



Supporting Information

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Multicenter Strategy for the Development of Catalytic Enantioselective Nucleophilic Alkylation to Ketones: Me₂Zn Addition to α -Ketoesters

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Methods

NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ¹H NMR, 125 MHz for ¹³C NMR. Chemical shifts in CDCl₃ were reported downfield from TMS (= 0) for ¹H NMR. For ¹³C NMR, chemical shifts were reported in the scale relative to CDCl₃ (77.00 ppm for ¹³C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. IR spectra were measured on a JASCO FT/IR-410 spectrometer. Mass spectra were measured on a JEOL BU-20 spectrometer. Enantiomeric excesses (ee) were determined by HPLC analyses. HPLC analyses were 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; column, DAICEL CHIRALPAK AD-H, AS-H, or DAICEL CHIRALCEL OD-H; mobile phase, hexane/2-propanol; flow rate, 1.0 mL/min.

Reagent supplies and preparations

In general, reactions were carried out in dry solvents purchased from KANTO CHEMICAL CO., INC., 2-8, Nihonbashi Honcho 3-chome, Chuo-ku, Tokyo, 103-0023, Japan (fax: +813-3279-5560, E-mail info@gms.kanto.co.jp) under an argon atmosphere, unless otherwise specified. Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Reagents were purified by standard methods before use unless otherwise specified.

Dimethylzinc in hexane (1.0 M) was purchased from KANTO CHEMICAL CO., INC. *trans*-4-

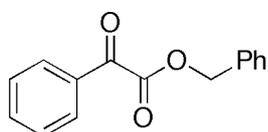
Hydroxy-L-proline and *cis*-4-hydroxy-L-proline were purchased from Aldrich and used as received.

Reagents listed below were purchased and purified by indicated methods prior to use:

Methyl benzoylformate (13a)	Acros	distillation (2 mmHg, 87-89 °C)
Ethyl benzoylformate (13b)	TCI	distillation (2 mmHg, 96-98 °C)
1-Methylisatin (13k)	Aldrich	recrystallization (toluene-hexane)

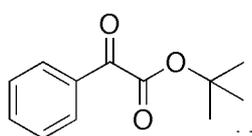
α -Ketoesters have been prepared in various methods, such as addition of Grignard reagents to oxalates (Rambaud, M.; Balasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, 564-566; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211-213), Friedel-Crafts reaction (Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407-6415), transition metal catalyzed reactions (Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513-13520; Rossi, R.; Carpita, A.; Pazzi, P.; Mannina, L.; Valensin, D. *Tetrahedron* **1999**, *55*, 11343-11364) and oxidation of alkynes (*Tetrahedron Lett.* **2002**, *43*, 2427-2430). For esterification of α -ketoacids, reaction with chloroformates is the simplest and the most reliable (Domagala, J. M. *Tetrahedron Lett.* **1980**, *21*, 4997-5000).

Compounds listed below were prepared according to literature procedures (or modified procedures) respectively.

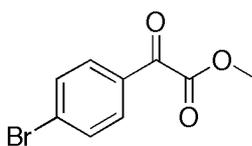


Benzyl benzoylformate (13c) (Domagala, J. M. *Tetrahedron Lett.* **1980**, *21*, 4997-5000): pale yellow oil, purified by distillation (0.1 mmHg, 160-162 °C); ¹H NMR (CDCl₃): δ 5.43 (s, 2H), 7.46-7.51 (m, 7H), 7.63-7.69 (m, 1H), 7.97-7.99 (m, 2H); ¹³C NMR (CDCl₃): δ 6.8, 127.7, 127.8, 127.9, 128.0,

129.1, 131.5, 133.5, 134.0, 162.7, 185.1; IR (neat) 1738, 1687, 1596, 1498, 1451, 1377, 1321, 1196, 1173, 991, 750, 696 cm⁻¹; EI-MS m/z 241 (M⁺), 212, 181, 167, 165, 152, 105 (PhCO⁺), 91 (Bn⁺), 77 (Ph⁺), 65, 52; Anal. Calcd. for C₁₅H₁₂O₃: C, 74.99, H, 5.03. Found: C, 74.77, 5.22.

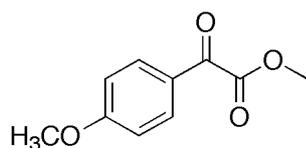


***t*-Butyl benzoylformate (13d)** (Kiesewetter, D. O. *Tetrahedron: Asymmetry* **1993**, *4*, 2183-2198): colorless oil, purified by distillation (0.1 mmHg, 93-95 °C). Spectra corresponded to the reported values.

