**Asymmetric Catalytic Mannich Reactions Catalyzed by Thiourea
Derivatives: Enantioselective Synthesis of β -Aryl- β -Amino Acids**

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Supporting Information

General Information. All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried, round bottom flasks fitted with rubber septa and/or glass stoppers. For Mannich reactions run at low temperatures, flasks were flushed with nitrogen, and the septa wrapped with Teflon® tape and parafilm to minimize the introduction of adventitious water. Stainless steel syringes or cannulae were used to transfer air or moisture-sensitive liquids.

Materials. Unless otherwise indicated, all compounds were purchased from Aldrich and/or Alfa Aesar. Commercial reagents were used as received with the following exceptions: toluene was distilled from sodium, tetrahydrofuran distilled from sodium/benzophenone ketyl, dichloromethane distilled from calcium hydride (CaH_2), triethylamine distilled from CaH_2 , and diisopropylethylamine (DIPEA) distilled from CaH_2 at 760 Torr. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations, see: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879). Racemic Mannich adduct samples for chiral HPLC analysis were prepared by combining imines and silyl ketene acetals at 23 °C in the absence of catalyst (for reaction conditions, refer to Sections II and V below). Flash chromatography was performed using silica gel 60 (230-400 mesh), purchased from EM Science.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker-300 (300 MHz), Varian Mercury-400 (400 MHz), Inova-500 (500 MHz), or an Inova-600 (600 MHz) NMR spectrometer at 20 °C. 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 7.26). 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; DMSO: δ 39.5). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants in Hertz (Hz), and assignment. 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), and assignment where appropriate. Mass spectroscopic data were obtained at the Harvard University

Mass Spectrometry Facility. Optical rotations were measured on a Jasco DIP 370 digital polarimeter (λ 589) using a 2-mL cell with a 1-dm path length. Chiral HPLC analysis was performed using a Hewlett-Packard 1050 HPLC. A Cryobath CB-80 constant temperature bath was used for low temperature Mannich reactions.

General Experimental Procedures:

I. Preparation of Solution Phase Catalyst.

6a. *Coupling of Boc-(L)-tert-leucine with Benzylamine, Followed by Deprotection.* A 200-mL flask was charged with Boc-(*L*)-tert-leucine (1.05 g, 4.53 mmol, 1.00 equiv) and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU, 1.72 g, 4.54 mmol, 1.00 equiv). Anhydrous dichloromethane (35 mL) was then added. After two minutes, anhydrous DIPEA (1.2 mL, 9.1 mmol, 2.0 equiv) and benzylamine (500 μL , 4.57 mmol, 1.00 equiv) were sequentially added. The reaction was allowed to stir 2 h, during which time the reaction mixture was observed to change from slightly heterogeneous to homogeneous—corresponding to consumption of HBTU. The reaction was then partitioned between dichloromethane (50 mL) and aqueous hydrochloric acid solution (1N, 30 mL). The organic layer was washed with 1N HCl (3 $\times$ 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting colorless oil was transferred to a 200-mL flask and redissolved in dichloromethane (25 mL). Trifluoroacetic acid (5.2 mL, 68 mmol, 15 equiv) was then added in one portion. After 1 h,

the reaction was slowly partitioned between dichloromethane (30 mL) and chilled, saturated aqueous sodium carbonate solution (5 °C, ~30 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a white solid (99% crude yield, 98% pure via ¹H NMR analysis), which was taken on without further purification to form the isothiocyanate.

Isothiocyanate¹ and Thiourea Formation. Crude, benzylamine-coupled *tert*-leucine was dissolved in a mixture of dichloromethane and saturated aqueous sodium bicarbonate solution (1:1, 90 mL). The flask was immersed in an ice bath and cooled to 5 °C with stirring. Once at 5 °C: stirring was stopped, and the layers allowed to separate. Thiophosgene (380 μL, 4.99 mmol, 1.10 equiv) was then added to the dichloromethane layer in one portion via syringe. Rapid stirring was subsequently commenced (~500 rpm), and the reaction was maintained at 5 °C for 20 min. The reaction mixture was then partitioned, and the aqueous layer extracted with dichloromethane (3 × 45 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give the isothiocyanate as a white solid in quantitative yield. Crude isothiocyanate was transferred to a 200-mL flask and dissolved in anhydrous dichloromethane (45 mL). (*R,R*)-1,2-diaminocyclohexane (628 mg, 5.50 mmol, 1.20 equiv) was then rapidly added in one portion at 23 °C with stirring. Reaction progress was monitored via IR, observing the disappearance of the isothiocyanate stretch at 2073 cm⁻¹. Quantitative conversion was observed after 20 min. The reaction was concentrated *in vacuo*. Crude ¹H NMR of the resulting solid revealed a 9:1 mixture of **6a** and a thiohydantoin byproduct. The product was purified via flash chromatography on silica gel (3 × 15 cm silica, 4% methanol in NH₃-saturated dichloromethane, R_f = 0.29, ninhydrin TLC visualization) to give **6a** as a white solid (1.3 g, 76% yield over 4 steps). mp 100-102 °C; IR (thin film, cm⁻¹) 3065 (m), 2934 (s), 2861 (m), 1649 (s, C=O), 1537 (s, C=S); ¹H NMR (500 MHz, CDCl₃, 20 °C) δ 7.36-7.27 (5H, m, ArH), 6.31 (1H, s, NH), 5.98 (1H, s, NH), 4.79 (1H, d, *J* = 6.8 Hz, CH(*t*Bu)), 4.53 (1H, dd, *J* = 6.1, 14.9 Hz, PhCH₂), 4.35 (1H, dd, *J* = 4.9, 14.6 Hz, PhCH₂), 2.53 (1H, m, CH(NH₂)), 2.00 (1H, d, *J* = 11.7 Hz, CHN thiourea), 1.85 (2H, m, CH₂ cycl), 1.80-1.64 (4H, m, CH₂ cycl + NH₂), 1.34-1.16 (m, 4H, CH₂ cycl), 1.08 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 183.0, 171.3, 137.8, 128.5, 127.7, 127.3, 66.6, 61.2, 55.3, 43.5, 34.7, 34.6, 32.1, 27.0, 26.84, 24.7; MS (ES) *m/z*: 377.0 [M]⁺.

6b. Compound **6b** was prepared on a 10.8-mmol scale utilizing the same procedure for the preparation of **6a**. The product was purified via flash chromatography on silica gel (4 × 16 cm silica, 10:1:0.1 dichloromethane/methanol/triethylamine, R_f = 0.37, ninhydrin TLC visualization) to give **6b** as a white solid (3.4 g, 86% yield over four steps). mp 92-94 °C; IR (thin film, cm⁻¹) 2932 (m), 2858 (w), 1624 (s, C=O), 1537 (s, C=S); ¹H NMR (500 MHz, CDCl₃, 20 °C; compound exists as a ~4.3:1 mixture of rotamers: the major rotamer is denoted by *) 7.42-7.20 (10H, m, ArH, ArH*), 5.75 (1H, d, *J* = 9.0 Hz, CH(*t*Bu)), 5.50 (1H, d, *J* = 7.5 Hz, CH(*t*Bu)*), 5.05 (1H, d, *J* = 15.5 Hz, PhCH₂), 4.98 (1H, d, *J* = 14.5 Hz, PhCH₂*), 4.64 (1H, d, *J* = 15.5 Hz, PhCH₂), 4.28 (1H, d, *J* = 14.5 Hz, PhCH₂*), 3.22 (3H, s, NCH₃*), 2.87 (3H, s, NCH₃), 2.57 (2H, m, CH(NH₂), CH(NH₂)*), 2.38 (4H, s, NH₂, NH₂*), 2.05 (2H, d, *J* = 12.0 Hz, CHN, CHN*).

¹ Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T.M.; Huang, S. *J. Am. Chem. Soc.* **1996**, *61*, 3929-3934.

thiourea), 1.88 (2H, d, $J = 10.0$ Hz, $\text{CH}_2(\text{CHNH}_2)$, $\text{CH}_2(\text{CHNH}_2)^*$), 1.71 (6H, m, $\text{CH}_2(\text{CHNH}_2)$, $\text{CH}_2(\text{CHNH}_2)^*$, $\text{CH}_2(\text{CHN})$, $\text{CH}_2(\text{CHN})^*$), 1.33-1.19 (8H, m, CH_2 , CH_2^* cycl) 1.09 (9H, s, $\text{C}(\text{CH}_3)_3^*$), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, 20 °C; compound exists as a mixture of rotamers) δ 182.9, 171.6, 171.4, 137.5, 137.1, 128.9, 128.4, 128.2, 128.1, 127.9, 127.7, 127.5, 127.1, 125.3, 59.4, 58.7, 54.2, 53.2, 50.2, 36.1, 35.8, 35.5, 34.3, 33.0, 31.4, 26.6, 26.5, 24.4, 24.3; MS (AP) m/z : 391.1 $[\text{M}]^+$.

1b. To a 100-mL flask: **6a** (940 mg, 2.5 mmol, 1.0 equiv) and 3-*tert*-butyl-5-pivaloyl-salicylaldehyde² (690 mg, 2.48 mmol, 0.99 equiv) were dissolved in anhydrous methanol (25 mL). The reaction mixture immediately turned bright yellow. After stirring 2 h at ambient temperature, volatiles were removed *in vacuo* to give **1b** (1.57 g; 99%). mp 144-146 °C; IR (thin film, cm^{-1}) 2961 (m), 2872 (m), 1751 (m, C=O), 1657 (s, C=N, C=O), 1535 (s, C=S); ^1H NMR (600 MHz, CDCl_3 , 20 °C) δ 13.65 (1H, s, ArOH), 8.19 (1H, s, $\text{CH}=\text{N}$), 7.28-7.14 (4H, ArH), 6.92 (1H, br, NH), 6.88 (2H, s, ArH), 6.66 (1H, br, NH), 4.85 (1H, br, $\text{CH}(t\text{Bu})$), 4.38 (1H, br d, $J = 9.9$ Hz, PhCH_2), 4.12 (1H, br, PhCH_2), 3.15 (1H, br, $\text{CH}(\text{N}=\text{C})$), 2.03 (1H, br, CHN thiourea), 1.80-1.52 (4H, m, CH_2 cycl), 1.48-1.20 (4H, m, CH_2 cycl), 1.35 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.32 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.91 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 177.8, 171.1, 165.0, 158.0, 141.8, 138.5, 137.6, 128.6, 127.5, 127.3, 122.7, 121.5, 118.2, 70.1, 66.1, 56.6, 43.4, 38.9, 34.8, 32.4, 30.0, 29.1, 28.9, 27.1, 27.0, 26.8, 23.6, 23.0; MS (ES) m/z : 637.0 $[\text{M}]^+$.

