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Novel Synthetic Organocatalytic Methodologies

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Ai miei genitori
e a mio fratello

Non credo possa esserci modo migliore di introdurre il lavoro di questi anni se non ringraziando con tutto il cuore chi lo ha reso possibile. Nell'incredibile dono che è la mia fortunatissima vita, sono da sempre circondata da persone davvero eccezionali, che mi hanno supportata in ogni momento, amato al di là delle circostanze e guardando oltre i miei limiti e le mie mille complicazioni, che non si sono mai arrese nello starmi vicino. A tutti voi va la mia più vera riconoscenza, grazie per esserci, grazie per essere stati parte di un'esperienza così intensa e significativa quale è stata il Dottorato.

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PREFACE

The objective of this PhD study was to apply organocatalytic synthetic methods for the regio- and stereoselective synthesis of highly functionalized compounds. We exploited different organocatalytic activation modes to peculiar substrates we identified as suitable building blocks for versatile products in enantiomerically enriched form. In particular the developed projects relied on stereoselective amino- and hydrogen bonding organocatalysis, employing β-nitroacrylates, β-trifluoromethylated nitroalkenes and 2,2,2-trifluoroethyl 2-[(1,3-dithian)-2-yl]-ethanthioate in combination with various reaction partners, thus finding entries to valuable intermediates suitable for further subsequent transformations.

The first Chapter of this thesis aim to give a general overview on those fields of organocatalysis related to the research topics studied in this PhD program, the second Chapter offers a literature background of the employed substrates.

Following five Chapters (3-7) and Appendix report the discussion on the obtained results.

SCIENTIFIC BACKGROUND

The primary importance of *chirality* as a fundamental requirement for life has become more and apparent. Each *chiral* entity, defined by Lord Kelvin as what "cannot be brought to coincide with its mirror image",[1] exists in two forms that are mirror images having the same scalar properties but opposite pseudo-scalar ones; these objects are indistinguishable in an *achiral* environment, but are expected to have a different behaviour in *unsymmetrical* surroundings.

Due to the ability of each enantiomer of differently interact with a properly polarized electromagnetic wave and to be selectively recognized by another chiral unit, chiral structures have a unique role in different areas of physics and chemistry. Many studies have been devoted to the development of chiral materials finding biomedical and bioanalytical applications and characterized by interesting properties such as chiroptical ones.[2] More generally, chiral molecules do hold a main position as numerous biological functions rely on the recognition between an unsymmetrical system and the correct stereoisomer. On these basis stereoisomers activities in pharmacologically active compounds can be completely different, one providing the highest therapeutic effect while the others being less active, inert or toxic. Despite a substantial quantity of chiral drugs is still sold in the racemic form - i.e. a mixture of enantiomers - the pharmaceutical industry needs to switch to the commercialization of single enantiomers; in fact, in 1992 FDA and in 1994 EU issued guidelines concerning the development of new chiral drugs, which mandate the development of enantiopure compounds.[3]

Development of strategies for preparing enantiomerically enriched chiral molecules represents therefore a field of very active research. Synthetic methods based on the use of chiral auxiliaries (chiral enantiomerically pure molecules covalently linked to a reaction partner to control the stereochemical outcome of a reaction and removed once the desired product is obtained) are gradually being abandoned in favour of *chiral catalysts*, regarded as a fundamental tool in the context of *Green Chemistry*.

Given the huge role that it had been playing in the last century in innovating and improving life quality, Chemistry has to be on the frontline in fulfilling sustainability. Thus, the concept of *Green Chemistry* has been set up not as a mere list of rules, but as a fundamental and more general idea for *greening* chemical processes.

Recognising the progressive deterioration of environment and natural resources, a special commission of the United Nations General Assembly (the World Commission on Environment and Development) released an official report entitled "Our Common Future" stating the concept of *sustainable development*. This has to be the leading principle for human development in all fields, allowing progress while preserving the "integrity, stability and beauty" of the natural system; "sustaining the ability of natural systems to continue to provide the natural resources and ecosystem services" is the principle that allows desirable future for next generations.[4]

To build sustainable competitiveness and growth, a continuous evolution in academic research and, as a direct consequence, in industry, is needed. This process of development must be supported by a

continuous active interaction with the so-called *enabling technologies*. It is worth noting that at least four out of the six Key Enabling Technologies (KETs) identified by the European Commission,[5] namely ICT, nanotechnology, advanced materials, manufacturing, space technology and biotechnology, are directly connected to Chemistry.

Several *advanced manufacturing* techniques can be collected within the class of the so-called *machine assisted* approaches. These include computation and visualization tools (founded on theoretical chemistry and supported by online databases, these allow a more rational experiments planning and a time-saving screening) advanced computer technology, downstream processing and analytical tools.[6] In addition to machineries needed to handle specific - and not so common - conditions, as those for supercritical fluids for operations under extremes of temperature and pressure, a more mainstream equipment is becoming more and more part of chemistry everyday life. The most common synthesis assisting techniques are ball milling, continuous-flow apparatus and microreactors, and ultrasound and microwave irradiation; besides, novel solvent systems have been introduced. Our group started integratign these techniques in every day research activity exploiting the effectiveness of microwave irradiation and investigating the suitability of novel reaction media

As already mentioned, within advanced development strategies for Green Chemistry, *catalytic* methodologies have gained significant importance, as they are meant to lower the energy needed by a transformation. Developments in this area lead to catalytic systems addressing the issues of chemo-regio- and stereoselectivity, allowing the direct synthesis of a desired product without passing through protection and deprotection steps. Thus, time and energy saving is achieved, and waste production, in terms of solvents and by-products, is reduced.

Catalysis was and is certainly fully exploited Nature, as all what is needed for life to flourish is produced with "incomparable efficiency and selectivity".

Catalytic strategies are classified according to the kind of application or to the structure of the catalyst, i.e. the molecule that "accelerates a chemical reaction without affecting the position of the equilibrium" on the basis of their aggregation state or their nature and composition.[7] Catalysts, promoting and controlling reaction selectivity, can be metal complexes, enzymes or organocatalysts. Specifically, in 2000 the term *organocatalysis* was coined by McMillan to identify reactions where catalysts are "organic compounds which do not contain a metal atom".

Perhaps better described as a process where a metal is not directly involved in the reaction mechanism, so to include also ferrocene-based organocatalysts,[8] organocatalysis is a continuously expanding field in organic chemistry. Relying on the use of relatively small molecules, typically cheap and readily accessible, easy to handle and non-toxic, organocatalysis finds economic- and eco-friendly applications. While organocatalysts' biocompatibility was previously mainly hypothesized, a recent study on different cell lines demonstrated this molecules are actually harmless over a wide range of concentrations, the only exception being a thiourea derivative.[9] Despite the high catalyst loading is often considered a requirement limiting organocatalysis viability in industry, the low cost of organocatalysts

as well as bypassing the problem of metals removal from final products make this approach nevertheless appealing[10] and highly selective organocatalytic synthesis of pharmaceutical compounds have already been reported and developed in large scale.[11,12]

1. REACTION MECHANISMS IN ORGANOCATALYSIS

1.1. Activation modes in organocatalysis

Stereoselective organocatalysis relies on different modes of substrate activation. This can be classified as *covalent* or *non-covalent* and further distinguished considering the molecular orbital involved (Figure 1.1).[13] It has to be mentioned that the same catalyst can operate through distinct modalities depending on the interacting substrate. Besides, organocatalysts featuring more than one active site, which are simultaneously activating two reaction partners or different positions of the same compound, have been developed and dubbed as *multifunctional*.
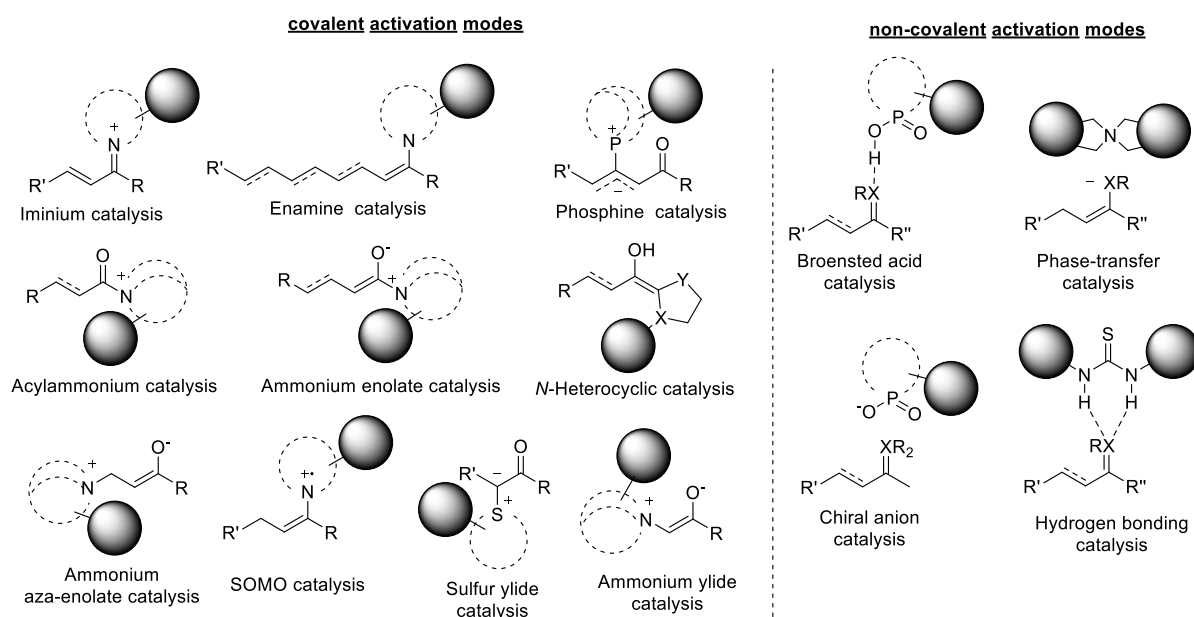

Figure 1.1

When the energy level of the lowest unoccupied molecular orbital of the substrate is lowered, nucleophilic attack is favoured. Within covalent catalysis, *iminium ion*, generated upon condensation of a (chiral) primary or secondary amine, is one of the most common intermediate exploited to make the LUMO of α,β-unsaturated compounds more accessible to electrophiles. To achieve carbonyl carbon activation of carboxylic acid derivatives, *acylammonium* catalysis is instead applied: initiated by the nucleophilicity of an acyltransfer organocatalyst, reactions including transesterifications, kinetic resolutions, desymmetrizations, and Steglich rearrangements have been reported. Activation of the LUMO orbital is also achieved by non-covalent *Brønsted acid* or *hydrogen bonding* catalysis, both based on substrate electronic depletion.

On the contrary, increasing of the energy level of the highest occupied molecular orbital enhances the nucleophilicity of the substrate. The most traditional approach is represented by *enamine* – subsequently estended to di- and trienamine catalysis: parallel to iminium ion mode, the first step of the catalytic cycle consists in the reaction between an amine catalyst and a carbonyl compound, followed by α-deprotonation and generation of an intermediate highly reactive towards electrophilic carbons or heteroatoms. Alternatively, a nucleophilic enolate equivalent (*ammonium enolate*) can be obtained

either by addition of a chiral tertiary amine catalyst to a ketene or through α-deprotonation of an acylammonium intermediate. A different kind of activated nucleophile is the *Breslow intermediate*; in this case, the α-carbon of an aldehyde acquires an electron rich character upon reaction with carbenes. As for non-covalent catalysis, HOMO activation is achieved *via phase-transfer* principle.

To rationally proceed towards further developments, a deeper understanding of the reaction mechanism is important. This can be achieved by both computational and experimental studies that, in the case of organocatalysis, are made easier by the inherent "robustness" of the catalyst, allowing the investigation of their chemical-physical properties and of the species generated during the catalytic cycle by means of spectroscopic and crystallographic techniques. Some catalytic intermediates, discrete and often stable, can be in fact isolated and characterized, but their role is not always apparent, as they can led to secondary catalytic species, on their turn *en route* or parasitic for product formation, or be spectators sometimes acting as catalyst reservoir.[14] Representative examples have been reported in the field of aminocatalysis (see the following Section).

Considering the extent and the freshness of this continuously upgrading subject, an exhaustive report on organocatalysis in all its aspects cannot be given within the present thesis work; herein, attention will be thus focused on presenting more in detail those activation modes on which the projects we developed in the course of this PhD studies were based.

1.2. <u>Aminocatalysis</u>

The roots of aminocatalysis, which can be considered as the starting block for the gold rush in organocatalysis,[15] are found in Knoevenagel's seminal discovery and mechanistic interpretation of his reaction over 100 years ago.[16] His observation that primary and secondary amines catalyze the aldol condensation of β-ketoesters or malonates with aldehydes or ketones inspired several subsequent works. In 1910, Dakin found that this reaction was also promoted by primary amino acids and Fischer and Marshall employed these catalysts in the aldol condensation of acetaldehyde. In 1930 Kuhn and Hoffer observed the effectiveness of secondary amines in catalying cross-aldol condensations ad six years later Kuhn et al. introduced piperidinium acetate as a particularly active catalyst for this reaction. Shortly after, Langenbeck, who reported the use of piperidinium acetate in the catalytic hydration of crotonaldehyde and of sarkosine for aldolization, started a an entire research program devoted to study organocatalysts ("die Organischen Katalysatoren"), their action mechanisms and their relationship to enzyme action. Based on these studies, Wieland and Miescher and Woodward et al. investigated intramolecular aldol reactions of diketones and dialdehydes catalyzed by piperidinium acetate, and proposed these to proceed via enamine intermediates, as confirmed by the mechanistic studies carried out by Spencer and co-workers in 1965. In the early '70, the Hajos-Parrish-Eder-Sauer-Wiechert reaction, i.e. the first stereoselective amino-catalyzed aldol condensation, was reported but not extensively discussed from a mechanistic point of view. Apart from sporadic examples, aminocatalysis remained rather unexplored for twenty years, when Yamaguchi and Taguchi proposed an iminium ion activation for their enantioselective Michael additions catalysed by proline. This was followed by studies on aldolase catalytic antibodies developed by Lerner and Barbas leading to first recognition of similarities between proline and type-I aldolases activation mechanism (Figure 1.2). Based on these considerations, Danishefsky encouraged further investigations on the Hajos-Parrish-Eder-Sauer-Wiechert reaction, employing the above mentioned antibodies 38C2 as catalysts. In 2000, experiments and argumentations collected over one century flowed into the official definition of the organocatalysis concept by McMillan[17] and List[18] groups (Scheme 1.1).
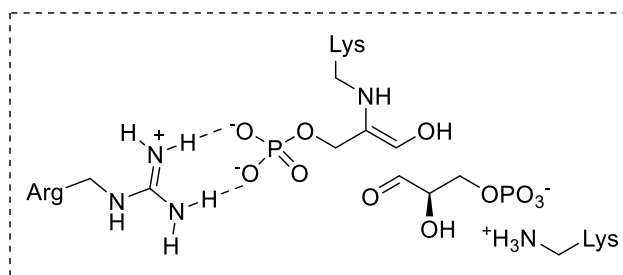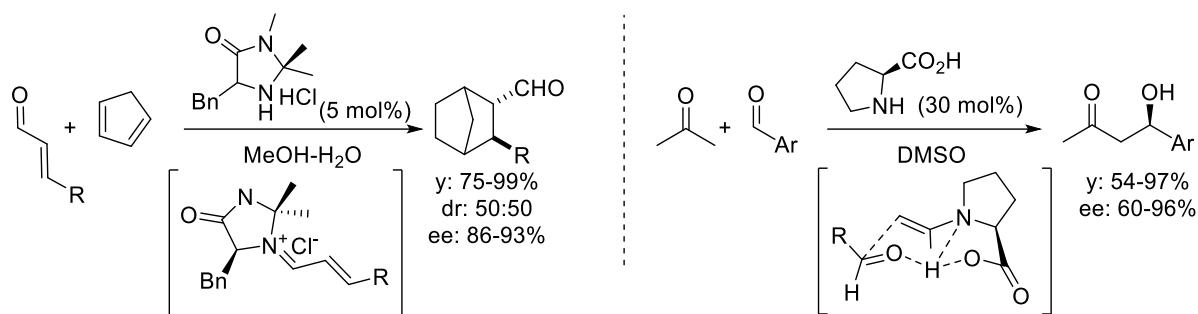

Figure 1.2

Scheme 1.1

In aminocatalysis, three main catalytic mechanisms are operating, based on HOMO (via enamine), LUMO (via iminium-ion) and SOMO activation (Figure 1.3). Stereoselectivity is given either by steric-shielding, in which one of the reactive intermediate faces is blocked by a bulky group, or by a hydrogen-bonding[19] directed approach, in which both substrate and reagent are simultaneously coordinated. In particular, in enamine-based catalytic processes a carbonyl compound is transformed into a more nucleophilic intermediate. Upon condensation between the catalyst and the substrate, forming an iminium ion that tautomerizes to the favoured nucleophilic enamine form, in contrast to what happens in the keto-enol equilibrium, mainly lying in the keto-form. The stronger nucleophilic character achieved thanks to the amine activation is not only due to the abundance of the enamine species, but also to the enamine HOMO energy that is higher than that of the corresponding enol, the less electronegative nitrogen lone-pair electrons being higher in energy than that of the more electronegative oxygen. Iminium ion catalysis acts lowering the substrate LUMO energy: when an α,β-carbonyl compound condenses with a chiral secondary amine, it forms a positively charged intermediate prone to electrophilic attack on the β-position. SOMO activation, instead, is based on the *in situ* generation of single electron species, generated through single electron oxidation of an enamine intermediated or by attack of a radical species.

The field evolved allowing stereoselective functionalization of position that are farther from the carbonyl group, thanks to the vinylogous activation of poly-unsaturated susbtrates (Figure 1.3).
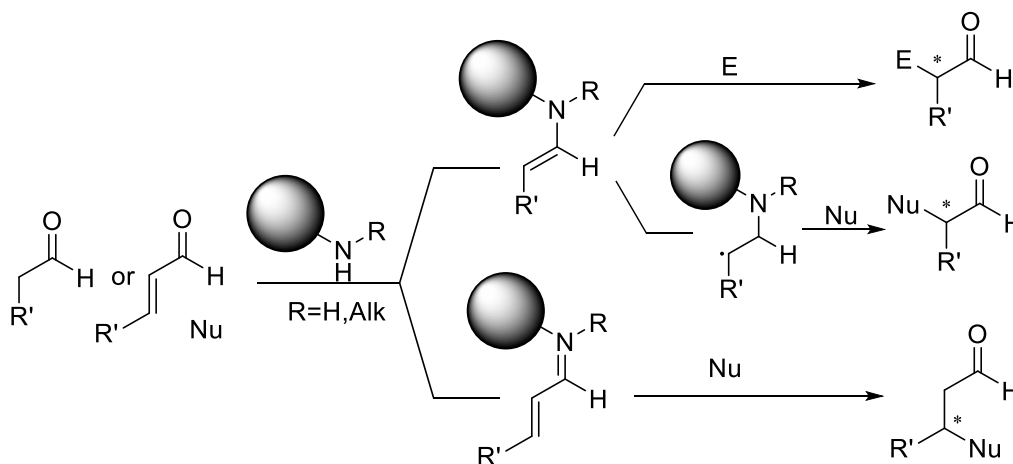

Figure 1.3

Besides the large number of new transformations developed in this field, in-depth investigations have been undertaken to gain an even more complete insights into the reaction mechanisms.

A paradigmatic case of study is the proline-catalyzed aldol reaction (Scheme 1.2). After seminal studies by Dunitz, Eschenmoser and co-workers,[20] in 2007 theoretical investigations on hemiacetal-, iminium-ion and enamine formation showed a lowering of the activation energies due to protic additives, so that a "proton-relay mechanism" was proposed. The enamine formation was investigated by Gschwind et al. by NMR techniques, performing the proline-catalysed self-aldol reaction of propionaldehyde under various conditions;[21] the *E*-s-trans enamine was proposed to be formed via an oxazolidinone, as observed by exchange spectroscopy and also confirmed by computational analysis by Sharma and Sunoj.[22]
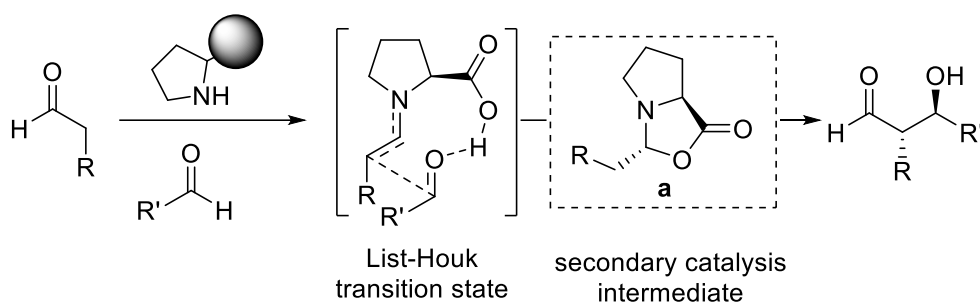
Scheme 1.2

Efforts have been also devoted to elucidate the role of the primary and secondary catalytic species in the addition of linear aldehydes to nitroolefins. After Seebach use of pre-formed enamines, the first catalytic stereoselective version of this reaction was reported by Hayashi and co-workers in 2005 (Scheme 1.3).[23] After crystallographic and spectroscopic studies on the enamine, Seebach, Hayashi, Blackmond and Pihko groups focused on the role of cyclobutane intermediate **b**: by both experimental and computational studies it resulted a rather stable catalyst tank, while dihydrooxazine oxides were revealed as the on-cycle participants.[24]
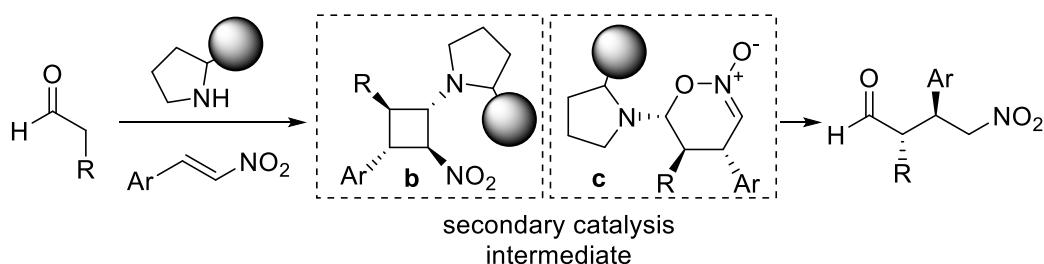
Scheme 1.3

Also iminium-ion based catalytic cycle has been the subject of mechanicistic investigation, confirming the importance of a protic additive in assisting a proton transfer that facilitates the formation of the hemiacetal intermediate and of water as proton shuttle for the enamine resulting after C-C bond formation. Moreover, kinetic measurements by Mayr group established an electrophilicity scale for iminium ions obtained from differently structured secondary amines, which revealed dominated by

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imidazolidinone-based ones (Figure 1.4, **a**).[25] Rationalization on the stereochemical outcome of the reaction has also been addressed through NMR and theoretical studies. These assessed the conformation of the catalysts, showing that steric shielding has to be ascribe to the benzyl substituent of oxazolidinone and to the TMS group in the Haiashi-Jørgensen prolinol. Additionally, the configuration of the iminium ion intermediate was elucidated being in an *E/Z* ratio > 9:1, the higher level of enantioselection justified by a kinetic resolution process operated by the nucleophile itself (Figure 1.4, **b**).[26]
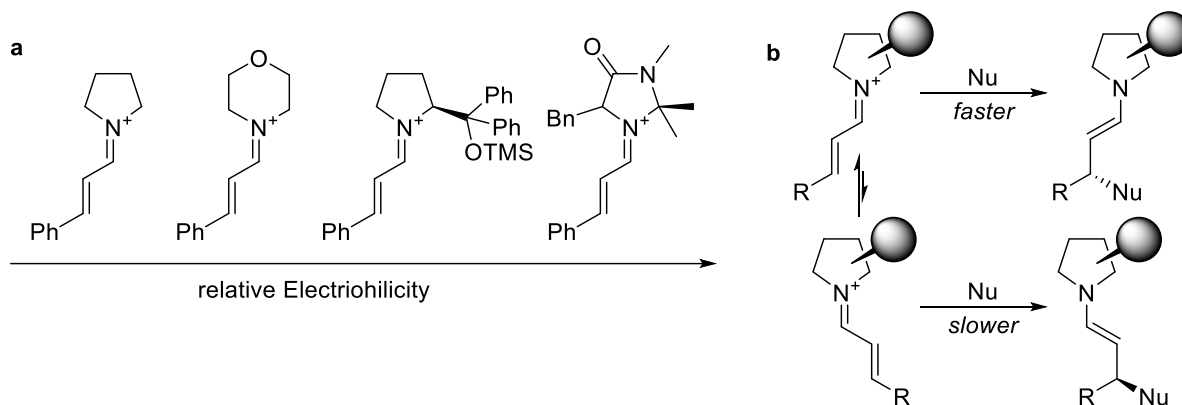

Figure 1.4

The relevance of gaining a good insight into the catalytic mechanism for new catalysts development can be appreciated considering that Jørgensen epoxidation of α,β-unsaturated aldehydes by hydrogen peroxide promoted by a diarylprolinol, proved to be accelerated by secondary intermediate peroxyhydrate working as phase-transfer catalyst (Scheme 1.4). The reaction proceeds through a cascade sequence started by an iminium ion, whose configuration was extensively investigated by Seebach group. While X-ray analysis of both single crystals and powder showed only the presence of the *E*-isomer, while NMR showed an E/Z equilibrium in which the Z isomer and less accessible for the nucleophile, as rationalized by DFT calculations [27]
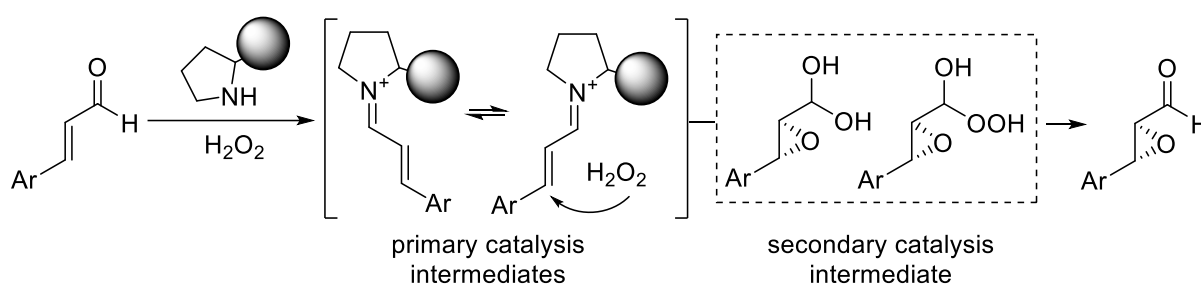
Scheme 1.4

On the basis of these results, Gilmur et al. designed a catalyst with a fluorine atom replacing TMS group, so that upon condensation with an α,β-unsaturated aldehyde, a transient β-fluoroiminium salt would be generated. This benefits from stabilizing hyperconjugative ($\sigma_{CH} \rightarrow \sigma_{CF*}$) and electrostatic interactions ($N^+ \cdots F^{\delta-}$) and, due to a gauche effect, one of the phenyl groups is located to effectively shield on of the two enantiotopic faces (Figure 1.4).[28] This hypothesis was validated by crystallographic and spectroscopic analyses of numerous isolated primary catalysis
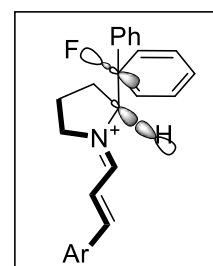

Figure 1.5

intermediates leading to the development of a novel catalyst for enantioselective epoxidation and aziridination; moreover, the fluorineiminium ion gauche effect was exploited to study the influence exerted by the phenyl group of MacMillan oxazolidinone in inducing stereoselection.

In addition to the more classical activation and stereoselection modes, some peculiar reactions, where the newly formed stereogenic centre is not belonging to the substrate covalently bound to the aminocatalyst but on the other reaction partner, should also be considered. In this case, the stereochemical outcome cannot be explained according to the previously mentioned schemes and new stereodifferentiation scenarios have to be evaluated. [29]

An example is given by acetaldehyde condensation with imines, where a stereocenter is formed on the moiety not activated by prolinol (Scheme1.5). According to calculation performed by Hayashi group in 2008, the stereochemical outcome of the reaction depends on electrostatic interactions arising between During the transition state of partially positively charged nitrogen atom in the aminocatalyst and the partially negatively charged oxygen atom in the amide group (Scheme 1.5).[30]
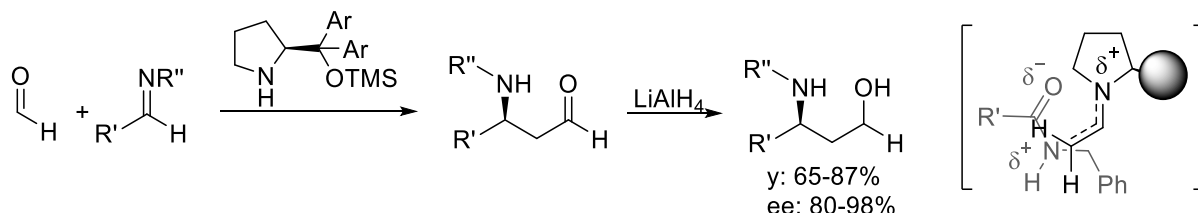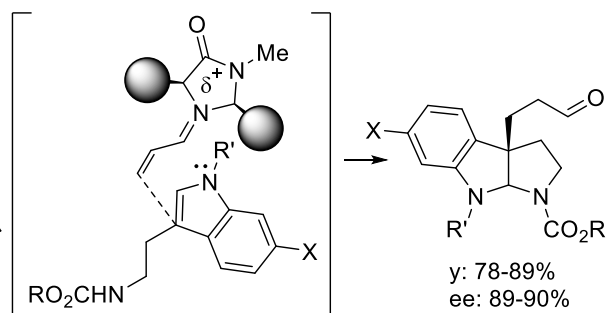

Scheme 1.5

Several other cases showing how stereoselectivity can be ruled by electrostatic interactions have been reported, including dienamine-mediated intramolecular [4+2]-cycloaddition, enantioselective Diels–Alder reactions (Scheme 1.6) and various iminium-ion promoted additions (Scheme 1.7).
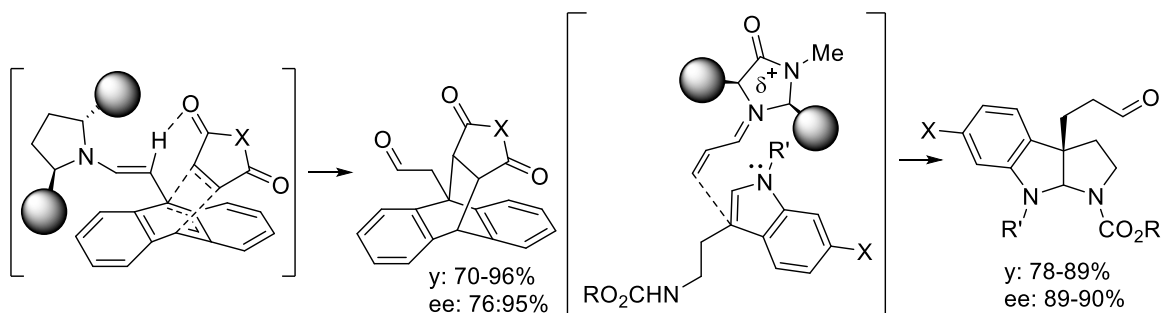
Scheme 1.6   **Scheme 1.7**

1.2.1. Primary amines as organocatalysts

Evolution in the field of aminocatalysis lead to the re-discovery of chiral primary amines as valuable catalysts. Involved in enzymatic processes, the catalytic effectiveness of primary amines was already recognized eighty years ago: in the 1930s, Kai J. Pedersen and Frank H. Westheimer noticed that in the decarboxylation of acetoacetate and the dealdolization of diacetone alcohol, primary amines were even better catalysts than their secondary counteroparts. In the early 1970s initial studies on

intramolecular aldol cyclizations established that natural amino acids other than proline, such as phenylalanine, were active as catalysts. However, the aminocatalysis scene has been dominated by cyclic secondary amines for the first 10 years, as the amazing first results obtained with proline were supported by the fundamental studies by Stork on the synthetic utility of enamines as nucleophiles, while primary amines suffer of less effective stabilization of the iminium ion intermediates by hyperconjugation and unfavourable imine-enamine equilibrium (Figure 1.6). On the other hand, extensive studies by Hine in 1978 showed how steric factors greatly affect the reactivity of secondary amines, which are less prone to condensation with α-branched aldehydes and ketones and faster in the subsequent hydrolysis. This is probably due to difficulties for tertiary enamines to achieve a planar conformation, required to maximize overlap between the π-orbital of the carbon–carbon double bond and the lone pair orbital on the nitrogen atom.[31]
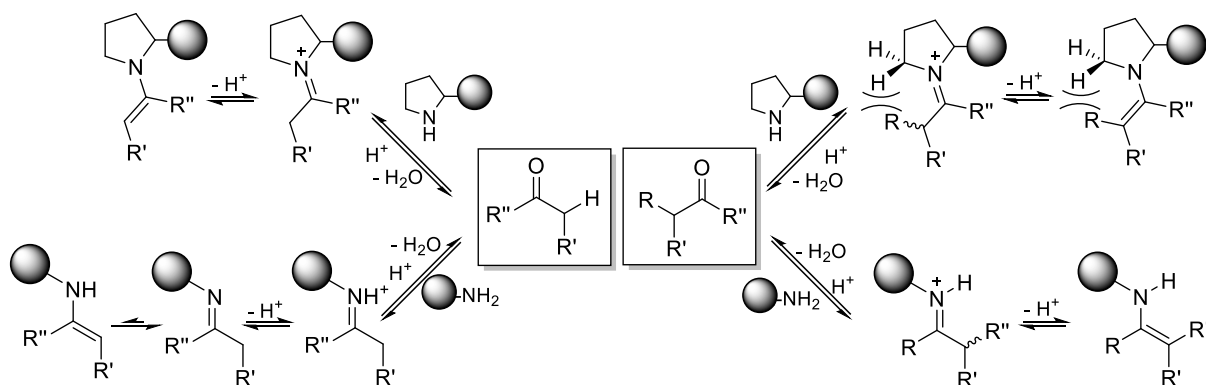

Figure 1.6

In particular, Hine focused on primary-tertiary vicinal diamines, as effective bifunctional catalysts. Studying the iminium ion-enamine equilibration occurring upon condensation between a primary amine and a carbonyl compound, deuterium exchange experiments showed intramolecular α-deprotonation and were followed by detailed investigations about the influence of amines structure on the process.[32]

Despite these bases, first works on the use of primary amines[33] as catalysts were published only in 2005, in a paper reporting the design of new primary-tertiary diamine skeletons (Figure1.7) and their use as organocatalysts for the stereoselective α-functionalization of branched compounds.[34]
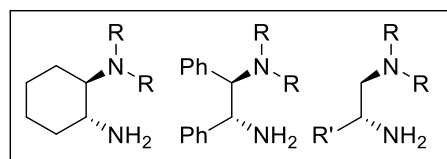

Figure 1.7

12

1.2.2.<u>Cinchona alkaloids derivatives as privileged scaffolds</u>

In the pool of chiral primary amines available as organocatalyst, derivatives of Cinchona alkaloids have an overwhelming role.

Cinchona alkaloids are natural products extracted from the bark of trees of the genus *Cinchona* that comprises about 40 species of trees or shrubs in the family Rubiaceae native to the Andes Mountains of South America. After isolation of quinine, accomplished by Pelletier and Caventou in 1820, about other 30 Cinchona alkaloids were isolated from Cinchona species, the four best known being quinine, cinchonidine, quinidine and cinchonine. Quinine, the main bioactive alkaloid extracted from Cinchona bark, was used as the sole cure for malaria and, in stopping this terrible disease, quinine was the first drug in the medical pharmacopoeia to cure a specific illness, thus bringing the revolution that lead to the foundation of chemotherapy. Over the years, Cinchona alkaloids also found applications as anticancer, analgesic, germicide, fungicide, insecticide, antibacterial agents, digestion stimulants, in the treatment of abnormal heartbeat and for relieving leg cramps; besides, they are used as bitter flavouring agents for some drinks.[35] Outside their medicinal use, they found application in all those field requiring a structure able to convey stereochemical information. Thus, referred to as "privileged structures" together with molecules as BINAP, BINOL and TADDOL,[36] they have been employed as surface modifiers, selectors for chromatographic separations, bases for the resolution of racemates, building blocks for supramolecular architectures, ligands for transition-metal complexes and organocatalysts. In particular, as far as their role as stereoselective catalysts, they have had a widespread diffusion, being considered as ideal compounds: abundantly provided by nature, they are commercially available at relatively moderate prices and bench-top stable and recoverable.

The basic scaffold characterizing all Cinchona alkaloids consists of two rigid ring moieties - an aromatic quinoline ring and an aliphatic quinuclidine ring - linked by two carbon-carbon single bonds; this structure contains five stereocentres, C3, C4, N1, C8 and C9, and in all the natural products the absolute configurations are (*S*)-N1, (*R*)-C3 and (*S*)-C4. Because the absolute configurations at the bridgeheads N1 and C4 of the quinuclidine bicyclic system are interdependent, the total number of stereoisomers for a series is only 16 and not 32 (2^5). Naturally occurring compounds, where the configuration of three out of the five stereocenters is fixed, exists in two diastereoisomeric forms that presents opposite configuration at C8 and C9 and that are referred to as *pseudo* or *quasi*-enantiomers (Figure 1.8).
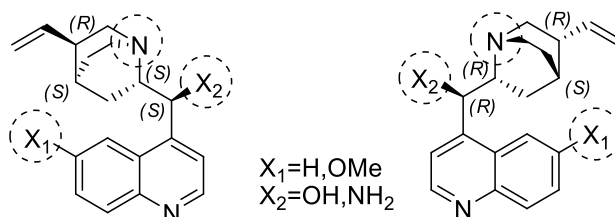

X_1=H,OMe
X_2=OH,NH$_2$

Figure 1.8

Because of the great flexibility of the Cinchona alkaloids' skeletons, lots of NMR, X-ray crystallography and computational studies have been devoted to gain a deeper insight into their conformational behaviour. The most important degrees of freedom were found to be the two torsional angles C3-C4-C9-C8 and C4-C9-C8-N, determining the relative orientation of the quinoline and quinuclidine moieties, accompanied by the orientation of the O-H and of the vinyl group and the conformation of the quinuclidine ring (left- or right-handed screw) (Figure 1.9).[37]
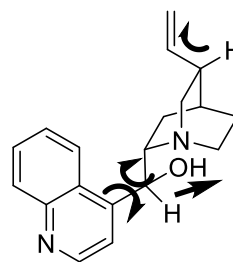

Figure 1.9

Two main conformations have been identified, namely *open* and *close*, differing in the orientation of the quinuclidine ring relative to the quinoline one, featuring C8-N and C9-C4' bonds staggered or eclipsed, respectively. Both open and close conformations, on their turn, can be *syn* or *anti* (Figure 1.10).
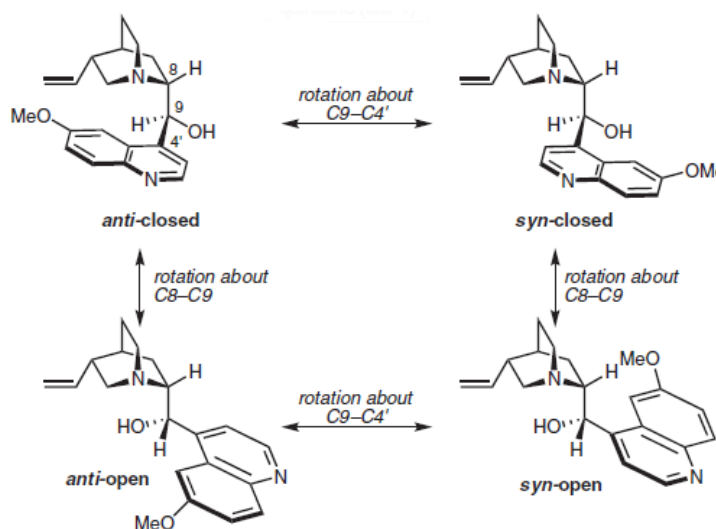

Figure 1.10

Relative stability of such conformers depends on different factors, as solvent polarity or bridged-head nitrogen protonation. Within a study about cinchonidine conformation dependence on solvent it was reported that conformational preferences are largely determined by the mutual repulsive interaction between the quinoline, quinuclidine, and hydroxyl moieties and by the Pauli repulsion between the oxygen atom and H5 and H1, respectively.

The polar solvent ability of stabilizing the two closed conformers relatively to the open ones was rationalized considering their different dipole moment, which is the most relevant quantity for the solvation interaction: dipole moment associated with the closed conformations is larger than that for the open ones. In ethanol, however, the population of the open conformer is much higher than what would be expected on the basis of its dielectric constant. This situation was warranted by the stabilizing hydrogen bond between the tertiary nitrogen and ethanol, which is more readily formed in the open than in the closed conformer. This hindrance, due to repulsion with the quinoline moiety, is less pronounced for smaller solvent molecules, such as water.

Protonation is to rigidify molecules, hindering rotation around C8-C9 and C4'-C9 bonds. Because of formation of inter- or intramolecular hyd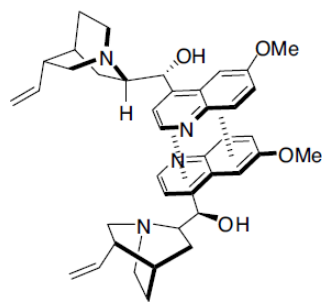rogen bond bridges involving the protonated quinuclidine nitrogen and the hydroxyl group or the counteranion, depending on the specific acid employed.

Several intermolecular aggregation phenomena have also been identified mainly by NMR experiments, investigating spectral parameters dependence on temperature and concentration; a dimeric π-π complex with roughly parallel quinoline rings was identified (Figure 1.11). These data were further supported by previous osmometric molecular weight determination, revealing the presence of aggregates when highly concentrated solutions were analysed.

Figure 1.11

A large number of derivatives of Cinchona alkaloids have been prepared functionalization of the oxygen atom on C6' of the aromatic ring or on C9, or by replacing it with an amino group; in particular, the C9-*epi* molecules are accessed either through a three steps synthesis,[38] or through a one-pot Mitsunobu-Staudinger reaction.[39]

As mentioned before, amino-Cinchona derivatives are probably the most common and efficient primary amines promoting highly stereoselective transformations with hindered substrates.

In agreement with typical aminocatalysis conditions, they operate in the presence of an acidic co-catalyst that activates the substrate's carbonyl moiety. In particular, a twofold excess of the acid is generally used for iminium ion promoted transformations of unsaturated substrates: in this way, protonation of the more basic tertiary amine occurs, and the resulting charged species is actually the catalytic active one, influencing the rate of imine formation through internal acid catalysis. Besides favouring the dehydration of the intermediate carbinolamines by proton transfer, the presence of a positive charge on the tertiary amine alters the electronic nature of the vicinal primary amine whose tendency to be on his turn protonated is lowered, thus facilitating its attack on the carbonyl compound. Moreover, changing the nature of the counteranion can have significant influences on the reaction stereoselectivity.[40]

First applications of these organocatalysts operating both through enamine and iminium-ion modes were published in 2007 and were followed closely by a large number of examples, showing how the use of these primary amines enabled previously inaccessible transformations.

One of the earliest examples of enamine catalysis was reported by McCooey and Connon and consisted in the conjugate addition of ketones and α-branched aldehydes to nitrostyrene promoted by amino-*epi*-hydroquinidine, which afforded the highest level of stereocontrol ever reached in aminocatalysis.[41] Interestingly, Michael adducts obtained from aldehydes and ketones had the same *syn* configuration but opposite absolute stereochemistry. Subsequently, List and co-workers reinvestigated

the intramolecular crotonic condensation of 2,6-heptandiones; also in this case a quinine derivative outperformed both proline and aldolase 38C2 (Scheme 1.8).[42]
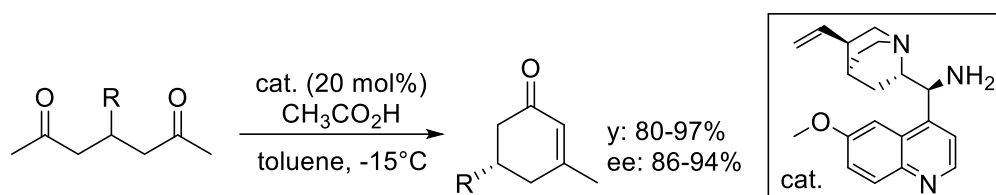
Scheme 1.8

This Cinchona alkaloid based activation of hindered bustrates was applied also to achieve C-N,[43] C-F[44] and C-O[45] bond formation, in all cases with good yields and enantioselectivity ranging from 80 to 99%.

The concept was then extended to vinylogous synthesis, developing even trienamine catalysis (Figure 1.12): in this case, HOMO-raising is propagated within α,β-γ,δ-unsaturated aldehydes and kenones allowing the rapid construction of cyclohexenyl rings with complete regioselectivity (Scheme 1.9).
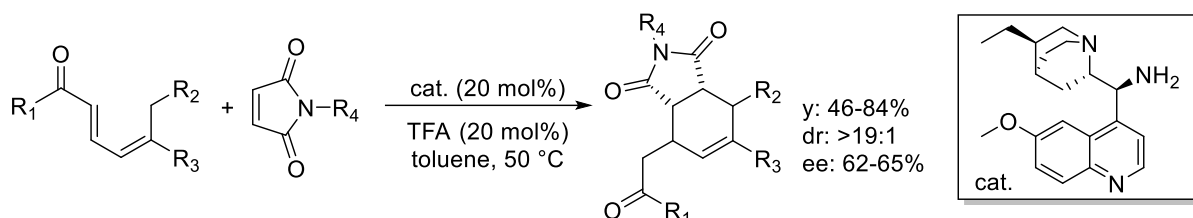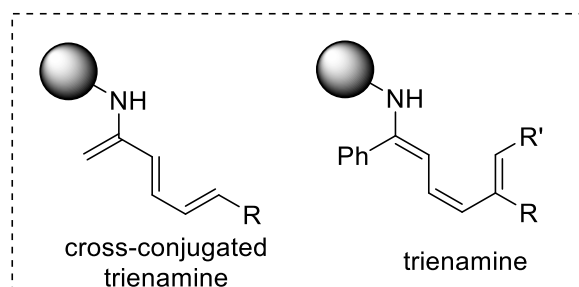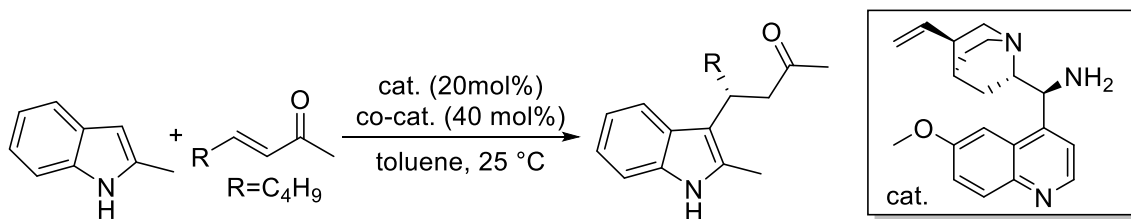

Scheme 1.9

Figure 1.12

As for iminium ion activation, an outstanding example is represented by the studies by Melchiorre group on the Friedel-Crafts alkylation of indoles (Scheme 1.10).[46] In this work it was found that the acidic co-catalyst is necessary and that its pK_a greatly influences the reaction rate as well as the level of stereoselectivity: a well-structured supramolecular catalytic assembly was built by means of electrostatic interactions and high stereocontrol was achieved thanks to hydrogen bonding stiffening and repulsive interactions with the counteranion (Figure 1.13).[47]
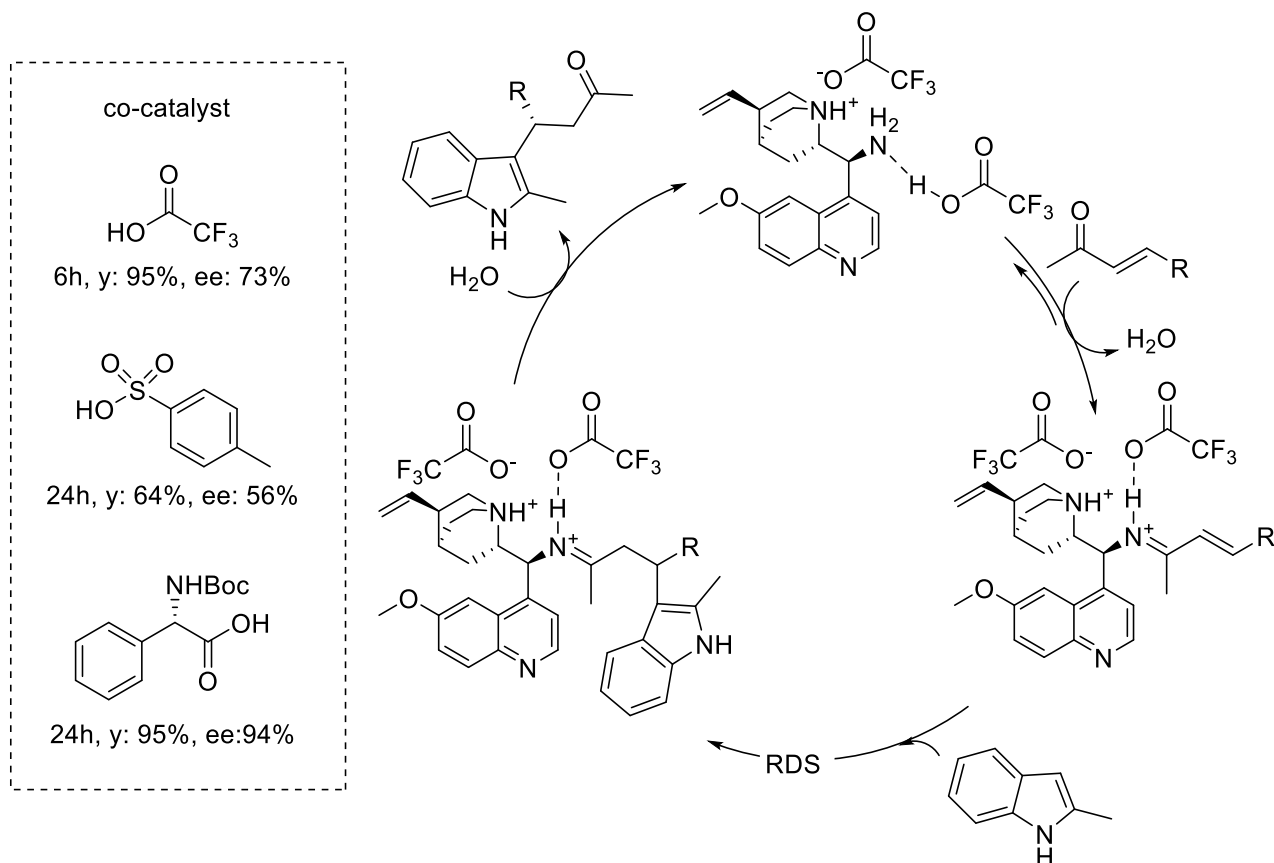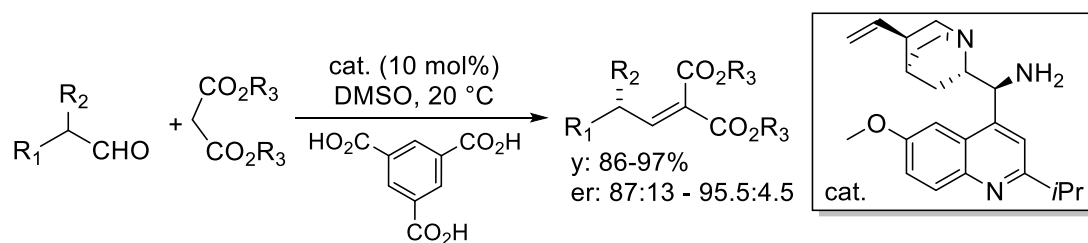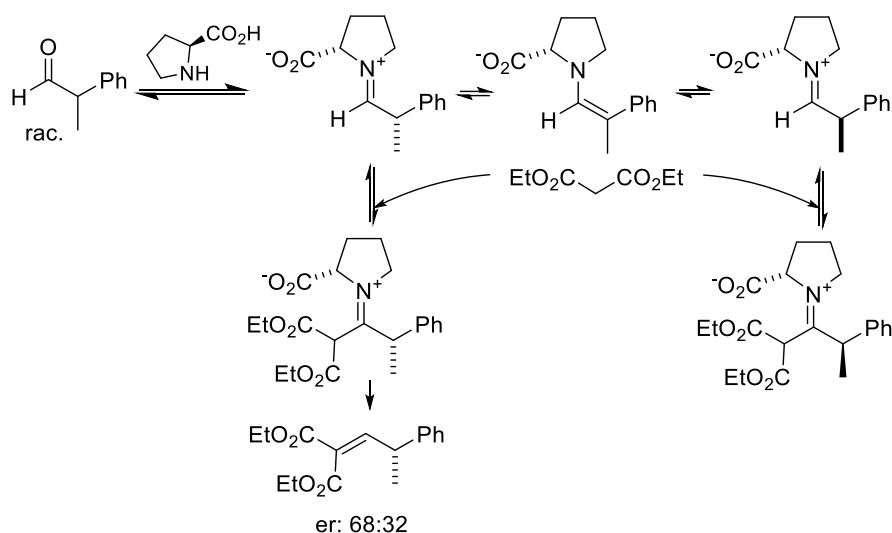
Scheme 1.10

Figure 1.13

In 2011, the use of Cinchona alkaloids derivatives allowed the first enantioselective Knoevenagel condensation (Scheme 1.11), based on a continuous racemization occurring through an iminium ion/enamine tautomerization (Scheme 1.12).[48]
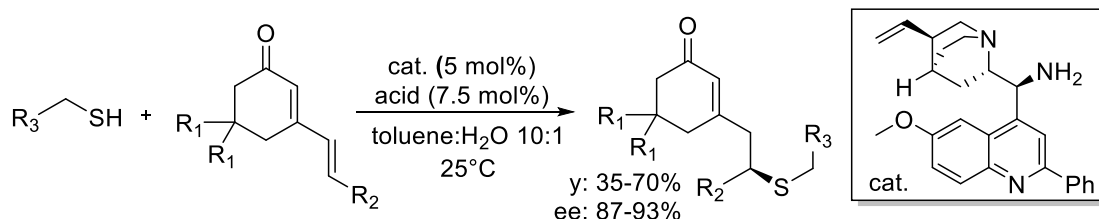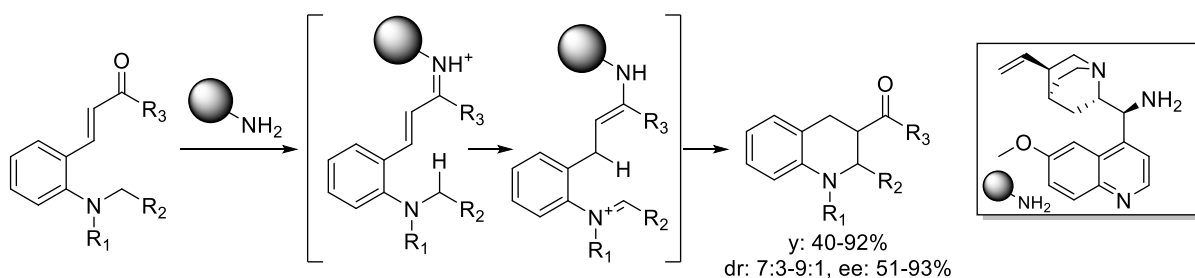

Scheme 1.11

Scheme 1.12

In the same year, an unprecedented sulfa-Michael addition of α-substituted enones was developed. Despite difficulties associated to the activation and control over such bulky substrates, not only excellent enantioselectivity was reached, but it was also possible to tune the *syn* or *anti* selectivity changing the nature of the acidic co-catalyst.[49]

The concept of iminium ion activation was also extended to achieve δ-stereoselective functionalization from α,β-γ,δ-unsaturated ketones. In fact, in 2012 the Melchiorre group reported one of the few examples of this kind of vinylogous approach, consisting in the 1,6-addition of alkyl thiols to cyclic enones (Scheme 1.13); although yields were lower than 70%, good enantioselectivity was achieved employing (L)-*N*-Boc-valine as co-catalyst.[50]

Scheme 1.13

More recently, a less common transformation promoted by the same chiral amine was reported: the synthesis of enantiopure tetrahydroquinoline derivatives through a 1,5-hydride transfer initiated by the formation of an iminium ion (Scheme 1.14). Employing a β-[ortho-(dialkylamino)aryl]-α,β-unsaturated ketone as substrate, the desired products were obtained in modest yield, dr and ee.[51]

Scheme 1.14

As elucidated in this Chapter, aminocatalysis proceeds activating the substrate by formation of covalent bonds upon condensation. However, for several transformations relying on this activation mode, the establishment of hydrogen bonds is nevertheless important for having a proper control over the stereochemical outcome. Indeed, proline itself, thanks to the carboxylic acid moiety, simultaneously coordinates the electrophile. This concept led to the development of novel bifunctional catalysts where covalent and non-covalent activation modes coexist.[52]

The herein reported strategies represent the foundations onto which organocatalyzed cascade sequences are built, allowing the stereocontrolled formation of more bonds in a unique synthetic operation, and creating, in a single step, molecular complexity from simple starting materials.

1.3. Cascade reactions

1.3.1. Taxonomy of cascade reactions

The identification of methods to straightforwardly access structurally and stereochemically complex molecules from simple starting materials is a central topic in organic synthesis. Complex molecular architectures can be afforded through a "stop and go" sequence of individual reactions and thanks to this approach almost all natural isolates have been obtained, although usually in small quantities and with high resources consumption in terms of materials, time and energy, implying high waste production and costs. In looking for alternative solutions, the main source of inspiration was again Nature, which builds complex molecules through continuous processes driven by transform-specific enzymes. The biocatalytic 'assembly line' takes place in a highly controlled environment, where regulatory systems, such as transport proteins, maintain the correct concentration of starting materials, reaction intermediates and products, and enzymes coexist in the same reaction medium without any deleterious interaction. An example of enzymatic cascade catalysis application can be represented by the biosynthesis of taxol, obtained in four cascade reactions from starting from the universal diterpene precursor geranylgeranyl diphosphate GGPP (Figure 1.14).[53]
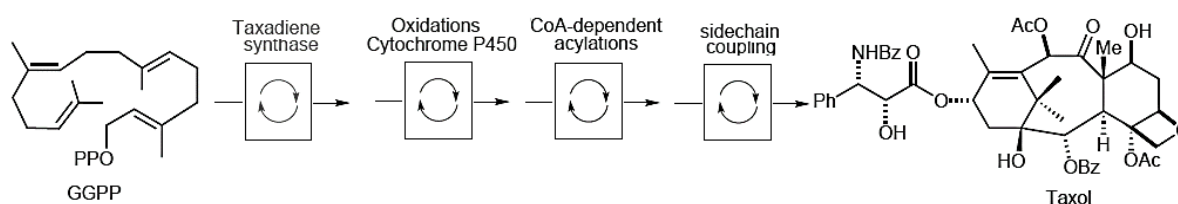

Figure 1.14

In the last three decades, numerous studies have been devoted to replace multistep synthesis with *tandem* reactions, where multiple transformations are combined into one synthetic operation. This strategy enables rapid increase in molecular complexity from readily available starting compounds, improving operational simplicity and making the process more feasible from both an economical and ecological point of view. Perfectly fit within the Green Chemistry concept, these strategies, which are atom-economical, often avoid time-consuming and costly protection/deprotection steps and are characterized by minimal waste generation, are not just interesting chemical exercises but already found important application in total synthesis.[54]

Several kinds of one-pot reactions have been developed, including both stoichiometric and catalytic strategies; in particular, *catalytic tandem reactions* are characterized by the presence of one or more catalysts operating in the same or in different cycles; consequently, many different definitions have been introduced trying to classify them. In Tietze's work, *domino catalysis* is defined as "a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts and in which subsequent reactions result as a consequence of the functionality in the previous step"[55] and Faber added that "each individual reaction belong tightly together and are rather difficult to perform in a stepwise fashion".[56] Additionally, Fogg stated that "the

transformations must be effected by a single catalytic mechanism"[57] and Chapman and Frost completed the definition saying that "a catalyst must be integral to both of the bond-forming transformations".[58] Previous to these specification Denmark (1996) integrated Tietze's work defying *tandem cascade reactions*, wherein each subsequent stage can occur by virtue of the structural change brought about by the previous step under the same reaction conditions; *tandem consecutive reactions*, wherein the first reaction is necessary but not sufficient for the tandem process, so external reagents or changes in reaction conditions are also required; *tandem sequential reactions*, wherein the second stage requires the addition of another reagent.[59]

The term domino was then placed side by side to *cascade*. When employed alone, this term is meant to indicate a transformation where a single catalyst subsequently build new bonds; however, it has been decorated with additional elements adapting its use to different situations, including those where more than one catalytic species is employed.

In fact, MacMillan and Walji introduced three other denominations to identify kinds of transformations that indeed are not clearly implied in the *domino catalysis* definition: *iterative cascade catalysis*, i.e. cascade catalysis involving one catalyst and one iterative reaction type (Scheme 1.15), *cascade catalysis based on multiple reaction types*, i.e. cascade catalysis involving one catalyst but multiple reaction types (Scheme 1.16) and *cycle-specific cascade catalysis*, i.e. cascade catalysis involving multiple catalysts and multiple reaction types (Scheme 1.17).[60] These partially overlap to Fogg definition of *tandem catalysis*, requiring more than one catalytic cycle, on its turn distinguished into *orthogonal catalysis* if more catalysts are required, and *assisted tandem* or *auto-tandem catalysis* depending on the fact that a chemical trigger is or not used to transform the catalyst or to cause a change in mechanism.[6]
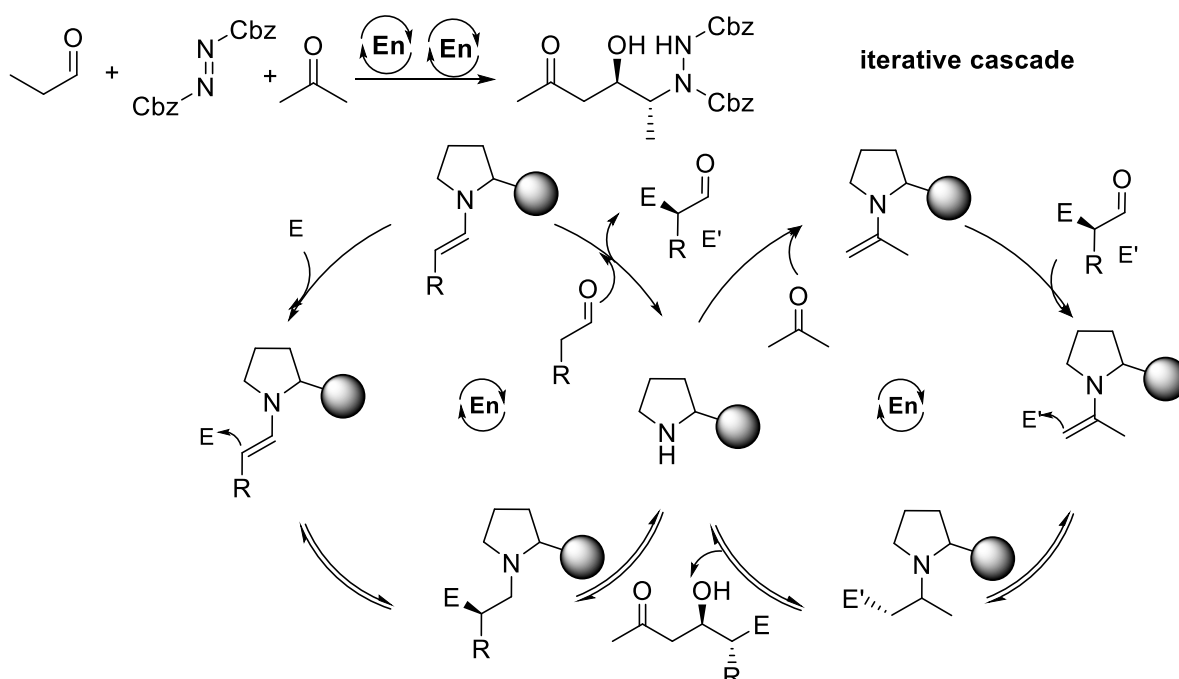
Scheme 1.15
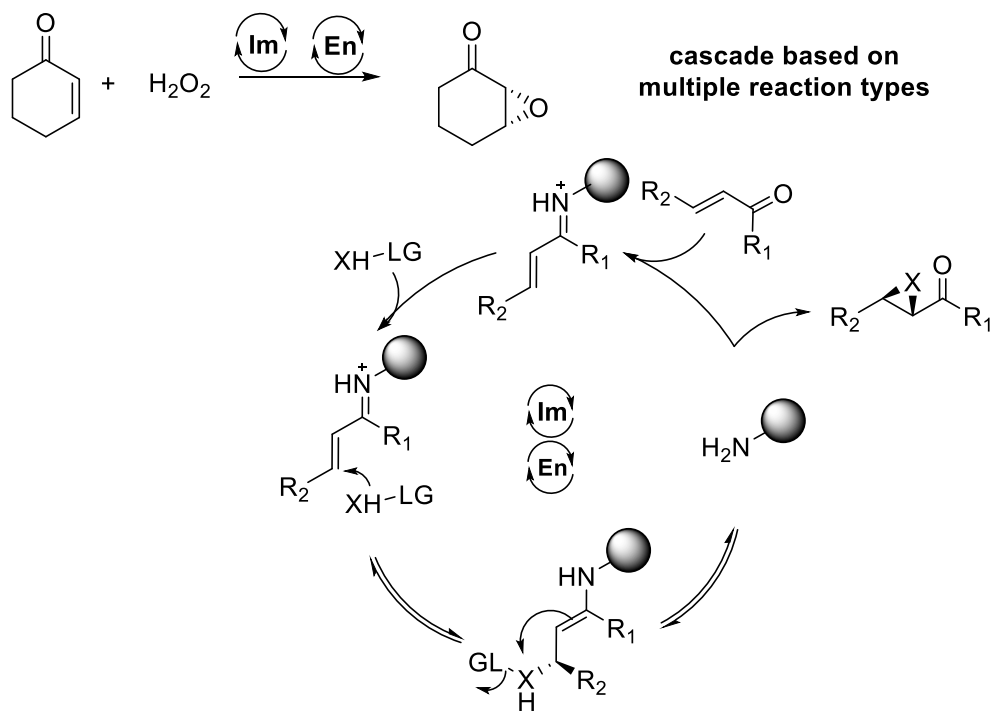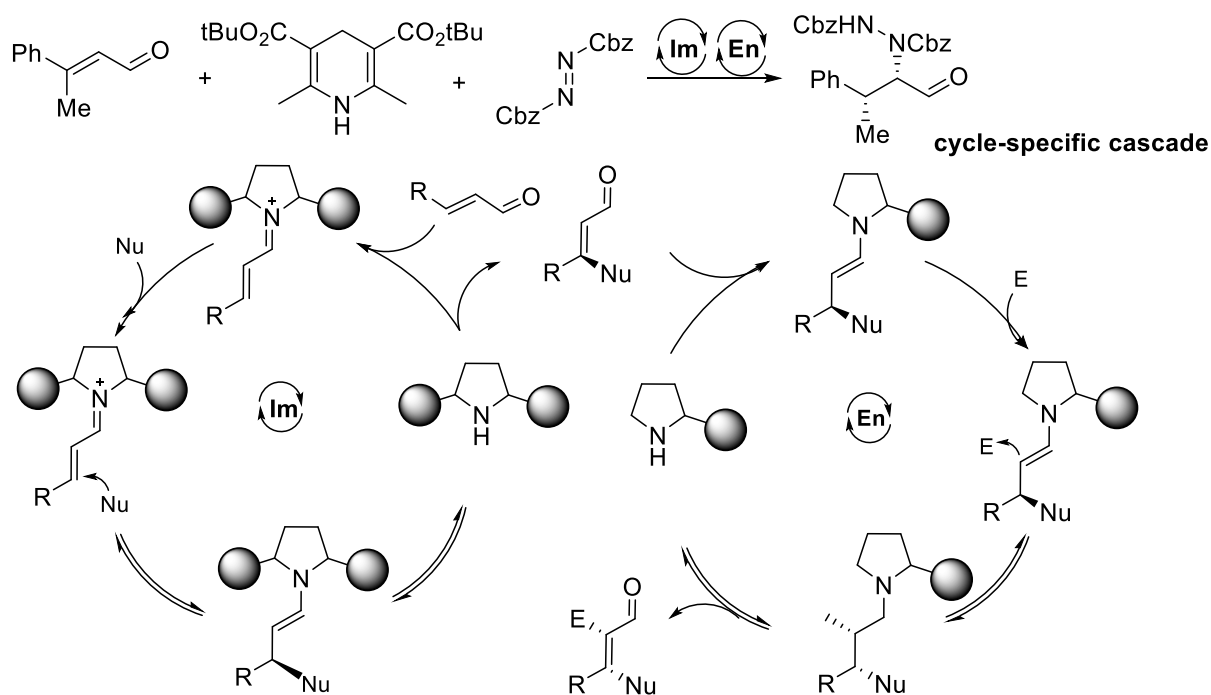
Scheme 1.16

Scheme 1.17

In 2005 Bazan group specified the concept of *concurrent tandem catalysis* (CTC), which involves the cooperative action of two or more catalytic cycles in a single reactor, and classified generic CTC cycles according to the number of unique catalytic cycles and the manner in which the products from each cycle are distributed in subsequent reactions (Figure 1.15).[61]
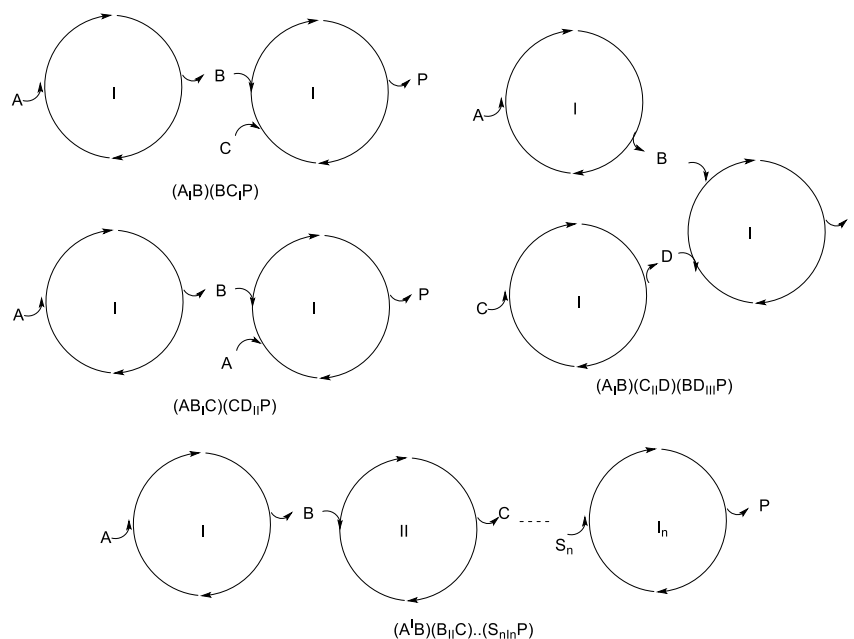
Figure 1.15

While being highly specific, these classification approaches lack in giving the direct macroscopic distinction between *organomulticatalysis* and *organocascade*, the difference lying in the number of catalysts, more or one, respectively, employed. This was adopted in 2014 by Volla et al. who, reviewing this field, pointed out double, triple and even quadruple cascades.[62]

A further specification within *organomulticatalysis* was given by Wende and Schreiner. The situation represented by the case $(A_IB)^{..}(S_{In}P)$, in which the intermediate generated from one catalytic cycle is the substrate for the subsequent one promoted by a different catalyst or by an independent catalytic moiety on the same catalyst, is precisely defined as *multicatalysis*. This strategy was also translated in the design of *multicatalysts*, i.e. a catalyst equipped with an appropriate spacers (Figure 1.16).[63]
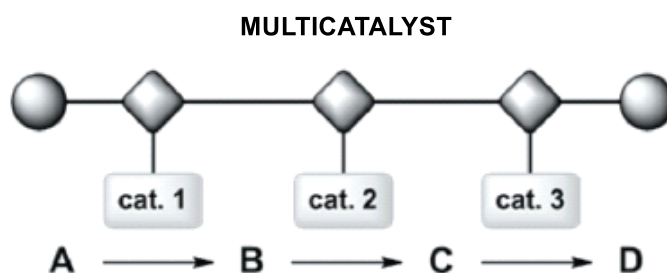
MULTICATALYST

Figure 1.16

Going back to the origin of this rather articulated taxonomy system, it is possible to notice that *multicatalysis* can be considered a kind of subgroup of domino reactions as defined by Tieze.

In 2012, Allen and McMillan made clear the difference between *double activation catalysis*, where two different catalysts activate the same starting material, and *synergistic catalysis*, where two different catalyst act on two different reaction partners (Figure 1.17).[64]
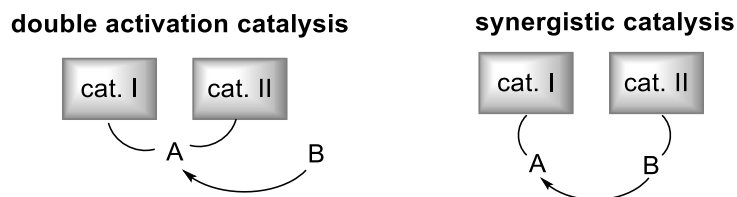

double activation catalysis   **synergistic catalysis**

Figure 1.17

Evaluating that conceptual differences among these tandem strategies do not exert a real impact on the anyway astonishing result they all achieve, *viz.* an enhanced effectiveness in constructing chemical complexity, Ambrosini and Lambert adopted the term *multicatalysis* with no specific connotation to encompass them all.[65]

A different systematic description and classification of one-pot reactions was introduced by Jorgensen group in 2011.[66] Considering that this kind of transformations have the ultimate goal of reducing time demand and waste production and have a evident link to industrial processes, the author proposed not to focus on the involved activation modes, but on the number of "manual operations", which is easily counted and may provide an indication of the complexity of the overall reaction and the required manual effort. This system relies on three parameters: *type*, indicating the position of the enantiodifferentiating manual operation; *order*, indicating total number of manual operations that are defined as "interruptions of the cascade by the addition of reagents or the removal of the solvent"; *fingerprint*, indicating the number of C-C (*m*) and C-X (*n*) bonds formed and abbreviate as *m*C*n*X. In particular, the authors proposed three *types* underlying the different "chemical purposes" on the basis of which the position of the stereoselective step is chosen. Specifically, in TypeA reactions (with asymmetric catalysis as the first manual operation) rapid assembly of structurally diverse chiral frameworks, subsequently modified by *in situ* modification may lead to highly complex target molecules; in this case, main concerns are racemization and decomposition of the assembled chiral framework. Instead, TypeC strategies (with asymmetric catalysis at the end of the sequence), are performed to avoid handling of delicate starting materials, reaching the stereoselective step as last one; in this case, success is threatened by contaminants somehow hampering the late-stage reaction. In the paper a flowchart is offered to make the assignement easier (Figure 1.17).
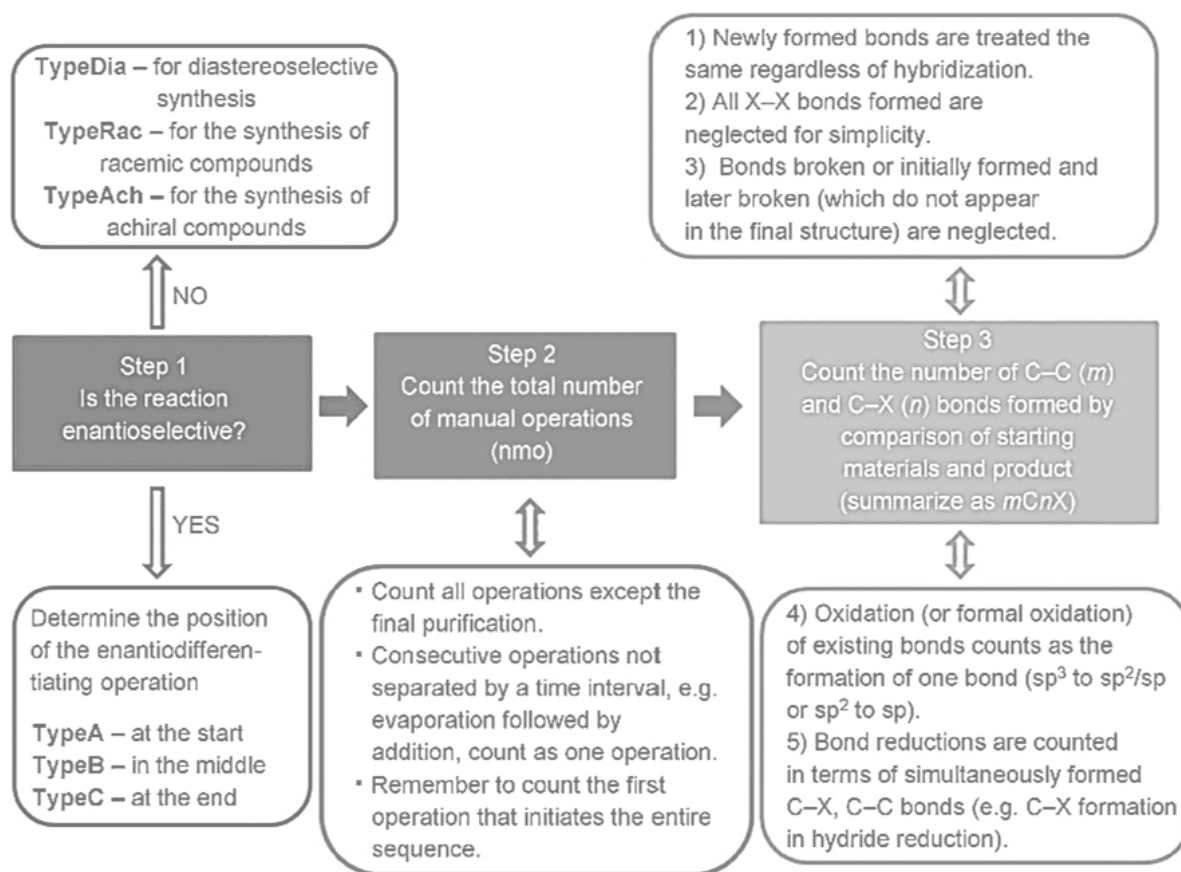
Figure 1.18

Moreover, they proposed new criteria to establish the efficiency of the one-pot reaction cascade: *yield per bond formed* (Y_{PBF}), which "defines the efficiency of the one-pot reaction by relating its yield to the number of bonds formed in the overall cascade"; *yield per manual operation* (Y_{PMO}), which "indicates the average yield of each single manual operation"; and *purification factor* (P_f), which indicates the number of purification steps saved passing from a stop-and-go to a one-pot protocol (Equation 1, 2 and 3).

$$Z = \sqrt[b]{\frac{Y}{100}} \times 100 \qquad Y_{PMO} = \sqrt[nmo]{\frac{Y}{100}} \times 100 \qquad P_f = nmo - 1 - n(INI) + x$$

**Equation 1**   **Equation 2**   **Equation 3**

Thanks to the remarkable analysis work carried out in the last 20 years, a deep insight in to the field of one-pot transformation has been obtained, even though sometimes scarifying directness and univocity.

1.3.2. Aminocatalytic cascade reactions

Within the context of this thesis works, attention was focused on stereoselective aminocatalytic sequences.[67] For sake of clarity, we will stick to the definition of domino reactions, as re-proposed by Pellissier [68] and by Enders et al.,[69] both using it mainly as a synonymous of cascade. In particular, Pellissier classified this transformations according to the reaction initiating the cycle, while Enders pointed out four different activation sequences, namely iminium-enamine, enamine-iminium enamine-enamine, iminium-iminium, besides other amine catalyzed "miscellaneous" ones. Reported below are both classical and recent examples on amino-catalyzed cascades, to elucidate basic mechanisms and to give an idea about the state of art.

The enamine-enamine pathway has not been largely explored and the major contributions in this filed come from Barbas group. In 2002 they reported the first organocatalytic assembly of carbohydrates and polyketides by means of a proline-catalyzed trimerization of simple aldehydes: a first self-aldolization reaction between two propanal molecules is followed by a cross-aldol reaction between two different aldehydes to achieve a substituted lactol, although in generally low yields and enantioselectivities (Scheme 1.18).[70]
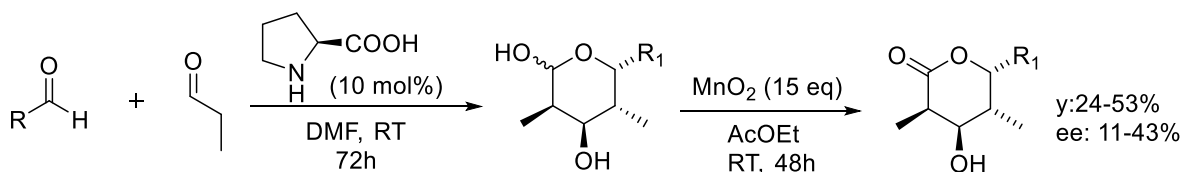
Scheme 1.18

Subsequently, these authors developed a three component sequence proceeding through α-amination and aldol condensation to obtain hydrazino aldols, in up to 99% ee, from acetone, azodicarboxylate and linear aldehydes.

In 2013 Portalier and co-workers extended this principle to developed a trienamine-enamine cascade to obtain a tricyclic motif, which can be found in natural products as Valeriananoid A, Penicillone A and Atropurpuran. The transformation starts with a trienamine mediated Diels-Alder condensation between a branched dienal and the oxidized hydroquinone and proceeds with an intramolecular conjugate addition, leading to the desired compounds in moderate yields and enantioselectivities ranging from 92 to 98% (Scheme 1.19).[71]
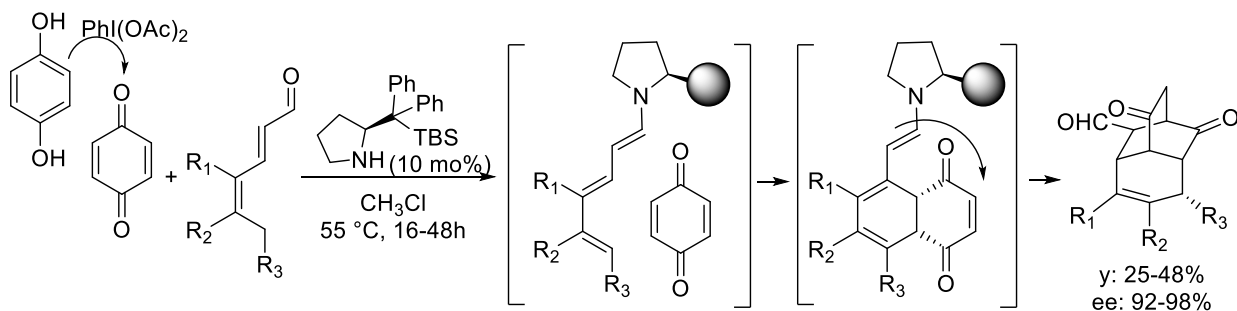
Scheme 1.19

A rather recent example of iminium-iminium cascade was reported by McMillan group. In 2013, they applied this strategy to the first enantioselective total synthesis of (-)-minovincine, referred to as a "biogenetic turntable" between the vindolinine and kopsinine classes of isolates, in nine reactions. The key step is the tetracycle formation promoted and controlled by a chiral imidazolidinone. After a [4+2] cycloaddition between an indole derivative and the chiral iminium ion derived from catalyst condensation with a butynone, an intramolecular Michal-type reaction occurs (Scheme 1.20).[72]
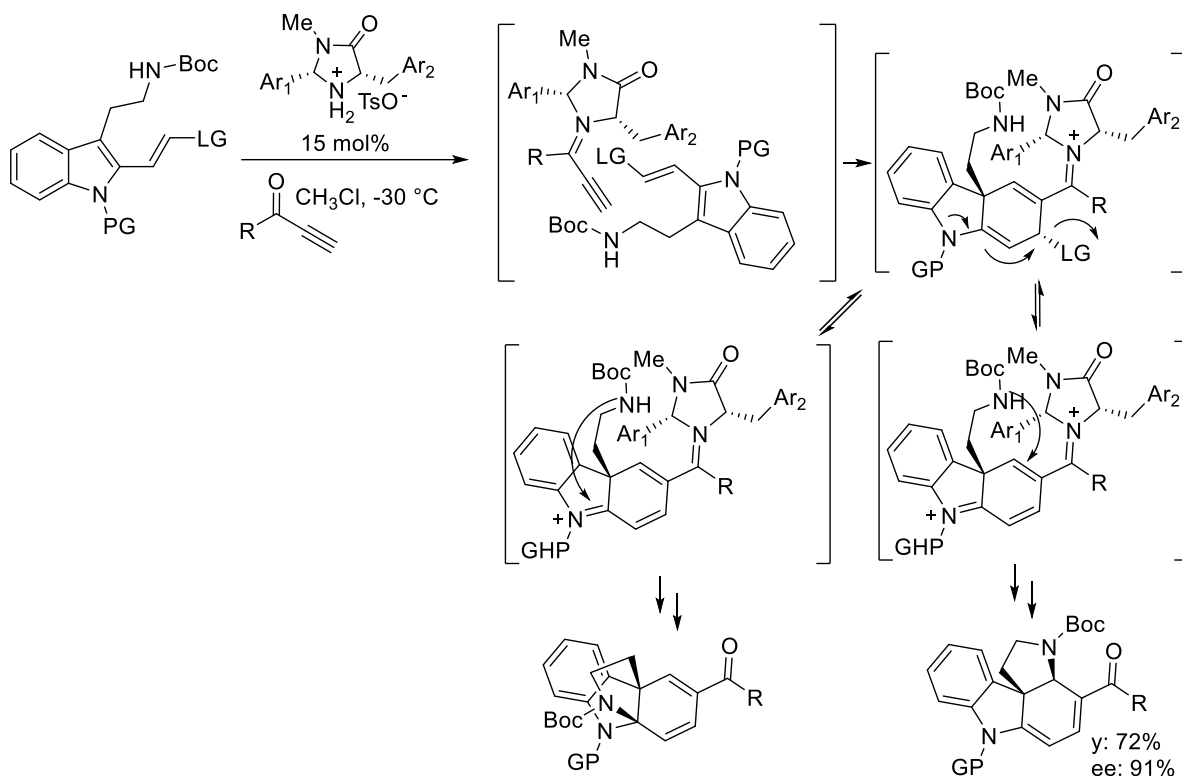
Scheme 1.20

Reactions proceeding through an iminium-enamine activation pathway can be also referred to as *domino reactions initiated by the Michael reaction*. Within this class, it is possible to make a further classification, identifying, among the others, Michael-Aldol, Michael-Michael and Michael-intramolecular heterocyclization rections.[68]

One of the first Michael-Aldol sequence was published in 2000 by Barbas and Bui, who employed proline to catalyse a stereoselective Robinson annulation for the synthesis of the Wieland–Miescher ketone starting from a vinyl ketone and a diketone (Scheme 1.21).[73] The Michael-aldol condensation sequence is initiated by iminium ion formation and completed by enamine promoted 1,2-addition.
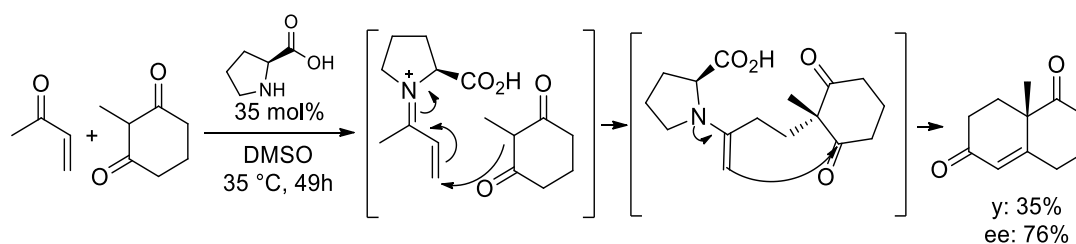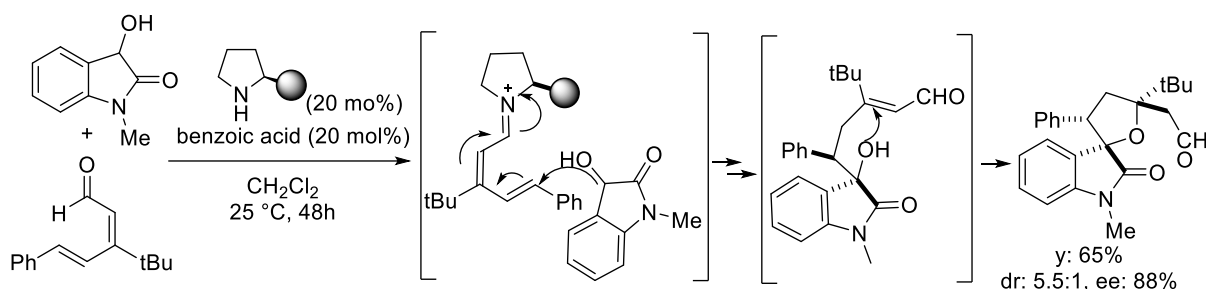

Scheme 1.21

Several examples exploiting this mechanicistic sequence to build new C-C, C-S and C-X bonds have been reported, the most of them employing aldehydes as substrates and proline or prolinol derived catalysts.[69,74]

Melchiorre and co-workers extended this method to the use of 2,4-dienals: thanks to the vinylogous activation of the γ position, the substrate was attacked by a 3-hydroxyl oxindole and tetrahydrofuran spirooxindole derivatives were obtained. High regio- and enantioselection were achieved thanks to a rational design of the substrate, bearing both a sterically demanding substituent on the enal β-position, to block the intermediate iminium ion in a specific configuration, and an aromatic δ-substituent, to avoid trienamine formation (Scheme 1.22).[75]

Scheme 1.22

In 2014, the stereoselective synthesis of chiral pyrrolizine-based triheterocycles was reported by Lee and Cho. In this sequence, the nitrogen atom of 2-(trifluoroacetyl)pyrroles acts as nucleophile towards the iminium ion generated upon condensation between 2-(trifluoroacetyl)pyrroles and the Haiashi-Jørgensen prolinol; the intermediate enamine then attacks the trifluoromethylated carbonyl group. Products were obtained in yields around 70%, >20:1dr and ee exceeding 90%.[76]

In the same year, the Bernardi group applied the same method to prepare 3,4-annulated indoles. Finding substrates with the proper electronic characteristics, where the electrowithdrawing power of C4 substituent was tuned to avoid suppression of the Friedel Craft step and to make the subsequent Michael adition possible, products were obtained in yield of about 75% and ee ranging from 91 to 99% (Scheme 1.23).[77]
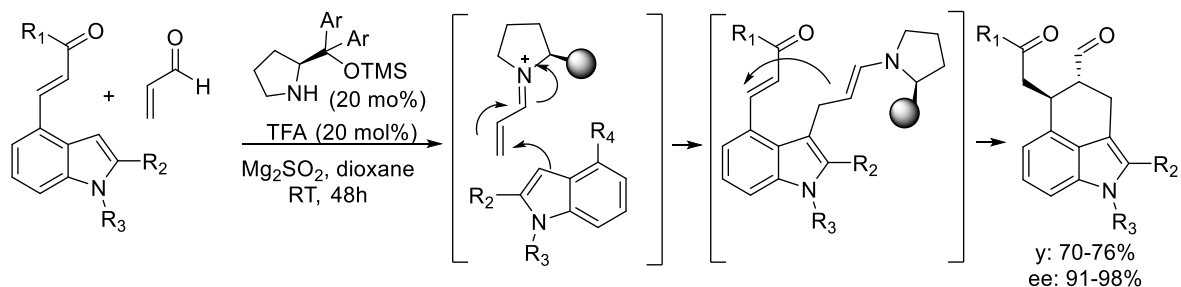
Scheme 1.23

With the massive re-introduction of primary amines from Cinchona alkaloids as organocatalysts, successful functionalization of cyclic ketones through this pathway was achieved: employing hydrogen peroxide, *N*-protected tosyloxycarbamates and bromonitromethane, epoxidation,[78] aziridination[79] and cyclopropanation[80] where performed with good yield and stereoselectivity (Scheme 1.24).
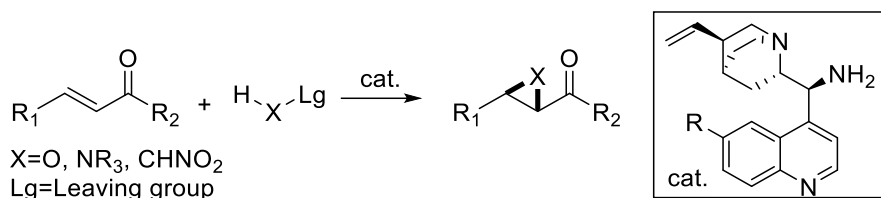
Scheme 1.24

In 2010 Wang et al. exploited this activation mode, to prepare spiroxiindoles from 2-hydroxyl-3-carboxy-indoles and enones.[81] One year after, Cai and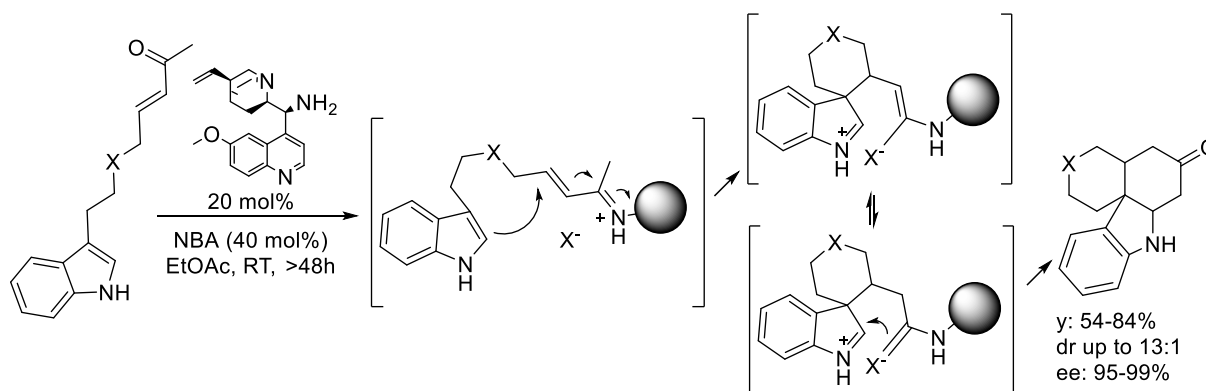 co-workers employed this strategy to build the tetracyclic core of indole derivatives; key to this transformation was the highest reactivity of the less substituted enamine intermediate (Scheme 1.25).[82]

Scheme 1.25

The reverse cascade sequence, i.e. the enamine-iminium one, found one of its first applications to build D-ring construction of indole alkaloids reported by Ohsawa and co-workers: after demonstrating the reactivity of simple ketones as proline-activable nucleophiles towards 9-tosyl-3,4-dihydro-β-carboline, employing 3-butenoneas substrate the initial Mannich reaction was followed by an aza-Michael one . [83]

Further extensions involved the use of different reaction partners,[84] including nitrosobenzene derivatives to achieve new C-N bonds.[85] Three components transformations were also developed: in 2006, Enders group obtained cyclohexane with four stereogenic centre from an enolizable aldehyde, a nitroalkene and an enone. Among the 16 possible stereoisomers, only two were obtained with diastereoselectivity ranging from 2:1 to 99:1 and enantiomeric excess up to 99% (Scheme 1.26).[86]
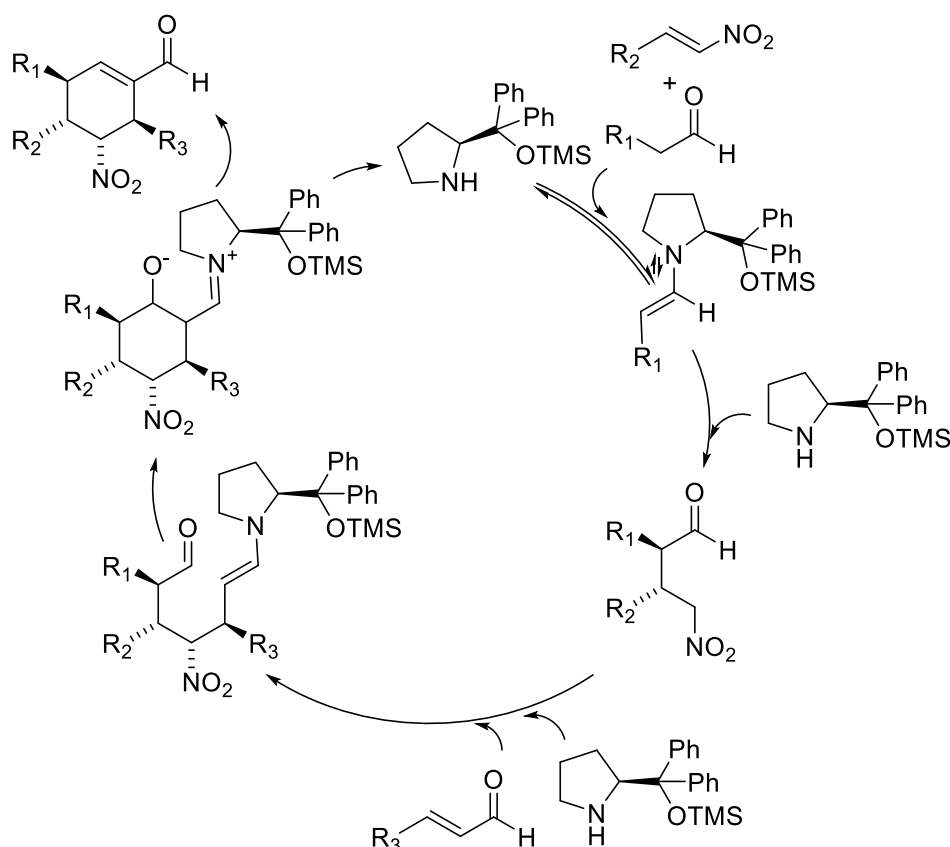
Scheme 1.26

Moreover, thanks to the use of primary amine catalysts, the use of substituted ketones as subtrates was made possible also in this kind of cascade. In particular, employing enones as substrates in combinations with proper Michael acceptors, complex cyclohexanones were obtained with good yield and excellent diastereoselectivity. In these transformations, the iminium ion generated upon condensation between the substrate and the catalysts tautomerizes to the corresponding enamine, prone to intramolecular attack by the electrophile (Scheme 1.27 and Figure 1.19).[87]

Scheme 1.27

dr: 6:1 - 19:1
ee: 94-99%

dr: 9:1 - 19:1
ee: 94-98%

dr: 7:1 - 19:1
ee: 96-98%
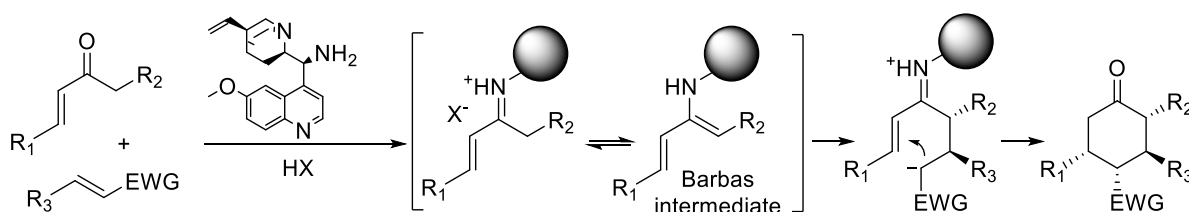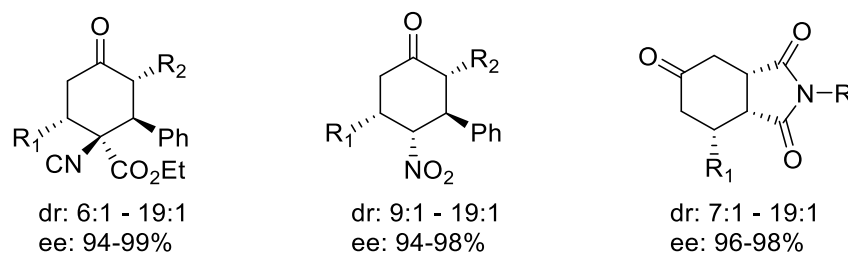
Figure 1.19

When secondary amines were employed to promote this transformation, the final cyclized product featured a different relative stereochemistry and enantioselectivity was quite low (Figure 1.20).
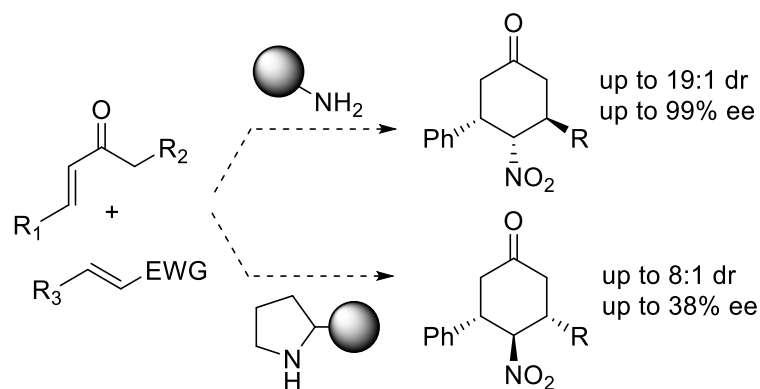
Figure 1.20

Employing unsaturated oxindole[88] and benzofuranone[89] derivatives as starting materials, spirocyclic compounds were obtained in moderate to good yields and up to 98% enantiomeric excess.

