Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

SCIENZE CHIMICHE

Ciclo XXV

NOVEL SYNTHETIC PROCEDURES IN ORGANOCATALYSIS

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Index

PART 1

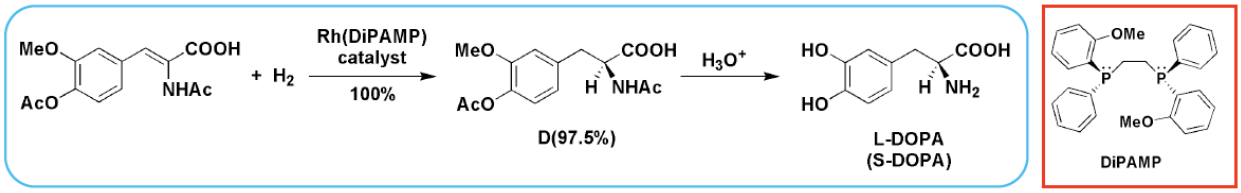
Design of new catalysts in organocatalysis

The main aim of my PhD project was to design and synthesize new pirrolidine organocatalysts.

Asimmetric Catalysis

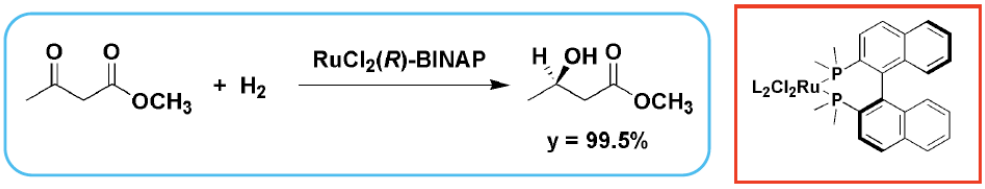
The term "asymmetric catalysis" refers to the set of chemical processes that allow a high stereochemical control of the reactions, by the use of sub-stoichiometric amount of enantiomerically pure chiral molecules as catalyst. The chirality of the molecules plays an important role in nature, science and technology: indeed, most of the physiological phenomena are driven by highly selective molecular interactions, where a chiral molecule (host) selectively recognizes two enantiomeric molecules (guest). The principle of asymmetric catalysis is based on the use of small amounts of a chiral catalyst able to give, in a stereoselective way, the desired product. The chiral catalyst promotes a reaction path where the two diastereoisomeric transition states have different activation energy, due to the discrimination between atoms, groups or faces of the molecule.

Knowles, Noyori and Sharpless, awarded with the Nobel Prize for chemistry in 2001, were among the first researchers to explore the field of asymmetric catalysis, demonstrating its usefulness in the processes for the synthesis of pharmaceuticals. In 1968, W. S. Knowles discovered that rhodium metal can be coordinated by a diphosphinic binder to carry out a chiral asymmetric catalysis of the hidrogenation reaction:[1] this observation rapidly led up to the development of an industrial process for the synthesis of L-DOPA, an amino acid used in the therapy of Parkinson's disease (*Scheme 1.1*).



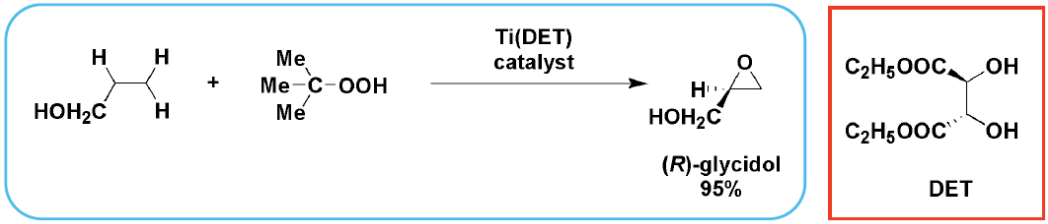
Scheme 1.1. Industrial sinthesys of L-DOPA

Once understood the importance of identifying excellent chiral ligands for highly selective asymmetric catalysis, Ryoji Noyori in 1974 developed the synthesis of BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), a di-phosphine with C2 symmetry. A new catalyst was developed, the Ru-BINAP, which is used for the synthesis of chemical compounds, pharmaceuticals, as well as new materials. Particularly important is its application to the synthesis of (R)1,2-propanediol in the production of the antibiotic Levofloxacin (*Scheme 1.2*).[2]



Scheme 1.2. Synthesis of (R)-1,2-propanediol.

In parallel with the development of catalytic asymmetric hydrogenation reactions, Barry Sharpless synthesized a new catalyst for another important class of transformations: the oxidation reactions.[3] Among the many discoveries made in this field, a special attention should be given to the asymmetric epoxidation reaction, catalyzed by a chiral titanium complex (*Scheme 1.3*). The epoxides are important intermediates for many syntheses, including those of drugs for blood pressure reduction.



Scheme 1.3. Asymmetric epoxidation reaction.

Starting from these early pioneering works, research on asymmetric catalysis has encountered an explosive growth especially in the last decade, in both academic and industrial sectors. To date, asymmetric catalysis represents an important branch of stereoselective synthesis and its high practicality is exploited in more and more industrial processes.

Asimmetric Organocatalysis

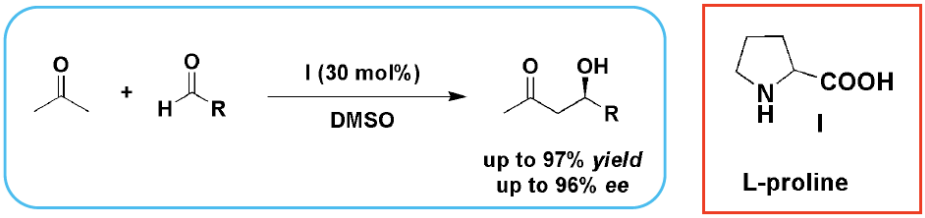
The use of small organic molecules as chiral catalysts is called 'organocatalysis'. At present, organocatalysis is considered an efficient and reliable strategy for the stereoselective preparation of a wide range of organic compounds: indeed, with respect to the classical methods (such as metal-catalysis, enzymatic catalysis and separation of enantiomers from racemic mixtures), it provides objective advantages in obtaining enantiopure products, since the catalysts:

- do not exhibit the toxicity problems associated with the use of metals (particularly advantageous in pharmaceutical chemistry);
- are readily available or synthesized from simple natural molecules;
- are stable to the air.

The high compatibility with aerobic conditions makes the reaction methodologies simple and safe, since the use of anhydrous solvents or inert atmosphere are not needed (the water and the air pose a serious risk when working with metal catalysts).

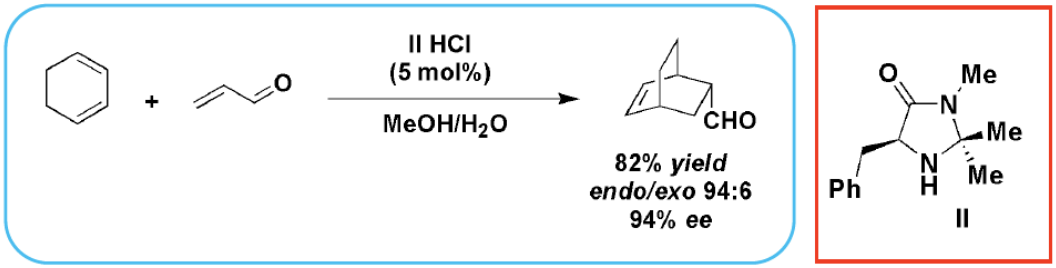
Although it was already known that small organic molecules can promote several changes in a stereoselective way,[4] the wherewithal of this approach was realized only in 2000 when, totally independently, List, Lerner and Barbas[5] on one side, and MacMillan and coworkers[6] on the other, published two different examples of organocatalysis promoted by chiral secondary amines, now known as "asymmetric aminocatalysis".

List, Lerner and Barbas showed that a catalytic amount acid L-proline (**I**) was capable of promoting a direct aldol reaction between a non-functionalized ketone, such as acetone, and a wide variety of aldehydes (*Scheme 1.4*). It was, thus, demonstrated that small organic molecules are able to promote the same reactions catalyzed by bio-organic molecules much larger (enzymes), in a similar manner.



Scheme 1.4. Aldol reaction promoted by L-proline.

Simultaneously, MacMillan described the first asymmetric Diels-Alder reaction catalyzed by a secondary amine, and demonstrated the efficiency of the imidazolidinone (**II**) in catalyzing the activation of aldehydes, α,β-unsaturated aldehydes (*Scheme 1.5*). In this circumstance, the term 'organocatalysis' was reintroduced in the literature, and the benefits of this newborn branch of catalysis were also described.



Scheme 1.5. Diels-Alder asymmetric reaction catalyzed by imidazolidinone (**II**).

The interest aroused by these two works has led to an exponential growth of studies on catalysis by secondary amines all over the world and the competition has accelerated the process of innovation and discovery.[7] New synthetic tools, that a few years earlier were considered inaccessible, were now revealed.

Due to its characteristics of generality, affordability, stability and non-toxicity, organocatalysis has encountered a wide acceptance not only in academia but also in industry, particularly in medicinal chemistry.

Critical for the success of organocatalysis in these fields was the identification of general protocols for the activation, induction and reactivity of the organic catalysts employed. An accurate study of these activation strategies has led to the discovery of new reactions and reactive species formed with a peculiar functional group able to participate in different stereoselective processes.

The importance of general methods of activation lies in their ease in being chosen and applied to new enantioselective synthesis or in the development of new catalysts families. This becomes evident when we consider that the 130 organocatalytic reactions published since 1998, are based on only four or five activation modes. At the same time, it is clear that the discovery of new strategies of activation is very important in all fields of catalysis.

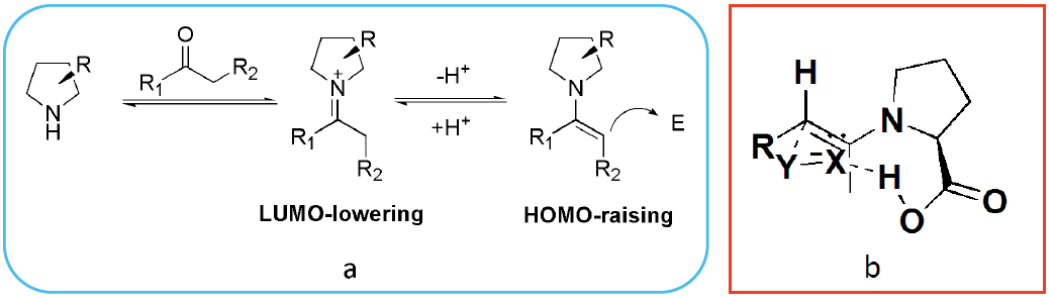
The four major activation procedures identified in aminocatalysis, able to promote so stereoselective formation of new bonds, are the following:[7]

Enamine catalysis:

The wide applicability of this activation comes from the studies of Barbas, Lerner and List,[5] that used the enamine to functionalize a carbonyl compound in α position. The reactive species is obtained by condensation of the reversible secondary chiral amine (organocatalyst) with the carbonyl compound. This reaction leads to the initial formation of the iminium cation, with a consequent lowering of the LUMO (Low Un-

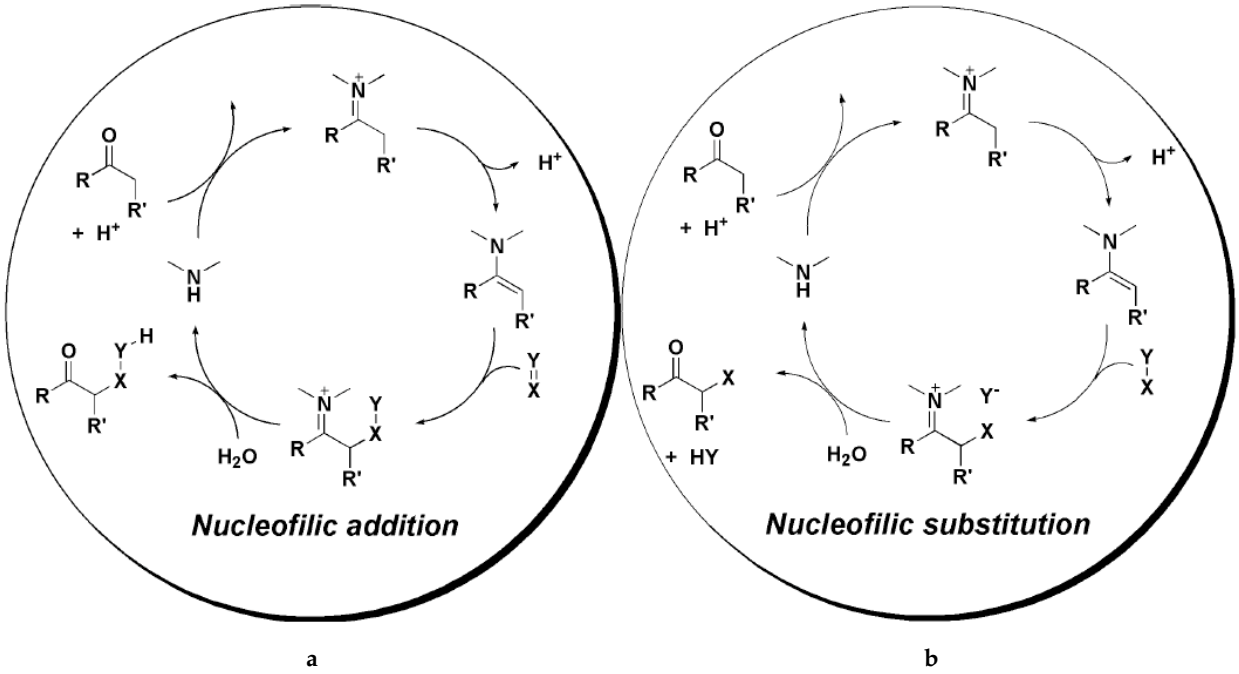
occupied Molecular Orbital) energy of the system; this leads to an increase of the proton acidity, therefore generating the nucleophilic enamine equivalent of the enolate (*Scheme 1.6a*).

A second contribution to activation is given by the coordination of the electrophilic partner, through hydrogen bonding or electrostatic interaction, by the carboxyl function present in the chiral catalyst, that stabilizes the transition state of the process and determines the stereoselectivity of the electrophilic attack (*Scheme 1.6b*).



Scheme 1.6. Enamine activation: a) activation HOMO b) coordination of the electrophilic.

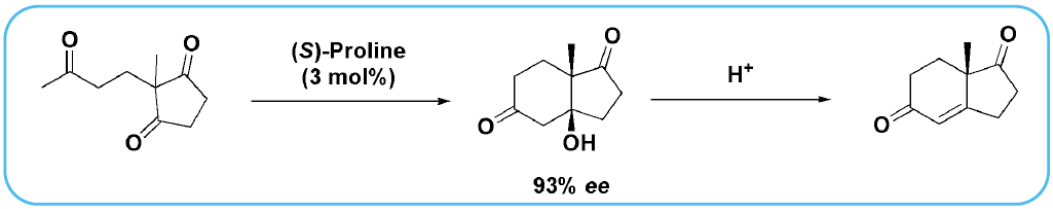
The enamine catalysis promotes two different types of reactions depending on the class of electrophiles used.[8] The electrophiles containing one double bond, such as aldehydes, imines, Mannich acceptors, are inserted in the C-H bond of the carbonyl compound through a nucleophilic addition reaction (*Scheme 1.7a*). Instead, single bonds with electrophiles, such as alkyl halides, react in a nucleophilic substitution reaction, giving a stoichiometric amount of co-product (*Scheme 1.7b*).



Scheme 1.7. Mechanisms of enamine catalysis.

The concept of enamine catalysis was developed starting from two important observations in the fields of organic chemistry and biochemistry.

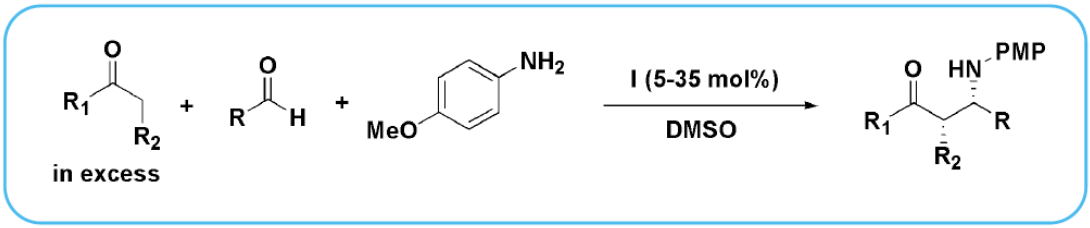
The first one is represented by the pioneering research of two industrial laboratories in the early '70s, that developed the so-called Hajos-Parrish-Eder-Sauer-Wiechert reaction, a stereoselective intramolecular aldol cyclization reaction catalyzed by a proline (*Scheme 1.8*).[9] This was the first demonstration that natural small molecules can act as highly enantioselective chiral catalysts in fundamental chemical transformations.



Scheme 1.8. Intramolecular stereo selective aldol reaction of cyclization.

The second observation comes from the studies of Lerner and Barbas, aimed at finding a new catalyst to promote intramolecular aldol reactions, similarly to the mechanism used by the natural enzyme aldolase type **I**.[10] The objective of the research was to to enhance the versatility of the enzyme aldolase, while preserving their exceptional catalytic efficiency.

Once elucidated the mechanistic aspect of the reaction, the principle of asymmetric enamine catalysis has been extended over the aldol reactions replacing the aldehyde with other electrophilic components, such as imines. The first reaction of asymmetric Mannich is reported from List in 2000: in this reaction, the compatibility between the conditions of catalysis via enamine was exploited together with the ability to generate in situ the imine, achieving with good results a direct three components reaction and a reversed stereoselectivity compared to that observed in the aldol condensation reaction (*Scheme 1.9*).[11]

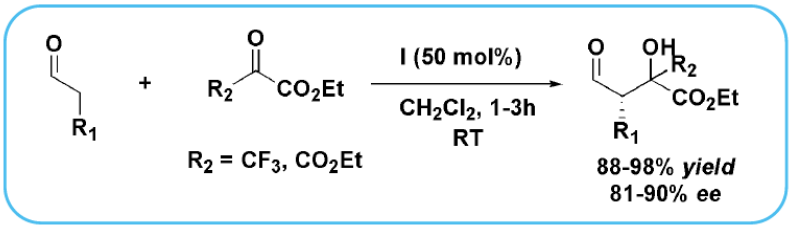


Scheme 1.9. Asymmetric Mannich reaction.

The demonstration of the efficiency of proline in activating different types of electrophiles promoting highly selective processes, strongly incentivated the search for new organic transformations applicable to catalysis via enamine, such as the Michael reaction.[12]

Thanks to Barbas' paper describing the autocondensation of acetaldehyde catalyzed by proline,[13] aldehydes quickly acquired a central role as donors in the organocatalysis, due to their high reactivity and versatility as building blocks.

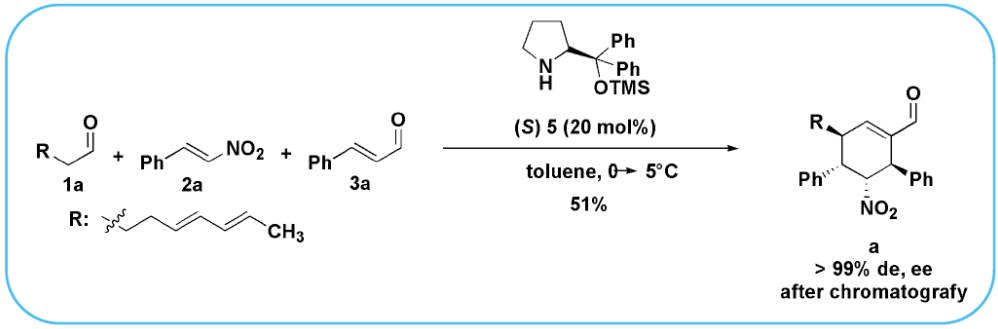
Following these observations, Jørgensen published the first asymmetric intermolecular addition of aldehydes to activated ketones (*Scheme 1.10*):[14] in his paper, indeed, he demonstrated that differently substituted ketones can be used for the fast synthesis of compounds with a quaternary center.



Scheme 1.10. Intermolecular and asymmetric direct aldol addition.

Secondarily, the range of applicability of proline to catalysis was extended beyond the formation process of the C-C bond, through a direct functionalization of aldehydes and ketones with different heteroatomic nucleophiles (α-amination, α-oxygenation, α-halogenation, α-sulfenilation). The formation of optically active molecules with one stereocenter directly bonded to a heteroatom in position adjacent to the carbonyl function, plays a key role in all the areas of organic chemistry. The first examples reported in literature, regarding effective and simple methods for a direct α-amination of highly enantioselective aldehydes,[15] were extended to ketones and α di-substituted aldehydes, then applied to the total synthesis of biologically active compounds.

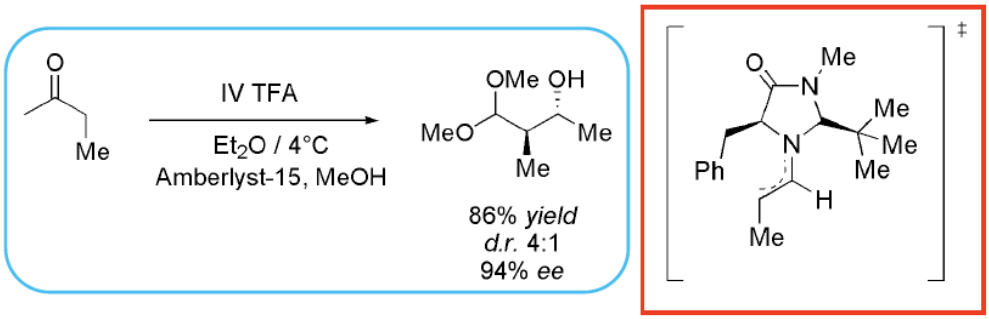
Following the excellent results with pyrrolidine skeleton catalysts, in recent years similar molecules with different substituents have been studied and developed. Among these, the Jørgensen catalyst catalyzes different types of nucleophilic attack ensuring good yields and excellent enantiomeric excesses.[16] The versatility of this catalyst, as well as the possibility to exploit it in a variety of reactions, favoured the use of Jørgensen catalyst in some processes so called "domino" (*Scheme 1.11*).[17]



Scheme 1.11. Domino process promoted by Jørgensen catalyst

Thanks to the formation of the active enaminic species and the high enantioselectivity of the catalyst, the domino reaction allows the formation of cyclic products containing up to five stereocenters, with an excellent stereocontrol.

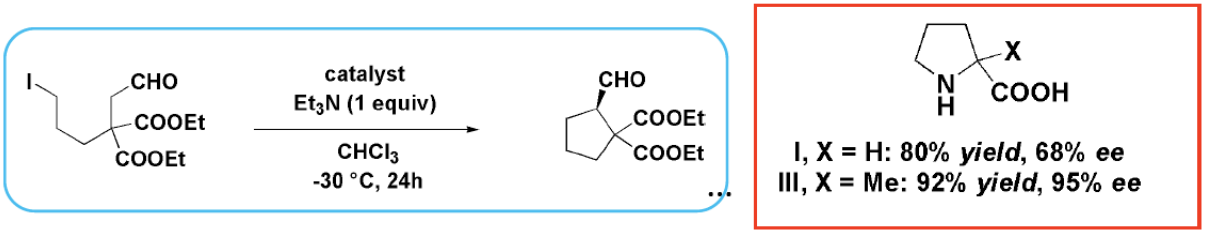
Another alternative to catalysis mediated by proline is represented by the use of MacMillan's imidazolidinone **II** and **IV**, which, in addition to activating carbonyl compounds as iminium ions, was found to be also a highly stereoselective enaminic catalyst (*Scheme 1.12*).[18]



Scheme 1.12. Application of MacMillan catalyst **IV**.

Computational studies indicated that the formation of an imine transition state precedes the formation of the C-C bond. On this basis, MacMillan suggested that the ability of a chiral amine to control the iminium geometry in the transition state is a crucial factor in the discrimination of the enantiofacial addition of the enamine.

The limited applicability of the enamine catalysis to electrophiles possessing a lone pair available, to allow the stereocontrol by the catalyst, was overcome by Vignola and List. Indeed, the two researchers discovered the first asymmetric intramolecular α-alkylation of halo-aldehydes via enamine catalysis, a highly useful unprecedented organocatalytic transformation. The proline and its derivative α-methylproline (**III**) are capable of cyclizing 6-halo-aldehydes to give cyclopentancarbaldehyde in excellent yields and enantiomeric excesses (*Scheme 1.13*).[19]



Scheme 1.13. Asymmetric catalysis via intramolecular enamine alkylation

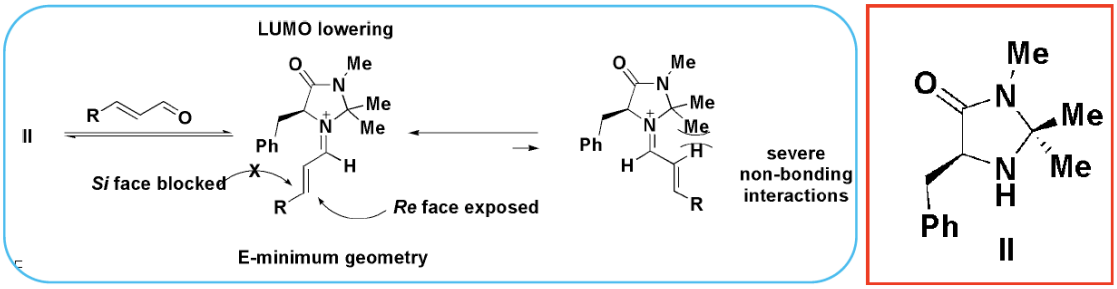
This first reaction of nucleophilic substitution opened a new line of research on catalysis by proline, contemporary solving the problems related to catalyst deactivation via the N-alkylation or possible racemization products.

Iminium catalysis:

This catalytic activation concept was introduced by MacMillan and co-workers with the asymmetric Diels-Alder reaction between α,β-unsaturated aldehydes and various dienes catalyzed by imidazolidinone (**II**). This new approach led to the development of a large number of asymmetric transformations involving unsaturated carbonyl compounds.[6]

The kind of organocatalytic activation derives from the reversible condensation of a secondary amine with an aldehyde to generate an unsaturated iminium ion intermediate. The latter induces an electronics redistribution that lowers the energy of the LUMO, increasing its susceptibility towards nucleophilic addition reactions, such as conjugated and pericyclic (LUMO activation). The success of this process lies in the catalytic ability of the iminium ion intermediate to discriminate effectively between the two faces of the electrophile: either through a control of the double bond configuration, favoring the E configuration with re-

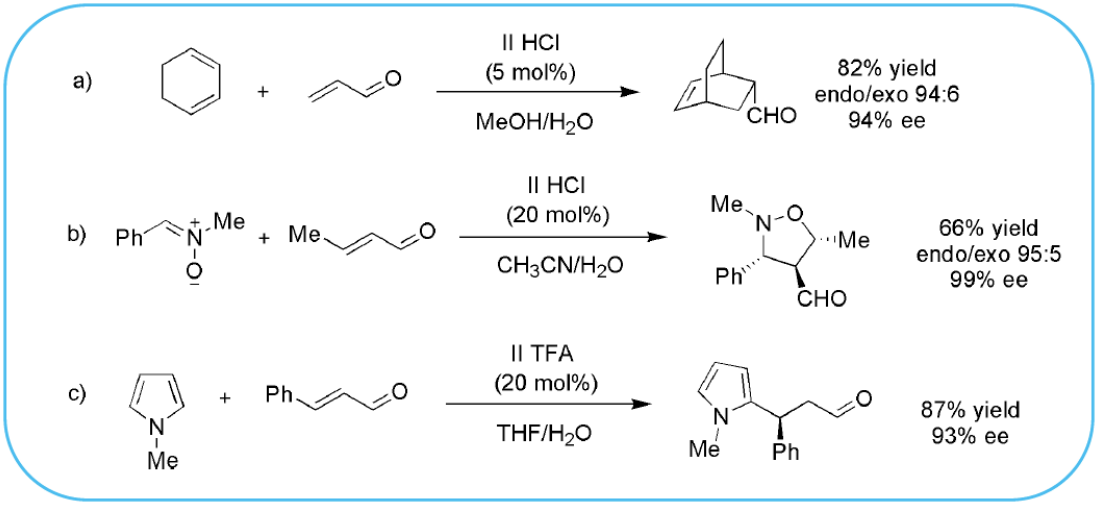
spect to Z; either through a control determined by steric and electronic factors, such as that due to the presence of a phenyl group on the catalyst that can interact with π electrons (*Scheme 1.14*).



Scheme 1.14. Activation mechanism of iminium catalysis.

The activated iminium exists predominantly in the E configuration so as to minimize destabilizing non-bonding interactions between the double bond of the substrate and the group gem-dimethyl of the catalyst. In addition, the configuration of imidazolidinone hides the π face of the intermediate with the benzyl group, leaving exposed the Re face and allowing the nucleophile attack in a highly enantioselective manner.

Further studies performed by MacMillan led to the application of catalysis by imidazolidinone to a wide range of α,β-unsaturated aldehydes transformations (*Scheme 1.15*).[20] It is important to note that the nature of the anion of the catalytically active salt is essential to modulate the reactivity and the stereoselectivity of the process.

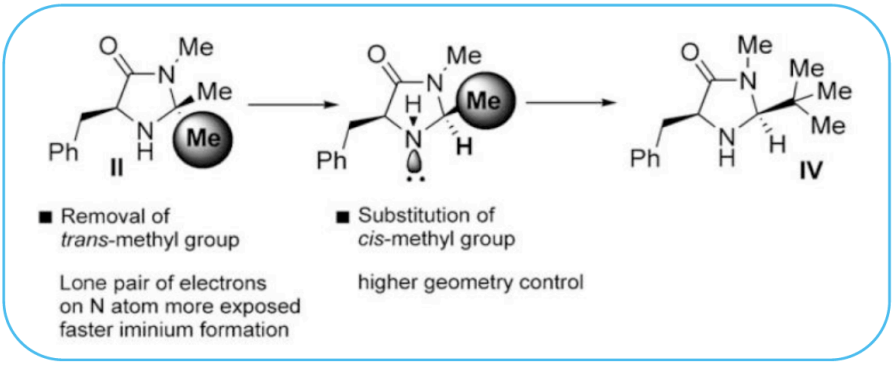


Scheme 1.15. Asymmetric catalysis by oxazolidinone II: a) Diels-Alder reaction,[5] b) cycloaddition [3 +2] with nitrone,[20a] c) Friedel-Crafts alkylation of pyrroles.[20b]

Thanks to the efficiency of imidazolidinone as a catalyst for the addition of pyrroles to unsaturated aldehydes,[20b] the organocatalytic Friedel-Crafts reaction was extended also to heteroatomic indoles and furanosidic derivatives.[21] Since these compounds are less activated nucleophiles, the design of a more responsive and versatile new catalyst was necessary. The kinetic studies on imidazolidinone **II** showed that the rate of reaction was dependant on both the formation of the iminium ion and the C-C bond, so a new catalyst was synthesized.

The replacement of the methyl group with a hydrogen atom has reduced the steric hindrance exerted on the lone pair of electrons on the nitrogen atom. In this way, its nucleophilic character, and consequently the

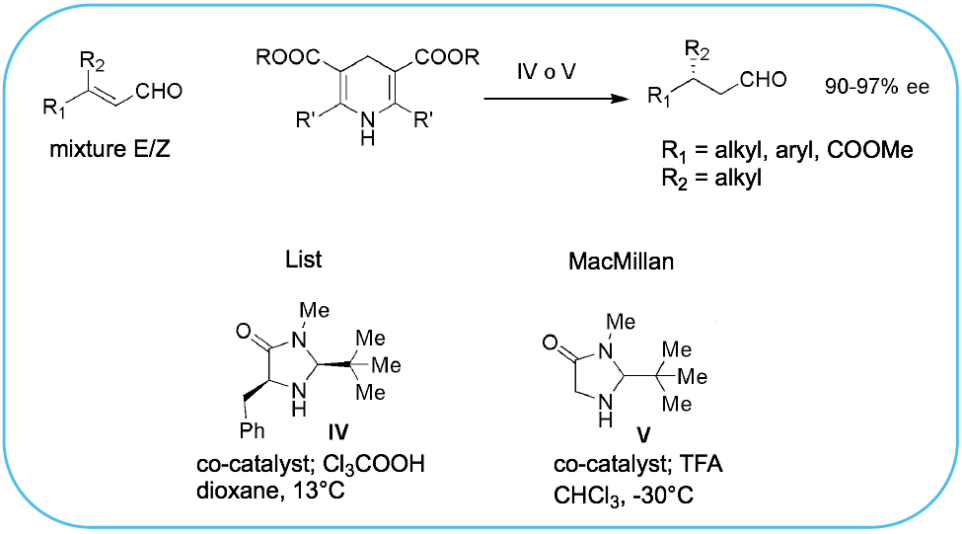
speed of the process, are enhanced, since the formation of the iminium ion is the rate determing step (rds). Similarly, the replacement of cis-methyl group with a bulkier substituent, such as tert-butyl, allows a better control on the geometry of the iminium ion and a better coverage of the blocked *Si* face (*Scheme 1.16*). Finally, the loss of the methyl group in the catalyst **IV** allows the nucleophilic attack to the *Re* face of the iminium ion intermediate, without being prevented from the steric hindrance.



Scheme 1.16. MacMillan catalyst **IV**.

One of the most important applications of this new catalyst was the asymmetric hydrogenation reaction of α,β-unsaturated aldehydes. In terms of sustainability, for instance, the advantage of using the new catalyst lies in the absence of metal impurities, which are present in the hydrogenation reactions catalyzed by metal complexes.

The research groups of MacMillan and List showed that the iminium catalysis is a good strategy for reducing enals with high enantioselectivity, using synthetic dihydropyridines of Hantzsch as hydrides donors (*Scheme 1.17*).[22]



Scheme 1.17. Enantioselective reduction via iminium catalysis

For this reaction, List used the imidazolidinone (**IV**), while MacMillan designed a new catalyst (**V**) aimed to increase the stereoselectivity and efficiency of the process. Interestingly, the E or Z configuration of the double bond in the α, β-unsaturated aldehyde don't affect the stereoselection of the process, leading to the same enantiomer in the product: this is probably due to the fast isomerization induced by the catalyst

(iminium-enamine equilibrium). These findings, that improve the importance of the process, contrast with the majority of hydrogenations mediated by metals, for which the configuration of the double bond affects the enantioselectivity of the reaction.

To extend this type of activation to Michael additions on α,β-unsaturated ketones, it was necessary to introduce new catalysts which might solve the problems related to the formation of highly congested iminium ions and the greater difficulty in controlling the configuration of the intermediate. The imidazolidinone (**VI**), proposed by MacMillan and co-workers, used for the first catalytic Diels-Alder reactions of simple ketones α,β-unsaturated[23] was not widely applicable.

Further expansion in the field of iminium catalysis involved asymmetric additions of acyclic enones, for which Jørgensen and co-workers introduced two new catalysts (**VII**) and (**VIII**)[24] (*Figure 1.1*).

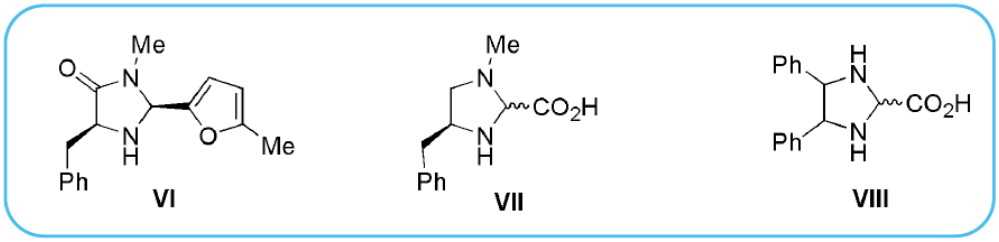


Figure 1.1. MacMillan (**VI**) and Jørgensen (**VII** and **VIII**) organocatalysts.

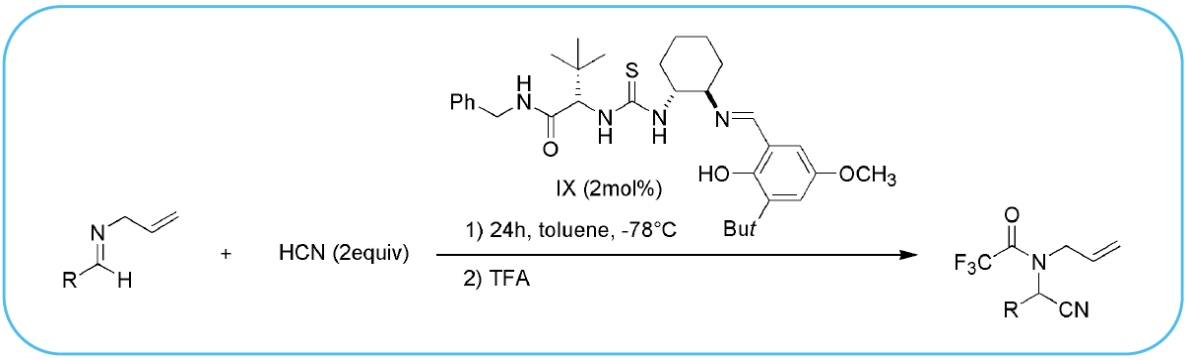
Exploiting these new and easily accessible organocatalysts, highly enantioselective conjugate additions to unsaturated ketones were promoted by various carbogenic nucleophiles, such as nitroalkanes,[24a] malonates,[24b] β-keto-ester[24c] or sulfones,[24d] allowing access to important building blocks for organic synthesis.

By the end of 2004, thanks to the contributions of MacMillan's and Jørgensen's research groups, iminium catalysis acquired a dominant role in asymmetric synthesis, consolidating a method for the catalytic asymmetric functionalization of β-unsaturated carbonyl compounds.

Hydrogen Bonding Catalysis:

At the end of the 90s, two independent studies by Jacobsen[25] and Corey[26] on asymmetric variant of the Strecker reaction, demonstrated, for the first time, the possibility to activate a substrate and coordinate its transition state using organocatalysts through well defined hydrogen bonds on electrophilic imines.

Jacobsen introduced a new organocatalyst (**IX**), obtained from a library of ureidic derivatives, consisting of L-amino acids and non-polar derivatives of salicylaldehyde 3-tert-butyl substituted. Its catalytic activity was demonstrated in the stereoselective formation of the adduct of Strecker, the N-allylbenzaldimine, using HCN as a cyanide source, obtaining the product in high yields and enantiomeric excesses (*Scheme 1.18*).[25]



Scheme 1.18. Stereoselective adduct formation with organ Strecker catalyst **IX**.

This new way of activation is based on the lowering of the LUMO orbital energy of the electrophilic substrate, achieved through the coordination of a lone electron pair present on the heteroatom by the two protons in the ureidic function of the catalyst (*Figure 1.2*).

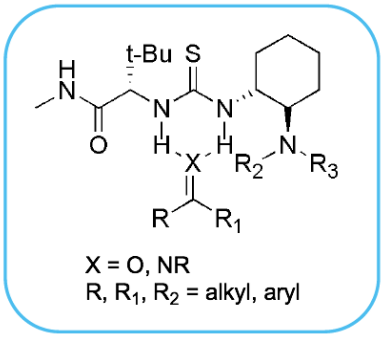


Figure 1.2. LUMO activation of the electrophilic substrate.

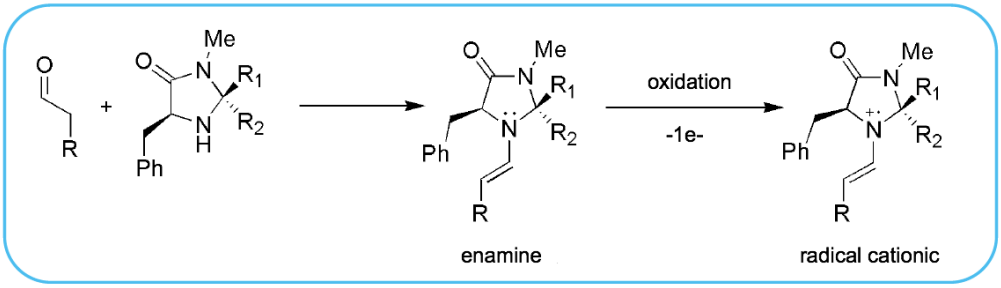
Jacobsen extended this activation mode to other important synthetic reactions, such as the Mannich reaction,[27] demonstrating the versatility of the enantioselective hydrogen bonding catalysis.

This powerful organocatalytic application became the basis for a large and dynamic research area, to such an extent that, nowadays, dozens of new synthetic protocols are based on this new method.

SOMO catalysis:

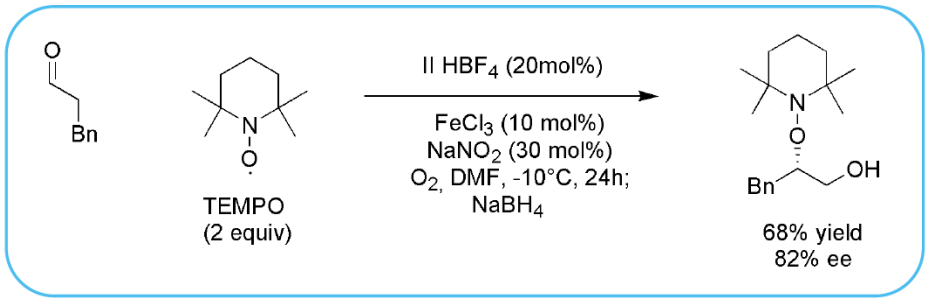
The organocatalytic activation concept defined "SOMO catalysis" (singly occupied molecular orbital) was recently introduced by two simultaneous works reported by MacMillan[28a,b] and Sibi[28c] and links two distant areas of organic chemistry: the organocatalysis and the radicals chemistry.

This way of activation is based on the oxidation of an electron-rich enamine (generated by the condensation of an aldehyde with a chiral amine) with a single electron and leads to the formation of a reactive radical cation with three π electrons. The electrophilicity of the singly occupied molecular orbital (SOMO) of this intermediate, allows its quick reaction on the α carbon of the corresponding enamine with a variety of weak carbon nucleophiles (SOMOphile), leading to alkylation products (*Scheme 1.19*).



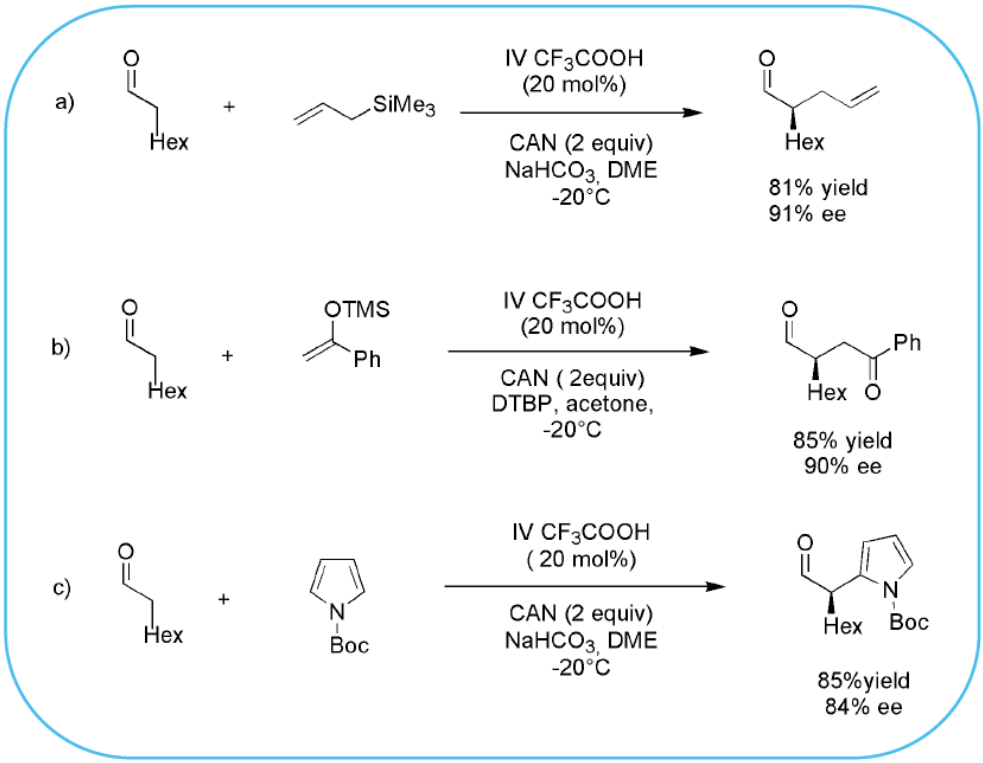
Scheme 1.19. SOMO activation.

Sibi and Hasegawa exploited the SOMO catalysis to perform a stereoselective α-oxygenation of aldehydes, using MacMillan's oxazolidinone (**II**) as catalyst and a substoichiometric quantity of $FeCl_3$ to the single-electron transfer (SET). The presence of $NaNO_2/O_2$ as co-oxidant has been used to generate the radical active intermediate of the enamine (*Scheme 1.20*).[28c] The use of TEMPO, a persistent radical reagent, intercepts the radical cationic species allowing the formation of the desired oxygenated product in good yield and enantioselectivity. Recent studies of MacMillan concerning the mechanism of the $FeCl_3$-catalyzed α-oxyamination of aldehydes are questioning this activation pathway assuming that is not a real SOMO.[29]



Scheme 1.20. Stereoselective α-oxygenation of aldehydes by SOMO catalysis.

MacMillan demonstrated the effectiveness of the new activation strategy by applying the SOMO catalysis to the α-alkylation of aldehydes, obtaining a highly enantioselective process[28a,b] in a new C-C bonds formation reaction. The radical cation intermediate is generated by enamine oxidation (formed by the condensation of an aldehyde with the second generation imidazolidinone catalyst (**IV**)) with cerium ammonium nitrate (CAN). After the reaction with the electron-rich organosilanes (alkylating agents), a second oxidation with CAN occurs, which is followed by the removal of the silyl group to obtain enantiopure α-functionalized aldehydes. This procedure has been applied to asymmetric α-allylation,[28a] α-enolation[28b] and α-arylation[28a] reactions of aldehydes, using the pyrrole N-Boc protected as SOMOphile (*Scheme 1.21*).



Scheme 1.21. SOMO catalysis in asymmetric reactions of α-allylation, α-enolation and α-arylation of aldehydes.

The α C of the aldehyde reacts with nucleophiles, for which it formally has a reversal reactivity of the intermediate enamine (umpolung), that allows to perform reactions otherwise prohibited with the classical catalytical processes. Expanding this strategy, new possibilities for the SOMO catalysis will be offered for different aldehydes, ketones and other classes of typical reagents in radical chemistry.

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New Ferrocenyl Pyrrolidine for Enamine Catalysis

In this chapter is presented the synthesis of new, effective ferrocenyl pyrrolidine catalysts bearing alkyl chains. In this catalyst the preferred conformation of pyrrolidine ring is imposed by the interaction between a ferrocene moiety and the two alkyl groups. In addition, it is proved that the enamine formed by these new organocatalysts is effective in benchmark organocatalytic reactions.

Introduction

The idea to use ferrocene as active framewotk to make new catalysts was has already been studied in our research group.[1] Ferrocenyl pyrrolidine was obtained by a direct nucleophilic substitution of optically enriched ferrocenyl alcohol with benzylcarbamate, in high yield and enantiomeric excess. Unfortunately, when we tried to perform the catalysis with this molecule, only racemic products were obtained in many of the organocatalytic reactions performed.

In the context of an European project,[2] our research group has designed new organocatalytic S_N1-type reactions, new approach to Tamiflu, and finally new organocatalysts. In this project, a specific, more successful design for the ferrocenyl organocatalyst was tried and described in this chapter. It is probably a semantic question to note that the molecule that was obtained contains an iron atom and is not a pure organocatalyst, following the discussion of the chapter 1. On the other hand, Greg Fu introduced very effective catalysts for organocatalysis and described the genesis, synthetic endeavor and performance of the new ferrocenyl organocatalysts.[3] However, in the ferrocene-containing catalysts, the iron center does not playing a role in the organocatalysis itself. It should be noted that the ferrocene moiety can act exclusively as a bulky group, with the metal iron centre being not involved in the reaction. As already shown in the previous chapter, most of the stereoselective organocatalytic reactions are based on the two basic activation modes[4] of enamino[5] and iminum catalysis,[6] as displayed by selected secondary amines bearing a pyrrolidine core.[7]

The nickname "work-horses"[8] in enantioselective organocatalysis was assigned to proline, proline derivatives or other five-membered heterocycles (structures **I-III**, *Figure 2.1*), due to their extensive use in this field. In particular the most commonly used diaryl-pyrrolidine derivatives, the Hayashi and Jørgensen organocatalysts,[9] are silylated at the O-atom (catalyst **II**), which allows for additional structural diversification by employing various R groups at Si. In this case, the presence of the aryl groups is required for the stereo direction. On the other hand, Palomo and co-workers[10] have demonstrated the use of pyrrolidine bearing long alkyl chain for reaction carried out in the presence of water. Maruoka has shown that a 2-tritylpyrrolidine is also a quite effective organocatalyst,[11] and more recently, Bolm, Christmann and Strohmann, have independently synthetized new organocatalysts based on silylated pyrrolidines.[12] In most of the examples cited, the presence of a diaryl or triaryl moiety is required to fix the conformation of the enamine, and to effectively shield one face from the attack of electrophiles.

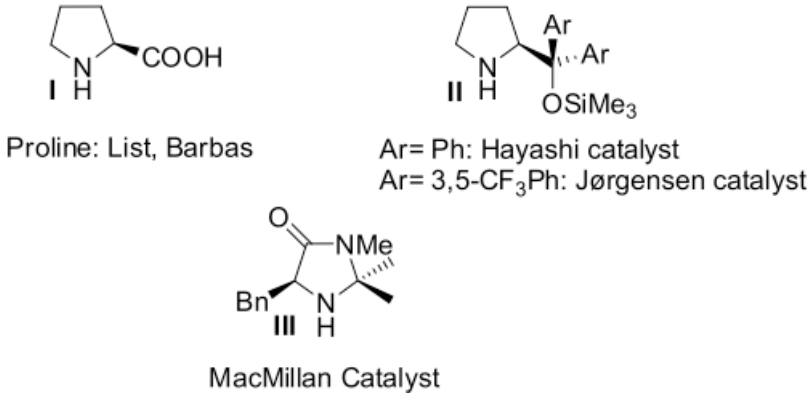


Figure 2.1. The catalysts extensively used as "working horse" in organocatalysis

The "geminal-diaryl effect" (stereodirection through conformational fixation) is a well-known result of bulky substituents, and it has been exploited throughout the field of stereoselective organic synthesis.[13] Not only are two aryl groups, like phenyl, capable of fixing the conformation around a neighbouring single bonds, but they also become powerful stereodirectors in chiral molecules, where the two aryl groups become diastereotopic, as in BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)[14] or in TADDOL (α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols).[15] Even in the modified Evans auxiliary DIOZ (3-(1-methylethyl)-5,5-diphenyloxazolidin-2-on), the diastereotopic Ph groups improve functional-group stereoselectivity.[16]

Our idea, proposed in the Cataflu.or[2] project and investigated in this chapter, was to introduce a ferrocene moiety in the chiral framework of pyrrolidine. In fact, ferrocene can be considered a "privileged framework" for the construction of effective chiral ligands.[17] Pyrrolidine bearing a ferrocene moiety has not been considered yet as a viable tool to control catalysts conformation in enamine/iminium catalysis.[18]

Results and Discussion

As mentioned in the introduction, a first attempt to generated an effective catalyst miserably failed. Therefore, in order to avoid another failure and to direct in some way our synthetic efforts we decided to use a different approach. As we have mentioned earlier, our aim was to prepare a new ferrocenyl pyrrolidine able to fix a conformation of enamine and shield, by a substituent, one enamine face. To designing some possible structures, we considered, at first, the frame of the Hayashi-Jørgensen catalyst, and we replaced the $OSiMe_3$ group with a ferrocenyl group. In order to avoid the preparation of many derivatives, and the attempts to separate the enantiomers by chemical resolution, we took advantage of a careful theoretical investigation for the initial design of the catalyst. This molecule possesses two mayor conformational degrees of freedom (CDF) associated to the dihedral angles ω, defined as C5-(C1-C6)-C7, and ϕ, defined as C1-(C6-C7)-N8 (*Figure 2.2*).

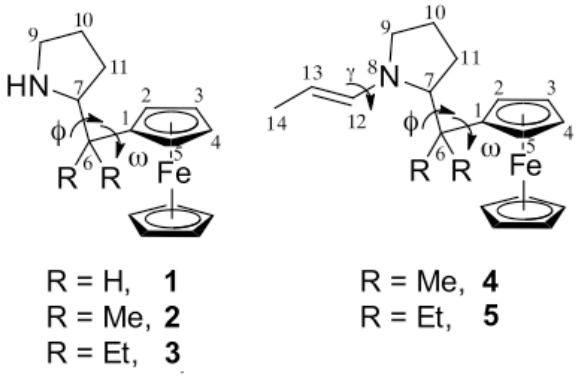


Figure 2.2. Geometrical parameters defining the conformational space of the ferrocenyl pyrrolidine catalyst

To discover the conformation equilibrium of the investigated catalyst, accurate QM calculations, performed by Dr. Marco Stenta (EPFL, Lausanne), were reemployed (RIJCOSX-B3LYP/def2-TZVPP optimization)(*Figure 2.3*). Here, only some of the major results of all the data and details obtained by Dr, Stenta are mentioned. The details of the choice of the functional for DFT calculation will not be discussed in this thesis: however, the theoretical investigation done by Dr. Stenta revealed precious to our approach, since, thanks to his work, we considerably reduced the time and efforts for the preparation of an effective catalyst. Since the full exploration of the conformational space of the enamine adduct would have required an overwhelming effort, a different strategy was put in place. The enamine was built stepwise by adding molecular fragments to an initial ferrocene; at each step, the relevant degrees of freedom were explored and the lowest conformer was underwent the following step. Besides a noticeable saving in computing time, this approach provided useful insights on the effects of each molecular fragment to the overall conformational equilibrium. Both metal-carbon (2.09 Å) and cyclopentadienyl carbon-carbon distances, obtained by optimization of eclipsed and staggered conformations of the unsubstituted ferrocene (model **Fe_1** and **Fe_2** in ES), were in close agreement with those reported previously.[19] The optimized staggered conformation (Fe-C = 2.081 Å, C-C = 1.422 Å) was used to build a tert-butyl derivative (model **M1**, ES) in order to study the energy difference between two possible rotamers **M1_1** and **M1_2** (ES). Geometry optimizations revealed that **M1_1** is a stable minimum on the potential energy surface (PES); no other stable conformers were individuated. The substitution of a methyl with the pyrrolidine ring increased the number of possible conformers. Three stable rotamers were identified by relaxed scan along the ϕ dihedral angle, with the three minima lying in an energy range as narrow as 1.44 kcal mol^{-1}. Alkyl and aryl groups were, then, introduced to assess the influence exerted on this conformational equilibrium by C6-substituents of different size and shape. We expected to find a direct and linear correlation between the size of the R groups and their capability in controlling the conformational equilibrium. Quite remarkably, we noticed that the energy spread of conformers was significantly reduced by aryl groups, while much smaller and simpler alkyl chains were able to favour only one conformer (**M3-S**, ES) over the possible ones. In particular, ethyl moieties showed the best compromise between effectiveness and size.

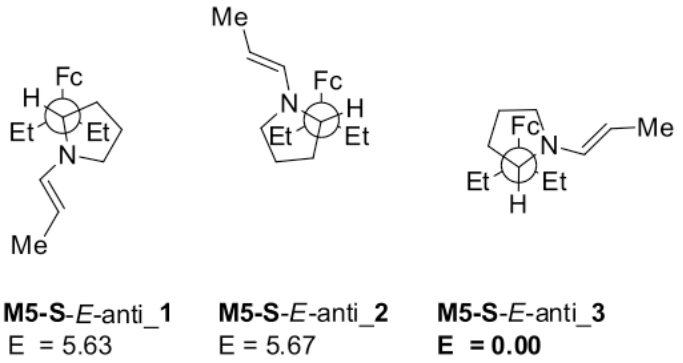
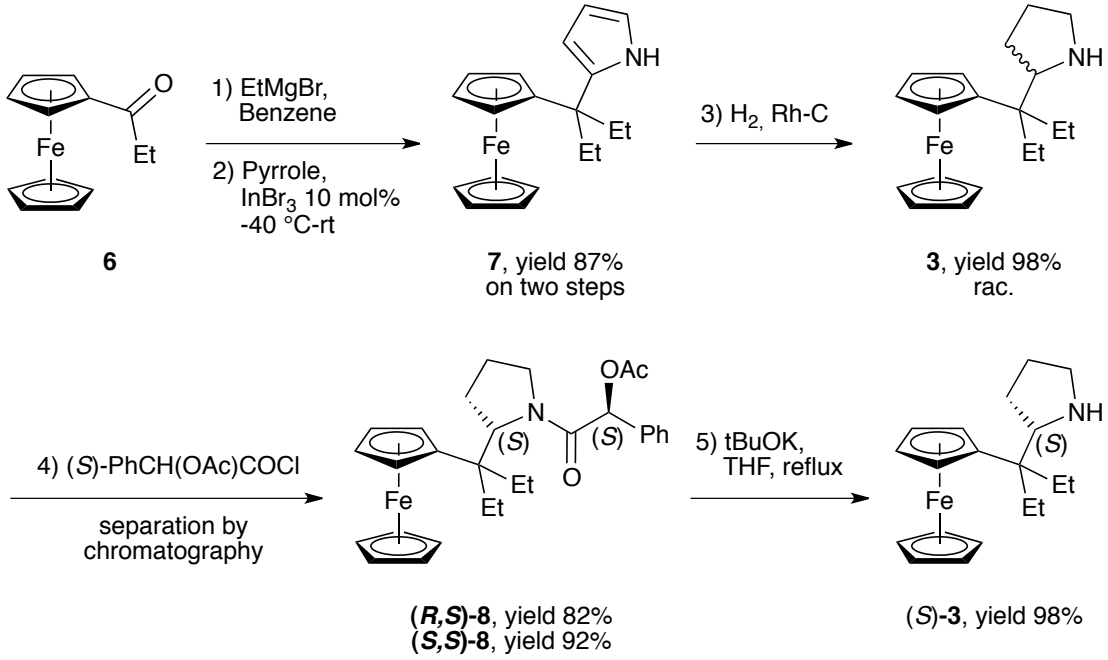


Figure 2.3. Preferred conformations of the enamine **5**, calculated at the RIJCOSX-B3LYP/def2-TZVPP level. Energies in kcal mol^{-1} (relative to the lowest energy structure)

The rotational equilibrium around the C6-C7 bond was investigated for both methyl- (**M4-S**, ES) and ethyl- (**M5-S**, ES) substituted enamine adducts. In the presence of methyl substituents, the energy spread between rotamers is as small as in the pyrrolidine substituted system (**M2-S**). The presence of an ethyl group strongly reduces the conformational freedom around this bond, as only one rotamer was predicted to be populated. In this rotamer, one of the ethyl groups is hindering the bottom face of the enamine **5**.

