Electronic Supplementary Material (ESI) for Chemical Communications

Organocatalytic asymmetric cyanation of isatin derived *N*-Boc ketoimines

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(Part I)

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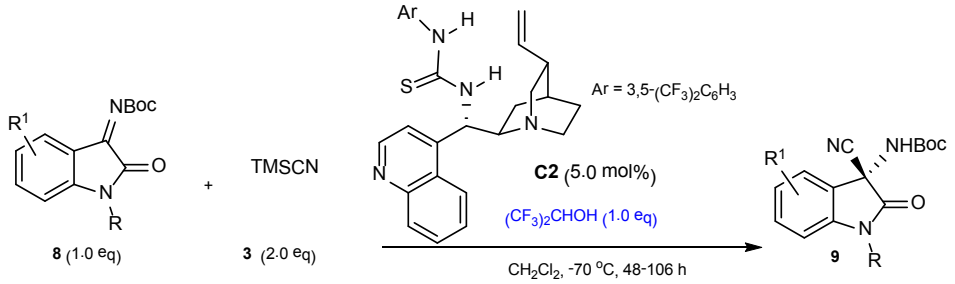
General: Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. The $[\alpha]_D$ was recorded using PolAAr 3005 High Accuracy Polarimeter. Infrared (IR) spectra were obtained using a Bruker tensor 27 infrared spectrometer.^{1}H and ^{13}C NMR spectra were obtained using a Bruker DPX-400 spectrometer. Chemical shifts are reported in ppm from $CDCl_3$ or $(CD_3)_2SO$ with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad.

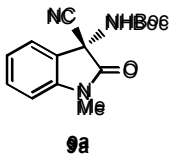
All reactions were carried out in air except noted. Anhydrous DCM was prepared by distillation over P_2O_5-CaH_2 prior to use. All the chiral (thio)urea catalysts were prepared using literature procedures.[1] All the isatins were commercially available or easily prepared using literature procedures.[2] The *N*-Boc ketoimines were prepared according to a literature method.[3]

[1] a) A. Berkessel, S. Mukherjee, T. N. Müller, F. Cleemann, K. Roland, M. Brandenburg, J.-M. Neudörfl, J. Lex, *Org. Biomol. Chem.*, 2006, **4**, 4319; b) G. Tárkányi, P. Király, S. Varga, B. Vakulya, T. Soós, *Chem. Eur. J.,* 2008, **14**, 6078; c) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.,* 2008, **73**, 3475; d) A. Peschiulli, C. Quigley, S. Tallon, Y. K. Gun'ko, S. J. Connon, *J. Org. Chem.,* 2008, **73**, 6409; e) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.,* 2005, **7**, 1967.
[2] For a review on the synthesis of isatins, see: da J. F. M. Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc.,* 2001, **12**, 273.
[3] W. Yan, D.Wang, J. Feng, P. Li, D. Zhao and R. Wang, *Org. Lett.*, 2012, **14**, 2512.

General procedure for the Strecker reaction of ketoimine 8 with TMSCN.

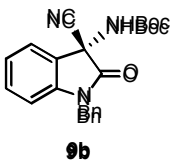


To a 10 mL vial were added catalyst **C2** (7.1 mg, 0.0125 mmol), ketoimines **8** (0.25 mmol) and $(CF_3)_2CHOH$ (25.0 μl, 0.25 mmol), followed by 1.0 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred vigorously at room temperature until the full dissolution of ketoimines **8**, and then cooled to -70 °C for about 30 minutes before TMSCN **3** (0.50 mmol, 67.0 μl) was added. After the addition of TMSCN **3**, the reaction was kept at -70 °C till the completion of ketoimines **8** by TLC analysis. The residue was directly subjected to column chromatography using petroleum ether/ethyl acetate (from 15:1 to 5:1) as the eluent, affording the desired product **9**.



9a

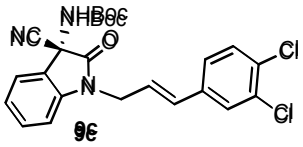
The reaction was run at -70 °C for 96 h, affording the product **9a** in 93% yield as yellow solid (m.p. 170-172 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 12.95 min, t_r (minor) = 17.47 min) gave the isomeric composition of the product: 98% ee, $[\alpha]^{25}_D$ = 31.2 (c = 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.29 (s, 3H), 5.51 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.18 (td, J = 7.6, 0.8 Hz, 1H), 7.44 (td, J = 7.6, 1.2 Hz, 1H), 7.84-7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.85, 153.51, 142.91, 131.25, 125.90, 124.66, 124.15, 114.50, 109.19, 82.14, 54.56, 27.95, 27.21; IR (ATR): 3316, 2923, 2853, 2245, 1725, 1705, 1610, 1491, 1469, 1370, 1255, 1151, 755; HRMS (ESI): Exact mass calcd for $C_{15}H_{17}N_3O_3$ $[M]^+$: 287.1270, Found: 287.1275.



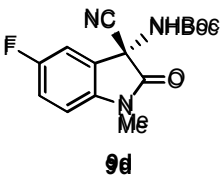
9b

The reaction was run at -70 °C for 48 h, affording the desired product **9b** in 95% yield as yellow solid (m.p. 76-78 °C); HPLC analysis (Chiralcel AS, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 24.19 min, t_r (minor) = 13.85 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D$ = 22.3 (c = 0.47, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 4.91-5.00 (m, 2H), 5.95 (s, 1H), 6.77 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.26-7.34 (m, 6H), 7.81-7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.18, 153.57, 142.04, 134.17, 131.09, 128.89, 127.96, 127.11, 125.97, 124.67, 124.15, 114.54, 110.21,

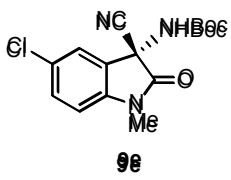
82.22, 54.72, 44.73, 27.98; IR (ATR): 3312, 2978, 2853, 2246, 1723, 1713, 1610, 1485, 1467, 1279, 1156, 752; HRMS (ESI): Exact mass calcd for $C_{21}H_{21}N_3O_3$ $[M]^+$: 363.1583, Found: 363.1588.



