THIOUREA-AMINE CATALYSED ASYMMETRIC SYNTHESIS OF FUNCTIONALISED EPOXIDES

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Abstract. *Bi- or multifunctional thiourea-amines are highly popular organocatalysts used for the C-C, C-N, and C-S bonds formation and in cascade reactions to prepare several heterocyclic compounds. More recently, thiourea-amines displayed useful catalytic activity to prepare functionalised epoxides via asymmetric epoxidation of electron-poor alkenes and kinetic resolution of racemic epoxides. In this personal account we present the results achieved by using this class of organocatalysts, which enabled the synthesis of a variety of functionalised epoxides in good to high yield, diastereo- and enantioselectivity. The optically active epoxides proved to be useful synthetic intermediates for further derivatization to heterocyclic or acyclic derivatives, bearing tertiary and quaternary stereocenters.*

Contents

1. Introduction

In the area of asymmetric organocatalysis, bifunctional and multifunctional thiourea-amines occupy a dominant position as promoters, clearly attested by the exponential number of reports published since the benchmark examples reported by Takemoto's[1] and Schreiner's[2] groups in 2003 (Figure 1).

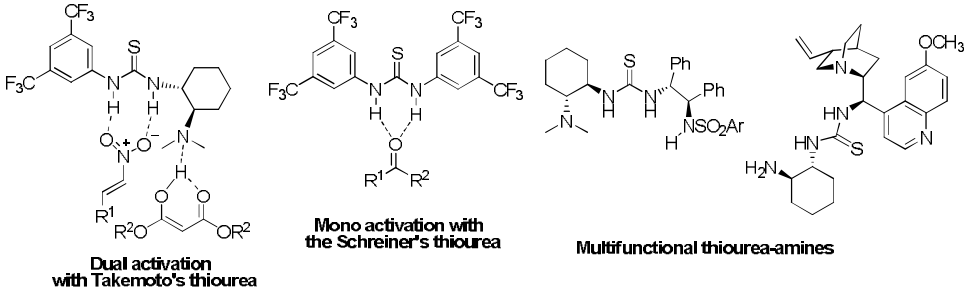


Figure 1. H-bonding as keystone concept in the activation of reagents by representative thiourea-derivatives.

The keystone concept in the activation mediated by these compounds is hydrogen-bonding.[3] The thiourea moiety, as double hydrogen-bonding donor, serves as general acid in the activation of typically, but not esclusively, carbonyl compounds, whereas the amine group works as Brønsted or Lewis base. According to the reaction mechanism and the nature of the reagents involved, more elaborated organocatalysts have been developed. More recently, different examples of multifunctional thiourea-amines bearing additional chiral moieties and hydrogen-bonding groups, have been disclosed and successfully applied in covalent as well as in noncovalent organocatalysis, expanding the basic concept of activation initially illustrated by Takemoto (Figure 1).[4] The presence of other additional H-bonding donor or acceptor groups in the promoter,

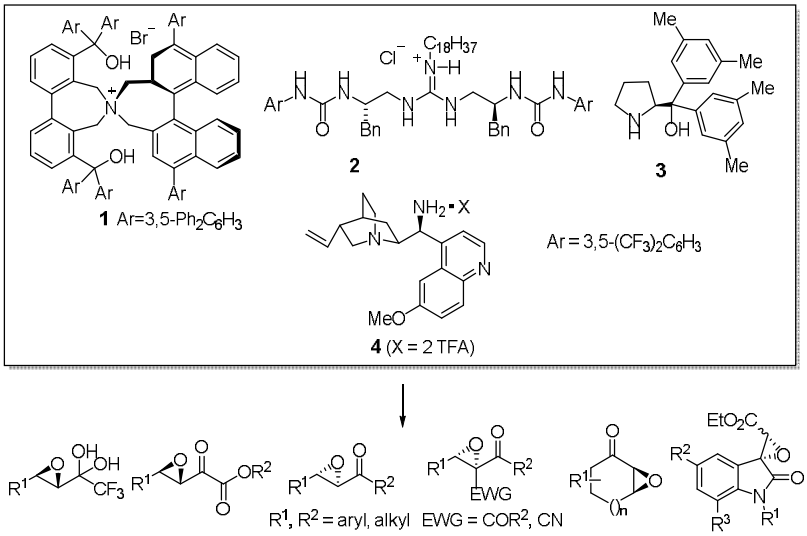
helped to establish additional H-bonding interactions useful to enhance the catalytic activity and the enantioselectivity. Although it is hard to have a defined picture of the mechanisms involved, especially in noncovalent organocatalysed reactions, DFT calcultations and experimental findings can give great support to rationalize the asymmetric induction and also to design new more efficient bi- and multifunctional organocatalysts suitable to solve unmet synthetic challenges.

