Synthesis T. Nishimura et al. Special Topic

Rhodium-Catalyzed Enantioselective Addition of Tricyclopropylboroxin to *N*-Sulfonylimines

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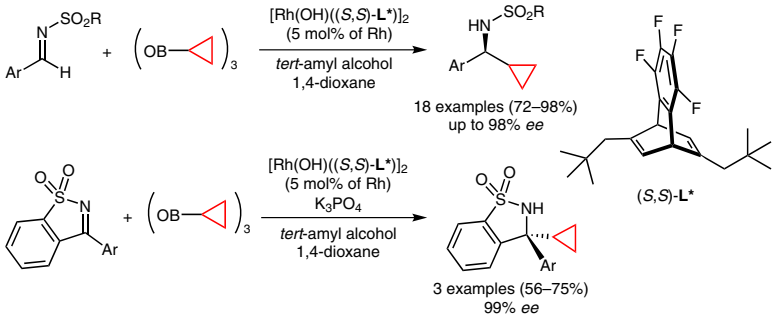

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Abstract A hydroxorhodium complex coordinated with a chiral diene ligand efficiently catalyzed the asymmetric addition of tricyclopropylboroxin to *N*-sulfonylimines in high yields and high enantioselectivities.

Key words asymmetric catalysis, addition reactions, rhodium, imines, cyclopropylation, ligands

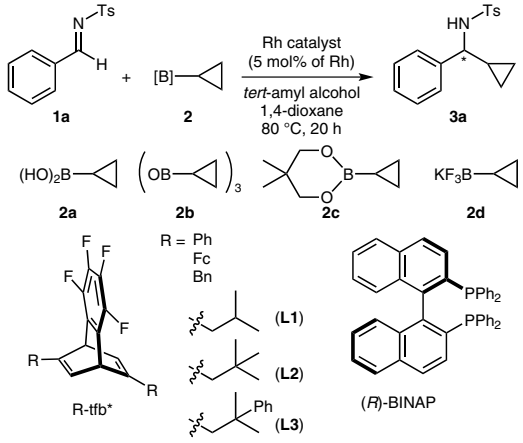
α-Chiral amines are important core units, often found in drugs and natural products, and their synthesis by enantioselective addition of organometallic reagents to imines has been developed as one of the most valuable transformations in organic synthesis.[1] There have been many reports on catalytic enantioselective alkylations and arylations of imines by organometallic reagents catalyzed by transition-metal complexes.[2] In this regard, the catalysis by rhodium complexes of the enantioselective addition of organoboron reagents to imines permits the synthesis of diverse α-chiral amines substituted with aryl or alkenyl groups with high enantioselectivity.[2f–q,3]

α-Cyclopropylbenzylamines are important core units of many biologically active compounds,[4] and their diastereoselective synthesis by using chiral auxiliaries on the imine nitrogen has been reported.[4] Asymmetric hydrogenation and hydrosilylation of ketimines are alternative approaches to chiral α-cyclopropylbenzylamines with high levels of enantioselectivity.[5] Recently, a palladium-catalyzed enantioselective addition of phenylboronic acid to imines generated in situ from cyclopropanecarbaldehyde to give α-cyclopropylbenzylamines was reported.[6] In this context, we recently reported that rhodium–chiral diene complexes catalyze the asymmetric 1,4-addition of cyclopropylboronic acid to electron-deficient alkenes, without suffering from β-hydrogen elimination.[7,8] Here, we report that similar catalytic conditions can be applied to the asymmetric cyclopropylation of *N*-sulfonylimines in a highly enantioselective manner. To the best of our knowledge, the catalytic enantioselective addition of cyclopropylated metal species to imines has not previously been reported.

