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Diaryl-2-pyrrolidinemethanols catalyzed enantioselective epoxidation of α,β-enones: new insight into the effect of structural modification of the catalyst on reaction efficiency

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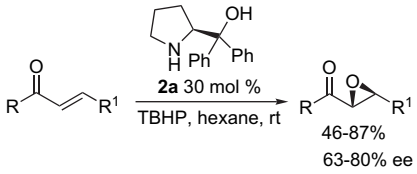
Abstract—Catalytic enantioselective epoxidation of α,β-unsaturated ketones promoted by diaryl-2-pyrrolidinemethanols and *tert*-butyl hydroperoxide (TBHP) is described. Investigation on structural modifications of the diaryl-2-pyrrolidinemethanols showed that fine tuning of the stereoelectronics of the substituents on the aryl moiety is important to achieve high efficiency. By employing a structurally optimized organocatalyst, significantly reduced loading (10 mol %) can be used to produce the epoxides in high yield and up to 90% ee at room temperature.

1. Introduction

Enantiomerically enriched α,β-epoxy ketones are versatile intermediates in organic synthesis and important synthetic pharmaceuticals.[1] Efficient asymmetric epoxidation reactions of α,β-unsaturated ketones, mainly chalcones, have been reported using chiral metal alkyl hydroperoxide systems.[2] Moreover, polyaminoacids[3] and cinchona alkaloids[4] have been used in the presence of hydrogen peroxide as an oxygen source under basic conditions. The development of simple, catalytic and environmentally benign methodologies to access optically pure compounds is a fundamental goal of current organic synthesis. Asymmetric organocatalysis[5] satisfies most of these requirements; low cost and easily accessible chiral organic molecules are able to catalyze an ever-increasing number of reactions under operational simplicity and mild conditions. In order to achieve good yields of products and satisfactory level of enantioselectivity, in most of the reactions, e.g., those promoted by proline-based compounds, 20–30 mol % of catalyst loading is generally employed. Thus, one of the most challenging goals in organocatalysis is to reduce catalyst loading to the level used in metal-catalyzed asymmetric synthesis (≤10 mol %).

Chiral diaryl-2-pyrrolidinemethanol ethers have been successfully employed as organocatalysts in different transformations such as C–C bond forming reactions,[6] functionalizations of carbonyl compounds[7] and epoxidation of α,β-unsaturated aldehydes.[8] On the other hand, the OH-free prolinols have met with poor success as promoters because of the formation of unreactive cyclic *N*,*O*-acetals with carbonyl compounds.[9] Very recently, the asymmetric vinylogous Michael addition reaction has been promoted by diaryl-2-pyrrolidinemethanols through the formation of iminium intermediates.[10] We have recently discovered that commercially available (*S*)-diphenyl-2-pyrrolidinemethanol **2a** and TBHP oxidize unsaturated α,β-ketones into the corresponding epoxides in good yield and enantioselectivity (up to 80% ee), using 30 mol % catalyst loading at room temperature (Scheme 1).[11]



Scheme 1.

In exploring the effects of structural modification on catalyst activity, investigation on stereoelectronic substitution on the phenyl moiety gave improved understanding of mechanism and more importantly a remarkable enhancement of the reaction efficiency.[12] Indeed, bis(3,5-dimethylphenyl)-((*S*)-pyrrolidin-2-yl)methanol **2b**, when employed at 20 mol % loading and 4 °C, afforded the epoxides in higher yield and ee (up to 92% ee). Nonlinear effects (NLE)[13] investigation using (*S*)-diphenyl-2-pyrrolidinemethanol **2a**, at different degrees of optical purity, afforded a linear relationship, suggesting the involvement of a single molecule of the catalyst in the enantiodifferentiating step. The postulated

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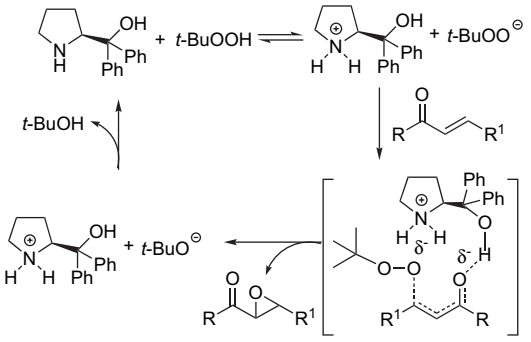


