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Asymmetric organocatalytic journey into the world of three-membered rings

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ABSTRACT

in this review the development of new organocatalytic methodologies for the asymmetric synthesis of small heterocycles, namely epoxides, cyclopropanes and aziridines will be illustrated. This topic covers our research, carried out in the last eleven years, using bifunctional organocatalysts derived from the chiral pool. The authors will highlight the challenges as well as the evolution on the catalyst structure necessary to overcome the limits of reactivity and stereocontrol, encountered during the research. This "catalytic evolution" has been always observed in catalysis and it can be easily traced back to what has been happening in the fascinating and rapidly evolving area of asymmetric organocatalysis.

1. Introduction

The organocatalytic approach to asymmetric organic synthesis favourably copes with the requirements of green and sustainable processes necessary to produce molecules under mild reaction conditions, low environmental impact and costs [1].

The preparation of chiral compounds is a crucial area of catalysis strictly related to the markets of pharmaceutical, agrochemical and materials industries to cite the most relevant. Hence, asymmetric organocatalysis is now considered the third pillar of asymmetric synthesis, displaying its power in concert with the well-established chiral-metal based and enzymatic catalysis. The organocatalysts can provide different activation strategies of the reagents, to form carbon-carbon and carbon-heteroatom bonds in a single step, or more interestingly, in cascade reactions to give complex (hetero)cyclic compounds bearing tertiary and quaternary stereocenters. The most intensively explored strategies are: 1) covalent activation of carbonyl compounds by secondary and primary amines, the so-called aminocatalysis to form chiral iminium and enamine intermediates [2]; 2) noncovalent activation of a great variety of pronucleophiles and electrofiles, through general acid-base catalysis, provided by bifunctional or more recently multifunctional organocatalysts based on cinchona alkaloids, amine-thioureas or squaramides, peptides [3]. In the noncovalent activation strategy polar and mostly H-bonding interactions, involved among the catalyst and the reagents, regulate the stereocontrolled formation of the products. This approach is likely the most challenging between the two, as intermediate species are not involved and it becomes difficult to design novel catalysts with improved activity. However, given the structural variety of organic promoters derived from L-proline, cinchona alkaloids and 1,2-diamines, it has been possible to successfully develop a great number of stereoselective methodologies for several carbon-carbon and carbon-heteroatom bonds formation under operationally simple and mild conditions. In the last decade, we have been interested in the asymmetric synthesis of three-membered rings, which are highly versatile building blocks frequently involved in the synthesis of natural compounds [4]. Moreover, the epoxide, aziridine and cyclopropane units are incorporated into the molecular scaffold of numerous bioactive products and pharmaceuticals.

To achieve this goal we exploited the noncovalent organocatalytic strategy for the activation of reagents, which has become a prominent area of asymmetric synthesis. The major focus has been on the synthesis of functionalised epoxides, followed by approaches directed to obtain cyclopropanes and aziridines. The review is organized according to our research developments achieved over the years, grouped according to catalysis mediated by diaryl prolinols and followed by the most recent use of cinchona or chiral 1,2-diamine derived thioureas.

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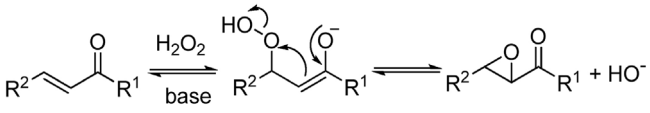
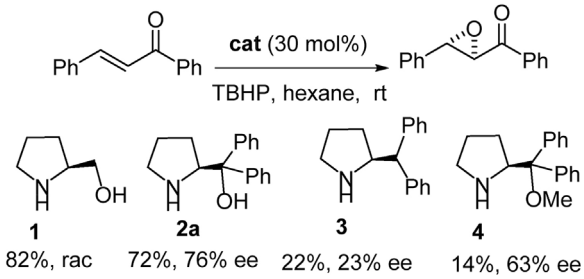
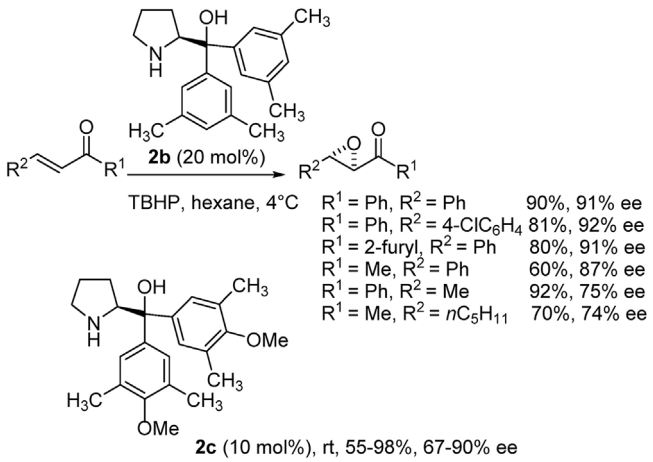


Scheme 1. The Weitz-Scheffer epoxidation.



Scheme 2. Asymmetric epoxidation of *trans*-chalcone with L-proline-based catalysts.



