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Article

Chiral Brønsted acid-catalyzed conjugate addition of indoles to azadienes: Enantioselective synthesis of hetero-triarylmethanes

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ABSTRACT

An efficient chiral Brønsted acid-catalyzed conjugate addition of indoles to azadienes has been successfully developed, which enables a facile approach to optically active hetero-triarylmethanes with excellent enantioselectivities and broad substrate scope. This chiral Brønsted acid catalytic system provides a new opportunity for the development of asymmetric reactions of azadienes.

1. Introduction

Aurone-derived azadienes have been regarded as a pivotal class of highly reactive intermediates in organic synthesis due to the driving force of aromatization [1–20]. In the past few years, only a few catalytic asymmetric processes of azadienes have been successfully developed on the basis of transition-metal catalysis and organo-catalysis [10–20]. Zhao and co-workers [10–12] disclosed palladium-catalyzed asymmetric formal cycloaddition of azadienes to prepare medium-sized compounds including benzofuran- fused nine-membered and ten-membered heterocycles. Organocatalytic systems for the asymmetric reactions of azadienes mainly focused on chiral amine, *N*-heterocyclic carbene (NHC), phosphine and bifunctional Brønsted base. In 2016, Zhao's group [13] reported chiral amine-catalyzed aza-Diels-Alder reactions of azadienes with aldehydes to afford tetrahydropyridines and NHC-catalyzed aza-Diels-Alder reactions of azadienes with α-chloroaldehydes to provide benzofuran-fused lactams. The catalytic systems, chiral amine and NHC, are complementary and made it possible to achieve diastereodivergent and highly stereoselective transformations. Ye and co-workers [14,15] developed NHC-catalyzed [4+3] annulation of azadienes with acyclic enals to deliver benzofuroazepinones with excellent stereoselectivities. The enantioselective amino-acid-derived phosphine-catalyzed formal [4+4] cycloaddition of azadienes with allene ketones to afford eight-membered structural motifs has been established by Lu's group [16]. Recently, chiral Brønsted bases have been used as highly enantioselective bifunctional catalysts for the asymmetric nucleophilic addition of phosphites, thiols and rhodanines to azadienes [17–19]. Additionally, the formal [4+2] cycloaddition of azadienes with malononitrile using bifunctional squaramide as catalyst has been realized by our group [20] (Scheme 1a). Although considerable

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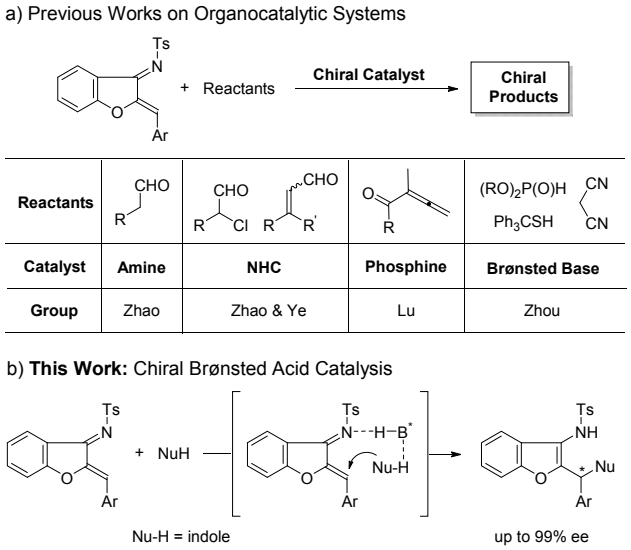


Scheme 1. Organocatalytic asymmetric reactions of azadienes.

progress has been achieved in asymmetric reactions of azadienes, the organocatalytic systems are still limited. Therefore, developing a new strategy for the asymmetric reactions of azadienes is still highly desirable.

Chiral Brønsted acids have been proved to be highly efficient and versatile catalysts for asymmetric transformations over the past decade [21–32]. Among these significant advances, chiral phosphoric acid-catalyzed Friedel–Crafts alkylation of electron-rich arenes is a facile and efficient approach for the construction of chiral hetero-triarylmethanes, which are ubiquitous and prevalent structural scaffolds in natural products, biologically active molecules and synthetic materials [33–58]. As our continuing efforts to the utilization of azadienes, we previously focused on chiral Brønsted base-catalyzed reactions of azadienes [17,18,20]. Considering that chiral Brønsted acids have been widely used to activate substrates through bifunctional catalysis mode, we envisioned that chiral Brønsted acid-catalyzed conjugate addition of indoles to azadienes could enable a facile approach to optically active hetero-triarylmethanes (Scheme 1b). To the best of our knowledge, chiral Brønsted acid catalysis has not been employed to the asymmetric reactions of azadienes. Herein, we reported bifunctional Brønsted acid-catalyzed conjugate addition of indoles to azadienes for the synthesis of chiral hetero-triarylmethanes with excellent enantioselectivities and broad substrate scope.

2. Experimental

2.1. General methods

Commercially available reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or DMSO–*d*6 on a 400 MHz instrument with tetramethylsilane (TMS) as internal standard. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by TLC analysis. Azadienes **1** could be conveniently synthesized from enones and sulfonamides according to the known literature procedures [13,16–18].

2.2. General procedure for catalytic enantioselective conjugate addition

To a solution of azadienes **1** (0.20 mmol) and chiral phosphoric acid (*R*)-TRIP (**A1**) (7.5 mg, 0.01 mmol) in mesitylene (3.0 mL) at –20 °C, indoles **2** (0.20 mmol) was added. The reaction was stirred at –20 °C for 2–3 d, which was monitored by thin-layer chromatography. The crude product was directly purified by silica gel column chromatography (eluent: hexanes/ethyl acetate = 10:1 to 5:1) to give the chiral hetero-triarylmethanes **3**.

(+)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3aa**): 95 mg, 96% yield, yellow solid, m.p. = 106–108 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 5:1), 89% ee, $[\alpha]^{20}_D$ = +93.36 (*c* 0.98, EtOAc). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.90 (s, 1H), 10.02 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.30–7.08 (m, 9H), 7.07–6.95 (m, 3H), 6.93–6.81 (m, 2H), 5.80 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6) δ 154.8, 152.6, 143.0, 140.9, 136.9, 136.2, 129.3, 128.2, 128.1, 126.7, 126.4, 126.2, 125.9, 124.2, 123.7, 122.7, 121.0, 119.8, 118.8, 118.5, 114.0, 113.1, 111.5, 111.3, 38.5, 20.9. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 21.2 min (major) and 23.9 min. HRMS calculated for $C_{30}H_{28}N_3O_3S$ $[M+NH_4]^+$ 510.1846, found: 510.1849.

