Orthogonal Synthesis of Indolines and Isoquinolines Via Aryne Annulation

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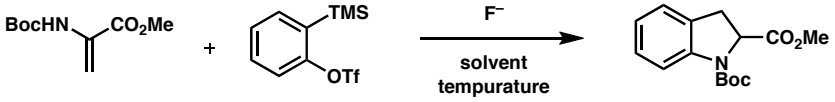
Materials and Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). 2-(trimethylsilyl)phenyl triflate was purchased from Sigma-Aldrich Chemical Company and used as received. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company and azeotropically dried three times from acetonitrile prior to use. Brine solutions are saturated aqueous sodium chloride solutions. Known dehydroamino ester starting materials were prepared by the methods of Kobayashi[1] or Parsons[2] unless otherwise specified. 3-methoxy-2-(trimethylsilyl)phenyl triflate,[3] 4-methyl-2-(trimethylsilyl)phenyl triflate,[4] 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate (**4**),[5] 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl triflate[6] and 4,5-difluoro-2-(trimethylsilyl)phenyl triflate[7] were prepared according to literature procedures. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively), with usage specified in each case, and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

Optimization of Reaction Conditions

Optimization of the indoline synthesis was performed by manipulating fluoride source, solvent, and concentration:

Table SI-1. *Optimization of indoline conditions*



Entry	*Aryne Equiv*	*F⁻ Source*	*Solvent*	*F⁻ Equiv*	*Conc. (M)*	*Temp. (°C)*	*% Yield*
1	1.5	CsF	MeCN	2.0	0.2	80 °C	35%
2	1.5	CsF	MeCN	2.0	0.2	25 °C	15%
3	1.5	KF / 18-Crown-6	THF	2.0	0.2	25 °C	44%
4	1.5	KF / 18-Crown-6	THF	2.0	0.2	40 °C	27%
5	1.0	KF / 18-Crown-6	THF	1.5	0.2	25 °C	16%
6	2.0	KF / 18-Crown-6	THF	2.0	0.2	25 °C	47%
7	2.0	TBAT	CH_2Cl_2	2.0	0.1	25 °C	53%
8	2.0	TBAT	THF	2.0	0.2	25 °C	45%
9	2.0	TBAT	THF	2.0	0.2	40 °C	33%
10	2.0	TBAT	THF	2.0	0.1	25 °C	45%
11	2.0	TBAT	THF	2.0	0.1	40 °C	22%
12	2.0	TBAT	THF	2.0	0.02	40 °C	47%
13	***2.0***	***TBAT***	***THF***	***2.0***	***0.02***	***25 °C***	***61%***

Optimization of the isoquinoline synthesis was performed by manipulating fluoride source, fluoride source equivalents, aryne equivalents, solvent, and concentration.

***Table SI-2**. Optimization of isoquinoline conditions*

Entry	*Aryne Equiv*	*F^- source*	*F^- Equiv*	*Solvent*	*Conc. (M)*	*Temp. (°C)*	*% Yield*
1	1.5	CsF	2.0	MeCN	0.2	25	57
2	1.5	CsF	2.0	MeCN	0.1	25	61
3	2.0	CsF	2.0	MeCN	0.2	25	65
4	1.5	CsF	2.0	MeCN	0.1	25	30
5	1.25	CsF	2.0	MeCN	0.2	25	50
6	1.25	CsF	2.0	THF	0.2	25	0
7	2.0	KF / 18-C-6	3.0	THF	0.2	25	36
8	1.5	KF / 18-C-6	2.0	THF	0.2	25	34
9	2.0	KF / 18-C-6	3.0	THF	0.2	40	40
10	2.0	TBAF	2.0	CH_2Cl_2	0.2	25	13
11	2.0	TBAT	2.0	CH_2Cl_2	0.2	25	71
12	2.0	TBAT	2.0	CH_2Cl_2	0.2	120	56
13	2.0	TBAT	2.0	THF	0.2	40	77
14	***2.0***	***TBAT***	***2.0***	***THF***	***0.01***	***25***	***87***

General Procedures

Method A:

To a solution of TBAT (0.756 g, 1.40 mmol, 2.0 equiv) and amido acrylate (0.10 g, 0.70 mmol) in THF (35 mL) was added silyl aryl triflate (0.340 mL, 1.40 mmol, 2.0 equiv) dropwise via syringe. The reaction was stirred under nitrogen at ambient temperature for 6 hours, at which point the reaction was concentrated under reduced pressure and purified via flash chromatography.

Method B:

To a solution of TBAT (0.756 g, 1.40 mmol, 2.0 equiv) and amido acrylate (0.10 g, 0.70 mmol) in THF (70 mL) was added silyl aryl triflate (0.340 mL, 1.40 mmol, 2.0 equiv) dropwise via syringe. The reaction was stirred under nitrogen at ambient temperature for 6 hours, at which point the reaction was concentrated under reduced pressure and purified via flash chromatography.

