Efficient synthesis of tetrahydronaphthalene- or isochroman-fused spirooxindoles using tandem reactions

Biao Wang,†a Hai-Jun Leng,†b Xue-Yuan Yang,a Bo Han,a Chao-Long Rao,b Li Liu,b Cheng Peng*a,c and Wei Huang*a

a State Key Laboratory Breeding Base of Systematic Research, Development and Utilization of Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, P. R. China. E-mail: huangwei@cdutcm.edu.cn

b Ministry of Education Key Laboratory of Standardization of Chinese Medicine, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, P. R. China. E-mail: pengcheng@cdutcm.edu.cn

† These authors contributed equally to this work.

Supporting Information

Table of Contents
1. General methods
2. General procedure for the synthesis of tetrahydronaphthalene-fused spirooxindole 4
3. General procedure for the synthesis of isochroman-fused spirooxindole 7
4. Procedure for the synthesis of drug-like spirocyclic products 8-12
5. Crystal data of 4a
6. NMR spectra
7. The preliminary investigation on the asymmetric versions of these tandem reactions
1. General methods

NMR data was obtained for $^1$H at 400 MHz, and for $^{13}$C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl$_3$ solution. ESI HRMS was performed on a Waters SYNAPT G2. Column chromatography was performed on silica gel (200-300 mesh) using an eluent of ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates; products were visualized using UV light and I$_2$. Melting points were determined on a Mel-Temp apparatus and were not corrected. All chemicals were used from Adamas-beta without purification unless otherwise noted.

2. General procedure for the synthesis of tetrahydronaphthalene-fused spirooxindole 4

The reaction was carried out with 3-ylideneoxindole 1 (0.3 mmol), 2-methyl-3,5-dinitrobenzaldehyde 2a (75.7 mg, 0.36 mmol) and TEA (8.4 μL, 0.06 mmol) in acetonitrile (4.0 mL) at 0 ºC for 4h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the cycloaddition product 3.

The protection of the hydroxyl group of the intermediate 3 gave the corresponding easily separable spirooxindole derivative 4. To a solution of the intermediate 3 in methylene chloride (4 mL) was added TMSCl (25.9 μL, 0.3 mmol) and imidazole (40.8 mg, 0.6 mmol). The mixture was stirred at 0 ºC for 30 min. The reaction was quenched with aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the tetrahydronaphthalene-fused spirooxindole 4.
4a was obtained as a white solid in 90% yield for two steps after flash chromatography. The dr value was calculated to be 90:10 by $^1$H NMR analysis of the crude reaction mixture. m.p. 197-200 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.76 (s, 1H), 8.56 (s, 1H), 7.38-7.22 (m, 7H), 7.05 (t, $J$ = 7.2 Hz, 1H), 6.77 (d, $J$ = 8.0 Hz, 1H), 5.17 (s, 1H), 4.88 (s, 2H), 3.96 (dd, $J$ = 16.0, 4.0 Hz, 1H), 3.68 (q, $J$ = 7.2 Hz, 2H), 3.33-3.20 (m, 2H), 0.60 (t, $J$ = 7.2 Hz, 3H), -0.21 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 176.5, 170.9, 148.4, 146.8, 144.7, 144.3, 137.5, 135.8, 129.6, 129.6, 128.9, 128.1, 127.9, 123.8, 123.6, 122.9, 118.8, 109.5, 74.6, 61.3, 54.8, 46.7, 44.4, 25.9, 13.5, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{31}$N$_3$O$_8$Si+Na 612.1778, found 612.1773.

4b was obtained as a white solid in 91% yield for two steps after flash chromatography. The dr value was calculated to be 92:8 by $^1$H NMR analysis of the crude reaction mixture. m.p. 180-182 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.75 (s, 1H), 8.56 (s, 1H), 7.35-7.08 (m, 7H), 6.68 (d, $J$ = 6.8 Hz, 1H), 5.80 (s, 1H), 5.12 (d, $J$ = 15.6 Hz, 1H), 4.56 (d, $J$ = 16.0 Hz, 1H), 4.32 (dd, $J$ = 10.0, 6.4 Hz, 1H), 4.13-4.10 (m, 1H), 3.99-3.90 (m, 2H), 3.54 (dd, $J$ = 18.0, 6.4 Hz, 1H), 0.97 (t, $J$ = 7.2 Hz, 3H), -0.11 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.8, 170.4, 148.1, 146.8, 146.3, 143.0, 137.4, 135.1, 130.8, 128.7, 127.7, 127.4, 126.9, 126.8, 125.3, 118.7, 118.2, 108.5, 71.7, 61.3, 54.9, 43.9, 42.4, 26.2, 13.7, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$BrSi+Na 690.0883, found 690.0885.

4c was obtained as a white solid in 88% yield for two steps after flash chromatography. The dr value was calculated to be 90:10 by $^1$H NMR analysis of the crude reaction mixture. m.p. 142-144 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.77 (s, 1H), 8.55 (s, 1H), 7.34-7.21 (m, 7H), 6.69 (d, $J$ = 8.4 Hz, 1H), 5.18 (s, 1H), 4.86 (s, 2H), 3.98 (dd, $J$ = 16.0, 4.0 Hz, 1H), 3.86-3.73 (m, 2H), 3.32-3.20 (m, 2H), 0.72 (t, $J$ = 7.2 Hz, 3H), -0.16 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 175.9, 170.6, 148.3, 146.7, 143.7, 143.1, 137.2, 135.2, 131.3, 129.3, 129.0, 128.2, 127.8, 124.1, 123.6, 119.0, 110.4, 74.3, 61.5, 54.8, 46.5, 44.5, 25.8, 13.6, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$ClSi+Na 646.1388, found 646.1391.
4d was obtained as a white solid in 86% yield for two steps after flash chromatography. The dr value was calculated to be 85:15 by $^1$H NMR analysis of the crude reaction mixture. m.p. 158-160 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.78$ (s, 1H), 8.55 (s, 1H), 7.39-7.28 (m, 7H), 6.64 (d, $J = 8.4$ Hz, 1H), 5.18 (s, 1H), 4.86 (s, 2H), 3.98 (dd, $J = 16.4$, 4.0 Hz, 1H), 3.86-3.75 (m, 2H), 3.32-3.18 (m, 2H), 0.73 (t, $J = 7.2$ Hz, 3H), -0.16 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 175.8$, 170.6, 148.3, 146.7, 143.7, 143.6, 137.2, 135.2, 132.3, 131.7, 129.0, 128.2, 127.7, 126.8, 123.8, 119.0, 115.2, 110.8, 74.3, 61.5, 54.7, 46.5, 44.4, 25.8, 13.6, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$BrSi+Na 690.0883, found 690.0880.