Our initial studies focused on the addition of various cyclopropylboron reagents to the *N*-tosylimine **1a** in the presence of various rhodium complexes in an attempt to find a suitable cyclopropyl transfer reagent (Table 1). Treatment of imine **1a** with cyclopropylboronic acid (**2a**, 3 equiv) in the presence of $[Rh(OH)(cod)]_2$ (cod = 1,5-cyclooctadiene; 5 mol% of Rh) in 1,4-dioxane at 80 °C for 20 hours gave the cyclopropylated product **3a** in 14% yield (Table 1, entry 1). The use of tricyclopropylboroxin (**2b**) with *tert*-amyl alcohol as a proton source improved the yield of **3a** to 33% (entry 2), whereas neither the cyclopropylboronate **2c** nor the trifluoroborate **2d** gave the cyclopropylated product (entries 3 and 4). A chlororhodium complex with K_3PO_4 as a base was not effective and gave a low yield of **3a** (entry 5). Enantioselective addition was achieved by the use of chiral diene ligands.[9] Among various chiral diene ligands based on a tetrafluorobenzobarrelene (tfb) framework[10,11] (entries 6–11), the neopentyl-substituted tfb ligand **L2**[7] showed a high enantioselectivity (93% ee) and gave **3a** in 59% yield (entry 10). Reaction for a prolonged reaction time (40 h) gave **3a** in 92% yield and 92% ee (entry 12). The rhodium-bisphosphine complex $\{Rh(OH)[(R)\text{-BINAP}]\}_2$, reported to be one of the most efficient catalysts for the enantioselective addition of arylboronic acids,[12] did not give the addition product at all (entry 13).

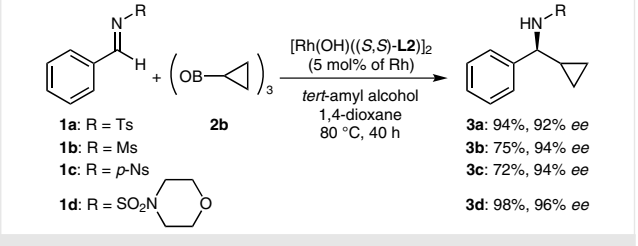
Besides the *N*-tosylimine **1a**, the *N*-mesylimine **1b**, the *N*-(4-nitrobenzenesulfonyl)imine **1c**, and the sulfamidate imine **1d** also reacted well to give the corresponding addition products **3b**–**d** in good to high yields and high enantioselectivities (Scheme 1).[13]

Table 1 Rhodium-Catalyzed Asymmetric Addition of Cyclopropylboron Reagents to Imine **1a**[a]



Entry	Catalyst	Reagent	Yield[b] (%)	ee[c] (%)
1[d]	$[Rh(OH)(cod)]_2$	**2a**	14	–
2	$[Rh(OH)(cod)]_2$	**2b**	33	–
3	$[Rh(OH)(cod)]_2$	**2c**	0	–
4	$[Rh(OH)(cod)]_2$	**2d**	0	–
5	$[RhCl(cod)]_2/K_3PO_4$[e]	**2b**	3	–
6	$\{Rh(OH)[(R,R)\text{-Ph-tfb}^*]\}_2$	**2b**	70	27
7	$\{Rh(OH)[(S,S)\text{-Fc-tfb}^*]\}_2$	**2b**	91	63
8	$\{Rh(OH)[(S,S)\text{-Bn-tfb}^*]\}_2$	**2b**	75	82
9	$\{Rh(OH)[(R,R)\text{-L1}]\}_2$	**2b**	67	88
10	$\{Rh(OH)[(R,R)\text{-L2}]\}_2$	**2b**	59	93
11	$\{Rh(OH)[(R,R)\text{-L3}]\}_2$	**2b**	48	93
12[f]	$\{Rh(OH)[(R,R)\text{-L2}]\}_2$	**2b**	92	92
13	$\{Rh(OH)[(R)\text{-BINAP}]\}_2$	**2b**	0	–

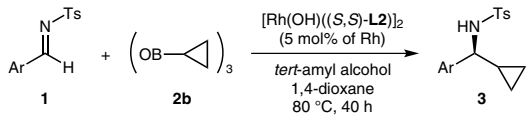
[a] Reaction conditions: **1a** (0.10 mmol), cyclopropylboron reagent (0.30 mmol of B), Rh catalyst (5 mol% of Rh), *tert*-amyl alcohol (0.30 mmol), 1,4-dioxane (0.4 mL), 80 °C, 20 h; for details, see Supporting Information.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Without *tert*-amyl alcohol.
[e] K_3PO_4 (0.10 mmol).
[f] For 40 h.



