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Supporting Information

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Enantioselective Thiourea-Catalyzed Acyl–Mannich Reactions of Isoquinolines

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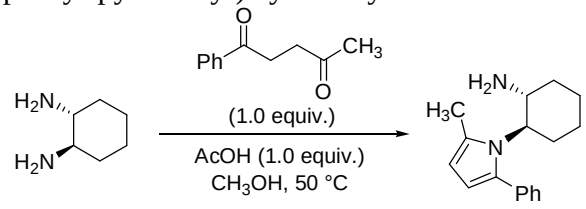
General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen, unless otherwise noted. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.

Materials. Commercial reagents were purchased from Sigma Aldrich, Fluka, Alfa Aesar, or Lancaster, and used as received with the following exceptions: diethyl ether and tetrahydrofuran were distilled from sodium at 760 Torr; dichloromethane was distilled from calcium hydride at 760 Torr.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (400 MHz), Inova-500 (500 MHz), or an Inova-600 (600 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.25). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hertz (Hz). Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Melting points were measured on a Mel-Temp apparatus, and are uncorrected. The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility. Chiral HPLC analysis was performed on a Shimadzu VP-series instrument. Chiral SFC analysis was performed on a Berger instrument.

(A) Preparation of Catalysts.[1]

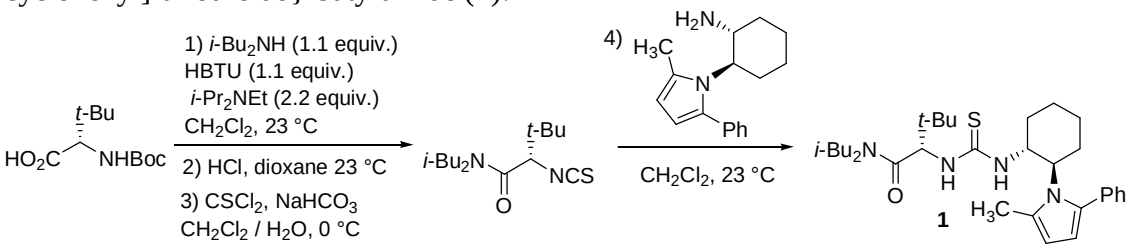
(*R*,*R*)-2-(2-Methyl-5-phenyl-pyrrol-1-yl)-cyclohexylamine:



84% yield

In a round-bottomed flask equipped with reflux condenser, acetic acid (179 μL, 3.13 mmol, 1.0 equiv.) and 5-phenyl-2,5-pentanedione (552 mg, 3.13 mmol, 1.0 equiv.) were added sequentially to a solution of (*R*,*R*)-diaminocyclohexane[2] (358 mg, 3.13 mmol) in methanol (16 mL). The mixture was heated to 50 °C and stirred for 12 hours, then cooled to 23 °C and concentrated *in vacuo*. The residue was partitioned between dichloromethane (50 mL) and 4M aqueous sodium hydroxide (20 mL). The organic phase was separated, and the aqueous extracted twice with dichloromethane (50 mL total volume). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (2% → 5% methanol in dichloromethane), yielding the product as a red oil (665 mg, 2.61 mmol, 84% yield) which gradually solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.30 (5H, m), 6.05 (1H, br s), 5.98 (1H, br s), 3.78–3.77 (1H, m), 3.23–3.19 (1H, m), 2.47 (3H, s), 2.03–1.95 (2H, m), 1.83–1.71 (2H, m), 1.35–1.20 (2H, m), 1.01–0.89 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$):
δ 137.4, 134.8, 129.8, 129.3, 128.6, 127.0, 109.8, 108.1, 64.8, 53.5, 35.6, 32.1, 26.2, 25.4, 15.6. IR (cm^{-1}, neat): 3366 (w), 3059 (w), 2931 (m), 2857 (m), 2236 (w), 1601 (s), 1514 (s), 1462 (s), 1385 (s), 1296 (s), 1028 (m), 910 (s). LRMS (CI): 254.5 (100%) $[M]^+$, 255.1 (50%) $[M+H]^+$.

(*S*,*R*,*R*)-*N*,*N*-Diisobutyl-3,3-dimethyl-2-{3-[2-(2-methyl-5-phenyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-butyramide (**1**):



Step 1: Diisopropylethylamine (958 μL, 5.5 mmol, 2.2 equiv.), then diisobutylamine (480 μL, 2.75 mmol, 1.1 equiv.) were added to a suspension of L-(*S*)-Boc-*tert*-leucine (578 mg, 2.5 mmol) and *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HBTU) (1.04 g, 2.75 mmol, 1.1 equiv.) in dichloromethane (25 mL) at 23 °C. The reaction was stirred for 28 hours at 23 °C, then diluted with diethyl

[1] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, *126*, 10558–10559.
[2] J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie, C. M. Zepp, *J. Org. Chem.* **1994**, *59*, 1939–1942.

ether (50 mL), and washed twice with 1M hydrochloric acid (50 mL) then twice with saturated aqueous sodium bicarbonate (50 mL), then once with brine. After drying over sodium sulfate, the solution was concentrated, yielding the crude product (contaminated with tetramethylurea) as a foam which was used in step 2 without further purification.
Step 2: Hydrogen chloride (6 mL, 4M in dioxane, excess) was added to crude Boc-2-amino-*N*,*N*-diisobutyl-3,3-dimethyl-butyramide (2.5 mmol), and the resulting solution stirred at 23 °C for 2 hours. The mixture was concentrated to yield (*S*)-2-amino-*N*,*N*-diisobutyl-3,3-dimethyl-butyramide hydrochloride (contaminated with tetramethylurea) as a foam, which was used in step 3 without further purification.
Step 3:
CAUTION*! Thiophosgene is a highly toxic compound.*
Saturated aqueous sodium bicarbonate (12.5 mL) was added to a solution of (*S*)-2-amino-*N*,*N*-diisobutyl-3,3-dimethyl-butyramide hydrochloride (2.5 mmol) in dichloromethane (12.5 mL) at 0 °C. The mixture was stirred for 5 minutes, then stirring was stopped and thiophosgene (210 μL, 2.75 mmol, 1.1 equiv.) was added to the organic (lower) phase by syringe. The resulting orange mixture was stirred at 0 °C for 20 minutes. Dichloromethane (20 mL) was added, and the organic portion separated. The aqueous was extracted twice with dichloromethane (20 mL). The combined organic extracts were dried over sodium sulfate and concentrated, yielding *N*,*N*-diisobutyl-2-isothiocyanato-3,3-dimethyl-butyramide (contaminated with tetramethylurea) as a solid, which was used in step 4 immediately and without further purification.
Step 4: (*R*,*R*)-2-(2-Methyl-5-phenyl-pyrrol-1-yl)-cyclohexylamine (820 mg, 3.22 mmol, 1.3 equiv.) was added by syringe as a dichloromethane solution (3 mL, with two 2.75 mL rinses) to a solution of *N*,*N*-diisobutyl-2-isothiocyanato-3,3-dimethyl-butyramide (2.5 mmol) in dichloromethane (4 mL) at 23 °C. The resulting solution was stirred at 23 °C for 13 hours, then concentrated. The residue was purified by chromatography on silica (5% → 10% ethyl acetate in hexanes), yielding the title compound as a white foam (1.22 g, 2.27 mmol, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.42 (2H, m), 7.36–7.31 (3H, m), 6.07 (1H, br s), 6.02 (1H, s), 5.86 (1H, s), 5.48 (1H, br s), 4.97 (1H, m), 4.35 (1H, br s), 3.97 (1H, m), 3.80 (1H, dd, J = 7.0, 13.0 Hz), 3.45–3.44 (1H, m), 3.01 (1H, dd, J = 7.5, 14.5 Hz), 2.58 (1H, dd, J = 8.0, 13.5 Hz), 2.47 (m, 3H), 2.26–2.17 (3H, br s), 2.02–1.98 (2H, m), 1.88–1.86 (1H, m), 1.73–1.70 (1H, m), 1.41–1.39 (1H, m), 0.97 (9H, s), 0.93 (6H, d, J = 6.5 Hz), 0.89 (6H, d, J = 6.5 Hz), 0.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.4, 172.2, 136.2, 134.5, 129.8, 129.3, 129.0, 127.2, 110.4, 108.9, 60.0, 56.6, 56.1, 53.9, 37.4, 33.9, 32.6, 28.2, 27.2, 27.2, 27.0, 25.9, 24.8, 21.0, 20.8, 20.7, 19.7, 15.5. IR (cm^{-1}, CH_2Cl_2 film): 3405 (br), 3055 (m), 2988 (w), 1630 (w), 1422 (w), 1265 (s), 897 (m). LRMS (CI): 410.3 (80%) $[M+H]^+$, 409.4 (100%) $[M–i\text{-}Bu_2NH]^+$.