The reaction was carried out at -70 °C for 48 h, affording the desired product **9c** in 90% yield as yellow solid (m.p. 69-71 °C); HPLC analysis (Chiralcel ADH, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 14.55 min, t_r (minor) = 13.15 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D$ = -19.2 (c = 0.65, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (s, 9H), 4.46-4.61 (m, 2H), 5.89 (s, 1H), 6.19 (dt, *J* = 21.6, 5.2 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.15-7.19 (m, 2H), 7.32-7.41 (m, 3H), 7.78 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.88, 153.39, 142.06, 136.00, 132.62, 131.62, 131.26, 130.95, 130.39, 128.29, 125.78, 125.55, 124.58, 124.26, 123.13, 114.49, 109.85, 82.30, 54.72, 42.57, 28.03; IR (ATR): 3342, 2924, 2853, 2246, 1712, 1611, 1467, 1366, 1158, 751; HRMS (ESI): Exact mass calcd for $C_{23}H_{21}N_3O_3Cl_2$ $[M]^+$: 457.0960, Found: 457.0968.

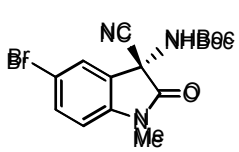


The reaction was carried out at -70 °C for 48 h. Column chromatography afforded the desired product **9d** in 92% yield as yellow solid (m.p. 148-149 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 9.92 min, t_r (minor) = 13.97 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D$ = 38.2 (c = 0.45, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9H), 3.28 (s, 3H), 5.51 (s, 1H), 6.19 (dd, *J* = 12.0, 3.6 Hz, 1H), 7.15 (td, *J* = 8.4, 2.4 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.62, 160.90, 158.47, 153.60, 139.01 (d, *J* = 2.0 Hz), 125.97 (d, *J* = 9.0 Hz), 117.8 (d, *J* = 24.0 Hz), 114.79, 114.55, 114.09, 109.99 (d, *J* = 8.0 Hz), 82.59, 54.63, 28.05, 27.47; IR (ATR): 3310, 2924, 2852, 2249, 1713, 1622, 1494, 1393, 1158, 817; HRMS (ESI): Exact mass calcd for $C_{15}H_{16}N_3O_3F$ $[M]^+$: 305.1176, Found: 305.1179.



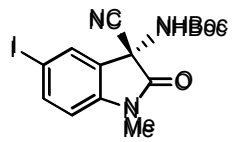
The reaction was carried out at -70 °C for 48 h. Column chromatography afforded the desired product **9e** in 84% yield as yellow solid (m.p. 147-149 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 9.29 min, t_r (minor) = 14.19 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D$ = 16.7 (c = 0.51, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9H), 3.28 (s, 3H), 5.51 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.84 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.50, 153.48, 141.58, 131.30, 129.66, 126.59, 126.00, 114.00, 110.24,

82.64, 54.47, 28.05, 27.44; IR (ATR): 3410, 2923, 2853, 2238, 1741, 1718, 1610, 1487, 1464, 1393, 1161, 852; HRMS (ESI): Exact mass calcd for $C_{15}H_{16}N_3O_3Cl$ $[M]^+$: 321.0880, Found: 321.0883.



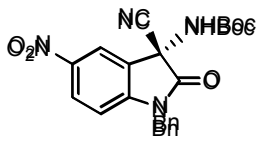
9f

The reaction was carried out at -70 °C for 48 h. Column chromatography afforded the desired product **9f** in 82% yield as yellow solid (m.p. 172-173 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 9.97 min, t_r (minor) = 14.01 min) gave the isomeric composition of the product: 97% ee, $[\alpha]^{25}_D$ = 40.2 (c = 0.44, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (s, 9H), 3.26 (s, 3H), 5.76 (s, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.40, 153.47, 142.06, 134.21, 129.21, 126.26, 116.75, 113.98, 110.69, 82.64, 54.38, 28.05, 27.41; IR (ATR): 3303, 2925, 2854, 2248, 1730, 1714, 1620, 1496, 1468, 1368, 1272, 1163, 858; MS (EI): 365 (M^+, 19), 367 ($[M+2]^+$, 20), 57 (100), 264 (60), 266 (59), 309 (52), 142 (29), 251 (23); HRMS (EI): Exact mass calcd for $C_{15}H_{16}N_3O_3{}^{79}Br$ $[M]^+$: 365.0375, Found: 365.0373.



9g

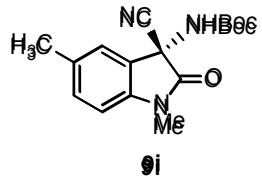
The reaction was carried out at -70 °C for 58 h. Column chromatography afforded the desired product **9g** in 91% yield as yellow solid (m.p. 151-153 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 11.53 min, t_r (minor) = 16.95 min) gave the isomeric composition of the product: 95% ee, $[\alpha]^{25}_D$ = -2.1 (c = 0.80, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9H), 3.26 (s, 3H), 5.50 (s, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.10 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.22, 153.40, 142.72, 140.10, 134.48, 126.47, 113.99, 111.18, 86.37, 82.60, 54.18, 28.03, 27.34; IR (ATR): 3314, 2926, 2854, 2248, 1740, 1714, 1604, 1484, 1417, 1393, 1353, 1252, 1156, 812; HRMS (ESI): Exact mass calcd for $C_{15}H_{16}N_3O_3I$ $[M]^+$: 413.0236, Found: 413.0237.