Experimental Data

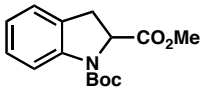


Table 1, Entry 1

Reaction performed via Method A. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 61% yield. R_f = 0.35 (30:70 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.5 Hz, 1H), 7.19 (d, *J* = 4.5 Hz, 1H), 7.12 (d, *J* = 4.2 Hz, 1H), 6.96 (t, *J* = 4.0 Hz, 1H), 4.89 (br t, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 10.2, 8.0 Hz, 1H), 3.51 (dd, *J* = 9.0, 2.5 Hz, 1H), 1.49 (br s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 152.2, 142.8, 134.0, 130.3, 128.2, 124.7, 122.5, 117.5, 81.7, 60.3, 52.2, 32.4, 28.6; IR (Neat Film, NaCl) 3066, 2928, 1754, 1603, 1485, 1289, 1319, 1277, 1203, 1169, 1046, 1022, 848, 751 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}NO_4$ [M]$^+$: 277.1314, found 277.1323.

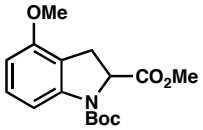


Table 1, Entry 2

Reaction performed via Method A. Purified by flash chromatography (SiO_2, 0:100 → 30:70 EtOAc/hexanes). 49% yield, isolated as a 2.3:1 mixture of inseparable 4- and 7-methoxyindolines. R_f = 0.21 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.0 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 3.6 Hz, 2H), 6.78 (d, *J* = 2.9 Hz, 1H), 5.08 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.55 (dd, *J* = 16.8, 5.0 Hz, 1H), 3.07 (d, *J* = 16.8, 1.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 153.5, 149.8, 133.4, 130.8, 125.7, 117.1, 112.8, 81.3, 62.6, 55.7, 53.1, 33.9, 28.3; IR (Neat Film, NaCl) 2976, 2838, 1733, 1695, 1609, 1595, 1490, 1461, 1367, 1275, 1164, 1027, 947, 867, 766 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{21}NO_5$ [M]$^+$: 307.1420, found 307.1418.

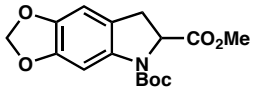


Table 1, Entry 3

Reaction performed via Method A. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 39% yield. R_f = 0.33 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.58 (s, 1H), 5.89 (s, 2H), 4.84 (d, *J* = 11.0 Hz, 1H) 2.78 (s, 1H), 3.55 (dd, *J* = 12.1, 5.7 Hz, 1H), 3.07 (d, *J* = 15.9, 1.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 151.9, 147.6, 143.3, 145.6, 128.2, 119.6, 105.0, 101.5, 98.3, 81.7, 61.7, 52.7, 33.0, 28.3; IR (Neat Film, NaCl) 2949, 1753, 1706, 1477, 1405, 1367, 1303, 1258, 1166, 1081, 1037, 938 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{19}NO_6$ [M]$^+$: 321.1212, found 321.1224.

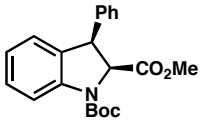


Table 1, Entry 4

Reaction performed via Method A. Purified by flash chromatography (SiO_2, 10:90 → 20:80 EtOAc/hexanes). 40% yield. R_f = 0.23 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.0 Hz, 1H), 7.48 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.37 (comp m, 4H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H) 3.86 (t, *J* = 5.3 Hz, 1H), 3.82 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 158.9, 155.8, 135.2, 133.9, 133.0, 130.2, 129.9, 129.6, 129.0, 128.8, 128.0, 120.9, 115.1, 80.9, 67.5, 52.8, 47.8, 21.4; IR (Neat Film, NaCl) 2947, 1723, 1707, 1638, 1600, 1496, 1448, 1391, 1366, 1245, 1170, 1143, 755, 692 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{23}NO_4$ $[M+H]^+$: 352.1549, found 352.1564. Relative stereochemistry of substituents at C(2) and C(3) confirmed by 1D NOESY NMR studies.

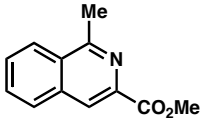


Table 2, Entry 1

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 87% yield. R_f = 0.33 (30:70 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.20 (d, *J* = 9.2, 1H), 7.97 (d, *J* = 6.7 Hz, 1H), 7.76 (app ddd, *J* = 5.2, 3.2, 1.9 Hz, 2H), 4.04 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 158.6, 141.4, 135.4, 131.0, 129.1, 128.6, 127.4, 125.4, 123.5, 51.5, 21.4; IR (Neat Film, NaCl) 2953, 1731, 1569, 1501, 1448, 1337, 1391, 1291, 1230, 1210, 795 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{11}NO_2$ $[M]^+$: 201.0790, found 201.0797.

