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Enantioselective Epoxidation of α,β-Enones Promoted by α,α-Diphenyl-L-prolinol as Bifunctional Organocatalyst

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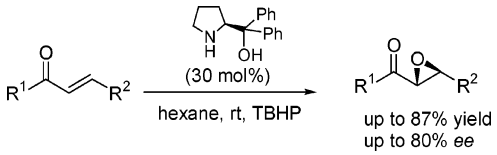
ABSTRACT



An operationally simple and mild protocol for the catalytic enantioselective epoxidation of α,β-unsaturated ketones has been estabilished using commercially available α,α-diphenyl-L-prolinol as bifunctional organocatalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant. The epoxides have been obtained in good yields and with up to 80% ee.

The development of efficient methods for the asymmetric epoxidation of α,β-enones is a major goal in organic synthesis since optically active epoxy ketones are among the most versatile building blocks for access to several natural products and pharmaceuticals.[1] A variety of valuable systems have been proposed for this reaction based on chirally modified metal alkyl peroxides[2] and optically pure alkyl hydroperoxides.[3] Hydrogen peroxide and various polyamino acids[1c,4] have also been used in this capacity, as have hydrogen peroxide and cinchona alkaloid combinations.[5] Asymmetric reactions promoted by small organic molecules is an emerging and still scarsely investigated area.[6] Being interested in the development of mild and convenient methodologies of epoxidation using renewable sources[7] or

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recyclable catalysts,[8] we were intrigued by the possibility that easily accessible amino alcohols could be exploited as bifunctional catalysts for the nucleophilic enantioselective epoxidation of α,β-enones. Herein, we report the first successful example of this transformation using commercially available α,α-diphenyl-L-prolinol and TBHP as the asymmetric oxidant.

L-Prolinol **1**[9] (Figure 1) was first examined for its ability

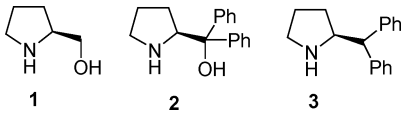
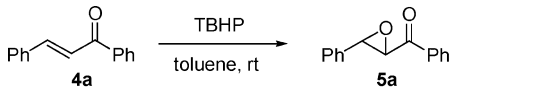


Figure 1. L-Proline-derived organocatalysts.

to promote the epoxidation of *trans*-chalcone **4a** with TBHP (1.2 equiv) in toluene at room temperature (Scheme 1).

Scheme 1. Epoxidation of *trans*-Chalcone **4a** by Catalysts **1** and **2**



Catalytic loadings of **1** (30 mol %) afforded racemic epoxide in modest yield. When α,α-diphenyl-L-prolinol **2** was used, diastereoisomerically pure *trans*-(2*R*,3*S*)-**5a** was isolated in 69% ee, although in low yield. Encouraged by this result, we screened various reaction conditions with a view to improving the efficiency of the epoxidation of model compound **4a** (Table 1).

The reaction was performed using 30 mol % of **2** in different solvents (entries 1−7). The epoxidation carried out in chloroform or dichloromethane (entries 1 and 2) was very sluggish, but satisfactory levels of enantioselectivity were observed. Tetrahydrofuran, polar and protic solvents afforded comparable results in terms of conversion, but the epoxide showed a poor ee (entries 3−5).

Since apolar and noncoordinating solvents furnished better results, the reaction was performed in hexane (entry 6). We were pleased to isolate, in reduced reaction time, (2*R*,3*S*)-**5a** in 53% yield and improved 76% ee. Cyclohexane proved to be equally efficient (entry 7). Hexane was then employed as the solvent of choice in further investigations of this reaction. More hindered cumene hydroperoxide (CHP) gave reduced conversion and enantioselectivity (entry 8). A

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(9) Amino alcohols have been previously reported to promote, in stoichiometric amounts, the epoxidation of electron-deficient alkenes to racemic epoxides: Masahiko, Y.; Noboru, K.; Satomi, T. Jpn. Patent JP 06092950 A2, 1994.