4e was obtained as a white solid in 92% yield for two steps after flash chromatography. The dr value was calculated to be 82:18 by $^1$H NMR analysis of the crude reaction mixture. m.p. 165-168 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.77$ (s, 1H), 8.55 (s, 1H), 7.34-7.28 (m, 5H), 7.04 (dd, $J = 8.0$, 2.8 Hz, 1H), 6.96 (td, $J = 8.8$, 2.4 Hz, 1H), 6.69 (q, $J = 4.4$ Hz, 1H), 5.17 (s, 1H), 4.87 (s, 2H), 3.98 (dd, $J = 15.6$, 3.2 Hz, 1H), 3.84-3.72 (m, 2H), 3.32-3.21 (m, 2H), 0.70 (t, $J = 7.2$ Hz, 3H), -0.16 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 176.10$, 170.7, 159.2 (d, $J_{CF} = 241.1$ Hz), 148.4, 146.8, 143.8, 140.7, 137.2, 135.4, 131.1 (d, $J_{CF} = 7.6$ Hz), 129.0, 128.1, 127.8, 123.9, 118.9, 115.7 (d, $J_{CF} = 23.2$ Hz), 112.0 (d, $J_{CF} = 24.3$ Hz), 110.0 (d, $J_{CF} = 7.6$ Hz), 74.4, 61.4, 55.1, 46.5, 44.5, 25.8, 13.6, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$FSi+Na 630.1684, found 630.1688.

4f was obtained as a white solid in 85% yield for two steps after flash chromatography. The dr value was calculated to be 80:20 by $^1$H NMR analysis of the crude reaction mixture. m.p. 185-188 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.89$ (s, 1H), 8.44 (s, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.41-7.30 (m, 5H), 6.80 (d, $J = 8.4$ Hz, 1H), 6.69 (s, 1H), 5.42 (d, $J = 15.6$ Hz, 1H), 5.31 (s, 1H), 4.68 (d, $J = 16.0$ Hz, 1H), 3.99 (dd, $J = 18.4$, 7.6 Hz, 1H), 3.89 (t, $J = 7.6$ Hz, 1H), 3.82-3.72 (m, 2H), 3.61 (dd, $J = 18.3$, 7.6 Hz, 1H), 0.80 (t, $J = 7.2$ Hz, 3H), 0.17 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 177.4$, 169.1, 149.7, 148.3, 146.2, 142.7, 142.5, 136.0, 133.7, 128.6, 127.8, 127.1, 126.8, 125.6, 124.2, 119.2, 118.9, 108.3, 73.9, 61.3, 54.5, 44.4, 44.3,
4g was obtained as a white solid in 85% yield for two steps after flash chromatography. The dr value was calculated to be 88:12 by $^1$H NMR analysis of the crude reaction mixture. m.p. 168-170 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.77$ (s, 1H), 8.54 (s, 1H), 7.3-7.29 (m, 5H), 7.16 (d, $J = 8.0$ Hz, 1H), 7.04 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.77 (d, $J = 1.6$ Hz, 1H), 5.13 (s, 1H), 4.85 (s, 2H), 3.96 (dd, $J = 16.0$, 3.6 Hz, 1H), 3.74 (q, $J = 7.2$ Hz, 2H), 3.31-3.19 (m, 2H), 0.70 (t, $J = 7.2$ Hz, 3H), -0.16 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 176.3$, 170.6, 148.3, 146.7, 145.9, 143.8, 137.2, 135.4, 135.1, 129.0, 128.2, 127.9, 127.7, 124.4, 123.8, 122.4, 118.9, 109.9, 74.3, 61.4, 54.4, 46.5, 44.4, 25.7, 13.6, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$Si+Na 657.1629, found 657.1633.

4h was obtained as a white solid in 81% yield for two steps after flash chromatography. The dr value was calculated to be 92:8 by $^1$H NMR analysis of the crude reaction mixture. m.p. 176-178 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.77$ (s, 1H), 8.53 (s, 1H), 7.35-7.28 (m, 5H), 7.20 (d, $J = 8.0$, 1.6 Hz, 1H), 7.10 (d, $J = 8.0$, 1H), 6.92 (s, 1H), 5.13 (s, 1H), 4.85 (s, 2H), 3.95 (dd, $J = 16.0$, 3.6 Hz, 1H), 3.74 (q, $J = 7.2$ Hz, 2H), 3.31-3.19 (m, 2H), 0.71 (t, $J = 7.2$ Hz, 3H), -0.16 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 176.2$, 170.6, 146.7, 146.0, 143.7, 137.2, 135.1, 129.0, 128.5, 128.2, 127.7, 125.5, 124.7, 123.8, 118.9, 112.6, 74.3, 61.4, 54.5, 46.4, 44.4, 25.7, 13.6, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$BrSi+Na 690.0886, found 690.0883.

