Supporting Information

Cu(I)-Catalyzed Direct Enantioselective Cross Aldol-Type Reaction of Acetonitrile

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General: NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR, 125.65 MHz for ^{13}C NMR and 202.35 MHz for ^{31}P NMR. Chemical shifts were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ^{31}P NMR were carried out with H_3PO_4 (= 0 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. All of cyanomethylation products are known compounds.[1-7] (*R*)–DTBM-SEGPHOS is provided by Takasago international corporation (Fax: +81-463-25-2084). Ligand **6** was synthesized following the reported procedures.[8]

General Procedure for Catalytic Enantioselective Direct Cyanomethylation of Aldehydes (Table 2, Entry 6). 3-Cyclohexyl-3-hydroxy-propionitrile (5f)[6]: (*R*)-DTBM-SEGPHOS (53.1 mg, 0.045 mmol) and CuO^{t}Bu (120 □L of 0.25 M THF solution, 0.03 mmol) were mixed and the solvent was evaporated under vacuum. The residue was dried under vacuum for 1 h. HMPA (0.6 mL) and CH_3CN (0.3 mL) were added. To the mixed solution, aldehyde **4f** was added slowly over 5 h by a syringe pump, and the mixture was stirred for further 10 min. 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 = 1/10–1/5) gave the product in 91% yield (42.4 mg). Ee was determined after conversion to the corresponding benzoyl ester (1.5 equiv of benzoylchloride in pyridine at room temperature). DAICEL CHIRALPAK OD-H, hexane/2-propanol 20/1, 1.0 ml/min, t_R 9.7 min (minor), 12.6 min (major). The absolute configuration was determined to be *S* by comparison of the optical rotations to the reported values[9]: $[\square]^{26}_{D} = -7.5$ (c 0.99, $CHCl_3$) (75% ee).

Spectroscopic data and HPLC conditions of the products:

3-Hydroxy-nonanenitrile (5a)[1]: Ee was determined after conversion to the corresponding benzoyl ester. DAICEL CHIRALCEL OD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R 8.6 min (minor), 10.9 min (major).

3-Hydroxy-undecanenitrile (5b)[2]: Ee was determined after conversion to the corresponding benzoyl ester. DAICEL CHIRALCEL OD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R 8.4 min (minor), 10.8 min (major).

3-Hydroxy-5-phenyl-pentanenitrile (5c)[3]: DAICEL CHIRALCEL AD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R 21.1 min (major), 23.0 min (minor).

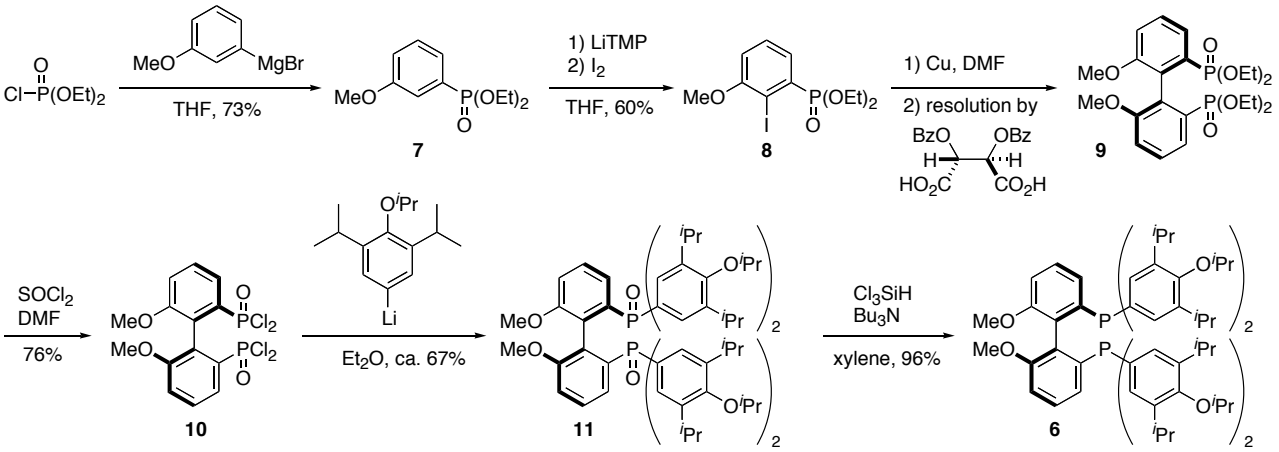
4-Cyclohexyl-3-hydroxy-butyronitrile (5d)[4]: Ee was determined after conversion to the corresponding benzoyl ester. DAICEL CHIRALCEL OD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R 7.4 min (minor), 10.3 min (major). $[\square]^{25}_{D} = +9.9$ (c 1.4, $CHCl_3$) (76% ee).