Table 1. Optimization of Reaction Conditions for the Epoxidation of **4a**[a]

entry	catalyst	solvent	oxidant	*t* (h)	yield (%) of **5a**[b]	ee (%) of **5a**[c] (config)[d]
1	**2**	$CHCl_3$	TBHP	96	5	65
2	**2**	CH_2Cl_2	TBHP	144	4	55
3	**2**	THF	TBHP	144	5	17
4	**2**	CH_3CN	TBHP	170	trace	nd[e]
5[f]	**2**	CH_3OH	TBHP	120	11	30
6	**2**	hexane	TBHP	48	53	76
7	**2**	*c*-C_6H_{12}	TBHP	48	46	76
8	**2**	hexane	CHP	94	51	55
9[g]	**2**	hexane	TBHP	62	71	70
10[f,h]	**2**	hexane	TBHP	102	80	78
11[i]	**2**	hexane	TBHP	44	27	67
12	**3**	hexane	TBHP	140	22	23

[a] Unless otherwise specified, the reaction was carried out at room temperature with 1.2 equiv of TBHP in the presence of 30 mol % of catalyst at $C = 0.2$ M of **4a**. [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis by using the chiral column Daicel Chiralcel OD. [d] Absolute configuration of **5a** was determined to be (2*R*,3*S*) by comparison of the HPLC retention times with those reported in the literature (see the Supporting Information). [e] Not determined. [f] 50 mol % catalyst was used in this reaction. [g] The reaction was performed at $C = 1$ M of **4a**. [h] The reaction was performed at 4 °C. [i] 30 mol % of tetrabutylammonium acetate was added.

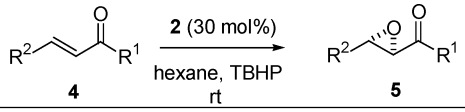
substantial improvement in the yield and a slightly reduced ee was observed under more concentrated reaction conditions (entry 9). Performing the epoxidation with 50 mol % of **2** at 4 °C had only a minimal effect on the level of selectivity, although a very good conversion was achieved (entry 10). When the reaction was carried out in the presence of the ionic additive tetrabutylammonium acetate (entry 11), the reaction rate was lowered (compare with entry 6) and the enantioselectivity moderately reduced. Notably, when the epoxidation was performed with catalyst **3** having no hydroxyl group, under conditions otherwise identical to those reported in entry 6, a dramatic loss was noted in both the catalytic activity and asymmetric induction (entry 12).

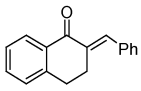
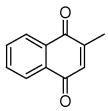
Having improved the reaction conditions to practically useful levels of stereocontrol, the optimized protocol, employing catalyst **2**, TBHP in hexane at room temperature, was applied to a variety of α,β-enones to study the general scope and limitations of the epoxidation method (Table 2).

In all of the examples (entries 1−10), diastereoisomerically pure *trans*-(2*R*,3*S*)-epoxides were obtained starting from *trans*-α,β-unsaturated ketones. Different types of electronic substitution on the phenyl ring of the carbonyl function furnished results comparable to those achieved in the epoxidation of **4a** (entries 2 and 3). More hindered β-naphthyl derivative was slowly converted to the epoxide in 64% ee (entry 4). Enones having para electron-donating or electron-withdrawing substituents on the β-phenyl group led to satisfactory results (entries 5 and 6), except for the *p*-NO_2-substituted chalcone, which did not react (entry 7).

Interestingly, the protocol can be successfully extended to substrates having an alkyl substituent either on the double bond or on the carbonyl carbon and to aliphatic α,β-unsaturated ketones (entries 8−10).

