Electronic Supplementary Information

Catalyst-free [3 + 2] Cyclization of Imines and Morita-Baylis-Hillman Carbonates: General Route to Tetrahydropyrrolo[2,1-*a*]isoquinolines and Dihydropyrrolo[2,1-*a*]isoquinolines

Xue Tang, [a,b] Ming-Cheng Yang,[a,b] Cui Ye,[a,b] Li Liu,[a,b] Hai-Lin Zhou,[b] Xiao-Jie Jiang,[b] Xiao-Lin You,[b] Bo Han [a,*] and Hai-Lei Cui [b,*]

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

[b] *Laboratory of Asymmetric Synthesis, Chongqing University of Arts and Sciences, 319 Honghe Ave., Yongchuan, Chongqing, 402160, P.R. China; E-mail: cuihailei616@163.com*

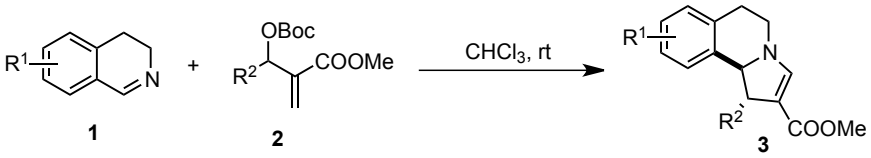
Table of Contents

1. **General methods:**

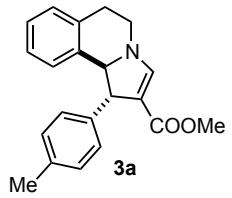
^{1}H NMR and ^{13}C NMR spectra were recorded at Bruker Avance 400. Chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants are given in Hz. ESI-MS analysis was performed using a Finnigan LCQ^{DECA} ion trap mass spectrometer.

All reagents and solvents were obtained from commercial sources and used without further purification. 3,4-Dihydroisoquinoline imines **1** and MBH carbonates **2** were prepared according to reported procedure.[1,2]

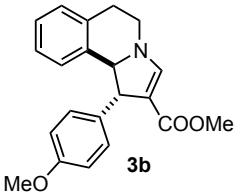
2. **General procedure for the synthesis of compounds 3:**



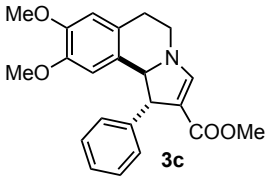
A mixture of 3,4-dihydro-isoquinoline imine **1** (0.2 mmol), MBH carbonate **2** (0.3 mmol) and $CHCl_3$ (1 mL) was stirred at room temperature without exclusion of air. Upon the consumption of imine **1** (monitored by TLC), the mixture was purified directly by a silica gel flash chromatography (PE/EtOAc) to afford compound **3**.



Compound 3a: White solid, 61.7 mg, 96% yield; m.p. 159-161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (m, 5H), 7.19-7.16 (m, 3H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 2.8 Hz, 1H), 4.32 (d, *J* = 3.6 Hz, 1H), 3.74 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.51 (s, 3H), 3.37 (td, *J* = 13.6, 3.6 Hz, 1H), 3.08-3.00 (m, 1H), 2.69 (dd, *J* = 16.0, 3.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 150.4, 142.1, 138.6, 136.2, 133.4, 129.4, 128.9, 127.2, 127.0, 126.7, 125.7, 108.7, 71.2, 56.0, 50.4, 44.9, 29.3, 21.1; IR (CH_2Cl_2, cm^{-1}) 1677, 1595, 1574, 1511, 1492, 1257, 1154; ESI-HRMS: calcd. for $C_{21}H_{22}NO_2^+$ $(M+H)^+$ 320.1645, found 320.1645.

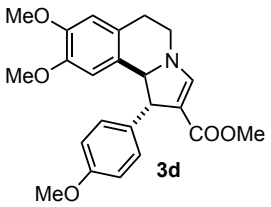


Compound 3b: White solid, 57.1 mg, 85% yield; m.p.113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.28-7.26 (m, 3H), 7.20-7.16 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.87 (d, *J* = 2.4 Hz, 1H), 4.31 (d, *J* = 3.2 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.52 (s, 3H), 3.38 (td, *J* = 12.8, 4.0 Hz, 1H), 3.09-2.97 (m, 1H), 2.70 (dd, *J* = 16.0, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.4, 150.3, 138.5, 137.3, 133.4, 128.9, 128.1, 127.2, 126.7, 125.7, 114.1, 108.9, 71.2, 55.6, 55.3, 50.4, 44.9, 29.3; IR (CH_2Cl_2, cm^{-1}) 1677, 1595, 1574, 1508, 1492, 1439, 1243, 1157; ESI-HRMS: calcd. for $C_{21}H_{22}NO_3^+$ $(M+H)^+$ 336.1594, found 336.1595.