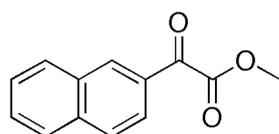


Methyl *p*-bromophenylglyoxylate (13e) (Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407-6415): To a solution of bromobenzene (2.11 mL, 20 mmol) and methyl chloro(oxo)acetate (2.58 mL 28 mmol, 1.4 equiv) in CH₂Cl₂ (40 mL, 0.50 M) at -5 °C, was added AlCl₃ (4.80 g, 36 mmol, 1.8 equiv) in small portions and warmed up to room temperature. After 20 min the reaction mixture turned to solution and was poured into ice water to quench, then conc. HCl aq. (~20 mL) was added.

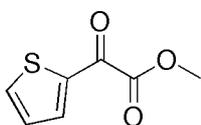
Extraction with CH₂Cl₂, washing with 1N NaOH aq., purification by a column chromatography (SiO₂, AcOEt/Hx, 1/4) and recrystallization from Hx gave the product in 37% yield as white needles. ¹H NMR (CDCl₃): δ 3.98 (s, 3H), 7.66-7.68 (m, 2H), 7.90-7.95 (m, 2H); ¹³C NMR (CDCl₃): δ 53.0, 130.7, 131.3, 131.5, 132.3, 163.4, 184.7; IR (neat) 1730, 1691, 1584, 1400, 1325, 1208, 1171, 1071, 1002, 843, 777, 669 cm⁻¹; EI-MS m/z 244 (M⁺, ⁸¹Br), 242 (M⁺, ⁷⁹Br), 216, 214, 185 (M⁺-COOCH₃, ⁸¹Br), 183 (M⁺-COOCH₃, ⁷⁹Br), 157 (⁸¹BrPh⁺), 155 (⁷⁹BrPh⁺), 104 (C₆H₄CO⁺), 74, 59; Anal. Calcd. for C₉H₇BrO₃: C, 44.47; H, 2.90. Found: C, 44.24; H, 3.02.



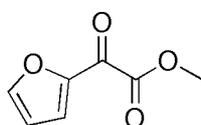
Methyl p-methoxyphenylglyoxylate (13f) (Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407-6415): To a suspension of AlCl₃ (1.85 g, 13.8 mmol, 1 equiv) in dichloroethane (13.8 mL, 1.0 M) cooled to -5 °C, was added methyl chloro(oxo)acetate (1.78 mL, 19.4 mmol, 1.4 equiv, over 5 min) followed by anisole (1.50 mL, 13.8 mmol, 1equiv, over 15 min). The reaction mixture was warmed up to room temperature and kept stirring overnight. It was poured into ice water to quench, followed by addition of conc. HCl aq. (~20 mL). Extraction with CH₂Cl₂, washing with 0.1N NaOH aq., purification by a column chromatography (SiO₂, CH₂Cl₂), and distillation (0.1 mmHg, 122-125 °C) gave the product in 56% yield as colorless solid. ¹H NMR (CDCl₃): δ 3.85 (s, 3H), 3.92 (s, 3H), 6.91-6.97 (m, 2H), 7.94-7.99 (m, 2H); ¹³C NMR (CDCl₃): δ 52.7, 55.6, 114.2, 125.4, 132.6, 164.3, 165.1, 184.4; IR (neat) 1731, 1671, 1600, 1512, 1439, 1319, 1269, 1224, 1167, 1025, 847, 798, 680 cm⁻¹; EI-MS m/z 194 (M⁺), 135 (M⁺-COOCH₃), 120 (M⁺-COOCH₃-CH₃), 107 (CH₃OC₆H₄⁺), 92 (OC₆H₄⁺), 77, 64, 63; Anal. Calcd. for C₁₀H₁₀O₄: C, 61.85; H, 5.19. Found: C, 62.07; H, 5.33.



Methyl 2-naphthylglyoxylate (13g): commercially available, can be prepared based on the literature procedure (Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883-2887; compare to the procedure for **13j**).

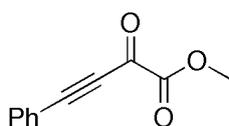


Methyl 2-thiophenylglyoxylate (13h) (Domagala, J. M. *Tetrahedron Lett.* **1980**, *21*, 4997-5000; compare to the procedure for **13i**. 2-Thiophenylglyoxylic acid was purchased from Aldrich): pale yellow solid, 82% yield; ¹H NMR (CDCl₃): δ 3.94 (s, 3H), 7.15-7.18 (m, 1H), 7.79-7.81 (m, 1H), 8.12-8.13 (m, 1H); ¹³C NMR (CDCl₃): δ 53.2, 128.7, 137.4, 137.6, 138.9, 161.9, 175.9; IR (neat) 1734, 1664, 1509, 1410, 1357, 1307, 1211, 1178, 1056, 986, 861, 732 cm⁻¹; EI-MS m/z 170 (M⁺), 142, 111 (M⁺-COOCH₃), 83 (C₄H₃S⁺), 57; Anal. Calcd. for C₇H₆O₃S: C, 49.40; H, 3.55. Found: C, 49.24; H, 3.71.