1c. Compound **1c** was prepared on a 2.56-mmol scale utilizing the same procedure for the preparation of **1b**. **1c** was obtained as a bright yellow solid (1.50 g; 99% yield). mp 124-125 °C; IR (thin film, cm^{-1}) 2957 (s), 2864 (w), 1630 (s, C=O, C=N), 1534 (s, C=S); ^1H NMR (600 MHz, CDCl_3 , 20 °C; compound exists as a ~4:1 mixture of rotamers: the major rotamer is denoted by *) δ 13.25 (2H, s, ArOH, ArOH*), 8.35 (1H, s, $\text{CH}=\text{N}^*$), 8.33 (1H, s, $\text{CH}=\text{N}$), 7.35-7.18 (10H, m, ArH, ArH*), 7.06 (1H, d, $J = 2.2$ Hz, ArH*), 7.05 (1H, d, $J = 2.6$ Hz, ArH), 6.41 (2H, br, NH, NH*), 6.08 (2H, br, NH, NH*), 5.70 (1H, br, $\text{CH}(t\text{Bu})$), 5.58 (1H, d, $J = 9.2$ Hz, $\text{CH}(t\text{Bu})^*$), 4.91 (1H, d, $J = 15.4$ Hz, PhCH_2), 4.86 (1H, d, $J = 14.6$ Hz, PhCH_2^*), 4.46 (1H, d, $J = 15.4$ Hz, PhCH_2), 4.18 (1H, d, $J = 14.3$ Hz, PhCH_2^*), 3.78 (2H, br, CHN , CHN^*), 3.09 (3H, s, CH_3^*), 2.78 (3H, s, CH_3), 2.14 (2H, m, CHN , CHN^*), 1.9-1.58 (8H, m, CH_2 , CH_2^* cycl), 1.50-1.27 (8H, m, CH_2 , CH_2^* cycl), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3^*$), 1.38 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.26 (9H, s, $\text{C}(\text{CH}_3)_3^*$), 1.25 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.89 (9H, s, $\text{C}(\text{CH}_3)_3^*$), 0.85 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, 20 °C; compound exists as a mixture of rotamers) δ 182.5, 171.4, 166.1, 157.5, 139.4, 137.4, 135.5, 128.3, 127.5, 127.0, 126.3, 126.1, 117.7, 69.6, 58.3, 56.3, 52.9, 50.0, 36.1, 35.7, 34.5, 33.8, 33.1, 31.3, 29.3, 26.5, 26.4, 23.5, 23.3; MS (AP) m/z : 607.2 $[\text{M}]^+$.

II. Enantioselective Mannich Reaction.

² Vachal, P.; Jacobsen, E.N. *Org. Lett.* **2000**, *2*, 867-870.

(R)-3-tert-butoxycarbonylamino-3-phenylpropionic acid isopropyl ester (5a). A 5-mL flask was charged sequentially with **1c** (15 mg, 0.025 mmol, 0.050 equiv) and anhydrous toluene (250 μ L). Benzaldehyde *N*-Boc imine **3a** (100 mg, 0.50 mmol, 1.0 equiv) was then added in one portion with stirring. Once the solution was homogeneous, the flask was immersed in a dry ice/acetone bath and cooled to -40 $^{\circ}$ C. Silyl ketene acetal **4c** (216 mg, 1.00 mmol, 2.00 equiv) was then slowly added along the flask wall over a ten-minute period. The flask was sealed under an atmosphere of nitrogen and stirred at -40 $^{\circ}$ C. After 48 h, excess silyl ketene acetal was quenched at -40 $^{\circ}$ C via the rapid addition of a 3M solution of trifluoroacetic acid in toluene (500 μ L; cooled to -20 $^{\circ}$ C prior to addition). The reaction was allowed to warm to ~ 5 $^{\circ}$ C, then partitioned between saturated aqueous sodium carbonate solution and dichloromethane (1:1, 2 mL). The aqueous layer was extracted with dichloromethane (3×2 mL), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified via flash chromatography on silica gel (2×11 cm silica, 2.5-10% ethyl acetate in hexanes, $R_f = 0.27$ (15% ethyl acetate in hexanes), KMnO₄ TLC visualization) to yield **5a** as a white, crystalline solid (146 mg, 95%) in 97% ee. Chiral HPLC (*R,R*-Whelk-01, 5% IPA in hexanes, 1.5 mL/min, $\lambda = 206$ nm) t_R (minor) = 6.8 min, t_R (major) = 12.5 min; $[\alpha]_D^{26} = +26.7^{\circ}$ ($c = 1.4$, CHCl₃); mp 52-53 $^{\circ}$ C; IR (thin film, cm⁻¹) 2980 (m), 2934 (w), 1717 (s, C=O), 1499 (m), 1171 (s, C-O); ¹H NMR (500 MHz, CDCl₃, 20 $^{\circ}$ C) δ 7.34-7.23 (5H, m, ArH), 5.47 (1H, br, NH), 5.10 (1H, br, CH), 4.93 (1H, sep, $J = 6.4$ Hz, CH(CH₃)₂), 2.84 (1H, br, CH₂), 2.76 (1H, dd, $J = 5.9, 15.1$ Hz, CH₂), 1.42 (9H, s, C(CH₃)₃), 1.15 (3H, d, $J = 6.3$ Hz, CH₃), 1.10 (3H, d, $J = 5.9$ Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃, 20 $^{\circ}$ C) δ 170.4, 154.9, 141.1, 128.5, 127.4, 126.1, 79.5, 68.1, 51.2, 41.2, 28.3, 21.6, 21.5; MS (AP) m/z : 308.1 [M]⁺.

Large Scale Experimental (10 mmol): A 50-mL flask was charged sequentially with **1c** (300 mg, 0.5 mmol, 0.05 equiv) and anhydrous toluene (5 mL). **3a** (2.0 g, 10 mmol, 1.0 equiv) was then added in one portion with stirring. Once the solution was homogeneous, the flask was immersed in a dry ice/acetone bath and cooled to -40 $^{\circ}$ C. Silyl ketene acetal **4c** (4.3 g, 20 mmol, 2.0 equiv) was then slowly added along the flask wall over a ten-minute period. The flask was placed under an atmosphere of nitrogen and stirred at -40 $^{\circ}$ C. After 48h, excess silyl ketene acetal was quenched at -40 $^{\circ}$ C via the rapid addition of a 3M solution of trifluoroacetic acid in toluene (10 mL; cooled to -20 $^{\circ}$ C prior to addition). The reaction was allowed to warm to ~ 5 $^{\circ}$ C, then partitioned between saturated aqueous sodium carbonate solution and dichloromethane (1:1, 40 mL). The aqueous layer was extracted with dichloromethane (3×20 mL), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified via flash chromatography on silica gel (5×16 cm silica, 2.5-15% ethyl acetate in hexanes, $R_f = 0.27$ (15% ethyl acetate in hexanes), KMnO₄ TLC visualization) to yield **5a** as a white, crystalline solid (2.9 g, 95%) in 97% ee.

(R)-3-tert-butoxycarbonylamino-3-(2-methylphenyl)propionic acid isopropyl ester (5b).

Reaction performed on a 0.5-mmol scale at -30 $^{\circ}$ C, using anhydrous toluene (250 μ L) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2×11.5 cm silica, 2.5-10% ethyl acetate in hexanes, $R_f = 0.30$ (15% ethyl acetate in hexanes), KMnO₄ TLC visualization) to yield **5b** as a white, crystalline solid (141 mg, 88%) in

91% ee. Chiral HPLC (*R,R*-Whelk-01, 5% IPA in hexanes, 1.5 mL/min, $\lambda = 206$ nm) $t_R(\text{minor}) = 6.0$ min, $t_R(\text{major}) = 7.2$ min; $[\alpha]_D^{26} = +34.9^\circ$ ($c = 1.4$, CHCl_3); mp 57-58 °C; IR (thin film, cm^{-1}) 2980 (m), 2932 (w), 1715 (s, C=O), 1495 (m), 1169 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.27-7.22 (1H, m, ArH), 7.19-7.13 (3H, m, ArH), 5.31 (2H, br, NH, CH), 4.91 (1H, sep, $J = 6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.80-2.70 (2H, br, CH_2), 2.42 (3H, s, Ar CH_3), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.15 (3H, d, $J = 6.0$ Hz, CH_3), 1.07 (3H, d, $J = 5.2$ Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.3, 154.8, 139.3, 135.5, 130.6, 127.4, 126.2, 124.9, 79.5, 68.1, 47.8, 40.5, 28.3, 21.6, 21.5, 19.1; MS (AP) m/z : 322.1 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(3-methylphenyl)propionic acid isopropyl ester (5c**).**

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (250 μL) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2×12 cm silica, 2.5-10% ethyl acetate in hexanes, $R_f = 0.32$ (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5c** as a pale, yellow oil (157 mg, 98%) in 94% ee.

Chiral HPLC (*R,R*-Whelk-01, 15% IPA in hexanes, 1.5 mL/min, $\lambda = 206$ nm) $t_R(\text{minor}) = 4.1$ min, $t_R(\text{major}) = 7.2$ min; $[\alpha]_D^{26} = +20.9^\circ$ ($c = 1.4$, CHCl_3); IR (thin film, cm^{-1}) 2980 (m), 2934 (w), 1715 (s, C=O), 1503 (m), 1171 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.22 (1H, t, $J = 7.7$ Hz, ArH), 7.09 (s, 1H, ArH), 7.08-7.03 (2H, m, ArH), 5.44 (1H, br, NH), 5.05 (1H, br, CH), 4.93 (1H, sep, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.81 (1H, dd, $J = 6.2, 14.8$ Hz, CH_2), 2.73 (1H, dd, $J = 6.2, 15.0$ Hz, CH_2), 2.32 (3H, s, CH_3), 1.42 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.15 (3H, d, $J = 6.2$ Hz, CH_3), 1.11 (3H, d, $J = 6.2$ Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.4, 154.9, 141.1, 138.1, 128.4, 128.1, 126.9, 123.1, 79.5, 68.0, 51.3, 41.4, 28.3, 21.6, 21.4; MS (AP) m/z : 321.9 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(4-methylphenyl)propionic acid isopropyl ester (5d**).**

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (250 μL) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2×12 cm silica, 2.5-10% ethyl acetate in hexanes, $R_f = 0.40$ (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5d** as a white solid (139 mg, 87%) in 96% ee.

Chiral HPLC (*R,R*-Whelk-01, 7% IPA in hexanes, 1.5 mL/min, $\lambda = 212$ nm) $t_R(\text{minor}) = 5.8$ min, $t_R(\text{major}) = 11.5$ min; $[\alpha]_D^{26} = +28.8^\circ$ ($c = 1.4$, CHCl_3); mp 79-80 °C; IR (thin film, cm^{-1}) 2980 (m), 2934 (w), 1719 (s, C=O), 1514 (m), 1171 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.18 (2H, d, $J = 8.1$ Hz, ArH), 7.11 (2H, d, $J = 8.1$, ArH), 5.43 (1H, br, NH), 5.06 (1H, br, CH), 4.92 (1H, sep, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.81 (1H, dd, $J = 6.2, 14.3$ Hz, CH_2), 2.73 (1H, dd, $J = 6.2, 14.6$ Hz, CH_2), 2.31 (3H, s, CH_3), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.15 (3H, d, $J = 6.3$ Hz, CH_3), 1.11 (3H, d, $J = 6.2$, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.4, 154.9, 138.2, 136.9, 129.1, 126.0, 79.4, 68.0, 51.0, 41.3, 28.3, 21.6, 21.0; MS (AP) m/z : 322.0 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(4-methoxyphenyl)propionic acid isopropyl ester (5e).

Reaction performed on a 0.5-mmol scale at 4 °C, using anhydrous toluene (250 μ L) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2 $\times$ 11.5 cm silica, 2.5-10% ethyl acetate in hexanes, R_f = 0.15 (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5e** as a white, crystalline solid (153 mg, 91%) in 86% ee. Chiral HPLC (*R,R*-Whelk-01, 15% IPA in hexanes, 1.5 mL/min, λ = 224 nm) t_R (minor) = 7.1 min, t_R (major) = 13.9 min; $[\alpha]_D^{26}$ = + 26.5° (c = 1.4, CHCl_3); mp 62-63 °C; IR (thin film, cm^{-1}) 2980 (w), 2936 (w), 1715 (s, C=O), 1514 (s), 1248 (s, C-O), 1171 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.20 (2H, d, J = 8.4 Hz, ArH), 6.83 (2H, d, J = 8.4 Hz, ArH), 5.40 (1H, br, NH), 5.02 (1H, br, CH), 4.91 (1H, sep, J = 6.2 Hz, $\text{CH}(\text{CH}_3)_2$), 2.80 (1H, dd, J = 6.6, 14.1 Hz, CH_2), 2.71 (1H, dd, J = 6.6, 15 Hz, CH_2), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.14 (3H, d, J = 6.2 Hz, CH_3), 1.10 (3H, d, J = 6.2 Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.4, 158.8, 154.9, 133.4, 127.3, 113.8, 79.4, 68.0, 55.1, 50.8, 41.3, 28.3, 21.6; MS (AP) m/z : 338.2 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)propionic acid isopropyl ester (5f).

