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Enantioselective catalytic epoxidation of α,β-enones promoted by fluorous α,α-diaryl-L-prolinols

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Abstract

Enantioselective (up to 87% ee) epoxidation of a variety of α,β-enones to form α,β-epoxy ketones is described using a series of fluorous α,α-diaryl-L-prolinols as bifuncational organocatalysts and *tert*-butyl hydrogenperoxide (TBHP) as an oxidant.
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Keywords: L-Prolinol; Fluorous catalyst; Asymmetric epoxidation; α,β-Enone

1. Introduction

Epoxides are found to be important intermediates in organic chemistry. The asymmetric epoxidation of functionalized and unfunctionalized olefins is emerging as a very versatile and important synthetic transformation in organic synthesis [1]. The Sharpless epoxidation for allylic alcohols and manganese–salen complexes developed by especially Jacobsen et al. for some kinds of unfunctionalized epoxides have opened up a brand-new field for organic chemistry [2]. Chiral epoxy ketones obtained by asymmetric epoxidation of α,β-unsaturated carbonyl compounds are versatile precursors to many natural products and drug molecules [3]. Therefore lots of methods have been introduced to this area. By use of heterometallic chiral catalysts such as lanthanoid complexes [4a–d] and enantioenriched-Ca complex [4e], α,β-enones could be epoxidized to the corresponding epoxides with hydrogen peroxide in high enantioselectivities. In the direction of heterogeneous catalysis, polymer-supported polypeptides [5a] were employed successfully in asymmetric epoxidation of α,β-enones while a truly recyclable, bifunctional nanocrystalline MgO [5b] demonstrated the same impressive effect. The catalytic asymmetric epoxidation of α,β-enones applying chiral phase-transfer catalysis [6] has also been achieved, and the epoxide products were generally obtained with high enantioselectivities.

Recently, asymmetric epoxidation of α,β-enones have been realized using L-prolinols as the organocatalyst [7]. Out of the concern for the recovery and reuse of the relatively costly catalysts, we have reported the preparation and use of chiral pyrrolidinylmethanol-based dendritic catalysts for this transformation [7d]. On the other hand, fluorous organocatalysts which are effective and easily recoverable for some asymmetric reactions have found rare applications in this field. We report herein the synthesis of a series of fluorous prolinols and their application in the enantioselective epoxidation of α,β-enones using *tert*-butyl hydrogenperoxide (TBHP) as an oxidant with moderate yields and up to 87% ee.

2. Results and discussion

Three fluorous prolinols (**1a**, **1d** and **1e**) and two fluorine-containing prolinols (**1b** and **1c**) were synthesized according to the reported methods (Scheme 1) [8]. And we performed a preliminary study on the catalytic properties of these catalysts in the asymmetric organocatalytic epoxidation of α,β-enones with TBHP in different solvents and temperature. 1,3-Diphenylpropenone **2b** was selected as a model compound to carry out these reactions. The results are shown in Table 1.

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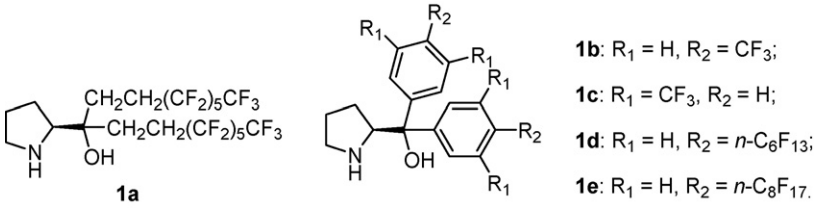


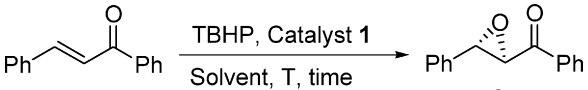
Scheme 1.

The reaction was carried out using 30 mol% of **1** in carbon tetrachloride at 0 °C or room temperature. Catalyst **1a** gave a very low enantioselectivity (Table 1, entry 1). When **1b** was used at 0 °C, diastereoisomerically pure *trans*-(2*R*,3*S*)-**3a** was isolated in 40% yield and 92% ee (Table 1, entry 2). However, the 3,5-bistrifluoromethyl substituted diaryl-L-prolinol **1c** gave a sluggish reaction and much lower enantioselectivity (Table 1, entry 3).