Methyl 2-furyl glyoxylate (13i) (Domagala, J. M. *Tetrahedron Lett.* **1980**, *21*, 4997-5000): Furyl glyoxylic acid (\square -oxo-2-furanacetic acid) is purchased from Fluka. To a solution of furyl glyoxylic acid (3.0 g, 21.4 mmol) in CH₂Cl₂ (21.4 mL, 1.0 M), were added triethylamine (2.98 mL, 21.4 mmol, 1equiv) and methyl

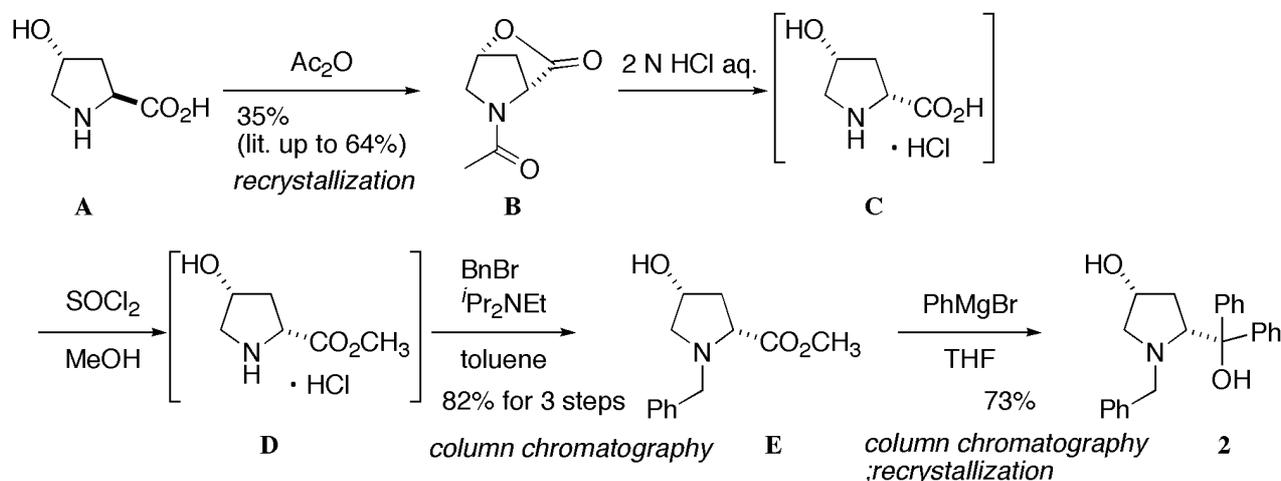
chloroformate (1.65 mL, 21.4 mmol, 1 equiv) successively at room temperature and the reaction mixture was kept stirring for 30 min. Quenching with H₂O, extraction with AcOEt, purification by a column chromatography (SiO₂, AcOEt/Hx, 1/2), and recrystallization from Hx gave the product in 71% yield as pale yellow solid. This compound can be purified by sublimation (2 mmHg, ~80 °C oil bath). ¹H NMR (CDCl₃): δ 3.97 (s, 3H), 6.47 (dd, *J* = 3.7, 1.5 Hz, 1H), 7.76 (dd, *J* = 3.7, 0.6 Hz, 1H), 7.78 (dd, *J* = 1.5, 0.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 53.1, 113.0, 124.9, 149.61, 149.66 161.3, 170.6; Other spectra corresponded to the reported values (Monenschein, H.; Drager, G.; Jung, A.; Kirschning, A. *Chem. Euro. J.* **1999**, *5*, 2270-2280; Goshima, K.; Maezono, N.; Tokuyama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3692-3698).