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (500 μ L) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2 $\times$ 12 cm silica, 2.5-10% ethyl acetate in hexanes, R_f = 0.30 (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5f** as a white, crystalline solid (143 mg, 88%) in 93% ee. Chiral HPLC (*R,R*-Whelk-01, 15% IPA in hexanes, 1.5 mL/min, λ = 224 nm) t_R (minor) = 5.7 min, t_R (major) = 10.2 min; $[\alpha]_D^{26}$ = + 17.4° (c = 1.4, CHCl_3); mp 42-43 °C; IR (thin film, cm^{-1}) 2982 (s), 2936 (w), 1719 (C=O), 1512 (s), 1173 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.28-7.22 (2H, m, ArH), 7.02-6.94 (2H, m, ArH), 5.52 (1H, br, NH), 5.05 (1H, br, CH), 4.91 (1H, sep, J = 6.2 Hz, $\text{CH}(\text{CH}_3)_2$), 2.79 (1H, dd, J = 6.2, 15.0 Hz, CH_2), 2.71 (1H, dd, J = 6.2, 15.0 Hz, CH_2), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.13 (3H, d, J = 6.2 Hz, CH_3), 1.09 (3H, d, J = 6.2, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.3, 163.2, 160.7, 154.9, 137.1, 127.8, 115.4, 115.2, 79.7, 68.2, 50.7, 41.2, 28.3, 21.6; MS (AP) m/z : 326.1 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(3-bromophenyl)propionic acid isopropyl ester (5g).

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (250 μ L) and **4c** (2 equiv). The product was purified via flash column chromatography on silica gel (2 $\times$ 12 cm silica, 2.5-10% ethyl acetate in hexanes, R_f = 0.25 (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5g** as a white, crystalline solid (185 mg, 96%) in 92% ee. Chiral HPLC (*R,R*-Whelk-01, 10% IPA in hexanes, 1.5 mL/min, λ = 208 nm) t_R (minor) = 4.7 min, t_R (major) = 8.9 min; $[\alpha]_D^{26}$ = + 18.9° (c = 1.4, CHCl_3); mp 54-55 °C; IR (thin film, cm^{-1}) 2980 (m), 2934 (w), 1717 (s, C=O), 1512 (m), 1168 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.43 (1H, s, ArH), 7.38-7.34 (1H, m, ArH), 7.24-7.14 (2H, m, ArH), 5.58 (1H, br, NH), 5.04 (1H, br, CH), 4.93 (1H, sep, J = 6.2 Hz, $\text{CH}(\text{CH}_3)_2$), 2.80-2.70 (2H, br, CH_2), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.15 (3H, d, J = 6.2 Hz, CH_3), 1.11 (3H, d, J = 6.2 Hz,

CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.1, 154.9, 143.7, 130.5, 130.1, 129.3, 124.9, 122.6, 79.8, 68.3, 50.8, 41.0, 28.3, 21.6; MS (AP) m/z : 385.9, 387.7 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(4-bromophenyl)propionic acid isopropyl ester (5h).

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (500 μL) and **4c** (2 equiv). The product was purified via flash column chromatography on silica gel (2×12 cm silica, 2.5-10% ethyl acetate in hexanes, R_f = 0.28 (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5h** as a white, crystalline solid (180 mg, 96%) in 94% ee. Chiral HPLC (*R,R*-Whelk-01, 10% IPA in hexanes, 1.5 mL/min, λ = 206 nm) $t_R(\text{minor})$ = 4.7 min, $t_R(\text{major})$ = 9.3 min; $[\alpha]_D^{26}$ = $+21.1^\circ$ (c = 1.4, CHCl_3); mp 97-98 °C; IR (thin film, cm^{-1}) 2980 (m), 2934 (w), 1715 (s, C=O), 1512 (m), 1489 (m), 1169 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.42 (2H, d, J = 8.8 Hz, ArH), 7.16 (2H, d, J = 8.3 Hz, ArH), 5.58 (1H, br, NH), 5.03 (1H, br, CH), 4.91 (1H, sep, J = 6.3 Hz, $\text{CH}(\text{CH}_3)_2$), 2.81-2.65 (2H, br, CH_2), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.14 (3H, d, J = 6.3 Hz, CH_3), 1.10 (3H, d, J = 5.9 Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.2, 154.9, 140.4, 131.6, 127.9, 121.2, 79.8, 68.3, 50.7, 40.9, 28.8, 21.6; MS (AP) m/z : 385.9, 387.6 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(1-naphthyl)propionic acid isopropyl ester (5i).

Reaction performed on a 0.52-mmol scale at -30 °C, using anhydrous toluene (260 μL) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2×12 cm silica, 2.5-10% ethyl acetate in hexanes, R_f = 0.29 (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5i** as a white, crystalline solid (173 mg, 93%) in 87% ee. Chiral HPLC (*R,R*-Whelk-01, 20% IPA in hexanes, 1.5 mL/min, λ = 224 nm) $t_R(\text{minor})$ = 6.9 min, $t_R(\text{major})$ = 16.1 min; $[\alpha]_D^{26}$ = $+13.7^\circ$ (c = 1.4, CHCl_3); mp 79-80 °C; IR (thin film, cm^{-1}) 2980 (m), 2934 (w), 1713 (s, C=O), 1512 (m), 1167 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 8.16 (1H, d, J = 8.8 Hz, ArH), 7.86 (1H, d, J = 8.0 Hz, ArH), 7.77 (1H, d, J = 8.0 Hz, ArH), 7.59-7.53 (1H, m, ArH), 7.52-7.40 (3H, m, ArH), 5.96 (1H, d, J = 5.6 Hz, NH), 5.56 (1H, d, J = 6.0 Hz, CH), 4.93 (1H, sep, J = 6.3 Hz, $\text{CH}(\text{CH}_3)_2$), 2.96 (2H, br, CH_2), 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.15 (3H, d, J = 6.4 Hz, CH_3), 1.02 (3H, d, J = 5.2 Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.4, 154.8, 136.8, 133.9, 130.6, 128.8, 128.2, 126.4, 125.7, 125.1, 122.9, 122.7, 79.6, 68.1, 47.5, 40.7, 28.3, 21.5; MS (AP) m/z : 358.1 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-(2-naphthyl)propionic acid isopropyl ester (5j).

Reaction performed on a 0.52-mmol scale at -30 °C, using anhydrous toluene (520 μL) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2×12 cm silica, 2.5-10% ethyl acetate in hexanes, R_f = 0.25 (15% ethyl acetate in hexanes), KMnO_4 TLC visualization) to yield **5j** as a white, crystalline solid (163 mg, 88%) in 96% ee. Chiral HPLC (Chiralpak AD, 2% IPA in hexanes, 1.5 mL/min, λ = 224 nm) $t_R(\text{minor})$ = 23.8 min, $t_R(\text{major})$ = 27.8 min; $[\alpha]_D^{26}$ = $+35.4^\circ$ (c = 1.4, CHCl_3); mp 82-83 °C; IR (thin film, cm^{-1}) 2980 (m), 1715 (s, C=O), 1508 (m), 1169 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ

7.66-7.60 (3H, m, ArH), 7.57 (1H, s, ArH), 7.32-7.22 (3H, m, ArH), 5.45 (1H, br, NH), 5.10 (1H, br, CH), 4.75 (1H, sep, $J = 6.2$ Hz, CH(CH₃)₃), 2.80-2.60 (2H, br, CH₂), 1.26 (9H, s, C(CH₃)₃), 0.97 (3H, d, $J = 6.2$ Hz, CH₃), 0.91 (3H, d, $J = 6.2$ Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 170.3, 155.0, 138.7, 133.2, 132.7, 128.4, 127.9, 127.5, 126.1, 125.8, 124.8, 124.4, 79.6, 68.1, 51.4, 41.2, 28.3, 21.6; MS (AP) m/z : 358.2 [M]⁺.

(*R*)-3-*tert*-butoxycarbonylamino-3-(2-furyl)propionic acid isopropyl ester (5k).

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (250 μ L) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2 $\times$ 12 cm silica, 2.5-10% ethyl acetate in hexanes, $R_f = 0.30$ (15% ethyl acetate in hexanes), KMnO₄ TLC visualization) to yield **5k** as a pale, yellow oil (125 mg, 84%) in 91% ee. Chiral HPLC (*R,R*-Whelk-01, 1.5% IPA in hexanes, 1.5 mL/min, $\lambda = 216$ nm) t_R (minor) = 11.4 min, t_R (major) = 12.9 min; $[\alpha]_D^{26} = +34.7^\circ$ ($c = 1.4$, CHCl₃); IR (thin film, cm⁻¹) 2980 (w), 2930 (w), 1721 (s, C=O), 1503 (m), 1169 (s, C-O); ¹H NMR (400 MHz, CDCl₃, 20 °C) δ 7.31 (1H, dd, $J = 0.73, 1.8$ Hz, furyl CH), 6.30-6.26 (1H, m, furyl CH), 6.17 (1H, d, $J = 2.9$ Hz, furyl CH), 5.4 (1H, br, NH), 5.16 (1H, br, CH), 4.96 (1H, sep, $J = 6.2$ Hz, CH(CH₃)₂), 2.85 (1H, dd, $J = 5.9, 15.4$ Hz, CH₂), 2.76 (1H, dd, $J = 6.2, 15.4$ Hz, CH₂), 1.43 (9H, s, C(CH₃)₃), 1.18 (3H, d, $J = 6.6$ Hz, CH₃), 1.16 (3H, d, $J = 6.2$ Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 170.1, 154.9, 153.7, 141.8, 110.2, 106.0, 79.7, 68.1, 45.6, 38.8, 28.3, 21.6; MS (AP) m/z : 298.1 [M]⁺.

(*R*)-3-*tert*-butoxycarbonylamino-3-(2-thienyl)propionic acid isopropyl ester (5l).

Reaction performed on a 0.5-mmol scale at -20 °C, using anhydrous toluene (250 μ L) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2 $\times$ 12 cm silica, 2.5-10% ethyl acetate in hexanes, $R_f = 0.16$ (10% ethyl acetate in hexanes), KMnO₄ TLC visualization) to yield **5l** as a white, crystalline solid (149 mg, 95%) in 92% ee. Chiral HPLC (*R,R*-Whelk-01, 2% IPA/hexanes, 1.5 mL/min, $\lambda = 234$ nm) t_R (minor) = 10.1 min, t_R (major) = 13.9 min; $[\alpha]_D^{26} = +31.9^\circ$ ($c = 1.4$, CHCl₃); mp 68-69 °C; IR (thin film, cm⁻¹) 2980 (m), 2934 (w), 1719 (s), 1499 (m), 1171 (s, C-O); ¹H NMR (400 MHz, CDCl₃, 20 °C) δ 7.17 (1H, dd, $J = 2.0, 4.2$ Hz, thienyl CH), 6.93-6.89 (2H, m, thienyl CH), 5.53 (1H, br, NH), 5.34 (1H, br, CH), 4.96 (1H, sep, $J = 6.2$ Hz, CH(CH₃)₂), 2.89 (1H, dd, $J = 6.1, 15.6$ Hz, CH₂), 2.82 (1H, dd, $J = 5.9, 15.4$ Hz, CH₂), 1.43 (9H, s, C(CH₃)₃), 1.17 (3H, d, $J = 6.2$ Hz, CH₃), 1.15 (3H, d, $J = 6.2$ Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 170.1, 154.7, 145.3, 126.7, 124.3, 123.9, 79.7, 68.2, 47.2, 41.2, 28.3, 21.6; MS (AP) m/z : 314.0 [M]⁺.

