantioselectivities. Also other kind of catalysis were tried for this reaction, and considered all, the results obtained are interesting.
Another aza-Michael reaction between OH-free hydroxylamines and nitrostyrene using cinchona alkaloid derived thioureas is briefly discussed.
Then our attention focused on Brønsted acid catalyzed transformations.
With this regard, the Prins cyclization, a reaction never accomplished in an enantioselective fashion up to date, is presented and developed. The results obtained are promising.
In the last part of this thesis the work carried out abroad is presented.
In Prof. Rueping laboratories, an enantioselective Nazarov cyclization using cooperative catalysis and the enantioselective desymmetrization of meso-hydrobenzoin catalyzed by Brønsted acid were studied.

Table of contents

Foreword

Nature is almost perfect. It took billions of years, but in the end life grew up not only effective and strong, but also elegant, complex, fascinating. And it's somehow surprising how the existence of complex creatures like living beings is fundamentally based on chemistry, made of chemistry. The functioning of living beings (or Life) is in the end nothing else than an ensemble of complex and intricate network of chemical interactions and reactions between more or less complex molecules. All of these complex chemical mechanisms are expressed by following the instructions encoded in a molecular manual, DNA, made with a surprisingly low Basis Set: four nitrogen bases derived from enantiopure deoxyribose. These bases combine to give two long molecules, which as well are paired, due to complementary interactions, to give a double helix. This double helix is screwed on itself, in a clockwise direction. The reason why the helix is forced to screw only in one direction lays basically on the enantiopurity of deoxyribose. Helicity is a kind of chirality, and DNA is enantiopure. Since that, the information encoded and expressed by DNA is chiral, and every molecule, every process, every interaction occurring in organisms is therefore chiral, enantiopure. So, Nature is chiral. The reason why it happened, and how, is nowadays object of big debate, but actually, despite the huge amount of work on it, it's still not known, and perhaps it will never be. But that's a fact we have to deal with: Nature is chiral, and complex, and elegant. As I told, almost perfect.

Driven by the need of making progress, grow and create welfare, humans developed, especially in the last two centuries, a fairly good expertise in the production of many types of chemicals, useful for their needs. Many of these chemicals are available in nature, but not in enough amount, and many others are unavailable, so their synthesis is necessary. Some of these molecules are not chiral, but many others are, and we have to consider this fact, especially in the synthesis of molecules that have to interact directly with our body, which, as seen, is chiral. Specifically, this is the case of pharmaceuticals, which have to improve our health conditions, and pesticides, which have to be toxic for pests, but not for everything else. While an enantiomer could have a good (or no) effect on our body or on the environment, the other could be just useless, or harmful, and so it must not be produced, or at least is must not be released in the environment or introduced in our bodies.

Hence, the importance for humans of producing enantiomerically pure molecules. Unfortunately, our technology is far away from Nature's perfection and the synthetic methodologies we developed are mostly scarcely effective and not enantioselective. So how can we do?

- Since Nature is chiral, the most conceptually simple way to produce enantioenriched compounds is starting from natural molecules, the so-called Chiral Pool. There are a lot these molecules readily available, but unfortunately most of the times it's difficult to obtain the products that we need directly from them. Often, what we need is fairly different from the structures available in Nature, and thus the synthetic elaboration becomes long, complicated, and there is always the possibility that we, with one of ours clumsy, not enantiospecific, achiral reaction, destroy the chirality created by nature.
- The second most conceptually simple way to produce enantioenriched compounds is the direct use of Nature's catalysts to perform our reactions. The use of enzymes, or directly microorganisms for industrial application is sometimes possible, and due

to the high activity and specificity of these catalysts it would be the best way to obtain a transformation. Unfortunately, enzymes are expensive, they require particular conditions to work well without degradation (water, relatively low temperature), but most importantly they are engineered by Nature to catalyze very specific transformations, and so they cannot be employed for all our purposes.

- Otherwise, we could think to perform our imperfect racemic synthesis and later try to obtain the separation of the two enantiomers somehow. Since the physical properties of two enantiomers are the same, we need chirality for this purpose, or with a solvent-consuming and expensive separation via chromatography on chiral columns, or, more easily, with chemical resolution of racemic mixtures. Here we take from the chiral pool enantiopure molecules which are reacted or interact with a racemic mixture. This allows the formation of diastereoisomers, which, being entities with different physical properties, can be separated with physical methods. The racemic resolution is currently widely used as a method to obtain enantiomerically pure compounds. A typical example is the selective crystallization of a diastereoisomer, leaving the other in solution. This process is often an acid-base reaction, reacting 0.5 eq. of a chiral base to crystallize a salt enantioenriched in the acidic component, or the opposite. The crystals are collected and the resolving agent removed, to give the title compound. Anyway, the other enantiomer which was produced in the synthesis, is in this way wasted, if not useful for something else, lowering the maximum yield of the process to 50%. For this reason many efforts are done to try to convert the “wrong” enantiomer into the desired one, and in order to save also more time and materials, if possible, this is performed directly in the same pot. This process is called dynamic kinetic resolution. Many dynamic kinetic resolutions are not just simple acid-base reactions, but more complex reactions, so they are more difficult to optimize. Anyway, simple optical resolution with a resolving agent provides in average reasonable yields and is nowadays the most widely used method to obtain enantiopure materials in industry.
- The fourth, and always more sophisticated method to obtain enantioselective synthesis, is to introduce at some point of the synthetic sequence a “piece of nature” as an enantiomerically pure chiral auxiliary. This is covalently introduced into the desired product structure, exploited to create a chiral center enantiospecifically, and then removed. With respect to optical resolution this method allows in principle a 100% yield, but it is more time- and material-consuming (two additional steps are required to introduce and remove the auxiliary), and chirality-wasting, because only sometimes the auxiliary can be recovered and used again, while often is destroyed in the removing step.
- The last and more sophisticated method to produce enantioenriched compounds is enantioselective catalysis. With this, humans try to mimic Nature, producing directly chiral molecules using chiral catalysts. It’s impossible for humans to produce such complex and efficient catalysts as enzymes, so our attention is focused on the use of smaller molecules, coming anyway from the chiral pool, used as they are or with some changes. The good catalytic activity of metals drove the humans to focus firstly on them massively. Complexes between certain metals and appropriate enantiopure organic ligands are formed, the latter creating the chiral environment necessary for the enantioselective transformation occurring at the metallic center. Metals are very useful catalysts: they are highly active and efficient, they give often good yields and enantiomeric excesses, and since many metals and ligands are available, a lot of their combination can be tried in the optimization of a reaction. Despite this effectiveness and versatility of metal complexes as enantioselective catalyst, some drawbacks have to be taken into account. Many useful metals are

expensive and/or toxic (Pd, Ru, Rh, Ni, Ir, …), and this limits their use in medicinal chemistry, since trace amounts of these metals can remain in the final product, thus adding risk to its use. Disposal of wastes containing these metals is therefore difficult and expensive, because they also can be pollutants. Then, metal based catalysts often require anhydrous and/or oxygen free conditions to work, complicating their use in terms of operational ease. Enantioselective transformations promoted by metal based catalysts are anyway object of tremendous studies in the academic community, and they are also applied in a growing number of industrial applications. But in the last 15 years academic research, for a combination of factors that we'll examine later, got interested and focused its attention on a different class of catalysts: organocatalysts. These are small organic molecules, in some cases the same or derived from the ones classically employed as ligands in metal catalysis, which can catalyze reactions on their own. Many achiral organic molecules such for instance organic bases or acids are used since a long time as catalysts, but recently the development of chiral organic molecules that can be used to obtain enantioselective transformation grew up tremendously, also with the discovery and development of many kind of new catalysts and activation modes. These catalysts are generally required in relatively high amount and require longer reaction times respect to metals. Nevertheless the number of transformations that they can catalyze is increasing every day, enantiomeric excesses can be very good, they are water and oxygen stable, and usually non-toxic. Since during the years a lot of improvements have been made, and a huge number of research groups got involved in this field, with a constantly growing number of publications, it's easy to expect further important developments and successes in this field during the following years.

The beautiful and fascinating phenomena occurring naturally, always pushed humans to try to mimic Nature, to try to reproduce these phenomena. In chemistry, enantioselective organocatalysis is probably the essence of this will. Building enantiopure molecules using small organic molecules is the attempt to reproduce, albeit in much smaller scale, the building of complex, harmonic and living architectures that Nature assembles using a sophisticated combination of DNA, enzymes, cofactors, neurotransmitters, and much more. Organocatalysis is only 15 years old: the challenge is only at the beginning.

Section 1

INTRODUCTION

1) Asymmetric organocatalysis[1]

The origin of asymmetric organocatalysis is much older than what we are used to think. The first known report about was out in 1912[2]. After his use in 1908[3] for trials to mimic enzymatic decarboxylation of camphocarboxylic acid, the German chemist Breding used cinchona alkaloids quinine **3** and quinidine **4** to catalyze the enantioselective addition of HCN to benzaldehyde, albeit in very low enantiomeric excess (*Figure 1.1*, **A**). Bredig observed that the products were optically active, but, with the methods known at that time, it was impossible to determine accurately the enantiomeric excess; anyway, it was esteemed to be lower than 10%. Even if the concept was new, enantioselective synthesis in general at that time was not yet considered central for chemical research, and so this paper didn't capture much the attention of the academic world. Anyway, sporadic reports on the field were out. For example in 1929[4] and 1932[5] kinetic resolution of carboxylic acids and alcohols, was reported respectively by a French and German chemist.
Organocatalysis was studied also in its non-asymmetric variant, despite employing chiral catalysts, for example in Knoevenagel condensation or aldol reaction, and such literature was also summarized in a book as early as 1949[6]. Then, in 1954[7] Prelog re-exhamined HCN addition to aldehydes, improving especially the understanding of the mechanism (*Figure 1.1*, **A**). A great breakthrough was made by Pracejus in 1960[8], in his acetylquinine **7** catalyzed synthesis of optically active methyl esters **8** from ketenes **6** and methanol (*Figure 1.1*, **B**). Here, an enantiomeric excess of 74% was obtained, showing for the first time that organocatalysis could be useful in enantioselective synthesis, and not only a curiosity. Another milestone in organocatalysis is the reaction that today is called the Hajos-Parrish-Eder-Sauer-Wieckert reaction (*Figure 1.1*, **C**). It is reported in 1971 in two different patents by scientist working at Hoffmann-La Roche[9] and Schering AG[10]. In this reaction proline **10** is used to catalyze an enantioselective intramolecular aldol reaction. While Hajos and Parrish use 3% of catalyst in DMF at r.t. obtaining the corresponding bicyclic aldol in 93% ee, Eder Sauer and Wieckert use higher loading and temperature, in combination with an acid, to obtain the dehydrated product with 71% ee. This was a high improvement in enantioselective organocatalysis, being all together the first report of an ee higher than 90%, the first proline catalyzed reaction (which, as we'll see later, will become widely used, together with its derivatives) and the first application of organocatalysis: in

[1] For this introduction, as well as for the rest of the document, three books as leading references were followed. (a) A. Berkessel, H. Groger. (2005). *Asymmetric Organocatalysis.* Weinheim: WILEY-VCH. (b) P. Dalko. (2007). *Enantioselective Organocatalysis.* Weinheim: WILEY-VCH. c) R. R. Torres. (2013). *Stereoselective organocatalysis: bond formation methodologies and activation modes*. JohnWiley & Sons, Inc., Hoboken, New Jersey. Please see them for further details.

[2] G. Breding, P.S. Fiske, *Biochem. Z.*, **1912**, *46*, 7.

[3] G. Breding, K. Fajans, Ber. *Deutsch. Chem. Ges.*, **1908**, *41*, 752–763.

[4] M.M. Vavon, P. Peignier, *Bull Soc. Fr.*, **1929**, *45*, 293.

[5] R. Wegler, *Liebigs Ann. Chem.*, **1932**, *498*, 62.

[6] W. Langenbeck, (1949), *Die Organische Katalysatoren und ihre Beziehungen zu den Fermenten, 2. Aufl*. Springer-Verlag.

[7] V. Prelog, M. Wilhelm, *Helv. Chim. Acta*, **1954**, *37*, 1634-1660.

[8] H. Pracejus, *Justus Liebigs Ann. Chem.*, **1960**, *634*, 9–22.

[9] (a) Hajos, Z. G. and Parrish, D. R., *Ger. Pat.*, July 29, **1971**, DE 2102623. (b) Z.G. Hajos, D.R. Parrish, *J. Org. Chem.*, **1974**, *39,* 1615-1621.

[10] (a) U. Eder, G. Sauer, R. Wiechert, *Ger. Pat.*, Oct 7, **1971**, DE 2014757. (b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl*., **1971**, *10*, 496.

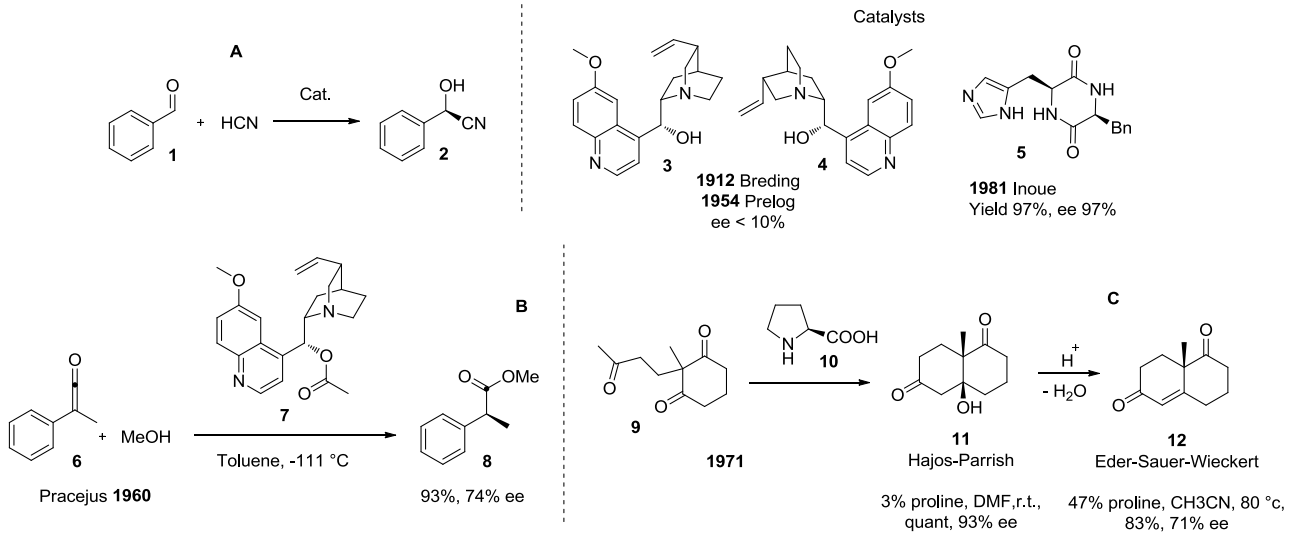


Figure 1.1: early milestones of enantioselective organocatalysis. **A**: Addition of HCN to benzaldehyde attempted by Bredig and Prelog, and finally achieved by Inoue was the first test and success in organocatalysis. **B**: For the first time, good enantioselectivity levels were achieved in this 1960 synthesis of enantioenriched ester by Pracejus. **C**: Hajos-Parrish-Eder-Sauer-Wieckert reaction, the milestone in proline-catalyzed aldolizations.

fact the reaction allows the enantioselective synthesis of the Wieland–Miescher ketone. An early application of this reaction in total synthesis is used by Woodward in his 1981 erythromycin synthesis[11]. In the same year a Japanese research group examined again the HCN addition to aldehydes, finally rising the eel to 97%, using a cyclic catalyst derived from histidine and phenylalanine[12] (*Figure 1.1*, **A**).
One year before the enantioselective Julia epoxydation of chalcones catalyzed by a polypeptide was published[13] (*Figure 1.2*, **A**). In 1984 alpha alkylation of alpha branched indanones was reported in the first example of enantioselective phase transfer catalysis using cinchona alkaloid ammonium quaternary salts[14], while in 1989 Kagan reported the first organocatalytic diels alder reaction[15]: reacting anthrone with maleimide, using quinine as catalyst, 61% of ee could be achieved in the product. At the same time that these really few reports on enantioselective organocatalysis were reported, metal-catalyzed enantioselective transformation grew up tremendously. A whole world made of many metal precursors, ligands and transformation had been developed and was still growing. Thinking about this, Peter Dalko, in one of his reviews, states:

> "Thus the concept of asymmetric catalysis has become almost synonymous with the use of metals in a chiral environment."[16]

By the way, the times were almost ready for organocatalysis, as again Peter Dalko says a few years later:

[11] R. B. Woodward *et al.*, *J. Am. Chem. Soc.*, **1981**, *103*, 3210-3213.
[12] J. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.*, **1981**, 229–230.
[13] S. Julià, J. Masana, J. C. Vega, *Angew. Chem.*, **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 929.
[14] U.-H. Dolling, P. Davis, E.J.J. Grabowski, *J. Am. Chem. Soc.*, **1984**, *106*, 446-447
[15] O. Riant, H. B. Kagan, *Tetrahedron Lett.*, **1989**, *30*, 7403.
[16] In: P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.*, **2001**, *40*, 3726-3748.

"Principally, asymmetric organocatalytic reactions were, for a long time, considered to be inefficient and limited in scope. In parallel, organometallic catalysts provided a flexible ground for all types of reaction, and thus received disproportionate emphasis. Although today the vast majority of reactions in asymmetric catalysis continue to rely on organometallic complexes, this picture is changing..."[17]

As we saw before, at this time, isolated but several examples of enantioselective organocatalytic reactions had been reported. Actually, many activation modes and reactions were developed, representing single discrete examples without a general background, like many little "black swan events"[18]. But in the end of 1990s something began to change. After the pollution prevention act in 1990, and the definition of atom economy and environmental impact factor in 1991[19] and 1992[20], in 1998 Anastas and Werner gave a big contribution to "green chemistry" with the definition of its 12 principles[21]. These are guidelines for the construction of more sustainable and eco-compatible chemical processes. Catalysis is expressively mentioned as one of the principles[22], as well as the selectivity of the process (including enantioselectivity). The design of reagents and catalysts less hazardous and toxic is another one.

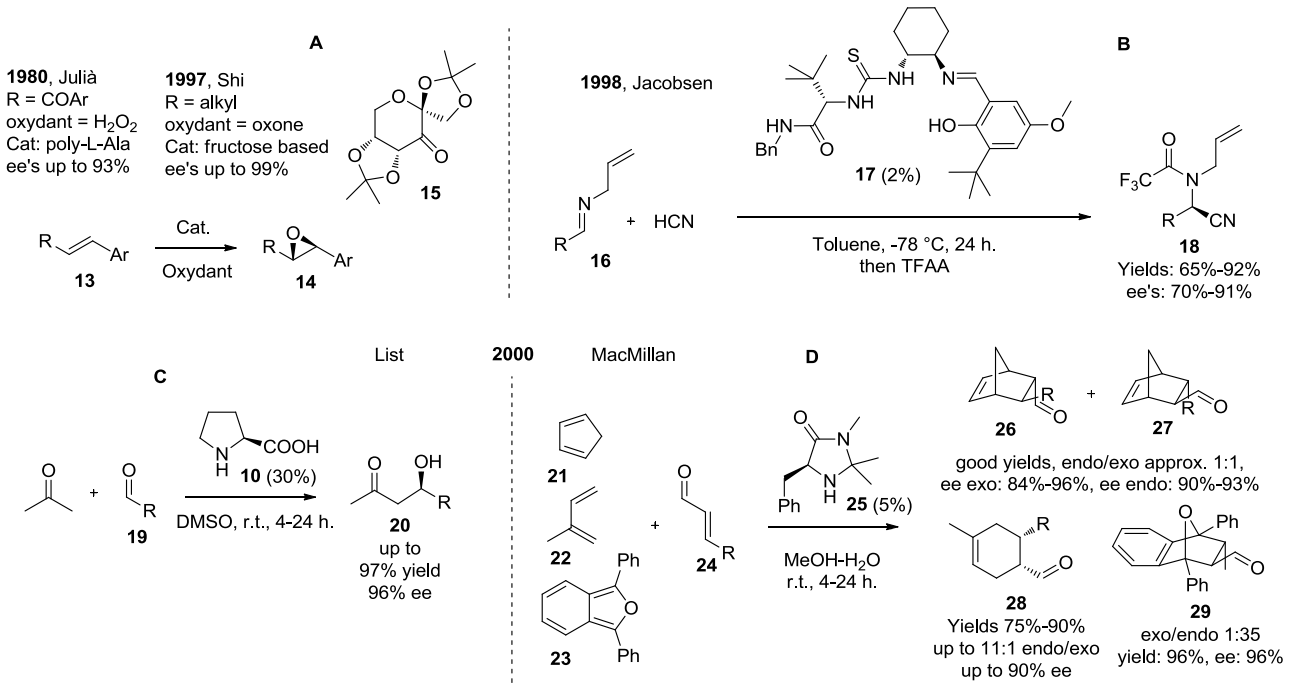


Figure 1.2: late milestones of organocatalysis. **A**: the first pioneering work by Julià on chalcone epoxidation, and the alkene epoxidation developed by Shi, which found many applications. **B**: HCN addition to allylimines developed by Jacobsen's group which after many effort found this thiourea-shiff base to be efficient. **C**: Chemo- and enantioselective cross-aldol reaction found by List in 2000. **D**: MacMillan's oxazolidinone catalyzes highly diastereo- and enantioselective diels alder on enals.

[17] In: P. Dalko. (2007). *Enantioselective Organocatalysis.* Weinheim: WILEY-VCH. Page 1.

[18] For the definition of the concept, but most of all for an illuminating reading see: W. A. Nugent, *Angew. Chem. Int. Ed.*, **2012**, *51*, 8936–8949.

[19] B. M. Trost, *Science*, **1991**, *254*, 1471–1477.

[20] (a) R. A. Sheldon, *Chem. Ind. (London)*, **1992**, 903-906; (b) R. A. Sheldon, *Chemtech*, **1994**, 38-47; (c) R. A. Sheldon, *Green Chem.*, **2007**, *9*, 1273-1283.

[21] P. T. Anastas, J. C. Warner, "Green Chemistry: Theory and Practice", (1998), Oxford University Press: New York.

[22] R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, (2007), WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.

While many metals are toxic and difficult to dispose, as mentioned before, organocatalysts are less toxic and easier to dispose. So, in principle, if equal in efficiency, organocatalysts are "greener" than metals. To this was added the fact that anyway in literature were present a number of examples that couldn't be ignored and that at the end of 1990s some of the currently major contributors to the field were at the beginning of their career, full of new ideas, and ready to embark in this new promising area. So, after a new organocatalytic epoxydation reaction reported by Shi[23] (*Figure 1.2*, **A**), in 1996 Enders reported for the first time the use of a chiral N-Heterocyclic Carbene (NHC) in an organocatalytic enantioselective transformation[24]. And in 1998 Eric Jacobsen performed again enantioselective HCN addition, but this time to aldimines, and with a new kind of catalysts, thioureas[25], which later became very popular (*Figure 1.2*, **B**). And then in the year 2000, the two current major contributors of aminocatalysis published their first papers on the topic. Benjamin List, together with Barbas and Lerner[26], made general the proline catalyzed aldolization pioneered by Hajos-Parrish-Eder-Sauer and Wieckert expanding the scope to many intermolecular reactions (*Figure 2*, **C**). David MacMillan (who coined the word "organocatalysis"[27]) designed the imidazolidinone catalysts that today bear his name, employing them in enantioselective Diels-Alder reaction on enals[28] (*Figure 2*, **D**).
Starting from this point organocatalysis gained much attention, and these seminal works prompted many others. In fact, this time for the first time, somebody looked for and found catalysts relied on general principles and activation modes, rather than single disconnected catalytic examples, discovering reactions with broad scope. The conventional wisdom that wanted organometallic catalysis to be the only one efficient in asymmetric synthesis was broken[18], and the door was open for a new "golden age" of organocatalysis[29].

[23] Z.-X. Wang, Y. Tu, M. Frohn, Y. Shi, *J. Org. Chem.*, **1997,** *62,* 2328-2329. (b) Z.-X. Wang, Y. Shi, *J. Org. Chem.*, **1997,** *62,* 8622-8623. (c) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.*, **1997,** *119,* 11224-11235.
[24] D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta*, **1996**, *79*, 1217-1221.
[25] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.*, **1998,** *120,* 4901-4902.
[26] B. List, R. A. Lerner, C. F. Barbas III, J. *Am. Chem. Soc.*, **2000**, *122*, 2395–2396.
[27] In: A. Berkessel, H. Groger. (2005). *Asymmetric Organocatalysis.* Weinheim: WILEY-VCH. Page XIII.
[28] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2000**, *122*, 4243–4244.
[29] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5138 – 5175.

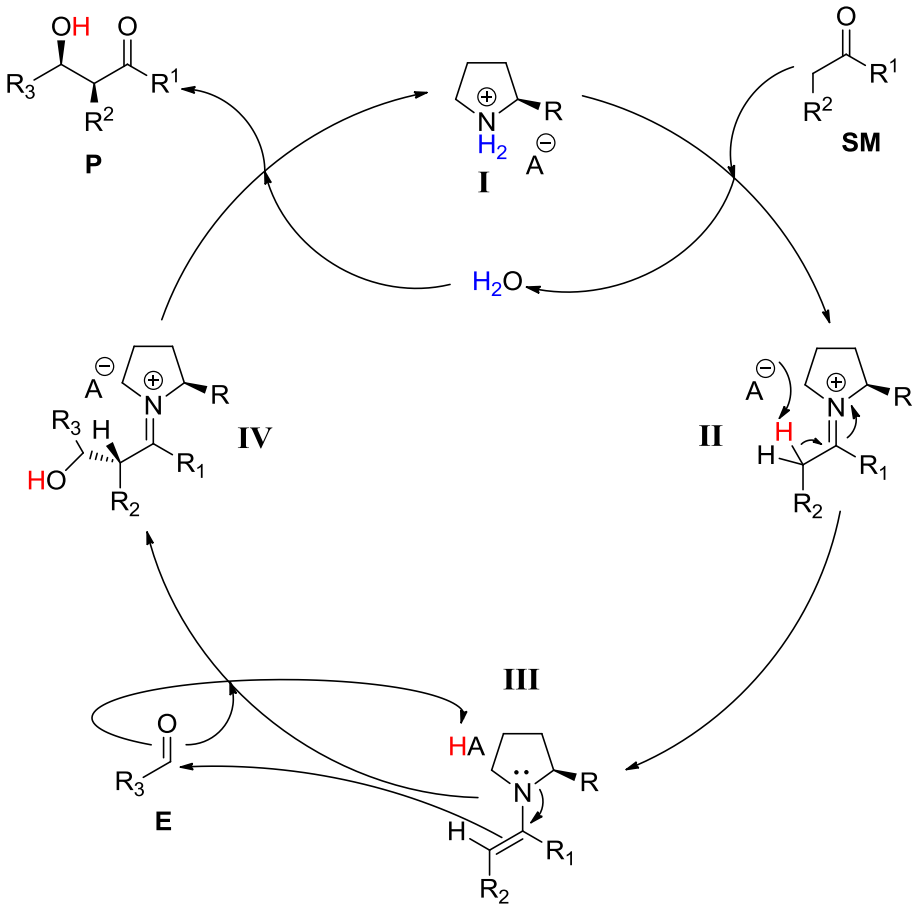
2) Activation modes and privileged catalysts

At the end of the last chapter we saw three examples where a thiourea, proline **10**, and an imidazolidinone were used as catalysts. Quickly, they and their derivatives became widely used for a great number of transformations. Thioureas, proline derivatives and imidazolidinones are nowadays families of catalysts, together with other ones appeared shortly after, like cinchona alkaloid derivatives, BINOL derivatives and chiral N-Heterocyclic Carbenes (NHC's). For each one of this classes, some particular catalysts have emerged as the ones giving better performance among the others. These are called privileged organocatalysts. Here below, each class of catalysts and some privileged catalysts are presented, divided by activation modes, and typical mechanisms are shortly discussed. Many organocatalysts are nucleophilic Lewis basic catalysts, and bind covalently the substrates in order to activate them. These are primary and secondary amine derivatives, phosphines and NHC's, and they are presented in the same section. Other catalysts do not bind covalently the substrates, like acidic or H-bonding catalysts as for example chiral Brønsted acids and thioureas. Also some other kinds of catalysts do not bind covalently the substrates: pure Brønsted basic catalysts and phase transfer catalysts (PTC's), and they are also grouped together. Finally, cooperative and bifunctional catalysis are presented.

2.1) Covalent catalysis

2.1.1) Primary and secondary amines

Primary and secondary amines are so much used in organocatalysis that their activation mose is one whole branch of organocatalysis, named aminocatalysis. The two examples reported by List and MacMillan (*Figure 1.2* **C** and **D**) are representative of two of the most widespread mechanisms in aminocatalysis. List's proline catalyzed aldolization proceeds *via* enamine, while MacMillan's organocatalysts works *via* iminium ion. These are the two key intermediates in the two mechanisms.
In enamine catalysis, the first step is the condensation of the catalyst (proline, or one of its derivatives in the figure) on the carbonyl compound **SM**, to give an iminium ion (*Scheme **2.1***, **II**), which is deprotonated to give the corresponding enamine (*Scheme **2.1***, **III**). The enamine **III** is the real nucleophile in the reaction and attacks the electrophile **E**, giving the iminium ion intermediate (*Scheme **2.1***, **IV**) that furnish the product and restores back the catalyst *via* hydrolysis.



*Scheme **2.1***: general mechanism of enamine catalysis.

So, enamine catalysis works via activation of the nucleophile and sometimes this kind of catalysis is called HOMO rising activation, watching it from a quantomechanical point of view. The catalyst's nitrogen donates electronic charge, allowing an easier reaction.
Actually, the concept of the reaction is not new at all, lying basically in the Stork enamminic synthesis[30], and in many other old achiral reaction like the Knoevenagel condensation[31]. Until 2000, nothing was done to obtain enantiomeric control, except in the Hajos-Parrish-Eder-Sauer-Wieckert reaction. The substituent R on the chiral center both controls the enamine geometry and causes steric hindrance, allowing the approach to the electrophile only by one side, creating enantiomeric excess. The enamine is a synthetic equivalent of the enolate. In enolate chemistry a stoichiometric amount of a strong base is generally required, and, typically, low temperatures are used to control enolate geometry. Since a net negative charge is present, metal enolates are formed and enantioselectivity must be achieved using chiral ligands on metal. Using chiral enamines as reaction intermediates allows the use of mild reaction conditions, room temperature operations and wet solvents, and achieving enantiocontrol. Proline **10** is a useful catalyst, but not satisfying for all the transformations. Its derivatives began to appear soon, like

[30] For the original paper see: G. Stork, S. R. Dowd, *J. Am. Chem. Soc.*, **1963**, *85*, 2178–2180. This reaction became a classic in organic synthesis and it's nowadays reported in every organic chemistry textbook.
[31] For the original paper see: E. Knoevenagel, *Ber. Dtsch. Chem. Ges.*, **1896**, *29*, 172; for an essay on the links between Knoevenagel's and other old scientist's work and modern aminocatalysis see: B. List, *Angew. Chem. Int. Ed.*, **2010**, *49*, 1730 – 1734. Moreover also this reaction became a classic in organic synthesis and it's nowadays reported in every organic chemistry textbook.

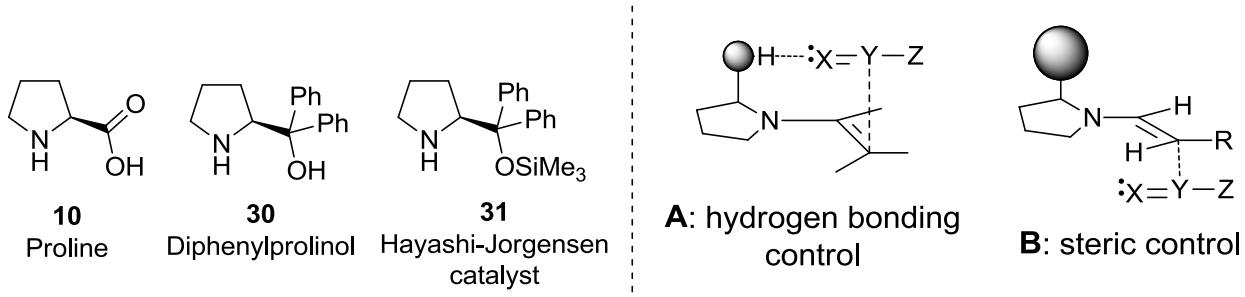


Figure 2.1: privileged enamine organocatalysts and activation modes.

diphenylprolinol **30** (*Fig. 2.1*), in which the carboxylic acid function is doubly alkylated to give a sterically hindered aminoalcohol. Another popular proline derivative is Hayashi-Jorgensen catalyst **31** (*Fig. 2.1*), the TMS-protected diphenylprolinol[32]. Developed in 2005 independently by the two researchers of which bears the name, this catalyst works in a different manner respect to proline **10** and diphenylprolinol **30**. In fact, while these two catalysts have a hydrogen bonding unit that can coordinate substrates (*Fig. 2.1*, **A**), enantioselectivity of Hayashi-Jorgensen **31** catalyst is given only by steric interactions (*Fig. 2.1*, **B**)[33]. Importantly, products arising from TS **A** and **B** possess opposite absolute configurations, as it is often experimentally reported[33]. Although these two enantiodetermining activation modes are widely reported an well explain the absolute configurations obtained for many products, the detailed mechanism of the enamine catalysis is still controversial, especially for proline. Whilst steric control together with defined *E* enamine geometry is generally accepted for diarylprolinol silyl ethers, activation modes in proline catalysis are still object of debate. Activation mode **A** was proposed for the first time by List in his first paper, who anyway was also reports that the only detectable intermediate in the reaction mixture is the corresponding oxazolidinone **II**, formed from the iminium ion **I**, thus before the enantiodetermining step (see scheme **2.2**)[26]. In List's model by the way this is a parasitic specie, with the only role to sequestrate the enamine, lowering the reaction rate. This model was confirmed by some computational studies by Houk who later collaborated also with List, to develop a mechanistic model and a transition state for the reaction[34]. Anyway, Seebach and co-workers suggested that this specie could be involved into the catalytic cycle otherwise[35]. This might be supported by the fact that oxazolidinones themselves are effective catalysts for aldolizations, giving the clue that they might be more than spectators in the process[36]. In fact not only hydrogen bonding control model **A** explains the observed absolute configurations of products. We said that the oxazolidinone is more stable, so the catalytic enamine could be formed starting from this one. Its opening should give the formation again of the zwitterion **III** (*Scheme **2.2***) and an intramolecular deprotonation might occur, giving rise to the *Z* enamine (**IV** in *Scheme **2.2***). Further carboxylate deprotonation by an external base would

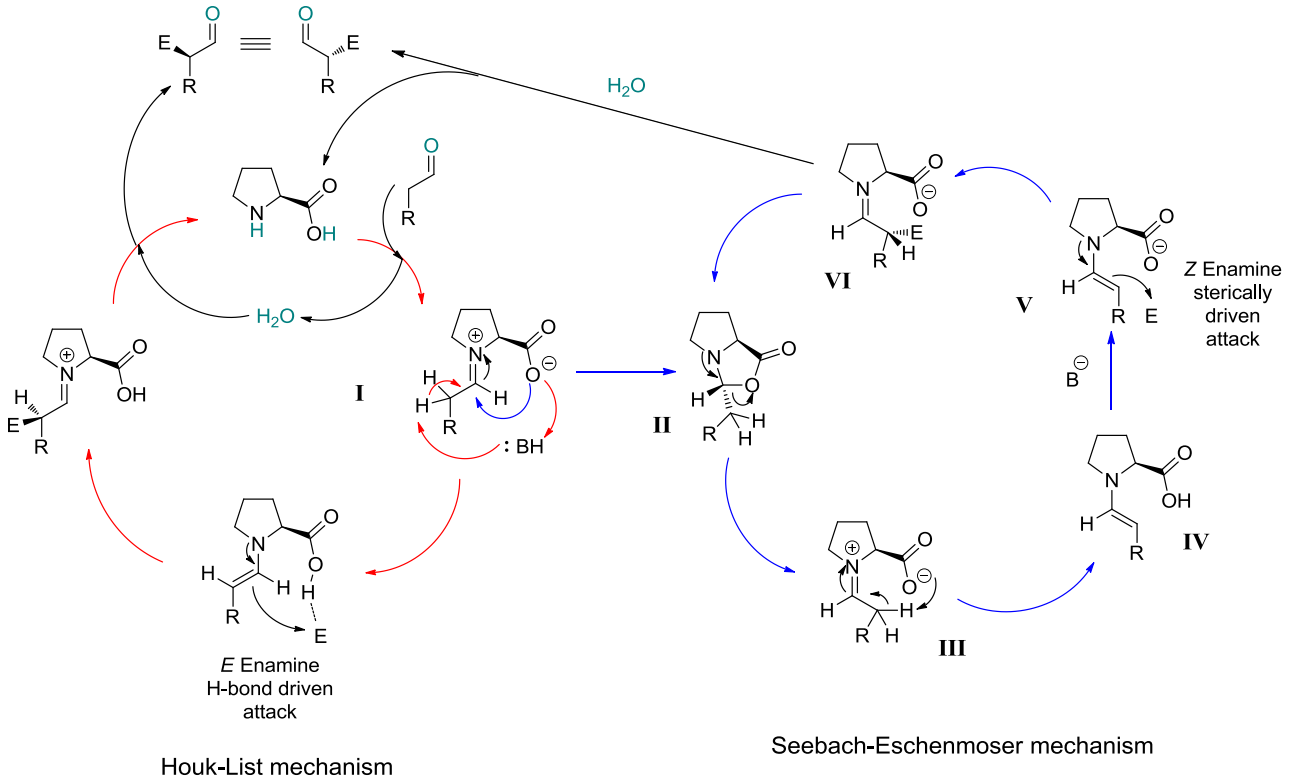
[32] a) J. Franzèn, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2005**, *127*, 18296-18304. b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.*, **2005**, *44*, 4212 –4215.

[33] C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.*, **2006**, *45*, 7876 – 7880.

[34] a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.*, **2001,** *123,* 11273-11283. b) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.*, **2001,** *123,* 12911–12912. c) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.*, **2003,** *125,* 16-17. d) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.*, **2003,** *125,* 2475–2479. e) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5839; f) F. R. Clemente, K. N. Houk, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5766-5768. g) D. A. Bock, C. W. Lehmann, B. List, *Proc, Nat. Acad. Sci. USA*, **2010**, *107*, 20636-20641.

[35] D. Seebach, A. K. Beck, M. D. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta*, **2007**, *90*, 425.

[36] C. Isart, J. Bures, J. Vilarrasa, *Tetrahedron Letters*, **2008**, *49*, 5414–5418.



Scheme **2.2**: comparison between List-Houk and Seebach-Eschenmoser model for proline-catalyzed enamine reactions

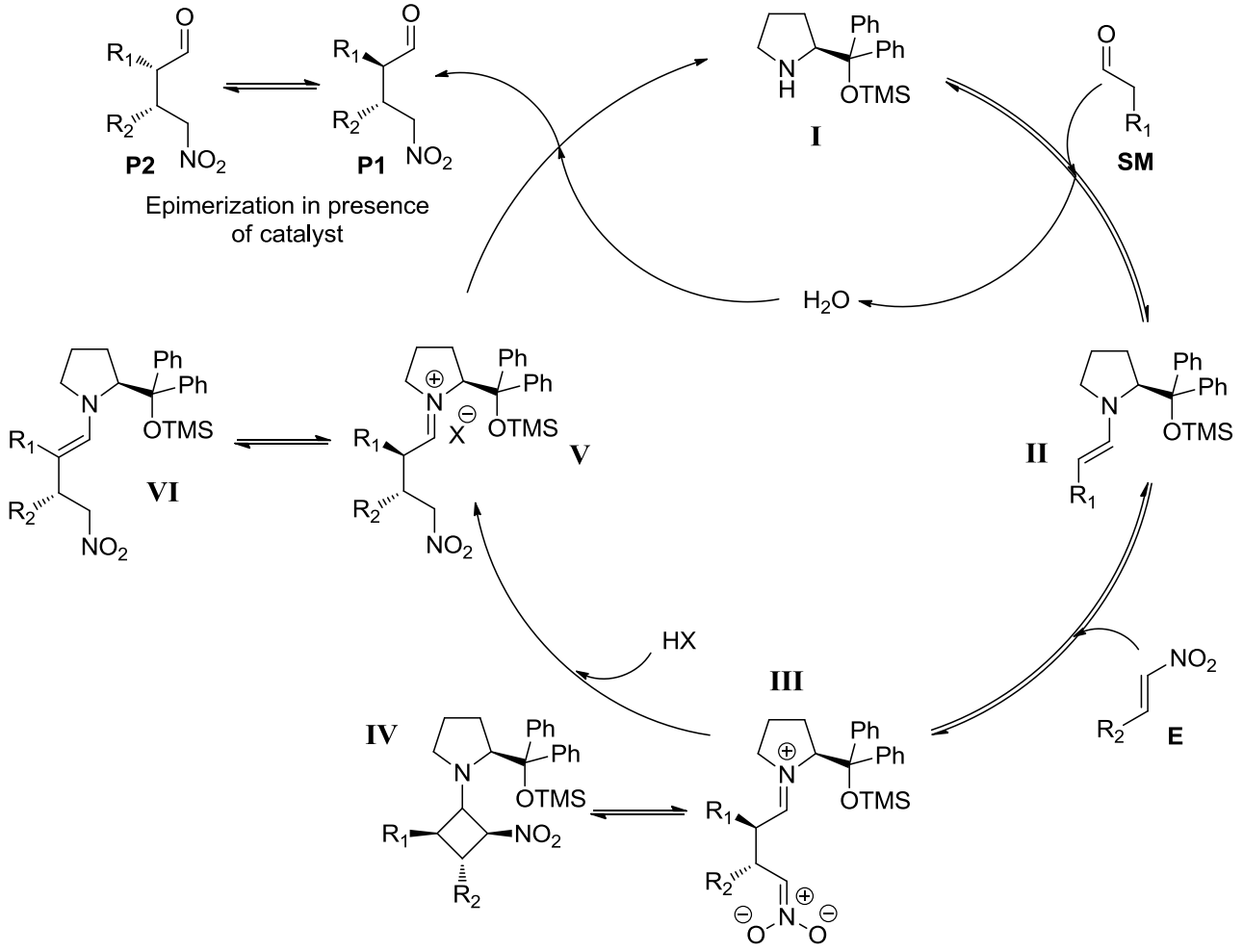
transform the carboxylate in a simple bulky group, allowing the electrophile approach by below the *Z* enamine, thus leading to the product with the same absolute configuration (Scheme **2.2**, **V** and **VI**). The problem is complicated also by further observation by Blackmond and co-workers of enantioselectivity switch in proline/prolinate salts catalyzed reactions[37]. At the present time no resolutive proofs have been furnished in favor of the one or of the other mechanism, possibly meaning that every reaction might work differently depending on substrates and conditions (mainly pH).

Another object of debate is in diarylprolinol silyl ethers catalyzed Michael additions to nitroolefines (see scheme **2.3**)[38]. After the enamine attack to the nitroalkene, an unstable zwitterionic intermediate **III** is formed, which likely collapses to give the corresponding cyclobutane **IV** with high levels of enantio- and diastereoselectivity. Anyway, for reaction completion a ring opening and protonation of the zwitterion, followed by iminium hydrolysis is necessary. This iminium ion **V**, anyway, might be deprotonated back to give the corresponding enamine **VI**, thus disrupting diastereoselectivity. The high observed d.r. would be given to the highly diastereoselective enamine protonation, as suggested Blackmond and co-workers[38b]. Even in this case no resolutive evidences have been furnished in favor of the one or of the other mechanism and the debate is not closed, showing that after 14 years from its discovery enantioselective enamine catalysis is still

[37] a) D. G. Blackmond, A. Moran, M. Hughes, A. Armstrong, *J. Am. Chem. Soc.*, **2010**, *132*, 7598. b) J. E. Hein, J. Burès, Y.-H. Lam, M. Hughes, K. N. Houk, A. Armstrong, D. G. Blackmond, *Org. Lett.*, **2011**, 13, 5644–5647.

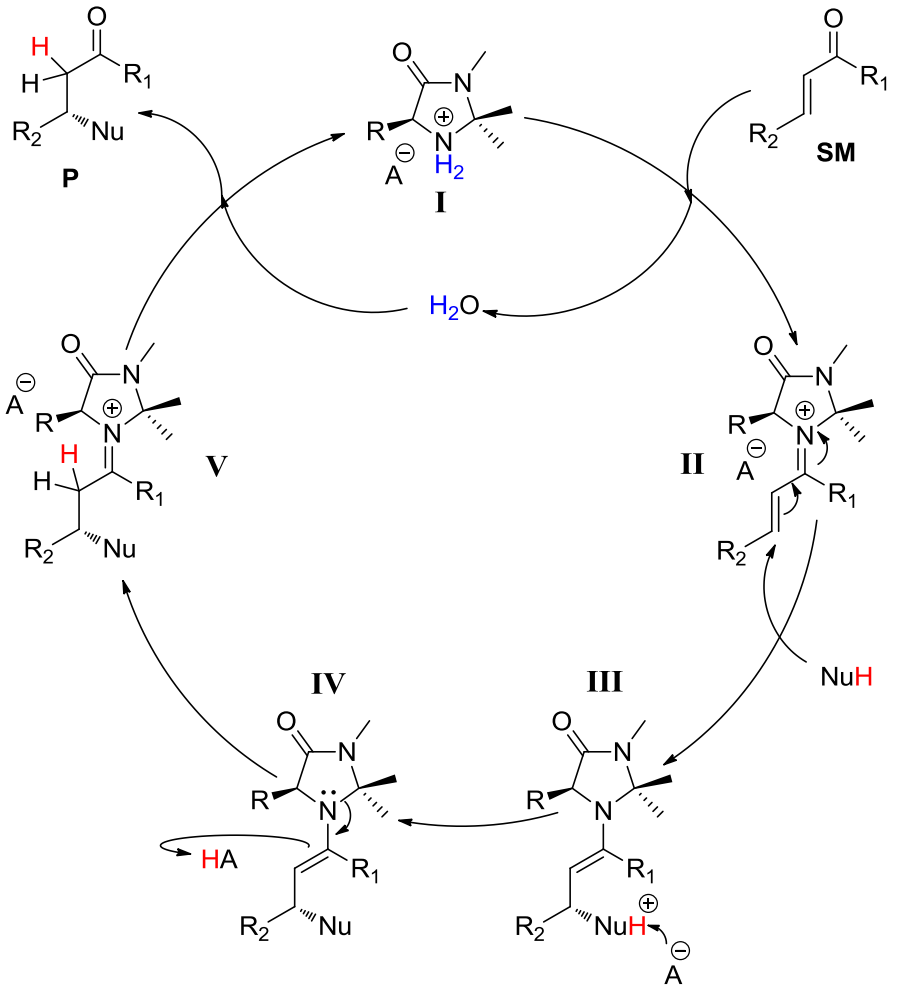
[38] Leading reference: C. Moberg, *Angew. Chem. Int. Ed.*, **2013**, *52*, 2160-2162. Original papers: a) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta*, **2011**, *94*, 719 – 745. b) J. Burès, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.*, **2011**, *133*, 8822 – 8825. c) J. Burès, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.*, **2012**, *134*, 6741 – 6750. d) D. Seebach, X. Sun, C. Sparr, M.-O. Ebert, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta*, **2012**, *95*, 1064 –1078.

challenging. Please note that both these discussions argue about proton transfer processes. It is known that many enamine catalyzed reactions are faster and more enantioselective using acidic additives, thus remarking the importance of proton transfers in enantioselective enamine catalysis.



Scheme **2.3**: mechanism of debate in diarylprolinol silyl ethers catalyzed Michael additions to nitroolefines.

MacMillan's imidazolidinones work mainly via iminium ion catalysis. In this kind of catalysis the iminium ion rising from the condensation of the catalyst on the substrate **SM** (Scheme **2.4**, **II**) reacts directly with a nucleophile present in the reaction mixture, and this generates an enamine (Scheme **2.4**, **III**). Further protonation of this enamine forms the iminium ion **V** and its hydrolysis gives back the catalyst and the product. The bases of this kind of catalysis rely also in old reactions but, also here for the first time enantioselectivity is achieved. Since a direct addition to the iminium ion carbon would just poison the catalyst, α,β unsaturated aldehydes or ketones are almost the only one electrophiles employed in this kind of catalysis, allowing the final hydrolysis with catalyst restoring. Thus, this is an activation of the electrophile, also mentioned sometimes as LUMO lowering (MacMillan himself is the first to talk about this in his first paper[28]), being the positively charged α,β unsaturated iminium ion a better electrophile than the corresponding aldehyde or ketone.



*Scheme **2.4***: general mechanism of iminium ion catalysis.

With this kind of mechanism, besides the first example of asymmetric Diels-Alder reaction and then many others, obviously this kind of activation mode has been employed extensively in every kind of Michael addition to α,β unsaturated aldehydes or ketones. Here enantioselectivity likely arise by a nucleophilic attack to the lower face of the *E* iminium ion, even if also in this case some considerations have been done regarding the mechanism and there is not complete certainty about it[39].

In both enamine and iminium ion activation, when employing secondary amines as catalysts, often the reaction does not work if ketones are used as Michael acceptors. This is principally due to the additional ketone alkyl group which causes too much steric hindrance, hampering the formation of the key enamine/iminium intermediate (*Fig. 2.2*, **A**). Thus, the less hindered primary amine moiety is often necessary for ketone activation (*Fig. 2.2*, **B**, left). Although catalysts derived from amino acids generally did not show good results, cinchona alkaloids derived primary amines proved to be effective and enantioselective catalysts, becoming in a few years the privileged catalysts for this kind of

[39] D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Šišak, T. Uchimaru, *Helv. Chim. Acta*, **2010,** *93*, 603-634.

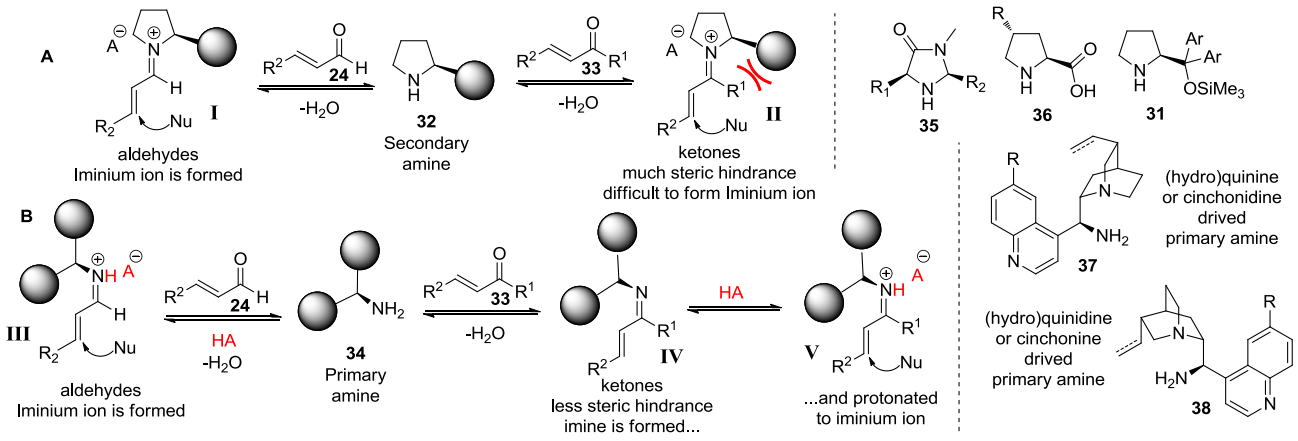


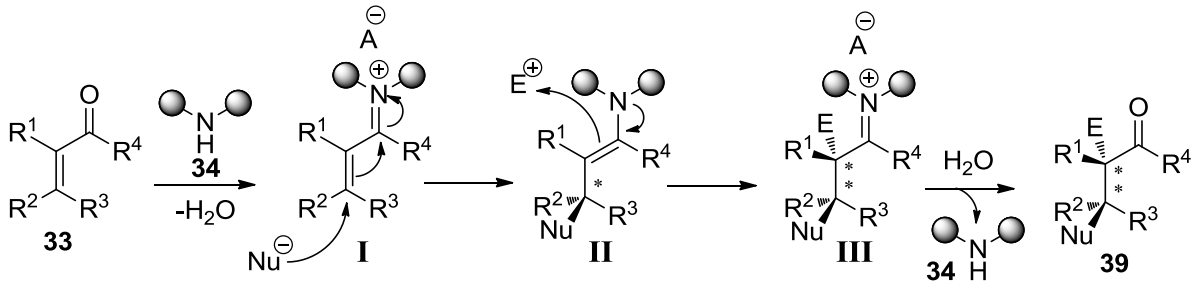
Figure 2.2. **A**, left: while the iminium ion **I** derived by secondary amines is readily formed with aldehydes, steric hindrance hampers its formation with ketones. **A**, right: general structure of some secondary amine derived privileged catalysts. **B**, left: the condensation of primary amines occurs easily with both aldehydes and ketones, to give the corresponding imines **III** and **IV**. An equivalent of acid is then required to form the iminium ion **V**. **B**, right: general structure of primary amine derived from cinchona alkaloids which became privileged catalysts in iminium ion activation of ketones.

activation (*Fig. 2.2*, **B**, right)[40]. Notably, in this case an equivalent of acid respect to the catalyst is required for the generation of the iminium ion (*Fig. 2.2*, **B**, in red), and since cinchona alkaloids possess an additional basic nitrogen atom, often the catalyst/acid ratio employed is 1:2. In this context, the nature and the amount of the acid are crucial, and can affect not only reactivity, but also selectivity. The choice of the acid is actually another variable to be taken into account, thus complicating the situation, but also giving another possible way for reaction optimization. Of course primary amines can activate also aldehydes, as well as examples of ketone activation by secondary amines are not missing (List aldolization is actually one of them). Not surprisingly, primary amines can be used in enamine catalysis as well.

It's easily possible to see how in the mechanism of enamine catalysis, iminium ion is present twice (Scheme **2.1**, **II** and **IV**), and in the mechanism of iminium ion catalysis enamine is present once (Scheme **2.4**, **III-IV**). This soon lead to the development of the so-called tandem and domino or cascade transformations[41], in which both the mechanisms are active at the same time using only one catalyst to operate more than one transformation in one pot. In a domino or cascade reaction, an electrophile activated via iminium ion can become a nucleophilic enamine after addition. This enamine can be captured by an appropriate electrophile, giving rise to a double functionalized product, in many cases with high enantiomeric excesses, adding thus value to the transformation. On the other way, an enamine addition product can become acidic enough to collapse onto the iminium ion formed as intermediate (scheme **2.5**).

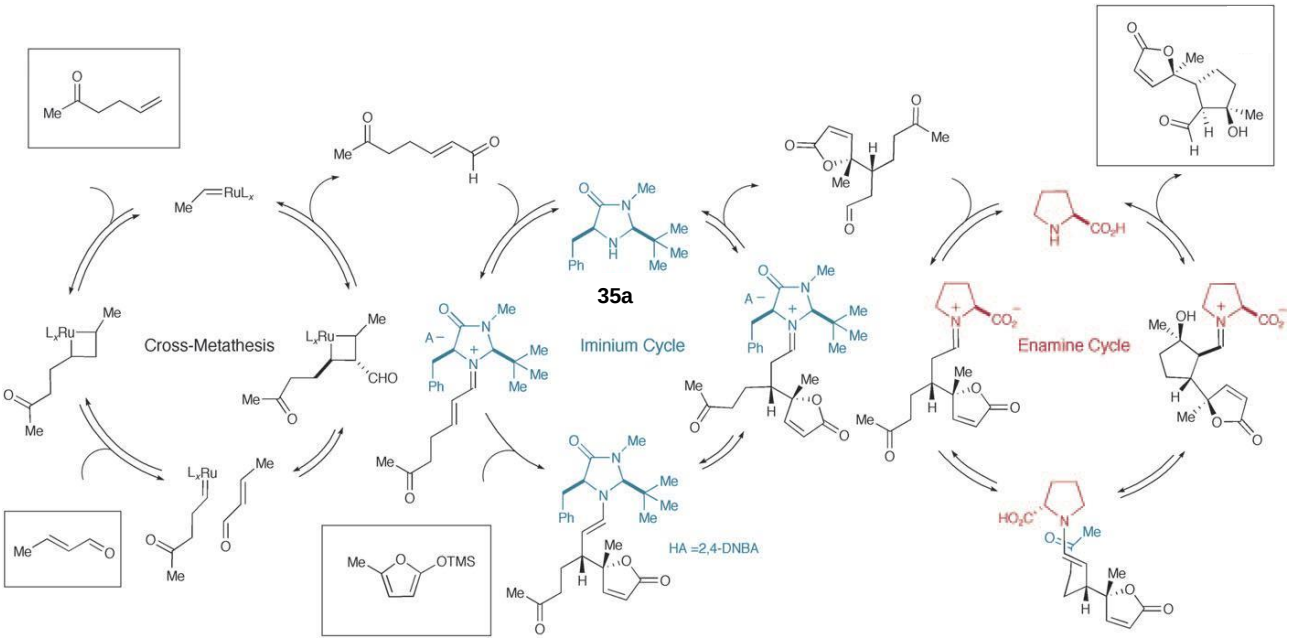
[40] a) Y.-C. Chen, *Synlett*, **2008**, 1919–1930., b) G. Bartoli, P. Melchiorre, *Synlett*, **2008**, 1759–1771. c) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.*, **2009**, 1807–1821. d) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol.*, **2011**, 1, 354–365. e) P. Melchiorre, *Angew. Chem. Int. Ed.*, **2012**, *51*, 9748–9770.

[41] a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.*, **2007**, *46*, 1570 – 1581. b) C. Grondal, M. Jeanty D. Enders, *Nat. Chem.*, **2010**, *2*, 167; d) B. Westermann, M. Ayaz S. S. van Berkel, *Angew. Chem. Int.Ed.*, **2010**, *49*, 846; e) Ł. Albrecht, H. Jiang, K. A. Jorgensen, *Angew. Chem. Int. Ed.*, **2011**, *50*, 8492-8509. f) H. Pellissier, *Adv. Synth. Catal.*, **2012**, *354*, 237 – 294. g) R. C. Wende, P. R. Schreiner, *Green Chem.*, **2012**, *14*, 1821–1849.



*Scheme **2.5***: tandem nucleophilic addition to an iminium ion and reaction with an electrophile of the resulting enamine.

Alternatively, in tandem processes these events are discrete, involving enamine catalysis, hydrolysis and then iminium, or two enamine, two iminium, and so on, up to the point of chemist's fantasy can achieve (a representative example is given in scheme **2.6**)[42]. Of course these transformations are not trivial, and must be well designed, otherwise they are not effective, resulting in mixture of products. Careful choice of catalysts, conditions and reactants can anyway give many valuable transformations, and a lot of paper had been published on the topic, also developing the concepts of triple and quadruple cascade. Enamine and iminium ion catalysis are strictly connected one to each other, being two sides of the same medal, or, as Benjamin List defined them in one of his review, the Yin and Yang of asymmetric aminocatalysis[43].

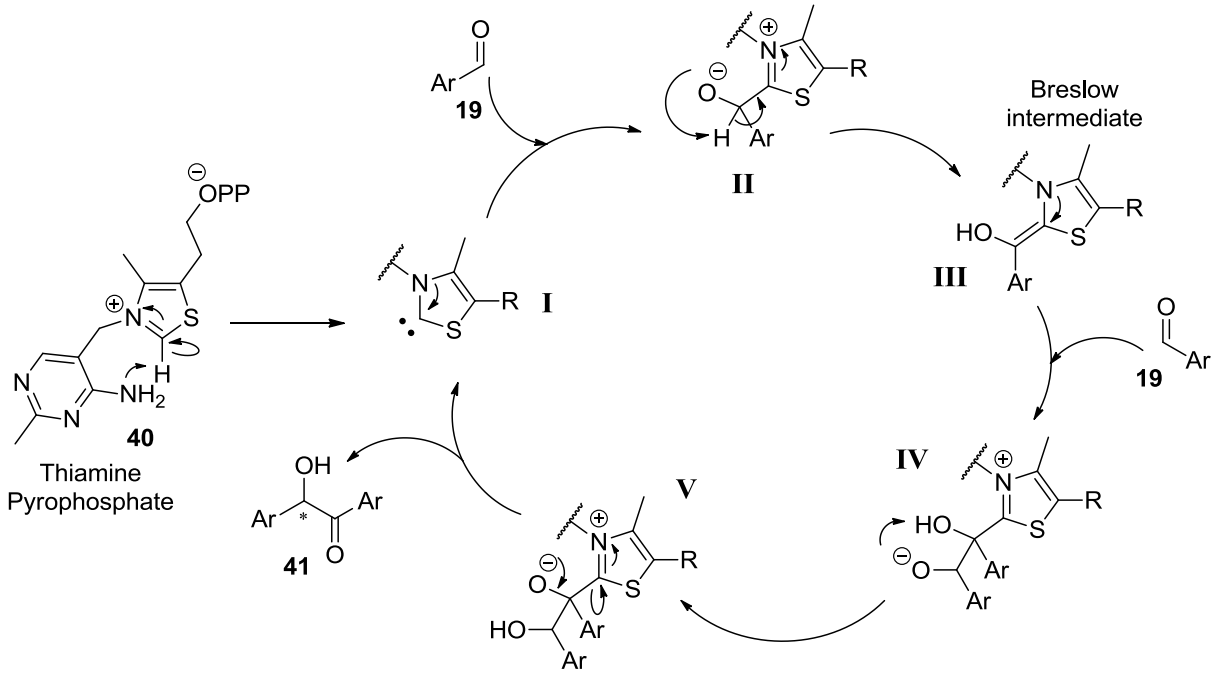


Scheme **2.6**: well-representative example of triple cascade catalysis with a combination of a cross-metathesis catalysts and two enantioselective organocatalysts, the firs working via iminium the second via enamine.

[42] Selected example given in scheme **2.6**: B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem. Int. Ed.*, **2009**, *48*, 4349 –4353.
[43] B. List, *Chem. Commun.*, **2006**, 819–824.

2.1.2) N-Heterocyclic Carbenes (NHCs)

After the first report by Enders in 1996[24], NHCs used as enantioselective organocatalysts grew tremendously after the re-discovery of organocatalysis in the 2000s. The inspiration is again biomimetic, since they are based on the working mechanism of the coenzyme thiamine pyrophosphate **40**, or vitamin B1, active in pyruvate dehydrogenase and in the formation of acetyl CoA. This coenzyme was found to catalyze the benzoin condensation for the first time in 1943[44] and the mechanism of this reaction was proposed for the first time by Breslow in 1957[45] (Scheme **2.7**).



Scheme **2.7**: the mechanism of the thiamine pyrophosphate catalyzed Benzoin reaction.

The basic unit of thiamine helps the deprotonation of the thiazole moiety, with the formation of a carbene (**I**). This is a highly nucleophilic specie and attacks the aldehyde, giving rise to the zwitterionic intermediate **II** that rearranges to the neutral enol **III** by proton transfer. This enol is called "Breslow intermediate", and remained elusive until recently, when particular Breslow intermediates have been isolated and characterized, thus confirming the presence of this intermediate in the catalytic cycle[46]. The Breslow intermediate can react with electrophiles, giving again a zwitterionic intermediate (**IV**) that, after another proton transfer, eliminates the thiazole as a leaving group, furnishing the Benzoin product **41** and restoring the catalyst.

[44] T. Ugai *et al., J. Pharm. Soc. Jpn.*, **63**, 296.

[45] R. J. Breslow, *J. Am. Chem. Soc.*, **1957**, *79*, 1762.

[46] a) B. Maji, M. Horn, H. Mayr, *Angew. Chem. Int. Ed.*, **2012**, *51*, 6231-6235. b) B. Maji, H. Mayr, *Angew. Chem. Int. Ed.*, **2012**, *51*, 10408-10412. c) H. Patel, N. S. Nemeria, L. A. Brammer, C. L. Freel Meyers, F. Jordan, *J. Am. Chem. Soc.*, **2012**, *134*, 18374–18379 d) A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer, J. H. Teles, *Angew. Chem. Int. Ed.*, **2012**, *51*, 12370-12374. e) A. Berkessel, V. R. Yatham, S. Elfert, .-M. Neudörfl, *Angew. Chem. Int. Ed.*, **2013**, *52*, 11158-11162.B. Maji, M. Horn, H. Mayr, *Angew. Chem. Int. Ed.*, **2013**, *52*, 11163-11167.

The studies on these kind of catalysts lead to the understanding that imidazole and triazole, especially if substituted with aromatic groups, can form more stable carbenes, helped by the fact that this carbene is aromatic. Many chiral molecules have been developed as enantioselective organocatalysts, but also in this case, some are privileged (*Fig.* 2.3, **A**). They are usually added to the reaction mixtures as azoluim salts, and then the carbene is generated in situ by the adding of an external base (*Fig.* 2.3, **B**).

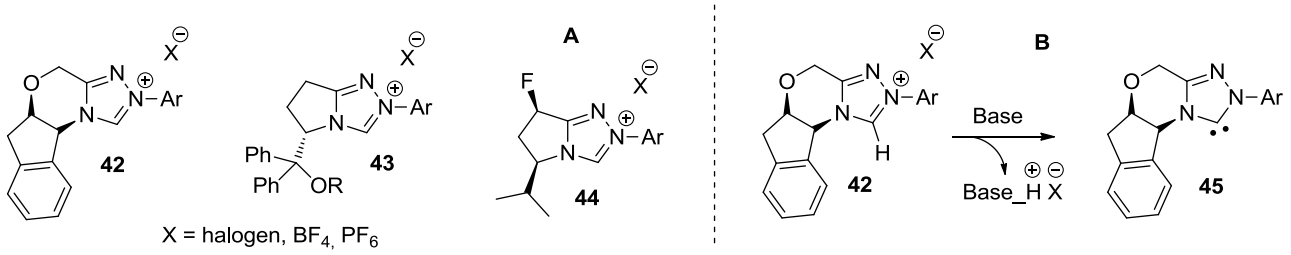


Figure 2.3: privileged NHC organocatalysts and their activation mode.

The use of this class of catalysts is particularly remarkable, because it gives access to the so-called "umpolung" reactivity (*Fig*. 2.4, **A**)[47]. In fact with this strategy carbonyl groups become nucleophilic, and it is also possible the formation of homoenolates (*Fig*. 2.4, **B**), opening the way to enantioselective umpolung reactions. It should be noted that the Breslow intermediate is actually an enol, but it reacts as an enamine, exploiting the electron donation of the nitrogen's lone pair, making NHC's, in the end, enamine catalysts, but umpolung (*Fig*. 2.4, **C**). Typical reactions catalyzed by NHC's are the Benzoin condensation and the Stetter reaction, but many other interesting reactions and also cascade transformations had been developed[48].

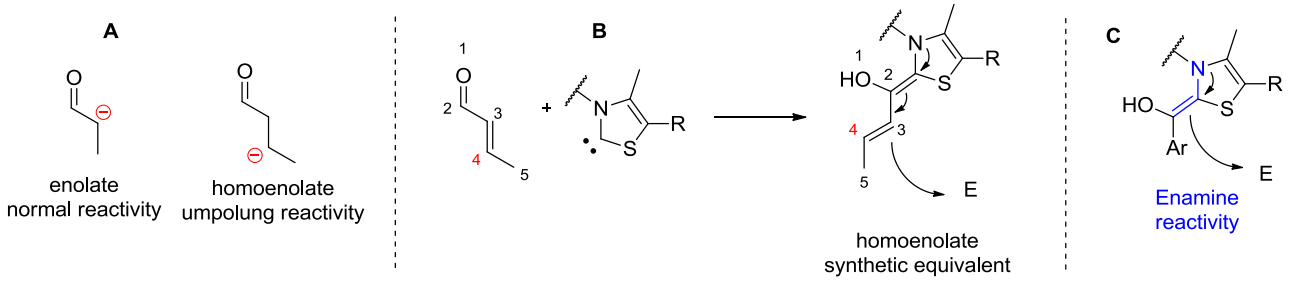
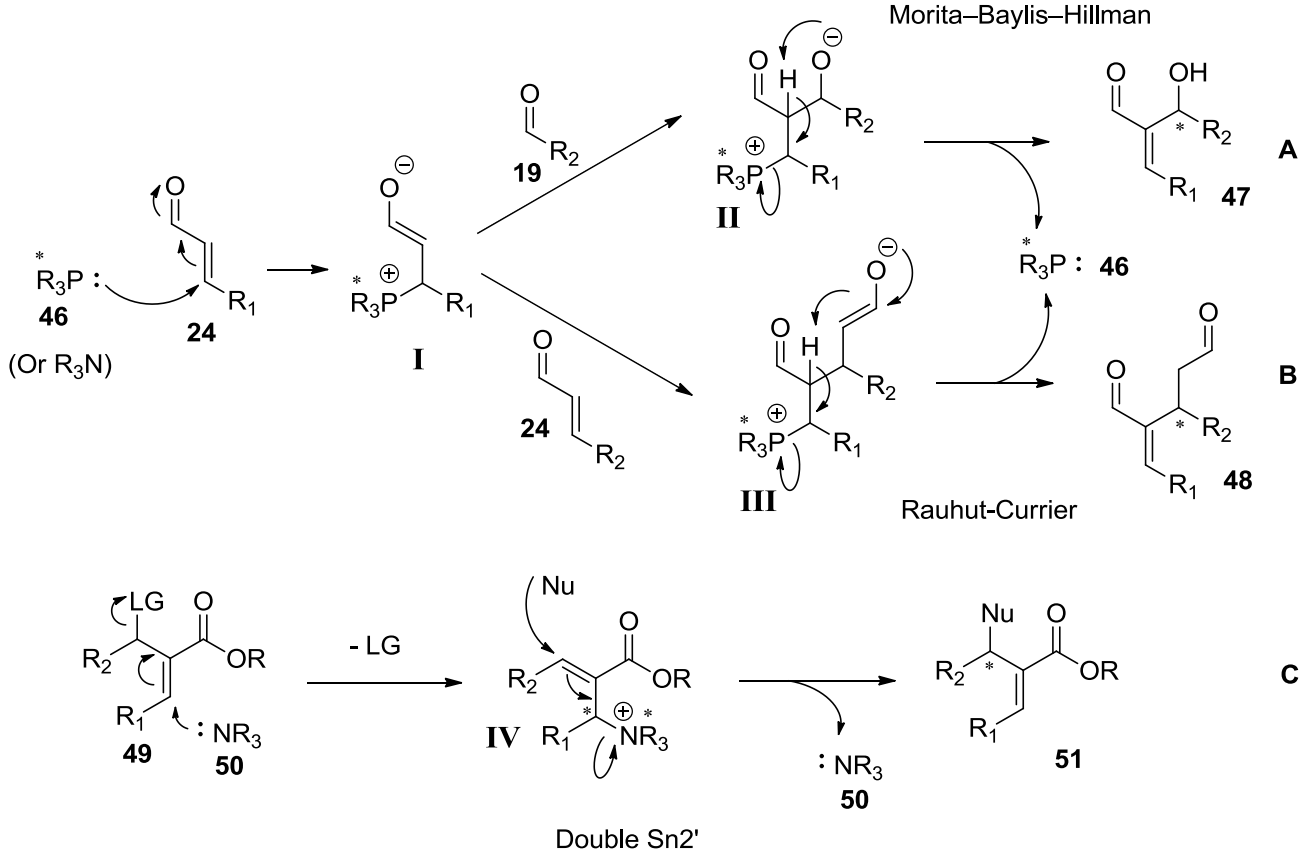


Figure 2.4. **A**: umpolung reactivity of carbonyl compounds. **B**: condensation of NHC on α,β-unsaturated carbonyl compounds give rise to Breslow intermediates synthetically equivalent to homoenolates. **C**: comparison of NHC reactivity to enamine reactivity.

[47] X. Bugaut, F. Glorius, Chem. Soc. Rev., 2012, **41**, 3511–3522.
[48] Selected reviews: a) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res*, **2011**, *44*, 1182-1185. b) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.*, **2012**, *51*, 314-325. c) X.-Y. Chen S. Ye, *Org. Biomol. Chem.*, **2013**, ***11***, 7991-7998.

2.1.3) Other covalent catalysts

There are other two categories of covalent catalysts which anyway are less employed, because they are able to catalyze essentially only a few transformations. These are phosphines and tertiary amines used as Lewis bases (as we will see later, tertiary amines can be used also as Brønsted bases). In the first class of transformation, the activation mode is always the same: the N or P atom attacks an electron-deficient double bond, creating a reactive specie, whose fate is different depending on the nature of the substrate. In Morita–Baylis–Hillman reaction (scheme 2.8, **A**) and Rauhut-Currier reaction (scheme 2.8, **B**)[49] a zwitterionic enolate (**I**) is formed in this way, which attacks a carbonyl compound **19** or an α,β-unsaturated carbonyl compound **24** respectively. Then the catalyst is released by a protin transfer which restores the double bond (scheme 2.8 **II** and **III**).
In double Sn2' reactions (scheme 2.8, **C**)[50] a leaving group in the allylic position gives rise to a positively charged Michael acceptor (**IV**), which is attacked by a nucleophile present in the reaction mixture with a second Sn2' reaction in which the catalyst acts as a leaving group, leading to the formal Sn2 product **51**. The most useful catalysts for these reactions are simple or dimeric cinchona alkaloid derivatives, 3-DMAP derived BINOL derivatives developed by Sasai, β-ICQD. Phosphines are mostly derived from BINOL or from amino acids (*Fig*. 2.5).



Scheme 2.8. Organocatalytic enantioselective Morita–Baylis–Hillman (**A**), Rauhut-Currier (**B**) and double Sn2' reactions (**C**).

[49] For an excellent review on organocatalytic enantioselective Baylis-Hillmann and Rauhut-Currier reactions see: Y. Wei, M. Shi, *Chem. Rev.*, **2013**, *113*, 6659−6690.
[50] For a review on the topic see: R. Rios, *Catal. Sci. Technol.*, **2012**, *2*, 267-278.

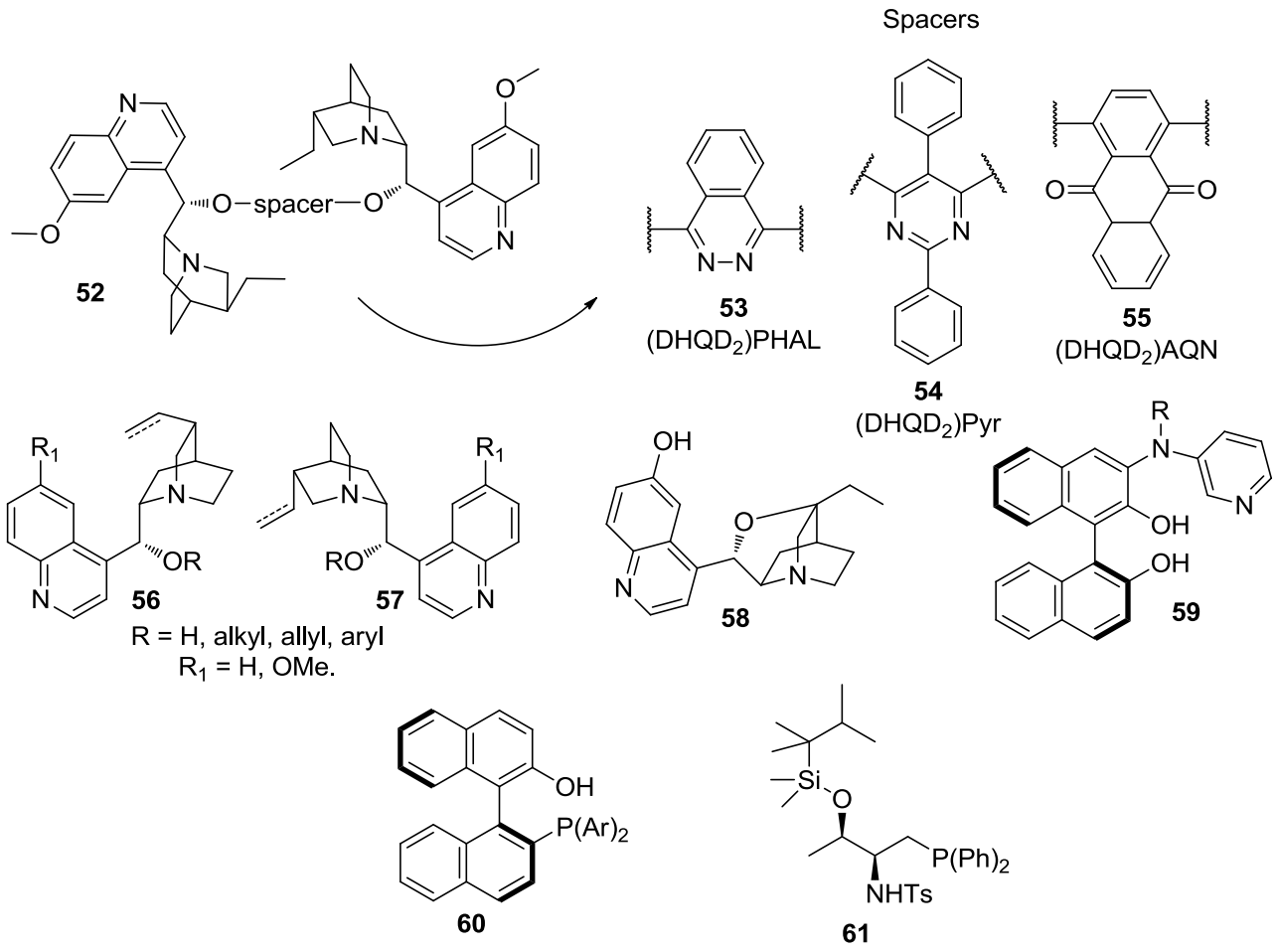


Figure 2.5. Privileged organocatalysts for nucleophilic catalysis.

2.2) Non-covalent catalysis

2.2.1) Phase-transfer and Brønsted base catalysis

Phase transfer catalysis is very particular, but also very fascinating, versatile and one of the most successful, both in academics and in industry. Here the catalysts are positive charged species, almost always chiral quaternary ammonium salts, and the catalysis requires a biphasic mixture, aqueous and organic solvent. *Figure 2.6* shows the mechanism, in which we call **SH** an enolizable substrate, but could be also any other specie that possess an acidic proton. In the aqueous phase is dissolved an inorganic base, typically an hydroxide, while the reactants are in the organic phase, and the catalyst **QX** at the interphase. When **SH** gets in contact with the aqueous phase is deprotonated, and stays at the interphase forming the corresponding metal enolate **KS**, releasing water in the aqueous phase. When this meets the chiral ammonium halogenide, a counterion exchange occurs, forming the metal halogenide **KX**, released in water, and the ammonium enolate **QS** as a chiral contact ion pair which stays in the organic phase. A real chiral recognition occurs and the catalyst and the enolate have complementary interactions. The net charges help the two ions not to dissociate and the enolate is forced to stay in a well-defined position, exposing only one of the two faces. In this way when this chiral contact ion pair meets the electrophile **RX**, a well-organized transition state is created, and an enantioselective addition is performed.

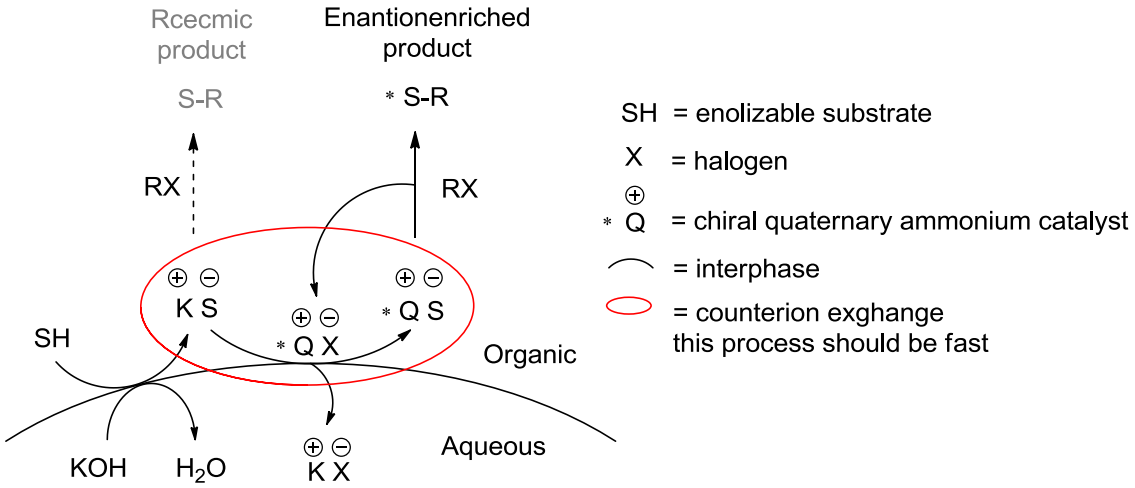


Figure 2.6: the phase transfer catalysis. The substrate **SH** is deprotonated at the interphase and the metal enolate **KS** undergoes a rapid counterion exchange (in red). Reaction of the so-formed chiral contact ion pair **QS** with an halogenide **RX** gives back the catalyst and forms the enantioenriched product.

The most important thing in this process is that, in order to avoid racemic reactions (*Fig*. 2.6, in gray), the counteranion exchange should be fast (*Fig*. 2.6, in red). Moreover, not only ionic interactions have to be considered, but there should be a network of other weak interactions that help to shield one of the enolate's faces. Finally, the electrophile should be able to interact with this ionic couple through other weak interactions, otherwise it will show one of its faces random. A disadvantage of this kind of catalysis is that one of the substrates must be enolizable, or anyway to have acidic protons.

The quaternary ammonium salts mostly used for this kind of catalysis are derived from cinchona alkaloids or from BINOL (*Fig*. 2.7, **A**). An impressive number of reactions have been catalyzed with these catalysts. Glycine derived iminoesters **65** are one of the most employed nucleophiles, because their enantioselective functionalization gives rise to enantioenriched non-natural amino-acid derivatives **67** (*Fig*. 2.7, **B**)[51].

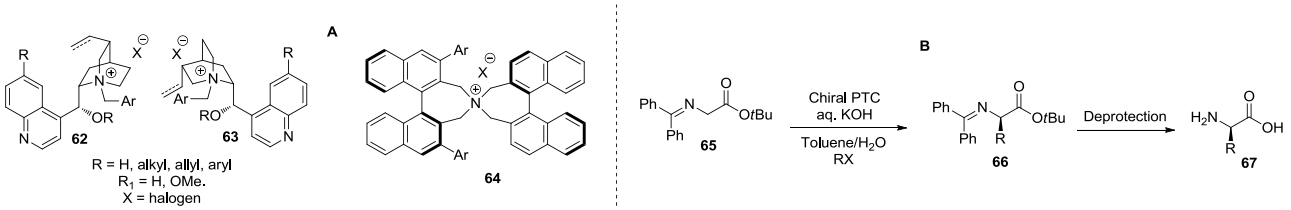


Figure 2.7. **A**: general structures of the two classes of privileged PTC's. **B**: general PTC alkylation of glycine derivative which became a test reaction for PTC's.

The working model for chiral Brønsted base catalysis is basically the same. Here homogeneous conditions are applied and no external bases are employed because the deprotonation of the substrate is performed directly by a chiral tertiary amine, forming thus the chiral ammonium enolate which than reacts with an electrophile. The practical advantage of this technique respect to PTC is balanced by the lower results sometimes obtained. While with PTC the proton is actually removed, here it stands on nitrogen, allowing proton transfer processes, possible hydrogen bindings with the solvent, and the missing of some important additional weak interactions. Privileged organocatalysts are derived from cinchona alkaloids, guanidines and the recently developed phosphoranes (called also "superbases") (*Fig*. 2.8). Moreover, many of these catalysts are bifunctional, and will be described later.

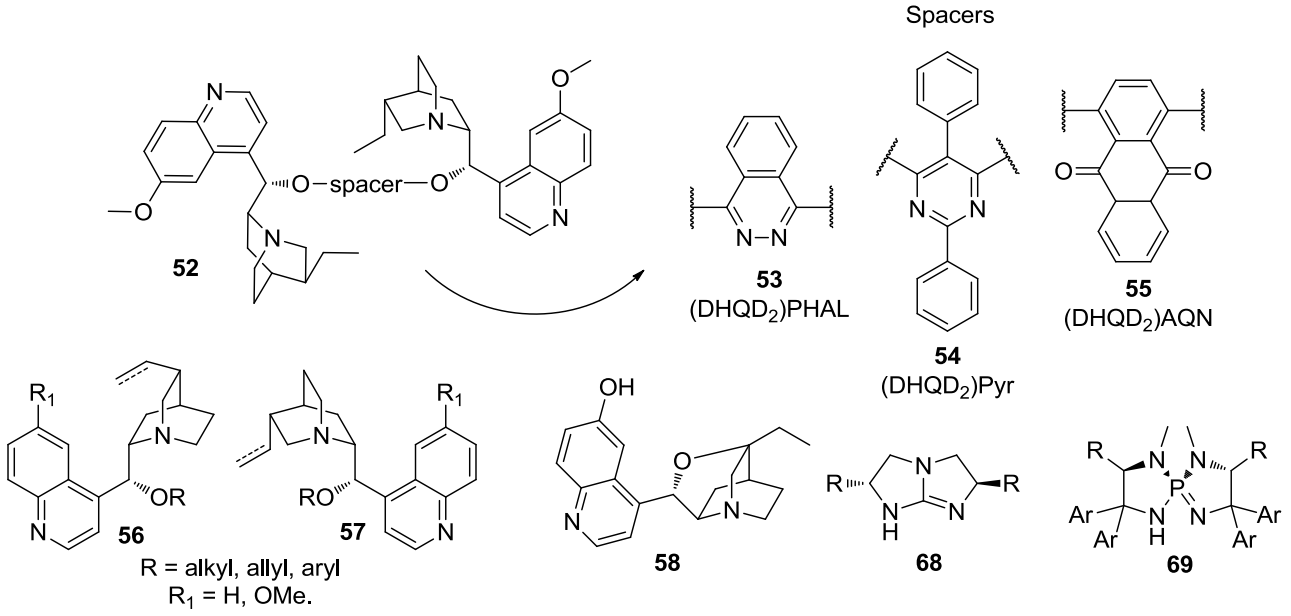


Figure 2.8: privileged Brønsted base catalysts.

[51] a) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.*, **2007**, *46*, 4222 – 4266. b) S. Shirakawa K. Maruoka, *Angew. Chem. Int. Ed.*, **2013**, *52*, 4312-4348.

2.2.2) Hydrogen-bonding catalysis

The secrets of the high catalytic activity and enantioselectivity of enzymes are basically two: the shape of the chiral pocket complementary to the transition state of the reaction, and the creation of a well-organized framework of hydrogen bonds. While such complex shape selectivity is difficult to obtain with artificial organocatalysts (and perhaps not convenient, since the structural complexity that must be possessed by the catalyst), using hydrogen bonds as anchoring, directing and catalytic units is a well-developed strategy in asymmetric organocatalysis. Hydrogen bonding donors can coordinate lone pairs of electron withdrawing groups (EWG) possessed by electrophiles. The stronger is the hydrogen bonding ability of the hydrogen bonding donor, the stronger is the interaction with an EWG. In this way the electron density is shifted towards the EWG, leaving uncovered other parts of the molecule, which becomes more electrophilic. So, this is an activation of the electrophile. Representative examples of single point hydrogen bond donors and double point hydrogen bonds, with relative bond strengths are depicted in figure 2.9 **A** (hydrogen atoms responsible for hydrogen bonding are depicted in red)[52]. Also a representative interaction between an hydrogen-bonding organocatalyst and various electrophiles is depicted in figure 2.9 **B**, and nitroalkenes are chose to represent enhanced electrophilicity of a compound if bound to an hydrogen-bonding organocatalyst (*Fig*. 2.9 **C)**.

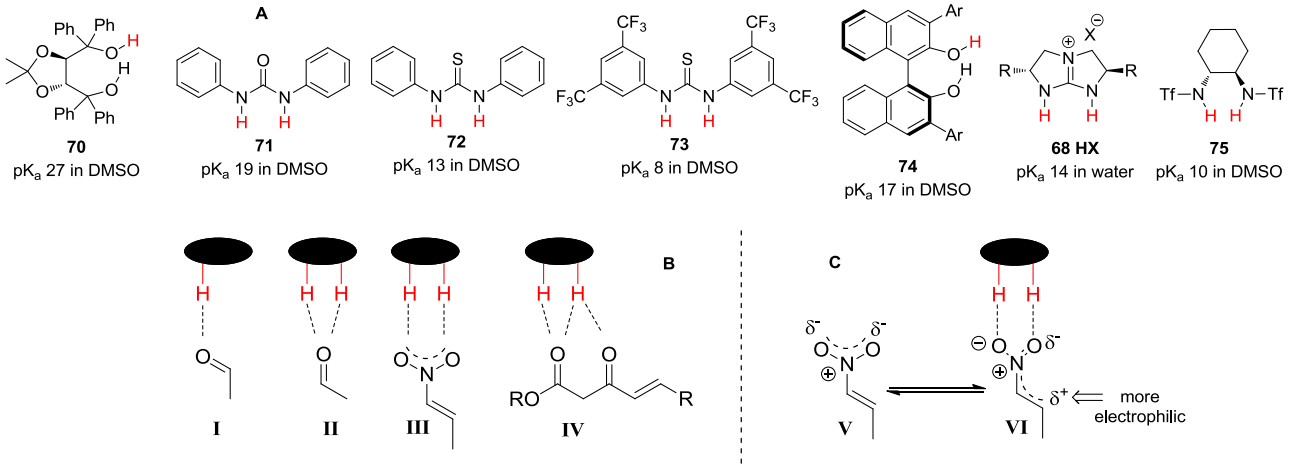


Figure 2.9. **A**: comparison of pK_a values of some kind of hydrogen bonding donor organocatalysts. The lower the pK_a value is, the higher is its hydrogen bonding donor character. EWG-substituted thioureas are more acidic than thioureas, which are more acidic than ureas. **B**: representative interactions between an H-bonding catalyst and some electrophiles. **C**: explicit graphic representation of enhanced electroplilicity in nitroalkenes bound to H-bonding organocatalysts. Hydrogen atoms responsible for hydrogen bonding are depicted in red.

Often, other interactions have to be taken into account in this kind of catalysis, like π-interactions, other hydrogen bonds and more, for a good outcome of the reactions. In fact, this is a weak interaction, and often is not enough to make the reaction occur, so a simultaneous activation of the electrophile or at least its coordination is necessary.

Thioureas are the most widely used H-bonding organocatalysts, especially as bifunctional organocatalysts. This class of catalysts will be described later, so here following in figure 2.10 are reported examples of privileged organocatalysts in which the H-bonding functionality is the main responsible for catalysis.

[52] Leading references: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.*, **2007,** *107*, 5713-5743. b) R. R. Knowels, E. N. Jacobsen, *Proc. Nat. Acad. Sci. USA*, **2010**, *107*, 20678-20685.

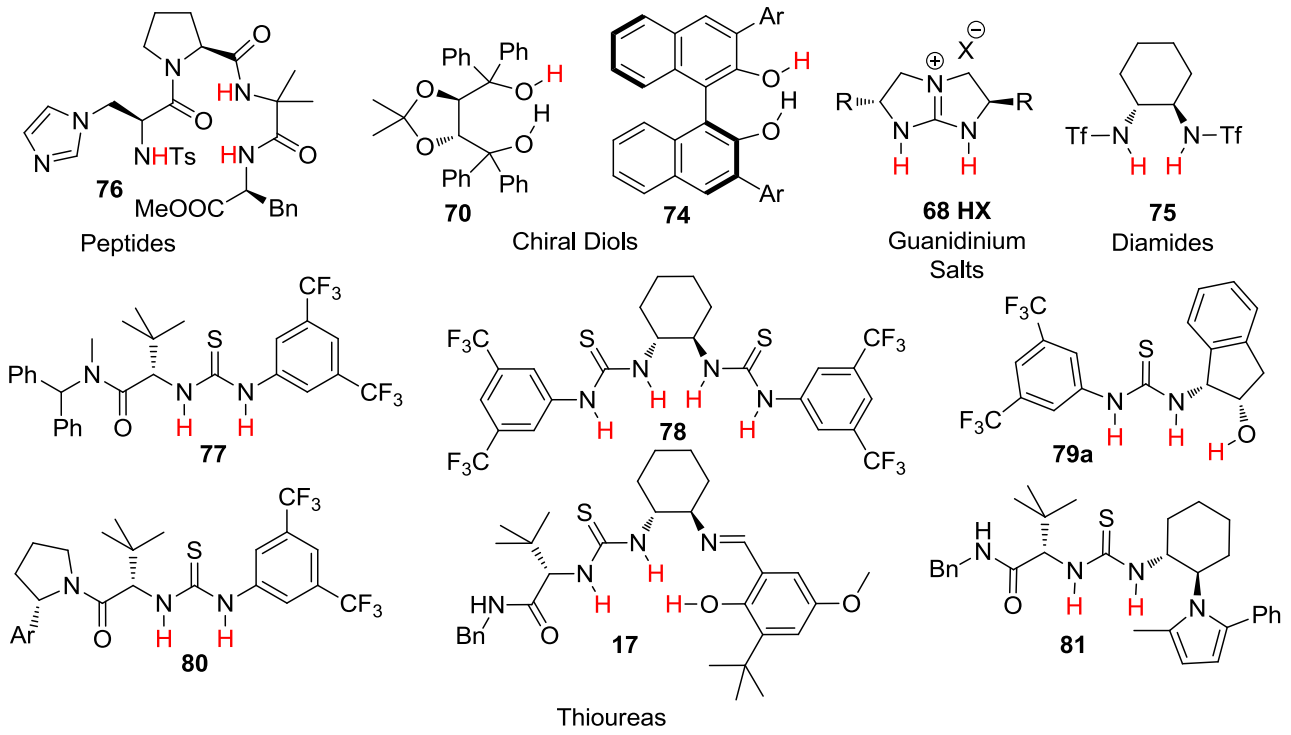
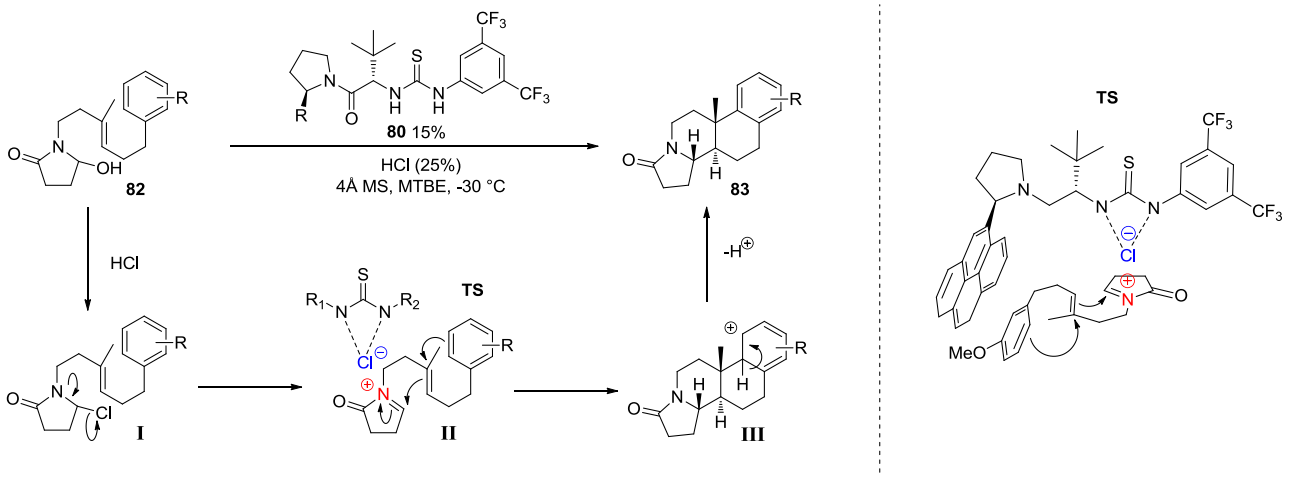


Figure 2.10: privileged hydrogen bonding organocatalysts

Thioureas are also well known as anion binders[53] and this has been exploited for a kind of catalysis called anion binding catalysis[54], where chiral thioureas bind an anion, and a prochiral cationic electrophile is associated to this complex, obtaining enantioselectivity using the thiourea as chiral template when the reaction occurs (Scheme **2.9**)[55].



Scheme **2.9**: chiral thiourea catalyzed polycyclization via anion binding catalysis and the proposed transition state for this reaction.

[53] Leading reference: Z. Zhang P. R. Schreiner, *Chem. Soc. Rev.*, **2009**, *38*, 1187–1198.
[54] Three recent excellent reviews included thiourea anion binding in more broad discussions on chiral counteranions in enantioselective catalysis. a) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem*, **2012**, *4*, 603-614. b) M. Mahlau, B. List, *Angew. Chem. Int. Ed.*, **2013**, *52*, 518-533. c) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.*, **2013**, *52*, 534-561.
[55] R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.*, **2010**, *132*, 5030-5032.

2.2.3) Chiral Brønsted acids

There is a big universe of acid catalyzed transformations. Proton is an highly effective catalyst for a huge number of transformations. Despite this, enantioselective Brønsted acid catalyzed reaction remained elusive for a long time. Common chiral acids are carboxylic acids, but they are not strong enough to catalyze many interesting transformations. Moreover, they are so many that it would have been impossible to identify a structure generally suitable for enantioselective catalysis. It also have to be considered that a great number of enantioselective metal catalyzed reactions are Lewis acids catalyzed, and considering the great diffusion of these transformation during the time, there was no such need of organocatalytic enantioselective acid catalysis, because metals were covering almost all the reaction spectrum. So, having a "chiral proton" remained a unmotivated wish for chemists for a long time. After the great re-discovering of organocatalysis in 2000 also this topic became interesting. Anyway, the chemistry's world had to wait until 2005 to see this goal achieved. In that year in fact Akiyama[56] and Terada[57] groups developed independently chiral BINOL based phosphoric acids for Mannich reactions. Since then, many different catalysts were employed and many different reactions were catalyzed. TADDOL, VAPOL, and SPINOL were also used as scaffolds, and the more acidic thiophosphoric acids, phosphoric acid triflimides, bis-sulphurylimides and bisphosphorylimides were developed. As a more detailed discussion on these catalysts will be reported later, here in figure 2.11 only the general structures of the catalysts are shown.

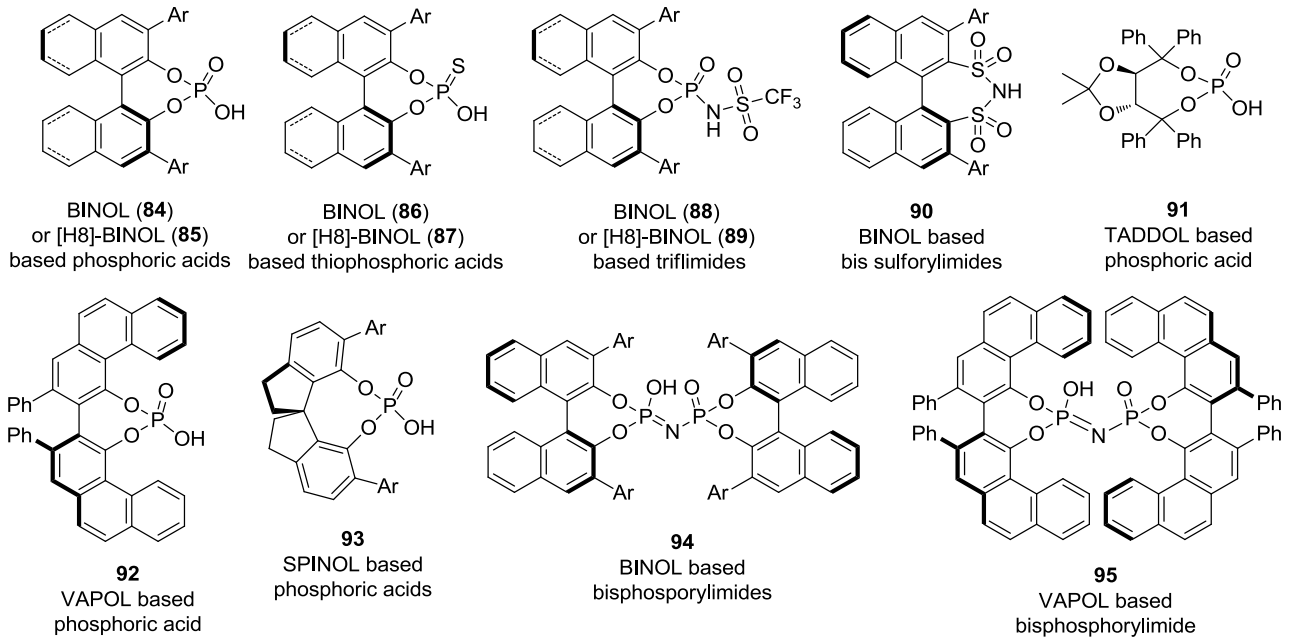


Figure 2.11: general structures of chiral Brønsted acid catalysts.

[56] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566–1568.
[57] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, **2004**, *126*, 5356-5357.

2.3) Dual activations

2.3.1) Bifunctional and cooperative organocatalysis

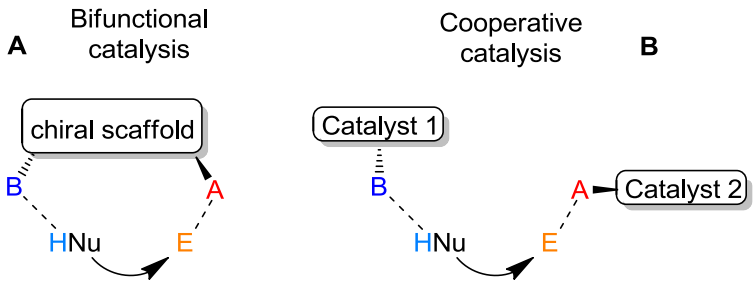


Figure 2.12. Schematic representation of bifunctional (**A**) and cooperative (**B**) catalysis.

When a catalyst incorporates two (or more) catalytic functionalities it is called bifunctional (or multifunctional) catalyst (Fig. 2.12, **A**). Since organic molecules have a lot of possible way of functionalization, two functionalities can be incorporated quite easily in the same catalyst structure, to give a bifunctional catalyst. As we saw, there are a lot of activation modes in organocatalysis, but of course to build an effective bifunctional organocatalyst the two catalytic centers must not react one with each other, or in other words, they have to be orthogonal. It all depends also on the kind of transformation we want to perform: the catalyst must be designed to be effective for that particular reaction. Many factors influence the outcome of a reaction: hydrogen bonds, interaction with the solvent, pH, catalyst poisoning, and so, thus everything must be fine-tuned, especially if two active sites on the same molecule have to perform two different kind of activation. Since that, not many classes of bifunctional organocatalysts can be general and widely employed. More generally, it is easier for a functional group performing an activation by weak interactions to be compatible with other functional groups. Usually these two active sites on the molecule activate respectively the nucleophile and the electrophile, so for example one is an acid unit and one is a basic unit. We saw that there is a big class of molecule able to activate electrophiles via weak interactions: hydrogen bonding catalysts. Moreover, we already said that these kind of catalysts often need an external activation of the nucleophile, so it's not surprising that most of the bifunctional organocatalysts are made by an hydrogen bonding unit, which helps to direct and anchor the electrophile, and a basic unit, which activate the nucleophile. The first example of bifunctional organocatalyst we met is proline **10**, as we said it's an enamine organocatalyst working with hydrogen bonding control (*Fig.* 2.1). Here following in *figure 2.13* a survey of privileged bifunctional organocatalysts and some activation modes are presented[58]. Thiourea units and the parent squaramides are often included as H-bond donors, as well as OH groups and amide protons, especially if substituted with EWG's. The basic functional groups are tertiary amines that act as Brønsted bases, or secondary/primary amines as enamine

[58] Leading references: primary and secondary amine derived thioureas and squaramides: a) L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett*, **2012**, *4*, 490-508. b) O. V. Serdyuk, C. M. Heckel and S.Tsogoeva, *Org. Biomol. Chem.*, **2013**, *11*, 7051-7071. c) M. Tsakos, C. G. Kokotos, *Tet. Lett.*, **2013**, *69*, 10199–10222. d) Ł. Albrecht, H. J., K, A, Jorgensen, *Chem. Eur. J.*, **2014**, *20*, 358-368. e) Cinchona alkaloid based thioureas and squaramides: S. J. Connon, *Chem. Commun.*, **2008**, 2499–2510. For a more detailed discussion please see section 1. e) Bifunctional phase transfer catalysts: J. Novacek, M. Waser, *Eur. J. Org. Chem.*, **2013**, *4*, 637–648. Also see ref. 51a for a broader discussion.

catalysts. CPA's are proposed to be bifunctional catalysts in some reactions because the phosphoryl oxygen can share one of its lone pair, while other kind of bifunctional organocatalysts are rarer.