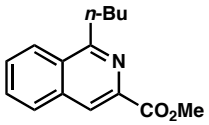


Table 2, Entry 2

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 76% yield. R_f = 0.40 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.18 (d, *J* = 9.6 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.70 (ddd, *J* = 5.0, 3.6, 2.3 Hz, 2H), 4.01 (s, 3H), 2.89 (d, *J* = 6.3 Hz, 2H), 1.63 (q, *J* = 5.2 Hz, 2H), 1.12 (app dt, *J* = 5.5, 3.3 Hz, 2H), 0.88 (t, *J* = 3.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 163.8, 141.4, 135.9, 131.0, 129.8, 129.1, 128.6, 126.0, 123.5, 53.5, 36.1, 33.2, 23.8, 14.3; IR (Neat Film, NaCl) 2855, 2870, 1721, 1449, 1293, 1246, 1213, 1175, 749 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{17}NO_2$ $[M]^+$: 243.1259, found 243.1256.

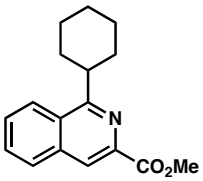


Table 2, Entry 3

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 EtOAc/hexanes). 65% yield. R_f = 0.49 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 8.44 (s, 1H), 8.28 (d, J = 4.3 Hz, 1H), 7.4 (d, J = 3.5 Hz, 1H), 7.73 (app dt, J = 5.2, 3.1 Hz, 2H), 4.02 (s, 3H), 3.59 (m, 1H), 1.98 (m, 8H), 1.57 (q, J = 5.1 Hz, 1H), 1.41 (q, J = 3.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.1, 140.7, 136.0, 129.9, 129.1, 127.8, 124.6, 122.2, 52.0, 42.1, 32.1, 27.1, 26.0; IR (Neat Film, NaCl) 2927, 2852, 1739, 1718, 1567, 1502, 1449, 1325, 1311, 1271, 1243, 1204, 1150, 1000, 780, 750 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{15}NO_2$ $[M]^+$: 269.1416, found 269.1424.

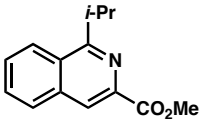


Table 2, Entry 4

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 66% yield. R_f = 0.37 (30:70 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 8.41 (s, 1H), 8.29 (d, J = 4.5 Hz, 1H), 7.96 (d, J = 3.5 Hz, 1H), 7.73 (app dt, J = 5.5, 3.3 Hz, 2H), 4.03 (s, 3H), 3.97 (m, 1H), 1.50 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 145.0, 140.8, 135.3, 130.4, 129.7, 129.3, 128.2, 125.2, 122.9, 53.0, 31.4, 22.7; IR (Neat Film, NaCl) 3965, 2929, 1718, 1565, 1501, 1449, 1323, 1267, 1221, 1207, 1150, 1117, 1077, 987, 781 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{15}NO_2$ $[M]^+$: 229.1103, found 229.1100.

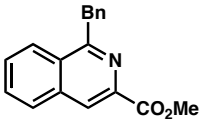


Table 2, Entry 5

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 30:70 EtOAc/hexanes). 72% yield. R_f = 0.47 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.20 (d, J = 6.7, 1H), 8.02 (d, J = 5.1 Hz, 1H), 7.74 (t, J = 7.1 Hz, 1H), 7.63 (t, J = 6.6 Hz, 1H), 7.22 (m, 4H), 7.18 (m, 1H), 4.80 (s, 2H) 4.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 163.7, 141.4, 139.5, 135.4, 131.7, 129.8, 129.1, 128.3, 128.0, 126.3, 124.0, 53.5, 42.9; IR (Neat Film, NaCl) 2946, 2929, 1731, 1716, 1551, 1455, 1380, 1301, 1230, 1210, 995 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{18}H_{15}NO_2$ $[M+H]^+$: 278.1103, found 278.1181.

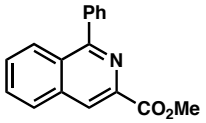


Table 2, Entry 6

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 10:90 EtOAc/hexanes). 55% yield. R_f = 0.52 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.71, (dd, J = 7.7, 4.3 Hz, 2H), 7.66 (d, J = 7.7 Hz, 1 H), 7.57 (t, J = 6.0 Hz, 1H), 7.53 (d, J = 6.8, 1H), 7.49 (t, J = 4.3 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 162.2, 141.2, 139.3, 137.7, 131.0, 130.4, 129.7, 128.6, 128.3, 128.2, 128.0, 127.8, 124.0; IR (Neat Film, NaCl) 2949, 1725, 1715, 1493, 1449, 1376, 1339, 1292, 1242, 1217, 1148, 1102, 997, 798, 766, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{13}NO_2$ $[M+H]^+$: 264.1025, found 264.1020.