Scheme 1 Effects of the substituent on the imine nitrogen

The results obtained in enantioselective additions of tricyclopropylboroxin (**2b**) to several imines **1** are summarized in Table 2. Aromatic imines substituted with various functional groups in the *ortho*-, *meta*-, and *para*-positions of the phenyl group (Table 2, entries 1–10), as well as those containing a naphthyl group (entries 11 and 12) or a ferrocenyl group (entry 13), gave the corresponding addition products in good to high yields and over 91% ee. The reaction of the 2-furyl-substituted imine **1r** gave the addition product **3r** in 75% ee (entry 14).

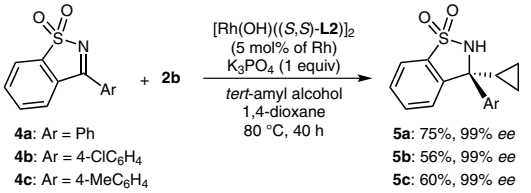
Table 2 Rhodium-Catalyzed Asymmetric Addition of Tricyclopropylboroxin to Imines **1**[a]



Entry	Ar	Product	Yield[b] (%)	ee[c] (%)
1	4-FC_6H_4 (**1e**)	**3e**	80	92
2	4-ClC_6H_4 (**1f**)	**3f**	76	91
3	4-BrC_6H_4 (**1g**)	**3g**	52	93
4	4-$F_3CC_6H_4$ (**1h**)	**3h**	91	94
5	4-Tol (**1i**)	**3i**	95	92
6	4-$MeOC_6H_4$ (**1j**)	**3j**	83	91
7	3-$MeOC_6H_4$ (**1k**)	**3k**	94	92
8	2-$MeOC_6H_4$ (**1l**)	**3l**	94	96
9	3,4,5-$(MeO)_3C_6H_2$ (**1m**)	**3m**	77	91
10	1,3-benzodioxol-5-yl (**1n**)	**3n**	65	94
11	2-naphthyl (**1o**)	**3o**	92	94
12	1-naphthyl (**1p**)	**3p**	95	98
13	Fc (**1q**)	**3q**	61	91
14	2-furyl (**1r**)	**3r**	90	75

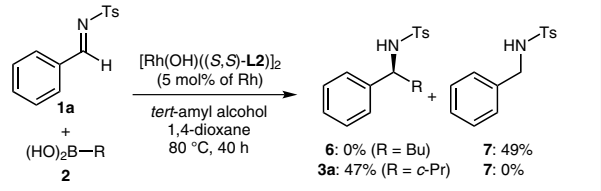
[a] Reaction conditions: **1a** (0.20 mmol), tricyclopropylboroxin (**2b**, 0.20 mmol), $[Rh(OH)[(S,S)\text{-L2}]]_2$ (5 mol% of Rh), *tert*-amyl alcohol (0.60 mmol), 1,4-dioxane (0.8 mL), 80 °C, 40 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

The present catalytic system can also be applied to addition reactions of ketimines to give the corresponding α-*tert*-chiral amines (Scheme 2). Thus, the reaction of cyclic *N*-sulfonyl ketimine **4a** with boroxin **2b** in the presence of K_3PO_4 as a base gave the α-*tert*-chiral amine **5a** in 75% yield with 99% ee.[14] A high enantioselectivity was also observed with ketimines **4b** and **4c** containing substituted phenyl groups.



Scheme 2 Asymmetric additions to ketimines

We tried to use alkylboron reagents other than tricyclopropylboroxin (**2b**) in the addition reactions of imines, but these reactions failed to give the corresponding addition products.[15,16] For example, no reaction was observed for cyclobutyl- or cyclopentylboronic acid. Butylboronic acid reduced the imine **1a** to give the benzylamine **7** in 49% yield (Scheme 3), probably through reduction of imine **1a** with a hydridorhodium species generated by β-hydrogen elimination from a butylrhodium complex.[7] In contrast, the formation of the reduced product **7** was not observed in the reaction using cyclopropylboronic acid (**2a**), implying that β-hydrogen elimination from the cyclopropylrhodium species does not take place under the present reaction conditions.



Scheme 3 Reduction caused by β-hydrogen elimination

In summary, by using a chiral diene ligand, we have developed a rhodium-catalyzed asymmetric addition of tricyclopropylboroxin to various aromatic imines with high enantioselectivity.