As previously described in Targets in Heterocyclic Systems by Marqués-López and Herrera,[5] thiourea-amines found interesting applications in asymmetric cascade synthesis to obtain a great variety of chiral heterocyclic compounds, most of them representing the core of different biologically active compounds. On the grounds of our main research interest in asymmetric oxidations,[6] some years ago we became interested in checking the activity of thioureas in the unexplored area of oxidation. In this chapter, we focus on the application of thiourea-amines as catalysts for the asymmetric synthesis of novel functionalized epoxides, bearing tertiary and quaternary stereocenters, via epoxidation. Moreover, the potential of thiourea-amines as organocatalysts in alternative non oxidative pathways involving kinetic resolution to produce optically active epoxides are also discussed.

2. Short and focused overview on asymmetric organocatalytic nucleophilic epoxidation

Undoubtedly, the asymmetric epoxidation of alkenes is to be considered the most effective and direct reaction to access a great number of optically active epoxides, thanks to the ready availaibility of differently substituted alkenes as reagents.[7] Chiral epoxides have undiscussed value as synthetic intermediate, thanks to the regio- and stereoselective ring-opening to give several functionalised building blocks bearing two-vicinal stereocenters.

Notable and highly useful metal-based systems have been developed over the last decades by Sharpless,[8] Katsuki,[9] Jacobsen,[10] Yamamoto[11] and organocatalytic systems disclosed by Shi[12] for the asymmetric epoxidation of allylic, homoallylic alcohols and unfuctionalised alkenes. Taking into account the epoxidation of electron-poor alkenes, besides the general chiral metal-based systems, such as those reported by Shibasaki,[13] in the last decade a significant contribution to the advancement of this area has been provided by the use of organocatalysts. Indeed, the most relevant achievements in the asymmetric epoxidation of α,β-unsaturated ketones concern the employment of novel phase transfer catalysts (PTC), beyond the known *Cinchona*-alkaloids based PTCs, such as compounds **1** and **2**, respectively reported by Maruoka's[14] and Nagasawa's[15] groups (Scheme 1).

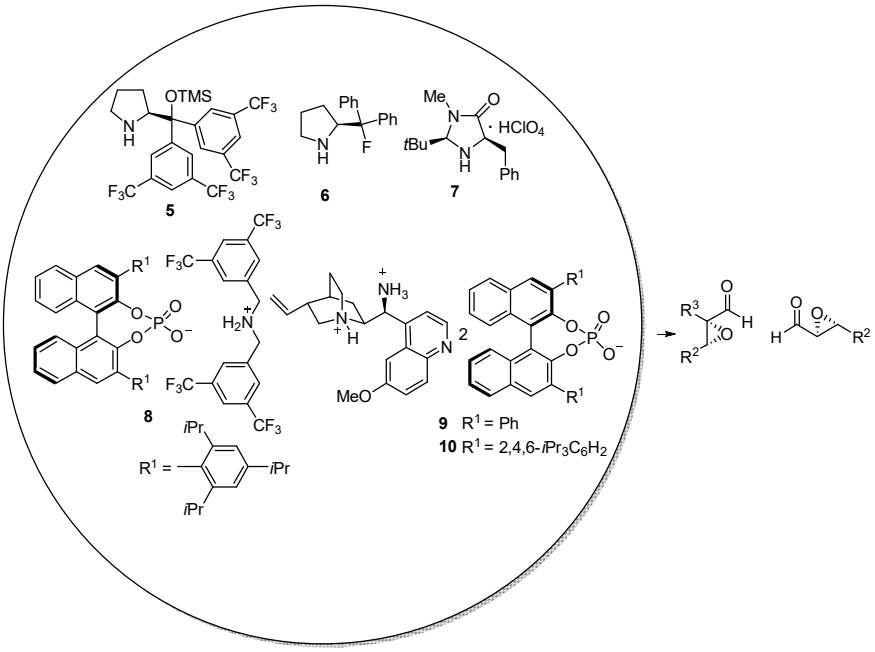


Scheme 1. Most recent promoters for the asymmetric organocatalyzed epoxidation of α,β-unsaturated ketones.

The appealing features of these catalysts are the high level of enantioselectivity (ees >90%) achieved for the epoxyketones, mainly derived from chalcones, low catalyst loading (1-3 mol%), and ready availability of the oxidants used (NaOCl and H_2O_2). It is interesting to note that in catalyst **2**, the urea groups were necessary for the reaction to proceed, indicating a synergic role of the urea moieties in the reagents activation. We disclosed that simple L-diaryl prolinols, such as commercially available **3**, can be used at 20 mol% loading for the epoxidation of α,β-unsaturated ketones with *tert*-butyl hydroperoxide (TBHP), affording the epoxides in good to high level of enantioselectivity.[16] With the help of experimental work and DFT calculations, we were able to assess that the reaction proceeds in a noncovalent fashion with a synergic activation of enone and TBHP by the hydroxy and amino groups via H-bonding interactions.[17] This and related systems have been applied further for the first asymmetric epoxidation of other useful classes of electron-poor alkenes.[18]

An important improvement in this area has been illustrated by the work of List's[19] and Deng's[20] group, who showed the ability of *Cinchona*-alkaloids derived primary amine **4** to catalyze the challenging epoxidation of cyclic and acyclic aliphatic enones with H_2O_2 or alkyl hydroperoxides, achieving excellent level of enantioselectivity (up to 99% ee). In this case the formation of a covalent chiral iminium intermediate was invoked, justifying the high level of stereocontrol.