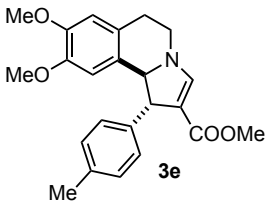
3c

Compound 3c: White solid, 61.0 mg, 84% yield; m.p. 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7,2 Hz, 2H), 7.30 (s, 1H), 7.28-7.24 (m, 1H), 6.71 (s, 1H), 6.53 (s, 1H), 4.85 (s, 1H), 4.30 (d, *J* = 3.2 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.74 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.52 (s, 3H), 3.35 (td, *J* = 12.8, 3.6 Hz, 1H), 3.03-2.92 (m, 1H), 2.63-2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 150.5, 148.4, 147.9, 145.1, 130.0, 128.8, 127.1, 126.8, 125.5, 111.4, 108.4, 108.2, 70.9, 56.4, 56.0, 55.9, 50.4, 44.9, 28.8; IR (CH_2Cl_2, cm^{-1}) 1675, 1598, 1512, 1494, 1463, 1453, 1254, 1155; ESI-HRMS: calcd. for $C_{22}H_{24}NO_4^+$ $(M+H)^+$ 366.1700, found 366.1700.



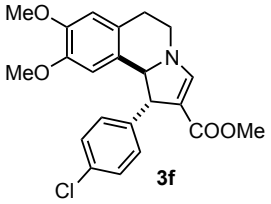
3d

Compound 3d: White solid, 68.7 mg, 87% yield; m.p. 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.70 (s, 1H), 6.53 (s, 1H), 4.81 (d, *J* = 2.4 Hz, 1H), 4.26 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.73 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.52 (s, 3H), 3.34 (td, *J* = 12.8, 4.0 Hz, 1H), 3.01-2.91 (m, 1H), 2.60 (dd, *J* = 16.0, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.5, 150.3, 148.4, 147.9, 137.4, 130.1, 128.1, 125.4, 114.2, 111.4, 108.6, 108.2, 70.9, 56.0, 55.9, 55.6, 55.3, 50.4, 44.9, 28.8; IR (CH_2Cl_2, cm^{-1}) 1676, 1598, 1508, 1462, 1440, 1245, 1154; ESI-HRMS: calcd. for $C_{23}H_{26}NO_5^+$ $(M+H)^+$ 396.1806, found 396.1805.



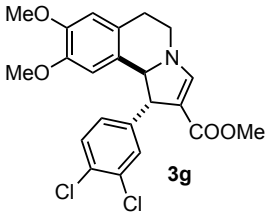
3e

Compound 3e: White solid, 62.6 mg, 82% yield; m.p. 110-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.28 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.71 (s, 1H), 6.53 (s, 1H), 4.83 (s, 1H), 4.27 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.73 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.52 (s, 3H), 3.34 (td, *J* = 12.8, 4.0 Hz, 1H), 3.01-2.93 (m, 1H), 2.60 (dd, *J* = 16.0, 3.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 150.3, 148.4, 147.9, 142.2, 136.3, 130.1, 129.5, 127.0, 125.4, 111.4, 108.5, 108.2, 70.9, 56.0, 56.0, 50.4, 44.9, 28.8, 21.1; IR (CH_2Cl_2, cm^{-1}) 1676, 1599, 1510, 1463, 1439, 1254, 1154; ESI-HRMS: calcd. for $C_{23}H_{26}NO_4^+$ $(M+H)^+$ 380.1856, found 380.1856.



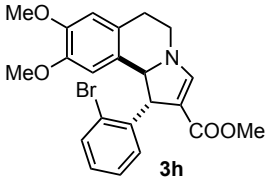
3f

Compound 3f: Pale yellow solid, 61.3 mg, 77% yield; m.p. 139-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.28 (s, 1H), 6.64 (s, 1H), 6.53 (s, 1H), 4.80 (d, *J* = 2.4 Hz, 1H), 4.27 (d, *J* = 3.6 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.74 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.52 (s, 3H), 3.35 (td, *J* = 13.6, 3.6 Hz, 1H), 3.01-2.92 (m, 1H), 2.61 (dd, *J* = 15.6, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 150.5, 148.5, 148.0, 143.7, 132.5, 129.7, 128.9, 128.5, 125.5, 111.5, 108.2, 108.1, 70.7, 56.0, 56.0, 55.8, 50.5, 44.9, 28.8; IR (CH_2Cl_2, cm^{-1}) 1677, 1598, 1514, 1488, 1463, 1439, 1254, 1155; ESI-HRMS: calcd. for $C_{22}H_{23}ClNO_4^+$ $(M+H)^+$ 400.1310, found 400.1313.



