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Hydroxytetraphenylenes as Chiral Ligands: Application to Asymmetric Darzens Reaction of Diazoacetamide with Aldehydes

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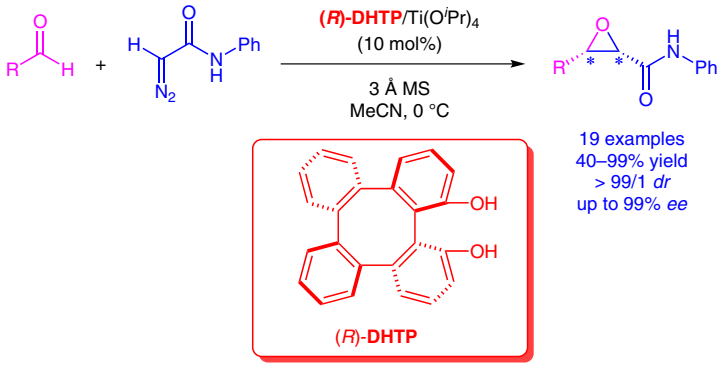
Dedicated to Professor Dr. Dieter Enders on the occasion of his 70th birthday.



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Abstract Hydroxytetraphenylenes with rigid conformations are potential candidates for employment as chiral ligands in asymmetric synthesis. Highly diastereo- and enantioselective Darzens reactions between aldehydes and diazo-*N*,*N*-dimethylacetamide were found to be catalyzed by a chiral titanium complex formed in situ from $Ti(O^iPr)_4$ and chiral 1,16-dihydroxytetraphenylene, leading to the formation of *cis*-glycidic amides in moderate to high yields with excellent enantiomeric purities (40–99% yield, up to 99% ee).

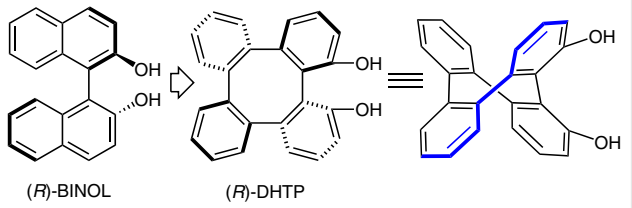
Key words asymmetric catalysis, tetraphenylene, chiral ligand, Darzens reaction, diazoacetamide

Over past decades, the area of asymmetric catalysis has continued to evolve at an accelerating speed.[1] Numerous chiral catalytic systems and a wide range of enantioselective transformations were developed in these endeavors. Despite significant advances, this field still lacks privileged chiral skeletons that highly match substrates and ligands like those host-guest interactions in enzymes. Furthermore, the structural features of these ligands responsible for reactivity and selectivity are not immediately clear. However, some trends can still be discerned. For instance, the 1,1′-binaphthyl skeleton is one of the most successful platforms in asymmetric catalysis, which could be ascribed to its structure with C_2-symmetry. In this regard, tetraphenylene was determined to be a non-planar molecule, featuring a distinct saddle-shaped framework.[2] The saddle-shaped geometry of tetraphenylene has been proved to be very rigid and stable, which was confirmed by the high-energy barrier to inversion by neutron diffraction studies as well as thermal experiments.[3] With this geometric rigidity, studies of tetraphenylene derivatives have led to their applications in asymmetric catalysis. In 2005, Wong reported phosphoramidites based on the tetraphenylene skeleton as chiral ligands in asymmetric hydrogenation, the α-acylaminoacrylates derivatives were hydrogenated in quantitative yields with excellent enantioselectivities of 94–99% ee.[4] Furthermore, tetraphenylene-based organocatalysts were also used in [4+2] cycloaddition between anthrone and maleimides by the Wong group.[5]

The asymmetric Darzens reaction is a powerful synthetic method to realize optically pure epoxides that have wide utilization in organic synthesis. Several elegant methods concerning the Darzens reaction are known to produce α,β-epoxycarbonyl compounds.[6–13] Earlier catalytic systems included phase-transfer catalysts of chiral quaternary cinchonium salts,[6] chiral crown ethers,[7] and a bis-ammonium salt derived from BINOL.[8] Chiral sulfur ylides were also employed to promote the Darzens reaction with or without metals.[9] In 2008, the research groups of Wulff and Maruoka reported axially chiral Brønsted acids in the asymmetric aziridination of diazoacetamides and imines, respectively.[10] North and co-workers utilized salen ligands in combination with various metals as Lewis acid catalysts to provide epoxy esters with moderate diastereoselectivities and enantioselectivities.[11] In 2009, Gong reported that dihydroxyl ligands of BINOL, in combination with titanium or zirconium metal, catalyzed the enantioselective Darzens reaction between diazoacetamides and aldehydes with excellent results.[12] Later, Sun screened various diol–Ti complexes in the asymmetric Darzens reaction, and noted that excellent enantioselectivity was achieved by the (+)-pinanediol ligand.[13]

In order to study the potential applications of tetraphenylenes, we recently reported several strategies to produce enantiopure hydroxytetraphenylenes.[2] In this connection, we describe herein the synthesis of 1,16-dihydroxytetraphenylenes (DHTP) as chiral ligands (Scheme 1).[14] The use of an (*R*)-DHTP/titanium(IV) complex as a chiral catalytic system in the asymmetric Darzens reaction between

diazoacetamides and aldehydes indeed led to the formation of epoxides in good yields with excellent enantioselectivities.



