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Catalysts' evolution in the asymmetric conjugate addition of nitroalkanes to electron-poor alkenes

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The conjugate addition of nitroalkanes to electron-poor alkenes is a widely used process which only in the late nineties of the last century has efficiently evolved in its asymmetric version. Synthetic protocols based on chiral organocatalytic methods have been largely exploited for the generation of optically pure γ-nitro derivatives through carbon–carbon bond formation. Chiral metal–ligand complexes have also been successfully employed for these conjugate additions, although their use in the synthesis of targeted bioactive compounds still appears rather limited. Most of the practical applications of the obtained adducts are based on the easy conversion of the nitro group into a primary amine directed to the preparation of nitrogen-containing structures. This review aims to provide a journey of the catalyst usage for the enantioselective conjugate addition of nitroalkanes to electron-poor olefins, from the early attempts to the latest achievements. The discussion is categorized according to the nature of different catalytic systems, and a final section reporting selected applications to targeted compounds is provided.

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1. Introduction

The conjugate addition of stabilized enolate anions to electron-poor alkenes has been firmly established as one of the leading synthetic processes since its discovery by Michael at the end of the nineteenth century. This reaction, essentially promoted by mildly basic conditions, has been largely employed for carbon–carbon bond formation and often represents the cornerstone for the assembling of complex structural frameworks.[1] The advent of catalyzed asymmetric synthesis has found in these conjugate additions an ideal benchmark to develop new chiral catalysts endowed with growing

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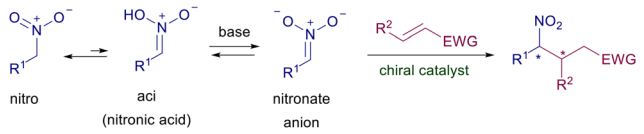
Roberto Ballini is Full Professor of Organic Chemistry at the University of Camerino (Italy) and Past President of the Organic Chemistry Division of the Italian Chemical Society (SCI). His scientific activity is mainly dedicated to organic synthesis, with a particular interest in the chemistry of nitroalkanes, including the formation of single and double C,C bonds and their conversion into other important functionalities. He is the author of about 300 papers, including a large number of review articles. Furthermore, he is editor of two books in the Green Chemistry Series by the RCS, Eco-Friendly Processes and Procedures of Fine Chemicals *and* Green Synthetic Processes and Procedures, *and the monographic book* Nitroalkanes: Synthesis, Reactivity and Applications *(Wiley-VCH).*

Alessandro Palmieri

Alessandro Palmieri obtained his Laurea degree cum laude *in Chemistry in 2002 at the University of Camerino (Italy) where, five years later, he received a PhD degree in Chemical Sciences. In 2008 he moved, as a visiting postdoctoral fellow, to the ITC Laboratory at the University of Cambridge (Prof. Steven V. Ley). In 2014 he was appointed associate professor in Organic Chemistry at the University of Camerino. His research interests involve (i) the chemistry of aliphatic nitro compounds, (ii) the realization of new one-pot protocols for generating and derivatizing heterocyclic systems, (iii) the preparation of solid supported reagents, and (iv) the development of new sustainable processes and (v) flow chemical protocols.*



Scheme 1 Aci-nitro equilibrium and conjugate addition to electron-poor alkenes.

levels of efficiency and sustainability.[2] Nitroalkanes, by virtue of the tautomeric aci-nitro equilibrium, can be easily converted into nitronate anions which are effective nucleophilic reagents toward several electrophiles including electron-poor alkenes (Scheme 1).[3]

In this reaction, one or more stereocenters can be generated, according to the nature of the reactants employed, and thus a diastereo- and/or enantiocontrol can be exerted on the corresponding adduct providing that a suitable chiral environment is applied. The synthetic versatility of the nitro group has been widely demonstrated over many years through its manifold transformations into other functional groups. The reduction of the nitro group into a primary amine is certainly the most practiced transformation and represents a flexible gateway to a plethora of nitrogenated compounds.[4] On the other hand, the nitro to carbonyl conversion, also known as the Nef reaction,[5] the reductive denitration and the nitrous acid elimination introducing an unsaturation into the molecular framework are complementary processes highlighting the powerful synthetic attributes of the nitro moiety.[6] The electrophilic character of the employed Michael acceptors is of crucial importance in leading to fast and efficient additions, and may substantially be tuned through a suitable choice of the nature of the electron-withdrawing group. α,β-Unsaturated carbonyls play a dominant role among Michael acceptors for their remarkable reactivity and for the electronic attributes of the carbonyl group. The electrophilicity of the carbonyl and the oxygen basic center have been conveniently used to generate covalent or electrostatic linkages with chiral catalysts in order to make their action more powerful. Other electron-withdrawing groups such as the cyano,[7] the arylsulfonyl and the phosphonyl groups have been used in the conjugate additions with nitroalkanes, but less frequently than their carbonyl counterparts.[8] A special mention can be made for nitroalkenes, which are the most reactive Michael acceptors and are used to generate 1,3-dinitro derivatives amenable for a subsequent reductive process leading to optically active 1,3-diamino compounds.[9]

The asymmetric procedures, which until twenty years ago still were in their infancy for this reaction, have been propelled by the need to ensure increasingly efficient catalytic devices to generate polyfunctionalized chiral compounds as pivotal intermediates in multistep synthetic protocols. This review is not intended to provide a comprehensive coverage of this topic, but aims to critically present the chiral catalyst developments from the early attempts to the latest achievements. The discussion privileges the presentation of the original procedure in which the catalyst was first used. Selected examples of other substrate combinations are reported only on the basis of their envisaged synthetic impact. Finally, the application of the discussed protocols to paradigmatic syntheses of targeted bioactive compounds is reported in the final section.

Marino Petrini

Marino Petrini obtained a Laurea degree in Chemistry in 1980 (University of Camerino, Italy). In 1983 he became a Research Associate at the University of Camerino and during the period 1987–88 he was a visiting scientist at the University of Montreal (Prof. S. Hanessian). In 1992 he was appointed Associate Professor and then Full Professor in Organic Chemistry at the University of Camerino. His research interests mainly deal with the following topics: synthesis and reactivity of aliphatic and aromatic nitro compounds; functionalization of azole derivatives; synthesis and reactivity of imino derivatives.

2. Organocatalyzed reactions

At the dawn of asymmetric conjugate additions involving nitroalkanes, purely organic molecules were the first optically active compounds tested as catalysts or promoters. The first example dates back to 1975, using quinine in the reaction of 1-tosylnitroethane with methyl vinyl ketone.[10] Later on, different organic molecules were progressively tested in this reaction, and the most used class of catalysts showing better performances are chiral secondary amines and ureas/amido compounds (Fig. 1). Interestingly, to these classes of nitrogen derivatives pertain complementary ways of action, since primary and secondary amines are known to act through covalent iminium ion catalysis activating the unsaturated carbonyls while ureas/amides enhance the reactivity of nitroalkanes. Compared with other amino derivatives, cinchona-derived chiral primary amines were introduced only at the end of the first decade of this century, including soon after peptide foldamers and aldolase biomimetic catalysts. Phase-transfer catalysts including chiral crown ethers and quaternary ammonium salts have been successfully employed through the years, although their use for practical purposes is totally surpassed by chiral pyrrolidine and thiourea-based catalysts.

2.1 Pyrrolidines and related derivatives

Chiral cyclic secondary amines are effective in the reaction of nitroalkanes with α,β-unsaturated carbonyls *via* pyrrolidinium ion catalysis which enhances the electrophilic character of the double bond towards the nitronate addition (Scheme 2). The

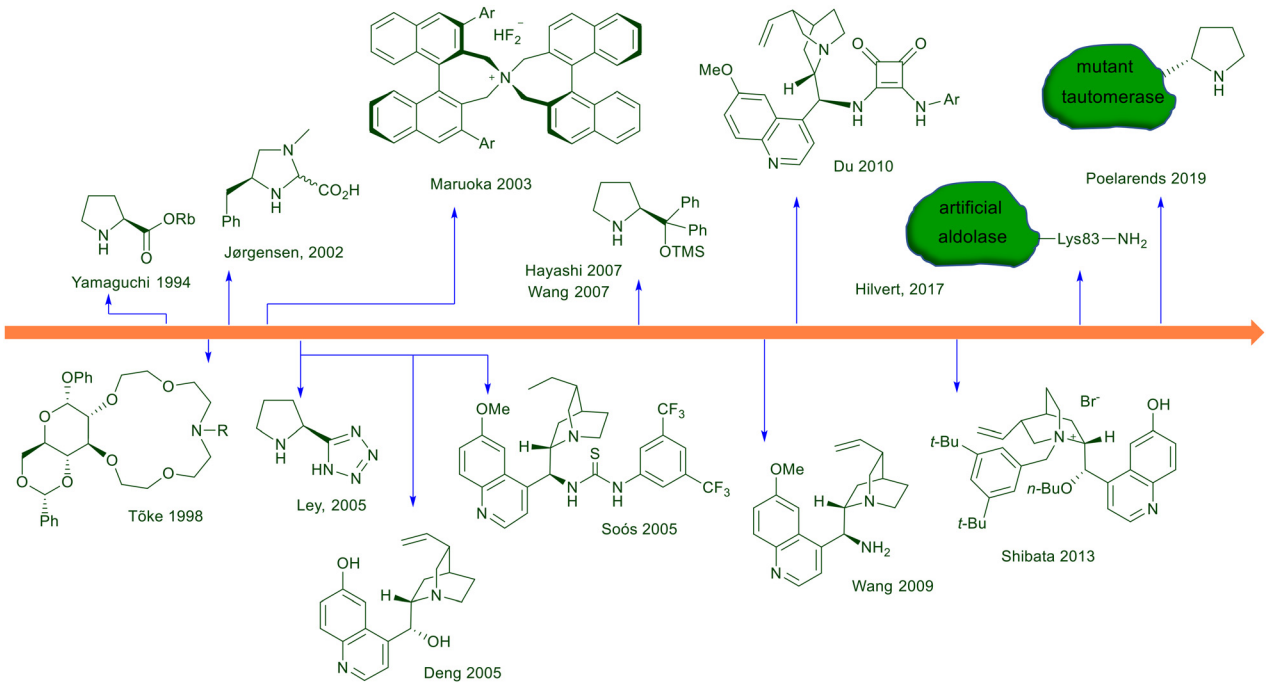
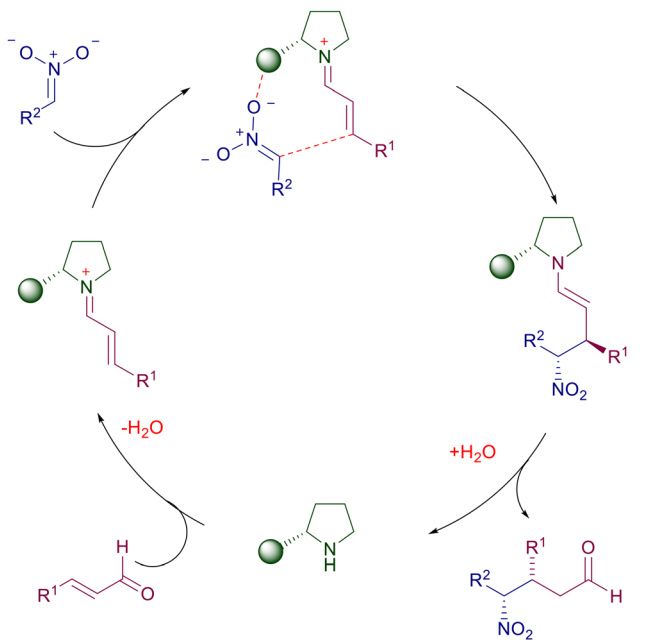


Fig. 1 Chronological development of organocatalysts employed for the asymmetric conjugate addition of nitroalkanes to electron-poor alkenes.

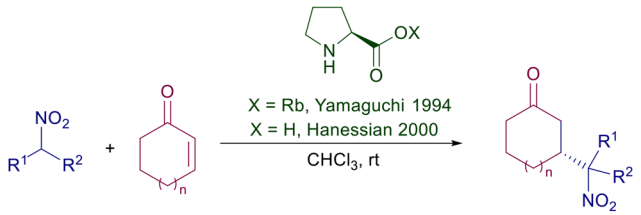


Scheme 2 Catalytic cycle for conjugate additions using chiral pyrrolidines.

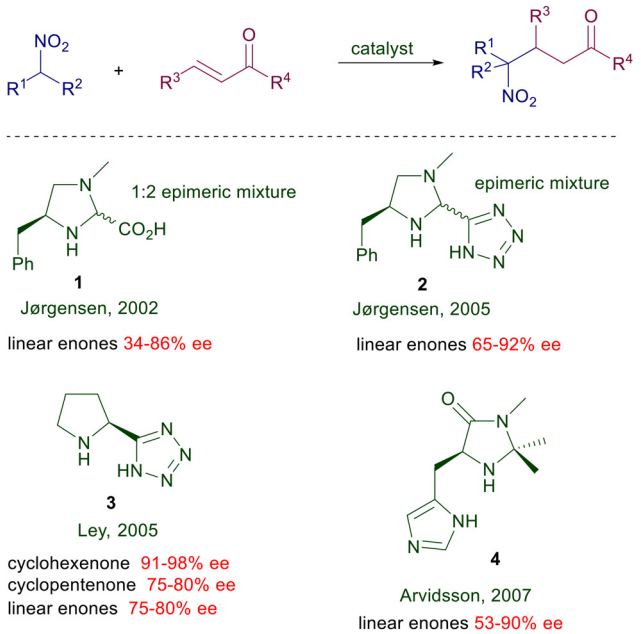
appendage of the pyrrolidine ring may exert a synergistic effect through hydrogen bonding with the oxygen atoms of the nitro moiety, enabling an appropriate stereofacial nucleophilic attack (cooperative intramolecular catalysis).

2.1.1 Proline and imidazolidine derivatives. Proline, a natural α-amino acid readily available in both enantiomeric forms, was the first chiral pyrrolidine employed as catalyst for the conjugate addition of nitroalkanes to enones. It was initially used as rubidium salt which was already proved to be effective in the classical Michael addition using malonate esters.[11] The preliminary results in the enantioselective reaction of nitroalkanes with linear or cyclic ketones were satisfactory (38–86% ee) considering the state of the art at that time.

Structural modifications of the pyrrolidine ring have also been attempted using 4-hydroxyproline derivatives and even the rubidium salt of (*S*)-azetidine-2-carboxylic acid, but the improvements were rather modest. A notable step forward was evidenced in the use of L-proline limitedly to the reaction of nitroalkanes with cycloalkenones introducing *trans*-2,5-dimethylpiperazine as an equimolar additive (Scheme 3).[12] The additive is instrumental in providing superior ee values using proline over its rubidium salt, although its role in the asymmetric process has not been ascertained. Interestingly, non-linear effects were observed with the use of the proline–dimethylpiperazine couple but not with proline rubidium salt. All these results indicate that proline alone is unable to provide a notable stereochemical bias, probably because of the limited ability of the carboxylate moiety to efficiently coordinate the nitronate anion. This item has been confirmed moving to imidazolidine derivatives bearing a carboxylic group (Scheme 4).[13] The Jørgensen's catalyst **1** is used as an epimeric mixture, showing that the effect brought by the carboxylic group is practically irrelevant on the stereochemical outcome since the *E* iminium ion intermediate is favored over the *Z* by 3 kcal mol^{-1} according to PM3 calculations. The tetrazole unit mimics the carboxylic group in several practical applications, and therefore a logical upgrade of the proline-based catalysts



Scheme 3 L-Proline and its rubidium salt in the reaction with cycloalkenones.

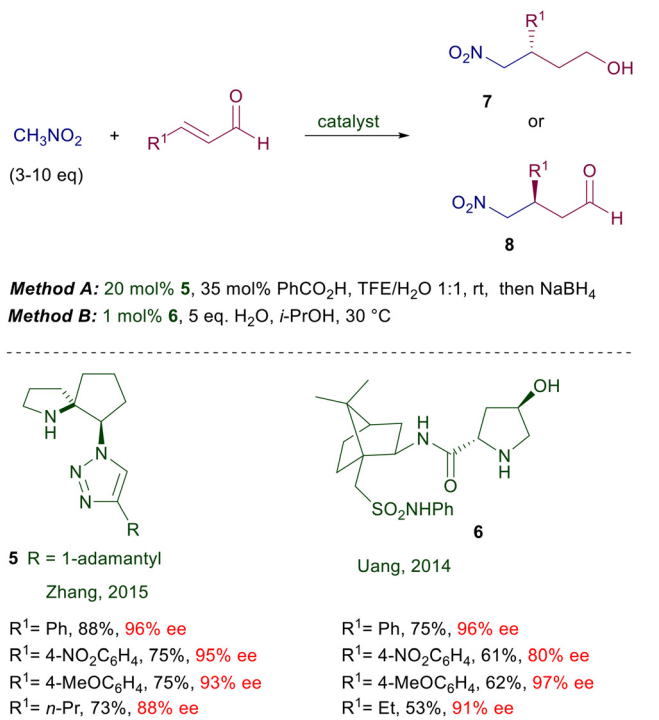


Scheme 4 Conjugate additions using pyrrolidines and imidazolidine catalysts.

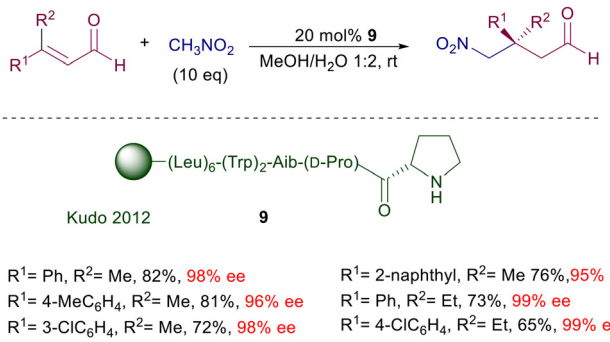
has involved the use of these tetrazole-containing catalytic systems. The results obtained using the chiral imidazolidine **2** are superior compared with those recorded with the acid analogue.[14] This trend is confirmed by the results obtained by Ley using the proline analogue **3** which is effective both on linear than cycloalkenone substrates.[15] The importance of the proximity effect exerted by the tetrazole unit is evidenced by the poor enantioselectivity (28% ee) obtained in the reaction of cyclohexenone with 2-nitropropane using a catalyst homologue of **3** in which the two heterocycles are connected by a methylene bridge.

These findings have spurred the exploitation of other surrogates of the carboxylic group such as the phosphonate group, but with limited success.[16] The behavior of imidazolidinone **4** obtained from L-histidine parallels that of chiral imidazolines also regarding the poor diastereoselectivity evidenced using primary nitroalkanes as reactants.[17] In the attempt to increase the stereochemical bias of the catalytic system, a rigid spiropyrrolidine embedding a triazole moiety **5** has been devised for the addition of nitromethane to enals (Scheme 5).[18] The nitro alcohol **7** obtained after reduction is formed with high enantioselectivity especially when 3-arylenals are used as substrates.

In the same reaction leading to nitro aldehyde **8**, the pyrrolidine–camphorsulfonamide catalyst **6** shows enhanced performances considering the very low charge employed.[19] Interestingly, addition of a few equivalents of water enables a sensible acceleration of the reaction, as also observed in related processes. According to the general mechanism reported in Fig. 1, a crucial role seems to be played by the acidic sulfonamide NH group in linking by hydrogen bonding the nitronate anion. It is worth noting that also for the latter catalysts the utilization of primary nitroalkanes affords the corresponding adducts with very poor diastereoselectivity, although with catalyst **6** the ee for each diastereomer is satisfactory (88–96% ee). Peptides bearing a terminal proline unit can also be involved in organocatalytic processes. The resin-supported peptide catalyst **9** has been employed for the enantioselective conjugate addition of nitromethane to β,β-disubstituted enals in hydroalcoholic solution (Scheme 6).[20] This catalyst features a helical portion made of



Scheme 5 Spiropyrrolidines and prolinamide-based organocatalysts.



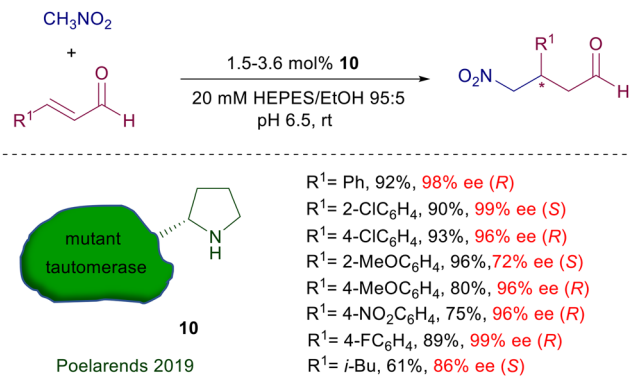
Scheme 6 Resin-bounded peptide catalyst bearing a terminal proline residue.

six leucine units and the non-proteinogenic 2-aminoisobutyric acid (Aib), which enhance the reaction rate and the enantioselectivity. At the end of the reaction the catalyst is just filtered off, but its reuse in further processes led to a notable conversion decrease probably caused by an oxidative deactivation. Enzymes bearing an *N*-terminal proline are the last developed biocatalytic systems containing this amino acid. The enzyme 4-oxalocrotonate tautomerase, specifically the F50A mutant species **10**, is able to catalyze the Michael addition of nitromethane to enals (Scheme 7).[21] The reaction is carried out in HEPES buffer (*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid) with a minimum amount of ethanol at room temperature.