9h

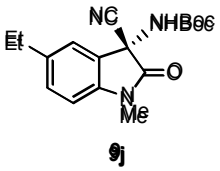
The reaction was carried out at -70 °C for 72 h. Column chromatography afforded the desired product **9h** in 81% yield as yellow oil; HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 10.29 min, t_r (minor) = 17.87 min) gave the isomeric composition of the product: 90% ee, $[\alpha]^{25}_D$ = -1.4 (c = 0.29, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9H), 4.98-5.10 (m, 2H), 6.10-6.11 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.30-7.38 (m, 5H), 8.24 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.59 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.45, 153.26, 147.61, 144.29,

133.20, 129.16, 128.44, 127.81, 127.16, 125.25, 121.24, 113.36, 110.29, 83.16, 54.36, 45.34, 28.01; IR (ATR): 3333, 2926, 2853, 2253, 1752, 1715, 1611, 1525, 1486, 1445, 1336, 1154, 730; MS (EI): 408 (M^+, 3), 409 ($[M+1]^+$, 1), 91 (100), 57 (25), 92 (11), 65 (8), 281 (6), 217 (5), 352 (5); HRMS (EI): Exact mass calcd for $C_{21}H_{20}N_4O_5$ $[M]^+$: 408.1434, Found: 408.1433.



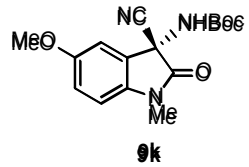
9i

The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9i** in 95% yield as yellow solid (m.p. 169-171 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 9.45 min, t_r (minor) = 16.34 min) gave the isomeric composition of the product: >99% ee, $[\alpha]^{25}_D$ = 16.3 (c = 0.32, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9H), 2.37 (s, 3H), 3.26 (s, 3H), 5.46 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.79, 153.57, 140.52, 134.07, 131.51, 126.67, 124.66, 114.65, 108.93, 82.11, 54.68, 28.01, 27.23, 20.98; IR (ATR): 3313, 2924, 2854, 2244, 1711, 1620, 1607, 1500, 1355, 1281, 1145, 1019, 827; HRMS (ESI): Exact mass calcd for $C_{16}H_{19}N_3O_3$ $[M]^+$: 301.1426, Found: 301.1430.



9j

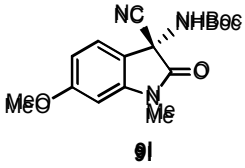
The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9j** in 92% yield as yellow solid (m.p. 144-146 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 8.47 min, t_r (minor) = 11.09 min) gave the isomeric composition of the product: 97% ee, $[\alpha]^{25}_D$ = 12.9 (c = 0.45, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (t, *J* = 7.6 Hz, 3H), 1.40 (s, 9H), 2.64 (q, *J* = 7.6 Hz, 2H), 3.24 (s, 3H), 5.78 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.83, 153.57, 140.69, 140.62, 130.38, 125.55, 124.77, 114.66, 108.99, 82.08, 54.69, 28.41, 27.97, 27.22, 15.66; IR (ATR): 3311, 2926, 2361, 1713, 1617, 1496, 1392, 1364, 1355, 1281, 1255, 1158, 853; HRMS (ESI): Exact mass calcd for $C_{17}H_{21}N_3O_3$ $[M]^+$: 315.1583, Found: 315.1588.



9k

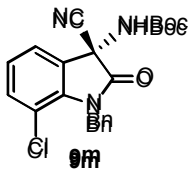
The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9k** in 90% yield as yellow solid (m.p. 149-151 °C); HPLC analysis (Chiralcel AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 31.19 min, t_r (minor) = 18.60 min) gave the isomeric composition of the product: 95% ee, $[\alpha]^{25}_D$ = 17.3 (c = 0.60, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (s, 9H), 3.24

(s, 3H), 3.80 (s, 3H), 5.75 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.94 (dd, J = 8.0, 2.8 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.53, 156.94, 153.62, 136.16, 125.75, 116.25, 114.54, 112.83, 109.78, 82.21, 55.87, 54.86, 28.01, 27.31; IR (ATR): 3276, 2924, 2853, 2243, 1742, 1686, 1610, 1523, 1497, 1465, 1286, 1033, 822; HRMS (ESI): Exact mass calcd for $C_{16}H_{19}N_3O_4$ $[M]^+$: 317.1376, Found: 317.1383.



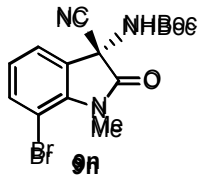
9l

The reaction was carried out at -30 °C for 72 h using $ClCH_2CH_2Cl$ as solvent. Column chromatography afforded the desired product **9l** in 94% yield as yellow oil; HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 14.23 min, t_r (minor) = 19.55 min) gave the isomeric composition of the product: 97% ee, $[\alpha]^{25}_D$ = 36.7 (c = 0.43, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (s, 9H), 3.23 (s, 3H), 3.83 (s, 3H), 5.70 (s, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.4, 2.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.38, 162.32, 153.63, 144.41, 127.32, 116.53, 114.79, 107.80, 97.12, 82.04, 55.62, 54.26, 28.02, 27.22; IR (ATR): 3320, 2928, 2851, 2248, 1716, 1622, 1506, 1468, 1369, 1252, 1156, 1081, 731; HRMS (ESI): Exact mass calcd for $C_{16}H_{19}N_3O_4$ $[M]^+$: 317.1376, Found: 317.1378.