2-{3-[2-(2,5-Dimethyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-*N*,*N*-diisobutyl-3,3-dimethyl-butyramide (Table 2, entry 1): The title compound was prepared according to general procedure A, and obtained as a white powder. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.26 (1H, br s), 5.74 (2H, m), 5.55 (1H, br s), 5.42 (1H, m), 4.36 (1H, m), 3.85–3.81 (1H, m), 3.78 (1H, dd, J = 13.2, 6.6 Hz), 3.52 (1H, dd, J = 7.2, 5.4 Hz), 3.50–3.46 (1H, m), 3.07 (1H, dd, J = 14.4, 7.2 Hz), 2.62 (1H, dd, J = 13.2, 8.4 Hz), 2.51 (1H, m), 2.39 (3H, br s), 2.26 (3H, br s), 2.08 (1H, m), 2.02–1.96 (2H, m), 1.92–1.90 (1H, m), 1.86–1.84 (1H, m), 1.50–1.46 (1H, m), 1.42–1.39 (1H, m), 1.34–1.30 (2H, m), 1.00 (9H, s), 0.97

(3H, d, J = 6.0 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 181.7, 138.6, 135.4, 109.0, 106.6, 60.4, 59.6, 56.6, 56.0, 53.8, 37.3, 34.2, 32.6, 28.1, 27.2, 26.9, 26.1, 24.9, 20.9, 20.7, 20.5, 19.6. IR (cm^{-1}, CH_2Cl_2 film): 3271 (w), 3054 (w), 2965 (m), 2872 (w), 1630 (m), 1524 (m), 1449 (m), 1265 (s).

2-{3-[2-(2,5-Diphenyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-*N*,*N*-diisobutyl-3,3-dimethyl-butyramide (Table 2, entry 2): The title compound was prepared according to general procedure A, and obtained as a white foam. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53–7.40 (10H, m), 6.29 (1H, br s), 6.14–6.08 (2H, m), 5.55 (1H, br s), 5.19 (1H, br s), 4.06–4.03 (1H, m), 3.83 (1H, dd, J = 13.8, 6.6 Hz), 3.62 (1H, br s), 3.54–3.50 (1H, m), 3.05 (1H, dd, J = 14.4, 7.2 Hz), 2.60 (1H, dd, J = 13.2, 8.4 Hz), 2.28–2.26 (1H, m), 2.11–2.08 (2H, m), 2.02–1.90 (2H, m), 1.73–1.71 (1H, m), 1.54–1.52 (1H, m), 1.16–1.14 (1H, m), 1.09 (9H, s), 1.02–1.00 (1H, m), 0.97 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 7.2 Hz), 0.92 (3H, d, J = 7.2 Hz), 0.92 (3H, d, J = 7.2 Hz), 0.80–0.78 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 181.2, 172.1, 137.0, 133.4, 131.6, 128.8, 128.4, 112.9, 110.0, 61.1, 60.6, 56.7, 54.0, 37.3, 34.1, 33.1, 32.8, 28.3, 27.3, 27.1, 26.1, 24.3, 21.1, 20.8, 20.6, 19.8. IR (cm^{-1}, CH_2Cl_2 film): 3374 (m), 3057 (w), 2961 (s), 2872 (m), 1683 (m), 1632 (s), 1518 (s), 1368 (s).

(B) Silyl Ketene Acetals.

1-(*Tert*-butyldimethylsilyloxy)-1-methoxyethene was purchased from Aldrich and used as received. 1-(*tert*-Butyldimethylsilyloxy)-1-butyloxyethene, 1-(*tert*-butyldimethylsilyloxy)-1-benzyloxyethene and 1-(*tert*-butyldimethylsilyloxy)-1-isopropoxyethene were prepared according to the literature procedure.[3]

(C) Preparation of Isoquinolines.

General procedure for preparation of (*tert*-butyl-dimethyl-silanyloxy)isoquinolines.

5-(*tert*-Butyl-dimethyl-silanyloxy)-isoquinoline:

To a suspension of 5-hydroxyisoquinoline (435 mg, 3.0 mmol) and imidazole (613 mg, 9.0 mmol, 3.0 equiv.) in *N*,*N*-dimethylformamide (1.0 mL) was added *tert*-butyldimethylsilyl chloride (678 mg, 4.5 mmol, 1.5 equiv.). The mixture was stirred at 23 °C for 50 hours, then partitioned between diethyl ether and brine. The aqueous phase was extracted twice with diethyl ether, and the combined organic extracts washed with brine, dried (magnesium sulfate) and concentrated. The residue was purified by chromatography on silica (33% ethyl acetate in hexanes), yielding the title compound as a pale yellow oil which gradually solidified (760 mg, 2.9 mmol, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (1H, s), 8.52 (1H, d, J = 6.0 Hz), 7.94 (1H, d, J = 6.0 Hz), 7.58 (1H, d, J = 8.0 Hz), 7.47 (1H, dd, J = 8.0, 8.0 Hz), 7.07 (1H, d, J = 8.0 Hz), 1.10 (9H, s), 0.30 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 150.7, 142.4, 130.5, 129.9, 127.3, 120.1, 116.4,115.3, 25.7, 18.3, –4.4. IR (CH_2Cl_2 film, cm^{-1}): 2957 (m), 2932 (m), 2888 (w), 2859 (m), 1584 (m), 1491 (m), 1431 (m), 1385 (m), 1321 (m), 1279 (s), 1171 (m), 1105 (m), 914 (s), 833 (s). LRMS (ESI): 260.1 (100%) $[M+H]^+$.

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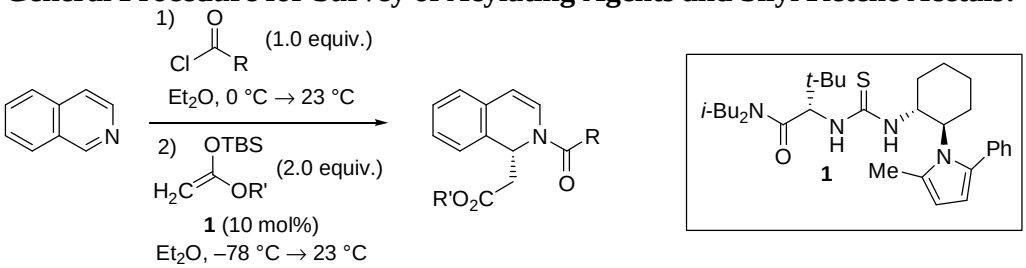
[3] A. G. Wenzel, E. N. Jacobsen. *J. Am. Chem. Soc*. **2002**, *124*, 12964–12965.

