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

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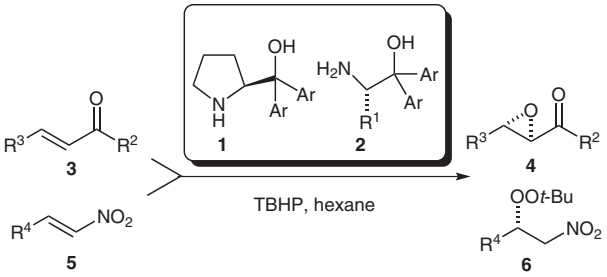
Abstract: The asymmetric oxyfunctionalization of alkenes is a fundamental process in synthetic organic chemistry. In this contribution, we review our findings on the enantioselective organocatalyzed oxidation of electron-poor alkenes. Readily or commercially available β-amino alcohols displayed catalytic 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 enals[4] and cyclic α,β-enones[5] have been successfully realized as well as the asymmetric β-peroxidation[6] and hydroperoxidation[7] 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 nitroalkenes[9] (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.



Scheme 1 Asymmetric epoxidation of α,β-enones **3** and β-peroxidation of nitroalkenes **5** catalyzed by the β-amino alcohol **1**, **2**/TBHP system (R^1 = alkyl)

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.[10] Polyleucine/hydrogen peroxide[11] and cinchona quaternary ammonium salts/sodium hypochlorite[12] 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.[13]

Stimulated by novel concepts on the activation of compounds offered by functional groups residing in small organic molecules,[14] 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–Scheffer[15] 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).[8a]

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

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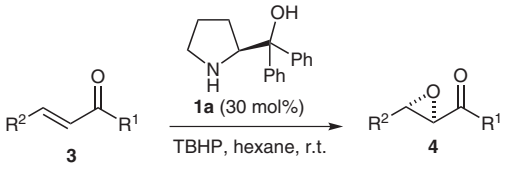


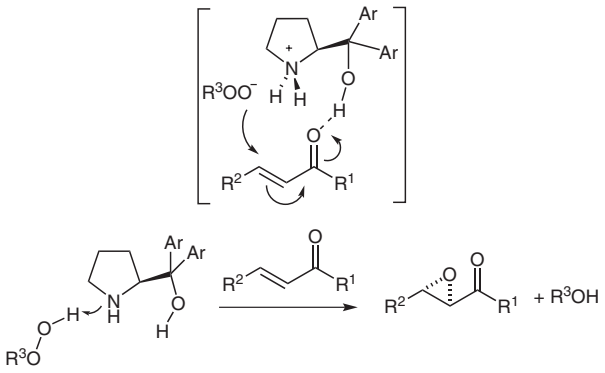
4a	R^1 = Ph, R^2 = Ph	72%, 75% ee
4b	R^1 = 3-MeC_6H_4, R^2 = Ph	70%, 78% ee
4c	R^1 = Ph, R^2 = 4-MeOC_6H_4	46%, 80% ee
4d	R^1 = Ph, R^2 = 4-ClC_6H_4	73%, 74% ee
4e	R^1 = Ph, R^2 = Me	87%, 63% ee
4f	R^1 = Me, R^2 = Ph	52%, 79% ee

Scheme 2 Enantioselective epoxidation of *trans*-α,β-enones **3a–f** catalyzed by the **1a**/TBHP system

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[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.

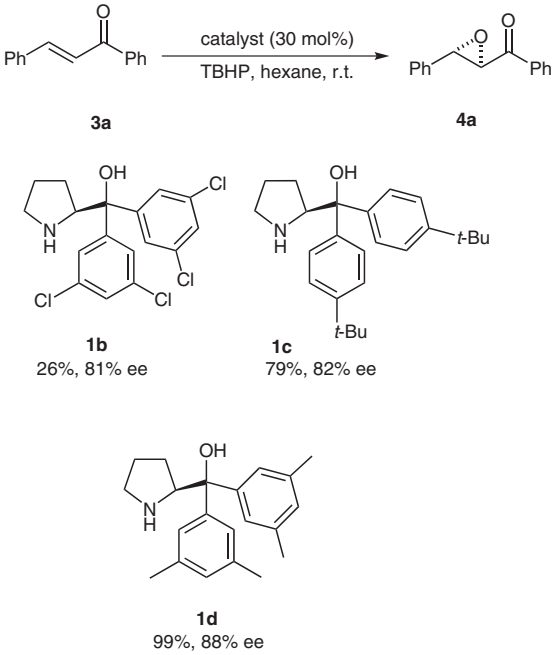


Scheme 3 Mode of dual activation of reacting partners in the nucleophilic epoxidation mediated by β-amino alcohol **1**

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,[17] were checked under standard conditions in the epoxidation of *trans*-chalcone (**3a**) (Scheme 4).