Scheme 1 Concept and design of chiral hydroxytetraphenylenes

As shown in Scheme 2, starting from the bis-pinacol ester of biphenyl-2,2′-diboronic acid (**1**)[15] and 2,2′-diiodo-6,6′-dimethoxybiphenyl (**2**),[16] the construction of 1,16-dimethoxytetraphenylene (**3**) was readily achieved by palladium-catalyzed double Suzuki reaction according to our recent report.[17] Next, demethylation by boron tribromide generated 1,16-dihydroxytetraphenylene (**4**) in an excellent yield of 98%. Resolution of racemic **4** was thus efficiently carried out by the use of a chiral stationary phase column (Daicel Chiralpak AD-H) on a preparative scale, giving both (*R*)-DHTP and (*S*)-DHTP in enantiomerically pure forms. The absolute configuration of (*R*)-DHTP (**L1**) and (*S*)-DHTP (**L2**) was determined by comparison of their optical rotations with known samples.[14] It is noteworthy that the synthesis of chiral 1,8,9,16-tetrahydroxytetraphenylenes [(*R*,*R*)- and (*S*,*S*)-THTP, viz. **L3** and **L4**] was also achieved according to our previous report (see Supporting Information).[18] Furthermore, chiral ligand **L5** was prepared via a double etherification reaction according to the literature procedure (see Supporting Information).[5]

With these hydroxytetraphenylenes **L1**–**L5** in hand, asymmetric Darzens reaction employing these chiral ligands was then assessed (Figure 1). Initially, we explored the Darzens reaction of diazo-*N*,*N*-dimethylacetamide (**6**) with benzaldehyde (**5a**) as a model reaction in dichloromethane at 0 °C by using 10 mol% of the titanium complex, which formed in situ between **L1**–**L5** and $Ti(O^iPr)_4$. Encouragingly, the reaction proceeded smoothly to generate *cis*-glycidic amide **7a** in 79% yield with 95% ee (Table 1, entry 1) by using a complex of **L1**/Ti(IV) (2:1) as the chiral catalyst. It is worth noting that this reaction exhibited excellent diastereoselectivities and the *trans*-diastereomer was not detectable by ^1H NMR spectroscopic analysis of the crude product. Additional studies on the stoichiometry of **L1** and $Ti(O^iPr)_4$ revealed that tuning the ratio of **L1**/$Ti(O^iPr)_4$ from 2:1 to 1:1 led to a slightly decreased enantioselectivities (Table 1, entries 2–4). Furthermore, we found that molecular sieves as additives had a positive effect on the yields of the desired products (Table 1, entries 5–7). Thus, the presence of 3-Å molecular sieves led to a higher yield and without obviously decreasing the enantioselectivity (Table 1,

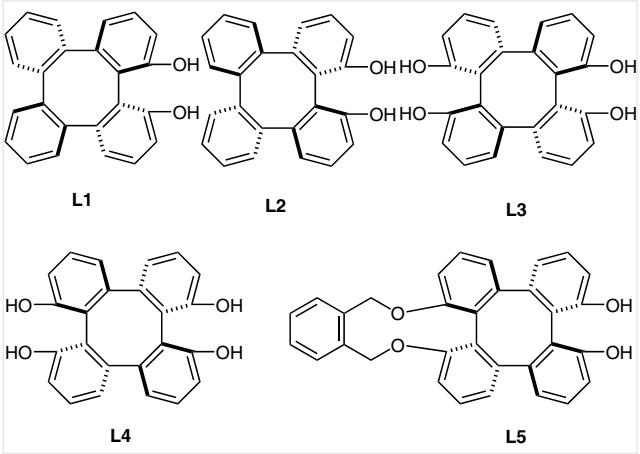
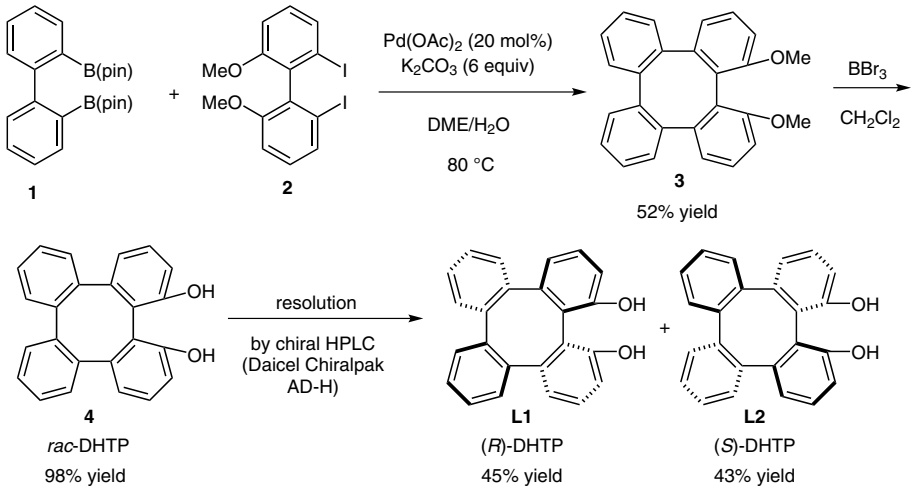
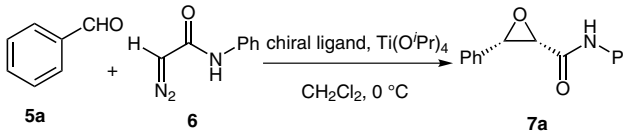


