

Regioselective Lithiation of Benzyl Imidazoles: Synthesis and Evaluation of New Organocatalysts for trans Diol Functionalization

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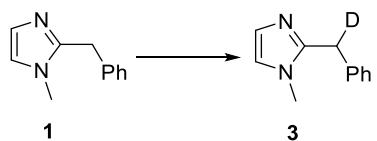
Electronic Supplementary Information

General: Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1} . ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Routine monitoring of reactions was performed using EM Science DC-Alufoilen silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel. Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by flame, then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.

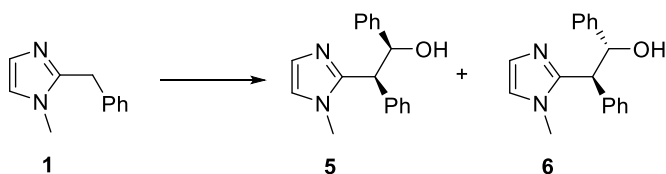
Lithiation of Benzyl Imidazoles and Their Addition to Select Electrophiles: Exploration of Reactivity and Diastereoselectivity

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Deuterated benzylimidazole 3: To a stirred solution of benzylimidazole **1** (25 mg, 0.145 mmol) in THF (0.95 mL) at -78°C was added sequentially *n*-BuLi (0.07 mL, 0.174 mmol, 2.5 M in hexanes). After 1 h was added and CD_3OD (0.006 mL, 5.8 mg, 0.291 mmol). After 2 h, the cold bath was removed and the reaction mixture was stirred at room temperature. The reaction mixture was concentrated *in vacuo* and the % deuterium incorporation was determined using crude ^1H NMR to be 87%.

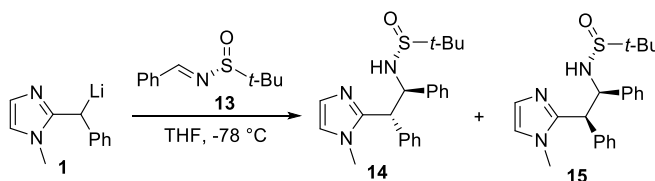


Alcohol 5 and 6. To a stirred solution of benzylimidazole **1** (2.4 g, 14.2 mmol) in THF (50 mL) at -78°C was added *n*-BuLi (5.7 mL, 14.2 mmol, 2.5 M in hexanes). After 1 h, benzaldehyde (**4**) (500 mg, 0.48 mL, 4.7 mmol) was added dropwise. After 2 h, the cold bath was removed and the reaction mixture was stirred at room temperature. After 10 h, the reaction was quenched by sat. aq. NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 X, 30 mL). The dried (MgSO_4) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 20-70% EtOAc / hexanes, to give **5** (441 mg, 1.6 mmol, 34%) as a white solid followed by **6** (761 mg, 2.7 mmol, 58%) as a white solid.

Alcohol 5. Mp $117\text{--}119^{\circ}\text{C}$; IR (neat) 3306, 3030, 1491, 1453 1283, 1140, 748, 104 cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 3.26 (s, 3 H), 4.07 (d, $J = 2.9\text{ Hz}$, 1 H), 5.66 (d, $J = 2.9\text{ Hz}$, 1 H), 6.75 - 6.77 (m, 2 H), 6.80 (d, $J = 1.3\text{ Hz}$, 1 H), 7.02 - 7.05 (m, 3 H), 7.09 - 7.12 (m, 2 H), 7.13 - 7.20 (m, 4 H) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 32.7, 50.7, 75.2, 120.8, 126.5, 126.6, 127.0, 127.2, 127.8, 129.9, 135.5, 141.4, 149.4 ppm; HRMS (EI+) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}$ (M+H) 279.14975, found 279.15000.