7-(*tert*-Butyl-dimethyl-silanyloxy)-isoquinoline:
After a reaction time of 42 hours, workup and purification as described above, the title compound was obtained as a pale yellow oil which gradually solidified (740 mg, 2.9 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 (1H, s), 8.40 (1H, d, J = 6.0 Hz), 7.71 (1H, d, J = 9.5 Hz), 7.57 (1H, d, J = 5.0 Hz), 7.29–7.27 (2H, m), 1.02 (9H, s), 0.26 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 151.1, 414.2, 131.4, 129.8, 128.0, 126.7, 120.0, 114.0, 25.6, 18.2, –4.4. IR (CH_2Cl_2 film, cm^{-1}): 2957 (m), 2932 (m), 2888 (w), 2859 (m), 1589 (m), 1502 (m), 1449 (m), 1385 (m), 1258 (m), 1217 (m), 970 (m), 932 (s), 841 (s). LRMS (ESI): 260.1 (100%) $[M+H]^+$.

Trifluoro-methanesulfonic acid isoquinolin-6-yl ester:
N-Phenylbis(trifluoromethanesulfonimide) (313 mg, 0.875 mmol, 1.25 equiv.) was added to a suspension of 6-hydroxyisoquinoline (102 mg, 0.70 mmol) and *N*,*N*-diisopropylethylamine (124 μL, 0.714 mmol, 1.02 equiv.) in methanol (1.5 mL) at 23 °C. The mixture was stirred for 20 hours, then concentrated. The residue was purified by chromatography on silica (10% ethyl acetate in dichloromethane), yielding the title compound as a colorless oil (102 mg, 0.37 mmol, 53% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.38 (1H, s), 8.68 (1H, d, J = 5.4 Hz), 8.15 (1H, d, J = 9.0 Hz), 7.80 (1H, d, J = 2.4 Hz), 7.58 (1H, d, J = 5.4 Hz), 7.55 (1H, dd, J = 9.0, 2.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.7, 150.2, 144.8, 136.5, 131.1, 127.6, 121.5, 120.7, 119.0 (q, $J_{C–F}$ = 320 Hz). IR: 3067 (w), 3032 (w), 1630 (m), 1427 (s), 1215 (s), 1142 (s), 959 (s), 839 (s). LRMS (ESI): 277.9 (90%) $[M+H]^+$.

(D) General Procedure for Survey of Acylating Agents and Silyl Ketene Acetals.



(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetic acid methyl ester (Table 1, entry 1):
In an oven-dried 2-dram vial, isoquinoline (11.6 μL, 0.10 mmol) was dissolved in diethyl ether (2.0 mL) and cooled to 0 °C. Acetyl chloride (7.1 μL, 0.10 mmol, 1.0 equiv.) was added by syringe, and the resulting white suspension warmed to 23 °C and stirred for 30 minutes, then cooled to –78 °C (dry ice/isopropanol bath). Catalyst **1** (5.4 mg, 0.010 mmol, 10 mol%), then 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (44 μL, 0.20 mmol, 2.0 equiv.) were added. The mixture was stirred while the dry ice/isopropanol bath was allowed to warm gradually to 23 °C over 14 hours. After the solvent was removed *in vacuo*, the residue was purified by chromatography on silica (20% → 33% ethyl acetate in hexanes), yielding the title compound as a colorless oil in 80% yield (20 mg) and 28% enantiomeric excess, as determined by SFC (Chiralpak AD-H, 15% methanol/CO_2, 4 mL/min, 50 °C, 292 nm; t_r(major) = 0.99 min, t_r(minor) = 1.15 min). ^{1}H NMR (600 MHz, $CDCl_3$): the compound exists as a 6.1:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 7.31–7.22 (3H, m), 7.14 (1H, d, J = 7.2 Hz), 6.67

(1H, dd, J = 7.2, 1.2 Hz), 6.19 (1H, dd, J = 7.2, 7.2 Hz), 6.02 (1H, d, J = 7.8 Hz), 3.66 (3H, s), 2.64 (1H, dd, J = 13.2, 7.8 Hz), 2.56 (1H, dd, J = 13.2, 6.0 Hz), 2.24 (3H, s). Representative signals corresponding to the minor rotamer: δ 7.19–7.14 (1H, m), 6.14 (1H, d, J = 7.8 Hz), 5.52 (1H, dd, J = 6.6, 6.6 Hz), 3.68 (3H, s), 2.78–2.69 (2H, m), 2.41 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 170.8, 168.8, 132.1, 131.7, 130.4, 129.9, 128.7, 128.4, 127.8, 127.5, 126.7, 125.8, 125.5, 125.1, 124.8, 124.1, 111.4, 110.5, 54.8, 52.1, 50.6, 40.0, 39.5, 21.7. IR (neat): 3018 (w), 2951 (m), 1732 (s), 1674 (s), 1628 (s), 1570 (m), 1352 (br), 1032 (m). LRMS (ESI): 246.0 (100%) $[M+H]^+$.

1-Methoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid benzyl ester (Table 1, entry 2):
After chromatography on silica (5% → 10% ethyl acetate in hexanes), the product was obtained as a colorless oil in 62% yield (21 mg) and 40% enantiomeric excess, as determined by SFC (Chiralpak OD-H, 5% methanol/CO_2, 4 mL/min, 50 °C, 289 nm; t_r(minor) = 4.52 min, t_r(major) = 5.10 min). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.45–7.33 (5H, m), 7.24–7.13 (3H, m), 7.11–7.08 (1H, m), 6.86 (1H, d, J = 7.5 Hz), 5.88 (1H, d, J = 7.5 Hz), 5.86 (1H, dd, J = 6.5, 6.5 Hz), 5.24 (2H, s), 3.59 (3H, s), 2.69 (1H, dd, J = 13.5, 7.5 Hz), 2.57 (1H, dd, J = 13.5, 7.0 Hz). Representative signals corresponding to the minor rotamer: δ 6.97 (1H, d, J = 8.0 Hz), 5.99 (1H, d, J = 8.0 Hz), 5.78 (1H, dd, J = 6.5, 6.5 Hz), 5.30 (1H, d, J = 12.0 Hz), 5.25 (1H, d, J = 12.0 Hz), 3.52 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 170.8, 170.4, 153.2, 152.8, 136.1, 135.9, 131.4, 131.3, 130.3, 130.1, 128.8, 128.6, 128.5, 128.4, 127.5, 127.3, 126.4, 126.2, 125.2, 125.1, 124.4, 124.3, 109.5, 109.1, 68.4, 68.3, 53.3, 52.9, 52.1, 52.0, 51.9, 51.8, 40.1, 39.7. IR (neat): 3034 (w), 2953 (m), 1723 (s), 1632 (s), 1456 (s), 1327 (s), 1250 (s). LRMS (ESI): 337.9 (100%) $[M+H]^+$.

