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Bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol: an Improved Organocatalyst for the Asymmetric Epoxidation of α,β-Enones

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Abstract: The asymmetric epoxidation of α,β-enones by the readily available bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol and *tert*-butyl hydroperoxide (TBHP) is described. Stereoelectronic substitution on the aryl moiety of diaryl-2-pyrrolidinemethanols was found to significantly affect the efficiency with respect to the previously reported (*S*)-diphenyl-2-pyrrolidinemethanol. Improved reactivity and enantioselectivity were achieved with bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol at reduced catalyst loading (20 mol %) with ees up to 94% for chalcone epoxides under mild reaction conditions, whereas (*S*)-diphenyl-2-pyrrolidinemethanol afforded a maximum ee of 80%. Interestingly, the methodology is applicable to the epoxidation of more challenging aliphatic or enolizable enones with good control of the asymmetric induction (up to 87% ee).

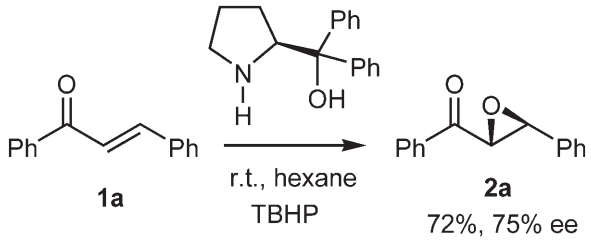
Keywords: amino alcohols; asymmetric epoxidation; α,β-enones; epoxides; organic catalysis

Introduction

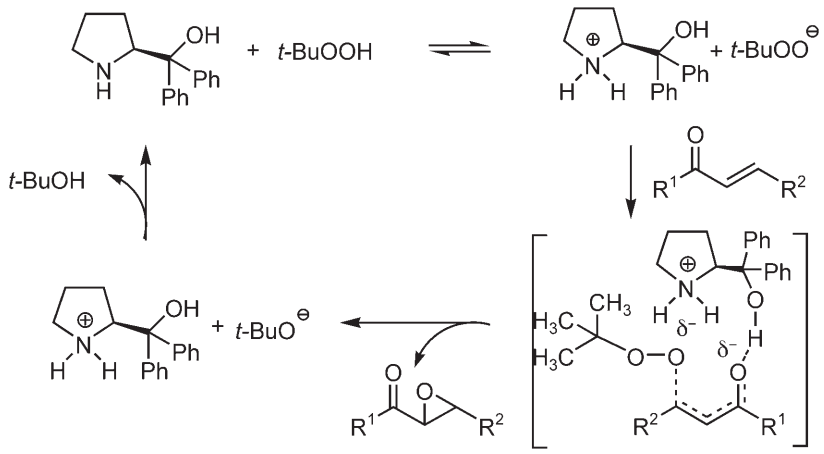
Asymmetric catalysis by small organic molecules, the so-called organocatalysis,[1] is a rapidly growing area, which has led to the development of efficient metal-free methodologies mainly for C–C bond-forming reactions. L-Proline and its derivatives are among the most studied organocatalysts reported up to now, which have shown wide applicability and generally good to high control of the asymmetric induction. With regards to oxidative transformations, few examples have been reported for proline-based organocatalysts. Electrophilic epoxidation of unfunctionalized alkenes, mediated by pyrrolidines and oxone or dioxirane, afforded the epoxides with up to 66% ee.[2] L-Proline and its analogues catalyzed the α-oxidation of aldehydes and ketones with up to >99% ee.[3] Very recently, the nucleophilic epoxidation of α,β-unsaturated aldehydes has been realized by using an *O*-protected diaryl-2-pyrrolidinemethanol and hydrogen peroxide as oxidant.[4] The valuable and difficult to obtain α,β-epoxy aldehydes have been isolated in high yields and excellent enantioselectivity (up to 98% ee).

In the past years, we have spent our efforts on developing epoxidation reactions based on renewable sources[5] or recyclable catalysts.[6] Enantiopure epoxides are important intermediates for drug design and natural products synthesis, hence new asymmetric versions for their production represent a fundamental target to be achieved by organic chemists.[7] In conjunction with our research interests, we have recently found that commercially available (*S*)-diphenyl-2-pyrrolidinemethanol and *tert*-butyl hydroperoxide (TBHP) promote the enantioselective epoxidation of α,β-enones (Scheme 1).[8]

The epoxides have been obtained in good yields and enantioselectivity (up to 80% ee) employing 30 mol % catalyst loading at room temperature in hexane. We have suggested a catalytic cycle for the nucleophilic epoxidation, where the amino alcohol plays the role of a bifunctional catalyst (Scheme 2). First, it activates *via* deprotonation the alkyl hydroperoxide by the Brønsted-basic secondary amine, thus generating a tight ion pair. Then, the hydroxy group of the catalyst activates and orientates the enone toward the attack of the alkyl peroxide anion to the β-carbon of the enone through hydrogen bonding with the carbonyl oxygen atom.