(+)-*N*-(2-((2-Methyl-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ab**): 91 mg, 90% yield, pale yellow solid, m.p. = 111–113 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 5:1), 79% ee, $[\alpha]^{20}_D$ = +74.66 (*c* 0.90, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.24–7.15 (m, 5H), 7.14–7.01 (m, 7H), 6.97–6.88 (m, 1H), 6.09 (s, 1H), 5.76 (s, 1H), 2.32 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 153.1, 144.1, 140.1, 136.6, 135.2, 132.9, 129.7, 128.4, 128.3, 127.9, 127.6, 126.6, 126.1, 124.3, 123.1, 121.3, 119.7, 119.3, 119.2, 113.4, 111.7, 110.4, 110.1, 38.7, 21.6, 12.4. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 10.6 min (major) and 13.0 min. HRMS calculated for $C_{31}H_{26}N_2NaO_3S$ $[M+Na]^+$ 529.1556, found: 529.1555.

(+)-Methyl-3-((3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)(phenyl)methyl)-1*H*-indole-4-carboxylate (**3ac**): 94 mg, 85% yield, white solid, m.p. = 113–114 °C, new compound, R_f = 0.10 (hexanes/ethyl acetate = 5:1), 89% ee, $[\alpha]^{20}_D$ = +119.14 (*c* 0.94, EtOAc). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.30 (d, *J* = 1.8 Hz, 1H), 10.13 (brs, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.25–7.06 (m, 6H), 7.01 (d, *J* = 7.0 Hz, 2H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.26 (s, 1H), 3.56 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 168.0, 156.4, 152.6, 142.6, 141.5, 137.5, 137.0, 129.2, 128.5, 127.7, 126.8, 126.3, 126.0, 124.1, 124.0, 122.8, 122.7, 121.3, 120.0, 119.8,

115.7, 113.8, 112.8, 111.3, 51.6, 38.9, 20.7. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 8.1 min and 24.6 min (major). HRMS calculated for $C_{32}H_{26}KN_2O_5S$ $[M+K]^+$ 589.1194, found: 589.1192.

(+)-*N*-(2-((5-Chloro-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ad**): 98 mg, 93% yield, white solid, m.p. = 109–110 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 5:1), 89% ee, $[\alpha]^{20}_D$ = +88.97 (*c* 0.98, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 10.05 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.27–7.10 (m, 8H), 7.07 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.02–6.95 (m, 3H), 5.77 (s, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.2, 152.6, 143.0, 140.6, 136.8, 134.7, 129.3, 128.2, 128.1, 127.2, 126.7, 126.6, 125.8, 125.6, 124.3, 123.1, 122.8, 121.0, 119.9, 117.9, 113.9, 113.3, 113.2, 111.3, 38.3, 20.8. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 9.9 min (major) and 12.1 min. HRMS calculated for $C_{30}H_{27}ClN_3O_3S$ $[M+NH_4]^+$ 544.1456, found: 544.1457.

(+)-*N*-(2-((5-Methoxy-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ae**): 96 mg, 92% yield, white solid, m.p. = 105–106 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 5:1), 92% ee, $[\alpha]^{20}_D$ = +89.51 (*c* 1.04, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.25–7.15 (m, 8H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.77 (d, *J* = 1.9 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 6.53–6.43 (m, 1H), 5.69 (s, 1H), 3.69 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.0, 153.3, 144.1, 140.2, 136.4, 131.5, 129.6, 128.6, 128.4, 127.5, 127.0, 126.9, 126.1, 124.4, 123.2, 119.6, 114.9, 113.1, 112.4, 112.0, 111.6, 101.5, 55.9, 39.8, 21.5. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 13.4 min (major) and 20.2 min. HRMS calculated for $C_{31}H_{25}N_2O_4S$ $[M-H]^-$ 521.1540, found: 521.1565.

(+)-*N*-(2-((5-(Benzyloxy)-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3af**): 105 mg, 88% yield, pale yellow solid, m.p. = 100–101 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate = 5:1), 88% ee, $[\alpha]^{20}_D$ = +77.74 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.41–7.29 (m, 6H), 7.25–7.16 (m, 8H), 7.13–7.08 (m, 1H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 6.35 (s, 1H), 5.65 (s, 1H), 4.94 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.3, 153.1, 144.0, 140.1, 137. 7, 136.3, 131.6, 129.5, 128.6, 128.5, 128.4, 127.8, 127.6, 127.5, 126.9, 126.8, 126.0, 124.3, 124.3, 123.1, 119.5, 115.0, 113.2, 113.0, 112.0, 111.6, 102.9, 70.8, 39.7, 21.4. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 18.1 min (major) and 22.2 min. HRMS calculated for $C_{37}H_{34}N_3O_4S$ $[M+NH_4]^+$ 616.2265, found: 616.2269.

(+)-4-Methyl-*N*-(2-((6-methyl-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)benzenesulfonamide (**3ag**): 91 mg, 90% yield, white solid, m.p. = 231–233 °C, new compound, R_f = 0.10 (hexanes/ethyl acetate = 5:1), 93% ee, $[\alpha]^{20}_D$ = +103.80 (*c* 0.92, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.34–7.28 (m, 2H), 7.23–7.16 (m, 4H), 7.14–7.05 (m, 5H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 1.8 Hz, 1H), 6.05 (s, 1H), 5.59 (s, 1H), 2.41 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.4, 144.1, 140.2, 136.9, 136.4, 132.4, 129.7, 128.6, 128.5, 127.7, 126.9, 126.2, 124.4, 123.2, 122.9, 121.7, 119.7, 119.2, 115.2, 113.2, 111.7, 111.3, 39.9, 21.8, 21.6. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 19.3 min and 21.2 min (major). HRMS calculated for $C_{31}H_{26}KN_2O_3S$ $[M+K]^+$ 542.1296, found: 542.1293.