9m

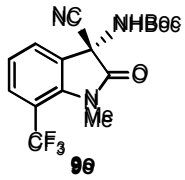
The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9m** in 91% yield as yellow solid (m.p. 108-110 °C); HPLC analysis (Chiralcel AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 23.64 min, t_r (minor) = 6.71 min) gave the isomeric composition of the product: 92% ee, $[\alpha]^{25}_D$ = 42.6 (c = 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9H), 5.39 (s, 2H), 5.95 (s, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.25-7.35 (m, 6H), 7.71 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.88, 153.35, 138.35, 136.01, 133.72, 128.67, 127.46, 127.25, 126.29, 125.04, 124.25, 116.41, 114.03, 82.60, 54.46, 46.11, 28.00; IR (ATR): 3313, 2924, 2853, 2248, 1732, 1715, 1603, 1497, 1465, 1367, 1153, 765; HRMS (ESI): Exact mass calcd for $C_{21}H_{20}N_3O_3Cl$ $[M]^+$: 397.1193, Found: 397.1196.



9n

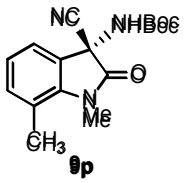
The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9n** in 90% yield as yellow solid (m.p. 160-162 °C); HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 5.33 min, t_r (minor) = 5.75 min) gave the isomeric composition of the product: 96%

ee, $[\alpha]^{25}_D$ = 73.7 (c = 0.91, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (s, 9H), 3.65 (s, 3H), 5.89 (s, 1H), 6.99-7.03 (m, 1H), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.70 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.46, 153.22, 140.45, 136.88, 127.45, 125.21, 124.67, 113.95, 103.20, 82.48, 54.30, 31.10, 27.97; IR (ATR): 3288, 2925, 2854, 2251, 1726, 1707, 1607, 1504, 1452, 1340, 1156, 749; HRMS (ESI): Exact mass calcd for $C_{15}H_{16}N_3O_3Br$ $[M]^+$: 365.0375, Found: 365.0378.



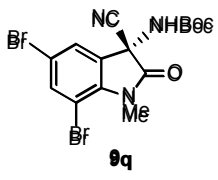
9o

The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9o** in 86% yield as yellow oil; HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 5.48 min, t_r (minor) = 5.93 min) gave the isomeric composition of the product: 93% ee, $[\alpha]^{25}_D$ = 34.3 (c = 0.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.36 (s, 9H), 3.48-3.49 (m, 3H), 5.94 (s, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.71-7.73 (m, 1H), 7.97 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.88, 153.23, 141.04, 129.08 (q, *J* = 11.5 Hz), 127.06, 124.26, 123.60, 121.56, 118.86, 113.77, 113.69 (q, *J* = 66.0 Hz), 82.64, 53.38, 30.10 (q, *J* = 13.0 Hz), 27.89; IR (ATR): 3331, 2980, 2852, 2249, 1750, 1716, 1599, 1457, 1422, 1338, 1121, 747; HRMS (ESI): Exact mass calcd for $C_{16}H_{16}N_3O_3F_3$ $[M]^+$: 355.1144, Found: 355.1152.



9p

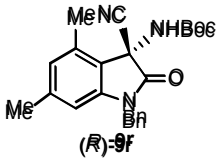
The reaction was carried out at -70 °C for 106 h. Column chromatography afforded the desired product **9p** in 90% yield as yellow solid (m.p. 178-179 °C); HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 10.79 min, t_r (minor) = 14.09 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D$ = 42.3 (c = 0.43, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 1.39 (s, 9H), 2.56 (s, 3H), 3.54 (s, 3H), 5.69 (s, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.13-7.15 (m, 1H), 7.61 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.67, 153.37, 140.70, 134.99, 125.30, 124.06, 123.65, 120.86, 114.61, 82.12, 54.37, 30.76, 28.02, 18.91; IR (ATR): 3281, 2925, 2853, 2252, 1703, 1602, 1510, 1457, 1363, 1255, 784; HRMS (ESI): Exact mass calcd for $C_{16}H_{19}N_3O_3$ $[M]^+$: 301.1426, Found: 301.1430.



9q

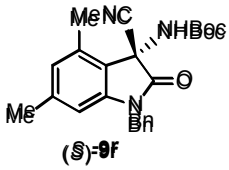
The reaction was carried out at -30 °C for 48 h using $ClCH_2CH_2Cl$ as solvent. Column chromatography afforded the desired product **9q** in 89% yield as yellow solid (m.p. 184-186 °C); HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 5.58 min, t_r (minor) = 6.06 min) gave the isomeric composition of the product: 90% ee, $[\alpha]^{25}_D$ = 31.8 (c = 0.49, MeOH); ^{1}H NMR (400 MHz,

$CDCl_3$): 1.40 (s, 9H), 3.64 (s, 3H), 5.84 (s, 1H), 7.69-7.70 (m, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.02, 153.19, 139.77, 138.87, 128.55, 127.85, 116.89, 113.47, 103.82, 82.92, 54.16, 31.16, 28.03; IR (ATR): 3391, 2979, 2926, 2232, 1741, 1718, 1570, 1490, 1453, 1247, 846; HRMS (ESI): Exact mass calcd for $C_{15}H_{15}N_3O_3Br_2$ $[M]^+$: 442.9480, Found: 442.9494.