1-Methoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (Table 1, entry 3):
After chromatography on silica (0% → 5% ethyl acetate in hexanes), the product was obtained as a colorless oil in 72% yield (31 mg) and 47% enantiomeric excess, as determined by SFC (Chiralpak OD-H, 5% methanol/CO_2, 4 mL/min, 50 °C, 288 nm; t_r(minor) = 2.33 min, t_r(major) = 2.79 min). ^{1}H NMR (600 MHz, $CDCl_3$): the compound exists as a 2.3:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.30–7.14 (3H, m), 7.13 (1H, d, J = 7.2 Hz), 6.91 (1H, dd, J = 7.8, 1.2 Hz), 5.96 (1H, d, J = 7.8 Hz), 5.83 (1H, dd, J = 7.2, 7.2 Hz), 3.69 (3H, s), 2.73 (1H, dd, J = 13.8, 7.8 Hz), 2.58 (1H, dd, J = 13.8, 6.6 Hz), 2.02 (3H, s), 1.97 (3H, s). Representative signals corresponding to the minor rotamer: δ 6.91 (1H, dd, J = 7.8, 0.6 Hz), 6.04 (1H, d, J = 7.8 Hz), 5.80 (1H, dd, J = 9.0, 4.8 Hz), 3.62 (3H, s), 2.81 (1H, dd, J = 14.4, 9.6 Hz), 2.67 (1H, dd, J = 14.4, 4.8 Hz), 2.06 (3H, s), 2.0 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 170.7, 170.3, 150.6, 150.3, 131.3, 131.1, 130.1, 130.1, 128.6, 128.5, 127.6, 127.3, 126.6, 126.4, 125.3, 125.2, 124.6, 124.4, 109.9, 109.5, 106.3, 90.2, 90.0, 53.3, 52.7, 52.2, 51.9, 39.7, 39.7, 21.9, 21.8, 21.7, 21.6. IR (neat): 3075 (w), 3003 (m), 2953 (m), 1724 (s), 1632 (s), 1572 (m), 1456 (s), 1248 (br), 1044 (s). LRMS (ESI): 406.0 (70%) $[M+H]^+$, 408.0 (60%) $[M+H]^+$, 410.0 (100%) $[M+H]^+$.

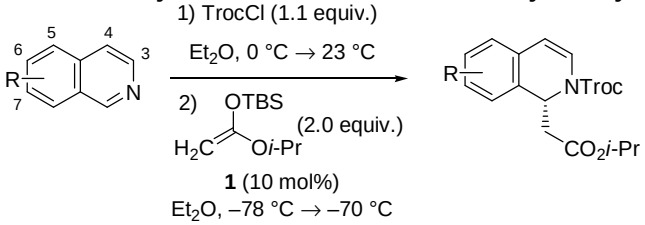
1-Methoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (Table 1, entry 4):
After chromatography on silica (5% → 10% ethyl acetate in hexanes), the product was obtained as a white solid in 73% yield (31 mg) and 64% enantiomeric excess, as determined by SFC (Chiralpak OD-H, 25% methanol/CO_2, 5 mL/min, 50 °C, 208 nm; t_r(minor) = 2.67 min, t_r(major) = 3.71 min). ^{1}H NMR (600 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.84–7.82 (2H, m), 7.71–7.62 (2H, m), 7.48–7.44 (2H, m), 7.40–7.34 (2H, m), 7.30–7.20 (3H, m), 7.15 (1H, d, J = 7.2 Hz), 6.88 (1H, d, J = 7.8 Hz), 5.99 (1H, d, J = 7.8 Hz), 5.90 (1H, dd, J = 7.2, 7.2 Hz), 4.58–4.55 (1H, m), 4.38–4.33 (1H, m), 3.66 (3H, s), 2.72 (1H, dd, J = 13.8, 7.2 Hz), 2.62 (1H, dd, J = 13.8, 6.6 Hz). Representative signals corresponding to the minor rotamer: δ 7.13 (1H, d, J = 7.2 Hz), 6.95 (1H, d, J = 7.8 Hz), 6.02 (1H, d, J = 7.8 Hz), 5.66 (1H, dd, J = 7.8, 5.4 Hz), 4.69 (1H, dd, J = 10.2, 6.0 Hz), 4.51 (1H, dd, J = 10.8, 6.6 Hz), 3.63 (3H, s), 2.68 (1H, dd, J = 13.8, 9.0 Hz), 2.43 (1H, dd, J = 14.4, 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 170.8, 170.5, 153.1, 152.8, 143.9, 143.8, 143.7, 141.6, 131.4, 130.9, 130.3, 130.1, 128.6, 128.4, 128.1, 127.6, 127.4, 127.2, 126.5, 125.3, 125.2, 125.2, 125.0, 124.1, 120.3, 120.3, 109.6, 109.4, 68.7, 68.5, 53.0, 52.9, 52.1, 51.9, 47.3, 39.7, 39.4. IR (neat): 3067 (m), 2951 (m), 1740 (s), 1634 (s), 1572 (m), 1285 (br), 984 (s). LRMS (ESI): 426.2 (100%) $[M+H]^+$.

1-Methoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 1, entry 5):
The product was obtained as a colorless oil in 66% yield (25 mg) and 82% enantiomeric excess, as determined by SFC (Chiralpak OD-H, 3% methanol/CO_2, 4 mL/min, 50 °C, 285 nm; t_r(minor) = 3.9 min, t_r(minor) = 4.2 min). α_D = –250° (c = 1.2 g/100 mL, ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.9:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.27–7.19 (3H, m), 7.11 (1H, d, J = 7.0 Hz), 6.92–6.90 (1H, m), 5.99 (1H, d, J = 7.5 Hz), 5.84 (1H, dd, J = 7.0 Hz, 7.0 Hz), 4.93 (1H, d, J = 12.5 Hz), 4.75 (1H, d, J = 12.5 Hz), 3.63 (3H, s), 2.71 (1H, dd, J = 14.0, 6.5 Hz), 2.62 (1H, dd, J = 14.0, 7.0 Hz). Representative signals corresponding to the minor rotamer: δ 6.05 (1H, d, J = 7.5 Hz), 4.85 (1H, d, J = 12.0 Hz), 3.61 (3H, s), 2.77 (1H, dd, J = 14.5, 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 170.5, 170.4, 151.6, 151.3, 131.3, 131.1, 129.9, 129.8, 128.7, 128.6, 127.8, 127.6, 126.5, 126.4, 125.5, 125.4, 124.5, 123.5, 110.7, 110.5, 95.2, 75.7, 75.6, 53.3, 53.2, 52.2, 52.0, 40.2, 39.6. IR (neat): 3023 (w), 2953 (m), 1726 (s), 1636 (s), 1292 (br), 934 (m). LRMS (ESI): 377.9 (95%) $[M+H]^+$, 379.9 (90%) $[M+H]^+$, 381.9 (30%), $[M+H]^+$, 394.9 (100%) $[M+NH_4]^+$, 396.9 (100%) $[M+NH_4]^+$, 398.9 (100%) $[M+NH_4]^+$.