4i was obtained as a white solid in 84% yield for two steps after flash chromatography. The dr value was calculated to be 85:15 by $^1$H NMR analysis of the crude reaction mixture. m.p. 96-98 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.77$ (s, 1H), 8.54 (s, 1H), 7.41-7.28 (m, 5H), 7.0-7.01 (m, 3H), 5.13 (s, 1H), 5.02 (dd, $J = 23.2$, 15.2 Hz, 2H), 3.95 (dd, $J = 15.6$, 3.2 Hz, 1H), 3.72-3.62 (m, 2H), 3.30-3.18 (m, 2H), 0.61 (t, $J = 7.2$ Hz, 3H), -0.19 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 176.3$, 170.6, 148.4, 147.6 (d, $J_{CF} = 243.6$ Hz), 146.8, 143.9, 137.3, 137.0,
132.8 (d, $J_{CF} = 3.5$ Hz), 131.4 (d, $J_{CF} = 8.5$ Hz), 128.7, 128.2 (d, $J_{CF} = 1.5$ Hz), 128.0, 123.8, 123.6, 123.6, 119.4 (d, $J_{CF} = 3.2$ Hz), 118.9, 117.8 (d, $J_{CF} = 19.5$ Hz), 74.8, 61.3, 46.9, 45.9 (d, $J_{CF} = 4.5$ Hz), 25.8, 13.5, -0.3 ppm; ESI HRMS: calcd. For C$_{30}$H$_{30}$N$_3$O$_8$Si +Na 630.1684, found 630.1682.

4j was obtained as a light yellow solid in 78% yield for two steps after flash chromatography. The dr value was calculated to be 86:14 by $^1$H NMR analysis of the crude reaction mixture. m.p. 154-156°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.76$ (s, 1H), 8.56 (s, 1H), 7.36-7.25 (m, 5H), 7.08 (s, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 7.9$ Hz, 1H), 5.16 (s, 1H), 4.86 (dd, $J = 23.6$, 15.6 Hz, 2H), 3.96 (dd, $J = 16.0$, 4.0 Hz, 1H), 3.75-3.66 (m, 2H), 3.32-3.18 (m, 2H), 2.31 (s, 3H), 0.62 (t, $J = 7.2$ Hz, 3H), -0.20 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 176.4, 170.9, 148.4, 146.7, 144.4, 142.2, 137.5, 135.9, 132.5, 129.7, 129.7, 129.0, 128.0, 128.0, 124.4, 123.8, 118.8, 109.3, 74.6, 61.2, 46.7, 44.4, 25.9, 21.3, 13.5, -0.3 ppm; ESI HRMS: calcd. For C$_{31}$H$_{33}$N$_3$O$_8$Si +Na 626.1935, found 626.1937.

4k was obtained as a white solid in 75% yield for two steps after flash chromatography. The dr value was calculated to be 80:20 by $^1$H NMR analysis of the crude reaction mixture. m.p. 185-187°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.81$ (s, 1H), 8.59 (s, 1H), 7.38 (t, $J = 7.2$ Hz, 1H), 7.38-7.25 (m, 10H), 7.04-6.96 (m, 2H), 6.32 (d, $J = 7.2$ Hz, 1H), 5.17 (s, 1H), 5.03 (d, $J = 15.2$ Hz, 1H), 4.10-3.95 (m, 3H), 3.47 (dd, $J = 16.8$, 11.6 Hz, 1H), -0.27 (s, 9H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta =$ 199.3, 177.1, 148.7, 146.9, 144.6, 144.4, 138.4, 137.0, 135.7, 133.4, 129.5, 129.2, 128.7, 128.6, 128.3, 128.2, 128.1, 125.1, 123.9, 123.3, 119.1, 109.3, 75.2, 55.3, 49.2, 44.7, 26.0, -0.2 ppm; ESI HRMS: calcd. For C$_{34}$H$_{33}$N$_3$O$_7$Si +Na 644.1829, found 644.1825.

4l was obtained as a semisolid in 52% yield for two steps after flash chromatography. The dr value was calculated to be 88:12 by $^1$H NMR analysis of the crude reaction mixture; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.16$ (d, $J = 8.4$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.36-7.25 (m, 6H), 7.19 (t, $J = 8.0$ Hz, 1H), 7.13 (d, $J = 7.6$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 7.6$ Hz, 1H), 4.95 (d, $J = 15.6$ Hz, 1H), 4.79 (d, $J = 15.6$ Hz, 1H), 4.70 (s, 1H), 3.99-3.91 (m, 1H), 3.86-3.78 (m, 2H), 3.66 (m, 2H), 2.31 (s, 3H), 0.62 (t, $J = 7.2$ Hz, 3H), -0.20 (s, 9H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta =$ 176.4, 170.9, 148.4, 146.7, 144.4, 142.2, 137.5, 135.9, 132.5, 129.7, 129.7, 129.0, 128.0, 128.0, 124.4, 123.8, 118.8, 109.3, 74.6, 61.2, 46.7, 44.4, 25.9, 21.3, 13.5, -0.3 ppm; ESI HRMS: calcd. For C$_{31}$H$_{33}$N$_3$O$_7$Si +Na 644.1829, found 644.1825.
3.71 (dd, $J = 17.2$, 12.0 Hz, 1H), 3.35 (dd, $J = 16.8$, 6.0 Hz, 1H), 0.86 (t, $J = 7.2$ Hz, 3H), -0.03 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 174.9$, 171.6, 145.9, 143.2, 142.5, 137.0, 135.4, 128.9, 128.8, 128.3, 128.2, 127.2, 127.0, 125.2, 123.9, 122.5, 121.5, 108.5, 72.2, 60.5, 52.4, 43.3, 41.9, 28.8, 13.2, -0.1 ppm; ESI HRMS: calcd. For C$_{30}$H$_{32}$N$_2$O$_6$Si+Na 567.1927, found 567.1929.

