**The First Catalytic, Asymmetric α -Additions of Isocyanides:
Lewis-Base-Catalyzed, Enantioselective Passerini-type Reactions**

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SUPPORTING INFORMATION

General Experimental

All reactions were performed in oven (140 °C) or flame-dried glassware under an inert atmosphere of dry N₂. All reaction temperatures correspond to internal temperatures measured with Teflon-coated thermocouples unless otherwise noted. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane (CaCl₂); methylene chloride (CaCl₂); ethyl acetate (K₂CO₃). Reaction solvents were distilled from the indicated drying agents: methylene chloride (P₂O₅); methanol (Mg). Diisopropylethylamine was freshly distilled from CaH₂. Flash column chromatography was performed using 230-400 mesh silica gel purchased from EM Science. SiCl₄ was purchased from Gelest and constantly distilled under nitrogen. Benzaldehyde, 4-tolualdehyde, 4-anisaldehyde, 4-trifluoromethylbenzaldehyde, 2-naphthaldehyde, 1-naphthaldehyde, 2-furaldehyde, (*E*)-cinnamaldehyde, (*E*)-2-methyl-cinnamaldehyde, hydrocinnamaldehyde, cyclohexanecarboxaldehyde were purchased from Aldrich and freshly distilled before use. Phenylpropargylaldehyde was prepared according to the literature procedure.¹ *tert*-Butyl isocyanide was purchased from Fluka and used as received. Tosylmethyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide were purchased from Aldrich and used as received. Ethyl isocyanoacetate was purchased from Aldrich and distilled before use. Phenyl isocyanide was prepared according to the literature procedure.²

¹H NMR, ¹³C NMR, ¹⁹F NMR spectra were recorded on a Varian Unity 400 (¹H, 400 MHz; ¹³C, 100 MHz; ¹⁹F, 376 MHz), Unity 500 (¹H, 500 MHz; ¹³C, 126 MHz). ¹H NMR and ¹³C

NMR spectra are referenced to residual chloroform (δ 7.26 ppm, ^1H ; δ 77.0 ppm, ^{13}C). ^{19}F NMR spectra are referenced externally to C_6F_6 . Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broadened). Coupling constants, J , are reported in Hertz. Mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Low-resolution electron impact (EI) mass spectra were obtained on a Finnigan-MAT CH-5 spectrometer with a typical ionization voltage of 70 eV. Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were obtained on Mattson Galaxy 5020 spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100%), m (medium, 34-66%), w (weak, 0-33%). The elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Bulb-to-bulb distillations were done on a Büchi GKR-50 Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures (ABT) and are uncorrected. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with potassium permanganate. Chiral stationary phase, supercritical fluid chromatography (CSP-SFC) was performed on a Berger Instruments SFC with built-in photometric detector (λ = 220 nm or 258 nm) using Daicel Chiralpak columns. Analytical capillary gas chromatography (GC) was performed on a Hewlett Packard 5890 Series II fitted with a flame ionization detector (H_2 carrier gas, 16 mL/min) using the following column: Astec (Chiraldex) BPH 30m x 0.25mm x 0.125 μm . The injector temperature was 225 $^\circ\text{C}$, the detector temperature was 300 $^\circ\text{C}$. Retention times (t_R) and peak ratios were determined with a Hewlett Packard 3396 Series II integrator. Analytical high pressure liquid chromatography (HPLC) was performed on a Hewlett Packard 1090 Series II Liquid Chromatograph with a built-in photometric detector (λ = 220 nm or 258 nm) using a Rexchrom (*S,S*)-Gem 1 column. Solvents for HPLC use were of spectroscopic grade and filtered before use. Retention times (t_R) and peak ratios were determined with a Hewlett Packard 3396 Series II integrator. All separation methods for chiral samples were calibrated with racemic samples. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were obtained on a Jasco DIP-360 digital polarimeter and are reported as follows: $[\alpha]_D^T$, concentration (c = g/100 mL), and solvent.

Experimental Procedures

General Procedure I. Pyridine *N*-Oxide Catalyzed Additions of *tert*-Butyl Isocyanide

A solution of *tert*-butyl isocyanide (1.2 equiv, 1.0 M in CH₂Cl₂) was added to a solution of an aldehyde (1.0 M in CH₂Cl₂ based on aldehyde), pyridine *N*-oxide (0.1 equiv), SiCl₄ (1.1 equiv) at −74 °C over 30 min via a syringe pump. After being stirred for the indicated time, the reaction mixture was warmed to room temperature and dropwise transferred to a vigorously stirred, ice-cold saturated aqueous solution of NaHCO₃ (20 mL). The mixture was stirred for 2 h further at room temperature. The white precipitate was filtered off through Celite and the filtrate was extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. Pyridine *N*-oxide was separated from the product by silica gel chromatography (EtOAc/hexane). Analytically pure product was obtained after recrystallization (benzene/heptane).

General Procedure II. Catalytic Asymmetric Additions of *tert*-Butyl Isocyanide

A solution of *tert*-butyl isocyanide (1.2 equiv, 1.0 M in CH₂Cl₂) was added to a solution of an aldehyde (1.0 M in CH₂Cl₂ based on aldehyde), chiral catalyst (0.05 equiv or 0.1 equiv), SiCl₄ (1.1 equiv), diisopropylethylamine (0.1 equiv) at −74 °C over the indicated time via a syringe pump. After being stirred for the indicated time, the reaction mixture was transferred dropwise to a vigorously stirred, ice-cold saturated aqueous solution of NaHCO₃ (20 mL). The mixture was stirred for 2 h at room temperature. The white precipitate was filtered off through Celite and the filtrate was extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The catalyst was separated from

the product by silica gel chromatography (EtOAc/hexane). Analytically pure product was obtained after sublimation or recrystallization (benzene/heptane).

***N*-tert-Butyl-2-hydroxy-2-phenylacetamide (**3a**)³**

Following General Procedure I, a mixture of benzaldehyde (104 μL , $d = 1.044$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 195 mg (94%) of **3a** was obtained as a white solid.

Data for ($\pm$)**3a**:

mp: 120–122 $^\circ\text{C}$

SFC: (*R*)-**3a**, t_R 4.68 min (49.9%); (*S*)-**3a**, t_R 5.15 min (50.1%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40 $^\circ\text{C}$, 2.5 mL min^{-1})

HMPA-Catalyzed Addition of *tert*-Butyl Isocyanide to Benzaldehyde

Following General Procedure I, a mixture of benzaldehyde (104 μL , $d = 1.044$, 1.0 mmol), HMPA (18 μL , $d = 1.030$, 0.1 mmol, 0.1 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 187 mg (90%) of **3a** was obtained as a white solid.

Optimization of Asymmetric Addition of *tert*-Butyl Isocyanide Catalyzed by **5a**

A. One-portion addition of *t*-BuNC. A solution of *tert*-butyl isocyanide (63 μ L, $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added in one portion to the cold solution of benzaldehyde (52 μ L, $d = 1.044$, 0.5 mmol), catalyst **5a** (22 mg, 0.025 mmol, 0.05 equiv), and SiCl_4 (63 μ L, $d = 1.483$, 0.55 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL) at -74°C . The mixture was stirred for 4 h at -74°C . After work-up and silica gel chromatography (10 mm column, 15 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 85 mg (83%) of **3a** was obtained as a white solid. The enantiomeric ratio was determined to be 9.8/90.2, (*R*)-**3a**/(*S*)-**3a**.

SFC: (*R*)-**3a**, t_R 4.60 min (9.8%); (*S*)-**3a**, t_R 4.94 min (90.2%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40°C , 2.5 mL min^{-1})

B. Two-hour addition of *t*-BuNC. A solution of *tert*-butyl isocyanide (63 μ L, $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added via a syringe pump to the cold solution of benzaldehyde (52 μ L, $d = 1.044$, 0.5 mmol), catalyst **5a** (22 mg, 0.025 mmol, 0.05 equiv), and SiCl_4 (63 μ L, $d = 1.483$, 0.55 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL) at -74°C over 2 h. The mixture was stirred further for 90 min at -74°C . After work-up and silica gel chromatography (10mm column, 15 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 97 mg (94%) of **3a** was obtained as a white solid. The enantiomeric ratio was determined to be 5.7/94.3, (*R*)-**3a**/(*S*)-**3a**.

SFC: (*R*)-**3a**, t_R 4.64 min (5.7%); (*S*)-**3a**, t_R 4.97 min (94.3%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40°C , 2.5 mL min^{-1})

C. With 30 mol% *i*-Pr₂NEt. A solution of *tert*-butyl isocyanide (63 μ L, $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added via a syringe pump to the cold solution of benzaldehyde (52 μ L, $d = 1.044$, 0.5 mmol), catalyst **5a** (22 mg, 0.025 mmol, 0.05 equiv), SiCl_4

(63 μL , $d = 1.483$, 0.55 mmol, 1.1 equiv), and diisopropylethylamine (27 μL , $d = 0.742$, 0.15 mmol, 0.3 equiv) in CH_2Cl_2 (0.5 mL) at -74°C over 3 h. The mixture was stirred further for 90 min at -74°C . After work-up and silica gel chromatography (10 mm column, 15 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 92 mg (89%) of **3a** was obtained as a white solid. The enantiomeric ratio was determined to be 1.9/98.1, (*R*)-**3a**/(*S*)-**3a**.