Methyl phenylethynylglyoxylate (13j): To a solution of dimethyl oxalate (5.66 g, 48 mmol, 3 equiv) in THF (150 mL, 0.32 M) cooled to -78 °C, was added over 5 min a solution of lithium phenylacetylide which was separately prepared from phenylacetylene (1.76 mL, 16 mmol) and *n*-BuLi (10.1 mL of 1.58 M soln. in hexane, 16 mmol) in THF (50 mL) at -78 °C. The reaction mixture was warmed up to room temperature and kept stirring overnight. Quenching with H₂O, extraction with AcOEt, and purification by column chromatographies (SiO₂, Et₂O/Hx, 1/10 for twice) gave the product in 17% yield as pale yellow needles. Suspicious to be light sensitive. ¹H NMR (CDCl₃): δ 3.94 (s, 3H), 7.39-7.42 (m, 2H), 7.49-7.52 (m, 1H), 7.64-7.66 (m, 2H); ¹³C NMR (CDCl₃): δ 53.7, 87.1, 98.1, 118.9, 128.8, 131.9, 133.8, 159.6, 169.1; IR (neat) 2198, 1745, 1677, 1595, 1489, 1443, 1300, 1301, 1251, 1081, 999, 951, 846, 760, 688 cm⁻¹; EI-MS *m/z* 188 (M⁺), 160, 158, 129 (M⁺-COOCH₃), 101 (PhCC⁺), 77 (Ph), 75, 74, 52; Anal. Calcd. for C₁₁H₈O₃: C, 70.11; H, 4.52. Found: C, 70.21; H, 4.29.

Synthesis of catalysts

Overview: The catalyst **2** was prepared in 5 steps (2 steps at shortest) starting from commercially available compounds.



(1R,4R)-5-Acetyl-2-oxa-5-aza-bicyclo[2,2,1]heptan-3-one (B) was prepared according to a literature procedure (Crose P. D.; Rosa C. L. *Tetrahedron: Asymmetry* **2002**, *13*, 197-201). A mixture of *trans*-4-hydroxy-L-proline (**A**, 10 g, 76.3 mmol, purchased from Aldrich) and acetic anhydride (60 mL, excess) was heated at 90 °C for 20 h to give the product in 35% yield as colorless cubes after recrystallization from MeOH-Et₂O (colorless cubes. lit. up to 64%).

cis-4-Hydroxy-D-proline hydrochloride (C): *cis*-4-Hydroxy-D-proline and its enantiomer are commercially available from Acros, Aldrich, Fluka, and many companies. For preparation of HCl salt, (1R,4R)-*N*-acetyl-2-oxa-5-aza-bicyclo[2,2,1]heptan-3-one (**B**, 1.50 g, 9.67 mmol) was dissolved in 2 N HCl aq. (9.7 mL) and heated to 100 °C for 4 h. The mixture was dried in vacuo to give a crude product **C** as a white solid. This crude mixture was used in the next step without further purification. ¹H NMR (CD₃OD): δ 2.34-2.50 (m, 2H), 3.37-3.45 (m, 2H), 4.50-4.55 (m, 2H).

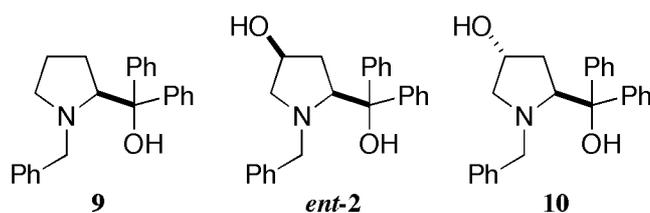
cis-4-Hydroxy-D-proline methyl ester hydrochloride (D): *cis*-4-Hydroxy-L-proline methyl ester is commercially available. For preparation: To a suspension of **C** (ca. 1.62 g, 9.67 mmol) in anhydrous MeOH (9.7 mL), was added SOCl_2 (705 μL , 9.67 mmol) at 0 °C to prepare a 2 N HCl in MeOH, and the mixture was heated to reflux for 4.5 h. The mixture was dried in vacuo to give a crude product **D** as a light brown oil. This crude mixture was used in the next step without further purification. ¹H NMR (CD₃OD): δ 2.35-2.51 (m, 2H), 3.37-3.42 (m, 2H), 3.84 (s, 3H), 4.53 (s, 1H), 4.59-4.60 (m, 1H).