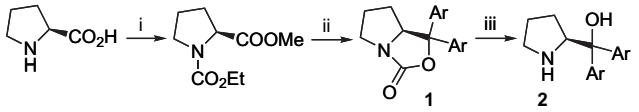
Figure 1. Proposed catalytic cycle for the epoxidation.

catalytic cycle for the epoxidation involves the formation of a ionic pair, made of *tert*-butyl hydroperoxide anion and ammonium cation, as the active species (Fig. 1).[11]

Further understanding of the catalyst activity, through fine-tuned stereoelectronic modifications on the phenyl ring, is important for the development of a more efficient and practical epoxidation reaction. Hence, in this study, novel modified diaryl-2-pyrrolidinemethanols were synthesized and tested as promoters for the epoxidation, which was successfully improved by using a more active organocatalyst at significantly reduced loading.

2. Results and discussion

Our preliminary investigation[12] on the effect of substituents on the phenyl ring showed that (i) electron-donating substituents at *para* and *meta* positions enhanced catalyst activity; (ii) substitution at *meta* positions was found to be beneficial for the enantioselectivity. These results reinforced the mechanistic hypothesis involving the ionic pair as active species (Fig. 1). In fact, the equilibrium for its formation would be favoured for those catalysts having electron-donating groups, which through inductive or mesomeric effects can increase amine basicity. In order to further improve our oxidative system, a more detailed analysis of the stereoelectronic effects on catalyst activity was undertaken. In the light of previous results,[12] *ortho*-substituted and *meta*-disubstituted catalysts with electron-donating groups were thought to be the most suitable compounds to prepare and check in the epoxidation. (*S*)-Diaryl-2-pyrrolidinemethanols are readily accessible starting from L-proline according to the general established procedures[14] (Scheme 2).



Ar=*o*-methyl-*p*-methoxyphenyl (**c**)
Ar=*o*,*p*-dimethoxyphenyl (**d**) 12%
Ar=*m*,*m*′-dimethoxy-p-methoxyphenyl (**e**) 49%
Ar=*m*,*m*′-di-*t*-butylphenyl (**f**) 31%
Ar=*m*,*m*′-dimethyl-*p*-methoxyphenyl (**g**) 68%

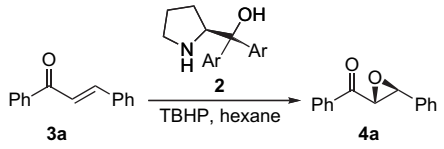
Scheme 2. Reagents and conditions: (i) ethyl chloroformate, K_2CO_3, MeOH, 0 °C to rt, 97%; (ii) ArMgBr, THF, 0–60 °C; (iii) KOH, EtOH/H_2O, reflux.

Grignard addition to (*S*)-proline-*N*-ethyl carbamate methyl ester did not furnish compound **1c**, while the *o*,*p*-dimethoxy substituted compound **1d** was obtained in 48% yield. This was probably due to the bigger steric congestion of the *o*-methyl substituent with respect to *o*-methoxy group at the reactive site of the organometallic reagent, which prevented the addition. Catalyst **2d** was isolated in 25% yield after hydrolysis. Next, sterically more encumbered groups were introduced at the *meta* positions and the corresponding compounds **2e**,**f** were obtained in 49% and 31% yield for the two steps, respectively. Finally, compound **2g** was obtained in good overall 68% yield.

Catalysts **2d**–**g** were then checked under the optimal conditions (TBHP 1.2 equiv, +4 °C, 20 mol % catalyst loading)[12] previously found for catalyst **2b** on *trans*-chalcone **3a** (Table 1, entry 1).