The asymmetric epoxidation of α,β-unsaturated aldehydes can be considered among the most challenging goals, solved for the first time in 2005 by Jørgensen and co-workers using a protected L-diaryl prolinol **5**/H_2O_2 system (Scheme 2).[21] Likewise, the involvement of chiral iminium ions intermediates attacked by the nuclephilic oxidant were suggested according to a Weitz-Scheffer mechanism. The epoxides were recovered in good to high diastereoselectivity and high ee values (up to 98% ee).



Scheme 2. Promoters for the asymmetric organocatalyzed epoxidation of α,β-unsaturated aldehydes.

Further studies were devoted to modify this scaffold to obtain new secondary chiral amines such as the fluorinated pyrrolidine-based organocatalyst **6**[22] and the imidazolidinone salt **7**[23] which behaved with similar performance. Interestingly, List applied a conceptually novel approach in asymmetric synthesis, named "asymmetric counteranion-directed catalysis" (ACDC),[24] in the epoxidation of enals catalysed by **8**/H_2O_2 system, which proceeded with high level of diastereo- and enantioselectivity.[25] When cationic intermediates

are involved in the reaction (such as iminium ions), it can proceed in enantioselective way when a chiral counteranion is incorporated into the catalytic system. In this case, the sterically encumbered counteranion governs the asymmetric induction. The same group developed more sophisticated system **9-10**/H_2O_2, combining 9-amino-9-deoxyepiquinine and (*R*)-BINOL-based phosphoric acid salts,[26] which enabled to succesfully extend the asymmetric epoxidation to β-disubstituted α,β-unsaturated aldehydes and α-substituted acroleins. Interestingly, dramatic matching/mismatching effects were observed when changing the absolute configuration of the phosphoric acid used.

It has to point out here that poly-L-alanine and poly-L-leucine (PLA/PLL)/H_2O_2 catalyzed asymmetric epoxidation of *trans*-chalcones, early reported in the 1980s by Juliá and Colonna, has been deeply studied and improved over the last decades.[27] This system has been frequently used as key-step in several total synthesis and it can be considered the epoxidizing system suitable for the widest substrate scope of electron-poor alkenes (Figure 2).[28] It has been successfully applied either to α,β-unsaturated carbonyl compounds or alkenes bearing other electron-withdrawing groups as reagents, with the exception of low reactive α,β-unsaturated esters and amides. This last class of alkenes still represent the most difficult to epoxidize with high level of stereoselectivities.

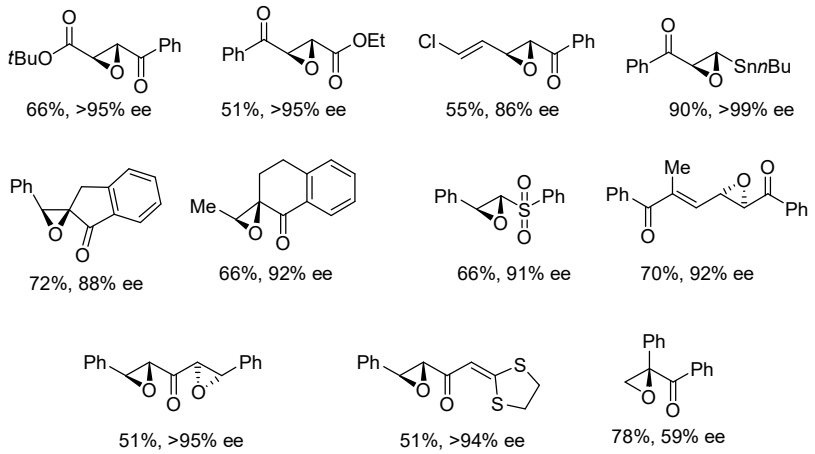


Figure 2. Representative substrate scope of the PLL catalysed asymmetric epoxidation.

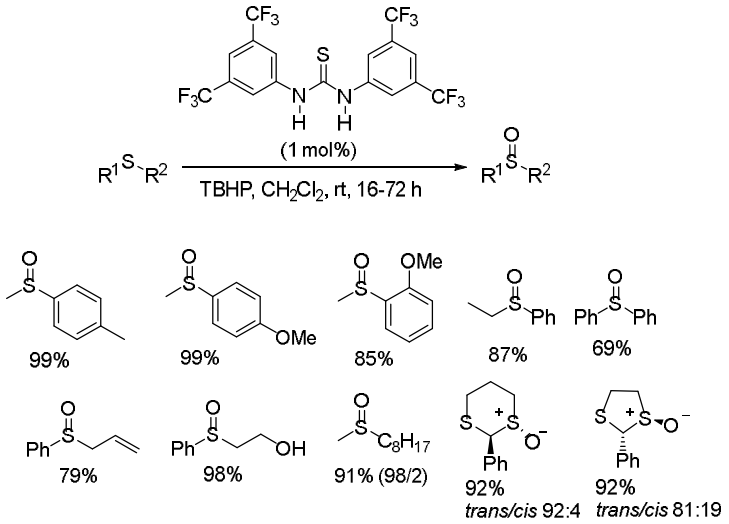
3. Thiourea-amine catalysed epoxidation of electron-poor alkenes