(+)-4-Methyl-*N*-(2-((7-methyl-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)benzenesulfonamide (**3ah**): 93 mg, 92% yield, white solid, m.p. = 190–192 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 5:1), 98% ee, $[\alpha]^{20}_D$ = +116.77 (*c* 0.93, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.24–7.07 (m, 8H), 7.05–6.90 (m, 4H), 6.79 (d, *J* = 1.6 Hz, 1H), 6.55–6.36 (m, 1H), 5.68 (s, 1H), 2.43 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 153.3, 144.0, 140.2, 136.3, 135.9, 129.6, 128.6, 128.4, 127.6, 126.9, 126.2, 126.1, 124.4, 123.3, 123.2, 122.9, 120.5, 120.0, 119.7, 117.3, 115.7, 113.0, 111.6, 39.9, 21.5, 16.6. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 12.8 min and 15.6 min (major). HRMS calculated for $C_{31}H_{25}N_2O_3S$ $[M-H]^-$ 505.1591, found: 505.1604.

(–)-*N*-(2-((1*H*-Indol-3-yl)(*o*-tolyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ba**): 94 mg, 93% yield, white solid, m.p. = 95–97 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate = 5:1), 93% ee, $[\alpha]^{20}_D$ = –54.68 (*c* 0.94, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.17–7.04 (m, 6H), 6.99–6.89 (m, 5H), 6.49 (d, *J* = 1.4 Hz, 1H), 6.00 (s, 1H), 5.74 (s, 1H), 2.17 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 153.3, 144.0, 138.5, 136.5, 136.4, 136.1, 130.6, 129.6, 128.5, 127.5, 127.1, 126.5, 126.2, 124.5, 124.0, 123.2, 122.5, 119.9, 119.9, 119.1, 114.8, 113.7, 111.6, 111.5, 37.1, 21.6, 19.6. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 12.2 min and 16.6 min (major). HRMS calculated for $C_{31}H_{26}KN_2O_3S$ $[M+K]^+$ 545.1296, found: 545.1291.

(+)-*N*-(2-((1*H*-Indol-3-yl)(*m*-tolyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ca**): 89 mg, 88% yield, white solid, m.p. = 236–238 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 5:1), 86% ee, $[\alpha]^{20}_D$ = +107.49 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.42–7.29 (m, 3H), 7.25–7.07 (m, 5H), 7.05–6.92 (m, 6H), 6.79 (d, *J* = 1.7 Hz, 1H), 6.37 (s, 1H), 5.61 (s, 1H), 2.26 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.4, 144.1, 140.1, 138.0, 136.4, 129.6, 129.3, 128.3, 127.8, 127.6, 126.6, 126.3, 125.6, 124.4, 123.6, 123.2, 122.3, 119.8, 119.7, 119.5, 115.3, 113.0, 111.7, 111.3, 39.8, 21.6, 21.5. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 11.7 min and 22.3 min (major). HRMS calculated for $C_{31}H_{26}KN_2O_3S$ $[M+K]^+$ 545.1296, found: 545.1300.

(+)-*N*-(2-((1*H*-Indol-3-yl)(*p*-tolyl)methyl)benzofuran-3-yl)-

4-methylbenzenesulfonamide (**3da**): 91 mg, 90% yield, pale yellow solid, m.p. = 103–104 °C, new compound, R_f = 0.30 (hexane s/ethyl acetate = 5:1), 89% ee, $[\alpha]^{20}_D$ = +17.50 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.02 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.37–7.28 (m, 3H), 7.24–7.17 (m, 2H), 7.14 (m, 2H), 7.05–6.97 (m, 7H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.24 (s, 1H), 5.60 (s, 1H), 2.30 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.9, 153.4, 144.1, 137.2, 136.5, 136.4, 136.4, 129.7, 129.2, 128.5, 127.6, 126.6, 126.2, 124.4, 123.5, 123.2, 122.4, 119.8, 119.7, 119.6, 115.5, 113.0, 111.6, 111.3, 39.5, 21.5, 21.2. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 11.9 min and 23.4 min (major). HRMS calculated for $C_{31}H_{26}KN_2O_3S$ $[M+K]^+$ 545.1296, found: 545.1292.

(+)-*N*-(2-((1*H*-Indol-3-yl)(4-isopropylphenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamidee (**3ea**): 95 mg, 89% yield, white solid, m.p. = 110–112 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate = 10:1), 90% ee, $[\alpha]^{20}_D$ = +142.99 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.90 (d, *J* = 1.7 Hz, 1H), 10.01 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.27–7.17 (m, 3H), 7.15–7.03 (m, 6H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.95–6.86 (m, 2H), 5.79 (s, 1H), 2.98–2.71 (m, 1H), 2.12 (s, 3H), 1.51–0.70 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 155.1, 152.6, 146.4, 143.0, 138.3, 137.0, 136.2, 129.3, 128.2, 126.7, 126.3, 126.0, 125.9, 124.1, 123.5, 122.7, 121.0, 119.7, 118.8, 118.5, 114.2, 112.9, 111.5, 111.3, 38.1, 33.0, 23.9, 23.8, 20.9. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 11.9 min and 20.3 min (major). HRMS calculated for $C_{33}H_{30}KN_2O_3S$ $[M+K]^+$ 573.1609, found: 573.1610.

(–)-*N*-(2-((1*H*-Indol-3-yl)(naphthalen-1-yl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3fa**): 97 mg, 89% yield, pale yellow solid, m.p. = 240–241 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 4:1), 96% ee, $[\alpha]^{20}_D$ = –88.39 (*c* 0.50, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.90 (s, 1H), 10.15 (s, 1H), 8.18–8.09 (m, 1H), 7.98–7.90 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.53–7.30 (m, 9H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.22–7.09 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.81–6.64 (m, 4H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 154.7, 152.7, 142.8, 137.2, 137.0, 136.3, 133.5, 131.0, 129.1, 128.7, 127.2, 126.5, 126.3, 126.1, 126.0, 125.5, 125.4, 124.5, 124.2, 123.8, 122.8, 121.2, 119.8, 118.7, 118.6, 114.5, 113.5, 111.6, 111.3, 35.2, 20.9. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 14.5 min and 22.9 min (major). HRMS calculated for $C_{34}H_{26}KN_2O_3S$ $[M+K]^+$ 581.1296, found:581.1301.