Scheme 1.



Scheme 2. Proposed catalytic cycle for the epoxidation.

The nature of diphenyl-2-pyrrolidinemethanol allows electronic and steric tuning of the catalyst by varying the substitution pattern on the aryl residue and this can help to shed more light on the factors affecting the catalytic activity and the enantioselectivity of this new oxidative system. Herein we report our investigation on the performance of different diaryl-2-pyrrolidinemethanols, which led to the development of a more effective system for the asymmetric epoxidation[9] of a broad variety of α,β-enones under mild and simple reaction conditions.

Results and Discussion

Variously substituted diaryl-2-pyrrolidinemethanols (Figure 1) were readily synthesized starting from L-proline following previously established procedures.[10]

In order to properly compare the efficiency of promoters **3b**–**g**, chalcone **1a** was treated under the reaction conditions previously optimized for **3a**,[8] employing 30 mol % of catalyst loading, 1.2 equivs. of TBHP in hexane at room temperature (Table 1).

The *p*-methoxyphenyl derivative **3b** (entry 2) afforded the (α*R*,β*S*)-epoxide **2a**, after a substantially reduced reaction time, in higher yield and similar ee, when compared to **3a** (entry 1). A better yield, but enhanced 82% ee, was observed when using more sterically encumbered *p*-*tert*-butylphenyl catalyst **3c** (entry 3). The *p*-phenyl residue on the benzene ring in **3d** reduced the reactivity with only a slight improvement in the enantioselectivity (entry 4). The sterically demanding β-naphthyl catalyst **3e** was slightly less reactive than **3a**, but the ee was not much affected (entry 5). With the 3,5-dichlorophenyl-modified compound **3f** the epoxidation rate was dramatically reduced, although the epoxide was recovered with improved 81% ee (entry 6). In contrast, the 3,5-dimethylphenyl catalyst **3g** afforded the epoxide in quantitative yield and 88% ee after the shortest reaction time (entry 7). It turned out that electronic properties of the substituents on the benzene ring noticeably influenced the catalytic activity of the diaryl-2-pyrrolidinemethanols, and electron-donating groups enhanced the conversion to the epoxide, while electron-withdrawing substituents were detrimental.

The effects on the asymmetric induction of the nature of the groups are less easily accountable; in fact, it appears that electronic character, steric size and the position of the groups in the benzene ring can be important in affecting the enantioselectivity. On the basis of the

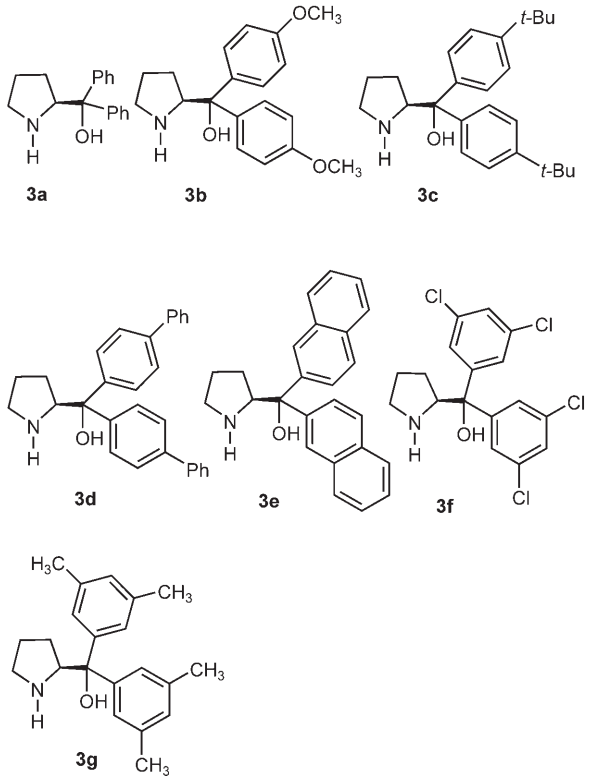
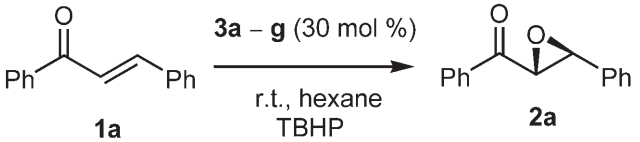


Figure 1.