All anaerobic and moisture-sensitive manipulations were carried out by standard Schlenk techniques under dry N_2. NMR spectra were recorded on a JEOL JNM ECA-600 spectrometer (600 MHz for ^{1}H; 150 MHz for ^{13}C) or a JEOL JNM LA-500 spectrometer (500 MHz for ^{1}H; 125 MHz for ^{13}C). Chemical shifts are referenced to the residual peaks of $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR. High-resolution mass spectra (TOF-MS) were obtained with a Bruker micrOTOF spectrometer. Flash column chromatography was performed on Silica Gel 60 N (spherical, neutral, Cica-Reagent). Preparative TLC was performed on Silica Gel 60 PF_{254} (Merck). Alumina (activated 200) for column chromatography was purchased from Nacalai Tesque.

Asymmetric Addition of Tricyclopropylboroxin (2b) to Imines 1; General Procedure

{Rh(OH)[(*S*,*S*)-**L2**]}$_2$ (4.8 mg, 0.010 mmol of Rh) and imine **1** (0.20 mmol) were placed in a Schlenk tube under N_2. A 0.50 M stock solution of tricyclopropylboroxin (**2b**) in 1,4-dioxane (0.40 mL, 0.20 mmol) together with *t*-amyl alcohol (66 µL, 0.60 mmol) and 1,4-dioxane (0.60 mL) were added to the Schlenk tube, and the mixture was stirred at 80 °C for 40 h. The mixture was then passed through a short column of alumina with EtOAc as eluent. The solvent was removed on a rotary evaporator and the residue was subjected to preparative TLC [silica gel, hexane–EtOAc] to give **3**. The ee of **3** was determined by chiral HPLC analysis.

N-[(*S*)-Cyclopropyl(phenyl)methyl]-4-toluenesulfonamide (3a)

[CAS Reg. No. 1797442-90-0 for (*R*)-**3a**]

Colorless solid; yield: 56.7 mg (94%); $[\alpha]_D^{20}$ –21 (*c* 0.99, $CHCl_3$) for 92% ee (*S*).

HPLC [Chiralpak AD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 28.0 min (*R*), 30.0 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.1 Hz, 2 H), 7.18–7.11 (m, 7 H), 4.95 (d, *J* = 5.4 Hz, 1 H), 3.70 (dd, *J* = 8.9, 5.4 Hz, 1 H), 2.37 (s, 3 H), 1.12–1.08 (m, 1 H), 0.52–0.45 (m, 2 H), 0.30–0.21 (m, 2 H).

N-[(*S*)-Cyclopropyl(phenyl)methyl]methanesulfonamide (3b)

[CAS Reg. No. 1376332-88-5 for *rac*-**3b**]

Colorless solid; yield: 33.8 mg (75%); $[\alpha]_D^{20}$ –6 (*c* 1.01, $CHCl_3$) for 94% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 20.9 min (*R*), 23.0 min (*S*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 4.73 (br s, 1 H), 3.23 (dd, *J* = 10.7, 6.5 Hz, 1 H), 2.63 (s, 3 H), 1.26–1.20 (m, 1 H), 0.74–0.66 (m, 1 H), 0.59–0.50 (m, 2 H), 0.40–0.36 (m, 1 H).

N-[(*S*)-Cyclopropyl(phenyl)methyl]-4-nitrobenzenesulfonamide (3c)

Colorless solid; yield: 47.9 mg (72%); $[\alpha]_D^{20}$ +32 (*c* 1.02, $CHCl_3$) for 94% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 60.4 min (*R*), 73.5 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.9 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.17–7.11 (m, 3 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 5.28–5.23 (m, 1 H), 3.82 (dd, *J* = 9.1, 5.4 Hz, 1 H), 1.18–1.12 (m, 1 H), 0.61–0.50 (m, 2 H), 0.38–0.30 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 149.5, 146.7, 139.2, 128.4, 128.2, 127.9, 127.0, 123.7, 63.3, 18.0, 4.8, 3.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{16}N_2NaO_4S$: 355.0723; found: 355.0717.

N-[(*S*)-Cyclopropyl(phenyl)methyl]morpholine-4-sulfonamide (3d)

Colorless solid; yield: 58.1 mg (98%); $[\alpha]_D^{20}$ +26 (*c* 1.01, $CHCl_3$) for 96% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 23.4 min (*R*), 26.2 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 5 H), 4.78 (br, 1 H), 3.68 (dd, *J* = 8.8, 4.8 Hz, 1 H), 3.43–3.33 (m, 4 H), 2.95–2.88 (m, 4 H), 1.23–1.17 (m, 1 H), 0.69–0.64 (m, 1 H), 0.57–0.48 (m, 2 H), 0.38–0.33 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 141.4, 128.6, 127.8, 127.0, 65.9, 63.2, 45.6, 18.5, 4.8, 4.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{20}N_2NaO_3S$: 319.1087; found: 319.1082.