With these results and considering the recycling of the fluorous prolinols, the catalysts of 4-perfluoroalkyl substituted L-prolinols **1d** and **1e** were tested with different solvents (Table 1, entries 4–9). At room temperature, 4-perfluoroalkyl substituted α,α-diaryl-L-prolinol **1d** and **1e** provided the product **3a** in 80 and 84% ee, respectively, with moderate yield when using carbon tetrachloride as a solvent (Table 1, entries 4 and 5). A better result was obtained when the epoxidation was carried out in *n*-hexane (Table 1, entries 6 and 7). However, when we tried to extend the scope of the substrates in *n*-hexane, some enones failed to dissolve well at room temperature. Reactions in toluene or α,α,α-trifluorotoluene gave comparable yields but lower enantioselectivities (Table 1, entries 8–10). Notably, the reaction performed in tetrahydrofuran (Table 1, entry 11) was totally inert to the epoxidation in our system. From these results, we concluded that using 30 mol% of catalyst **1e** and TBHP as an oxidant in carbon tetrachloride at room temperature was the optimal conditions for this epoxidation of α,β-enones.

Having optimized the reaction conditions, substrate generality was investigated. To demonstrate the scope and potential of catalyst **1e** for the organocatalytic epoxidation, a series of different substituted α,β-enones were tested under the optimized reaction conditions. The results are summarized in Table 2. Of all the examples examined (Table 2), the corresponding products *trans*-(2*R*,3*S*)-epoxides **3** were obtained as a single product in moderate to good enantioselectivities. Enones with substituent groups of different electronic nature on the carbonyl side afforded satisfactory results (Table 2, entries 5–12). Except for the *para*-nitro substituted one, enones with different substituents on the β-aryl moiety gave ee values above 75% (Table 2, entries 1–7). Most of these results were better than those obtained in our previously reported work using the dendritic catalysts [7e]. It is assumed that the reaction mechanism involves the ionic pair of *tert*-butyl hydroperoxide anion and ammonium cation as the

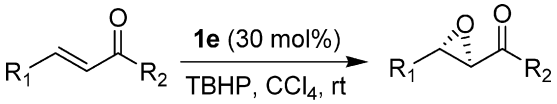
Table 1
Optimization of reaction conditions for asymmetric epoxidation of **2a**[a]

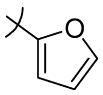


Entry	Catalyst	Solvent	*T* (°C)	Time (days)	Yield of **3a**[b] (%)	ee of **3a**[c] (%) (config.)[d]
1	**1a**	CCl_4	rt	8	58	12
2	**1b**	CCl_4	0	4	40	92
3	**1c**	CCl_4	0	6	10	66
4	**1d**	CCl_4	rt	4	60	80
5	**1e**	CCl_4	rt	8	65	84
6	**1d**	Hexane	rt	4	60	80
7	**1e**	Hexane	rt	8	62	87
8	**1d**	Toluene	rt	4	52	76
9	**1d**	$CF_3C_6H_5$	rt	8	62	74
10	**1e**	$CF_3C_6H_5$	rt	8	57	75
11	**1e**	THF	rt	4	Trace	nd[e]

[a] Unless otherwise specified, the reaction was carried out with 1.3 equiv. of TBHP in the presence of 30 mol% of catalyst.
[b] Isolated yield by flash column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using the chiral Daicel Chiralcel OD column.
[d] Absolute configuration of **3a** was determined to be (2*R*,3*S*) by comparison of the HPLC retention times with known data.
[e] Not determined.