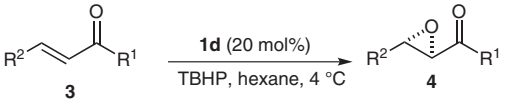
The presence of electron-withdrawing groups was detrimental to the catalyst activity, while compounds with



Scheme 4 Enantioselective epoxidation of *trans*-chalcone (**3a**) catalyzed by modified the prolinol **1b–d**/TBHP system

electron-donating groups **1c**,**d**, catalyzed the reaction with significantly higher efficiency when compared to catalyst **1a**.[8b]

Prolinol **1d** was chosen as the most effective promoter to develop an improved methodology. The formation of the epoxides **4a**,**c–g** in good to high yield and enantioselectivity was realized under reduced catalyst loading at 4 °C (Scheme 5).

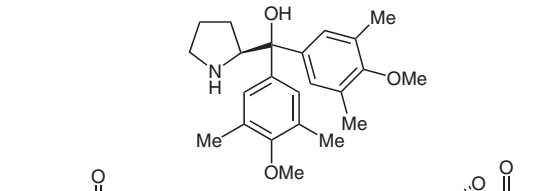


4a	R^1 = Ph, R^2 = Ph	90%, 91% ee
4c	R^1 = Ph, R^2 = 4-MeOC_6H_4	70%, 90% ee
4d	R^1 = Ph, R^2 = 4-ClC_6H_4	81%, 92% ee
4e	R^1 = Ph, R^2 = Me	92%, 75% ee
4f	R^1 = Me, R^2 = Ph	60%, 87% ee
4g	R^1 = Me, R^2 = $(CH_2)_4$Me	70%, 74% ee

Scheme 5 Enantioselective epoxidation of *trans*-α,β-enones **3a**,**c–g** catalyzed by the **1d**/TBHP system

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.

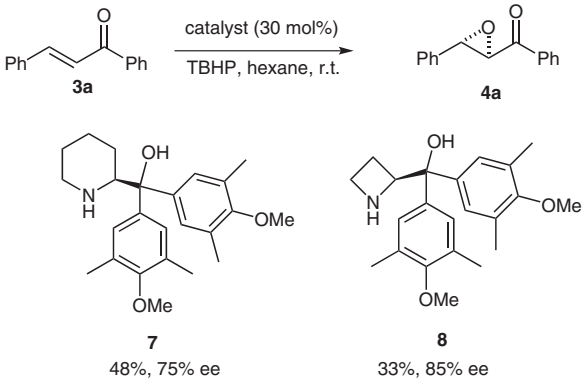
A deeper investigation, carried out to refine catalyst activity by modifications on the phenyl rings, showed that *ortho*-phenyl substituted prolinols were ineffective promoters.[8c] Sterically encumbered *tert*-butyl groups at *meta* positions completely inhibited the catalyst activity. The phenyl-trisubstituted 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).



4a	R^1 = Ph, R^2 = Ph	93%, 89% ee
4c	R^1 = Ph, R^2 = 4-MeOC_6H_4	61%, 87% ee
4d	R^1 = Ph, R^2 = 4-ClC_6H_4	88%, 87% ee
4f	R^1 = Me, R^2 = Ph	60%, 83% ee

Scheme 6 Enantioselective epoxidation of *trans*-α,β-enones **3a**,**c**,**d**,**f** catalyzed by the **1e**/TBHP system

Having optimized the phenyl substitution pattern, we turned our attention to the influence of the amine ring size on the catalyst performance.[8d] Six- and four-membered-ring compounds **7** and **8** were synthesized and used in the epoxidation of model compound **3a** (Scheme 7).