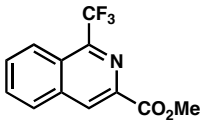


Table 2, Entry 7

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes). 57% yield. R_f = 0.22 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.42 (d, J = 7.9 Hz, 1H), 8.21 (d, J = 9.3 Hz, 1H), 7.91 (t, J = 8.4, Hz, 1H), 7.81 (t, J = 7.1 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 148.3, 135.9, 135.1, 132.1, 131.4, 130.6, 124.6, 122.1, 118.2, 54.5; IR (Neat Film, NaCl) 2924, 2102, 1730, 1643, 1462, 1275, 1252, 1155, 1126, 897, 726; HRMS (EI+) *m/z* calc'd for $C_{12}H_8F_3NO_2$ $[M]^+$: 255.0507, found 255.0500.

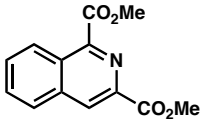


Table 2, Entry 8

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes). 51% yield. R_f = 0.21 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, J = 8.2 Hz, 1H), 8.78 (s, 1H), 8.05 (t, J = 3.5 Hz, 1H), 7.81 (m, 2H), 4.13 (s, 3H), 4.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.4, 149.1, 139.6, 136.3, 134.2, 131.0, 131.4, 128.4, 128.0, 127.2, 126.6, 53.6; IR (Neat Film, NaCl) 2959, 2924, 1725, 1713, 1449, 1300, 1251, 1232, 1205, 1146, 1055, 786, 760 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{11}NO_4$ $[M]^+$: 245.0688, found 245.0679.

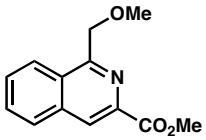


Table 2, Entry 9

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 25:75 → 50:50 EtOAc/hexanes). 68% yield. R_f = 0.50 (50:50 EtOAc/hexanes); ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.43 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.99 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.78 (ddd, *J* = 8.0, 6.0, 1.0 Hz, 1H), 7.77 (ddd, *J* = 9.0, 6.5, 1.5 Hz, 1H), 5.13 (s, 2H), 4.06 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 158.0, 140.4, 136.4, 131.2, 130.0, 128.9, 128.8, 126.4, 125.0, 75.5, 58.9, 53.2; IR (Neat Film, NaCl) 2950, 1736, 1718, 1450, 1295, 1248, 1210, 1100, 779 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974, found 232.0968.

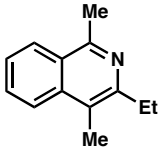


Table 2, Entry 10

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 20:80 EtOAc/hexanes). 72% yield. R_f = 0.45 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.52 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 3.00 (q, *J* = 7.8 Hz, 2H), 2.92 (s, 3H), 2.58 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 149.2, 129.5, 125.9, 125.3, 123.4, 29.3, 22.3, 14.3, 13.4; IR (Neat Film, NaCl) 2965, 1618, 1570, 1443, 1395, 1339, 1270, 755 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{15}N$ $[M]^+$: 185.1204, found 185.1266.

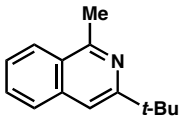


Table 2, Entry 11

Reaction Performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 4:96 Et_2O/hexanes). 83% yield. R_f = 0.73 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.0 Hz, 1H), 7.51 (t, *J* = 6.5 Hz, 1H), 7.45 (s, 1H), 2.95 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 157.2, 136.6, 129.4, 127.2, 125.9, 125.6, 125.3, 112.5, 36.9, 30.1, 22.6; IR (Neat Film, NaCl) 3058, 2954, 1626, 1573, 1481, 1390, 1356, 878, 748 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{17}N$ $[M]^+$: 199.1361, found 199.1363.

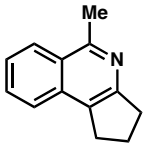
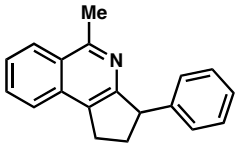


Table 2, Entry 12

Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 0:100 → 20:80 EtOAc/hexanes). 66% yield. R_f = 0.29 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.67 (app t, *J* = 7.5 Hz, 1H), 7.52 (app t, *J* = 7.5 Hz, 1H), 3.20 (app dd, *J* = 9.0, 8.0 Hz, 4H), 2.95 (s, 3H), 2.26 (app quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.4, 133.9, 130.1, 128.7, 126.6, 126.0, 125.7, 124.2, 35.1, 29.2, 22.7, 22.6; IR (Neat Film, NaCl) 2953, 1621, 1581, 1562, 1442, 1390, 1342, 1150, 755 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}N$ $[M]^+$: 183.1048, found 183.1033.



SI-1

Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 0:100 → 20:80 EtOAc/hexanes). 21% yield, isolated as a side product of the reaction to form Table 2, Entry 12. R_f = 0.80 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.72 (ddd, *J* = 8.3, 6.8, 1.0 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.27 (app t, *J* = 7.1 Hz, 2H), 7.19 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.14 (app d, *J* = 7.1 Hz, 2H), 4.62 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.36 (ddd, *J* = 15.9, 7.8, 7.3 Hz, 1H), 3.22 (ddd, *J* = 16.1, 9.0, 5.1 Hz, 1H), 2.91 (s, 3H), 2.85-2.77 (m, 1H), 2.26-2.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 157.5, 145.7, 135.5, 135.2, 130.3, 130.2, 128.7, 128.2, 128.1, 126.7, 126.4, 126.3, 126.2, 124.4, 52.6, 33.9, 27.8, 22.8; IR (Neat Film, NaCl) 3064, 2943, 1682, 1622, 1561, 1493, 1429, 1390, 1117, 1027, 758, 700 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{18}N$ $[M+H]^+$: 260.1439, found 260.1438.