As already mentioned, these sequences have been "elongated" so that even three and four consecutive steps can subsequently take place. Products are typically obtained with complete enantioselectivity and excellent diastereoselection, not just because of the effectiveness of the catalyst in directing the reaction, but also thanks to the conformational and steric bias characterizing the typically quite rigid and highly substituted structures of the obtained products.

1.4. <u>Hydrogen bonding organocatalysis</u>

Parallel to aminocatalysis, catalytic systems based on non-covalent bonds have been largely developed and finely modified in their electronic and steric properties, to guarantee strong interactions with the substrates and to create the proper steric environment to host a specific reaction. Due to the central role that non-covalent interactions hold in a wide variety of fields, including pharmaceutical design, supramolecular chemistry, molecular biology, sensing applications, materials and crystal engineering, lots of studies have been devoted to their elucidation and quantification.

As already stated in the first Section, several activation strategies are based on this concept, including non-covalent catalysis via phase transfer, Brønsted acids and bases, Lewis bases and hydrogen-bonding. Herein, we wish to give a deeper insight into hydrogen-bonding catalysis, especially focusing on the role of (thio)urea derivatives.

1.4.1. <u>Thiourea based hydrogen bonding catalysis</u>

The original recognition of (thio)urea as a bidentate hydrogen bonds donor catalysts dates back to seminal study by Hine and co-workers started in 1984.

From the X-ray structure of the isolated (1,8-biphenylenediol)-1,2,6-trimethyl-4-pyridone complex (Figure 1.21), the authors observed that both acidic protons were engaged in strong hydrogen bonds with the same basic atom.[90] As this was one of the few existing examples of such well defined interactions, they pursued on the topic, and thus prepared differently substituted biphenylenediol, studied acidity properties[91] and employed them as catalysts. Investigating diethylamine addition to phenyl glycidyl ether, they observed that the striking higher catalytic activity of their diol was not only due to pK_a value, but also and most importantly to the double coorination (Scheme 1.28).[92]

Figure 1.21

	pKa	Krel
R=Me	9.15	1.2
R=H	8.00	12.5
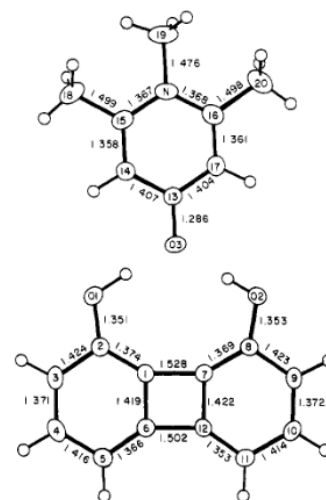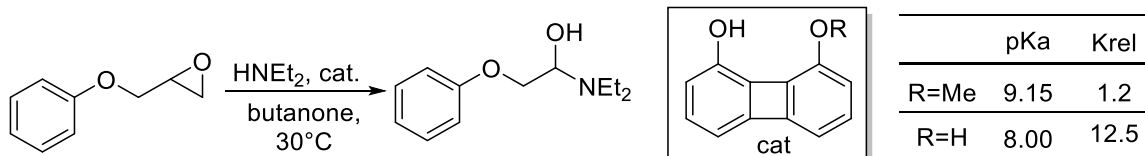
Scheme 1.28

Further evidences on the effectiveness of double hydrogen bonding activation subsequently came from Ekkundi group, who hypotetized double hydrogen-bond donation by biphenylenediol derivatives promoting Diels-Alder reactions,[93] and by Curran and co-workers, who were the first to use urea derivatives. Indeed, inspired by Etter observations about hydrogen bonds between *N,N'*-diarylureas and a variety of Lewis basic functional groups, they run allylation of cyclic α-sulfinyl radicals[94] and Claisen

rearrangement[95] in the presence of symmetric aryl urea derivatives noticing in both cases a rate acceleration effect.

Switching the main focus from ureas to thioureas, introduced as effective catalysts by Curran and recognized by Jacobsen to be superior with respect to urea ones in a systematic study on hydrogen-bonding directed stereoselective cyanation of imines,[96] Schreiner group undertook computational and NMR studies to give an evident demonstration about their activation mode.[97] Subsequently, a systematic study was carried out screening the activity of a large number of thiourea derivatives endowed with both alkyl and aryl, electron rich and poor *N,N'*-substituents, in promoting Diels-Alder reaction between cyclopentadiene and methyl vinyl ketone. It resulted that the thiourea-carbonyl complexation constant mainly derived from entropic effect; so, the more rigid the catalyst itself, the smaller the entropic penalty upon complexation (Figure 1.22). Thiourea derivatives almost completely displaced urea ones, due to their easier synthesis, higher solubility and lower tendency to auto-association.[98]
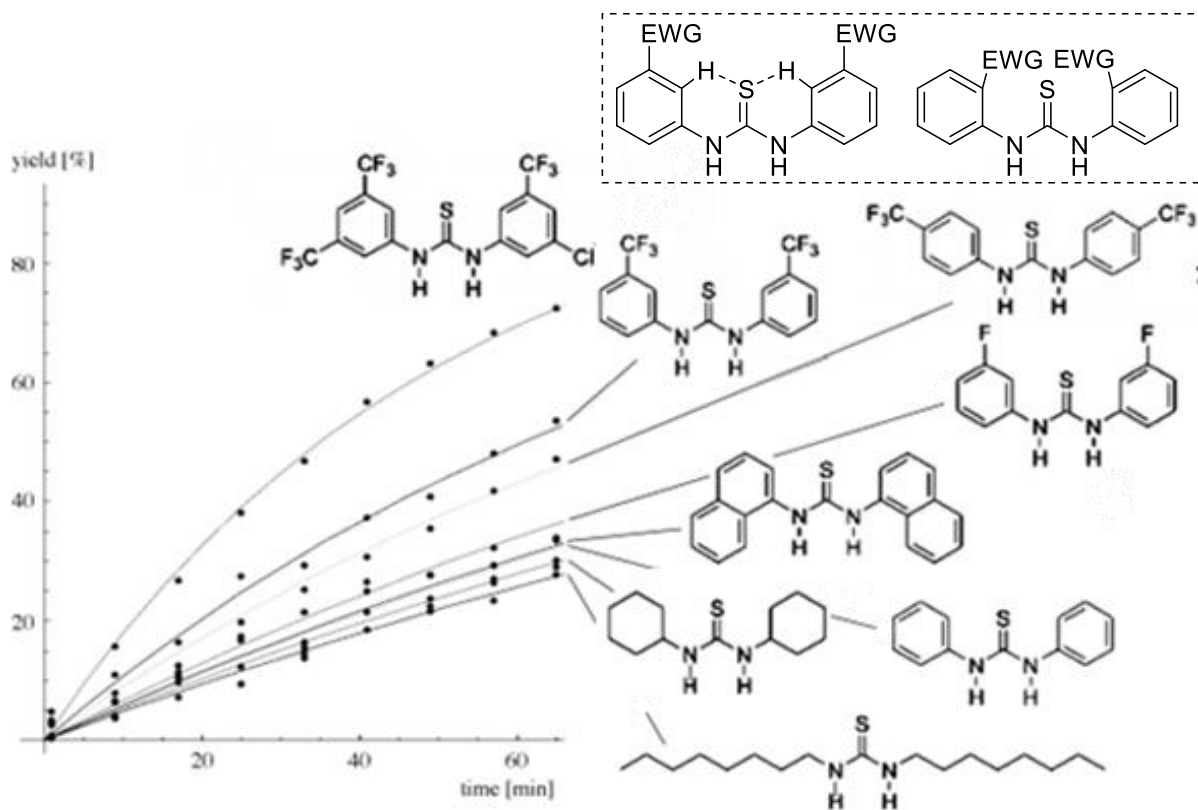

Figure 1.22 – adapted from *Chem. –Eur. J.,* **2003**, *9,* 407-414

Subsequent studies have been focused on the role of the 3,5-bis(trifluoromethyl)phenyl group, which has a deep influence on the electronic features of the catalysts.(Figure 1.23).

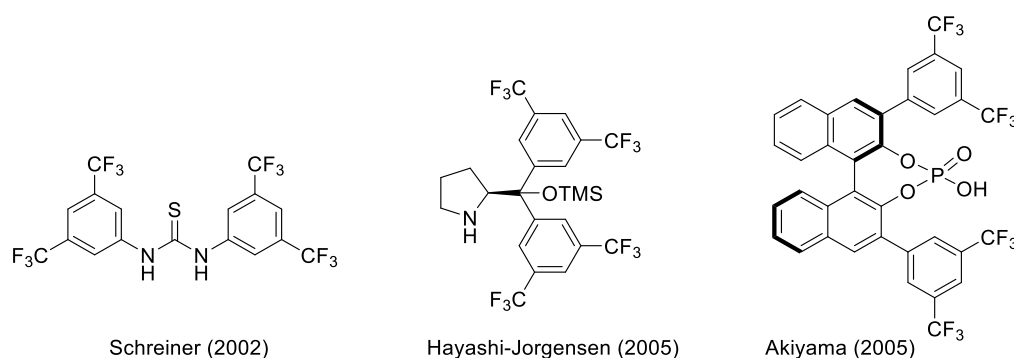Schreiner (2002)   Hayashi-Jorgensen (2005)   Akiyama (2005)

Figure 1.23

Catalysts containing these residues are typically more effective than the non-trifluoromethylated counterparts, a fact that has been rationalized considering that the 3,5-bis(trifluoromethyl)phenyl moiety can increase catalyst polarity, polarizability, acidity and π–π interactions. In particular, increased NH proton acidity and its beneficial effect on substrate coordination and, consequently, on reaction rate, were demonstrated in a physical organic study by Cheng group in 2010.[99] Two years later, Jakab and co-workers adopted a spectrophotometric method to establish the pK_a value of a

Figure 1.24

wide range of thiourea-based organocatalysts in DMSO. Due to their strong σ-electron withdrawing ability, each CF$_3$ group decreases the pK_a by approximately 1.2 units (Figure 1.24).[100] Moreover, the occurrence of CH−π stacking interactions between the "acidic" proton *ortho* to the CF$_3$ group and an aromatic ring of the coordinated substrate was demonstrated by two-dimensional NMR experiments and computational studies on a thiourea-benzoic acid complex.[101] The important role of the polar *ortho*-CH moiety, engaged in interactions with Lewis basic sites was demonstrated with low-temperature NMR and IR analysis, and supported by DFT calculations: in the presence of tetrahydropyranone, NH and *ortho*-CH proton NMR signals were strongly shifted down-field , and in the ^{19}F spectrum a coupling with proton next to the ring oxygen was detected; in addition, lactame bands in IR spectrum resulted redshifted (Figure 1.25).[102]
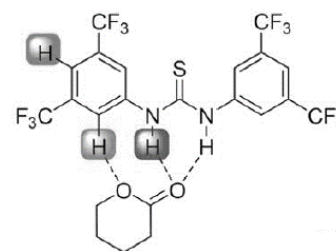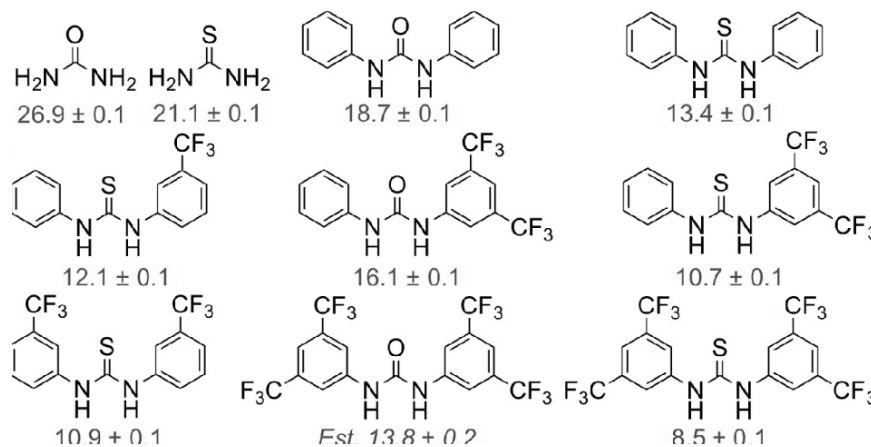

Figure 1.25 – adapted from *Org. Lett.* **2012**, *14*, 1724–1727

Even though maybe less apparent than interaction with Lewis bases, anions coordination by (thio)ureas are also significant. Once again in line with Nature systems, chemists designed molecular cages based on (thio)urea functionalities and took advantage of the formation of these (thio)urea-anion complexes to design catalytic reaction.[103] The hydrogen bonding ability of thiourea to oxyanions has been first demonstated by mechanicistic studies on carbonyl compounds acetalization, which was proved to proceed not through C=O activation but rather through orthoester heterolysis assisted by the catalyst. (Scheme 1.29).[104] Later on, Schreiner and Kotke applied this method to the thiourea catalyzed tetrahydropyranylation (THP-protection) of hydroxyl functionalities. In this reaction, the catalyst loading can be lowered from 1 to 0.001 mol%.[105] Several other reactions were based on the RO^--thiourea complexation, as addition of aliphatic amines, thiophenol and alcohols to epoxides; in addition, other anions, such as alides, cyanide, carboxylate, nitronate and enolates, revealed to be suitable for (thio)urea coordination.
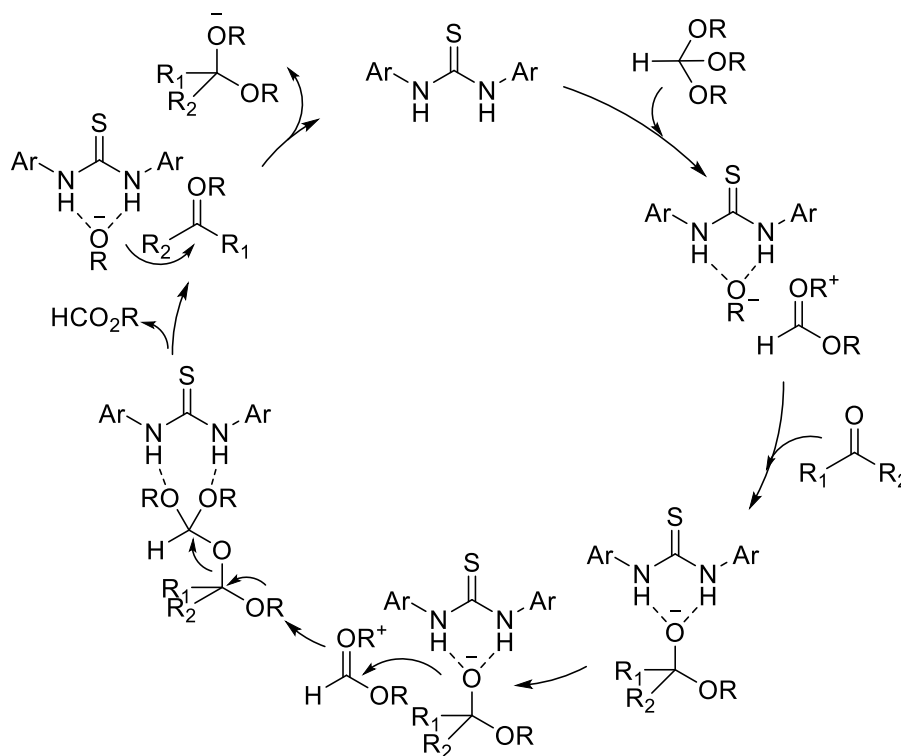
Scheme 1.29

Thus, given the high efficiency of these non-covalent interactions and, in particular, considering the activity of *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea, this molecule has been employed to promote a large variety of transformations. These include, besides those just mentioned, Friedel–Crafts alkylation, nucleophilic addition to nitrones, Baylis–Hillman reaction and reductions of aldimines and nitroolefines, recently reviewed by Zhang, Bao and Xing.[106]

In alternative approaches, acidifying groups different from the 3,5-bis(trifluoromethyl)phenyl one were evaluated. Jones, Pantos, Morrison, 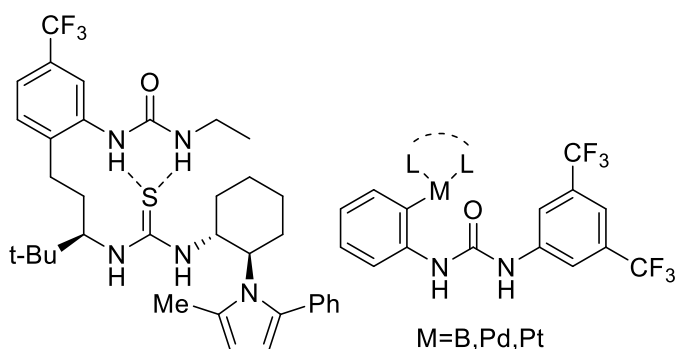and Smith achieved thiourea activation through internal coordination by urea,[107] while Mattson and co-workers introduced transition metals as substituent at the *ortho*-position of the aniline ring, thus being well directed to accept urea oxygen electron pair (Figure 1.26).[108] This group reported the application of such hybrid catalyst for the double α-arylation of nitrodiazoesters.[109]

Figure 1.26

Moreover, in the same decade asymmetric thiourea-based catalysts have been designed and employed to promote *stereoselective reactions*. First examples were reported by Jacobsen who, outside the main trend, employed a thiourea with *N,N'*-dialkyl substitutens, namely a *tert*-leucine and a diaminocyclohexane derivatives, to promote a stereoselective Strecker (Scheme 1.30) and acyl-Pictet–Spengler reaction.[110]
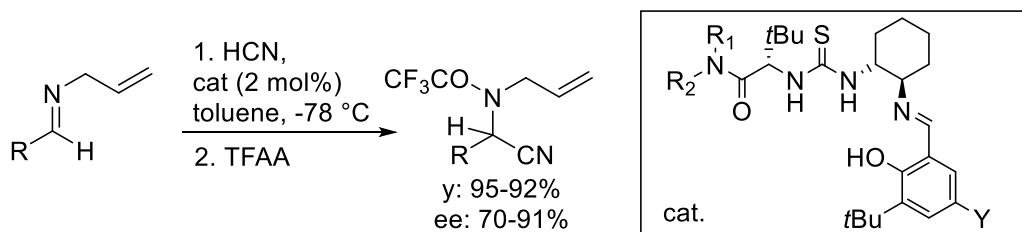
Scheme 1.30

1.4.2. Bifunctional catalysis

Considering the lability of hydrogen bonds, it is necessary that additional cooperative interactions take place between the catalyst and the reaction partners, so that the transformation can proceed through a transition state rigid enough to enclose reaction partners in the chiral environment created by the chiral catalyst. This issue has been discussed by Knowles and Jacobsen in 2010: presenting four model examples, they demonstrated the importance of multiple non-covalent interactions for the catalyst to achieve high stereoselection.[111] In this paper, cationic cyclization and Strecker reactions are reported as examples of thiourea catalysed transformations. Studying the enzymatic system that promotes olefins sequential additions to carbocations, the authors developed thiourea derivatives featuring an extended π-system to coordinate the cationic reactant and observed enantioselectivity increasing with increasing size of the aryl system (Scheme 1.31).[112] For the Strecker hydrocyanation, the catalyst of choice was endowed with an amino acid derived moiety, whose carbonyl group was actively involved in hydrogen bonds with the acidic proton of HCN.[113]
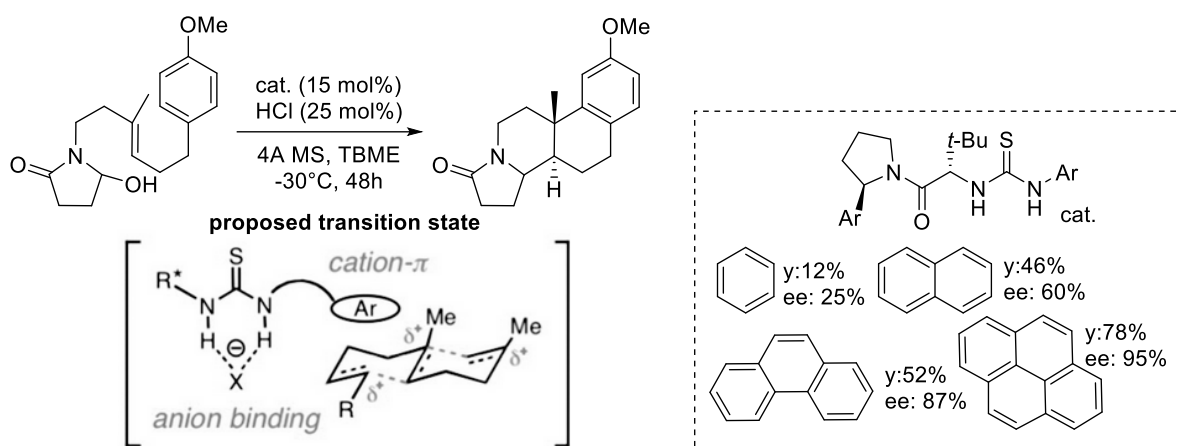
Scheme 1.31

The need for simultaneous interactions occurring to obtain a more rigid transition state thus enhancing enantioselection was the concept leading to the development of *polyfunctional organocatalysts*. Indeed, the idea of bifunctial catalyst was specifically defined when Lewis basic functional group was introduced along with hydrogen-bond donors within the same structure.

The first example in this direction was reported by Takemoto and co-workers in 2003, when they proved that it was necessary to employ a catalyst featuring both the *N*-3,5-bis(trifluoromethyl)phenyl thiourea and the *N,N;*-dimethyl diaminocyclohexane to obtain high activity and stereoselectivity in the diethymalonate addition to nitrostyrene (Scheme 1.32).[114] The hypothesized simultaneous activation of both reaction partners was first supported by the catalyst X-ray structure, showing that amino groups and thiourea N–H orient towards the same direction.
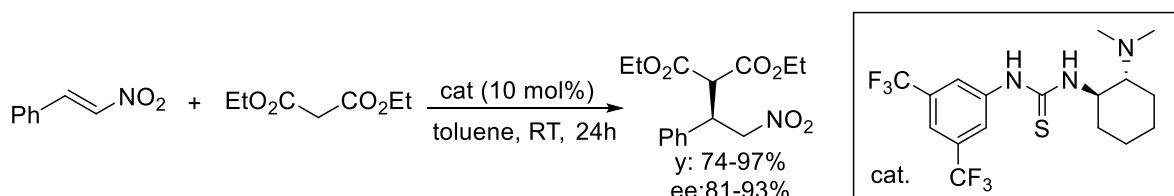
Scheme 1.32

Three years later, Papai's group undertook a detailed computational analysis on the addition of acetylacetone to nitrostyrene, promoted by Takemoto's catalyst, to define transition states through which the reaction proceeds. First, a conformational analysis on the catalyst itself was performed, showing that the conformation corresponding to that found in solid state is indeed more stable among the possible others, even if for just a few calories; so, it was considered likely that, in solution, the catalyst exists in equilibrium among severe conformers. Subsequently, catalyst coordination to each of the two reaction partners was evaluated separately, revealing that both nitrostyrene and acetylacetone coordinate through double hydrogen bonding to the thiourea group, and that the latter lays on a plain that is perpendicular to that of the catalyst; besides, enol coordination revealed helpful for enolate formation through deprotonation by the tertiary amine. Two different reaction pathways were then evaluated, depending on which reaction partner was coordinated to the thiourea moiety and which to the protonated amine (Figure 1.27). According to calculations that identified the C-C bond formation as the

rate determining step, both are feasible, but the one proceeding through enolate-thiourea coordination was slightly preferred.[115]
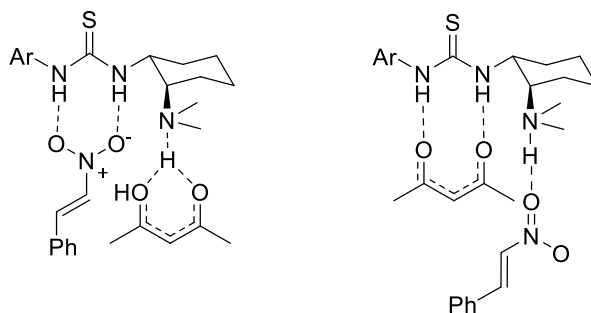
Figure 1.27

The same catalyst was then employed to promote malononitrile addition to unsaturated imides, Mannich reactions, and even polimerization. In addition, in 2005 Berkessel developed a dynamic kinetic resolution of racemic azalactones though allylic alcohol addition, where thiourea coordination to the substrate was demonstrated by ^{1}H NMR and control experiments with different catalysts confirmed the importance of bifunctionality.[116]

In the six years following Takemoto's breakthrough, [117] new model structures were developed by the groups of Nagasawa,[118] Soós[119] Dixon[120] and Connon,[121] Wang[122] and Jacobsen,[123] based not only on diaminocyclohexane but also on quinine and binaphtyl chiral scaffolds (Scheme 1.33).[124]
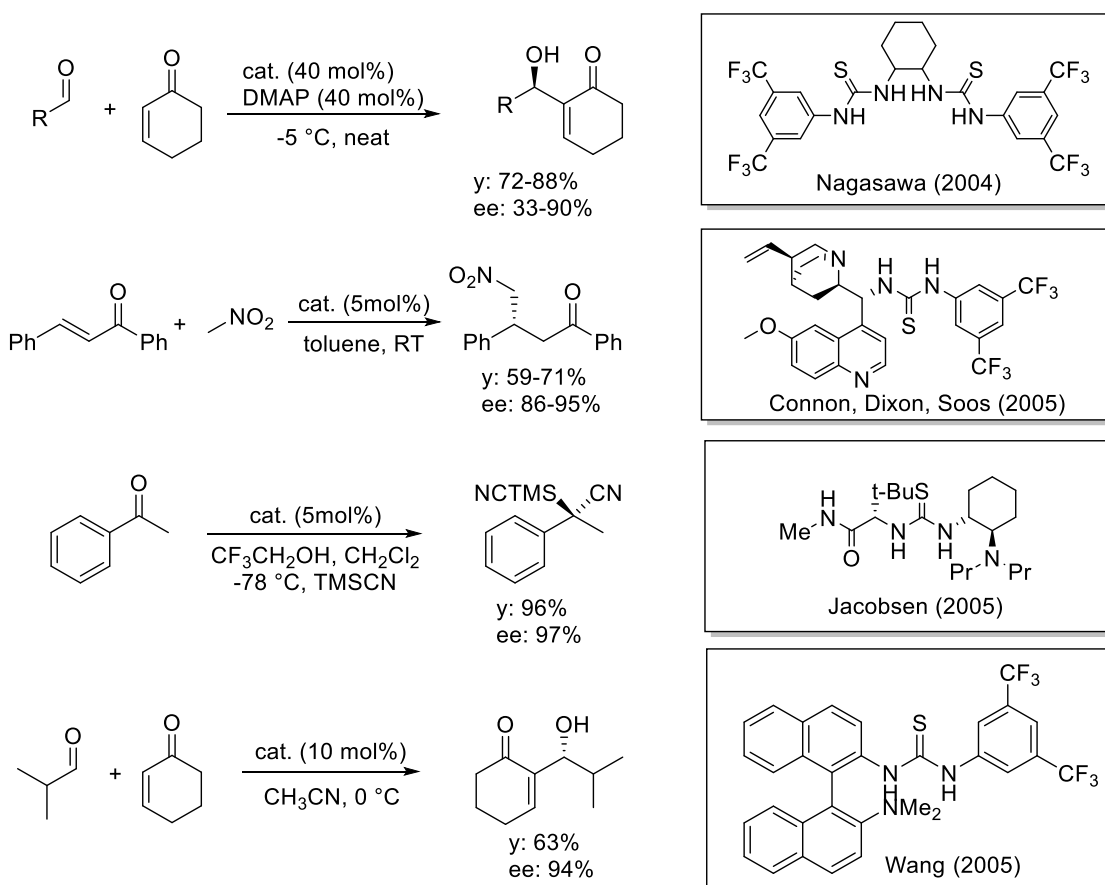
Scheme 1.33

Thanks to high robustness, versatility and high functional groups tolerance, these catalysts, possibly tailored considering ad-hoc specific requirements, found interesting applications. In particular, Cinchona alkaloids-thiourea derivatives have been successfully employed in a large variety of transformations, including domino processes;[125] the tens of reactions reported have been recently reviewed.[126] Theoretical calculations have been performed to elucidate the mode of action of these catalysts: DFT investigations on nitromethane addition to chalcone revealed that the reaction proceed through a three membered intermediate where the deprotonated nucleophile is coordinated by the thiourea moiety and the electrophile by the quinuclidine NH^+ group.

Citing just the most recent contributions, in 2014 Kaur et al. employed Cinchona alkaloids derived thioureas in the Friedel-Craft addition of phenols to isatine derivatives; coordinating both reaction partners, the catalysts affords the desired 3-hydroxyl-oxyndoles in about 80% yield and with enantiomeric excess ranging from 70 to 92%.[127] In 2015, Pang group developed a three-component cascade reactions of isatins, malononitrile and 2-hydroxynaphthalene-1,4-diones providing pyranonaphthoquinone fused spirooxindoles; the products were obtained in high yield and enantioselectivity. The reaction scope, however, could not be extended to β-keto nitriles. A detailed reaction mechanism was proposed, involving uncatalyzed condensation between malonitrle and isatin, followed by the simultaneous coordination of this intermediate by the thiourea group and establishment of a hydrogen bond between the teriary amine an the OH group of hydroxynaphthalene-1,4-dione (Scheme 1.34).[128]


y: traces-99%
ee: 81-97%
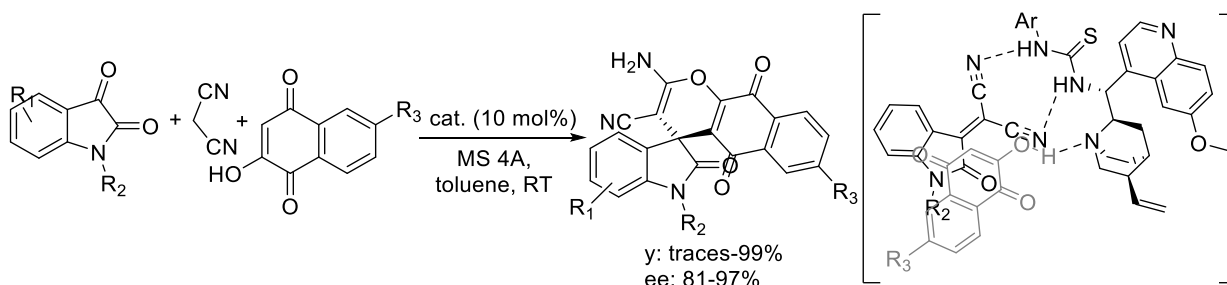
Scheme 1.34

Xu group reported a cascade reaction, involving the formation of three new bonds, for the synthesis of chromeno[4,3-b]pyrrolidines. With low catalyst loading (1 mol%) and in short reaction time (from 45 minutes to 5 hours) products were obtained in almost quantitative yield, >20:1 diastereoselection and 99% ee (Scheme 1.35).[129]
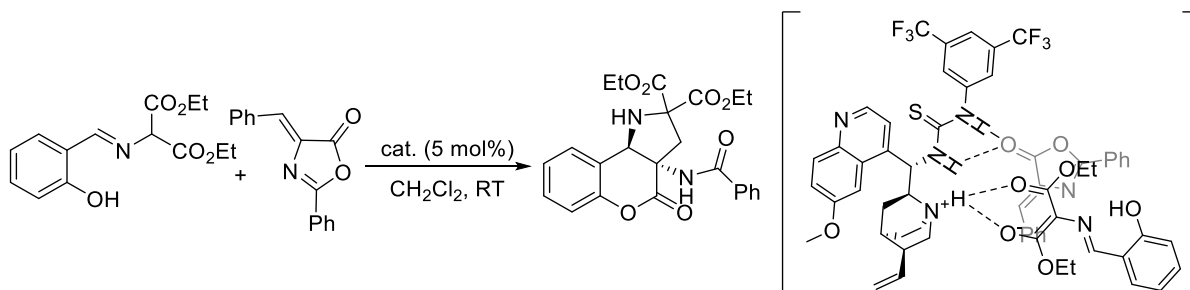
Scheme 1.35

The same catalyst was employed in 2015 by Huang and co-workers to promote substitution of 3-(1-tosylalkyl)indoles with oxindoles as key step in the total synthesis of (+)-Trigolutes B,[130] and by Bai et al. for the 1,4-addition of nitroalkanes to 2-furanones.[131] In a report by Das et al. the corresponding urea based catalyst promoted the Michael addition of nitrostyrene to 3-ketoprolines in ee ranging from 86 to 94% and good yield.[132] In the same period, Guang et al. showed that, thanks to bidentate hydrogen bonding coordination, *S*-phenyl thioesters can be deprotonated by quinuclidine group and attatck *N*-tosyl imines with high diastereo- and enantioselectivity; the best catalysts proved to be those where the (thio)urea group was grafted on the quinoline ring at C6' position (Scheme 1.36)[133]
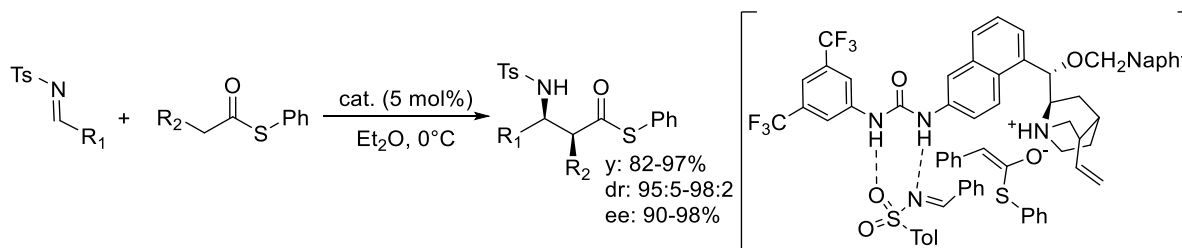
Scheme 1.36

In addition, thiourea-quinidine allowed stereoselective carbon-heteroatom bond formation.

Very recently, Matsubara group developed the formal hydration of γ-hydroxy-α,β-unsaturated carbonyl compounds with formaldehyde as oxygen-centered nucleophile; the reaction proceeded with good yield but moderate (ca. 70%) enantioselectivity.[134]

The authors besides used the urea derivative to obtain almost enantiopure isoquinoline *N*-oxides, in the first application of bifunctional organocatalysis to biaryls desimetrization by the introduction of a stereogenic axis (Scheme 1.37).[135]
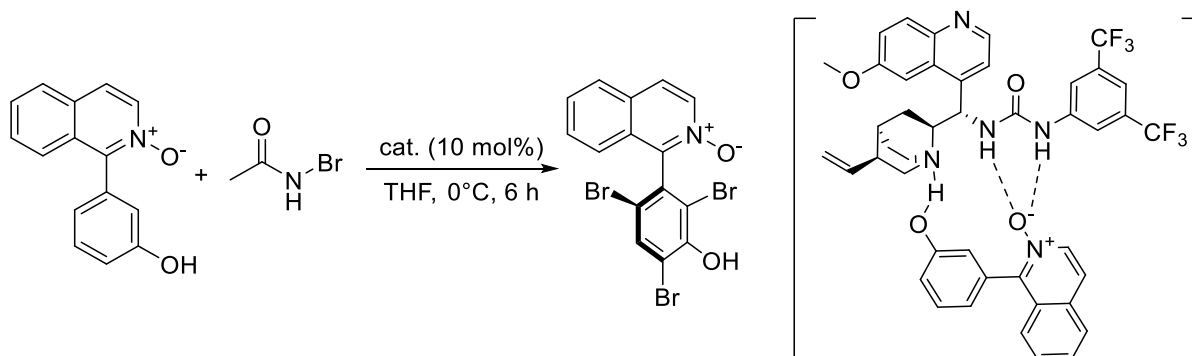
Scheme 1.37

Other bifunctional organocatalysts have been designed, featuring different chiral skeletons, as that of natural amino-alcohols[136] and sugars.[137,138] In 2014, Wang and co-workers employed an L-leucine-quinidine-thiourea catalyst for the sulfur-Michael addition of thioacetic acid to nitroalkenes with wide reaction scope and high yield, in up to 70% ee.[139] More recently, Ričko et al. synthetized a new class of bifunctional catalysts where a tertiary amino group is installed in different positions of a camphor moiety,[140] while Bharti and Parvin reported a new achiral thiourea derivative to promote the three component reaction of an aldehyde, 1,3-dimethyl-6-aminouracil and 2-hydroxy-1,4-naphthoquinone.[141] Serrano employed BINAM-bisthiourea catalyst in the highly enantioselective addition of a

formaldehyde hydrazone to aroyl and heteroaroyl phosphonates, leading to densely functionalized diazenes.[142]

Also for bifunctional structures the possibility of activating the thiourea function with groups other than 3,5-bis(trifluoromethyl)phenyl was investigated. After studies by Ellman and co-workers on the electron-withdrawing effect provided by the *N*-sulfinyl group, the suitability of *N*-sulfinylurea as bifunctional organocatalyst was evaluated in the aza-Henry reaction.[143] Subsequently, high enantioselectivity was reached in the addition of thioacids to nitrostyrene modulating the steric hindrance of sulphur substituent (Scheme 1.38).[144]
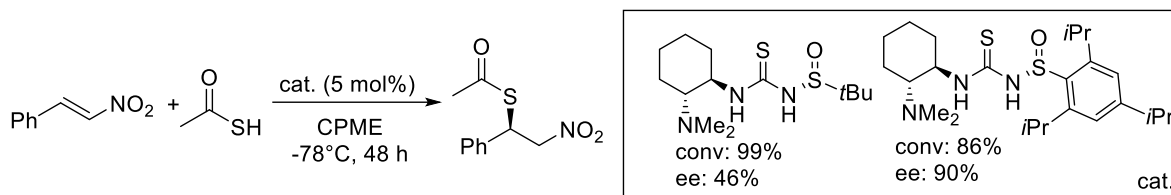
Scheme 1.38

With the aim of activating the (thio)urea group through functionalities other than 3,5-bis(trifluoromethyl)phenyl, internal Börnsted and Lewis acid assistance was 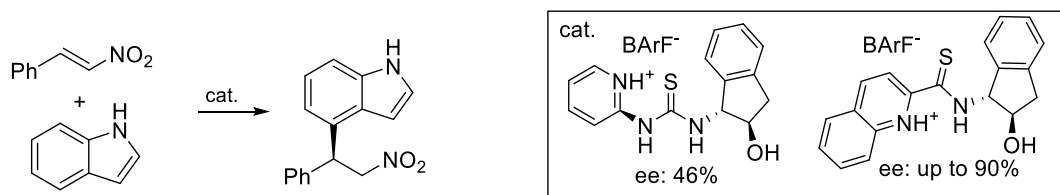explored. For instance, Siedel group installed a pyridiunium moiety, but obtained a significant improvement in the catalyst performance only when passing from thiourea to thioamide (Scheme 1.39).

Scheme 1.39

In further experiments, structures combining organocatalytic moieties working through covalent and non-covalent modes have been developed, outlining a slightly different concept of dual catalysis. In fact, catalysts embodying both a thiourea group and a secondary and, subsequently, primary amine were introduced, so that one reaction partner is activated though hydrogen bonds by the catalyst, simultaneously condensed with the other one.

Xiao group started an extended research program with the goal of developing new catalysts to achieve high stereoselectivity in aldol and Michael condensation. The leading idea was to create structures simultaneously operating through enamine and hydrogen bonding modes, thus simultaneaously activating both reaction partners. A systematic otpimization study was carried out so that the catalyst structure was optimal for each specific couple of substrates. So, depending on the branching level of the carbonyl compound a primary or secondary amine functionality was chosen, belonging to an unprotected diamino cyclohexane or to a pyrrolidine-derived moiety, respectively; hydrogen bond donors other than thiourea, including amide and sulfamide, were tested (Scheme n, selected examples).[145]
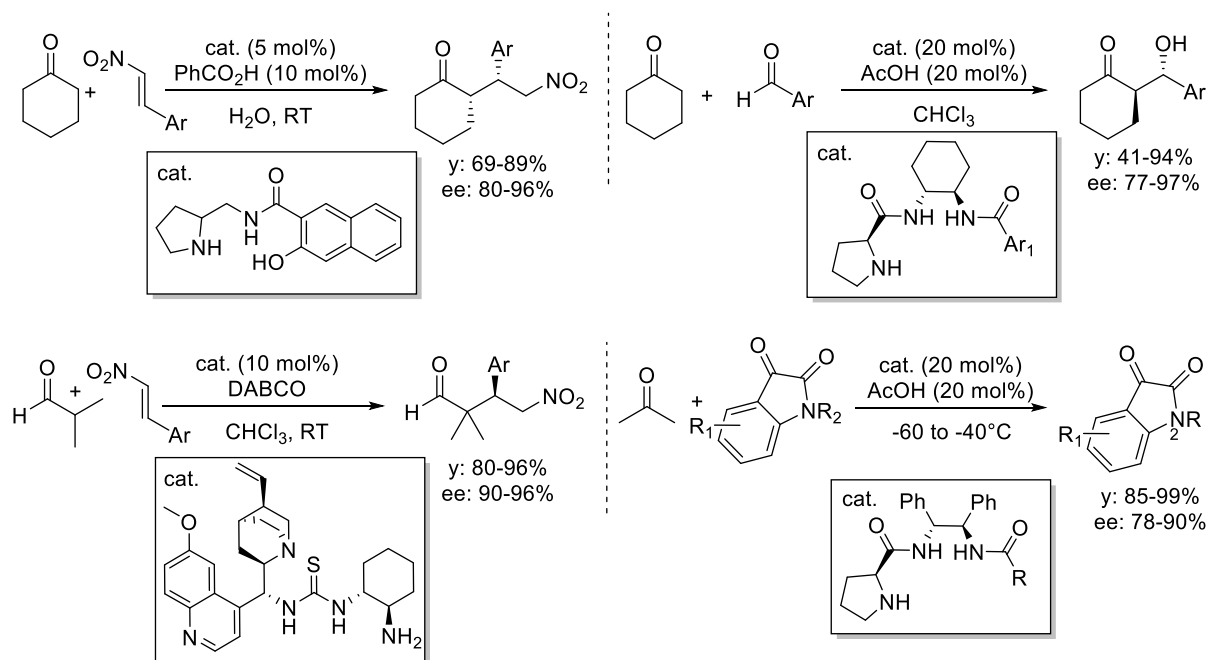
Scheme 1.40

Meanwhile, several groups focused on designing new bifunctional catalyst featuring free NH_2 group, being aware of the emerging potentiality of primary amines especially in the activation of hindered ketones. Thanks to the ready availability of chiral scaffold endowed with primary amine functionality, a wide variety of catalysts arose from the combination of these scaffolds (Figure 1.28, selected examples).[146]
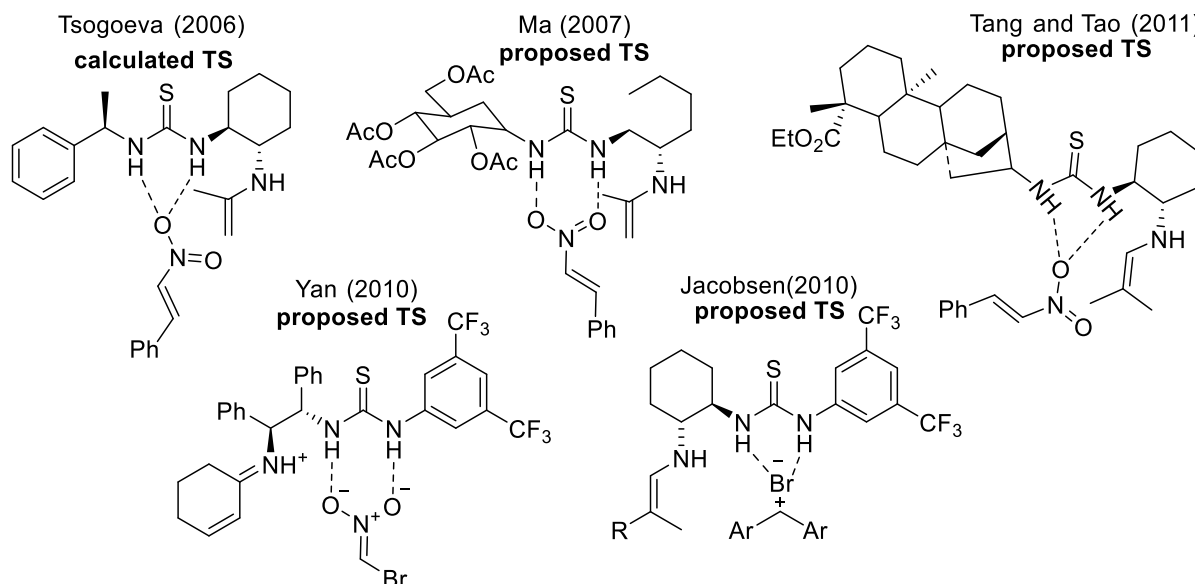
Figure 1.28

In particular, Tsogoeva developed 1-aryl ethylamines based catalysts for Michael addition,[147] while Jacobsen[148] demonstrated that a simplified version of his previously reported amino acid-diaminocyclohexane structure was also highly effective for this transformation. In 2007, Ma and co-workers prepared a new of class primary amine-thiourea catalysts based on saccharides and successfully employed them to promote the conjugate addition of aryl methyl ketones and cyclic ketones to styrenes

and phenyl nitrodiene.[149] Analogous results in this reaction were obtained with catalysts developed by the group of Wang in 2009, which were based on dehydroabietic amine; in this case, high yield and ee were achieved when branched ketones and amines were employed as nucleophiles. Besides nitroolefines, also enones proved to be suitable electrophiles for thiourea-promoted addition; in fact, despite being monodentate hydrogen bonding acceptors, they are effectively coordinated by the catalyst and reactions proceed with good stereocontrol. In a kind of reversed approach, Yan group performed high stereoselective cyclopropanantion of cyclohexenone with bromonitromethane through iminium ions activation. In 2013, Bastida and co-workers exploited a primary amine bifunctional catalyst for dienamine activation, promoting the vinylogous Michael addition of 3-methyl 2-cyclohexenone to α-keto esters.[150] Based on the anion-recognition abilitites of thiourea group, stereoselective α-alkylation of α-branched aldehydes and cyclizations have also been reported.

Taking advantage of the multifunctional nature of these catalysts, domino reactions have also been developed. In 2009, Xu and co-workers obtained 3-nitro-1,2-dihydroquinolines in up to 70% yield with up to 90% ee through a Michael-Henry cascade between 2-aminobenzaldehydes and nitroolefins.[151] In 2013, the Wang group reported a stereoselective Michael-cyclization sequence occurring with up to 90% ee.[152]

Also in the field of primary and secondary amino-(thio)urea catalsts, evolution never stopped and novel structures were continuously designed and tested. In 2015, He et al. synthetized the first diarylprolinol-thiourea catalyst (Figure 1.29), capable of promoting the conjugate addition of linear aldehydes to

Figure 1.29

nitrostyrene in up to 99% yield and 99% ee and with good diastereoselection (about 70:30).[153]
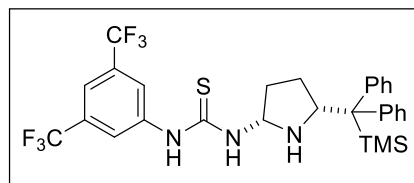
In addition to amines and hydroxyl groups, also phosphine functionalities have been associated to the thiourea one. The first example was reported in 2007 by Shi and Shi, who developed novel (thio)urea-phosphine derivatives based on an enantiomerically pure binaphtyl scaffold, for the stereoselective Morita-Baylis-Hillman reaction, proceeding with good enantioselectivity (ee up to 90%) in the presence of an acid co-catalyst. On the basis of NMR studies, a mechanicistic model was proposed involving phosphorus attack onto the double bond generating a zwitterionic species kept in a rigid conformation through hydrogen bonds (Scheme 1.14).[154] Higher enantioselectivity was then obtained by Yuan et al. with (thio)urea-phosphines featuring the diaminocyclohexane skeleton.[155]
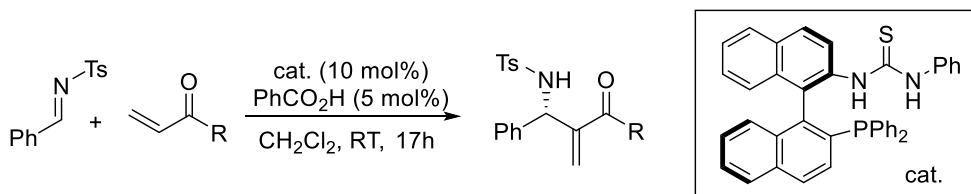
Scheme 1.41

In 2015, the same group employed this catalyst in the intramolecular Rauth-Currier transformation, affording two regioisomers in up to 99% ee (Scheme 1.42).[156]

y: 46-98%; ee: 70-99%
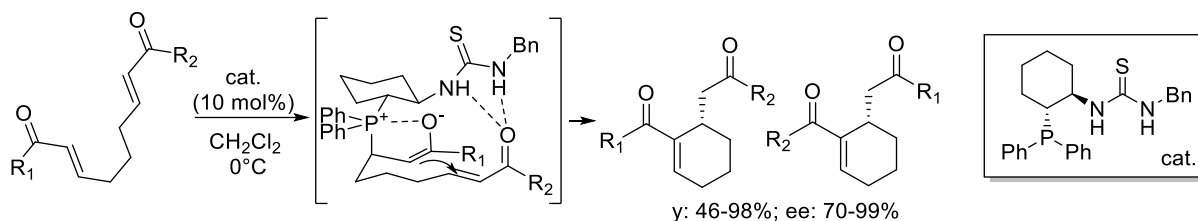
Scheme 1.42

Notably, in 2015 Schaufelberge and Ramström developed a dynamic combinatorial system to identify the best new bifunctional catalysts for a given reaction. Specifically, the authors evaluated the activity of catalysts which self-assembled in solution through the formation of an imine bond; so, they set up a catalytic system constituted by different aldehydes and primary amines, which were able to equilibrate generating all possible combination of catalysts structures (Scheme 1.43), to promote a Morita-Baylis-Hillman reaction. The identity of the best catalyst was uncovered through a dynamic deconvolution process, replacing potentially active components by inactive species.[157]

Ar=3,5-(CF$_3$)-Ph; X=H, NMe$_2$, PPh$_2$
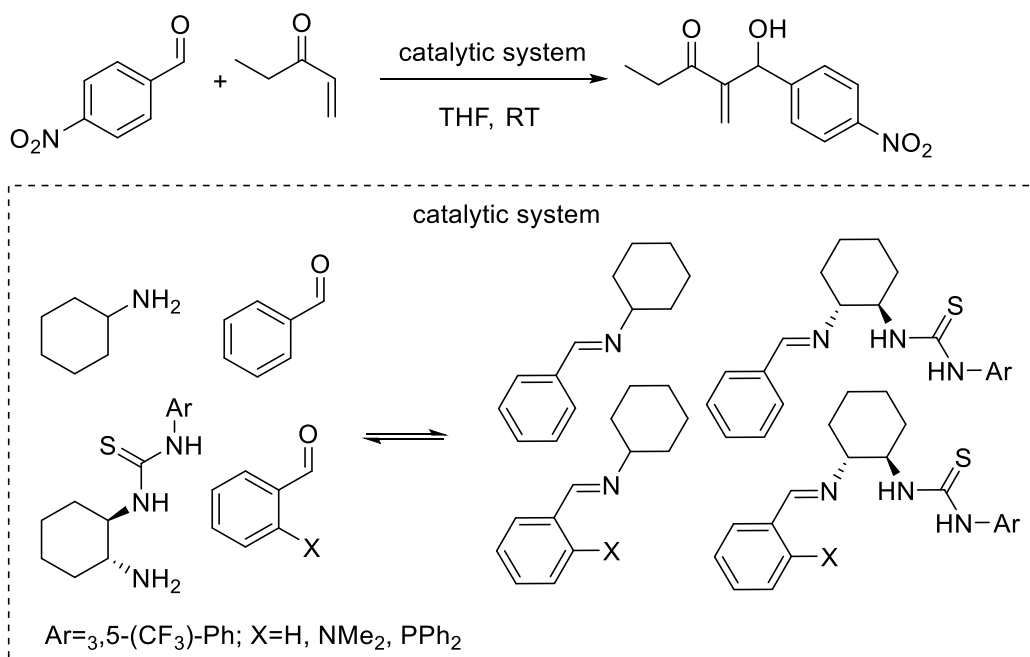
Scheme 1.43

The concept of bifunctional catalysis developed in the design of novel motifs able to engage an increasing number of weak interactions.[158]

The improved results reachable through this approach were demonstrated by Wang group, developing new diaminocyclohexane-thiourea derivatives featuring a further hydrogen bond donor group. While Takemoto's thiourea afforded the addition product between acetylacetone and nitrostyrene in 80% yield and 89% ee after 1 hour, the new catalyst, where a diphenylethenediamine moiety replaced the 3,5-bis(trifluoromethyl)phenyl one, achieved 97% yield and 93% ee in half the time; a further improvement in enantioselectivity was gained introducing a $NHSO_2Ar$ residue, able to establishe stronger interactions with the highly acidic NH proton. (Scheme 1.44)[159] Thanks to this catalyst, activation of less acidic α-aryl ketones was also possible and sulfa-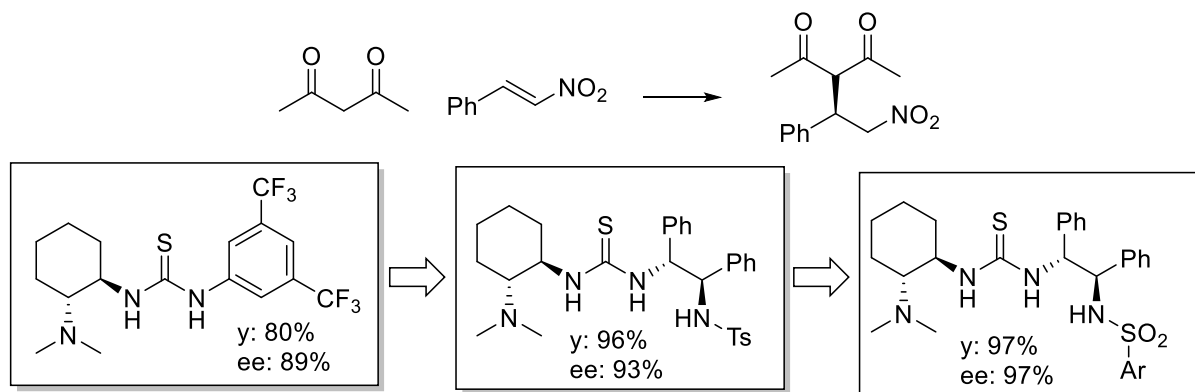Michael additions to differently substituted α,β-unsaturated ketones was successfully perfoermed.[160] Due to its high steric hindrance, the sulphonamide group limited the reaction scope to non-bulky nucleophiles; the problem was overcome replacing it with an OH group, which turned to be equally effective in hydrogen bonding donation.[161]

Scheme 1.44

An alternative way to develop the concept of polyfunctional organocatalysis acting through hydrogen bonding consists in the design of *self assembled multicomponent organocatalyst* and is once again inspired by biological systems. Generated *in situ* by hydrogen bonds among small organic molecules, this supramolecular systems allow an easy fine tuning achievable through the replacement of one of the components with no need for new catalyst synthesis.

Important contributions to this field were given by Bassil group, who studied various Mannich and Michel addition leading to product with quaternary stereogenic centres and supported the hypotesized transition states with DFT calculations. For instance, these authors found that employing a *t*-Bu-L-threonine-DMAP-sulfamide combination it was possible to promote addition of a branched aldehyde to N-phenyl phtalimide in 82% yield, 99:1 dr and 92% ee (Scheme 1.45).[162]

Scheme 1.45
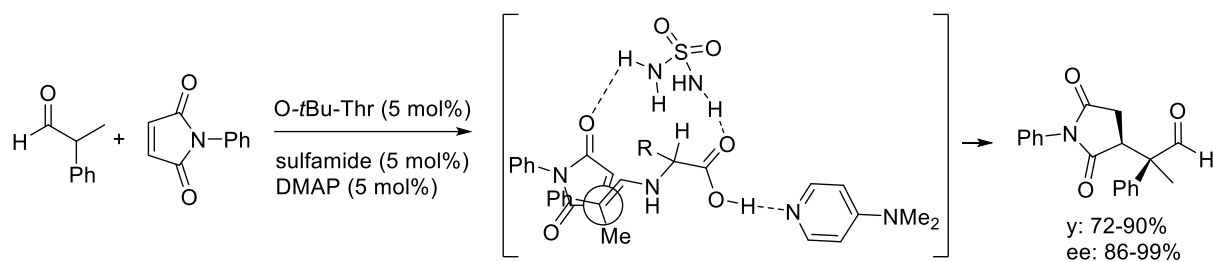
Following this approach, quinine ad quinidine derived thioureas were combined with L- and D-proline to create *self-assembled bifunctional catalytic systems*. As both the hydrogen-bonding and the enamine organocatalysts were readily available in two (*pseudo*)enantiomeric forms, the authors investigated all their possible combinations in promoting a double Michael addition, leading to cyclohexanes with four stereogenic centres, selectively leading a single diasteroisomer (Scheme 1.46).[163]

Scheme 1.46
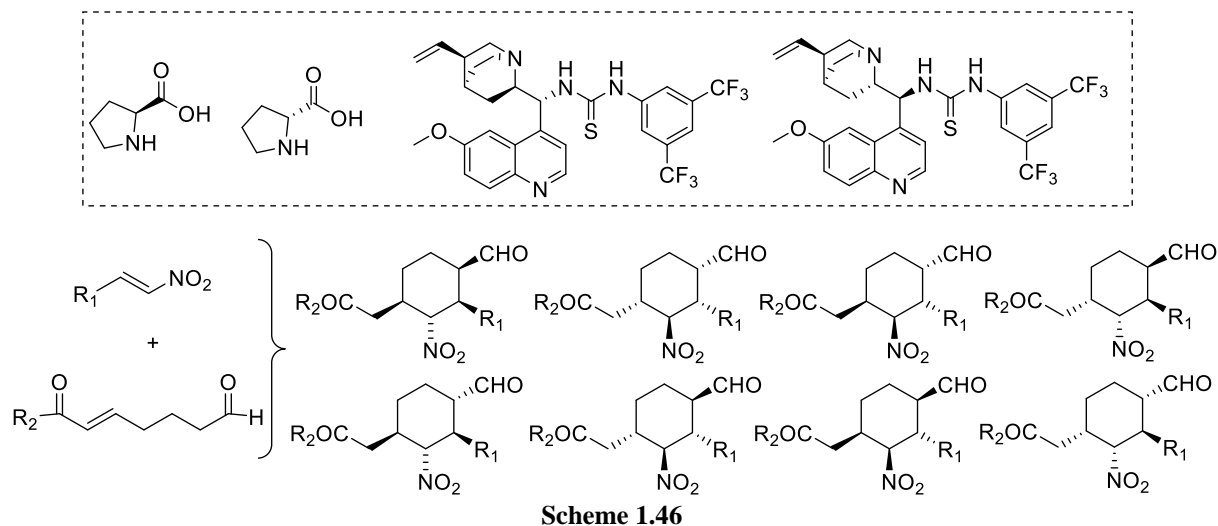
1.4.3.<u>Squaramides and further hydrogen bonding based organocatalysts</u>

In the shadow of the success of (thio)urea based organocatalysts, scaffolds based on different hydrogen bonds donor functionalities have been developed.[164]

The most close relatives to (thio)ureas are squaramides that, with respect to them, are characterized by higher scaffold rigidity, enhanced N–H acidity, longer H-H distance and inward converging N–H bond vectors (Figure 1.30).[165] In particular, in both thioureas and squaramides the nitrogen lone pair is delocalized, but only in the latter there is a further delocalization through the cyclobutenedione system.
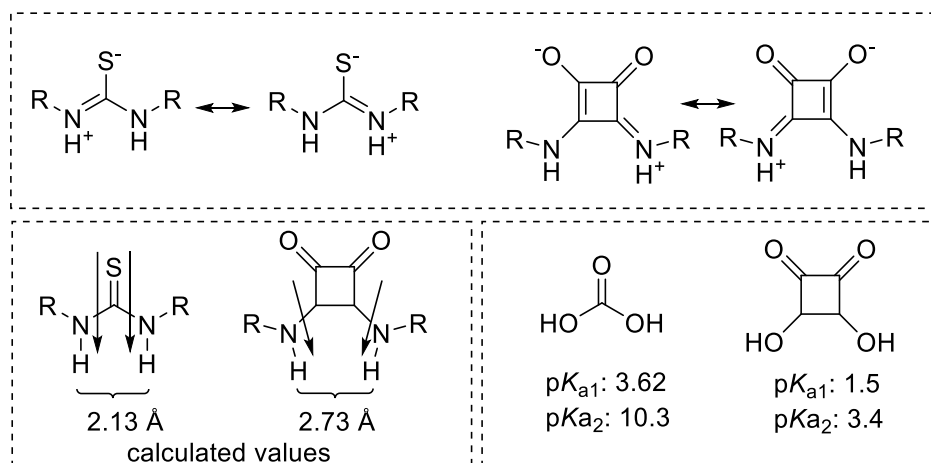
Figure 1.30

Derived from squaric acid, a very strong acid with a strong hydrogen bonding ability,[166] squaramides at first found successful applications in molecular recognition and it was only after the pioneering work by Rawal and co-workers that they started being employed as organocatalysts. As for the synthesis of non-symmetrical squaramides, this group published a one-pot method that, employing methanol as solvent of choice and requiring nothing more than subsequently adding the two desired primary amines, affords the desired products in yields ranging from 46 to <95%.[167]

Thus, different squaramide-based chiral structures have been prepared. They featured, among the others, amino-cinchona, amino alcohol, diaminocylohexane and binaphtyl scaffolds. Primary, secondary and tertiary amine-squaramide bifunctional catalysts have been designed and used in different stereoselective transforamtions, mainly including 1,2- and 1,4-addition with high stereoselectivity.

Several works about squaramides catalysed reactions have been and are still reported, witnessing important role of these organocatalysts.[168] Limiting our survey to woks published in the early 2015,[169] representative examples include: addition of naphtoquinone to enoyilpyridine;[170] α-chlorination of silyl ketene acetals;[171] the Michael addition of oxindoles to α,β-unsaturated phosphonates,[172] of pyrazolone to 3-nitro-2H-chromene,[173] of 3-pyrrolyl-oxindoles[174] and diketones[175] to nitrostyrenes and of α-nitrophosphonates to enones;[176] the 1,3-dipolar cycloaddition between maleimides and *in situ* generated isatin-derived azomethine ylides[177] (Scheme 1.47). Notably, BINAM-based squaramides,

employed in the α-amination of β-dicarbonyl compounds and α-cyanoacetates, were effectively recycled and re-used upon simple precipitation (Scheme 1.48).[178]
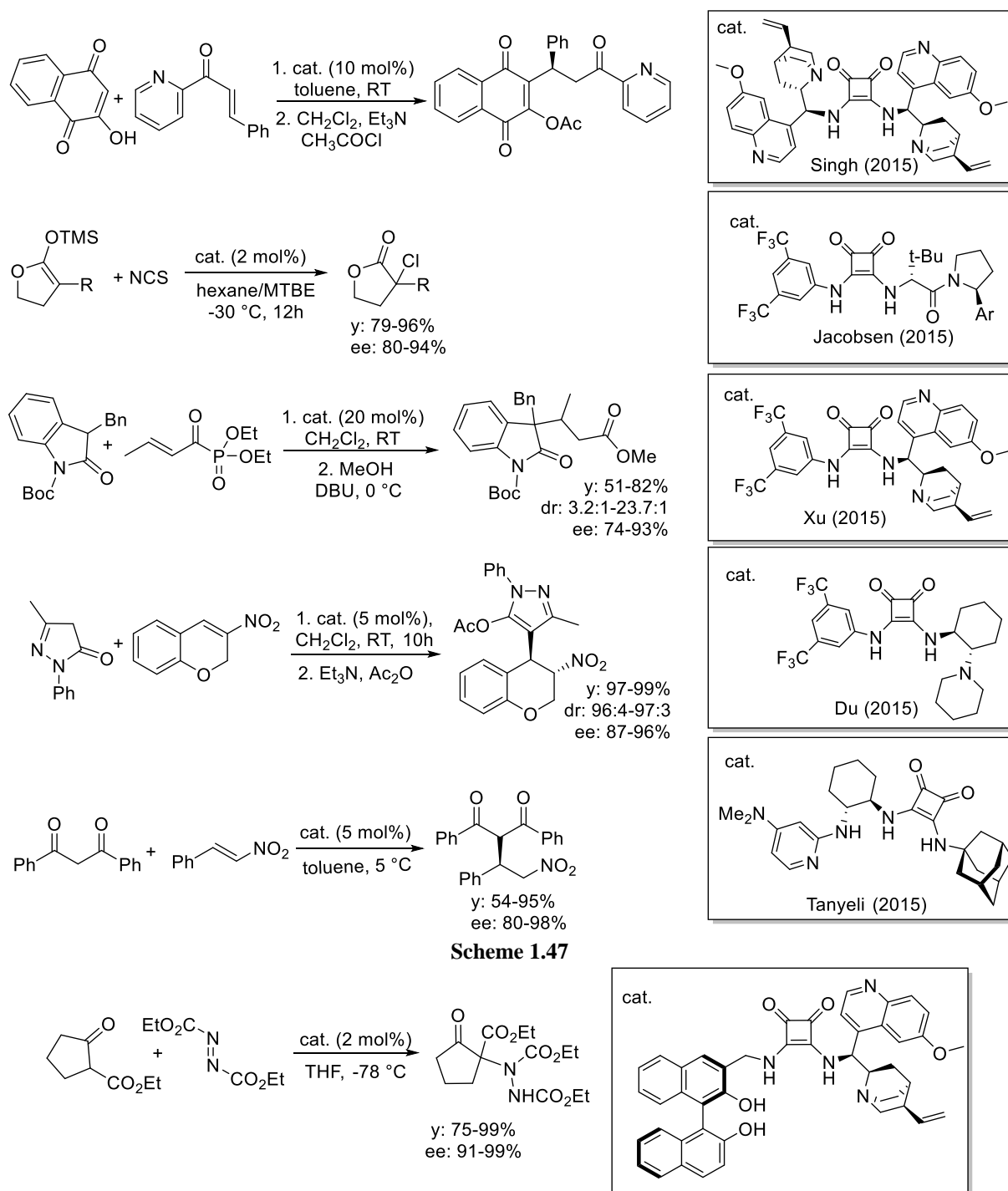
Scheme 1.47

Scheme 1.48

Bifunctional squaramide-based organocatalysts revealed also effective in promoting cascade reactions;[179] after the review by Chauhan and co-workers covering up to 2014,[180] several other works have been published. For instance, Zhu, Wang et al. exploited a squaramide-tertiary amine derived from a Cinchona alkaloid for the one-pot synthesis of CF₃-containig chromanes[181] and pyrano-pyrazoles.[182] The same catalyst was also employed in some three component reactions: Lin group obtained poly-substituted spirocyclohexane oxindoles via a Michael–Michael–aldol sequence,[183] while Chauhan and

co-workers prepared cyclohexane derivatives featuring six stereogenic centres.[184] All these transformations proceed with excellent stereocontrol.

Phosphine functionalities have been also coupled to the squaramide unit to obtain bifunctional organocatalysts which proved effective in the Morita-Baylis-Hillman reaction. Dong et al. developed a series of highly tuneable phosphine-squaramides from commercially available amino alcohols, promoting the MBH transformation between *N*-alkyl isatines and acrylate esters with excellent enantioselectivity (Scheme 1.49).[185]
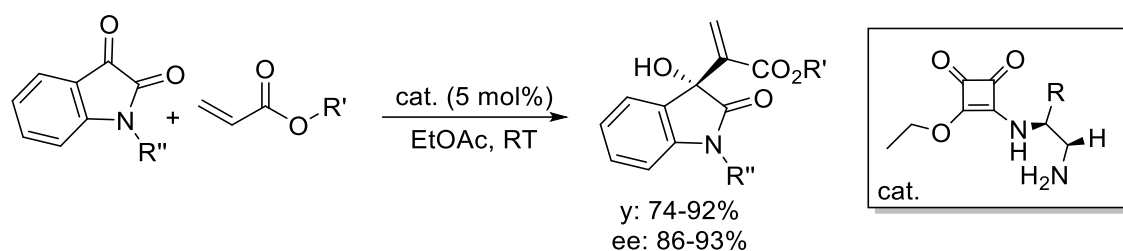
Scheme 1.49

The use of phosphorus based functional groups is not unusual in hydrogen bonding organocatalysis. A recent example is given by the bifunctional organocatalyst featuring a phoshponium and a hydroxyl group. This has been employed in the addition of carbon dioxide to epoxides. In particular, the bests results were obtained with iodide ion as counteranion, long alkyl chains as phosphorus substituents and when PR_4 and OH groups were connected through a two carbon atoms long linker: as the two groups were hypothesized to coordinate to the epoxidic oxygen, a transient six membered ring could thus be formed.[186]

Several other scaffolds the proved to be effective organocatalysts operating through hydrogen bonding have been developed,[187] but a detailed discussion is out of the scope of this Introduction (Figure 1.29, representative examples).
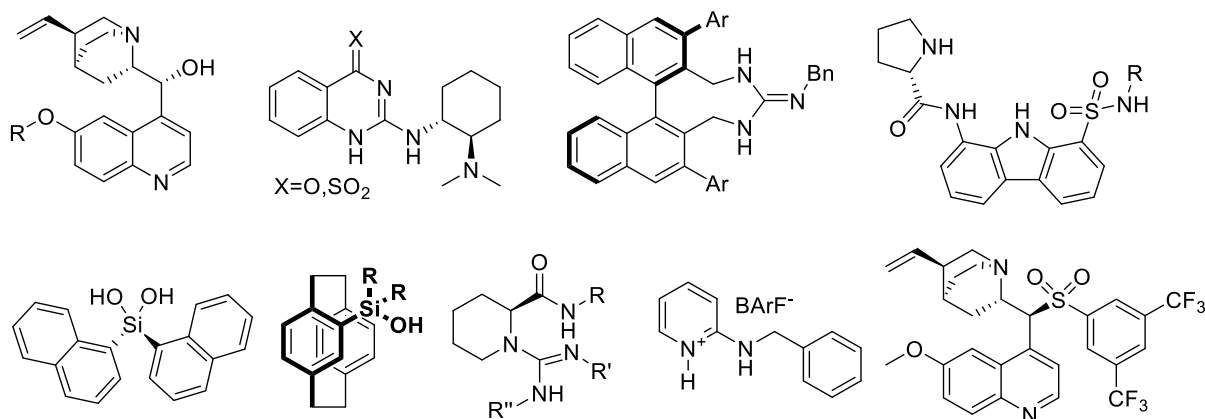

Figure 1.31

1.4.4.Hydrogen bonding organocatalysis *on water*

Considering the high polarity of water molecules, hydrogen bonding organocatalysis could be expected to fail in this medium, that can disrupt the network of non-covalent interactions that need to be established between the organocatalyst and the substrates. However, outstanding examples contradicted this hypothesis. In 2006, Schreiner showed "his" achiral thiourea to promote epoxides opening way more effectively in water than in organic solvents, supporting experimental results with DFT calculations. Thus, even under hydrogen bonding catalysis conditions, the already known "hydrophobic effect" (i.e. formation of a concentrated organic phase by aggregation of organic reaction partners in water) is active (Figure 1.32).[188] On the basis of this seminal
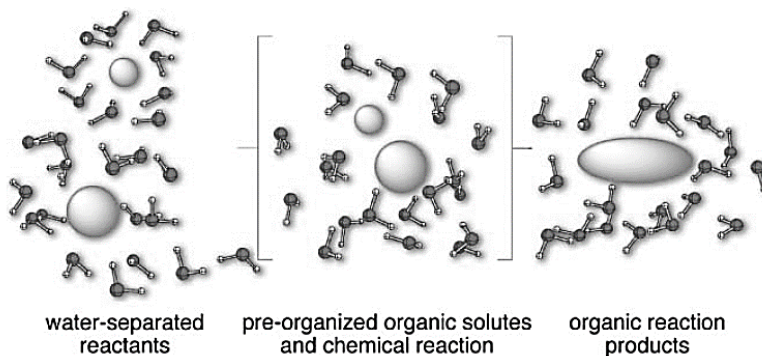
water-separated reactants — pre-organized organic solutes and chemical reaction — organic reaction products

Figure 1.32

work, Song group studied the effect of brine as solvent for the conjugate addition of acetylacetone to nitrostyrene promoted by thiourea and squaramide, the latter proving to be more selective.[189] The reaction was significantly faster in the aqueous salt solution than in CH_2Cl_2 (10 minutes *vs* 4 hours) and complete enantioselectivity was nevertheless achieved. Dependence of rate acceleration on hydrophobic interactions was shown by the rate decrease observed upon addition of $LiClO_4$, known to hamper the hydrocarbon solubility in water.[190] A three component aza-Henry reaction in a biphasic system was then implemented. Also in this case, squaramides afforded higher yield and stereoselectivity.[191] In 2015, chiral squaramides were employed in the "on water" Michael addition of dicarbonyl compounds to nitroolefines; catalyst's activity depended on its extent of hydrophobicity: when dihydroquinine-derived squaramide were employed, up to 0.01 mol% loading was sufficient to obtain quantitative conversion and high enantioselectivity in less than one hour. This method was scaled up for the synthesis of a pharmacologically active compound in which the catalyst recovered by simple precipitation and filtration.[192] In the same year, Guo et al. reported the first conjugate addition of tritylthiol to *in situ* generated *ortho*-quinone methides in almost quantitative yield and up to 98:2 er; the reaction was catalysed by chiral squaramides in water as medium (Figure 1.33).[193]
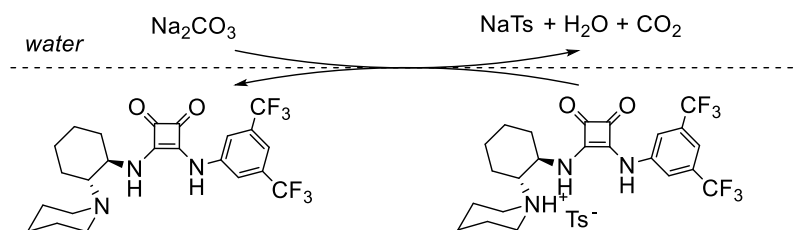
Figure 1.33

1.4.5.Studies on hydrogen bonding power quantification

Despite the wide range of application of hydrogen-bonding catalysts, the issue of quantifying the electrophilic activation they exerted was not tackled and a rough estimation of the hydrogen-bonding strength was given by ΔpK_a values between the donor and the acceptor. In 2014 Walvoord, Huynh and Kozlowski implemented a colorimetric method to evaluate the relative reactivity of several organocatalysts. The strategy was based on the use of a small organic sensor, whose UV−Vis absorption profile significantly changed upon coordination (Figure 1.34). So, sensor's absorbance was measured while adding increasing quantities of a hydrogen-bonding donor and it was observed that, before saturation, a single signal was obtained – rather than two signals belonging to the complexed and non-complexd species which are present in solutions. This indicates a rapid equilibration of the two species and made possible the direct determination of binding constants. Results obtained with this method were in line with experimental evidences about relative effectiveness of different catalysts in Diels-Alder and Friedel-Crafts reactions, and prove to be more reliable than pK_a-based evaluation, as they are more dependent on effective coordination ability.[194]
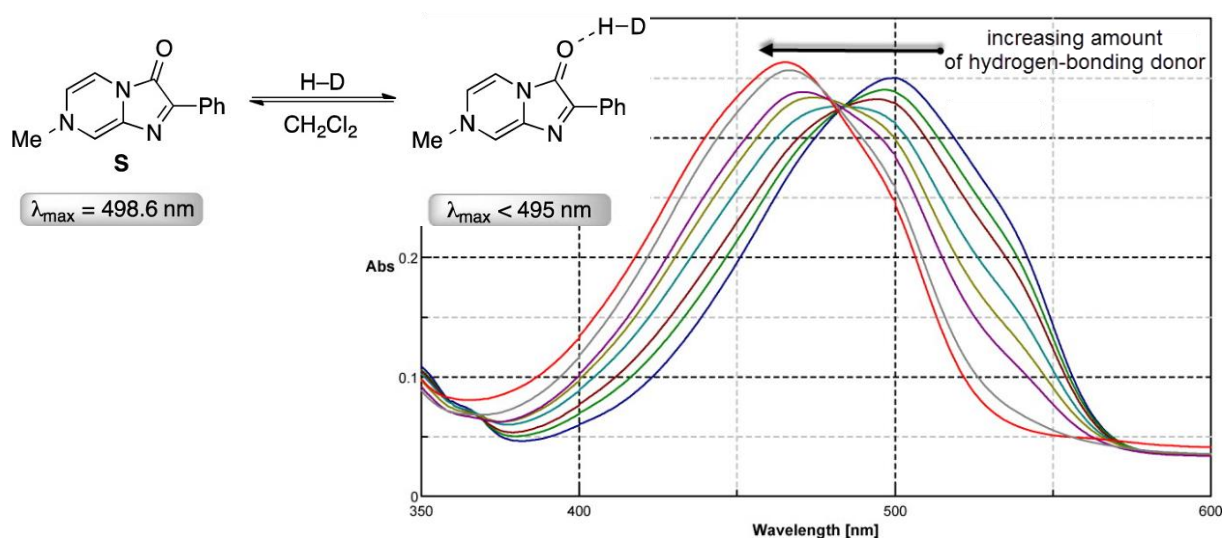
Figure 1.34

2. SUBSTRATES AS VERSATILE PRECURSORS OF HIGHLY FUNCTIONALIZED COMPOUNDS

In our search for innovative synthetic methods, the aim was that of identifying straightforward entries to functionalized products in enantiomerically enriched form. Thus, the main approach we followed consisted in the identification of suitable starting materials, featuring peculiar groups, and in their use in organocatalytic transformations.

In particular, we used nitroacrylates as electron poor compounds featuring two different and reactive functionalities in a vicinal position, β-trifluoromethylated nitroalkenes due to the increasing importance that fluorinated groups are gaining in the pharmaceutical field, and 2,2,2-trifluoroethyl 2-[(1,3-dithian)-2-yl]-ethanthioate as activated thioester and acyl anion mimic.

2.1. <u>Nitroacrylates as precursors of pluripotent compounds</u>

Characterized by the simultaneous presence of a nitro and an ester group, nitroacrylates are still underexploited but interesting substrates that can give direct access to highly functionalized relevant products as e.g. β-amino acids.

Nitraocrylates can be prepared according to two main strategies: direct nitration of acrylates (Scheme 2.1)[195] (not very common as it requires rather harsh reaction conditions) and the much milder dehydration of nitroalcohols (Scheme 2.2).[196] The latter method has been recently improved by Palmieri and co-workers developing a sustainable protocol where hydroxyl mesilation with MsCl and elimination with excess of trimethylamine under inert conditions are replaced by Amberlyst-promoted OH acetylation followed by elimination triggered by KF-Al$_2$O$_3$; an in-flow version of this transformation has also been developed.[197]
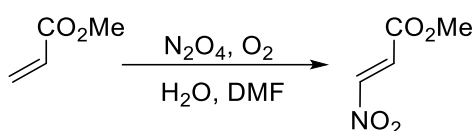
Scheme 2.1   **Scheme 2.2**

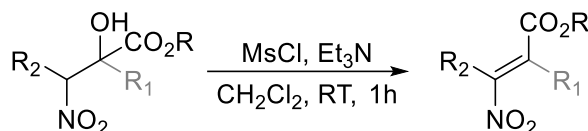Extensive studies[198] have been dedicated to nitroacrylates as electrophiles giving the *anti*-Michael addition product with complete regioselectivity. Different nucleophiles were used, including amines,[199] nitroalkanes,[200] hydrazine and β-diketones.[201] When performed under basic conditions, the conjugate addition step is followed by HNO$_2$ elimination (Scheme 2.3). [202]
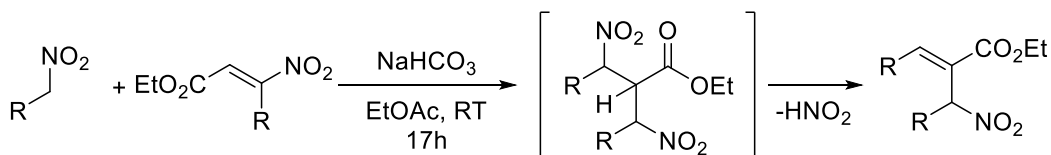
Scheme 2.3

In the presence of Lewis acids, also indoles proved to be effective nucleophiles.[203] The procedure was improved by Ballini and co-workers, who employed basic Al$_2$O$_3$ as promoter,[204] while Bartoli achieved similar results with a CeCl$_3$/NaI/SiO$_2$ system.[205] A single stereoselective example was reported in 2008 as a part of a work about chiral thiourea promoted indole addition to nitroolefins; the product was obtained in 80% yield and 95% ee (Scheme 2.4).[206] A more detailed study on this reaction was carried out by Weng et al.: under nickel catalysis and in the presence of chiral ligands, indole Friedel-Craft addition to nitroacrylates occurred in high yield and ee between 89 and 96%.[207]
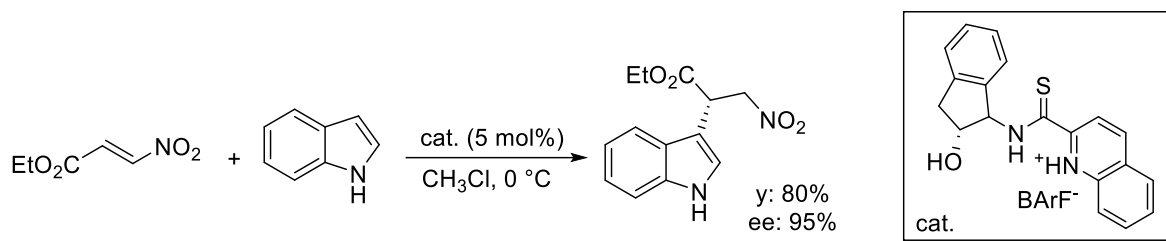
Scheme 2.4

Zhong and coworkers employed 3-alkylidene oxindoles as vinylogous nucleophiles for nitroacrylates which were activated through hydrogen bonds by chiral organocatalysts; a squaramide derivative revealed more effective than thiourea based catalysts affording the products with good yield and 86-96% ee (Scheme 2.5).[208, 209]
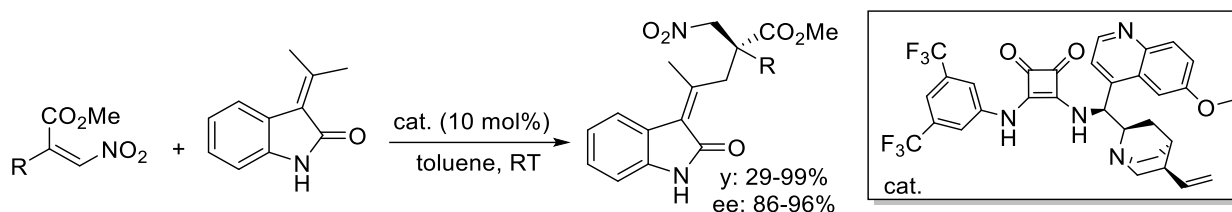
Scheme 2.5

Organocatalytic versions of aldehyde addition to nitroacrylates have also been developed. Using diarylprolinol derivatives[210] as promoters, Zhu, Yu and Ma studied the addition of aldehydes to nitroacrylates *via* enamine activation, obtaining in high yield and almost complete enantioselectivity 1,4-nitroaldhydes subsequently transformed into chiral cyclic amino acids.[211]

Methyl-nitroacrylate reacted with γ,δ-unsaturated aldehydes to form an intermediate, obtained in 92% yield, 98:2 dr and 95% ee, which could underwent a [3+2]-heterocyclization triggered by a base and TMSCl, in analogy to what was done for the corresponding product obtained from nitrostyrene (Scheme 2.6).[212]
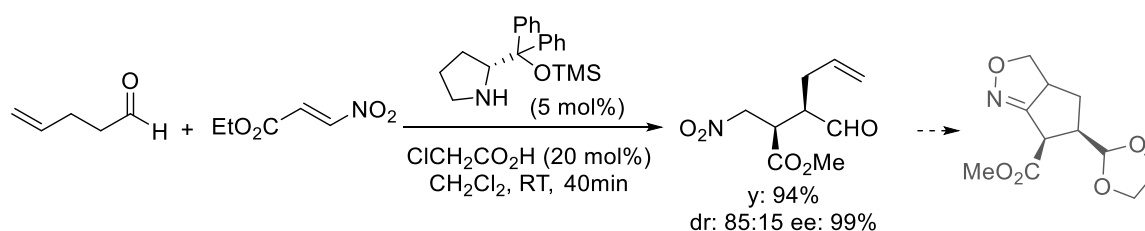
Scheme 2.6

One-pot synthesis have also been developed. Examples of these procedures were reported in 2011 by both Hayashi[213] and Xu[214] and by Jorgensen[215] group, describing the preparation of a direct precursor of (-)-Oseltamivir (Scheme 2.7) and of a polycyclic hexahydrocyclopenta[b]quinolone (Scheme 2.8), respectively.
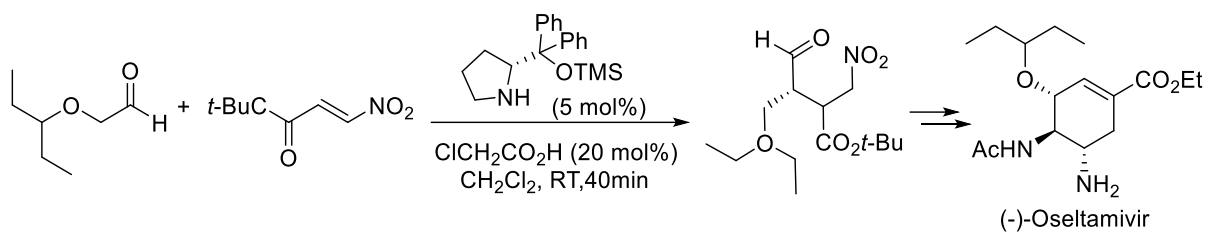
Scheme 2.7
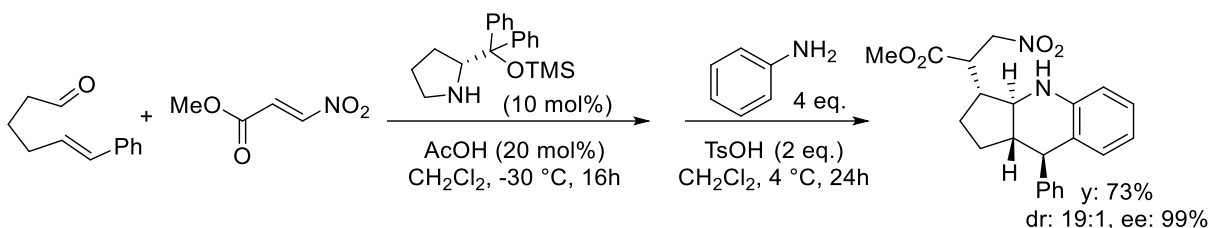
Scheme 2.8

More recently, Wennemers successfully accomplished a highly stereoselective addition of aldehydes to α-substituted-β-nitroacrylates through a tripeptide-catalysed transformation that allowed to generate all-carbon quaternary stereocentres (Scheme 2.9).[216]
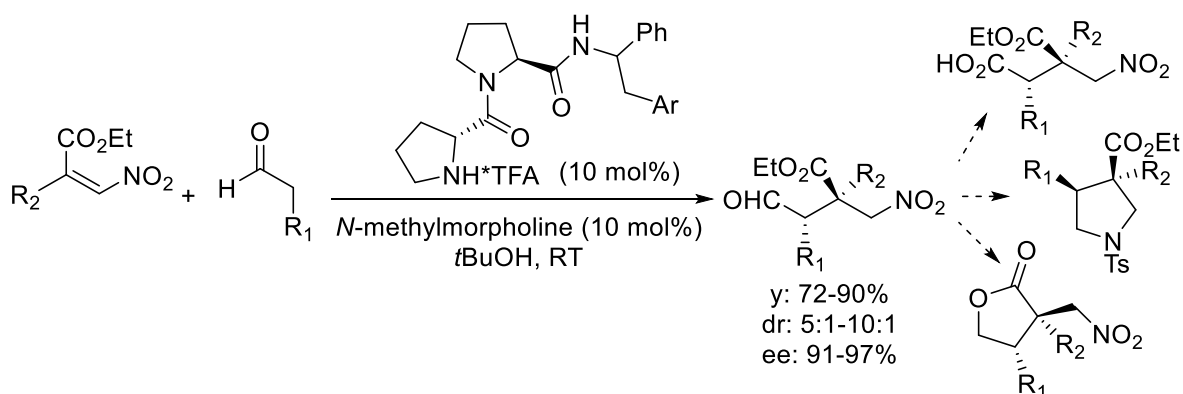
Scheme 2.9

In 2010 cyclic enones, activated as extended dienamines by primary amine catalysts, were employed as nucleophiles for nitroacrylates to afford γ-functionalized products in 58% yield and 90% ee.[217]

Nitroacrylates have been also employed as substrates in new carbon-heteroatom bond construction. In 2009, Lu and co-workers reported the stereoselective C-S bond formation through thiol attack catalysed by *epi*-quinine-thiourea, obtaining the desired product in 92% ee and 98% yield.[218] One year later, the same group used an *O*-alkylated quinine derivative to promote the enantioselective conjugate addition of oximes to β-nitroacrylates, enantioselectivly generating a new C-O bond;[219] yields between 77 and 93% and above 90% were achieved (Scheme 2.10).[220]
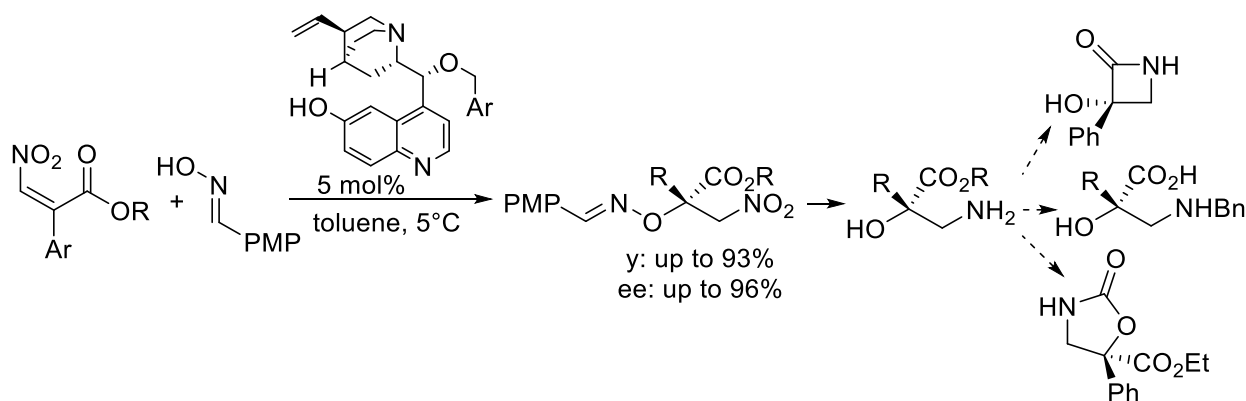
Scheme 2.10

Due to the strongly electrondeficient character of their double bond, nitroacrylates found also several applications as dienophiles in cycloaddition reactions.