(+)-*N*-(2-((1*H*-Indol-3-yl)(4-methoxyphenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamidee (**3ga**): 99 mg, 95% yield, tan solid, m.p. = 94–96 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 5:1), 76% ee, $[\alpha]^{20}_D$ = +125.16 (*c* 0.60, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.99 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.33–7.25 (m, 3H), 7.21-7.09 (m, 4H), 7.08–7.02 (m, 2H), 7.00–6.95 (m, 3H), 6.76 (s, 1H), 6.74–6.69 (m, 2H), 6.23–6.10 (m, 1H) 5.57 (s, 1H), 3.73 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.5, 156.0, 153.4, 144.1, 136.4, 132.3, 129.7, 129.6, 127.6, 126.6, 126.2, 124.4, 123.4, 123.2, 122.4, 119.8, 119.7, 119.6, 115.7, 113.9, 112.8, 111.7, 111.3, 55.3, 39.1, 21.5. HPLC: Chiralcel IA column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 13.5 min (major) and 16.6 min. HRMS calculated for $C_{31}H_{26}KN_2O_4S$ $[M+K]^+$ 561.1245, found: 561.1250.

(+)-*N*-(2-((3-Bromophenyl)(1*H*-indol-3-yl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ha**): 105 mg, 92% yield, white solid, m.p. = 116–118 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 5:1), 91% ee, $[\alpha]^{20}_D$ = +78.28 (*c* 1.05, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.06 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.42–7.29 (m, 4H), 7.26–7.18 (m, 4H), 7.17–7.08 (m, 3H), 7.08–7.00 (m, 3H), 6.88 (d, *J* = 1.6 Hz, 1H), 6.14 (s, 1H), 5.65 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.2, 153.4, 144.2, 142.6, 136.4, 131.6, 130.1, 130.0, 129.7, 127.6, 127.4, 126.4, 126.1, 124.7, 123.6, 123.4, 122.6, 122.5, 120.0, 119.6, 119.4, 114.8, 113.2, 111.8, 111.4, 39.3, 21.6. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 12.0 min and 18.4 min (major). HRMS calculated for $C_{30}H_{22}BrN_2O_3S$ $[M-H]^-$ 569.0540, found: 569.0541.

(+)-*N*-(2-((3-Chlorophenyl)(1*H*-indol-3-yl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ia**): 95 mg, 90% yield, pale yellow solid, m.p. = 234–236 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 4:1), 92% ee, $[\alpha]^{20}_D$ = +139.12 (*c* 0.80, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.98 (d, *J* = 1.7 Hz, 1H), 10.12 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.28–7.13 (m, 7H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.96–6.88 (m, 4H), 5.80 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 153.7, 152.8, 143.5, 143.1, 136.7, 136.3, 132.9, 130.1, 129.4, 127.9, 127.0, 126.7, 126.6, 126.0, 125.8, 124.5, 123.9, 123.0, 121.3, 120.1, 118.8, 118.7, 113.5, 113.4, 111.7, 111.5, 38.2, 20.9. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 11.7 min and 17.0 min (major). HRMS calculated for $C_{30}H_{23}ClKN_2O_3S$ $[M+K]^+$ 565.0749, found: 565.0746.

(+)-*N*-(2-((4-Chlorophenyl)(1*H*-indol-3-yl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3ja**): 95 mg, 90% yield, white solid, m.p. = 230–232 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate = 5:1), 95% ee, $[\alpha]^{20}_D$ = +94.62 (*c* 0.95, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.07 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 8.1 Hz, 2H), 7.25–7.08 (m, 9H), 7.05–6.95 (m, 3H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.46 (s, 1H), 5.70 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.5, 153.4, 144.2, 138.8, 136.4, 136.3, 132.7, 130.0, 129.7, 128.6, 127.6, 126.4, 126.0, 124.6, 123.6, 123.3, 122.5, 120.0, 119.6, 119.5, 115.0, 113.1, 111.7, 111.4, 39.1, 21.5. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 60/40, flow = 0.8 mL/min, retention time 13.2 min and 22.8 min (major). HRMS calculated for $C_{30}H_{23}ClKN_2O_3S$ $[M+K]^+$ 565.0749, found: 565.0745.

(+)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)-5-methylbenzofuran-3-yl)-4-methylbenzenesulfonamide (**3ka**): 90 mg, 89% yield, yellow solid, m.p. = 233–234 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 5:1), 84% ee, $[\alpha]^{20}_D$ = +86.44 (*c* 0.45, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 10.91 (s, 1H), 9.91 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.27–7.13 (m, 6H), 7.12–6.94 (m, 4H), 6.93–6.84 (m, 2H), 6.81 (s, 1H), 5.79 (s, 1H), 2.24 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 155.5, 151.2, 143.1, 141.1, 137.2,

136.4, 131.7, 129.4, 128.3, 128.1, 126.9, 126.5, 126.3, 126.0, 125.2, 123.8, 121.1, 119.5, 118.9, 118.6, 114.2, 112.9, 111.6, 110.9, 38.6, 20.9, 20.8. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 19.3 min (major) and 24.1 min. HRMS calculated for $C_{31}H_{25}N_2O_3S$ [M-H]$^-$ 505.1591, found: 505.1608.

(+)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)-6-methylbenzofuran-3-yl)-4-methylbenzenesulfonamide (**3la**): 93 mg, 90% yield, yellow solid, m.p. = 214–216 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 5:1), 91% ee, $[\alpha]^{20}_D$ = +70.85 (*c* 0.47, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.26–7.17 (m, 5H), 7.17–7.11 (m, 4H), 7.05–6.99 (m, 3H), 6.99–6.94 (m, 1H), 6.81 (d, *J* = 1.7 Hz, 1H), 6.05 (s, 1H), 5.60 (s, 1H), 2.40 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 153.8, 144.1, 140.3, 136.4, 136.4, 134.8, 129.7, 128.6, 128.5, 127.7, 126.9, 126.6, 124.6, 123.6, 123.5, 122.5, 119.9, 119.5, 119.2, 115.5, 113.0, 111.9, 111.3, 39.9, 21.7, 21.6. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 22.1 min (major) and 26.7 min. HRMS calculated for $C_{31}H_{25}N_2O_3S$ [M-H]$^-$ 505.1591, found: 505.1627.