Table 2. Catalytic Enantioselective Epoxidation of α,β-Enones Promoted by **2** and TBHP[a]



entry	R^1	R^2	t(h)	yield%[b]	ee% (config.)[c,d]
1	Ph	Ph	94	72	75 (2*R*,3*S*)
2	*p*-Br-C_6H_4	Ph	98	72	74 (2*R*,3*S*)
3	*m*-Me-C_6H_4	Ph	135	70	78 (2*R*,3*S*)
4	β-Naphthyl	Ph	133	27	64 (2*R*,3*S*)
5[e]	Ph	*p*-MeO-C_6H_4	190	46	80 (2*R*,3*S*)
6	Ph	*p*-Cl-C_6H_4	105	73	74 (2*R*,3*S*)
7	Ph	*p*-NO_2-C_6H_4	120	trace	nd[f]
8[g]	Me	Ph	186	52	79 (3*R*,4*S*)
9	Ph	Me	114	87	63 (2*R*,3*S*)
10[g]	Me	$PhCH_2CH_2$	185	75	66 (3*R*,4*S*)
11			235	trace	nd[f]
12[g]			182	76	14 (2*S*,3*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of TBHP in the presence of 30 mol % of **2** at $C = 0.2$ M of **4**. [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis using chiral columns Daicel Chiralcel OD and Chiralpak AD. [d] Absolute configurations of **5** were determined by comparison of the HPLC retention times or optical rotations with those reported in the literature (see the Supporting Information). [e] The reaction was carried out at $C = 0.6$ M of **4**. [f] Not determined. [g] 50 mol % catalyst was used in this reaction.

The conformationally fixed *s-cis*-β-benzilidene-α-tetralone (entry 11) proved to be completely unreactive, while the rigid *s-trans* vitamin K_3 was fairly converted to the (2*S*,3*R*)-epoxide although in low ee (entry 12).[10] These data indicate that stereoelectronic requirements and conformational prerequisites of enones are important features for the reactivity and the enantiocontrol.

To gain insight into the mechanism of the epoxidation, we next investigated nonlinear effects[11] using α,α-diphenyl-L-prolinol **2** of different degrees of optical purity (Figure 2).

Within experimental error, a linear effect in the epoxidation of **4a** was observed under the conditions reported in Table 1, entry 6. This correlation strongly indicates that a single molecule of the catalyst is involved in the enantiodifferentiating step.

(10) The *s-trans* conformation of the enone moiety might be preferentially adopted in the epoxidation reaction, although a noncoplanar enone geometry cannot be excluded.

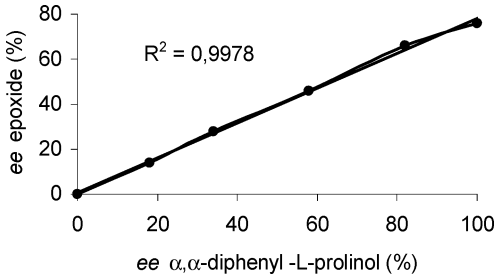
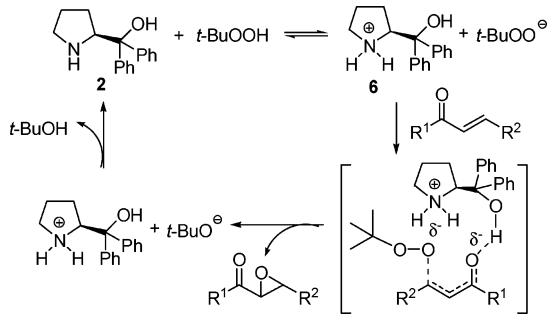


Figure 2. Linear effect in the α,α-diphenyl-L-prolinol-mediated epoxidation of chalcone **4a**. R = correlation coefficient.

On the basis of the experimental data, we suggest that α,α-diphenyl-L-prolinol serves as bifunctional catalyst giving rise to the simultaneous activation of the enone and the alkyl hydroperoxide by the hydroxy and amino groups, respectively (Scheme 2).[12]

Scheme 2. Proposed Catalytic Cycle



Catalyst **2** activates the nucleophile by deprotonation of TBHP,[13] thus generating *tert*-butyl hydroperoxide anion and the corresponding ammonium cation **6**, which in hexane constitute a tight ion pair.