SFC: (*R*)-**3a**, t_R 4.67 min (1.9%); (*S*)-**3a**, t_R 5.03 min (98.1%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40°C , 2.5 mL min^{-1})

D. Optimized conditions. A solution of *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to the cold solution of benzaldehyde (104 μL , $d = 1.044$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.5 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL , $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at -74°C over 4 h. The mixture was stirred for 90 min at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 199 mg (96%) of **3a** was obtained as a white solid. The enantiomeric ratio was determined to be 0.1/99.9, (*R*)-**3a**/(*S*)-**3a**. The absolute configuration was deduced to be *S* according to the sign of optical rotation.^{3a}

Data for (*S*)-(+)-**3a**:

mp: $83\text{--}84^\circ\text{C}$ (benzene)

^1H NMR: (400 MHz, CDCl_3)

7.32–7.38 (m, 5 H, aryl); 5.80 (bs, 1 H, NH); 4.89 (s, 1 H, HC(2)); 4.89 (bs, 1 H, OH); 1.32 (s, 9 H, 3 X $\text{H}_3\text{C}(2'')$)

SFC: (*R*)-**3a**, t_R 4.64 min (0.1%); (*S*)-**3a**, t_R 4.93 min (99.9%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40°C , 2.5 mL min^{-1})

Opt. Rot.: $[\alpha]_D^{24} +28.8$ ($c = 0.54$, MeOH)

Analysis: $\text{C}_{12}\text{H}_{17}\text{NO}_2$ (207.27)

Calcd: C, 69.54; H, 8.27; N, 6.76%

Found: C, 69.47; H, 8.35; N, 6.97%

Catalyst Survey for the Asymmetric Addition of *tert*-Butyl Isocyanide to Benzaldehyde

Following General Procedure II, a solution of *tert*-butyl isocyanide (63 μ L, $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added to the cold solution of benzaldehyde (52 μ L, $d = 1.044$, 0.5 mmol), catalyst **5b** (21 mg, 0.025 mmol, 0.05 equiv), SiCl_4 (63 μ L, $d = 1.483$, 0.55 mmol, 1.1 equiv), and diisopropylethylamine (9 μ L, $d = 0.742$, 0.05 mmol, 0.1 equiv) in CH_2Cl_2 (0.5 mL) at -74°C over 3 h. The mixture was further stirred for 90 min at -74°C . After work-up and silica gel chromatography (10 mm column, 15 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 97 mg (93%) of **3a** was obtained as a white solid. The enantiomeric ratio was determined to be 3.6/96.4, (*R*)-**3a**/(*S*)-**3a**.

SFC: (*R*)-**3a**, t_R 4.56 min (3.6%); (*S*)-**3a**, t_R 4.86 min (96.4%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40°C , 2.5 mL min^{-1})

Following General Procedure II, a solution of *tert*-butyl isocyanide (63 μ L, $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added to the cold solution of benzaldehyde (52 μ L, $d = 1.044$, 0.5 mmol), catalyst **5c** (22 mg, 0.025 mmol, 0.05 equiv), SiCl_4 (63 μ L, $d = 1.483$, 0.55 mmol, 1.1 equiv), and diisopropylethylamine (9 μ L, $d = 0.742$, 0.05 mmol, 0.1 equiv) in CH_2Cl_2 (0.5 mL) at -74°C over 3 h. The mixture was stirred for 90 min further at -74°C . After work-up and silica gel chromatography (10 mm column, 15 g SiO_2 , R_f 0.22, EtOAc/hexane, 3/1), 89 mg (86%) of **3a** was obtained as a white solid. The enantiomeric ratio was determined to be 4.4/95.6, (*R*)-**3a**/(*S*)-**3a**.

SFC: (*R*)-**3a**, t_R 4.63 min (4.4%); (*S*)-**3a**, t_R 4.94 min (95.6%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40°C , 2.5 mL min^{-1})

***N*-tert-Butyl-2-hydroxy-2-(4-methylphenyl)acetamide (3b)**

Following General Procedure I, a mixture of 4-tolualdehyde **2b** (118 μL , $d = 1.019$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.20, EtOAc/hexane, 3/1), 188 mg (87%) of **3b** was obtained as a white solid. White needle-like crystals of **3b** (150 mg, 69%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for (±)-3b:

mp: 119.5-120 $^\circ\text{C}$ (benzene/heptane)

^1H NMR: (400 MHz, CDCl_3)

7.16-7.24 (m, 4 H, aryl); 5.50 (bs, 1 H, NH); 4.86 (d, $J = 3.4$, 1 H, HC(2)); 3.60 (d, $J = 3.4$, 1 H, OH); 2.35 (s, 3 H, $\text{H}_3\text{C}(5')$); 1.32 (s, 9 H, 3 X $\text{H}_3\text{C}(2'')$)

^{13}C NMR: (100 MHz, CDCl_3)

171.39 (C(1)), 138.35 (C(1')), 136.92 (C(4')), 129.57 (C(3')), 126.79 (C(2')), 73.98 (C(2)), 54.49 (C(1'')), 28.62 (C(2'')), 21.19 (C(5'))

IR: (CHCl_3)

3612 (m), 3413 (s), 3008 (s), 2977 (s), 2929 (m), 2873 (w), 1675 (s), 1614 (s), 1523 (s), 1481 (m), 1392 (m), 1367 (m), 2929 (m), 1265 (s), 1232 (w), 1076 (w)

TLC: R_f 0.20 (EtOAc/hexane, 3/1)

SFC: (*R*)-**3b**, t_R 5.28 min (49.3%); (*S*)-**3b**, t_R 5.89 min (50.7%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, 40 $^\circ\text{C}$, 3.0 mL min^{-1})

MS: (FI, 70 eV)

221 (100), 222 (15)

Analysis: C₁₃H₁₉NO₂ (221.30)

Calcd: C, 70.56; H, 8.65; N, 6.33%

Found: C, 70.58; H, 8.78; N, 6.44%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μ L, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of 4-tolualdehyde **2b** (118 μ L, *d* = 1.019, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 μ L, *d* = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, *d* = 0.742, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 4 h. The mixture was stirred for 4 h further at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.20, EtOAc/hexane, 3/1), 210 mg (91%) of **3b** was obtained as a white solid. An analytically pure sample was obtained after sublimation (75 °C/0.5 mm Hg).

Data for (+)-**3b**:

mp: 77-79 °C

SFC: (*R*)-**3b**, *t_R* 5.28 min (0%); (*S*)-**3b**, *t_R* 5.89 min (100%) (Chiracel AD, 4.5% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Opt. Rot.: [α]_D²⁴ +28.5 (*c* = 0.735, MeOH)

Analysis: C₁₃H₁₉NO₂ (221.30)

Calcd: C, 70.56; H, 8.65; N, 6.33%

Found: C, 70.58; H, 8.78; N, 6.44%

N-*tert*-Butyl-2-hydroxy-2-(4-methoxyphenyl)acetamide (**3c**)

Following General Procedure I, a mixture of 4-methoxybenzaldehyde **2c** (136 mg, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl₄ (125 μ L, *d* = 1.483, 1.1 mmol, 1.1

equiv), and *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.22, EtOAc/hexane, 65/35), 218 mg (92%) of **3c** was obtained as a white solid. White plate-like crystals of **3c** (171 mg, 70%) were obtained after recrystallization from a 3/7 mixture of benzene and heptane.

Data for ($\pm$)-**3c**:

mp: $96\text{--}97^\circ\text{C}$ (benzene/heptane)

^1H NMR: (400 MHz, CDCl_3)

6.89–7.23 (m, 4 H, Aryl); 5.75 (bs, 1 H, NH); 4.85 (d, $J = 3.4$, 1 H, HC(2)); 3.81 (s, 3 H, H_3C (5')); 3.59 (d, $J = 3.7$, 1 H, OH); 1.32 (s, 9 H, 3 $\times$ H_3C (2'))

^{13}C NMR: (100 MHz, CDCl_3)

171.53 (C(1)), 159.71 (C(4')), 132.07 (C(1')), 128.21 (C(2')), 114.24 (C(3')), 73.71 (C(2)), 55.26 (C(1'')), 51.40 (C(5')), 28.62 (C(2''))

IR: (CHCl_3)

3606 (m), 3411 (s), 3008 (s), 2969 (s), 2937 (s), 2910 (s), 2873 (m), 2838 (m), 1672 (s), 1612 (s), 1587 (w), 1511 (s), 1457 (s), 1394 (s), 1367 (s), 1303 (m), 1249 (s), 1197 (s), 1035 (s), 948 (s), 906 (w), 862 (w)

TLC: R_f 0.22 (EtOAc/hexane, 65/35)

SFC: (*R*)-**3c**, t_R 2.99 min (49.9%); (*S*)-**3c**, t_R 3.43 min (50.1%) (Chiracel AD, 8.0% MeOH in CO_2 , 125 bar, 40°C , 3.0 mL min^{-1})

MS: (FI, 70 eV)

237 (100), 238 (15)

Analysis: $\text{C}_{13}\text{H}_{19}\text{NO}_3$ (237.29)

Calcd: C, 65.80; H, 8.07; N, 5.90%

Found: C, 65.61; H, 8.12; N, 6.03%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to a cold solution of 4-methoxybenzaldehyde **2c** (136 mg, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl_4

(125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL , 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at -74°C over 4 h. The mixture was stirred for 4 h further at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.22, EtOAc/hexane, 65/35), 211 mg (89%) of **3c** was obtained as a white solid. An analytically pure sample was obtained after sublimation ($100^\circ\text{C}/0.5$ mm Hg).

