Supporting Information

Direct Catalytic Aldol-Type Reactions Using RCH₂CN

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General: NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ¹H NMR, 125.65 MHz for ¹³C NMR, and 470.4 MHz for ¹⁹F NMR. Chemical shifts were reported downfield from TMS (= 0) for ¹H NMR. For ¹³C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ¹⁹F NMR were carried out with trifluoroacetic acid (= -79 ppm) as an external standard. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC analysis was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; mobile phase, hexane-2-propanol. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Normal glassware can be used to conduct the reactions in this manuscript. CuF•3PPh₃•2EtOH was synthesized following the reported procedure.¹ (EtO)₃SiF was purchased from Azmax Co. Ltd. (Fax: +81-436-20-2665) and used after distillation. **3a**,² **3h**,² **3i**,³ **3j**,⁴ **3k**,⁵ and **3l**³ are known compounds.

Effect of TMSCH₂CN Slow Addition on CuF-Catalyzed Cyanomethylation

Entry	Slow addition time (h)	Yield (%)
1	0	40
2	2.5	50
3	4.5	75
4	7.5	54

General Procedure for Copper Fluoride Catalyzed Cyanomethylation by TMSCH₂CN (Table 1, entry 6): To a solution of CuF•3PPh₃•2EtOH (9.6 mg, 0.01 mmol) in THF (0.4 mL), **2f** (58.5 mg, 0.40 mmol) and (EtO)₃SiF (89 μ L, 0.48 mmol) were added in an ice bath. To the mixed solution, TMSCH₂CN (66 μ L, 0.48 mmol) was added slowly over 1 h by a syringe pump. After 6 h, 3HF•NEt₃ (0.3 mL) was added for desilylation (ca. 1 h). Satd. NaCl was added and the product was extracted with AcOEt. The combined organic layer was washed with satd. NaHCO₃, and dried over Na₂SO₄. Filtration, evaporation, and purification through silica gel column chromatography (AcOEt/hexane = 1/3~1/2) gave pure **3f** in 98% yield. Spectroscopic data for new compounds are as follows.

3-(4-Chlorophenyl)-3-hydroxybutyronitrile (3b): ¹H NMR (500 MHz, CDCl₃) δ : 7.4 (m, 2H), 7.3 (m, 2H), 2.81 (d, *J* = 12.4 Hz, 1H), 2.77 (d, *J* = 12.4 Hz, 1H), 2.55 (brs, 1H), 1.74 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ : 29.1, 33.7, 72.1, 117.0, 126.0, 128.8, 133.9, 143.1; IR (neat, cm⁻¹) 3441, 2253; MS *m/z* 196 (*M*⁺); HRMS Calcd for C₁₀H₁₀ClNO (*M*⁺) 196.0529. Found 196.0532.

3-(4-Methylphenyl)-3-hydroxybutyronitrile (3c): ¹H NMR (500 MHz, CDCl₃) δ : 1.74 (s, 3H), 2.35 (s, 3H), 2.77 (d, *J* = 16.5 Hz, 1H), 2.82 (d, *J* = 16.5 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 20.95, 29.11, 33.64, 72.34, 117.31, 124.30, 129.33, 137.75, 141.65; IR (neat, cm⁻¹) 3446, 2254; MS *m/z* 176 (*M*⁺+1); HRMS Calcd for C₁₁H₁₄NO (*M*⁺+1) 176.1075. Found 176.1080.

3-(4-Methoxyphenyl)-3-hydroxybutyronitrile (3d): ¹H NMR (500 MHz, CDCl₃) δ : 1.74 (s, 3H), 2.76 (d, *J*

= 16.8 Hz, 1H), 2.81 (d, J = 16.8 Hz, 1H), 3.81 (s, 3H), 6.90 (d, J = 8.9 Hz, 2H), 7.40 (d, J = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 29.10, 33.74, 55.28, 72.15, 113.92, 117.34, 125.73, 136.72, 159.17; IR (neat, cm^{-1}) 3445, 2253; MS m/z 192 (M^+ +1); HRMS Calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_2$ (M^+ +1) 192.1025. Found 192.1025.

