Applications of Asymmetric Hydrosilylations Mediated by Catalytic (DTBM-SEGPHOS)CuH

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Supporting Information

Representative Procedure for the Asymmetric Hydrosilylation of Aryl Ketones using *R*-(-)-(DTBM-SEGPBOS)CuH: (*R*)-methyl-4-hydroxy-4-phenylbutanoate (2; Table 1, entry a).

To a flame-dried 10 mL round-bottom flask (RBF) equipped with a magnetic stir bar and purged with argon in a glovebox were added CuCl (1.5 mg, 0.015 mmol, 1.0 mol %) and NaO-*t*-Bu (1.4 mg, 0.015 mmol, 1.0 mol %), (*R*)-(-)-DTBM-SEGPBOS (0.88 mg, 7.5×10^{-4} mmol, 0.05 mol %), and 1.5 mL of toluene at rt. The mixture was stirred for 30 min before being cooled to -78 °C. PMHS (0.39 mL, 6.0 mmol, 4 equiv) was added to the RBF and the mixture was stirred for 15 min. In a separate 10 mL pear-bottomed flask (PBF) were combined methyl-4-oxo-4-phenylbutanoate (0.26 mL, 1.50 mmol), *t*-BuOH (80 μ L, 1.50 mmol), and THF (1.5 mL) under argon, and the mixture was cooled to -78 °C. The contents of the PBF were transferred via cannula to the RBF, and the reaction was monitored by TLC. Upon completion (2 h), the reaction was quenched with 2.5 M aqueous KF (10 mL) and Et₂O (10 mL) and stirred for 3 h. The biphasic mixture was separated, and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined extracts were washed with brine and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography (20% EtOAc/hexanes) to yield 264 mg (92%) of a colorless oil. Comparison of spectral data with known literature values confirmed the identity of the product.¹ Chiral GC analysis (Chiraldex B-DM column, 140 °C) indicated an ee of 99.4%.

(*R*)-1-(Fluoro[2,3-*c*]pyridin-5-yl)ethanol (4; Table 1 entry b). The representative procedure was used with the following amounts of reagents: 1-(fluoro[2,3-*c*]pyridin-5-yl)ethanone (160 mg, 1.0 mmol), CuCl (2.0 mg, 0.020 mmol, 2.0 mol %) and NaO-*t*-Bu (1.9 mg, 0.020 mmol, 2.0 mol %), (*R*)-(-)-DTBM-SEGPBOS (3.0 mg, 2.5×10^{-3} mmol, 0.25 mol %), *t*-BuOH (53 μ L, 1.0 mmol, 1.0 equiv), PMHS (0.26 mL, 4.0 mmol), THF (1.0 mL) and toluene (1.0 mL). The

reaction was quenched with 2.5 M aqueous NaOH rather than KF. The title compound (141 mg, 88%) was isolated as a colorless oil. Comparison of spectral data with known literature values confirmed the identity of the product.² Chiral GC analysis (Chiraldex B-DM column, 80 °C) indicated an ee of 97.1%.

(*R*)-1-(3-(Trifluoromethyl)phenyl)ethanol (6; Table 1, entry c). The representative procedure was used with the following amounts of reagents: 3-trifluoromethylacetophenone (376 mg, 2.0 mmol), CuCl (4.0 mg, 0.04 mmol, 2.0 mol %) and NaO-*t*-Bu (3.8 mg, 0.04 mmol, 2.0 mol %), (*R*)-(-)-DTBM-SEGPHOS (3.0 mg, 2.5×10^{-4} mmol, 0.25 mol %), *t*-BuOH (190 μ L, 2.0 mmol, 1.0 equiv), PMHS (130 μ L, 2.0 mmol), toluene (2.0 mL). The reaction was quenched with 2.5 M aqueous NaOH. The title compound (354.2 mg, 95%) was isolated as a colorless oil. Comparison of spectral data with known literature values confirmed the identity of the product.³ Chiral GC analysis (Chiraldex BDM column, 80 °C) indicated an ee of 95.3%.

(*R*)-1-(3,5-bis(Trifluoromethyl)phenyl)ethanol (8; Table 1, entry d). The representative procedure was used with the following amounts of reagents: 3,5-bis(trifluoromethyl)-acetophenone (256.1 mg, 1.0 mmol), Cu(OAc)₂•H₂O (2.0 mg, 0.01 mmol, 1.0 mol %), *R*-(-)-DTBM-SEGPHOS (2.9 mg, 2.5×10^{-4} mmol, 0.25 mol %), *t*-BuOH (80 μ L, 1.0 mmol, 1.0 equiv), PMHS (130 μ L, 2.0 mmol), and toluene (3.0 mL). The reaction was quenched with 2.5 M aqueous NaOH. The title compound (244 mg, 98%) was isolated as a colorless oil. Comparison of spectral data with known literature values confirmed the identity of the product.⁴ Chiral GC analysis (Chiraldex B-DM column, 70 °C) indicated an ee of 91.7%.