4m was obtained as a semisolid in 58% yield for two steps after flash chromatography. The dr value was calculated to be 85:15 by $^1$H NMR analysis of the crude reaction mixture. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.21$ (d, $J = 8.4$, 1H), 8.14 (s, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.43-7.41 (m, 2H), 7.35-7.27 (m, 3H), 7.06 (t, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.61 (t, $J = 7.6$ Hz, 1H), 5.63 (d, $J = 7.6$ Hz, 1H), 5.25 (d, $J = 4.8$ Hz, 1H), 4.69 (d, $J = 15.6$ Hz, 1H), 3.88 (dd, $J = 9.2$, 5.6 Hz, 1H), 3.65-3.52 (m, 3H), 3.26 (dd, $J = 17.2$, 9.2 Hz, 1H), 0.52 (t, $J = 7.2$ Hz, 3H), 0.15 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 178.1$, 170.1, 147.1, 144.5, 142.8, 140.5, 135.7, 128.6, 128.6, 128.3, 127.7, 127.6, 126.8, 124.1, 122.6, 122.0, 120.8, 108.7, 74.2, 60.9, 56.1, 44.9, 44.3, 28.1, 13.2, 0.2 ppm; ESI HRMS: calcd. For C$_{30}$H$_{32}$N$_2$O$_6$Si+Na 567.1927, found 567.1931.
3. General procedure for the synthesis of isochroman-fused spirooxindole 7

The reaction was carried out with isatin 5 (0.3 mmol), 2-methyl-3,5-dinitro-benzaldehyde 2a (0.36 mmol) and TEA (0.06 mmol) in acetonitrile (4.0 mL) at room temperature for 1 h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the hemiacetal 6.

Hemiacetal 6 were oxidized to the corresponding stable isochroman-fused spirooxindole 7. To a solution of 6 in toluene (4 mL) was added PCC (107.8 mg, 0.5 mmol). The mixture was stirred for 1 h at 60 °C. The solid was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residual was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to give the isochroman-fused spirooxindole 7.

7a was obtained as a white solid in 79% yield for two steps after flash chromatography. m.p. 171-172 °C; 1H NMR (600 MHz, CDCl3): δ = 9.28 (s, 1H), 9.12 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.38-7.27 (m, 4H), 7.23-7.17 (m, 3H), 6.82 (d, J = 7.8 Hz, 1H), 4.79 (dd, J = 33.6, 15.6 Hz, 2H), 4.02 (d, J = 19.2 Hz, 1H), 3.81 (d, J = 19.2 Hz, 1H) ppm; 13C NMR (100 MHz, CDCl3): δ = 172.4, 160.8, 147.9, 147.0, 142.5, 137.2, 134.3, 132.0, 129.8, 129.1, 128.7, 128.2, 127.2, 125.3, 124.7, 124.3, 124.2, 110.5, 79.3, 44.2, 32.4 ppm; ESI HRMS: calcd. For C23H15N3O7+Na 468.0808, found 468.0803.

7b was obtained as a white solid in 81% yield for two steps after flash chromatography. m.p. 212-214 °C; 1H NMR (600 MHz, CDCl3) δ 9.31 (s, 1H), 9.16 (s, 1H), 7.35-7.29 (m, 4H), 7.25-7.20 (m, 3H), 6.77 (d, J = 7.8 Hz, 1H), 4.82-4.70 (m, 3H), 3.73 (d, J = 19.2 Hz, 1H) ppm; 13C NMR (100 MHz, CDCl3): δ = 172.2, 160.4, 147.9, 147.0, 144.4, 137.3, 133.8, 133.1, 129.5, 129.2, 128.8, 128.4, 128.3, 127.2, 124.4, 123.1, 120.6, 109.5, 80.1, 44.3, 29.4 ppm; ESI HRMS: calcd. For C23H15N3O7Br+Na 545.9913, found 545.9916.
7c was obtained as a white solid in 78% yield for two steps after flash chromatography. m.p. 160-162 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 9.28\) (s, 1H), 9.13 (s, 1H), 7.48 (s, 1H), 7.34-7.28 (m, 4H), 7.20 (d, \(J = 7.2\) Hz, 2H), 6.74 (d, \(J = 8.4\) Hz, 1H), 4.77 (dd, \(J = 46.2, 15.2\) Hz, 2H), 4.00 (d, \(J = 18.6\) Hz, 1H), 3.81 (d, \(J = 19.2\) Hz, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
\[\delta = 172.1, 160.3, 147.9, 147.1, 140.9, 136.7, 133.8, 131.9, 129.7, 129.6, 129.2, 128.8, 128.4, 127.2, 126.8, 125.3, 124.4, 111.6, 79.0, 44.3, 32.2\) ppm; ESI HRMS: calcd. For C\(_{23}\)H\(_{14}\)N\(_3\)O\(_7\)Cl+Na 502.0418, found 502.0421.

7d was obtained as a white solid in 70% yield for two steps after flash chromatography. m.p. 162-163 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.29\) (s, 1H), 9.15 (s, 1H), 7.63 (d, \(J = 1.6\) Hz, 1H), 7.49 (dd, \(J = 8.4, 1.6\) Hz, 1H), 7.37-7.29 (m, 3H), 7.24-7.13 (m, 2H), 6.69 (d, \(J = 8.4\) Hz, 1H), 4.77 (dd, \(J = 35.2, 15.6\) Hz, 2H), 4.00 (d, \(J = 18.8\) Hz, 1H), 3.81 (d, \(J = 19.2\) Hz, 1H) ppm; \(^{13}\)C NMR (150 MHz, CDCl\(_3\)):
\[\delta = 172.0, 160.3, 147.8, 147.1, 141.4, 136.7, 134.7, 133.7, 129.6, 129.2, 128.8, 128.4, 128.0, 127.2, 127.1, 124.4, 116.8, 112.0, 78.9, 44.3, 32.2\) ppm; ESI HRMS: calcd. For C\(_{23}\)H\(_{14}\)N\(_3\)O\(_7\)Br+Na 545.9913, found 545.9911.