Table 1. Asymmetric epoxidation of **1a** promoted by **3a**–**g**.



Entry	3	Time [h]	Yield [%][a]	ee [%][b]
1[c]	**3a**	94	72	75
2	**3b**	65	85	76
3	**3c**	90	79	82
4	**3d**	90	48	78
5	**3e**	87	60	77
6	**3f**	70	26	81
7	**3g**	60	99	88

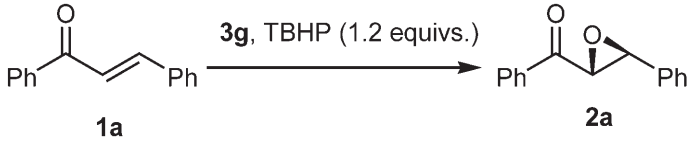
[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC on chiral column Daicel Chiralcel OD. The absolute configuration ($\alpha R,\beta S$) was determined by comparison of the HPLC retention times with those in the literature.
[c] Yield and ee reported in ref.[8]

mechanistic hypothesis proposed for the reaction, namely the ionic pair made up of the *tert*-butyl hydroperoxide anion and the ammonium cation being the active species for the epoxidation, increased conversion is expected when using more basic pyrrolidinemethanol compounds. Indeed, catalysts with electron-donating substituents on the benzene ring (entries 2, 3 and 7) were more efficient than unsubstituted **3a** and far more active than electron-withdrawing substituted **3f**, favouring amine protonation by means of inductive or electronic effects.[2c,11] Another key factor, which can influence the catalytic activity, is the enhanced solubility of alkyl-substituted compounds **3b**, **c**, **g** in the reaction solvent. In fact, while reaction mixtures appeared homogeneous when using catalysts **3b**, **c**, **g**, heterogeneous reaction mixtures were observed employing catalysts **3d**, **e**, **f**. It is interesting to note that bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol (**3g**) has been recently reported as a very efficient ligand for the highly enantioselective cyanosilylation of aldehydes[12] and Diels–Alder reaction.[13]

Next, we optimized the parameters for the epoxidation of **1a** using the best candidate **3g** (Table 2). As previously observed in the epoxidation promoted by **3a**,[8] apolar solvents provided high enantioselectivity (entries 1 and 2), although the conversion was modest.[14] Hexane was proved to be the best solvent (Table 1, entry 7) and it has to be pointed out that the enantioselectivity was maintained at the same level when using 10 mol % of the catalyst (Table 2, entry 3).

Under these conditions, a set of experiments was performed in the presence of hydrogen bonding donors as additives.[15] The epoxidation was carried out adding 10 mol % of commercially available (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol [(−)-TADDOL] as a competitive activator of the enone carbonyl group (entry 4). TADDOLs were recently employed as hydrogen bonding donors capable of activating the dienophile carbonyl group in the enantioselective hetero-Diels–Alder reaction.[16] The epoxide was

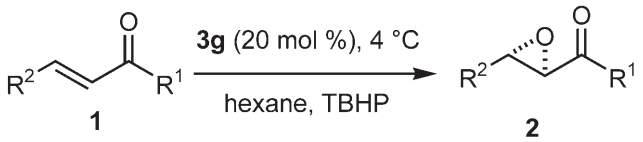
Table 2. Bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol (**3g**)-catalyzed epoxidation of **1a** under various conditions.

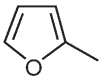
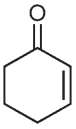
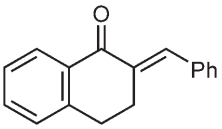


Entry	Solvent	Catalyst loading [mol %]	*T* [°C]	Time [h]	Yield [%][a]	ee [%][b]
1	toluene	30	r.t.	72	40	86
2	$CHCl_3$	30	r.t.	264	39	78
3	hexane	10	r.t.	95	61	88
4[c]	hexane	10	r.t.	96	65	85
5[d]	hexane	10	r.t.	98	66	85
6[e]	hexane	10	r.t.	96	–	–
7	hexane	20	−6	130	46	94
8[f]	hexane	20	4	99	80	91

[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC on chiral column Daicel Chiralcel OD. The absolute configuration ($\alpha R,\beta S$) was determined by comparison of the HPLC retention times with those reported in the literature.
[c] The reaction was carried out in the presence of 10 mol % of (−)-TADDOL.
[d] The reaction was carried out in the presence of 10 mol % of phenol.
[e] The reaction was carried out in the presence of 10 mol % of benzoic acid.
[f] The reaction was carried out at C = 0.7 M of **1a** instead of C = 0.2 M.