Table 2
Catalytic enantioselective epoxidation of α,β-enones promoted by **1e**[a]



Entry	R_1	R_2	Time (days)	Yield[b] (%)	Product	ee[c] (%)
1	Ph	Ph	8	65	**3a**	84
2	*p*-Cl-C_6H_4	Ph	8	63	**3b**	80
3	*p*-CH_3-C_6H_4	Ph	8	50	**3c**	75
4	*p*-NO_2-C_6H_4	Ph	8	64	**3d**	65
5	*p*-CH_3-C_6H_4	*p*-Cl-C_6H_4	8	56	**3e**	77
6	*p*-Cl-C_6H_4	*p*-CH_3O-C_6H_4	8	41	**3f**	83
7	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	8	65	**3g**	79
8	Ph		8	56	**3h**	81
9	Ph	*p*-Cl-C_6H_4	8	61	**3i**	80
10	Ph	*p*-Br-C_6H_4	8	60	**3j**	82
11	Ph	*p*-CH_3O-C_6H_4	8	31	**3k**	80
12	Ph	*p*-F-C_6H_4	8	67	**3l**	83

[a] The reaction was carried out with 1.3 equiv. of TBHP in the presence of 30 mol % of catalyst **1e**.
[b] Isolated yields by column chromatography.
[c] Enantiomeric excess was determined by chiral HPLC (see the experimental section).

Table 3
Recycling of catalyst **1e** in the epoxidation of α,β-enone **2a**

Run	Time (days)	Yield (%)[a]	ee (%)[b]
1	8	65	84
2	8	63	83
3	8	64	82
4	8	62	82

[a] Isolated yield.
[b] Determined by chiral HPLC.

active species [7a–d]. The electron-withdrawing perfluoroalkyl group decreases the amine basicity to retard the reaction.

Funabiki et al. have reported a novel method to recover the fluorous catalyst **1a** without the use of any fluorous solvents or silica gel by simply cooling the organic phase followed by filtration [8f]. In our experiments, a similar method was used to recover **1e** (see the experimental section), and the recovered catalyst **1e** could be reused at least three times with little or no loss of activity and enantioselectivity (Table 3).

3. Conclusion

In summary, we have reported an enantioselective asymmetric epoxidation for α,β-enones using easily accessible and recoverable fluorous α,α-diaryl-L-prolinol **1e** as a catalyst and TBHP as an oxidant. Moderate to good enantioselectivities have been obtained for a number of substrates with a variety of substituted groups, using a relatively operationally simple protocol without any protection and additional treatment.

4. Experimental

General: ^{1}H NMR spectra were recorded on Bruker AM-300 or Varian Mercury 300 (300 MHz) spectrometer with TMS as an internal standard. ^{19}F NMR spectra were recorded on Bruker AM-300 or Varian Mercury 300 (282 MHz) spectrometer with $CFCl_3$ as an external standard. ^{13}C NMR spectra were recorded on Bruker DPX-300 (75.5 MHz) or DPX-400 (100.7 MHz) spectrometer. All the reagents were obtained from commercial source. THF, Et_2O and DMSO were freshly distilled over CaH_2 before use. Carbon tetrachloride was used as received.

4.1. Typical procedure for the prearation of fluorous α,α-diaryl-L-prolinols

4.1.1. 2-[Bis-(perfluorohexyl-ethyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester

A solution of (perfluorohexyl) ethylmagnesium iodide (9.80 g, 21 mmol) in dry ether (30 mL) was added over 20 min to a mixture of magnesium (503 mg, 22 mmol) and a few iodine crystals in ether (5 mL). This mixture was stirred at room temperature for 3 h followed by adding a solution of (*S*)-proline-*N*-ethyl carbamate methyl ester (704 mg, 3.5 mmol) in dry ether (20 mL) within 20 min. After stirring for 24 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl solution. After separation of the organic layer, the aqueous layer was extracted with ether (3× 20 mL). After drying the combined organic layers over anhydrous Na_2SO_4 followed by evaporation of the solvent under reduced pressure, a yellow liquid was obtained. Column chromatography (hexane/ethyl acetate 5:1) gave the product 1.41 g in 47% yield as a colorless liquid.