(+)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-nitrobenzenesulfonamide (**3ma**): 92 mg, 88% yield, pink solid, m.p. = 127–128 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate = 5:1), 75% ee, $[\alpha]^{20}_D$ = +61.73 (*c* 0.46, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.83–7.69 (m, 4H), 7.52–7.39 (m, 2H), 7.35–7.26 (m, 3H), 7.24–7.18 (m, 3H), 7.20–7.09 (m, 4H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.67–6.55 (m, 1H), 5.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 153.5, 149.8, 144.5, 139.8, 136.1, 128.6, 128.4, 127.2, 126.3, 125.8, 125.0, 123.9, 123.7, 123.2, 122.9, 120.1, 119.7, 118.9, 115.2, 112.1, 111.9, 111.6, 39.6. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 18.5 min and 22.9 min (major). HRMS calculated for $C_{29}H_{25}N_4O_5S$ [M+NH$_4$]$^+$ 541.1540, found: 541.1543.

(+)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)benzofuran-3-yl) methanesulfonamide (**3na**): 72 mg, 86% yield, pink solid, m.p. = 110–112 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 5:1), 85% ee, $[\alpha]^{20}_D$ = +96.94 (*c* 0.72, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.79–7.59 (m, 1H), 7.48–7.37 (m, 4H), 7.36–7.26 (m, 5H), 7.25–7.22 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.24 (s, 1H), 6.11 (s, 1H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 153.5, 140.2, 136.5, 128.7, 127.2, 126.6, 126.0, 124.8, 123.8, 123.6, 122.6, 120.0, 119.4, 119.3, 115.3, 113.1, 112.0, 111.5, 40.2, 40.1. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 24.9 min (major) and 28.3 min. HRMS calculated for $C_{24}H_{20}N_2NaO_3S$ [M+Na]$^+$ 439.1087, found: 439.1085.

(+)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)benzofuran-3-yl) methanesulfonamide (**3oa**): 83 mg, 80% yield, yellow solid, m.p. = 175–177 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate = 5:1), 83% ee, $[\alpha]^{20}_D$ = +84.74 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (d, *J* = 1.6 Hz, 1H), 9.93 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.27–7.12 (m, 8H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 2.1 Hz, 1H), 6.66 (s, 2H), 5.67 (s, 1H), 2.39 (s, 6H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 152.7, 141.8, 140.8, 138.5, 136.3, 134.3, 131.5, 128.2, 128.1, 126.5, 126.4, 126.2, 124.2, 123.5, 122.9, 121.1, 119.7, 118.7, 118.5, 113.9, 112.6, 111.5, 111.4, 38.7, 22.7, 20.3. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 70/30, flow = 0.8 mL/min, retention time 12.2 min and 18.1 min (major). HRMS calculated for $C_{32}H_{32}N_3O_3S$ [M+NH$_4$]$^+$ 538.2159, found: 538.2156.

(*S*)-(–)-*N*-(2-((1*H*-Indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3fh**): 104 mg, 93% yield, pink solid, m.p. = 145–146 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate = 5:1), 99% ee, $[\alpha]^{20}_D$ = –92.99 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.52–7.42 (m, 2H), 7.41–7.35 (m, 1H), 7.33–7.27 (m, 2H), 7.25–7.12 (m, 3H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.93 (t, *J* = 7.7 Hz, 3H), 6.57 (d, *J* = 1.8 Hz, 1H), 6.35 (s, 1H), 6.00 (s, 1H), 2.46 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 153.4, 144.0, 136.4, 136.1, 136.0, 134.0, 131.4, 129.6, 128.9, 127.9, 127.6, 126.4, 126.4, 126.4, 126.0, 125.7, 125.6, 124.5, 124.1, 123.7, 123.3, 123.2, 120.6, 120.3, 120.1, 116.8, 115.6, 114.0, 111.6, 36.8, 21.6, 16.7. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 18.0 min (major) and 21.1 min. HRMS calculated for $C_{35}H_{32}N_3O_3S$ [M+NH$_4$]$^+$ 574.2159, found: 574.2161.

(+)-*N*-(2-((4-Chlorophenyl)(7-methyl-1*H*-indol-3-yl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (**3jh**): 100 mg, 92% yield, pink solid, m.p. = 124–126 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate = 5:1), 98% ee, $[\alpha]^{20}_D$ = +102.66 (*c* 0.30, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.24–7.15 (m, 4H), 7.13–6.93 (m, 8H), 6.85 (s, 1H), 6.26 (s, 1H), 5.69 (s, 1H), 2.47 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 153.4, 144.2, 138.8, 136.4, 136.0, 132.7, 130.0, 129.7, 128.6, 127.7, 126.0, 126.0, 124.6, 123.3, 123.2, 123.2, 120.5, 120.3, 119.5, 117.2, 115.6, 113.1, 111.7, 39.2, 21.5, 16.7. HPLC: Chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 75/25, flow = 0.8 mL/min, retention time 29.1 min and 31.4 min (major). HRMS calculated for $C_{31}H_{29}ClN_3O_3S$ [M+NH$_4$]$^+$ 558.1613, found: 558.1614.

(+)-4-Methyl-*N*-(2-((1-methyl-1*H*-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)benzenesulfonamide (**3ai**): 50 mg, 49% yield, white solid, m.p. = 229–231 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 10:1), 49% ee, $[\alpha]^{20}_D$ = +54.25 (*c* 0.40, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.28–7.08 (m, 9H), 6.99–6.87 (m, 3H), 6.84 (s, 1H), 5.81 (s, 1H), 3.69 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 152.7, 142.9, 140.8, 136.9, 136.6, 129.2, 128.3, 128.1, 127.9, 126.7, 126.5, 126.5, 125.9, 124.2, 122.8, 121.1, 119.9, 119.0, 118.6, 113.3, 113.1, 111.3, 109.6, 38.4, 32.2, 20.8. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 25.1 min and 28.0 min (major). HRMS calculated for $C_{31}H_{26}N_2NaO_3S$ [M+Na]$^+$ 529.1556, found: 529.1554.

4-Methyl-*N*-(2-(phenyl(1*H*-pyrrol-3-yl)methyl)benzofuran-3-yl)benzenesulfonamide (**3aj**): 55 mg, 62% yield, pink solid, m.p. = 256–257 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 10:1), 1% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.29–7.25 (m, 1H), 7.25–7.21 (m, 4H), 7.19–7.09 (m, 3H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.76–6.67 (m, 1H), 6.19–6.02 (m, 2H), 5.91 (s, 1H), 5.76 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.6, 153.4, 144.4, 139.0, 136.5, 130.0, 129.9, 128.7, 128.7, 127.7, 127.4, 125.5, 124.7, 123.1, 118.9, 118.1, 113.3, 111.9, 108.3, 107.9, 41.4, 21.7. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 70/30, flow = 0.7 mL/min, retention time 6.9 min (major) and 7.6 min. HRMS calculated for $C_{26}H_{23}N_2O_3S$ $[M+H]^+$ 443.1424, found: 443.1421.