Data for (+)-3c:

mp: 103-104 $^\circ\text{C}$

SFC: (*R*)-**3c**, t_R 3.00 min (1.7%); (*S*)-**3c**, t_R 3.44 min (98.3%) (Chiracel AD, 8.0% MeOH in CO_2 , 125 bar, 40°C , 3.0 mL min^{-1})

Opt. Rot.: $[\alpha]_D^{24} +30.9$ ($c = 0.755$, MeOH)

Analysis: $\text{C}_{13}\text{H}_{19}\text{NO}_3$ (237.29)

Calcd: C, 65.80; H, 8.07; N, 5.90%

Found: C, 65.47; H, 8.14; N, 6.09%

***N*-tert-Butyl-2-hydroxy-2-(4-trifluoromethylphenyl)acetamide (3d)**

Following General Procedure I, a mixture of 4-(trifluoromethyl)benzaldehyde **2d** (137 μL , $d = 1.275$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.11, EtOAc/hexane, 3/1), 235 mg (87%) of **3d** was obtained as a white solid. White crystals of **3d** (180 mg, 65%) were obtained after recrystallization from a 1/4 mixture of benzene and heptane.

Data for (±)-**3d**:

mp: 135-136 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

7.58 (AB quartet, *J* = 8.6, 4 H, Aryl); 5.93 (bs, 1 H, NH); 4.97 (d, *J* = 3.9, 1 H, HC(2)); 3.59 (d, *J* = 3.9, 1 H, OH); 1.32 (s, 9 H, 3 X H₃C(2''))

¹⁹F NMR: (376 MHz, CDCl₃)

-62.77

¹³C NMR: (100 MHz, CDCl₃)

170.34 (C(1)), 143.70 (C(1')), 130.52 (q, *J* = 32.8, C(4')), 126.95 (C(2')), 125.66 (q, *J* = 3.8, C(3')), 123.95 (q, *J* = 271.6, (C(5')), 73.59 (C(2)), 51.56 (C(1'')), 28.57 (C(2''))

IR: (CHCl₃)

3612 (m), 3411 (s), 2998 (m), 2971 (m), 2935 (m), 2908 (m), 2873 (m), 1679 (s), 1672 (s), 1619 (m), 1523 (s), 1456 (m), 1419 (m), 1394 (m), 1367 (s), 1326 (s), 1276 (m), 1213 (m), 1168 (s), 1132 (s), 1068 (s), 1018 (m), 842 (w)

TLC: *R_f* 0.11 (EtOAc/hexane, 3/1)

SFC: (*R*)-**3d**, *t_R* 2.54 min (50.0%); (*S*)-**3d**, *t_R* 3.52 min (50.0%) (Chiracel AD, 4.5% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

MS: (EI, 70 eV)

277 (2), 276 (14), 275 (47), 176 (3), 175 (46), 101 (6), 100 (100)

Analysis: C₁₃H₁₆F₃NO₂ (275.27)

Calcd: C, 56.72; H, 5.86; N, 5.09%

Found: C, 56.86; H, 6.11; N, 5.19%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μL, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to the cold solution of 4-(trifluoromethyl)benzaldehyde **2d** (137 μL, *d* = 1.275, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 μL, *d* = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL, *d* = 0.742, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 4 h. The mixture

was stirred further for 4 h at $-74\text{ }^{\circ}\text{C}$. After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.11, EtOAc/hexane, 3/1), 245 mg (89%) of **3d** was obtained as a white solid. An analytically pure sample was obtained after sublimation ($80\text{ }^{\circ}\text{C}/0.5\text{ mm Hg}$).

Data for (+)-**3d**:

mp: $87\text{--}88\text{ }^{\circ}\text{C}$

SFC: (*R*)-**3d**, t_R 2.12 min (3.5%); (*S*)-**3d**, t_R 3.02 min (96.5%) (Chiracel AD, 4.5% MeOH in CO_2 , 125 bar, $40\text{ }^{\circ}\text{C}$, 3.0 mL min^{-1})

Opt. Rot.: $[\alpha]_D^{24} +18.5$ ($c = 0.625$, MeOH)

Analysis: $\text{C}_{13}\text{H}_{16}\text{F}_3\text{NO}_2$ (275.27)

Calcd: C, 56.72; H, 5.86; N, 5.09%

Found: C, 56.62; H, 5.78; N, 5.13%

***N*-tert-Butyl-2-hydroxy-2-(2-naphthyl)acetamide (3e)**

Following General Procedure I, a mixture of 2-naphthaldehyde **2e** (156 mg, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was stirred for 4 h at $-74\text{ }^{\circ}\text{C}$. After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.17, EtOAc/hexane, 3/1), 230 mg (90%) of **3e** was obtained as a white solid. White crystals of **3e** (204 mg, 80%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for ($\pm$)-**3e**:

mp: $118\text{--}119\text{ }^{\circ}\text{C}$ (benzene/heptane)

^1H NMR: (400 MHz, CDCl_3)

7.45–7.87 (m, 7 H, aryl); 5.72 (bs, 1 H, NH); 5.06 (d, $J = 3.7$, 1 H, HC(2)); 3.88 (d, $J = 3.4$, 1 H, OH); 1.31 (s, 9 H, 3 X $\text{H}_3\text{C}(2'')$)

¹³C NMR: (100 MHz, CDCl₃)

171.15 (C(1)), 137.21 (C(2')), 133.35 (C(9') or C(10')), 133.2 (C(9') or C(10')), 129.01 (C(8')), 128.03 (C(3')), 127.76 (C(4')), 126.50 (C(5')), 126.40 ((C(1') or C(6')), 126.34 (C(6') or C(1')), 124.01 (C(7')), 74.23 (C(2)), 51.63 (C(1'')), 28.62 (C(2''))

IR: (CHCl₃)

3612 (m), 3413 (m), 3010 (m), 2973 (m), 1677 (s), 1602 (s), 1523 (s), 1425 (w), 1394 (w), 1367 (m), 1278 (w), 1267 (m), 1234 (w), 1170 (w), 1124 (w), 1079 (m), 877 (w)

TLC: *R_f* 0.17 (EtOAc/hexane, 3/1)

SFC: (*R*)-**3e**, *t_R* 3.71 min (50.3%); (*S*)-**3e**, *t_R* 4.58 min (49.7%) (Chiracel AD, 10.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

MS: (FI, 70 eV)

258 (19), 257 (100)

Analysis: C₁₆H₁₉NO₂ (257.33)

Calcd: C, 74.68; H, 7.44; N, 5.44%

Found: C, 74.65; H, 7.70; N, 5.61%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 µL, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to the cold solution of 2-naphthaldehyde **2e** (156 mg, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 µL, *d* = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 µL, *d* = 0.742, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 4 h. The mixture was stirred for 4 h further at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.17, EtOAc/hexane, 3/1), 242 mg (93%) of **3e** was obtained as a white solid. An analytically pure sample was obtained after sublimation (90 °C/0.5 mm Hg).

Data for (+)-3e:

mp: 94-96 °C

SFC: (*R*)-**3e**, t_R 3.73 min (0.3%); (*S*)-**3e**, t_R 4.58 min (99.7%) (Chiracel AD, 10% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Opt. Rot.: $[\alpha]_D^{24} +44.9$ ($c = 0.96$, MeOH)

Analysis: C₁₆H₁₉NO₂ (257.33)

Calcd: C, 74.68; H, 7.44; N, 5.44%

Found: C, 74.60; H, 7.54; N, 5.66%

***N*-tert-Butyl-2-hydroxy-2-(1-naphthyl)acetamide (3f)**

Following General Procedure I, a mixture of 1-naphthaldehyde **2f** (136 μ L, $d = 1.150$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (2.0 mL) was stirred for 8 h at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.26, EtOAc/hexane, 7/3), 223 mg (87%) of **3f** was obtained as a white solid. White crystals of **3f** (183 mg, 71%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for ($\pm$)-**3f**:

mp: 133-133.5 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

8.09-8.12 (m, 1 H, H(C(4'))); 7.84-7.89 (m, 2 H, H(C(2')) and H(C(3'))); 7.44-7.53 (m, 4 H, Aryl); 5.72 (bs, 1 H, NH); 5.46 (d, $J = 3.7$, 1 H, HC(2)); 3.96 (d, $J = 3.4$, 1 H, OH); 1.27 (s, 9 H, 3 X H₃C(2''))

¹³C NMR: (100 MHz, CDCl₃)

171.78 (C(1)), 134.95 (C(1')), 134.23 (C(10')), 131.06 (C(9')), 129.57 (C(5')),

128.81 (C(4')), 127.00 (C(7')), 126.62 (C(6')), 126.00 (C(3')), 125.20 (C(2')), 123.89 (C(8')), 73.03 (C(2)), 51.62 (C(1')), 28.48 ((C(2'))

IR: (CHCl₃)

3602 (w), 3413 (s), 3052 (w), 3010 (s), 2971 (s), 2935 (m), 1675 (s), 1598 (s), 1521 (s), 1456 (m), 1394 (m), 1367 (m), 1265 (m), 1234 (w), 1169 (w), 1101 (m), 1064 (m), 1020 (w), 944 (w)

TLC: *R_f* 0.26 (EtOAc/hexane, 7/3)

HPLC: (*S*)-**3f**, *t_R* 6.57 min (49.6%); (*R*)-**3f**, *t_R* 13.82 min (50.4%) (Rexchrom (*S,S*) BETA-GEM 1, hexane/isopropanol, 7/3, 1.0 mL min⁻¹).