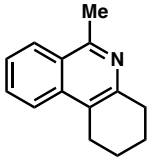
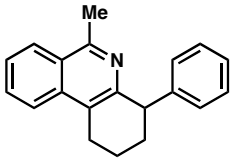


Table 2, Entry 13

Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 67% yield. R_f = 0.33 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.53 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 3.04 (app dd, *J* = 5.0, 2.0 Hz, 4H), 2.92 (s, 3H), 1.95 (app quintet, *J* = 3.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 148.9, 135.7, 129.9, 126.3, 126.0, 125.8, 123.2, 122.7, 33.0, 24.9, 23.4, 23.0, 22.6; IR (Neat Film, NaCl) 2930, 1616, 1570, 1443, 1392, 1332, 1030, 754 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{15}N$ $[M]^+$: 197.1204, found 197.1213.



SI-2

Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 14% yield, isolated as a side product of the reaction to form Table 2, Entry 13. R_f = 0.84 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.73 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.23 (app t, *J* = 7.1 Hz, 2H), 7.16 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.00 (app d, *J* = 7.1 Hz, 2H), 4.48 (app t, *J* = 4.6 Hz, 1H), 3.23 (dt, *J* = 16.9, 4.9 Hz, 1H), 3.05 (dt, *J* = 16.9, 8.3 Hz, 1H), 2.84 (s, 3H), 2.29-2.21 (m, 1H), 2.08 (app dq, *J* = 13.4, 4.2 Hz, 1H), 1.88-1.83 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 149.6, 146.6, 135.6, 135.2, 130.4, 130.0, 129.3, 128.2, 126.4, 126.3, 126.2, 125.9, 124.5, 123.0,

47.5, 32.4, 25.0, 22.7, 18.4; IR (Neat Film, NaCl) 3066, 2934, 1615, 1590, 1492, 1446, 1390, 1332, 1117, 1029, 756, 700 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{20}H_{20}N$ $[M+H]^+$: 274.1596, found 274.1608.

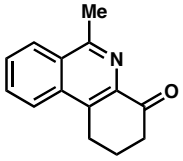


Table 2, Entry 14

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 1:1 EtOAc/hexanes). 66% yield. R_f = 0.21 (1:1 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.8 Hz, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 6.1 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 3.38 (t, *J* = 6.8 Hz, 2H), 3.04 (s, 3H), 2.86 (d, *J* = 7.6, 2H), 2.33 (quintet, *J* = 4.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 158.6, 141.2, 136.0, 134.7, 130.9, 129.7, 128.9, 126.8, 124.7, 39.2, 25.2, 23.1, 22.5; IR (Neat Film, NaCl) 2944, 1682, 1628, 1407, 1385, 1164, 1129, 1031, 906, 759 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$: 211.0997, found 211.0994.

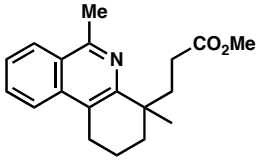


Table 2, Entry 15

See below for synthesis of the enamide substrate **SI-4**. Purified by flash chromatography (SiO_2, 5:95 Et_2O/hexanes). 71% yield. R_f = 0.48 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.0 Hz, 1H), 3.62 (s, 3H), 3.11 (dt, *J* = 16.5, 5.5 Hz, 1H), 2.99-2.93 (m, 1H), 2.90 (s, 3H), 2.33 (app d, *J* = 12.0 Hz, 2H), 2.08 (app d, *J* = 12.0 Hz, 2H), 2.02-1.90 (comp m, 2H), 1.85 (td, *J* = 13.0, 3.0 Hz, 1H), 1.74-1.69 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 155.6, 153.9, 135.2, 129.3, 125.8, 125.5, 125.4, 122.9, 122.4, 51.4, 38.7, 36.5, 34.7, 29.9, 28.2, 25.5, 22.5, 18.9; IR (Neat Film, NaCl) 2934, 1737, 1570, 1439, 1205, 1171, 1118, 756, 710 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$: 298.1807, found 298.1796.

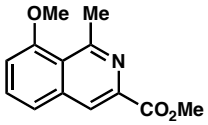


Table 3, Entry 1

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 20:80 EtOAc/hexanes). 66% yield. R_f = 0.32 (30:70 EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.03 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 159.8, 158.3, 140.6, 138.6, 131.4, 122.8, 121.8, 121.0, 109.0, 55.9, 53.0, 29.2; IR (Neat Film, NaCl) 2936, 2852, 1734, 1708, 1616, 1566, 1455, 1435, 1363, 1275,

1252, 1214, 1140, 1088, 1012, 787 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}NO_3$ $[M]^+$: 231.0895, found 231.0889.