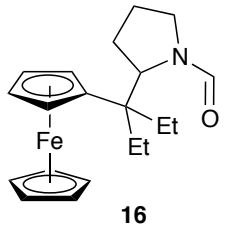
Based on the theoretical analysis, We selected the diethyl ferrocenyl pyrrolidine **3** as a candidate for the synthetic evaluation. The synthesis of the enantiomerically pure **3** was devised as reported in *Scheme 2.1*.



Scheme 2.1. Synthesis of racemic and enantioenriched ferrocenylpyrrolidine

The ferrocenyl ethyl ketone **6**[20] was transformed in a straightforward manner to the tertiary alcohol, that was treated with pyrrole in the presence of a catalytic amount of $InBr_3$ (10 mol%) to give the desired **7** in high yield.[21] No trace of β-pyrrole isomer was detected. Due to the reactivity of pyrrole the reaction was conducted using an excess of pyrrole at low temperature. The compound **7**, after chromatographic purification, was hydrogenated with 1 atm of hydrogen by using rhodium on graphite[22] as catalyst to give the racemic pyrrolidine **3** in high yield: this was, then, separated by the synthesis of the corresponding *O*-acetyl-

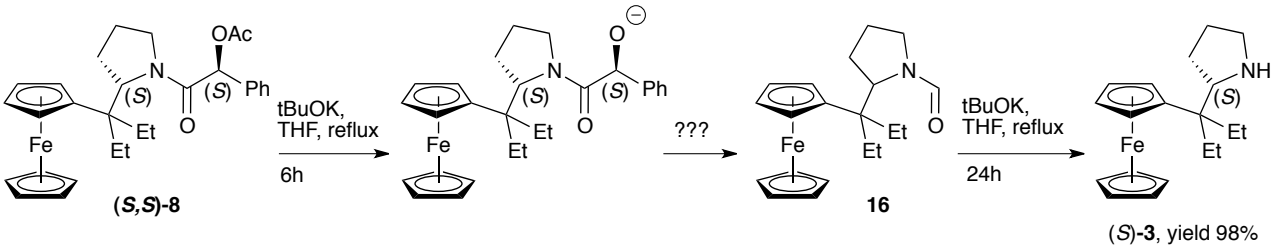
mandelic amide **8**. The mandelic amide was chosen on the basis of the previous experience gained by our group.[23] The chromatographic separation by preparative TLC was quite straightforward. The hydrolysis of the isolated diasteroisomers of **8** revealed quite difficult. In standard reaction conditions and in the presence of excess of KOH or NaOH no reaction was observed. However, by the treatment of the amide with an excess of *t*BuOK in THF at refluxing condition[24] for 36 hours, we were able to cleave the amide bond. Unexpected and intringuing is the mechanism of the reaction, which is probably determined by a two steps cleavage. In fact, we were able to isolate, as a partial product of the hydrolysis, the corresponding formyl ferrocenyl pyrrolidine **16** (*Figure 2.4*).



16

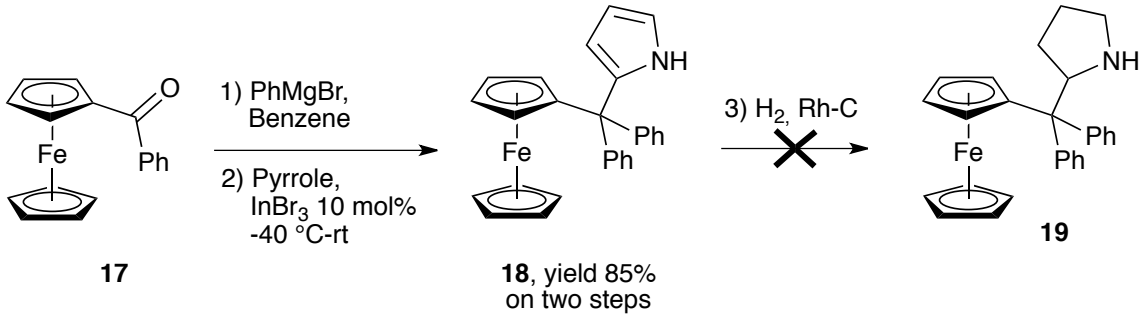
Figure 2.4

It's quite hard to propose a reasonable mechanism for the cleavage. The acetyl group is immediately cleaved in the reaction conditions and probably the anionic intermediated is transformed in the corresponding formyl pyrrolidine. If the reaction is heated for prolonged reaction time, the intermediate decomposes to the desired ferrocenyl compound that was isolated after quenching with water. We tried to propose several mechanisms aimed at explaining this particular hydrolysis, but further experimental work with deuterated products is necessary in order to give a rational explanation for this crucial transformation (*Scheme 2.2*). In any case, the desired enantioenriched 2-(diethylferrocenyl)pyrrolidine **3** was isolated in satisfactory yields.



Scheme 2.2

However other attempts were made to produce different catalysts bearing two phenyl groups, such as the catalys **19** (*Scheme 2.3*). Unfortunately, the reduction of the pyrrole was not possible in many of the reaction conditions and catalyst tried, probably due to the enhanced sterical hindrance.



Scheme 2.3

The absolute (*S*,*S*) configuration of the more retained diastereoisomer was established by X-ray analysis (ES for further detail). The X-ray structure of the mandelate was almost identical to the structure of the lowest energy conformer (*Figure 2.5*).

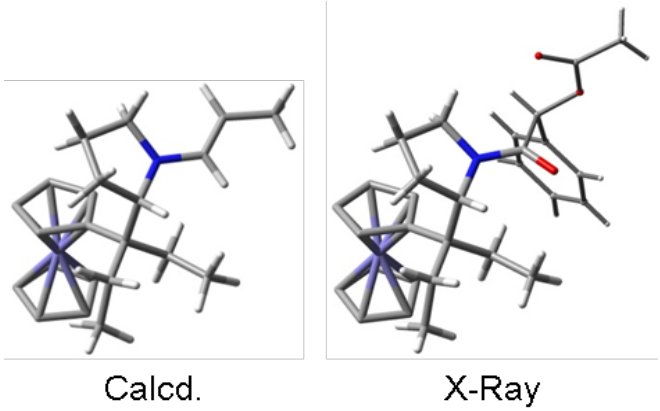
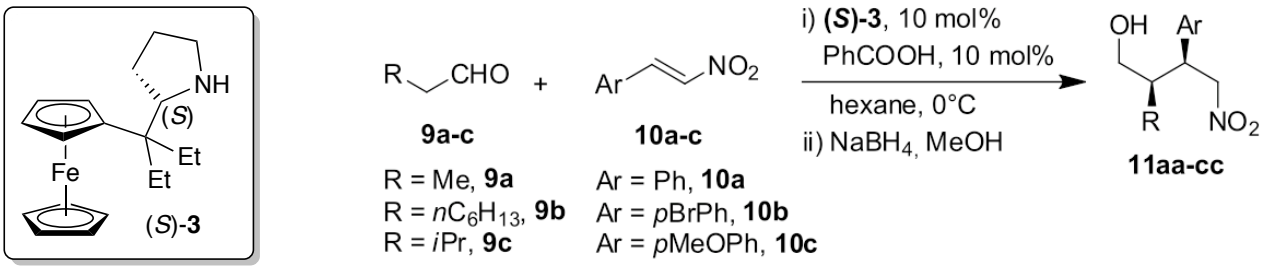


Figure 2.5. Configurational determination of the slow eluted amide obtained by reaction of **3** with (*S*)-OAc-mandelic chloride

Next, (*S*)-2-(diethylferrocenyl)pyrrolidine **3** (96-99% ee as proven by its HPLC analysis after derivatization to the corresponding 3,5-dinitrophenylamide; see ES for details), was used in stereoselective organocatalytic reactions. We select the asymmetric Nitro-Michael addition[25] reactions of aldehydes **10a,c** to nitro alkene **11a,c** (*Table 2.1*).

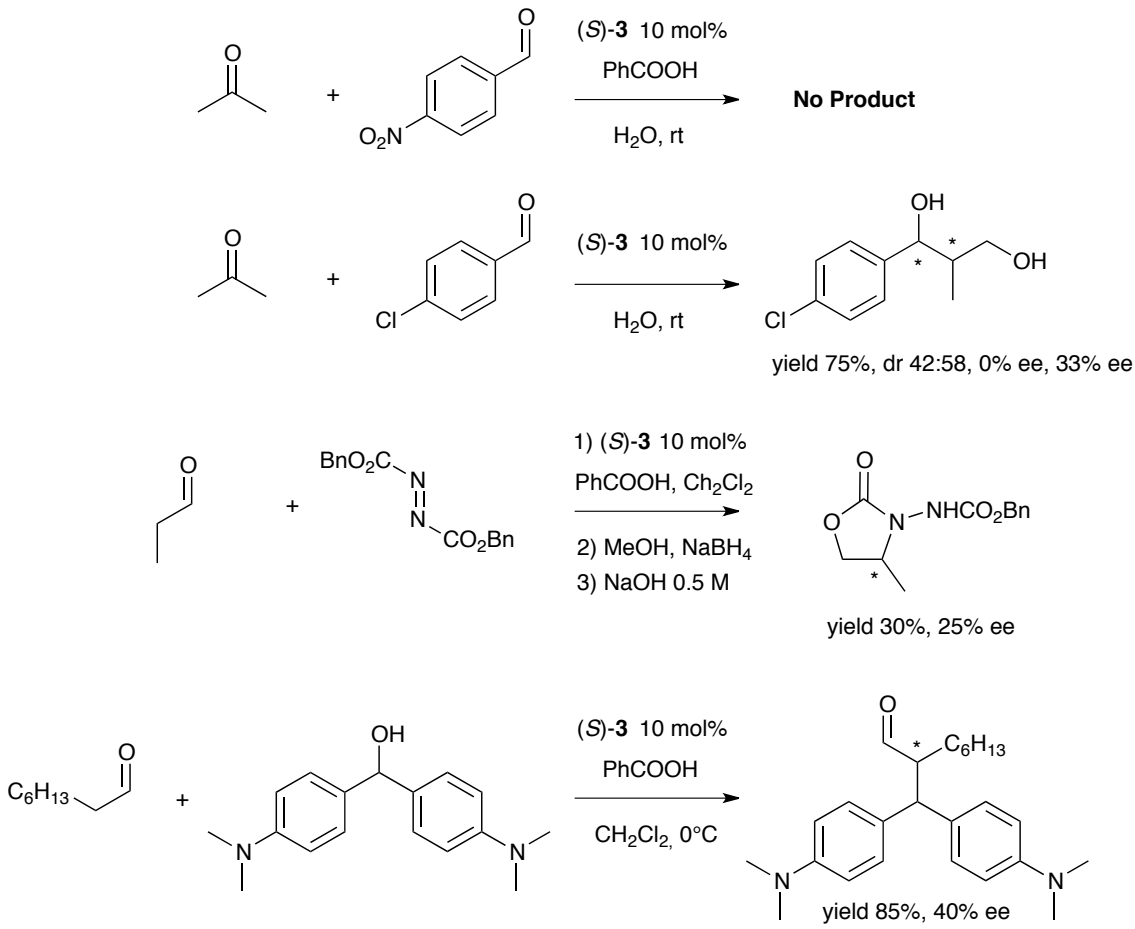
Table 2.1. Organocatalytic addition of aldehydes to nitroalkenes promoted by **3.**



Entry[a]	Product	T, h	Yield[%][b]	d.r.[c]	*ee* % *syn*[d]
1	**11aa**	14	73	8:1	88
2[e]	**11aa**	14	75	8:1	95
3	**11ba**	16	70	10:1	88
4	**11ca**	60	74	24:1	89
5	**11ab**	20	98	30:1	87
6	**11ac**	40	98	12:1	91

[a] The reactions were performed at 0 °C with 1 equiv. of nitroalkene **11**, 10 equiv. of aldehyde **10**, in the presence of 10 mol% of catalyst (S)-**3** (96% ee) and the reactions were run until completion checked by TLC (16-60 h). [b] Yield after chromatographic purification. [c] For all the reactions the d.r. (syn vs anti) was measured by 1H-NMR and HPLC analysis. [d] Determined by chiral HPLC analysis. [e] (S)-**3** of 99% ee was used for the reaction.

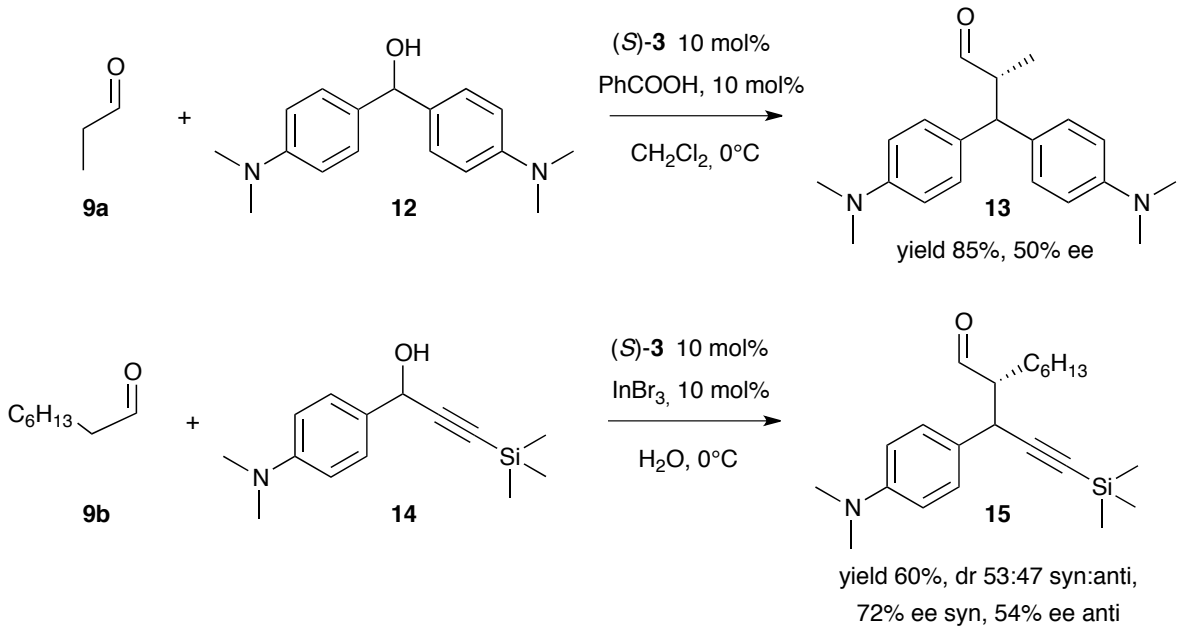
Solvent screening experiments showed that hexane is the optimal solvent, as it gives the best results in terms of stereoselectivity and yield. To our delight, the excellent results, obtained under selected reaction conditions (*Table 2.1*), confirmed our hypothesis about the ability of the catalyst in discriminating one face of the enamine. However we have investigated also the aldolic and azo-coupling reaction (*Scheme 2.4*) and in this case the enantiomeric excess obtained in the model reaction was quite modest.



Scheme 2.4

It should be noted that, differently from the Hayashi-Jørgensen catalyst, the ferrocenyl compound **3** is a remarkably robust and recoverable catalyst, and is not easily decomposed by acids or bases. In the cataflu.or project,[2] we proposed the use of S_N1-type reaction if organocatalysis. Recently, the direct substitution of allylic, benzylic, and tertiary alcohols has been achieved via an S_N1-type reaction with a catalytic amount of Brønsted or Lewis acids.[26] When a new stereogenic center is formed, most of these transformations produce the desired product in racemic form, as carbenium ions are involved.[27] Although diastereoselective addition to a prostereogenic carbenium ion, generated by suitable precursors, was described recently, stereoselective processes involving an S_N1-type of reaction were still an unexplored research area. The arsenal of activation modes available in organocatalysis[28] can be used to set up suitable reaction conditions in which chiral nucleophiles (enamine catalysis) or chiral electrophiles (iminium catalysis, chiral counter-ion catalysis) can be easily generated.

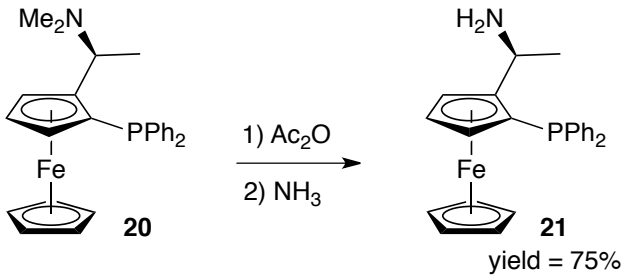
The use of organocatalytic stereoselective S_N1-type reactions was recently described. An overview of the recent results and the new directions opened up along with the most recent results in this new research area was recently reported.[29] In the catalytic S_N1-type of reaction, a carbenium ion is generated in the presence of an organocatalyst able to form enamine catalysis. Therefore, We tested the performance of **3** in organocatalytic S_N1-type alkylations[30] of enamines with bis[4-(dimethylamino)phenyl] methanol (*Scheme 2.5*). This alcohols is a benchmark reagent in this kind of organocatalytic reaction. The key-steps in many organocatalytic cycles are electrophile–nucleophile combinations and will be detailed in the next chapter.



***Scheme* 2.5.** S_N1–type reaction of the alcohols **12** and **14** with the aldehydes **9a** and **9b** promoted by 10 mol% of the catalyst **3**

Dr. Marco Stenta has also performed some preliminary DFT calculations in order to clarify the selectivity of the nitro-Michael reaction and to understand how the ferrocene moiety is exercising the effective shield of one face of the enamine. It is worth to mention that the theoretical investigation of the reaction, recently performed, showed some surprises and revealed once more that organocatalytic reactions are just apparently quite simple.[31] The conformational constraints imposed by ferrocene also drive the conformation of the ethyl groups, thus resulting in the effective screening of one face of the enamine intermediate. The less hindered enamine face reacts with the nitroderivative giving a zwiterrionic intermediate. These results confirm the effective shield of the ferrocene group determined by its capability to control conformational issues in the enamine intermediate.

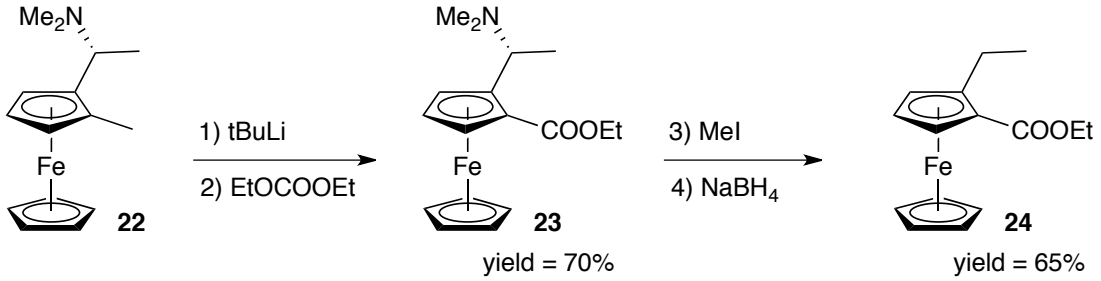
Further studies were carried on with other ferrocene derivatives. First of all, the compound **20** (available by a generous gift of "JSM Catalysis") was used to generate the primary amine **21** (*Scheme 2.6*)



***Scheme* 2.6**

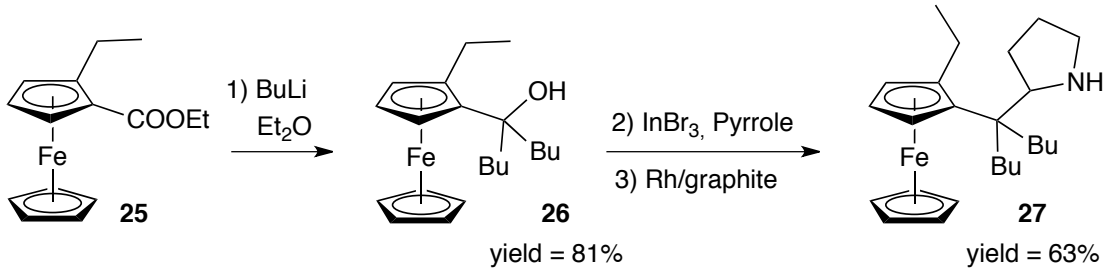
The catalyst **21** was used in the S_N1-type reaction of ketone with alcohols, with the hope to generate the corresponding enamine of ketones. Although the desired product was observed by TLC and by GC analysis, many other by-products were present in the reaction mixture. In addition, both the yield and the enantiomeric excess of the isolated product were quite poor. The other compound **22**, generously given by "JSM Catalysis", was transformed into the compound **23**, by lithiation with tert-BuLi and following reaction with

diethyl carbonate. Then the compound was alkylated with MeI and the trimethylamino group eliminated by a reduction with $NaBH_4$ (*Scheme 2.7*).



Scheme 2.7

We tried to avoid the separate diasteroisomeric amides, previously used for the synthesis of the catalyst **3,** (*Scheme 2.8*) by the synthesis of different enantioenriched ferrocenyl precursors. By starting from the compound **25**, the synthesis of the desired compound **27** was obtained following the reaction scheme described earlier.

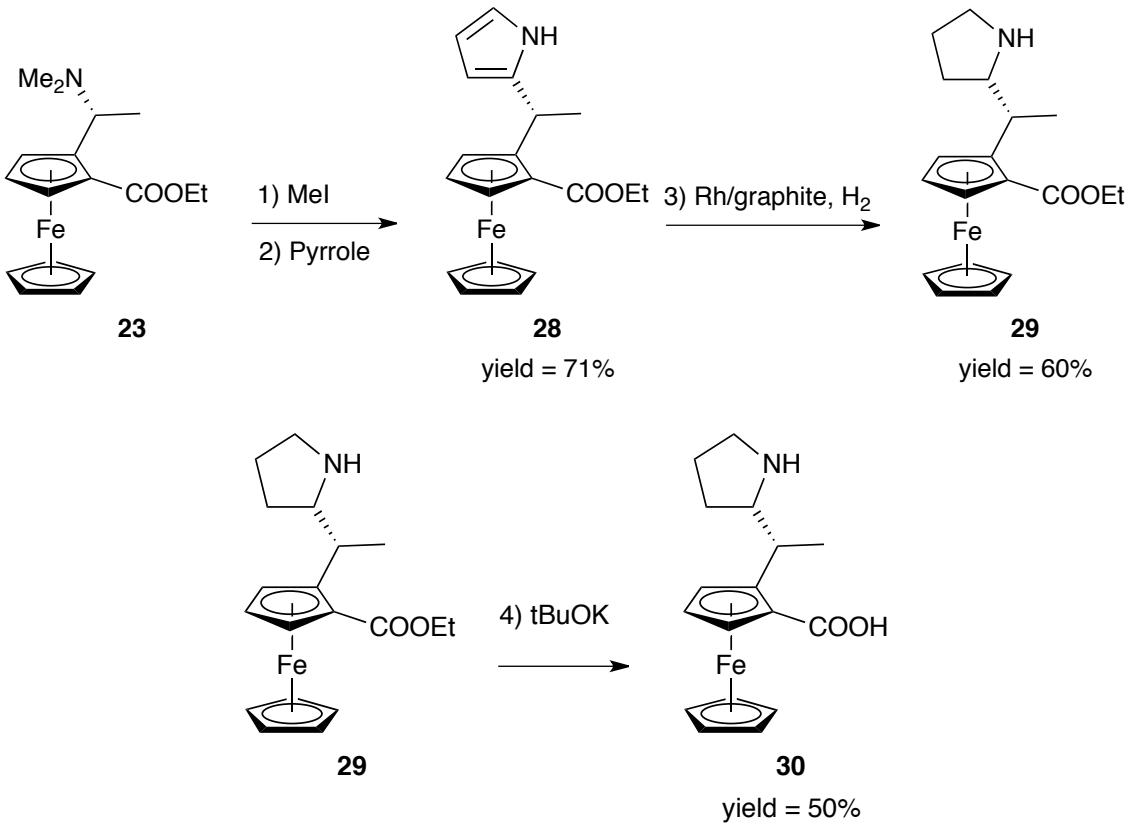


Scheme 2.8

Unfortunately, the compound **27** was obtained as an inseparable mixture of two diastereoisomers and the synthesis didn't give a preferential formation for one diastereoisomer. As expected by the reaction of **27** as catalyst in nitro-Michael afforded very modest results (dr 89:11, ee 11% for the *syn*, 4% for the *anti*). Probably, this was determined by the presence of the two diastereoisomers and by the not effective shielding of the face of the enamine.

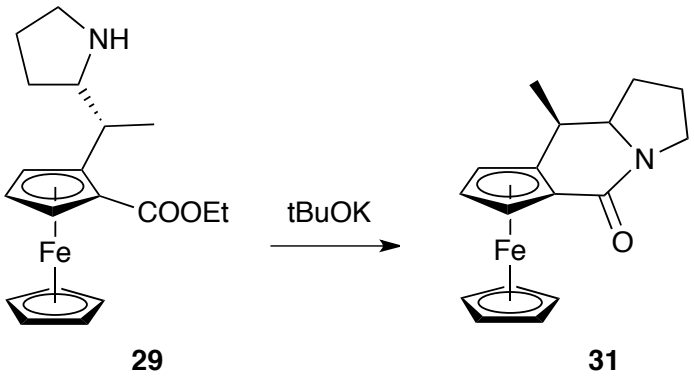
We tried to separate the obtained diastereoisomers by attempting some functionalizations as already done for catalyst **3**, but in this case the two diastereoisomers were not separable.

Starting from the product 23, We tried to prepare another derivative, with the aim to separate the obtained diastereoisomers without using a derivatization (*Scheme 2.9*).



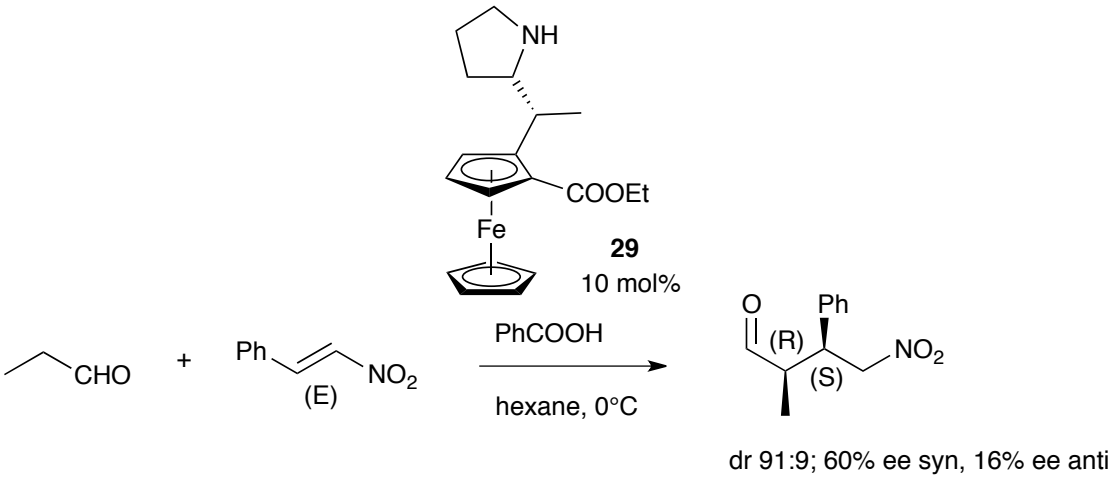
Scheme 2.9

Interestingly, the direct substitution of the ammonium salt occurs with pyrrole at 90 °C, without any use of Lewis acids. The reaction occurs with retention of stereochemistry at the stereogenic center. The successive hydrolysis of **29** was quite complicate and occurred only in the reaction conditions that were optimized for the synthesis of **3**. In this case, the two diastereoisomeric amino acids derivatives **30** were separable by TLC. However, when the reaction was repeated and investigated again, only the formation of a cyclic by-product **31** was observed. We tried several time to repeat the hydrolysis, but the undesired product always prevailed (*Scheme 2.10*). At present, We have no possible and easy explanation for the failure of the reproducibility of the reaction.



Scheme 2.10

Taking into account the difficulties encountered with the separation of the compounds, We decided to perform the model nitro-Michael reaction with the catalyst **29** (*Scheme 2.11*)

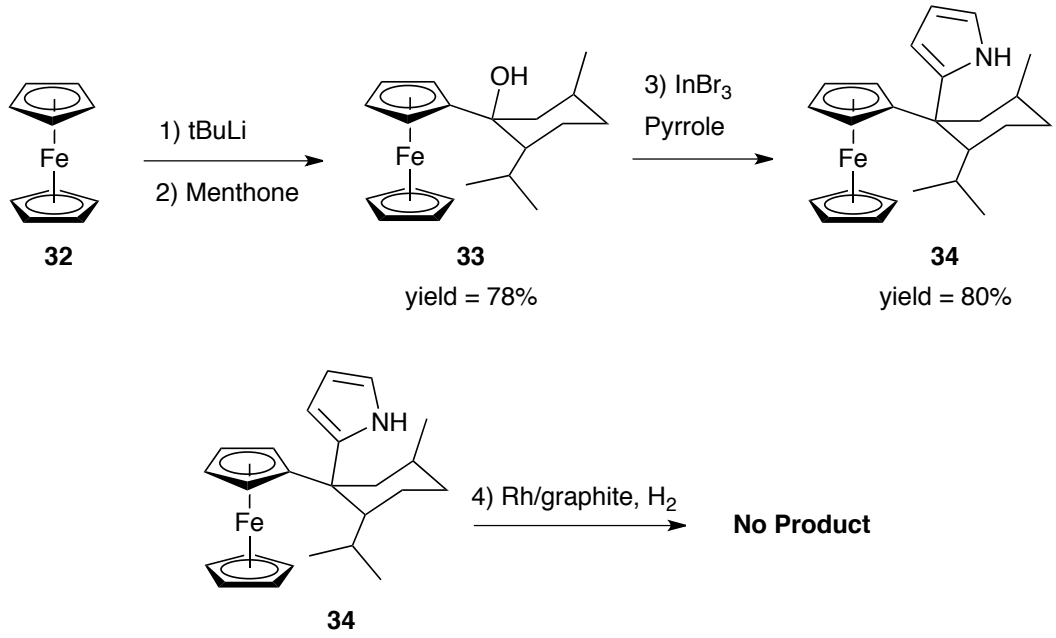


Scheme 2.11. Nitro-Michael model reactions

The enantiomeric excesses obtained were quite low compared to the previous results. The presence of a planar stereogenic unit (introducing an ester group we obtained one favored diastereoisomer) did not improve our results. Probably, in this case the presence of the ester group favours the reaction and exerts a selection on the enamine face. Once again, if the diastereoisomers are not separated after the reduction, the effectiveness of the catalyst is quite modest.

As the main problem to overcome was to avoid the separation of diastereoisomer, we tried another strategy: the reaction of the ferrocene with a chiral ketone, to obtain a mixture of diastereoisomeric alcohol. Whether the alcohols are separable or not, it's not important, because the successive reaction, in which a carbenium ion is formed, is controlled by the presence of the groups at the stereogenic carbon and, starting from the mixture, is stereoconvergent. The nucleophilic addition of nucleophiles to chiral carbenium ion has been investigated by Bach.[32]

The chiral ketone We selected was the commercially available (-)-Menthone. The addition of the ferrocene to the ketone is quite straightforward and occurs to give the compounds as a mixture of diastereoisomers (*Scheme2.12*).



Scheme 2.12

The reaction of the alcohol **33** with pyrrole was carried out with indium and the reduction of pyrrole was attempted with Rh/graphite, as previously described. Unfortunately, due to the major sterical hindrance, the reaction was not successful. Increasing the pressure of hydrogen did not give any reaction. For future investigation, our group wants to study this and other reactions with chiral electrophiles more in detail, in order to take advantage of the ferrocene moiety for the synthesis of different effective organocatalysts.

Conclusions

In conclusion, we developed a new 2-(diethylferrocenyl)pyrrolidine catalyst, active in benchmark organocatalytic reactions. The ferrocenyl moiety, in combination with simple ethyl chains, is capable of fixing the enamine conformation addressing the approach trajectory of the nucleophile reaction partner. The results presented here represent an interesting proof-of-concept, showing for the first time the remarkable effectiveness of the ferrocenyl moiety in providing enantioselectivity through conformational selection. This approach could be viably employed in the rational design of ligands for organometallic or organocatalytic reactions.

Experimental Section

General Methods.

^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian MR 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: m/z (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Determination of enantiomeric excess were performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using a Daicel Chiralpak columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and n-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (NaD line), specific rotation was expressed as deg $cm^3g^{-1}dm^{-1}$ and concentration as gcm^{-3}. Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected.

Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification. Deuterated Chloroform was used as received without further purification.

Conformational Investigation of Ferrocenyl derivatives.

On the basis of the commonly accepted catalytic mechanism for the reaction discussed, the chiral pyrrolidine (catalyst) forms a covalent adduct with the nucleophilic substrate (an aldehyde in *Figure 2.5*). The resulting enamine reacts with the electrophilic reaction partner to generate an iminium ion, the hydrolysis of which yields the product(s) and restores the catalyst. The level of stereogenic control depends on the geometry of the enamine intermediate; this, in turn, affects the approach trajectory of the incoming electrophile. Substituent and other factors determine the stereogenic outcome of the reaction by stabilizing different transition states for the reaction between enamine and its electrophilic partner. In all cases, the conformational freedom of the enamine intermediate should be restrained to achieve a reasonably high stereocontrol. In fact, a too flexible structure can easily access a multitude of different conformations, each with different geometrical and electronic features. Such a flexible structure is thus incapable of selecting a unique approach trajectory of the electrophile. In other terms a system existing in different conformational states does not stabilizes one single transition state for the reaction, with the results that different products (stereoisomers) are obtained. In order to exert a control on the reaction outcome the conformational freedom of the substituents of the catalyst has to be restrained. The use of bulky groups has been proposed as a possible strategy to obtain a conformational population dominated by a single species. As a matter of fact the strategy is not simple and the use of bulkier (and more complex) substituents can have the opposite effect, thus populating a plethora of local minima, each contributing with mixed effects to the reaction.

As confirmed by many recent studies in the field, computational chemistry can help rationalizing the effects of substituents in this family of organocatalytic reactions.[33] What's more, molecular modeling can provide guidelines to rationally design catalysts with desired properties, thus avoiding or, at least, limiting the need of blind substituent screening at the lab bench, with a strong saving of resources.

A rational approach based on quantum chemistry was adopted in this case to design a pyrrolidine catalyst featuring a 1,1-disubstituted-ferrocenylmethyl group (*FC, Figure 2.7*). In particular the attention focused on the nature of the two R substituents of the methyl group: the goal of the computational investigation was set to find the smallest and simplest decoration capable of achieving good stereocontrol in the reaction with benchmark substituents. In order to do so, the conformational freedom of several systems, each featuring different R groups, was investigated in silico, and the best candidates were sent forth for synthesis and then for catalysis tests. The results from calculations suggested that substituents larger than ethyl have a detrimental effect on the conformational uniqueness of the enamine intermediate. On the other hand, hydrogen and methyl provided no sufficient control in the orientation of the ferrocenyl moiety with respect to the pyrrolidine ring. As it turned out from experiment, a pair of ethyl substituents provides the optimal compromise between size/complexity and conformational control. In this case a single conformer dominates the conformational population, as confirmed by the X-ray structure of the mandelate derivative (*Figure 2.5*).

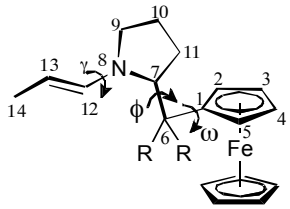


Figure 2.6. Schematic representation of ferrocenyl derivatives (FC) investigated

FC molecules possess two major conformational degrees of freedom (CDF) associated to the dihedral angles ω, defined as C5-(C1-C6)-C7, and ϕ, defined as C1-(C6-C7)-N8 (*Figure 2.6*). To reduce the complexity of the problem ad to avoid a full conformational search on each compound, the preferred conformational basins were individuated using a "progressive growth" approach: the conformational preference of progressively complex molecules was defined on the basis of the results obtained with simpler models. Both metal-carbon (2.09 Å) and cyclopentadienyl carbon-carbon distances obtained by RIJCOSX-B3LYP/def2-TZVPP optimization of eclipsed and staggered conformations of un-substituted ferrocene (model Fe_1 and Fe_2 in *Figure 2.7*) were in close agreement with those reported previously.[19] The optimized eclipsed conformation (Fe-C = 2.081 Å, C-C = 1.422 Å) was used to build a tert-butyl derivative to study the energy difference between rotamers M1_1 and M1_2 (*Figure 2.7*). Geometry optimization revealed the M1_1 to be a stable minimum on the potential energy surface (PES). On the contrary, conformation M1_2 was identified as a transition state ($\Delta E‡$ = 3.8 kcal mol^{-1}) by performing a relaxed scan along the ω angle (followed by TS optimization); no other stable conformers were individuated.

The addition of a pyrrolidine ring to the C6 atom leads to a chiral center and increases the number of possible conformers. The model M2-S (S referring to the absolute configuration of the C7 carbon atom, S) was used to investigate the conformational preference across ϕ. Three stable rotamers were identified by relaxed scan along the ϕ dihedral angle; further geometry optimization showed the three minima to lie in an energy range as narrow as 1.44 kcal mol^{-1}, with M2-S_2 being the most populated conformer (*Table 2.3*). Methyl groups (model M3-S) were introduced in place of ethyl groups (of M2-S) to assess the influence the size of C6 substituents exerts on this conformational equilibrium. The energy spread of the three stable rotamers, as located by geometry optimization, was larger for M3-S than for M2-S, as caused by the size of R

groups. Moreover the conformational population is shifted in favor of M3-S due to the combined effect of the size of R groups and ferrocenyl moiety.

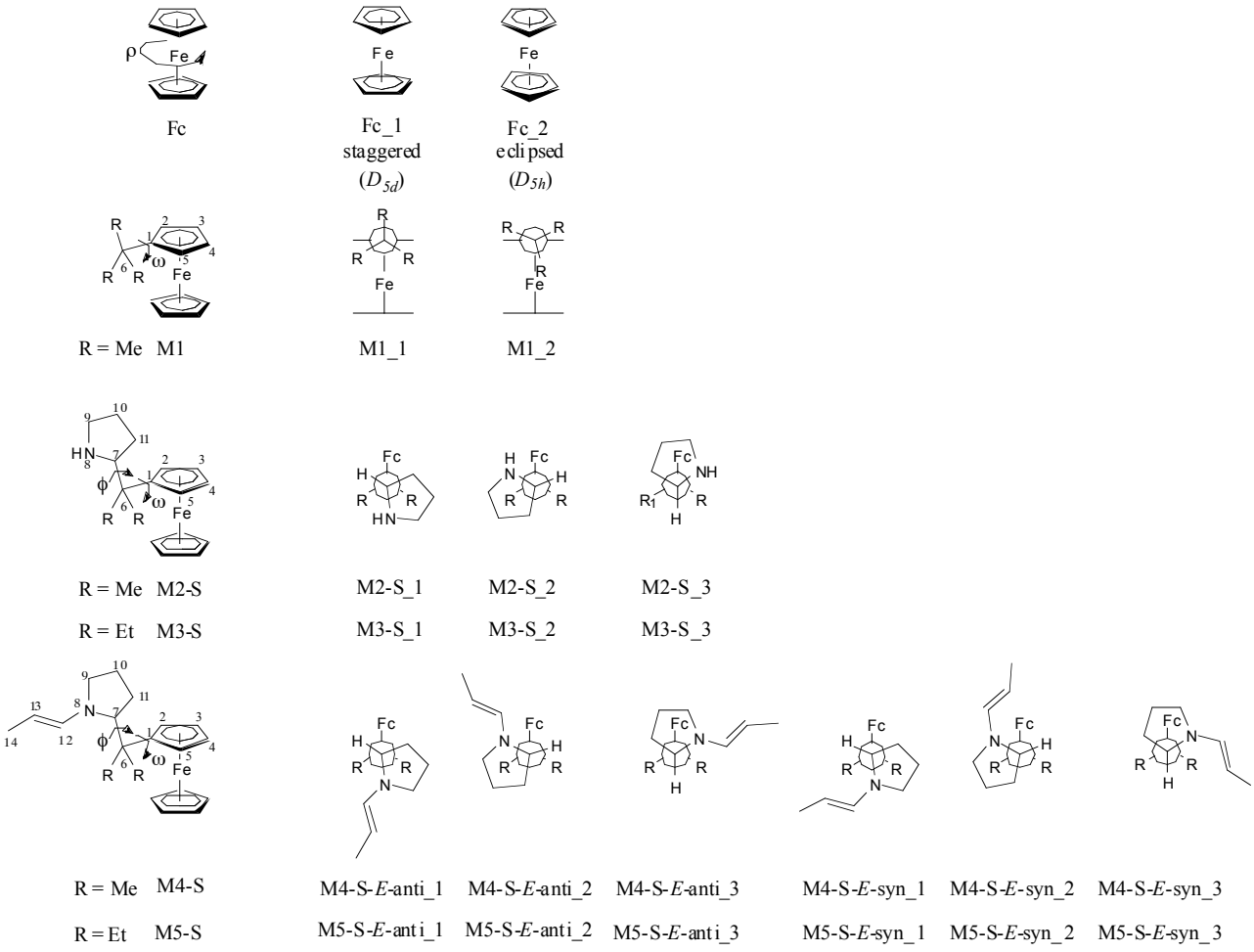


Figure 2.7. Schematic representation of the model systems used to investigate the conformational equilibrium along the dihedral angles ω and ϕ (M5-S models corresponds to the molecule discussed in the main text).

The rotational equilibrium around the C6-C7 bond was investigated for both methyl- (M4-S) and ethyl- (M5-S) substituted enamine adducts. The Z double bond configuration was not modeled as considered significantly less stable than the E configuration and the isomerization barrier too high to allow spontaneous equilibration. The partial double bond character of the N8-C12 bond reduces the conformational freedom along the γ dihedral angle to two possible minima, denoted as anti and syn according to the relative position of C7 and C13 with respect to N8-C12. The syn configuration of the N8-C12 destabilizes the system of about 2-4 kcal mol^{-1} (*Table 2.2*), due to the steric interference between the double bond and the substituted C7 atom. For both M4-S and M5-S models three stable conformers were individuated along the ϕ dihedral angle. In the presence of methyl substituents the energy spread between rotamers is as small as in the pyrrolidine substituted system (M2-S). The presence of two ethyl groups strongly reduces the conformational freedom around this bond, as only one rotamer is predicted to be populated.

Having established the main geometry of the catalyst, a whole conformational search on the relative disposition of the two ethyl groups was desirable. In order to reduce the computational time, the M4S_E-Anti_3 was taken as a starting geometry, and the 9 available dispositions were generated by the substitution of two

hydrogen atoms with methyl groups. The geometries were then optimized at the B3LYP/LANL2DZ level (*Table 2.2*).

Table 2.2. Calculated energies for the available dispositions of the ethyl groups, calculated at the B3LYP/LANL2DZ level (gas phase). The relative stability of each isomer with respect the most stable one is reported in kcal mol-1 (atom numbering C1′, C1″, C2′, C2″ refer to the CH_2 and CH_3 of the two ethyl groups, respectively).

conformation	C_7-C_6-$C_{1'}$-$C_{2'}$ dihedral angle	C_7-C_6-$C_{1''}$-$C_{2''}$ dihedral angle	Energy (E_h)	ΔE (kcal mol^{-1})
1-1	**-173**	**66**	**-1035.011989**	**0.00**
1-2	-173	-174	-1035.003982	5.02
1-3	-173	-53	-1035.004033	4.99
2-1	-61	61	-1035.008517	2.18
2-2	-61	172	-1035.009470	1.58
2-3	-61	-71	-1035.005224	4.24
3-1	64	62	-1035.004786	4.52
3-2	64	170	-1035.003603	5.26
3-3	64	-74	-1035.000418	7.26

Table 2.3. Energies, reported in hartree, are calculated at the RIJCOSX-B3LYP/def2-TZVPP level (gas phase). The relative stability of each isomer with respect the most stable one is reported in kcal mol^{-1}. Isomer population was computed using a standard Boltzmann distribution (T = 300 K) in conjunction with the calculated potential energy of each isomer.

	Energy (E_h)	ΔE (kcal mol^{-1})	Popul. (%)	ω (°)	ϕ (°)	γ (°)
M1_1	-1808.312074	0.00	100	86		
M1_2	-1808.306000	3.81	a)			
M2_1	-1980.444294	0.77	20	93	177	
M2_2	-1980.445529	0.00	70	82	62	
M2_3	-1980.443709	1.14	10	78	-67	
M3_1	-2059.082014	2.32	2	85	170	
M3_2	-2059.082231	2.18	2	72	51	
M3_3	-2059.085708	0.00	96	78	-59	
M4-S-*E*-anti_1	-2097.201937	0.21	34	94	177	-165
M4-S-*E*-anti_2	-2097.201289	0.61	17	81	59	-161
M4-S-*E*-anti_3	-2097.202268	**0.00**	48	81	-66	-166
M4-S-*E*-syn_1	-2097.197946	2.71	1	96	175	10
M4-S-*E*-syn_2	-2097.195819	4.05	0	88	59	13
M4-S-*E*-syn_3	-2097.198526	2.35	1	81	-67	13
M5-S-*E*-anti_1	-2175.837444	5.63	0	96	174	-165
M5-S-*E*-anti_2	-2175.837376	5.67	0	79	50	-161
M5-S-*E*-anti_3	**-2175.844626**	**0.00**	**100**	**83**	**-61**	**-165**
M5-S-*E*-syn_1	-2175.833235	8.27	0	96	173	14
M5-S-*E*-syn_2	-2175.831432	9.40	0	85	47	9
M5-S-*E*-syn_3	-2175.839082	4.60	0	82	-59	9
	-2175.846412					

a) M1_2 constitutes a transition state

The best geometry obtained (conformation 1-1) was than optimized again using the RIJCOSX-B3LYP/def2-TZVPP level, to be compared with the previously optimized structures. When compared with the X-ray structure of the mandelate adduct, this geometry showed to be almost identical to the experimental one. This identity confirmed the accuracy and reliability of the theoretical approach.

Reaction Intermediates.

As shown in recent literature, two intermediates are involved in the Michael addition of aldehydes to Nitro-alkenes when a secondary amine catalyst is used. They correspond to a six-membered dihydrooxazine ring and to a cyclobutane.[34] The benchmark reaction reported in the main text employs catalyst **3** with benzoic acid as co-catalyst. To confirm the existence of the same intermediates, the geometries were first optimized by QM/MM methods to find the best geometry of the interaction between the intermediate and benzoic acid. The resulting structures were then optimized at the B3LYP/LANL2DZ, and vibrational analysis confirmed they are energy minima (*Figure 2.8*). In the present case the dihydrooxazine intermediate was calculated to be more stable than cyclobutane.

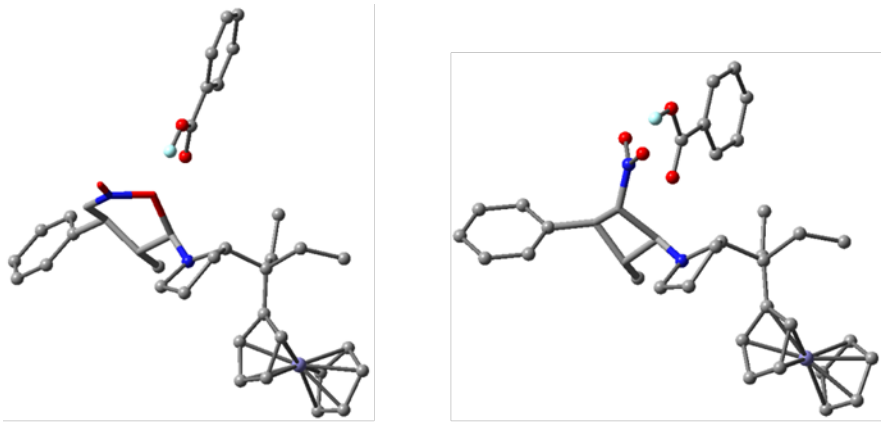


Figure 2.8. Optimized structures of the dihydrooxazine and ciclobutane intermediate, coordinated with one molecule of benzoic acid.

Methods

The conformational equilibrium of selected compounds was detailed by means of full geometry optimizations and relaxed scan calculations conducted at the density functional theory (DFT) level. The nature of all found critical points was confirmed by means of analytical or numerical frequency calculations. DFT/B3LYP was preferred over more accurate, but computationally expensive, approaches such as MP2 or CCSD(T) on the basis of benchmark calculations performed on ferrocene.[33] Moreover, DFT/B3LYP have been successfully employed for both enamine intermediate characterization and transition state identification in the study of prolinol-catalyzed α-heteroatom functionalization of aldehydes.[35] Plain DFT/B3LYP was considered unfit for studying compounds characterized by extended intermolecular π-π interactions, due to the B3LYP functional underestimation of Van der Waals interactions.[36] Instead of using MP2 or other post-Hartree-Fock approaches, an empirical correction to the B3LYP functional was employed in such cases.[37]

The COBRAMM[38] suite of program was used to combine the GAUSSIAN03 (revision E.01)[39] geometry optimization driver[40] with the DFT calculations performed by the software ORCA (release 2.8). The B3LYP functional was employed in conjunction with the def2-TZVPP[41] basis set (BS2) to investigate the conformational potential energy surface (PES) of compound **3**. The cheaper but still accurate def-SVP[42] basis set (BS1) was employed do investigate the conformational equilibrium of some model compounds. Since small or null solvent effects were observed in preliminary benchmark calculations on the same compounds, all reported results refer to gas-phase calculations. The "Resolution of Identity" (RI) approximation was adopted to speed up the DFT calculations using the RIJCOSX algorithm[43] was employed in conjunction with B3LYP hybrid functional; in all cases appropriate auxiliary basis sets were employed. B3LYP/LanL2DZ calculations were used for the optimization of the conformations due to the relative dispositions of the ethyl groups, and to optimize the geometries of the two intermediates.

Preparation and structural analysis of enamine

A careful 1-D NOESY study performed on the stable enamine confirmed the E geometry of the enamine, with a conformation that confirmed the structure calculated by DFT, thus ratifying the reliability of the theoretical studies.

A sample of the enamine **5** was obtained by adding 0.36 mg of freshly distilled propanal (as 2 mg/mL solution in DMSO[d6]) inside an NMR sample containing 2.0 mg of catalyst **3** dissolved in 0.5 mL of DMSO[d6] (eurisotop, < 0.02% water). The sample was then transferred into the probe head of a 600 MHz spectrometer kept at 25 °C. The formation of the enamine was followed by monitoring the grow of the signal at 6.05 ppm. After 180 min the conversion was > 80% (*Figure 2.9*).

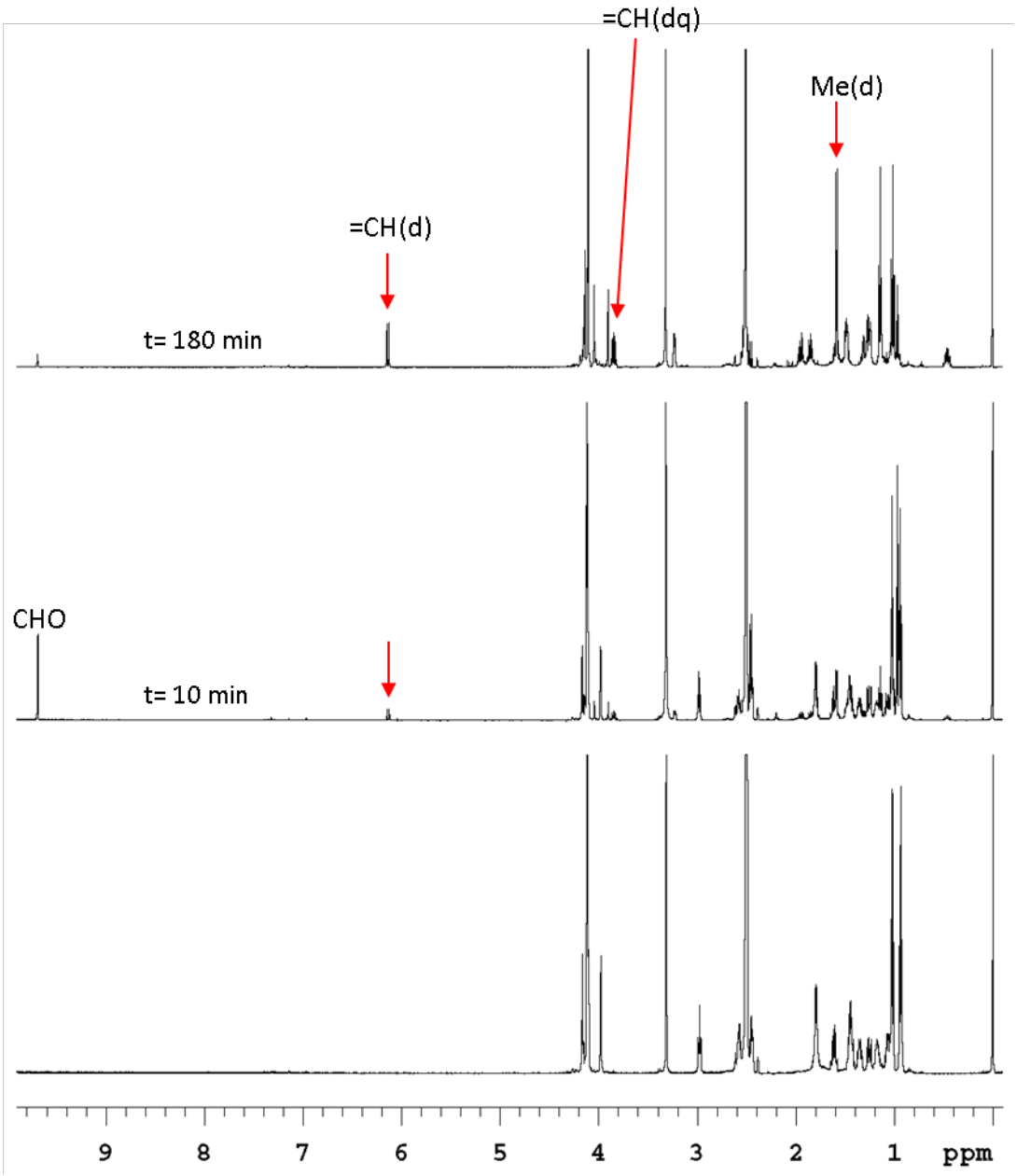


Figure 2.9. Bottom: ^{1}H spectrum of catalyst **3** (600 MHz in DMSO[d6]). Middle trace: ^{1}H spectrum 10 min after the addition of propanal. Top trace: ^{1}H spectrum after 180 minutes.

The sample was then subjected to COSY and 1D-NOESY experiment to ascertain the structural features of the enamine. COSY spectrum showed that the signal at 6.05 (doublet, J=14.0 Hz) was coupled with the signal at 2.8 ppm and with the doublet at 1.60 ppm (methyl) (*Figure 2.10*).