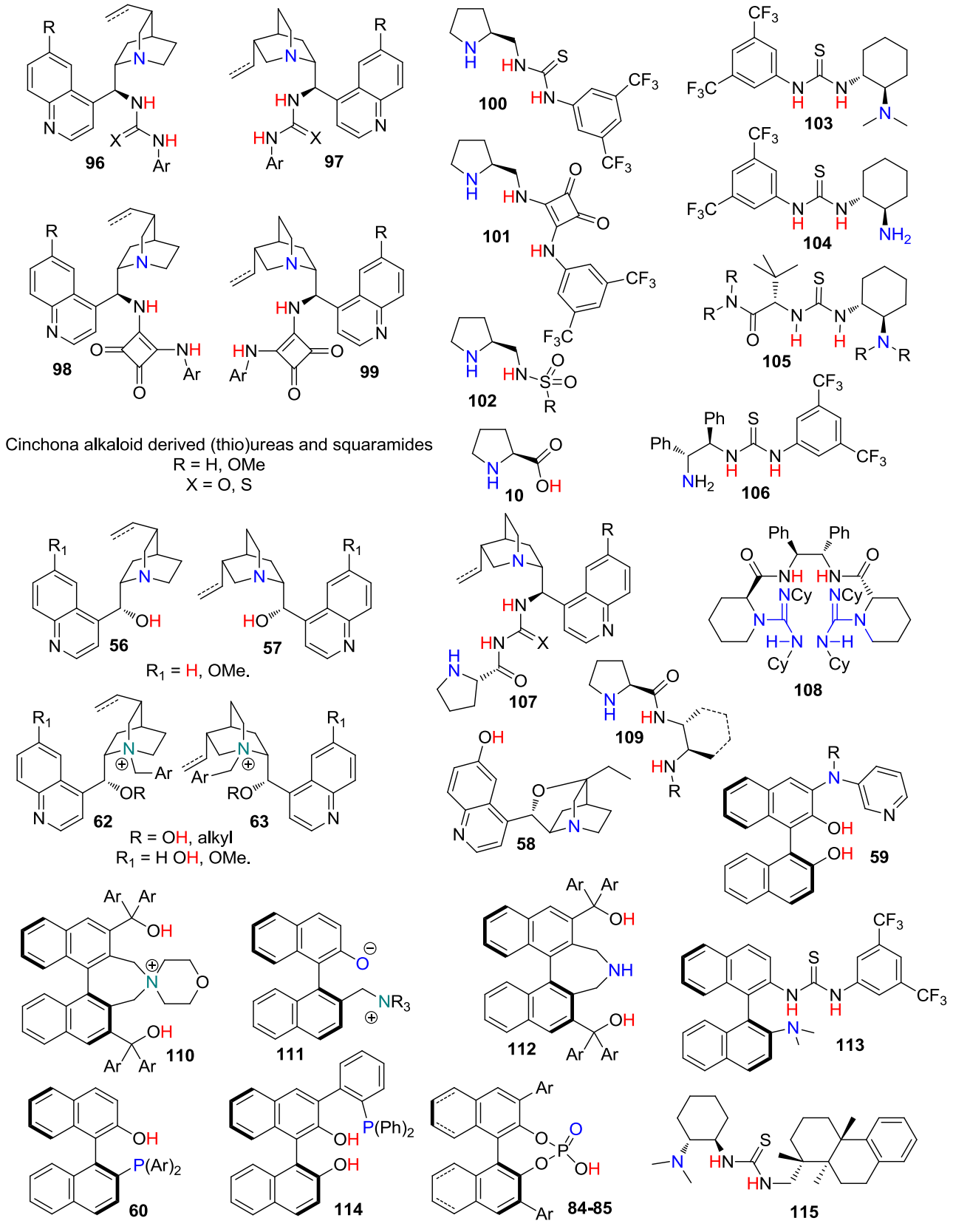
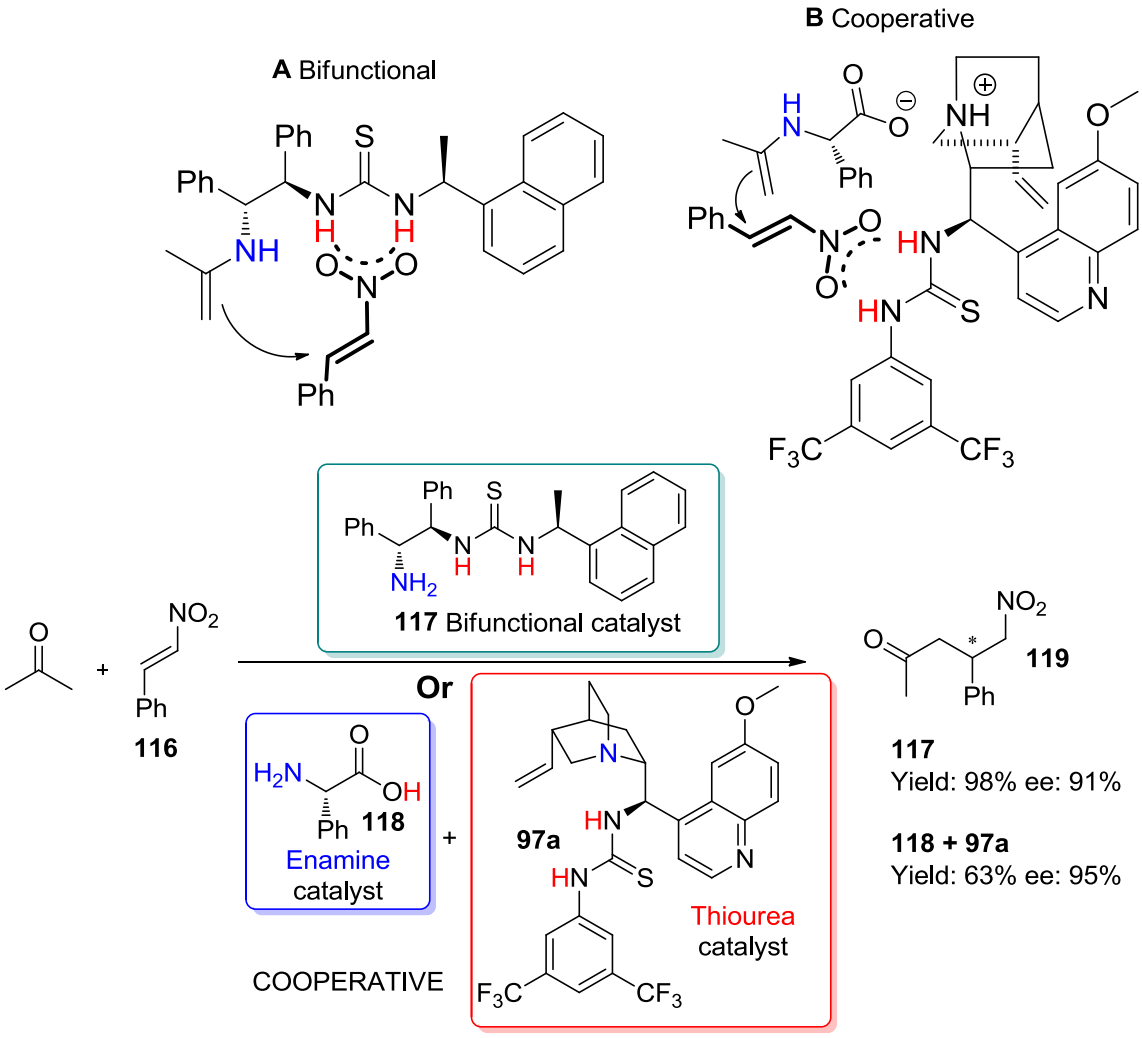


Figure 2.13: privileged bifunctional organocatalysts: basic sites in blue, acid sites in red, other catalytic units in green.

When two distinct organocatalysts are involved at the same time in the reaction transition state and both help the reaction to occur, they act in a cooperative way and therefore the catalysis is called cooperative (Fig. 2.12, **B**). Here the advantage of the operational simplicity of just mixing two catalysts is balanced by the difficulty to obtain a working system because in this case four entities (two catalysts and two reactants) have to be in the same place at the same time and in the right position, while in bifunctional catalysis the two catalytic units were on the same molecule, arranged in a particular and defined position. In cooperative catalysis this is not possible and so other factors (like solvent, concentration, and so) are crucial for a good reaction outcome. Sometimes anyway better results can be obtained respect to other catalytic systems.
The two catalysts mixed can be any appropriate combination of the ones we saw previously. In scheme **2.10** the results and the transition states for bifunctional or cooperative catalyzed Michael addition of acetone to nitrostyrene are compared[59].



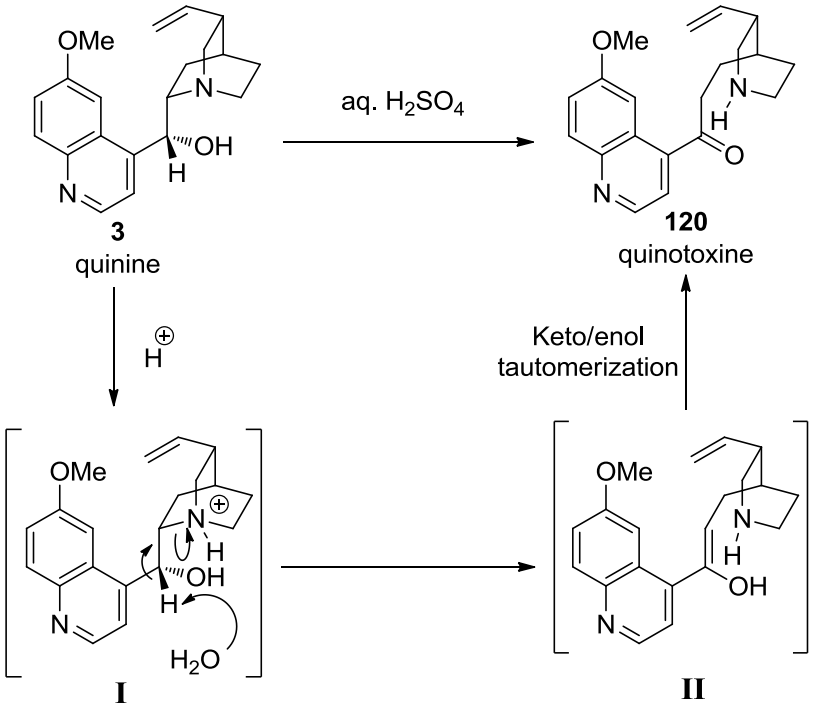
Scheme **2.10**: results of the same reaction catalyzed by two different catalytic systems, the first bifunctional and the second cooperative, each with the corresponding transition states. Both the reactions show good results.

[59] a) Bifunctional catalysis: S. B. Tsogoeva S. Wei, *Chem. Commun.*, **2006**, 1451–1453. b) Cooperative catalysis: T. Mandal C.-G. Zhao, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7714 –7717.

3) Cinchona alkaloids in organocatalysis[60]

3.1) A brief history[61]

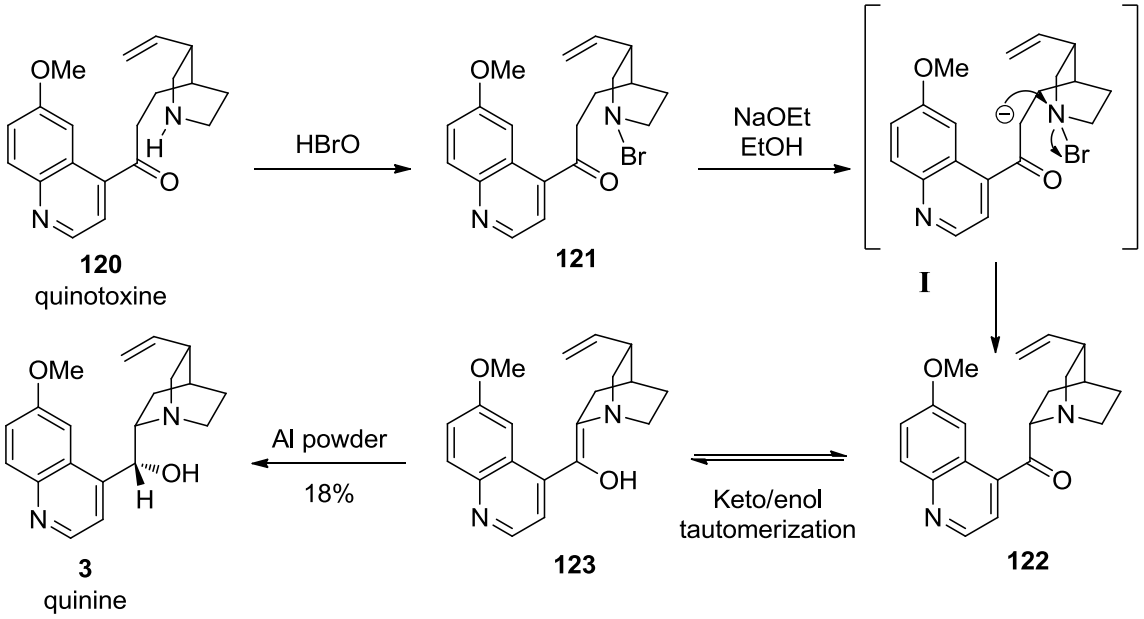
The story of cinchona alkaloids, in particular quinine, is deeply interconnected with human history, and quinine is undoubtedly one of the most important molecules ever.
Quinine and related molecules are alkaloids present in the bark of cinchona trees, growing originally in the forests located in the Andes mountains, between Venezuela and Colombia. The natives of that area apparently always used the extracts of the bark as medicines against fever, and were the ones that introduced this cure to Spanish colonies in the early 1600s. It's wide spread told that the wife of the Count of Chinchòn, Viceroy of this part of the Spanish colonies, was cured from ague in an almost miraculous way using this alkaloid, and for this reason she decided the introduction of cinchona bark for medical use in Europe in 1639. Although this story is nowadays considered as a legend, the European name of the plant was established as "cinchona", and this remained until today.



Scheme **3.1**: Pasteur's degradation of quinine to quinotoxine.

[60] For this introduction, as well as for the rest of the chapter, the following leading references were followed: a) C. E. Song, (2009). *Cinchona alkaloids in synthesis and catalysis.* WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. b) E. M. O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron*, **2011**, *67*, 1725-1762.

[61] The story of quinine and especially about the debate in its first total synthesis, which I personally found exciting and instructive, covers more than 150 years of chemistry and involves some big names of chemistry during all the eras. It provides an opportunity to jump in the past and know these characters and their story, offering a sight on chemistry during time. I strongly recommend the reading of the following ref. a, and at least a sight to ref b. Also refs c and d point out the importance of telling this story to young chemists. a) T. S. Kaufman, E. A. Rùveda, *Angew. Chem. Int. Ed.*, **2005**, *44*, 854 – 885. b) J. I. Seeman, *Angew. Chem. Int. Ed.*, **2007**, *46*, 1378 – 1413. c) T. S. Kaufman, E. A. Rùveda, *Chem. Educator*, **2004,** *9*, 172-176. d) K. Ap. F. D. Souza, P. A. Porto , *J. Chem. Educ.*, **2012**, *89*, 58–63.

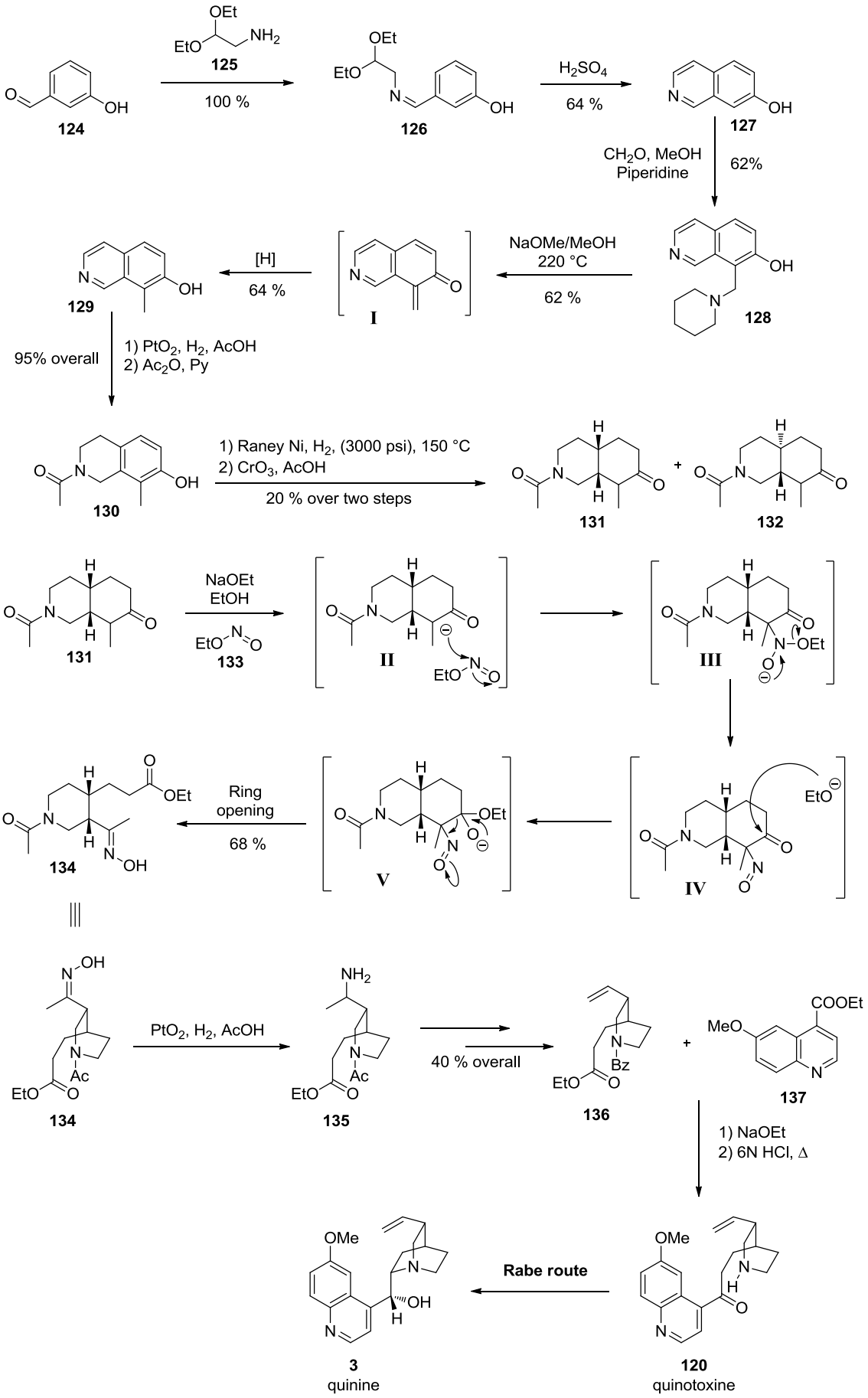


Scheme **3.2**: The "Rabe route" to quinine starting from quinotoxine.

Widely used for centuries as the main remedy against malaria, quinine and related alkaloids began to be studied by many scientists and also by chemists. After the discovery by Pasteur of the degradation of quinine to quinotoxine in 1853[62] (scheme **3.1**), the inverse pathway was reported in 1918 by Rabe (scheme **3.2**), yet unfortunately with an experimental procedure poorly described[63]. Rabe couldn't imagine how much controversy this fact would have generated during the following years. In fact since the great importance of the molecule, many chemists tried to accomplish the total synthesis of quinine. The first ones that claimed to be successful were the legendary R. B. Woodward and his colleague W. E. Doering, firstly in 1944, and then in 1945 with a longer report[64]: thus in the middle of world war II (scheme **3.3**). The news of the synthetic production of quinine was of huge impact in society: this has been claimed as a great achievement in science by many newspapers, and R. B. Woodward and W. E. Doering gained a lot of popularity in the academic ambient and out. The reason was simple:

> "During WWII quinine supplies, which were considered critical for the allied forces, suddenly became scarce, thus causing thousands of soldiers to die after becoming infected with malaria during the campaigns in Africa and the Pacific. The cinchona plantations established in Java by the Dutch were the major sources of the European reserves of quinine, which were stored in Amsterdam. However, the German capture of Holland in 1940 and the Japanese military invasion of Java in 1942 abruptly cut these vital supplies."[65]

[62] L. Pasteur, C. R. Hebd., *Seances Acad. Sci.*, **1853**, *37*, 162.
[63] P. Rabe, K. Kindler, *Ber. Dtsch. Chem. Ges.*, **1918**, *51*, 466 – 467.
[64] a) R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.*, **1944**, *66*, 849. b) R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.*, **1945**, *67*, 860 – 874.
[65] In ref. 61a, page 866.



Scheme **3.3**: schematic representation of Woodward-Doering synthesis of quinine

The achievement of a total synthesis of quinine was a message of great impact to the rest of the world, giving the impression that a natural source of quinine for malaria treatment would not have to be needed anymore for USA and allies.
Yet, actually, the Woodward-Doering synthesis of quinine was practically not possible on large scale. Moreover, and most importantly, the Woodward-Doering synthesis of quinine was a formal synthesis. There's in fact no doubt that they could obtain the quinotoxine starting from cheap and readily available starting materials[66], but for the conversion of quinotoxine to quinine they completely relied on Rabe procedure, not trying to reproduce it. Anyway, the huge clamor about the publication stopped in its tracks any academic discussion about that. Only Gilbert Stork, at that time a student at Wisconsin university, asked details to Woodward with a letter (Woodward was in Harvard), which however was never answered and apparently nothing else happened until 2001. In that year, 55 years after the first synthesis, Stork accomplished the first stereoselective synthesis of quinine[67] (other synthesis appeared in the meantime, but not stereoselective) arguing at the same time, in that and other articles, the hypothesis that the effective possibility to obtain quinine via synthesis was not real in 1944, principally due to Rabe procedure, claiming the first total synthesis of quinine as a myth[68]. The debate was on fire for years, but surprisingly until 2007 no one tried to reproduce the Rabe route to quinine, or at least nobody reported this effort. So in 2008 a paper was out by Aaron C. Smith and Robert M. Williams publishing their studies about the reproducibility of this procedure[69]. Although in a first moment they couldn't reproduce the last step of the synthesis, (reduction of quininone **122** to quinine **3** with Al powder) subsequently they found some Al(III) impurities present in Al powder to be crucial to obtain quinine in the yields reported by Rabe (≈ 15%), closing in this way (forever?) the debate 90 years after the original Rabe publication[70]. Despite Woodward passed away prematurely in 1979, William E. Doering was still alive (the paper is in fact dedicated to him) and could finally know that his formal total synthesis of quinine was actually right.

[66] As part of the chapter on Gilbert Stork quinine synthesis, Woodward-Doering synthesis is described and explained in detail in: K. C. Nicolaou, S. A. Snyder, (2003), Classics in total synthesis II: More Targets, Strategies, Methods. Wiley-WHC, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Chapter 15.

[67] G. Stork, D. Niu, A. Fujimoto, E. R. Koft, J. M. Balkovec, J. R. Tata, G. R. Dake, *J. Am. Chem. Soc.*, **2001**, *123,* 3239-3242.

[68] M. Rouhi, *Chem. Eng. News*, **2001**, *79*, 54 – 56. See also ref. 61 and letters by G. Stork: a) *Chem. Eng. News*, **2001**, **79**, 8. b) G. Stork, *Chem. Eng. News*, **2000**, *78*, 8.

[69] A. C. Smith, R. M. Williams, *Angew. Chem. Int. Ed.*, **2008**, *47*, 1736 –1740.

[70] P. Ball, *Nature*, **2008**, *451*, 1065-1066.

3.2) Cinchona alkaloids: properties and applications

As we saw in the first chapter, the first attempt to enantioselective organocatalysis was out in 1912 by Breding[2]. In this paper the natural cinchona alkaloids quinine and quinidine were used to induce enantiomeric excess in the product of HCN addition to benzaldehyde. Albeit the ee was very low, Breding recognized that the two cinchona alkaloids induced opposite enantiodiscrimination, since the optical rotation in the final product was opposite.
This is the first observation of what later was recognized to be a general trend in cinchona alkaloid enantioselective catalysis. For this reason quinine and quinidine are called "pseudoenantiomers", because, when used as catalysts, they generally induce opposite absolute configuration in the product formed. In fact, even though they might appear as enantiomers, they are diastereoisomers, or, better, epimers at C8 and C9 carbon atoms, while the absolute stereochemistry of the other chiral centers is the same (see *figure 3.1*). It is worth noting that these alkaloids, having a tertiary nitrogen included in an asymmetric substituted bicyclic system, show a quite rare example of chiral nitrogen. The way they are presented in *figure 3.1* will be the standard in all this text, and remarks their nature of pseudoenantiomers. Other parent molecules of the cinchona alkaloid family exist as pair of pseudoenantiomers and they are also used in catalysis: cinchonidine and cinchonine lacks the methoxy substituent on the quinoline ring, while cupreine and cupreidine (not naturally occurring but readily available from quinine and quinidine) have instead an OH substituent in that position. Finally, all the corresponding dihydro- derivatives exist, having the original vinyl group hydrogenated: some of them are naturally occurring, others are not, but readily available from the parent alkaloid via hydrogenation, some of them are widely used as catalysts, others are not. For completeness, all the derivatives are reported in *figure 3.1*, though many of them will not appear anymore in this thesis.

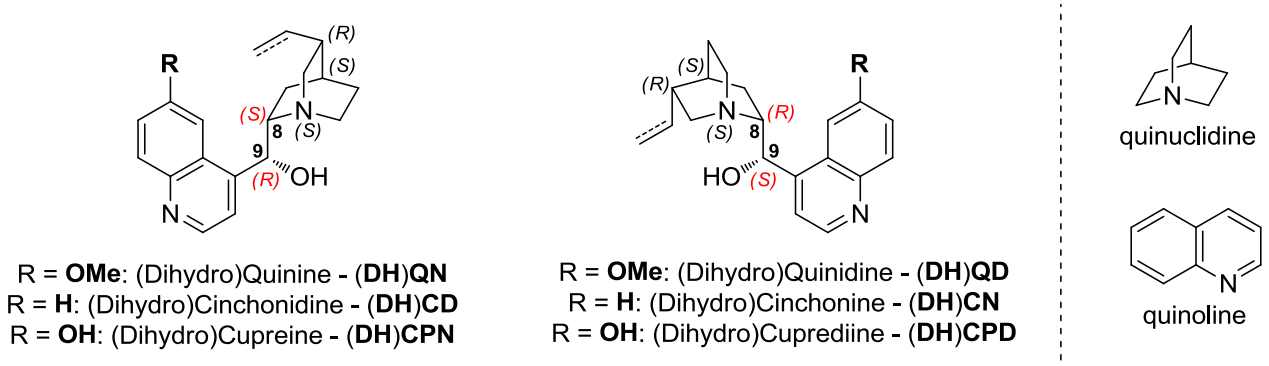


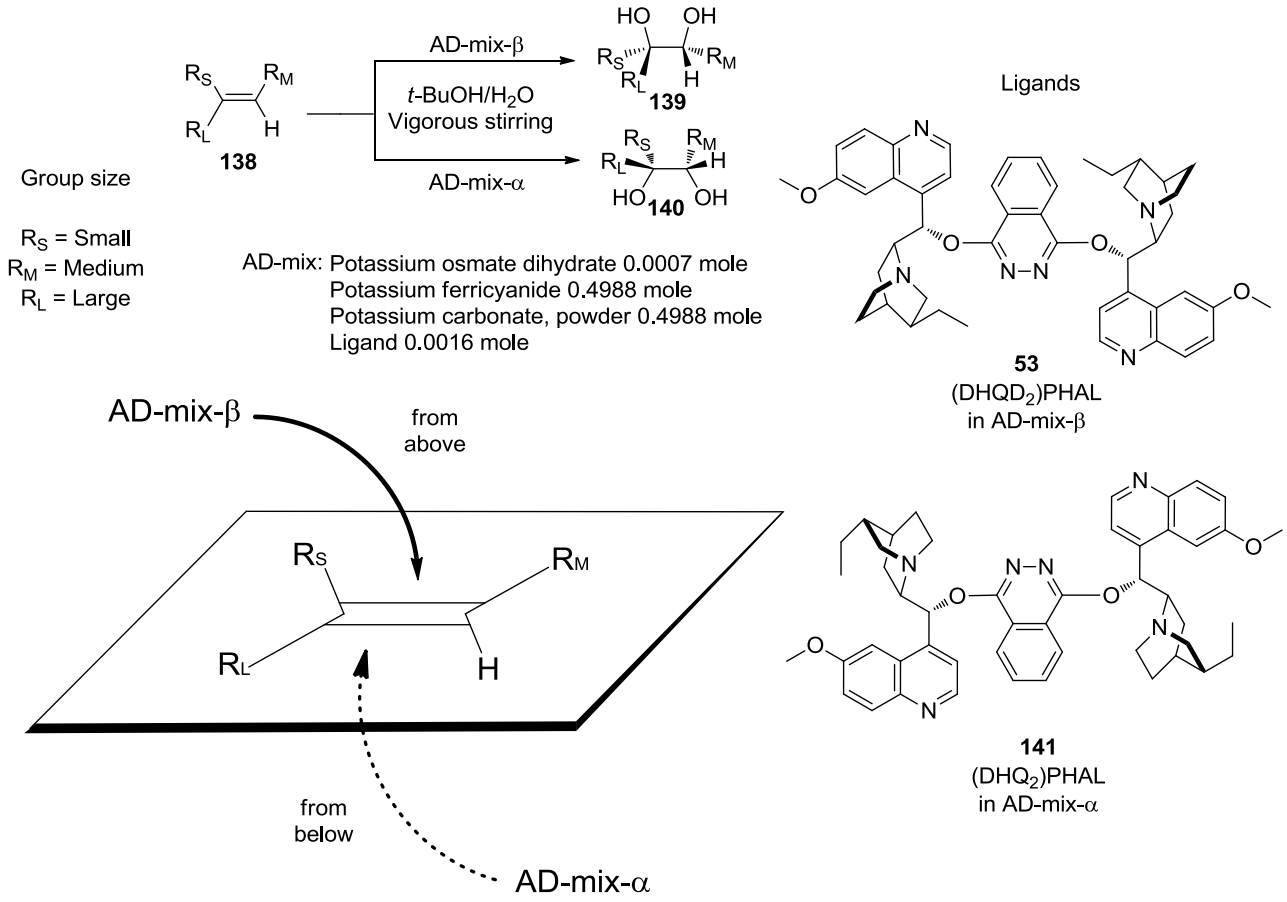
Figure 3.1: General structures and names of some cinchona alkaloids and derivatives.

As we saw in **chapter 2.3**, cinchona alkaloids themselves can be considered as bifunctional catalysts, due to their double nature of Lewis/Brønsted bases and Hydrogen-bonding donors. As we also saw in **chapter 2**, they can be derivatized in many ways and thus used in many activation modes. They and their derivatives can be used as:

- iminium/enamine organocatalysts
- nucleophilic organocatalysts
- phase transfer organocatalysts

- general base/bifunctional organocatalysts
- bifunctional (thio)ureas/squaramides

The easy availability of both the pseudoenantiomeric forms and the versatility of cinchona alkaloid scaffold, featuring many functional groups and possibilities for derivatizations, makes this family of catalysts one of the most widespread in enantioselective organocatalysis. It is also worth noting anyway that cinchona alkaloids are also used as ligands in enantioselective metal-catalyzed transformations[71]. Probably the most famous example is the Sharpless asymmetric dihydroxylation of olefins, which uses dimeric cinchona alkaloid derivatives as chiral ligands for Osmium to induce chirality in the final products[72]. Although also in this case the mechanism has been controversial[73], mnemonic rules have been established to predict the absolute configuration in the final product, and today mixtures of oxidant, Osmium precursor and ligand called AD-mix-α and AD-mix-β are commercially available and ready to use (*Fig*. 3.2).



[71] See ref. 60. See also: L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.*, **2012**, *3*, 942-958.

[72] a) E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder, K. B. Sharpless, *J. Am. Chem. Soc.*, **1988**, *110*, 1968-1970. b) H.-L. Kwong, C. Sorato, Y. Ogino, H. Chen, K. B. Sharpless, *Tetrahedron Lett.*, **1990**, *31*, 2999-3002. c) K. B. Sharpless *et al.*, *J. Org. Chem.*, **1992**, *57*, 2768-2771. d) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.*, **1994**, *94*, 2483-2547. See also ref. 60.

[73] Also this is another saga that went on for many years. Whereas this document is not about metal catalysis it is not reported here, anyway the following reference are leading if you are interested: a) oxidations catalyzed by other metals: D. V. Deubel, G. Frenking, P. Gisdakis, W. A. Herrmann, N. Rösch, J. Sundermeyer, *Acc. Chem. Res.*, **2004,** *37*, 645-652. b) review on the topic: G. Drudis-Solé, G. Ujaque, F. Maseras, A. Lledós, *Topics Organomet. Chem.*, **2005**, *12*, 79–107. c) presentation at Baran group meeting: http://www.scripps.edu/baran/images/grpmtgpdf/Seiple_Sept_10.pdf d) study on TS by the synthesis of tailor-made catalysts: B. B. Loray, S. K. Singh, V. Bhushan, *Ind. J. Chem.*, **2002**, *41B*, 1226-1233.

Figure 3.2: procedure, ligands, AD-mix composition and mnemonic rule for Sharpless enantioselective dihydroxylation of olefins.

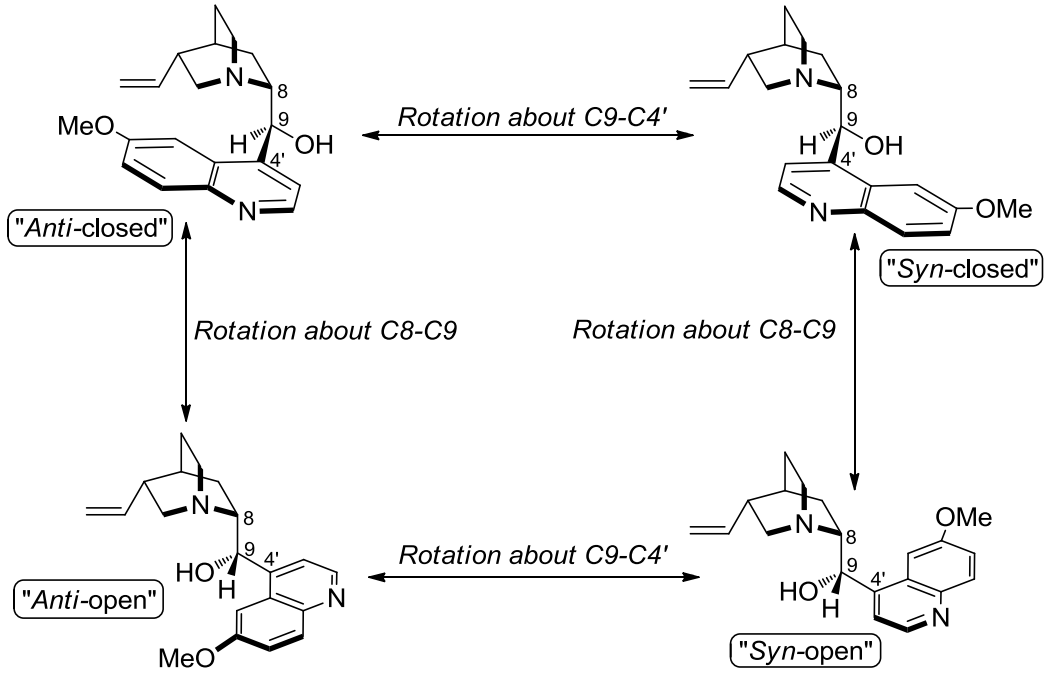


Figure 3.3: main conformations of cinchona alkaloids in solution.

Cinchona alkaloids catalytic performance is affected by their conformation in solution. This is object of many studies over the literature focused on the improvement of results. A study by Sharpless and co-workers in 1989 showed the four conformations in *figure 3.3* as the main in solution[74]. Further studies revealed that in apolar solvents the "*anti-open*" conformation is preferred, while in polar solvents the "*syn*" conformations (more polar) gain importance[75]. By the way, in every solvent, if the quinuclidinic nitrogen is protonated the "*anti-closed*" conformation is the most stable[76]. Other many studies on amides[77], fluorinated derivatives[78], thioureas[79] ethers[80] and amines[81] have been performed. The reason of all these studies is clear: the conformation adopted by the cinchona alkaloid in solution is a key point to understand and rationalize the results in terms of enantioselectivity[82]. Free OH groups in the natural alkaloid or other groups installed may play a key role, driving the attack of one of the reactants and have to be taken into account. More generally trying to force the cinchona scaffold in one conformation using

[74] G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless**,** *J. Am. Chem. Soc.***, 1989**, *111,* 8069-8076.
[75] T. Bürgi, A. Baiker, *J. Am. Chem. Soc.*, **1998**, *120*, 12920-12926.
[76] R. A. Olsen, D. Borchardt, L. Mink, A. Agarwal, L. J. Mueller, F. Zaera, *J. Am. Chem. Soc.*, **2006**, *128*, 15594-15595.
[77] H. Brunner, P. Schmidt, M. Prommesberger, *Tetrahedro*n, **2000**, *11*, 1501-1512.
[78] a) G. K. S. Prakash, F. Wang, M. Rahm, J. Shen, C. Ni, R. Haiges, G. A. Olah, *Angew. Chem. Int. Ed.*, **2011**, *50*, 11761-11764. b) G. K. S. Prakash, F. Wang, C. Ni, J. Shen, R. Haiges, A. K. Yudin, T. Mathew, G. A. Olah, *J. Am. Chem. Soc.*, **2011**, *133*, 9992–9995. c) E.-M. Tanzer, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Chem. Eur. J.*, **2012**, *18*, 2006-2013.
[79] J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem.*, **2012**, *77*, 9813−9825,
[80] a) H. Yang, M. W. Wong, *J. Am. Chem. Soc.*, **2013**, *135*, 5808–5818. b) H. Li, X. Liu, F. Wu, L. Tang, L. Deng, *Proc. Nat. Acad. Sci. USA*, **2010**, *107*, 20625-20629.
[81] Supporting information of: X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc.*, **2011**, *133*, 17934–17941.
[82] M. Aune, A. Gogoll, O. Matsson, *J. Org. Chem.*, **1995**, *60*, 1356-1364. See also ref. 75, 80.

appropriate substituents and reaction conditions is a strategy to drive the reaction outcome.

3.3) Cinchona alkaloid derived primary amines[40,60b] and thioureas[58e]

3.3.1) Catalysts sintheses

The procedure for the synthesis of Cinchona alkaloid derived primary amines (scheme **3.4 A**) was reported for the first time in 1995, and then improved[83]. It is a one-pot protocol involving a Mitsunobu azidation[84] and a subsequent Staudinger reduction[85], in which the primary amines are generally obtained as hydrochlorides in typical yields of 50%-70%. The Mitsunobu reaction allows a clear Sn_2 mechanism and a complete inversion of the stereocenter at C-9 position is obtained in this way when the azide attacks the C9 carbon after the OH has been transformed in situ in a leaving group. The so-obtained intermediate **I** reacts with another equivalent of PPh_3 in the first step of Staudinger reduction to give the phosphorous pentavalent intertmediate **II**, which undergoes hydrolysis to give the free corresponding primary amines. In many cases, protonation with HCl and crystallization afford pure hydrochloride crystals, which can be stored. The free amine can be obtained after washing with NH_4OH. This protocol is very convenient, since no chromatography is required, but only estraction, evaporation and crystallization. Moreover in one step, and aproximatively three days the catalyst can be obtained ready for use. This makes the procedure very convenient. The compound obtained in this way is epimeric at C9 respect to the original cinchona alkaloid used.

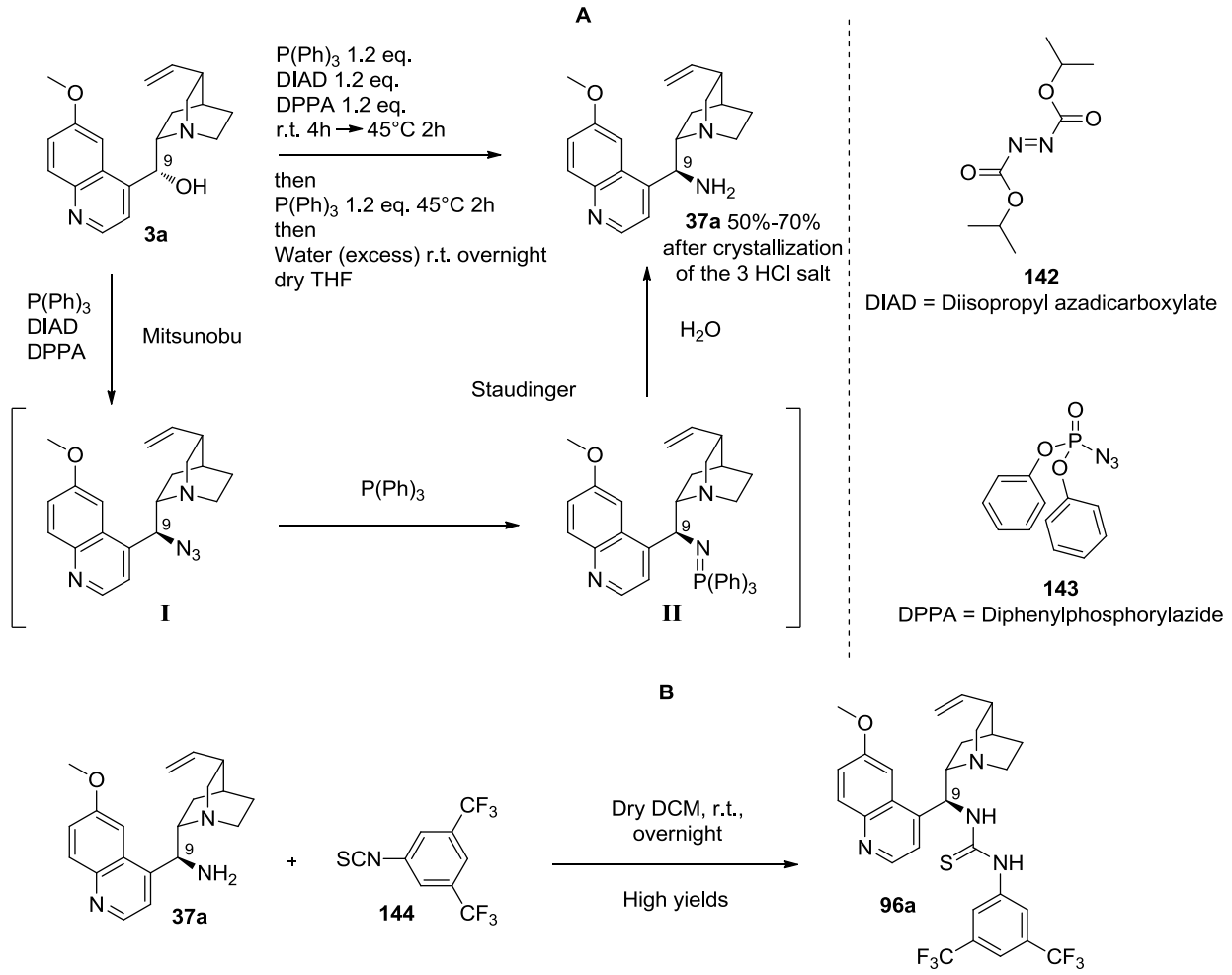
The corresponding thioureas are prepared from the primary amines in a simple and high yielding reaction with the corresponding isothiocyanate (scheme **3.4 B**)[86] which is also convenient since these useful bifunctional catalyst can be obtained in only two steps. In scheme **3.4** quinine is chosen as representative cinchona alkaloid and 3,5-*bis*-(trifluoromethyl)phenyl isothiocyanate are chosen as representative, but the procedure is generally applicable to all the other cinchona alkaloids and isothiocyanates. The inversion of the absolute configuration at C9 during the Mitsunobu reaction is very important because when Cinchona alkaloid derived primary amines and thioureas with the original absolute configuration were synthesized, the reaction outcome was generally worse[58e].

[83] a) H. Brunner, J. Bügler, B. Nuber, *Tet. Asymm.*, **1995**, *6*, 1699-1702. b) B. Vakulya, S. Varga, A. Csámpai, T. Soos, *Org. Lett.* **2005**, *7*, 1967. c) S. H. McCooey, S. J. Connon, *Org. Lett.*, **2007**, *9*, 599-602. d) C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre. *Nat. Protoc.*, **2013**, *8*, 325–344.

[84] a) O. Mitsunobu, Y, Yamada, *Bull. Chem. Soc. Jpn.,* **1967**, *40***,** 2380–2382. b) D. L. Hughes, R. A., Reamer, J. J., Bergan, E. J. J. Grabowski, *J. Am. Chem. Soc.*, **1988**, *110*, 6487–6491. c) H. Loibner, E. Zbiral, *Helv. Chim. Acta*, **1976**, *6*, 2100-2114. d) B. Lal, B. N. Pramanik, M. S. Manhas, A. K. Bose, *Tet. Lett.*, **1977**, *18*, 1977–1980. e) D. L. Hughes, *Org. React.,* **1992**, *42*, 335–656.

[85] a) H. Staudinger, J. Meyer, *Helv. Chim. Acta*, **1919**, *2*, 635. b) Y. G. Gololobov, *Tetrahedron*, **1981**, *37***,** 437.

[86] a) B.J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett*, **2005**, *4*, 603–606. b) B. Vakulya, S. Varga, A. Csàmpai, T. Soòs, *Org. Lett.*, **2005**, *7*, 1967-1969. c) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.*, **2005**, 4481-4483. d) S. H. McCooey, S. J. Connon, *Angew. Chem., Int. Ed.*, **2005**, *44*, 6367-6370.



Scheme **3.4**: **A**: Mitsunobu/Staudinger reaction one pot for the synthesis of cinchona alkaloid derived primary amines. **B**: the formation of the corresponding thioureas.

3.3.2) Cinchona alkaloid derived primary amines

As we saw in *section 2.1.1*, using a primary amine in place of a secondary one leads to an effective activation of ketones. In fact, despite acetone is readily activated by proline, limited examples have been reported of ketone activation by secondary amines. Steric reasons are involved in this fact (*Fig*. 3.4, **A**), but also better reactivity of the derived enamines and iminium ion due to better orbital overlap reasons[87]. In fact steric hindrance force the enamines and iminium ions derived from secondary amines to rotate and this reduces the overlap of π orbital, crucial for a good reactivity in both enamine and iminium catalysis (*Fig*. 3.4, **B**). With primary amines, instead, this doesn't happen, allowing better reactivity (*Fig*. 3.4, **C**). Anyway, the reactivity of primary amines is lower respect to secondary amines (especially to cyclic ones) due to the lower nucleophilicity of the first ones.

[87] See ref. 40e.

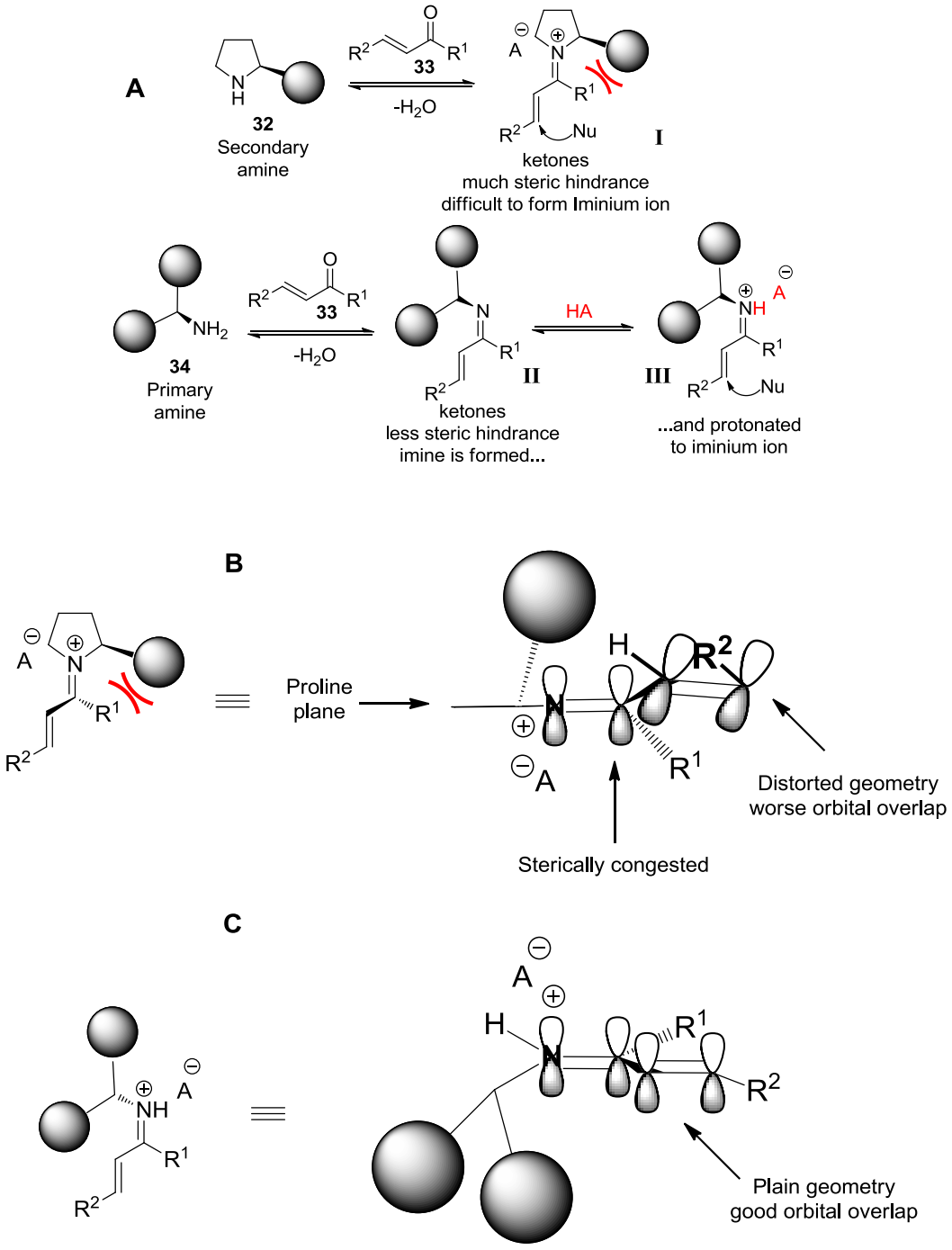
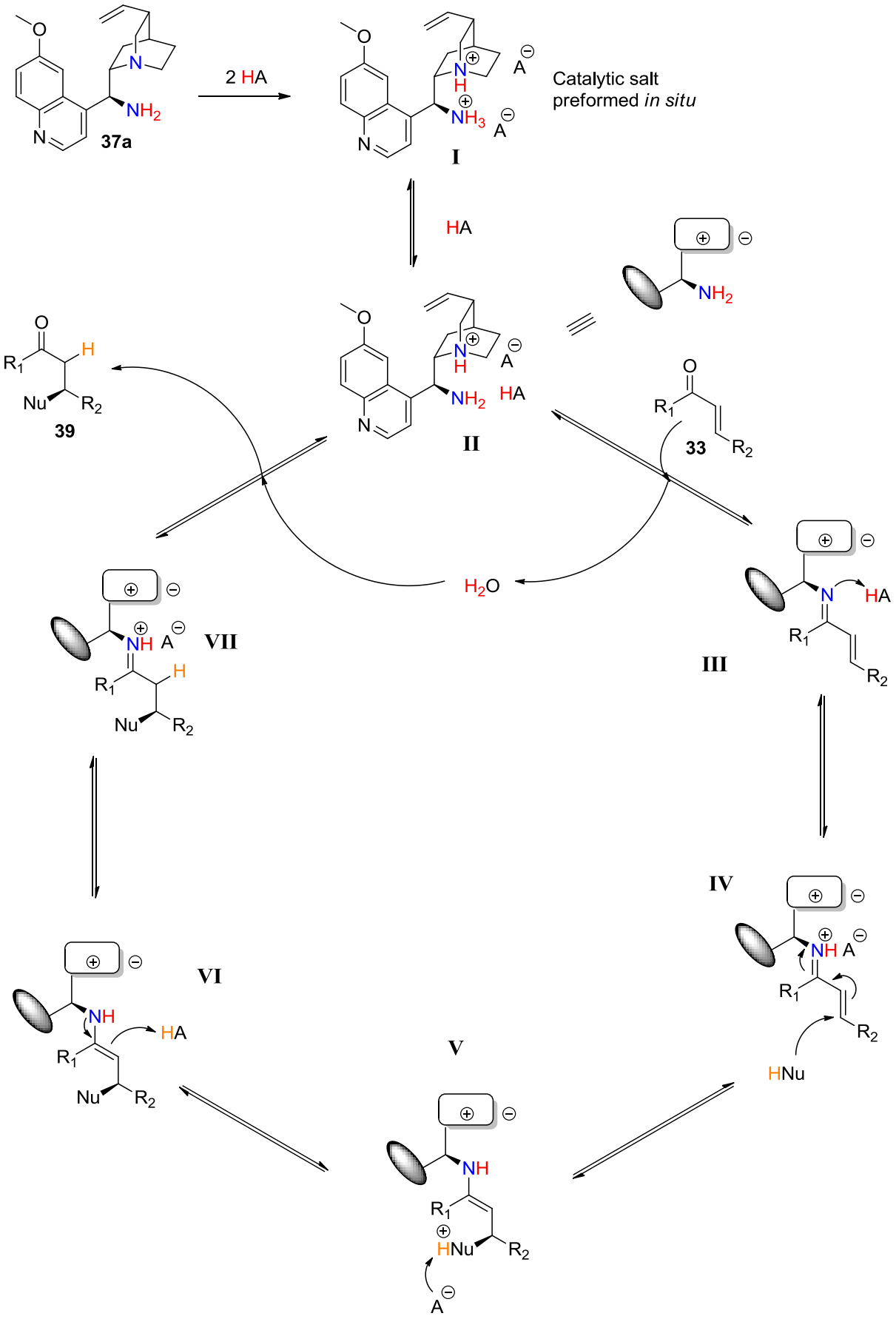


Figure 3.4: steric hindrance and overlap factors in condensation of secondary and primary amines with ketones.



Scheme **3.5**: mechanism of iminium ion catalysis using cinchona alkaloid primary amines as catalysts: focus on proton transfer.

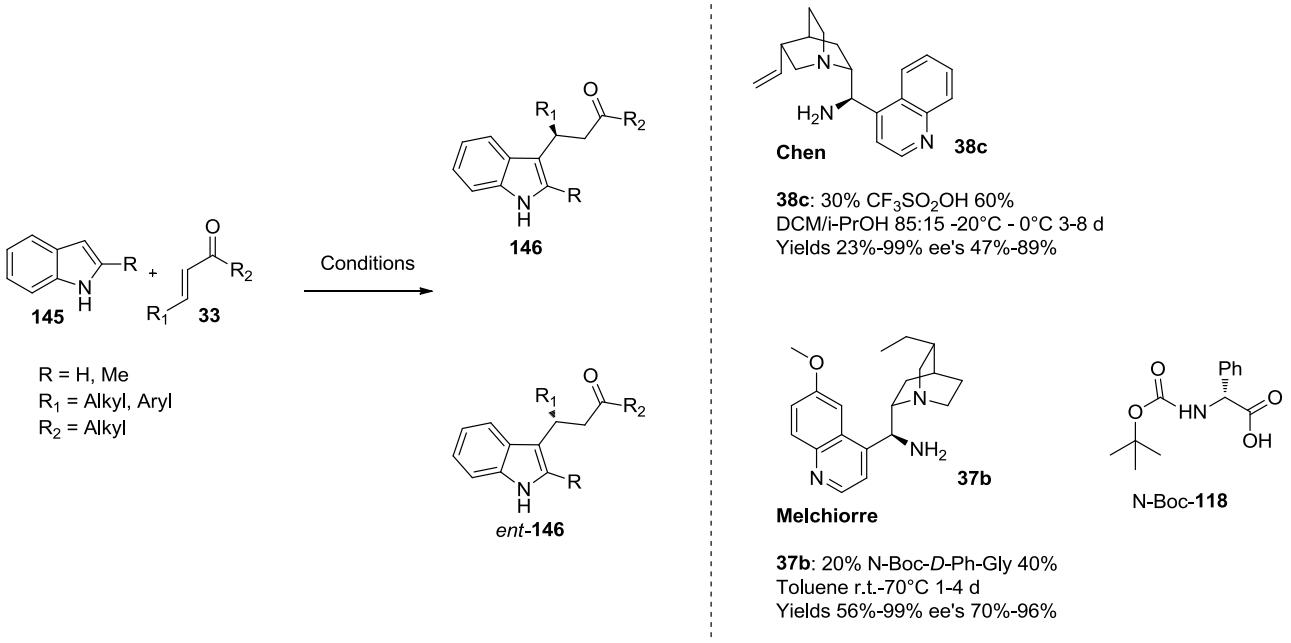
Using primary amines as catalysts generally requires an acidic co-catalyst, otherwise the reaction does not occur. This is true in particular for Cinchona alkaloid derived primary amines, which possess an additional highly basic tertiary nitrogen atom. The first equivalent of acid "quenches" this nitrogen to form an ammonium salt. If one wants to perform enamine catalysis, this is generally enough (moreover, the proton located on tertiary nitrogen may help carbonyl condensation). For iminium ion catalysis, as we told in *section 2.2.1, figure 2.2*), a second equivalent of acid is required to generate the iminium ion, otherwise the simple imine is formed. Since this thesis is focused on iminium ion catalysis, in scheme **3.5** a catalytic cycle of iminium ion catalysis using cinchona alkaloid derived primary amines is presented. Usually a real "catalytic salt" is formed in situ before adding the reactants, using 1:2 ratio of amine/acid (scheme 3.5, **I**). The third quinolinic nitrogen is generally considered not enough basic to be involved. Thus, it is clear since this point that the acid used plays a key role in catalysis. Firstly, an equilibrium must exist between the catalytic salt and the dissociated amine/acid form **II**, otherwise of course the amine cannot perform the condensation on carbonyl (**III**). By the way this acid should be strong enough to protonate the imine to iminium ion afterwards (**IV**), otherwise the catalysis is not effective. Moreover in all the other steps of the mechanism, there are proton transfers (**III, V, VI,** and of course in the condensation to give **III** and in the final hydrolysis to restore **II**), and the acid might be involved, increasing reaction rate or driving the nucleophile's attack by coordination. In all of this, we have to consider that the tertiary nitrogen, protonated, bears another counteranion of the same acid and this might not be a simple spectator. Steric hindrance, coordinating ability (e.g. hydrogen-bonding-donor/acceptor properties) and other factors give to the acidic co-catalyst a key role in iminium ion catalyzed reaction using primary amines. Thus, iminium ion catalysis with primary amines can be difficult to optimize due to that, but the careful choice of the acid can also be a tool to fine tune the reaction outcome.

Cinchona alkaloid derived primary amines were firstly used as aminocatalysts in 2007 when by three different research groups turned the attention on these catalysts independently[88]. While Connon and co-workers used them in enamine catalysis[88d], Chen and co-workers[88a,b] and Melchiorre and co-workers[88c] used them in iminium ion activation. Interestingly Chen and co-workers[88b] and Melchiorre and co-workers[88c] reported simultaneously the same reaction: the first organocatalytic highly enantioselective Friedel-Crafts (FC) alkylation of indoles with enones (scheme **3.6**). Until the same reaction had been accomplished with aldehydes[89], it had remained elusive with ketones. Though indoles are quite reactive nucleophiles, this transformation is valuable because a new Aryl-alkyl C-C bond is formed and also because indole core is widespread found in natural products and biologically active substances[90].

[88] Iminium ion activation: a) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y.Wu, J. Zhu, J.-G. Deng, *Angew. Chem. Int. Ed.*, **2007**, *46*, 389 – 392 b) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.,* **2007**, *5*, 816–821. c) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.,* **2007**, *9*, 1403–1405. Enamine activation: d) S. H. McCooey, S. J. Connon, *Org. Lett*. **2007**, *9*, 599 – 602.

[89] J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173.

[90] For some recent reviews: a) W. Gul, M. T. Hamann, *Life Sciences*, **2005**, *78*, 442– 453. b) A. J. Kochanowska-Karamyan, Mark T. Hamann, *Chem. Rev.* **2010,** *110,* 4489–4497. c) M. Ishikura, K. Yamada T. Abe, *Nat. Prod. Rep*., 2010, **27**, 1630–1680. d) V. Sharma, P. Kumar, D. Pathak, *J. Heterocyclic Chem.*, **2010**, *47*, 491-502. e) M. d'Ischia, A. Napolitano, A. Pezzella, *Eur. J. Org. Chem.,* **2011**, 5501–5516 f) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. lvarez, *Chem. Eur. J.*, **2011**, *17*, 1388–1408. g) S. Biswal, U. Sahoo, S. Sethy, H. K. S. Kumar, M. Banerjee, *Asian J. Pharm. Clin. Res.,* **2012,** *5*, 1-6. h) M. Ishikura, Takumi Abe, T. Choshi, S. Hibino, *Nat. Prod. Rep.*, **2013**, *30*, 694-752. i) N. Kumar Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. Kumar Verma, E. H. Choi, *Molecules*, **2013**, *18*, 6620-6662.

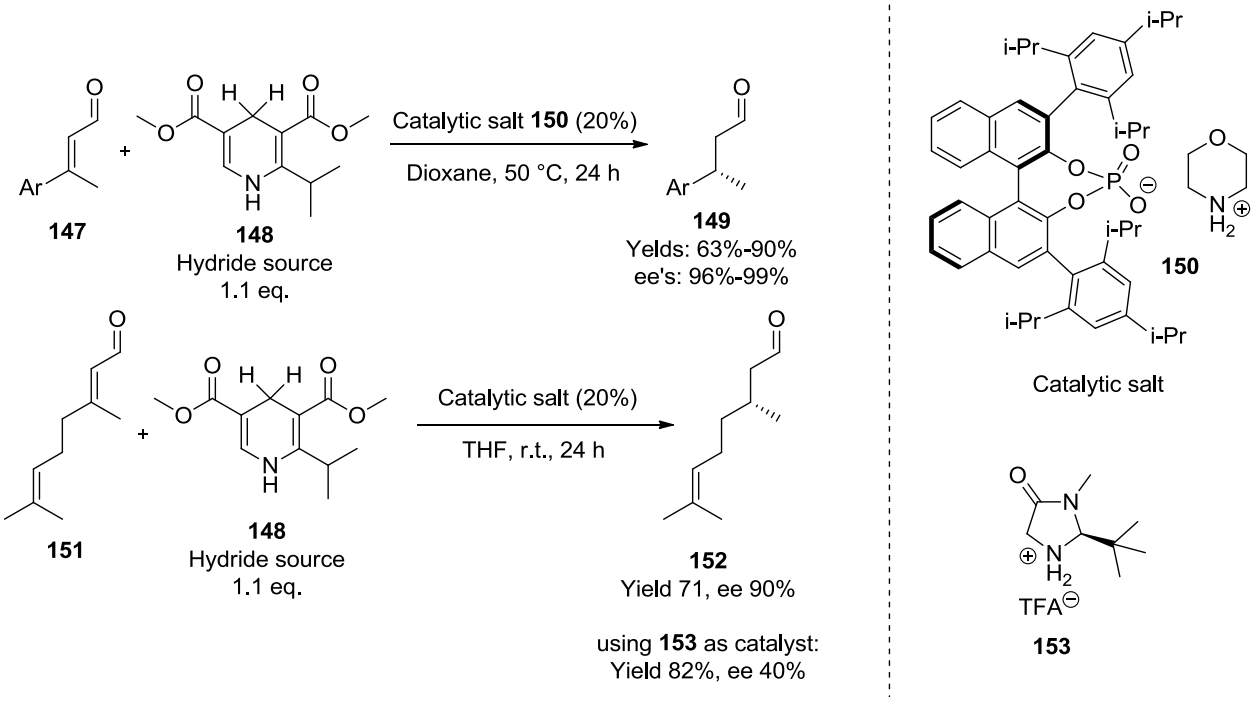


Scheme **3.6**: the first two examples of enantioselective organocatalytic F-C alkylations of indoles with enones catalyzed by cinchona alkaloid derived primary amines.

3.3.2.1) Asymmetric Counteranion Directed Catalysis

We already discussed the counteranion effect in iminium ion catalysis. In the example by Melchiorre in scheme **3.6** the acid used to form the iminium ion is chiral, leading to the formation of a chiral counteranion. This clearly affect the stereochemical outcome of the reaction since during optimization with achiral counteranions a maximum ee of 65% was obtained, while using the chiral N-Boc-**118** as acid ee increased up to 93%. However, most likely the chiral catalyst is still the major responsible for enantiodiscrimination since using racemic or the opposite enantiomer of N-Boc-**118** gave the product with just slightly lower ee. But in other examples the counteranion effect was much more substantial. The asymmetric catalysis where the only chiral object performing enantiodiscrimination is a counteranion is called asymmetric counteranion directed catalysis, and was invented by Benjamin List in 2006 (Scheme **3.7**)[91]. In this example the enantioselective iminium ion catalyzed transfer hydrogenation of enals with Hantsch ester was obtained by using a catalytic salt of morpholine with a chiral phosphoric acid serving as counteranion, thus only the latter created the chiral environment for the asymmetric reaction. Other catalyst combinations, based on chiral amines gave worse results. This concept had been applied to a number of different transformations and today is generally considered as an established activation mode[54].

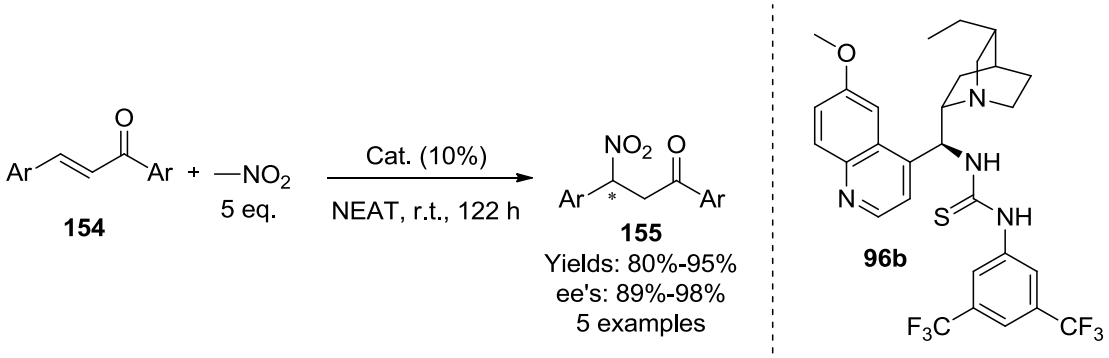
[91] S. Mayer, B. List, *Angew. Chem. Int. Ed.*, **2006**, *45*, 4193 –4195.



Scheme 3.7: the first asymmetric counteranion directed catalysis appeared in literature.

3.3.3) Cinchona alkaloid based thioureas

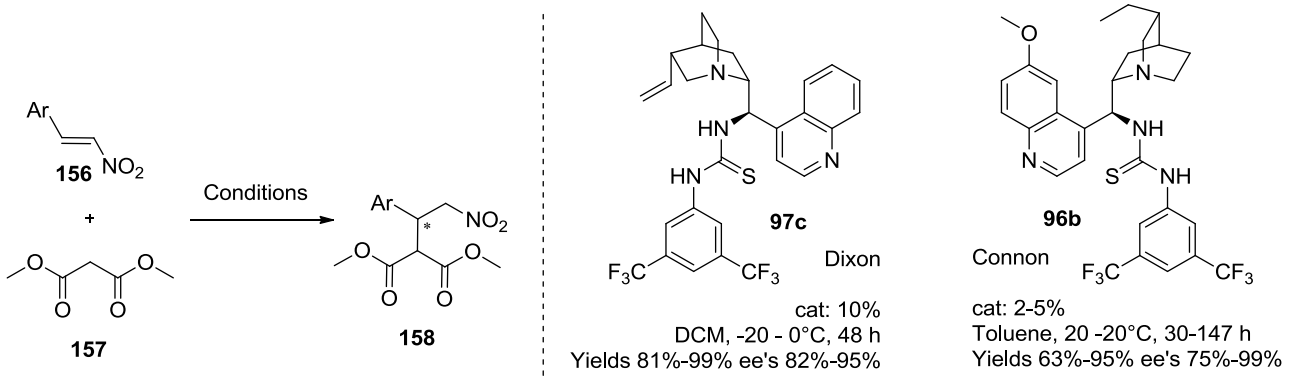
These kind of thioureas began to appear in 2005, two year after Takemoto first report of bifunctional organocatalysts based on cyclohexanediamine[92]. The first report was by Chen that revealed a Michael addition of thiophenols α,β-unsaturated imides, albeit with low enantioselectivity. The first to report high levels of enantioselectivity was Soòs which applied these catalysts to the enantioselective addition of nitroalkanes to chalcones[86b]. In this reaction both quinine and epiquinine were ineffective, showing that a simple Brønsted base catalysis can't be employed. So, they switched their attention to the corresponding thiourea derivatives. Surprisingly, the catalyst with the same absolute configuration of the natural alkaloid was also not effective in catalysis (*Fig.* 3.5, **A**). On the contrary, 9-epi-9-thioureido cinchona alkaloids derivatives were effective in promoting the transformation, with the best being the hydroquinine derivative (scheme **3.8**). Curiously, in this paper only 5 examples are reported for the scope.



Scheme 3.8. The first example of highly enantioselective cinchona alkaloid derived thiourea transformation.

[92] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.*, **2003**, *125*, 12672–12673.

In the same year, and almost at the same time, Dixon[86c] and Connon[86d] independently reported the enantioselective addition of dimethylmalonate to nitroalkenes catalyzed by cinchona alkaloid derived thioureas (scheme **3.9**). Also, in this case, simple cinchona alkaloids and the thioureas with the natural absolute configuration didn't give a reaction or high enantioselectivities (*Fig.* 3.5, **A**), while their C-9 epimers were highly effective and enantioselective. The nature of bifunctional catalyst was also discussed.



Scheme 3.9. The addition of dimethyl malonate to nitroolefins independently developed by Dixon and Connon.

In these three first reports, the high affinity of thiourea moiety for the nitro group was already shown. The thioureas, in fact, not only can activate electrophilic nitroalkenes **I**, but can also stabilize the nitronate anion, which is formed from nitroalkanes before nucleophilic addition **III**, and from nitroalkenes after they underwent electrophilic attack **II** (*Fig.* 3.5, **B**).

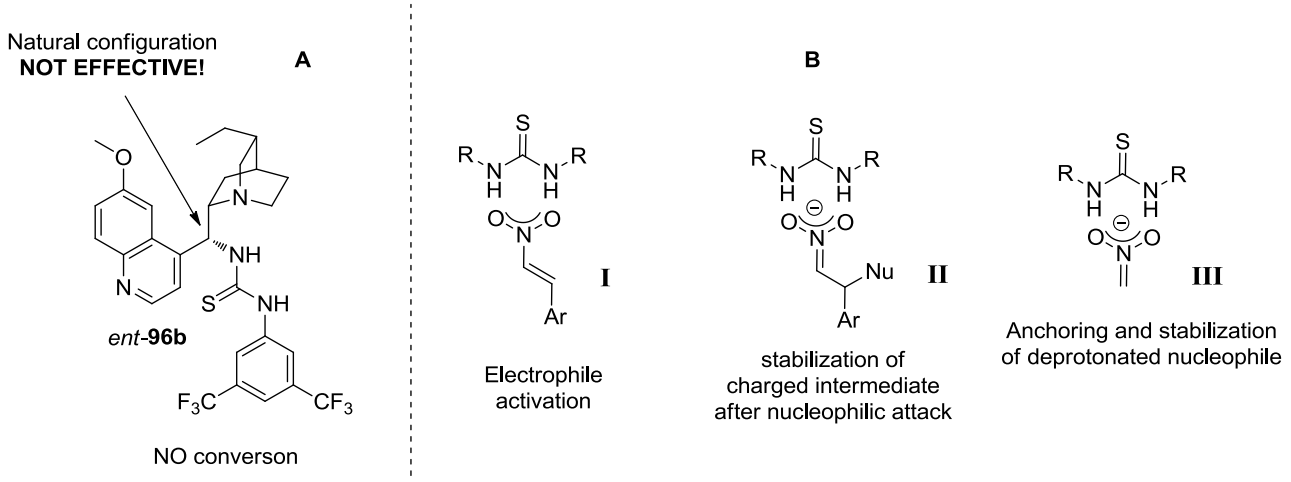


Figure 3.5: as a general trend, thioureas derived from cinchona alkaloid with the natural configuration at C9 are not reactive in catalysis (**A**). **B**: the bifunctional role of the thiourea moiety, activating electrophiles **I**, stabilizing negatively charged nucleophiles **III** or intermediates **II**.

After these three seminal papers, many reactions were developed, and the field grew tremendously. As soon as 2008 a review on the topic appeared[58e], and it has been calculated that in 2013 more than 100 reactions were published[93]. Anyway, nitrocompounds remained privileged substrates during time[94].

[93] Y. Xi, X. Shi, *Chem. Commun.*, **2013**, *49,* 8583-8585.
[94] L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis*, **2013**, *45*, 2627-2648.

3.3.3.1) Some theory

In 2012 Schreiner measured the pK_a values of some ureas and thioureas in DMSO[95]. Firstly he investigated the differences between achiral ureas and thioureas, to understand the difference in pK_a. Then he also focused on the influence on pK_a variation upon introduction of the popular electron withdrawing $–CF_3$ group on the aryl substituent. As we can see in *figure 3.6*, generally, ureas are less acidic than thioureas of about 5 pK_a units. Every $–CF_3$ group introduced on the aryl substituents decreases pK_a roughly of 1.2 units. In this way a quite wide acidity range is obtained, from 18.7 of diphenyl urea **71** to 8.5 of Schreiner's catalyst **73**.

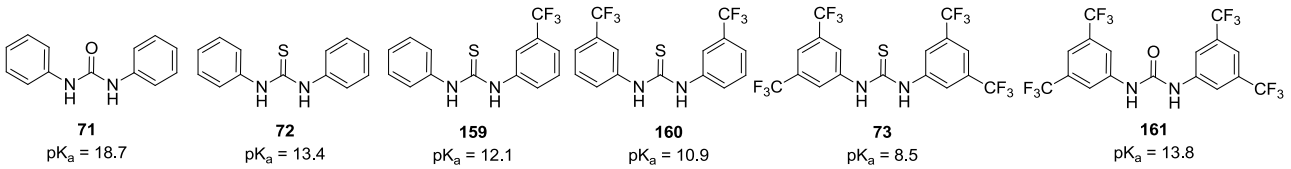


Figure 3.6: pK_a values of some achiral ureas and thioureas in DMSO measured by Schreiner and co-workers. Thioureas are 5 pK_a units more acidic then the corresponding ureas and every additional $–CF_3$ group on phenyl ring decreases pK_a roughly of 1.2 units.

Subsequently, he focuses on measurements for some chiral privileged thiourea organocatalysts. 3,5-bis-trifluoromethylphenyl substituted thioureas lay all in a narrow range between 10.7 and 13.6 pK_a units. Non-aromatic thioureas are around of pK_a 18-19 (see *figure 3.7*). Surprisingly, the basic/acid nature of other functional groups does not affect the pK_a values in a predictable way: the most acidic catalyst **113** bears a tertiary, although aromatic, amine functionality, while the cinchona alkaloid derived thiourea **96a**, which possess the highly basic tertiary nitrogen on quinuclidine ring, have a pK_a of 12.3, lower for example that the one showed by Ricci's catalyst *ent*-**79a**, bearing an additional weakly acid secondary OH. Takemoto catalyst **103**, also possessing a tertiary amine is instead the least acidic among 3,5-bis-trifluoromethylphenyl substituted thioureas.

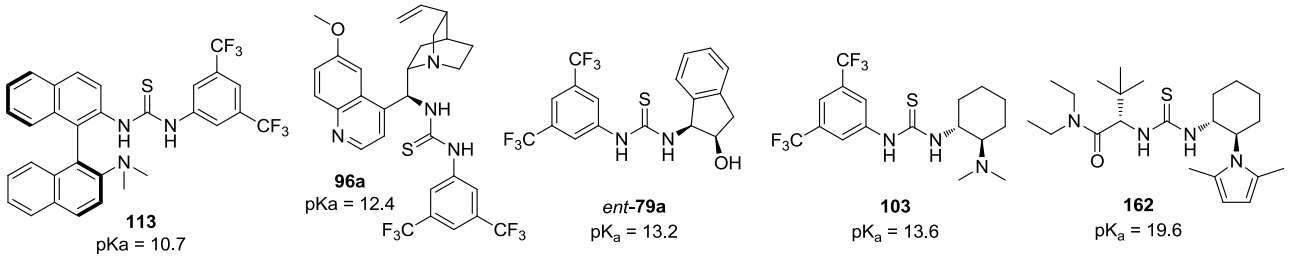


Figure 3.7: pK_a values for some chiral privileged thiourea organocatalysts measured by Schreiner and co-workers in DMSO (selected examples). Surprisingly, the basic/acid nature of the other functional groups does not affect the acidity as expected.

3,5-bis-trifluoromethylphenyl substituents not only enhance the acidity of the thioureidic protons, but they remarkably affect the binding properties of thiourea activating the proton located in the *ortho*-position with respect to the thiourea itself. In 2012, in fact, again Schreiner, showed the high affinity and binding properties of 3,5-bis-trifluoromethylphenyl

[95] G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.*, **2012**, *14*, 1724–1727.

substituted thioureas with respect to 3,5-dimethylphenyl substituted ones[96]. In principle, for thioureas, 2 conformations in solution can exist: the E-Z and Z-Z conformations. 3,5-dimethylphenyl thiourea prefers E-Z while 3,5-bis-trifluoromethylphenyl thiourea displays only the Z-Z conformation at r.t. and so the spectrum is symmetric (at lower temperatures E-Z conformation becomes detectable). When mixing the two thioureas with valerolactone **163** different phenomena are observed (*figure 3.8*). No change in the ^{1}H NMR spectrum was observed when 3,5-dimethylphenyl thiourea was mixed with it (*Fig*. *3.8*, (a) and (b)). Even computational calculations, IR measurements and MS analysis didn't show changes, proving that an adduct is not formed. On the contrary, when 3,5-bis-trifluoromethylphenyl thiourea was used, changes in the ^{1}H NMR spectrum were observed (*Fig*. *3.8*, (c) and (d)). The thioureidic protons are shifted downfield by 1.5 ppm, but more interestingly also the aromatic protons are shifted: in particular the signal belonging to the *ortho*-proton also shifts downfield by 0.8 ppm (*Fig*. *3.8*, (d)). This shift can be interpreted as the proof of a binding, because if the proton is deshielded it's attracted by something outside the molecule, as for example a Lewis basic site of another molecule, binding it. So, if on one hand this might be expected for thioureidic protons, this large chemical shift of the ortho proton on the phenyl ring is an important finding. This means that this proton contributes to the thiourea binding to the lactone. Everything was confirmed by MS and computational studies.

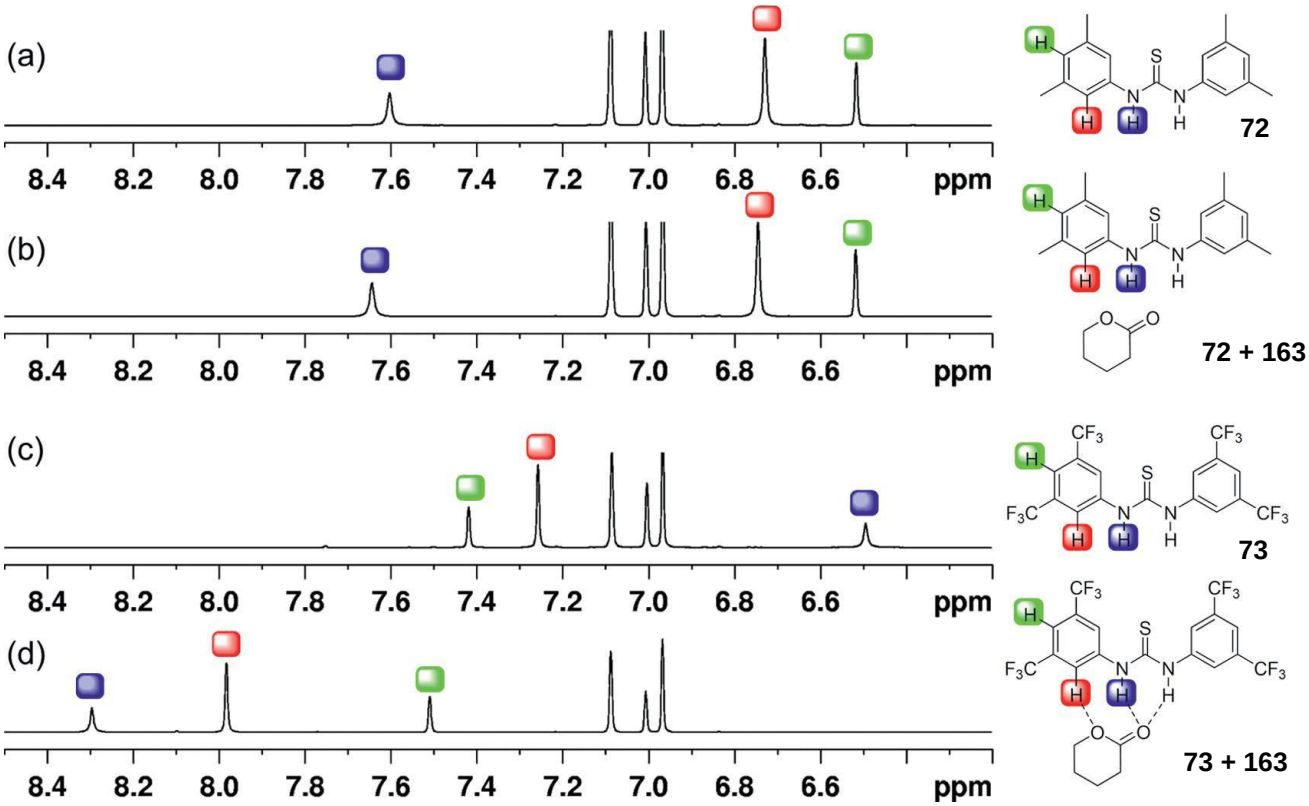


Figure 3.8. Spectra of the 3,5-dimethylphenyl thiourea alone (a) and mixed with valerolactone (b). No relevant changes in the spectrum are obtained. Instead, when 3,5-bis-trifluoromethylphenyl thiourea was used, the thioureidic protons and the *ortho*-proton marked in red shifted downfield considerably (compare (c) and (d)). This means that these two protons are involved in binding.

[96] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.,* **2012**, 5919–5927.

NOESY spectra (*Fig*. 3.9) shows also how this adduct is formed: the carbonyl oxygen binds the thioureidic protons and the other oxygen binds the *ortho*-proton. This is confirmed by the NOE effect observed between this proton and the two CH_2-O protons of **163**, as well as by the one observed between the two protons in α to the carbonyl and the thioureidic protons. Further confirmations are given by the NOE effect observed between the two CH_2-O protons of the lactone and fluorine, as well as by MS and computational studies. All the experiments were repeated with other substrates, with similar results. This finding may be important for the development of new reactions or catalysts.

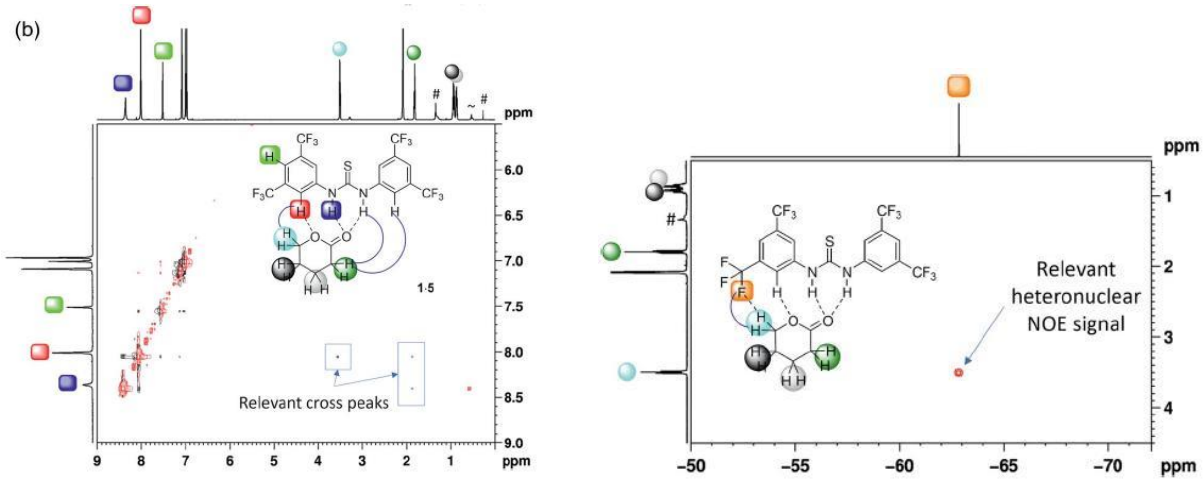


Figure 3.9: NOESY NMR spectroscopy of the adduct 3,5-bis-trifluoromethylphenyl thiourea/ valerolactone showing the conformation of the adduct.

Another case of study about cinchona alkaloid derived thioureas is given by Wang in his 2012 computational study about vinylogous addition of a α,β-unsaturated butyrolactam to chalcone[97]. Until that moment, two different transition state were proposed for this reaction: in the first (*Fig*. 3.10, **A**) the electrophile binds both thioureidic protons and a contact ion pair Nu^--Cat^+ is formed. In the second (*Fig*. 3.10, **B**), the deprotonated nucleophile binds the thiourea, and chalchone forms an H-bond with Cat^+. In the course of his study Wang finds that the transition state might involve a deprotonated nucleophile bound to one of the thioureidic protons and to the protonated tertiary nitrogen; the electrophile instead is bound only to the other thioureidic proton (*Fig*. 30, **C**). In the same study he re-investigates also the addition of nitromethane to chalchones reported by Soòs (Scheme **3.8**)[86b] and finds the same kind of interaction (*Fig*. 30, **D**). It's worth noting that in this work the interaction with the ortho-proton of 3,5-bis-trifluoromethylphenyl moiety was not considered, but in the transition state that Wang found the electrophile is in the right position to perform also this weaker interaction.

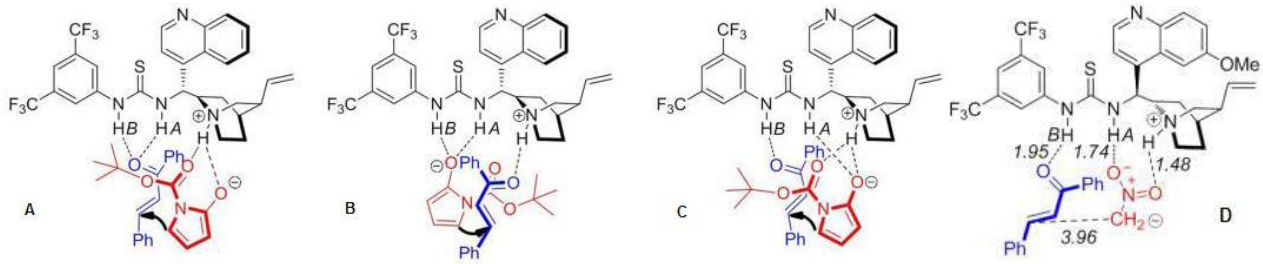
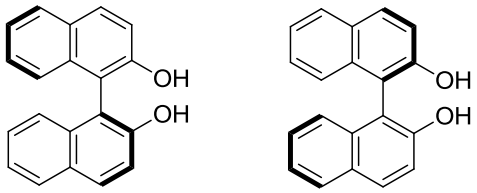


Fig 30: previously proposed transition states for the vinylogous addition of an α,β-unsaturated butyrolactam to chalcone (**A** and **B**) and the one found by Wang (**C**). The same TS should be involved also in the addition of nitromethane to chalchone reported by Soòs (**D**).

[97] J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem.*, **2012**, *77*, 9813−9825.

4) BINOL derived Chiral Phosphoric Acids in asymmetric catalysis

4.1) BINOL: a history of successes[98].



164
(*S*)-BINOL

ent-**164**
(*R*)-BINOL

2,2'-hydroxy-1,1'-binaphthyl, known as BINOL is perhaps the most famous and widely employed C_2-symmetric atropoisomeric scaffold in asymmetric catalysis. Unlike cinchona alkaloids, this is not a naturally occurring compound. It was synthesized for the first time probably in 1873 but until another report by Pummerer in 1926 its structure was still unclear[99]. It was known that it was chiral[100] but for a long time its synthesis was only racemic: the first preparation and characterization of enantiomerically enriched BINOL appeared only in 1971 through resolution of the corresponding phosphoric acid with cinchonine (!)[101].The chirality possessed by BINOL is a special kind of chirality named axial chirality or atropoisomerism[102]. It consists in a chirality generated by a hindered rotation around one bond (from ancient Greek *atropos*: *a-* meaning not, without, and *tropos* meaning turn). In fact in BINOL the rotation about 1-1' bond is hampered by steric hindrance of the two 8,8' hydrogen atoms on one side (*Fig*. 4.1 **B** left) and by one of those hydrogen and the OH group on the other side (*Fig*. 4.1 **B** right). Thus the rotation is blocked and this generates chirality. There is an empirical rule to determine the configuration (*Fig.* 4.2): one should look through C1-C1' bond and see the groups leaning out. One binaphthyl plane would be ahead, the other behind. Priority must be assigned to

[98] Leading references for this introduction: a) L. Pu, *Chem. Rev.*, **1998**, *98*, 2405-2494. b) E. N. Jacobsen, A. Pfaltz. H. Yamamoto. (1999) *Comprehensive Asymmetric Catalysis I-III*. Springer-Verlag Berlin Heidelberg New York. c) P Kočovský, Š. Vyskočil, M. Smrčina, *Chem. Rev.* **2003,** *103,* 3213-3245. d) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.,* **2003,** *103,* 3155-3211. e) J. M. Brunel, Chem. Rev. **2007,** 107, PR1-PR45. f) Q. L. Zhou. (2011). *Privileged Ligands and Catalysts*. WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

[99] The first report by Von Richter apparently is just a mention of what was told by the Russian chemist Dianin at a meeting. Anyway, since the structure of BINOL was not clear, somebody refers to Pummerer as the first one who synthesized it. a) V. von Richter, *Chem. Ber.,* **1873**, *6*, 1252. b) R. Pummerer, E. Prell, A. Rieche, *Chem. Ber.,* **1926**, *59*, 2159.

[100] Axial chirality had been predicted by Vant'Hoff and only later the possibility of separation of two atropoisomers was shown in 6,6'-dinitro-2,2'-diphenic acid: a) J. H. van't Hoff, *Arch. Neerl. Sci. Exactes Nat.,* **1874**, *9*, 445. b) G. H. Christie, J. H. Kenner, *J. Chem. Soc.,* **1922**, 614.

[101] J. Jacques, C. Fouquey, *Tetrahedron Lett.,* **1971**, 4617.

[102] The first one who refers to axial chirality with the word "atropoisomerism" was Kuhn, talking about the paper in ref. 99b: a) R. Kuhn, "Molekulare Asymmetrie," in K. Freudenberg, *Stereochemie*. (1933) Franz Deutike: Leipzig, Germany, 1933; p 803. b) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds.* (1994) Wiley: New York. pp 1142-1147.

the groups both ahead and behind (*Fig. 4.2*, **I, II**). Than draw an arrow starting from the group with the major priority ahead, going towards the group with minor priority ahead without passing from the side bearing the group with major priority behind (if necessary, it's possible to pass from the group with minor priority behind, see *Fig. 4.2*, **III**). If the arrow is clockwise it's R, otherwise it's S.

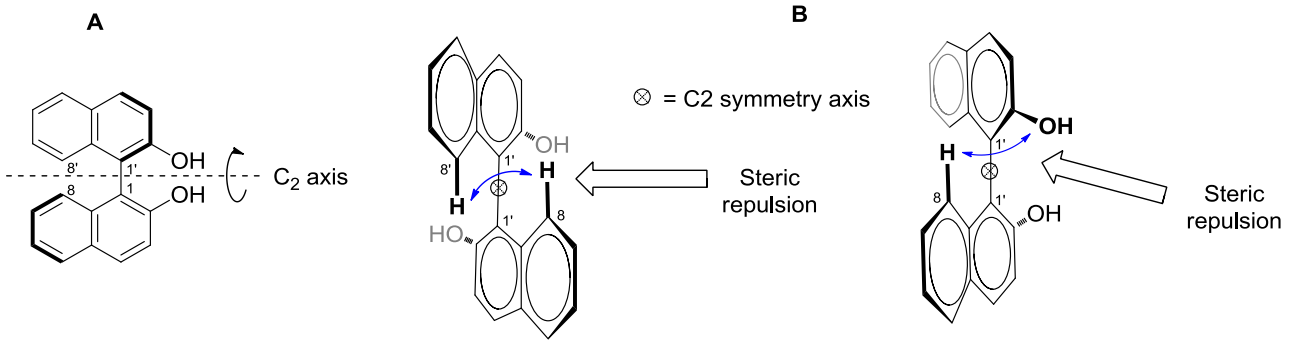


Figure 4.1: symmetry properties (**A**) and reason for BINOL chirality (**B**).

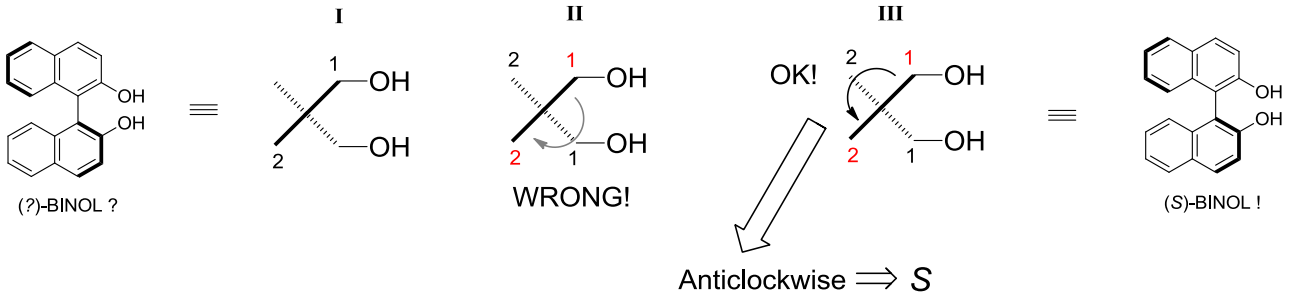


Figure 4.2: how to determine BINOL configuration. **I**: assign priority to the groups ahead. **II**: assign priority behind. **II-III**: draw an arrow to go from the group 1 to group 2 ahead without passing through 1 behind (like in **II**), but passing through 2 behind (like in **III**).

However a mnemonic rule for BINOL could be that, having OH groups on the right, if the ring in the upper left is above, that is (*S*)-BINOL. As we can clearly see from pictures **I, II** and **III** in *figure 4.2*, the two planes on which the two naphthyls lay cross one to each other to form an angle. This is called *dihedral angle* and its value is crucial for enantioselective catalysis, since the size of the chiral pocket is strictly related to the width of this angle. The lower is the angle value, the smaller is the pocket, and the opposite. In asymmetric metal catalysis the ligand should fit to the metal and clamp it if the fit is not perfect (taking into account the metal's molecular orbital geometry), thus in different metal complexes this angle can vary. In *figure 4.3* we see BINOL and some of its derivatives. If in BINOL the dihedral angle is 80.8°, in BINAP, due to the bulky $-P(Ph)_2$ substituents, is 90°, and in BINOL hydrogenphosphate, strained by the additional ring, is only 57.77°[103] (see *figure 4.3*).

[103] To the best of my knowledge, this is the only dihedral angle reported on phosphoric acid derivatives, and it actually belongs to the salt formed by BINOL hydrogenphosphate with an amine, so in the free acid it may vary a little: E. J. Wang, G. Y. Chen, *Acta Cryst.*, **2011**, *E67*, o91

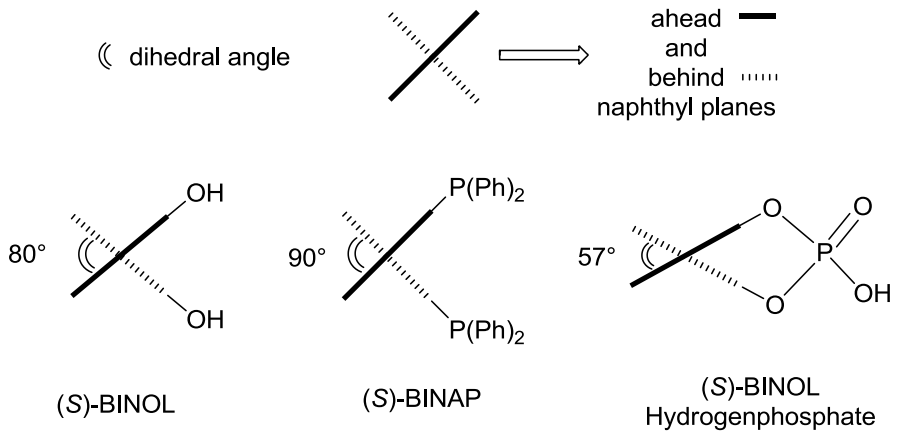
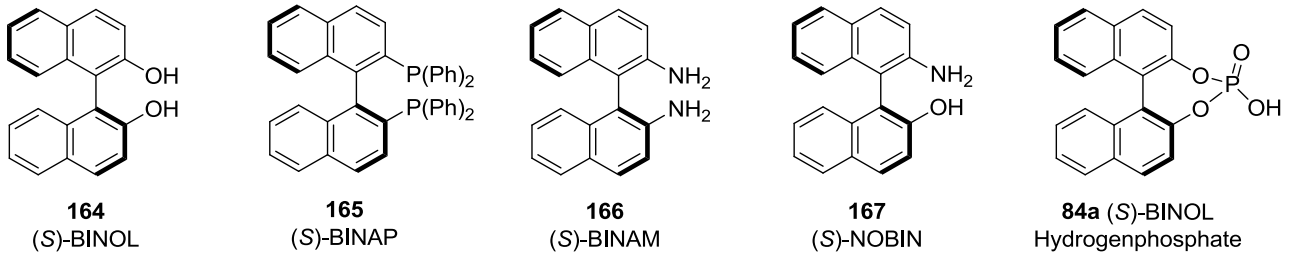


Figure 4.3: dihedral angle and some representation of BINOL derived compounds in perspective.

BINOL possesses a C_2 symmetry axis (*Fig.* 4.1, **A**), that means that rotating the molecule by 180 degrees clockwise or anticlockwise along that axis would give the molecule itself. This means that, despite its chirality, BINOL is somewhat symmetric. For example, ^{1}H NMR spectrum of BINOL shows only half of the protons, being *number* and *number'* protons equivalent, thus with the same chemical shifts. Turning BINOL upside down results in the same spatial arrangement of the atoms, unlike it happens for its non-symmetric derivatives (such as NOBIN, see figure 4.4).

> "C2 symmetry is attractive because it reduces the number of possible catalyst-substrate arrangements and, consequently, the number of competing reaction pathways by a factor of two. This can have a beneficial effect on the enantioselectivity and, moreover, facilitates a mechanistic analysis and identification of the factors responsible for enantiocontrol".[104]



164 (*S*)-BINOL | **165** (*S*)-BINAP | **166** (*S*)-BINAM | **167** (*S*)-NOBIN | **84a** (*S*)-BINOL Hydrogenphosphate

Figure 4.4: BINOL and some of its most widespread derivatives.

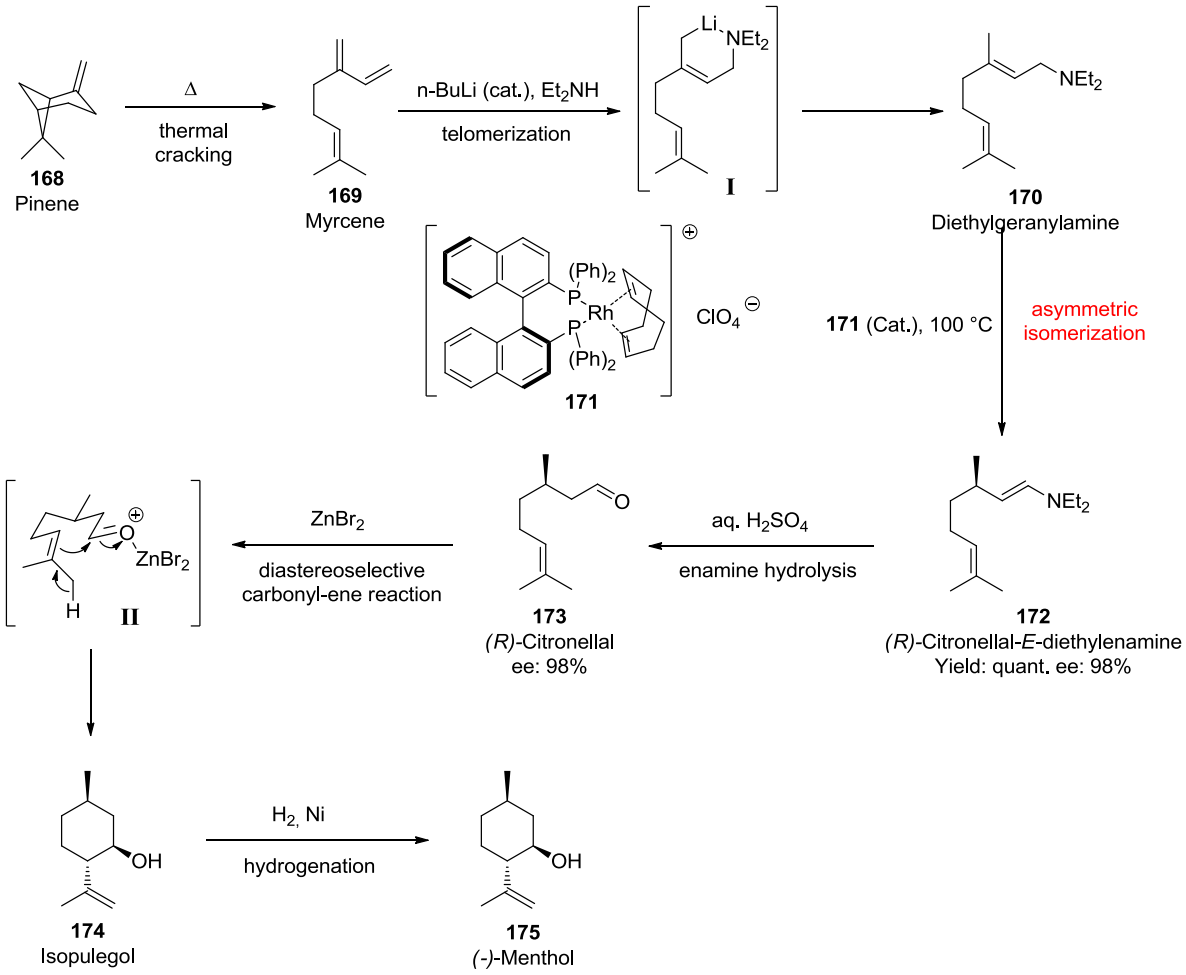
In figure 4.4 are shown some common BINOL derivatives. While BINOL **164**, BINAP **165** and BINAM **166** are symmetric, NOBIN **167** is not and BINOL hydrogenphosphate **84a** (the simplest chiral phosphoric acid) is formally not. But the way it's represented shouldn't deceive. It looks like unsymmetric, but the rapid equilibrium shifting the acidic proton between the two phosphoryl oxygen atoms gives to this compound a real C_2 symmetry.

After the establishment of a convenient method for its resolution in 1971, BINOL was applied in two different reports that showed its particular utility as enantiomerically pure compound: between 1974 and 1978 Cram, with an impressive work, used BINOL derived polycyclic crown ethers as chiral anion binders and in 1979 Noyori showed its utility in reduction of carbonyl compounds[105,106]. Since that moment, BINOL chemistry

[104] In ref. 98b, page 2.

[105] a) D. J. Cram et al., *J. Org. Chem.,* **1878***, 43, 1930-1946.* b) D. J. Cram, J. M. Cram, *Acc. Chem. Res.*, **1978**, *11*, 8–14. and reference therein.

grew exponentially, as well as synthesis and application of its derivatives[98]. Cram contributed significantly to the development of the synthesis of 3,3' derivatives, used later as chiral ligands in transition metal and Lewis acid catalyzed transformations[98]. On the other side as early as 1980 Noyori used the BINOL derivative BINAP in the asymmetric hydrogenation of olefins[107], a particularly challenging transformation at that time, and since that moment it became (one of) the most popular ligands in asymmetric metal catalysis[98]. The development of this ligand, useful for a broad scope of highly enantioselective hydrogenations, and its use in 1984 for the first enantioselective industrial synthesis (synthesis of menthol **175**, at the Japanese chemical company Takasago, working in strict contact with Noyori himself[108]) accounts for the half of the 2001 Nobel prize shared by the Japanese scientist with Knowles for enantioselective reductions (the other half of the prize went actually to Sharpless for enantioselective oxidation reactions, one of which is the dihydroxylation using Osmium and cinchona alkaloids derivatives that we saw in *figure 3.2*). The key step for enantioselectivity in Takasago synthesis (scheme **4.1**) of menthol is the RhBINAP complex **171** catalyzed isomerization of a double bond of diethyl geranylamine **170** to give enamine **172**, which will be hydrolyzed to citronellal **173** in the following step. The chirality created in this way is then maintained in the stereoselective cyclization of **173** to isopulgeol **174**, easily converted to menthol **175** via reduction.



Scheme **4.1**: Takasago process for enantioselective industrial synthesis of Menthol, 1984.

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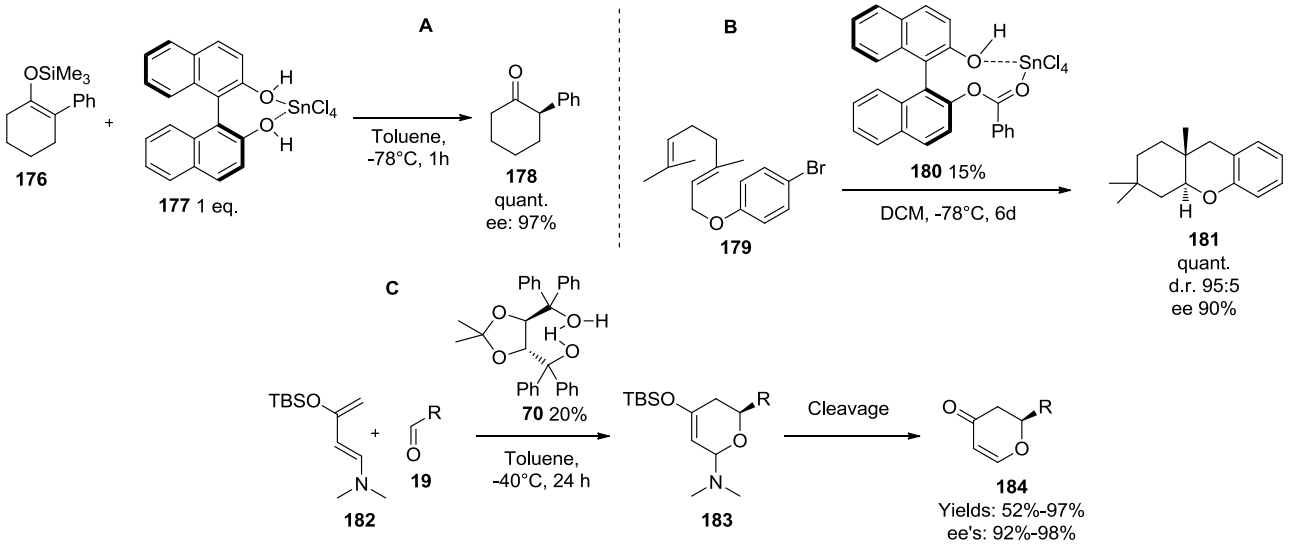
[106] R. Noyori, I. Tomino, Y. Tanimoto, *J. Am. Chem. Soc.*, **1979**, *101*, 3129–3131.

[107] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.,* **102**, *1980*, 7932–7934.

[108] K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, T. Otsuka, *J. Am. Chem. Soc.,* **1984,***106,* 5208-5217**.**

The extensive work of Yamamoto on enantioselective acid catalyzed reactions brought him to recognize in 1994 that the complex of BINOL with $SnCl_4$ is a Brønsted acid and not a Lewis acid, since it could perform enantioselective potonation of silyl enol ethers[109] (scheme **4.2**, **A**). Unfortunately, there was no way to regenerate the acid and so a stoichiometric amount of BINOL was used. Many similar examples were out, but only one was really catalytic: the enantioselective polycyclization of geraniol derivatives **179**[110] (scheme **4.2**, **B**). This kind of catalysis is called Lewis Acid Assisted Brønsted acid catalysis, because the near Lewis Acid helps in increasing the acidity of the Brønsted acid attracting on itself negative charge from one of the BINOL oxygen. The same technique is used also in 2003 by Rawal (scheme **4.2**, **C**) but in this case he uses a Brønsted acid Assisted Brønsted acid catalysis, where the acidity of a proton is increased by another proton[111]. The chiral scaffold used is TADDOL in which is known a hydrogen bond between the two oxygen atoms, having a proton more acidic than the other. Whether the latter it's not BINOL and somebody would refer this example as Hydrogen bonding catalysis, Brønsted acidic catalysts based on a C2 symmetric scaffold were developed and the times were ready for real asymmetric Brønsted acid catalysis.



Scheme **4.2**. **A**: the first recognition that a BINOL complex acts as a Brønsted acid. **B** asymmetric polycyclization via Lewis Acid Assisted Brønsted acid catalysis. **C**: Brønsted acid Assisted Brønsted acid catalysis by TADDOL. They can all three be considered as early attempts to asymmetric Brønsted acid catalysis.