Alcohol 6. Mp $183\text{--}184^{\circ}\text{C}$; IR (neat) 3134, 3102, 1491, 1454, 1282, 1062, 752, 698 cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 3.19 (s, 3 H), 4.16 (d, $J = 7.5\text{ Hz}$, 1 H), 5.30 (d, $J = 7.5\text{ Hz}$, 1 H), 5.97 (br. s., 1 H), 6.77 (d, $J = 1.5\text{ Hz}$, 1 H), 6.90 - 6.94 (m, 2 H), 7.05 (d, $J = 1.3\text{ Hz}$, 1 H), 7.11 - 7.22 (m, 8 H) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 32.7, 52.5, 78.0, 121.1, 126.8, 126.9, 127.1, 127.5, 128.0128.6, 128.8, 138.4, 141.9, 148.3 ppm; HRMS (EI+) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}$ (M+H)

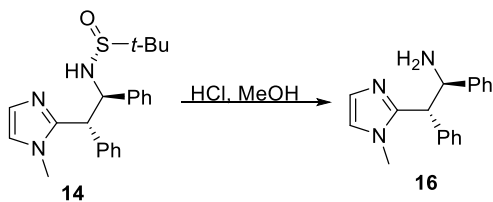
279.14975, found 279.14878.



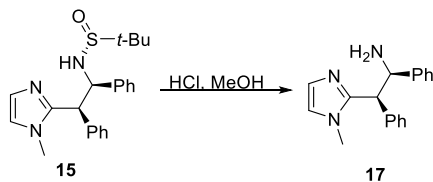
Sulfonamides 14, 15. To a stirred solution of the known benzyl imidazole ¹⁸ (1.65 g, 9.57 mmol) in THF (6 mL) at -78°C was added solution of n-BuLi (3.83 mL, 9.57 mmol, 2.5 M in hexanes). After 30 min, a solution sulfinamine²⁷ (1.00 g, 4.79 mmol) in THF (5 mL) at rt was added dropwise. After 4 h, the reaction was quenched by sat. aq. NH₄Cl (20 mL) and extracted with DCM (3 X 30 mL). The dried (MgSO₄) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 40-80% EtOAc / DCM, to give sequentially **14** (807 mg, 2.1 mmol, 44%) followed by **15** (726 mg, 1.9 mmol, 40 %) both as white solids.

Sulfonamides 14: [α]_D²³ = +137.1° (*c* = 1.0, CHCl₃); Mp 178-180°C; IR (neat) 3648, 3227, 2957, 229, 1739, 1494, 1454, 1065, 699 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 1.07 (s, 9 H), 3.22 (s, 3 H), 4.53 (d, *J* = 7.0 Hz, 1 H), 4.97 (t, *J* = 6.8 Hz, 1 H), 6.41 (d, *J* = 6.6 Hz, 1H), 6.72 (s, 1 H), 7.04 (s, 1 H), 7.12 - 7.25 (m, 8 H) 7.30 (d, *J* = 7.5 Hz, 2 H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 22.6, 32.5, 50.2, 56.6, 65.9, 120.9, 127.1, 127.2, 127.7, 128.25, 128.33, 128.5, 128.8, 138.8, 140.2, 146.7 ppm; HRMS (EI⁺) calcd. for C₂₂H₂₇N₃OS (M+H) 382.19531, found 382.19343.

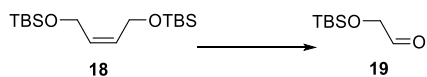
Sulfonamides 15: [α]_D²³ = -96.1° (*c* = 1.0, CHCl₃); Mp 174-175°C; IR (neat) 3227, 2954, 1739, 1492, 1455, 1056, 700 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 0.93 (s, 9 H), 3.22 (s, 3 H), 4.13 (d, *J* = 4.8 Hz, 1 H), 4.34 (d, *J* = 9.7 Hz, 1 H), 5.20 (dd, *J* = 9.7, 4.8 Hz, 1 H), 6.54 (d, *J* = 1.3 Hz, 1 H), 6.90 (d, *J* = 1.3 Hz, 1 H), 7.18 - 7.21 (m, 1 H), 7.22 - 7.27 (m, 3 H), 7.31 - 7.35 (m, 4 H), 7.48 - 7.51 (m, 2 H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 22.3, 32.4, 50.5, 56.4, 64.5, 120.3, 127.3, 127.7, 127.9, 128.0, 128.4, 128.6, 129.7, 137.9, 140.5, 146.7 ppm; HRMS (EI⁺) calcd. for C₂₂H₂₇N₃OS (M+H) 382.19531, found 382.19339.