Table 3. Bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol (**3g**)-catalyzed asymmetric epoxidation of α,β-enones.



Entry	Substrate **1**			Time [h]	Yield [%][a]	ee [%][b]	Catalyst **3a**	
	R^1	R^2					Yield [%][f]	ee [%][f]
1	Ph	Ph	**1a**	112	90	91	72	75
2	*p*-BrC_6H_4	Ph	**1b**	217	81	92	72	74
3	*m*-MeC_6H_4	Ph	**1c**	139	98	89	70	78
4[c]	Ph	*p*-$MeOC_6H_4$	**1d**	126	70	90 (99)	46	80
5	Ph	*p*-MeC_6H_4	**1e**	178	75	90	–	–
6	Ph	*p*-ClC_6H_4	**1f**	165	81	92	73	74
7[d]	Ph	*p*-$NO_2C_6H_4$	**1g**	178	90	82 (89)	<5	–
8		Ph	**1h**	177	80	91	–	–
9[e]	Me	Ph	**1j**	220	60	87	52	79
10	Ph	Me	**1k**	147	92	75	87	63
11	Ph	$PhCH_2CH_2$	**1i**	160	87	79	–	–
12	Ph	*i*-Pr	**1l**	292	83	34	–	–
13	Me	$CH_3(CH_2)_4$	**1m**	264	70	74	–	–
14[d]			**1n**	284	38	6[g]	–	–
15[d]			**1o**	243	16	75	<5	–

[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC on Daicel Chiralcel OD and Chiralpak AD chiral columns. The absolute configuration (α*R*,β*S*) was determined by comparison of the HPLC retention times or optical rotation with those in the literature. The value in parentheses refers to ee after one recrystallization.
[c] The reaction was carried out at room temperature using 30 mol % of **3g**.
[d] The reaction was carried out at room temperature.
[e] 30 mol % of **3g** was used in this reaction.
[f] Yields and ees reported in ref.[8]
[g] The ee was determined by optical rotation measurement. The absolute configuration was (α*R*,β*R*).

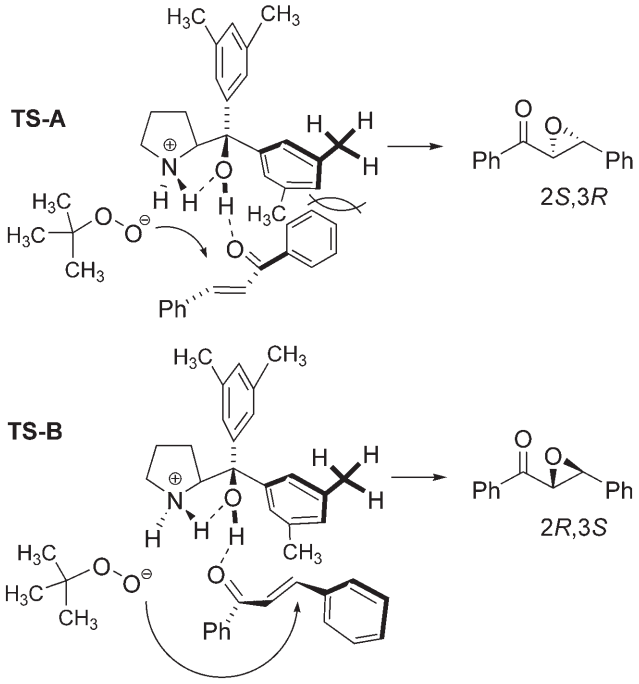
isolated in comparable yield and slightly decreased enantioselectivity with respect to the reaction performed in the absence of additive (entry 3). Then, as a blank experiment, the epoxidation was performed by using 10 mol % of pyrrolidine and 10 mol % of (−)-TADDOL, in order to verify if any asymmetric induction could be provided when the basic and the hydrogen bonding donor functionalities were present in separate compounds. After 93 h the racemic epoxide was recovered in 45% yield. The epoxidation was not much affected when adding 10 mol % of phenol as the additive (entry 5). As expected, when adding 10 mol % of the more acidic benzoic acid, the epoxidation did not proceed (entry 6). When employing 20 mol % of catalyst loading at −6 °C, the epoxide was isolated in 94% ee, but the catalyst activity was markedly depressed (entry 7). Finally, a right compromise to obtain high asymmetric induction and conversion in an acceptable reaction time was achieved performing the reaction under more concentrated conditions at 4 °C (entry 8).