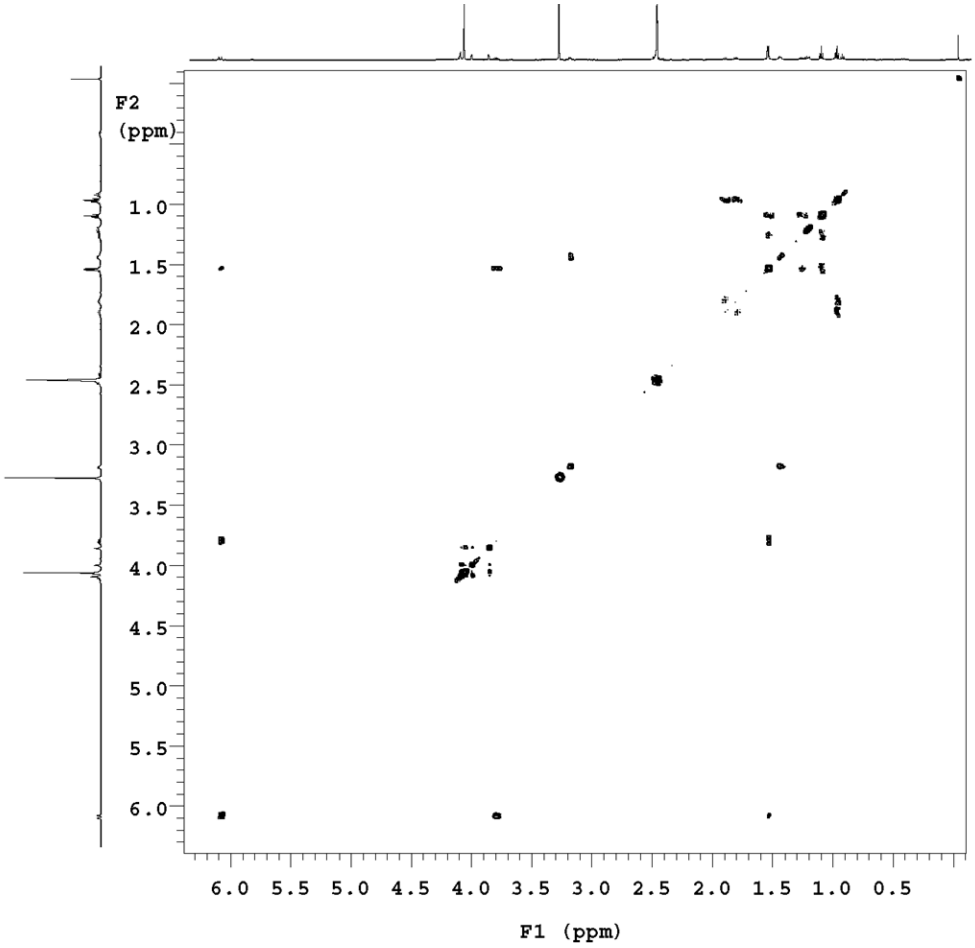


Figure 2.10. COSY spectrum of the enamine sample.

1D-NOESY spectrum obtained with the DPFGSE-NOE sequence by saturating the signal at 6.05 ppm yelded strong NOE on the methyl at 1.60 ppm, thus confirming the E-geometry of the enamine. The NOEs observed on the CH-N signal at 3.22 ppm and on the CH_3 and CH_2 of one ethyl group confirmed the disposition of the enaminic CH towards the stereogenic centre. *Figure 2.11* shows the observed NOE on the calculated structure.

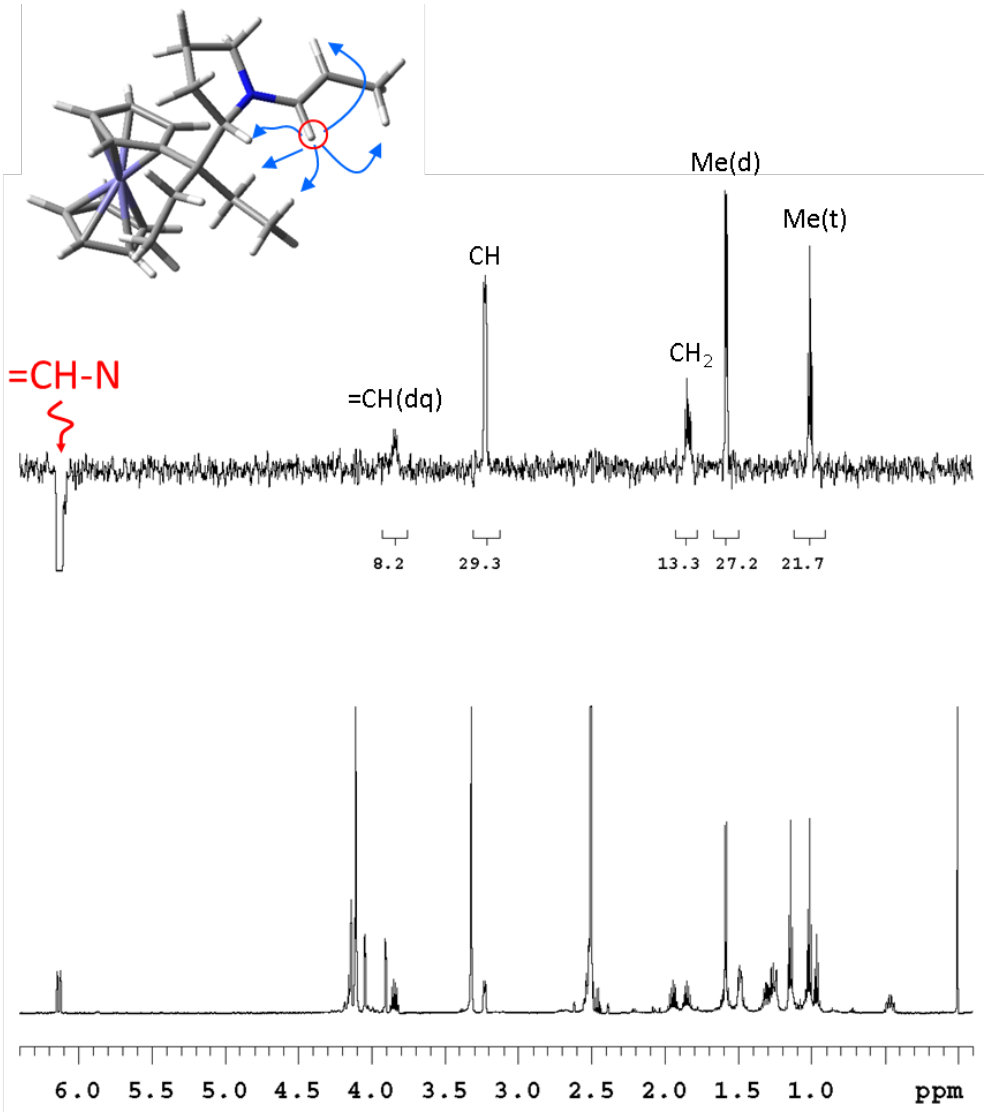
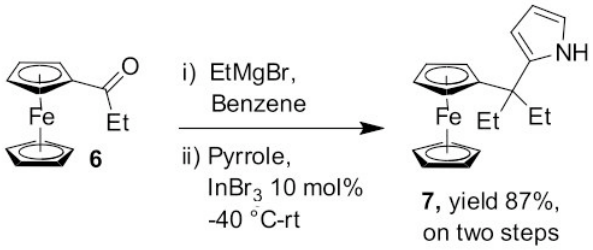


Figure 2.11. Bottom: control spectrum of the enamine. Top: DPFGSE-NOE spectra on saturation of the enaminic CH. Blue arrow in the 3D structure indicate the observed NOEs.

Procedure for the synthesis of catalyst

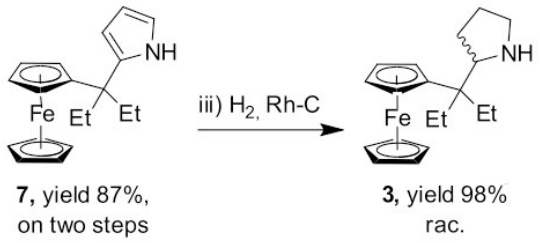
Preparation of 7



In a two necks flask with nitrogen atmosphere the ferrocenylethyl ketone (572 mg, 2.36 mmol, 1 equiv) was dissolved in a mixture of THF (0.5 mL) and 97% Benzene (4 mL). Ethyl magnesium bromide (3.3 mL, 3.3 mmol, 1.4 equiv.) was added at 0 °C and the reaction was allowed to warm to room temperature and stirred for 90 minutes. The reaction was quenched by addition of water. The organic phase was separated and the aqueous phase was extracted with ethyl acetate/brine. The organic phase were collected, than concentrated at reduced pressure to afford dark orange oil as crude product in 97% yield. ^{1}H NMR (400 MHz, CDCl3, 25 °C); δ 4.22 (s, 5H), 4.18 (s, 4H), 1.75 (m, 4H), 0.84 (t, 6H, J = 7.70Hz) ppm. ^{13}C NMR (100.76 MHz, CDCl3, 25 °C); δ 110.1 (1C), 73.0 (1C), 68.3 (5C), 67.6 (2C), 66.4 (2C), 31.6 (2C), 8.1 (2C).

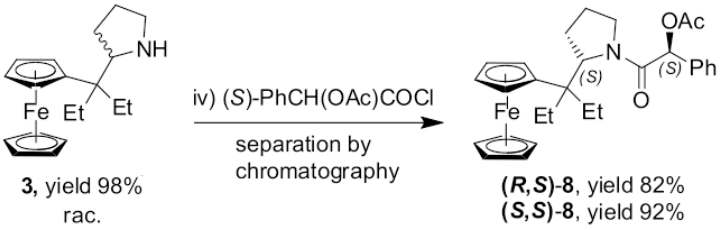
The compound obtained was used for the successive reaction without further purification for the successive reaction with pyrrole. In a sealed vial with nitrogen atmosphere ferrocenyl alcohol obtained in the previous reaction (620 mg, 2.3 mmol, 1 equiv) was dissolved in neat pyrrole (7.0 mL, 0.1 mol, 50 equiv). A 0.3M solution of $InBr_3$ in CH3CN (1.4 mL, 0.46 mmol, 0.2 equiv) was added at -30 °C and the reaction mixture was stirred for 15 hours covered with an aluminum foil to protect the reaction from the light. The reaction mixture was allowed to warm at room temperature and then the excess of pyrrole was distillated at reduced pressure. The crude product obtained was purified by flash chromatography (cyclohexane/ethyl acetate 9:1) affording the desired product as an orange oil in 90% yield. ^{1}H NMR (400 MHz, CDCl3, 25 °C); δ 9.30 (bs, 1H), 6.81-6.76 (m, 1H), 6.18 (q, 1H, J = 2.7, 6.1Hz), 6.02-5.99 (m, 1H), 4.23 (s, 5H), 4.19-4.15 (m, 2H), 3.92-3.88 (m, 2H), 1.96-1.77 (m, 4H), 0.70 (t, 6H, J = 7.1Hz) ppm. ^{13}C NMR (100.76 MHz, CDCl3, 25 °C); δ 115.3 (1C), 107.1 (1C), 105.9 (1C), 69.0 (1C), 68.6 (1C), 68.6 (5C), 67.2 (2C), 67.1 (2C), 66.7 (1C), 32.4 (2C), 9.0 (2C).

Preparation of rac. 3.



In a two necks flask connected to a hydrogen balloon (1 atm) ferrocenyldiethylpyrrole 7 (431 mg, 1.34 mmol, 1 equiv) was dissolved in a mixture of MeOH (7 mL) and acetic acid (1 mL). Rhodium on graphite catalyst (10% mol, 55 mg, 0.134 mmol, 0.1 equiv) was added at the reaction mixture and after vacuum, the flask was purged with hydrogen. The reaction mixture was stirred for 15 hours. The reaction was stopped and the hydrogen replaced by air. After filtration over celite® a saturated solution of $NaHCO_3$ was added. After neutralization, the MeOH was evaporated under reduced pressure and the aqueous residue was extracted with diethyl ether (3 x 8 mL). The organic phases were collected, and evaporated under reduced pressure to give a solid product in yield of 98% in racemic form, that was further purified by crystallization with dichloromethane and diethyl ether. ^{1}H NMR (400 MHz, CDCl3, 25 °C) δ 6.89-5.87 (bs, 1H), 4.32 (s, 1H), 4.27 (s, 1H), 4.22 (s, 1H), 4.20 (s, 5H), 4.07 (s, 1H), 3.45 (t, 1H, J = 8.2Hz), 3.22-3.00 (m, 1H), 2.69-2.45 (m, 1H), 2.13-1.36 (m, 8H), 1.13 (dt, 6H) ppm. ^{13}C NMR (100.76 MHz, CDCl3, 25 °C) δ 92.2 (1C), 69.1 (5C), 67.8 (1C), 67.4 (1C), 66.8 (1C), 65.8 (1C), 64.6 (1C), 45.6 (1C), 41.5 (1C), 27.5 (1C), 27.2 (1C), 26.2 (1C), 24.2 (1C), 8.8 (1C), 8.5 (1C). HMRS: calc. for $C_{19}H_{27}FeN$ = 325.14929; found: 325.14933

Preparation of 8.



In a three necks flask with nitrogen atmosphere ferrocenyl diethyl pyrrolidine catalyst (150 mg, 0.46 mmol, 1 equiv) was dissolved in dichloromethane (2 mL). Pyridine (0.11 mL, 1.38 mmol, 3 equiv), DMAP (3mg, 0.023 mmol, 0.05 equiv) were added at 0 °C. and (S) O-acetylmandelic chloride (0.55 mL, 0.70 mmol, 1.5 equiv) was added dropwise at 0 °C as a solution 1M in dichloromethane. After 15 hours stirring the reaction was quenched with HCl 1N and the mixture was extracted with dichloromethane (2 x 8mL). The organic phases were collected, dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product that was purified by preparative chromatography on silica

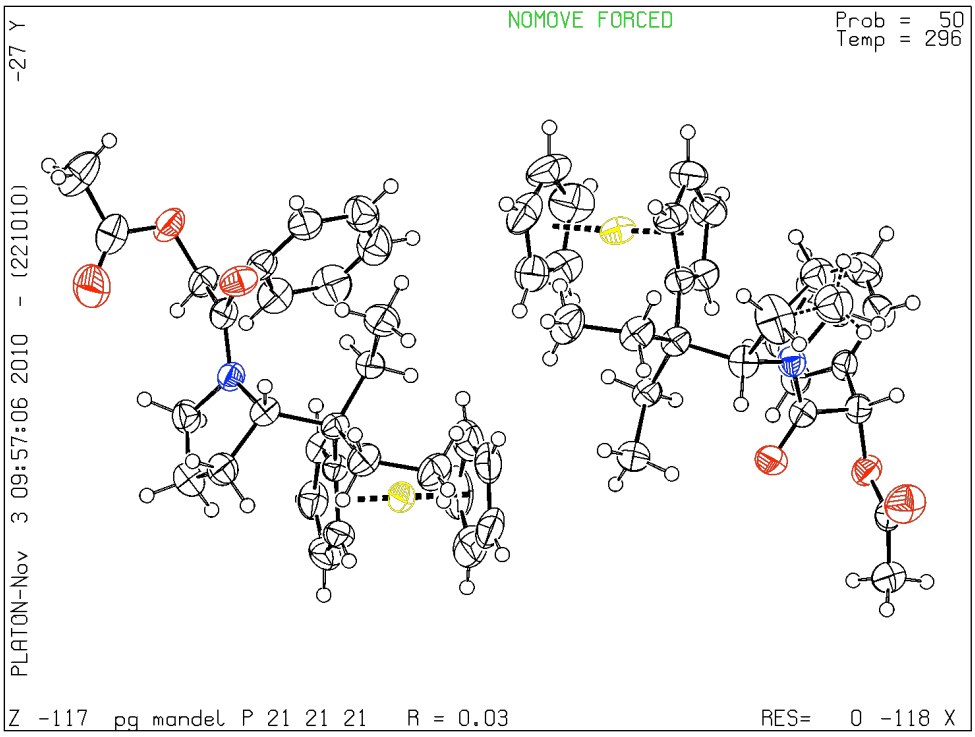
(cyclohexane/ethyl acetate 9:1, 2 times) and the desired (R,S)(first eluted diastereoisomer) and (S,S) (second eluted diastereoisomer) diastereoisomeric amides were obtained in 75% yield.

(S,S)-8: ^{1}H NMR (400 MHz, CDCl3, 25 °C); δ 7.46-7.39 (m, 2H), 7.37-7.29 (m, 3H), 5.85 (s, 1H), 4.48 (s, 1H),4.39 (q, 1H, J = 3.6, 8.9Hz), 4.17 (s, 1H), 4.15 (s, 5H), 4.11 (s, 1H), 4.05 (s, 1H), 3.02-2.93 (m, 1H), 2.42-2.32 (m, 1H), 2.19 (s, 3H), 1.96-1.85 (m, 2H), 1.75-1.59 (m, 2H), 1.58-1.44 (m, 2H), 1.23-1.08 (m, 6H), 0.97-0.87 (m, 2H) ppm. ^{13}C NMR (100.76 MHz, CDCl3, 25 °C); δ 170.7 (1C), 167.7 (1C), 133.7 (1C), 129.2 (1C), 128.8 (2C), 128.7 (2C), 95.3 (1C), 75.3 (1C), 69.0 (5C), 68.0 (1C), 67.2 (1C), 66.8 (1C), 66.1 (1C), 62.1 (1C), 46.6 (1C), 43.9 (1C), 30.9 (1C), 27.7 (1C), 25.1 (1C), 23.6 (1C), 20.9 (1C), 9.2 (1C), 9.1 (1C). ESI-MS: m/z = 502.1 $[M+H]^+$, 524.2 $[M+Na]^+$.

(R,R)-8: ^{1}H NMR (400 MHz, [D3]CHCl3, 25 °C) δ 7.56-7.49 (m, 2H), 7.49-7.43 (m, 3H), 6.00 (s, 1H), 4.46 (q, 1H, J = 3.9, 8.1Hz), 3.99 (s, 5H), 3.97 (s, 1H), 3.94 (s, 1H), 3.72 (s, 1H), 3.52-3.42 (m, 1H), 2.83 (s, 1H), 2.29-2.19 (m, 1H), 2.18 (s, 3H), 1.70-1.35 (m, 8H), 1.13-1.03 (m, 6H) ppm. ^{13}C NMR (100.76 MHz, [D3]CHCl3, 25 °C) δ 170.8 (1C), 169.1 (1C), 134.5 (1C), 129.1 (1C), 128.7 (2C), 128.4 (2C), 94.8 (1C), 74.8 (1C), 68.7 (5C), 66.9 (1C), 66.6 (1C), 66.6 (1C), 66.0 (1C), 62.1 (1C), 47.5 (1C), 44.0 (1C), 27.7 (1C), 26.3 (1C), 24.5 (1C), 24.0 (1C), 20.8 (1C), 9.2 (1C), 9.0 (1C). ESI-MS: m/z = 502.1 $[M+H]^+$, 524.2 $[M+Na]^+$.

The absolute configuration of the two stereogenic centers of the second eluted diastereoisomer was established by X-ray analysis.

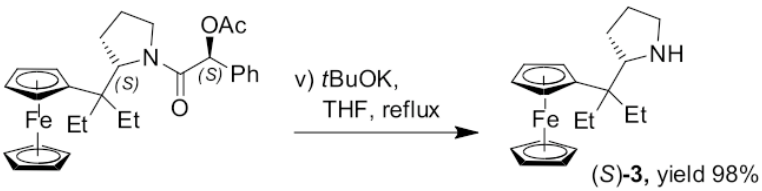
Crystal Data for compound 8



Molecular formula: $C_{29}H_{35}NO_3Fe$, M_r = 501.43, orthorhombic, space group $P2_12_12_1$ (No. 14), a = 10.4037(15), b = 16.013(2), c = 30.288(4) Å, V = 5045.8(13) Å^3, T = 298(2) K, Z = 8, ϱ_c = 1.320 g cm^{-3}, F(000) = 2128, graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å), μ(Mo$K\alpha$) = 0.628 mm^{-1}, orange plates (0.4 × 0.3 × 0.15 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9117 – 0.7872), 2400 frames, exposure time 15 s, 1.85 ≤ θ ≤ 28.75, –13≤ h ≤ 13, –20 ≤ k ≤ 20, –40 ≤ l ≤ 40, 58717 reflections collected, 12340 independent reflections (R_{int} = 0.0359), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELXTL

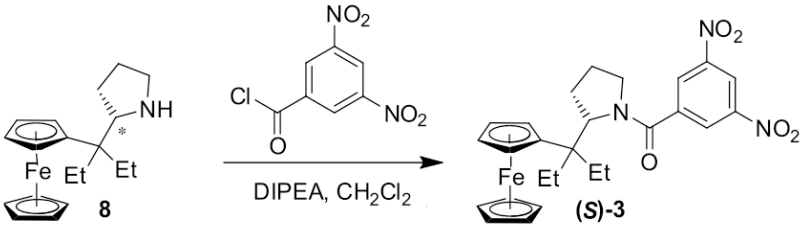
6.10), hydrogen atoms refined with a riding model, data / restraints / parameters = 12340/ 0 / 620, $S(F^2)$ = 1.031, $R(F)$ = 0.0418 and $wR(F^2)$ = 0.0823 on all data, $R(F)$ = 0.0320 and $wR(F^2)$ = 0.775 for 2965 reflections with $I > 4\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0429P)^2 + 0.4913P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.234 and –0.256 e Å^{-3}. Flack parameter[44] for *S*,*S* configuration: -0.014(8). The crystal cell contains two independent molecule, one of which shows disorder on one carbon atom of the pyrrolidine ring.

Synthesis of (S)-3.



In a sealed vial under nitrogen atmosphere the diasteroisomeric amides (111 mg, 0.22 mmol, 1 equiv) were dissolved in THF (4 mL) and subjected to hydrolysis by adding a large excess of *t*BuOK (987 mg, 8.8 mmol, 40 equiv). The reaction mixture was vigorously stirred for 96 hours at 95 °C. The reaction was cooled to rt, then quenched with water. The mixture was extracted with water/ethyl acetate (3 x 4mL) then the organic phases were collected, dried over Na_2SO_4, and then evaporated under reduced pressure. The crude product obtained was purified by flash chromatography (dichloromethane/methanol/ammonium hydroxide 9:0.8:0.2) to provide the enantiopure products in 98% yields as an orange powder. ^{1}H and ^{13}C NMR are reported for racemic **3.**

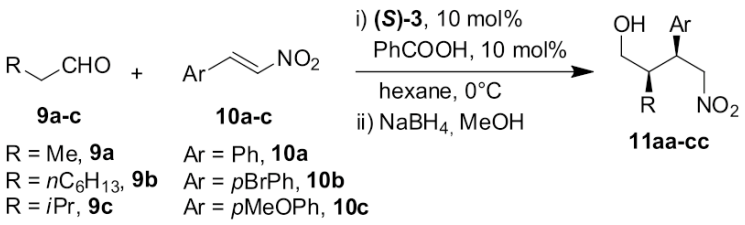
The enantiomeric excess of 3 was determined by synthesis of the corresponding 3,5 dinitrophenylbenzoate.



In a two necks flask with nitrogen atmosphere the enantiopure ferrocenyl diethyl pyrrolidine catalyst (9 mg, 0.028 mmol, 1 equiv) was dissolved in dichloromethane (1.0 mL, 0.03 M).

3,5-dinitrobenzoylchloride (19 mg, 0.083 mmol, 3 equiv.) and DIPEA (0.042 mL, 0.083 mmol, 3 equiv) were added to the reaction mixture. After 15 hours the solvent was evaporated, the organic phase was extracted with diethyl ether and then concentrated. The enantiomeric excess of (*R*)-enantiomer and (*S*)-enantiomer was measured directly on the crude product by chiral HPLC analysis: IB column; *n*-hexane/*i*-propanol 75:25; flux = 0.5 mL/min; T = 30 °C.

General procedure for the synthesis of compounds 11aa, 11ba, 11ca, 11ab, 11ac.



In a vial the enantioenriched catalyst (S)-3 (3.3 mg, 0.01 mmol, 0.05 equiv) was dissolved in hexane, then the nitro alkene (0.2 mmol, 1 equiv) and benzoic acid (1.2 mg, 0.01 mmol, 0.05 equiv) were added. The mixture was cooled to 0 °C and then the aldehyde (2 mmol, 10 equiv) was added at 0 °C. The reaction mixture was stirred at 0 C° temperature for 10 to 24 hours. The reaction was quenched at 0 °C by the addition of HCl (1 mL, 1 N), then the mixture was extracted with diethyl ether (2 x 3mL). The organic phases were collected, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was analyzed with chiral HPLC: IA column; *n*-hexane/*i*-propanol 95:5; flux = 1.0 mL/min; T = 30 °C. The crude product was then purified by flash chromatography on silica (cyclohexane/ethyl acetate) gives the pure products in 90 to 99% yield.

Spectroscopic data of the purified compounds are in agreement with the published data :

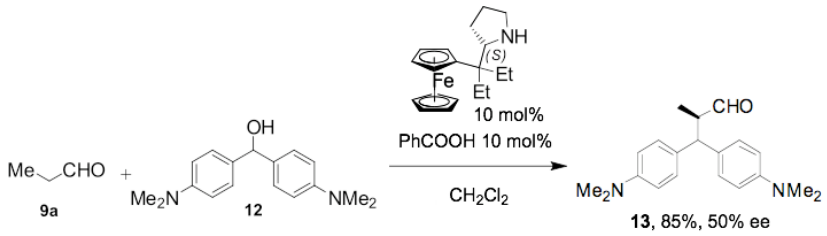
11aa, 11ca: a) J. M. Betancort, C. F. Barbas, III, *Org. Let.* **2001**, *3*, 3737. b) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611. c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147.

11ba: Q. Tao, G. Tang, K. Lin, Y.-F. Zhao, Chirality 20:833–838 (2008)

11ab: Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, Angew. Chem. Int. Ed. 2005, 44, 4212 –4215

11ac: c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147.

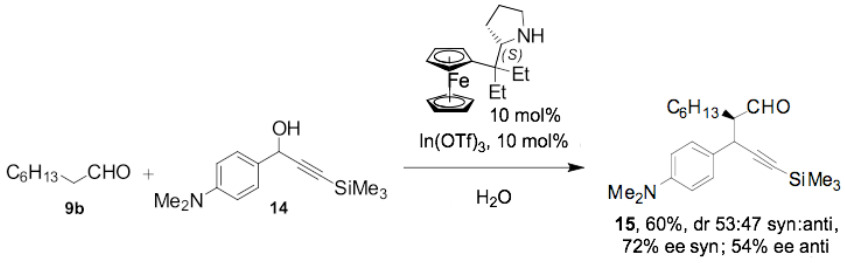
Synthesis of 13



In a air opened vial the enantioenriched catalyst (S)-3 (3.3 mg, 0.01 mmol, 0.1 equiv) was dissolved in Dichloromethane, the benzhydrylic alcohol 12 (27 mg, 0.1 mmol, 1 equiv) and benzoic acid (1.2 mg, 0.01 mmol, 0.1 equiv) were added. The aldehyde (0.3 mmol, 3 equiv) was added at 0 °C and the reaction mixture was stirred at that temperature for 18 hours. HCl (1 mL, 1 N) was then added, the mixture was extracted with diethyl ether and concentrated. The crude product was analysed with chiral HPLC: IA column; *n*-hexane/*i*-propanol 95:5; flux = 1.0 mL/min; T = 30 °C. At last purification by flash chromatography on silica (dichloromethane/diethyl ether 90:10) gives the pure products in 85% yield.

Spectroscopic data are in agreement with the published data: P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed.* **2009**, *48*, 1313 –1316.

Synthesis of 15



In a vial the enantiopure catalyst (S)-3 (3.3 mg, 0.01 mmol, 0.1 equiv) was added to the water, the propargylic alcohol 14 (27 mg, 0.1 mmol, 1 equiv), the benzoic acid (1.2 mg, 0.01mmol, 0.1 equiv) and the Indium Triflate (0.01 mmol, 0.1 equiv) were added. The aldehyde (0.3 mmol, 3 equiv) was added at 0 °C and the reaction mixture was stirred at that temperature for 18 hours. The mixture was reduced with $NaBH_4$ in methanol at 0 °C for 20 minutes. Purification by flash chromatography on silica (cyclohexane /diethyl ether 7:3) gives the pure products in 60% yield. The pure product was analysed with chiral HPLC: IC column; *n*-hexane/*i*-propanol from 99:1 to 90:10 in 30 minutes 95:5; flux = 0.5 mL/min; T = 30 °C.

Spectroscopic data are in agreement with the published data: R. Sinisi, M. V. Vita, A. Gualandi, E. Emer, P. G. Cozzi *Chem. Eur. J.* **2011**, *17*, 7404 – 7408.

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Towards novel organocatalytic strategies

In this chapter a new effective chiral pyrrolidine organocatalyst was prepared by the use of simple, and practical alkylation of nitroalkanes that take place with benzylic, benzhydrylic and propargylic alcohols in trifluoroethanol. A variety of different nitroalkanes bearing functional groups can be used in this S_N1-type reaction affording the desired products in quantitatively yields. Different highly functionalized chiral compounds obtained by organocatalytic nitro-Michael reaction react with the selected alcohols with high selectivity.

Electrophiles and nucleophiles: a new reactivity profile

For a long time, carbocationic species were considered unstable, highly reactive and barely useable to promote controlled reactions in a stereoselective way. Nevertheless, in 2001, Professor Herbert Mayr[1]

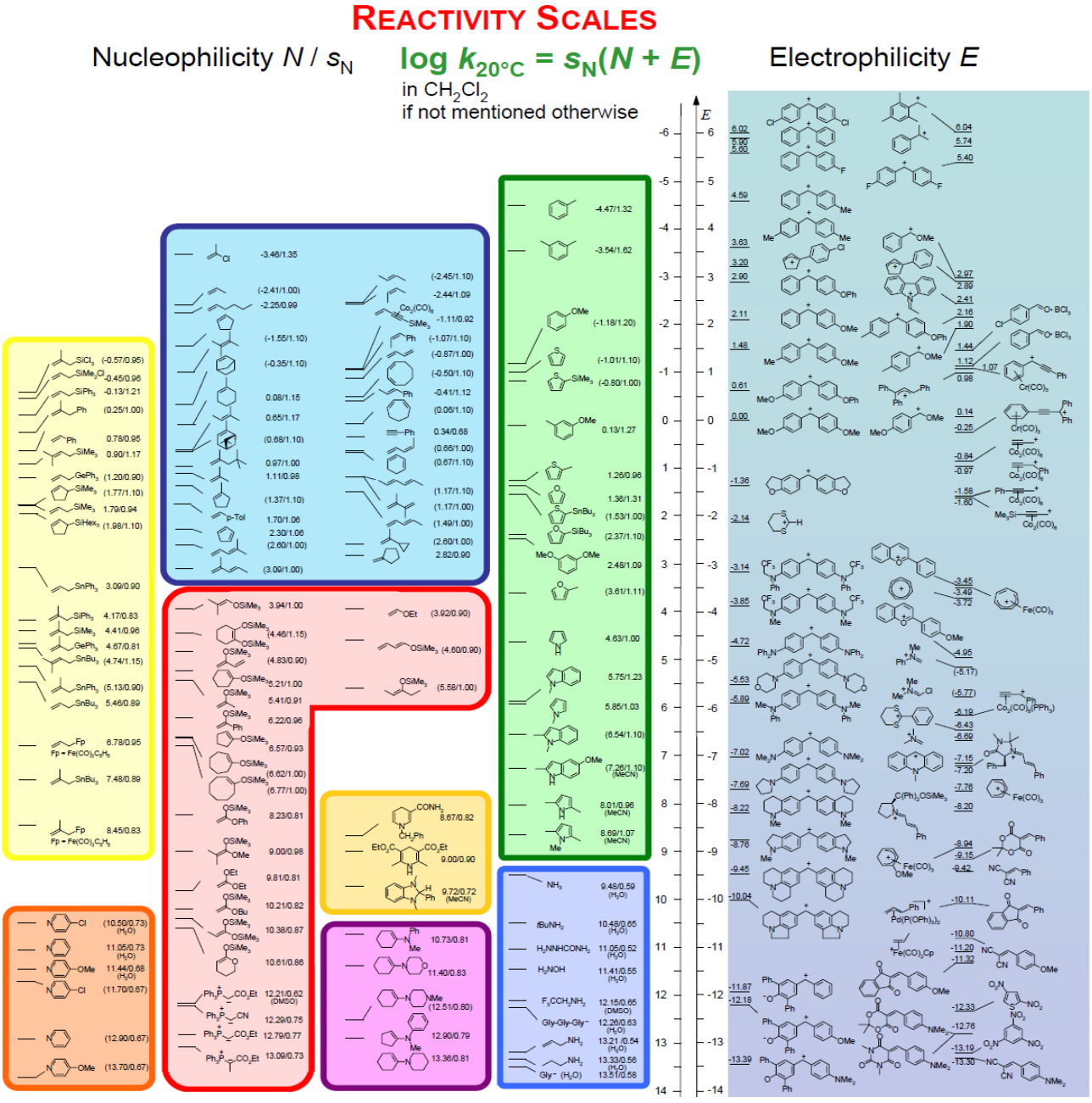


Figure 3.1. Mayr reactivity scale: electrophilic to the right and nucleophilic to the left.

described a wide scale of reactivity for different diarylcarbenic ions (*Figure 3.1*, right) to which a parameter of electrophilicity (E) was experimentally assigned on the basis of electronic factors, since the steric factor is negligible. By varying the nature of the aryl substituents in the para- and meta- position, the reactivity can vary within a range of 16 orders of magnitude: for example, a nucleophile that reacts in one minute with a derivative of the benzhydryl ion (E = 2.11) on top of the scale, would need 20 billion years (not possible to determine experimentally!) to react with the lithium bis-(lilolidin-8-yl) carbenium (E -10.04), at the bottom of the scale (*Figure 3.2*).[1]

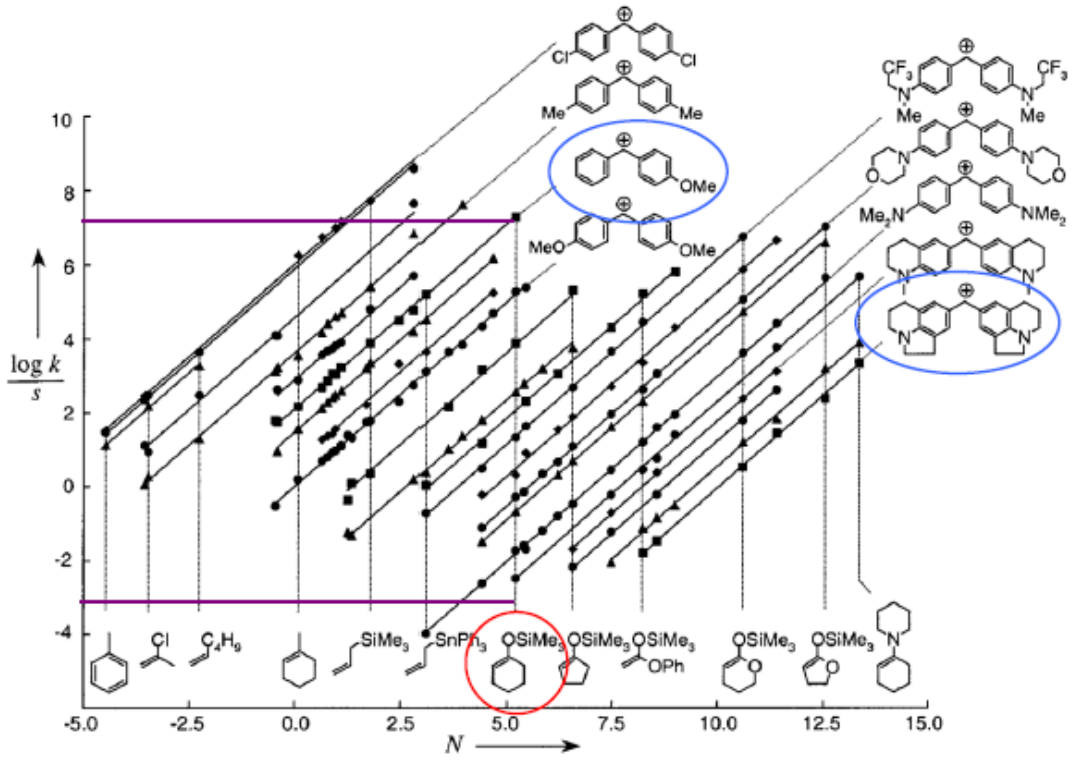


Figure 3.2. Diagram that defines the reactivity of electrophiles.

Similarly, a comparable scale of reactivity (scale of nucleophilicity) was built for various aromatic or π system containing nucleophiles (*Figure 3.1*, left side), based on the parameters of nucleophilicity (N) and Specific nucleophilicity (s), which both depend on steric and electronic factors. In this case, the nucleophilicity of the compounds increases from top to bottom of the scale. The result is a graphical representation that allows to immediately get a sense of the effectiveness of a reaction. Indeed, the nucleophiles on top of the scale cannot react with the electrophiles on the bottom, while the nucleophiles in the lower positions of the scale can react instantaneously with the electrophiles on top. Therefore, to perform a kinetically relevant reaction, electrophiles and nucleophiles placed at similar levels on the scale of Mayr must be combined.

The wherewithal of this classification lies in the possibility to quantitatively predict the rate of reaction of a combination between any electrophile and nucleophile by simply solving the following logarithmic equation (1), based on just three experimental parameters (E, N and s):

$$\log k\ (20\ ^\circ\ C) = s\ (N + E) \qquad (1)$$

The kinetics of many reactions for the formation of C-C bonds were determined in this manner. The results are resumed in a diagram that combines the different nucleophile-electrophile pairs that come into

play. Moreover, this scheme allows to predict other possible reactions which have not yet been tested, since it specifies the ranges of nucleophilicity and electrophilicity that can be combined in order to proceed reactions with speed control (*Figure 3.3*).[2]

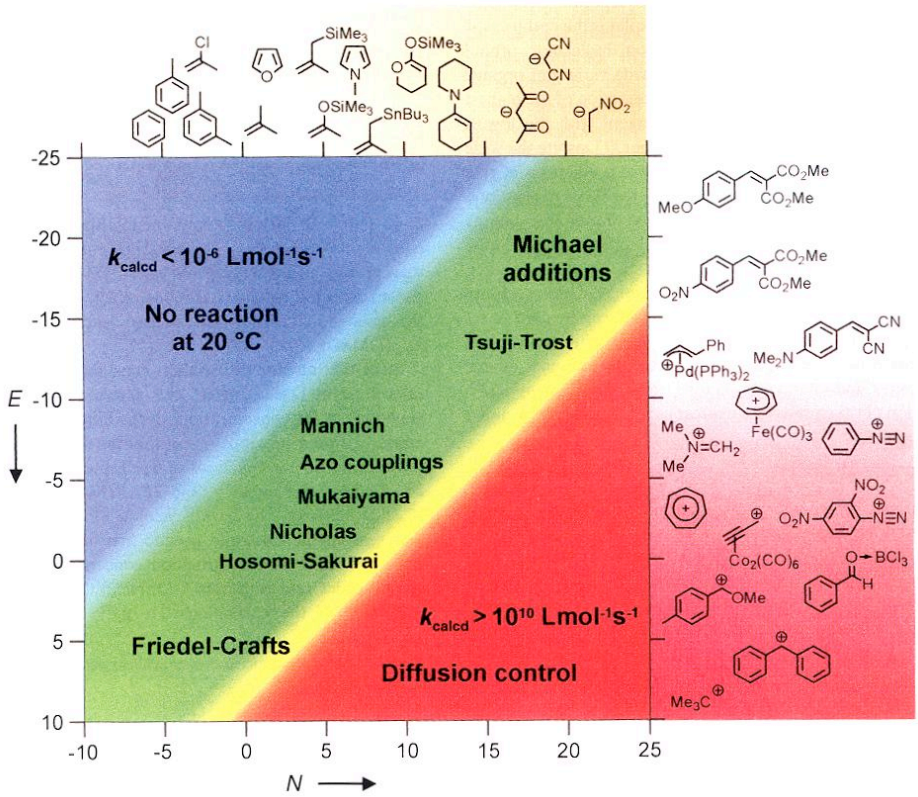


Figure 3.3. Diagram of possible reactions between nucleophilic and electrophilic according to their reactivity.

The Mayr table can be used in a fast and practical way, for the qualitative evaluation of the rate of a reaction without necessarily solving the logarithmic equation (1). To this aim, Mayr defined a general rule according to which an electrophile can react with a nucleophile at room temperature in a reasonable time if E+N>-5 (2). This generalization is based on the fact that a 1 M mixture of both reagents requires a second order rate constant of k>10^{-4} M^{-1} s^{-1} to give a 50% conversion in less than 3 hours, and that this condition is realized when E+N>-5.7/-3.3, for a slope between 0.7 and 1.2.

Introduction

Recently Mayr has expanded his studies involving organocatalysis. Starting from all of these usefull Mayr′s works, my research group has made many studies on the possibility to generate stable carbenium ion from alcohols in Alkylation reactions.[3] Two new lines of research have thus been opened: the first on a new direct reaction of this species and the second on stereoselective organocatalytic alkylations that will be discussed in the chapter 4.

The *E*-values for many carbenium ions have been determined and served as a guide for the appropriate choice of alcohols for our reactions. Their stability is strictly connected to the presence of aryl, alkenyl, or alkynyl groups linked to the carbenium ionic center. For this reason, sometimes the phrase ‘π-activated alcohol’[4a,b] is used in the literature for these type of compounds. However, a substituent in the *para*-position of an aryl group linked to the carbenium atom strongly affects the electrophilicity of the ion. The table intro-

duced by Mayr (*Figure 3.1*) offers a more-practical comprehensive definition of the stability and reactivity of carbenium ions. Carbenium compounds with $E > 0$ (benzhydrylium ion) are practically impossible to isolate and store and are transiently generated at low temperatures, sometimes using very specialized techniques.[4c] Because isolated carbenium ions of this type are difficult to handle, S_N1-type reactions involving these ions can be quite limited in scope. However, benzylic, propargylic, and allylic alcohols can form carbenium ions in the presence of Lewis or Brønsted acids, generating adapted electrophiles. In general, strongly electron-donating substituents such as NMe_2 enhance the stability of the carbenium ion, and those ions located at –7 on the Mayr scale are air- and bench- stable for months. Conversely, benzylic carbocations have moderate stability and high reactivity and, therefore, are capable of reacting with a large variety of nucleophiles. After looking carefully at the Mayr table, we were able to select the right alcohols for our scope (*Figure 3.4*).

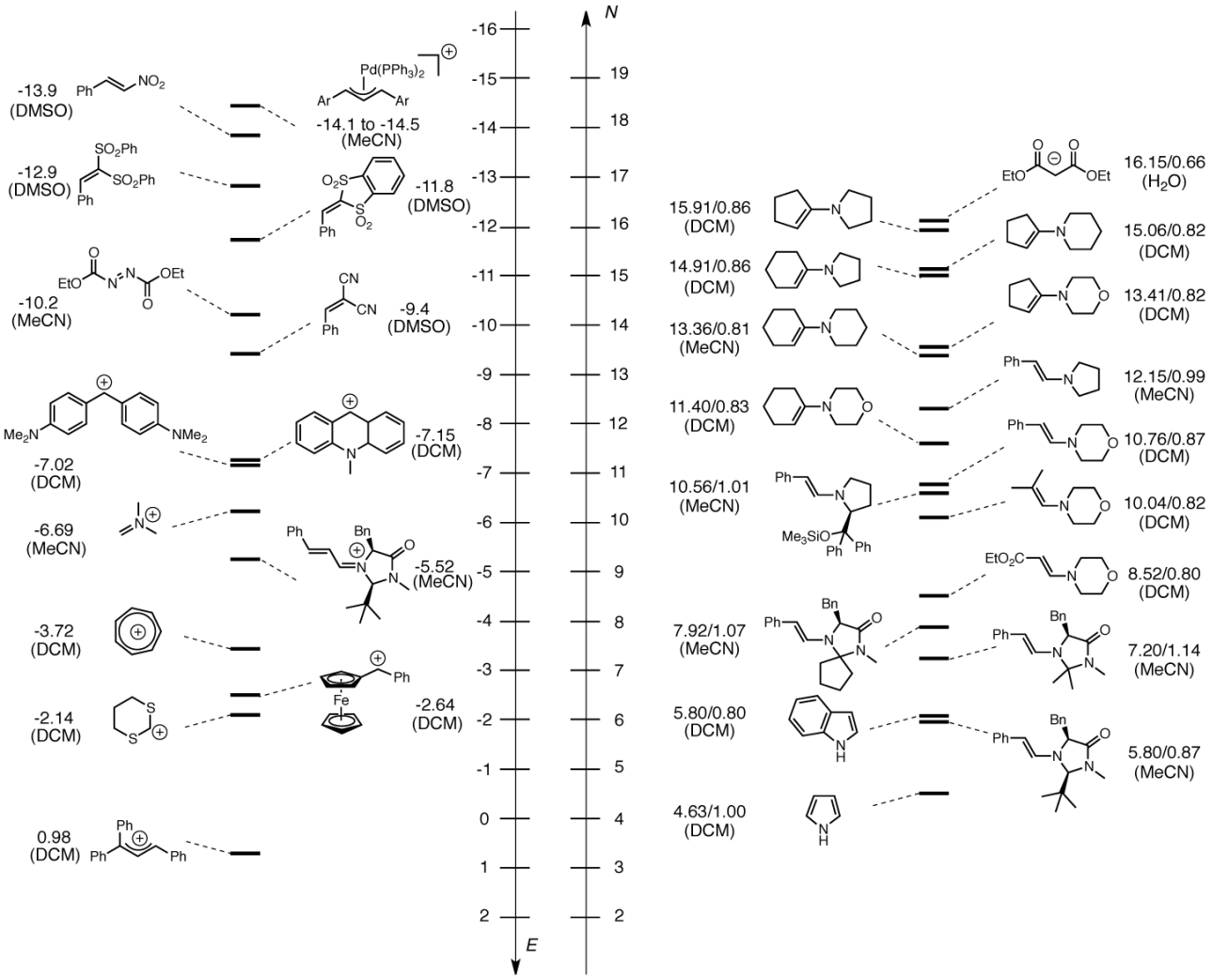


Figure 3.4

The principal idea, that we want to develop here, is to mate the reactivity of these carbocations with that of nitro compounds with the aim of obtaining highly functionalized products thanks to the versatility of the nitro group. Infact, deprotonated nitroalkanes are an important class of ambident anions, widely used in organic synthesis.[5] Their application in diverse chemical transformations results in their frequent use in

total synthesis.[6] Recently, nitro derivatives have found also applications in organocatalysis,[7] principally in Michael and Henry type reactions.[8] However, the simple alkylation of nitro derivatives has been found to be quite troublesome.[9] In fact, the intrinsic preference for attack of the oxygen at nitronate anions is so large that irreversible S_N2 reactions with a variety of alkylating agents generally proceed in this manner.[10] As a consequence of the failure to achieve C-alkylation of nitronate anions by simple substitution reactions,[11] Seebach et al. developed a method for the α-alkylation of nitroalkanes, which proceeds via doubly deprotonated nitroalkanes.[12]

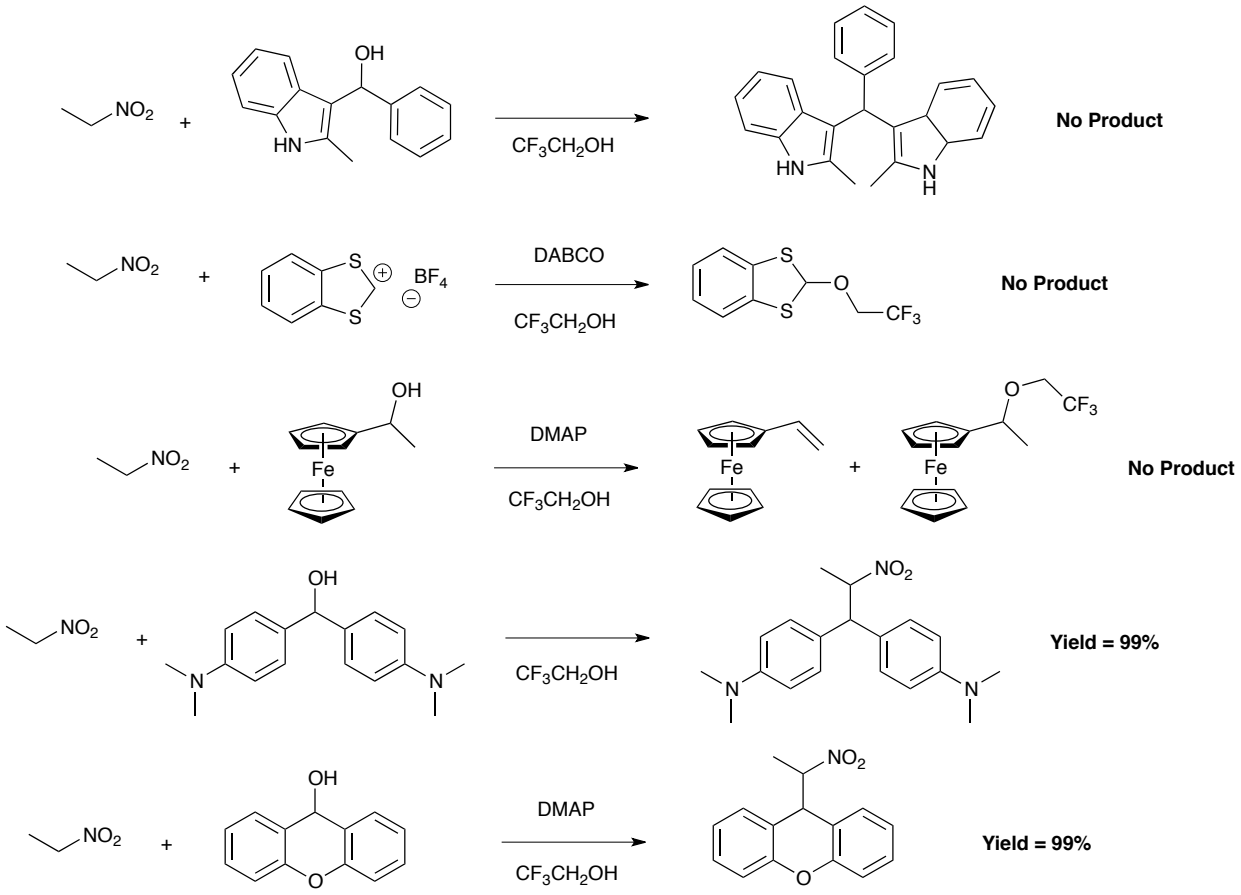
The next results demonstrate that a variety of different nitroalkanes bearing functional groups can be used in this S_N1-type reaction affording the desired products in quantitatively yields, if you are able to choose the right carbocation and the right conditions.

Results and Discussion

From past experiences we know that Trifluoroethanol (TFE) and Hexafluoroisopropanol (HFIP) are solvents with unique properties.[13] In particular their high ionizing power and low nucleophilicity has made them the media in which to perform nucleophilic opening of oxiranes,[14] intramolecular electrophilic addition to C-C bonds,[15] and aromatic electrophilic substitution.[16] These reactions are conducted in the absence of any other activating agents or Lewis acids. Recently, it was shown that HFIP could be employed as a medium and an activator for a number of classical C–C bond forming reactions, using carbonyl compounds and their acetals.[17]

We reasoned that the acidic properties and low nucleophilicity of TFE probably made it capable of forming carbenium ions from benzhydrylic alcohols.[18]

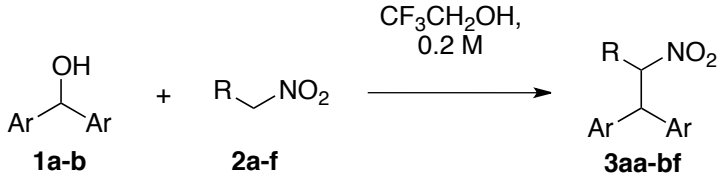
The first step was to test a series of carbocations in the presence of nitroalkanes in different conditions. The results obtained are reported in the *Scheme 3.1*.

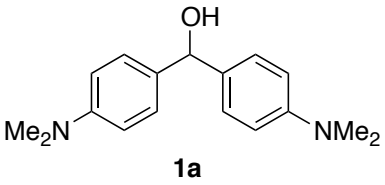


Scheme 3.1

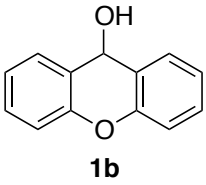
On the basis of these results we selected the alcohols 4,4'-bis(dimethylamino)-benzhydrol and 9*H*-xanthen-9-ol, positioned at -7 and -1.5 of the Mayr scale respectively,[19] as the best candidates for the reactions with many different nitroderivatives (*Table 3.1*)

Table 3.1. Addition of alcohols **1a-b** to various nitroderivatives **2a-f** in TFE.





1a



1b

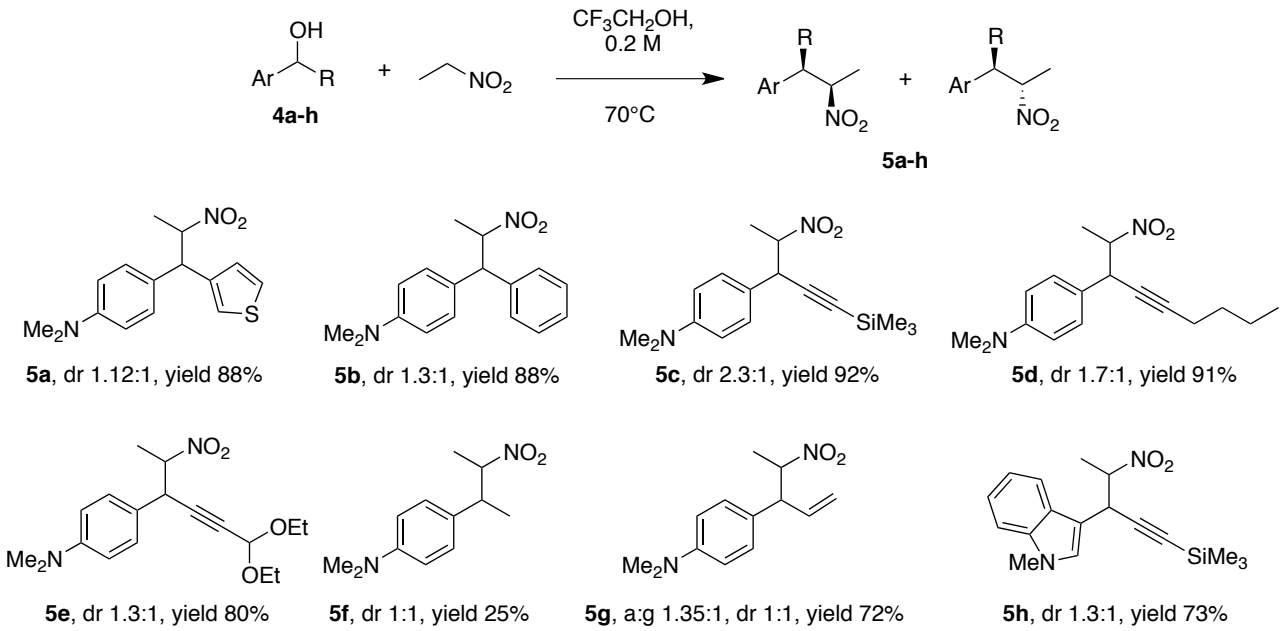
2a, R = Me
2b, R = nBu
2c, R = CH_2OH
2d, R= COOMe
2e, R= CH_2CH_2COOMe
2f, R = CH_2OTHP

Entry[a]	Time (h)	RCH_2NO_2	Product	Yield[b]
1	16	**2a**	**3aa**	99
2	20	**2b**	**3ab**	99
3	20	**2c**	**3ac**	99
4	3	**2d**	**3ad**	99
5	20	**2e**	**3ae**	95
6	70	**2f**	**3af**	99
7[c]	70	**2a**	**3ba**	99
8[c]	23	**2b**	**3bb**	99
9[c]	20	**2c**	**3bc**	62
10[c]	48	**2c**	**3bc**	99
11[c]	48	**2d**	**3bd**	99
12[c]	20	**2e**	**3be**	60
14[c]	48	**2e**	**3be**	99
15[c]	20	**2f**	**3bf**	65

[a] The reactions were performed at 25 °C with 0.1 mmol of 1a-b, 3 equiv. of nitroderivative 2a-f, and the reactions were run until completion by TLC (16-24 h). [b] Yield after chromatographic purification. [c] The reactions were performed at 25 °C with 1 equiv. of 1b, 3 equiv. of nitroderivative 2a-f and in the presence of 0.2 equiv. of DMAP as a catalyst.

The nitroderivatives **2a-f** were shown to give excellent yields with alcohol **1a**. In all the cases, no by-product derived from *O*-alkylation were identified in the crude reaction mixture. The reactions are very convenient, being performed in air at rt and generating water as the only by-product.[20] In the case of the alcohol **1b**, a more electrophilic carbenium ion is produced, a base additive is necessary in order to perform the reaction. We have screened various organic and inorganic bases and found out that the addition of DMAP was necessary to perform the reaction. It is worth underlying that the addition of Brønsted acids or bases to nitroderivatives in the presence of the alcohols **1a** using 5-10 equivalent of nitromethane gave no reaction. The isolated carbenium ion as tetrafluoroborate salts was not reactive with the nitroethane when the reaction was performed in the presence of DABCO. With all acid and base combinations examined, this highlights the simple conditions that we have found. The reaction tolerates the presence of many functional group and un-protected primary alcohols can also be present.

As many stabilized carbenium ion can be generated within the useful limit in the Mayr scale established with the model substrates, we have found that other benzhydrylic, benzylic, and propargylic alcohols react in the reaction conditions at 70 °C, as is highlighted in the *Scheme 3.2*.