The hydroxyl group of the diarylmethanol moiety of **2** appears to activate the enone by hydrogen bonding to the carbonyl group.[14,15] The polar-electrostatic interactions of the three partners provide a valuable organizational template that

(11) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 4000. (b) Kagan, H. B. *Adv. Synth. Catal.* **2001**, *343*, 227. (c) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402.

(12) Activation of the enone via iminium ion formation is less reasonably expected to occur under these reaction conditions, given the unreactive nature of enone carbonyls and the absence of an acid catalyst.

(13) (a) pK_a of pyrrolidine= 11.3: Ohwada, T.; Hirao, H.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 7486. (b) pK_a of TBHP= 12.4: Richardson, W. H.; Hodge, V. F. *J. Org. Chem.* **1970**, *35*, 4012.

(14) Wynberg first reported a transition-state complex comprising all three species (thiol, enone, and the catalyst) in the asymmetric Michael addition of thiols to cyclic enones mediated by quinine as bifunctional catalyst: Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

(15) For studies on hydrogen bonds acting in a Lewis acid fashion, see: (a) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (b) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. (c) Scheiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (d) Bordwell, F. G.; Ji, G. *J. Am. Chem. Soc.* **1991**, *113*, 8398. (e) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072.

correctly positions the enone for conjugate addition of the *tert*-butyl hydroperoxide anion. The hydrogen-bond-stabilized enolate then attacks the O−O bond intramolecularly giving rise to epoxide ring closure and elimination of the *tert*-butoxy anion, according to the accepted mechanism for the nucleophilic epoxidation.[16] Finally, the *tert*-butoxy anion regenerates catalyst **2**.[17]

It is noteworthy that good facial control was observed in the epoxide formation, taking into account that no covalent bonds are involved in the activation of both reagents by such a small organocatalyst. This proposition is confirmed by the dramatic solvent effects displayed in the epoxidation (Table 1). In fact, polar, protic and coordinating solvents, which solvate the ion pair, disrupt its rigidity, giving rise to a conformationally flexible system of much less efficiency and selectivity.

The competitive formation by exchange of the unreactive ion pair made of ammonium cation **6**/acetate anion and the low-reacting ion pair made of sterically hindered quaternary tetrabutylammonium cation/*tert*-butyl hydroperoxy anion[18] explains the suppressed reactivity and the slightly decreased enantioselectivity observed when using the additive tetrabutylammonium acetate (Table 1, entry 11). Hydrogen bonding has been shown to be fundamental for the catalytic efficiency and the enantiocontrol, as clearly demonstrated when employing α,α-diphenyl-L-proline **3**, which proved to be a very poor catalyst (Table 1, entry 12).

In conclusion, we have disclosed a new methodology for the catalytic asymmetric epoxidation of a broad variety of α,*β*-enones mediated by the bifunctional organocatalyst α,α-L-diphenyl prolinol. The reaction is operationally simple and does not require inert atmospheres or temperature manipulation, and the epoxides are readily isolated by flash chromatography without further workup to obtain good enantioselectivity. Moreover, depending on the choice of both commercially available, α,α-L- or α,α-D-diphenylprolinol, either enantiomer of the epoxide can be prepared. Research efforts are now directed at improving the reaction by employing stereoelectronically modified α,α-L-diarylprolinols, which should help to better define the elements crucial for the reactivity and asymmetric induction.

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Supporting Information Available: Experimental procedures, ee determination of chiral epoxy ketones by HPLC, and ^{1}H NMR and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Bunton, C. A.; Minkoff, G. J. *J. Chem. Soc., Chem. Commun.* **1979**, 665. (b) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428. (c) Wynberg, H.; Pluim, H. *J. Org. Chem.* **1980**, *45*, 2498.

(17) Background oxidation of catalyst **2** was checked in absence of the enone [**2** (30 mol %)/TBHP (1.2 equiv) in hexane at room temperature for 115 h]. ^{1}H NMR analysis of the crude reaction mixture showed no significant degradation of **2** under the reaction conditions.

(18) The epoxidation of **4a** with the tertiary *N*-benzyl L-prolinol under the usual conditions (rt, hexane, TBHP, 90 h) furnished traces of the epoxide.