Seminal studies by Danishefsky demonstrated that the cycloaddition reaction[221] with activated dienes proceeds with high regioselectivity[222] and later investigations were aimed to improve the *endo/exo* cycloaddition products ratio.[223] Reactions with cyclopentadiene (Scheme 2.11)[224] and furan[225] were exploited to obtain precursors of cyclic amino acids.
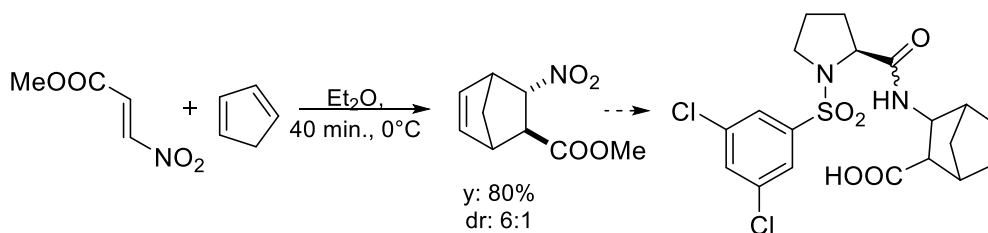
Scheme 2.11

Stereoselective versions of these transformations have been developed, relying on the use of chiral auxiliaries linked either to the diene[226] or to the dienophiles;[227] an example of enantioselective catalysed reaction employing proton-activated chiral oxazaborolidine cations was also reported (Scheme 2.12).[228]
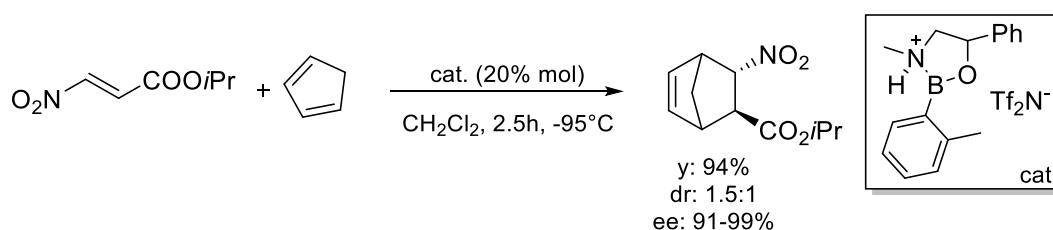
Scheme 2.12

Studies on the enantioselective reduction of the C=C double bond of nitroacrylates was also reported, even if this transformation was much more investigated on alkyl and aryl substituted nitroalkenes.

After the bioreduction with *Saccharomyces carlsbergensis* old yellow enzyme developed by Stewart,[229] List applied to these substrates the transfer hydrogenation previously developed by his group

for the stereoselective reduction of nitrostyrenes. Using a chiral thiourea as organocatalyst and Hantzsch ester as hydride donor, the corresponding β-carboxy nitroalkanes were obtained in yield higher than 80% and ee ranging from 89 to 95% (Scheme 2.13).[230]
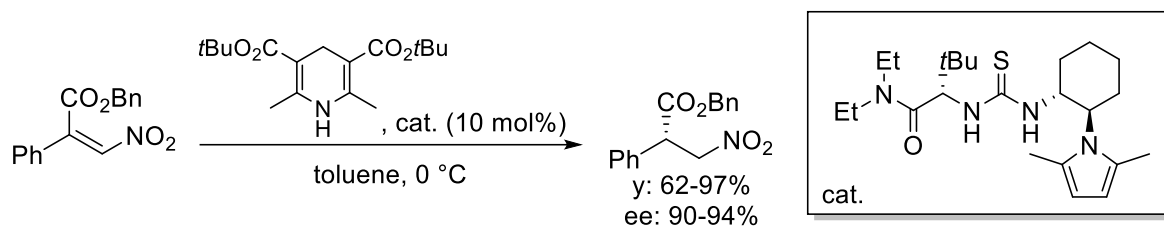
Scheme 2.13

Further enzymatic[231] and organocatalytic[232] methodologies were subsequently published, followed by the enantioselective hydrogenation promoted by an iridium catalyst featuring chiral ligands. Under optimized conditions, the reduced compounds were obtained in 92-98% ee. Based on the use of a transition metal, this method represents a valuable alternative to the previous ones, requiring a lower catalyst loading and being superior from the atom-economy point of view.[233]

Due to the close proximity of two highly reactive functional groups and to the low stability of the reaction interemdiates, nitroacrylates can easily undergo spontaneous cascade transformations, thus leading to cyclized products. This has been exploited for the synthesis of cyclic and heterocyclic compounds[234] as decorated anilines,[235] oxopiperazine,[236] pyrazoles,[237] indoles,[238] quinoxalinones[239] and pyrroles[240] (Figure 1.33). In 2012, Anderson and co-workers obtained enantioenriched functionalized pyrrolidinone derivatives through a stereoselective copper mediated β-alkylation[241] by organozinc[242] reagents followed by intramolecular lactamization (Scheme 2.14).[243]
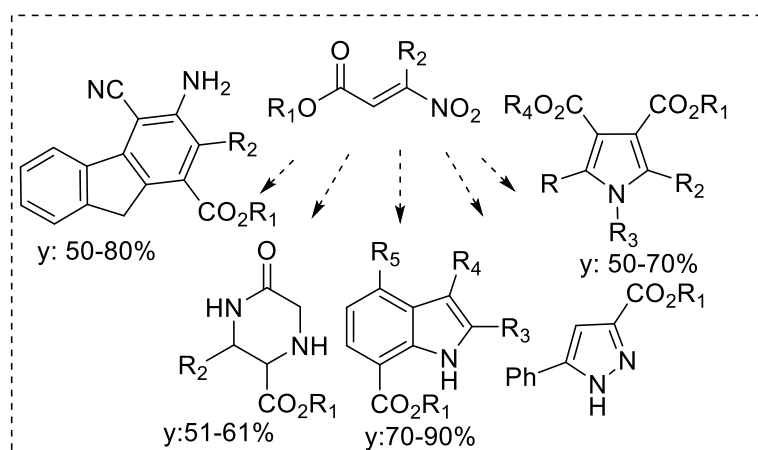
Figure 2.1
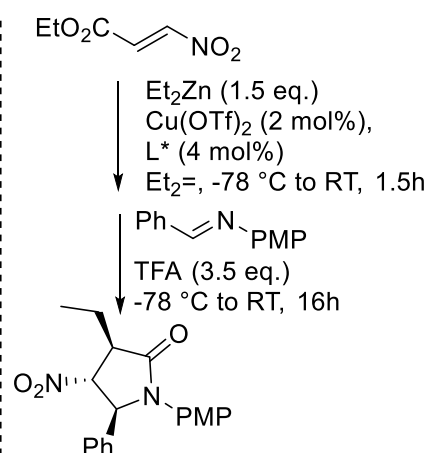
Scheme 2.14

2.2. <u>Organofluorine compounds</u>

Fluorine is the least abundant halide in natural compounds, but it has been gradually recognized that its presence plays a fundamental role in tuning molecules physicochemical properties and activity.

Fluorination can impart molecules a behaviour strongly deviating from that of the non-fluorinated counterparts, because of the peculiar steric and electronic characteristics of the fluorine atom, larger than a proton - its Van der Waals radius (1.47 Å) lies between that of oxygen (1.57 Å) and hydrogen (1.20 A°) - and much more electronegative - F=4.0 and H=2.1 on Pauling's scale -. Besides, fluorine participates in hydrogen-bonding interactions as acceptor but with a much lower energy than an O···H hydrogen bond (2-3 *versus* 5-10 kcal mol^{-1}). Cambridge structural database surveys showed that there are a considerable number of short contacts between covalent fluorine and other atoms including H, C, O, and F. [244,245]

By virtue of the interesting characteristic of flurininated groups, fluorine-containing molecules play a role in several fields.

Fluorine inclusion in a bioactive molecule has a strong impact on its effectiveness, simultaneously modulating electronic, lipophilic and steric parameters, which can critically influence both the pharmacodynamic and pharmacokinetic properties. Because of its high electronegativity, fluorine improves oral bioavailability modulating the pK_a of adjacent groups and decreases lipophilicity when introduced in saturated alkyl groups. In contrast, lipophilicity increases with fluorination and polyfluorination of position conjugated to unsaturated moieties, due to F orbital overlap with π-bonds. The strong fluorine electron withdrawing power also influences molecules conformation and electrostatic interactions and affects drugs reactivity inducing different metabolic pathways, for example deactivating substrates towards oxidation or increasing hydrolytic stability.[246]

After Fried and Sabo demonstration that cortisone fluorination causes an increased activity and selectivity, in 1957 the antineoplastic agent 5-fluorouraicil was introduced as one of the first fluorinated drugs. At present fluorine-containing molecules more than 25% of the total amount of drugs[247] and more than 30% of the agrochemicals. Fluorine introduction as a substituent in the drug discovery process has allowed accessing pharmaceutically active compounds that have replaced their non-fluorinated counterparts. Two outstanding examples are Falsodex, a pentafluorinated 7-α-alkylsulfinyl analogue of Tamoxifen, used in the treatment of hormone dependent breast cancer, and the Flurithromycin, fluorinated analogue of the antibiotic Erythromycin.

There are also several CF$_3$ containing dugs, as Efavirenz, used in the treatment of HIV infection, Telcalgepant, employed in the treatment of the neurovascular disorder migraine[248] and Prozac, whose trifluoromethyl group in the *para* position of the phenol ring increases the potency of this antidepressant by 6-fold with respect to its parent compound (Figure 2.2).
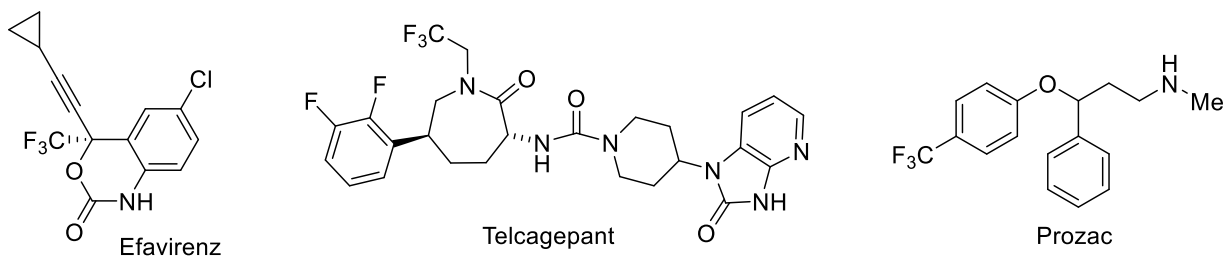
Figure 2.2

More recently developed trifluoromethylated bioactive compounds include metallocenes derived from hexafluoroacetone, which have been evaluated as anticancer agents observing that the presence of the CF$_3$ group was crucial for the cytotoxic effect,[249] and the pentacycle introduced by Merck for the treatment of the postmenopausal symptom, where the CF$_3$ substituent at the α-position of the enone is one of its key structural features.[250]

Fluorinated moieties have also been used for the preparation of metabolically stable peptide analogues (Figure 2.3). The fluorovinyl group has been recognized as a hydrolytically stable replacement for a peptide bond, mimicking its electronic characteristics better than the non-fluorinated vinyl function. An alternative strategy consists in replacing amide bond with a trifluoroethylamine, where the trifluoromethyl group, the C-CF$_3$ being substantially isopolar with the C=O even though not an as good hydrogen bond acceptor, is connected through a near 120° angle to a hydrolytically stable and poorly basic amine.[251] The high electron density on CF$_3$ and the sp^3 backbone carbon connected to it make this kind of structures related to the tetrahedral intermediate involved in the peptide bond hydrolysis mediated by proteases. Besides, retropetpides featuring the trifluoroethylamino unit adopt a highly stable turn-like conformation, probably thanks to the presence of the bulky CF$_3$ group.[252]
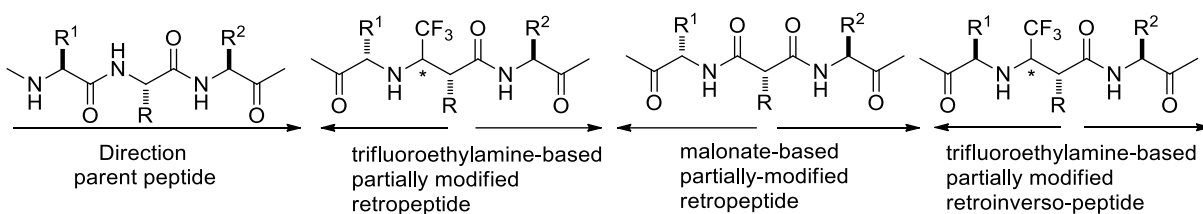
Figure 2.3

2.2.1. Fluorinated Nitroalkenes

Among the several fluorinated substrates, we focused our attention on nitroalkenes, as direct precursors of chiral amines featuring a β-CF$_3$ substituent. CF$_3$-substituted nitroolefins have been extensively employed as dienophiles in Diels-Alder reactions[253] (Scheme 2.15) and as electrophiles in Friedel-Crafts reactions[254] (Scheme 2.16) or, more extensively, in Michael-type additions.
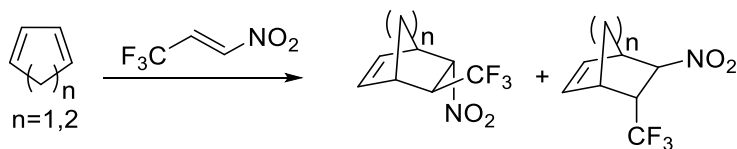
Scheme 2.15
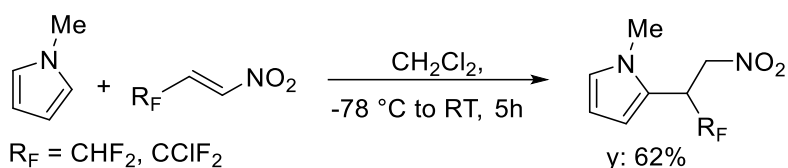
Scheme 2.16

Various non-stereoselective conjugate additions to β-CF$_3$ nitroalkenes have been reported, using primary and secondary amines,[255] imines derived from 2-hydroxy acetophenone,[256] morpholinoalkene[257] and enamines[258] as nucleophiles. When 1-trifluoromethyl-1,3-diketoenes were used, the Michael reaction is followed by detrifluoroacetylation and β-CF$_3$-γ-nitroketones are obtained (Scheme 2.17).[259]
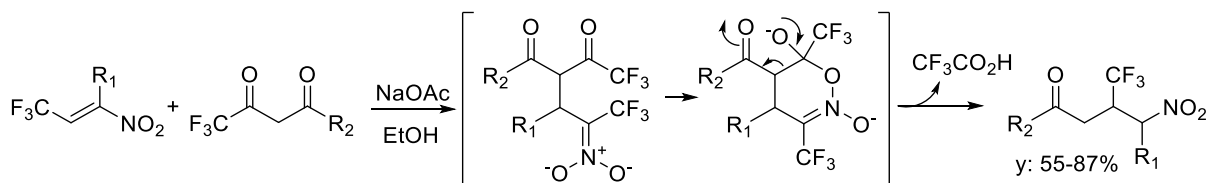
Scheme 2.17

In 2012, the first three-component Grob synthesis affording fully substituted β-trifluoromethyl pyrroles in up to 69% yield has been reported by Korotaev et al. (Scheme 2.18).[260]
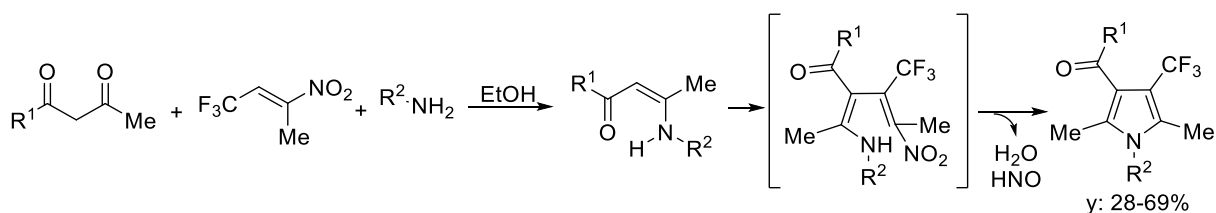
Scheme 2.18

Several works report the use of trifluoromethylated nitroalkenes in combination with chiral reaction partners to afford β-nitro-trifluoromethylated products in a stereoselective way. Typical examples include the use of trifluoromethyl nitroalkenes in the synthesis of trifluoromethylated peptide analogues, using enantiopure α-amino acids as nucleophiles. In a work by Zanda and Volonterio it was pointed out that the diastereoselectivity of the process depended on the base employed, on its stoichiometry, on the solvent and on the nature of the α-substituent of the AA (Scheme 2.19).[261]
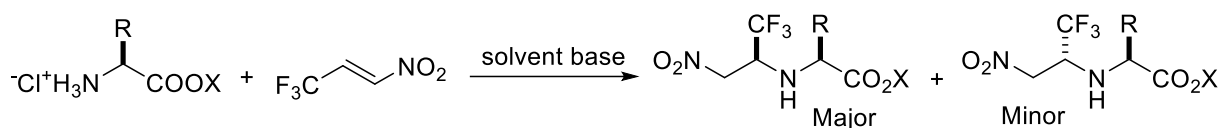
Scheme 2.19

The same approach was used in the synthesis of Enkephalines mimics (single example in Scheme 2.20), bringing a trifluoroethylamino group that makes this structure resistant against endopeptidases but preserving the analgesic activity that characterizes the parental endogenous opioid pentapeptide.[262]
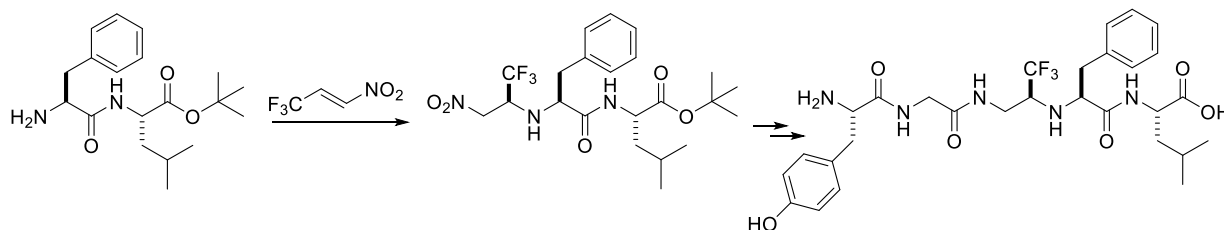
Scheme 2.20

Diastereoselective 1,4-additions not related to peptide chemistry were also reported. In 2006 Turconi et al. studied the stereoselective addition of an enantiopure nitrogen nucleophile to trans-3,3,3-trifluoro-nitropropene promoted by different achiral bases, obtaining products in high yield and up to 92% ee (Scheme 2.21).[263] This group employed also chiral amines achieving a good stereoselectivity addition to the same nucleophile without additional bases.[264]
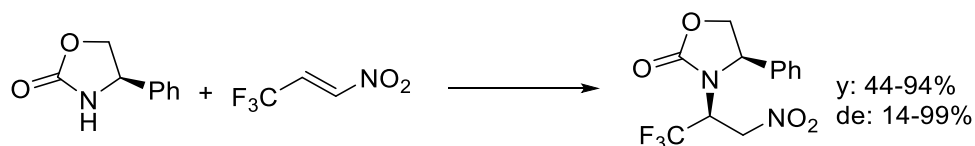
Scheme 2.21

Apart from strategies exploiting chiral auxiliaries, stereoselective catalytic ones have been developed.

Within a study on Michael reaction between carbonyl compounds and nitroolefins catalyzed by *N*-alkyl-2,2'-bipyrrolidine derivatives by Alexakis group, propionaldehyde addition to *trans*-3,3,3-trifluoro-nitropropene was found to give 42% yield and 91% ee after one day at room temperature.[265]

A single example of organocatalyzed aldehyde conjugate addition to this alkene was reported by Jacobsen group in 2006. The reaction was promoted by a thiourea-based bifunctional catalyst (Scheme 2.22) affording the desired product in low yield (34%) but high diastero- and enantioselection (dr>50:1, 97% ee).[266]
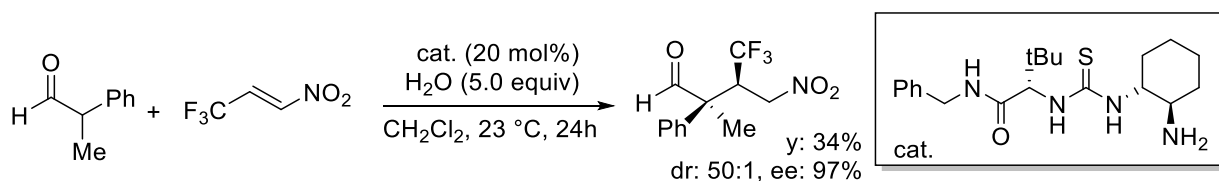
Scheme 2.22

Konno group reported the 1,4-arylation using aryl boranes on CF$_3$ containing unsaturated compound using (*S*)-BINAP as chiral ligand for Rh in 2008. When *trans*-3,3,3-trifluoro-nitropropene

was employed as substrate, the product was obtained in moderate yield but as racemate (Scheme 2.23).[267] Five years later, the authors extended their work to organostannaes.[268]
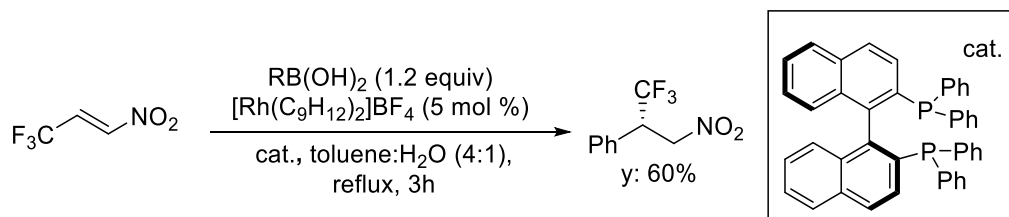
Scheme 2.23

Ni(ClO)$_4$-bisoxazoline complexes were employed to promote the enantioselective Michael type Friedel-Crafts alkylation of indoles with β-trifluoromethylate nitroalkenes (up to 95% yield and 97% ee) by Gao et al. (Scheme 2.24),[269] and one year later 3-substitued oxyndoles were employed by Zhao and co-workers as nucleophiles in the organocatalyzed addition to the same nitroolefins (typically, 90% yield, 20:1 dr and >95% ee) (Scheme 2.25).[270]
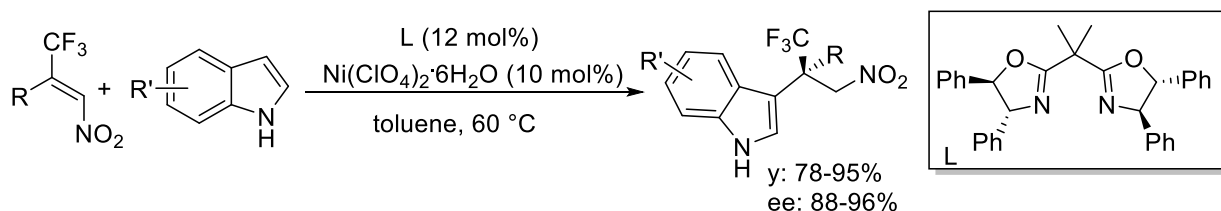
Scheme 2.24
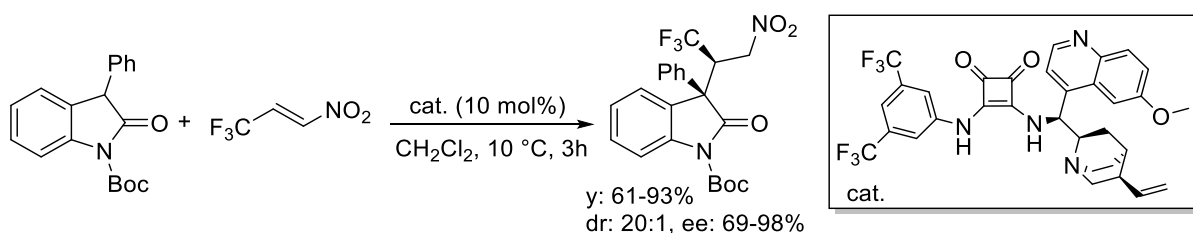
Scheme 2.25

In 2014, Chen, Xiao and co-workers published the first stereoselective intermolecular oxa-Michael addition of oximes to β-CF$_3$-β-disubstituted nitroalkenes catalyzed by a Cinchona alkaloid derived thiourea; CF$_3$-containing oxime ethers were obtained in up to 87% yield and 95:5 enantiomeric ratio (Scheme 2.26).[271]
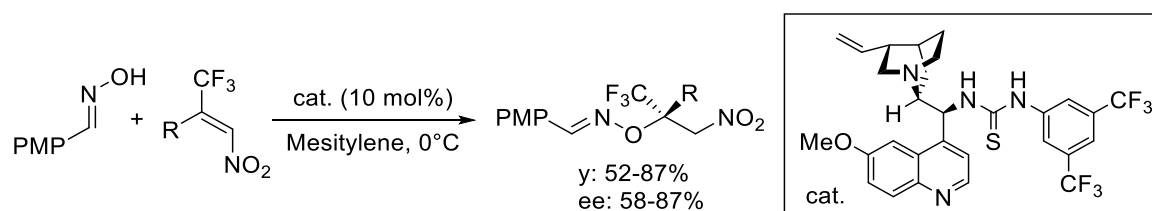
Scheme 2.26

The same organocatalyst was used by Chen et al. (2014) to promote the vinylogous conjugate addition of 3-alkylidene oxindoles β-CF$_3$-β-disubstituted nitroolefins yielding all-carbon quaternary

stereocenters in very efficient and stereoselective fashion (up to 93% yield, >20:1 dr and >99% ee) (Scheme 2.27).[272]
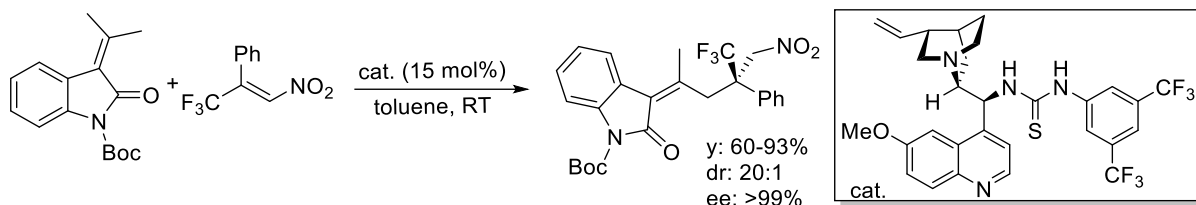
Scheme 2.27

Trans-3,3,3-trifluoro-1-nitropropene was also employed as Michael acceptor for β-dicarbonyl compounds. For this reaction, reported by Liu group in 2014, the best catalyst was a cinchonidine derivative, whose hydroxyl function on C9 is protected as carbonate; products were afforded in good yields and up to 99% enantioselection (Scheme 2.28).[273]
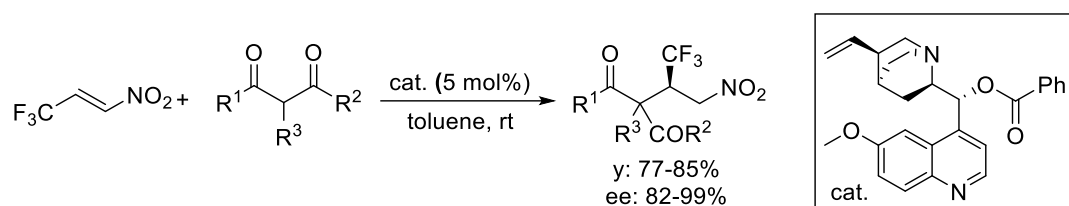
Scheme 2.28

Despite the effectiveness of β-trifluoromethylated nitroalkenes as Michael acceptors, a single example on hydride attack, i.e. C=C reduction, has been published and dates back to 1956; this work reported the successful use of metal hydrides leading to nitroalkanes with no nitro group reduction.[274]

In 2015, the field was independently entered by the research group of Bernardi and Mazzanti (Scheme 2.29)[275] and by ours. Employing Hantzsch ester as hydride source in the presence of a chiral thiourea based organocatalyst, the reaction was performed in a stereoselective way (see Chapter 6).
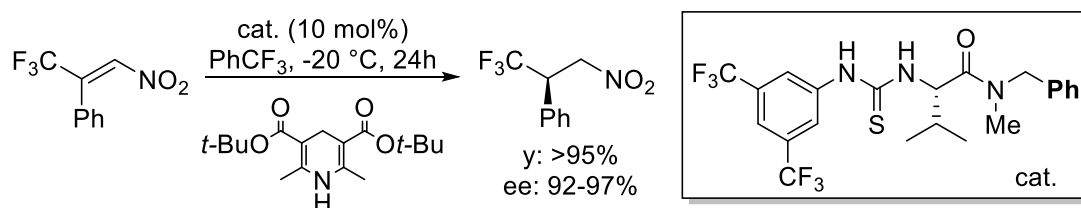
Scheme 2.29

2.2.2. <u>Preparation of trifluoromethylated amines</u>

Due to the increasingly great number of bioactive chiral molecules featuring a stereogenic carbon atom linked to the CF$_3$ group, several studies have been devoted to obtain these compounds in an enantiomerically enriched form. Particular attention was focused on chiral amines, as these play a fundamental role in medicinal chemistry.

A possible approach consists in the stereoselective construction of C-CF$_3$ bond. In 2013, Yasu, Koike and Akita developed the first visible light-driven intermolecular aminotrifluoromethylation of alkenes promoted by the photoredox catalyst [Ru(bpy)$_3$](PF$_6$)$_2$, an highly efficient and regioselective one-step reaction that gives access to a variety of β-trifluoromethylamides in up to 82% yield and 89:11 dr (Scheme 2.30).[276]
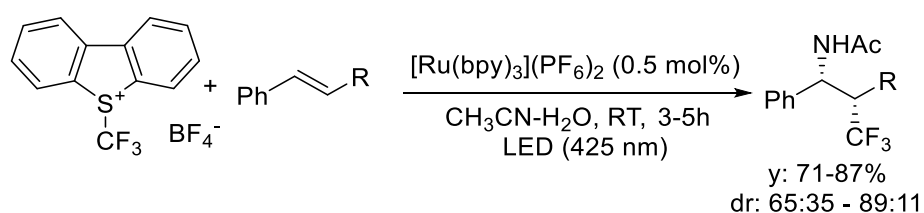
Scheme 2.30

An alternative strategy involves the use of trifluoromethylated prochiral compounds as substrates in stereoselective reactions. These have been reviewed by Ma and co-workers in 2011 and include the use of trifluoroacetaldheyde, trifluoropyruvates, trifluoroacetoacetate, trifluoromethyl ketones,[277] trifluoromethyl olefins, trifluoropropionic acid and their derivatives.[278]

In an example by Lin group (2013), enantiomerically enriched α-trifluoromethylated amines were obtained through dynamic kinetic resolution using Pt/Al$_2$O$_3$, for starting amines isomerization, and *Candida Antarctica* lipase B to selectively obtain the amide of one of the two enantiomeric starting amines (Scheme 2.31).[279]
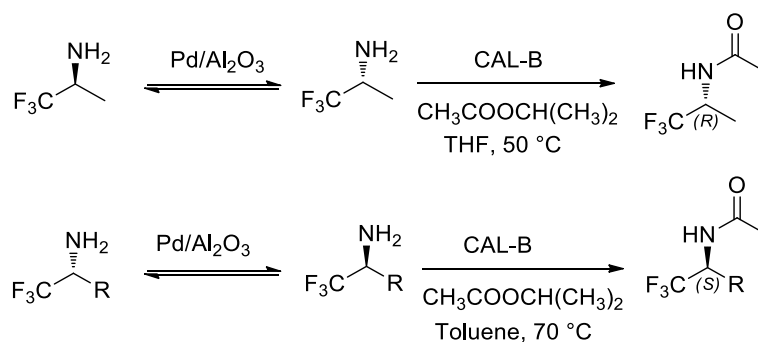
Scheme 2.31

Lately, enantiomerically enriched trifluoromethyl alcohols have been obtained by means of bioreduction occurring within whole cells. The efficiency of the process was improved immobilizing

thee on calcium alginate spheres without loss of enantioselectivity.[280] Turgut group described ketone reduction by borane promoted by chiral β-hydroxyamides: while moderate enantioselection was reached using non-fluorinated substrates, 2,2,2-trifluoroacetophenone afforded racemic products.[281]

In 2014, the stereoselective allylic amination of racemic allyl esters containing the trifluoromethyl group was reported by Kawatsura and Itoh group using the Pd(C₃H₅)Cl]₂/(S)-BINAP/AgPF₆ system as catalyst. The reaction proceeds through the nitrogen nucleophile attack of the π allylpalladium complex and a high selective dynamic kinetic resolution between the α- and the γ-amination products. Allylic α-trifluoromethylated amines were obtained in up to 98 yield and 93% enantiomeric excess (Scheme 2.32).[282]
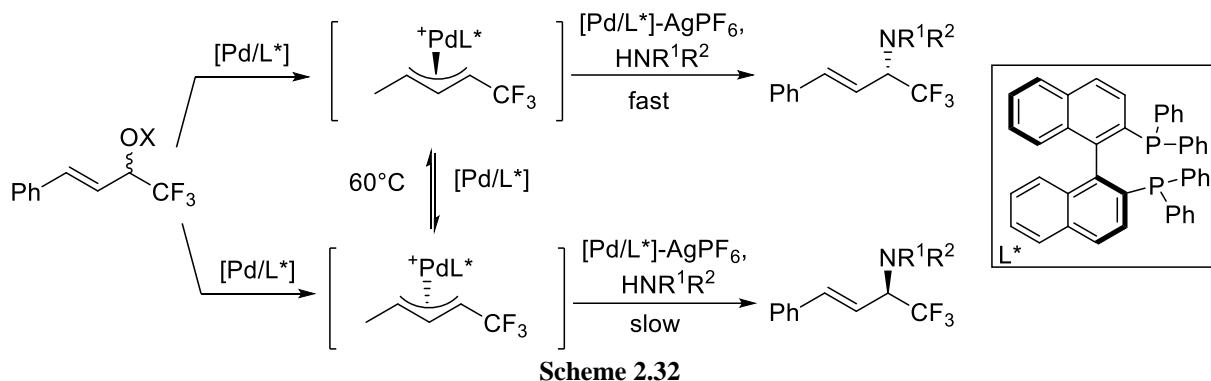
Scheme 2.32

In this context, our group reported the stereoselective reduction of trifluoromethylated *N*-protected imines using HSiCl₃ as hydride donor and a chiral Lewis base as catalyst (Scheme 2.33).[283]

Specifically, for the stereoselective reduction of C=N in fluorinated substrates, chiral picolinamides derived from ephedrine, binaphthyl diamine and prolinol as well as (*S*)-prolinol-derived phosphoroamides and chiral biphosphine oxides were tested. Working at 0 °C in dichloromethane, the ephedrine derived picolinamide proved to be the catalyst of choice, affording chiral amines in yields from 70 to 91% and typical enantioselectivity of 90%. According to the tentative model of stereoselection proposed, silicon is coordinated by the pyridine nitrogen and by the amidic group, while face selectivity depends on steric interaction between the pyridine ring and the aryl group of the substrate.

Scheme 2.33
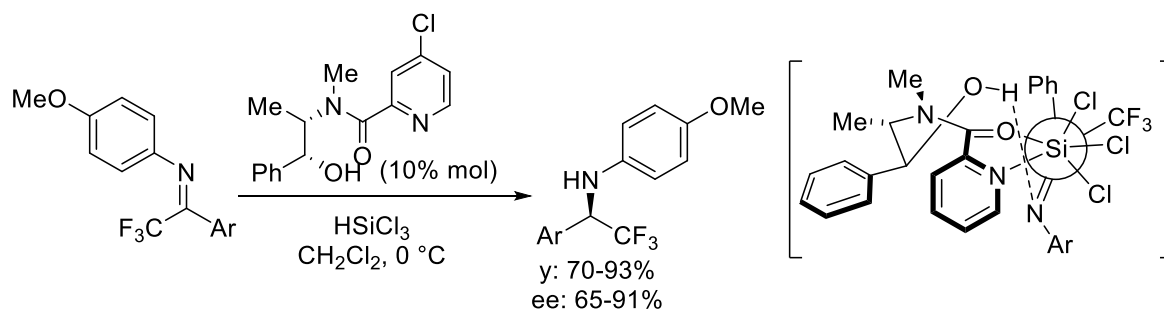
2.3. <u>A tailor-made activated thioester</u>

A considerable part of our research work was focused on the use of a peculiar nucleophile, namely 2,2,2-trifluoroethyl 2-[(1,3-dithian)-2-yl]-ethanthioate, ad hoc designed to address the need of high reactivity and diverse functionality. Indeed, exploiting this molecule gives access to compounds featuring high potentiality in terms of possible transformations, as the thioester moiety can be either hydrolized or transesterified and the dithiane ring can be removed to deliver a carbonyl functionality. With this premises, we investigated the suitability of this nucleophile in stereoselective metal free 1,4-additions (Scheme 2.34).

In particular, this methodology can be counted among those designed to somehow circumvent the issue of organocatalytic esters addition. Besides, if the dithiane group is transformed into a carbonyl one without affecting the stereochemical integrity of the compound, the organocatalytic addition can be seen as a stereoselective introduction of an acyl anion mimic.
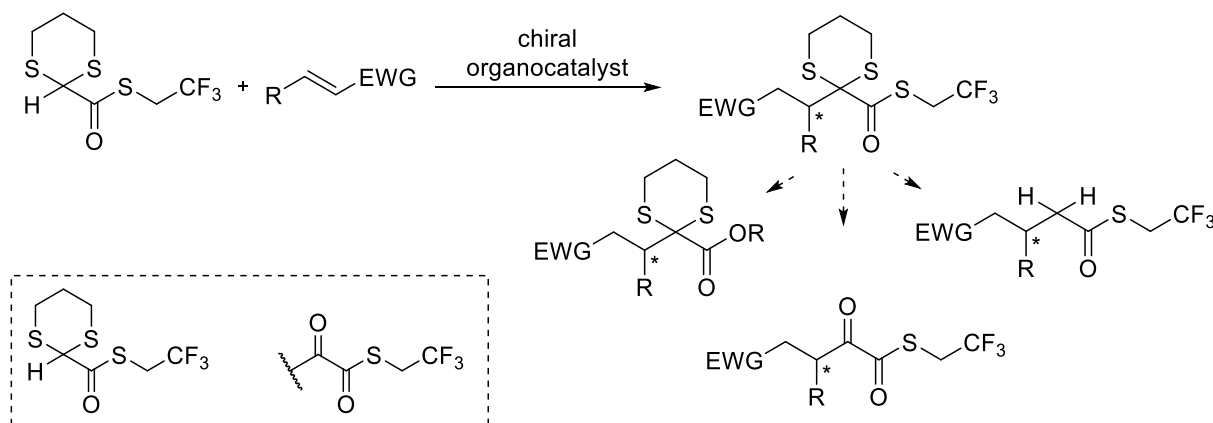
Scheme 2.34

2.3.1. Addition of activated esters

The development of stereoselective addition of esters in either aldol, Mannich or Michael-type reactions is still a challenging topic in organocatalysis. The difficulty of realizing such transformations arises from the need to find a successful strategy for the activation of these substrates as nucleophiles. In fact, α-protons (pK_a ~19) of carboxylic esters are characterized by a lower acidity than that (pK_a 16–17) necessary for amine bases activation. Besides, esters are not feasible for an enamine-based approach. In Nature, esters addition results from enzymatic activation of malonic acid half thioesters (MAHTs) (Figure 2.4, **a**) in decarboxylative Claisen condensation to synthetize polyketides and fatty acids.[284]
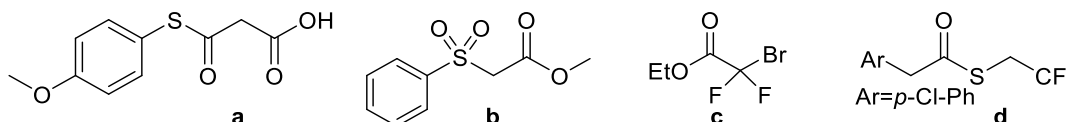
Figure 2.4

Following this kind of strategy, some groups have studied catalytic stereoselective transformations with MAHTs, exploiting either organometallic[285] or metal-free catalysis; being activated substrates, thioesters are versatile building blocks that can be transformed into amides, aldehydes, α-ketoalkynes, and ketones. In the organocatalytic field, Ricci's group realized an enantioselective decarboxylative addition to N-tosyl protected imines to afford β-amino thioesters in up to 79% ee using a Cinchona derivative as catalyst.[286] Wennemers exploited a Cinchona-urea catalyst to promote the enantioselective 1,4-addition to nitroolefins; the reaction was run under mild conditions and products were obtained in good yield and in up to 90% ee.[287] Imrpovements in this transformation were achieved by Bae et al. thanks to the use of squaramide based organocatalyst.[288] The author developed a metal-free strategy also for the stereoselective aldol addition of this nucleophile; a sulfonamide hydrogen bond donor was necessary to achieve ees higher than 90%.[289] A mechanicistic investigation through ^{1}H NMR studies was subsequently carried out by Fagnou group, revealing the base-catalysed addition of MAHT occurs reversibly prior to CO_2 elimination.[290]

In the subsequent years, other kinds of activated nucleophiles have been prepared. Wang and Li used the carbonylmethyl 2-pyridinylsulfone (Figure 2.4, **b**) in a Michael reaction with enals promoted by prolynol-based catalysts; the sulfone group can be readily removed under mild reaction conditions without affecting enantioselectivity of the final products.[291] Meanwhile, Kim's group employed ethyl bromodifluoroacetate in a copper-promoted conjugated addition to different kind of electrophiles (Figure 2.4, **c**).[292]

An alternative approach was proposed by Barbas, who tuned the electronic properties at the thioester to activate α-proton removal. He introduced the use of trifluoroethyl thioesters as nucleophilic substrates suitable for enantioselective activation by amines[293] (Figure 2.4, **d**). Our group used this same substrate as esters in aldol reactions promoted by a chiral Lewis acid generated by coordination of catalytic amounts of a chiral phosphine oxide to $SiCl_4$.[294]

2.3.2.<u>Stereoselective introduction of an acyl anion moiety</u>

The addition an acyl anion mimic in a stereoselective way is one of the still open challenges in organic synthesis.

Indeed, possibilities in synthesis design have been multiplied by the introduction of *umpolung* strategies,[295] firstly developed by Corey and Seebach in the '60. Consisting in the reversal of functional groups natural reactivity, this approach found main application in the establishment of acyl anion synthons, equivalents of this being, according to the original classification, acetal-type protected compounds (**a**), vinyl ether type protected acyl anions (**b**), unprotected acyl or acyl-analogous derivatives (**c**) and aldehyde hydrazones (**d**) (Figure 2.5).[296,297]
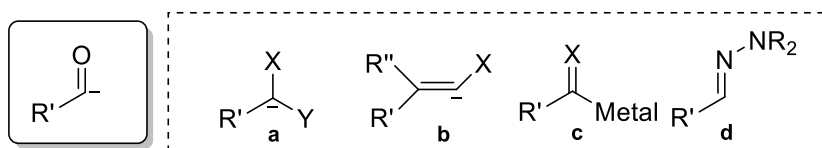
Figure 2.5

The milestone in the field of acyl anon introduction is represented by the Corey-Seebach reaction, which gave access to α-hydroxyaldehydes through lithiodithiane addition and subsequent hydrolysis (Scheme 2.35).[298] This strategy has widely been applied for the synthesis of complex molecules, as quinoline-substituted dihydropyridines[299] or ribitylaminolumazines derivatives.[300]
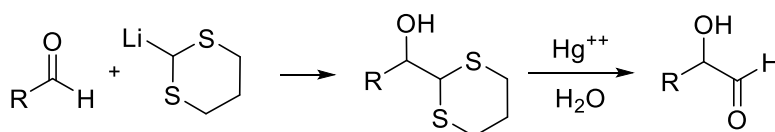
Scheme 2.35

The stereoselective introduction of the dithiane moiety was achieved not only when occurring on chiral substrates,[301] but also thanks to the employment of chiral acyl anion synthons (Scheme 2.36). In particular, the chiral dithiane dioxide afforded the corresponding α-dithio aldehyde as single diastereoisomer when deprotonated by NaHMDS, the origin of complete enantioselectivity being sodium coordination to oxygen atoms.[302] In addition, enantiopure 2-lithio-*N*-Boc-thiazolidines[303] have been prepared and used in the addition to non-enolizable aldheydes with high yield and dr around 70%; also in this case counteranion coordination is determinant for stereoselectivity.
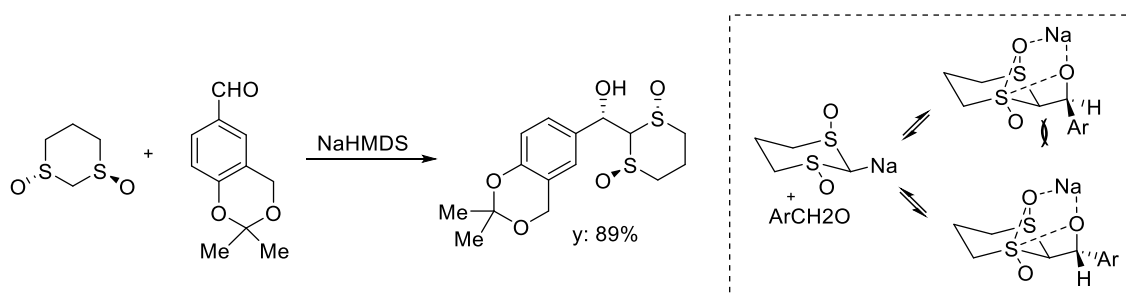
Scheme 2.36

Few catalytic versions of the metallated dithiane based methodology have been reported; two recent examples (2014) are the Pd-promoted synthesis of diaryl ketones by Yucel and Walsh and the conjugate addition to enones, proceeding through a fluorodesilylation mechanism, by Denmark group[304] (Scheme 2.36).
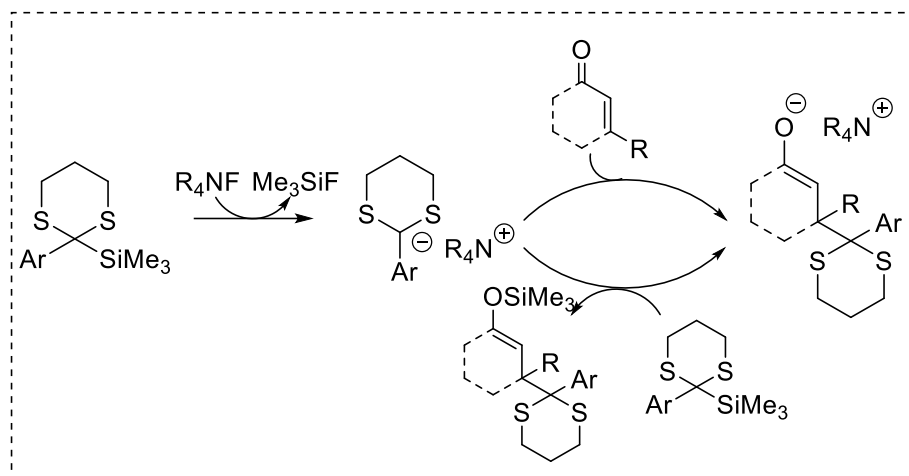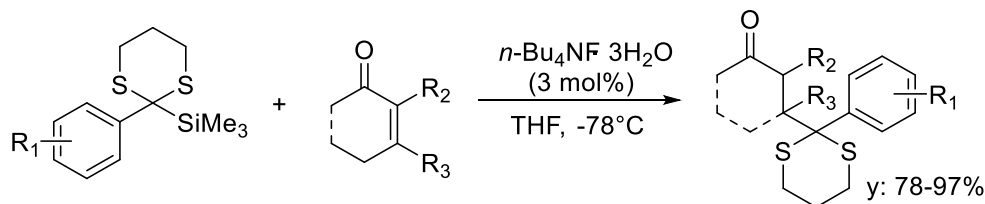
Scheme 2.37

The most ancient example of polarity inversion is represented by cyanide promoted benzoin condensation and dates back to 1903.[305] This method has not been abandoned: a recent example was reported by Johnson's group in 2003, employing KCN as catalyst in the cross silyl benzoin reaction between acylsilanes and aldehydes reported by the same group.[306]

In a related approach, cyanohydrines[307] have been used as stoichiometric acyl anion equivalents, building blocks in the total synthesis of complex compounds.[308] Stereoselection can be controlled either by the substrate[309,310] or by a chiral catalyst (Scheme 2.38).[311]
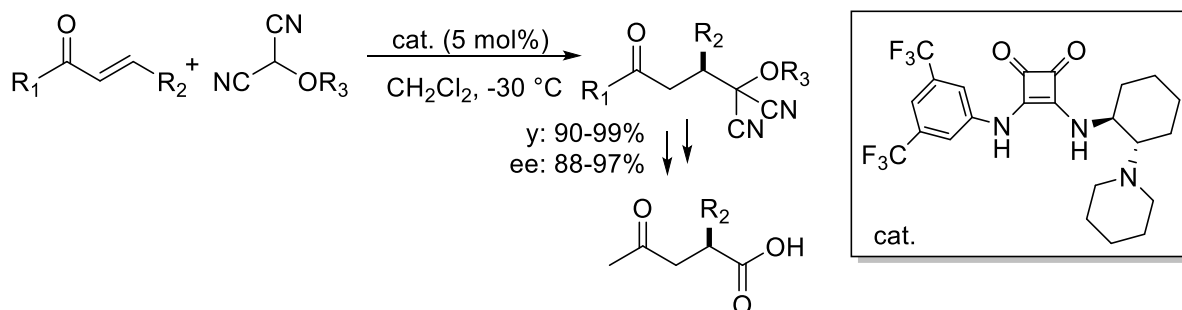
Scheme 2.38

A chiral equivalent of cyanide anion is represented by metallophosphites. In 2004 these were employed in an enantioselective cross silyl benzoin reaction, affording α-ketosilylethers in up to 87% ee;[312] in the catalytic cycle the catalyst acts consecutively as nucleophile, anion stabilizing group and

finally leaving group. Metallophosphines were involved successfully also in the Stetter reactions, exhibiting higher reactivity than their NHC-derived counterparts.[313]

Alternatively, catalysts affording masked acyl anion **a** are nucleophilic phosphines[314] typically working through the formation of Lewis adducts, namely phosphonium (di)enolate zwitterions, upon attack at electron-poor nuclei. In most of the cases these tertiary phosphine activate the β-position of conjugated systems, generating active intermediates that react with allenes in annulations. A different application of these catalysts was reported in 2015 by Haugen an co-workers, who developed the synthesis of *N*-acyl hydrazine through addition of 1,2-dicarbonyls to diazenes (Scheme 2.39).[315]
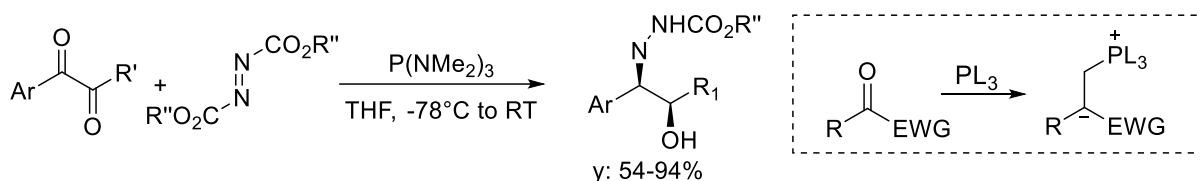
Scheme 2.39

As far as vinyl ether type acyl anion **b**, classical precursors are azalactones, which were recognised to be nucleophilic acylating equivalent of formaldehyde, reacting with both electrophilic olefins and aldehydes in moderate to good yield.[316] These have been employed in stereoselective additions relying on hydrogen bonds: in 2009, Uraguchi reported the use of spiro-aminophosphoranes that spontaneously assembled with phenols creating a supramolecular catalytic system promoting the conjugate addition to enones in up to 98% ee (Scheme 2.40).[317]
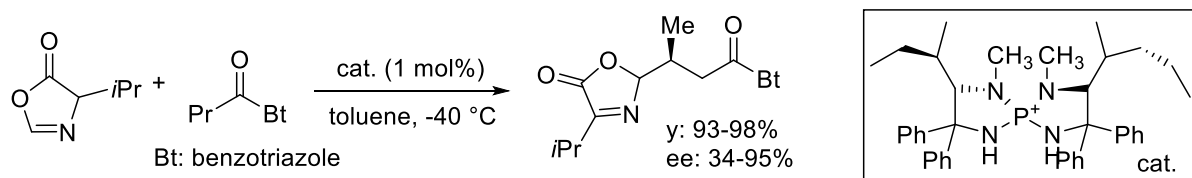
Scheme 2.40

Catalytic strategies have also been developed also for the *in situ* generation of type **b** intermediate. A widely applied approach involves the use of by *N*-heterocyclic carbenes (NHC) as catalysts.[318] The first report by Stetter, on the conjugate addition of the Breslow intermediate affording 1,4-dicarbonyl compounds, set the stage for a large number of different developments,[319] including the use of different acyl unit sources,[320,321] as well as the investigation of different catalytic systems, such as three-membered carbenes[322] and thiazolium salts immobilized on monolithic microreactors[323] or enzymes.[324] Finely tuning the nature of the carbene, it has also been possible to selectively obtain the acyl anion over the homoenolate intermediate, which is likewise available when employing enals as substrates, obtaining pyrazole derivatives upon [4+1] condensation with hydrazones.[325] In addition, synergistic NHC and palladium catalysis has been investigates, allowing direct allylation of aldehydes by attack of the *in situ* generated acyl nucleophile to an electrophilic allylpalladium complex.[326]

Employing chiral carbenes, enantioselective reactions have also been moulded; in designing proper catalysts, the triazolium scaffold was preferred over the thiazolium and imidazolium ones, being more tailorable thanks to the highest number of sites available for structural and electronic modifications (Figure 2.6).[327]
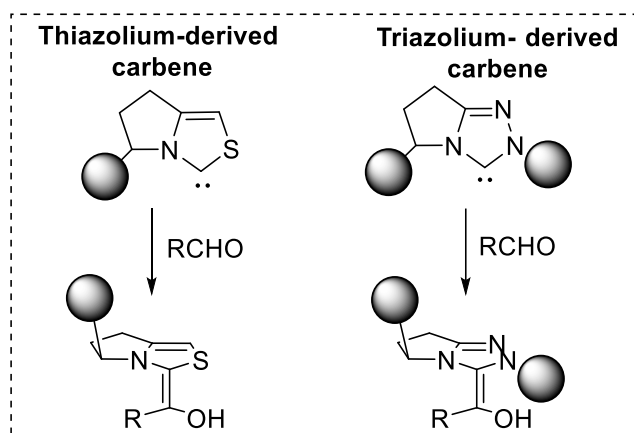
Figure 2.6

As for stereoselective benzoin condensation, first attempts by Sheehan group (1966) prompted a series of subsequent studies that gradually[328] brought the enantioselection level from 2 to 95%.[329] Research on stereoselectivity in the Stetter transformation started in 1996 by Enders et al., who obtained a chromanone derivative in 69% yield and 56% ee;[330] eight years later, the same group reported poor ees in the synthesis of 1,4-dicarbonyl compounds (Scheme 2.41).[331,332]
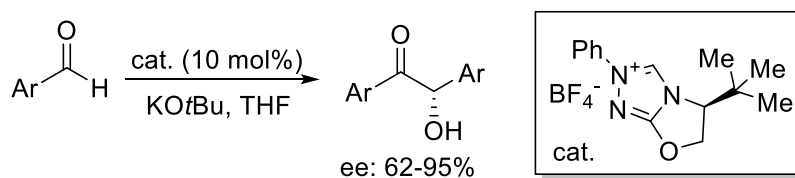
Scheme 2.41

Recent developments have also been achieved in the use of unmasked acyl equivalents **c**: in 2014, Lee and co-workers reported their application in the palladium mediated synthesis of ketones, where the acyl organometallic reagent was prepared *in situ* and reacted under mild conditions (Scheme 2.42) thus avoiding the tedious and harsh reactions previously required.[333]
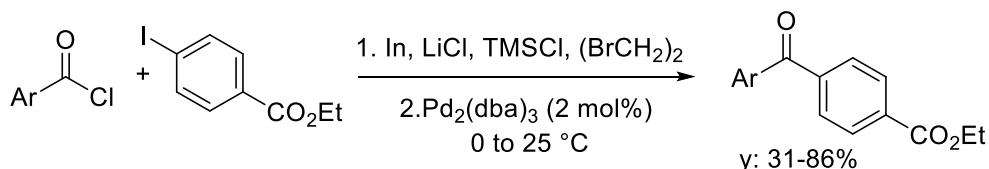
Scheme 2.42

The employment of aldehydes acyl hydrazones **d** is based on the fact that these compounds feature a nucleophilic character at the β-position, due to conjugative interaction between the C=C bond and the amino lone pair. Being kind of "aza-enamines", especially when substituted with electron donating

amino groups, they undergo a large series of β-functionalizatons with electrophilic reaction partners (Figure 2.7).[334]
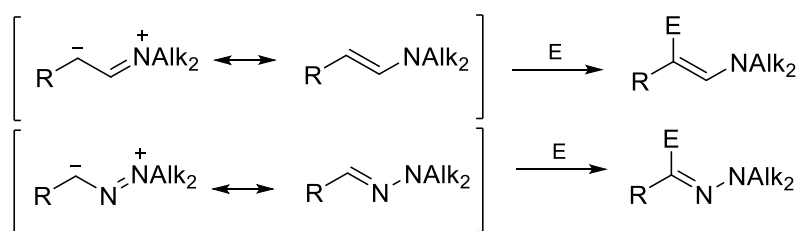
Figure 2.7

Employing chiral auxiliaries, a wide range of diastereoselective nucleophilic addition has been developed, both on α,β-unsaturated compounds (including nitroalkenes, enones, unsaturated lactones and alylidenmalonates) as well as on carbonyl compounds as aldehydes, trifluoromethylated ketones and α-amino acids. When achiral hydrazones were used, good levels of enantioselection were achieved applying stereoselective organocatalysis through hydrogen bonding or iminium ion[335] activation of the electrophile.[336]

In parallel to the use of acyl anion mimics, various strategies for the introduction of the carbonyl unit have been developed, not involving polarity reversal but relying on the "conventional" addition of various functional groups and their subsequent transformation.

Besides the most traditional examples as NO_2 conversion,[337] ozonolysis[338] or CN hydrolysis[339] (for which improved methodologies have recently been reported) or the unconventional methanolysis of the nitro(phenylsulfonyl)methyl moiety,[340] C-C oxidative cleavage methodologies are also available, including degradation of chiral aminonitrile derivatives,[341] copper(II) mediated deacylation[342] and primary amines promoted C-C breaking in aldehydes (Scheme 2.43).[343]

Scheme 2.43

72
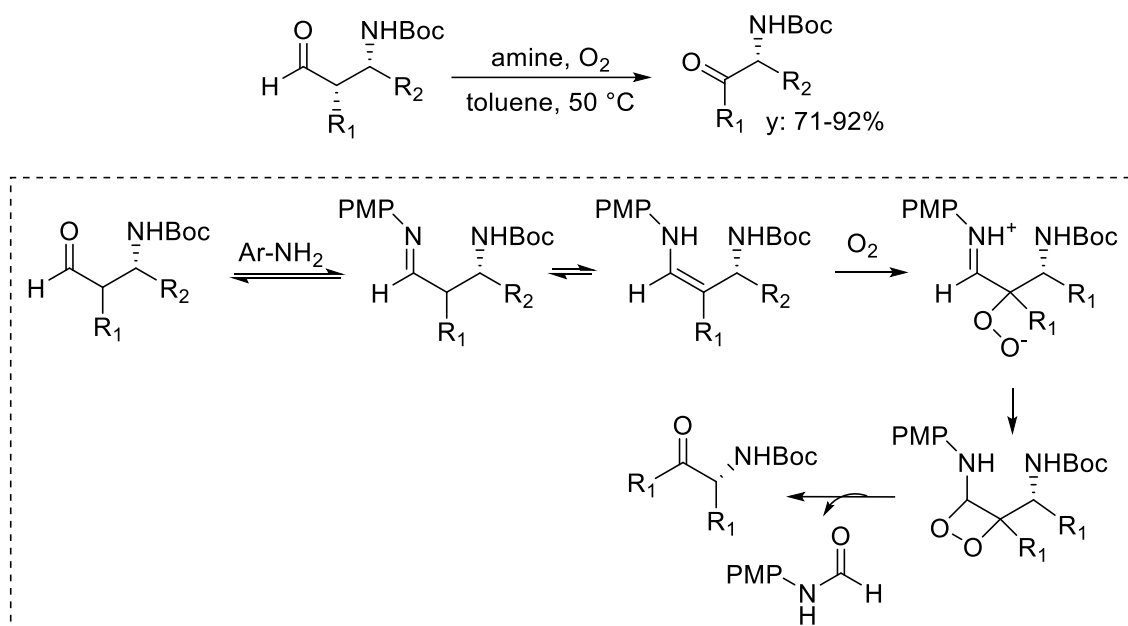
RESULTS AND DISCUSSION

As already mentioned, the herein reported insight into amino- and hydrogen bonding catalysis, as well as the rather complete introduction on specific substrates, was meant to contextualise and support the research projects developed during this PhD study.

In particular, in this thesis work we reported on (i) an aminocatalytic cascade between nitroacrylates and enones, optimization studies and extension of this transformation to hindered susbtrates, (ii) a stereoselective addition of activated nucleophiles to nitroacrylates promoted by chiral hydrogen bonding catalysts, the stereoselective conjugate addition of a peculiar 2-carboxythioester-1,3-dithiane to (iii) nitrostyrene derivatives (iv) and to enones, (v) the synthesis of enantiomerically enriched trifluoromethylated nitroalkanes starting from the corresponding olefins and (vi) on the use of innovative reaction media, namely Deep Eutectic Solvents, for stereoselective organocatalytic reaction. In addition, a Chapter is dedicated to investigations on organophotocatalytic reactions carried out at University of Regensburg, under the scientific supervision of Professor Burkhard König.

3. STEREOSELECTIVE CONJUGATE ADDITION OF DIENAMINE ACTIVATED ENONES TO β-NITROACRYLATES

3.1. Stereoselective synthesis of highly functionalized chiral 2-nitro-cyclohexane carboxylic esters via catalytic dienamine addition to β-substituted-β-nitroacrylates

Despite the field of organocatalytic cascade reactions has largely been investigated, we noticed that nitroacrylates have been often neglected in favour of the cognate nitroalkenes. We thus focused our attention on these compounds that, even though less easy to prepare, feature a futher functional group in addition to the nitro one and give access to more highly functionalized and versatile products.

In particular, we envisaged to use β-substituted-β-nitroacrylates in an amino-catalysed double Michael addition sequence with α,β-unsatured ketones, to obtain cyclohexanones featuring three contiguous stereocentres – including a quaternary one (Scheme 3.1).
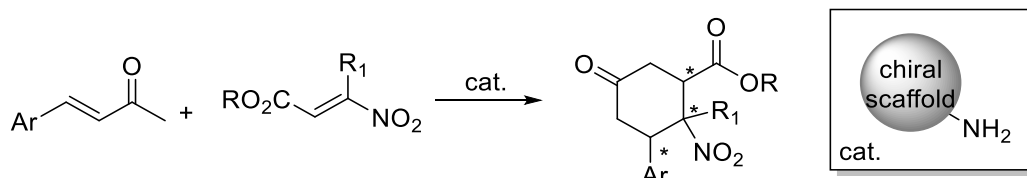
Scheme 3.1

Our strategy was based on the generation of a chiral dienamine by condensation between an enone and a chiral primary amine followed by reaction of the obtained intermediate with the β-position of the nitroacrylates thus forming a zwitterionic species where a second new C-C bond should form by intramolecular reaction (Figure 3.1).
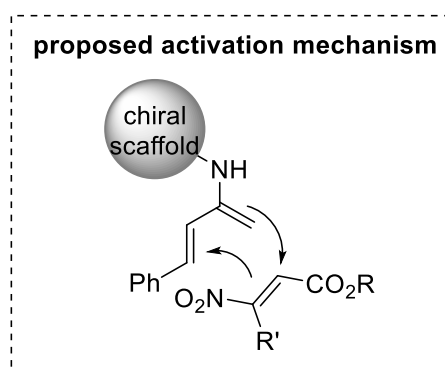
Figure 3.1

The chiral cyclohexanones thus obtained are direct precursors of chiral six membered cyclic[344] β-amino acids,[345] which have always been regarded as molecules of great interest because of their presence in many natural products[346] and biologically active compounds.[347] Cyclic β-AA have been employed as scaffold in the synthesis of glycomimetics[348] and as starting materials for more complex heterocycles. Moreover, they are constituents of β-peptides, unnatural oligomers characterized by a high resistance to enzyme-catalyzed hydrolysis[349] and often presenting discrete and predictable folding propensities. Indeed, β-peptides containing cyclic β-amino acid residues display a higher intrinsic tendency to adopt

a regular secondary structure (helix, sheet and turn) than acyclic residues do. These protease-resistant backbones could deliver protein-like functions as biomolecular recognition and catalysis and were used as building blocks in peptide nanotubes.[350] In this class of AA, hydroxyl-substituted β-amino acids are of considerable importance because of their increased water solubility and their occurrence in biologically active compounds.[351] In fact, they can be transformed into heterocycles or β-lactams and can be seen as advanced intermediates for the synthesis of some alkaloids derivatives in the lycorine, crinine and caranine series (Figure 3.2). In addition, cyclic β-amino acids found application in chiral alcohol resolution.[352]
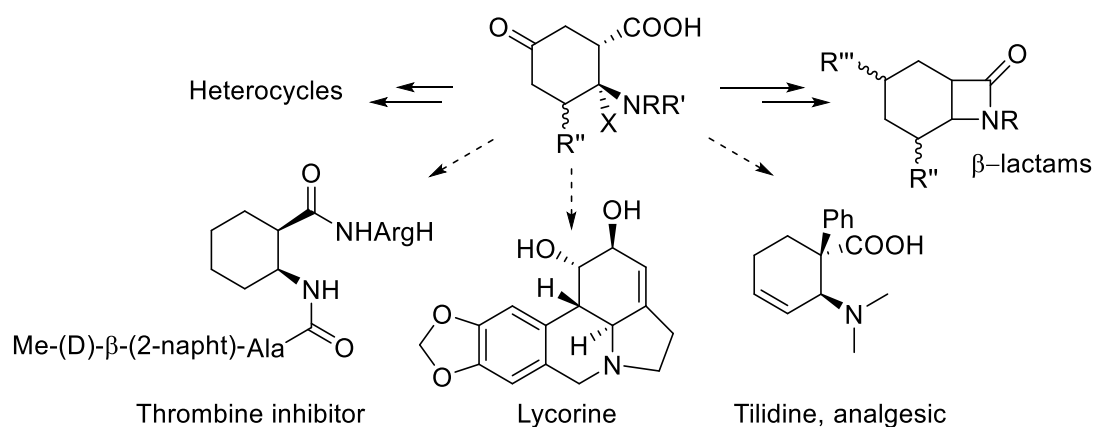
Figure 3.2

The aminocatalyzed reaction we designed was related to the cycloaddition between enones and nitrostyrenes promoted by 9-amino-*epi*-Cinchona alkaloids derivatives reported by Melchiorre group,[87] and to several previous transformations catalysed by proline derivatives. As already mentioned in Chapter 1, the primary amine promoted reaction was considered to proceed through a stepwise pathway rather than via a Diels-Alder type cycloaddition (Scheme 3.2), as supported by experimental evidences. In fact, solvents as MeOH and H_2O completely suppressed reactivity, while Diel-Alder reactions are known to be accelerated by these polar media. More convincingly, intermediate of the first Michale type addition was isolated as by-product from the reaction mixture (Figure 3.3).
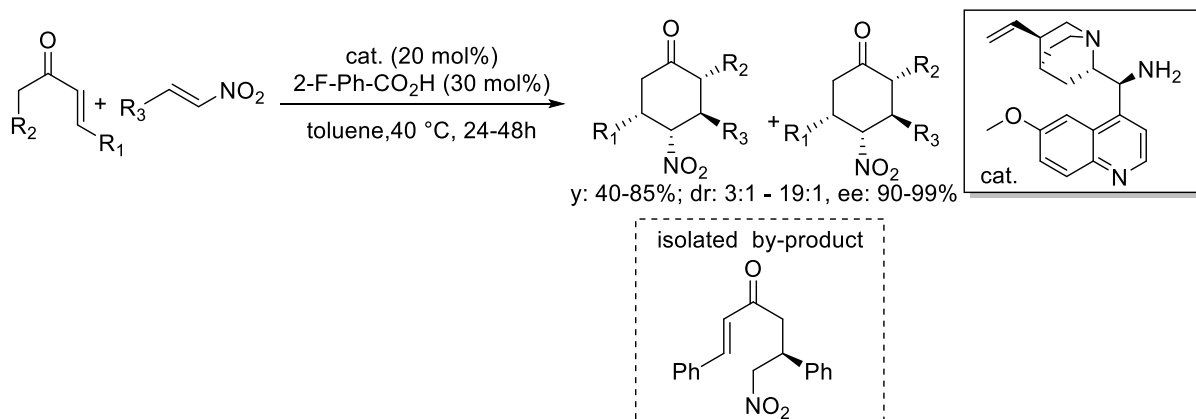
Scheme 3.2
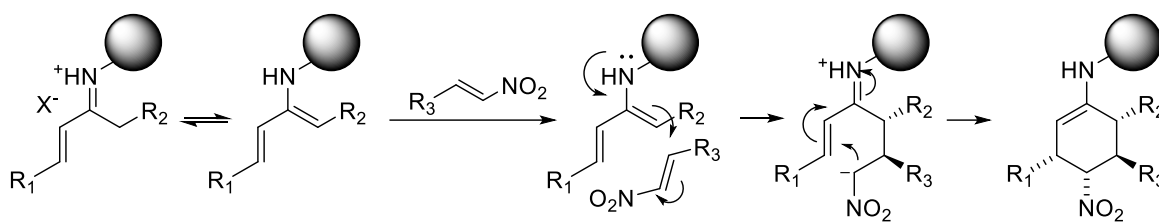
Figure 3.3

For the synthesis of bicyclic hexanones derivatives, obtained from cyclohexenones and nitroalkenes in the presence of substoichiometric amounts of chiral pyrrolidines, instead, two different pathways were proposed (Scheme 3.3), i.e. both the double Michael sequence (Figure 3.4)[353] and the concerted one (Figure 3.5).[354] However, the latter was more plausible, as no conjugate addition intermediate was observed and ESI-MS analysis confirmed the formation of two of the supposed transient species.[355,356]
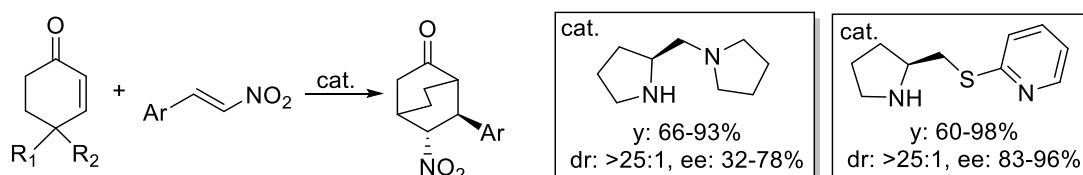
Scheme 3.3
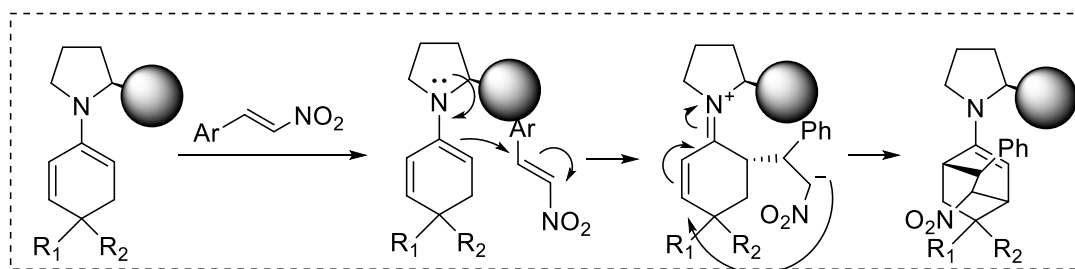
Figure 3.4
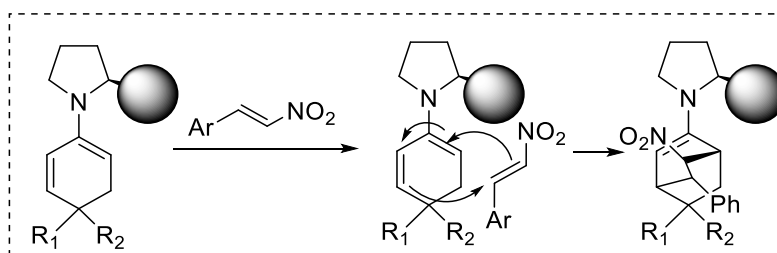
Figure 3.5

Based on this background, we tested the effectiveness of both primary and secondary amines in promoting the reaction between a linear enone and β-substituted-β-nitroactrylates (Scheme 3.1)

As for the nitroacrylates synthesis,[a] a three step procedure turned to be the most convenient one.[357] This involves nitroalkane attack onto glyoxylic acid under basic conditions, esterification via acyl chloride formation and one-pot mesylation-elimination (Scheme 3.4).[b]
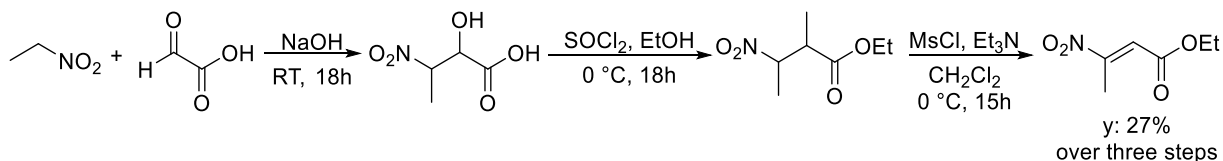
Scheme 3.4

The reaction between (*E*)-3-ethyl-3-nitro ethylacrylate and 4-phenyl-2-butanone was investigated as model reaction. This was typically performed in toluene at 40 °C, in the presence of 0.2 equivalents of catalyst and 0.3 equivalents of an acid co-catalyst (Scheme 3.5; products are represented with the absolute configuration obtained with quinine derivative as catalyst).
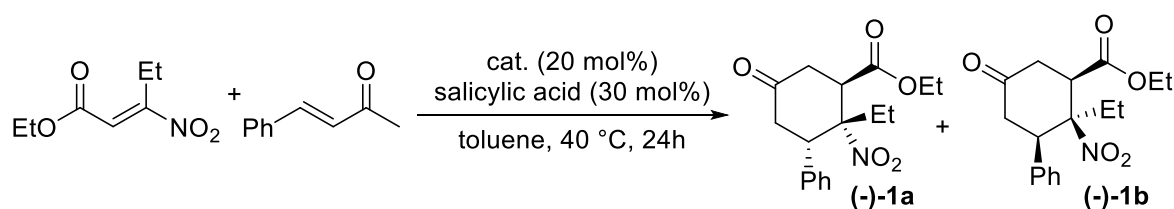
Scheme 3.5

Nor the commercially available Hayashi-Jørgensen catalyst neither the proline/pyridine derivative[c] afforded any product, probably because of steric requirements of both reaction partner. In addition, it seems reasonable to hypothesize that nitroacrylates, being less reactive than nitrostyrenes, require some sort of Lewis acid activation that is not offered by these catalysts.

Interesting results were instead obtained with amino-quinidine: under standard conditions, only two out of the four possible diastereoisomers formed, in 30:70 dr and with 88 and 85% ee. When the *pseudo*-enantiomeric catalyst, deriving from quinine, was used, even higher – and opposite – enantioselectivity (97% and 95% ee) with similar dr (80:20). Equally configured primary amines featuring different substituens on the quinoline ring were tested, to obtain results comparable (Figure 3.6); this suggested that the heteroaromatic ring of the catalyst is oriented so that its C6' position is far enough from the reaction core not to influence its outcome.

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[a] Several nitroacrylates have been prepared by Prof. Alessandro Palmieri and co-workers, in University of Camerino.

[b] Optimization studies on nitroacrylates synthesis were carried out by Davide Parravicini during his master thesis work.

[c] The secondary amine tested was obtained from proline, as a shorter synthesis starting from prolinol failed:
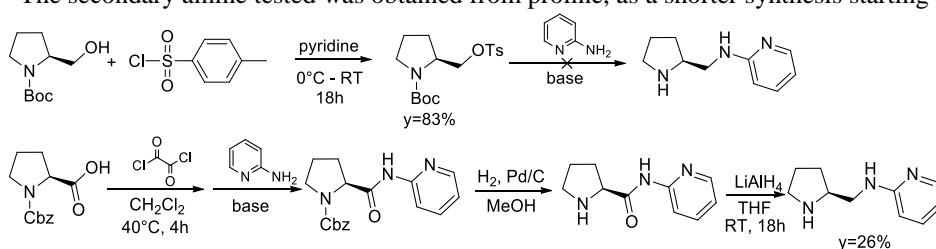
The high stereoselectivity obtained suggests the reaction proceeds through a rigid transition state, where it is reasonable to hypothesize a non-covalent interaction between the protonated quinuclidine moiety and the nitro group of the electrophile (Figure 3.7). Therefore, the formation of the first new C-C bond occurs in a chiral environment where both reaction partners are kept in a specific orientation being simultaneously bound to the catalyst; the second stereocentre is generated within a strained structure, where a strong conformational bias helps to control the final product configuration.

A
y:82%, dr: 30:70
ee: (+) 88% - 85%

B
y:72%, dr: 20:80
ee: (-) 97% - 95%

C
y: 43%, dr: 30:70
ee: (-) 95% - 92%

D
y: 70%, dr: 50:50
ee: (-) 83% - 90%

E
y: 87%, dr: 30:70
ee: (-) 92% - 96%
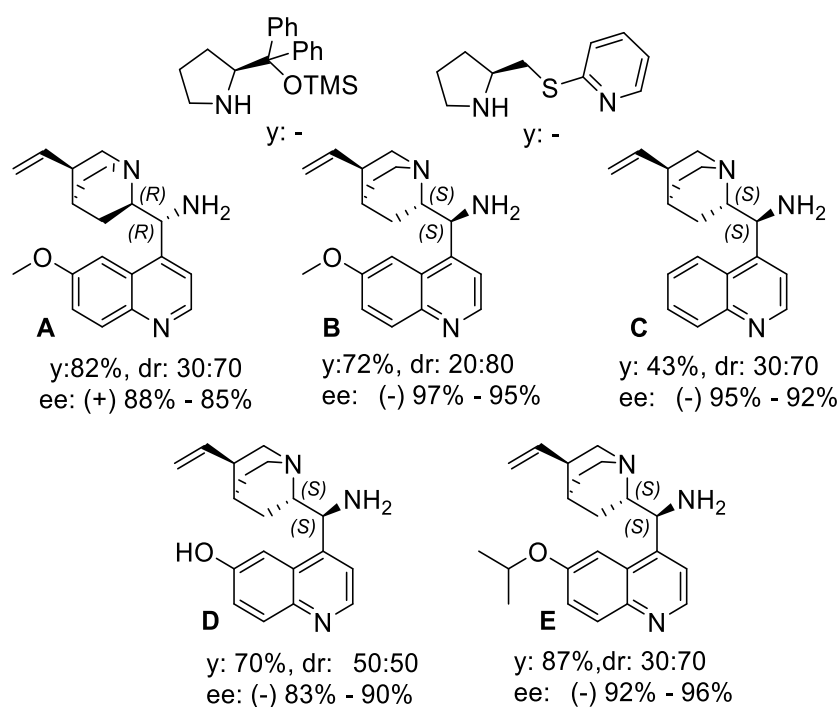
Figure 3.6 – dr indicates **1a**:**1b** ratio; **1a** - **1b** enantiomeric excesses are reported.
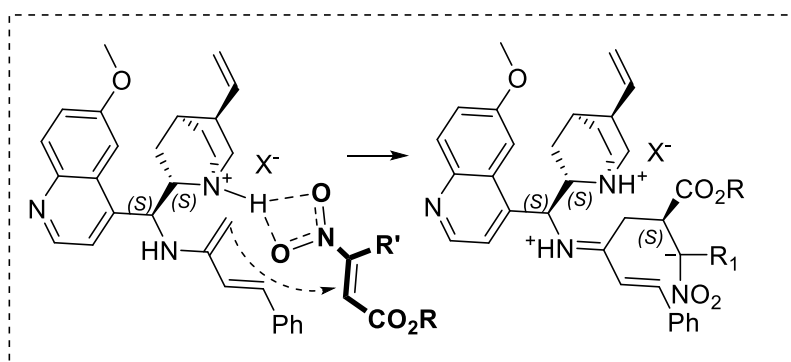
Figure 3.7

Looking for the best experimental conditions, several parameters were investigated (Table 3.1). Reaction temperature did not show any appreciable influence, as changing it from 5 °C to 60 °C led to the products in almost the same yields and enantiomeric excesses; the result remained virtually unchanged also when the reaction time was changed from 24 to 48 hours. As for the solvent, toluene proved to be the best choice and dichloromethane did not compromise significantly the stereoselectivity. A drop in both enantioselection and yield was registered instead when running the reaction in DMSO, probably because the high polarity of the solvent interferes with the polar interactions in the transition

state; in pure water high levels of ee were observed, although the yields were low likely because of solubility issues.
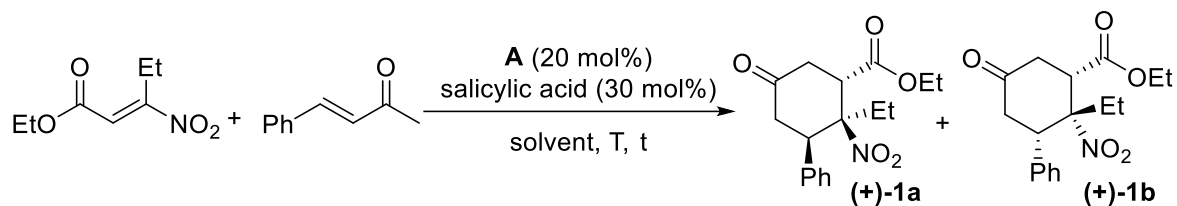
Scheme 3.6

solvent	T (°C)	t (h)	ketone/nitroacrylate	y (%)	dr (1a:1b)	ee (%) (1a-1b)
toluene	40	48	2/1	42	33:67	(+) 92-87
toluene	60	48	2/1	55	48:52	(+) 94-81
toluene	RT	48	2/1	72	33:67	(+) 96-93
toluene	5	48	2/1	60	20:80	(+) 93-92
toluene	40	24	2/1	82	33:67	(+) 88-85
toluene	40	48	1/2	80	50:50	(+) 70-75
toluene	40	48	1/1	57	33:67	(+) 95-90
CH$_2$Cl$_2$	40	48	2/1	80	25:75	(+) 87-83
EtOH	40	48	2/1	70	30:70	(+) 91-78
DMSO	40	48	2/1	40	50:50	(+) 77-76
H$_2$O	40	48	2/1	37	15:85	(+) 91-87
H$_2$O	5	48	2/1	24	9:91	(+) 90-93

Table 3.1

The effect on the yield exerted by the acidic additive, which proved to be necessary for the reaction, depended both on its acidity and on its structure. However, a clear correlation between co-catalyst activity and pK_a value cannot be observed, as the best results were obtained with salicylic acid, whose pK_a is intermediate among the other co-catalysts tested (Table 3.2). Some effects of the additive on the stereochemical outcome were also observed; for instance, the use of 4-hydroxybenzoic acid instead of 2-hydroxybenzoic acid caused a decrease in the enantioselectivity for both isomers, suggesting that the OH group could be involved in the transition state through hydrogen bonding interactions.

acidic co-catalyst	acid p$K_{a(DMSO)}$	y (%)	dr (1a:1b)	ee (%) (1a-1b)
-	-	-	-	-
2-OH-benzoic	6.8[358]	82	30:70	(+) 88-85
Acetic	12.3	37	50:50	(+) 95-70
(R)-BPA[a]	~ 3.5[359]	65	20:80	(+) 62-80
(S)- BPA[a]	~ 3.5	63	25:75	(+) 40-89
2-F-benzoic	~ 10[360]	61	47:53	(+) 93-78
2-F-benzoic[b]	~ 10	60	33:67	(-) 90-88
4-OH-benzoic	7.1[361]	50	48:52	(+) 83-72

Table 3.2 – Reactions were performed on the model substrate (ketone:nitroacrylate 2:1) in toluene (1M) at 40 °C for 48 hours in the presence of catalyst **A** (20 mol%). [a]BPA: 1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate. [b]Reaction performed in the presence of catalyst **B**.

The general applicability of the methodology was then investigated. Therefore, enones with different substituents at C4 position, including an electron rich and poor phenyl group, an heteroaromatic ring and an alkyl chain, were employed in combination with (E)-ethyl β-ethyl nitroacrylate. In all cases, excellent enantioselectivity were obtained, often exceeding 90%. Yields decreased passing from 2-thiopenyl to 1-(4-bromo)-phenyl butenone, probably due to the decreasing electron donating ability of the aromatic residue, resulting in a diminished reactivity at the conjugated C1 position of the reactive dienamine; the even lower reactivity of 2-pentenone could be ascribable both to the weakness of the +M effect exterted by the methyl group on the dienamine intermediate and to the possibility of formation of a non reactive linear dienamine (Figure 3.8).

cat. **A** - y: 53%, dr: 45:55, ee: (+) 93%-81%
cat. **B** - y: 40%, dr: 47:53, ee: (-) 94%-92%

cat. **A** - y: 80%, dr: 12:88, ee: (+) 91%-90%
cat. **B** - y: 77%, dr: 25:75, ee: (-) 97%-98%

cat. **A** - y: 21%, dr: 25:75, ee: (+) 97%-87%
cat. **B** - y: 22%, dr: 47:53, ee: (-) 97%-93%
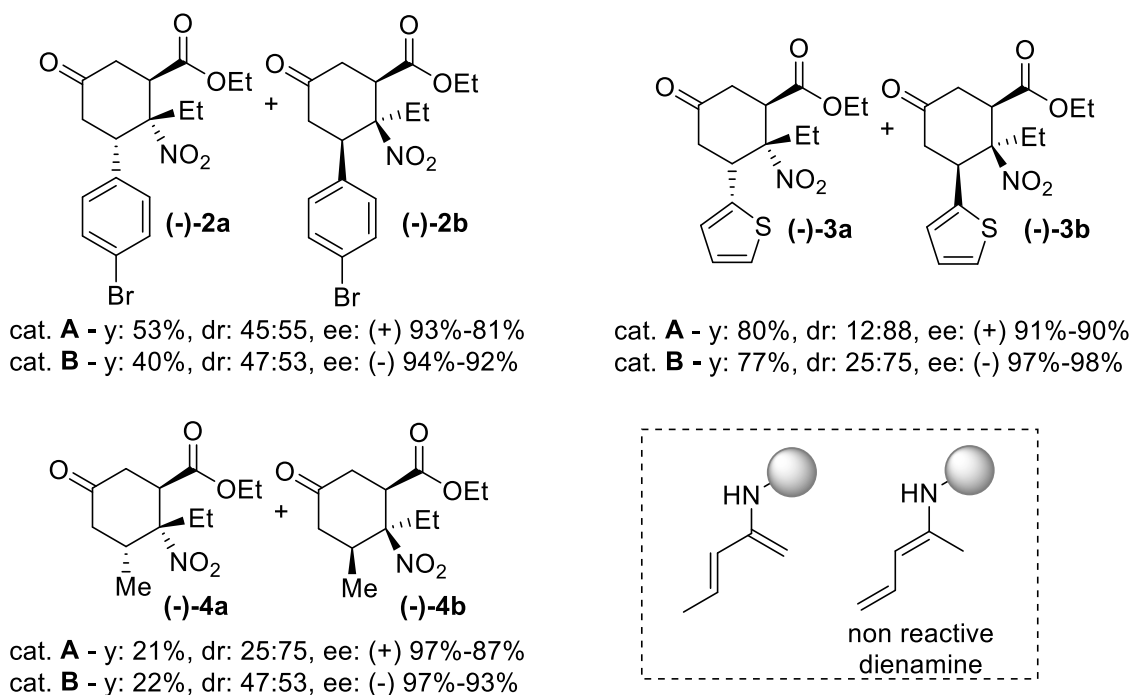
Figure 3.8 - Reactions were performed in toluene (1M) at 40 °C for 48 hours in the presence of catalyst **A** or **B** (20 mol%) and salicylic acid (30 mol%).