1-Benzyloxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 1, entry 6):
After chromatography on silica (0% → 5% ethyl acetate in hexanes), the product was obtained in 80% yield (38 mg) and 73% enantiomeric excess, as determined by SFC (Chiralpak OD-H, 15% methanol/CO_2, 4 mL/min, 50 °C, 283 nm; t_r(minor) = 2.29 min,

t_r(minor) = 2.55 min). α_D = –179° (c = 0.85 g/100 mL, ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.41–7.35 (5H, m), 7.30–7.27 (1H, m), 7.21–7.13 (3H, m), 6.94–6.92 (1H, m), 6.02 (1H, d, J = 7.8 Hz), 5.91–5.89 (1H, m), 5.13 (1H, d, J = 12.0 Hz), 5.06 (1H, d, J = 12.0 Hz), 4.86 (1H, d, J = 12.0 Hz), 4.79 (1H, d, J = 12.0 Hz), 2.88–2.77 (1H, m), 2.72 (1H, dd, J = 13.8 Hz, 7.2 Hz). Representative signals corresponding to the minor rotamer: δ 6.07 (1H, d, J = 8.4 Hz), 5.13–5.06 (2H, m), 4.90 (1H, d, J = 12.0 Hz), 4.84 (1H, d, J = 12.0 Hz), 2.88 (1H, dd, J = 14.4, 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 170.0, 169.8, 151.5, 151.2, 135.8, 135.6, 131.2, 131.0, 129.9, 129.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 127.8, 127.6, 126.5, 125.5, 125.4, 124.5, 123.5, 110.7, 110.5, 95.2, 75.7, 75.5, 67.0, 66.8, 53.3, 53.2, 40.4, 39.8. IR (neat): 3034 (w), 2957 (w), 1728 (s), 1654 (m), 1456 (m), 1246 (s), 1126 (s), 1047 (m), 781 (m). LRMS (ESI): 453.7 (18%) $[M+H]^+$, 455.7 (20%) $[M+H]^+$, 457.7 (5%) $[M+H]^+$, 470.8 (40%) $[M+NH_4]^+$, 472.8 (40%) $[M+NH_4]^+$, 474.8 (12%) $[M+NH_4]^+$.

(E) General Procedure for Acyl-Mannich Reactions Catalyzed by 1.



1-Isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 1):

In an flame-dried round-bottomed flask, isoquinoline (61 μL, 97% pure, 0.50 mmol) was dissolved in diethyl ether (5.0 mL) and cooled to 0 °C. 2,2,2-Trichloroethyl chloroformate (76 μL, 98% pure, 0.55 mmol, 1.1 equiv.) was added dropwise by syringe, and the resulting white suspension warmed to 23 °C and stirred for 30 minutes, then cooled to –78 °C (dry ice/isopropanol bath). Catalyst **1** (26.9 mg, 0.050 mmol, 10 mol%) in diethyl ether (4.0 mL + 1.0 mL rinse volume), then 1-(*tert*-butyldimethylsilyloxy)-1-isopropoxyethene (216 mg, 1.0 mmol, 2.0 equiv.) was added. The reaction mixture was warmed to –70 °C (isopropanol bath equipped with immersion cooler) and stirred 14 hours. Cooling was stopped and the bath allowed to warm to 23 °C over 3 hours. After the solvent was removed *in vacuo*, the residue was purified by chromatography on silica (0% → 5% ethyl acetate in hexanes), yielding the title compound as a colorless oil (161 mg, 0.40 mmol, 80% yield) The enantiomeric excess was determined to be 86% by chiral SFC (Chiralpak OD-H, 5% methanol/CO_2, 5 mL/min, 50 °C, 285 nm. t_r(minor): 2.23 min, t_r(major): 2.66 min.) α_D = –240° (c = 1.1 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.26–7.17 (3H, m), 7.10 (1H, d, J = 7.5 Hz), 6.90 (1H, d, J = 7.5 Hz), 5.99 (1H, d, J = 8.0 Hz), 5.84–5.82 (1H, m), 4.97–4.88 (2H, m), 4.78 (1H, d, J = 12.0 Hz), 2.67–2.58 (2H, m), 1.20 (3H, d, J = 6.0 Hz), 1.16 (3H, d, J = 6.5 Hz). Representative signals corresponding to the minor rotamer: δ 6.90 (1H, d, J = 7.5 Hz), 6.04 (1H, d, J = 8.0 Hz), 4.82 (1H, d, J = 11.5 Hz), 2.77 (1H, dd, J = 14.0, 9.0 Hz), 1.11 (3H, d, J = 5.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both

rotamers: δ 169.6, 169.5, 151.6, 151.2, 131.4, 131.2, 129.9, 129.8, 128.6, 128.5, 127.7, 127.5, 126.7, 126.6, 125.5, 125.3, 124.5, 123.6, 110.7, 110.6, 95.2, 95.2, 75.7, 75.6, 68.4, 68.4, 53.3, 53.1, 40.8, 40.1, 22.0, 22.0, 21.9, 21.9. IR (neat): 3063 (w), 2980 (m), 2936 (w), 1728 (s), 1651 (s), 1452 (m), 1262 (m), 1109 (m), 968 (w). HRMS (ES): Expected for $[C_{17}H_{18}Cl_3NO_4+H]^+$: 406.0380. Found: 406.0380.

3-Methyl-1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 2):
The product was obtained as a colorless oil (159 mg, 0.38 mmol, 75% yield) after column chromatography on silica gel, (2.5% → 5% ethyl acetate in hexanes). The enantiomeric excess was determined to be 94% by chiral SFC (Pirkle (*R,R*)-Whelk-01, 2% methanol/CO_2, 50 °C2 mL/min, 285 nm. t_r(major): 16.6 min, t_r(minor): 17.8 min.) α_D = –320° (c = 1.1 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.16 (3H, m), 7.09 (1H, d, J = 7.5 Hz), 5.01–4.96 (2H, m), 4.61 (1H, d, J = 11.5 Hz), 6.15 (1H, s), 5.90 (1H, dd, J = 9.0, 6.0 Hz), 2.82 (1H, ddd, J = 14.0, 9.0, 2.0 Hz), 2.49 (1H, dd, J = 14.0, 6.0 Hz), 2.35 (3H, s), 1.24 (3H, dd, J = 6.5, 2.0 Hz), 1.20 (3H, dd, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 151.1, 133.8, 132.7, 130.4, 128.0, 125.3, 124.6, 115.5, 94.9, 75.5, 68.1, 54.3, 38.8, 29.6, 21.8, 21.7. IR (neat): 2980 (m), 2934 (w), 1728 (s), 1642 (m), 1398 (m), 1316 (m), 1260 (m), 1115 (m). LRMS (ESI): 419.8 (98%) $[M+H]^+$, 421.8 (100%) $[M+H]^+$, 423.8 (30%) $[M+H]^+$, 436.8 (100%) $[M+NH_4]^+$, 438.9 (100%) $[M+NH_4]^+$, 440.8 (30%) $[M+NH_4]^+$.

4-Bromo-1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 3):
The product was obtained as a colorless oil (192 mg, 0.40 mmol, 79% yield) after column chromatography on silica gel, (0% → 5% ethyl acetate in hexanes). The enantiomeric excess was determined to be 91% by chiral SFC (Chiralpak OD-H, 5% methanol/CO_2, 4 mL/min, 50 °C, 285 nm. t_r(minor): 3.0 min, t_r(major): 4.6 min.) α_D = –190° (c = 1.1 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.5:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.52 (1H, d, J = 7.5 Hz), 7.35 (1H, dd, J = 8.5, 8.5 Hz), 7.28–7.20 (3H, m) 5.83 (1H, dd, J = 7.5, 7.5 Hz), 4.96–4.92 (1H, m), 4.92 (1H, d, J = 12.5 Hz), 4.76 (1H, d, J = 12.5 Hz), 2.69–2.61 (2H, m), 1.20 (3H, d, J = 6.5 Hz), 1.16 (3H, d, J = 6.5 Hz). Representative signals corresponding to the minor rotamer: δ 4.82 (1H, d, J = 11.5 Hz), 2.78 (1H, dd, J = 15.0, 8.5 Hz), 1.11 (3H, d, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 169.3, 169.2, 150.9, 150.4, 131.6, 131.3, 129.1, 129.0, 128.9, 128.8, 126.5, 126.4, 125.6, 125.5, 125.4, 124.4, 106.0, 105.8, 95.0, 75.8, 75.7, 68.7, 68.6, 53.6, 53.3, 41.0, 40.3, 22.0, 21.0, 21.9. IR (neat): 3010 (w), 2982 (m), 1728 (s), 1624 (m), 1400 (s), 1316 (s), 1130 (s), 762 (m). LRMS (ESI): 483.8 (15%) $[M+H]^+$, 485.8 (30%) $[M+H]^+$, 487.8 (20%) $[M+H]^+$, 500.8 (50%) $[M+NH_4]^+$, 502.8 (100%) $[M+NH_4]^+$, 504.8 (60%) $[M+NH_4]^+$.