(*R*)-3-*tert*-butoxycarbonylamino-3-(3-quinoliny)propionic acid isopropyl ester (5m).

Reaction performed on a 0.5-mmol scale at -30 °C, using anhydrous toluene (1 mL) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2 $\times$ 15 cm silica, 2.5-5% methanol in dichloromethane, $R_f = 0.60$ (10% methanol in dichloromethane), UV TLC visualization) to yield **5m** as a pale, yellow oil (177 mg, 99%)

in 96% ee. Chiral HPLC (Chiralpak AD, 15% IPA in hexanes, 1.5 mL/min, $\lambda = 206$ nm) $t_R(\text{minor}) = 12.7$ min, $t_R(\text{major}) = 15.6$ min; $[\alpha]_D^{26} = +36.4^\circ$ ($c = 1.4$, CHCl_3); IR (thin film, cm^{-1}) 2980 (s), 2936 (w), 1713 (s, C=O), 1516 (s), 1499 (s), 1169 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.87 (1H, d, $J = 2.2$ Hz, ArH), 8.08-8.02 (2H, m, ArH), 7.75 (1H, dd, $J = 1.5$, 8.1 Hz, ArH), 7.68-7.62 (1H, m, ArH), 5.54-7.48 (1H, m, ArH), 5.83 (1H, br, NH), 5.29 (1H, br, CH), 4.90 (1H, sep, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.96-2.84 (2H, br, CH_2), 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.12 (3H, d, $J = 6.2$ Hz, CH_3), 1.05 (3H, d, $J = 6.2$ Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 170.0, 154.9, 149.6, 147.4, 134.0, 132.9, 129.3, 129.1, 127.7, 127.6, 126.8, 79.9, 68.5, 49.4, 40.6, 28.2, 21.5; MS (AP) m/z : 359.1 $[\text{M}]^+$.

(R)-3-tert-butoxycarbonylamino-3-(3-pyridyl)propionic acid isopropyl ester (5n).

Reaction performed on a 0.53-mmol scale at -30 $^\circ\text{C}$, using anhydrous toluene (270 μL) and **4c** (2 equiv). The product was purified via flash chromatography on silica gel (2×14 cm silica, 2.5-5% methanol in dichloromethane, $R_f = 0.57$ (10% methanol in dichloromethane), UV TLC visualization) to yield **5n** as a pale, yellow oil (162 mg, 99%) in 98% ee.

Chiral HPLC (Chiralpak AD, 5% IPA in hexanes, 1.5 mL/min, $\lambda = 206$ nm) $t_R(\text{minor}) = 25.6$ min, $t_R(\text{major}) = 28.0$ min; $[\alpha]_D^{26} = +18.9^\circ$ ($c = 1.4$, CHCl_3); IR (thin film, cm^{-1}) 2980 (m), 2935 (w), 1715 (s, C=O), 1520 (m), 1169 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.54 (1H, d, $J = 1.8$ Hz, ArH), 8.47 (1H, dd, $J = 1.1$, 4.8 Hz, ArH), 7.60 (1H, dt, $J = 1.8$, 8.1 Hz, ArH), 7.21 (1H, dd, $J = 4.8$, 7.7 Hz, ArH), 5.76 (1H, br, NH), 5.09 (1H, br, CH), 4.90 (1H, sep, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.82-2.66 (2H, br, CH_2), 1.37 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.12 (3H, d, $J = 6.2$ Hz, CH_3), 1.07 (3H, d, $J = 6.2$ Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 170.0, 154.9, 148.7, 148.0, 136.8, 133.8, 123.3, 79.8, 68.4, 49.2, 40.6, 28.2, 21.5; MS (AP) m/z : 309.1 $[\text{M}]^+$.

Large Scale Experimental (5 mmol, 2 equiv silyl ketene acetal): A 20-mL flask was charged sequentially with **1c** (150 mg, 0.25 mmol, 0.050 equiv) and anhydrous toluene (2.5 mL). 3-pyridine carboxaldehyde *N*-(Boc) imine **3n** (1.0 g, 5.0 mmol, 1.0 equiv) was then added in one portion with stirring. Once the solution was homogeneous, the flask was immersed in a dry ice/acetone bath cooled to -30 $^\circ\text{C}$. **4c** (2.16 g, 10 mmol, 2.0 equiv) was then added slowly along the flask wall over a ten-minute period. The flask was sealed under an atmosphere of nitrogen and stirred at -30 $^\circ\text{C}$. After 48 h, excess silyl ketene acetal was quenched at -30 $^\circ\text{C}$ via the rapid addition of a 3M solution of trifluoroacetic acid in toluene (5 mL; cooled to -20 $^\circ\text{C}$ prior to addition). The reaction was allowed to warm to ~ 5 $^\circ\text{C}$, then partitioned between saturated aqueous sodium carbonate solution and dichloromethane (1:1, 20 mL). The aqueous layer was extracted with dichloromethane (3×15 mL), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified via flash chromatography on silica gel (3×19 cm silica, 2.5-5% methanol in dichloromethane), $R_f = 0.57$ (10% methanol in dichloromethane), UV TLC visualization) to yield **5n** as a pale, yellow oil (1.49 g, 97%) in 98% ee.

Large Scale Experimental (5 mmol, 1.2 equiv silyl ketene acetal): Reaction performed utilizing the same procedure listed above, adding 1.2 equiv silyl ketene acetal **4c** (1.3 g, 6.0 mmol). After 48 h at -30 $^\circ\text{C}$, excess silyl ketene acetal was quenched via the rapid addition of a 3M solution of

trifluoroacetic acid in toluene (3.0 mL; cooled to $-20\text{ }^{\circ}\text{C}$ prior to addition). Reaction was worked up and chromatographed as above to yield **5n** (1.53 g, 99%) in 98% ee.

III. Silyl Ketene Acetal Preparation.

*Note: 1-methyl-2-pyrrolidinone (NMP; distilled from CaH_2) can be readily substituted for DMPU to yield identical results

1-(tert-butyldimethylsilyloxy)-1-isopropoxyethylene (4c). *n*-Butyllithium (2.5M in hexanes; 13.2 mL, 33.0 mmol, 1.10 equiv) was added dropwise to a solution of freshly distilled diisopropylamine (5.0 mL, 36 mmol, 1.2 equiv) in anhydrous tetrahydrofuran (75 mL) at $0\text{ }^{\circ}\text{C}$. The flask was maintained at $0\text{ }^{\circ}\text{C}$ for 20 min, then immersed in a dry ice/acetone bath at $-78\text{ }^{\circ}\text{C}$. Isopropyl acetate (3.5 mL, 30 mmol, 1.0 equiv) was then added dropwise (neat) over a ten-minute period. The reaction was stirred 30 min at $-78\text{ }^{\circ}\text{C}$. 1,3-Dimethyl-3,4,5,6,-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 6 mL) was then added dropwise, followed by *tert*-butyldimethylsilyl chloride (5.0 g, 33 mmol, 1.2 equiv; dissolved in 8 mL anhydrous tetrahydrofuran). The reaction was stirred for an additional 30 min at $-78\text{ }^{\circ}\text{C}$, then slowly allowed to warm to ambient temperature over a 1 h period. The solvent was removed *in vacuo*, and the resulting residue was taken up in pentane (200 mL) and washed successively with water ($1 \times 100\text{ mL}$), saturated aqueous copper sulfate (CuSO_4 ; $1 \times 100\text{ mL}$), saturated aqueous sodium bicarbonate solution ($1 \times 100\text{ mL}$), and brine ($1 \times 100\text{ mL}$). The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude product in quantitative yield (~95% pure via ^1H NMR). Crude silyl ketene acetal was further purified via distillation (bp $78\text{--}80\text{ }^{\circ}\text{C}$ at 10 Torr) to yield **4c** as a colorless liquid (6.0 g, 93%). IR (thin film, cm^{-1}) 2932 (s), 2860 (s), 1651 (s, C=C), 1274 (s); ^1H NMR (400 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$) δ 4.12 (1H, sep, $J=6.2\text{ Hz}$, $\text{CH}(\text{CH}_3)_2$), 3.27 (1H, d, $J=2.2\text{ Hz}$, $=\text{CH}_2$), 3.09 (1H, d, $J=2.2\text{ Hz}$, $=\text{CH}_2$), 1.25 (6H, d, $J=5.9\text{ Hz}$, $\text{CH}(\text{CH}_3)_2$), 0.93 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.17 (6H, s, SiCH_3); ^{13}C NMR (100 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$) δ 159.7, 69.8, 61.5, 25.7, 21.6, 18.1, -4.5 ; MS (CI) m/z : 217 $[\text{M}]^+$.

1-(tert-butyldimethylsilyloxy)-1-methoxyethylene (4a). Reaction performed on a 30-mmol scale. Purification via distillation (bp $74\text{--}76\text{ }^{\circ}\text{C}$ at 23 Torr) yielded **4a** as a colorless liquid (4.85 g, 86%). IR (thin film, cm^{-1}) 2959 (m), 2934 (m), 2861 (m), 1655 (s, C=C), 1447 (w), 1281 (s); ^1H NMR (600 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$) δ 3.52 (3H, s, CH_3O), 3.22 (1H, d, $J=2.6\text{ Hz}$, $=\text{CH}_2$), 3.09 (1H, d, $J=2.6\text{ Hz}$, $=\text{CH}_2$), 0.92 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.16 (6H, s, SiCH_3); ^{13}C NMR (100 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$) δ 162.3, 60.1, 55.0, 25.6, 18.1, -4.8 ; MS (EI) m/z : 189 $[\text{M}]^+$.

1-(*tert*-butyldimethylsilyloxy)-1-ethoxyethylene (4b). Reaction performed on a 30-mmol scale.

Purification via distillation (bp 70-72 °C at 10 Torr) yielded **4b** as a colorless liquid (5.77 g, 95%). IR (thin film, cm⁻¹) 2934 (m), 2861 (m), 1657 (s, C=O), 1474 (m), 1277 (s); ¹H NMR (600 MHz, CDCl₃, 20 °C) δ 3.74 (2H, q, *J* = 7.0 Hz, CH₂CH₃), 3.22 (1H, d, *J* = 2.6 Hz, =CH₂), 3.05 (1H, d, *J* = 2.6 Hz, =CH₂), 1.29 (3H, t, *J* = 7.2 Hz, CH₃), 0.93 (9H, s, C(CH₃)₃), 0.17 (6H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 161.2, 63.3, 60.3, 25.6, 18.1, 14.3, -4.6; MS (EI) *m/z*: 318.9 [M + TBS]⁺, 202.9 [M]⁺.

1-(*tert*-butyldimethylsilyloxy)-1-*tert*-butoxyethylene (4d). Reaction performed on a 30-mmol scale to give crude silyl ketene acetal in quantitative yield after workup. Further

purification via distillation (bp 73-75 °C at 5 Torr) yielded **4d** as a colorless liquid (4.5 g, 65%). *Note: product loss due to partial decomposition during distillation.* IR (thin film, cm⁻¹) 2934 (s), 2861 (s), 1651 (s, C=C), 1474 (m), 1368 (m), 1254 (s); ¹H NMR (400 MHz, CDCl₃, 20 °C) δ 3.47 (1H, d, *J* = 1.5 Hz, =CH₂), 3.45 (1H, d, *J* = 1.5 Hz, =CH₂), 1.34 (9H, s, OC(CH₃)₃), 0.93 (9H, s, C(CH₃)₃), 0.18 (6H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 157.7, 78.0, 72.7, 28.5, 25.7, 18.0, -4.8; MS (EI) *m/z*: 230.8 [M]⁺.