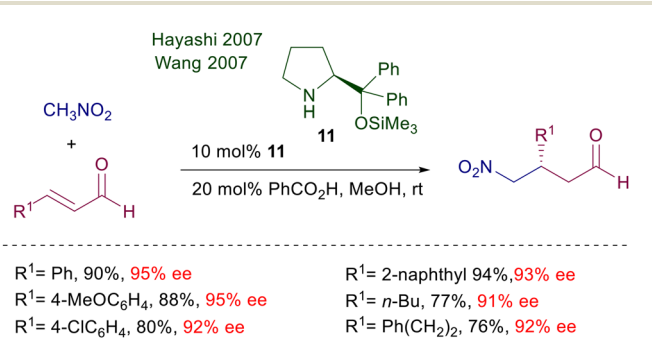
Interestingly, the absolute stereochemistry of the resulting γ-nitroaldehyde is affected by the position of the substituent in the aryl ring, being *S* with *ortho*-substituents and *R* with *meta* and *para* substituted aryls. This effect is probably due to a relocation of the aryl group in the enzyme active pocket or a stereofacial shielding effect. The ability of this enzyme to catalyze crossed aldol condensations as well has been exploited in a four-step biocatalytic cascade synthesis of γ-nitrobutyric acids starting from acetaldehyde and arylaldehydes. The initially formed enal reacts with nitromethane, and finally the resulting γ-nitroaldehyde is oxidized to the acid by oxygen catalyzed by the NAD^+/NADH redox couple. Engineered tetrameric streptavidin has been recently used for the same purpose, leading to encouraging results for the reaction of nitromethane with cinnamaldehyde.[22]

2.1.2 Prolinol derivatives. Structural modifications of the proline system also included the synthesis of diarylprolinol derivatives formerly used for the preparation of chiral oxazaborolidines and subsequently employed as catalysts in other processes including conjugate additions.[23] Particularly, since its first trials *O*-trimethylsilyldiphenyl prolinol **11** proved very effective in the conjugate addition of nitromethane to enals (Scheme 8).[24,25] Interestingly, neither unprotected diarylprolinol nor trifluoromethylarylprolinol gave results comparable with **11**. Furthermore, the reaction efficiency is greatly enhanced using methanol or ethanol as solvents and benzoic acid as additive. The reactivity of primary nitroalkanes also leads to excellent results in terms of enantioselectivity, but no diastereoselectivity can be recorded. Later on, the same catalyst **11** was used under slightly different reaction conditions for the same reaction without any notable improvement.[26] The reduced reactivity of α,β-unsaturated esters over enals and the inability to use the iminium ion catalytic approach with them led to the development of synthetic protocols for the one-pot oxidative esterification of the obtained γ-nitroaldehyde to the corresponding γ-nitroesters with NBS in methanol.[27]

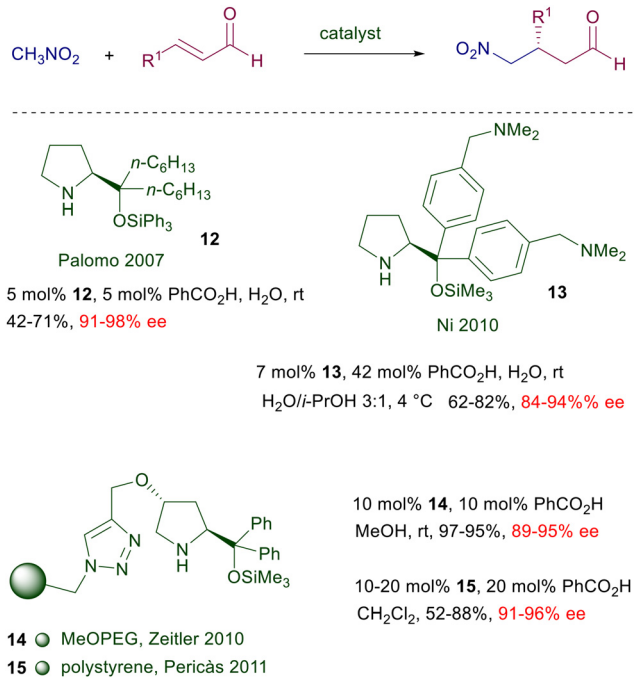
Despite the excellent results obtained with prolinol **11**, a number of structural modifications have been proposed in order to carry out the reactions in water, or for recovering and recycling the catalyst (Scheme 9). Catalyst **12** has been designed with the aim of increasing its water compatibility and the steric constraint improving the *E* geometry of the intermediate iminium ion.[28] The hexyl linear chain and the *O*-triphenylsilyl group provide better results over other shorter or longer alkyl chains in the catalyst. In order to increase the water solubility of the catalyst, a tertiary amino group was applied as substituent of the aryl groups in catalyst **13**.[29] The superior solubility over other catalysts is produced by the formation of an ammonium salt with benzoic acid, which in this scope is used in a larger amount than usual. The catalyst can also be recycled, keeping the aqueous solution for subsequent reactions, maintaining a good level of enantioselectivity but with prolonged reaction times and a drop in the chemical yield. The immobilized catalyst **14** prepared from 4-hydroxy-



Scheme 7 Tautomerase catalyst embedding a proline residue.



Scheme 8 The classical and efficient *O*-trimethylsilyldiphenyl prolinol catalyst.



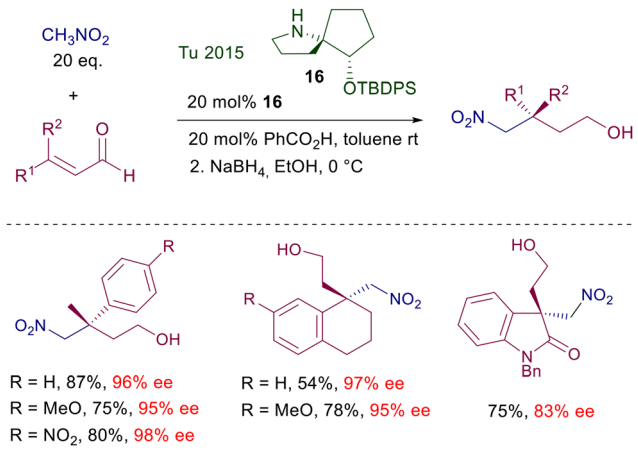
Scheme 9 Structural modifications of chiral prolinol catalysts.

proline shows good performances in terms of enantioselectivity and recyclability.[30] Notably, the crude products obtained after simple work-up do not require further purification. A related polystyrene-bound catalyst **15** gives similar results but its recyclability has not been tested.[31] Attempts to improve the catalytic activity by introducing imidazolium salts into the 4-hydroxyprolinol systems, thus generating ionic liquids, have not given significant results.[32] The first successful generation of quaternary stereocenters by reaction of nitromethane with β,β-disubstituted enals using proline derivatives was carried out employing a chiral spiropyrrolidine catalyst **16** (Scheme 10).[33] Subsequent reduction of the aldehyde ensures stability of the corresponding nitro alcohols and prevents the products from undergoing a retro-Michael reaction.

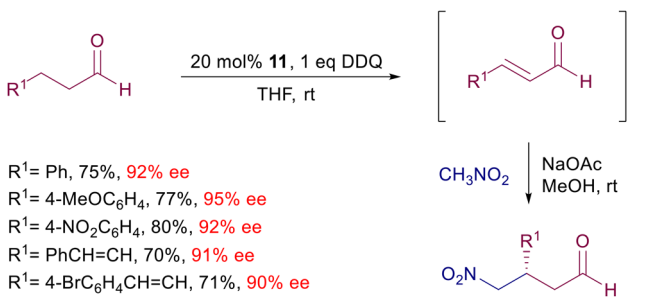
The process shows a notable efficiency level and can be applied to several functionalized substrates. The stereochemical bias offered by the rigid bicyclic framework is probably far superior to simple prolinols, and parallels the behavior further observed with triazole catalyst **5**. A notable drawback in this protocol stems from the elaborate multistep synthesis required to prepare catalyst **16** which obviously cannot take advantage of the chiral pool as many other pyrrolidine-based catalysts.

The limited stability of enals led to the development of an interesting protocol involving the one-pot oxidation of alkanals to enals followed by the conjugate addition of nitromethane (Scheme 11).[34] Catalyst **11** generates the enamine intermediate of the alkanal, which is promptly oxidized by DDQ to the corresponding enal. Sodium acetate provides the basic milieu for the subsequent addition of nitromethane *via* the usual iminium ion. Interestingly, application of this procedure to γ,δ-unsaturated aldehydes leads to the β-regioselective addition of nitromethane to the intermediate dienal.

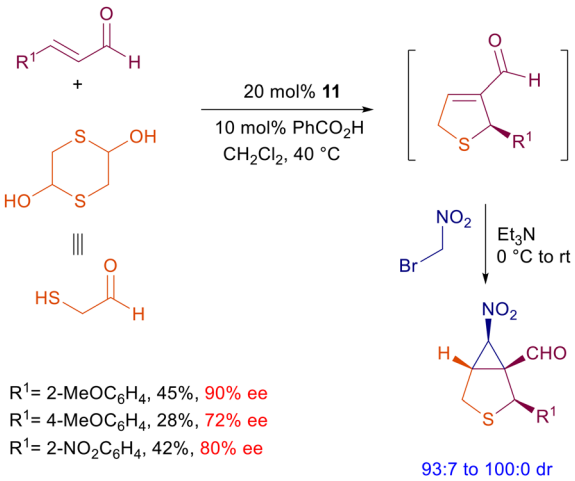
The wide success of prolinol **11** as a pyrrolidine-based catalyst for several applications can be ascribed to its ease of preparation from proline and the rewarding results obtained in terms of chemical yield and enantioselectivity. A still standing problem associated with **11** and related catalysts is practically the lack of diastereoselectivity detected using primary nitroalkanes. However, the involvement of functionalized nitroalkanes in cascade or tandem processes often leads to better stereodefined products, probably because of a thermodynamic equilibration of the α-nitro stereocenter which is more notable in cyclic products. Eventually, this equilibration can be forced toward the more stable stereoisomer by an added base in a further step. Bromonitromethane has been involved in several synthetic processes for the preparation of chiral nitrocyclopropane derivatives.[35] Recently, this reagent was used in a one-pot process for the preparation of bicyclic derivatives embedding the nitrocyclopropane moiety (Scheme 12).[36] The whole process consists of a preliminary sulfa-Michael reaction of 2-mercaptoacetaldehyde generated by its dimer with enals followed by an intramolecular aldol condensation. The reaction, catalyzed by prolinol **11**, affords a chiral dihydrothiophene intermediate which undergoes a



Scheme 10 Spiropyrrolidine embedding a silyl ether appendage.



Scheme 11 One-pot oxidative conversion of aldehydes into enals followed by conjugate addition of nitromethane catalyzed by prolinol **11**.

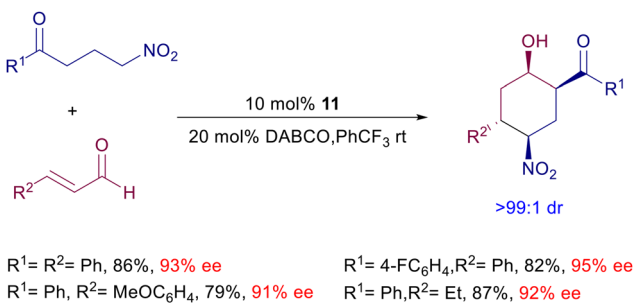


Scheme 12 Synthesis of nitrocyclopropane derivatives.

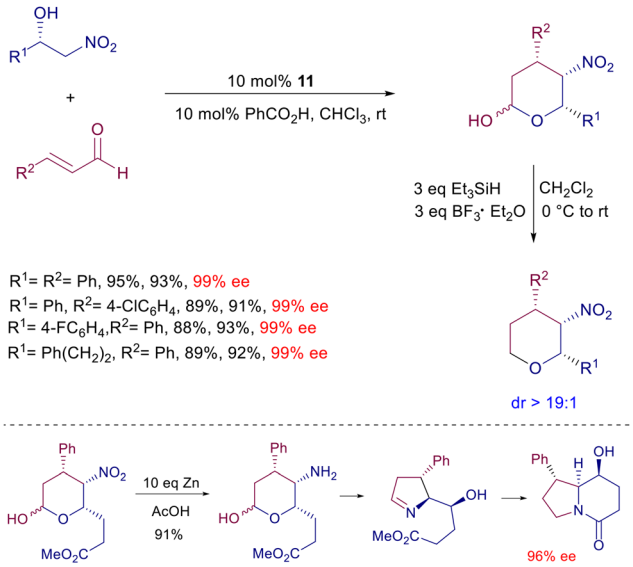
tandem conjugate addition-nucleophilic substitution to the final bicyclic derivative. The chiral prolinol is supposed to be active in both steps *via* iminium ion catalysis. The modest chemical yields recorded seem to be associated with the first step, which also affects the enantioselectivity of the target products which are, however, obtained with high diastereoselectivity. 2-Aryl-3-nitrocyclopentancarboxaldehydes can be prepared by reaction of 3-bromonitropropane with enals using catalyst **11** following the Michael-nucleophilic substitution strategy.[37] Remarkably, the reaction conditions enable outstanding control in the formation of three stereocenters including the labile α-nitro one by thermodynamic equilibration.

The conjugate addition of γ-nitroketones to enals can be coupled with an intramolecular aldol reaction leading to densely functionalized nitrocyclohexanol derivatives (Scheme 13).[38] Four stereocenters are generated in a single synthetic operation with an outstanding level of diastereoselectivity and satisfactory ee values. This process is also possible starting from allylic alcohols as enal precursors exploiting an *in situ* preliminary oxidation using the TPAP/NMO couple.

Optically active nitro alcohols obtained by an asymmetric Henry reaction can be used as substrates in the enantio-



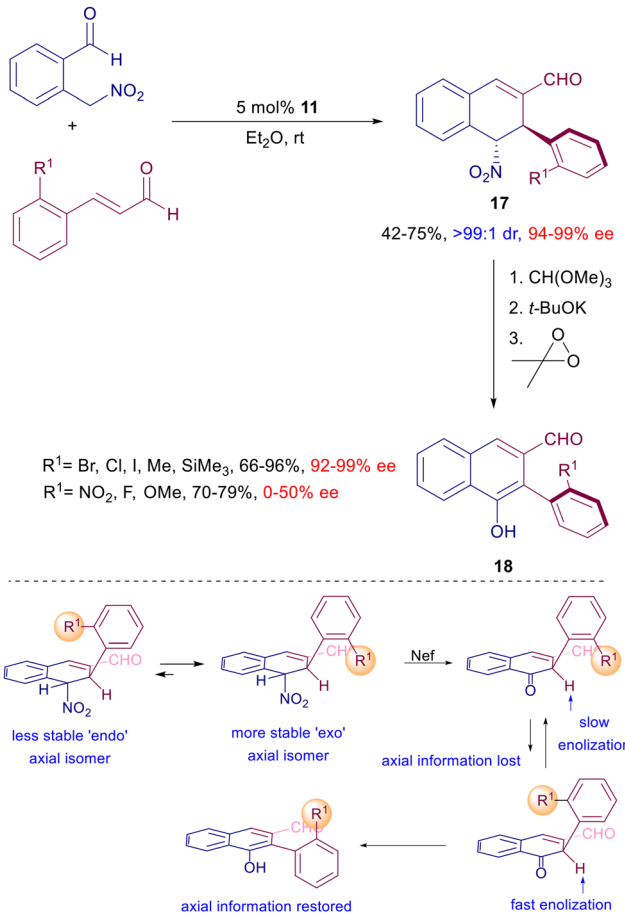
Scheme 13 Tandem conjugate addition/aldol reactions catalyzed by chiral prolinol **11**.



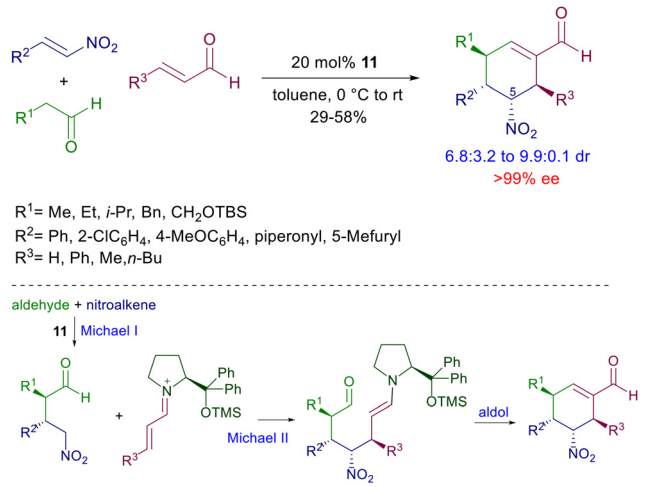
Scheme 14 Synthesis of nitrolactols and their application to the preparation of optically active indolizinones.

selective reaction with enals catalyzed by prolinol derivative **11** (Scheme 14).[39] The initially formed conjugate adducts undergo a spontaneous cyclization leading to an epimeric mixture of the corresponding lactols. The high diastereo- and enantioselectivity of the process is evidenced by the subsequent reductive conversion of the lactols by triethylsilane, *via* oxonium ion intermediate, giving enantiopure tetrahydropyrans. The synthetic usefulness of these derivatives has been demonstrated converting a specific lactol bearing an ester appendage to a chiral indolizinone compound by zinc reduction under acidic conditions. This very efficient conversion involves a cascade process entailing the nitro group reduction, intramolecular imination, imine reduction and final lactamization. The reaction of 2-nitromethylbenzaldehyde with *ortho*-substituted 3-arylenals catalyzed by **11** offers an additional intriguing aspect beyond the expected asymmetric induction of the obtained products (Scheme 15).[40]

Besides the two formed stereocenters, dihydronaphthalenes **17** feature additional axial chiral information controlled by the thermodynamic stability of the '*exo*' rotamer over the '*endo*' one. The nitro to carbonyl conversion (Nef reaction), after carbonyl protection, of compounds **17** affords naphthalenone intermediates in which the axial chiral information is lost, but since the '*endo*' rotamer is enolized faster than the '*exo*' one, the axial chiral information is restored in the final biaryls **18**. It should be observed that this effect tends to considerably decrease with the reduced dimensions of the *ortho* substituents. The conjugate addition of nitroalkanes can also be included in multistep processes involving other nitro derivatives as substrates. In a seminal paper, Enders and co-workers elaborated a procedure entailing a three-component coupling of aldehydes, enals and nitroalkenes catalyzed by **11** leading to the formation of cyclohexene carbaldehydes controlling the



Scheme 15 Enantioselective synthesis of optically active biaryls catalyzed by **11**.



Scheme 16 Three-component coupling involving a cascade Michael–Michael–aldol condensation catalyzed by **11**.

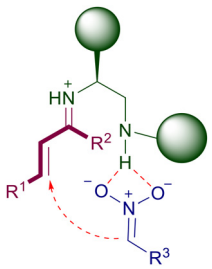


Fig. 2 Catalytic action of chiral 1,2-diamino compounds in the conjugate addition of nitroalkanes with enones.

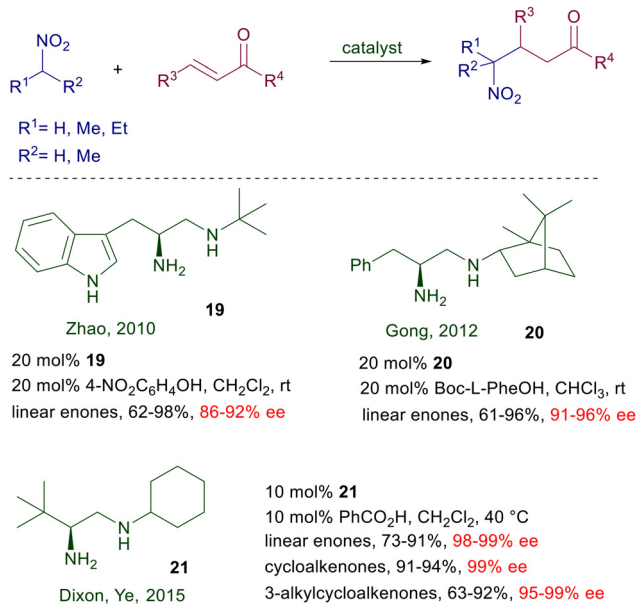
generation of four stereocenters (Scheme 16).[41] The obtained diastereomeric mixture was epimeric at C-5 with an outstanding level of enantioselectivity for each stereoisomer. The cascade process involves a preliminary conjugate addition of the aldehyde to the nitroalkene *via* enamine catalysis followed by the usual addition of the resulting γ-nitroaldehyde to the enal *via* iminium ion catalysis. The catalytic cycle ends with the ring closure by aldol condensation. This strategy has been subsequently implemented using other functionalized nitroalkenes for the preparation of polycyclic derivatives.[42]

2.2 Primary amines and peptides

The iminium ion catalysis can also be exploited using primary amines providing that an acid co-catalyst is added.[43] These catalysts have been particularly developed for the conjugate additions of nitroalkanes to enones, which require a more reactive amino derivative to generate the active iminium ion. Particularly, the vast majority of the catalysts employed are actually 1,2-diamines in which the second nitrogen atom is a secondary or a tertiary amine. Thus, the catalytic action is jointly provided by the two amino groups according to the general interaction depicted in Fig. 2. The secondary or tertiary amino group interacts with the nitronate anion through hydrogen bonding, enabling the appropriate proximity effect required for an efficient addition.

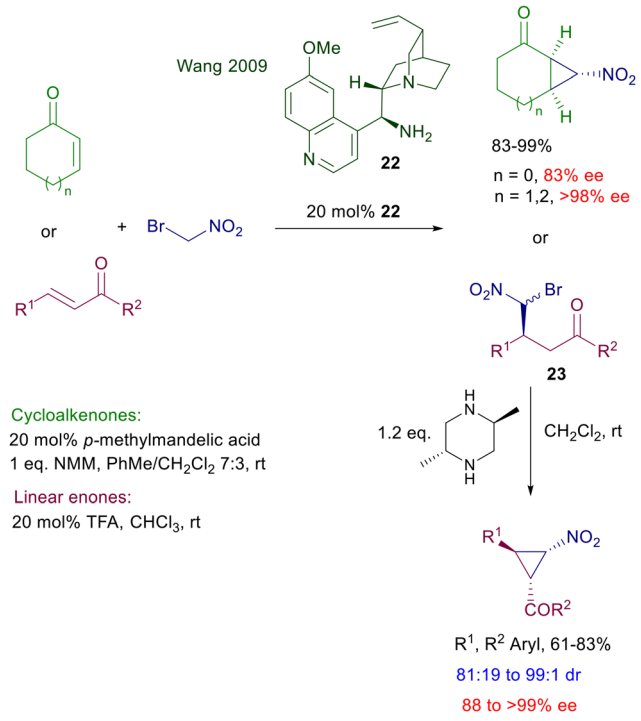
Chiral 1,2-diamines obtained from α-amino acids have been tested for the conjugate addition of nitroalkanes with enones (Scheme 17). The L-tryptophan-derived catalyst **19** was proved to be effective for the reaction of 2-nitropropane with linear enones.[44] Enforcement of the chirality by introducing a camphor residue in catalyst **20** and *N*-Boc-phenylalanine as additive was attempted with only modest improvements.[45]

Increasing the steric crowding around the primary amino group in catalyst **21** proved very effective in leading to an excellent enantioselectivity for the reaction of nitromethane with linear enones and cycloalkenones even bearing a C-3 substituent.[46] The latter protocol thus allows an efficient entry to γ-nitroketone derivatives featuring quaternary stereocenters to be used as intermediates for the synthesis of sesquiterpenoid skeletons. Primary amines derived from cinchona alkaloids are probably the most employed diamino derivatives for these conjugate additions.[47] The pseudoenantiomeric relationship between the quinine and quinidine series enables a versatile access to both enantiomeric forms of the possible adducts. The acidic cocatalyst plays a fundamental role by protonation of the quinuclidine moiety, affecting the rate of formation of



Scheme 17 Catalytic activity of various chiral 1,2-diamines.