The reaction conditions that proved optimal for **1a** were found to be general for a variety of α,β-enones (20 mol % of **3g**, 1.2 equivs. of TBHP at 4 °C in hexane) and the results are summarized in Table 3. Chalcones having either electron-donating or electron-withdrawing substituents on the phenyl rings and heteroaromatic groups were converted into the epoxides in high yield and ee (entries 1–8). The less reactive compound **1d**

was treated at room temperature with 30 mol % of the catalyst and the epoxide was thus isolated in good yield and high ee (entry 4). Compound **1g**, which did not react when using catalyst **3a**,[8] was now converted into the epoxide at room temperature in high yield and very good ee (entry 7). The ees in both cases can be significantly increased after one recrystallization (entries 4 and 7). Thanks to the mild reaction conditions, more challenging enones having an alkyl substituent either on the double bond or on the carbonyl carbon and aliphatic substrates were selectively epoxidized (entry 9–13) with good asymmetric induction except when a sterically demanding alkyl substituent was present (entry 12).[17] In all the examples (entries 1–13 and 15), diastereoisomerically pure *trans*-epoxides[18] have been obtained preferentially enriched in the (α*R*,β*S*) enantiomer. Bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol (**3g**) proved superior for the epoxidation of α,β-enones when compared to the previously employed catalyst **3a** (Table 3). Finally, in order to point out the influence of the structural features of the enones, conformationally fixed *s-trans*-cyclo-2-hexenone and *s-cis*-benzylidene-α-tetralone were treated under the usual conditions at room temperature (entries 14 and 15). Both substrates reacted sluggishly, but while the epoxycyclohexanone was obtained in poor ee, the (2*R*,1′*S*)-epoxide **2o** was isolated in 75% ee. These results suggest that, in the enantiodifferentiating step, enones could preferentially adopt the *s-cis* conformation, although the coplanarity of the aryl group attached to the carbonyl seems to be detrimental for the reactivity.

With the intention of gaining better insight into the mechanism of the reaction, compound **1a** was epoxidized under the usual conditions with catalyst **3g**, TBHP (1.2 equivs.) in $CDCl_3$ at room temperature and the catalyst loading was progressively increased with reaction time from 30 up to 100 mol %. ^1H NMR and ^{13}C NMR spectra of the reaction mixture were recorded after each addition up to two days reaction time. Iminium ion intermediates have not been detected by NMR analyses and the same result has been obtained when carrying out the reaction in C_6D_6 as the solvent. On the other hand, the alternative activation of the enone *via* iminium ion formation would be less reasonably expected to occur under these reaction conditions, given the unreactive nature of enone carbonyls and the absence of an acid catalyst. These observations support that the epoxidation would proceed *via* the formation of an ion pair as the true catalytic species (Scheme 2).[19] In the light of all results,[20] we propose two hypothetical transition states **A** and **B** to account for the observed sense of the enantioselectivity (Scheme 3).

Hydrogen bonding was shown to be fundamental for the reactivity as well as for the asymmetric induction, as previously demonstrated by the fact that (*S*)-2-diphenylmethylpyrrolidine was a very poor catalyst.[8] Competitive optically pure and achiral hydrogen bonding donors did not particularly affect the epoxidation (Table 2, entries 4 and 5), indicating the selective and coordinated action of the basic and hydroxy functionalities of catalyst **3g** in the reaction. When these functionalities are not in the same molecular scaffold, a reduced reactivity and, most of all, a poor control of the asymmetric induction can be observed, as demonstrated by carrying out the epoxidation using pyrrolidine/(−)-TADDOL as the catalytic system. Furthermore, while prolinol promoted the epoxidation, *N*-benzylprolinol did not catalyze the reaction.[8] It is likely that an intramolecular hydrogen bonding in the ammonium cation, between the oxygen of the hydroxy group and the proximal ^+N–H group, might render the proton of the hydroxy group more acidic. Consequently, it would be more susceptible to take part in an intermolecular hydrogen bonding with the oxygen of the carbonyl moiety, so activating the enone and providing the right orientation for the nucleophilic attack.[21] Moreover, since a tertiary ammonium cation was not able to catalyze the reaction, it seems that simple electrostatic interactions between the ammonium cation and *tert*-butyl hydroperoxide anion might not adequately stabilize the ion pair, the protonated secondary ammonium cation being necessary.[22]



Scheme 3. Postulated transition states.