The epoxidation of **3a**, using the *o*,*p*-dimethoxy substituted catalyst **2d**, afforded **4a** in very low yield and low enantioselectivity (entry 2). Although we expected the trisubstituted catalyst **2e** to be less reactive than **2b**, because of electron-withdrawing inductive effect of the methoxy groups at *meta* positions, the slightly bigger *m*-methoxy substituents were not beneficial for the enantioselectivity (entry 3). Interestingly, the activity of catalyst **2f**, bearing sterically encumbered *m*-*tert*-butyl groups, was completely inhibited (entry 4). These results showed that *ortho*-type substitution is detrimental in all respects, probably because of steric effect on the OH group, which prevented activation via hydrogen bonding with the enone carbonyl moiety. Substitution at the *meta* positions proved to be crucial for catalyst performance. Small or major modifications of the substituent nature, with respect to the methyl group of **2b**, were deleterious (entries 3 and 4). Thus, methyl substitution at the *meta* positions would seem optimal to achieve high enantioselectivity. We then studied the epoxidation with the trisubstituted promoter **2g**. This compound should have had improved activity with respect to **2b** due to the introduction of additional electron-donating *p*-methoxy groups and had a comparable impact on enantioselectivity. The epoxidation was carried

Table 1. Asymmetric epoxidation of **3a** by **2**/TBHP system



Entry	**2** (mol %)	*T* (°C)	*t* (h)	Yield **4a** (%)[a]	ee **4a** (%)[b]
1[c]	**b** (20)	+4	112	90	91 (α*R*,β*S*)
2	**d** (20)	+4	112	9	43 (α*R*,β*S*)
3	**e** (20)	+4	86	37	86 (α*R*,β*S*)
4	**f** (20)	+4	90	<5	—
5	**g** (15)	+4	106	70	92 (α*R*,β*S*)
6	**g** (10)	rt	110	93	89 (α*R*,β*S*)
7[c]	**b** (10)	rt	95	61	88 (α*R*,β*S*)
8[d]	**a** (30)	rt	94	72	75 (α*R*,β*S*)
9	**g** (5)	rt	120	77	88 (α*R*,β*S*)
10	**g** (2)	rt	120	47	83 (α*R*,β*S*)

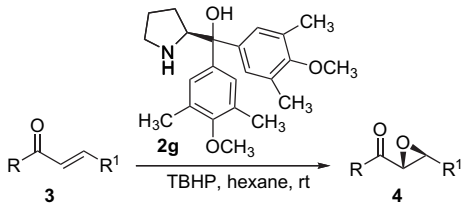
[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC on chiral column. Absolute configuration (α*R*,β*S*) was determined by comparison of the HPLC retention times with those in the literature.
[c] Yield and ee are reported in Ref. 12.
[d] Yield and ee are reported in Ref. 11.

out at lower catalyst loading (15 mol %) under the same conditions and the epoxide was isolated in good yield and high ee (entry 5). A better comparison on catalysts activity can be gained by comparing the results obtained at 10 mol % loading, working at room temperature (entries 6 and 7). After similar reaction times, the epoxide was isolated in comparable ee, but a higher yield was achieved when using catalyst **2g**. The relevance of the substitution pattern on catalyst efficiency can be clearly observed when comparing the results with those obtained using the original promoter **2a** at 30 mol % (entry 8). It is worth noting that the amount of catalyst **2g** could be further reduced to 2 mol % (entries 9 and 10) without particularly affecting the enantioselectivity, although the yield of **4a** decreased.

Having established that **2g** proved about equal to **2b** (compare entries 1 and 6), but at half the catalyst loading (10 mol %) we next screened a series of α,β-enones under the conditions reported in entry 6 of Table 1 (Table 2).

Epoxides of chalcones bearing electron-donating or withdrawing groups on the phenyl rings were obtained in good to high yield and high ee (entries 1–8). Predictably, the conversion was somewhat decreased for chalcones having electron-donating substituent on the β-phenyl ring (entries 4 and 5). Although the epoxide of the *o*-substituted β-phenyl ring **4i** was obtained with decreased ee (entry 9), it is worth noting that the same reaction when carried out by 30 mol % of the commercial promoter **2a** was considerably slower and the product was obtained in modest yield and significantly reduced ee (entry 10). Finally, the epoxidation of more challenging alkyl substituted α,β-unsaturated ketones led to the formation of the epoxides in good ee (entries 11–13).

