Highly Enantioselective Cyanosilylation of Aldehydes Catalyzed by a Chiral Oxazaborolidinium Ion.

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Supplementary Materials

Materials and Methods. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F₂₅₄ precoated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 µm particle size). NMR spectra were recorded on Varian Innova-500, or Mercury-400 instruments and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on Avatar 360 FT-IR spectrometer. Gas chromatography (GC) analyses were performed on Hewlett-Packard 6850 Series GC System equipped with flame ionization detector using a J & W Scientific Cyclosil-B (30 m x 0.25 mm) or Chiraldex γ-TA (30 m x 0.25 mm) column. Toluene was distilled from sodium. Trimethylsilyl cyanide, benzaldehyde, *o*-tolualdehyde, anisaldehyde and pivaldehyde were distilled from calcium hydride. Cyclohexanecarboxaldehyde and heptaldehyde were distilled from magnesium sulfate.

General Procedure for the Preparation and Use of Chiral Catalyst. A 100-mL, two-necked, round-bottomed flask equipped with a stir bar, a glass stopper and a 50-mL pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 4Å molecular sieves,¹ and functioning as a Soxhlet extractor) fitted on top with a reflux condenser and a nitrogen inlet adaptor was charged with (*S*)-(-)-α,α-dimethyl-2-pyrrolidinemethanol² (188.0 mg, 0.608 mmol), tri-*o*-tolylboroxine³ (71.4 mg, 0.202 mmol) and 25 mL of toluene. The resulting solution was heated

¹ Molecular sieves (pellets) were dried *in vacuo* at ca. 200 °C with a gas burner for 10 min prior to use.

² Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, 56, 751-762.

³ Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, 124, 3808-3809.

to reflux (bath temperature $\sim 145\text{ }^{\circ}\text{C}$). After 3 h, the reaction mixture was cooled to *ca.* $60\text{ }^{\circ}\text{C}$ and the addition funnel and the condenser were quickly replaced with a short-path distillation head. The mixture was concentrated by distillation (air-cooling) to a volume of *ca.* 5 mL. This distillation protocol was repeated three times by re-charging with 3 x 5 mL of toluene. The solution was then allowed to cool to room temperature to give the oxazaborolidine precursor solution (0.608 mmol) in toluene (*ca.* 5 mL). To the solution at $-25\text{ }^{\circ}\text{C}$ was added trifluoromethanesulfonimide (0.20 M solution in toluene, freshly prepared, 2.5 mL, 0.5 mmol) dropwise. After 10 min at $-25\text{ }^{\circ}\text{C}$, a colorless homogeneous catalyst solution was ready for use in the cyanosilylation reactions.

To triphenylphosphine oxide (293 mg, 1.05 mmol) was added a catalyst solution in toluene (7.5 mL) at $0\text{ }^{\circ}\text{C}$ and it was stirred for 5 min until triphenylphosphine oxide dissolved in toluene completely. Trimethylsilyl cyanide (0.752 mL, 5.64 mmol) was added to the catalyst solution in one portion and an aldehyde (5 mmol) solution in toluene (3~5 mL) was dropwise added to the solution for 1 hr. Then the reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ for the time indicated in Table 1 and monitored by ^1H NMR or TLC.

Method 1 (Direct hydrolysis to cyanohydrin): When it was judged to be complete, 2N HCl (5 mL) and ethyl acetate (5 mL) were added and the resulting mixture was stirred vigorously for 2 hr. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined extract was dried over anhydrous Na_2SO_4 and evaporated, affording a residue that was purified by flash chromatography⁴ to obtain pure cyanohydrins.

Method 2 (Isolation of TMS protected cyanohydrin): When it was judged to be complete, volatile materials were evaporated *in vacuo* and water (5 mL) and pentane (5 mL) were added.

⁴ After elution of the cyanohydrin, the ligand-containing fractions were eluted with 10% MeOH- CH_2Cl_2 and concentrated *in vacuo*. This material was dissolved in diethyl ether and hydrolyzed by stirring with aqueous 2N NaOH solution for 2 h. The organic phase was collected, concentrated and purified by column chromatography (elution with EtOAc) to afford pure ligand (95-97% recovery).