N-[(*S*)-Cyclopropyl(4-fluorophenyl)methyl]-4-toluenesulfonamide (3e)

[CAS Reg. No. 1108697-86-4 for *rac*-**3e**]

Colorless solid; yield: 51.1 mg (80%); $[\alpha]_D^{20}$ –20 (*c* 1.02, $CHCl_3$) for 92% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 22.4 min (*R*), 26.1 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.1 Hz, 2 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 7.10–7.07 (m, 2 H), 6.84 (t, *J* = 8.5 Hz, 2 H), 5.17 (br s, 1 H), 3.66 (dd, *J* = 8.9, 5.4 Hz, 1 H), 2.38 (s, 3 H), 1.09–1.03 (m, 1 H), 0.53–0.45 (m, 2 H), 0.29–0.18 (m, 2 H).

N-[(*S*)-(4-Chlorophenyl)(cyclopropyl)methyl]-4-toluenesulfonamide (3f)

Colorless solid; yield: 50.9 mg (76%); $[\alpha]_D^{20}$ –20 (*c* 1.01, $CHCl_3$) for 91% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 21.9 min (*R*), 24.6 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 7.11 (d, *J* = 8.2 Hz, 2 H), 7.01 (d, *J* = 8.1 Hz, 2 H), 5.35 (br, 1 H), 3.64 (dd, *J* = 8.1, 6.1 Hz, 1 H), 2.39 (s, 3 H), 1.10–1.02 (m, 1 H), 0.54–0.44 (m, 2 H), 0.27–0.17 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 143.2, 139.0, 137.5, 133.1, 129.3, 128.3, 128.2, 127.1, 61.9, 21.4, 18.0, 4.4, 3.7.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}ClNNaO_2S$: 358.0639; found: 358.0637.

N-[(*S*)-(4-Bromophenyl)(cyclopropyl)methyl]-4-toluenesulfonamide (3g)

Colorless solid; yield: 39.4 mg (52%); $[\alpha]_D^{20}$ –13 (*c* 0.49, $CHCl_3$) for 93% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 25.6 min (*R*), 29.7 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 6.99 (d, *J* = 8.2 Hz, 2 H), 5.04 (br s, 1 H), 3.62 (dd, *J* = 8.9, 5.2 Hz, 1 H), 2.40 (s, 3 H), 1.08–1.02 (m, 1 H), 0.55–0.45 (m, 2 H), 0.28–0.19 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 143.3, 139.4, 137.5, 131.3, 129.3, 128.6, 127.1, 121.3, 62.1, 21.5, 18.0, 4.4, 3.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}BrNNaO_2S$: 402.0134; found: 402.0136.

N-{(*S*)-Cyclopropyl[4-(trifluoromethyl)phenyl]methyl}-4-toluenesulfonamide (3h)

Colorless solid; yield: 67.0 mg (91%); $[\alpha]_D^{20}$ –7 (*c* 1.01, $CHCl_3$) for 94% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 20.8 min (*R*), 23.7 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.1 Hz, 2 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 5.00 (br s, 1 H), 3.67 (dd, *J* = 7.0, 4.8 Hz, 1 H), 2.35 (s, 3 H), 1.11–1.05 (m, 1 H), 0.55–0.50 (m, 1 H), 0.54–0.49 (m, 1 H), 0.33–0.29 (m, 1 H), 0.27–0.23 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.3, 143.3, 137.3, 129.5 (q, *J* = 33 Hz), 129.3, 127.3, 127.1, 125.1 (q, *J* = 4 Hz), 124.0 (q, *J* = 271 Hz), 62.3, 21.3, 18.1, 4.5, 3.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{18}F_3NNaO_2S$: 392.0903; found: 392.0910.

