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

Huan-Ping Xie, Bo Wu, Xin-Wei Wang, Yong-Gui Zhou*

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China
University of Chinese Academy of Sciences, Beijing 100049, China

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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.

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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 α-chloroaldehydes to provide 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
without further purification. 1H NMR and 13C NMR spectra were recorded at room temperature in DMSO-d6 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 (eluents: hexanes/ethyl acetate = 10:1 to 5:1) to give the chiral hetero-triarylmethanes 3.

(+)−N−2−(2-Methyl−1H-indol−3−yl)(phenyl)methyl)benzofuran−3−yl)−4−methylbenzenesulfonamide (3ab): 91 mg, 96% yield, yellow solid, m.p. = 106−113 °C, new compound, Rf = 0.25 (hexanes/ethyl acetate 5:1), 89% ee, [α]20D = +93.36 (c 0.98, EtOAc). 1H NMR (400 MHz, DMSO-d6) 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); 13C NMR (100 MHz, DMSO-d6) 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, 20.0. HPLC: Chiralcel IC column, 254 nm, 30 °C, n-hexane/2-propanol = 90/10, flow = 0.7 mL/min, retention time 12.4 min (major) and 13.0 min. HRMS calculated for C31H26N2NaO3S [M+Na]+ 530.1844, found 530.1849.

(+)−N−2−(2-Methyl−1H-indol−3−yl)(phenyl)methyl)benzofuran−3−yl)−4−methylbenzenesulfonamide (3ab): 91 mg, 96% yield, yellow solid, m.p. = 111−113 °C, new compound, Rf = 0.30 (hexanes/ethyl acetate = 5:1), 79% ee, [α]20D = +74.66 (c 0.98, EtOAc). 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 156.5, 155.5, 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, 111.7, 111.0, 110.1, 83.7, 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 C32H28NaO3S [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, Rf = 0.10 (hexanes/ethyl acetate = 5:1), 89% ee, [α]20D = +119.14 (c 0.94, EtOAc). 1H NMR (400 MHz, DMSO-d6) 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); 13C NMR (100 MHz, DMSO-d6) 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,
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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).


(+)–4-Methyl-N-(3-Chloro-4-H-indol-3-yl)(phenyl)methylbenzofuran-3-yl-4-methylbenzenesulfonamide (3aH): 93 mg, 92% yield, white solid, m.p. = 190–192 °C, new compound, R_0 = 0.30 (hexanes/ethyl acetate = 5:1), 98% ee, [α]_D^20 = +116.77 (c 0.93, EtOAc). H NMR (400 MHz, CDCl3) δ 7.34–7.25 (m, 8H), 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, 4H), 6.59 (s, 1H), 3.69 (s, 3H), 2.21 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 155.8, 153.4, 144.1, 140.2, 133.6, 129.6, 128.6, 128.4, 127.5, 127.0, 126.9, 126.1, 124.4, 123.2, 122.9, 120.5, 119.6, 114.9, 113.1, 112.0, 111.6, 105.5, 39.9, 21.5, 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 C31H26KN2O3S [M]+: 505.1591, found: 505.1604.

(+)–N-(2-((6-Methyl-1H-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3a): 94 mg, 93% yield, white solid, m.p. = 95–97 °C, new compound, R_0 = 0.25 (hexanes/ethyl acetate = 5:1), 93% ee, [α]_D^20 = −54.68 (c 0.94, EtOAc). H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 154.5, 153.3, 144.0, 138.5, 136.5, 136.4, 136.1, 130.6, 129.8, 128.5, 127.1, 126.5, 126.2, 124.5, 124.0, 122.3, 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 C31H26KN2O3S [M]+: 545.1296, found: 545.1291.