Thioureas demonstrated to be good H-bonding donors, able to activates different compounds, behaving like Lewis acids, thus increasing the electrophilicity of the reagents involved in the activation (Figure 1). At the time we started our investigation, no examples of thioureas in the area of asymmetric oxidations had been reported. To check the suitability of their application as catalysts, we envisioned alkyl hydroperoxides could be electrophilically activated toward nucleophilic reagents such as sulfides by using a thiourea as an H-bonding donor.[29] Indeed, we disclosed that Schreiner's thiourea promoted the chemoslective oxidation of sulfides to sulfoxides at 1 mol% loading working at room temperature in CH_2Cl_2 (Scheme 3).

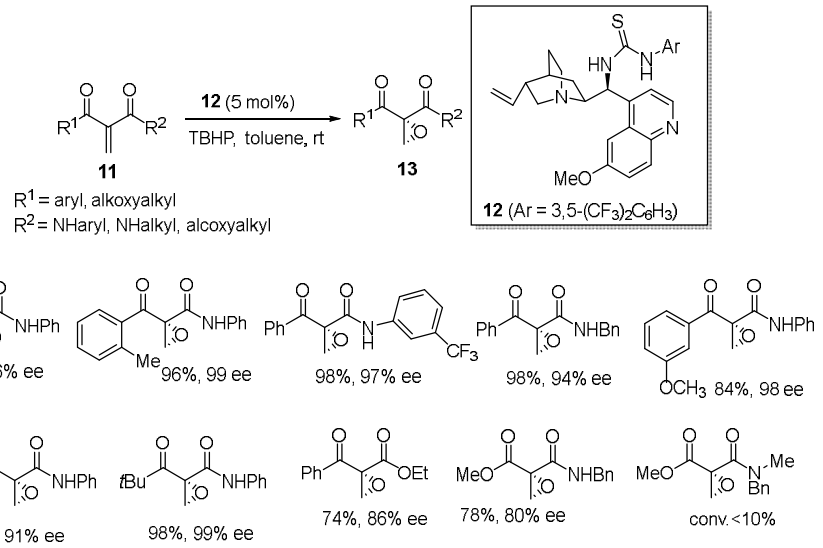
A variety of sulfoxides were obtained with high chemoselectivity in good to high yield. First attempts to investigate the stereoselectivity showed that 2-phenly-1,3-dithiane and dithiolane were converted into the *trans*-monosulfoxides with comparable stereocontrol to metal-based oxidative systems. The thiourea proved to be stable under the conditions employed in the oxidation, as checked in a blank experiment. These results encouraged us to explore the activity of optically active bifunctional thiourea amines in asymmetric epoxidation of electron-poor alkenes. As previously described, a lot of space for the development of new asymmetric epoxidation of di- and trisubstituted electron-poor alkenes, bearing two-electron-withdrawing groups, was available, as these classes of alkenes were not investigated.

We speculated that thiourea amines would be suitable promoters for the nucleophilic epoxidation, able to activate the alkene via H-bonding and the nucleophilic hydroperoxide via deprotonation by the amine

group. Given the importance of terminal epoxides in organic synthesis, we decide to start our investigation with α-aroyl acrylamides and acrylates **11** (Scheme 4).[30]



Scheme 3. Thioureas in electrophilic oxidation of sulfides to sulfoxides.



Scheme 4. Asymmetric epoxidation of α-aroyl acrylamides and acrylates with cinchona thiourea/TBHP.

Terminal alkenes of type **11** are challenging to epoxidize, being highly reactive Michael acceptors and prone to polymerization as side-process. Easily available thiourea amine **12** worked efficiently at room temperature and at 5 mol% loading to give the epoxides **13**, bearing a quaternary stereocenter, in generally high yield and enantiomeric excess. In the case of acrylates and carbamoyl acrylates, the reaction proceeded slowly and a sligth decrease of the enantioselectivity was observed. The presence of the amide N-H proton in the alkene demonstrated to have a fundamental role in promoting the reaction. It likely served to

preorganize the alkene through H-bonding, as attested by the absence of reactivity of carbamoylacrylates bearing a tertiary amide group.

The bifunctional nature of the catalyst was necessary to accelerate the reaction. DFT calculations helped to suggest the formation of a neutral ternary complex among catalyst, alkene, and TBHP, in which the secondary amide group of the alkene activates the substrate blocking its geometry via an intramolecular hydrogen-bonding with the carbonyl group (Figure 3).