Nitroacrylates with various alkyl groups in β-position and different ester residues were also tested, but no deep difference in terms of yield and selectivity were observed. When β-unsubstitued nitroacrylates were employed, no reaction occurred (Figure 3.9). This last result was unexpected, as no a priori differences in reactivity with respect to the β-alkylated counterparts could be envisaged. A possible rationalization involves poor stability of this electrophile under the reaction conditions, as no starting material was recovered from the reaction mixture; however, further experiments would be needed to confirm this hypothesis.

cat. **A** - y: 67%, dr: 33:67, ee: (+) 83%-86%
cat. **B** - y: 60%, dr: 30:70, ee: (-) 96%-94%

cat. **A** - y: 67%, dr: 20:80, ee: (+) 90%-84%
cat. **B** - y: 60%, dr: 12:88, ee: (-) 88%-92%

cat. **A** - y: 67%, dr: 30:70, ee: (+) 91%-77%
cat. **B** - y: 60%, dr: 32:68, ee: (-) 93%-90%

y: -
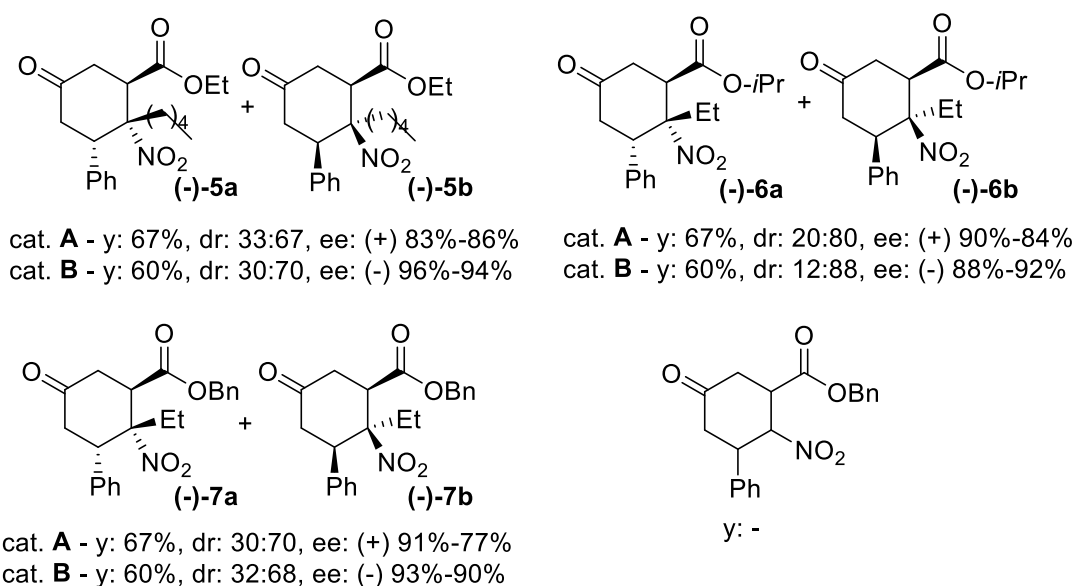
Figure 3.9 - Reactions were performed in toluene (1M) at 40 °C for 48 hours in the presence of catalyst **A** or **B** (20 mol%) and salicylic acid (30 mol%).

The relative configuration of the products was established by NMR studies, while the absolute configuration was determined to be 1*R*, 2*S*, 3*R* for the major isomer of the 4-Br phenyl derivative thanks to X-ray analysis (Figure 3.10). Interestingly, it was observed that in the major isomer obtained the nitro and the ester group are in a *cis* disposition and does not reflect that of the starting nitroacrylate. This observation strongly suggests that diastereoisomer **b** is not obtained through a Diels-Alder-like mechanism.

Ar=4-Br-Ph
major diastereoisomer
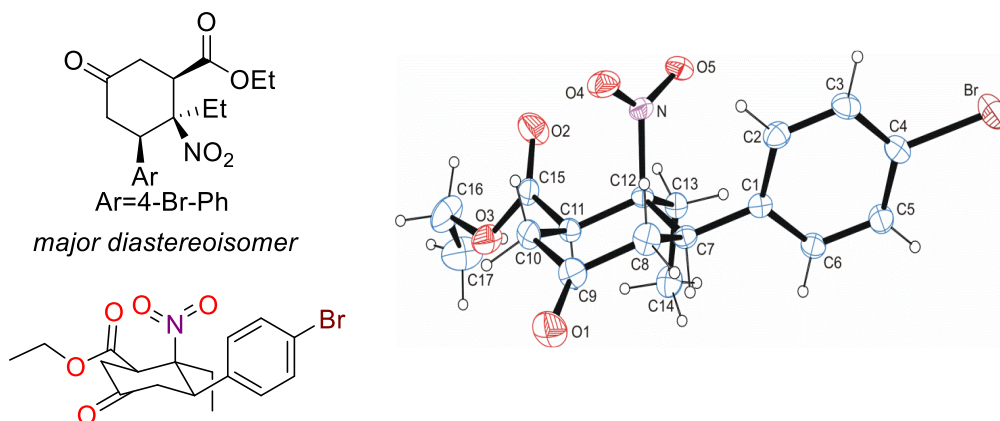
Figure 3.10

A further proof against a concerted pathway was obtained observing that the same diastereomeric ratio was obtained starting from a Z-configured nitroacrylate.[d] It was thus reasonable to envisage a stepwise mechanism, involving a double Michael addition sequence, rather than a [4+2] cycloaddition.

According to the proposed reaction mechanism (Figure 3.11), catalyst condensation with the α,β-unsaturated ketone generates the imine intermediate **i** that, in the presence of the acidic co-catalyst, is protonated to give the corresponding iminium ion. This species is characterized by an increased acidity of the α-protons, and the conjugated base drives the tautomerization towards the conjugated dienamine **ii**, i.e. the active nucleophile attacking the nitroacrylate. The thus formed iminium ion exhibits two conformers **iii** and **iv** generated upon rotation around the single bond. Due to the steric hindrance of the α-alkyl substituted nitro derivative and to stabilization of the negative charge, both species exist for a time long enough to allow ring closure; so, from this two zwitterionic intermediates the two diasteroisomeric products are formed.
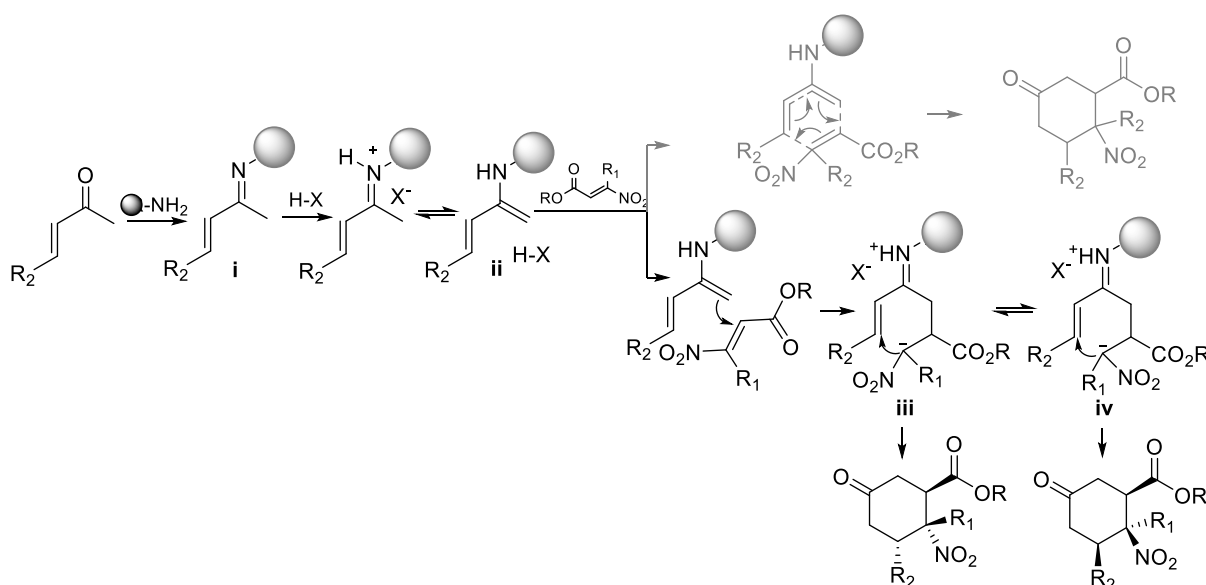
Figure 3.11

Finally, the synthetic versatility of the functionalized 2-nitro-cyclohexanone carboxylic ester derivatives was investigated; the two diasteroisomers were separated through column chromatography, and subjected to different reduction protocols.

It resulted that the C=O function of the major isomer can be selectively reduced with $NaBH_4$ affording the corresponding alcohol **8** as a single isomer. Reduction of both the nitro and the ketone could be accomplished to afford compound **11** using $NaBH_4/NiCl_2$ (Scheme 3.8). Applying the Zn/acid procedure to reduce the nitro group, N-hydroxyl β-lactam **9** was obtained. Treating cyclohexanol **8** and hydroxylamide **9** with $NaBH_4$, led to N-OH-lactam **10** (Scheme 3.7).

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[d] Z-configured nitroacrylate was obtained through photocatalyzed isomerization.
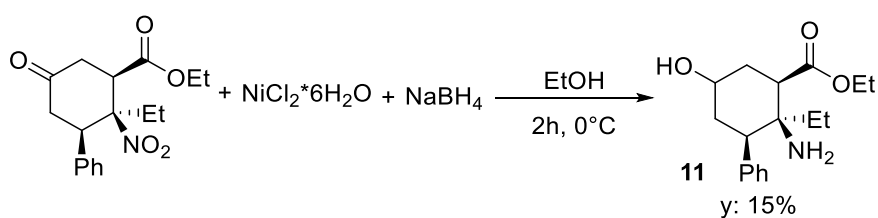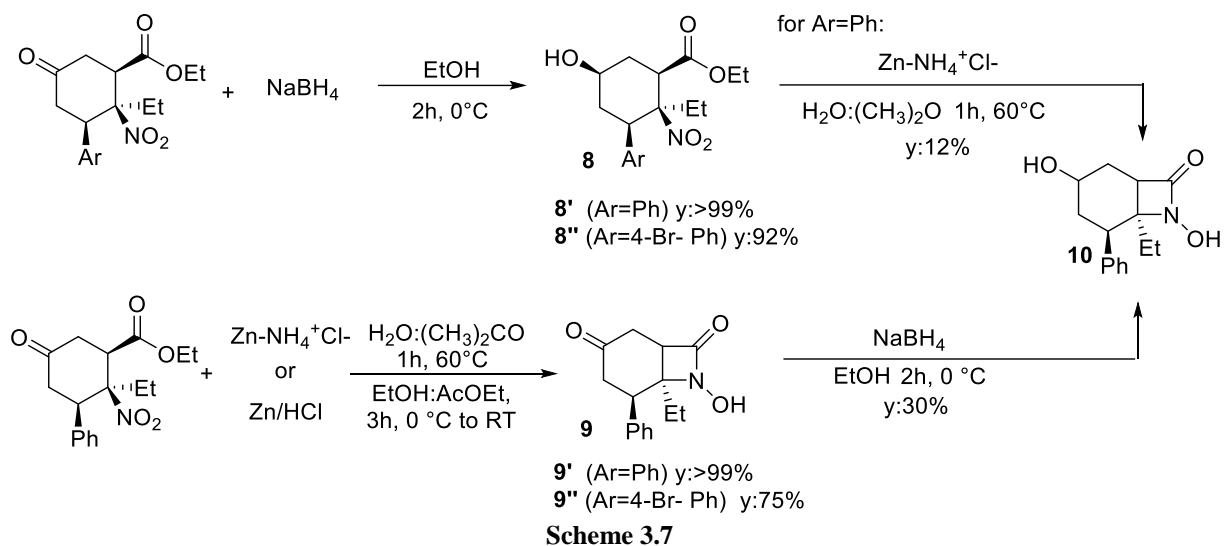
Scheme 3.7

Scheme 3.8

Reaction of cyclohexanones **1a** and **2a** with $LiAlH_4$ produced diol **12** that manteined its NO_2 function. Further reductions with Zn/NH_4Cl or Zn/HCl led to compounds **13** and **15**, respectively (Scheme 3.9).
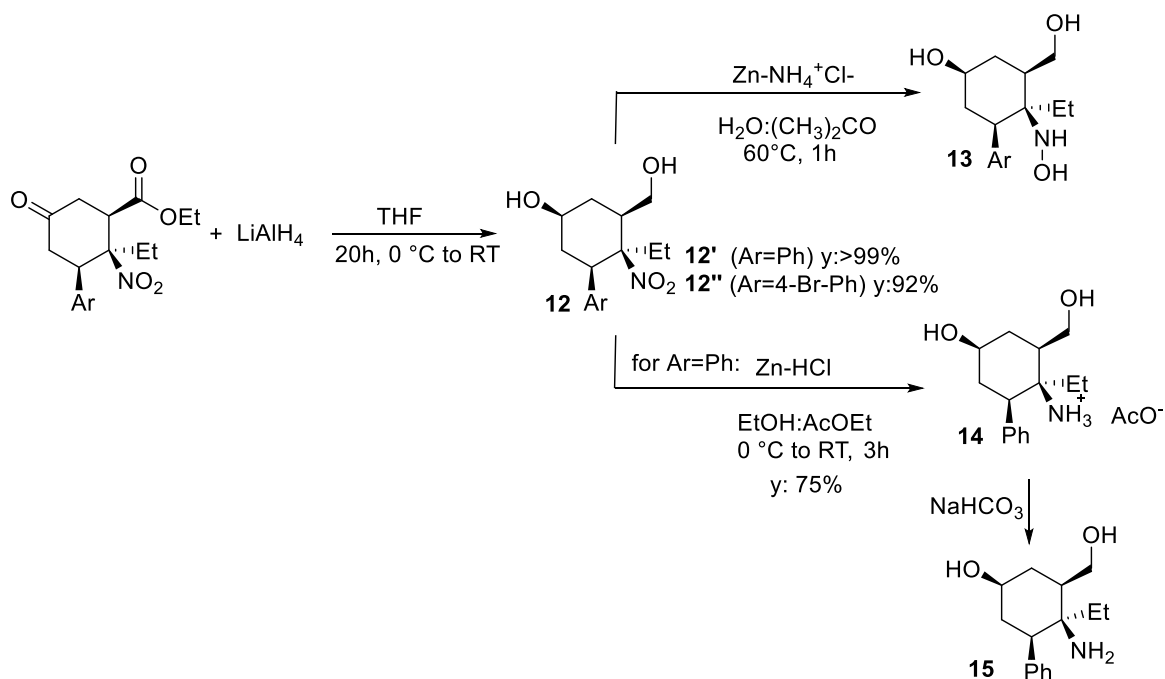
Scheme 3.9

Noteworthy, applying the zinc-acid reducing system on the minor isomer **1b** led to functionalized cyclohexane **16**, which is the product of a Clemmensen-type reduction[e] of the carbonyl group (Scheme 3.10).
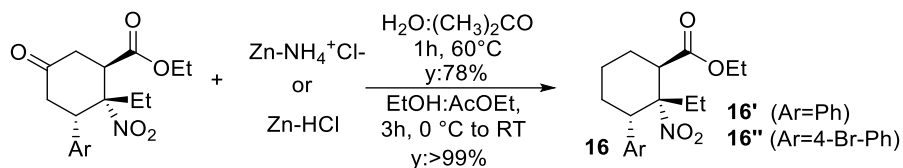
Scheme 3.10

In conclusion, we developed an organocatalytic cascade to obtain 4-nitro cyclohexanones 3-carboxylic esters bearing one quaternary and two tertiary stereocentres as two diastereoisomers in high yields and up to 98% ee. This compounds were further transformed into several polyfunctional molecules.[362]

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[e] Clemmensen-type reductions proceeding in the absence of Hg-amalgam have already been reported.

3.2. <u>Synthesis of highly decorated chiral 2-nitro-cyclohexane carboxylic esters through microwave-assisted organocatalyzed cascade reactions</u>

To improve the good results obtained, further studies were devoted to this one-pot synthesis of functionalized cyclohexanones starting from nitroacrylates.

Indeed, the reaction time was quite long and a discrepancy between isolated yield and conversion determined through ¹H NMR was observed - the first being typically 15-20% lower than the latter. This suggested the likely occurrence of undesired reaction pathways, leading to minor by-products that, however, have not been spectroscopically identified in the crude and not isolated in the chromatographic purification. So, further studies were devoted to conditions optimization on a model reaction promoted by the quinine-derived catalyst **B**, which previously afforded the best results (Scheme 3.11).
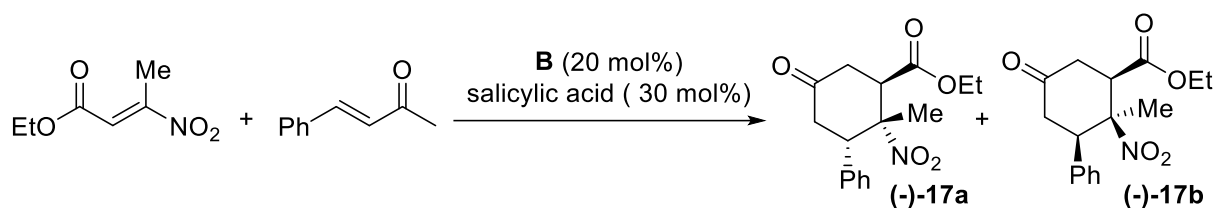
Scheme 3.11

Time dependence was evaluated stopping the reaction after short reaction times. After 30 minutes at 40 °C, ¹H NMR analysis revealed a conversion of 52% while the isolated yield was 48%; after 2 hours and in the same conditions, 73% conversion was reached, just slightly lower than that obtained in 48 hours (80%). These results seemed to support the idea that the desired reaction is quite fast, reaching a stationary state. At this stage, however the nitroacrylate, which is the limiting reagent, is not completely consumed and unwanted events could take place.

As our aim was to obtain equal or better yields in shorter reaction time, the exploitation of microwaves appeared an interesting choice.

Microwave technology,[363] implemented in organic chemistry since the middle of the '80s,[364] is based on the application of radiations in the microwaves range causing a temperature increase and a rate acceleration. A rationalization for this acceleration effect can be given considering the Arrhenius equation, where both the pre-exponential factor *A*, describing molecular mobility, and the free energy of activation $\Delta E^{\ddagger}$ could be affected (Equation 4).

$$k = Ae^{-\frac{\Delta E^{\ddagger}}{RT}}$$

Equation 4

For the amino-quinine catalysed reaction between (*E*)-ethyl β-methyl-β-nitroacrylate we thus set up a typical experiment where after a 10 minutes period during which the chiral catalyst (0.2 equivalents)

85

and the acid (0.3 equivalents) were stirred at room temperature, the two reaction partners were added and the mixture was subjected to 300W microwave irradiation at 40 °C.

It was observed that the best diastereomeric ratio (**17a**:**17b** 20:80) was obtained after 15 minutes, decreasing over longer reaction time: this behaviour may be rationalized considering the catalyst possibility to induce an equilibrating retro-cyclization. Yields increased from 59% to 72% after 30 minutes, to decrease again after 45 minutes, a trend paralleling that observed under standard thermal conditions and supporting again the hypothesis of side pathways occurrence. Passing from 40 to 80 °C and changing the solvent from toluene to ethanol did not bring significant changes, while employing the *quasi*-enantiomeric catalyst **B** caused a decrease in both efficiency and enantioselectivity, while diastereoselection switched in favour of the usually minor product (Table 3.3).

cat.	solvent	T (°C)	t	conv.[a] (%)	y (%)	dr (17a:17b)	ee (%) (17a:17b)
B	toluene	40 °C	15 min	55	59	1:4	80-93
B	toluene	40 °C	30 min	73	72	1:3	75-93
B	toluene	40 °C	45 min	79	60	1:3	78-94
B	toluene	80 °C	2 h	nd	52	1:1.5	93-75
B	EtOH	80 °C	2 h	nd	56	1:2	87-63
A	EtOH	80 °C	2 h	nd	38	2:1	79-27

Table 3.3 - Reactions were performed in the presence of catalyst A or B (20 mol%) and salicylic acid (30 mol%) under microwave irradiation. [a]Conversion determined by ^{1}H NMR analysis on the crude.

Despite its efficiency, MW heating did not allow cyclization between (*E*)-4-phenylbutenone and the unsubstituted (*E*)-benzyl β-nitroacrylate, that already proved unreactive under classical heating conditions. However, the application of microwave technology enabled also the extension of the procedure to C1 substituted enones, which were unreactive under classical conditions (Scheme 3.12).
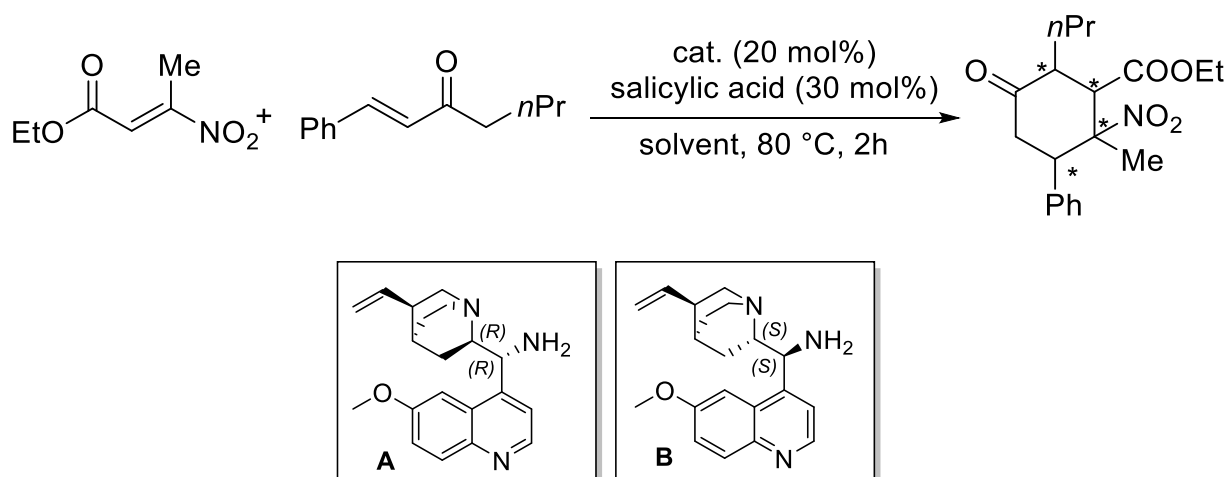
Scheme 3.12

In particular, (*E*)-1-phenyl-2-hepten-3-one was reacted with ethyl (*E*)-3-nitrobut-2-enoate in the presence of 9-amino-epi-quinine and salicylic acid; the desired products were detected only by applying microwave heating. At first, the reaction was run at 80 °C in polar solvents. The cyclized product,

featuring four contiguous stereocenters, was obtained in modest yields as a mixture of only two out of the eight possible diasteroisomers and ee up to 87%. Different concentrations, reaction times or solvents did not lead to any significant improvement. Since monitoring the reaction by ^{1}H NMR revealed that no improvement in conversion could be achieved running the reaction for longer times, a reaction time of 2 hours was considered the best compromise (Table 3.4).

The relative configuration of the stereocentres was assigned by NMR experiments, while the absolute configuration was assumed to remain unchanged with respect to that of products **17** (Figure 3.12). Diastereomeric ratio was slightly in favour of isomer **18b**, featuring all substituents - except for the nitro group - in equatorial position.[f]
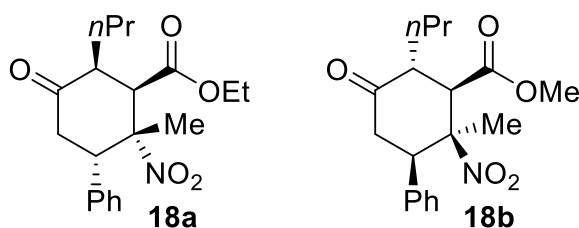
Figure 3.12

cat.	solvent	t (h)	conc.	P (W)	conv.[a] (%)	y (%)	dr (18a:18b)	ee (%) (18a:18b)
B	EtOH	2	0.8M	100	35	25	40:60	91-nd
A	EtOH	2	0.8M	100	nd	22	60:40	97-nd
B	H$_2$O	2	0.8M	100	-	-	-	-
B	toluene	2	0.8M	300	24	23	55:45	93-nd
B	EtOH	2	0.08M	100	33	30	50:50	-
B	toluene	2	0.8M	100	23	nd	45:55	nd
B	toluene	6	0.8M	100	26	nd	50:50	nd
B	EtOH	6	0.8M	100	33	nd	50:50	nd

Table 3.4 - Reactions were performed in the presence of catalyst **A** or **B** (20 mol%) and salicylic acid (30 mol%) under microwave irradiation. [a]Conversion determined by ^{1}H NMR analysis on the crude.

A temperature increase from 40 °C to 60 °C improved the yield that however was lowered again when heating to 80 °C. The use of acetonitrile was tested at 60 °C afforded poorer results as far as both yield and ee. Different reaction times were also tested at 60 °C, and it was observed that yields were only marginally higher when the reaction was allowed to proceed for 2 hours instead of 30 minutes. Further increase in time did not produce any improvement. Diastereomeric ratio was only slightly dependent from these parameters, as was enantiomeric excess (Table 3.5).

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[f] The enantiomeric excess for this diasteroisomer has been determined by ^{1}H NMR experiments using a chiral europium salt (Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]), as no proper HPLC or GC elution conditions for enantiomers separation were found.

cat.	solvent	T (°C)	t (h)	conv.[a] (%)	y (%)	dr (18a:18b)	ee (%) (18a:18b)
B	toluene	40	2	27	19	45:55	97-nd
B	toluene	60	2	33	30	45:55	98-nd
A	toluene	60	2	14	13	50:50	95-nd
B	CH₃CN	60	2	15	11	50:50	79-83
B	toluene	80	2	24	23	55:45	93-nd
B	toluene	60	0,5	30	23	50:50	99-91
B	toluene	60	2	33	30	45:55	98-nd
B	toluene	60	3	40	31	50:50	98-nd

Table 3.5 - Reactions were performed in the presence of catalyst **A** or **B** (20 mol%) and salicylic acid (30 mol%) under microwave irradiation. [a]Conversion determined by ^{1}H NMR analysis on the crude.

Noting that the yields did not exceed catalyst's loading, we thought that probably a single catalytic cycle occurred, due to an excessive stability of the enamine intermediates (**v**, **vi**) formed after the second cascade Michael addition (Figure 3.13).
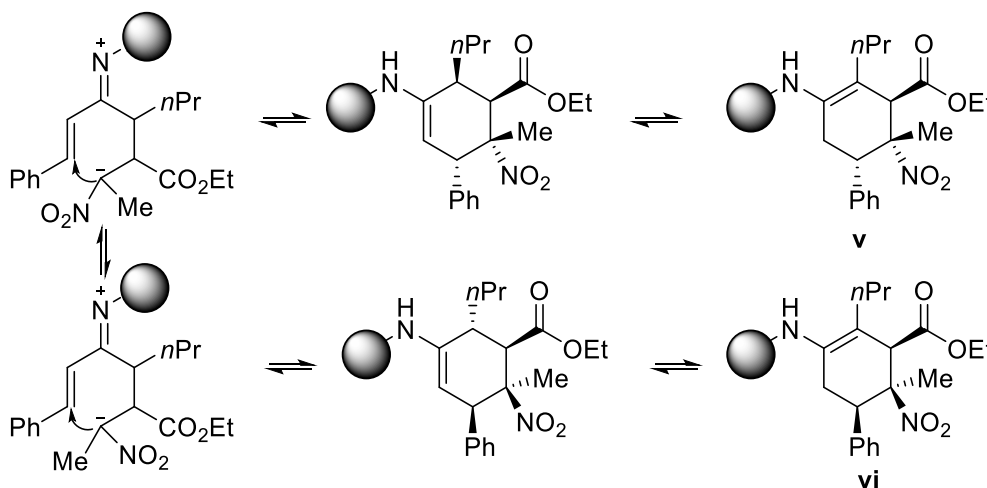
Figure 3.13

Thus, we envisioned that this equilibrium can be favourably shifted forward by adding an electrophile trapping the interemdiate. Through a control experiment on the model enone, we first established that p-nitro-benzaldehyde did not react with the *in situ* generated dienamine. Thus, we the effect of this additive was tested on the model reaction run operating under classical heating conditions; however, a side reaction took place (Scheme 3.13).
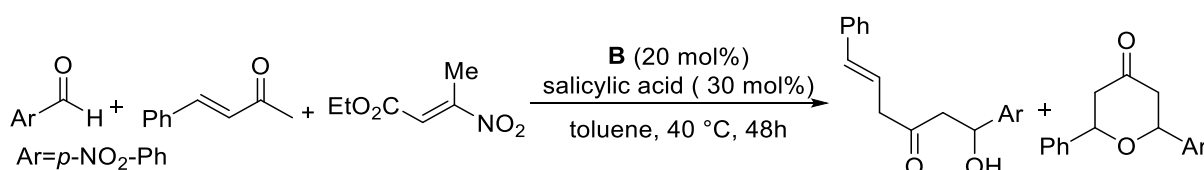
Scheme 3.13

Microwave technology revealed decisive also in the synthesis of highly functionalized cyclohexanones **19**, obtained by reacting ethyl nitroacrylate with (*E*)-1,4-diphenylbut-3-en-2-one. In particular, product formation was observed only at temperature as high as 100 °C (Scheme 3.14 and Table 3.6).
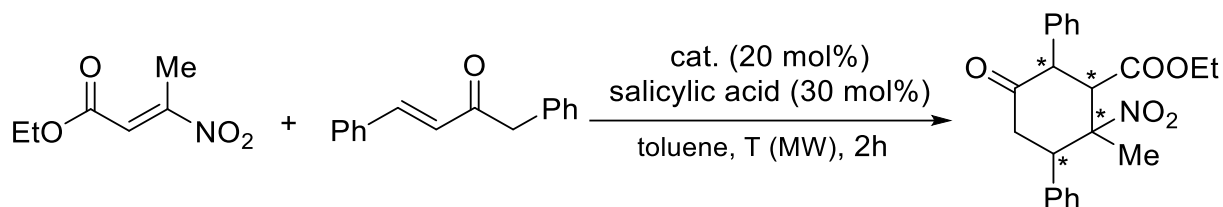
Scheme 3.14

Also in this case, only two diastereoisomers were formed. Relative configuration, defined through ^{1}H NMR experiments, did not reflect that obtained with previously employed enones: indeed, products **19a** and **19b** were epimer at the quaternary stereogenic centre, while all the other substituents were in the same disposition. Absolute configuration was assigned considering that the stereocentre featuring the ester group, which is the first formed in the reaction cascade, is defined by the catalyst in a way analogous to that observed in the case of on 4-phenylbutenone (Figure 3.14).
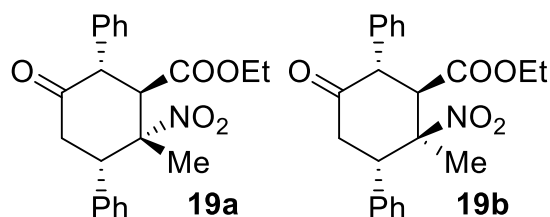
Figure 3.14

cat.	T (°C)	conv. (%)	y (%)	dr (19a:19b)	ee (%) (19a:19b)
B	60	10	nd	nd	nd
B	80	22	14	80:20	95-rac.
B	100	34	21	60:40	93-14
A	100	17	13	60:40	92-28

Table 3.6

After having established that hindering the ketone at C1 causes a decrease in yields, the effect of butenone substitution at C3 was studied (Scheme 3.15). By reacting 3-methyl-4-phenyl-3-buten-2-one with ethylntroacrylate, only traces of the desired products were obtained running the reaction in toluene at 80°C. Changes in solvent and temperature did not bring any improvement (Table 3.7).
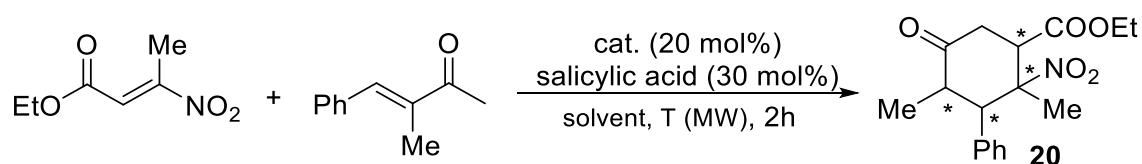
Scheme 3.15

T (°C)	P (W)	solvent	y (%)
60	300	toluene	nd
80	300	toluene	5
80	100	EtOH	5
60	200	CH$_3$CN	nd

Table 3.7

Summarizing, an in-depth study on the stereoselective organocatalyzed cascade between nitroacrylates and ketones has been performed. In particular, the use of microwave technology allowed to find optimized conditions, affording cleaner reactions in shortened time with no loss in enantioselectivity, and to employ C1 substituted enones leading to cyclohexenones with four contiguous stereogenic centre in only two out of the eight possible diastereoisomers and with excellent enantioselectivity.[365]

4. ORGANOCATALYTIC STEREOSELECTIVE ADDITION OF ACTIVATED NUCLEOPHILES TO β-NITROACRYLATES

Even though a really large number of reactions promoted by hydrogen bonding organoatalysts are conjugate additions employing nitroalkenes as electrophiles, at the best of our knowledge only few examples have been reported using nitroacrylates. As already mentioned in Chapter 2, these are indeed interesting substrates bringing into the final product two functional groups that are highly reactive and versatile for further transformations.[366]

Therefore, we decided to investigate some organocatalytic reactions in which variously substituted β-nitroacrylates were combined with activated nucleophiles such as active methylene compounds (Scheme 4.1).
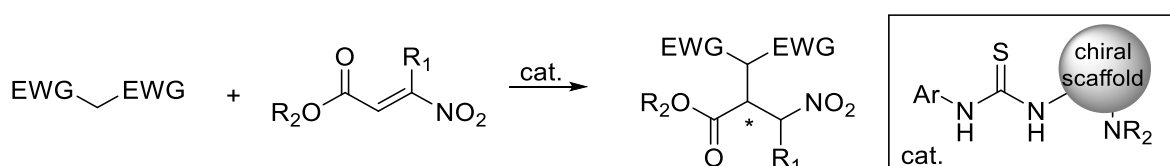
Scheme 4.1

To control the stereochemical outcome of the reaction we relied on bifunctional chiral structures capable of coordinating both the nucleophile and the electrophile by H-bonds formation (Figure 4.1).
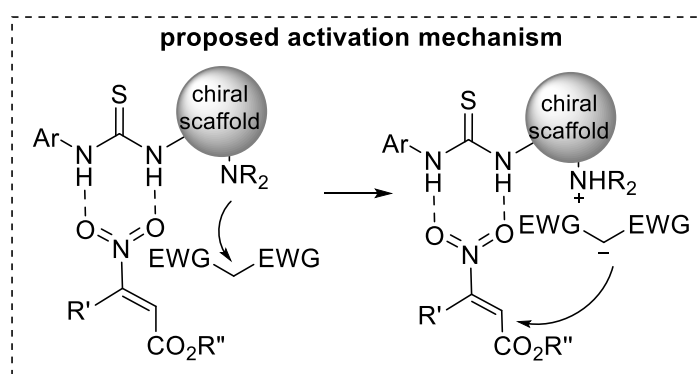
Figure 4.1

Our first aim was that of developing a stereoselective version of β-dicarbonyl compounds conjugate addition, reported in 2009 by Palmieri et al. to proceed in high yield (75-95%) with a catalytic amount of potassium carbonate (Scheme 4.2).[367]
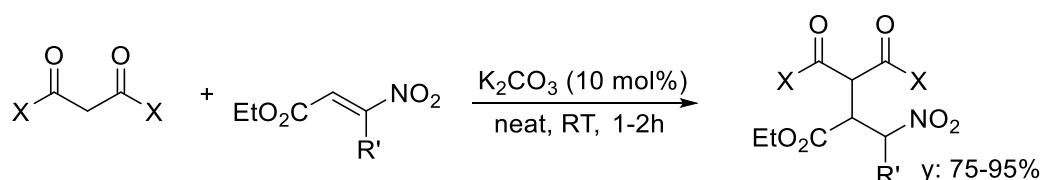
Scheme 4.2

Thus, we first addressed this study investigating diketones addition to ethyl β-ethyl-β-nitroacrylate employing two well established thiourea organocatalysts, namely the quinine derivative **F** and Takemoto catalyst **G** (Figure 4.2).
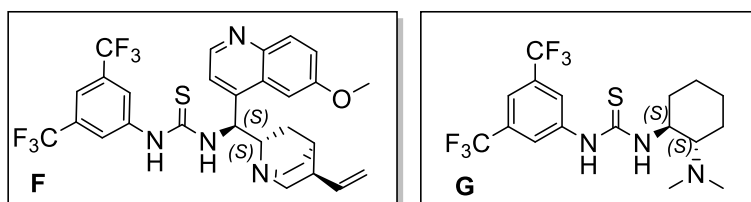
Figure 4.2

While diethyl malonate proved to be completely unreactive, the addition product with acetyl acetone was obtained in fair yield and diastereoselectivity; however it was not possible to determine the value of the enantiomeric excess through HPLC on chiral stationary phase, probably because of the keto-enol tautomerism led to the simultaneous presence of multiple species in solution (Scheme 4.3).
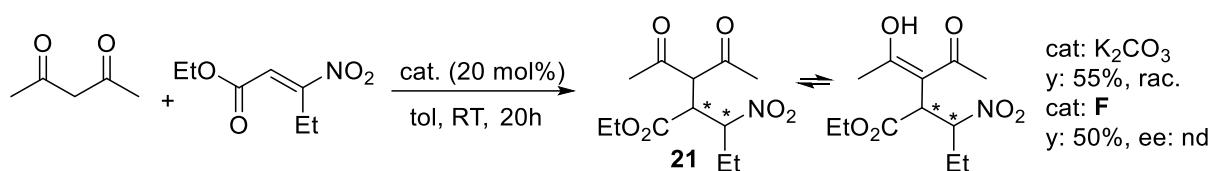
Scheme 4.3

As a preliminary demonstration of the versatility of these compounds, we focused on a possible transformation of the diketo-unit. Thus, by reaction of **21** with hydrazine the corresponding pyrazole ring was obtained, which is contained in many pharmaceutically active products (Scheme 4.4).[368] Besides, this structural transformation made the compounds suitable for HPLC analysis, so that it was possible to determine the enantiomeric excess for both diastereoisomers **22a** and **22b**. As the pyrazole-formation reaction is expected to proceed with no epimerization, it was reasonable to assume that this ee values completely reflect the enantioselectivity of the organocatalytic conjugate addition.
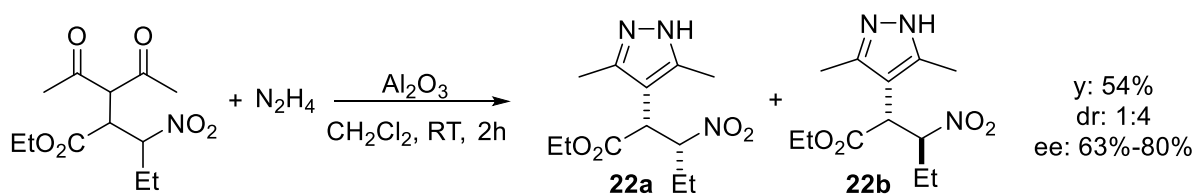
Scheme 4.4

To work with more stable products, we switched to α-methyl substituted acetylacetone as nucleophile, so to preclude the formation of the conjugated enolic form of the diketone moiety in the final product (Scheme 4.5). With this electrophile, yields and dr were lower than those previously observed, but for one of the two diastereoisomers an enantiomeric excess as high as 89% was obtained.
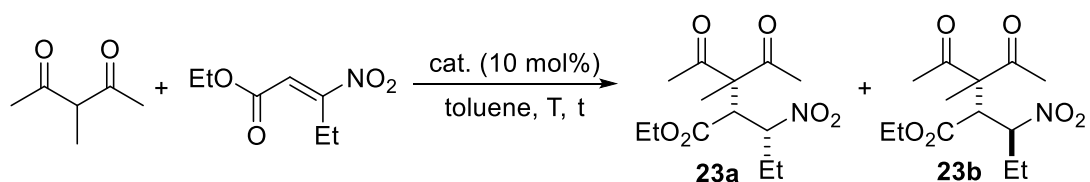
Scheme 4.5

Neither extension of the reaction time nor an increase in concentration led to improvementsin the results. Rather, it was observed that the reaction was completely hampered by higher temperatures, by stoichiometry inversion involving the use of nitroacrylate as limiting reactant and by the use of an increased nucleophile loading. As expected, a more effective control over the stereochemical outcome was achieved when running the reaction at 0 °C, while the yield remained low (Table 4.1).

cat.	T (°C)	t (h)	yield (%)	dr (23a:23b)	ee (%) (23a-23b)
F	25	20	35	33:67	70-73
F[a]	25	20	15	43:57	70-79
F	25	96	27	35:65	73-71
F[b]	25	20	<5	nd	nd
G	25	20	41	32:68	83-89
H	25	20	-	-	-
F[c]	25	48	-	-	-
F	0	48	25	37:63	90-93
G	0	48	37	30:70	nd-83
I	0	48	57	15:85	33-85

Table 4.1 - Reactions were performed in toluene (0.17M) with ketone:nitroacrylate 3:1. [a]Reaction performed in toluene in 0.1M concentration. [b]Reaction performed with ketone:nitroacrylate 1:3. [c]Reaction performed with ketone:nitroacrylate 50:1.
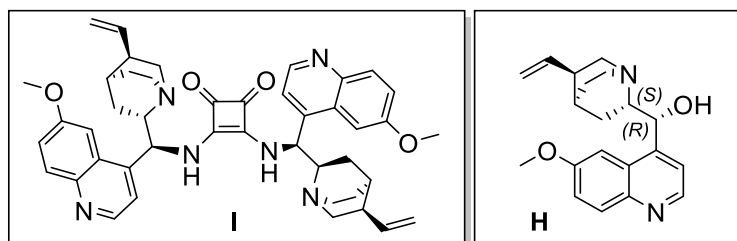
Figure 4.3

The use of squaramide-quinine derivative **I** led to higher yield and enhanced diastereoselectivity but to slightly diminished enantiomeric excesses. The different hydrogen bonding pattern offered by natural quinine (**H**), instead, revealed unsuitable for promoting the desired reaction, probably due to an ineffective nitro group coordination and/or by the lack of the simultaneous activation of both reaction partners.

The use of 3-methyl-2,4-pentadione was extended to differently substituted nitroacrylates (Figure 4.4). In all cases moderate to good diastero- and enantioselection were obtained, but yields did not

exceed 35%. These results showed that not only the ester group was not involved in interactions determining the reaction outcome, as it was almost expected considering that the ester moiety should not be directed towards the catalyst's coordination site, but also that the TS is probably not tight enough to differentiate between β-substitutents, as neither the obtained diastereomeric ratio nor the enantiomeric excesses are influenced by the size and shape of the β-alkyl chains.

y: 35%, dr: 36:64, ee: 81%-87%   y: 31%, dr: 34:66, ee: 75%-90%

Pn=pentyl
y: 30%, dr: 36:64, ee: 83%-89%   y: 325%, dr: 42:58, ee: 55%-77%
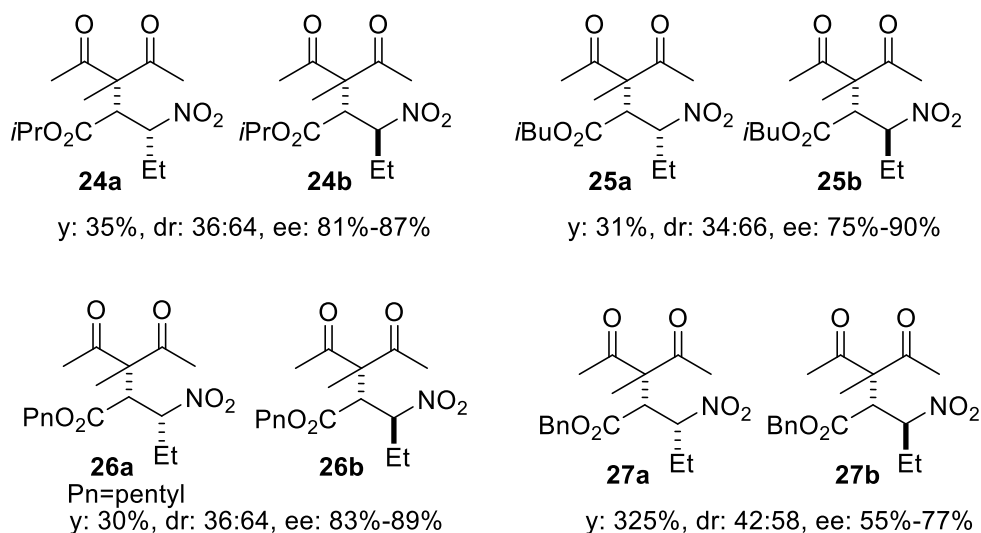
Figure 4.4 – Reactions were performed in toluene (0.17 M) at 0 °C for 40 hours with ketone:nitroacrylate 3:1 ration and in the presence of cat. F (10 mol%).

The possibility of employing differently structured nucleophiles was then investigated. To this end nitromethane and phtalimide[369] were selected on the basis of an activation mode analogous to that hypothesized for β-ketones, based on the simultaneous coordination of the electrophile by the thiourea moiety and of the deprotonated nucleophile with the protonated basic group.

However, MeNO$_2$ revealed unreactive and with phtalimide the *in situ* elimination of HNO$_2$ from the product occurred, leading to an α-phtalimido acrylate as only product (Figure 4.5).

y: 25%   y: -
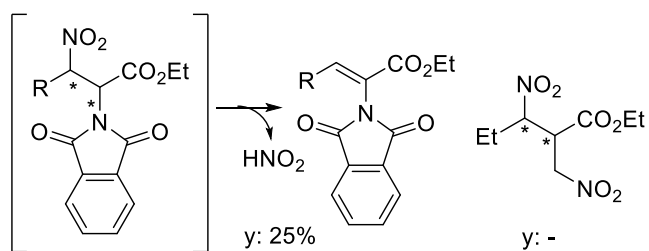
Figure 4.5

Ethylnitroacetate and ethyl 2-nitropropanoate[370] were then employed, aiming to exploit HNO$_2$ elimination to obtain conjugated chiral compounds otherwise achievable through a stereoselective Baylis-Hillman reaction (Scheme 4.6).
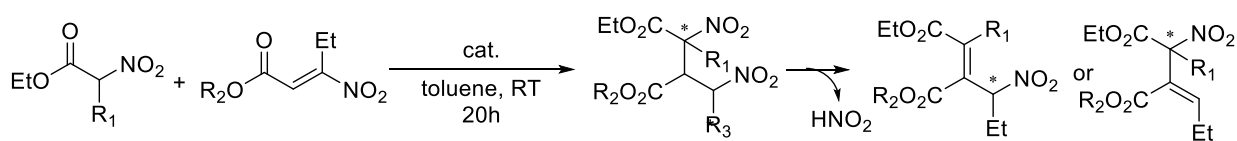
Scheme 4.6

However, no product formation was obtained with both the α-substituted and unsubstituted nucleophile in the presence of catalyst **F**.

Catalyst **F** was also tested in the reaction with indole derivatives as Michael donors (Scheme 4.7).[371] While indole reacted with high yield but no stereoselectivity was imparted, the reaction with *N*-methyl indole occurred in only 33% yield (Table 4.2). The addition of an acid co-catalyst increased the yield to 81% but low enantioselection was observed.[372] The use of a chiral acid additive, such as binaphthyl-derived phosphoric acid (PA) allowed an increase in the ee up to 53%, but no indication of a possible matching pair with the catalyst emerged. Obtaining the known compound **29** allowed the assignment of products relative configuration, which was then extended to the products derived from the addition of diketones to nitroacrylates.
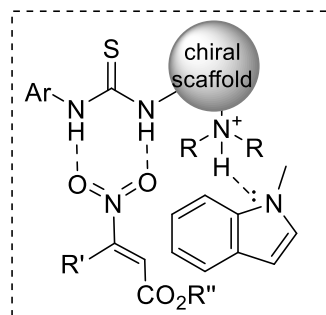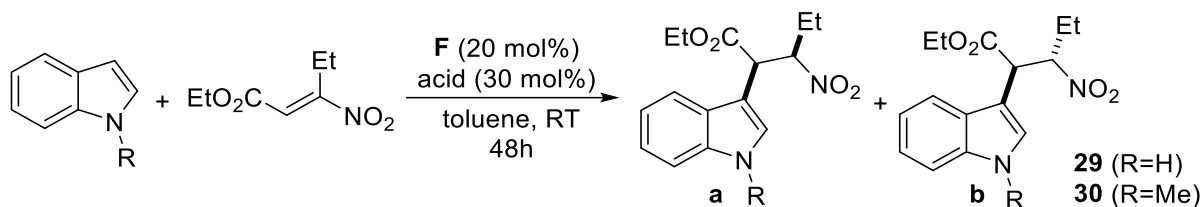
Scheme 4.7

R	acid	yield (%)	dr (a:b)	ee (%) (a-b)
H	-	73	50:50	<5%
Me	-	33	40:60	<5%
Me	salicylic	81	49:51	27-33
Me	salicylic	25	43:57	37-40
Me	(+)-PA	93	55:45	25-45
Me	(-)-PA	67	48:52	13-53
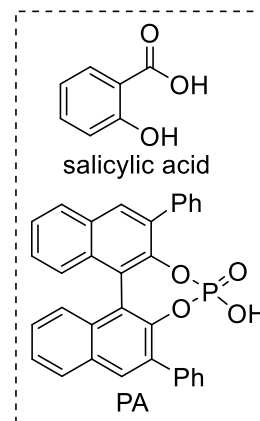
Table 4.2

To summarize, the stereoelective addition of activated nucleophiles to nitroacrylates have been carried out. Bifunctional organocatalysts afforded enantioselectivities up to 93%, but the poor chemical yields represents major drawback of the process.[373]

5. METAL-FREE STEREOSELECTIVE CONJUGATE ADDITION OF AN ACTIVATED THIOESTER

5.1. Stereoselective reaction of 2-carboxythioesters-1,3-dithiane with nitroalkenes: an organocatalytic strategy for the asymmetric addition of a glyoxylate anion equivalent

Nitroalkenes, which already proved to be suitable as substrates for reactions promoted by bidentate hydrogen bonding catalysts, are compounds of great synthetic interest, as they can undergo lots of different transformations, such as Nef and Meyer reactions, nucleophilic displacement, reduction to amino group and conversion into a nitrile oxide.[374]

Thus, we decided to extend the range of their reactivity studying the Michael addition of the activated ester featuring a dithiane ring (see Chapter 2); according to our reaction design, stereoselectivity could be obtained thanks to hydrogen bonding organocatalysis (Scheme 5.1).
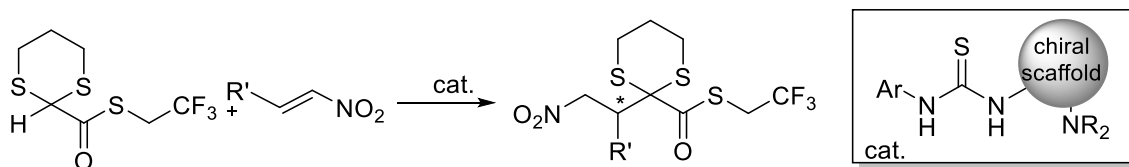
Scheme 5.1

Thanks to the peculiarity of the chosen nucleophile, the formed addition products would have be prone to a wide spectrum of subsequent transformations, involving nitro group reduction, intramolecular amidation and dithiane removal (Figure 5.1).

possible product transformations
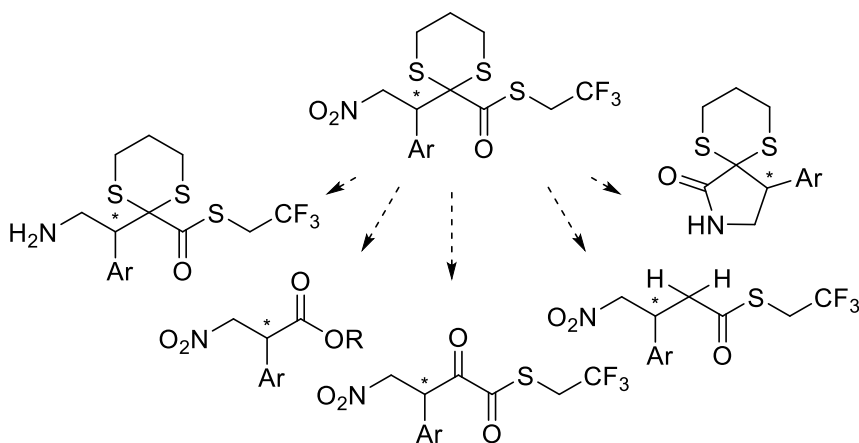
Figure 5.1

Our working hypothesis was based on a possible bidentate coordination by thiourea moiety of the catalyst to the substrate, which was thus kept into a chiral environment and activated towards the attack of the nucleophile, while forming an ion pair with a basic group (Figure 5.2).
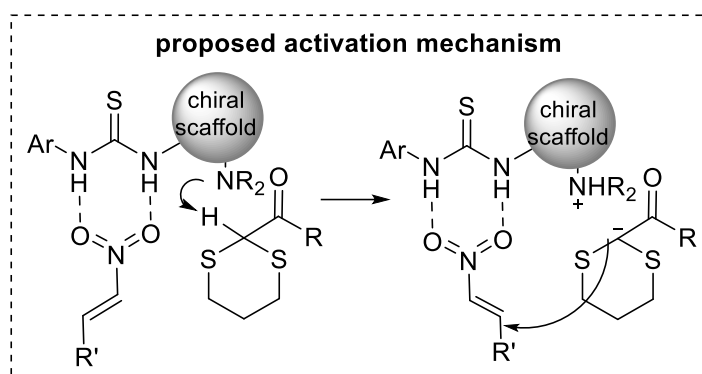
Figure 5.2

In a first investigation on the feasibility of the proposed transformation, the thiourea organocatalyst based on the quinine scaffold (**F**) was employed. The family of bifunctional organic catalysts created from a 9-amino-9-deoxy-*epi*-Cinchona alkaloid skeleton, developed by Dixon group, was already tested in the dimethyl malonate Michael addition to β-nitrostyrene, showing the superiority of bidentate hydrogen bond donors.[120]

A preliminary screening of different nucleophiles featuring the same 1,3-dithianyl-ester backbone showed that the presence of the strong electron withdrawing group on the ester was necessary to have a proper reactivity (Scheme 5.2 and Table 5.1). In fact, commercially available 1,3-dithiane-2-ethylcarboxylate did not react at all with nitrostyrene. The corresponding *S*-phenyl thioester showed poor reactivity, affording the corresponding addition product **32** in low yields even after prolonged reaction times, although with remarkable 89% enantioselectivity. The desired addition product **33** was obtained from the pyridine derived thioester in high yield, but it was not stable enough to allow enantiomeric excess determination. When 2-*S*-trifluoroethyl carboxy-thioester-1,3-dithiane was employed, compound **31** was obtained in 71% yield and 87% ee.
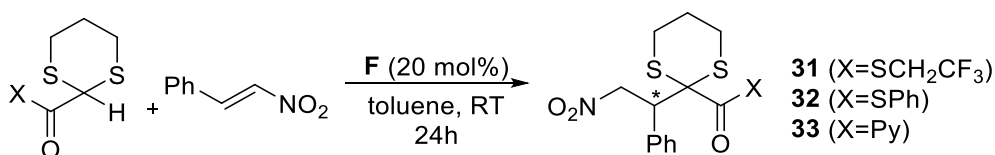
Scheme 5.2
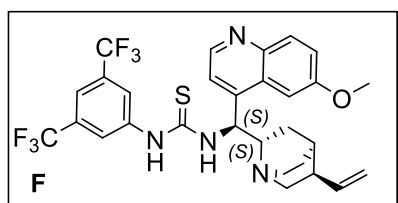
X	yield (%)	ee (%)
SCH$_2$CF$_3$	70	86
SPh	16	89
OEt	-	-
SPy	41	n.d.

Table 5.1

These first experiments thus allowed to identify 2,2,2-trifluoroethyl 2-[(1,3-dithian)-2-yl]-ethanthioate as the nucleophile of choice.

This compound was easily synthesized[g] in two steps, namely basic hydrolysis a esterification promoted by condensing agents, starting from the commercially available ethyl ester (Scheme 5.3).
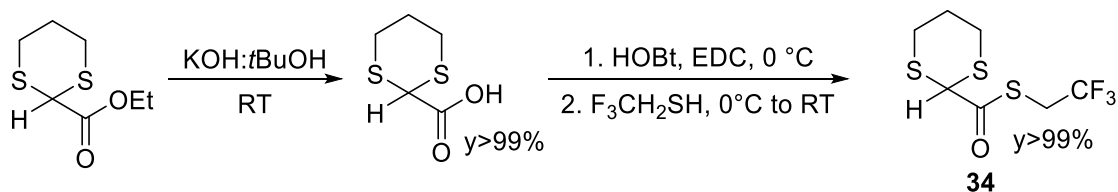
Scheme 5.3

Literature survey shoved compound **34** has been recently employed in a domino conjugate addition-cyclization for the synthesis of functionalized dihydropyranones; using KOH as base and benzyltriethylammonium chloride as phase transfer catalyst the products were obtained in yield mainly ranging from 70 to 85%. Subsequent reduction with Ni-Raney or nickel chloride allowed dithiane moiety removal (Scheme 5.4).[375]
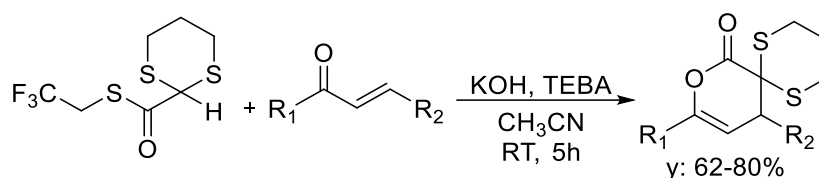
Scheme 5.4

The activated dithiane-thioester **34** was then employed in the conjugate addition to nitrostyrene in the presence of different catalysts under standard conditions (Scheme 5.5).
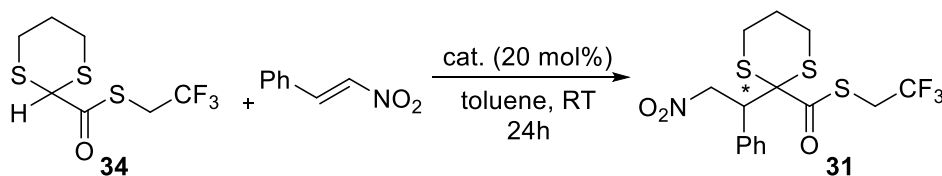
Scheme 5.5

Of the two prolinol derived Brønsted bases tested at first (Figure 5.3), only the non trifluoromethylated one afforded the addition product, albeit with low enantioselection. This result can be rationalized considering that the ionic couple formed upon the envisaged deprotonation by the chiral secondary amine is not tight enough and/or the chiral space that should have been created around the reaction centre was not sterically biased enough to control the reaction outcome.
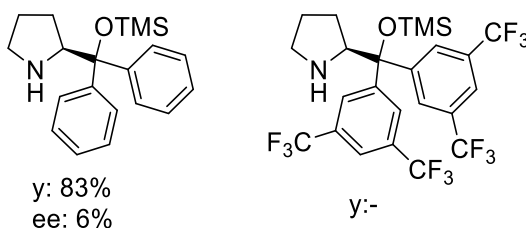
Figure 5.3

As Cinchona alkaloids are known to act also as bifunctional hydrogen bonding organocatalysts,[376] we tested natural quinine, its C6' demethoxylated analogue and both the 9-*epi*-amino counterparts; however, products were obtained in moderate yield and zero to low enantioselectivity. Transition states involving coordination of both reaction partners can be envisaged, but bidentate coordination of the nitro group could involve a looser ion pair between the catalyst and the deprotonated nucleophile (Figure 5.4). Low enantioselectivity could thus be due to an inefficient simultaneous coordination of the two partners.
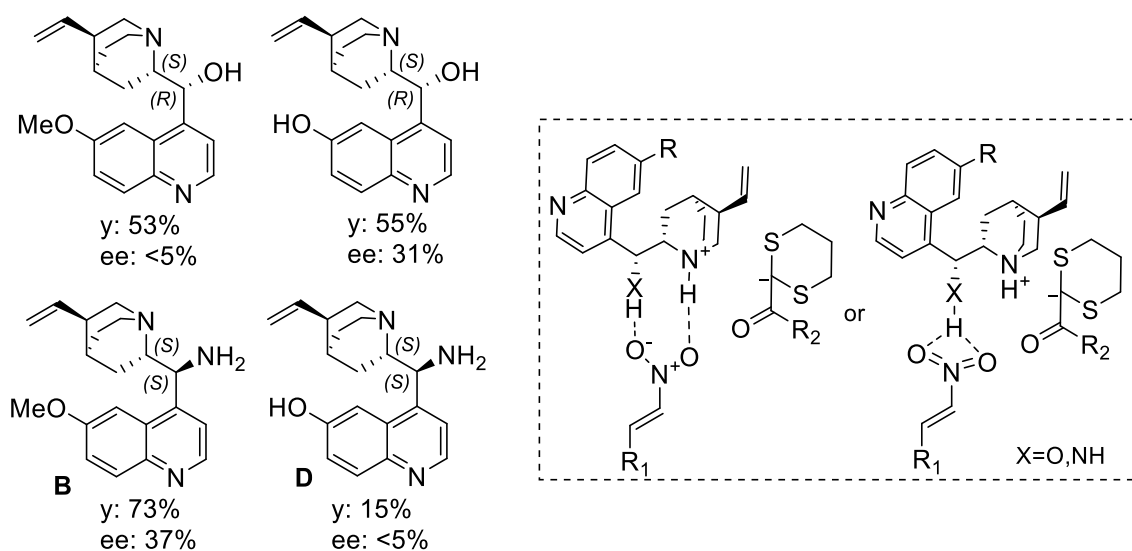
Figure 5.4

When Takemoto's thiourea **G** was employed, the product was isolated in higher yield but lower enantioselectivity than that observed with the cinchona derived catalyst **F**. These results confirmed quinine derived scaffold as a good candidate to control the stereochemical outcome of this reaction. When the *quasi* enantiomeric catalyst **F'** was employed, the addition product of opposite absolute configuration was obained in comparable yield and marginally lower enantioselectivity. Analogous of catalyst **F** differing in substitution on the quinoline core as well as some squaramide derivatives were tested. With the cinchonidine derivative **F1** a little decrease in enantioselection was observed, while using **F2** and **F3** a drop in the product ee occurred; the detrimental effect of the free OH group can be rationalized hypothesizing the formation of competing hydrogen bonding patterns. The crucial role of the thiourea group was then made clear by unsatisfactory results obtained with all the squaramide based catalysts **L1**, **L2** and **L3**, which afforded almost no enantiocontrol (Figure 5.5). Finally, the need for a basic functionality within the catalyst structure was demonstrated observing that with the L-valine-thiourea derivative **M** no reaction occurred (Figure 5.6).
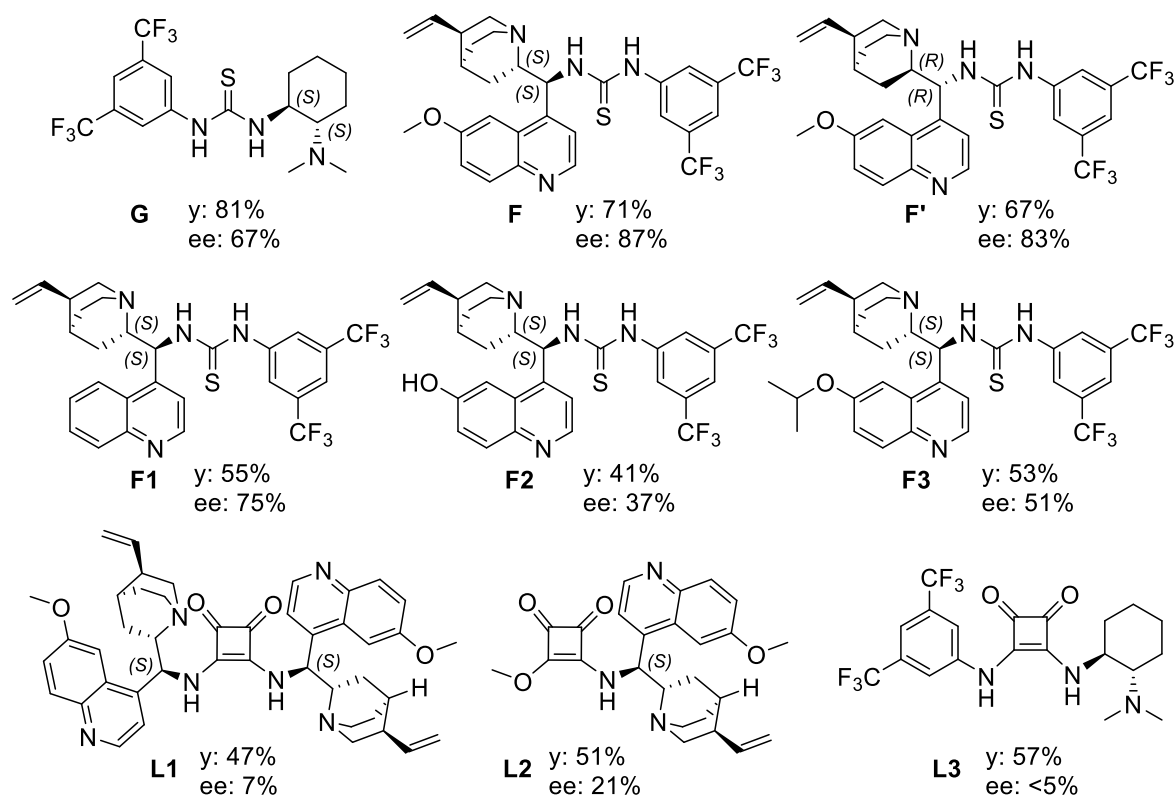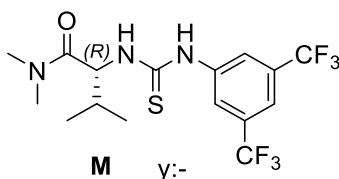
Figure 5.5

Figure 5.6

As catalyst **F** proved to be the best one, this was employed to establish reaction conditions (Table 5.2). Effects of solvent and temperature were first investigated. As expected, the best results were obtained in toluene and dichloromethane, solvents that do not interfere with the hydrogen bond network established between the catalyst and the reaction partners. Passing from 25 to 0 °C as reaction temperature led to an improvement in the level of enantioselection, while heating up to 50 °C did not have a significant influence. In addition, it was possible to lower the catalyst loading to 5 mol% without suffering from an excessive drop in the yield. We also studied the influence of concentration on the reaction outcome, to find that an increase from 0.1 M to 0.5 M did not led to any significant change in yields and enantioselection. Thus, in toluene at 0 °C, product **31** was obtained in 60% yield and 92% ee.

solvent	T (°C)	yield (%)	ee (%)
toluene	25	71	87
CH$_2$Cl$_2$	25	55	80
CH$_3$CN	25	80	41
hexane	25	75	57
Et$_2$O	25	73	67
toluene	0	60	92
toluene	-20	61	66
toluene	50	71	83
toluene[a]	25	55	81
toluene[b]	25	47	80

Table 5.2 - Reactions were carried out with nitroalkene:dithiane 1:2 in the presence of catalyst **F** (20 mol%) in toluene (0.1M) for 20 hours. [a]Reaction run in the presence of **F** (10 mol%). [b]Reaction run in the presence of **F** (5 mol%).

Working under the best conditions, the reaction scope was then investigated (Figure 5.7).
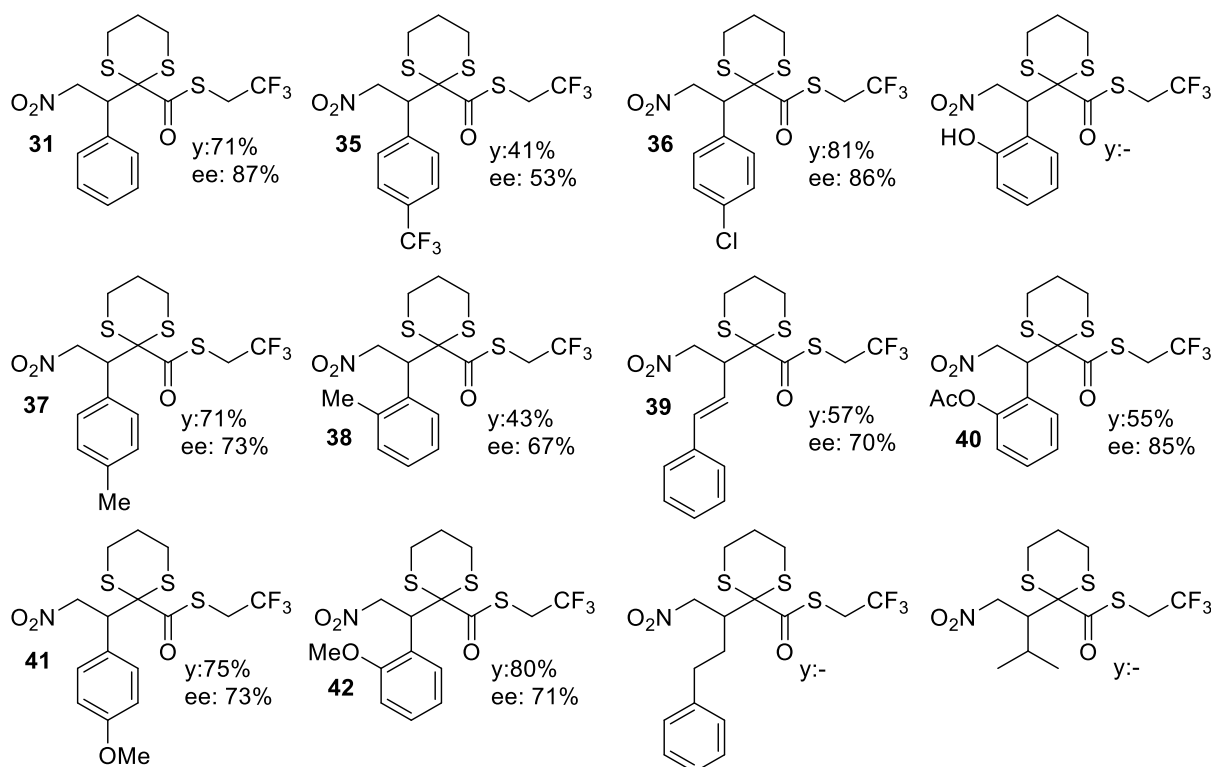
Figure 5.7 - Reactions were carried out with nitroalkene:dithiane 1:2 in the presence of catalyst **F** (20 mol%) in toluene (0.1M) at RT for 20 hours.

It turned out that good yields and ees were obtainable with nitrostirenes featuring both electron donating or withdrawing group either in the *ortho* or in the *para* position. However, *o*-OH-nitrostyrene was unreactive, a fact that we attributed to the formation of undesired hydrogen bonds, which possibly prevented proper coordination and thus activation by the catalyst. This hypothesis was supported by introducing an acetyl protection on this substrate, that allowed the organocatalytic Michael addition to proceed smoothly and with high enantioselectivity. With 4-nitro-1-phenyl butadiene the reaction

occurred exclusively on the C=C directly bound to NO$_2$ in good yield and ee were achieved. Alkyl substituted nitroalkenes, instead, did not afford any product. This unsatisfactory result was not unexpected, as these substrates are known to be less reactive than conjugated nitroolefines. A rationalization was offered by Rai and Namboothiri through computational studies supporting previous kinetic ones.[377] The rational was based on the consideration that in Michael addition to nitroalkenes the transition state is not an intermediate structure between that of the reactant and the product, but was proved to have a partial radical character along with partial charge (Scheme 5.6). So, when the nitroalkene features a β-substituent able to stabilize the radical centre at the benzylic position, its reactivity will be enhanced.
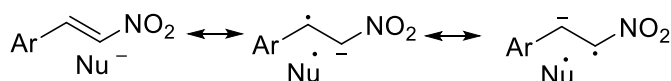
Scheme 5.6

Once the new organocatalytic reaction was established, the possibility of further transforming the addition products obtained was investigated.

First, we focused on finding proper conditions for nitro group reduction with the aim to develop an expeditious entry to baclofen, a GABA$_B$ receptor agonist used in the treatment of spasticity and alcohol dependence.[378] For this reduction, neither HSiCl$_3$[379] nor Na$_2$S, NiCl$_2$ combined with NaBH$_4$ were effective. In fact, adding a 0.6 M solution of trichlorosilane in dichloromethane to the substrate, dissolved in dichloromethane, at 0 °C and stirring the mixture overnight at the same temperature, afforded only the starting material. An increase in the temperature after the reducing agent addition did not allow obtaining the desired amine. Treating the substrate, dissolved in ethanol, with 5 equivalents of Na$_2$S at 0 °C for 4 hours, only the formation of degradation products was observed; idle was also the attempt with nickel chloride and sodium borhydride, which were expected to for an intermediate nickel borhydryde species active in ethanol at 0 °C in two hours. Howvever, when H$_2$ pressure was applied on the substrate dissolved in ethyl acetate at room temperature in the presence of palladium over carbon, an incompletely reduced *N*-hydroxyl lactam was obtained. Powder zinc and ammonium chloride, refluxed for 1 hour with the substrate in a 5:1 acetone:water mixture, afforded the same hidroxylamine product (Scheme 5.7).
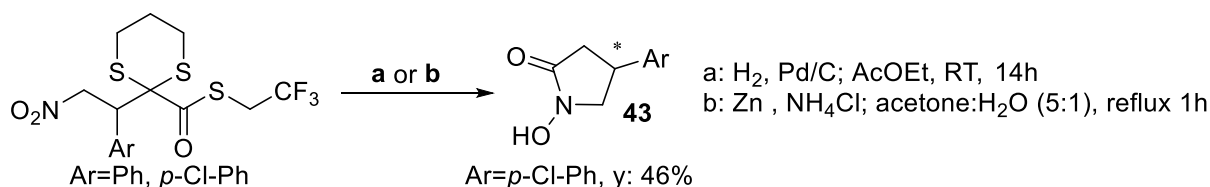
Scheme 5.7

Eventually, complete conversion of NO$_2$ to the primary amine was achieved applying Anderson procedure,[380] where the reducing system is represented by powder zinc and 6M HCl. After the substrate was dissolved in a 5:4 ethanol:ethyl acetate mixture at 0 °C, the reagents were added and the mixture

reacted at room temperature for three hours. Formation of the NH_2 function was immediately followed by ring closure forming a five membered lactam. This procedure allowed also the simultaneous dithiane ring reductive removal, leading in a single step from the oganocatalytically obtained product to the precursor of a known pharmacologically active compound (Scheme 5.8).
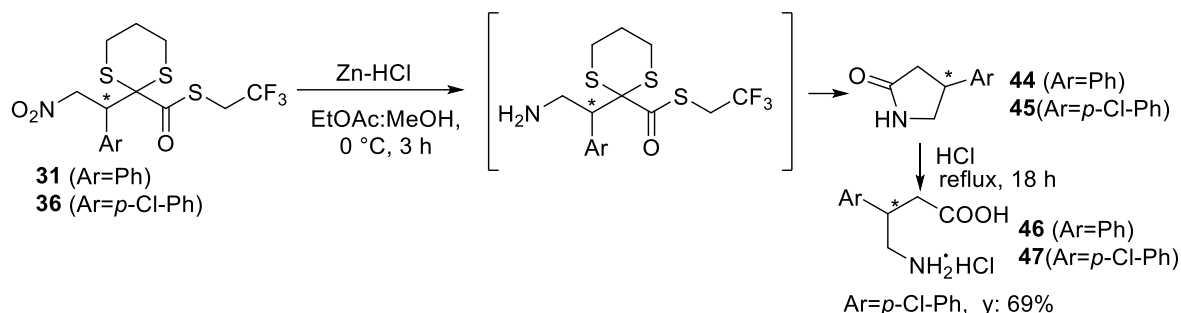
Scheme 5.8

Through chemical correlation, it was then possible to establish the absolute configuration of compound **47**, from which that of addition products can be derived. Comparing the optical rotation value of the known compound with that reported in literature, the *S* configuration was assigned to the stereocenter, thus showing that the organocatalized Michael addition, promoted by the quinine and by the (*S,S*)-diaminocyclohexane derived thioureas **F** and **G**, afforded preferentially the *S*-enantiomer. It was also verified that by employing (*R,R*)-diaminocyclohexane-derived catalyst, addition products characterized by the (*R*)-configuration were obtained.

According to the experimental results and to our working hypotesis, a stereoselection model was proposed where the coordination of both reaction partners to the bifunctional catalyst is envisaged, in this model the substrate nitro group is hydrogen bonded by the thiourea moiety and by the charged quinuclidine nitrogen possibly forming an ion pair with the nucleophile (Figure 5.8).
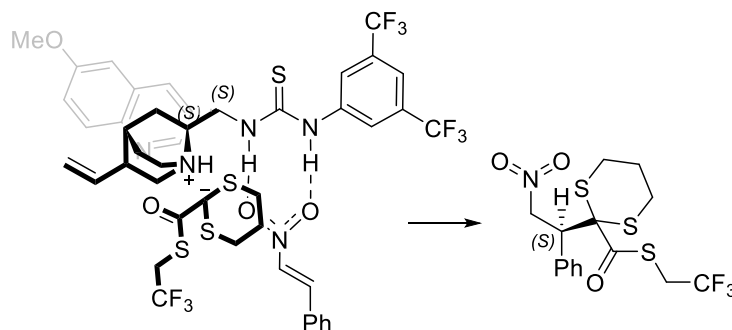
Figure 5.8

We then studied the development of the dithiane of **31**, **35** and **36** into the carbonyl group. A modification of the Corey procedure, based on the use of *N*-bromosuccinimide in acetone, achieved the quantitative conversion of the addition products into the corresponding α-keto thioesters **48**-**50** (Scheme 5.9).
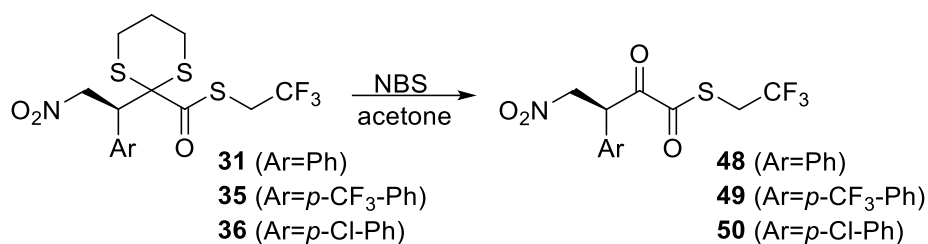
Scheme 5.9

The thioester to ester transesterification was not as straightforward as expected and, as a matter of fact, the desired α-keto esters were never obtained. In fact, acidic conditions let the starting material unchanged, while basic conditions led to its degradation, probably due to the high acidity of protons in the α-position with respect to the nitro group. Thus, procedures based on the use of transition metals, supposed to coordinate the sulphur atom facilitating the removal of the thiol group, were tested. Interestingly and quite unexpectedly, both silver and mercury salts afforded the corresponding β-nitro ester with no loss in the enantiomeric excess. Thus, a sample of (*R*)-**31** (53% ee) was quantitatively transformed into the α-ketothioester **48**, which then gave the known (*R*)-β-nitro methylester **51** in 70% yield, its absolute configuration reflecting that of the starting compound **31** without appreciable variation in the ee value (Scheme 5.10).
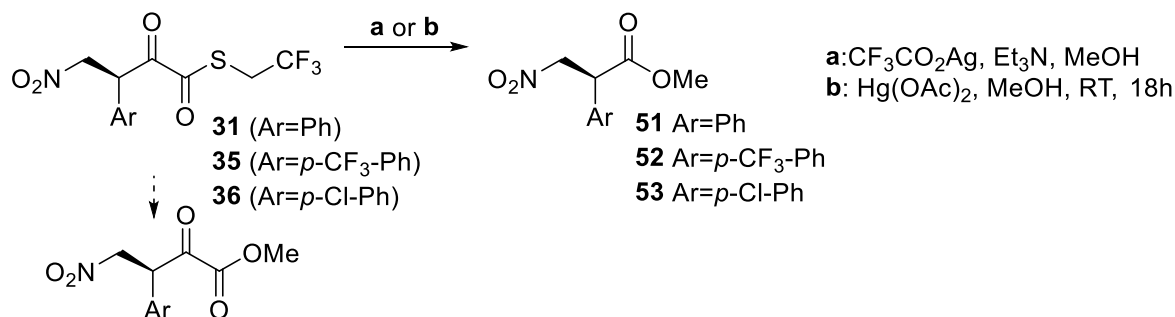
Scheme 5.10

The mechanism of the metal promoted decarbonylation has not been elucidated yet, but probably it involves metal coordination to both carbonyl oxygen atoms and nucleophilic attack by methanol.

To verify if the zinc mediated removal of the dithiane moiety proceeded through unmasking of the carbonyl group followed by a Clemmensen-type reduction, which is know to work also in the absence of Hg amalgam, a α-keto thioester was subjected to the Zn-HCl procedure; however, the expected five membered lactam was not obtained (Scheme 5.11). Even though this experiment was a proof against this mechanicistic hypothesis, it cannot be considered as conclusive.
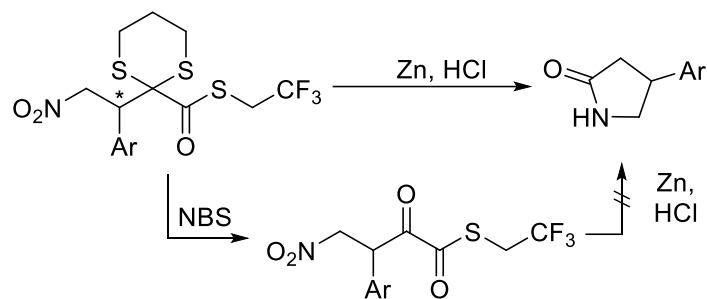
Scheme 5.11

In conclusion, the enantioselective conjugate addition of a newly activated thioester has been performed reaching good yields and enantioselectivity up to 92% thanks to bifunctional organocatalysts. It was also demonstrated that the employed nucleophile can act as an acyl anion mimic; thus, this methodology represents an entry to highly functionalized, enantiomerically enriched products, such as γ-nitro-β-aryl-α-keto thioesters, valuable precursors of a wide variety of chiral organic compounds.[381]

5.2. Primary amines promoted stereoselective conjugate addition of an acyl anion mimic to α,β-unsaturated ketones

Consistently with the aim of obtaining versatile compounds in enantiomerically enriched form, we investigated the conjugate addition of the activated dithiane-thioester **34**, characterized by the presence of multiple functionalities, to simple enones. To promote this transformation and control its stereochemical outcome, we exploited primary amines activation of the substrate as chiral iminium ion. As already reported in the previous section of this chapter, the final compound can be subjected to further synthetic elaborations (Figure 5.9).
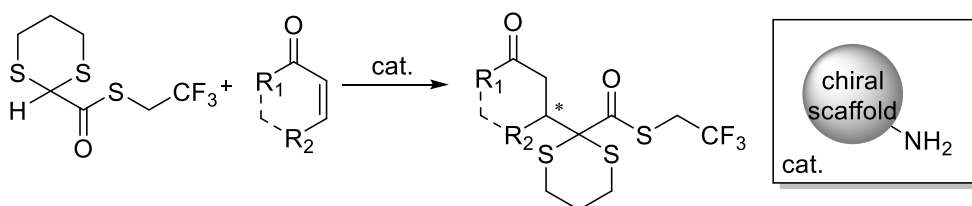
Scheme 5.12

possible product transformations
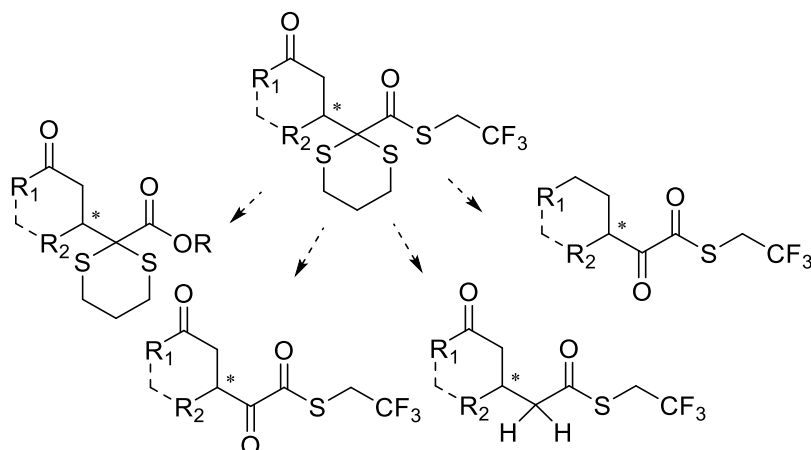
Figure 5.9

According to our hypothesis, the reaction should proceed through condensation between the enone and the primary amine, forming the activated electrophile, i.e. the chiral iminium ion, which is attacked by the nucleophile on its turn deprotonated by the quinuclidine functionality. Thus, in analogy to the thiourea promoted addition to nitroalkenes, the thioester approach is directed by electrostatic coordination to the protonated tertiary amine (Figure 5.10).
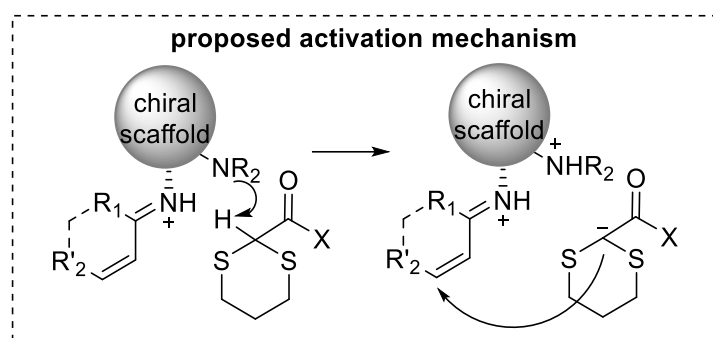
Figure 5.10

First studies were carried out on the model reaction between *S*-(2,2,2-trifluoroethyl) 1,3-dithiane-2-carbothioate and cyclohexenone (hopefully more reactive than open-chain enones) in the presence of primary amines derived from Cinchona alkaloids and of salicylic acid as co-catalyst (Scheme 5.13). Remarkably, the quinidine derived thiourea **A** afforded the desired compound in good yield and 91% ee.
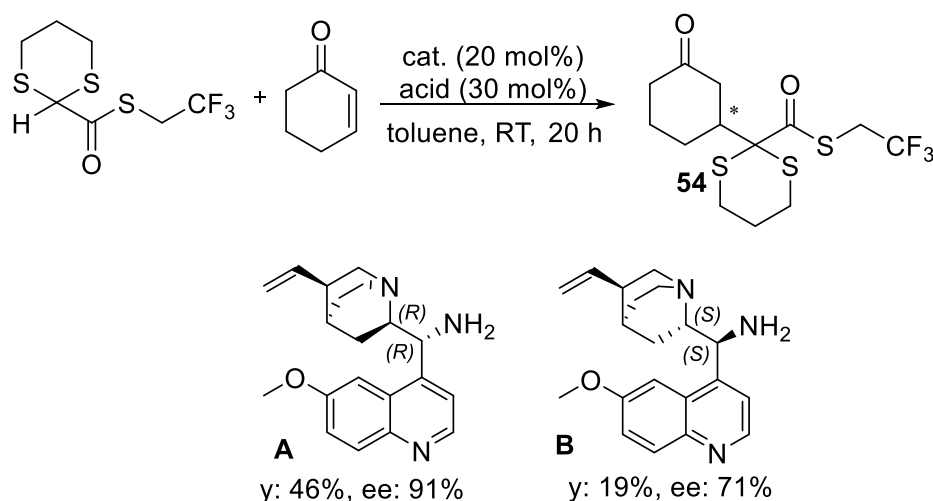
Scheme 5.13

We then investigated the role of the acidic co-catalyst, which proved to be necessary. Two chiral acids, namely *N*-Boc-(L)-phenyl glycine and *N*-Cbz-(L)-serine were thus tested in combination with the best performing amine, but no improvements were observed. Trifluoroacetic acid, despite being commonly employed as additive in reactions proceeding through this same activation mode, revealed completely uneffective (Table 5.3). It has to be mentioned that typical conditions for iminium ion catalysis call for 0.3 equivalents of the acid; however, we reasoned that the excess of acidic additive with respect to the catalyst could cause complete protonation of the quinuclidine moiety that must remain basic to deprotonate the nucleophile. Thus, in first experiments, only 0.1 equivalents of the co-catalyst was used. When the acid amount was raised to 30 mol%, however, performances of the worse performing catalyst **B** improved (Table 5.3). This behaviour could be rationalized hypothesizing that the acidic co-catalyst, besides promoting the formation of the active electrophilic species - i.e. the iminium ion - is involved in a hydrogen bonding network; as the two catalysts **A** and **B** are indeed

diasteroisomers, it is no wonder that different acid concentrations are needed to establish the best non-covalent interactions framework.

acid	p$K_{a(H2O)}$	acid eq.	cat.	y (%)	ee (%)
-	-		**B**	-	-
salicylic	+ 2.9	0.1	**B**	19	71
salicylic	+ 2.9	0.1	**A**	46	91
N-Boc-(L)-phenyl glycine	+ 3.5	0.1	**A**	-	-
N-Cbz-(L)-serine	+ 2.2	0.1	**A**	23	87
salicylic	+ 2.9	0.3	**B**	21	92
TFA	- 0.25	0.3	**B**	-	-

Table 5.3

Microwave irradiation was applied in the attempt to improve the yield. Indeed, raising the temperature to 40 °C under MW, the product was obtained 70% yield with 95% ee in 2 hours. A decrease in reaction time to 1 hour provoked a lowering of the yield back to 46% (Table 5.4).
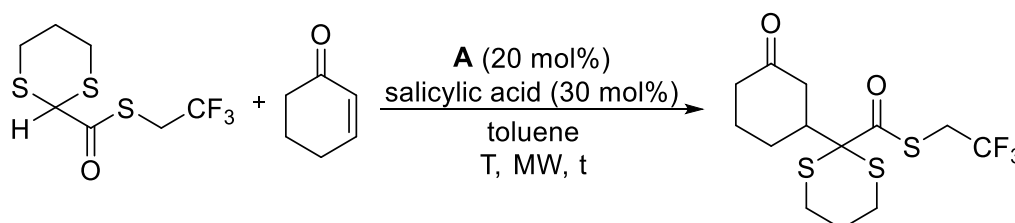
Scheme 5.14

t (h)	T (°C)	yield (%)	ee (%)
20[a]	RT	46	91
2[a]	40 MW	70	95
1	40 MW	45	97

Table 5.4 [a]Reaction run with 10 mol% of acid.

A further improvement in yields was achieved employing a 3.5 moles excess of the starting enone, while increasing its amountto 13 mol. equivalents led to slightly worse results (Table 5.5).

x eq.	solvent	yield (%)	ee (%)
1.5	toluene	70	95
3.5	toluene	80	97
3.5[a]	toluene	82	87
13	-	68	89

Table 5.5 - [a]Reaction run in the presence of catalyst **B**.

When the the catalytic system, catalyst loading was reduced to 5 mol%, while keeping constant the catalyst/product ratio the enantiomeric excess remained constantly high and the yield decreased with the catalyst amount (Table 5.6).

cat. eq.	acid eq.	y (%)	ee (%)
0.2	0.3	80	97
0.1	0.15	45	93
0.05	0.075	34	95

Table 5.6 All reactions were run with 3.5 equivalents of enone in the presence of catalyst **B** (20 mol%) at 40 °C under MW for 2 hours.

Different solvents were also tested. All solvents employed proved to be inferior to toluene, the most significant drop in enantioselection occurring in ethanol, confirming that the non covalent interactions between the quinuclidine and the deprotonated nucleophile do have a role in controlling the formation of the new C-C bond (Table 5.7).

solvent	cat.	yield (%)	ee (%)
toluene	**A**	80	(+) 97
toluene	**B**	82	(-) 87
ethanol	**B**	61	(-) 65
ethanol	**A**	24	(+) 65
hexane	**B**	18	(-) 85
hexane	**A**	23	(+) 85
acetonitrile	**B**	70	(-) 69
acetonitrile	**A**	49	(+) 75
toluene	**D'**	52	(-) 85
toluene[a]	**D'**	89	(-) 94
toluene	**C'**	96	(-) 97
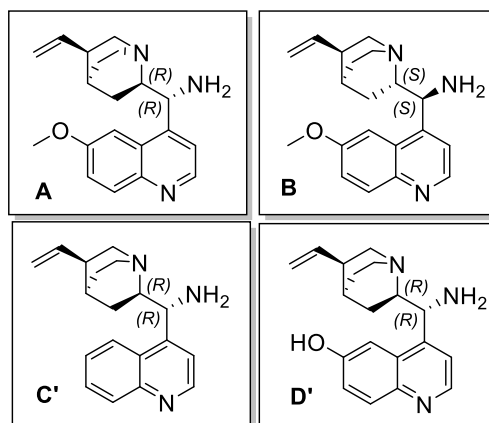
Table 5.7 All reactions were run with 3.5 equivalents of enone in the presence of catalyst (20 mol%) and salicylic acid (30 mol%) at 40 °C under MW for 2 hours. [a]Concentration of the reaction mixture 0.038M (typical conditions: 0.1M).

Finally, when the cinchonine derivative **C'** and the quinidine derivative **D'**, featuring different groups at C6', were used, the change in the outcome was not dramatic.