N-[(*S*)-Cyclopropyl(4-tolyl)methyl]-4-toluenesulfonamide (3i)

Colorless solid; yield: 60.2 mg (95%); $[\alpha]_D^{20}$ –32 (*c* 1.01, $CHCl_3$) for 92% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 19.8 min (*R*), 23.0 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 7.00 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 5.10–5.02 (m, 1 H), 3.65 (dd, *J* = 8.5, 5.8 Hz, 1 H), 2.38 (s, 3 H), 2.28 (s, 3 H), 1.12–1.06 (m, 1 H), 0.52–0.43 (m, 2 H), 0.28–0.19 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 142.9, 137.8, 137.5, 137.1, 129.2, 128.9, 127.1, 126.8, 62.2, 21.4, 21.0, 18.0, 4.4, 3.6.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{21}NNaO_2S$: 338.1185; found: 338.1183.

N-[(*S*)-Cyclopropyl(4-methoxyphenyl)methyl]-4-toluenesulfonamide (3j)

[CAS Reg. No. 1108697-85-3 for *rac*-**3j**]

Colorless solid; yield: 55.1 mg (83%); $[\alpha]_D^{20}$ –28 (*c* 1.03, $CHCl_3$) for 91% ee (*S*).

HPLC [Chiralpak AD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 44.5 min (*R*), 47.7 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.2 Hz, 2 H), 7.16 (d, *J* = 8.1 Hz, 2 H), 7.03 (d, *J* = 8.2 Hz, 2 H), 6.70 (d, *J* = 8.1 Hz, 2 H), 4.87 (br, 1 H), 3.76 (s, 3 H), 3.66 (dd, *J* = 8.8, 5.5 Hz, 1 H), 2.38 (s, 3 H), 1.11–1.05 (m, 1 H), 0.52–0.42 (m, 2 H), 0.27–0.20 (m, 2 H).

N-[(*S*)-Cyclopropyl(3-methoxyphenyl)methyl]-4-toluenesulfonamide (3k)

Colorless solid; yield: 63.3 mg (94%); $[\alpha]_D^{20}$ –26 (*c* 1.00, $CHCl_3$) for 92% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 28.2 min (*R*), 40.3 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 7.10 (t, *J* = 8.1 Hz, 1 H), 6.73–6.69 (m, 2 H), 6.60 (s, 1 H), 5.00 (br s, 1 H), 3.68 (s, 3 H), 3.67 (dd, *J* = 8.9, 6.1 Hz, 1 H), 2.37 (s, 3 H), 1.12–1.06 (m, 1 H), 0.54–0.46 (m, 2 H), 0.32–0.24 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.5, 143.0, 142.0, 137.8, 129.3, 129.2, 127.1, 119.3, 112.9, 112.4, 62.5, 55.0, 21.4, 18.1, 4.4, 3.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{21}NNaO_3S$: 354.1134; found: 354.1133.

N-[(*S*)-Cyclopropyl(2-methoxyphenyl)methyl]-4-toluenesulfonamide (3l)

[CAS Reg. No. 1108697-89-7 for *rac*-**3l**]

Colorless solid; yield: 62.3 mg (94%); $[\alpha]_D^{20}$ –6 (*c* 0.99, $CHCl_3$) for 96% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 22.4 min (*R*), 24.4 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.1 Hz, 2 H), 7.09 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.00 (d, *J* = 8.1 Hz, 2 H), 6.83 (dd, *J* = 7.5, 1.3 Hz, 1 H), 6.72 (t, *J* = 7.5 Hz, 1 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 5.68 (br, 1 H), 3.72 (s, 3 H), 3.66 (t, *J* = 9.2 Hz, 1 H), 2.29 (s, 3 H), 1.35–1.29 (m, 1 H), 0.55–0.49 (m, 1 H), 0.41–0.35 (m, 2 H), 0.24–0.19 (m, 1 H).

N-[(*S*)-Cyclopropyl(3,4,5-trimethoxyphenyl)methyl]-4-toluenesulfonamide (3m)

Colorless solid; yield: 60.5 mg (77%); $[\alpha]_D^{20}$ –4 (*c* 1.00, $CHCl_3$) for 91% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 41.4 min (*R*), 49.0 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 6.27 (s, 2 H), 5.34 (br, 1 H), 3.77 (s, 3 H), 3.68 (s, 6 H), 3.67 (dd, *J* = 8.9, 6.1 Hz, 1 H), 2.35 (s, 3 H), 1.12–1.07 (m, 1 H), 0.57–0.46 (m, 2 H), 0.34–0.29 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.9, 143.0, 138.0, 137.1, 136.0, 129.1, 127.1, 103.9, 62.8, 60.7, 55.8, 21.4, 18.0, 4.4, 3.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{25}NNaO_5S$: 414.1346; found: 414.1355.