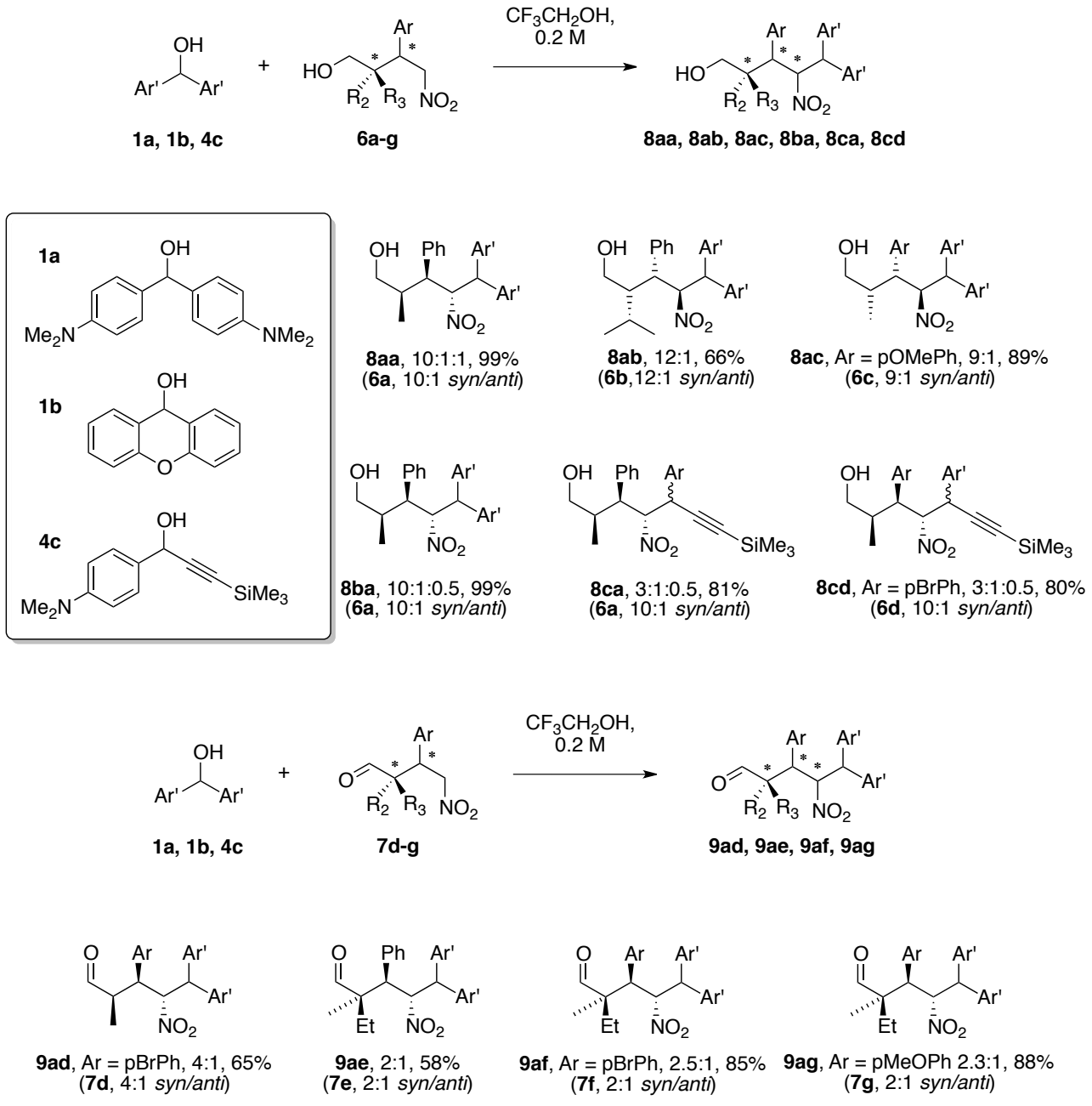


Scheme 3.2. Reaction of the alcohols **4a-h** with nitroethane in trifluoroethanol.

Not symmetric phenyldimethylammino-benzhydrylic substrates substituted with aryl or heteroaryl group are reactive in the reaction conditions giving high yield of product but with poor diastereoselectivity. Moderate level of simple diastereoselection were recorded alkynyl derivatives. The presence of the *p*NMe_2 substituent as an activating group was important in order to observe the formation of the desired product in good yield, but it is not mandatory, as other alcohols able to form stabilized carbenium ion in the range of -7 and -1 could be used.[21] For example indole alkynyl substrates can form quite stabilized carbenium ion[22] and are suitable substrates. In addition, the presence of the activating *p*NMe_2 moiety is not a limitation for the chemistry, as is possible to take advantage of its presence to introduce further functional groups, by nickel[23] or palladium[24] catalyzed reactions. Other alcohols, such as 1,3-diphenylprop-2-en-1-ol, are reactive as well, but the formation of ether by-product, obtained by the attack of the alcohol to the carbenium ion, is the predominant side product in this case. Also different benzylic substrates (i.e. Ar = *p*NMe_2Ph, R = *n*Bu) are reactive in the reaction conditions, but in this case the formation of alkene as the by-products, through elimination of water, is predominant.

Organocatalytic Michael and Henry type reactions gave simple stereoselective access to useful densely functionalized building blocks. Nitroderivatives obtained through organocatalytic reactions have found an increasing application in total synthesis. The organocatalyzed Michael addition of functionalized aldehydes to nitroalkenes is a key step in the total synthesis of the Tamiflu® and ABT 341.[25] Therefore, we wondered if such enantioenriched and accessible building blocks could be employed in the alkylation reaction performed in TFE. We were pleased to discover that the reaction was possible and it was also highly diastereoselective. The compounds **6a-c** and **7d** were obtained through standard organocatalytic procedures described by Hayashi[26] in high ee's (*syn*:*anti* 10:1 to 12:1).[27] The flash chromatography purification of

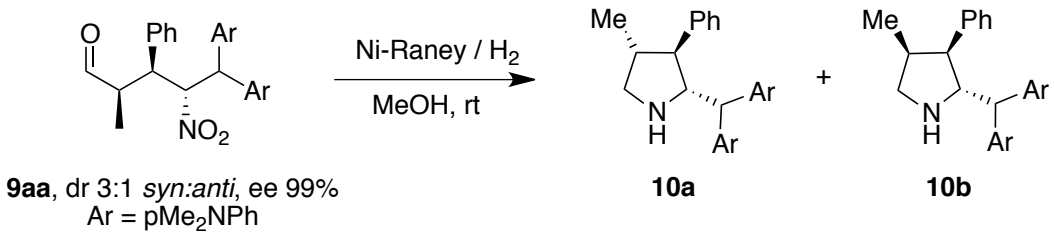
these compounds, performed by our group, gave a loss of dr ratio compared to the results obtained by Hayashi.[28] When the aldehyde was reduced to the corresponding alcohol prior to chromatography, the dr obtained were in line with those in Hayashi's paper. Nevertheless, in both cases the inseparable mixtures of diastereoisomers were used in the nitro alkylation reaction in order to evaluate the diastereoisomeric stereoselectivity of the reaction (*Scheme 3.3*).



Scheme 3.3. Highly diastereoselective addition of enantioenriched nitroderivatives **6a-g** and **7d-g** to alcohols **1a**, **1b** and **4c**. Conversion were determined by ^{1}H NMR.

By employing the Hayashi protocol, the enantiomeric excesses obtained are up to 99%, with just two steroisomers of the four possible present in the mixtures (*syn* and *anti* diastereoisomers of the nitro Michael reaction). In the alkylation reaction performed in TFE during 20-70h (see ES), alcohols that are not able to form the carbenium ion are recovered unconsumed after the reaction, and they do not need to be protected.

Four diasteroisomers can be formed by this alkylation reaction performed in TFE; *syn-syn, syn-anti, anti-syn, anti-anti*. In all the substrates investigated we have found (in the limitation of the NMR, GCMS, and HPLC-ESI-MS detections) the predominant presence of two favoured diastereoisomers. Starting from dr mixture of 10:1 it was possible to recognize the presence of another diastereoisomer as a minor component of the crude reaction mixture (**8aa** and **8ba**). The reaction is highly diastereoselective and the stereogenic center formed in the alkylation reaction is obtained with high stereocontrol (up to 9-10:1 *anti/syn*). The variation in the ratio between the starting and final diastereoisomers is inferred by the different reactivity between the *syn* (major diastereoisomer) and the *anti* (minor diastereoisomer) of the starting material. In fact, the reaction of the compound **7a** (*syn/anti* 2:1) with **1a** in TFE at 0 °C was not complete after 24h, and the observed ratio of **9aa** was 4:1. On the other hand, when the compound **7f** (*syn/anti* 2:1) was treated with **1a** in TFE at -20 °C for 18 days, the dr of the final mixture (50% conversion) was 4:1. The substrates **7e-g** were obtained using a thiourea catalyst, following the protocol established by Jacobsen.[29] As reported by Jacobsen, the d.r. obtained in this reaction is moderate. However, the more hindered substrates undergo alkylation in TFE, in a diastereoselective reaction. No evidence for the presence of the other two diastereoisomers was obtained by ^{1}H NMR or HPLC-ESI-MS. The reaction is also possible with the alcohol **4c**, but a mixture of diastereoisomers is obtained. The reaction of chiral nitroderivative with alcohols **1a-b** and **4c** is another example of diastereoselective S_N1 type reaction. Quite recently Bach has exploited diastereoselective alkylation[30] by S_N1-type reactions[31] in which chiral carbenium ions are formed and reacted with various nucleophiles. The relative anti-configuration of the newly formed stereogenic center was established by 'NOE' correlation on 400 and 600 MHz NMR on a cyclic product obtained by reduction of the nitro group (*Scheme 3.4*, see ES). The reaction of **7a** (*syn/anti* 3:1, 99% ee) in TFE gave the corresponding product **9aa** which was purified by chromatography and treated with Ni-Raney in MeOH at 20 °C in the presence of H_2. The corresponding pyrrolidine **10a** was isolated in 60% yield in high enantiomeric excess after chromatographic purification.



Scheme 3.4. Cyclization of derivative **9aa** by Ni-Raney in MeOH.

Although the precise role of TFE in the diastereoselective reaction is not clear at the present time,[32] we can suggest a model for the formation of the major stereoisomer. We assume that the sterical hindrance of the carbenium ion, generated by the action of TFE, is attached by the nitro derivative while avoiding sterical interaction with the aryl groups on the alpha-carbon (*Figure 3.5*).

It is worth adding that the cyclization procedure gives simple access to α-substituted pyrrolidines that might serve as potential organocatalysts.

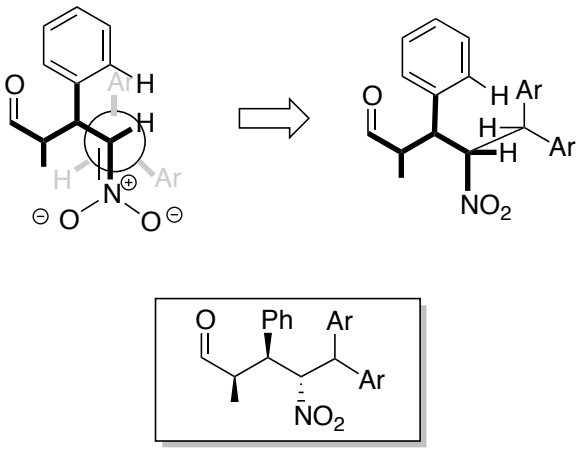
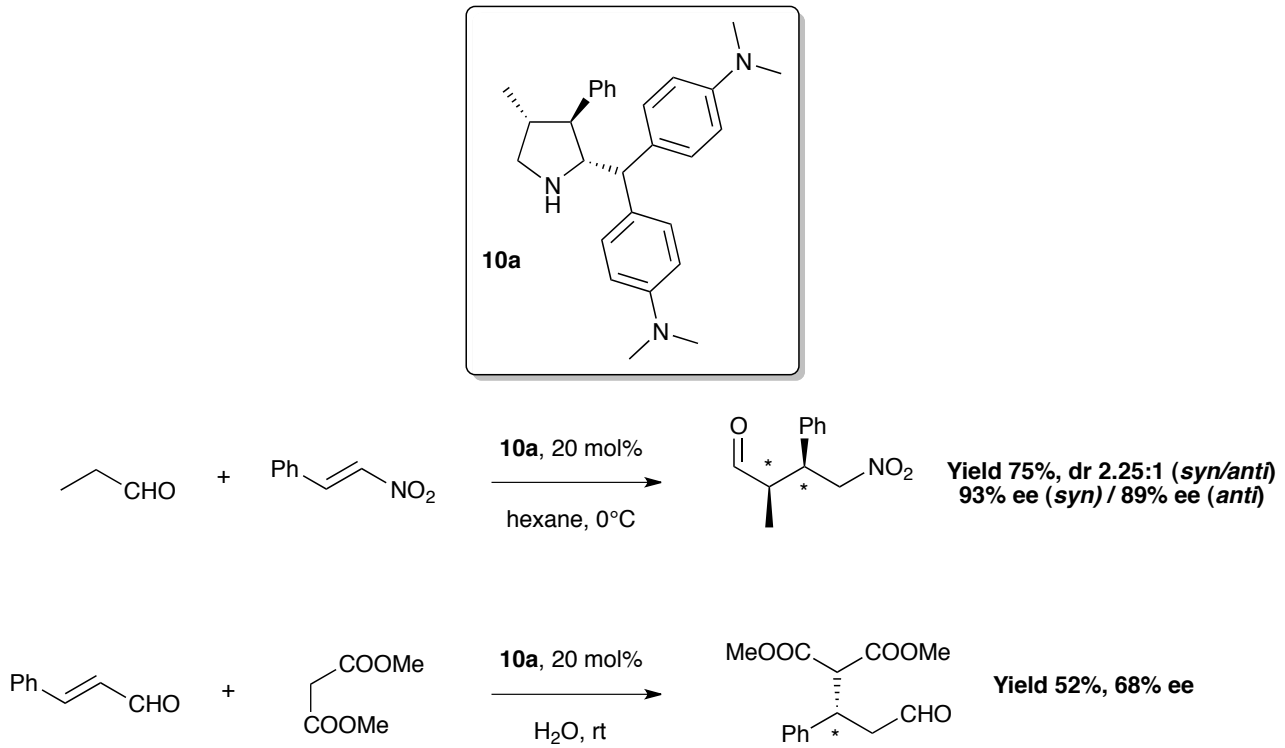


Figure 3.5. Stereochemical model for the addition of chiral nitro derivatives to benzhydrylic alcohols.

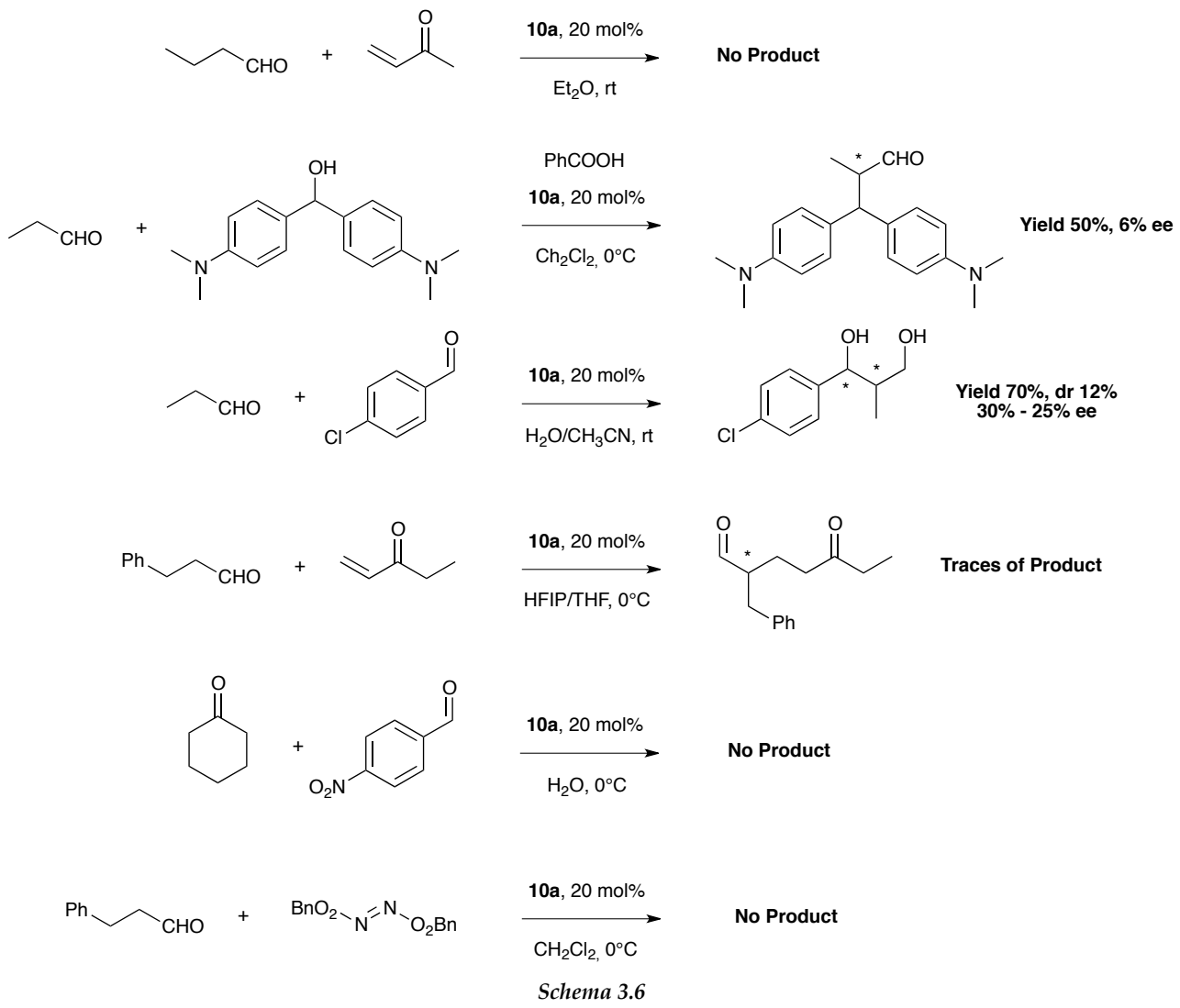
To shown the potentially of the newly synthesized catalysts **10a**,[33] we have explored its use in standard organocatalytic reactions (*Scheme 3.5*).

The best results were obtained in the Michael and nitro-Michael reaction:



Scheme 3.5. Organocatalytic reactions performed in the presence of 20 mol% of the pyrrolidine catalyst **10a**.

In other type reactions the catalyst has not led to the formation of products or gave quite low enantiomeric excesses (*Schema 3.6*).



Schema 3.6

Conclusions

In conclusion, we have described the first addition of nitroderivatives to alcohols. The reaction tolerates a range of functional groups and was performed using TFE as reaction solvent. Acyclic chiral nitroderivatives undergo alkylation of carbenium ion formed by alcohols in a highly diastereoselective fashion. Hindered secondary amines can be prepared from these adducts in a straightforward manner, giving access to functionalized, useful organocatalytic chiral pyrrolidines. A family of new pyrrolidines bearing sterogenic centers and functional groups can be readily accessible by this methodology.[34]

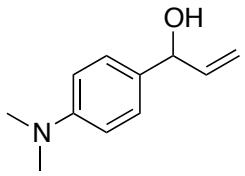
Experimental Section

General Methods.

^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian MR 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: *m/z* (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Determination of enantiomeric excess were performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using a Daicel Chiralpak columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line), specific rotation was expressed as deg $cm^3g^{-1}dm^{-1}$ and concentration as gcm^{-3}. Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected.

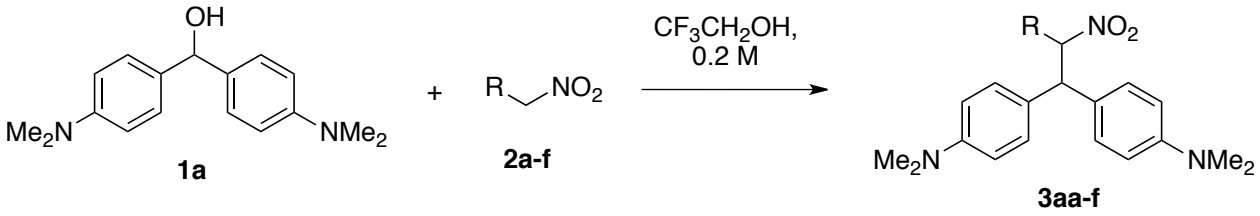
Materials: All reactions were carried out in sealed vials in open air without nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification. Compounds **1a,b** and **2a-g** are commercially available. Hayashi catalyst ((*R*) and (*S*) α,α-diphenyl prolinol trimethyilsilyl ether) is commercially available (Aldrich). Trifluoroethanol was used as received without further purification. Compounds **4a-b,f**,[35] **4c-e**[36] and were prepared according to the literature procedure. Spectral characterization for compound **4f** was already reported.[37]

Procedure for the synthesis of compound 4f: 1-(4-(dimethylamino)phenyl)prop-2-en-1-ol



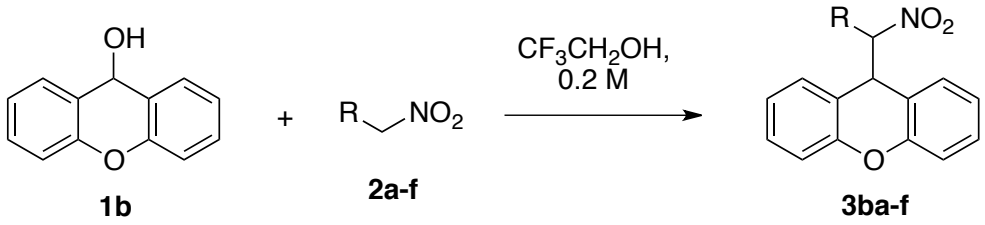
To a stirred solution of 4-(dimethylamino)benzaldehyde (2 mmol, 298 mg) in THF (5 mL) at -78 °C a solution of vinylmagnesium bromide (2.2 mmol, 1 M in THF, 2.2 mL) was added dropwise. The reactione mixture was slowly warmed at 0 °C and stirring until no further conversion take place (controlled by TLC). The reaction was worked up with aq. solution of NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted twice with EtOAc (20 mL). The collect organic layers were dried over Na_2SO_4 and concentrated under reduce pressure obtain an orange oil. The residue was purified by flash chromatography (cyclohexane:Et_2O; 7/3) to give **4f** as yellow oil. (1.7 mmol, 304 mg, 86% Yield.). ^{1}H NMR (400 MHz, $[D_3]CHCl_3$, 25 °C) δ 7.23 (d, 2H, J = 8.6Hz, 2ArH), 6.77 (d, 2H, J = 8.9Hz, 2ArH), 6.06 (ddd, J = 5.9Hz, J = 10.4Hz, J = 17.1Hz, CH=), 5.32 (ddd, J = 1.5Hz, J = 1.5Hz, J = 17.1Hz, $=CH_2$), 5.09 (ddd, J = 1.5Hz, J = 1.5Hz, J = 10.3Hz, $=CH_2$), 5.09 (bd, 1H, J = 5.9 Hz, 1ArCHOH), 2.94 (s, 6H, $2NCH_3$), 2.36 (bs, 1H, OH) ppm. ^{13}C NMR (100.76 MHz, $[D_3]CHCl_3$, 25 °C) δ 150.2 (C), 140.5 (CH), 130.7 (C), 127.3 (CH), 114.0 (CH_2), 112.5 (CH), 74.8 (CH), 40.5 (CH_3) ppm.

General procedure for the synthesis of compounds 3aa-f



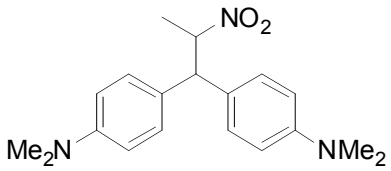
In an air-open vial the 4,4'-bis(dimethylamino)-benzhydrol **1a** (27 mg, 0.1 mmol, 1 equiv) was dissolved in triufluoroethanol (0.2 mL, 0.5 M). The nitroalkane (0.5 mmol, 5 equiv.) was added and the reaction was stirred at room temperature for the indicated time. The reaction mixture was than concentrated to afford crude product that was purified by flash chromatography (Cyclohexane/AcOEt 7:3-1:1) to provide pure product.

General procedure for the synthesis of compounds 3ba-f



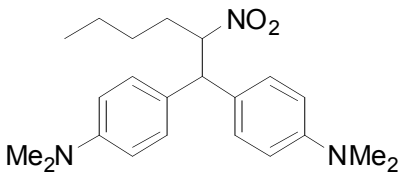
In an air-open vial 9*H*-xanthen-9-ol (20 mg, 0.1 mmol, 1 equiv) and DMAP (3 mg, 0.025 mmol, 0.25 equiv) were dissolved in trifluoroethanol (0.2 mL, 0.5 M). Nitroalkane (0.5 mmol, 5 equiv.) was added to the reaction mixture and the reaction was stirred at room temperature until disappear of **1b** checked by TLC. The reaction mixture was then concentrated under reduced pressure and the crude reaction mixture was purified by flash chromatography (Cyclohexane/AcOEt 7:3-1:1) to provide the pure product.

4,4′-(2-Nitropropane-1,1-diyl)bis(N,N-dimethylaniline), 3aa.



^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.13 (d, 2H, J = 8.8Hz, 2ArH), 7.10 (d, 2H, J = 8.8Hz, 2ArH) 6.65 (d, 2H, J = 8.8Hz, 2ArH), 6.61 (d, 2H, J = 8.8Hz, 2ArH), 5.24-5.34 (m, 1H, CHNO$_2$), 4.22 (d, 1H, J = 11.3Hz, 1ArHAr), 2.90 (d, 12H, J = 12.6Hz, 4NCH$_3$), 1.50 (d, 3H, J = 5.6Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 128.8 (C), 128.0 (C), 113.1 (CH), 112.9 (CH), 87.6 (CH), 54.9 (CH), 40.7 (CH$_3$), 27.1 (CH$_3$). ESI-MS: *m/z* = [M+H]$^+$, 260.1 [M+Na]$^+$, [2M+Na]$^+$.

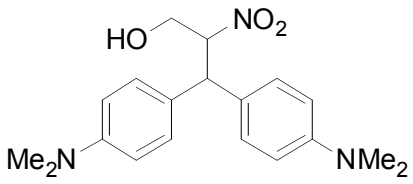
4,4′-(2-Nitrohexane-1,1-diyl)bis(N,N-dimethylaniline), 3ab.



^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.14 (d, 2H, J = 8.8Hz, 2ArH), 7.10 (d, 2H, J = 8.8Hz, 2ArH), 6.65 (d, 2H, J = 8.8Hz, 2ArH), 6.60 (d, 2H, J = 8.8Hz, 2ArH), 5.18-5.15 (m, 1H, CHNO$_2$), 4.20 (d, 1H, J = 11.4Hz, 1ArHAr), 2.88 (d, 12H, J = 12.5 Hz, 1ArHAr), 2.88 (d, 12H, J = 15.2Hz, 4NCH$_3$), 1.94-1.85 (m, 1H, CH$_2$), 1.72-1.64 (m, 1H, CH$_2$), 1.37-1.20(m, 4H, CH$_2$CH$_2$), 0.84-0.80 (t, 3H, J = 7.0Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.5 (C),

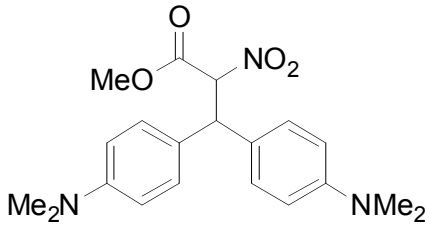
128.4 (C), 127.9 (CH), 112.9 (CH), 92.7 (CH), 54.1 (CH), 40.5 (CH_3), 32.7 (CH_2), 28.1 (CH_2), 21.9 (CH_2), 13.7 (CH_3).

3,3-bis(4-(Dimethylamino)phenyl)-2-nitropropan-1-ol, 3ac.



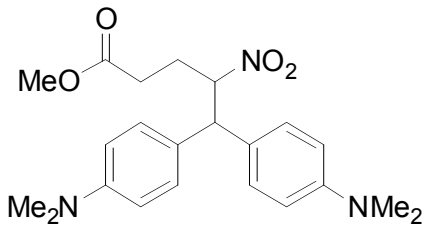
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.15 (d, 2H, J = 8.8Hz 2ArH), 7.12 (d, 2H, J = 8.8Hz 2ArH), 6.64 (d, 2H, J = 8.8Hz 2ArH), 6.62 (d, 2H, J = 8.9Hz, 2ArH), 5.38-5.32 (m, 1H, $CHNO_2$), 4.31 (d, 1H, J = 11.7Hz, 1ArHAr), 3.95 (dd, 1H, J = 8.0, 12.3Hz, CH_2OH), 3.38 (dd, 1H, J = 12.3, 2.9Hz, CH_2OH), 2.86 (d, 12H, J = 10.0Hz, 4NCH_3) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.8 (C), 128.1 (CH), 127.2 (C), 113.0 (CH), 93.3 (CH), 63.5 (CH_2), 50.4 (CH), 40.6 (CH_3).

Methyl 3,3-bis(4-(dimethylamino)phenyl)-2-nitropropanoate, 3ad.



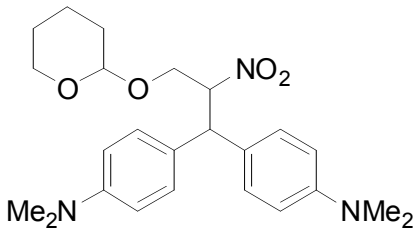
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.14 (d, 2H, J = 8.8Hz, 2ArH), 7.09 (d, 2H, J = 8.8Hz, 2ArH), 6.62 (d, 2H, J = 8.8 2ArH), 6.61 (d, 2H, J = 8.8 2ArH), 5.83 (d, 1H, J = 12.0Hz, $CHNO_2$), 4.83 (d, 1H, J = 12.0Hz, 1ArHAr), 3.61 (s, 1H, CH_3O), 2.89 (d, 12H, J = 2.3Hz, 4NCH_3) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 164.2 (CO), 149.9 (C), 128.1 (CH), 126.6 (C), 112.8 (CH), 91.9 (CH), 53.5 (CH_3), 50.9 (CH), 40.5 (CH_3).

Methyl 5,5-bis(4-(dimethylamino)phenyl)-4-nitropentanoate, 3ae



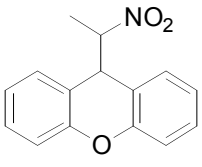
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.14 (d, 2H, J = 8.8Hz, 2ArH), 7.13 (d, 2H, J = 8.8Hz, 2ArH), 6.66 (d, 2H, J = 8.8Hz, 2ArH), 6.60 (d, 2H, J = 8.8Hz, 2ArH), 5.36-5.30 (m, 1H, $CHNO_2$), 4.21 (d, 1H, J = 11.4Hz, 1ArHAr), 3.66 (s, 1H, CH_3O), 2.82 (d, 12H, J = 14.7Hz, 4NCH_3), 2.40-2.26 (m, 2H, CH_2CO), 2.16-2.10 (m, 2H, CH_2) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 172.5 (CO), 149.7 (C), 128.1 (CH), 127.6 (C), 112.9 (CH), 91.8 (CH), 54.1 (CH_3), 51.9 (CH), 40.6 (CH_3), 30.2 (CH_2), 28.1 (CH_2). HMRS found 399.21566; $C_{22}H_{29}N_3O_4$ requires: 399.215807.

4,4′-(2-Nitro-3-((tetrahydro-2H-pyran-2-yl)oxy)propane-1,1-diyl)bis(N,N-dimethylaniline), 3af.



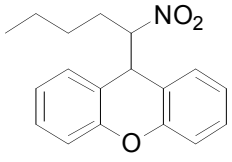
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.18-7.10 (m, 4H, 4ArH), 6.66-6.60 (m, 4H, 4ArH), 5.51-5.44 (m, 1H, $CHNO_2$), 4.58-4.54 (m, 1H, OCHO), 4.23 (d, 1H, J = 11.4Hz, 1ArHAr), 3.92-3.83 (m, 1H, CCH_2), 3.82-3.72 (m, 1H, OCH_2), 3.63-3.54 (m, 1H, OCH_2CH_2), 3.52-3.42 (m, 1H, OCH_2CH_3), 2.87 (d, 12H, J = 10.5Hz, 4NCH_3), 1.80-1.65 (m, 2H, CH_2CHO_2), 1.63-1.47 (m, 2H, CH_2CH_2) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.7 (C), 128.0 (CH), 127.4 (C), 112.8 (CH), 97.4 (CH), 91.2 (CH), 67.2 (CH_2), 61.3 (CH_2), 51.0 (CH), 40.6 (CH_3), 30.1 (CH_2), 25.3 (CH_2), 18.4 (CH_2). ESI-MS: *m/z* = 428.5 $[M+H]^+$, 855.8 $[2M+H]^+$.

9-(1-Nitroethyl)-9H-xanthene, 3ba.



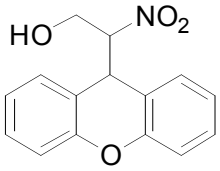
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.35-7.26 (m, 4H, 4ArH), 7.18-7.09 (m, 4H, 4ArH), 4.76 (d, 1H, J = 6.0Hz, $CHNO_2$), 4.65-4.58 (m, 1H, 1$CHNO_2$), 1.25 (d, 3H, J = 6.7Hz, CH_3) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 152.8 (C), 129.3 (CH), 128.6 (CH), 124.1 (CH), 118.8 (C), 117.0 (CH), 88.3 (CH), 44.2 (CH), 14.0 (CH_3).

9-(1-Nitropentyl)-9H-xanthene, 3bb.



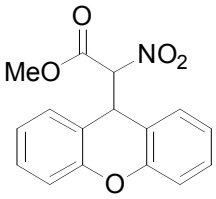
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.35-7.24 (m, 2H, 2ArH), 7.20-7.14 (m, 4H, 4ArH), 7.12-7.06 (m, 2H 2ArH), 4.48 (d, 1H, J = 7.6Hz, CHNO$_2$), 4.45-4.38 (m, 1H, 1CHNO$_2$), 1.93-1.80 (m, 1H, CH$_2$), 1.54-1.42 (m, 1H, CH$_2$), 1.22-0.98 (m, 4H, CH$_2$CH$_2$), 0.73(t, 3H, J = 8.4Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 152.9 (C), 129.3 (CH), 129.5 (CH), 123.7 (C), 120.0 (C), 117.0 (CH), 93.7 (CH), 44.5 (CH), 29.3 (CH$_2$), 28.0 (CH$_2$), 22.0 (CH$_2$), 13.7 (CH$_3$).

2-Nitro-2-(9H-xanthen-9-yl)ethanol, 3bc.



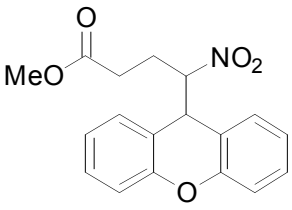
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.42-7.38 (m, 2H, 2ArH), 7.33-7.24 (m, 4H, 4ArH), 7.22-7.17 (m, 2H, 2ArH), 4.89 (d, 1H, J = 7.4Hz, ArHAr), 4.66 (dt, 1H, J = 2.6, 7.7Hz, CHNO$_2$), 3.93 (dd, 1H, J = 7.8, 12.8Hz, CH$_2$OH), 3.81 (dd, 1H, J = 2.2, 13.0Hz, CH$_2$OH), 2.17 (bs, 1H, OH) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 153.1 (C), 129.5 (CH), 128.6 (CH), 124.1 (C), 119.0 (C), 117.2 (CH), 93.6 (CH), 60.1 (CH$_2$), 40.9 (CH).

Methyl-2-nitro-2-(9H-xanthen-9-yl)acetate, 3bd.



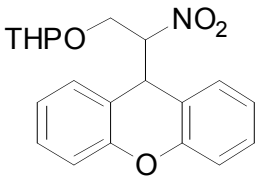
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.34-7.22 (m, 4H, 4ArH), 7.17 (d, 2H, J = 8.0Hz, ArH), 7.12-7.05 (m, 2H, 2ArH), 5.06 (q, 2H, J = 9.0, 21.7Hz, CHCH), 3.61 (s, 3H, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 163.3 (CO), 153.2 (C), 129.7 (CH), 128.8 (CH), 123.9 (C), 119.9 (C), 117.3 (CH), 92.1 (CH), 53.6 (CH$_3$), 41.5 (CH). ESI-MS: *m/z* = 317.3 [M+H2O]$^+$, 322.3 [M+Na]$^+$.

Methyl-4-nitro-4-(9H-xanthen-9-yl)butanoate, 3be



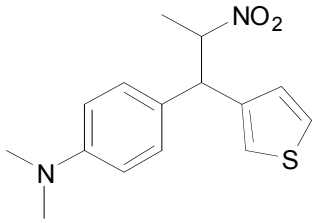
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.36-7.23 (m, 3H, 3ArH), 7.20-7.10 (m, 5H, 5ArH), 4.65-4.57 (m, 2H, CHCH), 3.57 (s, 3H, CH$_3$), 2.30-2.20 (m, 1H, CH$_2$CH), 2.19-2.07 (m, 2H, CH$_2$CO), 1.95-1.86 (m, 1H, CH$_2$CH) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 172.2 (CO), 152.9 (C), 129.4 (CH), 128.6 (CH), 123.9 (C), 119.1 (C), 117.2 (CH), 92.5 (CH), 51.9 (CH$_3$), 44.3 (CH), 30.2 (CH$_2$), 24.2 (CH$_2$).

9-(1-Nitro-2-((tetrahydro-2H-pyran-2yl)oxy)ethyl)-9H-xanthene, 3bf.



^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.35-7.20 (m, 3H, 3ArH), 7.18-7.05 (m, 5H, 5ArH), 4.80-4.67 (m, 1H, ArHAr), 4.66-4.58 (m, 1H, CHNO$_2$), 4.50-4.41 (m, 1H, OCHO), 4.19-1.04 (m, 1H, CH$_2$O), 3.80-3.74 (m, 1H, CH$_2$O), 3.69-3.54 (m, 1H, CH$_2$O), 3.48-3.33 (m, 1H, CH$_2$O), 1.72-1.35 (m, 6H, CH$_2$CH$_2$CH$_2$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 152.9 (C), 129.5 (CH), 128.6 (CH), 123.9 (C), 119.2 (C), 117.1 (CH), 98.0 (CH), 92.0 (CH), 64.7 (CH$_2$), 61.6 (CH$_2$), 41.5 (CH), 30.1 (CH$_2$), 25.3 (CH$_2$), 18.5 (CH$_2$). HMRS found 355.14173; $C_{20}H_{21}N_1O_5$ requires: 355.141974.

N,N-dimethyl-4-(2-nitro-1-(thiophen-3-yl)propyl)aniline (Major diasteroisomer), 5a

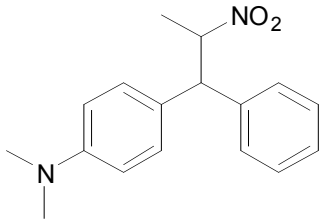


The reaction was performed under the general conditions described for 20 h. Yield 88% as a mixture of diastereoisomers. D.r. 1.12:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.15-7.22 (m, 3H, ArH), 6.93-6.99 (m, 1H, ArH), 6.85-6.90 (m, 1H, ArH), 6.70 (d, 2H, J = 8.6Hz, 2ArH), 5.18-5.26 (m, 1H, CHNO$_2$), 4.63 (d, 1H, J = 5.7Hz, 1ArCHAr), 2.95 (s, 6H, 2NCH$_3$), 1.48 (d, 3H, J = 6.5Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.9 (C), 143.8 (C), 128.8 (CH), 126.9 (CH), 126.0 (C), 125.3 (CH), 124.7 (CH), 112.7 (CH), 88.4 (CH), 50.9 (CH), 40.4 (CH$_3$), 19.0 (CH$_3$) ppm.

(minor diastereoisomer): 7.15-7.22 (m, 3H, ArH), 6.93-6.99 (m, 1H, ArH), 6.85-6.90 (m, 1H, ArH), 6.66 (d, 2H, J = 8.8Hz, 2ArH), 5.18-5.26 (m, 1H, CHNO$_2$), 4.61 (d, 1H, J = 6.1Hz, 1ArCHAr), 2.91 (s, 6H, 2NCH$_3$), 1.59 (d, 3H, J = 6.6Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.8 (C), 143.0 (C), 128.1 (CH), 126.7 (CH), 126.0 (C), 124.7 (CH), 124.6 (CH), 112.6 (CH), 87.7 (CH), 50.6 (CH), 40.4 (CH$_3$), 19.1 (CH$_3$) ppm.

N,N-dimethyl-4-(2-nitro-1-phenylpropyl)aniline, (Major diasteroisomer), 5b

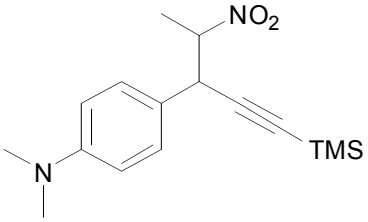


The reaction was performed under the general conditions described for 20 h. Yield 88%. D.r.1.3:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.24-7.32 (m, 5H, ArH), 7.18 (d, 2H, J = 8.5Hz, 2ArH), 6.68 (d, 2H, J = 8.6Hz, 2ArH), 5.33-5.39 (m, 1H, CHNO$_2$), 4.33 (d, 1H, J = 11.3Hz, 1ArCHAr), 2.91 (s, 6H, 2NCH$_3$), 1.53 (d, 3H, J = 6.6Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.6 (C), 140.0 (C), 128.9 (CH), 128.7 (CH), 127.9 (CH), 127.0 (CH), 126.7 (C), 112.7 (CH), 87.1 (CH), 55.5 (CH), 40.7 (CH$_3$), 19.2 (CH$_3$) ppm.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.24-7.32 (m, 5H, ArH), 7.13 (d, 2H, J = 8.9Hz, 2ArH), 6.63 (d, 2H, J = 9.0Hz, 2ArH), 5.33-5.39 (m, 1H, CHNO$_2$), 4.33 (d, 1H, J = 11.3Hz, 1ArCHAr), 2.88 (s, 6H, 2NCH$_3$), 1.49 (d, 3H, J = 6.4Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.7 (C), 140.5 (C), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.1 (CH), 127.1 (C), 112.8 (CH), 87.0 (CH), 55.4 (CH), 40.7 (CH$_3$), 19.3 (CH$_3$) ppm.

N,N-dimethyl-4-(4-nitro-1-(trimethylsilyl)pent-1-yn-3-yl)aniline, (Major diasteroisomer), 5c

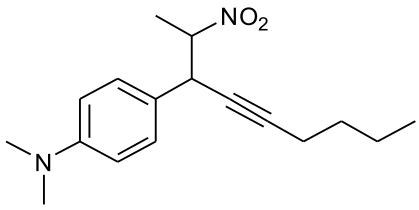


The reaction was performed under the general conditions described for 4 h at 70°C. Yield 92% as a mixture of diasteroisomers. D.r. 2.3:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.20 (d, 2H, J = 8.6Hz, 2ArH), 6.70 (d, 2H, J = 8.6Hz, 2ArH), 4.61-4.63 (m, 1H, CHNO$_2$), 4.33 (d, 1H, J = 7.9 Hz, 1ArCHCC), 2.96 (s, 6H, 2NCH$_3$), 1.64 (d, 3H, J = 6.7Hz, 1CH$_3$), 0.19 (s, 9H, 3CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 150.2 (C), 128.6 (CH), 123.4 (C), 112.6 (CH), 101.9 (C), 91.1 (C), 87.6 (CH), 43.0 (CH), 40.4 (CH$_3$), 16.0 (CH$_3$), -0.12 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.16 (d, 2H, J = 8.6Hz, 2ArH), 6.68 (d, 2H, J = 8.6Hz, 2ArH), 4.71-4.73 (m, 1H, CHNO$_2$), 4.16 (d, 1H, J = 8.2 Hz, 1ArCHCC), 2.95 (s, 6H, 2NCH$_3$), 1.40 (d, 3H, J = 6.5Hz, 1CH$_3$), 0.17 (s, 9H, 3CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 150.3 (C), 129.2 (CH), 122.1 (C), 112.5 (CH), 103.2 (C), 89.9 (C), 87.6 (CH), 42.7 (CH), 40.4 (CH$_3$), 16.4 (CH$_3$), -0.15 (CH$_3$) ppm.

N,N-dimethyl-4-(2-nitronon-4-yn-3-yl)aniline, (Major diasteroisomer), 5d

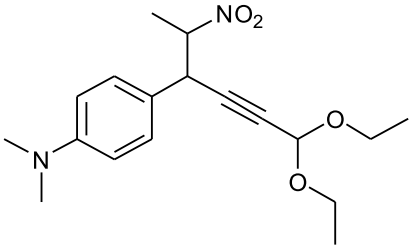


The reaction was performed under the general conditions described for 4 h at 70 °C. Yield 91% as a mixture of diasteroisomers. D.r. 1.7:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.20 (d, 2H, J = 8.7Hz, 2ArH), 6.65-6.70 (m, 2ArH), 4.64-4.70 (m, 1H, CHNO$_2$), 4.06 (dt, 1H, J = 2.1 Hz, J = 8.7 Hz,1ArCHCC), 2.93 (s, 6H, 2NCH$_3$), 2.18 (td, 2H, J = 2.4 Hz, J = 6.9 Hz,CH$_2$CC), 1.38-1.54 (m, 4H, CH$_2$CH$_2$), 1.36 (d, 3H, J = 6.8Hz, 1CH$_3$), 0.90 (t, 3H, J = 7.2Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 150.2 (C), 129.1 (CH), 123.3 (C), 112.4 (CH), 88.1 (CH), 85.4 (C), 77.4 (C), 42.0 (CH), 40.4 (CH$_3$), 21.7 (CH$_3$), 18.3 (CH$_3$), 16.6 (CH$_2$), 15.5 (CH$_2$), 13.5 (CH$_2$) ppm.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.15 (d, 2H, J = 8.7Hz, ArH), 7.00 (dd, 2H, J = 8.7Hz, J = 10.1Hz, ArH), 4.57-4.72 (m, 1H, CHNO$_2$), 4.31 (dt, 1H, J = 2.1 Hz, J = 7.3 Hz,1ArCHCC), 2.93 (s, 6H, 2NCH$_3$), 2.23 (td, 2H, J = 2.4 Hz, J = 6.8 Hz,CH$_2$CC), 1.38-1.54 (m, 4H, CH$_2$CH$_2$), 1.58 (d, 3H, J = 6.6Hz, 1CH$_3$), 0.92 (t, 3H, J = 7.5Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 150.0 (C), 128.5 (CH), 124.3 (C), 112.4 (CH), 87.6 (CH), 86.6 (C), 75.8 (C), 42.2 (CH), 40.5 (CH$_3$), 21.9 (CH$_3$), 18.4 (CH$_3$), 16.6 (CH$_2$), 15.5 (CH$_2$), 13.5 (CH$_2$) ppm.

4-(6,6-diethoxy-2-nitrohex-4-yn-3-yl)-N,N-dimethylaniline, (Major diasteroisomer), 5e

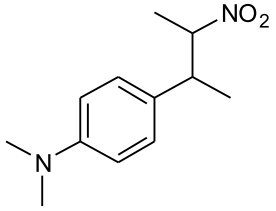


The reaction was performed under the general conditions described for 4 h at 70 °C. Yield 80% as a mixture of diasteroisomers. D.r. 1.3:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.13 (d, 2H, J = 8.7Hz, 2ArH), 6.65-6.68 (m, 2H, ArH), 5.27 (d, 1H, J = 1.3Hz, CHO), 4.62-4.76 (m, 1H, CHNO$_2$), 4.18 (dd, 1H, J = 1.3Hz, J = 7.6Hz, 1ArCHCC), 3.66-3.76 (m, 2H, OCH$_2$), 3.51-3.60 (m, 2H, OCH$_2$), 2.94 (s, 6H, 2NCH$_3$), 1.34 (d, 3H, J = 7.0Hz, 1CH$_3$), 1.18-1.24 (m, 6H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 150.3 (C), 129.3 (CH), 121.7 (C), 112.6 (CH), 91.1 (CH), 87.3 (CH), 83.0 (CH), 80.6 (C), 61.0 (CH$_2$), 60.0 (CH$_2$), 42.1 (CH), 40.5 (CH$_3$), 16.8 (CH$_3$), 15.2 (CH$_3$) ppm.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.18 (d, 2H, J = 8.7Hz, 2ArH), 6.65-6.68 (m, 2H, ArH), 5.30 (d, 1H, J = 1.3Hz, CHO), 4.62-4.76 (m, 1H, CHNO$_2$), 4.36 (dd, 1H, J = 1.3Hz, J = 7.6Hz, 1ArCHCC), 3.66-3.76 (m, 2H, OCH$_2$), 3.51-3.60 (m, 2H, OCH$_2$), 2.93 (s, 6H, 2NCH$_3$), 1.64 (d, 3H, J = 7.0Hz, 1CH$_3$), 1.18-1.24 (m, 6H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 150.2 (C), 129.8 (CH), 122.8 (C), 112.6 (CH), 91.4 (CH), 87.4 (CH), 81.8 (CH), 81.7 (C), 61.0 (CH$_2$), 60.9 (CH$_2$), 41.9 (CH), 40.5 (CH$_3$), 16.3 (CH$_3$), 15.2 (CH$_3$) ppm.

N,N-dimethyl-4-(3-nitrobutan-2-yl)aniline, (Major diasteroisomer), 5f

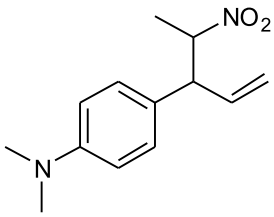


The reaction was performed under the general conditions described for 20 h. Yield 15% as a mixture of disteroisomers. D.r. 1.7:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.05 (d, 2H, J = 8.7Hz, 2ArH), 6.71 (d, 1H, J = 8.7Hz, 2ArH), 4.56-4.63 (m, 1H, CHNO$_2$), 3.09-3.18 (m, 1H, ArCH), 2.95 (s, 6H, 2NCH$_3$), 1.33 (d, 3H, J = 6.7Hz, 1CH$_3$), 1.29 (d, 3H, J = 7.1Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 149.6 (C), 128.2 (CH), 122.3 (C), 112.8 (CH), 89.6 (CH), 43.9 (CH), 40.5 (CH$_3$), 18.9 (CH$_3$), 18.1 (CH$_3$) ppm.

(minor diastereoisomer): Yield 10%. ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.05 (d, 2H, J = 8.5Hz, 2ArH), 6.69 (d, 1H, J = 8.5Hz, 2ArH), 4.62-4.75 (m, 1H, CHNO$_2$), 3.323 (q, 1H, J = 7.1Hz, 2ArH), 2.93 (s, 6H, 2NCH$_3$), 1.53 (d, 3H, J = 6.8Hz, 1CH$_3$), 1.30 (d, 3H, J = 7.3Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 149.8 (C), 127.9 (CH), 126.9 (C), 112.6 (CH), 89.1 (CH), 43.1 (CH), 40.5 (CH$_3$), 16.2 (CH$_3$), 16.1 (CH$_3$) ppm.

N,N-dimethyl-4-(4-nitropent-1-en-3-yl)aniline, (Linear, Major diasteroisomer), 5g

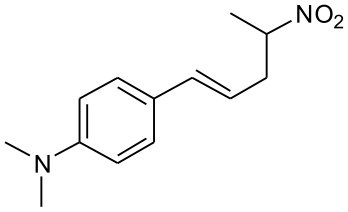


The reaction was performed under the general conditions described for 4 h at 70°C. Yield 72% as a mixture od stereo- and diasteroisomers. D.r. 1:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.04-7.08 (m, 2ArH), 6.67-6.72 (m, 2ArH), 5.82-6.03 (m, 1H, CH=), 5.08-5.23 (m, 2H, =CH$_2$), 4.75-4.87 (m, 1H, CHNO$_2$), 3.77 (dd, 1H, J = 9.0Hz, J = 9.0Hz, ArCH), 2.95 (s, 6H, 2NCH$_3$), 1.37 (d, 3H, J = 6.7Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.9 (C), 136.6 (CH), 128.6 (C), 126.2 (C), 118.2 (CH), 112.4 (CH), 87.9 (CH), 54.2 (CH), 40.5 (CH$_3$), 17.4 (CH$_3$) ppm.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.04-7.08 (m, 2ArH), 6.67-6.72 (m, 2ArH), 5.82-6.03 (m, 1H, CH=), 5.08-5.23 (m, 2H, =CH$_2$), 4.75-4.87 (m, 1H, CHNO$_2$), 3.62 (dd, 2H, J = 8.9Hz, J = 10.9Hz, ArCH), 2.93 (s, 6H, 2NCH$_3$), 1.58 (d, 3H, J = 5.6Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.8 (C), 135.5 (CH), 128.1 (C), 125.8 (C), 118.0 (CH), 112.9 (CH), 87.2 (CH), 54.1 (CH), 40.5 (CH$_3$), 17.8 (CH$_3$) ppm.

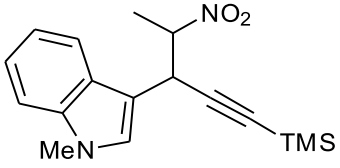
(E)-N,N-dimethyl-4-(4-nitropent-1-en-1-yl)aniline, (Unbranched), 5g



The reaction was performed under the general conditions described for 20 h.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.24 (d, 2H, J = 9.0Hz, 2ArH), 6.67-6.72 (m, 2ArH), 6.41 (d, 1H, J = 16.0Hz, 1H, CH=), 4.60-4.6 (m, 1H, =CH), 4.75-4.87 (m, 1H, CHNO$_2$), 2.95 (s, 6H, 2NCH$_3$), 2.75-2.86 (m, 1H, CH$_2$NO$_2$), 2.60-2.67 (m, 1H, CH$_2$NO$_2$), 1.59 (d, 3H, J = 5.9Hz, 1CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.9 (C), 134.4 (CH), 127.2 (C), 126.2 (C), 118.1 (CH), 112.7 (CH), 83.3 (CH), 40.5 (CH$_3$), 38.7 (CH$_2$), 17.4 (CH$_3$) ppm.

1-methyl-3-(4-nitro-1-(trimethylsilyl)pent-1-yn-3-yl)-1H-indole, (Major diasteroisomer), 5h

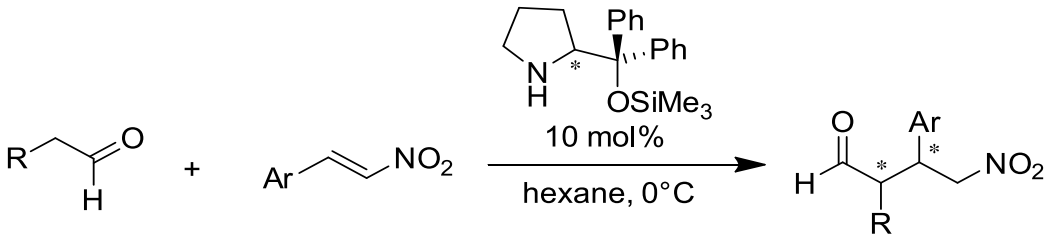


The reaction was performed under the general conditions described for 4h at 70°C. Yield 73%. D.r. 1.3:1

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.78 (m, 1H, ArH), 7.24-7.31 (m, 2H, 2ArH), 7.03-7.09 (m, 1H, ArH), 7.01 (s, 1H, ArH), 4.86-4.93 (m, 1H, CHNO$_2$), 4.74 (d, 1H, J = 7.3Hz, ArCH), 3.71 (s, 3H, NCH$_3$), 1.65 (d, 3H, J = 6.7Hz, 1CH$_3$), 0.19 (s, 9H, 3CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 137.4 (C), 127.2 (CH), 126.7 (C), 121.5 (CH), 119.5 (CH), 118.3 (CH), 114.5 (CH), 109.6 (CH), 101.4 (C), 90.4 (C), 85.7 (CH), 35.9 (CH$_3$), 32.7 (CH), 15.7 (CH$_3$), -0.09 (CH$_3$) ppm.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.78 (m, 1H, ArH), 7.24-7.31 (m, 2H, 2ArH), 7.17-7.11 (m, 1H, ArH), 6.91 (s, 1H, ArH), 4.86-4.93 (m, 1H, CHNO$_2$), 4.51 (d, 1H, J = 8.4Hz, ArCH), 3.74 (s, 3H, NCH$_3$), 1.46 (d, 3H, J = 6.6Hz, 1CH$_3$), 0.17 (s, 9H, 3CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 137.3 (C), 128.0 (CH), 125.7 (C), 122.1 (CH), 119.9 (CH), 118.7 (CH), 114.5 (CH), 109.7 (CH), 101.4 (C), 90.4 (C), 85.4 (CH), 35.9 (CH$_3$), 32.9 (CH), 17.0 (CH$_3$), -0.18 (CH$_3$) ppm.

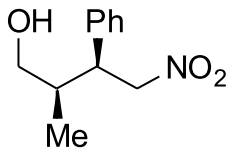
General procedure for the synthesis of compounds 6a-d and 7d



To a hexane solution of the nitroolefin (1.0 mmol, 1 equiv) and Hayashi catalyst (34 mg, 0.1 mmol, 0.1 equiv) was added an aldehyde (10 mmol, 10 equiv) at 0°C. After stirring the reaction mixture at 0°C for

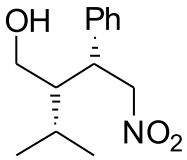
4-8 hours, the reaction was quenched by the addition of aq. 1N HCl. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated under reduced pressure to give an oil that was purified by flash chromatography (cyclohexane/AcOEt 7:3-1:1).

