Asymmetric Oxidations of Electron-Poor Alkenes Promoted by the β-Amino Alcohol/TBHP System

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Abstract: The asymmetric oxyfunctionalization of alkenes is a fundamental process in synthetic organic chemistry. In this contribution, we review our findings on the enantioselective organocatalyzed oxidation of electron-poor alkenes. Readily or commercially available β-amino alcohols displayed catalytic activity in the asymmetric epoxidation of α,β-enones and β-peroxidation of nitroalkenes with tert-butyl hydroperoxide (TBHP) as the oxidant. The corresponding epoxides and peroxides were isolated in good to high yield and enantioselectivity.

Key words: α,β-enones, epoxides, peroxides, α,α-diaryl-L-prolinols, nitroalkenes

The development of novel oxidative systems able to catalyze the enantioselective epoxidation of alkenes is one of the most important research areas of synthetic organic chemistry. Metal-catalyzed asymmetric systems have played a prominent role in alkene epoxidation,1 but lately, organocatalyzed methodologies have rapidly progressed.2 Very recently, improvements and, most of all, important new achievements have been attained in the epoxidation and β-oxyfunctionalization of electron-poor alkenes by using readily accessible organic promoters.3 Indeed, the first examples of enantioselective epoxidation of challenging compounds such as enals4 and cyclic α,β-enones5 have been successfully realized as well as the asymmetric β-peroxidation6 and hydroperoxidation7 of α,β-unsaturated ketones using secondary and primary amines as the organocatalysts.

In this context, we recently found that commercially or readily accessible diarylprolinols 1 and primary β-amino alcohols 2 catalyze the epoxidation of α,β-enones in the presence of tert-butyl hydroperoxide (TBHP) as the oxygen source.8 Moreover, this simple catalytic system could be applied to realize an unprecedentedly reported asymmetric β-peroxidation of nitroalkenes8 (Scheme 1). Epoxides 4 and peroxides 6 could be obtained in good to high yield and enantioselectivity (70–92% ee).

Our findings on the enantioselective epoxidation of α,β-unsaturated ketones and the β-peroxidation of nitroalkenes catalyzed by β-amino alcohols and tert-butyl hydroperoxide as the oxygen source are reviewed.

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Enantioselective Epoxidation of α,β-Enones Catalyzed by the β-Amino Alcohol/TBHP System

The epoxidation of α,β-enones has been accomplished either by using asymmetric metal-catalyzed protocols or by employing organocatalyzed oxidative versions.9 Polyleucine/hydrogen peroxide10 and cinchona quaternary ammonium salts/sodium hypochlorite11 systems are illustrative of the most effective organocatalytic systems. These methodologies, originally discovered more than two decades ago, have been recently the subject of renewed interest.12 Stimulated by novel concepts on the activation of compounds offered by functional groups residing in small organic molecules,13 we targeted these to develop a simple oxidative system for the nucleophilic asymmetric epoxidation of α,β-enones. According to the mechanism of the Weitz–Scheffer15 epoxidation, a bifunctional system was thought to be able to promote the epoxidation. In particular, the presence of a chiral base and an additive with hydrogen-bonding donating groups would simultaneously activate the oxidant and the enone, respectively. After checking a variety of different combinations, we disclosed that the epoxidation of trans-α,β-enones 3a–f, catalyzed by commercially available α,α-diphenylprolinol (1a) with tert-butyl hydroperoxide, proceeded in an enantioselective way at room temperature in hexane to give epoxides 4a–f (Scheme 2).16a

The epoxides 4 were isolated in good yield and enantioselectivity. Polar, protic, halogenated, and ethereal media proved to be unsuitable solvents. The reaction did not proceed when using hydrogen peroxide as the oxidant. The
epoxidation carried out with modified compound 1a devoid of the hydroxy group furnished poor results in terms of activity and enantioselectivity, thus showing the crucial role played by this group in the catalysis.

The investigation on nonlinear effects\textsuperscript{16} in the epoxidation of trans-chalcone (3a) employing enantiomerically enriched 1a, showed a linear correlation, which suggested that one molecule of catalyst 1a is likely to have been involved in the enantiodiscriminating step.

A dual activation of the reagents provided by organocatalyst 1a has been proposed as illustrated in Scheme 3.

After deprotonation of the pronucleophile, the resultant ammonium ion would remain coordinated to the peroxy-anion, while the enone would be activated and properly orientated for the conjugate addition via hydrogen bonding with the hydroxy group. Then, ring closure to the epoxide occurs with the elimination of the tert-butoxy anion, which deprotonates the ammonium ion regenerating the catalyst.