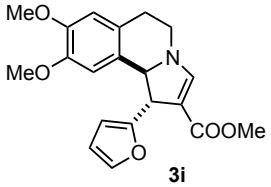
3g

Compound 3g: White solid, 78.6 mg, 90% yield; m.p. 79-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.26-7.24 (m, 1H), 6.60 (s, 1H), 6.53 (s, 1H), 4.79 (s, 1H), 4.23 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.74 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.52 (s, 3H), 3.35 (td, *J* = 13.2, 4.0 Hz, 1H), 3.00-2.91 (m, 1H), 2.61 (dd, *J* = 15.6, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 150.8, 148.5, 148.1, 145.4, 132.8, 130.7, 130.7, 129.2, 129.1, 126.7, 125.6, 111.5, 108.0, 107.7, 70.6, 56.1, 56.0, 55.6, 50.6, 45.0, 28.8; IR (CH_2Cl_2, cm^{-1}) 1676, 1597, 1514, 1466, 1440, 1255, 1158; ESI-HRMS: calcd. for $C_{22}H_{22}Cl_2NO_4^+$ $(M+H)^+$ 434.0920, found 434.0920.



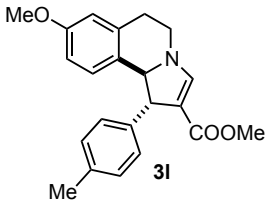
3h

Compound 3h: White solid, 50.8 mg, 57% yield; m.p. 162-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.36 (s, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 6.52 (s, 1H), 4.87 (d, *J* = 2.4 Hz, 1H), 4.76 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.75 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.51 (s, 3H), 3.35 (td, *J* = 12.8, 3.6 Hz, 1H), 3.03-2.95 (m, 1H), 2.62 (dd, *J* = 16.0, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 150.8, 148.4, 147.8, 143.4, 132.8, 129.5, 128.9, 128.3, 125.2, 123.2, 111.2, 109.4, 109.3, 71.1, 56.1, 56.0, 54.3, 50.6, 45.0, 28.9; IR (CH_2Cl_2, cm^{-1}) 1678, 1598, 1514, 1463, 1438, 1256, 1154; ESI-HRMS: calcd. for $C_{22}H_{23}BrNO_4^+$ $(M+H)^+$ 444.0805, found 444.0805.



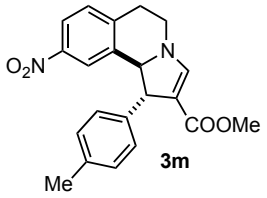
3i

Compound 3i: White solid, 58.3 mg, 83% yield; m.p. 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 6.65-6.64 (m, 2H), 6.52 (s, 1H), 6.42 (d, *J* = 1.2 Hz, 1H), 4.82 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.81-3.75 (m, 4H), 3.55 (d, *J* = 5.2 Hz, 1H), 3.47 (dt, *J* = 12, 4.4 Hz, 1H), 3.17-3.11 (m, 1H), 2.91-2.84 (m, 1H), 2.74 (dt, *J* = 15.2, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 153.6, 148.3, 147.3, 144.4, 143.3, 127.0, 124.1, 112.4, 111.0, 104.9, 97.0, 96.4, 65.4, 56.1, 56.0, 56.0, 53.4, 51.5, 28.2; IR (CH_2Cl_2, cm^{-1}) 1678, 1598, 1511, 1463, 1440, 1254, 1156; ESI-HRMS: calcd. for $C_{20}H_{22}NO_5^+$ $(M+H)^+$ 356.1493, found 356.1493.



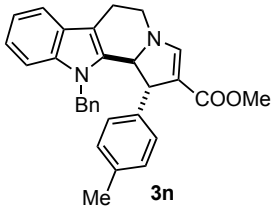
3l

Compound 3l: White solid, 49.8 mg, 71% yield; m.p. 58-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 4.84 (d, *J* = 2.4 Hz, 1H), 4.28 (d, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.72 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.52 (s, 3H), 3.39-3.32 (m, 1H), 3.06-2.97 (m, 1H), 2.66 (dd, *J* = 16.0, 2.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ165.9, 158.2, 150.4, 142.1, 136.1, 134.7, 130.6, 129.4, 127.0, 126.8, 113.7, 113.4, 108.7, 70.9, 56.0, 55.3, 50.4, 44.8, 29.6, 21.1; IR (CH_2Cl_2, cm^{-1}) 1680, 1597, 1500, 1428, 1261, 1159; ESI-HRMS: calcd. for $C_{22}H_{24}NO_3^+$ $(M+H)^+$ 350.1751, found 350.1751.