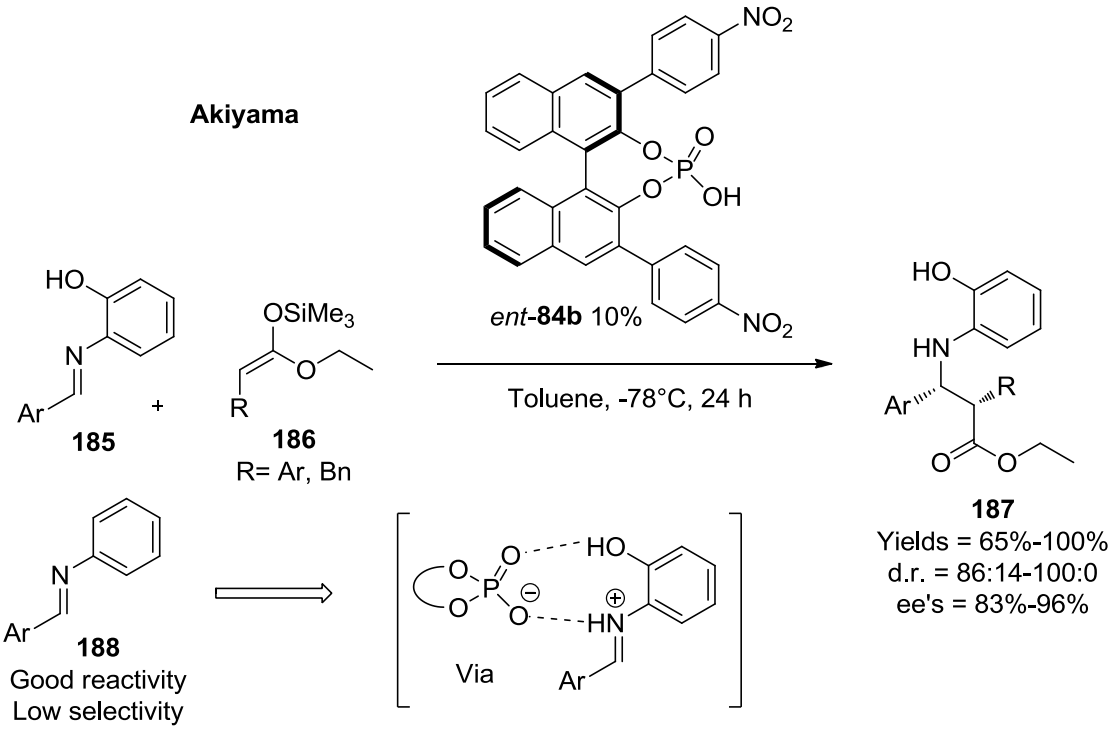
[109] K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.*, **1994**, *116*, 11179–11180.

[110] a) K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.,* **1999,** *121,* 4906-4907. b) S. Nakamura, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.,* **2000,** *122,* 8131-8140.

[111] a) Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature*, **2003**, *424*, 146. b) A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5846–5850.

4.2) Chiral Phosphoric Acids

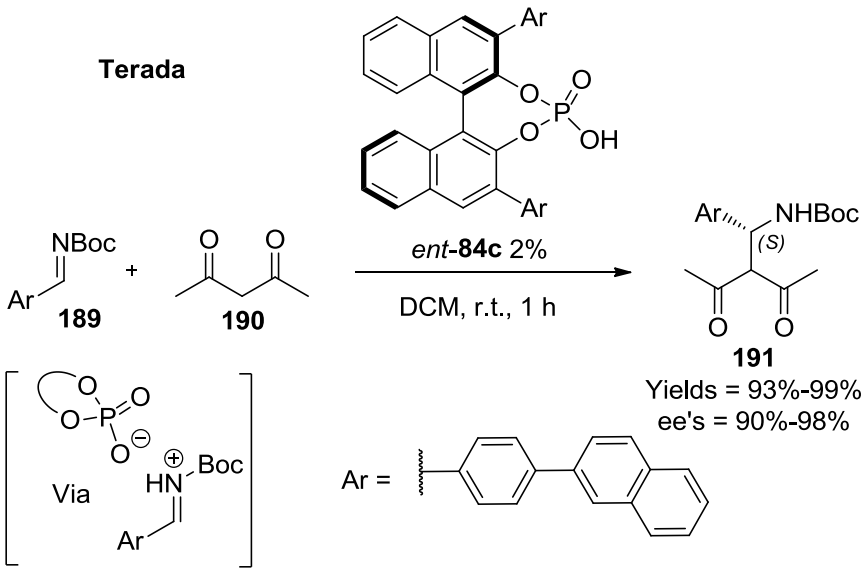
The era of phosphoric acids began in 2004 when Akiyama and Terada groups reported independently enantioselective Mannich reactions[112]. Akiyama reported the addition of silyl ketene acetals **186** to aryl aldimines **185** (scheme **4.3**). The reaction takes place at low temperature and 10% of catalyst *ent*-**84b**, evaluated among others, is enough to catalyze the transformation in 24 h. The authors point out that the *ortho*-hydroxyphenyl moiety on the nitrogen is crucial for the stereochemical outcome of the reaction: when a simple phenyl substituent is employed the ee dropped to 39%. This suggests an activation mode where the imine is protonated, but also the *ortho*-hydroxy group is involved in the transition state, perhaps with a hydrogen bond to the phosphoryl oxygen (see scheme **4.3**). This renders the chiral phosphoric acid a bifunctional catalyst, where the proton is the real activator and the oxygen serves as anchoring moiety to create an ordered transition state.



Scheme **4.3**: Akiyama seminal work on enantioselective Brønsted acid catalyzed Mannich reactions.

Conversely, in Terada's example the activation mode appears to be different. The reaction is again a Mannich addition to arylimines, but performed in this case with acetylacetone (scheme **4.4**). The reaction occurs in very mild condition, short times and with low catalyst loadings. Since in this case the imine does not bear any hydrogen bonding unit, it appears that in this case just the protonation of the imine is responsible for catalysis. In a short time we will see that it's not exactly like this.

[112] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566 –1568. b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, **2004**, *126*, 5356-5357.



Scheme **4.4**: Terada seminal work on enantioselective Brønsted acid catalyzed Mannich reactions.

The best catalyst *ent*-**84c** bears two very bulky substituents in the 3 and 3' position on BINOL backbone. This will become a very common feature for chiral phosphoric acid and related catalysts, as well as it's been for a long time a feature for BINOL based ligands for metals. The reason why most of the times it's important to have bulky substituents on these positions is that in this way they point towards the active site of the catalyst, creating a chiral environment for the reaction to occur. Often the authors of the papers talk about a "chiral pocket" inside which the reaction occurs. The more bulky the substituents are, the smaller is the pocket, and the easier is the reaction to control. That's why often simple phenyl or substituted phenyls are not enough to achieve good enantiocontrol. Often 2-naphthyl, phenanthryl, anthracenyl and $SiPh_3$ are used as substituents (*figure 4.5*). One substituent in particular, the 2,4,6-triisopropylphenyl moiety, proved to be very effective in many cases, and became so popular that a name was given to the corresponding phosphoric acid: it's nowadays called TRIP (**84h**, *figure 4.5*). This acid gain so much attention that in three years since its introduction by Benjamin List, it deserved a review on its use and became commercially available from Sigma-Aldrich[113]. Anyway there is not a general rule that states that the bulkier is the acid, the better is enantioselectivity.

> "It is particularly noteworthy that the catalytic activity and stereoselectivity imparted by these catalysts can change dramatically with the reactions and substrates, making a prediction of the catalytic behavior of chiral phosphoric acids quite difficult"[114].

Every reaction needs a different size and shape of the chiral pocket, and sometimes also slight modifications of the catalyst structure lead to dramatic changes in enantioselectivity, so a catalyst screening is generally required for reaction optimization.

[113] a) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem. Int. Ed.,* **2005**, *44*, 7424. b) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta,* **2008***, 41,* 31-39.
[114] B. List, In ref. 113b.

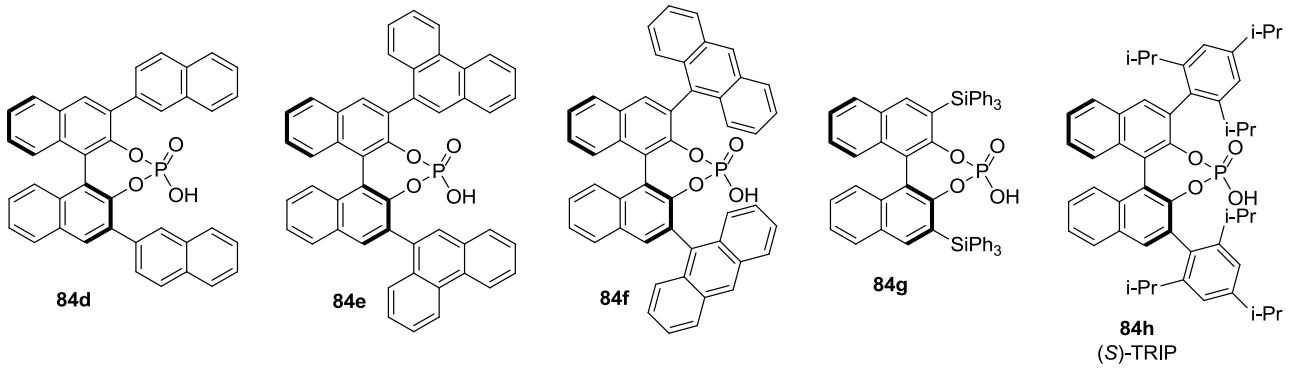
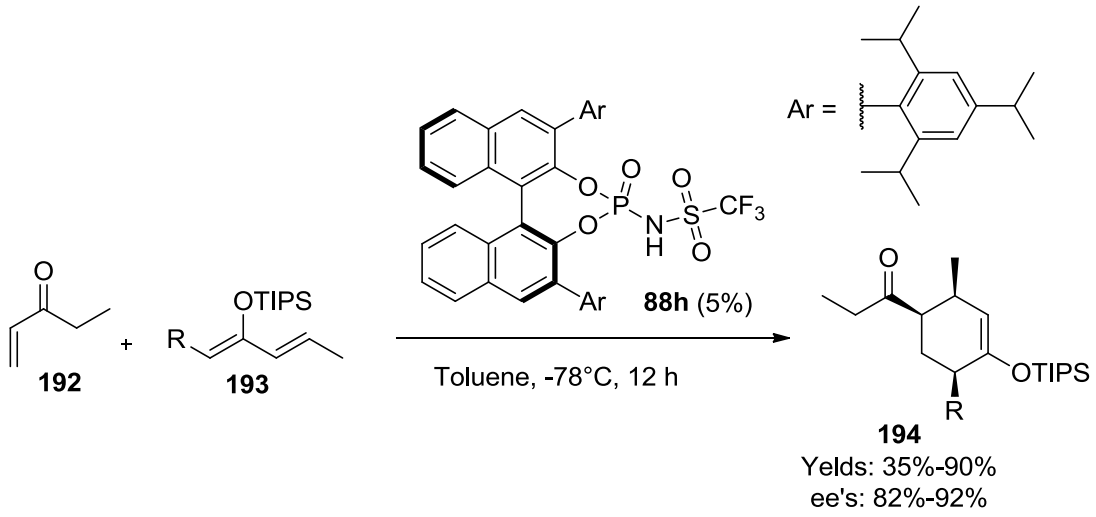


Figure *4.5*: some of the most commonly used chiral phosphoric acids with bulky substituents including TRIP.

Phosphoric acids became popular in activation of imines, α-ketoesters, and generally of good electrophiles. Their moderate acidity doesn't allow them to activate more challenging electrophiles such as aldehydes and ketones.

Anyway in 2006 Yamamoto introduced their corresponding triflimides, as stronger Brønsted acids[115]. In fact the additional trifluoromethanesulfonyl moiety makes the compounds more acidic due to its electron withdrawing nature. In this way Brønsted acid catalyst were able to perform new reactions which require stronger activation. For example Yamamoto applies these catalysts in Diels-Alder reactions between dienes **193** and ethyl vinyl ketones **192** probably with direct carbonyl activation[116] (scheme **4.5**).

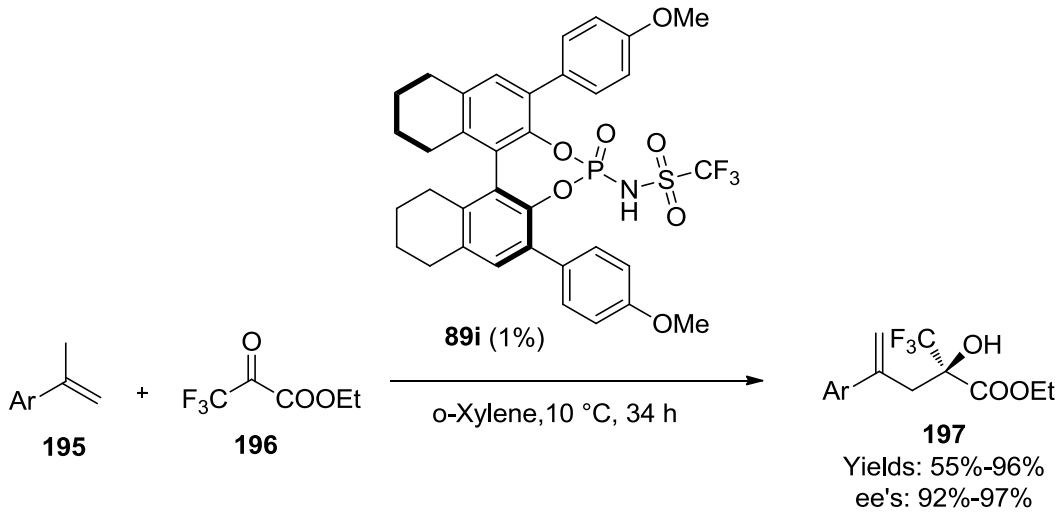


Scheme **4.5**: Yamamoto designs a new highly acidic catalyst: phosphoric acid triflimide.

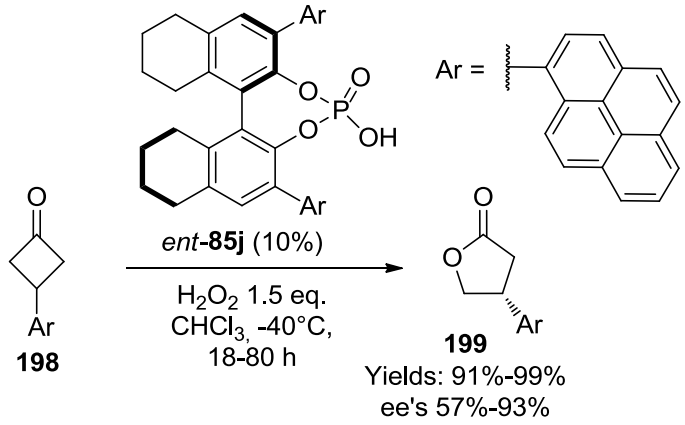
[115] D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.*, **2006**, *128*, 9626-9627.

[116] The authors did not propose an activation model, but showed that triflimides are silylated in reaction conditions, more or less quickly depending on the substituents. This silylated species, anyway, are not catalytic, ruling out silylium catalysis. Bulkiness of the catalyst employed results in slow silylation, and this is actually the reason of high catalytic activity of the catalyst employed.

Since this moment Brønsted acids were used to promote more challenging transformations. One relevant example is the carbonyl-ene reaction developed by Rueping and co-workers[117]. In this case the highly electrophilic trifluoropyruvate **196** is used, but it's reacted with relatively weak nucleophiles as alkenes **195**. A survey of methyl styrenes was reacted with trifluoropyruvate **196** with good yields and selectivities (scheme **4.6**). Other two interesting features of this paper were the observed extensive dimerization of styrenes in chlorinated solvents, probing high acidity of the catalysts, and the mention that low reactivity was obtained employing calcium salts of the phosphoric acid triflimides, ruling out their involvement in catalysis. Although it's not clear the reason of this mention, the author says that more detailed studies would have been reported in due to course.



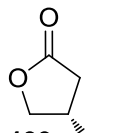
Scheme **4.6**: Rueping's carbonyl-ene reaction: a difficult transformation.



During optimization

with catalyst purified via flash chromatograpy:
65% Yield, 88% ee in 43 h

with catalyst washed with 4 n HCl:
99% Yield, 88% ee in 18 h

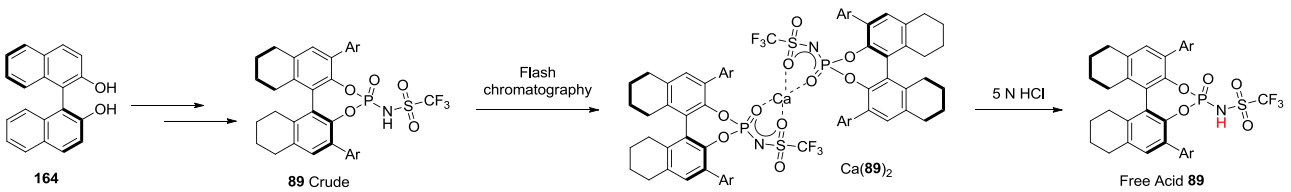


Scheme **4.7**: desymmetrizative Baeyer-Williger reaction disclosed by Ding. During optimization he realizes that washing the catalyst with HCl results in higher catalyst activity.

[117] M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem. Int. Ed.*, **2008**, *47*, 6798–6801.

In the same year Ding and co-workers report a remarkable enantioselective desymmetrizative Baeyer-Williger oxidation of meso-cyclobutanones **198**[118]. After an impressive optimization of the catalyst and of reaction conditions, they found the H8-BINOL derived catalyst *ent*-**85j** bearing very bulky pyrenyl substituents as the optimal for the title reaction. Interestingly, the last step of the optimization is the use of the catalyst washed with HCl: whether enantioselectivity is not affected, reactivity is enhanced. The authors explain this as a possible removal of unspecified impurities (scheme **4.7**).

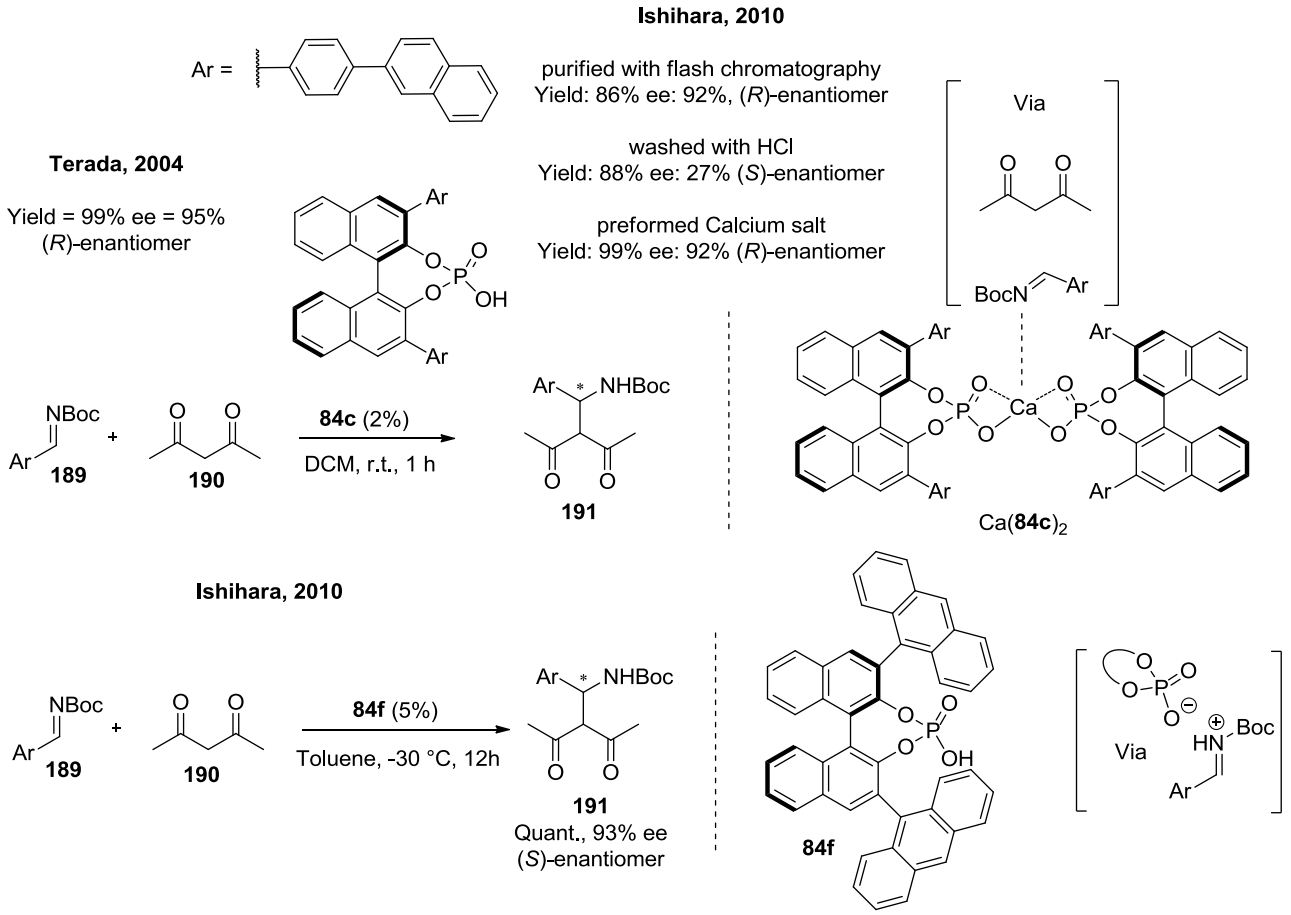
Actually in 2010 Rueping and co-workers reported the detailed studies announced two years before[119]. In a valuable and comprehensive study on the synthesis and characterization of H8-BINOL based triflimides **89**, the authors realize that after column chromatography only the corresponding calcium salt Ca(**89**)$_2$ is obtained, with two triflimide counteranions chelating the metal. Since no calcium derivatives were used during the synthesis, they inferred that calcium came from the silica gel used for purification by column chromatography. Anyway, after washing with 5 N HCl, pure metal free Brønsted acids were obtained, as confirmed by X-ray and EDX experiments (scheme **4.8**).



Scheme **4.8**: Rueping, 2010. After their synthesis, purification of H8-triflimides **89** by flash chromatography on silica gel gives the calcium salt Ca(**89**)$_2$ because silica contains calcium impurities. By the way, washing this material with 5 N HCl restores the metal free catalyst.

In the same year many other experiments dealing with this problem were out. The most impressive was reported by Ishihara and co-workers about Mannich addition to aldimines (Scheme **4.9**)[120]. During their studies to expand the scope of this reaction, apparently they encountered problems. In this way they decided to re-examine Terada's 2004 results (scheme **4.4**). They suddenly realized that, if working with HCl washed catalyst, in the conditions reported by Terada the reaction was sluggish, giving the opposite enantiomer of the product **191**, with low ee. Anyway the reaction was working well with the same catalyst if not washed with HCl after purification on silica gel. Thus they deduced that some metal impurity contained in the silica actually catalyzes the reaction. After a screening of different metals, they found the calcium salt Ca(**84c**)$_2$ as the catalytically active specie. In the same context, they also found the right conditions for a metal-free reaction using catalyst **84f**.

[118] S. Xu, Z. Wang, X. Zhang, X. Zhang, Kuiling Ding, *Angew. Chem. Int. Ed.*, **2008**, *47*, 2840–2843.
[119] M, Rueping, B, J. Nachtsheim, R. M. Koenigs, W, Ieawsuwan, *Chem. Eur. J.*, **2010**, *16*, 13116–13126.
[120] M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem. Int. Ed.*, **2010**, *49*, 3823–3826.



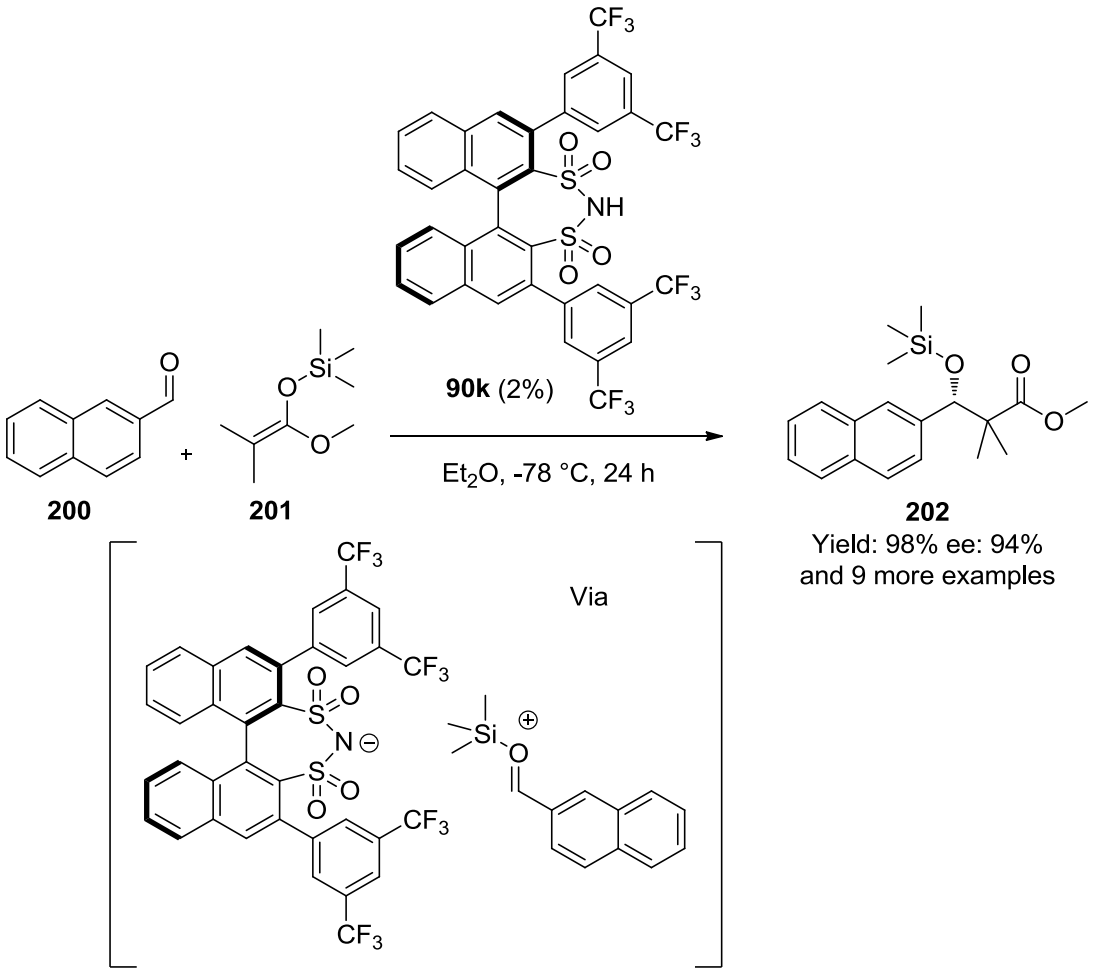
Scheme **4.9**: Ishihara in 2010 re-examines Terada's 2004 results. He finds that the material purified via flash chromatography on silica gel is highly catalytic and enantioselective, furnishing the same results reported by Terada. By the way, this material is most likely not the free phosphoric acid, but the corresponding calcium salt, which, if prepared on purpose and used as catalyst gives roughly the same result. Conversely, the metal free acid, washed with HCl, gives poor results. It's actually possible to catalyze the reaction with a metal free phosphoric acid, but the 3-3' substituents and the conditions have to be changed.

This result clearly points out the attention on how much is important washing the catalysts with HCl after their purification by flash chromatography on silica gel.
In 2010, anyway, Terada himself re-investigate some of his reactions, confirming some results, disproving others[121]. Also List points out the importance of washing TRIP with HCl after purification on column for a good performance of the catalyst[122].
After this important issue had been emphasized, it was clear to everyone the importance of washing catalysts with HCl after purification. In fact, every reaction outcome could be affected also by small amounts of metal salts, if they are highly catalytically active. Conversely, Brønsted acid catalyzed reaction may be sluggish if considerable amounts of metal impurities are present. Moreover, composition of metal impurities in silica gel may vary on the suppliers, and so the product obtained from column chromatography is not always the calcium salt, but other metals may be there. Therefore, for chiral phosphate catalyzed reactions, the acid must be washed after chromatography, and then the metal complex must be made on purpose.

[121] M. Terada, K. Kanomata, *Synlett,* **2011**, *9*, 1255–1258.
[122] M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett,* **2010**, *14*, 2189–2192.

Recently other more acidic BINOL based Brønsted acid were out, able to catalyzed new transformations.

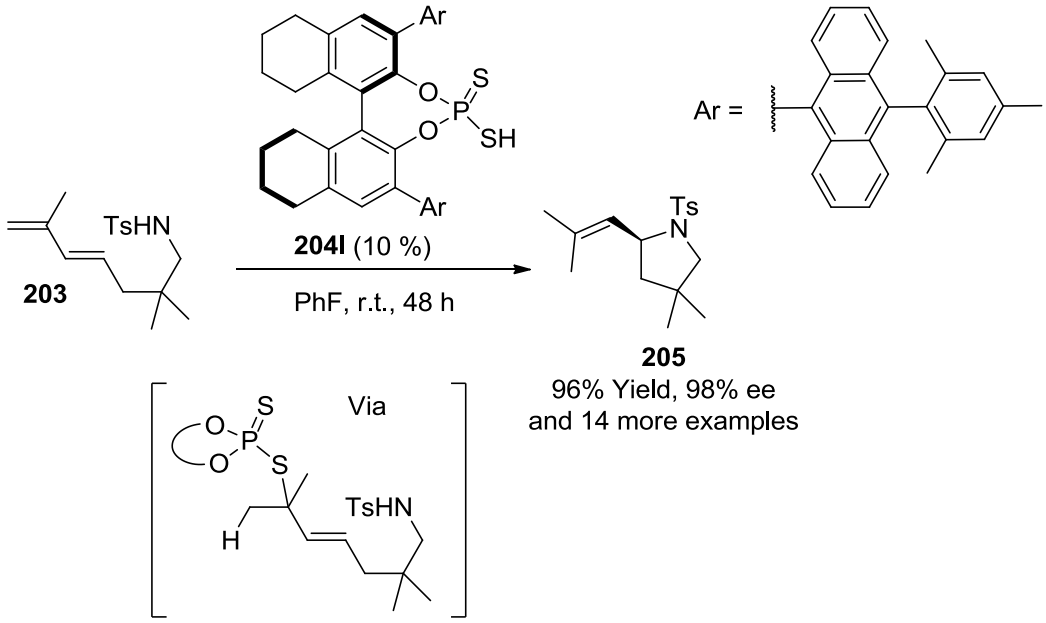
In 2009 List reported the chiral bis-sulfonamides **90** as highly active and enantioselective catalyst for Mukaiyama-aldol reactions[123]. This catalyst is highly active and enantioselective where all the other BINOL based Brønsted acids fail. These catalysts seems to have a particular affinity to silicon, as an N-silylated specie is proposed to be involved in the reaction mechanism and to be the actual catalyst in the transformation (scheme **4.10**). This trend is confirmed by other following reports, where sylilated reagents were employed.



Scheme **4.10**: list discloses enantioselective catalysis by bis-sulfonamides, apparently having affinity with silicon.

[123] P. Garcìa-Garcìa, F. Lay, P. Garcìa-Garcìa, C. Rabalakos, B. List, *Angew. Chem. Int. Ed.*, **2009**, *48*, 4363 –4366.

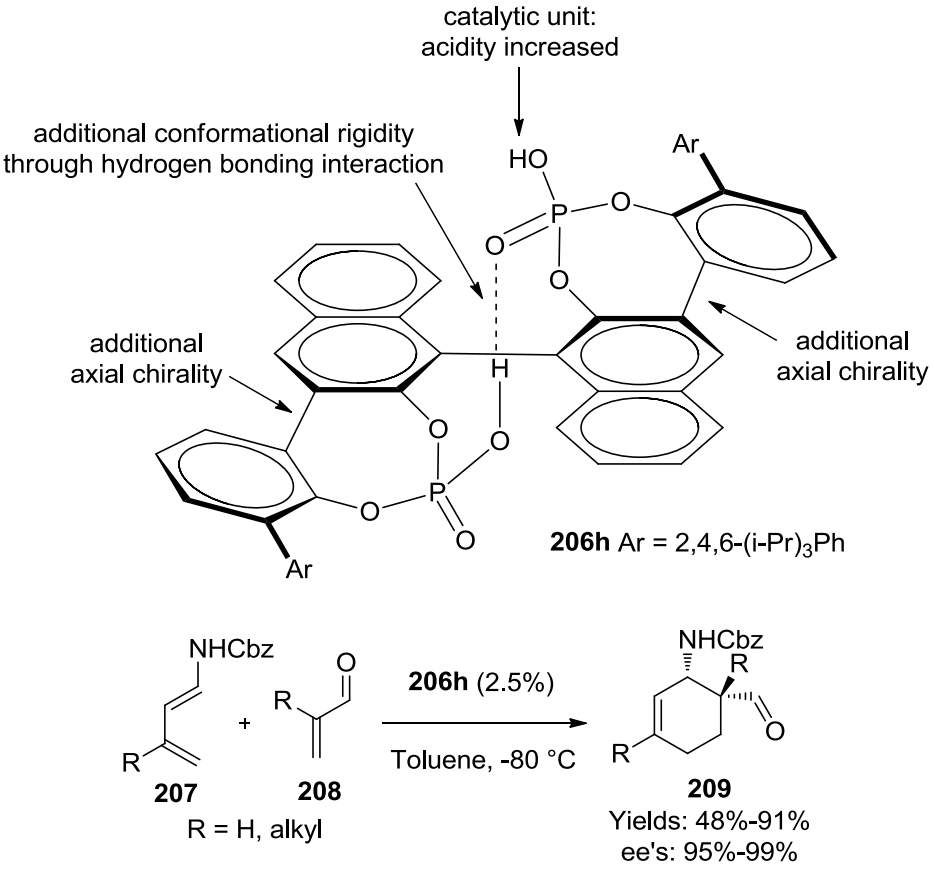
In 2011 Dean Toste reported the first organocatalytic enantioselective hydroamination[124]. The reaction, until that time a prerogative of metal catalysis, was catalyzed by a new dithiophosphoric acid **204l**, with a new, covalent, activation mode (scheme **4.11**). The catalyst, due to its highly acidity, activates the substrate firstly by protonation of the double bond, then, due to the relatively high nucleophilicity of sulfur, reacting with the carbocation formed in this way. A covalent bond between the catalyst sulfur atom and the previously carbocationic carbon is created in this way (see scheme **4.11**). The thiophosphate acts finally as a leaving group in the ring closing step, where the nitrogen attacks the double bond and the latter shifts expelling the dithiophosphate, leading to the hydroamination product **205**.



Scheme 4.11. Toste publishes in Nature the first organocatalytic enantioselective hydroamination. The catalyst is a highly acidic thiophosphoric acid, developed on purpose, enough acidic to protonate the double bond and with a counterion enough nucleophilic to quench the carbocation. It serves as a leaving group upon the attack of the amine, and so the catalyst is restored.

In the same year Terada designed new bisphosphoric acids **206**[125]. Two ortho-hydroxy substituents in aryl groups located in 3 and 3' allows the formation of these acids. The main feature is that of the two protons, only one is responsible for catalysis, while the other one is bridging with the other phosphoryl oxygen, creating a rigid framework, enhancing acidity of the catalytic proton, and giving directionality to the system (scheme **4.12**). This is a clear example of Brønsted acid assisted Brønsted acid catalysis. The reaction is an enantioselective Diels-Alder on aldehydes with dienamines, and the enantioselectivities are all impressively high.

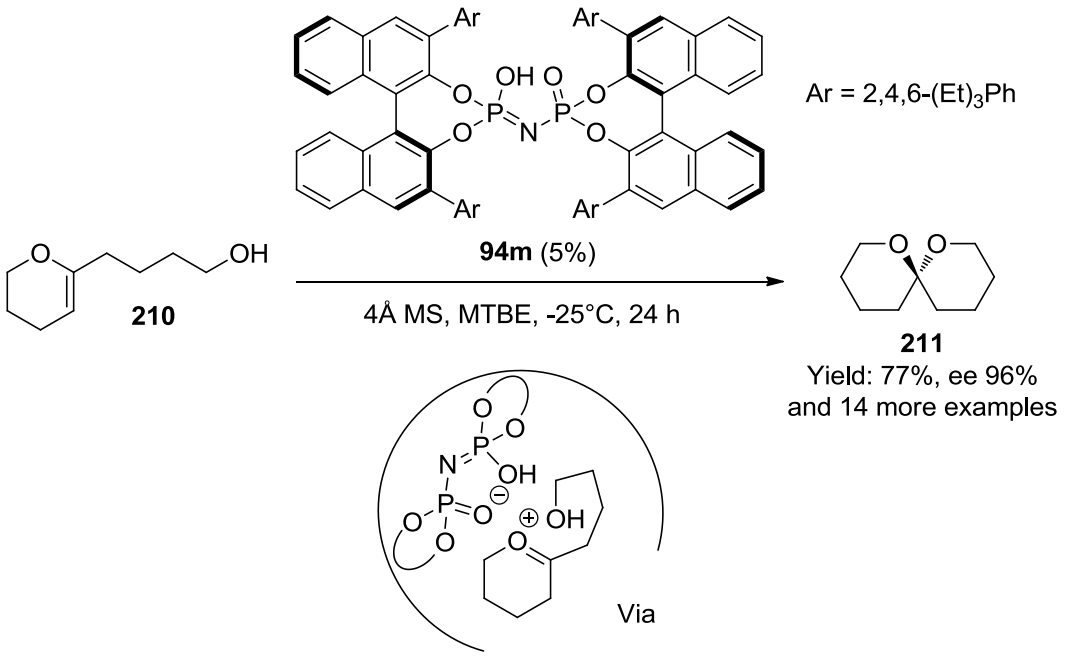
[124] N. D. Shapiro, V. Rauniyar, G. L. Hamilton, J. Wu, F. D. Toste, *Nature*, **2011**, *470*, 245-250.
[125] N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto, M. Terada, *J. Am. Chem. Soc.*, **2011**, *133*, 19294–19297.



Scheme **4.12**. The bisphosphoric acid developed by Terada, exploiting an internal hydrogen bond, creates a rigid structure, and forms a cavity ideal to accomplish enantioselective reactions. R = 2,4,6-triisopropylphenyl.

In 2012 again List reported new, highly acidic, extremely encumbered bisphosphorylimides **94** for the highly challenging spiroketalization of enol ethers[126]. The acidic proton has been shown to be bridging by the two oxygen atoms, and not on the nitrogen as expected. The four bulky substituents confer to this catalyst a defined structure similar to an enzyme pocket, where the spirocyclization of the small enol ethers **210** used can occur enantioselectively (scheme 4.13).

[126] I. Coric, B. List, *Nature*, **2012**, *483*, 315-319.



Scheme **4.13**: the latest arrived in chiral Brønsted acids family are bisphosphorylimides **94m** developed by List. The very big steric bulkiness hinders the catalytic site inside a chiral pocket in an enzyme-like working mechanism. And so the challenging asymmetric spiroketalization of small enol ethers **210** can be accomplished.

Having a look to the survey of reactions and concepts just presented above, it's clear that during the years the developments of chiral Brønsted acids were numerous and outstanding. The always deeper understanding of their nature, the reasoning on their structure, the acidity improvements, creating of frameworks and refining the structure of the chiral pocket led the chemists to accomplish new and always more challenging transformations. The importance of these findings are clearly shown by the great interest in the field, with many publications and groups working on these catalysts. Moreover, recently the most outstanding results were published in the best journals for a scientist: Nature and Science. This means that this field has still a lot to give, and for sure in the future many important and exciting findings will be reported.

4.2.1) Some theory

From the topics covered in the previous section two key features of chiral Brønsted acids emerged, determining their reactivity and their selectivity: acidity, which most likely allows them to activate more challenging substrates, and bulkiness of substituents, determining enantioselectivity. By the way we also said that is difficult to anticipate whether reactivity or enantioselectivity will be good using a particular catalyst, and a catalyst screening is generally required. Despite this fact will continue to be true probably forever, somebody tried to develop models and experiments to anticipate, or at least to better understand the reaction outcome, shedding light on mechanisms and species involved into them. First of all, since these catalysts are acid, an acidity scale is useful. Surprisingly, for many years the acidity of these compounds was related just to the one of the achiral surrogate diphenylphosphate **255** (commonly used as achiral catalyst, to test whether if a system shows reactivity under phosphoric acid catalysis or not), with a known pK_a of 1.9 in water. Triflimides, sulphonamides, and so were defined just "more acidic" due to the known

decreasing in pK_a values in molecules bearing trifluoromethanesulphonyl substituents respect to the corresponding not bearing them. Only in 2011 a systematic experimental study on Brønsted acidities of these compounds was carried out for the first time[127]. Berkessel and O'Donoghue developed an acidity scale in DMSO of some phosphoric acid derivatives, also belonging to different classes like: chiral phosphoric acids chiral triflimides, bis-sulfonamides and bis-sulforylimides. The acids cover a narrow 2.63-4.22 pK_a range being the electron poor **84k** the most acidic and the electron rich *ent*-**84h** the least (*Fig*. *4.6*). An acid based on [H_8]-BINOL (**85a**) showed to be less acidic than the corresponding BINOL based **84a** by roughly 0.8 points (*Fig*. *4.6*). Surprisingly, the corresponding triflimide *ent*-**88h** resulted only 0.9 pK_a units more acidic than TRIP *ent*-**84h** (*Fig*. *4.6*). This is really surprising since the different reactivity of phosphoric acids and their corresponding triflimides had always been rationalized until that time with a much higher acidity of the latter. Phosphoric acid triflimides have experimentally shown to activate much better some challenging substrates respect to the acids. Many triflimide catalyzed reactions don't work with phosphoric acids, if using those particular substrates. But, since this low acidity difference, Berkessel and O'Donoghue conclude that other factors may determine this high reactivity difference. Bis-sulfonamides and bis-sulforylimides are more acidic, but still in pK_a values between 1.7-2.0.

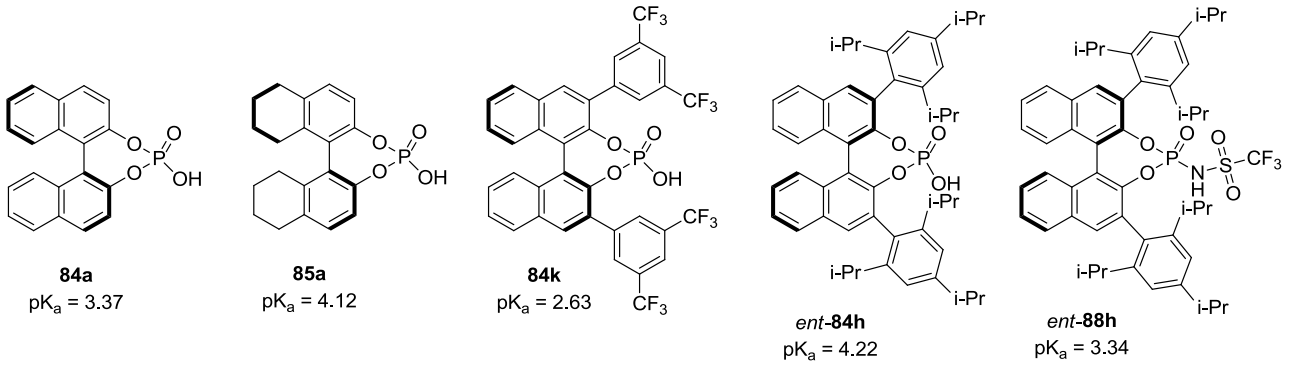


Figure 4.6: pK_a values of some chiral Brønsted acid catalysts in DMSO according to Berkessel and O'Donoghue.

Based on Berkessel and O'Donoghue work, Li and Cheng in 2013 developed a computed acidity scale for such compounds in DMSO[128]. They used some of their experimental values to develop a general computational method to predict the acidity of other acids. Other than the acids investigated in the previous work, also thio and bis-thioacids were exhamined (*figure 4.7*). BINOL based Bis-thioacids **204** (-4.2/-3.2) are in general more acidic than thioacids **212** (-3.0/-1.9), which are more acidic than thioacids **86** (0.9/1.9) which are more acidic than phosphoric acids **84** (1.9/4.9, with the only exception of the highly electron withdrawing 3,3' pentafluorophenyl substituent: pK_a = 1.3). The wider is the aromatic scaffold, the higher is the acidity, as VAPOL **92** and analogues are more acidic than BINOL **84**, which is more acidic than SPINOL **93** and [H_8]-BINOL **85** derivatives. As expected, acids based on the non-aromatic TADDOL **91** are the weakest, except the highly electron withdrawing tetrakistrifluoromethyl derivative. Interestingly, in this work triflimides, bis-sulfonamides and bis-sulforylimides were not considered. The authors well correlate the acidities of some compounds with the Curtin-Hammett parameters regarding electron withdrawing/donating properties, showing linear dependency. They also discuss a

[127] P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudörfl, A. Berkessel, AM. C. O'Donoghue, *Chem. Eur. J.*, **2011**, *17*, 8524-8528.
[128] C. Yang, X.-S. Xue, J.-L. Jin, X. Li, J.-P. Cheng, *J. Org. Chem.*, **2013**, *78*, 7076−7085.

very few examples in literature in which reactivity, and, remarkably, enantioselectivity seems to be related to the strength of the acids. Anyway these examples are limited and do not cover all the literature.

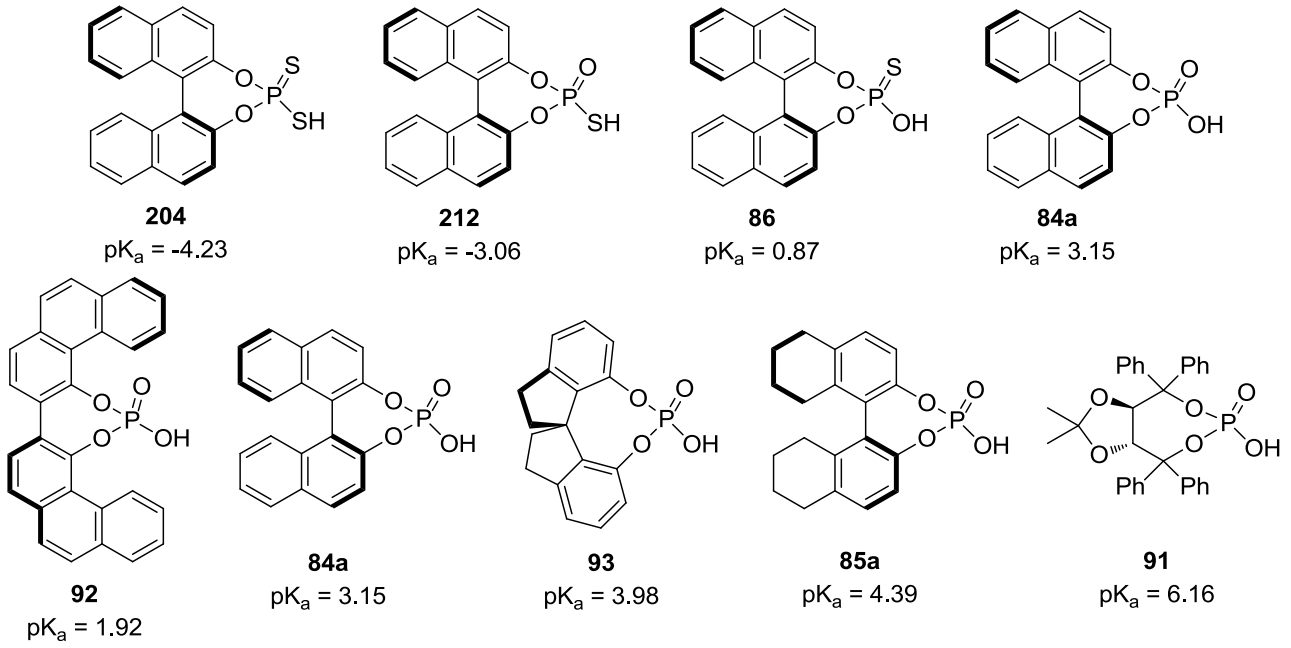


Figure 4.7: pK_a values of some chiral Brønsted acid catalysts in DMSO calculated by Li and Cheng.

In the same year Rueping and Leito came out with a new acidity scale for chiral Brønsted acids[129]. This time the values were measured in dry acetonitrile (see *figure 4.8* for some of them). Phosphoric acids are in the pK_a range of 12.5/14. Again, [H_8]-BINOL derivatives **85** show higher pK_a values than corresponding BINOL **84**. Electronic properties of aromatic 3,3' substituents well fit the Curtin-Hammett parameters, as acid **84o**, is more acidic than acid **84n**, which is more acidic than TRIP **84h**. Until this point, Rueping and Leito's work is according to the previous two. But, then, the acidities for triflimides are strikingly different. According to Rueping and Leito they lay in a pK_a range between 6.3/6.9, that is roughly 6 pK_a unit lower than the one for the corresponding phosphoric acids. Since the correlation between pK_a values DMSO and acetonitrile is linear with a slope roughly one, this huge difference between the two acidity scales seems to be inexplicable.

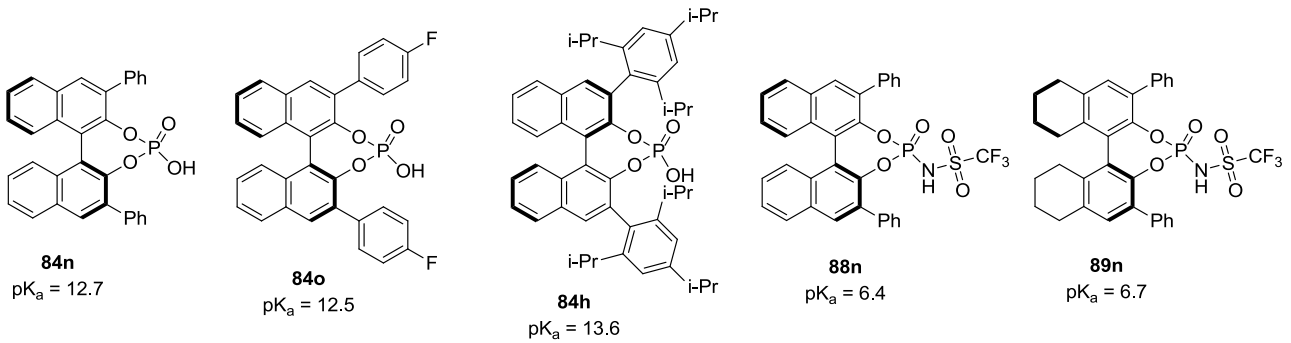


Figure 4.8: pK_a values of some chiral Brønsted acid catalysts in acetonitrile according to Rueping and Leito. Sharp contrast for triflimide acidity was observed compared to Berkessel and O'Donoghue work. Here triflimides resulted much more acidic.

[129] K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping, I. Leito, *Angew. Chem. Int. Ed.*, **2013**, *52*, 11569-11572.

For example if a phosphoric acid, like TRIP **84h** have a pK_a value of roughly 4 in DMSO, the corresponding triflimide **88h** should have a pK_a value of roughly -2 in that solvent, but Berkessel and O'Donoghue measured a value of 3.34. Rueping and Leito try to give a reason to this huge difference in pK_a. Summarizing, probably Berkessel and O'Donoghue did not choose the right method for this kind of analysis. When the acid becomes too strong, probably DMSO solvates the proton, which is not protonating the indicator used for the measurements, leading to an underestimated indicator-H concentration, and thus to a higher pK_a value. Moreover water, that Berkessel and O'Donoghue used in trace amounts, can change considerably the pK_a value as well. Dry acetonitrile hasn't got these problems, and thus leads to a better acidity scale. Anyway a detailed discussion is given in supporting information of Rueping and Leito's work.
In summary, probably Rueping and Leito's acidity scale is reliable for every pK_a value, while Berkessel and O'Donoghue only for acid of medium strength. It's worth noting that Li and Cheng based their computational method on the acidity of these medium-strength acids, and thus their predicted acidities may be correct. Anyway more detailed studies are probably needed and we will see if this discrepancy will become a controversy or not.
Concerning the catalytic activity of these compounds, Rueping and Leito observed a linear correlation between the acidities of the catalysts and the reaction rate of a Nazarov cyclization reaction, showing that the stronger is the acid, the faster is the reaction. Anyway no information is given about the reaction's enantiomeric excess.

Apart of the exact pK_a value of a catalyst, it might be interesting to know which are the involved species in a given reaction, such as intermediates. Moreover, the question if phosphoric acid catalyzed reactions are Brønsted acid catalyzed or more similar to an activation via hydrogen bonding is still open. For this reason in 2011 Rueping and Gschwind investigated the species formed when mixing diphenylphosphate and some imines via NMR[130] (*Fig*. 4.9). While at r.t. only one peak was observed, at 280 K this one split in three different peaks and at 240 K they found the optimum conditions to study the system. These three species were each one different from the free imine and the free acid. By means of proton-heteronuclear coupling experiments, firstly one of them was established to be the OH---N hydrogen bonding complex, than the other two were identified as the O^----HN^+ protonated imine and the solvolyzed HN^+ protonated imine alone. Thus all the three species exists in solution with a ratio of OH---N:O^----HN^+:HN^+ of 0.38/0.62/0.08. these values changed when a ketimine and an electron poor ketimine were employed. A ratio of OH---N:O^----HN^+:HN^+ of 0.42/0.58/0.18 was observed for the ketimine and OH---N:O^----HN^+:HN^+ of 0.51/0.49/0.11 was observed for the electron poor ketimine. This growing for the OH---N signal accounts for a lower basicity of the ketimines, in particular for the electron poor one, and a growing of H-bonding nature of the complex more than ionic nature. Also the chemical shifts of NH proton in NH complexes grew, meaning a farer proton from the nitrogen, and the chemical shifts of OH proton decreased, meaning of a nearer proton from the catalyst oxygen. Interestingly a strong temperature dependence was observed in those complexes distribution, until when it was possible: the OH---N character increase with temperature and, following the slopes for the line obtained at low temperature, it should be the major at r.t. for all the three complexes; for sure it's like that for the electron poor ketimine which shows a steep slope. Therefore, both hydrogen bonding complex and protonated imine exist in solution at 240 K, with a slight preference for the protonated imine. For the electron poor ketimine, at r.t. only the hydrogen bonding complex should exist and therefore it should be the reactive specie, while for the other two imines, also NH species should exist at r.t., and it's not possible

[130] M. Fleischmann, D. Drettwan, E. Sugiono, M. Rueping, R. M. Gschwind, *Angew. Chem. Int. Ed.*, **2011**, *50*, 6364-6369.

even to speculate which one is the reactive one. This experiments anyway showed that for chiral phosphoric acid a mechanism of clear imine protonation for their activation is at least not always true.

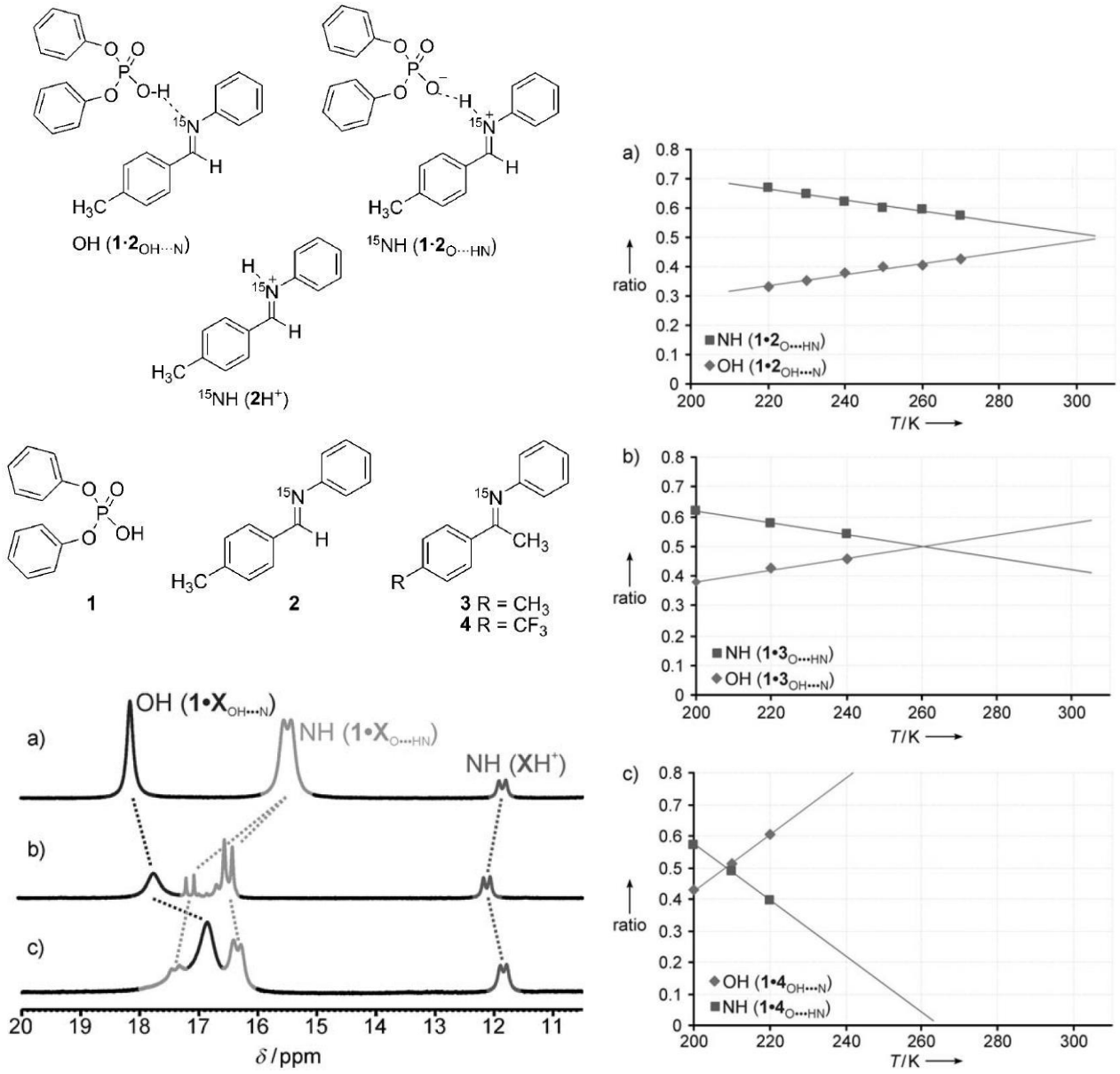


Figure 4.9: complexes found, Imines used, ^{1}H NMR spectra and temperature dependence in the study by Rueping and Gschwind.

Trying to predict the ee of a reaction somehow would be valuable in chiral Brønsted acids catalyzed transformations, since a screening of catalyst would be avoided. For this reason Simòn and Goodman developed an empirical model on this purpose, then supported by computational methods[131]. This model is generally working for the addition of nucleophiles to imines, when phosphoric acids acts like bifunctional catalysts. Considered bulkiness of the catalyst, the imine can offer the *re* or *si* face depending on steric hindrance of its groups, and this can be rationalized. Sometimes the imine is forced to have a Z configuration, which gives the opposite enantiomer respect to E configuration, and also in these cases prediction is possible. If to this we add the consideration that some

[131] L. Simon, J. M. Goodman, *J. Org. Chem*., **2011**, *76*, 1775–1788.

nucleophiles prefer always one side because they are big, mixing all these three factors appropriately, it's possible to predict the absolute configuration of the product of a given reaction (*Fig*. *4.10*).

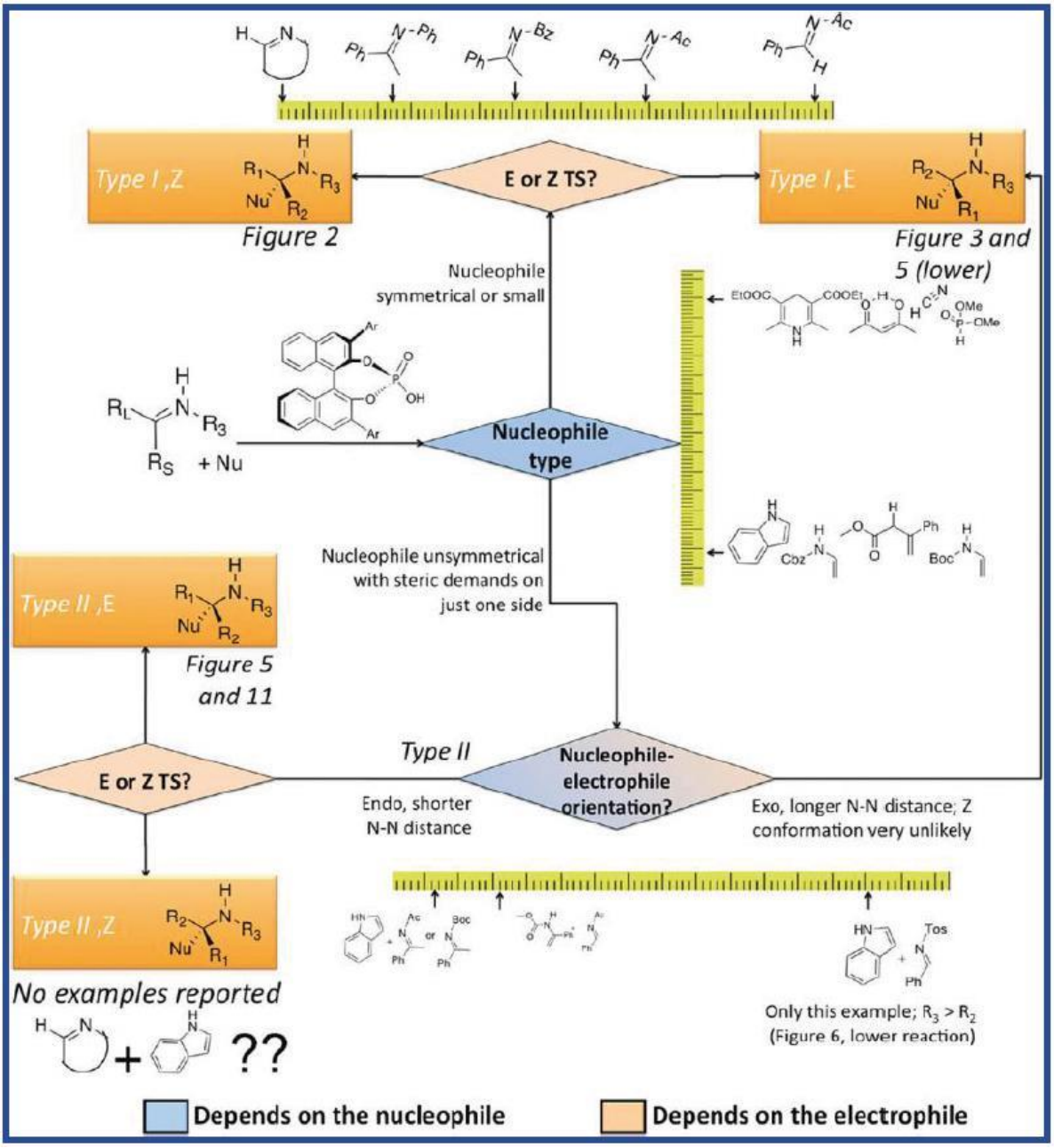


Figure 4.10. Synthesis of Simòn and Goodman work.

Another interesting way to predict a reaction outcome is the development of a model that can tell us which catalyst is the best for a given transformation. Akiyama and co-workers tried to do it for the atroposelective bromination of biaryls, via ^{1}H NMR studies[132] (Fig. **4.11**). They reasoned that in solution an adduct between the substrate and the catalyst might be formed, and so a difference in proton chemical shift might be observed, since they become diastereotopic. They speculated that the difference in chemical shift would have been proportional to the reaction ee, due to the strong affinity of the catalyst with the

[132] K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Sci.*, **2013**, *4*, 4235-4239.

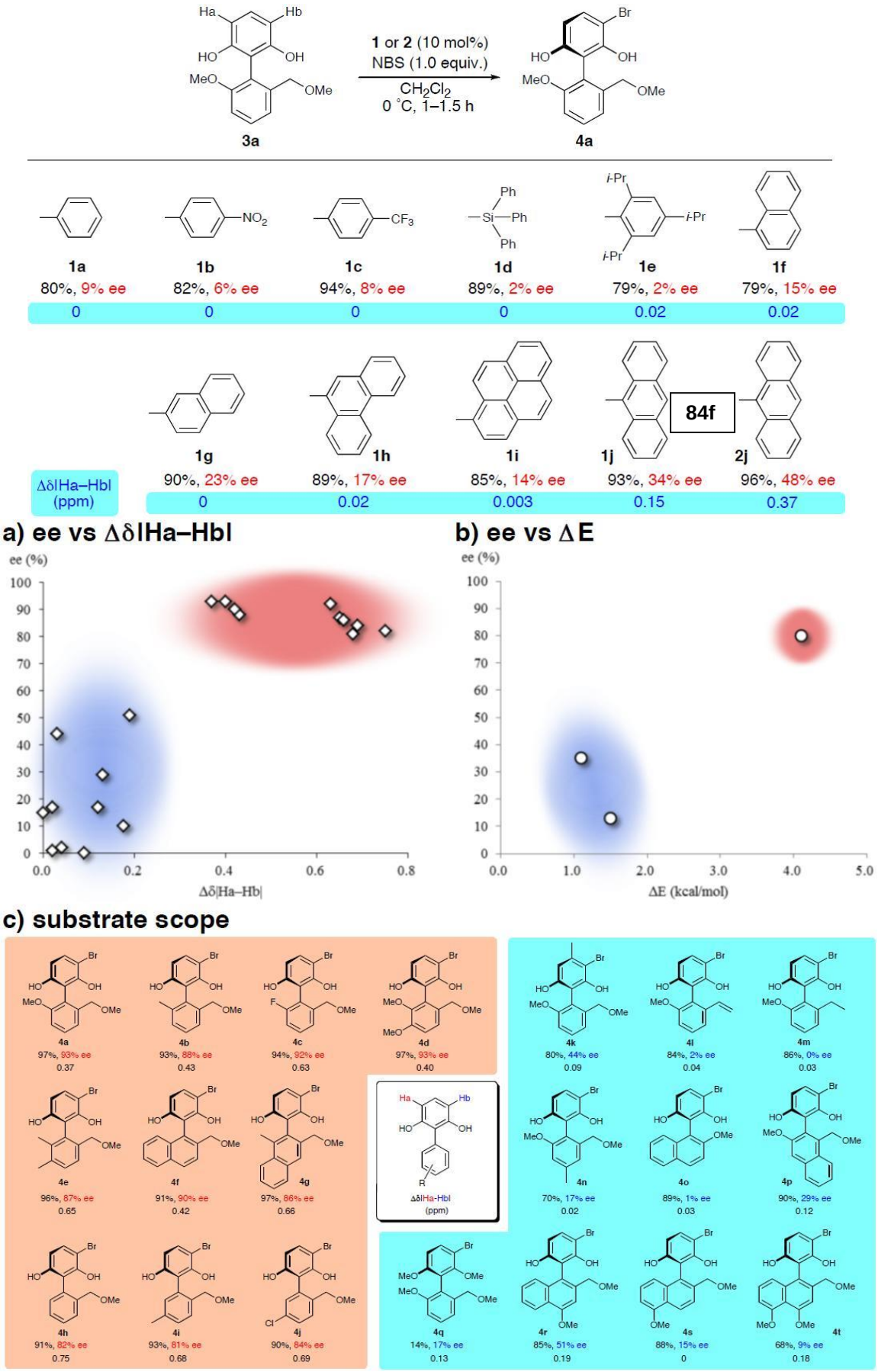
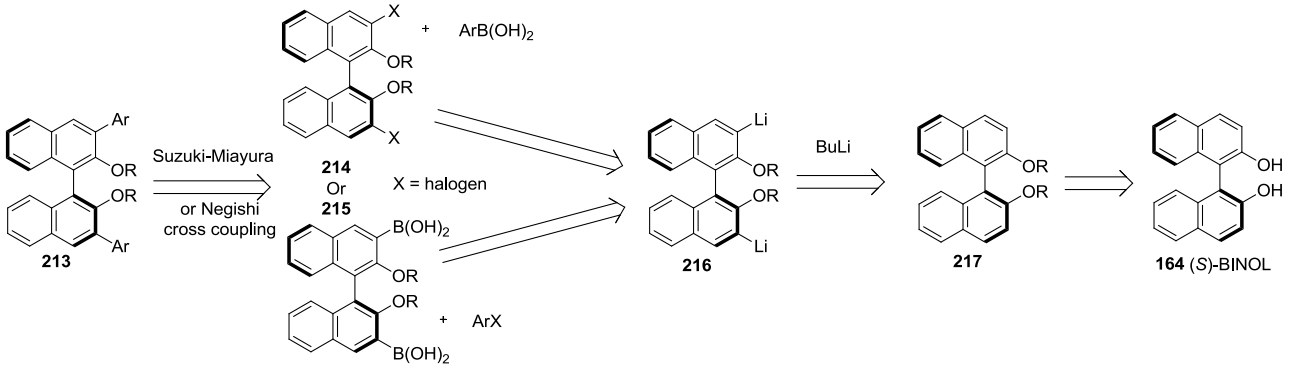


Figure 4.11: correlation between differences in chemical shifts of the diastereotopic protons and the enantiomeric excesses in Akiyama's work.

substrate, which would give rise to a tight complex and so a better splitting of diastereotopic protons. Recording ^{1}H NMR of the substrate with many catalysts resulted in many spectra where no or only negligible changes were observed, except **84f**, giving a separation of 0.15 ppm. Switching to the corresponding [H_8]BINOL derivative results in an enhancement of peak separation to 0.37 ppm. Actually, performing the real screening of the catalysts no one gave an ee better than 23%, except **84f** which gave 34% ee, and the corresponding [H_8]BINOL derivative which gave 48% ee (*Fig*. 4.11, above). Further optimization of reaction conditions allowed the achievement of an ee up to 93%. In the same way the authors exhamined the scope of the reaction: based on the difference of chemical shifts in the ^{1}H NMR of the catalyst with many substrates, they were able to predict which ones would have given good enantiomeric excesses and which ones would have given bad ones. It should be pointed out that the method is not quantitative. Catalysts that did not show peak separation gave (low) enantioselectivities anyway. In substrate scope is also clear that the relationship is not linear, but there are two areas in the graphic: the red one contains high ee substrates with high differences of chemical shifts in the diastereotopic proton, the blue one contains low ee substrates with low differences of chemical shifts in the proton (*Fig*. 33, below). Roughly, substrates with high ee have a difference in chemical shifts of more than 0.4 ppm, and substrates with low ee have a difference in chemical shifts of less than 0.2 ppm on the diastereotopic proton. This means that ^{1}H NMR spectroscopy could be a tool to have a clue on the right catalyst to use for a given transformation.

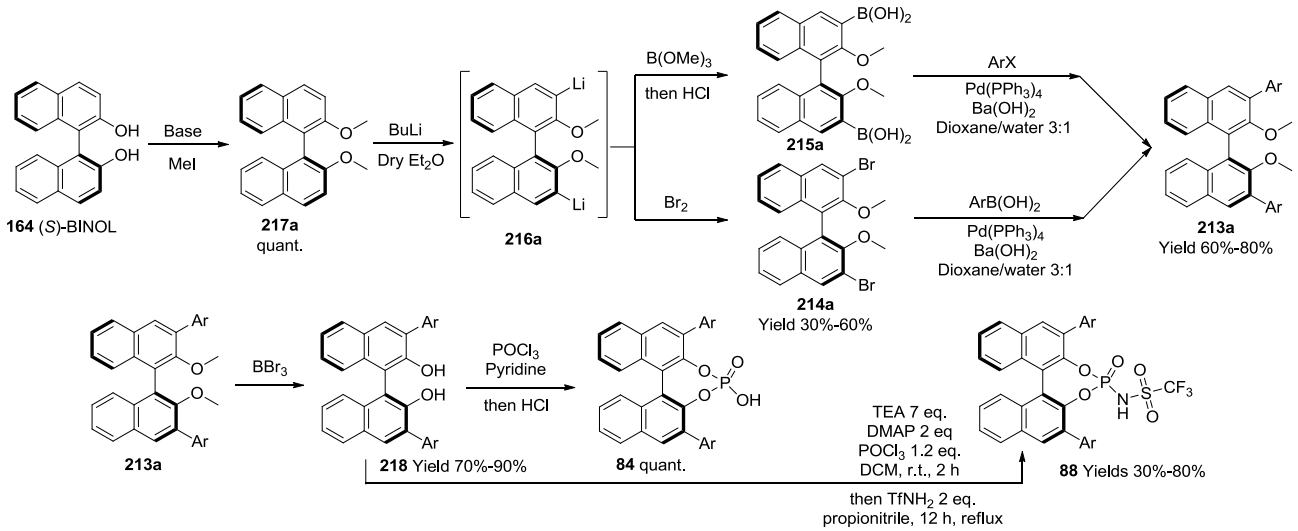
4.2.2 Catalysts synthesis

Here below in schemes **4.14**, **4.15** and **4.16** a brief description of chiral BINOL based phosphoric acids and chiral triflimides is presented, as they are the catalysts used in this study. The general approach is always the same, but during time reagents and conditions have been developed to obtain more effective synthesis. The key step is the introduction of the aryl moieties in 3 and 3' position of BINOL skeleton. This is obtained with a Suzuki-Miayura cross coupling, or with a Negishi cross coupling for the sterically demanding 2,4,6-triisopropyl substituent in the synthesis of TRIP. Therefore whether the 3,3' bis-halogenide **214** or bis-boronic acid BINOL derivative **215** must be synthesized from BINOL. The procedure for both these derivatizations involve the formation of the corresponding lithiate with BuLi and quenching with the appropriate reagent. For this reason, BINOL must be protected. This protecting group must be removed after the cross coupling step and at this point the corresponding phosphoric acid could be formed via phosphorylation.



Scheme **4.14**. Retrosynthetic pathway for the key intermediate 3,3' aryl derivative.

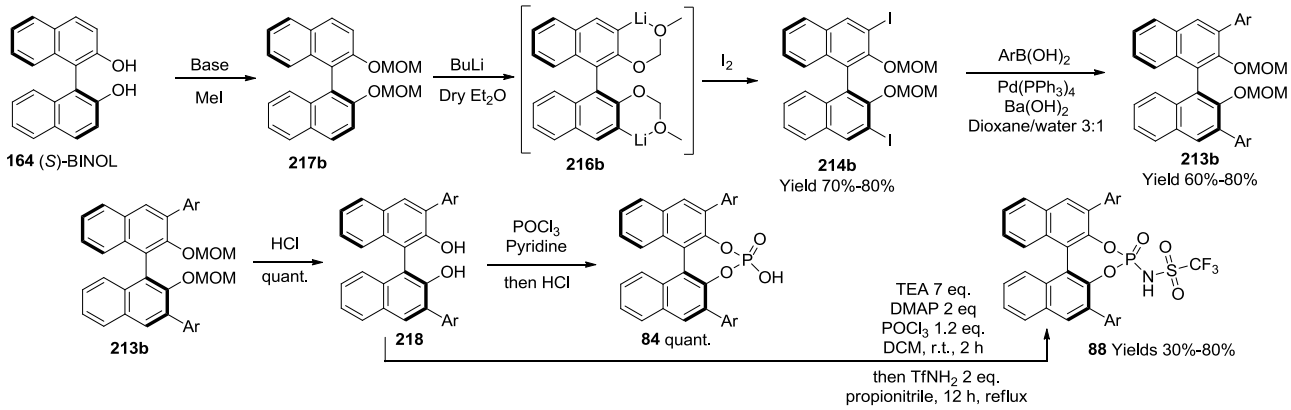
Triflimides are not synthesized from the phosphoric acids, but a one pot procedure is available starting from the corresponding diol.
Typically, in cross coupling procedures, the boronic acid is used in excess, so it's more convenient to synthesize the 3,3' bis-halogenide BINOL **214**, and use an aryl boronic acid for the coupling, avoiding BINOL waste. This is true for all the acid except TRIP, for which Suzuki coupling is not working, due to the steric hindrance. In this case, a Ni-catalyzed Negishi cross coupling using freshly prepared 2,4,6-triisopropylmagnesium bromide is performed. 3,3'-DibromoBINOL **214a** was used at the beginning as halogenide. By the way its synthesis is difficult, sometimes leading to no reaction or low yields, probably highly sensitive to the dryness grade of the solvent. It also has to be considered that the first synthetic routes towards 3,3'-DibromoBINOL employed simple methyl as a protecting group for phenolic OH (**217a**). Anyway the protecting group MOM is more effective (**217b**) because it can assist ortho-lithiation in the following step, chelating and thus stabilizing the lithiate, later quenched by the halogen. This could enhance the bromination efficiency, however it's possible to state that ortho iodination is more effective. A procedure is available in literature where the reported yield of **214b** is 93%. I personally carried out the reaction a few times, finding it reliable: a yield >70% was always obtained. The cross coupling step is generally carried out in the same conditions, and MOM deprotection is always quantitative, as its introduction. Conversely, sometimes methyl deprotection with BBr_3 is less effective: BBr_3 is a highly reactive compound and releases HBr. Thus, not only is hazardous to use, but also sometimes can destroy rubber made septa or tubes, allowing atmospheric water to enter and stopping the reaction before its completion.



Scheme **4.15**. First generation synthesis of chiral BINOL based phosphoric acids and triflimides.

Considered all this, MOM protection followed by iodination is generally recommended for the synthesis of these catalysts. The Suzuki cross coupling of course is not always quantitative, depending on groups, but yields are generally satisfying. The Negishi cross coupling for the synthesis of TRIP instead requires highly dry solvents and an effective formation of the Grignard reagent, which is not trivial. Due to the bulky groups the coupling itself is difficult, lowering the yields also to 30% sometimes. Anyway, the use of di-iodo derivative in place of di-bromo derivative enhanced chemical yields for the cross coupling step, due to the higher reactivity of aryl iodides in cross coupling reactions. The last phosphorylation step leading the phosphoric acid is generally quantitative. Not the same

can be told for the triflimide formation. The one pot procedure for its formation developed by Yamamoto in 2006 is still today the only one available in the literature. By the way for some substituents it doesn't work properly. For example the sterically demanding big aromatic groups anthracenyl and phenanthryl the yields are low.
Trifluoromethanesulfonamide is not a good nucleophile, and the steric hindrance is also a problem. Often, adventitious water hydrolyzes the in situ formed chloride to the corresponding acid (valuable product, but not the desired one!). Even if dry propionitrile (used as co-solvent to enhance the mixture's boiling point) is used, the yields are in some cases relatively low, and probably also dry triethylamine would be needed.



Scheme **4.16**. Second generation synthesis of chiral BINOL based phosphoric acids and triflimides. MOM protecting group provides stabilization to the lithiate, and thus diiododerivative is formed in high yields. Iodine is also more reactive than bromine in cross couplings, and then MOM is easier to remove respect to methyl, using less hazardous reagents.

A general consideration that must be made concerns purification. Generally, in all the steps, the main reaction byproduct is the mono-derivative of BINOL. This leads, especially in the iodination and Suzuki coupling steps, to mixtures of mono- and bis- BINOL derivatives that must be separated. Generally, these compounds possess very narrow differences in r.f. an chromatography columns become long and tedious. Anyway, separation must be achieved, because the mono- derivatives are reactive in the further steps, and lead to the formation of an always increasing number of undesired products. If working on a big scale, purification of 3,3'-Bisaryl diols and acids by crystallization is recommended, because yellow/brownish unidentified impurities are always obtained, even after chromatography. Finally, as we saw previously with egregious examples, washing the catalysts with HCl after purification via chromatography is required to be sure to have in hand the metal free phosphoric acid/triflimide and not the corresponding calcium/magnesium salt.
The synthesis of [H_8]-BINOL derivatives involves partial hydrogenation of BINOL as the first step, but then is easier, protective group free and generally more high yielding, respect to the one for BINOL derivatives. This synthesis is well described in ref. 119. Detailed references for the syntheses are Ref. 112-126 and in the following experimental sections (ref. 192).

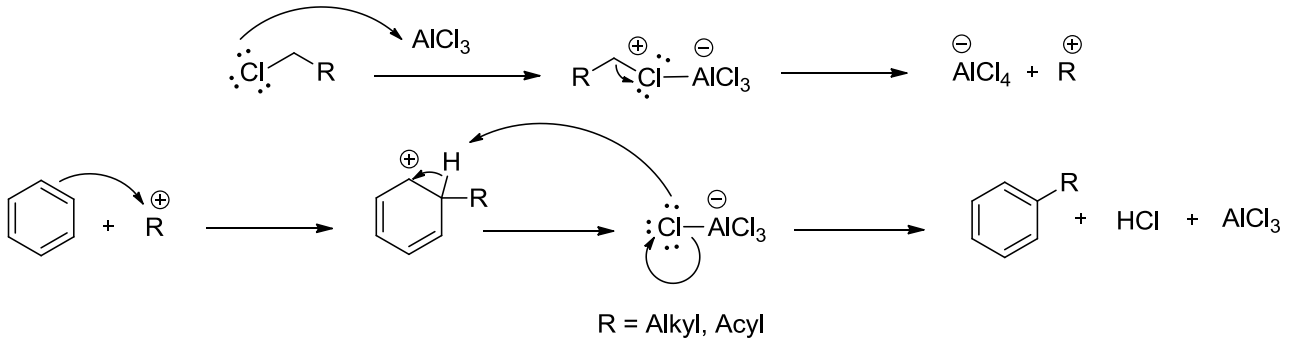
Section 2

The projects and their aims

5) The enantioselective Friedel-Crafts alkylation/acetalization cascade of naphthols with α,β-unsaturated cyclic ketones[133]

5.1) historical background and organocatalysis

The Friedel-Crafts alkylation is one of the so-called electrophilic aromatic substitutions, often associated to the Friedel-Crafts acylation. It was discovered by Charles Friedel and James Mason Crafts in 1877 with three consecutive reports[134], still in the times when the structure of Benzene and related compounds was recently proposed and the reasons of their scarce reactivity was still unclear[135]. Using powerful Lewis acids as promoters, Friedel and Crafts succeeded in the introduction of alkyl chains and acyl groups on an aromatic ring, where up to those times only heteroatoms had been introduced (Scheme **5.1**).

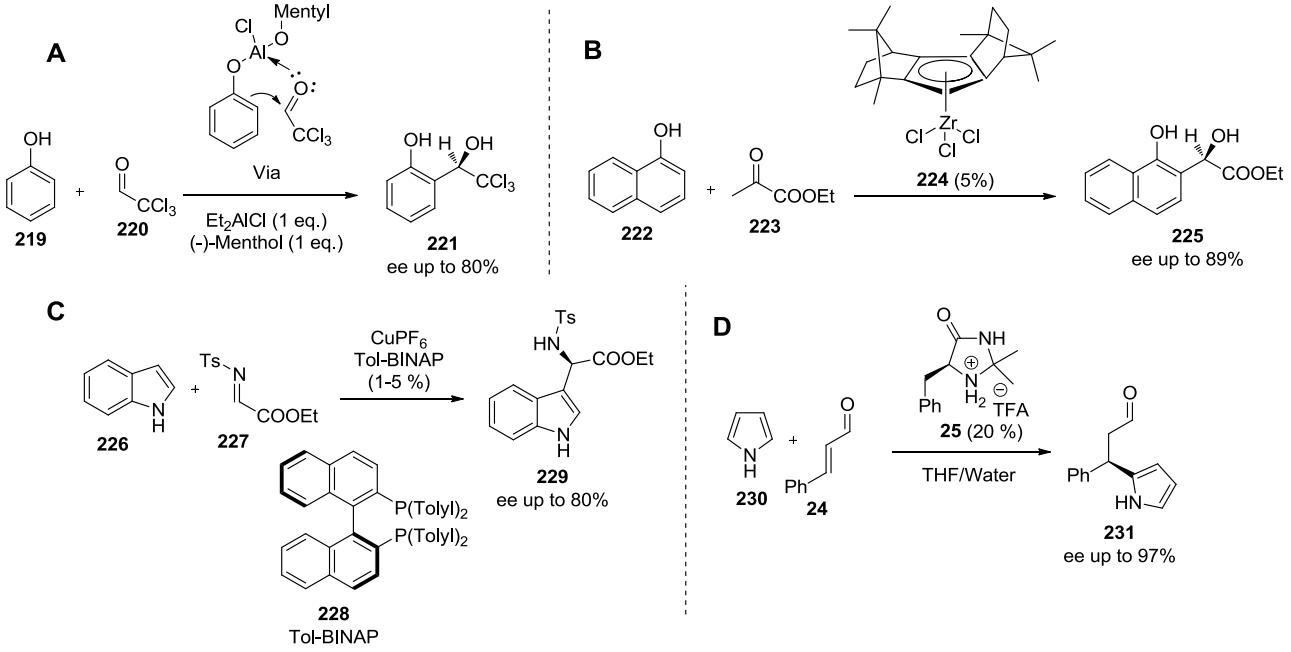


Scheme 5.1: general Friedel-Crafts alkylation reaction.

Since that time the Friedel-Crafts alkylation grew and became one of the most used, powerful and convenient strategies for the synthesis of aromatic compounds, and now is largely described in every organic chemistry's textbook. Nowadays aromatic compounds represent about one third of the chemical production[136], and since they are so ubiquitous, some of them need also, for some reasons, to be obtained in enantiomerically enriched form. Logically one of the most powerful methods to achieve this goal is the enantioselective synthesis, and of course the enantioselective Friedel-Crafts alkylation is one of the most attractive ways to do it, because of the direct introduction of an aromatic moiety on another one, thus creating a new C-C bond.
Despite the long history of the reaction, its first asymmetric variant appeared only in 1985, when an Italian research group reported an enantioselective alkylation of phenols with chloral using a chiral Al-based reagent[137] (Scheme **5.2**, **A**). The first catalytic example,

[133] Enrico Paradisi, Paolo Righi, Andrea Mazzanti, Silvia Ranieri, Giorgio Bencivenni, *Chem. Commun.*, **2012,** 48**,** 11178-11180. Cover: *Chem. Commun.*, **2012,** *48***,** 11153-11153. Highlighted in: *ChemInform***, 2013,** *44***,** March 19. *Synfacts*, **2012**; *8*, 1259.
[134] (a) Friedel, C. and Crafts, J.-M. Comptes Rendus de l'Academie des Sciences Paris, **1877**, *84*, 1450–1454; (b) Friedel, C. and Crafts, J.-M. Comptes Rendus de l'Academie des Sciences Paris, **1877**, *84*, 1392–1395; (c) Friedel, C. and Crafts, J.-M. Comptes Rendus de l'Academie des Sciences Paris, **1877**, *85*, 74–77.
[135] Kekulé, F. A. *Bulletin de la Société Chimique de Paris*, **1865**, *3*, 98–110.
[136] Taylor, R. (1990) Electrophilic Aromatic Substitution, Wiley, Chichester.
[137] Bigi, F., Casiraghi, G., Casnati, G., Sartori, G., Gasparri Fava, G. and Ferrari Belicchi, M. *J. Org. Chem.* **1985**, *50*, 5018–5022.

which used a Zr-based catalyst with a camphor-derived ligand appeared in 1990[138] (Scheme **5.2**, **B**). Anyway, the reports on enantioselective Friedel-Crafts alkylation remained sporadic until 1999, when copper-based catalysts appeared[139] (Scheme **5.2**, **C**), and then in 2001 the first organocatalytic enantioselective Friedel-Crafts alkylation was reported by MacMillan[140] (Scheme **5.2**, **D**). Enals were used as electrophiles and activated via iminium ion towards the attack of pyrrole, an electron rich arene.

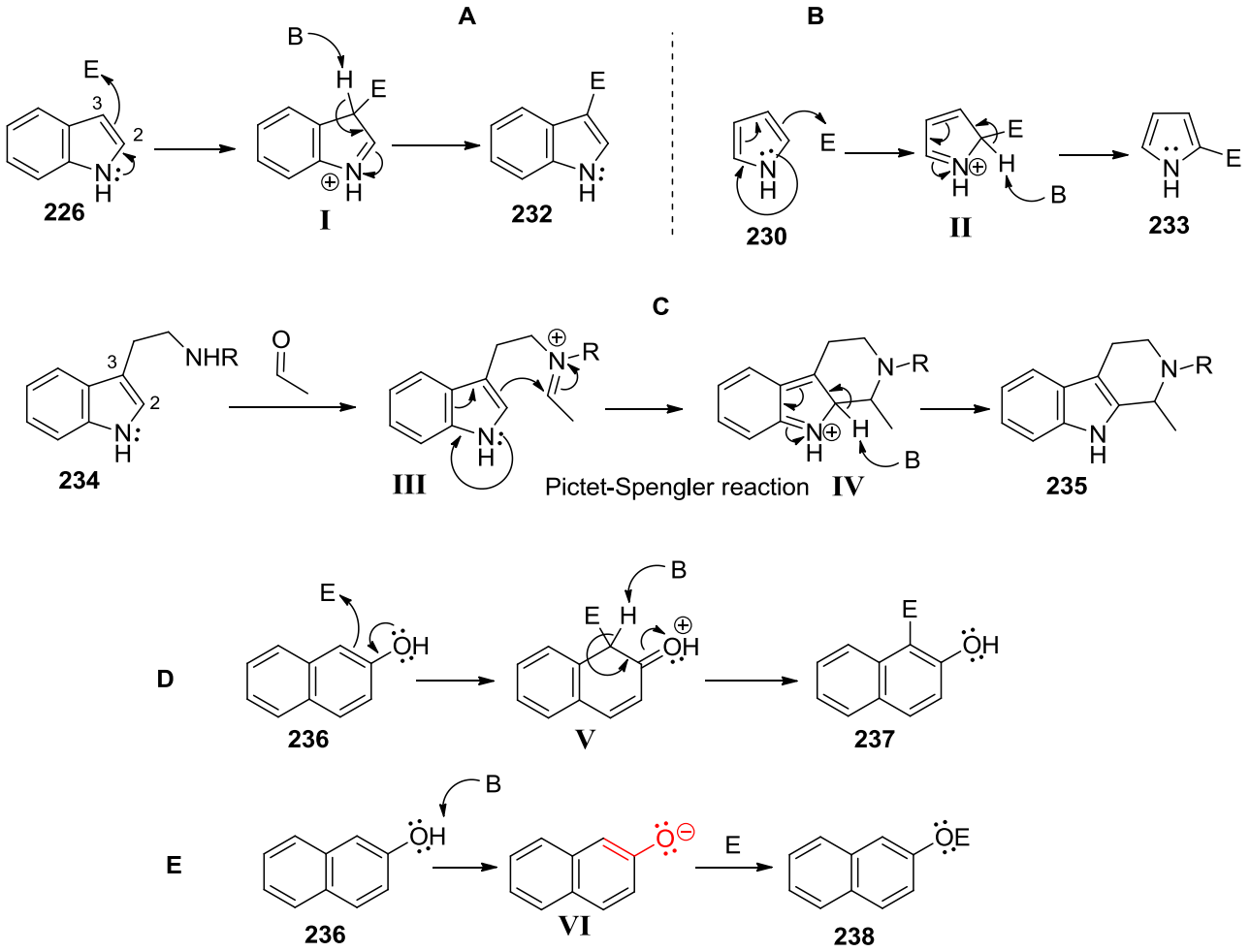


Scheme **5.2**. **A**: The first enantioselective Friedel-Crafts alkylation in which was used a stoichiometric amount of a chiral aluminium complex as reactant (1985). **B**: The first catalytic enantioselective Friedel-Crafts alkylation using a Zr-complex (1990). **C**: The first enantioselective Friedel-Crafts alkylation on indoles using a chiral Copper complex as catalyst. Cu-based catalysts became quite popular for the enantioselective Friedel-Crafts alkylations after this publication (1999). **D**: The first organocatalytic enantioselective Friedel-Crafts alkylation which prompted the use of organocatalysts in this transformation (2001).

Since then, numerous reactions were reported to be enantioselective, either employing metals or organocatalysts[141,142]. Regarding organocatalytic enantioselective Friedel-Crafts alkylations some kind of aromatic rings were reacted with several electrophiles, many methods and kind of catalysts were employed[143]. Generally, heteroaromatic or anyway electron rich arenes were employed, because simple benzenes are too much inert to react at the relatively low temperatures required for enantioselective reactions. So, for example, highly reactive indoles are the mostly used compounds for enantioselective Friedel-Crafts alkylations, followed by pyrroles and naphthols. Phenols and anilines are also quite

[138] Erker, G.; van der Zeijden, A. A. H. *Angew. Chem. Int. Ed.* **1990**, *29*, 512.
[139] Johannsen, M. *Chem. Commun.*, **1999**, 2233–2234.
[140] Paras, N. A., MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001,** *123,* 4370-4371.
[141] Poulsen, T.B. and Jørgensen, K.A. *Chem. Rev*, **2008**, *108*, 2903–2915.
[142] (a) *Catalytic Asymmetric Friedel-Crafts Alkylations*, ed. M. Bandini and A. Umani Ronchi, Wiley-VCH, Weinheim, 2009. (b) Poulsen, T.B. and Jørgensen, K.A. *Chem. Rev*, **2008**, *108*, 2903–2915.
[143] For some recent reviews see: (a) Terrasson, V., de Figueiredo, R. M., Campagne, J. M. *Eur. J.Org. Chem.* **2010**, 2635; (b) You, S.-L., Cai, Q., Zeng, M. *Chem. Soc. Rev.,* **2009**, *38*, 2190. (c) Zeng, M., You, S.-L., *Synlett*, **2010**, *9*, 1289–1301. (d) Bartoli, G., Bencivenni, G., Dalpozzo, R., *Chem. Soc. Rev.,* **2010**, *39*, 4449–4465. (e) P. Chauhan, S. S. Chimni, *RSC Adv.*, **2012**, *2*, 6117–6134.

common nucleophiles, while other kind of aromatic rings are almost lacking[134a]. Basically all the organocatalytic enantioselective Friedel-Crafts reactions rely on the activation of the electrophilic partner, since the direct activation of an aromatic ring is difficult. Coordination of the non-aromatic protons possessed by phenols, naphthols and heteroaromatics, like indoles and pyrroles, is often crucial for the good outcome of the reaction, and anyway the intrinsic nucleophilicity of the arenes is always important. For instance indoles are largely employed because their high nucleophilicity. In fact the delocalization of the lone pair on nitrogen renders the 3 position highly nucleophilic (Scheme **5.3**, **A**). Moreover, this breaks only partly its aromaticity as the other ring is unaffected by this movement of electron. Anyway, if 3 position is blocked, the indole can still react in 2 position, as it happens for example in Pictet-Spengler reactions (Scheme **5.3**, **C**). Aromaticity is broken but then restored with a deprotonation. The same happens when pyrroles are reacted, anyway they are quite nucleophilic (Scheme **5.3**, **B**). Naphthols are also electron-rich, since here the delocalization of OH electron occurs (Scheme **5.3**, **D**). We can fully understand their reactivity with an enolate like mechanism, but is should be pointed out that, since they are aromatic and aromaticity must be broken during the reaction, clean deprotonation of naphthols typically results in their O-alkylation (Scheme **5.3**, **E**). Other electron rich arenes are anilines, phenols and some kind of furans.



Scheme **5.3**: reactivity of electron rich arenes. **A**: high reactivity of indoles in position 3 through delocalization of nitrogen lone pair. **B**: the same reactivity on pyrroles, there aromaticity is completely broken. **C**: the Pictet-Spengler reaction, an example of indole nucleophilicity in 2 due to the 3 position blocked. **D**: F-C reaction of naphthols with involvement of oxygen lone pair. **E**: as opposite for enolate chemistry (the supposed enolate is in red), a base, makes more nucleophilic the oxygen than the carbon in naphthols.

A large number of examples of enantioselective organocatalytic FC-alkylations have been carried out with indoles. Two reviews were published on the topic[144] and later many other examples were out. Alkylation of carbonyl compounds is difficult because they tend to undergo a second reaction, giving rise to achiral products (a remarkable overcoming of this problem is the design of atropoisomeric products made by Rueping and co-workers[145]). Anyway one of the first enantioselective organocatalytic FC-alkylations catalyzed by simple cinchona alkaloids is on these substrates[146]. The alkylation of imines is easier: it can be performed in many ways, but has become during the years a kind of test reaction for the evaluation of new phosphoric acid catalysts (around 15 papers were published on the topic[147]). These catalysts, together with thioureas were largely employed also for nitroalkene activation[148]. For the activation of enals, instead, secondary amines were used, employing MacMillan[149] or secondary amines organocatalysts[150]. These are valuable catalysts for the activation of enals, and many kind of electron-rich arenes other than indoles were reacted with enals using them, but not naphthols[151]. Moreover, these

[144] Ref. 143d and: M. Zeng, S. L. You, *Synlett.*, **2010**, *9*, 1289-1301.

[145] M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed.*, **2008**, *47*, 593 –596.

[146] a) Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem. Int. Ed.,* **2005**, *44*, 3086. b) H. Li, Y.-Q. Wang, L. Deng, *Org. Lett.,* **2006**, *8*, 4063.

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[149] a) J. F. Austin, D.W.C. MacMillan, *J. Am. Chem. Soc.*, **2002**, *124*, 1172–1173. b) C.-F. Li, H. Liu, J. Liao, Y.-J. Cao, X.-P. Liu, W.-J. Xiao, *Org. Lett.*, **2007**, *9*, 1847–1850. c) Y.-C. Guo, D.-P. Li, Y.-L. Li, H.-M. Wang, W.-J. Xiao, *Chirality*, **2009**, *21*, 777–785. d) H. D. King, Z. Meng, D. Denhart, R. Mattson, R. Kimura, D. Wu, Q. Gao, J. E. Macor, *Org. Lett.*, **2005**, *7*, 3437–3440. e) Y. R. Chi, S. T. Scroggins, J.M.J. Frechet, *J. Am. Chem. Soc.*, **2008**, *130*, 6322–6323. f) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2005**, *127*, 15051-15053. g) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5482–5487. j) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2009**, *131*, 13606–13607.

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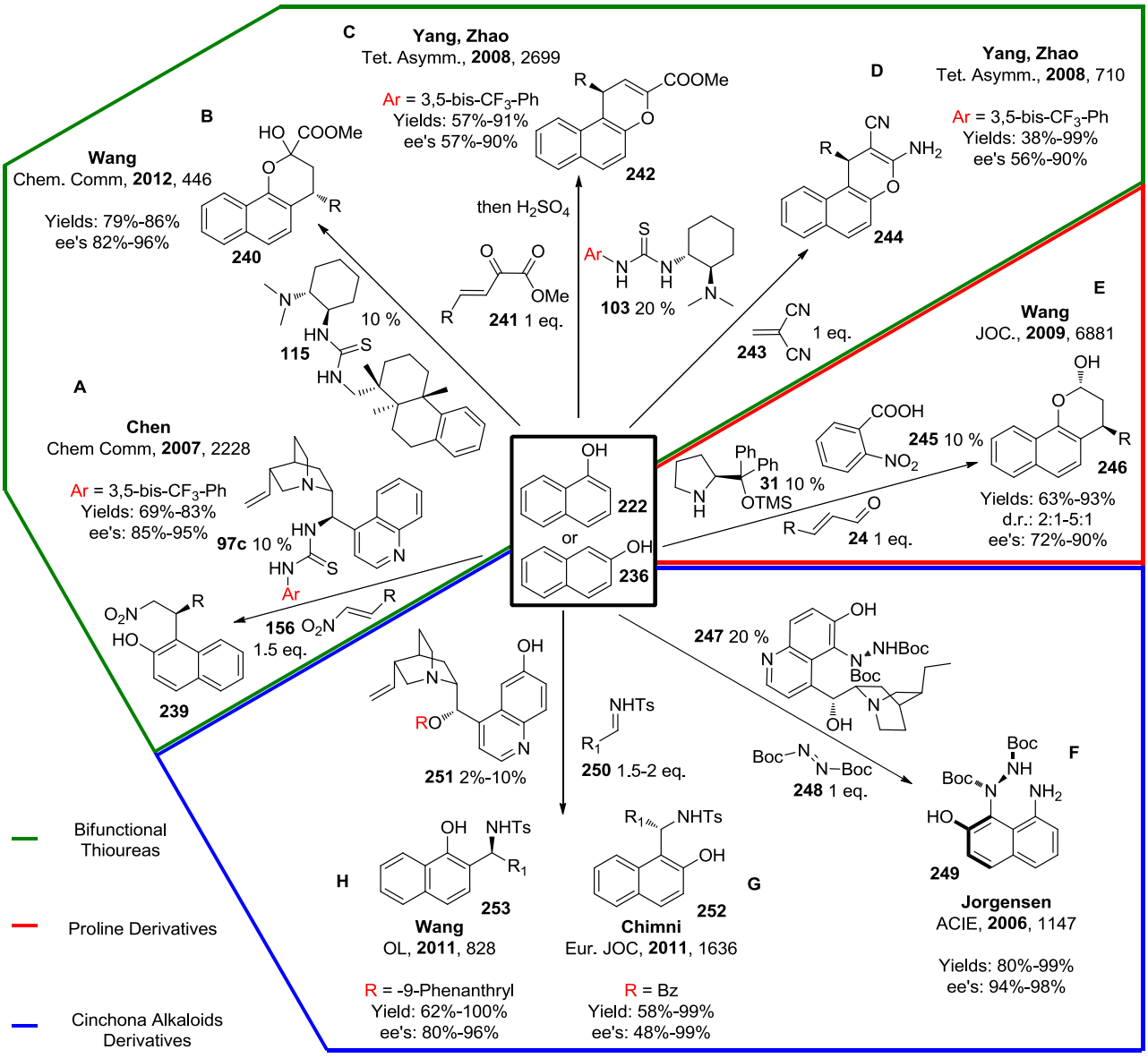
catalysts are not able to activate enones, for which, as we saw, primary amines are required. In this context, while the field is growing rapidly, only the two examples by Melchiorre and Chen seen in section **3.3.2** concern about a Friedel-Crafts reaction, and both are using indoles as nucleophiles. Less electron rich arenes have never been employed.

5.1.1) Naphthols in organocatalytic Friedel-Crafts reactions



Scheme **5.4**: overview of all organocatalytic FC reactions on naphthols until 2011.

C.-F. Li, H. Liu, J. Liao, Y.-J. Cao, X.-P. Liu, W.-J. Xiao, *Org. Lett.*, **2007**, *9*, 1847. k) Y.-C. Guo, D. -P. Li, Y.-L. Li, H.-M. Wang, W.-J. Xiao, *Chirality*, **2009**, *21*, 777. Other arenes and cascade reactions: l) S. P. Brown, Doctoral Dissertation, California Institute of Technology Pasadena, CA, 2005. m) S. Lee, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2007**, *129*, 15438. n) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2005**, *127*, 15051.

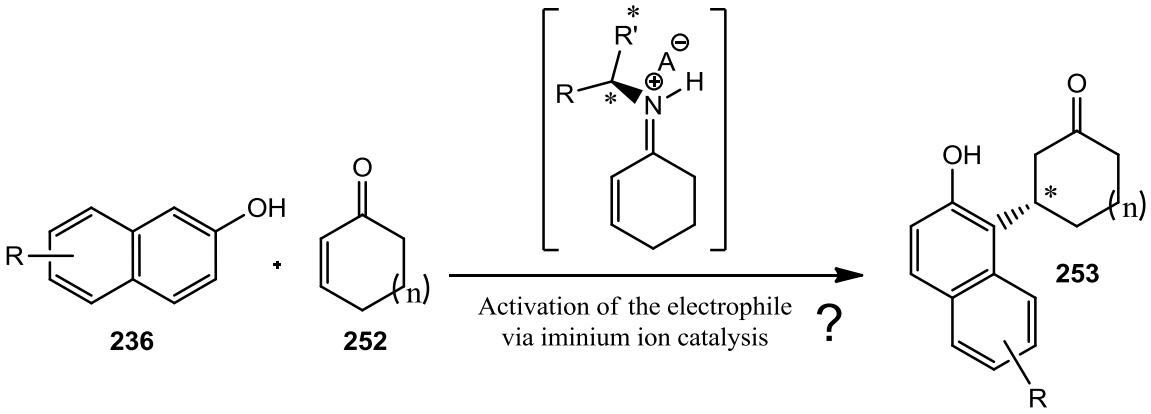
Despite, as we saw, the first organocatalytic enantioselective FC-alkylation was reported in 2001, naphthols appeared as nucleophiles only in 2006, in a paper that until now remains the only example of organocatalytic enantioselective FC-amination of naphthols (scheme **5.4**, **F**)[152]. This reaction is also a rare example of organocatalytic enantioselective formation of non-biaryl atropoisomers. In fact, amination of β-naphthol with azodicarboxylates results in the sterically hindered compounds **249**, with hampered rotation about C-N bond. Whilst the reaction product in this case have rotamers, that can interconvert at r.t., 8-substituted β-naphthols give rise to real atropoisomers stable at r.t.. 8-amino-β-naphthol was chosen as substrate, and during the catalyst screening, in which mainly cinchona alkaloid were employed, Jorgensen and co-workers realized that the catalyst itself was aminated in the reaction conditions. So they decided to synthesize some modified cinchona alkaloids on purpose, to test them in the reaction. They were pleased to find that one of them, **247**, catalysed the reaction efficiently, giving rise to highly eanantioenriched products, and it was the best catalyst for this transformation.
The first organocatalytic enantioselective FC-alkylation of naphthols was reported in 2007 by Chen, using the cinchona alkaloid based thiourea **97c** (scheme **5.4**, **A**)[153]. The reaction involves β-naphthols and nitroalkenes that, as we saw, are readily and efficiently activated by thioureas. Results are generally good.
In 2008 Yang and Zhao published two papers on the enantioselective FC-alkylation of β-naphthols and cyclization cascade. The first was on α,α-dicyanoolefines **243** as electrophiles to obtain the corresponding aminated naphthopyrans **244** (scheme **5.4**, **D**)[154], in the second they used β,γ-unsaturated α-ketoesters **241** as electrophiles to obtain substituted naphthopyrans **242** after an acid-catalyzed dehydration (scheme **5.4**, **C**)[155]. Despite in both papers sometimes good enantioselectivities could be obtained, in many cases they were moderate.
Enals were firstly employed as electrophiles in 2009 in a paper by Wang and co-workers (scheme **5.4**, **E**)[156]. This is the first and, up to 2011, only one example of iminium ion catalyzed enantioselective FC-alkylation on α-naphthols. The Hayashi-Jorgensen catalyst **31** was used in combination with *o*-nitrobenzoic acid which gave the best reactivity and enantioselectivity. The alkylation products underwent subsequent ring closure to give the corresponding cyclic hemiacetal **246** without further operations. Generally, moderate diastereoselectivity and good enantioselectivities are obtained.
In 2012 two organocatalytic enantioselective FC-alkylation of naphthols with imines were out almost at the same time. In both cases cupreidine-derivatives **251** were used as catalysts, with the only difference in the protective group used for C9-OH group. In the paper by Wang and co-workers (scheme **5.4**, **H**)[157] mainly α-naphthols were used, while in Chimni (scheme **5.4**, **G**)[158] paper mainly β-naphthols were used. Generally, good enantioselectivities were obtained.
In 2012 Wang and co-workers report the highly enantioselective FC-alkylation of α-naphthols with β,γ-unsaturated α-ketoesters using the bifunctional thiourea organocatalyst **115** derived from Rosin, developed in their laboratories (scheme **5.4**, **G**)[159]. Yields and ee's were generally good to very good and anyway better that the one obtained by Yang

[152] S. Brandes, M. Bella, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1147–1151.
[153] T.-Y Liu, H.-L. Cui, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Chem. Commun.*, **2007**, 2228–2230.
[154] X.-S. Wang, G.-S. Yang, G. Zhao, *Tet. Asymm.*, **2008**, *19*, 709–714.
[155] X.-S. Wang, C.-W Zheng, S.-L. Zhao, Z. Chai, G. Zhao, G.-S. Yang, *Tet. Asymm.*, **2008**, *19*, 2699–2704.
[156] L. Hong, L. Wang, W. Sun, K. Wong, R. Wang, *J. Org. Chem.*, **2009**, *74*, 6881–6884.
[157] G. Liu, S. Zhang, H. Li, T. Zhang, W. Wang, *Org. Lett.*, **2011**, *13*, 828-831.
[158] P. Chauhan, S. S. Chimni, *Eur. J. Org. Chem.,* **2011**, 1636–1640.
[159] X. Jiang, L. Wu, Y. Xing, L. Wang, S. Wang, Z. Chen, R. Wang, *Chem. Commun.,* **2012**, *48*, 446–448.

and Zhao in their similar paper. While Yang and Zhao reported only example involving β-naphthols, Wang focuses mainly on α-naphthols, with some examples on β-naphthols. Moreover in his paper hemiketal products **240** are not dehydrated. Enantioselectivities are generally very good.
Yang and Zhao and Wang papers are the only ones on organocatalytic enantioselective FC-alkylation of naphthols with ketones, but the highly electrophilic β,γ-unsaturated α-ketoesters can be activated by thioureas via anion binding. The same can't happen if simple ketones are employed: iminium ion activation is required. The only iminium ion catalyzed enantioselective FC-alkylation of naphthols up to 2011 was the one carried out by Wang on enals[156].