(*R*)-**9r**

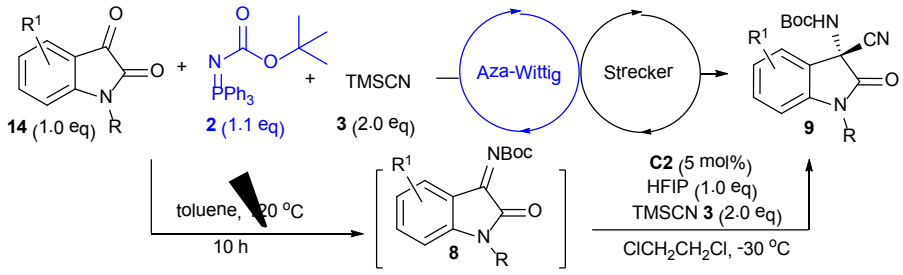
The reaction was carried out at -70 ^oC for 106 h. Column chromatography afforded the desired product **9r** in 89% yield as yellow oil; HPLC analysis (Chiralcel OZ-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 7.09 min, t_r (minor) = 7.93 min) gave the isomeric composition of the product: 95% ee, $[\alpha]^{25}_D$ = 21.6 (c = 0.55, MeOH); ^1H NMR (400 MHz, $CDCl_3$): 1.45 (s, 9H), 2.20 (s, 3H), 2.29 (s, 3H), 5.19 (s, 2H), 5.91 (s, 1H), 6.87 (s, 1H), 7.21-7.27 (m, 3H), 7.31-7.35 (m, 2H), 7.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.16, 153.52, 137.57, 136.15, 135.55, 134.00, 128.92, 127.41, 125.49, 125.34, 124.16, 120.65, 114.81, 82.13, 54.59, 46.03, 28.03, 20.61, 18.42; IR (ATR): 3319, 2979, 2931, 2248, 1712, 1603, 1483, 1454, 1367, 1156, 728; HRMS (ESI): Exact mass calcd for $C_{23}H_{25}N_3O_3$ $[M]^+$: 391.1896, Found: 391.1905.



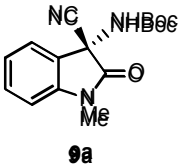
(*S*)-**9r**

The reaction was carried out at -70 ^oC for 120 h using **C4** as catalyst. Column chromatography afforded the desired product **9r** in 65% yield as yellow oil; HPLC analysis (Chiralcel OZ -H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 8.31 min, t_r (minor) = 7.55 min) gave the isomeric composition of the product: 94% ee, $[\alpha]^{25}_D$ = -21.3 (c = 3.10, MeOH); The data of product (*S*)**-9r** are the same as (*R*)**-9r** in the above.

General procedure for the one-pot tandem aza-Wittig/Strecker reaction.

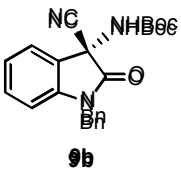


To a 10 mL seal tube were added isatins **14** (0.25 mmol), phosphazene **2** (103.7 mg, 0.275 mmol), followed by 1.0 mL of anhydrous toluene. The reaction mixture was stirred vigorously at 120 °C until the most of isatins **14** was completed (about 10 h), and cooled to room temperature. The toluene was removed under reduced pressure. Then catalyst **C2** (7.1 mg, 0.0125 mmol) and $(CF_3)_2CHOH$ (HFIP) (25.0 μl, 0.25 mmol) was added. Followed by 1.0 mL of anhydrous $ClCH_2CH_2Cl$ and then cooled to -30 °C for about 30 minutes before the TMSCN **3** (0.50 mmol, 67.0 μl) was added. After the addition of TMSCN **3**, the reaction was kept at -30 °C till the completion of ketoimines by TLC analysis. The residue was directly subjected to column chromatography using petroleum ether/ethyl acetate (from 15:1 to 5:1) as the eluent, affording the desired product **9**.



9a

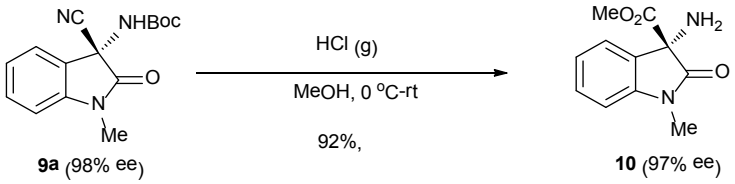
The reaction was run at -30 °C for 72 h, affording the product **9a** in 81% yield as yellow solid; HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 12.39 min, t_r (minor) = 16.54 min) gave the isomeric composition of the product: 95% ee, $[\alpha]^{25}_D = 28.6$ (c = 0.49, MeOH).



9b

The reaction was run at -30 °C for 58 h, affording the desired product **9b** in 86% yield as yellow solid; HPLC analysis (Chiralcel AS, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 21.39 min, t_r (minor) = 12.39 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D = +20.5$ (c = 0.73, MeOH)**.**

The preparation of amino acid ester 10 from 9a[4]

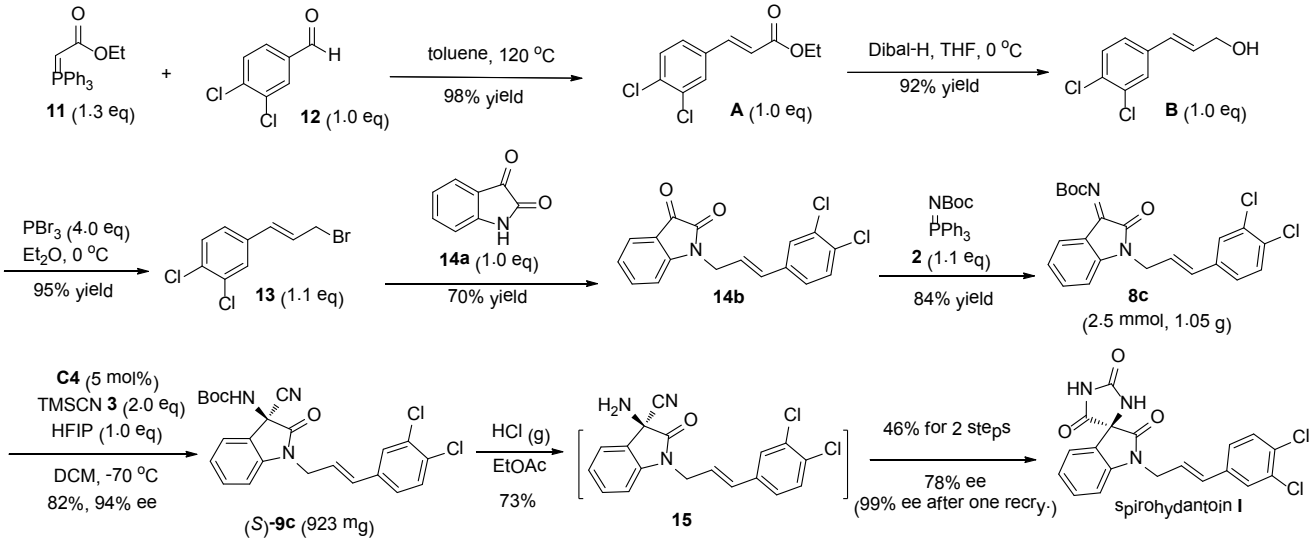


9a (98% ee) **10** (97% ee)