MS: (FI, 70 eV)

258 (18), 257 (100)

Analysis: C₁₆H₁₉NO₂ (257.33)

Calcd: C, 74.68; H, 7.44; N, 5.44%

Found: C, 74.52; H, 7.35; N, 5.61%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μL, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of 1-naphthaldehyde **2f** (136 μL, *d* = 1.150, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 μL, *d* = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 4 h. The mixture was stirred for 8 h further at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.26, EtOAc/hexane, 7/3), 236 mg (92%) of **3f** was obtained as a white solid. An analytically pure sample was obtained after sublimation (110° C/0.5 mm Hg).

Data for (+)-**3f**:

mp: 113-116 °C

HPLC: (*S*)-**3f**, *t_R* 6.64 min (92.2%); (*R*)-**3f**, *t_R* 14.05 min (7.8%) (Rexchrom (*S,S*) BETA-GEM 1, hexane/isopropanol, 7/3, 1.0 mL min⁻¹)

Opt. Rot.: [α]_D²⁴ +40.8 (*c* = 0.66, MeOH)

Analysis: C₁₆H₁₉NO₂ (257.33)

Calcd: C, 74.68; H, 7.44; N, 5.44%

Found: C, 74.60; H, 7.54; N, 5.66%

***N*-tert-Butyl-2-hydroxy-2-(2-furyl)acetamide (3g)**

Following General Procedure I, a mixture of 2-furaldehyde **2g** (83 μ L, $d = 1.160$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ was stirred for 4 h at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.29, EtOAc/hexane, 2/1), 147 mg (76%) of **3g** was obtained as a white solid. White crystals of **3g** (124 mg, 63%) were obtained after recrystallization from a 1/4 mixture of benzene and heptane.

Data for ($\pm$)-**3g**:

mp: 83-84 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

7.41 (m, 1 H, HC(5'')); 6.39 (t, $J = 3.4$, 1 H, HC(4'')); 6.37 (dd, $J = 3.4$, 1.7, 1 H HC(3'')); 5.88 (bs, 1 H, NH); 4.99 (bs, 1 H, HC(2'')); 3.68 (d, $J = 3.7$, 1 H, OH); 1.36 (s, 9 H, 3 X H₃C(2''))

¹³C NMR: (100 MHz, CDCl₃)

168.59 (C(1'')), 152.10 (C(2'')), 142.92 (C(5'')), 110.62 (C(4'')), 108.27 (C(3'')), 67.64 (C(2'')), 51.80 (C(1'')), 28.64 (C(2''))

IR: (CHCl₃)

3683 (m), 3604 (w), 3415 (m), 3020 (s), 2979 (m), 2935 (w), 2873 (w), 1681 (s), 1581 (w), 1525 (s), 1477 (m), 1456 (m), 1423 (m), 1367 (m), 1216 (s), 1149 (m), 1068 (w), 1012 (m), 929 (m)

TLC: R_f 0.29 (EtOAc/hexane, 2/1)

GC: (S)-**3g**, t_R 42.17 min (49.5%); (R)-**3g** t_R 42.82 min (50.5%) (Chiraldex BPH, 114 °C, 20 psi)

MS: (EI, 70 eV)
198 (15), 197 (100)

Analysis: $C_{10}H_{15}NO_3$ (197.23)

Calcd: C, 60.90; H, 7.67; N, 7.10%

Found: C, 60.70; H, 7.72; N, 7.10%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to a cold solution of 2-furaldehyde **2g** (83 μ L, $d = 1.160$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), $SiCl_4$ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at -74 °C over 4 h. The mixture was stirred for 4 h further at -74 °C. After work-up and silica gel chromatography (20mm column, 60 g SiO_2 , R_f 0.29, EtOAc/hexane, 2/1), 163 mg (83%) of **3g** was obtained as a white solid. An analytically pure sample was obtained after sublimation (100 °C/0.5 mm Hg).

Data for (+)-**3g**:

mp: 103-104.5 °C

GC: (S)-**3g**, t_R 42.69 min (95.9%); (R)-**3g**, t_R 43.28 min (4.1%) (Chiraldex BPH, 114 °C, 20 psi)

Opt. Rot.: $[\alpha]_D^{24} +15.5$ ($c = 0.53$, MeOH)

Analysis: $C_{10}H_{15}NO_3$ (197.23)

Calcd: C, 60.90; H, 7.67; N, 7.10%

Found: C, 60.77; H, 7.64; N, 7.12%

***N*-tert-Butyl-2-hydroxy-4-phenyl-3-butenamide (3h)**

Following General Procedure I, a mixture of (*E*)-cinnamaldehyde **2h** (126 μL , $d = 1.048$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.26, EtOAc/hexane, 2/1), 170 mg (73%) of **3h** was obtained as an off-white solid. White crystals of **3h** (132 mg, 57%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for ($\pm$)-3h**:**

mp: 93-94 $^\circ\text{C}$ (benzene/heptane)

^1H NMR: (400 MHz, CDCl_3)

7.27-7.42 (m, 5 H, aryl); 6.74 (d, $J = 15.9$, 1 H, HC(4)); 6.25 (dd, $J = 15.8$, 3.0, 1 H, HC(3)); 5.95 (bs, 1 H, NH); 4.58 (d, $J = 6.8$, 1 H, HC(2)); 3.41 (bs, 1 H, OH); 1.37 (s, 9 H, 3 X $\text{H}_3\text{C}(2'')$)

^{13}C NMR: (100 MHz, CDCl_3)

170.89 (C(1)), 135.96 (C(1')), 133.28 (C(4)), 128.60 (C(3')), 128.11 (C(3)), 127.16 (C(4')), 126.71 (C(2')), 72.97 (C(2)), 51.49 (C(1'')), 28.70 (C(2''))

IR: (CHCl_3)

3614 (m), 3413 (m), 3006 (m), 2973 (m), 2935 (m), 1678 (s), 1521 (s), 1456 (m), 1394 (w), 1367 (m), 1276 (w), 1236 (w), 1216 (w), 1108 (m), 1072 (w), 968 (m)

TLC: R_f 0.26 (EtOAc/hexane, 2/1)

SFC: (*S*)-**3h**, t_R 2.35 min (50.2%); (*R*)-**3h**, t_R 2.77 min (49.8%) (Chiracel AD, 10.0% MeOH in CO_2 , 125 bar, 40 $^\circ\text{C}$, 3.0 mL min $^{-1}$)

MS: (FI, 70 eV)

234 (16), 233 (100), 232 (3), 231 (16), 207 (3), 148 (2)

Analysis: C₁₄H₁₉NO₂ (233.31)

Calcd: C, 72.07; H, 8.21; N, 6.00%

Found: C, 71.91; H, 8.23; N, 6.06%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μ L, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of *trans*-cinnamaldehyde **2h** (126 μ L, *d* = 1.048, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 μ L, *d* = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, *d* = 0.742, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 4 h. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.26, EtOAc/hexane, 2/1), 188 mg (81%) of **3h** was obtained as a white solid. An analytically pure sample was obtained after sublimation (70 °C/0.5 mm Hg).

Data for (-)-**3h**:

mp: 71-74 °C

SFC: (*R*)-**3h**, *t_R* 2.35 min (2.2%); (*S*)-**3h**, *t_R* 2.77 min (97.8%) (Chiracel AD, 10.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Opt. Rot.: [α]_D²⁴ -7.2 (*c* = 1.055, MeOH)

Analysis: C₁₄H₁₉NO₂ (233.31)

Calcd: C, 72.07; H, 8.21; N, 6.00%

Found: C, 71.75; H, 8.13; N, 6.04%

N-*tert*-Butyl-2-hydroxy-3-methyl-4-phenyl-3-butenamide (**3i**)

Following General Procedure I, a mixture of (*E*)-2-methylcinnamaldehyde **2i** (140 μ L, *d* = 1.047, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl₄ (125 μ L, *d* = 1.483, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μ L, *d* = 0.735, 1.2 mmol, 1.2 equiv) in

CH₂Cl₂ (2.0 mL) was stirred for 4 h at –74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.28, EtOAc/hexane, 3/1), 211 mg (86%) of **3i** was obtained as a white solid. White crystals of **3i** (185 mg, 75%) were obtained after recrystallization from a 1/4 mixture of benzene and heptane.