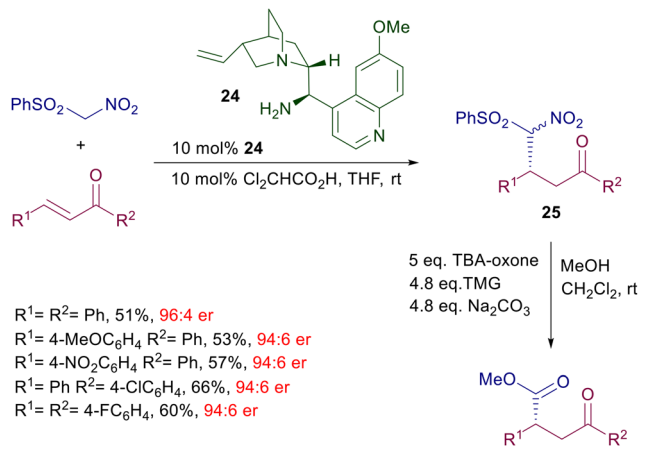
the intermediate imine. Furthermore, the cocatalyst can be suitably used to modify the steric shielding through appropriate modulation of its anionic structure. Quinine-derived amine **22** was selected as the most effective catalyst for the nitrocyclopropanation of enones using bromonitromethane (Scheme 18).[48] Cycloalkenones are directly converted into bicyclic derivatives in the presence of *N*-methylmorpholine (NMM), which assists the final ring closure by nucleophilic displacement of the bromide anion. The enantioselectivity is satisfactory for cyclopentenone and excellent for cycloalkenone homologues as substrates.



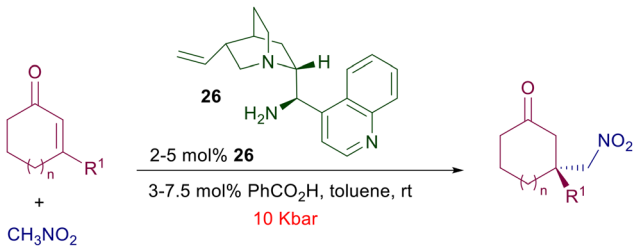
Scheme 18 Synthesis of chiral nitrocyclopropane derivatives.

Linear enones require two separate steps to afford the corresponding nitrocyclopropane derivatives with satisfactory enantioselectivity. The initial adduct **23** is obtained with poor diastereoselectivity but excellent enantioselectivity for each formed diastereomer. Among different bases, *trans*-2,5-dimethylpiperazine has been identified as the best promoter for the ring closure, leading to the cyclopropane derivatives in good diastereo- and enantioselectivity. The reaction of phenylsulfonylnitromethane with enones catalyzed by quinidine derivative **24** has been employed for the two-step synthesis of optically active 2-aryl-γ-ketoesters (Scheme 19).[49] Catalyst **24** affords the expected adducts **25** in an enantiocomplementary fashion compared with its pseudoenantiomer **22** for the synthesis of **23**, thus confirming that the same mechanism is operative for both functionalized nitromethane derivatives. Conversion of nitro ketone **25** into the target ketoesters is carried out through an oxidative Nef reaction using tetrabutylammonium-oxone, thus realizing a formal conjugate addition of an acyl anion synthon to enones.

The influence of pressure has been evaluated in the enantioselective addition of nitromethane to 3-substituted cycloalkenones catalyzed by cinchonine-derived amine **26** (Scheme 20).[50] At normal pressure (1 bar) the reaction is practically ineffective (1–9% yield), contrary to what was observed in the same process catalyzed by chiral diamine **21** (Scheme 17). However, by increasing the pressure to 10 kbar a notable improvement in the chemical yield was recorded. It should be observed that the pressure applied has no effect on the enantioselectivity of the reaction, which is very high even at 1 bar, but only affects the yield of the reaction. The same effect is evidenced for the nitromethane addition to some β,β-disubstituted linear enones.

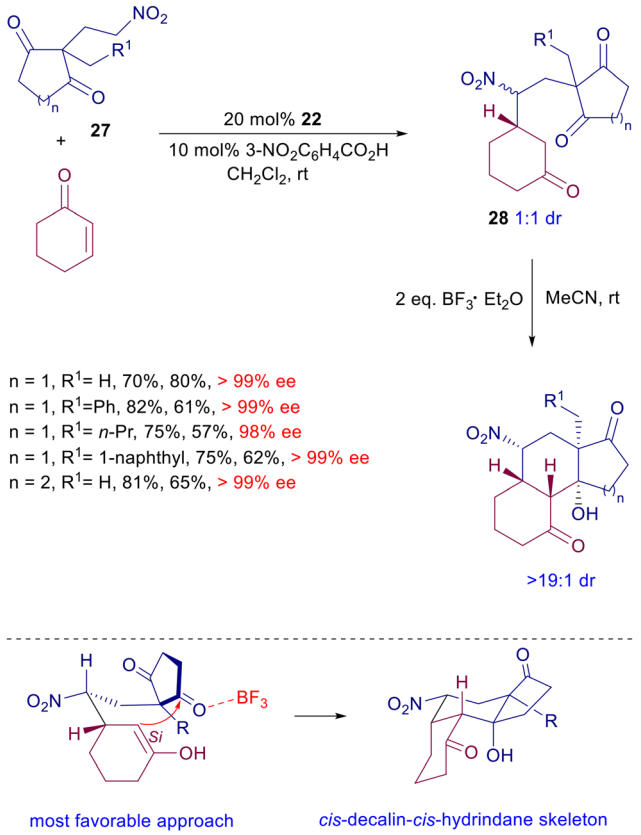


Scheme 19 Synthesis of chiral 4-oxoesters by conjugate addition/Nef reaction.



Scheme 20 Conjugate addition of nitromethane to 3-substituted cycloalkenones catalyzed by cinchonine-derived amine **26**.

Ready access to the uncommon *cis*,*cis*-tricyclic diterpenoid skeleton can be achieved by reaction of functionalized nitroethylcycloalkanediones **27** with cyclohexenone in the presence of chiral diamine catalyst **22** (Scheme 21).[51] Adducts **28** are formed as an equimolar epimeric mixture with excellent control of the ring stereocenter. The subsequent intramolecular aldol reaction, catalyzed by boron trifluoride etherate, affords the target tricyclic derivatives with outstanding stereocontrol, considering that in the six-membered ring transition state, the most favorable approach entails a pseudoequatorial position of the nitro group and attack of the enolate *Si* side to the ketone.

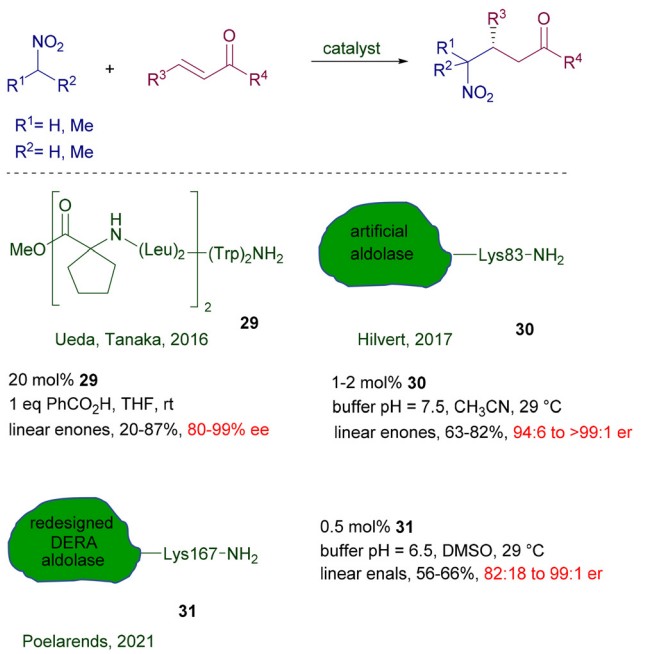


Scheme 21 Synthesis of *cis*,*cis*-tricyclic diterpenoid derivatives by a tandem conjugate addition/aldol condensation catalyzed by quinine-derived amine **22**.

Biocatalytic methods can be applied in these reactions using peptides and enzymes providing that free primary amino residues are present in the molecular framework. Peptide foldamer **29** having a helical structure has been used for the addition of nitroalkanes to linear enones using a terminal tryptophan residue as catalytic site (Scheme 22).[52] The catalyst charge parallels that of most organocatalyzed procedures, and the enantioselectivity obtained is high for several of the reported examples. Artificial aldolase RA95.5-8 **30** created by computational design is very effective in the reaction of nitromethane with linear enones at low catalyst charge.[53] As for many enzymatic procedures, careful pH and temperature controls are mandatory for suitable catalytic activity, which has been evaluated to occur at the level of the lysine-83 residue. A redesigned aldolase **31** from 2-deoxy-D-ribose-5-phosphate aldolase (DERA) has been recently introduced for the addition of nitromethane to enals.[54] The new version of the DERA enzyme differs from the original one by twelve amino acids and appears 190-fold more active at a very reduced catalyst charge. Also for this enzyme, the active site is attributable to the primary amino group of the lysine-167 residue.

2.3 Thioureas as bifunctional catalysts

Functionalized chiral ureas exert their catalytic activity in a complementary fashion to amino derivatives, activating the nitroalkane towards the conjugate addition. The activation is due to the strong hydrogen bonding established between the acidic NH of urea and the oxygen atoms of the nitro group.



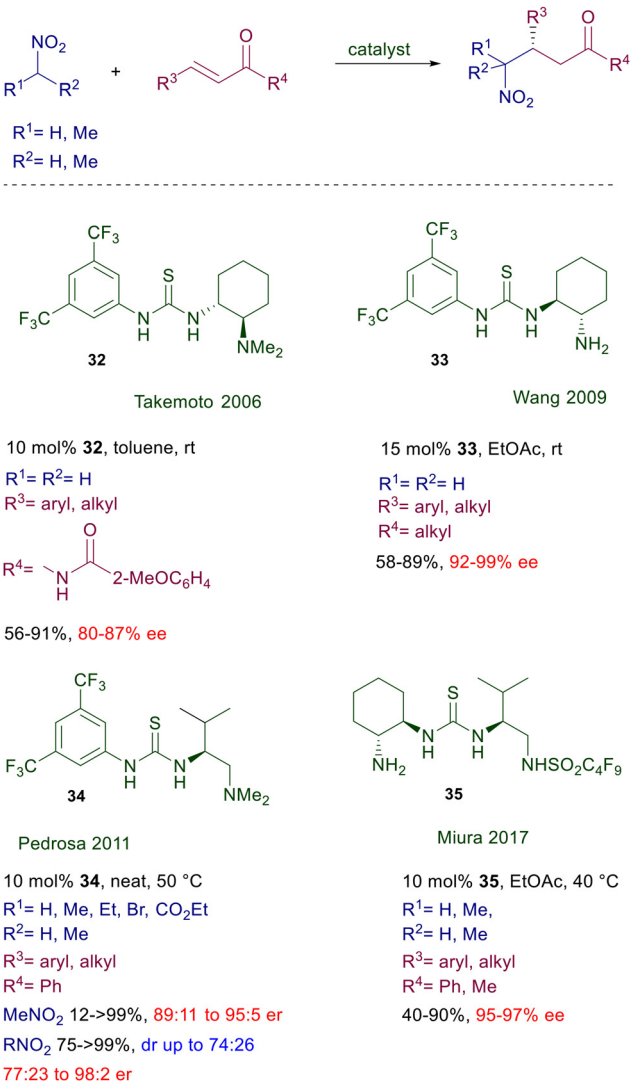
Scheme 22 Chiral peptide foldamers and aldolases as biocatalysts.

The acidity of these NH bonds is superior in thioureas, which are thus preferred to ureas as catalysts. Furthermore, the reduced electronegativity of sulfur compared with that of oxygen makes the self-association by hydrogen bonding among thiourea molecules less favorable, thus enhancing the catalytic activity. The interactive model is totally based on the hydrogen bonding network among the bifunctional catalyst and the substrate according to Fig. 3. The protonated amino group is instrumental in providing the necessary interaction with the Michael acceptor, generating an electrophilic catalysis and ensuring the required proximity effect.

In 2003, a chiral bifunctional thiourea was introduced by Takemoto and co-workers for the conjugate addition of malonates to nitroalkenes,[55] but only three years later the same catalyst **32** was used for the addition of nitromethane to α,β-unsaturated imides (Scheme 23).[56] Thus, the use of catalyst **32** in these conjugate additions was anticipated by a cinchona-derived thiourea one year before (*vide infra*).

The catalytic activity of **32** was ascribed to the activation of the imide moiety rather than the nitromethane by hydrogen bonding with the NH of thiourea, although no evidence for this assumption has been provided. Furthermore, the presence of a 2-methoxy group in the aryl substituent of the imide was proved to be mandatory for an optimal enantioselectivity. Later on, a structural modification was introduced converting the tertiary amino group into a primary one in catalyst **33**.[57] The performance of this catalyst is superior compared with its previous analogue, and although activation of the enone carbonyl by hydrogen bonding with the NH groups of the catalyst has been proposed, the concomitant iminium ion formation and nitroalkane activation appears to be the most probable mechanism. In any event, catalyst **34**, developed as a further modification of the Takemoto's catalyst **32**, is also effective on simple enones and functionalized nitroalkanes.[58] Theoretical studies on this catalyst suggest the general assumption that the nitroalkane is activated by the thiourea NH groups and the enone by the protonated tertiary amine as depicted in Fig. 3. The recently developed bifunctional catalyst **35** includes in its structure an acidic sulfonamide group and a primary amine.[59] This catalyst affords high ee values in the corresponding adducts, and it is correctly proposed that activation of the enone occurs *via* iminium ion while activation of the nitroalkane is brought about by a joint action of the three acidic NH groups. The asymmetric conjugate addition of nitroalkanes to nitroalkenes affords 1,3-dinitro derivatives which are direct precursors of optically active 1,3-diamines (Scheme 24). Thiourea catalyst **36**, featuring a binaphthyl chiral scaffold, gives good results in the asymmetric reaction of primary nitroalkanes with nitrostyrene derivatives.[60] The thiourea and the 2-aminopyridyl catalytic sites jointly provide the activation of the reactants through a closely related hydrogen bonding mechanism. Interestingly, the observed diastereoselectivity is superior compared with that recorded in similar reactions with enones, that barely exceeds the value of 3 : 2. Satisfactory results are also obtained in the same process using the more traditional catalyst **37**, for which generally high values of diastereo- and enantioselectivity are recorded.[61]

The reaction of 2-nitrocyclohexanone with nitrostyrenes required the elaboration of a different thiourea derivative considering that classical catalysts such as **32** were proved to be



Scheme 23 Chiral bifunctional thioureas as catalysts.

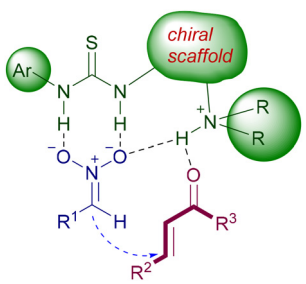
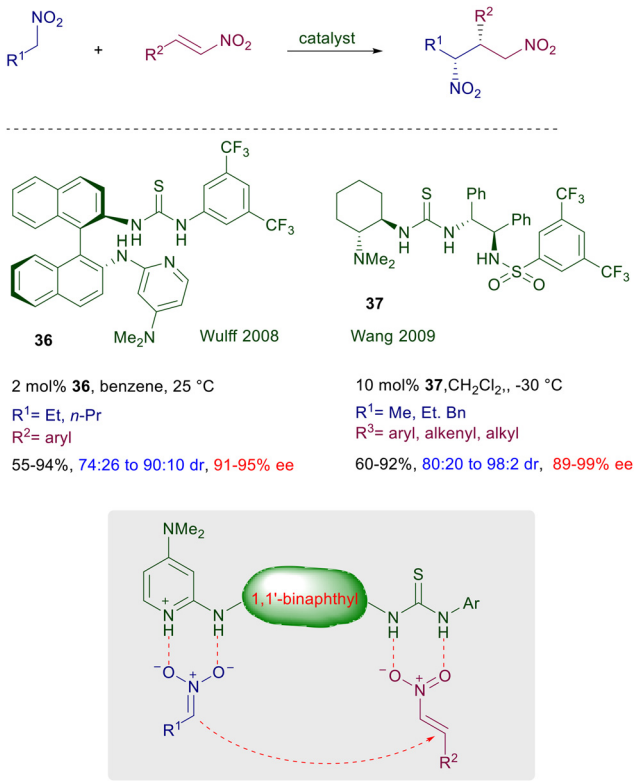


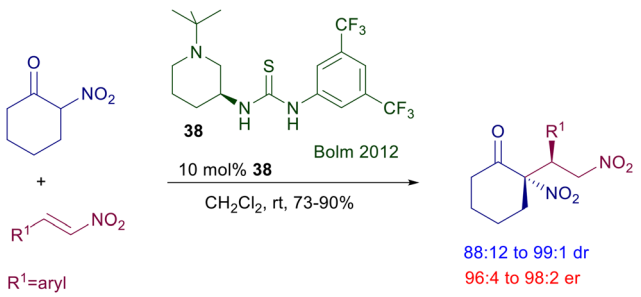
Fig. 3 Mechanism of activation of the reactants by chiral bifunctional thioureas.



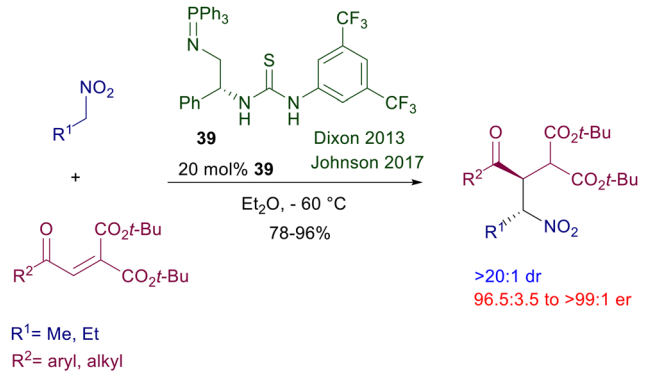
Scheme 24 Conjugate addition of nitroalkanes to nitroalkenes catalyzed by bifunctional chiral catalysts **36** and **37**.

poorly effective in this process (Scheme 25).[62] Catalyst **38**, featuring a piperidine unit, was highly active in this conjugate addition, leading to the corresponding dinitro derivatives with diastereo- and enantioselectivity.

Increasing the basic character of the catalyst has a notable impact on the efficiency of the reactions involving nitroalkanes. Iminophosphorane-based thiourea catalyst **39** was originally designed for enantioselective nitro-Mannich reactions,[63] but is also very effective for the conjugate addition of nitroalkanes to enone diesters (Scheme 26).[64] The corresponding adducts are practically obtained as single diastereomers and with very good enantioselectivity.



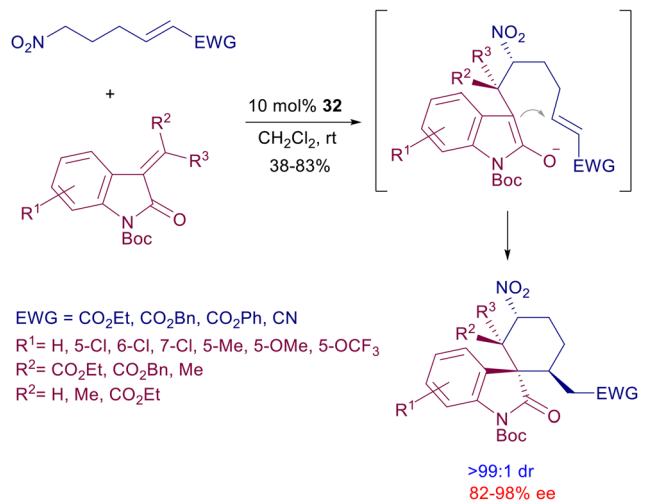
Scheme 25 Conjugate addition of 2-nitrocyclohexanone to nitroalkenes.



Scheme 26 Chiral iminophosphorane-thiourea catalyst in the reaction of nitroalkanes with enone diesters.

These relatively simple bifunctional catalysts have been involved in the synthesis of complex structural entities, exploiting cascade processes such as that displayed in Scheme 27.[65] Nitroalkanes bearing a terminal electron-poor alkene react with 3-alkylideneoxindoles in the presence of catalyst **32** leading to a tricyclic derivative with outstanding diastereoselectivity. The process entails a preliminary nitro-Michael reaction followed by ring closure of the intermediate enolate to the electron-poor alkene. The utilization of the lower homologue (C4) of the nitroalkane in the same reaction occurs with poor diastereoselectivity using catalyst **32**, but a notable improvement can be achieved by moving to cinchona-derived thiourea catalysts (*vide infra*).