Next our efforts were directed to improving the performance of the epoxidizing system. To this end, different aryl-substituted prolinols 1b–d, readily synthesized starting from L-proline,\textsuperscript{17} were checked under standard conditions in the epoxidation of trans-chalcone (3a) (Scheme 4).

The presence of electron-withdrawing groups was detrimental to the catalyst activity, while compounds with electron-donating groups 1c,d, catalyzed the reaction with significantly higher efficiency when compared to catalyst 1a.\textsuperscript{8b} Prolinol 1d was chosen as the most effective promoter to develop an improved methodology. The formation of the epoxides 4a–g in good to high yield and enantioselectivity was realized under reduced catalyst loading at 4 °C (Scheme 5).

It is interesting to note that this system can be successfully employed for the epoxidation of challenging compounds such as alkyl, aryl, and dialkyl ketones.

A deeper investigation, carried out to refine catalyst activity by modifications on the phenyl rings, showed that ortho-phenyl substituted prolinols were ineffective promoters.\textsuperscript{8c} Sterically encumbered tert-buty! groups at meta positions completely inhibited the catalyst activity. The phenyl-trisubstituted compound 1e proved to be more active than promoter 1d and it could be conveniently used at 10 mol% loading at room temperature (Scheme 6).
Having optimized the phenyl substitution pattern, we turned our attention to the influence of the amine ring size on the catalyst performance. Six- and four-membered-ring compounds 7 and 8 were synthesized and used in the epoxidation of model compound 3a (Scheme 7).

In both cases, their efficiency was lower than that observed for compound 1e. Indeed, the activity was markedly reduced, although the asymmetric induction was slightly affected.

In order to have a comprehensive idea of the effectiveness of β-amino alcohols as catalysts in the enantioselective epoxidation of α,β-enones, easily accessible primary, secondary, and tertiary β-amino alcohols 9a–e and 2a–c and were checked in the epoxidation of 3a (Scheme 8).

Primary β-amino alcohols were able to catalyze the epoxidation of 3a in modest yield and low enantioselectivity. Interestingly, as previously observed when using α,α-diarylprolinols 1, the activity and the enantioselectivity of primary β-amino alcohols 2a–c, readily accessible from α-amino acid esters, could be significantly tuned by modifying the substitution pattern of the phenyl rings. The primary amine 9d, devoid of the hydroxy group, showed itself to be a poor catalyst, thus confirming the importance of the hydroxy moiety in the catalysis. Acyclic secondary and tertiary β-amino alcohols 9c–e were unsuitable promoters.

The epoxidation carried out with catalysts 1d and 9d in the presence of different acids as co-catalysts did not proceed. These findings supported our mechanistic hypothesis based on the formation of an ion pair as the reactive species, rather than the generation of an iminium ion of the enone as an intermediate.
plane. Conformer C, having the intramolecular hydrogen bond with the N–H bond on the opposite side of the ring plane, proved to be 3.6 kJ/mol less stable than A.

In the case of the acyclic catalyst 2c, conformers B and D are almost comparable since they have an energy difference of 0.6 kJ/mol. The energy differences observed suggest that conformer A would be likely involved in the ion pair during the epoxidation, thus affording a univocal stereochemical control. On the other hand, conformers B and D would be reasonably active in the epoxidation, which would give rise to an average result in terms of enantioselectivity. The result achieved in the epoxidation of 3a promoted by catalyst 1f, having the protected hydroxy group, could be explained by taking into account the formation of the intramolecular hydrogen bond in the ammonium ion (Scheme 9).

![Figure 1 DFT-calculated ammonium conformers of catalysts 1e and 2c](image)

**Scheme 9** Enantioselective epoxidation of trans-chalcone (3a) catalyzed by the 1f/TBHP system

Although a dramatic reduction of the catalyst activity was observed, the ammonium ion involved in the ion pair would be conformationally blocked, thus leading to an almost comparable control of the enantioselectivity with respect to catalyst 1a.

**Enantioselective β-Peroxidation of trans-Nitroalkenes Catalyzed by β-Amino Alcohols/TBHP System**

Among conjugate additions, the oxa-Michael addition represents one of the most difficult processes to realize. The major problems associated with this transformation are the low nucleophilicity and strong basicity of the oxygen nucleophiles as well as the reversibility of the conjugate addition. Moreover, the polymerization of the alkene can be easily observed. Indeed, only a few examples of stereo-selective oxa-Michael addition have been successfully accomplished.