5.2) project discussion

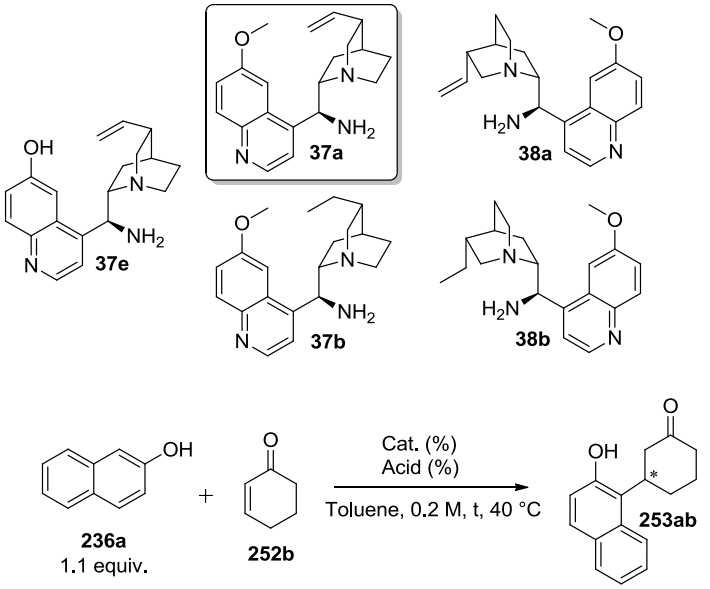
With all this background in mind, we wondered whether it was possible to perform an enantioselective F-C alkylation on naphthols using simple enones as Michael acceptors. The inspiration are the works of 2007 by Chen and Melchiorre seen in section **3.3.2**[88b,88c], who used cinchona alkaloid, derived primary amines for the enantioselective F-C of indoles with enones. Our aim was to perform the same reaction with the same activation mode, but using the more challenging naphthols as nucleophiles. We decided to start with b-naphthols because noteworthy they are more reactive than a-naphthols. Moreover, cyclic enones were selected as suitable electrophiles, because usually their conformational rigidity allows a better control of enantioselectivity (scheme **5.5**).



Scheme **5.5**: working hypothesis for the enantioselective F-C alkylation of cyclic enones with naphthols.

So, we started the catalyst screening trying some cinchona alkaloid primary amines in combination with TFA at 40°C using toluene as solvent, since this combination usually gives reactivity in iminium ion catalysis. Since, as we told, a ratio 1:2 amine/acid is often used in these reactions, we started using a combination of 20% of amine and 40% of acid. All the catalysts tried showed reactivity and interestingly almost the same enantioselectivity (*Tab. 5.1*, entries **4-8**). Cupreidine derivative **37e**, however, gave poor yields (*Tab. 5.1*, entry **4**), while on the other hand quinine derived primary amine **37a** showed good reactivity and a slight better enantioselectivity among the others (Tab *5.1*, entry **5**). For this reason, this catalyst was selected for further screening of amine/acid

ratio. Decreasing amine/acid ratio to 1:1 dramatically decreased reactivity and selectivity (Tab *5.1*, entry **9**). Increasing amine/acid ratio to 1:3 instead improved reactivity, but selectivity was worse (Tab *5.1*, entry **10**). In control experiments the reaction was shown not to take place using only the amine or only the acid, as well as background reaction was absent (Tab *5.1*, entries **1-3**). This confirmed that both the amine and the acid are necessary for the reaction to occur.



Entry	Cat. (20%)	Acid (40%)	t (d)	Yield %	ee %
1	-	-	2	0	-
2	**38a**	-	2	-	-
3	-	TFA	2	0	-
4	**37e**	TFA	2	12.5	45
5	***37a***	***TFA***	***4***	***87***	***49***
6	**37b**	TFA	4	89	45
7	**38a**	TFA	4	42	-45
8	**38b**	TFA	2	60	-45
9	**38b**	TFA (20%)	2	28	-15
10	**38a**	TFA (60%)	4	96	-33

Table 5.1: evaluation of catalyst combination for the enantioselective iminium ion catalyzed F-C alkylation of naphthols with enones.

During this screening, only ^{1}H NMR on the products were performed. Since the reaction showed to be promising, we decided to carry out further analyses to fully characterize the product. Surprisingly, when a ^{13}C NMR analysis was performed on the product, no carbonyl carbons were detected (*Fig. 5.1*, red circle). This was intriguing because the ^{1}H NMR was reasonable for the desired product, and also MS gave the right value for MW. We also noticed in the ^{13}C NMR a peak around 100 ppm, which in the product shouldn't be there, but it's a characteristic value for the acetals (*Fig. 5.1*, light blue circle). In this way we realized to have in our hands, not the desired product, but the corresponding bicyclic hemi-acetal (*Fig. 1*, above). This implies two consequences, clear if we draw the product with the cyclohexane in perspective, like in *Figure* 1: first, the naphthol is forced to be axial with respect to the cyclohexane ring. The formation of a cyclic product with two

substituents in equatorial would be impossible. This is remarkable because usually substituents on a cyclohexane are more stable if in the equatorial position. Second, a single diastereoisomer is always formed, since if the naphthol attacks on one side, the ring closure can occur only by one side of the carbonyl, and also in this case the closure on the other side would be geometrically impossible. With these information in mind, we realize to have in our hands a highly valuable transformation, and we went on with the screening also more interested and intrigued.

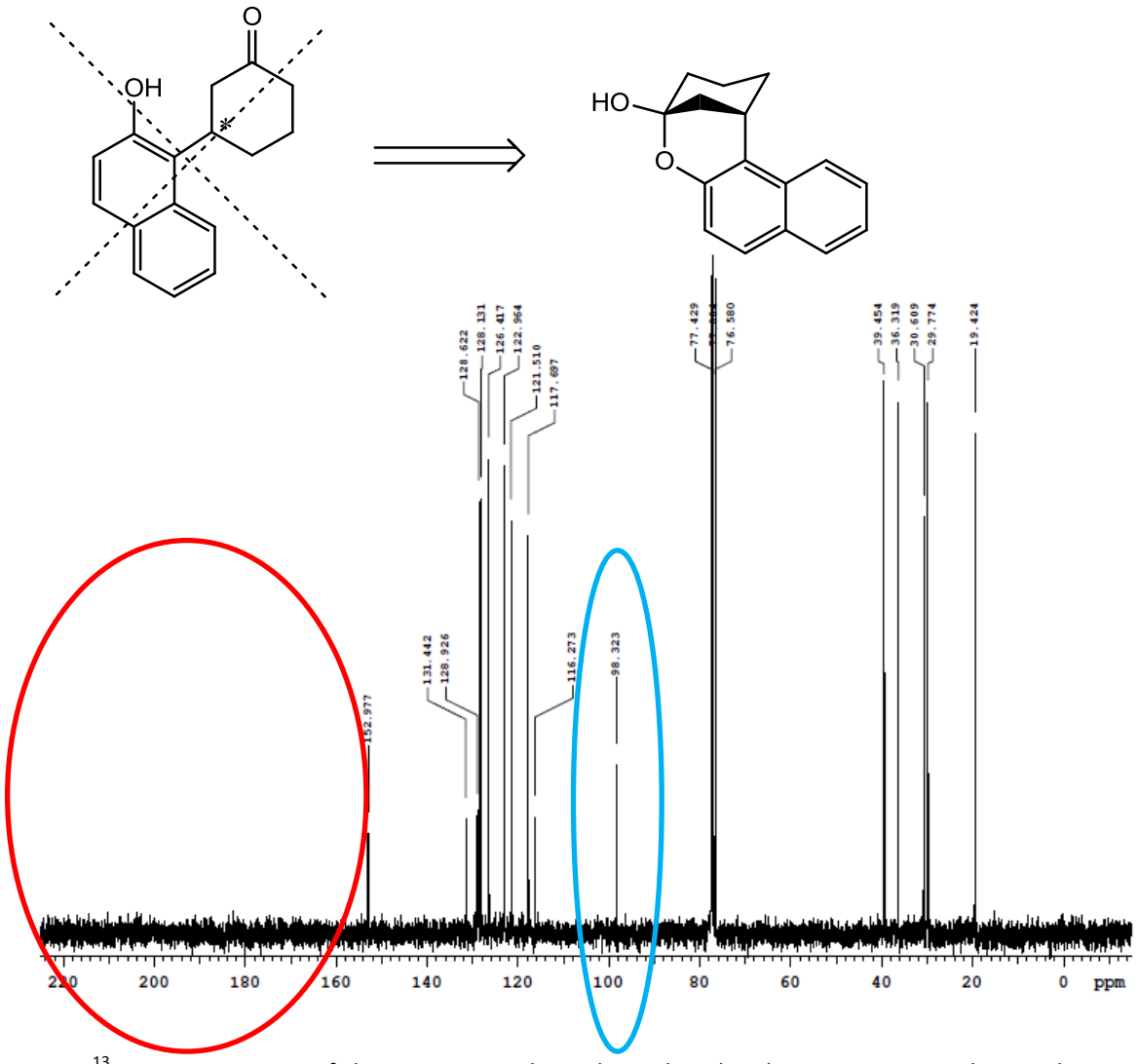
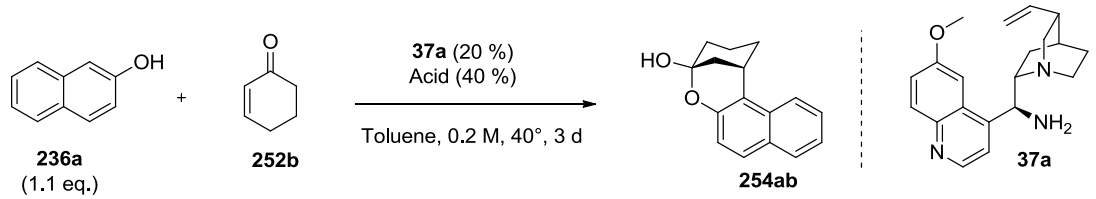
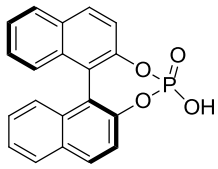


Figure. 5.1: ^{13}C NMR sperctrum of the reaction product. The carbonyl carbon is missing, and instead is present an acetalic carbon. This, combined with all the other data in our hand, led us to understand we had the bicyclic hemi-acetal. This product is particular: the naphthol is forced to be axial and only one diastereoisomer can exist.

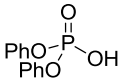
We performed next the acid screening. As you can see in *Tab. 5.2*, strong acids like p-TsOH or phosphoric acids give low yelds (entries **1-3**). A weak acid like benzoic acid also don't give good results, but a benzoic acid substituted with electron withdrawing groups like *o*-fluorobenzoic acid gave a better ee respect to TFA (*Tab. 5.2*, entries **4,5**). We tried more benzoic acids with electron withdrawing groups, and whether the stronger 3,5-dinitrobenzoic acid gave lower selectivity respect to the one with only an electron withdrawing group (*Tab. 5.2*, entries **6-9**), o-nitrobenzoic acid was the best improving enantioselectivity up to 74% (*Tab. 5.2*, entry **7**). The same selectivity was obtained with salicylic acid (*Tab. 5.2*, entry **10**). So we tried stronger salicylic acids and 5-nitrosalicylic



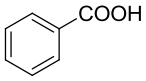
236a (1.1 eq.) + **252b** → **254ab**; **37a**



84a (*S*)-BINOL hydrogenphosphate

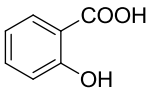


255 diphenylphosphate (DPP)

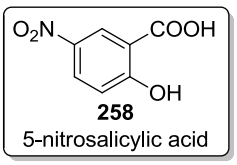


256 Benzoic acid

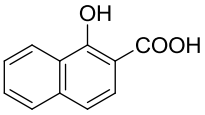
Entry	Acid	Yield (%)	ee (%)
1	TFA	87	49
2	p-TsOH	0	-
3	*(R)*-BINOL-hydrogenphosphate	12	n.d.
4	DPP	43	19
5	Benzoic Acid	29	32
6	o-fluorobenzoic acid	61	57
7	o-nitrobenzoic acid	82	74
8	p-nitrobenzoic acid	58	71
9	3,5-dinitrobenzoic Acid	28	56
10	Salicylic Acid	45	74
11	Thiosalicylic acid	57	53
12	3-nitrosalicylic acid	61	73
13	***5-nitrosalicylic acid***	***78***	***82***
14	2-hydroxy-1-naphtoic acid	58	78
15	1-hydroxy-2-naphtoic acid	81	76



257 Salicylic acid

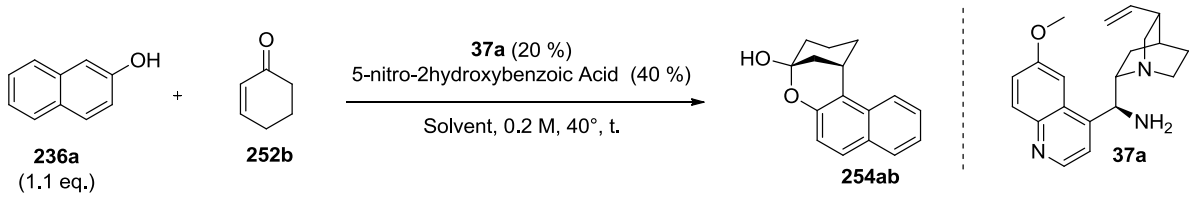


258 5-nitrosalicylic acid



259 1-hydroxy-2-naphthoic acid

Table 5.2: acid co-catalyst optimization for the enantioselective F-C alkylation acetalization cascade of natphthols with enones. On the left and right some of the acid used.



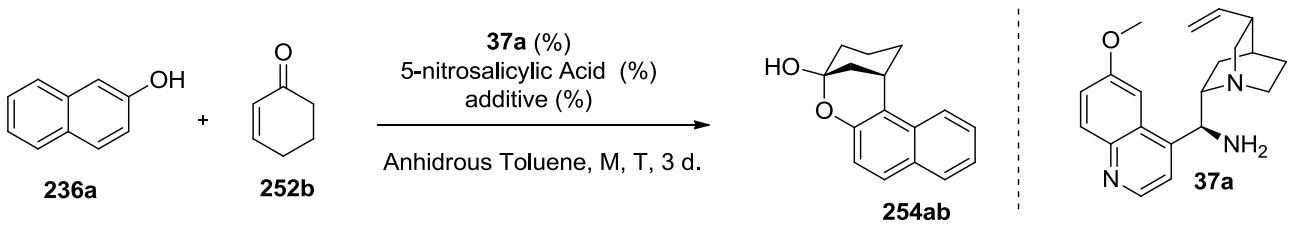
236a (1.1 eq.) + **252b** → **254ab**; **37a**

Entry	Solvent	t (d)	Yield (%)	ee (%)
1	Hexane	2	18	52
2	Et_2O	3	6	n.d.
3	MTBE	2	5	n.d.
4	*Toluene*	*3*	*78*	*82*
5	p-Xylene	3	43	68
6	Clorobenzene	3	89	79
7	Fluorobenzene	2	46	80
8	DCM	3	47	80
9	$CHCl_3$	2	52	80
10	1,2-DCE	3	24	76
11	THF	3	0	-
12	dioxane	2	12	n.d.
13	EtOAc	3	16	n.d.
14	HFIP	2	0	-
15	MeOH	3	0	-
16	Water	3	43	46
17	Toluene/Brine 1:1	3	83	73
18	***Dry Toluene***	***3***	***90***	***84***

Table 3: solvent screening for the enantioselective F-C alkylation acetalization cascade of natphthols with enones.

acid **258** was found promising, giving an enantioselectivity of 82% (*Tab. 5.2*, entry **13**). The other two bigger naphthoic acids didn't show better results (*Tab. 5.2*, entries **14,15**). At this point we were quite satisfied of our preliminary result and we continued the optimization with the solvent screening.

Very non-polar and very polar solvents gave poor reactivity (*Tab. 5.3*, entries **1-3** and **11-15**). An exception was water (*Tab. 5.3* entry **16**), so we tried a biphasic system toluene/brine to enhance the ionic strength of the reaction medium (*Tab. 5.3* entry **17**). Actually the result was not bad, but not as good as the one gave by toluene itself (*Tab. 5.3*, entry, **4**), which was our starting point from the previous optimization. Generally, good selectivities could be obtained in aromatic and chlorinated solvents, but yields were higher in aromatic ones (*Tab. 5.3*, entries **4-7** and **8-10**). By the way no solvent gave better enantioselectivity than toluene. Since the reaction with toluene/brine 1:1 gave slight decreased ee, we thought that water could have a detrimental role on its value and for this reason we tried anhydrous toluene as solvent. Actually, a slight improvement of both yield and ee could be obtained (compare entry **4** and **18** in *Tab. 5.3*). We decided to perform all the other reactions with this solvent. Since the reaction works slightly better in dry toluene than in normal one, we decided to investigate the possibility that a certain amount of water could be beneficial, since of course the amount of water in "wet" toluene is unknown. Total elimination of water with powdered 4Å molecular sieves completely suppressed the reaction (*Tab. 5.4*, entry **3**). This might be expected, because water is formed in the first step of the catalytic cycle but is necessary in the last step to restore the catalyst.

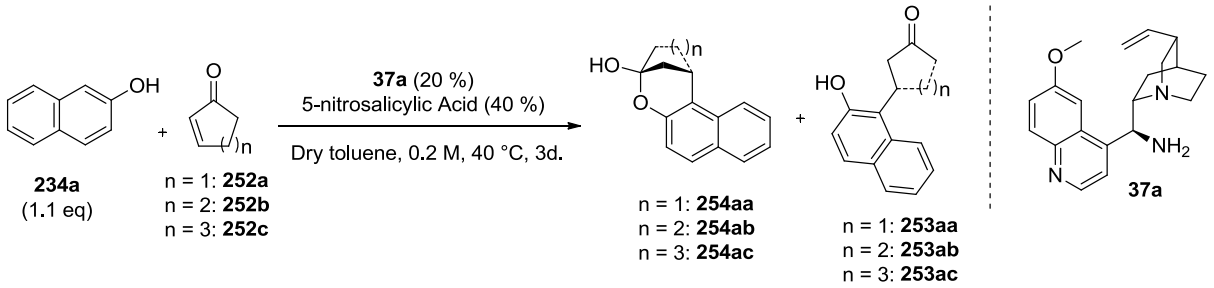


236a + **252b** → **254ab**; **37a**

Entry	Eq. 1	% cat.	% acid	M	T(°C)	Additive	Yield (%)	ee (%)
1	1.1	20	40	0.2	40	Water (3 eq.)	70	81
2	***1.1***	***20***	***40***	***0.2***	***40***	**-**	***90***	***84***
3	1.1	20	40	0.2	40	MS 3Å powder	0	**-**
4	1.1	20	20	0.2	40	-	31	76
5	1.1	20	60	0.2	40	-	67	80
6	1.1	20	40	0.1	40	-	61	78
7	1.1	20	40	0.4	40	-	88	81
8	1.1	20	40	0.2	0	-	0	-
9	1.1	20	40	0.2	25	-	52	81
10	1.1	20	40	0.2	60	-	91	80
11	3	20	40	0.2	40	-	Quant.	84
12	3	10	20	0.2	40	-	38	84

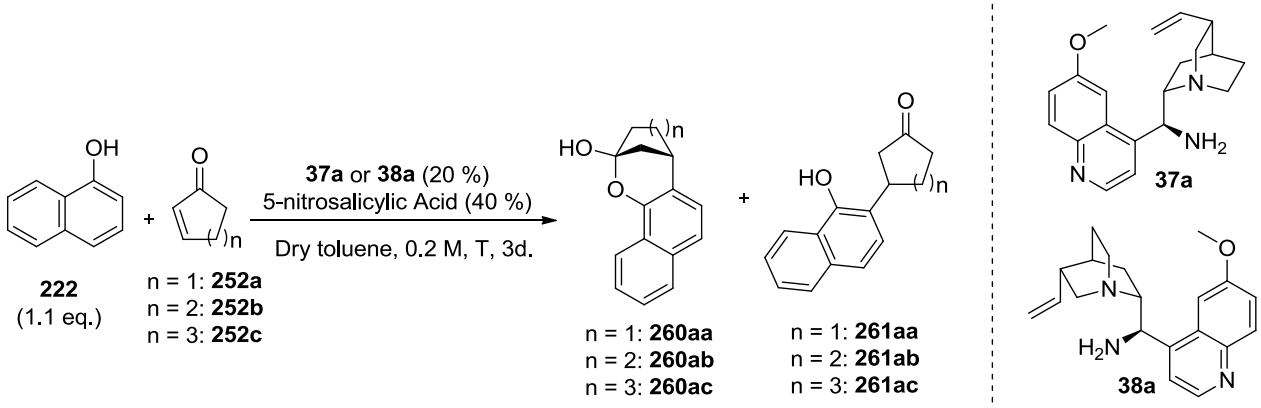
Table 5.4: further optimization of reaction conditions. * toluene wasn't anhydrous

If water is absent this last hydrolysis can't occur and the catalyst is poisoned. Anyway, this might not the only reason why the reaction is not working with molecular sieves as additive. For example one of the reactant could be adsorbed by the sieves. Also adding 3 eq. of water didn't give better results, so it could be speculated that the equivalent of water generated in the catalytic cycle is just the right amount required for a good reaction outcome (*Tab. 5.4*, entry **1**). Since we performed the catalyst/acid ration screening with TFA, we decided to carry it out also with this acid, because different results could be obtained. Actually, the results were not bad, but not comparable with entry **2** (*Tab. 5.4*, entries **4,5**). Further concentration and temperature screening didn't improve the results (*Tab. 5.4*, entries **6-7** and **8-10**). We observed a faster reaction using 3 equivalents of β-naphthol, and so we thought that in this way we could decrease the catalyst loading (*Tab. 5.4*, entry **11**). However, working with 3 eq. of β-naphthol, 10% of catalyst and 20% of acid the yield was low (*Tab. 5.4*, entry **12**). In summary, the best conditions for this reaction remained the ones in entry **2**, which we used to try the reaction scope.



Entry	starting	products	254:253	Overall Yield	ee (major)
1	**252a**	**254aa/253aa**	3:1	30	53
2	**252b**	**254ab/253ab**	100:0	93	84
3	**252c**	**254ac/254ac**	100:0	66	73

Table 5.5: reaction of β-naphthol with cyclopentenone, cyclohexenone and cyclopentenone.

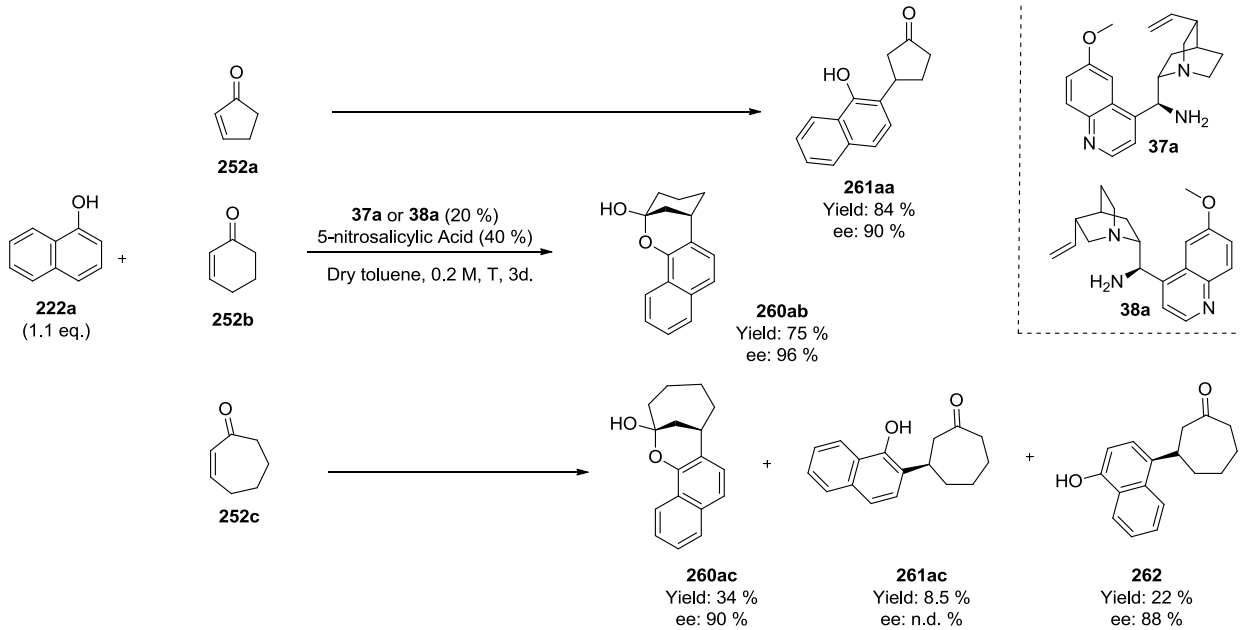


Entry	Starting	Product	closed:open	Overall Yield	ee (Major)
1	**252a**	**260aa/261aa**	0:100 (0:100)	63 (84)	90 (90)
2	**252b**	**260ab/261ab**	100:0 (100:0)	75 (63)	96 (94)
3	**252c**	**260ac/261ac**	1:1 (4:1)	35 (42)	92 (90)

Table 5.6: reaction of b-naphthol with cyclopentenone, cyclohexenone and cyclopentenone. Values in parentesys are obtained with catalyst **38a**.

In *table 5.5* are summarized the results for the reaction of β-naphthol with enones with various ring size. Unfortunately, cyclopentenone **252a** and cycloheptenone **252c** didn't give results as good as cyclohexenone **252b**. Yields were low and ee's only moderate. Moreover, the reaction between β-naphthol and cyclopentenone (*Tab. 5.5*, entry **1**) was found to give a mixture of products **254aa**, closed as an hemi-acetal and **253aa**, open, with a ratio of 3:1. These products were separable: the ee given is for **253aa**, but the ee for **254aa** was similar. This situation will happen for other products. I will refer to them as "open" and "closed" products.

In *table 5.6* the results for the reaction of α-naphthol with enones with various ring size are summarized. Since no other method to produce the racemic products was available, we had to perform the reactions with both the pseudoenatiomeric catalysts **37a** and **38a** and then mix a bit of the two enantioenriched products to obtain a racemic sample for the HPLC. In this way we realized that sometimes the results obtained with **38a** were better. So, values for this catalyst are given in parenthesis in this and in the following tables. We were pleased to find high enantiomeric excesses for the α-naphthol derivatives; however the nature of the products was different. While the reaction using cyclpentenone gave exclusively the "open" product **261aa**, (*Tab. 5.6*, entry **1**) the cyclohexenone derivative was obtained esclusively in the "closed" form **260ab** (*Tab. 5.6*, entry **2**). Compare to what happened with β-naphthol: in that case the reaction product with cyclopentenone was also open, even if only partly (*Tab. 5.5*, entry **1**) and the reaction product with cyclohexenone was all closed (*Tab. 5.5*, entry **2**). The case of cycloheptenone **252c** was even more complicated: an uninseparable mixture of "open" and "closed" products **260ac** and **261ac** was obtained (on the contrary, products **254aa**, and **253aa** in *table 5*, were separable), and the yield was lowered by the presence of another product, formed in 22% of yield (see scheme **5.6** for clarity). Investigation on the nature of this product lead us to find that in this reaction also the 4-substituted product **262** was obtained. Actually this is interesting, because even if it's known that also 4 position of α-naphthol is reactive, this is much less common. In fact in our reaction this kind of product was obtained only in this case. No other ketone, in combination with no other α-naphthol derivative ever gave 4-substituted products. Anyway we were curious about the possible enantiomeric excess of **262**, so we produced a racemic sample and then performed the HPLC analysis on it. It was very interesting to find an ee of 88% for **262**, close to the one obtained for the product arising from the attack in 2 position (*Table 5.6*, entry **3**).



Scheme **5.6** : graphical summary of what happened reacting α-naphthol with enones of various ring size.

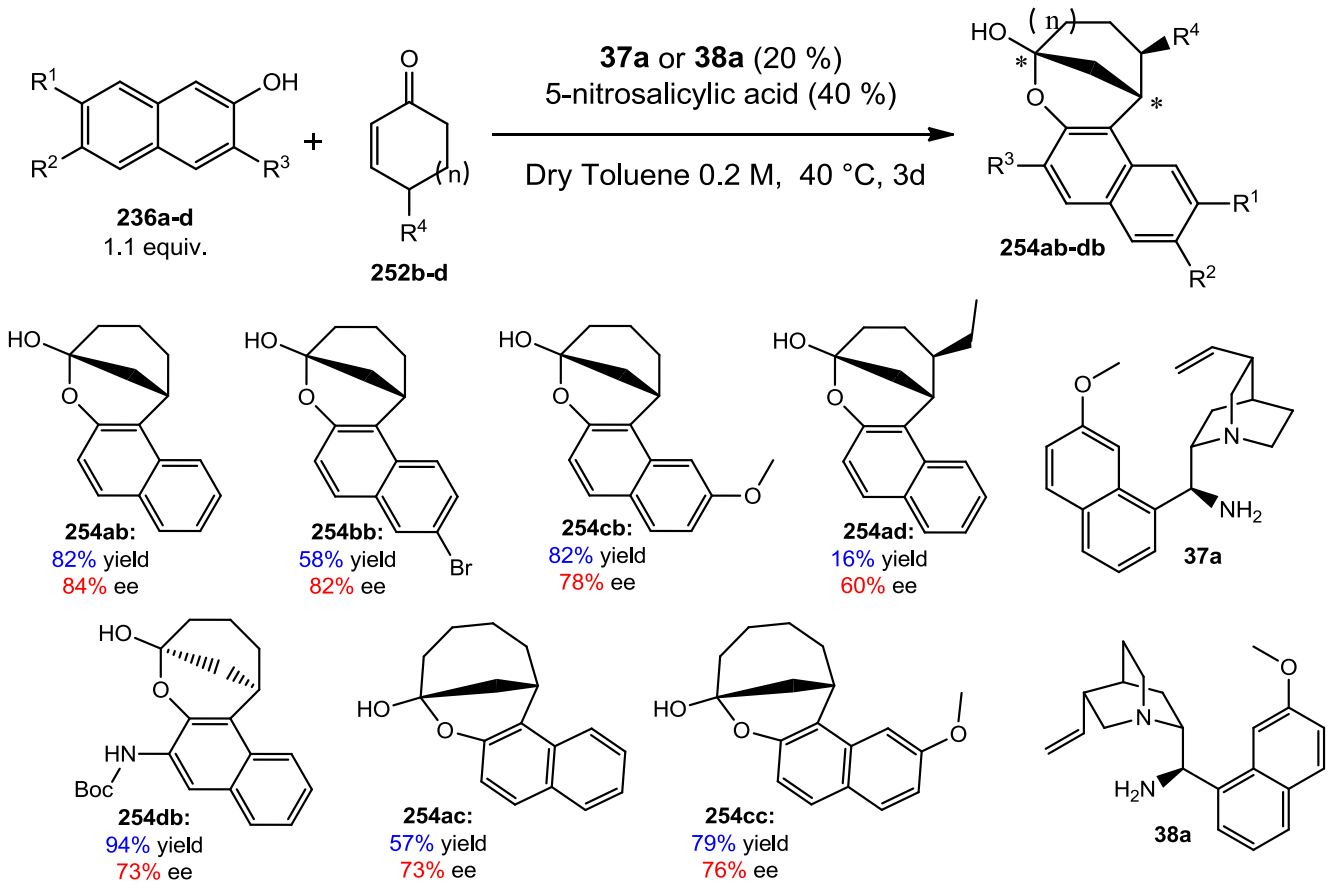


Figure 5.2: reaction scope on b-naphthols.

Next we performed the scope on β-naphthols by reacting some β-naphthol derivatives with some enones. Yields and ee's were generally quite good, except for product **254ad**, obtained in poor yield and ee. Products and results are summarized in *figure 2*. Products **254ab** and **254ac** are repeated and can be found also in *table 5.5*.

Then we performed the scope also on α-naphthol derivatives. The results are summarized in *figure 3*. In this figure the results in *table 5.6* are not repeated. Notably, the ee's are generally better compared to β-naphthols, with values above 90% ee. It is possible to note that if using substituted cyclohexenones as Michael acceptors yields are low; by the way in these reactions something special happened. In fact, the starting materials 4-ethyl cyclohexenone **252d** and 5-phenyl cyclohexenone **252e** are chiral, and we used them in a racemic form. So, both enantiomers were present in the reaction mixture, and in both cases the two enantiomers behave differently under the reaction conditions, giving two different results. When using **252d** a kinetic resolution occurred, instead when using **252e** the two enantiomers gave two different reaction products (**260ae** and **261ae** in *figure 5.3*).

When product **260ad** was obtained and purified, we realized that it did not show diastereoisomers. No other products were observed in this reaction. This was somehow unexpected: since the starting material was chiral but racemic in principle two diastereoisomers should be obtained. We concluded that only one of the two enantiomers of the starting material reacted, and thus a kinetic resolution occurred. We confirmed the relative configuration of the product **260ad** via NOE experiments (see *Figure 5.4*). Remarkably, the ethyl substituent is in the axial position respect to the cyclohexane. The so-formed product is therefore a cyclohexane with three substituents in the axial position, which highly unlikely is the thermodynamically most stable one, so for his formation a

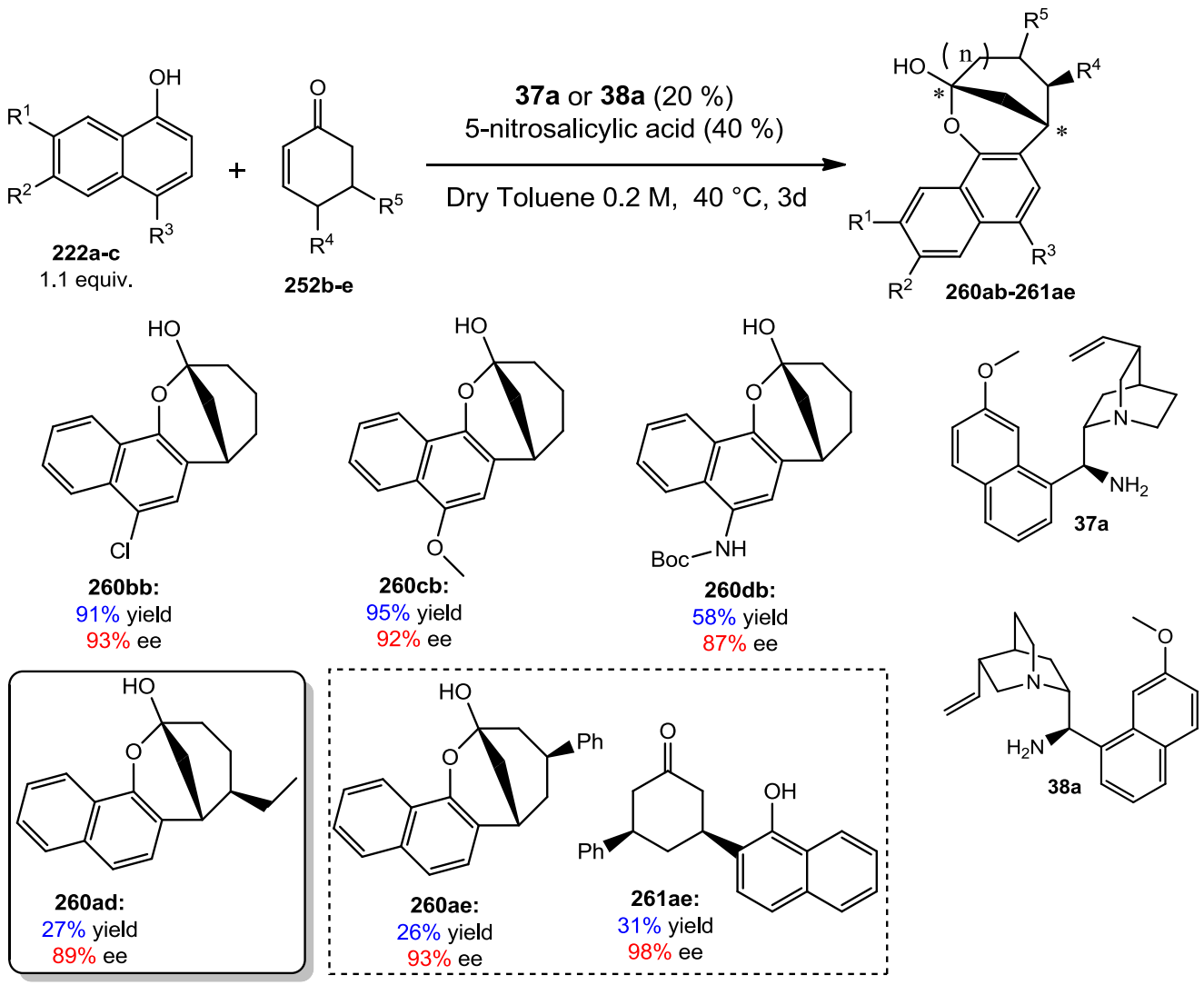


Figure 5.3: reaction scope on α-naphthols.

catalyst controlled kinetic process must be involved. Probably, somehow the transition state in this reaction has a particular steric hindrance, that hampers the attack of the naphthol if an equatorial group is present on the 4-position of the cyclohexane ring. A computational calculation to create a stereochemical model, or other experiments to better understand this process would be necessary to better understand the phenomenon, but they were out of the aim of the work. Anyway a model with a possible explanation of this kinetic resolution due to the steric hindrance of the ethyl group is given in *Figure 5.5*, anyway please note that this model is completely speculative, and more detailed studies would be necessary to confirm it: conformations of cyclohexane have to be taken into account, and it is anyway possible that the catalyst moiety, and not only the ethyl group, is responsible for this particular reaction pathway. Moreover, unfortunately it was not possible to recover the unreacted starting material, in order to confirm its structure and measure its ee.

Also the reaction between α-naphthol and **252e** in principle should give diastereoisomers, since also this starting material is chiral but racemic. Actually, in this reaction two products were obtained but ^{1}H and ^{13}C NMR spectra showed that they were not diastereoisomers, but the closed and open products **260ae** and **261ae**, each one not showing diastereoisomers.

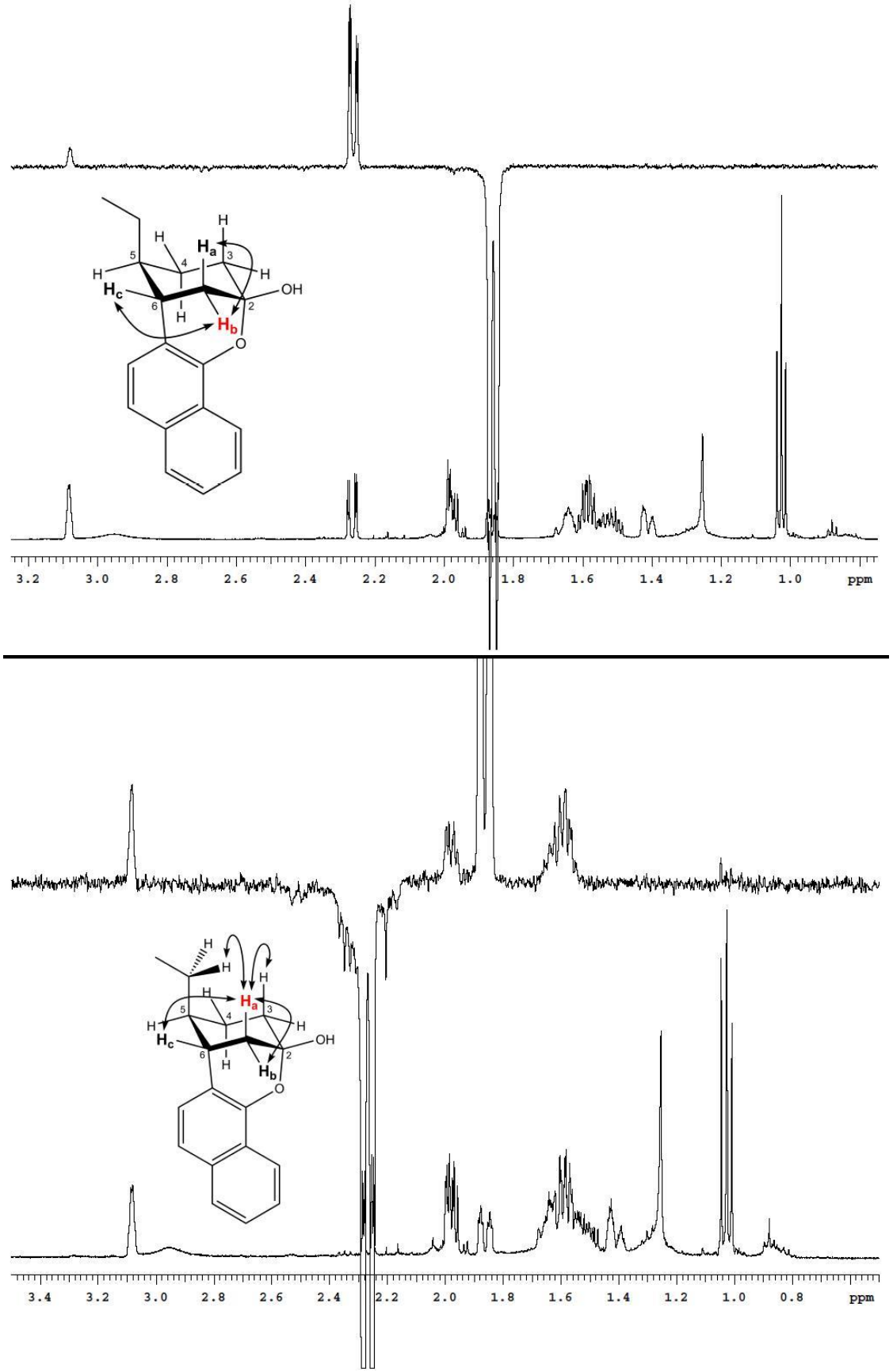


Figure 5.4: NOE experiments on product **260ad**. After understanding signals given by Ha and Hb with NOE on Hc, the same experiment were performed on this two protons. One of them (Hb) coupled only with the benzylic and the germinal proton. The other (Ha) shows coupling with the axial proton on C3 and with the two protons on ethyl group, which is therefore axial.

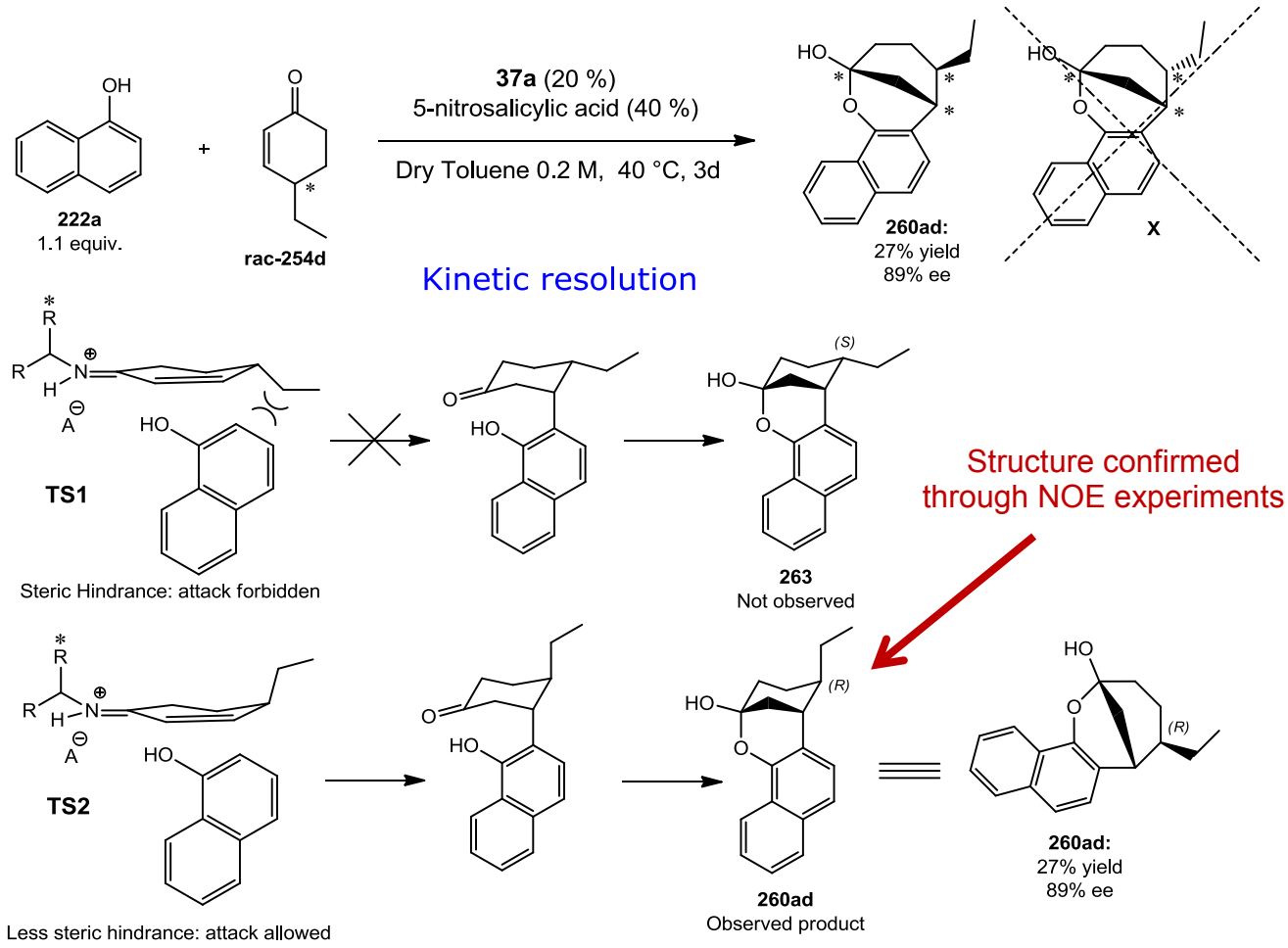


Figure 5.5: speculative model for the transition states for the reaction of 4-ethyl cyclohexenone and a-naphthol. In TS1 the steric hindrance is too high and the attack can't occur. In TS2, having the ethyl in axial position, the space is enough. By the way in TS1 not only the ethyl moiety, but also the catalyst moiety might be responsible of the steric hindrance.

Intrigued by this finding we analysed the structures of these products, again with NOE spectra. These are showed in *figures 5.6 and 5.7*. The two different pathways can be rationalized this time reasoning on the relative stability of the two products formed (see *figure 5.8*). Here the preference of the additional phenyl ring to be equatorial is determining for the reaction outcome: in fact, when the ring closure gives a structure in which the phenyl ring is equatorial it occurs to give product **260ae**. When, instead, it would give product **264**, having the phenyl substituent in the axial position, inversion of the cyclohexane ring occurs, in order to give a compound with both the substituents in the equatorial position, and in this way ring closure is impossible and so the simple "open" **261ae** is obtained. In other words, due to the relative stereochemistry of product **260ae** the two substituents must be one axial and one equatorial: in this way the evidently thermodynamically favoured ring closure leading to the naphthol in axial position is favoured, also because it leaves the phenyl in the equatorial position. On the contrary, for product **261ae** the relative stereochemistry allows the formation of a compound with two substituents in the equatorial position, and thus much more thermodynamically stable that the corresponding closed product with both the substituents in axial position. Thus, actually, the two diastereoisomers were obtained, but one of the two is more stable as closed as a hemiacetal, the other one prefers to stay "open".

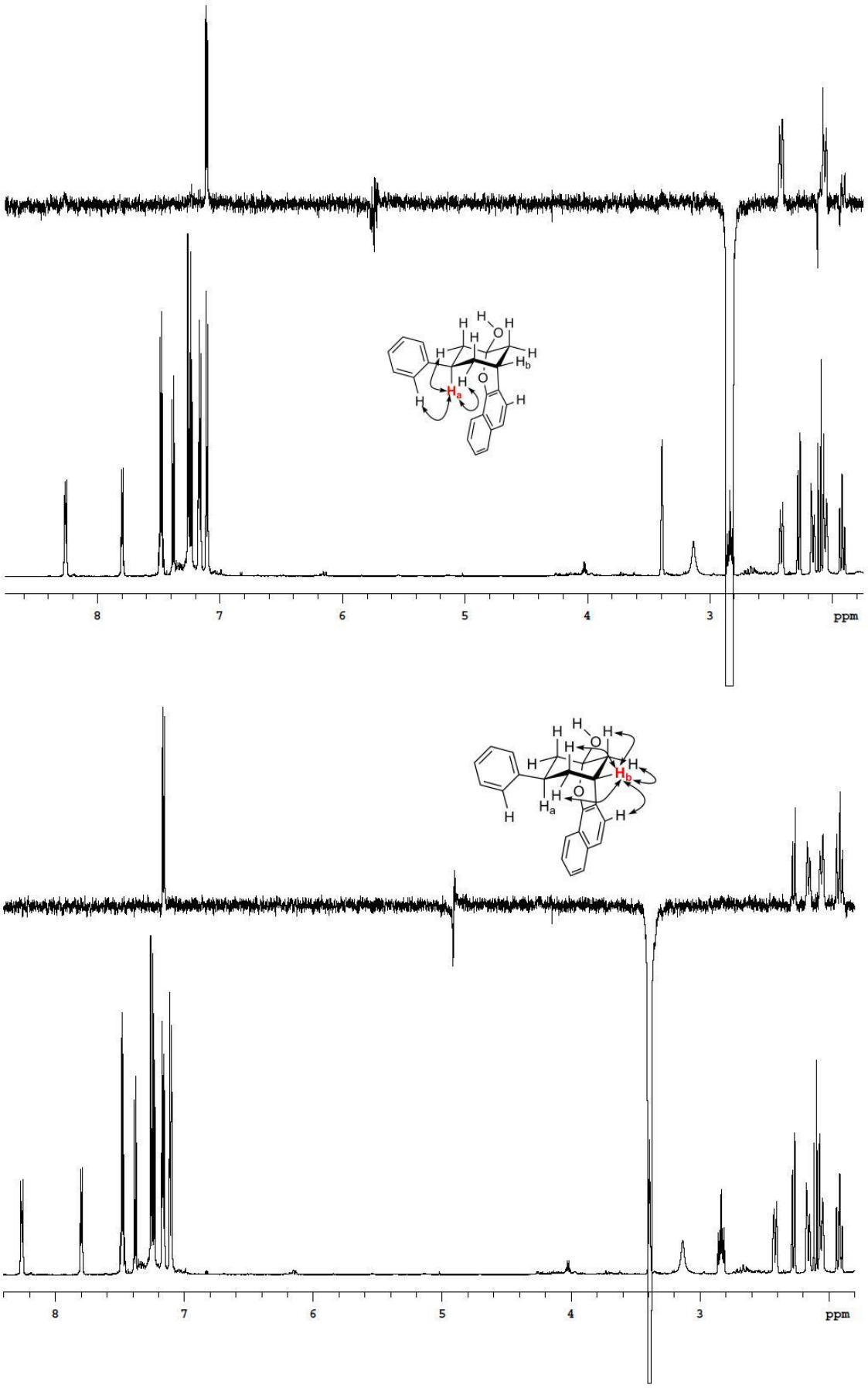


Figure 5.6: NOE spectra for product **260ae**. Benzylic Ha has only a few NOE couplings, compatible with its axial position. More couplings are observed for Hb, which is near to many protons, duo to its equatorial position.

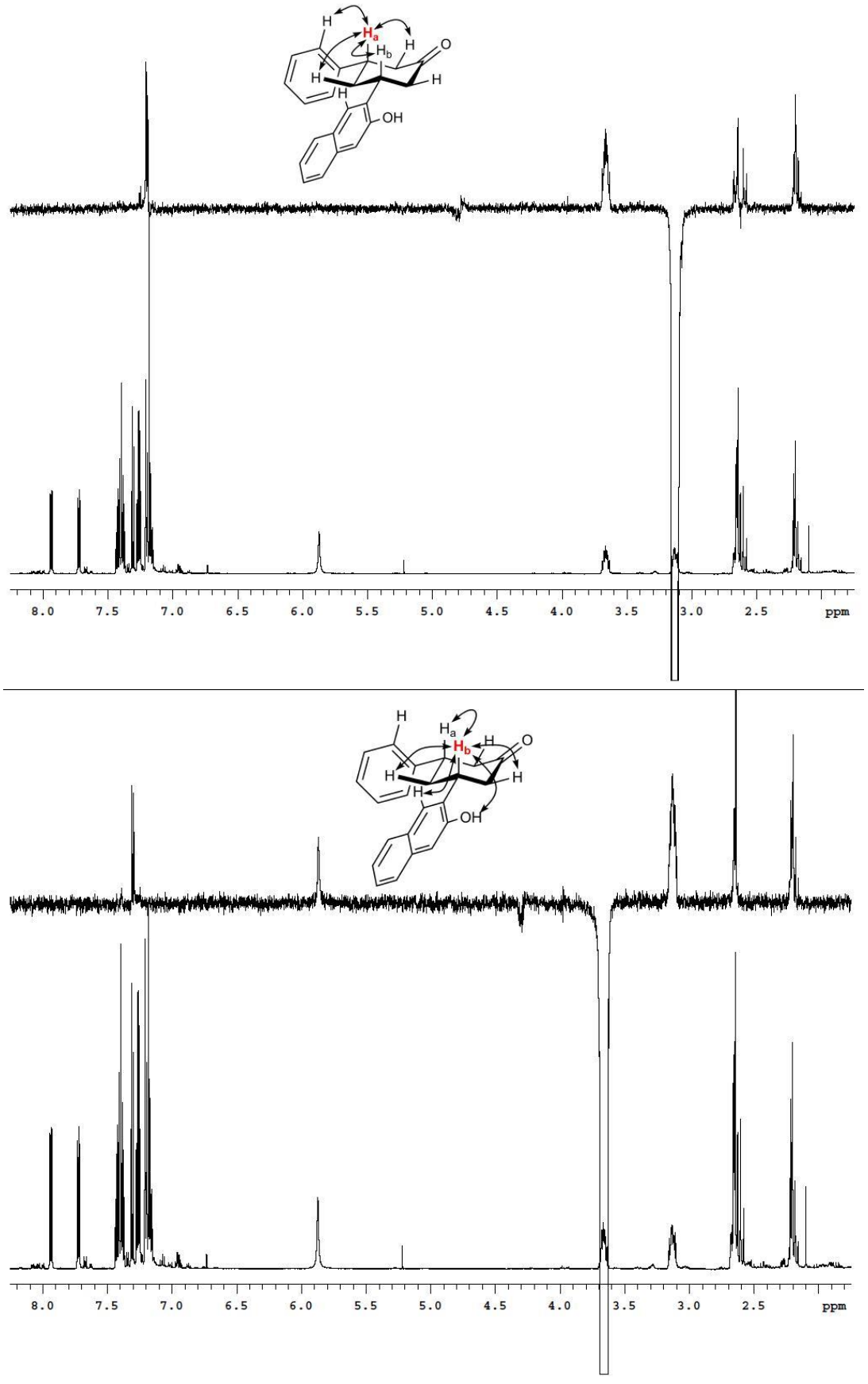


Figure 5.7: NOE spectra for product **261ae**. Benzylic Ha and Hb strongly correlate one to each other, meaning that they are both axial. This allows to the larger phenyl and naphthyl substituents to be axial and to the structure to be more stable. In this way hemi-acetalization cannot occur.

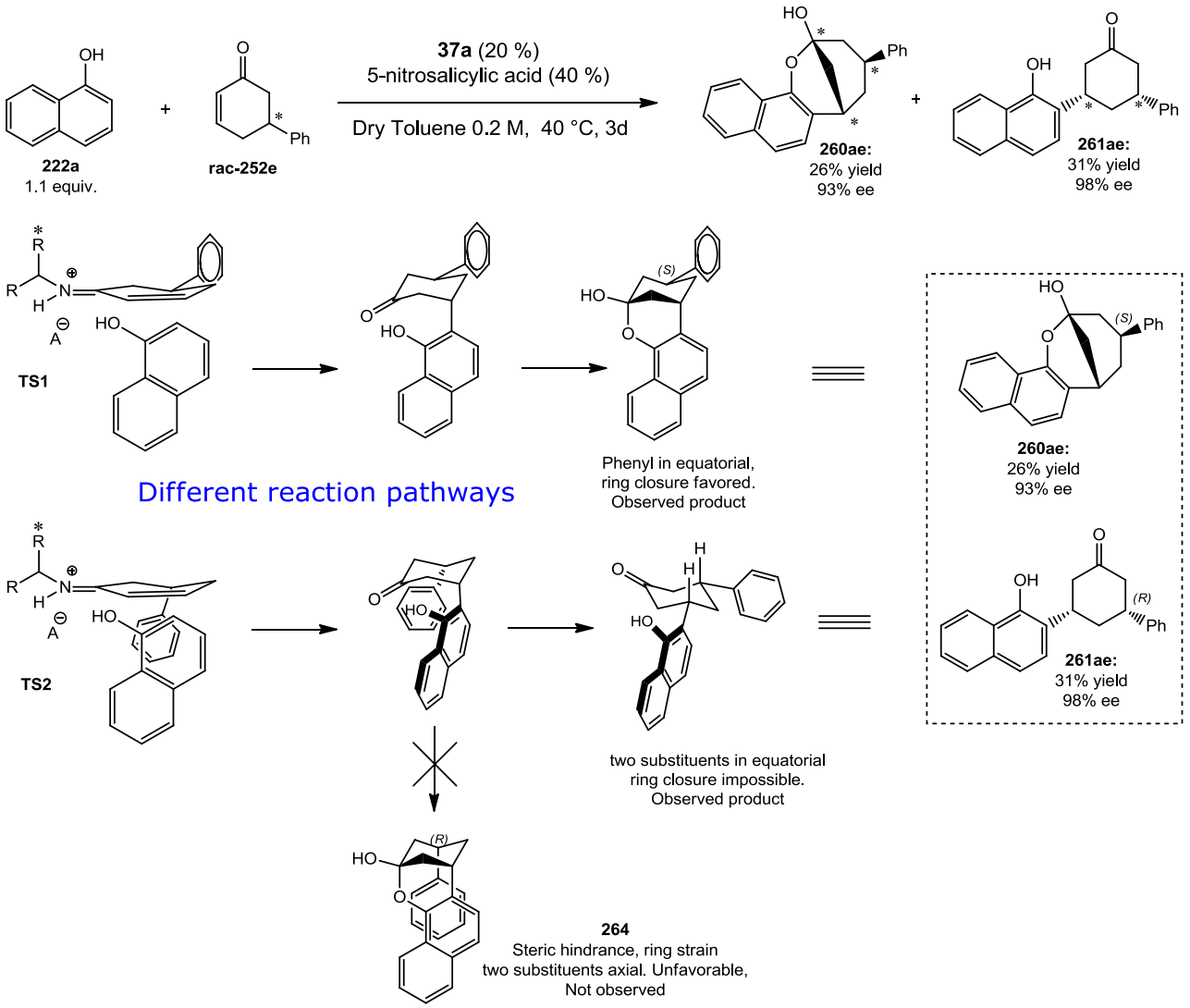
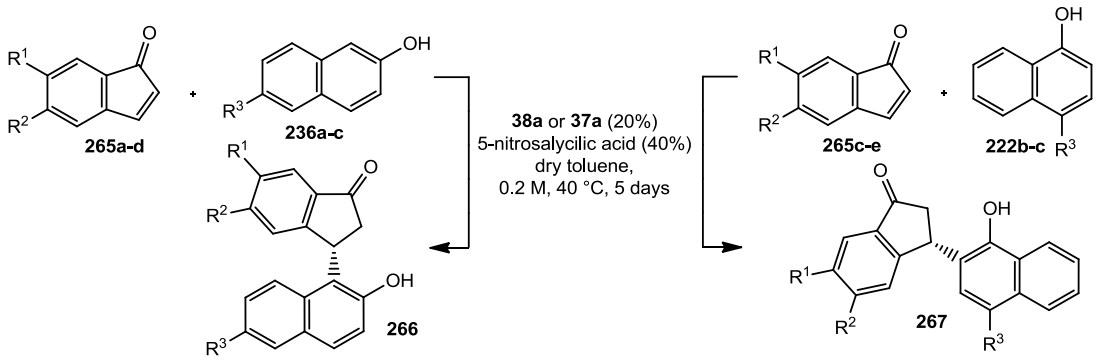


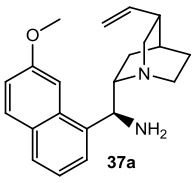
Figure 5.8: graphical explanation of the two different pathways observed for the two enantiomers in the reaction of 5-phenyl cyclohexnone with α-naphthol.

Another class of ketones reactive under these conditions are indenones **265**. These substrates are big and thus sterically hindered, so they are seldom employed as Michael acceptors. In our catalytic system, instead, they are also able to react with naphthols, despite in slightly longer reaction times (5 days). Anyway, yields are good to very good and ee's are excellent, often above 90%. Some indenones were synthesized and reacted with α- and β-naphthols. Like happened for other 5-membered rings, these compounds didn't undergo hemiacetalization cascade but were all "open", maybe because of the additional conformational strain given by the phenyl ring. Interestingly, for these class of substrates catalyst **38a**, the pseudo-enantiomer of catalyst **37a** generally gave better results. Yields and ees for indenones are summarized in *table 7*.

Arrived at this stage we successfully applied iminium ion catalysis for the enantioselective F-C alkylation of cyclic enones with naphthols. We were also curious about other substrates. For example we wanted to know what happened if acyclic enones were used as Michael acceptors. *E*-Pentenone and *E*-Nonenone **33a** and **33b** were chosen as substrates and the reaction was tried both with α- and β-naphthol, with both catalyst **37a** and **38a**, in the standard conditions. Results are summarizes in *Tables 5.8 and 5.9*.



Entry	Product	R^1	R^2	R^3	Yield (%)	ee (%)
1	**266aa**	H	H	H	63	95
2	**Ent-266aa**	H	H	H	68	85
3	**266ab**	Me	H	H	97	90
4	**266bc**	H	F	Br	83	90
5	**266cd**	H	Cl	MeO	84	81
6	**267bc**	H	F	Cl	60	90
7	**267ce**	MeO	H	MeO	92	94
8	**267cd**	H	Cl	MeO	83	90



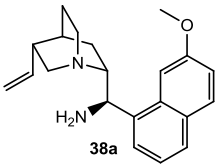
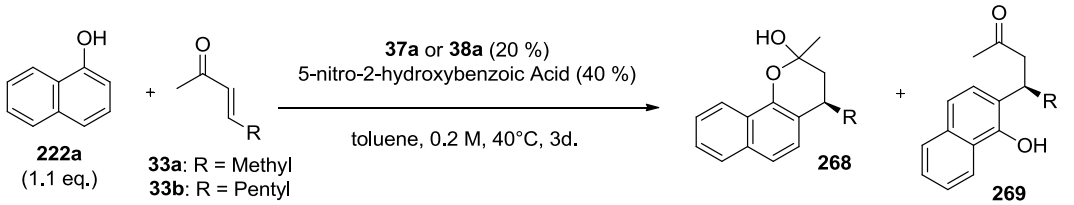
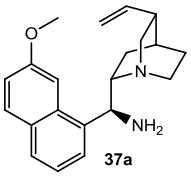


Table 5.7: results obtained reacting a- and b-naphthols with indenones.





Entry	Starting	Cat.	268:269	d.r.	Overall Yield	Ee (Major)
1	**33a**	**37a**	0:100 (0:100)	n.a.	68 (71)	41 (44)
2	**33b**	**37a**	1:1.83 (1:1.85)	n.d.	57 (38)	33 (34)

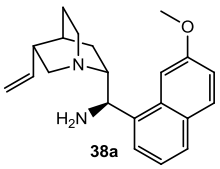
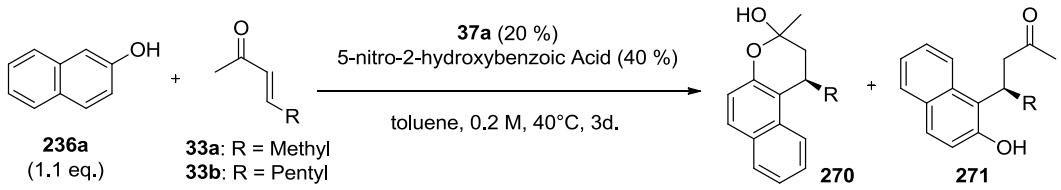


Table 5.8: attempts of F-C alkylation of α-naphthol with linear ketones. Values in parenthesis are obtained with catalyst **38a**. n.a.: not applicable. n.d.: not determined.

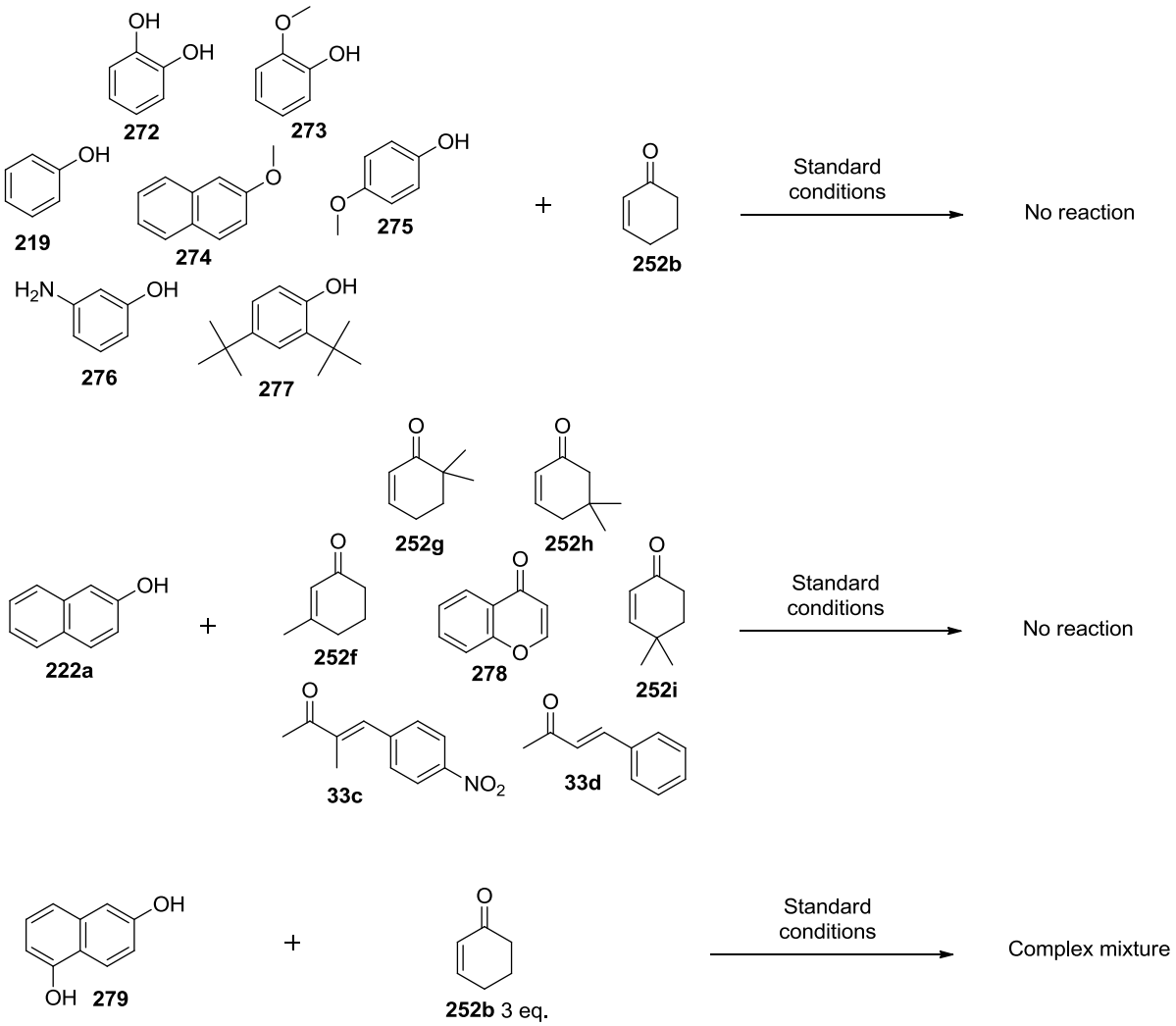


Entry	R	Cat.	270:271	d.r.	Overall Yield	Ee (Major)
EP 251	**33a**	**37a**	100:0 (100:0)	2.7:1 (2.85:1)	41 (42)	n.s. (n.s.)
EP 253	**33b**	**37a**	100:0	n.a.	11 (12)	n.d. (n.d.)

Table 5.9: attempts of F-C alkylation of β-naphthol with linear ketones. Values in parenthesis are obtained with catalyst **38a**. n.a.: not applicable. n.d.: not determined. n.s.: not separable.

Reaction of α-naphthol with **33a** gave exclusively the "open" product in good yields but unfortunately with scarce ee. Reaction of α-naphthol with **33b** gave a mixture of "open" and "closed" products, which were separable, with a slight preference for the "open" one. On this one, the ee was determined, but it was again poor, as well as the yield (*Tab 5.8*). Results employing α-naphthol were even worse (*Tab 5.9*). With **33a** actually the yield was reasonable, and the product was all closed. In this case, since the ketone was linear and so not forced to give a single diastereoisomer, a d.r. existed, and found to be 2.7:1 or 2.85:1 for catalyst **38a**. Anyway, despite many chiral HPLC columns were tried, an effective separation for the two enantiomers couldn't be found, and ee was not determined. Finally, reaction of α-naphthol with **33b** gave the product in very low yield, and the ee was not determined. We therefore stopped our work and concluded that for linear ketones another optimization would have to be done, but it was out of our aims.

During our studies other reactions proved to be uneffective. In scheme **5.7** they are summarized. As you can see, phenols, electron poor naphthols, and more linear enones were not reactive. In addition, 2-methoxynaphthalene **274** was not reactive, thus suggesting that the naphtholic proton plays a key role in the reaction mechanism, although this role is unknown. Doubly substituted cyclohexenones also were not effective, confirming that even a small steric hindrance is crucial for the outcome of this transformation. Finally, reacting 5-hydroxy-1-naphthol **279** with 3 equivalents of cyclohexenone resulted in a complex mixture.



Scheme **5.7**: summary of all the uneffective reactions.

5.2.1) Conclusion and future challenges

In summary, the first iminium ion catalyzed Friedel-Crafts alkylation/acetalization cascade of naphtholes with cyclic enones was developed. 20% of a cinchona alkaloid derived primary amine and 40% of 5-nitrosalicylic acid was used as catalyst combination. The reaction gave the desired products in reasonable time, good yields and enantiomeric excesses. Both α- and β-naphthols participate in this transformation, with α-naphthols giving generally slightly better enantiomeric excesses. Indenones, seldom used as Michael acceptors, can also be employed as electrophiles, giving in slightly prolonged reaction times good yields and selectivities. Interesting phenomena occurred when mono-substituted cyclohexenones were employed: in one case, a kinetic resolution of a racemic substrate took place and in another case the two enantiomers of another racemic substrate reacted differently.
Unfortunately, the reaction is limited to those enones not too much sterically congested, and linear enones gave bad yields and ee, suggesting that a new optimization would be necessary for these substrates. Phenols and 2-methoxynaphthalene were not reactive under these reaction conditions.

5.3) EXPERIMENTAL SECTION

General informations.

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian inova 300, at 300 MHz and 75 MHz respectively, Varian mercury 400, at 400 MHz and 100 MHz respectively, or Varian inova 600, at 600 MHz and 150 MHz respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CDCl_3$, DMSO-d_6). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. $CDCl_3$ was passed over a short pad of alumina before use. Coupling constants are given in Hz. When 2D-NMR were not performed, the carbon types were determined from DEPT ^{13}C NMR experiments. NOE spectra were recorded using the DPFGSE-NOE sequence[160] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. High Resolution Mass spectra (HRMS) were obtained from the Department of Organic Chemistry "A. Mangini" Mass Spectroscopy facility, on a Thermo-Finnigan MAT 95 XP spectrometer. X-ray data were acquired at the Department of Physical and Inorganic Chemistry X-ray Crystallography facility, on a Bruker APEX-2 difractometer. Optical rotations were measured on a Perkin-Elmer 341 polarimeter and reported as follow: $[\alpha]_D^{rt}$ (c in g per 100 mL, solvent). Thin Layer Chromatography (TLC) was performed on commercially available Fluka TLC plates on aluminium or PET foils with fluorescent indicator at 254 nm,

[160] (a) K. Stott, J. Stonehouse, J. Keeler, T.-L. Hwand, A. Shaka, *J. Am. Chem. Soc.* 1995, **117**, 4199. (b) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Resonance* **1997**, *125*, 302. (c) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Resonance* **1999**, *141*, 191. (d) See also: Claridge, T.D.W. *High Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.

using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents.
Purification of the products was carried out by flash chromatography (FC) on silica gel (Aldrich, 230-400 mesh) according to the method of Still[161]. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Materials

All the commercially available reagents and solvents were used without any further purifications; otherwise, where necessary, they were purified as recommended[162]. Chiral primary amine catalysts 9-amino(9-deoxy)*epi*-quinine **37a** and its *pseudo*-enantiomer 9-amino(9-deoxy)*epi*-quinidine **38a** were synthesized according to literature procedures[163].
All the ketones and the naphthols were purchased from Sigma-Aldrich or Alfa Aesar and used as received. Compounds **252d**-**e**[164] and **265a-d**[165] were prepared following the literature procedures *Tert-butyl (3-hydroxynaphthalen-2-yl)carbamate* **236d** was synthesized according to the literature procedure[166].
Tert-butyl (4-hydroxynaphthalen-1-yl)carbamate **222d** was synthesized as follows:

In a flame-dried flask equipped with a condenser and a magnetic stirring bar, triethylamine (0.344 ml, 1 eq.) was added to a 0.5 M solution of 4-amino-1-naphthol hydrochloride (2.56 mmol, 0.5 g, 1 eq.) in anhydrous THF (5.11 ml). The reaction mixture was left to stir at r.t. for 5 min. Then di-*tert*-butyl dicarbonate (0.558 g, 1 eq.) was added as a solid and the reaction mixture was stirred and refluxed for three days. Then it was cooled to room temperature and the solvent was removed in vacuo. The crude product was purified through flash chromatography on silica gel (Hex/EtOAc 70:30) to give a violet solid, which was crystallized from Et_2O/Hex to afford **222d** in 57% yield as a pink solid.
^{1}H NMR (300 MHz, $CDCl_3$)[167]: δ 1.58 (s, 9H), 6.41 (d, 1H, J = 7.8 Hz), 6.49 (bs, 1H), 6.71 (bs, 1H), 7.22 (d, 1H, J = 8.1 Hz), 7.40 (t, 1H, J = 8.2 Hz), 7.51 (dt, 1H, J_a = 8.2 Hz, J_b = 1.5 Hz), 7.84 (d, 1H, J = 8.4 Hz), 8.05 (d, 1H, J = 8.4 Hz).

[161] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[162] W. L. F. Armarego, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
[163] (a) S. H.; McCooey, S. J.; Connon. *Org. Lett*. **2007**, *9*, 599-602; (b) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2007**, *46*, 7667 –7670. Please see also ref. 83.
[164](a) B.-D. Chong, Y.-I. Ji, S.-S. Oh, J.-D. Yang, W. Baik, S. Koo *J. Org. Chem*. 1997, **62**, 9323; (b) Y. Ergün, N. Bayraktar, S. Patir, G. Okay, *J. Hetrocyclic Chem.* 2000, **37**, 11.
[165] a) L. Minuti, A. Taticchi, E. Gacs-Baitz, A. Marrocchi, *Tetrahedron*, 1995, **51**, 8953; b) E. Zimmerman, V. Suryanarayan, *Eur. J. Org. Chem.* 2007, 4091.
[166] *S. Kumar, D. Hernandez, B. Hoa, Y. Lee, J.-S. Yang, A. McCurdy, Org. Lett.*, **2008**, *10*, 3761.
[167] Bachir Latli, *J. Label Compd. Radiopharm.* 2004; **47**, 847.

Determination of diastereomeric ratios and enantiomeric purity.

Diastereomeric ratios was determined by ^{1}H NMR spectroscopy of the crude product. Enantiomeric excesses were determined, after purification, through HPLC analysis on chiral stationary phase performed on an Agilent 1100-series instrumentation using Daicel Chiralpak AD-H, Daicel Chiralpak AS-H, Daicel Chiralcel OD-H, Daicel Chiralcel OJ-H, Phenomenex Lux-Amilose 2 and Phenomenex Lux-Cellulose 2 columns. Racemic samples of compounds **254ab, 254ac**, **260ab**, **260ac**, **266aa** were obtained performing the reaction with *p*-anisidine 30 mol% and 5-nitrosalicylic acid 60 mol% as catalyst combination. All the other racemic samples were prepared by mixing the two product antipodes obtained performing the reaction with catalyst 9-amino(9-deoxy)*epi*-quinine **37a** and its *pseudo*-enantiomer 9-amino(9-deoxy)*epi*-quinidine **38a** separately.

Conformational analysis and absolute configuration determination.

Good crystals suitable for X-ray diffraction were obtained for compound **266cd** by slow evaporation of a methanol solution. The anomalous scattering determination of the absolute configuration was possible thanks to the presence of the chlorine atom. The *S* configuration was determined for the selected crystal, and its relationship to the major enantiomer obtained with ent-A catalyst, was confirmed by means of enantioselective HPLC analysis of the very same crystal used for X-ray analysis (this was not straightforward, since the crystals were obtained from a 81% ee mixture of enantiomers). The crystal cell contained two conformations of the *S* enantiomers, that were different in the orientation of the OMe group on the naphthalene ring (see below for refinement details).

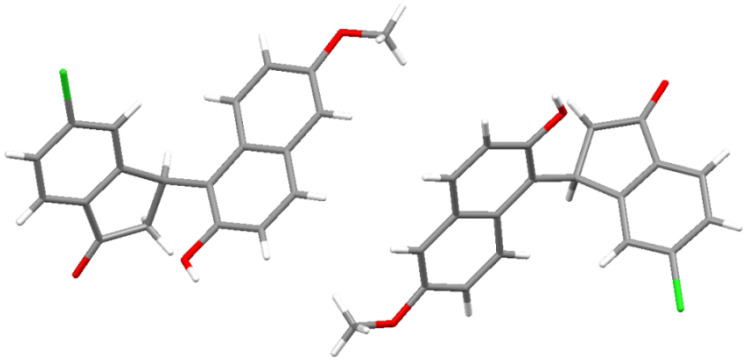
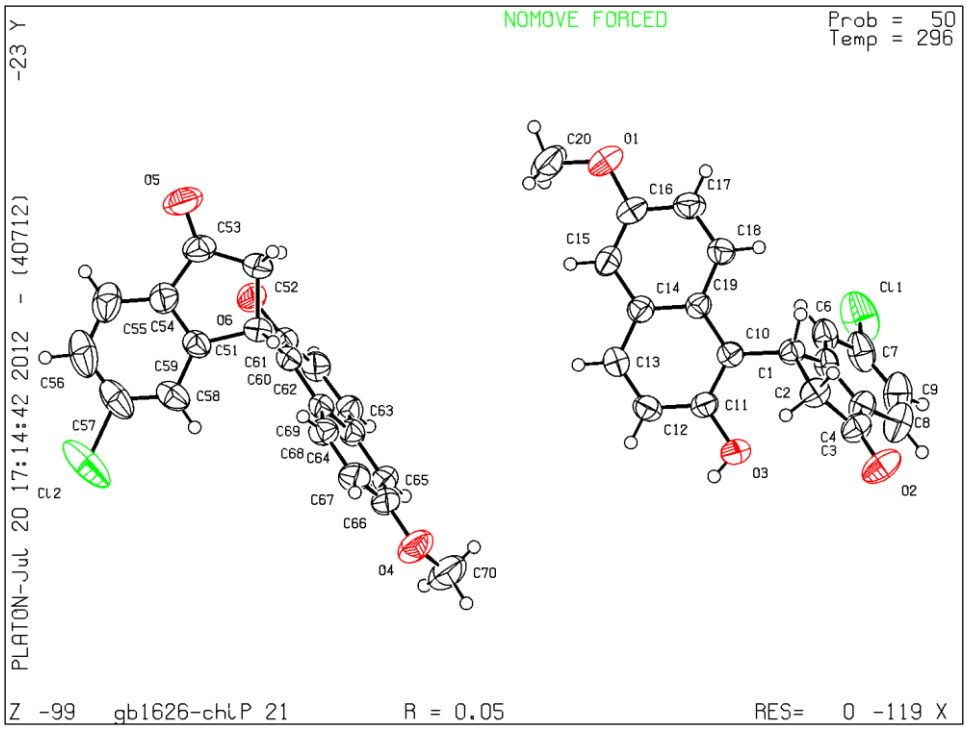


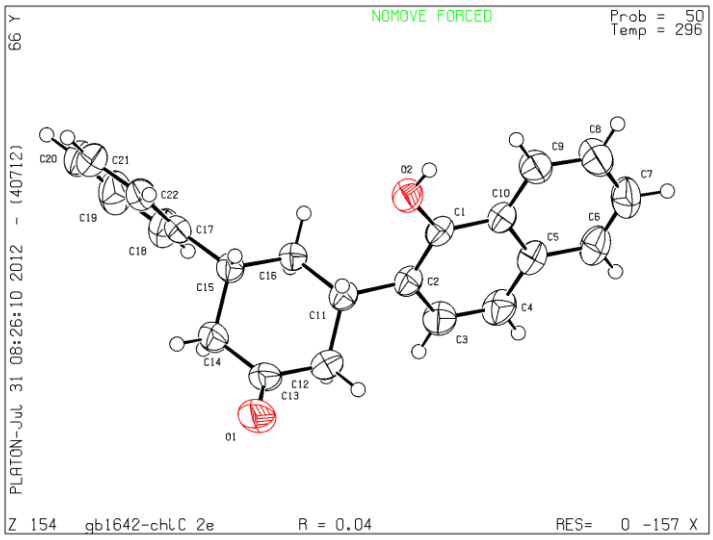
Figure S1: X-Ray structure of **266cd** Two different conformations with the same *S* absolute configuration represent the asymmetric unity.

Crystal data for 266cd



Molecular formula: $\mathbf{C}_{20}H_{15}ClO_4$, MW 338.77. Monoclinic, space group $P2_1$, a = 8.6325(13), b = 8.6693(13), c = 22.017(3), β = 92.146(2). V = 1646.6(4) Å^3, T = 298(2) °K, Z = 4, ρ_c = 1.367 g cm^{-3}, F(000) = 2762, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.247 mm^{-1}, colorless sticks (0.40 × 0.15 × 0.10 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9078 – 0.9758), 2400 frames, exposure time 20 s, 1.85 ≤ θ ≤ 27.40, −11≤ h ≤ 11, −11 ≤ k ≤ 11, −28 ≤ l ≤ 28, 7373 reflections collected, 5444 independent (R_{int} = 0.0277), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97), hydrogen atoms refined with a riding model except for the hydroxyl hydrogen that was experimentally located; data / restraints / parameters = 7373/ 1 / 441, $S(F^2)$ = 1.044, $R(F)$ = 0.0634 and $wR(F^2)$ = 0.1258 on all data, $R(F)$ = 0.0454 and $wR(F^2)$ = 0.1124 for 5444 reflections with $F_0 > 4\sigma(F_0)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0646P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.186 and −0.293 e Å^{-3}. Flack parameter: 0.02(6). The unit cell contains two different conformation belonging to the same chirality, that are different because of the different disposition of the OMe group. CCDC-893970 CIF file contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for 261ae

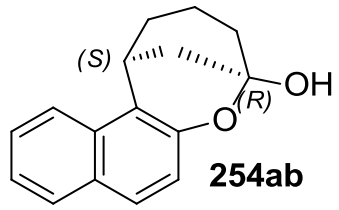


Molecular formula: $\mathbf{C}_{22}H_{20}ClO_2$, MW 316.38. Monoclinic, space group C2, a = 19.582(3), b = 6.4957(10), c = 15.898(2), β = 123.3630(10). V = 1688.9(4) Å^3, T = 298(2) °K, Z = 4, ρ_c = 1.244 g cm^{-3}, F(000) = 672, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.078 mm^{-1}, colorless plates (0.40 × 0.40 × 0.20 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9845 – 0.9694), 2400 frames, exposure time 15 s, 1.53 ≤ θ ≤ 27.49, –25≤ h ≤ 25, –8 ≤ k ≤ 8, –20 ≤ l ≤ 20, 9738 reflections collected, 3846 independent (R_{int} = 0.0201), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97), hydrogen atoms refined with a riding model except for the hydroxyl hydrogen that was experimentally located; data / restraints / parameters = 3846/ 1 / 221, $S(F^2)$ = 1.025, $R(F)$ = 0.0440 and $wR(F^2)$ = 0.0879 on all data, $R(F)$ = 0.0360 and $wR(F^2)$ = 0.827 for 3296 reflections with $F_0 > 4\sigma(F_0)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0379P)^2 + 0.3168P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.127 and –0.125 e Å^{-3}. Flack parameter: -0.6(11). CCDC-894320 CIF file contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the Friedel-Crafts alkylation-acetalization cascade of naphthols with α,β–unsaturated cyclic ketones

In a screw-capped vial equipped with a Teflon coated magnetic stir bar an anhydrous toluene solution of 9-amino(9-deoxy)*epi*-quinine **37a** (0.04 mmol, 0.2 eq., 20 mol%) and 2-hydroxy-5-nitrobenzoic acid (0.08 mmol, 0.4 eq., 40 mol%) was prepared under argon. After 5 min α,β-unsaturated ketone (0.2 mmol, 1 eq.) was added. The resulting yellow solution was stirred for further 5 minutes then β- or α-naphthol (0.22 mmol, 1.1 eq) was added and stirring was continued for 72 hours at 40 °C. the Then the septum was replaced, the vial was refilled with argon, and quickly closed with the screw-cap. The vial was placed at 40°C in a pre-heated oil bath and stirring was continued for 72 hours. Subsequently the reaction mixture was diluted with an 1:1 mixture of Et_2O/DCM, passed through a short plug of silica gel and solvent was evaporated in vacuo to give the crude product which was purified through flash chromatography on silica gel.

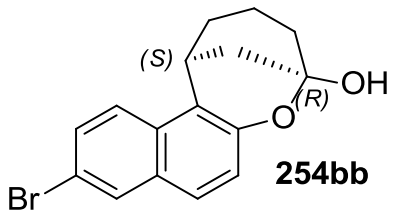
(1*S*,5*R*)-2,3,4,5-tetrahydro-1*H*-1,5-methanonaphtho[2,1-b]oxocin-5-ol 254ab:



254ab

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 80:20) as a white solid in 82% yield and 84% ee. **HPLC analysis**: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 95:5, flow rate 0.65 mL/min, T = 20 °C, λ = 230 nm, τ_{minor} = 20.0 min τ_{major} = 30.1 min. **$[\alpha]_D^{rt}$:** +106.7 (*c* 3.96, $CHCl_3$, 84% ee). **HRMS** calculated for $C_{16}H_{16}O_2$: 240.11503, found 240.11537. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 1.43 (tt, J_a = 13.7 Hz, J_b = 4.8 Hz, 1H), 1.55-1.66 (m, 1H), 1.74 (tt, J_a = 13.1 Hz, J_b = 3.8 Hz, 1H), 1.86 (td, J_a = 14.4 Hz, J_b = 5.5 Hz, 1H), 1.89-7.99 (m, 1H), 2.00-2.09 (m 1H), 2.11-2.20 (m, 1H), 2.19 (dd, J_a = 12.4 Hz, J_b = 2.9 Hz, 1H), 2.92 (bs, 1H), 3.86 (m, 1H), 7.07 (d, J = 8.2, 1H), 7.31 (td, J_a = 7.5 Hz, J_b = 1.1 Hz, 1H), 7.47 (td, J_a = 7.7 Hz, J_b = 1.5 Hz, 1H), 7.63 (d, J = 8.9, 1H), 7.76 (d, J = 8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 19.4 (CH_2), 29.8 (CH_2), 30.6 (CH), 36.3 (CH_2), 39.4 (CH_2), 98.3 (C), 116.3 (C), 117.7 (CH), 121.5 (CH), 123.0 (CH), 126.4 (CH), 128.1 (CH), 128.6 (CH), 128.9 (C), 131.4 (C), 153.0 (C).

(1*S*,5*R*)-10-bromo-2,3,4,5-tetrahydro-1*H*-1,5-methanonaphtho[2,1-b]oxocin-5-ol 254bb (Table 2, entry 2):

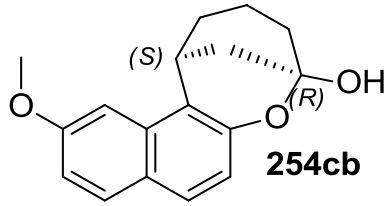


254bb

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 80:20) as a white solid in 58% yield and 82% ee. **HPLC analysis**: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 90:10, flow rate 0.65 mL/min, T = 20 °C, λ = 230 nm, τ_{minor} = 12.9 min τ_{major} = 15.1 min. **$[\alpha]_D^{rt}$:** +76.8 (*c* 0.6, $CHCl_3$, 82% ee). **HRMS** calculated for $C_{16}H_{15}BrO_2$: 318.02554, found 318.02526. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 1.38 (tq, J_a = 14.1 Hz, J_b = 4.4 Hz, 1H), 1.58-1.67 (m, 1H), 1.75 (tt, J_a = 13.2 Hz, J_b = 4.4 Hz, 1H), 1.84-1.93 (m, 2H), 2.02-2.08 (m, 1H), 2.17 (d, J = 13.5 Hz, 1H), 2.20 (dd, J_a = 12.3 Hz, J_b = 2.9 Hz, 1H), 2.9 (bs, 1H), 3.8 (m, 1H), 7.08 (d, J = 9.2, 1H),

7.51-7.56 (m, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 2.0 Hz, 1H). **^{13}C-NMR (150 MHz, $CDCl_3$):** *δ* 19.3 (CH_2), 29.8 (CH_2), 30.6 (CH), 36.1 (CH_2), 39.3 (CH_2), 98.4 (C), 116.5 (C), 116.6 (C), 118.8 (CH), 123.3 (CH), 127.2 (CH), 129.6 (CH), 130.0 (CH), 132.1 (C), 130.5 (C), 153.3 (C).

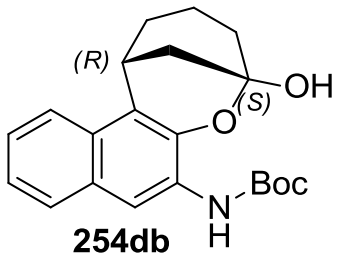
(1*S*,5*R*)-11-methoxy-2,3,4,5-tetrahydro-1*H*-1,5-methanonaphtho[2,1-b]oxocin-5-ol 254cb:



254cb

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 80:20) as a white solid in 82% yield and 78% ee. **HPLC analysis**: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 9:1, flow rate 0.65 mL/min, T = 20 °C, λ = 230 nm, τ_{minor} = 15.97 min τ_{major} = 24.92 min. **$[\alpha]_D^{rt}$:** +105 (*c* 1.10, $CHCl_3$, 78% ee). **HRMS** calculated for $C_{17}H_{18}O_3$: 270.125595, found 270.12562. **^{1}H-NMR (400 MHz, $CDCl_3$):** *δ* 1.34-1.49 (m, 1H), 1.55-1.67 (m, 1H), 1.73 (tt, J_a = 13.0 Hz, J_b = 3.8 Hz, 1H), 1.85 (dt, J_a = 13.4 Hz, J_b = 5.3 Hz, 1H), 1.90-1.99 (m, 1H), 2.0-2.09 (m, 1H), 2.11-2.22 (m, 2H), 3.06 (brs, 1H), 3.73-3.78 (m, 1H), 3.91 (s, 3H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, J_a = 8.7 Hz, J_b = 2.5 Hz, 1H), 7.11 (brd, *J* = 2.4 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** *δ* 19.4 (CH_2), 29.4 (CH_2), 30.8 (CH), 36.4 (CH_2), 39.4 (CH_2), 55.3 (CH_3), 98.2 (C), 101.0 (CH), 114.7 (CH), 115.2 (CH), 115.3 (C), 124.2 (C), 127.8 (CH), 130.1 (CH), 132.7 (C), 153.6 (C), 158.4 (C).

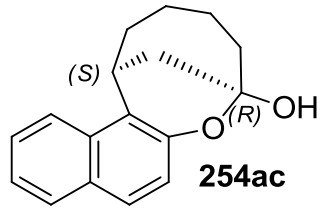
tert-butyl ((1*R*,5*S*)-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1,5-methanonaphtho[2,1-b]oxocin-7-yl)carbamate 254db:



254db

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/EtOAc 9:1) as a pink solid in 94% yield and 73% ee. **HPLC analysis**: Daicel Chiralpak AD-H column; Hex/i-PrOH 9:1, flow rate 0.7 mL/min, T = 25 °C, λ = 230 nm, τ_{minor} = 10.9 min τ_{major} = 15.3 min. **$[\alpha]_D^{rt}$:** -56.6 (c 1.39, $CHCl_3$, 73% ee). **HRMS** calculated for $C_{21}H_{25}NO_4$ 355.17836, found 355.17882. **^{1}H-NMR (400 MHz, $CDCl_3$):** *δ* 1.37 (tt, J_a = 13.6 Hz, J_b = 5.0 Hz, 1H), 1.58 (s, 10H), 1.72 (tt, J_a = 13.0 Hz, J_b = 3.8 Hz, 1H), 1.85 (td, J_a = 13.4 Hz, J_b = 5.2 Hz, 1H), 1.85-1.96 (m, 1H), 2.01-2.10 (m 1H), 2.14-2.22 (m, 1H) 2.21 (dd, J_a = 12.0 Hz, J_b = 3.2 Hz, 1H), 3.67 (bs, 1H), 3.78 (m, 1H), 7.27-7.41 (m, 3H) 7.66-7.77 (m, 2H), 8.41 (bs 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** *δ* 19.3 (CH_2), 28.4 (CH_3), 29.6 (CH_2), 30.7 (CH), 36.4 (CH_2), 39.2 (CH_2), 80.6 (C), 99.5 (C), 113.1 (CH), 116.1 (C), 121.0 (CH), 123.6 (CH), 124.6 (CH), 126.5 (C), 126.8 (C), 128.3 (CH), 129.2 (C), 143.0 (C), 152.8 (C).

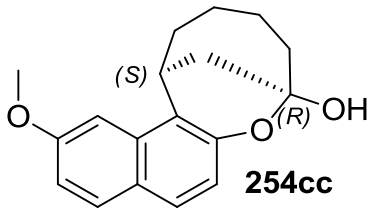
(8*R*,13*S*)-8,9,10,11,12,13-hexahydro-8,13-methanonaphtho[2,1-b]oxonin-8-ol 254ac:



254ac

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 85:15) to give a yellow solid in 57% yield and 73% ee. **HPLC analysis**: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 95:5, flow rate 0.65 mL/min, T = 20 °C, λ = 230 nm, τ_{minor} = 20.8 min τ_{major} = 33.1 min. **$[\alpha]_D^{rt}$:** +20.9 (c 0.54, $CHCl_3$, 73% ee). **HRMS** calculated for $C_{17}H_{18}O_2$ 254.13068, found 254.13044. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 1.42-1.68 (m, 4H), 2.00-2.31 (m, 5H), 2.58 (dd, J_a = 13.8 Hz, J_b = 1.7 Hz, 1H), 2.79 (s, 1H), 3.73 (m, 1H), 7.07 (d, J = 8.9 Hz, 1H), 7.34 (dt, J_a = 7.5 Hz, J_b = 1.1 Hz, 1H), 7.49 (dt, J_a = 8.3 Hz, J_b = 1.5 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 22.3 (CH_2), 25.1 (CH_2), 28.7 (CH), 33.8 (CH_2), 37.0 (CH_2), 43.0 (CH_2), 100.4 (C), 117.8 (C), 118.7 (CH), 122.3 (CH), 123.1 (CH), 126.3 (CH), 128.3(CH), 128.7(CH), 129.4 (C), 131.6 (C), 151.2 (C).

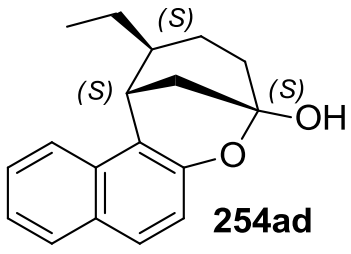
(8*R*,13*S*)-2-methoxy-8,9,10,11,12,13-hexahydro-8,13-methanonaphtho[2,1-b]oxonin-8-ol 254cc:



254cc

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 85:15) to give a yellow solid in 79% yield and 76% ee. **HPLC analysis**: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 9:1, flow rate 0.7 mL/min, T = 23 °C, λ = 230 nm, τ_{minor} = 16.0 min τ_{major} = 33.7 min. **$[\alpha]_D^{rt}$:** + 41.5 (*c* 0.54, $CHCl_3$, 76% ee). **HRMS** calculated for $C_{18}H_{20}O_3$ 284.14125, found 284.14163. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 1.54 (m, 4H), 2.04 (m, 2H), 2.19, (m, 3H), 2.54 (d, J = 14.4 Hz, 1H), 2.90 (br. s, 1H), 3.59, (m, 1H), 3.91 (s, 3H), 6.91 (d, J = 8.8 Hz, 1H), 7.00 (dd, J_a = 8.8 Hz, J_b = 2.6 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 22.6 (CH_2), 25.4 (CH_2), 29.1 (CH), 33.5 (CH_2), 37.3 (CH_2), 43.3 (CH_2), 55.5 (CH_3), 100.6 (C), 102.4 (CH), 114.9 (CH), 116.5 (CH), 117.2 (C), 124.9 (C), 128.3 (CH), 130.5 (CH), 152.1 (C), 158.5 (C).

(1*S*,2*S*,5*S*)-2-ethyl-2,3,4,5-tetrahydro-1*H*-1,5-methanonaphtho[2,1-b]oxocin-5-ol 254ad:

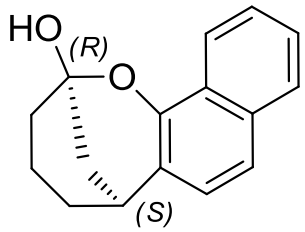


254ad

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 85:15) to give a yellow oil in 16% yield and 60% ee. **HPLC analysis**: Phenomenex Lux-Amilose 2 column; Hex/i-PrOH 85:15, flow rate 0.4 mL/min, T = 23°C, λ = 230 nm, τ_{minor} = 13.9 min τ_{major} = 15.7 min. **$[\alpha]_D^{rt}$:** + 6.7 (*c* 0.285; $CHCl_3$, 60% ee). **HRMS** calculated for $C_{18}H_{20}O_2$ 268.14633, found

268.14658. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 1.11 (t, J = 7.6 Hz, 3H), 1.43 (m, 1H), 1.67, (m, 3H), 1.84 (m, 1H), 1.96 (dd, J_a = 4.0 Hz, J_b = 1.4 Hz, 1H), 2.00 (dd, J_a = 5.34 Hz, J_b = 2.5 Hz, 1H), 2.34 (dd, J_a = 12.7 Hz, J_b = 2.9 Hz, 1H), 2.88 (s, 1H), 3.69 (s, 1H), 7.07 (d, J = 9.1 Hz, 1H), 7.31 (m, 1H), 7.47 (m, 1H), 7.63, (d, J = 9.0 Hz, 1H), 7.76 (d, J = 8.23 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H). **^{13}C-NMR (150 MHz, $CDCl_3$):** δ 12.6 (CH_3), 23.1 (CH_2), 24.2 (CH_2), 30.8 (CH_2), 34.0 (CH), 35.1 (CH_2), 39.0 (CH), 99.5 (C), 117.7 (CH), 117.8 (C), 121.3 (CH), 122.9 (CH), 126.4 (CH), 128.1 (CH), 128.7 (CH), 128.9 (C), 131.3 (C), 152.9 (C).

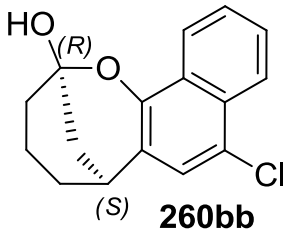
(2*R*,6*S*)-3,4,5,6-tetrahydro-2*H*-2,6-methanonaphtho[1,2-b]oxocin-2-ol 260ab:



260ab

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 85:15) to give a white solid in 73% yield and 96% ee. **HPLC analysis**: Phenomenex Lux-Amilose 2 column; Hex/i-PrOH 95:5, flow rate 0.65 mL/min, T = 20 °C, λ = 230 nm, τ_{minor} = 14.5 min τ_{major} = 16.1 min. **$[\alpha]_D^{rt}$:** -28.9 (c 3.60, $CHCl_3$, 96% ee). **HRMS** calculated for $C_{16}H_{16}O_2$ 240.11503, found 240.11537. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 1.33-1.47 (m, 1H), 1.54-1.63 (m, 1H), 1.67-1.81 (m, 2H) 1.85 (dt, 1H, J_a = 13.7 Hz, J_b = 5.5 Hz), 2.05 (m, 1H), 2.14 (dd, 1H, J_a = 12.2 Hz, J_b = 2.6 Hz), 2.18 (d, 1H, J = 13.3 Hz), 2.98 (bs, 1H), 3.28 (m, 1H), 7.11 (d, 1H, J = 8.2), 7.33 (d, 1H, J = 8.2), 7.44 (m, 2H), 7.75 (m, 1H), 8.21 (m, 1H). **^{13}C-NMR (150 MHz, $CDCl_3$):** δ 18.7 (CH_2), 31.5 (CH_2), 35.3 (CH), 36.5 (CH_2), 39.1 (CH_2), 99.1 (C), 118.5 (C), 119.4 (CH), 121.7 (CH), 123.8 (C), 125.7 (CH), 125.7 (CH), 126.1 (CH), 127.4 (CH), 133.5 (C), 150.3 (C).

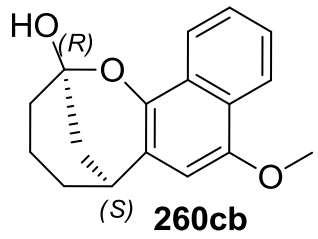
(2*R*,6*S*)-8-chloro-3,4,5,6-tetrahydro-2H-2,6-methanonaphtho[1,2-b]oxocin-2-ol 260bb:



260bb

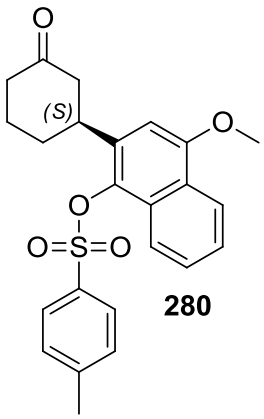
The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 80:20) to give a white solid in 91% yield and 93% ee. **HPLC analysis**: Daicel Chiralpak AD-H column; Hex/i-PrOH 95:5, flow rate 0.7 mL/min λ = 214 nm, τ_{major} = 18.27 min, τ_{minor} = 19.37 min. **$[\alpha]_D^{rt}$:** -14.99 (c 0.99, $CHCl_3$, 93% ee). **HRMS** calculated for $C_{16}H_{15}O_2Cl$ 274.076059, found 274.07611. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 1.29-1.46 (m, 1H), 1.53-1.64 (m, 1H), 1.64-1.78 (m, 2H), 1.84 (dt, 1H, J_a = 13.6 Hz, J_b = 5.3 Hz), 2.00-2.23 (m, 3H), 3.17-3.23 (m, 1H), 3.23-3.25 (brs, 1H), 7.16 (s, 1H), 7.49 (m, 1H), 7.55 (m, 1H), 8.15 (m, 1H), 8.22 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 18.6 (CH_2), 31.3 (CH_2), 35.1 (CH), 36.2 (CH_2), 39. (CH_2), 99.3 (C), 118.9 (C), 122.0 (C), 122.1 (CH), 124.1 (CH), 124.7 (C), 125.7 (CH), 125.8 (CH), 126.7 (CH), 130.2 (C), 149.4 (C).

(2*R*,6*S*)-8-methoxy-3,4,5,6-tetrahydro-2*H*-2,6-methanonaphtho[1,2-b]oxocin-2-ol 260cb (Table 3, entry 3):



260cb

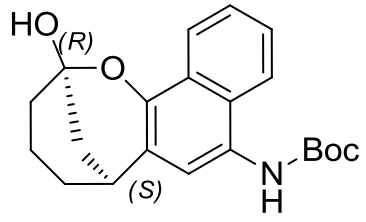
The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 70:30) to give a white solid in 95% yield and 92% ee. **HPLC analysis**: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 87:13, flow rate 0.7 mL/min, T = 15 °C, λ = 230 nm, τ_{minor} = 10.63 min τ_{major} = 17.68 min. **HRMS** calculated for $C_{17}H_{18}O_3$ 270.125595, found 270.12566. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 1.25-1.40 (m, 1H), 1.43-1.52 (m, 1H), 1.55-1.80 (m, 3H), 1.93-2.02 (m, 2H), 2.02-2.07 (m, 1H), 3.04-3.10 (m, 1H), 3.14 (brs, 1H), 3.84 (s, 3H), 6.31 (s, 1H), 7.31-7.42 (m, 2H), 8.03-8.10 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 18.8 (CH_2), 31.3 (CH_2), 35.8 (CH), 36.6 (CH_2), 39.2 (CH_2), 55.7 (CH_3), 98.6 (), 104.0 (CH), 117.4 (C), 121.4 (CH), 121.6 (CH), 124.4 (C), 125.0 (CH), 125.1 (C), 125.7 (CH), 144.0 (C), 148.8 (C).