2.3. Experiment at gram scale

To a solution of azadiene **1a** (939 mg, 2.5 mmol) and chiral phosphoric acid (*R*)-TRIP (**A1**) (90.7 mg, 0.125 mmol) in mesitylene (37.5 mL) at –20 °C, indole **2a** (292 mg, 2.5 mmol) was added. The reaction was stirred at –20 °C for 48 h. The crude product was directly purified by silica gel column chromatography (eluent: hexanes/ethyl acetate = 10:1 to 5:1) to give the desirable chiral hetero-triarylmethane **3aa**, 1.166 g, 95% yield, 90% ee. HPLC: Chiralcel IC column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 90/10, flow = 0.7 mL/min, retention time 20.7 min (major) and 23.3 min (minor).

2.4. Synthetic transformation of compound (–)-*3fh*

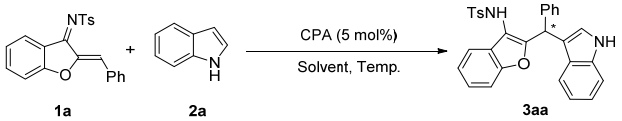
Under nitrogen atmosphere, to a solution of (–)-**3fh** (99% ee, 55 mg, 0.10 mmol) in anhydrous tetrahydrofuran, triethylamine (12.2 mg, 0.12 mmol) and 4-dimethylaminopyridine (DMAP, 12.2 mg, 0.10 mmol) were added in sequence at 0 °C, and then TsCl (23.0 mg, 0.12 mmol) in tetrahydrofuran was added dropwise. The reaction was monitored by thin-layer chromatography. After the starting material disppeared, the solvent was removed under reduced pressure. Then water was added and the mixture was extracted with dichloromethane, The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (dichloromethane/hexanes 1/2 to 1/1) to give the product (–)-**4** (60 mg, 85%) as white solid.

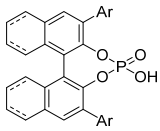
(*S*)-(–)-4-Methyl-*N*-(2-((7-methyl-1*H*-indol-3-yl)(naphthalen-1-yl)methyl)benzofuran-3-yl)-*N*-tosylbenzenesulfonamide (**4**): 60 mg, 85% yield, white solid, m.p. = 260–261 °C, new compound, R_f = 0.60 (hexanes/ethyl acetate = 5:1), 99% ee, $[\alpha]^{20}_D$ = –244.58 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.07 (d, *J* = 8.5 Hz, 1H), 7.96 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.68–7.59 (m, 1H), 7.54–7.41 (m, 2H), 7.39–7.32 (m, 3H), 7.19–7.12 (m, 3H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.04–6.91 (m, 4H), 6.74 (s, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 2H), 2.46 (s, 3H), 2.38 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.6, 153.2, 145.4, 144.6, 137.7, 136.3, 135.9, 135.9, 134.1, 131.7, 129.5, 129.4, 129.0, 128.7, 128.5, 127.9, 126.6, 126.5, 126.4, 126.3, 125.7, 125.7, 124.9, 124.7, 124.3, 123.3, 122.7, 120.2, 120.0, 119.4, 118.1, 116.1, 112.7, 112.0, 36.9, 21.8, 21.5, 16.7. HPLC: chiralcel AD-H column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 80/20, flow = 0.7 mL/min, retention time 19.3 min and 25.4 min (major). HRMS calculated for $C_{42}H_{38}N_3O_5S_2$ $[M+NH_4]^+$ 728.2247, found: 728.2257.

3. Results and discussion

At the outset, azadiene **1a** and indole **2a** were chosen as model substrates for condition optimization. To our delight, the reaction proceeded smoothly in 10 min to give the anticipated product with 90% isolated yield and 67% ee by employing chiral BINOL-based phosphoric acid (*R*)-**A1** as catalyst (Table 1, entry 1). A series of solvents were evaluated, and it was found that solvent played a crucial role in controlling the enantioselectivity of the reaction (entries 1–6). Polar solvents such as tetrahydrofuran exhibited poor enantioselectivity (entry 3). Mesitylene proved to be the most favourable solvent in view of reactivity and enantioselectivity (entry 6). Subsequently, various chiral phosphoric acids including BINOL and H8-BINOL skeletons were explored (entries 6–11). (*R*)-TRIP (**A1**) was the most efficient catalyst, providing the desired product **3aa** with 81% ee (entry 6). To further improve the enantioselectivity, the effect of temperature was examined (entries 12 and 13). When the reaction temperature was decreased to –20 °C, a higher enantioselectivity (89%) was obtained and the reactivity could be maintained by extending

Table 1
The evaluation of reaction parameters [a].