7e was obtained as a white solid in 80% yield for two steps after flash chromatography. m.p. 185-186 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 9.30\) (s, 1H), 9.15 (s, 1H), 7.35-7.27 (m, 3H), 7.23 (dd, \(J = 20.4, 7.2\) Hz, 3H), 7.07 (t, \(J = 8.4\) Hz, 1H), 6.75 (dd, \(J = 9.0, 4.2\) Hz, 1H), 4.78 (dd, \(J = 45.6, 15.6\) Hz, 2H), 3.99 (d, \(J = 18.6\) Hz, 1H), 3.82 (d, \(J = 18.6\) Hz, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
\[\delta = 172.3, 160.4, 159.7 (d, \text{J}_{\text{CF}} = 253.5\) Hz), 147.9, 147.2, 138.4, 136.8, 133.9, 129.7, 129.2, 128.8, 128.4, 127.2, 126.7 (d, \text{J}_{\text{CF}} = 7.8\) Hz), 124.4, 118.5 (d, \text{J}_{\text{CF}} = 23.3\) Hz), 113.0 (d, \text{J}_{\text{CF}} = 25.2\) Hz), 111.5 (d, \text{J}_{\text{CF}} = 8.9\) Hz), 79.2, 44.4, 32.3 ppm; ESI HRMS: calcd. For C\(_{23}\)H\(_{14}\)N\(_3\)O\(_7\)F+Na 486.0713, found 486.0715.
**7f** was obtained as a white solid in 79% yield for two steps after flash chromatography. m.p. 183-185 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.93 (s, 1H), 8.75 (s, 1H), 8.32 (d, $J$ = 2.0 Hz, 1H), 8.28 (dd, $J$ = 8.8, 3.0 Hz, 1H), 7.39-7.31 (m, 3H), 7.23-7.21 (m, 2H), 6.90 (d, $J$ = 8.8 Hz, 1H), 4.90 (s, 2H), 3.73 (d, $J$ = 18.8 Hz, 1H), 3.50 (d, $J$ = 18.4 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 178.1, 160.5, 148.3, 147.1, 146.9, 144.7, 140.2, 133.3, 131.8, 129.5, 129.4, 128.7, 127.6, 127.1, 127.0, 120.4, 120.4, 110.2, 92.0, 44.6, 33.0 ppm; ESI HRMS: calcd. For C$_{23}$H$_{14}$N$_4$O$_7$+Na 513.0658, found 513.0662.

**7g** was obtained as a white solid in 74% yield for two steps after flash chromatography. m.p. 143-145 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.27 (s, 1H), 9.13 (s, 1H), 7.42-7.29 (m, 4H), 7.22-7.15 (m, 3H), 6.82 (d, $J$ = 1.6 Hz, 1H), 4.76 (dd, $J$ = 27.2, 15.6 Hz, 2H), 3.99 (d, $J$ = 18.8 Hz, 1H), 3.79 (d, $J$ = 19.2 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 172.4, 160.5, 147.9, 147.2, 143.7, 138.1, 136.8, 133.7, 129.7, 129.3, 128.8, 128.4, 127.2, 125.7, 124.4, 124.2, 123.6, 111.2, 78.8, 44.4, 32.2 ppm; ESI HRMS: calcd. For C$_{23}$H$_{14}$N$_{3}$O$_7$Cl+Na 502.0418, found 502.0415.

**7h** was obtained as a white solid in 70% yield for two steps after flash chromatography. m.p. 192-194 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.26 (s, 1H), 9.12 (s, 1H), 7.37-7.28 (m, 5H), 7.22-7.20 (m, 2H), 6.97 (s, 1H), 4.75 (dd, $J$ = 25.6, 15.6 Hz, 2H), 3.98 (d, $J$ = 18.8 Hz, 1H), 3.79 (d, $J$ = 18.8 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 172.3, 160.5, 147.9, 147.1, 143.8, 136.8, 133.7, 129.6, 129.2, 128.8, 128.4, 127.2, 127.2, 126.0, 125.9, 124.4, 124.2, 113.9, 78.9, 44.3, 32.1 ppm; ESI HRMS: calcd. For C$_{23}$H$_{14}$N$_3$O$_7$Br +Na 545.9913, found 545.9915.
7i was obtained as a white solid in 80% yield for two steps after flash chromatography. m.p. 175-177 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.27 \text{ (s, 1H)}, 9.13 \text{ (s, 1H), 7.33-7.14 \text{ (m, 8H)}, 4.92 \text{ (dd, } J = 33.2, 15.6 \text{ Hz, 2H), 3.97 \text{ (d, } J = 18.8 \text{ Hz, 1H)} \) ppm; \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 172.3, 160.4, 147.9, 147.6 \text{ (d, } J_{CF} = 245.6 \text{ Hz), 147.1, 136.7, 135.4, 129.7, 129.2 \text{ (d, } J_{CF} = 9.4 \text{ Hz), 128.9, 128.7, 128.2, 128.0 \text{ (d, } J_{CF} = 3.1 \text{ Hz), 127.5 \text{ (d, } J_{CF} = 1.5 \text{ Hz), 125.2, 125.2, 124.4, 120.6 \text{ (d, } J_{CF} = 3.4 \text{ Hz), 120.2 \text{ (d, } J_{CF} = 19.5 \text{ Hz), 79.1 \text{ (d, } J_{CF} = 2.6 \text{ Hz), 45.9 \text{ (d, } J_{CF} = 4.7 \text{ Hz), 32.4 \text{ ppm; ESI HRMS: calcd. For C}_{23}\text{H}_{14}\text{N}_3\text{O}_7\text{F}+\text{Na} 486.0713, found 486.0717.}