N-[(*S*)-1,3-Benzodioxol-5-yl(cyclopropyl)methyl]-4-toluenesulfonamide (3n)

Colorless solid; yield: 45.9 mg (65%); $[\alpha]_D^{20}$ –31 (*c* 1.01, $CHCl_3$) for 94% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 34.9 min (*R*), 41.9 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.1 Hz, 2 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 6.63–6.55 (m, 3 H), 5.89 (d, *J* = 1.4 Hz, 1 H), 5.87 (d, *J* = 1.4 Hz, 1 H), 5.08 (br s, 1 H), 3.58 (dd, *J* = 8.5, 5.8 Hz, 1 H), 2.38 (s, 3 H), 1.08–1.01 (m, 1 H), 0.54–0.44 (m, 2 H), 0.27–0.19 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.5, 146.8, 143.0, 137.7, 134.4, 129.2, 127.2, 120.4, 107.8, 107.2, 100.9, 62.4, 21.4, 18.1, 4.5, 3.7.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{19}NNaO_4S$: 368.0927; found: 368.0932.

N-[(*S*)-Cyclopropyl(2-naphthyl)methyl]-4-toluenesulfonamide (3o)

Colorless solid; yield: 64.7 mg (92%); $[\alpha]_D^{20}$ –20 (*c* 1.01, $CHCl_3$) for 94% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 32.5 min (*R*), 38.8 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76–7.75 (m, 1 H), 7.65–7.63 (m, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.45–7.42 (m, 3 H), 7.24 (dd, *J* = 8.5, 1.7 Hz, 1 H), 6.97 (d, *J* = 8.1 Hz, 2 H), 5.02 (br s, 1 H), 3.87 (dd, *J* = 8.5, 5.8 Hz, 1 H), 2.22 (s, 3 H), 1.23–1.17 (m, 1 H), 0.60–0.55 (m, 1 H), 0.53–0.48 (m, 1 H), 0.37–0.29 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 142.9, 137.6, 137.5, 133.0, 132.7, 129.1, 128.1, 127.8, 127.5, 127.1, 126.0, 125.9, 125.8, 124.7, 62.7, 21.3, 18.0, 4.5, 3.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{21}NNaO_2S$: 374.1185; found: 374.1176.

N-[(*S*)-Cyclopropyl(1-naphthyl)methyl]-4-methylbenzenesulfonamide (3p)

[CAS Reg. No. 1108697-87-5 for *rac*-**3p**]

Colorless solid; yield: 66.8 mg (95%); $[\alpha]_D^{20}$ +18 (*c* 0.84, $CHCl_3$) for 98% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 27.8 min (*R*), 37.6 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04–7.99 (m, 1 H), 7.79–7.76 (m, 1 H), 7.67 (d, *J* = 7.5 Hz, 1 H), 7.46–7.42 (m, 4 H), 7.34 (d, *J* = 6.8 Hz, 1 H), 7.27 (t, *J* = 8.2 Hz, 1 H), 6.92 (d, *J* = 7.5 Hz, 2 H), 5.30 (br, 1 H), 4.61 (t, *J* = 6.5 Hz, 1 H), 2.26 (s, 3 H), 1.43–1.37 (m, 1 H), 0.56–0.50 (m, 1 H), 0.46–0.41 (m, 1 H), 0.34–0.29 (m, 1 H), 0.27–0.23 (m, 1 H).

N-[(*S*)-Cyclopropyl(ferrocenyl)methyl]-4-toluenesulfonamide (3q)

Yellow solid; yield: 50.5 mg (61%); $[\alpha]_D^{20}$ –13 (*c* 1.02, $CHCl_3$) for 91% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 24.9 min (*S*), 27.6 min (*R*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 4.85 (br s, 1 H), 4.17 (s, 5 H), 4.13 (s, 1 H), 4.11 (s, 1 H), 4.01 (s, 1 H), 3.92 (d, *J* = 1.3 Hz, 1 H), 3.48 (t, *J* = 7.8 Hz, 1 H), 2.44 (s, 3 H), 1.13–1.07 (m, 1 H), 0.59–0.53 (m, 1 H), 0.40–0.37 (m, 1 H), 0.31–0.24 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 143.2, 138.6, 129.6, 127.1, 90.7, 68.5, 68.1, 68.0, 67.5, 66.4, 56.8, 21.5, 16.8, 4.2, 3.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{23}FeNNaO_2S$: 432.0691; found: 432.0687.