3-Hydroxy-5-methyl-hexanenitrile (5e)[5]: Ee was determined after conversion to the corresponding benzoyl ester. DAICEL CHIRALCEL OD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R 8.6 min (minor), 12.7 min (major).

3-Hydroxy-4,4-dimethyl-5-phenyl-pentanenitrile (5g)[5]: DAICEL CHIRALCEL OD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R = 23.8 min (minor) and 46.4 min (major).

3-Hydroxy-3-phenylpropionitrile (5h)[7]: DAICEL CHIRALCEL AS-H, hexane/2-propanol 20/1, 0.8 mL/min, t_R = 51.2 min (minor) and 54.4 min (major).

Ligand **6** was synthesized via the following synthetic scheme. Compounds **7**–**10** are known synthetic intermediates.[8]



(3-Methoxyphenyl)phosphonic acid diethyl ester (7): A solution of 3-bromoanisole (25.2 g, 135 mmol) in THF (65 mL) was added dropwise to Mg (3.5 g, 144 mmol) and a small tip of I_2. After stirring at rt for 3 h, the Grignard reagent solution was cooled to –78 ºC, and diethylchlorophosphate (25.0 g, 145 mmol) in THF (55 mL) was added dropwise. The reaction temperature was gradually increased to rt, and the reaction was continued for 16 h. The solvent was evaporated to half amount, and H_2O was added. Products were extracted with AcOEt/hexane = 1/1 x 3 times, and the combined organic layer was washed with saturated NaCl. After concentration of the organic layer, purification by SiO_2 column chromatography (eluent: AcOEt/hexane = 1/2) gave **7** in 73% yield (24.0 g). ^{1}H NMR ($CDCl_3$) □ 1.33 (t, *J* = 7.0 Hz 6H), 3.85 (s, 3H), 4.05–4.17 (m, 4H), 7.09 (m, 1H), 7.32–7.40 (m, 3H).

(2-Iodo-3-methoxyphenyl)phosphonic acid diethyl ester (8): A hexane solution of BuLi (1.56 M in hexane, 75 mL, 117 mmol) was added to a solution of tetramethylpiperidine (24 mL, 142 mmol) in THF (100 mL) at –78 ºC. The temperature was increased to –20 ºC, and the solution was stirred for 1 h. After re-cooling to –78 ºC, cold solution (–78 ºC) of **7** in THF (100 mL) was added, and the deprotonation was performed for 30 min. To this aryllithium, I_2 (25 g, 100 mmol) in THF (50 mL) was added, and the temperature was increased gradually to rt. After 16 h, saturated NH_4Cl and H_2O were added, and products were extracted with AcOEt. After concentration, purification through SiO_2 column chromatography (eluent: acetone/hexane = 1/10) followed by recrystallization from toluene/hexane = 1/5 gave **8** in 60% yield (21.8 g). ^{1}H NMR ($CDCl_3$) □ 1.37 (t, *J* = 7.0 Hz, 6H), 3.92 (s, 3H), 4.11–4.23 (m, 4H), 6.98 (d, *J* = 8.3 Hz, 1H), 7.40 (m, 1H), 7.63 (m, 1H).

(*R*)–[6'-(Diethoxyphosphoryl)-6,2'-dimethoxybiphenyl-2-yl]phosphonic acid diethyl ester (9): Cu powder (6.5 g, 102 mmol) was added to a solution of **8** (19.7 g, 53 mmol) in DMF (50 mL), and the whole was stirred at 140 ºC for 2 h. After cooling to rt, solvent was evaporated at 70 ºC, and the residue was dissolved in CH_2Cl_2 (50 mL). Precipitate was filtrated, and the residue was washed with CH_2Cl_2. The combined organic layer was washed with saturated NH_4Cl x 3 times, and concentrated to give the racemate. Part of the crude racemates (12.3 g, 25 mmol) was resolved by salt formation with (+)-dibenzoyltartaric acid (9.5 g, 26.5 mmol) in Et_2O to give pure (*R*)–isomer salt (2.95 g, 48%: the absolute configuration was temporarily assigned based on the analogy of ligand **6** to DTBM-SEGPHOS and the absolute configuration of the nitrile aldol product). Conversion of the salt to **9** was performed by washing a CH_2Cl_2 solution of the salt with saturated $NaHCO_3$. Enantiomeric purity was checked by chiral HPLC analysis. DAICEL CHIRALCEL OD-H, hexane/2-propanol 20/1, 1.0 mL/min, t_R = 19.4 min (*S*) and 22.2 min (*R*). ^{1}H NMR ($CDCl_3$) □ 1.12 (t, *J* = 8.3 Hz, 6H), 1.17 (t, *J* = 8.3 Hz, 6H), 3.71 (s, 6H), 3.77–3.94 (m, 8H), 7.10 (d, *J* = 8.3 Hz), 7.42 (ddd, *J* = 4.9, 7.9, 8.3 Hz, 1H), 7.56 (ddd, *J* = 0.9, 7.9, 13.8 Hz, 1H); ^{31}P NMR ($CDCl_3$) □ 18.1.