Figure 1 Chiral hydroxytetraphenylenes employed in asymmetric Darzens reaction



Scheme 2 Synthesis of (*R*)-DHTP and (*S*)-DHTP

Table 1 Screening the Reaction Conditions for Asymmetric Darzens Reaction[a]



5a 6 7a

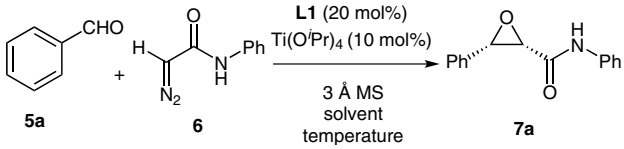
Entry	Ligand	Ratio ligand/Ti	Additive	Yield[b] (%)	ee (%)[c]
1	**L1**	2.0:1	none	79	95 (*S*,*S*)
2	**L1**	1.5:1	none	75	93 (*S*,*S*)
3	**L1**	1.2:1	none	87	91 (*S*,*S*)
4	**L1**	1.0:1	none	87	77 (*S*,*S*)
5	**L1**	1.5:1	4 Å MS	92	91 (*S*,*S*)
6	**L1**	1.5:1	3 Å MS	89	93 (*S*,*S*)
7	**L1**	1.5:1	5 Å MS	89	90 (*S*,*S*)
8	**L1**	2.0:1	3 Å MS	83	95 (*S*,*S*)
9	**L3**	1.0:1	none	47	65 (*S*,*S*)
10	**L4**	1.0:1	none	84	–68 (*R*,*R*)[d]
11	**L4**	2.0:1	none	52	–57 (*R*,*R*)[d]
12	**L5**	2.0:1	none	55	–68 (*R*,*R*)[d]

[a] *Reaction conditions*: **5a** (0.24 mmol), **6** (0.2 mmol), $Ti(O^iPr)_4$ (0.02 mmol), CH_2Cl_2 (2 mL), 0 °C, 12–24 h; under an argon atmosphere.
[b] Isolated yield.
[c] The ee values were determined by HPLC analysis using a chiral column.
[d] Opposite configuration of **7a** was obtained.

entry 1 vs entry 8). An evaluation of titanium(IV) complexes formed by different hydroxytetraphenylenes **L3**–**L5** showed that the **L1**/Ti(IV) complex was the most efficient catalyst, offering the highest enantioselectivity while the complexes of **L3**–**L5** only afforded **7a** in moderate ee values. The relative and absolute configurations of the products were determined by both specific rotation values and high performance liquid chromatography (HPLC) data in comparison with their respective literature values.[12]

Subsequently, in order to enhance ee value of the desired product **7a**, we started to screen solvents. As shown in Table 2, halogenated solvents such as dichloromethane, chloroform, and 1,2-dichloroethane gave yields in the range of 83–91% and enantioselectivities of 92–95% (Table 2, entries 1–3). Non-polar solvent such as toluene provided a sluggish reaction, although the enantioselectivity remained at 90% ee (Table 2, entry 4). Diethyl ether increased both the yield and enantioselectivity (95% yield with 97% ee) while tetrahydrofuran only gave an ee value of 85% (Table 2, entries 5 and 6). A much lower yield of 6% with a moderate ee of 65% was observed when methanol was used as the solvent (Table 2, entry 7). Fortunately, a polar solvent, namely acetonitrile, afforded the best yield of 95% with an excellent enantioselectivity of 98% ee (Table 2, entry 8). Consequently, an investigation of the temperature effect on the reaction performance was carried out in acetonitrile. It was found that the temperature of 0 °C resulted in the highest level of yield and enantioselectivity (Table 2, entries 8–10).

Table 2 Effect of Solvent and Temperature on the Asymmetric Darzens Reaction[a]



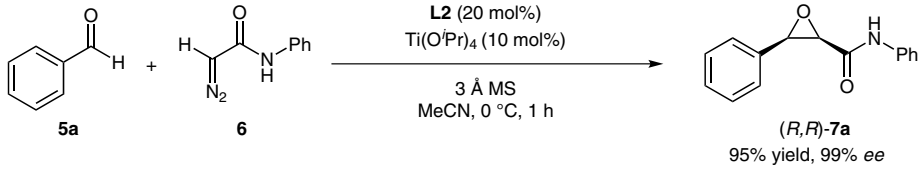
5a 6 7a

Entry	Solvent	Time (h)	Temp (°C)	Yield[b] (%)	ee (%)[c]
1	CH_2Cl_2	12	0	83	95
2	$CHCl_3$	10	0	89	92
3	DCE	10	0	91	95
4	toluene	25	0	64	90
5	Et_2O	10	0	95	97
6	THF	20	0	93	85
7	MeOH	48	0	6	65
8	MeCN	1	0	95	98
9	MeCN	1	25	92	98
10	MeCN	5	–20	92	96

[a] Reaction conditions: **5a** (0.24 mmol), **6** (0.2 mmol), **L1** (0.04 mmol), $Ti(O^iPr)_4$ (0.02 mmol), solvent (2 mL), 3-Å MS (200 mg); under an argon atmosphere.
[b] Isolated yield.
[c] The ee values were determined by HPLC analysis using a chiral column.