The chiral 1,2-diamino framework required for the preparation of the thiourea catalysts comes from chiral *trans*-1,2-cyclohexanamine or from synthetic manipulation of amino acid derivatives. As already discussed in Section 2.2, optically active 1,2-diamino derivatives can also be obtained from cinchona alkaloids through a stereospecific conversion of the sec-



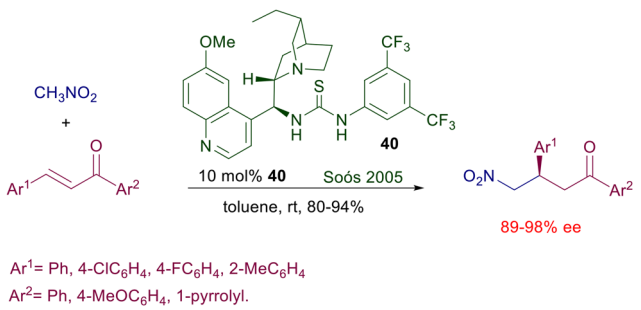
Scheme 27 Synthesis of chiral spiroxindoles by double conjugate addition.

ondary hydroxy group into a primary amine. The thiourea moiety is then built up on the primary amine, leading to the bifunctional catalyst. In devising the structural elements to be embedded in these cinchona-thiourea catalysts, an essential motif like the 2,4-trifluoromethylphenyl group that proved effective in Takemoto's catalyst was included. Thus dihydroquinine-derived bifunctional catalyst **40** was the first thiourea derivative employed for the reaction of nitromethane to chalcones and α,β-unsaturated-*N*-acylpyrroles (Scheme 28).[66]

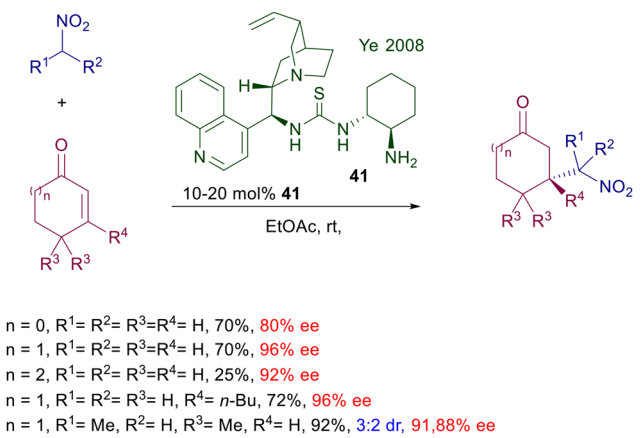
Interestingly, the features of this catalyst are effective for many synthetic purposes, so that a limited number of structural modifications have been introduced over time. A first important change was made by substituting the bistrifluoromethylphenyl moiety with a (*R*,*R*)-cyclohexyldiamino group in catalyst **41** (Scheme 29).[67] This catalyst has been employed for the conjugate addition of nitroalkanes to various cycloalkenones.

The enantiofacial preference for the attack of nitromethane to cyclohexenone is dictated by the stereochemistry of the (*R*,*R*)-cyclohexyldiamino group, considering that the catalyst bearing the *S*,*S* unit affords the other enantiomer of the product. This is congruent with the formation of an iminium ion intermediate, as observed with catalysts bearing a primary amino group. Catalyst **41** can also be used on linear enone derivatives, but the enantioselectivity is slightly lower compared with cycloalkenones. Another significant change was introduced in catalyst **42**, in which the cinchona system is spaced from the thiourea by a L-threonine moiety (Scheme 30).[68] This structural modification allows better performances over similar catalysts in the conjugate addition of 1-fluoronitroalkanes to nitroalkenes. It is not clear what the effect is brought by the threonine unit in which the hydroxy group is protected with a cumbersome *t*-butyldiphenylsilyl group, except that it can increase the steric constraint around the reactants in the transition state.

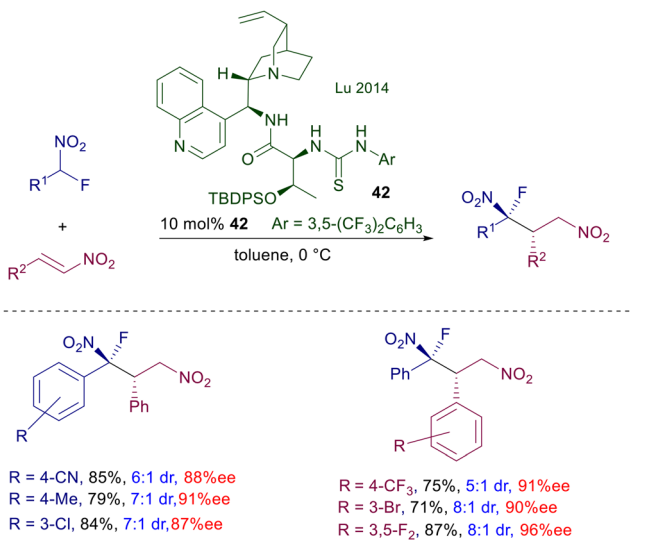
A double Michael reaction of a α,β-unsaturated-ω-nitroester to nitrostyrenes has been envisaged using catalyst **40** under mild reaction conditions (Scheme 31).[69] After the first conjugate addition the resulting intermediate nitronate anion undergoes a further Michael addition with the acrylate moiety, leading to a dinitrocyclohexane derivative with satisfactory control of the four generated stereocenters. The formed dinitro derivatives can be converted in a three-step process into tetracyclic compounds that feature the α-lycorane skeleton. The level of architectural complexity can be driven until the formation of polycyclic structures featuring several stereocenters with overall good diastereo- and enantiocontrol. The three-component coupling of nitromethane with chromene and oxindole compounds in the presence of quinidine-thiourea catalyst **43** affords hexahydroxanthone derivatives through a formal [2 + 1 + 3] annulation process (Scheme 32).[70] The overall process starts with a conjugate addition of nitromethane to the alkylideneoxindole, thus generating the first stereocenter. A second Michael addition of the nitroxindole enol to the chromone unit provides the installation of three further stereocenters, but the last nitroaldol Henry reaction finally leads to the target hexahydroxanthone featuring six stereocenters.



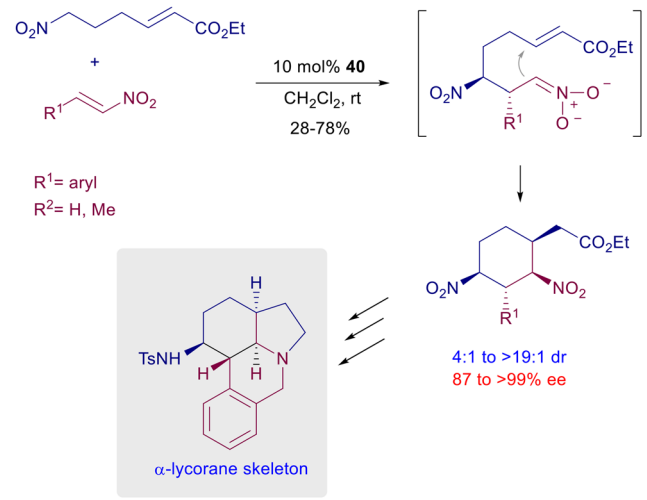
Scheme 28 Dihydroquinine-derived bifunctional catalyst in the reaction of nitromethane with chalcones.



Scheme 29 Cinchonidine-cyclohexane diamine mixed thiourea catalyst in the conjugate addition of nitroalkanes with cycloalkenones.



Scheme 30 Cinchonidine-threonine mixed thiourea catalyst in the conjugate addition of 1-fluoronitroalkanes with nitroalkenes.



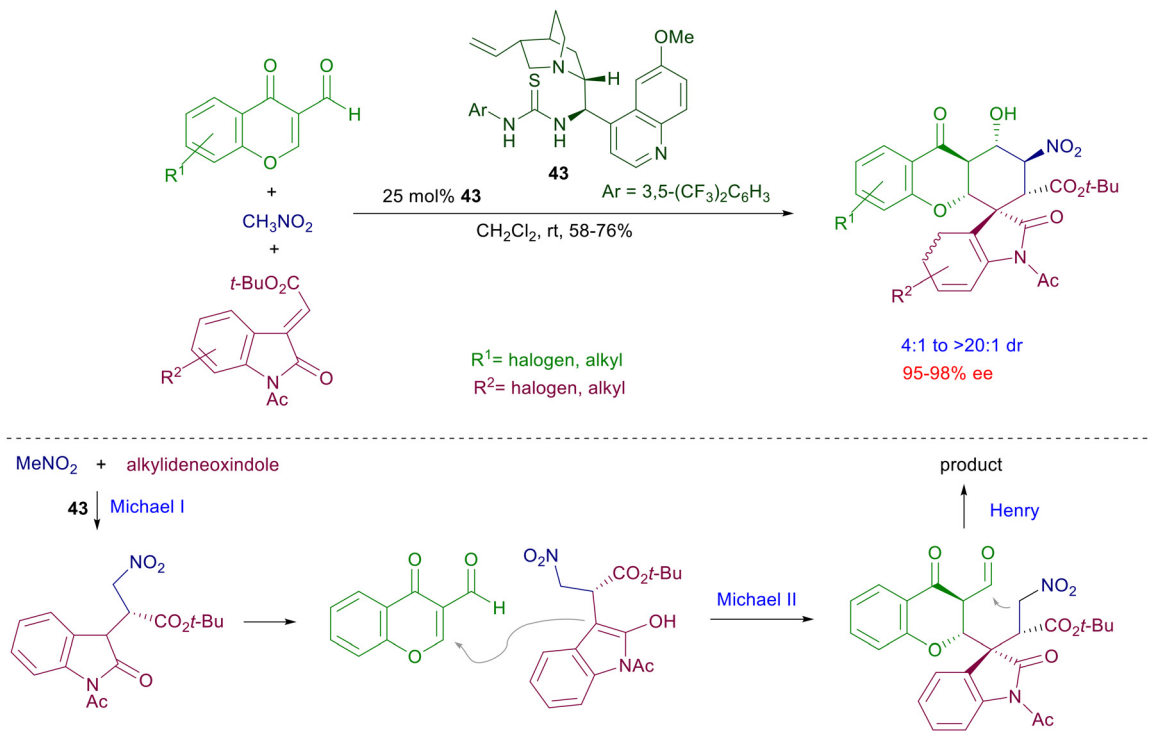
Scheme 31 Double asymmetric conjugate addition catalyzed by chiral thiourea **40**.

A formal alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones has been realized using nitroalkanes as the alkyl source in the presence of quinine-derived urea catalyst **44** (Scheme 33).[71] This is one of the rare examples where the urea group shows a superior catalytic activity compared with the thiourea analogue. The large number of examples reported includes the use of nitroalkanes and 1,3-diones embedding useful amino and oxygenated functional groups. The alkylative process is based on the well-known aptitude of β-nitrocarbonyl derivatives in undergoing loss of nitrous acid generating α,β-unsaturated derivatives.[6] Thus, the selective enantiofacial attack of the nitronate anion to the enedione substrate affords the expected Michael adduct, which upon loss of nitrous acid initially gives the exocyclic unsaturated cyclopentane-1,3-dione. Formation of the final product **45** is then ensured by a thermodynamically driven hydrogen shift.

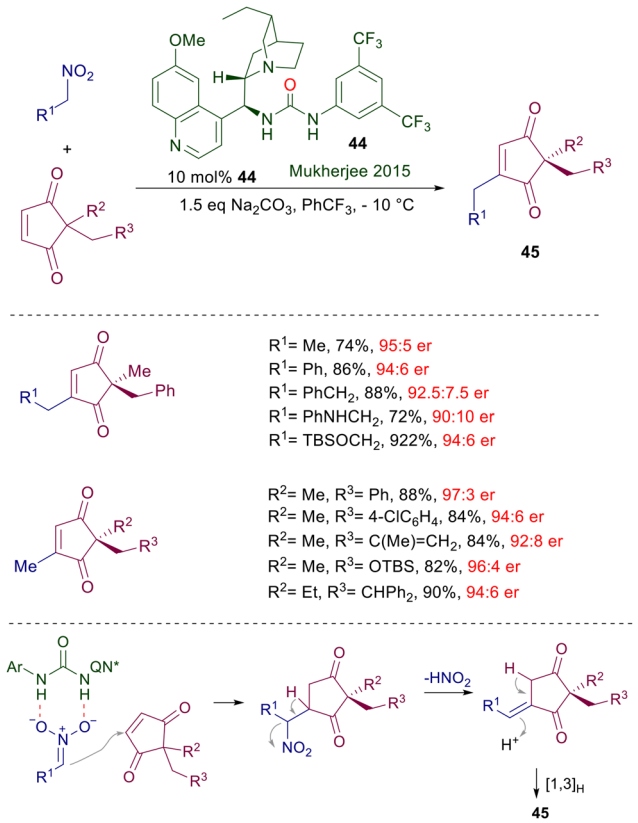
A recent example of cooperative heterocatalysis has been reported in the Michael addition of nitro alcohols with 2-hydroxycinnamaldehydes jointly catalyzed by chiral bisthiourea **46** and prolinol **11** (Scheme 34).[72] The resulting products are tricyclic nitroacetal derivatives obtained with good enantioselectivity but variable diastereoselectivity depending on the nature of the substituents on the nitro alcohol. The presence of α-substituents ($R^1 \neq H$) or small substituents on carbinol [R^2 = H or $-(CH_2)_3-$] usually affords epimeric mixtures of products. The cooperative action of the catalysts involves the hydrogen bonding interaction of the thiourea NH with the nitronate and the phenolic oxygen atom while the prolinol acts through the usual iminium ion catalysis. The initially formed dihydroxynitroaldehydes can be acetalyzed under acidic conditions to afford the target products.

2.4 Squaramide catalysts

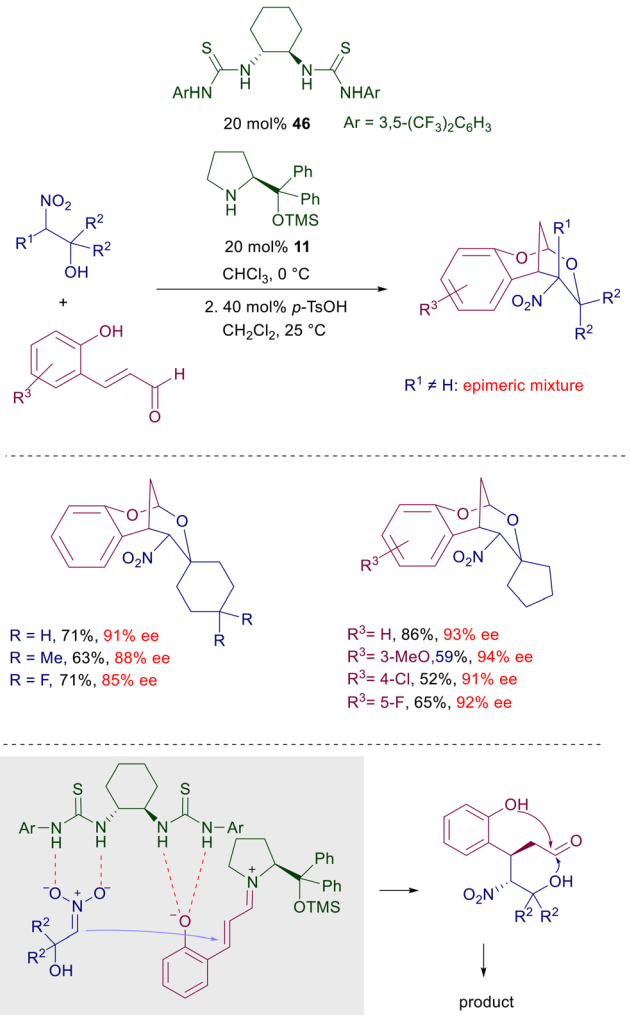
Squaramides are derivatives of squaric acid largely employed in a notable number of applications in material chemistry and drug design as bioisosteres.[73] The structural features of squaramides closely resemble those of thioureas, although the H–H



Scheme 32 Three-component cascade process catalyzed by chiral thiourea **43** leading to spiroxindole derivatives.



Scheme 33 Alkylative desymmetrization of cyclopentendione derivatives catalyzed by quinine-derived chiral urea **44**.



Scheme 34 Cooperative heterocatalysis in the conjugate addition of nitro alcohols to 2-hydroxycinnamaldehydes.

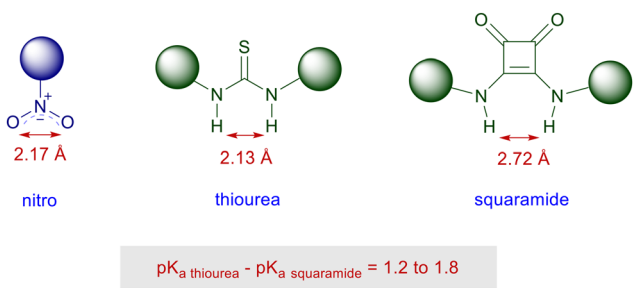
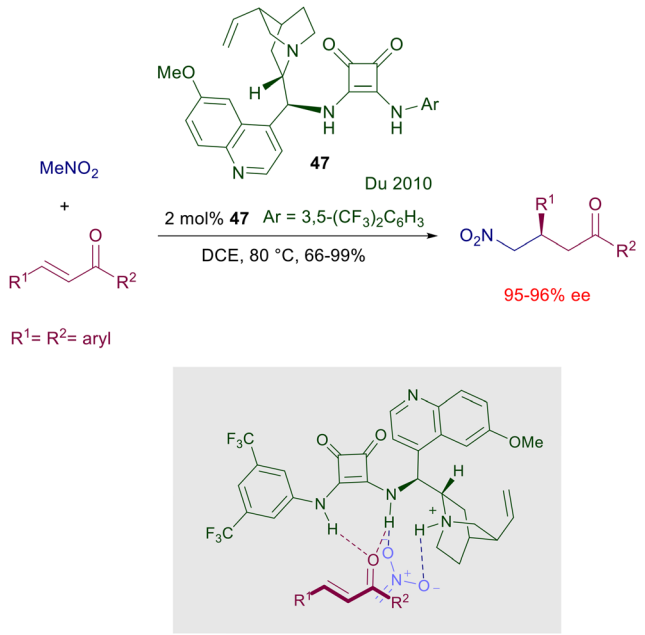


Fig. 4 Structural features of nitro, thiourea and squaramide derivatives.

interatomic distance is superior in the squaramide system by ~0.6 Å (Fig. 4).[74] A further analogy can be found in the acidity level of the NH bonds which, however, is fairly superior in squaramides than in thioureas.[75] This allows squaramide to establish stronger hydrogen bonding with functionalities commonly involved in thiourea-catalyzed reactions such as nitro, carbonyl, carboxylates and imino groups.[76]

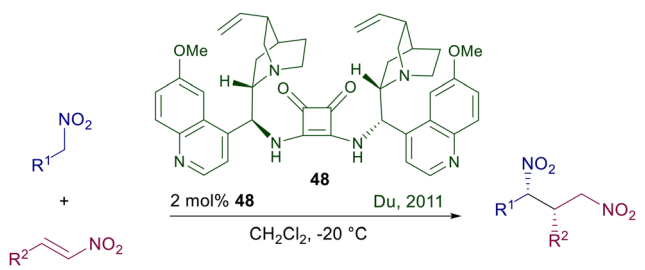
In 2008, the results previously obtained using chiral thioureas inspired the development of a chiral bifunctional squaramide catalyst embedding a cinchonine-derived amine and a substituted benzylamine which was effective in the asymmetric Michael reaction of 1,3-diketones with nitroalkenes.[74a] A couple of years later, the first enantioselective addition of nitromethane to enones was reported using the related quinine-derived catalyst **47** (Scheme 35).[77] The reaction is effective even with a reduced catalyst charge, although a relatively high temperature must be applied. Modest results have been obtained using 2-cyclohexen-1-one as substrate and, as expected, the utilization of a chiral squaramide embedding the pseudoenantiomeric quinidine-derived amine afforded the corresponding (*S*)-adducts. Interestingly, in the plausible transition state depicted for this process the interaction of the enone carbonyl oxygen with the squaramide is privileged over that of the nitromethane, which appears mostly activated by the ammonium salt.

Asymmetric procedures catalyzed by bifunctional squaramides bearing cinchona-derived amines are largely predominant over related methods using different chiral amines. Furthermore, in optimization studies where thiourea and squaramide catalysts are comparatively evaluated for the conjugate addition of nitroalkanes to electron-poor alkenes, the latter catalysts very often show better performances. The cata-



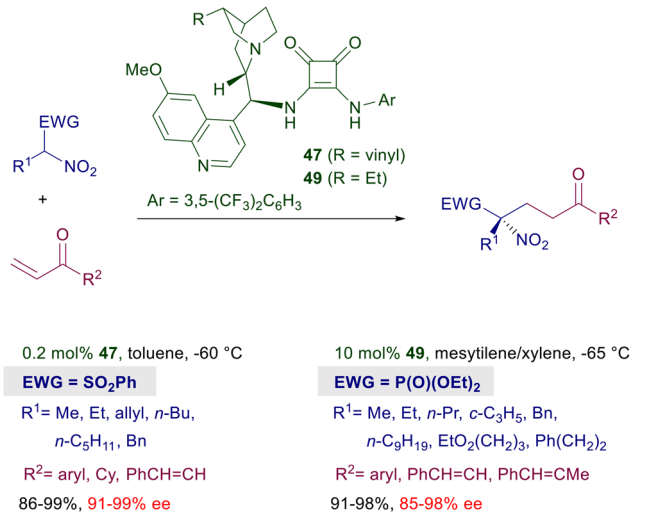
Scheme 35 The first enantioselective conjugate addition of nitromethane to chalcones catalyzed by a quinine-derived squaramide catalyst **47**.

lyst activity can be further increased by moving to biscinchona-squaramide catalyst **48** featuring a C_2-symmetry which is effective in the conjugate addition of nitroalkanes to nitroalkenes (Scheme 36).[78] The diastereoselectivity observed in this reaction is satisfactory with *para*-substituted nitrostyrenes, but decreases when the substituent occupies the *ortho* position. The enantioselectivity is always excellent with all nitrostyrenes employed except with alkyl-substituted nitroalkenes, which provide disappointing results. Nitroalkanes bearing an additional electron-withdrawing group at the α-position can be efficiently added to enones using cinchona-derived squaramides (Scheme 37). A direct comparison of these squaramide



R1= Me, R2= Ph, 94%, 95:5 dr, 97% ee
R1= Me, R2= 4-FC6H4, 94%, 94:6 dr, 96% ee
R1= Me, R2= 2-ClC6H4, 83%, 88:12 dr, 95% ee
R1= Me, R2= *i*-Pr, 16%, 67:33 dr, 80% ee
R1= Et, R2= 4-MeOC6H4, 64%, 92:8 dr, 97% ee

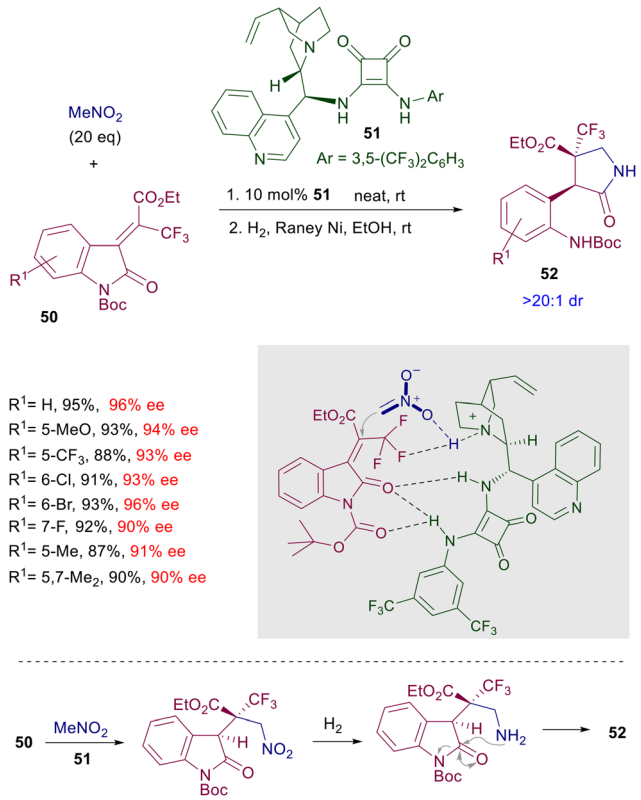
Scheme 36 Asymmetric conjugate addition of nitroalkanes to nitroalkenes catalyzed by biscinchona-squaramide catalyst **48**.