In a 10.0 mL three-necked flask, **9a (**50.9 mg, 0.18 mmol, 98% ee) and 2.0 mL of anhydrous methanol were added under N_2. The resulting mixture was stirred at 0 ^oC for 10 mins, and then dried HCl gas was bubbled slowly for 10 min. The resulting reaction mixture was stirred at room temperature overnight until the completion of **9a** by TLC analysis. The solvent was removed under reduced pressure, and 5.0 mL of saturated aqueous solution of $NaHCO_3$ was added. The mixture was \extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2/ethyl acetate = 10/1 as the eluent) to give product **10** (35.6 mg) in 92% yield as yellow solid (m.p. 105-107 ^oC); HPLC analysis [Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 14.55 min, t_r (minor) = 17.24 min)] gave the isomeric composition of the product: 97% ee; $[\alpha]^{25}_D$ = -110.1 (c = 0.80, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (brs, 2H), 3.24 (s, 3H), 3.67 (s, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.30-7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.32, 170.37, 144.16, 130.13, 128.53, 123.37, 123.28, 108.79, 65.12, 53.32, 26.63; MS (EI): 220 (M^+, 4), 161 (100), 57 (18), 71 (12), 162 (11), 118 (11), 69 (10), 83 (10), 97 (10); HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_3$ $[M]^+$: 220.0848, Found: 220.0847.

[4] A. Sacchetti, A. Silvani, F. G. Gatti, G. Lesma, T. Pilati and B. Trucchi, *Org. Biomol. Chem.,* 2011, **9**, 5518.

The total synthesis of spirohydantoin I.



(*E*)-ethyl 3-(3,4-dichlorophenyl)acrylate A: A seal tube was charged with compound **11** (8.46 g, 24.3 mmol), aldehyde **12** (3.31 g, 18.7 mmol) and 10 mL of toluene. The resulting solution was stirred for 6 h at 120 °C, then the mixture was cooled to room temperature and directly subjected to silica gel column chromatography (petroleum ether/ethyl acetate = 50/1 as the eluent) to give product (*E*)-ethyl 3-(3,4-dichlorophenyl)acrylate **A** as white soild (4.50 g, 18.4 mmol) in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (t, J = 7.2 Hz, 3H), 4.27 (q, J = 12.0 Hz, 2H), 6.41 (d, J = 16.0 Hz, 1H), 7.33-7.35 (m, 1H), 7.45-7.47 (m, 1H), 7.54-7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 166.26, 141.70, 134.46, 134.04, 133.17, 130.80, 129.52, 126.90, 120.14, 60.70, 14.21.

(*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-ol B: Under nitrogen, a 150 mL three-necked round bottom flask was charged with (*E*)-α,ß-unsaturated ester **A** (18.8 mmol, 4.6 g) and anhydrous THF (30 mL). Then DIBAL-H (41.4 mmol, 1 M solution in hexanes, 41.4 mL) was injected slowly over 15 minutes from a syringe at 0 °C. The resulting solution was stirred at 0 °C for 1 h. Then the reaction mixture was carefully quenched by the slow addition of saturated aqueous solution of NH_4Cl. The white solid material formed was filtered through the celite. The filtrate was concentrated under reduced pressure. The crude residue was subjected to flash chromatography (petroleum ether/ ethyl acetate = 4/1) affording 3.51 g of (*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-ol **B** as a white solid in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 2.20 (brs, 1H), 4.30-4.31 (m, 2H), 6.30-6.37 (m, 1H), 6.48-6.52 (m, 1H), 7.14-7.19 (m, 1H), 7.33-7.37 (m, 1H), 7.41-7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 136.81,

132.63, 131.20, 130.58, 130.43, 128.29, 128.09, 125.53, 63.11.

(*E*)-4-(3-bromoprop-1-enyl)-1,2-dichlorobenzene 13: Under nitrogen, a 100 mL three-necked round bottom flask was charged with (*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-ol **B** (15.3 mmol, 3.1 g) and anhydrous Et_2O (30 mL). Then PBr_3 (61.2 mmol, 5.8 mL) was injected slowly over three portions at 0 ^oC. The resulting solution was stirred at 0 ^oC for 2 h. Then the reaction mixture was carefully quenched by the slow addition of saturated aqueous solution of $NaHCO_3$. The resulting solution was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1 as the eluent) to give product (*E*)-4-(3-bromoprop-1-enyl)-1,2-dichlorobenzene **13** (3.85 g, 95% yield) as colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 4.12 (d, J = 7.6 Hz, 2H), 6.35-6.42 (m, 1H), 6.52-6.56 (m, 1H), 7.19-7.21 (m, 1H), 7.38-7.41 (m, 1H), 7.45-7.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 135.75, 132.63, 131.86, 131.79, 130.40, 128.23, 127.09, 125.71, 32.37.