Assuming that enones reacted in the preferential *s-cis* conformation, in **TS-A** a strong steric interaction can be envisaged between the phenyl ring attached to the carbonyl function and one of 3,5-dimethylphenyl groups of the catalyst, which shields the *Re*-face of the C–C double bond. In **TS-B** the phenyl ring at the β-position

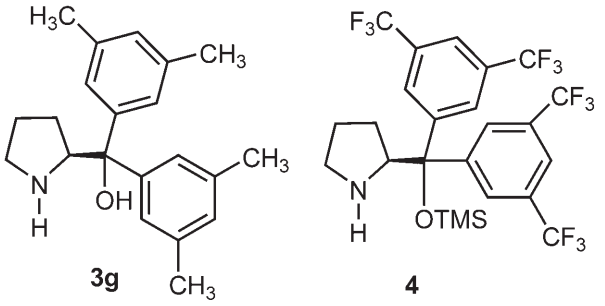


Figure 2. L-Proline-derived catalysts active in the epoxidation of enones and enals (TMS = trimethylsilyl).

points away from the 3,5-dimethylphenyl group, which effectively shields the opposite face of the enone. **TS-B** should be favoured in view of the minimized steric interactions and the attack on the *Re*-face by the *tert*-butyl hydroperoxy anion would afford the (α*R*,β*S*)-epoxide predominantly, as experimentally observed.

It is interesting to note at this point that the structurally and electronically different diaryl-2-pyrrolidinemethanols **3g** and **4**[4] (Figure 2) promote the nucleophilic asymmetric epoxidation of α,β-enones and α,β-unsaturated aldehydes, respectively. Two distinct pathways are reasonably involved during the epoxidation reactions. In the last case, the formation of an iminium ion, by reaction of **4** and aldehyde, was proposed to occur as the reactive intermediate undergoing the nucleophilic attack of the oxidant at the β-carbon.[4a]

Conclusion

In summary, investigations on the stereoelectronic substitution of the phenyl rings of amino alcohol **3a** led to the discovery that the easily accessible bis(3,5-dimethylphenyl)-(*S*)-pyrrolidin-2-ylmethanol (**3g**) catalyzes the asymmetric epoxidation of α,β-enones with enhanced efficiency. The data obtained give better support to the mechanistic hypothesis proposed for the reaction with the amino alcohol **3g** playing the role of a bifunctional organocatalyst. Compared to the previously reported **3a**, significant improvements have been achieved: 1) reduced catalyst loading can be used (20 mol %); 2) high yields and enantioselectivity (up to 94% ee) are obtained. Attractive features of this organocatalytic transformation, that could be of interest for an industrial point of view, are that the reactions are carried out under mild conditions at 4 °C, with no particular precautions in the absence of inert atmosphere, anhydrous solvents and the epoxides are directly isolated by flash chromatography. The epoxidation of aliphatic or enolizable substrates, apart from chalcones, occurred selectively and with good control of the asymmetric induction, which is a positive distinguishing feature of this system giving it a wider applicability. Low reaction rates remain the main drawback, which unfortunately still represent an aspect in common with several other organocatalytic processes.

Experimental Section

General Remarks

Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer at room temperature in $CDCl_3$ as solvent. Optical rotations were performed on a Jasco Dip-1000 digital polarimeter using the Na lamp. All commercially available reagents were purchased from Aldrich. α,β-Enones which were not commercially available were prepared *via* aldol condensation using standard conditions.[23] Hexane of HPLC grade was used as solvent. Catalysts **3b**–**g**, prepared according to reported procedures, have been previously described in the literature.[10] All epoxides are known compounds, their analytical data were identical to those reported in the literature.[17,24] The absolute configuration of the predominant enantiomer was determined by comparison with the HPLC retention times (Waters 486, UV detector) using Daicel Chiralcel OD and Daicel Chiralpak AD columns or with optical rotations reported in the literature.[17,24] The enantioselectivities were determined by chiral HPLC analysis.

General Procedure for Asymmetric Epoxidation of α,β-Enones

TBHP (5–6 M decane solution, 33 μL, 0.18 mmol) was added to a stirred solution of catalyst **3g** (9.2 mg, 0.03 mmol) and enone **1** (0.150 mmol) in hexane (0.215 mL) at 4 °C. Stirring was maintained for the time indicated in Table 3. The crude reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 99/1) to provide the epoxy ketone **2**.