Moreover, (*R*,*R*)-**7a** was obtained in high yield with excellent enantioselectivity (95% yield, 99% ee) when **L2** (*S*)-DHTP) was used as the chiral ligand (Scheme 3).

Under the optimized reaction conditions, we then explored the substrate scope of aldehydes in Darzens reaction (Table 3). Benzaldehyde derivatives bearing electron-withdrawing substituents at either *para* or *meta* positions pro-



5a 6 (*R*,*R*)-**7a**
95% yield, 99% *ee*

Scheme 3 Synthesis of (*R*,*R*)-**7a**. *Reagents and conditions*: **5a** (0.24 mmol), **6** (0.2 mmol), **L2** (0.04 mmol), $Ti(O^iPr)_4$ (0.02 mmol), MeCN (2 mL), 0 °C, 3 Å MS (200 mg) under an argon atmosphere.

vided *cis*-epoxides in good yields of 88–99% with excellent enantioselectivities (95–99% ee; Table 3, entries 2–5). However, in the case of *p*-fluorobenzaldehyde, the product was obtained in 78% yield with a moderate ee value of 70% (Table 3, entry 6). Electronically rich and neutral aromatic aldehydes were also employed in the Darzens reaction, affording the desired products **7g–l** in moderate to good yields with excellent enantioselectivities (Table 3, entries 7–12). Interestingly, the heteroaromatic aldehyde **5m** was also tolerated in this reaction with the yield of 88% and excellent ee value of 99% (Table 3, entry 13). The extension of the substrate scope to aliphatic aldehydes including linear and branched aliphatic aldehydes was also rather successful, giving the glycidic amides **7n–s** in 41–95% yields with 80–99% ee (Table 3, entries 14–19).

Table 3 Reaction Scope for Asymmetric Darzens Reaction[a]

Entry	R	Product	Yield[b] (%)	ee (%)[c]
1	Ph	**7a**	95	98
2	4-$O_2NC_6H_4$	**7b**	99	99
3	3-$O_2NC_6H_4$	**7c**	88	98
4	4-ClC_6H_4	**7d**	91	95
5	4-BrC_6H_4	**7e**	87	98
6	4-FC_6H_4	**7f**	78	70
7	4-MeC_6H_4	**7g**	83	96
8	3-MeC_6H_4	**7h**	60	74
9	2-MeC_6H_4	**7i**	40	92
10	3-$MeOC_6H_4$	**7j**	92	97
11	2-naphthyl	**7k**	75	99
12	1-naphthyl	**7l**	72	98
13	pyridin-2-yl	**7m**	88	99
14	Cy	**7n**	41	80
15	Pr	**7o**	92	99
16	^iPr	**7p**	56	98
17	C(Et)=CH_2	**7q**	95	98
18	Bn	**7r**	66	98
19	CH_2CH_2Ph	**7s**	94	97

[a] Reaction conditions: **5** (0.24 mmol), **6** (0.2 mmol), **L1** (0.04 mmol), $Ti(O^iPr)_4$ (0.02 mmol), MeCN (2 mL), 0 °C, 3 Å MS (200 mg), 1–24 h; under an argon atmosphere.
[b] Isolated yield.
[c] The ee values were determined by HPLC analysis using a chiral column.

In conclusion, we disclose in this article an asymmetric Darzens reaction between aldehydes and diazo-*N*,*N*-dimethylacetamide by using a chiral Lewis acid catalyst formed in particular from (*R*)-DHTP and titanium(IV) isopropoxide, solely giving *cis*-glycidic amides in good yields with excellent enantioselectivities. This protocol tolerated a broad range of structurally diverse aldehydes, including aromatic, unsaturated, and aliphatic aldehydes. The current protocol provides an important alternative to prepare epoxy amides with high enantiomeric purity. It is believed that the chiral hydroxytetraphenylenes will be suitable for the preparation of more catalysts and a wide range of catalytic asymmetric reactions will be discovered by using these catalytic systems. The studies in this direction are underway in our laboratories.