280

Compound **260cb** (50 mg, 0.185 mmol) has been reacted with TsCl (70.54 mg, 0.37 mmol, 2 equiv) in the presence of Et_3N (52 μL, 0.37 mmol, 2 equiv.) and DMAP (50% mol, 0.0925 mmol, 11.30 mg) in 4 ml of dichloromethane for 2 days. The reaction mixture was poured into water (10 ml) and extracted 2 times with 10 ml of dichloromethane. After evaporation of the solvent compound **280** was obtained in 50 yield. **$[\alpha]_D^{rt}$:** -40.5 (*c* 0.44, $CHCl_3$, 92% ee). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 1.51-1.71 (m, 1H), 1.73-1.90 (m, 1H), 1.96-2.17 (m, 2H), 2.27-2.53 (m, 7H), 3.41 (m, 1H), 4.02 (s, 3H), 6.67 (s, 1H), 7.33-7.39 (m, 2H), 7.39-7.47 (m, 2H), 7.75-7.82 (m, 1H), 7.82-7.88 (m, 2H), 8.15-8.22 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 21.7 (CH_3), 25.4 (CH_2), 31.8 (CH_2), 38.2 (CH), 41.1 (CH_2), 47.6 (CH_2), 55.7 (CH_3), 101.1 (CH), 121.9 (CH), 122.7 (CH), 125.3 (C), 125.7 (CH), 127.3 (CH), 128.2 (CH), 128.8 (C), 130.0 (CH), 133.7 (C), 134.1 (C), 135.9 (C), 145.5 (C), 154.6 (C), 209.9 (C).

tert-butyl ((2R,6S)-2-hydroxy-3,4,5,6-tetrahydro-2H-2,6-methanonaphtho[1,2-b]oxocin-8-yl)carbamate 260db:

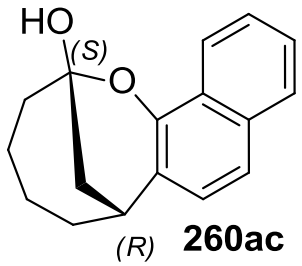


260db

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst and the title compound was obtained in 58% yield determined by ^{1}H-NMR using CH_2Br_2 as internal standard. Compound **260db** was purified by flash chromatography on silica gel (eluent mixture Hex/Et_2O 60:40) to give a pink solid in 87% ee. Further purification was carried out through preparative HPLC (AD-H column, Hex/i-PrOH 8:2, flow rate 20 mL/min) to give a white solid. **HPLC analysis**: Daicel Chiralpak AD-H column; Hex/i-PrOH 8:2, flow rate 1 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 8.6 min, τ_{minor} = 13.3 min. **$[\alpha]_D^{rt}$:** - 11.0 (*c* 0.82, $CHCl_3$, 87% ee). **HRMS** calculated for $C_{21}H_{25}NO_4$ 355.17836, found 355.17882. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 1.42 (tt, 1H, J_a = 13.5 Hz, J_b = 4.5 Hz), 1.54 (s, 10H), 1.70 (tt, 1H, J_a = 13.5 Hz, J_b = 3.7 Hz), 1.79-1.86 (m, 1H), 1.84 (td, 1H, J_a = 13.1 Hz, J_b = 5.3 Hz), 2.01-2.06 (m, 1H), 2.11-2.19 (m, 2H), 2.96 (s, 1H), 3.28 (m, 1H), 6.56 (s, 1H), 7.39-7.54 (m, 3H), 7.80 (d,

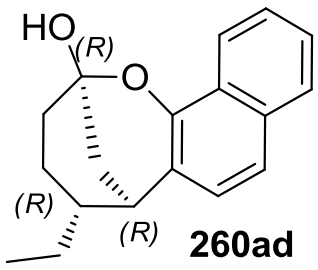
1H, *J* = 8.7 Hz), 8.24 (d, 1H, *J* = 8.1 Hz). **^{13}C-NMR (100 MHz, $CDCl_3$):** *δ* 17.8 (CH_2), 27.4 (CH_3), 30.3 (CH_2), 34.3 (CH), 35.5 (CH_2), 38.1 (CH_2), 79.3 (C), 98.1 (C), 117.2 (C), 119.8 (C), 121.3 (CH), 122.4 (C), 123.0 (C), 123.9 (C), 124.2 (2×CH), 125.0 (2 CH), 146.9 (C).

(2*S*,7*R*)-2,3,4,5,6,7-hexahydro-2,7-methanonaphtho[1,2-b]oxonin-2-ol 260ac:



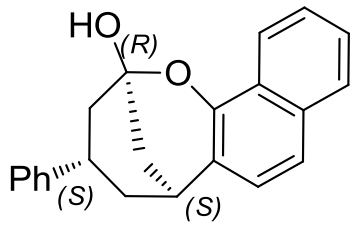
The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was obtained in 34% yield determined by ^{1}H-NMR using CH_2Br_2 as internal standard together with a 8% of Friedel-Crafts alkylation compound. Compound **260ac** was purified from crude mixture by flash chromatography on silica gel (eluent mixture Hex/Et_2O 8:2) in 90% ee. **HPLC analysis:** Phenomenex Lux-Amilose 2 column; Hex/i-PrOH 95:5, flow rate 0.7 mL/min, T = 20 °C, λ = 230 nm, τ_{minor} = 30.3 min τ_{major} = 34.5 min. **$[\alpha]_D^{rt}$:** +48.0 (*c* 0.375; $CHCl_3$, 90% ee). **HRMS** *calcd.* for $C_{16}H_{16}O_2$ 240.11503, found 240.11537. **^{1}H NMR (300 MHz, $CDCl_3$) of 5ca with traces of Friedel-Crafts alkylation compound:** *δ* 1.29-1.38 (m, 1H), 1.49-1.55 (m 2H), 1.61-1.71 (m, 1H), 1.83-1.93 (m 1H), 2.03-2.09 (m, 1H), 2.09-2.17 (m, 1H), 2.17-2.25 (m, 2H), 2.58 (d, 1H, *J* = 13.6 Hz), 2.99 (bs, 1H), 2.25 (m, 1H), 7.23 (d, 1H, *J* = 8.1 Hz), 7.40 (d, 1H, *J* = 8.2 Hz), 7.43-7.48 (m, 2H), 7.75-7.79 (m, 1H), 8.22-8.27 (m, 1H). **^{13}C-NMR (150 MHz, $CDCl_3$) of 5ca with traces of Friedel-Crafts alkylation compound:** *δ* 22.0 (CH_2), 25.0 (CH_2), 32.3 (CH), 34.3 (CH_2), 37.0 (CH_2), 42.4 (CH_2), 100.3 (C), 118.5 (C), 119.1 (CH), 120.8 (CH), 124.1 (C), 124.2 (CH), 124.8 (C), 125.3 (CH), 126.3 (CH), 132.3 (C), 147.4 (C).

(2*R*,5*R*,6*R*)-5-ethyl-3,4,5,6-tetrahydro-2H-2,6-methanonaphtho[1,2-b]oxocin-2-ol 260ad:

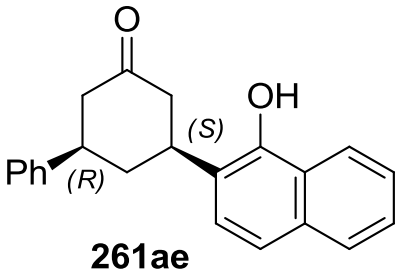


The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 9:1) to give a yellow oil in 27%and 89% ee. **HPLC analysis**: Daicel Chiralcel OJ-H; flow rate 0.7 ml/min, Hex/i-PrOH 9:1, λ = 230 nm, 23°C, τ_{minor} = 24.5 min τ_{major} = 32.3 min. **$[\alpha]_D^{rt}$:** -60.1 (*c* 0.27; $CHCl_3$, 89% ee). **HRMS** calculated for $C_{18}H_{20}O_2$ 268.14633, found 268.14658. **^{1}H-NMR (400 MHz, $CDCl_3$):** *δ* 1.04 (t, 3H, *J* = 7.6 Hz), 1.48-1.46 (m, 1H), 1.48-1.70 (m, 5H), 1.85-1.91 (m, 1H), 1.96-2.02 (m, 2H), 2.28 (dd, 1H, J_a = 12.6 Hz, J_b = 2.7 Hz), 2.95 (s, 1H), 3.10 (m, 1H), 7.14 (d, 1H, *J* = 8.2 Hz), 7.35 (d, 1H, *J* = 8.2 Hz), 7.41-7.49 (m, 2H), 7.74-7.79 (m, 1H), 8.20-8.25 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** *δ* 12.7 (CH_3), 22.1 (CH_2), 24.2 (CH_2), 31.2 (CH_2), 34.7 (CH_2), 39.1 (CH), 41.2 (CH), 99.2 (C), 119.4 (CH), 120.2 (C), 121.6 (CH), 123.8 (C), 125.0 (CH), 125.6 (CH), 126.1 (CH), 127.4 (CH), 133.4 (C), 150.1 (C).

(2*R*,4*S*,6*S*)-4-phenyl-3,4,5,6-tetrahydro-2*H*-2,6-methanonaphtho[1,2-b]oxocin-2-ol 260ae and (3*S*,5*R*)-3-(1-hydroxynaphthalen-2-yl)-5-phenylcyclohexanone 261ae:



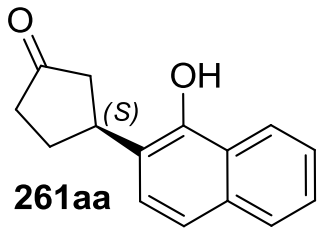
260ae



261ae

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. Compounds **260ae** and **261ae** were isolated after 5 days by flash chromatography on silica gel (eluent mixture Hex/Et_2O 70:30) in 26% yield and 93% ee and 31% yield and 98% ee respectively (57% overall yield). **HPLC analysis:** for compound **260ae** Daicel Chiralpak AD-H column; Hex/i-PrOH 95:5, flow rate 0.75 mL/min λ = 214 nm, τ_{major} = 32.69 min, τ_{minor} = 35.13 min; for compound **261ae** Daicel Chiralpak AD-H column; Hex/i-PrOH 80:20, flow rate 0.75 mL/min λ = 214 nm, τ_{major} = 14.39 min, τ_{minor} = 16.19 min. $\mathbf{[\alpha]_D^{rt}}$ for **260ae**: -133.8 (*c* 0.447; $CHCl_3$, 93% ee); $\mathbf{[\alpha]_D^{rt}}$ for **261ae**: +19.2 (*c* 0.47; $CHCl_3$, 98% ee). **HRMS** *calcd.* for $C_{22}H_{20}O_2$ 316.14633, found 316.14661. **^{1}H-NMR (400 MHz, $CDCl_3$) 260ae:** *δ* 1.92 (dt, 1H, J_a = 12.7 Hz, J_b = 3.2 Hz), 2.02-2.19 (m, 3H), 2.27 (dd, 1H, J_a = 12.3 Hz, J_b = 2.8 Hz), 2.38-2.46 (m, 1H), 2.84 (m, 1H), 3.13 (brs, 1H), 3.36-3.42 (m, 1H), 7.08-7.13 (m, 2H), 7.14-7.19 (m, 2H), 7.21-7.25 (m, 2H), 7.38 (d, 1H, *J* = 8.3 Hz), 7.44-7.51 (m, 2H), 7.77-7.82 (m, 1H), 8.23-8.29 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$) 260ae:** *δ* 35.3 (CH), 36.1 (CH_2), 36.5 (CH), 39.6 (CH_2), 46.4 (CH_2), 99.3 (C), 118.9 (C), 119.7 (CH), 121.7 (CH), 123.8 (C), 125.2 (CH), 125.8 (CH), 126.0 (CH), 126.3 (CH), 127.0 (CH), 127.4 (CH), 128.4 (CH), 133.6 (C), 144.3 (C), 150.1 (C). **^{1}H-NMR (400 MHz, $CDCl_3$) 261ae:** *δ* 2.20-2.35 (m, 2H), 2.60-2.80 (m, 4H), 3.21 (m, 1H), 3.74 (m, 1H), 5.93 (brs, 1H), 7.21-7.31 (m, 3H), 7.32-7.42 (m, 3H), 7.43-7.54 (m, 3H), 7.81 (m, 1H), 8.01 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$) 261ae:** *δ* 37.3 (CH), 39.3 (CH_2), 44.0 (CH), 47.3 (CH_2), 48.6 (CH_2), 120.1 (CH), 121.1 (CH), 123.9 (C), 124.1 (CH), 124.5 (C), 125.8 (CH), 125.9 (CH), 126.6 (CH), 126.9 (CH), 128.1 (CH), 128.8 (CH), 133.3 (CH), 143.9 (CH), 147.6 (CH), 210.8 (C).

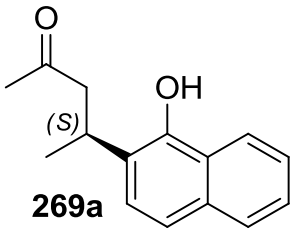
(*S*)-3-(1-hydroxynaphthalen-2-yl)cyclopentanone 261aa:



261aa

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinine **37a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 70:30) to give a yellow solid in a 63% yield and 90% ee. **HPLC analysis:** Daicel Chiralpak AS-H; Hex/i-PrOH 85:15, flow rate 0.7 ml/min, λ = 230 nm, 25°C, τ_{major} = 23.1 min, τ_{minor} = 29.2 min. **$\mathbf{[\alpha]_D^{rt}}$:** -56.0 (*c* 0.67; $CHCl_3$, 90% ee). **HRMS** *calcd.* for $C_{16}H_{16}O_2$ 226.09938, found 226.09952. **^{1}H-NMR (400 MHz, $CDCl_3$):** *δ* 2.06-2.30 (m, 2H), 2.30-2.60 (m, 4H), 2.75 (dd, 2H, J_a = 17.8 Hz, J_b = 7.8 Hz), 3.84-3.98 (m, 1H), 5.51 (s, 1H), 7.35 (d, 1H, *J* = 8.6 Hz), 7.44-7.57, (m, 3H), 7.84 (d, 1H, *J* = 8.1 Hz), 7.99 (dm, 1H, *J* = 8.1 Hz). **^{13}C-NMR (100 MHz, $CDCl_3$):** *δ* 28.7 (CH_2), 34.2, 35.4 (CH_2), 35.9, 37.8 (CH_2), 37.9, 39.2, 43.8 (CH_2), 118.7 (CH), 120.0 (CH), 120.4 (C), 122.0 (C), 123.3 (C), 123.4 (CH), 124.1, 124.4, 124.6, 124.8 (CH), 126.5, 127.2 (CH), 132.9 (CH), 147.2 (C), 218.2 (C).

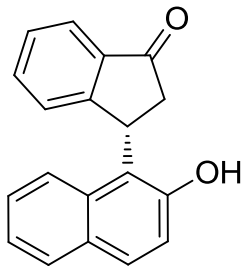
(*S*)-4-(1-hydroxynaphthalen-2-yl)pentan-2-one 269a:



269a

The reaction was performed following the general procedure using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hex/Et_2O 70:30) to give a yellow solid in 71% yield and 44% ee. **HPLC analysis:** Daicel Chiralpak AD-H; flow rate 0.7 ml/min, Hex/i-PrOH 96:4, λ = 230 nm, 25°C, τ_{major} = 47.7 min, τ_{minor} = 52.5 min. **$[\alpha]_D^{rt}$:** + 25 (*c* 1.39; $CHCl_3$, 44% ee). **HRMS** *calcd.* for $C_{16}H_{16}O_2$ 228.11503, found 228.11533. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 1.39 (d, 3H, J = 7.4 Hz), 2.13 (s, 3H), 2.73 (dd, 1H, J_a = 16.6 Hz, J_b = 8.7 Hz), 2.89 (dd, 1H, J_a = 16.5 Hz, J_b = 5.2 Hz), 4.12 (m, 1H), 5.65 (s, 1H), 6.77 (d, 1H, J_a = 7.6 Hz), 7.18 (d, 1H, J = 7.5 Hz), 7.45-7.60 (m, 2H), 8.10 (d, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.3 Hz). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 21.4 (CH_3), 29.3 (CH), 30.4 (CH_3), 51.8 (CH_2), 108.0 (CH), 122.4 (CH), 122.5 (CH), 122.6 (C), 122.9 (CH), 124.8 (CH), 124.9 (C), 126.5 (CH), 132.1 (C), 134.3 (C), 150.1 (C), 208.5 (C).

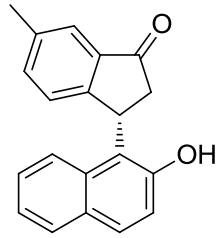
(S)-3-(2-hydroxynaphthalen-1-yl)-2,3-dihydro-1H-inden-1-one 266aa:



266aa

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/AcOEt 80:20) as a white solid in 63% yield and 95% ee. **HPLC analysis**: Daicel Chiralcel OD-H, Hex/i-PrOH 90:10, flow rate 0.7 ml/min, λ = 254 nm: τ_{major} = 16.32 min, τ_{minor} = 21.18 min. **HRMS** calculated for $C_{19}H_{14}O_2$ 274.09938, found 274.09907. **$[\alpha]_D^{rt}$** = -118.9 (*c* 0.45; DMSO, 95% ee). **^{1}H-NMR (400 MHz, DMSO d_6):** 70:30 mixture of conformational diastereosiomers *A* (major) and *B* (minor); δ 2.84 (dd, J_a = 19.4 Hz, J_b = 5.0 Hz, $1H_B$), 2.95 (dd, J_a = 18.6 Hz, J_b = 3.4 Hz, $1H_A$), 3.08 (dd, J_a = 18.6 Hz, J_b = 8.2 Hz, $1H_A$), 3.19 (dd, J_a = 19.2 Hz, J_b = 8.3 Hz, $1H_B$), 5.51 (m, $1H_A$), 5.70 (m, $1H_B$), 6.77 (d, J = 9.0 Hz, $1H_B$), 7.0 (dd, J_a = 16.7 Hz, J_b = 7.7 Hz, $2H_A$), 7.05-7.09 (m, $2H_B$), 7.12-7.16 (m, $1H_B$), 7.30 (d, J = 9.1 Hz, $1H_B$), 7.32-7.41 (m, $2H_A$), 7.43-7.52 (m, $1H_A$ + $1H_B$), 7.53-7.58 (m, $1H_A$ + $1H_B$), 7.67 (d, J = 7.7 Hz, $1H_A$), 7.71 (d, J = 8.7 Hz, $1H_A$), 7.75 (d, J = 8.9 Hz, $1H_B$), 7.77 (d, J = 8.1 Hz, $1H_B$), 7.81 (d, J = 7.6 Hz, $1H_B$), 7.84 (d, J = 8.2 Hz, $1H_A$), 8.38 (d, J = 8.7 Hz, $1H_A$). 9.43 (s, $1H_A$), 10.08 (s, $1H_B$). **^{13}C-NMR (100 MHz, DMSO d_6):** δ 34.55 (CH), 35.5 (CH), 42.8 (CH_2), 43.4 (CH_2), 117.6 (CH), 117.9 (C), 118.6 (CH), 119.6 (C), 122.0 (CH), 122.1 (CH), 122.2 (CH), 122.4 (CH), 122.4 (CH), 123.2 (CH), 125.3 (CH), 125.6 (CH), 125.8 (CH), 126.7 (CH), 126.8 (CH), 127.4 (CH), 128.1 (C), 124.4 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 131.6 (C), 133.6 (C), 134.4 (CH), 135.3 (CH), 136.3 (C), 136.6 (C), 152.6 (C), 153.6 (C), 158.8 (C), 159.6 (C), 205.2 (C), 206.3 (C).

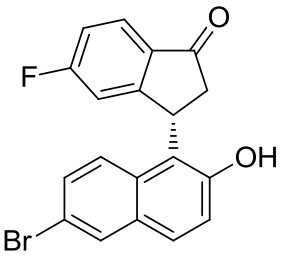
(*S*)-3-(2-hydroxynaphthalen-1-yl)-6-methyl-2,3-dihydro-1*H*-inden-1-one 266ab:



266ab

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/AcOEt 80:20) as a white solid in 97% yield and 90% ee. **HPLC analysis**: Daicel Chiralcel OJ-H, Hex/i-PrOH 90:10, flow rate 1.0 ml/min, λ = 254 nm: τ_{minor}= 26.63 min, τ_{major} = 35.26 min. **HRMS** calculated for $C_{20}H_{16}O_2$ 288.11503, found 288.11535. $[\alpha]_D^{rt}$ = -288.3 (*c* 0.80; DMSO, 90% ee). **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** 65:35 mixture of conformational diastereosiomers *A* (major) and *B* (minor); *δ* 2.35 (s, 3H$_A$), 2.38 (s, 3H$_B$), 2.83 (dd, J_a = 19.3 Hz, J_b = 4.9 Hz, 1H$_B$), 2.96 (dd, J_a = 18.4 Hz, J_b = 3.6 Hz, 1H$_A$), 3.06 (dd, J_a = 18.6 Hz, J_b = 7.9 Hz, 1H$_A$), 3.13-3.23 (m, 1H$_B$), 5.44 (m, 1H$_A$), 5.66 (m, 1H$_B$), 6.80 (d, *J* = 8.4 Hz, 1H$_B$), 6.91 (d, *J* = 7.8 Hz, 1H$_A$), 6.96 (d, *J* = 7.8 Hz, 1H$_B$), 7.00 (d, *J* = 8.7 Hz, 1H$_A$), 7.03-7.09 (m, 1H$_B$), 7.10-7.16 (m, 1H$_B$), 7.26-7.40 (m, 1H$_A$ + 2H$_B$), 7.47 (s, 1H$_A$), 7.49-7.57 (m, 1H$_A$), 7.60 (s, 1H$_B$), 7.66-7.79 (m, 1H$_A$), 7.80-7.86 (m, 1H$_A$), 8.36 (d, *J* = 8.5 Hz, 1H$_A$), 9.41 (brs, 1H$_A$), 10.06 (brs, 1H$_B$). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** mixture of conformers *δ* 20.5 (CH_3), 20.6 (CH_3), 30.7 (CH), 34.2 (CH), 43.1 (CH_2), 43.7 (CH_2), 117.7 (C), 117.9 (CH), 118.7 (CH), 119.8 (C), 122.0 (CH), 122.1 (CH), 122.2 (CH), 122.4 (CH), 122.5 (CH), 123.1 (CH), 125.0 (CH), 125.3 (CH), 125.8 (CH), 126.7 (CH), 128.1 (C), 128.3 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 131.7 (C), 133.6 (C), 135.4 (CH), 136.2 (C), 136.4 (CH), 136.5 (C), 136.9 (C), 153.0 (C), 153.6 (C), 156.2 (C), 157.0 (C), 205.1 (C), 206.3 (C).

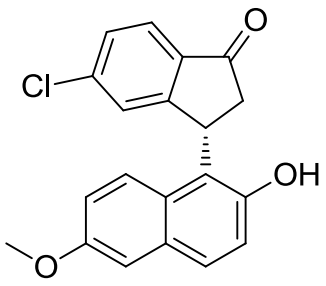
(*S*)-3-(6-bromo-2-hydroxynaphthalen-1-yl)-5-fluoro-2,3-dihydro-1H-inden-1-one 266bc:



266bc

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/AcOEt 70:30) as a white solid in 83% yield and 90% ee. **HPLC analysis**: Daicel Chiralcel OD-H, Hex/i-PrOH 95:5, flow rate 0.7 ml/min, λ = 214 nm: τ_{major} = 28.23 min, τ_{minor} = 33.48 min. **ESI-MS:** 393 (M + Na)$^+$, 395 (M + Na)$^+$. $[\alpha]_D^{rt}$ = -205.4 (*c* 0.91, DMSO, 90% ee). **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** 73.5:26.5 mixture of conformational diastereosiomers *A* (major) and *B* (minor); *δ* 2.82 (dd, J_a = 19.3 Hz, J_b = 5.1 Hz, 1H$_B$), 2.90 (dd, J_a = 18.5 Hz, J_b = 3.5 Hz, 1H$_A$), 3.11 (dd, J_a = 18.4 Hz, J_b = 8.1 Hz, 1H$_A$), 3.21 (dd, J_a = 19.2 Hz, J_b = 8.2 Hz, 1H$_B$), 5.45 (m, 1H$_A$), 5.68 (m, 1H$_B$), 6.70 (d, *J* = 9.3 Hz, 1H$_B$), 6.74-6.84 (m, 1H$_A$ + 1H$_B$), 7.07 (d, *J* = 8.9 Hz, 1H$_A$), 7.21 (m, 1H$_A$), 7.26-7.38 (m, 2H$_B$), 7.62 (dd, J_a = 9.2 Hz, J_b = 2.2 Hz, 1H$_A$), 7.70-7.78 (m, 2H$_A$ + 1H$_B$), 7.88 (dd, J_a = 8.6 Hz, J_b = 5.4 Hz, 1H$_B$), 8.06 (d, *J* = 2.1 Hz, 1H$_B$), 8.10 (d, *J* = 2.2 Hz, 1H$_A$), 8.30 (d, *J* = 9.4 Hz, 1H$_A$), 9.75 (brs, 1H$_A$ + 1H$_B$). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** mixture of conformers *δ* 34.5 (CH), 35.6 (CH), 43.2 (CH_2), 43.7 (CH_2), 111.7 (d, CH, J_{C-F} = 22.3 Hz), 111.9 (d, CH, J_{C-F} = 22.3 Hz), 114.9 (d, CH, J_{C-F} = 23.4 Hz), 115.3 (C), 115.8 (d, CH, J_{C-F} = 23.4 Hz), 117.3 (C), 119.1 (CH), 119.4 (C), 119.8 (CH), 124.5 (CH), 124.7 (CH), 125.0 (d, CH, J_{C-F} = 10.2 Hz), 126.2 (d, CH, J_{C-F} = 10.8 Hz), 128.0 (CH), 128.7 (d, CH, J_{C-F} = 34.6 Hz), 129.4 (C), 129.5 (CH), 130.2 (CH), 130.3 (d, C, J_{C-F} = 32.5 Hz), 130.9 (C), 132.2 (C), 133.1 (C), 133.4 (d, C, J_{C-F} = 1.5 Hz), 153.6 (C), 154.3 (C), 161.9 (d, C, J_{C-F} = 9.7 Hz), 162.4 (d, C, J_{C-F} = 9.6 Hz), 165.1 (C), 165.6 (C), 167.6 (C), 168.1(C), 203.1(C), 204.2(C).

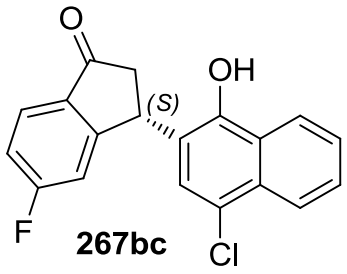
(*S*)-5-chloro-3-(2-hydroxy-6-methoxynaphthalen-1-yl)-2,3-dihydro-1H-inden-1-one 266cd:



266cd

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/Et_2O 70:30) as a white solid in 84% yield and 81% ee. **HPLC analysis**: Daicel Chiralpak AD-H, Hex/i-PrOH 90:10, flow rate 0.75 ml/min, λ = 254 nm: τ_{minor} = 23.19 min, τ_{major} = 25.66 min. **HRMS** calculated for $C_{20}H_{15}O_3Cl_1$ 338.070974, found 338.07133. $\mathbf{[\alpha]_D^{rt}}$ determined on the product obtained in the reaction with 9-amino(9-deoxy)*epi*-quinine **A** as catalyst = +141.5 (*c* 0.9; DMSO, 78% ee). **^{1}H-NMR (400 MHz, DMSO-d_6):** 75:25 mixture of conformational diastereosiomers *A* (major) and *B* (minor); δ 2.83 (dd, J_a = 19.3 Hz, J_b = 4.9 Hz, $1H_B$), 2.93 (dd, J_a = 18.6 Hz, J_b = 3.5 Hz, $1H_A$), 3.10 (dd, J_a = 18.6 Hz, J_b = 8.1 Hz, $1H_A$), 3.21 (dd, J_a = 19.4 Hz, J_b = 8.4 Hz, $1H_B$), 3.75 (s, $3H_B$), 3.86 (s, $3H_A$), 5.45 (m, $1H_A$), 5.68 (m, $1H_B$), 6.67 (d, J = 9.3 Hz, $1H_B$), 6.81 (dd, J_a = 9.3 Hz, J_b = 2.6 Hz, $1H_B$), 6.95-7.04 (m, $2H_A$ + $1H_B$), 7.17-7.32 (m, $2H_A$ + $2H_B$), 7.43 (dd, J_a = 8.2 Hz, J_b = 1.9 Hz, $1H_A$), 7.51 (m, $1H_B$), 7.60-7.71 (m, $2H_A$ + $1H_B$), 7.81 (d, J = 8.3 Hz, $1H_B$), 8.26 (d, J = 9.5 Hz, $1H_A$), 9.26 (s, $1H_A$), 9.88 (s, $1H_B$). **^{13}C-NMR (100 MHz, DMSO-d_6):** mixture of conformers δ 34.5 (CH), 35.6 (CH), 43.1 (CH_2), 43.6 (CH_2), 54.9 (CH), 55.1 (CH), 107.0 (CH), 108.0 (CH), 117.2 (C), 118.1 (CH), 118.4 (CH), 119.0 (CH), 119.1 (CH), 119.4 (C), 123.6 (C), 123.7 (CH), 124.0 (CH), 125.0 (CH), 125.1 (C), 125.2 (CH), 126.5 (C), 127.3 (CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.7 (C), 129.1 (C), 130.2 (C), 135.2 (C), 135.4 (C), 139.2 (C), 140.2 (C), 151.2 (C), 152.0 (C), 154.4 (C), 154.9 (C), 160.8 (C), 161.4 (C), 203.8 (C), 204.9 (C).

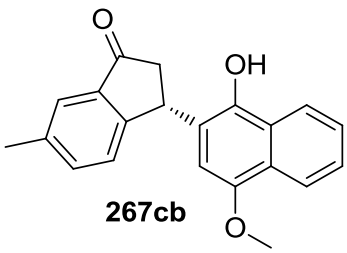
(*S*)-3-(4-chloro-1-hydroxynaphthalen-2-yl)-5-fluoro-2,3-dihydro-1H-inden-1-one 267bc:



267bc

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/Et_2O 60:40) as a white solid in 60% yield and 90% ee. **HPLC analysis**: Daicel Chiralcel OD-H, Hex/i-PrOH 95:5, flow rate 0.75 ml/min, λ = 214 nm: τ_{minor} = 21.63 min, τ_{major} = 24.11 min. **ESI-MS:** 327 $(M + 1)^+$, 329 $(M + 1)^+$, 349 $(M + Na)^+$, 351 $(M + Na)^+$. $\mathbf{[\alpha]_D^{rt}}$ = -119.6 (*c* 0.78; DMSO, 90% ee). **^{1}H-NMR (400 MHz, DMSO-d_6):** δ 2.78 (dd, J_a = 9.0 Hz, J_b = 4.0 Hz, 1H), 3.24 (dd, J_a = 19 Hz, J_b = 8.2 Hz, 1H), 5.12 (m, 1H), 7.09 (dd, J_a = 8.9 Hz, J_b = 2.1 Hz, 1H), 7.24-7.34 (m, 2H), 7.55-7.68 (m, 2H), 7.80 (dd, J_a = 8.5 Hz, J_b = 5.3 Hz, 1H), 8.06 (m, 1H), 8.30 (m, 1H), 9.83 (s, 1H). **^{13}C-NMR (100 MHz, DMSO-d_6):** δ 38.4 (CH), 44.7 (CH_2), 119.9 (d, CH, J_{C-F} = 22.1 Hz), 115.9 (d, CH, J_{C-F} = 23.7 Hz), 121.4 (C), 122.8 (CH), 123.6 (CH), 124.7 (C), 125.4 (d, CH, J_{C-F} = 10.7 Hz), 126.1 (CH), 126.6 (CH), 126.7 (C), 127.3 (CH), 129.8 (C), 133.3 (d, C, J_{C-F} = 1.3 Hz), 149.5 (C), 161.0 (d, C, J_{C-F} = 9.7 Hz), 165.2 (C), 167.8 (C), 203.5 (C).

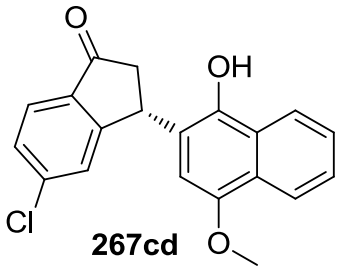
(*S*)-3-(1-hydroxy-4-methoxynaphthalen-2-yl)-6-methyl-2,3-dihydro-1*H*-inden-1-one 267cb:



267cb

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/Et_2O 75:25) as a white solid in 92% yield and 94% ee. **HPLC analysis**: Daicel Chiralpak AD-H, Hex/i-PrOH 90:10, flow rate 0.75 ml/min, λ = 214 nm: τ_{major} = 18.33 min, τ_{minor} = 20.09 min. **HRMS** calculated for $C_{21}H_{18}O_3$ 318.12559, found 318.12592. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** mixture of conformers δ 2.78 (dd, J_a = 18.8 Hz, J_b = 3.9 Hz, 1H), 3.18 (dd, J_a = 19.0 Hz, J_b = 8.0 Hz, 1H), 3.75 (s, 3H), 5.11 (m, 1H), 6.45 (s, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.42-7.54 (m, 4H), 8.04 (m, 1H), 8.16 (m, 1H), 8.85 (s, 1H). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ 20.6 (CH_3), 38.1 (CH), 44.9 (CH_2), 55.5 (CH_3), 104.3 (CH), 121.3 (CH), 122.1 (CH), 122.5 (CH), 124.4 (C), 124.5 (C), 125.0 (CH), 125.7 (CH), 126.3 (CH), 126.7 (C), 136.0 (CH), 136.6 (C), 137.0 (C), 143.0 (C), 148.6 (C), 155.7 (C), 205.6 (C).

(*S*)-5-chloro-3-(1-hydroxy-4-methoxynaphthalen-2-yl)-2,3-dihydro-1*H*-inden-1-one 267cd (Table 4 entry 8):



267cd

The reaction was performed following the general procedure on using 9-amino(9-deoxy)*epi*-quinidine **38a** as catalyst. The title compound was isolated by flash chromatography on silica gel (eluent mixture Hexane/Et_2O 70:30) as a white solid in 83% yield and 90% ee. **HPLC analysis**: Daicel Chiralcel OD-H, Hex/i-PrOH 95:5, flow rate 0.75 ml/min, λ = 214 nm: τ_{minor} = 32.18 min, τ_{major} =38.27 min. **ESI-MS:** 361 $(M + Na)^+$, 363 $(M + Na)^+$. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ 2.90 (dd, J_a = 19.0 Hz, J_b = 4.0 Hz, 1H), 3.20 (dd, J_a = 19.0 Hz, J_b = 8.1 Hz, 1H), 3.81 (s, 3H), 5.11 (m, 1H), 6.59 (s, 1H), 7.40-7.58 (m, 3H), 7.72 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.88 (s, 1H). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ 44.3 (CH_2), 38.1 (CH), 55.6 (CH_3), 104.8 (CH), 121.4 (CH), 122.1 (CH), 123.8 (C), 124.4 (CH), 124.7 (C), 125.2 (CH), 126.2 (CH), 126.8 (C), 128.0 (CH), 135.2 (C), 139.7 (C), 143.1 (C), 148.7 (C), 160.3 (C), 204.4 (C).

All the other products were not fully characterized.

6) Aza-Michael additions to electron poor double bonds[168]

6.1) introduction

Actually, the Aza-Michael reaction, namely the conjugate addition of nitrogen nucleophiles to electron deficient double bonds, was discovered before the reaction we usually call Michael addition, which is the conjugate addition of carbon nucleophiles to electron deficient double bonds[169] (*Fig*. *6.1*). By the way, Michael addition had always more attracted chemists because it gives the important possibility to create new C-C bonds. So, the Michael reaction has always been studied extensively, much more than its heteroatom based counterparts, such as aza-Michael, and is another or those reactions that nowadays can be found in every organic chemistry textbook.

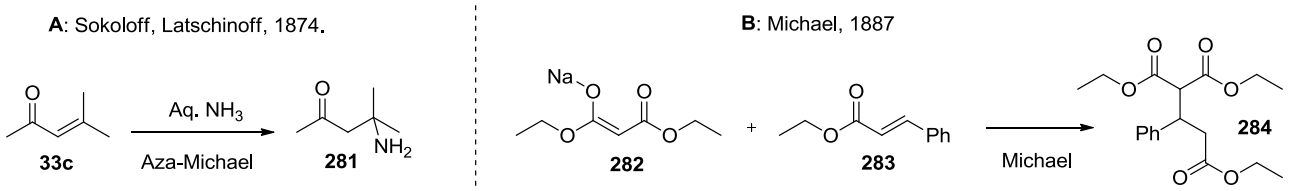


Figure 6.1: the first reports of Aza-Michael (**A**) and Michael (**B**) addition.

The amount of literature on Michael reaction is enormous. Reaction of enolizable or easily deprotonable substrates (aldehydes, ketones, enamines, malonates, nitroalkanes, dicyanomalonates, and so on) to electrophiles like enals, enones, α–β-unsaturated esters, alkylidene malonates, dicyanoolefines, nitroolefines and more are considered Michael reactions. These electrophiles are also partner in aza-Michael reactions, which uses amines, amides, nitrogen-based heteroaryl and more as nucleophiles. As, clearly, stereocenters are formed in these reactions, asymmeteic variants are highly desirable. Since this thesis is about organocatalysis, other methods will be omitted in this introduction. The earliest examples of organocatalytic enantioselective Michael additions were reported in 1973 and 1975[170]. Since then, and particularly starting form the year 2000

[168] For reviews on stereoselective aza-Michael, organocatalytic aza-Michael, and its application to the synthesis of chiral compounds see: a) P. R. Krishna, A. Sreeshailam, R. Srinivas, *Tetrahedron*, **2009**, *65*, 9657–9672. b) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.*, **2009**, *15*, 11058–11076. c) Z. Amara, J. Caron, D. Joseph, *Nat. Prod. Rep.*, **2013**, *30*, 1211–1225.

[169] Aza-Michael: a) N. Sokoloff, P. Latschinoff, *Ber. Dtsch. Chem. Ges.*, **1874**, *7*, 1384–1387; b) W. Heintz, N. Sokoloff, P. Latschinoff, *Ber. Dtsch. Chem. Ges.*, **1874**, *7*, 1518–1520; c) P. R. Haeseler, *Org. Synth.*, **1926**, *6*, 28–30. Michael: d) A. Michael, *J. Prakt. Chem.*, **1887**, *35*, 349.

[170] a) B. Långström, G. Bergson, *Acta Chem. Scand*. **1973**, *27*, 3118–3132. b) H. Wynberg, R. Helder, *Tetrahedron Lett*. **1975**, *46*, 4057–4060. Better results in: c) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244.

a huge amount of literature was published. Since then also this is not in the aim of this dissertation, the reader is referred to books[1] and reviews[171] appeared recently.

The first aza-michael addition, instead, appeared in 1996[172] catalyzed by a titanium complex (*Fig. 6.2*, **A**). The first organocatalytic variant, was developed in 2000 by Miller[173], who reported that peptide **292** catalyzed conjugate azidation of pyrrolidinone derived imides **290** (*Fig. 6.2*, **B**). Then, in 2006[174], MacMillan reported another important example, designing a nucleophile not competing with its catalyst in the formation of iminium ions (*Fig. 6.2*, **C**).

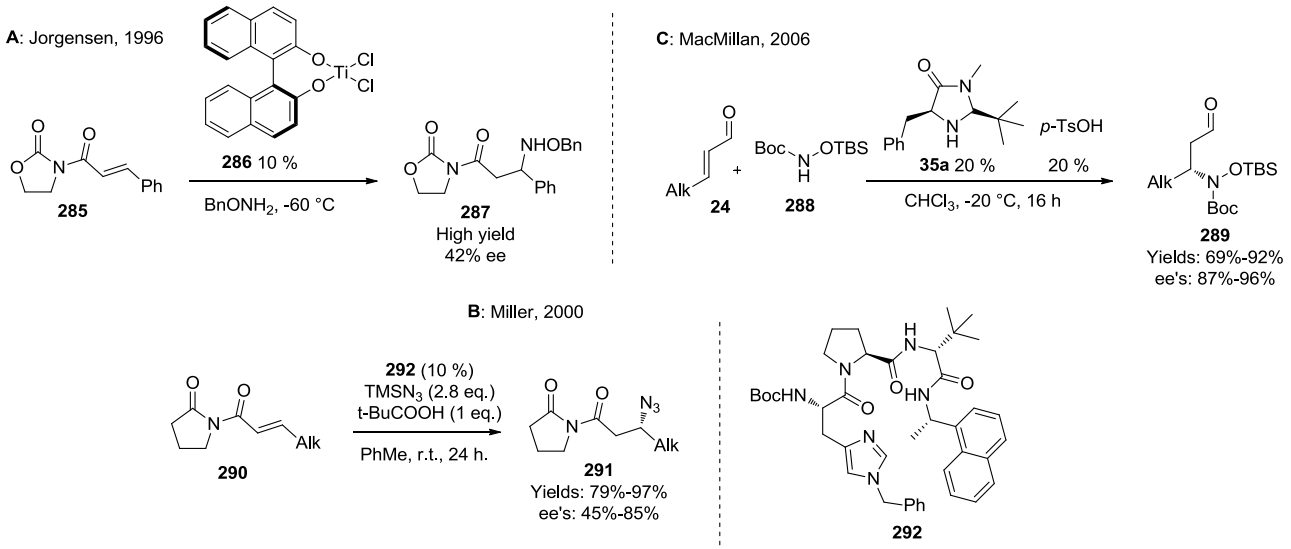


Figure 6.2: The first asymmetric metal catalyzed (**A**) and organocatalytic (**B, C**) AM reactions.

In fact, a free amine could in principle form an iminium ion with the reaction partner **24**, an enal, and catalyze the racemic reaction. Actually, the nature itself of amines as nucleophiles is a great challenge in organocatalysis: simple amines are scarcely employed. In fact, using aminocatalysis they can compete in the formation of iminium ions/enamines and catalyze racemic reactions (*Fig*. *6.3*, **A**). They are not enough acidic to be deprotonated in general base or phase transfer catalysis (*Fig*. *6.3*, **B**). They react with Brønsted acid catalysts to form stable and inert salts (*Fig*. *6.3*, **C**). So, often, reactive or relatively acidic amides are used, as well as N-nucleophilic heteroarenes, especially azoles oh hydroxylamine derivatives. Also, anilines (relatively weak bases) can be employed quite easily (*Fig*. *6.3*, **D**).

[171] a) S. B. Tsogoeva, *Eur. J. Org. Chem.*, **2007**, 1701; b) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry*, **2007**, *18*, 299; c) J. L. Vicario, D. Badia, L. Carrillo, Synthesis, **2007**, 2065; d) M. Thirumalaikumar, *Org. Prep. Proced. Int.*, **2011**, *43*, 67. e) Y. Zhang, W. Wang, *Catal. Sci. Technol.*, **2012**, ***2***, 42–53.
[172] L. Falborg, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans.*, **1996**, *1*, 2823–2826.
[173] T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem. Int. Ed.*, **2000**, *39*, 3635-3638.
[174] Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.***, 2006**, *128*, 9328-9329.

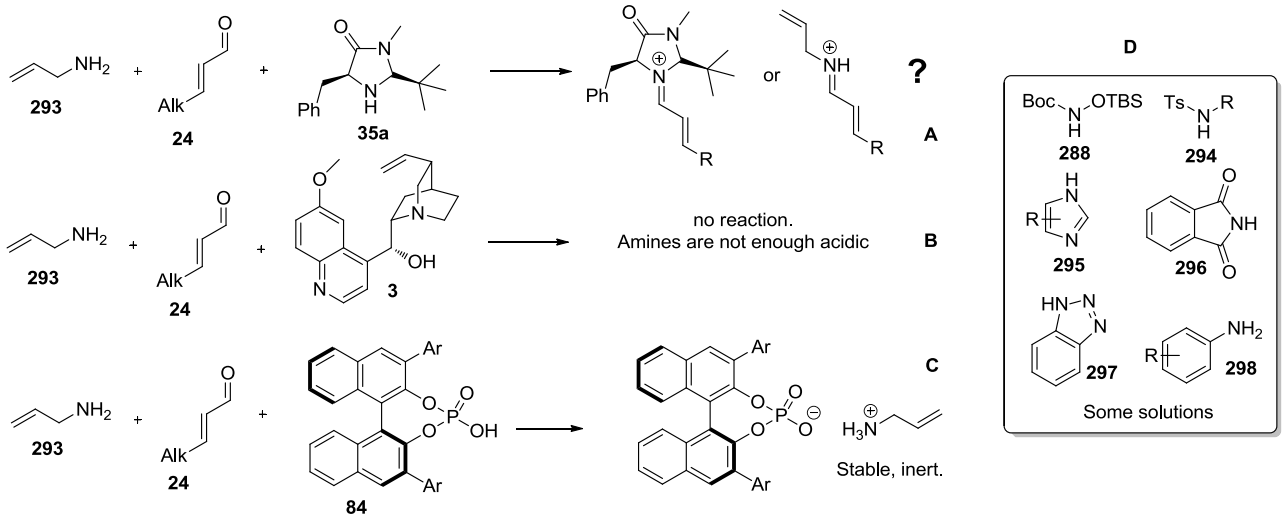


Figure 6.3: problems encountered reacting amines under the catalysis of the mostly used classes of organocatalysts and on the right some amine surrogate nucleophiles used to overcome the problem.

So, during the years many asymmetric aza-Michael reactions were published. Again, MacMillan organocatalysts are king in enal activation toward a large amount of N-nucleophiles[175]. In this field, a large amount of work was done with enones, via iminium ion catalysis[176], using bifunctional thioureas[177] or others[178].
We saw before how for the Friedel-Crafts reaction a lot was done with indoles. By the way, indoles have also a nucleophlic nitrogen, but it is not as much reactive as C3 carbon. Therefore, when reacting an indole with an electrophile, usually FC-alkylation at the C-3 carbon occurs (*Fig. 6.4*, **A**). To obtain functionalization at nitrogen usually C3 position must be blocked with an alkyl chain, in order to avoid deprotonation (*Fig. 6.4*, **D**). In this way, rearomatization cannot occur, and the F-C reaction is disfavored. Anyway there are examples in literature where 3-substituted indoles undergo initial FC-reaction and then

[175] See ref. 168b and additionally: a) W. Sun, G. Zhu, L. Hong, R. Wang, *Chem. Eur. J.*, **2011**, *17*, 13958-13952. b) Takuya Yokosaka, Akinari Hamajima, Tetsuhiro Nemoto, Yasumasa Hamada, *Tet. Lett.*, **2012**, *53*, 1245–1248. c) A. Desmarchelier, V. Coeffard, X. Moreau, C. Greck, *Chem. Eur. J.*, **2012**, *18*, 13222-13225. d) A. Pou, A. Moyano, *Eur. J. Org. Chem*, **2013**, *15*, 3103-3111.
[176] a) X. Lu, L. Deng, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7710–7713. b) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem. Int. Ed.*, **2008**, *47*, 8703–8706. c) G. Luo, S. Zhang, W. Duan, W. Wang, *Synthesis*, **2009**, 1564–1572. d) S. Gogoi, C.-G. Zhao, D. Ding, *Org. Lett.*, **2009**, *11*, 2249–2252. e) S. Fustero, C. del Pozo, C. Mulet, R. Lazaro, M. Sànchez-Rosellò, *Chem. Eur. J.*, **2011**, *17*, 14267-14272. e) C. Zeng, H. Liu, M. Zhang, J. Guo, S. Jiang, S. Yu, *Synlett*, **2012**, *23*, 2251-2254. f) R. Kapoor, R. Chawla, S. Singh, L. D. S. Yadav, *Synlett*, **2012**, *23*, 1321-1326. g) W. Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu, J. Ye, *Org. Lett.*, **2013**, *15*, 4524–4527. h) H.-J. Lee, C.-W. Cho, *J. Org. Chem.*, **2013**, *78*, 3306–3312. j) P. Li, F. Fang, J. Chen, J. Wang, *Tetrahedron: Asymmetry*, **2014**, *25*, 98–101. k) H.-J. Lee, C.-W. Cho, *Eur. J. Org. Chem.*, **2014**, *2*, 387-394.
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other transformations occurs cascade[179]. Moreover, indoles are nucleophilic also in C2 position, as we saw in section **5.1**, and also this reactivity is possible when C3 position is blocked (Pictet-Spengler reactivity is an example[180], see *figure 6.4* **C**).

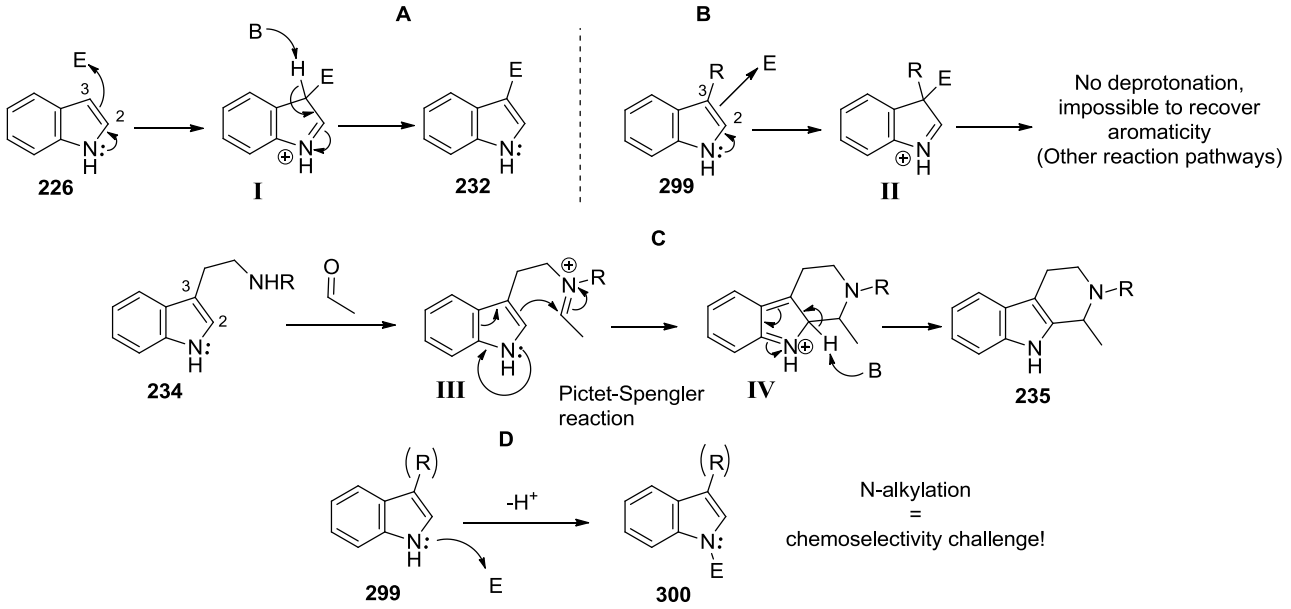

Figure 6.4: **A**: the most reactive position of indoles is C3, due to the delocalization of Nitrogen lone pair. **B**: when C3 position is blocked, deprotonation is impossible, and the reaction takes other pathways. **C**: for example, C2 position is also reactive, liki in Pictet-Spengler reaction. **D**: N-alkylation is therefore difficult.

Thus, the N-alkylation of indoles is a considerable chemoselectivity challenge, and the reports on the field are limited (see *figure 6.5* for a summary).

There are two reports on simple intermolecular indole addition to electrophiles. The first is by Chen in 2009 (*Fig. 6.5*, **A**)[181]. Simple indoles can undergo aza-Michael reaction on MBH-carbonates **49** when the dimeric cinchona alkaloid catalyst $(DHQD)_2PHAL$ **53** is employed. Formal S_n2 reaction occurs via double S_n2' pathway as depicted in SECTION **2.1.3**. Generally, good yields and selectivities are obtained. The second example was reported in 2011 by Huang (*Fig. 5*, **B**)[182]. After isomerization of α,β-unsatureted lactams **301** under the catalysis of a chiral Brønsted acid, the indole can attack the so formed cyclic N-acyliminium ion, to give the corresponding products **300a** in very good ee's.

[179] This pathway is active in dearomatization reactions. For a review on this topic please see: C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.*, **2012**, *51*, 12662–12687.

[180] For a recent excellent review on all aspects of Pictet-Spengler reaction see: J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.*, **2011**, *50*, 8538–8564.

[181] H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang, Y.-C. Chen, *Angew. Chem. Int. Ed.*, **2009**, *48*, 5737-5740.

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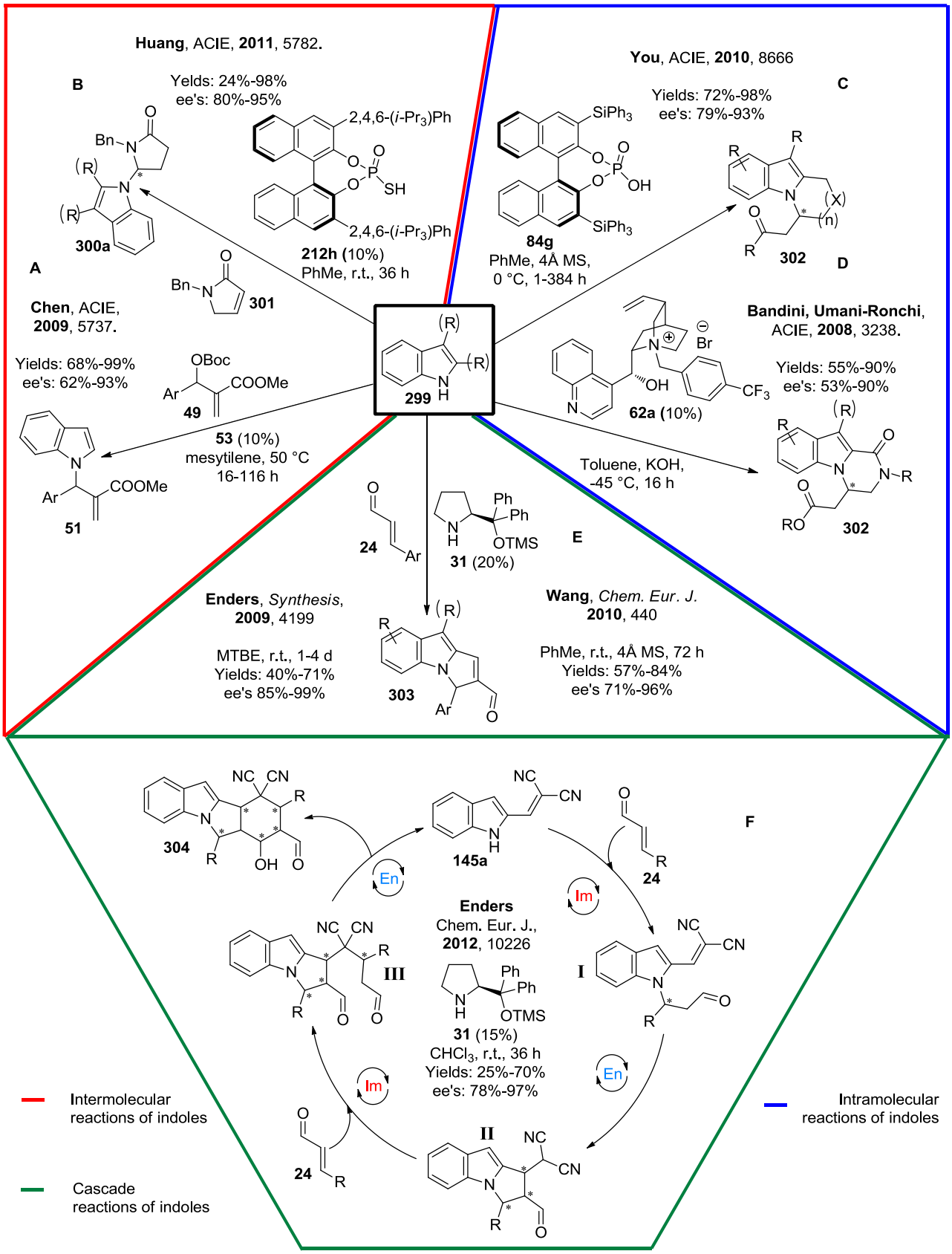


Figure 6.5: all the organocatalytic aza-Michael addition on indoles reported to date.

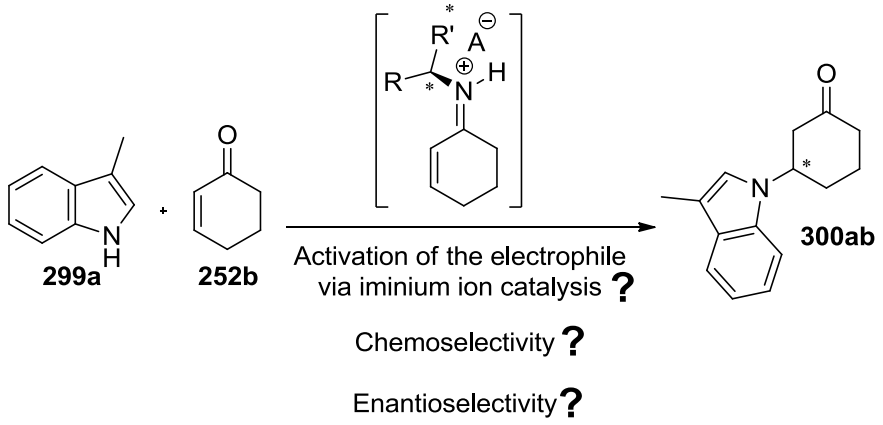
Two reports are present for the intramolecular indole alkylation. The first is by Bandini and Umani-Ronchi in 2008 (*Fig. 5*, **D**)[183]. A cinchona alkaloid based phase transfer catalyst promotes intramolecular N-alkylation of esters located on a chain bound to the C2 position of indoles. In this way a new 6-membered ring was created to give the tricyclic products **302** in moderate to very good ee's. The same approach was used in 2010 by You in a phosphoric acid catalyzed N-alkylation of enones (*Fig. 5*, **C**)[184]. Generally good to very good yields and ee's of the corresponding tricyclic product **302** are obtained when the catalyst **84g** is used. It's worth noting that all the other phosphoric acid catalysts tried gave poor enantiomeric excesses. Across the years 2009 and 2010, the groups of Enders and Wang independently reported the same reaction: an iminium ion catalyzed aza-Michael addition of 2-acyl-indoles to enals and subsequent enamine catalyzed ring closure/dehydration (*Fig. 5*, **E**)[185]. Although very different conditions were used, the catalyst is the same (**31**), and the results are quite similar. Finally, in 2012 Enders reports a quadruple cascade reaction when the first step is an intramolecular aza-Michael reaction of appropriately designed indoles on enals (*Fig. 5*, **F**)[186]. It's not surprising that some yields are quite low because they are calculated on the whole process, which consists of many steps. Anyway, ee's are very good also in this case.

In this survey of reactions involving indoles, remarkably, in only one case a substituent must be present at C-3 indole carbon to make the reaction work properly (*Fig. 5*, **C**). In the other examples the reactions can be performed also if this position is free, so they feature a remarkable chemoselectivity feature, in some cases difficult to explain. We saw that various aza-michael reaction on indoles can be catalyzed in different ways, with catalysts working with different activation modes, depending also on electrophiles. Although the general trend that sees secondary amines as privileged catalysts for aldehyde activation, it seems that indole N-activation can be performed with many kind of catalysts. By the way this field looks like underexplored, maybe due to the disproportionate attention given to the parent C-C bond forming reaction, maybe due to the fact that aza-Michael addition is more challenging. Anyway, such a small number of example regarding indoles, is somewhat surprising because the indole core is widespread in natural and bioactive products, as well as drugs and synthetic intermediates[90]. Therefore, the indole moiety is one of those more studied in chemistry since ever, especially in enantioselective catalysis, as we told before in the previuos section.
Moreover, among the methods in *figure 6.5*, there is an example of enantioselective aza-Michael functionalization of indoles with enones (*Fig. 5*, **C**). It is a phosphoric acid catalyzed ring closure, that is a intramolecular reaction. The corresponding intermolecular reaction doesn't exist.
We also saw before that for enone activation primary amines are commonly used, where secondary fails. Anyway, this approach for asymmetric aza-michael addition of indoles to enones has never been used[187].
Always interested in enantioselective primary amine catalysis, we decided to investigate this reactivity, and embarked in the following project, with the aim of perform the first iminuim ion catalyzed enantioselective aza-Michael addition of indoles to enones.

[183] M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.*, **2008**, *47*, 3238-3241.
[184] Q. Cai, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.*, **2008**, *49*, 8666-8669.
[185] a) D. Enders, C. Wang, G. Raabe, *Synthesis*, **2009**, 4119-4124. b) L. Hong, W.-S. Sun, C.-X. Liu, L. Wang, R. Wang, *Chem. Eur. J.*, **2010**, *16*, 440-444.
[186] D. Enders, A. Greb, K. Deckers, P. Selig, C. Merkens, *Chem. Eur. J.*, **2012**, *18*, 10226–10229.
[187] This approach, anyway, was used for reacting enones with other nucleophiles. See ref 165.

6.2) The aza-Michael reaction of indoles with enones

6.2.1) part I: iminium ion catalyzed enantioselective addition of 3-methyl indole to cyclohexenone



Scheme **6.1**: working hypothesis for enantioselective addition of 3-methyl indole to cyclohexenone.

With the same reasoning that we made for FC-alkylation, we selected cyclic enones as suitable substrate for a first optimization because of their enhanced conformational rigidity. To overcome, at least in the beginning, the chemoselectivity problem due to a possible C-3 alkylation, we chose 3-methyl indole as a model nucleophile for this reaction (Scheme **6.1**).

We begun with a screening of amines that could possibly catalyze the reaction. The acid chosen for the generation if the iminium ion was TFA and the solvent toluene, because often iminium ion catalysis works in these conditions. An achiral base did not catalyze the reaction (*Tab.1*, entry **4**), as well as **307** or **308** (*Tab.1*, entries **12-13**). The two BINAM derived amines **305** and **306** showed reactivity but not selectivity (*Tab.1*, entries **9-11**). Only when cinchona alkaloid derived primary amines were employed, things begun to change: Hydroquinine and cupreine derived primary amines **37b** and **37e** showed reasonable reactivities, but Hydroquinine derivative was the most reactive (*Tab.1*, entries **5** and **8**). Good selectivity was found for Hydroquinidine derived primary amine **38b**, but reactivity was very low (*Tab.1*, entry **6**).

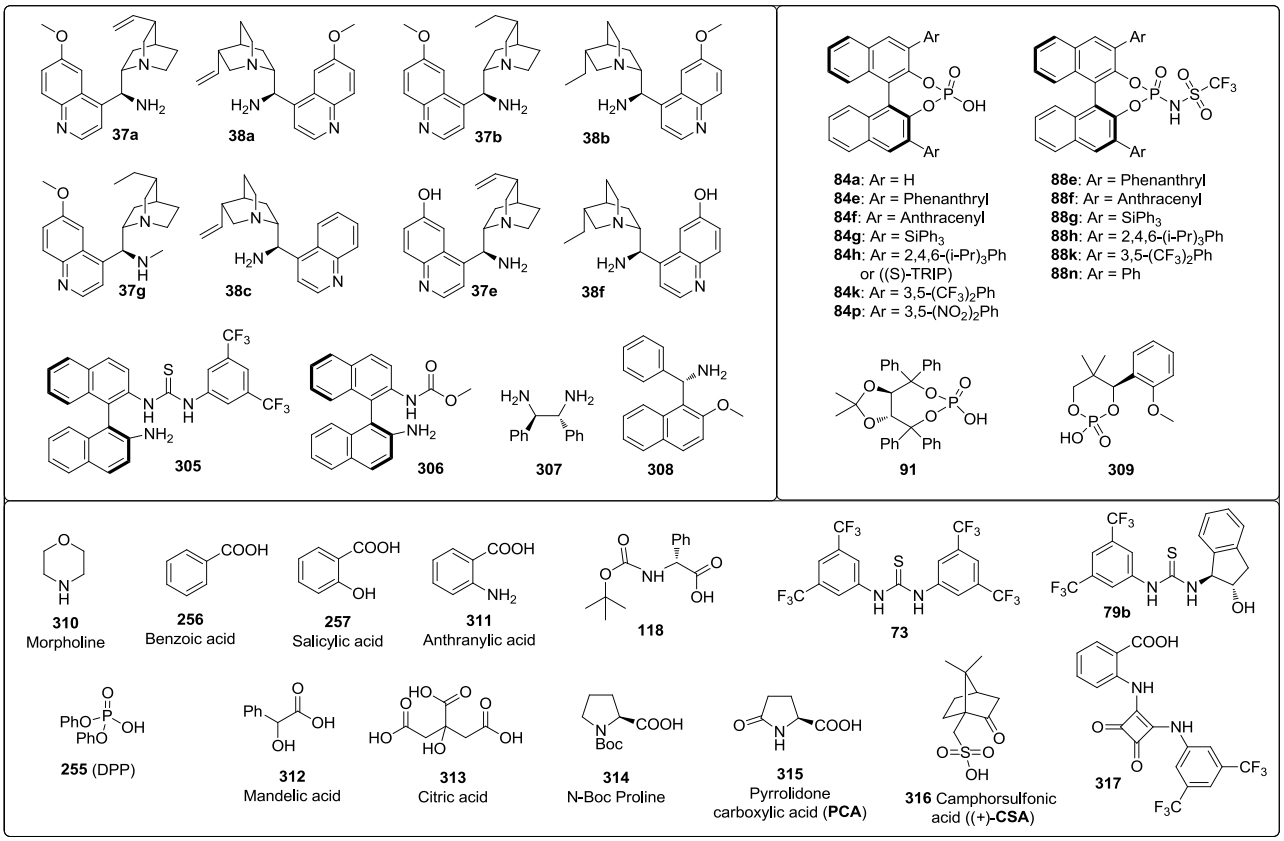
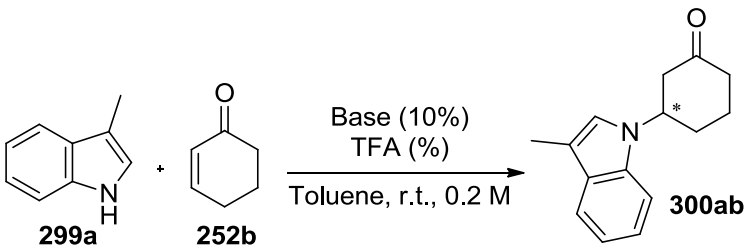


Figure 2: all the catalysts used in this study.



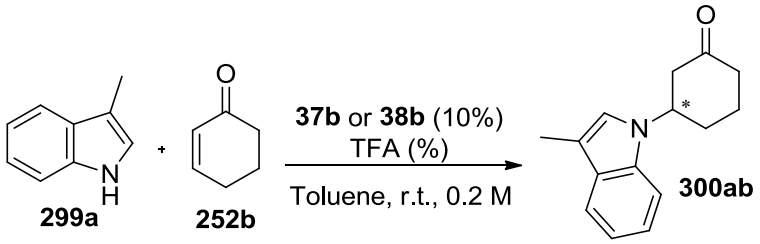
Entry	3/4	Base	% TFA	T (d)	Yield (%)	ee (%)
1	1.2 : 1	-	-	3	0	-
2	1.2 : 1	**37b**	-	3	0	-
3	1.2 : 1	-	20	5	0	0
4[a,b]	2 : 1	**BnNH$_2$**	20	5	Low	0
5	1.2 : 1	**37b** (20%)	40	2	83	56
6	1 : 5	**38b**	20	13	80	-72
7	1.2 : 1	**37g**	20	3	14	n.d.
8	1.2 : 1	**37e** (20%)	40	2	44	60
9	1.2 : 1	**305**	10	3	26	0
10	1.2 : 1	**305**	20	3	43	0
11	1.2 : 1	**306**	20	3	46	10
12	1.2 : 1	**307**	[d]20	3	0	-
13[a,c]	2 : 1	**308**	20	5	Low	0

Table 6.1: First catalyst screening for the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone. a: temperature was raised to 50 °C during the reaction due to low conversion. b: cyclopentenone was used as ketone. c: DCM was used as solvent. d: *p*-nitrobenzoic acid was used as acid additive.

Since it was not clear which one was the best catalyst, we screened the amine/acid ratio for two of them, varying also the reagent stoichiometry. In *table 6.2* we can see two major general trends:

1) a higher selectivity but lower reactivity is observed if decreasing the indole equivalents (compare entries **1** and **2**; **3** and **4**; **5**, **6** and **7**; **9** and **10**).
2) a higher selectivity is obtained decreasing the TFA loading, with the best result obtained when using a 1:1 ratio amine/acid (compare entries **1-2**, with **3-4**, and **5-7**; entries **9-10** with **11** and **12**).

As expected, the pseudoenantiomeric catalysts **37b** and **38b** give the product epimers (the opposite sign in the ee means that the opposite enantiomer was formed), but surprisingly, although the selectivity was higher, quinidine derived primary amines showed very low reactivities respect to quinine derived ones (entries **9-12** and **14**). Since a 1:1 ratio of amine and acid was the best, some other catalysts were tried with this ratio (entries **13-15**). Among them, quinine derivative **37a** was the best, but its dihidro- derivative **37b** was anyway still slightly more selective (entry **2**), and so was chosen as the best for further optimization. A reaction carried out at 0 °C showed only a slight improvement of ee, but the yield was considerably lower (entry **8**). So, conditions in entry **2** were considered to be the best, and we submitted further optimization using them.

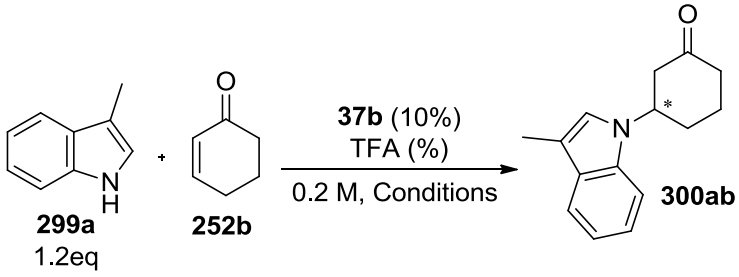


Entry	3/4	Base	% TFA	t (d)	Yield (%)	ee (%)
1	2 : 1	**37b**	10	3	70	66
2	***1.2 : 1***	***37b***	***10***	***3.5***	***66***	***70***
3	4 : 1	**37b**	15	1	92	60
4	1.2 : 1	**37b**	15	2	44	68
5	2 : 1	**37b**	20	n.d.	n.d.	58
6	1.2 : 1	**37b** (20%)	40	2	83	56
7	1 : 5	**37b**	20	4	66	68
8[a]	1.2 : 1	**37b** (20%)	40	2	47	60
9	2 : 1	**38b**	10	3	25	-76
10	1 : 5	**38b**	10	5	28	-76
11	4 :1	**38b**	15	3	55	-70
12	1 : 5	**38b**	20	13	80	-72
13	1.2 : 1	**37a**	10	3	77	68
14	1.2 : 1	**38a**	10	3	25	-72
15	1.2 : 1	**38c**	10	3	46	68

Table 6.2: optimization of base/acid ratio and reagent stoichiometry. a: reaction carried out at 0 °C.

We next moved to solvent screening. As observed also for the F-C reaction, generally aromatic and chlorinated solvents showed reactivity, with chlorinated giving slightly better reactivities, but aromatic giving slightly better selectivities (*Tab. 6.3*, entries **1-2** and **6-7**). Also according to what observed in F-C reaction, non-polar or very polar solvents didn't

show reactivity (*Tab. 6.3*, entries **4**, **7-8** and **10-11**). Also if using the enone as solvent the reaction doesn't work (*Tab. 6.3*, entry **3**). Water showed some reactivity, but with only moderate levels of enantioselectivity (*Tab. 6.3*, entry **12**), while EtOAc gave actually the best ee level, but the yield was very low (*Tab. 6.3*, entry **9**), and in comparison the use of toluene was considered the most convenient. In addition to toluene, also other solvents were tried at 0 °C, but without ee improvements (*Tab. 6.3*, entries **13-15**). So, the conditions in entry **1** were considered the best for further optimization.

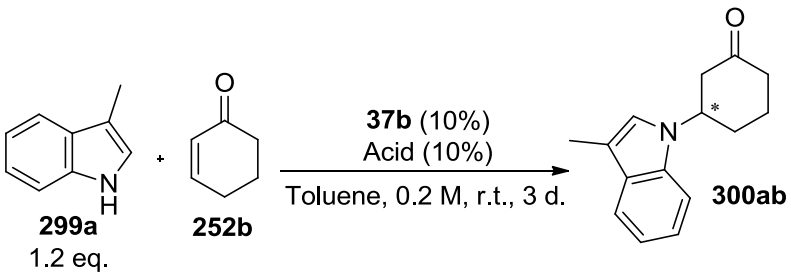


Entry	Solvent	% TFA	T	t (d)	Yield (%)	ee (%)
1	***toluene***	***10***	***r.t.***	***3.5***	***66***	***70***
2	THN	10	r.t.	3	61	70
3	NEAT	20	r.t.	10	0	-
4	Et_2O	10	r.t.	3	0	-
5	DCM	10	r.t.	3	74	60
6	$CHCl_3$	10	r.t.	3	80	54
7	THF	10	r.t.	3	0	-
8	acetone	15	r.t.	3	0	-
9	EtOAc	10	r.t.	3	26	74
10[a]	acetonitrile	15	r.t.	5	0	-
11	DMF	20	r.t.	5	0	-
12	H_2O	20	r.t.	5	42	-50
13[b]	toluene	40	0 °C	2	47	60
14	p-xilene	10	0 °C	3	50	40
15	DCM	10	0 °C	3	32	52

Table 6.3: solvent screening for the the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone. a: HQD-NH_2 was used as catalyst. b) 20% of amine catalyst was used. THN = tetrahydronaphthalene.

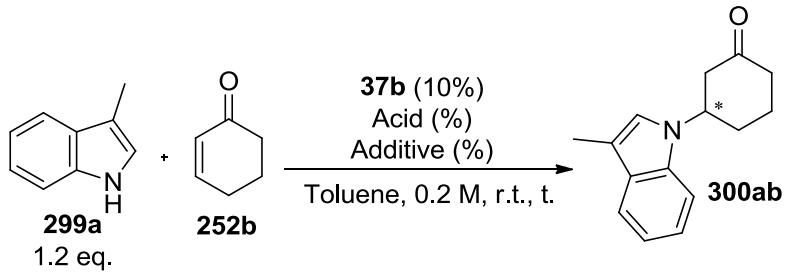
After the best solvent was established, we next moved to acid screening (*Table 6.4*). In addition to TFA, other strong acetic acids were tried, but no-one with better results. Interestingly, in this serie, the stronger is the acid, the best is ee (compare entries **1-4**). Benzoic acid derivatives showed no or poor reactivity or poor selectivity when used in 1:1 ratio with the amine (entries **5-9**), but this changes if increasing the loading to 20%-30% when good yields and selectivities were obtained using 5-NO_2-Salicylic acid, the same that gave good results in F-C reaction (entries **10-11**). Other acids of different nature gave no or poor yields (entries **12-18**). Thus, again, the first row of the table has the best results.

Later, with all the optimization steps already performed, some additives, like inorganic salts, thiourea additives and 4Å MS were evaluated (*Table 6.5*). Some, actually gave good yields and moderate selectivities, but not comparable to the ones obtained in Toluene with 10% of TFA. It is important to note that with 4Å MS the reaction did not work.



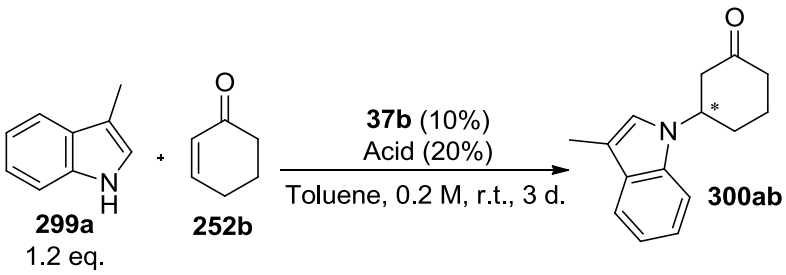
Entry	Acid	Yield (%)	ee (%)
1[a]	***TFA (10%)***	***66***	***70***
2	CA (10%)	5	44
3	DCA (10%)	61	50
4	TCA (10%)	61	68
5	Benzoic acid **256** (10%)	0	-
6	*p*-nitrobenzoic acid (10%)	0	-
7	3,5-dinitrobenzoic acid (10%)	8	68
8[b]	Salicylic acid **257** (40%)	40	17
9	5-nitrosalicilyc acid **258** (10%)	8	0
10	5-nitrosalicilyc acid **258** (20%)	70	60
11	5-nitrosalicilyc acid **258** (30%)	67	60
12	Anthtranilic acid **311** (10%)	0	-
13	Anthtranilic acid **311** (20%)	0	-
14	Citric acid **313**	0	-
15	**317** (10%)	0	-
16	DPP **255** (10%)	33	54
17	p-TsOH (10%)	16	64
18	$HClO_4$ (10%)	0	-

Table 6.4: Screening for acids in the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone. a: reaction time was 3.5 days. b) CPN-NH_2 (20 %) was used as catalyst. CA = Chloroacetic acid. DCA = Dichloroacetic acid. TCA = Trichloroacetic acid.



Entry	Acid (%)	Additive (%)	t (d)	Yield (%)	ee (%)
1	CH_3COOH (10%)	CH_3COONa (10%)	3	0	-
2	TFA (20%)	TBAB (20%)	3	17	61
3	TFA (10%)	CsF (10%)	3	50	70
4	KHF_2 (10%)[a]		3	0	-
5	Q-NH_2·3HCl[b]	**73** (30%)	4	0	-
6	TFA (10%)	**73** (10%)	3	61	45
7	TFA (20%)	**73** (20%)	3	88	45
8	TFA (20%)	**79b** (20%)	2	86	52
9	TFA (20%)	4Å MS	3	0	-

Table 6.5: Screening for additives in the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone. a: the commercially available salt KHF_2 was used as HF + KF source. b: this salt was used in place of catalyst/acid combination. Of course HQ-NH_2 in this entry was not used.



Entry	Acid (20%)	Yield (%)	ee (%)
1[a]	TFA (10%)	66	70
2	(±)-**312**	mixture	-
3	(*S*)-**312**	mixture	-
4[b,c]	**118** (40%)	50	40
5	**314**	0	-
6	(*S*)-**315**	0	-
7	(+)-**316**	38	63
8[c]	***(S)-TRIP (84h)***	***30***	***-80***

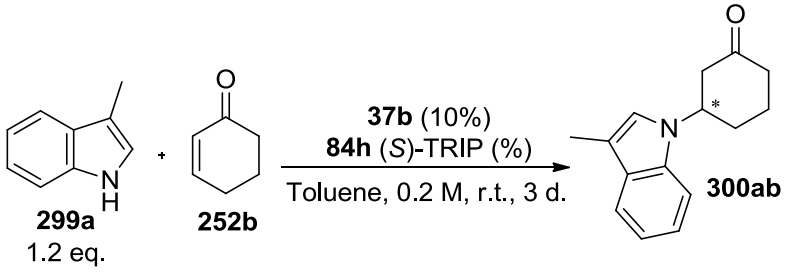
Table 6.6: Screening for chiral acids in the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone. a: reaction time 3.5 days. b: 20% of HQ-NH_2 was used. c: reaction time 2 days.

At this point, before stopping optimization, we thought that a chiral acid could be beneficial in our case, as it was for the F-C reaction of indoles to enones developed by Melchiorre and co-workers[85c]. There are quite much and different chiral acids to try, especially amino-acid derivatives and the aforementioned phosphoric acids. We decided to try some of them, including phosphoric acids, despite the result given by their achriral precursor DPP were poor (*table 6.4*, entry **15**).
To this regard, it should be noted that chiral acid and chiral amine combination of catalysts give diastereoisemoeric catalytic salts that lead to different results. So, in principle both enantiomer should be tried for each acid. Anyway we decided to screen some acid to see if we could observe reactivity, and to think later about this problem. In fact, additionally to the acid also other amines would have to be tried because the catalysts that we use are not enantiomeric but pseudoenantiomeric. With this in mind we performed a preliminary screening of chiral acids. Unfortunately, many of these were unreactive or lead to mixtures of products (*Tab. 6.6*, entries **2-3**, **5-6**). Moderate reactivity and selectivity were observed with N-Boc-**118** and **316** (*Tab.6. 6*, entries **4**, **7**). But when we turned our attention on chiral phosphoric acids and tried the widely used TRIP, an 80% ee was obtained (*Tab. 6.6*, entry **8**). Although the yield was low, this result was considered promising since it was the highest ee obtained. Moreover, it's worth noting that using (*S*)-TRIP in combination with **37b** we obtained the opposite enantiomer with respect to the one obtained with TFA. Intrigued by these findings, we decided to investigate more this chemistry.

First of all we optimized again the ratio between the catalyst and the amine, since with a different acid a different ratio could be the best. Actually, the ratio that we tried at the beginning was not the same we were using with TFA, but this was an advantage: in fact a 1:2 ratio catalyst/acid is the best for (*S*)-TRIP, while a 1:1 was the best for TFA. Using 10%, 15%, or 40% of (*S*)-TRIP results in lower ee, despite yields are higher (*Table 6.7*).

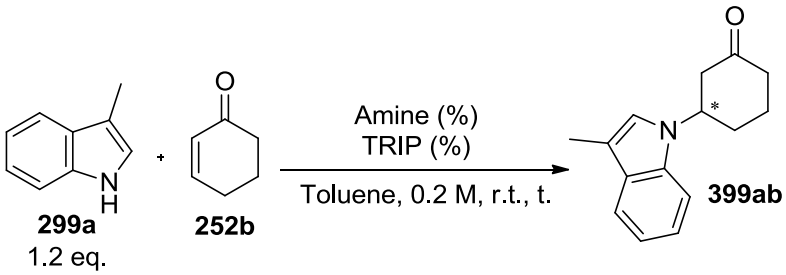
At this point, we had in our hands the optimal amine/acid ratio to perform a screening of two pseudoenantiomeric amines with both the enantiomers of the chiral acid. This is

necessary, since the cinchona alkaloid derived primary amines form diastereoisomeric salts with one or the other enantiomer of the acids. Additionally, since the two amines are pseudo-enantiomers and not real enantiomers, 4 different diastereoisomeric salts would be formed, and we expected each one to give different results in catalysis. The amine and the enantiomer of the acid wihich for the catalyst combination giving best results are called "matched" couple. The other catalytic salt, giving worse results, is called "mismatched" couple.



Entry	% (*S*)-TRIP	Yield (%)	ee (%)
1	(*S*)-TRIP (10%)	52	-62 (AD-H)
2	(*S*)-TRIP (15%)	80	-70 (AD-H)
***3*[a]**	***(S)-TRIP (20%)***	***30***	***-80 (AD-H)***
4	(*S*)-TRIP (30%)	82	-66 (AD-H)

Table 6.7: optimization of (*S*)-TRIP loading. a: reaction time: 2 days.

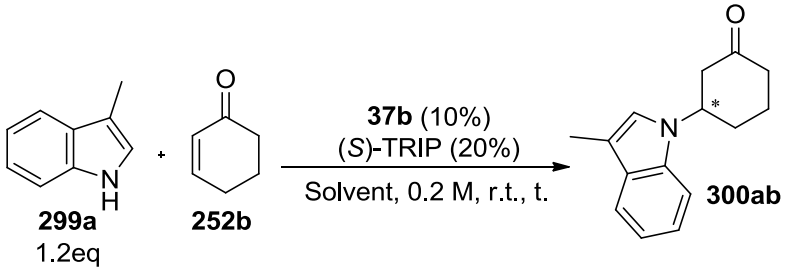


Entry	Amine (%)	Acid (%)	t (d)	Yield (%)	ee (%)
1	**37b** (20%)	TFA (40%)	2	83	56
2	**37b *(10%)***	***84h ((S)-TRIP) (20%)***	***2***	***30***	***-80***
3	**37b** (10%)	*ent*-**84h** ((*R*)-TRIP) (20%)	3	32	66
4[a]	**38b** (10%)	TFA (20%)	13	80	-72
5	**38b** (10%)	**84h** ((*S*)-TRIP) (20%)	2.5	40	16
6	**38b** (10%)	*ent*-**84h** ((*R*)-TRIP) (20%)	3	50	52

Table 6.8: study on Matched/Mismatched catalyst combinations in ACDC aza-Michael addition of 3-methyl indole to cyclohexenone. a: ratio 3/4 was 1:5.

In *table 6.8* are given the results for these studies on matched and mismatched couples. For comparison, also results obtained with TFA are reported. Again, the first choice revealed to be the best, because the couple **37b** (10%) – **84h** (20%) is the matched couple. By the way, it's interesting to see how the reaction's stereochemistry is completely acid-controlled, since changing the enantiomer of the acid, changes also the enantiomer of the product (T*ab. 6.8*, entries **2-3**). In this way, we can refer to this transformation as an

Asymmetric Cunteranion Directed Catalysis. Regarding **38b**, results are generally poorer. In this case, as somehow expected, the matched couple is formed with (*R*)-TRIP (T*ab. 6.8*, entry **6**), but despite a decent yield, the ee is only moderate. Also in this case the major enantiomer of the product is the opposite respect to what obtained with TFA. The ee obtained with (*S*)-TRIP is very low (T*ab. 6.8*, entry **5**), and the best selectivity for ths amine is still given by using TFA as acid.



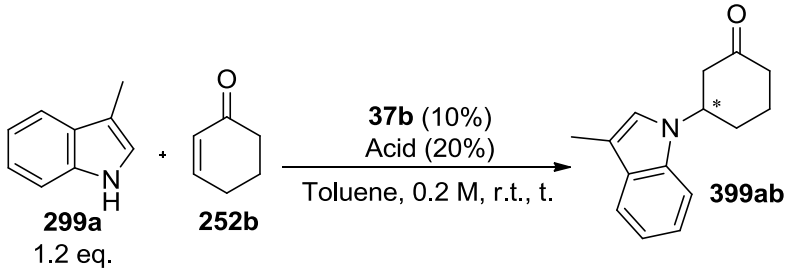
Entry	Solvent	3/4	t (d)	Yield (%)	ee (%)
1	*n*-hexane	2 : 1	2	90	-6
2	***toluene***	***1.2 : 1***	***2***	***30***	***-80***
3	p-xylene	1.2 : 1	3	91	-72
4	PhF	1.2 : 1	3	78	-60
5	DCM	2 : 1	3	53	56
6	EtOAc	1.2 : 1	3	36	43
7[a,b]	THF	2 : 1	5	n.d.	2
8	ethanol	2 : 1	2	68	-10
9	Water	1.2 : 1	3	76	- 50
10	Toluene/ water 1:1	2 : 1	2.5	70	-69
11[c]	Toluene	1.2 : 1	3	24	-48

Table 6.9: solvent screening for ACDC aza-Michael addition of 3-methyl indole to cyclohexenone. a: cycloheptenone was used as enone. b: temperature was raised to 50 °C during the reaction due to its low rate. c: 30 mg of powdred 4Å MS were used as additive.

We soon realized that for this reaction a new optimization was needed. After the establishment of an amine/acid ratio and the identification of the matched couple, we performed a solvent screening again. The results, summarized in *table 6.9*, are difficult to rationalize. Three solvents, hexane, THF and ethanol give very low ee's (entries **1**, **7** and **8**). There is a big performance difference between toluene and other aromatic solvents concerning the reaction rate; the ee, instead is still higher in toluene (entries **2-4**). Moderate reactivity and selectivity was observed in DCM and EtOAc, by the way it's worth noting that in these two solvents the opposite enantiomer of the product was obtained (entries **5-6**). Interestingly, reactivity and selectivity were quite good in water, as well as in a mixture toluene/water 1:1 (entries **9-10**). Importantly, when using 4Å MS as additive, an enantioselectivity drop is obtained (entry **11**).

The best result at this point was still the first one that we found. But of course TRIP is not the only phosphoric acid that can be tried. Since we saw in section **4.2** that the results can vaty a lot using these acids, we decided the synthesis of a small library of compounds to try to find the better acid for this transformation. In the end, a fairly good number of catalysts were synthesized and they were all evaluated in this ACDC. It's noteworthy that

the two aryl substituents on the 3,3'- position of BINOL strongly influence the reaction outcome and the results can be very different. It is also noteworthy that the results given by triflimides can be very different respect to the ones given by the corresponding phosphoric acids. Therefore, it is not surprising if such a thing happen, but the results in *table 6.10*, which summarizes the chiral phosphoric acid screening for the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone, are puzzling.



Entry	Acid	t (d)	Yield (%)	ee (%)
1	(*S*)-TRIP (**84h**)	2	30	-80
2	**84a**	3	20	12
3[a]	**84k** (10%)	3	32	36
4	**84k**	1	47	70
5	**84e**	3	84	-60
6[b]	[b]	3	34	-85
7	**84f**	3	43	42
8	**84g**	2.5	n.d.	76
9	**84p**	3	0	-
10[c]	**91** (15%)	3	47	38
11	**309**	3	76	44
12[d]	**88h**	3	0	-
13	**88h**	3	15	-90
14[d,e]	***88h (40%)***	***3***	***36***	***-90***
15	**88e**	3	8	29
16	**88f**	10	14	33
17[f]	**88g**	6	47	-30
18	*ent*-**88k**	3	0	-
19	**88n**	3	18	-20

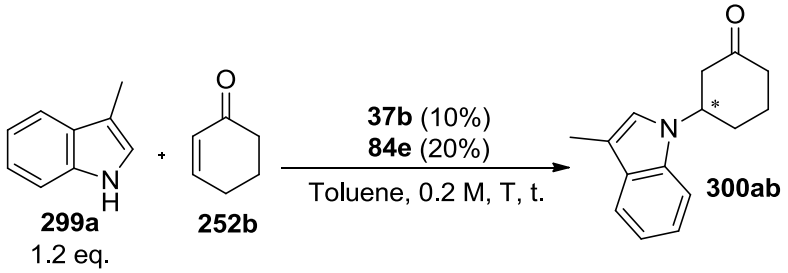
Table 6.10: Screening for chiral phosphoric acids and triflimides in the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone. a: 10% of acid was used. b: see text for an explaination. c: 15% of acid was used. d: 20% of HQ-NH_2 was used. e: 40% of acid was used. f: temperature was raised to 50 °C during the reaction due to its low rate.

Two preliminary general considerations are:

1) despite the BINOL backbone is the same, many of these acids gave again the opposite enantiomer with respect to TRIP (entries **5**, **6**, **13-14**, **17** and **19** are exceptions).
2) yields are often below 50% (entries **5**, and **11** are exceptions).

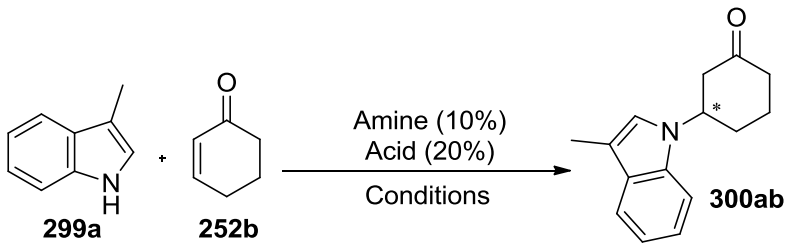
BINOL hydrogenphosphate **84a** gave poor ee (entry **2**), and using catalyst **84k** a 1:2 ratio was confirmed to be optimal for the system (entries **3-4**). Acid **84e** is one of the best in yield and selectivity, giving the same product enantiomer as TRIP (entry **5**). Entry **6**

deserves a particular discussion. Initially, this reaction was carried out believing to have in hand the acid **84f**. After the reaction was carried out and result was obtained, we realized that the structure of the catalyst did not match the literature reported spectra. After further analyses, mass spectrometry let us understand that the material we had produced was not the phosphoric acid, but the corresponding phosphoric acid chloride. It's worth mentioning that after a short time we found this material decomposed into unidentified byproducts, by the way the reaction should have been carried out with the chloride. Therefore, it's quite surprising to see conversion in this reaction, that remarkably overcomes the results obtained with TRIP. We speculated that a bit of acid could be formed in situ via chloride hydrolysis by adventitious water. By the way, when acid **84f** was synthesized, its structure confirmed, and used in the reaction, the results were strikingly different and the opposite enantiomer of the product was obtained, with low ee (entry **7**). This result is inexplicable and obscure, and these findings would have required further investigation, but the low amount of catalyst we had, the impossibility of exactly reproducing the conditions of entry **6**, and the next findings led us to omit this issue.
We found another acid giving good ee (**84g**, entry **8**), and two instead leading to poor selectivities (entries **10**-**11**), while reaction with acid **84d** just did not work (entry **9**). Then we switched our attention to phosphoric acid triflimides.
The triflimide **88h**, bearing the same substituent as TRIP, was found to give an also lower yield, but a 90% ee (entry **13**). Since these compounds are more acidic than the corresponding phosphoric acids, we speculated that lower yield was due to that and we tried to reduce amine/acid ratio to 1:1, but unfortunately with no results (entry **12**). So we tried to increase the yield by simply increasing the catalyst loading. Actually, the yield increased, but it remained stuck on low levels (entry **14**). Poor yields afflict also all the other triflimides, that anyway gave also low ee's (entries **15-19**).
As further optimization, we studied the temperature effect with the catalyst **84e**, available in quite large amount in our laboratories. By the way, as it is possible to see in *table 6.11*, r.t. is the best temperature both for yields and enantioselectivities.
In *table 6.12* are reported some miscellaneous trials made during the course of our studies, including one for a "real" ACDC, where the amine is not chiral, but without good results (entry **4**).



Entry	T (°C)	t (d)	Yield (%)	ee (%)
1	0	4 d	38	-40
2	r.t.	3 d	84	-60
3	40	2 d	77	-36

Table 6.11: temperature effect on ACDC using phosphoric acid **1g** in the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone.



Entry	Solvent	3/4	Amine (10%)	Acid (20%)	T (°C)	t (d)	Yield (%	ee (%)
1	toluene	1.2 : 1	**37e**	**84h**	r.t.	1	n.d.	9
2	toluene	1.2 : 1	**38f**	**84h**	r.t.	5	67	32
3	toluene	1.2 : 1	**310** (1 eq.)	**84h**	r.t.	2.5	0	0
4	toluene	1.2 : 1	p-OMe-aniline	*ent*-**84h**	r.t. → 50°	7	0	-
5	dioxane	2 : 1	**37b**	**1c**	r.t. → 50°	5	80	50

Table 6.12: Miscellaneous trials in in the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone with phosphoric acids as counteranions.

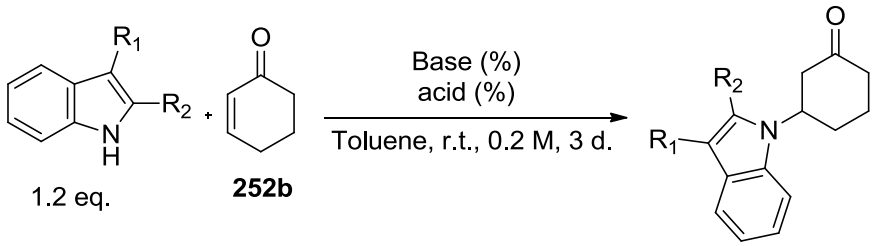
After this huge amount of work we decided that was reasonable to stop the reaction optimization, because it was considered hard to get better results for this reaction. Further improvement would have required more catalyst or acid screening, but their synthesis, especially, the preparation of phosphoric acids and triflimides, is not trivial, quite long and sometimes low yielding. Too many efforts for the preparation of considerable amount of acids should have been made, and then results were anyway not guaranteed.

Thus, for the iminium ion catalyzed aza-Michael addition of 3-methyl indole to cyclohexenone, we could summarize that:

1) a catalytic system giving acceptable yields and ee's was established to be HQ-NH_2 / TFA in ratio 1:1 in toluene as the solvent.
2) an alternative catalytic system using **37b** / **84h** in a ratio 1:2 and toluene as solvent gives excellent enantioselectivities, but unfortunately low yields.

Anyway, we were curious about the reaction outcome with other substrates and other kind of catalysis.

6.2.2) part II: iminium ion catalysis on other substrates



1.2 eq. **252b**

300ab-300eb

226: $R_1 = R_2 = H$
299b : $R_1 = R_2 = Me$
299c : $R_1 = Bn$ $R_2 = H$
299d : $R_1 = R_2 = -(CH_2CH_2CH_2CH_2)-$
299e: Carbazole

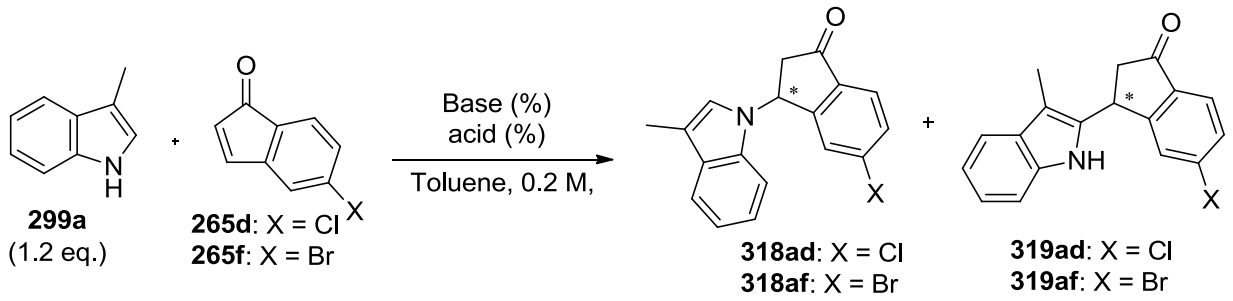
Entry	Indole	Base (%)	Acid (%)	Product	Yield (%)	ee (%)
1	**226**	HQ-NH_2 (10)	(S)-TRIP (20)	-	0	-
2	**299b**	HQ-NH_2 (10)	(S)-TRIP (20)	**13**	30	0
3	**299b**	HQD-NH_2 (10)	TFA (10)	**13**	25	-12
4	**299b**	HQD-NH_2 (10)	TFA (20)	**13**	25	0
5[a,b]	**299b**	HQ-NH_2 (10)	TFA (20)	**13**	20	62
6[a]	**299b**	HQD-NH_2 (10)	TFA (20)	**13**	66	-90
7[a]	**299b**	HQD-NH_2 (10)	TFA (20)	**13**	62	60
8[a]	**299b**	HQD-NH_2 (10)	TFA (20)	**13**	59	62
9	**299c**	HQ-NH_2 (10)	TFA (10)	**14**	42	n.d.
10	**299c**	HQ-NH_2 (10)	(S)-TRIP (20)	**14**	73	60
11	**299d**	HQ-NH_2 (10)	TFA (10)	**15**	44	31
12	**299d**	HQD-NH_2 (10)	TFA (10)	**15**	44	47
13	**299e**	HQ-NH_2 (10)	TFA (10)	**16**	25	40
14	**299e**	HQD-NH_2 (10)	TFA (10)	**16**	26	0
15[c]	**299e**	HQD-NH_2 (10)	TFA (10)	**16**	35	0

Table 6.13: other indoles tried in the aza-Michael addtiton to cyclohexenone. a: 5 eq. of cyclohexenone were used. b: reaction time 4 days. c: EtOAc was used as the solvent.

With all the previous work in hand we tried the reaction using some indoles more. *Table 6.13* summarizes the results.

Simple indole is not reactive (entry **1**) and 2,3-dimethylindole has low reactivity and selectivity in the optimized conditions (entries **2-4**). Only when a 1:2 ratio of amine/acid was used in combination with 5 eq of ketone, good yields and selectivities were obtained (entries **5-8**). Using **38b** as base this time in entry **6** lead to our delight to a very high ee. Unfortunately, this result was not reproducible, as you can observe in entries **7** and **8**. Anyway the reaction usinfg 5 eq. of ketone features an impressive enantioselectivity difference respect to the ones carried out with 1.2 eq (compare entries **2-4** and **5-8**). Employing 3-benzyl indole as starting material, using (S)-TRIP as acid, good yields and selectiviteis were observed, but not comparable to the ones seen in the previous section with 3-methyl indole (entries **9-10**). Using carbazole and tetrahydrocarbazole moderate yields and selectivities were obtained (entries **11-15**).

Since indenones were good substrates for the F-C reaction, we decided to try them in the aza-Michael reaction. Results are summarized in *table 6.14*.

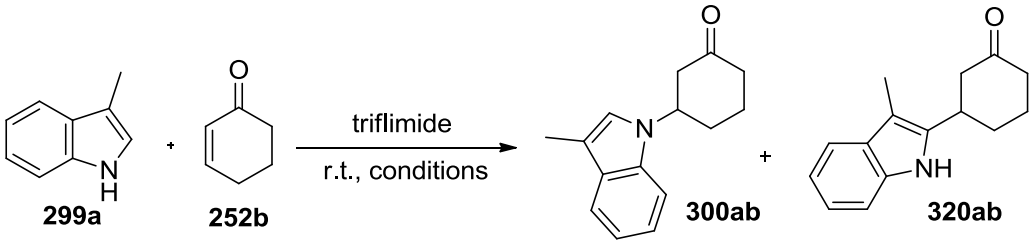


Entry	Indenone	Catalyst (%)	t	T (°C)	Yield 318 (%)	ee 318 (%)	Yield 319 (%)	ee 319 (%)
1	**265d**	**37b** (10) TFA (10)	3 d	r.t.	16	52	22	26
2	**265d**	**38b** (10) TFA (10)	5 d	r.t.	20	64	30	53
3	**265d**	**37b** (10) TFA (20)	4 d	35	26	40	44	36
4	**265d**	**37b** (10) o-FBA (20)	4 d	r.t.	0	-	0	-
5	**265d**	**37b** (10) 5-NO_2-SA **258** (20)	3 d	r.t.	0	-	0	-
6	**265d**	**37b** (10) DPP **255** (20)	5 d	r.t.	24	55	15	27
7	**265d**	***37b (10)*** ***84h ((S)-TRIP) (20)***	***3 d***	***r.t.***	***32***	***-94***	***16***	***-72***
8[a]	**265d**	**37b** (10) TFA (20)	5 d	r.t.	0	-	-	-
8	**265f**	**37b** (10) TFA (20)	6 d	r.t.-->50[b]	low	42	low	27
9	**265f**	**37b** (10) **84h** (*S*)-TRIP (20)	6 d	r.t.-->50 [b]	low	78	low	14

Table 6.14: aza-michael addition of 3-methyl indole to indenones. a: 2,3-dimethylindole was used as nucleophile. b: the temperature was increased to 50 °C during the reaction due to its low rate. o-FBA = ortho-flurorobenzoic acid. 5-NO_2-SA = 5-nitrosalycilic acid

Since in the adition of 3-methyl indole to cyclohexenone the aza-michael product was the only one observed, we were surprised and a bit disappointed when we saw that in this reaction indenones **265** gave also the corresponding products **319** arising from a C-2 F-C alkylation of indole. If using the optimized conditions with TFA, this is the major product, obtained in quite low to moderate enantioselectivities (entries **1-3**). Ratios of A-M/F-C products **318/319** were rougly 2:3 and anyway the combined yields of A-M and F-C products were only moderate. Changing to benzoic acid derivatives as acidic partners resulted in no reaction (entries **4-5**), while again (*S*)-TRIP improved the results (entry **7**): using this acid, a ratio of 2:1 in favor of the A-M product was observed an remarkably the enantioselectivity was raised up to 94%. Interestingly the F-C product had lower, but still acceptable enantiomeric excess. Since this result was promising but in this reaction there was poor chemoselectivity, we hoped to get better results avoiding this problem by using 2,3-dimethylindole as substrate (entry **8**). Unfortunately, this reaction, repeated twice, didn't show conversion. Finally, another indenone was employed, but its reactivity was very low and low yields were obtained even if rising the temperature and with prolonged reaction times (entries **8-9**). A sample of product could anyway be obtained, but HPLC analysis revealed lower enantioselectivities compared to the one obtained with the other indenone.
Despite the high enantiomeric excess obtained in entry **7**, the low chemoselectivity of the reaction led us to give up, combined also with matters of time and catalyst availability.

6.2.3) part III: Brønsted acid catalysis



Entry	299a : 252b	Catalyst (%)	Solvent	t (h)	Yield 300ab (%)	ee 300ab (%)	Yield 320ab (%)
1	1.2 : 1	**88h** (20)	Toluene	3	45	20	n.d.
2	1.2 : 1	**88h** (20)	Toluene	7	62	20	n.d.
3[a]	1.2 : 1	**88h** (20)	Toluene	45	40	20	n.d.
4[a]	1.2 : 1	**88h** (20)	$CHCl_3$	42	45	20	n.d.
5	1.2 : 1	**88h** (5)	MTBE	72	20	27	10
6	1.2 : 1	**88n** (20)	Toluene	3	56	5	32
7	1 : 1.2	**88n** (20)	Toluene	5.5	65	4	23
8	1 : 1.2	**88n** (20)	$CHCl_3$	3	67	8	30
9	1 : 1.2	**88n** (20)	EtOAc	38	44	0	44
10	1 : 1.2	**88n** (20)	MTBE	22	61	20	35
11	1 : 1.2	**88n** (20)	THF	44	42	12	40
12	1 : 1.2	**88n** (20)	Dioxane	72	26	10	n.d.
13	1 : 1.2	**88n** (20)	MeOH	3	0	-	0
14[b]	1 : 1.2	**88n** (20)	DMF	32	0	-	0
15	1 : 1.2	**88g** (20)	Toluene	72	80	20	12
16	1 : 1.2	**88g** (20)	MTBE	72	n.d.	12	n.d.
17	1 : 1.2	**88g** (20)	THF	-	-	-	-
18	1 : 1.2	**88g** (20)	Water	72	n.d.	-7	n.d.
19	1 : 1.2	**88k** (20)	MTBE	72	65	0	32
20	1.2 : 1	**88e** (2)	Toluene	72	62	4	27
21	1.2 : 1	**88f** (5)	Hexane	72	39	20	22
22	1.2 : 1	**88f** (5)	Et_2O	72	64	32	16
23	***1.2 : 1***	***88f (5)***	***MTBE***	***72***	***50***	***34***	***5***
24	1.2 : 1	**88f** (10)	Toluene	6	68	29	25
25	1.2 : 1	**88f** (2)	Toluene	96	70	28	20
26[c]	1.2 : 1	**88f** (2)	Toluene	72	0	-	
27[d]	1.2 : 1	**88f** (2)	Toluene	144	9	30	n.d.
28	1 : 0	TsOH (20)	Toluene	15	-	-	-
29	0 : 1	TsOH (20)	Toluene	15	-	-	-
30	1.2 : 1	TsOH (20)	Toluene	15	73	-	27
31[e]	1.2 : 1	TsOH (20)	Toluene	72	0	-	0

Table 6.15: results of the Brønsted acid catalyzed aza-Michael addition of 3-methyl indole to cyclohexenone. a: reaction temperature = -20 °C. b: reaction temperature raised to 60 °C during the reaction due to its low rate. c: powdred 4Å MS (30 mg) were used as additive. d: reaction temperature was initially -78 °C and then raised to -30 °C during the reaction due to its low rate. e: 2,3 dimethylindole was used as substrate.

While we were trying triflimides as counteranions in iminium ion catalysis, we thought that the increased acidity of these compounds could be enough to make possible a Brønsted acid catalysis for this reaction. Actually, when we tried the addition of 3-methyl indole to cyclohexenone using 20% of the catalyst **88h**, the results were surprising (*Tab. 6.15*, entry **1**). Within 5 min. the reaction mixture from colorless changed to an orange/red color and then became violet. After only three hours we observed a good conversion by TLC, but another product was formed together with the aza-Michael product. We decided to stop the reaction and see the results. After purification we measured a promising 20% of ee on the aza-Michael product and decided to further optimize the reaction. Here, the byproduct yield was not measured, but it was identified as the corresponding Friedel-Crafts product **320ab** arising from the attack of indole in C-2 position.