5-Bromo-1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 4):
The product was obtained as a colorless oil (187 mg, 0.39 mmol, 77% yield) after column chromatography on silica gel (0% → 5% ethyl acetate in hexanes). The enantiomeric

excess was determined to be 87% by chiral SFC (Chiralpak OD-H, 5% methanol/CO_2, 4 mL/min, 50 °C, 285 nm. t_r(minor): 2.8 min, t_r(major): 3.6 min.) α_D = –250° (c = 1.0 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.48 (1H, d, J = 8.5 Hz), 7.16 (1H, dd, J = 6.5, 6.5 Hz), 7.05 (1H, d, J = 8.5 Hz), 6.99 (1H, d, J = 6.5 Hz), 6.35 (1H, d, J = 8.5 Hz), 5.99 (1H, d, J = 8.0 Hz), 5.80 (1H, dd, J = 6.0, 6.0 Hz), 4.99–4.94 (1H, m), 4.89 (1H, d, J = 12.0 Hz), 4.79 (1H, d, J = 12.0 Hz), 2.65–2.62 (2H, m), 1.20 (3H, d, J = 6.5 Hz), 1.16 (3H, d, J = 6.5 Hz). Representative signals corresponding to the minor rotamer: δ 6.40 (1H, d, J = 8.0 Hz), 4.84 (1H, d, J = 12.0 Hz), 2.78 (1H, dd, J = 14.5, 9.5 Hz), 1.11 (3H, d, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 169.3, 169.3, 151.4, 151.0, 133.1, 133.0, 132.7, 132.6, 129.7, 129.6, 128.6, 128.3, 126.3, 125.9, 125.9, 125.3, 121.0, 120.9, 109.1, 95.1, 75.8, 75.7, 68.6, 53.3, 53.1, 40.5, 39.7, 22.0, 21.9. IR (neat): 3111 (w), 2980 (s), 2874 (m), 1730 (s), 1632 (s), 1557 (m), 1385 (s), 1273 (s), 1119 (s), 932 (m), 767 (s). LRMS (ESI): 483.8 (20%) $[M+H]^+$, 485.8 (40%) $[M+H]^+$, 487.8 (25%) $[M+H]^+$, 500.8 (50%) $[M+NH_4]^+$, 502.8 (100%) $[M+NH_4]^+$, 504.8 (70%) $[M+NH_4]^+$.

5-(*tert*-Butyl-dimethyl-silanyloxy)-1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 5):
The product was obtained as colorless oil (209 mg, 0.39 mmol, 77% yield) after column chromatography on silica gel (1.25 → 2.5% ethyl acetate in hexanes). The enantiomeric excess was determined to be 83% by chiral HPLC (Chiralpak OD-H, 1% isopropanol/hexanes, 0.7 mL/min, 220 nm. t_r(minor): 8.6 min, t_r(major): 10.4 min.) α_D = –130° (c = 1.1 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.05 (1H, d, J =8.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.72 (1H, d, J = 7.5 Hz), 6.29 (1H, d, J = 7.5 Hz), 5.80–5.77 (1H, m), 4.95–4.90 (1H, m), 4.91 (1H, d, J = 12.0 Hz), 4.76 (1H, d, J = 12.0 Hz), 2.65–2.56 (2H, m), 1.20 (3H, d, J = 6.5 Hz), 1.16 (3H, d, J = 6.5 Hz), 1.03 (9H, s), 0.24 (3H, s), 0.22 (3H, s). Representative signals corresponding to the minor rotamer: δ 7.03 (1H, d, J = 8.0 Hz), 6.72 (1H, d, J = 8.0 Hz), 6.35 (1H, d, J = 8.0 Hz), 4.94 (1H, d, J = 11.5 Hz), 2.73 (1H, dd, J = 14.0, 9.5 Hz), 1.20 (3H, d, J = 6.5 Hz), 1.11 (3H, d, J = 6.5 Hz), 1.03 (9H, s), 0.24 (3H, s), 0.20 (3H, s) ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 169.3, 169.1, 151.3, 150.9, 150.3, 150.2, 132.7, 132.6, 127.9, 127.7, 123.2, 122.3, 121.2, 121.1, 119.3, 119.2, 118.6, 118.3, 105.6, 105.4, 95.0, 94.9, 75.4, 75.2, 68.0, 68.0, 52.9, 52.7, 40.3, 39.6, 25.7, 21.7, 21.6, 21.6, 18.2, –4.3, –4.3, –4.4, –4.4. IR (neat): 2980 (m), 2957 (m), 2932 (m), 2859 (m), 1728 (s), 1632 (w), 1574 (m), 1468 (s), 1385 (s), 1271 (s), 1125 (s). LRMS (ESI): 535.8 (90%) $[M+H]^+$, 537.8 (85%) $[M+H]^+$, 539.8 (30%) $[M+H]^+$, 552.9 (90%) $[M+NH_4]^+$, 554.9 (100%) $[M+NH_4]^+$, 555.9 (30%) $[M+NH_4]^+$.

5-Nitro-1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 6):
The product was obtained as yellow solid (161 mg, 0.36 mmol, 71% yield) after column chromatography on silica gel (0% →5% ethyl acetate in hexanes). The enantiomeric excess was determined to be 71% by chiral SFC (Chiralpak OD, 5% methanol/CO_2, 4 mL/min, 50 °C, 285 nm. t_r(minor): 2.98 min, t_r(major): 3.54 min.) α_D = –100° (c = 1.1

g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.8:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.94 (1H, d, J = 7.5 Hz), 7.51 (1H, d, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 7.14 (1H, d, J = 8.5 Hz), 6.76 (1H, d, J = 8.5 Hz), 5.92–5.89 (1H, m), 4.96–4.90 (1H, m), 4.92 (1H, d, J = 12.0 Hz), 4.80 (1H, d, J = 12.0 Hz), 2.73–2.63 (2H, m), 1.20 (3H, d, J = 6.5 Hz), 1.15 (3H, d, J = 6.5 Hz). Representative signals corresponding to the minor rotamer: δ 7.30 (1H, t, J = 7.5 Hz), 7.15 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 8.5 Hz), 5.02 (1H, d, J = 12.0 Hz), 4.82 (1H, d, J = 12.0 Hz), 2.87 (1H, dd, J = 15.0, 10.0 Hz), 1.11 (3H, d, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 168.7, 168.6, 150.7, 150.4, 144.7, 144.6, 133.2, 133.0, 131.7, 128.8, 127.8, 127.1, 126.9, 124.9, 124.8, 124.6, 104.2, 104.1, 94.6, 75.6, 68.5, 52.8, 52.5, 39.8, 39.1, 29.6, 21.6, 21.6. IR (CH_2Cl_2 film): 2982 (m), 2938 (w), 1728 (s), 1626 (m), 1528 (s), 1385 (s), 1273 (s), 1126 (s). LRMS (ESI): 450.8 (30%) $[M+H]^+$, 452.8 (30%) $[M+H]^+$, 454.8 (10%) $[M+H]^+$, 467.8 (90%) $[M+NH_4]^+$, 469.8 (100%) $[M+NH_4]^+$, 471.8 (30%) $[M+NH_4]^+$.