(2*R*, 3*S*)-2-methy-4-nitro-3-phenyl-butan-1-ol, 6a



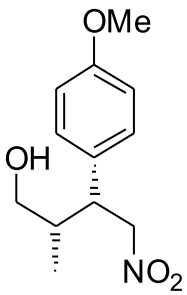
The compound was obtained following the procedure described by Hayashi et al.[38] The typical experimental procedure: Propanal (10 equiv) was added to a solution of nitrostyrene (1 equiv) and the (S)-Hayashi catalyst (10 mol%) in hexane (1M) at 0 °C. After the reaction mixture has been stirred for 5 h at that temperature, the reaction was diluted with MeOH and $NaBH_4$ in excess was added at 0 °C. After 1 hour the reaction was quenched by the addition of aqueous 1N HCl. MeOH was evaporated under reduced pressure and the reaction mixture was diluted with AcOEt. The organic phase was separated and the aqueous phase was extracted three times with AcOEt, and the combined organic phases were dried (Na_2SO_4), and purified by flash chromatography to afford the Michael adduct as a clear oil: syn/anti 10:1 (by 1H NMR spectroscopy of the crude mixture), 99% ee (by HPLC of the corresponding aldehyde on a chiral phase: chiralcel OD-H column, λ=214 nm, iPrOH/hexane 1:10, 1.0 mL min^{-1}; tR=30.0 min (major), 35.4 min (minor). ^{1}H NMR and ^{13}C were in agreement with the described compound.

(2*R*, 3*R*)-2-isopropyl-4-nitro-3-phenyl-butan-1-ol, 6b



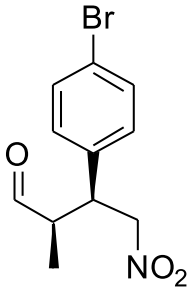
Title compound was prepared from (*E*)-β-nitrostyrene and isovaleraldehyde according to general procedure described by Hayashi et al.[38] using the (*R*)-Hayashi catalyst (10 mol%) After completion the reaction was diluted with MeOH and $NaBH_4$ in excess was added. The reaction was stirred at 0 °C for 1 hour, then it was quenched by the addition of aqueous 1N HCl. MeOH was evaporated under reduced pressure and the reaction mixture was diluted with AcOEt. The organic phase was separated and the aqueous phase was extracted three times with AcOEt, and the combined organic phases were dried (Na_2SO_4), and purified by flash chromatography to afford the Michael adduct as a clear oil: syn/anti 12:1 (by 1H NMR spectroscopy of the crude mixture), 99% ee (by HPLC of the corresponding aldehyde). Spectroscopic data are in agreement with the published data.

(2*S*, 3*R*)-3-(4-methoxyphenyl)2-methyl-4-nitrobutan-1-ol, 6c



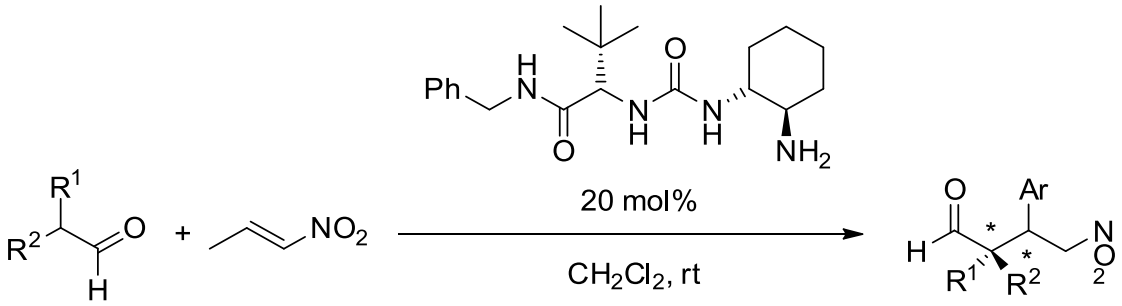
Title compound was prepared from 1-methoxy-4-(2-nitrovinyl)-benzene and propanal according to general procedure described by Hayashi et al.[38] using the (*R*)-Hayashi catalyst (10 mol%) After completion the reaction was diluted with MeOH and $NaBH_4$ in excess was added. The reaction was stirred at 0 °C for 1 hour, then it was quenched by the addition of aqueous 1N HCl. MeOH was evaporated under reduced pressure and the reaction mixture was diluted with AcOEt. The organic phase was separated and the aqueous phase was extracted three times with AcOEt, and the combined organic phases were dried (Na_2SO_4), and purified by flash chromatography to afford the Michael adduct as a clear oil: syn/anti 9:1 (by 1H NMR spectroscopy of the crude mixture), 99% ee (by HPLC of the corresponding aldehyde). Spectroscopic data are in agreement with the published data

(2*R*, 3*S*)-3-(4-Bromophenyl)2-methyl-4-nitrobutan-1-ol, 7d



Title compound was prepared from 1-bromo-4-(2-nitrovinyl)-benzene and propanal according to general procedure described by Hayashi et al.[38] using the (*S*)-Hayashi catalyst (10 mol%). Enantiomeric excess of the product obtained: 99%ee (by HPLC of the crude aldehyde). The crude Michael adduct was purified by flash chromatography to afford the desired compound as a clear oil: syn/anti 4:1 (by 1H NMR spectroscopy of the crude mixture). Spectroscopic data are in agreement with the published data.

General procedure for the synthesis of compounds 7e-g



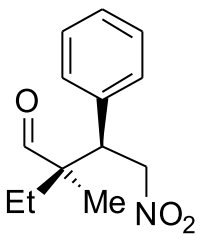
7e-g

The reaction was performed by employing a primary thiourea catalyst described by Jacobsen.[39]

Under a positive pressure of nitrogen at room temperature, thiourea catalyst (20 mol%) was added to a vial and CH_2Cl_2 was added. 2-methylbutanal (2 equiv) and water (5 equiv) were added to the vial by siringe. The resulting solution was stirred for few minutes then (*E*)-*β*-nitrostyrene (1 equiv) was added. The vial was sealed with a septum and the reaction was stirred for 24 h at room temperature.

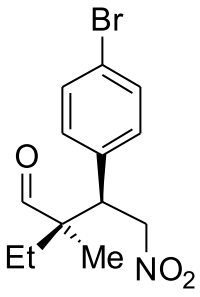
Aqueous hydrochloric acid solution (1M, 7 mL) was added to the reaction flask, and the resulting biphasic mixture was stirred vigorously for 5 min at room temperature. The biphasic mixture was transferred to a separating funnel, and additional portions of dichloromethane and 1M HCl were added. The phases were separated, and the aqueous layer was washed with dichloromethane. The organic layers were combined and washed with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow residue was purified by chromatography on silica (Cyclohexane/Ether 95:5), providing the title compound as a light yellow liquid in 78 % yield in 2:1 diastereomeric ratio.

(2*R**,3*R**)-2-ethyl-2-methyl-4-nitro-3-phenylbutanal, 7e



^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 9.54 (s, 1H, CHO), 7.36-7.27 (m, 3H, 3ArH), 7.22-7.16 (m, 2H, 2ArH), 4.87-4.74 (m, 1H, CH_2NO_2), 4.64-4.60 (m, 1H, CH_2NO_2), 1.63-1.43 (m, 2H, CH_2CH_3), 1.11 (s, 3H, CH_3), 0.81 (t, 3H, J = 7.4Hz, CH_2CH_3) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 205.8 (CO), 135.8 (C), 129.7(CH), 129.2 (CH), 128.6 (CH), 76.8 (CH_2), 52.2 (C), 47.9 (CH), 28.5 (CH_2), 15.8 (CH_3), 8.6 (CH_3). Enantiomeric excesses of the diastereoisomers obtained was not determined.

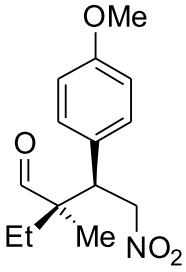
(2*R*,3*R*)-3-(4-bromophenyl)-2-ethyl-2-methyl-4-nitrobutanal, 7f



The resulting crude product was purified by chromatography on silica (Cyclohexane/AcOEt 9:1), providing the title compound as a light yellow liquid in 40 % yield in 2:1 diastereomeric ratio.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 9.50 (s, 1H, CHO), 7.50-7.38 (m, 2H, 2ArH), 7.14-7.00 (m, 2H, 2ArH), 4.88-4.68 (m, 1H, CH_2NO_2), 4.77-4.56 (m, 1H, CH_2NO_2), 3.82-3.68 (m, 1H, CHAr), 1.63-1.44 (m, 2H, CH_2CH_3), 1.09 (s, 3H, CH_3), 0.82 (t, 3H, J = 7.8Hz, CH_2CH_3) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 205.1 (CO), 134.6 (C), 132.1 (CH), 130.9 (CH), 122.4 (C), 76.6 (CH_2), 51.8 (C), 46.9 (CH), 28.2 (CH_2), 15.6 (CH_3), 8.2 (CH_3). Enantiomeric excesses of the diastereoisomers obtained was not determined.

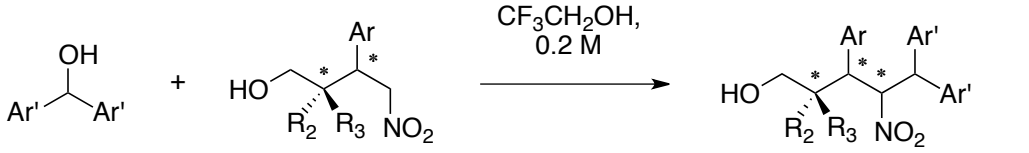
(2*R*,3*R*)-2-ethyl-3-(4-methoxyphenyl)-2-methyl-4-nitrobutanal, 7g



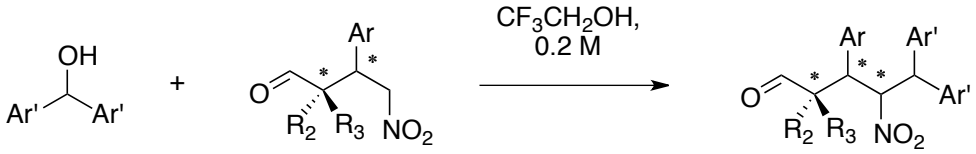
The resulting crude product was purified by chromatography on silica (Cyclohexane/AcOEt 9:1), providing the title compound as a light yellow liquid in 56 % yield in 1.9:1 diastereomeric ratio.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 9.52 (s, 1H, CHO), 7.15-7.05 (m, 2H, 2ArH), 6.89-6.80 (m, 2H, 2ArH), 4.85-4.68 (m, 1H, CH_2NO_2), 4.76-4.54 (m, 1H, CH_2NO_2), 3.78 (s, 3H, OCH_3), 3.77-3.68 (m, 1H, CHAr), 1.65-1.46 (m, 2H, CH_2CH_3), 1.08 (s, 3H, CH_3), 0.80 (t, 3H, J = 7.5Hz, CH_2CH_3) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 205.7 (CO), 159.5 (C), 130.4(CH), 127.2 (C), 114.2(CH), 77.0 (CH_2), 55.4 (CH_3), 52.1 (C), 46.9 (CH), 28.1 (CH_2), 15.4 (CH_3), 8.2 (CH_3). Enantiomeric excesses of the diastereoisomers obtained was not determined.

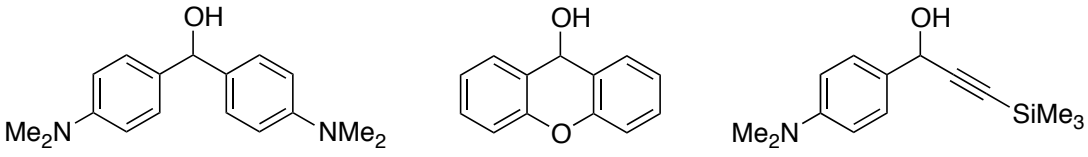
General procedure for the synthesis of compounds 8aa-8hd and 9ad-ag



1a, 1b, 4c **6a-g** **8aa, 8ab, 8ac, 8ba, 8ca, 8cd**



1a, 1b, 4c **7d-g** **9ad, 9ae, 9af, 9ag**

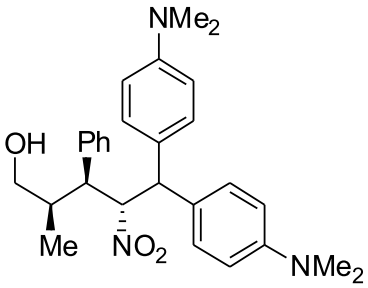


1a **1b** **4c**

In an air-open vial the nitroalkane derivative **6a-g** or **7d-g** (0.1 mmol, 1 equiv) was dissolved in trifluoroethanol (TFE) (0.2 mL, 0.5 M). The 4,4'-Bis(dimethylamino)-benzhydrol **1a** (29 mg, 0.11 mmol, 1.1 equiv) was added and the reaction was stirred room temperature for 24-48 h. The reaction mixture was concentrated and the crude reaction mixture was purified by flash chromatography (Cyclohexane:AcOEt 7/3)

to provide the pure products as mixtures of diastereoisomer. The dr ratio was evaluated by ^{1}H NMR and GCMS analysis on the crude reaction mixture before chromatography.

(2*R*,3*S*,4*R*)-5,5-bis(4-(dimethylamino)phenyl)-2-methyl-4-nitro-3-phenylpentan-1-ol, (Major diasteroisomer), 8aa

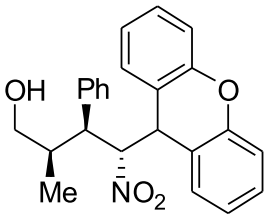


The reaction was performed under the general conditions described in ES for 20 h. Yield 75%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.18-7.14 (m, 3H, 3ArH), 7.02 (d, 2H, J = 8.8Hz, 2 ArH), 6.98 (d, 2H, J = 9.4Hz, 2ArH), 6.97 (d, 2H, J = 8.8Hz, 2ArH), 6.57 (d, 2H, J = 8.8Hz, 2ArH), 6.46 (d, 2H, J = 8.8Hz, 2ArH), 5.78 (dd, 1H, J = 9.6, 7.6Hz CHNO$_2$), 4.22 (d, 1H, J = 7.5Hz, 1ArHAr), 3.63 (dd, 1H, J = 9.7, 3.2Hz ArCH), 3.30-3.26 (m, 1H, CH$_2$OH), 3.16-3.08 (m, 1H, CH$_2$OH), 2.85 (d, 12H, J = 12.7Hz, 4NCH$_3$), 1.97-1.94 (m, 1H, CHCH$_2$), 1.10 (bs, 1H, OH), 0.81 (d, 3H, J = 6.9Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.3 (C), 135.9 (C), 130.0 (CH), 129.2 (CH), 128.0 (CH), 127.3 (C), 126.9 (CH), 112.4 (CH), 93.9 (CH), 65.8 (CH$_2$), 53.1 (CH), 48.1 (CH), 40.4 (CH$_3$), 36.8 (CH), 12.1 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 6.13 (dd, 1H, CHNO$_2$), 0.62 (d, 3H, CH$_3$) ppm.

(2*R*,3*S*,4*R*)-2-methyl-4-nitro-3-phenyl-4-(9*H*-xanthen-9-yl)butan-1-ol, (Major diastereoisomer), 8ba

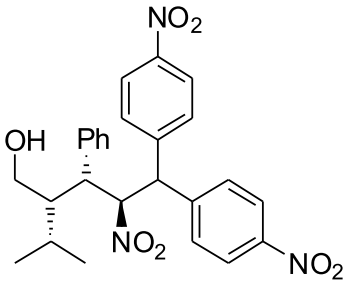


The reaction was performed under the general conditions described in ES for 70 h. Yield 76%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.44-7.40 (m, 3H, 3ArH), 7.36-7.32 (m, 1H, 1ArH), 7.30-7.20 (m, 5H, 5ArH), 7.12-7.00 (m, 4H, 4ArH), 5.32 (dd, 1H, J = 12.4, 2.8Hz CHNO$_2$), 4.40 (d, 1H, J = 2.6Hz, 1ArHAr), 3.80 (dd, 1H, J = 5.6, 11.0Hz, ArCH), 3.21-3.18 (dd, 1H, J = 9.1, 10.8Hz, CH$_2$OH), 3.05-3.00 (m, 1H, CH$_2$OH), 1.77-1.65 (m, 1H, CHCH$_3$), 1.40 (bs, 1H, OH), 0.72 (d, 3H, J = 7.0Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 153.1 (C), 134.5 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 127.9 (CH), 123.3 (CH), 120.9 (C), 117.1 (CH), 96.2 (CH), 65.5 (CH$_2$), 45.2 (CH), 41.4 (CH), 36.8 (CH), 11.0 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 4.35 (d, 1H, 1ArHAr), 0.69 (d, 3H, CH$_3$) ppm.

(2*R*,3*S*,4*S*)-2-isopropyl-4-nitro-5,5-bis(4-(dimethylamino)phenyl)-3-phenylpentan-1-ol (Major diastereoisomer), 8ab

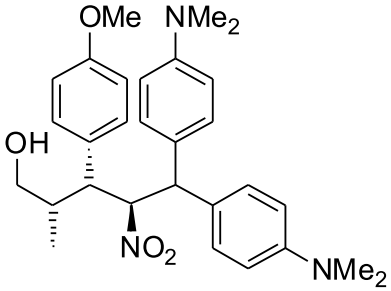


The reaction was performed under the general conditions described in ES for 20 h. Yield 75%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.23-7.18 (m, 3H, 3ArH), 7.07-6.99 (m, 6H, 6ArH), 6.54 (d, 4H, J = 8.8Hz, 4ArH), 5.93 (dd, 1H, J = 9.0, 6.7Hz, CHNO$_2$), 4.27 (d, 1H, J = 9.1Hz, 1ArHAr), 3.80-3.72 (m, 1H, CH$_2$OH), 3.64 (t, 1H, J = 6.2Hz, CHAr), 3.58-3.48 (m, 1H, CH$_2$OH), 2.85 (d, 12H, J = 8.0Hz, 4NCH$_3$), 1.82-1.72 (m, 1H, CH$_2$), 1.37 (bs, 1H, OH), 0.90 (d, 3H, J = 6.9Hz, CH$_3$), 0.25 (d, 3H, J = 6.9Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) 149.6 (C), 138.1 (C), 129.8 (CH), 129.0 (CH), 128.3 (CH), 127.2 (C), 113.0 (CH), 112.7 (CH), 94.5 (CH), 60.9 (CH$_2$), 52.6 (CH), 48.3 (CH), 47.2 (CH), 40.6 (CH$_3$), 26.7 (CH), 23.8 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 6.09 (dd, 1H, CHNO$_2$), 0.48 (d, 3H, J = 6.9Hz, CH$_3$) ppm.

(2*R*,3*S*,4*S*)-5,5-bis(4-(dimethylamino)phenyl)-3-(4-methoxyphenyl)-2-methyl-4-nitropentan-1-ol (Major diastereoisomer), 8ac

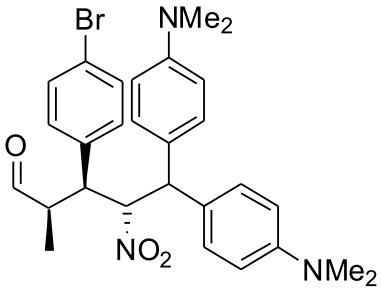


The reaction was performed under the general conditions described in ES for 20 h. Yield 89%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.03 (d, 2H, J = 8.8Hz, ArH), 6.95 (d, 2H, J = 8.8Hz, ArH), 6.87 (d, 2H, J = 8.8Hz, ArH), 6.68 (d, 2H, J = 8.8Hz, ArH) , 6.57 (d, 2H, J = 8.8Hz, ArH), 6.46 (d, 2H, J = 8.8Hz, ArH), 5.73 (dd, 1H, J = 9.7, 7.7Hz, CHNO$_2$), 4.20 (d, 1H, J = 7.6Hz, 1ArHAr), 3.77 (s, 3H, CH$_3$), 3.59 (dd, 1H, J = 9.7, 3.7Hz, CHAr), 3.24 (dd, 1H, J = 10.8, 5.5Hz, CH$_2$OH), 3.08 (dd, 1H, J = 10.8, 8.2Hz, CH$_2$OH), 2.84 (d, 12H, J = 11.3Hz, 4NCH$_3$), 1.98-1.85 (m, 1H, CHCH$_3$), 0.81 (t, 3H, J = 6.9Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 158.5 (C), 149.4 (C), 131.2 (CH), 128.9 (CH), 128.8 (C), 127.7 (C), 113.6 (CH), 112.6 (CH), 94.2 (CH), 66.0 (CH$_2$), 55.3 (CH$_3$), 53.3 (CH), 47.7 (CH), 40.6 (CH$_3$), 37.0 (CH), 12.2 (CH$_3$); ESI-MS: *m/z* = 317.3 [M+H2O]$^+$, 322.3 [M+Na]$^+$.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 6.08 (dd, 1H, CHNO$_2$), 0.81 (t, 3H, J = 6.9Hz, CH$_3$) ppm.

(2*R*,3*S*,4*R*)-3-(4-bromophenyl)-5,5-bis(4-(dimethylamino)phenyl)-2-methyl-4-nitropentanal (Major diastereoisomer), 9ad

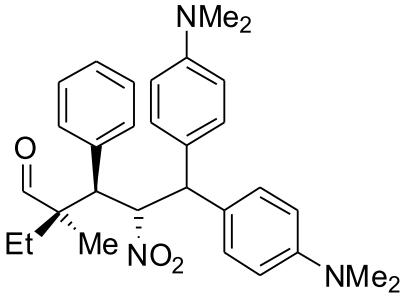


The reaction was performed under the general conditions described in SI for 45 h. Yield 65%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.61 (s, 1H, CHO), 7.31 (d, 2H, J = 8.4Hz, ArH), 7.05 (d, 2H, J = 8.8Hz, ArH), 7.00 (d, 2H, J = 8.8Hz, ArH), 6.77 (d, 2H, J = 8.4Hz, ArH), 6.55 (d, 2H, J = 8.8Hz, ArH), 6.54 (d, 2H, J = 8.8Hz, ArH), 5.63 (dd, 1H, J = 5.3, 10.8Hz, CHNO$_2$), 4.27 (d, 1H, J = 10.9Hz, 1ArHAr), 3.75 (dd, 1H, J = 7.8, 5.4Hz, CHAr), 2.85 (d, 12H, J = 11.4Hz, 4NCH$_3$), 2.75-2.65 (m, 1H, CHCH$_3$), 0.83 (t, 3H, J = 7.1Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 201.9 (CO), 149.7 (C), 137.1 (C), 131.6 (CH), 130.8 (CH), 129.1 (CH), 128.0 (C), 121.6 (C), 112.3 (CH), 92.9 (CH), 53.3 (CH), 47.4 (CH), 40.6 (CH$_3$), 31.1 (CH), 12.6 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.53 (s, 1H, CHO), 5.93 (dd, 1H, CHNO$_2$), 4.19 (d, 1H, 1ArHAr), 1.10 (t, 3H, J = 7.1Hz, CH$_3$) ppm.

(2*R*,3*R*,4*S*)-5,5-bis(4-(dimethylamino)phenyl)-2-ethyl-2-methyl-4-nitro-3-phenylpentanal (Major Diastereoisomer), 9ae

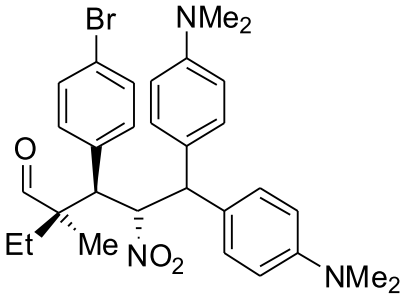


The reaction was performed under the general conditions described in SI for 70 h. Yield 58%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.35 (s, 1H, CHO), 7.28-7.24 (m, 3H, 3ArH), 7.03-6.89 (m, 6H, 6ArH), 6.57 (d, 2H, J =8.8Hz, 2ArH), 6.52 (d, 2H, 8.8Hz, 2ArH), 5.69 (dd, 1H, J = 6.4, 10.0Hz CHNO$_2$), 4.05 (d, 1H, J = 6.2Hz, 1ArHAr), 3.75 (d, 1H, J = 10.0Hz ArCH), 2.88 (d, 12H, J = 14.3Hz, 4NCH$_3$), 1.28 (t, 3H, J = 4.3Hz, CH$_3$), 0.57 (t, 3H, J = 7.5Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 203.1 (CO), 149.4 (C), 136.3 (C), 130.1 (CH), 128.8 (CH), 128.4 (CH), 127.7 (C), 126.2 (CH), 112.3 (CH), 92.9 (CH), 60.5 (CH), 53.3 (C), 52.2 (CH), 40.6 (CH$_3$), 29.9 (CH$_2$), 11.8 (CH$_3$), 7.9 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.37 (s, 1H, CHO), 5.81 (dd, 1H, CHNO$_2$), 3.80 (d, 1H, J = 10.0Hz ArCH) ppm.

(2*R*,3*R*,4*S*)-3-(4-bromophenyl)-5,5-bis(4-(dimethylamino)phenyl)-2-ethyl-2-methyl-4-nitropentanal. (Major diastereoisomer), 9af

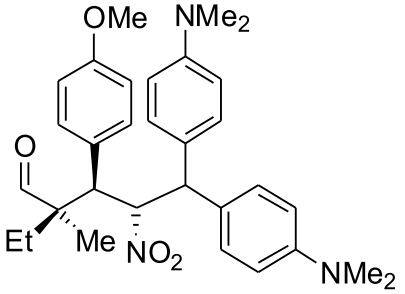


The reaction was performed under the general conditions described in SI for 20 h. Yield 88%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.32 (s, 1H, CHO), 7.23 (d, 2H, J = 10.2Hz, 2ArH), 6.98 (d, 2H, J = 8.8Hz, 2ArH), 6.80 (d, 4H, J = 8.6Hz, 4ArH), 6.54 (d, 2H, J = 8.8Hz, 2ArH), 6.44 (d, 2H, J = 8.8Hz, 2ArH), 5.63 (dd, 1H, J = 8.9, 9.6Hz, CHNO$_2$), 3.99 (d, 1H, J = 9.6Hz, 1ArHAr), 3.71 (d, 1H, J = 7.0Hz, CHAr), 2.86 (d, 12H, J = 3.8Hz, 4NCH$_3$), 1.37-1.18 (m, 2H, CH$_2$), 1.15 (s, 3H, CH$_3$), 0.57 (t, 3H, J = 7.5Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 202.7 (CO), 149.8 (C), 135.2 (C), 131.3 (CH), 129.5 (CH), 128.7 (CH), 126.7 (C), 121.5 (C), 112.5 (CH), 92.7 (CH), 54.4 (CH), 52.7 (CH), 52.6 (C), 40.6 (CH$_3$), 30.0 (CH$_2$), 12.1 (CH$_3$), 7.9 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.30 (s, 1H, CHO), 5.48 (dd, 1H, J = 8.9, 9.6Hz, CHNO$_2$), 0.42 (t, 3H, J = 7.5Hz, CH$_3$) ppm.

(2*R*,3*R*,4*S*)-5,5-bis(4-(dimethylamino)phenyl)-2-ethyl-3-(4-methoxyphenyl)-2-methyl-4-nitropentanal. (Major diastereoisomer), 9ag

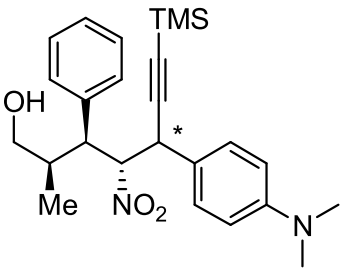


The reaction was performed under the general conditions described in SI for 20 h. Yield 85%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.32 (s, 1H, CHO), 7.00-6.93 (m, 2H, 2ArH), 6.93-6.82 (m, 4H, 4ArH), 6.76-6.62 (m, 2H, 2ArH), 6.59-6.47 (m, 4H, 4ArH), 5.62 (dd, 1H, J = 6.6, 10.1Hz, CHNO$_2$), 4.06-4.00 (m, 1H, 1ArHAr), 3.80 (s, 3H, CH$_3$), 3.67 (d, 1H, J = 10.1Hz, CHAr), 2.86 (d, 12H, J = 12.8Hz, 4NCH$_3$), 1.40-1.30 (m, 2H, CH$_2$), 1.14 (s, 3H, CH$_3$), 0.56 (t, 3H, J = 7.5Hz, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 203.2 (CO), 159.0 (C), 149.8 (C), 130.0 (CH), 128.8 (CH), 128.0 (C), 126.5 (C), 112.8 (CH), 112.3 (CH), 93.0 (CH), 55.3 (CH), 53.4 (C), 53.0 (CH), 51.8 (C), 40.6 (CH$_3$), 29.8 (CH$_2$), 11.8 (CH$_3$), 7.9 (CH$_3$); ESI-MS: *m/z* = 518.5 [M+H]$^+$, 1035.9 [2M+Na]$^+$.

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 9.33 (s, 1H, CHO), 5.74 (dd, CHNO$_2$), 0.75 (t, 3H, J = 7.5Hz, CH$_3$) ppm.

(2*R*,3*S*,4*R*)-5-(4-(dimethylamino)phenyl)-2-methyl-4-nitro-3-phenyl-7-(trimethylsilyl)hept-6-yn-1-ol. (Major diastereoisomer), 8ha

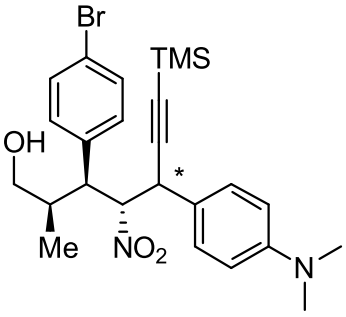


The reaction was performed under the general conditions described in SI for 6 h at 50°C. Yield 81%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 7.43-7.19 (m, 5H, 5ArH), 7.07 (d, 2H, J = 8.6Hz, 2ArH), 6.63 (d, 2H, J = 8.6Hz, ArH), 5.12 (dd, 1H, J = 12.1, 4.1Hz, CHNO$_2$), 4.16 (dd, 1H, J = 12.1, 3.5Hz, CHAr), 3.79 (d, 1H, J = 4.1Hz, 1ArHCC), 3.30-3.24 (m, 1H, CH$_2$OH), 3.23-3.10 (m, 1H, CH$_2$OH), 2.92 (s, 6H, 2NCH$_3$), 1.75-1.55 (m, 1H, CHCH$_3$), 0.88 (d, 3H, J = 7.0Hz, CH$_3$), 0.25 (s, 9H, 3 CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 150.1 (C), 134.9 (C), 129.7 (CH), 128.7 (CH), 128.2 (CH), 127.8 (CH), 127.0 (C), 112.6 (CH), 101.0 (C), 93.7 (CH), 91.5 (C), 65.8 (CH$_2$), 47.2 (CH), 40.5 (CH$_3$), 36.8 (CH), 29.7 (CH), 11.4 (CH$_3$), 0.02 (CH$_3$).

(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 6.86 (d, 2H, J = 8.9Hz, 2ArH), 6.56 (d, 2H, J = 8.9Hz, ArH), 5.42 (dd, 1H, J = 10.4, 5.0Hz, CHNO$_2$), 4.00 (d, 1H, J = 5.0Hz, 1ArHCC), 3.54 (dd, 1H, J = 10.4, 4.3Hz, CHAr), 3.38-3.24 (m, 1H, CH$_2$OH), 3.23-3.17 (m, 1H, CH$_2$OH), 2.92 (s, 6H, 2NCH$_3$), 1.94-1.84 (m, 1H, CHCH$_3$), 0.80 (d, 3H, J = 7.0Hz, CH$_3$), 0.16 (s, 9H, 3 CH$_3$) ppm.

(2*R*,3*S*,4*R*)-3-(4-bromophenyl)-5-(4-(dimethylamino)phenyl)-2-methyl-4-nitro-7-(trimethylsilyl) hept-6-yn-1-ol. (Major diastereoisomer), 8hd

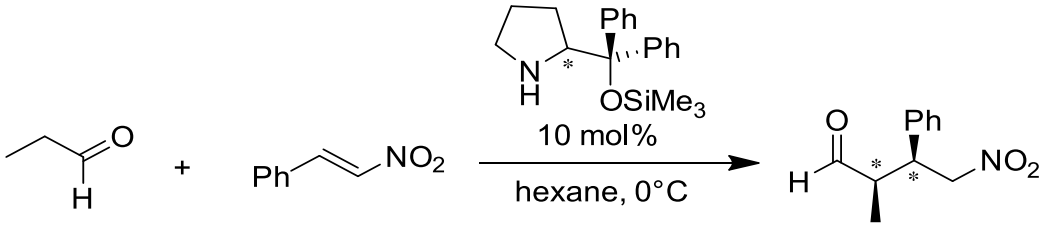


The reaction was performed under the general conditions described in SI for 6 h at 50 °C. Yield 80%.

^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.50 (d, 2H, J = 8.2Hz, 2ArH), 7.14 (d, 2H, J = 8.2Hz, 2ArH), 7.04 (d, 2H, J = 8.8Hz, 2ArH), 6.61 (d, 2H, J = 8.8Hz, 2ArH), 5.07 (dd, 1H, J = 12.0, 4.4Hz, CHNO$_2$), 4.15 (dd, 1H, J = 12.0, 3.4Hz, CHAr), 3.76 (d, 1H, J = 4.3Hz, 1ArHCC), 3.34-3.24 (m, 1H, CH$_2$OH), 3.10-3.00 (m, 1H, CH$_2$OH), 2.92 (s, 6H, 2NCH$_3$), 1.76-1.57 (m, 1H, CHCH$_3$), 0.83 (d, 3H, J = 7.0Hz, CH$_3$), 0.24 (s, 9H, 3 CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 150.2 (C), 133.9 (C), 131.8 (CH), 131.4 (CH), 128.3 (CH), 121.7 (C), 112.5 (CH), 112.1 (C), 100.8 (C), 93.3 (CH), 91.6 (C), 65.4 (CH$_2$), 46.5 (CH), 40.5 (CH$_3$), 36.6 (CH), 29.7 (CH), 11.2 (CH$_3$), 0.01 (CH$_3$).

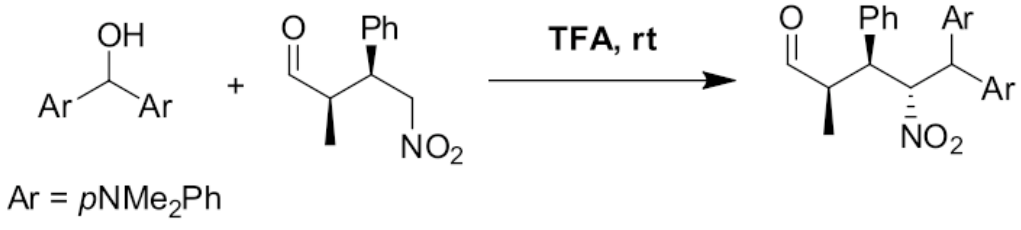
(minor diastereoisomer): ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.41 (d, 2H, J = 8.1Hz, 2ArH), 7.02 (d, 2H, J = 8.1Hz, ArH), 6.85 (d, 2H, J = 8.8Hz, 2ArH), 6.53 (d, 2H, J = 8.8Hz, 2ArH), 5.33 (dd, 1H, J = 10.3, 5.5Hz, CHNO$_2$), 4.03 (d, 1H, J = 5.5Hz, 1ArHCC), 3.64 (dd, 1H, J = 10.3, 4.7Hz, CHAr), 3.41-3.34 (m, 1H, CH$_2$OH), 3.16-3.10 (m, 1H, CH$_2$OH), 2.92 (s, 6H, 2NCH$_3$), 1.93-1.80 (m, 1H, CHCH$_3$), 0.77 (d, 3H, J = 6.9Hz, CH$_3$), 0.17 (s, 9H, 3 CH$_3$) ppm.

Preparation of the organocatalysts 10



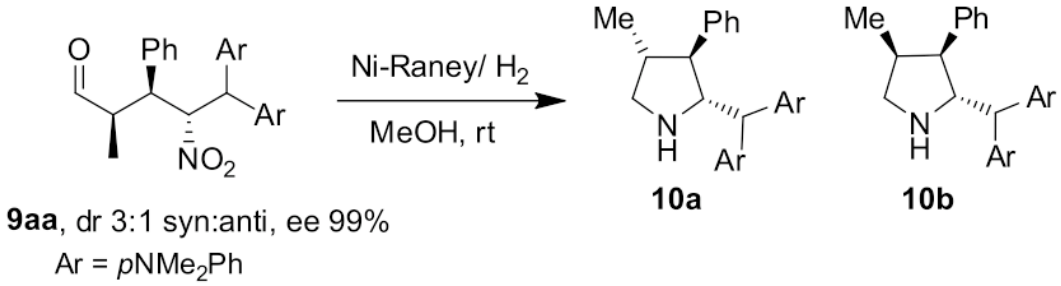
The compound was obtained following the procedure described by Hayashi et al.[38] The typical experimental procedure: Propanal (10 mmol.) was added to a solution of nitrostyrene (1 mmol) and the (*S*)-Hayashi catalyst (34 mg, 10 mol%) in hexane (1M) at 0 °C. After the reaction mixture had been stirred for 5 h at that temperature, the reaction was quenched by the addition of aqueous 1N HCl. The organic phase was separated and the aqueous phase was extracted three times with AcOEt, and the combined organic phases were dried (Na$_2$SO$_4$), and purified by flash chromatography (Cyclohexane/AcOEt 7:3) to afford the Michael adduct as a clear oil: syn/anti 3:1 (Before the column the dr ratio measured by 1H NMR was 24:1) (by 1H NMR spectroscopy of the crude mixture), 99% ee (by HPLC of the corresponding aldehyde on a chiral phase: chiralcel OD-H column, l=214 nm, iPrOH/hexane 1:10, 1.0 mLmin1; tR=30.0 min (major), 35.4 min (minor).

Preparation of 9aa



In an air-open vial the 4,4'-Bis(dimethylamino)-benzhydrol (1.0 mol, 1.2 equiv) was dissolved in triufluoro-ethanol (5 mL, 0.4 M). The nitroalkane (1.58 mol, 1 equiv.) was added and the reaction was stirred at room temperature for 40 hours. The reaction mixture was than concentrated to afford a crude product that was purified by flash chromatography (Cyclohexane/AcOEt 8:2) to provide the desired product as a mixture of diastereoisomers (syn:anti 3:1). ^{1}H-NMR and ^{13}C-NMR identical to the published product.[38]

Procedure for the synthesis of the pyrrolidine 10a,b.



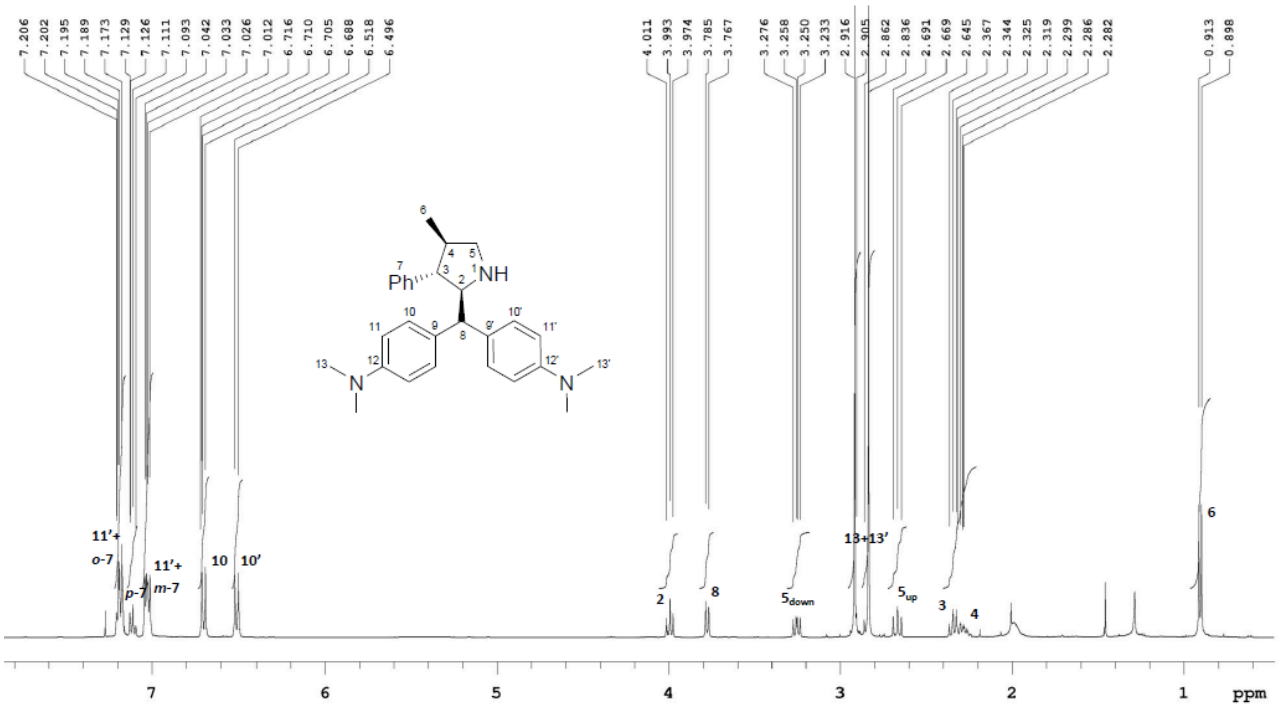
9aa, dr 3:1 syn:anti, ee 99%
Ar = *p*NMe$_2$Ph

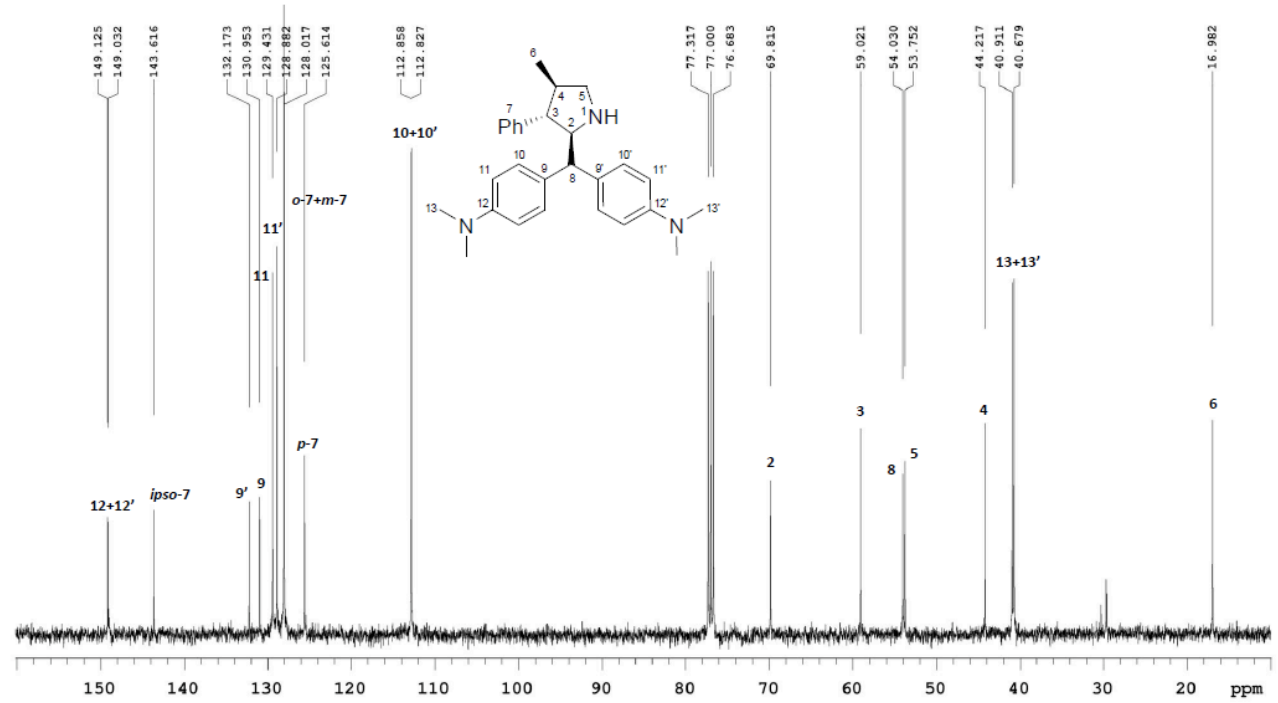
To a MeOH solution of the mixture of diastereoisomers **7aa** (0.42 mol, 1 equiv) was added Ni-Raney (2.1 mol, 5 equiv) at room temperature. After stirring the reaction mixture for 24 hours under hydrogen atmosphere, the reaction was opened to air filtered and the MeOH was evaporated under reduced pressure. The mixture was diluted with AcOEt (3 mL) The organic phase was separated and the aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered, concentrated and the crude was purified by flash chromatography (AcOEt/MeOH 95:5) to provide the **8a** as pure products. Yield 51%.

10a: ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ: 7.21-7.17 (m, 4H, CH), 7.13-7.09 (m, 1H, CH), 7.04-7.01 (m, 4H, CH), 6.70 (d, J = 8.8Hz, 2H, CH), 6.51 (d, J = 8.8Hz, 2H, CH), 4.00 (t, J = 7.4Hz, 1H, CH), 3.77 (d, J = 7.2Hz, 1H, CH), 3.25 (dd, J = 10.2, 7.0Hz, 1H, CH$_2$), 2.92 (s, 6H, CH$_3$), 2.84 (s, 6H, CH$_3$), 2.68 (dd, J = 10.2, 8.6Hz, 1H, CH$_2$), 2.37-2.26 (m, 2H, CH), 0.89 (d, J = 6.4 Hz, 3H, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ:149.1 (C), 149.0 (C), 143.6 (C), 132.2 (C), 131.0 (C), 129.4 (CH), 128.9 (CH), 128.0 (4CH), 125.6 (CH), 112.9 (CH), 112.8 (CH), 69.8 (CH), 59.0 (CH), 54.0 (CH), 53.8 (CH$_2$), 44.2 (CH), 40.9 (CH$_3$), 40.7 (CH$_3$), 17.0 (CH$_3$). HMRS found 413.28311; $C_{28}H_{35}N_3$ requires: 413.283097.

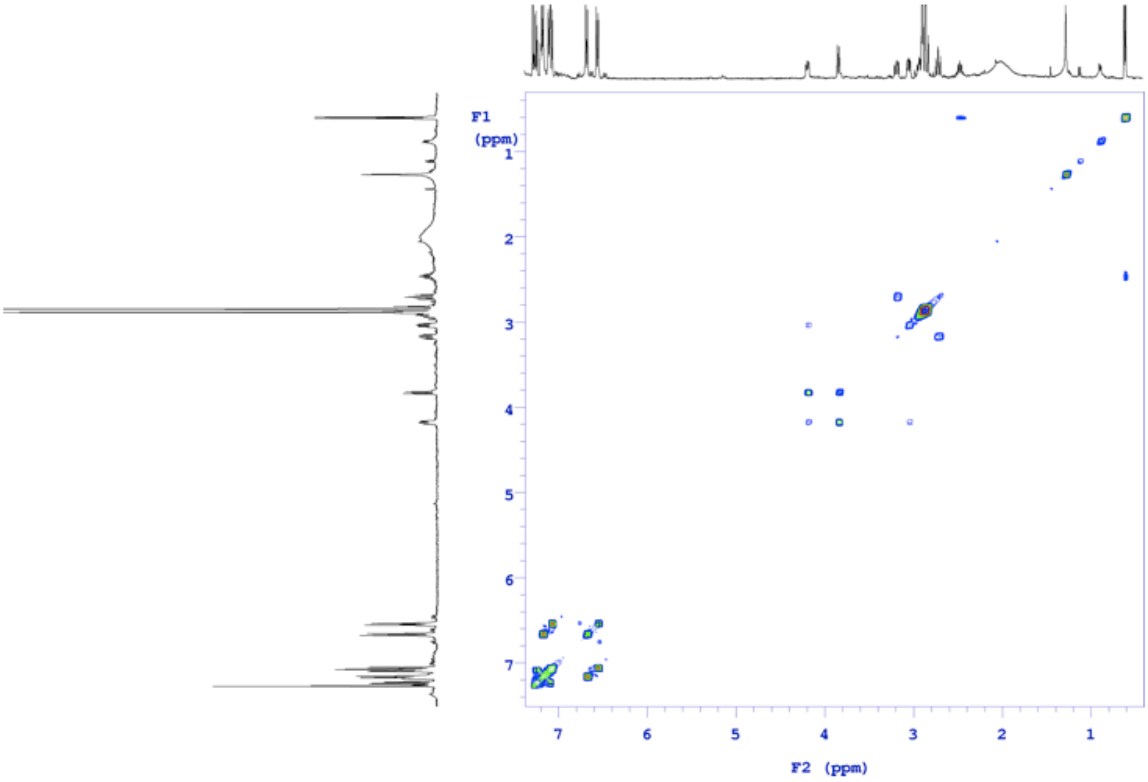
10b: ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ: 7.24 (t, J = 7.4Hz, 2H, CH), 7.18-7.15 (m, 3H, CH), 7.09-7.05 (m, 4H, CH), 6.66 (d, J = 8.0Hz, 2H, CH), 6.54 (d, J = 8.4Hz, 2H, CH), 4.19-4.16 (m, 1H, CH), 3.83 (d, J = 8.8Hz, 1H, CH), 3.17 (dd, J = 10.2, 7.0Hz, 1H, CH$_2$), 3.04 (dd, J = 8.4Hz, J = 5.2Hz, 1H, CH), 2.88 (s, 6 H, CH$_3$), 2.84 (s, 6 H, CH$_3$), 2.71 (t, J = 10.2Hz, 1H, CH), 2.49-2.43 (m, 1H, CH), 0.60 (d, J = 6.4Hz, 3H, CH$_3$) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 149.2 (C), 149.0 (C), 141.8 (C), 132.2 (C), 130.6 (C), 129.4 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 125.8 (CH), 112.9 (CH), 112.8 (CH), 67.9 (CH), 54.8 (CH), 53.4 (CH), 53.1 (CH), 40.8 (CH$_3$), 40.7 (CH$_3$), 37.2 (CH), 14.7 (CH$_3$).

Compound 10a (Major diastereoisomer) (400MHz, $CDCl_3$)

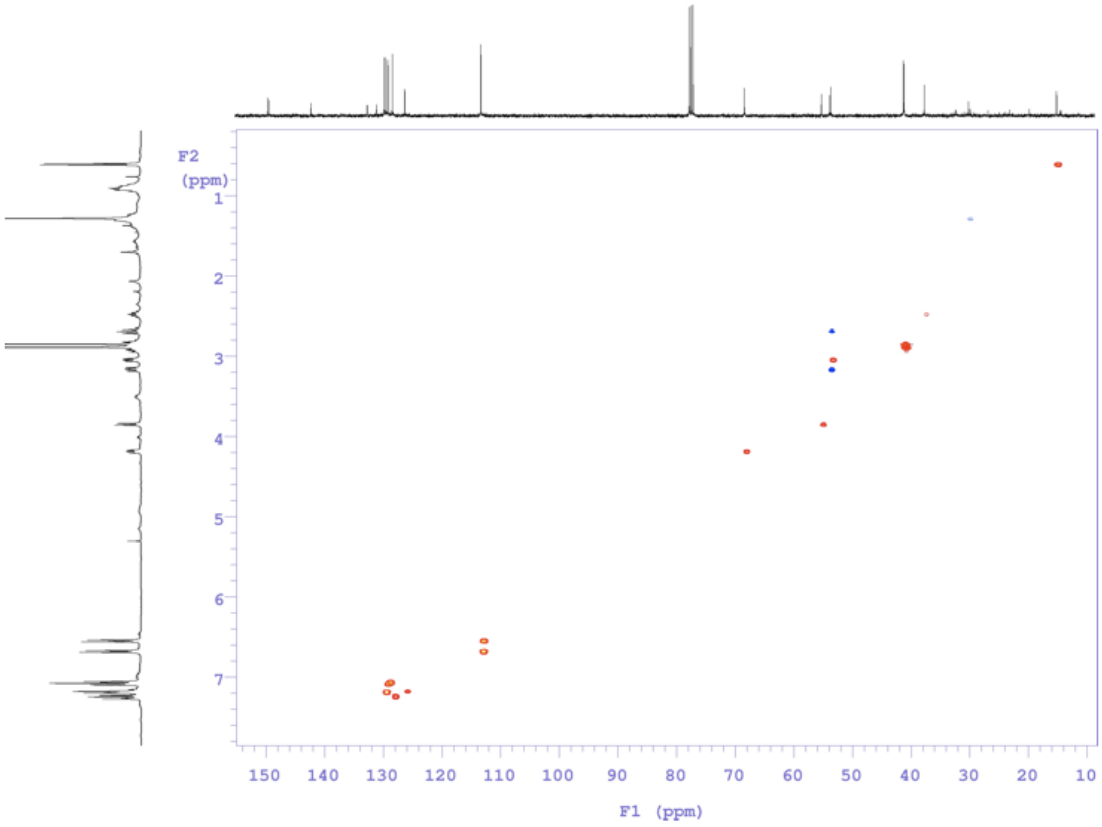




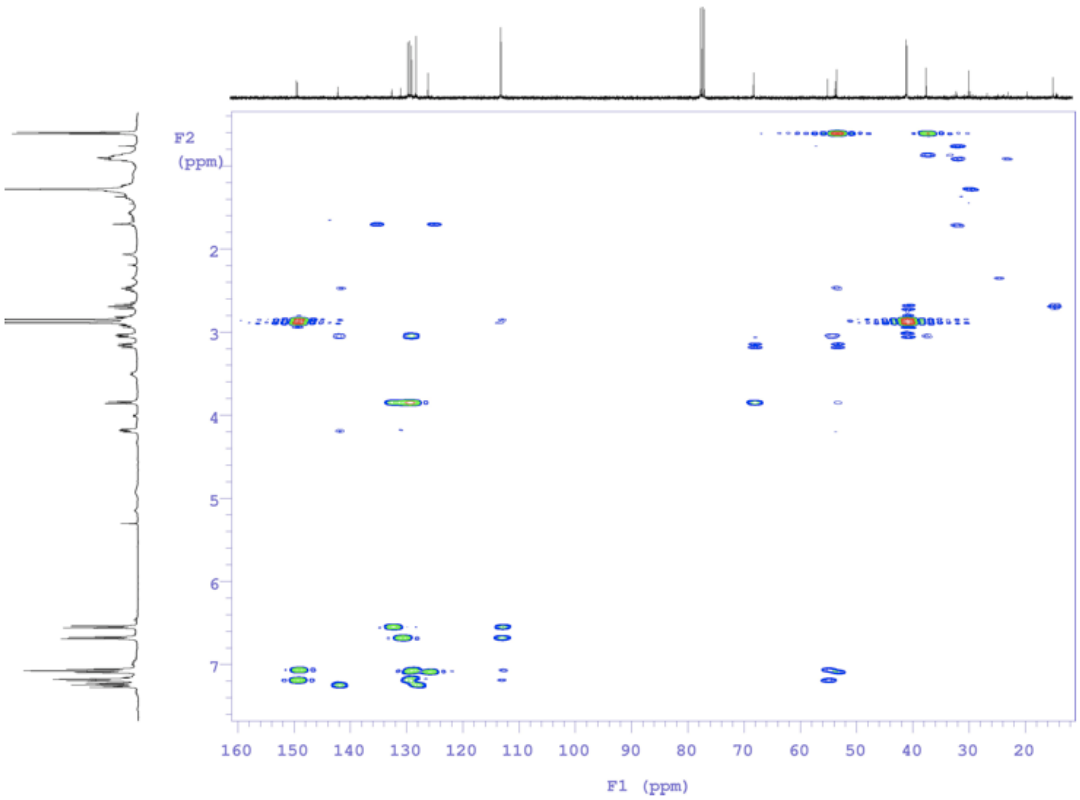
gCOSY


F1
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

gHSQC

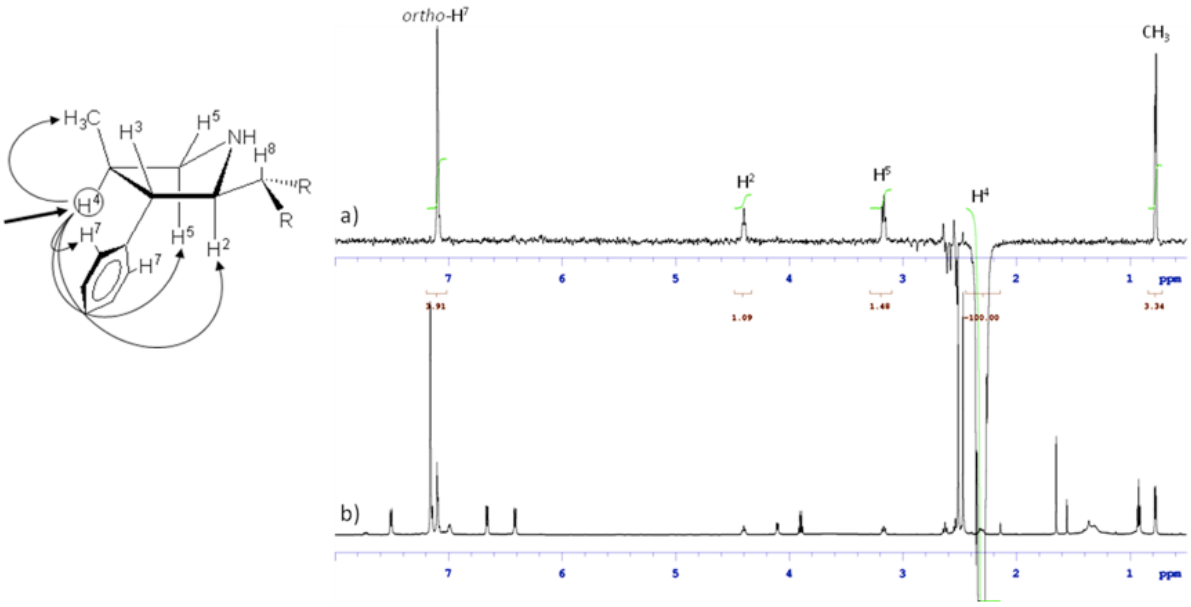

F2
(ppm)
1
2
3
4
5
6
7
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
F1 (ppm)

gHMBC

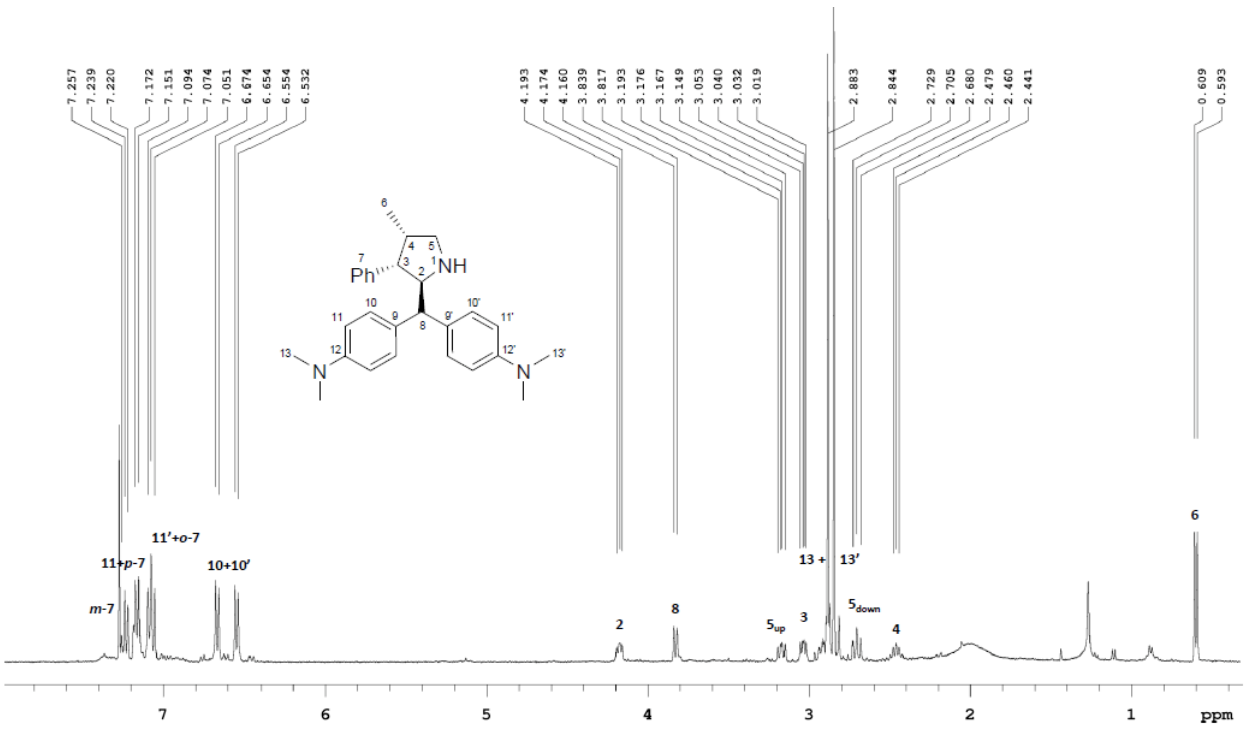


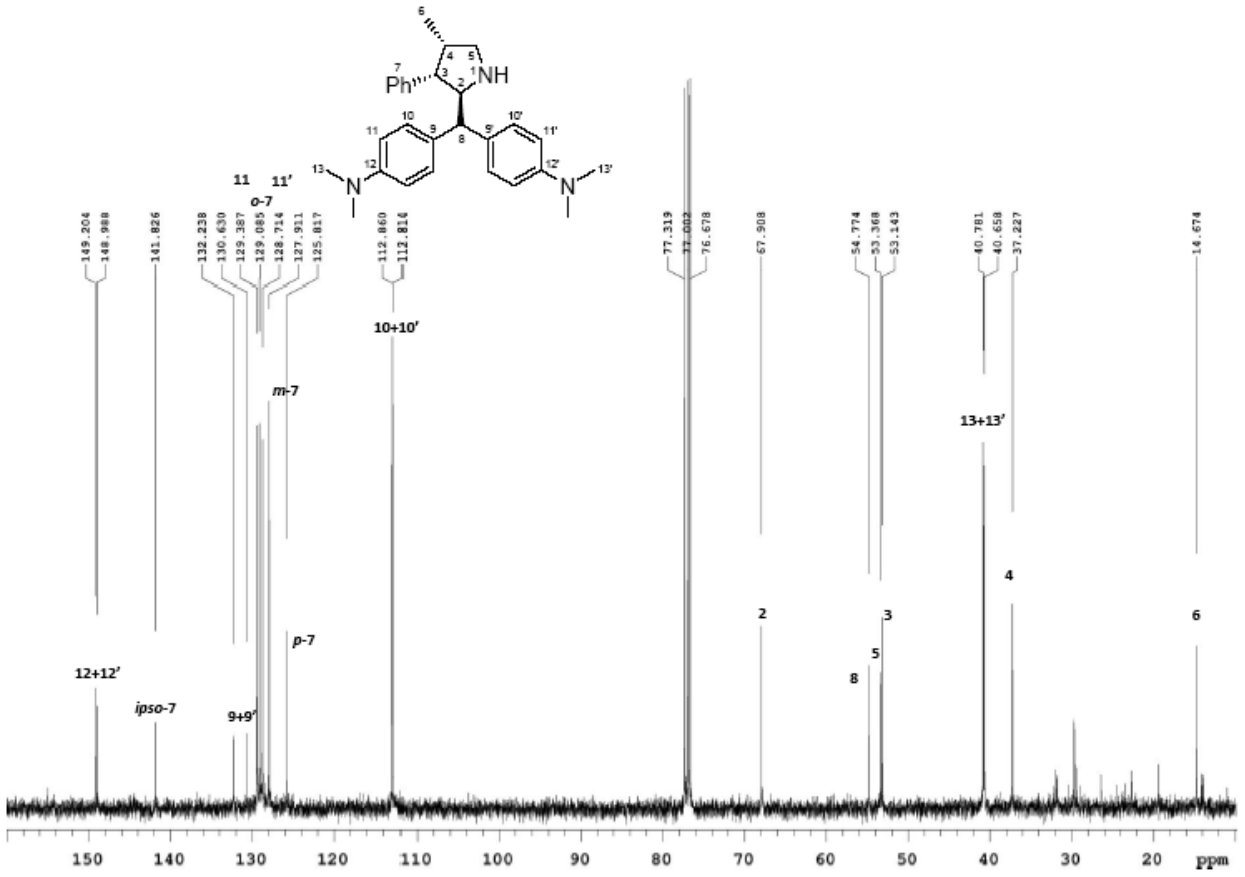
Determination of the relative configuration of the isolated product 10a.