Data for (±)-**3i**:

mp: 125.5-126.0 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

7.25-7.41 (m, 5 H, aryl); 6.62 (s, 1 H, HC(4)); 5.78 (bs, 1 H, NH); 4.48 (d, *J* = 3.4, 1 H, HC(2)); 3.89 (d, *J* = 3.2, 1 H, OH); 1.83 (s, 3 H, H₃C(5')); 1.39 (s, 9 H, 3 X H₃C(2''))

¹³C NMR: (100 MHz, CDCl₃)

170.90 (C(1)), 137.17 (C(1') or C(3)), 136.61 (C(1') or C(3)), 130.58 (C(4)), 128.93 (C(3')), 128.29 (C(2')), 127.11 ((C(4')), 77.80 (C(2)), 51.64 (C(1'')), 28.65 (C(2'')), 12.23 (C(5''))

IR: (CHCl₃)

3411 (s), 3010 (s), 2971 (s), 2935 (m), 2912 (m), 2873 (m), 1678 (s), 1523 (s), 1492 (m), 1456 (s), 1393 (s), 1367 (s), 1274 (s), 1232 (s), 1178 (m), 1083 (s), 1016 (s), 950 (m), 919 (m)

TLC: *R_f* 0.28 (EtOAc/hexane, 3/1)

SFC: (*S*)-**3i**, *t_R* 7.24 min (49.8%); (*R*)-**3i**, *t_R* 7.95 min (50.2%) (Chiracel AD, 4.5% MeOH in CO₂, 125 bar, 40 °C, 2.5 mL min⁻¹).

MS: (FI, 70 eV)

248 (15), 247 (100)

Analysis: C₁₅H₂₁NO₂ (247.33)

Calcd: C, 72.84; H, 8.56; N, 5.66%

Found: C, 72.83; H, 8.67; N, 5.88%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μL, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to the cold solution of (*E*)-2-methylcinnamaldehyde **2i** (140 μL, *d* = 1.047, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol,

0.05 equiv), SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at $-74\text{ }^{\circ}\text{C}$ over 4 h. The mixture was stirred for 4 h further at $-74\text{ }^{\circ}\text{C}$. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.28, EtOAc/hexane, 3/1), 212 mg (86%) of **3i** was obtained as a white solid. The enantiomeric ratio was determined to be 67.4/32.6, (*S*)-**3i**/(*R*)-**3i**. Analytically pure sample (165 mg, 67%), which has an enantiomeric ratio of 59.4/40.6, (*S*)-**3i**/(*R*)-**3i**, was obtained after recrystallization from a 1/4 mixture of benzene and heptane.

Data for (–)-**3i**:

mp: 112–113 $^{\circ}\text{C}$ (benzene/heptane)

SFC: (*S*)-**3i**, t_R 7.27 min (67.4%); (*R*)-**3i**, t_R 7.97 min (32.6%) (Chiracel AD, 4.5% MeOH in CO₂, 125 bar, 40 $^{\circ}\text{C}$, 2.5 mL min^{–1}) (before recrystallization)

SFC: (*S*)-**3i**, t_R 7.22 min (59.4%); (*R*)-**3i**, t_R 7.93 min (40.6%) (Chiracel AD, 4.5% MeOH in CO₂, 125 bar, 40 $^{\circ}\text{C}$, 2.5 mL min^{–1}) (after recrystallization)

Opt. Rot.: $[\alpha]_D^{24} -4.1$ ($c = 3.815$, EtOH/conc. HCl, 95/5)

Analysis: C₁₅H₂₁NO₂ (247.33)

Calcd: C, 72.84; H, 8.56; N, 5.66%

Found: C, 72.80; H, 8.61; N, 5.80%

***N*-tert-Butyl-2-hydroxy-4-phenyl-3-butyramide (3j)**

Following General Procedure I, a mixture of phenylpropargyl aldehyde **2j** (125 μ L, $d = 1.047$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (2.0 mL) was stirred for 4 h at $-74\text{ }^{\circ}\text{C}$. The mixture was poured into an ice-cold saturated aqueous solution of KF (20 mL) with vigorous stirring. The mixture was stirred at rt for 1 h and

then was extracted with CH₂Cl₂ (4 X 10 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The product **3j** (197 mg, 85%) was obtained as a pale yellow solid after silica gel column chromatography (20 mm column, 60 g SiO₂, *R_f* 0.26, EtOAc/hexane, 3/1). White crystals of **3j** (153 mg, 66%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for (±)-**3j**:

mp: 127-128 °C (benzene/heptane)

SFC: (S)-**3j**, *t_R* 4.96 min (50.0%); (S)-**3j**, *t_R* 5.58 min (50.0%) (Chiracel AD, 5.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 µL, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of phenylpropargyl aldehyde **2j** (125 µL, *d* = 1.047, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), and SiCl₄ (125 µL, *d* = 1.483, 1.1 mmol, 1.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 4 h. The mixture was stirred further for 4 h at -74 °C and then poured into an ice cold saturated aqueous solution of KF (20 mL) with vigorous stirring. The mixture was stirred at rt for 1 h and then was extracted by CH₂Cl₂ (4 X 10 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. After silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.26, EtOAc/hexane, 3/1), 177 mg (76%) of **3j** was obtained as a pale yellow solid. An analytically pure sample was obtained after sublimation (90 °C/0.5 mm Hg).

Data for (+)-**3j**:

mp: 94-96 °C

¹H NMR: (400 MHz, CDCl₃)

7.32-7.47 (m, 5 H, aryl); 6.12 (bs, 1 H, NH); 4.89 (d, *J* = 2.9, 1 H, HC(2)); 3.60 (bs, 1 H, OH); 1.41 (s, 9 H, 3 X H₃C(2''))

¹³C NMR: (100 MHz, CDCl₃)

167.99 (C(1)), 131.85 (C(2')), 128.84 (C(4')), 128.27 (C(3')), 121.80 (C(1')), 85.87 (C(3) or C(4)), 85.46 (C(3) or C(4)), 62.90 (C(2)), 51.83 (C(1'')), 28.55 (C(2''))

IR: (CHCl₃)

3602 (m), 3411 (s), 2973 (m), 2225 (w), 1689 (s), 1523 (s), 1490 (s), 1456 (s),
1394 (s), 1367 (s), 1278 (s), 1232 (m), 1085 (m), 815 (m)

TLC: *R_f* 0.26 (EtOAc/hexane, 3/1)

SFC: (*S*)-**3j**, *t_R* 4.99 min (77.0%); (*R*)-**3j**, *t_R* 5.61 min (23.0%) (Chiracel AD, 5.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

MS: (EI, 70 eV)

233 (1), 232 (6), 231 (8), 175 (14), 174 (12), 132 (36), 131 (100), 103 (19)

Opt. Rot.: [α]_D²⁴ +10.0 (*c* = 1.765, EtOH/conc. HCl, 95/5)

Analysis: C₁₄H₁₇NO₂ (231.29)

Calcd: C, 72.70; H, 7.41; N, 6.06%

Found: C, 72.63; H, 7.42; N, 5.92%

N-*tert*-Butyl-2-hydroxy-4-phenylbutamide (**3k**)

Following General Procedure I, a solution of *tert*-butyl isocyanide (125 μ L, *d* = 0.735, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of hydrocinnamaldehyde **2k** (132 μ L, *d* = 1.019, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and SiCl₄ (125 μ L, *d* = 1.483, 1.1 mmol, 1.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 8 h. The mixture was stirred for 8 h further at -74 °C. After silica gel column chromatography (20 mm column, 60 g SiO₂, *R_f* 0.21, EtOAc/hexane, 3/1), 209 mg (89%) of **3k** was obtained as a white solid. White crystals of **3k** (168 mg, 71%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for (±)-3k**:**

mp: 86-87 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

7.20-7.29 (m, 5 H, aryl); 6.20 (bs, 1 H, NH); 3.97-4.02 (m, 1 H, HC(2)); 3.00 (bs, 1 H, OH); 2.75 (t, $J = 7.2$, 2 H, H₂C(4)); 1.89-2.13 (m, 2 H, H₂C(3)); 1.37 (s, 9 H, 3 X H₃C(2''))

¹³C NMR: (100 MHz, CDCl₃)

172.97 (C(1)), 141.35 (C(1')), 128.46 (C(3') and C(4')), 125.99 (C(2')), 71.49 (C(2)), 50.97 (C(1'')), 36.63 (C(4)), 31.19 (C(3)), 28.70 (C(2''))

IR: (CHCl₃)

3619 (m), 3407 (s), 3008 (s), 2969 (s), 2932 (m), 1670 (s), 1525 (s), 1496 (s), 1456 (m), 1367 (s), 1282 (s), 1232 (m), 1174 (m), 1095 (m), 1074 (m), 825 (m)

TLC: R_f 0.21 (EtOAc/hexane, 3/1)

SFC: (*R*)-**3k**, t_R 4.05 min (50.3%); (*S*)-**3k**, t_R 5.28 min (49.7%) (Chiracel AD, 5.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

MS: (FI, 70 eV)

236 (19), 235 (100)

Analysis: C₁₄H₁₉NO₂ (235.32)

Calcd: C, 71.46; H, 8.99; N, 5.95%

Found: C, 71.53; H, 8.96; N, 6.14%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μL, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of hydrocinnamaldehyde **2k** (132 μL, $d = 1.019$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 μL, $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL, $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 8 h. The mixture was stirred further for 8 h at -74 °C. After work-up and silica gel column chromatography (20 mm column, 60 g SiO₂, R_f 0.21, EtOAc/hexane, 3/1), 217 mg (92%) of **3k** was obtained as a white solid. An analytically pure sample (199 mg, 84%) was obtained after sublimation (70 °C/0.5 mmHg).