3-Hydroxy-3-phenylpentanenitrile (3e): ^1H NMR (500 MHz, CDCl_3) δ : 0.81 (t, J = 7.3 Hz, 3H), 2.03 (q, J = 7.3 Hz, 2H), 2.43 (s, 1H), 2.84 (s, 2H), 7.28–7.34 (m, 2H), 7.35–7.43 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 7.70, 32.42, 34.12, 75.01, 117.29, 124.87, 127.74, 128.60, 142.67; IR (neat, cm^{-1}) 3457, 2253; MS m/z 176 (M^+ +1); HRMS Calcd for $\text{C}_{11}\text{H}_{14}\text{NO}$ (M^+ +1) 176.1075. Found 176.1080.

3-Hydroxy-3-methyl-5-phenylpent-4-enenitrile (3f): ^1H NMR (500 MHz, CDCl_3) δ : 1.56 (s, 3H), 2.39 (s, 1H), 2.66 (s, 2H), 6.30 (d, J = 15.9 Hz, 1H), 6.72 (d, J = 15.9 Hz, 1H), 7.23–7.29 (m, 1H), 7.29–7.35 (m, 2H), 7.36–7.41 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 27.79, 32.06, 71.05, 117.12, 126.66, 128.16, 128.65, 129.64, 132.44, 135.73; IR (neat, cm^{-1}) 3445, 2254; MS m/z 188 (M^+ +1); HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{NO}$ (M^+ +1) 188.1075. Found 188.1072.

3-Hydroxy-3-methyloctanenitrile (3g): ^1H NMR (500 MHz, CDCl_3) δ : 0.90 (t, J = 7.0 Hz, 3H), 1.27–1.42 (m, 9H), 1.57–1.65 (m, 2H), 2.05 (brs, 1H), 2.49 (d, J = 16.5 Hz, 1H), 2.53 (d, J = 16.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 13.89, 22.45, 23.40, 26.57, 31.14, 31.90, 41.42, 71.08, 117.72; IR (neat, cm^{-1}) 3444, 2253; MS m/z 156 (M^+ +1); HRMS Calcd for $\text{C}_9\text{H}_{18}\text{NO}$ (M^+ +1) 156.1388. Found 156.1396.

Hydrolysis of the Nitrile to β -Hydroxycarboxylic Acids (Scheme 2).⁶ From Ketone Cyanomethylation

Product 3a: NaOH (0.21 g, 5.3 mmol) was dissolved in H_2O (1.8 mL) and 30% H_2O_2 aq. (0.6 mL) was added. This solution was added to **3a** (38.8 mg, 0.24 mmol), and the mixture was stirred for 1 h at rt, followed by stirring at 50 °C for 6 h. After cooling in an ice bath, 3 M HCl was added till acidic. The product was extracted with AcOEt, and the combined organic layer was dried over Na_2SO_4 . Filtration, evaporation, and purification by preparative TLC (AcOEt/hexane/AcOH = 20/20/1) gave the product in 78% yield (34 mg).

From Aldehyde Cyanomethylation Product 3h: To **3h** (44.7 mg, 0.30 mmol), 3M NaOH aq. (2.2 mL) and 30% H_2O_2 aq. (0.8 mL) were added, and the mixture was stirred for 14 h at rt. 3 M HCl was added to acidify the solution. The product was extracted with AcOEt, and the combined organic layer was dried over Na_2SO_4 . Filtration, evaporation, and purification by preparative TLC (AcOEt/hexane/AcOH = 10/10/1) gave the product in 70% yield (35 mg).

General Procedure for CuO'Bu Catalyzed Direct Cyanomethylation of Aldehyde (Table 3, Entry 6):

CuO'Bu (0.03 mmol, 60 μL in THF) and dppe (18 mg, 0.045 mmol) were mixed and dried under vacuum for 1 h. To the residue, DMSO (0.3 mL), propionitrile (0.3 mL), and **2h** (30 μL , 0.3 mmol) were added to start the reaction. After 2 h, satd. NH_4Cl was added, and the product was extracted with AcOEt. The combined organic layer was washed with satd. NaCl aq., and dried over Na_2SO_4 . Filtration, evaporation, and purification by silica gel column chromatography gave the product in 90% yield (44 mg).