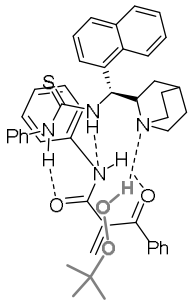
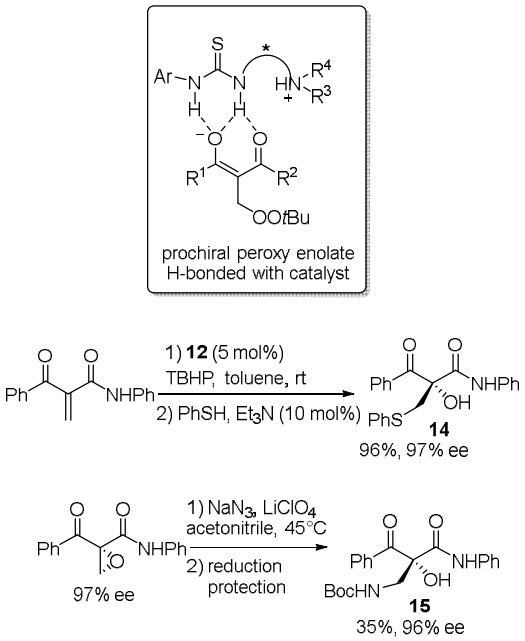


Figure 3. Computed model of the neutral ternary complex among reagents and simplified catalyst.

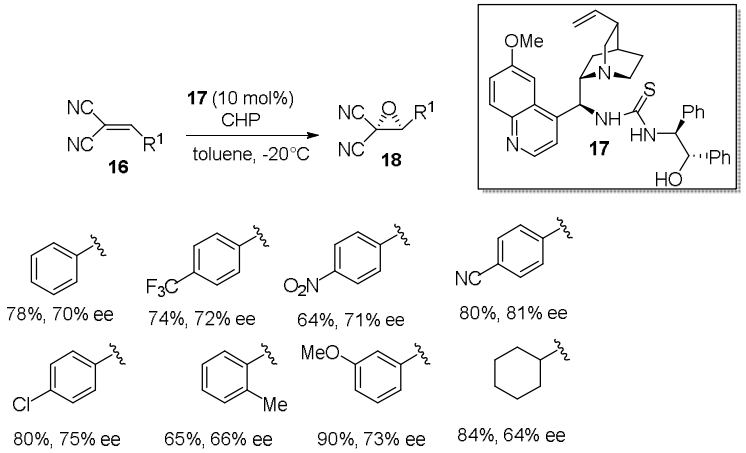
Mechanistically, the interesting feature of this system is that the stereogenic centre was formed in the second step of the Weitz-Scheffer reactive pathway (Scheme 5). Indeed, a first deprotonation of TBHP would form the peroxyanion, followed by its conjugate addition to the alkene to give the prochiral peroxy enolate hydrogen-bonded by the thiourea group of the chiral catalyst, which in the ring-closure step would give highly selective formation of (*R*)-epoxide. Given the high regioselectivity observed in ring-opening reactions of terminal epoxides, the synthesis of functionalised scaffolds containing a quaternary stereocenter was demonstrated via a one-pot fashion from the alkene or from the optically active epoxide.



Scheme 5. Reactive peroxy enolate thiourea-amine complex and synthetic elaboration of epoxides.

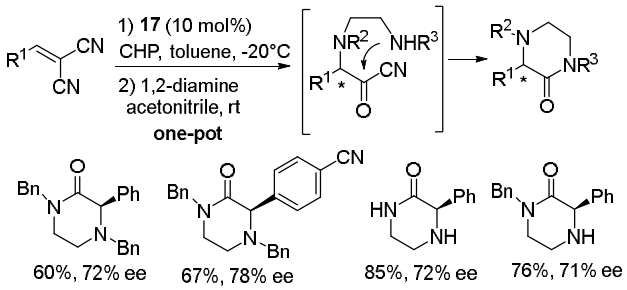
Hydroxy sulfide **14** or *N*-Boc-α-hydroxy-β-amino acid derivative **15**, were obtained in good to high yield and excellent enantioselectivity.

The development of stereoselective epoxidation of alkenes, bearing modest H-bonding acceptors groups, is particularly critical under noncovalent activation. Consequently, it was necessary to design organocatalysts able to engage more effectively in hydrogen-bonding network with the alkene and the oxidant. Following this line, we became interested in developing a first asymmetric epoxidation of alkylidene malononitriles **16**. These readily available alkenes, are reactive Michael acceptors but the cyano group is a weak H-bonding acceptor. Satisfactory results were achieved by using multifunctional quinine-derived thiourea **17**, bearing additional stereocenters and hydrogen-bonding donor group (Scheme 6).[31]



Scheme 6. Asymmetric epoxidation of alkylidenemalononitriles with cinchona thiourea/CHP system.

A significant influence of matching and mismatching effects was observed on the stereochemical outcome of the reaction when checking a variety of thiourea-amines. Catalyst **17** proved to be more effective than **12**, which also confirmed the importance of additional groups present in the organocatalyst. Aryl and alkyl substituted alkenes were epoxidized in good yield and moderate to satisfactory level of enantioselectivity when using cumyl hydroperoxide (CHP) as the oxidant in toluene at -20°C. *gem*-Dicyanoepoxides **18** can be considered synthetic equivalent of dication ketenes, when reacted with binucleophilic reagents to give a variety of interesting heterocyclic compounds such as imidazoles, 1,4-benzoxazin-2-ones, 3-substituted piperazin-2-ones. Hence, a one-pot asymmetric epoxidation/ring-opening reaction with diamines to access enantioenriched 3-substituted piperazin-2-ones was developed under mild reaction conditions (Scheme 7). This class of compounds show a wide range of biological activities and only a few asymmetric approaches have been developed so far.