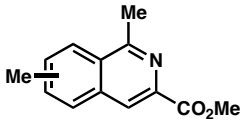


Table 3, Entry 2

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 20:80 EtOAc/hexanes). 59% yield as a 1:1 mixture of isomers. R_f = 0.40 (30:70 EtOAc/hexanes); Isolated as 1:1 mixture of isomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.00 (s, 1H), 8.34 (s, 1H), 8.04 (s, 1H), 8.02 (s, 1H), 7.90, (s, 2H), 7.82 (s, 1H), 7.80, (s, 1H), 7.67 (s, 2H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H) 4.02 (s, 6H), 2.99 (d, *J* = 1.8 Hz, 6H), 2.57 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 167.1, 159.3, 158.9, 141.6, 140.1, 139.9, 133.8, 133.6, 132.0, 129.1, 128.5, 128.0, 127.8, 125.9, 125.0, 123.8, 122.6, 53.3, 23.1, 22.1, 21.9; IR (Neat Film, NaCl) 2951, 1718, 1438, 1392, 1287, 1245, 1212, 1116, 1009, 818 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}NO_2$ $[M]^+$: 215.0946, found 215.0898.

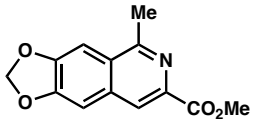


Table 3, Entry 3

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 63% yield. R_f = 0.25 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.31 (s, 1H), 7.06 (s, 1H), 5.87 (s, 2H), 3.85 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 150.2, 149.3, 141.3, 133.6, 121.9, 104.2, 101.0, 100.7, 68.3, 51.7, 29.8, 22.2; IR (Neat Film, NaCl) 2903, 2833, 1755, 1609, 1522, 1461, 1430, 1244, 1170, 1026, 931, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{11}NO_4$ $[M]^+$: 245.0688, found 245.1003.

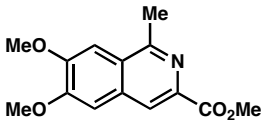


Table 3, Entry 4

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 60% yield. R_f = 0.34 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.34 (s, 1H), 7.20 (s, 1H), 4.08 (s, 3H), 4.05 (s, 6H), 4.03 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 156.6, 154.2, 152.1, 139.7, 132.1, 125.8, 123.9, 111.8, 105.2, 56.1, 51.5, 21.4; IR (Neat Film, NaCl) 2952, 2840, 1730, 1618, 1511, 1465, 1426, 1256, 1161, 1028, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{15}NO_4$ $[M]^+$: 261.1001, found 261.1012.

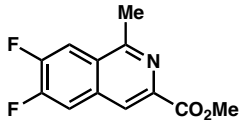
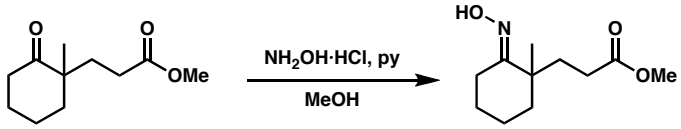


Table 3, Entry 5

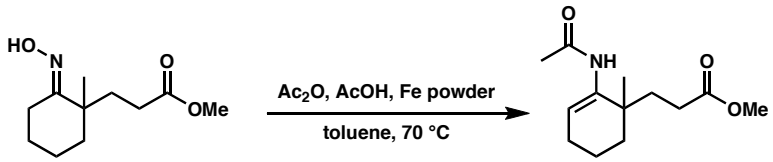
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 30:70 EtOAc/hexanes). 66% yield. R_f = 0.29 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.93 (dd, J = 8.0, 1.9 Hz, 1H), 7.70 (t, J = 8.7 Hz, 1H), 4.05 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 122.23, 115.1, 114.9, 113.9, 113.0, 60.7, 53.3, 31.3, 23.2, 21.4, 14.5; IR (Neat Film, NaCl) 2920, 1716, 1514, 1426, 1281, 1258, 1228, 1181, 1144, 1125, 928, 851, 792, 738, 611 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{23}NO_2$ [M]$^+$: 237.0601 found 237.0591.