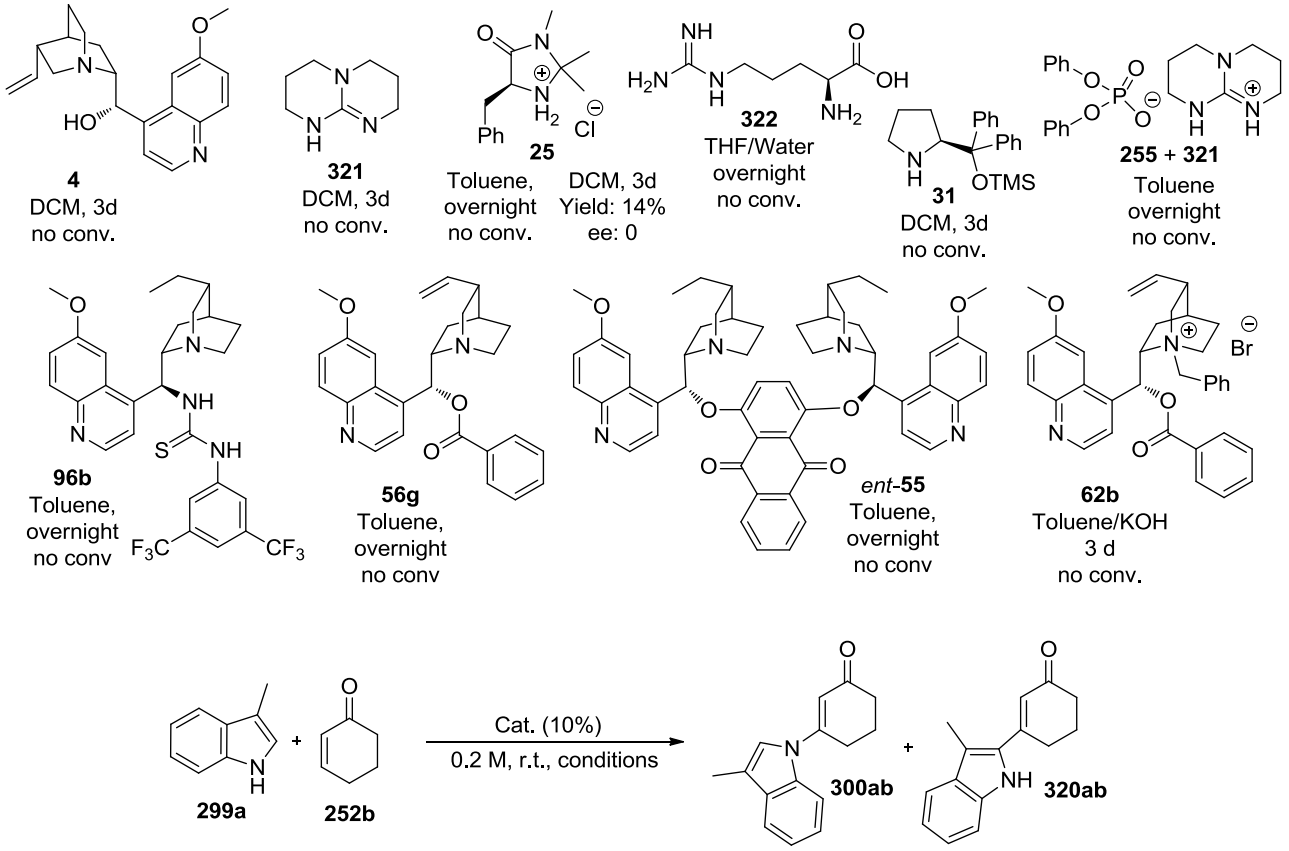
Some general considerations for the next entries.

1) In all the reaction that worked, the mixture's color changed form colorless to orange/red and then became violet. Someone in the end was blue.
2) since our target was the aza-Michael product, the yield of the F-C product was determined to determine the selectivity, but the ee was not.

Full conversion in the same reaction was observed in 7 hours (*Tab. 6.15*, entry **2**), and since the reaction was so fast, we tried to repeat it at low temperature. The reaction rate was lower, but unfortunately the ee didn't change (*Tab. 6.15*, entry **3**). Two solvents were also tried and MTBE dhowed a slight improvement in ee (*Tab. 6.15*, entries **4-5**). At this point we decided to perform a wide solvent screeining with catalyst **88h**, available in quite large amounts in our laboratory. All the solvents except highly polar ones showed reactivity and the best selectivity was given again by MTBE (*Tab. 6.15*, entries **6-14**). Anyway this didn't happen with catalyst **88g**: the reactivity was much lower, and we found toluene to give the best selectivity (*Tab. 6.15*, entries **15-18**). Catalysts **88k** and **88e** didn't give high ee (*Tab. 6.15*, entries **19-20**), while catalyst **88f** was the best in terms of ee (*Tab. 6.15*, entries **21-27**). Also the reactivity was very good, as with 10% of the catalyst the reaction was complete in 6 h (*Tab. 6.15*, entry **24**) and we could decrease the loading to 2%, even if 4 days of time were required (*Tab. 6.15*, entry **25**). Anyway the ee was only 30% and working with molecular sieves or at lower temperature didn't lead to improvements (*Tab. 6.15*, entries **26-27**). MTBE proved to be the best solvent again and actually entry **23**, in which it's used, is the best of all the table. Anyway, the ee was not that good and a mixture of products **300ab** and **320ab** was obtained. For this reason we had to stop the project at this point. The only other optimization possible would have been the synthesis and evaluation of other catalysts, but this opration would have been too much time consuming for our efforts. Only other four reactivity trials were carried out: stirring only the indole or only the enone with TsOH, the purple/violet color was not observed (*Tab. 6.15*, entries **28-29**), while instead was observed in the racemic reaction (*Tab. 6.15*, entry **30**). This means that this is the colour possessed by a reaction intermediate. The nature of this intermediate is not clear, and everything is complicated also by the observation that the substrate 2,3-dimethyl indole is not reactive using this kind of catalysis (*Tab. 6.15*, entry **31**). More detailed mechanicistic experiment would have been required to understand the process, and then to try to optimize more the reaction but all considered, they were not in our aims.

6.2.4) part IV: miscellaneous

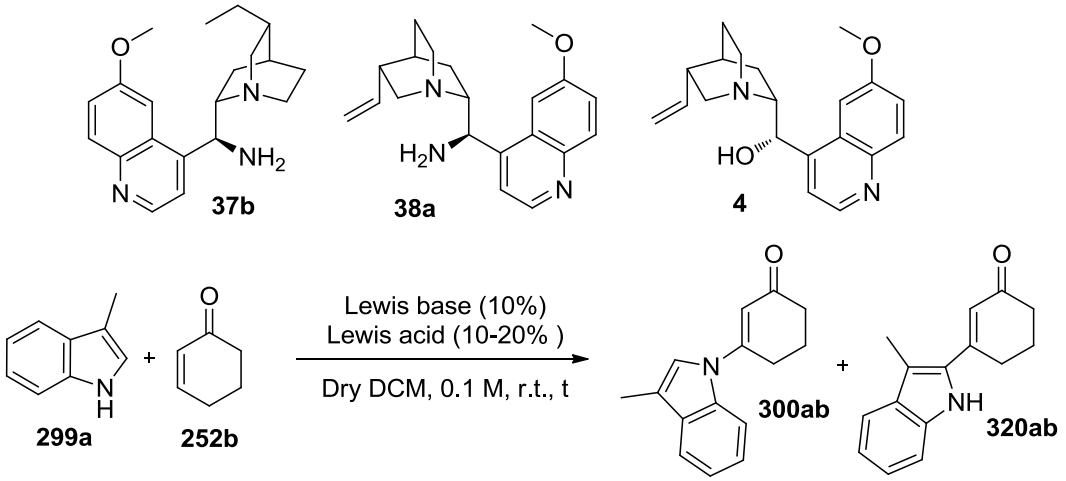
During the work on enantioselective aza-michael addition of 3-Methyl indole to cyclohexenone many kind of catalysis were tried but not effective. Free quinine, Brønsted bases, bifunctional thioureas, PTC, and a combination DPP/TBD were not able to promote the reaction. A little conversion was observed with MacMillan's catalyst **25**, but no ee was obtained. These results are reported in scheme **6.2**.



Scheme **6.2**: failed catalyses for the enantioselective aza-michael addition of 3-Methyl indole to cyclohexenone.

In the study of this reaction we wanted also to wkow whether if Lewis acids could be responsible for iminium ion formation other that Brønsted acids. So in this case this would be anyway iminium ion catalysis, but the acid used for iminium in formation would be metallic. Also simple quinine was tried because this catalysis was reported in a paper (*Tab. 6.16* entry **1**)[167d], but no results were obtained. The same TMSCl as acid didn't give the product as well (*Tab. 6.16* entry **2**). Next, we investigated some Lewis acids equimolar respect to the amine catalyst in toluene (*Tab. 6.16* entries **3-6**). The poor results obtained prompted us to switch to Dry DCM as solvent and to try also a 1:2 ratio between the catalyst and the acid. Lewis acids $Sc(OTf)_3$, $InBr_3$ and AgOTf were used with both 10% and 20% in combination with 10% of catalyst (*Tab. 6.16* entries **7-8**, **9-10**, and **12-13**). Two of them did not lead to a reaction if used in 10% mol (*Tab. 6.16* entries **9** and **12**). With $Sc(OTf)_3$ different results were obtained using 10% and 20% of the acid: in entry **7** the aza-Michael product is the major, in entry **8** is the opposite. ee's are generally better for the F-C product, albeit quite low. With $InBr_3$ and AgOTf prevalence of A-M adduct was observed but the ee's were also quite low; moreover $InBr_3$ showed wery low yields and

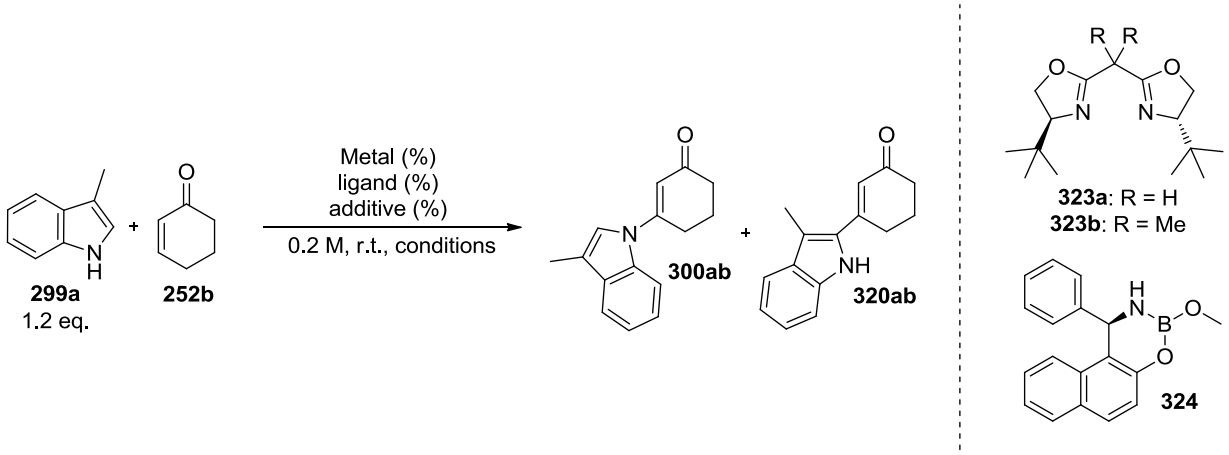
AgOTf showed poor chemoselectivities (*Tab. 6.16* entries **10** and **13**). Using $In(OTf)_3$ in place of $InBr_3$ lead to acceptable yields but again no chemoselectivity and no ee (*Tab. 6.16* entry **11**). Among the other acids tried, only TMSOTf, $MgBr_2 \cdot Et_2O$ and BF_3 showed reactivity (*Tab. 6.16* entries **14**, **16** and **19-20**). Anyway, in all the cases quite low yields, chemo- and enantioselectivities were observed. The only exception was the ee of the FC product observed with BF_3. For this reason the reaction was repeated with 1 eq of BF_3 to try to favor the F-C product formation. Actually this happened, but ee dropped, suggesting a racemic background reaction catalyzed by BF_3 only (*Tab. 6.16* entry **20**).



entry	Lewis base	Lewis acid (%)	t	Yield 300ab (%)	ee 300ab (%)	Yield 320ab (%)	ee 320ab (%)
1	**4**	TMSCl (20%)	4 d	0	-	0	-
2	**38a**	TMSCl (20%)	4 d	0	-	0	-
3[a]	**37b**	$Sc(OTf)_3$ (10%)	5 d	22	0	0	-
4[a]	**37b**	$InBr_3$ (10%)	5 d	0	-	0	-
5[a]	**37b**	$CeCl_3$ (10%)	5 d	0	-	0	-
6[a]	**37b**	I_2 (10%)	5 d	0	-	0	-
7	**37b**	$Sc(OTf)_3$ (10%)	3 d	36	2	15	17
8	**37b**	$Sc(OTf)_3$ (20%)	3 d	19	5	50	12
9	**37b**	$InBr_3$ (10%)	3 d	0	-	0	-
10	**37b**	$InBr_3$ (20%)	3 d	9	27	0	-
11	**37b**	$In(OTf)_3$ (20%)	3 d	36	1	31	2
12	**37b**	AgOTf (10%)	3 d	0	-	0	-
13	**37b**	AgOTf (20%)	3 d	36	16	16	19
14	**37b**	TMSOTf (20%)	3 d	18	9	8	12
15	**37b**	$Pd(OAc)_2$ (20%)	3 d	0	-	0	-
16	**37b**	$MgBr_2 \cdot Et_2O$ (20%)	3 d	21	14	6	24
17	**37b**	$B(OH)_3$ (20%)	3 d	0	-	0	-
18	**37b**	$B(OMe)_3$ (20%)	3 d	0	-	0	-
19	**37b**	$BF_3 \cdot Et_2O$ (20%)	3 d	13	2	6	34
20	**37b**	$BF_3 \cdot Et_2O$ (100%)	overnight	15	0	53	0
21	**37b**	$(Ph)_3CCl$ (20%)	overnight	0	-	0	-
22	**37b**	$SnCl_2$ (20%)	overnight	0	-	0	-
23	**37b**	$ZnBr_2$ (20%)	overnight	0	-	0	-
24	**37b**	$(Ph)_3ZnCl$ (20%)	overnight	0	-	0	-

Table 6.16: trying to use Lewis acids to form the iminium ion. a: dry Toluene was used as solvent.

These poor results obtained lead us to conclude that using Lewis acids to form the iminium ion is not a good method for the catalysys of this reaction.
Curiosity lead us to carry out some trials also in Lewis acid catalysis. The results are summarized in *table 6.17*.



Entry	Solvent	Metal (%)	Ligand (%)	Additive (%)	t	Yield 300ab (%)	ee 300ab (%)	Yield 320ab (%)	ee 320ab (%)
1	DCM	CuCl (8)	**323a** (10)	$AgSbF_6$ (16)	3 d	11	2	30	30
2	DCM	CuCl (8)	**323b** (10)	$AgSbF_6$ (16)	3 d	0	-	0	-
3[a]	DCM	$Cu(OTf)_2$ (4)	**88e** (8)	Ag_2CO_3 (4)	2 d	0	-	0	-
4[a]	DCM	CuCl (4)	**88e** (8)	Ag_2CO_3 (4)	2 d	0	-	0	-
5[a]	DCM	$MgBr_2{\cdot}Et_2O$ (4)	**88e** (8)	Ag_2CO_3 (4)	2 d	0	-	0	-
6	Toluene	$Mg(Ot\text{-}Bu)_2$ (10)	**88h** (20)	-	2 d	0	-	0	-
7	Toluene	-	-	TsOH (10)	18 h	73	-	27	-
8	Toluene	-	**324** (10)	TFA (10)	3 d	0	-	0	-
9	Toluene	-	**324** (10)	TsOH (10)	1 h	37	0	49	0

Table 6.17: some Lewis acid catalysis for the aza-Michael addition of 3-Methyl indole to Cyclohexenone. a: powdred 4Å MS (30 mg) were used as additive.

Of all the catalyst combination used only entry **1** and **8** showed reactivity. CuBOX catalysis (entry **1**), with $AgSbF_6$ as additive used for halide extraction, provided in three days a mixture 1:3 of products **300ab** and **320ab**, with the first nearly racemic and the second in 30% of ee. Trying to form *in situ* Cu or Mg phosphates to use them in catalysis resulted in no reaction (entries **2-5**). The use of oxazaborolidine **324** in combination with TFA did not lead to a reaction, but if used in combination with TsOH resulted in a very fast but not chemo and enantioselective reaction (entries **8-9**). It must be pointed out, anyway, that TsOH perform racemic catalysis, so this result might be due to this, albeit in this reaction time is much longer and the product ration is different (entry **7**).

Anyway, since these poor results, in the end the project of an enantioselective aza-Michael addition of indoles to enones was definitively abandoned.

6.2.5) EXPERIMENTAL SECTION.

General experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian inova 300, at 300 MHz and 75 MHz respectively, Varian mercury 400, at 400 MHz and 100 MHz respectively, or Varian inova 600, at 600 MHz and 150 MHz respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. $CDCl_3$ was passed over a short pad of alumina before use. Coupling constants are given in Hz. The carbon types were determined from DEPT ^{13}C NMR experiments. NOE spectra were recorded using the DPFGSE-NOE sequence[188].
Optical rotations are determined using a Perkin Elmer 341 instrument with sodium lamp and are reported as follows: $[\alpha]^{^{\circ}C}_{D}$ (*c* in g per 100 mL, solvent).
Thin Layer Chromatography (TLC) was performed on commercially available Fluka TLC plates on aluminium or PET foils with fluorescent indicator at 254 nm, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents.
Purification of the products was carried out by flash chromatography (FC) on silica gel (Aldrich, 230-400 mesh) according to the method of Still[189].
Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Materials

All the commercially available reagents and solvents were used without any further purifications; otherwise, where necessary, they were purified as recommended[190].
Compounds **73, 305, 308** and **317** were synthesyzed according to literature procedures[191].
Phosphoric acid catalysts and triflimides were prepared according according to literature procedures[192].
For catalysts **25** and **31** please see ref. 28 and 32.

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[188] (a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwand, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (b) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Resonance* **1997**, *125*, 302. (c) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Resonance* **1999**, *141*, 191. (d) See also: Claridge, T.D.W. *High Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.

[189] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

[190] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

[191] For compound **73** see: a) P. R. Schreiner, A. Wittkopp, *Org. Lett.*, **2002**, *4*, 217–220. b) for compound **305** see: G. Bartoli, G. Bencivenni, P. Galzerano, B. Giannichi, A. Mazzanti, P. Melchiorre, F. Pesciaioli, L. Sambri, *Chem. Eur. J.*, **2009**, *15*, 7846-7849. c) for compound **308** see: M. Betti, *Gazz. Chim. Ital.*, **1900**, *30 II*, 301. Another synthesis: d) C. Cardellicchio, C. Ciccarella, F. Naso, E. Schingaro, F. Scordari, *Tetrahedron: Asymmetry*, **1998**, *9*, 36667-3675.e) for compound **317** see: J. Valgeirsson, E. Ø. Nielsen, D. Peters, C. Mathiesen, A, S. Kristensen, U. Madsen, *J. Med. Chem.* **2004,** *47,* 6948-6957.

[192] a) T. R. Wu, L. Shen, J. M. Chong, *Org. Lett.*, **2004**, *6*, 2701–2704. b) R. R. Milburn, S. M. S. Hussain, O. Prien, Z. Ahmed, V. Snieckus, *Org. Lett.*, **2007**, *9*, 4403–4406. c) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566 –1568. d) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, 2004, *126*, 5356-5357. e) M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett,* **2010**, *14*, 2189–2192. f) V. Rauniyar, J. Wang, H. Burks, F. D. Toste, *J. Am. Chem. Soc.*, **2011**, *133*, 8486–8489. g) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.*, **2006**, *128*, 9626-9627.

For the other catalysts in sceme **6.2** please see section 6.3.1.
Chiral primary amine catalysts were synthesized according to literature procedures. Please see ref. 83 and 163.
Compounds **118, 255, 256, 257, 307, 309, 310, 311, 312, 313, 314, 315, 316, 321, 322, 323a** and **323b** are commercially available. Compound **306** was already present in our laboratories. Compound **79b** was kindly provided by Dr. Luca Bernardi.
All the ketones and the indoles were purchased from Sigma-Aldrich or Alfa Aesar and used as received, except indenones, which were prepared according to literature procedures[193].

General procedure for the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone via iminium ion

9-*epi*-9-amino-9-deoxyquinine (**A**) or 9-*epi*-9-amino-9-deoxy quinidine (***ent*-A**) (0.01 or 0.02 mmol, 0.1 or 0.2 eq.) and TFA (0.01 mmol, 0.1 eq) or (*S*)-TRIP (0.02 mmol, 0.2 eq.) were introduced into a screw-capped vial equipped with a magnetic stir bar. Toluene (0.5 ml, 0.2 M) was added and stirring was continued for 5 min., followed by addition of cyclohexenone (0.1 mmol, 1 eq.). Then, stirring was continued for other 5 min., and 3-methyl indole (0.12 mmol, 1.2 eq) was added. The vial was closed and stirring was continued for three days.
Subsequently the reaction mixture was diluted with an 1:1 mixture of Et_2O/DCM, passed through a short pad of silica and the solvent was evaporated in vacuo to give the crude product which was purified through flash chromatography on silica gel.

Reaction on the other substrates were performed with similar procedures

General procedure for the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone via Brønsted acid or oxazaborolidine catalysis

3-Methyl indole (1.2 eq.) was added to a solution of chclohexenone (1 eq.) and the triflimide catalyst in the solvent and the mixture was stirred for the given time. Then the solvent was evaporated in vacuo and the products purified through flash chromatography on silica gel.

The procedure for oxazaborolidine catalysis is similar, except than TFA or TsOH were also added to the mixture after the catalyst.

General procedure for the enantioselective aza-Michael addition of 3-methyl indole to cyclohexenone via iminium ion using Lewis acids as acids.

HQ-NH_2 (0.01 mmol, 0.1 eq.) was introduced into a test tube, which then was put into a glovebox. The lewis acid (0.01 or 0.02 mmol, 0.1 or 0.2 eq.) was added, the test tube was covered with a serum cap and then removed form the glovebox. Dry DCM or dry Toluene (0.5 ml) was then added via syringe and the mixture was stirred 1 h. then cyclohexenone (0.1 mmol, 1 eq.) was added via syringe and the mixture was stirred further 5-10 min. Then a solution of 3-Methyl indole (0.12 mmol, 1.2 eq.) in 0.5 ml of Dry DCM or dry Toluene was

[193] a) L. Minutia, A. Taticchi, E. Gacs-Baitz, A. Marrocchia, *Terahedron*, **1995**, *51*, 8953-8958. b) H. E. Zimmerman, V. Suryanarayan, *Eur. J. Org. Chem.,* **2007**, 4091–4102.

added an the mixture was stirred fo the given time. Subsequently the reaction mixture was diluted with an 1:1 mixture of Et_2O/DCM, passed through a short pad of silica and the solvent was evaporated in vacuo to give the crude product which was purified through flash chromatography on silica gel.

Procedure for CuBOX catalysis (table 17, entry 1)

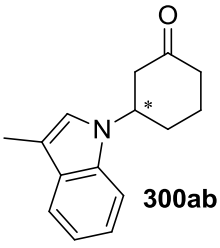
In a test tube containing a stir bar was placed $CuCl_2$ (0.008 mmol, 8%) with no precaution to exclude moisture and air. The schlenck was covered with a serum cap, flame dried in vacuo and then backfilled with argon upon cooling. Then the tube was put into a glovebox and the ligand (0.01 mmol, 10%) was added. The tube was covered with a serum cap, removed from the glovebox and 0.5 ml of dry DCM were added under argon. This solution was stirred at r.t. for 2 hours. Meanwhile, $AgSbF_6$ (0.016 mmol, 16%) stored in the glovebox was added to a different vial, which was also covered with a serum cap and removed from the glovebox. To this vial was also added dry DCM (0.5 ml) under argon and this solution was transferred via syringe under argon to the tube containing the copper and the ligand. The so-obtained mixture was stirred in the absence of light for 2 hours, then cyclohexenone (0.1 mmol, 1 eq.) was added, the mixture stirred further 5 min. and finally a solution of 3-methyl indole (0.12 mmol, 1.2 eq.) in 1 ml of dry DCM was added to the reaction mixture via syringe. The so-obtained mixture was stirred fot the required time, then diluted with an 1:1 mixture of Et_2O/DCM, passed through a short pad of silica and the solvent was evaporated in vacuo to give the crude product which was purified through flash chromatography on silica gel.

Procedure for Lewis acid catalysis (table 17, entry 2-5)

For entry **2-5** a literature procedure was followed[194].
For entry **6** another literature procedure was followed[195].

Characterization of compounds

3-(3-methyl-1H-indol-1-yl)cyclohexanone 300ab (green oil)



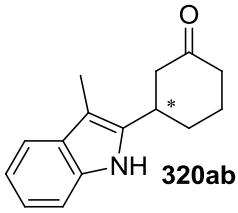
300ab

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.77 (m, 1H), 2.14 (m, 2H), 2.28 (m, 1H), 2.32 (s, 3H), 2.41 (m, 1H), 2.51 (m, 1H), 2.76 (m, 1H), 2.86 (m, 1H), 4.62 (m, 1H), 6.96 (s, 1H), 7.12 (dt, 1H, J_a = 7.64 Hz; J_b = 0.16 Hz), 7.21 (dt, 1H, J_a = 7.97 Hz; J_b = 1.22 Hz), 7.29 (d, 1 H, J = 8.29 Hz), 7.57 (d, 1 H, J = 7.86 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 9.7 (CH_3), 22.3 (CH_2), 31.6 (CH_2), 40.9 (CH_2), 48.3 (CH_2), 53.9 (CH), 109.0 (CH), 111.5 (C), 119.1 (CH), 119.3 (CH), 121.2 (CH), 121.7 (CH), 128.8 (C), 135.6 (C), 208.3 (C).

ESI-MS: calcd: 227; found: 250 (M+Na).
HPLC analysis: on a Daicel Chiralpak AD-H column; Hex/i-PrOH 9:1, flow rate 0.6 mL/min, T = 25 °C, λ = 210 nm, τ_{major} = 11.1 min. τ_{minor} = 11.7 min. (using the catalyst combination HQ-NH_2 – (*S*)-TRIP).
$[\alpha]_D^{rt}$ = - 24 (*c* = 0.59, $CHCl_3$, ee = 56% (*Tab. 2*, entry **2**)).

[194] K. Saito, Y. Kajiwara, T. Akiyama, *Angew. Chem. Int. Ed.*, **2013**, *52*, 13284-13288.
[195] M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem. Int. Ed.*, **2010**, *49*, 3823–3826.

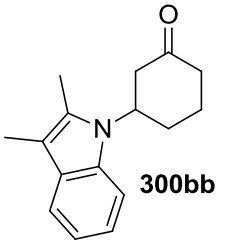
3-(3-methyl-1H-indol-2-yl)cyclohexanone 320ab (red oil)



320ab

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.83 (m, 2H), 2.09 (m, 2H), 2.23 (s, 3H), 2.35 (m, 1H), 2.53, (m, 3H), 3.34, (m, 1H), 7.12 (m, 2H), 7.28 (m, 1H), 7.50 (m, 1H), 8.01 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 8.6 (CH_3), 25.5 (CH_2), 31.1 (CH_2), 36.5 (CH), 41.3 (CH_2), 47.3 (CH_2), 106.6 (C), 110.5 (CH), 118.4 (CH), 119.3 (CH), 121.5 (CH), 129.2 (C), 135.3 (C), 136.1 (C), 210.8 (C).
ESI-MS: calcd: 227; found: 282 (M+MeOH+Na) and 298 (M+MeOH+K).
HPLC analysis: on a Daicel Chiralpak AD-H column; Hex/i-PrOH 8:2, flow rate 0.6 mL/min, T = 25 °C, λ = 210 nm, τ_{major} = 12.6 min. τ_{minor} = 11.5 min.

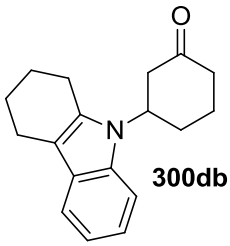
3-(2,3-dimethyl-1H-indol-1-yl)cyclohexanone 300bb (red crystals)



300bb

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.70, (tq, 1H, J_a = 14.13 Hz; J_b = 3.84 Hz), 2.09 (m, 1H), 2.17 (m, 1H), 2.22 (s, 1H), 2.33 (s, 1H), 2.42 (m, 1H), 2.52 (m, 1H), 2.63 (m, 2H), 3.31, (t, 1H, J = 13.8 Hz), 4.49 (m, 1H), 7.09 (m, 2H), 7.42, (d, 1H, J = 8.02 Hz), 7.50, (d, 1H, J = 4.32 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 8.9 (CH_3), 11.1 (CH_3), 22.8 (CH_2), 30.1 (CH_2), 40.9 (CH_2), 46.9 (CH_2), 54.4 (CH), 107.4 (C), 110.5 (CH), 118.6 (CH), 118.8 (CH), 120.6 (CH), 129.7 (C), 131,7 (C), 134.2 (C), 208.5 (C).
ESI-MS: calcd: 241; found: 264 (M+Na).
HPLC analysis: on a Daicel Chiralpak AD-H column; Hex/i-PrOH 98:2, flow rate 0.55 mL/min, T = 25 °C, λ = 210 nm, τ_{major} = 17.3 min. τ_{minor} = 16.5 min.
$[\alpha]_D^{rt}$ = + 3.9 (*c* = 3.66, $CHCl_3$).

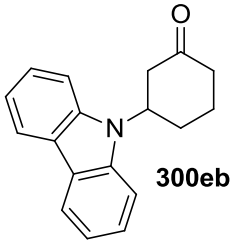
3-(3,4-dihydro-1H-carbazol-9(2H)-yl)cyclohexanone 300db (yellow foam)



300db

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.79 (tq, J_a = 13.78 Hz; J_b = 4.30 Hz), 1.84 (m, 2H), 1.93 (m, 2H), 2.16 (m, 2H), 2.42 (td, J_a = 13.78 Hz; J_b = 3.01 Hz), 2.51 (m, 1H), 2.62 (m, 1H), 2.7, (t, 4H, J = 5.60 Hz), 3.26 (t, 1h, J = 13.80 Hz), 4.45, (m, 1H), 7.09 (m, 2H), 7.41 (d, 1H, J = 8.29 Hz), 7.47 (d, 1H, J = 7.69 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.0 (CH_2), 22.8 (CH_2), 22.9 (CH_2), 23.3 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 40.9 (CH_2), 47.1 (CH_2), 54.1 (CH), 110.3 (C), 110.4 (CH), 118.3 (CH), 118.9 (CH), 120.7 (CH), 128.4 (C), 134.6 (C), 134.7 (C), 208.4 (C).
ESI-MS: calcd: 267; found: 290 (M+Na).
HPLC analysis: on a Daicel Chiralpak AD-H column; Hex/i-PrOH 95:5, flow rate 0.6 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 12.1 min. τ_{minor} = 11.5 min.
$[\alpha]_D^{rt}$ = + 11.9 (*c* = 2.81, $CHCl_3$).

3-(9H-carbazol-9-yl)cyclohexanone 300eb (white foam)

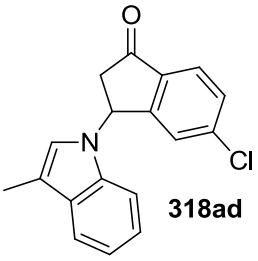


300eb

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.80 (tq, J_a = 14.0 Hz; J_b = 3.90 Hz), 2.21 (m, 2H), 2.50, (dt, 1H, J_a = 15.21 Hz; J_b = 6.43 Hz), 2.58, (d, 1H, J = 15.79 Hz), 2.74, (m, 2H), 3.43, (t, 1h, J = 15.59 Hz), 4.85, (m, 1H), 7.24, (t, 2H, J = 8.06 Hz), 7.43, (t, 2H, J = 8.06 Hz), 7.49 (d, 2H, J = 8.06 Hz), 8.10, (d, 2H, J = 8.06 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 22.8 (CH_2), 29.3 (CH_2), 40.9 (CH_2), 45.8 (CH_2), 54.0 (CH_3), 109.7 (CH), 119.3 (CH), 120.6 (CH), 123.6 (C), 125.7 (CH), 239.1 (C), 208.3 (C).
ESI-MS: calcd: 263; found: 286 (M+Na).
HPLC analysis: on a Daicel Chiralpak AD-H column; Hex/i-PrOH 9:1, flow rate 0.6 mL/min, T = 25 °C, λ = 254 nm, τ_{major} = 15.4 min. τ_{minor} = 14.1 min.
$[\alpha]_D^{rt}$ = - 10.6 (*c* = 2.19, $CHCl_3$).

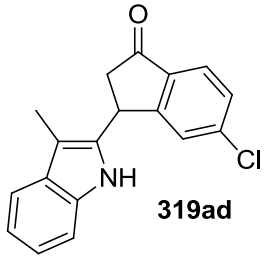
5-chloro-3-(3-methyl-1H-indol-1-yl)-2,3-dihydro-1H-inden-1-one 318ad (orange foam)



318ad

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.28 (s, 3H), 2.84 (dd, 1H J_a = 19.33 Hz; J_b = 3.87 Hz), 3.32 (dd, 1H J_a = 18.47 Hz; J_b = 8.16 Hz), 6.06 (dd, 1H, J_a = 7.83 Hz; J_b = 3.92 Hz), 6.64 (s, 1H), 7.18, (m, 3H), 7.37 (s, 1H), 7.50 (dd, 1H, J_a = 8.56 Hz; J_b = 0.92 Hz), 7.59, (d, 1H, J = 7.64 Hz), 7.81 (d, 1H, J = 7.95 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 9.6 (CH_3), 44.6 (CH_2), 53.3 (CH), 109.0 (CH), 121.6 (C), 119.5 (CH), 119.6 (CH), 122.1 (CH), 122.6 (CH), 124.8 (CH), 126.4 (CH), 129.4 (C), 130.5 (CH), 135.3 (C), 136.3 (C), 142.2 (C), 154.2 (C), 200.9 (C).
ESI-MS: calcd: 295; found: 318 (M+Na).
HPLC analysis: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 9:1, flow rate 0.7 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 21.8 min. τ_{minor} = 26.1 min. (using the catalyst combination HQ-NH_2 – (*S*)-TRIP).
$[\alpha]_D^{rt}$ = - 22.3 (*c* = 1.785, $CHCl_3$, ee 55 (*Tab*. 14, entry 6)).

5-chloro-3-(3-methyl-1H-indol-2-yl)-2,3-dihydro-1H-inden-1-one 319ad (yellow solid)



319ad

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.36 (s, 3H), 2.80 (dt, 1H, J_a = 19.47 Hz; J_b = 4.49 Hz), 3.29 (dd, 1H, J_a = 19.47 Hz; J_b = 8.24 Hz), 4.90, (dd, 1H, J_a = 8.37 Hz; J_b = 4.28 Hz), 7.14 (m, 2H), 7.22 (m, 1H), 7.30 (m, 1H), 7.38 (m, 1H), 7.55 (m, 1H), 7.68 (t, 1H, J = 8.51 Hz), 7.80 (br s, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 8.6 (CH_3), 35.6 (CH), 44.3 (CH_2), 109.1 (C), 110.7 (CH), 118.6 (CH), 119.6 (CH), 122.2 (CH), 124.7 (CH), 126.9 (CH), 128.9 (C), 129.3 (CH), 133.4 (C), 135.0 (C), 135.7 (C), 142.1 (C), 157.3 (C), 203.8 (C).
ESI-MS: calcd: 295; found: 318 (M+Na).
HPLC analysis: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 8:2, flow rate 0.7 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 13.0 min. τ_{minor} = 22.5 min. (using the catalyst combination HQ-NH_2 – (*S*)-TRIP).
$[\alpha]_D^{rt}$ = - 11.6 (*c* = 1.785, $CHCl_3$, ee 27 (*Tab*. 14, entry 6)).

The other products were not fully characterized.

6.3) The aza-Michael reaction (part V): addition of OH-free hydroxylamines to nitroalkenes

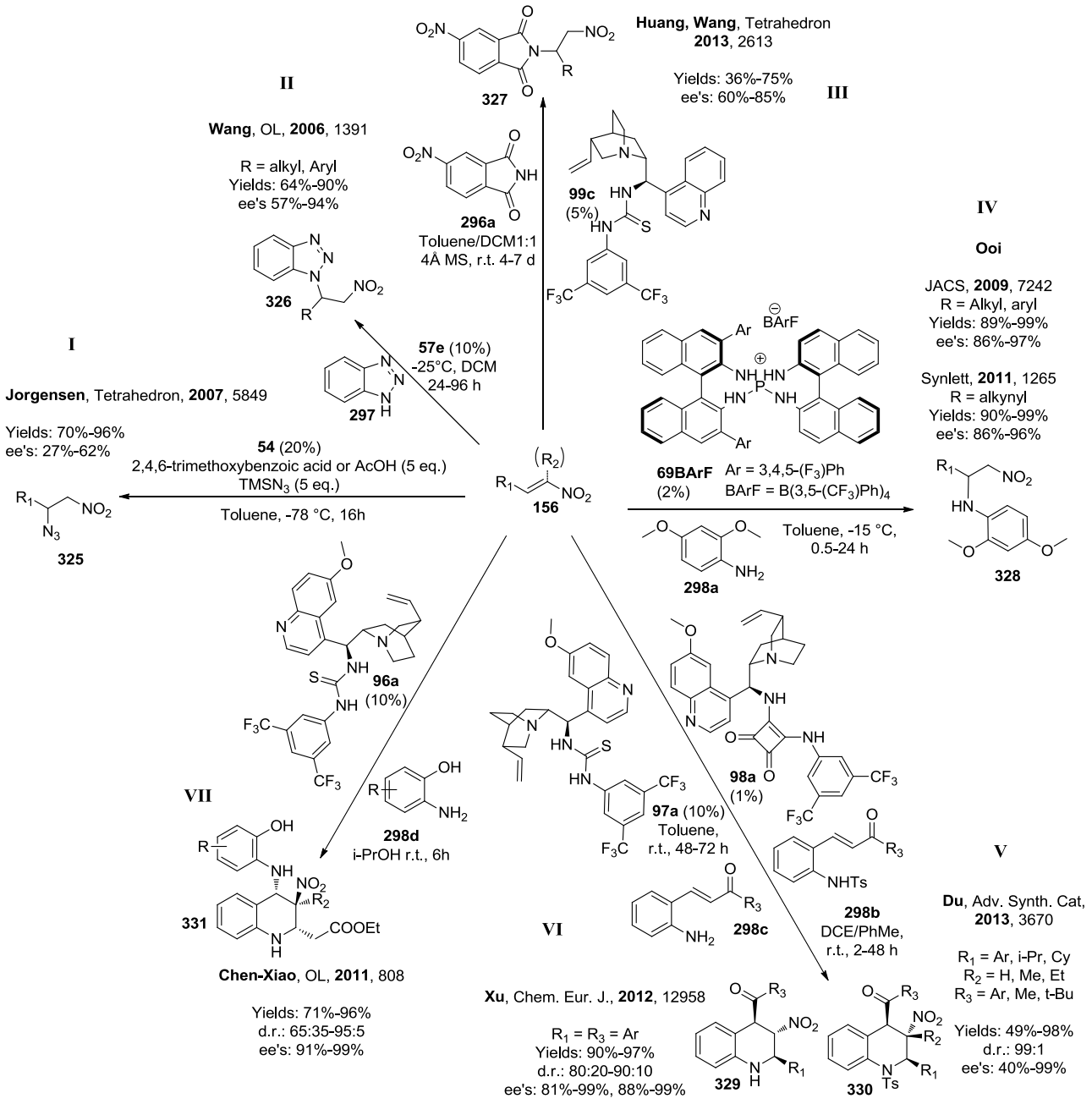
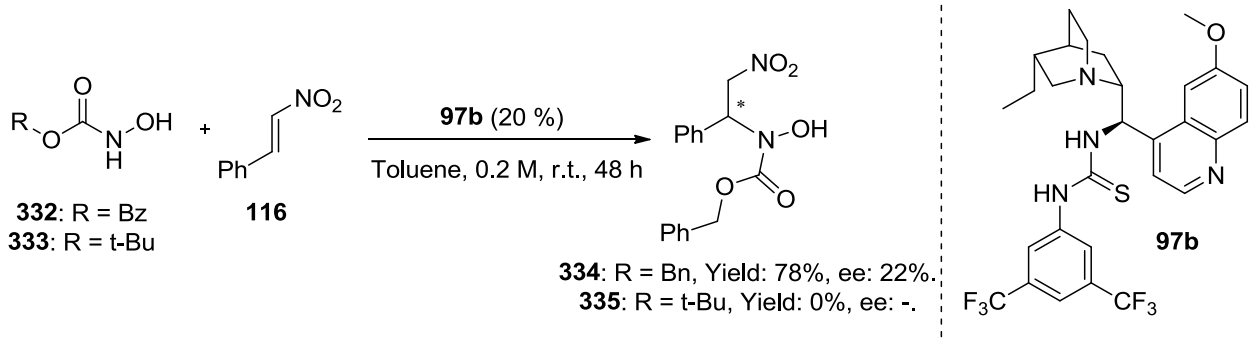


Figure 6.3: all the organocatalytic enantioselective AM additions to nitroalkenes reported to date.

If talking about nucleophiles in aza-Michael, the use of indoles is scarce, when talking about electrophiles we observed that nitroalkene chemistry in this field was underexplored. In this context, thioureas, widely used for their activation, were surprisingly not much employed. For instance, the first example of AM on nitroalkenes was reported in 2006 and involved the use of simple cupreidine as catalyst for the additions of benzotriazoles to nitroalkenes (*Fig.6.3*, **II**)[196]. The second 2007 example by Jorgensen is the azidation of

[196] J. Wang, H. Li, L. Zu, W. Wang, *Org. Lett.*, **2006**, *8*, 1391-1394.

nitroalkenes, but the results were not very good (*Fig. 6.3*, **I**)[197]. Ooi showed with two consecutive reports[198] that BINOL-based phosphonium BArFates **69BArF** are highly effective and selective catalysts for the AM addition of electron rich anilines to nitroalkenes (*Fig. 6.3*, **IV**). Addition of nitromaleimides to these electrophiles was reported in 2013 by Huang and Wang using thioureas as organocatalysts, but the results were not very good also in this example (*Fig. 6.3*, **III**)[199]. Only recently, effective use of thioureas and squaramides in aza-Michael addition were possible, curiously always in domino reactions. In 2011 Chen and Xiao reported the effective addition of ortho-hydroxy anilines to nitroalkenes with subsequent cyclization on imines (*Fig. 6.3*, **VII**)[200]. The products **331** formed in this way bear a quaternary stereocenter, and are obtained in generally good yields and ee's. using the same strategy, Xu and Du reported respectively in 2012[201] and 2013[202] an aza-Michael-Michael cascade cyclization to obtain enantioenriched substituted tetrahydroquinolines **329** and **330** with three chiral centers (*Fig. 6.3*, **V** and **VI**). In Xu's work the catalyst is a thiourea, in Du's work thr catalyst is a squaramide (both derived from cinchona alkaloids) and the carbon bearing the nitro-functionality is a quaternary stereocenter. In both cases yields and selectivities are very good.
Some quite used nucleophiles for these transformations are protected hydroxylamines. They can be doubly protected[203], or NH_2-free[204] or OH-free[205] and they were employed in many reactions using many catalysts. Simple hydroxylamines have never been used. Anyway the number of electrophiles employed is narrow and nitroalkenes have never been used. For this reason we thought that an aza-Michael addition of hydroxylamine derivatives to nitroalkenes could be a highly valuable and challenging transformation.



Scheme **6.3**: starting material evaluation for the enantioslective aza-Michael addition of OH-free hydroxylamines to nitrostyrene.

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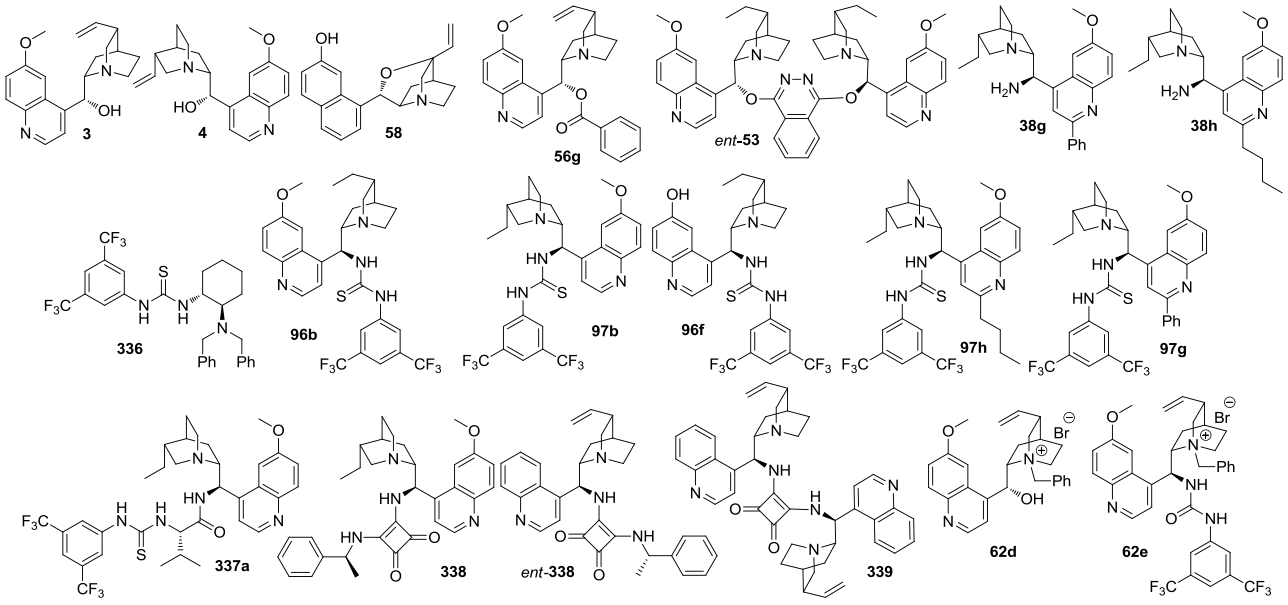
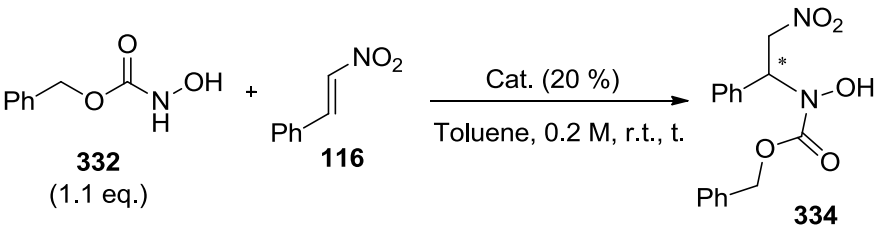
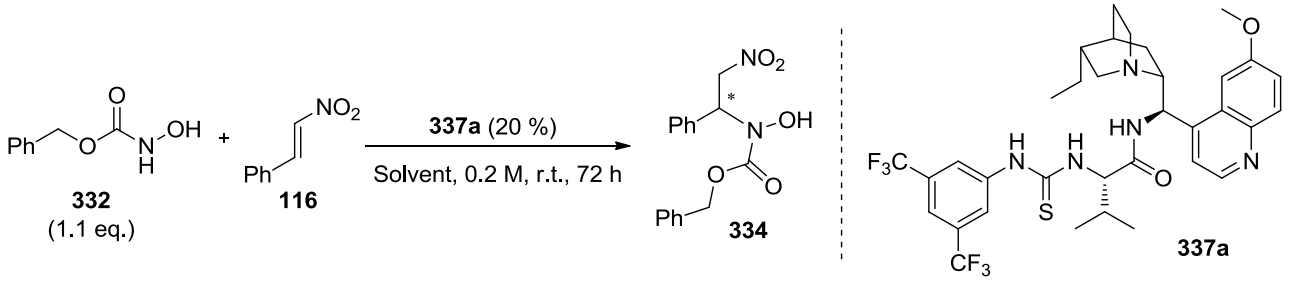




entry	Cat.	t (h)	Yield (%)	ee (%)
1	-	48	0	-
2	**3**	48	Quant.	9
3	**4**	48	Quant.	9
4	**58**	72	92	20
5	**56g**	72	29	5
6	*ent*-**53**	72	56	3
7	**38g**	72	47	5
8	**38h**	72	41	0
9	**336**	72	24	9
10	**96b**	72	79	21
11	**97b**	48	78	22
12	**96f**	48	99	13
13	**97h**	72	89	22
14	**97g**	72	82	15
15	**337a**	72	99	24
16	**338**	72	43	32
17	*ent*-**338**	72	92	10
18	**339**	72	59	5
19	**62d**	72	14	0
20	**62e**	72	63	6

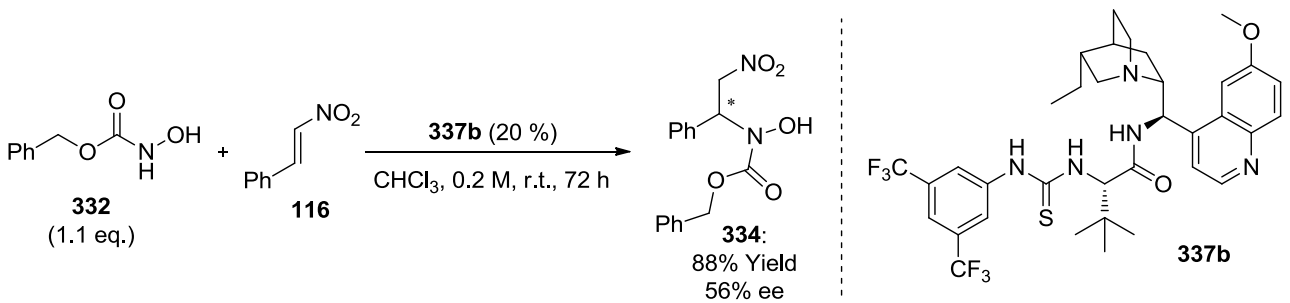
Table 6.18: catalyst evaluation for the enantioslective aza-Michael addition of OH-free hydroxylamines to nitrostyrene.

In scheme **6.3** it's possible to see the first preliminary trials on the starting material evaluation. N-Cbz hydroxylamine **332** shows reactivity and some enantioselectivity in toluene at room temperature using the cinchona alkaloid derived thiourea **97b** as catalyst. Conversely, N-Boc hydroxylamine **333** is not reactive under these reaction conditions. **333** was then chosen for the reqiured catalyst screening in the same conditions, which is reported in *table 6.18*. Qunine **3** and quinidine **4** gave the product in excellent yields but with low ee's (entries **2-3**). The others Brønsted base catalysts (entries **4-9**) did not generally show good yields and ee's, with the only exception of β-ICD **58** (entry **4**) which gave 20% of ee and a nearly quantitative yield in three days. The Takemoto-like catalyst **336** also did not gaive good results (entry **9**), while a better reaction outcome was obtained using cinchona alkaloid-derived bifuctional thiourea or squaramide organocatalysts **96b**-*ent*-**338** (entries **10-17**). It is interesting to note that the two best catalysts bear two chiral scaffolds: catalyst **337a** (entry **15**) is a cinchona alkaloid-derived thiourea with a chiral linker based on Valine and gives an excellent yield and 24% of ee. Catalyst **338** is a cinchona alkaloid-derived squaramide with (*S*)-phenylethylamine as a chiral scaffold on the other side (entry **16**). It gives the best ee, but since the yield was only 43% in three days, catalyst **337a** was chosen for further screening. Entry **1** confirms no background reaction.



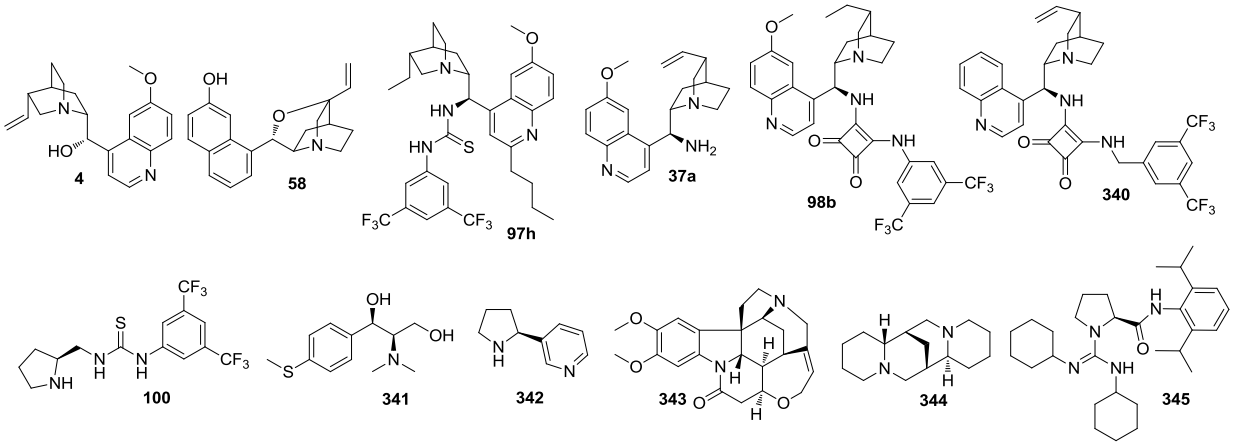
Entry	Solvent	Yield (%)	ee (%)
1	Toluene	99	24
2	PhCl	95	20
3	MTBE	24	21
4	$CHCl_3$	88	35
5	THF	0	-
6	EtOAc	57	22
7	i-PrOH	low	n.d.
8	MeOH	low	n.d.

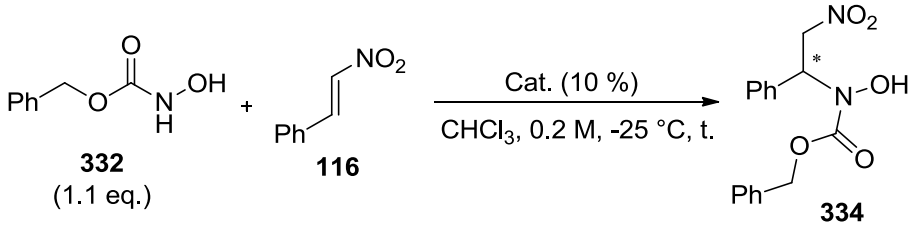
Table 6.19: Solvent screening for the enantioslective aza-Michael addition of OH-free hydroxylamines to nitrostyrene.



Scheme **6.4**: switching to t-leucine as linker in thioureidic part of the molecule.

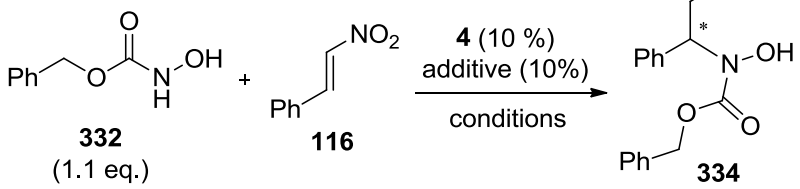
Table 6.19 shows the solvent screening: as other times happeed, the best reactivity is in aromatic and chlorinated solvents (entries **1-2** and **4**) with chloroform giving the best ee (entry **4**). Ethers and alcohols show low reactivity (entries **3**, **5**, **7-8**), ethyl acetate gives moderate yields and ee's not comparable with chloroform (entry **4**). $CHCl_3$ was then chosen as the best solvent and selected for further catalyst screening. First of all, catalyst **337b**, analogue to **337a** but having a *tert*-leucine linker, was tried in chloroform at room temperature. The higher steric hindrance ot the *t*-Bu group led to a remarkable increasing in enantioselectivity up to 56% (scheme **6.4**). Subsequently, some catalysts already used (*Tab. 6.20*, entries **1-3**) and new ones (*Tab. 6.2*, entries **4-12**) were screened at -25 °C, since the reactivity in Brønsted base catalysis was good. The results with the new catalysts were not satisfying, since all of them showed low reactivity except sparteine **344**, which however gave a racemic product (*Tab. 6.20*, entry **11**). Among the catalysts tried also at r.t., Brønsted basic catalysts **3** and **4** lead to a significative ee improvement (compare entries **1-2** of *Tab. 6.20* with entries **3-4** of *Tab. 6.18*), while bifunctional thiourea **97h** didn't (compare entry **3** of *Tab. 6.20* with entry **13** of *Tab. 6.18*).

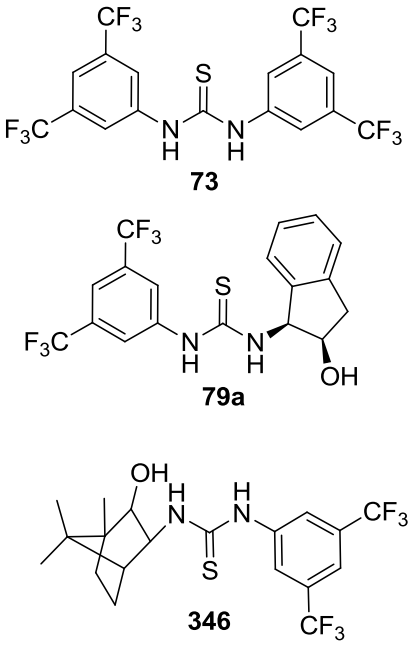




Entry	Cat	t (d)	Yield (%)	ee (%)
1	**4**	3	70	28
2	**58**	7	47	43
3	**97h**	7	47	18
4	**37a**	7	low	n.d.
5	**98b**	7	low	n.d.
6	**340**	7	low	n.d.
7	**100**	7	low	n.d.
8	**341**	7	34	0
9	**342**	7	0	-
10	**343**	7	24	24
11	**344**	4	81	0
12	**345**	4	0	-

Table 6.20: further catalyst screening at -25 °C.





Entry	Solvent	Additive	T (°C)	t (h)	Yield (%)	ee (%)
1	Toluene	**-**	r.t.	48	99	9
2	$CHCl_3$	**73**	r.t.	20	99	8
3	$CHCl_3$	**79a**	r.t.	14	97	14
4	$CHCl_3$	**346**	r.t.	14	94	6
5	$CHCl_3$	**-**	-25	72	70	28
6	$CHCl_3$	**79a**	-20	48	84	22
7	Toluene	**79a**	-25	96	81	27
8	$CHCl_3$	**79a**	-25	72	89	26

Table 6.21: cooperative catalysis for the enantioselective aza-michael addition of OH-free hydroxylamines to nitroalkenes.

Since Brønsted bases gave high reactivity and bifunctional thioureas gave better selectivity, also a cooperative approach was briefly tried for this reaction, combining bases and thioureas. Quinidine **4** was chosen as Brønsted basic catalyst, and a small library of non-basic thioureas was used. In the beginning apparently using thiourea **79a** better results could be obtained respect to the reaction carried out with only quinidine **4** as catalyst (compare entries **1** and **3** of *table 6.21*), but it has to be pointed out that the solvents were different. Actually, when triying the reaction at lower temperature in the same solvent, the results were comparable (compare entries **5** and **8** of *table 6.21*), and so we considered that cooperative catalysis could not offer better results respect to Brønsted base or bifunctional catalysis.

For mainly a reason of time, more trials could not be carried out for this project, leaving the latter at this point.

6.3.1 EXPERIMENTAL SECTION

General experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian inova 300, at 300 MHz and 75 MHz respectively, Varian mercury 400, at 400 MHz and 100 MHz respectively, or Varian inova 600, at 600 MHz and 150 MHz respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. $CDCl_3$ was passed over a short pad of alumina before use. Coupling constants are given in Hz. The carbon types were determined from DEPT ^{13}C NMR experiments. NOE spectra were recorded using the DPFGSE-NOE sequence[206].
Optical rotations are determined using a Perkin Elmer 341 instrument with sodium lamp and are reported as follows: $[\alpha]^{^{\circ}C}_{D}$ (*c* in g per 100 mL, solvent).
Thin Layer Chromatography (TLC) was performed on commercially available Fluka TLC plates on aluminium or PET foils with fluorescent indicator at 254 nm, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents.
Purification of the products was carried out by flash chromatography (FC) on silica gel (Aldrich, 230-400 mesh) according to the method of Still[207].
Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Materials

All the commercially available reagents and solvents were used without any further purifications; otherwise, where necessary, they were purified as recommended[208].
N-Boc-, N-Cbz-hydroxylamine **332** and **333** and nitrostyrene were purchased from alpha aesar company. Catalysts **3**, **4**, *ent*-**53**, **342**, **343** and **344** are commercially available.
Catalysts **337a**, **337b**, **338**, *ent*-**338** and **331** were already available in our laboratory.
Thioureas **73**, **79a** and **346** were kindly provided by Dr. Luca Bernardi.
Chiral primary amine catalysts 9-*epi*-9-amino-9-deoxyquinine and its *pseudo*-enantiomer 9-*epi*-9-amino-9-deoxyquinidine were synthesized according to literature procedures[209].
All the other catalysts were prepared according to literature procedures[210].

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[206] (a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwand, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (b) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Resonance* **1997**, *125*, 302. (c) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Resonance* **1999**, *141*, 191. (d) See also: Claridge, T.D.W. *High Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.

[207] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

[208] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

[209] (a) S. H.; McCooey, S. J.; Connon. *Org. Lett*. **2007**, *9*, 599-602; (b) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2007**, *46*, 7667 –7670.

[210] a) for catalyst 5**8**: Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.,* **1999,** *121,* 10219-10220. b) for catalyst **9**: H. Pracejus, H. Maetje, *J. Prakt. Chem.,* **1964**, *24,*195. c) for catalysts **38g** and **38h**: d) A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem. Int. Ed.*, **2011**, *50*, 1707 –1710. e) for catalyst **336**: N. R. Amarasinghe, P. Turner, M. H. Todd, *Adv. Synth. Cat.*, **2012**, *354*, 2954-2958. f) for thioureas **96b, 97b, 96f, 97h** and

General procedure for the enantioselective aza-Michael addition of N-Cbz-hydroxylamine to nitrostyrene

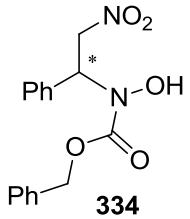
The catalyst (10% or 20%, 0.01 or 0.02, mmol) was added to a stirred solution of N-Cbz-hydroxylamine (1.1 eq., 0.11 mmol) and nitrostyrene (1 eq., 0.1 mmol) in the required solvent (0.5 ml, 0.2 M) and stirred at the given temperature for the given time. Then the mixture was plugged on a short pad of silica gel using a 1:1 mixture of DCM/Et_2O to remove the catalyst. then the product was further purified through flash chromatography on silica gel (eluent mixture: 8:2 Hex/EtOAc) to give the pure product **4** as a white solid.

General procedure for the enantioselective aza-Michael addition of N-Cbz-hydroxylamine to nitrostyrene via cooperative catalysis.

Quinidine (0.1 eq., 0.01 mmol) and the thiourea used as additive (0.1 eq., 0.01 mmol) were placed in a screw-capped vial and dissolved in the reaction solvent (0.5 ml, 0.2 M) with stirring. Subsequently, N-Cbz-hydroxylamine (1.1 eq., 0.11 mmol) and nitrostyrene (1 eq., 0.1 mmol) were added, the vial was closed and the reaction mixture was stirred at the given temperature for the given time. Then the mixture was plugged on a short pad of silica gel using a 1:1 mixture of DCM/Et_2O to remove the catalyst. then the product was further purified through flash chromatography on silica gel (eluent mixture: 8:2 Hex/EtOAc) to give the pure product **4** as a white solid.

Product characterization

benzyl hydroxy(2-nitro-1-phenylethyl)carbamate 334



334

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4,65 (dd, 1H, J_a = 4,7 Hz, J_b = 13,2 Hz;); 5,10 (d, 1H, J = 12,2 Hz); 5,16 (d, 1H, J = 12,2 Hz); 5,18 (dd, J_a = 10,2 Hz, J_b = 13,2 Hz); 5,89 (dd, 1H , J_a = Hz, J_b = 10,2 Hz); 7,27 (m, 2H); 7,33 (m, 8H); 7,53 (bs, 1H).
^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 60,2 (CH); 68,8 (CH_2); 74,7 (CH_2); 127,7 (CH); 128,1 (CH); 128,5 (CH); 128,6 (CH); 129 (CH); 130 (CH); 134,6 (C); 135,3 (C); 157,4 (CO).

ESI-MS: calcd.: 315; found: 316 (M+H).
Melting point: 106,5-107,4 °C.

HPLC analysis: on chiralcel OJ-H column, eluent mixture: Hex/i-PrOH 70:30, flow: 1 ml/min, λ = 254 nm, T = 25 °C, τ_{max} = 35 min.; τ_{min} = 22 min.

97g the same general procedures can be followed: g) B.J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett*, **2005**, *4*, 603–606. h) B. Vakulya, S. Varga, A. Csàmpai, T. Soòs, *Org. Lett.*, **2005**, *7*, 1967-1969. i) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.*, **2005**, 4481-4483. j) S. H. McCooey, S. J. Connon, *Angew. Chem., Int. Ed.*, **2005**, *44*, 6367-6370. k) for catalyst **339**: J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang, C. E. Song, *Chem. Commun.,* **2009**, 7224-7226. l) for catalyst **62d**: S. Wu, W. Zeng, Q. Wang F.-X. Chen, *Org. Biomol. Chem.*, **2012**, *10*, 9334-9337. m) for catalyst **62e**: D. J. Dixon *et al.*, *Org. Lett.*, **2012**, *14*, 2492–2495. n) for catalyst **98b**: W. Yang, D.-M. Du, *Org. Lett.*, **2010**, *12*, 5450. o) for catalyst **340**: J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.*, **2008**, *130*, 14416–14417. p) for catalyst **100**: C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.,* **2006**, *8*, 2901-2904. q) for catalyst **345**: L. Wu, G. Li, Q. Fu, L. Yu, Z. Tang, *Org. Biomol. Chem.*, **2013**, *11*, 443-447.

Crystal structure

We were able to obtain crystals of product **334** in order to confirm its truucture. The ORTEP diagram at 50% probability is shown below.

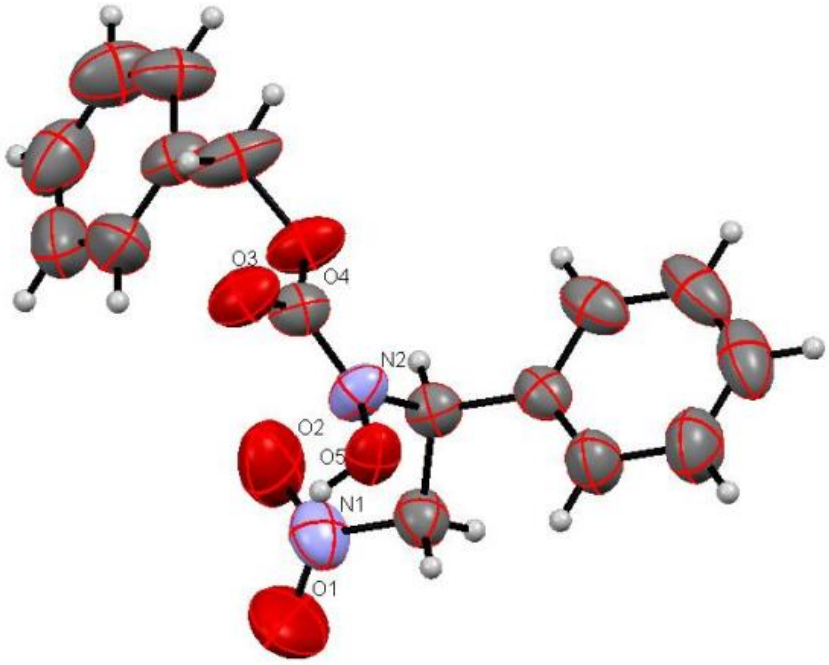
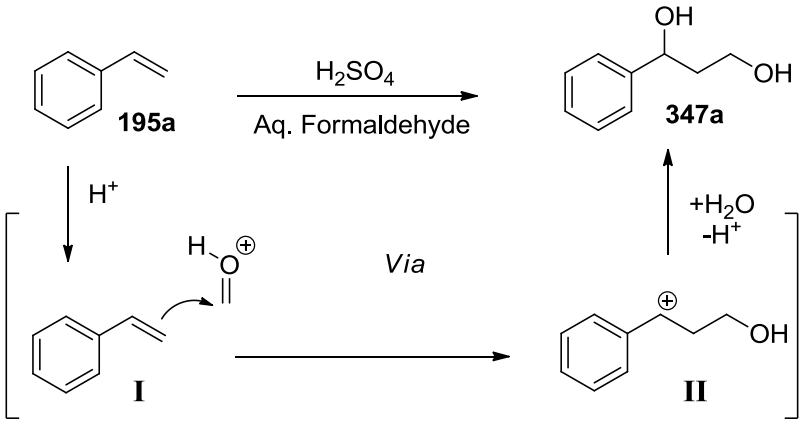


Figure 1: crystal structure of product **334**.

7) The Prins cyclization[211]

7.1) introduction

The Prins cyclyzation is a variant of the Prins reaction, discovered in 1919 by the Dutch chemist Hendrik Jacobus Prins[212]. In this reaction styrene was reacted with formaldehyde under acqueous acidic conditions to obtain the corresponding 1,3-diol **347a**. The generally accepted mechanism involves protonation of formaldehyde and subsequent nucleophilic attack of the alkene on the so-formed oxocarbenium ion (**I**) with the formation of carbocation (**II**), which is quenched by water giving the final product (see scheme **7.1**).



Scheme **7.1**: the first 1919 report on Prins reaction and the assumed mechanism.

Since this reaction in principle can be carried out between any alkene and any aldehyde, it is often mentioned as one of the most powerful ways to create new C-C bonds. Moreover, changing the reaction conditions results in different pathways, since the intermediate carbocation can be also trapped by an external nucleophile, lose a proton or even react with another equivalent of aldehyde, to give 1,3 dioxanes **349** (*Fig. 7.1*).

[211] Reviews concerning Prins reaction and Prins cyclization: a) E. Arundale, L. A. Mikeska, *Chem. Rev.*, **1952**, *51*, 505-555. b) D. R. Adams, S. P. Bhatnagar, *Synthesis*, **1977**, 661-673. c) Snider, B. B. In Comprehensive Organic Synthesis; Trost, B., Fleming, I., Heathcook, C. H., Eds.; Pergamon: New Yok, NY, 1991; Vol. 2, pp 527–561. d) I. Pastor, M. Yus, *Curr. Org. Chem.*, **2007**, *11*, 925-957. e) E. A. Crane, K. A. Scheidt, *Angew. Chem. Int. Ed.*, **2010**, *49*, 8316–8326. f) C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron*, **2010**, *66*, 413–445.

[212] a) H. J. Prins, *Chem. Weekbl.* **1919**, *16*, 1072; b) H. J. Prins, *Chem. Weekbl.* **1919**, *16*, 1510.

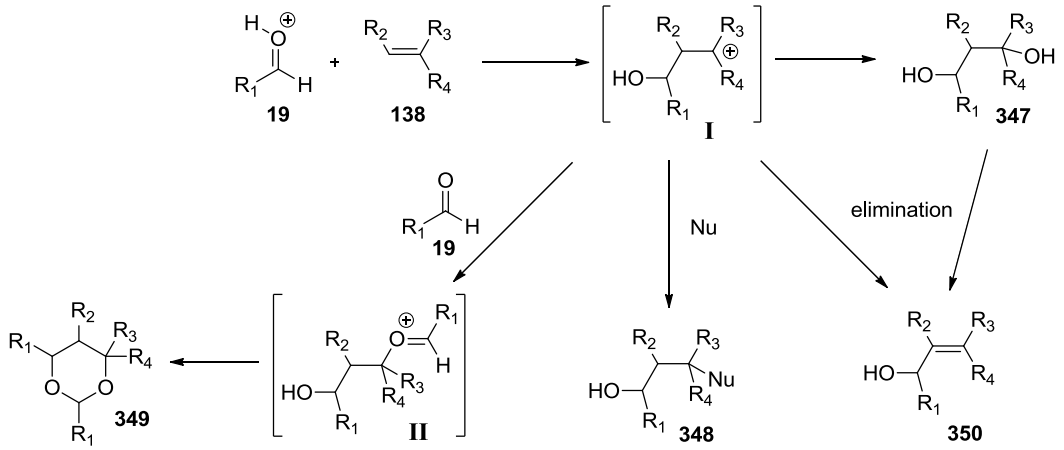
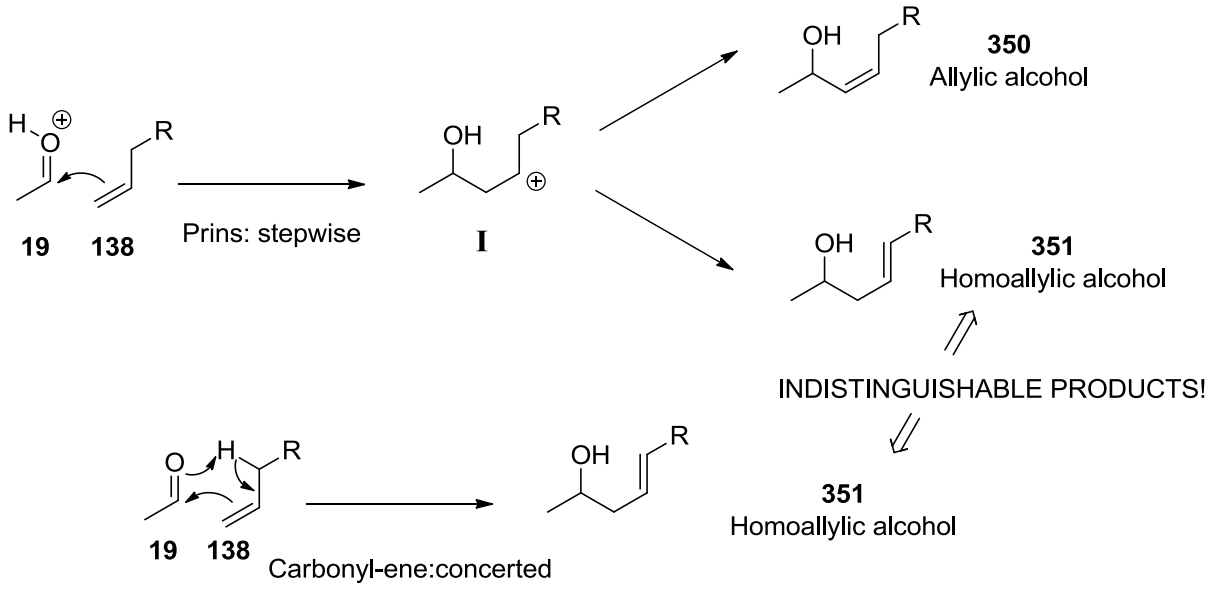
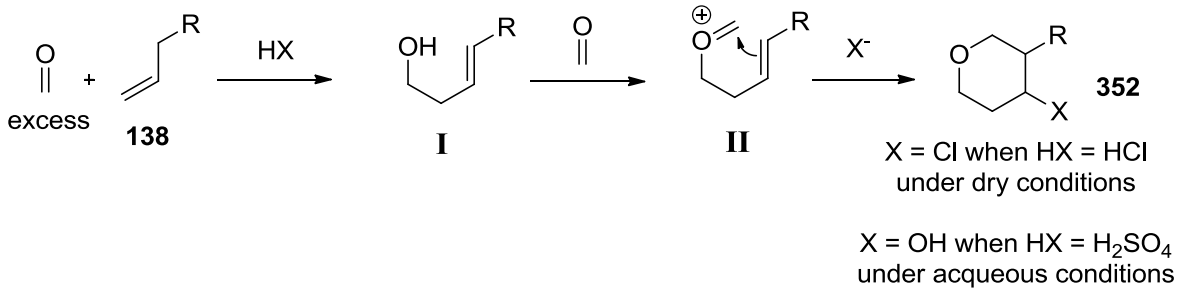


Figure 7.1: the different destinies of the key carbocationic intermediate **I** in Prins-type reactions.

For this reason, the reaction is considered at the same time powerful, but challenging, because sometimes even careful control of reaction conditions can lead to product mixtures. Three things have to be pointed out: first of all also Lewis acid can catalyze this reaction, and actually they are more often employed respect to Brønsted acids. The second is that the formation of dihydropyrans gives cyclic products, but this is not the reaction called Prins cyclization. The last is that when allylic or homoallylic alcohol are the main products often is not possible to distinguish if the carbocation undergoes direct proton elimination of first hydration to give **347** and subsequent water elimination (both mechanisms are possible in acidic conditions). Moreover, the homoallylic alcohol product **350** is also the same product arising from a concerted ene reaction and in that case it's impossible to say which one of the two mechanisms is operative (see scheme **7.2**). Usually ene reactions are concerted thermal processes, but there are many examples of catalytic ene reactions. The mechanism should be anyway concerted, even if stepwise processes cannot be ruled out, at least in some cases. So, if the main product is an homoallylic alcohol, ene and Prins reaction have to be considered the same reaction (scheme **7.2**).



Scheme **7.2**. It's impossible to distinguish weather if a Prins or a carbonyl-ene reaction is occurring when the main product is the homoallylic alcohol: the two reactions have to be considered as the same.



Scheme **7.3**: the first Prins cyclizations.

The Prins cyclization is a particular Prins reaction where the reacting alkene is an homoallylic alcohol. This reaction was firstly reported in 1955 by Hanschke and Gendorf[213] and then in 1969-70 by Stapp[214].
They reported that when reacting alkenes with more than one equivalent of formaldehyde, the major products were tetrahydropyrans. Depending on the nature of the acid used, chlorinated or hydroxy-substituted tetrahydropyranes were obtained (scheme **7.3**). The transformation consists in two subsequent Prins reactions, the first occurring on protonated formaldehyde and giving the homoallyl alcohol **I** as product after deprotonation. The second Prins reaction occurred intramolecularly on the oxocarbenium ion **II** formed by condensation of the alcohol onto a second aldehyde equivalent and subsequent water loss. The double bond attacks the oxocarbenium ion to give a cyclic tetrahydropyran **352** in the process that today is called Prins cyclization. Then the incoming carbocation is quenched by chloride if the acid used is HCl and by water if the acid used is sulfuric acid in acqueous conditions (scheme **7.3**).

In *figure 7.2* is shown a general mechanism for the Prins cyclization between an aldehyde (benzaldehyde is used as example) and an allylic alcohol. In the example given in *figure 7.2*, a generic Brønsted acid is used as the catalyst: this is useful for further development of this thesis, but it must be pointed out that also Lewis acids can be used as well, and actually they are in general more used respect to Brønsted acids.

Firstly, the aldehyde is activated by protonation (**I**), and the homoallylic alcohol attacks the protonated aldehyde to give a positively charged hemiacetal (**II**). Formal proton transfer gives the intermediate **III**, which undergoes water loss and forms the oxocarbenium ion **IV** thanks to the lone pair on the oxygen previously belonging to the alcohol (in blue). This oxocarbenium ion undergoes Prins cyclization to give the carbocation **V** which is quenched by water (**VI**). Finally a proton loss stores back the catalyst and gives the product **VII**.

[213] E. Hanschke, O. Gendorf, *Chem. Ber.*, **1955**, *88*, 1053-1061.
[214] a) P. R. Stapp, *J. Org. Chem.*, **1969**, *34*, 479-485; b) P. R. Stapp, *J. Org. Chem.*, **1970**, *35*, 2419-2420.

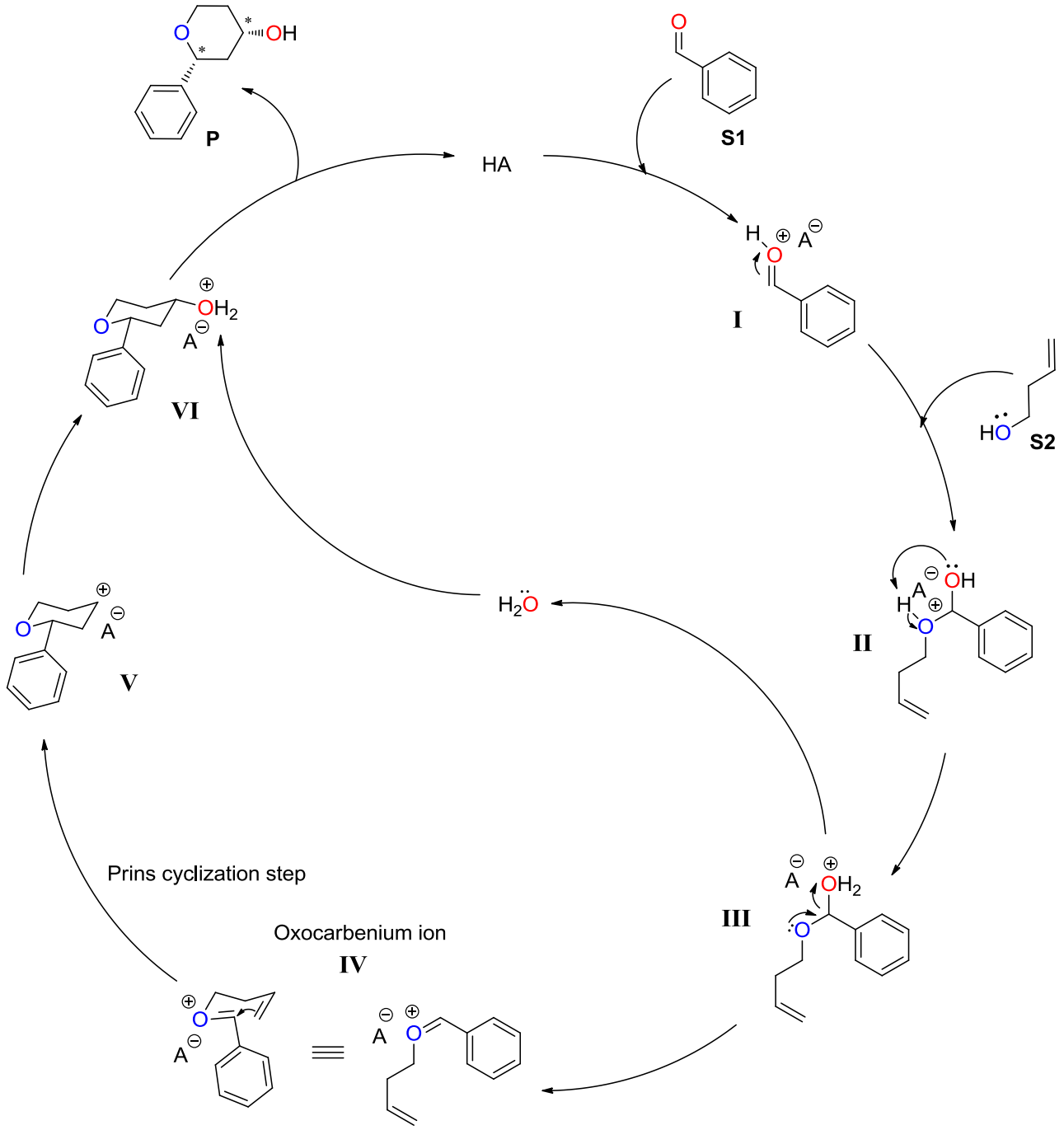


Figure 7.2: general mechanism of Brønsted acid catalyzed Prins cyclization.

Also here it's necessary to do some general considerations:

1) as you can see since the first protination to the end, all intermediates are positively charged. Always keeping in mind that proton transfer processes are equilibriums and that passing from intermediate **II** to intermediate **III** most likely requires the participation of an external base, is clear since now that a contact ion pair is present for the whole reaction having A^- as the counteranion. In principle, being this counteranion chiral, might lead to an enantioselective reaction.

2) The final product often is the thermodynamically more stable, bearing the substituents in *cis*- configuration, since in this way they are both in the equatorial position.
3) The key step here is the cyclization step and thus the oxocarbenium ion is the key intermediate. As before, for Prins reaction, the carbocation was.

Unfortunately, to all the different reaction pathways possible for the carbocation that we saw before, and possible also here, in the case of Prins cyclyzation the oxocarbenium ion can also undergo different reaction pathways, thus complicating the picture, and making the reaction even more challenging than before. This is well explained in *figure 7.3*, which summarizes all the possible reaction pathways that this reaction can undergo. In this hypothesis the starting homoallylic alcohol **351** is enantioenriched, and, as you can see, all the competitive reaction pathways of the Prins cyclization destroy chirality.

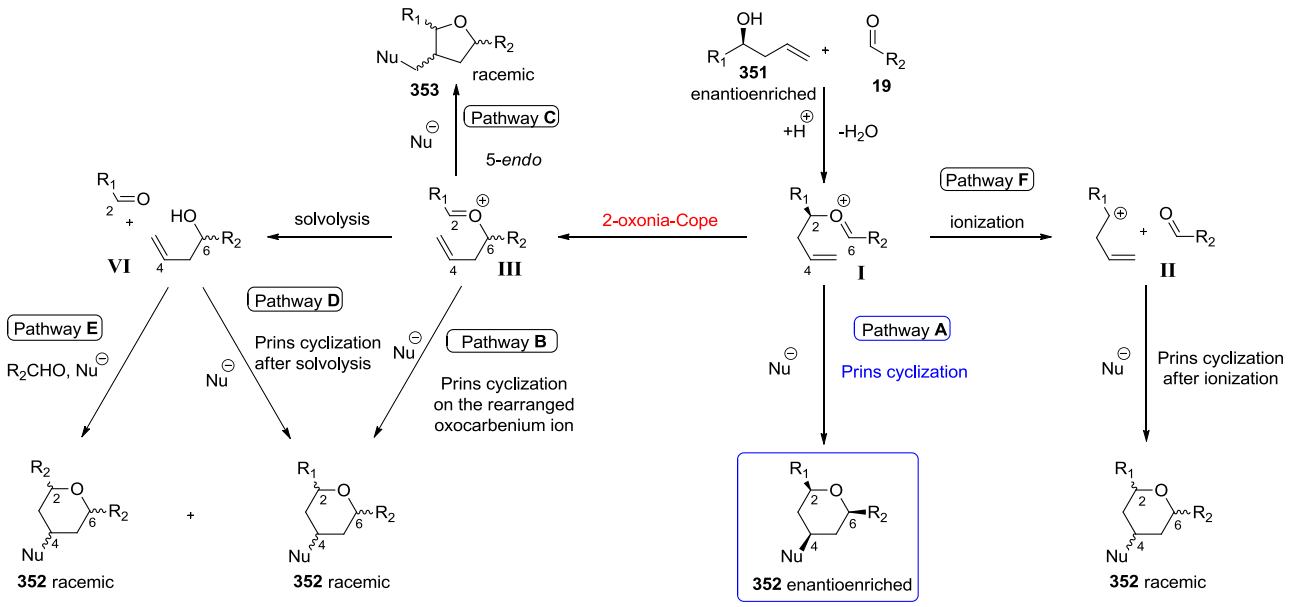
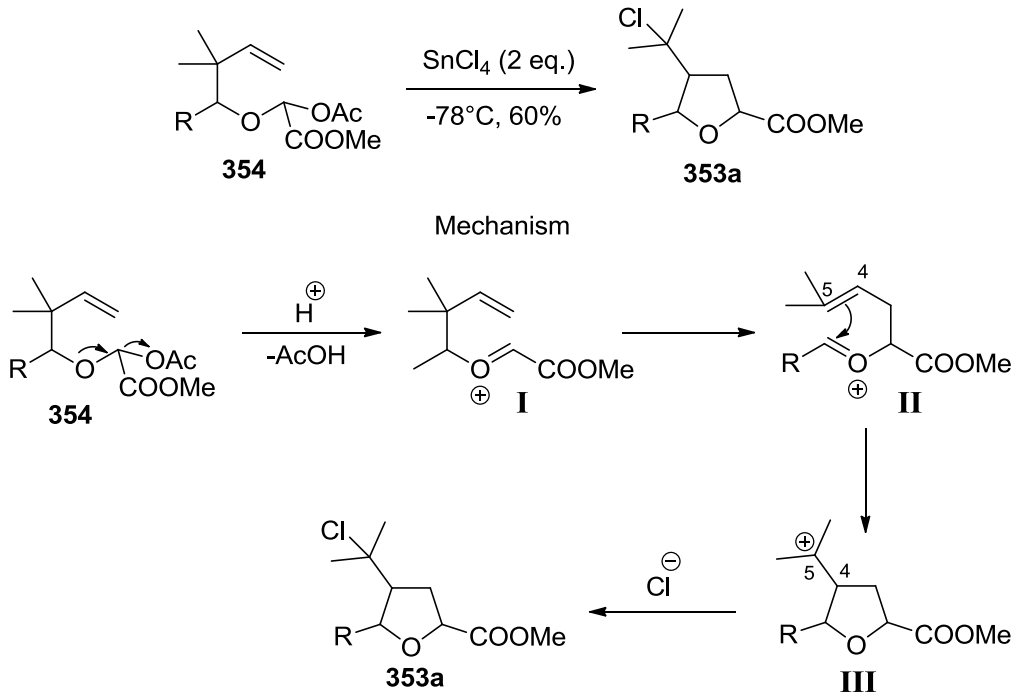


Figure 7.3: many problematic reaction pathways in the Prins cyclization reaction of enantiopure homoallylic alcohols.

In *figure 7.3*, on the right you can see the key oxocarbenium ion **I** and more right one racemization pathway called “pathway F”, which consists in ionization (**II**). But one of the biggest problems encountered in apptempts to stereoselective Prins cyclyzations is the competitive 2-oxonia cope sigmatropic rearrangement. This destroys the chiral center forming another oxocarbenium ion **III**, which can then undergo racemic Prins cyclization (“Pathway B”) or solvolysis, which leads to other undesired products (“Pathways D”) or other kind of cyclizations (“Pathway C”). The involvement of 2-oxonia cope sigmatropic rearrangement during Prins-type cyclization was firstly observed and studied by Hiemstra and Speckamp, who concluded that this kind of rearrangement should be involved in Prins cyclization of α-methoxycarbonyl oxycarbenium ions **II**[215]. In this reaction they observed a five memdered ring product **353a** arising from the cyclyzation of the rearranged oxocarbenium ion **II**, favoured by the formation of a tertiary carbocation **III** (scheme **7.4**).

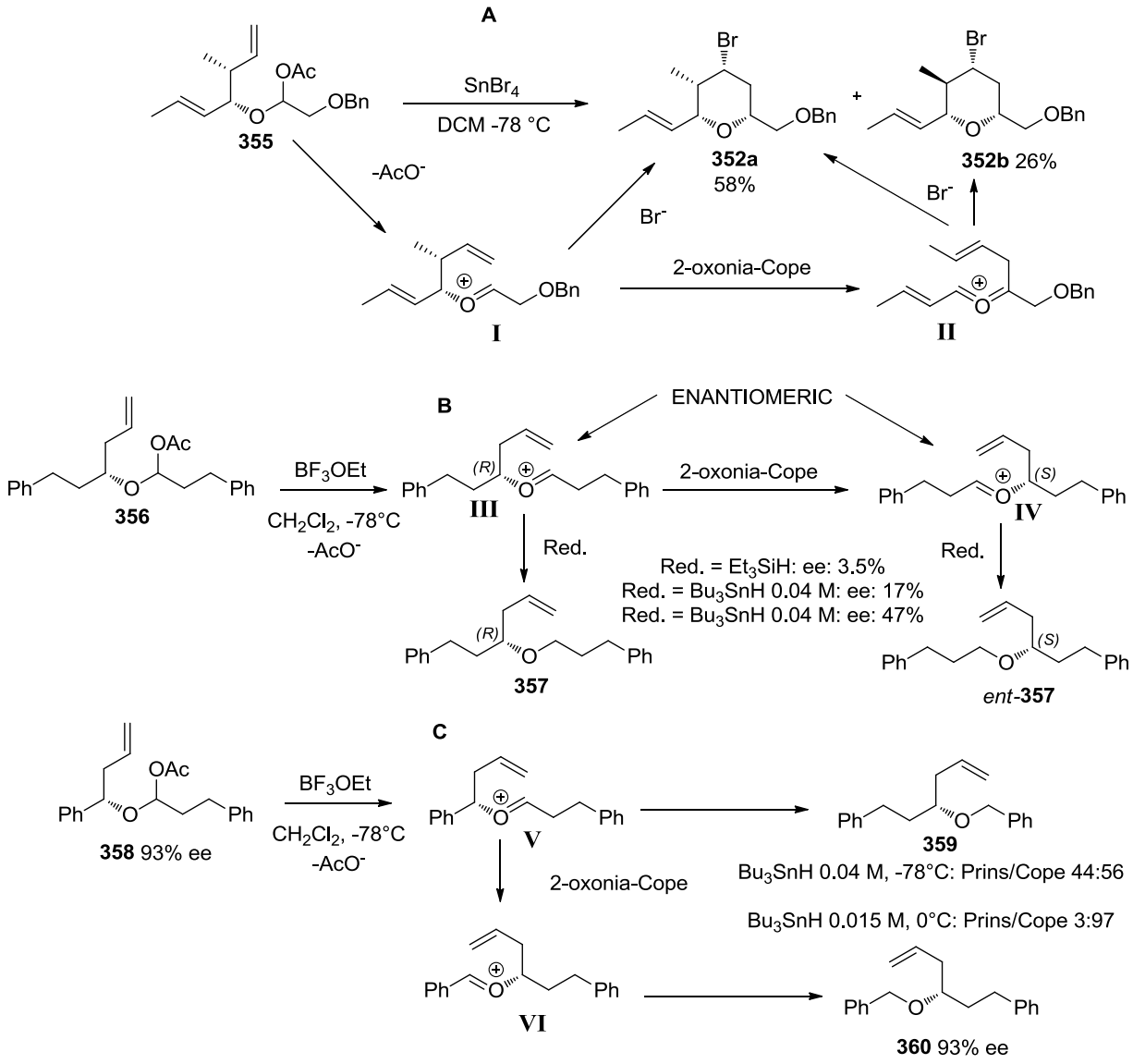
[215] a) L. D. Lolkema, H. Hiemstra, C. Semeyn, W. N. Speckamp, *Tetrahedron*, **1994**, *50*, 7115; b) L. D. Lolkema, C. Semeyn, L. Ashek, H. Hiemstra, W. N. Speckamp, *Tetrahedron*, **1994**, *50*, 7129.



Scheme **7.4**: Hiemstra and Speckamp work in which 5-exo cyclization of the rearranged oxocarbenium ion after 2-oxonia-Cope is favoured by the formation of a tertiary carbocation as intermediate.

Oxonia-Cope rearrangements were responsible for racemization of a possible precursor of ratjadone in a 2001 study by Rychnowsky[216]. Unexpected partial racemization was observed in the Prins cyclization of the enantiopure acethoxy precursor **355** and this was ascribed to 2-oxonia-Cope rearrangements (scheme **7.5**, **A**). To prove this mechanism a reducing agent was employed in the reaction conditions using the same enantiopure acethoxy ether **355**. If Prins cyclization directly occurs after the elimination of the acethoxy group, an enantiopure product should be obtained. Since extensive racemization was instead observed, the authors conclude that 2-oxonia-Cope rearrangement is fast in those reaction conditions (scheme **7.5**, **B**). The racemization extent is higher when weak and diluted reducing agents were used, confirming that during time continuous group scrambling due to consecutive 2-oxonia-Cope rearrangements leading racemization occurs. In the same paper they also find an enantiospecific 2-oxonia-Cope rearrangement and exploit this for an enantioselective synthesis. The formation of a benzylic oxocarbenium ion **VI**, claimed more stable, is invoked for a good reaction control. Prins product is also present, but its formation is suppressed at relatively high temperatures and reductant concentrations (scheme **7.5**, **C**).

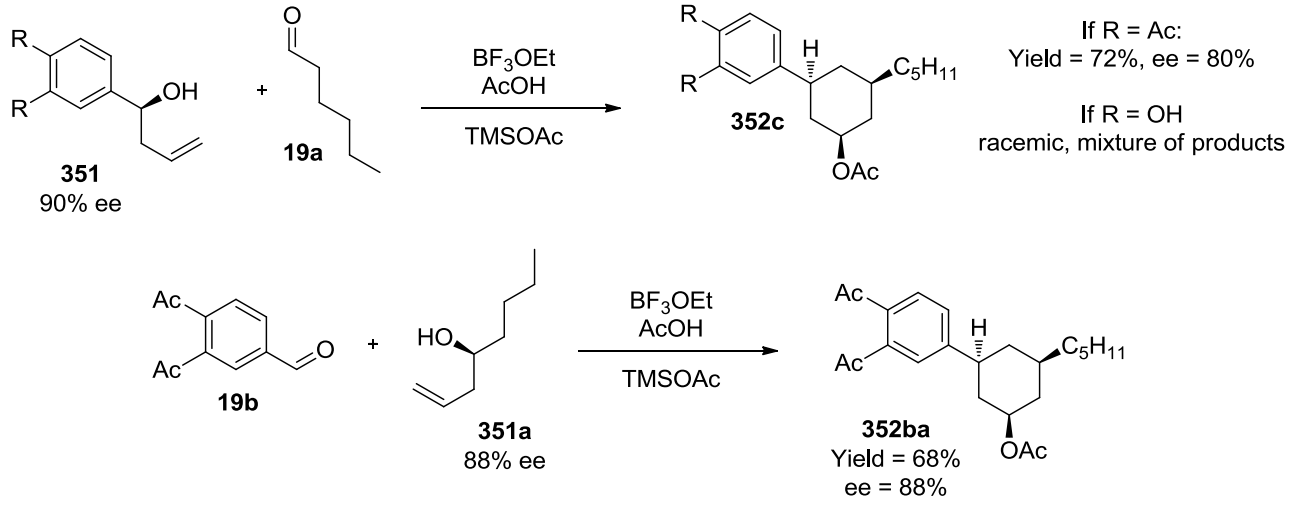
[216] S. D. Rychnovsky, S, Marumoto, J. J. Jaber, *Org. Lett.*, **2001**, *3*, 3815-3818.



Scheme **7.5**: Rychnovsky studies on racemization induced by oxonia-Cope processes ion Prins cyclization.

Also Willis and co-workers encounter racemization in their studies on Prins cyclization between homoallylic benzylic alcohols and aldehydes (scheme **7.6**). In this study, they also find other reactions and racemization pathways, finding aromatic aldehydes in the mixture, resulting from the solvolysis of the oxocarbenium ion generated after the 2-oxonia Cope rearrangement[217]. This is supported by ^{18}O labeling studies[218]. An important conclusion, anyway, is that oxonia-Cope rearrangements are favored when the aryl group of the homoallylic benzylic alcohol is electron rich, while lower reaction rates and higher amounts of the Prins product were formed with electron withdrawing groups on the phenyl ring. In another study Willis finds no racemization in Prins cyclization on enantiopure starting materials both using homoallylic benzylic alcohols with electron-withdrawing groups and alkyl-aldehydes or simple homoallylic alcohols with aryl aldehydes bearing electron-withdrawing groups on the aryl substituent[219] (scheme **7.6**).

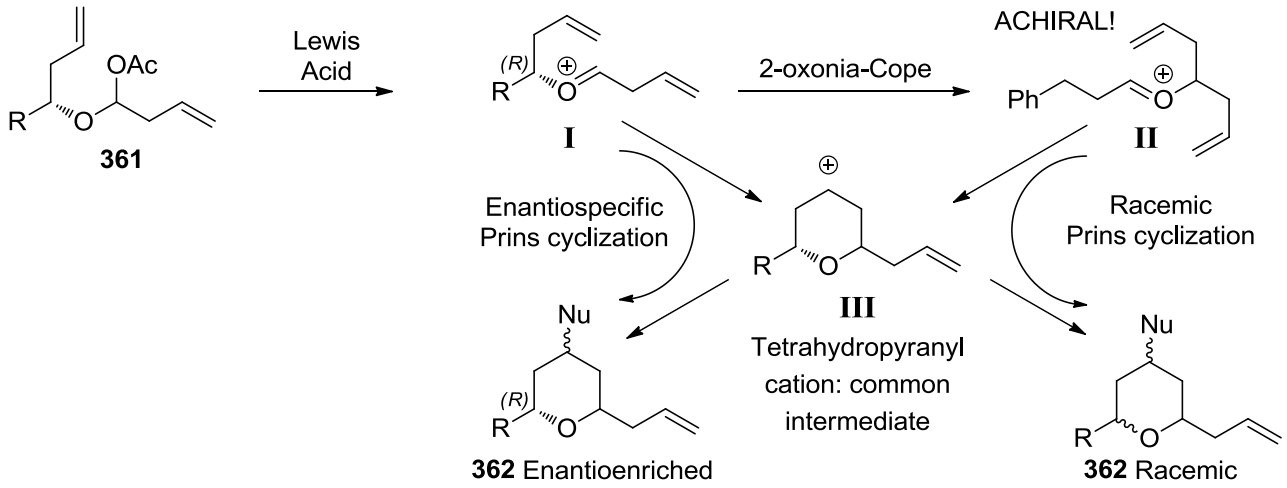
[217] S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker, C. L. Willis, *Org. Lett.*, **2002**, *4*, 577-580.
[218] S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker, C. L. Willis, *Org. Lett.*, **2002**, *4*, 3047-3410.
[219] C. S. Barry, N. Bushby, J. R. Harding, R. A. Hughes, G. D. Parker, R. Roe, C. L. Willis, *Chem Commun.*, **2005**, 3727-3729.



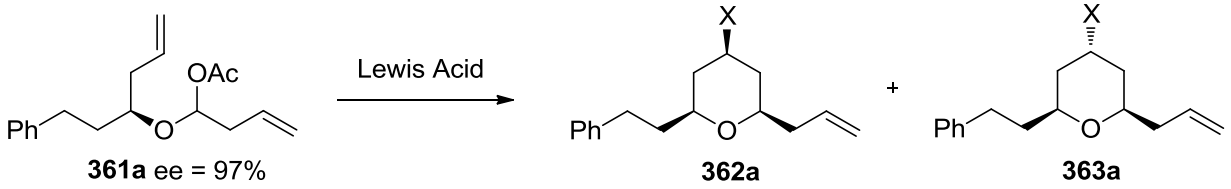
Scheme **7.6**: studies by Willis on the reaction course when using electron-donating or electron withdrawing groups on the phenyl substituents on homoallylic benzylic alcohol. When electron-donating groups are used, a mixture of products is obtained and the Prins product was racemic, revealing a fast 2-oxonia-cope process. When electron-withdrawing groups are used the Prins cyclization is favored leading to good retention of absolute configuration. The same happens if alkyl homoallylic alcohol and aromatic aldehyde are used.

A big work on Prins reaction mechanism was made by Rychnowsky and co-workers. They discovered another solvolysis pathway for enantioenriched tetrahydropyranyl mesilates[220]. But most importantly they published a paper in which important and extensive studies on Prins reaction mechanism and related 2-oxonia-Cope rearrangements were involved[221]. Rychnowsky designed an experiment in which an enantioenriched acethoxyether **361** would give the corresponding oxocarbenium ion **I** (scheme **7.7**). Direct Prins cyclization of **I** affords enantioenriched product. 2-oxonia-Cope rearrangement would instead give an achiral oxocarbenium **II**, destroying chirality for sure. This was made in order to exclude the possibility of an enantiospecific 2-oxonia-Cope rearrangements. In this way, the enantiomeric excess measured on the final product is a direct evidence of the different reaction rate between the Prins and the oxonia-Cope reactions. The diastereoisomeric ratio of the final product after the attack of a nucleophile, on the other hand, is determided by other factors, such as steric hindrance and the counteranion. The results were very interesting (see *table A*). First of all, the Lewis acid employed deeply influences the reaction outcome: $SnBr_4$, taken as the reference, and many others, including Brønsted acids, gave very poor enantiomeric excesses and a moderate preference for the all-cis product **362a**. A completely different result was obtained with TMSBr: the product **363a** arising from the axial attack of the bromide was the major, and was obtained in 79% ee (ee of the starting material was 97%, *Tab. A*, entry 6). The reaction outcome was not affected by the temperature and the concentration of the nucleophile (not shown) and generally polar solvents gave lower ee's and much higher preference for **362** respect to apolar ones (compare entries **2, 3** and **4** of *table A*).

[220] R. Jasti, S. D. Rychnovsky, *Org. Lett.*, **2006**, 10, 2175-2178.
[221] R. Jasti, C. D. Anderson, S. D. Rychnovsky, *J. Am. Chem. Soc.*, **2005**, *127*, 9939-9945.



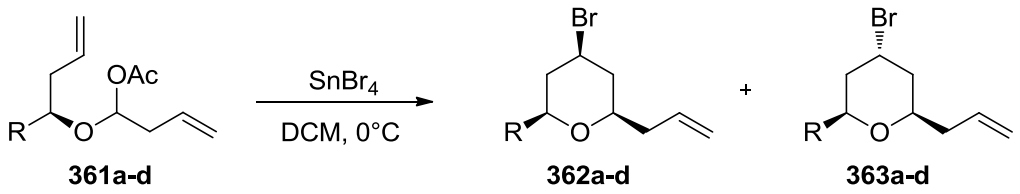
Scheme **7.7**: the experiment designed by Rychnowsky to study the Prins cyclization mechanism.



Entry	Lewis Acid	X	Solvent	T (°C)	Yield (%)	362a:363a	eel 362a (%)	eel 363a (%)
1	$SnBr_4$	Br	DCM	-78	93	1.8:1.0	8	9
2	$SnBr_4$	Br	DCM	0	90	3.0:0	9	10
3	$SnBr_4$	Br	Hexanes	0	64	3.1:1.0	31	36
4	$SnBr_4$	Br	$MeNO_2$	0	82	11:1.0	0	0
5	$SnCl_4$	Cl	DCM	0	81	3.7:1.0	7	8
6	TMSBr	Br	DCM	0	85	1.0:14	-	79
7	$BF_3{\cdot}OEt_2$	Ac	Hexanes	0	52	> 19:1.0	13	-
8	TFA	TFA	DCM	0	92	> 19:1.0	5	-

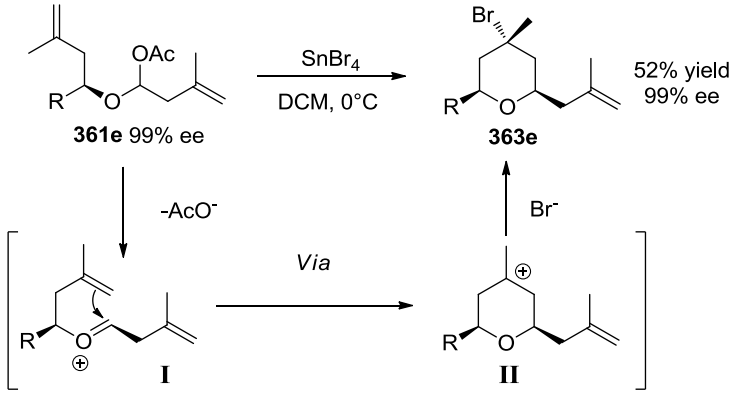
Table A: Rychnowsky's work on different lewis acid catalyzed studies on Prins cyclization mechanism.

The obtained results suggests that 2-oxonia-Cope rearrangement is a fast process in this reaction but there are some ways to suppress it. The results clearly indicates, also, that the reactivity, and not the concentration of the counteranion is crucial for the reaction outcome. In fact, using $SnBr_4$ a tin"ate" complex would be formed as counteranion and so in that case bromide is less reactive. If using TMSBr, the counteranion is a simple bromide and it's much more reactive, quenching the carbocation just after the Prins cyclization. This explains also the solvent effect: apolar solvents generate tight ion pairs and the quenching is faster, allowing higher Prins reaction rate, and thus higher ee's. All these findings suggest that Prins cyclization is a stepwise process, with the formation of a tetrahydropyranyl carbocation as a key intermediate, wich then subsequently have many destinies, depending on the occurrence or not of 2-oxonia-Cope rearrangements.
Substituent influence was also exhamined and a vynil group, stabilizing the oxocarbenium ion arising from the rearrangement, led to a racemic product. Electron-withdrawing groups, instead, destabilize that oxocarbenium ion more than the original one. Higher energy of the tetrahydropyranyl cation makes it more reactive and axial trapping is then more favoured (*table B*).