3m

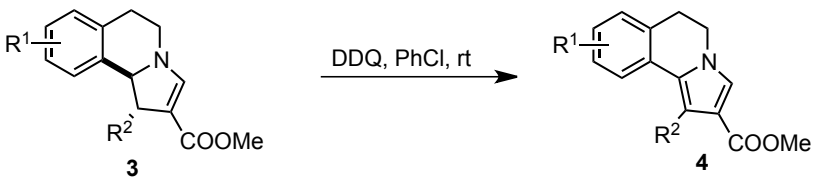
Compound 3m: White solid, 29.7 mg, 41% yield; m.p. 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 1.6 Hz, 1H), 8.04 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (m, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 4.90 (s, 1H), 4.32 (d, *J* = 3.2 Hz, 1H), 3.80 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.52 (s, 3H), 3.43-3.39 (m, 1H), 3.14-3.05 (m, 1H), 2.82 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.9, 147.2, 141.1, 140.9, 140.2, 136.8, 130.0, 129.7, 126.9, 121.6, 121.2, 109.9, 70.8, 56.1, 50.6, 44.2, 29.2, 21.1; IR (CH_2Cl_2, cm^{-1}) 1680, 1600, 1521, 1437, 1344, 1258, 1160; ESI-HRMS: calcd. for $C_{21}H_{21}N_2O_4^+$ $(M+H)^+$ 365.1496, found 365.1496.



3n

Compound 3n: White solid, 40.5 mg, 90% yield (0.1 mmol scale); m.p. 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 1H), 7.22-7.21 (m, 3H), 7.13-7.11 (m, 4H), 7.10-7.08 (m, 4H), 6.80-6.79 (m, 2H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 17.2 Hz, 1H), 5.08 (s, 1H), 4.28 (d, *J* = 3.2 Hz, 1H), 3.82 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.47 (s, 3H), 3.33-3.25 (m, 1H), 3.01-2.93 (m, 1H), 2.85 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.6, 141.4, 137.5, 137.0, 136.4, 134.2, 129.3, 128.7, 127.4, 127.2, 126.9, 126.0, 122.0, 119.7, 118.3, 111.0, 110.1, 108.5, 68.5, 52.7, 50.4, 47.6, 45.7, 22.5, 21.1; IR (CH_2Cl_2, cm^{-1}) 1680, 1603, 1511, 1495, 1464, 1452, 1437, 1261, 1150; ESI-HRMS: calcd. for $C_{30}H_{29}N_2O_2^+$ $(M+H)^+$ 449.2224, found 449.2223.

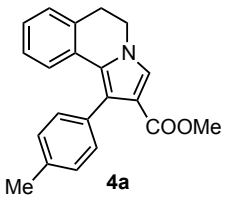
3. General procedure for the synthesis of compounds 4:



3 **4**

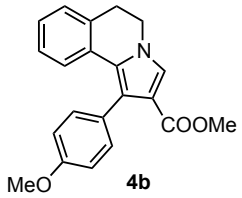
To a mixture of **3** (0.1 mmol) in PhCl (1.0 mL) was added DDQ (0.12 mmol) at room temperature. The resulting reaction mixture was stirred at rt. After compound **3** was consumed (monitored by TLC), the reaction was then washed with aq NaOH and

brine. The organic layer was concentrated and the residue was purified directly by a silica gel flash chromatography (PE/EtOAc) to give compound **4**.



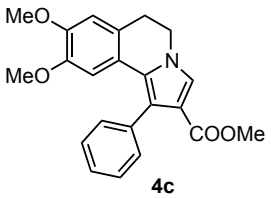
4a

Compound 4a: White solid, 25.9 mg, 82% yield; m.p. 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.15 (m, 2H), 7.14-7.11 (m, 2H), 7.09-7.04 (m, 1H), 6.96-6.92 (m, 1H), 6.85-6.82 (m, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 3.55 (s, 3H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 136.4, 132.6, 131.7, 130.3, 129.0, 128.9, 128.0, 126.9, 126.1, 125.9, 124.4, 123.2, 114.4, 50.7, 45.0, 29.9, 21.4; IR (CH_2Cl_2, cm^{-1}) 1711, 1604, 1578, 1552, 1522, 1461, 1441, 1228, 1182; ESI-HRMS: calcd. for $C_{21}H_{19}NO_2^+$ $(M+H)^+$ 340.1313, found 340.1312.



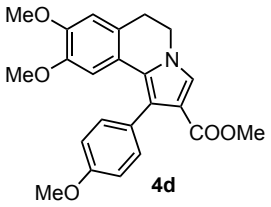
4b

Compound 4b: White solid, 27.7 mg, 90% yield; m.p. 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 6.8 Hz, 1H), 6.96-6.93 (m, 4H), 4.11 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.67 (s, 3H), 3.09 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 158.7, 131.7, 131.5, 129.0, 128.0, 127.8, 127.0, 126.9, 126.1, 125.9, 124.3, 122.8, 114.4, 113.6, 55.2, 50.7, 45.0, 29.9; IR (CH_2Cl_2, cm^{-1}) 1709, 1604, 1575, 1552, 1521, 1510, 1461, 1440, 1240, 1180; ESI-HRMS: calcd. for $C_{21}H_{20}NO_3^+$ $(M+H)^+$ 334.1438, found 334.1437.