N-[(*S*)-Cyclopropyl(2-furyl)methyl]-4-toluenesulfonamide (3r)

Colorless solid; yield: 52.3 mg (90%); $[\alpha]_D^{20}$ –25 (*c* 1.01, $CHCl_3$) for 75% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 254 nm]: t_R = 21.5 min (*R*), 24.7 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 7.14 (s, 1 H), 6.14 (dd, *J* = 3.1, 1.7 Hz, 1 H), 6.00 (d, *J* = 3.1 Hz, 1 H), 5.07 (br, 1 H), 3.91 (t, *J* = 7.8 Hz, 1 H), 2.38 (s, 3 H), 1.23–1.17 (m, 1 H), 0.55–0.47 (m, 2 H), 0.34–0.24 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.7, 142.9, 141.9, 137.8, 129.3, 127.0, 109.9, 106.9, 55.6, 21.4, 15.8, 3.8, 3.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{17}NNaO_3S$: 314.0821; found: 314.0824.

(3*S*)-3-Cyclopropyl-3-phenyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide (5a)

[CAS Reg. No. 1504627-57-9 for (*R*)-**5a**]

Colorless solid; yield: 21.4 mg (from the reaction of 0.10 mmol of **4a**; 75%); $[\alpha]_D^{20}$ +62 (*c* 0.53, $CHCl_3$) for 99% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 4:1), flow: 0.5 mL/min, 254 nm]: t_R = 15.7 min (*R*), 18.1 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.4 Hz, 1 H), 7.61–7.54 (m, 4 H), 7.37–7.31 (m, 3 H), 7.21 (d, *J* = 7.4 Hz, 1 H), 4.38 (s, 1 H), 0.90–0.84 (m, 1 H), 0.77–0.71 (m, 1 H), 0.70–0.65 (m, 1 H), 0.60–0.47 (m, 2 H).

(3*S*)-3-(4-Chlorophenyl)-3-cyclopropyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide (5b)

Colorless solid; yield: 35.8 mg (56%); $[\alpha]_D^{20}$ +51 (*c* 1.05, $CHCl_3$) for 99% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 9:1), flow: 0.5 mL/min, 230 nm]: t_R = 27.1 min (*S*), 36.9 min (*R*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.5 Hz, 1 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.51 (d, *J* = 8.9 Hz, 2 H), 7.32 (d, *J* = 8.9 Hz, 2 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 4.44 (s, 1 H), 1.68–1.61 (m, 1 H), 0.89–0.82 (m, 1 H), 0.75–0.68 (m, 1 H), 0.57–0.48 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 143.3, 141.5, 134.6, 134.4, 133.6, 129.6, 129.1, 128.7, 124.9, 121.3, 67.9, 19.8, 3.1, 1.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{14}ClNNaO_2S$: 342.0326; found: 342.0317.

(3*S*)-3-Cyclopropyl-3-(4-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide (5c)

Colorless solid; yield: 35.9 mg (60%); $[\alpha]_D^{20}$ +48 (*c* 0.68, $CHCl_3$) for 99% ee (*S*).

HPLC [Chiralcel OD-H (hexane–*i*-PrOH, 4:1), flow: 0.5 mL/min, 254 nm]: t_R = 21.9 min (*R*), 33.9 min (*S*).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.5 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.44 (d, *J* = 8.2 Hz, 2 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 4.37 (s, 1 H), 2.33 (s, 3 H), 1.68–1.62 (m, 1 H), 0.87–0.71 (m, 1 H), 0.74–0.68 (m, 1 H), 0.58–0.53 (m, 1 H), 0.51–0.45 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.3, 140.2, 138.5, 134.4, 133.5, 129.6, 129.3, 127.1, 124.9, 121.2, 68.3, 21.0, 19.7, 3.2, 0.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_2S$: 322.0872; found: 322.0868.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561605.

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