Data for (-)-3k:

mp: 74-78 °C

SFC: (*R*)-**3k**, t_R 4.09 min (18.1%); (*S*)-**3k**, t_R 5.86 min (81.9%) (Chiracel AD, 5.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Opt. Rot.: $[\alpha]_D^{24} -22.7$ ($c = 1.07$, MeOH)

Analysis: C₁₄H₂₁NO₂ (235.32)

Calcd: C, 71.46; H, 8.99; N, 5.95%

Found: C, 71.45; H, 9.05; N, 6.10%

***N*-tert-butyl-2-hydroxy-2-cyclohexylacetamide⁴ (3l)**

Following General Procedure I, a mixture of cyclohexanecarboxaldehyde **2l** (121 μ L, $d = 0.926$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (2.0 mL) was stirred for 24 h at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.35, EtOAc/hexane, 3/1), 152 mg (72%) of **3l** was obtained as a white solid. White crystals of **3l** (120 mg, 50%) were obtained after recrystallization from a 1/3 mixture of benzene and heptane.

Data for ($\pm$)-3l**:**

mp: 122-123 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

6.24 (bs, 1 H, NH); 3.78 (m, 1 H, HC(2)); 2.95 (bs, 1 H, OH); 1.08-1.78 (m, 11 H, cyclohexyl); 1.36 (s, 9 H, 3 X H₃C(2''))

¹³C NMR: (100 MHz, CDCl₃)

172.35 (C(1)), 76.06 (C(2)), 51.01 (C(1'')), 41.78 (C(1')), 29.58, 28.78 (C(2'')), 26.33, 26.12, 26.00, 25.68

IR: (CHCl₃)

3627 (m), 3405 (s), 3002 (s), 2969 (s), 2931 (s), 2856 (s), 1660 (s), 1527 (s), 1479

(m), 1452 (s), 1394 (m), 1365 (m), 1280 (m), 1232 (m), 1189 (w), 1112 (m), 993 (w)

TLC: R_f 0.35 (EtOAc/hexane, 3/1)

GC: (S)-**3I**, t_R 17.80 min (49.4%); (R)-**3I**, t_R 18.46 min (50.6%) (Chiraldex BPH, 150 °C, 20 psi)

MS: (FI, 70 eV)

215 (4), 214 (23), 213 (3), 213 (100), 212 (2), 81 (3)

Analysis: C₁₂H₂₃NO₂ (213.32)

Calcd: C, 67.57; H, 10.86; N, 6.57%

Found: C, 67.53; H, 11.05; N, 6.76%

Following General Procedure II, a solution of *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to the cold solution of cyclohexanecarboxaldehyde **2I** (121 μ L, $d = 0.926$, 1.0 mmol), catalyst **5a** (85 mg, 0.10 mmol, 0.1 equiv), SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 12 h. The mixture was stirred for 12 h further at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.35, EtOAc/hexane, 3/1), 113 mg (53%) of **3I** was obtained as a white solid. An analytically pure sample was obtained after sublimation (100 °C/0.5 mm Hg).

Data for (–)-**3I**:

mp: 118–120 °C

GC: (S)-**3I**, t_R 17.81 min (87.1%); (R)-**3I**, t_R 18.49 min (12.9%) (Chiraldex BPH, 150 °C, 20 psi)

Opt. Rot.: $[\alpha]_D^{24} -39.2$ ($c = 0.905$, MeOH)

Analysis: C₁₂H₂₃NO₂ (213.32)

Calcd: C, 67.57; H, 10.86; N, 6.57%

Found: C, 67.52; H, 10.86; N, 6.65%

***N*-(1,1,3,3-Tetramethylbutyl)-2-hydroxy-4-phenylbutamide (3m)**

Following General Procedure I, 1,1,3,3-tetramethylbutyl isocyanide **1e** (210 μ L, $d = 0.799$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to a cold solution of hydrocinnamaldehyde **2k** (132 μ L, $d = 1.019$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and SiCl_4 (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv) in CH_2Cl_2 (1.0 mL) at -74°C over 8 h. The mixture was stirred for 8 h further at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.27, EtOAc/hexane, 4/1), 244 mg (84%) of **3m** was obtained as colorless oil. Bulb-to-bulb distillation provided 240 mg (82%) of analytically pure **3m**.

Data for ($\pm$)-3m:

bp: 200°C (0.5 mm Hg)

^1H NMR: (400 MHz, CDCl_3)

7.20-7.31 (m, 5 H, aryl); 6.22 (bs, 1 H, NH); 3.96-4.00 (m, 1 H, HC(2)); 2.60-2.79 (m, 2 H, $\text{H}_2\text{C}(4)$); 2.61 (dd, $J = 5.1$, 1 H, OH); 1.86-2.19 (m, 2 H, $\text{H}_2\text{C}(3)$); 1.73 (s, 2 H, $\text{H}_2\text{C}(2'')$); 1.42 (s, 6 H, 2 X $\text{H}_3\text{C}(5'')$); 1.00 (s, 9 H, 3 X $\text{H}_3\text{C}(4'')$)

^{13}C NMR: (100 MHz, CDCl_3)

172.33 (C(1)), 141.30 (C(1')), 128.48 (C(3') and C(4')), 126.02 (C(2')), 71.66 (C(2)), 54.95 (C(1'')), 52.11 (C(3'')), 36.46 (C(4)), 31.64 (C(3)), 31.48 (C(2'')), 31.41 (C(5'')), 29.00 (C(5'')), 28.92 (C(4''))

IR: (CHCl_3)

3622 (m), 3397 (s), 2992 (s), 2958 (s), 2871 (s), 1658 (s), 1602 (s), 1529 (s), 1496 (s), 1479 (s), 1454 (s), 1388 (m), 1367 (s), 1155 (m), 1095 (m), 827 (m)

TLC: R_f 0.27 (EtOAc/hexane, 4/1)

SFC: (*R*)-**3m**, t_R 1.52 min (50.0%); (*R*)-**3m**, t_R 1.84 min (50.0%) (Chiracel AD, 15.0% MeOH in CO_2 , 125 bar, 40°C , 3.0 mL min^{-1})

MS: (EI, 70 eV)

292 (2), 291 (6), 220 (34), 187 (40), 180 (16), 114 (11), 58 (100)

Analysis: C₁₈H₂₉NO₂ (291.43)

Calcd: C, 74.18; H, 10.03; N, 4.81%

Found: C, 74.44; H, 10.12; N, 5.01%

Following General Procedure II, a solution of 1,1,3,3-tetramethylbutyl isocyanide **1e** (210 μ L, d = 0.799, 1.2 mmol, 1.2 equiv) in CH₂Cl₂ (1.0 mL) was added via a syringe pump to a cold solution of hydrocinnamaldehyde **2k** (132 μ L, d = 1.019, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl₄ (125 μ L, d = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, d = 0.742, 0.1 mmol, 0.1 equiv) in CH₂Cl₂ (1.0 mL) at -74 °C over 8 h. The mixture was stirred for 8 h further at -74 °C. After work-up and silica gel chromatography (20 mm column, 60 g SiO₂, *R_f* 0.27, EtOAc/hexane, 4/1), 252 mg (87%) of **3m** was obtained as colorless oil. Bulb-to-bulb distillation provided 244 mg (84%) of analytically pure **3m** (200 °C/ 0.5 mm Hg).

Data for (-)-3m:

SFC: (*R*)-**3m**, *t_R* 1.56 min (30.0%); (*S*)-**3m**, *t_R* 1.87 min (70.0%) (Chiracel AD, 15.0% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Opt. Rot.: [α]_D²⁴ -12.5 (*c* = 3.1, MeOH)

Analysis: C₁₈H₂₉NO₂ (291.43)

Calcd: C, 74.18; H, 10.03; N, 4.81%

Found: C, 74.00; H, 10.21; N, 4.97%

***N*-Phenyl-2-hydroxy-2-phenylacetamide (**3n**)⁵**

Following General Procedure I, a mixture of phenyl isocyanide **1b** (122 mg, 1.2 mmol), benzaldehyde (104 μL , $d = 1.044$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv) was stirred for 4 h at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.37, EtOAc/hexane, 1/1), 173 mg (76%) of **3n** was obtained as a white solid. An analytically pure sample was obtained after recrystallization from benzene.

Data for ($\pm$)-3n**:**

mp: 148-149 $^\circ\text{C}$ (benzene)

SFC: (*S*)-**3n**, t_R 5.35 min (49.9%); (*R*)-**3n**, t_R 6.49 min (50.7%) (Chiracel AD, 10% MeOH in CO_2 , 125 bar, 40 $^\circ\text{C}$, 3.0 mL min^{-1})

Following General Procedure II, phenyl isocyanide **1b** (122 mg, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to a cold solution of benzaldehyde (104 μL , $d = 1.044$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL , $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at -74°C over 4 h. The mixture was stirred for 4 h further at -74°C . After work-up and silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.37, EtOAc/hexane, 1/1), 186 mg (82%) of **3n** was obtained as a white solid. An analytically pure sample was obtained after sublimation (140 $^\circ\text{C}$ /0.5 mm Hg).