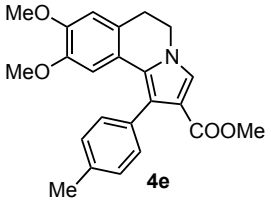
4c

Compound 4c: White solid, 23.0 mg, 63% yield; m.p. 139-140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ7.41-7.40 (m, 4H), 7.36 (s, 1H), 7.33-7.30 (m, 1H), 6.66 (s, 1H), 6.40 (s, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.66 (s, 3H), 3.28 (s, 3H), 3.03 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 147.5. 147.3. 136.2, 130.8, 128.2, 127.2, 127.0, 125.5, 124.0, 121.6, 121.5, 114.1, 111.1, 107.6, 56.0, 55.1, 50.8, 45.1, 29.3; IR (CH_2Cl_2, cm^{-1}) 1709, 1606, 1550, 1508, 1484, 1463, 1443, 1227, 1186; ESI-HRMS: calcd. for $C_{22}H_{21}NO_4^+$ $(M+Na)^+$ 386.1368, found 386.1371.



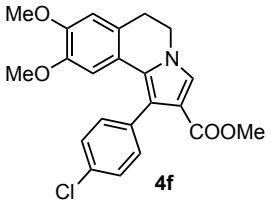
4d

Compound 4d: White solid, 33.5 mg, 85% yield; m.p. 161-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.8 Hz, 2H), 7.31 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 6.48 (s, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.67 (s, 3H), 3.35 (s, 3H), 3.02 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 158.7, 147.6, 147.3, 131.8, 128.2, 127.2, 125.4, 124.0, 121.7, 121.2, 114.2, 113.7, 111.1, 107.7, 55.9, 55.3, 55.1, 50.7, 45.1, 29.2; IR (CH_2Cl_2, cm^{-1}) 1710, 1608, 1577, 1550, 1503, 1481, 1462, 1440, 1215, 1184; ESI-HRMS: calcd. for $C_{23}H_{24}NO_5^+$ $(M+H)^+$ 394.1649, found 394.1649.



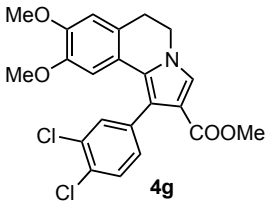
4e

Compound 4e: White solid, 19.4 mg, 61% yield; m.p. 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.66 (s, 1H), 6.44 (s, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 3.66 (s, 3H), 3.30 (s, 3H), 3.02 (t, *J* = 6.4 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 147.5, 147.3, 136.4, 133.0, 130.6, 128.8, 127.1, 125.3, 123.9, 121.6, 114.1, 111.1, 107.8, 55.9, 54.9, 50.7, 45.1, 29.2, 21.2; IR (CH_2Cl_2, cm^{-1}) 1710, 1610, 1554, 1519, 1489, 1443, 1226, 1186; ESI-HRMS: calcd. for $C_{23}H_{24}NO_4^+$ $(M+H)^+$ 378.1700, found 378.1700.



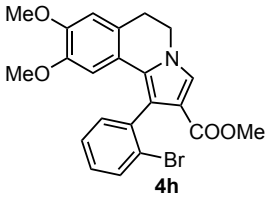
4f

Compound 4f: White solid, 30.0 mg, 75% yield; m.p. 154-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 5H), 6.68 (s, 1H), 6.37 (s, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 3.67 (s, 3H), 3.36 (s, 3H), 3.03 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 147.6, 147.5, 134.6, 132.9, 132.3, 128.3, 127.3, 125.6, 124.2, 121.2, 120.1, 114.0, 111.2, 107.6, 56.0, 55.1, 50.8, 45.1, 29.2; IR (CH_2Cl_2, cm^{-1}) 1706, 1610, 1550, 1504, 1482, 1453, 1442, 1226, 1184; ESI-HRMS: calcd. for $C_{22}H_{21}ClNO_4^+$ $(M+H)^+$ 398.1154, found 398.1154.