7j was obtained as a white solid in 65% yield for two steps after flash chromatography. m.p. 181-183 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.28 \text{ (s, 1H)}, 9.13 \text{ (s, 1H), 7.34-7.15 \text{ (m, 7H), 6.70 \text{ (d, } J = 8.0 \text{ Hz, 1H)}, 4.76 \text{ (dd, } J = 28.8, 15.6 \text{ Hz, 2H), 4.01 \text{ (d, } J = 19.2 \text{ Hz, 1H), 3.79 \text{ (d, } J = 19.2 \text{ Hz, 1H), 2.36 \text{ (s, 3H) ppm; ESI HRMS: calcd. For C}_{24}\text{H}_{17}\text{N}_3\text{O}_7\text{Na} 482.0964, found 482.0965.}

7k was obtained as a white solid in 72% yield for two steps after flash chromatography. m.p. 180-182 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.28 \text{ (s, 1H), 9.13 \text{ (s, 1H), 7.50 \text{ (t, } J = 8.0 \text{ Hz, 2H), 7.23 \text{ (t, } J = 7.6 \text{ Hz, 1H), 6.94 \text{ (d, } J = 8.0 \text{ Hz, 1H)}, 3.99 \text{ (d, } J = 18.8 \text{ Hz, 1H), 3.75 \text{ (d, } J = 18.8 \text{ Hz, 1H)}, 3.15 \text{ (s, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): } \delta = 172.3, 160.8, 147.9, 147.1, 143.3, 137.2, 132.1, 129.9, 128.7, 125.3, 124.6, 124.2, 124.2, 109.4, 79.3, 32.3, 26.5 \text{ ppm; ESI HRMS: calcd. For C}_{17}\text{H}_{11}\text{N}_3\text{O}_7\text{Na} 392.0495, found 392.0497.}

11
71 was obtained as a white solid in 78% yield for two steps after flash chromatography. m.p. 160-162 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.23$ (s, 1H), 9.11 (s, 1H), 7.47 (dd, $J = 15.2, 7.6$ Hz, 2H), 7.21 (t, $J = 7.6$ Hz, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 5.82-5.73 (m, 1H), 5.27-5.23 (m, 2H), 4.22 (d, $J = 5.2$ Hz, 2H), 4.01 (d, $J = 18.8$ Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 172.0, 160.7, 147.9, 147.1, 142.6, 137.2, 132.0, 130.1, 129.9, 128.7, 125.3, 124.7, 124.3, 124.1, 118.9, 110.3, 79.2, 42.8, 32.4 ppm; ESI HRMS: calcd. For C$_{19}$H$_{13}$N$_3$O$_7$+Na $^{418.0651}$, found 418.0652.

4. Procedure for the synthesis of drug-like spirocyclic products 8-12

The reaction was carried out with olefinic indenedione (70.3 mg, 0.3 mmol), 2-methyl-3,5-dinitro-benzaldehyde 2a (75.7 mg, 0.36 mmol) and TEA (8.4 $\mu$L, 0.06 mmol) in acetonitrile (4.0 mL) at 0 °C for 4h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the cycloaddition product. To a solution of the intermediate in methylene chloride (4 mL) was added TMSCl (25.9 $\mu$L, 0.3 mmol) and imidazole (40.8 mg, 0.6 mmol). The mixture was stirred at 0 °C for 30 min. The reaction was quenched with aqueous NaHCO$_3$, extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the tetrahydronaphthalene-fused spirocyclic indenedione 8 in 78% yield. The dr value was calculated to be 84:16 by $^1$H NMR analysis of the crude reaction mixture. m.p. 174-176 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.88$ (s, 1H), 8.68 (s, 1H), 7.99 (d, $J = 7.6$ Hz, 1H), 7.88-7.78 (m, 3H), 7.18 (br s, 5H), 5.58 (s, 1H), 4.13 (dd, $J = 19.2, 12.0$ Hz, 1H), 3.86 (dd, $J = 12.4, 6.0$ Hz, 1H), 3.70 (dd, $J = 19.2, 5.6$ Hz, 1H), 0.12 (s, 9H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 201.5, 200.4, 148.4, 146.2, 143.7, 143.3, 143.0, 138.1, 137.1, 135.9, 135.5, 128.7, 128.3, 128.0, 125.0, 122.8, 122.7, 118.9, 74.4, 61.2, 44.1, 31.2, -0.1 ppm; ESI HRMS: calcd. For C$_{27}$H$_{34}$N$_2$O$_7$Si+Na $^{539.1250}$, found 539.1252.
The reaction was carried out with olefinic pyrazolone (78.7 mg, 0.3 mmol), 2-methyl-3,5-dinitro-benzaldehyde 2a (75.7 mg, 0.36 mmol) and TEA (8.4 μL, 0.06 mmol) in acetonitrile (4.0 mL) at 0 °C for 4h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the cycloaddition product. To a solution of the intermediate in methylene chloride (4 mL) was added TMSCl (25.9 μL, 0.3 mmol) and imidazole (40.8 mg, 0.6 mmol). The mixture was stirred at 0 °C for 30 min. The reaction was quenched with aqueous NaHCO₃, extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the tetrahydronaphthalene-fused spirocyclic pyrazolone 9 in 75% yield. The dr value was calculated to be 80:20 by ¹H NMR analysis of the crude reaction mixture. m.p. 232-234 °C; ¹H NMR (400 MHz, CDCl₃): δ = 8.74 (s, 1H), 8.59 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.36 (m, J = 7.8 Hz, 2H), 7.27 (d, J = 3.2 Hz, 3H), 7.20 (d, J = 6.8 Hz, 3H), 5.30 (s, 1H), 4.09 (dd, J = 20.4, 13.6 Hz, 1H), 3.53-3.41 (m, 2H), 2.11 (s, 3H), 0.28 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 170.9, 158.2, 147.8, 146.0, 141.3, 137.8, 137.4, 137.1, 129.0, 128.5, 128.2, 126.6, 125.6, 125.1, 118.8, 118.7, 73.1, 61.0, 43.1, 30.4, 14.0, 0.3 ppm; ESI HRMS: calcd. For C₂₈H₂₈N₄O₆Si+Na 567.1676, found 567.1673.