$[\alpha]_D^{24}$: −24 (*c* = 1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 1H), 4.24–4.14 (m, 2H), 4.02 (t, *J* = 8.4 Hz, 1H), 3.87-3.76 (m, 1 H), 3.27–3.174 (m, 1 H), 2.59–2.28 (m, 2H), 2.25–2.01 (m, 3H), 1.96–1.64 (m, 6 H), 1.32–1.27 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.46 (t, *J* = 10.7, 6F), −114.21 to −114.44 (m, 4F), −121.87 (s, 4F), −122.86 (s, 4F), −123.50 (s, 4F), −126.05 to −126.17 (m, 4F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 121.3, 118.7, 115.9, 111.5, 111.2, 110.9, 74.4, 65.7, 62.6, 48.4, 28.3, 28.0, 25.5, 25.3, 25.1, 24.3, 14.4; IR (KBr) ν 3307, 2963, 1668, 1418, 1385, 1260, 1020 cm^{-1}; ESI–MS (*m/z*): 866.0 (M^+ + 1); HRMS (MALDI): *m/z*: calcd. for $C_{24}H_{21}F_{26}NO_3Na$: 888.0986; found: 888.0998 $[M + Na]^+$.

4.1.2. Bis-(2-perfluorohexyl-ethyl)-pyrrolidin-yl-methanol (**1a**) [8f]

To a mixture of 2.5 M KOH in 15 mL of MeOH and 5 mL α,α,α-trifluorotoluene was added 2-[bis-(perfluorohexyl-ethyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (740 mg, 0.9 mmol), and it was stirred and refluxed for 24 h. After removal of the organic solvent, the residue was mixed with 20 mL of water, and extracted with CH_2Cl_2 (4× 20 mL). The combined organic phases were washed with brine (2× 20 mL) and dried over anhydrous Na_2SO_4. Removal of the organic solvent gave the crude product. Column chromatography (hexane/ethyl acetate 1:2) gave the product **1a** 340 mg in 51% yield as a white solid.

Mp: 49–50 °C; $[\alpha]_D^{20}$: −6.0 (*c* = 0.6 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (t, *J* = 7.5 Hz, 1H), 3.10–3.02 (m, 1H), 2.90–2.83 (m, 1H), 2.26–1.95 (m, 4H), 1.89–1.58 (m, 10H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.81 (t, *J* = 8.46 Hz, 6F), −114.24 to −114.71 (m, 4F), −121.92 (s, 4F), −122.88 (s, 4F), −123.31 (s, 4F), −126.08 to −126.21 (m, 4F); ^{13}C NMR δ 121.7, 118.9, 118.1, 115.3, 111.0, 107.0, 71.8, 63.4, 46.9, 27.2, 26.8, 25.7, 25.5, 25.2, 24.6. IR (KBr) ν 3379, 3331, 2967, 2879, 1474, 1367, 1320, 1236, 1192, 1142, 1056 cm^{-1}; ESI–MS (*m/z*): 794.2 (M^+ + 1); elemental analysis calcd. (%) for $C_{29}H_{17}F_{26}NO$: C, 39.16; H, 1.93; N, 1.57. Found: C, 39.38; H, 2.13; N, 1.55. HRMS (MALDI): *m/z*: calcd. for $C_{21}H_{18}F_{26}NO$: 794.0949; found: 794.0968 $[M + H]^+$.

4.1.3. 1,1-Bis-(4-perfluorohexyl-phenyl)-tetrahydro-pyrrolo[1,2-c]oxazol-3-one [8d,e]

A solution of 1,4-dibromobenzene (2.45 g, 104 mmol) in dry THF (50 mL) was added over 20 min to a mixture of magnesium turnings (2.50 g, 104 mmol) and a few iodine crystals in dry THF (5 mL). This mixture was stirred at rt for 3 h before a solution of (*S*)-proline-*N*-ethyl carbamate methyl ester (8.60 g, 42 mmol) in dry THF (20 mL) was added within 20 min. After stirring for 4 h at rt, the reaction mixture was quenched with saturated NH_4Cl solution. After separation of the organic layer, the aqueous layer was extracted with ether (3× 40 mL). After drying the combined organic layers over

anhydrous Na_2SO_4 followed by evaporation of the solvent, a yellow solid was obtained. Purification by column chromatography (hexane/ethyl acetate: 10:1) gave the desired ester as a white solid. This ester (874 mg, 2 mmol) and freshly activated copper powder (576 mg, 9 mmol) was then dissolved in dry DMSO (20 mL) under N_2 atmosphere. At 120 °C, perfluorohexyl iodide (2.00 g, 6 mmol) in 10 mL of dry DMSO was added over 30 min. After stirring for 24 h at the same temperature, the reaction mixture was cooled to room temperature and diluted with 30 mL of diethyl ether. Then the mixture was filtered through a celite pad and washed with diethyl ether (4 × 40 mL), The organic layer was washed with brine (2 × 40 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate 6: 1) to give the product in 72% yield as a white solid.