Synthesis of Additional Substrates



SI-3

To a solution of ketoester (1.36 g, 6.86 mmol) in MeOH (27 mL) was added NH_2OH·HCl (1.21 g, 17.4 mmol, 2.5 equiv) and pyridine (9.75 mL, 121 mmol, 17.6 equiv). The reaction was stirred at ambient temperature under nitrogen for 30 h, at which point it was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed sequentially with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to a pink oil. Purification by flash chromatography (SiO_2, 10:90 EtOAc:hexanes) provided oxime **SI-3** as a colorless oil (1.22 g, 83% yield). R_f = 0.33 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 3.66 (s, 3H), 3.01 (dt, J = 14.5, 4.5 Hz, 1H), 2.31 (dt, J = 10, 5 Hz, 1H), 2.19-2.11 (comp m, 2H), 2.04 (ddd, J = 14.5, 11.0, 5.0 Hz, 1H), 1.77-1.58 (comp m, 5H), 1.50-1.42 (comp m, 2H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 163.9, 51.6, 40.0, 39.9, 32.5, 29.1, 25.8, 23.7, 21.1, 20.7; IR (Neat Film, NaCl) 3313, 2933, 2863, 1738, 1438, 1375, 1197, 1173, 936 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{19}NO_3$ [M]$^+$: 213.1365, found 213.1367.

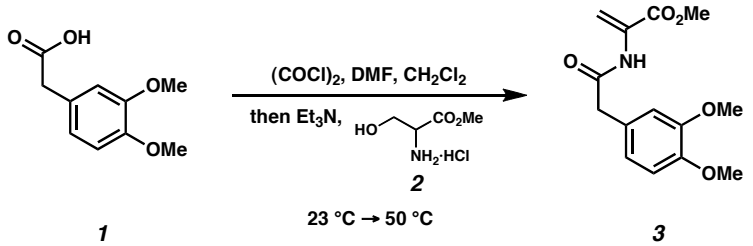


SI-4

Reaction performed according to the method of Burk.[1] Acetic anhydride (7.0 mL, 74.1 mmol, 2.8 equiv) was added dropwise to a solution of oxime **SI-3** (5.61 g, 26.3 mmol) in toluene (45 mL) over a period of 5 min. After an additional 5 min, acetic acid (4.5 mL, 78.6 mmol, 3.0 equiv) was added dropwise over 2 min, followed by 325 mesh iron powder (2.94 g, 52.6 mmol, 2.0 equiv). A reflux condenser was attached and the mixture was heated to 70 °C under a nitrogen atmosphere for 4 h, during which time the color changed from dark grey to orange-brown. The reaction was cooled to ambient

temperature and passed through a plug of Celite. The filtrate was diluted with EtOAc (100 mL) and washed with saturated aqueous sodium bicarbonate (2 x 100 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to a yellow oil. Purification by flash chromatography (SiO_2, 25:75 → 60:40 EtOAc:hexanes) provided acetamide **SI-4** (3.74 g, 60% yield) as a colorless oil. R_f = 0.21 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (br s, 1H), 6.16 (t, J = 4.0 Hz, 1H), 3.68 (s, 3H), 2.33 (dd, J = 9.5, 7.0 Hz, 1H), 2.26-2.09 (comp m, 3H), 2.05 (s, 3H), 1.88-1.82 (m, 1H), 1.64-1.56 (comp m, 4H), 1.44-1.39 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 168.8, 135.7, 120.1, 51.8, 37.0, 34.7, 33.8, 29.0, 26.0, 24.8, 24.5, 18.6; IR (Neat Film, NaCl) 3301, 2934, 1738, 1672, 1658, 1531, 1436, 1371, 1272, 1198, 1173, 1001 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{13}H_{21}NO_3$ $[M]^+$: 239.1521, found 239.1527.

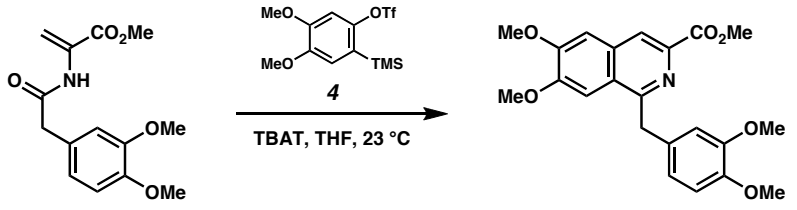
Total Synthesis of Papaverine



Methyl (3,4-dimethoxyphenyl)acetamidoacrylate (3)

Oxalyl chloride (2.6 mL, 29.8 mmol, 2.3 equiv) was slowly added to a solution of acid **1** (5.55 g, 28.3 mmol, 2.2 equiv) in CH_2Cl_2 (40 mL), followed by DMF (0.10 mL, 1.29 mmol, 0.1 equiv). The solution was stirred at ambient temperature for 40 min, during which time it bubbled vigorously and the color changed from pale to bright yellow. In a separate flask, serine methyl ester·HCl (2.02 g, 13.0 mmol) was suspended in CH_2Cl_2 (120 mL), and Et_3N (5.91 mL, 42.0 mmol, 3.2 equiv) and DMAP (77.6 mg, 0.64 mmol, 0.05 equiv) were added. The mixture was stirred for 15 min until all solids had dissolved. The solution of acid chloride in the first flask was then transferred into the second flask via cannula under nitrogen over a period of 10 min, during which time the color of the serine methyl ester solution changed from colorless to orange. The reaction was maintained at ambient temperature under nitrogen for 2.5 h, at which time an additional portion of Et_3N (2.0 mL, 14.3 mmol, 1.1 equiv) was added. A reflux condenser was attached and the reaction was heated to 50 °C for 20 h. After cooling to ambient temperature, the solids were filtered off under vacuum and the filtrate was diluted in CH_2Cl_2 (100 mL), washed with saturated aqueous sodium bicarbonate (150 mL), brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. In order to retrieve excess acid **1**, the aqueous layer was acidified with concentrated HCl (5 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a pale yellow solid (crude **1**). Purification of the original yellow oil by flash chromatography (SiO_2, 25:75 → 45:55 EtOAc/hexanes) provided enamide **3** (2.43 g, 67% yield) as a colorless oil. R_f = 0.51 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (br s,