The reaction was carried out with ninhydrin (53.4 mg, 0.3 mmol), 2-methyl-3,5-dinitro-benzaldehyde 2a (75.7 mg, 0.36 mmol) and TEA ((8.4 μL, 0.06 mmol) in acetonitrile (4.0 mL) at room temperature for 1h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the hemiacetal. To a solution of hemiacetal and triethyl silane (47.9 μL, 0.3 mmol) in DCM (5 mL) was added BF₃·Et₂O (44.4 μL, 0.36 mmol). The mixture was stirred at 0 °C for 2 h. The reaction was quenched with aqueous NaHCO₃, extracted
with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1). The isochroman-fused spirocyclic indenedione 10 was obtained in 71% yield after flash chromatography. m.p. 194-196 °C; ¹H NMR (400 MHz, CDCl₃): δ = 8.82 (s, 1H), 8.27 (s, 1H), 8.05 (dd, J = 5.6, 3.2 Hz, 2H), 7.97 (dd, J = 5.6, 3.2 Hz, 2H), 5.32 (s, 2H), 3.48 (s, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 196.2, 148.7, 146.0, 140.2, 138.9, 137.2, 132.9, 124.5, 124.3, 123.8, 123.4, 118.9, 65.4, 27.4 ppm; ESI HRMS: calcd. For C₁₇H₁₀N₂O₇+Na 377.0386, found 377.0388.

The reaction was carried out with alloxan (48.0 mg, 0.3 mmol), 2-methyl-3,5-dinitrobenzaldehyde 2a (75.7 mg, 0.36 mmol) and TEA (8.4 μL, 0.06 mmol) in acetonitrile (4.0 mL) at room temperature for 1h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the hemiacetal. To a solution of hemiacetal and triethyl silane (47.9 μL, 0.3 mmol) in DCM (5 mL) was added BF₃·Et₂O (44.4 μL, 0.36 mmol). The mixture was stirred at 0 °C for 2 h. The reaction was quenched with aqueous NaHCO₃, extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1). The isochroman-fused spirocyclic pyrimidinetrione 11 was obtained in 60% yield after flash chromatography. m.p. 226-228 °C; ¹H NMR (400 MHz, CDCl₃): δ = 8.83 (s, 1H), 8.72 (s, 1H), 8.64 (s, 1H), 8.29 (s, 1H), 5.17 (d, J = 15.6 Hz, 1H), 5.00 (dd, J = 11.2, 2.8 Hz, 1H), 3.49 (d, J = 18.0 Hz, 1H), 3.26 (dd, J = 18.4, 10.8 Hz, 1H) ppm; ¹³C NMR (100 MHz, DMSO): δ = 150.4, 148.2, 145.7, 145.2, 144.0, 138.9, 135.4, 135.1, 123.7, 70.9, 67.5, 31.6 ppm; ESI HRMS: calcd. For C₁₁H₇N₄O₈+Na 359.0240, found 359.0244.

The reaction was carried out with acenaphthenequinone (54.7 mg, 0.3 mmol), 2-methyl-3,5-
dinitro-benzaldehyde 2a (75.7 mg, 0.36 mmol) and TEA (8.4 μL, 0.06 mmol) in acetonitrile (4.0 mL) at room temperature for 1h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to afford the hemiacetal. To a solution of hemiacetal and triethyl silane (47.9 μL, 0.3 mmol) in DCM (5 mL) was added BF₃·Et₂O (44.4 μL, 0.36 mmol). The mixture was stirred at 0 °C for 2 h. The reaction was quenched with aqueous NaHCO₃, extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1). The isochroman-fused spirocyclicacenaphthylenone 12 was obtained in 74% yield after flash chromatography. m.p. 224-226°C; ¹H NMR (600 MHz, CDCl₃): δ = 8.83 (s, 1H), 8.31 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.99 (t, J = 7.8 Hz, 2H), 7.80 (t, J = 7.8 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 5.49 (d, J = 16.8 Hz, 1H), 5.25 (d, J = 16.2 Hz, 1H), 3.67 (d, J = 19.2 Hz, 1H), 3.60 (d, J = 18.6 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 200.2, 149.0, 146.0, 141.8, 139.5, 137.6, 134.3, 132.5, 130.9, 130.4, 128.8, 128.7, 126.5, 123.3, 122.9, 120.8, 118.7, 64.9, 31.1 ppm; ESI HRMS: calcd. For C₂₀H₁₂N₂O₆+Na 399.0593, found 399.0595.
5. Crystal data of 4a