Table 2. Catalytic asymmetric epoxidation of **3** by **2g**/TBHP system[a]



Entry	R, R^1	**3**	*t* (h)	Yield **4** (%)[b]	ee **4** (%)[c]
1	Ph, Ph	**a**	110	93	89
2	*p*-BrC_6H_4, Ph	**b**	172	98	86
3	*m*-$CH_3C_6H_4$, Ph	**c**	137	87	89
4	Ph, *p*-CH_3	**d**	153	80	86
5[d]	Ph, *p*-OCH_3	**e**	120	61	87
6	Ph, *p*-CN	**f**	170	65	86
7	2-Furyl, Ph	**g**	179	78	90
8	Ph, *p*-Cl	**h**	167	88	87
9[e]	Ph, *o*-Cl	**i**	76	70	69
10[f]	Ph, *o*-Cl	**i**	143	45	34
11[d]	CH_3, Ph	**j**	216	55	83
12	Ph, CH_3	**k**	119	95	67
13	Ph, $(CH_2)_2$Ph	**l**	162	80	71

[a] Molar ratios: **3**/**2g**/TBHP 1:0.10:1.2.
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC on chiral columns. Absolute configuration (α*R*,β*S*) was determined by comparison of the HPLC retention times with those in the literature.
[d] 20 mol % was used in this reaction.
[e] 15 mol % was used in this reaction.
[f] The reaction was carried out with 30 mol % of **2a**.

3. Conclusion

In summary, careful choice of stereoelectronic phenyl substitution is necessary in order to improve the activity of diaryl-2-pyrrolidinemethanols as promoters in asymmetric epoxidation of α,β-enones. Electron-rich derivative **2g**, easily obtained in good overall yield from L-proline, proved to be a more active catalyst than previously reported analogues and it could be employed at 10 mol % level, which is considerably lower than firstly reported (30 mol % loading). The optimized catalytic epoxidation reaction afforded epoxides in good to high yield and high ee at room temperature.

4. Experimental

4.1. General

All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of argon. THF was freshly distilled before use from $LiAlH_4$. 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 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. FTIR spectra were recorded as a thin film on NaCl plates using Bruker Vector 22 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. All commercially available reagents were purchased from Aldrich. Petrol ether (PE) refers to light petroleum ether (bp 40–60 °C). α,β-Enones which were not commercially available were prepared via aldol condensation using standard conditions.[15] Hexane of HPLC grade was used as solvent for the epoxidation. The absolute configuration of the predominant enantiomer of epoxides was determined by comparison with the HPLC retention times, using Daicel Chiralcel OD and Daicel Chiralpak AD columns, as reported in the literature. (*S*)-Proline-*N*-ethyl carbamate ethyl ester was prepared according to the literature.[16]

4.2. General procedure for the preparation of carbamates 1 from (*S*)-proline-*N*-ethyl carbamate methyl ester

Magnesium turnings (251 mg, 10.3 mmol) were placed in a dried two-necked round-bottom flask attached with a reflux condenser under argon atmosphere. After adding dry THF (3 mL) and few iodine crystals to the reaction vessel, the turnings were left under stirring for 2 h. Aryl bromide (9.4 mmol) in dry THF (8 mL) was added dropwise in 15 min. The mixture was then refluxed under stirring for 45 min. After cooling the reaction mixture at 0 °C, a solution of (*S*)-proline-*N*-ethyl carbamate methyl ester (805 mg, 4 mmol) in THF (18 mL) was cannulated into the reaction vessel. The resulting mixture was warmed up to room temperature gradually and then heated up to 60 °C. After stirring

overnight, the reaction was quenched with saturated ammonium chloride solution (50 mL) extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography typically eluting with mixtures of PE/ethyl acetate 90/10 to 50/50 afforded the corresponding carbamate **1**.

4.2.1. Carbamate 1d. Compound **1d** was obtained in 48% yield as white gum; $[\alpha]_D^{24}$ −118.1 (*c* 1.25, $CHCl_3$); ν_{max}/cm^{-1} 2945, 1743, 1463, 1209, 798, 750; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, d, *J*=8.5 Hz), 6.94 (1H, d, *J*=8.5 Hz), 6.51–6.43 (3H, m), 6.39–6.34 (1H, m), 4.53 (1H, dd, *J*=9.6, 6.6 Hz), 3.82 (3H, s), 3.78 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.67–3.59 (1H, m), 3.30–3.22 (1H, m), 2.09–2.00 (1H, m), 1.98–1.89 (1H, m), 1.75–1.68 (1H, m), 1.50–1.42 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.6, 159.8, 157.6, 129.7, 128.3, 124.1, 120.6, 103.9, 103.5, 99.1, 99.0, 86.7, 69.4, 55.4, 55.2, 55.1, 44.9, 28.0, 25.9; MS (ESI$^+$, *m*/*z*): 422 [(M+Na$^+$), 28%], 438 [(M+K$^+$), 35%], 400 [(M+H$^+$), 20%]; Anal. Calcd (%) for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.29; H, 6.20; N, 3.42.