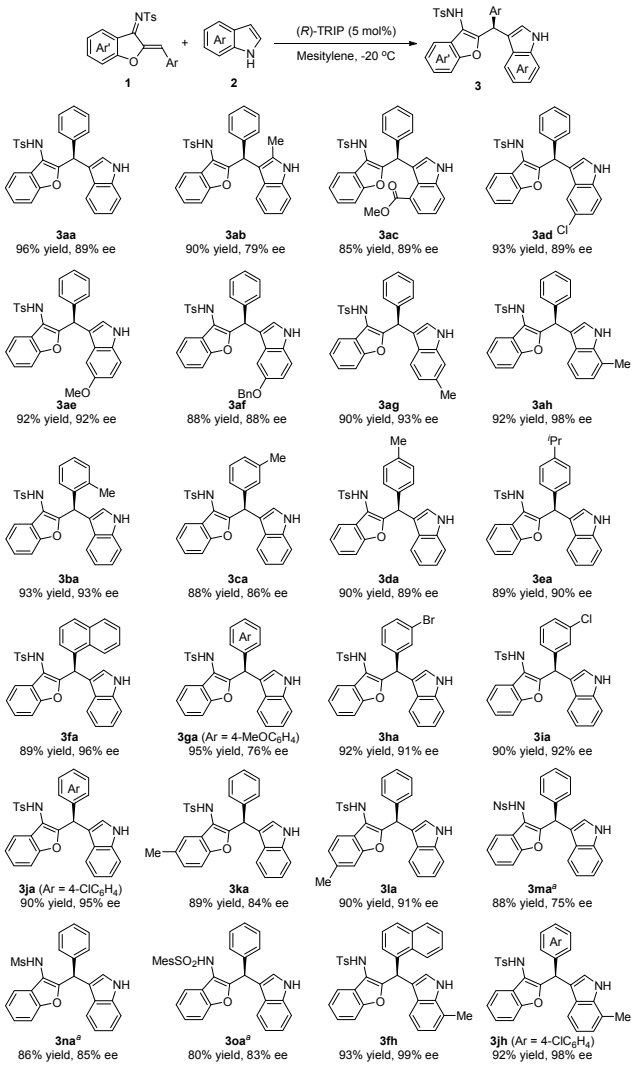


(*R*)-**A1**: Ar = 2,4,6-^{i}Pr$_3$-C$_6$H$_2$
(*S*)-**A2**: Ar = Ph
(*S*)-**A3**: Ar = SiPh$_3$
(*S*)-H$_8$-**A4**: Ar = Ph
(*R*)-H$_8$-**A5**: Ar = Anthracenyl
(*R*)-H$_8$-**A6**: Ar = 2,4,6-Me$_3$-C$_6$H$_2$

Entry	Solvent	CPA	Temp. (°C)	Yield [b] (%)	ee [c] (%)
1	CH_2Cl_2	(*R*)-**A1**	30	90	67
2	$CHCl_3$	(*R*)-**A1**	30	88	44
3	THF	(*R*)-**A1**	30	82	3
4	Toluene	(*R*)-**A1**	30	92	74
5	*p*-Xylene	(*R*)-**A1**	30	86	79
6	Mesitylene	(*R*)-**A1**	30	90	81
7	Mesitylene	(*S*)-**A2**	30	86	3
8	Mesitylene	(*S*)-**A3**	30	88	21
9 [d]	Mesitylene	(*S*)-**A4**	30	92	8
10	Mesitylene	(*R*)-**A5**	30	90	54
11	Mesitylene	(*R*)-**A6**	30	94	48
12	Mesitylene	(*R*)-**A1**	0	88	87
13	Mesitylene	(*R*)-**A1**	–20	92	89

[a] Reaction conditions: azadiene **1a** (0.10 mmol), indole **2a** (0.10 mmol), CPA (5 mol%), solvent (1.5 mL).
[b] Isolated yield.
[c] Determined by HPLC.

the reaction time to 48 h (entry 13). Therefore, the optimal condition was established: using (*R*)-TRIP as catalyst and mesitylene as solvent to perform the reaction at –20 °C. After establishing the optimal conditions, we examined the scope of conjugate addition of indoles **1** to azadienens **2** and the results are depicted in Scheme 2. In general, the reaction performed very well, delivering the corresponding chiral hetero-triarylmethanes in good yields and enantioselectivities. Various indoles were suitable for the conjugate addition. Steric properties of substituents on indole had an obvious influence on the enantioinduction. When a methyl group was introduced at the 2-position of the indole, the desired adduct **3ab** was obtained in moderate enantioselectivity. Good enantioselectivities and yields were achieved for indoles with both electron-donating and electron-withdrawing substituents at the 5-position. The reaction of 5-chloroindole with azadiene could provide adduct **3ad** with 89% ee and 93% yield. It was worth noting that using 7-methylindole as nucleophile, the corresponding product **3ah** was acquired in excellent enantioselectivity and yield. Further research was focused on a wide array of azadienes. The steric properties of the substituents on the aromatic ring had only marginal effect on yields and enantioselectivities. For example, the reaction furnished the target products **3ba** and **3da** in 93% and 89% ee, respectively. However, probably owing to electronic effects, the introduction of electron-donating methoxy group at the *para*-position of the aromatic ring resulted in the decreased ee value, and moderate enantioselectivity of **3ga** was delivered. The azadienes with methyl substituent at the 5- or 6-position of benzofuryl ring were also suitable reaction partners, giving the corresponding products **3ka** and **3la** in 84% and 91% ee, respectively. When the reaction temperature was increased to 0 °C, sulfonylimines **3m**–**3o** were transformed successfully with moderate to good enantioselectivities. Notably, the conjugate addition of azadienes **3f** and **3j** with 7-methylindole proceeded smoothly, achieving excellent enantioselectivities and yields. Moreover, the addition of pyrrole to azadiene performed well with high reactivity albeit with very low enantioselectivity (1% ee) (see the Supporting Information for details).

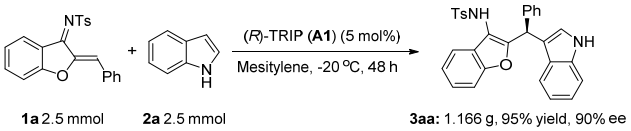


Scheme 2. Substrate scope. Conditions: azadienes **1** (0.20 mmol), indoles **2** (0.20 mmol), (*R*)-TRIP (**A1**) (5 mol%), mesitylene (3.0 mL), –20 °C, 48–72 h. [a] 0 °C, 48 h.

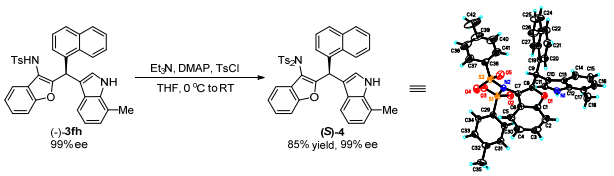
In order to further demonstrate the practicality of this methodology, the conjugate addition of indole **2a** to azadiene **1a** was conducted at gram scale, giving the desired product in 95% yield and 90% ee without noticeable loss of yield and enantioselectivity (Scheme 3).

The additional tosylation of hetero-triarylmethane (–)-**3fh** with *p*-tosyl chloride, delivering the *N*,*N*-bistosylamide (–)-**4** with good yield and without loss of enantiopurity (Scheme 4). The absolute configuration of compound (–)-**4**, which was recrystallized from dichloromethane and *n*-hexane as a colorless crystal, was unambiguously determined to be *S* by X-ray crystallographic analysis [59] (Scheme 4). Therefore, the absolute configuration of hetero-triarylmethane (–)-**3fh** was assigned as (*S*)-(–)-**3fh**.