Empirical formula: \( \text{C}_{30}\text{H}_{31}\text{N}_{3}\text{O}_{8}\text{Si} \)
Formula weight: 589.67
Temperature/K: 150(2)
Crystal system: orthorhombic
Space group: P\text{b}c\text{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a/\text{Å} )</td>
<td>12.4185(4)</td>
<td></td>
</tr>
<tr>
<td>(b/\text{Å} )</td>
<td>19.1948(7)</td>
<td></td>
</tr>
<tr>
<td>(c/\text{Å} )</td>
<td>24.2024(9)</td>
<td></td>
</tr>
<tr>
<td>(\alpha/\degree )</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>(\beta/\degree )</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>(\gamma/\degree )</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Volume/Å\(^3\): 5769.1(4)
\(Z\): 8
\(\rho_{\text{calc}}/\text{g/cm}^3\): 1.358
\(\mu/\text{mm}^{-1}\): 0.138
\(F(000)\): 2480.0
Crystal size/mm\(^3\): 0.491 × 0.148 × 0.139
Radiation: MoK\(\alpha\) (\(\lambda = 0.71073\))

2\(\Theta\) range for data collection/\(\degree\): 6.334 to 55.04
Index ranges: -16 ≤ \(h\) ≤ 16, -24 ≤ \(k\) ≤ 24, -31 ≤ \(l\) ≤ 31
Reflections collected: 85112
Independent reflections: 6620 [\(R_{\text{int}} = 0.0933, R_{\text{sigma}} = 0.0446\)]
Data/restraints/parameters: 6620/0/383
Goodness-of-fit on \(F^2\): 1.028
Final R indexes [\(I > \sigma (I)\)]: \(R_1 = 0.0519, wR_2 = 0.1343\)
Final R indexes [all data]: \(R_1 = 0.0902, wR_2 = 0.1567\)
Largest diff. peak/hole / e Å\(^{-3}\): 0.53/-0.24
6. NMR spectra
Irradiation Ha at 5.30 ppm, no signal at 4.08 ppm.
7. The preliminary investigation on the asymmetric versions of these tandem reactions

Table S1. Screening the optimal bifunctional organocatalyst for the asymmetric synthesis of chiral tetrahydronaphthalene-fused spirooxindolesa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>48</td>
<td>49</td>
<td>90:10</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>48</td>
<td>31</td>
<td>92:8</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>48</td>
<td>40</td>
<td>85:15</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>72</td>
<td>30</td>
<td>80:20</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>72</td>
<td>25</td>
<td>82:18</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>72</td>
<td>35</td>
<td>90:10</td>
<td>-46</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>48</td>
<td>43</td>
<td>88:12</td>
<td>-60</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>48</td>
<td>47</td>
<td>90:10</td>
<td>-85</td>
</tr>
</tbody>
</table>

a Unless noted otherwise, reactions were performed with 1c (0.15 mmol), 2a (0.3 mmol), catalyst (10 mol%) and 4Å MS (40 mg) in dichloromethane (0.5 mL) at 0 °C for the time shown in the Table. b Yield of isolated 4c. c Calculated based on 1H NMR analysis of the crude reaction mixture. d Determined by HPLC analysis on chiral column (Chiralpak OD-H column, hexane/2-propanol = 90/10, 1.0 mL/min, t_major = 11.14 min, t_minor = 17.12 min).
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret. Time (detected)</th>
<th>Area</th>
<th>Ret. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a</td>
<td>11.14</td>
<td>588.697</td>
<td>60.20</td>
<td>1345.600</td>
<td>n.a</td>
</tr>
<tr>
<td>2</td>
<td>n.a</td>
<td>17.18</td>
<td>874.739</td>
<td>49.70</td>
<td>835.108</td>
<td>n.a</td>
</tr>
</tbody>
</table>

---

**Diagram:**

- **Peak 1:** n.a.
- **Peak 2:** n.a.

---

### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret. Time (detected)</th>
<th>Area</th>
<th>Ret. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a</td>
<td>11.14</td>
<td>1164.788</td>
<td>97.22</td>
<td>1695.694</td>
<td>n.a</td>
</tr>
<tr>
<td>2</td>
<td>n.a</td>
<td>17.12</td>
<td>33.958</td>
<td>9.79</td>
<td>8.978</td>
<td>n.a</td>
</tr>
</tbody>
</table>

---

**Diagram:**

- **Peak 1:** n.a.
- **Peak 2:** n.a.

---

**Note:**

- **4c racemate**
- **4c chiral**
Table S2. Screening the optimal bifunctional organocatalyst for the asymmetric synthesis of chiral isochroman-fused spirooxindoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>72</td>
<td>30</td>
<td>-30</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>72</td>
<td>25</td>
<td>-40</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>72</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>48</td>
<td>40</td>
<td>-80</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>48</td>
<td>35</td>
<td>-55</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>48</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>48</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>48</td>
<td>51</td>
<td>72</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless noted otherwise, reactions were performed with 5a (0.15 mmol), 2a (0.3 mmol), catalyst (10 mol%) and 4Å MS (40 mg) in dichloromethane (0.5 mL) at 0 °C for the time shown in the Table. <sup>b</sup> Yield of isolated 4c. <sup>c</sup> Determined by HPLC analysis on chiral column (Chiralpak AD-H column, hexane/2-propanol = 80/20, 1.0 mL/min, t<sub>minor</sub> = 32.04 min, t<sub>major</sub> = 40.88 min).
In the preliminary screening studies (Table S1 and S2), we examined a number of chiral bifunctional tertiary amine-hydrogen-bond donor catalysts (Cat. a-h). This led to the identification of thiourea-based bifunctional organocatalyst a as the optimal catalyst for the synthesis of chiral tetrahydronaphthalene-fused spirooxindole with high stereoselectivity and in moderate yields (Table S1, entry 1). Meanwhile, the squaramide-cinchona bifunctional catalyst f could provide chiral isochroman-fused spirooxindole with high enantioselectivity (Table S2, entry 6).