4.2.2. Carbamate 1e. Compound **1e** was obtained in 59% yield as dark yellow gum; $[\alpha]_D^{24}$ −134.3 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} 2940, 1749, 1418, 1128, 756; δ_H (400 MHz, $CDCl_3$) 6.73 (2H, s), 6.58 (2H, s), 4.47 (1H, dd, *J*=10.5, 5.4 Hz), 3.84 (12H, s), 3.83 (6H, s), 3.80–3.71 (1H, m), 3.30–3.25 (1H, m), 2.06–1.98 (1H, m), 1.93–1.86 (1H, m), 1.79–1.73 (1H, m), 1.25–1.15 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.3, 153.2, 153.0, 138.7, 138.1, 137.3, 135.6, 103.6, 102.8, 85.8, 77.3, 69.3, 60.8, 56.3, 56.2, 46.1, 29.0, 24.8; MS (ESI$^+$, *m*/*z*): 498 [(M+K$^+$), 12%], 460 [(M+H$^+$), 35%]; Anal. Calcd (%) for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.60; H, 6.49; N, 3.14.

4.2.3. Carbamate 1f. Compound **1f** was obtained in 65% yield as yellow gum; $[\alpha]_D^{25}$ −82.2 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2963, 1749, 1476, 1248, 754; δ_H (400 MHz, $CDCl_3$) 7.38 (2H, d, *J*=1.4 Hz), 7.35–7.33 (1H, m), 7.30–7.28 (1H, m), 7.24 (2H, d, *J*=1.4 Hz), 4.48 (1H, dd, *J*=10.5, 5.3 Hz), 3.77–3.70 (1H, m), 3.26–3.20 (1H, m), 2.01–1.95 (1H, m), 1.94–1.85 (1H, m), 1.84–1.74 (1H, m), 1.29 (36H, s), 1.16–1.10 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.9, 150.7, 150.4, 143.4, 139.6, 122.1, 122.0, 121.0, 119.7, 119.6, 86.8, 70.7, 45.9, 34.9, 31.4, 29.3, 24.8; MS (ESI$^+$, *m*/*z*): 526 [(M+Na$^+$), 12%], 504 [(M+H$^+$), 35%]; Anal. Calcd (%) for $C_{34}H_{49}NO_2$: C, 81.06; H, 9.80; N, 2.78. Found: C, 81.18; H, 9.68; N, 2.66.

4.2.4. Carbamate 1g. Compound **1g** was obtained in 84% yield as yellow gum; $[\alpha]_D^{24}$ −168.8 (*c* 1.54, $CHCl_3$); ν_{max}/cm^{-1} 2947, 1752, 1484, 1227, 1012, 756; δ_H (400 MHz, $CDCl_3$) 7.14 (2H, s), 6.98 (2H, s), 4.50 (1H, dd, *J*=10.5, 5.5 Hz), 3.75–3.68 (1H, m), 3.69 (6H, s), 3.26–3.20 (1H, m), 2.27 (6H, s), 2.25 (6H, s), 2.01–1.94 (1H, m), 1.93–1.82 (1H, m), 1.70–1.55 (1H, m), 1.14–1.07 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.7, 156.7, 156.1, 138.6, 135.6, 130.8, 130.6, 126.2, 125.7, 85.5, 59.6, 46.0, 28.9, 24.7, 16.3; MS (ESI$^+$, *m*/*z*): 434 [(M+K$^+$), 15%], 396 [(M+H$^+$), 100%]; Anal. Calcd (%) for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.73; H, 7.27; N, 3.44.

4.3. General procedure for the hydrolysis of carbamates to (*S*)-diaryl-2-pyrrolidinemethanols 2

A solution of **1** (2.2 mmol), KOH (2.4 g, 43 mmol), EtOH (10 mL) and H_2O (2.0 mL) was heated overnight at 80 °C (in some examples up to two days time was necessary to complete conversion of starting material as assessed by TLC analysis). After cooling to room temperature, EtOH was removed under reduced pressure, and the aqueous layer was extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography typically eluting with mixtures of PE/ethyl acetate 80/20 to pure ethyl acetate afforded compounds **2**.