(*R*)-3-Chloro-1-phenylpropan-1-ol (10; Table 1, entry e). The representative procedure was used with the following amounts of reagents: 3-chloro-1-phenylpropan-1-one (337 mg, 2.0 mmol), CuCl (2.0 mg, 0.020 mmol, 2.0 mol %) and NaO-*t*-Bu (1.9 mg, 0.020 mmol, 2.0 mol %),

(*R*)-(-)-DTBM-SEGPPOS (1.2 mg, 1.0×10^{-3} mmol, 0.05 mol %), *t*-BuOH (107 μ L, 2.0 mmol, 1.0 equiv), PMHS (0.52 mL, 4.0 mmol), toluene (4.0 mL), and THF (1.0 mL). The reaction was quenched with 2.5 M aqueous NaOH rather than KF. The title compound (321.4 mg, 98%) was isolated as a white crystalline solid (mp 42.5-43.5 °C). Chiral GC analysis (Chiraldex GTA column, 125 °C) indicated an ee of 92.0%; R_f = 0.41 (20% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3): δ = 7.22 (bm, 5H), 4.84 (dd, J = 8.4 Hz, J = 8.0 Hz, 1H), 3.64 (dd, J = 6.0 Hz, J = 5.6 Hz, 1H), 3.46 (dd, J = 6.0 Hz, J = 5.6 Hz, 1H), 2.13 (dt, J = 8.4 Hz, J = 6.0 Hz, 1H), 2.02 (bs, 1H), 1.98 (dt, J = 8.0 Hz, J = 6.0 Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ = 143.84, 128.81, 128.57, 128.07, 126.15, 125.95, 71.41, 41.91, 41.55. HRMS (ESI+/TOF): m/z calcd for $\text{C}_9\text{H}_{11}\text{ClO}$ 170.0498, found 170.0492.

(*R*)-2-Phenyl-1-(thiazol-2-yl)ethanol (12; Table 1, entry f). The representative procedure was used with the following amounts of reagents: 2-phenyl-1-(thiazol-2-yl)ethanone (50.8 mg, 0.25 mmol), CuCl (0.25 mg, 2.5×10^{-3} mmol, 1.0 mol %) and NaO-*t*-Bu (0.24 mg, 0.25×10^{-3} mmol, 1.0 mol %), (*R*)-(-)-DTBM-SEGPPOS (0.15 mg, 1.25×10^{-4} mmol, 0.25 mol %), *t*-BuOH (13.4 μ L, 0.25 mmol, 1.0 equiv), PMHS (65 μ L, 1.0 mmol), toluene (0.30 mL) and THF (0.7 mL). The reaction was quenched with 2.5 M aqueous NaOH rather than KF. The title compound (51.3 mg, 100%) was isolated as a colorless oil. Chiral GC analysis (Chiraldex GTA column, 145 °C) indicated an ee of 89.3%; R_f = 0.21 (20% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3): δ = 7.76 (s, 1H), 7.23-7.34 (bm, 7H), 5.22 (q, J = 4.0 Hz, J = 8.8 Hz, 1H), 3.375 (dd, J = 4.0 Hz, J = 13.6 Hz, 1H), 3.10 (dd, J = 8.8 Hz, J = 13.6 Hz, 1H), 3.05 (bs, 1H); ^{13}C NMR (400 MHz, CDCl_3): δ = 174.59, 142.56, 127.02, 129.88, 128.86, 127.17, 119.21, 72.94, 44.74. HRMS (ESI+/TOF): m/z calcd for $\text{C}_{11}\text{H}_{11}\text{NOS}$ ($\text{M} + \text{H}$) $^+$ 206.0634, found 206.0642.

(S)-1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol (14; Table 1, entry g). The representative procedure was used with the following amounts of reagents: 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone (255 mg, 1.0 mmol), CuCl (2.0 mg, 0.02 mmol, 2.0 mol %) and NaO-*t*-Bu (1.9 mg, 0.02 mmol, 2.0 mol %), *R*-(-)-DTBM-SEGPHOS (2.9 mg, 2.5×10^{-4} mmol, 0.25 mol %), *t*-BuOH (90 μ L, 1.0 mmol, 1.0 equiv), PMHS (130 μ L, 2.0 mmol), toluene (2.0 mL) and THF (1.0 mL). The reaction was quenched with 2.5 M aqueous NaOH. The title compound (231.4 mg, 90%) was isolated as a colorless oil. Comparison of spectral data with known literature values confirmed the identity of the product.⁵ Chiral GC analysis (Chiraldex GTA column, 155 °C) indicated an ee of 86.1%.

¹ Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546.

² Wishka, D. G.; Graber, D. R.; Seest, E. P.; Lester, A.; Dolak, F. H.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851.

³ Tanaka, K.; Katsurada, M.; Ohno, F.; Shiga, Y.; Oda, M.; Miyagi, M.; Takehara, J.; Okano, K. *J. Org. Chem.* **2000**, *65*, 432.

⁴ Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A. et al. *J. Am. Chem. Soc.* **2003**, *125*, 2129.

⁵ Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110 .