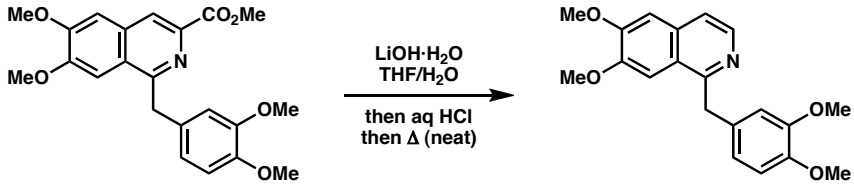
1H), 6.86 (s, 1H), 6.86 (d, J = 19.0 Hz, 1H), 6.82 (d, J = 19.5 Hz, 1H), 6.60 (s, 1H), 5.85 (d, J = 1.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.61 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 164.4, 149.4, 148.5, 130.8, 126.4, 121.6, 112.3, 111.6, 108.7, 55.9, 55.8, 52.9, 44.5; IR (Neat Film, NaCl) 3368, 2955, 1725, 1687, 1514, 1441, 1327, 1263, 1158, 1027 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{17}NO_5$ $[M]^+$: 279.1107, found 279.1118.



3 *5*

Methyl 1-(3'4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline-3-carboxylate (5)

To a solution of methyl (3,4-dimethoxyphenyl)acetamidoacrylate **3** (156 mg, 0.56 mmol, 2.0 equiv) in THF (20 mL) was added TBAT (166 mg, 0.31 mmol, 1.1 equiv) followed by silyl aryl triflate **4** (100 mg, 0.28 mmol) in THF (8 mL). The solution was stirred at ambient temperature under nitrogen for 72 h, at which point it was concentrated under reduced pressure to a yellow oil. Purification by flash chromatography (SiO_2, 50:50 → 60:40 EtOAc/hexanes) provided isoquinoline **5** (77.6 mg, 70% yield) as tan solid. R_f = 0.15 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 6.78 (app d, J = 6.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 1H), 4.63 (s, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 158.2, 152.8, 151.5, 149.0, 147.6, 139.6, 133.0, 132.0, 124.8, 122.4, 120.5, 111.9, 111.1, 106.5, 104.8, 56.1, 56.0, 55.8, 55.7, 52.8, 42.8; δ; IR (Neat Film, NaCl) 2951, 2835, 1730, 1618, 1511, 1465, 1426, 1256, 1161, 1028, 733 cm^{-1}; HRMS (ES+) m/z calc'd for $C_{22}H_{23}NO_6$ $[M+H]^+$: 398.1604, found 398.1584.



5 ***Papverine (6)***

Papaverine (6)

To a solution of isoquinoline ester **5** (20.0 mg, 50 μmol) in THF (1 mL) was added a solution of $LiOH{\cdot}H_2O$ (10.6 mg, 253 μmol, 5.0 equiv) in H_2O (0.5 mL). The biphasic mixture was vigorously stirred at ambient temperature under nitrogen for 3 h. The mixture was then concentrated under reduced pressure to remove the organic solvent and the aqueous layer was diluted with H_2O (1 mL). The pH was adjusted to 4 with conc. HCl (20 μL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a solid tan foam. The vial containing the crude foam under nitrogen was then heated by passing intermittently through a Bunsen burner flame over 45 sec. The resulting brown oil was purified by flash chromatography (SiO_2, 40:60 → 60:40

EtOAc/hexanes) to provide papaverine **6** (10.5 mg, 61% yield) as a yellow solid. R_f = 0.10 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.5 Hz, 1H), 7.43 (d, *J* = 5.5 Hz, 1H), 7.35 (s, 1H), 7.06 (s, 1H), 6.82 (app d, *J* = 7.0 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.54 (s, 2H), 4.01 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 150.5, 147.8, 147.1, 145.6, 139.2, 131.5, 130.4, 121.0, 118.6, 116.8, 109.9, 109.2, 103.4, 102.3, 54.1, 54.0, 53.9, 53.8, 40.4; IR (Neat Film, NaCl) 2930, 2832, 1511, 1478, 1421, 1269, 1235, 1158, 1026, 855 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{20}H_{21}NO_4$ $[M+H]^+$: 340.1549, found 340.1553.

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