Scheme 3. Asymmetric epoxidation of *trans*-chalcone with L-diaryl prolinol/TBHP system.

2. Prolinols catalysed reactions

Asymmetric epoxidation of alkenes is at the forefront of research in organic synthesis [5]. Chiral oxiranes are found in several natural products and biologically active compounds, being important building blocks in total synthesis to access after stereocontrolled ring-opening reaction, highly versatile 1,2-funtionalised alcohols [6]. Our interest in this area dates back the end of 1990s, when we investigated the use of new achiral and enantiopure alkyl hydroperoxides in titanium/tartrate [7] and vanadium/hydroxamic acid [8] catalysed asymmetric epoxidation/kinetic resolution of allylic alcohols and base-catalysed asymmetric epoxidation of α,β-unsaturated ketones [9].

With the advent of organocatalysis, which can be framed into the more general field of sustainable chemistry, we considered highly stimulating the possibility to set up new methodologies by using small organic molecules as the catalysts. We targeted the asymmetric synthesis of small (hetero)cyclic compounds starting with epoxides. In particular, we became interested in the asymmetric epoxidation of electron-poor alkenes, given the great variety of functionalised epoxides accessible and useful for further synthetic elaborations [10]. Over the years, several groups devoted their attention to prevalently studying asymmetric epoxidation reactions of *trans*-α,β-unsaturated ketones. Hence, taking into account the great variety of disubstituted and trisubstituted electron-poor alkenes, potentially susceptible of epoxidation, we envisaged a lot of room for further improvement in this area.

The general approach for the synthesis of epoxides, starting from electron-poor alkenes, involves the formation of a nucleophilic oxidant, as firstly reported in 1921 by Weitz and Scheffer in the epoxidation of α,β-unsaturated carbonyl compounds (Scheme 1) [11].

According to this two-step mechanism, we thought a bifunctional organocatalyst, bearing Brønsted acid and base moieties, might catalyse the asymmetric epoxidation of α,β-unsaturated ketones by activation of the hydroperoxide pronucleophile via general base catalysis and the ketone via general acid catalysis in the first oxa-Michael addition step. To test this hypothesis, readily accessible L-proline derivatives were checked as bifunctional organocatalysts in the epoxidation of *trans*-chalcone with *tert*-butyl hydroperoxide (TBHP) in hexane at room temperature (Scheme 2) [12]. Pleasingly, the epoxidation worked, showing that activity and enantioselectivity were deeply influenced by the presence or absence of the hydroxy group. L-Diphenyl prolinol **2a** proved to be the most effective yielding the epoxide with 76% see [13]. The presence of acid additives or the use of 30% hydrogen peroxide and urea hydrogen peroxide as oxygen sources as well as the use of polar media, prevented the reaction to occur. The epoxidation of different α,β-unsaturated ketones catalysed by 30 mol% of compound **2a** with TBHP, under conditions reported in Scheme 2, afforded *trans*-epoxides in good yield and up to 80% ee, although after prolonged reactions times (up to 7 days).

In order to increase the efficiency of this simple system, diaryl prolinols substituted onto the aromatic rings were easily synthesized starting from L-proline and checked in the epoxidation. A significant improvement of the epoxidation was achieved when using 20 mol% of commercially available, more sterically demanding prolinol **2b** (Scheme 3).

The epoxides were recovered after shorter reaction times in higher yield and enantioselectivity (up to 92% ee) working at 4 °C [14]. Further enhancement of the catalytic acitivity could be achieved by using 10 mol% loading of substituted prolinol **2c**, working at room temperature (Scheme 3) [15]. Under these conditions, the conversion to the epoxides was good and the enantioselectivity maintained, as a further demonstration that the catalytic activity of diaryl prolinols could be tuned by modifying the steric and electronic features of the aromatic groups. In order to assess the impact of the organocatalyst structure on the stereocontrol, the optimized aromatic pattern of catalyst **2c** was maintained, whereas the size of the cyclic amine was modified (Scheme 4). The epoxidation performed on model *trans*-chalcone by four- and six-membered catalysts showed that ring size is fundamental to assure catalyst activity and level of enantioselectivity [16]. Indeed, prolinol **2c** proved to be the most effective. Moreover, although modest ee values were observed, simple primary β-amino alcohols, synthesized from commercially available α-amino acid esters, were also found to promote the epoxidation.

According to the experimental findings and aided by a computational study, we proposed a general acid/base activation of the reagents in the epoxidation mediated by diaryl prolinols [17]. In agreement with the Weitz-Scheffer mechanism, the first oxa-Michael addition of the peroxide was found to be the rate- and stereoselectivity determining-step, followed by a fast ring-closure step to the epoxide. The transition states **TS-I** and **TS-II**, computed for the oxa-Michael addition of *trans*-1-phenylbut-2-en-1-one with TBHP, catalysed by prolinol **2a** are illustrated in Scheme 5. The oxa-Michael addition would preferentially occur via the most energetically favored **TS-II**, showing a more staggered conformation for the C—O forming-bond as well as a more effective H-bonding

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