Data for **3n:**

mp: 147-149 $^\circ\text{C}$

^1H NMR: (400 MHz, CDCl_3)

8.12 (bs, 1 H, NH); 7.10-7.53 (m, 10 H, aryl); 5.18 (d, $J = 3.4$, 1 H, HC(2)); 3.41 (d, $J = 3.4$, 1 H, OH)

TLC: R_f 0.37 (EtOAc/hexane, 1/1)

SFC: (*S*)-**3n**, t_R 5.28 min (73.2%); (*R*)-**3n**, t_R 6.43 min (26.8%) (Chiracel AD, 10% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹).

Opt. Rot.: $[\alpha]_D^{24} +2.4$ ($c = 2.43$, EtOH/conc. HCl, 95/5)

Analysis: C₁₄H₁₃NO₂ (227.26)

Calcd: C, 73.99; H, 5.77; N, 6.16%

Found: C, 73.86; H, 5.76; N, 6.20%

(2-Hydroxy-2-phenylacetyl-amido)-acetic acid ethyl ester (3o**)⁵**

Ethyl isocyanoacetate **1c** (135 μL , $d = 1.150$, 1.2 mmol, 1.2 equiv) was added in one portion to a solution of benzaldehyde (104 μL , $d = 1.044$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and SiCl₄ (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv) in CH₂Cl₂ (5.0 mL) at -74 °C. The mixture was stirred at -74 °C for 24 h and then was quenched by pouring into an ice-cold saturated aqueous solution of NaHCO₃ (20 mL) with vigorous stirring. After being stirred for 2 h at rt, the white precipitate was filtered off through Celite and the filtrate was extracted with CH₂Cl₂ (4 X 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. After silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.32, EtOAc/hexane, 1/2), 171 mg (72%) of **3o** was obtained as a white solid. White crystals of **3e** (104 mg, 44%) were obtained after recrystallization from a 1/1 mixture of benzene and heptane.

Data for ($\pm$)-3o**:**

mp: 97-99 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

7.33-7.49 (m, 5 H, aryl); 6.73 (bs, 1 H, NH); 5.11 (s, 1 H, HC(2)); 4.19 (q, $J = 8.1$, 2 H, H₂C(2')); 4.03 (qd, $J = 18.4, 5.7$, 2 H, H₂C(1')); 3.51 (bs, 1 H, OH); 1.26 (t, $J = 7.1$, 3 H, H₃C(3'));

TLC: R_f 0.32 (EtOAc/hexane, 2/1)

SFC: (*R*)-**3o**, t_R 3.87 min (49.9%); (*R*)-**3o**, t_R 4.95 min (50.1%) (Chiracel AD, 15% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹)

Ethyl isocyanoacetate **1c** (135 μ L, $d = 1.15$, 1.2 mmol, 1.2 equiv) was added in one portion to a solution of benzaldehyde (104 μ L, $d = 1.044$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), and SiCl₄ (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv) in CH₂Cl₂ (5.0 mL) at -74 °C. The mixture was stirred at -74 °C for 24 h and then was quenched by pouring into an ice-cold saturated aqueous solution of NaHCO₃ (20 mL) with vigorous stirring. After being stirred for 2 h at rt, the white precipitate was filtered off through Celite and the filtrate was extracted by CH₂Cl₂ (4 X 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The product **3o** (197 mg, 83%) was obtained as an off-white solid after silica gel chromatography (20 mm column, 60 g SiO₂, R_f 0.32, EtOAc/hexane, 2/1). White crystals of **3o** (154 mg, 65%) were obtained after recrystallization from a 1/1 mixture of benzene and heptane.

Data for (+)-**3o**:

mp: 80-82 °C (benzene/heptane)

SFC: (*R*)-**3o**, t_R 3.87 min (16.7%); (*S*)-**3o**, t_R 4.95 min (83.3%) (Chiracel AD, 15% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹) (before recrystallization)

SFC: (*R*)-**3o**, t_R 3.77 min (19.2%); (*S*)-**3o**, t_R 4.85 min (80.8%) (Chiracel AD, 15% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min⁻¹) (after recrystallization)

Opt. Rot.: $[\alpha]_D^{24} +18.6$ ($c = 1.07$, MeOH)

Analysis: C₁₄H₁₃NO₂ (237.25)

Calcd: C, 60.75; H, 6.37; N, 5.90%

Found: C, 60.38; H, 6.33; N, 5.90%

***N*-(Tosylmethyl)-2-hydroxy-4-phenylbutamide (3p)**

Tosylmethyl isocyanide **1d** (235 mg, 1.2 mmol, 1.2 equiv) was added in one portion to a solution of benzaldehyde (104 μ L, $d = 1.044$, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and SiCl_4 (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv) in CH_2Cl_2 (5.0 mL) at -74°C . The mixture was stirred at -74°C for 24 h and then was quenched by pouring into an ice-cold saturated aqueous solution of NaHCO_3 (20 mL) with vigorous stirring. After being stirred for 2 h at rt, the white precipitate was filtered off through Celite and the filtrate was extracted with CH_2Cl_2 (4 X 20 mL). The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. The product **3p** (220 mg, 69%) was obtained as a fluffy white solid after silica gel chromatography (20 mm column, 60 g SiO_2 , R_f 0.36, EtOAc/hexane, 2/1). White crystals of **3p** (190 mg, 60%) were obtained after recrystallization from a 1/1 mixture of benzene and heptane.

Data for ($\pm$)-**3p**:

mp: 118–119 $^\circ\text{C}$ (benzene/heptane)

SFC: (*R*)-**3p**, t_R 4.87 min (49.9%); (*S*)-**3p**, t_R 6.10 min (50.1%) (Chiracel AD, 15% MeOH in CO_2 , 125 bar, 40°C , 3.0 mL min^{-1})

Tosylmethyl isocyanide **1d** (235 mg, 1.2 mmol, 1.2 equiv) was added in one portion to a solution of benzaldehyde (104 μ L, $d = 1.044$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), and SiCl_4 (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv) in CH_2Cl_2 (5.0 mL) at -74°C . The mixture was stirred at -74°C for 24 h and then was quenched by pouring into an ice-cold saturated aqueous solution of NaHCO_3 (20 mL) with vigorous stirring. After being stirred for 2 h at rt, the white precipitate was filtered off through Celite and the filtrate was extracted with CH_2Cl_2 (4 X 20 mL). The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. The product **3p** (255 mg, 80%) was obtained as a white solid after silica gel

chromatography (20 mm column, 60 g SiO₂, *R_f* 0.36, EtOAc/hexane, 2/1). White crystals of **3p** (211 mg, 66%) were obtained after recrystallization from a 1/1 mixture of benzene and heptane.

Data for (–)-**3p**:

mp: 117–119 °C (benzene/heptane)

¹H NMR: (400 MHz, CDCl₃)

7.60 (d, *J* = 8.1, 2 H, HC(2'')); 7.15–7.38 (m, 5 H, aryl); 7.18 (d, *J* = 8.1, 2 H, HC(3'')); 7.15 (bs, 1 H, NH); 5.01 (d, t, *J* = 3.4, 1 H, HC(2)); 4.56–4.77 (m, 2 H, H₂C(1'')); 3.03 (bs, 1 H, OH); 2.39 (s, 3 H, H₃C(5''))

¹³C NMR: (100 MHz, CDCl₃)

171.76 (C(1)), 145.62 (C(1')), 138.53, 138.55, 130.13, 129.09, 129.06, 128.88, 126.79, 74.35 (C(2)), 60.03 (CH₂Tos), 21.95 (Me(C(4'')))

IR: (CHCl₃)

3622 (m), 3397 (s), 2992 (s), 2958 (s), 2871 (s), 1658 (s), 1602 (s), 1529 (s), 1496 (s), 1479 (s), 1454 (s), 1388 (m), 1367 (s), 1155 (m), 1095 (m), 827 (m)

TLC: *R_f* 0.36 (EtOAc/hexane, 2/1)

SFC: (*R*)-**3p**, *t_R* 4.87 min (11.5%); (*S*)-**3p**, *t_R* 6.10 min (88.5%) (Chiracel AD, 15% MeOH in CO₂, 125 bar, 40 °C, 3.0 mL min^{–1})

MS: (FI, 70 eV)

320 (50), 319 (100)

Opt. Rot.: [*α*]_D²⁴ –2.21 (*c* = 0.73, MeOH)

Analysis: C₁₆H₁₇NO₄S (319.38)

Calcd: C, 60.17; H, 5.37; N, 4.39%

Found: C, 59.90; H, 5.27; N, 4.38%

General Procedure III. Conversion of Imidoyl Chlorides to Methyl Esters

A. A solution of *tert*-butyl isocyanide (1.2 equiv, 1.0 M in CH₂Cl₂) was added to a solution of an aldehyde (1.0 M in CH₂Cl₂ based on aldehyde), catalyst **5a** (0.05 equiv), SiCl₄ (1.1 equiv), diisopropylethylamine (0.1 equiv) at -74°C over the indicated time via a syringe pump. After being stirred further for the indicated time, dry MeOH (2.5 mL) was added dropwise to the reaction mixture at -74°C . After being stirred for 40 minutes at -74°C , the mixture was transferred dropwise to a vigorously stirred, ice-cold saturated aqueous solution of NaHCO₃ (20 mL) and was stirred for 2 h further at room temperature. The white precipitate was filtered off over Celite and the filtrate was extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The catalyst was separated from the product by silica gel column chromatography (EtOAc/hexane).