Scheme 7. One-pot asymmetric epoxidation/ring-opening with diamines.

We propose the alkene would be H-bonded with NH and the OH groups of the thiourea and the CHP would be strongly engaged in H-bonding interaction with the basic quinuclidine nitrogen. In this chiral ensemble, the peroxide addition would occur onto the *Si*-face of the olefin, to give the enolate which would afford the (*S*)-epoxide by ring-closure (Figure 4).

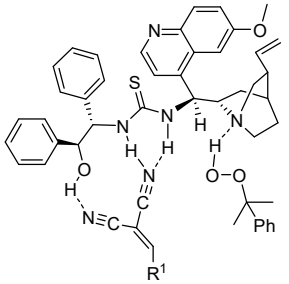
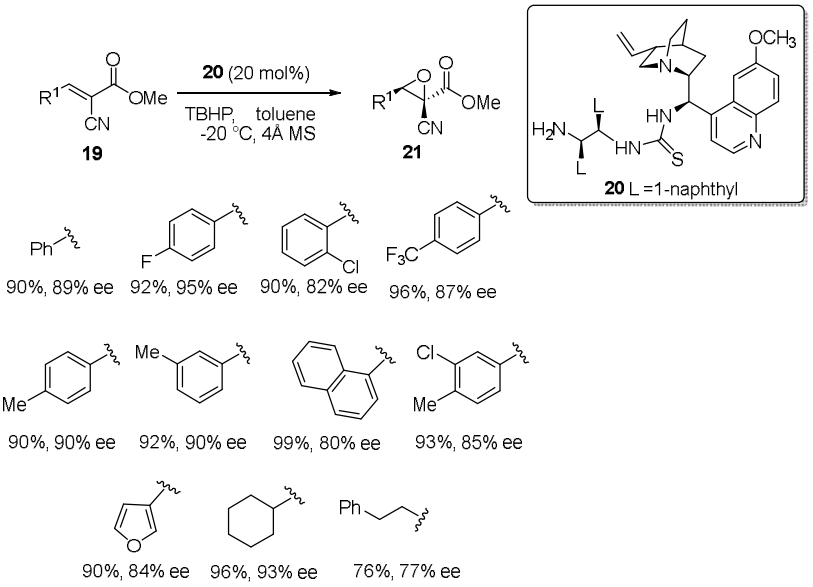


Figure 4. Postulated transition state of the asymmetric epoxidation of alkylidenemalononitriles.

These results prompted us to investigate this catalytic system for the asymmetric epoxidation of α-cyano-α,β-unsaturated esters **19**. As a general remark, only a few examples of asymmetric epoxidation of -α,β-unsaturated esters are present in the literature, which is not surprising since these alkenes are only moderately reactive either for electrophilic or nucleophilic oxidative systems. The corresponding glycidic esters are epoxides of significant synthetic interest as illustrated by their elaboration to prepare pharmaceuticals such as the blood pressure lowering agent Diltiazem,[32] phenylisoserine Taxol side-chain.[32] Among the multifunctional organocatalysts screened in the epoxidation, *epi*-quinidine/dinaphthyl ethylendiamine derived thiourea **20** was found the most active and enantioselective, when working at 20 mol% loading in toluene at -20°C (Scheme 8).[33] The reaction proceeded with good substrate scope to give the aryl and alkyl substituted glycidic esters **21** in excellent yield and high enantioselectivity.



Scheme 8. Asymmetric epoxidation of α-cyano-α,β-unsaturated esters with cinchona derived thiourea/TBHP system.

A tentative transition state model for the oxa-Michael addition step, which should be the rate- and stereoselectivity-determining step of the process has been proposed (Figure 5). A fast ring closure to the epoxide would be in line with the observed complete control of the diastereoselectivity. The NH_2 and thiourea groups are important in tuning the enantioselectivity likely via cooperative H-bonding engagement with the cyano and ester groups of alkene **19**.

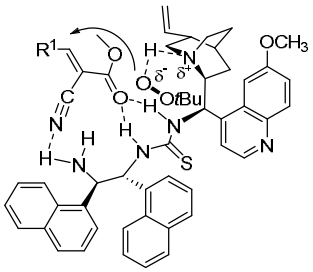
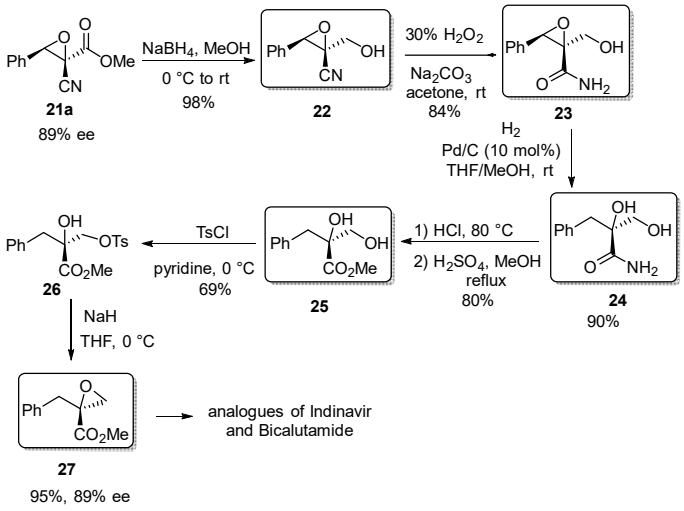


Figure 5. Postulated transition state of the asymmetric epoxidation of α-cyano-α,β-unsaturated esters.