Amine 16. To a stirred solution of sulfonamide **14** (800 mg, 2.10 mmol) in MeOH (10 mL) at 0°C was added concentrated HCl (0.5 mL, 6.3 mmol) dropwise. After 10 h, the solvent was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 5% MeOH / DCM, to give **16** (580 mg, 2.1 mmol, 99%) as a colorless oil. $[\alpha]_D^{23} = +183.3^\circ$ ($c = 1.0$, solvent); IR (neat) 3368, 3298, 3028, 1601, 1491, 1283, 749, 700 cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 2.38 (br. s., 3 H), 3.31 (s, 3 H), 4.09 (d, $J = 9.2$ Hz, 1 H), 4.81 (d, $J = 9.2$ Hz, 1 H), 6.76 (s, 1 H), 6.84 - 6.91 (m, 2 H), 7.06 (br. s., 4 H), 7.14 (br. s., 5 H) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 32.6, 53.0, 121.0, 126.7, 127.2, 127.3, 127.7, 128.1, 128.2, 128.7, 138.7, 142.8, 148.2 ppm; HRMS (EI⁺) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_3$ (M+H) 278.16572, found 278.16624.



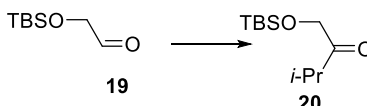
Amine 17. To a stirred solution of sulfonamide **15** (400 mg, 1.05 mmol) in MeOH (10 mL) at 0°C was added concentrated HCl (0.25 mL, 3.14 mmol) dropwise. After 10 h, the solvent was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 5% MeOH / DCM, to give **17** (290 mg, 1.05 mmol, 99%) as a colorless oil. $[\alpha]_D^{23} = -88.5^\circ$ ($c = 1.0$, CHCl_3); IR (neat) 3347, 3287, 3135, 1617, 1488, 779, cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 1.77 (br. s., 2 H), 3.12 (s, 3 H), 4.09 (d, $J = 7.5$ Hz, 1 H), 4.95 (d, $J = 7.5$ Hz, 1 H), 6.59 (d, $J = 1.3$ Hz, 1 H), 6.97 (d, $J = 1.3$ Hz, 1 H), 7.18 - 7.27 (m, 6 H), 7.28 - 7.32 (m, 4 H) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 32.5, 52.1, 59.4, 120.2, 127.15, 127.25, 127.26, 127.4, 128.1, 128.6, 129.5, 138.0, 143.8, 148.2 ppm; HRMS (EI⁺) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_3$ (M+H) 278.16572, found 278.16623.



Aldehyde 19. To a stirred solution of the known alkene **18**²⁸ (7.6 g, 24.0 mmol) in a acetone water mixture (65 mL, 1:1) at rt was added sequentially NMO (8.4 g, 71.9 mmol) and potassium osmate (44.0 mg, 0.12 mmol). After 10 h, the reaction was quenched by NaHSO_3 (200 mg). After 30 min, the reaction was extracted with ethyl acetate (3 X 50 mL). The dried

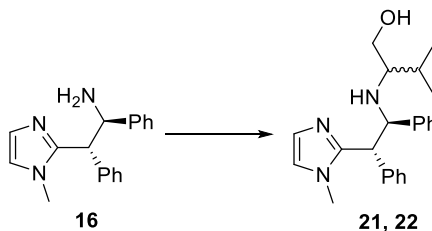
(NaSO₄) extract was concentrated *in vacuo* passed through short column of silica gel to give the crude diol, which was used in the next step without further purification.

A solution of this crude diol (24.0 mmol) in DCM (20 mL) was added to a suspension of NaIO₄ (8.4 g, 39.1 mmol, loaded onto 30 g of silica gel) in DCM (100 mL). After 24 h, the mixture was filtered and the silica gel was washed with DCM (3 X 50 mL) and concentrated *in vacuo* to give the known aldehyde **19**²⁶ as colorless oil (6.5 g, 18.5 mmol, 77%). ¹H NMR (700 MHz, CDCl₃) δ 0.11 (s, 6 H), 0.93 (s, 9 H), 4.21 (d, *J* = 0.9 Hz, 2 H) 9.70 (t, *J* = 0.9 Hz, 1 H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ -5.3, 18.5, 25.9, 69.8, 202.5 ppm.