All reactions were carried out under an atmosphere of argon and solvents were dried according to established procedures. Schlenk tubes were all flamed and cooled before use. All reagents were purchased from J&K or Aldrich Co., Ltd. Benzaldehyde, butyraldehyde, and isobutyraldehyde were distilled before use. Other aldehydes were used without further purification. Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). HPLC analysis was performed on a DIONEX UltiMate 3000, NO.8074238, ThermoScientific. Chiral HPLC data for the epoxidation products could be obtained using a Chiralcel OD or Chiralpak AD-H column. These chiral columns were purchased from Daicel Chemical Industries, Ltd. Optical rotations were measured on an Autopol I polarimeter. ^1H and ^{13}C NMR spectra were measured with Agilent 400 (400 MHz) spectrometer and Agilent 500 (500 MHz) (samples in $CDCl_3$ with TMS as the internal standard). LR-MS were recorded with Agilent GC-MS 5975C, or Agilent 1100 LC-MSD SL. All melting points were determined using a digital melting point apparatus and are uncorrected. The starting diazo-*N*,*N*-dimethylacetamide was prepared according to reported procedures.[13]

Asymmetric Darzens Reactions; General Procedure

To a 25-mL Schlenk tube equipped with a magnetic stirrer, in which the air was replaced by argon, was added (*R*)-DHTP (13.4 mg, 0.04 mmol), MeCN (2 mL), and $Ti(O^iPr)_4$ (6 μL, 0.02 mmol). The mixture was stirred at r.t. for 1 h. Then 3-Å molecular sieves (200 mg) were added. The resulting orange solution was cooled to 0 °C, and then aldehyde (0.24 mmol) and diazoacetamide (0.2 mmol) were introduced into the reaction system under an argon atmosphere. The mixture was stirred at 0 °C. After completion of the reaction (monitored by TLC), H_2O (0.1 mL) was added to the mixture to quench the reaction. After evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 15:1–1:1) to yield pure products.

N,3-Diphenyloxirane-2-carboxamide (7a)

Flash column chromatography (petroleum ether/EtOAc, 5:1); colorless solid; yield: 46 mg (95%); mp 104–105 °C (Lit.[12a] 101–103 °C); 98% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 80:20, flow rate 1.0 mL/min, T = 30 °C, 214 nm): t_R = 14.70 (major), 12.16 min (minor)]; $[\alpha]_D^{27}$ +18.6 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (br s, 1 H), 7.42–7.40 (m, 2 H), 7.34–7.27 (m, 3 H), 7.23–7.14 (m, 4 H), 7.07–7.03 (m, 1 H), 4.43 (d, *J* = 4.8 Hz, 1 H), 3.92 (d, *J* = 4.8 Hz, 1 H).

LRMS (ESI): *m*/*z* = 240.1 [$C_{15}H_{13}NO_2$ + H]$^+$, 262.1 [$C_{15}H_{13}NO_2$ + Na]$^+$.

3-(4-Nitrophenyl)-*N*-phenyloxirane-2-carboxamide (7b)

Flash column chromatography (petroleum ether/EtOAc, 2:1); yellowish solid; yield: 56 mg (99%); mp 170–172 °C (Lit.[12a] 166–169 °C); 99% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 15.67 (major), 8.39 min (minor)]; $[\alpha]_D^{27}$ +49.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2 H), 7.61–7.58 (br s, 1 H), 7.60 (d, *J* = 8.7 Hz, 2 H), 7.23–7.20 (m, 4 H), 7.10–7.06 (m, 1 H), 4.47 (d, *J* = 5.2 Hz, 1 H), 4.01 (d, *J* = 4.8 Hz, 1 H).

LRMS (ESI): *m*/*z* = 285.1 [$C_{15}H_{12}N_2O_4$ + H]$^+$, 307.1 [$C_{15}H_{12}N_2O_4$ + Na]$^+$.

3-(3-Nitrophenyl)-*N*-phenyloxirane-2-carboxamide (7c)

Flash column chromatography (petroleum ether/EtOAc, 4:1); colorless solid; yield: 50 mg (88%); mp 152–154 °C (Lit.[13] 146–147 °C); 98% ee [HPLC (Daicel Chiralpak AD-H, *n*-hexane/^{i}PrOH, 60:40, flow rate = 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 10.81 (major), 8.73 min (minor)]; $[\alpha]_D^{27}$ +16.7 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 8.15–8.12 (m, 1 H), 7.75–7.70 (m, 2 H), 7.53–7.49 (t, *J* = 8.0 Hz, 1 H), 7.25–7.20 (m, 4 H), 7.09–7.06 (m, 1 H), 4.48 (d, *J* = 4.8 Hz, 1 H), 4.01 (d, *J* = 4.8 Hz, 1 H).

LRMS (ESI): *m*/*z* = 285.1 [$C_{15}H_{12}N_2O_4$ + H]$^+$, 307.0 [$C_{15}H_{12}N_2O_4$ + Na]$^+$.

3-(4-Chlorophenyl)-*N*-phenyloxirane-2-carboxamide (7d)

Flash column chromatography (petroleum ether/EtOAc, 4:1); colorless solid; yield: 50 mg (91%); mp 136–138 °C (Lit.[12a] 141–143 °C); 95% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 9.94 (major), 7.24 min (minor)]; $[\alpha]_D^{27}$ +23.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (br s, 1 H), 7.35–7.21 (m, 8 H), 7.10–7.06 (m, 1 H), 4.38 (d, *J* = 4.8 Hz, 1 H), 3.92 (d, *J* = 4.8 Hz, 1 H).

LRMS (ESI): *m*/*z* = 274.1 [$C_{15}H_{12}ClNO_2$ + H]$^+$, 296.0 [$C_{15}H_{12}ClNO_2$ + Na]$^+$.