cis-N-Benzyl-4-hydroxy-D-proline methyl ester (E): To a suspension of **D** (ca. 1.76 g, 9.67 mmol) in toluene (9.7 mL), were added $i\text{Pr}_2\text{NEt}$ (4.21 mL, 24.2 mmol) and benzyl bromide (1.27

mL, 10.6 mmol), and the mixture was heated at 110 °C for 6 h. Meanwhile the mixture turned into a biphasic clear solution. Quenching with NaHCO₃ aq., extraction with AcOEt and purification by a column chromatography (SiO₂, AcOEt/Hx, 1/1) gave the product **E** as a light brown oil in 82% yield for 3 steps from **B**. ¹H NMR (CDCl₃): δ 1.91-1.95 (m, 1H), 2.35-2.42 (m, 1H), 2.60 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.00 (d, *J* = 9.8 Hz, 1H), 3.31-3.33 (br, 1H), 3.32 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.62 (s, 3H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.86 (d, *J* = 13.0 Hz, 1H), 4.20-4.27 (m, 1H), 7.23-7.30 (m, 5H); ¹³C NMR (CDCl₃): δ 39.1, 51.9, 58.0, 61.6, 63.2, 70.7, 127.1, 128.1, 128.9, 137.8, 175.3; [α]_D²⁴ +51.1 (*c* 2.72, CHCl₃); IR (neat) 3421, 1736, 1496, 1438, 1378, 1205, 1085, 752, 702 cm⁻¹; MS *m/z* 235 (M⁺), 176 (M⁺-COOCH₃), 91 (Bn⁺), 77 (Ph⁺), 65, 58; EI-HRMS Calcd. for C₁₃H₁₇NO₃ 235.1208 (M⁺), Found 235.1206.

(3*R*,5*R*)-1-Benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-ol (2): To a solution of **E** (700 mg, 2.98 mmol) in THF (8.5 mL), was added PhMgBr (1.04 M in THF, 11.4 mL, 11.9 mmol) over 5 min at -78 °C and the mixture was kept stirring for 3 h at room temperature. Quenching with NaHCO₃ aq., extraction with AcOEt and purification by a column chromatography (SiO₂, AcOEt/Hx, 1/1) gave the product **2** in 83% yield as a white powder. Further purification by recrystallization (AcOEt-Hx) gave a white powder in 73% yield overall. ¹H NMR (CDCl₃): δ 1.74-1.77 (m, 1H), 2.36-2.42 (m, 1H), 2.48 (dd, *J* = 10.5, 3.8 Hz, 1H), 2.95 (d, *J* = 8.2 Hz, 1H), 2.98 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.05 (d, *J* = 12.5 Hz, 1H), 3.26 (d, *J* = 12.5 Hz, 1H), 4.09-4.12 (m, 1H), 4.15 (dd, *J* = 10.4, 3.0 Hz, 1H), 5.17 (bs, 1H), 7.01 (d, *J* = 6.7 Hz, 2H), 7.12-7.32 (m, 9H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H); ¹³C NMR (CDCl₃): δ 38.7, 60.4, 63.7, 69.8, 70.0, 77.7, 125.5, 125.7, 126.5, 126.7, 127.0, 128.2, 128.29, 128.33, 128.6, 138.8, 145.9, 146.9; [α]_D²³ -97.3 (*c* 1.00, CHCl₃); IR (neat) 3397, 1597, 1494, 1449, 1377, 1180, 1124, 1029, 963, 829, 749, 700, 640 cm⁻¹; MS *m/z* 359 (M⁺), 346, 323, 246, 232, 217, 201, 182 (Ph₂CO⁺), 176 (M⁺-Ph₂COH), 159 (M⁺-Ph₂COH-OH), 105 (PhCO⁺), 91 (Bn⁺), 77 (Ph⁺), 68 (C₄H₆N⁺), 65; Anal. Calcd. for C₂₄H₂₅NO₂: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.04; H, 6.99; N, 3.88.

(2*S*)-1-Benzyl-2-(hydroxydiphenylmethyl)-pyrrolidine (9) was prepared according to a literature procedure (Hedenstroem, E.; Andersson, F.; Hjalmarsson, M. *J. Chem. Soc., Perkin Trans. I* **2000**, 1513-1518). **(3*S*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-ol (*ent*-**2**)** and **(3*R*,5*S*)-1-benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-ol (10)** were prepared from *cis*-4-hydroxy-L-proline and *trans*-4-hydroxy-D-proline respectively according to the procedure for **2**.



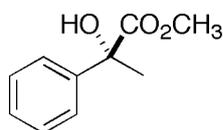
Preparation of racemic compounds

Racemic compounds **13a-k** were prepared by reactions between corresponding α -ketoesters and dimethylzinc (2 equiv) in CH_2Cl_2 or toluene at room temperature in the presence of 20-30 mol % ZnI_2 as a catalyst. The products were obtained in 50-90% yields.