IV. Imine Preparation³

***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)benzylamine (7a).** A 500-mL flask was charged with *tert*-butyl carbamate (10.0 g, 85.5 mmol, 1.00 equiv) and benzenesulfinic acid sodium salt (28 g, 170 mmol, 2.0 equiv). Solids were suspended in a solution of methanol in water (1:2, 250 mL). Benzaldehyde (13.0 mL, 128 mmol, 1.50 equiv) was then added in one portion, followed by formic acid (98%, 6.4 mL). The reaction was allowed to stir 48 h at 23 °C, during which time the product precipitated as a white solid. **7a** was isolated via Büchner funnel filtration and purified via trituration with water and diethyl ether. After drying *in vacuo*, **7a** was obtained as a white solid (23.6 g, 80%). IR (thin film, cm⁻¹) 2981 (m), 1698 (s), 1508 (s), 1310 (s), 1145 (s); ¹H NMR (400 MHz, CDCl₃, 20 °C) δ 7.92 (2H, d, *J* = 7.3 Hz, ArH), 7.67-7.61 (1H, m, ArH), 7.57-7.61 (2H, m, ArH), 7.49-7.38 (5H, m, ArH), 5.95 (1H, br d, *J* = 11.0 Hz), 5.88 (1H, br d, *J* = 10.3 Hz), 1.25 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 153.5, 136.9, 133.9, 129.8, 129.7, 129.4, 129.0, 128.9, 128.7, 81.1, 73.9, 27.9.

³ Procedure adapted from: Kanazawa, A. M.; Denis, J.; Greene, A. E. *J. Org. Chem.* **1994**, 59, 1238-1240.

Benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (3a). A 250-mL, 3-neck flask was charged with anhydrous potassium carbonate (12.4 g, 90.0 mmol, 6.00 equiv) and anhydrous sodium sulfate (15 g). The solids were placed under vacuum and flame-dried. Once cool, **7a** (5.2 g, 15 mmol, 1.0 equiv) was added under a positive stream of nitrogen, followed by anhydrous tetrahydrofuran (140 mL). The flask was capped with a water-cooled reflux condenser under an atmosphere of nitrogen and heated to reflux with stirring. After 15 h, the reaction was cooled to ambient temperature and the solids removed via filtration through a fine, glass frit. The filtrate was concentrated *in vacuo* and dried under high vacuum to give imine **3a** as a colorless oil (3.07 g, 100%). IR (thin film, cm^{-1}) 2980 (w), 1717 (s, C=O), 1633 (m, C=N), 1270 (s), 1152 (s); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.88 (1H, s, CH=N), 7.93-7.90 (2H, m, ArH), 7.57-7.54 (1H, m, ArH), 7.49-7.43 (2H, m, ArH), 1.59 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 169.7, 162.6, 134.0, 133.5, 130.2, 128.8, 82.3, 27.9; MS (AP) m/z : 206.1 [M]⁺.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-2-methylbenzylamine (7b).** Reaction performed on a 42.6-mmol scale utilizing the same procedure for the preparation of **7a**. After 3 days, **7b** was isolated as a white solid (11.1 g, 73%) after trituration. IR (thin film, cm^{-1}) 1705 (m, C=O), 1319 (m), 1144 (s); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 7.96-7.88 (2H, m, ArH), 7.70-7.60 (1H, m, ArH), 7.60-7.50 (2H, m, ArH), 7.49-7.41 (1H, m, ArH), 7.36-7.19 (3H, m, ArH), 6.25 (1H, br d, J = 10.5 Hz), 5.77 (1H, br d, J = 10.1 Hz), 2.45 (3H, s, ArCH₃), 1.25 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 153.5, 138.1, 137.3, 133.9, 130.8, 129.7, 129.3, 129.0, 127.6, 126.5, 81.1, 69.6, 28.0, 19.7.

***o*-Tolualdehyde *N*-(*tert*-butoxycarbonyl)imine (3b).** Reaction performed on a 6-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3b** was isolated as a colorless oil (1.29 g, 98%). IR (thin film, cm^{-1}) 2980 (w), 1711 (s, C=O), 1624 (m, C=N), 1599 (m), 1267 (s), 1155 (s); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 9.22 (1H, s, CH=N), 8.08 (1H, d, J = 7.7 Hz, ArH), 7.45-7.39 (1H, m, ArH), 7.30-7.20 (2H, m, ArH), 2.58 (3H, s, ArCH₃), 1.59 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 168.1, 163.0, 140.8, 133.2, 132.0, 131.1, 128.7, 126.3, 82.2, 27.9, 19.2; MS (AP) m/z : 220.1 [M]⁺.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-3-methylbenzylamine (7c).** Reaction performed on a 42.6-mmol scale utilizing the same procedure for the preparation of **7a**. After 3 days, **7c** was isolated as a white solid (13.8 g, 89%) after trituration. IR (thin film, cm^{-1}) 2980 (w), 1699 (s, C=O), 1507 (m), 1310 (s), 1146 (s); ^1H NMR (500 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 7.92 (2H, d, J = 7.8 Hz, ArH), 7.64 (1H, t, J = 7.3 Hz, ArH), 7.56-7.51 (2H, m, ArH), 7.32-7.28 (1H, m, ArH), 7.27-7.21 (3H, m, ArH), 5.89 (1H, br d, J = 10.7 Hz), 5.77 (1H, br d, J = 10.7 Hz), 2.37 (3H, s, ArCH₃), 1.25 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 153.4, 138.6, 137.0, 133.9, 130.7, 129.7, 129.5, 129.4, 129.0, 128.6, 126.0, 81.1, 73.9, 28.0, 21.4.

***m*-Tolualdehyde *N*-(*tert*-butoxycarbonyl)imine (3c).** Reaction performed on a 6-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3c** was isolated as a colorless oil (1.31 g, 100%). IR (thin film, cm^{-1}) 2980 (w), 1719 (s, C=O), 1638 (s, C=N), 1370 (s), 1242 (s), 1150 (s); ^1H NMR (600 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.86 (1H, s, CH=N), 7.78 (1H, s, ArH), 7.67 (1H, d, J = 6.8 Hz, ArH), 7.38-7.33 (2H, m, ArH), 2.39 (3H, s, ArCH₃); 1.58 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 170.1, 162.6, 138.7, 134.4, 134.0, 130.1, 128.7, 128.0, 82.2, 27.9, 21.1; MS (AP) m/z : 220.0 $[\text{M}]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-4-methylbenzylamine (7d).** Reaction performed on a 42.6-mmol scale utilizing the same procedure for the preparation of **7a**. After 2 days, **7d** was isolated as a white solid (13.5 g, 88%) after trituration. IR (thin film, cm^{-1}) 2980 (w), 1701 (s, C=O), 1507 (m), 1310 (s), 1142 (s); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 7.92 (2H, d, J = Hz, ArH), 7.64 (1H, t, J = 7.0 Hz, ArH), 7.53 (2H, t, J = 7.6 Hz, ArH), 7.33 (2H, d, J = 7.7 Hz, ArH), 7.22 (2H, d, J = 8.0 Hz, ArH), 5.90 (1H, br d, J = 10.6 Hz), 5.77 (1H, d, J = 10.6 Hz), 2.37 (3H, s, ArCH₃), 1.24 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 153.4, 140.0, 137.0, 133.8, 129.4, 129.0, 128.7, 126.7, 81.1, 73.7, 28.0, 21.3.

***p*-Tolualdehyde *N*-(*tert*-butoxycarbonyl)imine (3d).** Reaction performed on a 8.3-mmol scale utilizing the same procedure the preparation of **3a**. After 15 h, **3d** was isolated as a colorless oil (1.73 g, 95%). IR (thin film, cm^{-1}) 2980 (w), 1713 (m, C=O), 1609 (m, C=N), 1256 (m), 1154 (s); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.87 (1H, s, CH=N), 7.81 (2H, d, J = 8.1 Hz, ArH), 7.26 (2H, d, J = 7.7 Hz, ArH), 2.41 (3H, s, ArCH₃), 1.58 (9H, s, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 170.0, 162.8, 144.6, 131.5, 130.3, 129.6, 82.1, 27.9, 21.8; MS (AP) m/z : 220.0 $[\text{M}]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(4-methylphenylsulfonyl)-4-methoxybenzylamine (7e).**⁴ A 250-mL flask was charged with *tert*-butyl carbamate (3.5 g, 30 mmol, 1.0 equiv) and *p*-toluenesulfinic acid sodium salt (6.9 g, 39 mmol, 1.3 equiv). Solids were suspended in a solution of methanol in water (1:9, 30 mL). *p*-Methoxybenzaldehyde (4.4 mL, 36 mmol, 1.2 equiv) was then added in one portion, followed by formic acid (98%, 5.2 mL). The reaction was allowed to stir 9 h at 23 $^\circ\text{C}$, during which time the product precipitated as a white solid. **7e** was isolated via Büchner funnel filtration and purified via trituration with water and diethyl ether. After drying *in vacuo*, **7e** was obtained as a white solid (10.0 g, 82%). IR (thin film, cm^{-1}) 2836 (w), 1713 (s, C=O), 1511 (s), 1314 (s), 1253 (s), 1141 (s); ^1H NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 7.78 (2H, d, J = 7.7 Hz, ArH), 7.36 (2H, d, J = 8.8 Hz, ArH), 7.31 (2H, d, J = 8.1 Hz, ArH), 6.92 (2H, d, J = 8.8 Hz, ArH), 5.85 (1H, br d, J = 11.0 Hz), 5.79 (1H, br d, J =

⁴ Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622-2636.

10.6 Hz), 3.81 (3H, s, OCH₃), 2.41 (3H, s, CH₃), 1.25 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 160.7, 153.5, 144.8, 133.9, 130.2, 129.6, 129.4, 121.8, 114.1, 80.9, 73.4, 55.3, 27.9, 21.6.

***p*-Methoxybenzaldehyde *N*-(*tert*-butoxycarbonyl)imine (3e).** Reaction performed on a 7.0-mmol scale utilizing the same procedure for the preparation of **3a**. After 24 h, **3e** was isolated as a white solid (1.61 g, 98% yield). IR (thin film, cm⁻¹) 2980 (m), 2937 (m), 1708 (s, C=O), 1628 (s, C=N), 1366 (s), 1256 (s), 1167 (m), 1027 (s); ¹H NMR (400 MHz, CDCl₃, 20 °C) δ 8.88 (1H, s, CH=N), 7.88 (2H, d, *J* = 8.8 Hz, ArH), 6.96 (2H, d, *J* = 8.8 Hz, ArH), 3.87 (3H, s, OCH₃), 1.58 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 169.8, 164.1, 162.8, 132.5, 126.9, 114.3, 81.8, 55.5, 27.9; MS (AP) *m/z*: 236.0 [M]⁺.

***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-fluorobenzylamine (7f).** Reaction performed on a 53.7-mmol scale utilizing the same procedure for the preparation of **7a**. After 3 days, **7f** was isolated as a white solid (12.1 g, 62%) after trituration. IR (thin film, cm⁻¹) 1713 (s, C=O), 1510 (m), 1316 (m), 1144 (m); ¹H NMR (400 MHz, CDCl₃, 20 °C) δ 7.92 (2H, d, *J* = 7.7 Hz, ArH), 7.65 (1H, t, *J* = 7.6 Hz, ArH), 7.54 (2H, t, *J* = 7.6 Hz, ArH), 7.48-7.41 (2H, m, ArH), 7.10 (2H, t, *J* = 8.4 Hz, ArH), 5.93 (1H, br d, *J* = 10.8 Hz), 5.82 (1H, br d, *J* = 10.8 Hz), 1.24 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 164.8, 162.3, 153.4, 136.6, 134.0, 130.9, 130.8, 129.4, 129.1, 125.8, 116.0, 115.7, 81.3, 73.1, 27.9.