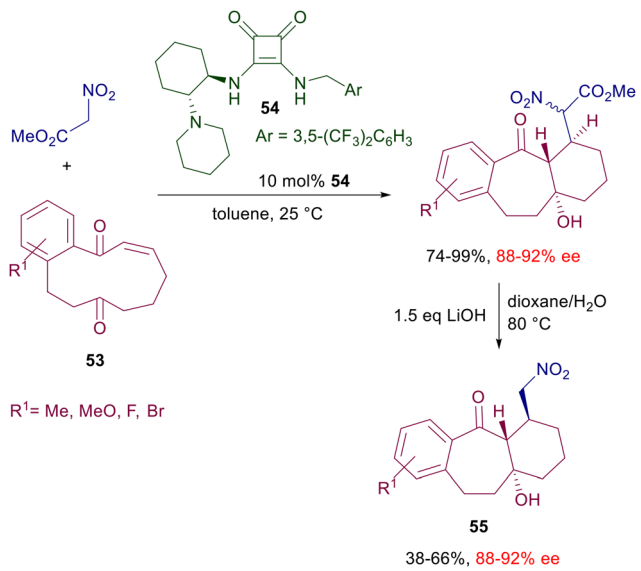
Scheme 37 Enantioselective conjugate addition of activated nitroalkanes to enones.

catalysts with structurally related thiourea derivatives shows a superior catalytic activity of the former compounds often resulting in a reduced catalyst charge and low reaction temperature. Nitrosulfonyl derivatives react with terminal enones in the presence of just 0.2 mol% of catalyst **47** leading to the corresponding adducts in good yield and excellent enantioselectivity.[79] Similarly, nitrophosphonates can be added to terminal enones using catalyst **49** under similar reaction conditions, giving ketophosphonates which upon selective reduction of the nitro group easily afford α,α-disubstituted aminophosphonic acid derivatives.[80]

An effective asymmetric synthesis of pyrrolidinones **52** can be realized in a two-step procedure reacting alkylideneoxindoles **50** with nitromethane in the presence of cinchonidine-derived squaramide **51** (Scheme 38).[81] The nitro group of the initially formed adduct is reduced by catalytic hydrogenation, and the resulting primary amine is then involved in a thermodynamically controlled transamidation leading to the target pyrrolidinone **52** as a single diastereomer and very good ee value. The trifluoromethyl group in the electrophile seems to play an essential role in enhancing the steric constraint of the transition state through an additional hydrogen bonding with the ammonium ion. As a matter of fact, the oxindole **50** lacking the ethyl ester group still gives a product with high enantioselectivity (95% ee), while the substrates in which the trifluoromethyl is substituted by a methyl or a hydrogen atom evidence a notable drop in the ee value (74% and 51% ee). The reduced reactivity of nitromethane with particular enones can be overcome using nitroacetate derivatives endowed with a higher enolizability. The addition of methyl nitroacetate to cyclic diketoenones **53** occurs smoothly at 25 °C in the presence of diamine-derived squaramide **54**, which was found superior to thioureas as well as cinchona-derived squaramides (Scheme 39).[82]



Scheme 38 Asymmetric synthesis of pyrrolidinones **52**.

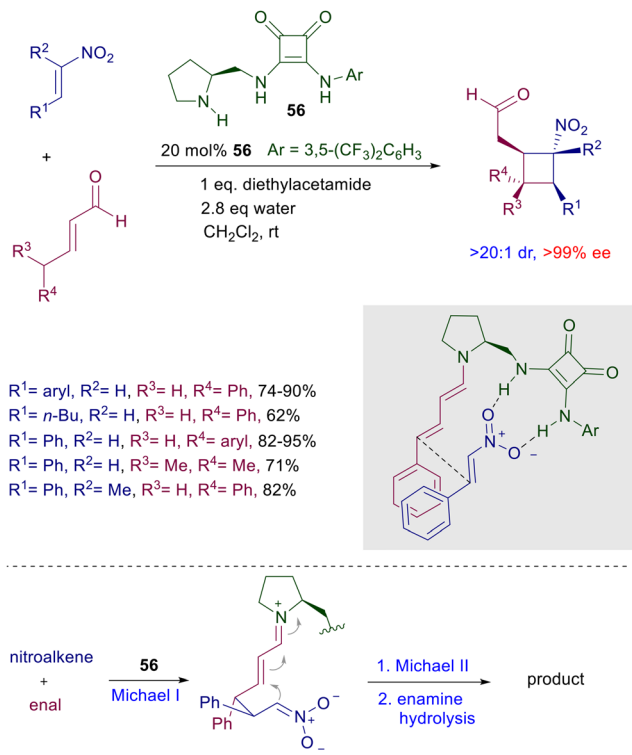


Scheme 39 Asymmetric tandem conjugate addition/aldol reaction catalyzed by squaramide **54**.

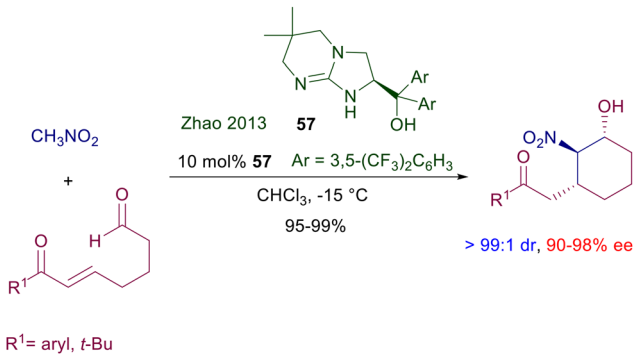
The chiral catalysts ensure a very good enantiocontrol in the conjugate addition, while a substrate control is believed to be operative in the subsequent intramolecular aldol condensation leading to the target tricyclic compounds. As always occurs, no stereocontrol is possible at the rather acidic nitroester stereocenter, so that these products are obtained as a 2 : 1 epimeric mixture.[83] In any event, basic decarboxylative hydrolysis of these compounds finally affords nitromethyl derivatives **55** as a result of a formal addition of nitromethane to diketoenones **53**. Reaction of nitroalkenes with enals in the presence of bifunctional pyrrolidine-squaramide catalyst **56** affords nitrocyclobutane derivatives through a formal [2 + 2] cycloaddition (Scheme 40).[84] The process occurs with perfect control of the four stereocenters generated in the cyclobutanation reaction involving a double conjugate addition with dienamine-iminium ion intermediates. The reactants' arrangement leading to the first Michael addition is favored by the hydrogen bonding of the nitro group with the squaramide moiety and by the π-stacking interaction between the aryl groups. The second Michael addition occurs between the nitronate anion and the vinylogous iminium ion leading, after enamine hydrolysis, to the final product.

2.5 Amidines, guanidines and related catalysts

The activation mode of the nitro group by hydrogen bonding with protonated amidines and guanidines closely resembles that with thioureas and squaramides, and has been confirmed by isolation and characterization of the complex between phenylnitromethane and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[85] The first chiral guanidine catalyst that featured a C_2-symmetrical bicyclic structure was devised several years ago and gave low ee values for the reaction of nitroalkanes with methyl vinyl ketone.[86] More recently, chiral bicyclic guanidine



Scheme 40 Formal [2 + 2] cycloaddition of nitroalkenes to enals catalyzed by bifunctional squaramide **56**.



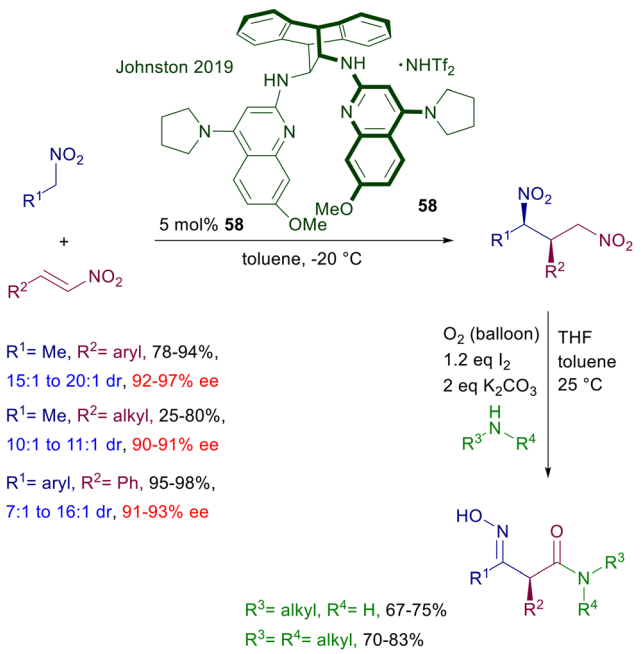
Scheme 41 Chiral bicyclic guanidine **57** as catalyst for the tandem conjugate addition/aldol condensation of nitromethane to oxoenals.

57 was revealed to be very effective in a tandem nitroaldol-Michael addition of nitromethane to 7-oxohept-5-enals (Scheme 41).[87] Control experiments demonstrated that the nitroaldol process occurs first and is followed by the conjugate addition leading to the ring closure.

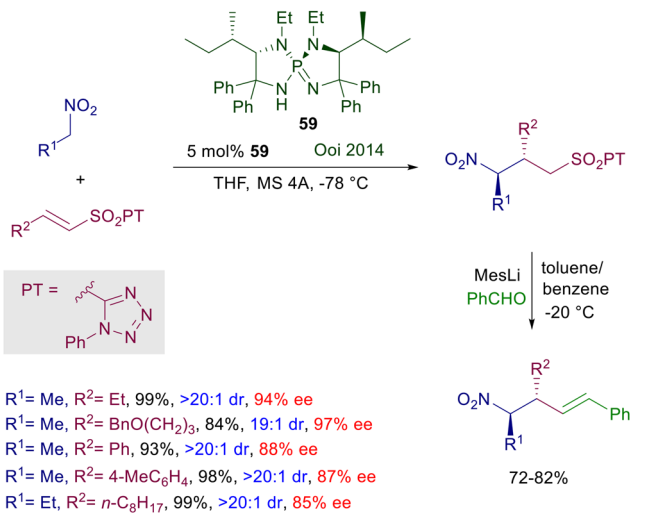
The anthracene-derived chiral bisamidine **58** has been recently introduced as catalyst for the conjugate addition of nitroalkanes to nitroalkenes (Scheme 42).[88] The reaction is particularly effective with nitrostyrenes and affords with satisfactory *syn* diastereoselectivity the corresponding 1,3-dinitro derivatives. Catalyst **58** is used as triflimidic acid salt since the free base does not bring about significant levels of stereoselectivity in the formation of 1,3-dinitro derivatives, and this aspect stresses the bifunctional nature of the catalytic action provided. An original application of the obtained adducts involves a double oxidative Nef reaction,[5] using the molecular oxygen–iodine couple in the presence of primary and secondary amines to generate 3-hydroxyiminoalkanamides with full retention of the original C2 configuration. Triaminoiminophosphoranes show an enhanced basic character and similarly to guanidines and amidines are able to deprotonate nitroalkanes, establishing strong hydrogen bonding interactions with the corresponding nitronate anions. Chiral triaminoiminophosphorane **59** catalyzes the conjugate addition of nitroalkanes to vinylsulfones leading to the corresponding nitrosulfonyl derivatives with excellent diastereocontrol (Scheme 43).[89] The observed enantioselectivity for the obtained adducts is better for 2-alkyl substituted vinylsulfones compared with their aryl analogues. A structural implementation of the target 3-sulfonylnitro derivatives has been proposed through a Julia–Kocienski olefination generating 3-nitroalkenyl compounds arising from an overall formal allylation of the initially employed nitroalkanes. To this scope, the nitrosulfonyl derivatives were treated with the bulky mesityllithium (MesLi) in order to ensure a regioselective kinetic deprotonation of the less acidic α-sulfonyl hydrogen atoms. Reaction with benzaldehyde resulted in the formation of 3-alkenylnitro compounds with substantial retention of the original configuration of stereocenters.

2.6 Cinchona alkaloids

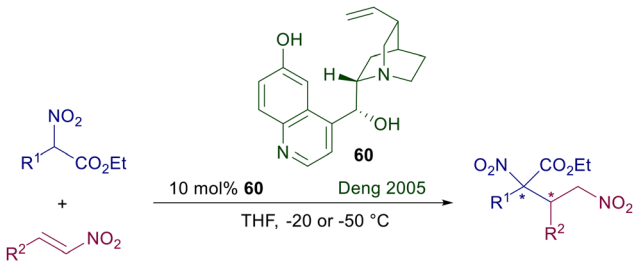
Quinine was the first chiral catalyst employed in the seventies of the last century for the conjugate addition of nitroalkanes to enones,[10] but other cinchona alkaloids were soon after used with relatively modest results.[90] It is therefore evident that the structural features of cinchona alkaloids hardly allow appropriate interactions with the nitroalkane–enone couple to provide a satisfactory enantiofacial discrimination.[91] The first successful application of cinchona alkaloids was found in the utilization of cupreine **60** as catalyst for the conjugate addition of 2-nitroesters to nitroalkenes (Scheme 44).[92] Although the



Scheme 42 Asymmetric synthesis of 3-hydroxyiminoalkanamides.



Scheme 43 Conjugate addition of nitroalkanes to vinyl sulfones catalyzed by chiral triaminoiminophosphorane **59**.



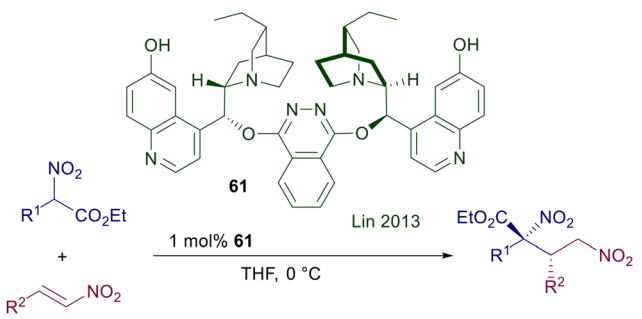
R^1= Me, R^2= Ph, 78%, 92:8 dr, 92% ee
R^1= Me, R^2= *n*-C_5H_{11}, 78%, 93:7 dr, 92% ee
R^1= Et, R^2= Ph, 77%, 95:5 dr, 96% ee

Scheme 44 Asymmetric conjugate addition of nitroesters to nitroalkenes catalyzed by cupreine **60**.

absolute configuration of the stereocenters was not evaluated, the obtained adducts were formed with high diastereo- and enantioselectivity. The free hydroxy group in the quinoline ring and the ester group in the nitro derivative seem to play an essential role in establishing an appropriate hydrogen bonding network leading to the target products. As a matter of fact, reaction of unfunctionalized nitroalkanes with nitroalkenes catalyzed by cupreidine, the pseudoenantiomer of **60**, leads only to modest results in terms of enantioselectivity (67–86% ee).[93]

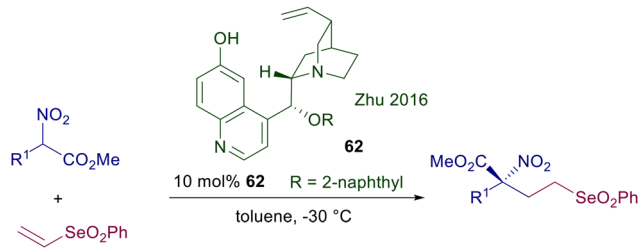
Later on, the same process was carried out using catalyst **61** based on two molecules of demethyldihydroquinine tethered by a phthalazine unit (Scheme 45).[94] The catalyst is active even at 1 mol% concentration and gives satisfactory results with nitrostyrenes as well as linear nitroalkenes.

Conversion of the aliphatic hydroxy group of cupreine into the 2-naphthyl ether derivative **62** also provides a notable improvement in the enantioselectivity of the conjugate addition of functionalized nitroesters to vinylselenones



R^1= Me, R^2= aryl, 88-99%, 89:11 to 99:1 dr, 94-98% ee
R^1= Me, R^2= PhCH=CH, 95%, 91:9 dr, 95% ee
R^1= Me, R^2= alkyl, 71-91%, 91:9 to 94:6 dr, 96-97% ee
R^1= Et, R^2= Ph, 92%, 91:9 dr, 96% ee

Scheme 45 Asymmetric conjugate addition of nitroesters to nitroalkenes catalyzed by biscinchona-phthalazine **61**.



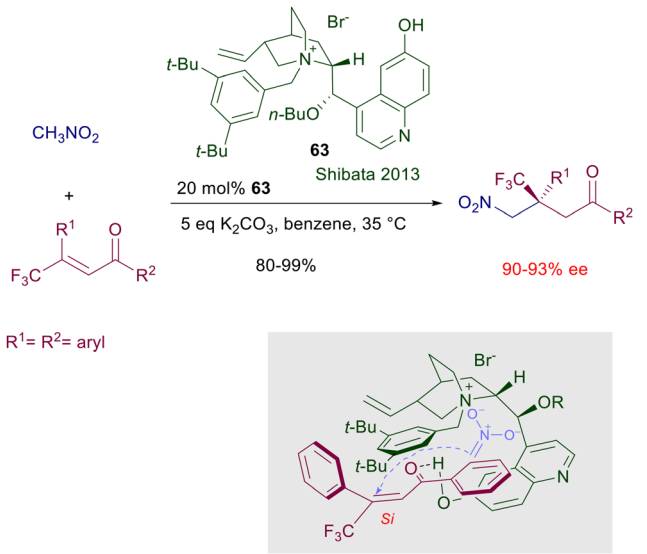
R^1= Me, 96%, 98:2 er
R^1= CH_2=$CHCH_2$, 97%, 95:5 er
R^1= $MeO_2C(CH_2)_2$,>99%, 93:7 er
R^1= $Me(O)C(CH_2)_2$,84%, 96:4 er
R^1= Bn, 95%, 91:9 er

Scheme 46 Enantioselective conjugate addition of nitroesters to vinyl selenones.

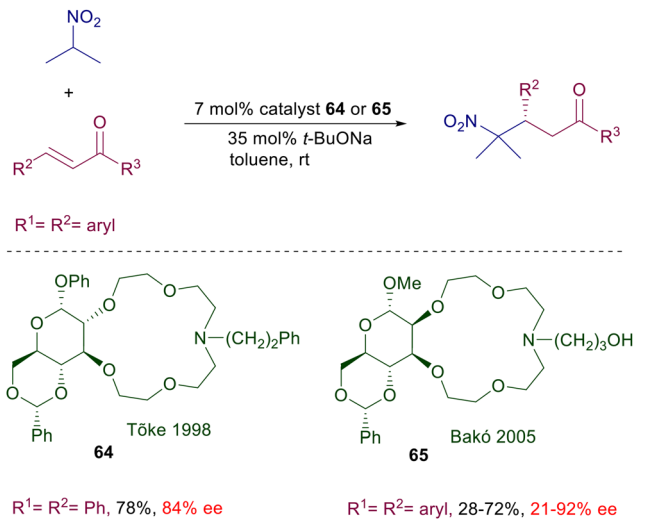
(Scheme 46).[95] Considering that the phenylselenonyl moiety is an excellent leaving group in eliminations and nucleophilic substitution reactions, the target selenonyl nitro esters are potentially useful building blocks for the preparation of α,α-difunctionalized amino acid derivatives.

2.7 Phase-transfer catalysts

Ammonium and phosphonium salts bearing large substituents were originally designed to act as anion carriers in biphasic systems, enabling a dramatic rate enhancement of the corresponding ionic processes. In asymmetric synthesis, the role played by ammonium salts in phase-transfer catalysis (PTC) is to provide a chiral environment around tightly bonded anionic reactants involved in nucleophilic addition or substitution reactions.[96] The main ionic bond provided by the ammonium moiety can be obviously assisted by further hydrogen bonding with additional polar groups present in the catalyst and in the reactants.[97] The development of ammonium salts as phase-transfer catalysts for conjugate additions took place in parallel with the use of cinchona alkaloids for the same purpose. Early attempts to use quinine *N*-benzylic salts for the conjugate addition of nitromethane and chalcones in a biphasic system gave only very modest results.[98] Only quite recently cupreidine derivative **63** has been successfully employed in the conjugate addition of nitromethane to 3-trifluoromethyl chalcones (Scheme 47).[99] In the proposed transition state the ammonium ion is supposed to interact with the nitronate anion in which enantiofacial attack to the chalcone derivative is biased by π-stacking and hydrogen bonding interactions. Conceptually different phase-transfer catalysts based on monoaza-15-crown-5 ethers derived from D-glucose were introduced in the late nineties for the conjugate addition of 2-nitropropane to chalcones (Scheme 48).[100] The activity of catalyst **64** is based on the ability of the azacrown ether in complexating the sodium cation, providing the formation of a ionic pair with the nitronate anion. The reaction gives interesting results with chalcone (R^1 = R^2 = Ph), but very modest levels



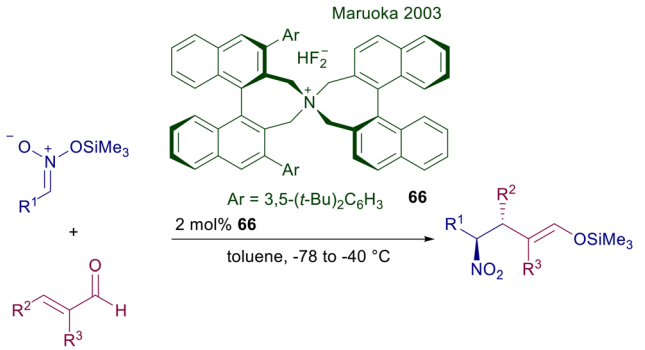
Scheme 47 Cinchona-derived ammonium salt **63** as phase-transfer catalyst.