The catalytic enantioselective addition of dimethylzinc to α -ketoesters

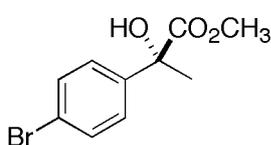
General procedure:

To a solution of the catalyst **2** (7.2 mg, 0.020 mmol) in toluene (0.45 mL), was added dimethylzinc (1.0 M in hexane, 18 μL , 0.018 mmol) and the resulting solution was kept stirring for 30 min at room temperature. i -PrOH (4.13 μL in 0.050 mL toluene) was then added and stirring was continued for further 30 min. The mixture was cooled to -20 $^\circ\text{C}$ and substrate α -ketoester (0.20 mmol) was added, followed by the addition of dimethylzinc (1.0 M in hexane, 482 μL , 0.482 mmol) dropped slowly over 30 h using a syringe pump. The reaction vessel has to be sealed strictly not to lose volatile dimethylzinc. 12 h after the end of the addition, the reaction mixture was quenched by 10% citric acid aq. Extraction with AcOEt and purification by a column chromatography (SiO_2 , AcOEt/Hx, 1/8 to 1/4) gave a product. Enantiomeric excesses (ee) were determined by chiral HPLC analyses. For solid compounds as substrates, the catalyst was prepared in 0.30 mL toluene and substrates were added as solutions in 0.20 mL toluene. For 1-methylisatin (**13k**) as a substrate, the catalyst was prepared in 0.50 mL toluene and the substrate was added directly as a solid.



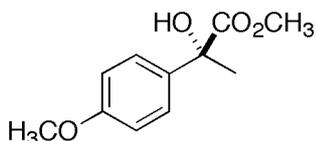
(R)-Methyl 2-hydroxy-2-phenylpropionate (14a): colorless oil; ^1H NMR (CDCl_3): δ 1.79 (s, 3H), 3.75 (s, 1H), 3.77 (s, 3H), 7.28-7.31 (m, 1H), 7.34-7.37 (m, 2H), 7.54-7.56 (m, 2H); ^{13}C NMR (CDCl_3): δ 26.7, 53.2, 75.8, 125.1, 127.8, 128.3, 142.7, 176.1; $[\alpha]_{\text{D}}^{25}$ -58.0 (c 1.39, CHCl_3 , 92% ee), $[\alpha]_{\text{D}}^{24}$ -4.6 (c

1.17, MeOH, 92% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_{R} 9.7 min (minor) and 10.7 min (major); IR (neat) 3502, 1732, 1447, 1256, 1148, 1096, 1071, 976, 733, 699, 658 cm^{-1} ; EI-MS m/z 180 (M^+), 163 (M^+-OH), 121 ($\text{M}^+-\text{COOCH}_3$), 105, 91, 77; EI-HRMS Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_3$ 180.0786 (M^+), Found 180.0784. The absolute configuration was assigned compared with a reported value (Whitman, C. P.; Craig, J. C.; Kenyon, G. L. *Tetrahedron* **1985**, *41*, 1183-1192), which was confirmed by comparison with that of a prepared compound by methanolysis of a known chiral cyanohydrin (Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908-9909).

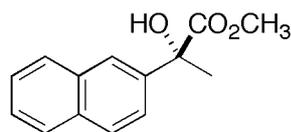


Methyl 2-(4-bromophenyl)-2-hydroxypropionate (14e): colorless oil; ^1H NMR (CDCl_3): δ 1.76 (s, 3H), 3.78 (s, 3H), 3.81 (s, 1H), 7.42-7.49 (m, 4H); ^{13}C NMR (CDCl_3): δ 26.8, 53.4, 75.4, 122.0, 127.1, 131.4, 141.7, 175.7; $[\alpha]_{\text{D}}^{24}$ -39.3 (c 0.760, CHCl_3 , 85% ee); HPLC (DAICEL

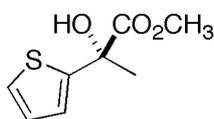
CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R 10.1 min (minor) and 11.1 min (major); IR (neat) 3495, 1732, 1487, 1456, 1397, 1255, 1150, 1079, 1010, 976, 829, 756, 715 cm^{-1} ; EI-MS m/z 260 (M^+ , ^{81}Br), 258 (M^+ , ^{79}Br), 201 ($M^+ - \text{COOCH}_3$, ^{81}Br), 199 ($M^+ - \text{COOCH}_3$, ^{79}Br), 183, 185, 157 ($^{81}\text{BrPh}^+$), 155 ($^{79}\text{BrPh}^+$), 121, 105, 102; EI-HRMS Calcd. for $\text{C}_{10}\text{H}_{11}^{81}\text{BrO}_3$ 259.9871 (M^+), Found 259.9870.