mp: 123–124 °C; $[\alpha]_D^{26}$: −64.0 (c = 1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.55 (m, 8H), 4.56 (dd, J = 5.9 Hz, 11.1 Hz, 1H), 3.81–3.74 (m, 1H), 3.32–3.24 (m, 1H), 2.11–1.98 (m, 1H), 1.98–1.88 (m, 1H), 1.82–1.74 (m, 1H), 1.18-1.08 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.75 (t, J = 10.6 Hz, 6F), −110.71 to −110.87 (m, 4F), −121.45 to −121.69 (m, 8F), −122.76 (s, 4F), −126.08 (s, 4F); IR (KBr) ν 1754, 1290, 1242, 1207, 1145, 1121, 1094 cm^{-1}; ESI–MS (m/z): 916.0 (M^+ + 1); Elemental analysis calcd. (%) for $C_{30}H_{15}F_{26}NO_2$: C, 39.36; H, 1.65; N, 1.53. Found: C, 39.34; H, 1.64; N, 1.47.

4.1.4. Bis-(4-perfluorohexyl-phenyl)-pyrrolidin-yl-methanol (**1d**) [8d]

To a mixture of 2.5 M KOH in 15 mL of MeOH and 5 mL of α,α,α-trifluorotoluene was added 1,1-bis-(4-perfluorohexyl-phenyl)-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (740 mg, 0.8 mmol), and then the mixture was stirred and refluxed for 4 h. Then the mixture was concentrated under reduced pressure. The residue was mixed with water (30 mL), and extracted with CH_2Cl_2 (4× 40 mL). The organic layer was separated, washed with brine (2× 20 mL) and dried over Na_2SO_4. Removal of the organic solvent gave the product **1d** (658 mg in 92% yield) as a white solid.

mp: 99–100 °C; $[\alpha]_D^{26}$: −25.0 (c = 1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.55–7.48 (m, 4H), 4.80 (br s, 1H), 4.30 (t, J = 7.6 Hz, 1H), 3.10–2.95 (m, 2H), 1.78–1.59 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.42 (s, 6F), −111.13 (m, 4F), −122.12 ∼ −122.34 (m, 8F), −123.42 (s, 4F), −126.74 (s, 4F); IR (KBr) ν 1293, 1193, 1145, 1122, 1018 cm^{-1}; ESI–MS (m/z): 890.0 (M^+ + 1); Elemental analysis calcd. (%) for $C_{29}H_{17}F_{26}NO$: C, 39.16; H, 1.93; N, 1.57. Found: C, 39.38; H, 2.13; N, 1.55.

4.1.5. Bis-(4-perfluorooctyl-phenyl)-pyrrolidin-yl-methanol (**1e**) [8d]

White solid; mp: 112–113 °C; $[\alpha]_D^{25}$: −3.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.55–7.50 (m, 4H), 4.30 (t, J = 7.6 Hz, 1H), 3.10–2.95 (m, 2H), 1.78–1.54 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.90 (t, J = 10.6 Hz, 6F), −110.52 to −110.74 (m, 4F), −121.41 to −121.66 (m, 4F), −122.19 to −122.66 (m, 12F), −122.96 (s, 4F), −126.13 to −126.32 (m, 4F); IR (KBr) ν 3389, 1301, 1202, 1150, 1116, 1091 cm^{-1}.

4.1.6. α,α-Bis-(4-trifuloromethylphenyl)-L-prolinol (**1b**) [8a]

White solid; mp: 84–85 °C; $[\alpha]_D^{25}$: −51.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48–1.56 (m, 2H), 1.64–1.71 (m, 2H), 2.89–2.96 (m, 2H), 4.23 (t, J = 7.6 Hz, 1H), 7.46–7.56 (m, 6H), 7.62–7.64 (m, 2H); IR (KBr) ν 3360, 2927, 2855, 1616, 1461, 1415, 1325, 1165, 1125, 1069, 1018, 907, 837 cm^{-1}.