Ketone 20. To a stirred solution of aldehyde **19** (0.5 g, 2.9 mmol) in THF (6 mL) at -78°C was added sequentially isopropyl magnesium bromide dropwise (2.9 mL, 8.6 mmol, 3.0 M in THF). After 2 h, the reaction was allowed to warm to rt. After 12 h, the reaction was quenched by sat. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (3 X 30 mL). The dried (NaSO₄) extract was concentrated *in vacuo* to give the corresponding alcohol, which was used without further purification.

To solution of this alcohol in ethyl acetate (10 mL) was added IBX²⁹ (1.0 g, 3.5 mmol). After 24 h reflux under argon, the mixture was filtered through short plug of celite®, the solvent was concentrated to give ketone **20** (609.0 mg, 2.8 mmol, 98%) as colorless oil. ¹H NMR (700 MHz, CDCl₃) δ 0.09 (s, 6 H), 0.92 (s, 9 H), 1.09 (s, 3 H), 1.10 (s, 3 H), 2.89 (spt, *J* = 6.9 Hz, 1 H) 4.26 (s, 2 H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ -5.4, 18.1, 18.5, 25.9, 36.3, 68.2, 214.3 ppm.

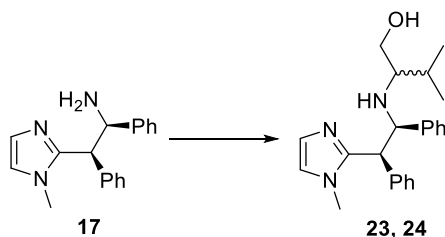


Alcohol 21 & 22. To a stirred solution of amine **16** (150 mg, 0.54 mmol) in THF (1 mL) at rt was added sequentially Ti(*i*-PrO)₄ (31 mg, 32 μL, 0.11 mmol) and ketone **20** (175 mg, 175 μL, 0.81 mmol). After 1 h, methanol (1 mL) was added. The reaction mixture was cooled to 0°C and NaBH₃CN (102 mg, 1.63 mmol) was added. After 10 h, the reaction was quenched

by water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The dried (NaSO₄) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give inseparable mixture of diastereomers. This mixture was redissolved in methanol (1 mL) cooled to 0 °C, and concentrated HCl (81 µL, 1.05 mmol) was added dropwise. After 12 h, the solvent was concentrated *in vacuo*. The remaining solid was dissolved in water (5 mL) and extracted with DCM (2 X 10 mL). The aq. layer was basified with NaOH (as determined by litmus paper) and extracted with ethyl acetate (3 X 20 mL). The dried (NaSO₄) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 80% EtOAc / hexanes, to give **21** (70 mg, 0.19 mmol, 36%) as a white solid followed by **22** (71 mg, 0.20 mmol, 36%) as a white solid at 10% MeOH/ EtOAc.

Alcohol 21: $[\alpha]_D^{23} = +145.2^\circ$ ($c = 1.3$, CHCl₃); Mp 151-152°C; IR (neat) 3336, 3292, 3029, 2955, 1668, 1489, 1455, 1413, 1071, 751, 700 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 0.80 (d, $J = 7.0$ Hz, 3 H), 0.89 (d, $J = 7.0$ Hz, 3 H), 1.24 - 1.27 (m, 1 H), 1.55 (sxt, $J = 7.0$ Hz, 1 H), 2.01 - 2.04 (m, 1 H), 3.24 (s, 3 H), 3.58 (dd, $J = 12.3, 3.1$ Hz, 1 H), 4.03 (d, $J = 9.7$ Hz, 1 H), 4.07 (dd, $J = 12.3, 3.1$ Hz, 1 H), 4.72 (d, $J = 10.1$ Hz, 1 H), 6.65 - 6.68 (m, 2 H), 6.79 (d, $J = 1.3$ Hz, 1 H), 6.99 - 7.02 (m, 3 H), 7.07 - 7.13 (m, 6 H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 20.3, 30.8, 32.8, 51.9, 60.5, 61.3, 63.9, 121.5, 126.7, 126.8, 127.0, 127.7, 128.2, 128.7, 128.9, 138.6, 141.6, 148.6 ppm; HRMS (EI+) calcd. for C₂₃H₃₀N₃O (M+H) 364.23889, found 364.23960.