4g

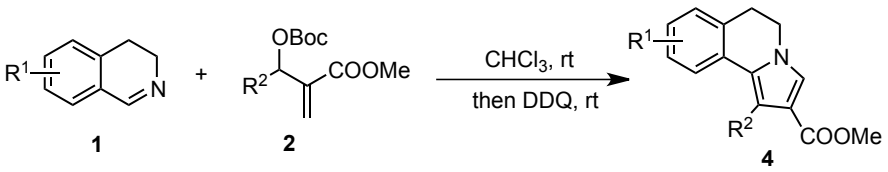
Compound 4g: White solid, 33.5 mg, 77% yield; m.p. 153-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.28 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.69 (s, 1H), 6.39 (s, 1H), 4.09 (t, *J* = 6.8 Hz, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 3.39 (s, 3H), 3.03 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 147.8, 147.7, 136.3, 132.7, 132.0, 130.9, 130.6, 130.0, 127.5, 125.8, 124.5, 120.9, 118.7, 114.0, 111.3, 107.5, 56.0, 55.2, 50.8, 45.1, 29.2; IR (CH_2Cl_2, cm^{-1}) 1707, 1611, 1544, 1524, 1501, 1473, 1441, 1228, 1187; ESI-HRMS: calcd. for $C_{22}H_{20}Cl_2NO_4^+$ $(M+H)^+$ 432.0764, found 432.0764.



4h

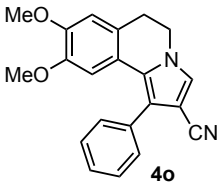
Compound 4h: White solid, 33.0 mg, 75% yield; m.p. 176-179 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J*= 8.4 Hz, 1H), 7.38 (s, 1H), 7.37-7.34 (m, 2H), 7.23-7.20 (m, 1H), 6.67 (s, 1H), 6,30 (s, 1H), 4.13 (dd, *J* = 8.4, 6.0 Hz, 2H), 3.84 (s, 3H), 3.65 (s, 3H), 3.31 (s, 3H), 3.11-3.06 (m, 1H), 3.00 (td, *J* = 11.4, 5.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 147.8, 147.5, 137.8, 132.6, 132.5, 128.8, 127.4, 127.2, 126.0, 125.3, 123.9, 121.4, 120.0, 114.3, 111.1, 106.9, 56.0, 55.2, 50.9, 45.1, 29.2; IR (CH_2Cl_2, cm^{-1}) 1708, 1611, 1553, 1524, 1503, 1463, 1440, 1186; 1ESI-HRMS: calcd. for $C_{22}H_{20}BrNO_4^+$ $(M+Na)^+$ 464.0473, found 464.0479.

4. General Procedure for the one pot synthesis of compounds 4:



1 **2** **4**

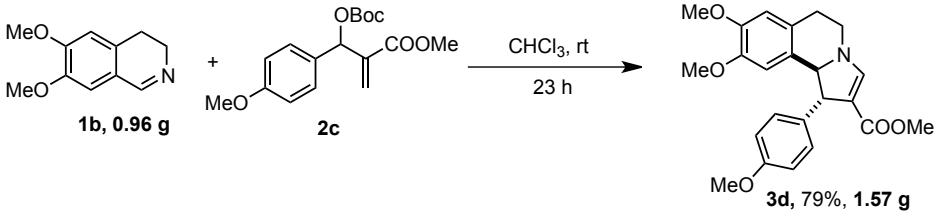
A mixture of 3,4-dihydro-isoquinoline imine **1** (0.2 mmol), MBH carbonate **2** (0.3 mmol) and $CHCl_3$ (1 mL) was stirred at room temperature without exclusion of air. Upon the consumption of imine **1** (monitored by TLC), DDQ (0.24 mmol) was added at room temperature. The resulting reaction mixture was stirred at rt. After compound **3** was consumed (monitored by TLC), the reaction was then washed with aq NaOH and brine. The organic layer was concentrated and the residue was purified directly by a silica gel flash chromatography (PE/EtOAc) to give compound **4**.



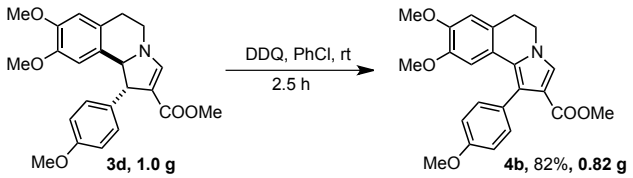
4o

Compound 4o: Pale yellow solid, 45.0 mg, 68% yield; m.p. 130-133 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.45-7.41 (m, 2H), 7.35 (d, J = 7.2 Hz, 1H), 7.21 (s, 1H), 6.70 (s, 1H), 6.69 (s, 1H), 4.09 (t, J = 6.4 Hz, 2H), 3.87 (s, 3H), 3.38 (s, 3H), 3.05 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 147.8, 133.5, 129.9, 128.7, 127.7, 126.7, 126.4, 124.4, 122.7, 120.6, 116.4, 111.2, 107.8, 94.0, 56.0, 55.3, 45.3, 29.1; IR (CH_2Cl_2, cm^{-1}) 2219, 1604, 1554, 1508, 1485, 1464, 1443, 1217, 1170; ESI-HRMS: calcd. for $C_{21}H_{19}N_2O_2^+$ $(M+H)^+$ 331.1441, found 331.1441.