1-Isopropoxycarbonylmethyl-6-trifluoromethanesulfonyloxy-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 7):
The reaction was carried out on 0.25 mmol scale, and the product obtained as a colorless oil (93 mg, 0.168 mmol, 67% yield) after column chromatography on silica (5% ethyl acetate in hexanes). The enantiomeric excess was determined to be 83% by chiral SFC (Pirkle (S,S)-Whelk-01, 1% methanol/CO_2, 4 mL/min, 50 °C, 295 nm, t_r(minor): 7.1 min, t_r(major): 8.7 min.) α_D = –150° (c = 1.9 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.6:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.31 (1H, d, J = 8.5 Hz), 7.10–7.07 (1H, m), 7.02–7.01 (2H, m), 5.96 (1H, d, J = 8.0 Hz), 5.86 (1H, dd, J = 6.0, 6.0 Hz), 4.95–4.90 (1H, m), 4.91 (1H, d, J = 11.5 Hz), 4.70 (1H, d, J = 11.5 Hz), 2.68–2.59 (2H, m), 1.19 (3H, d, J = 6.5 Hz), 1.14 (3H, d, J = 6.5 Hz). Representative signals corresponding to the minor rotamer: δ 7.06–7.03 (1H, m), 6.01 (1H, d, J = 8.0 Hz), 5.00 (1H, d, J = 11.5 Hz), 4.80 (1H, d, J = 11.5 Hz), 2.80 (1H, dd, J = 14.5, 9.5 Hz), 0.97 (3H, d, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 169.2, 169.2, 151.4, 150.9, 149.6, 149.5, 132.6, 132.4, 131.1, 131.0, 128.7, 128.7, 126.8, 125.8, 119.9, 119.7, 118.9 (q, J_{C-F} = 320 Hz), 118.9 (q, J_{C-F} = 320 Hz), 117.8, 117.7, 108.9, 108.8, 95.0, 95.0, 75.9, 75.7, 68.7, 68.7, 52.7 52.5, 40.5, 39.7, 25.9, 25.9, 21.9, 21.8. IR (neat): 2984 (m), 2941 (w), 1730 (s), 1638 (m), 1410 (s), 1252 (s), 1130 (s), 918 (m). LRMS (ESI): 553.8 (65%) $[M+H]^+$, 555.8 (60%) $[M+H]^+$, 557.8 (20%) $[M+H]^+$, 569.8 (60%) $[M+NH_4]^+$, 571.8 (50%) $[M+NH_4]^+$, 573.8 (20%) $[M+NH_4]^+$.

7-(*tert*-Butyl-dimethyl-silanyloxy)-1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (Table 3, entry 8):
The product was obtained as pale yellow oil (232 mg, 0.43 mmol, 86% yield) after column chromatography on silica gel (0% →2.5% ethyl acetate in hexanes). The enantiomeric excess was determined to be 60% by chiral HPLC (Chiralpak OD-H, 1% isopropanol/hexanes, 0.7 mL/min, 220 nm. t_r(major): 7.7 min, t_r(minor): 8.2 min.) α_D = –100° (c = 1.1 g/100 mL, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 6.98–6.97 (1H, m), 6.87 (1H, d, J = 7.5 Hz), 6.72–6.71 (2H, m), 5.94 (1H, d, J = 7.5 Hz), 5.78–

5.73 (1H, m), 4.98–4.93 (1H, m), 4.89 (1H, d, J = 12.5 Hz), 4.76 (1H, d, J = 12.5 Hz), 2.65–2.56 (2H, m), 1.21 (3H, d, J = 6.5 Hz), 1.19 (3H, d, J = 6.5 Hz), 0.97 (9H, s), 0.19 (6H, s). Representative signals corresponding to the minor rotamer: δ 6.78 (1H, d, J = 8.0 Hz), 5.99 (1H, d, J = 8.0 Hz), 4.98 (1H, d, J = 12.0 Hz), 4.79 (1H, d, J = 12.0 Hz), 2.75 (1H, dd, J = 14.5, 9.0 Hz), 1.14 (3H, d, J = 6.5 Hz), 0.97 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 169.2, 169.1, 155.1, 154.9, 151.2, 150.9, 132.7, 132.5, 126.3, 126.3, 123.0, 122.2, 121.2, 119.6, 119.5, 118.3, 118.1, 110.1, 95.0, 75.3, 75.2, 68.0, 68.0, 52.8, 52.7, 40.7, 39.8, 25.5, 21.7, 21.6, 21.6, 18.0, 18.0, –4.5, –4.6. IR (neat): 2957 (m), 2932 (m), 2888 (w), 2859 (m), 1728 (s), 1638 (w), 1501 (m), 1265 (s), 1126 (s), 841 (s). LRMS (CI): 535.9 (40%) $[M+H]^+$, 537.9 (40%) $[M+H]^+$, 539.8 (15%) $[M+H]^+$, 552.9 (40%) $[M+NH_4]^+$, 554.9 (40%) $[M+NH_4]^+$, 555.9 (150%) $[M+NH_4]^+$.

(F) Survey of Solvents for Acyl-Mannich Reactions Catalyzed by 1.

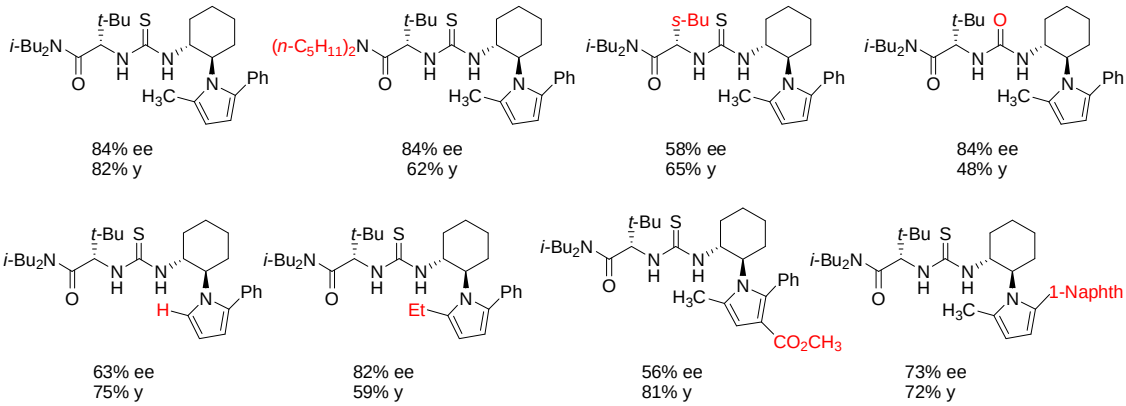
Solvent survey was carried out according to general procedure D, with the following modifications:
1. The reaction temperature was –65 °C.
2. 1.0 equivalent of trichloroethyl chloroformate was used.
3. Reactions were quenched by addition of sodium methoxide (0.5 M in methanol, 1.0 equiv.) after 14 hours.
4. Quenched reaction mixtures were diluted to homogeneity with dichloromethane and analyzed by GC, then passed through a short silica plug (10% ethyl acetate in hexanes), concentrated, and analyzed by SFC.

solvent	**% yield**[1]	**% ee**
dichloromethane	66	2
toluene	81	74
t-butyl methyl ether	42	89
diethyl ether	57	87

[1] Yield by GC assay, using dodecane as a quantitative internal standard.