We performed a control experiment to gain insight into the plausible mechanism. When *N*-methylindole **2i** was used as nucleophile to react with azadiene **1a** under the above standard conditions, the addition product **3ai** was obtained in only 49% yield and 49% ee by extending the reaction time to 120 h (Eq. 1). This result suggested the free N-H moiety of indole might provide a hydrogen-bonding interaction with the phos-



Scheme 3. Scale-up experiment.



Scheme 4. Synthetic transformation of compound (–)-**3fh** and X-ray crystal structure of compound (–)-**4**.

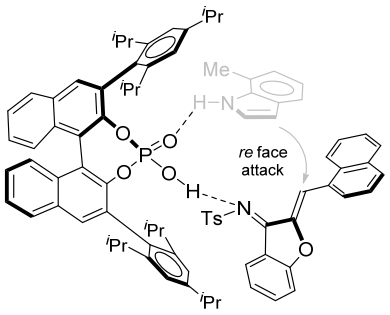
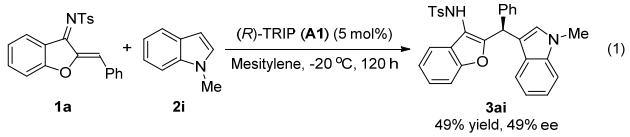


Fig. 1. A plausible transition state.

phoryl oxygen atom of chiral phosphoric acid catalyst.



On the basis of the above experimental results, we proposed a plausible transition-state model to explain the absolute configuration structure of hetero-triarylmethane products (Fig. 1). The chiral phosphoric acid simultaneously activated azadiene and indole *via* dual hydrogen-bonding interaction. The triisopropyl phenyl groups at the 3,3'-positions of the catalyst shielded the *si*-face of azadiene, and the conjugate addition preferentially occurred at the *re*-face of azadiene, affording *S*-configured hetero-triarylmethane product.

4. Conclusions

We have successfully developed an efficient chiral Brønsted acid-catalyzed conjugate addition of indoles to azadienes for the preparation of structurally important optically active hetero-triarylmethanes with excellent enantioselectivities and broad substrate scope. This chiral Brønsted acid catalytic system provides a new opportunity for the development of asymmetric reactions of azadienes. Further explorations on the application of this strategy are ongoing in our laboratory.

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Graphical Abstract

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Chiral Brønsted acid-catalyzed conjugate addition of indoles to azadienes: Enantioselective synthesis of hetero-triarylmethanes

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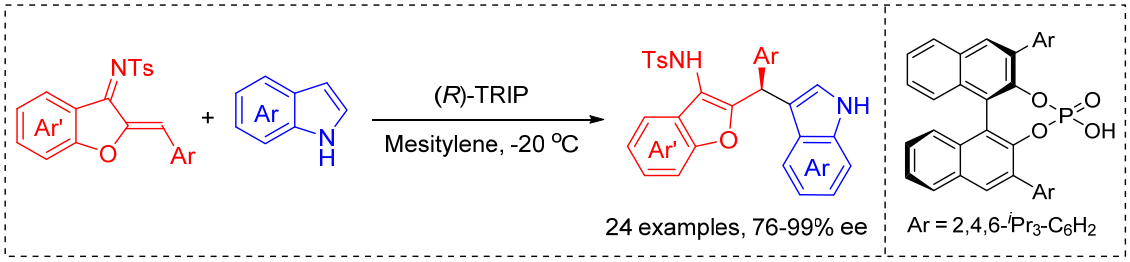

An efficient chiral Brønsted acid-catalyzed conjugate addition of indoles to azadienes has been successfully developed, which enables a facile approach to optically active hetero-triarylmethanes with excellent enantioselectivities and broad substrate scope. This chiral Brønsted acid catalytic system provides a new opportunity for the development of asymmetric reactions of azadienes.

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手性布朗斯特酸催化吲哚与氮杂二烯的共轭加成反应对映选择性合成杂三芳基甲烷

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摘要: 呋喃酮衍生的氮杂二烯具有恢复芳香性的特点, 是一类重要的高活性中间体. 近年来, 呋喃酮衍生的氮杂二烯的不对称催化反应已经取得重要进展, 并且发展了多种有效的催化体系, 包括过渡金属催化体系、手性胺催化体系、氮杂环卡宾催化体系、手性膦催化体系以及手性布朗斯特碱催化体系. 这些催化体系丰富了氮杂二烯的不对称反应类型如亲核加成和环合反应, 同时为具有生物活性结构单元的合成提供了新的途径. 尽管在有机催化中手性布朗斯特酸是一类非常重要的催化剂, 已成功应用于不对称催化反应中, 然而手性布朗斯特酸在氮杂二烯中间体不对称化学中的应用却未见报道. 为了进一步丰富氮杂二烯的不对称反应类型和构建更多的具有生物活性的结构单元, 发展新的催化体系应用于氮杂二烯的不对称反应具有重要意义.

基于本课题组之前对氮杂二烯不对称催化反应的研究, 本文发展了一种手性布朗斯特酸催化吲哚与氮杂二烯的共轭

加成反应对映选择性合成杂三芳基甲烷的方法. 通过对催化剂、溶剂和温度的筛选, 得到了最优反应条件: 使用在3,3'-位引入大位阻的2,4,6-三异丙基苯基取代的BINOL衍生的手性磷酸作为催化剂, 均三甲苯为溶剂, 反应温度为–20 ºC. 该反应具有较好的普适性, 共合成了24个手性杂三芳基甲烷化合物, 分离收率是80%–96%, 最高对映选择性可达99%. 为了提高该合成方法的实用性, 进行了克级规模反应. 实验结果表明, 氮杂二烯和吲哚的用量由0.20 mmol增加至2.5 mmol时, 不对称共轭加成反应仍能以优秀的对映选择性(90%)和收率(95%)得到目标产物, 对映选择性可以保持.

总之, 我们采用手性磷酸作为有机催化剂成功实现了吲哚与氮杂二烯的高对映选择性共轭加成反应, 合成了一系列光学活性的杂三芳基甲烷化合物, 为手性杂三芳基甲烷化合物的合成提供了一种新的有效方法, 为新药的开发奠定了基础. 该反应操作简单、条件温和并且底物适用范围广. 手性布朗斯特酸催化体系为氮杂二烯不对称催化反应的发展提供了新的机会.

关键词: 共轭加成; 杂三芳基甲烷; 氮杂二烯; 吲哚; 手性布朗斯特酸

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