(+)–N-(2-((6-Methyl-1H-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3a): 94 mg, 93% yield, white solid, m.p. = 190–192 °C, new compound, R_0 = 0.30 (hexanes/ethyl acetate = 5:1), 98% ee, [α]_D^20 = +116.77 (c 0.93, EtOAc). H NMR (400 MHz, CDCl3) δ 7.34–7.25 (m, 8H), 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, 4H), 6.59 (s, 1H), 3.69 (s, 3H), 2.21 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 155.8, 153.4, 144.1, 140.2, 133.6, 129.6, 128.6, 128.4, 127.5, 127.0, 126.9, 126.1, 124.4, 123.2, 122.9, 120.5, 119.6, 114.9, 113.1, 112.0, 111.6, 105.5, 39.9, 21.5, 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 C31H26KN2O3S [M]+: 505.1591, found: 505.1604.

(+)–N-(2-((6-Methyl-1H-indol-3-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3a): 94 mg, 93% yield, white solid, m.p. = 190–192 °C, new compound, R_0 = 0.30 (hexanes/ethyl acetate = 5:1), 98% ee, [α]_D^20 = +116.77 (c 0.93, EtOAc). H NMR (400 MHz, CDCl3) δ 7.34–7.25 (m, 8H), 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, 4H), 6.59 (s, 1H), 3.69 (s, 3H), 2.21 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 155.8, 153.4, 144.1, 140.2, 133.6, 129.6, 128.6, 128.4, 127.5, 127.0, 126.9, 126.1, 124.4, 123.2, 122.9, 120.5, 119.6, 114.9, 113.1, 112.0, 111.6, 105.5, 39.9, 21.5, 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 C31H26KN2O3S [M]+: 505.1591, found: 505.1604.
uran-3-yl)-4-methylbenzenesulfonamide (3da): 91 mg, 90% yield, pale yellow solid, m.p. = 103–104 °C, new compound, Rf = 0.30 (hexane/ethyl acetate = 5:1), 89% ee, [α]D20 = +17.50 (c 0.40, EtOAc). νM (400 MHz, DMSO-d6) 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). νC NMR (100 MHz, CDCl3) 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 C23H25KN2O3S [M+K]+: 561.1245, found: 561.1250.

(+)–N-[(1H-indol-3-yl)-(4-isopropylphenyl)methyl]benzofuran-an-3-yl)–4-methylbenzenesulfonamide (3ea): 95 mg, 92% yield, white solid, m.p. = 116–118 °C, new compound, Rf = 0.20 (hexanes/ethyl acetate = 5:1), 91% ee, [α]D20 = +78.28 (c 1.05, EtOAc). νM (400 MHz, DMSO-d6) 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). νC NMR (100 MHz, CDCl3) δ 155.2, 153.4, 144.2, 142.6, 136.4, 131.6, 131.0, 130.0, 129.7, 127.6, 127.4, 126.4, 126.1, 124.7, 123.6, 122.6, 122.5, 122.0, 119.6, 119.4, 114.8, 113.2, 111.8, 114.9, 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 C23H23BrN2O3S [M−H]−: 569.0540, found: 569.0541.

(–)–N-[(1H-indol-3-yl)-(4-isopropylphenyl)methyl]benzofuran-an-3-yl)–4-methylbenzenesulfonamide (3ea): 95 mg, 90% yield, pale yellow solid, m.p. = 234–236 °C, new compound, Rf = 0.35 (hexanes/ethyl acetate = 4:1), 92% ee, [α]D20 = +139.12 (c 0.80, EtOAc). νM (400 MHz, DMSO-d6) δ 10.90 (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). νC NMR (100 MHz, DMSO-d6) δ 153.7, 152.8, 145.3, 143.1, 136.7, 136.3, 132.9, 130.1, 129.4, 127.9, 127.0, 126.7, 126.6, 125.9, 124.1, 123.5, 122.7, 121.0, 119.7, 118.8, 118.5, 114.2, 112.9, 111.5, 111.3, 39.1, 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 11.7 min and 17.0 min (major). HRMS calculated for C23H23BrN2O3S [M−H]−: 569.0549, found: 569.0541.
136.4, 131.7, 129.4, 128.3, 128.1, 126.9, 126.5, 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-ProOH = 90/10, flow = 0.7 mL/min, retention time 19.3 min (major) and 24.1 min. HRMS calculated for C_{21}H_{24}NO_{10}S [M-H]– 505.1591, found: 505.1608.