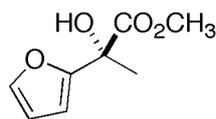
Methyl 2-hydroxy-2-(4-methoxyphenyl)propionate (14f): white solid; ^1H NMR (CDCl_3): δ 1.76 (s, 3H), 3.756 (bs, 1H), 3.760 (s, 3H), 3.80 (s, 3H), 6.88 (d, $J = 8.9$ Hz, 2H), 7.46 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (CDCl_3): δ 26.6, 53.2, 55.2, 75.3, 113.6, 126.4, 134.8, 159.1, 176.3; $[\alpha]_D^{25} -45.0$ (c 0.945, CHCl_3 , 92% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R 14.4 min (minor) and 16.1 min (major); IR (neat) 3502, 1733, 1683, 1600, 1511, 1457, 1301, 1252, 1179, 1163, 1112, 1030, 835, 615 cm^{-1} ; EI-MS m/z 210 (M^+), 194, 151 ($M^+ - \text{COOCH}_3$), 135, 121, 109, 92, 77; EI-HRMS Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_4$ 210.0892 (M^+), Found 210.0891.



Methyl 2-hydroxy-2-(2-naphthyl)propionate (14g): white solid; ^1H NMR (CDCl_3): δ 1.89 (s, 3H), 3.78 (s, 3H), 3.88 (s, 1H), 7.47-7.49 (m, 2H), 7.64 (dd, $J = 8.7, 2.0$ Hz, 1H), 7.81-7.86 (m, 3H), 8.03 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 26.6, 53.3, 75.9, 123.4, 124.1, 126.2, 127.5, 128.1, 128.3, 132.8, 133.0, 140.0, 176.1; $[\alpha]_D^{25} -31.6$ (c 1.51, CHCl_3 , 80% ee), $[\alpha]_D^{24} -12.7$ (c 0.820, MeOH, 80% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R 16.6 min (minor) and 18.9 min (major); IR (neat) 3494, 1732, 1599, 1506, 1436, 1373, 1245, 1140, 976, 859, 821, 752 cm^{-1} ; EI-MS m/z 230 (M^+), 213 ($M^+ - \text{OH}$), 171 ($M^+ - \text{COOCH}_3$), 155, 141, 127 (Naph $^+$), 115, 101, 86, 84, 77, 63, 58, 51; EI-HRMS Calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_3$ 230.0943 (M^+), Found 230.0942. The optical rotation supports a tentative assignment of the absolute configuration (Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149-154).

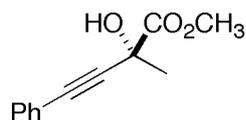


Methyl 2-hydroxy-2-(2-thiophenyl)propionate (14h): colorless oil; ^1H NMR (CDCl_3): δ 1.83 (s, 3H), 3.82 (s, 3H), 4.02 (s, 1H), 6.96-6.98 (m, 1H), 7.06-7.07 (m, 1H), 7.23-7.24 (m, 1H); ^{13}C NMR (CDCl_3): δ 27.8, 53.5, 74.3, 124.1, 125.0, 127.0, 147.4, 175.2; $[\alpha]_D^{22} -51.5$ (c 1.55, CHCl_3 , 96% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R 10.6 min (minor) and 11.4 min (major); IR (neat) 3325, 1735, 1445, 1435, 1372, 1262, 1234, 1198, 1141, 1092, 1029, 974, 846, 705 cm^{-1} ; EI-MS m/z 186 (M^+), 168, 155 ($M^+ - \text{OCH}_3$), 127 ($M^+ - \text{COOCH}_3$), 109, 83 ($\text{C}_4\text{H}_3\text{S}^+$); EI-HRMS Calcd. for $\text{C}_8\text{H}_{10}\text{O}_3\text{S}$ 186.0351 (M^+), Found 186.0351.



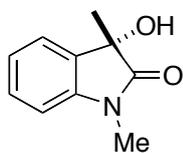
Methyl 2-(2-furyl)-2-hydroxypropionate (14i): colorless oil; ^1H NMR

(CDCl₃): δ 1.78 (s, 3H), 3.79 (s, 1H), 3.80 (s, 3H), 6.34-6.35 (m, 2H), 7.367-7.373 (m, 1H); ¹³C NMR (CDCl₃): δ 23.7, 53.4, 71.9, 106.6, 110.3, 142.5, 154.5, 174.5; $[\alpha]_D^{25}$ -23.6 (c 0.675, CHCl₃, 53% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 99/1, 1.0 mL/min) t_R 22.8 min (minor) and 27.1 min (major); IR (neat) 3501, 1738, 1677, 1503, 1452, 1372, 1265, 1141, 1013, 975, 921, 885, 817, 748, 599 cm⁻¹; EI-MS m/z 170 (M⁺) 153 (M⁺-OH), 111 (M⁺-COOCH₃), 95, 84, 68, 65, 59, 53; EI-HRMS Calcd. for C₈H₁₀O₄ 170.0579 (M⁺), Found 170.0581.