4.1.7. α,α-Bis-(3,5-ditrifuloromethylphenyl)-L-prolinol (**1c**)

White solid; mp: 117–118 °C; $[\alpha]_D^{26}$: −51.0 (c = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51–1.63 (m, 2H), 1.75-1.82 (m, 2H), 3.04–3.08 (m, 2H), 4.35 (t, J = 7.6 Hz, 1H), 5.07 (b, 1H), 7.77 (s, 2H), 7.96 (s, 2H), 8.04 (s, 2H), IR (KBr) ν 3356, 2949, 2871, 1604, 1463, 1370, 1279, 1173, 1139, 1035, 901, 845 cm^{-1}.

4.2. Typical procedure for the asymmetric epoxidation of α,β-enones

To a solution of the α,β-enone **2a** (21 mg, 0.1 mmol) and the catalyst **1e** (32 mg, 30 mol%) in CCl_4 (0.5 mL) was added TBHP (0.13 mmol, 25 uL) at room temperature. The mixture was stirred for the indicated time. After evaporation of the solvent, the reaction mixture was dissolved in hot methanol (1 mL) and then was kept at −5 °C for 24 h. Then the supernatant layer was removed by syringe. The residue was washed with cold methanol and dried under vacuum at room temperature to give the catalyst **1e** as a white solid 24 mg, in 74% recovery yield. The organic solvent was removed under vacuum, and the residue was purified by flash chromatography on silia gel (petroleum ether: diethyl ether 40: 1) to give the pure epoxide **3a** 13 mg in 65% yield.

4.2.1. trans-(2R,3S)-Epoxy-1,3-diphenyl-propan-1-one (**3a**) [9a,b]

$[\alpha]_D^{26}$: −132.0 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 1H), 4.23 (s, 1 H), 7.32-7.45 (m, 7H), 7.54 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 7.8 Hz, 2H). HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 16.6 min (2*S*,3*R*), t_R = 17.8 min (2*R*,3*S*).

4.2.2. trans-(2R,3S)-Epoxy-3-(4-chlorophenyl)-1-phenyl-propan-1-one (**3b**) [9a]

$[\alpha]_D^{26}$: −181.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 1H), 4.27 (s, 1H), 7.26–7.38 (m, 4H), 7.51–7.53 (m, 2H), 7.65 (t, J = 7.8 Hz, 1H), 8.01 (dd, J = 7.8, 1.2 Hz, 2H). HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 55: 1 hexane: *i*-PrOH, 0.75 mL/min; t_R = 50.5 min (2*S*,3*R*), t_R = 53.6 min (2*R*,3*S*).

4.2.3. trans-(2R,3S)-Epoxy-3-(4-methylphenyl)-1-phenyl-propan-1-one (**3c**) [9]

$[\alpha]_D^{26}$: −170.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (d, J = 1.6 Hz, 1H), 4.31 (d, J = 1.7 Hz, 1H),

7.21–7.29 (m, 4H), 7.49 (t, J = 7.5 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 8.00 (dd, J = 8.1, 1.2 Hz, 2H). HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 0.50 mL/min; t_R = 15.6 min (2*S*,3*R*), t_R = 17.1 min (2*R*,3*S*).

*4.2.4. trans-(2R,3S)-Epoxy-3-(4-nitrophenyl)-1-phenyl-propan-1-one (**3d**) [9a]*

$[\alpha]_D^{26}$: −74.0 (c = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 1H), 4.29 (s, 1H), 7.50–7.66 (m, 5H), 8.02 (d, J = 7.8 Hz, 2H); 8.28 (d, J = 8.1 Hz, 1H). HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 46.2 min (2*S*,3*R*), t_R = 59.5 min (2*R*,3*S*).