Entry	Starting material	R group	eel 361 (%)	Yield (%)	362:363	eel 362 (%)	eel 363 (%)
1	361a	$PhCH_2CH_2$-	97	80	3.0:1.0	9	10
2	361b	Vinyl-	92	66	19:1.0	0	-
3	361c	$TBDPSOCH_2$-	98	69	1.0:1.5	57	56
4	361d	$ClCH_2$-	99	55	1.0:4.0	96	96

Table B: substituent effects.



Scheme **7.8**: stabilizing tetrahydropyranyl cation.

Moreover, an experiment clearly shows that when there is the possibility to form a tertiary tetrahydropyranyl cation, this happens, and it is so stable that 2-oxonia-Cope rearrangement does not occur, leading to complete conservation of ee (scheme **7.8**).
Another work by Rychnowsky is focused on Brønsted acid catalyzed reactions. The results are similar, except for the influence of the temperature: in this case lowering the temperature leads to higher ee conservation, suggesting a slow rate of 2-oxonia-Cope rearrangements at low temperature[222].

After all these information, we can recap the major features of the Prins cyclization, and especially how to suppress, at least partially, the competitive 2-oxonia-Cope rearrangement:

1) Prins cyclization is a stepwise process that proceeds through an oxocarbenium ion and then through a tetrahydropyranyl cation.
2) 2-oxonia-Cope rearrangement competes often with Prins cyclization. This leads to the formation of another oxocarbenium ion, but finally to the same tetrahydropyranyl cation and the same product.
3) therefore, this is not a problem until enantioenriched alcohols are used in the reaction: in this case the 2-oxonia-Cope rearrangement can destroy chirality.
4) methods to favor direct Prins cyclization pathway can be:

[222] R. Jasti, S. D. Rychnovsky, *J. Am. Chem. Soc.*, **2006**, *128*, 13640-13648.

a. the design of reagents that lead to particularly stable intermediates for the Prins cyclization pathways. Some can be: conjugated, or benzylic oxocarbenium ions, the latests especially if substituted with EWG's. EWG's in the α position respect to the oxocarbenium carbon. Tertiary tetrahydropyranyl cations.
b. decreasing the reaction temperature.
c. careful choice of solvent (better if apolar) and catalyst (lewis acids leading to reactive counteranions, like, for example TMSBr).

Using these guidelines is possible to design diastereoselective and enantiospecific Prins cyclizations, as we saw in some examples and many others are present in the literature[223]. But surprisingly enantioselective Prins cyclizations are virtually absent in literature. This is particularly strange because the reaction is versatile and powerful: new C-C bonds are formed, tetrahydropyrane scaffold, an important backbone in naturally occurring and biologically active compounds[224], is synthesized. Moreover, many variants of this reaction have been developed during years[225]. Despite this, the enantioselective Prins cyclization remains elusive and has never been reported[226]. For this reason, we thought it was worth to explore the possibility of such a reaction, and we embarked in trials for enantioselective Prins cyclization.

[223] See ref. 211.

[224] a) Ed.K.C. Majumdar, S.K. Chattopadhyay. (*2011*). Heterocycles in Natural Product Synthesis. Wiley-VCH Verlag & Co. KGaA. Chapter 5. b) A. K. Ghosh, D. D. Anderson, *Fut. Med. Chem.*, **2011**, *3*, 1181-1197.

[225] An excellent classification of the different kind of Prins cyclization is done in ref. 211f.

[226] Some enantioselective reactions are claimed "Prins" in the literature, but actually they are two special cases of ene reaction and an oxa-pictet-spengler reaction. For reference see: a) H. Nakamura, K. Ishihara, H. Yamamoto, *J. Org. Chem.* **2002**, *67*, 124-5137. b) C. A. Mullen, M. R. Gagnè, *Org. Lett*. **2006**, *4*, 665-668. c) V. M. Lombardo, C. D. Thomas, K. A. Scheidt, *Angew. Chem. Int. Ed.*, **2013**, *52*, 12910-12914.

7.2) The enantioselective Prins cyclization: the concept and the attempts

Since this reaction is acid catalyzed, considered that for all the reacton mechanism positively charged species are involved and aware about to the previously discussed importance of the counteranion in the reaction outcome, we thought that chiral BINOL based Brønsted acids might be enantioselective catalysts for this reaction. Our idea was then to design a reaction in all similar to the one depicted in scheme **7.2**. In this case HA is a chiral acid and therefore the counteranion A^- is chiral, and induces enantioselectivity in the Prins cyclization step (**IV** → **V**) through a contact ion pair. We can call this activation also Asymmetric Ion Pair Catyalysis (*figure 4*)[54].

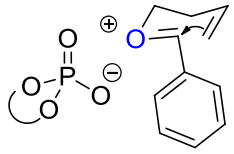
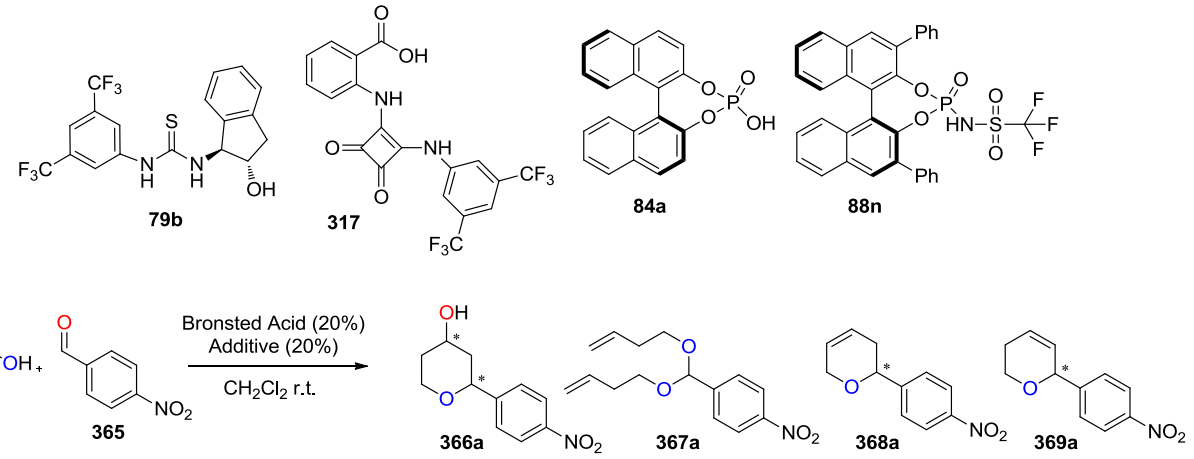


Figure 4: hypothesis of an asymmetric counteranion directed Prins cyclization.

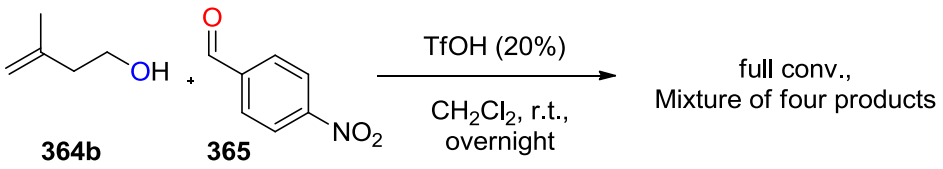
For the firs trials we chose the simplest homoallylic alcohol **364a**, and *p*-nitrobenzaldehyde **365** to try to ensure a little more reactivity. We initially screened some chiral and non-chiral acid to try to test reactivity. Unfortunately, the results were not encouraging: in many cases no conversion was obtained, using moderate acids (*table 7.1*, entries **1, 2, 6, 7, 11, 14**), or the simple aldehyde acetal **367a** was obtained (*table 7.1*, entries **3, 4, 5, 8, 9, 12, 13, 18**). When stronger acids were used, sometimes complex mixtures were obtained (*table 7.1*, entries **10, 16**), sometimes other products were formed, albeit in low yields (*table 7.1*, entries **15, 17**). Two of these products were probably the dehyderated products **368a** and **369a**, and the other ones were not charachterized. Anyway, the yields were low and the reaction was substantially not satisfying. No accurate charachterization was carried out in this stage and no enantiomeric excess was measured.



Entry	Acid	Additive/Conditions	Conv.	Product	Yield
1	-	-	0	-	-
2	**79b**	-	0	-	-
3	**317**	-	25	**367a**	n.d.
4	**255** (DPP)	-	11	**367a**	n.d.
5	**84a**	-	16	**367a**	n.d.
6	**84a**	**(1:1 DCM/H_2O)**	0	-	-
7	TFA	-	0	-	-
8	**88n**	-	20	**367a**	n.d.
9	p-TsOH	**-**	17	**367a**	n.d.
10	p-TsOH	**Toluene, 70 °C**	n.d.	Mixture	-
11	TfOH	-	50	decomposition	-
12	TfOH	4Å MS	31	**367a**	-
13	TfOH	4Å MS, **Toluene 70 °C**	27	**367a**	-
14	HCl	**1**, then I_2	0	-	-
15	$HClO_4$	-	80	**368a + 369a** + decomposition	20
16	$HClO_4$	**79b**	60	Complex mixture	-
17	$HClO_4$	**84a**	44	**368a + 369a** + another unknown product	12 + 34
18	$HClO_4$	**84a**, Powdred 4Å MS (30 mg)	10	**367a**	n.d.

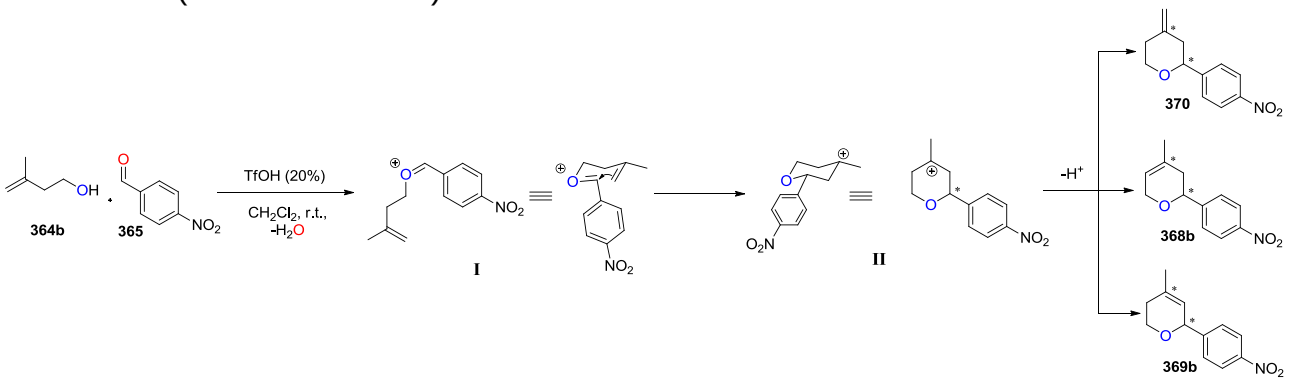
Table 7.1: first attempts to Brønsted acid catalyzed Prins cyclization.

In order to obtain a clean reaction we started thinking to change the starting materials. After having exhemined the literature and found the rules listed before, we supposed that our problem could be the alcohol **364a**, which was not enough reactive. We speculated that simply using 3-methyl-3-pentene-1-ol **364b**, the situation could change, because in the mechanism, after cyclization, a tertiary tetrahydropyranyl cation would have been formed. When we submitted the reaction using 20% of TfOH as catalyst, interestingly we obtained full conversion in a short time (scheme **7.9**). The reaction mixture was quite complicated, anyway we thought interesting to try a purification, at least partial, to understand what we obtained and considering the possibility to further improve the reaction in the future.



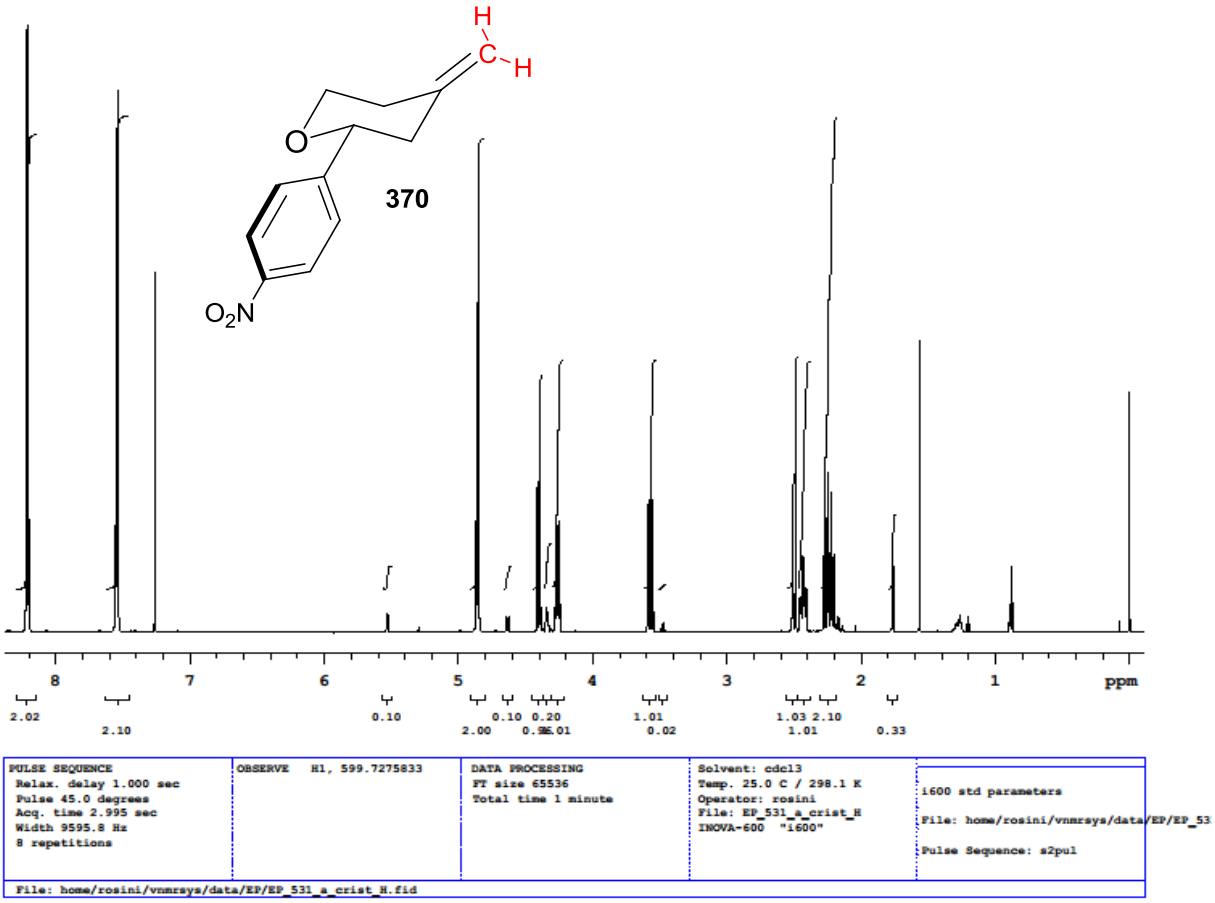
Scheme **7.9**: the first trial using 3-methyl-3-pentene-1-ol as alcohol.

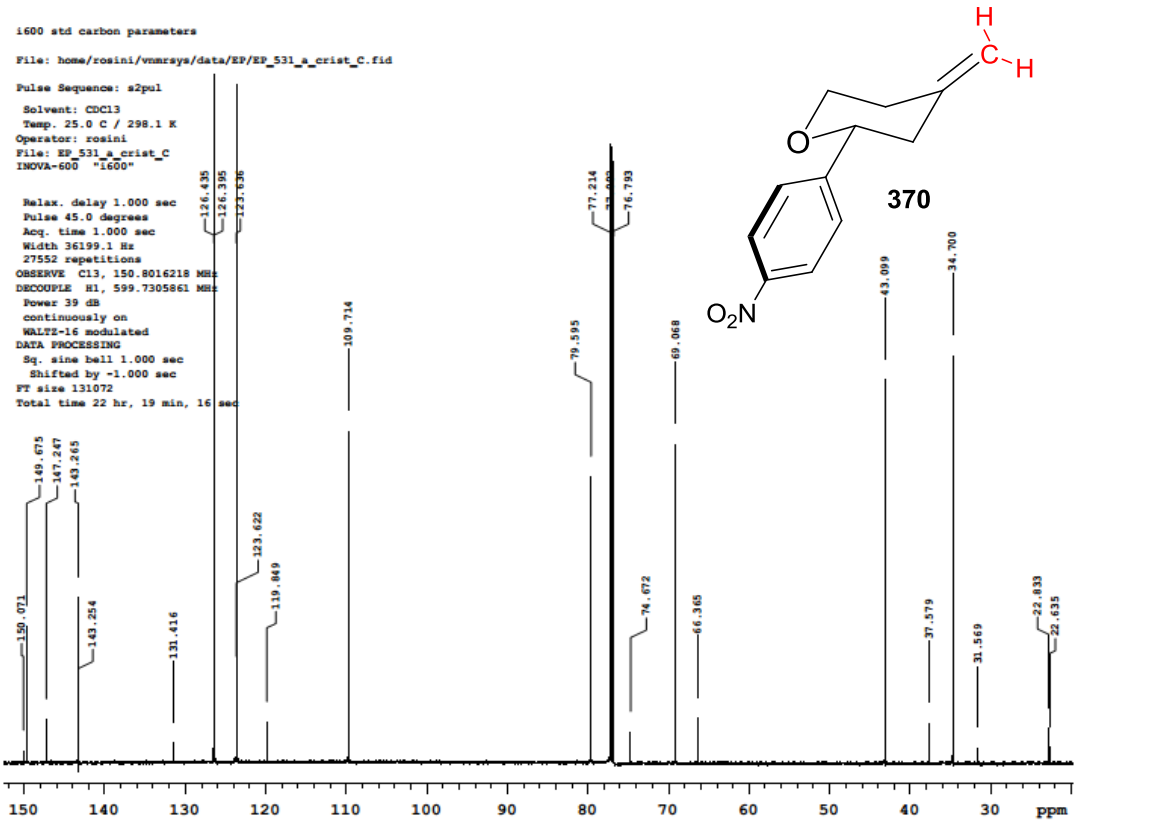
It is worth noiting that on TLC three spots were visible, and only later we understood that the first one consisted actually in an inseparable mixture of two products. Moreover, the second spot was very difficult to separate from the first. The third spot was more polar, and largely the minor: for this reason we decided not to charachterize it. This situation, actually makes the column very tedious. Honestly, for some time we went on with trials having only partial charachterization and a full one was obtained only later, but in the end this did not affect the good interpretation of the results. A reaction on quite big scale was necessary for a full understanding of the reaction outcome. As told, the first TLC spot is a mixture of two products, but the second, albeit quite difficult to isolate, is a pure product. We suddenly understood that these three products must be the three isomeric alkenes **370**, **368b** and **369b** arising by the Prins cyclization followed by deprotonation of the so-formed tetrahydropyranyl cation. Water, apparently, is too weak as nucleophile to quench the carbocation (see scheme **7.10**).

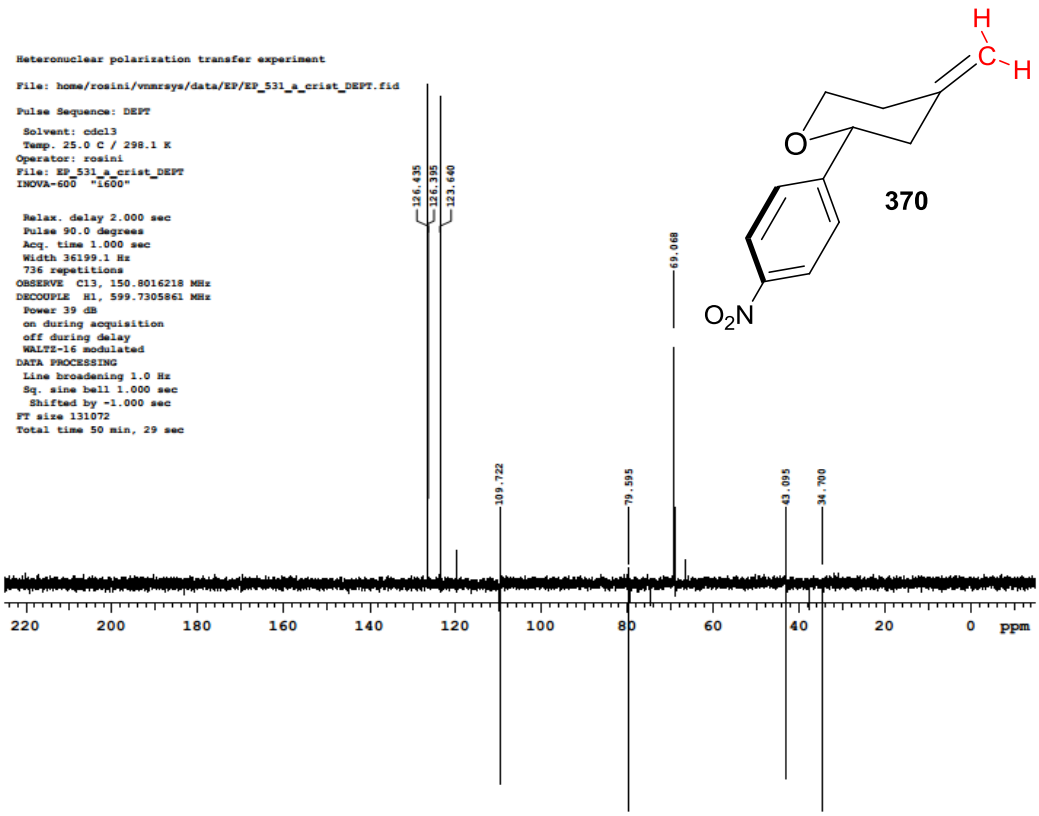


Scheme 10: formation of products **370, 368b** and **369b**.

We soon guessed that one of the two products in the first TLC spot had to be the exo-methylene product **370**, since by integration in the ^{1}H NMR spectrum we could see two set of signals, and in one there was a vinilic signal integrating for two protons. Moreover a vinylic CH_2 could be detected in the DEPT spectrum, thus giving us the evidence that product **370** was one of the ones in the first TLC spot (see *figures 7.5, 7.6* and *7.7*). Moreover, we realized that in the isolated first TLC spot the material obtained was not all the same: it was possible to see some small white crystals surrounded by a yellow oil. Thus, we tried to separate the two products by crystallization. After some trials, a sample with a quite high amount of purity of **370** was obtained (see the experimental section for details). The following spectra given for the characterization of **370** were obtained in thes way.

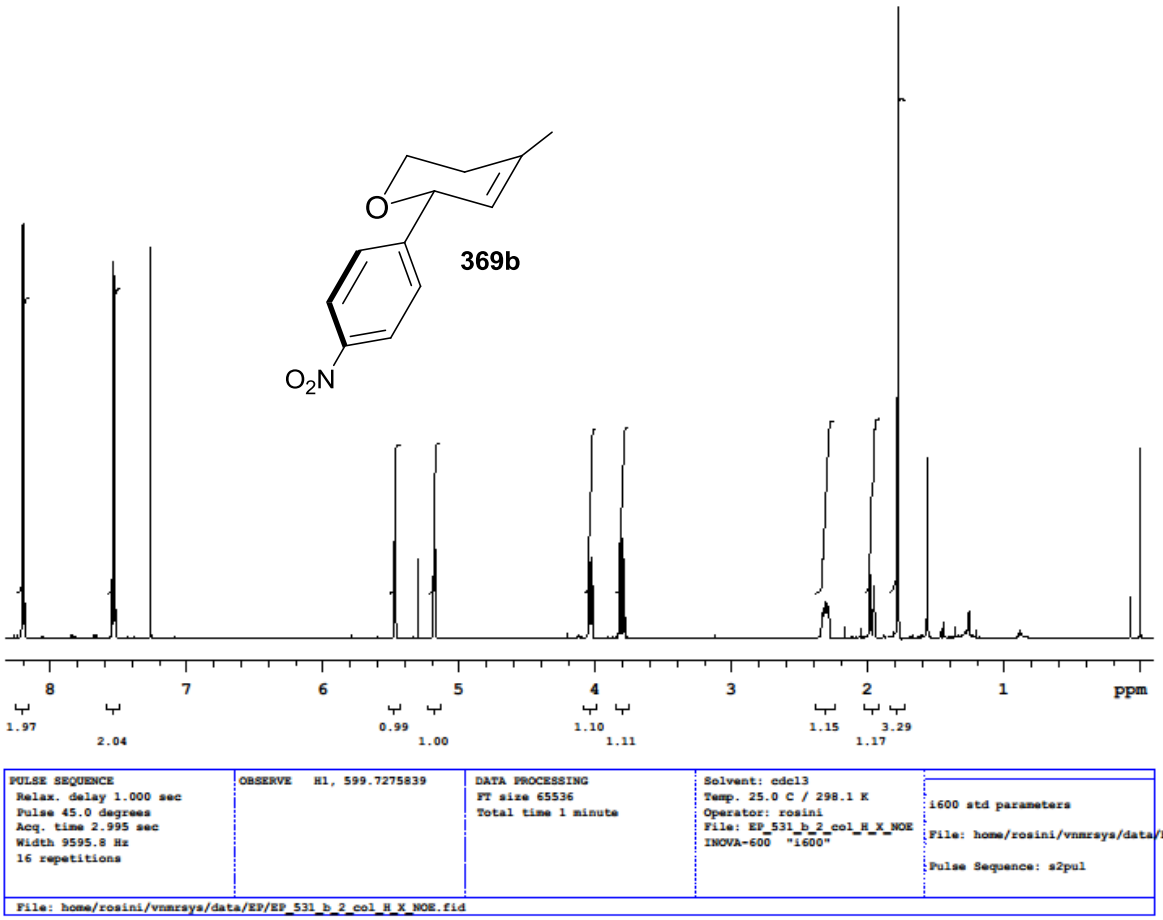

H
C
H
O
370
O2N
8
7
6
5
4
3
2
1
ppm
2.02
2.10
0.10
2.00
0.10
0.20
0.95
1.01
0.02
1.03
2.10
1.01
0.33
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.995 sec
Width 9595.8 Hz
8 repetitions
OBSERVE H1, 599.7275833
DATA PROCESSING
FT size 65536
Total time 1 minute
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: rosini
File: EP_531_a_crist_H
INOVA-600 "i600"
i600 std parameters
File: home/rosini/vnmrsys/data/EP/EP_53
Pulse Sequence: s2pul
File: home/rosini/vnmrsys/data/EP/EP_531_a_crist_H.fid

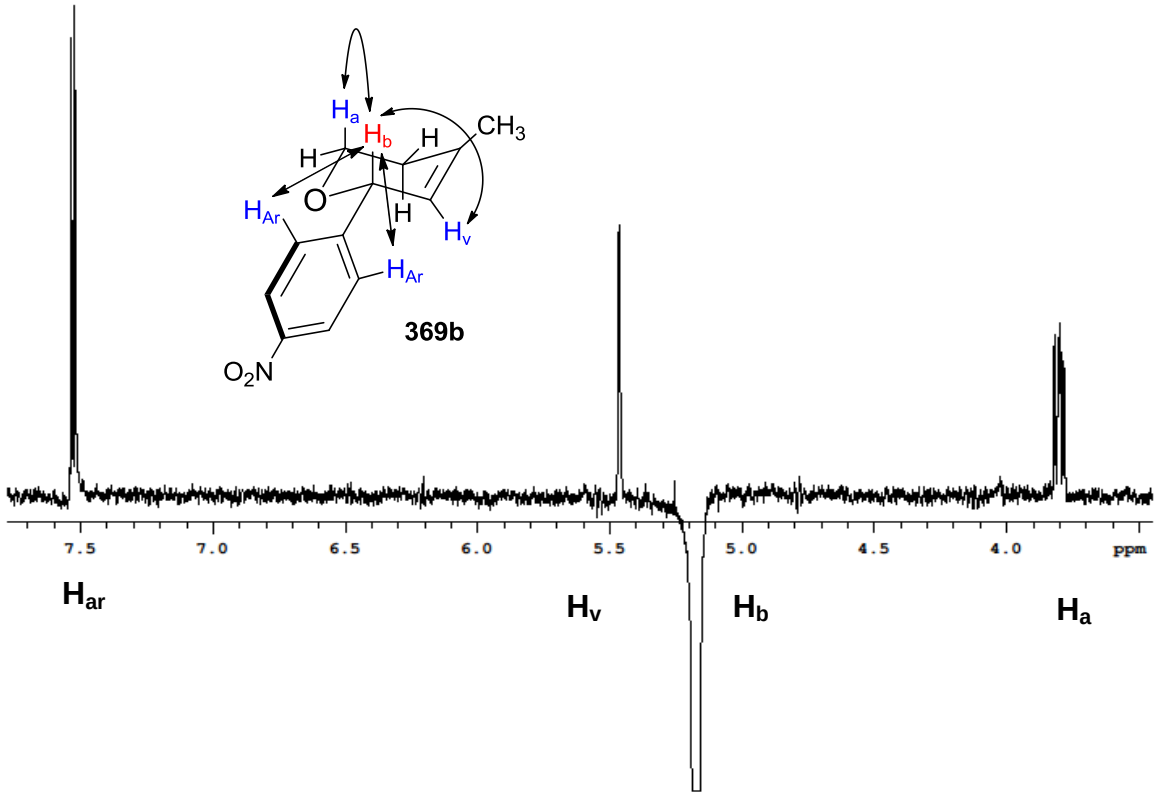

i600 std carbon parameters
File: home/rosini/vnmrsys/data/EP/EP_531_a_crist_C.fid
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: rosini
File: EP_531_a_crist_C
INOVA-600 "i600"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 36199.1 Hz
27552 repetitions
OBSERVE C13, 150.8016218 MHz
DECOUPLE H1, 599.7305861 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.000 sec
Shifted by -1.000 sec
FT size 131072
Total time 22 hr, 19 min, 16 sec
H
C
H
O
370
O2N
126.435
126.395
123.636
77.214
76.793
109.714
79.595
69.068
43.099
34.700
149.675
147.247
143.265
123.622
119.849
150.071
143.254
131.416
74.672
66.365
37.579
31.569
22.833
22.635
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

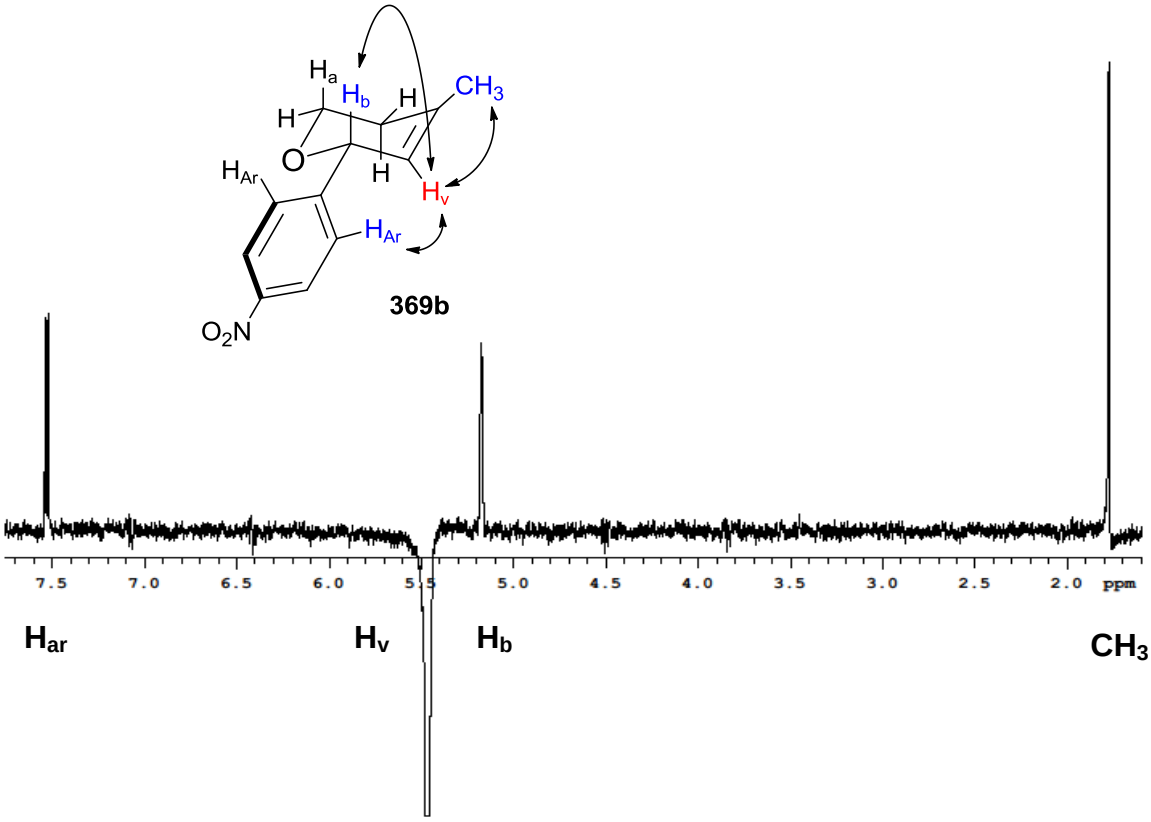


Figures 5, 6, and 7. NMR Spectra for compound **12**.

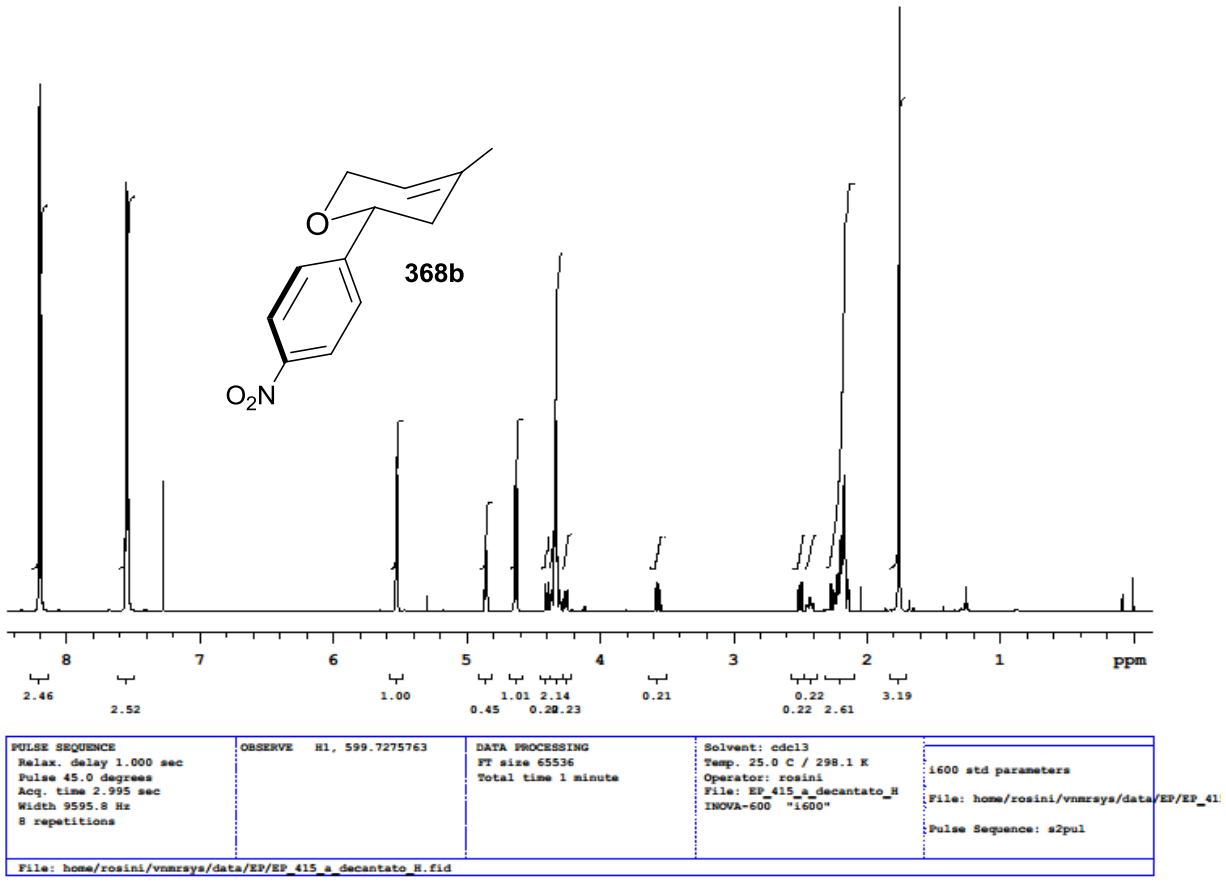
Albeit not as much pure, also the other compound present in the first TLC spot was obtained from the mother liquor of crystallization of **370**. It was still not clear wheater if it was **368b** or **369b**. Its purity extent was probably enough for a reasonable characterization, but, since it was not the best, to avoid any mistake we decided to perform a full characterization on the isolated second TLC spot (even if it was the minor product) and then deduce and confirm the structure of the other product only later.
So, we considered the compound in the second TLC spot. Its ^{1}H NMR spectrum is reported in *figure 7.8*. Quite logically the two protons between 5 and 5.5 ppm belong to the benzylic and the vynilic ones, and the two signals around 4 ppm belong to the protons in α to the oxygen. The reasoning is simple: since the possible structures are **368b** or **369b**, if irradiating the benzylic proton results in NOE effect on the vynilic one, the two protons are one next to the other, and the product is **369b**. Of course also the opposte must happen. On the contrary, if no NOE effect can be seen, the product must be **368b**. Irradiating the proton at 5.18 ppm results in NOE signals on the proton at 5.47 ppm, on one aromatic proton and on an ethereal one, thus clearly indicating that this is the benzylic proton H_b of product **369b**, which stays in the axial position, because it's near an ethereal proton, of course H_a (*Fig. 7.9*). To confirm that, also NOE on the signal at 4.47 ppm, which should be the vynilic one, was performed, obtaining without surprise NOE effect on the proton at 5.18 ppm, H_b, on one aromatic and on the methyl group around 2 ppm (*Fig. 7.10*). For confirmation, NOE spectra were performed on the mother liquor of the crystallized **370**, which, at this point, should contain **369b**. Despite, as told, the product is dirty of **370** and the NOE spectra are not perfect, the proton at 4.61 ppm, if irradiated, does not show signals around 5.5 ppm, where the vinylic proton should be (*Fig. 7.12*). This signal is compatible with the axial benzylic proton H_b of **369b**. For the vynilic proton at 5.51 ppm, things are also clearer, since no benzylic and no aromatic protons can be seen, but a strong NOE effect displayed by the vicinal etereal protons H_a and the methyl group around 2 ppm, confirms the structure of the product to be the one of **369b** (*Fig. 7.13*).

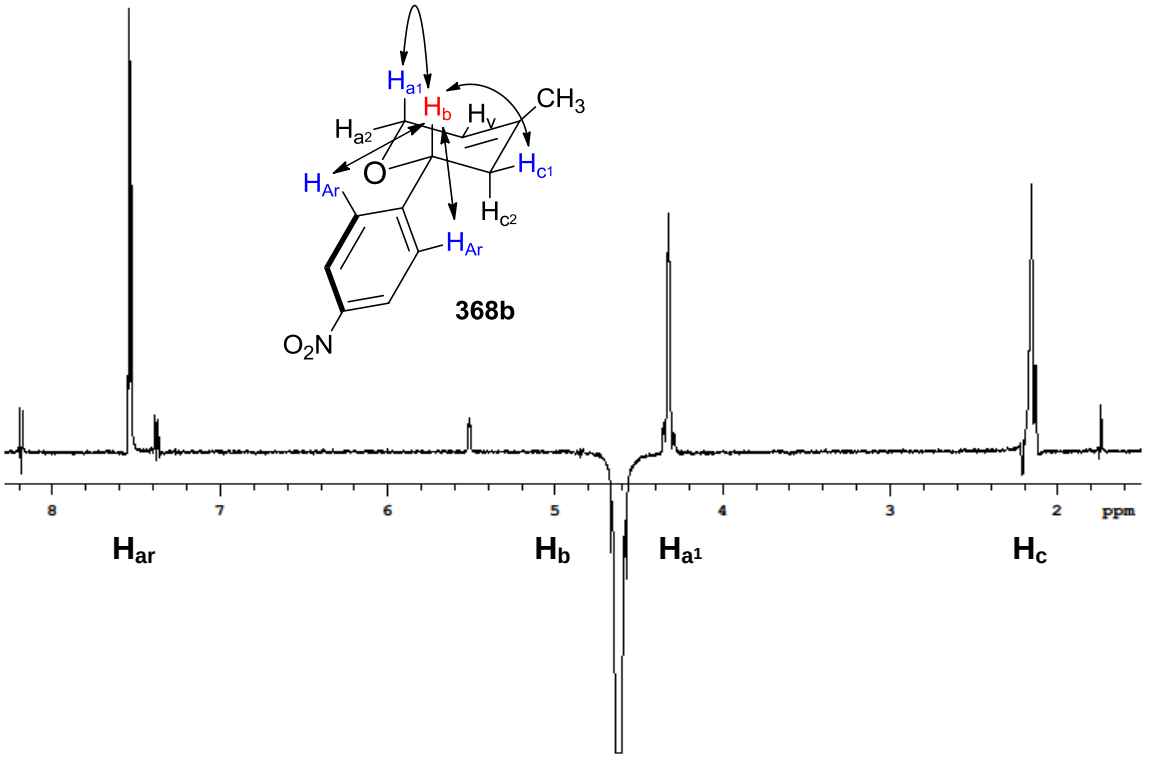

O
O2N
369b
8
7
6
5
4
3
2
1
ppm
1.97
2.04
0.99
1.00
1.10
1.11
1.15
1.17
3.29
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.995 sec
Width 9595.8 Hz
16 repetitions
OBSERVE H1, 599.7275839
DATA PROCESSING
FT size 65536
Total time 1 minute
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: rosini
File: EP_531_b_2_col_H_X_NOE
INOVA-600 "i600"
i600 std parameters
File: home/rosini/vnmrsys/data/EP/EP_53
Pulse Sequence: s2pul
File: home/rosini/vnmrsys/data/EP/EP_531_b_2_col_H_X_NOE.fid

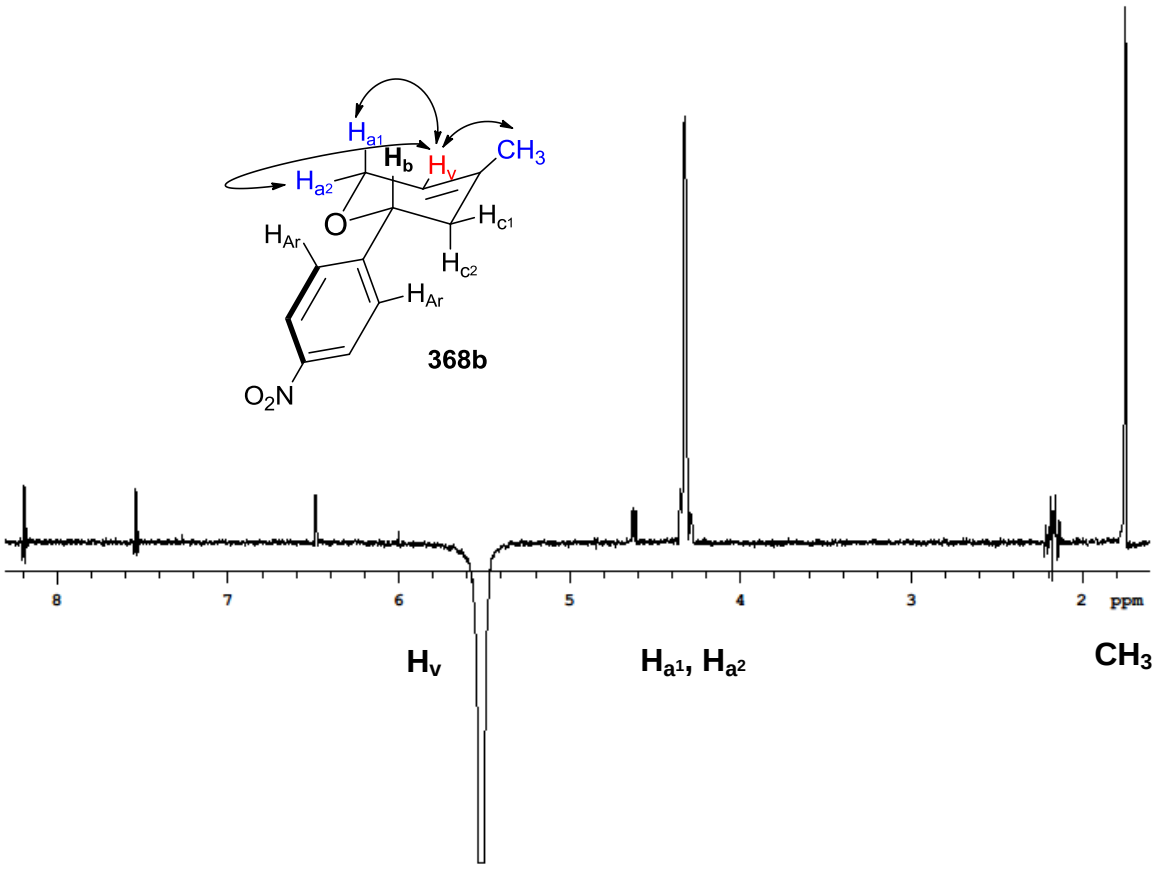

Ha
Hb
H
H
CH3
O
HAr
H
Hv
HAr
O2N
369b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
Har
Hv
Hb
Ha



Figures 7.8, 7.9 and 7.10: 1H NMR and NOE spectra of compound **369b**.

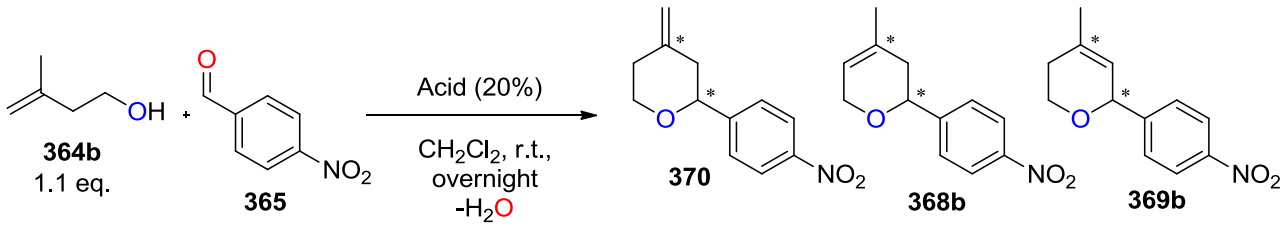






Figures *7.11, 7.12 and 7.13*: 1H NMR and NOE spectra of compound **368b**.

After this charachterization it was possible a complete assignment of the ^{1}H NMR signals also on the ^{1}H NMR of the crude mixture, therefore, using an internal standard it was possible to calculate the yield directly with NMR comparing the integration of the peaks: in this way even if two of the products were unseparable, all the yields were calculated. Moreover, we found condition for the separation of the enantiomers all the products in the same chiral column on the HPLC at the same time. Since pure samples of racemic **370** and **369b** were available, it was possible to assign every peak in the HPLC, and so to calculate enantiomeric excesses even on mixtures. This simplified dramatically the operations necessary to obtainthe results. Anyway, as we will see, product **369b** is largely minor in many reaction and its ee was almost never determined.
We are now able to give the right product distribution for racemic catalysis (*table 7.2*).

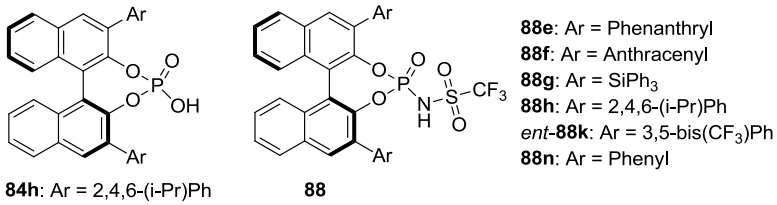


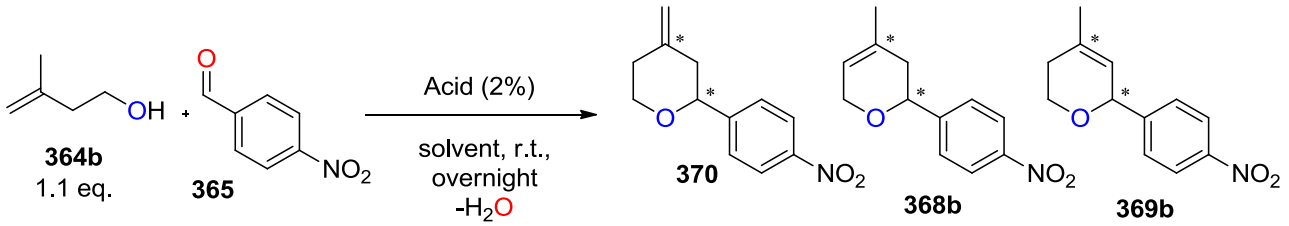
Entry	Acid	Conv.	Yield 370 (%)	Yield 368b (%)	Yield 369b (%)
1	TfOH	100	29	43	26
2	TMSOTf	100	39	49	12

Table 7.2: yields of the three products of the Prins cyclyzation exhamined.

With these results in our hand, we were ready to try enantioselective catalysis. Results are summarized in *table 7.3*. First of all, we tried a chiral phosphoric acid catalyst in DCM: unfortunately, when using the popular acid **84h** ((*S*)-TRIP) the reaction didn't show conversion (*Tab. 7.3*, entry **2**). When we switched to the more acidic triflimides we could see conversion using 2-5 mol% of catalyst in all the cases except for **88g** (*Tab. 7.3*, entry **5**). Low conversion was observed for **88n** which gave also a nearly racemic product (*Tab. 7.3*, entry **8**). Using catalysts **88e, 88f,** and **88k** remarkably increased the yield, with product **370** that becomes largely the major and product **369b** which is produced in trascurable amounts (*Tab. 7.3*, entries **3**, **4** and **7**). Moreover, ee's increase also, and actually catalyst **88e** gives interesting results with a promising ee (23%, *Tab. 7.3*, entry **3**). The best ee's among all (*Tab. 7.3*, entry **6**: 35% for **370** and 40% for **368b**) are anyway given by catalyst **88h**, but in this case the yields are lower and there is a lower preference for the formation of product **370** (with **88e** the ratio **370/368b** was 7:1, here is only 2:1; compare *table 7.3*, entries **3** and **6**).
Even if not the best for the enantioselectivity, catalyst **88e** was chosen for a solvent screening because of moderate enantioselectivity, high conversion and regioselectivity and also its availability in higher amounts. We found, anyway that changing the solvent does not affect much the reaction outcome (*Tab. 7.3*, entries **9-13**): in every solvent the ratio **370/368b** was 2:1-3:1 and ee's were generally similar. Ethyl acetate gave slightly better results respect to DCM for product **370**, and toluene did the same for product **368b** (*Tab. 7.3*, entries **9** and **12**). For this reason we repeated the reaction in these solvents using **88h** (*Tab. 7.3*, entries **14-15**). We found toluene to give comparable results with DCM and ethyl acetate giving less selectivity. Moreover, using powdred 4Å MS as additive

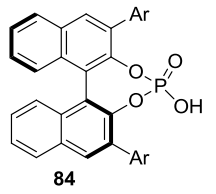
resulted in no reaction and decreasing the temperature disappointingly gave very low yields (*Tab. 7.3*, entries **16-17**).





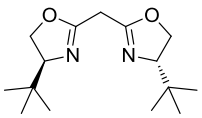
Entry	Cat (2%)	Solv.	t	Conv.	Yield 370 (%)	*ee 370 (%)*	Yield 368b (%)	*ee 368b (%)*	Yield 369b (%)	ee *369b* (%)
1	TfOH (20%)	DCM	16 h	100	29	-	43	-	26	-
2	**84h**	DCM	4 d	0	-	-	-	-	-	-
3	***88e***	*DCM*	*5 d*	*94*	*76*	*23*	*10*	*23*	*8*	*n.d.*
4	**88f**	DCM	3 d	93	73	*2*	12	*18*	7	n.d.
5	**88g** (5%)	DCM	1 d	0	-	-	-	-	-	-
6	***88h***	***DCM***	***3 d***	***61***	***37.5***	***35***	***16.6***	***40***	***7.3***	***n.d.***
7	*ent*-**88k** (5%)	DCM	5 d	91	72	*14*	20	*4*	3	n.d.
8	**88n** (5%)	DCM	3 d	36	n.d.	*4*	n.d.	*0*	n.d.	n.d.
9	**88e**	PhMe	3 d	99	66	*19*	24	*24*	9	n.d.
10	**88e**	Et_2O	3 d	63	48	*22*	16	*11*	6	n.d.
11	**88e**	THF	3 d	75	40	*22*	21	*0*	10	n.d.
12	**88e**	EtOAc	3 d	97	65	*25*	23	*22*	12	n.d.
13	**88e**	Etylen Glycol	3 d	0	-	-	-	-	-	-
14	**88h** (5%)	PhMe	3 d	50	30	*35*	15	*44*	5	n.d.
15	**88h** (5%)	EtOAc	3 d	70	42	*29*	26	*n.d.*	9	n.d.
16[a]	**88h** (5%)	DCM	16 h	0	-	-	-	-	-	-
17[b]	**88e**	DCM	4 d	47.5	15	*n.d.*	7	*n.d.*	3.5	n.d.

Table 7.3: chiral Brønsted acid catalyzed Prins cyclization. a: powdred 4Å MS (25 mg) were used as additive. b: reaction temperature was -30 °C.

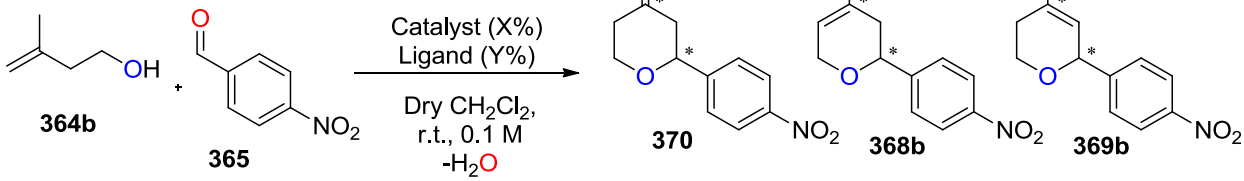


84

84e: Ar = Phenanthryl
84h: Ar = 2,4,6-(i-Pr)Ph



323c

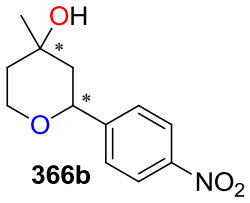


364b + 365 → 370 + 368b + 369b

Entry	Cat.	Ligand	t	Conv.	Yield 370 (%)	ee 370 (%)	Yield 368b (%)	ee 368b (%)	Yield 369b (%)	ee 369b (%)
1	TMSOTf (10%)	-	2 h	100	39	-	49	-	12	-
2	TMSCl	QD	Overnight	0	-	-	-	-	-	-
3	TMSCl	QD-NH2	Overnight	0	-	-	-	-	-	-
4	$Mg(O^t\text{-}Bu)_2$	**84h**	Overnight	0	-	-	-	-	-	-
5	$BF_3 \bullet Et_2O$ (5%)	**84e** (5%)	5 d	See text						
6	TMSOTf (5%)	**84e** (5%)	Overnight	99	42	0	45	0	14	n.d.
7	$In(OTf)_3$ (2%)	**84e** (6%)	3 d	97	35	0	37	0	11.5	0
8	$Sc(OTf)_3$ (2%)	**84e** (6%)	3 d	99	40	0	40	0	14	0
9	$CuCl_2$ (8%) $AgSbF_6$ (16%)	**323c** (10%)	3 d	Complex Mixture	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
10[a]	Ag_2CO_3 (4%) $Cu(OTf)_2$ (4%)	**84e** (8%)	2 d	0	-	-	-	-	-	-
11[a]	Ag_2CO_3 (4%) $CuCl_2$ (4%)	**84e** (8%)	2 d	0	-	-	-	-	-	-
12[a]	Ag_2CO_3 (4%) $MgBr_2 \bullet Et_2O$ (4%)	**84e** (8%)	2 d	0	-	-	-	-	-	-

Table 7.4: Lewis acid catalyzed Prins cyclization. a : powdred 4Å MS (30 mg) were used as additive.

For comparison, also some trials in Lewis acid catalysis were performed for this reaction (*table 7.4*). The only entries which gave good conversion and interpretable results were entries **6-8**, when compound **84e** was used in combination with lewis acid to try cooperative catalysis. In this cases the products are racemic: the reaction is probably catalyzed only by the racemic Lewis acid, even if we observed changes in the color of the reaction mixtures which might indicate the formation of complex species. When CuBOX catalysis was tried a very complex mixture was obtained (entry **9**). When BF_3•Et_2O was used, instead, another product was formed in quite low yield (entry **5**). After analysis via ^1H NMR spectroscopy, we made the hypothesis that this material could be the real Prins cyclization product **366** in 1:1 diastereomeric mxture, but the low yield and the lack of time didn't allow us a full charachterization of the latter (see *figure 7.14*).



366b

Figure 7.14: the real Prins cyclization product, probably obtained in low yield and as 1:1 diastereoisomeric mixture in entry **5** of Tab. 7.4.

After obtaining this results, mainly for reasons of time, we had to interrupt the project, but it's worth noting that it was not abandoned. Many other things can be made in order to try to optimize the reaction, and could be very interesting options for its the future development, like screening other catalysts, or change starting materials, maybe using also other approaches.
Here everything we can do is a small mechanicistic consideration: as you can see, enantioselective catalysis gives mainly product **370** and only low amounts of product **369b**. In a thermodynamically controlled reaction, with a stepwise mechanism, no other entities are involved in the cyclization step and the chiral counteranion creates the chiral environment but mechanicistically is only a spectator. The formation of the tetrahydropyranyl cation would be followed by random deprotonation, giving rise to a statistic mixture of products like happened in *table 7.1* for racemic catalysis. In this context, the sometimes high preference for the formation of **370** respect to the others, is somehow counterintuitive, since it's also the less substituted alkene, thus thermodynamically disfavored. Moreover the second major product is **368b**. If we think about the mechanism, these are the two products that could arise by an hypothetic concerted mechanism, where the proton is taken by the counteranion at the same time of ring closure (*Fig. 7.15,* **A**). For product **369b**, this mechanism is not possible, and a proton form that position can be lost only after the ring closure by the tetrahydropyranyl cation (*Fig. 7.15,* **B**). We can conclude that, since product **369b** is present, stepwise mechanism is surely operative, but being this product the minor, and the other two the major ones, this particular reaction might proceed partially with a concerted mechanism (*figure 15*). On the other hand, as we saw in the introduction, counteranions have a big influence on the Prins reaction outcome. So the different behavior of racemic and chiral catalysts might be ascribed even to other factors, e.g. the simple steric hindrance of the counteranion. So, the hypothesis of the concerted mechanism is completely speculative and more insightful mechanicistic studies would have to be performed to get some more clues on the elucidation of the latter, but this was out of the aim of this work.

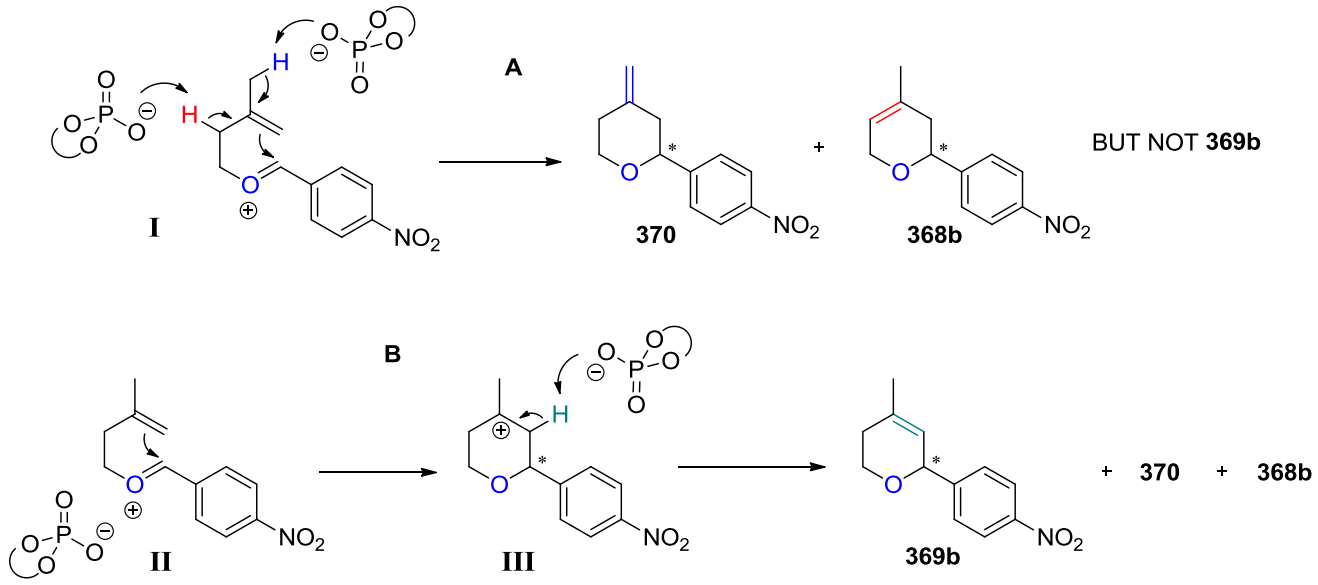


Figure 7.15: hypothesis for concerted (**A**), and stepwise (**B**) mechanism for Brønsted acid catalyzed Prins cyclization. In a concerted mechanism product **369b** can't be formed: it must arise from a stepwise mechanism involving the tetrahydropyranyl cation. Anyway, the high preference for the enantioselective reaction for the other products, especially **370**, lead us to the idea that also concerted mechanism is operative for this particular reaction together with the stepwise one.

7.3) EXPERIMENTAL SECTION

General experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian inova 300, at 300 MHz and 75 MHz respectively, Varian mercury 400, at 400 MHz and 100 MHz respectively, or Varian inova 600, at 600 MHz and 150 MHz respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. $CDCl_3$ was passed over a short pad of alumina before use. Coupling constants are given in Hz. The carbon types were determined from DEPT ^{13}C NMR experiments. NOE spectra were recorded using the DPFGSE-NOE sequence[227].
Optical rotations are determined using a Perkin Elmer 341 instrument with sodium lamp and are reported as follows: $[\alpha]^{^{\circ}C}_{D}$ (*c* in g per 100 mL, solvent).
Thin Layer Chromatography (TLC) was performed on commercially available Fluka TLC plates on aluminium or PET foils with fluorescent indicator at 254 nm, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents.
Purification of the products was carried out by flash chromatography (FC) on silica gel (Aldrich, 230-400 mesh) according to the method of Still[228].
Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Materials

All the commercially available reagents, solvents, catalysts and ligands were used without any further purifications; otherwise, where necessary, they were purified as recommended[229].
Phosphoric acid catalysts and triflimides were prepared according according to literature procedures[230]. Compound **323c** is commercially available. For compounds **79b** and **317** please see section **6.3.1**.

Determination of yields and enantiomeric purity.

Chemical yields were determined by ^{1}H NMR spectroscopy of the crude product using CH_2Br_2 as internal standard. Enantiomeric excesses were determined, after purification, through HPLC

[227](a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwand, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (b) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Resonance* **1997**, *125*, 302. (c) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Resonance* **1999**, *141*, 191. (d) See also: Claridge, T.D.W. *High Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.
[228] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[229] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
[230] a) T. R. Wu, L. Shen, J. M. Chong, *Org. Lett.*, **2004**, *6*, 2701–2704. b) R. R. Milburn, S. M. S. Hussain, O. Prien, Z. Ahmed, V. Snieckus, *Org. Lett.*, **2007**, *9*, 4403–4406. c) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566 –1568. d) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, 2004, *126*, 5356-5357. e) M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett,* **2010**, *14*, 2189–2192. f) V. Rauniyar, J. Wang, H. Burks, F. D. Toste, *J. Am. Chem. Soc.*, **2011**, *133*, 8486–8489. g) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.*, **2006**, *128*, 9626-9627. Please see also ref.112-126.

analysis on chiral stationary phase performed on an Agilent 1100-series instrumentation using a Phenomenex Lux-Cellulose 2 column. Racemic samples of compounds **370**, **368b** and **369b** were obtained performing the reaction with 20 % of TfOH as catalyst.

General procedure for the Brønsted acid catalyzed Prins cyclization.

Chiral BINOL-based triflimide (0.002 mmol, 0.02 eq.) was introduced into a screw-capped vial and then subsequently p-nitrobenzaldehyde (0.1 mmol, 1 eq.), the solvent (0.5 ml, 0.2 M), and the alcohol (0.11 mmol, 1.1 eq.) were added, and the reaction mixture was stirred fo the given time. Then it was plugged on a short pad of silica gel to remove the catalyst (eluent 1:1 Hex/EtOAc) and the yield was measured via NMR using an internal standard. After that, the mixture was further purified via flash chromatography on silica gel (eluent mixture 98:2 Hex/Et_2O) to give a mixture of products **370** and **368b** as an heterogeneous mixture of colorless crystals and an orange oil and pure product **369b** as an orange oil.

General procedure for the racemic reaction to obtain pure samples for charachterization.

TfOH (0.1 mmol, 0.2 eq.) was added to a solution of p-nitrobenzaldehyde (0.5 mmol, 1 eq.), and alcohol (0.55 mmol, 1.1 eq.) in 2.5 ml of DCM (0.2 M) and the reaction mixture was stirred overnight. Then it was plugged on a short pad of silica gel to remove the catalyst (eluent 1:1 Hex/EtOAc) and the yield was measured via NMR using an internal standard. After that, the mixture was further purified via flash chromatography on silica gel (eluent mixture 98:2 Hex/Et_2O) to give a mixture of products **370** and **368b** as an heterogeneous mixture of colorless crystals and an orange oil and pure product **369b** as an orange oil. The mixture of **370** and **368b** was then dissolved in the minimum amount of DCM, hexane was added, and the flask was left open, until the formation of colorless crystals happened. The mother liquor was decanted in another flask and the crystals were further washed twice with hexane. In this way a sample of **370** having 95% purity and a sample of **368b** having 75% purity were obtained.

General procedure for the Lewis acid catalyzed Prins cyclization (*table 7.4*, entry **5-8**)

Chiral BINOL-based triflimide (0.005-0.006 mmol, 0.05-0.06 eq.) was introduced into a test tube, which then was put into a glovebox. The lewis acid (0.02 or 0.05 mmol, 0.02 or 0.05 eq.) was added, the test tube was covered with a serum cap and then removed form the glovebox. Dry DCM (0.5 ml) was then added via syringe and the mixture was stirred 1 h. Then p-nitrobenzaldehyde (0.1 mmol, 1 eq.) was added via syringe as a solution in 0.5 ml do dry DCM and the mixture was stirred further 5-10 min. Then 3-methyl-3-pentene-1-ol (0.11 mmol, 1.1 eq.) was added via syringe and the mixture was stirred fo the given time. Subsequently the reaction mixture was diluted with an 1:1 mixture of Hex/EtOAc, passed through a short pad of silica and the solvent was evaporated in vacuo to give the crude product which was purified through flash chromatography on silica gel.

Procedure for CuBOX catalysis (*table 7.4*, entry 9)

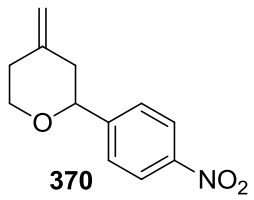
In a test tube containing a stir bar was placed $CuCl_2$ (0.008 mmol, 8%) with no precaution to exclude moisture and air. The schlenck was covered with a serum cap, flame dried in vacuo and then backfilled with argon upon cooling. Then the tube was put into a glovebox and the ligand (0.01 mmol, 10%) was added. The tube was covered with a serum cap, removed from the glovebox and 0.5 ml of dry DCM were added under argon. This solution was stirred at r.t. for 2 hours. Meanwhile, $AgSbF_6$ (0.016 mmol, 16%) stored in the glovebox was added to a different vial, which was also covered with a serum cap and removed from the glovebox. To this vial was also added dry DCM (0.5 ml) under argon and this solution was transferred via syringe under argon to the tube containing the copper and the ligand. The so-obtained mixture was stirred in the absence of light for 2 hours, then a solution of p-nitrobenzaldehyde in 0.5 ml of dry DCM was added (0.1 mmol, 1 eq.) was added, the mixture stirred further 5 min., and finally 3-methyl-3-pentene-1-ol (0.11 mmol, 1.1 eq.) was added via syringe. The so-obtained mixture was stirred fot the required time, then diluted with an 1:1 mixture of Hex/EtOAc, passed through a short pad of silica and the solvent was evaporated in vacuo to give the crude product which was purified through flash chromatography on silica gel.

Procedure for Lewis acid catalysis (*table 17*, entry 2-5)

For entry **10-12** a literature procedure was followed[231].
For entry **4** another literature procedure was followed[232].

Characterization of products

4-methylene-2-(4-nitrophenyl)tetrahydro-2H-pyran (370), colorless crystals.

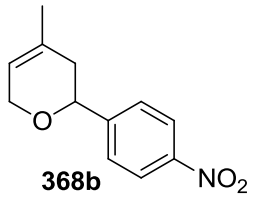


370

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.21 (d, 1H, J = 12.6 Hz), 2.26 (d, 1H, J = 15.0 Hz), 2.43, (M, 1H), 2.50 (td, 1H, J_a = 13.4 Hz, J_b = 2.1 Hz), 3.57, (ddd, 1H, J_a = 12.5 Hz, J_b = 10.5 Hz, J_c = 2.6 Hz), 4.26 (dd, 1H, J_a = 11.1 Hz, J_b = 5.8 Hz), 4.40 (dd, 1H, J_a = 11.4 Hz, J_b = 2.6 Hz), 4.86 (dq, 2H, J_a = 9.25 Hz, J_b = 1.8 Hz), 7.54 (d, 2H, J = 8.5 Hz), 8.46 (d, 2H, J = 8.5 Hz).
^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 34.7 (CH_2), 43.1 (CH_2), 69.1 (CH_2), 79.6 (CH), 109.7 (CH_2), 123.6 (CH), 126.4 (CH), 143.3 (C), 147.2 (C) 149.7 (C).
ESI-MS: calcd. 219; found 274 (M+MeOH+Na).
HPLC analysis: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 98:2, flow rate 0.55 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 22.6 min. τ_{minor} = 25.9 min.

[231] K. Saito, Y. Kajiwara, T. Akiyama, *Angew. Chem. Int. Ed.*, **2013**, *52*, 13284-13288.
[232] M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem. Int. Ed.*, **2010**, *49*, 3823–3826.

4-methyl-2-(4-nitrophenyl)-3,6-dihydro-2H-pyran (368b), orange oil.

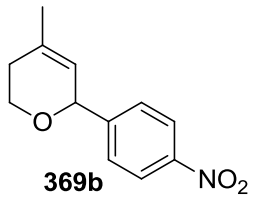


368b

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.76 (s, 3H), 2.19 (m, 2H), 4.34, (m, 2H), 4.63 (dd, 1H, J_a = 9.9 Hz, J_b = 4.3 Hz), 5.52, (s, 1H), 7.55 (d, 2H, J = 8.0 Hz), 8.20 (d, 2H, J = 8.0 Hz).
^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 22.8 (CH_3), 37.6 (CH_2), 66.4 (CH_2), 74.7 (CH), 119.8 (CH), 123.6 (CH), 126.4 (CH), 131.4 (C), 147.2 (C), 150.1 (C).
ESI-MS: calcd. 219; found 274 (M+MeOH+Na).
HPLC analysis: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 98:2, flow rate 0.55 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 29.9 min. τ_{minor} = 28.5 min.

The two products were fully characterized because the racemic reaction was carried out on a bigger scale, and the separation of the two product was possible by selective crystallization of **12**. This was not possible on the enantioenriched products, since the enantioselective catalysis was performed in a smaller scale. The rotatory power was therefore measured on a mixture of products **12** and **13** in a 2:1 ratio.
$[\alpha]_D^{rt}$ = + 2.4 (c = 1.225, $CHCl_3$).

4-methyl-6-(4-nitrophenyl)-3,6-dihydro-2H-pyran (369b), yellow oil.



369b

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.79 (s, 3H), 1.98 (m, 1H), 2.32 (m, 1H), 3.81 (ddd, 1H, J_a = 11.1 Hz, J_b = 9.2 Hz, J_c = 4.1 Hz),, 4.04 (ddd, 1H, J_a = 11.2 Hz, J_b = 5.6 Hz, J_c = 3.2 Hz), 5.19 (m, 1H), 5.48 (m, 1H), 7.54, (d, 2H, J = 8.1 Hz), 8.21 (d, 2H, J = 8.1 Hz).
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 23.2 (CH_3), 29.7 (CH_2), 63.5 (CH_2), 75.2 (CH), 121.8 (CH), 123.6 (CH), 127.8 (CH), 134.1 (C), 147.3 (C), 149.4 (C).
ESI-MS: calcd. 219; found 274 (M+MeOH+Na).
HPLC analysis: Phenomenex Lux-Cellulose 2 column; Hex/i-PrOH 98:2, flow rate 0.55 mL/min, T = 25 °C, λ = 230 nm, τ_{major} = 23.3 min. τ_{minor} = 32.2 min.
$[\alpha]_D^{rt}$ = - 7.3 (c = 1.225, $CHCl_3$).

Projects carried out abroad

The following two projects were carried out during my experience of six months in the laboratories of Prof. Dr. Magnus Rueping:

Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1
52074 Aachen
Germany

8) The Nazarov cyclization of electron-rich arenes

8.1) introduction

The Nazarov cyclization takes its name from the Russian chemist Ivan Nazarov. Although the process was known also before, the intensive studies carried out by Nazarov since 1941 gave to this reaction much attention and consideration[233]. This reaction always attracted organic chemists because its products are cyclopentenones, highly valuable intermediates in organic syntheses. The generally accepted mechanism (*Figure 8.1*) is as follows: the starting material is a divinilketone **I** which under the action of a Lewis acid can generate the corresponding divinylcation **II**. This intermediate then undergoes a 4π-electrocyclization. This transformation has been recognized as a pericyclic reaction, which follows the Woodward and Hoffman rules[234]. Thus the reaction must occur with a conrotatory mechanism, since the disrotatory mechanism is forbidden for symmetry reasons. As a valuable consequence of this mechanism, this reaction occurs with a well-defined stereochemical outcome, forming only the corresponding *trans*-cyclopentdienyl cations **III**. Unfortunately, one of these stereocenters is lost during the deprotonating step which gives the cross dienolate **IV**, which is protonated to the desired ciclopentenone **V**.

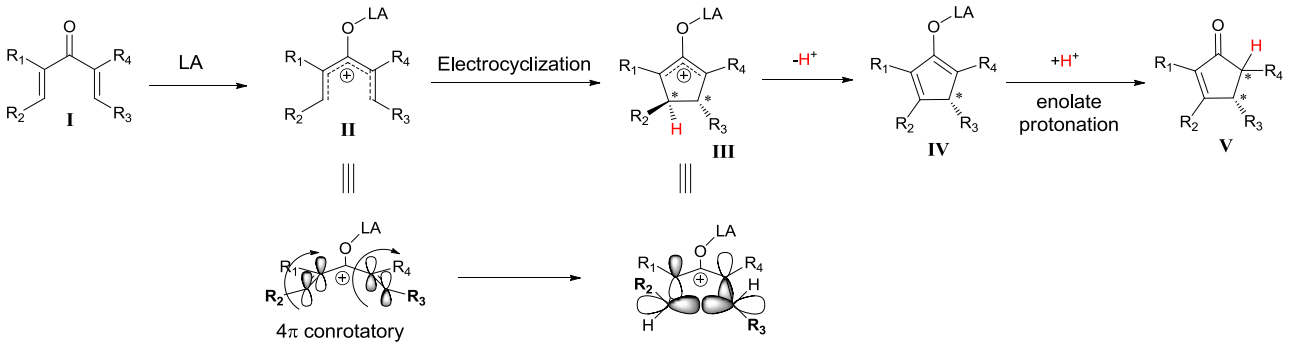


Figure 8.1: the mechanism of the Nazarov cyclization.

During the first years the effectiveness of this transformation remained elusive, and the old reviews describe the Nazarov cyclization as challenging and difficult to control[235]. Classically, some drawbacks were:

- lacking in the control of the position of the double bond: this might be achieved if one of the double bonds would be more substituted than the other, or if one of the R

[233] For the first paper by Nazarov, to which many others followed, see: I. N. Nazarov, I. I.Zaretskaya, I*zv. Akad. Nauk. SSSR, Ser. Khim.*, **1941**, 211–224.

[234] a) Woodward, R. B. *Chem. Soc. Special Publication No. 21*, **1967**, 237–239. b) C. W. Shoppee, R. E. Lack, *J. Chem. Soc.*, **1969**, 1346–1349. c) C. W. Shoppee, B. J. A. Cooke, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2271–2276. d) C. W. Shoppee, B. J. A. Cooke, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1026–1032.

[235] a) C. Santelli-Rouvier, M. Santelli, *Synthesis*, **1983**, 429–442. b) S. E. Denmark, In: B. M. Trost, I. Fleming, Eds.; (1991) *Comprehensive Organic Synthesis*; Pergamon: Oxford, *5*, page 751. c) K. L. Habermas, S. E. Denmark, T. K. Jones, (1994) *Org. React. (N.Y.)*, *45*, 1–158.

groups stabilizes carbocations, driving deprotonation, or, additionally, if one of the proton is more acidic than the others. If none of this conditions is satisfied, the deprotonation is statistical, and can lead to both cyclopentenones.

- Typically stoichiometric or superstoichiometric of strong Lewis or Brønsted acid promoters are required.
- One stereocenter is lost during the process
- Seldom the last protonation step is diastereoselective
- Depending on the nature of carbocationic intermediate, side reactions, like Wagner-Meerwein rearrangement, can occur leading to undesired products.

During the time achievements in the understanding of the mechanism and in controlling the reactions were obtained. For example Denmark used silyl groups to control the formation of the double bond (*Fig. 8.2*, **A**)[236]: the silyl acts as a "electrofugal" leaving group allowing the well-determined formation of a double bond. Denmark himself studied systematically the substituent effect on the Nazarov cyclization[237], while other groups developed the fluorine driven Nazarov cyclization (*Fig. 8.2*, **B**)[238] and the interrupted Nazarov cyclization[239], where the cyclopentadienyl cation is trapped with a nucleophile (*Fig. 8.2*, **D**). Than in 2003 many groups realized that α-alkoxy substituents improved the reaction efficiency and let it be catalytic due to the electron donating nature of the alkoxy moiety and its ability to further stabilize the cyclopentadienyl cation, also driving the loss of a proton[240]. This strategy is also called polarized Nazarov cyclization (*Fig. 8.2*, **C**).

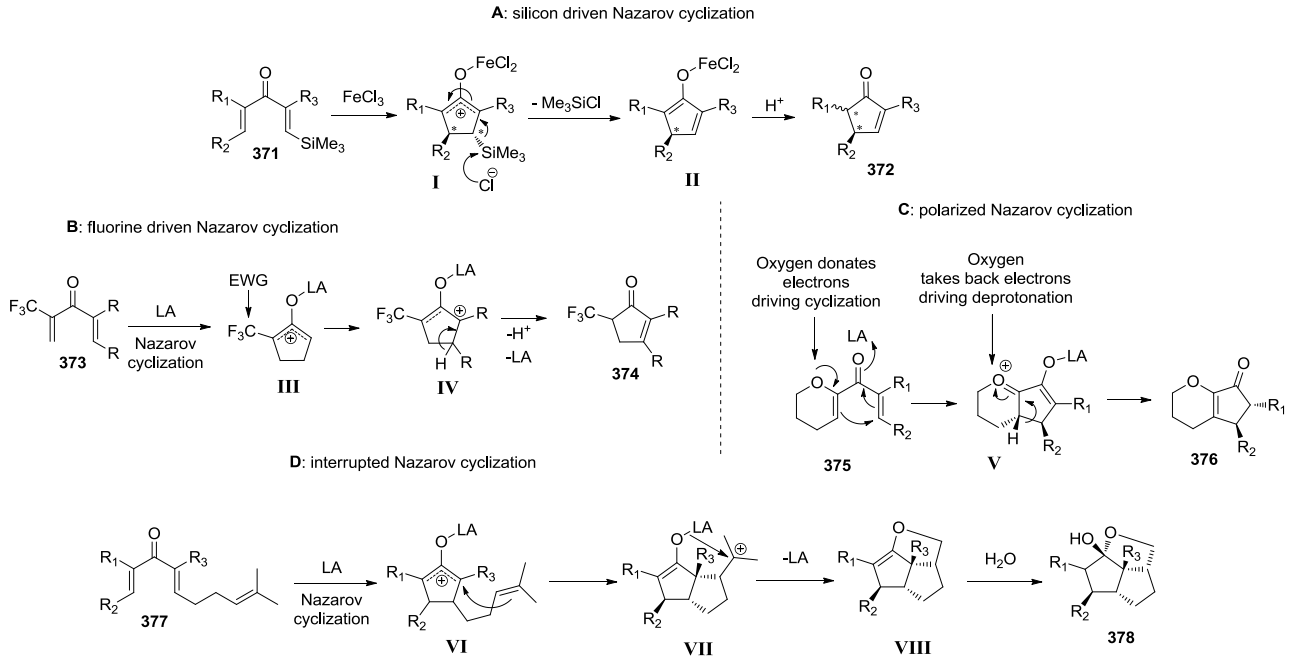


Figure 8.2: different Nazarov cyclization variant allowing stereocontrol.

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[236] S. E. Denmark, T. K. Jones, *J. Am. Chem. SOC.,* **1982,** *104,* 2642-2645.

[237] S. E. Denmark, K. L. Habermas, G. A. Hite, *Helv. Chim. Acta*, **1988**, *71*, 168–194.

[238] a) J. Ichikawa, S. Miyazaki, M. Fujiwara, T. Minami, *J. Org. Chem.*, **1995**, *60*, 2320–2321. b) J. Ichikawa, S. Miyazaki, M. Fujiwara, T. Okauchi, T. Minami, *Synlett*, **1998**, 927–929. c) J. Ichikawa, *Pure Appl. Chem.*, **2000**, *72*, 1685–1689.

[239] For West's seminal work, to which many others followed, see: (a) J. A. Bender, A. E. Blize, C. C. Browder, S. Giese, F. G. West, *J. Org. Chem.,* **1998**, *63*, 2430.

[240] a) W. He, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.,* **2003**, *125*, 14278- 14279; addition/correction *J. Am. Chem. Soc,.* **2004**, *126*, 10493. b) G. X. Liang, S. N. Gradl, D. Trauner, *Org. Lett.,* **2003**, *5*, 4931. c) C. Bee, E. Leclerc,M. A. Tius, *Org. Lett.,* **2003**, *5*, 4927. d) E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, P. Venturello, *J. Org. Chem.,* **2003**, *68*, 9728.

This prompted many groups to further study the reaction and many publications appeared and reviewed[241]. Development of stereoselective and/or catalytic[242] version of the reaction were done. Recently, asymmetric variants appeared[243].
Asymmetric Nazarov cyclization is a torquoselectivity problem, that means that a direction of rotation (clockwise or anticlockwise) have to be selected by the control of a chiral entity. This problem is not trivial. The first asymmetric Nazarov cyclization was reported in 1999 and a chiral auxiliary was used[244] (*Fig. 8.3*, **A**). In 2003 the first catalytic enantioselective reation was reported using the chiral Sc-PyBOX complex **381**, but the yield and ee were only moderate[245] (*Fig. 8.3*, **B**). In the same year the first highly enantioselective Nazarov cyclization was reported, but, with only one exception, a stoichiometric amount of a chiral complex was required[246] (*Fig. 8.3*, **C**). The first really catalytic highly enantioselective process based on Nazarov cyclization was reported in 2004, although the enantioselective step was actually the final protonation of the cyclic enolate[247] (*Fig. 8.3*, **D**).

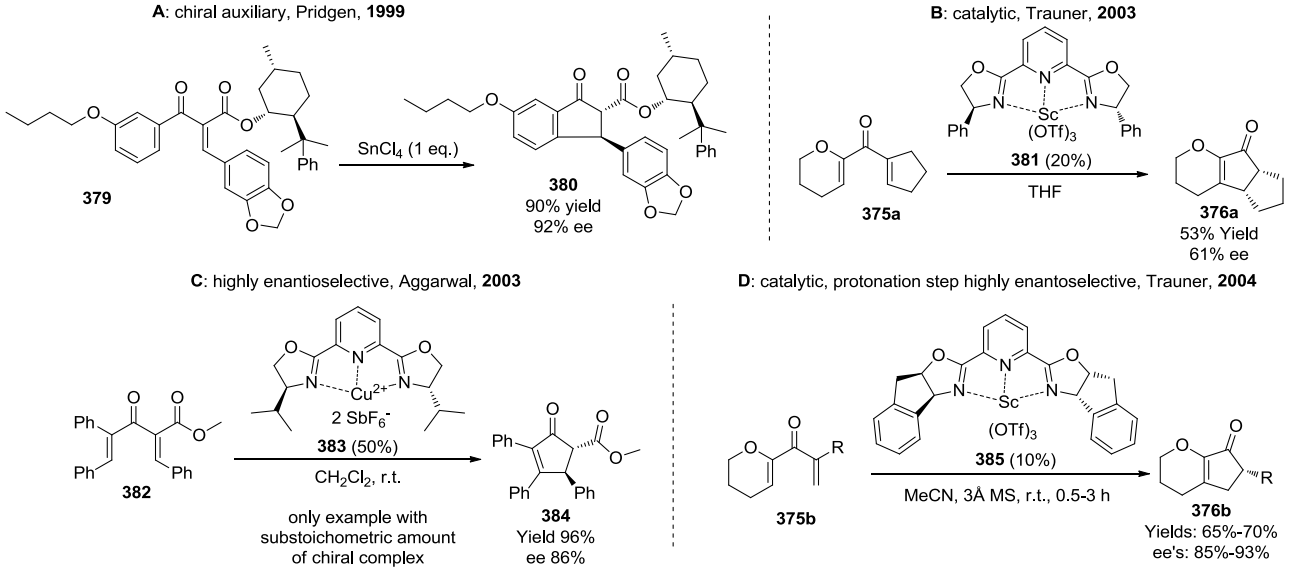


Figure 8.3: early examples of asymmetric Nazarov cyclizations.

The reason why enantiocontrol in this reaction is so difficult is clear: forcing the rotation occurring in one or in the other direction means forcing one substituent to undergo a determined rotation in only one direction by hampering the other one with a steric hindrance. Since coordination is on one side of the molecule, and substituents are on the other one, they are far away, and stereocontrol is difficult. Protonation, instead happens next to the reaction centre, and can be contolled in an easier way (*Fig*. *8.4*).

[241] Reviews: a) A. J. Frontier, C. Collison, *Tetrahedron*, **2005**, *61*, 7577 –7606. b) M. A. Tius, *Eur. J. Org. Chem.*, **2005**, 2193 –2206. c) H. Pellissier, *Tetrahedron*, **2005**, *61*, 6479– 6517.
[242] Review: T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem*, **2011**, *3*, 1531–1548.
[243] Review: N. Shimada, C. Stewart, M. A. Tius , *Tetrahedron*, **2011**, *67*, 5851-5870.
[244] L. N. Pridgen, K. Huang, S. Shilcrat, A. Tickner-Eldridge, C. DeBrosse, R. C. Haltiwanger, *Synlett*, **1999**, *10*, 1612–1614.
[245] G. Liang, S. N. Gradl, D. Trauner, *Org. Lett.*, **2003**, *5*, 4931–4934.
[246] V. K. Aggarwal, A. J. Belfield, *Org. Lett.,* **2003,** *5*, 5075-5078.
[247] G. Liang, D. Trauner, *J. Am. Chem. Soc.*, **2004**, *126*, 9544–9545.

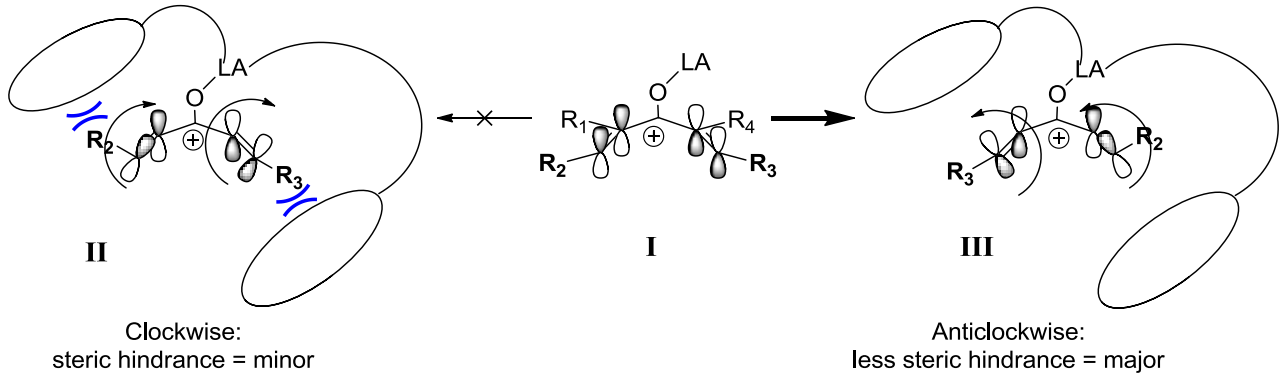
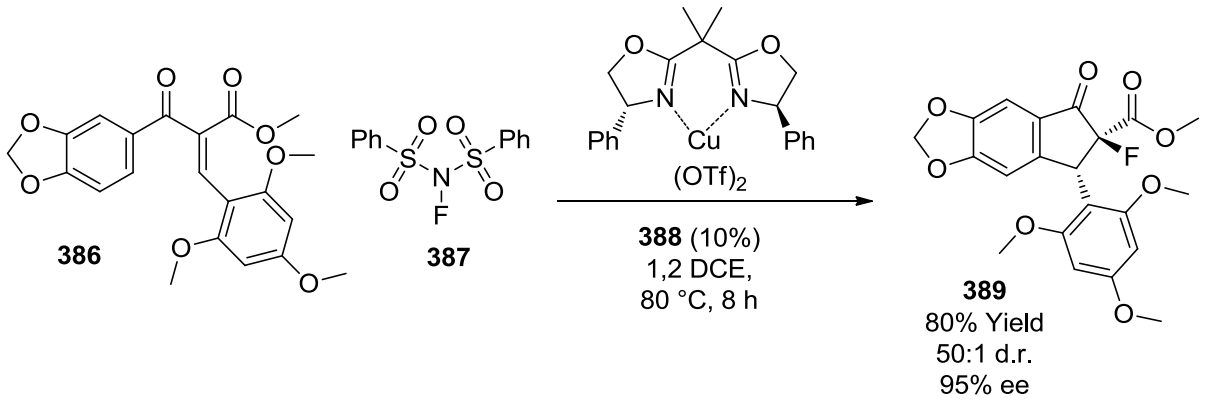


Figure 8.4: torquoselectivity problem in asymmetric Nazarov cyclization. In the example represented the steric hindrance of the chiral catalyst hampers clockwise Nazarov cyclization (left) and allows it occurring in anticlockwise direction (right) because in this case the substituents go far away from the bulky moiety.



Scheme **8.1**: tandem enantioselective Nazarov Cyclization/electrophilic fluorination on aryl vinyl ketones developed by Ma.

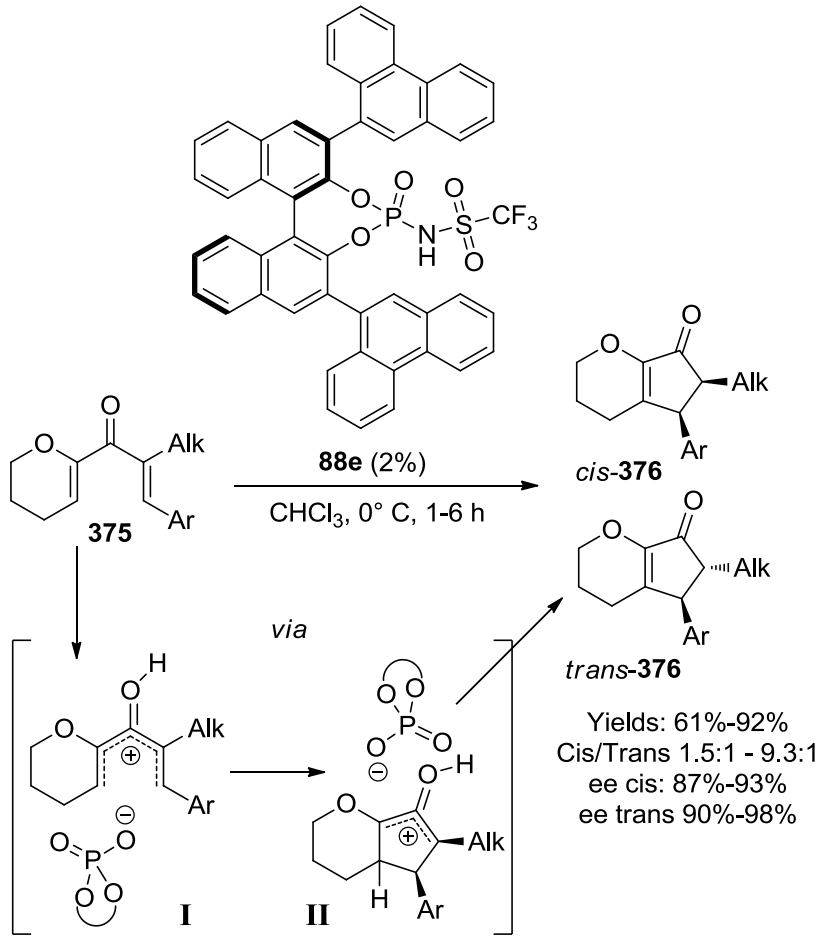
Anyway, later also more effective cyclization catalyzed by metal Cu-TOX, Cr-SALEN, or Ni-pigiphos complexes were developed[248], among which a remarkable tandem enantioselective Nazarov Cyclization/electrophilic fluorination on aryl vinyl ketones[249]. Anyway the reaction was developed in its racemic variant, and then only a few examples were reported to be enantioselective (scheme **8.1**). Importantly, the simple Nazarov Cyclization on these substrates was not reported.

[248] a) P. Cao, C. Deng, Y.-Y. Zhou, X.-L. Sun, J.-C. Zheng, Z. Xie, Y. Tang, *Angew. Chem. Int. Ed.*, **2010**, *49*, 4463–4466. b) G. E. Hutson, Y. E. Turkmen, V. H. Rawal, *J. Am. Chem. Soc.*, **2013**, *135*, 4988–4991. c) I. Walz, A. Togni, *Chem. Commun.*, **2008**, 4315-4317.

[249] J. Nie, H.-W. Zhu, H.-F. Cui, M.-Q. Hua, J.-A. Ma, *Org. Lett.*, **2007,** *9*, 3053-5056.

8.1.1) Nazarov cyclization and phosphoric acid triflimides

In 2007 Rueping and co-workers published the first of a series of papers about the enantioselective organocatalytic Nazarov Cyclization catalyzed by chiral Brønsted acids[250]. The strategy of polarization was adopted, and the mechanism involves carbonyl activation via protonation and formation of a chiral contact ion pair, with the chiral phosphate as a counteranion which creates the chiral environment for the reaction to occur (Scheme **8.2**). Also the deprotonation is catalyst-driven, creating diastereoselectivity and restoring the catalyst. Notably in this reaction only 2 mol%. of catalyst were employed to get the products in good yields and ee's in reasonable times. Despite this was only the first of several papers, the enantioselective Nazarov Cyclization on aryl vinyl ketones was never achieved[251].

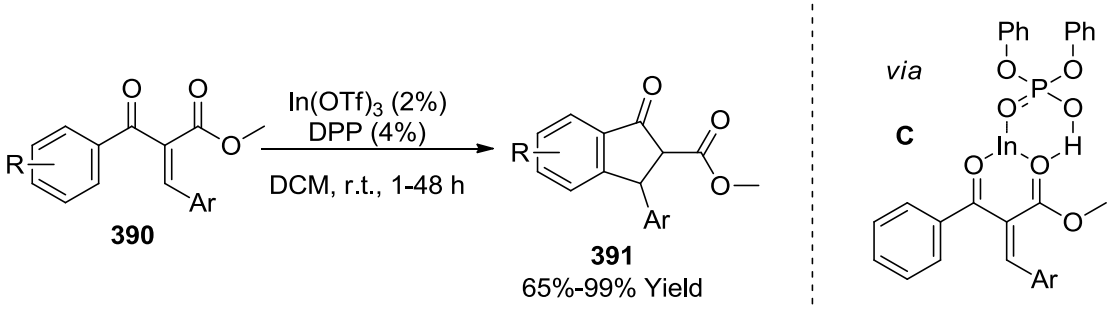


Scheme **8.2**: the first organocatalytic enantioselective Nazarov cyclization reported by Rueping and co-workers.

[250] M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2097–2100.

[251] a) M. Rueping, W. Ieawsuwan, *Adv. Synth. Catal.*, **2009**, *351*, 78–84. b) M. Rueping, W. Ieawsuwan, *Chem. Commun.*, **2011**, *47*, 11450–11452 c) S. Raja, W. Ieawsuwan, V. Korotkov, M. Rueping, *Chem. Asian J.*, **2012**, *7*, 2361–2366. d) A. Das, C. M. R. Volla, I. Atodiresei, W. Bettray, M. Rueping, *Angew. Chem. Int. Ed.*, **2013**, *52*, 8008–8011. Notably, phosphorodithioic acids are not effective in this transformation: e) G. Pousse, A. Devineau, V. Dalla, L. Humphreys, M.-C. Lasne, J. Rouden, J. Blanchet, *Tetrahedron*, **2009**, *65*, 10617-10622. There is only one example in literature of effective organocatalytic Nazarov cyclization which does not involve strong Brønsted acids as catalysts: f) A. K. Basak, N. Shimada, W. F. Bow, D. A. Vicic, M. A. Tius, *J. Am. Chem. Soc.*, **2010**, *132*, 8266-8267.

In 2013 Luo published a study about the Nazarov Cyclization on aryl vinyl ketones catalyzed by a binary acid catalytic system: a combination of $In(OTf)_3$ and DPP proved to be highly efficient in promoting this transformation[252]. It was shown that both the Lewis and the Brønsted acid were necessary to effectively catalyze the reaction: in fact using them separately the latter was not working or very slow. So this is a clear example of cooperative catalysis between a metal and an organic acid, and the authors proposed also a working model (scheme **8.3**). Since DPP is the common achiral surrogate of phosphoric acids, enantioselective catalysis using chiral BINOL based phosphoric acid was tried, but the authors declared that no enantiomeric excesses could be obtained.

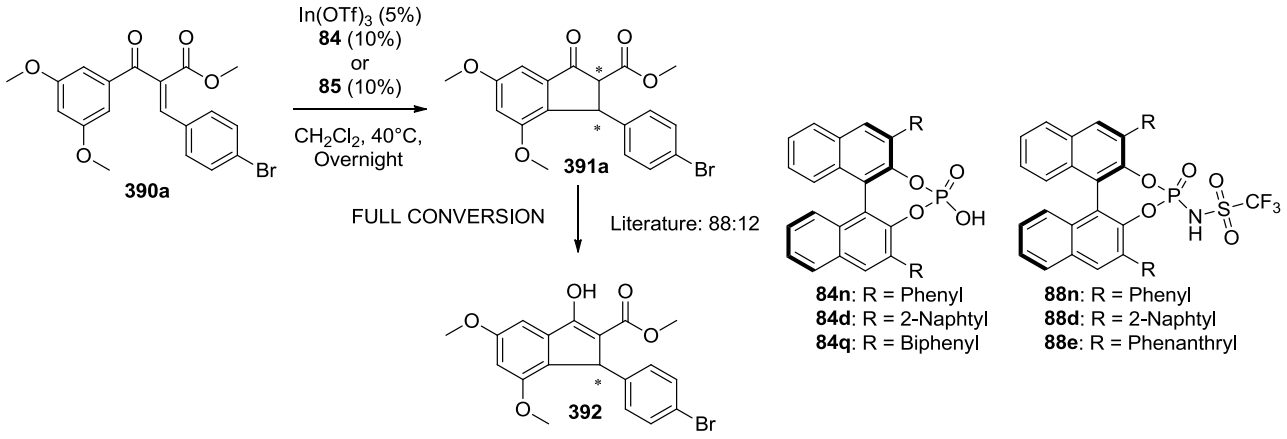


*Scheme **8.3***: The highly efficient Nazarov Cyclization on aryl vinyl ketones via binary acid strategy reported by Luo and co-workers.

[252] Z.-G. Xi, L. Zhu, S. Luo, J. P. Cheng, *J. Org. Chem.*, **2013**, *78*, 606–613.

8.2) The enantioselective Nazarov Cyclization on aryl vinyl ketones: In-catalysis

This reaction was already tried previously in the Rueping group using metal catalysis. The optimal conditions for a reaction were established, but then when the scope was tried fluctuating results were obtained, with ee's between 0% and 98%. For this reason, after Luo's paper appeared in literature we decided to try this approach, leaving the previous one. A first screening of a combination of $In(OTf)_3$ with some chiral phosphoric acid and triflimides was performed in dry CH_2Cl_2 at 40 °C overnight (scheme **8.4**).



Scheme **8.4**: Early work on enantioselective Nazarov Cyclization on aryl vinyl ketones.

Five of six reaction were complete overnight, only the chiral phosphoric acid with the phenyl substituent did not work. After purification we realized by ^{1}H NMR spectroscopy that the product was in equilibrium with its enolic form. A ratio of roughly 85:15 was present in all the samples, but for one of them the enol was even the major form (see *figure 8.5*). When these products were analyzed via HPLC two peaks were obtained, but one was extremely broad and in the various analyses had different retention times (*figure 8.6*). We had the suspect that this was due to the enolic form, and that this maybe could alter the HPLC result. The observation that just standing at r.t. for some days on the bench the product underwent partial decarboxylation suggested us that for a reliable analysis this could be exploited to our advantage. So studies for an effective decarboxylation protocol were begun. At the beginning HCl was found to be effective and the first decarboxylations were performed with this method (scheme **8.5**, above). Anyway the reaction was not clean and some small impurities could not be separated from the product; these ones in the in the HPLC gave peaks really near to the product's one. For this reason, later another decarboxylation protocol using DABCO was established (scheme **8.5**, below). Anyway, the ee was proved not to change with the two different decarboxylation protocols, so the results obtained with both were reliable.
After this preamble, some general considerations: firstly, the decarboxylation destroys one chiral center. Anyway the keto/enol tautomerization naturally destroyed this center, giving rise to the most thermodynamically stable *trans* isomer, which is the only one that could be detected in the ^{1}H NMR spectra. In the tables given below, the conversion determined via ^{1}H NMR spectroscopy on the crude Nazarov product is given as indicator of the reaction efficiency. The crude mixture was directly subjected to decarboxylation, and only the decarboxylation product was purified. Typical yields of decarboxylation are 75%-80%.

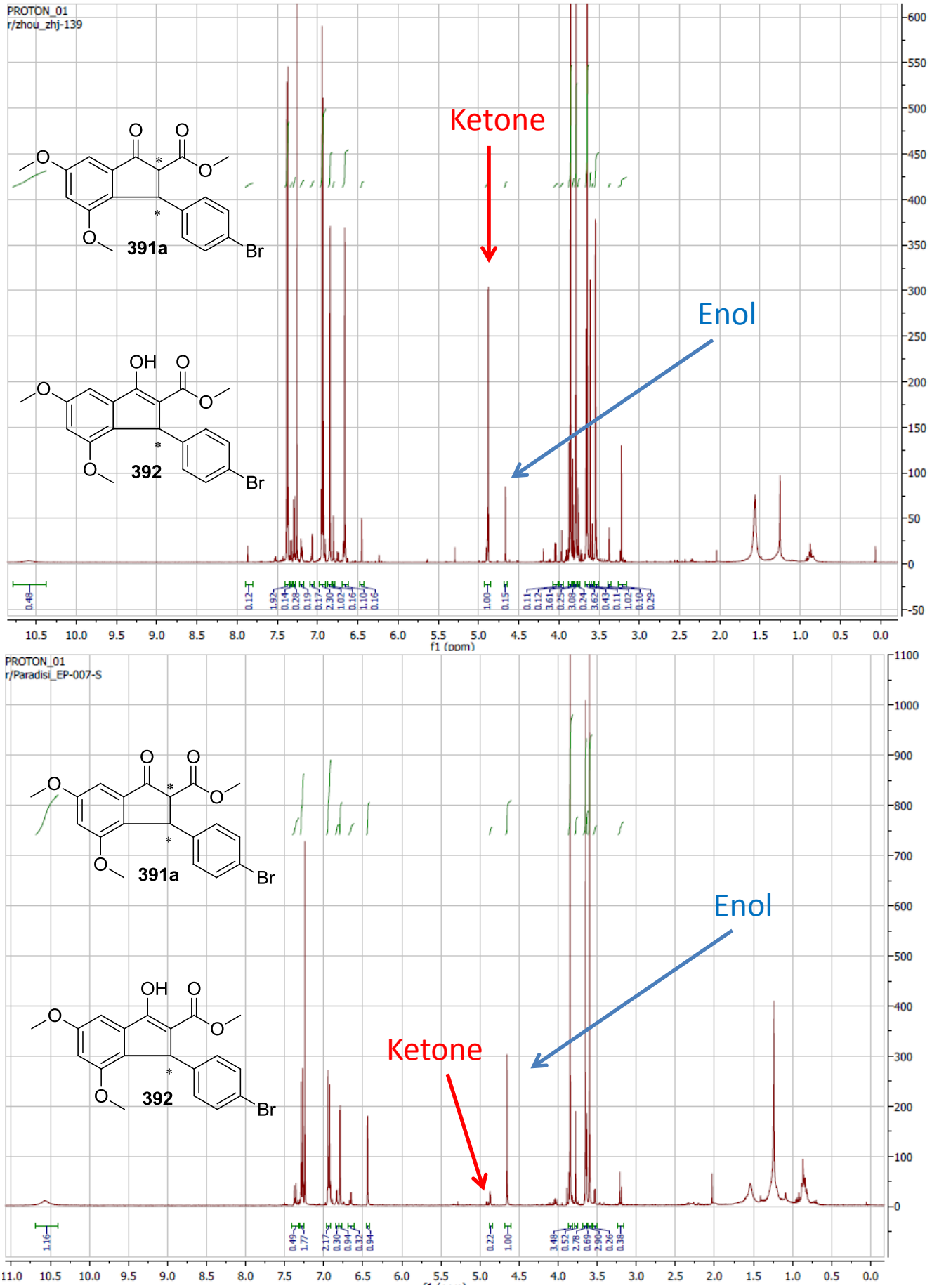
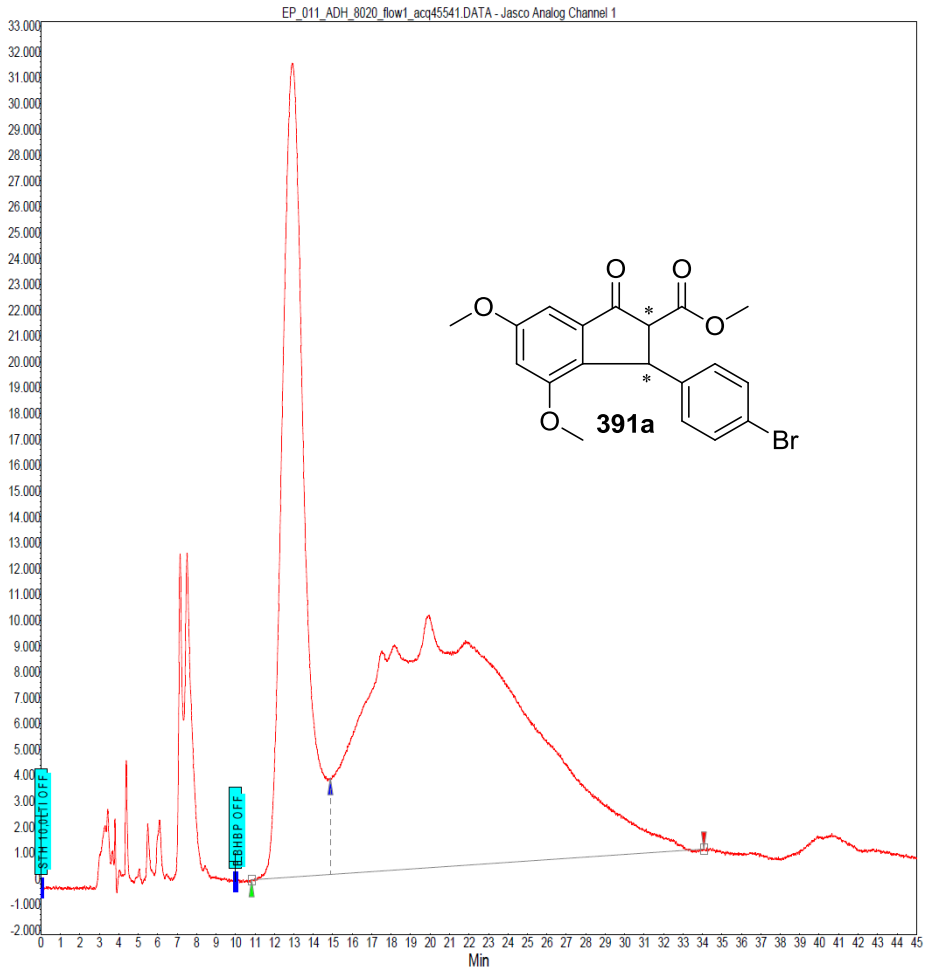


Figure 8.5: Two ^{1}H NMR spectra of reaction product showing its keto/enol tautomerization.