NOESY1D (400 MHz, $CDCl_3$) obtained using a DPFGSE-NOE sequence with a 50 Hz 'r-snob' pulse and a mixing time of 1 s. The frequency of proton H^4 was irradiated. The *sin*-relationship between H^4 and H^3 protons was confirmed by the positive NOE response of the H^3 frequency. No NOE effect was found for H^2, confirming the *anti*-relationship between the two nuclei. Discrete positive NOE was unexpectedly observed for the proton H^8, apparently quiet far from proton H^4. This effect can be justified by assuming the most stable conformation having the proton H^8 directed towards the center of the five-membered ring.

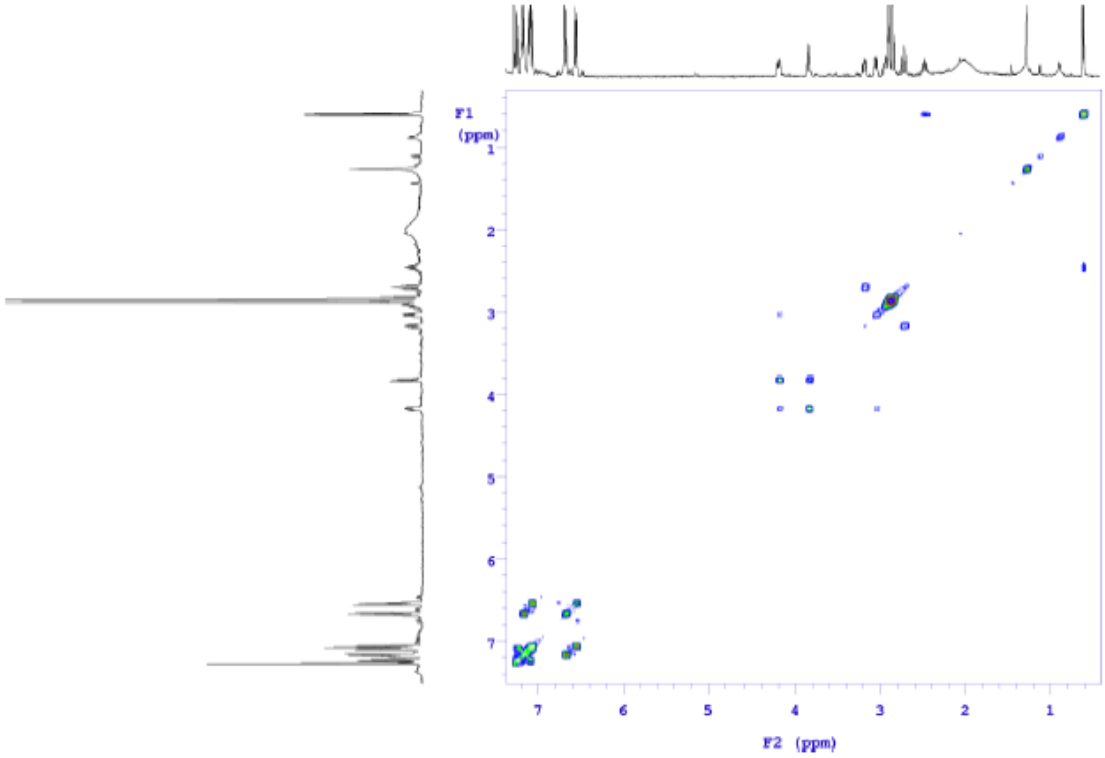


Compound 10b(Minor diastereoisomer) (400MHz, CD3Cl)

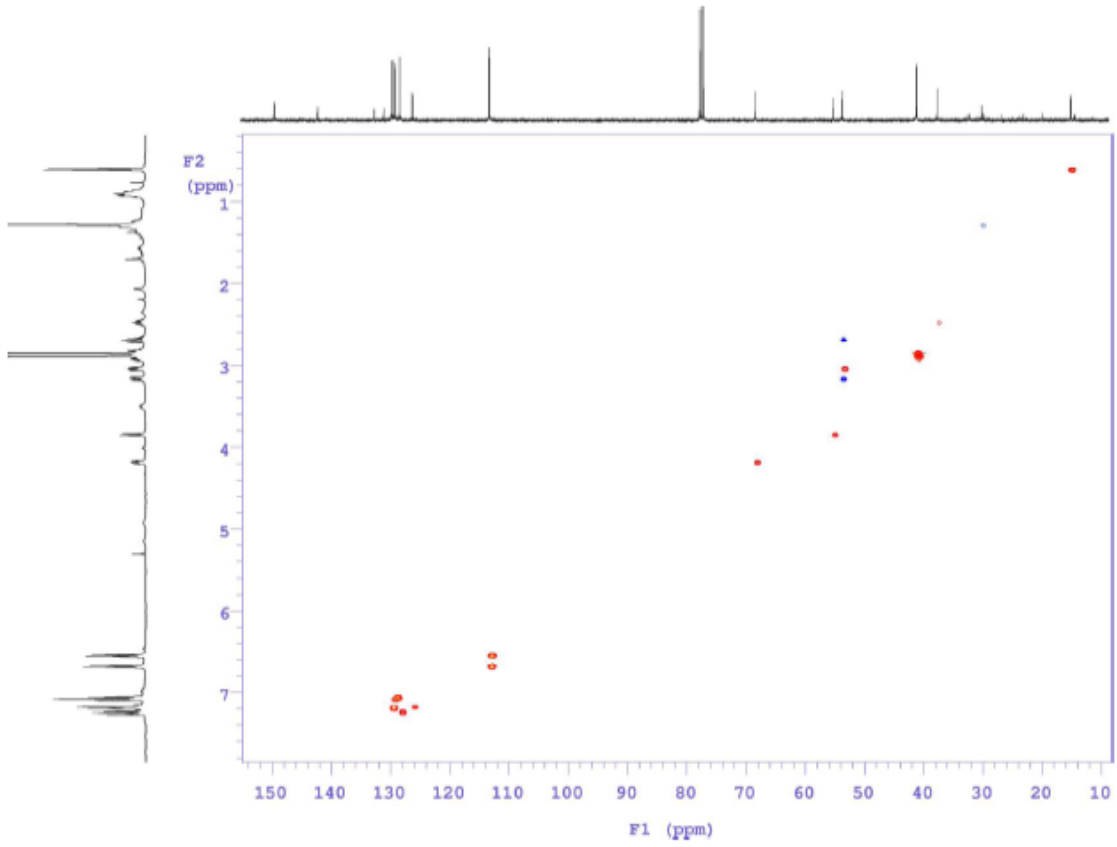




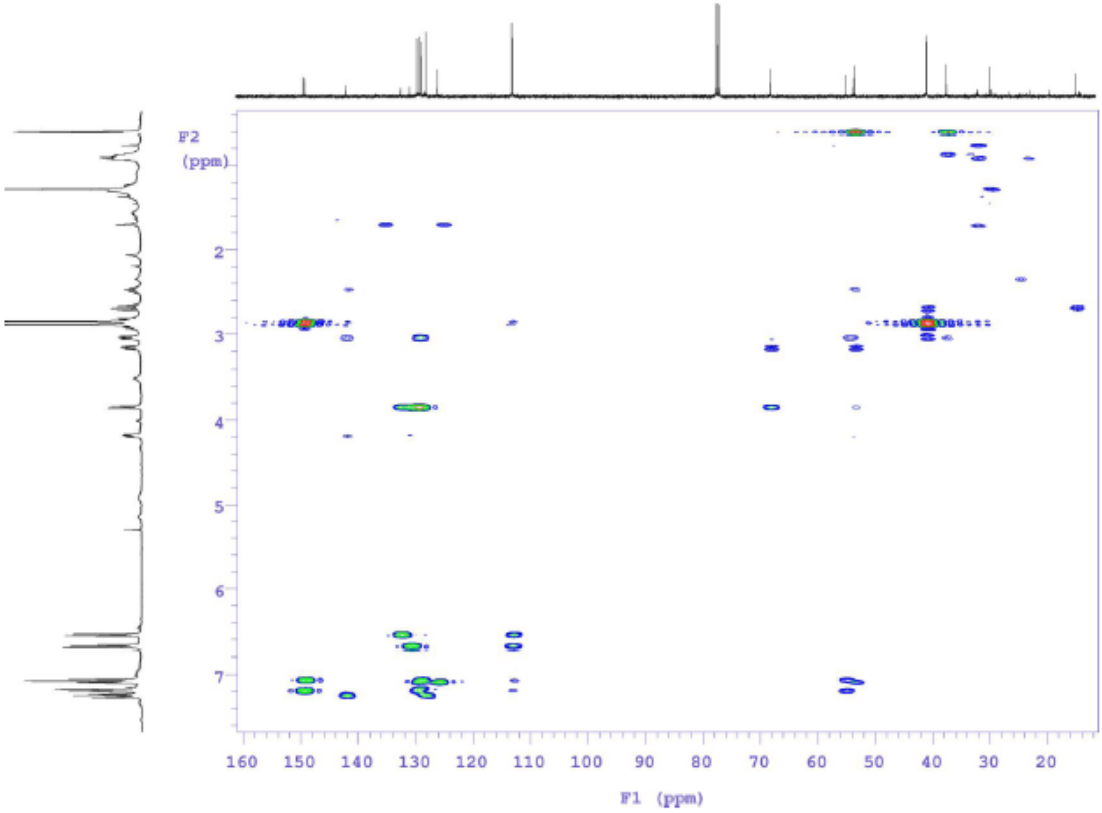
gCOSY


F1
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)

gHSQC


F2
(ppm)
1
2
3
4
5
6
7
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
F1 (ppm)

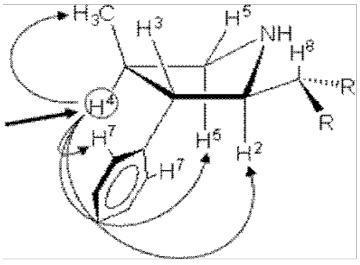
gHMBC

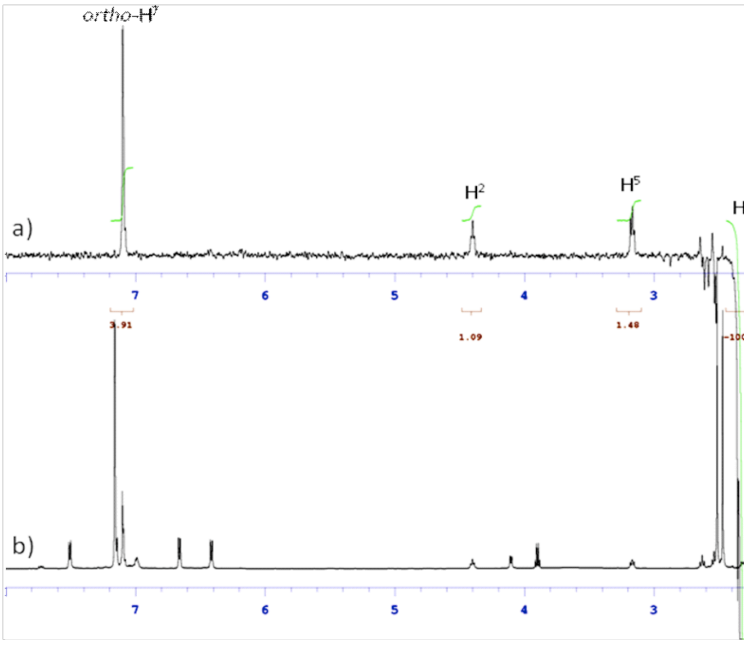


Determination of the relative configuration of the isolated product 10b.

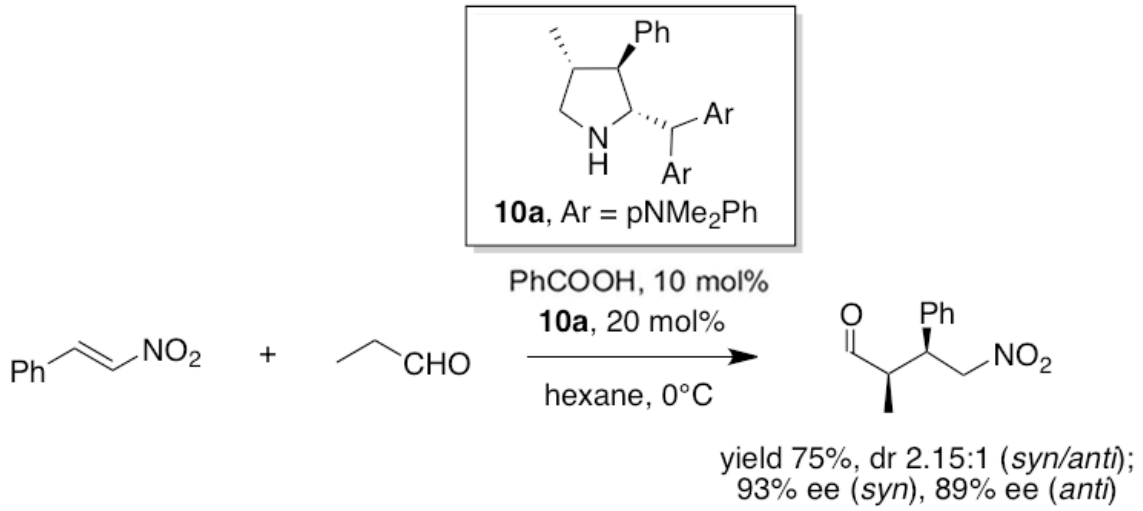
a) NOESY1D (600 MHz, CD_6D_6) obtained using a DPFGSE-NOE sequence with a 50 Hz 'r-snob' pulse and a mixing time of 1 s. The frequency of proton H^4 was irradiated. The NOE responses on H^2, H^5 and ortho-H^7 allowed the assignment of the sin-relationship between H^4 and H^2 and the anti-relationship between H^4 and H^3. Being the carbon bearing phenyl group and H^3 proton stereodinamically defined, the absolute configuration of all the stereocenters can be assigned.

b) ^1H NMR (600 MHz, CD_6D_6)



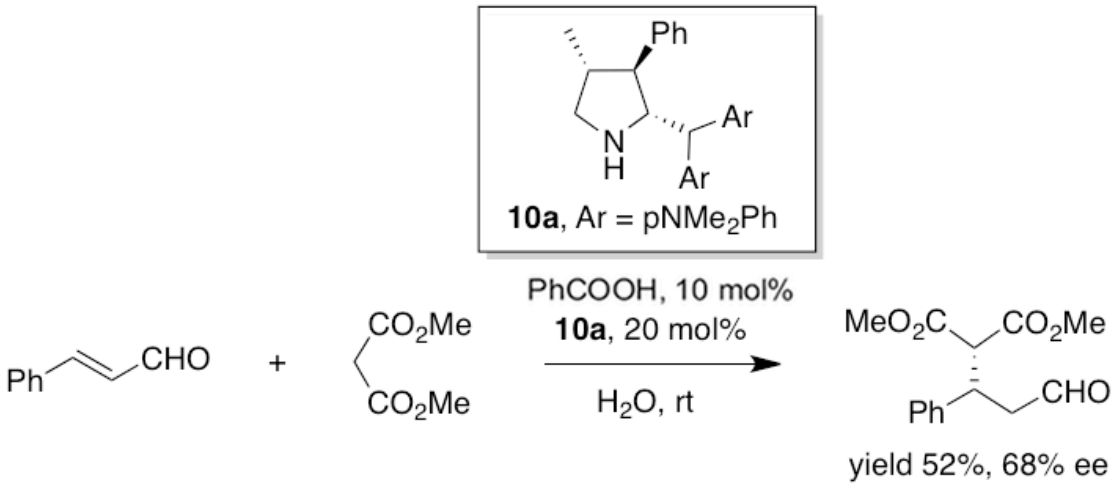


Organocatalytic reaction promoted by the new organocatalysts 10a



Propanal (1 mmol, 10 equiv) was added to a solution of nitrostyrene (0.1 mmol, 1 equiv) benzoic acid (0.05 mmol, 5 equiv) and the catalyst **10a** (10 mol%) in hexane (0.3 M) at 0 °C. After the reaction mixture has been stirred for 24 h at that temperature, it was quenched by the addition of aqueous 1N HCl. The organic phase was separated and the aqueous phase was extracted three times with AcOEt, and the combined organic phases were dried (Na_2SO_4), and purified by flash chromatography to afford the Michael adduct as a clear oil: syn/anti 2.25:1 (by 1H NMR spectroscopy of the crude mixture), 93:89% ee (by HPLC of the corresponding aldehyde on a chiral phase: chiralcel OD-H column, l=214 nm, iPrOH/hexane 1:10, 1.0 mLmin1; ; tR=21.8 min (minor syn), 26.7 (minor anti), 30.0 min (major syn), 35.4 min (major anti). ^{1}H NMR and ^{13}C were in agreement with the described compound.

Procedure for the organocatalytic addition of malonates to α,β-unsaturated aldehydes



The catalyst **10a** (10 mol%) was added to a stirred suspension of the α,β-unsaturated aldehyde (0.1 mmol, 10 equiv) and benzoic acid (0.05 mmol, 5 equiv) in water. After the addition of dimethyl malonate (0.01 mmol, 1 equiv) the reaction mixture was stirred for 40 h and then AcOEt was added. The organic phase was separated and the aqueous phase was extracted with AcOEt. The organic phases were collected, dried over

Na_2SO_4, evaporated under reduced pressure to give an oil purified by flash chromatography (Cyclohexane/AcOEt 7:3) on silica gel. Spectroscopic data are in agreement with the published data.[40] Colorless liquid. Yield: 52% ^{1}H NMR (CDCl3) d 9.61 (t, 3J = 1.6 Hz, 1H), 7.33–7.22 (m, 5H), 4.04 (m, 1H), 3.78 (d, 3J = 2.5 Hz, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 2.94 (m, 2H). 13C NMR (CDCl3) d 199.8, 168.2, 167.6, 139.5, 128.6, 127.8, 127.4, 57.0, 52.6, 52.3, 47.2, 39.3. HRMS: $C_{14}H_{16}O5$ [M+Na]+ calcd: 287.0895, found: 287.0882. $[\alpha]_D$ 23 = -17.2 (c = 0.6, CHCl3, 68% ee).

References

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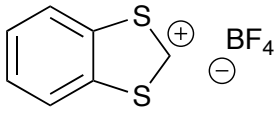
PART 2

Direct Formylation of Organoboron Aromatic Compounds

The second purpose of my project was to study in deep the reactivity of 1,3-benzodithiolylium tetrafluoroborate as stabilized carbocation in new metal-free and organocatalytic reactions. In this chapter is presented the Facile and Direct Formylation of Organoboron Aromatic Compounds with Benzothiolilyum Tetrafluoroborate. The direct C-C bond forming reaction between boronic acid and a stable carbenium ion is described without any catalysts or transition metal salts. The reaction is dictated by the nucleophilic properties of boronic derivatives.

The benzodithiolylium tetrafluoroborate salt

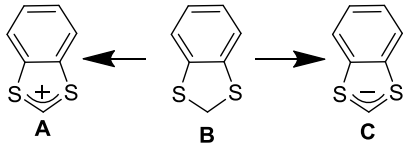
Continuing the work reported in the previous chapter, we focused on the study of one of the most useful stabilized carbocation. The benzodithiolylium salt is quite electrophylic and it is generally used as readily available synthon in a large series of transformations for organic synthesis (*Figure 4.1*). It gives the possibility to functionalise the molecules after lithiation and successive alkylation with other electrophiles, or by reductive or oxidative cleavage.



1

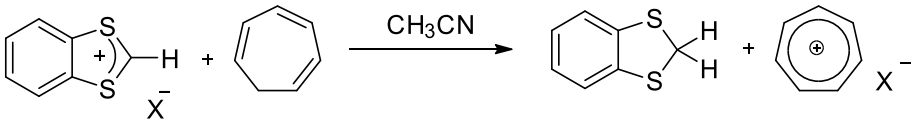
Figure 4.1. The benzodithiolylium tetrafluoroborate salt

The heterocyclic compound 1.3 benzodithiol **B** is particularly useful for the design of synthetic routes through the carbocationic form **A**, prepared by the exchange of a hydride with triphenilic carbocation salt,[1] or the carbanionic species **C** (equivalent of an acyl-anion), by treating it with a strong base such as n-butyllithium (*Scheme 4.1*).[2]



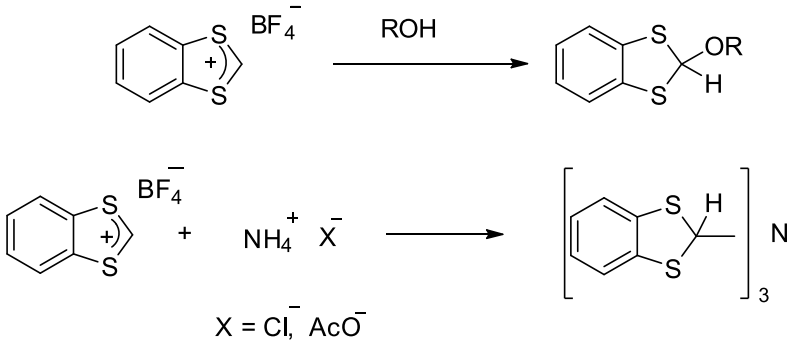
Scheme 4.1

The carbocationic form is particularly interesting, since it is strongly stabilized by a 10 π electron system that relocate the positive charge and confer to the system an aromatic connotation, allowing it to exclusively react with nucleophiles in position 2. The benzothiazolium tetrafluoroborate salt is stable and commercially available. In the Mayr scale, it is positioned approximately at -3.5: therefore, its stability is comparable to that of the tropylium, in fact, in the presence of tropylium, a hydride is ripped to the 1,3 benzodithiolylium giving tropylium salt (*Scheme 4.2*).[3]



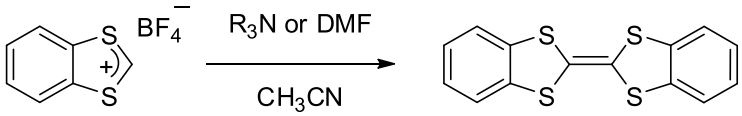
Scheme 4.2

In the reactions with oxygen or nitrogen nucleophiles, it gives the products confirming the unique position of nucleophilic attack (*Scheme 4.3*).[4]



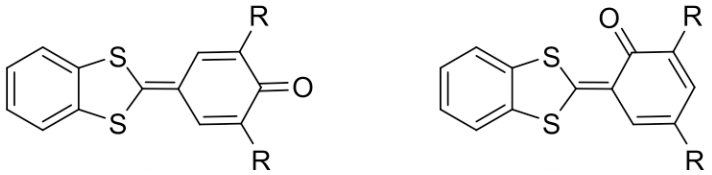
Scheme 4.3

In the presence of organic bases, such as tertiary amines, the formation of fulvenic systems takes place due to the dimerization of carbene with the carbocation. For this reason, organic bases should not be used in the organocatalytic alkylation reaction, which will be discussed in the next chapter (*Scheme 4.4*).



Scheme 4.4

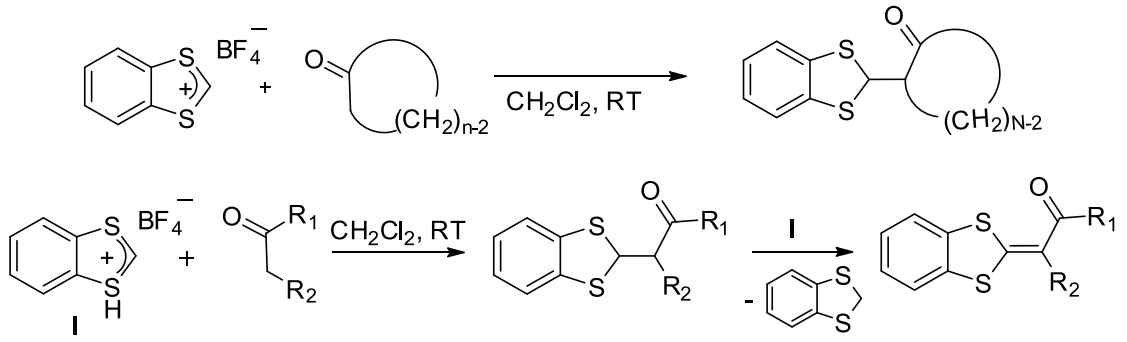
In the case of 2,6 or 2,4 di-substituted phenols, followed by treatment with triethylamine, **D** and **E** are obtained (*Figure 4.2*):[5]



D **E**

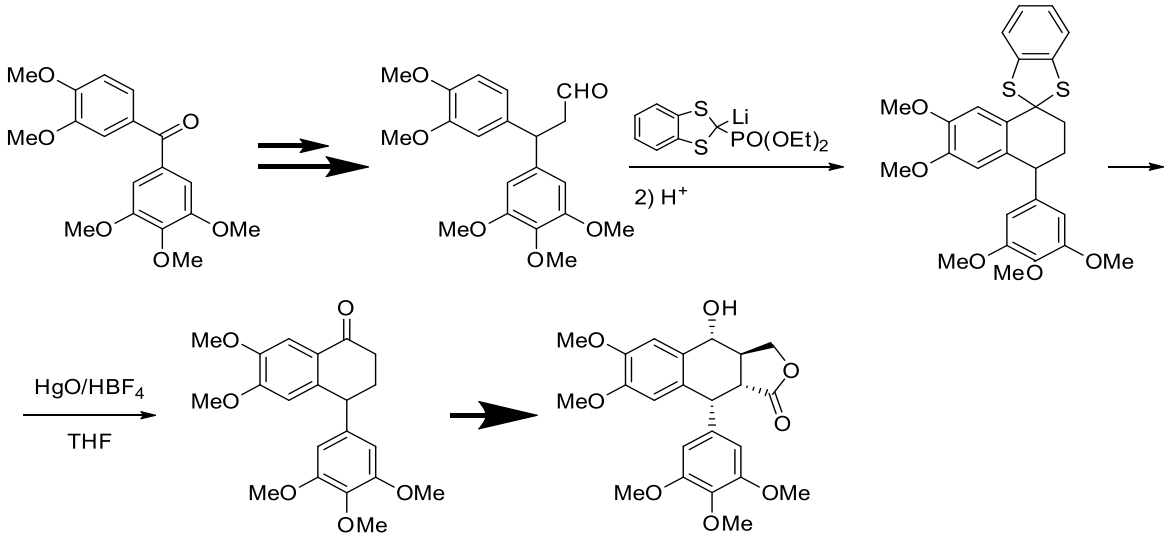
Figure 4.2

The reaction between enolizable substrates in the presence of acids such as for ketones is also described in the literature (*Scheme 4.5*).[6]



Scheme 4.5

1,3-benzodithiolilyum tratrafluoroborate **1** gives access to useful intermediates which can be transformed into the corresponding aldehyde, ketone, or acid groups. Reactions with phosphorus nucleophiles, in which the 1,3-benzodithiolylium tetrafluoroborate is used as an intermediate in total synthesis, are proposed by Rigby, demonstrating its versatility (*Scheme 4.6*).[7]



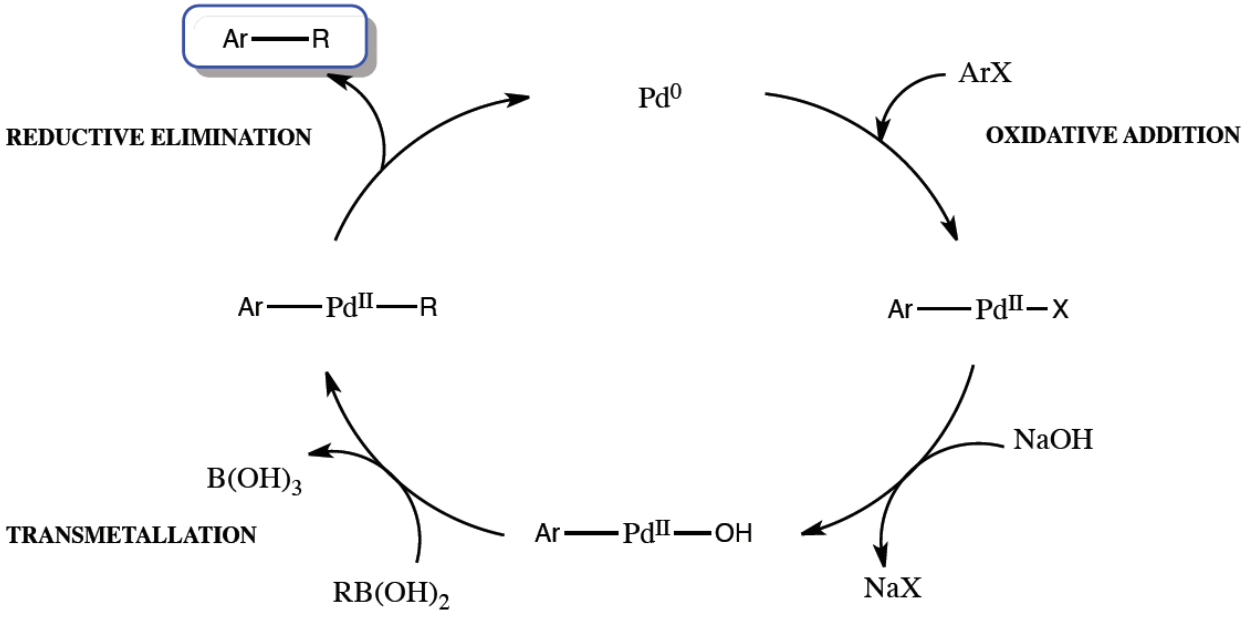
Scheme 4.6

The benzodithiole heterocycle **1** has found a number of particularly striking applications in the rapidly evolving field of organocatalysis.[8] We have reported the highly enantioselective α-alkylation of aldehydes[9] and subsequent stereoselective construction of quaternary stereogenic centres that will be discussed in the next chapter.[10] The stability of **1**, the possibility of metallating the benzodithiole and subsequently reacting it with an alkylating agent followed by the simple elimination of this group by treatment with Raney Nickel, prompted us to investigate the reactivity of **1** with a range of organoboron reagents.

The Suzuki Reaction

The chemistry of boron has long been of interest to organic chemists; from the awarding of the Nobel Prize for Chemistry to H. C. Brown in 1979 for pioneering research into organoboranes, to A. Suzuki's share in the 2010 Nobel Prize for palladium-catalysed cross coupling reactions involving boronic acids, the variety and potential of boron chemistry continues to attract much attention in the research world. The awarding of the later of these two Nobel Prizes has focused interest on the synthetic scope of boronic acids in a variety of contexts beyond that of metal mediated cross coupling reactions.

Suzuki's eponymous reaction has given synthetic chemists an incredibly powerful tool with which to affect such controlled construction and has facilitated the synthesis of many high value target molecules.[11] The use of organoboron reagents is what sets this method apart from other transition metal catalysed cross coupling reactions; the analogous Stille coupling (organotin), Kumada coupling (organomagnesium) and Negishi coupling (organozinc) all employ organometallic reagents of relatively high toxicity.[12] As well as their relative lack of toxicity, organoboranes offer a number of marked advantages in terms of their relative ease of preparation, with a number of methods established that include mild and in situ conditions, as well as their relative ease of isolation.[13]



Scheme 4.7. General catalytic cycle for the Suzuki reaction

The reaction mechanism of the Suzuki reaction has been studied in depth, with a generally accepted catalytic cycle for the reaction having been well established. As shown in *Scheme 4.7*, the first step is an oxidative addition of the aryl halide to the palladium metal centre. A ligand exchange is then presumed to take place followed by the base driven activation of the boronic acid and subsequent transmetallation. The trans-organic ligands are then posited to undergo an isomerisation resulting in a cis-geometry followed by a reductive elimination to give the coupled product. The scope and limitations of this reaction have been thoroughly investigated and are well documented.[14] The ready accessibility of boronic acids must be considered as one of the primary reasons for the success of the Suzuki reaction, particularly in the pharmaceutical industry, and wealth of methods exists for the synthesis of boronic acids from a variety of starting materials.[15]

In early 2012, Mayr et al. published a series of kinetic studies into the nucleophilicity of organoboron compounds with the goal of establishing his nucleophilicity parameter as a guide in the designing of transition metal-free carboncarbon bond forming reactions.[16] A particularly interesting feature of this study was the establishment of novel nucleophilicity parameters for designing transition metal-free C-C bond forming

reactions. Based on the rule of thumb for nucleophile-electrophile combinations (as already seen in the previous chapter).[17] In the context of organic synthesis, high nucleophilic reactivity and functional group tolerance are opposing properties of organometallic compounds. Organolithium reagents, for example, are highly nucleophilic and as such react with most electrophiles,[18] whilst organosilicon compounds demonstrate a much lower reactivity, tolerating the majority of functional groups but usually requiring base activation in order to react. The need to balance reactivity and selectivity in synthetic sequences involving a number of functionalities often precludes the use of either of these types of reagents. Organoboron compounds however are positioned in between the two in terms of nucleophilicity vs. functional group tolerance; many are useful partners in non-catalysed C-C bond forming reactions with various electrophiles, whilst others demonstrate a remarkable tolerance of a variety of functional groups and are valuable substrates in Suzuki-Miyaura type Pd-catalysed cross coupling reactions.[19] While aryl and alkenyl trifluoroborates, as well as trialkoxyborates, have been used in the absence of transition metals,[20] arylboronic acids and arylboronates are commonly used in the presence of Lewis basic additives.[21] The formation of boron "ate complexes" and their successive reaction with carbon electrophiles such as iminium ions, Michael acceptors and stabilised carbocations, have recently been explored.[22]

Mayr has quantified the change in nucleophilicity upon quaternisation of the boron centre when moving from the boronic acid or pinacol ester to any of the other protected functional groups. In considering 5-substituted furan rings, the nucleophilic reactivity of the organic residue increases by about three orders of magnitude in the case of the intramolecular coordination of an amino group and by almost ten orders of magnitude in the case of intramolcular alkoxide coordination. The trifluoroborate moiety is considerably less reactive than the trialkyloxyborate functional group, increasing the nucleophilicity (relative to the pinacol protected boronic acid) by a factor of 104.

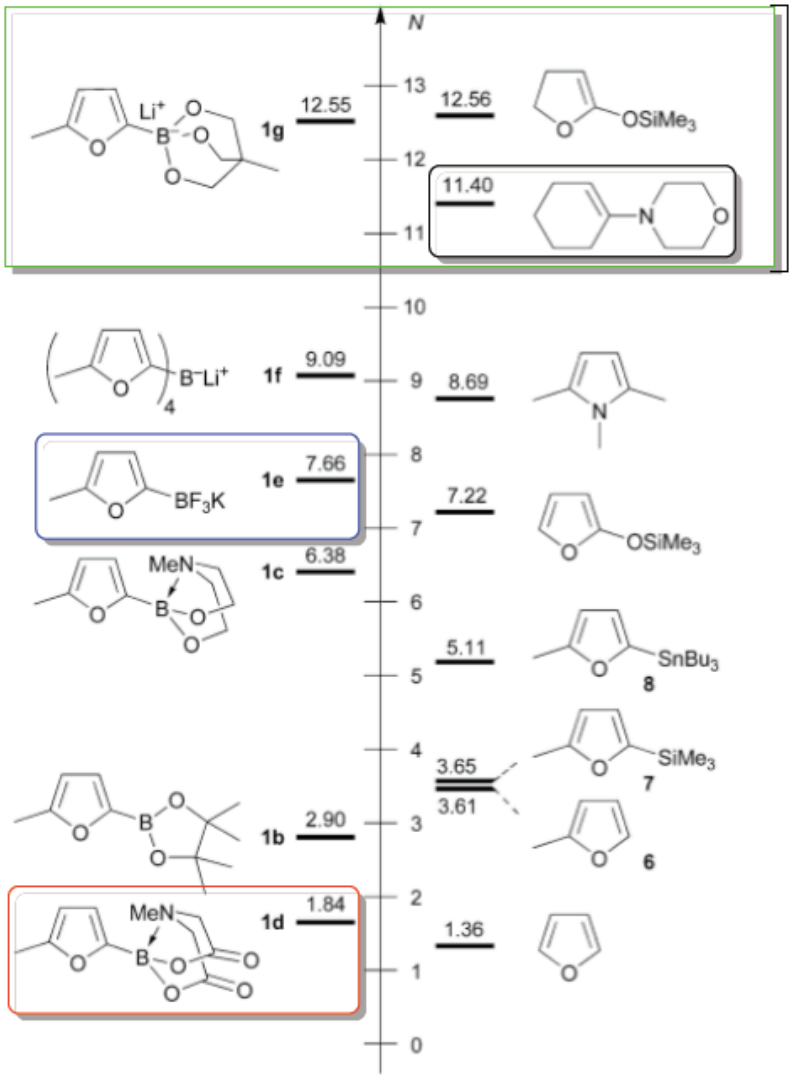


Figure 4.3. The nucleophilicity of boronic derivatives according to Mayr-scale rationalization.

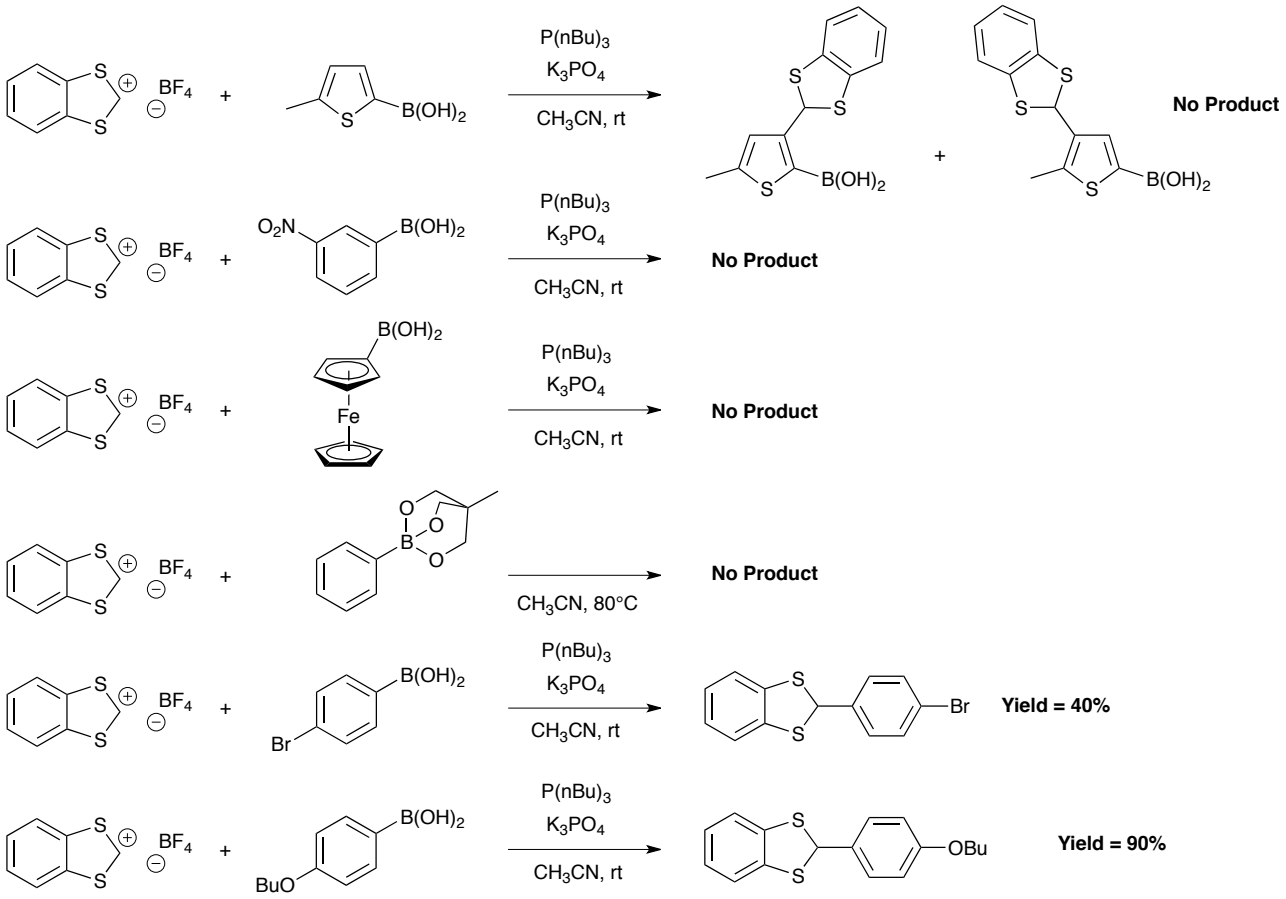
On the basis of the measured range in the nucleophilicity parameter of organoboron reagents, Mayr highlighted the possible scope for organoboron compounds in new, reasonably tolerant, and functional group compatible organic transformations, avoiding the use of transition metals.[23]

While transition metal-free C-C bond forming reactions utilising organoboronates as the nucleophilic partner to a stabilised carbenium ion are not well established in the literature, they are of potentially great interest to industry and academia. The Mayr scale[24] and relation provide a base from which an element of systematic rational design can join the chemical intuition that guided previous efforts in this area of organic synthesis (*Figure 4.3*).

The idea shown below is to develope the direct reaction of the carbocation 1,3-benzodithiolylium with some boronic substrates promoting a metal-free Suzuki reaction. This appear to be facilitated by the wide range of nucleophilic boronate compounds from which to choose that Mayr has reported.

Results and Discussion

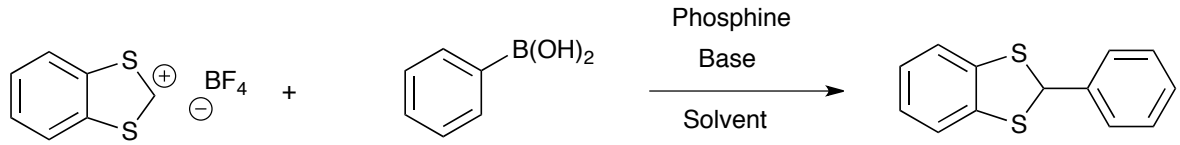
We start by testing some reactions under the standard conditions reported by Suzuki (phosphine and base) in the absence of the Pd based catalyst. These tests have led to some encouraging results (*Scheme 4.8*):



Scheme 4.8

Subsequently we carried out a screening in order to determine the best conditions to carry out a standard reaction (*Table 4.1*):

Table 4.1



Entry[a]	Solvent	Base	Phosphine	Temp., (°C)	Yield (%)[b]
1	CDCl3	K3PO4	P(nBu)	rt	0
2	CH_3CN	K3PO4	P(nBu)	80	0
3	Toluene	K3PO4	P(nBu)	110 (MW)	0
4	Toluene	/	/	110	0
5	Toluene	/	P(nBu)	110	0
6	Toluene	K3PO4	/	110	30
7	Toluene	K3PO4	P(nBu)	110	0
8	Toluene	K3PO4	Pd(PPh3)4	110	0
9	Toluene	NaH2PO4	Pd(PPh3)4	110	0
10	Toluene H2O	+K3PO4	/	110	0
11	Toluene	K3PO4	/	110	0
12	Toluene	NaH2PO4	/	110	0
13	Toluene	NaHCO3	/	110	0
14	Toluene	tBuOOK	/	110	0
15	CH_3CN	K3PO4	P(PhF5)3	rt	29
16	CH_3CN	K3PO4	P(Ph)3	rt	61

With the aim of increasing the yield of the reactions we decided to change the boronic species among those studied by Mayr.

Trifluoroborate salts

Potassium trifluoroborate salts are particularly interesting protecting groups for boronic acids (*Figure 4.4*). Pyrimidisation of the boron centre attenuates the reactivity associated with the planar sp^2 boron centre in boronic acids, rendering the molecules indefinitely stable to air and water.

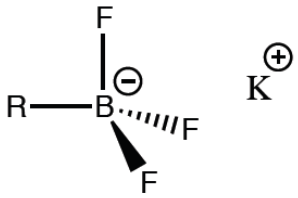


Figure 4.4. The trifluoroborate protecting group

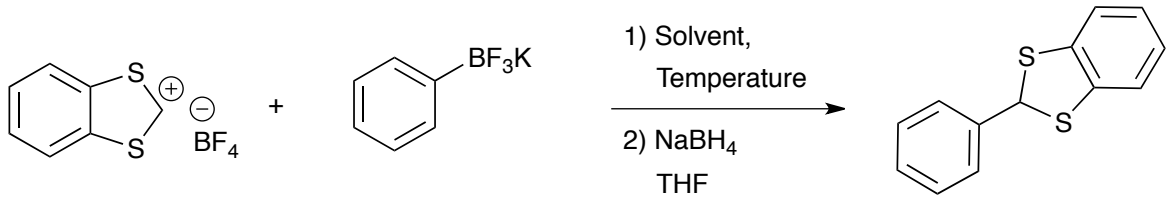
A number of possible routes have been developed to access organotrifluoroborates depending on the nature of the organic residue. In 1995, Vedejs et al. published a highly efficient method using aqueous potassium hydrogen difluoride (KHF_2) as a fluorinating reagent for purified boronic acids.[25] It is not necessary to pass through the purified boronic acid in order to access the corresponding trifluoroborate salt

though, other methods have been established, including transmetallation, hydroboration and C-H activation.[18]

The activation of the BF_3 group is sufficient for the organocatalytic Friedel Crafts alkylation of the α,β-unsaturated iminium ion (-10 < E < -5) as described by MacMillan.[26]

From an inspection of the Mayr nucleophilicity parameters published for the organoboron reagents,[16] the aryltrifluoroborate salts are seen to exhibit moderate nucleophilicity (*Figure 4.3*). The more nucleophilic boron 'ate' complexes were not suitable for the carbenium ion as the alcohol in equilibrium with the 'ate' complex is presumed to intercept the carbenium ion. The desired compounds were obtained after the reduction of the carbenium ion intermediate with $NaBH_4$. The optimisation procedure was conducted with 2.5 equivalents of potassium phenyltrifluoroborate as the nucleophilic reagent due to the ease of access to this compound. The process of optimising the reaction involved a solvent screening with the results shown in *Table 4.2*; the use of acetonitrile as a solvent resulted in significantly higher conversion when compared to the other solvents tested: dichloroethane, toluene and dioxane. No traces of product were identified when DMF was used. It was found that the conversion did not increase after the reaction temperature was raised above 80 °C in each of the solvents tested and as such 80 °C was selected as the optimum reaction temperature.

Table 4.2. Reaction conditions for the direct formylation of **2a** with the electrophilic reagent **1**.



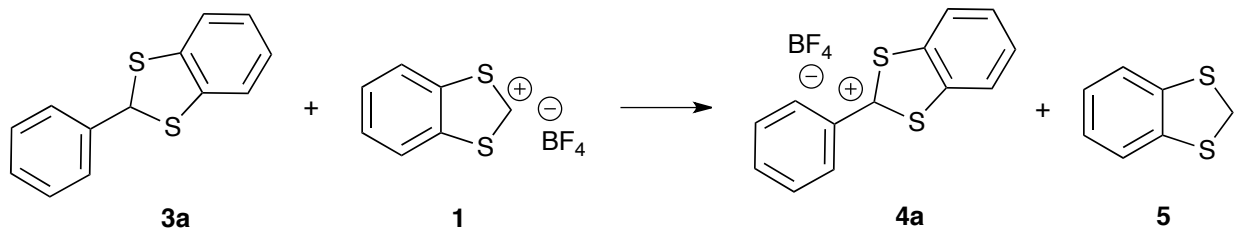
1 2.5 equiv | **2a** 1.0 equiv | **3a**

Entry[a]	T (h)	Solvent	Temp. (°C)	Conversion (%)[b]
1	16	DCE	80	60
2	48	DMF	80	0
3	24	THF	80	10
4	24	Dioxane	80	17
5	16	Toluene	80	50
6	16	CH_3CN	rt	73
7[c]	10	CH_3CN	80	80

[a] The reaction was conducted under nitrogen atmosphere for the indicated time. [b] After ^{1}H-NMR of the crude reaction mixture.

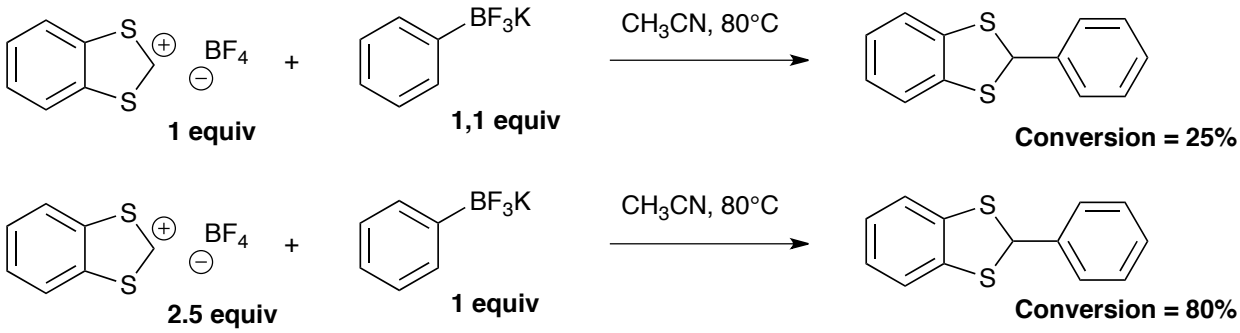
After optimisation, it was determined that the reaction of potassium phenyltrifluoroborate and 1,3-benzodithiolylium tetrafluoroborate in CH_3CN afforded the desired coupled product with high conversion

and satisfactory isolated yield. Although the reaction was effective at room temperature, longer reaction times were necessary to achieve a satisfactory conversion. The chemical properties of CH_3CN are not thought to affect the reaction rate; Mayr has observed only minor changes in the rate of the reaction in CH_3CN when compared to CH_2Cl_2, thereby excluding the possibility that the acetonitrile coordinates to the sp^2 boron centre. The number of equivalents of **1** is important in driving the reaction to the desired product.



Scheme 4.9. Formation of the most stable cationic compounds by hydride shift.

It is well known that the carbenium ion can be obtained by CH hydride shift.[27] As soon the aryl benzodithiole (**3a**) is obtained, the product is transformed into the corresponding cationic compound (**4a**, *Scheme 4.9*); in order to drive the reaction towards the formation of the more stabilized cation (**4a**), almost 2.5 equivalents of **1** are necessary, this has been perceived by intuition after H-NMR analysis of the crudes and after the consequent test reported in *Scheme 4.10*.

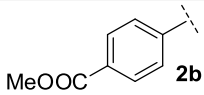
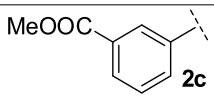
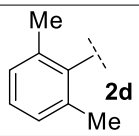
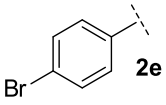
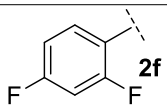
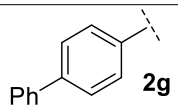
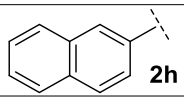
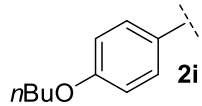
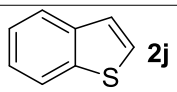
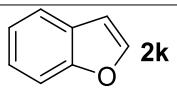


Scheme 4.10

It is worth adding that cationic form **4a** obtained is air stable and can be isolated by filtration. In order to isolate the compound in its neutral form, the crude reaction mixture was reduced with $NaBH_4$, affording the desired **3a** in high yields. The isolation of a number of products proved to be challenging due to their tendency to form stabilized cations. Fortunately, preparative TLC on neutral-Al_2O_3 resulted in only minor decomposition (formation of the carbenium ion by hydride shift).