(−)-N-{[(1H-Indol-3-yl)(phenyl)methyl]-6-methylbenzofuran-3-yl}-4-methylbenzenesulfonamide (3ia): 93 mg, 90% yield, yellow solid, m.p. = 214–216 °C, new compound, R_{f} = 0.35 (hexanes/ethyl acetate = 5:1), 91% ee, [α]_{D}^{20} = +70.85 (c 0.47, EtOAc). νH 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); 13C NMR (100 MHz, CDCl_{3}) δ 154.8, 153.8, 144.1, 140.3, 136.4, 134.8, 129.7, 128.6, 128.5, 127.7, 126.9, 126.6, 124.6, 123.6, 123.5, 122.7, 119.9, 119.5, 119.2, 115.5, 113.0, 111.9, 111.3, 39.7, 21.7, 21.6. HPLC: Chiralcel IC column, 254 nm, 30 °C, n-hexane/i-ProOH = 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_{2}O_{3}S [M–H]– 505.1608.
4-Methyl-N-[2-(phenyl[1H-pyrrol-3-yl]methyl)benzofuran-3-yl]benzenesulfonamide (3a): 55 mg, 62% yield, pink solid, m.p. = 256–257 °C, new compound, R = 0.30 (hexanes/ethyl acetate = 10:1), 1% ee. 1H NMR (400 MHz, CDCl3) δ 8.62 (s, 1H), 7.54–7.41 (m, 2H), 7.39–7.32 (m, 3H), 7.19–7.12 (m, 3H), 7.09–7.03 (m, 2H), 6.46 (d, J = 7.5 Hz, 2H), 5.91 (s, 1H), 5.76 (s, 1H), 2.37 (s, 3H); 13C NMR (100 MHz, CDCl3) 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, 128.9, 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: chiral 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 C42H35N3O5S2 [M+H]+: 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 HBINOL 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

<table>
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<tr>
<th>Entry</th>
<th>Solvent</th>
<th>CPA (Temp.)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>(R)-A1</td>
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<td>THF</td>
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*Reaction conditions: azadiene 1a (0.10 mmol), indole 2a (0.10 mmol), CPA (5 mol%), solvent (1.5 mL).*

*Isolated yield.*

* 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 azadienes 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, sulfonylumines 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).

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 re-cristallized 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 configuratiue 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
Phosphoryl oxygen atom of chiral phosphoric acid catalyst.

\[
\begin{align*}
\text{(R)-TRIP (Af)} & \quad (5 \text{mol\%}) \\
\text{Mesitylene, -20°C, 120h} & \quad \text{TsNHAr, 45\% yield, 45\% ee}
\end{align*}
\]

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.

References


Graphical Abstract


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

Huan-Ping Xie, Bo Wu, Xin-Wei Wang, Yong-Gui Zhou*
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences

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.
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

谢焕平,a,b 吴 波,a 王新维,a 周永贵,a*

a中国科学院大连化学物理研究所催化基础国家重点实验室，辽宁大连116023
b中国科学院大学，北京100049

摘要：呋喃酮衍生物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、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催化反应类型和构建更多的具有生物活性的结构单元，发展新的催化体系用于氮杂二烯的不对称催化反应具有重要意义。

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的催化体系。
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 ℃。该反应具有较好的普适性，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，氯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氯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氯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; 氯杂二烯; 吲哚; 手性布朗斯特酸


*通讯联系人. 电话/传真: (0411)84379220; 电子信箱: ygzhou@dicp.ac.cn

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