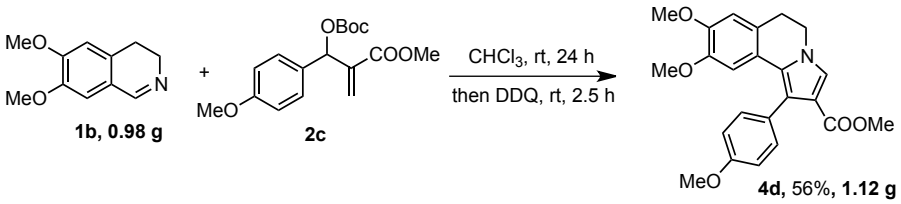
5. Gram-scale reaction:



A mixture of 3,4-dihydro-isoquinoline imine **1b** (0.96 g, 5.0 mmol, 1 equiv), MBH carbonate **2** (1.77 g, 5.5 mmol, 1.1 equiv) and $CHCl_3$ (15 mL) was stirred at room temperature without exclusion of air. After imine **1** was consumed (monitored by TLC), the mixture was concentrated and the residue was purified directly by a silica gel flash chromatography (PE/EtOAc = 3/2) to afford compound **3d** as white solid (1.57g, 79% yield).

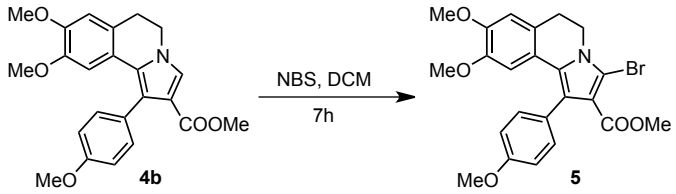


To a mixture of compound **3d** (1.0 g, 2.53 mmol, 1 equiv) in PhCl (22 mL) was added DDQ (0.689 g, 3.04 mmol, 1.2 equiv) and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was then diluted with DCM, washed with aq NaOH and brine, and dried with Na_2SO_4. After concentrated, the residue was purified by a silica gel flash chromatography (PE/EtOAc = 7/3) to afford compound **4b** as pale yellow solid (0.82 g, 82% yield).



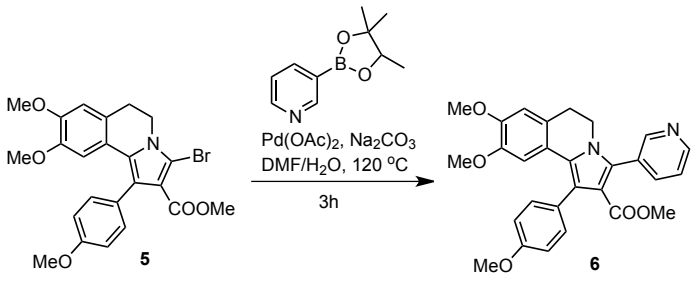
A mixture of 3,4-dihydro-isoquinoline imine **1b** (0.98 g, 5.1 mmol, 1 equiv), MBH carbonate **2** (1.82 g, 5.6 mmol, 1.1 equiv) and $CHCl_3$ (10 mL) was stirred at room temperature without exclusion of air. Upon the consumption of imine **1** (monitored by TLC), DDQ (1.42 g, 6.2 mmol, 1.2 equiv) was added. The resulting reaction mixture was stirred at room temperature for 2.5 h (monitored by TLC). The reaction mixture was then diluted with DCM, washed with aq NaOH and brine, and dried with Na_2SO_4. After concentrated, the residue was purified by a silica gel flash chromatography (PE/EtOAc = 7/3) to afford compound **4b** as pale yellow solid (1.12 g, 56% yield).

6. Synthesis of compound 5:



To a solution of **4b** (1 eq, 0.1 mmol, 39.3 mg) in DCM (1 mL) was added NBS (1.1 eq, 0.11 mmol, 19.6 mg). The resulting mixture was stirred at rt for 7 h. Then the mixture was purified by a silica gel flash chromatography (Hexane/EtOAc = 3/1 to 2/1) to give compound **5** as white amorphous solid (40.5 mg, 95% yield); m.p. 142-144 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.66 (s, 1H), 6.38 (s, 1H), 4.14 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.64 (s, 3H), 3.31 (s, 3H), 3.01 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 158.8, 147.6, 147.5, 131.8, 128.3, 128.3, 124.1, 122.1, 121.2, 114.3, 113.7, 110.8, 108.1, 107.6, 55.9, 55.3, 55.1, 50.9, 43.4, 28.8; IR (CH_2Cl_2, cm^{-1}) 1704, 1611, 1571, 1554, 1517, 1497, 1475, 1459, 1451, 1227, 1189; ESI-HRMS: calcd. for $C_{23}H_{23}BrNO_5^+$ $(M+H)^+$ 472.0754, found 472.0754.