3-(4-Bromophenyl)-*N*-phenyloxirane-2-carboxamide (7e)

Flash column chromatography (petroleum ether/EtOAc, 3:1); colorless solid; yield: 55 mg (87%); mp 170–172 °C (Lit.[12a] 167–169 °C); 98% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 254 nm): t_R = 10.74 (major), 7.49 min (minor)]; $[\alpha]_D^{27}$ +22.0 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (br s, 1 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.29–7.21 (m, 6 H), 7.10–7.06 (m, 1 H), 4.35 (d, *J* = 4.8 Hz, 1 H), 3.92 (d, *J* = 4.8 Hz, 1 H).

LRMS (ESI): *m*/*z* =318.0 [$C_{15}H_{12}BrNO_2$ + H]$^+$, 341.9 [$C_{15}H_{12}BrNO_2$ + Na]$^+$.

3-(4-Fluorophenyl)-*N*-phenyloxirane-2-carboxamide (7f)

Flash column chromatography (petroleum ether/EtOAc, 3:1); colorless solid; yield: 40 mg (78%); mp 114–116 °C (Lit.[12a] 106–108 °C); 70% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 254 nm): t_R = 8.83 (major), 7.02 min (minor)]; $[\alpha]_D^{27}$ +9.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (br s, 1 H), 7.37–7.35 (m, 2 H), 7.24–7.16 (m, 4 H), 7.07–6.97 (m, 3 H), 4.36 (d, *J* = 4.8 Hz, 1 H), 3.90 (d, *J* = 4.4 Hz, 1 H).

LRMS (ESI): *m*/*z* = 258.1 [$C_{15}H_{12}FNO_2$ + H]$^+$.

N-Phenyl-3-*p*-tolyloxirane-2-carboxamide (7g)

Flash column chromatography (petroleum ether/EtOAc, 5:1); colorless solid; yield: 42 mg (83%); mp 130–132 °C (Lit.[13] 127–128 °C); 96% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 9.41 (major), 7.42 min (minor)]; $[\alpha]_D^{27}$ +24.2 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (br s, 1 H), 7.29–7.20 (m, 6 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.07–7.04 (m, 1 H), 4.39 (d, *J* = 4.8 Hz, 1 H), 3.90 (d, *J* = 4.8 Hz, 1 H), 2.28 (s, 3 H).

LRMS (ESI): *m*/*z* = 254.1 [$C_{16}H_{15}NO_2$ + H]$^+$, 276.1 [$C_{16}H_{15}NO_2$ + Na]$^+$.

N-Phenyl-3-*m*-tolyloxirane-2-carboxamide (7h)

Flash column chromatography (petroleum ether/EtOAc, 5:1); colorless solid; yield: 30 mg (60%); mp 103–106 °C; 74% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 8.40 (major), 7.34 min (minor)]; $[\alpha]_D^{27}$ +19.6 (*c* 1.00, CH_2Cl_2).

IR (KBr): 3333, 1673, 1595, 1520, 1442, 804, 775, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (br s, 1 H), 7.24–7.16 (m, 7 H), 7.08–7.04 (m, 2 H), 4.40 (d, *J* = 4.8 Hz, 1 H), 3.91 (d, *J* = 4.8 Hz, 1 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 138.4, 136.1, 132.7, 129.6, 129.0, 128.6, 127.1, 125.0, 123.5, 120.3, 58.8, 56.7, 21.4 (two carbons overlapped).

LRMS (ESI): *m*/*z* = 254.1 [$C_{16}H_{15}NO_2$ + H]$^+$, 276.0 [$C_{16}H_{15}NO_2$ + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}O_2N$: 254.1176; found: 254.1175.

N-Phenyl-3-*o*-tolyloxirane-2-carboxamide (7i)

Flash column chromatography (petroleum ether/EtOAc, 5:1); colorless solid; yield: 20 mg (40%); mp 90–92 °C; 92% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 8.57 (major), 8.09 min (minor)]; $[\alpha]_D^{27}$ +38.0 (*c* 1.00, CH_2Cl_2).

IR (KBr): 3302, 2923, 1667, 1598, 1547, 1443, 756, 712, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2 H), 7.20–7.08 (m, 7 H), 7.05–7.01 (m, 1 H), 4.37 (d, *J* = 4.5 Hz, 1 H), 3.99 (d, *J* = 4.5 Hz, 1 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 136.8, 136.0, 131.4, 130.4, 129.0, 128.7, 125.9, 125.8, 124.9, 120.4, 58.3, 56.4, 18.8.

LRMS (ESI): *m*/*z* = 254.1 [$C_{16}H_{15}NO_2$ + H]$^+$, 276.0 [$C_{16}H_{15}NO_2$ + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}O_2N$: 254.1176; found: 254.1175.