Preparation of isatin derivative 14b: Under nitrogen, a 100 mL three-necked round bottom flask was charged with isatin **14a** (9.7 mmol, 1.43 g) and anhydrous DMF (30 mL). Then NaH (11.6 mmol, 464 mg, 60% in mineral oil) was added slowly over two portions at 0 ^oC. The resulting solution was stirred at 0 ^oC for 0.5 h. Followed by the addition (*E*)-4-(3-bromoprop-1-enyl)-1,2-dichlorobenzene **13** (11.6 mmol, 3.01 g) dropwise. The resulting mixture was stirred at 0 ^oC for 1.0 h, and carefully quenched by the slow addition of saturated aqueous solution of NaCl (30 mL). The yellow solid formed was filtered and washed with petroleum ether and cold Et_2O. The yellow solid was recrystallized using petroleum ether/acetone, affording the desired product **14b** (2.25 g) in 70% yield.^1H NMR (400 MHz, DMSO-d_6): 4.46 (d, J = 4.4 Hz, 2H), 6.39-6.45 (m, 1H), 6.68-6.72 (m, 1H), 7.09-7.14 (m, 2H), 7.39-7.41 (m, 1H), 7.51-7.65 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): 183.82, 158.57, 150.94, 138.67, 137.60, 131.93, 131.24, 130.38, 129.68, 128.62, 126.88, 126.18, 125.01, 123.88, 118.21, 111.59, 41.65. IR (ATR): 2974, 2890, 1806, 1725, 1610, 1469, 1370, 983, 754; MS (EI): 331 (M^+, 10), 332 (M^+, 2), 146 (100), 115 (31), 148 (29), 90 (26), 149 (19), 150 (18), 185 (17); HRMS (EI): Exact mass calcd for $C_{17}H_{11}NO_2Cl_2$ $[M]^+$: 331.0167, Found: 331.0169.

Preparation of *N*-Boc ketoimine 8c: A 10 mL seal tube was charged with isatin **14b** (1.97 mmol, 656.3 g), iminophosphorane **2** (2.17 mmol, 656.3 g), anhydrous toluene (3.0 mL) and 1,4-dioxane (1.0 mL). The resulting mixture was stirred at 120 ^oC for 10 h until most of **14b** was completed. Then the

reaction mixture was cooled to room temperature, and directly subjected to silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 as the eluent) to give product *N*-Boc ketoimine **8c** (1.65 mmol, 0.72 g) in 84% yield as yellow soild.^{1}H NMR (400 MHz, DMSO-d_6): 1.51 (s, 9H), 4.46 (d, J = 4.8 Hz, 2H), 6.36-6.42 (m, 1H), 6.63 (d, J = 16.0 Hz, 1H), 7.07-7.14 (m, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.51-7.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.28, 157.13, 153.43, 147.83, 137.41, 136.43, 131.97, 131.14, 130.51, 130.29, 128.65, 126.92, 126.08, 124.25, 123.97, 119.16, 111.37, 83.20, 41.95, 28.19. IR (ATR): 2981, 2853, 2397, 1735, 1719, 1675, 1611, 1468, 1367, 1351, 1142, 746; MS (EI): 430 (M^+, 3), 57 (100), 147 (83), 115 (52), 185 (49), 145 (37), 150 (33); HRMS (EI): Exact mass calcd for $C_{22}H_{20}N_2O_3Cl_2$ $[M]^+$: 430.0851, Found: 430.0853.

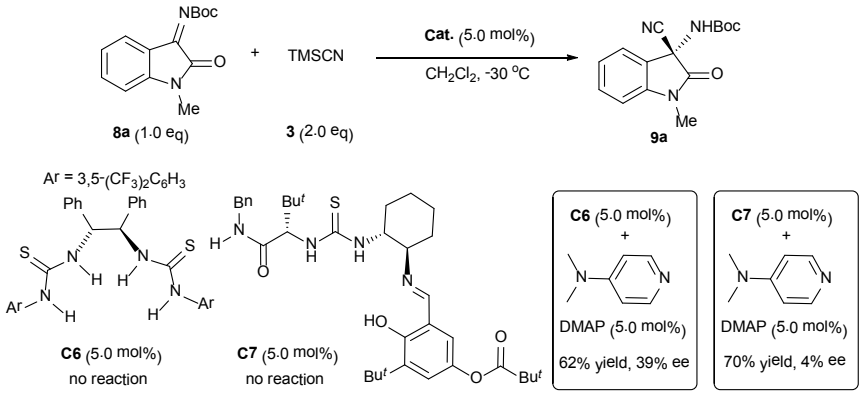
Preparation of α-amino nitrile (*S*)-9c: To a 10 mL vial were added catalyst **C4** (71.0 mg, 0.125 mmol), *N*-Boc ketoimine **8c** (2.5 mmol, 1.05 g) and HFIP (250.0 µl, 2.5 mmol), followed by 5.0 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred vigorously at room temperature until the full dissolution of ketoimine **8c**, and then cooled to -70 ^{o}C for about 30 minutes before the TMSCN **3** (5.0 mmol, 650.0 µl) was added. The reaction was kept at -70 ^{o}C till the completion of N-Boc ketoimine **8c** by TLC analysis. The residue was directly subjected to column chromatography using petroleum ether/ethyl acetate (from 8:1) as the eluent, affording the desired product α-amino nitrile (*S*)**-9c** (2.03 mmol, 0.93 g) in 81% yield as yellow solid. HPLC analysis [Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 13.63 min, t_r (minor) = 15.19 min)] gave the isomeric composition of the product: 94% ee; $[\alpha]^{25}_{D}$ = +26.7 (c = 0.42, MeOH); The ^{1}H and ^{13}C NMR of product (*S*)**-9c** are similar to that of (*R*)**-9c** shown above**.**

Preparation of α-amino nitrile 15: In a 10.0 mL three-necked flask, α-amino nitrile (*S*)**-9c (**113.0 mg, 0.24 mmol, 94% ee) and 2.5 mL of anhydrous ethyl acetate were added under N_2. The resulting mixture was stirred at 0 ^{o}C for 10 mins, and then dried HCl gas was bubbled slowly for 9 min until the completion of (*S*)**-9c** by TLC analysis. The reaction was carefully quenched by the slow addition of saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2/ethyl acetate = 10/1-1/2 as the eluent) to give product **15** (60.5 mg) in 73% yield as white solid. Product **15** was not stable enough, and was immediately used for the next step.