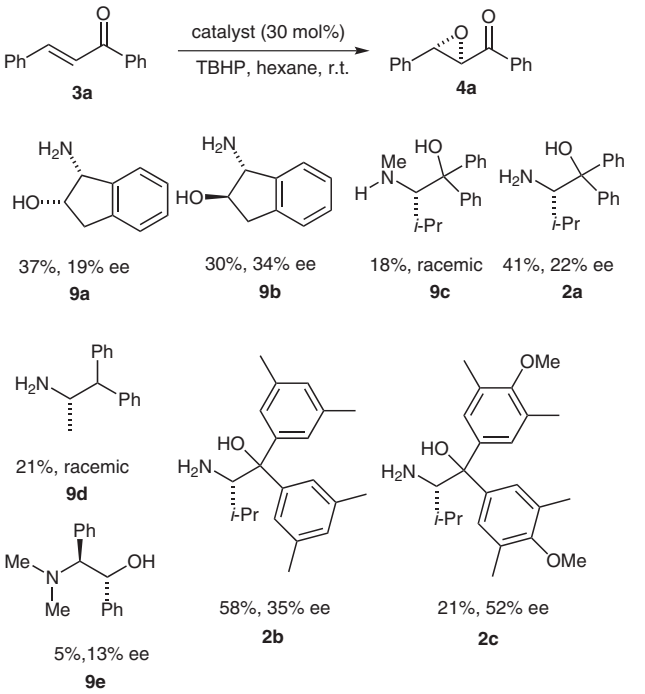
Scheme 7 Enantioselective epoxidation of *trans*-chalcone (**3a**) catalyzed by the modified secondary amino alcohol **7**, **8**/TBHP system

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.



Scheme 8 Enantioselective epoxidation of *trans*-chalcone (**3a**) catalyzed by the β-amino alcohols **9** and **2**/TBHP system

The different catalytic activity showed by primary, secondary, and tertiary β-amino alcohols in the epoxidation of α,β-enones can be explained by taking into account factors affecting the formation and the stability of the ion pair. In an apolar medium, hydrogen bonding interactions play a fundamental role in the stabilization of polar species. Stronger localized ammonium ions are generated starting from primary β-amino alcohols, which can more efficiently stabilize the *tert*-butyl peroxyanion. Ion pair destabilization increases when going from secondary to tertiary β-amino alcohols, whose sterically more crowded ammonium ions less effectively stabilize the anion, giving rise to a looser ion pair. Intramolecular hydrogen bonding interaction between the NH and the vicinal oxygen of the OH group are known to stabilize charged ammonium ions derived from β-amino alcohols and block their conformations.[18] The structures of the most stable ammonium ion conformers of promoters **1e** and **2c** were then calculated in the gas-phase by using B3LYP density functional theory (Figure 1).

Most stable conformer **A** of catalyst **1e** shows an intramolecular hydrogen bond between the oxygen of the OH group with the N–H bond from the same side of the ring

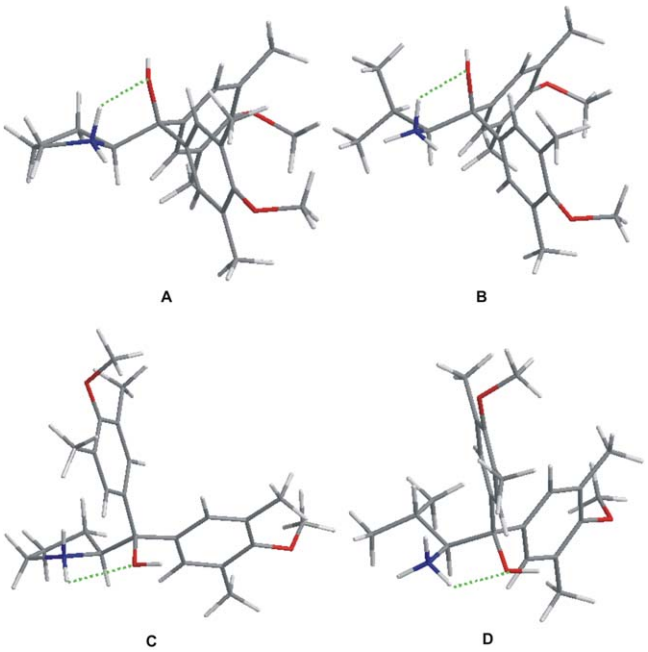
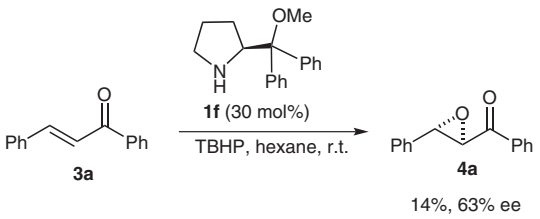


Figure 1 DFT-calculated ammonium conformers of catalysts **1e** and **2c**

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).