Starting from a model epoxide, chemo- and regioselective transformation showed the synthetic value of this novel class of optically enriched epoxides to prepare, without racemization, products of great interest (Scheme 9). Reduction with $NaBH_4$ yielded selectively the cyano epoxy alcohol **22**. The previously reported stoichiometric Sharpless Ti/tartrate mediated asymmetric epoxidation of poorly reactive 2-cyanoallylic alcohols afforded compounds of type **22** in modest conversions.[34] Epoxide **22** was hydrolysed to the corresponding *cis*-α-amido epoxide **23** in 84% yield, which was regioselectively ring-opened, under hydrogenation conditions, to give the α,β-dihydroxy amide **24**, bearing a tetrasubstituted carbon, in 90% yield. This compound was readily transformed into methyl ester **25**. Products of type **24** and **25** can be accessed by Sharpless asymmetric dihydroxylation of the corresponding 2-substituted acrylates or acrylamides with variable level of asymmetric induction. Tosylation of diol **25** followed by base-promoted ring-closure afforded challenging terminal epoxy methyl ester **27** in 65% two-step overall yield and 89% ee, attesting that no racemization occurred over the entire sequence. (*S*)-Epoxide **27** is a particularly attractive and versatile compound, used as building block for the synthesis of a new class of HIV-1 protease inhibitors, analogues of Indinavir.[35]



Scheme 9. Synthetic elaborations of glycidic esters **21**.

Moreover, (*S*)-epoxide **27** can be employed as key-intermediate for the synthesis of Bicalutamide-like molecules, which displayed promising activity toward prostate cancer cell lines.[36]

4. Thiourea-amine catalysed kinetic resolution of racemic epoxides

Nucleophilic kinetic resolution of racemic epoxides is an important tool when chiral epoxides cannot be obtained through classical asymmetric methods.[37] In an ideal process of kinetic resolution, the two enantiomers have to significantly differ in reaction rates, as measured by the stereoselectivity factor ($S = k_{rel} = k_{fast}/k_{slow}$). To be of practical utility and achieve the 50% maximum theoretical yield and high enantiocontrol *S* needs to be at least equal to 50. The most notable examples of effective kinetic resolution of epoxides are exemplified by the Ti/tartrate-catalyzed Katsuki-Sharpless epoxidation of secondary allylic alcohols, which enabled to obtain both unreacted enantioenriched secondary allylic alcohols and epoxyalcohol products in nearly ideal yields and high enantioselectivities.[38] Terminal racemic epoxides are also kinetically resolved in an excellent way by using Co(III)- and Cr(III)-salen catalysts as one of the most effective method to obtain this class of optically active epoxides.[39]

The asymmetric epoxidation of nitroalkenes demonstrated to be a difficult goal to achieve according to the paucity of examples reported in the literature,[40] although these epoxides can be regioselectively ring-opened to prepare interesting derivatives.[41] To achieve this goal, we first checked simple bifunctional organocatalysts such as L-diaryl prolinols in the asymmetric epoxidation of *trans*-nitroalkenes with TBHP.[42] Unexpectedly, the formation of *tert*-butyl peroxy adducts was observed in good enantiocontrol (up to 84% ee). Hence, a different strategy was applied, we thought to proceed via kinetic resolution of racemic starting material by amines as the nucleophiles. Based on literature's work on regioselective ring-opening,[41] our working hypothesis conceived the formation of α-amino ketones and unreacted enantioenriched epoxides occurring in the presence of a thiourea-amine as the promoter. This class of promoters was thought to be suitable, in view of their ability to establish H-bonding interactions with nitro group, as firstly reported by Takemoto and coworkers. The amine group in the organocatalyst would interact via general base with the nucleophile to give the preferential regioselective ring-opening of one enantiomer of the α-nitroepoxide.

A first enantioselective synthesis of β-aryl-substituted α-nitroepoxides was developed via an aminolytic kinetic resolution with aniline promoted by cinchonidine-derived thiourea **29** (Scheme 10).[43] Although the stereoselectivity factors for this process were modest ($3 < S < 7$) and underestimated by the concomitant occurrence of the background ring-opening pathway, taking place in absence of catalyst **29**, the α-nitroepoxides were recovered in acceptable yield and good to high enantioselectivity. The α-amino ketones **31** were isolated in good yields, but poor enantioselectivity was expected according to the modest value of stereoselectivity factors.