(*R*)–[6'-(Dichlorophosphoryl)-6,2'-dimethoxybiphenyl-2-yl]phosphonic acid dichloride (10): $SOCl_2$ (3.6 mL, 49 mmol) and DMF (380 □L) were added to **9** (2.45 g, 5.0 mmol), and the mixture was stirred under

reflux for 3.5 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (10 mL). Filtration through celite pad, evaporation of solvent, and crystallization with hexane gave **10** as white powder (1.7 g, 76%). ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H), 7.23 (d, J = 8.2 Hz, 1H), 7.59 (dd, J = 6.2, 15.6 Hz, 1H), 7.67 (dd, J = 8.2, 20 Hz, 1H); ^{31}P NMR ($CDCl_3$) δ 34.1.

6,6'-Bis-[bis(4-isopropoxy-3,5-diisopropylphenyl)phosphinoyl]-2,2'-dimethoxybiphenyl (11): A hexane solution of ^{t}BuLi (1.43 M, 4.4 mL) was added to a solution of 5-bromo-2-isopropoxy-1,3-diisopropylbenzene (1.0 g, 3.3 mmol) in Et_2O (20 mL) at –78 ºC, and the temperature was increased to –40 ºC. This aryllithium solution was added to a solution of **10** (200 mg, 0.45 mmol) in Et_2O (20 mL) at –78 ºC, and the mixture was warmed gradually to rt. A saturated NH_4Cl solution was added, and products were extracted with AcOEt. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated. Partial purification through SiO_2 column chromatography gave **11** in ca. 67% yield (355 mg).

(1*S*)-2,6'-Bis[bis(3,5-diisopropyl-4-isopropoxyphenyl)phosphanyl]-6,2'-dimethoxybiphenyl (ligand 6): Cl_3SiH (230 μL, 2.3 mmol) was added to a solution of **11** (340 mg, 0.29 mmol) and Bu_3N (540 μL, 2.3 mmol) in xylene (4 mL), and the mixture was heated under reflux for 3 h. After cooling to rt, 30% NaOH aq (2 mL) was added, and the mixture was stirred at 60 ºC for 1 h. After cooling, products were extracted with AcOEt x 3 times, and the combined organic layer was washed with saturated $NaHCO_3$, NH_4Cl, and NaCl aqueous solutions successively. Concentration and purification through SiO_2 column chromatography (hexane to AcOEt/hexane = 1/20) gave **6** in 96% yield (321 mg). **6 w**as further purified by recrystallization from MeOH. ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 5.4 Hz 12H), 1.00 (d, J = 5.4 Hz 12H), 1.08 (d, J = 5.4 Hz, 3H), 1.13 (d, J = 5.4 Hz 12H), 1.23-1.31 (m, 24H), 3.01 (s, 6H), 3.23 (sept, J = 5.4 Hz, 4H), 3.30 (sept, J = 5.4 Hz, 4H), 4.02 (sept, J = 5.0 Hz 2H), 4.08 (sept, J = 5.0 Hz 2H), 6.68 (d, J = 6.5 Hz 2H), 6.74-6.78 (m, 2H), 6.95-7.03 (m, 8H), 7.22 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.2, 22.36, 22.41, 23.90, 23.95, 24.0, 24.3, 26.55, 26.60, 31.6, 54.9, 75.77, 75.80, 110.61, 126.2, 127.7, 128.9 (t, J = 10.8 Hz), 130.6 (t, J = 11.9 Hz), 132.3-132.4 (m), 133.1-133.4 (m), 134.4-134.6 (m), 139.9-140.1 (m), 141.1-141.3 (m), 151.0, 151.6, 157.6 (t, J = 6.2 Hz); ^{31}P NMR ($CDCl_3$) δ –15.1; MS m/z 1152 ($M+H^+$); HRMS Calcd for $C_{74}H_{105}O_6P_2$ ($M+O_2+H^+$) 1183.7279. Found 1183.7280. IR (neat) 2965, 1460 cm^{-1}.

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