Scheme 48 Monoaza-15-crown-5 ethers as phase transfer catalysts.

of enantioselectivity are recorded with other chalcone derivatives. Attempts to use related azacrown ethers derived from D-mannose such as catalyst **65** did not provide significantly enhanced results except for single chalcones as substrates.[101]

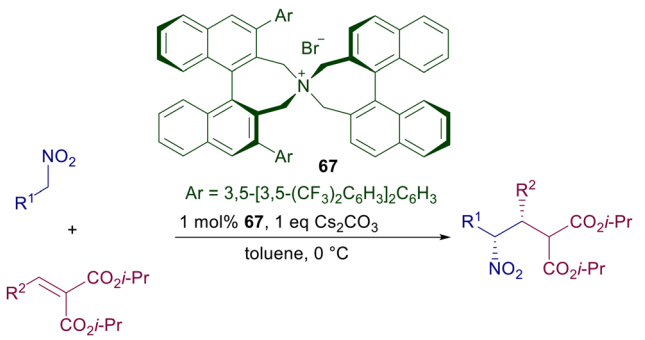
A truly effective quaternary ammonium salt catalyst was introduced by Maruoka in 2003 for the conjugate addition of silyl nitronates to enals (Scheme 49).[102] The bisbinaphthylammonium difluoride **66** is particularly active at low charge in toluene and at low temperature, allowing the diastereoselective synthesis of the *anti*-adducts that can be recovered as the corresponding silyl enol ethers. Mild acidic hydrolysis of these silyl enol ethers allows regeneration of the carbonyl function almost quantitatively without any erosion of the original stereochemical attributes.



Scheme 49 Asymmetric conjugate addition of silyl nitronates to enals catalyzed by bisbinaphthylammonium difluoride **66**.

The same catalyst with marginal modifications, mainly regarding the aryl substituents of the binaphthyl system, has been used for the conjugate addition of other functionalized nitroalkanes with various Michael acceptors. In the reaction portrayed in Scheme 50, nitroalkanes have been made to react with diisopropyl arylidenemalonates in the presence of chiral ammonium bromide **67**, leading to the corresponding *syn*-adducts with satisfactory diastereo- and enantioselectivity.[103] This process represents an interesting case of matching–mismatching interactions since the ee values recorded for the minor *anti* stereoisomer are considerably lower compared with those of the *syn*.

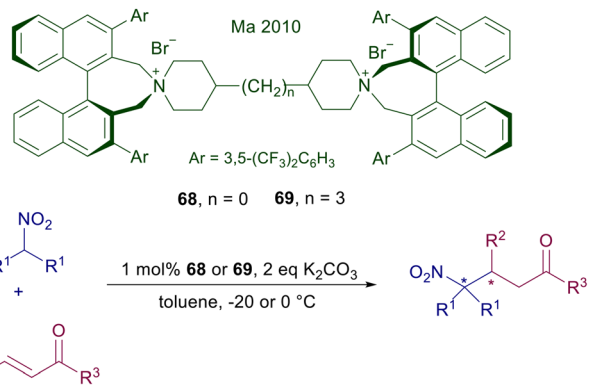
The synthetic versatility and high performances of catalysts of type **66** have been subsequently confirmed in the reaction of nitroalkanes with cycloalkenones,[104] and silyl nitronates with



Scheme 50 Chiral ammonium salt **67** in the conjugate addition of nitroalkanes to arylidene malonates.

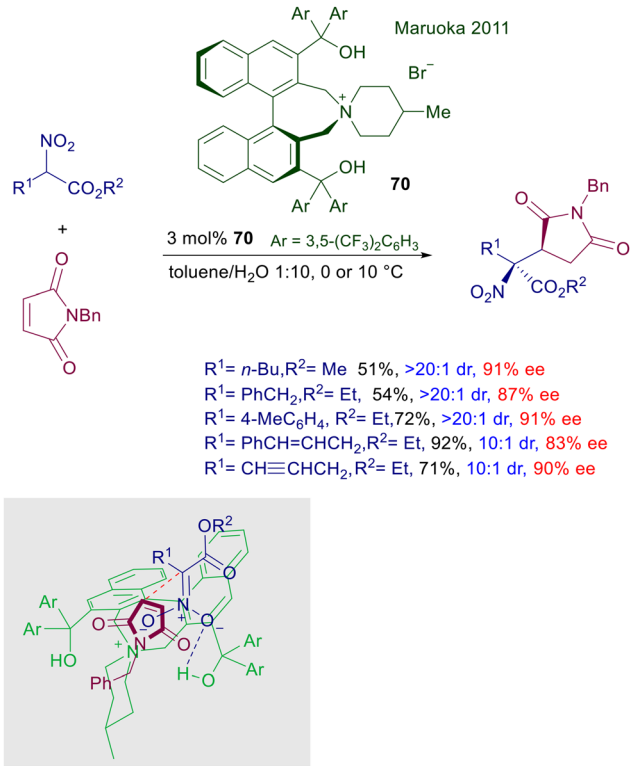
nitroalkenes.[105] These quaternary ammonium catalysts are monofunctional in nature, only allowing the activation of the nitronate anion thus excluding any interaction with the electron-poor olefin. This aspect has been revealed as problematic in the reaction of secondary nitroalkanes with enones, since the above discussed catalysts fail to provide significant levels of asymmetric induction in these reactions. Thus a bifunctional catalyst embedding two ammonium ions has been devised with the aim to provide the activation of both reactants, overcoming this limitation. The bisammonium bromides **68** and **69**, built up by tethering two binaphthylammonium units, are excellent catalysts in the conjugate addition of secondary nitroalkanes with enones (Scheme 51).[106] A peculiar aspect in the utilization of these catalysts is that a simple modification of the length of the tether enables a complete reversal of the stereochemical bias, thus allowing the preparation of both enantiomers of the resulting γ-nitroketones in a formal enantiodivergent process. A rationale for this behavior has not been provided, although it could be associated with the rotational rigidity of catalyst **68** featuring a diazaspiroundecane system compared with catalyst **69** tethered by a propyl framework.

The enantioselective addition of nitroacetate esters to maleimide has been devised using a different version of the old-fashioned catalysts **66** embedding a couple of binaphthyl units (Scheme 52).[107] Catalyst **70** includes two diarylmethanol frameworks, which would enhance the interactions with the nitronate anion thus favoring the enolization process. As a matter of fact, this is a base-free protocol carried out under the classical PTC conditions in a toluene/water biphasic system. Interestingly, the use of mild bases is not only unnecessary, but proved to be detrimental for the reaction as well as the use of homogeneous conditions using a single organic phase. In the proposed transition state, the attack of nitronate anion on the prochiral imide occurs selectively on the *Re* side of the unsaturation in order to minimize the clashing interactions with the left-sided diarylmethanol group.



R^1	R^2	R^3	Cat.	yield (%)	er (conf)
Me	Ph	Ph	**68**	95	98.5:1.5 (*R*)
Me	Ph	Ph	**69**	99	99.9:0.1 (*S*)
Me	4-FC_6H_4	Ph	**68**	92	97.1:2.9 (*R*)
Me	4-FC_6H_4	Ph	**69**	94	97.9:2.1 (*S*)
Me	Ph	4-BrC_6H_4	**68**	83	98.2:1.8 (*R*)
Me	Ph	4-BrC_6H_4	**69**	97	99.1:0.9 (*S*)
-$(CH_2)_4$-	Ph	Ph	**68**	80	96.2:3.8 (*R*)
-$(CH_2)_4$-	Ph	Ph	**69**	98	98.3:1.7 (*S*)

Scheme 51 Enantiodivergent conjugate addition of tertiary nitroalkanes to chalcones catalyzed by differently tethered ammonium salts **68** and **69**.



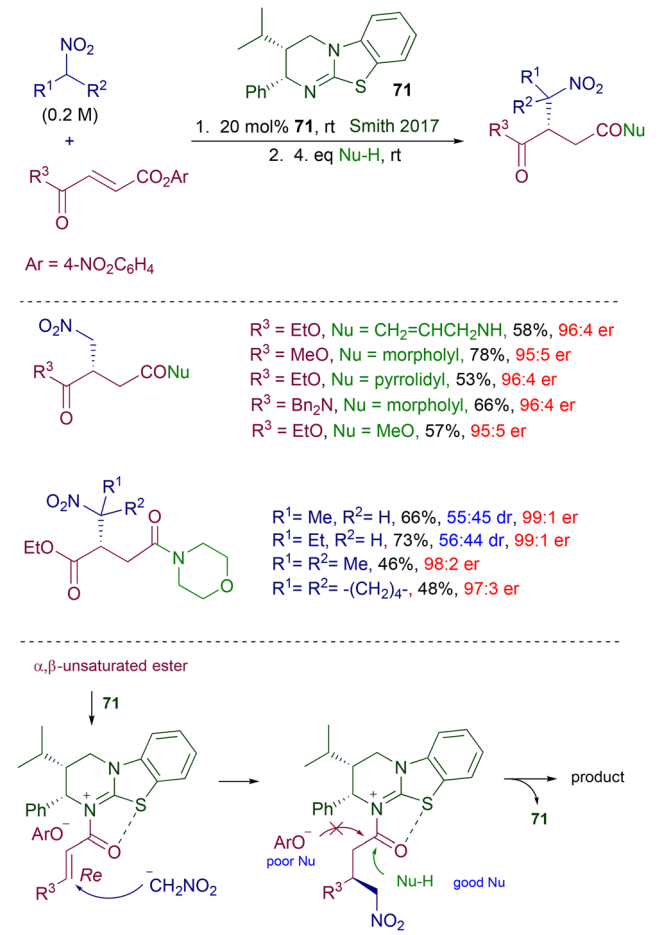
Scheme 52 Asymmetric conjugate addition of nitroesters to maleimides catalyzed by chiral ammonium salt **70**.

2.8 Acylammonium ion and NHC catalysis

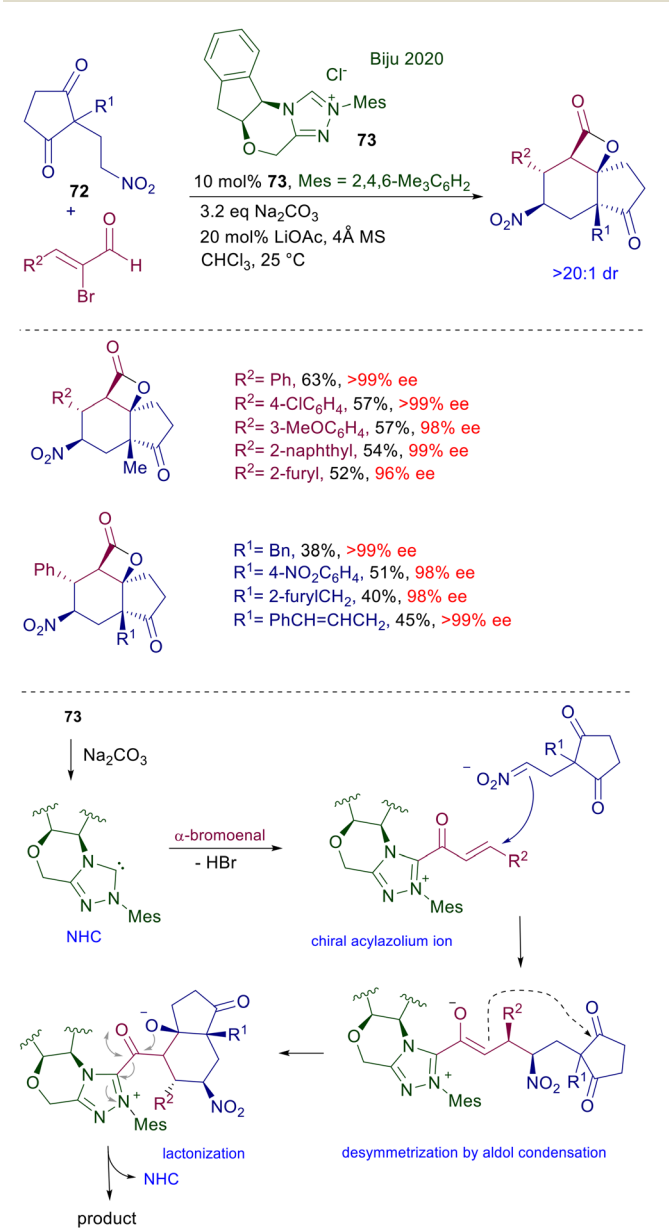
Among Michael acceptors, α,β-unsaturated esters are seldom used in organocatalyzed asymmetric reactions because of their reduced reactivity over the parent carbonyl derivatives and the poor efficiency of the activating modes provided by classical organocatalytic systems. Particularly, the enhancement in the reactivity of nitroalkanes provided by the usual hydrogen bonding with the chiral catalyst is generally inadequate for a suitable reaction with α,β-unsaturated esters. In this context, the activation of the acyl moiety by its temporary conversion into an acylammonium salt using a suitable chiral Lewis base catalyst represents an efficient strategy to allow these esters to be used as electrophiles in conjugate additions.[108] The effectiveness of this approach has been demonstrated in the reaction of nitroalkanes with fumaric acid derivatives in the presence of chiral dihydroimidazo-benzothiazole **71**

(Scheme 53).[109] According to the proposed mechanism, reaction of the fumaric acid diester with catalyst **71** chemoselectively generates an acylammonium salt on the acyl moiety bearing the better leaving group (*p*-nitrophenoxide). The conformation of the acylammonium ion intermediate is locked by a sulfur–oxygen interaction caused by the electron-withdrawing effect exerted by the positive nitrogen atom on sulfur. Thus, the subsequent attack of the nitronate anion occurs regio- and stereoselectively to the *Re* face of the alkenyl framework. The phenoxide counteranion is poorly effective as a nucleophile, and thus in order to ensure an appropriate catalyst turnover stronger nucleophiles such as primary or secondary amines or alkanols are subsequently added to obtain the target products. The enantiomeric ratios for the obtained products are satisfactory even when primary nitroalkanes are used as reactants, providing the final products as an almost equimolar mixture of diastereomers. In a related approach, the same catalyst **71** has been used for the conjugate addition of triisopropylsilyl nitronates with anhydrides of fumaric acid monoesters.[110] The resulting adducts are obtained as triisopropyl esters, making unnecessary the utilization of external nucleophiles as in the original protocol. However, reaction parameters such as atom economy and process mass intensity (PMI) are not very favorable due to the waste of half of the anhydride reactants.

The reaction of *N*-heterocyclic carbenes (NHC) with α-haloenals represents a powerful method for the preparation of α,β-unsaturated acylazolium salts showing an enhanced reactivity as Michael acceptors towards a large variety of nucleophiles. 2-Nitroethylcyclopentandione **72** reacts with 2-bromoenals in the presence of chiral triazolium salt pre-catalyst **73**, leading to tricyclic lactones with an outstanding control of the five contiguous generated stereocenters (Scheme 54).[111] Under basic conditions, triazolium salt **73** is converted into the corresponding NHC, which upon reaction



Scheme 53 Enantioselective conjugate addition of nitroalkanes to fumaric acid derivatives *via* chiral acylammonium ion intermediate.



Scheme 54 Chiral NHC-catalyzed conjugate additions using pre-catalyst **73**.

with the α-bromoenal affords the α,β-unsaturated acylazolium salt intermediate. Nitroalkane **72** undergoes a conjugate addition with the acylazolium salt, leading to a chiral enolate anion intermediate which, through an intramolecular aldol condensation, enables a desymmetrization of the 1,3-cyclopentandione moiety. The last step is a lactonization reaction releasing the target tricyclic compound with concomitant regeneration of the NHC, thus closing the catalytic cycle.

3. Organometallic complexes-catalyzed reactions

The development of synthetic procedures based on the use of chiral organometallic complexes for the conjugate addition of nitroalkanes to electron-poor alkenes has initially run parallel with that of organocatalytic methods. A selected number of metal–ligand couples have been envisaged for these conjugate additions and since the substrate–catalyst interaction is based on strong coordinating bonding, the results are often rewarding in terms of asymmetric induction (Fig. 5). Notwithstanding, to date the utilization of organometallic catalysts still remains underdeveloped compared with the synthetic protocols based on the use of organocatalysts. Interestingly, there are some metallic complexes based on aluminium which, after an initial success, have been neglected, while those based on lanthanum are rather recurrent throughout the years. The same observation can be made for magnesium, nickel and zinc-based complexes, which more recently have been superseded by copper and scandium complexes. Among chiral ligands bisoxazolines are undoubtedly the most employed derivatives, widely known for their chelating aptitude, although chiral *N*-oxides, biphosphines and Schiff base ligands have been successfully used in the conjugate addition of nitroalkanes to electron-poor olefins. The discussion of various metal–ligand complexes follows the chronological order in which they first appeared in the literature for these conjugate additions.

3.1 Nickel and cobalt complexes

In a couple of papers that appeared more than thirty years ago the first conjugate addition of nitromethane to enones catalyzed by chiral nickel and cobalt complexes was reported.[112] Ni $(acac)_2$ and $Co(acac)_2$ were coupled with various ligands including chiral 2,2′-bipyridines, 1,10-phenanthrolines, prolinamdes, prolinamines and prolinol. The nickel complexes were found to be particularly effective in the reaction of nitromethane with chalcones, leading to a maximum value of 60.9% ee evaluated by comparison with the optical rotation of the enantiomerically pure adduct. The first successful method for the addition

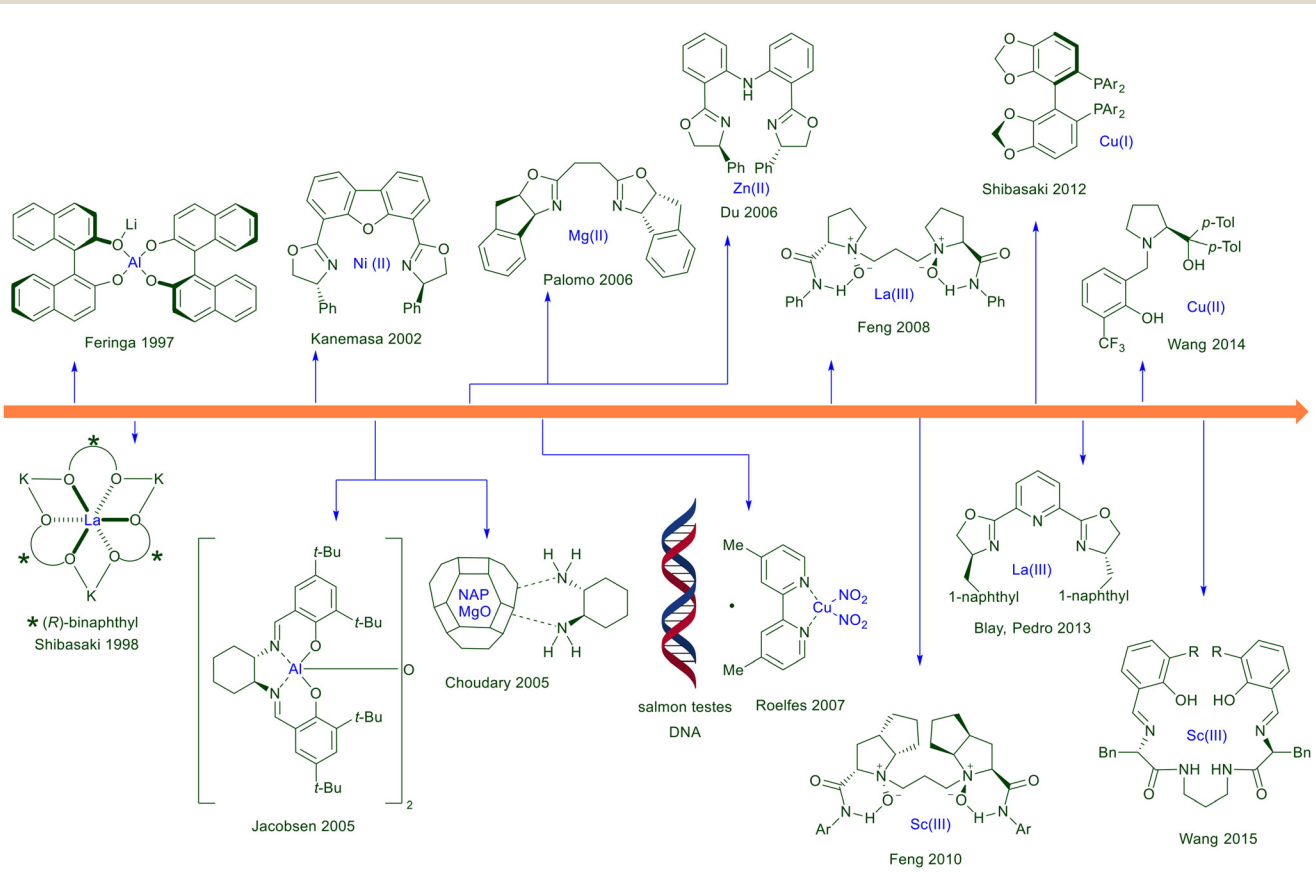
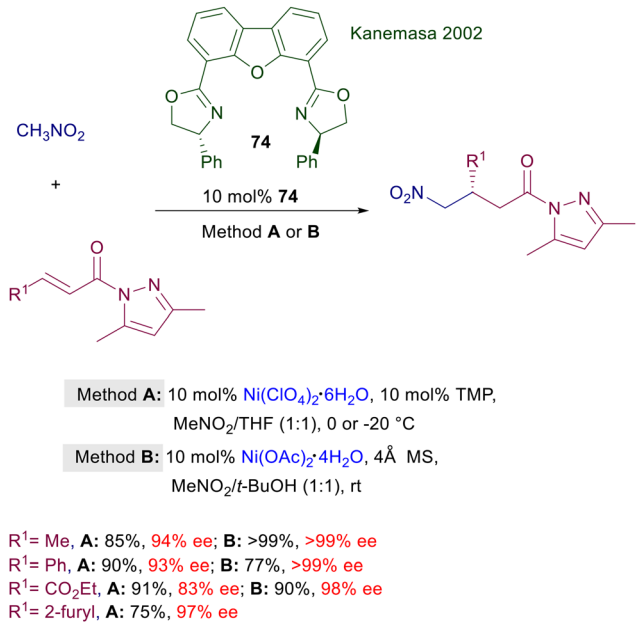
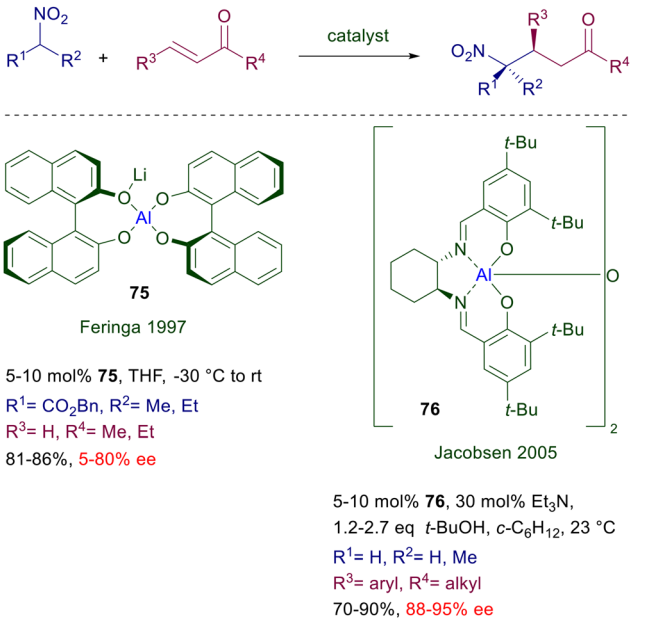


Fig. 5 Chronological development of metal–chiral ligand complexes employed for the asymmetric conjugate addition of nitroalkanes to electron-poor alkenes.