7. Synthesis of compound 6

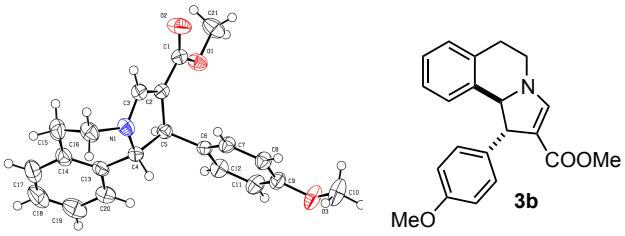


A mixture of compound **5** (1 eq, 0.05 mmol, 21.4 mg), $Pd(PPh_3)_4$ (0.1 eq, 0.005 mmol, 5.8 mg), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2 eq, 0.1 mmol, 20.5 mg) and Na_2CO_3 (2 eq, 0.1 mmol, 10.6 mg) in DMF (0.4 mL) and H_2O (0.1 mL) was stirred at 120 ^oC for 3 h. Then the reaction mixture was cooled to rt, diluted with EtOAc, washed with sat Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by a silica gel flash chromatography (Hexane/EtOAc/Et_3N = 30/30/1) to give compound **6** as white amorphous solid (20.8 mg, 88% yield); m.p. 192-193 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67-8.65 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 4.8, 7.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 6.49 (s, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.43 (s, 3H), 3.35 (s, 3H), 2.95 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.7, 151.1, 149.2, 147.5, 147.5, 138.3, 132.7, 131.8, 128.5, 128.1, 127.5, 124.5, 122.8, 121.7, 121.5, 114.2, 113.8, 110.9, 108.1, 55.9, 55.3, 55.1, 50.6, 42.6, 29.2; IR (CH_2Cl_2, cm^{-1}) 1703, 1612, 1555, 1517, 1488, 1463, 1441, 1224, 1167; ESI-HRMS: calcd. for $C_{28}H_{27}N_2O_5^+$ $(M+H)^+$ 471.1915, found 471.1914.

Reference:

(1) T. O. Ronson, C. Kitsiou, W. P. Unsworth, R. J. K. Taylor, *Tetrahedron.,* **2016,** *72,* 6099-6106.
(2) J. Feng, X. Lu, A. Kong, X. Han, *Tetrahedron.,* **2007,** *63,* 6035-6041.

8. Crystal data of Compound 3b:



Bond precision: C-C = 0.0021 A Wavelength=0.71073

Cell: a=5.5044(9) b=9.9935(17) c=32.218(5)
alpha=90 beta=91.006(3) gamma=90
Temperature: 296 K

	Calculated	Reported
Volume	1772.0(5)	1772.0(5)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C21 H21 N O3	C21 H21 N O3
Sum formula	C21 H21 N O3	C21 H21 N O3
Mr	335.39	335.39
Dx,g cm-3	1.257	1.257
Z	4	4
Mu (mm-1)	0.084	0.084
F000	712.0	712.0
F000'	712.33	
h,k,lmax	7,12,41	7,12,41
Nref	4074	3996
Tmin,Tmax		
Tmin'		

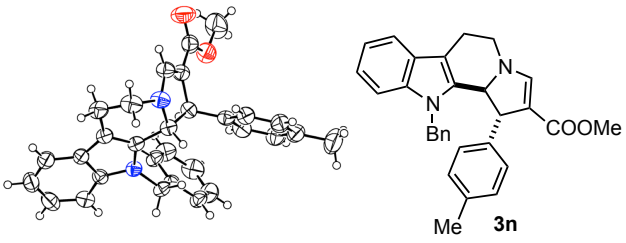
Correction method= Not given

Data completeness= 0.981 Theta(max)= 27.527

R(reflections)= 0.0468(3365) wR2(reflections)= 0.1186(3996)

S = 1.080 Npar= 229

9. Crystal data of Compound 3n:



Bond precision: C-C = 0.0040 A Wavelength=0.71073

Cell: a=9.6403(16) b=12.825(2) c=20.041(3)
alpha=83.205(2) beta=77.161(2) gamma=89.737(2)
Temperature: 296 K

	Calculated	Reported
Volume	2398.3(7)	2398.3(7)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	4(C30 H28 N2 O2), H2 O	4(C30 H28 N2 O2), H2 O
Sum formula	C120 H114 N8 O9	C120 H114 N8 O9
Mr	1812.19	1812.19
Dx,g cm-3	1.255	1.255
Z	1	1
Mu (mm-1)	0.079	0.079
F000	962.0	962.0
F000'	962.39	
h,k,lmax	12,16,25	12,16,25
Nref	9779	9671
Tmin,Tmax		
Tmin'		

Correction method= Not given

Data completeness= 0.989 Theta(max)= 26.372

R(reflections)= 0.0606(5220) wR2(reflections)= 0.1654(9671)

S = 0.994 Npar= 626