The aqueous layer was extracted with pentane (3 x 5mL).⁵ The combined extract was dried over anhydrous Na₂SO₄, cooled down to -20 °C to remove residual triphenylphosphine oxide, filtered through glass filter and concentrated to afford the corresponding TMS protected cyanohydrin which was pure enough for the most purposes.

The corresponding racemic products for the determination of enantioselectivity were prepared by using ethylaluminum dichloride (10 mol %) as a Lewis acid catalyst.

Determination of Enantioselectivity and Absolute Configuration of the Cyanohydrins Reported in Tables 1.

Table 1, entry 1: Enantioselectivity of TMS ether was determined by GC analysis (γ -TA, 120 °C, 22 psi); retention times: 10.53 (major), 10.88 min (minor). The absolute configuration was determined by the sign of optical rotation: $[\alpha]_D^{23} +45.3$ (c 2.0, CHCl₃, 95% ee). [lit. $[\alpha]_D^{24} +36.8$ (c 2.0, CHCl₃) for *R*-enantiomer in 85 % ee]; Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, 58, 1515-1522.

Table 1, entry 2: Enantioselectivity of TMS ether was determined by GC analysis (Cyclosil B, 150 °C, 25 psi); retention times: 23.44 (minor), 24.45 min (major). The absolute configuration was determined by the sign of optical rotation: $[\alpha]_D^{23} +39.9$ (c 2.0, CHCl₃, 91% ee). [lit. $[\alpha]_D +21.3$ (c 1.0, CHCl₃) for *R*-enantiomer in 51% ee]; Matthews, B. R.; Jacson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, 41, 1697-1709.

Table 1, entry 3: Enantioselectivity was determined by conversion to the (*R*)-MTPA ester derivative and ¹H NMR integration (500 MHz, CDCl₃): δ 3.57 (d, 3H, J = 1.0 Hz, major), 3.45 (d, 3H, J = 0.5 Hz, minor). The absolute configuration was assigned by the sign of optical

⁵ After pentane extraction, the aqueous solution was treated with aqueous 2N NaOH solution and extracted with diethyl ether. The combined extract was dried over Na₂SO₄, concentrated to afford a mixture of ligand and triphenylphosphine oxide. Triphenylphosphine oxide was removed by treatment with hexanes to give pure ligand (95-97% recovery).

rotation: $[\alpha]_D^{23} +43.2$ (c 2.0, CHCl_3 , 90% ee). [lit. $[\alpha]_D^{24} +41.7$ (c 1.4, CHCl_3) for *R*-enantiomer in 91% ee]; Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, 58, 1515-1522.

Table 1, entry 4: Enantioselectivity of TMS ether was determined by GC analysis (γ -TA, 140 °C, 22 psi); retention times: 27.04 (minor), 27.64 min (major). The absolute configuration was determined by the sign of optical rotation: $[\alpha]_D^{23} +31.5$ (c 1.0, CHCl_3 , 97% ee). [lit. $[\alpha]_D +16.6$ (c 0.8, CHCl_3) for *R*-enantiomer in 52% ee]; Matthews, B. R.; Jacson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, 41, 1697-1709.

Table 1, entry 5: Enantioselectivity of TMS ether was determined by GC analysis (Cyclosil B, 90 °C, 25 psi); retention times: 36.59 (minor), 37.27 min (major). The absolute configuration was determined by the sign of optical rotation: $[\alpha]_D^{23} +8.2$ (c 2.0, CHCl_3 , 90 % ee). [lit. $[\alpha]_D^{24} +6.1$ (c 3.8, CHCl_3) for *R*-enantiomer in 65% ee]; Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, 58, 1515-1522.

Table 1, entry 6: Enantioselectivity of TMS ether was determined by GC analysis (γ -TA, 70 °C, 22 psi); retention times: 8.12 (major), 8.38 min (minor). The absolute configuration was determined by the sign of optical rotation: $[\alpha]_D^{23} +17.5$ (c 1.0, CHCl_3 , 91% ee). [lit. $[\alpha]_D^{24} +14.5$ (c 1.0, CHCl_3) for *R*-enantiomer in 70% ee]; Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, 58, 1515-1522.

Table 1, entry 7: Enantioselectivity of TMS ether was determined by GC analysis (γ -TA, 100 °C, 22 psi); retention times: 11.20 (minor), 13.11 min (major). The absolute configuration was determined by the sign of optical rotation: $[\alpha]_D^{23} +12.4$ (c 2.0, CHCl_3 , 91% ee). [lit. $[\alpha]_D^{21} -13.3$ (c 1.0, CHCl_3) for *S*-enantiomer in 98% ee]; Hamashima, Y.; Swada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, 121, 2641-2642.