***p*-Fluorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine (3f).** Reaction performed on a 9.9-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3f** was isolated as a white solid (2.20 g, 100%). IR (thin film, cm⁻¹) 2982 (m), 1715 (s), 1634 (m, C=N), 1370 (m), 1148 (m); ¹H NMR (300 MHz, CDCl₃, 20 °C) δ 8.85 (1H, s, CH=N), 7.96-7.90 (2H, m, ArH), 7.18-7.12 (2H, m, ArH), 1.58 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 168.4, 167.3, 164.7, 162.4, 132.6, 132.5, 130.4, 116.3, 116.1, 82.4, 27.9; MS (AP) *m/z*: 224.1 [M]⁺.

***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-3-bromobenzylamine (7g).** Reaction performed on a 42.6-mmol scale utilizing the same procedure for the preparation of **7a**. After 2 days, **7g** was isolated as a white solid (10.3 g, 57%) after trituration. IR (thin film, cm⁻¹) 2980 (w), 1711 (s, C=O), 1520 (m), 1310 (m), 1142 (s); ¹H NMR (600 MHz, CDCl₃, 20 °C) δ 7.92 (2H, d, *J* = 7.8 Hz, ArH), 7.67 (1H, t, *J* = 7.0 Hz, ArH), 7.58-7.54 (4H, m, ArH), 7.40 (1H, d, *J* = 7.8 Hz, ArH), 7.29 (1H, t, *J* = 8.0 Hz, ArH), 5.89 (1H, br d, *J* = 10.7 Hz), 5.71 (1H, br d, *J* = 10.7 Hz), 1.26 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, 20 °C) δ 153.3, 136.6, 134.2, 132.9, 132.1, 131.8, 130.2, 129.4, 129.1, 127.7, 122.8, 81.5, 73.1, 28.0.

***m*-Bromobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**3g**).** Reaction performed on a 5.4-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3g** was isolated as a colorless oil (1.50 g, 98%). IR (thin film, cm^{-1}) 2980 (w), 1719 (s, C=O), 1630 (m, C=N), 1256 (s), 1154 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 8.77 (1H, s, CH=N), 8.10 (1H, t, J = 1.8 Hz, ArH), 7.80-7.76 (1H, m, ArH), 7.68-7.64 (1H, m, ArH), 7.34 (1H, t, J = 7.9 Hz, ArH), 1.58 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 167.8, 162.1, 136.2, 136.0, 132.2, 130.3, 129.0, 123.1, 82.6, 27.9; MS (AP) m/z : 283.9, 285.8 $[\text{M}]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-4-bromobenzylamine (**7h**).** Reaction performed on a 42.6-mmol scale utilizing the same general procedure for the preparation of **7a**. 1.2 equiv 4-bromobenzaldehyde was used. After 2 days, **7h** was isolated as a white solid (10.3 g, 57%) after extensive trituration. IR (thin film, cm^{-1}) 1694 (s, C=O), 1505 (m), 1310 (s), 1142 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.91 (2H, d, J = 7.6 Hz, ArH), 7.72-7.62 (1H, m, ArH), 7.58-7.51 (4H, m, ArH), 7.32 (2H, d, J = 8.2 Hz, ArH), 5.89 (1H, br d, J = 10.7 Hz), 5.70 (1H, br d, J = 10.7 Hz), 1.25 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 153.4, 136.6, 134.1, 131.9, 130.4, 129.4, 129.1, 128.9, 124.3, 81.4, 73.2, 27.9.

***p*-Bromobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**3h**).** Reaction performed on a 3.5-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3h** was isolated as a white solid (955 mg, 96%). IR (thin film, cm^{-1}) 2980 (w), 1715 (s, C=O), 1632 (s, C=N), 1589 (s), 1256 (s), 1154 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 8.81 (1H, s, CH=N), 7.77 (2H, d, J = 8.4 Hz, ArH), 7.60 (2H, d, J = 8.4 Hz, ArH), 1.58 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 168.4, 162.3, 132.9, 132.2, 131.4, 128.5, 82.5, 27.9; MS (AP) m/z : 283.9, 285.9 $[\text{M}]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-*C*-naphthalen-1-yl-methylamine (**7i**).** Reaction performed on a 49-mmol scale utilizing the same procedure for the preparation of **7a**. After 3 days, **7i** was isolated as a white solid (5.9 g, 30%) after trituration. IR (thin film, cm^{-1}) 2980 (w), 1703 (s, C=O), 1310 (s), 1142 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 8.14 (1H, d, J = 8.4 Hz, ArH), 7.99 (2H, d, J = 7.7 Hz, ArH), 7.94 (1H, d, J = 8.1 Hz, ArH), 7.88 (1H, d, J = 8.1 Hz, ArH), 7.79 (1H, d, J = 7.0 Hz, ArH), 7.66-7.48 (6H, m, ArH), 6.88 (1H, br d, J = 10.6 Hz), 5.98 (1H, br d, J = 10.6 Hz), 1.27 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 153.6, 137.3, 133.9, 133.6, 131.7, 130.5, 129.4, 129.0, 128.8, 127.2, 127.0, 126.6, 126.1, 125.1, 122.8, 81.2, 69.0, 28.0.

1-Naphthaldehyde *N*-(*tert*-butoxycarbonyl)imine (3i**).** Reaction performed on a 5.7-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3i** was isolated in 95% yield (1.38 g). IR (thin film, cm^{-1}) 2980 (m), 1711 (s, C=O),

1613 (s, C=N), 1254 (s), 1157 (s); ^1H NMR (500 MHz, CDCl_3 , 20 °C) δ 9.55 (1H, s, $\text{CH}=\text{N}$), 8.92 (1H, d, $J = 8.4$ Hz, ArH), 8.19 (1H, d, $J = 7.0$ Hz), 8.05 (1H, d, $J = 8.4$ Hz, ArH), 7.91 (1H, d, $J = 7.7$ Hz, ArH), 7.68-7.63 (1H, m, ArH), 7.60-7.54 (2H, m, ArH), 1.63 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 169.0, 162.8, 134.3, 133.7, 131.9, 131.8, 129.3, 128.8, 128.1, 126.5, 125.1, 123.9, 82.2, 28.0; MS (AP) m/z : 256.0 $[\text{M}]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-*C*-naphthalen-2-yl-methylamine (7j).** Reaction

performed on a 42.6-mmol scale utilizing the same procedure for the preparation of **7a**. After 2 days, **7j** was isolated as a white solid (9.2 g, 54%) after trituration. IR (thin film, cm^{-1}) 1699 (s, C=O), 1505 (m), 1310 (s), 1140 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.97-7.80 (6H, m, ArH), 7.65 (1H, t, $J = 7.3$ Hz, ArH), 7.58-7.48 (5H, m, ArH), 6.10 (1H, br d, $J = 10.6$ Hz), 5.89 (1H, br d, $J = 10.6$ Hz), 1.27 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 153.5, 136.9, 134.0, 133.7, 132.9, 129.5, 129.1, 129.0, 128.6, 128.3, 127.7, 127.2, 127.1, 126.7, 125.5, 81.3, 74.1, 28.0.

2-Naphthaldehyde *N*-(*tert*-butoxycarbonyl)imine (3j). Reaction performed on a 5.7-mmol

scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3j** was isolated as a white solid (1.45 g, 100%). IR (thin film, cm^{-1}) 2980 (m), 1713 (s, C=O), 1620 (s, C=N), 1368 (m), 1249 (s), 1151 (s); ^1H NMR (500 MHz, CDCl_3 , 20 °C) δ 9.05 (1H, s, (1H, s, $\text{CH}=\text{N}$), 8.30 (1H, s, ArH), 8.10 (1H, dd, $J = 1.4$, 8.9 Hz, ArH), 7.95 (1H, d, $J = 7.8$ Hz, ArH), 7.89 (2H, t, $J = 8.5$ Hz, ArH), 7.62-7.54 (2H, m, ArH), 1.60 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125 MHz, CDCl_3 , 20 °C) δ 170.0, 162.7, 136.0, 134.2, 132.8, 131.8, 129.2, 128.8, 128.6, 128.0, 126.9, 124.0, 82.3, 27.9; MS (AP) m/z : 256.1 $[\text{M}]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-furfurylamine (7k).** Reaction performed on a

42.6-mmol scale utilizing the same procedure for the preparation of **7a**. After 2 days, **7k** was isolated as a white solid (7.94 g, 55%) after trituration. IR (thin film, cm^{-1}) 2983 (m), 1703 (s, C=O), 1309 (s), 1143 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.89 (2H, d, $J = 7.3$ Hz, ArH), 7.64 (1H, t, $J = 7.3$ Hz, ArH), 7.53 (2H, t, $J = 7.7$ Hz, ArH), 7.47 (1H, s, furyl H), 6.57 (1H, d, $J = 3.3$ Hz, furyl H), 6.43-6.41 (1H, m, furyl H), 6.03 (1H, br d, $J = 10.6$ Hz), 5.88 (1H, br d, $J = 10.6$ Hz), 1.27 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 153.3, 144.2, 142.9, 136.5, 134.0, 129.5, 129.0, 112.2, 111.1, 81.3, 68.9, 27.9.

Furfural *N*-(*tert*-butoxycarbonyl)imine (3k). Reaction performed on a 7.4-mmol scale utilizing

the same procedure for the preparation of **3a**. After 15 h, **3k** was isolated as a pale, yellow oil (1.37 g, 95%). IR (thin film, cm^{-1}) 2981 (m), 1712 (s), 1625 (s, C=N), 1247 (s), 1158 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 8.75 (1H, s, $\text{CH}=\text{N}$), 7.67 (1H, s, furyl H), 7.21 (1H, d, $J = 3.7$ Hz, furyl H), 6.58 (1H, dd, $J = 1.46$, 3.30, furyl H), 1.54 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20

°C) δ 162.1, 157.4, 150.7, 148.1, 121.3, 113.0, 82.1, 27.8; MS (EI) m/z : 196.0 $[M]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-*C*-thiophen-2-yl-methylamine (7l).**

performed on a 57-mmol scale utilizing the same procedure for the preparation of **7a**. After 3 days, **7l** was isolated as tan solid (8.8 g, 44%) after trituration. IR (thin film, cm^{-1}) 1707 (s, C=O), 1512 (m), 1310 (s), 1144 (s); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.92 (2H, d, J = 7.7 Hz, ArH), 7.64 (1H, t, J = 7.3 Hz, ArH), 7.53 (2H, t, J = 7.7 Hz, ArH), 7.40 (1H, d, J = 5.1 Hz, thienyl H), 7.26 (1H, br, thienyl H), 7.05 (1H, t, J = 4.2 Hz, thienyl H), 6.20 (1H, br d, J = 10.3 Hz), 5.76 (1H, br d, J = 10.6 Hz), 1.24 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 153.2, 136.3, 134.0, 131.3, 129.5, 129.3, 129.0, 127.7, 127.3, 81.3, 70.1, 27.9.

Thiophene-2-carboxaldehyde *N*-(*tert*-butoxycarbonyl)imine (3l).