3-(3-Methoxyphenyl)-*N*-phenyloxirane-2-carboxamide (7j)

Flash column chromatography (petroleum ether/EtOAc, 3:1); colorless solid; yield: 50 mg (92%); mp 100–101 °C (Lit.[12a] 104–108 °C); 97% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, *T* = 30 °C, 214 nm): t_R = 9.99 (major), 8.57 min (minor)]; $[\alpha]_D^{27}$ +24.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (br s, 1 H), 7.25–7.18 (m, 5 H), 7.08–7.04 (m, 1 H), 6.99 (d, *J* = 7.6 Hz, 1 H), 6.94 (s, 1 H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 1 H), 4.40 (d, *J* = 4.8 Hz, 1 H), 3.90 (d, *J* = 4.8 Hz, 1 H), 3.73 (s, 3 H).

LRMS (ESI): *m*/*z* = 270.1 [$C_{16}H_{15}NO_3$ + H]$^+$, 292.0 [$C_{16}H_{15}NO_3$ + Na]$^+$.

3-(Naphthalen-2-yl)-*N*-phenyloxirane-2-carboxamide (7k)

Flash column chromatography (petroleum ether/ EtOAc, 4:1); colorless solid; yield: 43 mg (75%); mp 148–150 °C (Lit.[12a] 143–145 °C); 99% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, T = 30 °C, 214 nm): t_R = 12.23 (major), 9.55 min (minor)]; $[\alpha]_D^{27}$ +33.5 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.80–7.76 (m, 3 H), 7.63 (br s, 1 H), 7.50–7.43 (m, 3 H), 7.15–7.08 (m, 4 H), 7.00–6.96 (m, 1 H), 4.57 (d, J = 4.8 Hz, 1 H), 4.00 (d, J = 4.8 Hz, 1 H).

LRMS (ESI): m/z = 290.1 $[C_{19}H_{15}NO_2 + H]^+$, 312.1 $[C_{19}H_{15}NO_2 + Na]^+$.

3-(Naphthalen-1-yl)-N-phenyloxirane-2-carboxamide (7l)

Flash column chromatography (petroleum ether/EtOAc, 5:1); colorless solid; yield: 41 mg (72%); mp 142–145 °C (Lit.[12a] 153–158 °C); 98% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 60:40, flow rate 0.7 mL/min, T = 30 °C, 214 nm): t_R = 11.33 (major), 8.56 min (minor)]; $[\alpha]_D^{27}$ +125.4 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.4 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.61–7.50 (m, 3 H), 7.44–7.36 (m, 2 H), 7.14–7.10 (m, 2 H), 7.02–6.96 (m, 3 H), 4.80 (d, J = 4.4 Hz, 1 H), 4.16 (d, J = 4.4 Hz, 1 H).

LRMS (ESI): m/z = 290.1 $[C_{19}H_{15}NO_2 + H]^+$, 312.1 $[C_{19}H_{15}NO_2 + Na]^+$.

***N*-Phenyl-3-(pyridin-2-yl)oxirane-2-carboxamide (7m)**[12a]

Flash column chromatography (petroleum ether/EtOAc, 1:1); colorless oil, yield: 42 mg (88%); 99% ee [HPLC (Daicel Chiralpak OD, hexane/^{i}PrOH, 80:20, flow rate 0.7 mL/min, T = 30 °C, 254 nm): t_R = 17.04 (major), 24.22 min (minor)]; $[\alpha]_D^{27}$ +67.3 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (br s, 1 H), 8.58 (d, J = 4.8 Hz, 1 H), 7.67 (dt, J = 1.5, 7.5 Hz, 1 H), 7.45–7.41 (m, 3 H), 7.29–7.20 (m, 3 H), 7.08–7.05 (m, 1 H), 4.40 (d, J = 4.5 Hz, 1 H), 3.97 (d, J = 4.5 Hz, 1 H).

LRMS (ESI): m/z = 241.1 $[C_{14}H_{12}N_2O_2 + H]^+$.

3-Cyclohexyl-*N*-phenyloxirane-2-carboxamide (7n)[12a]

Flash column chromatography (petroleum ether/EtOAc, 20:1); colorless oil, yield: 20 mg (41%); 80% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 90:10, flow rate 0.7 mL/min, T = 30 °C, 214 nm): t_R = 16.56 (major), 13.50 min (minor)]; $[\alpha]_D^{27}$ +19.5 (c 1.00, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (br s, 1 H), 7.55 (d, J = 8.5 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 3.64 (d, J = 4.5 Hz, 1 H), 3.00 (dd, J = 4.5, 9.0 Hz, 1 H), 1.99–1.96 (m, 1 H), 1.75–1.63 (m, 4 H), 1.25–1.11 (m, 6 H).

LRMS (ESI): m/z = 246.1 $[C_{15}H_{19}NO_2 + H]^+$, 268.1 $[C_{15}H_{19}NO_2 + Na]^+$.

***N*-Phenyl-3-propyloxirane-2-carboxamide (7o)**[12a]

Flash column chromatography (petroleum ether/EtOAc, 10:1); colorless oil, yield: 38 mg (92%); 99% ee [HPLC (Daicel Chiralpak OD, hexane/^{i}PrOH, 80:20, flow rate 0.7 mL/min, T = 30 °C, 254 nm): t_R = 8.81 (major), 15.29 min (minor)]; $[\alpha]_D^{27}$ +35.6 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (br s, 1 H), 7.55 (d, J = 7.6 Hz, 2 H), 7.36 (t, J = 7.6 Hz, 2 H), 7.16 (t, J = 7.6 Hz, 1 H), 3.63 (d, J = 4.4 Hz, 1 H), 3.29 (dt, J = 5.2, 6.0 Hz, 1 H), 1.62–1.58 (m, 4 H), 0.99–0.95 (m, 3 H).