We thought it would be interesting to investigate the application of the diarylprolinols/tert-butyl hydroperoxide system in the epoxidation of nitroalkenes. Unexpectedly, the model reaction carried out on trans-nitrostyrene 5a with catalyst 1a and tert-butyl hydroperoxide afforded the enantioselectively enriched β-peroxide 6a (Scheme 10).

![Scheme 10](image)

**Scheme 10** Enantioselective β-peroxidation of trans-nitrostyrene 5a catalyzed by the 1a/TBHP system

Peroxide 6a has been previously isolated as an intermediate in the oxidation of nitrostyrenes to α-nitroacetophenones. Our reaction represents the first asymmetric route to this type of compounds. Enantioselectively enriched acyclic peroxides are very difficult to be obtained and only a few examples have been reported.

After screening of the reaction parameters and catalysts activity, compound 1d was found to be the most effective in methylcyclohexane as the solvent at –18 °C (Scheme 11).

![Scheme 11](image)

**Scheme 11** Enantioselective β-peroxidation of trans-nitroalkenes 5 catalyzed by the 1d/TBHP system

Peroxides 6 were recovered in moderate to good yield and fairly good asymmetric induction. Compounds 6 can be synthetically exploited to produce enantioenriched β-amino alcohols 10, which are widely used building blocks and ligands in asymmetric synthesis as well as pharmaceutical targets. Catalytic hydrogenation of products 6 allowed direct isolation of β-amino alcohols 10 in high yield and only slightly decreased enantioselectivity (Scheme 12).
These findings can be framed under the previously suggested mechanistic pathway illustrated for the epoxidation. Catalyst 1d serves as bifunctional promoter, via deprotonation of tert-butyl hydroperoxide to generate the contact ion pair. Then, the intermolecular hydrogen bonding between the catalyst hydroxy group and the oxygen of nitro group would orientate the nitroalkene favoring the peroxyanion attack to its Si face (Scheme 13).

In conclusion, easily accessible β-amino alcohols have been showed to be useful promoters in the catalytic asymmetric epoxidation of α,β-enones and the β-peroxidation of nitroalkenes, affording the products in good to high yield and enantioselectivity. A bifunctional activation of the reagents provided by β-amino alcohols has been proposed. It is interesting to point out that they operate via noncovalent catalysis in contrast to covalent catalysis, via enamine/iminium intermediates formation, generally displayed by L-proline derivatives.24 An analogy can be rather found with the mechanism of action provided by cinchona alkaloids in Michael addition reactions pioneered by Winberg over 20 years ago.25

All reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light, by exposure to iodine vapor, or by phosphomolybdic acid/ethanol spray test. Flash chromatography was performed on Merck silica gel 60 (particle size 0.040–0.063 mm). All commercially available reagents were purchased from Aldrich.

**Epoxidation of trans-α,β-Enones; General Procedure**

A sample vial was charged with trans-α,β-ene (0.15 mmol), the β-amino alcohol (0.045 mmol) and hexane (0.300 mL) at r.t. TBHP (5–6 M soln in decane; 37 μL, 0.21 mmol) was then added. After monitoring by TLC, the crude reaction mixture was directly purified by flash chromatography on silica gel (PE–Et₂O, 99:1) to provide the epoxy ketone 4. All epoxides are known compounds, their analytical data were identical to those reported in the literature.8 Enantiomeric excess was determined by chiral HPLC using Daicel Chiralcel OD and Daicel Chiralpak AD columns.8

**β-Peroxidation of trans-Nitroalkenes; General Procedure**

A sample vial was charged with trans-nitroalkene (0.15 mmol), catalyst 1d (9.3 mg, 0.03 mmol) and methylcyclohexane (or methylcyclohexane–toluene, 3:1) (1.0 mL). TBHP (5–6 M soln in decane; 40 μL, 0.23 mmol) was then added to the stirring solution at –18 °C. The reaction was monitored by TLC. Unsoluble polymeric by-products were formed during the reaction. The solvent was removed under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel, eluting with mixtures of PE and PE–Et₂O (98:2) to provide peroxide 6. Residual nitroalkene isolated with the peroxide 6 (which is in general slightly more mobile on TLC than the corresponding nitroalkene) was removed by precipitation in hexane at low temperature. Peroxides 6 are known compounds, their analytical data were identical to those reported in the literature.9 Enantiomeric excess was determined by chiral HPLC using Daicel Chiralcel OD-H and Daicel Chiralpak AS-H columns.9

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**References**