Physical Data of the Cyanohydrins:

(R)-2-Hydroxy-2-phenylacetonitrile (Table 1, entry 1). The physical and spectral data were identical to those previously reported for this compound⁶: ¹H NMR (500 MHz, CDCl₃) δ 7.49-7.51 (m, 2H), 7.40-7.43 (m, 3H), 5.50 (s, 1H), 2.04 (brs, 1H) ; ¹³C NMR (125 MHz, CDCl₃) δ 135.2, 129.6, 129.0 (x2), 126.6 (x2), 118.9, 63.3, 18.6; [α]_D²³ +45.3 (c 2.0, CHCl₃, 95 % ee).

(R)-2-Hydroxy-2-*o*-tolylacetonitrile (Table 1, entry 2). ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, 1H, *J* = 8.0, 1.4 Hz), 7.33 (ddd, 1H, *J* = 8.0, 8.0, 1.4 Hz), 7.27 (ddd, 1H, *J* = 7.6, 7.6, 1.0 Hz), 7.23 (d, 1H, *J* = 7.6 Hz), 5.61 (s, 1H), 3.61 (brs, 1H), 2.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.1, 133.0, 131.2, 129.9, 126.9, 126.6, 118.7, 61.5, 18.6; FTIR (neat) 2361, 2340, 1021, 749; LRMS (CI) calcd for [C₉H₉NO] ([M]⁺):147; found 147 ; [α]_D²³ +39.9 (c 2.0, CHCl₃, 91% ee).

(R)-2-Hydroxy-2-(4-methoxyphenyl)acetonitrile (Table 1, entry 3). The physical and spectral data were identical to those previously reported for this compound⁶: ¹H NMR (500 MHz, CDCl₃) δ 7.45-7.48 (m, 2H), 6.94-6.97 (m, 2H), 5.49 (d, 1H, *J* = 6.5 Hz), 3.84 (s, 3H), 2.42 (d, 1H, *J* = 6.5 Hz); [α]_D²³ +43.2 (c 2.0, CHCl₃, 90% ee).

4-((R)-cyano(hydroxy)methyl)benzonitrile (Table 1, entry 4). The physical and spectral data were identical to those previously reported for this compound⁶: ¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 9.0 Hz), 5.66 (d, 1H, *J* = 7.0 Hz), 2.80 (d, 1H, *J* = 6.5 Hz); [α]_D²³ +31.5 (c 1.0, CHCl₃, 97% ee).

(R)-2-Cyclohexyl-2-hydroxyacetonitrile (Table 1, entry 5). The physical and spectral data were identical to those previously reported for this compound⁶: ¹H NMR (500 MHz, CDCl₃) δ 4.24 (d, 1H, *J* = 6.5 Hz), 3.74 (brs, 1H), 1.86 (t, 2H, *J* = 13.0 Hz), 1.77-1.80 (m, 2H), 1.67-1.73 (m, 2H), 1.03-1.0 (m, 5H); [α]_D²³ +8.2 (c 2.0, CHCl₃, 90% ee).

⁶ Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, 58, 1515-1522.

(R)-2-Hydroxy-3,3-dimethylbutanenitrile (Table 1, entry 6). The physical and spectral data were identical to those previously reported for this compound⁶: ¹H NMR (500 MHz, CDCl₃) 4.13 (s, 1H), 2.46 (brs, 1H), 1.08 (s, 9H); [α]_D²³ +17.5 (c 2.0, CHCl₃, 91% ee).

(R)-2-Hydroxyoctanenitrile (Table 1, entry 7). The physical and spectral data were identical to those previously reported for this compound⁷: ¹H NMR (400 MHz, CDCl₃) 4.48 (brt, 1H, *J* = 6.8 Hz), 2.24 (brs, 1H), 1.83-1.88 (m, 2H), 1.47-1.54 (m, 2H), 1.24-1.39 (m, 6H), 0.89 (t, 3H, *J* = 7.2 Hz); [α]_D²³ +12.4 (c 2.0, CHCl₃, 91% ee).

⁷ Hamashima, Y.; Swada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641-2642.