LRMS (ESI): m/z = 206.1 $[C_{12}H_{15}NO_2 + H]^+$, 228.1 $[C_{12}H_{15}NO_2 + Na]^+$.

3-Isopropyl-*N*-phenyloxirane-2-carboxamide (7p)[12a]

Flash column chromatography (petroleum ether/EtOAc, 10:1); colorless oil, yield: 23 mg (56%); 98% ee [HPLC (Daicel Chiralpak AD-H, hexane/^{i}PrOH, 80:20, flow rate 0.7 mL/min, T = 30 °C, 214 nm): t_R = 8.19 (major), 7.79 min (minor)]; $[\alpha]_D^{27}$ +29.4 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (br s, 1 H), 7.56 (d, J = 7.6 Hz, 2 H), 7.36 (t, J = 7.6 Hz, 2 H), 7.16 (t, J = 7.6 Hz, 1 H), 3.65 (d, J = 4.4 Hz, 1 H), 2.97 (dd, J = 4.8, 9.6 Hz, 1 H), 1.53–1.47 (m, 1 H), 1.16 (d, J = 6.4 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H).

LRMS (ESI): m/z = 206.1 $[C_{12}H_{15}NO_2 + H]^+$, 228.1 $[C_{12}H_{15}NO_2 + Na]^+$.

***N*-Phenyl-3-(but-1-en-2-yl)oxirane-2-carboxamide (7q)**

Flash column chromatography (petroleum ether/EtOAc, 10:1); colorless oil, yield: 41 mg (95%); 98% ee [HPLC (Daicel Chiralpak OD, hexane/^{i}PrOH, 80:20, flow rate 0.7 mL/min, T = 30 °C, 254 nm): t_R = 9.99 (major), 10.99 min (minor)]; $[\alpha]_D^{27}$ +11.4 (c 1.00, CH_2Cl_2).

IR (KBr): 3337, 2970, 1667, 1596, 1527, 1444, 1315, 950, 936, 818, 755, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (br s, 1 H), 7.45 (d, J = 8.0 Hz, 2 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.14 (t, J = 7.6 Hz, 1 H), 5.16 (d, J = 1.0 Hz, 1 H), 5.05 (d, J = 1.0 Hz, 1 H), 3.75 (m, 2 H), 2.17–2.10 (m, 2 H), 1.06–1.02 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 143.2, 136.5, 129.1, 124.9, 119.9, 111.5, 59.8, 56.5, 26.2, 12.0.

LRMS (ESI): m/z =206.1 $[C_{13}H_{15}NO_2 + H]^+$, 228.1 $[C_{13}H_{15}NO_2 + Na]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{16}O_2N$: 218.1176; found: 218.1175.

3-Benzyl-*N*-phenyloxirane-2-carboxamide (7r)

Flash column chromatography (petroleum ether/EtOAc, 8:1); colorless solid; yield: 33 mg (66%); mp 85–86 °C (Lit.[12a] 81–82 °C); 98% ee [HPLC (Daicel Chiralpak OD, hexane/^{i}PrOH, 80:20, flow rate 0.7 mL/min, T = 30 °C, 254 nm): t_R = 13.82 (major), 20.16 min (minor)]; $[\alpha]_D^{26}$ +31.6 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (br s, 1 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.38–7.31 (m, 4 H), 7.27–7.25 (m, 3 H), 7.17–7.14 (m, 1 H), 3.72 (d, J = 4.8 Hz, 1 H), 3.48 (dd, J = 6.9, 5.2 Hz, 1 H), 2.96 (d, J = 6.0 Hz, 2 H).

LRMS (ESI): m/z = 254.1 $[C_{16}H_{15}NO_2 + H]^+$, 276.0 $[C_{16}H_{15}NO_2 + Na]^+$.

3-Phenethyl-*N*-phenyloxirane-2-carboxamide (7s)[12a]

Flash column chromatography (petroleum ether/EtOAc, 8:1); colorless oil, yield: 50 mg (94%); 97% ee [HPLC (Daicel Chiralpak OD, hexane/^{i}PrOH, 80:20, flow rate 0.7 mL/min, T = 30 °C, 254 nm): t_R = 13.35 (major), 19.26 min (minor)]; $[\alpha]_D^{26}$ +35.4 (c 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (br s, 1 H), 7.54 (d, J = 8.8 Hz, 2 H), 7.36–7.33 (m, 2 H), 7.29–7.25 (m, 2 H), 7.21–7.12 (m, 4 H), 3.64 (d, J = 4.4 Hz, 1 H), 3.29–3.28 (m, 1 H), 2.84 (t, J = 7.6 Hz, 2 H), 1.98–1.87 (m, 2 H).

LRMS (ESI): m/z = 268.1 $[C_{17}H_{17}NO_2 + H]^+$, 290.1 $[C_{17}H_{17}NO_2 + Na]^+$.

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Supporting Information

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