***trans*-(2*R*,3*S*)-Epoxy-1,3-diphenylpropan-1-one (2a):**[17a] ^{1}H NMR (400 MHz): δ = 4.08 (d, J = 1.9 Hz, 1H), 4.29 (d, J = 1.9 Hz, 1H), 7.35–7.63 (m, 8H), 8.00–8.03 (m, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH 98/2, flow rate 1.0 mL/min): t_r(2*S*,3*R*) = 17.3 min, t_r(2*R*,3*S*) = 18.5 min.

***trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(4-bromophenyl)propan-1-one (2b):**[24a] ^{1}H NMR (400 MHz): δ = 4.05 (d, J = 1.9 Hz, 1H), 4.22 (d, J = 1.9 Hz, 1H), 7.33–7.41 (m, 5H), 7.60–7.65 (m, 2H), 7.86–7.90 (m, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH, 95/5, flow rate 0.8 mL/min): t_r(2*R*,3*S*) = 20.2 min, t_r(2*S*,3*R*) = 22.6 min.

***trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(3-methylphenyl)propan-1-one (2c):**[24b] ^{1}H NMR (400 MHz): δ = 2.41 (s, 3H), 4.07 (d, J = 1.9 Hz, 1H), 4.29 (d, J = 1.9 Hz, 1H), 7.34–7.82 (m, 9H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH 30/1, flow rate 0.8 mL/min): t_r(2*S*,3*R*) = 17.8 min, t_r(2*R*,3*S*) = 18.8 min.

***trans*-(2*R*,3*S*)-Epoxy-3-(4-methoxyphenyl)-1-phenyl-1-propanon-1-one (2d):**[24a] ^{1}H NMR (400 MHz): δ = 3.80 (s, 3H),

4.02 (d, $J=2.0$ Hz, 1H), 4.28 (d, $J=2.0$ Hz, 1H), 6.86–6.96 (m, 2H), 7.23–7.34 (m, 2H), 7.40–7.63 (m, 3H), 7.96–8.04 (m, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min): $t_r(2S,3R)=21.7$ min, $t_r(2R,3S)=23.1$ min.

***trans*-(2*R*,3*S*)-Epoxy-3-(4-methylphenyl)-1-phenyl-1-propanon-1-one (2e):**[24k] ^{1}H NMR (400 MHz): δ = 2.38 (s, 3H), 4.04 (d, $J=1.8$ Hz, 1H), 4.27 (d, $J=1.8$ Hz, 1H), 7.25–8.10 (m, 9H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min): $t_r(2S,3R)=17.1$ min, $t_r(2R,3S)=19.6$ min.

***trans*-(2*R*,3*S*)-Epoxy-3-(4-chlorophenyl)-1-phenyl-1-propanon-1-one (2f):**[24c] ^{1}H NMR (400 MHz): δ = 4.06 (d, $J=1.8$ Hz, 1H), 4.24 (d, $J=1.8$ Hz, 1H), 7.25–7.68 (m, 7H), 7.97–8.05 (m, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH, 55/1, flow rate 0.5 mL/min): $t_r(2S,3R)=54.5$ min, $t_r(2R,3S)=57.0$ min.

***trans*-(2*R*,3*S*)-Epoxy-3-(4-nitrophenyl)-1-phenyl-1-propanon-1-one (2g):**[24k] ^{1}H NMR (400 MHz): δ = 4.21 (d, $J=1.8$ Hz, 1H), 4.27 (d, $J=1.8$ Hz, 1H), 7.45–8.30 (m, 9H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH, 80/20, flow rate 0.8 mL/min): $t_r(2S,3R)=35.9$ min, $t_r(2R,3S)=40.3$ min.

***trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(2-furyl)-1-propan-1-one (2h):**[24g] ^{1}H NMR (400 MHz): δ = 4.13 (d, $J=1.8$ Hz, 1H), 4.15 (d, $J=1.8$ Hz, 1H), 6.59–6.60 (m, 1H), 7.29–7.37 (m, 5H), 7.45–7.47 (m, 1H), 7.66–7.68 (m, 1H); HPLC (Chiralpak AD, λ 254 nm, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min): $t_r(2S,3R)=15.3$ min, $t_r(2R,3S)=16.8$ min.

***trans*-(3*R*,4*S*)-Epoxy-4-phenylbutan-2-one (2j):**[17a,24e] ^{1}H NMR (400 MHz): δ = 2.18 (s, 3H), 3.49 (d, $J=2.0$ Hz, 1H), 4.00 (d, $J=2.0$ Hz, 1H), 7.19–7.46 (m, 5H); HPLC (Chiralpak AD, λ 254 nm, hexane/*i*-PrOH, 98/2, flow rate 1.0 mL/min): $t_r(3R,4S)=10.9$ min, $t_r(3S,4R)=13.7$ min.