4.3.1. Bis(2,4-dimethoxyphenyl)((*S*)-pyrrolidin-2-yl)methanol 2d. Compound **2d** was obtained in 25% yield as yellow gum; $[\alpha]_D^{24}$ −83.5 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} 3463, 2938, 1462, 1209, 1031, 833, 754; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, d, *J*=8.7 Hz), 7.54 (1H, d, *J*=8.7 Hz), 6.56–6.51 (1H, m), 6.49–6.45 (1H, m), 6.36–6.25 (2H, m), 5.13 (1H, t, *J*=8.4 Hz), 3.75 (3H, s), 3.73 (3H, s), 3.63 (3H, s), 3.51 (3H, s), 3.09–3.00 (2H, m), 1.91–1.76 (3H, m), 1.58–1.55 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.1, 157.6, 156.5, 131.4, 129.6, 127.8, 127.6, 124.4, 123.1, 104.3, 103.7, 99.8, 99.1, 76.9, 62.0, 55.7, 55.4, 55.2, 47.4, 26.8, 25.2; MS (ESI$^+$, *m*/*z*): 374 [(M+H$^+$), 18%], 356 [(M−17), 100%]; Anal. Calcd (%) for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.68; H, 7.20; N, 3.61.

4.3.2. Bis(3,4,5-trimethoxyphenyl)((*S*)-pyrrolidin-2-yl)methanol 2e. Compound **2e** was obtained in 83% yield as yellow gum; $[\alpha]_D^{23}$ −60.3 (*c* 1.17, $CHCl_3$); ν_{max}/cm^{-1} 3450, 2940, 1458, 1128, 756; δ_H (400 MHz, $CDCl_3$) 6.81 (2H, s), 6.73 (2H, s), 4.14 (1H, t, *J*=7.8 Hz), 3.85 (6H, s), 3.84 (6H, s), 3.80 (6H, s), 3.04–2.90 (2H, m), 1.77–1.53 (4H, m); δ_C (100 MHz, $CDCl_3$) 152.9, 152.7, 143.5, 140.7, 136.7, 136.5, 103.7, 103.2, 102.8, 72.9, 64.8, 60.7, 56.2, 56.1, 46.6, 26.4, 25.3; MS (ESI$^+$, *m*/*z*): 434 [(M+H$^+$), 10%], 416 [(M−17), 100%]; Anal. Calcd (%) for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.62, H, 7.30; N, 3.15.

4.3.3. Bis(3,5-di-*tert*-butylphenyl)((*S*)-pyrrolidin-2-yl)methanol 2f. Compound **2f** was obtained in 48% yield as yellow gum; $[\alpha]_D^{22}$ −58.2 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} 3417, 2963, 1392, 1248, 757; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J*=1.4 Hz), 7.35 (2H, d, *J*=1.4 Hz), 7.26 (1H, s), 7.18 (1H, s), 4.73 (1H, t, *J*=7.8 Hz), 2.33–2.27 (1H, m), 2.25–2.15 (1H, m), 1.94–1.88 (1H, m), 1.75–1.55 (3H, m), 1.32 (18H, s), 1.24 (18H, s); δ_C (100 MHz, $CDCl_3$) 150.7, 150.4, 143.1, 142.4, 122.1, 120.5, 119.9, 119.2, 78.2, 66.2, 46.2, 35.0, 34.9, 31.6, 26.6, 24.7; MS (ESI$^+$, *m*/*z*): 478 [(M+H$^+$), 100%], 460 [(M−17), 60%]; Anal. Calcd (%) for $C_{33}H_{51}NO$: C, 82.96; H, 10.76; N, 2.93. Found: C, 82.85; H, 10.66; N, 2.85.