The single case of an aryltrifluoroborate bearing an electron-donating group that has demonstrated a successful conversion to the corresponding coupled product in good yield was extended to other aryltrifluoroborates (*Table 4.3*).

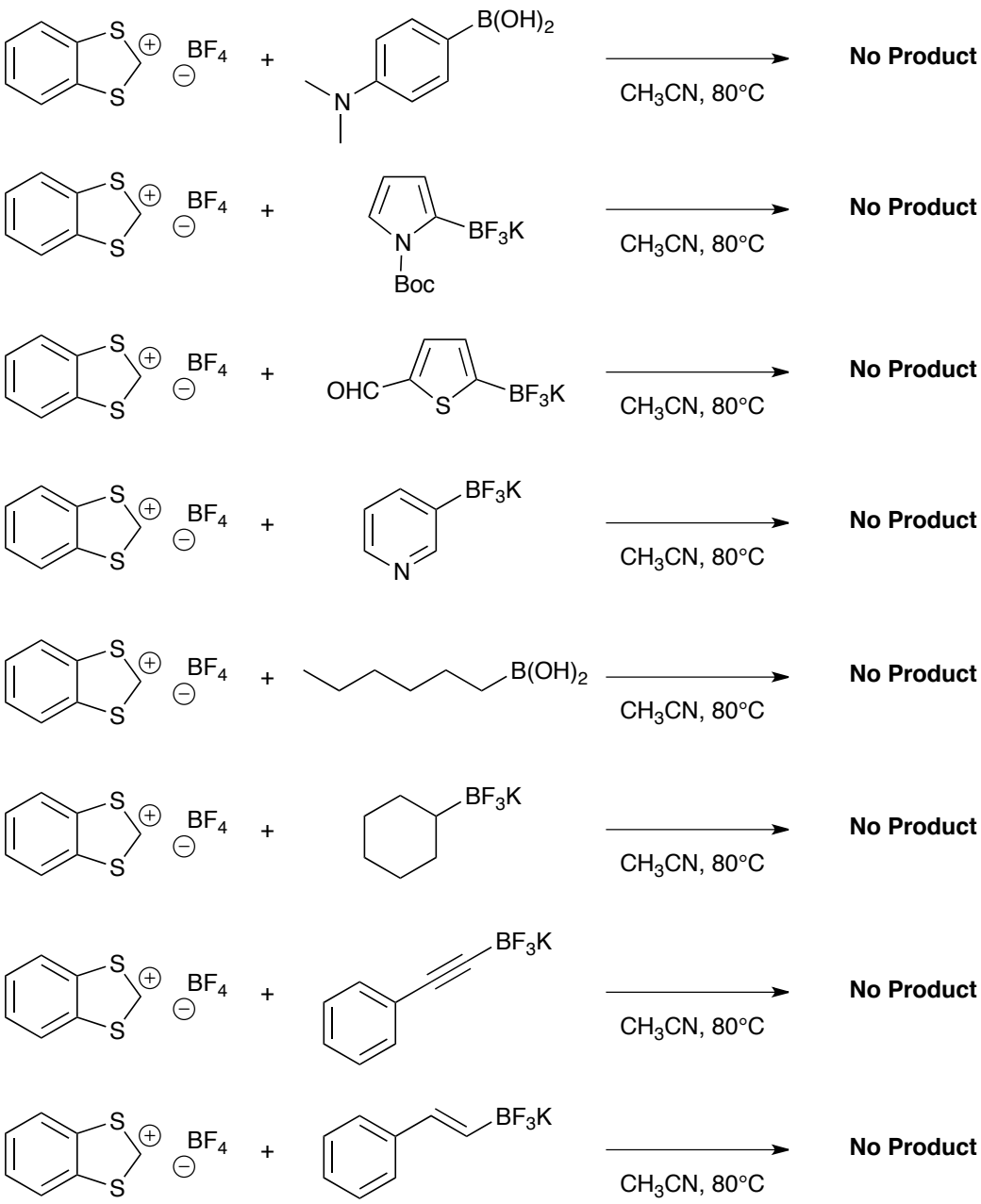
Table 4.3. Addition of the benzodithiolylium **1** to electron rich and electron poor aryltrifluoroborates.

Entry[a]	$ArBF_3K$	Product	Yield [%][b]
1		**3b**	45(30)
2		**3c**	52(32)
3		**3d**	68(40)
4		**3e**	68(33)
5		**3f**	64[c]
6		**3g**	85(70)
7		**3h**	100(72)
8		**3i**	87(67)
9		**3j**	98(30)
10		**3k**	99(84)

[a] All the reactions were conducted in CD_3CN. [b] The conversion were determined by ^{1}H-NMR in CD_3CN on the crude reaction mixture. The isolated yield after chromatographic purification on neutral Al_2O_3 are reported in parenthesis. [c] The product was obtained as inseparable mixture with the benzodithiol **5**.

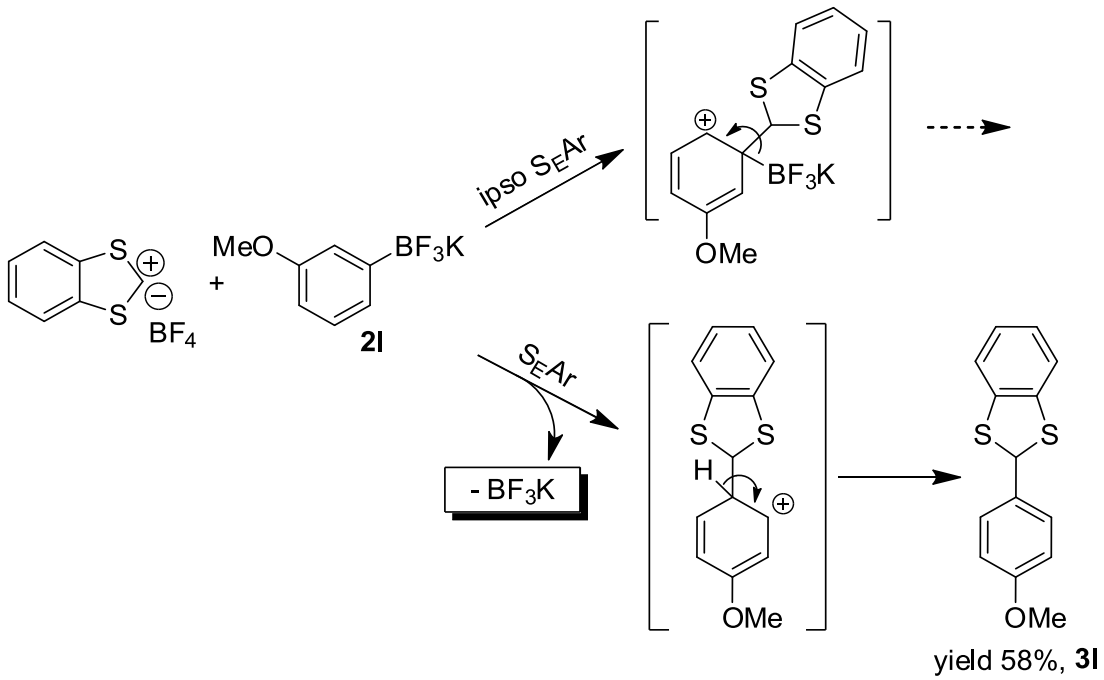
All the trifluoroborate salts were prepared from the commercially available boronic acid following the simple procedure described by Molander.[28] Electron donating groups (**2g-i**) on the aromatic ring system are seen to result in both better conversion to the coupled product and a better yield of isolated product when compared to electron withdrawing groups (**2b, 2c**). This can be explained by the increased nucleophilicity of the organic residue in the case of an activated ring system bearing electron donating groups as opposed to a relatively deactivated ring in the case of a ring bearing electron withdrawing groups. The reaction also proved to be tolerant of halide functionalities; both **2e** and **2f** were coupled with a high conversion, while only **3e** was successfully isolated as a pure product.

Strongly electron deficient aromatic substrates (pyridine, formylthiophenes, etc.)[29] proved to be unreactive under the reaction conditions studied, as well as all aliphatic compounds tested (*Schema 4.11*).



Scheme 4.11

The compounds were purified by preparative TLC on neutral-Al_2O_3. The facile formation of the cation by hydride shift can be advantageously used for the preparation of new hydridic reagents for organocatalytic reduction.[27] The ipso Friedel-Crafts electrophilic aromatic substitution mechanism is presumed to be the prevalent reaction pathway in this class of reaction. Mayr et al. report that changing the counter ion in the reactions of a number of borates with a benzhydrylium cation does not result in a significant change in the rate of reaction.[16] This indicates a rate determining C-C bond forming step in which the C-B bond is not yet fully broken, a result fully consistent with the Friedel Crafts S_EAr mechanism. However, as the electron rich aromatic compounds can also react directly with **1**,[4] we examined the possibility of a competition between activating effects and trifluoroborate ipso-activation. The 3-methoxyphenylboronic **2l** (*meta* substituted) acid was readily transformed into the corresponding *para* substituted **3l** (*Scheme 4.12*).



Scheme 4.12. Reactions of electron rich boronic acid derivative.

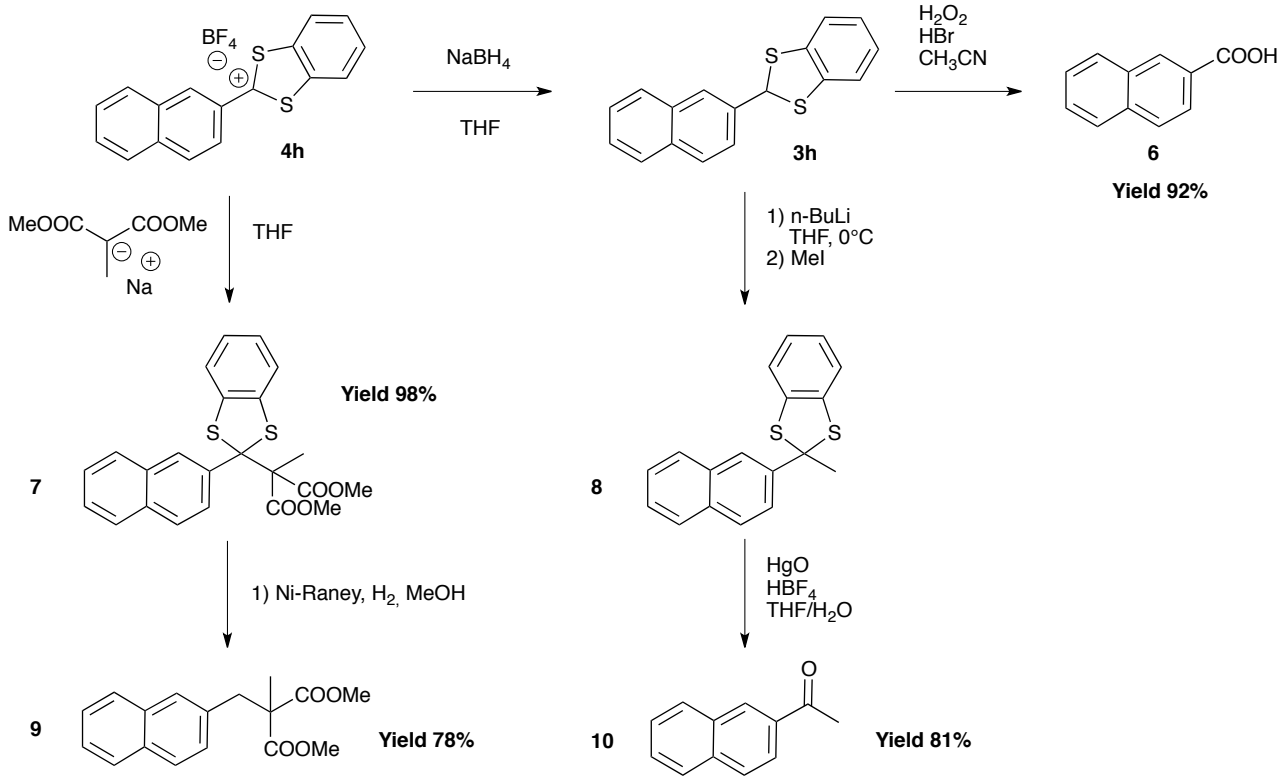
Two possible explanations are suggested. The first is based on the idea of a *para*-directed Friedel Crafts electrophilic aromatic substitution mechanism with a separate step or concomitant hydrogen transfer and elimination of the trifluoroborate moiety. Another possible explanation for the observed regiochemistry of this substituted product can be offered based on an examination of selected results from other electrophilic aromatic substitution reactions reported in the literature involving trifluoroborate salts.[17] In their investigation of the nitrosation of substituted aryl and heteroaryltrifluoroborates, Molander et al.[18] noted a number of cases in which the attempted substitution reaction actually resulted in the undesired protodeboronation of the aryl or heteroaryltrifluoroborate compound. If this mechanism were to have occurred, methoxybenzene would then be free in the presence of the electrophilic **1**, but this was not observed.[19]

The versatility of the benzodithiol after its introduction is illustrated in *Scheme 4.13*. Separate direct reactions of the electrophilic compound **4h** with strong nucleophilic compounds such enamines,[8] at 80 °C did not result in any further coupling product as determined by ^{1}H-NMR analysis after 17 hours. The even more strongly nucleophilic malonate anion, however, proved to be sufficiently reactive to overcome the strong stabilization of **4h.**

The benzodithiol group can easily be alkylated with electrophiles following treatment with *n*BuLi. Starting from the aryltrifluoroborate, aromatic ketones can be obtained easily. The benzothiol group can also be oxidised to the corresponding carboxylic acid. The benzodithiol is not only the masked form of the corresponding aldehyde, ketone or acid, but it is also possible to eliminate the group by hydrogenation. This particular transformation is illustrated by a stepwise synthesis. Moreover the direct formation of the carbenium ion before reduction with $NaBH_4$ can be advantageously used for successive additions of nucleophiles. This transformation can be accomplished with a one pot, two-steps procedure. It is worth adding that the electrophilicity of the intermediated cations like **4a** is not very high; this limited capacity to behave like a powerful electrophile restricts the range of nucleophiles that can be used for intercepting these arylbenzodithi-

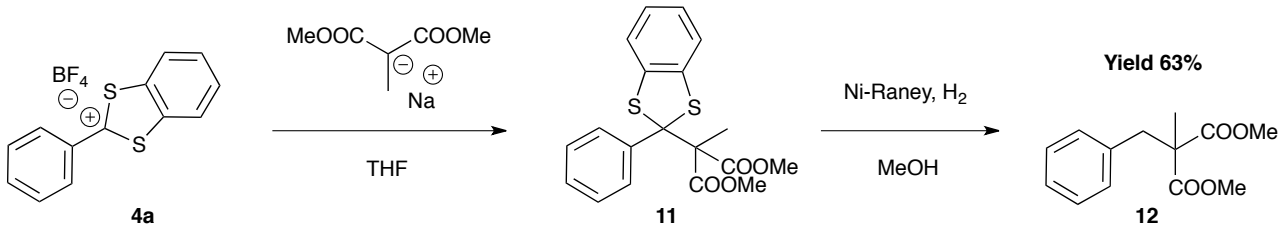
olylium cations.[33] Only very reactive nucleophiles, positioned at or below 18 on the Mayr scale[23] can be used in order to observe a reaction.

We have also performed a C-C bond forming reaction by introducing the anion of dimethyl 2-methylmalonate (prepared by addition of NaH in THF) to the compound **4h**. The irreversible formation of a C-C bond and the stability of the resultant structure are the driving forces for obtaining a good yield of the desired product **7**. Interestingly, the treatment of **7** with Ni-Raney resulted in the elimination of benzodithiole and the reduction of the less substituted benzene ring.



Scheme 4.13. Multistep reaction sequences utilizing the chameleonic benzodithiol group.

When the reaction was repeated on compound **11,** the elimination of the benzodithiole group occurred without any side reaction (*Schema 4.14*).



Scheme 4.14

Conclusions

In conclusion, by taking advantage of the results from the kinetic and synthetic studies described by Mayr, we were able to design a simple and effective procedure for the direct formylation of arylte-

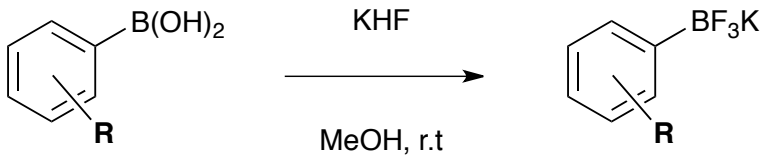
trafluoroborate salts. The coupling of a range of aryl and heteroaryl trifluoroborate salts with 1,3-benzodithiolylium tetrafluoroborate, a stabilised and functionalisable carbocation, has been attempted. Electron rich ring systems and polyaryl compounds were successfully coupled to the stabilised carbocation in moderate to good yield while electron deficient rings as well as certain simple aliphatic and heteroaromatic substrates were not seen to couple efficiently and often decomposed during the isolation process on alumina.

The advantage in introducing the benzodithiole group stems from its chameleonic nature; this group can be advantageously used for further transformations. The cationic aryl benzodithiol compounds, accessible via the direct reaction of **1**, are potentially of use in materials science. In future it will be possible to expand the scope of this chemistry by studying related reactions involving a variety of boronic acids and suitable carbenium ion precursors.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian MR 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: *m/z* (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel or with Neutral Al_2O_3. Determination of enantiomeric excess were performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using a Daicel Chiralpak columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line), specific rotation was expressed as deg $cm^3g^{-1}dm^{-1}$ and concentration as gcm^{-3}. Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected.
Materials: All reactions were carried out in sealed vials with nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification. Deutereted Chloroform was used as received without further purification.

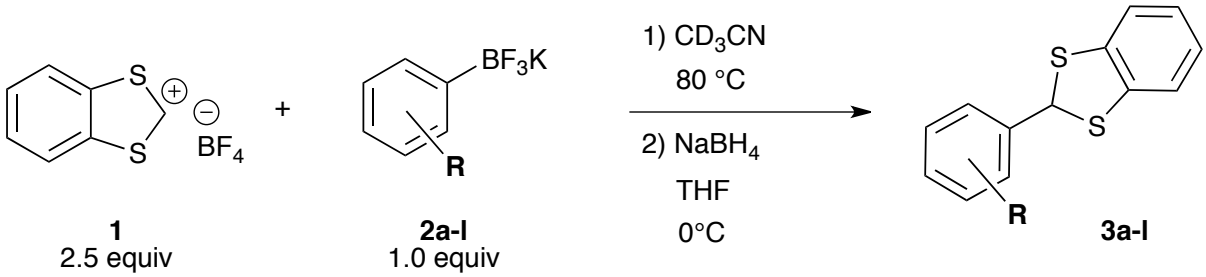
General procedure for the synthesis of compounds 2a-l



2a-l

In an air-open flask the boronic acid (1.0 mmol, 1 equiv) was dissolved in methanol (2 mL, 0.5 M). KHF_2 (3.5 mmol, 3.5 equiv.) was added and the reaction was stirred at room temperature for 24-48 hours. The MeOH was than evaporated under reduced pressure and acetone was added (10 mL, only the product is soluble in acetone). The organic phase was collected and concentrated under reduced pressure to afford the desired aryltrifluoroborate salts.

General procedure for the synthesis of compounds 3a-l



1
2.5 equiv

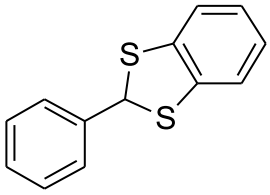
2a-l
1.0 equiv

3a-l

In a flask under nitrogen atmosphere 1,3-benzodithiolylium tetrafluoroborate (60 mg, 0.25 mmol, 2.5 equiv) were dissolved in deuterated acetonitrile-d^3 (1.0 mL, 0.25 M). The aryltrifluoroborate salt (0.1 mmol, 1 equiv.) was added to the solution and the reaction mixture was stirred at 80 °C until the maximum conversion (checked by direct ^{1}H-NMR on the crude reaction mixture) was obtained. The reaction was then concentrated under reduced pressured and obtained solid was washed with diethyl ether (2 x 2mL). It was possible to obtain the product **4a-l** by evaporation of the solvent, addition of ether and filtration. The carbocation product was obtained with excellent purity. THF (1.0 mL) was added to the solid, followed by $NaBH_4$ (3 equiv.) at 0 °C. The reaction mixture was stirred for 1-2 hours then quenched with the minimum amount of water and extracted with diethyl ether. The organic phases were collected, dried over Na_2SO_4 and then evaporated under reduced pressure to give crude product, that was purified by preparative chromatography on neutral-Al_2O_3 using cyclohexane as eluent to provide the pure product.

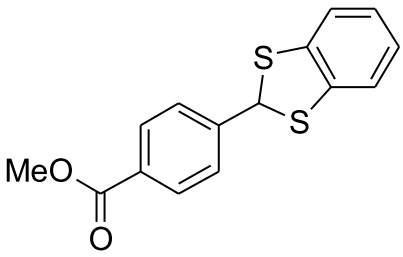
Spectral data of compounds 3a-l

3a: 2-phenylbenzo[*d*][1,3]dithiole



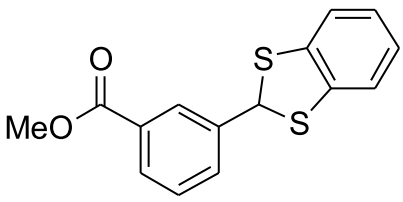
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.55 (dd, 2H, J = 2.0, 7.4 Hz), 7.37-7.29 (m, 3H), 7.21 (dd, 2H, J = 3.0, 5.8Hz), 7.06 (dd, 2H, J = 3.0, 5.8Hz), 6.20 (s, 1H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 139.9 (1C), 137.5 (2C), 128.8 (1C), 128.7 (2C), 127.1 (2C), 125.8 (2C), 121.9 (2C), 56.5 (1C). HMRS calcd for $C_{13}H_{10}S_2$: 230.02239.

3b: methyl 4-(benzo[*d*][1,3]dithiol-2-yl)benzoate



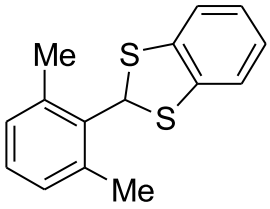
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.98 (d, 2H, J = 8.4Hz), 7.58 (d, 2H, J = 8.4Hz), 7.22 (dd, 2H, J = 3.0, 5.8Hz), 7.07 (dd, 2H, J = 3.0, 5.8Hz), 6.13 (s, 1H), 3.91 (s, 3H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 198.0 (1C), 151.0 (1C), 137.2 (2C), 130.1 (2C), 127.0 (2C), 126.0 (2C), 125.7 (1C), 122.0 (2C), 55.6 (1C), 52.2 (1C). HMRS calcd for $C_{15}H_{12}O_2S_2$: 288.02787.

3c: methyl 3-(benzo[*d*][1,3]dithiol-2-yl)benzoate



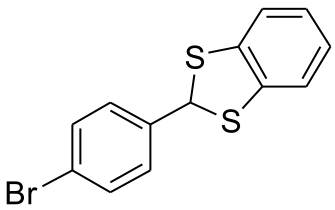
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 8.17 (s, 1H), 7.97 (d, 1H, J = 7.8Hz), 7.79 (d, 1H, J = 7.8Hz), 7.41 (t, 1H, J = 7.8Hz), 7.21 (dd, 2H, J = 3.3, 5.8Hz), 7.07 (dd, 2H, J = 3.3, 5.8Hz), 6.21 (s, 1H), 3.91 (s, 3H), ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 166.5 (1C), 140.6 (1C), 137.2 (2C), 131.6 (1C), 130.5(1C), 129.9 (1C), 129.0 (1C), 128.2 (1C), 125.9 (2C), 122.0 (2C), 55.9 (1C), 52.2 (1C). HMRS calcd for $C_{15}H_{12}O_2S_2$: 288.02787.

3d: 2-(2,6-dimethylphenyl)benzo[*d*][1,3]dithiole



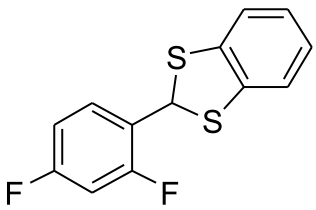
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.34-7.22 (m, 1H), 7.21-7.09 (m, 3H), 7.08-6.98 (m, 4H), 2.63 (s, 6H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 139.0 (2C), 131.1 (1C), 129.8 (2C), 128.6 (2C), 125.9 (1C), 125.4 (2C), 121.8 (2C), 52.1 (1C), 21.8 (2C). HMRS calcd for $C_{15}H_{14}S_2$: 258.05369.

3e: 2-(4-bromophenyl)benzo[*d*][1,3]dithiole



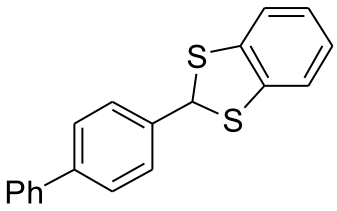
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.47-7.38 (m, 4H), 7.20 (dd, 2H, J = 3.2, 5.8Hz), 7.07 (dd, 2H, J = 3.2, 5.8Hz), 6.09 (s, 1H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 139.3 (1C), 137.1 (2C), 131.8 (2C), 128.7 (2C), 125.9 (2C), 125.6 (1C), 122.0 (2C), 55.6 (1C). HMRS calcd for $C_{13}H_9BrS_2$: 307.93290.

3f: 2-(2,4-difluorophenyl)benzo[*d*][1,3]dithiole



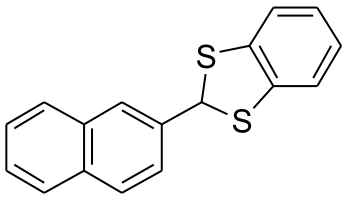
The compound was obtained as a mixture with the benzodithiole. Chromoatographic purification was not possible in this as case as in many different eluent mixture the compounds were not separable. ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.73-7.64 (m, 1H), 7.24 (dd, 2H, J = 3.3, 5.9Hz), 7.08 (dd, 2H, J = 3.3, 5.9Hz), 6.85-6.75 (m, 2H), 6.26 (s, 1H) ppm. HMRS calcd for $C_{13}H_8F_2S_2$: 266.00355.

3g: 2-([1,1′-biphenyl]-4-yl)benzo[*d*][1,3]dithiole



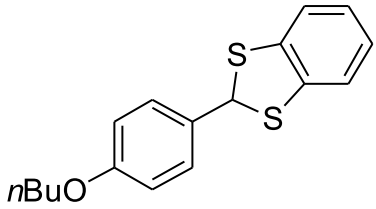
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.62 (d, 2H, J = 8.0Hz), 7.59-7.52 (m, 4H), 7.44 (d, 2H, J = 8.0Hz), 7.35 (t, 1H, J = 7.3Hz), 7.23 (dd, 2H, J = 3.3, 5.8Hz), 7.08 (dd, 2H, J = 3.3, 5.8Hz), 6.24 (s, 1H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 141.8 (1C), 140.5 (1C), 139.0 (1C), 137.6 (2C), 128.9 (2C), 127.6 (1C), 127.5 (4C), 127.2 (2C), 125.9 8 (2C), 122.0 (2C), 56.3 (1C). HMRS calcd for $C_{19}H_{14}S_2$: 306.05369.

3h: 2-(naphthalen-2-yl)benzo[*d*][1,3]dithiole



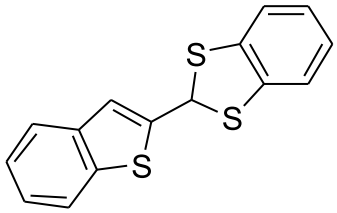
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.89 (s, 1H), 7.85-7.77 (m, 3H), 7.73 (d, 1H, J = 8.8Hz), 7.48 (dd, 2H, J = 3.3, 6.2Hz), 7.23 (dd, 2H, J = 3.3, 5.9Hz), 7.07 (dd, 2H, J = 3.3, 5.9Hz), 6.37 (s, 1H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 137.6 (2C), 137.1 (1C), 133.4 (1C), 132.5 (1C), 129.0 (1C), 128.1 (1C), 127.7 (1C), 126.5 (2C), 125.9 (2C), 124.9 (2C), 122.0 (2C), 56.8 (1C). HMRS calcd for $C_{17}H_{12}S_2$: 280.03804.

3i: 2-(4-butoxyphenyl)benzo[*d*][1,3]dithiole



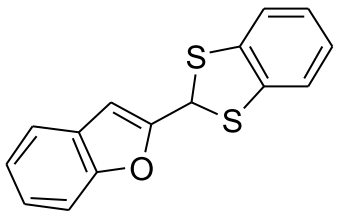
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.48 (d, 2H, J = 8.7Hz), 7.17 (dd, 2H, J = 3.3, 5.7Hz), 7.03 (dd, 2H, J = 3.3, 5.7Hz), 6.82 (d, 2H, J = 8.7Hz), 6.22 (s, 1H), 3.93 (t, 2H, J = 6.5Hz), 1.79-1.67 (m, 2H), 1.52-1.40 (m, 2H), 0.95 (t, 3H, J = 7.4Hz) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 159.5 (1C), 137.7 (2C), 131.1 (1C), 128.4 (2C), 125.7 (2C), 121.9 (2C), 114.6 (2C), 67.7 (1C), 56.6 (1C), 31.2 (1C), 19.2 (1C), 13.8 (1C). HMRS calcd for $C_{17}H_{18}OS_2$: 302.07991.

3j: 2-(benzo[*b*]thiophen-2-yl)benzo[*d*][1,3]dithiole



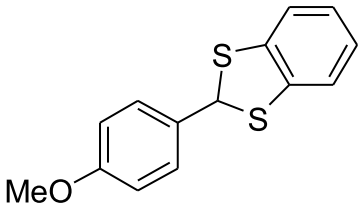
^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.77-7.70 (m, 1H), 7.70-7.63 (m, 1H), 7.33-7.28 (m, 2H) 7.29-7.21 (m, 3H), 7.13-7.4 (m, 2H), 6.37 (s, 1H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 145.3 (1C), 139.8 (1C), 138.8 (1C), 136.7 (1C), 126.0 (2C), 125.8 (1C), 124.9 (1C), 124.5 (1C), 123.8 (1C), 122.4 (2C), 122.3 (2C), 52.2 (1C). HMRS calcd for $C_{15}H_{10}S_3$: 285.99446.

3k: 2-(benzo[b]furan-2-yl)benzo[*d*][1,3]dithiole



^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.50-7.39 (m, 2H), 7.29-7.21 (m, 3H), 7.17 (t, 1H, J = 7.2Hz) 7.11-7.00 (m, 2H), 6.78 (s, 1H), 6.02 (s, 1H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 155.4 (1C), 155.3 (1C), 136.4 (2C), 127.9 (1C), 125.9 (2C), 124.7 (1C), 123.0 (1C), 122.4 (2C), 121.2 (1C), 111.4 (1C), 104.8 (1C), 48.3 (1C). HMRS calcd for $C_{15}H_{10}OS_2$: 270.01731.

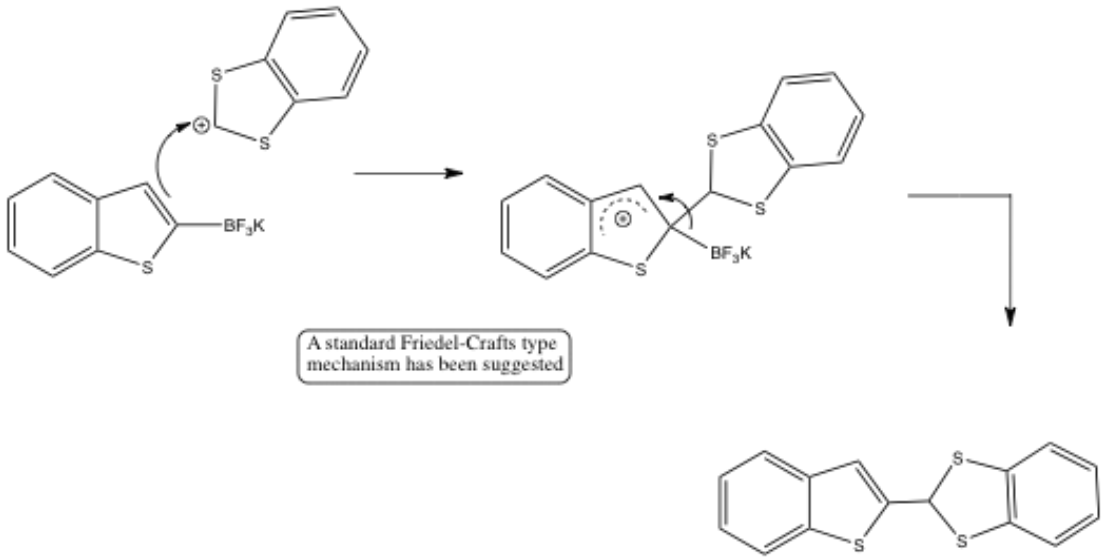
3l: 2-(4-metoxyphenyl)benzo[*d*][1,3]dithiole



^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 7.49 (d, 2H, J = 8.7Hz), 7.19 (dd, 2H, J = 3.2, 5.8Hz), 7.04 (dd, 2H, J = 3.2, 5.8Hz), 6.84 (d, 2H, J = 8.7Hz), 6.23 (s, 1H), 3.79 (s, 3H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25 °C) δ 159.9 (1C), 137.7 (2C), 131.5 (1C), 128.4 (2C), 125.7 (2C), 121.8 (2C), 114.0 (2C), 56.5 (1C), 55.3 (1C). HMRS calcd for $C_{14}H_{12}OS_2$: 260.03296.

Ipso substitution assignment of compound 3j

The evidence strongly suggests the Friedel-Crafts type regioselectivity demonstrated in the 2-substituted product. The proposed mechanism for the reaction between the stabilised carbocation **1** and the trifluoroborate activated π nucleophile:



Scheme 4.15. A suggested mechanism for the Friedel Crafts type ipso-substitution

This reaction mechanism could feasibly allow for the formation of a 3-substituted product.

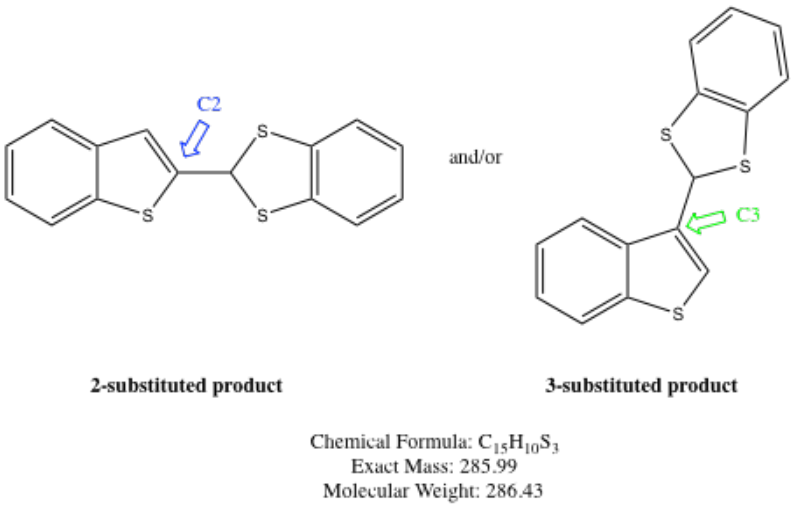


Figure 4.5. Two possible regioisomers from the coupling reaction

The ^{1}H NMR spectrum obtained for compound **3j** (400 MHz, $[D_3]CHCl_3$, 25 °C), beyond supporting the formation of a single coupled product, does not allow for a conclusive assignment of the regioisomer gained in the reaction between benzothiophene-2-boronic acid and the 1,3-benzodithiolylium cation.

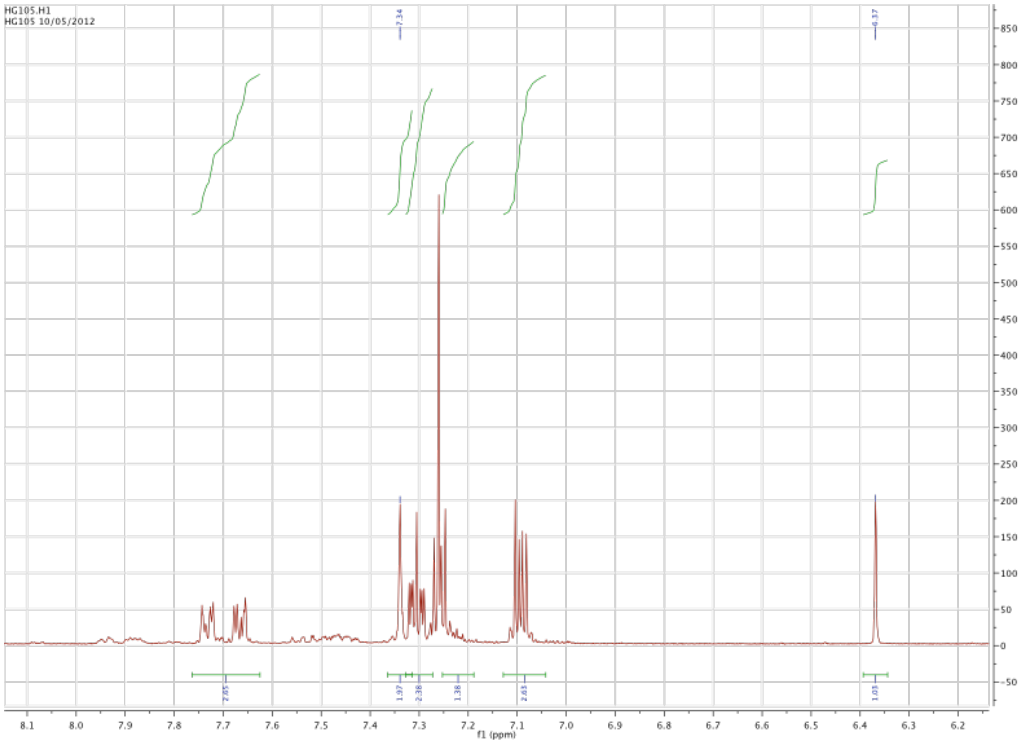


Figure 4.6. ^{1}H NMR spectrum recorded for product **3l**

The assignment of the compound's structure is partly facilitated by an examination of the characteristic peaks in the ^{1}H NMR spectrum:

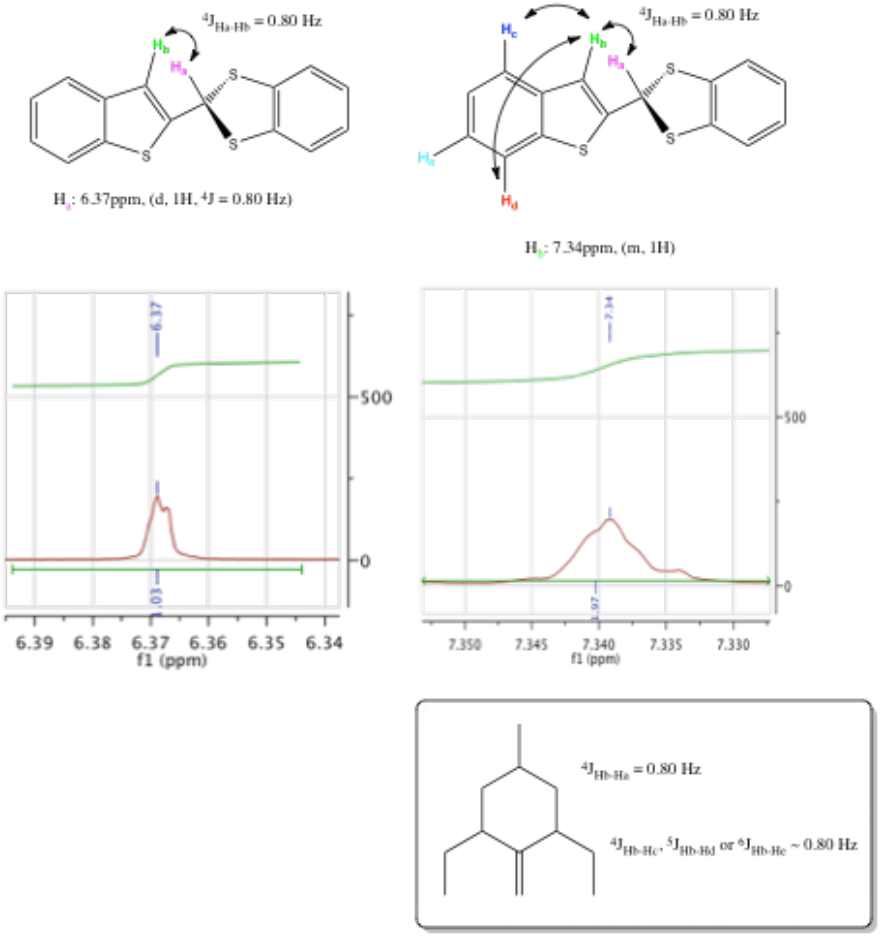


Figure 4.7. Physical origin of the coupling seen in the ^{1}H NMR spectrum

The doublet at 6.37 ppm is as expected and can be accounted for by the coupling between the H_a and H_b nuclei in the 2-substituted product or that between the H_x and H_y nuclei in the 3-substituted product (as shown in the relevant diagrams). The ^1H multiplet at 7.34 cannot, however, be conclusively assigned. The broadness of the signal masks the fine structure to the extent that it was necessary to consider other NMR methods in order to assign regioselectivity. The second order coupling could feasibly occur with any of the hydrogens close by. The intrinsic width of the NMR signals was identified as ~ 0.8 Hz and as such it is not surprising that the fine structure was not resolvable (altering this by more careful manual shimming and by examining the exponential vs. Gaussian breakdown of the signal did not offer much more in the way of useful information).

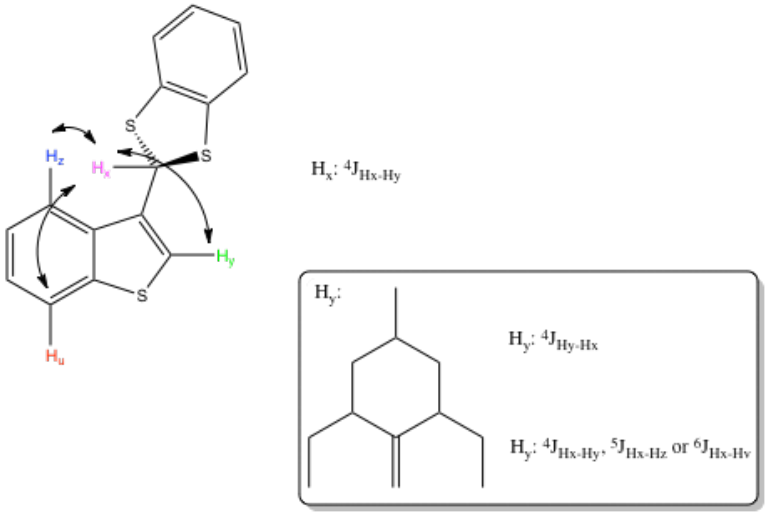


Figure 4.8. Physical origin of the coupling seen in the ^1H NMR spectrum

1D-NOESY ^1H NMR

The NOESY relies on an exploitation of the Nuclear Overhauser Effect (the through space transfer of nuclear spin polarisation from one nuclear spin population to another via cross relaxation during the mixing period) to establish correlations.

The NOESY experiment is performed in a one-dimensional fashion by pre-selecting individual resonances (or a range of resonances, typically in the order of ~25 Hz). The spectra are read with the pre-selected nuclei giving a large, negative signal while nuclei in the immediate vicinity are identified by weaker, positive signals (as shown on the superimposed spectra below).

1D-NOESY (400 MHz, $[D_3]CHCl_3$, 25 °C, Sequence = 50 Hz, Mixing Time = 1 s) was identified as a possible means by which a more convincing elucidation of the structure could be achieved. The dithiolynium hydrogen (H_a or H_x depending on the structure) was irradiated in order to identify the hydrogens to which this nucleus couples.

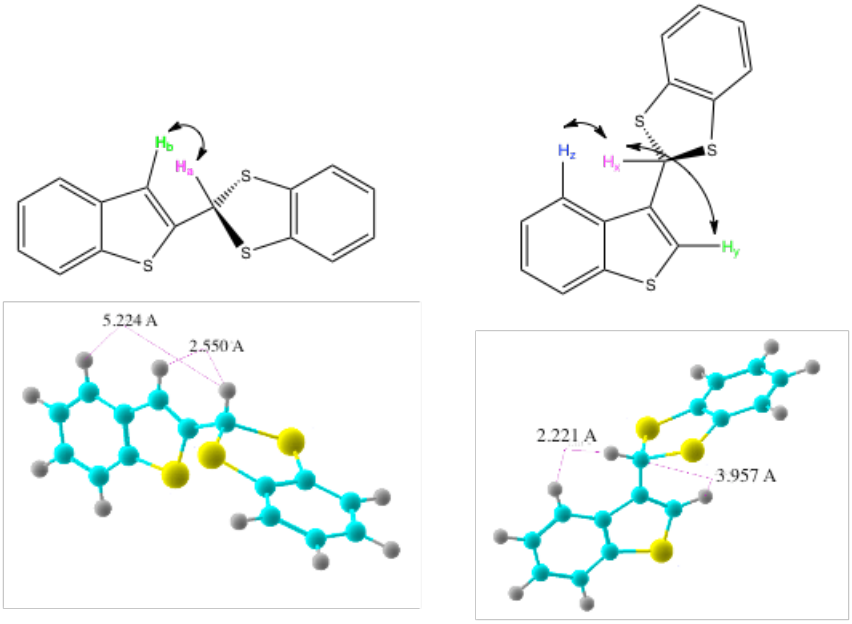


Figure 4.9. Molecular mechanical simulations of the 2- and 3-substituted products showing H-H distances

A crude molecular mechanics simulation ([PCMODEL7.5, FF:MMX], the simplicity of which is justified by the single degree of freedom represented by the carbon-carbon bond formed in the reaction between two rigid substructures) was carried out in order to determine which hydrogens in each structure were close to the irradiated hydrogen (through space) and therefore which would give rise to a signal in the NOESY analysis. The carbon-carbon bond formed in the reaction is free to rotate and so in the 3-substituted structure, the molecular geometry would likely oscillate between the two low energy conformers (separated in energy by less than half a cal.) and consequently have a mean position close to two hydrogens – this would give rise to two signals. Of these two signals, the peak corresponding to the aromatic hydrogen (H_z) would be expected to display a greater intensity in the NOESY spectrum due to the fact that it is expected, on average, to be closer through space to the irradiated hydrogen than the allylic hydrogen (H_y). This is not the case; in fact only a single peak is seen, which would be expected in the case of the 2-substituted product (all other hydrogen's are too far from the irradiated hydrogen to be reasonably expected to give rise to a signal).

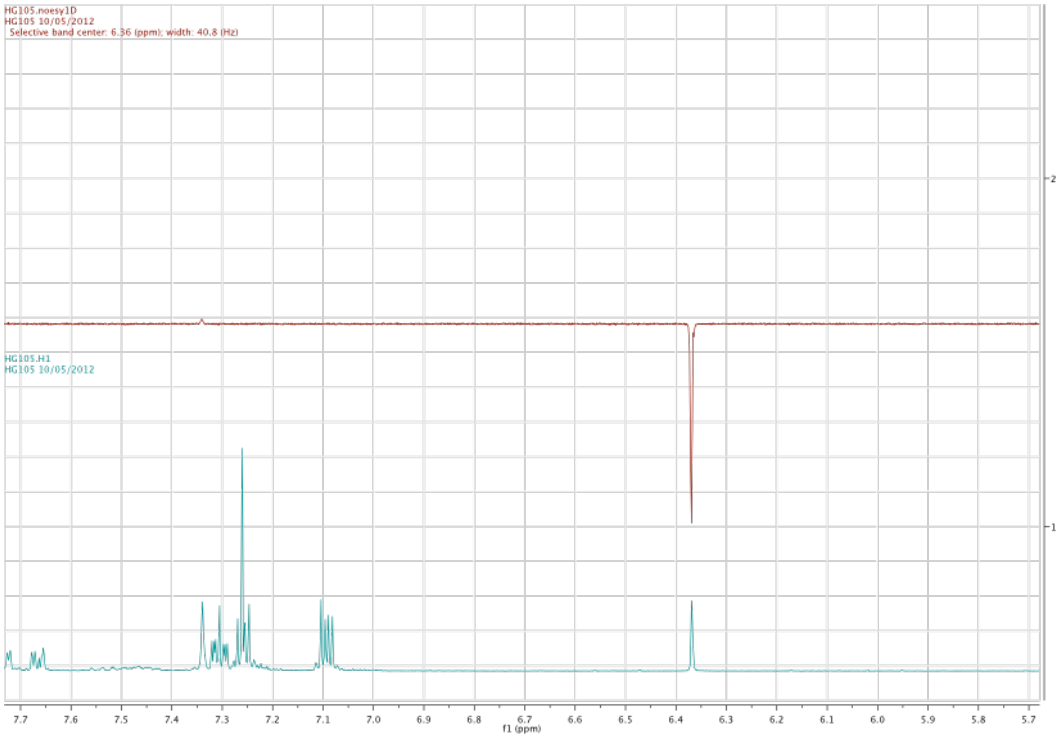
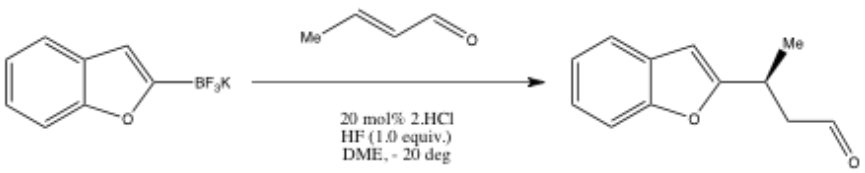


Figure 4.10. Overlap of 1D NOESY ^{1}H NMR spectrum and ^{1}H NMR spectrum for the product obtained

The analysis and structural assignment is supported by the characterization of analogous compounds in the literature. In 2007, D. MacMillan reported a Friedel-Crafts type regioselectivity with analogous trifluoroborate activated heterocyclic systems: S. Lee and D. W . C. MacMillan, *J. Am. Chem. Soc.,* **2007**, 129, 15438-15439.



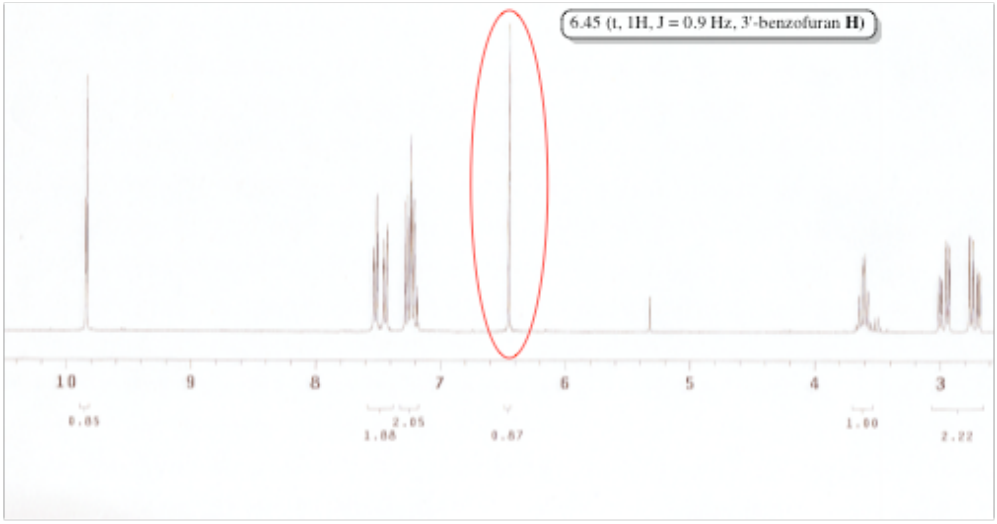


Figure 4.11. Key singlet signal in an analogous 2-substituted molecule

While even more convincing were analogous benzothiophenes synthesised by C. Bryan et al.: C. S. Bryan, J. A. Braunger, and M. Lautens, *Angew. Chem. Int. Ed.*, **2009**, 48, 7064 –7068.

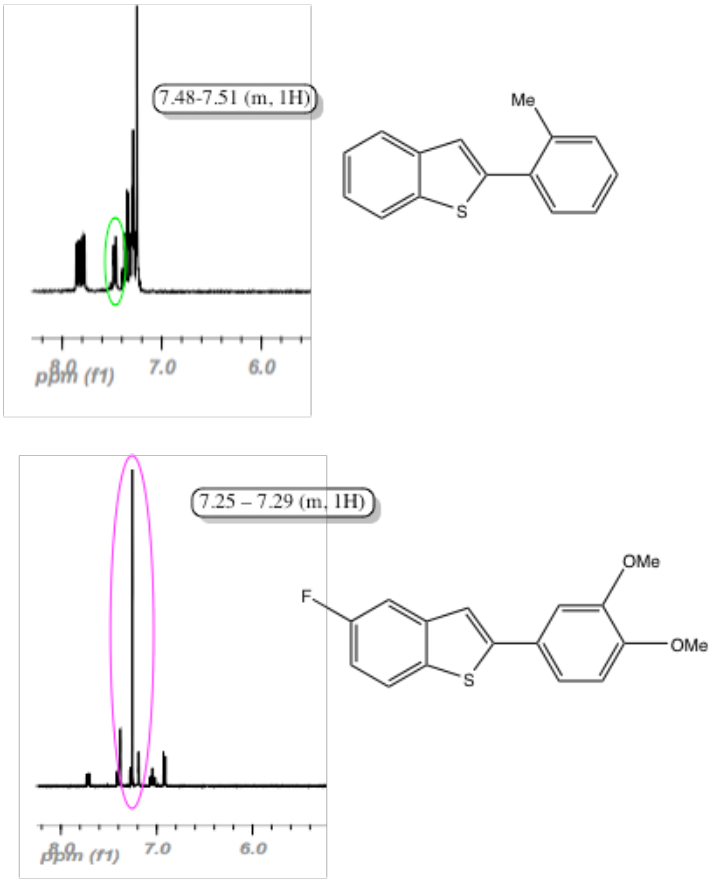
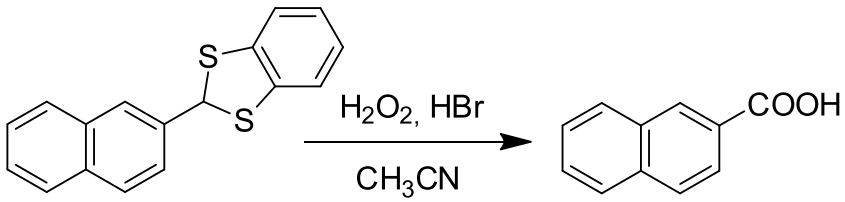


Figure 4.12. Key singlet signal in an analogous 2-substituted molecule

Synthesis of 6

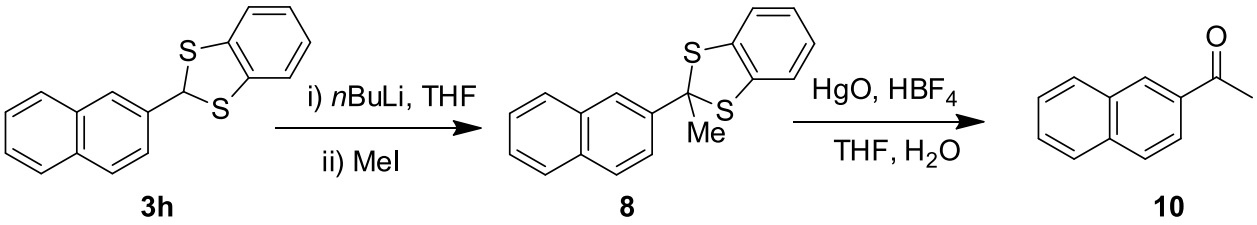


3h **6**

In an air-open flask 2-(naphthalen-2-yl)benzo[*d*][1,3]dithiole (30 mg, 0.1 mmol, 1 equiv.) was dissolved in CH_3CN (1.0 mL, 0.1 M) and a solution of 70% H_2O_2 (0.57 mL, 0.4 mmol) followed by HBr (0.022 mL, 0.2 mmol, 2 equiv.) were added at room temperature. After 24 hours the reaction was quenched by the addition of $NaHSO_3$ (1 mL of saturated solution) and $NaHCO_3$ (5 mL of saturated solution). The aqueous phase was extracted with diethyl ether (2 x 5mL). The aqueous phase was acidified with HCl (5 mL, 1N) until pH = 1 and extracted with ethyl acetate (2 x 5 mL). The organic phases were collected, evaporated under reduced pressure to give a pure product obtained in 92% yield.

Spectroscopic data are in agreement with the published data: D. Yang, H. Yang and H. Fu *Chem. Commun., 2011,* 47, 2348-2350.