3-Hydroxy-5-methylhexanenitrile (3m): ^1H NMR (500 MHz, CDCl_3) δ : 0.92 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.34 (ddd, J = 4.3, 8.9, 13.7 Hz, 1H), 1.54 (ddd, J = 5.5, 9.2, 13.7 Hz, 1H), 1.75 (m, 1H), 2.15 (brs, 1H), 2.44 (dd, J = 6.4, 16.8 Hz, 1H), 2.54 (dd, J = 4.6, 16.8 Hz, 1H), 4.00 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 21.80, 23.09, 24.54, 26.61, 45.52, 65.97, 117.67; IR (neat, cm^{-1}) 3435, 2252.

General Procedure for Catalytic Enantioselective Direct Cyanomethylation of Aldehydes (Scheme 4).

3-Hydroxy-4,4-dimethyl-5-phenylpentanenitrile (3n): (*R*)-DTBM-SEGPHOS (53.1 mg, 0.045 mmol) and CuO'Bu (60 μL of 0.5 M THF solution, 0.03 mmol) were mixed and the solvent was evaporated under vacuum. The residue was dried under vacuum for 1 h. DMF (0.3 mL) and CH_3CN (0.3 mL) were added, and the mixture was cooled in an ice bath. Aldehyde **2n** was added and the mixture was stirred for 48 h at 4 °C. Satd. NH_4Cl was added and the product was extracted with AcOEt. The combined organic layer was washed with satd. NaCl aq., and dried over Na_2SO_4 . Filtration, evaporation, and purification by silica gel column chromatography (AcOEt/hexane = 1/5–1/3) gave the product in 45% yield (27.4 mg). The ee was determined by chiral HPLC analysis (CHIRALCEL OD-H, isopropanol/hexane = 1/20, 1 mL/min, t_r = 23.8 min (minor) and 46.4 min (major). ^1H NMR (500 MHz, CDCl_3) δ : 0.93 (s, 3H), 1.01 (s, 3H), 2.58 (m, 4H), 2.82 (d, J =

13.2 Hz, 1H), 3.77 (dd, $J = 3.1, 9.5$ Hz, 1H), 7.23 (brd, $J = 7.3$ Hz, 2H), 7.3–7.38 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 21.63, 21.65, 23.21, 38.68, 44.51, 73.55, 119.03, 126.35, 128.03, 130.56, 137.59; IR (neat, cm^{-1}) 3446, 2253; $[\alpha]_{\text{D}}^{22} -0.82$ (c 1.18, EtOH).

3-Hydroxy-3-phenylpropionitrile (3h): The ee was determined by chiral HPLC analysis (CHIRALPAK AS-H, isopropanol/hexane = 1/20, 0.8 mL/min, $t_{\text{R}} = 51.2$ min (minor) and 54.4 min (major). The absolute configuration was determined by comparison of the optical rotation: $[\alpha]_{\text{D}}^{22} = -24.2$ (c 2.34, EtOH) (43% ee).⁷

General Procedure for Catalytic Enantioselective Cyanomethylation of Ketones Using TMSCH_2CN (Scheme 4). 3-Hydroxy-3-phenyl-butyronitrile (3a): $\text{CuF}\cdot 2\text{H}_2\text{O}$ (1.4 mg, 0.01 mmol) and (*S*)-*p*-tol-BINAP (13.6 mg, 0.02 mmol) were dissolved in MeOH (0.35 mL), and the mixture was heated to reflux for 2 h. The solvent was evaporated under vacuum, and the residue was azeotropically dried by addition of toluene (0.5 mL) and evaporation. After drying the residue for 1 h under vacuum, degassed THF (0.4 mL) was added, followed by the addition of **2a** (47 μL , 0.40 mmol), $(\text{EtO})_3\text{SiF}$ (89 μL , 0.48 mmol), and TMSCH_2CN (66 μL , 0.48 mmol) at -30 °C. After 85 h, workup and purification following the general procedure described above gave the product in 48% yield. The ee was determined by chiral HPLC analysis (CHIRALCEL OD-H, isopropanol/hexane = 1/20, 1 mL/min, $t_{\text{R}} = 26.7$ min (minor) and 32.9 min (major). The absolute configuration was determined by converting to the corresponding 3-hydroxycarboxylic acid via hydrolysis (see Scheme 2), and comparison of the optical rotation: $[\alpha]_{\text{D}}^{23} = +3.0$ (c 0.96, solvent) (43% ee).⁸

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