4.3.4. Bis(3,5-dimethyl-4-methoxyphenyl)((*S*)-pyrrolidin-2-yl)methanol 2g. Compound **2g** was obtained in 81% yield as pale yellow gum; $[\alpha]_D^{25}$ −48.1 (*c* 1.15, $CHCl_3$); ν_{max}/cm^{-1} 3446, 2946, 1484, 1224, 1136, 756; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, s), 7.09 (2H, s), 4.18 (1H, t,

J=7.6 Hz), 3.66 (6H, s), 3.00–2.89 (2H, m), 2.25 (6H, s), 2.24 (6H, s), 1.75–1.67 (2H, m), 1.62–1.53 (2H, m); δ_C (100 MHz, $CDCl_3$) 155.3, 155.2, 143.3, 140.6, 130.1, 129.8, 126.8, 126.7, 126.0, 125.7, 76.4, 64.5, 59.4, 46.6, 26.2, 25.4, 16.3; MS (ESI$^+$, m/z): 370 [(M+H$^+$), 10%], 352 [(M−17), 100%]; Anal. Calcd (%) for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.65; H, 8.53; N, 3.70.

4.4. General procedure for the asymmetric epoxidation of α,β-enones

To a stirred solution of catalyst **2g** (5.5 mg, 0.015 mmol) and α,β-enone **3** (0.150 mmol) in hexane (300 μL) at room temperature was added TBHP (5–6 M decane solution, 33 μL, 0.18 mmol). Stirring was maintained for the time indicated in Table 2. The crude reaction mixture was directly purified by flash chromatography on silica gel (PE/diethyl ether 99/1) to provide the epoxy ketone **4**. Epoxides data were as described previously.[2c,11,12,17–23]

4.5. Determination of enantiomeric excess for epoxy ketones 4

4.5.1. *trans*-(2*R*,3*S*)-Epoxy-1,3-diphenylpropan-1-one 4a.[2c] 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.

4.5.2. *trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(4-bromophenyl)-propan-1-one 4b.[17] 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.

4.5.3. *trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(3-methylphenyl)-propan-1-one 4c.[4f] 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.

4.5.4. *trans*-(2*R*,3*S*)-Epoxy-3-(4-methylphenyl)-1-phenyl-1-propan-1-one 4d.[18] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=17.1 min, t_R(2*R*,3*S*)=19.6 min.

4.5.5. *trans*-(2*R*,3*S*)-Epoxy-3-(4-methoxyphenyl)-1-phenyl-1-propan-1-one 4e.[17] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=21.7 min, t_R(2*R*,3*S*)=23.1 min.

4.5.6. *trans*-(2*R*,3*S*)-Epoxy-3-(4-cyanophenyl)-1-phenyl-1-propan-1-one 4f.[19] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 90/10, flow rate 0.9 mL/min, t_R(2*S*,3*R*)=35.0 min, t_R(2*R*,3*S*)=38.3 min.

4.5.7. *trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(2-furyl)-1-propan-1-one 4g.[20] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min, t_R(2*S*,3*R*)=15.3 min, t_R(2*R*,3*S*)=16.8 min.

4.5.8. *trans*-(2*R*,3*S*)-Epoxy-3-(4-chlorophenyl)-1-phenyl-1-propan-1-one 2h.[21] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 55/1, flow rate 0.5 mL/min, t_R(2*S*,3*R*)=54.5 min, t_R(2*R*,3*S*)=57.0 min.

4.5.9. *trans*-(2*R*,3*S*)-Epoxy-3-(2-chlorophenyl)-1-phenyl-1-propan-1-one 2i.[4f] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 96/4, flow rate 1.0 mL/min, t_R(2*R*,3*S*)=10.1 min, t_R(2*S*,3*R*)=11.5 min.

4.5.10. *trans*-(3*R*,4*S*)-Epoxy-4-phenylbutan-2-one 4j.[2c] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 98/2, flow rate 1.0 mL/min, t_R(3*R*,4*S*)=10.9 min, t_R(3*S*,4*R*)=13.7 min.

4.5.11. *trans*-(2*R*,3*S*)-Epoxy-1-phenylbutan-1-one 4k.[22] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 94/6, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=10.7 min, t_R(2*R*,3*S*)=11.6 min.

4.5.12. *trans*-(2*R*,3*S*)-Epoxy-5-phenylpentanophenone 4l.[23] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 20/1, flow rate 1.0 mL/min, t_R(2*R*,3*S*)=16.6 min, t_R(2*S*,3*R*)=18.3 min.

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References and notes

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