7.4-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3l** was isolated as a pale, yellow oil (1.50 g, 96%). IR (thin film, cm^{-1}) 1709 (s, C=O), 1605 (s, C=N), 1240 (s), 1154 (s); ^1H NMR (500 MHz, CDCl_3 , 20 °C) δ 9.08 (1H, s, $\text{CH}=\text{N}$), 7.68-7.65 (2H, m, thienyl H), 7.18-7.16 (1H, m, thienyl H), 1.57 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 163.6, 162.1, 140.2, 137.1, 134.2, 128.3, 82.1, 27.9; MS (AP) m/z : 212.1 $[M]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-*C*-quinolin-3-yl-methylamine (7m).**

performed on a 29-mmol scale utilizing the same general procedure for the preparation of **7a**. 1.1 equiv 3-quinolinecarboxaldehyde was used. After 2 days, **7m** was isolated as a white solid (6.4 g, 55%) after trituration. IR (thin film, cm^{-1}) 1703 (s, C=O), 1507 (m), 1310 (s), 1142 (s); ^1H NMR (500 MHz, CDCl_3 , 20 °C) δ 8.94 (1H, br, ArH), 8.31 (1H, br, ArH), 8.13 (1H, d, J = 8.8 Hz, ArH), 7.98 (2H, d, J = 7.3 Hz, ArH), 7.83 (1H, d, J = 7.8 Hz, ArH), 7.79-7.75 (1H, m, ArH), 7.68 (1H, t, J = 7.3 Hz, ArH), 7.60-7.55 (3H, m, ArH), 6.17 (1H, br d, J = 10.7 Hz), 6.05 (1H, br d, J = 10.3 Hz), 1.26 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 153.4, 149.9, 148.4, 136.5, 134.3, 130.7, 129.5, 129.4, 129.3, 128.2, 127.4, 127.3, 123.4, 81.6, 72.0, 28.0.

3-quinolinecarboxaldehyde *N*-(*tert*-butoxycarbonyl)imine (3m).

mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3m** was isolated as white solid (1.46 g, 100%). IR (thin film, cm^{-1}) 2980 (s), 1713 (s, C=O), 1632 (s, C=N), 1370 (s), 1252 (s), 1155 (s); ^1H NMR (500 MHz, CDCl_3 , 20 °C) δ 9.39 (1H, d, J = 2.2 Hz, ArH), 9.05 (1H, s, $\text{CH}=\text{N}$), 8.61 (1H, d, J = 1.8 Hz, ArH), 8.13 (1H, d, J = 8.4 Hz, ArH), 7.90-7.87 (1H, m, ArH), 7.83-7.78 (1H, m, ArH), 7.62-7.57 (1H, m, ArH), 1.60 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 167.3, 162.0, 150.1, 149.9, 139.4, 132.0, 129.6, 129.0, 127.6, 127.1, 126.8, 82.7, 27.8; MS (AP) m/z : 257.0 $[M]^+$.

***N*-(*tert*-butoxycarbonyl)- α -(phenylsulfonyl)-*C*-pyridin-3-yl-methylamine (**7n**).** Reaction performed on a 42.7-mmol scale utilizing the same procedure for the preparation of **7a**. After 3 days, **7n** was isolated as white solid (11.9 g, 80%) after trituration. IR (thin film, cm^{-1}) 1717 (m, C=O), 1310 (m), 1144 (s); ^1H NMR (300 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 8.70-8.67 (2H, m, ArH), 7.93 (2H, d, J = 8.3 Hz, ArH), 7.86-7.83 (1H, m, ArH), 7.68 (1H, t, J = 7.0 Hz, ArH), 7.57 (2H, t, J = 7.5 Hz, ArH), 7.39-7.35 (1H, m, ArH), 5.97 (2H, br, NH, CH), 1.25 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 153.4, 150.9, 150.0, 136.3, 136.2, 134.3, 129.5, 129.2, 126.3, 123.5, 81.6, 71.8, 28.0.

3-pyridinecarboxaldehyde *N*-(*tert*-butoxycarbonyl)imine (3n**).** Reaction performed on a 15-mmol scale utilizing the same procedure for the preparation of **3a**. After 15 h, **3n** was isolated as yellow oil (3.09 g, 100%). IR (thin film, cm^{-1}) 1721 (s, C=O), 1640 (s, C=N), 1271 (s), 1155 (s); ^1H NMR (400 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 9.00 (1H, d, J = 2.2 Hz, ArH), 8.87 (1H, s, CH=N), 8.76 (1H, dd, J = 1.83, 4.8 Hz, ArH), 8.27 (1H, dt, J = 1.8, 8.1 Hz, ArH), 7.40 (1H, dd, J = 4.8, 8.1 Hz, ArH), 1.58 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 $^\circ\text{C}$) δ 166.7, 162.0, 153.9, 152.2, 135.8, 129.8, 123.9, 82.8, 27.8; MS (AP) m/z : 207.1 $[\text{M}]^+$.

V. Variation of Silyl Ketene Acetal Alkoxy Group Substitution in the Mannich Reaction (Table 1 Data).

(*R*)-3-*tert*-butoxycarbonylamino-3-phenylpropionic acid methyl ester.

To a flame-dried, 1/2-dram vial: **1b** (8.0 mg, 0.013 mmol, 0.050 equiv) was dissolved in anhydrous toluene (125 μL). Imine **3a** (51 mg, 0.25 mmol, 1.0 equiv) was then added in one portion with stirring, followed by silyl ketene acetal **4a** (94 mg, 0.50 mmol, 2.0 equiv). Reaction was allowed to stir at ambient temperature, monitoring via GC (relative to 5 mol% dodecane as an internal standard). 90% conversion was observed at 5.5 h. Excess silyl ketene acetal was quenched at -20 $^\circ\text{C}$ via the addition of a 3M solution of trifluoroacetic acid in toluene (250 μL ; cooled to -20 $^\circ\text{C}$ prior to addition). The reaction was allowed to warm to ~ 5 $^\circ\text{C}$, then partitioned between saturated aqueous sodium carbonate solution and dichloromethane (1:1, 2 mL). The aqueous layer was extracted with dichloromethane (3×2 mL), and the combined extracts dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. A small aliquot was purified via flash chromatography on silica gel (0.5×7 cm silica, 2.5-10% ethyl acetate in hexanes). Analysis via chiral HPLC (Chiralcel OD, 5% IPA in hexanes, 1.5 mL/min, λ = 203

nm) $t_R(\text{major}) = 6.5$ min, $t_R(\text{minor}) = 7.7$ min) revealed product to be present in 54% ee. IR (thin film, cm^{-1}) 2976 (w), 1726 (s, C=O), 1684 (s, C=O), 1518 (s), 1165 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.36-7.22 (5H, m, ArH), 5.47 (1H, br, NH), 5.10 (1H, br, CH), 3.61 (3H, m, OCH_3), 2.95-2.75 (2H, br, CH_2), 1.42 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 171.4, 155.0, 141.1, 128.6, 127.5, 126.1, 79.7, 51.7, 51.2, 40.7, 28.3; MS (ES) m/z : 280.0 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-phenylpropionic acid ethyl ester.

Reaction was performed on a 0.25-mmol scale, adding silyl ketene acetal **4b** (101 mg, 0.5 mmol, 2 equiv). 90% conversion was observed at 3.5 h. After reaction quench and workup, a small aliquot was purified via flash chromatography on silica gel (0.5 $\times$ 7 cm silica, 2.5-10% ethyl acetate in hexanes). Analysis via chiral HPLC (Chiralcel OD, 2% IPA in hexanes,

1.5 mL/min, $\lambda = 206$ nm) $t_R(\text{major}) = 8.2$ min, $t_R(\text{minor}) = 9.6$ min) revealed product to be present in 63% ee. IR (thin film, cm^{-1}) 2980 (w), 1719 (s, C=O), 1499 (m), 1169 (s, C-O); ^1H NMR (500 MHz, CDCl_3 , 20 °C) δ 7.35-7.20 (5H, m, ArH), 5.45 (1H, br, NH), 5.09 (1H, br, CH), 4.04 (2H, q, $J = 7.2$ Hz, OCH_2), 2.90-2.70 (2H, br, CH_2), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.14 (3H, t, $J = 7.1$ Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.9, 155.0, 141.2, 128.6, 127.5, 126.1, 79.6, 60.7, 51.2, 41.0, 28.3, 14.0; MS (ES) m/z : 294.0 $[\text{M}]^+$.

(*R*)-3-*tert*-butoxycarbonylamino-3-phenylpropionic acid isopropyl ester.

Reaction was performed on a 0.25-mmol scale, adding silyl ketene acetal **4c** (110 mg, 0.50 mmol, 2.0 equiv). 93% conversion was observed at 2 h. After reaction quench and workup, a small aliquot was purified via flash chromatography on silica gel (0.5 $\times$ 7 cm silica, 2.5-10% ethyl acetate in hexanes). Analysis via chiral HPLC (*R,R*-Whelk-01, 5% IPA in hexanes,

1.5 mL/min, $\lambda = 206$ nm) $t_R(\text{minor}) = 6.8$ min, $t_R(\text{minor}) = 12.5$ min) revealed product to be present in 68% ee. Refer to Section II for characterization data.

Reaction at -40 °C. To a flame-dried, 5-mL flask: **1b** (8.0 mg, 0.0125 mmol, 0.050 equiv) was dissolved in anhydrous toluene (125 μL). Imine **3a** (51 mg, 0.25 mmol, 1.0 equiv) was then added in one portion. Reaction was cooled to -40 °C. Silyl ketene acetal **4c** (94 mg, 0.50 mmol, 2.0 equiv) was then slowly added along the flask wall over a ten-minute period. Reaction was maintained at -40 °C, monitoring via GC (relative to 5 mol% dodecane as an internal standard). 88% conversion was observed at 48 h. Excess silyl ketene acetal was quenched at -40 °C via the addition of a 3M solution of trifluoroacetic acid in toluene (250 μL ; cooled to -20 °C prior to addition). The reaction was allowed to warm to ~5 °C, then partitioned between saturated aqueous sodium carbonate solution and dichloromethane (1:1, 2 mL). The aqueous layer was extracted with dichloromethane (3 $\times$ 2 mL), and the combined extracts dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. A small aliquot was purified via flash chromatography on silica gel (0.5 $\times$ 7 cm silica, 2.5-10% ethyl acetate in hexanes). Analysis via chiral HPLC revealed product to be present in 90% ee.

(R)-3-*tert*-butoxycarbonylamino-3-phenylpropionic acid *tert*-butyl ester.

Reaction was performed on a 0.25-mmol scale, adding silyl ketene acetal **4d** (115 mg, 0.50 mmol, 2.0 equiv). 91% conversion was observed at 25.5 h. After reaction quench and workup, a small aliquot was purified via flash chromatography on silica gel (0.5 × 7 cm silica, 2.5-10% ethyl acetate in hexanes). Analysis via chiral HPLC (*R,R*-Whelk-01, 5% IPA in hexanes, 1.5 mL/min, λ = 206 nm) t_R (minor) = 4.4 min, t_R (minor) = 7.9 min) revealed product to be present in 51% ee. IR (thin film, cm^{-1}) 2978 (m), 1713 (s, C=O), 1499 (m), 1163 (s, C=O); ^1H NMR (400 MHz, CDCl_3 , 20 °C) δ 7.30-7.20 (5H, m, ArH), 5.50 (1H, br, NH), 5.06 (1H, br, CH), 2.80-2.60 (1H, br, CH_2), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.33 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , 20 °C) δ 170.1, 155.0, 141.4, 128.4, 127.3, 126.2, 81.0, 79.4, 51.4, 42.1, 28.3, 27.8; MS (AP) m/z : 322.1 $[\text{M}]^+$.

VI. Confirmation of Stereochemistry

Preparation of (S)-3-*tert*-Butoxycarbonylamino-3-phenylpropionic Acid Methyl Ester via the Arndt-Eistert⁵ Reaction.