B. A solution of *tert*-butyl isocyanide (1.2 equiv, 1.0 M in CH₂Cl₂) was added to a solution of an aldehyde (1.0 M in CH₂Cl₂ based on aldehyde), pyridine-*N*-oxide (0.1 equiv), SiCl₄ (1.1 equiv) at -74°C over 30 min via a syringe pump. After being stirred further for the indicated time, dry MeOH (2.5 mL) was added dropwise to the reaction mixture at -74°C . After being stirred for 40 minutes at -74°C , the mixture was transferred dropwise to a vigorously stirred, ice-cold saturated aqueous solution of NaHCO₃ (20 mL) and stirred for 2 h further at room temperature. The white precipitate was filtered off over Celite and the filtrate was extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. Pyridine-*N*-oxide was separated from the product by silica gel column chromatography (EtOAc/hexane).

(S)-(+)-Methyl-2-hydroxy-2-phenylacetate (6**)⁶**

Following General Procedure III A, a solution of *tert*-butyl isocyanide (125 μ L, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to the cold solution of benzaldehyde (104 μ L, $d = 1.044$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl_4 (125 μ L, $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μ L, $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at -74°C over 4 h. The mixture was stirred for 4 h at -74°C . Work-up with the methanol quench provided 160 mg (97%) of **6** after silica gel column chromatography (20 mm column, 60 g SiO_2 , R_f 0.31, EtOAc/hexane, 3/1), Bulb-to-bulb distillation provided 158 mg (95%) of **6** as colorless oil, which solidified upon standing. The absolute configuration was deduced to be *S* according to the sign of optical rotation.

Data for (+)-6**:****mp:** 56-58 $^\circ\text{C}$ **bp:** 120 $^\circ\text{C}$ (0.5 mm Hg) **^1H NMR:** (400 MHz, CDCl_3)7.33-7.44 (m, 5 H, aryl); 5.18 (d, $J = 5.3$, 1 H, HC(2)); 3.77 (s, 3 H, OCH_3); 3.42 (d, $J = 4.7$, 1 H, OH)**TLC:** R_f 0.31 (EtOAc/hexane, 3/1)**SFC:** (*S*)-**6**, t_R 3.97 min (99.9%); (*R*)-**6**, t_R 4.31 min (0.1%) (Chiracel AS, 1.4% MeOH in CO_2 , 125 bar, 40 $^\circ\text{C}$, 2.5 mL min^{-1})**Opt. Rot.:** $[\alpha]_D^{24} +143.2$ ($c = 0.57$, MeOH)

Following General Procedure III B, a solution of *tert*-butyl isocyanide (63 μ L, $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added via a syringe pump to the cold solution of benzaldehyde (52 μ L, $d = 1.044$, 0.5 mmol), pyridine-*N*-oxide (4.7 mg, 0.05 mmol, 0.1 equiv), SiCl_4 (63 μ L, $d = 1.483$, 0.55 mmol, 1.1 equiv) at -74°C over 30 min via a syringe pump. The

mixture was stirred for 4 h at $-74\text{ }^{\circ}\text{C}$. Work-up following the methanol quench provided 69 mg (83%) of **6** after silica gel column chromatography (20 mm column, 60 g SiO_2 , R_f 0.31, EtOAc/hexane, 3/1).

Data for (+)-**6**:

SFC: (S)-**6**, t_R 3.93 min (49.9%); (R)-**6**, t_R 4.31 min (50.1%) (Chiracel AS, 1.4% MeOH in CO_2 , 125 bar, $40\text{ }^{\circ}\text{C}$, 2.5 mL min^{-1})

(2S,3E)-(+)-Methyl 2-hydroxy-2-phenyl-3-butenolate (7**)**⁷

Following General Procedure III A, a solution of *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to the cold solution of (*E*)-cinnamaldehyde **2h** (126 μL , $d = 1.048$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL , $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at $-74\text{ }^{\circ}\text{C}$ over 4 h. The mixture was stirred for 4 h at $-74\text{ }^{\circ}\text{C}$. Work-up following the methanol quench provided 136 mg (71%) of **7** after silica gel column chromatography (20 mm column, 60 g SiO_2 , R_f 0.25, EtOAc/hexane, 3/1). Bulb-to-bulb distillation provided 132 mg (69%) of **7** as colorless oil. The absolute configuration was deduced to be *S* according to the sign of optical rotation.

Data for (+)-**7**:

bp: $140\text{ }^{\circ}\text{C}$ (0.5 mm Hg)

^1H NMR: (400 MHz, CDCl_3)

7.23-7.37 (m, 5 H, aryl); 6.81 (d, $J = 15.9$, 1 H, HC(4)); 6.25 (dd, $J = 15.8, 5.7$, 1 H, HC(3)); 4.85 (d, $J = 5.6$, 1 H, HC(2)); 3.83 (s, 3 H, OCH_3); 3.35 (bs, 1 H, OH)

GC: (S)-**7**, t_R 37.92 min (97.9%); (R)-**7**, t_R 38.61 min (2.1%) (Chiraldex BPH, $93\text{ }^{\circ}\text{C}$, 20 psi)

Opt. Rot.: $[\alpha]_{\text{D}}^{24} +112.3$ ($c = 0.524$, MeOH)

Following General Procedure III B, a solution of *tert*-butyl isocyanide (63 μL , $d = 0.735$, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added via a syringe pump to the cold solution of (*E*)-cinnamaldehyde **2h** (63 μL , $d = 1.048$, 0.5 mmol), pyridine-*N*-oxide (4.8 mg, 0.05 mmol, 0.1 equiv), SiCl_4 (63 μL , $d = 1.483$, 0.55 mmol, 1.1 equiv) at -74°C over 30 min via a syringe pump. The mixture was stirred for 4 h at -74°C . Work-up following the methanol quench provided 71mg (74%) of **7** after silica gel column chromatography (20 mm column, 60 g SiO_2 , R_f 0.25, EtOAc/hexane, 3/1).

Data for ($\pm$)-**7**:

GC: (*S*)-**7**, t_{R} 37.80 min (49.4%); (*R*)-**7**, t_{R} 38.54 min (50.6%) (Chiraldex BPH, 93°C , 20 psi)

(*S*)-(+)-Methyl-2-hydroxy-4-phenylbutanoate (8**)⁸**

Following General Procedure III A, a solution of *tert*-butyl isocyanide (125 μL , $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump to a cold solution of hydrocinnamaldehyde (132 μL , $d = 1.019$, 1.0 mmol), catalyst **5a** (43 mg, 0.05 mmol, 0.05 equiv), SiCl_4 (125 μL , $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL , $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) at -74°C over 8 h. The mixture was stirred for 8 h at -74°C . Work-up following a methanol quench provided 171 mg (88%) of **8** after silica gel column chromatography (20 mm column, 60 g SiO_2 , R_f 0.25, EtOAc/hexane, 3/1). Bulb-to-bulb distillation provided 170 mg (88%) of **8** as colorless oil. The absolute configuration was deduced to be *S* according to the sign of optical rotation.

Data for (+)-**8**:

bp: 140°C (0.5 mm Hg)

¹H NMR: (400 MHz, CDCl₃)

7.18-7.31 (m, 5 H, aryl); 4.19-4.21 (m, 1 H, H(C(2))); 3.76 (s, 3 H, OCH₃); 2.72-2.80 (m, 2 H, H₂(C(4))); 2.75 (s, 1 H, OH); 1.91-2.17 (m, 2 H, H₂(C(3)))

SFC: (*S*)-**8**, *t*_R 3.37 min (81.8%); (*R*)-**8**, *t*_R 3.69 min (18.2%) (Chiracel AS, 2.5% MeOH in CO₂, 125 bar, 40 °C, 2.5 mL min⁻¹)

Opt. Rot.: [α]_D²⁴ +21.1 (*c* = 0.524, CHCl₃)

Following General Procedure III B, a solution of *tert*-butyl isocyanide (63 μL, *d* = 0.735, 0.6 mmol, 1.2 equiv) in CH₂Cl₂ (0.5 mL) was added via a syringe pump to the cold solution of hydrocinnamaldehyde (66 μL, *d* = 1.019, 0.5 mmol), pyridine-*N*-oxide (4.7 mg, 0.05 mmol, 0.1 equiv), SiCl₄ (63 μL, *d* = 1.483, 0.55 mmol, 1.1 equiv) at -74 °C over 8 h via a syringe pump. The mixture was stirred for 8 h further at -74 °C. Work-up following the methanol quench provided 81 mg (83%) of **6** after silica gel column chromatography (20 mm column, 60 g SiO₂, *R*_f 0.28, EtOAc/hexane, 3/1).

Data for (±)-**8**:

SFC: (*S*)-**8**, *t*_R 3.39 min (50.5%); (*R*)-**8**, *t*_R 3.71 min (49.5%) (Chiracel AS, 2.5% MeOH in CO₂, 125 bar, 40 °C, 2.5 mL min⁻¹)

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