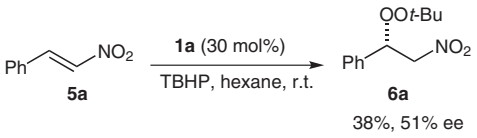
Scheme 9 Enantioselective epoxidation of *trans*-chalcone (**3a**) catalyzed by the **1f**/TBHP system

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,[19] the oxa-Michael addition represents one of the most difficult process 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 stereoselective oxa-Michael addition have been successfully accomplished.[20]

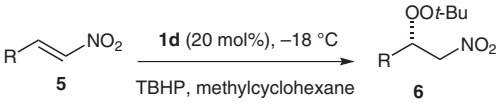
We thought it would be interesting to investigate the application of the diarylprolinols/*tert*-butyl hydroperoxide system in the epoxidation of nitroalkenes. Unexpectedly, the model reaction carried out on *trans*-nitrostyrene **5a** with catalyst **1a** and *tert*-butyl hydroperoxide afforded the enantiomerically enriched β-peroxide **6a** (Scheme 10).[9]



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.[21] Our reaction represents the first asymmetric route to this type of compounds. Enantiomerically enriched acyclic peroxides are very difficult to be obtained and only a few examples have been reported.[22]

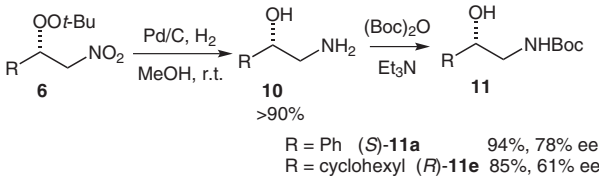
After screening of the reaction parameters and catalysts activity, compound **1d** was found to be the most effective in methylcyclohexane as the solvent at –18 °C (Scheme 11).



6a	R = Ph	72%, 84% ee
6b	R = 3,4-$(Me)_2C_6H_3$	70%, 83% ee
6c	R = 4-ClC_6H_4	80%, 84% ee
6d	R = 3-furyl	45%, 83% ee
6e	R = cyclohexyl	73%, 72% ee

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.[23] Catalytic hydrogenation of products **6** allowed direct isolation of β-amino alcohols **10** in high yield and only slightly decreased enantioselectivity (Scheme 12).



Scheme 12 Synthetic elaboration of peroxides **6**

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-enone (0.150 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–Et_2O, 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–Et_2O (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]

Acknowledgment

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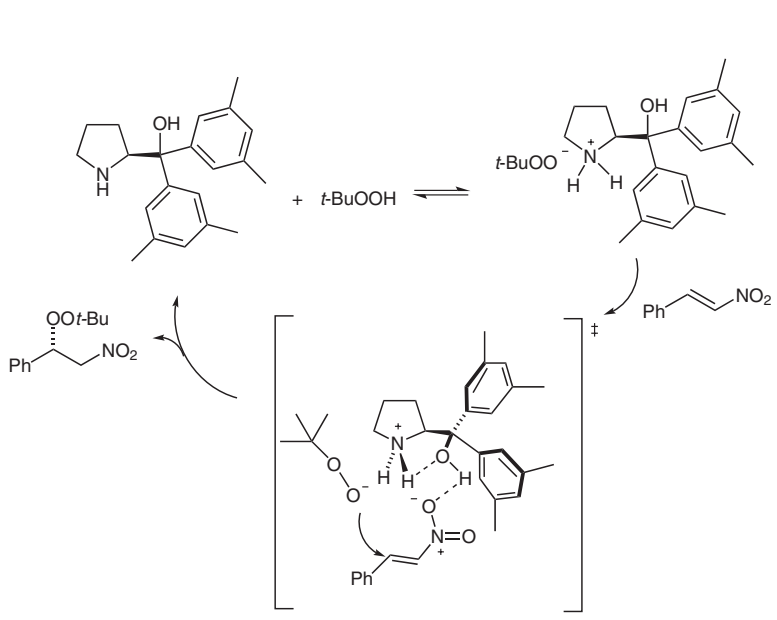

Scheme 13 Proposed catalytic cycle for the β-peroxidation

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