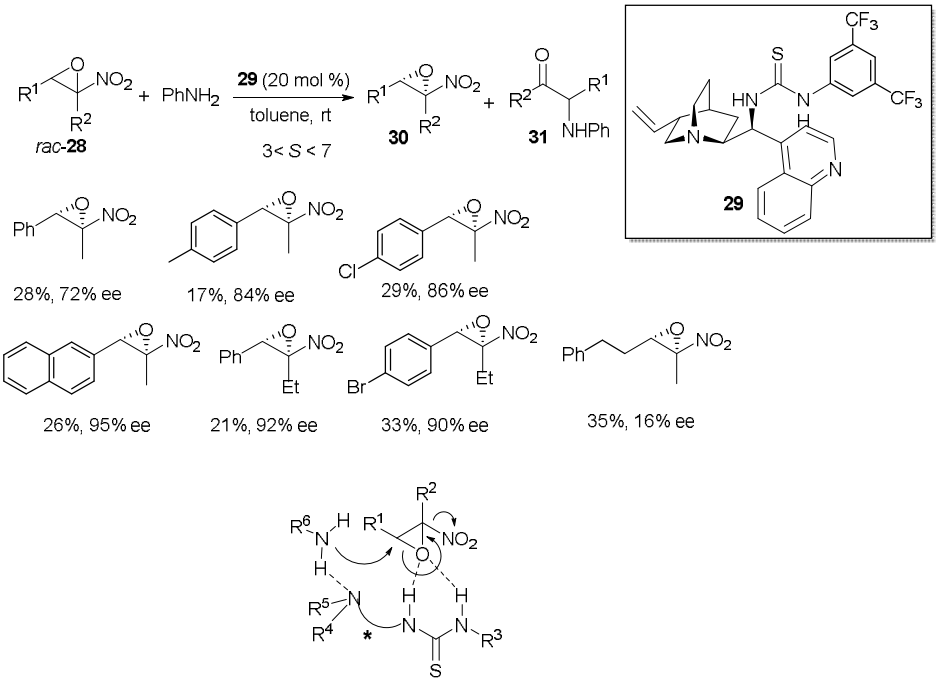
As an application of the synthetic utility of enantioenriche epoxides **30**, compound **28a** was converted into synthetically useful building block *anti*-1,2-amino alcohol **32**, via a one-pot diastereoselective ring-opening reaction with pyrrolidine, followed by reduction of the ketone intermediate. Thiols and 1,2-diamines are also useful nucleophiles in the ring-opening process to obtain pharmaceutically important targets, such as quinoxalines, prepared via an organocatalyzed kinetic resolution of α-nitroepoxides (Scheme 11).

Although the kinetic resolution at present is not suitable for applications due to modest efficiency, a facile access to chiral non racemic α-nitroepoxides has been devised as an alternative route to the asymmetric epoxidation.[44] Moreover, other nucleophiles and more effective bi- and multifunctional organocatalysts are likely employable to improve the outcome of this process.

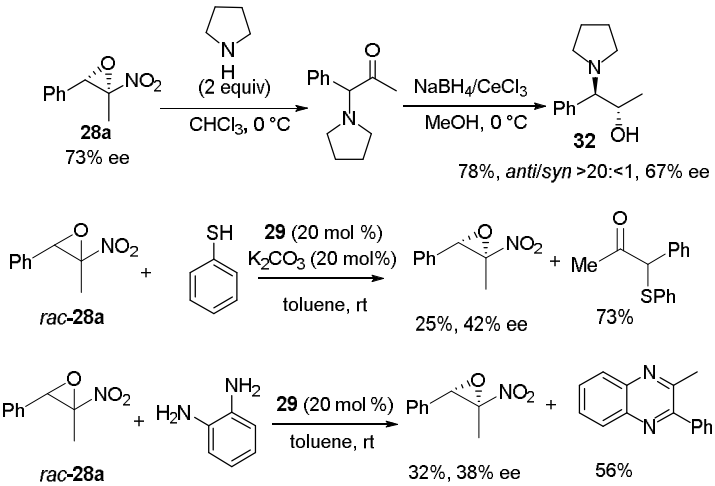
5. Conclusions

Thiourea-amines demonstrated to be highly useful bifunctional organocatalysts in domino processes to form heterocycles of different ring size and stereocenters. More recently, we have attested their ability to catalyse the asymmetric epoxidation of electron-poor alkenes, expanding the dimension of heterocycles accessible, by using this class of readily or commercially available organocatalysts. The kinetic resolution of racemic epoxides is an uncommon tool to obtain optically active epoxides and it is certainly an option which deserves further investigation. The synergic presence of an acid and a basic group and other H-bonding donors in these organocatalysts opens the opportunity to tune their activity and the enantioselectivity. Future

research in this area will show applications of thiourea-amines in asymmetric epoxidation to prepare more challenging epoxides, thus extending further their still underexplored catalytic power.



Scheme 10. Aminolytic kinetic resolution of α-nitroepoxides catalysed by cinchonidine derived thiourea.



Scheme 11. One-pot elaboration of enantioenriched α-nitroepoxide into *anti*-1,2-amino alcohol and other nucleophiles used in the kinetic resolution.

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