The notable results obtained employing cyclohexenone were unfortunately not reproduced on other substrates (Figure 5.11). Among the linear and cyclic enones tested, only chalcone and cyclopentenone did react, the latter giving the product with high enantioselectivity. 2- and 3-methyl cyclohexenones were probably too hindered, while 1,2- and 1,4-naphtoquinones were probably not suitable from an electronic point of view.
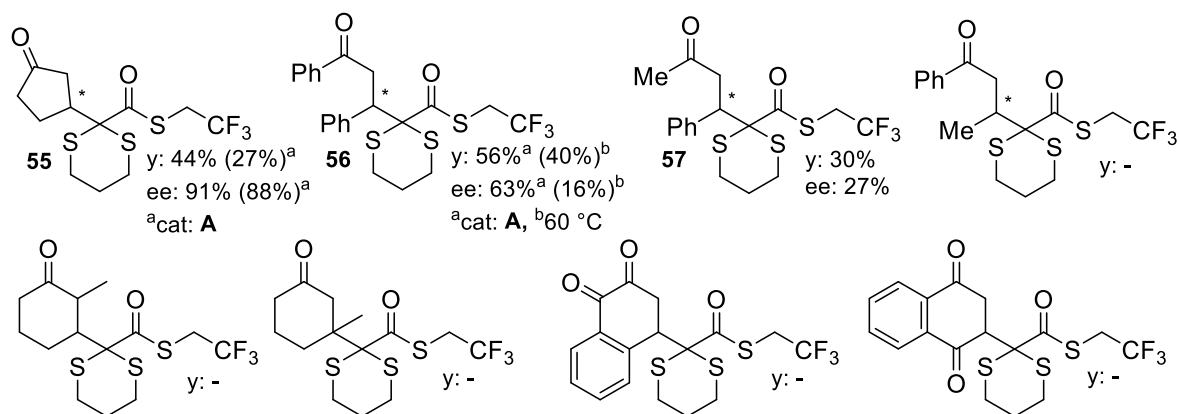
Figure 5.11 – Reactions were performed in the presence of catalyst C' (20 mol%) and salicylic acid (30 mol%) under MW for 2 hours.

With the reaction products in hand, we explored the possibility of chemically transforming the obtained reaction products.

To achieve carbonyl deprotection we mainly relied on the use of *N*-bromsuccinimide; this ketone derivatives revealed less suitable for this kind of reaction than the dithiane-nitrostyrene derivatives (see previous section), therefore a systematic screening of reaction conditions was needed (Scheme 5.15). We referred to Corey extensive studies devoted to this specific reaction, where the author demonstrated the superiority of halosuccinimides with respect to mercuric chloride for the hydrolysis of dithiane in substrates featuring unsaturated bond or oxygenated substituents and identified silver nitrate and sterically hindered pyridines as optimal additives (Table 5.8).[382]
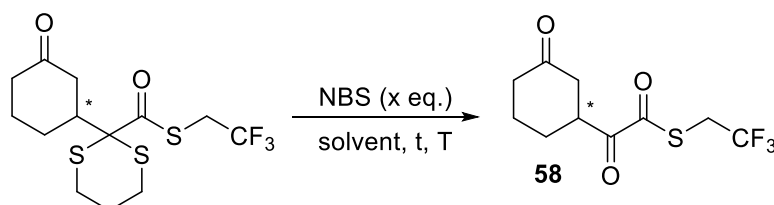
Scheme 5.15

x eq.	solvent	t (h)	T	y (%)
2	Acetone/ H_2O (97%)	2	0 °C	-
2	CH_3CN/H_2O (80%)	18	RT	-
5	Acetone/ H_2O (97%)	2	0 °C	13%
5	CH_3CN/ H_2O (80%)	18	RT	-
10	Acetone/ H_2O (97%)	2	0 °C	19%
10	CH_3CN/ H_2O (80%)	18	RT	40%
6[a]	CH_3CN/ H_2O (80%)	1	RT	-
6[a]	CH_3CN/ H_2O (80%)	15min	RT	-

Table 5.8 - [a]Reaction run in the presence of $AgNO_3$ (6.3 eq.) and dimethyl pyridine (16 eq.).

Our tests revealed that working in an acetonitrile:water 80:20 mixture with 10 equivalents of NBS, it is possible to obtain the desired compound in 40% yield upon overnight stirring at room temperature. The addition of $AgNO_3$ and dimehtyl pyridine proved not to be helpful (Scheme 5.15 and Table 5.8). As an alternative, we begun investigating the effectiveness of Selectfluor™, already reported to transform 1,3-dithiane containing compounds into the corresponding aldehydes with high efficiency under mild conditions.[383]

Differently from compound **31**, the cyclohexane-dithiane derivative **54**, proved prone to transesterification affording the desired γ-keto methylester in 60% yield upon treatment with 2 equivalents of silver triflate[h] (Scheme 5.16). Under acidic conditions, ester hydrolysis to carboxylic acidwas attempted under both acid and basic conditions. While under acidic conditions the starting material was recovered unchanged, the use of LiOH caused its complete degradation.
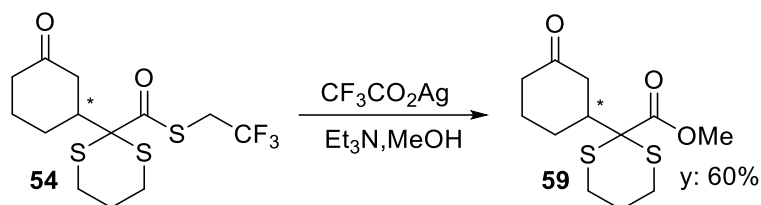
Scheme 5.16

First trials were also carried out to reductively remove the dithiane ring to obtain a chiral cyclohexanone functionalized with an alkyl chain. In fact, compound **54** was treated with $NiCl_2*6H_2O$ and $NaBH_4$ at 0 °C using either DMF or MeOH as solvent; however, no formation of the desired product was observed (Scheme 5.17).
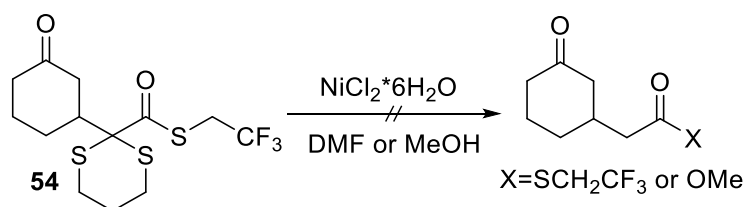
Scheme 5.17

Summarizing, excellent level on enantioselectivity were achieved in the conjugate addition of a peculiar activated thioester to α,β-unsaturated enones promoted by Cinchona alkaloids derived primary amines, even though the reaction scope was rather narrow. First investigations on addition products synthetic elaborations were performed, and an α,γ-keto ester as well as a 1,2,5-tricarbonyl compound were successfully obtained. Further studies are need to optimize and extend 1,3-dithianlyl-1,4-keto thioester transformations.

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[h] CF_3CO_2Ag integrity revealed determinant for the transformation to be succesfull.

6. STEREOSELECTIVE REDUCTION OF β-TRIFLUOROMETHYL NITROALKENES CATALYZED BY CHIRAL BIFUNCTIONAL ORGANOCATALYSTS

As already detailed in Chapter 2, trifluoromethyl-containing amines are getting an increasing important role, especially in the pharmaceutical field. In this context, our group developed straightforward methods for the preparation of enantiomerically enriched amines featuring a CF_3 group both in the α- and in the β-position. The two strategies rely on organocatalytic stereoselective reductions of easily available trifluoromethylated substrates (Scheme 6.1 and 6.2).

Scheme 6.1

Scheme 6.2
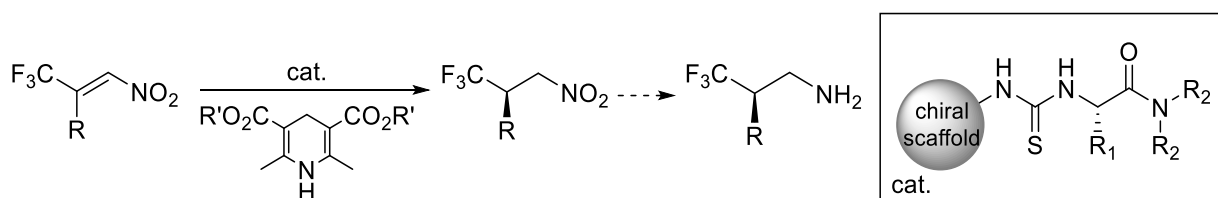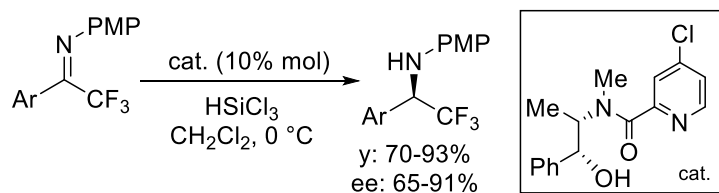
In this Chapter, we will discuss on the reduction of trifluoromethylated nitroalkenes by Hantzsch ester, controlled by a thiourea based bifunctional organocatalyst.

On the bases of what is known about these kind of transformations and relying on the thiourea-NO_2 interaction, we hypothesized this reaction could proceed through the simultaneous coordination of both reaction partners with the catalyst that features both a hydrogen bond donor and acceptor site (Figure 6.1).

Figure 6.1
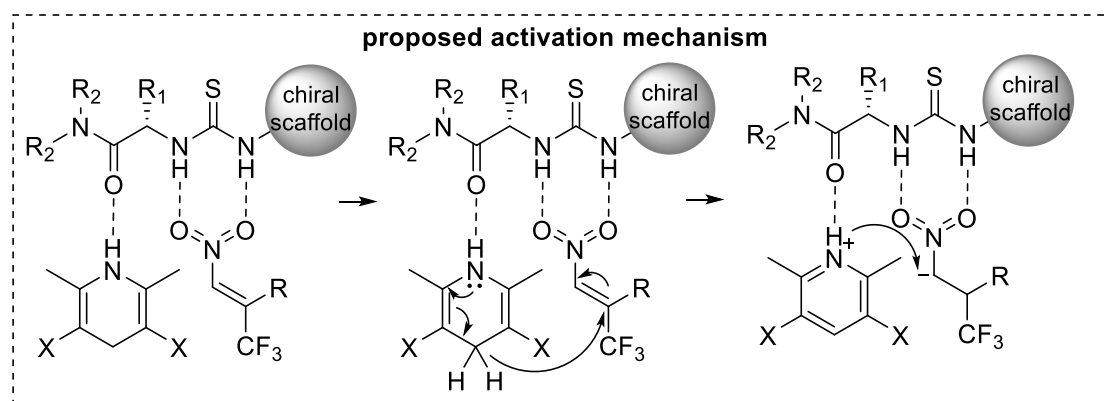
To accomplish nitroolefins reduction several strategies have been reported, including biotransformations carried out by enzymes or yeasts,[384] and metal catalysed hydrogenation,[385] and hydride transfer from different sources as PMHS[386], Ph$_3$SiH[387], HCO$_2$H[388] and Hantzsch ester.

Hantzsch ester is a mimic of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) (Figure 6.2), ubiquitous cofactors mediating a very wide variety of redox processes in living organisms. These compounds are endowed with the nucleosidic element that enables molecular recognition of a specific enzymatic environment wherein selective reduction might occur and the dihydropyridine ring of the nicotinamide subunit which can deliver a hydride species from C4 position with concomitant aromatization of the heterocycle yielding the oxidized form of the coenzyme, NAD(P)$^+$.[389]
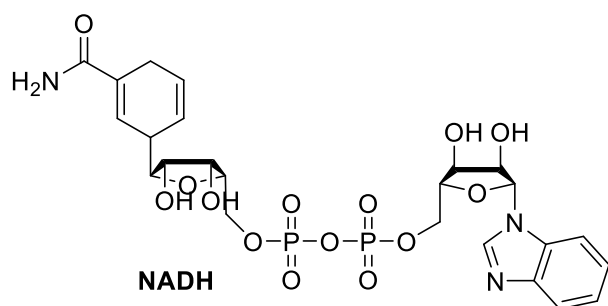
Figure 6.2

Just characterized by the dihydropyridine core, Hantzsch ester is able to act as a reducing agent working through an analogous mechanism: aromatization to the pyridine form is the driving force for hydride loss from C4, followed by deprotonation (Scheme 6.3).
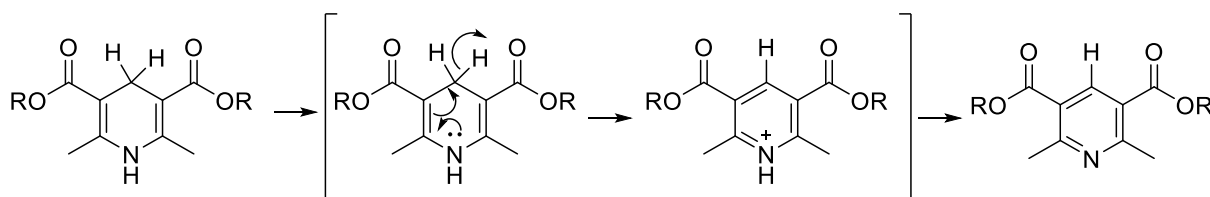
Scheme 6.3

This reducing agent has been used for the stereoselective catalysed reduction of C=N in imines and C=C in unsaturated aldehydes and ketones and in nitroolefins. In a recent example by Meggers group, chiral iridium complexes were used to promote nitroalkanes formation in excellent yields and enantioselection typically exceeding 95% with 0.3 mol% catalyst loading. In the organometallic model complex, a coordinated 5-amino-3-(2-pyridyl)-1H-pyrazole acts as a double hydrogen-bond donor for the nitro group of the substrate, whereas a hydroxymethyl substituent on the benzoxazole ligand coordinates the incoming nucleophile acting as a hydrogen-bond acceptor (Scheme 6.4).[390]
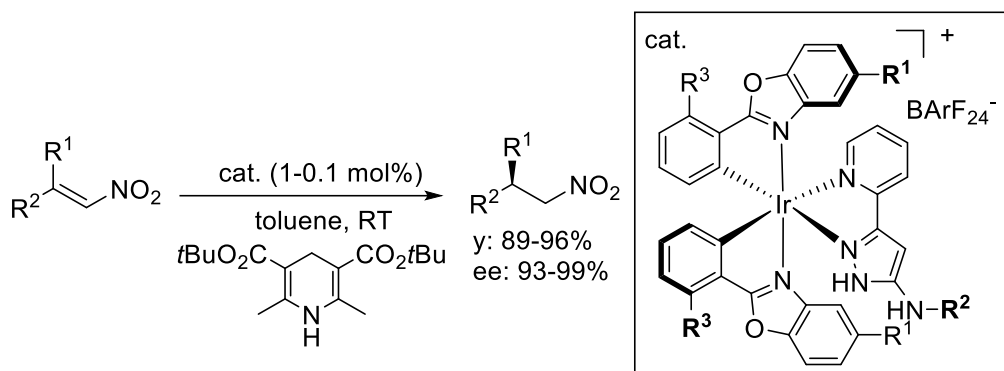
Scheme 6.4

The iridium catalyst design was inspired to thiourea-based organocatalysts that have been successfully employed in this kind of reactions.

In 2007, List and co-workers published the organocatalyzed stereoselective reduction of nitroalkenes affording the corresponding enantiomerically enriched nitroalkanes in often quantitative yield and up to 96% enantiomeric excess. The most efficient catalyst features a thiourea moiety linked to the (L)-*tert*-leucine diethylamide and to the *N*-pyrrole derivative of (*R,R*)-diaminocyclohexane (Scheme 6.5).[391]
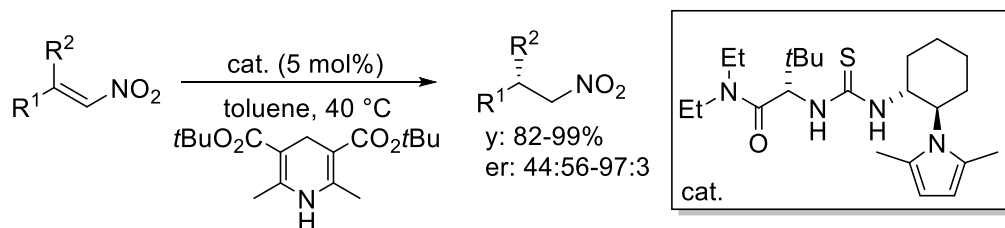
Scheme 6.5

So-called "planar-chiral" thioureas were synthetized and used by Schneider et al. to promote nitroolefin transfer hydrogenation. However, ee lower than 24% have been obtained (Scheme 6.6).[392]
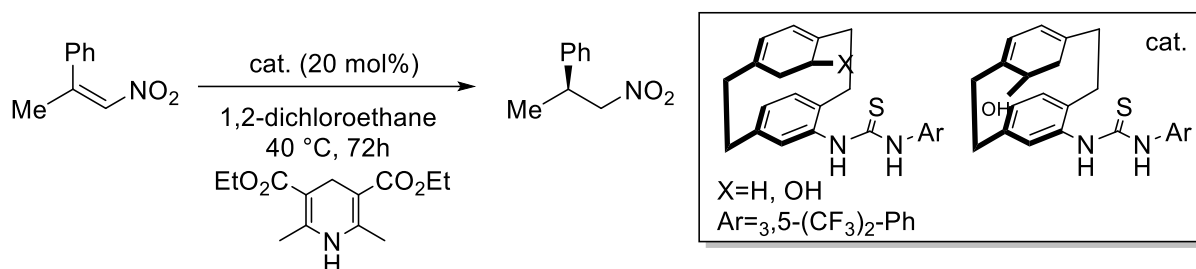
Scheme 6.6

In 2013, Anderson and Koovits reported the first stereoselective tandem reductive nitro-Mannich reaction promoted by a valine-derived thiourea organocatalysts, affording α-nitro amines in up to 89% yield, 95:5 dr and 98% ee. The reaction proceeds through Hantzsch ester hydride delivering followed by Henry type attack of the formed anionic intermediate onto the imine (Scheme 6.7).[393]
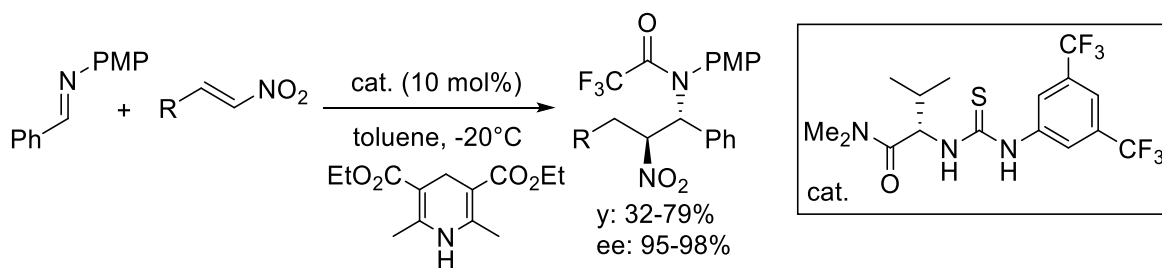
Scheme 6.7

We reasoned that trifluoromethylated nitroalkenes deserve particular attention for their unique substitution pattern.

As illustrated di Chapter 2, these substrates have already been employed as dienophiles in Diels-Alder reactions and as electrophiles in Michael-type additions. Besides their use in combination with chiral reaction partners, which is the typical approach for the preparation of peptidomimetics, these substrates have also been employed in stereoselective catalytic strategies.

However, when we started this project, no strategy for β-trifluoromethylated nitroolefins reduction has been reported so far, except for that by Shechter, Ley and Roberson (1956) relying on the use of complex hydrides. In this work the authors demonstrated that sodium trimethoxyborhydride, lithium borhydride, sodium borhyidride and lithium aluminium hydride are optimal reagents for reducing the C=C double bond without affecting the nitro group. Even under the best reaction conditions, however, they observed the formation of polynitroalkanes due to a side Michael type addition occurring between the negatively charged nitroalkane intermediate generated by after hydride addition and the unreacted nitroalkene.[274]

This gap in the field was simultaneously noticed by the group of Bernardi and Mazzanti[275] and by ours, thus undertaking independent investigations to establish a stereoselective organocatalytic procedure to obtain enantioenriched β-CF$_3$-nitroalkanes from the corresponding alkenes. Inspired by the works on nitroolefines[388] and nitroacrylates[230] reduction by List group, the C=C reduction in β-CF$_3$-nitroalkanes through transfer hydrogenation promoted by a chiral bifunctional catalyst was investigated (Scheme 6.8).
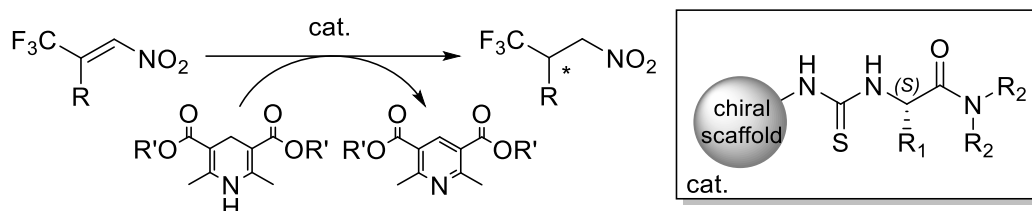
Scheme 6.8

The substrates can be prepared in two steps starting from the corresponding α-trifluoromethyl ketones through nitroalkane attack followed by one-pot chloride substitution and base-promoted elimination (Scheme 6.9). Due to the high volatility of these alkene, they were all purified through flash column chromatography employing low-boiling diethyl ether:pentane mixtures as eluents.
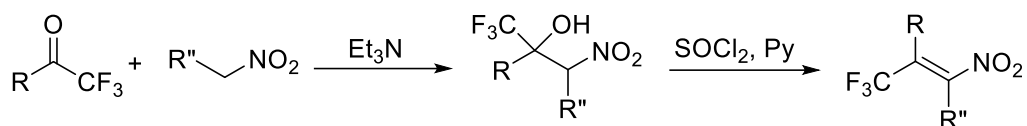
Scheme 6.9

We screened differently structured hydrogen bonding organocatalysts in the model reduction of β-trifluoromethyl-β-nitrostyrene by the commercially available Hantzsch ester, carried out in deuterated benzene at room temperature to make possible the direct ^{1}H NMR analysis of the crude reaction mixture (Scheme 6.10 and Figure 6.3).
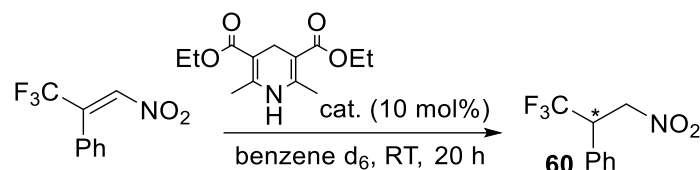
Scheme 6.10
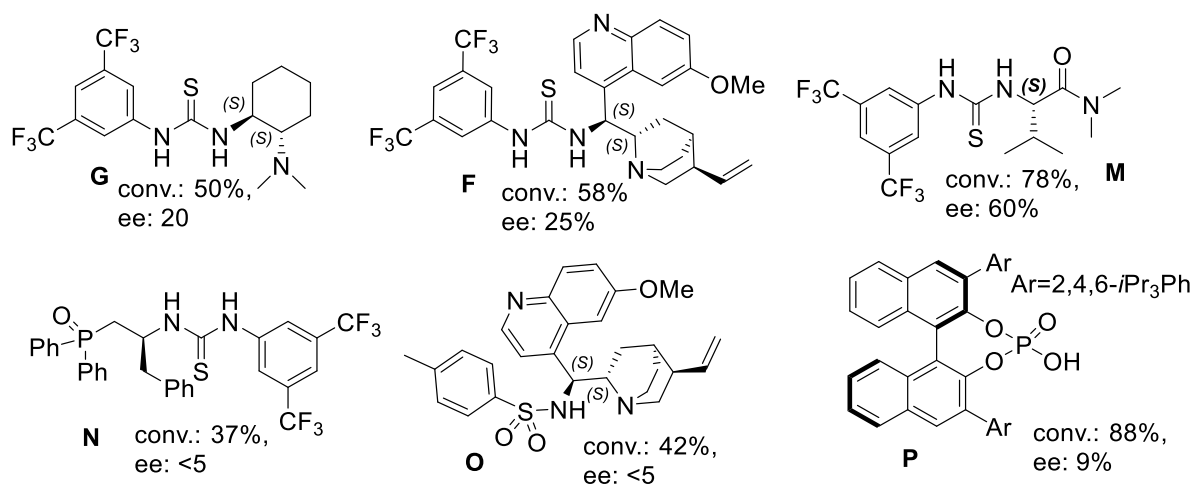
Figure 6.3

In agreement with previously published results, the higher level of enantioselectivity was achieved with a thiourea-amino acid based catalyst, which outperformed not only monodentate hydrogen bonding donors as sulfonamide or phosphoric acid, but also other thiourea derivatives featuring different chiral backbones.

A systematic investigation was thus undertaken testing the performances of a series of derivatives featuring this thiourea-AA skeleton and classifiable in to two main families differing for the presence of an aromatic or aliphatic *N*- substituent (Figure 6.3).

Figure 6.4

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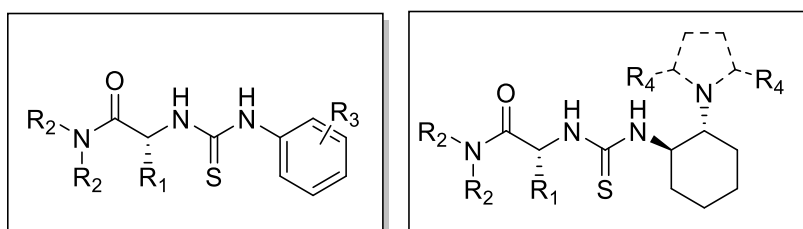
All structures were readily prepared from commercially available and rather cheap starting materials following straightforward and well established procedures (Scheme 6.11): *N*-protected amino acids were transformed into the corresponding amides and the subsequently released primary amines condensed with aryl isothiocyanate (pathway **a**) or transformed into an NCS group to be reacted with an alkyl primary amine (pathway **b**).
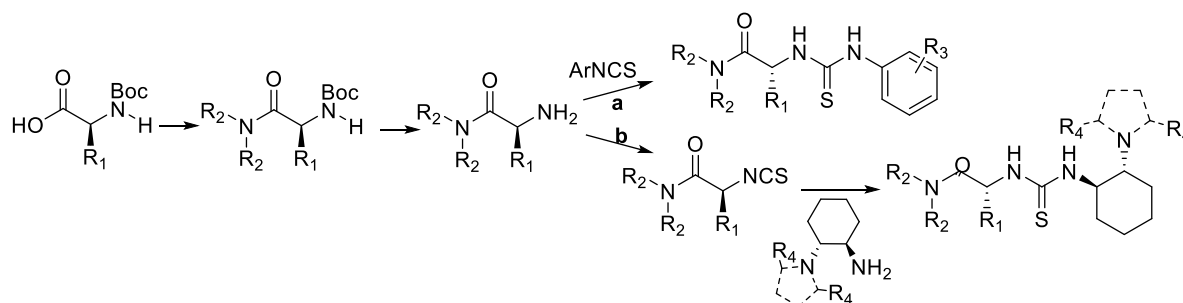
Scheme 6.11

The catalysts screening was therefore performed and a first rationalization of data was proposed using a transition state model supprted by DFT calculations (see below).[i]

Among the catalysts of the first class, the best ones revealed those featuring a L-valine derived amide and a 3,5-bis(trifluoromethyl)phenyl group, namely **M** and **M1** (Figure 6.5).
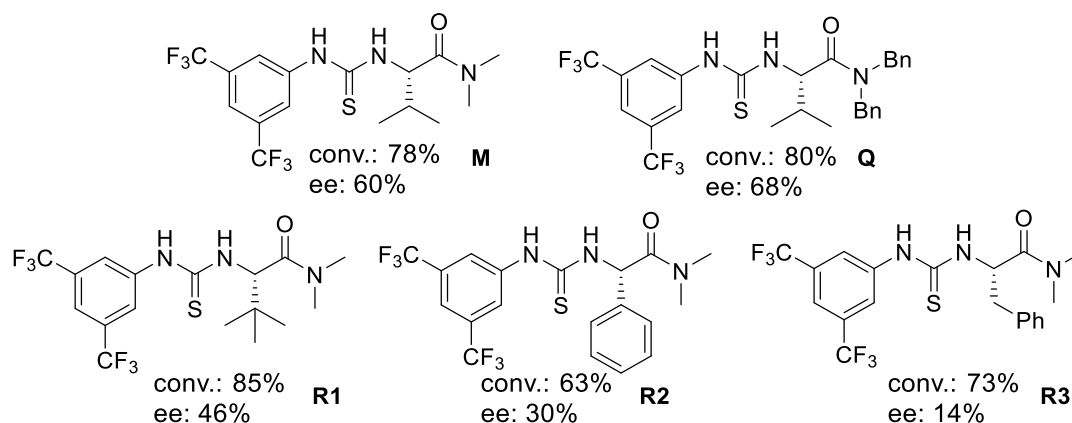
Figure 6.5

Lower enantiocontrol but comparable yield was offered by *tert*-leucine (**R1**), phenylalanine (**R2**) and phenylglycine (**R3**) derivatives. This result that can be explained considering the importance of the amino acid α-substituent not only in shielding one of the substrate enantiofaces, but also in stabilizing the catalyst skeleton in a single rotamer. In fact, as rotation around the N-αC bond is free, two different conformations, orienting Hanztsch ester – and thus hydride delivering – on both nitrostyrene faces can be adopted. In particular, the rotamer leading to *Si* face attack is destabilized by steric interactions between α- and *N*-substituents; thus, the more effective the α-substituent hindrance, the higher the difference in energy between the two catalyst's conformers and, therefore, the stronger the preference for H[-] attack on one of two enantiofaces. Poor performances of phenylalanine and phenylglycine derived catalysts can be thus due to inefficiency of the flat phenyl and of the flexible benzyl groups in blocking

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[i] Mechanicistic rationalization and DFT studies were performed by Manuel Orlandi.

the structure in a specific conformation. Lower enantioselectivity offered by *tert*-leucine with respect to valine is instead unexpected and unexplained, considering the high steric demand of the *t*Bu moiety (Figure 6.6).
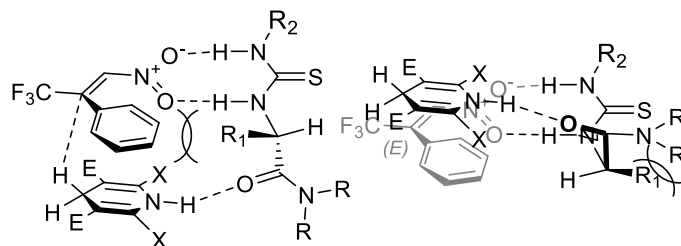
Figure 6.6

With the thioureas catalyst **T1**, **T2** and **T3** where the amino acid was substituted by an amino alcohol moiety the product was always obtained as racemate (Figure 6.7). This result can be rationalized considering less effective coordination of the Hantzsch ester by the catalyst OH group, less powerful than the carbonyl one as hydrogen bond acceptor. Replacing the 3,5-$(CF_3)_2$-Ph group with aryl or alkyl substituted phenyl ring (catalysts **S1** and **S2**) did not lead to a decrease in conversion but to a drop in the ee level.
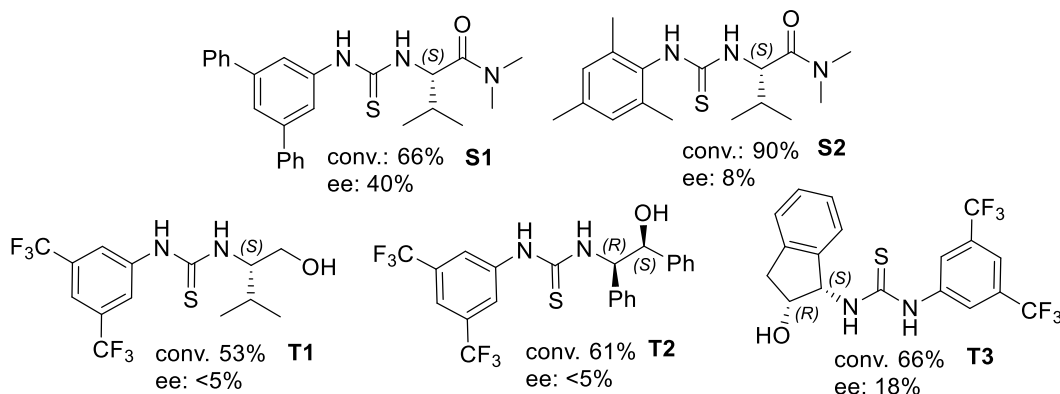
Figure 6.7

Under the same conditions, cyclohexanediamine derived catalysts **U1**-**V3** proved to be more effective in controlling the stereochemical outcome of the reaction (Figure 6.8). Also in this case, higher ees were achieved with L-valine moieties. The effect of different *N*-cyclohexane substituent was also investigated: while methyl groups revealed not suitable for obtaining high enantioselection, an improvement was achieved with phtalimide protection (catalysts **V2** and **V3**); however, ees lower than 60% where achieved, maybe because of the presence of the two further amide C=O groups allowing the establishment of hydrogen boding networks others than the desired one. To identify the best cooperating couple of enantiomers from each of the two chiral molecules embedded in the catalyst's structure, (*S*)-

valine was combined with both (*R,R*)- and (*S,S*)-diaminocyclohexane. The latter was found to form the *matched* couple.
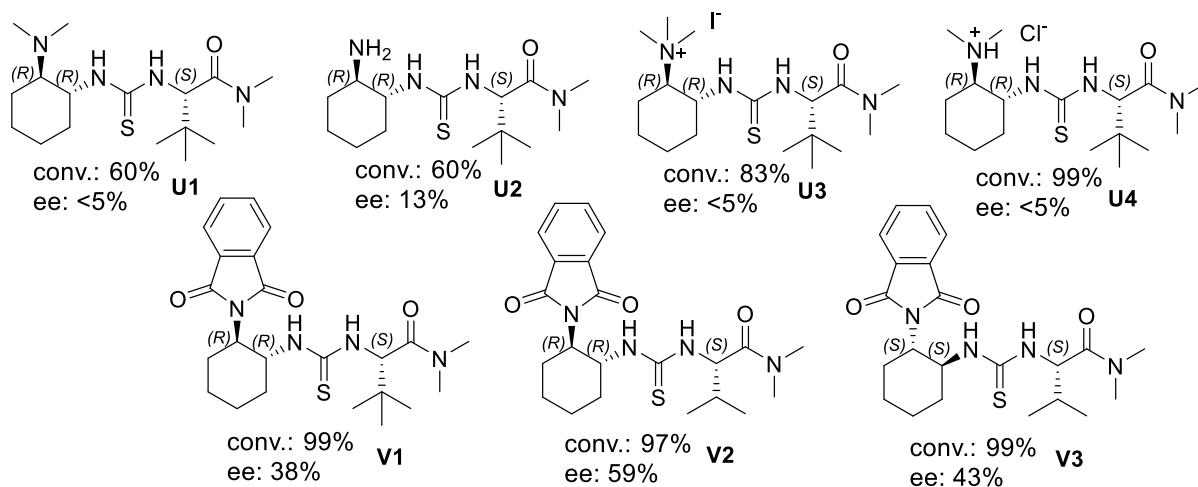
Figure 6.8

Much higher enantiomeric excess was obtained with *N*-pyrrole substituted structures; in this case, the presence of α-phenyl group on the pyrrole ring (catalyst **Z**) revealed detrimental, probably due to an excessive steric demand, as space around the thiourea functionality may be so hindered that prevents a proper coordination of the nitro group (Figure 6.9).
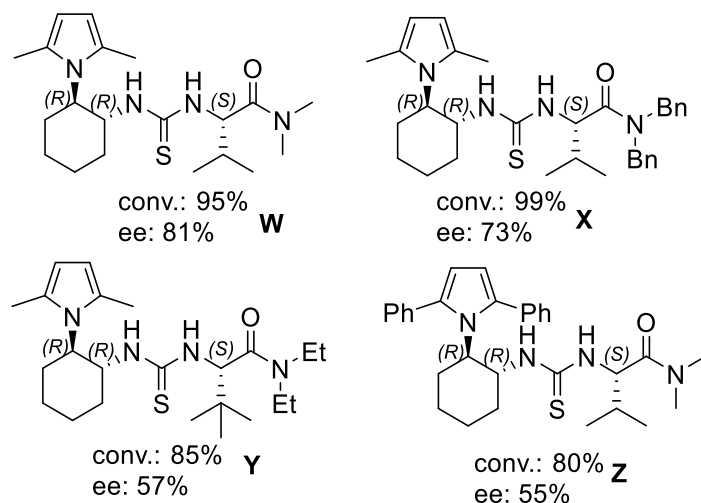
Figure 6.9

Once identified the best performing catalysts in the two families, a preliminary study on the reaction conditions was carried out. Different apolar solvents as well as the lowering temperature to 0 °C did not have a significant effect on the results (Table 6.1).
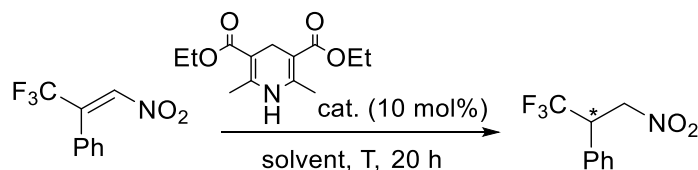
Scheme 6.12

cat.	solvent	T (°C)	yield (%)	ee (%)
M	hexane	25	85	71
M	CH_2Cl_2	25	90	62
M	toluene	0	76	75
M	hexane	0	5	61
M	CH_2Cl_2	0	45	68
V2	CH_2Cl_2	0	50	60
W	CH_2Cl_2	0	60	80

Table 6.1

An ultimate improvement was achieved thanks to the use of a modified Hantzsch ester (HE'), where *tert*-buthyl groups replaced ethyl ones. This dihydropyridine is known to have enhanced reducing power; in fact, the bulky *t*Bu units force the central core in a slightly tilted conformation, where the nitrogen lone pair partially overlaps do the C4-H bond, which intensifies H-nucleophilicity (Figure 6.10).[394]
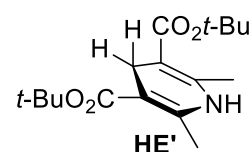
Figure 6.10

This reducing agent was used in combination with diaminocyclohexane derived thioureas. As expected, polar and protic solvent interfered with the non-covalent interactions needed for stereoselection (Table 6.2).

cat.	solvent	T (°C)	yield (%)	ee (%)
W	toluene	25	>99	71
X	toluene	25	>99	81
W	CH_2Cl_2	0	>99	78
W	THF	0	>99	9
W	EtOH	0	>99	6
W	hexane	0	>99	80

Table 6.2 - Reactions were performed with HE' (1.3 eq.) in the presence of 10 mol% of the catalyst for 20 hours.

The higher activity of HE' allowed lower the reaction temperature to -50 °C; this implied a marginal loss in yield, but the level of conformational rigidity needed to overcome 90% ee was finally achieved (Table 6.3).

cat.	solvent	T (°C)	yield (%)	ee (%)
W	toluene	-78	-	-
W	CH_2Cl_2	-15	>99	77
X	CH_2Cl_2	-15	>99	74
W	CH_2Cl_2	-50	>99	77
W	toluene	-50	61	87
X	toluene	-50	71	93
X	hexane	-50	50	71
W	hexane	-50	70	83

Table 6.3 - Reactions were carried out with HE' (1.3 eq.) in the presence of 10 mol% of the catalyst for 20 hours.

Once the best conditions were identified, the reaction scope was examined using differently substituted aryl and alkyl nitroalkenes; with one of the latter, a remarkable level of ee (97%) was achieved (product **66**, Figure 6.11).
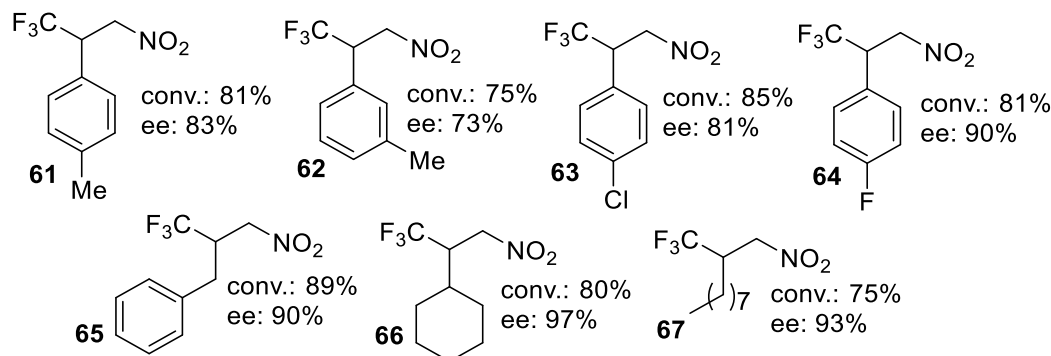
Figure 6.11 - Reactions were carried out with HE' (1.3 eq.) in the presence of cat. **X** (10 mol%) at -50 °C for 20 hours.

To establish the absolute configuration of the reduced products, we transformed one of the obtained nitroalkanes into a known amine[395] through nitro group reduction and reductive amination. Comparing the α_D value with the literature one, in was established that the used catalyst deriving from (*R,R*)-diamino cyclohexane led to an (*R*)-configured product (Scheme 6.13).
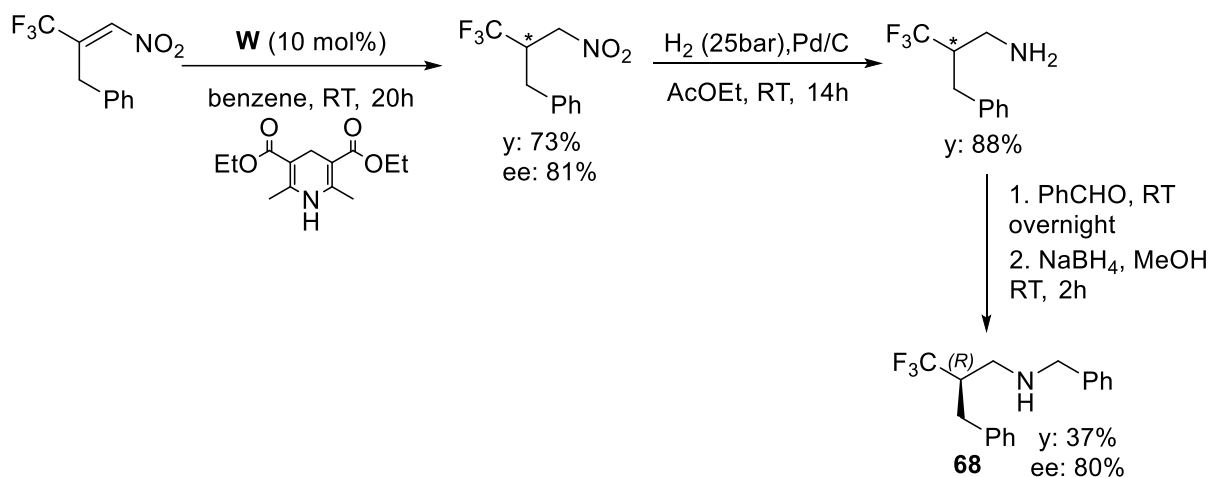
Scheme 6.13

To have a deeper insight of the structure of the transition state through which the reaction proceeds, computational studies were carried out.[j] Preliminary conformational analysis on the catalysts underlined high structural rigidity: only three conformations for catalyst **W** and a unique conformation for catalyst **Y** appeared energetically allowed. The analysed TSs have been identified based on the assumption of coordination of the nitro group to the thiourea moiety and of the Hantzsch ester NH group to the catalyst carboxyamide group.

Comparing the two competing transition states involving catalyst **W**, it is possible to notice that in the TS leading to the minor *S* enantiomer the pyrrole moiety experience a repulsive interaction with the

[j] The transition states (TSs) leading to the formation of both (*R*)-and (*S*)-**60**, for the reaction with both catalysts **W** and **Y**, have been located at a B3LYP/6-31G(d) level of theory; finer electronic energies have successively been obtained increasing the basis set up to 6/311+(2df,2pd) with two different functionals: B3LYP and M062X.

phenyl group of the nitroalkene. Additionally, it was observed that the nitroolefin C2 in TS-**S**W is closer to the bulky diaminocyclohexane moiety than it is in TS-**R**W; therefore the reducing agent, that needs to approach this electrophilic carbon atom to release the hydride, is forced in a hindered region where its ester group repulsively interacts with the 2,5-methyl pyrrole substituents (Figure 6.12).
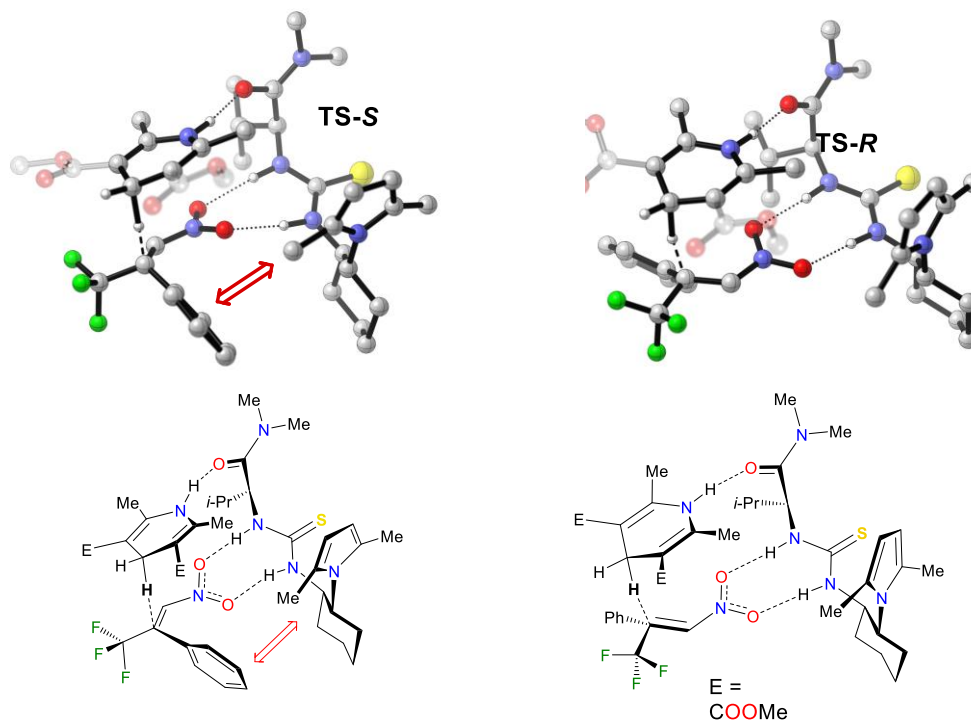
Figure 6.12

Moreover, aiming to understand the unsatisfying performance of the *tert*-leucine derivative, at first glance unjustified, a comparison was made between the favoured transition states, i.e. those leading to the *R* enantiomer. It was observed that with both catalysts **Y** and **W** a repulsive interaction may occur between the phenyl nitroalkene ring and *i*Pr or *t*Bu groups. However, it is only with the *i*Pr substituted catalyst that this destabilizing interaction can be avoided (Figure 6.13).
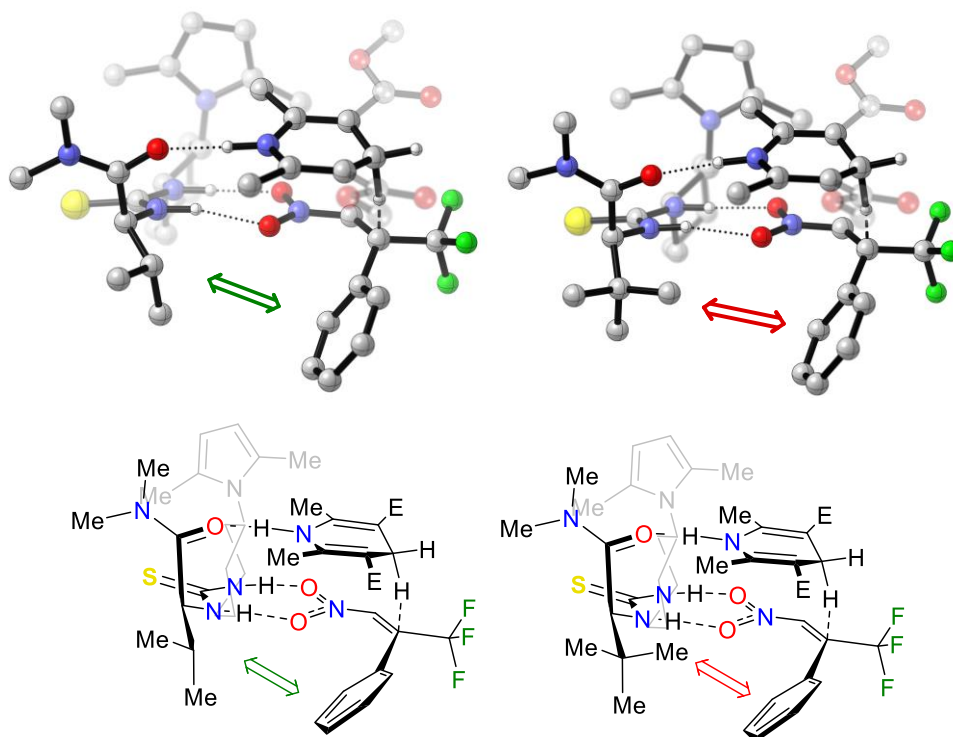
Figure 6.13

A tentative rationalization for the higher ee observed in the reduction of alkyl-substituted nitroalkenes was based on a possible CH$_3$-π interaction occurring in the disfavoured TSs between the methyl group of the 2,5-dimethyl pyrrole moiety an the aryl β-substituent of the substrate. This stabilizing interaction might lower the difference in energy between TS-*S* and TS-*R*. When the β-aryl group is replaced by an alkyl one, this positive interaction cannot occur and hence, the TSs leading to the *R* and *S* enantiomer should be energetically more differentiated. The possible role of this kind of interaction was confirmed by performing a non-covalent interaction (NCI) analysis with the NCIPLOT software.[396] A large region of weak positive interaction due to the expected CH$_3$-π interaction was evident between the phenyl ring and the catalyst's methyl substituent (Figure 6.14).
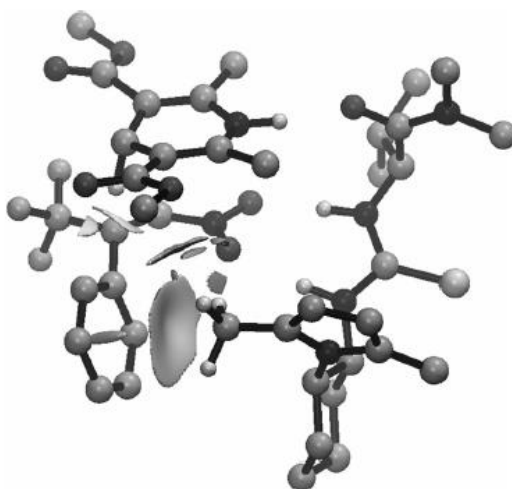
Figure 6.14

The calculated Gibbs free energies and the prediction of the enantioselectivities were also computed. Since the B3LYP functional is known to give a poor description of long-range dispersive interactions, a better prediction of the enantiomeric excesses was obtained with M06-2X. In particular, a remarkably good agreement between calculated and experimental ee obtained with catalyst **Y** has been achieved with M06-2X (43 vs. 57% ee). Noteworthy, both the DFT functionals predict higher TSs energy differences for catalyst **W** compared to **Y**, thus confirming the valine-derivative **W** to be the best catalyst.

Possible extension of this reaction to α,β-disubstituted-β-trifluoromethyl nitroalkenes has also been preliminary investigated (Scheme 6.14).
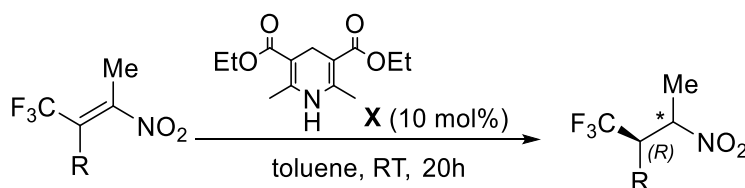
Scheme 6.14

It is worth mentioning that the stereoselective reduction of nitrostyrene derivatives featuring an α-substituent is still considered a challenging transformation that requires a controlled protonation step and leads to the formation of a rather labile stereocentre; indeed, to the best of our knowledge, no organocatalytic example of this reaction has been reported so far.[397] The substrates were obtained as a differently enriched mixture of isomers. They were shown be configurationally unstable and involved in an equilibrium (Scheme 6.15).[k] Due to this equilibration, H-H NOESY experiments were not decisive for attributing the *E/Z* configuration of the substrates.
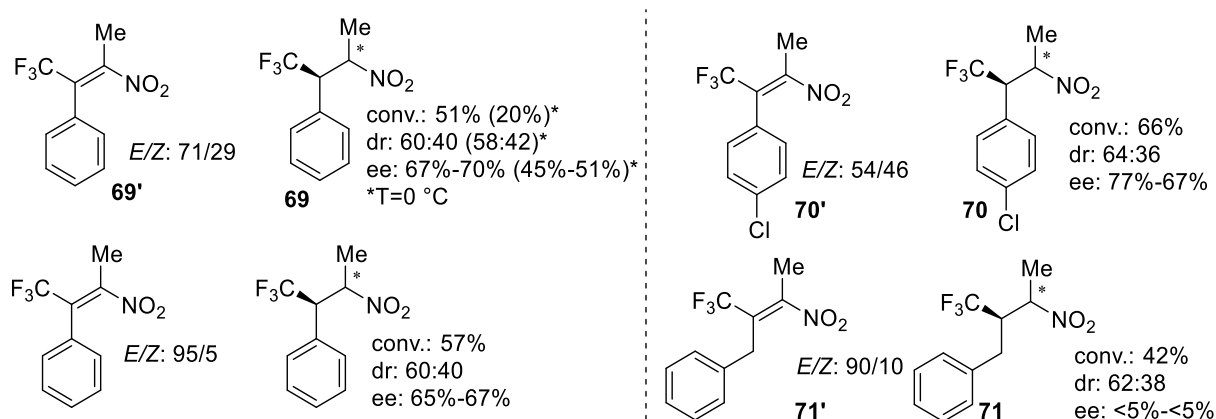
Scheme 6.15

Almost identical results in terms of yield, dr and ee were obtained in the enantioselective reduction of **69'**, independently from the diastereoisomeric ratio of the starting nitroalkene. The β-trifluoromethyl-α-methyl-substituted nitroalkanes were obtained in modest yields and low diastereoisomeric ratio, but with an appreciable level of enantioselectivity for both isomers. The absence of diastereoselection can

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[k] A change in the diastereoisomeric ratio of the two isomers, from roughly 50:50 to 90:10 was observed for all compounds to take place in few days, even when the isomeric mixture was kept neat at 8 °C.

be rationalized considering that employed catalyst is probably not suitable for effectively controlling the re-protonation step, which is expected to occur very rapidly after H$^-$ delivery. Even enantioselectivity level was not a high as it was obtained for compounds **61**-**67**, probably because the α-substituent establishes destabilizing steric interactions with the catalyst (Figure 6.15).
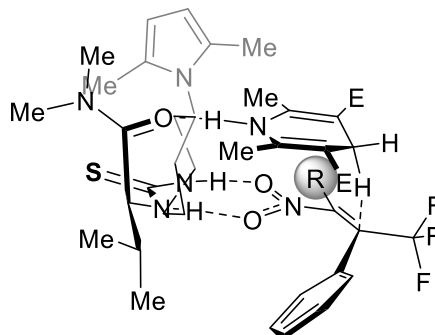
Figure 6.15

As already mentioned, in the same period also Martinelli and co-workers developed an organocatalytic system to perform the C=C reduction of β-CF$_3$-nitroolefines in a stereoselective way. The authors identified an aryl-substituted thiourea as the best performing catalyst, showing enantiocontrol was dependent on the substituents on the amide portion of the catalyst; in particular, the highest ees were obtained with *N*-unsymmetrically substituted valine derivatives. Working at -20 °C in trifluorotoluene, products were afforded with enantioselectivity ranging from 85 to 97% (Scheme 6.16).
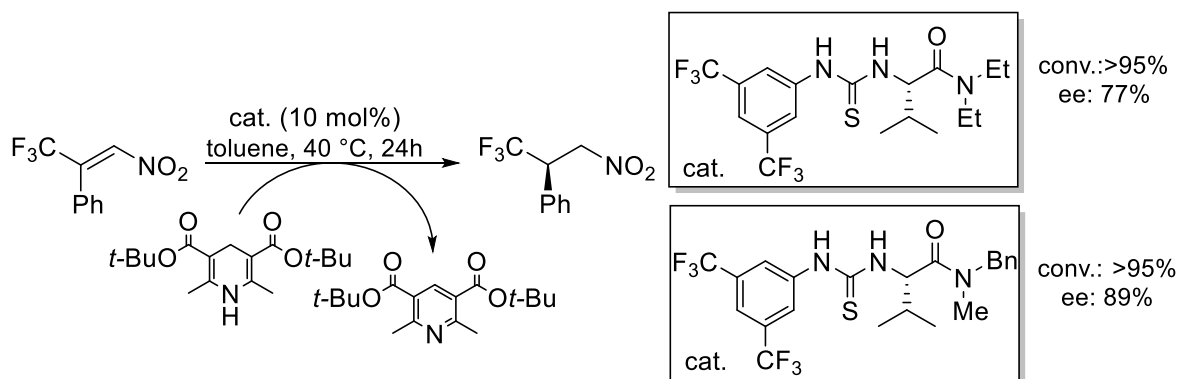
Scheme 6.16

In conclusion, the enantioselective organocatalytic reduction of β-trifluoromethylated nitroalkenes was accomplished on both β-aryl- and β-alkyl-substituted substrates, in up to 97% ee. The absolute configuration of the chiral obtained nitroalkanes was established through chemical correlation, thus also demonstrating that this methodology offers a valuable entry for a straightforward synthesis of enantiomerically pure β-trifluoromethylated amines. Moreover, the stereochemical outcome of the reaction and the behaviour of the thiourea-based bifunctional catalyst were rationalized based on computational analysis.[398]

7. DEEP EUTECTIC SOLVENT AS NOVEL REACTION MEDIA FOR STEREOSELECTIVE ORGANOCATALYTIC REACTIONS

Meeting the requirements for sustainable development is a challenge all research studies have to deal with, carrying out innovation that fulfils the need of preserving current resources to guarantee a healthy progress for future generations. Within the design and engineering of chemical processes, this implies evaluations on whole life-cycles, aiming to identify suitable alternative to methods and substances that can be considered *hazardous* towards living beings and environment;[399] one of the main objective consists in finding new *green* solvents, as harmless as possible and suitable for the use at the industrial level.

A breakthrough in this direction was represented by the possibility of employing easily obtainable eutectic mixture as effective solvents for a growing number of different applications. This concept was introduced in 2003 by Abbott and co-workers who reported on room temperature liquid mixtures of amides and quaternary ammonium salts,[400] thus opening the door on a new research field swarming of till unexplored opportunities.[401] Several studies have been devoted to find new combination of neutral hydrogen bond donors and acceptors[402] leading to either Low-Transition-Temperature Mixtures (LTTMs) or Deep Eutectic Solvents (DESs), depending on their phase transition being identified by a melting point or by a glass transition, respectively.

Whether derived from ammonium derivatives and metal salts or organic compound endowed with acidic hydrogen atoms (type I to IV DES),[403] sugars and urea ("sweet" eutectic mixtures) or amino or carboxylic acids and choline chloride (NAtural DESs),[404] these solvents are simply prepared by thermal mixing and require no purification, their low cost and ready accessibility being the main strong points with respect to ionic liquids.[405] Besides, differently from the ionic liquids, LTTMs composition is not limited by stoichiometry and their properties, including freezing point, density, viscosity, polarity, molar heat capacity and conductivity, can be tuned varying the nature and the ratio of the mixed components. Correlations have been found between mixture composition and chemical-physic behaviour, which nevertheless remain partially unpredictable. Despite low melting mixtures have been demonstrated not to be completely biodegradable and non-toxic[406] and further investigations are needed to assess their *greenness* extent,[407] they are generally referred to as bio- and environmental benign, due to their natural metabolites based composition, low volatility and non-flammability. These promising low environmental impact features, together with the ad hoc tailored nature, make these solvents fit for large-scale purposes. Increasing number of investigations are focused on LTTMs and DESs in process technologies, including separation procedures[408] as CO_2 dissolution[409] and biomass processing,[410] materials preparation,[411] metal treatments, electrochemistry, biomedical techniques and environment-preservation methods, as desulfurization procedures.[412]

Even if DESs have not been extensively employed in organic synthesis yet, several advantages associated to their use have been observed, as their properties are easily tuneable to meet specific reaction requirements and they offer convenient products isolation possibilities by organic phase

extraction or even precipitation upon addition of water, which is subsequently removed restoring a reusable deep eutectic mixture.

In different kinds of transformations DESs typically afford increased reaction rates and yield. Collected and classified in recent reviews, these transformations include multi-component and metal-catalysed C-C bond formation and hydrogenation reactions. In the last year, Mallardo and co-workers reported the *ortho*-lithiation/functionalization of diaryltetrahydrofurans proceeding in choline-derived mixtures with high yield and complete regioselectivity;[413] an efficient Au(I) catalysed γ-alkynoic acids cycloisomerisation, carried out in ChCl-urea, at room temperature and open air, was published by Alvarez group.[414] Biocatalytic processes[415] have also been performed in these solvents having positive effects on substrate dissolution and enzyme stability. Besides, exploiting their acid or basic character, DES were demonstrated to simultaneously play the role of reaction media and catalyst in acid or base catalysed transformations.[416]

At the best of our knowledge, however, only a single example of the use of DESs in organocatalysis has been reported. In this work by María group, an enzyme-secondary amine cascade allows alcohol oxidation to acetaldehyde, subsequently undergoing cross aldol condensation; the whole process takes place in a choline chloride/glycerol medium and the DES-enzyme-organocatalyst system was recycled up to six times, although partial extraction of the proline derivative in the solvent used for product separation was observed (Scheme 7.1).[417]
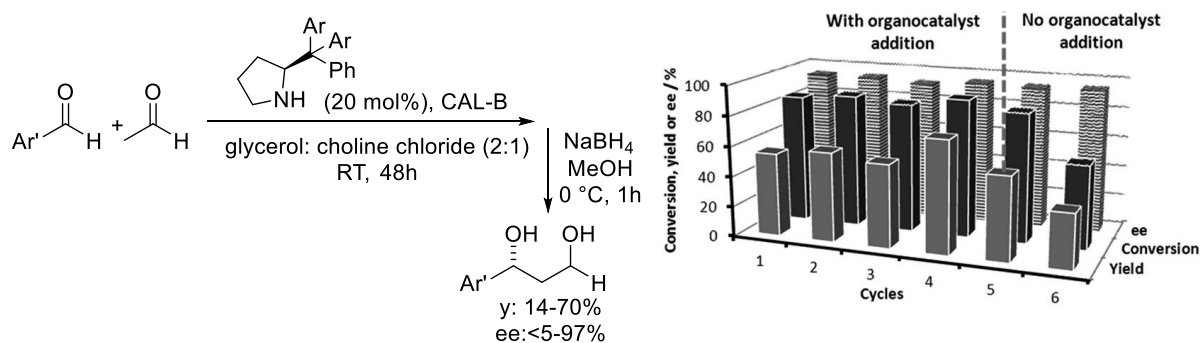
Scheme 7.1

Our aim was that of exploiting these innovative *eco-friendly solvents* in organocatalysis, which is already regarded as one of the most powerful tools of Green Chemistry, thus expanding the widely-recognized sustainability of this approach.

In particular, we studied primary amines promoted stereoselective transformations proceeding through different pathways in three diverse choline-based DES (Table 7.1) and we compared results with those previously obtained in conventional solvents.

	components	molar ratio
DES A	CHOLINE CHLORIDE : UREA	1:2
DES B	CHOLINE CHLORIDE : FRUCTOSE : H$_2$O	1:1:1
DES C	CHOLINE CHLORIDE : GLYCEROL	1:2

Table 7.1

We initially focused on the conjugate addition of isobutyraldehyde to nitrostyrene, proceeding by an enamine activation mode; the reaction is promoted by a primary amine derived from a Cinchona alkaloid, in the presence of an acidic co-catalyst (Scheme 7.2).
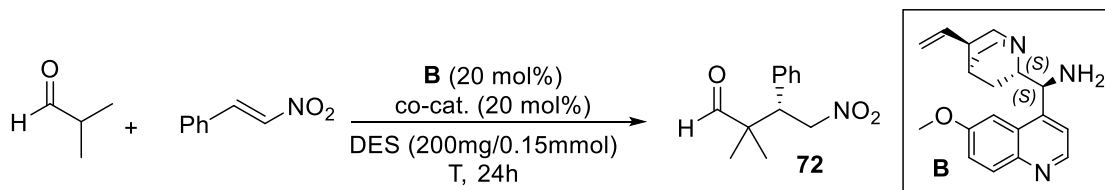
Scheme 7.2

solvent	co-cat.	T (°C)	conv.[b] (%)	ee (%)
DES A	benzoic acid	25	73	80
DES B	benzoic acid	25	>99	81.5
DES B	-	25	>99	95
DES C	benzoic acid	25	>99	62
DES C	benzoic acid	0	26	21
DES C	-	0	-	-
DES B	benzoic acid	50	>99	85
DES A	benzoic acid	50	>99	81
DES A	-	50	>99	88
-[a]	benzoic acid	25	92	89

Table 7.2 - [a]Literature reported result:[417] the reaction was performed neat and promoted by the amino-quinidine catalyst **A**. [b]Conversion determined by ^{1}H NMR analysis on the crude.

In all tested DESs, good conversions and satisfying levels of enantioselectivity, comparable to literature reports,[418] were achieved. Unexpectedly, temperature lowering proved to be detrimental not only in terms of yield but also of enantioselectivity, while carrying out the reaction at 50 °C better yields were achieved with no loss in ee (Table 7.2).

Further parameters were then investigated (Table 7.3). The concentration of the reaction mixture seems to have an effect on the reaction rate, but not a remarkable influence on the enantioselection of the transformation; indeed, higher yields were obtained operating in a 1 M solution rather than in 0.1 M solutions. A similar trend was also observed in toluene, but the reactions proved to be slower than those run in DES B. In particular, it was observed that the use of a low melting mixture as medium had a significant impact on the reaction progress. In fact, working in the absence of the acidic co-catalyst, which is typically required, product formation was roughly three folds faster than in toluene for low concentrated mixtures. These results are consistent with a positive cooperative effect of the DES system with the chiral catalyst in promoting the transformation, suggesting either an active involvement in the reaction mechanism (through the establishment of hydrogen bonds activating the substrate but not interfering with enantiocontrol) or the formation of a concentrated hydrophobic phase, constituted by the starting materials and the catalyst.

solvent	conc.	t (h)	conv.[a] (%)	ee (%)
DES B	1 M	3	65	91
		5	89	95
		20	>99	95
toluene	1 M	3	45	95
		5	67	98
		20	nd	nd
DES B	0.1 M	3	27	nd
		5	47	89
toluene	0.1 M	3	9	nd
		5	15	97
H_2O	1 M	3	25	61
glycerol	1 M	3	21	91

Table 7.3 - Reactions were carried out with aldehyde:nitrosturene 5:1 in the presence of **B** (20 mol%), but with no co-catalyst, at RT. [a]Conversion determined by ^{1}H NMR analysis on the crude.

The possibility of recycling the precious chiral catalyst was also examined. These experiments were based on the different solubility properties the amino-quinine derivative exhibited in DESs and in other organic solvents. In fact, when the reaction was interrupted adding a 7:3 hexane:diisopropyl ether mixture, the product was quantitatively extracted while the catalyst remained in the DES phase. Recycling tests showed indeed that the solvent-catalyst system remains unaltered over multiple reaction cycles. A decrease in yields, observed at the third recycle, was ascribed to a partial transfer of the catalyst in the organic solvent. No drop in the enantiomeric excess was observed, confirming that the catalyst activity was not affected (Table 7.4).

Further studies were performed to optimize the recyclability of the chiral catalyst, turning out that it was possible to improve the productivity of the recycling protocol by shortening the reaction time to only 2 hours.

recycle	t (h)	conv.[a] (%)	ee (%)
-	24	>99	95
1st	24	>99	93
2nd	24	37	92
-	5	89	95
1st	5	88	92
2nd	5	44	91
-	2	57	95
1st	2	55	95
2nd	2	55	93
3rd	2	38	93
4th	2	27	92

Table 7.4 - Reactions were carried out with aldehyde:nitrosturene 5:1 in the presence of **B** (20 mol%), but with no co-catalyst, at RT. [a]Conversion determined by ^{1}H NMR analysis on the crude.

To demonstrate the general applicability of DESs as solvents in organocatalytic reactions, we performed other two stereoselective transformations catalysed by the same primary amine **B** but proceeding through different activation mechanisms.

The addition of α,β-unsaturated ketones to *E*-nitroacrylates was studied (see Chapter 3). Conditions analogous to the previous ones were applied and products were obtained in yield, diastereomeric ratio and enantiomeric excess in agreement with those obtained in toluene (Scheme 7.3 and Table 7.5).
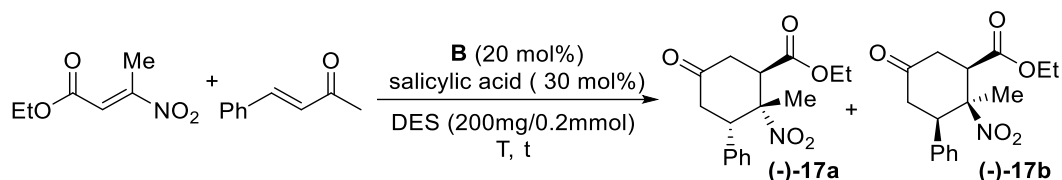
Scheme 7.3

solvent	T (°C)	t (h)	conv. (%)	dr (17a:17b)	ee (%) (17a:17b)
DES A	50	20	40	67:33	97-62
DES B	50	20	37	75:25	93-55
DES C	50	20	37	70:30	91-55
toluene	50	20	57	66:34	92-38
DES C	0	20	60	72:28	80-66
DES B	50[a]	2	-	-	-
DES B[b]	50	2	-	-	-
DES A	50[a]	2	-	-	-
DES A[c]	50[b]	2	46	76:24	94-72

Table 7.5 - [a]Reactions were performed under microwave irradiation. [b]Reactin performed in the absence of the acid co-catalyst. [c]3 equivalents of enone were employed.

The high heating efficiency of microwave irradiation, formerly applied in toluene to accelerate this already fast transformation,[419] revealed not to be compatible with the deep eutectic solvents. In this case, the presence of the co-catalyst proved necessary, as the catalytic cycle is initiated by an imine-dienamine tautomerization, promoted by the conjugate base of the acid.

Deep eutectic solvents revealed also suitable reaction media for stereoselective transformations based on iminium-ion activation, allowing the synthesis of the anticoagulant drug warfarin **73**. Yields ranged from very low to moderate, and good level of enantioselectivity, which revealed highly dependent on the temperature, was achieved (Scheme 7.3 and Table 7.6).[420]
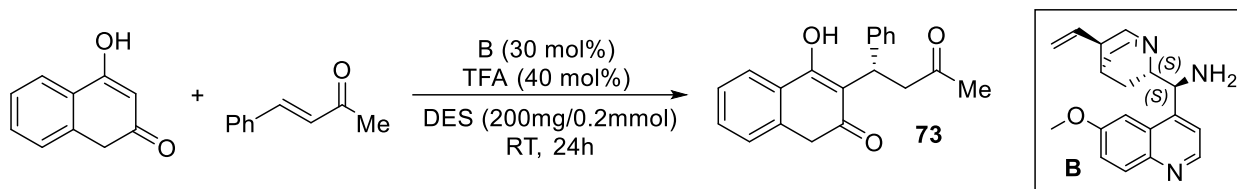
Scheme 7.4

solvent	conv.[c] (%)	ee (%)
DES A	52	86
DES A[a]	36[b]	11
DES B	40	66
DES C	18	62

Table 7.6 - [a]The reaction was performed at 50°C. [b]Isolated yield. [c]Conversion determined by ^{1}H NMR analysis on the crude.

In conclusion, three different eutectic mixtures were screened as representative DES systems; studying three model reactions catalysed by different mechanisms, excellent yields and stereoselectivities were obtained. Moreover, the recyclability of the chiral catalyst by a simple extraction protocol was successfully accomplished.[421]

EXPLORATIVE STUDIES IN PHOTOCATALYSIS

Brief overview on photochemistry and photocatalysis

To achieve a development that is as much sustainable as possible, it is also necessary to face the problem of energy supply. A futuristic light on the topic was cast by Giacomo Ciamician in 1912 when, a paper entitled *The Future of Photochemistry*, he pointed out the possibility of developing technologies to directly harvest energy from sunlight and convert it into fuels and chemicals. This visionary proposal of using sunlight as renewable, abundant and safe source of energy and chemical potential, despite not being fully realized yet, has been gradually embraced, firstly with remarkable progresses in radiation transformation into electricity and fuels, and subsequently with the development of what we can generally assess as *photochemical synthesis*. Indeed, a proper recognition of photochemistry as an individual science, where light unique activation cannot be replaced by other forms, as heating, occurred thanks to the Ciamician assertion that there are specific reactions promoted by "light and light alone". Two years later, Bodenstein stated that a photochemical reactions involves *electronic isomers* of ground states, i.e. electronically excited states, featuring an own peculiar reactivity.

Despite the take-off of this field required some time, significant photochemical transformations are known since decades and have been included as key steps in the synthesis of natural products;[422] stereoselective reactions promoted by UV direct sensitizations have also been developed.[423]

Right after *photochemistry*, *photocatalysis* was born, defining light promoted reactions where the photon energy was not incorporated in the final product and, later on, referring to reactions requiring the simultaneous presence of light and a catalyst and reactions involving the reagent excited states.[424] Due to the lack of visible light absorption by many organic molecules, visible light absorbing compounds, able to collect visible light photons and then to interact with a wide range of substrates *via* energy or electron transfers, have been employed being defined as *photocatalysts*. The photocatalyst can interact with a substrate through *photosensitization*, i.e. ceding energy, or through s*ingle electron transfer*, which can occur in two opposite directions. In fact, in the excited state the molecule becomes both a better oxidant and reductant, as the singularly occupied SOMOs, which are the previous LUMO and HOMO, are more prone either to donate or to accept an electron.[425] As for the nature of the photocatalyst, this can be an organometallic or a purely organic molecule. Most common metal-based visible light photocatalysts are polypyridyl complexes of ruthenium and iridium, both giving stable excited states that live long enough to engage in bimolecular electron-transfer reactions.[426] Despite featuring excellent photophysical properties, these complexes brings typical metal-associated disadvantages, including high costs and potential toxicity.[427] Therefore, also in the field of photocatalysis, organic catalysts emerged as effective alternative; previously employed as pigments and analytical indicators, organo-photocatalysts in some cases proved even better than the metallic ones.[428] One of the main exponents of organic photocatalysts family, including methylene blue, pyrylium,

quinolinium and acridinium salts, is eosin Y, a green light absorbing molecule successfully promoting reactions passing through both oxidative and reductive pathways.[429]

Photocatalysis finds an increasing number of synthetic applications;[430] the latest and more challenging strategies involve the cooperation among more catalysts and/or catalytic cycles to establish otherwise inaccessible reaction pathways. One of the most recent approaches involves the combination of organo- and photocatalysts.[431] An early report in this field by Rueping et al. showed the productive combination of the photooxidative generation of tetraisoquinoline-derived iminium ions with organocatalytic enamine catalysis. [432] A different approach was reported by McMillan and co-workers; these authors developed a variation of the SOMO based strategy, where a chiral enamine is attacked by a radical formed upon reductive cleavage by single electron donation from an excited photocatalysts[433]

In a work by Zleiter group, the reductive bisenone cyclization was reported (Scheme A.1); the reaction proceeded *via* ketyl radical formation promoted by eosyn Y in combination with a hydrogen bond donor organocatalysts. This study demonstrated the suitability of an organic dye replacing [Ru(bpy)$_3$]$^{2+}$ to generate the active radical intermediate in the presence of an organocatalysts acting as a Lewis acid. Reaction scope investigation showed that the methodology was feasible also for unsymmetrical systems.[434]
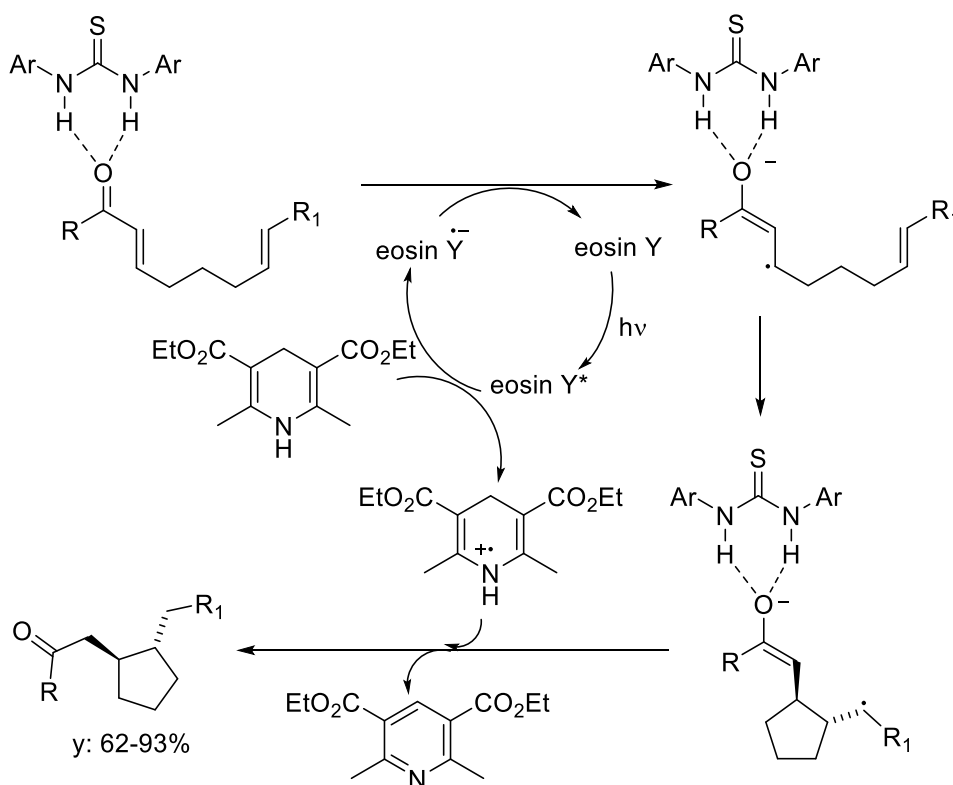
Scheme A.1

The following sections report on two different projects, both relying on the use of photocatalysis to explore possible novel reaction pathways.

Cooperative organo-photocatalytic system for the stereoselective light-induced C-C bond formation in nitro group containing substrates

As already mentioned, the cooperative application of different catalytic methods gives potential access to novel reaction pathways, opening new lines of investigation. In particular, the aim of this project was that of combining photocatalysis[435] together with stereoselective organocatalytic methodologies to access novel synthetic strategies for the preparation of enantiomerically enriched compounds through a metal-free visible light mediated process.[436]

Our working proposal relied on the employment of organic dyes as catalysts to induce an electron transfer to a substrate interacting with a relatively simple organic molecule used in substoichiometric amount; if a chiral organocatalyst is employed and manages to control the bond-formation step that follows the photochemical event, enantioselectivity could be induced. We focused on the use of nitroalkenes and nitroalkanes as substrates; these are precursors and building blocks of a wide array of molecules, largely employed in Michael reactions and cycloadditions, but rarely exploited in photochemistry.[437] Our aim was to investigate transformations where hydrogen-bonding coordination of the nitro-group directed the reactivity of photochemically generated radicals creating an asymmetric environment around the reaction centres.

Nitrostyrene single electron reduction

A first part of the study was focused on the use of nitroalkenes in a photochemically induced cyclization processes, where α,β-unsaturated ketones have already been successfully employed (Scheme A.2). Considering the electronic parallelism between these two classes of compounds, it was reasonable to propose these substrates to undergo an analogous mechanism;[438] besides, the possibility of activating nitroalkenes simultaneously controlling the stereochemical pattern of their reactivity - thanks to organocatalysts endowed with correctly positioned hydrogen bond donors - is well known (Scheme A.3).[439]
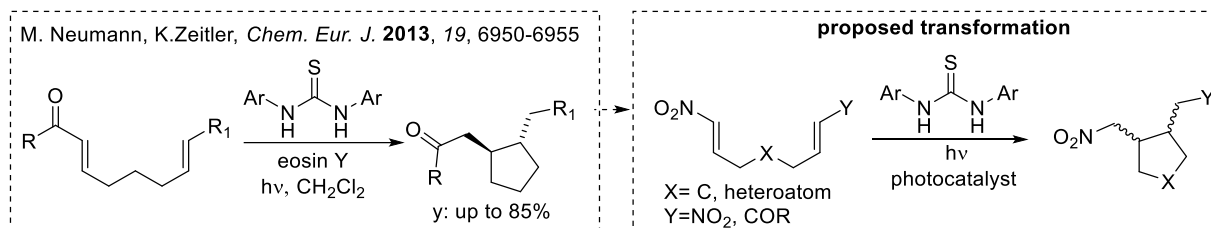
Scheme A.2
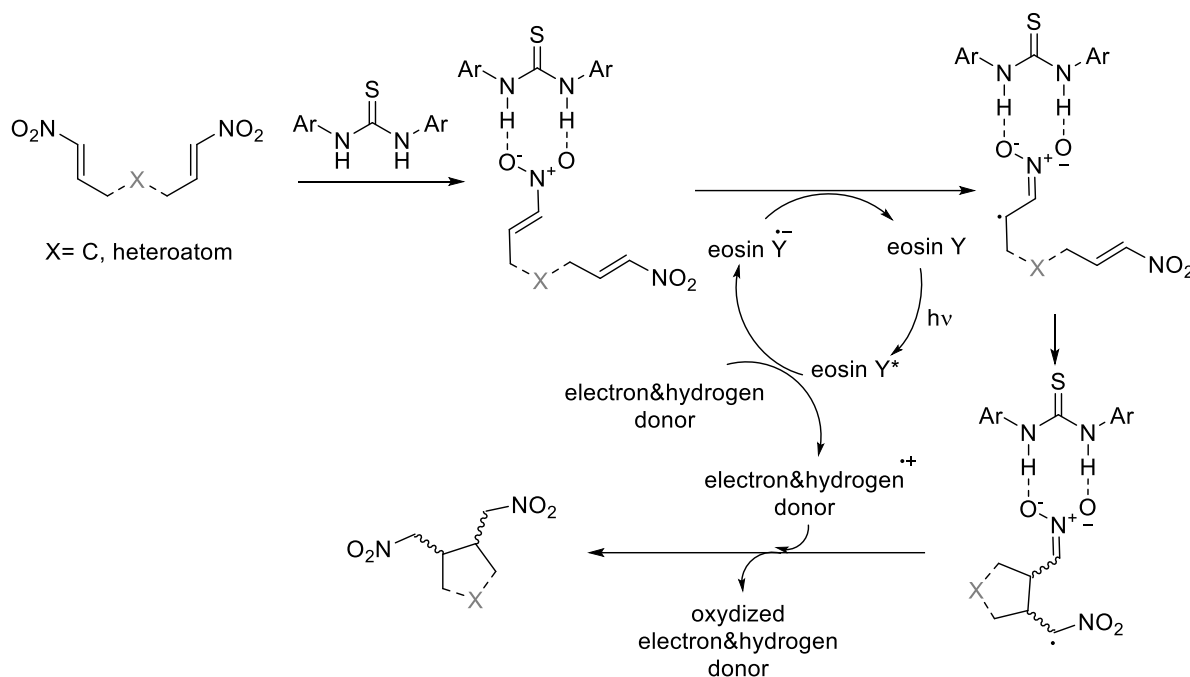
Scheme A.3

Preliminary experiments were carried out on an intermolecular reaction (Scheme A.4), employing a commercially available substrate as starting material (**sm**). Unsubstituted nitrostyrene was subjected to green and blue light irradiation in the presence of a photocatalyst and of an additive able to act both as electron and hydrogen donor, testing the influence of an achiral thiourea-based organocatalyst (**A0**). Different conditions were screened, and the formation of the homocoupling product **74**[440] was observed.
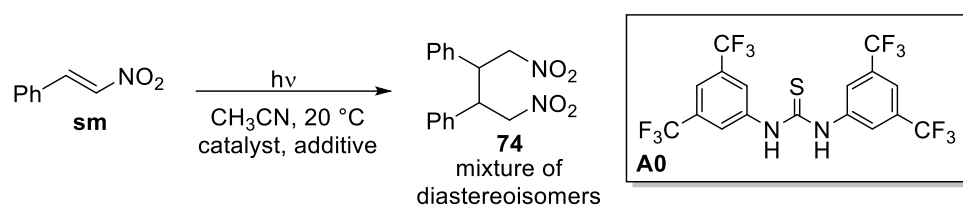
Scheme A.4

light[a]	catalyst and additive	[A_74/A_sm]					
DARK	(*i*Pr)₂NEt (2 eq.)	3.5h	2.5				
	(*i*Pr)₂NEt (2 eq.) + Eosin Y (0.1 eq.)	24h	>1%				
	A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.)	24h	-				
	A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.) + Eosin Y (0.1 eq.)	3.5h					
	HE (1.1 eq.)	3h	18% reduction product[b]				
	(Ph)₃N (2 eq.)	3h	-				
	ASCORBIC ACID (2 eq.)	3h	-				
GREEN	-	3.5h	-	7h	-	22h	-
	DIPEA (2 eq.)	3.5h	13	7h	15	22h	14
	Eosin Y (0.1 eq.)	3.5h	-	7h	-	22h	-
	(*i*Pr)₂NEt (2 eq.) + Eosin Y (0.1 eq.)	3.5h	64	7h	72	22h	67
	(*i*Pr)₂NEt (2 eq.) + Eosin Y (0.05 eq.)	1h	26	2h	26	4h	73
	(*i*Pr)₂NEt (2 eq.) + Eosin Y (0.025 eq.)	1h	25	2h	28	4h	35
	(*i*Pr)₂NEt (2 eq.) + Eosin Y (0.01 eq.)	1h	37	2h	34	4h	37
	HE[c] (1.1 eq.) + Eosin Y (0.025 eq.)	3h					
	(Ph)₃N (2 eq.) + Eosin Y (0.025 eq.)	3h	-				
	ASCORBIC ACID (2 eq.) + Eosin Y (0.025 eq.)	3h	6				
	A0 (0.1 eq.)	3h	-	6h	-	24h	-
	A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.)	3h	13	6h	15	24h	13
	A0 (0.1 eq.) + Eosin Y (0.1 eq.)	3h	-	6h	-	24h	-
	A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.) + Eosin Y (0.1 eq.)	3h	83	6h	87	24h	75
BLUE	-	1.15h	-	3h	-	24h	-
	(*i*Pr)₂NEt (2 eq.)	1.15h	28	3h	37	24h	43
	Ru (0.1 eq.)	1.15h	-	3h	-	24h	-
	(*i*Pr)₂NEt (2 eq.) + Ru(bpy)₃ (0.1 eq.)	1.15h	6	3h	3	24h	75
	A0 (0.1 eq.)	1.15h	-	3h	-	24h	-
	A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.)	1.15h	40	3h	98	24h	98
	A0 (0.1 eq.) + Ru(bpy)₃ (0.1 eq.)	1.15h	-	3h	10	24h	<1
	A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.) + Ru(bpy)₃ (0.1 eq.)	1.15h	23	3h	20	24h	-

Table A.1 - The ratio of GC areas attributed to compound **74** and to starting material was evaluated. [a]Light was provided by LEDs. [b]The formation of the nitroalkane deriving from C=C reduction on nitrostyrene was observed. [c]HE=Hantzsch ester.

These experiments proved the possibility of using nitrostyrene in photocatalytic reactions, as no significant amount of by-products was detected. In particular, the formation of the reductive coupling

product **74** was observed when using diisopropylethylamine as donor, while triphenylamine and ascorbic acid proved to be uneffective under these conditions, also due to solubility issues.

However, the organocatalyst revealed not to have a predominant role in the reaction outcome, as nitrostyrene was active both as electron- and as Michael-acceptor without the need of the further activation provided by coordination with **A0**. As lowering eosin Y amount from 10% to 1% did not clearly slow down the observed homocoupling, it was reasonable to suppose that the organocatalyst should have a rather limited role in controlling the substrate reactivity under these conditions; further optimization studies are necessary to minimize the background reaction.

The possibility of exploiting the radical anion, which is supposed to be generated upon electron donation from eosin Y$^{\cdot-}$ to nitrostyrene, as an *in situ* formed nucleophile reacting with electron poor compounds was also explored (Scheme A.4). An excess of potential electrophiles was therefore employed under those reaction conditions that were expected to lead to the formation of the reactive species from the substrate (Scheme A.5).
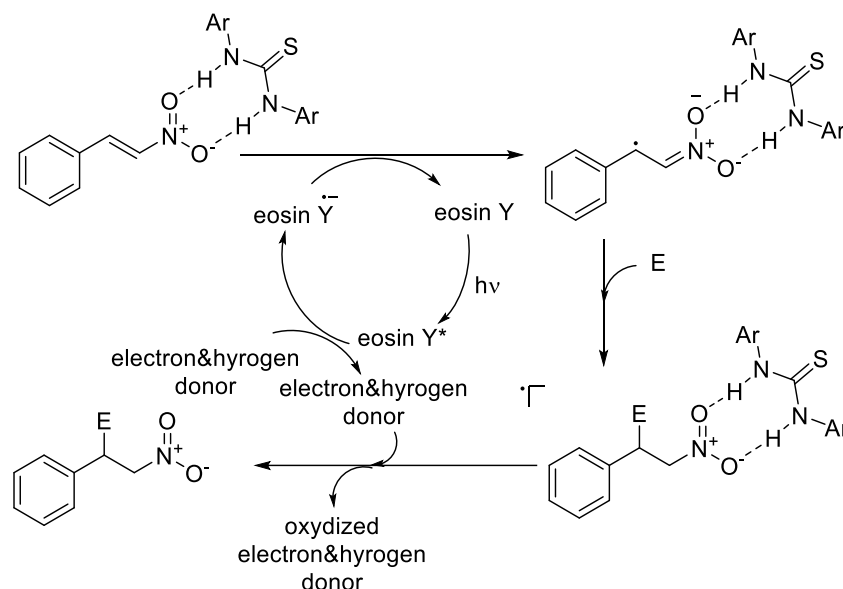
Scheme A.5

Different solvents were used trying to address solubility problems, but neither with 4-phenylbutenone nor with cylohexenone, benzaldehyde or *N*-chlorosucinimide the desired cross-coupling product was formed (Scheme A.6 and Table A.2). This results demonstrated that nitrostyrene reacts faster with respect to the partner compound, showing the highest tendency to allocate a negative charge and the highest reactivity as Michael acceptor.

Scheme A.6
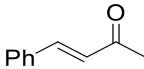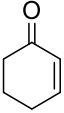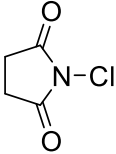
E	catalyst, additive	solvent	detected product[a]
	-	CH_3CN	
	Eosin Y (0.025 eq.)	CH_3CN	
	(iPr)$_2$NEt (2 eq.) + Eosin Y (0.025 eq.)	CH_3CN	**74**
	HE (1.1 eq.) + Eosin Y (0.025 eq.)[b]	CH_3CN	**74**
	(Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)[b]	CH_3CN	-
	ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)[b]	CH_3CN	**74**
	1-[2,4-(OMe)$_2$Ph]-methanol (4 eq.) + Eosin Y (0.05 eq.)[b]	CH_3CN	-
	(Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH_3CN + H_2O	-
	A0 (0.1 eq.) + DIPEA (2 eq.) + Eosin Y (0.05 eq.)[b]	CH_3CN	**74**
	A0 (0.1 eq.) + HE (1.1 eq.) + Eosin Y (0.05 eq.)[b]	CH_2Cl_2	-
	A0 (0.1 eq.) + (Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	A0 (0.1 eq.) + ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	A0 (0.1 eq.) + ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH_3CN + H_2O	-
	A0 (0.1 eq.) + 1-[2,4-(OMe)$_2$Ph]-methanol (4 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	(iPr)$_2$NEt (2 eq.) + Eosin Y (0.025 eq.)	CH_3CN	**74**
	(Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	A0 (0.1 eq.) + DIPEA (2 eq.) + Eosin Y (0.05 eq.)	CH_3CN	**74**
	A0 (0.1 eq.) + (Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	(iPr)$_2$NEt (2 eq.) + Eosin Y (0.025 eq.)	CH_3CN	-
	(Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	A0 (0.1 eq.) + DIPEA (2 eq.) + Eosin Y (0.05 eq.)	CH_3CN	-
	A0 (0.1 eq.) + (Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	(Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-
	A0 (0.1 eq.) + (Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	CH_2Cl_2	-

Table A.2 – Reactions were performed with 10 equivalents of the electrophile under N_2 atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude. [b]Reactions performed with 2 equivalents of enone.