(S)-3-(*tert*-butoxycarbonylamino)-1-diazo-3-phenylpropan-2-one. To a 300 mL, 3-neck flask under an atmosphere of nitrogen: Boc-(D)-phenylglycine (>99% ee, 2.00 g, 7.96 mmol, 1.00 equiv) was dissolved in anhydrous tetrahydrofuran (40 mL). The flask was cooled to -5 °C (ice/aqueous sodium chloride bath). Distilled triethylamine (1.10 mL, 7.96 mmol, 1.00 equiv) and ethylchloroformate (760 μL , 8.0 mmol, 1.0 equiv) were then sequentially added. (Note: A white precipitate formed upon ethylchloroformate addition) After 15 min at -5 °C, diazomethane⁶ (~1.5 equiv; freshly prepared ethereal solution) was slowly added to the flask (using a smooth plastic funnel) until an intense yellow color persisted. The flask was then slowly allowed to warm to ambient temperature and stirred for an additional 3 h. Upon reaction completion, excess diazomethane was destroyed via the addition of a few drops acetic acid. The reaction was then concentrated to ~10 mL and partitioned between water and diethyl ether (1:1, 250 mL). The ethereal layer was washed sequentially with saturated aqueous sodium bicarbonate (1 × 75 mL), saturated aqueous ammonium chloride (1 × 75 mL), and brine (1 × 75 mL), then

⁵ (a) Gademann, K. Ph.D. Dissertation, Eidgenössische Technische Hochschule, Zürich, Switzerland, 2000.

(b) Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217-1228 and references therein.

⁶ Prepared utilizing the Diazald® procedure. Refer to: *Diazald®*, *MNNG and Diazomethane Generators*; Technical Information Bulletin Number AL-180; Aldrich Chemical Company: Milwaukee, WI, 1993. (CAUTION!: diazomethane is a highly toxic, carcinogenic, and explosive compound that exists as a gas at room temperature. Avoid contact and inhalation. While handling: rough edges, which can potentially cause detonation, should also be avoided.

dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting residue was purified via flash chromatography on silica gel (1:5 ethyl acetate/pentane, R_f = 0.19, UV TLC visualization) to give product as a viscous, yellow oil (1.70 g, 81%). ^1H NMR data correspond to the reported literature values.⁷

(S)-3-tert-butoxycarbonylamino-3-phenylpropionic acid methyl ester. To a 100-mL round bottom flask under an atmosphere of nitrogen: diazoketone (1.43 g, 5.19 mmol, 1.00 equiv) was dissolved in anhydrous methanol (21 mL). The flask was completely covered with aluminum foil to exclude light and cooled to $-25\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath. Silver benzoate (130 mg, 0.57 mmol, 0.11 equiv) dissolved in anhydrous triethylamine (1.7 mL, 12 mmol, 2.3 equiv) was then added dropwise with minimal exposure to light. The cold bath was removed, and the flask was allowed to slowly warm to ambient temperature. The reaction was stirred an additional 3 h, carefully avoiding exposure to light. Solvent was subsequently removed *in vacuo*, and the residue partitioned between ethyl acetate (125 mL) and saturated sodium bicarbonate solution (100 mL). The organic layer was washed with saturated aqueous ammonium chloride (1 $\times$ 100 mL) and brine (1 $\times$ 100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting residue was purified via flash chromatography on silica gel (1:5 ethyl acetate/pentanes, R_f = 0.31, KMnO_4 TLC visualization) to yield product as a white, crystalline solid (1.33 g, 92%). Chiral HPLC (Chiralcel OD, 5% IPA in hexanes, 1.5 mL/min, λ = 203 nm) $t_R(\text{minor})$ = 6.2 min, $t_R(\text{major})$ = 7.8 min) revealed product to be present in 78% ee.⁸ $[\alpha]_D^{26} = -26.9^{\circ}$ (c = 1.4, CHCl_3), in accordance with the reported literature value;⁹ mp $89\text{--}91\text{ }^{\circ}\text{C}$; IR (thin film, cm^{-1}) 2976 (w), 1726 (s, C=O), 1684 (s, C=O), 1518 (s), 1165 (s, C-O); ^1H NMR (400 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$) δ 7.36–7.22 (5H, m, ArH), 5.47 (1H, br, NH), 5.10 (1H, br, CH), 3.61 (3H, m, OCH_3), 2.95–2.75 (2H, br, CH_2), 1.42 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$) δ 171.4, 155.0, 141.1, 128.6, 127.5, 126.1, 79.7, 51.7, 51.2, 40.7, 28.3; MS (ES) m/z : 280.0 $[\text{M}]^+$.

(R)-3-tert-butoxycarbonylamino-3-phenylpropionic acid methyl ester. To a 25-mL, flame-dried flask: (R)-3-tert-butoxycarbonylamino-3-phenylpropionic acid isopropyl ester **5a** (300 mg,

⁷ Païs, M.; Sarfati, R.; Jarreau, F.-X.; *Bull. Soc. Chim. France* **1973**, 331–334.

⁸ *N*-Boc-(D)-Phenylglycine partially racemized during formation of the mixed anhydride.^{5b}

⁹ Alcon, M.; Canas, M.; Poch, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1994**, 35, 1589–1592.

0.98 mmol, 1.0 equiv, 97% ee; prepared utilizing Mannich reaction, ref Section II) was dissolved in anhydrous methanol (10 mL). Sodium methoxide (159 mg, 2.94 mmol, 3.00 equiv) was then added in one portion with stirring. An additional 2 mL anhydrous methanol was used to wash all sodium methoxide off the flask wall into the reaction. Reaction was allowed to stir overnight. After 12 h, 100% conversion observed via TLC: R_f (starting material) = 0.27, R_f (product) = 0.20 (15% ethyl acetate in hexanes, KMnO_4 TLC visualization). The reaction was slowly partitioned between dichloromethane and 10% aqueous citric acid (1:1, 60 mL). The aqueous layer was extracted with dichloromethane (3×20 mL), and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a white, crystalline solid (272 mg, 99%), analytically pure via ^1H NMR. Chiral HPLC (Chiralcel OD, 5% IPA in hexanes, 1.5 mL/min, $\lambda = 203$ nm) t_R (major) = 6.0 min, t_R (minor) = 7.0 min) revealed product to be present in 98% ee. $[\alpha]_D^{26} = +26.7^\circ$ ($c = 1.4$, CHCl_3), in accordance with the reported literature values;¹⁰ mp 94-95 °C.

¹⁰ (a) Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett.* **1998**, 39, 5951-5954. (b) Hanessian, S.; Sanceau, J. -Y. *Can. J. Chem.* **1996** 74; 4, 621-624.

HPLC Conditions: *R,R*-Whelk-01, 5% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.486	NM	0.3887	1.56389e4	670.46267	49.7723
2	12.435	NM	0.8806	1.57820e4	298.70062	50.2277

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.873	NM	0.3334	816.84692	40.82814	1.6057
2	12.519	NM	0.9843	5.00551e4	847.52612	98.3943

HPLC Conditions: *R,R*-Whelk-01, 5% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.001	BV	0.2940	1.22693e4	622.43451	49.5224
2	7.363	VB	0.3686	1.25060e4	505.50311	50.4776

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.015	BV	0.2885	1062.38403	57.24332	4.5660
2	7.209	VB	0.3568	2.22047e4	909.74683	95.4340

HPLC Conditions: *R,R*-Whelk-01, 15% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.046	NM	0.1961	1.04241e4	886.06012	50.0741
2	7.291	NM	0.4515	1.03933e4	383.66608	49.9259

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.075	NM	0.1962	694.12549	58.97563	3.1003
2	7.180	NM	0.4587	2.16949e4	788.34357	96.8997

HPLC Conditions: *R,R*-Whelk-01, 7% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=212,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.163	BB	0.2881	5997.30273	306.68063	50.9691
2	12.925	BB	0.7001	5769.24609	117.64062	49.0309

Signal 1: DAD1 B, Sig=212,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.789	MM	0.2965	288.94073	16.24217	1.8677
2	11.514	MM	0.7844	1.51815e4	322.58093	98.1323

Chiral HPLC: *R,R*-Whelk-01, 15% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 B, Sig=224,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.009	MM	0.4622	2.58287e4	931.28650	49.8177
2	14.261	MM	1.1563	2.60177e4	375.00919	50.1823

Signal 1: DAD1 B, Sig=224,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.137	MM	0.4541	2977.74731	109.30268	6.9663
2	13.904	MM	1.1722	3.97672e4	565.41650	93.0337

HPLC Conditions: *R,R*-WheIk-01, 15% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.727	NM	0.3487	8564.97266	409.40500	50.6987
2	10.387	NM	0.7001	8328.88281	198.27998	49.3013

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.768	NM	0.2907	750.30713	43.01879	3.6773
2	10.180	NM	0.7124	1.96534e4	459.79730	96.3227

HPLC Conditions: *R,R*-Whelk-01, 10% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.734	BB	0.2524	1.68728e4	1002.06714	50.3674
2	8.866	BB	0.5300	1.66267e4	464.02338	49.6326

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.706	BB	0.2335	1108.84241	72.88181	3.9442
2	8.540	BB	0.4887	2.70045e4	802.22534	96.0558

HPLC Conditions: *R,R*-Whelk-01, 10% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.776	HM	0.2554	9352.85937	610.26312	50.2765
2	9.710	HM	0.6566	9249.97070	234.79477	49.7235

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.742	BB	0.2453	1299.13489	80.07018	3.1412
2	9.205	BB	0.6055	4.00590e4	978.80353	96.8588

HPLC Conditions: *R,R*-Whelk-01, 20% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 B, Sig=224,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.666	MM	0.4826	3.03521e4	1048.21570	50.2220
2	16.755	MM	1.3388	3.00837e4	374.51367	49.7780

Signal 1: DAD1 B, Sig=224,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.883	VB	0.4258	2850.56543	98.44540	6.7159
2	16.096	PB	1.1098	3.95947e4	519.13275	93.2841

HPLC Conditions: Chiralpak AD, 2% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 B, Sig=224,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.869	PV	1.3124	7.23910e4	748.48279	49.6322
2	28.057	VP	1.7512	7.34640e4	630.57587	50.3678

Signal 1: DAD1 B, Sig=224,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.753	MM	1.4095	1282.61389	15.16641	1.9957
2	27.798	MM	1.8894	6.29861e4	555.60590	98.0043

HPLC Conditions: *R,R*-Whelk-01, 1.5% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 B, Sig=216,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.341	VV	0.6099	2.71681e4	652.36279	48.5465
2	13.281	VB	0.7653	2.87949e4	533.85431	51.4535

Signal 1: DAD1 B, Sig=216,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.378	NH	0.6406	1429.72473	37.19984	4.3606
2	12.918	NH	0.9353	3.13576e4	558.79340	95.6394

HPLC Conditions: *R,R*-Whelk-01, 2% IPA/hexanes, 1.5 mL/min

Signal 1: DAD1 B, Sig=234,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.601	BB	0.4928	2.33560e4	700.85126	50.4719
2	13.694	PB	0.7537	2.29193e4	438.54318	49.5281

Signal 1: DAD1 C, Sig=234,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.078	NM	0.4847	960.94342	33.04245	3.7016
2	13.920	NM	0.8982	2.49995e4	463.86823	96.2984

HPLC Conditions: Chiralpak AD, 15% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.217	BP	0.5628	2.31575e4	632.95978	49.4621
2	15.106	VV	0.7800	2.36612e4	482.61182	50.5379

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.254	MM	0.4961	1258.20020	42.27315	1.8559
2	15.026	VV	0.8104	6.65381e4	1305.93005	98.1441

HPLC Conditions: Chiralpak AD, 5% IPA in hexanes, 1.5 mL/min

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.061	BV	1.0497	2.47659e4	367.75961	49.7693
2	28.090	VB	1.2610	2.49955e4	302.19254	50.2307

Signal 1: DAD1 A, Sig=206,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.552	NM	0.7818	243.08406	5.18233	0.9679
2	27.987	NM	1.3979	2.48714e4	296.53973	99.0321