***trans*-(2*R*,3*S*)-Epoxy-1-phenylbutan-1-one (2k):**[24d] ^{1}H NMR (400 MHz): δ = 1.52 (d, $J=5.2$ Hz, 3H), 3.23 (dq, $J=2.0$, 5.2 Hz, 1H), 3.98 (d, $J=2.0$ Hz, 1H), 7.48–7.65 (m, 3H), 7.99–8.03 (m, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH, 94/6, flow rate 0.8 mL/min): $t_r(2S,3R)=10.7$ min, $t_r(2R,3S)=11.6$ min.

***trans*-(2*R*,3*S*)-Epoxy-5-phenylpentanophenone (2i):**[24f] ^{1}H NMR (400 MHz): δ = 2.00–2.22 (m, 2H), 2.72–3.00 (m, 2H), 3.20 (ddd, $J=2.0$, 5.3, 7.3 Hz, 1H), 3.98 (d, $J=2.0$ Hz, 1H), 7.08–7.37 (m, 5H), 7.45 (t, $J=7.5$ Hz, 2H), 7.60 (t, $J=7.5$ Hz, 1H), 7.83 (d, $J=7.3$ Hz, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH, 20/1 flow rate 1.0 mL/min, $t_r(2R,3S)=16.6$ min, $t_r(2S,3R)=18.3$ min.

***trans*-(2*R*,3*S*)-Epoxy-4-methylpentanophenone (2l):**[24e,f] ^{1}H NMR (400 MHz): δ = 1.07 (d, $J=6.9$ Hz, 3H), 1.11 (d, $J=6.9$ Hz, 3H), 1.72–1.84 (m, 1H), 2.97 (dd, $J=2.0$, 6.0 Hz, 1H), 4.07 (d, $J=2.0$ Hz, 1H), 7.47–7.56 (m, 2H), 7.58–7.66 (m, 1H), 8.02 (d, $J=8.6$ Hz, 2H); HPLC (Chiralcel OD, λ 254 nm, hexane/*i*-PrOH, 98/2, flow rate 1.0 mL/min): $t_r(2S,3R)=7.5$ min, $t_r(2R,3S)=8.8$ min.

***trans*-(3*R*,4*S*)-Epoxynonan-2-one (2m):**[17a,24e] ^{1}H NMR (400 MHz): δ = 0.89 (m, 3H), 1.20–1.75 (m, 8H), 2.06 (s, 3H), 3.07 (dt, $J=2.0$, 5.0 Hz, 1H), 3.18 (d, $J=2.0$ Hz, 1H); HPLC (Chiralpak AD, λ 280 nm, hexane/*i*-PrOH, 100/1, flow rate 0.4 mL/min): $t_r(3R,4S)=15.6$ min, $t_r(3S,4R)=17.5$ min.

(2*R*,3*R*)-Epoxycyclohexan-1-one (2n):[24i,j] $[\alpha]_D^{28}$: +9.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 1.65–1.73 (m, 1H), 1.83–2.14 (m, 3H), 2.23–2.31 (m, 1H), 2.51–2.59 (m, 1H), 3.22 (d, $J=4.0$ Hz, 1H), 3.58–3.61 (m, 1H).

(2*R*,1′*S*)-Epoxy-2-(1′-phenylmethyl)-1-tetralone (2o):[24e,h] ^{1}H NMR (400 MHz): δ = 1.86 (dt, $J=4.3$, 13.5 Hz, 1H), 2.45 (dt, $J=8.6$, 13.5 Hz, 1H), 2.83 (dd, $J=4.3$, 8.6 Hz, 2H), 4.37 (s, 1H), 7.22 (d, $J=7.6$ Hz, 1H), 7.34–7.40 (m, 6H), 7.51–7.55 (m, 1H), 8.10–8.14 (m, 1H); HPLC (Chiralpak AD, λ 254 nm, hexane/*i*-PrOH, 90/10, flow rate 0.5 mL/min): $t_r(2R,1'S)=23.3$ min, $t_r(2S,1'R)=27.9$ min.

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[21] The negative charge of the enolate, developed in the transition state at the oxygen of the carbonyl group after the nucleophilic attack at the β-carbon, would be poorly stabilized in apolar hexane, and consequently the formation of the enolate disfavoured. However, in this case, it can be efficiently stabilized by hydrogen bonding and electrostatic interaction with the positively charged nitrogen of the catalyst.

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