*4.2.5. trans-(2R,3S)-Epoxy-3-(4-methylphenyl)-1-(4-chlorophenyl)-propan-1-one (**3e**) [7c]*

$[\alpha]_D^{26}$: −148.0 (c = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.04 (d, J = 1.8 Hz, 1H), 4.24 (d, J = 2.1 Hz, 1H), 7.21–7.27 (m, 4H), 7.46 (dd, J = 7.0, 1.8 Hz, 2H), 7.96 (dd, J = 6.6, 2.1 Hz, 2H). HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 17.1 min (2*R*,3*S*), t_R = 19.3 min (2*S*,3*R*).

*4.2.6. trans-(2R,3S)-Epoxy-3-(4-chlorophenyl)-1-(4-methoxylphenyl)-propan-1-one (**3f**) [8a]*

$[\alpha]_D^{26}$: −105.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.05 (s, 1H), 4.21 (s, 1H), 6.96 (d, J = 8.7 Hz, 2H); 7.29-7.39 (m, 4H), 8.00 (d, J = 7.8 Hz, 2H). HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 34.0 min (2*S*,3*R*), t_R = 43.1 min (2*R*,3*S*).

*4.2.7. trans-(2R,3S)-Epoxy-1,3-bis-(4-chlorophenyl)-propan-1-one (**3g**) [9a]*

$[\alpha]_D^{26}$: −153 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 1H), 4.19 (s, 1H), 7.26–7.40 (m, 4H), 7.47 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H). HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 19.4 min (2*S*,3*R*), t_R = 21.9 min (2*R*,3*S*).

*4.2.8. trans-(2R,3S)-Epoxy-3-phenyl-1-furan-2yl-propan-1-one (**3h**) [9c]*

$[\alpha]_D^{26}$: −151.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (d, J = 1.8, 2H), 6.6 (dd, J = 3.6, 1H), 7.35-7.41 (m, 5H), 7.46 (d, 1H), 7.68 (dd, J = 1.8, 1H). HPLC separation conditions: Chiralcel AD, 20 °C, 254nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 24.8 min (2*S*,3*R*), t_R = 27.3 min (2*R*,3*S*).

*4.2.9. trans-(2R,3S)-Epoxy-3-phenyl-1-(4-chlorophenyl)-propan-1-one (**3i**) [9a]*

$[\alpha]_D^{26}$: −151.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (d, J = 1.8 Hz, 1H), 4.25 (d, J = 1.5 Hz, 1H), 7.37-7.49 (m, 7H), 7.96–7.99 (m, 2H). HPLC separation conditions: Chiralcel OJ, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 26.0 min (2*R*,3*S*), t_R = 31.4 min (2*S*,3*R*).

*4.2.10. trans-(2R,3S)-Epoxy-3-phenyl-1-(4-bromophenyl)-propan-1-one (**3j**) [7a,9b]*

$[\alpha]_D^{26}$: −139.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 1H), 4.23 (s, 1H), 7.26–7.40 (m, 5H), 7.63 (d, J = 7.5 Hz, 2H), 7.96 (d, J = 6.9 Hz, 2H). HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 95: 5 hexane: *i*-PrOH, 0.75 mL/min; t_R = 35.3 min (2*R*,3*S*), t_R = 38.1 min (2*S*,3*R*).

*4.2.11. trans-(2R,3S)-Epoxy-3-phenyl-1-(4-methoxylphenyl)-propan-1-one (**3k**) [9a]*

$[\alpha]_D^{24}$: −184.0 (c = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88(s, 3H), 4.07 (s, 1H), 4.26 (s, 1H), 6.96 (d, J = 7.8 Hz, 2H); 7.39 (s, 5H), 8.02 (d, J = 8.1 Hz, 2H). HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 1.00 mL/min; t_R = 31.4 min (2*S*,3*R*), t_R = 33.3 min (2*R*,3*S*).

*4.2.12. trans-(2R,3S)-Epoxy-3-phenyl-1-(4-fluorophenyl)-propan-1-one (**3l**) [9a]*

$[\alpha]_D^{26}$: −102.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 1H), 4.17 (s, 1H), 7.10 (t, J = 8.4 Hz, 2H), 7.33 (s, 5H), 7.80 (t, J = 6.4 Hz, 2H). HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 90: 10 hexane: *i*-PrOH, 0.60 mL/min; t_R = 22.8 min (2*R*,3*S*), t_R = 27.8 min (2*S*,3*R*).

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