Alcohol 22: $[\alpha]_D^{23} = +109.9^\circ$ ($c = 1.0$, CHCl₃); Mp 109-111°C; IR (neat) 3310, 2956, 2926, 1491, 1455, 1282, 700 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 0.83 (d, $J = 7.0$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H), 1.97 - 2.05 (m, 1 H), 2.35 - 2.40 (m, 1 H), 3.19 (t, $J = 9.7$ Hz, 1 H) 3.33 - 3.36 (m, 1 H) 3.37 (s, 3 H) 4.10 - 4.16 (m, 1 H), 4.73 (d, $J = 9.68$ Hz, 1 H), 6.80 (s, 1 H), 6.82 - 6.86 (m, 2 H), 6.99 - 7.02 (m, 3 H), 7.07 (s, 1 H), 7.08 - 7.16 (m, 5 H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 17.0, 19.8, 27.6, 32.6, 52.2, 60.4, 60.8, 64.5, 121.3, 126.6, 127.3, 127.4, 128.1, 128.2, 128.7, 128.8 ppm; HRMS (EI+) calcd. for C₂₃H₃₀N₃O (M+H) 364.23889, found 364.24037.

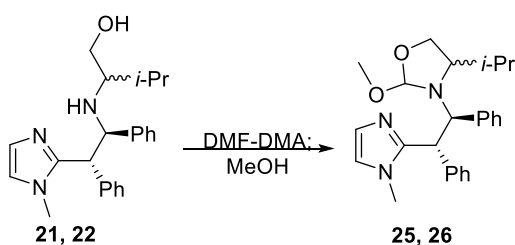


Alcohol 23 & 24. To a stirred solution of amine **17** (286 mg, 1.03 mmol) in THF (1 mL) at rt was added sequentially $\text{Ti}(\text{iPrO})_4$ (59 mg, 61 μL , 0.21 mmol) and ketone **20** (335 mg, 340 μL , 1.55 mmol). After 1 h, methanol (1 mL) was added. The reaction mixture was cooled to 0°C and NaBH_3CN (195 mg, 3.10 mmol) was added. After 10 h, the reaction was quenched by water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The dried (NaSO_4) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 20-40% EtOAc / hexanes, to give inseparable mixture of diastereomers. This mixture was redissolved in methanol (1 mL) and cooled to 0°C , concentrated HCl (0.8 mL, 10.1 mmol) was added dropwise. After 12 h, the solvent was concentrated *in vacuo*. The remaining solid was dissolved in water (5 mL) and extracted with DCM (2 X 10 mL). The aq. layer was basified with NaOH (as determined by litmus paper) and extracted with ethyl acetate (3 X 20 mL). The dried (NaSO_4) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 50-80% EtOAc / hexanes, to give **23** (39 mg, 0.11 mmol, 20%) as a colorless oil followed by **24** (33 mg, 0.09 mmol, 17%) as a white solid.

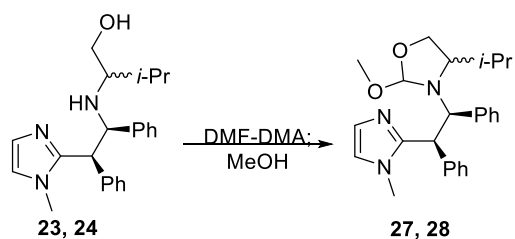
Alcohol 23: $[\alpha]_{\text{D}}^{23} = -78.5^\circ$ ($c = 1.0$, CHCl_3); Mp $131\text{--}135^\circ\text{C}$; ^1H NMR (700 MHz, CDCl_3) δ 0.49 (d, $J = 7.0$ Hz, 3 H), 0.65 (d, $J = 7.0$ Hz, 3 H), 1.87 (td, $J = 7.0, 4.4$ Hz, 1 H), 2.29 (dt, $J = 8.7, 4.2$ Hz, 1 H), 3.01 (t, $J = 9.5$ Hz, 1 H), 3.12 (s, 3 H), 4.06 (d, $J = 9.7$ Hz, 1 H), 4.69 (d, $J = 9.7$ Hz, 1 H), 6.45 (s, 1 H), 6.90 (s, 1 H), 7.14 - 7.17 (m, 1 H), 7.19 - 7.22 (m, 2 H), 7.28 (t, $J = 7.5$ Hz, 1 H), 7.31 (d, $J = 7.5$ Hz, 2 H), 7.36 (t, $J = 7.7$ Hz, 2 H), 7.62 (d, $J = 7.0$ Hz, 2 H) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 16.4, 19.3, 27.3, 32.3, 51.3, 60.3, 60.6, 64.5, 119.98, 127.2, 127.5, 127.8, 128.20, 128.22, 1289.0, 129.3, 138.2, 142.1, 147.3 ppm; HRMS (EI⁺) calcd. for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}$ (M+H) 364.23889, found 364.23719.