Preparation of spirohydantoin I[4]: To a solution of **15** (55.1 mg, 0.16 mmol) in 3.0 mL of dry CH_2Cl_2 was added chlorosulfonyl isocyanate (CSI) (16.0 μl, 0.16 mmol). After the reaction mixture was stirred at room temperature for 10 min, CH_2Cl_2 was removed under pressure, and then 3.0 mL of 2 N HCl was added. The suspension was heated to reflux for 2 h. Once the mixture cooled to room temperature, the reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2/ethyl acetate = 5/1 as the eluent) to give product spirohydantoin **I** (29.5 mg) as white solid in 46% yield for two steps. HPLC analysis (Chiralcel AD-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 230 nm; t_r (major) = 18.44 min, t_r (minor) = 15.31 min) gave the isomeric composition of the product: 79% ee, which could be easily improved to 99% by a single recrystallization. $[\alpha]^{25}_D$ = +10.0 (c = 1.30, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.51 (d, *J* = 4.4 Hz, 2H), 6.41 (dt, *J* = 16.0, 4.8 Hz, 1H), 6.51 (d, *J* = 16.0, 1H), 7.12-7.15 (m, 2H), 7.35-7.42 (m, 3H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 8.72 (s, 1H), 11.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.38, 171.26, 158.20, 143.88, 137.40, 132.09, 131.43, 131.41, 130.60, 129.32, 128.61, 126.93, 125.92, 125.27, 124.74, 124.13, 110.67, 69.81, 42.01; IR (ATR): 3424, 3332, 2923, 2854, 1786, 1726, 1606, 1568, 852; HRMS (ESI): Exact mass calcd for $C_{19}H_{13}N_3O_3Cl_2$ $[M]^+$: 401.0334, Found: 401.0337. Reported rotation for (*S*)-spirohydantoin **I** $[\alpha]_D^{20}$ = +16.2 (c = 0.50, MeOH).[4] Accordingly, the absolute configuration of the spirohydantoin **I** we synthesized was assigned to be *S*.

The control experiments and the proposed stereochemical model.

The control experiment: Some control experiments were conducted to learn more about the reaction mechanism. It was found the use of tertiary amine as the Lewis base catalyst was very important for this reaction, as either thiourea catalyst **C6** or **C7** alone failed to catalyze this reaction at all (Scheme 2). Even in the presence of 1.0 equiv of MeOH,[5] Jacobsen's thiourea catalyst **C7** still failed, despite it had been established as a powerful catalyst for the Strecker reaction of benzyl amine derived ketoimines.[5] However, the combination of chiral thiourea catalysts **C6** or **C7** with equal amount of achiral tertiary amine DMAP, the reaction worked well, and product **9a** could be obtained in 39% or 4% ee, as shown in Scheme 1. These results suggested the bifunctional catalysis nature of this reaction, with tertiary amine activating TMSCN and thiourea activating ketoimine **8**.

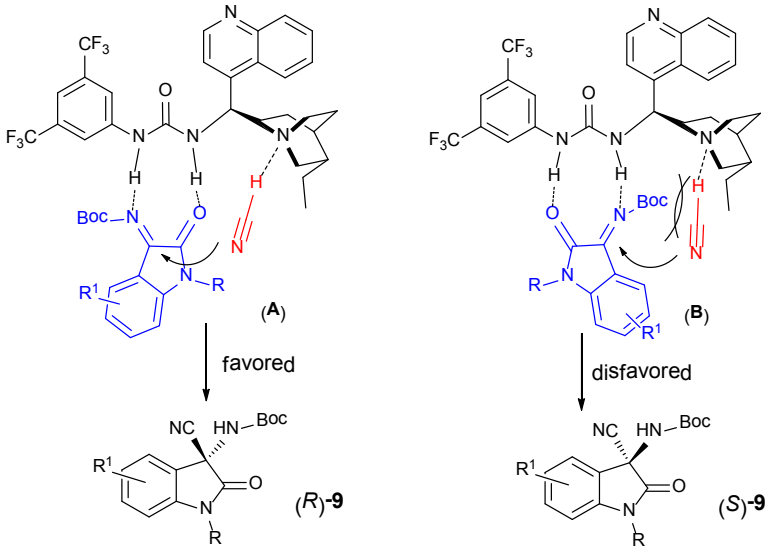


Scheme 1 Control experiments.

The proposed stereochemical model: By comparing the sign of optical rotation of with literature report,[4] the absolute configuration of the spirohydantoin **I** that we synthesized was assigned to be *S*. Accordingly, the absolute configuration of compound **9c** obtained by using catalyst **C4** was assigned to be *S*, and that of product **9** obtained by using catalyst **C2** was tentatively assigned to be *R* by analogy. Based on the absolute configuration of the product **9**, a plausible mechanism was proposed for the observed enantiofacial control of this reaction when using catalyst **C2**. As shown in scheme 2, the activation of in situ generated HCN by the tertiary amine in the cinchonidine thiourea catalyst backbone to react with *N*-Boc ketoimine **8** which was activated by the thiourea part of the catalyst **C2** through H-bonding interaction. Among the two possible orientations, the isatin was organized to

[5] P. Vachal and E. N. Jacobsen, *Org. Lett.,* 2000, **2**, 867.

avoid the unfavorable interaction between Boc group ring and the nucleophile, which made the attack of the cyanide from the *Re* face of the isatin ketoimine favorable to afford *R*-enantiomer as the major product.



Scheme 2: Proposed stereochemical model.