As DIPEA already demonstrated not to be involved in this kind of mechanism, acting only as an electron donor allowing dimer **74** formation, different tertiary amines were screened. With *N*-Me-pyrrolidine traces of the desired product were observed; however, the reaction proved to be poorly reproducible and compound **77** was indeed never isolated. In none of the other investigated cases the derided products were obtained (Scheme A.11 and Table A.5).
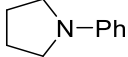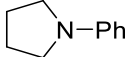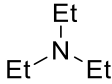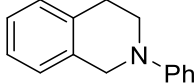
amine	amine eq.	atmosphere	detected product[a]
	2	N$_2$	-
	2	Air	**74** + *traces*[d]
	1	Air	**74**
(pyrrolidine) N—Ph	5	Air	**74**
	2	Air[b]	**74**
	2	N$_2$[c]	*traces*[d]
	2	Air[c]	-
N—Ph	2	N$_2$	**74** + *traces*[d]
	2	Air	**74** + *traces*[d]
Et / N(Et)Et	2	N$_2$	**74** + *traces*[d]
	2	Air	**74** + *traces*[d]
(tetrahydroisoquinoline) N—Ph	2	N$_2$	*traces*[d]
	2	Air	*traces*[d]

Table A.3 - [a]The Presence of product detected by ^{1}H NMR of the crude. [b]Reaction performed in the absence of catalyst **A0**. [c]Reactions performed in the dark. [d]Minor signals attributable to the desired products were observed, however no purification allowed their isolation.
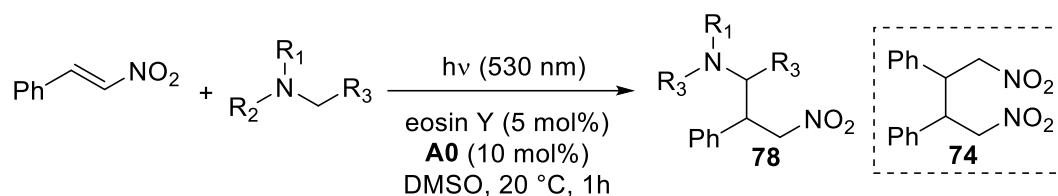
Scheme A.7

To have a preliminary demonstration that the coupling reaction leading to compound **74** proceeded through a radical mechanism, *N*-methylpyrrole was employed, as its ability of rapidly reacting with substrates featuring an uncoupled electron is well known (Scheme A.7).
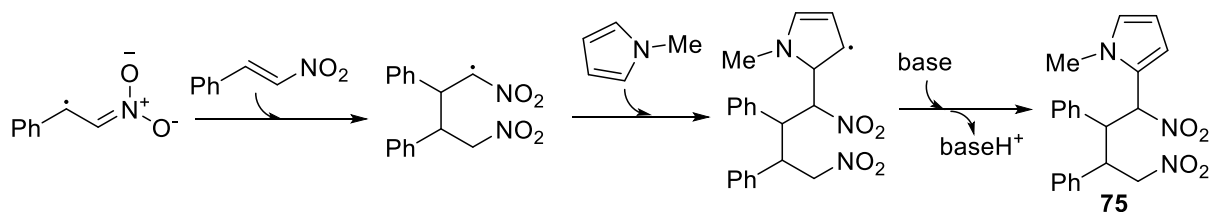
Scheme A.8

The formation of the desired compound **75** was never observed under the tested conditions, while a tiny amount of compound **76** was observed when triphenylamine was used in combination with thiourea **A0** (Scheme A.8 and Table A.3). A control experiment, performed in the absence of the photocatalyst, afforded - although less efficiently - the same product; thus, a simple conjugated addition of the electronrich heteroaromatic compound can be envisioned as a competitive process.
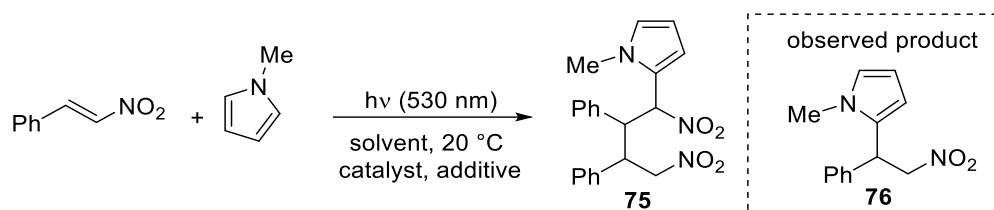
Scheme A.9

catalyst, additive	solvent	detected product[a]
A (0.1 eq.) + (Ph)₃N (2 eq.)	CH₂Cl₂	-
(*i*Pr)₂NEt (2 eq.) + Eosin Y (0.025 eq.)	CH₃CN	**-**
HE (1.1 eq.) + Eosin Y (0.025 eq.)	CH₃CN	-
(Ph)₃N (2 eq.) + Eosin Y (0.05 eq.)	CH₂Cl₂	-
ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH₂Cl₂	-
ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH₃CN + H₂O	**74**
ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH₃CN	**74**
2,4-(MeO)₂Ph-1-CH₂OH (4 eq.) + Eosin Y (0.05 eq.)	CH₃CN	-
A0 (0.1 eq.) + HE (1.1 eq.) + Eosin Y (0.05 eq.)	CH₃CN	**74**
A0 (0.1 eq.) + (*i*Pr)₂NEt (2 eq.) + Eosin Y (0.05 eq.)	CH₃CN	**74**
A0 (0.1 eq.) + (Ph)₃N (2 eq.) + Eosin Y (0.05 eq.)	CH₂Cl₂	**76** (23%)
A0 (0.1 eq.) + (Ph)₃N (2 eq.)	CH₂Cl₂	**76** (10%)
A0 (0.1 eq.) + ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH₂Cl₂	**76** (23%)
A0 (0.1 eq.) + ASCORBIC ACID (2 eq.) + Eosin Y (0.05 eq.)	CH₃CN + H₂O	**74**
A0 (0.1 eq.) + 2,4-(MeO)₂Ph-1-CH₂OH (4 eq.) + Eosin Y (0.05 eq.)	CH₃CN	-

Table A.4 – Reactions performed in the presence of 10 equivalents of *N*-Me-pyrrole under N₂ atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude.

No starting material conversion occurred also when 2,2-diphenylethylene, another typical radical trapping reagent, was employed (Scheme A.9 and Table A.4).
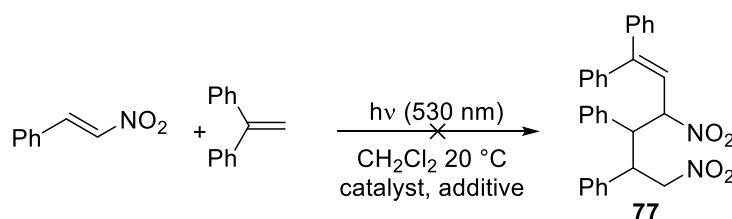
Scheme A.10

catalyst, additive	detected product[a]
(Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	-
A0 (0.1 eq.) + (Ph)$_3$N (2 eq.) + Eosin Y (0.05 eq.)	-

Table A.5

Despite these experiments were unsuccessful and so no experimental proof of the formation of the radical intermediates was obtained. However, considering that the reaction is not proceeding in the absence of light and that formation of product **74** can not be rationalized within a classical ionic pathway, a radical mechanism was reasonably assumed as responsible for this reaction.

Subsequently, preliminary experiments were performed to investigate the opportunity to employ an *in situ* generated electrophile for trapping the radical anion that derives from nitrostyrene single electron reduction. In particular, experiments were set up to observe the possible attack of nitroalkanoate, obtained upon e$^-$ donation by reduced eosin Y, onto the iminium ion that is expected to be formed by a tertiary amine single electron oxidation and subsequent deprotonation (Scheme A.10).[441]
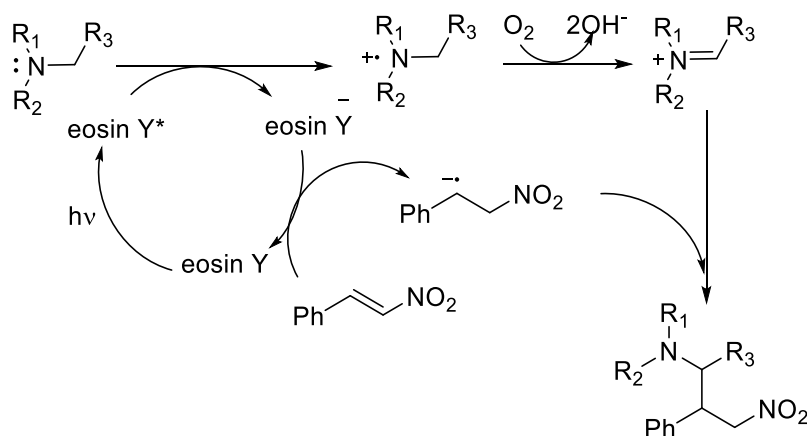
Scheme A.11

Nitrostyrene as Michael acceptor for neutral radical species

Aware of the fact that the high reactivity of nitrostyrene was not easily tuneable, we decided to use a different approach to access C-C bond formation occurring between two different substrates. Thus, a second part of this project was focused on the possibility to restrict the role of nitrostyrene to that of a Michel acceptor for a radical species.

According to our working proposal, the use of compounds known to rapidly interact with the photocatalyst should have prevented electron donation to nitrostyrene. Therefore, two different diazonium salts and α-bromomalonate were chosen as starting material for this purpose.
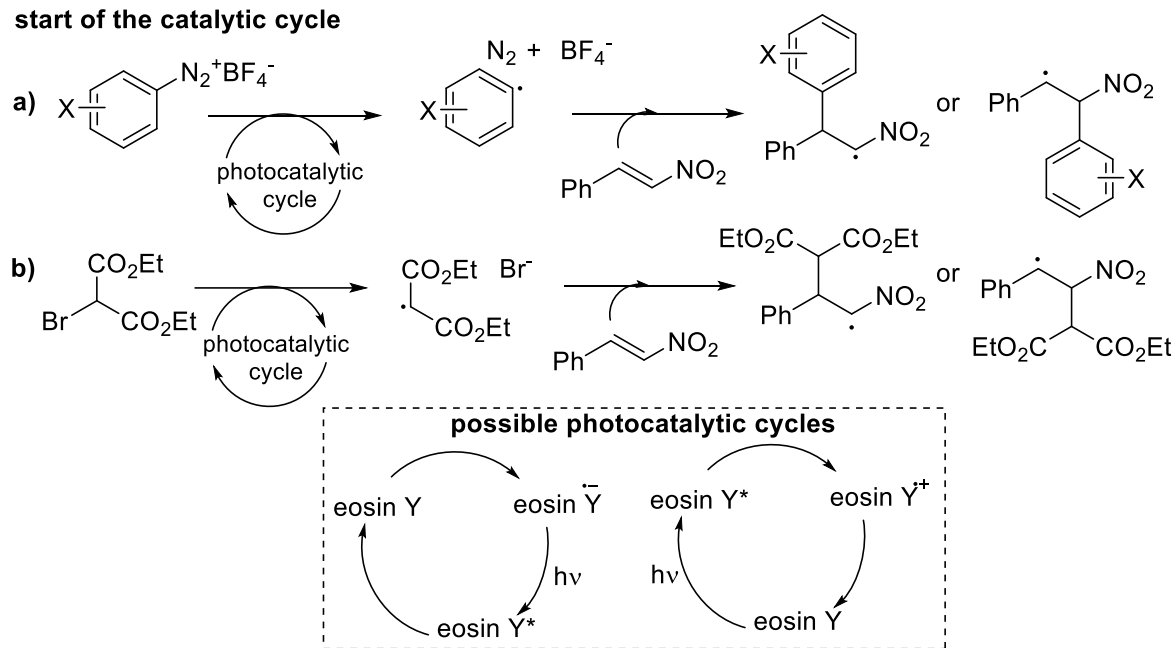
Figure A.1

In the hypothesized reaction mechanism, an intermediate nitroalkane is formed; this species features an unpaired electron that can react with a hydrogen atom or with a trapping reagent (Figure A.2). To explore both these possibilities, experiments were carried out employing Hantzsch ester, as both electron and H⁺ donor, and *N*-Me-pyrrole, to achieve the formation of two different C-C bonds.
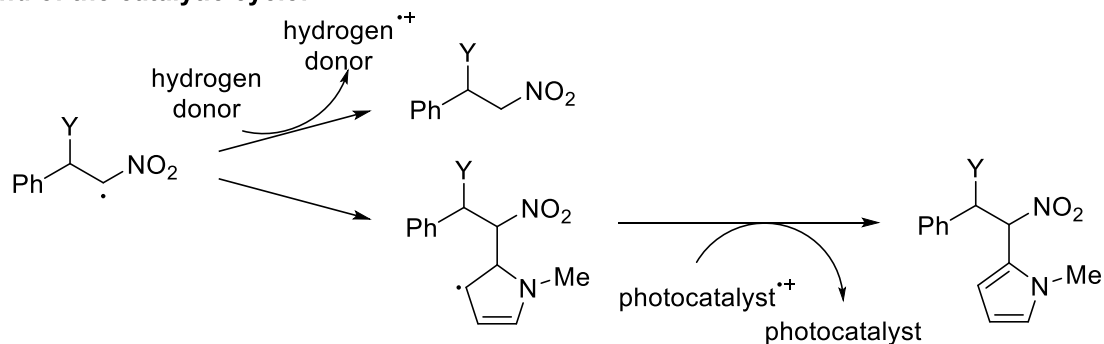
Figure A.2

When diazonium salts[442] where employed in the presence of the hydrogen donor, i.e. Hantzsch ester or DIPEA, in acetonitrile, no nitrostyrene conversion was observed, but traces of by-product was detected.
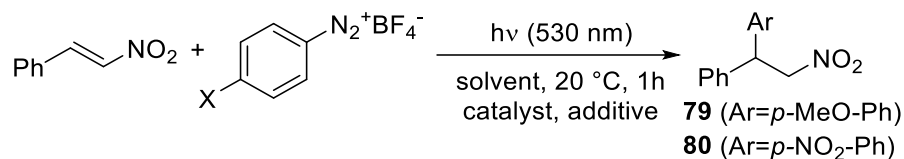
Scheme A.12

X	catalyst, additive	solvent	detected product[a]
NO$_2$	(iPr)$_2$NEt (2 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
NO$_2$	HE (1.5 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
NO$_2$	HE (1.5 eq.) + Eosin Y (0.05 eq.)	DMSO	-
NO$_2$	A0 (0.1 eq.) + DIPEA (2 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
NO$_2$	A0 (0.1 eq.) + HE (1.5 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
NO$_2$	A0 (0.1 eq.) + HE (1.5 eq.) + Eosin Y (0.05 eq.)	DMSO	-
MeO	(iPr)$_2$NEt (2 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
MeO	HE (1.5 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
MeO	HE (1.5 eq.) + Eosin Y (0.05 eq.)	DMSO	-
MeO	A0 (0.1 eq.) + DIPEA (2 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
MeO	A0 (0.1 eq.) + HE (1.5 eq.) + Eosin Y (0.05 eq.)	CH$_3$CN	-
MeO	A0 (0.1 eq.) + HE (1.5 eq.) + Eosin Y (0.05 eq.)	DMSO	-
NO$_2$	Eosin Y (0.05 eq.)	DMSO	**81**
MeO	Eosin Y (0.05 eq.)	DMSO	**82**
NO$_2$	-	DMSO	-
MeO	-	DMSO	-

Table 0.6 - Reactions were performed using an equimolar amount of nitrostyrene and diazonium salt under N$_2$ atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude.

Changing the solvent to DMSO, which was reported to afford best results in analogous reactions, a non-symmetrically disubstituted styrene was obtained.[1]
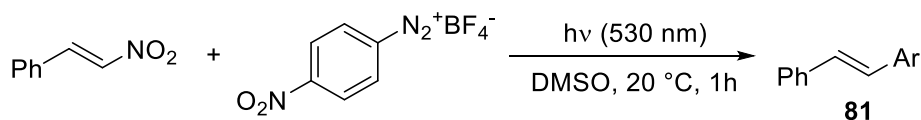
Scheme A.13

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[1] When the *p*-methoxy-substituted diazonium salt was employed as starting material, a different product was detected; in particular, considering ^{1}H NMR spectra of the crude, formation of compound **82** can be hypothesized (~15% with respect to nitrostyrene), but as this structural identification has not been confirmed by GC-MS(EI) analysis.
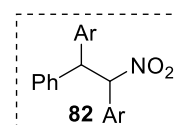
A plausible mechanism could involve the release of the nitrogen dioxide radical to restore a completely conjugated pattern; single electron donation from NO$_2\cdot$ could be involved to regenerate the neutral catalyst (Figure A.3).
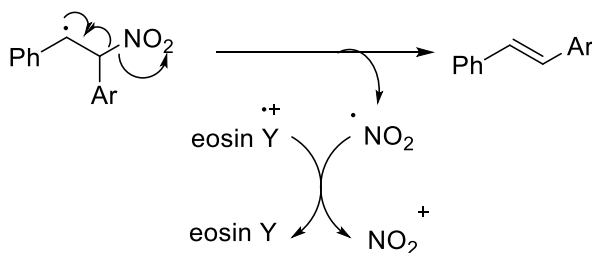
Figure A.3

To explore the possibility of closing the hypothesized catalytic cycle with a second C-C bond formation, *N*-methylpyrrole was used instead of Hantzsch ester (Scheme A.21). Under these conditions, LC-MS(ESI) and ^{1}H NMR analysis on the crude suggest partial conversion of the starting materials into the undesired compound **84**. Additionally, control experiments proved eosin Y not to be necessary in this transformation (Scheme A.14).
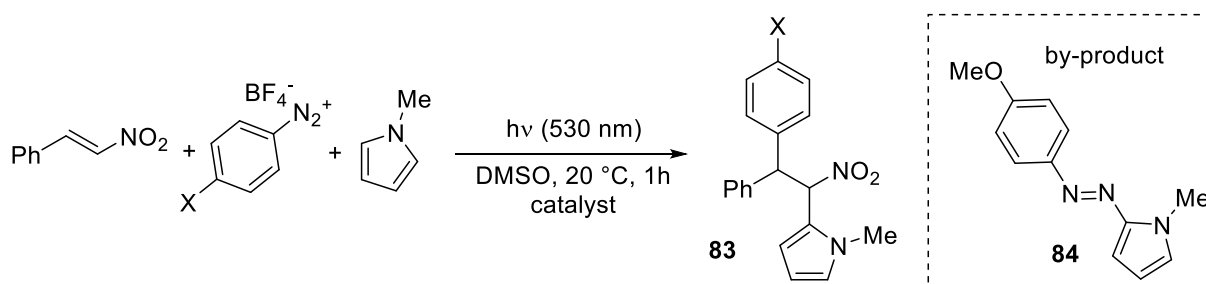
Scheme A.14

X	catalyst	detected product[a]
NO$_2$	**A0** (0.1 eq.) + Eosin Y (0.05 eq.)	**84**
MeO	**A0** (0.1 eq.) + Eosin Y (0.05 eq.)	**84**
NO$_2$	Eosin Y (0.05 eq.)	**84**
MeO	Eosin Y (0.05 eq.)	**84**
NO$_2$	-	**84**
MeO	-	**84**

Table A.7 - Reactions were performed using an equimolar amount of nitrostyrene, diazonium salt and *N*-Me-pyrrole, under N$_2$ atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude.

To generate an alternative radical in principle able to attack nitrostyrene, diethyl bromomalonate[443] was employed (Scheme A.15). No heterocoupling reaction occurred neither with Hantzsch ester nor with 2,6-dimethylpyridine,[m] while DIPEA afforded the undesired product **86**[444] through an acid-base reaction (Table A.8).

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[m] Using 2,6-dimethylpyridine the reductive-cyclization product **74** was obtained thanks to hydrogen abstraction from the solvent.
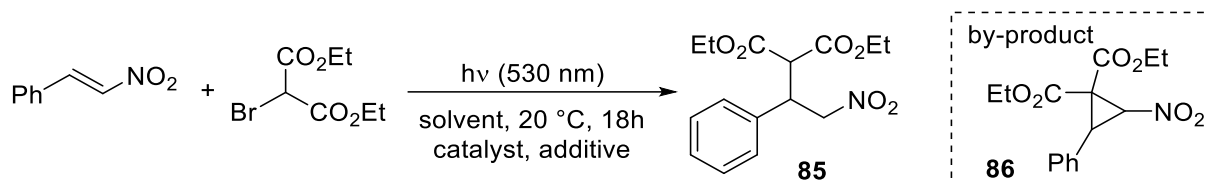
Scheme A.15

catalyst, additive	solvent	detected product[a]
A0 (0.1 eq.) + H.E. (1.5 eq.) + Eosin Y (0.05 eq.)	DMSO	**74**
A0 (0.1 eq.) + (*i*Pr)$_2$NEt (2 eq.) + Eosin Y (0.05 eq.)	DMSO	**86**
(*i*Pr)$_2$NEt (2 eq.) + Eosin Y (0.05 eq.)	DMSO	**86**
A0 (0.1 eq.) + Lutidine (2 eq.) + Eosin Y (0.05 eq.)	DMSO	**74**
A0 (0.1 eq.) + Lutidine (2 eq.) + Eosin Y (0.05 eq.)	DMF	**74**
A0 (0.1 eq.) + (*i*Pr)$_2$NEt (2 eq.) + Eosin Y (0.05 eq.)[b]	DMSO	**86**
(*i*Pr)$_2$NEt (2 eq.) + Eosin Y (0.05 eq.)[b]	DMSO	**86**

Table 0.8 - Reactions were performed using an equimolar amount of nitrostyrene and diethyl bromomalonate under N$_2$ atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude. [b]Reactions performed in the dark.

When the reaction was carried out in the presence of *N*-Me-pyrrole aiming to a further C-C bond formation (product **87**), only compound **88**, deriving form nucleophilic attack of deprotonated bromomalonate onto nitrostyrene, was detected. This result suggested that quenching of the anionic intermediate through H^{+} delivery by protonated lutidine was the fastest process under these conditions (Scheme A.16 and Table A.9).
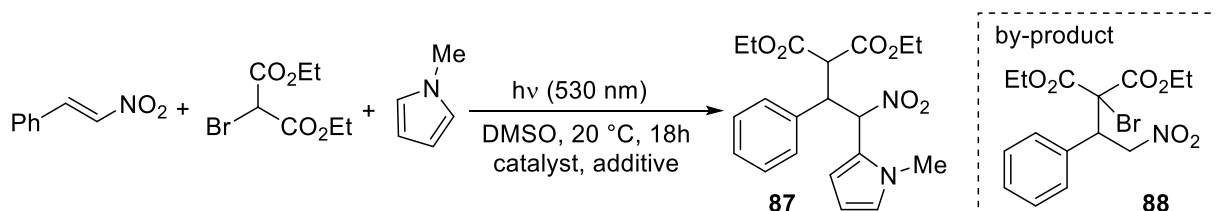
Scheme A.16

donor/catalyst	detected product[a]
A0 (0.1 eq.) + Ph$_3$N (2 eq.) + Eosin Y (0.05 eq.)	**-**
A0 (0.1 eq.) + ASCORBIC ACID (1.5 eq.) + Eosin Y (0.05 eq.)	-
A0 (0.1 eq.) + lutidine (2 eq.) + Eosin Y (0.05 eq.)	**88**

Table 0.9 - Reactions were performed using an equimolar amount of nitrostyrene, diethyl bromomalonate and *N*-Me-pyrrole under N$_2$ atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude.

Nitroalkanoate single electron oxidation

In parallel to the first to studies, focused on the use of nitroalkenes as substrates for phocatalytic reactions, a third part of the project was developed, devoted to the investigation of nitroalkanes reactivity under irradiation. In particular, the possible single-electron oxidation of an anionic intermediate formed upon nitroalkane deprotonation was examined (Figure A.4).[445]
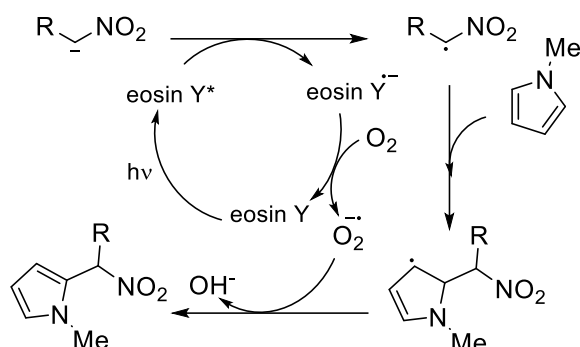
Figure A.4

Three different nitroalkanes were employed in the presence of bases harder to oxidize than the *in situ* generated nitroalkanoate. Reactions were performed both under air, as oxygen is expected to be needed for closing the catalytic cycle, and under N_2 atmosphere in the presence of an oxidant (Scheme A.17 and A.18). None of the explored conditions led to the formation of the desired compounds **89** (Table A.10 and A.11)
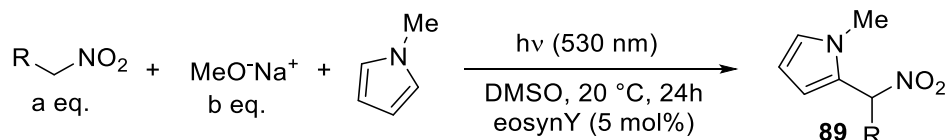
Scheme A.17

susbtrate	catalyst	a	b	atm.	solvent	detected product[a]
	Eosin Y (0.05 eq.)	1	0.8	Air	DMSO	-
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	1	0.8	Air	DMSO	-
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	1	0.8	N_2	DMSO	-
⟋NO₂	Eosin Y (0.025 eq.)	10	1	Air	-	*traces*[b]
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	10	1	Air	-	*traces*[b]
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	10	1	N_2	-	-
	Eosin Y (0.025 eq.)[b]	10	1	Air		*traces*[b]
	Eosin Y (0.05 eq.)	1	0.8	Air	DMSO	-
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	1	0.8	Air	DMSO	-
Ph⟋NO₂	Eosin Y (0.025 eq.)	10	1	Air	-	-
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	10	1	Air	-	-
	Eosin Y (0.025 eq.)[b]	10	1	Air	-	-
⟋NO₂	Eosin Y (0.025 eq.)	10	1	Air	DMSO	-
	Eosin Y (0.025 eq.)[b]	10	1	Air	DMSO	-

Table A.10 - [a]The Presence of product detected by ^{1}H NMR of the crude. [b]Minor signals attributable to the desired products were observed..
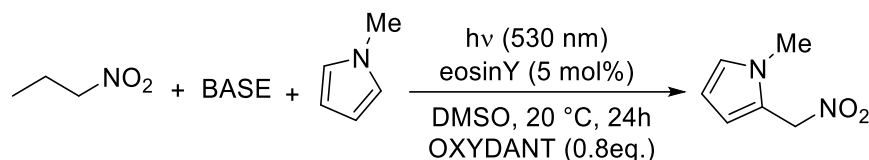
Scheme A.18

BASE	OXYDANT	organocatalyst	detected product[a]
Et₃N	NH₄S₂O₈	A0 (0.1 eq.)	-
Et₃N	NH₄S₂O₈	-	-
Et₃N	nitrobenzene	A0 (0.1 eq.)	-
Et₃N	nitrobenzene	-	-
Et₃N[b]	nitrobenzene	A0 (0.1 eq.)	-
lutidine	NH₄S₂O₈	A0 (0.1 eq.)	-
lutidine	NH₄S₂O₈	-	-
lutidine	nitrobenzene	A0 (0.1 eq.)	-
lutidine	nitrobenzene	-	-

Table A.11 - Reactions were performed with 10 equivalents of nitropropane, 5 equivalents of *N*-Me-pyrrole and 1 equivalent of base under N_2 atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude. [b]The reaction was performed under blue light irradiation using Ru(bpy)₃ as photocatalyst.

A parallel approach where the nitroalkanoate was generated upon nucleophilic attack onto nitrostyrene was also studied (Figure A.5).
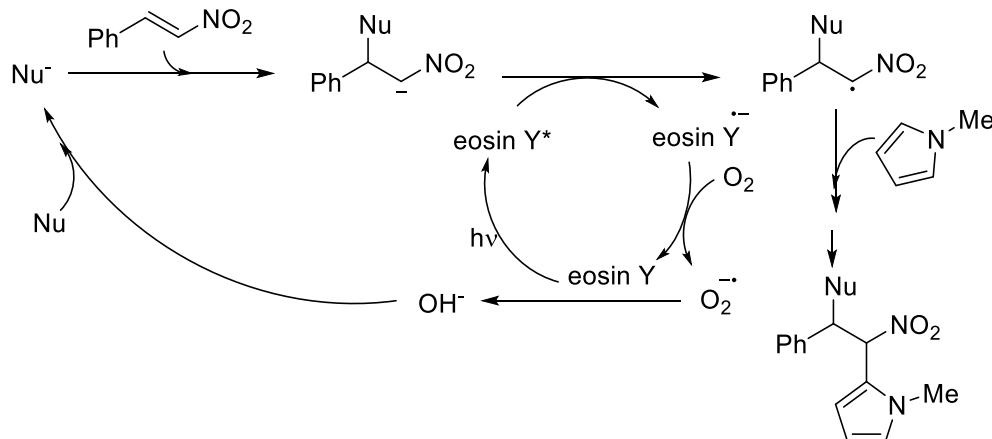
Figure A.5

Preliminary experiments were carried out, employing nitromethane and 3-methyl acetylacetone in in the presence of *N*-Me-pyrrole (Scheme A.19). When the reaction was performed under air, a catalytic amount of base for activating the nucleophile was used, to replace the hydroxyl group expected to be generated from oxygen. However, none of the experiments led to the formation of the desired products **90**.
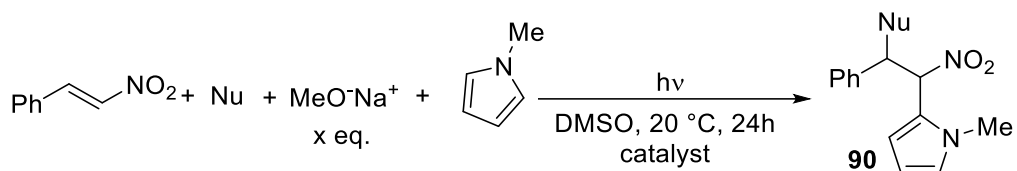
Scheme A.19

Nu	catalyst	x eq	atm.	detected product[a]
$CH_3CH_2NO_2$ (shown as structure)	**A0** (0.1 eq.) + Eosin Y (0.025 eq.)	0.2	Air	-
	A0 (0.1 eq.) + Eosin Y (0.025 eq.)	1	N_2	-
(acetylacetone structure with Me)	Eosin Y (0.05 eq.)	0.2	Air	**-**

Table A.12 - Reactions were performed with 5 equivalents of *N*-Me-pyrrole under N_2 atmosphere. [a]The Presence of product detected by ^{1}H NMR of the crude.

Conclusions

In conclusion, preliminary investigations on nitro-containing compounds as substrates for photocatalytic transformations have been carried out. In particular, nitrostyrene and diffetent nitroalkanes have been employed in reactions proceeding through different catalytic cycles, involving either electron donation or abstraction from the excited state of the photocatalyst. To explore the possibility of a synergyc cooperation between a photo- and an organocatalyst, experiments were performed in the presence of substoichiometric amount of a thiourea-based compound.

Based on the explorative results obtained so far, further experiments can be designed to channel nitroalkanes and nitroalkenes within organophotocatalytic cycles, directing their behaviour through conditions tuning and hydrogen-bonding organocatalyst employment.

To obtain heterocoupled product upon e- injection onto nitrostyrene, substrates featuring different electronic characteristics, including differently substituted enones,[446] could be employed. Optimization of reaction conditions for slowing down background dimerization could led to the use of chiral organocatalyst to control the stereochemical outcome.

CONCLUSIONS

In the herein reported research work rather successful applications of stereoselective organocatalysis have been developed. Enantioenriched compounds featuring more than one functionality have been straightforwardly obtained, thus giving a further proof of concept that simple strategies can represent direct entries to valuable molecules. As already demonstrated in literature, besides being directly employed in the preparation of biologically active compounds, organocatalytic methods can be envisaged as part of longer synthetic routes to access complex structures.

According to our opinion, this PhD study offers solid examples of robustness, versatility and effectiveness of stereoselective organocatalytic strategies, which have been applied to interesting starting materials and in innovative reaction media, thus giving a reliable contribution to expand the boundaries of this field.

EXPERIMENTAL SECTION

General Methods

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Melting point were determined with Branstead Electrothermal 9100 capillary melting point apparatus. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300) or at 500 MHz (Bruker Advance 500). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl$_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, or on 500 MHz spectrometers (Bruker Advance 500) operating at 125 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl$_3$, δ = 77.0 ppm). ^{19}F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. Fluorine chemical shifts are reported in ppm (δ) relative to CF$_3$Cl. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell with a length of 1 dm.

Catalysts preparation

Synthesis of thiourea-based bifunctional catalysts derived from Cinchona alkaloids

Products were prepared according to literature procedures; analytical data were in agreement with literature ones.

BBr$_3$ $\left[\begin{array}{l}\text{R=OMe } \textbf{F}\\ \text{R=OH } \textbf{G} \text{ y:83\%}\end{array}\right.$

BBr$_3$ $\left[\begin{array}{l}\text{R=OMe } \textbf{H} \quad \text{y:90\%}\\ \text{R=OH } \textbf{I} \quad \text{y:67\%}\\ \text{R =O}i\text{Pr} \quad \text{y: 97\%}\end{array}\right.$

R=H   **C**   y:63%
R=OMe **A**   y:69%
R=O*i*Pr **D**   y: 20%
R=OH   **E**   y: 40%
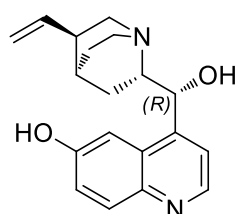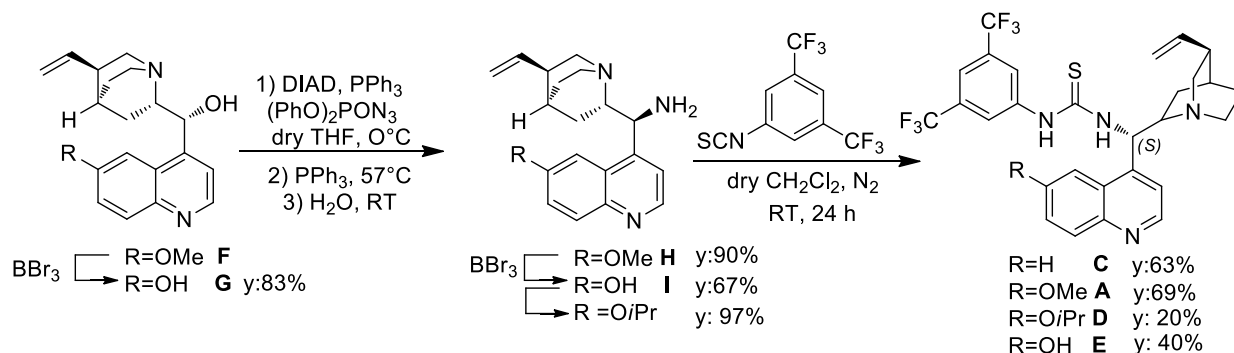
Rf = 0.33 (CH$_2$Cl$_2$/MeOH = 95/5 + 1mL NH$_4$OH) [n]

^{1}H-NMR (300 MHz, CD$_3$OD) δ: 8.56 (d, J = 4.6 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 4.6 Hz, 1H), 7.32-7.27 (m, 2H), δ 5.76-5.65 (m, 1H), 5.51 (d, J = 3.3 Hz, 1H), 4.95-4.84 (m, 2H), 3.71-3.62 (m, 1H), 3.10-3.02 (m, 1H), 2.73-2.60 (m, 2H), 2.37-2.23 (bs, 1H), δ 1.88-1.75 (m, 3H), 1.77 (br s, 1H), 1.59-1.51 (m, 1H), 1.45-1.36 (m, 1H).

Catalyst B [o]
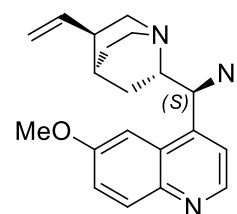
Rf = 0.41 (EtOAc/MeOH = 50/50 + 1mL NH$_4$OH)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 8.69 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.65 (bs, 1H), 7.40 (d, J = 4.4 Hz, 1H), 7.32 (dd, J = 9.2, 2.4 Hz, 1H), 5.80-5.7 (m, 1H), δ 4.97-4.89 (dd, J = 13.6, 9.9 Hz, 2H), 4.53 (d, J = 10.1 Hz, 1H), 3.90 (s, 3H), 3.26-3.16 (m, 2H), 2.98-3.07 (m, 1H), δ 2.79-2.69 (m, 2H), 2.22 (br s, 1H), 2.03 (bs, 2H), 1.56-1.50 (m, 3H), 1.36-1.43 (m, 1H), 0.80-0.68 (m, 1H).

Catalyst D [p]
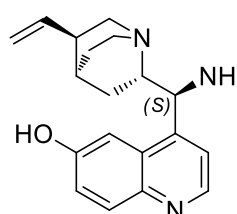
Rf = 0.22 (CH$_2$Cl$_2$/MeOH = 50/50 + 1mL NH$_4$OH)

^{1}H-NMR (300 MHz, CDCl$_3$): δ 8.59-8.56 (m, 1H), 7.95 (dd, J = 9.1, 1.9 Hz, 1H), 7.53 (bs, 1H), 7.31-7.25 (m, 2H), 7.29 (dd, 1H), 5.77-5.63 (m, 1H), 4.45-4.12 (m), 3.19-3.11 (m, 1H), 3.07-2.94 (m, 2H), 2.73-2.60 (m, 2H), 2.19 (bs, 1H), 1.49-1.36 (m, 4H), 0.65-0.59 (m, 1H).

[n] T. Furuya, A. E. Storm, T. Ritter, *J. Am. Chem. Soc.*, **2009**, *131*, 1662-1663.

[o] C. G. Oliva, A. M. S. Silva, D. I. S. P. Resende, F. A. A. Paz, José A. S. Cavaleiro, *Eur. J. Org. Chem.,* **2010**, 3449-3458.

[p] W. C., W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int, Ed.*, **2007**, *46*, 7667-7670.
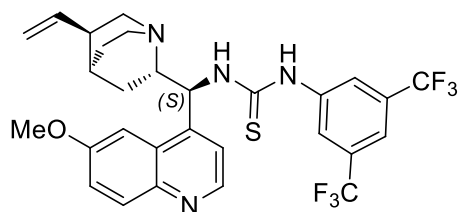
Catalyst Fq

Rf = 0.6 (CH₂Cl₂/MeOH = 96/4)

¹H-NMR (300 MHz, CDCl₃) δ: 8.69 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.86 (s, 2H), 7.68 (s, 2H), 7.42 (dd, J = 9.2, 2.6 Hz, 1H), 7.29 (s, 1H), 5.93 (bs, 1H), 5.76-5.65 (m, 1H), 5.07 (d, J = 4.9, 1H), 5.03 (bs, 1H), 3.99 (s, 3H), 3.46 (bs, 2H), 3.24 (dd, *J* = 13.8, 10.1 Hz, 1H), 2.90-2.79 (m, 2H), 2.42 (bs, 1H), 1.78-1.74 (m, 3H), 1.53-1.43 (m, 1H), 1.04-0.99 (m, 1H).

Catalyst F1[7]
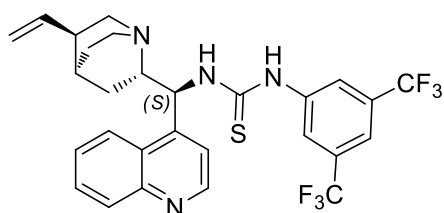
Rf = 0.35 (CH₂Cl₂/MeOH = 95/5)

¹H-NMR (300 MHz, CDCl₃) δ: 8.73 (bs, 1H), 8.40 (d, J = 6.3 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.81 (s, 2H), 7.71-7.66 (m, 1H), 7.63-7.57 (m, 2H), 7.24 (d, J = 5.4 Hz, 1H), 5.86 (bs, 1H), 5.68-5.57 (m, 1H), 4.97-4.91 (m, 2H), 3.30-3.20 (m, 3H), 3.14-3.06 (m, 1H), 2.73-2.68 (bs, 2H), 2.28 (bs, 1H), 1.72-1.62 (m, 3H), 0.95-0.83 (m, 1H).

Catalyst F3r
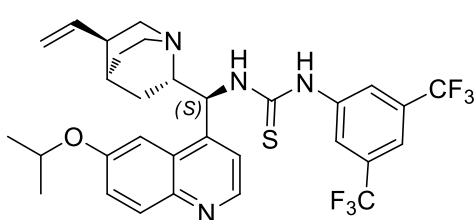
Rf = 0.33 (CH₂Cl₂/MeOH = 94/6)

¹H NMR (300 MHz, CDCl₃) δ: 8.72 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.97 (s, 2H), 7.72 (bs, 1H), 7.60 (s, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.37 (d, J = 9.3, 2.2 Hz, 1H), 6.19 (bs, 1H), 5.68-5.56 (m, 1H), 5.06-5.00 (m, 2H), 4.79-4.71 (m, 1H), 3.77-3.60 (m, 2H), 3.32 (dd, J = 13.6, 10.5 Hz, 1H), 2.97-285 (m, 2H), 2.48-2.46 (m, 1H), 1.85 (bs, 3H), 1.49-1.59 (m, 1H), 1.42 (d, J = 6.0 Hz, 6H), 1.07 (d, J = 11.1 Hz, 1H).

Catalyst F2s
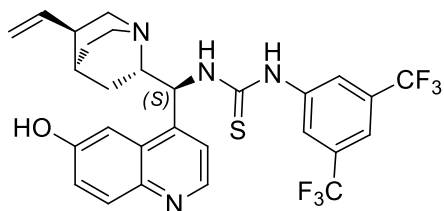
Rf = 0.37 (CH₂Cl₂/MeOH = 94/6)

¹H NMR (300 MHz, CD₃OD) δ: 8.67 (s, 1H), 8.20 (s, 2H), 7.90 (s, 2H), 7.74 (s, 1H), 7.60 (s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 9.4 Hz, 1H), 5.84 (bs, 1H), 5.21-5.08 (m, 2H), 4.29-4.17 (m, 2H), 3.66-5.87 (m, 1H), 3.40-3.28 (m, 3H), 2.74 (bs, 1H), 1.99-1.91 (m, 3H), 1.70 (bs, 1H), 1.18-1.12 (m, 1H).

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[q] C. B. Tripathi, S. Kayal, S. M., *Org. Lett.*, **2012**, *14,* 3296-3299.

[r] J. Li, T. Du, G. Zhang, Y. Peng, *Chem. Commun.*, **2013**, *49,* 1330-1332.

[s] T. Zhang, L. Cheng, S. Hameed, L. Liu, D. Wang, Y.-J. Chen, *Chem. Commun.*, **2011**, *47*, 6644-6646.

Synthesis of squaramide-based bifunctional catalysts derived from Cinchona alkaloids

Catalyst L2
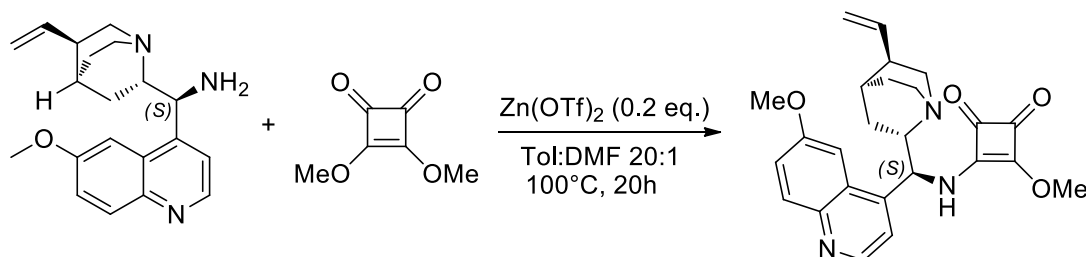
^{1}H NMR (300 MHz, CD$_3$OD) δ: 8.72 (d, J = 4.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.61 (d, J = 4.8 Hz, 1H), 7.44 (dd, J = 9.2, 2.6 Hz, 1H), 6.36 (d, J = 11.2 Hz, 1H), 6.04-5.95 (m, 1H), 5.23-5.14 (m, 2H), 4.00 (s, 6H), 3.59-3.52 (m, 1H), 3.00-3.17 (m, 2H), 2.69 (bs, 1H), 1.82-1.93 (m, 5H), 0.99-0.92 (m, 1H).

^{1}H NMR (300 MHz, CD$_3$OD) δ: 189.22 (s), 188.07 (s), 167.90 (s), 159.35 (s), 147.02 (s), 135.91 (s), 130.36 (s), 129.36 (s), 123.13 (s), 118.96 (s), 116.85 (s), 100.36 (s), 67.58 (s), 66.02 (s), 55.36 (s), 51.88 (s), 48.32, 37.54, 29.16, 26.01 (s), 24.17 (s).

Catalyst L1^t

y: 26%
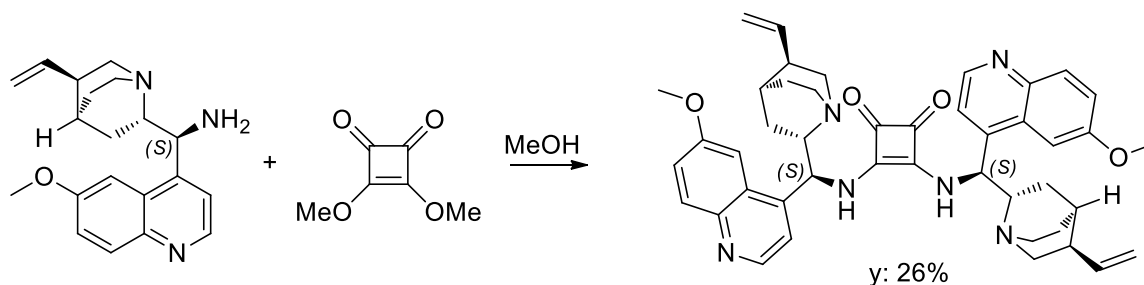
^{1}H NMR (300 MHz, DMSO) δ: 8.81 (d, J = 4.2 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.87-7.79 (m, 2H), 7.58 (d, J = 4.4 Hz, 1H), 7.46 (d, J = 9.1 Hz, 1H), 6.01-5.84 (m, 2H), 5.01-4.93 (m, 2H), 3.94 (s, 3H), 3.25-3.12 (m, 3H), 3.08-3.01 (m, 1H), 2.50 (bs, 1H), 2.24-2.15 (m, 1H), 1.52-1.43 (m, 4H), 0.56-0.44 (m, 1H).

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^{t} J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang, C. E. Song, *Chem. Commun.*, **2009**, 7224-7226.

Synthesis of bifunctional catalysts derived from diaminocyclohexane

Catalyst G (Takemoto catalyst)[u]
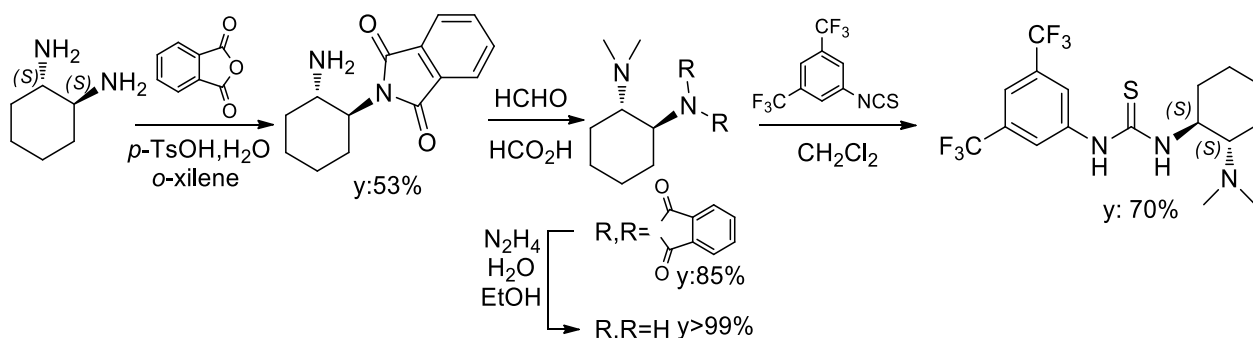
Rf = 0.23 (CH$_2$Cl$_2$/MeOH = 9/1)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.92 (s, 2H), 7.63 (s, 1H), 3.99 (bs, 1H), 2.68 (bs, 1H), 2.45 (s, 7H), 2.40 (s, 1H), 2.00-1.97 (m, 1H), 1.93-1.89 (m, 1H), 1.82-1.78 (m, 1H), 1.40-1.17 (m, 4 H).

Catalyst L3[v]
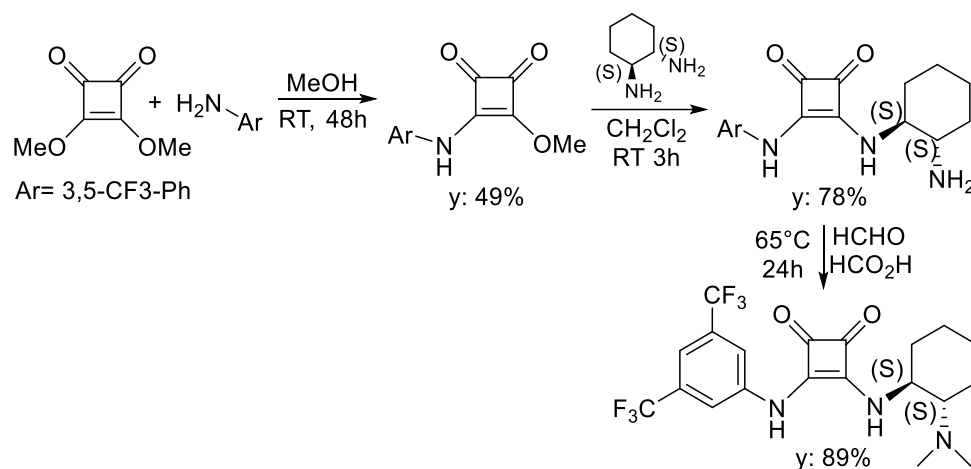
^{1}H NMR (300 MHz, CD$_3$OD) δ 7.81 (s, 2H), 7.33 (s, 1H), 4.11-3.94 (m, 1H), 2.57-2.44 (m, 1H), 2.30-2.27 (m, 1H), 2.33 (s, 3H), 1.98-1.75 (m, 3H), 1.60-1.49 (m, 1H), 1.45-1.27 (m, 1H).

[u] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.*, **2003**, *125*, 12672-12673; for ^{1}H NMR spectrum in CDCl$_3$ see T.-Y. Liu, J. Long, B.-J Li, L. Jiang, R. Li, Y. Wu, L.-S. Dingb, Y.-C. Chen, ***Org. Biomol. Chem. 2006***, *4,* 2097-2099.

[v] Wen Yang, and Da-Ming Du, *Adv. Synth. Catal.* **2011**, *353*, 1241-1246.

Synthesis of thiourea-based catalysts derived from amino acids

Catalysts were prepared according to literature procedures,[w] involving condensation between isothiocyanate function, built on the starting amino acid, and a proper diaminocyclohexane derivative.
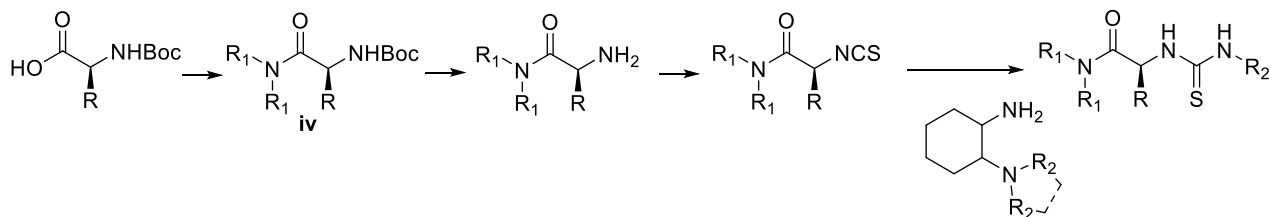
DIAMINOCYCLOHEXANE DERIVATIVES SYNTHESIS
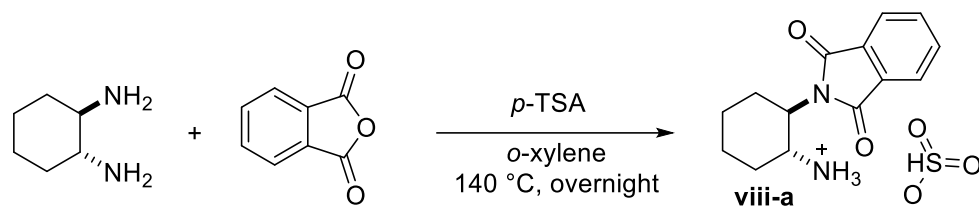
Freshly crystallised phtalic anhydride (1 eq., 6 mmol) and diaminocyclohexane (1 eq., 6 mmol) were added to a 0.2M refluxing solution of *p*-toluensolfonic acid (1 eq., 6 mmol) in *o*-xylene. The mixture was stirred at 140 °C overnight. After this period, it was allowed to room temperature; the formed white solid was filtered and washed with *o*-xylene. The product was obtained as a white sold in 81% yield and it was used in the subsequent step without further purification.
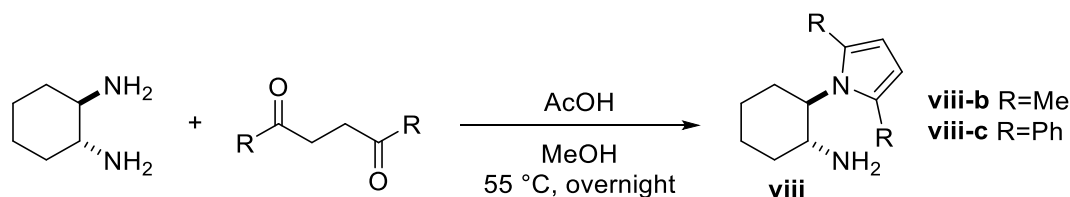
Acetic acid (1 eq., 0.7 mmol) and 2,6-hexaandione or 1,2-dibenzoyilethane (1 eq., 0.7 mmol) were added to a 0.2M solution of diaminocyclohexane (1 eq., 0.7 mmol) in methanol. The reaction mixture was heated to 50 °C and stirred overnight. After this period, it was allowed to cool to room temperature the solvent was removed under reduced pressure. The reaction mixture was treaded with 5.5M NaOH and extracted with CH$_2$Cl$_2$; the combined organic phases were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The product was purified through flash column chromatography on silica gel.

[w] a) G. C. Anderson, P. J. Koovits, *Chem. Sci.* **2013**, *4*, 2897-2901; b) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872-15883; c) J. M. Andrés, R. Manzano, R. Pedrosa, *Chem. Eur. J*, **2008**, *14*, 5116-5119; d) Nolwenn J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976-8977.

AMINO ACID DERIVED ISOTHIOCYANATE SYNTHESIS

STEP 1a - *transformation of the starting amino acid into the corresponding N,N.dimtheylamide.*[6a,b]

iv-a: R=*i*Pr
iv-b: R=*t*Bu
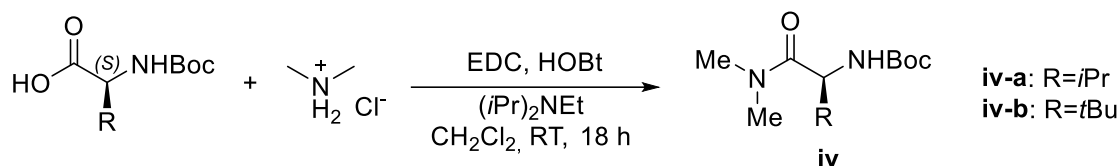
N,N-Diisopropylethylamine (1.5 eq., 2.1 mmol) was added to a 0.1M solution of the *N*-Boc-(L)-amino acid (1 eq., 1.38 mmol), HOBt (1.1 eq., 1.5 mmol), EDC (1.1 eq., 1.5 mmol) and *N,N*-dimethylamine hydrochloride (1.1 eq. 1.5 mmol) in CH_2Cl_2. The reaction mixture was stirred at room termperature overnight, then treated with 1N HCl and with $NaHCO_3$ ss. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Amide **iv-a** and **iv-a** were formed in quantitative yield and used in the subsequent step without further purification.

STEP 1b - *transformation of the starting amino acid into the corresponding N,N.dibenzylamide.*[6c]

iv-c: R=*i*Pr
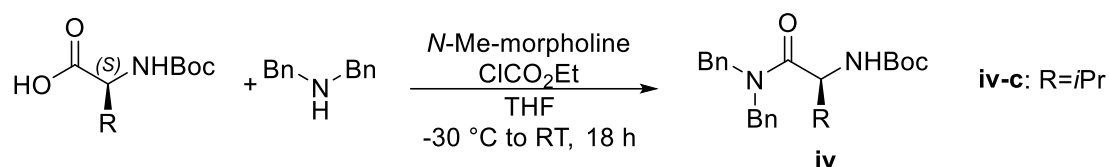
N-Me-morpholine (2 eq., 2.8 mmol) was slowly added to a 0.5M solution of the proper *N*-Boc-(L)-amino acid (1 eq., 1.4 mmol) in THF, kept under inert atmosphere, at -30 °C; after 15 minutes, ethyl chloroformate (1 eq., 1.4 mmol) was added. The reaction mixture was stirred at -30 °C for 30 minutes, after which dibenzylamine (1 eq., 1.4 mmol) was added. The reaction mixture was allowed to warm room temperature and stirred overnight. After this period, the solvent was removed and the crude mixture dilute with AcOEt and extracted with Na_2CO_3ss the organic phase was washed with 0.1M HCl. Amide **iv-c** was used in the subsequent step without further purification.

STEP 1c - *transformation of the starting amino acid into the corresponding N,N-diehtylamide.*[6d]

iv-d: R=*t*Bu
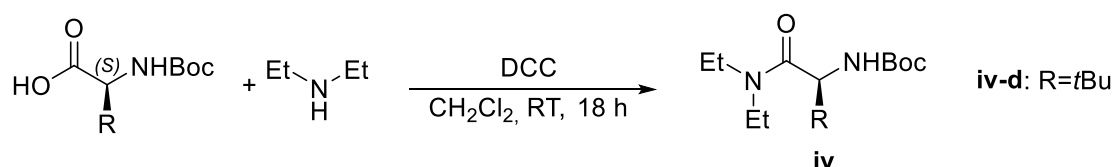
N,N-diethylamine (2 eq., 0.8 mmol) was added, under N_2 atmosphere, to a 0.1M solution of *N*-Boc-(L)-tert-leucine (1 eq., 0.4 mmol) and DCC (1.2 eq, 0.5 mmol) in dry CH_2Cl_2 at room temperature; the reaction mixture was stirred overnight. After this period, the solid residue was filtered off and the solved removed under reduced pressure. Amide **iv-d** was used in the subsequent step without further purification.

STEP 2
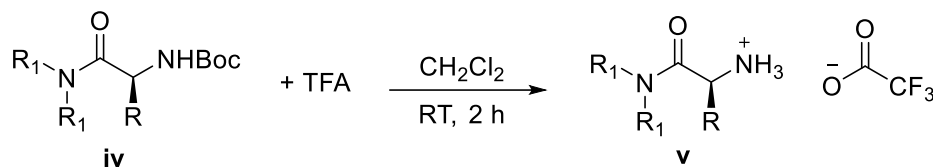
TFA (10 eq., 2 mmol) was added to a 0.3M solution of amide **iv** (1 eq., 0.2 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred for 2 hours, after which it was concentrated under reduced pressure. Product **v** was obtained in quantitative yield and used in the subsequent step without further purification.

STEP 3
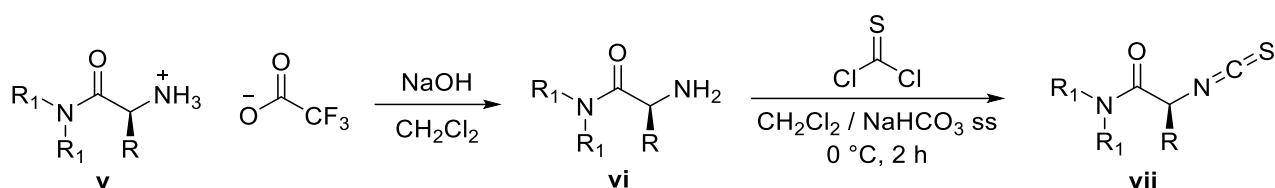
The trifluoroacetate salt of the amino acid derived amide (**v**) was diluted in CH_2Cl_2 and treated with a stoichiometric amount of 5.5M NaOH. The solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the corresponding amide – featuring free NH_2.

To a 0.05M solution of amide **vi** (1 eq., 0.5 mmol) in CH_2Cl_2:$NaHCO_3$ ss 1:1, kept at 0°C, thiophosgene (1.1 eq., 0.55 mmol) was added directly into the organic phase. The reaction mixture was stirred for 2 hours at 0 °C; after this period, the organic phase was separated and the aqueous one extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Typically, complete conversion of the starting material into the corresponding isothiocyanate **vii** was observed; otherwise, the product was purified through flash column chromatography on silica gel using hexane:AcOEt 8:2 as eluent.

<u>FINAL CATALYSTS SYNTHESIS THROUGH THIOUREA BOND FORMATION</u>
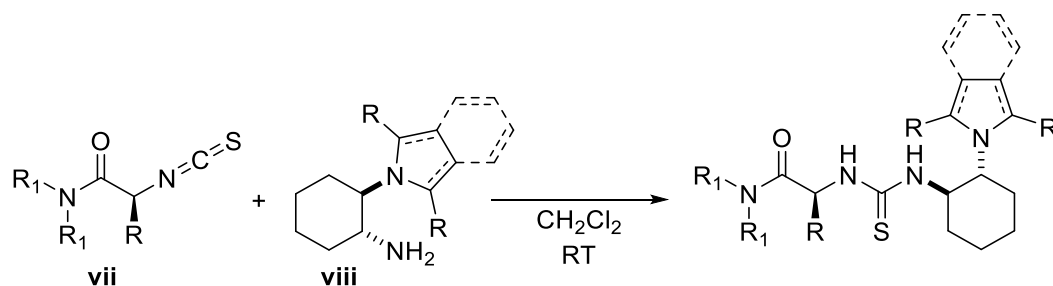
Working under inert atmosphere, a 0.1M solution of the proper diaminocyclohexane derivative **viii** (1.2 eq., 0.18 mmol) in CH_2Cl_2 was added to a solution of the amino acid derived isothiocyanate **vii** (1 eq., 0.15 mmol) in CH_2Cl_2 at room temperature. The reaction mixture was stirred 48 hours and subsequently concentrated under reduced pressure. The product was purified though flash column chromatography on silica gel. Reported yields are referred to the last step.

Catalysts characterization

(*S*)-2-(3-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)thioureido)-*N,N*,3-trimethylbutanamide[x] (U1)
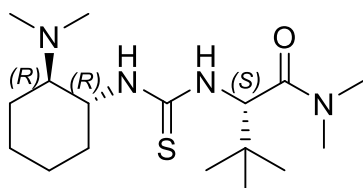
The product was purified through flash column chromatography using a mixture 9:1 CH_2Cl_2:MeOH with 1% NH_4OHaq. as eluent and obtained in 64% yield.

Rf = 0.153 (9:1 CH_2Cl_2:MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.27 (d, J = 8.8 Hz, 1H), 6.43 (bs, 1H), 5.39 (d, J = 8.8 Hz, 1H), 3.85 (s, 2H), 3.24 (s, 3H), 2.93 (s, 3H), 2.70 (s, 1H), 2.42 (s, 6H), 1.92-1.71 (m, 4H), 1.39- 1.17 (m, 3H), 1.04 (s, 9H).

Corresponding salts (catalysts 2 and 4) were prepared reacting this compound with HCl in Et$_2$O and MeI, respectively.

(*S*)-2-(3-((1*R*,2*R*)-2-aminocyclohexyl)thioureido)-*N,N*,3,3-tetramethylbutanamide[y] (U2)

The product was purified through flash column chromatography using a mixture 94:6 CH_2Cl_2:MeOH as eluent and obtained in 40% yield.

Rf = 0.15 (94:6 CH_2Cl_2:MeOH).

MS Mass (ESI+) m/z calc. for $C_{15}H_{30}N_4O_1S_1$: 314.21, found 315.1 [M+H]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.28 (d, J = 6.4 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 5.20 (d, J = 8.0 Hz, 1H), 4.32 (d, J = 9.9 Hz, 1H), 3.26 (s, 3H), 3.26-3.16 (m, 1H), 2.97 (s, 3H), 2.38-2.30 (m, 2H), 1.79-1.70 (m, 2H), 1.61-1.57 (m, 1H), 1.36-1.21 (m, 3H), 1.03 (s, 9H).

^{13}C NMR (75 MHz, CDCl3) δ: 183.43 (s), 172.80 (s), 60.59 (s), 56.45 (s), 54.62 (s), 50.76 (s), 38.79 (s), 36.55 (s), 35.63 (s), 31.94 (s), 30.86 (s), 26.83 (s), 24.25 (s).

(*S*)-2-(3-((1*R*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl)thioureido)-*N,N*,3,3-tetramethylbutanamide (V1)
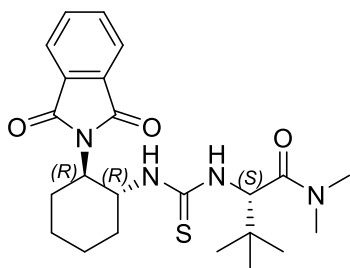
The product was purified through flash column chromatography using a mixture 94:6 CH_2Cl_2:MeOH as eluent and obtained in 23% yield.

Rf = 0.48 (98:2 CH_2Cl_2:MeOH).

$[\alpha]_D^{28}$ = -28.70 (*c* 0.21, CHCl$_3$).

MS Mass (ESI+) m/z calc. for $C_{23}H_{32}N_4O_3S_1$: 444.22, found 467.4 [M+Na]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.79-7.76 (m, 2H), 7.69-7.65 (m, 2H), 6.36 (d, J = 9.3 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 5.45 (d, J = 9.3 Hz, 1H), 4.66 (bs, 1H), 3.98 (td, J = 11.9, 3.8 Hz, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 2.3-2.25 (m, 2H), 1.86-1.77 (m, 3H), 1.57-1.40 (m, 1H), 1.35-1.24 (m, 2H), 0.90 (s, 9H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 182.13 (s), 171.65 (s), 168.59 (s), 133.83 (s), 131.82 (s), 123.36 (s), 60.19 (s), 54.69 (s), 53.59 (s), 38.30 (s), 35.98 (s), 35.48 (s), 33.49 (s), 26.48 (s), 25.21 (s), 24.52 (s).

[x] D. F. Fuerst, N. E. Jacobsen, *J. Am. Chem. Soc*. **2005**, *127*, 8964-8965.

[y] P. Vachal; N. E. Jacobsen, *J. Am. Chem. Soc*. **2002**, *124*, 10012-10014.

(*S*)-2-(3-((1*R*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl)thioureido)-*N*,*N*,3-trimethylbutanamide (V2)
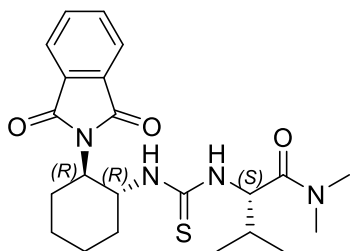
The product was purified through flash column chromatography using a mixture 99:1 CH_2Cl_2:MeOH as eluent and obtained in 50% yield.

Rf = 0.50 (98:2 CH_2Cl_2:MeOH).

$[\alpha]_D^{28}$ = -34.98 (*c* 0.23, $CHCl_3$).

HRMS Mass (ESI+) m/z calc. for $C_{22}H_{30}N_4O_3S_1Na_1^+$: 453.19308, found: 453.19310 [M + Na].

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83-7.79 (m, 2H), 7.70-7.65 (m, 2H), 6.77 (bs, 1H), 6.31 (bs, 1H), 5.31-5.25 (m, 1H), 4.76 (bs, 1H), 3.96 (td, J = 11.8, 3.9 Hz, 1H), 2.98 (s, 3H), 2.88 (s, 3H), 2.42 (bs, 1H), 2.25 (d, J = 10.8 Hz, 1H), 1.98-1.87 (m, 1H). 1.87-1.76 (m, 3H), 1.58-1.44 (m,1H), 1.38-1.17 (m, 2H), 0.81 (d, J = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.79 (s), 172.05 (s), 168.04 (s), 133.11 (s), 131.50 (s), 122.75 (s), 58.32 (s), 54.27 (s), 53.25 (s), 37.13 (s), 35.14 (s), 32.88 (s), 31.73 (s), 28.59 (s), 24.85 (s), 24.04 (s), 18.37 (s), 17.71 (s).

(*S*)-2-(3-((1*S*,2*S*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl)thioureido)-*N*,*N*,3-trimethylbutanamide (V3)
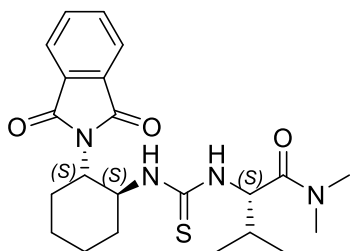
The product was purified through flash column chromatography using a mixture 98:2 CH_2Cl_2:MeOH as eluent and obtained in 26% yield.

Rf = 0.26 (98:2 CH_2Cl_2:MeOH).

$[\alpha]_D^{28}$ = +66.87 (*c* 0.21, $CHCl_3$).

MS Mass (ESI+) m/z calc. for $C_{22}H_{30}N_4O_3S_1$: 430.20, found 453.4 [M+Na]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78-7.65 (m, 2H), 7.68-7.65 (m, 2H), 7.39 (bs, 1H), 6.80 (bs, 1H), 5.31-5.25 (m, 1H), 5.04 (bs, 1H), 3.90 (td, J = 12.1, 3.5 Hz, 1H), 3.20 (s, 3H), 3.05 (s, 3H), 2.71-2.61 (m, 1H), 2.22-2.15 (m, 1H), 1.91-1.72 (m, 4H), 1.58-1.45 (m, 1H), 1.33-1.15 (m, 2H), 0.75 (d, J = 6.7 Hz, 3H), 0.54 (d, J = 6.5 Hz, 3H).

13C NMR (75 MHz, CDCl3) δ: 182.49 (s), 173.70 (s), 168.62 (s), 133.44 (s), 132.07 (s), 122.96 (s), 58.34 (s), 55.33 (s), 54.14 (s), 38.10 (s), 36.06 (s), 33.38 (s), 32.26 (s), 28.59 (s), 25.69 (s), 24.68 (s), 18.83 (s), 17.81 (s).

(S)-2-(3-((1R,2R)-2-(2,5-dimethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-N,N,3-trimethylbutanamide (W)
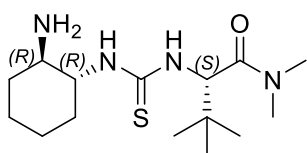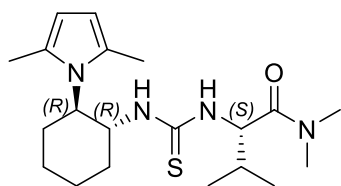
The product was purified through flash column chromatography using a mixture 6:4 hexane:ethyl acetate as eluent and obtained in 56% yield.

$Rf = 0.28$ (98:2 CH_2Cl_2:MeOH).

$[\alpha]_D^{28} = +30.37$ (c 0.25, $CHCl_3$).

MS Mass (ESI+) m/z calc. for $C_{20}H_{34}N_4O_1S_1Na_1$: 401.23455, found 401.23477 [M+Na]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.72 (bs, 1H), 6.37 (bs, 1H), 5.71 (s, 2H), 5.29 (bs, 1H), 4.45 (bs, 1H), 3.80 (td, J = 11.5, 4.4 Hz, 1H), 3.17 (s, 3H), 2.96 (s, 3H), 2.43-2.12 (m, 6H), 2.04-1.77 (m, 5H), 1.44-1.12 (m, 4H), 0.90 (dd, J = 6.7, 1.8 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.95 (s), 172.82 (s), 128.99(s), 127.15 (s), 108.38 (s), 105.89 (s), 59.68 (s), 59.40 (s), 59.89 (s), 37.96 (s), 35.72 (s), 31.99 (d, J = 150.1 Hz), 25.85 (s), 24.76 (s), 18.98 (s), 18.70 (s), 15.32 (s), 13.60 (s).

(S)-2-(3-((1R,2R)-2-(2,5-dimethyl-pyrrolyl)cyclohexyl)thioureido)-N,N-diethyl-3,3-imethylbutanamide[6c] (Y)
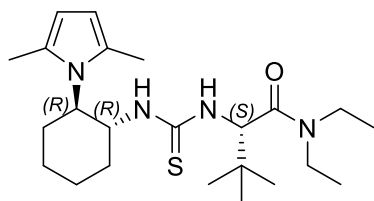
The product was purified through flash column chromatography using a mixture 8:2 hexane:ethyl acetate as eluent and obtained in 56% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.67 (bs, 1H), 5.92 (bs, 1H), 5.69 (s, 2H), 5.47 (d, J = 9.1 Hz, 1H), 4.53 (m, 1H), 3.88-3.75 (m, 1H), 3.71-3.60 (m, 1H), 3.35 (dq, J = 14.4, 7.1 Hz, 1H), 3.08 (dq, J = 14.0, 7.1 Hz, 1H), 2.51 (d, J = 12.9 Hz, 1H), 2.29-2.15 (m, 6H), 1.96-1.71 (m, 4H), 1.68-1.66 (m, 1H), 1.49-1.35 (m, 2H), 1 1.26 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H).

(*S*)-*N*,*N*-dibenzyl-2-(3-((1*R*,2*R*)-2-(2,5-dimethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-3-ethylbutanamide (X)
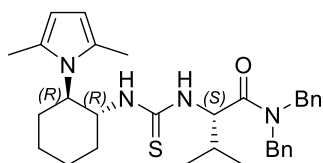
The product was purified through flash column chromatography using a mixture 85:15 hexane:ethyl acetate as eluent and obtained in 54% yield.

Rf = 0.15 (8:2 hexane:ethyl acetate).

$[\alpha]_D^{24}$= -15.86 (*c* 0.33, CHCl$_3$).

MS Mass (ESI+) m/z calc. for C$_{32}$H$_{42}$N$_4$O$_1$S$_1$: 530.31, found 553.5 [M+Na]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7,39-7,3 (m, 6H), 7.23 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 6.40 (d, J = 8.6 Hz, 1H), 6.00 (bs, 1H), 5.75 (s, 2H), 4.73 (d, J = 14.8 Hz, 1H), 4.61 (s, 2H), 4.48-4.44 (m, 1H) 4.38 (d, J = 14.8 Hz, 1H), 3.84 (td, J = 11.1, 4.6 Hz, 1H), 2.55-2.20 (m, 7H), 2.10-1.82 (m, 6H), 1.55-1.39 (m, 2H), 0.89 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 181.71 (s), 172.35 (s), 136.14 (s), 135.48 (s), 12827 (s), 128.10 (s), 127.65 (s), 127.29 (s), 126.97 (s), 108.24 (s), 105.50 (s), 59.06 (s), 55.71 (s), 49.75 (s), 47.58 (s), 33.49 (s), 31.64 (s), 31.33 (s), 29.14 (s), 25.29 (s), 24.19 (s), 18.90 (s), 17.57 (s), 14.36 (s), 13.40 (s).

(*S*)-2-(3-((1*R*,2*R*)-2-(2,5-diphenyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-*N*,*N*,3-trimethylbutanamide (Z)
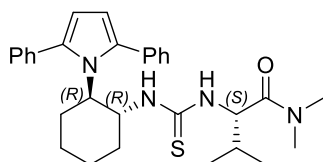
The product was purified through flash column chromatography using a mixture 7:3 hexane:ethyl acetate as eluent and obtained in 33% yield.

Rf = 0.21 (7:3 hexane:ethyl acetate).

$[\alpha]_D^{28}$= -3.02 (*c* 1.0, CHCl$_3$).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.54-7.52 (d, J = 7.3 Hz, 4H), 7.48-7.39 (m, 6H), 6.22 (s, 2H), 6.03 (d, J = 8.0 Hz, 1H), 5.51-5.46 (m, 1H), 5.40 (d, J = 6.1 Hz, 1H), 4.05-3.96 (m, 1H), 3.60 (bs, 1H), 3.20 (s, 3H), 2.95 (s, 3H), 2.22 (d, J = 13.0 Hz, 2H), 2.12-2.05 (m, 2H), 1.91 (qd, J = 12.7, 3.5 Hz, 1H), 1.81-1.69 (m, 2H), 1.55 (d, J = 12.3 Hz, 1H), 1.20-1.00 (m, 1H), 1.06 (d, J = 3.6 Hz, 3H), 1.04 (d, J = 3.6 Hz, 3H), 0.95-0.75 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 181.20 (s), 171.81 (s), 130.06 (s), 127.80 (s), 127.27 (s), 110.39 (s), 60.29 (s), 58.72 (s), 55.93 (s), 37.15 (s), 35.01 (s), 33.38 (s), 32.58 (s), 31.67 (s), 25.28 (s), 23.56 (s), 18.64 (s), 17.86 (s).

<u>Stereoselective synthesis of highly functionalized chiral 2-nitro-cyclohexane carboxylic esters via catalytic dienamine addition to β-substituted-β-nitroacrylates</u>

<u>Materials</u>

Commercial grade reagents and solvents were used without further purification. Chiral primary amine catalysts A-E were prepared from commercially available quinine and quinidine, following literature procedures.[z] α,β-Unsaturated ketones were purchased from Aldrich used as received or synthesized following the literature procedures.[aa] Nitroacrylates were prepared according to literature procedures.[bb]

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[z] a) C. G. Oliva, A. M. S. Silva, D. I. S. P. Resende, F. A. A. Paz, José A. S. Cavaleiro, *Eur. J. Org. Chem.,* **2010**, 3449–3458. b) H. Brunner, J. Bügler, B. Nuber, *Tetrahedron: Asymmetry*, **1995**, *6*, 1699-1702. c) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int. Ed.,* **2007**, *46*, 7667 –7670. d) A. Berkessel, M. Guixà, F. Schimdt, J. M. Nrudorfl, *Chem. Eur. J.*, **2007**, *13*, 4483-4498.

[aa] J. Hu, S. Chen, Y. Sun, J. Yang, Y. Rao, *Org. Lett.*, **2012**, *14*, 5030-5033.

[bb] A. Palmieri, S. Gabrielli, R. Ballini, *Green. Chem.*, **2013**, *15*, 2344-2348.

General procedure for organocatalytic reactions
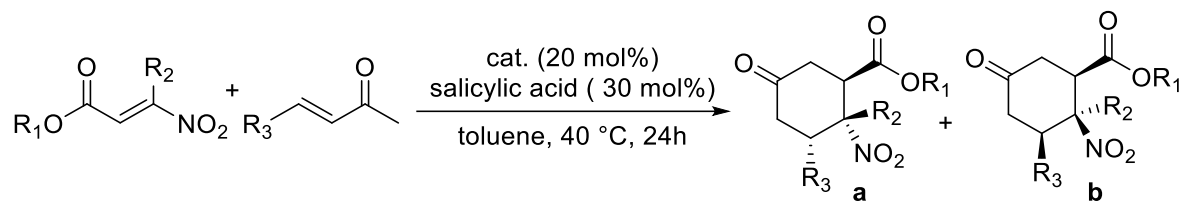
The primary amine catalyst (0.2 eq.) and the acidic co-catalyst (0.3 eq.) were dissolved in dry solvent (1M solution) under N_2 atmosphere and stirred at room temperature for 10 minutes. After this period, the α,β-unsaturated ketone and the nitroacrylate were added. The reaction mixture was heated to the desired temperature and stirred for the reported time, after which solvent was removed at reduced pressure. Cyclohexanone derivatives were isolated by flash column chromatography on silica gel. The diastereomeric ratio was determined by ^{1}H NMR analysis on the crude mixture; the enantiomeric ratio was determined by HPLC on chiral stationary phase.

The absolute configuration of the major enantiomer of ethyl 3-(4-bromophenyl)-2-ethyl-2-nitro-5-oxocyclohexanecarboxylate (Table 3, entries 5-6-7, *cis* isomer b) obtained with catalyst B (9-deoxy-9-amino-epiquinine) was determined to be 1*R*, 2*S*, 3*R* by X-ray analysis; in the product characterization section and in figures associated to NMR spectra only the major enantiomer obtained with catalyst B is shown.

Products characterization

Ethyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (1a)
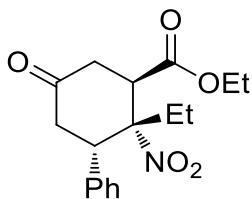
The product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

R_f = 0.25 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.33-7.29 (m, 3H), 7.12- 7.06 (m, 2H), 4.33-4.17 (m, 2H), 4.07 (dd, J = 13.4, 4.2 Hz, 1H), 3.91 (dd, J = 7.3, 3.4 Hz, 1H), 3.36 (dd, J = 16.8, 7.3 Hz, 1H), 3.01 (dd, J = 15.9, 13.4 Hz, 1H), 2.67-2.57 (m, 2H), 2.12 (ept, J = 7.5 Hz, 1H), 1.83 (sex, J = 7.5 Hz, 1H), 1.31 (t, 3 H, J = 7.2 Hz, 3H), 0.95 (t, 3H, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.70 (s), 171.63 (s), 136.60 (s), 129.16 (s), 128.38 (s), 93.18 (s), 61.94 (s), 47.05 (s), 46.26 (s), 42.61 (s), 40.57 (s), 29.08 (s), 13.98 (s), 7.91 (s).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{21}$NO$_5$Na$_1$$^+$: 342.13119, found: 342.13211 [M + Na].

ν (cm^{-1}): 3019.98 (Ph), 1729.83 (C=O), 1654.62 (C=O), 1541.81 (NO$_2$), 1336.43 (NO$_2$).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+) enantiomer, obtained with catalyst **A**: t_R 13.15 min (minor), t_R 19.35 min (major); (-) enantiomer, obtained with catalyst **B**: t_R 13.52 min (major), t_R 20.32 min (minor).

$[\alpha]_D^{23}$= -8° (ee 97%, c: 0.23, CHCl$_3$).

Ethyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (1b)

The product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

Rf = 0.17 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl3) δ: 7.32-7.30 (m, 3H), 7.06-7.03 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.36-3.41 (m, 3H), 3.33 (dd, J = 13.3, 5.5 Hz, 1H), 2.79 (dd, 1H, J = 15.2, 5.3 Hz), 2.57-2.54 (m, 1H), 2.13 (sex, J = 7.5 Hz, 1H), 1.87 (sex, J = 7.5 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3) δ: 205.46 (s), 168.65 (s), 135.63 (s), 128.63 (s), 128.23 (s), 127.31 (s), 90.07 (s), 61.35 (s), 46.22 (s), 45.96 (s), 42.84 (s), 40.02 (s), 25.32 (s), 13.43 (s), 8.63 (s).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{21}$NO$_5$Na$_1$$^+$: 342.13119, found: 342.13099 [M + Na].
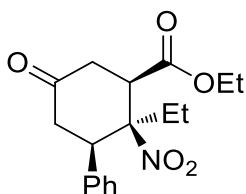
ν (cm^{-1}): 3019.01 (Ph), 1717.3(C=O), 1653.66 (C=O), 1544.7 (NO$_2$).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t_R 26.11 min (major), 29.29 min (minor); (-)-enantiomer, obtained with catalyst **B**: t_R 26.01 min (minor), 28.83 min (major).

$[\alpha]_D^{23}$= -20.5° (ee 88%, c: 0.38, CHCl$_3$).

Ethyl 3-(4-bromophenyl)-2-ethyl-2-nitro-5-oxocyclohexanecarboxylate (2a)
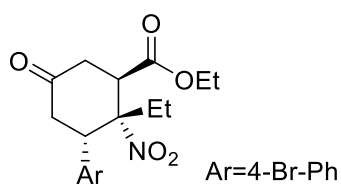
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

Rf = 0.27 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.48 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 4.35-4.19 (m, 2H), 4.07 (dd, J = 13.6, 4.1 Hz, 1H), 3.93 (dd, J = 7.4, 3.1 Hz, 1H), 3.36 (dd, J = 16.6, 7.3 Hz, 1H), 2.95 (dd, J = 15.6, 13.5 Hz, 1H), 2.69-2.55 (m, 2H), 2.10 (sex, J = 7.5 Hz, 1H), 1.82 (sex, J = 7.5 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.02 (s), 171.62 (s), 135.67 (s), 131.53 (s), 130.87 (s), 122.53 (s), 93.08 (s), 62.03 (s), 46.49 (s), 46.10 (s), 42.49 (s), 40.52 (s), 29.26 (s), 13.98 (s), 7.86 (s).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{22}$N$_1$O$_5$Br$_1$Na$_1$$^+$: 420.04171, found: 420.04173 [M + Na].

ν (cm^{-1}): 2983.35 (Ph), 1737.55 (C=O), 1683.55 (C=O), 1540.85 (NO$_2$), 1361.5 (NO$_2$), 756.92 (Ph).

The enantiomeric excess was determined by HPLC with Daicel Chiralcell OD-H column, eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 19.87 min (minor), t$_R$ 29.57 min (major); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 19.49 min (major), t$_R$ 30.29 min (minor).

$[\alpha]_D^{30}$= -27.8° (ee 94%, *c*: 0.49, CHCl$_3$).

(1*R*, 2*S*, 3*R*,)-Ethyl 3-(4-bromophenyl)-2-ethyl-2-nitro-5-oxocyclohexanecarboxylate (2b)

The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as white solid. Crystals suitable for X-ray analysis were obtained by crystallization from iPr$_2$O.

mp: 113.7-115.5 °C.

Rf = 0.15 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.48 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.53 (dd, J = 15.3, 13.3 Hz, 1H), 3.41-3.33 (m, 2H), 3.33 (dd, J = 13.3, 5.5 Hz, 1H), 2.82 (ddd, J = 15.3, 5.4, 1.6 Hz, 1H), 2.61-2.49 (m, 1H), 2.18 (sex, J = 7 Hz, 1H), 1.85 (sex, J = 7 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 204.82 (s), 168.44 (s), 134.56 (s), 131.78 (s), 128.90 (s), 122.31 (s), 89.86 (s), 61.38 (s), 45.80 (s), 45.62 (s), 42.60 (s), 39.89 (s), 25.27 (s), 13.37 (s), 8.54 (s).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{22}$N$_1$O$_5$Br$_1$Na$_1$$^+$: 420.04171, found: 420.04170 [M + Na].
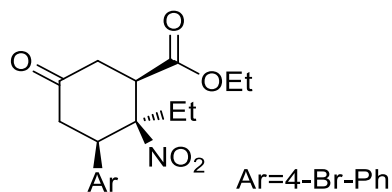
ν (cm^{-1}): 2969.84 (Ph), 1736.58 (C=O), 1652.7 (C=O), 1540.85 (NO$_2$), 1358.6 (NO$_2$), 735.45 (Ph).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column, eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 28.88 min (major), t$_R$ 37.97 min (minor); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 28.56 min (minor), t$_R$ 37.87 min (major);

$[\alpha]_D^{25}$= -35.7° (ee 92%, *c*: 0.31, CHCl$_3$).

Ethyl 2-ethyl-2-nitro-5-oxo-3-(thiophen-2-yl)cyclohexanecarboxylate (3a)
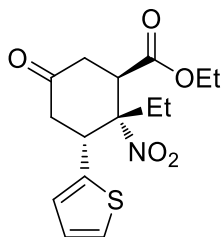
The product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.3 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.29 (d, J = 5.3 Hz, 1H), 7.00 (dd, J = 5.6, 3.6 Hz, 1H), 6.91 (d, J = 3.4 Hz, 1H), 4.38 (dd, J = 12.3, 4.7 Hz, 1H), 4.30-4.19 (m, 2H), 3.92 (dd, J = 6.9, 3.9 Hz, 1H), 3.16-2.99(m, 2H), 2.78 (ddd, J = 16.2, 4.7, 1.6 Hz, 1H), 2.65 (ddd, J = 16.7, 3.9, 1.6 Hz, 1H), 2.27 (sex, J = 7.5 Hz, 1H), 1.97 (sex, J = 7.5 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 204.37 (s), 171.36 (s), 139.32 (s), 127.60 (s), 126.73 (s), 125.76 (s), 93.04 (s), 62.04 (s), 46.28 (s), 44.44 (s), 42.67 (s), 40.30 (s), 29.33 (s), 13.98 (s), 8.14 (s).

HRMS Mass (ESI+) m/z calc. for C$_{15}$H$_{19}$NO$_5$S$_1$Na$_1^+$: 348.08761, found: 348.08768 [M + Na].

ν (cm^{-1}): 3019.01 (Ph), 1737.55 (C=O), 1683.55 (C=O), 1540.85 (NO$_2$), 1361.5 (NO$_2$), 756.92 (Ar).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column, eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t_R 16.33 min (minor), t_R 19.33 min (major); (-)-enantiomer, obtained with catalyst **B**: t_R 16.33 min (major), t_R 20.49 min (minor).

$[\alpha]_D^{30}$ = -8.3° (ee 97%, *c*: 0.13, CHCl$_3$).

Ethyl 2-ethyl-2-nitro-5-oxo-3-(thiophen-2-yl)cyclohexanecarboxylate (3b)
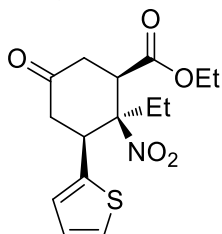
The product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

Rf = 0.18 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.24 (d, J = 5.1 Hz, 1H), 6.96 (dd, J = 3.7, 4.9 Hz, 1H), 6.83 (d, J = 3.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.73 (dd, J = 13.5, 5.0 Hz, 1H), 3.55-3.38 (m, 2H), 3.29 (dd, J = 13.5, 4.6 Hz, 1H), 2.78-2.69 (m, 2H), 2.21 (sex, J = 7.5 Hz, 1H), 2.07 (sex, J = 7.5 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 204.98 (s), 168.86 (s), 138.06 (s), 127.29 (s), 126.21 (s), 125.29 (s), 91.10 (s), 61.94 (s), 46.05 (s), 44.89 (s), 41.88 (s), 40.04 (s), 25.95 (s), 13.90 (s), 9.00 (s).

HRMS Mass (ESI+) m/z calc. for C$_{15}$H$_{19}$N$_1$O$_5$SNa$_1^+$: 348.08761, found: 348.08770 [M + Na].

ν (cm^{-1}): 2981.41 (Ar), 1743.33(C=O), 1717.3 (C=O), 1540.85 (NO$_2$), 772.35 (Ar).

The enantiomeric excess was determined by HPLC with Daicel Chiralcell OD-H column, eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min, detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t_R 21.60 min (minor), t_R 26.93 min (major), (-)-enantiomer, obtained with catalyst **B**: t_R 21.60 min (major), t_R 27.85 min (minor).

$[\alpha]_D^{30}$ = -38.3° (ee 98%, *c*: 0.57, CHCl$_3$).

Ethyl 2-ethyl-3-methyl-2-nitro-5-oxocyclohexanecarboxylate (4a)
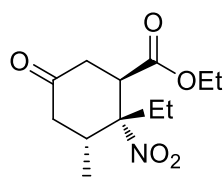
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

Rf = 0.37 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.25-4.13 (m, 2H), 3.87 (t, J = 5.9 Hz, 1H), 2.97 (dd, J = 16.8, 6.8 Hz, 1H), 2.92-2.80 (m, 1H), 2.55 (dd, J = 16.5, 5.2 Hz, 1H), 2.48-2.27 (m, 3H), 1.89 (sex, J = 7.5, 1H), 1.27 (t, J = 6.2 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 206.46 (s), 172 (s), 93.5 (s), 61.80 (s), 46.09 (s), 44.51 (s), 40.32 (s), 35.89 (s), 28.09 (s), 16.04 (s), 13.96 (s), 8.10 (s).

MS Mass (ESI+) m/z calc. for $C_{12}H_{19}N_1O_5Na_1^+$: 280.13, found: 280.2 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS-3 column, eluent: 8:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 20.02 min (minor), t$_R$ 27.02 min (major); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 20.01 min (major), t$_R$ 27.79 min (minor).

Ethyl 2-ethyl-3-methyl-2-nitro-5-oxocyclohexanecarboxylate (4b)
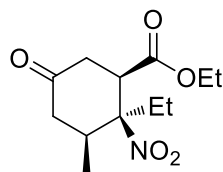
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

Rf = 0.36 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.17 (q, J = 6.9 Hz, 2H), 3.34-3.15 (m, 2H), 2.75-2.66 (m, 2H), 2.44.-2.27 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.00-0.95 (m, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 206.46 (s), 169.22 (s), 91.51 (s), 61.77 (s), 46.13 (s), 44.24 (s), 40.38 (s), 35.20 (s), 25.67 (s), 15.31 (s), 13.94 (s), 8.91 (s).

HRMS Mass (ESI+) m/z calc. for $C_{12}H_{19}N_1O_5Na_1^+$: 280.11554, found: 280.11611 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column, eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 16.69 min (minor), t$_R$ 19.04 min (major); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 16.34 min (minor), t$_R$ 18.25 min (major).

Ethyl 2-nitro-5-oxo-2-pentyl-3-phenylcyclohexanecarboxylate (5a)
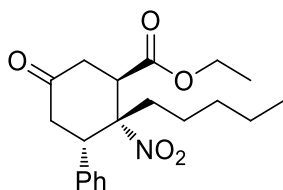
The product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

Rf = 0.38 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.39-7.35 (m, 3H), 7.14-7.08 (m, 2H), 4.32-4.19 (m, 2H), 4.06 (dd, J = 13.4, 4.0 Hz, 1H), 3.92 (dd, J = 7.3, 3.6 Hz, 1H), 3.36 (dd, J = 16.5, 7.3 Hz, 1H), 3.03-2.98 (m, 1H), 2.68-2.63 (m, 1H), 2.04-2.00 (m, 1H), 1.79-1.74 (m, 1H), 1.33-1.15 (m, 9H), 0.83 (t, J = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.87 (s), 171.69 (s), 136.58 (s), 129.13 (s), 128.61 (s), 128.40 (s), 92.79 (s), 61.97 (s), 47.16 (s), 47.64 (s), 40.60 (s), 35.93 (s), 31.72 (s), 22.97 (s), 22.29 (s), 14.06 (s), 13.87 (s).

HRMS Mass (ESI+) m/z calc. for C$_{20}$H$_{27}$N$_1$O$_5$Na$_1^+$: 384.17814, found: 384.17971 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 9.38 min (minor), t$_R$ 10.81 min (major); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 9.29 min (major), t$_R$ 10.89 min (minor).

$[\alpha]_D^{25}$= -14.7° (ee 96%, *c*: 0.06, CHCl$_3$).