Alcohol 24: $[\alpha]_{\text{D}}^{23} = -124.7^\circ$ ($c = 1.0$, CHCl_3); Mp $158\text{--}162^\circ\text{C}$; ^1H NMR (700 MHz, CDCl_3) δ 0.82 (d, $J = 6.6$ Hz, 3 H), 0.84 (d, $J = 6.6$ Hz, 3 H), 1.71 (sxt, $J = 7.0$ Hz, 1 H), 1.96 (dt, $J = 7.9, 2.2$ Hz, 1 H), 3.10 (s, 3 H), 3.55 (dd, $J = 12.0, 0.9$ Hz, 1 H), 4.00 (dd, $J = 12.0, 2.9$ Hz, 1 H), 4.11 (d, $J = 3.1$ Hz, 1 H), 4.92 (d, $J = 2.6$ Hz, 1 H), 6.69 (d, $J = 7.4$ Hz, 2 H), 6.76 (d, $J = 1.3$ Hz, 1 H), 7.03 (d, $J = 1.3$ Hz, 1 H), 7.12 (dd, $J = 7.0, 2.2$ Hz, 2 H), 7.16 - 7.19 (m, 2 H), 7.21 - 7.25 (m, 4 H) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 20.3, 30.4, 33.0, 51.4, 58.5, 59.9,

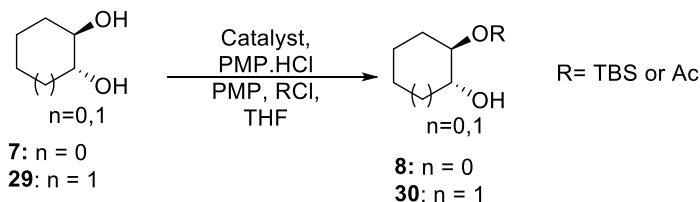
60.7, 121.1, 126.4, 127.1, 127.2, 127.7, 127.9, 128.5, 129.9, 136.1, 142.9, 149.0 ppm; HRMS (EI+) calcd. for C₂₃H₃₀N₃O (M+H) 364.23889, found 364.23609.



Oxazollidine 25, 26. To a stirred solution of alcohol **21** or **22** (40 mg, 0.1 mmol) in MeOH (1 mL) at rt was added DMF-DMA (131 mg, 147 μ L, 1.11 mmol). After 3 h, the solvent was concentrated and fresh MeOH (1 mL) was added. After an additional 3 h, the solvent was evaporated and the crude product was used without purification.



Oxazole 27, 28. To a stirred solution of alcohol **23** or **24** (60 mg, 0.17 mmol) in MeOH (1 mL) at rt was added DMF-DMA (196 mg, 221 μ L, 1.65 mmol). After 3 h, the solvent was concentrated and fresh MeOH (1 mL) was added. After an additional 3 h, the solvent was evaporated and the crude product was used without purification.



General procedure for diol desymmetrization. A solution of the diol (0.40 mmol), the organocatalyst (0.080 mmol, 20 mol%), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (2.3 mg, 0.012 mmol, 3 mol%) in anhydrous THF (0.50 mL) was added to an oven-dried glass reaction vial. The reaction mixture was stirred at room temperature for 10 min. 1,2,2,6,6-pentamethylpiperidine (87 mL, 0.48 mmol, 1.2 equiv) was added, followed by addition of a solution of tert-butylchlorodimethylsilane (120 mg, 0.80 mmol, 2.0 equiv) or acetyl chloride (63 mg, 0.80 mmol, 2.0 equiv) in anhydrous THF (0.50 mL). After stirring at room temperature for 4 h, reaction mixture was quenched by addition of N,N-diisopropylethylamine (200 mL) and methanol (60 mL). The mixture was stirred at room temperature for 10 min,

and was then concentrated under reduced pressure. Flash column chromatography on silica gel (hexanes/EtOAc=20/1) afforded pure product as colorless oil.