Scheme 55 Ni(II)-Bisoxazoline complex catalyzes the conjugate addition of nitromethane to α,β-unsaturated acylpyrazoles.



Scheme 56 Asymmetric conjugate additions catalyzed by Al(III)-complexes.

of nitromethane to α,β-unsaturated acylpyrazoles was accomplished using Ni(II) complexes of bisoxazoline ligand **74** (Scheme 55). In the original procedure,[113] the aqua complex obtained using nickel perchlorate hexahydrate (method A) was used in combination with 2,2,6,6-tetramethylpiperidine (TMP) as activator, since the metallic aqua complex alone was catalytically inactive. Later on, a modified procedure (method B) was introduced, changing the nature of the complex by using nickel acetate tetrahydrate and replacing TMP with 4 Å molecular sieves.[114] The second procedure was more effective in leading to the target compounds with improved ee values, although both methods employ a very large excess of nitromethane used as cosolvent in the reaction. Recently, a chiral nickel-diamine complex supported on a mesoporous silica composite (MCM-41) has been introduced for the conjugate addition of malonate esters to nitroalkenes.[115] This catalyst is also effective in the Michael addition of nitromethane to alkylidene malonates, but the observed enantioselectivity never exceeds the value of 86% ee.

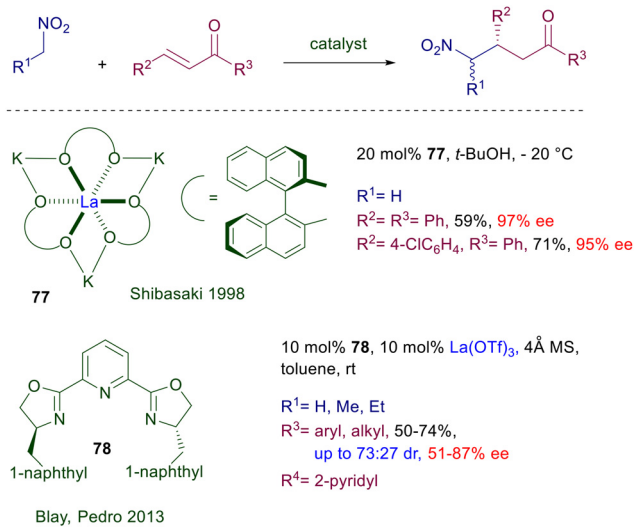
3.2 Aluminium complexes

The first aluminium complex employed as catalyst for the conjugate addition of nitroalkanes to enones was a mixed Li–Al alkoxide **75** obtained by reaction of chiral BINOL with lithium aluminium hydride (Scheme 56).[116] This catalyst was used for the reaction of a couple of nitroesters with enones, with generally modest results in term of ee values and, as expected, the enantioselectivity could be improved at low temperature. Spectroscopic studies have revealed that the effective catalyst is actually a mixture of aluminium complexes in solution. A more effective chiral [(salen)Al]$_2$O catalyst **76** has been subsequently developed for the reaction of nitroalkanes with enones at room temperature.[117] The use of an added base is necessary for a suitable conversion and, as usually observed, nitroethane affords an equimolar mixture of diastereomers.

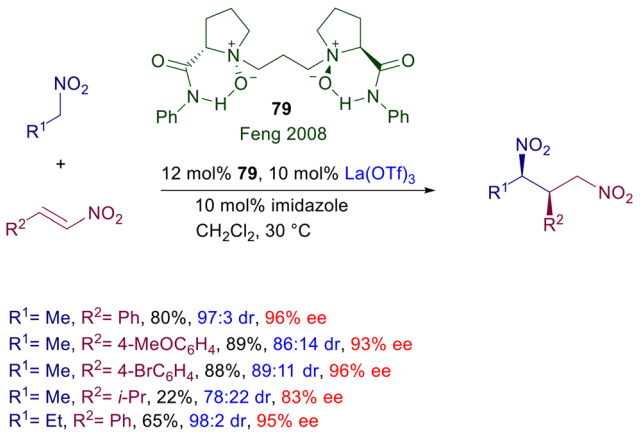
3.3 Lanthanum complexes

Chiral heterobimetallic complexes of La(III)–alkali metals with BINOL are particularly effective in the nitroaldol reaction as well as other nucleophilic addition processes.[118] The heterobimetallic complex **77** obtained by reaction of (*R*)-BINOL with lanthanum(III) triisopropoxide and potassium bis(trimethylsilyl)amide has been used to demonstrate that this catalyst is also potentially useful for the conjugate addition of nitromethane to enones (Scheme 57).[119] Curiously, in spite of the excellent results obtained with a couple of enones, the use of this catalyst has not been further expanded to other substrate–reagent combinations. The lanthanum complex obtained using bisoxazoline **78** as chiral ligand has been tested for the same purpose, but the results obtained in the reaction of nitromethane and other primary nitroalkanes with enones are less encouraging.[120]

Chiral *N*,*N*-dioxides developed by Feng and co-workers are particularly versatile catalysts since they can be used as organocatalysts as well as metal ligands in several asymmetric processes.[121] The features of the catalyst can be appropriately tuned by changing the ring size of the two *N*-oxide subunits and the length of tethering connection. Chiral dioxide **79** acts as an effective ligand for lanthanum(III) triflate in the conjugate addition of nitroalkanes to nitroalkenes (Scheme 58).[122] The reaction has been tested with a couple of nitroalkanes and nitrostyrenes, leading to the corresponding adducts with satisfactory diastereoselectivity and generally high ee values.



Scheme 57 La(III)-complexes in the conjugate addition of nitroalkanes to enones.

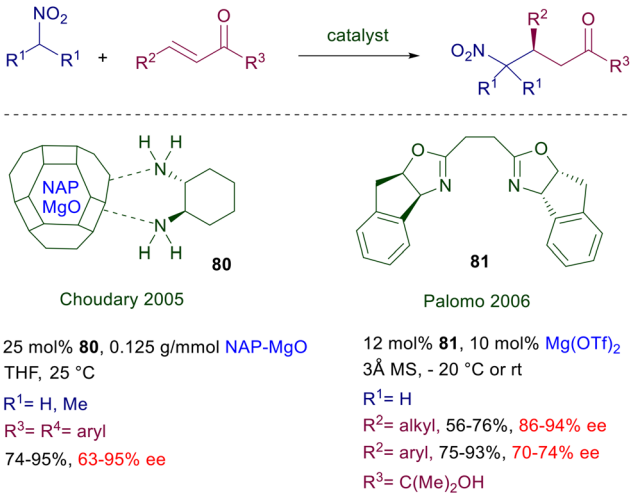


Scheme 58 Asymmetric conjugate addition of nitroalkanes to nitroalkenes catalyzed by La(III)-dioxide complex.

Modest results are evidenced using a linear nitroalkene both in terms of yield and stereoselectivity.

3.4 Magnesium complexes

The chelating ability of the magnesium cation was evaluated in a couple of papers more than fifteen years ago, exploiting two different magnesium-containing compounds interacting with chiral ligands. Nanocrystalline magnesium oxide (NAP-MgO) was used as ligand for (*R*,*R*)-1,2-diaminocyclohexane **80** as catalyst for the addition of nitromethane and 2-nitropropane to chalcones (Scheme 59).[123] The results obtained using this protocol are not particularly remarkable, with the exception of a single example. The NAP-MgO can be recycled up to five times after heating at high temperature, maintaining the same performance for the best observed process. The complex of chiral bisoxazoline **81** with magnesium triflate is

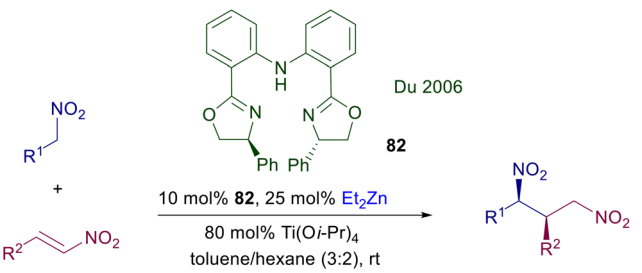


Scheme 59 Enantioselective conjugate addition of nitroalkanes to enones using Mg(II)-complexes.

effective in the addition of nitromethane to α′-hydroxy enones (R^3 = $C(Me)_2OH$).[124] Interestingly, Michael acceptors bearing alkyl substituents give better results compared with aryl-substituted ones. The dimethylcarbinol group in the target adducts acts as a dummy substituent, since by oxidative cleavage with sodium periodate it can provide access to the corresponding γ-nitroacids or γ-nitroaldehydes maintaining the same enantiopurity of the corresponding substrates.

3.5 Copper and zinc complexes

The first enantioselective conjugate addition of nitroalkanes to nitroalkenes was carried out using the zinc(II) complex with bisoxazoline **82** (Scheme 60).[125] The required zinc cation was generated by diethylzinc upon activation with titanium tetraisopropoxide. The reaction is *syn* selective and affords the corresponding 1,3-dinitro derivatives with satisfactory levels of enantioselectivity. To date, this is the only available asym-

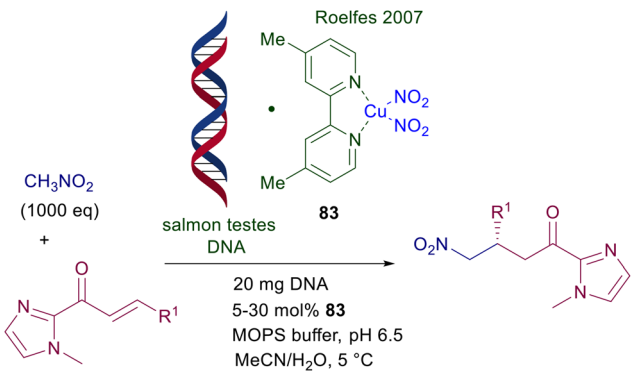


Scheme 60 Asymmetric synthesis of 1,3-dinitro derivatives by a Zn(II)-bisoxazoline complex.

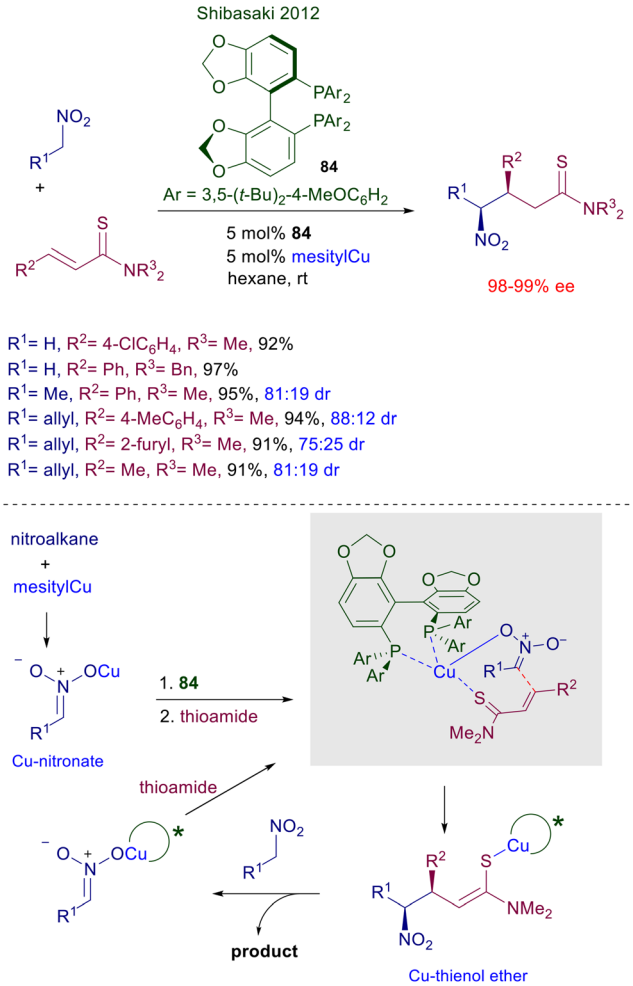
metric conjugate addition involving nitroalkanes which employs a zinc complex as catalyst.

The use of copper complexes in these conjugate additions was introduced with an unusual protocol involving salmon testes DNA as chiral element associated with copper(II)-bipyridine complex **83** (Scheme 61).[126] The exact nature of the interaction between DNA and the achiral copper complex is unknown, but the bipyridine ligand is mandatory for a successful reaction since no asymmetric induction was observed using only the DNA/copper(II) nitrate couple. A large excess of nitromethane is required for an effective conversion, and the enantioselectivity is constantly below 90% ee but with just one example (R^1 = 2-BrC_6H_4, 94% ee). A more effective chiral copper complex has been devised using (*R*)-DTBM-Segphos **84** in combination with mesitylcopper for the conjugate addition of nitroalkanes with α,β-unsaturated thioamides (Scheme 62).[127] The mesitylcopper initially reacts with the nitroalkane, generating a copper nitronate which in the presence of the phosphine ligand **84** leads to an organometallic complex. Subsequent interaction of the copper complex with the sulfur atom of the thioamide paves the way for a preferential *syn* diastereoselective conjugate addition which occurs with outstanding levels of enantioselectivity.

The addition reaction results in the formation of an intermediate copper thioenol ether, which upon reaction with the nitroalkane delivers the final product and generates the chiral copper nitronate, thus ensuring an efficient catalyst turnover. It should be observed that this catalytic system is highly chemoselective for α,β-unsaturated thioamide substrates, since the corresponding amides or enones are unaffected in competitive cross experiments. The copper(I) complex with prolinol-derived ligand **85** is a valuable catalyst for the conjugate addition of nitroacetate esters to β,γ-unsaturated α-ketoesters (Scheme 63).[128] As is commonly observed, no stereocontrol is possible at the very easily enolizable α-nitro carbon, but the



Scheme 61 Salmon testes DNA/Cu(II)-bipyridine complex as catalyst in conjugate additions of nitromethane to enones.

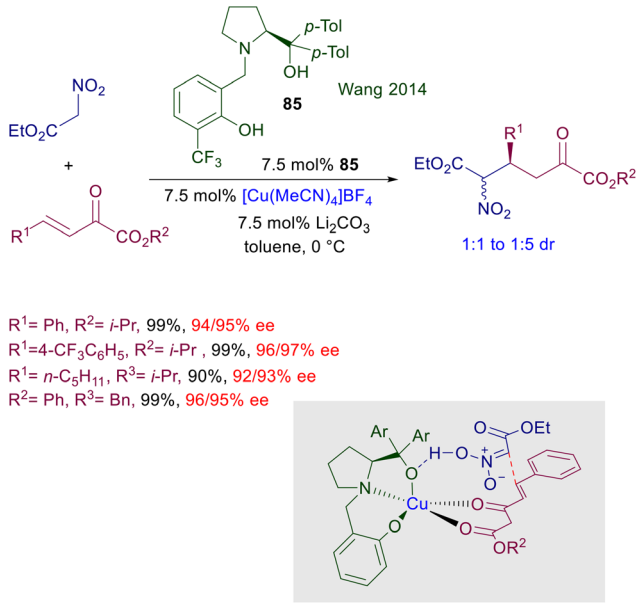


Scheme 62 Asymmetric conjugate addition of nitroalkanes to unsaturated thioamides catalyzed by Cu(I)-DBTM-Segphos.

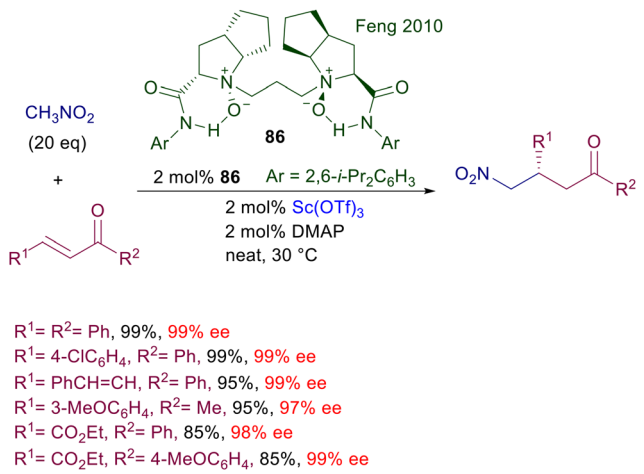
enantioselectivity recorded for both diastereoisomers formed is very good. The hydroxy groups in the ligand are able to coordinate the copper atom with further assistance from the pyrrolidine nitrogen atom. In the plausible transition state, the arrangement of the reactants leading to the observed stereochemical outcome is caused by the β-ketoester coordination with the copper and by the hydrogen bonding of the nitronic acid with the diarylmethanol group. A related copper(II) complex with the same ligand has been subsequently used for the conjugate addition of nitroalkanes to 4-alkylidenpyrrolidin-2,3-diones in water, with excellent stereoselectivity.[129]

3.6 Scandium complexes

The complex between chiral *N*,*N*-dioxide **86** and scandium(III) triflate gives superior results over complexes of other metal triflates (La, Sm, Y, Yb) with the same ligand in the reaction of nitromethane with enones and 4-oxo-4-arylbutenoates (Scheme 64).[130] The chemical yields and the enantioselectivity obtained for the corresponding adducts are really outstanding for the use of nitromethane, but this protocol has not been



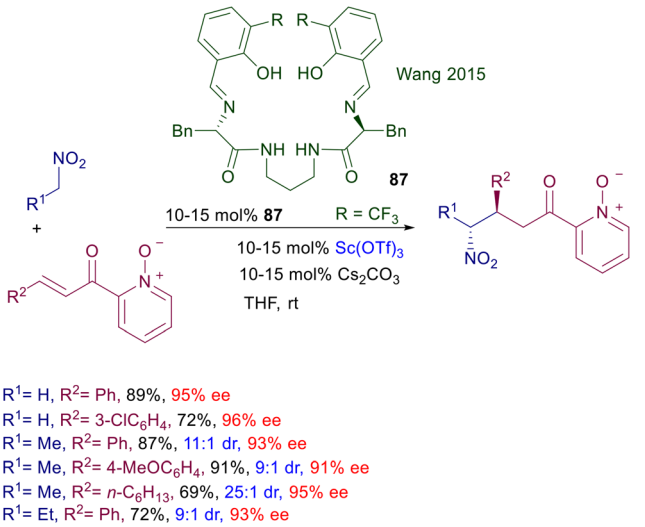
Scheme 63 Cu(I)–ligand **85** complex for the enantioselective reaction of ethyl nitroacetate with unsaturated ketoesters.