Ethyl 2-nitro-5-oxo-2-pentyl-3-phenylcyclohexanecarboxylate (5b)
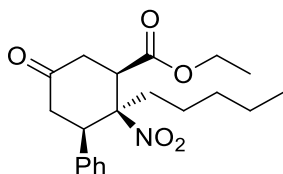
The product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

Rf = 0.25 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.34-7.32 (m, 3H), 7.05-7.02 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.49-3.35 (m, 4H), 2.79 (dd, J = 15.4, 5.0 Hz, 1H), 2.6-2.48 (m, 1H), 2.16-2.05 (m, 1H), 1.81-1.43 (m, 1H), 1.41-1.23 (m, 9H), 0.90 (t, J = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 206.03 (s), 169.19 (s), 136.13 (s), 129.08 (s), 128.74 (s), 127.77 (s), 90.32 (s), 61.83 (s), 47.15 (s), 46.98 (s), 43.34 (s), 40.56 (s), 32.74 (s), 31.76 (s), 24.37 (s), 22.28 (s), 13.96 (s), 13.86 (s).

HRMS Mass (ESI+) m/z calc. for C$_{20}$H$_{27}$NO$_5$Na$_1^+$: 384.17814, found: 384.17964 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralcell OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 11.12 min (major), t$_R$ 14.12 min (minor); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 11.60 min (minor), t$_R$ 14.71 min (major).

$[\alpha]_D^{25}$= -13.4° (ee 94%, *c*: 0.31, CHCl$_3$).

Isopropyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (6a)
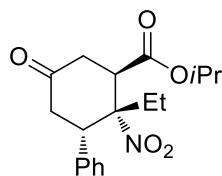
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

Rf = 0.49 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.41-7.44 (m, 3H), 7.15-7.04 (m, 2H), 5.12 (quin, J = 6.2 Hz, 1H), 4.11 (d, J = 11.5 Hz, 1H), 3.88 (d, J = 7.3 Hz, 1H), 3.40 (dd, J = 16.8, 7.4 Hz, 1H), 3.03 (t, J = 14.7 Hz, 1H), 2.63 (d, J = 16.1 Hz, 2H), 2.15 (sex, J = 7 Hz, 1H), 1.84 (sex, J = 7 Hz, 1H), 1.35-1.23 (m, 6H), 0.97 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.77 (s), 171.11 (s), 136.66 (s), 129.16 (s), 128.37 (s), 93.17 (s), 69.81 (s), 47.14 (s), 46.45 (s), 42.62 (s), 40.61 (s), 29.12 (s), 21.56 (s), 21.46 (s), 7.92 (s).

HRMS Mass (ESI+) m/z calc. for C$_{18}$H$_{23}$N$_1$O$_5$Na$^+$: 356.14684, found: 356.14748 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpack AD column, eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 10.21 min (minor), t$_R$ 15.18 min (major); (-)-enantiomer, obtained with catalyst **B**: t$_R$ 10.24 min (major), t$_R$ 15.26 min (minor).

$[\alpha]_D^{26}$= -8.5° (ee 88%, *c*: 0.14, CHCl$_3$).

Isopropyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (6b)
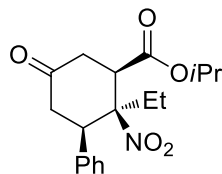
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R$_f$ = 0.25 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.39-7.33 (m, 3H), 7.10-7.06 (m, 2H), 5.05 (sex, J = 6.3 Hz, 1H), 3.61-3.39 (m, 3H), 3.31 (dd, J = 13, 5 Hz, 1H), 2.80 (dd, J = 15.4, 5.5 Hz, 1H), 2.65-2.52 (m, 1H), 2.18 (sex, J = 7 Hz, 1H), 1.89 (sex, J = 7.5 Hz, 1H),1.30-1.23 (m, 6H), 1.09 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 206.10 (s), 168.60 (s), 136.11 (s), 129.10 (s), 128.69 (s), 127.77 (s), 90.51 (s), 69.70 (s), 43.35 (s), 40.46 (s), 25.76 (s), 21.52 (s), 21.42 (s), 9.09 (s).

HRMS Mass (ESI+) m/z calc. for C$_{18}$H$_{23}$N$_1$O$_5$Na$_1$$^+$: 356.14684, found: 356.14750 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column, eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t$_R$ 20.63 min (major), t$_R$ 31.49 min (minor); (-)-enantiomer, obtained with catalyst **B**:t$_R$ 21.55 min (minor), t$_R$ 31.87 min (major).

(+)-enantiomer$[\alpha]_D^{26}$= +20.4° (ee 84%, *c*: 0.45, CHCl$_3$).

Benzyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (7a)

The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.43 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.42-7.41 (m, 5H), 7.33-7.30 (m, 4H), 7.03-7.00 (m, 2H), 5.24 (d, J = 3.8 Hz, 1H), 4.09 – 3.93 (m, 2H), 3.36 (dd, J = 16.7, 7.2 Hz, 1H), 3.01 (dd, J = 15.7, 13.5 Hz, 1H), 2.74 – 2.54 (m, 2H), 2.03 (sex, J = 7.5 Hz, 1H), 1.67 (sex, J = 7.5 Hz, 1H), 0.88 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.55 (s), 171.31 (s), 136.50 (s), 134.63 (s), 129.14 (s), 128.84 (s), 128.32 (s), 93.17 (s), 67.77 (s), 46.92 (s), 46.19 (s), 42.57 (s), 40.43 (s), 28.98 (s), 7.88 (s).

HRMS Mass (ESI+) m/z calc. for C$_{22}$H$_{23}$N$_1$O$_5$Na$_1^+$: 404.14684, found: 404.14762 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column, eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+)-enantiomer, obtained with catalyst **A**: t_R 19.52 min (minor), t_R 24.64 min (major); (-)-enantiomer, obtained with catalyst **B**: t_R 19.51 min (major), t_R 24.84 min (minor).

$[\alpha]_D^{26}$ = -10.3° (ee 91%, *c*: 0.42, CHCl$_3$).

Benzyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (7b)

The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.33 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.40-7.33 (m, 8H), 7.11-7.05 (m, 2H), 5.17 (s, 2H), 3.63-3.36 (m, 4H), 2.83 (dd, J = 15.0, 5.4 Hz, 1H), 2.64-2.52 (m, 1H), 2.11 (sex, J = 7.5 Hz, 1H), 1.86 (sex, J = 7.5 Hz, 1H), 1.04 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 206.25 (s), 169.30 (s), 136.38 (s), 135.20 (s), 129.54 (s), 129.17 (s), 128.85 (s), 128.22 (s), 90.98 (s), 68.02 (s), 47.10 (s), 46.84 (s), 43.69 (s), 40.91 (s), 26.19 (s), 9.53 (s).

HRMS Mass (ESI+) m/z calc. for C$_{22}$H$_{23}$N$_1$O$_5$Na$_1^+$: 404.14684, found: 404.14743 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack IB column, eluent: 7:3 Hex/IPA; 0.8 mL/min flow rate, detection: 220 nm; (+)-enantiomer, obtained with catalyst **A**: t_R 10.87 min (major), t_R 14.47 min (minor); (-)-enantiomer, obtained with catalyst **B**: t_R 11.03 min (minor), t_R 14.47 min (major).

For (+)-enantiomer: $[\alpha]_D^{26}$ = +15.5° (ee 78%, *c*: 0.45, CHCl$_3$).

PROCEDURE A: CARBONYL REDUCTION[cc]

To a stirred solution of ethyl 2-ethyl-2-nitro-5-oxo-3-arylcyclohexanecarboxylate (1 eq.) in ethanol (4.4 mL each 0.1 mmol of substrate), NaBH$_4$ (1.5 eq.) was added. The reaction mixture was stirred at 0 °C for 2 hours, after which a saturated solution NH$_4$$^+Cl^-$ (0.5 mL each 0.1 mmol of substrate) was added. The mixture was stirred for 1 hour and the solvent was removed. The residue was dissolved in water and extracted with Et$_2$O. The combined organic phases were dried over anhydrous Na$_2$S0$_4$ and the solvent was removed under reduced pressure.
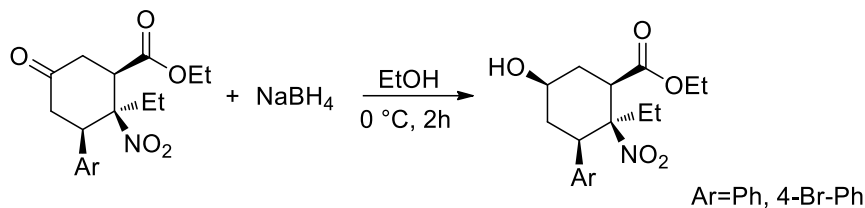
Ethyl 2-ethyl-5-hydroxy-2-nitro-3-phenylcyclohexanecarboxylate (8')
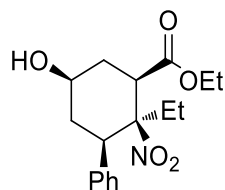
The product was obtained as a white solid in quantitative yield.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.31-7.28 (m, 3H), 7.09-7.06 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.89 (hept, J = 4.7 Hz, 1H), 3.04 (t, J = 13.0 Hz, 1H), 3.02 (t, J = 13.5 Hz, 1H), 2.67 (q, J = 12.6 Hz, 1H), 2.53 (ddd J = 13.0, 11.9 Hz, 1H), 2.43-2.37 (m, 1H), 2.19-2.01 (m, 2H), 1.91 (sex, J = 7.5 Hz, 1H), 1.81 (bs, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.24 (s), 137.48 (s), 128.72 (s), 128.15 (s), 90.53 (s), 68. 88 (s), 61.36 (s), 45.98 (s), 36.18 (s), 34.10 (s), 26.02 (s), 13.95 (s), 9.40 (s).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{23}$NO$_5$Na$_1$$^+$: 344.14684, found: 344.14746 [M + Na].

ν (cm^{-1}): 3370.96 (OH), 1737.55 (C=O), 1717.3 (C=O), 1540.85 (NO$_2$), 754.03 (Ph).

Ethyl 3-(4-bromophenyl)-2-ethyl-5-hydroxy-2-nitrocyclohexanecarboxylate (8'')

The product was obtained as a white solid in 92% yield.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.43 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 3.93-3.82 (m, 1H), 3.05-2.96 (m, 2H), 2.65 (q, 12.3 Hz, 1H), 2.54-2.37 (m, 2H), 2.12 (hept, J = 7.6 Hz, 1H), 2.02-1.98 (m, 1H), 1.87 (sex, J = 7.4 Hz, 1H), 1.72 (bs, 1H), 1.25 (t, J = 6.9 Hz, 4H), 1.05 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.03 (s), 136.46 (s), 131.90 (s), 129.81 (s), 122.24 (s), 90.36 (s), 68.73 (s), 61.43 (s), 45.87 (s), 45.44 (d, J = 32.5 Hz), 36.07 (s), 34.04 (s), 26.02 (s), 13.93 (s), 9.36 (s).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{22}$N$_1$O$_5$Br$_1$Na$_1$$^+$: 422.05736, found: 422.05734 [M + Na].
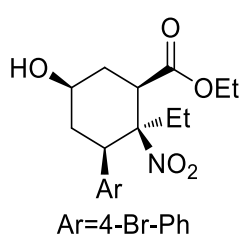
[cc] A. G. Schultz , R. E. Taylor, *J. Am. Chem. Soc.*, **1992**, *114*, 3937–3943.

To a stirred solution of ethyl 2-ethyl-2-nitro-5-oxo-3-arylcyclohexanecarboxylate (1 eq.) in acetone/H$_2$O (5:1, 6 mL each 0.07 mmol of substrate), powder Zn (12 eq.) and solid NH$_4$Cl (3 eq.) were added at room temperature. The reaction mixture was heated at 60 °C for 1 hour, after which it was cooled to room temperature and concentrated under reduced pressure. The mixture was treated with water and extracted with CH$_2$Cl$_2$. The combined organic phases were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure.

Application of PROCEDURE B on *cis* isomer: nitro group reduction
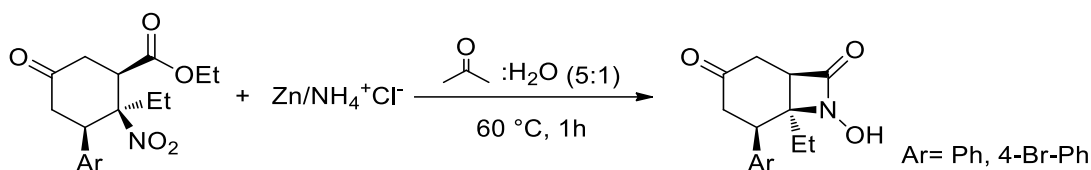
6-Ethyl-N-hydroxy-5-phenyl-7-azabicyclo[4.2.0]octane-3,8-dione (9')
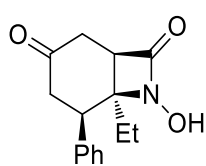
The product was obtained as a deliquescent pale yellow solid in quantitative yield.

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.40-7.35 (m, 3H), 7.29-7.28 (m, 2H), 6.45 (bs, 1H), 3.29-3.24 (m, 2H), 3.09 (dd, J = 16.4, 14.4, Hz, 1H), 2.99 (dd, J = 17.3, 3.9 Hz, 1H), 2.76 (dd, J = 17.4, 7.2 Hz, 1H), 2.55 (dd, J = 16.8, 3.6 Hz, 1H), 1.67 (q, J = 7.4 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 206.66 (s), 176.95 (s), 137.20 (s), 128.93 (s), 128.83 (s), 128.06 (s), 65.95 (s), 45.03 (s), 43.37 (s) 42.94 (s), 37.58 (s), 29.95 (s), 13.37 (s), 8.5 (s).

HRMS Mass (ESI+) m/z calc. for C$_{15}$H$_{17}$N$_1$O$_3$Na$_1^+$: 282.11006, found: 282.11005 [M + Na].

5-(4-bromophenyl)-6-ethyl-7-hydroxy-7-azabicyclo[4.2.0]octane-3,8-dione (9'')
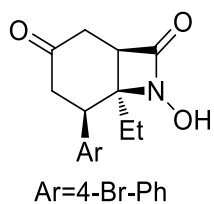
The product was obtained as a pale yellow solid in 75% yield.

mp: 118.5-121.3 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.47 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 3.22-3.16 (m, 2H), 3.02-2.88 (m, 2H), 2.70 (dd, J = 17.5, 7.1 Hz, 1H), 2.46 (dd, J = 17.0, 3.3 Hz, 1H), 1.60 (q, J = 7.5 Hz, 2H), 1.05 (t, J = 7.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 206.25 (s), 177.44 (s), 136.31 (s), 131.72 (s), 130.88 (s), 121.98 (s), 65.66 (s), 44.31 (s), 43.15 (s), 42.74 (s), 37.69 (s), 29.87 (s), 8.25 (s).

HRMS Mass (ESI+) m/z calc. for C$_{15}$H$_{16}$N$_1$O$_3$Br$_1$Na$_1^+$: 360.02058, found: 360.02120 [M + Na].

[dd] M. F. Jacobsen, J. E. Moses, R. M. Adlington, J. E. Baldwin, *Org. Lett.,* **2005**, *7*, 641-644.

Application of PROCEDURE B on *trans* isomer: carbonyl reduction
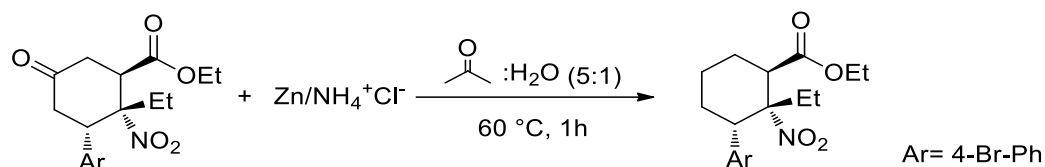
Ethyl 3-(4-bromophenyl)-2-ethyl-2-nitrocyclohexanecarboxylate (16)
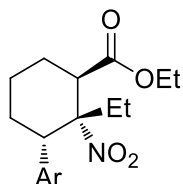
The product was purified by flash column chromatography on silica gel with a 98:2 CH_2Cl_2/MeOH mixture as eluent. The product was obtained as a white deliquescent solid in 78% yield.

R_f = 0.58 (98:2 CH_2Cl_2/MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.36 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 4.28-4.13 (m, 2H), 3.52 (bs, 1H), 3.25 (dd, J = 9.8, 6.7 Hz, 1H), 2.44-2.22 (m, 3H), 1.87 (bs, 1H), 1.46-1.20 (m, 7H), 0.87-0.72 (m, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 174.23 (s), 141.30 (s), 131.41 (s), 131.13 (s), 120.57 (s), 96.59 (s), 60.84 (s), 47.05 (s), 41.75 (s), 39.49 (s), 36.27 (s), 24.77 (s), 14.34 (s), 8.59 (s).

HRMS Mass (ESI+) m/z calc. for $C_{17}H_{23}N_1O_4Br_1^+$: 384.08050, found: 384.08086 [M + H]; calc. for $C_{17}H_{23}N_1O_4Br_1Na_1^+$: 406.06244, found: 406.06307 [M + Na].

PROCEDURE C: ZN/HCL MEDIATED REDUCTION[ee]

To a stirred solution of 4-ethyl-3-(hydroxymethyl)-4-nitro-5-phenylcyclohexanol (197 mg, 0.71 mmol) in AcOEt (21 mL) and EtOH (28 mL), 6M HCl (6 mL, 36 eq.) was added. The reaction mixture was cooled to 0 °C and powder zinc (2.3 g, 50 eq.) was added in three portions over 10 minutes. The reaction mixture was allowed to reach room temperature and stirred for 2 hours, after which additional powder zinc (25 eq.) was added. The mixture was stirred at room temperature for 1 hour, after which solvent were removed reduced pressure. The mixture was quenched with an oversaturated solution of $NaHCO_3$ and extracted with AcOEt. The aqueous layer (containing insoluble zinc salts) was filtered over celite and washed with AcOEt. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed at reduced pressure. The desired product was obtained as acetic acid salt as a red oil in 75% yield.

Application of PROCEDURE C on *cis* isomer: nitro group reduction
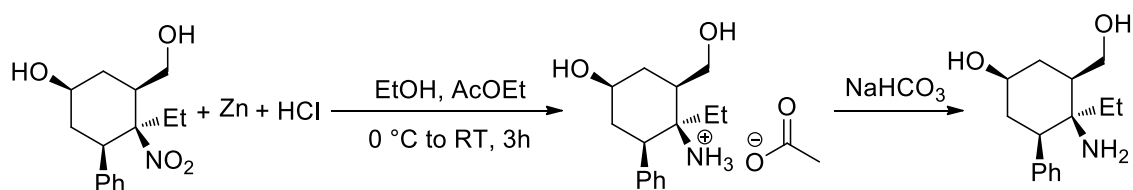
4-Amino-4-ethyl-3-(hydroxymethyl)-5-phenylcyclohexanol (acetic acid salt) (14)

^{1}H NMR (300 MHz, MeOD) δ: 7.44-7.34 (m, 3H), 7.28 (d, J = 7.0 Hz, 2H), 4.14 (dd, J = 11.2, 2.7 Hz, 1H), 3.97-3.88 (m, 1H), 3.72 (d, J = 11.2 Hz, 1H), 3.36-3.32 (m, 2H), 3.24 (dd, J = 12.8, 4.6 Hz, 1H), 2.14-2.03 (m, 7H), 1.92-1.84 (m, 1H), 1.82-1.69 (m, 1H), 1.46 (sex, J = 7.4, 1H), 1.09 (t, J = 7.5 Hz, 3H).
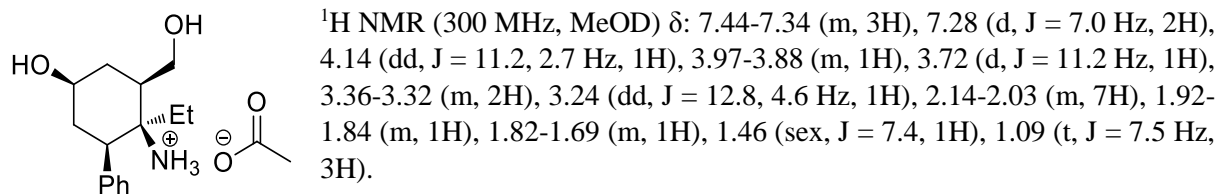
^{13}C NMR (75 MHz, MeOD) δ: 175.59 (s), 137.51 (s), 128.48 (s), 128.07(s), 127.34 (s), 126.79 (m), 67.47 (s), 62.63 (s), 61.98 (s), 43.87 (s), 37.14 (s), 35.66 (s), 33.17 (s), 25.90 (s), 19.72 (s), 6.39 (s).

[ee] J. C. Anderson, A. Noble, D. A. Tocher, *J. Org. Chem.*, **2012**, *77*, 6703-6727.

4-Amino-4-ethyl-3-(hydroxymethyl)-5-phenylcyclohexanol (15)

The product was treated with an oversaturated solution of NaHCO$_3$ and extracted with ethyl acetate. The desired amine was obtained as a light red oil.
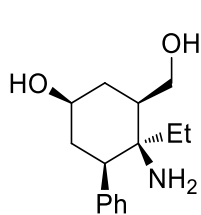
^{1}H NMR (300 MHz, MeOD) δ: 7.32-7.72 (m, 5H), 3.85 (dd, J = 10.9, 4.3 Hz, 1H), 3.65-3.75 (m, 1H), 3.60 (d, J = 11.1 Hz, 1H), 3.29 (bs, 2H), 2.86 (dd, J = 13.3, 3.4 Hz, 1H), 2.07-1.94 (m, 2H), 1.87-1.81 (m, 1H), 1.76-1.70 (m, 1H), 1.52-1.41 (m, 1H), 1.07-0.96 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, MeOD) δ: 140.82 (s), 128.52 (s), 127.85 (s), 126.46 (s), 69.01 (s), 63.23 (s), 56.12 (s), 46.59 (s), 40.09 (s), 36.81 (s), 33.79 (s), 28.60 (s), 6.67 (s).

HRMS Mass (ESI+) m/z calc. for C$_{15}$H$_{24}$N$_1$O$_2^+$: 250.18016, found: 250.180310 [M + H].

Application of PROCEDURE C on *trans* isomer: carbonyl reduction
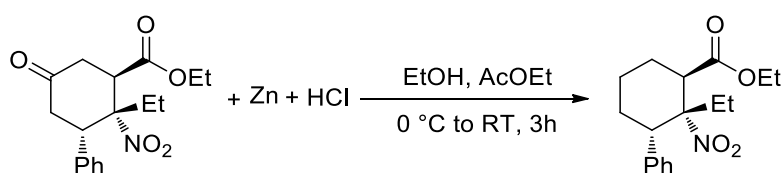
Ethyl 2-ethyl-2-nitro-3-phenylcyclohexanecarboxylate (16')
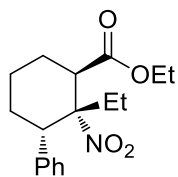
The product was obtained as a yellow solid in quantitative yield.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.30-7.24 (m, 5H), 4.33-4.18 (d, J = 43.2 Hz, 5H), 3.54 (bs, 1H), 3.26 (dd, J = 9.3, 7.0 Hz, 2H), 2.46-2.36 (m, 3H), 2.20 (bs, 1H), 1.35 (m, 7H), 0.83 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 170.11 (s), 137.16 (s), 130.33 (s), 128.68 (s), 127.87 (s), 102.97 (s), 62.18 (s), 46.44 (s), 41.14 (s), 38.48 (s), 32.09 (s), 22.14 (s), 14.54 (s), 8.82 (s), 1.19 (s).

MS Mass (ESI+) m/z calc. for C$_{17}$H$_{23}$N$_1$O$_4$: 305.37, found: 306.4 [M+H].

PROCEDURE D: CARBONYL AND NITRO GROUPS SIMULTANEOUS REDUCTION[ff]
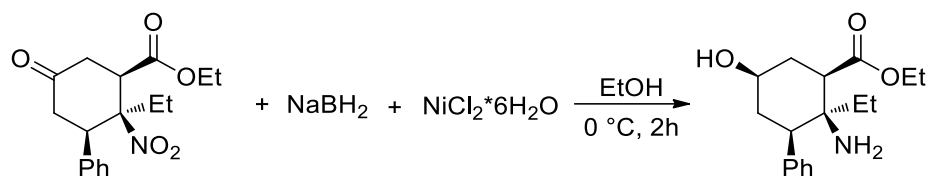
To a stirred solution of ethyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (28.5 mg, 0.089 mmol) and $NiCl_2 \cdot 6H_2O$ (121.2 mg, 0.089 mmol) in EtOH (500 μL), $NaBH_4$ (37.1 mg, 0.98 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, after which it was quenched with brine. The solution was extracted with CH_2Cl_2; the combined organic phases were dried over anhydrous Na_2SO_4, filtered through celite and subsequently over a pad of silica gel, elueting with AcOEt. The solvent was removed under reduced pressure. The desired product was purified by flash column chromatography on silica gel, using the mixture 98:2 CH_2Cl_2/MeOH as eluent. The desired product was obtained as a colourless oil in 15% yield.

Ethyl 2-amino-2-ethyl-5-hydroxy-3-phenylcyclohexanecarboxylate (11)
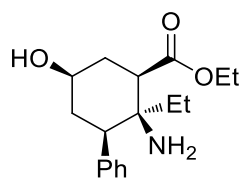
$R_f = 0.46$ (98:2 CH_2Cl_2/MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.27 (m, 5H), 4.23-4.15 (m, 2H), 3.83-3.74 (m 1H), 3.65 (t, J = 3.0 Hz, 1H), 2.91 (d, J = 5.6 Hz, 1H), 2.77 (dd, J = 13.0, 3.3 Hz, 1H), 2.71 (dd, J = 12.9, 3.6 Hz, 1H), 2.39 (q, J = 12.2 Hz, 1H), 2.17 (q, J = 11.3 Hz, 1H), 2.09-2.02 (m, 1H), 1.95-1.89 (m, 1H), 1.31-1.15 (m, 5H), 0.95 (t, J = 7.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.94 (s), 140.80 (s), 128.94 (s), 128.55 (s), 128.22 (s), 127.03 (s), 124.09 (s), 69.46 (s), 60.48 (s), 54.84 (s), 51.80 (s), 47.08 (s), 37.19 (s), 33.86 (s), 30.92 (s), 14.18 (s), 8.51 (s).

HRMS Mass (ESI+) m/z calc. for $C_{17}H_{26}N_1O_3^+$: 292.19072, found: 292.19063 [M + H]; calc. for $C_{17}H_{25}N_1O_3Na_1^+$: 314.17266, found 314.17260 [M + Na].

[ff] P. S. Hynes, P. A. Stupple, D. J. Dixon, *Org. Lett.,* **2008**, *10*, 1389-1391.

PROCEDURE E: CARBONYL AND ESTER GROUPS SIMULTANEOUS REDUCTION
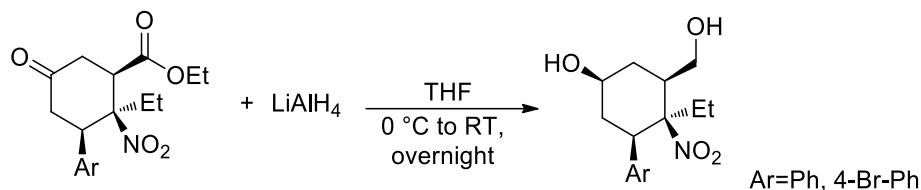
To a stirred suspension of LiAlH₄ (3 eq.) in THF (1 mL each 0.2 mmol of substrate), a solution of compond **3b** (1 eq.) in THF was added at 0 °C. The reaction was stirred at room temperature for 18 hours, after which it was cooled to 0 °C and quenched with water. The solution was extracted with CH_2Cl_2 and the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure.

4-Ethyl-3-(hydroxymethyl)-4-nitro-5-phenylcyclohexanol (12')
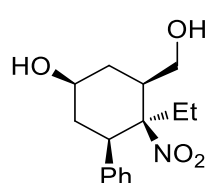
$R_f = 0.08$ (1:1 hexane/AcOEt).

The desired product was obtained as a white solid in 92%; diastereomeric ratio: 10:1.

^{1}H NMR (300 MHz, CDCl₃) δ: 7.32-7.26 (m, 3H), 7.10-7.07 (m, 2H), 3.93-3.83 (m, 1H), 3.77 (dd, J = 10.7, 3.0 Hz, 1H), 3.51 (dd, J = 10.6, 6.2 Hz, 1H), 3.10 (dd, J = 13.2, 3.9 Hz, 1H), 2.57 (dt, J = 12.8, 11.6 Hz, 1H), 2.30-2.18 (m, 3H), 2.10-2.03 (m, 1H), 2.15 (t, J = 7.5 Hz, 1H), 1.85 (sex, J = 7.5 Hz, 1H), 1.09 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl₃) δ: 138.50 (s), 128.71 (s), 128.29 (s), 127.93 (s), 93.11 (s), 69.31 (s), 62.60 (s), 46.13 (s), 41.18 (s), 36.86 (s), 33.73 (s), 24.81 (s), 9.34 (s).

HRMS Mass (ESI+): m/z calc. for: $C_{15}H_{21}N_1O_4Na_1^+ = 302.13628$, found: 302.13623 [M + Na].

3-(4-Bromophenyl)-4-ethyl-5-(hydroxymethyl)-4-nitrocyclohexanol (12'')
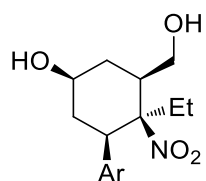
The desired product was purified by flash column chromatography on silica gel using a mixture 95:5 CH_2Cl_2/MeOH as eluent.

The desired product was obtained in 40% yield.

$R_f = 0.13$ (95:5 CH_2Cl_2/MeOH).

^{1}H NMR (300 MHz, CDCl₃) δ: 7.42 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 3.91-3.81 (m, 1H), 3.74 (dd, J = 10.9, 3.0.Hz, 1H), 3.45 (dd, J = 10.9, 6.0 Hz, 1H), 3.07 (dd, J = 13.2, 3.8 Hz, 1H), 2.50 (q, J = 12.8 Hz, 2H), 2.30 – 2.10 (m, 4H), 2.03-1.99 (m, 1H), 1.78 (sex, J = 7.4 Hz, 1H), 1.06 (t, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl₃) δ: 137.13 (s), 131.86 (s), 129.97 (s), 121.95 (s), 93.09 (s), 69.01 (s), 62.16 (s), 45.53 (s), 41.14 (s), 36.62 (s), 33.49 (s), 24.75 (s), 9.27 (s).

HRMS Mass (ESI+) m/z calc. for: $C_{15}H_{20}N_1O_4Br_1Na_1^+$: 380.04679, found: 380.04712 [M + Na].

Synthesis of 6-ethyl-3,7-dihydroxy-5-phenyl-7-azabicyclo[4.2.0]octan-8-one

6-Ethyl-3,7-dihydroxy-5-phenyl-7-azabicyclo[4.2.0]octan-8-one (**10**) was obtained through two different synthetic pathways:
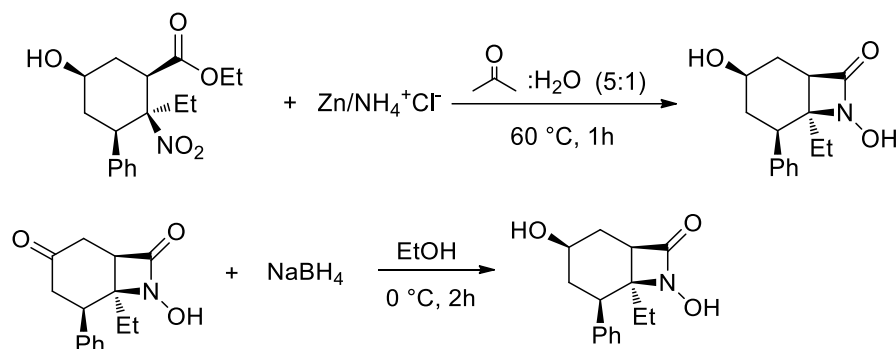
i. nitro-group reduction on ethyl 2-ethyl-5-hydroxy-2-nitro-3-phenylcyclohexanecarboxylate (PROCEDURE C);

ii. carbonyl reduction on 6-ethyl-N-hydroxy-5-phenyl-7-azabicyclo[4.2.0]octane-3,8-dione (PROCEDURE A).
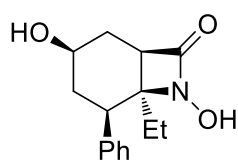
The desired product was purified by flash column chromatography on silica gel using the mixture 98:2 CH_2Cl_2/MeOH as eluent.

The product was isolated as a white solid in 12% yield (pathway i) and 30% yield (pathway ii).

R_f = 0.16 (98:2 CH_2Cl_2/MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.32-7.21 (m, 5H), 3.88-3.79 (m, 1H), 3.00 (dd, J = 12.6, 4.8 Hz, 1H), 2.76 (dd, J = 11.3, 6.8 Hz, 1H), 2.35-2.26 (m, 1H), 2.21-2.10 (m, 1H), 2.09-2.01 (m, 1H), 1.88 (q, J = 12.9 Hz, 1H), 1.65 (sex, J = 7.6 Hz, 1H), 1.56 (bs, 1H), 1.43 (sex, J = 7.1 Hz, 1H), 0.93 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 138.98 (s), 128.83 (s), 128.45 (s), 127.61 (s), 68.07 (s), 65.86 (s), 43.96 (s), 37.62 (s), 32.94 (s), 29.36 (s), 8.50 (s).

HRMS Mass (ESI+) m/z calc. for $C_{15}H_{19}N_1O_3Na_1^+$: 284.12571, found: 284.12575 [M + Na].

Single crystal structural determination of ethyl 3-(4-bromophenyl)-2-ethyl-2-nitro-5-oxocyclohexanecarboxylate
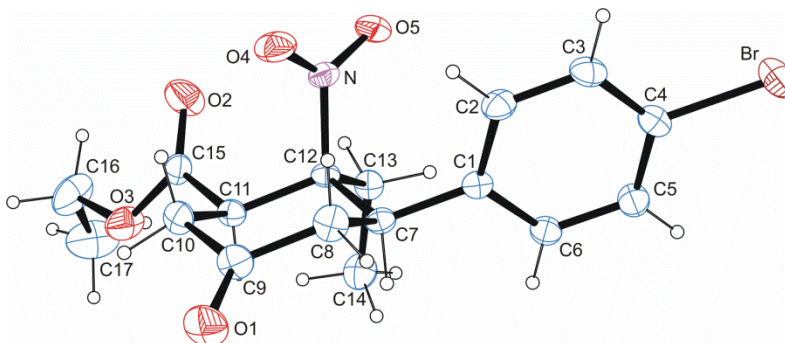
ORTEP plot of the 4-Br phenyl derivative with atom numbering scheme. Displacement ellipsoids at 20% probability level.

Single crystals suitable for X-ray structure determination were obtained by precipitation from diisopropyl ether. The intensity data were collected on a Bruker Smart Apex CCD area detector using graphite-monochromated Mo Ka radiation ($\lambda = 0.71073$ Å). Data reduction was made using SAINT programs; absorption corrections based on multiscan were obtained by SADABS. The structure was solved by SHELXS-97 and refined on F^2 by full-matrix least-squares using SHELXL-97. All the non-hydrogen atoms were refined anisotropically, hydrogen atoms were included as 'riding' and not refined. The isotropic thermal parameters of H atoms were fixed at 1.2 (1.5 for methyl groups) times the equivalent thermal parameter of the atoms to which corresponding H atoms are bonded.

Crystal data and results of the refinement: colourless plate 0.45x0.18x0.05 mm, $M_r = 398.25$, monoclinic, space group P2₁, $a = 10.8855(10)$ Å, $b = 6.5177(6)$ Å, $c = 13.0512(13)$ Å, $\beta = 107.140(1)°$, $V = 884.84(14)$ Å^3, $Z = 2$, $T = 296(2)$ K, $\mu = 2.348$ mm^{-1}. 13092 measured reflections, 3523 independent reflections, 2928 reflections with $I > 2\sigma(I)$, $3.26 < 2\theta < 52.42°$, $R_{int} = 0.0237$. Refinement on 3523 reflections, 219 parameters. Flack parameter for determination of the absolute configuration = -0.015(11). Final $R = 0.0388$, $wR = 0.0886$ for data with $F^2 > 2\sigma(F^2)$, $S = 1.046$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.738$, $\Delta\rho_{min} = -0.434$ eÅ^{-3}. Crystallographic data (excluding structure factors) for the compound have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 965651. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Synthesis of highly decorated chiral 2-nitro-cyclohexane carboxylic esters through microwave-assisted organocatalyzed cascade reactions

Materials

Commercial grade reagents and solvents were used without further purification. Chiral primary amine catalysts I and II were prepared from commercially available quinine and quinidine, following literature procedures.[gg] Substrates were prepared according to literature procedures, as specified below.

[gg] H. Brunner, J. Bügler, B. Nuber, *Tetrahedron: Asymmetry*, **1995**, *6*, 1699-1702.

General procedure for organocatalytic reactions
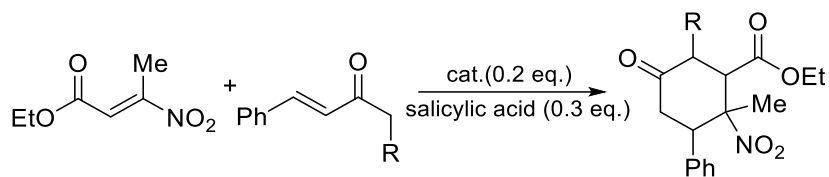
GENERAL PROCEDURE FOR THE "IN FLASK" REACTION

The primary amine catalyst (0.2 eq.) and salicylic acid (0.3 eq.) were dissolved in dry solvent (1M solution) under N_2 atmosphere and stirred at room temperature for 10 minutes. After this period, the α,β-unsaturated ketone (2 eq.) and the nitroacrylate (1 eq.) were added. The reaction mixture was heated to the desired temperature and stirred for the reported time, after which solvent was removed under reduced pressure.

GENERAL PROCEDURE FOR THE MICROWAVE-ASSISTED REACTION

The primary amine catalyst (0.2 eq.) and the salicylic acid (0.3 eq.) were dissolved in dry solvent (0.8 solution) in a vial and stirred at room temperature for 10 minutes. After this period, the α,β-unsaturated ketone and the nitroacrylate were added. The stirred reaction mixture was subjected to constant microwave irradiation, heated to the desired temperature and with the desired power, for the reported time. Solvent was removed under reduced pressure.

PRODUCTS ISOLATION AND CHARACTERIZATION

Cyclohexanone derivatives were isolated by flash column chromatography on silica gel.

The diastereomeric ratio was determined by ^{1}H NMR analysis on the crude mixture and confirmed by the isolated quantities; the enantiomeric ratio was determined by HPLC on chiral stationary phase.

The relative configuration was determined by NMR experiments.

The absolute configuration was assumed to remain unchanged with respect to that of products deriving from (E)-4-phenylbut-3-en-2-one and β-substituted-β-nitroacrilates.[hh]

In the product characterization section and in figures associated to NMR spectra only the major enantiomer obtained with catalyst **B** (9-amino-9-deoxy-*epi*-quinine) is shown.

[hh] E. Massolo, M. Benaglia, R. Annunziata, A. Palmieri, G. Celentano, A. Forni, *Adv. Syn. Catal.* **2014**, *356*, 493-500.

Products characterization

Ethyl 2-methyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (17a)
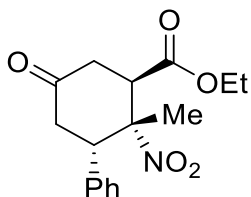
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

R_f = 0.14 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.36-7.33 (m, 3H), 7.12-7.08 (m, 2H), 4.21 (qd, J = 7.1, 1.6 Hz, 2H), 3.87 (dd, J = 9.5, 5.5 Hz, 1H), 3.65 (dd, J = 9.8, 5.2 Hz, 1H), 3.24 (dd, J = 16.7, 9.8 Hz, 1H), 3.09 (dd, J = 17.1, 5.4 Hz, 1H), 2.75 (dd, J = 16.8, 5.2 Hz, 1H), 2.65 (dd, J = 17.1, 9.5 Hz, 1H), 1.83 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 206.03 (s), 170.48 (s), 136.37 (s), 128.91 (s), 128.60 (s), 128.47 (s), 89.97 (s), 61.81 (s), 49.08 (s), 46.44 (s), 42.41 (s), 39.48 (s), 21.26 (s), 13.97 (s).

MS Mass (ESI+) m/z calc. for C$_{16}$H$_{19}$N$_1$O$_5$: 305.13, found: 306.1 [M + H]; 328.1 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (-) enantiomer, obtained with catalyst **B**: t_R 17.19 min (major), t_R 20.29 min (minor); (+) enantiomer, obtained with catalyst **A**: t_R 16.86 min (minor), t_R 19.18 min (major).

$[\alpha]_D^{23}$ = +15.46° (c: 1.52, CHCl$_3$, ee 78% obtained with 9-amino-9-*epi*-quinidine – cat. **A**).

Ethyl 2-methyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (17b)
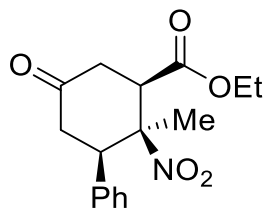
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

Rf = 0.09 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl3) δ: 7.36-7.33 (m, 3H), 7.09-7.06 (m, 2H), 4.28-4.13 (m, 2H), 3.56-3.41 (m, 1H+1H), 3.28-3.15 (m, 1H+1H), 2.82 (ddd, J = 15.6, 5.6, 1.7 Hz, 1H), 2.57 (ddd, J = 15.5, 4.5, 1.8 Hz, 1H), 1.58 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3) δ: 205.92 (s), 169.22 (s), 135.79 (s), 129.02 (s), 128.81 (s), 128.23 (s), 86.80 (s), 61.93 (s), 51.62 (s), 51.37 (s), 43.09 (s), 40.66 (s), 23.29 (s), 13.95 (s).

MS Mass (ESI+) m/z calc. for C$_{16}$H$_{19}$N$_1$O$_5$: 305.13, found: 306.0 [M + H]; 328.2 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralcell ODH column; eluent: 8:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (-) enantiomer, obtained with catalyst **B**: t_R 19.12 min (minor), 34.15 min (major). (+) enantiomer, obtained with catalyst **A**: t_R 18.55 min (major), 34.61 min (minor);

$[\alpha]_D^{23}$ = +10.82° (c: 0.86, CHCl$_3$, ee 93%, obtained with 9-amino-9-*epi*-quinidine – cat. **A**).

Ethyl-2-methyl-2-nitro-5-oxo-3-phenyl-6-propylcyclohexane-1-carboxylate (18a)
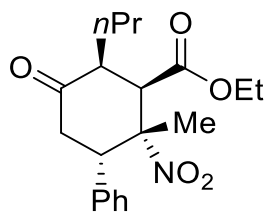
The product was purified by flash column chromatography on silica gel with a 20:1 hexane/ethyl acetate mixture as eluent. The product appears as a yellow oil.

R_f = 0.45 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.34-7.28 (m, 3H), 7.19-7.17 (m, 2H), 4.36-4.19 (m, 2H), 3.92 (dd, J = 13.7, 4.9 Hz, 1H), 3.58-3.46 (m, 1H+1H), 3.26-3.20 (m, 1H) 2.67 (dd, J = 14.7, 5.1 Hz, 1H), 1.98-1.92 (m, 1H), 1.56 (s, 3H), 1.44-1.28 (m, 5H), 1.53-1.05 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 206.44 (s), 170.14 (s), 136.47 (s), 129.14 (s), 128.72 (s), 128.35 (s), 89.85 (s), 73.15 (s), 61.92 (s), 57.12 (s), 48.72 (s), 46.78 (s), 43.43 (s), 28.28 (s), 27.61(s), 23.45 (s), 20.22 (s), 14.20 (s), 14.00 (s).

HRMS Mass (ESI+) m/z calc. for $C_{15}N_1O_5Na_1^+$: 370.16249, found: 370.16284 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack IB column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (+) enantiomer, obtained with catalyst **B**: t_R 12.25 min (major), minor enantiomer not detected; (-) enantiomer, obtained with catalyst **A**: t_R 12.51 min (minor), t_R 13.11 min (major).

$[\alpha]_D^{23}$=+11.84° (*c*: 1.15, CHCl$_3$, ee 98%, obtained with 9-amino-9-*epi*-quinine – cat. **B**).

Ethyl-2-methyl-2-nitro-5-oxo-3-phenyl-6-propylcyclohexane-1-carboxylate (18b)
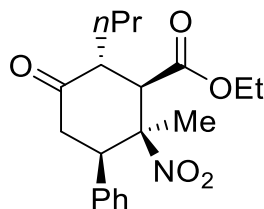
The product was purified by flash column chromatography on silica gel with a 20:1 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

R_f = 0.41 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.37-7.35 (m, 3H), 7.11-7.08 (m, 2H), 4.29-4.18 (m, 2H), 3.743.64 (m, 1H+1H), 3.21 (dd, J = 14.0, 5.0 Hz, 1H), 2.92 (d, J = 12.8 Hz, 1H), 2.60 (dd, J = 15.1, 5.0 Hz, 1H), 1.78-1.65 (m, 2H), 1.51 (s, 3H), 1.41-1.25 (m, 3H),1.29 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 207.44 (s), 168.95 (s), 135.94 (s), 129.11 (s), 128.76 (s), 128.60 (s), 128.24 (s), 88.40 (s), 61.82 (s), 57.90 (s), 52.43 (s), 47.45 (s), 43.81 (s), 29.71 (s), 23.44 (s), 20.17 (s), 14.27 (s).

MS Mass (ESI+) m/z calc. for $C_{19}H_{25}N_1O_5$: 347.41, found: 370.4 [M + Na].

Suitable HPLC conditions for determine the enantiomeric excess have not been found.

$[\alpha]_D^{23}$= -49.87° (*c*: 0.81, CHCl$_3$, ee nd, obtained with 9-amino-9-*epi*-quinine – cat. **B**).

Ethyl-2-methyl-2-nitro-5-oxo-3-phenyl-6-propylcyclohexane-1-carboxylate (19a and 19b)
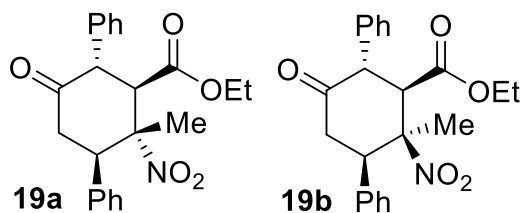
Products were purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. Products mixture appears as a yellow solid.

R_f = 0.19 (8:2 hexane/ethyl acetate).

The two diasteroisomers were not separated, but the different fractions from column chromatography were differently enriched, thus it has been possible to at least partially assign ^{1}H and ^{13}C NMR signal to the MINOR and MAJOR isomer.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.44-7.16 (m, 10H$_{MINOR}$+10H$_{MAJOR}$) 4.88 (d, J = 13.2 Hz, 1H$_{MINOR}$), 4.12 (AB system-part A, J = 12.5 Hz, 1H$_{MAJOR}$), 4.03 (AB system-part B, J = 12.5 Hz, 1H$_{MAJOR}$), 3.90-3.80 (m, 3H$_{MAJOR}$+2H$_{MINOR}$), 3.46-3.39 (m, 2H$_{MINOR}$) 3.40 (d, J = 13.1 Hz, 1H$_{MINOR}$), 3.18 (ABX system-part A, J = 17.6, 7.9 Hz, 2H$_{MAJOR}$), 3.00 (ABX system-part B, J = 17.6, 6.0 Hz, 2H$_{MAJOR}$), 2.78 (ABX system-part A, J = 15.5, 4.9 Hz, 1H$_{MINOR}$), 2.01 (s, 3H$_{MAJOR}$), 1.28 (s, 3H$_{MINOR}$), 0.88 (td, J = 7.1, 2.4 Hz, 3H$_{MINOR}$+3H$_{MAJOR}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.15 (s), 170.22 (s), 136.38 (s), 134.99 (s), 129.40 (s), 128.99 (s), 128.65 (s), 128.51 (s), 127.98 (s), 91.45 (s), 61.27 (s), 56.11 (s), 51.93 (s), 49.40 (s), 41.98 (s), 21.71 (s), 13.55 (s).

MS Mass (ESI+) m/z calc. for C$_{22}$H$_{23}$N$_1$O$_5$: 381.43, found: 404.3 [M + Na].

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose4 column; eluent: 7:3 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; MAJOR diastereoisomer, enantiomer obtained with catalyst **B**: t$_R$ 21.52 min (major), t$_R$ 24.75 min (minor); enantiomer obtained with catalyst **A**: t$_R$ 21.62 min (minor), t$_R$ 23.62 min (major); MINOR diastereoisomer, enantiomer obtained with catalyst **B**: t$_R$ 17.07 min (minor), t$_R$ 18.58 min (major); enantiomer obtained with catalyst **A**: t$_R$ 16.20 min (major), t$_R$ 18.28 min (major).

General procedure for nitroacrylate synthesis

The product was obtained in a three step synthesis based on literature procedures.[ii] Products' analytical data were in agreement with literature ones.

STEP 1
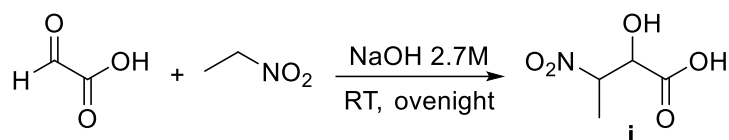
To the commercial solution of glyoxylic acid in H_2O (50% w/w) (1 eq.) 2.7M NaOH (0.7 eq. for each mmol) was added dropwise at room temperature. The solution was stirred for 5 minutes, then the proper nitroalkenes was added and the reaction was stirred at room temperature overnight. The reaction mixture was cooled to 0 °C and treated with H_2SO_4 10% aq. till acid pH was reached; the aqueous layer was extracted with AcOEt (6x) and the combined organic phases dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was used in the subsequent step without further purification.

STEP 2
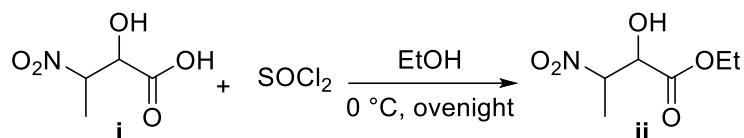
A 1M solution of alcohol **i** in ethanol was prepared and the reaction mixture was cooled to 0 °C. $SOCl_2$ (2 eq.) was added and the mixture was stirred at 0°C overnight. The solvent was removed under reduced pressure to give the desired product, which was used in the subsequent step without further purification.

STEP 3
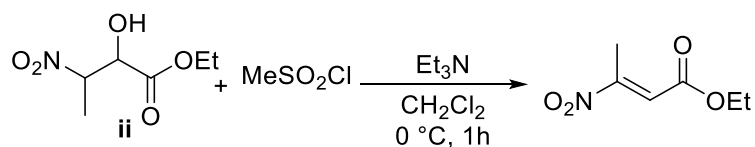
A 1M solution of the β-nitro-α-hydroxylester **ii** (1 eq.) in dry CH_2Cl_2 was cooled to 0 °C under N_2 atmosphere. After adding mesyl chloride (1.5 eq.), triethylamine (3 eq.) was added dropwise (5 mL over 15 minutes). The mixture was stirred for 1 hour, during which the solution turned brown. After this period, H_2O was added and the aqueous phase was extracted with Et_2O. The combined organic phases were treated with an oversaturated solution of $CuSO_4$ (20 mL for 13 mmol of stating material), then washed with an oversaturated solution of $NaHCO_3$ and with brine. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified through flash column chromatography on silica gel using a CH_2Cl_2:Hexane 7:3 mixture as eluent (R_f= 0.5 in hexane:AcOEt 8:2) and isolated in 28% yield over three steps.

[ii] M. Yoshida, E. Masaki, H. Ikehara, S. Hara, *Org. Biomol. Chem.* **2012**, *10*, 5289-5297.

Procedure for enones synthesis

STEP 1[jj]
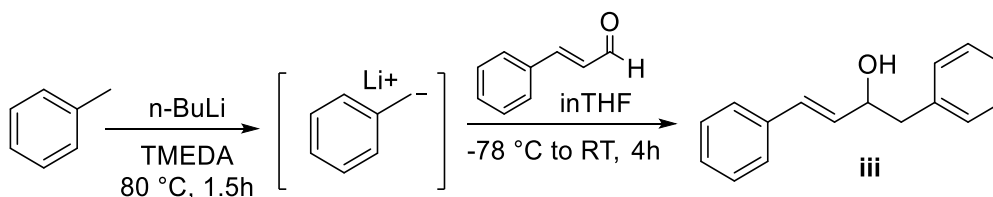
To a solution of TMEDA (1 eq.) in dry toluene (35 mL for 13 mmol of TMEDA), buthyllitium (1 eq.) was added under N_2 atmosphere. The reaction mixture was heated to 80 °C and stirred for 1.5 hours, during which it fast turned to dark red. After this period, the mixture was allowed to reach room temperature and then cooled to -78 °C. A 0.7M solution of cinnamaldehyde in dry THF was added dropwise and the solution assumed a yellow colour. The temperature was then brought to 0 °C and the mixture was stirred for 15 minutes, after which it was allowed to reach room temperature and stirred for further 4 hours. An oversaturated solution of $NaHCO_3$ was then added and extracted with THF. The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil. The product was purified through flash column chromatography on silica gel using an hexane:AcOEt 9:1 mixture as eluent (R_f= 0.30 in hexane:AcOEt 8:2) and isolated in 56% yield.

STEP 2[kk]
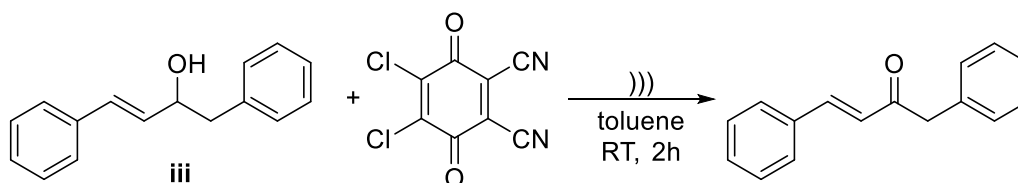
To a 0.5M solution of the allylic alcohol **iii** dry toluene, DDQ was added. The reaction mixture was subjected to ultrasound irradiation for 2 hours, after which it was treated with an oversaturated solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a pink oil. The product was purified through flash column chromatography on silica gel using an hexane:AcOEt 95:5 mixture as eluent (R_f= 0.28 in hexane:AcOEt 9:1) and isolated in 82% yield

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[jj] C. D. Broaddus, *Journal of Organic Chemistry* **1970**, *35*, 10-15.
[kk] K. Peng, F. Chen, X. She, C, Yang, Y. Cui, X. Pan, *Tetrahedron Letters* **2005**, *46*, 1217-1220.

STEP 1[ll]
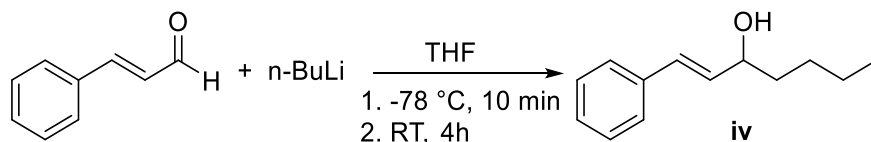
To a 0.3M stirred solution of *n*-BuLi (1.3 eq.) in dry Et$_2$O, a 1M solution of cinnamaldehyde in dry Et$_2$O was added at -78 °C under N$_2$ atmosphere. The reaction mixture was stirred at this temperature for 10 minutes, after which it was allowed to gradually reach room temperature and stirred for further 4 hours. An oversaturated solution of NaHCO$_3$ was added till the solution red colour disappeared. The mixture was diluted with H$_2$O and extracted with Et$_2$O. The combined organic phases were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the product was purified through flash column chromatography on silica gel using an hexane:AcOEt 9:1 mixture as eluent (R$_f$= 0.30 in hexane:AcOEt 9:1) and isolated in 79% yield.

STEP 2[4]

To a 0.5M solution of the allilyc alcohol **iv** dry toluene, DDQ (2 eq.) was added. The reaction mixture was subjected to ultrasound irradiation for 2 hours, after which it was treated with an oversaturated solution of NaHCO$_3$. The aqueous phase was extracted with CH$_2$Cl$_2$ and the combined organic phases were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to give violet solid. The product was purified through flash column chromatography on silica gel using an hexane:AcOEt 8:2 mixture as eluent (R$_f$= 0.50 in hexane:AcOEt 8:2) and isolated in 85% yield. [mm]

[ll] A. B. Smith III, R. Tong, W. Kim, W. A. Maio, *Angew. Chem. Int. Ed.n* **2011**, *50*, 8904-8907.

Organocatalytic Stereoselective addition of activated nucleophiles to β-nitroacrylates

Materials

Commercial grade reagents and solvents were used without further purification. Chiral catalysts A, B, D ,E were prepared following literature procedures.[nn] Catalyst C (quinine) was purchased from Aldrich and used as received. Nitroacrylates were prepared according to literature procedures.[oo]

[nn] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc*., **2003**, *125*, 12672-12673, Y. Takemoto, *Org. Biomol. Chem,* **2005**, *3*, 4299-4321; J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang, C. E. Song, *Chem.Commun*., **2009**, 7224-7226; S. H. McCooey and S. J. Connon, *Angew. Chem. Int. Ed*., 2005, **44**, 6367-6370.

[oo] A. Palmieri, S. Gabrielli, R. Ballini, *Green. Chem*., **2013**, *15*, 2344-2348; M.Yoshida, E. Masaki, H. Ikehara, S. Hara, *Org. Biomol. Chem.*, 2012, **10**, 5289-5297.

General procedure for organocatalytic reactions
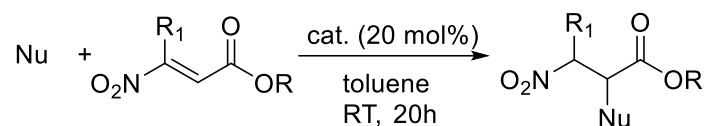
The bifunctional catalyst (0.1 eq.) and the nitroacrylate were dissolved in dry solvent (typically, 0.17 M solution) under N2 atmosphere and stirred for 10 minutes. After this period, the proper nucleophile was added. The reaction mixture was stirred at the desired temperature for the reported time, after which solvent was removed at reduced pressure. Products were isolated by flash column chromatography on silica gel. The diastereomeric ratio was determined by ^{1}H NMR analysis on the crude mixture; the enantiomeric ratio was determined by HPLC on chiral stationary phase.

Tentative assignment of products relative configuration

The organocatalyzed addition of indole to ethyl 3-nitropent-2-enoate was performed obtaining compound **29**, known in literature. Based on analytical datapp, the relative configuration of the two diastereoisomers was assigned to products deriving from the reaction of N-Me-indole with the same nitroacrylate and extended to the products derived from the addition of diketones to nitroacrylates.

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pp T. Arai, A. Awata, M. Wasai, N. Yokoyama, H. Masu, *J. Org. Chem.* **2011**, *76*, 5450-5456.

Products characterization

Ethyl 3-acetyl-3-methyl-2-(1-nitropropyl)-4-oxopentanoate (23a, 23b)
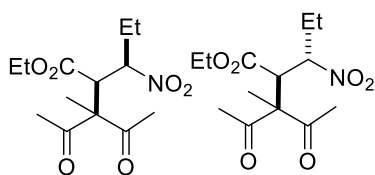
The products were purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The mixture of diastereoisomers appears as an oil.

$R_f = 0.35$ (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.49-4.39 (m, 1H$_{Major}$+1H$_{Minor}$), 4.22-4.11 (m, 2H$_M$+2H$_{Minor}$), 4.08-4.03 (m, 1H$_{Majpr}$ +1 H$_{Minor}$), 2.27- 2.15 (m, 1H$_{Majpr}$ +1H$_{Minor}$), 2.18 (s, 3H$_{Major}$), 2.16 (s, 3H$_{Minor}$), 2.15 (s, 3H-$_{Major}$), 2.10 (s, 1H$_{Minor}$), 2.06-1.92 (m, 1H$_{Major}$ +1H$_{Minor}$), 1.66 (s, 3H$_{Minor}$), 1.63 (s, 3H$_{Major}$), 1.37-1.18 (m, 3H$_{Major}$ +3H$_{Minor}$), 1.01 (t, J = 7.3 Hz, 3H$_{Major}$), 0.92 (t, J = 7.3 Hz, 3H$_{Minor}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 204.90 (s), 169.83 (s), 89.60 (s), 87.03 (s), 68.81 (s), 61.89 (s), 61.71 (s), 51.04 (s), 50.52 (s), 27.80 (s), 26.82 (s), 26.67 (s), 25.06 (s), 14.93 (s), 13.92 (s), 13.82 (s), 10.77 (s).

HRMS Mass (ESI+) m/z calc. for $C_{13}H_{21}N_1O_6Na_1^+$: 310.12611, found: 310.12636 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS-3 column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t_R 8.14 min (minor), t_R 8.99 min (major); minor diastereoisomer: t_R 8.54 min (major), t_R 9.54 min (minor).

Isopropyl 3-acetyl-2-(-1-nitropropyl)-4-oxopentanoate (24a, 24b)

MIXTURE OF DIASTEREOISOMERS

The products were purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The mixture of diastereoisomers appears as an oil.

$R_f = 0.53$ (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.05 (sex, 1H$_{Major}$+1H$_{Minor}$), 4.49 (pent, 1H$_{Major}$), 4.28-4.39 (m, 1H$_{Minor}$), 4.06 (d, J = 4.2 Hz, 1H$_{Major}$+1H$_{Minor}$), 2.28-2.18 (m, 1H$_{Major}$+1H$_{Minor}$), 2.21 (s, 3H$_{Major}$), 2.19 (s, 3H$_{Minor}$), 2.04-1.98 (m, 1H$_{Major}$+1H$_{Minor}$), 1.71 (s, 3H$_{Minor}$), 1.66 (s, 3H$_{Major}$), 1.28-1.26 (m, 6H$_{Major}$+6H$_{Minor}$), 1.04 (t, J = 7.4 Hz, 3H$_{Major}$), 0.92-0.86 (m, 3H$_{Minor}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 205.24 (s), 204.36 (s), 169.42 (s), 89.84 (s), 70.14 (s), 69.11 (s), 50.67 (s), 31.10 (s), 29.87 (s), 27.90 (s), 26.94 (s), 21.74 (s), 15.09 (s), 10.97 (s).

MS Mass (ESI+) m/z calc. for $C_{14}H_{23}NO_6$: 301.34, found: 324.3 [M+Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS-3 column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t_R 6.35 min (minor), t_R 6.99 min (major); minor diastereoisomer: t_R 6.66 min (major), t_R 7.25 min (minor).

Isopentyl 3-acetyl-2-(-1-nitropropyl)-4-oxopentanoate (25a, 25b)
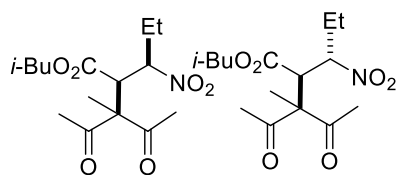
MIXTURE OF DIASTEREOISOMERS

The products was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The mixture of diastereoisomers appears as an oil.

R_f = 0.2 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.54-4.41 (m, 1H$_{Major}$+1H$_{Minor}$), 4.19-4.08 (m, 3H$_{Major}$+3H$_{Minor}$), 2.31-2.18 (m, 1H$_{Major}$+1H$_{Minor}$), 2.23 (s, 3H$_{Major}$), 2.21 (s, 3H$_{Minor}$), 2.19 (s, 3H$_{Major}$), 2.14 (s, 3H$_{Minor}$), 2.09-1.95 (m, 1H$_{Major}$+1H$_{Minor}$), 1.79-1.64 (m, 1H$_{Major}$+1H$_{Minor}$), 1.71 (s, 3H$_{Minor}$), 1.64 (s, 3H$_{Major}$), 1.57-1.50 (m, 1H$_{Major}$+1H$_{Minor}$)1.05 (t, J = 7.4 Hz, 2H$_{Major}$+2H$_{Minor}$), 0.99-0.93 (m, 6H$_{Major}$+6H$_{Minor}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 206.90 (s), 204.89 (s), 204.96 (s), 89.57 (s), 86.87 (s), 77.16 (s), , 77.15 (s), 68.80 (s), 50.53 (s), 51.13 (s), 50.60 (s), 36.73(s), 27.76 (s), 26.76 (s), 25.21 (s), 24.88 (s), 22.13 (s), 22.24 (s), 14.95 (s), 10.74 (s).

MS Mass (ESI+) m/z calc. C$_{16}$H$_{27}$NO$_6$: 329.18 found: 352.2 [M+Na].

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose2 column; eluent: 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t$_R$ 12.69 min (minor), t$_R$ 15.06 min (major); minor diastereoisomer: t$_R$ 14.27 min (major), t$_R$ 17.55 min (minor).

Ethyl 2-(3-methyl-2,4-dioxopentan-3-yl)-3-nitrooctanoate (26a, 26b)
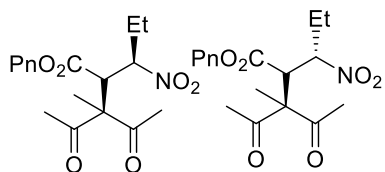
Pn=pentyl
MIXTURE OF DIASTEREOISOMERS

The products was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The mixture of diastereoisomers appears as an oil.

R_f = 0.5 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.58-4.50 (m, 1H$_{Major}$+1H$_{Minor}$), 4.24-4.23 (m, 2H$_{Major}$+2H$_{Minor}$), 4.08 (d, J = 6.8 Hz, 2H$_{Minor}$), 4.03 (d, J = 3.7 Hz, 2H$_{Major}$), 2.22-2.18 (m, 1H$_{Major}$+1H$_{Minor}$), 2.19 (s, 3H$_{Major}$), 2.18 (s, 3H$_{Minor}$), 2.16 (s, 3H$_{Major}$), 2.11 (s, 3H$_{Minor}$), 1.95-1.95 (m, 1H$_{Major}$+1H$_{Minor}$), 1.67 (s, 3H$_{Minor}$), 1.64 (s, 3H$_{Major}$), 0.89 (m, 3H$_{Minor}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 169.83 (s), 88.14 (s), 85.56 (s), 61.85 (s), 61.67 (s), 51.13 (s), 50.78 (s), 34.36 (s), 31.43 (s), 30.87 (s), 29.66 (s), 26.77 (s), 25.73 (s), 22.23 (s), 14.90 (s), 13.80 (s).

MS Mass (ESI+) m/z calc. C$_{16}$H$_{27}$NO$_6$: 329.18 found: 352.2 [M+Na].

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose-2 column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t$_R$ 7.55 min (minor), t$_R$ 8.45 min (major); minor diastereoisomer: t$_R$ 7.89 min (major), t$_R$ 8.08 min (minor).

Benzyl 3-acetyl-3-methyl-2-(-1-nitropropyl)-4-oxopentanoate (27a, 27b)
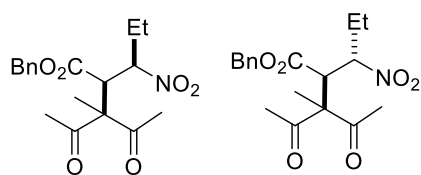
MIXTURE OF DIASTEREOISOMERS

The products were purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The mixture of diastereoisomers appears as an oil.

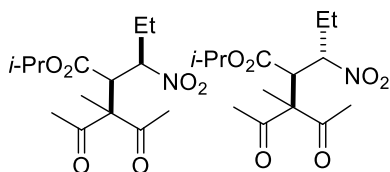R_f = 0.30 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.36-7.13 (m, 5H$_{Major}$+5H$_{Minor}$), 4.61 (pent, J = 3.75, 1H$_{Major}$), 4.58-4.48 (m, 1H$_{Minor}$), 4.27-4.67 (m, 2H$_{Major}$+2H$_{Minor}$ +1H$_{Minor}$), 4.09 (d, J = 2.8 Hz, 7H), 2.82-2.66 (m, 3H), 2.61-2.49 (m, 2H), 2.42-2.25 (m, 2H), 2.21 (s, 3H$_{Major}$), 2.17 (s, 3H$_{Minor}$), 2.16 (s, 3H$_{Major}$+3H$_{Minor}$), 1.95-1.82 (m, 1H$_{Minor}$), 1.62 (s, 3H$_{Minor}$), 1.59 (s, 3H$_{Major}$), 1.28 (m, 3H$_{Major}$+3H$_{Minor}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 204.80 (s), 204.53 (s), 204.39 (s), 204.05 (s), 169.71 (s), 169. 46 (s), 139.28 (s), 139.28 (s), 128.69 (s), 128.46 (s), 126.58 (s), 87.22 (s), 84.52 (s), 69.07 (s), 68.83 (s), 61.96 (s), 61.79 (s), 51.00 (s), 50.80 (s), 36.06 (s), 33.04 (s), 32.37 (s), 29.69 (s), 26.85 (s), 26.58 (s), 26.46 (s), 14.83 (s), 13.86 (s).

MS Mass (ESI+) m/z calc. for C$_{19}$H$_{25}$NO$_6$: 363.40, found: 386.4 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS-3 column; eluent: 9:1 Hex/IPA; flow rate: 0.5 mL/min; detection: 210 nm; major diastereoisomer: t_R 15.79 min (minor), t_R 17.58 min (major); minor diastereoisomer: t_R 16.79 min (major), t_R 18.78 min (minor).

Ethyl 3-acetyl-2-(1-nitropropyl)-4-oxopentanoate (21)
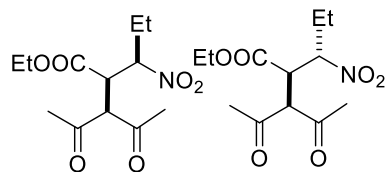
MIXTURE OF DIASTEREOISOMERS

The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as an oil. Products analytical data are in agreement with those reported in literature.[qq]

Benzyl 3-acetyl-2-(nitromethyl)-4-oxopentanoate (28)
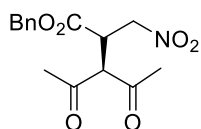
The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as an oil.

R_f = 0.17 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.36 (m, 5H), 5.17 (s, 3H), 4.77 (s, 3H), 4.43 (d, J = 7.8 Hz, 1H), 3.94-3.88 (m, 1H), 2.37 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 200.94 (s), 169.57 (s), 128.73 (s), 73.20 (s), 68.17 (s), 65.20 (s), 42.34 (s), 30.71 (s).

MS Mass (ESI+) m/z calc. for C$_{15}$H$_{17}$NO$_6$: 307.30, found: 330.3 [M+Na].

The enantiomeric excess was determined by HPLC with Phenomenex Lux-3u Cellulose2 column; eluent: 7:3 Hex/IPA; flow rate: 0.8 mL/min; detection: 220 nm; t_R 15.19 min (major), t_R 25.81 min (minor).

[qq] R. Ballini, G.Bosica, A. Palmieri, K. Bakhtiari, *Synlett*, **2009**, *2*, 268-270.

Ethyl 2-(1H-indol-3-yl)-3-nitropentanoate (29a, 29b)

The products were purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

Minor diastereoisomer 29a
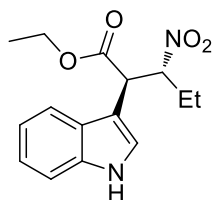
The product appears as a white solid.

R_f = 0.27 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.15 (bs, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.26 – 7.09 (m, 3H), 5.25-5.10 (dt, J = 10.3, 6.7 Hz, 1H), 4..43-4.04 (m, 2H), 2.20-1.98 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.06 (s, 3H).

Major diastereoisomer 29b
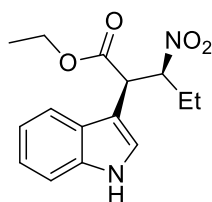
The product appears as a white solid.

R_f = 0.20 (8:2 hexane/ethyl acetate).

1H NMR (300 MHz, CDCl3) δ: 8.29 (bs, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.27-7.15 (m, 3H), 5.24 (ddd, *J* = 12.1, 8.4, 4.0 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.23-4.00 (m, 2H), 1.84-1.65 (m, 2H), 1.15 (d, J = 7.1 Hz, 2H), 0.85 (d, J = 7.4 Hz, 2H).

Ethyl 2-(1-methyl-indol-3-yl)-3-nitropentanoate (30a, 30b)

The products were purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

Minor diastereoisomer 30a
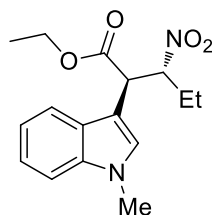
The product appears as a white solid.

mp: 97.3-100.5 °C

R_f = 0.37 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.69 (d, J = 7.9 Hz, 1H), 7.34-7.24 (m, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.06 (s, 1H), 5.25-5.17 (m, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.25-4.13 (m, 1H), 4.04-3.98 (m, 1H), 3.78 (s, 3H), 1.88-1.63 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 171.33 (s), 137.13 (s), 127.97 (s), 126.61 (s), 122.39 (s), 119.98 (s), 119.12 (s), 109.70 (s), 106.54 (s), 89.37 (s), 61.55 (s), 45.63 (s), 32.92 (s), 25.02 (s), 13.95 (s), 9.51 (s).

MS Mass (ESI+) m/z calc. for C$_{16}$H$_{20}$N$_2$O$_4$: 304.14, found 327.3 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralcel OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t_R 10.51 min (minor), t_R 16.23 min (major).

Major diastereoisomer 30b
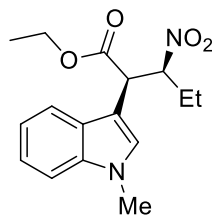
The product appears as a white solid.

mp: 113.6-114.5 °C

R_f = 0.45 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.71 (d, J = 7.9 Hz, 1H), 7.30-7.09 (m, 3H), 7.07 (s, 1H), 5.18 (td, J = 10.3, 3.6 Hz, 1H), 4.42 (d, J = 10.6 Hz, 1H), 4.26-4.15 (m, 1H), 4.14-4.04 (m, 1H), 3.73 (s, 3H), 2.21-1.90 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.65 (s), 136.89 (s), 127.96 (s), 126.56 (s), 122.10 (s), 119.75 (s), 119.09 (s), 109.47 (s), 106.73 (s), 91.52 (s), 61.59 (s), 47.01 (s), 32.86 (s), 26.18 (s), 14.04 (s), 10.44 (s).

MS Mass (ESI+) m/z calc. for C$_{16}$H$_{20}$N$_2$O$_4$: 304.14, found 327.3 [M + Na].

The enantiomeric excess was determined by HPLC with Daicel Chiralcel OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t_R 8.04 min, t_R 9.95 min.

Procedure for pyrazole synthesisrr and product characterization
Ethyl 2-(3,5-dimethyl-1H-pyrazol-4-yl)-3-nitropentanoate (22a, 22b)

MIXTURE OF DIASTEREOISOMERS

MIXTURE OF DIASTEREOISOMERS
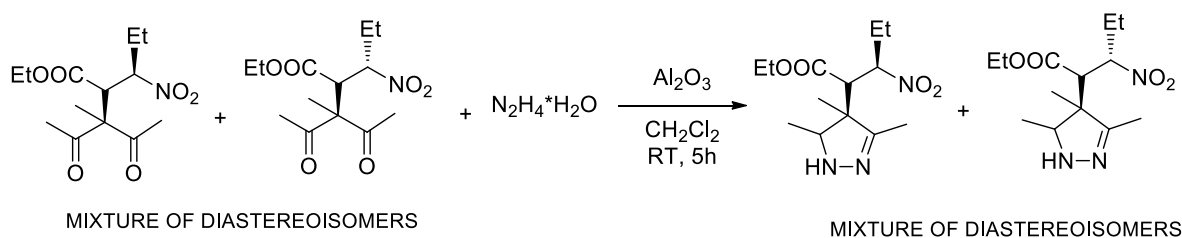
To a stirred solution of ethyl 3-acetyl-2-(1-nitropropyl)-4-oxopentanoate (mixture of diastereoisomers) (0.344 mmol, 1 eq.) in dry CH_2Cl_2 (300 μl), Al_2O_3 (Brockmann II-III) (0.2 eq.) was added at room temperature. hydrazine monohydrate (1 eq.) was added to the suspension. The reaction was stirred at room temperature for 2.5 hours, after which hydrazine monohydrate (0.5 eq.) was added again and stirred for 2.5 hours at room temperatue. The reactin mixture was treated with H2O and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.

The products were purified by flash column chromatography on silica gel with a 95:5 CH_2Cl_2/MeOH mixture as eluent. The mixture of diastereoisomers appears as a deliquescent yellow solid.

R_f = 0.21 (7:3 hexane/CH_2Cl_2).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.13 (m, 1H$_{Major}$+1H$_{Minor}$), 4.23 (d, J = 11.3 Hz, 1H$_{Major}$+1H$_{Minor}$), 4.19-3.96 (m, 2H$_{Major}$+2H$_{Minor}$), 2.30 (s, 6H$_{Major}$+6H$_{Minor}$), 1.86-1.76 (m, 1H$_{Major}$+1H$_{Minor}$), 1.70-1.63 (m, 1H$_{Major}$+1H$_{Minor}$), 1.36-1.26 (m, 3H$_{Minor}$), 1.20 (t, J = 7.1 Hz, 3H$_{Major}$), 1.09-0.95 (m, 3H$_{Minor}$), 0.90 (t, J = 7.4 Hz, 3H$_{Major}$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.47 (s), 143.09 (s), 108.01 (s), 87.49 (s), 61.57 (s), 43.64 (s), 24.73 (s), 13.95 (s), 11.37 (s), 9.45 (s).

HRMS Mass (ESI+) m/z calc. for $C_{12}H_{18}N_3O_4^-$: 268.13028, found: 268.13035 [M -H].

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Amylose-2 column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; major diastereoisomer: t_R 10.04 min (minor), t_R 12.3 min (major); minor diastereoisomer: t_R 8.58 min (minor), t_R 8.86 min (major).

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rr F. Texier-Boullet, B. Klein, J. Hamelin, *Synthesis*, **1986**, 409-411.

Stereoselective reaction of 2-carboxythioesters-1,3-dithiane with nitroalkenes: an organocatalytic strategy for the asymmetric addition of a glyoxylate anion equivalent

General procedure for organocatalytic reactions
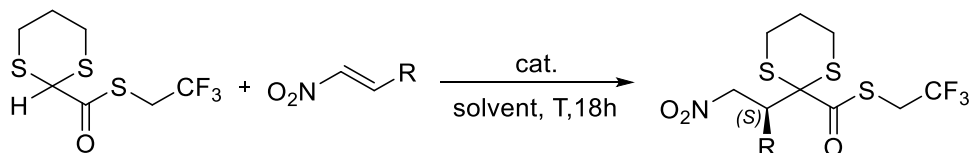
The proper nitrostyrene derivative (0.076 mmol), dithianilthioester (0.152 mmol) and the catalyst (0.0152 mmol, 0.2 eq.) were dissolved in the proper dry solvent - typically, toluene - (1 mL). The reaction mixture was stirred at the desired temperature for 18 hours after which the solvent was removed at reduced pressure. Products were isolated by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). The enantiomeric ratio was determined by HPLC on chiral stationary phase, terms "major" and "minor" being referred respectively to the majority and the minority enantiomer obtained with quinine-derived catalysts, characterized by (*S*) configuration at C9, and with catalysts derived from (*S*,*S*)-diaminocyclohexane. The absolute configuration was determined through chemical correlation.

Characterization of Michael addition products

2,2,2-trifluoroethyl 4-nitro-3-phenyl-2-[(1,3-dithian)2-yl]-butanethioate (31)
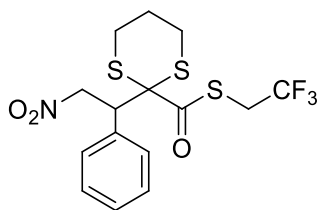
Rf = 0.37 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.30 (s, 5H), 5.26 (AB system-part A, J = 13.7, 3.7 Hz, 1H), 5.08 (AB system-part B, J = 13.7, 10.9 Hz,1H), 4.17 (dd, J = 10.9, 3.6 Hz, 1H), 3.51-3.32 (m, 2H), 2.97-2.85 (m, 2H), 2.81-2.77 (m, 2H), δ 2.11-2.028 (m, 1H), 1.93-1.80 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -65.99 (t, J = 9.2 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 195.99 (s), 132.29 (s), 129.58 (s), 128.59 (s), 127.97 (s), 124.20 (q, J = 274.6 Hz), 76.96 (s), 66.72 (s), 51.87 (s), 32.85 (q, J = 33.3 Hz), 28.04 (s), 27.54 (s), 22.53 (s).

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose2 column; eluent: 95:5 Hexane/2-Propanol; flow rate: 0.8 mL/min; detection: 210 nm; t$_R$ 8.33 min (major), t$_R$ 9.05 min (minor).

HRMS Mass (ESI+) m/z calc. for C$_{19}$H$_{19}$N$_1$O$_3$S$_3$F$_3$Na$_1^+$: 428.04193, found: 428.04193 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(trifluoromethyl)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (35)

Rf = 0.43 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.56 (AB system-part A, J = 8.2 Hz, 2H), 7.44 (AB system-part B, J = 8.2 Hz, 2H), 5.26 (AB system-part A, J = 14.0, 3.5 Hz, 1H), 5.05 (AB system-part B, J = 11.0, 3.7 Hz, 1H), 4.22 (dd, J = 11.0, 3.7 Hz, 1H), 3.54-3.35 (m, 2H), 2.99-2.87 (m, 2H), 2.84-2.77 (m, 2H), 2.12-2.04 (m, 1H), 1.95-1.79 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -63.35 (s), -66.11 (t, J = 9.7 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 195.79 (s), 136.40 (s), 131.00 (s), 129.57 (s), 124.93 (s), 124.04 (q, J = 273.5 Hz), 123.33(q, J = 289.11), 121.40 (s), 76.46 (s), 66.25 (s), 51.45 (s), 32.81 (q, J = 33.6 Hz), 27.96 (s), 27.53 (s), 22.40 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t$_R$: 9.02 min (major), t$_R$: 10.52 min (minor).

$[\alpha]_D^{23}$ = (c 0.174, CHCl$_3$, e.e. 53%).

HRMS Mass (ESI+) m/z calc. for C$_{16}$H$_{15}$N$_1$O$_3$S$_3$F$_6$Na$_1^+$: 502.00105, found: 502.00189 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(chloro)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (36)
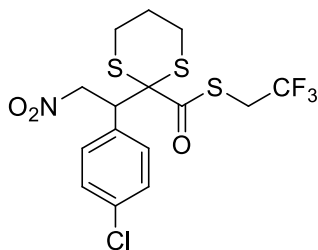
Rf = 0.47 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.28 (m, 4H), 5.23 (AB system-part A, J = 13.8, 3.6 Hz, 1H), 5.02 (AB system-part B, J = 13.8, 11.1 Hz, 1H), 4.15 (dd, J = 11.0, 3.5 Hz, 1H), 3.57-3.41 (m, 2H), 3.05-2.88 (m, 2H), 2.86-2.78 (m, 2H), 2.14-2.06 (m, 1H), 1.96-1.81 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -66.06 (t).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 196.39 (s), 135.25 (s), 131.31 (s), 130.91 (s), 128.76 (s), 124.65 (q, J = 274.5 Hz), 77.22 (s), 66.97 (s), 51.72 (s), 33.41 (q, j = 33.8 Hz), 28.53 (s), 28.04 (s), 22.98 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 11.27 min (major), t_R: 12.60 min (minor).

$[\alpha]_D^{23}$ = + 8.726 (c 0.324, CHCl$_3$, e.e. 69%).

HRMS Mass (ESI+) m/z calc. for C$_{15}$H$_{15}$N$_1$O$_3$S$_3$F$_3$Na$_1^+$: 467.97, found: 467.97582 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[4-(methyl)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (37)
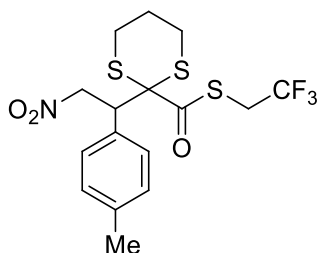
Rf = 0.42 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.17 (AB system-part A, J = 8.0 Hz, 2H), 7.09 (AB system-part B, J = 8.1 Hz, 2H), 5.20 (AB system-part A, J = 13.6, 3.7 Hz, 1H), 5.03 (AB system-part B, J = 13.5, 10.9 Hz, 1H), 4.12 (dd, J = 10.9, 3.6 Hz, 1H), 3.51-3.38 (m, 2H), 2.97-2.85 (m, 2H), 2.82-2.79 (m, 2H), 2.30 (s, 3H), 2.01-2.08 (m, 1H), 1.93-1.82 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -65.98 (t, J = 8.8 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 196.49 (s), 139.02 (s), 129.61 (s), 129.38 (s), 129.23 (s), 124.73 (q, J = 274.6 Hz), 76.75 (s), 67.40 (s), 52.04 (s), 33.49 (q, J = 33.7 Hz), 28.60 (s), 28.07 (s), 23.11 (s), 21.12 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.24 min (major), t_R: 10.42 min (minor).

$[\alpha]_D^{23}$ = + 5.566 (c 0.1796, CHCl$_3$, e.e. 73%).

HRMS Mass (ESI+) m/z calc. for C$_{16}$H$_{18}$N$_1$O$_3$S$_3$F$_3$Na$_1^+$ 448.02931, found: 448.03026 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[2-(methyl)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (**38**)
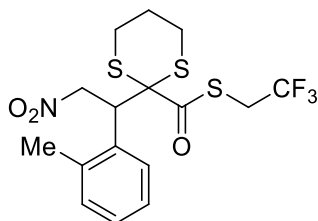
Rf = 0.39 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.48-7.45 (m, 1H), 7.23-7.16 (m, 3H), 5.11 (AB system-part A, J = 13.5, 3.5 Hz, 1H), 4.97 (AB system-part B, J = 12.2 Hz, 1H), 4.59 (dd, J = 10.8, 3.2 Hz, 1H), 3.63-3.40 (m, 2H), 3.03-2.88 (m, 2H), 2.83-2.76 (m, 2H), 2.46 (s, 3H), δ 2.11-2.06 (m, 1H), 1.97-1.84 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -66.25 (t, J = 9.0 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 197.34 (s), 138.62 (s), 131.90 (s), 131.04 (s), 128.79 (s), 127.75 (s), 126.52 (s), 126.18 (s), 124.69 (q, J = 274.5 Hz), 77.26 (s), 67.77 (s), 46.44 (s), 33.64 (q, J = 33.0 Hz), δ 28.46 (s), 23.02 (s), 20.14 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 8.89 min (major), t_R: 10.20 min (minor)

$[\alpha]_D^{23} = -9.793$ (c 0.22, CHCl$_3$, e.e. 67%).

HRMS Mass (ESI+) m/z calc. for C$_{16}$H$_{18}$N$_1$O$_3$S$_3$F$_3$Na$_1^+$ 448.02931, found: 448.03034 [M + Na].

(*E*)-2,2,2-trifluoroethyl 3-nitromethyl-2-[(1,3-dithian)-2-yl]-5-phenyl-pent-4-en-thioate (**39**)
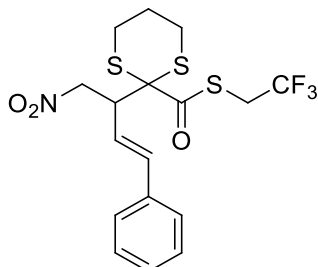
Rf = 0.31 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.34-7.28 (m, 5H), 6.55 (d, J = 15.6 Hz, 1H), 6.09 (dd, J = 15.6, 9.8 Hz, 1H), 4.98 (AB system-part A, J = 12.8 Hz, 1H), 4.63 (AB system-part B, J = 11.8 Hz, 1H), 3.73-3.55 (m, 3H), 3.02-2.92 (m, 2H), 2.85-2.81 (m, 2H), 2.13-2.10 (m, 1H), 1.95-1.86 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -66.31 (t, J = 9.1 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 195.59 (s), 137.05 (s), 135.08 (s), 128.05 (s), 127.94 (s), 126.33 (s), 124.18 (q, J = 274.4 Hz), 119.93 (s), 76.05 (s), 66.19 (s), 50.05 (s), 32.77 (q, J = 33.6 Hz), 27.82 (s), 27.52 (s), 22.88 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 9.52 min (major), t_R: 11.45 min (minor).

$[\alpha]_D^{23} = +50.55$ (c 0.182, CHCl$_3$, e.e. 71%).

HRMS Mass (ESI+) m/z calc. for C$_{17}$H$_{18}$N$_1$O$_3$S$_3$ F$_3$Na$_1^+$: 460.02931, found: 460.03053.

2,2,2-trifluoroethyl 4-nitro-3-[2-(acetoxy)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (40)
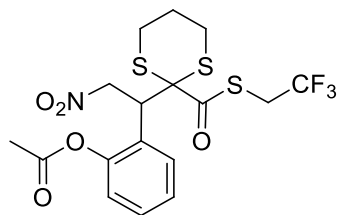
Rf = 0.31 (7:3 hexane:ethyl acetate)

1H-NMR (300 MHz, CDCl$_3$) δ: 7.57 (dd, J = 7.7, 1.1 Hz, 1H), 7.34 (td, J = 7.8, 1.6 Hz 1H), 7.24-7.22 (m, 1H), 7.16 (d, J = 8.1 Hz, 1H), 5.15 (AB system-part A, J = 13.8, 3.8 Hz, 1H), 4.94 (AB system-part B, J = 13.8, 10.3 Hz, 1H), 4.71 (dd, J = 10.1, 3.8 Hz, 1H), 3.37-3.31 (m, 2H), 2.97-2.87 (m, 2H), 2.81-2.73 (m, 2H), 2.38 (s, 3H), 2.09-2.01 (m, 1H), 1.93-1.81 (m, 1H).
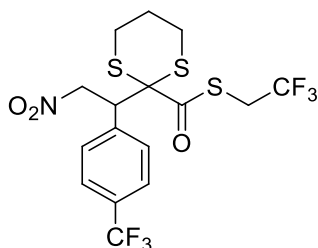
^{19}F-NMR (300 MHz, CDCl$_3$) δ: -66.30 (t).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 196.69, 170.17, 151.34, 131.33, 129.49, 128.12, 127.50, 126.16, 120.36, 76.74, 67.24, 51.60, 32.57 (q), 28.75, 28.11, 23.12, 20.89.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 18.55 min (minor), t_R: 21.15 min (major)

$[\alpha]_D^{23}$ = - 14.82 (c 0.244, CHCl$_3$, e.e. 85%).

2,2,2-trifluoroethyl 4-nitro-3-[4-(methoxy)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (41)
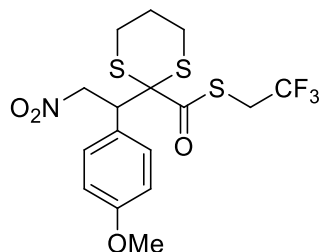
Rf = 0.31 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.21 (AB system-part A, J = 8.0 Hz, 2H), 6.80 (AB system-part B, J = 8.1 Hz, 2H), 5.18 (AB system-part A, J = 13.1 Hz, 1H), 5.00 (AB system-part B, J = 12.1 Hz, 1H), 4.09 (d, J = 10.8 Hz, 1H), 3.76 (s, 3H), 3.50-3.38 (m, 2H), 2.96-2.86 (m, 2H), 2.80-2.76 (m, 2H), 2.09-2.04 (m, 1H), 1.92-1.80 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -65.98 (t, J = 9.6 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 195.55 (s), 160.04 (s), 130.71 (s), 124.49 (s), 124.73 (q, J = 274.4 Hz), 113.88 (s), 76.86 (s), 67.45 (s), 55.17 (s), 51.77 (s), 33.43 (q, J = 33.5 Hz), 28.59 (s), 28.07 (s), 23.11 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 9:1 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 13.69 min (major), t_R: 15.78 min (minor).

$[\alpha]_D^{23}$ = + 3.062 (c 0.288, CHCl$_3$, e.e. 73%). HRMS Mass (ESI+) m/z calc. for $C_{16}H_{18}N_1O_4S_3F_3Na_1^+$ 464.02423, found: 464.02536 [M + Na].

2,2,2-trifluoroethyl 4-nitro-3-[2-(methoxy)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (42)
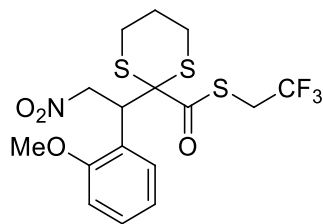
Rf = 0.41 (7:3 hexane:ethyl acetate)

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.37-7.34 (m, 1H), 7.29 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.21 (AB system-part A, J = 13.4, 3.9 Hz, 1H), 5.10 (AB system-part B, 1H), 4.80-4.78 (m, 1H), 3.81 (s, 3H), 3.47 (q, J = 10.0 Hz, 2H), 3.00-2.77 (m, 4H), 2.09-2.03 (m, 1H), 1.92-1.83 (m, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$) δ: -66.09 (t, J = 8.8 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 196.55 (s), 157.95 (s), 130.20 (s), 124.79 (q, J = 274.6 Hz), 121.75 (s), 120.47 (s), 111.27 (s), 76.33 (s), 67.84 (s), 55.53 (s), 33.60 (q, J = 33.0 Hz), 28.75 (s), 28.11 (s), 23.12 (s).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS-3 column; eluent: 9:1 Hex/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t_R: 30.78 min (minor), t_R: 34.22 min (major)

$[\alpha]_D^{23}$ = - 11.80 (c 0.122, CHCl$_3$, e.e. 71%).

HRMS Mass (ESI+) m/z calc. for C$_{16}$H$_{18}$N$_{1}$O$_4$S$_3$F$_3$Na$_1$$^+$: 464.02423, found: 464.02526 [M + Na].