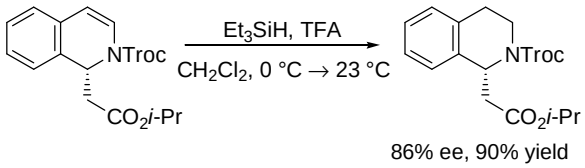
(G) Survey of Catalysts for the Enantioselective Acyl-Mannich Reaction:

Catalyst survey was carried out according to general procedure D, with the following modifications:
1. The reaction temperature was –65 °C.
2. 1.5 equivalents of trichloroethyl chloroformate were used.
3. Reactions were quenched by addition of sodium methoxide (0.5 M in methanol, 1.0 equiv.) after 14 hours.
4. Quenched reaction mixtures were diluted to homogeneity with dichloromethane and analyzed by GC, then passed through a short silica plug (10% ethyl acetate in hexanes), concentrated, and analyzed by SFC.



(H) Preparation of racemic samples for HPLC analysis.
To a solution of isoquinoline (0.1 mmol) in dichloromethane (1.0 mL) at –78 °C were added, sequentially, acylating agent (0.1 mmol, 1.0 equiv.) and silyl ketene acetal (0.15 mmol, 1.5 equiv.). The resulting solution was stirred at –78 °C for 5 minutes, then warmed to 23 °C and stirred for 14 hours. Solvent was removed *in vacuo* and the residue was purified by chromatography on silica (ethyl acetate/hexanes).

(I) Ionic hydrogenantion of enamide:
1-Isopropoxycarbonylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester.

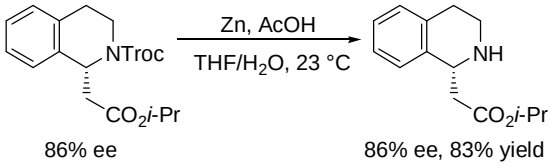


86% ee, 90% yield

Triethylsilane (1.0 mL, excess) and trifluoroacetic acid (0.50 mL, excess) were added sequentially to a solution of 1-isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (97 mg, 0.238 mmol, 86% ee) in dichloromethane (5.0 mL) at 0 °C. The solution was allowed to warm to 23 °C and stirred for 18 hours. Volatiles were removed in vacuo and the residue purified by chromatography on silica (10% ethyl acetate in hexanes), yielding the title compound as a colorless oil (88 mg, 0.215 mmol, 90% yield). The enantiomeric excess was determined to be 86% by chiral SFC (Chiralpak AS, 2% methanol/CO_2, 2 mL/min, 50 °C, 220 nm, t_r(major) 8.09 min, t_r(minor) 8.98 min). α_D = –45° (c = 0.7 g/100 mL, ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$): the compound exists as a 1.4:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: δ 7.24–7.17 (4H, m), 5.73–5.69 (1H, m), 5.05–5.01 (1H, m), 4.87 (1H, d, J = 12.0 Hz), 4.74 (1H, d, J = 12.0 Hz), 4.19 (ddd, J = 13.2, 4.8, 4.8 Hz), 3.60–3.53 (1H, m), 3.05–2.97 (1H, m), 2.91 (2H, m), 2.79 (1H, m), 1.26–1.24 (6H, m). Representative signals corresponding to the minor rotamer: δ 4.84 (2H, s), 4.08 (1H, ddd, J = 13.2, 5.4, 5.4 Hz), 2.95 (1H, dd, J = 15.0, 6.6 Hz), 1.22 (3H, d, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ 189.9, 170.0, 153.7, 136.0, 135.9, 134.2, 134.0, 129.2, 127.6, 127.5, 127.3, 127.1, 126.8, 75.4, 75.4, 68.5, 68.5, 52.7, 52.6, 43.0, 42.2, 39.7, 39.1, 28.7, 28.3, 22.0, 21.9. IR (neat): 2982 (m), 1723

(s), 1427 (m), 1244 (m), 1125 (m), 1047 (m), 972 (w). LRMS (CI): 407.8 (90%) $[M+H]^+$, 409.8 (100%) $[M+H]^+$, 411.8 (35%) $[M+H]^+$.

(J) Reductive cleavage of trichloroethyl carbamate.
(1,2,3,4-Tetrahydro-isoquinolin-1-yl)-acetic acid isopropyl ester:



86% ee 86% ee, 83% yield

Acetic acid (49 μL, 0.863 mmol, 5.2 equiv., then zinc dust (54 mg, 0.830 mmol, 5.0 equiv.) were added to a solution of 1-isopropoxycarbonylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloro-ethyl ester (68 mg, 0.166 mmol) in 1:1 THF/H_2O (1.2 mL) at 23 °C. The mixture was stirred at 23 °C for 6 hours, then diluted with water. Saturated aqueous sodium carbonate was added, and the mixture extracted three times with dichloromethane (total volume 50 mL), then three times with ethyl acetate (total volume 35 mL). The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica (5% methanol in dichloromethane), yielding the title compound as a colorless oil (32 mg, 0.137 mmol, 83% yield). The enantiomeric excess was determined to be 86% by chiral SFC (Chiralpak OD-H, 2% (0.2% triethylamine/methanol)/CO_2, 4 mL/min, 50 °C, 208 nm t_r(minor) 4.65 min, t_r(major) 5.19 min). α_D = +73° (c = 1.6 g/100 mL, ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.09 (4H, m), 5.06 (1H, septet, J = 6.5 Hz), 4.45 (1H, dd, J = 9.5, 3.5 Hz), 3.21 (1H, ddd, J = 12.5, 5.5, 5.0 Hz), 3.04–2.99 (1H, m), 2.89–2.82 (2H, m), 2.78–2.75 (1H, m), 2.72 (1H, dd, J = 15.5, 9.5 Hz), 2.37 (1H, br s), 1.24 (6H, t, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 137.9, 135.7, 129.7, 126.5, 126.1, 126.1, 68.2, 53.0, 41.8, 41.0, 30.1, 22.1, 22.1. IR (neat): 3351 (w), 2980 (m), 2930 (m), 2834 (m), 1726 (s), 1454 (m), 1373 (m), 1178 (m), 1109 (s). LRMS (CI): 234.0 (100%) $[M+H]^+$.

(K) Determination of absolute configuration.
(1,2,3,4-Tetrahydro-isoquinolin-1-yl)-acetic acid isopropyl ester (86% ee) was converted to (1,2,3,4-tetrahydro-isoquinolin-1-yl)-acetic acid methyl ester (3.0 equiv. NaOMe, MeOH, 23 °C). Characterization data were in agreement with literature values. α_D = +79° (c = 0.36 g/100 mL, $CHCl_3$). Literature α_D for (*R*)-(1,2,3,4-tetrahydro-isoquinolin-1-yl)-acetic acid methyl ester: +95° (95% ee, c = 1.0 g/100 mL, $CHCl_3$).[4]

[4] Y. Takeuchi, Y. Kamada, K. Nishimura, H. Nishioka, M. Nishikawa, *Chem. Pharm. Bull*. **1994**, *42*, 796–801.