Scheme 64 Enantioselective conjugate addition of nitromethane to chalcones catyalyzed by Sc(III)-*N*,*N*-dioxide complex.

evaluated for the same process using primary or secondary nitroalkanes. In any event, chiral *N*,*N*-dioxides of type **79** and **86** have been proposed as ligands of gadolinium(III) in the catalyzed reaction of nitroalkanes with enones, giving excellent ee values but an almost complete lack of diastereoselectivity.[131]

With the aim of increasing the level of diastereoselectivity obtainable in the reaction of nitroalkanes with enone derivatives a new chiral ligand **87**, particularly suited to accommodate early-transition metals like scandium(III), has been designed (Scheme 65).[132] The ligand ability of the C_2-symmetric Schiff base **87** is coupled with the insertion of a pyridyl *N*-oxide moiety in the Michael acceptor, which would ensure a



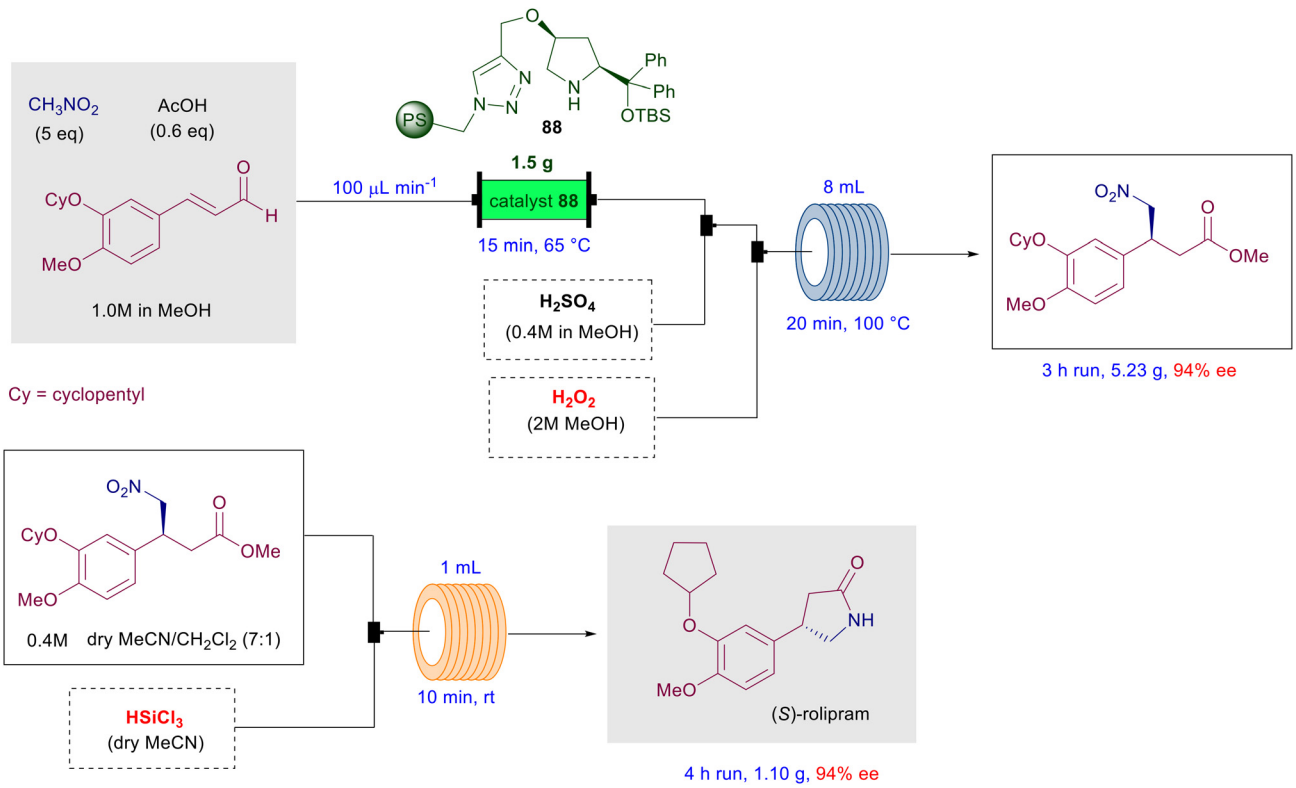
Scheme 65 Sc(III)-Schiff base **97** complex catalyzes the asymmetric conjugate addition of nitroalkanes to pyridine *N*-oxide enones.

strong coordination with the metal cation in the transition state. These combined effects lead to a satisfactory *anti* diastereoselectivity in the reaction of primary nitroalkanes with the employed substrate and a generally good level of enantioselectivity including the use of nitromethane as reactant.

4. Selected synthetic applications

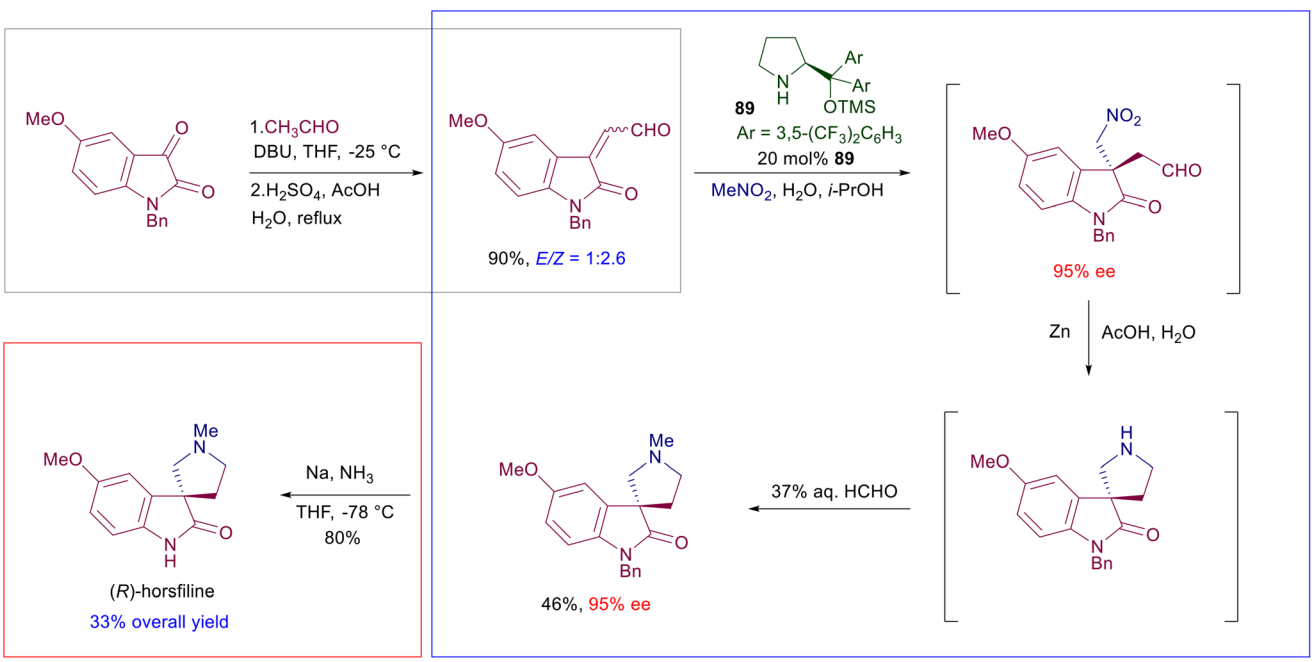
The asymmetric conjugate addition of nitroalkanes to various Michael acceptors has been particularly employed in preliminary stages of multistep processes in order to generate the embryonic element of chirality required to build up the whole optically active molecule. Soon after the introduction of the early protocols for the asymmetric synthesis of γ-nitrocarbonyl derivatives, the preparation of small bioactive compounds such as the $GABA_B$ receptor agonist baclofen or the enzyme inhibitor rolipram has been used to highlight the importance of these methods. Recently, the advent of telescoped continuous flow chemistry has provided a technical tool for the efficient synthesis of (*S*)-rolipram using a polystyrene-bound prolinol-derived catalyst **88** (Scheme 66).[133] The enantioselective conjugate addition of nitromethane to the appropriate functionalized enal, catalyzed by the immobilized chiral catalyst **88**, is followed by the oxidation–esterification step carried out in a heated coil reactor using the *in situ* generated persulfuric acid.

The intermediate γ-nitroester is obtained in 94% ee and is submitted to a metal-free reductive process in a coil reactor using trichlorosilane, leading to (*S*)-rolipram after spontaneous lactamization. Efficient and sustainable protocols for the synthesis of bioactive compounds also entail a limitation in the work-up and purification operations, exploiting one-pot transformations. The total synthesis of the spiroxindole



Scheme 66 Telescoped flow chemical process for the enantioselective synthesis of (*S*)-rolipram.

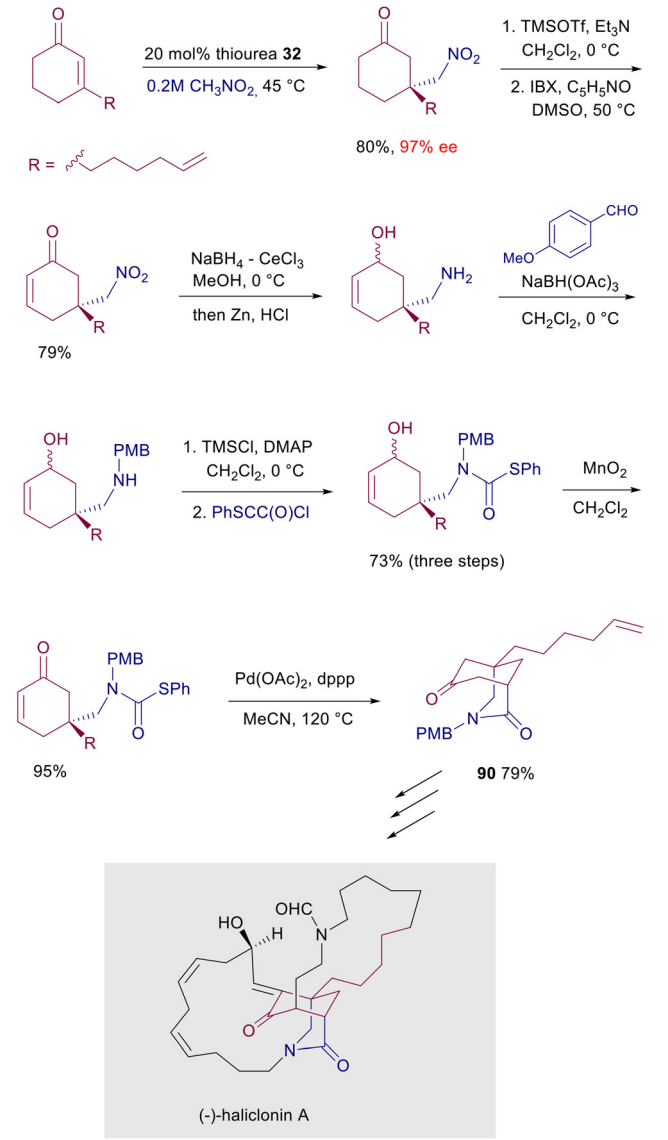
(–)-horsfiline has been carried using six synthetic transformations grouped in two one-pot processes and a final cleavage, resulting in an overall yield of 33% of the enantiopure target product starting from the oxindole substrate (Scheme 67).[134] The initial aldol condensation between the oxindole and acetaldehyde requires two steps, including the acid-promoted de-



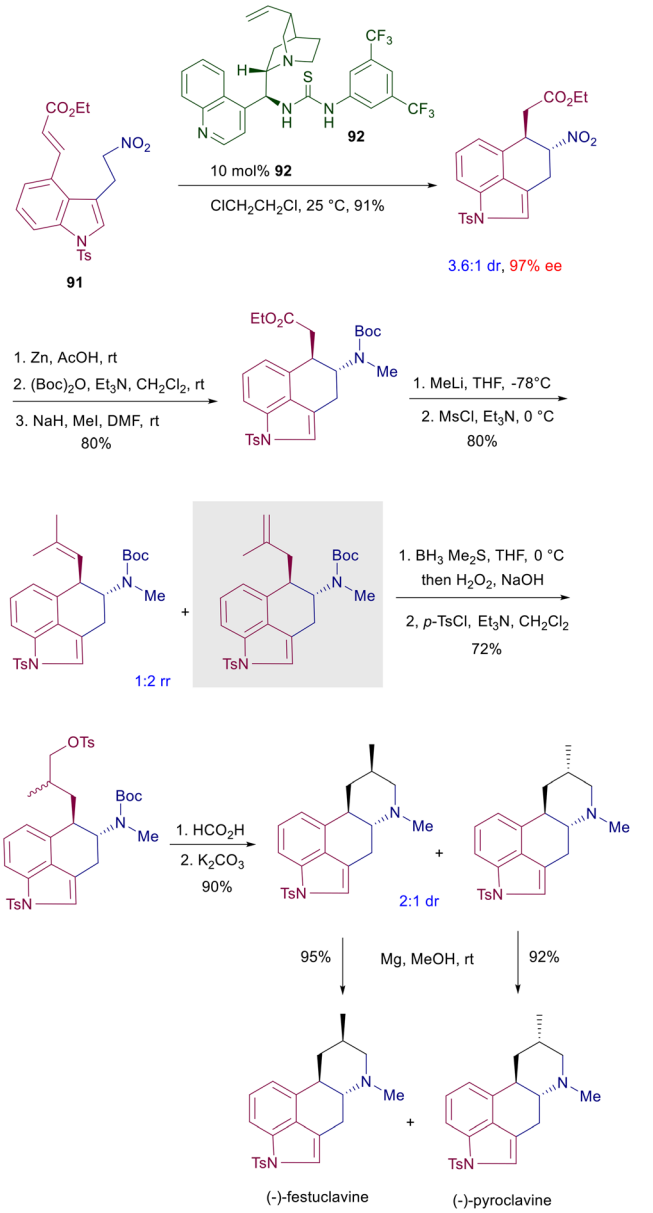
Scheme 67 Total synthesis of (*R*)-horsfiline by one-pot processes.

hydration, which can be realized in a one-pot fashion. The enantioselective conjugate addition of nitromethane to the isolated α,β-unsaturated aldehyde is carried out using chiral diarylprolinol **89** followed by reduction of the nitro group just by adding zinc metal, acetic acid and water to the solution. Formation of the primary amine is coupled with intramolecular imination and further reduction leading to the spirocyclic derivative. The *N*-methylation of the pyrrolidine ring by aqueous formaldehyde takes advantage of the presence of zinc metal used in the previous step, ultimately leading to the *N*-benzylated horsfiline in 46% overall yield from the enal substrate. The cleavage of the *N*-benzyl group is finally carried out by a Birch electron transfer reaction using sodium metal/ammonia, giving (*R*)-horsfiline in good overall yield. The same approach has been used to prepare the demethoxylated analogue of (−)-horsfiline named (−)-coerulescine in 46% overall yield and 94% ee.

The macrocyclic alkaloid (−)-haliclonin A, isolated from a marine sponge, showed promising cytotoxic activity against the K562 leukemia cell line. The core of this natural product is represented by the aza-bicyclic derivative **90**, which was obtained starting from 3-(5-hexenyl)-2-cyclohexen-1-one (Scheme 68).[135] Reaction of the cyclohexenone with nitromethane employed as a solvent in the presence of the Takemoto's chiral thiourea **32** led to the formation of the corresponding adduct in good yield and enantioselectivity. After the oxidative regeneration of the α,β-unsaturated system, selective reduction of the carbonyl group using the Luche pro-



Scheme 68 Synthesis of the macrocyclic alkaloid (−)-haliclonin.

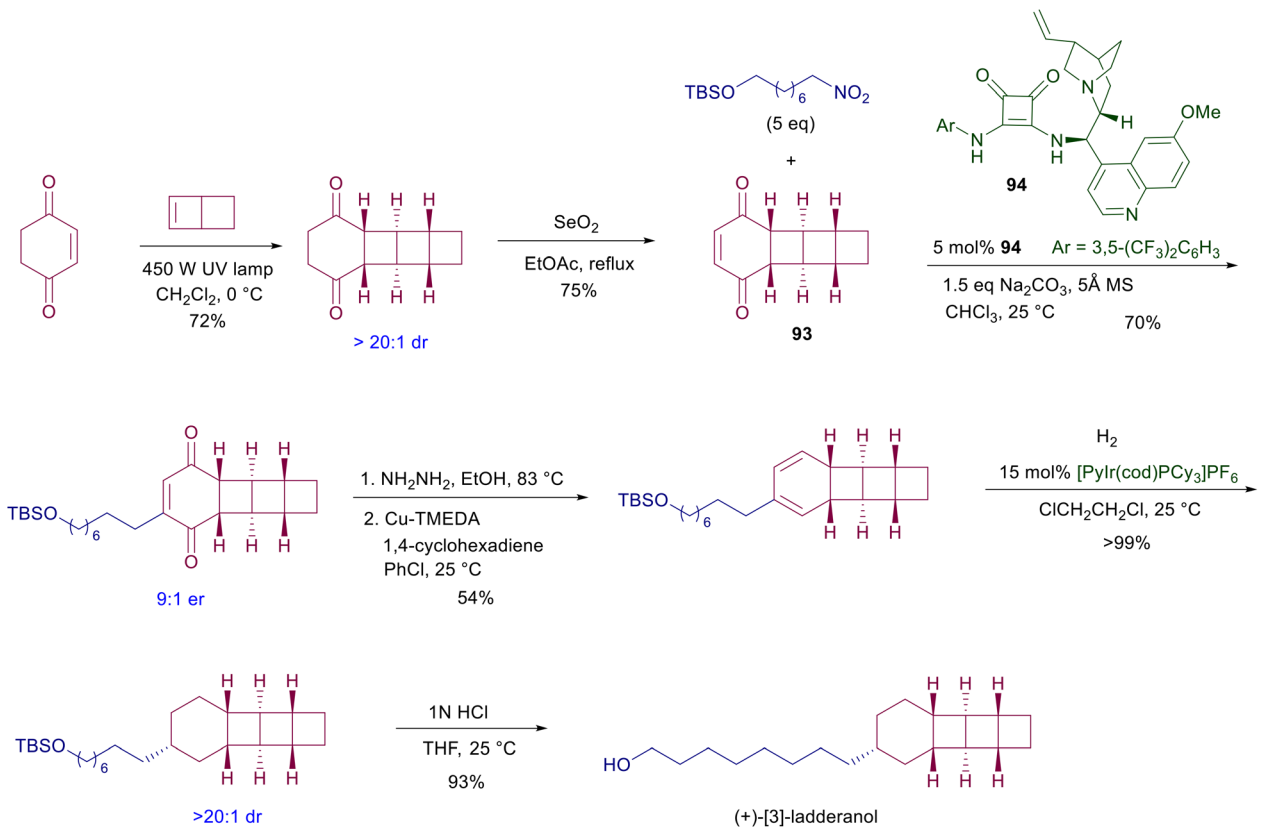


Scheme 69 Synthesis of the ergot alkaloids (−)-festuclavine and (−)-pyroclavine.

tocol and zinc-promoted reduction of the nitro group gave an amino alcohol intermediate. Protection of the primary amino group as *p*-methoxybenzyl (PMB) derivative was accomplished by reductive amination followed by amidation with phenylchlorothioformate. After oxidation of the allylic alcohol to the enone moiety, the last step to intermediate **90** was carried out by a Pd(II)-catalyzed cyclization using 1,3-bis(diphenylphosphino)propane (dppp) as ligand. After several steps compound **90** was converted into (−)-haliclonin A, thus confirming the structural assignment of the isolated natural product.

The enhanced pharmacological profile of many alkaloids of the ergot family led to the development of many procedures for their asymmetric synthesis. Considering the common structural motif of these alkaloids, a unifying strategy consists of the synthetic elaboration of 4-substituted 3-(2-nitroethyl) indoles, easily obtainable by Friedel–Crafts reaction of indoles with nitroalkenes (Scheme 69).[136] Particularly, (−)-festuclavine and (−)-pyroclavine, which show an epimeric relationship, have been prepared by a preliminary intramolecular conjugate addition of nitroindole **91** in the presence of chiral bifunctional thiourea catalyst **92**. This reaction allows the generation of two stereocenters of the three present in the target products, with a satisfactory level of diastereo- and enantioselectivity.

The adopted synthetic strategy entailed the reductive transformation of the nitro group into a protected *N*-methylamino derivative and the installation of an isopropenyl side chain, which proved rather troublesome by nucleophilic methylation-elimination since a regioisomeric mixture of alkenyl compounds was formed. The required 2-methylallyl regioisomer was submitted to a hydroboration–oxidation followed by *O*-tosylation with poor stereocontrol which, however, enabled the formation of the epimeric couple of *N*-tosylated natural products by nucleophilic displacement by the *N*-deprotected amino group. The target alkaloids were obtained after final deprotection of the indole nitrogen atom. The procedure devised for the alkylative desymmetrization of *meso*-cyclopenten-1,3-diones portrayed in Scheme 33 has been successfully employed for the total synthesis of (+)-[3]-ladderanol, a component of natural ladderane phospholipids (Scheme 70).[137] The cyclohexenedione **93** required for the asymmetric conjugate addition was prepared by [2 + 2] photocycloaddition of cyclohex-2-ene-1,4-dione with bicyclo[2.2.0]hex-2-ene followed by oxidation with selenium dioxide. Reaction of **93** with an appropriate nitroalkane in the presence of bifunctional squaramide catalyst **94** gave the expected optically active cyclohexenedione in 9 : 1 er. Subsequently, carbonyl reduction of the 1,3-dienone system led to the corresponding cyclohexadiene derivative, which upon a highly diastereoselective hydrogenation using the Crabtree's catalyst afforded the *O*-protected ladderanol. The natural (+)-[3]-ladderanol was finally obtained by hydrolytic cleavage of the silylated hydroxy group.



Scheme 70 Total synthesis of (+)-[3]-ladderanol by alkylative desymmetrization of tetracyclic derivative **93** as a key step.

5. Conclusions and outlook

The conjugate addition of nitroalkanes to electron-poor alkenes is an old-fashioned process widely used to generate γ-nitro-functionalized derivatives to be mainly used as a gateway to γ-amino compounds. The asymmetric version of this reaction was introduced almost fifty years ago, but only in the last couple of decades has it achieved notable results in terms of diastereo- and enantioselectivity. Synthetic protocols based on the use of chiral organocatalyst are preeminent over those employing chiral metal–ligand complexes, especially regarding the practical application to targeted compounds. The success of organocatalyst-based procedures is to be found in the stability and easy handling of these purely organic molecules and their good performances even at low catalyst charge. A large majority of the organocatalysts employed for this purpose are obtained by relatively simple structural modifications of natural compounds coming from the chiral pool such as amino acids and alkaloids. Very often, the most effective catalysts are those evidencing a simple structure, as in the case of chiral diarylprolinols easily obtained from proline in a few synthetic steps. A notable advance has been introduced exploiting the use of bifunctional thiourea and squaramide-based catalysts, enabling the efficient activation of both reactants participating in the conjugate addition. The last systems developed are peptide foldamers and engineered aldolase enzymes whose primary amine and pyrrolidine amino acid residues are able to effectively catalyze this conjugate addition. On the side of the metal complexes, new chiral ligands have been developed to ensure better results, with traditional metals used for this purpose like copper, scandium and lanthanum. For some of these metal complexes the presence of additional chelating groups in the Michael acceptor is often required in order to obtain satisfactory results. Among chiral ligands employed, *N*,*N*-dioxides, diphosphines and Schiff base derivatives appear to be the most effective systems for these processes. The procedures presented in this report clearly indicate that although a high level of enantiocontrol is very often observed with these methods, the achievable diastereoselectivity is still largely unsatisfactory. The high ee values recorded for each diastereomeric couple indicate that a thermodynamic equilibration involving the acidic α-nitro hydrogen atoms could be responsible for the reduced level of diastereoselectivity observed. As a matter of fact, high diastereomeric ratios are frequently evidenced in cascade processes, leading to cyclic derivatives featuring superior sterical constraints. The selected examples of targeted applications reported in the second-last section are paradigmatic of the synthetic potential of the discussed procedures for these conjugate additions, which are expected to provide new and exciting results in the future.

Author contributions

Roberto Ballini: visualization, writing – original draft and writing – review & editing. Alessandro Palmieri: visualization, writing – original draft and writing – review & editing. Marino Petrini: conceptualization, visualization, writing – original draft and writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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