Baclofen synthesis
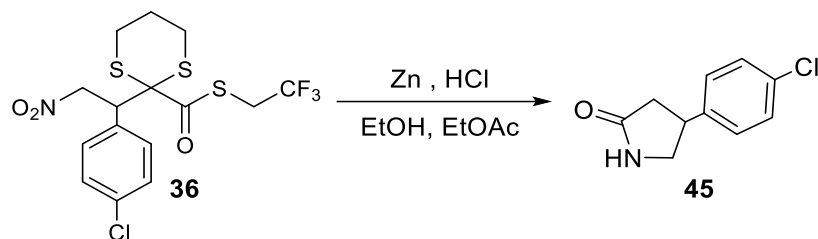
Compound **36** (1.34 mmol) was dissolved in ethanol and 53.8 mL) and ethyl acetate (40 mL); the solution was cooled to 0 °C and stirred for 10 minutes, after which 6M HCl (11.6 mL) was added. The solution was vigorously stirred while powder zinc (66.8 mmol) was added in three portions over 10 min. The reaction mixture was stirred at room temperature for 2 hours; after this period powder zinc (33.4 mmol) was added in one portion and the resultant grey suspension was stirred at room temperature for a further 1 hour. The organic solvent was removed under vacuum and the aqueous solution was quenched with an oversaturated solution of NaHCO$_3$. The aqueous layer was washed five times with ethyl acetate. The combined organic phases were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Purification through flash column chromatography on silica gel (98:2 CH$_2$Cl$_2$:MeOH) afforded the desired product **45** as a white solid (0.926 mmol, 69% yield).

Rf = 0.38 (94:6 CH$_2$Cl$_2$:MeOH)

^{1}H-NMR (300 MHz, CDCl$_3$):δ: 7.34 (AB system-part A, J = 8.3 Hz, 2H), 7.17 (AB system-part B, J = 8.2 Hz, 2H), 3.74 (t, 1H), 3.65 (m, 1H), 3.38 (t, 1H), 2.75 (AB system-part A, 1H), 2.43 (AB system-part B, 1H).

^{19}F-NMR (300 MHz, CDCl$_3$): no signal

^{13}C-NMR (75 MHz, CDCl$_3$) δ: 177.90, 140.69, 129.24, 128.98, 128.12, 49.55, 39.59, 38.01.

$[\alpha]_D^{23}$ = + 18.35 (c 0.306, CHCl$_3$).

MS Mass (ESI+) m/z calc. for C$_{10}$H$_{10}$Cl$_1$N$_1$O$_1$Na$_1^+$ 218.23, experimental 218.10.
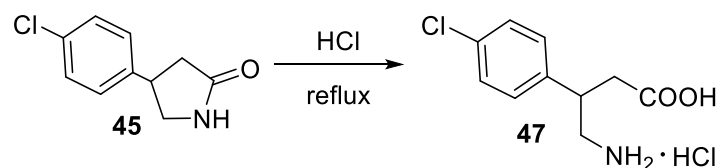
A solution of product **45** (1.34 mmol) in 6M HCl (3.3 mL) was refluxed for 18 hours. After this period the solvent was removed under reduced pressure and baclofen hydrochloridric salt **47** was isolated as a white solid (0.48 mmol, 73% yield).

^{1}H-NMR (300 MHz, CD$_3$OD) δ: 7.35 (m, 4H), 3.32 (m, 2H), 3.18 (m, 1H), 2.80 (AB system-part A, 1H), 2.67 (AB system-part B, 1H).

^{13}C-NMR (75 MHz, CD$_3$OD) δ: 173.95, 138.63, 134.25,δ 130.20, 129.80,44.36,40.57, 38.74.

HMRS Mass (FAB +) m/z calc. for: C$_{10}$H$_{13}$Cl$_2$N0$_2^+$: 214.06, found: 214.0637.

Determination of the absolute configuration

The sense of enantioselection the stereoselective organocatalyzed conjugate addition reaction was determined through chemical correlation.

45   **36**
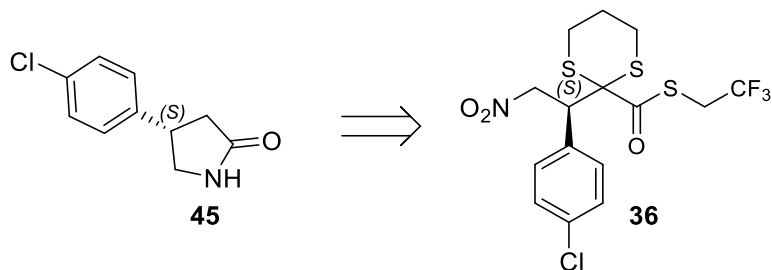
2,2,2-trifluoroethyl 4-nitro-3-[4-(chloro)phenyl]-2-[(1,3-dithian)-2-yl]-butanethioate (compound **11**), obtained with quinine-derived catalyst A, was transformed into the known compound **18** (direct precursor of baclofen, compound **19**) through one-pot nitro group reduction and lactonization and simultaneous loss of the dithiane moiety.

Optical rotation of the product was measured ($[\alpha]_D^{23} = + 18.35$, c 0.306, CHCl$_3$) and compared with literature data ($[\alpha]_D^{23} = +21.8$, c 0.5, CH$_2$Cl$_2$).[ss]

Compound **18** - and, as a consequence, compound **36** - was assigned (*S*)-configuration.

[ss] K. L. Jensen, P. H. Poulsen, B. S. Donslund, F. Morana, K. A. Jørgensen, *Org. Lett*., **2012**, *14*, 1516-1519.

General procedure for the synthesis of β-aryl-α-ketothioesters and of the corresponding β-nitro-α-aryl-esters

STEP 1[tt]
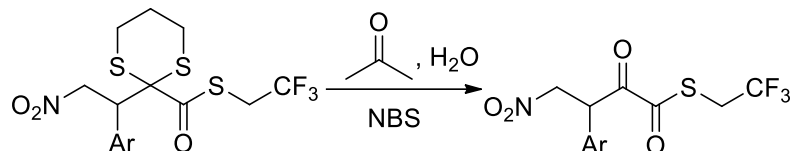
To a stirred solution of *N*-bromosucinimide (10 eq.) in aqueous 97% acetone (1.85 mL for 1 mmol of NBS) at 0 °C a solution of the proper 2,2,2-trifluoroethyl 4-nitro-3-aryl-2-[(1,3-dithian)2-yl]-butanethioate (1 eq.) in acetone (4 mL for 1 mmol of carboxythioester) was added dropwise. The solution turned yellow to limpid orange and after some minutes faded to pale yellow. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. After this period, the reaction mixture was treated with an oversatured aqueous solution of Na_2SO_3 and extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Products were used in the subsequent step without further purification.

STEP 2[uu]
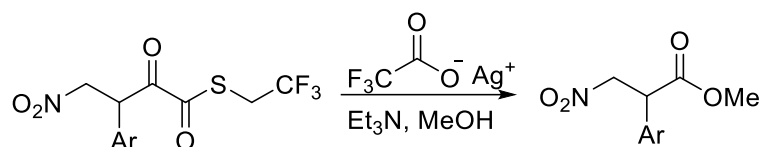
To a stirred solution in dry methanol (0.1 mL for 0.057 mmol of substrate), of the β-nitro-α-ketothioester (1 eq.), obtained in the previous step, CF_3CO_2Ag (1.2 eq.) and triethylamine (1 eq.) were added at room temperature. A yellow precipitate was formed. After ten minutes, water was added and the crude reaction product was extracted three times with ethyl acetate The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.

[tt] E. J. Corey, B. W. Erickson, *J. Org. Chem.*, **1971**, *36*, 3553-3560.
[uu] I. Shina, Y. Fukuda, T. Ishii, H. Fujisawa, T. Mukaiyama, *Chem. Lett.*, **1998**, 831-832.

Characterization of β-aryl-α-ketothioesters and of the corresponding β-nitro-α–aryl-esters

2,2,2-trifluoroethyl 4-nitro-3-phenyl-2-oxo-butanethioate (48)
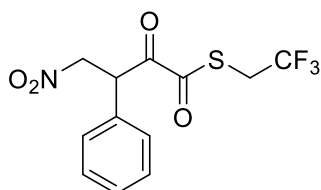
Rf = 0.53 (8:2 hexane:ethyl acetate))

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.42-7.39 (m, 3H), 7.27-7.24 (m, 2H), 5.36 (dd, J = 10.3, 4.4 Hz, 1H), 5.23 (dd, J = 14.8, 10.3 Hz, 1H), 4.68 (dd, J = 14.8, 4.4 Hz, 1H), 3.60 (q, J = 9.6 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 188.71 (s), 186.04 (s), 133.00 (s), 129.33 (s), 128.90 (s), 128.33 (s), 127.61 (s), 127.40 (q, J = 274.9 Hz), 73.97 (s), 48.10 (s), 30.04 (q, J = 34.5 Hz).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.45 (t, J = 9.6 Hz).

Methyl 3-nitro-2-phenylpropanoate (51)[vv]
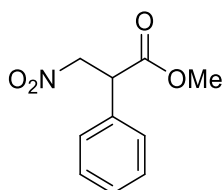
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.40-7.36 (m, 3H), 7.30-7.27 (m, 2H), 5.13 (dd, J = 14.5, 9.8 Hz, 1H), 4.57 (dd, J = 14.5, 5.2 Hz, 1H), 4.47 (dd, J = 9.8, 5.2 Hz, 1H), 3.76 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcell OD-H column, eluent 95:5 Hexane/2-Propanol; flow 1 mL/min; detection: 210 nm; t$_R$: 23.00 min (major), t$_R$: 59.40 min (minor).

Alternative HPLC analysis conditions: column: Phenomenex Lux Cellulose2; eluent 8:2 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t$_R$: 9.07 min (minor), t$_R$: 11.41 min (major).

[vv] H. Liu, J. Xu, D. M. Du, *Org. Lett.*, **2007**, *9*, 4725-4728.

2,2,2-trifluoroethyl 4-nitro-3-[4-(trifluoromethyl)phenyl]-2-oxo-butanethioate (49)
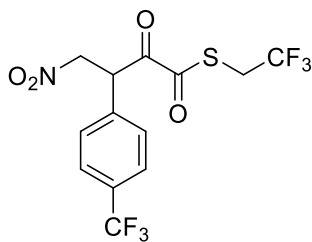
Rf = 0.60 (8:2 hexane:ethyl acetate)

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.68 (AB system-part A, J = 8.2 Hz, 2H), 7.42 (AB system-part B, J = 8.2 Hz, 2H), 5.44 (dd, J = 10.0, 4.8 Hz, 1H), 5.24 (dd, J = 15.0, 10.0 Hz, 1H), 4.75-4.67 (m, 1H), 3.61 (q, J = 9.6 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 188.88 (s), 186.46 (s), 135.36 (s), 133.81 (s), 129.32 (s), 130.20 (q, J = 16.3), 129.127.88 (q, J = 276.80 Hz), 127.56 (q, J = 284.8 Hz), 126.83 (s), 74.27 (s), 48.32 (s), 30.64 (q, J = 34.8 Hz).

Methyl 3-nitro-2-[4-(trifluoromethyl)-phenyl]-propanoate (52)
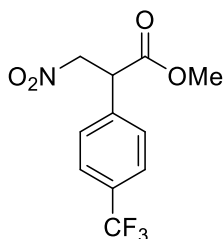
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.67 (AB system-part A, *J* = 8.1 Hz, 2H), 7.44 (AB system-part B, *J* = 8.0 Hz, 2H), 5.14 (dd, *J* = 14.2, 8.9 Hz, 1H), 4.61 (dd, *J* = 19.3, 5.1 Hz, 1H), 4.60-4.52 (m ,2H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.24 (s), 136.99 (s), 128.46 (s), 126.41 (s), 125.83 (s), 75.36 (s), 52.97 (s), 48.41(s).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -76.20 (s).

2,2,2-trifluoroethyl 4-nitro-3-[4-(chloro)phenyl]-2-oxo-butanethioate (50)
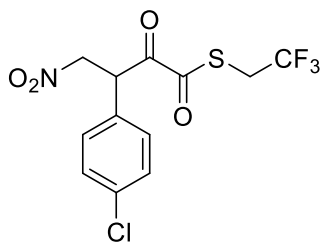
Rf = 0.63 (8:2 hexane:ethyl acetate)

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 5.31 (dd, J = 10.0, 4.7 Hz, 1H), 5.16 (dd, J = 14.8, 10.0 Hz, 1H), 4.64 (dd, J = 14.9, 4.8 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 188.41 (s), 185.98 (s), 135.26 (s), 133.61 (s), 129.60 (s), 73.79 (s), 47.39 (s), 30.06 (q, J = 34.6 Hz).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.44 (t, J = 9.6 Hz).

Methyl 3-nitro-2-[4-(chloro)phenyl]-propanoate (53)
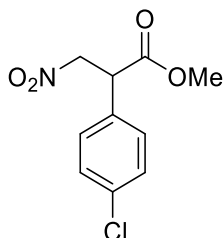
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.37 (AB system-part A, J = 8.5 Hz, 1H), 7.23 (AB system-part B, J = 8.5 Hz, 1H), 5.09 (dd, J = 14.6, 9.5 Hz, 1H), 4.56 (dd, J = 14.6, 5.5 Hz, 1H), 4.44 (dd, J = 9.5, 5.6 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.69 (s), 135.33 (s), 131.59 (s), 129.61 (s), 129.29 (s), 75.33 (s), 53.02 (s), 48.00 (s).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Phenomenex Lux Cellulose2; eluent 8:2 Hexane/2-Propanol; flow 0.8 mL/min; detection: 210 nm; t$_R$: 9.81 min (minor), t$_R$: 13.69 min (major).

2,2,2-trifluoroethyl 2-[(1,3-dithian)-2-yl]-ethanthioate preparation
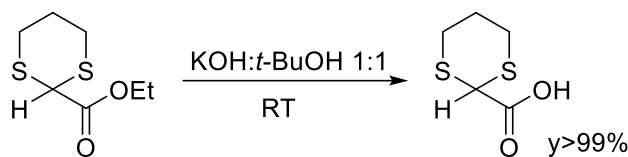
A solution of ethyl 2-[(1,3-dithian)-2-yl]-acetate (1.92 g, 10 mmol) in a 1:1 mixture of 1N KOH (10 mL) and *tert*-butanol (10 mL) was stirred overnight at room temperature. The alcohol was removed under reduced pressure and the aqueous phase was acidified with 2N HCl. The mixture was extracted with ethyl acetate (4 x 50 mL) and the solvent was removed under reduced pressure to give 1.5 g of solid dithiane carboxylic acid (mp 115-116°C). The ^{1}H NMR spectra was in agreement with that reported in the literature.
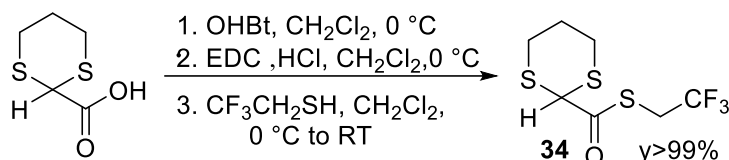
To a solution of carboxylic acid (821 mg, 5 mmol) in dry CH_2Cl_2 (25 mL) HOBt (709 mg, 5.25 mmol) was added at 0 °C, and the resulting solution was stirred for 10 minutes at the same temperature. After this period, EDC•HCl (1.01 g, 5.25 mmol) was added at 0 °C and the mixture was stirred for 30 minutes at the same temperature. Finally, 2,2,2-trifluoroethanethiol (638 mg, 5.50 mmol) was added at 0 °C, and the mixture was allowed to warm to room temperature. After being stirred overnight, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the desired compound was obtained as a white solid (1.25 g, 95%).

Mp: 56-57 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.62 (q, J = 9.8 Hz, 2H), 3.16-3.24 (m, 2H), 2.60-2.68 (m, 2H), 1.96-2.20 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.7 (s), 124.0 (q, J = 272.0 Hz), 49.5 (s), 31.8 (q, J = 1.4 Hz), 26.4 (s), 24.7 (s).

^{19}F-NMR (282 MHz, $CDCl_3$) δ: -67.2 (t).

ν (cm^{-1}) (KBr) 2998, 2970, 2934, 2907, 1698, 1686, 1400, 1307, 1270, 1237, 1131, 1081, 1009, 992, 910, 764.

$C_7H_9F_3OS_3$ (262.34): calc. C, 32.05, H, 3.46; found C, 32.14, H, 3.47.

Nitrostyrene derivatives preparation
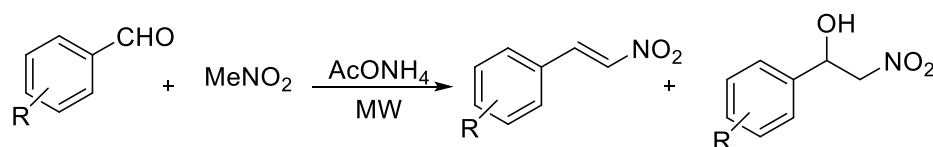
A stirred mixture of the proper aldehyde (1 eq.), ammonium acetate (0.3 eq.) and nitromethane (55 eq.) was subjected to 200W microwave irradiation and heated to 90 °C for 1 hour. Constant microwave irradiation and simultaneous air-cooling (2 bar) were applied during the entire reaction time. After this period, the mixture was treated with an oversaturated aqueous solution of NaHCO3 and extracted with CH2Cl2. The combined organic phases were dried over anhydrous Na2SO4 and the solvent was removed under reduced pressure. This procedure typically brought to the formation of a mixture of the desired nitrostyrene derivative and of the nitroalcohol; the two products were separated through flash column chromatography on silica gel (9:1 hexane:ethyl acetate) and nitroalcohols were subjected to subsequent dehydration.
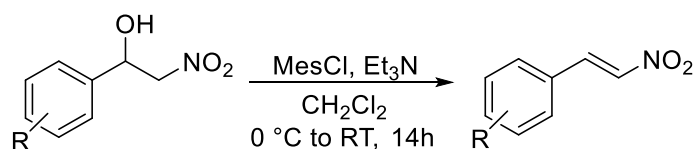
The proper nitroalcohol was dissolved in CH₂Cl₂; the solution was cooled to 0 °C and stirred for 10 minutes. After this period, triethylamine (4 eq.) and methanesulfonyl chloride (3 eq.) were added dropwise. The resulting mixture was stirred at room temperature for 14 hours, after which the reaction mixture was quenched with water; the aqueous layer was separated and washed three times with CH₂Cl₂. The combined organic phases were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). Products' analytical data were in agreement with literature.

R	Yield (%)
p- CF₃	51
p- Cl	52
p- CH₃	53
o- CH₃	79
p- OMe	37
o- OMe	>99
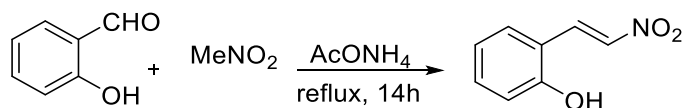
A stirred mixture of the salicylic aldehyde (1 eq.), ammonium acetate (1.1 eq.) and nitromethane (100 eq.) was refluxed for 14 hours. After this period, nitromethane was removed under reduced pressure and the mixture was treated with H_2O and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. After purification through flash column chromatography on silica gel (9:1 hexane:ethyl acetate) the desired nitrostyrene derivative (*E*)-2-(2-nitrovinyl)phenol was obtained as yellow solid (46% yield).
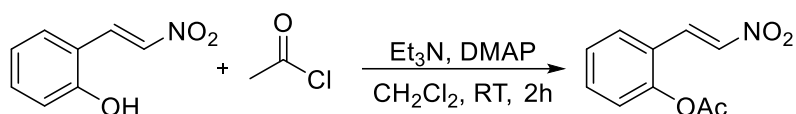
To a stirred solution of the previously prepared nitrostyrene derivative (*E*)-2-(2-nitrovinyl)phenol (1 eq.) 4-dimethylaminopyridine (0.1 eq.), triethylamine (2 eq.) and acetyl chloride (1.5 eq.) were added dropwise at 0 °C. The mixture was stirred for 2 hours and after this period it was quenched with an oversaturated solution of $NaHCO_3$; the aqueous layer was separated and washed diethyl ether. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification though flash column chromatography on silica gel (9:1 hexane:ethyl acetate) afforded compound **16** as a yellow solid (36% yield).
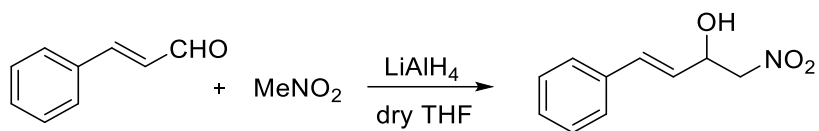
A solution of lithium aluminium hydride (0.179 mmol) in dry tetrahydrofuran (7 mL) was cooled to 0 °C and stirred for 30 minutes. After this period, nitromethane (0.485 mL) was added and the reaction mixture was stirred at 0 °C for 30 minutes. Cinnamaldehyde (1.79 mmol) was added dropwise and the reaction mixture was stiredr at 0 °C for 14 hours, after which the reaction mixture was quenched with 1M HCl; the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). The desired nitroalcohol was obtained as a yellow oil (1.29 mmol, 72% yield).[ww]
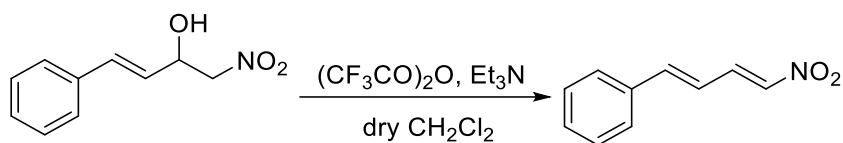
Nitroalcohol (1.29 mmol) was dissolved under inert atmosphere in CH_2Cl_2; the solution was cooled to 0 °C and stirred for 10 minutes. After this period, 2,2,2-trifluoroacetic anhydride (1.37 mmol) and triethylamine (2.73 mmol) were added. The reaction mixture was stirred under inert atmosphere at room temperature for 2 hours, after which it was treated with an oversaturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic phases were washed with an oversaturated solution of NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (9:1 hexane:ethyl acetate). Nitrostyrene derivative **17** was isolated as a yellow solid.

Product's analytical data were in agreement with literature.

[ww] S. Belot, A. Massaro, A. Tenti, A. Mordini, A. Alexakis, *Org. Lett.*, **2008**, *10*, 4557-4560.

Primary amines promoted stereoselective conjugate addition of an acyl anion mimic to α,β-unsaturated ketones

General procedure for organocatalytic reactions
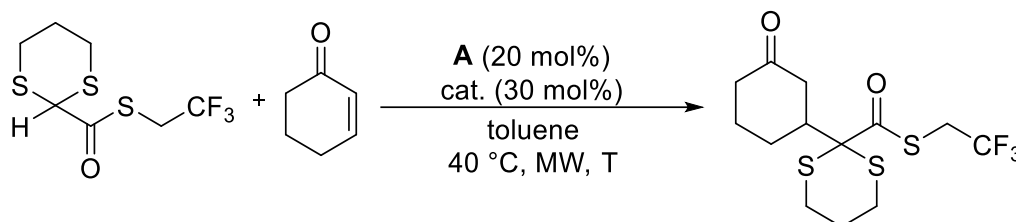
GENERAL PROCEDURE FOR "IN FLASK" REACTIONS

To a solution of dithianilthioester (0.15 mmol), catalyst (0.015 mmol) and co-catalyst in dry toluene (1.5 mL), cyclohexenone (0.23 mmol) was added. The resulting mixture was stirred under inert atmosphere for 20 hours at room temperature. After this reaction time, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (eluent: Hexane/EtOAC = 8/2). The enantiomeric excess was determined by HPLC on chiral stationary phase.

GENERAL PROCEDURE FOR THE MICROWAVE-ASSISTED REACTIONS

The primary amine catalyst, the co-catalytic acid and the dithianilthioester (0.15 mmol) were dissolved in dry toluene (excepted for the neat reaction) in a vial; subsequently, the α,β-unsaturated ketone was added. The stirred reaction mixture was heated to the desired temperature under constant microwave irradiation for the desired time. After this period, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 8/2). The enantiomeric excess was determined by HPLC on chiral stationary phase.

Products characterization

S-(2,2,2-trifluoroethyl) 2-(3-oxocyclohexyl)-1,3-dithiane-2-carbothioate (54)
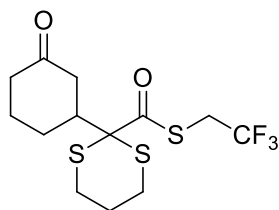
The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

R_f = 0.25 (8:2 hexane/EtOAc).

^{1}H NMR (300 MHz,CDCl$_3$) δ: 3.61 (t, J=8 Hz, 2H), 2.92 (q, J = 8 Hz), 2.78 (q, J = 8 Hz, 1H), 2.62 (d, J=8 Hz), 2.51 (t, J = 8 Hz), 2.37 (t, J=8 Hz), 2.25 (q, J= 8 Hz), 2.12 (t, J=8 Hz), 1.9 (q, J=8 Hz).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.46 (t, J = 8 Hz).

^{13}C NMR(75 MHz,CDCl$_3$) δ : 209.10 (s), 196.61 (s), 128.74 (t, J=60 Hz), 123.02 (s), 69.17 (s) 53.40 (s), 46.92 (s), 42.97 (s), 40.98 (s), 32.17 (q, J=30 Hz), 30.91 (s), 28.22 (s), 26.53 (s), 24.14 (d, J=30 Hz).

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (-) enantiomer, obtained with 9-amino-9-*epi*-quinine (catalyst **B**): t_R 12.21 min (major), t_R 14.44 min (minor); (+) enantiomer, obtained with 9-amino-9-*epi*-quinidine (catalyst **A**): t_R 12.15 min (minor), t_R 14.15 min (major).

MS Mass (ESI+) m/z calc. for C$_{13}$H$_{17}$S$_3$O$_2$F$_3$: 358.34, found: 359.4 [M + H]; 381.3 [M + Na].

$[\alpha]_D^{23}$= -3.79° (*c*: 0.73, CHCl$_3$, ee 93% obtained with 9-amino-9-*epi*-quinine - cat **B**).

$[\alpha]_D^{23}$= +4.52° (*c*: 0.39, CHCl$_3$, ee 93% obtained with 9-amino-9-*epi*-quinidine - cat **A**).

Melting point: 70-73°C

S-(2,2,2-trifluoroethyl) 2-(3-oxocyclopentyl)-1,3-dithiane-2-carbothioate (55)
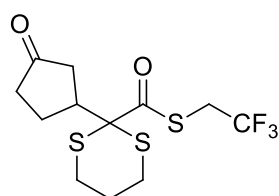
The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

R_f = 0.21 (8:2 hexane/EtOAc).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.65 (q, J=8 Hz, 2H), 2.92 (q, J = 8 Hz, 2H), 2.83 (q, 2H), 2.56 (q, J=8 Hz, 1H), 2.42 (q, J = 8 Hz), 2.15 (m, 3H), 1.94 (m, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.51 (t, J = 8 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 214.96 (s), 196.45 (s), 124.09 (t, J=250 Hz), 67.40 (s), 44.94 (s), 39.53 (s), 37.86 (s), 32.63 (q, J=30 Hz), 27.77 (s), 27.60 (s), 23.66 (s), 23.41 (s).

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-*epi*-quinine (catalyst **B**): t_R 19.09 min (major), t_R 17.7 min (minor); enantiomer obtained with 9-amino-9-*epi*-quinidine (catalyst **A**): t_R 17.70 min (minor), t_R 16.37 min (major).

MS Mass (ESI+) m/z calc. for C$_{12}$H$_{15}$S$_3$O$_2$F$_3$: 344.24, found: 345.3 [M + H]; 367.2 [M + Na].

S-(2,2,2-trifluoroethyl) 2-(3-oxo-1,3-diphenylpropyl)-1,3-dithiane-2-carbothioate (56)
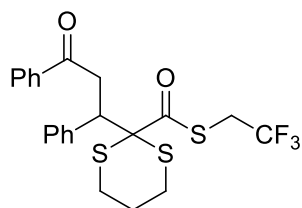
The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as a light yellow oil.

R_f = 0.30 (8:2 hexane/EtOAc).

^{1}H NMR(300 MHz,CDCl$_3$) δ:7.93 (d, J = 8 Hz, 2H), 7.56-7.24 (m, 8H), 4.18 (t, J=8 Hz, 1H), 3.85 (d, J=8 Hz, 2H), 3.48 (dq, J = 8 Hz, 2 Hz, 2H), 2.93 (t, 2H), 2.79 (t, 2H), 2.08 (q, 1H), 1.90 (q, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 133.09 (s), 129.78 (s), 128.53 (s), 128.03 (s), 127.94 (s), 49.63 (s), 40.47 (s), 33.44 (q, J = 33.3 Hz), 28.68 (s), 28.28 (s), 23.44 (s). *C=O and CF$_3$ are not visible*

^{19}F NMR (282 MHz,) δ: -65.95 (t, J = 8 Hz).

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-*epi*-quinidine (catalyst **A**): t$_R$ 15.63 min (minor), t$_R$ 9.67 min (major).

S-(2,2,2-trifluoroethyl) 2-(3-oxo-1-phenylbutyl)-1,3-dithiane-2-carbothioate (57)
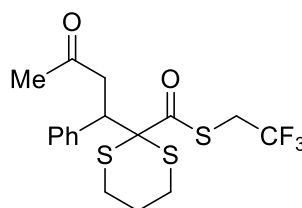
The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as a light yellow oil.

R_f = 0.25 (9:1 hexane/EtOAc).

^{1}H NMR (300 MHz,CDCl$_3$) δ: 7.32-7.29 (m, 2H), 7.26-7.24 (m, 3H), 3.91 (dd, J = 9.6, 3.9 Hz, 1H), 3.44 (qd, J = 10.0, 2.4 Hz, 2H), 3.32-3.15 (m, 2H), 2.94-2.80 (m, 2H), 2.77-2.67 (m, 2H), 2.03 (s, 3H), 2.00-1.97 (m, 1H), 1.89-1.77 (m, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -65.99 (t, J=8 Hz).

^{13}C NMR (75 MHz,CDCl$_3$) δ: 205.10 (s), 197.10 (s), 136.84 (s), 129.72 (s), 128.00 (s), 127.36 (q, J = 276 Hz), 69.75 (s), 49.39 (s), 45.10 (s), 33.39 (q, J = 33.0 Hz), 28.62 (s), 28.27 (s), 28.27 (s), 23.43 (s)

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-*epi*-quinidine (catalyst **A**): t$_R$ 14.26 min (minor), t$_R$ 15.53 min (major).

Procedure for the synthesis of the α-ketothioesters
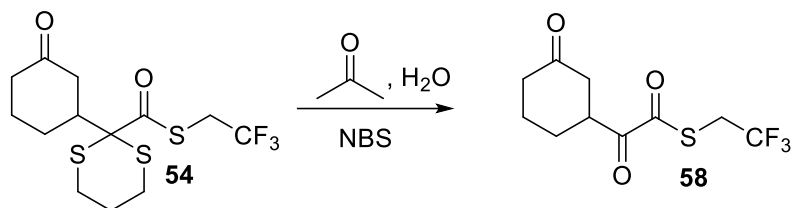
To a stirred solution of *N*-bromosucinimide (10 eq.) in aqueous 97% acetone (1.85 mL for 1 mmol of NBS) at 0 °C a solution of thioester **54** (1 eq.) in acetone (4 mL for 1 mmol of carboxythioester) was added. The solution turned yellow to limpid orange and after some minutes faded to pale yellow. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After this period, the reaction mixture was treated with an oversatured aqueous solution of Na_2SO_3 and extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Products were used in the subsequent step without further purification.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.72-3.54 (m, 3H), 2.65-2.28 (m, 4H), 2.19-2.06 (m, 2H), 1.92-1.79 (m, 1H), 1.73 (ddd, J = 13.1, 10.3, 2.5 Hz, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.48 (t, J = 9.6 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 207.92 (s), 193.70 (s), 187.61 (s), 53.39 (s), 43.92 (s), 41.06 (s), 40.81 (s), 26.74 (s), 24.57 (s).

Procedure for the synthesis of the γ-ketoester
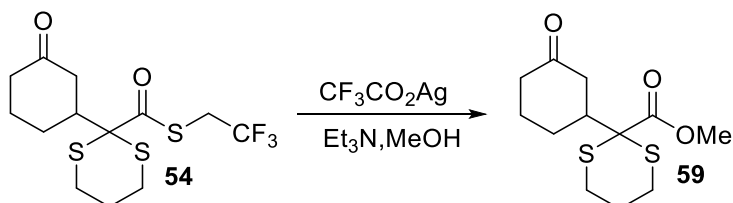
To a solution of thioester **54** in methanol (43 mmol in 210 μL), Et$_3$N (1 eq., 0.12 mmol) and AgCO$_2$CF$_3$ (2 eq., 53 mmol) were added; the reaction mixture was stirred for 2 hours at room temperature. After this period, the reaction mixture was treated with H$_2$O and extracted with EtOAc. The combined organic phases were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The The crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 9/1). The desired product was obtained in 60 % yield.

Rf = 0.57 (9:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.84 (s, 3H), 3.29-3.17 (m, 2H), 2.78-2.71 (m, 2H), 2.64-2.49 (m, 3H), 2.44-2.39 (m, 1H), 2.33-2.22 (m, 1H), 2.17-2.07 (m, 3H), 1.94-1.74 (m, 2 H), 1.69-1.54 (m, 1H)

^{13}C NMR (75 MHz, CDCl$_3$) δ: 210.05 (s), 170.79 (s), 58.67 (s, 1C), 53.10 (s), 45.26 (s), 43.13 (s), 41.09 (s), 27.88 (s), 26.66 (s), 24.64 (s), 24.55 (s).
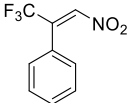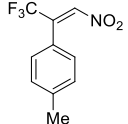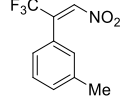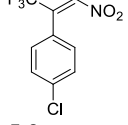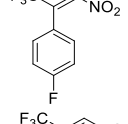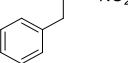
Stereoselective reduction of β-trifluoromethyl nitroalkenes catalyzed by chiral bifunctional organocatalysts

General procedure for organocatalytic reactions
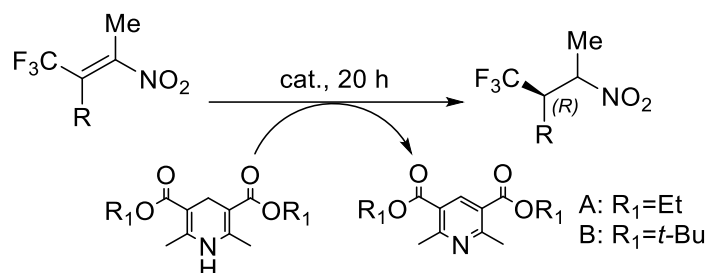
The β-trifluoromethyl nitroalkene derivative (1 eq.) and the catalyst (0.1 eq.) were dissolved in the dry solvent (1M solution) under nitrogen atmosphere and stirred for 10 minutes at the desired temperature; Hantzsch ester (A: 1 eq.; B: 1.3 eq. due to higher tendency to oxidation) was added as a solid and the mixture stirred for 20 hours at constant temperature. The solvent was then removed under reduced pressure and products were isolated by flash column chromatography on silica gel using the mixture 99:1 hexane:ethyl acetate. When low-boiling substrates were employed – yielding low boiling products – only the crude mixture was analysed. For routine analysis, the product was isolated through preparative thin layer chromatography. All products obtained appear as colourless oils. Substrate conversion into the desired product, *i.e.* the corresponding β-trifluoromethyl nitroalkane, was determined through ^{1}H and ^{19}F NMR. Enantiomeric excess was determined by HPLC on chiral stationary phase. The absolute configuration was determined through chemical correlation.

Substrate	TOLUENE		HEXANE	
	conv.	ee	conv.	ee
	76%	93%	64%	51%
	68%	83%	68%	67%
	58%	73%	62%	39%
	84%	90%	69%	56%
	81%	90%	61%	28%
	88%	90%	72%	68%

General procedure for non-stereoselective reductio[n][xx]
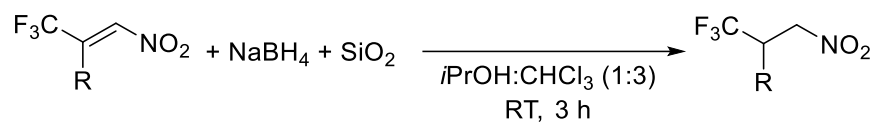
NaBH$_4$ (4 eq., 0.6 mmol) and SiO$_2$ (50 mg for 0.15 mmol of substrate) were subsequently added to a solution of the the β-trifluoromethyl nitroalkene derivative (1 eq., 0.15 mmol) in 1:3 iPrOH:CHCl$_3$ (0.5 mL and 1.5 mL for 0.15 mmol of substrate) at room temperature. The reaction mixture was stirred for 3 hours, after which it was quenched with 1M HCl and extracted with CH$_2$Cl$_2$ or Et$_2$O - depending on products boiling point; the combined organic phases were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Products were obtained in quantitative yield.

[xx] P. Astolfi, L. Charles, D. Gigmes, L. Greci, C. Rizzoli, F. Sorana, P. Stipa, *Org. Biomol. Chem.*, **2013,** *11*, 1399-1406.

Reduction products characterization

2-phenyl-2-(trifluoromethyl)-nitroethane[yy] (60)
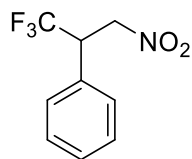
Rf = 0.43 (9:1 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.42-7.38 (m, 3H), 7.35-7.31(m, 2H), 4.97 (AB system – part A, 1H), 4.82 (AB system – part B, 1H), 4.39-4.26 (m, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.38 (d, J = 8.6 Hz).

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose-1 column with SecurityGuard cartridge; eluent: 9:1 Hex/IPA; flow rate: 1 mL/min detection: 210 nm; t$_R$ 3.88 min (major), t$_R$ 6.32 min (minor).

$[\alpha]_D^{22}$= +30.94 (c 0.45, CHCl$_3$, ee 67%).

2-(4-methylphenyl)-2-(trifluoromethyl)-nitroethane (61)
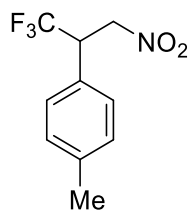
Rf = 0.448 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.21 (s, 4H), 4.96 (AB system – part A, J = 13.6, 5.8 Hz, 1H), 4.81 (AB system – part B, J = 13.6, 9.0 Hz, 1H), 4.35-4.22 (n, 1H), 2.35 (s, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.53 (d, J = 8.7 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 134.22 (s), 129.42 (s), 128.07 (s), 124.51 (q, J = 279.3 Hz), 73.45 (s), 47.26 (q, J = 27.4 Hz), 22.08 (s).

$[\alpha]_D^{24}$= +39.67 (c 0.3, CHCl$_3$, ee 78%).

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose-1 column with SecurityGuard cartridge; eluent: 99:1 Hex/IPA; flow rate: 1 mL/min; detection: 210 nm; t$_R$ 7.68 (minor), t$_R$ 13.17 (minor).

[yy] A. Morigaki,T. Tanaka, T. Myiabe, T. Ishihara, T. Konno, *Org. Biomol. Chem.*, **2013,** *11*, 586-594.

2-(3-methylphenyl)-2-(trifluoromethyl)-nitroethane (62)
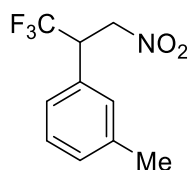
Rf = 0.49 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.35-7.20 (m, 3H), 7.12 (bs, 1H), 4.96 (AB system – part A, J = 13.7, 5.8 Hz, 1H), 4.82 (AB system – part B, J = 13.7, 8.8 Hz, 1H), 4.35-4.22 (m, 1H), 2.37 (s, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.34 (d, J = 8.7 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 138.59 (s), 129.80 (s), 128.96 (s), 128.58 (s), 125.15 (s), 124.49 (q, J = 278.3 Hz), 73.40 (s), 47.54 (q, J = 28.6 Hz), 20.78 (s).

$[\alpha]_D^{24}$= +20.29 (*c* 0.16, CHCl$_3$, ee 39%).

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose-1 column with SecurityGuard cartridge; eluent: 9:1 Hex/IPA; flow rate: 1 mL/min; detection: 210 nm; t$_R$ 2.92 (major), t$_R$ 4.50 (minor).

2-(4-chlorophenyl)-2-(trifluoromethyl)-nitroethane (63)
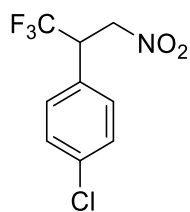
Rf = 0.39 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.40 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 4.97 (AB system – part A, J = 13.8, 5.5 Hz, 1H), 4.80 (AB system – part B, J = 13.8, 9.3 Hz, 1H), 4.39-4.26 (m, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.38 (d, J = 8.6 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 135.40 (s), 129.57 (s), 129.07 (s), 127.93 (s), 124.17 (q, J = 278.3 Hz), 73.12 (s), 47.06 (q, J = 28.8 Hz).

$[\alpha]_D^{24}$= +30.34 (*c* 0.32, CHCl$_3$, ee 78%).

The enantiomeric excess was determined by HPLC with Phenomenex Lux 3u Cellulose-1 column with SecurityGuard cartridge; eluent: 9:1 Hex/IPA; flow rate: 1 mL/min; detection: 210 nm; t$_R$ 4.69 (major), t$_R$ 7.05 (minor).

2-(4-fluorophenyl)-2-(trifluoromethyl)-nitroethane (64)
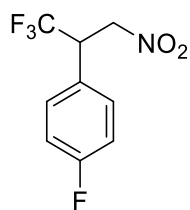
Rf = 0.35 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.35-7.30 (m, 2H), 7.11 (t, J = 8.4 Hz, 2H), 4.97 (AB system – part A, J = 13.7, 5.5 Hz, 1H), 4.80 (AB system – part B, J = 13.6, 9.3 Hz, 1H), 4.39-4.25 (m, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.56 (d, J = 8.5 Hz, 3F), -111.68 (s, 1F).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 164.46 (s), 130.14 (s), 130.03 (s), 127.23 (q, J = 169.4 Hz), 116.05 (s), 115.76 (s), 73.29 (s), 46.93 (q, J = 28.7 Hz).

$[\alpha]_D^{24}$ = +32.21 (c 1.4, CHCl$_3$, ee 88%).

The enantiomeric excess was determined by HPLC with Phenomenex Lux Cellulose-4 column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t$_R$ 8.33 (minor), t$_R$ 8.75 (major).

3-phenyl-2-(trifluoromethyl)-nitropropane (65)
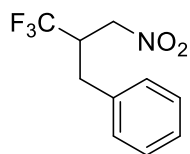
Rf = 0.43 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.42-7.29 (m, 3H), 7.26-7.23 (m, 2H), 4.58 (AB system – part A, J = 14.2, 7.7 Hz, 1H), 4.33 (AB system – part B, J = 14.2, 4.7 Hz, 1H), 3.59-3.44 (m, 1H), 3.24 (dd, J = 14.4, 4.9 Hz, 1H), 2.71 (dd, J = 14.4, 10.3 Hz, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -71.32 (d, J = 7.8 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 135.07 (s), 129.18 (s), 129.02 (s), 127.74 (s), 126.22 (q, J = 286.5 Hz), 71.97 (s), 43.73 (q, J = 26.9 Hz), 31.79 (s).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AS3 column; eluent: 9:1 Hex/IPA; flow rate: 1 mL/min detection: 230 nm; t$_R$ 6.67 min (major), t$_R$ 7.40 min (minor).

$[\alpha]_D^{25}$ = -14.44 (c 0.32, CHCl$_3$, ee 81%).

2-cyclohexyl-2-(trifluoromethyl)-nitroethane (66)
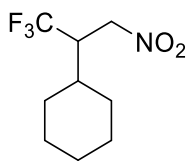
^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.57 (AB system – part A, J = 14.3, 7.0 Hz, 1H), 4.47 (AB system – part B, J = 14.3, 5.1 Hz, 1H), 3.18-3.02 (m, 1H), 2.14-2.00 (m, 1H), 1.86-1.69 (m, 5H), 1.40-1.10 (m, 5H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -67.51 (d, J = 9.5 Hz).

^{13}C NMR (75 MHz, CD$_2$Cl$_2$) δ: 123.01 (q, J = 243.7 Hz), 71.42 (s), 47.01 (q, J = 26.0 Hz), 36.27 (s), 30.46 (s), 28.95 (s), 26.34 (s), 26.15 (s), 25.76 (s).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack AD column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t$_R$ 4.96 (minor), t$_R$ 6.49 (major).

2-heptyl-2-(trifluoromethyl)-nitroethane (67)
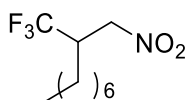
^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.60 (AB system – part A, J = 13.9, 6.6 Hz, 1H), 4.38 (AB system – part B, J = 14.0, 6.1 Hz, 1H), 3.19-3.06 (m, 1H), 1.82-1.70 (m, 1H), 1.64-1.33 (m, 11H), 0.88 (t, J = 6.6 Hz, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -70.99 (d, J = 8.3 Hz).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 126.30 (q, J = 280.2 Hz), 73.25 (s), 41.99 (q, J = 27.3 Hz), 29.19 (s), 28.83 (s), 26.22 (s), 22.55 (s), 14.01 (s).

The enantiomeric excess was determined by HPLC with Daicel Chiralpack OJ-H column; eluent: 95:5 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t$_R$ 5.19 (major), t$_R$ 5.53 (minor)

1-methyl-2-phenyl-2-(trifluoromethyl)-nitroethane (69)
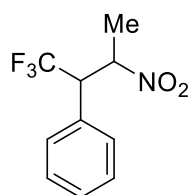
60:40 diastereomeric mixture

Rf = 0.30 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.43-7.41 (m, 2H$_{MINOR+MAJOR}$), 7.38-7.36 (m, 1H$_{MINOR+MAJOR}$), 7.29-7.25 (m, 2H$_{MINOR+MAJOR}$), 5.16 (q, J = 6.7 Hz, 1H$_{MINOR}$), 5.13 (q, J = 6.8 Hz, 1H$_{MAJOR}$), 4.16-4.07 (m, 1H$_{MAJOR}$), 4.02-3.87 (m, 1H$_{MINOR}$), 1.84 (dq, J = 6.7, 1.5 Hz, 3H$_{MINOR}$), 1.36 (d, J = 6.8 Hz, 3H$_{MAJOR}$).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -63.89 (d, J = 8.9 Hz, 3F$_{MINOR}$), -68.15 (d, J = 8.3 Hz, 3F$_{MAJOR}$).ù

^{13}C NMR (75 MHz, CDCl$_3$) δ: 131.80 (s, MAJOR+MINOR), 128.93 (s, MAJOR), 128.80 (s, MAJOR), 128.56 (s, MINOR), 128.24 (s, MINOR), 124.66 (q, J = 281.4 Hz, MAJOR+MINOR), 83.76 (s, MINOR), 80.81 (s, MAJOR), 53.18 (q, J = 27.9 Hz, MINOR), 52.99 (d, J = 27.2 Hz, MAJOR), 31.01 (s, MINOR), 22.08 (s, MAJOR), 18.27 (s, MINOR), 17.77 (s, MAJOR).

The enantiomeric excess was determined by HPLC with Phenomenex Lux Cellulose-4 column; eluent: 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; MINOR DIASTEREOISOMER: t$_R$ 5.67 (minor), t$_R$ 5.87 (major); MAJOR DIASTEREOISOMER: t$_R$ 6.63 (major), t$_R$ 7.08 (minor).

1-methyl-2-(4-chlorophenyl)-2-(trifluoromethyl)-nitroethane (70)
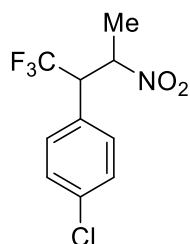
70:30 diastereomeric mixture

Rf = 0.7 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.42-7.34 (m, 2H$_{MINOR+MAJOR}$), 7.24-7. (m, 2H$_{MINOR+MAJOR}$), 5.16-5.02 (m, 1H$_{MINOR}$+1H $_{MAJOR}$), 4.14 (p, J = 8.6 Hz, 1H $_{MAJOR}$), 3.99-3.87 (m, 1H$_{MINOR}$), 1.83 (dd, J = 6.7, 1.4 Hz, 3H$_{MINOR}$) 1.37 (d, J = 6.8 Hz, 3H $_{MAJOR}$).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -64.06 (d, J = 8.5 Hz, 3F$_{MINOR}$), -68.19 (d, J = 8.2 Hz, 3F$_{MAJOR}$).

The enantiomeric excess was determined by HPLC with Phenomenex Lux Cellulose-4 column; eluent: 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; MINOR DIASTEREOISOMER: t$_R$ 5.77 (minor), t$_R$ 6.04 (major); MAJOR DIASTEREOISOMER: t$_R$ 6.81 (major), t$_R$ 7.23 (minor).

1-methyl-3-phenyl-2-(trifluoromethyl)-nitropropane (71)
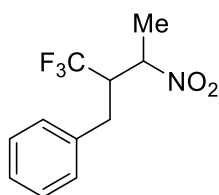
66:34 diastereomeric mixture

Rf = 0.31 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.84-7.59 (m, 2H$_{MINOR+MAJOR}$), 5.52-5.41 (m, 1H$_{MINOR}$), 5.28-5.17 (m, 1H$_{MAJOR}$), 4.19-4.02 (m, 1H$_{MAJOR}$), 3.97-3.88 (m, 1H$_{MINOR}$), 3.65 (dd, J = 14.7, 5.1 Hz, 1H$_{MAJOR}$), 3.43 (dd, J = 13.3, 7.2 Hz, 1H$_{MINOR}$), 3.31 (dd, J = 14.5, 6.1 Hz, 1H$_{MINOR}$), 3.16 (dd, J = 14.8, 10.0 Hz, 1H$_{MAJOR}$), 2.10 (d, J = 7.0 Hz, 3H$_{MAJOR}$), 1.79 (d, J = 6.7 Hz, 3H$_{MINOR}$).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.57 (d, J = 8.5 Hz, 3F $_{MAJOR}$), -67.87 (d, J = 7.5 Hz, 3F$_{MINOR}$).

The enantiomeric excess was determined by HPLC with Phenomenex Lux Cellulose-4 column; eluent: 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; MINOR DIASTEREOISOMER: t$_R$ 10.02, t$_R$ 10.42, MAJOR DIASTEREOISOMER: t$_R$ 4.07, t$_R$ 5.50.

Determination of the absolute configuration

Absolute configuration was determined through chemical correlation, transforming compound **15e** into the known compound **16**[zz] through three subsequent transformations – namely, NO$_2$ reduction, imine formation and C=C reduction – that do not affect the stereochemical integrity of the starting material, as confirmed by HPLC analysis on chiral stationary phase.
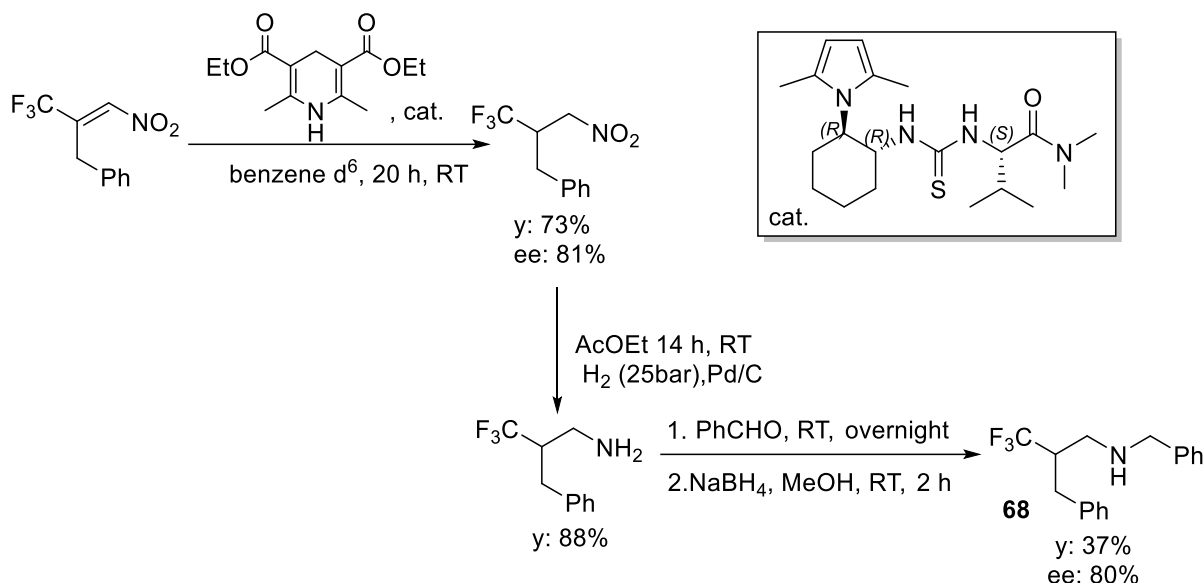
NO$_2$ REDUCTION PROCEDURE

In a Parr Multireactor vial, Pd/C (10% w/w) (180 mg for 0.32 mmol of substrate) was added to a solution of the susbtrate in AcOEt (8 ml). The mixture was stirred under H$_2$ pressure (25 bar) for 14 hours at room temperature. The crude then was filtered over a celite pad and the solvent was removed under reduced pressure. Product **16** was obtained in 88% yield and used in the subsequent step without further purification.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.40-7.21 (m, 5H), 3.04 (dd, J = 13.9, 4.9 Hz, 1H), 2.92-2.91 (m, 2H), 2.76 (dd, J = 14.1, 9.7 Hz, 1H), 2.63-2.52 (m, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.60 (d, J = 8.9 Hz).

IMINE FORMATION PROCEDURE

Benzaldehyde (1.5 eq., 0.42 mmol) was added to a 1M solution of the intermediate amine (1 eq., 0.28 mmol) in dry CH$_2$Cl$_2$ over molecular sieves under N$_2$ atmosphere. After stirring the reaction mixture at room temperature overnight, it was filtered over celite pad. The solvent was removed under reduced pressure; the product (Rf 0.58, CH$_2$Cl$_2$:MeOH) was used in the subsequent step without further purification.

[zz] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875-10877.

<u>IMINE REDUCTION PROCEDURE</u>

NaBH$_4$ (1 eq., 0.28 mmol) was added to a 0.2M solution of intermediate imine (1 eq., 0.28 mmol) in MeOH. The reaction mixture was stirred at room temperature for 2 hours, after which it was treated with NH$_4^+$Cl$^-$ ss and extracted first with AcOEt (10 mL) and finally with CH$_2$Cl$_2$ (10 mL). The combined organic phases were dried over Na2SO4 and the solvent was removed under reduced pressure. The product was purified through flash column chromatography on silica gel using the mixture 78:14:5: 2 hexane:AcOEt:CH$_2$Cl$_2$:NH$_4$OH as eluent. Product 68 was obtained in 35% yield over two steps.
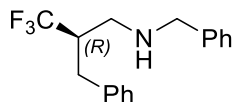
Rf: 0.46 (78:14:5: 2 hexane:AcOEt:CH$_2$Cl$_2$:NH$_4$OH)

$[\alpha]_D^{26}$ = - 36.4 (*c* 0.63, CHCl$_3$)

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.35-7.20 (m, 10H), 3 .73 (AB system – part A, J = 13.3 Hz, 1H), 3.67 (AB system – part B, J = 13.3 Hz, 1H), 3.04 (ABX system, J = 13.9, 4.5 Hz, 1H), 2.89-2.77 (m, 3H), 2.67-2.52 (m, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -69.84 (d, J = 8.7 Hz).

General procedure for β-trifluoromethylated nitroalkenes synthesis

Nitroolefins preparation followed a two steps typical procedure: nitromethane attack on the proper trifluoromethylated ketone followed by formal water elimination.[aaa]
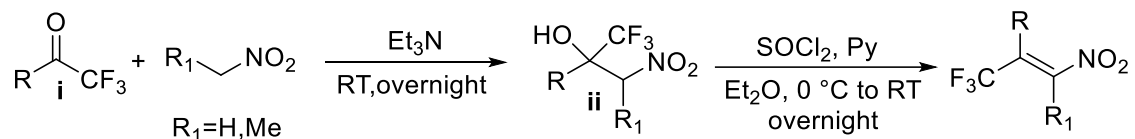
STEP 1

Triethylamine (1.5 eq., 1.5 mmol) was added to a solution of the proper ketone (1 eq., 1 mmol) in MeNO$_2$ or EtNO$_2$ (0.5M) at room temperature. After overnight stirring, the reaction mixture was treated with 1M HCl and extracted with Et$_2$O. For high boiling products, the combined organic phases were concentrated under reduced pressure, while, when low boiling ketones (i. e. those featuring an alkyl chain) were used, nitromethane was eliminated though careful distillation at reduced pressure (10 torr). The desired α-trifluoromethylated-β-nitro alcohol **ii** were typically obtained in quantitative yield and used in the subsequent step without further purification.

STEP 2

Thionyl chloride (1.5 eq.) and pyridine (2 eq.) were subsequently added to a 1M solution of the obtained α-trifluoromethylated-β-nitro alcohol **ii** in Et$_2$O at 0 °C (the addition was performed at room temperature for substrate 14f). The reaction mixture was allowed to room temperature, stirred overnight and subsequently treated with 1M HCl and extracted with Et$_2$O. For high boiling products, the combined organic phases were concentrated under reduced pressure, while with alcohols deriving from low boiling ketones the solvent was removed by nitrogen flow. Nitroalkenes were purified by flash column chromatography on silica gel using the mixture 99:1 hexane:ethyl acetate as eluent. All nitroalkenes prepared appear as yellow oils, typically featuring acrid smell and irritating to eyes.

[aaa] J. R. Gao, H. Wu, B. Xiang, W. B. Yu, L. Han, Y. X. Jia, *J. Am. Chem. Soc.*, **2013**,*135*, 2983-2986.

General procedure for α-trifluoromethylated ketone synthesis[bbb]
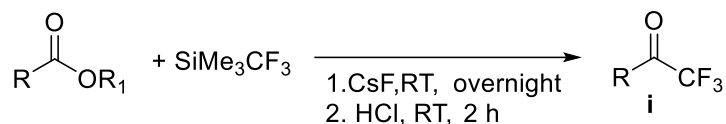
SiMe$_3$CF$_3$ (1.05 eq., 5.25 mmol) and CsF (0.1 eq, 0.5 mmol) were added to the proper ester (1 eq., 5 mmol) at room temperature under nitrogen atmosphere; the reaction mixture was stirred overnight. After this period, 4M HCl was added and the mixture stirred at room temperature for further 2 hours, then extracted with Et$_2$O. The collected organic phases were dried over Na$_2$SO$_4$; for low boiling products, the solvent was removed flowing N$_2$.

1,1,1-trifluorononan-2-one
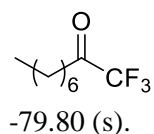
The product was observed in 79% conversion by ^{1}H NMR analysis. The crude was used directly in the subsequent step. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.73 (t, J = 7.2 Hz, 2H), 1.68-1.65 (m, 4H) 1.29-1.17 (m, 6H), 0.93-0.89 (m, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ: -79.80 (s).

[bbb] R. P. Singh, G. Cao, R. L. Kirchmeier, J. M. Shreeve, *J. Org. Chem.,* **1999**, *64*, 2873-2876.

Substrate characterization

(*E*)-2-phenyl-2-(trifluoromethyl)-nitroethene

Yield: 53%

Rf = 0.63 (9:1 hexane:ethyl acetate).
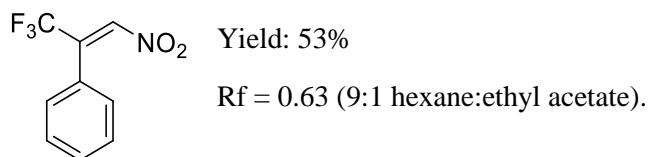
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.52 (s, 1H), 7.50-7.42 (m, 3H), 7.30 (d, J = 7.1 Hz, 2H).

^{19}F NMR (282 MHz, CDCl$_3$) δ -67.19 (s).

(*E*)-2-(4-methylphenyl)-2-(trifluoromethyl)-nitroethene

Yield: 35%

Rf = 0.44 (98:2 hexane:ethyl acetate).
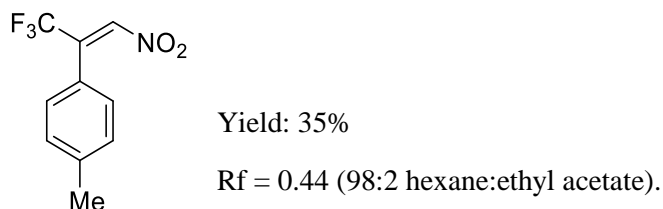
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.49 (s, 2H), 7.24 (AB system – part A, 2H), 7.19 (AB system – part B, 2H), 2.39 (s, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -67.70 (s).

(*E*)-2-(3-methylphenyl)-2-(trifluoromethyl)-nitroethene

Yield: 38%

Rf = 0.44 (98:2 hexane:ethyl acetate).
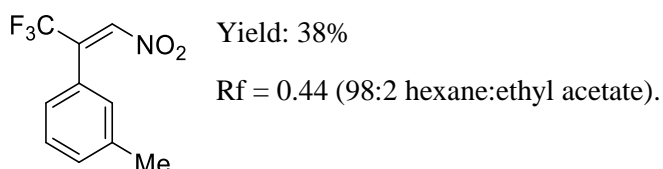
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.52 (s, 1H), 7.39-7.30 (m, 2H), 7.12 (bs, 2H), 2.41 (s, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -67.16 (s).

(*E*)-2-(4-chlorophenyl)-2-(trifluoromethyl)-nitroethene
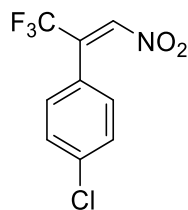
Yield: 21%

Rf = 0.44 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.52 (s, 1H), 7.44 (AB system – part A, J = 8.4 Hz, 2H), 7.24 (AB system – part B, J = 7.1 Hz, 2H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -67.18 (s).

(*E*)-2-(4-fluorophenyl)-2-(trifluoromethyl)-nitroethene
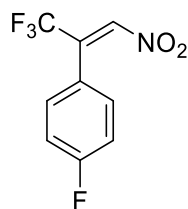
Yield: 24%

Rf = 0.44 (98:2 hexane:ethyl acetate).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.56 (s, 1H), 7.35-7.29 (m, 2H), 7.22-7.17 (m, 2H).

^{19}F NMR (282 MHz, CDCl$_3$) δ -67.31 (s, 3F), -109.43 (s, 1F).

(*E*)-3-phenyl-2-(trifluoromethyl)-nitropropene
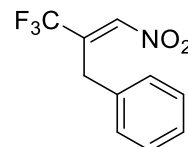
Yield: 23%

Rf = 0.64 (9.6:0.4 hexane:ethyl acetate)

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.48 (s, 1H), 7.37-7.21 (m, 5H), 4.05 (s, 2H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.93 (s).

(*E*)-2-cyclohexyl-2-(trifluoromethyl)-nitroethene

Yield: 28%

Rf = 0.43 (hexane)
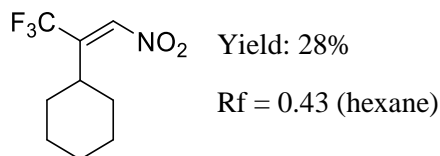
^{1}H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.34 (s, 1H), 3.12 (t, J = 11.9 Hz, 1H), 2.21-2.02 (m, 1H), 1.93-1.83 (m, 2H), 1.73-1.77 (m, 2H), 1.65-1.53 (m, 3H), 1.42-1.36 (m, 2H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -63.52 (s).

^{13}C NMR (75 MHz, CD$_2$Cl$_2$) δ: 141.11 (q, J = 27.8 Hz), 123.10 (q, J = 277.8 Hz), 37.87 (s), 30.04 (s), 26.28 (s), 25.41 (s).

(*E*)-2-heptyl-2-(trifluoromethyl)-nitroethene

Rf = 0.39 (hexane)
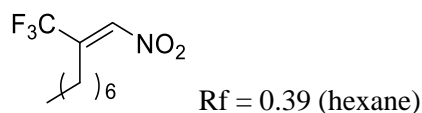
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.34 (s, 1H), 2.63 (dd, J = 9.3, 6.8 Hz, 2H), 1.66-1.56 (m, 2H), 1.39-1.32 (m, 8H), 0.89 (t, J = 6.5 Hz, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -68.31 (s).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 139.82 (s), 122.88 (q, J = 276.5 Hz), 31.55 (s), 29.64 (s), 28.63 (s), 28.09 (s), 26.03 (s), 22.52 (s), 13.96 (s).

1-methyl-2-phenyl-2-(trifluoromethyl)-nitroethene (69')

95:5 diastereomeric ratio

Yield: 28%

Rf = 0.41 (98:2 hexane:ethyl acetate)
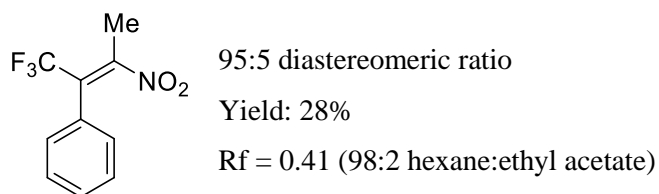
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.39-7.34 (m, 1H), 7.24-7.21 (m, 1H), 2.53 (q, J = 2.3 Hz, 1H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -59.27 (s, 3F$_{MAJOR}$), -71.88 (s, 3F$_{MINOR}$).

1-methil-2-(4-chlorophenyl)-2-(trifluoromethyl)-nitroethene (70')
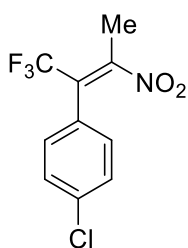
46:54 diastereomeric ratio

Yield: 10%

Rf = 0.43 (98:2 hexane:ethyl acetate)

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.02 (d, J = 8.6 Hz, 2H$_{MINOR}$), 7.54 (d, J = 8.7 Hz, 2H$_{MINOR}$), 7.36 (d, J = 8.5 Hz, 2H$_{MAJNOR}$), 7.17 (d, J = 8.4 Hz, 2H$_{MAJNOR}$), 2.53 (q, J = 2.5 Hz, 3H$_{MAJOR}$), 0.87 (s, 3H$_{MINOR}$).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -59.38 (s, 3F$_{MAJOR}$), -72.06 (s,3F$_{MINOR}$).

1-methil--3-phenyl-2-(trifluoromethyl)-nitropropene (71')
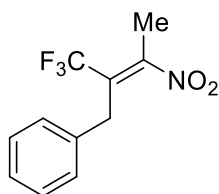
Yield: 5%

Rf = 0.3 (98:2 hexane:ethyl acetate)

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.33-7.22 (m, 5H), 3.62 (s, 2H), 2.49 (s, 3H).

^{19}F NMR (282 MHz, CDCl$_3$) δ: -59.15 (s).

Deep Eutectic Solvent as novel reaction media for stereoselective organocatalytic reactions

Materials

Commercial grade reagents and solvents were used without further purifications. Quinine (anhydrous, technical grade 98%), *trans*-β-nitrostyrene (technical grade 97%), trifluoroacetic acid (99%), were purchased from Sigma-Aldrich. Silica (Apex Prepsil Silica Media 8 μm) was purchased from Grace.

Trans-ethyl-3-nitrobut-2-enoate[1] was prepared according to published procedures.

Isobutyraldehyde, was purified by distillation under atmospheric pressure and under nitrogen atmosphere before use. Cyclohexanone and was purified by distillation under reduced pressure before use.

4-Hydroxycoumarin was recrystallized from EtOAc before use; benzalacetone was recrystallized from hexane before use.

DES Preparation

The employed Deep Eutectic Solvents (DESs) [DES A choline chloride/urea 1/2; DES B choline chloride fructose/water 1/1/1; DES C choline chloride /glycerol 1/2)] were prepared by gentle heating under stirring at 70 °C for 15 min the corresponding individual components until a clear solution was obtained.

Determination of DES B density

Density of DES B was determined to be 1.21 g/mL.

For this determination, the DES (1.21 g) was weighed directly in a 1 mL volumetric flask.

Addition of a carbonyl compound to nitrostyrene: substrate activation *via* enamine
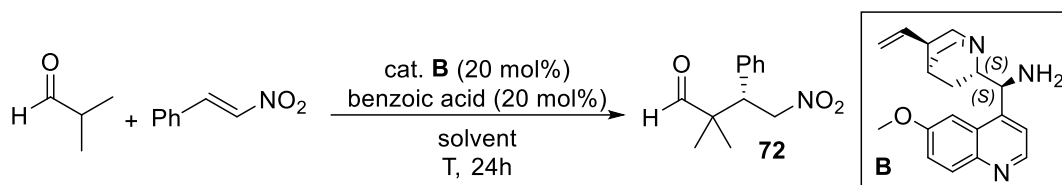
GENERAL PROCEDURE FOR STEREOSELECTIVE ORGANOCATALYZED CONJUGATE ADDITION IN DES

Catalyst **B** (17 mg, 0.053 mmol, 20 mol%) and benzoic acid (0.053 mmol 20 mol%; while investigating reaction conditions, it was observed that the desired product is formed even in the absence of the benzoic acid – see Table 2) were dissolved in the desired DES (353.3 mg – for optimization studies about reaction concentration in DES see Table 3) and kept under stirring; after 5 minutes, freshly distilled isobutyraldehyde (1.325 mmol, 5 eq) was added and the reaction mixture was kept under stirring for further 5 minutes. Nitrostyrene (0.265 mmol, 1 eq) was finally added and the reaction mixture was stirred for the reported time at the desired temperature (see Table 2 and 3). After this period, the mixture was treated with water and the desired product was extracted with Et_2O. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

When the reaction was subjected to microwave irradiation, it was run in proper MW vial.

GENERAL PROCEDURE FOR STEREOSELECTIVE ORGANOCATALYZED CONJUGATE ADDITION IN TOLUENE

Catalyst **Q** (10 mg, 0.031 mmol, 20 mol%) and benzoic acid (0.031 mmol, 20 mol%; while investigating reaction conditions, it was observed that the desired product is formed even in the absence of the benzoic acid – see Table 2) were dissolved in toluene (0.17 mL); after 5 minutes, freshly distilled isobutyraldehyde (0.77 mmol, 5 eq) was added and stirred for further 5 minutes. After this period, nitrostyrene (0.155 mmol, 1 eq) was added. The reaction mixture was kept under constant stirring for 24 hours at the desired temperature (see Table 2) and finally quenched with HCl (10% aqueous solution) (2 mL). The product was extracted with EtOAC. The collected organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

General procedure for recycle experiments

Catalyst **B** (43 mg, 0.133 mmol, 20 mol%) and benzoic acid (0.133 mmol, 20 mol%) were dissolved in the desired DES (886.7 mg) and kept under stirring; after 5 minutes freshly distilled isobutyraldehyde (3.325 mmol, 5 eq) was added and the reaction mixture was kept under stirring for further 5 minutes. Nitrostyrene (0.665 mmol, 1 eq) was finally added and the reaction mixture was stirred for the reported time at room temperature (see Table 4). After this period, hexane/iPr$_2$O 7/3 (1 mL) was added and the mixture stirred for further 2 minutes. The stirring was stopped to allow phase separation. The organic layer was removed through settling and the solvent was removed under reduced pressure; this procedure was repeated twice.

The desired product, extracted through this procedure in the organic phase, was purified by flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

The catalytic system (i.e. catalyst and acidic co-catalyst) was regenerated by benzoic acid addition (20 mol%), in the DES phase, where catalyst **B** was still dissolved. Thus, a further reaction was performed within this DES, where isobutyraldehyde (5 eq.) and *trans*-β-nitrostyrene (1 eq.) were added. This reaction mixture was subjected to the above described procedure and further reaction cycles were repeated within the same DES phase.
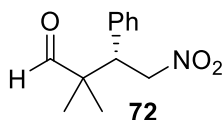
Compound **2** was purified by flash column chromatography on silica gel (eluent: Hexane/EtOAC = 9/1) to afford a colorless oil; analytical data are in agreement with the reported ones[5].

TLC R$_f$ = 0.27 (Hexane/EtOAC = 9/1, stained blue with phosphomolibdic acid)
^{1}H-NMR (300 MHz, CDCl$_3$): δ 9.55 (s, 1H), 7.35-7.20 (m, 5H), 4.88 (dd, J=12.9, 11.3 Hz, 1H), δ 4.72 (dd, J=13.0, 4.3 Hz, 1H), 3.81 (dd, J=11.2, 4.3 Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H).
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent hexane/iPrOH = 8/2, flow rate 0.8 mL/min, λ=210 nm, τ$_{minor}$=12.5 min, τ$_{major}$=17.2 min.

Addition of nitroacrylate to benzalacetone: substrate activation *via* dienamine
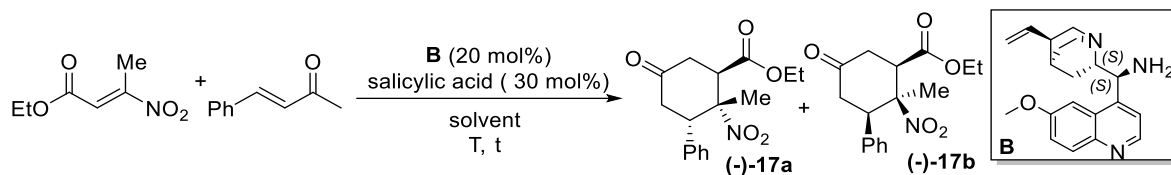
<u>GENERAL PROCEDURE FOR STEREOSELECTIVE ORGANOCATALYZED CONJUGATE ADDITION IN DES</u>

Catalyst **B** (20 mg, 0.063 mmol, 20 mol%), salicylic acid (0.094 mmol, 30 mol%) and *trans*-ethyl-3-nitrobut-2-enoate (0.314 mmol, 1 eq) were dissolved in the desired DES (314 mg) and stirred for 10 minutes; benzalacetone (0.628 mmol, 2 eq) was finally added. The reaction mixture was stirred at the desired temperature for the reported time (see Table 5) and after this period was treated with water. The desired product was extracted with Et_2O. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

When the reaction was subjected to microwave irradiation, it was run in proper MW vial.[6]

<u>GENERAL PROCEDURE FOR STEREOSELECTIVE ORGANOCATALYZED CONJUGATE ADDITION IN TOLUENE</u>

Catalyst **B** (12 mg, 0.038 mmol, 20 mol%), salycilic acid (0.057 mmol, 30 mol%) and *trans*-ethyl-3-nitrobut-2-enoate (0.19 mmol, 1 eq) were dissolved in dry toluene (0.19 mL) under N_2 atmosphere and stirred for 10 minutes. After this period, benzalacetone (0.38 mmol, 2 eq) was added. The reaction mixture was stirred at the desired temperature for 20 hours, after which solvent was removed under reduced pressure. The desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

Addition of 4-hydroxycoumarin to benzalacetone (synthesis of (*S*)-Warfarin): substrate activation *via* iminium ion
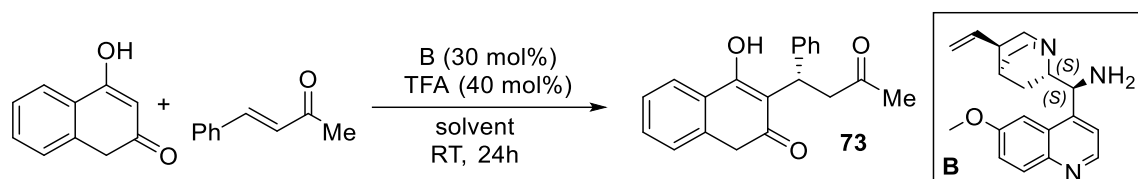
<u>GENERAL PROCEDURE FOR STEREOSELECTIVE ORGANOCATALYZED CONJUGATE ADDITION IN DES</u>

Catalyst **B** (10 mg 0.031 mmol, 20 mol%), benzalacetone (0.31 mmol, 2 eq) 4-hydroxycoumarin (0.155 mmol, 1 eq) and trifluoroacetic acid (0.062 mmol, 40 mol%) were dissolved in the desired *DES* (155 mg). The reaction mixture kept under constant stirring for 24 hours at room temperature. After this period, the reaction mixture was treated with water and the desired product was extracted with Et_2O. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified by flash column chromatography on silica gel using the mixture hexane/EtOAC 70/30 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

<u>GENERAL PROCEDURE FOR STEREOSELECTIVE ORGANOCATALYZED CONJUGATE ADDITION IN CH_2Cl_2</u>

Catalyst **B** (0.02 mmol, 20 mol%), 4-hydroxycoumarin (0.1 mmol, 1eq), benzalacetone (0.15 mmol, 2 eq) and trifluoroacetic acid (0.04 mmol, 40 mol%) were dissolved in CH_2Cl_2 (2 mL) for 12 hours at room temperature. After this period, the reaction mixture was quenched by adding 1M HCl (0.5 mL). After this period, the reaction mixture was treated with water and the desired product was extracted with EtOAC. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 70/30 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

73
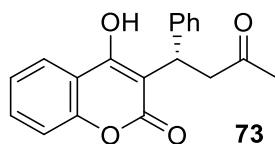
Compound **73** was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 70/30) to afford a white-off solid; analytical data are in agreement with the reported ones.[8]

TLC R_f = 0.28 (Hexane/EtOAC = 70/30, stained yellow with $KMnO_4$)

Compound **73** was found to exist in rapid equilibrium with hemiketal form in solution. The equilibrium is rapid enough so that the two forms are not observed during HPLC analysis using the mixture of hexane/iPrOH containing 0.1% TFA as eluent; however, both forms are visible in the ^{1}H NMR spectrum.[55]
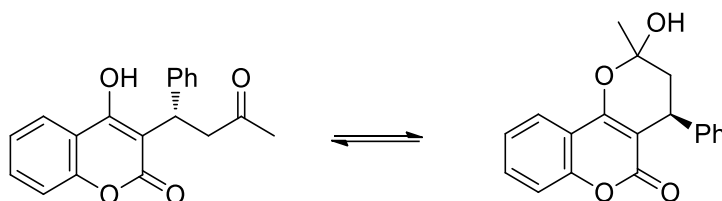
^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.95 (dd, J=13.5, 7.9 Hz, 1H$_a$+1H$_b$), 7.84 (d, J=8.0 Hz, 1H$_a$), 7.59-7.50 (m, 2H$_a$+1H$_b$), 7.39-7.21 (m, 5H$_a$+7H$_b$), 4.71-4.74 (d, J=8.3 Hz, 1H$_b$), 4.32 (dd, J =6.4, 2.8 Hz, 1H$_a$), 4.22-4.11 (m, 1H$_a$+1H$_b$), 3.89 (dd, J = 19.6, 10.2 Hz, 1H$_b$), 3.37-3.23 (m, 2H$_{a+b}$), 2.6-2.5 (m, 3.56H$_{a+b}$), 2.07-1.99 (m, 2.30H$_{a+b}$), 1.74 (s, 3H$_a$), 1.70 (s, 3H$_b$).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralpack AD column: eluent hexane/iPrOH = 8/2 +0.1% TFA, flow rate 0.8 mL/min, λ=280 nm, τ$_{minor}$=7.7, τ$_{major}$=18.8 min min.

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[55] The two forms are present in an approximately 70:30 ratio; the most and the less abundant form are indicated as **a** and **b**, respectively, in the ^{1}H NMR signals report.

Explorative studies in photocatalysis

General conditions

Reagents were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar, Acros, Fluka or VWR) and were used without further purification. Solvents were used as p.a. grade and, when necessary, were dried over activate MS and stored under N2 atmosphere. Industrial grade of solvents was used for automated flash column chromatography.

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated aluminium plates and visualized using UV light or colouring agents. Flash chromatography was carried out on silica gel (230-400 mesh).

^{1}H NMR spectra were recorded on 300 MHz (Bruker AC 300) or at 400 MHz (Bruker AC 400); proton chemical shifts are reported in ppm (δ) with the solvent reference relative internal standard (CDCl$_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker AC 300) operating at 75 MHz, or on 400 MHz spectrometers (Bruker AC 400) operating at 101 MHz, with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) with the respective solvent resonance as the internal standard (CDCl$_3$, δ = 77.0 ppm). Abbreviations are used to indicate signal multiplicity: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, and m = multiplet.

Absorption spectra were performed on a Varian Cary BIO 50 UV-vis/NIR spectrometer or an Agilent 8453 UV-vis spectrometer with a 10 mm Hellma® quartz fluorescence cuvette at room temperature.

GC measurements were performed on a GC 7890 from Agilent Technologies. Data were elaborated with Agilent ChemStation.[56]

The mass measurements were performed at the Central Analytical Laboratory of the University of Regensburg. LC-MS: Agilent QTof 6540 (MS), Agilent UHLPC (HLPC). GC-MS: Finningan MAT 710A (MS), Agilent 6890M(GC) or Jeol AccuTOF (MS), Agilent 7890B (GC).

CV measurements were performed with the three-electrode potentiostat galvanostat PGSTAT302N from Metrohm Autolab using a glassy carbon working electrode, a platinum wire counter electrode, a silver wire as a reference electrode and TBATFB 0.1 M as supporting electrolyte. The potentials were achieved relative to the Fc/Fc+ redox couple with ferrocene as internal standard.

Microwave promoted reactions were carried out in a CEM Discover® S-Class microwave reactor using 10 mL glassware capped vial.

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[56] V. V. Pavlishchuk, A. W. Addison, *Inorganica Chimica Acta* **2000**, *298*, 97-102.

General procedure for catalysis tests

For catalysis test requiring air exclusion, solid starting materials were added in a 5-mL-crimp top vial in which, after sealing, inert atmosphere was created through three cycles vacuum/ N_2. Dry solvent (unless otherwise stated, 0.1M solutions were prepared) was introduced *via* syringe; liquid reagents were finally added under stirring - transferred *via* syringe from a sealed vial, in which they were stored under N_2 atmosphere, to the reaction mixture. Two rapid vacuum/N_2 cycles were applied before subjecting the reaction mixture to stirring and constant light irradiation by LED.

For catalysis test performed under air atmosphere, the solvent was added to solid starting materials in a 5-mL open vial; liquid reagents were finally added *via* syringe under stirring. The reaction mixture was stirred under constant light irradiation by LED. When necessary, reaction progress was monitored through TLC or GC.

After the stated reaction time, irradiation was interrupted and the crude was concentrated under reduced pressure – when the reaction was carried out in low-boiling solvents, the solvent was directly evaporated, while when high-boiling solvents were used, the crude was treated with deionized H_2O and extracted with CH_2Cl_2 or Et_2O. The crude was analysed by ^1H NMR and eventually by GC/MS or LC/MS techniques.

Products identification:

In the screening experiments carried out so far, products have not been isolated but their presence in the crude has been determined through diagnostic signals:

anti isomer
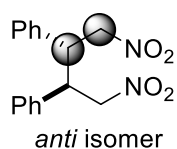
^1H NMR (300 MHz, CDCl$_3$) δ: 6.78 (dd, J = 7.8, 1.7 Hz, 2H), 4.72 (ABX, J = 13.1, 7.1 Hz, 1H), 4.55 (ABX,, J = 13.1, 7.7 Hz, 1H), 3.98-3.87 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 129.15 (s), 77.29 (s), 45.50 (s).

syn isomer
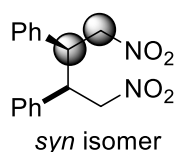
^1H NMR (300 MHz, CDCl$_3$) δ: 6.78 (dd, J = 7.8, 1.7 Hz, 2H), 4.55-4.47 (m, 1H), 4.21 (dd, J = 12.8, 3.8 Hz, 1H), 3.77-3.75 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ: 129.15 (s), 79.09 (s), 47.45 (s).
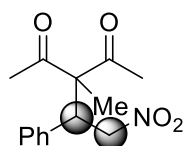
^1H NMR (300 MHz, CDCl$_3$) δ: 4.88 (ABX, J = 13.4, 10.9 Hz, 1H), 4.78 (ABX, J = 13.4, 3.7 Hz, 1H), 4.23 (ABX, J = 10.9, 3.7 Hz, 1H).
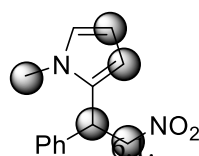
^1H NMR (300 MHz, CDCl$_3$) δ: δ 6.62-6.58 (m, 2H), 6.13 (d, J = 6.7 Hz, 2H), 4.97 (ABX, J = 11.3, 7.7 Hz, 1H), 4.92-4.85 (m, 1H), 4.76 (ABX, J = 11.3, 6.8 Hz, 1H), 3.36 (s, 3H).[57]

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[57] X. W. Dong, T. Liu, Y. Z. Hu, X. Y. Liu, C. M. Che, *Chem. Commun.* **2013**, *49*, 7681-7683.

Procedure for thiourea A0 synthesis[58]
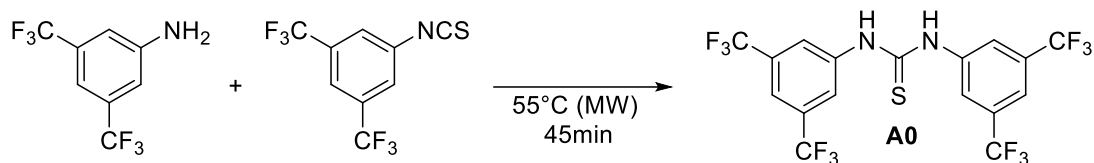
In a microwave reactor vessel, 3,5-bis(trifluoromethyl)aniline (1.1 eq., 2.18 mmol, 340 μL) was added to neat 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1 eq., 1.98 mmol, 360 μL); the reaction mixture was stirred at room temperature and subsequently heated to 55 °C and kept under stirring and costant MW irradiation for 45 minutes. After this period, the obtained solid was filtered and washed with ice-cooled CH_2Cl_2. The product was obtained as a white solid in 77% yield.

^{1}H NMR (300 MHz, DMSOd[6]) δ: 10.66 (s, 1H), 8.20 (s, 2H), 7.88 (s, 1H).

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[58] A. K. Qaroush,a A. S. Al-Hamayda, Y. K. Khashman, S. I. Vagin, C. Trolla, B. Rieger, *Catal. Sci. Technol.*, **2013**, *3*, 2221-2226.

Absorption measurements

The UV-Vis absorption spectra of nitrostyrene shows no absorption band between 400 and 800 nm; this spectroscopic behaviour guaranties that no direct excitation of this substrate occurs upon irradiation provided by green (530 nm) and blue (455 nm) LED.
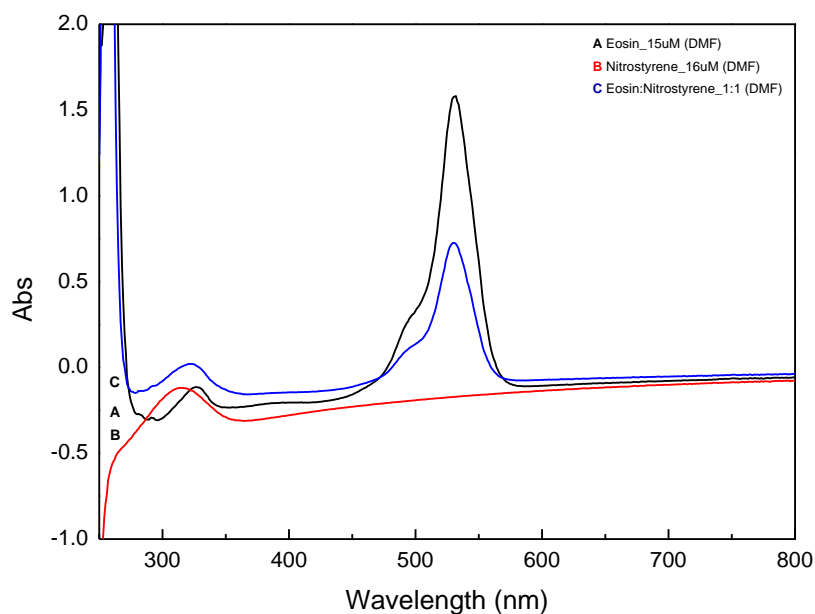
Interactions between nitrostyrene and the thiourea-based organocatalyst are not proved by the UV-Vis absorption spectra: when analysing the behaviour of an equimolar mixture of the two molecules, any new absorption band, eventually attributable to an intermolecular complex, can be observed; changing the solvent from the highly polar DMF, which could interfere in the hydrogen bonding network, to CH_3CN does not cause any evident variation.
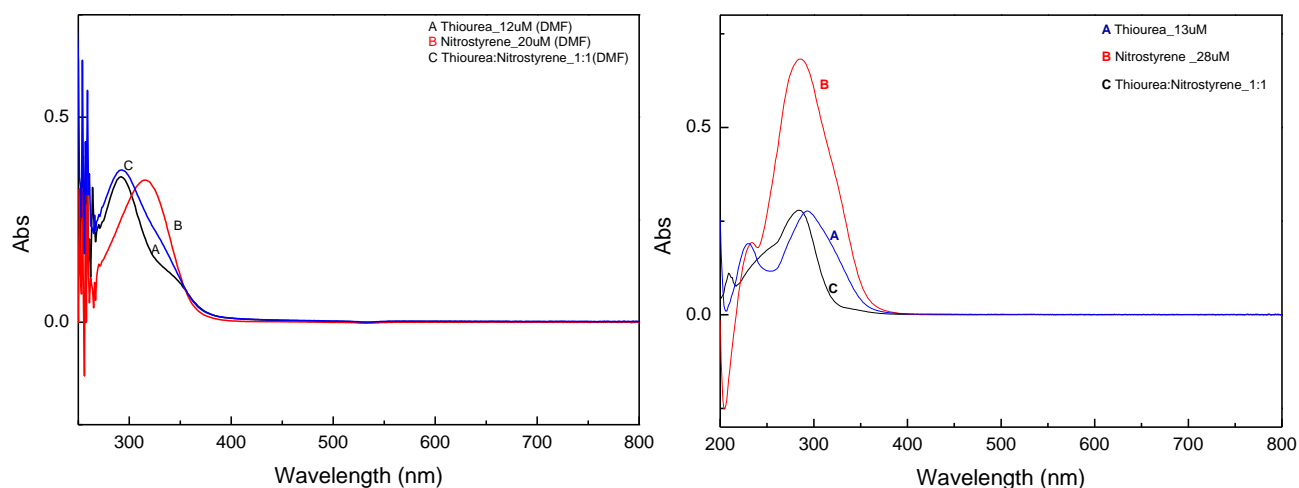
Further measurement will be required for characterizing the spectroscopic behaviour of reaction mixtures undergoing interesting transformations.

Cyclic voltammetry measurements

Cyclic voltammetry measurements allowed the determination of nitrostyrene and thiourea reduction potential. Besides, when a 1:1 mol. mixture of the substrate and the organocatalyst was measured, a new reduction peak appeared, characterized by a less negative value. This electrochemical evidence can be considered as proof for the formation of an intermolecular complex, where a lower amount of energy is required for electron donation to the substrate thanks to the electron withdrawing effect of the organocatalyst coordinated to it.
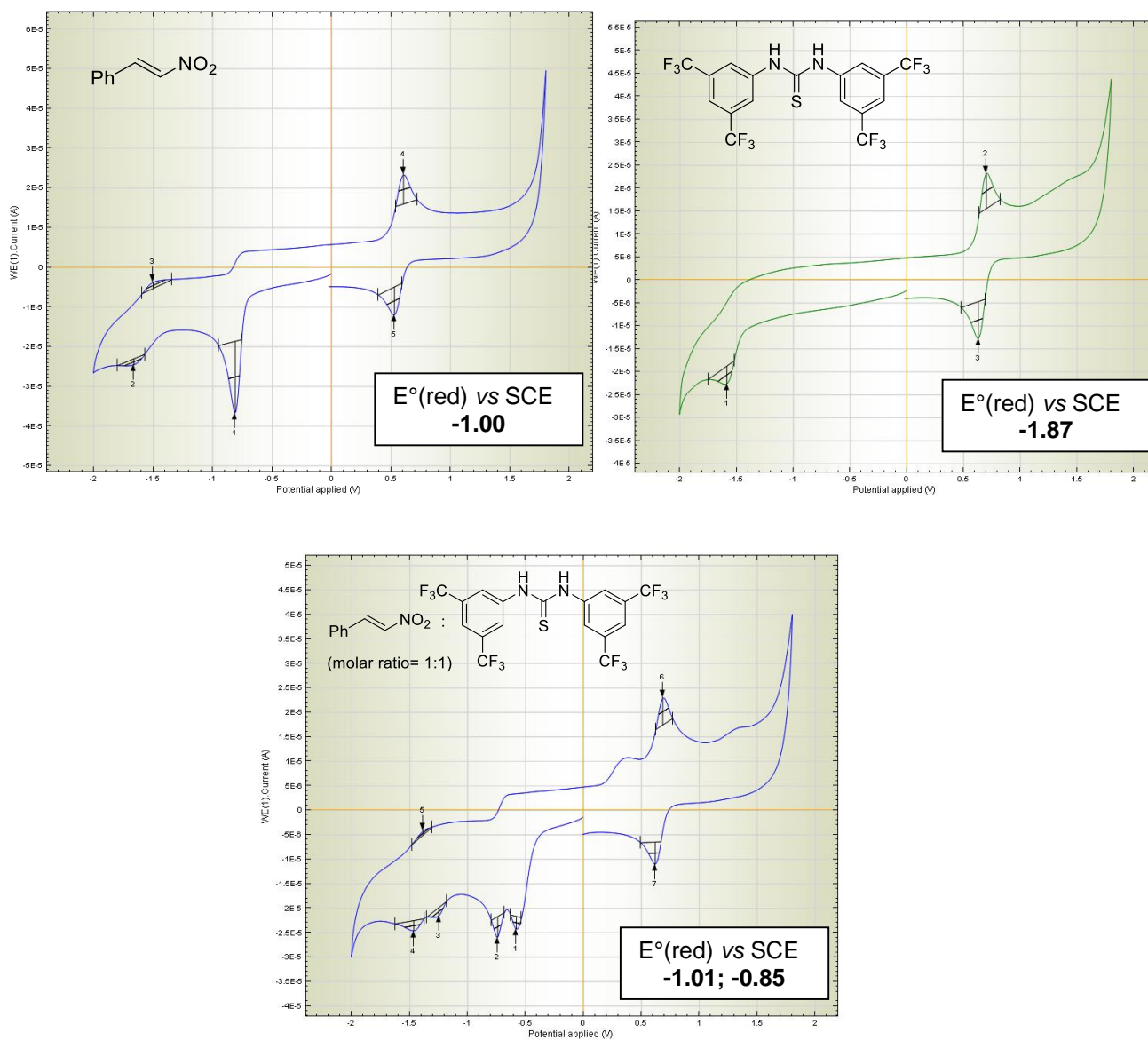
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