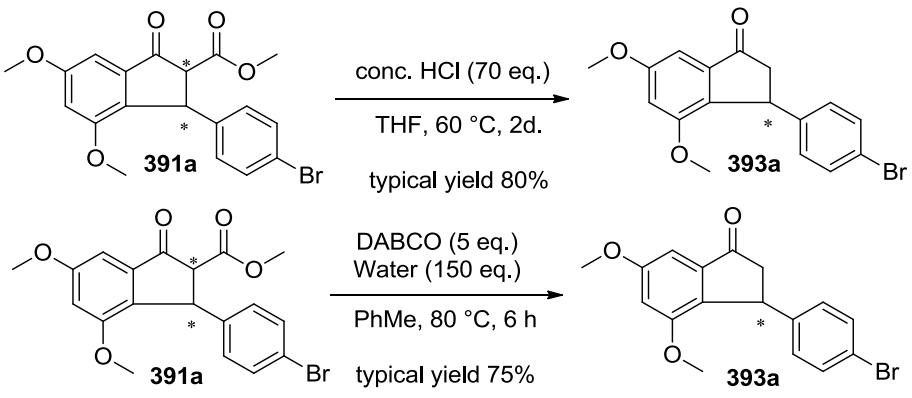
Chromatogram : EP_011_ADH_8020_flow1_acq45541

Data file: EP_011_ADH_8020_flow1_acq45541.DATA
Method: HPLC2_ADH_8020_flow1_acq45
Date: 18.02.2013 16:18:42



Index	Name	Start	Time	End	Ret. time Offset	Quantity	Height	Area	Area %
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10,832	12,917	14,876	0,000	31,16	31492,3	42130,9	31,159
2	UNKNOWN	14,876	19,925	34,075	0,000	68,84	9757,2	93080,2	68,841
Total						100,00	41249,4	135211,1	100,000

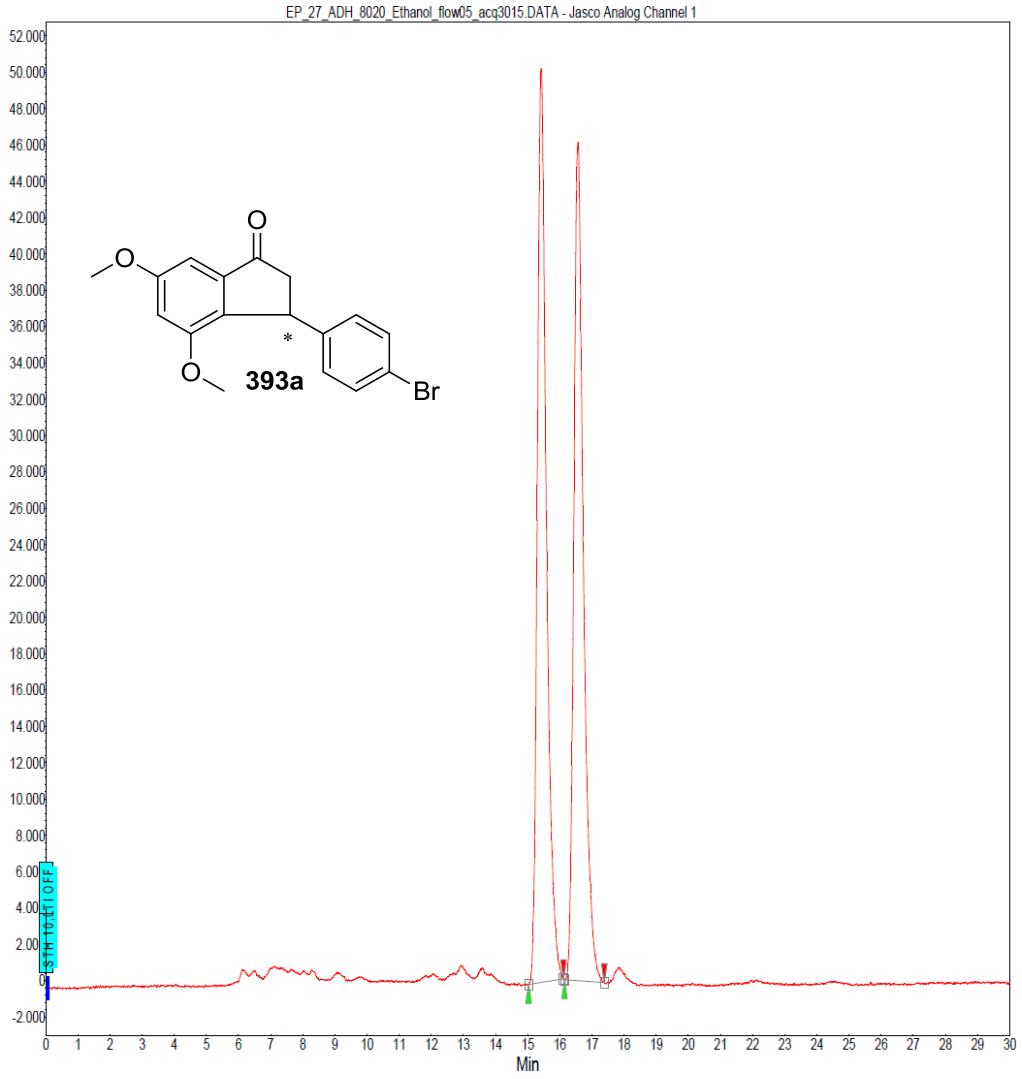
Figure 8.6: an HPLC spectrum of Nazarov cyclization reaction product clearly showing problems likely due to product showing keto/enol tautomerization.



Scheme **8.5**. The two decarboxylation protocols used, the first at the beginning of the work, the second later. The ee of the product proved to be the same, but in the second case the reaction was cleaner.

Chromatogram : EP_27_ADH_8020_Ethanol_flow05_acq3015

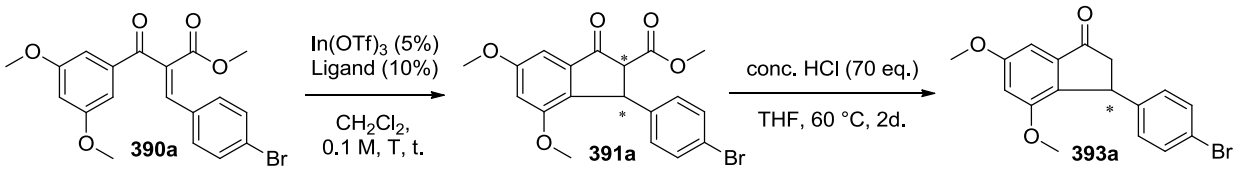
Data file: EP_27_ADH_8020_Ethanol_flow05_acq3015.DATA
Method: HPLC2_ADH_8020_Ethanol_flow05_acq30
Date: 09.03.2013 20:37:56



Index	Name	Start	Time	End	Ret. time Offset	Quantity	Height	Area	Area %
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15,031	15,417	16,116	0,000	50,72	50309,2	16573,9	50,715
2	UNKNOWN	16,147	16,567	17,386	0,000	49,28	46124,3	16106,6	49,285
Total						100,00	96433,5	32680,5	100,000

Figure 8.7: an HPLC spectrum of decarboxylation product clearly showing sharp and reliable peaks.

So, after having established the appropriate decarboxylation protocol, reliable HPLC analyses could be performed (*Fig. 8.7*). The results of the first screening revealed that the chiral phosphoric acid bearing a biphenyl substituent in 3 and 3' position, and the chiral triflimide bearing a phenanthryl substituent in 3 and 3' position were the best ligands in terms of enantioselectivity, giving each the opposite enantiomers of the product (*Table 8.1* entries **3,6**).



Entry	ligand	Ar	T °C	t	Conv. 1°step	ee (%)
1	**84n**	Phenyl	40	overnight	< 5%	-
2	**84d**	2-naphthyl	40	overnight	full	4
3	**84q**	Biphenyl	40	overnight	full	9
4	**88n**	Phenyl	40	overnight	full	rac
5	**88d**	2-naphthyl	40	overnight	full	2
6	**88e**	Phenanthryl	40	overnight	full	-14
7	**88e**	Phenanthryl	r.t.	38 h	full	-40
8	**84q**	Biphenyl	r.t.	48 h	full	44
9	**88q**	Biphenyl	r.t.	18 h	< 5%	-
10	**85q**	Biphenyl	r.t.	18 h	full	-9
11	**86q**	Biphenyl	r.t.	18 h	60%	-9
12	**84k**	3,5-bis-CF_3-Ph	r.t.	26 h	full	6
13	**84r**	1-naphthyl	r.t.	48 h	< 5%	-
14	**84q**	Biphenyl	0	5 days	< 5%	-
15	**84q** (15%)	Biphenyl	0	5 days	54%	22
16[a]	**84q** (15%)	Biphenyl	r.t.	overnight	0	-

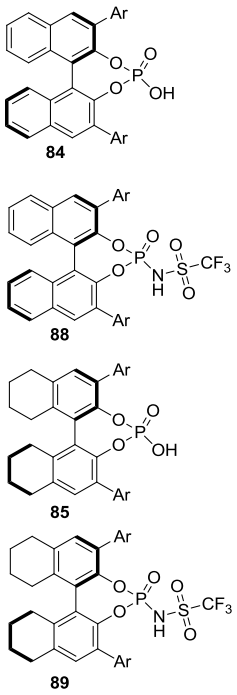
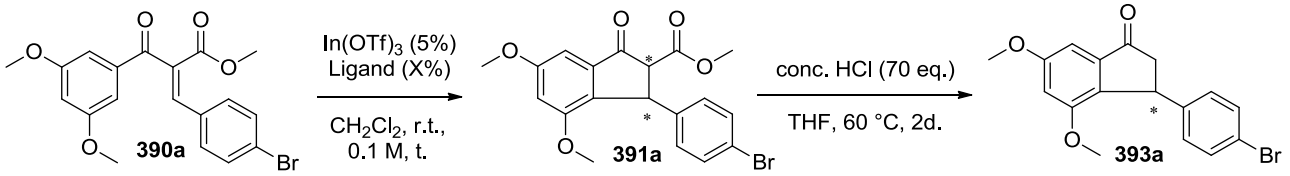


Table 8.1: first optimization for In-catalyzed Nazarov cyclization. *a*: activated 4Å MS were used as additive.

The ee could be increased performing the reaction at room temperature with these two ligands (*Tab. 8.1*, entries **7** and **8**), but no better results could be obtained at 0 °C (*Tab. 8.1*, entries **14-15**), with molecular sieves as additive (*Tab. 8.1*, entry **16**), or using other ligands, also based on octahydro BINOL scaffold (*Tab. 8.1*, entries **9-13**). For this reason these two ligands were chosen for further investigation about the optimal molar ratio between $In(OTf)_3$ and the ligand.



Entry	ligand	Ar	X	t	Conv. 1°step	ee (%)
1	**84q**	Biphenyl	5	22 h	full	54
2	**84q**	Biphenyl	10	48 h	full	44
3	**84q**	Biphenyl	15	22 h	full	68
4	**88e**	Phenanthryl	5	42 h	full	-52
5	**88e**	Phenanthryl	10	38 h	full	-40
6	**88e**	Phenanthryl	15	6 d	70%	-30

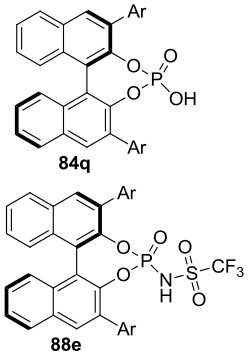
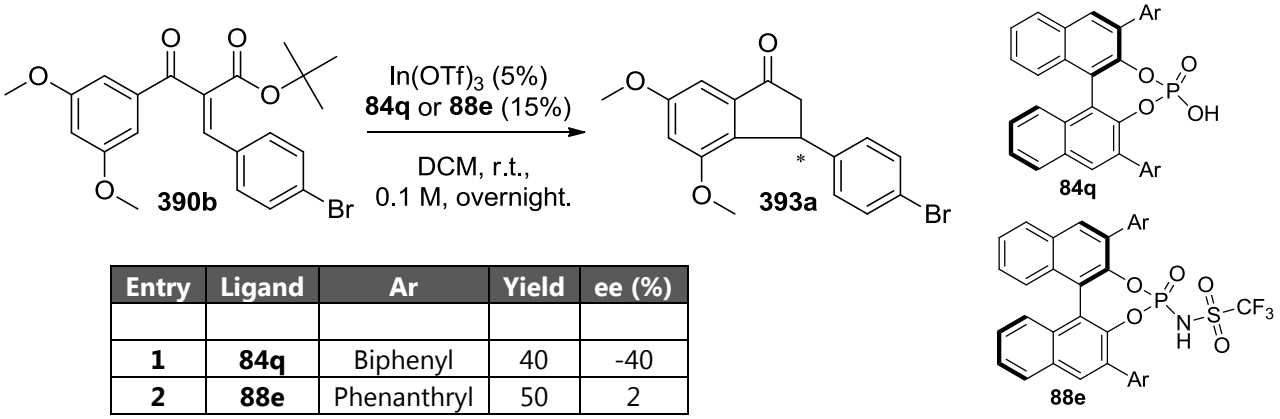


Table 8.2: optimization of the In/ligand ratio using ligands **84q** and **88e**.

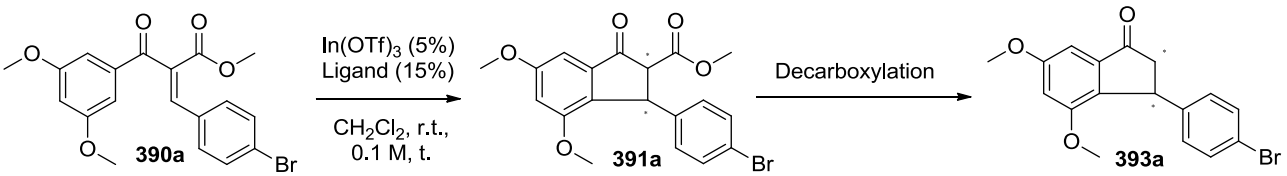
Different trends were obtained for the phosphoric acid and the triflimide, being 1:1 the optimal ratio between $In(OTf)_3$ and triflimide (*Tab. 8.2*, entry **4**), and 1:3 the optimal ratio between $In(OTf)_3$ and the chiral phosphoric acid. The latter combination gives the best enantiomeric excess among all (68%) (*Tab. 8.2*, entry **3**).
With ligands **84q** and **88e**, a starting material bearing O-tBu ester moiety **390b** was also tried: interestingly it gave directly the decarboxylated product in moderate yields and with the opposite absolute configuration, but ee's were not better that the ones provided using **390a** (*Table 8.3*).



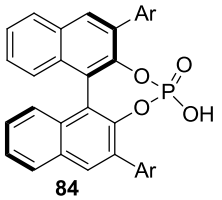
Entry	Ligand	Ar	Yield	ee (%)
1	**84q**	Biphenyl	40	-40
2	**88e**	Phenanthryl	50	2

Table 8.3: results obtained using the starting material bearing O-tBu ester.

With the optimal starting material and $In(OTf)_3$/ligand ratio in hand, other ligands, were screened for this In-catalyzed Nazarov cyclization, but no one gave better results compared to the biphenyl substituted one (*table 8.4*).



Entry	ligand	Ar	t	Conv. 1°step	ee (%)
1	**84d**	2-naphthyl	26 h	full	29
2	**84e**	Phenanthryl	overnight	0	-
3	**84i**	4-OMe-Ph	44 h	full	17
4	**84k**	3,5-bis-CF_3-Ph	26 h	full	6
5	**84o**	p-FPh	48 h	full	22
6	**84q**	biphenyl	22 h	full	68
7	**84r**	1-naphthyl	48 h	< 5%	-
8	**84s**	p-tBuPh	25 h	93 %	23
9	**85q**	biphenyl	overnight	0	-



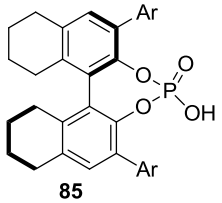
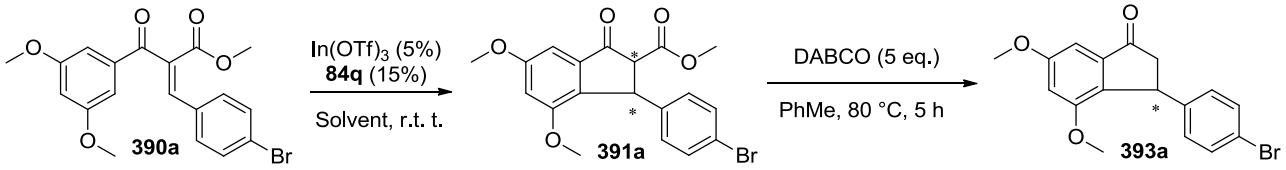


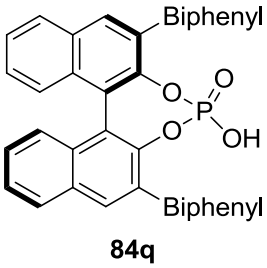
Table 8.4: more ligand's screening.

Since the ligand **84q** showed to be the best, solvent and concentration screening was performed using $In(OTf)_3$/**84q** as the catalyst combination. Some aromatic and chlorinated solvents were tried, and the best ones also at different concentration (*table 8.5*). No big difference in the enantiomeric excess was observed using different solvents at different

concentration, except when using DCM, which showed a value of 15% higher than all the other solvents (entry **1**).



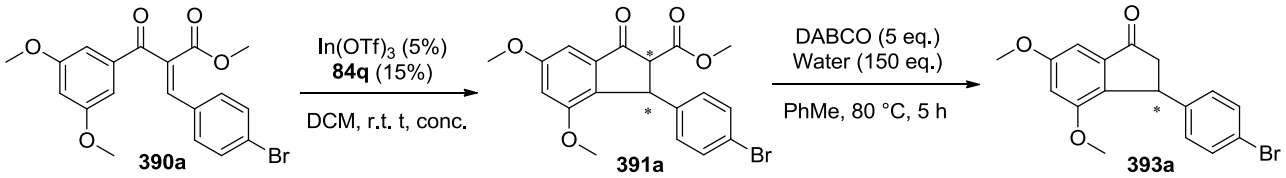
Entry	solvent	Time (h)	Conc.	Yield (%)	ee (%)
1	DCM	22	0.1 M	Full conv.	68
2	1,2-DCE	42	0.06 M	91	42
3	$CHCl_3$	20	0.06 M	87	53
4	$CHCl_3$	25	0.1 M	Full conv.	51
5	PhCl	64	0.06 M	57	54
6	PhMe	42	0.06 M	91	52
7	PhMe	25	0.1 M	Full conv.	45
8	o-Xylene	42	0.06 M	90	45



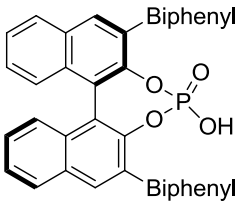
84q

Table 8.5: solvent screening.

Also more surpisingly, the concentration of the reaction apparently really matters, having 0.1 M. as the very best (*table 8.6*).



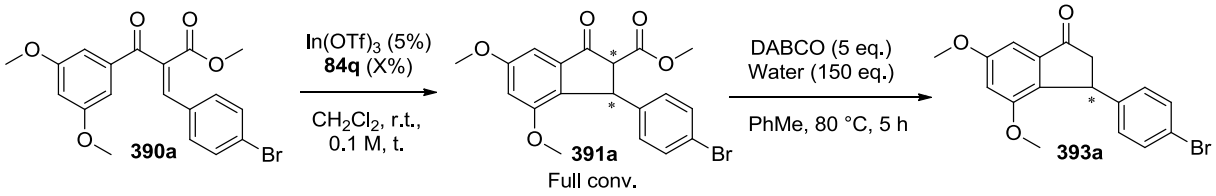
Entry	concentration	Time (h)	Yield (%)	ee (%)
1	0.05 M	18 h	85	24
2	0.1 M	22 h	Full conv.	68
3	0.2 M	18 h	85	40



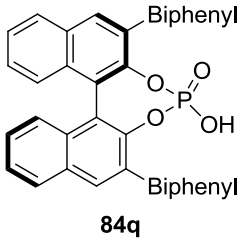
84q

Table 8.6: concentration screening.

These results seemed quite strange, because it seemed like there was one trial (*table 8.2* entry **3**) much better than the others. This led us to perform some reproducibility trials. Actually, repeating the best entry we had until that moment, gave only 33% of ee (*Table 8.7*, entry **3**, trial 2). After having distilled DCM again, we decided to repeat the In/ligand ratio screening, speculating about some mistakes did at that stage, but still we couldn't reproduce the result. (*Table 8.7*). In *Table 8.7* trial **3** an 1:3 ratio between the catalyst and the ligand is the worst. So, if this is the real result, we should have worked maybe in other conditions, as for example using ligand **88e** in ratio 1:1 with $In(OTf)_3$, (cfr. *Table 8.7* entry **3** trial 3 and *Table 8.2* entry **4**) or maybe in another solvent (cfr. *Table 8.7* entry **3** trial 3 and *Table 8.5*). so we realized that probably the real ee was lower that what we thought and we might have wasted a lot of time. This was very disappointing.



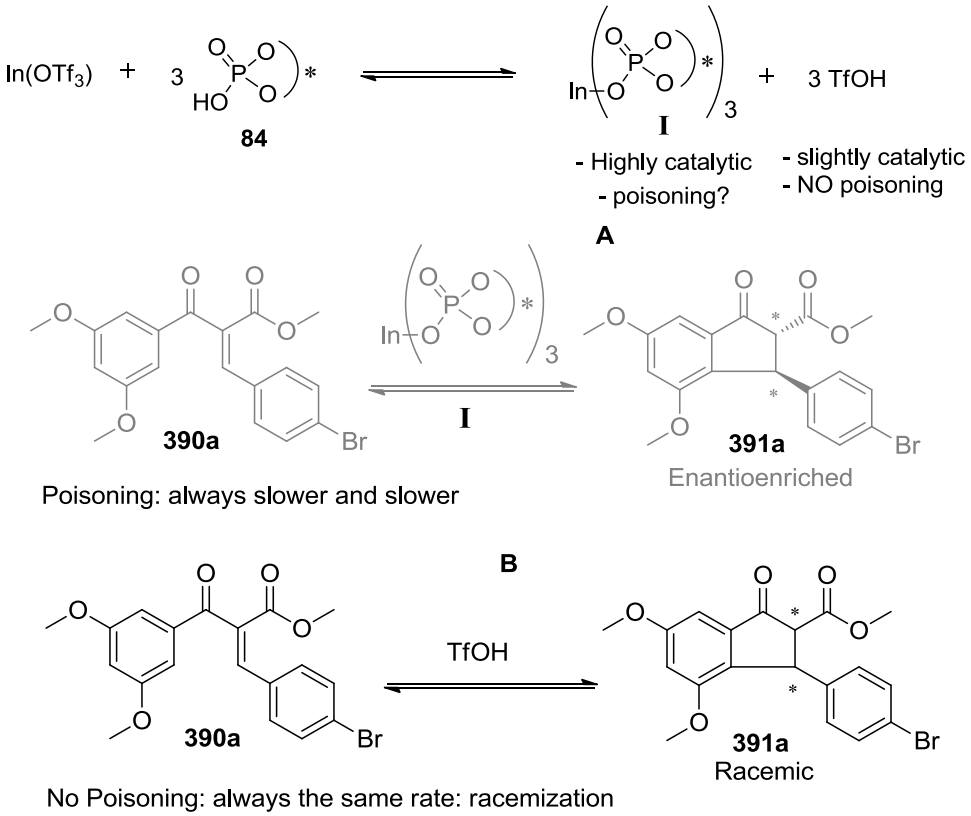
Entry	% 1a	Time Trial 1	ee (%) Trial 1	Time Trial 2	ee (%) Trial 2	Time Trial 3	ee (%) Trial 3
1	5	22 h	54	-	-	overnight	44
2	10	overnight	44	-	-	overnight	44
3	15	22 h	68	26 h	33	overnight	41



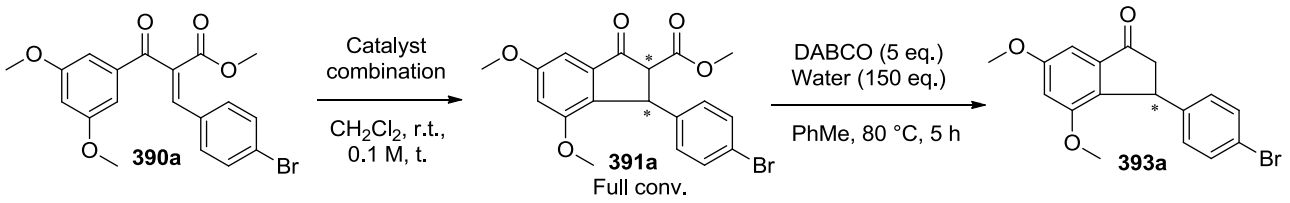
84q

Table 8.7: reproducibility trials varying the In/ligand ratio.

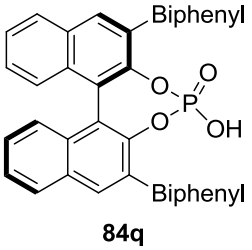
To try to explain the obtained results we envisioned the possibility of a TfOH catalyzed racemic reaction, which is parallel to the enantioselective process, but also can destroy the enantiomeric excess in case where the reaction is an equilibrium and poisoning of the catalytic complex occurs (scheme **8.6**). To this purpose we set up two experiments: in the first one the reaction was plugged as soon as it was finished; in the second the reaction mixture was stirred for two days more after completion. As you can see in table 8.8 actually there is a difference in ee, which may indicate that this racemization pathway is active, but this does not completely explain the lower ee observed respect to the best result obtained ever (*Tab. 8.2*, entry **3**: 68% of ee). Anyway in a control experiment (*Tab. 8.8* entry 4) catalysis by TfOH (leading to a racemic product) was confirmed.



Scheme **8.6**: hypothesis of poisoning of the catalytic complex and racemization via racemic retro-Nazarov/Nazarov cyclization pathway catalyzed by in situ formed TfOH.



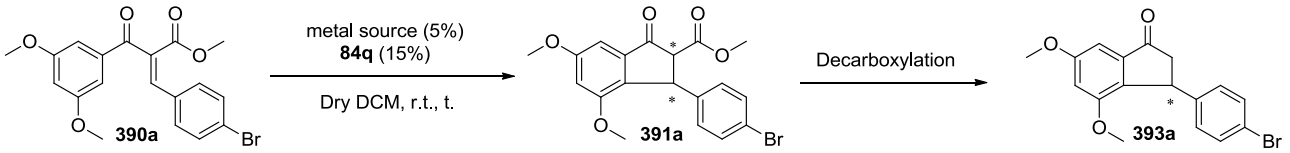
Entry	Catalyst combination	Time for full conversion	ee
1	$In(OTf)_3$ (5%) **84q** (15%)	12 h	40
2	$In(OTf)_3$ (5%) **84q** (15%)	12 h (stirred for 2 days)	30
3	$In(OTf)_3$ (5%) **84q** (15%) 2,6-lutidine (15%)	No reaction	
4	TfOH	overnight	-



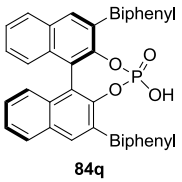
84q

Table 8.8: studies about possible poisoning and racemization pathways.

Since this reproducibility problem had emerged, maybe due to a poisoning of the catalyst, or to a parallel TfOH-catalyzed racemic reaction, other metal sources were investigated. The metal source screening revealed $Cu(OTf)_2$ as an interesting metal precursor: despite the long reaction time, the enantiomeric excess obtained was high (*Tab. 8.9*, entry **4**).



Entry	Metal source	time	Conc.	Conv.	ee %
1	$In(OTf)_3$	22 h	0.1 M	Full	68
2	$In(OTf)_3$	overnight	0.1 M	Full	41
3	$In(Br)_3$	Easter	0.06 M	96 %	29
4	$Cu(OTf)_2$ (10% of ligand)	7 d	0.06 M	60 %	85
5	$Sc(OTf)_3$	39 h	0.1 M	96 %	10
6	$Ca(NTf_2)_2$ (10% of ligand)	8 d	0.1 M	27 %	6



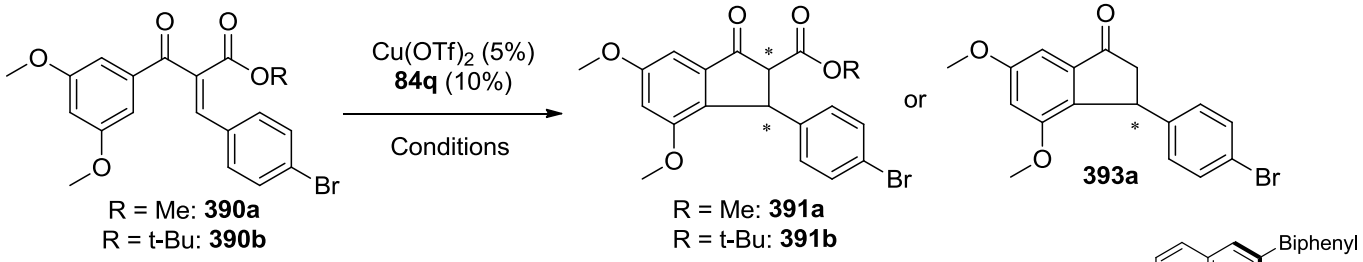
84q

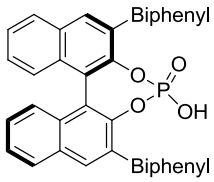
Table 8.9: evaluation of the metal source.

Considering all the problens had with Indium and this promising result in hand, we decided to stop with In-catalysis and focus our attention into Cu-catalysis.

8.2.1) Cu-catalyzed Nazarov cyclization

With the lacking of reproducibility of In-catalysis in mind, for Cu-catalysis reproducibility was firstly checked. In this case we were able to repeat the result for the enantiomeric excess, but a different reactivity was observed, probably due to evaporation of the solvent in entry **1** of table 8.9, which concentrated the solution (*Tab 8.10*, entries **1** and **2**).





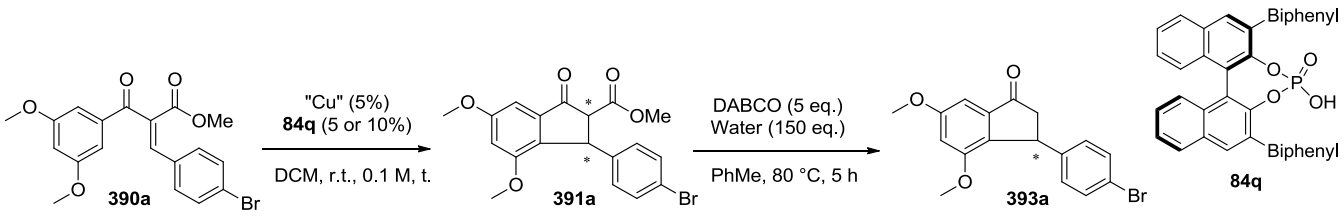
84q

Entry	R	Solvent	T (°C)	Conc. (M)	Time	Product	Conv. (%)	ee
1	**390a**	DCM	r.t.	0.06	7 d	**391a**	60	85
2	**390a**	DCM	r.t.	0.1	7 d	**391a**	31	88
3	**390a**	$CHCl_3$	50	0.2	3 d	**391a**	full	50
4	**390a**	$CHCl_3$	r.t.	0.05	7 d	-	0	-
5	**390a**	DCE	r.t.	0.05	7 d	**391a**	22	91
6	**390a**	$PhCF_3$	r.t.	0.05	7 d	**391a**	51	83
7	**390b**	$CHCl_3$	r.t.	0.05	7 d	**391b** + **393a** (3:1)	8	n.d.
8	**390b**	DCE	r.t.	0.05	7 d	**391b** + **393a** (3:2)	25	42
9	**390b**	$PhCF_3$	r.t.	0.05	7 d	**391b** + **393a** (1.3:1)	46	31

Table 8.10: Cu-catalyzed Nazarov cyclization. N.d. = not determined.

For a further investigation of the reaction, two starting materials and three solvents were tried. While **390b** gave poor selectivity (*Table 9.10*, entries **7-9**), **390a** gave generally good ee's, with the best result when working in 1,2 DCE (91%, *Table 9.10*, entry **5**).
Anyway, reaction time is very long and conversion is very low in all cases.

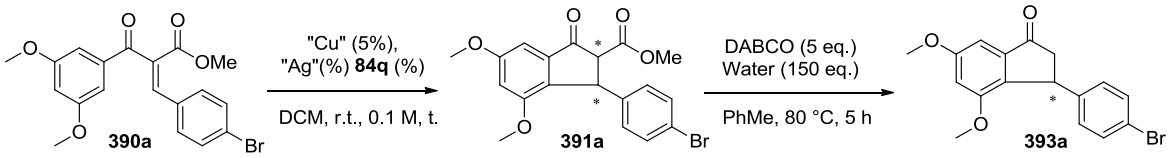
We evaluated DCM as the solvent with the best compromise between reactivity and enantioselectivity, and decided further screening of copper sources for this transformation (*table 8.11*).
Initially, $(CuOTf)_2 \cdot PhH$ seemed to be faster than $Cu(OTf)_2$ (*table 8.11*, entry **4**), but trying to repeat the reaction didn't give the same result, also when 6 or 10 mol% of ligand were used (*table 8.11*, entry **5-7**). Anyway a screening of Cu(I) and Cu(II) salts was performed, but no other one showed reactivity. To the reactions using copper chlorides, two different additives containing silver were added. While addition of Ag_2CO_3 to $CuCl_2$ and the ligand didn't lead to any reactivity (*table 8.11*, entry **15**), upon addition of $AgSbF_6$ to the reaction mixture containing CuCl and the ligand the color turned bright yellow, and then the reaction proceeded smoothly with a promising ee (*table 8.11*, entry **14**).



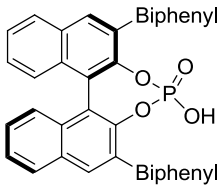
Entry	"Cu"	% A	Additive	time	Conv. (%)	ee (%)
1	$Cu(OTf)_2$ (0.06 M)	10	-	7 d	60	85
2	$Cu(OTf)_2$	10	-	7 d	31	88
3	$Cu(OTf)_2$	10	2,6-lutidine (10 % + 10 %)	2 d	0	-
4	$(CuOTf)_2$·PhH (2.5 %)	5	-	3 d	57	84
5	$(CuOTf)_2$·PhH (2.5 %)	5	-	10 d	33	n.d.
6	$(CuOTf)_2$·PhH (2.5 %)	6	-	7 d	53	83
7	$(CuOTf)_2$·PhH (2.5 %)	10	-	7 d	35	84
8	$Cu(MeCN)_4PF_6$	5	-	3 d	0	-
9	$Cu(MeCN)_4PF_6$	10	-	overnight	0	-
10	$Cu(acac)_2$	10	-	overnight	0	-
11	CuBr·SMe_2	5	-	overnight	0	-
12	CuOAc	5	-	overnight	0	-
13	$CuOAc_2$	10	-	overnight	0	-
14	CuCl	5	$AgSbF_6$ (5 %) added after 3 days	No reaction/ overnight	full	48
15	$CuCl_2$	10	Ag_2CO_3 (10%) added after 3 days	3 + 1 d	0	-

Table 8.11: screening of Cu salts, various conditions and discovery of Cu-Ag cooperative catalysis.

Interested by this huge reactivity improvement, we tried to find better conditions for this Cu/Ag catalysis. Repeating the reaction adding $AgSbF_6$ since the beginning lead to a slight improvement of ee, while using $CuCl_2$ as the copper salt, an higher amount of ligand or a lower amount of $AgSbF_6$ didn't (*table 8.13*, entries **2-5**).



Entry	"Cu"	% A	"Ag"	time	Conv. (%)	ee (%)
1	CuCl	5	$AgSbF_6$ (5 %) added after 3 days	No reaction/ overnight	full	48
2	CuCl	5	$AgSbF_6$ (5 %)	3 h	full	59
3	CuCl	10	$AgSbF_6$ (5 %)	5.5 h	97	52
4	CuCl	5	$AgSbF_6$ (2.5 %)	22 h	95	4
5	$CuCl_2$	10	$AgSbF_6$ (10 %)	overnight	full	20
6	-	-	$AgSbF_6$ (5 %)	3 h	50 (then blocked)	-
7	-	5	$AgSbF_6$ (5 %)	22 h	89	1
8	-	5	$AgSbF_6$ (5 %)	5.5 h	89	1
9	-	5	AgOTf (5 %)	7 d	38	20
10	-	-	AgTRIP (5%)	2 d	0	-
11	CuCl	5	AgOTf (5 %)	4 d	< 5	n.d.
12	CuCl	5	$AgNTf_2$ (5 %)	11 h	88	4
13	CuCl	5	$AgBF_4$ (5 %)	8 h	< 5	n.d.
14	CuCl	5	$AgPF_6$ (5 %)	8 h	< 5	n.d.
15	CuCl	5	NaBArF (5 %)	8 h	< 5	n.d.
16	CuBr	5	$AgBF_4$ (5 %)	6 h	95	2
17	$CuBr{\cdot}SMe_2$	5	$AgBF_4$ (5 %)	6 h	full	0
18	CuI	5	$AgBF_4$ (5 %)	6 h	97	0

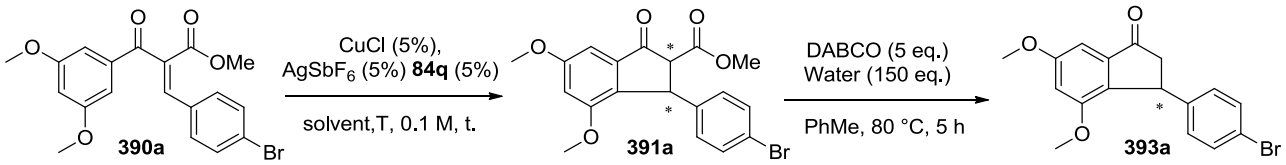


84q

Table 8.13: optimization of Cu-Ag catalysis.

It has to be noted that $AgSbF_6$ itself was confirmed to be an active racemic catalyst, even if the reaction was blocked at 50% conv. (*table 8.13*, entry **6**). The reaction is complete in a short time using $AgSbF_6$ in combination with the chiral ligand, but it's still racemic while using AgOTf a low reactivity and selectivity was observed (*table 8.13*, entries **7-9**).
Further screening of other silver salts (and NaBArF) in combination with CuCl or other copper salts in combination with $AgSbF_6$ gave no reactivity or no selectivity (*table 8.13*, entries **11-18**).
So, CuCl (5%), $AgSbF_6$ (5%) and ligand **84q** (5%) showed to be the best catalyst combination and a small solvent screening was performed (*table 8.14*). 1,2 DCE showed to be a good solvent in terms of reactivity, but surprisingly a racemic mixture was obtained. Aromatic solvents showed slower reactivity and selectivity, as well as the reaction at 0 °C (*table 8.14* entry **4**). As observed also for In-catalysis, 4Å molecular sieves seem to suppress the reaction (*table 8.14* entry **5**).

These poor results during optimization, considered also all the previous work, in the end led us to stop completely this project of the Nazarov cyclization of electron rich arenes, even if with Cu catalysis we never tried to change the ligand.



Entry	Solvent	T	additive	time	Conv.	ee
1	1,2 DCE	r.t.	-	4 h	full	0
2	Toluene	r.t.	-	3 d	65	2
3	Chlorobenzene	r.t.	-	3 d	75	7
4	DCM	r.t.	4 Å MS	3 d	0	-
5	DCM	0°C	-	3 d	63	21

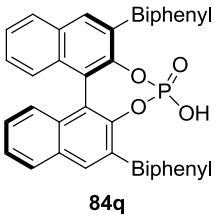


Table 8.14: brief solvent, temperature and additive screening

8.2.2) Miscellaneous

During the work on enantioselective Nazarov cyclization of electron rich arenes, also iminium ion catalysis and brønsted acid catalysis were tried, each one with no results.

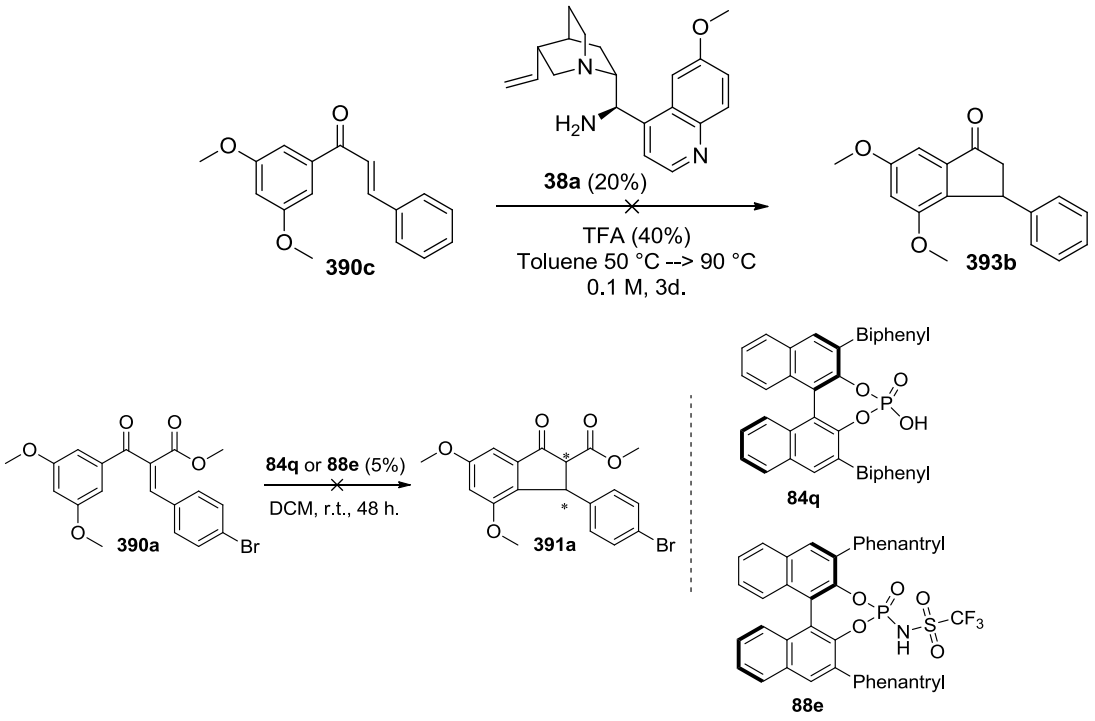


Figure 9.9: failed organocatalytic trials on enantioselective Nazarov cyclization of electron rich arenes.

8.3) EXPERIMENTAL SECTION

General

All commercially available compounds were used as provided without further purification. Solvents were technical grade and distilled prior to use. All the solvents used in catalysis reactions were dried as recommended[253]. 4Å molecular sieves were purchased from Sigma-Aldrich as 3.2 mm size pellets and grinded before use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualised by irradiation with UV light and developed with $KMnO_4$. Flash column chromatography was performed using silica gel (Macherey Nagel, particle size 0.040-0.063 mm) according to the method of Still[254]. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Solvent mixtures are understood as volume/volume. ^{1}H-NMR and ^{13}C-NMR were recorded on Varian Gemini 300 MHz, Inova 400 MHz or 600 MHz spectrometers in $CDCl_3$ and are reported relative to the solvents residual 1H-signal ($CHCl_3$, δ(H) 7.26). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet); coupling constants (*J*) are in Hertz (Hz). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. CHIRALCEL OJ-H; eluent: *n*-hexane/2-propanol. The chiral HPLC methods were calibrated with the corresponding racemic mixtures.

General procedure for the In-catalyzed Nazarov cyclization and Cu-catalyzed Nazarov cyclization:

In a schlenck flask containing a stir bar was placed the phosphoric acid or triflimide ligand (0.0050 or 0.0075 mmol, 10 or 15%), then the schlenck was introduced into the glovebox and $In(OTf)_3$ or $Cu(OTf)_2$ (0.0025 mmol, 5%) was added. The schlenck was covered with a septum, removed from the glovebox, 0.2 ml of dry DCM were added via syringe, and the solution was stirred for 0.5 - 1 h. Then the starting material (0.05 mmol) was dissolved in 0.3 ml of dry DCM and this solution was transferred to the schlenck via syringe under argon and the so-obtained yellow reaction mixture was stirred for the required time at r.t.. After this, the reaction mixture was plugged on a short pad of silica and directly subjected to decarboxylation.

General procedure for the Cu-Ag catalyzed Nazarov cyclization:

In a schlenck flask containing a stir bar was placed the phosphoric acid ligand (0.0050 mmol, 10%) then the schlenck was introduced into the glovebox and $Cu(OTf)_2$ (0.0025 mmol, 5%) and $AgSbF_6$ (0.0025 mmol, 5%) were added. The schlenck was covered with a septum, removed from the glovebox, 0.2 ml of dry DCM were added via syringe, and the solution was stirred in the absence of light for 0.5 h. Then the starting material (0.05 mmol) was dissolved in 0.3 ml of dry DCM and this solution was transferred to the schlenck via syringe under argon to the catalyst solution and the so-obtained bright yellow reaction mixture was stirred for the required time at r.t. in the absence of light. After this, the reaction mixture was plugged on a short pad of silica and directly subjected to decarboxylation.
All the reactions with other dry solvents or metal precursors were performed with similar procedures.

[253] W. L. F.Armarego, D.D.Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
[254] W.C.Still, M.Kahn, A.J.Mitra, *J.Org.Chem.* **1978**, *43*, 2923.

General procedure for the HCl promoted decarboxylation of Nazarov cyclization products.

The crude Nazarov cyclization product (0.05 mmol) placed in a pressure cap vial was dissolved in THF (0.5 ml) and 50 equiv. of conc HCl were added. Then the vial was capped and this mixture was warmed to 60°C overnight. The mixture was cooled, transferred in a separatory funnel and quenched with sat. aq. $NaHCO_3$. The mixture was extracted with DCM twice, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (eluent Hex/EtOAc 10:1 or 94:6 if still the starting material of the Nazarov cyclization was present) to give the title compound as a white solid (typical yield: 80%).

General procedure for the DABCO promoted decarboxylation of Nazarov cyclization products.

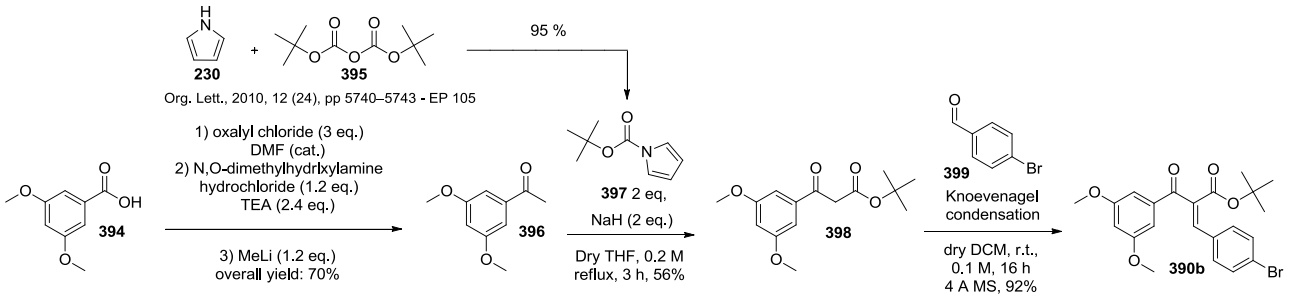
The crude Nazarov cyclization product (0.05 mmol) was placed in a pressure cap vial, DABCO (0.25 mmol, 5 eq.) was added an then everithing was dissolved in toluene (1 ml). Water (135 μl, 150 eq.) was then added, the vial was capped and this mixture was heated at 80°C for 6 h. Then it was cooled, transferred in a separatory funnel and quenched with 1 M HCl. The mixture was extracted with DCM twice, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (eluent Hex/EtOAc 10:1 or 94:6 if still the starting material of the Nazarov cyclization was present) to give the title compound as a white solid (typical yield: 75%).
This second protocol gave cleaner ^{1}HNMR and chiral HPLC spectra and in the end for this reason was preferred to the other.

Materials.

For the synthesis of chiral phosphoric acid catalysts please see ref. 112-126 and 192.
For the synthesis of **38a** please see ref 83 and 163.
For the synthesis of **390a** please see ref. 251.
For the synthesis of **390b** see the scheme below.
For the synthesis of **390c** a literature procedure was followed[255].

Preparation of 390b

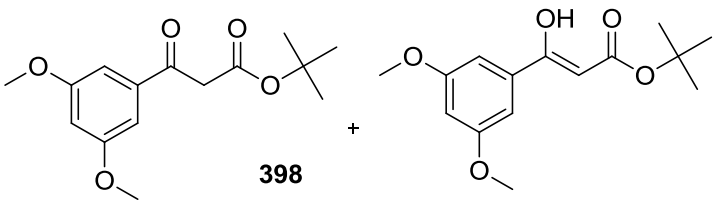
t-Butyl 1*H*-pyrrole-1-carboxylate was prepared according to the literature procedure given in the scheme below. For the rest of the synthesis was followed the general procedure used in ref 252.



[255] V. Kumar, S. Kumar, M. Hassan, H. Wu, R. K. Thimmulappa, A. Kumar, S. K. Sharma, V. S. Parmar, S. Biswal, S. V. Malhotra, *J. Med. Chem.*, **2011**, *54*, 4147–4159.

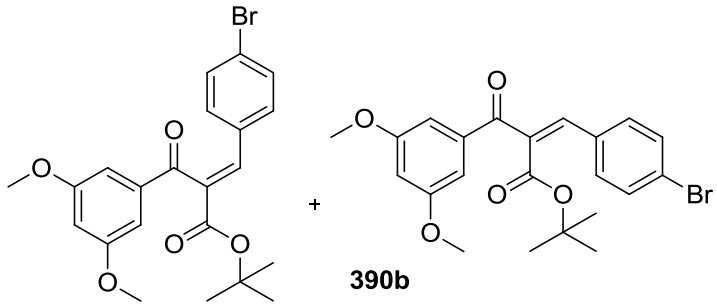
Characterization of new compounds.

This compound was obtained as a mixture ketone/enol 5:1



ketone:

^{1}HNMR: (400 MHz, $CDCl_3$) δ = 1.42 (s, 9H), 3.79 (s, 6H), 3.83 (s, 2H), 6.63 (t, J = 2.4 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 2H). **^{13}CNMR**: (400 MHz, $CDCl_3$) δ =27.8 (CH_3), 42.4 (CH_2), 55.5 (CH_3), 81.2 (C), 105.8 (CH), 106.1 (CH), 138.0 (C), 160.8 (C), 166.6 (C), 192.6 (C). enol: **^{1}HNMR**: (400 MHz, $CDCl_3$) δ = 1.51 (s, 9H), 3.78 (s, 6H), 5.52 (s, 1H), 6.51 (t, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 12.66 (s, 1H). **^{13}CNMR**: (400 MHz, $CDCl_3$) δ = 28.3 (CH_3), 55.3 (CH_3), 81.2 (C), 89.2 (CH), 103.4 (CH), 103.8 (CH), 135.7 (C), 160.7 (C), 170.6 (C), 173.0 (C).

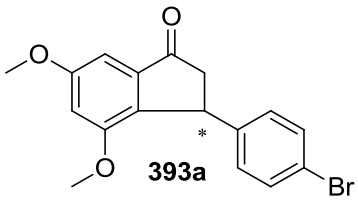


This compound was obtained as a mixture Z/E 3:1.

Z: **^{1}HNMR**: (400 MHz, $CDCl_3$) δ = 1.37 (s, 9H), 3.77 (s, 6H), 6.64 (t, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 2H) 7.20 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 2H), 7.36 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 2H), 7.73 (s, 1H). **^{13}CNMR**: (400 MHz, $CDCl_3$) δ = 22.8 (CH_3), 55.5 (CH_3), 82.4 (C), 106.2 (CH), 106.5 (CH), 124.6 (C) 131.4 (CH), 131.9 (C) 132.0 (CH), 133.7 (C), 138.2 (C), 140.2 (CH), 161.0 (C), 163.6 (C), 195.0 (C).

E: **^{1}HNMR**: (400 MHz, $CDCl_3$) δ = 1.40 (s, 9H), 3.79 (s, 6H), 6.63 (t, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 2H), 7.28 (s, 1H), 7.39 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 2H), 7.50 (dt, J_1 = 8.4 Hz, J_2 = 2 Hz, 2H).

^{13}CNMR: (400 MHz, $CDCl_3$) δ = 27.7 (CH_3), 55.5 (CH_3), 83.0 (C), 105.0 (CH), 106.6 (CH), 124.8 (C), 131.2 (CH), 131.7 (CH), 132.3 (C), 135.7 (C), 139.2 (C), 141.5 (CH), 160.7 (C), 165.7 (C), 192.9 (C).



data for NMR spectra of this compound were unfortunately lost.

Chiral HPLC analysis: Daicel Chiralpak AD-H; flow rate 0.5 ml/min., Hex/EtOH 80:20, λ = 230 nm, r.t., τ_{minor} = 16.7 min, τ_{major} = 15.5 min.

All the other compounds were not fully characterized.

9) Desymmetrization of meso compounds

9.1) introduction

A meso compound is a stereoisomerically pure compound possessing stereocenters, but superimposable with its mirror image due to the presence in its structure of a C_2 symmetry plane. For this reason the title compound results achiral and optically inactive. This C_2 symmetry plane passes in the middle of the molecule[256], dividing it in two parts, each one superimposable with the other. The molecule's symmetry destroys chirality. Typically, meso compounds have parent chiral molecules. For example, in *figure 9.1* the compound hydrobenzoin can exist in two diastereoisomers. The *trans* is chiral, having two enantiomers, the *cis*, instead, is a meso compound because it's superimposable with its mirror image.

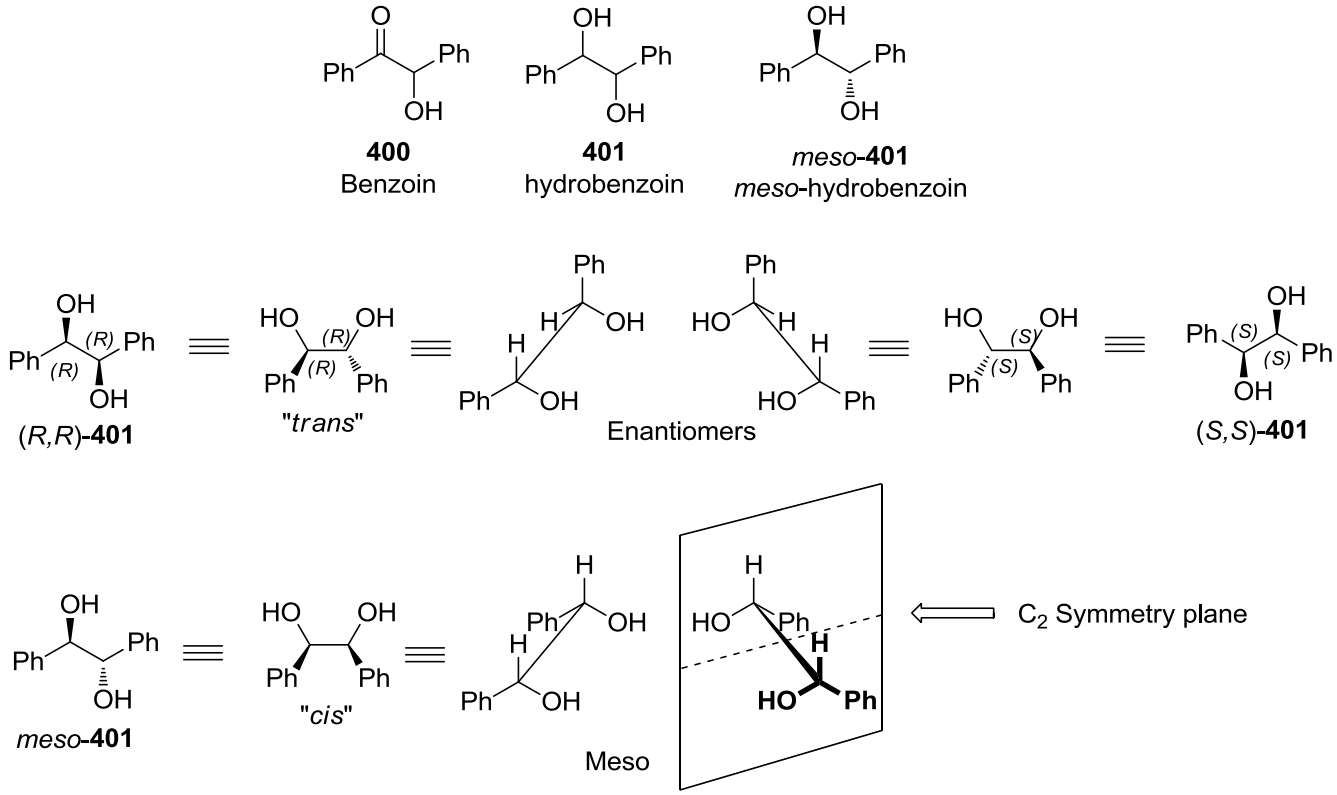


Figure 9.1: hydrobenzoin as representative compound possessing a diastereoisomer with two optically active enantiomers and an achiral meso form.

[256] Here's the origin of the name meso: from the greek *mesos*, meaning "middle, located in the middle".

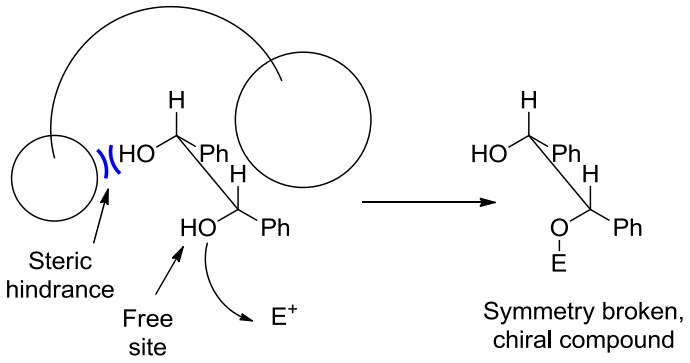


Figure 9.2: schematic representation of an asymmetric chiral catalyst breaking symmetry of a meso compound, allowing discrimination of the two enantiotopic functional groups.

Enantioselective functionalization of meso compounds is sometimes compared kinetic resolution, but actually is really different: the relative stereochemistry of a meso compound is fixed and the enantioselectivity achieved is a problem of sitoselectivity of one of the two enantiotopic functional groups by symmetry breaking (*figure 9.2*). Moreover, enantioselective desymmetrization is more convenient, since the theoric yield could be 100%.

Due to their importance in organic synthesis, methods for the preparation of enantioenriched chiral diols always had much attention in research. We saw in section 3.2 that enantioselective Osmium-catalyzed dihydroxylation of alkenes is considered an important reaction and partly determined the 2001 Nobel prize for Sharpless. Regarding organocatalytic enantioselective desymmetrization of chiral diols, many methods have been applied and many catalysts[257]. By the way, the vast majority of the currently available desymmetrization methods are based on activation of an electrophile by a chiral nucleophilic catalyst, to give a chiral, positively charged intermediate. The diol then attacks this intermediate in an enantioselective fashion and so the chiral desymmetrized product is released, together with the restored catalyst (*figure 9.3, **A***). Many tertiary amines like 4-dimethylaminopyridine derivatives **404**, N-alkyl-proline derivatives **405**, N-alkyl-imidazole derivatives **410** and cinchona alkaloid derivatives **408** were used. Other nucleophilic catalysts for diols desymmetrization are phosphines **405** and aminophosphines **411**, and some examples of oxidative diol desymmetrization using NHC's were reported (*figure 9.3,* **B**). One of the most used class of catalysts are isothioureas **409**. Most of the reactions are acyl transfer reactions, to give acetyl or benzoyl esters, namely alcohol protecting groups.

[257] Review: M. D. Dìaz-de-Villegas, J. A. Gàlvez, R. Badorrey, M. P. Lòpez-Ram-de-Vìu, *Chem. Eur. J.*, **2012**, *18*, 13920–13935.

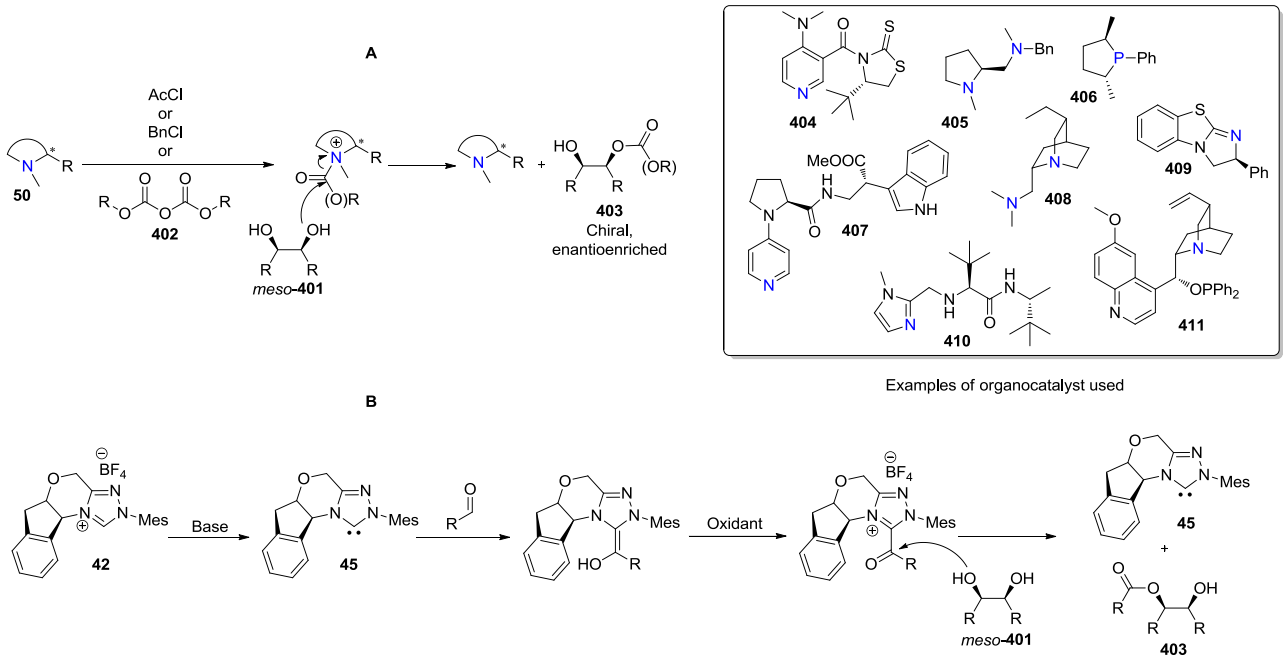
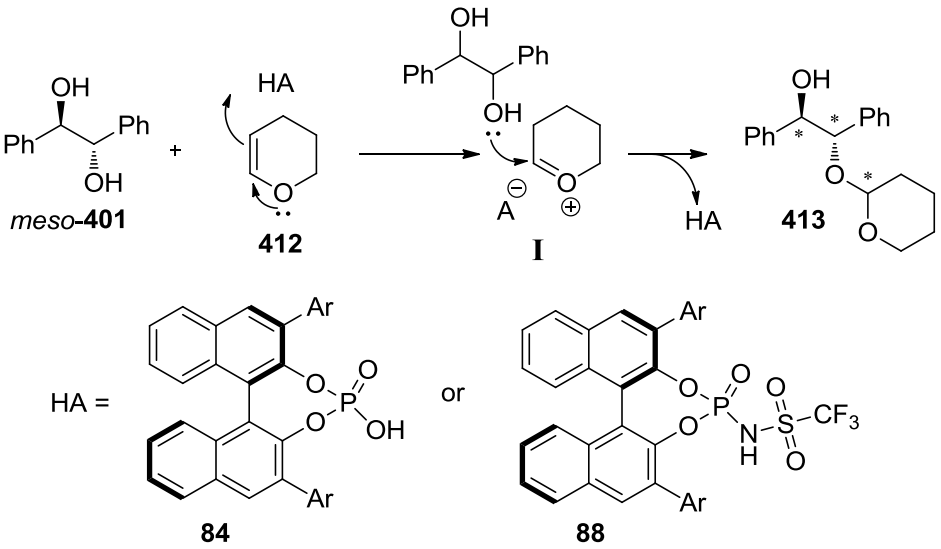


Figure 9.3: common activation modes in desymmetrization of meso diols. **A**: acyl transfer via chiral acyl ammonium intermediates. **B**: in situ formation of acyl intermediates via oxidation of Breslow intermediates.

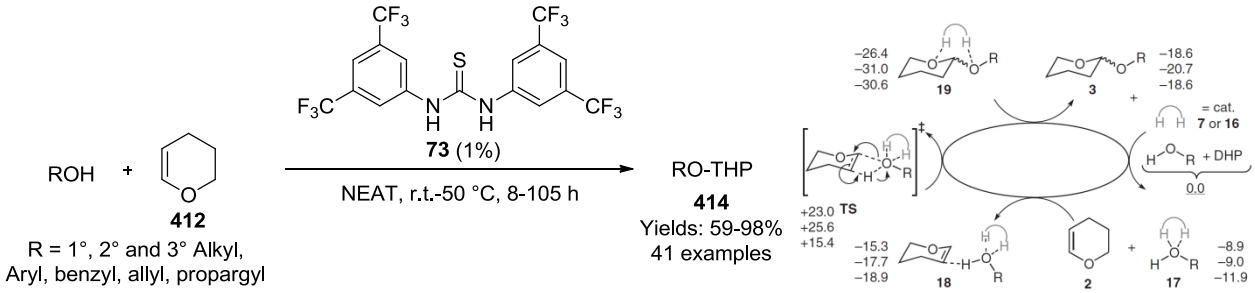
As you can easily see, these methods (many of then highly enantioselective bay the way) are all based of acyl introduction and on nucleophilic catalyisis. There are a few reports of sylil ether formation, but the catalysis is still nucleophilic. Asymmetric desymmetrization of chiral diols via Brønsted acid catalysis has naver been reported to date, but it would be highly valuable, because it would be complementary to the latter, being useful, for instance, in case diols would bear groups highly sensitive to nucleophiles.

To design an effective enanatioselective Brønsted acid catalyzed desymmetrization of diols it is necessary to find a reagent that can be introduced on a diol via this kind of catalysis. A protecting group for alcohols classically introduced via acid catalysis is the tetrahydropyranyl group. This is introduced using dihydropyrane **412** as reagent, which under Brønsted acid catalysis is protonated to the corresponding oxocarbenuim ion **I**, an highly electrophilic specie that undergoes nucleophilic attack by the diol (scheme **9.1**). Introduced and removed under relatively mild acidic conditions, this protecting group is extremely useful when it's impossible to introduce in the molecule protecting groups that need nucleophilic conditions because the molecule is sensitive to nucleophiles. On the other hand, the introduction of this protecting group creates diastereoisomers because an additional chiral center is created on the tetrahydropyranyl moiety during the reaction. Sometimes this fact could help in elucidating some complex structures, but often is considered a drawback, because it complicates the spectra, the purification operations and influences further reactivity of the molecule. By the way, considered its large use and application, its relatively easy removal and its orthogonality to other protecting groups, we judged this to be the group of choice to begin a study on enanatioselective Brønsted acid catalyzed desymmetrization of diols (scheme **9.1**).



Scheme 1: working hypothesis of desymmetrizative tetrahydropyranylation of meso dols: please note the formation of an additional stereocenter on the tetrahydropyranyl moiety.

Additionally to Brønsted acid catalysis, in literature also thiourea catalyzed introduction of THP group is reported. In 2007 Schreiner reports[258] that an achiral thiourea can also efficiently and rapidly catalyze alcohol tetrahydropyranylation in a mild and general way and with good selectivities. The author propose also an activation mode (scheme **9.2**). For this reason in the final part of the project we also tried catalysis with chiral thioureas.

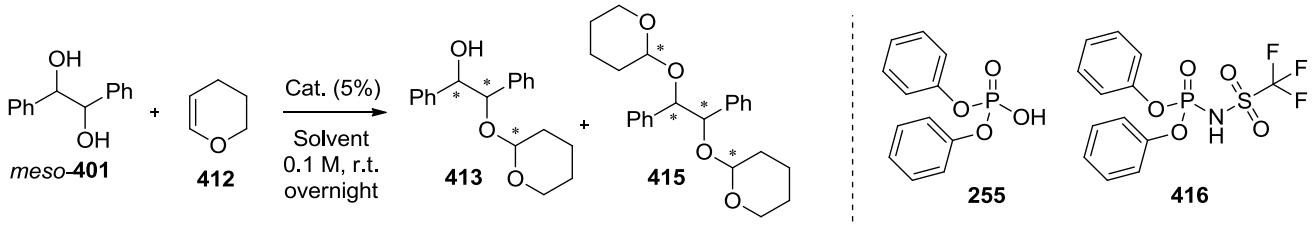


Scheme **9.2**: Schreiner's general thiourea catalyzed tetrahydropyranylation of alcohols and possible transition state.

[258] M. Kotke, P. R. Schreiner, *Synthesis*, **2007**, *5*, 779–790.

9.2) Enanatioselective Brønsted acid catalyzed desymmetrization of meso-Hydrobenzoin

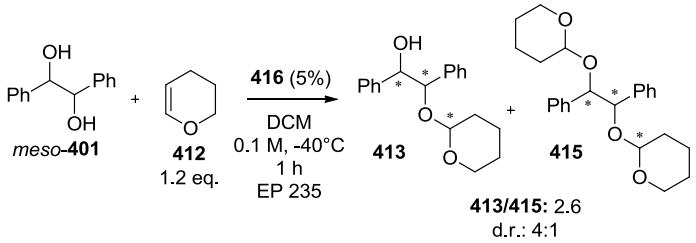
We embarked in this project using as model substrate meso-hydrobenzoin, that we showed before for the general explaination on desymmetrization. The first trials with racemic catalysts showed good reactivity for both the achiral phosphoric acid **255** and the achiral superacid **416** (*Table 9.1*). For the latter, reactivity was shown in every solvent, while for **255** only DCM and toluene worked. Anyway the reaction mixture was quite messy, showing many spots on TLC and a messy NMR spectrum of the crude, especially for **416** catalyzed reactions. A mixture of products **413** and **415** was obtained, each one in diastereoisomeric mixtures. In this regard, it should be noted since now that all values obtained via NMR in all the following tables are esteems, due to overlapping peaks in the spectra.



Entry	Catalyst	Solvent	413/415	d.r. of A	NMR Yield of A (%)
1	**255**	Hexane	0.59	n.d.	n.d.
2	**255**	Toluene	2.54	1:1	86
3	**255**	Et_2O	-	-	0
4	**255**	DCM	1.96	2.36:1	80
5	**255**	EtOAc	-	-	Low
6	**255**	THF	-	-	0
7	**416**	Toluene	1.5	3:1	56
8	**416**	Et_2O	1.47	3:1	59
9	**416**	DCM	1.6	3.35:1	59
10	**416**	EtOAc	1.9	2.89:1	43

Table 9.1: racemic solvent trials for the desymmetrization of meso hydrobenzoin

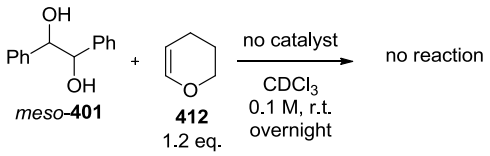
Since the formation of the product **415** was clear, a kinietic study was tried, but already in the first reaction after 1 h full conversion of DHP was observed using **416** as catalyst (scheme **9.1**).



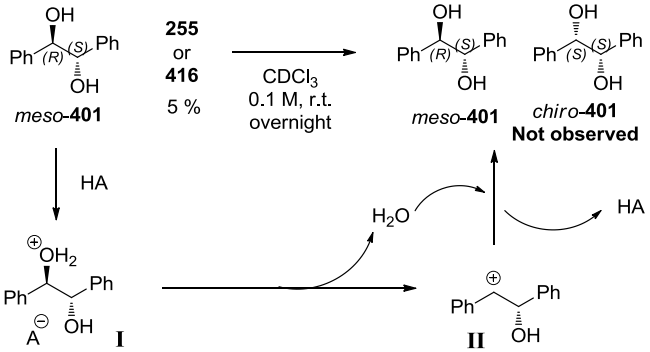
Scheme **9.1**: Reaction using **416** at -40°C

Anyway from this reaction it was possible to isolate most of the reaction products. At least two **415** byproducts, one meso and one not, are formed, and **413** is obtained as a couple

of diastereoisomers partly separable. Another unknown byproduct could be isolated (for more information about, see the last page, product **428**).
To understand why the reaction is so messy, leading also byproducts, some control experiments were performed. It was confirmed that without catalyst no background reaction occurs (scheme **9.2**) and that racemization of starting material leading to the opposite diastereoisomer was not taking place (scheme **9.3**).

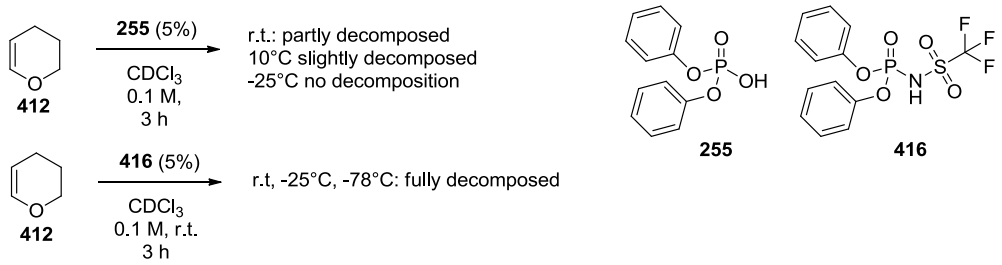


Scheme **9.2**: checking for background reaction.



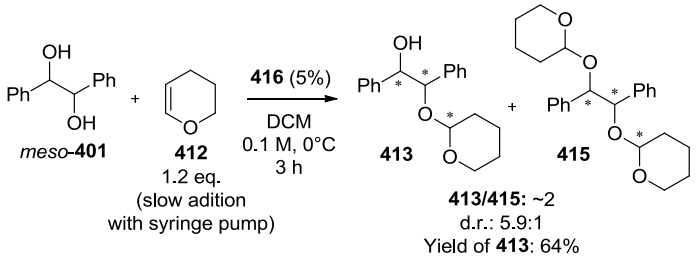
Scheme **9.3**: checking for possible racemization pathway.

Finally, it was found that dihydropyrane undergoes into a fast decomposition using **416** as the catalyst at every temperature, while using **255** already at 10 °C ths decomposition was little (scheme **9.4**).



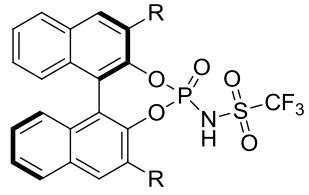
Scheme **9.4**: decomposition of **412** using **255** and **416** at different temperatures catalyst. EP239-240

To try to reduce this decomposition, a reaction was tried adding DHP slowly in solution with the syringe pump. Despite the results in terms of chemoselectivity and d.r. were not so different, this could be considered an improvement, because the reaction was cleaner. By the way the reported ratio **413/415** is still underestimated due to overlapping peaks (scheme **9.5**).

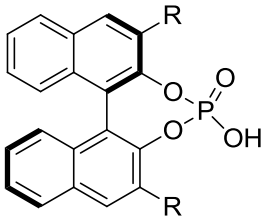


Scheme 5: ASA catalyzed reaction adding slowly DHP at 0°C.

With these results in hand we decided to try an enantioselective reaction using a BINOL based phosphoric acid and a triflimide with the same substituent on the 3 and 3' positions of the BINOL (*table 9.2*, entries **1** and **2**).
Even if regarding selectivity the triflimide gave slightly better results, we preferred to screen phosphoric acid as catalysts because of the higher ratio **413/415**.
So we screened four different catalysts in two solvents. It should be noted since now that the order in which the diastereoisomers are written is important, since in some reactions one is the major, and in other reactions the major is the second one. Toluene showed generally better enantioselectivities, and in many cases the second diastereoisomer shows better ee values. Anyway the two catalysts **84k** and **84i** showed promising enantioselectivities, **84i** on the second diastereoisomer, **84k** in both (*table 9.2*, entries **8** and **9**).

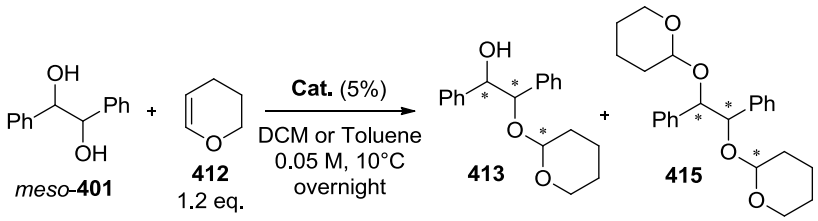


88q R= Biphenyl



84

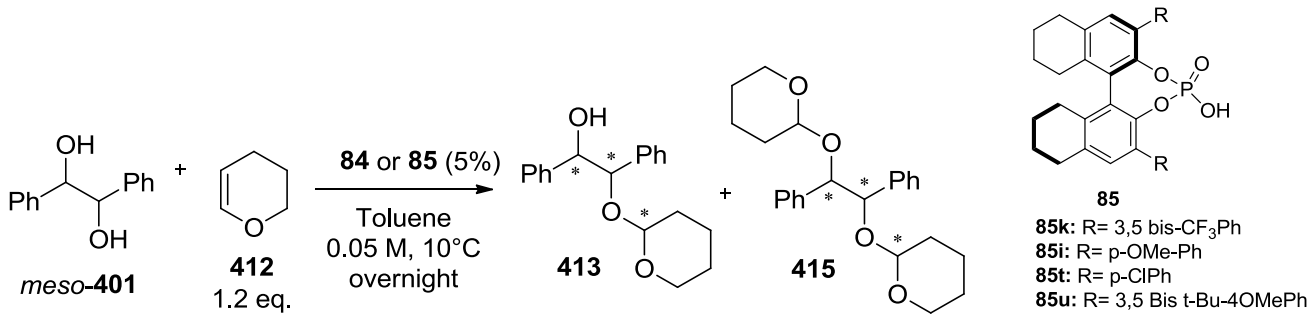
84n: R= Phenyl
84k: R= 3,5 bis-CF_3Ph
84i: R= p-OMe-Ph
84e: R= Phenanthryl
84q: R= Biphenyl
84r: R= 1-Naphthyl
84d: R= 2-Naphthyl
84o: R= p-FPh



Entry	Catalyst	Solvent	413/415	NMR d.r. of 413	HPLC d.r. of 413 ee	NMR yield (%)	Isolated yield (%)
1	**84q (2 %)**	DCM	> 20	1 : 1.34	1 : 1.04 0/-7	N.D.	32
2	**88q** *	DCM	1.97	3.1 : 1	4.5 : 1 -3/-10	N.D.	47
3	**84n**	DCM	1.59	3.11 : 1	3 : 1 0/-6	50	31
4	**84k**	DCM	1.35	5.28 : 1	5.25 : 1 3/-7	36	20
5	**84i**	DCM	2.53	2.11 : 1	2.12 : 1 -3/-11	56	39
6	**84e**	DCM	> 20	1.03 : 1	1.27 : 1 -5/-18	40	30
7	**84n**	Toluene	2.84	1.3 : 1	1.12 : 1 1/-16	55	38
8	**84k**	Toluene	1.5	4 : 1	2.4 : 1 26/-25	38	21
9	**84i**	Toluene	4	1.1 : 1	1 : 1 -9/-36	52	32
10	**84e**	Toluene	-	-	-	0	0

Table 9.2: evaluation of some catalysts for the enantioselective desymmetrization of meso hydrobenzoin. *(conditions: 1% of catalyst, -78°C, slow addition of DHP with syringe pump over 30 min).

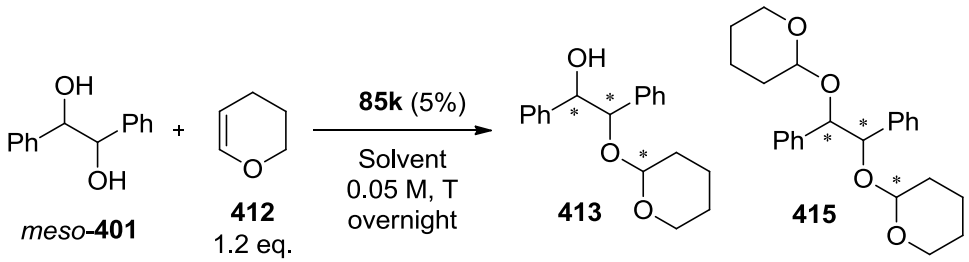
Since catalysts **84k** and **84i** showed to be the best, we tried the corresponding octahydro BINOL derivatives, together with some other catalysts (*table 9.3*). As catalyst **85i** only slightly improved the results obtained with the corresponding **84i** (compare *Tab. 9.2*, entry **9** and *Tab. 9.3* entry **5**), the catalyst **85k**, corresponding to **84k**, showed surprisingly different results (compare *Tab. 9.2*, entry **8** and *Tab. 9.3* entry **4**). Respect to **84k**, using **85k** the major diastereomer was the opposite, albeit the d.r. was only 1:1.3, and it was obtained in 70% of ee. All the other catalysts tried in *table 3* didn't give better results.



Entry	Catalyst	413/415	NMR d.r. of 413	HPLC d.r. of 413 ee	NMR yield (%)	Isolated yield (%)
1	**84r**	3	1.4 : 1	1.5 : 1 -15/-23	67	59
2	**84d**	3.3	1.46 : 1	1.44 : 1 -11/-31	74	52
3	**84o**	2.5	1.5 : 1	1.38 : 1 -1/-18	71	50
4	**85k**	7	1:1.4	1 : 1.3 6/-70	65	62
5	**85i**	> 20	1 : 1.6	1 : 1.2 -9/-40	84	63
6	**85t**	5.4	1 : 1.35	1 : 1.27 -4/-37	63	42
7	**85u**	> 20	1 : 1.2	1.2 : 1 -7/-8	24	39

Table 9.3: more optimization for the enantioselective desymmetrization of meso hydrobenzoin

With this good result in hand we performed more screening of conditions and solvent. Both decreasing the temperature and adding 4Å molecular sieves increased the enantiomeric excess (*table 9.4*, entries **2** and **3**), but the reaction at -10 °C was very slow, giving only 18% of yield in three days (*table 9.4*, entry **3**). A small solvent screening revealed that o-Xylene is also a good solvent if we consider selectivity (*table 4*, entry **4**), so the reaction was tried in this solvent at 0 °C with 4Å molecular sieves, and the same was done using toluene; this was done to try to combine the best conditions (*table 9.4*, entries **7-8**). The reactions proceeded smoothly and the best solvent was o-Xylene which gave 91% of ee on the second diastereoisimer. Unfortunately here a low **413/415** ratio was observed. The last trial was a reaction at low temperature in o-Xylene which didn't improve the enantioselectivity (*table 9.4*, entry **9**).

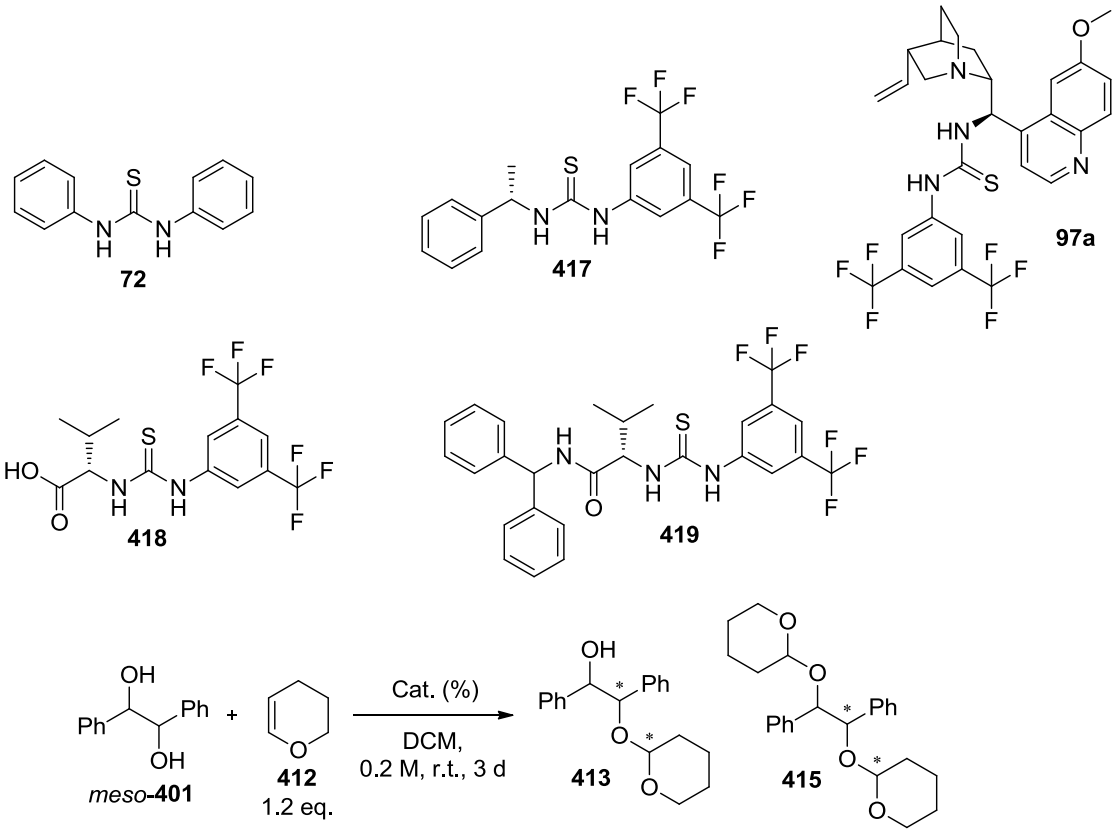


Entry	Solvent	T (°C)	Additive	413/415	NMR d.r. of 413	HPLC d.r. of 413/ ee	NMR yield (%)	Isolated yield (%)
1	Toluene	10	-	7	1:1.1	1 : 1.3 6/-70	66	62
2	Dry Toluene	10	4Å MS	8	1 : 1.3	1 : 1.2 +4/-83	67	46
3	Toluene	-10	-	4.5	1 : 1.4	1 : 2.1 +3/-82	14	18
4	o-Xylene	10	-	6	1 : 1.14	1 : 1.17 6/-71	64	48
5	Chlorobenzene	10	-	9	1 : 1.13	1 : 1 2/-54	81	53
6	Trifluorotoluene	10	-	4	1.2 : 1	1 : 1 -3/-44	44	31
7	Toluene	0	4Å MS	1.6	1 : 1.36	1 : 1.3 9/-88	77	58
8	o-Xylene	0	4Å MS	1.2	1.1 : 1	1 : 2.1 14/-91	61	56
9	o-Xylene	-20	4Å MS	1.3	2.5 : 1	n.d. n.d./-89	n.d.	42

Table 9.4: optimization of solvent and additive. *: reaction time: 3d. **: reaction time 36 h.

9.2.1) Thiourea catalyzed desymmetrization of meso diols using enol ethers

This reaction was tried als under thiourea catalysis, since a racemic trial showed reactivity (*table 9.5*, entry **1**). The cinchona alkaloid-based thiourea **97a** didn't show reactivity. Speculating that this could be due to the basicity of quinuclidine core, the same reaction with 1 and 2 equivalents of benzoic acid with respect to the catalyst was tried, but still no reactivity was observed (*table 9.5*, entries **4-6**). Surprisingly, even adding benzoic acid to catalyst **417**, which alone showed reactivity but poor selectivity, suppressed the reaction (*table 9.5*, entries **2-3**). Including the acid moiety into the catalyst (**418**), instead, lead to the formation of the product in good yields, but again with poor selectivity, as well as using a catalyst bearing an amide moiety (**419**) (*table 9.5*, entries **7-8**). In summary thiourea catalysis didn's seem to be effective.

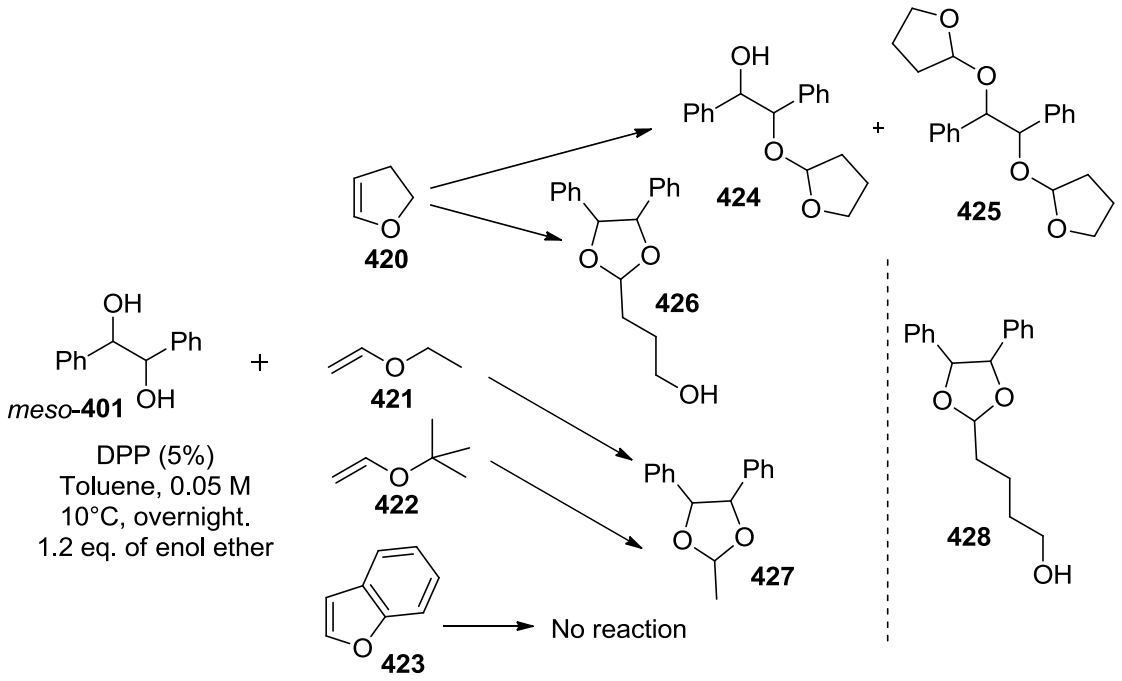


Entry	Cat (mol%)	additive	413/415	NMR d.r.	NMR Yield (%)	HPLC d.r./ ee	Isolated Yield (%)
1	**72** (10)	-	>20	1 : 1.1	58	-	50
2	**417** (5)	-	>20	1 : 1.1	n.d.	1 : 1 4/-6	51
3	**417** (10)	PhCOOH (10%)	-	-	-	-	No reaction
4	**97a** (10)	-	-	-	-	-	No reaction
5	**97a** (10)	PhCOOH (10%)	-	-	-	-	No reaction
6	**97a** (10)	PhCOOH (20%)	-	-	-	-	No reaction
7	**418** (10)	-	5.5	1 : 1	85	1 : 1 0/-5	64
8	**419** (10)	-	2.6	1.6 : 1	73	1.7 2/-3	44

*Table **9.5***: attempting thiourea-catalyzed desimmetryzation of meso-hydrobenzoin.

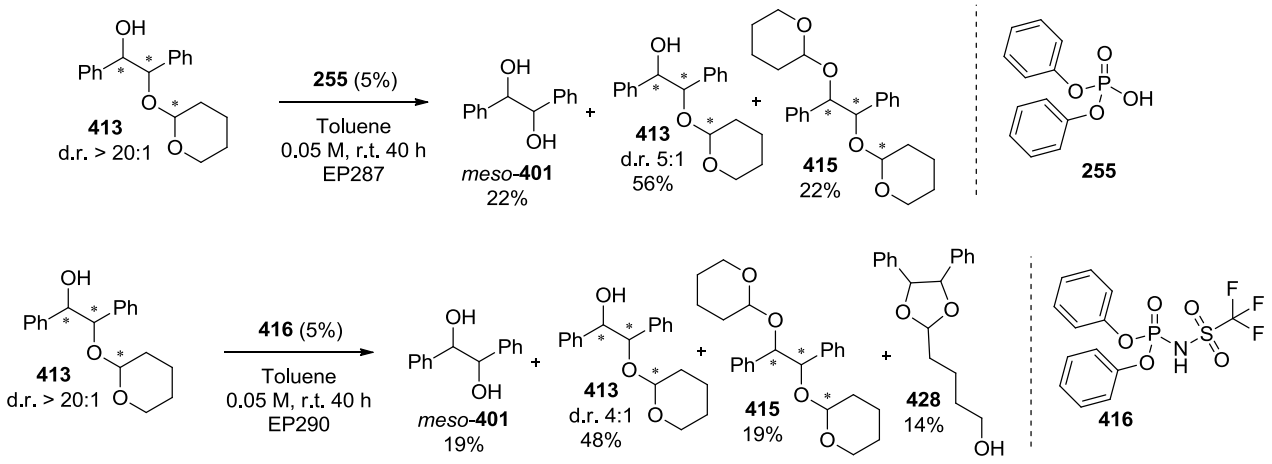
In the end, we switched our attention also on other enol ethers (scheme **6**). Using acyclic enol ethers **421** and **421** only the cyclic byproduct **427** was formed. It arises from a cyclization of the other OH of the diol on the acetalic carbon with the elimination of the corresponding alcohol. The reaction employing **420** gave three spots separable by column chromatography. The first one should be a mixture of products **425**, the second and the third could be the two diastereoisomers of product **424**, but one or both could also be or contain byproduct **426**. Since this studies were performed at the very end of my stay, further investigation would be needed to confirm the structures, because a simple ^{1}H NMR spectrum was not determining (scheme **9.6**). Also in the HPLC some peaks could be separated, but we can't be sure that they are the enantiomers of the desired product.

Finally, no reaction was observed employing benzofuran (**423**) as the enol ether. At least these results gave us a clue on the nature of the unidentified byproduct in the monoprotection of meso-hydrobenzoin with dihydropyran catalyzed by triflimides: it could be compound **428**.



Scheme 6: last trials with other enol ethers.

In the end, it's worth noting that the reaction showed to be an equilibrium: stirring the product **413** with both the catalysts **255** and **416** for 40 h at r.t. resulted in a mixture of starting material, product and byproduct **415**, together with another set of unknown signals. With the catalyst ASA also the unidentified byproduct that might be **428** was observed. The d.r. also changed considerably (scheme **9.7**).



Scheme **9.7**: studies on the reversibility of the reaction.

9.3) EXPERIMENTAL SECTION

General

All commercially available compounds were used as provided without further purification. Solvents were technical grade and distilled prior to use. Toluene and o-Xylene were dried by distillation from benzophenone/Na. 4Å molecular sieves were purchased from Sigma-Aldrich as 3.2 mm size pellets and grinded before use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualised by irradiation with UV light and developed with $KMnO_4$. Flash column chromatography was performed using silica gel (Macherey Nagel, particle size 0.040-0.063 mm) according to the method of Still[259]. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Solvent mixtures are understood as volume/volume. ^{1}H-NMR and ^{13}C-NMR were recorded on Varian Gemini 300 MHz, Inova 400 MHz or 600 MHz spectrometers in $CDCl_3$ and are reported relative to the solvents residual 1H-signal ($CHCl_3$, δ(H) 7.26). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet); coupling constants (*J*) are in Hertz (Hz). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. CHIRALCEL OJ-H; eluent: *n*-hexane/2-propanol. The chiral HPLC methods were calibrated with the corresponding racemic mixtures.

Determination of yields, diastereomeric ratios and 413/415 ratios

All these data were estimated via ^{1}HNMR spectroscopy of the crude. Yields were calculated using a known amount of mesitylene as internal standard. Diastereomeric ratios and **413/415** ratios were determined by adequate integration of the peaks on the crude ^{1}HNMR spectra.

General procedure for the desymmetrization of meso-hydrobenzoin with enol ethers.

In a screw capped vial equipped with a stirring bar were placed the catalyst (0.005 mmol, 5%) and meso-hydrobenzoin (0.1 mmol). Toluene (2 ml) and dihydropyrane (0.12 mmol, 1.2 eq.) were added and the reaction was stirred at r.t. or at 10 °C overnight. The reaction mixture was then plugged on a short pad of silica and the product was purified through flash chromatography on silica gel (eluent mixture: Hex/EtOAc 10:1) to give a white solid, which was the pure desired product obtained as a mixture of diastereoisomers.

General procedure for the desymmetrization of meso-hydrobenzoin with enol ethers using molecular sieves.

Grinded 4Å molecular sieves (30 mg) were placed in a screw capped shclenck tube equipped with a stirring bar which was covered with a septum. The molecular sieves were activated by flame drying in vacuo and the tube was refilled with argon upon cooling. Then the catalyst

[259] W.C.Still, M.Kahn, A.J.Mitra, *J.Org.Chem.* **1978**, *43*, 2923.

(0.005 mmol, 5%) and meso-hydrobenzoin (0.1 mmol) were quickly added as solids. Dry Toluene or o-Xylene (2 ml) and dihydropyrane (0.12 mmol, 1.2 eq.) were added via syringe and the reaction was stirred at the indicated temperature for the required time. The reaction mixture was then plugged on a short pad of silica and the product was purified through flash chromatography on silica gel (eluent mixture: Hex/EtOAc 10:1) to give a white solid, which was the pure desired product obtained as a mixture of diastereoisomers.

General procedure for the desymmetrization of meso-hydrobenzoin with enol ethers catalyzed by superacids.

The catalyst (0.005 mmol, 5%), meso-hydrobenzoin (0.1 mmol) and DCM (1 ml) were introduced into a screw capped shclenck tube equipped with a stirring bar which was covered with a septum and placed in a cooling bath at the indicated temperature. On the other side, dihydropyrane (0.12 mmol, 1.2 eq.) was dissolved in 1 ml of DCM. This solution was transferred into a syringe and added to the schlenck tube during 30 min. using a syringe pump. The reaction mixture was stirred for further 1 h and then plugged on a short pad of silica. The product was then purified through flash chromatography on silica gel (eluent mixture: Hex/EtOAc 10:1) to give a white solid, which was the pure desired product obtained as a mixture of diastereoisomers.

General procedure for the desymmetrization of meso-hydrobenzoin with enol ethers catalyzed by thioureas.

In a screw capped vial equipped with a stirring bar were placed the thiourea catalyst (0.01 mmol, 10%) and meso-hydrobenzoin (0.1 mmol). DCM (0.5 ml) and dihydropyrane (0.12 mmol, 1.2 eq.) were added and the reaction was stirred at r.t. for three days. The solvent was then removed *in vacuo* and the product was purified through flash chromatography on silica gel (eluent mixture: Hex/EtOAc 10:1) to give a white solid, which was the pure desired product obtained as a mixture of diastereoisomers.

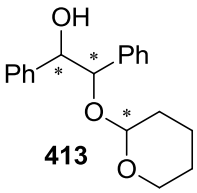
Materials

Compounds *meso*-**401**, **412** and **420-423** are commercially available.
Phosphoric acid catalysts were prepared following literature procedures[112-1126, 192].
Catalyst **72** is commercially available. Catalyst **416** was already present in our laboratories.
Catalysts **97a**[83], **417**[260], **418**[261] and **419**[262] were prepared according to the procedures described in the literature.

[260] *Aust. J. Chem.* **2008**, 61, *364–375*.
[261] *Org. Biomol. Chem.*, **2008**, 6, *2054-2057.*
[262] *J. Am. Chem. Soc.*, **2009**, 131 (42), *15358–15374*.

Characterization of new compounds.

413, first diastereoisomer



^{1}HNMR (600 MHZ, $CDCl_3$): δ = 1.38 (m, 1H), 1.46 (m, 2H), 1.60 (m, 2H), 1.74 (m, 1H), 2.73 (bs, 1H), 3.30 (m, 2H), 4.47 (t, *J* = 3.5 Hz, 1H), 4.83 (d, *J* = 5.8 Hz, 1H), 4.89 (d, *J* = 5.8 Hz, 1H), 7.25 (m, 10H). **^{13}CNMR (600 MHZ, $CDCl_3$):** δ = 19.1 (CH_2), 25.3 (CH_2), 30.6 (CH_2), 62.0 (CH_2), 77.2 (CH), 81.5 (CH), 95.8 (CH), 127.3 (2 CH), 127.4 (CH), 127.6 (2 CH), 127.9 (CH), 128.0 (2 CH), 128.1 (2 CH), 137.9 (C), 140.6 (C). **Chiral HPLC analysis**: Daicel Chiralcel OJ-H; flow rate 0.6 ml/min., Hex/i-PrOH 85:15, λ = 230 nm, r.t., τ_1 = 12.2 min, τ_2 = 27.1 min.

413, second diastereoisomer

This diastereoisomer couldn't be isolated, but was obtained always in mixture with the first one. Anyway, knowing the signals of the first diastereoisomer, in ^{1}H NMR it's possible to understand the signal of the second, in it ^{13}C NMR is not possible.
This second diastereoisomer was the one that had high enantiomeric excess.
^{1}HNMR (400 MHZ, $CDCl_3$): δ = 1.40 (m, 6H), 2.05 (bs, 1H), 3.14 (ddt, J_1 = 14.8 Hz, J_2 = 5.6 Hz, J_3 = 2 Hz, 1 H), 3.33 (dt, J_1 = 15.2 Hz, J_2 = 4 Hz, 1 H), 4.34 (t, *J* = 3.1 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.76 (d, *J* = 1.4 Hz, 1H), 7.25 (m, 10H).
Chiral HPLC analysis: Daicel Chiralcel OJ-H; flow rate 0.6 ml/min., Hex/i-PrOH 85:15, λ = 230 nm, r.t., τ_{minor} = 13.8 min, τ_{major} = 14.8 min.

I could not understand which diastereoisomer was the first and which was the second.

All the other compounds were not fully characterized.

Post scriptum

Three years working in chemistry lab teached me that chemistry may be tyring.
There is always something to do in the chemistry lab: one coud never stop, in principle.
Time is a precious resource, and, in order not to waste it, we are pushed to fill
every minute doing something, even little things like cleaning or tiding up.
When I started this experience I didn't know well what to expect. Just some months before,
I was thinking that the Ph.D was just another course of study, when people were always on books
and doing exams like in the Bachelor or Master. I realized I was completely wrong during my
Master thesis. I saw Ph.D students working in the lab and supervising my work.
I saw them, doing research, and teaching, and being also the lab managers.
I realized that being a Ph.D student is like a job, a manual job more than an intellectual one.
After all these years studying, I really wanted to work, to demonstrate that all these years
were useful, that besides learning I could be able also to produce something.
For this reason I accepted enthusiastically my Ph.D position. Suddently I realized how much work
there is to do in a chemistry lab, and we are back to the first speech: lacking of time.
It is never enough to do everything you wish, and this pushes you to work faster, and in this way
chemistry becomes tyring. I am not complaining, this is that kind of good tyring:
At the end of the day I felt many times satisfied and surprised for how many the things I coud do in
one day, working so fast. The amount of work not always results in the same amount of good
results, and this is disappointing, but it's our job, I suppose.
After these three years, anyway, I realize that it's not possible to go so fast forever.
I slowly understood the importance of studying a subject, to get all the possible knowledge about.
I have a T-shirt on which is written: knowledge is power. And this is true. If you have knowledge
you can rationally think to what you are doing, and develop a methodology.
And with this methodology you can work efficiently and save a lot of time, going directly to the
point. This is what I learned in three years of Ph.D. This, and a bit of chemistry, I hope.

Because I was always so busy, I have a little regret concerning my Ph.D: relationship with people.
I couldn't know deeper my colleagues, couldn't share ideas and experiences as I wished.
I was surrounded by many nice people, and for sure each of them deserved more attention.
Despite this, many beautiful moments passed and many memories will stay forever in my mind.
The time spent abroad, in Germany deserves a special mention. There, I not only learned
much interesting chemistry, new methodologies and other ways to work, which for sure opened my
mind. I also demonstated that I could live in a foreign country, having a language completely
unknown to me, with not many problems. Since my house was just next to the faculty,
since my position was not the one of "lab manager", I could live my life there more as a student,
create friendships, go out often and enjoy the life both in the lab and outside.
I have to admit that my life there was made easy by the amazing people I met, always helpful and
nice. Everytime I think about Aachen it's an emotion and I whish to be there.
At the beginning also in this case I didn't know what to expect.
Now I know that it could have been much worse, and I feel really lucky when I think about that
experience.
A small note for all my Italian friends: Germany is a beautiful country, not only an efficient one.
There are many beautiful places and cities in Germany and people are really amazing.
They are maybe more reserved than Italians, but not cold, and they are really helpful:
many times I got helped even without asking.

One last consideration: during these years making chemistry I felt prompted, surprised, sad, frustrated, satisfied, angry, determined, stressed and inspired. But never bored. Science, research, chemistry, has this prerogative: it's interesting, fascinating, creates wonder, both in the discovery of a new reaction, or just looking amazed to some nice crystals. This is what should push scientists in research: curiosity, passion and wonder of discovery. Sometimes I think academic research is too much target oriented: this is a must in industry, but academic should be more knowledge oriented, because everything can be useful: knowledge, as I told, is power. From this point of view I think I can be satisfied, Because in these years, anyway, I could explore many sides of organic chemistry, and for this reason I have to be grateful to my supervisors that let me do it, also allowing me to develop my ideas. I hope I can be so much lucky also in the future and find a job that I like and that gives me this freedom. Many boring job exists, also in chemistry. I hope to avoid this. Our job is a huge part of our life, I think we must like it, or our life is not satisfying.

Enrico Paradisi.

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