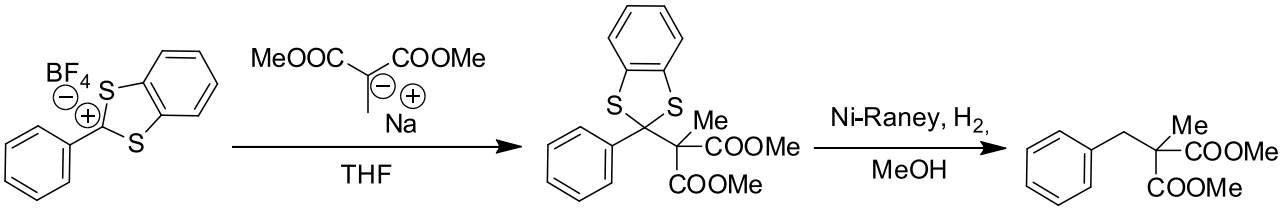
Synthesis of 10



3h **8** **10**

In a two necks flask under nitrogen atmosphere 2-(naphthalen-2-yl)benzo[*d*][1,3]dithiole (30 mg, 0.1 mmol, 1 equiv) was dissolved in THF (1.0 mL, 0.1 M). *n*-Butyllithium (0.2 mmol, 2 equiv.) was added dropwise at 0 °C, until a persistent yellow color was obtained. The reaction mixture was stirred at 0 °C for 15 minutes then MeI (0.5 mmol, 0.5 equiv.) was added dropwise to the reaction mixture. The reaction was controlled by GC-MS, quenched by the addition of water and extracted with diethyl ether (3 x 2mL). The organic phases were collected, evaporated under reduced pressure to give an oil. Crude product was dissolved in THF (1.0 mL) and a suspension of HgO (0.8 mmol, 0.8 equiv) in H_2O (1 mL) was added to the solution followed by HBF_4 (0.2 mL, 0.2 mL/mmol). After 15 hours $NaHCO_3$ was added until basic pH, and the reaction mixture was filtrated through Celite and washed with diethyl ether The reaction mixture was extracted with diethyl ether (2 x 3mL) and the organic phases were collected, and evaporated under reduced pressure. The crude product obtained was purified by flash chromatography on silica (Cyclohexane/Ethyl Acetate 95:5) to provide the pure product in 81% yield.
Spectroscopic data are in agreement with the published data: N. Havare and D. A. Plattner *Org. Lett.*, **2012**, *14*, 5078–5081.

General procedure for the synthesis of malonates 9, 12



4a **11** **12**

In a two necks flask under nitrogen atmosphere containing NaH (20 mg, 0.5 mmol, 5 equiv) THF was added (1 mL). Methyl-dimethylmalonate (0.073 mL, 0.55 mmol, 5.5 equiv.) was subsequently added dropwise at 0 °C. After 20 minutes the reaction mixture was added dropwise by cannula to a solution of 2-phenylbenzo[*d*][1,3]dithiolylium tetrafluoroborate **4a** (77 mg, 0.1 mmol, 1 equiv.) dissolved in THF (0.5 mL, 0.05 M) under nitrogen atmosphere, and reaction mixture was stirred 15 hours at room temperature.

The reaction was quenched by the addition of H_2O (2 mL) and extracted with diethyl ether (2 x 3 mL). The organic solvent was collected, evaporated under reduced pressure and the crude product was dissolved in MeOH (3 mL), Ni-Raney (500 mg, slurry in water) was added and the reaction was stirred under H_2 atmosphere. After 48h the reaction mixture was filtered through Celite washed with MeOH. The MeOH was evaporated and H_2O/diethyl ether were added. The aqueous phase was extracted with diethyl ether (2 x 3mL). The organic phases were collected, evaporated under reduced pressure to give the crude product that was purified by flash chromatography on silica (Cyclohexane/Diethyl Ether 95:5) to provide the pure product in 63% yield.
Spectroscopic data are in agreement with the published data: F. Bjoerkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, and P. Szmulik, *Tetrahedron*, **1985**, *41*, 7, 1347-1352.

The compound **9** was prepared according to the procedure reported **12**. The pure product was obtained in 78% yield. ^{1}H NMR (400 MHz, [D$_3$]CHCl$_3$, 25°C) δ 6.94 (d, 1H, J = 7.6 Hz), 6.82-6.75 (m, 2H), 3.73 (s, 6H), 3.15 (s, 2H), 2.76-2.64 (m, 4H), 1.81-1.72 (m, 4H), 1.34 (s, 3H) ppm. ^{13}C NMR (100.76 MHz, [D$_3$]CHCl$_3$, 25°C) δ 172.5 (2C), 137.0 (1C), 136.2 (1C), 132.3 (1C), 130.8 (1C), 128.9 (1C), 127.1 (1C), 54.9 (1C), 52.4 (2C), 40.9 (1C), 29.4 (1C), 29.0 (1C), 23.2 (2C) 19.7 (1C).

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Particularly, heteroaromatic and aromatic electron poor substrates. For example with 3-pyridineBF_3K, PhCCF_3K, vinylBF_3K, alkylBF_3K we observed no reaction.

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[33] For the more electrophilic 2-phenyl-1,3-dithiolan-2-ylium cation, Mayr has described the reactions with different nucleophiles, (enamines, allylsilane, silyl enolates) successfully predicting the observed rate. It is important to mention that this cation is less stabilized and positioned at -6.25 on the Mayr scale, while aryl compounds bearing cationic **1** are much less electrophilic: Mayr, O. Kuhn, M. F. Gotta, M. Patz, *J. Phys. Org. Chem.* **1998**, *11*, 642-654.

Stereoselective Alkylation of α-Substituted Aldehydes

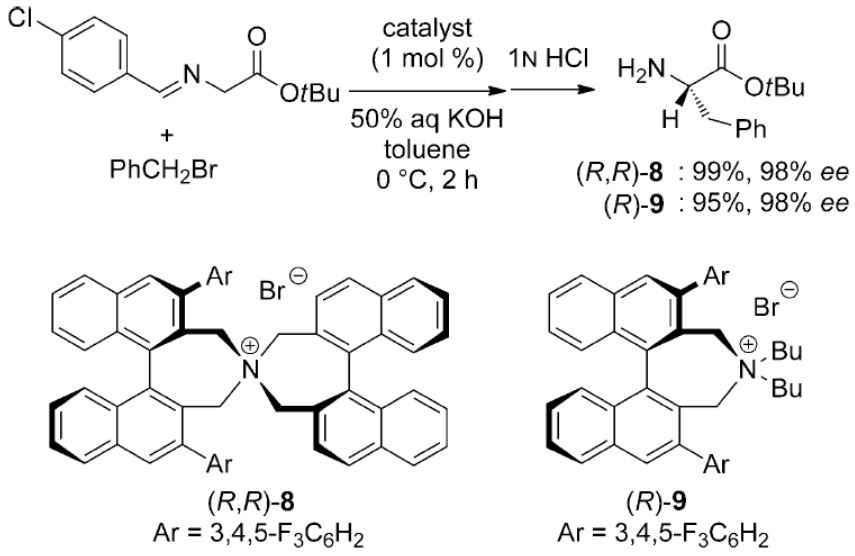
Continuing the work on stabilized carbocations previously shown, in this chapter I present the results obtained in the study of the reactivity of 1,3-benzodithiolylium tetrafluoroborat salt in organocatalytic enamine-mediated α-alkylation of α-substituted aldehydes for the stereoselective construction of quaternary stereogenic centers.

Introduction

Recently, in our research group has been established the possibility of using stable carbenium ions generated from alcohols in alkylation reactions[1] in the presence of MacMillan catalysts.[2] We have also performed enantioselective alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate.[3] The scope of this work is to expand what we have already done to the α-substituted aldehydes with the aim of build controlled quaternary stereogenic centers.

The formation of quaternary stereocenters in the synthesis of a complex molecule is a rather challenging transformation.[4] Even more difficult is the control of their absolute and relative configurations. In recent years, the development of new and exciting methodologies in organocatalysis[5] have furnished new reactions for targeting the asymmetric formation of quaternary stereogenic centers.[6] All these new methodologies are appealing, since they offer excellent stereocontrol and operate under mild operative conditions. It is also important to note that the use of transition metals are, in general, avoided.[7]

The direct asymmetric intermolecular α-alkylation of carbonyls remains a difficult and hot topic in organocatalysis.[8] The alkylation of activated carbonyl substrates was developed by Merck laboratories[9] with the invention of a quite useful asymmetric phase-transfer catalysis (PTC),[10] that was employed for preparative purposes achieving high stereoselectivity. The quaternary cinchona alkaloids employed at first as asymmetric PTC were later replaced by more active and stereoselective catalysts developed by Maruoka.[11a] An example is the synthesis of optically active α-amino acid derivatives in high chemical yield and excellent enantioselectivity under mild liquid–liquid phase-transfer conditions using binaphthylmodified chiral quaternary ammonium bromides (*Scheme 5.1*). Several of these reactions have been applied to the asymmetric synthesis of biologically active compounds, including natural products.[11b]



Scheme 5.1. The preparation of optically active α-amino acid derivatives by chiral phasetransfer catalysis.

Although some innovative strategies have been described,[12] the development of a new general enamine-mediated α-alkylation of α-substituted aldehydes has received scarcely attention.[1,12d]

Quite recently, Aggarwal and coworkers[13] have presented a general organometallic strategy for the preparation of stereogenic centers. This outstanding procedure, that start with available enantiopure alcohol has allowed the possibility of introducing a quaternary center in stereoselective fashion starting from a common precursor. The idea that we want to borrow to translate in the language of organocatalysis was to apply a general and simple methodology for preparation of an intermediate that, through practical and simple reactions can give the possibility to introduce many different groups and to vary the chemistry.

This idea can be simply pursued by the application of our benzodithiol chemistry. In fact, the introduction of the benzodithiol (*Figure 5.1*) in stereoselective fashion can gave the possibility to construct the desired quaternary stereogenic center and to install many groups after lithiation and successive alkylation or by reductive or oxidative cleavage of the benzodithiol group (as already discuss in the previuos chapter).

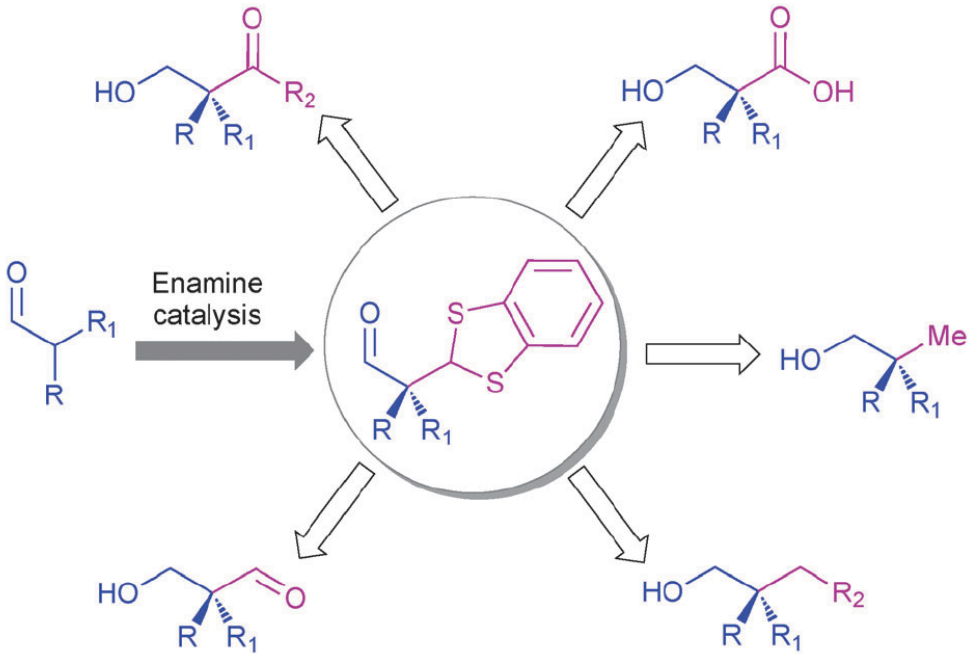
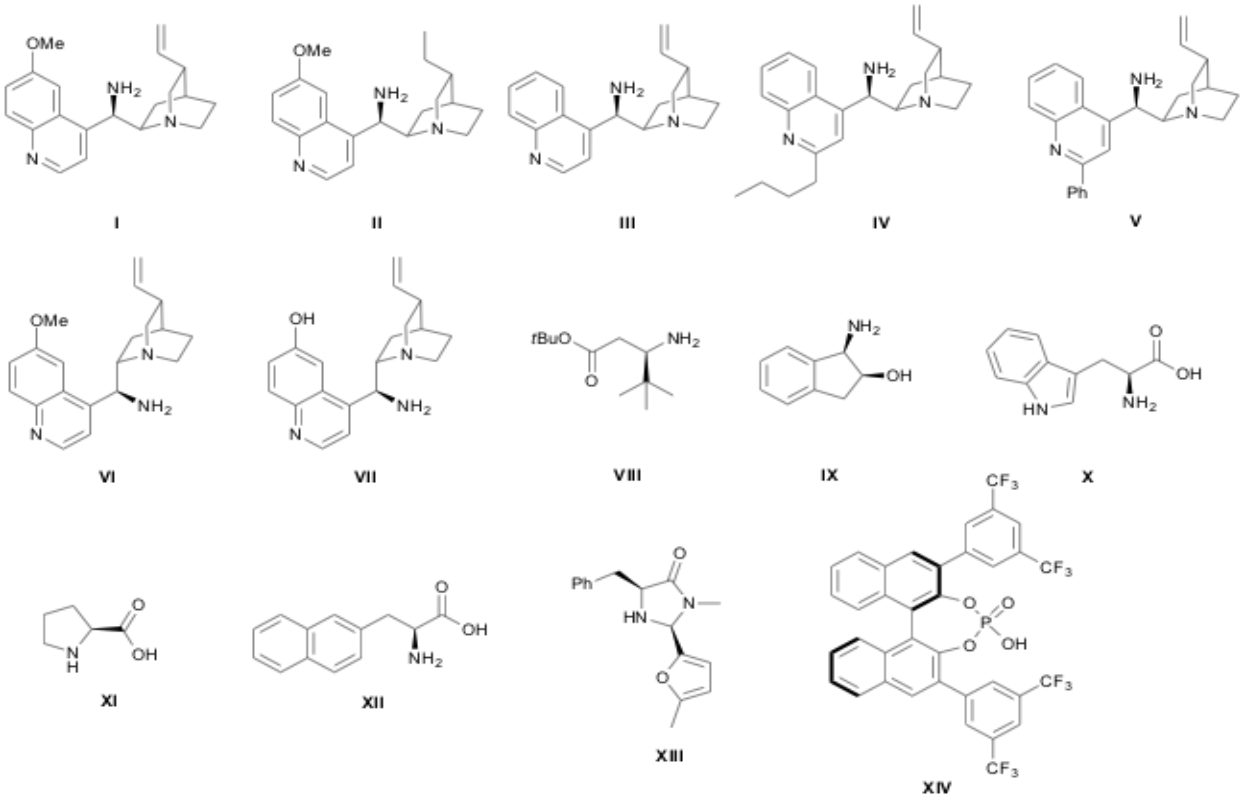


Figure 5.1 Stereoselective formylation for the preparation of quaternary stereogenic centers.

Results and Discussion

Primary amines efficiently catalyzed Michael reactions with α-substituted aldehydes.[14] In order to find the optimal reaction conditions, we started our preliminary investigation using phenylpropionaldehyde **1a** as a model substrate in the presence of the commercially available 1,3-benzodithiolylium tetrafluoroborate **2** and several aminoacids (such as L-triptophan, proline and others). Different primary amine and imidazolidinone were also tested, all giving disappointing results (*Table 5.1*):

Table 5.1. Catalyst effect[a]

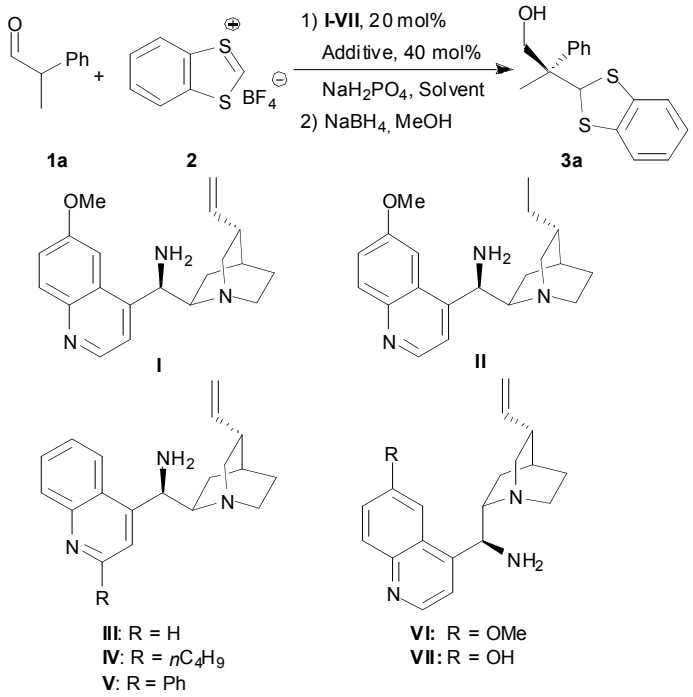


Entry	Catalyst	Acid (mol%)	Solvent	er
1	**I**	(-)-CSA (40)	CH_3CN/H_2O 1/1	92:8
2	**II**	(-)-CSA (40)	CH_3CN/H_2O 1/1	89.5:10.5
3	**III**	(-)-CSA (40)	CH_3CN/H_2O 1/1	90.5:9.5
4	**IV**	(-)-CSA (40)	CH_3CN/H_2O 1/1	90:10
5	**V**	(-)-CSA (40)	CH_3CN/H_2O 1/1	84.5:15.5
6	**VI**	(-)-CSA (40)	CH_3CN/H_2O 1/1	11:89
7	**VII**	(+)-CSA (40)	CH_3CN/H_2O 1/1	21.5:78.5
8	**VIII**	(+)-CSA (20)	CH_3CN/H_2O 1/1	50:50
9	**IX**	(+)-CSA (20)	CH_3CN/H_2O 1/1	57:43
10	**X**	PNBA[b] (20)	CH_3CN	57:43
11	**X**	PNBA[b] (20)	CH_3CN/H_2O 1/1	47:53
12	**X**	-	CH_3CN/H_2O 1/1	44:56
13	**XI**	-	CH_3CN/H_2O 1/1	47:53
14	**XI**	-	CH_3CN	50:50
15	**XII**	(-)-CSA (20)	CH_3CN/H_2O 1/1	48.5:51.5
16	-	(-)-CSA (20)	CH_3CN/H_2O 1/1	50:50
17	**XIII**	(-)-CSA (20)	CH_3CN/H_2O 1/1	60:40

[a] The reactions were performed at 0°C with 1 equiv. of **2**, 3 equiv. of aldehyde **1a** in the presence of 20 mol% of catalysts **I-XIII**, with 2 equiv. of NaH_2PO_4 and 20 mol% o 40% mol of acid as a co-catalyst in 500 µL of solvent at 0°C. The reactions were run until completion, as determined by TLC (16–24 h). [b] *p*-nitrobenzoic acid.

It is worth mentioning that Melchiorre has provided evidence that the catalysts derived from cinchona alkaloids (**I-VII**)[15] were compatible with the carbenium ion. We therefore investigated these primary amines and were pleased to find out that these catalysts were able to transmit the chiral information in a better way (*Table 5.2*).

Table 5.2. Optimisation of reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Yield[b]	er[c]
1	**I**	**(-)-CSA**	**CH_3CN/H_2O**	**90**	**92:8**
2	**II**	(-)-CSA	CH_3CN/H_2O	84	89.5:10.5
3	**III**	(-)-CSA	CH_3CN/H_2O	84	90.5:9.5
4	**IV**	(-)-CSA	CH_3CN/H_2O	85	90:10
5	**V**	(-)-CSA	CH_3CN/H_2O	86	84.5:15.5
6	**VI**	(-)-CSA	CH_3CN/H_2O	87	11:89
7	**VII**	(+)-CSA	CH_3CN/H_2O	68	21:79
8	**VI**	(-)-CSA	CH_3CN/H_2O		nd
9	**I**	(-)-CSA	CH_2Cl_2	83	31.5:68.5
10	**I**	(-)-CSA	CH_3CN	86	83:17
11	**I**	(-)-CSA	H_2O	77	77.5:22.5
12	**I**	(+)-CSA	CH_3CN/H_2O	88	91:9
13	**VI**	PhCOOH	CH_3CN/H_2O	58	37:63
14	**VI**	PTSA	CH_3CN/H_2O	69	14:86
15	**VI**	TfOH	CH_3CN/H_2O	72	12:88
16	**VI**	*N*-Boc-*D*-Phe	CH_3CN/H_2O	79	12.5:87.5

[a] The reactions were carried out with 1 equiv. of **2**, 3 equiv. of **1a** in the presence of 20 mol% of catalysts **I-VII**, 40 mol% of additive and with 2 equiv. of NaH_2PO_4 in 500 µL of solvent at 0°C. [b] Determined by ^1H NMR [c] (*R*)-**3a**:(*S*)-**3a** ratio determined by HPLC (see ES).

However, still the results were not satisfactory, and a series of reaction conditions, considering solvent, temperature, and additive were screened. In the optimized conditions the reactions were performed in a 1:1 mixture of CH_3CN/H_2O as reaction solvent, at 0 °C, in the presence of NaH_2PO_4 as a base.

Table 5.3. Base effect[a]

Entry	Catalyst	Solvent	Base	er
1	**I**	CH_2Cl_2	Imidazole	50:50
2	**VI**	CH_3CN/H_2O 1/1	Na_2HPO_4	59:41
3	**VI**	CH_3CN/H_2O 1/1	$NaHCO_3$	55.5:44.5

[a] The reactions were performed at 0°C with 1 equiv. of **2**, 3 equiv. of aldehyde **1a** in the presence of 20 mol% of catalysts **I-VI**, with 2 equiv. of base and 40% mol of (-)-CSA as a co-catalyst in 500 µL of solvent. The reactions were run until completion, as determined by TLC (16–24 h).

Table 5.4. Solvent effect[a]

Entry	Catalyst	Solvent	er
1	**I**	CH_2Cl_2	31.5:68.5
2	**VI**	Toluene/CH_3CN 5/1	46.5:53.5
3	**VI**	Hexane/CH_3CN 5/1	50:50
4	**I**	CH_3CN	83:17
5	**I**	H_2O	72.5:27.5
6	**I**	CH_3CN/H_2O 1/1	92:8
7	**I**	CH_3CN/H_2O 9/1	92:8
8	**I**	CH_3CN/H_2O 1/9	89:11
9	**I**	[Bmim]OTf	28.5:71.5
10	**I**	C_2H_5CN/H_2O 1/1	86.5:13.5
11	**I**	CH_3CN/D_2O 1/1	90:10
12	**I**	Dioxane/H_2O 1/1	81.5:18.5
13	**I**	THF/H_2O 1/1	78.5:21.5
14	**I**	DME/H_2O 1/1	73.5:26.5
15	**I**	TBME/H_2O 1/1	84:16
16	**I**	Toluene/H_2O 1/1	71:29
17	**I**	DMF/H_2O 1/1	89:11
18	**I**	DMSO	54:46
19	**I**	DMSO/H_2O 1/1	82.5:17.5

[a] The reactions were performed at 0°C with 1 equiv. of **2**, 3 equiv. of aldehyde **1a** in the presence of 20 mol% of catalysts **I-VI**, with 2 equiv. of NaH_2PO_4 and 40% mol of (-)-CSA as a co-catalyst in 500 µL of solvent. The reactions were run until completion, as determined by TLC (16–24 h).

Table 5.5. Temperature effect[a]

Entry	Catalyst	T (°C)	er
1	**I**	0	92:8
2	**I**	25	90.5:9.5
3	**VI**	0	11:89
4	**VI**	-13	11.5:88.5

[a] The reactions were performed with 1 equiv. of **2**, 3 equiv. of aldehyde **1a** in the presence of 20 mol% of catalysts **I-VI**, with 2 equiv. of NaH_2PO_4 and 40% mol of (-)-CSA as a co-catalyst in 500 μL of CH_3CN/H_2O 1/1. The reactions were run until completion, as determined by TLC (16–24 h).

Table 5.7. Concentration effect[a]

Entry	Catalyst (mol%)	Acid (mol%)	Note	er
1	**I** (5)	(-)-CSA (10)	-	87:13
2	**I** (20)	(-)-CSA (40)	10 eq. di aldehyde	86:14
3	**I** (20)	(-)-CSA (40)	[Carbocation] = 0.1 M	92:8
4	**I** (20)	(-)-CSA (40)	[Carbocation] = 0.05 M	90.5:9.5
5	**I** (20)	(-)-CSA (40)	[Carbocation] = 0.2 M	91:9

The reactions were performed at 0°C with 1 equiv. of **2**, 3 equiv. of aldehyde **1a** in the presence of catalysts **I**, with 2 equiv. of NaH_2PO_4 and and (-)-CSA as a co-catalyst in 500 μL of CH_3CN/H_2O 1/1. The reactions were run until completion, as determined by TLC (16–24 h).

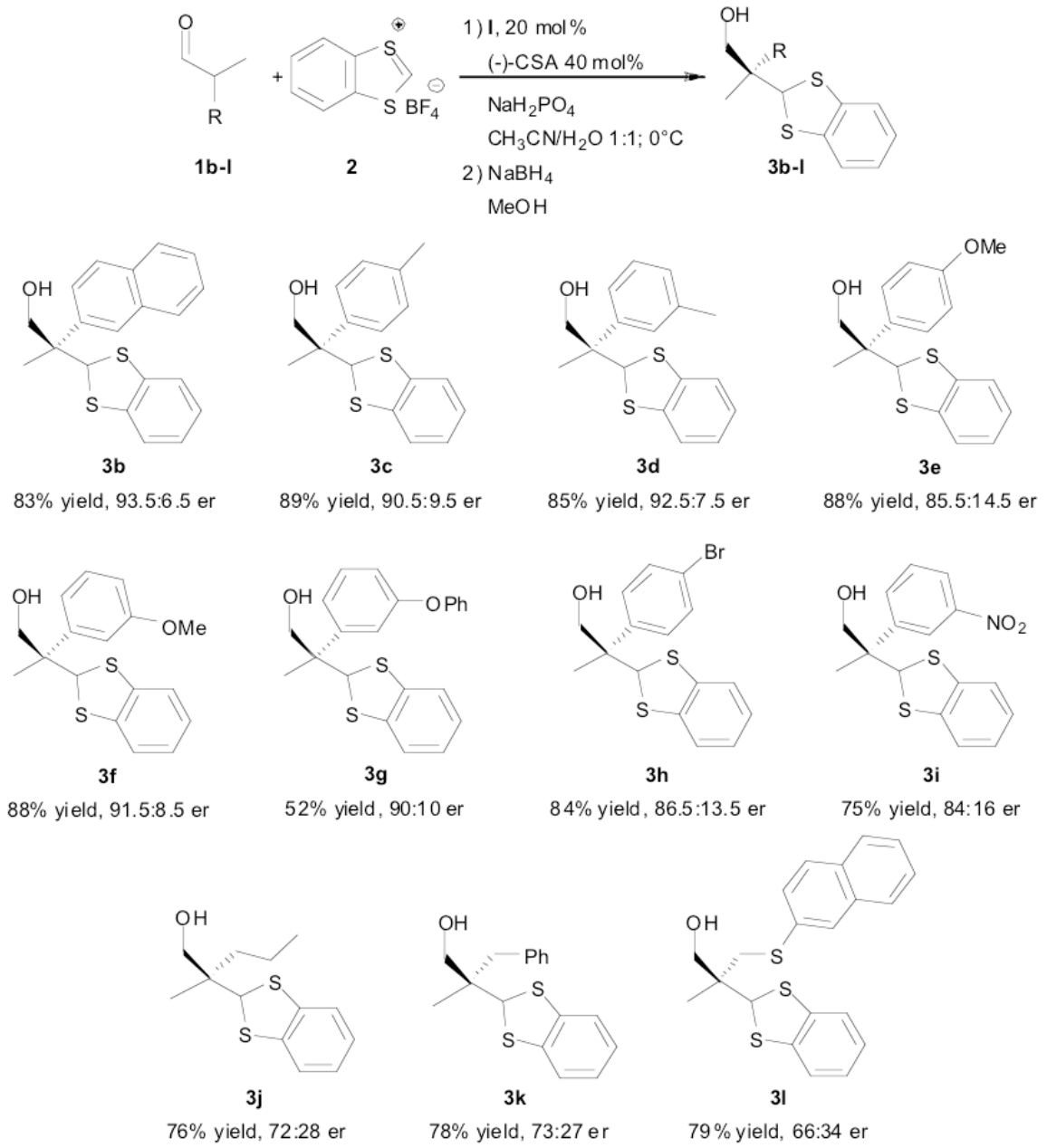
It is noteworthy that the solvent controls the enantiofacial selectivity of the reaction (entry 9 *vs* entry 10), as result of the delicate conformation of cinchona alkaloid framework.[16] After testing several acidic additives able to enhanced both reactivity and the selectivity, we observe that (-)-CSA as chiral acid[17] gave the best results in term of stereoselectivity. We have also prepared and tested the primary amines **IV** and **V** following the procedure developed by Hintermann,[18] but the enantiomeric excess was not enhanced.

Table 5.6. Acid effect[a]

Entry	Catalyst (mol%)	Acid (mol%)	er
1	**I** (20)	Benzioc acid (40)	63:37
2	**I** (20)	PNBA[b] (40)	68.5:31.5
3	**VI** (20)	*N*-Boc-*L*-His (40)	14:86
4	**VI** (20)	*N*-Boc-*D*-Phe (40)	12.5:87.5
5	**VI** (20)	*N*-Boc-*L*-Phe (40)	13.5:86.5
6	**VI** (20)	*L*-Tartaric acid (40)	39:61
7	**VI** (20)	(*R*)-Mandelic acid (40)	35:65
8	**VI** (20)	PTSA (40)	14:86
9	**VI** (20)	(+)-Canforic acid	12.5:87.5
10	**VI** (20)	**XIV** (40)	50:50
11	**VI** (20)	TfOH (40)	12:88
12	**I** (20)	(-)-CSA (40)	91:9
13	**I** (20)	(+)-CSA (40)	92:8
14	**VI** (20)	-	13:87
15	**VI** (20)	(-)-CSA (20)	15.5:84.5
16	**VI** (20)	(-)-CSA (40)	11:89
17	**VI** (20)	(-)-CSA (80)	12.5:87.5
18	**VI** (20)	(+)-CSA (40)	17.5:82.5
19	**VII** (20)	(+)-CSA (40)	21.5:78.5
20	**VII** (20)	**XIV** (40)	44:56
21	**III** (20)	HCl (40)[c]	91:9
22	**III** (20)	(-)-CSA (40)	90.5:9.5

[a] The reactions were performed at 0°C with 1 equiv. of **2**, 3 equiv. of aldehyde **1a** in the presence of 20 mol% of catalysts **I-IV**, with 2 equiv. of NaH_2PO_4 and different amount of acid as a co-catalyst in 500 µL of CH_3CN/H_2O 1/1. The reactions were run until completion, as determined by TLC (16–24 h). [b] *p*-nitrobenzoic acid. [c] Aqueous solution.

The optimized reaction conditions were applied to a series of aldehydes (*Scheme 5.2*). The substituents presents on the aldehydic substrates are crucial to determine the outcome of the reaction. Particularly, increasing the hindrance of the aromatic substituents gave disappointing results. In fact, *ortho* substituted aromatic groups were blocking the reactivity of the branched aldehydes. However, different branched aldehydes were alkylated in good yield and with good enantiomeric excess. Interestingly, moderate enantiomeric excesses were obtained with α,α-dialkyl aldehydes (3j-l). The absolute configuration of the newly formed quaternary center was established by chemical correlation.

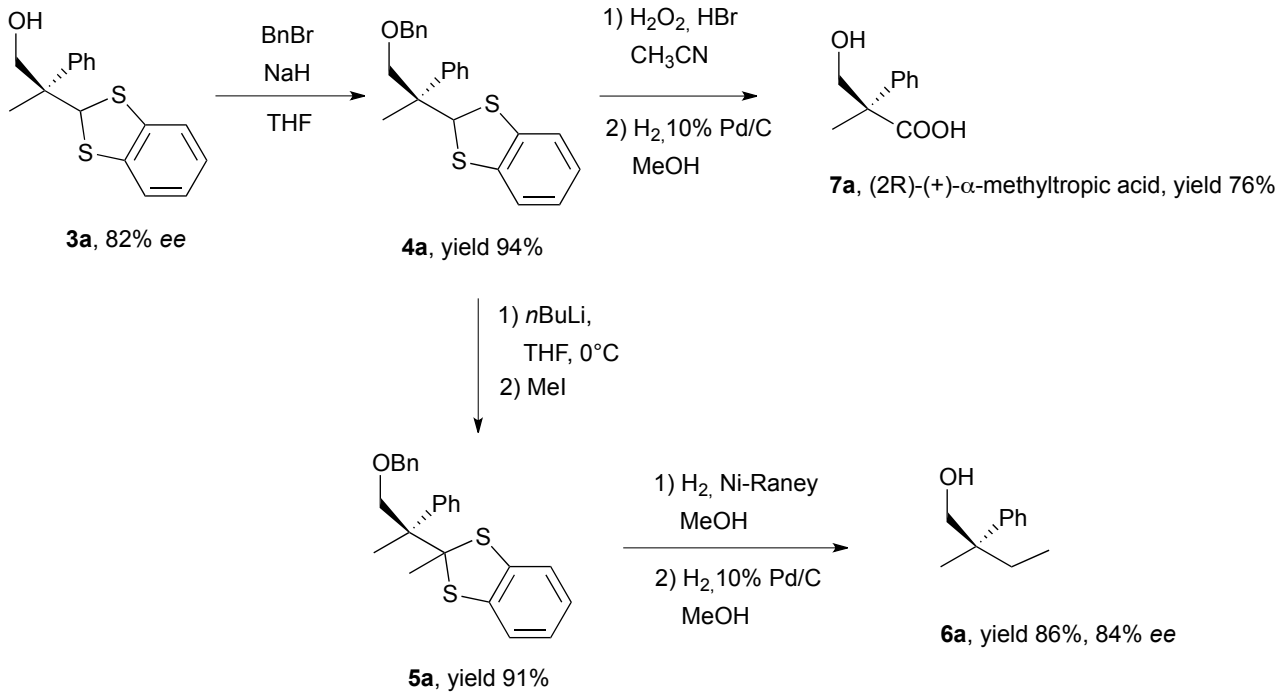


Scheme 5.2. Scope of the reaction with different α-substituted aldehydes.

The advantage of the benzodithiole as a versatile and chameleonic synthetic group was fully explored in a series of transformation performed with the derivative **1a**, similar to those seen in the previous chapter.

1a was protected by reduction and successive benzylation. The resulting **4a** was treated with *n*-BuLi at 0 °C and alkylated with MeI. Finally, by treatment with Ni-Raney[19] the compounds **6a** was obtained without loss of enantiopurity, and the absolute configuration of the product was determined.

We have applied our chemistry to the synthesis of a natural product. The compound **4a** can be straightforwardly transformed in the (2*R*)-(+)-α-methyltropic acid,[20] by direct oxidation of the benzodithiol to the corresponding acid and debenzylation of the hydroxyl group (*Scheme 5.3*).



Scheme 5.3. Synthesis of (2*R*)-(+)-α-methyltropic acid from the compound **4a**.

Conclusions

In conclusion, we have reported a simple and general methodology for the enamine-mediated α-alkylation of α-substituted aldehydes, previously an unresolved problem in organocatalysis. It was possible to construct many quaternary stereogenic center on different aldehyde and install many functional groups after the wide range of possible derivatisation of the benzodithiol group. Synthetic work towards the synthesis of more hindered carbenium ions, could be developed in the future, in order to improve the stereoselection of this synthetic methodology.

Experimental Section

General Methods

^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). Chromatographic purification was done with 240-400 mesh silica gel. Determination of enantiomeric ratio was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using a Daicel Chiralpak columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line), specific rotation was expressed as deg $cm^3g^{-1}dm^{-1}$ and concentration as gcm^{-3}. Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected. Materials: All reactions were carried out under inert gas and under anhydrous conditions. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and used avoiding purification.

Aldehydes **1a** and **1j** are commercially available. Aldehydes **1b-f** and **1i** were prepared according to reported methodologies.[21] The analytical data for **1b**, **1c**, **1f**, **1h**,[21] **1d**,[22] **1e**,[23] **1i**,[24] were consistent with the literature. **1g** was prepared according to literature.[25]

Preparation of *Cinchona* catalysts:

catalyst **I-III** and **VI-VII**, were prepared according to the literature procedure.[26] **IV** and **V** were prepared using Hintermann procedure[27] followed by Connon method.[26] The analytical data for **I**,[28] **II**,[25] **III**,[29] **VI**,[30] **VII**,[31] and were consistent with the literature.

IV (45%); The desired product was isolated by flash column chromatography (CH_2Cl_2/CH_3OH/NH_4OH = 95/5/1) as sticky solid; $[\alpha]_D^{20}$ +79.6 (*c* 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.96 (t, *J* = 7.3 Hz, 3H), 1.40-1.49 (m, 3H), 1.53-1.60 (m, 3H), 1.76-1.84 (m, 3H), 2.12 (bs, 3H), 2.27 (q, *J* = 7.9 Hz, 1H), 2.90-3.08 (m, 7H), 4.74 (m, 1H), 5.05 (dt, *J* = 1.4 Hz, *J* = 8.3 Hz, 1H), 5.09 (m, 1H), 5.86 (ddd, *J* = 7.0 Hz, *J* = 10.9 Hz, *J* = 17.4 Hz, 1H), 7.47 (bs, 1H), 7.51 (ddd, *J* = 1.4 Hz, *J* = 7.0 Hz, *J* = 8.2 Hz, 1H), 7.67 (ddd, *J* = 1.3 Hz, *J* = 6.9 Hz, *J* = 8.2 Hz, 1H), 8.07 (dd, *J* = 1.1 Hz, *J* = 8.3 Hz, 1H), 8.27 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 13.9, 22.7, 25.0, 26.6, 27.6, 32.2, 39.1, 39.6, 47.4, 49.5, 114.5, 119.7, 123.0, 125.4, 125.2, 128.1, 129.7, 140.5, 148.3, 148.7, 162.9; HMRS found M^+, 349.25151; $C_{23}H_{31}N_3$ requires: 349.25180.

V (51%); The desired product was isolated by flash column chromatography (CH_2Cl_2/CH_3OH/NH_4OH = 95/5/1) as white solid; mp 54 °C (from MeOH); $[\alpha]_D^{20}$ +129.6 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 0.94-1.02 (m, 1H), 1.16-1.21 (m, 2H), 1.53-1.60 (m, 2H), 2.23-2.30 (m, 3H), 2.94-3.11 (m, 5H), 4.83 (d, *J* = 8.1 Hz, 1H), 5.08 (dt, *J* = 1.6 Hz, *J* = 10.6 Hz, 1H), 5.10-5.12 (m, 1H), 5.88 (ddd, *J* = 6.8 HZ, *J* = 10.6 Hz, *J* = 17.2 Hz, 1H), 7.44-7.49 (m, 1H), 7.52-7.59 (m, 3H), 7.73 (ddd, *J* = 1.2 HZ, *J* = 6.9 Hz, *J* = 8.4 Hz, 1H), 8.11 (bs, 1H), 8.19-8.23 (m, 3H), 8.32 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 24.9, 25.3, 26.6, 27.6, 39.6, 47.4, 49.4, 50.4, 114.5, 117.5, 123.0, 126.0, 126.7, 127.5, 128.7, 129.1, 129.2, 130.6, 139.6, 140.5, 148.6, 149.5, 157.1; HMRS found M^+, 369.22019; $C_{25}H_{27}N_3$ requires: 369.22050.

Preparation of aldehyde 1l:

Following the procedure of Vedejes et al.[32] A mixture of 2-naphthalenethiol (3.6 mmol, 581 mg) and methacrolein (3.6 mmol, 300 µL) was refluxed with triethylamine (0.5 mL) for 3h. Solvent was removed under reduce pressure. Flash chromatography (cyclohexane/ethyl acetate, 95/5) of the residue give **1l** (571 mg, 69%) as sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.29 (d, J = 7.3 Hz, 3H), 2.7 (m, 1H), 3.00 (dd, J = 6.8 Hz, J = 13.2 Hz, 1H), 3.00 (dd, J = 6.4 Hz, J = 13.2 Hz, 1H), 7.42-7.50 (m, 3H), 7.73-7.79 (m, 4H), 9.71 (d, J = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 13.5, 34.5, 45.8, 125.9, 126.6, 127.1, 127.7, 128.0, 128.7, 132.0, 132.9, 133.7, 202.8; HMRS found M^+, 230.07610; $C_{14}H_{14}OS$ requires: 230.07654.

Enantioselective α-alkylation of aldehydes

General procedure: A vial was charged with **I** (0.02 mmol, 6 mg), (-)-CSA (0.04 mmol, 9 mg), acetonitrile (0.25 mL) and water (0.25 mL). The mixture was cooled at 0 °C, 1,3-benzodithiolylium tetrafluoroborate **2** (0.1 mmol, 24 mg), NaH_2PO_4 (0.2 mmol, 24 mg) and **1a** (0.3 mmol, 40 µL) were added. The mixture was stirred for 24 hours at the same temperature and a saturated solution of $NaHCO_3$ (1 mL) was added and the mixture was diluted with AcOEt (3mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 3 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure. The residue was diluted in MeOH (1 mL) and $NaBH_4$ (0.4 mmol, 15 mg) was slowly added at 0 °C. After 30 minutes, silica was added and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate = 9/1) to give **3a**.

3a (26 mg, 90%); er = 92:8; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40 °C, λ = 232, 254 nm: τ*major* = 23.2 min, τ*minor* = 25.7 min; $[\alpha]_D^{20}$ -7.1 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.51 (s, 3H), 3.78 (d, J = 11.1 Hz, 1H), 4.01 (d, J = 11.1 Hz, 1H), 5.64 (s, 1H), 6.93-6.95 (m, 2H), 7.06-7.08 (m, 1H), 7.14-7.16 (m, 1H), 7.29 (dt, J = 1.4 Hz, J = 7.3 Hz, 1H), 7.35-7.40 (m, 2H), 7.43-7.46 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 16.9, 50.1, 60.6, 68.7, 121.4, 121.6, 125.1, 125.2, 127.2 (2C), 127.3, 128.6 (2C), 138.1, 141.9 (2C); HMRS found M^+, 288.06401; $C_{16}H_{16}OS_2$ requires: 288.06426.

3b (28 mg, 83%); er = 93.5:6.5; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel IA column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40 °C, λ = 232, 254 nm: τ*major* = 30.1 min, τ*minor* = 27.9 min; $[\alpha]_D^{20}$ -104.2 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.62 (s, 3H), 3.80 (d, J = 11.2 Hz, 1H), 4.11 (d, J = 11.2 Hz, 1H), 5.78 (s, 1H), 6.92-6.98 (m, 2H), 7.05-7.08 (m, 1H), 7.15-7.17 (m, 1H), 7.49-7.53 (m, 2H), 7.59 (dd, J = 2.1 Hz, J = 11.7 Hz, 1H), 7.82-7.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 20.0, 50.3, 60.6, 68.7, 121.5, 121.6, 124.6, 125.1, 125.3, 126.2, 126.8, 127.4, 128.2, 128.3, 132.4, 133.1, 138.0, 138.1, 139.5; HMRS found M^+, 338.07963; $C_{20}H_{18}OS_2$ requires: 338.07991.

3c (27 mg, 89%); er = 90.5:9.5; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40 °C, λ = 232, 254 nm: τ*major* = 15.7 min, τ*minor* = 17.8 min; $[\alpha]_D^{20}$ -108.7 (*c* 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.49 (s,

3H), 2.35 (s, 3H), 3.75 (d, J = 11.3 Hz, 1H), 3.99 (d, J = 11.3 Hz, 1H), 5.65 (s, 1H), 6.94-6.98 (m, 2H), 7.07-7.09 (m, 1H), 7.15-7.18 (m, 1H), 7.19-7.21 (m, 2H), 7.32-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 16.8, 20.9, 49.8, 60.8, 68.7, 121.4, 121.6, 125.1, 12.0, 129.4, 137.0, 138.1, 138.8; HMRS found M^+, 302.07969; $C_{17}H_{18}OS_2$ requires: 302.07991.

3d (26 mg, 85%); er = 92.5:7.5; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 18.3 min, τ_{minor} = 15.7 min; $[\alpha]_D^{20}$ -78.7 (*c* 0.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.56 (s, 3H), 2.38 (s, 3H), 3.76 (dd, J = 6.8 Hz, J = 11.1 Hz, 1H), 3.99 (dd, J = 5.9 Hz, J = 11.1 Hz, 1H), 5.65 (s, 1H), 6.93-6.99 (m, 2H), 7.06-7.11 (m, 2H), 7.14-7.16 (m, 1H), 7.22-7.29 (m, 3H); ^{13}C NMR (25 MHz, $CDCl_3$, 25°C): δ= 16.9, 21.7, 50.0, 60.7, 68.8, 121.5, 121.6, 124.2, 125.1, 125.2, 127.9, 128.1, 128.5, 138.2, 141.8, 151.0; HMRS found M^+, 302.07968; $C_{17}H_{18}OS_2$ requires: 302.07991.

3e (28 mg, 88%); er = 85.5:14.5; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 27.2 min, τ_{minor} = 29.5 min; $[\alpha]_D^{20}$ -44.8 (*c* 2.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.48 (s, 3H), 3.75 (d, J = 11.0 Hz, 1H), 3.81 (s, 3H), 3.97 (d, J = 11.0 Hz, 1H), 5.59 (s, 1H), 6.87-6.92 (m, 2H), 6.94-6.98 (m, 2H), 7.05-7.09 (m, 1H), 7.13-7.19 (m, 1H), 7.34-7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 17.0, 49.4, 55.2, 61.0, 68.7, 113.9 (2C), 121.4, 121.6, 125.1, 125.2, 128.3 (2C), 133.6, 138.0, 138.1, 158.6; HMRS found M^+, 318.07459; $C_{17}H_{18}O_2S_2$ requires: 318.07482.

3f (28 mg, 88%); er = 91.5:8.5; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) sticky solid; The er was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 23.1 min, τ_{minor} = 18.4 min; $[\alpha]_D^{20}$ -47.9 (*c* 3.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.46 (s, 3H), 3.72 (d, J = 10.6 Hz, 1H), 3.80 (s, 3H), 3.95 (d, J = 10.6 Hz, 1H), 5.60 (s, 1H), 6.80 (ddd, J = 0.8 Hz, J = 2.5 Hz, J = 8.4 Hz, 1H), 6.90-6.97 (m, 2H), 6.98-7.01 (m, 2H), 7.04-7.07 (m, 1H), 7.12-7.14 (m, 1H), 7.29 (t, J = 8.0 Hz, 1H)6.87-6.92 (m, 2H), 6.94-6.98 (m, 2H), 7.05-7.09 (m, 1H), 7.13-7.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 16.8, 50.2, 55.2, 60.5, 68.7, 111.8, 114.1, 119.4, 121.4, 121.6, 125.1, 125.2, 129.5, 138.1, 138.2, 143.6, 159.7; HMRS found M^+, 318.07455; $C_{17}H_{18}O_2S_2$ requires: 318.07482.

3g (20 mg, 52%); er = 90:10; desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OF column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 17.7 min, τ_{minor} = 10.3 min; $[\alpha]_D^{20}$ -49.3 (*c* 0.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.46 (s, 3H), 1.59 (bs, 1H), 3.78 (d, J = 11.4 Hz, 1H), 3.99 (d, J = 11.4 Hz, 1H), 5.54 (s, 1H), 6.88 (ddd, J = 1.0 Hz, J = 2.4 Hz, J = 8.9 Hz, 1H), 6.95-6.97 (m, 2H), 6.99-7.02 (m, 2H), 7.07-7.10 (m, 1H), 7.12-7.17 (m, 3H), 7.20 (ddd, J = 1.0 Hz, J = 1.8 Hz, J = 7.9 Hz, 1H), 7.28-7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 17.1, 50.1, 50.0, 60.4, 68.4, 117.4, 118.4, 118.7 (2C), 121.4 (2C), 121.6, 122.1, 123.3, 125.2, 125.3, 129.6, 129.8 (2C), 138.0, 144.0, 157.1, 157.2; HMRS found M^+, 380.09020; $C_{22}H_{20}O_2S_2$ requires: 380.09047.

3h (31 mg, 84%); er = 86.5:13.5; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 21.1 min, τ_{minor} = 19.7 min; $[\alpha]_D^{20}$ -60.2 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.46 (s, 3H), 3.78 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 5.53 (s, 1H), 6.94-6.99 (m, 2H), 7.06-7.08 (m, 1H), 7.11-7.14 (m, 1H), 7.32-7.35 (m, 2H), 7.44-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 17.1, 49.8, 60.3, 68.2, 125.5, 121.6, 125.2, 125.3, 129.1 (2C), 131.4 (2C), 137.8, 137.9 (2C), 140.8; HMRS: no ionization was observed.

3i (25 mg, 75%); er = 84:16; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 7/3) as sticky solid; The er was determined by HPLC analysis Daicel Chiralcel IA column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 27.3 min, τ_{minor} = 29.1 min; $[\alpha]_D^{20}$ -46.4 (*c* 0.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.55 (s, 3H), 3.96 (d, *J* = 10.6 Hz, 1H), 4.09 (d, *J* = 10.6 Hz, 1H), 5.40 (s, 1H), 6.87-6.91 (m, 2H), 7.00-7.06 (m, 2H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.83 (ddd, *J* = 1.0 Hz, *J* = 1.9 Hz, *J* = 8.0 Hz, 1H), 8.03 (ddd, *J* = 1.0 Hz, *J* = 1.9 Hz, *J* = 8.0 Hz, 1H), 8.4 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 18.0, 49.7, 59.9, 67.3, 121.4, 121.5, 122.1, 122.8, 125.3, 128.5, 133.8, 137.5 (2C), 143.4, 147.8; HMRS found M^+, 333.04908; $C_{16}H_{15}NO_3S_2$ requires: 333.04933.

3j (19 mg, 76%); er = 72:28; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 95/5) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel IC column: hexane/*i*-PrOH 98:2, flow rate 0.50 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 27.2 min., τ_{minor} = 25.5 min; $[\alpha]_D^{20}$ -28.0 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 0.93 (t, *J* = 7.3 Hz, 3H), 0.94 (s, 3H), 1.27-1.39 (2H), 1.44-1.49 (m, 2H), 1.61 (bs, 1H), 3.58 (d, *J* = 11.3 Hz, 1H), 3.66 (d, *J* = 11.3 Hz, 1H), 5.26 (s, 1H), 6.97-7.01 (m, 2H), 7.16-7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 14.9, 17.0, 17.8, 36.8, 41.1, 62.9, 66.4, 121.6 (2C), 125.2, 125.3, 138.1, 138.2; HMRS found M^+, 254.07971; $C_{13}H_{18}OS_2$ requires: 254.07991.

3k (24 mg, 78%); er = 73:27; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 95/5) as colourless oil; The er was determined by HPLC analysis Daicel Chiralcel OJ column: hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 10.6 min, τ_{minor} = 11.9 min; $[\alpha]_D^{20}$ -24.3 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 0.91 (s, 3H), 2.80 (d, *J* = 13.3 Hz, 1H), 2.85 (d, *J* = 13.3 Hz, 1H), 3.51 (d, *J* = 11.1 Hz, 1H), 3.59 (d, *J* = 11.1 Hz, 1H), 5.20 (s, 1H), 7.00-7.02 (m, 2H), 7.20-7.25 (m, 4H), 7.27-7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 17.4, 39.7, 45.8, 60.9, 65.4, 121.7, 125.2, 125.3 (2C), 126.5, 128.2 (2C), 130.6 (2C), 137.3, 138.2, 138.2; HMRS found M^+, 302.07913; $C_{17}H_{18}OS_2$ requires: 302.07991.

3l (30 mg, 79%); er = 66:34; The desired product was isolated by flash column chromatography (cyclohexane/ethyl acetate = 9/1) as sticky solid; The er was determined by HPLC analysis Daicel Chiralcel OJ column: hexane/*i*-PrOH 50:50, flow rate 0.5 mL/min, 40°C, λ = 232, 254 nm: τ_{major} = 29.5 min, τ_{minor} = 37.8 min; $[\alpha]_D^{20}$ -31.3 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.06 (s, 3H), 3.28 (d, *J* = 12.6 Hz, 1H), 3.34 (d, *J* = 12.6 Hz, 1H), 3.75 (s, 2H), 5.36 (s, 1H), 7.00-7.04 (m, 2H), 7.19-7.21 (m, 2H), 7.43-7.51 (m, 3H), 7.74-7.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 17.2, 39.9, 46.8, 59.5, 65.8, 121.6, 121.7, 125.4 (2C), 125.9, 126.7, 127.1, 127.4, 127.5, 127.7, 128.6, 131.9, 133.7, 134.1, 138.1 (2C); HMRS found M^+, 384.06796; $C_{21}H_{20}OS_3$ requires: 384.06763.

Protection of hydroxyl group: To a suspension of NaH (1.3 mmol, 52 mg of a 60% suspension in mineral oil) in anhydrous THF (3 mL) a solution of **3a** (0.65 mmol, 187 mg) in THF (1 mL) was slowly added at 0°C. After 30 minutes benzylbromide (1.0 mmol, 116 µL) was added and the mixture was stirred at room temperature for 18 hours. Water (5 mL) was slowly added and the mixture was diluted with Et_2O (3mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure. Flash chromatography (cyclohexane/ethyl acetate, 9/1) of the residue give **4a** (231 mg, 94%) as colourless oil. $[\alpha]_D^{20}$ -42.6 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.45 (s, 3H), 3.61 (d, *J* = 9.2 Hz, 1H), 3.78 (d, *J* = 9.2 Hz, 1H), 4.48 (s, 2H), 5.70 (s, 1H), 6.88-6.94 (m, 2H), 7.02-7.05 (m, 1H), 7.07-7.10 (m, 1H), 7.22-7.35 (m, 8H), 7.47-7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 17.5, 48.9, 60.8, 73.5, 75.8, 121.4, 121.5, 125.0, 125.1, 127.1 (2C), 127.5 (2C), 127.7 (2C), 128.1 (2C), 128.5 (2C), 138.2, 138.5, 138.6, 142.9; HMRS found M^+, 378.11092; $C_{23}H_{22}OS_2$ requires: 378.11121.

Alkylation of benzodithiol: A solution of *n*BuLi (0.033 mmol, 206 µL, 1.6 M in hexanes) was added dropwise to a solution of **4a** (0.3 mmol, 112 mg) in anhydrous in THF (2 mL) at 0°C. The mixture turns to orange colour. After 5 minutes methyl iodide (1.5 mmol, 76 µL) was added and the solution became colourless. The solution was stirred for 5 minutes and then water (1 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure. Flash chromatography (cyclohexane/ethyl acetate = 9/1) of the residue give **5a** (107 mg, 91%) as colourless oil. $[\alpha]_D^{20}$ -15.7 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 1.78 (s, 3H), 1.82 (s, 3H), 4.06 (d, *J* = 9.4 Hz, 1H), 4.26 (d, *J* = 9.4 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 6.95-6.99 (m, 2H), 7.10-7.13 (m, 2H), 7.28-7.35 (m, 8H), 7.49-7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ= 22.6, 29.4, 49.4, 73.4, 76.9, 122.1, 122.2, 125.0, 125.1, 127.1, 127.4, 127.5, 127.6 (3C), 128.1 (2C), 128.2 (2C), 136.8, 137.9, 138.1, 141.1; HMRS found M^+, 392.12656; $C_{24}H_{24}OS_2$ requires: 392.12686.

Reductive removal of benzodithiol group: To a solution of **5a** (0.08 mmol, 31 mg) in methanol (1 mL), Ni-Raney (0.450 g, slurry in water) was added and the reaction was kept under H_2 atmosphere (1 atm). After 18h the reaction mixture was filtered through a Celite pad and the organic solvent was removed under reduce pressure. The residue was diluted with AcOEt, the organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). The residual was dissolved in MeOH (5 mL), 10% Pd/C (10 mg) was added and the reaction was kerp under hydrogen atmosphere for 18h. The reaction mixture was filtered through a Celite pad and the organic solvent was removed under reduce pressure. Flash chromatography (cyclohexane/ethylacetate, 8/2) of the residue give **6a** (11.3 mg, 86%) as colourless oil. All spectra data were consistent with the literature.[33] $[\alpha]_D^{20}$ -2.9 (*c* 0.5 in $CHCl_3$); lit.: $[\alpha]_D^{20}$ -3.6 (*c* 0.8 in $CHCl_3$, ee = 83%).[34] Absolute configuration was confirmed by comparison of the chiral HPLC retention time (Daicel Chiralcel OF column: hexane/*i*-PrOH 90:10, flow rate 0.50 mL/min, 40°C, λ = 214 nm: τ*major*(*R*) = 21.0 min, τ*minor*(*S*) = 26.4 min;) in the literature.[31]

Oxidative removal of benzodithiol group, synthesis of (*2R*)-(+)-α-methyltropic acid: To a solution of **4a** (0.08 mmol, 30 mg) in acetonitrile (1 mL) at 0°C, 30% H_2O_2 (320 µL) was added. 40% HBr (0.16 mmol, 21 µL) was slowly added and the reaction mixture was raised at room temperature. After 4h $Na_2S_2O_5$ (1.0 g), was slowly added at 0°C and the mixture was diluited with AcOEt (5 mL). Water (0.25 mL) and

$NaHCO_3$ aq. were added until pH 8.0. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). HCl (0.1M) was added to the aqueous phase until pH=2 and AcOEt was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure to give a colourless oil. The residual was dissolved in MeOH (5 mL), 10% Pd/C (10 mg) was added and the reaction was kept under hydrogen atmosphere for 18h. The reaction mixture was filtered through a Celite pad and the organic solvent was removed under reduce pressure. Flash chromatography (cyclohexane/ethylacetate/acetic acid, 1/1/0.05) of the residue give **7a** (10.9 mg, 76%) as colourless oil. Spectroscopy data are in according with literature.[35] $[\alpha]_D^{20}$ +20.5 (*c* 0.2 in $CHCl_3$); lit.: $[\alpha]_D^{20}$ +21.3 (*c* 0.7 in $CHCl_3$).[36]

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