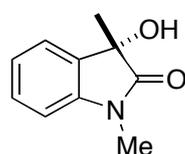
Methyl 2-hydroxy-2-phenylethynylpropionate (14j): colorless oil; ¹H NMR (CDCl₃): δ 1.79 (s, 3H), 3.52 (s, 1H), 3.89 (s, 3H), 7.29-7.35 (m, 3H), 7.43-7.45 (m, 2H); ¹³C NMR (CDCl₃): δ 27.8, 53.8, 68.3, 84.0, 88.2, 121.9, 128.3, 128.8, 131.9, 173.2; $[\alpha]_D^{25}$ -47.4 (c 1.04, CHCl₃, 59% ee); HPLC

(DAICEL CHIRALPAK AS-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R 16.8 min (minor) and 18.5 min (major); IR (neat) 3464, 2235, 1743, 1490, 1445, 1370, 1253, 1146, 1123, 1076, 977, 957, 758, 691 cm⁻¹; EI-MS m/z 204 (M⁺), 145 (M⁺-COOCH₃), 129, 115, 102 (PhCCH⁺), 77 (Ph⁺), 75; EI-HRMS Calcd. for C₁₂H₁₂O₃ 204.0786 (M⁺), Found 204.0785. The absolute configuration was determined to be (*R*) after conversion to the corresponding ethyl ester (2 N HCl aq. in EtOH, room temperature for 15 h, 71% yield, $[\alpha]_D^{25}$ -29.6 (c 0.57, CHCl₃, 59% ee)), and through the comparison of the optical rotation to the reported data (Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451).



(S)-3-Hydroxy-1,3-dimethyl-1,3-dihydroindol-2-one (14k): white solid; ¹H NMR (CDCl₃): δ 1.61 (s, 3H), 3.19 (s, 3H), 3.50 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 7.09-7.12 (m, 1H), 7.31-7.34 (m, 1H), 7.42 (d, *J* = 7.3 Hz, 1H); ¹³C NMR (CDCl₃): δ 24.8, 26.2, 73.7, 108.5, 123.2, 123.4, 129.5, 131.5, 142.7, 178.7; $[\alpha]_D^{22}$ -52.0 (c 1.26, CHCl₃, 76% ee);

HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol 9/1, 1.0 mL/min) t_R 16.1 min (minor) and 20.0 min (major); IR (neat) 3405, 1699, 1618, 1496, 1471, 1384, 1355, 1239, 1123, 1099, 943, 756, 700 cm⁻¹; EI-MS m/z 177 (M⁺), 162 (M⁺-CH₃), 159, 149 (M⁺-CO), 134, 132, 130, 121, 116, 106, 91, 77; EI-HRMS Calcd. for C₁₀H₁₁NO₂ 177.0790 (M⁺), Found 177.0790. The absolute configuration was determined after the following conversion, and through the comparison of the sign (-) of the optical rotation to the reported data (Yu, Q.; Li, Y.; Luo, W.; Brossi, A. *Heterocycles* **1993**, *36*, 1791).



1) AcCl, py, CH₂Cl₂, 100%

2) Pb(OAc)₄, TFA

3) MeI, K₂CO₃, acetone

4) NaOH aq., MeOH

1% (3 steps)

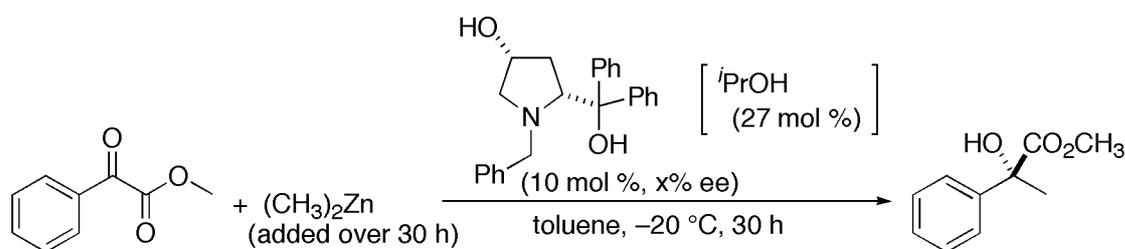


Nonlinear effects study

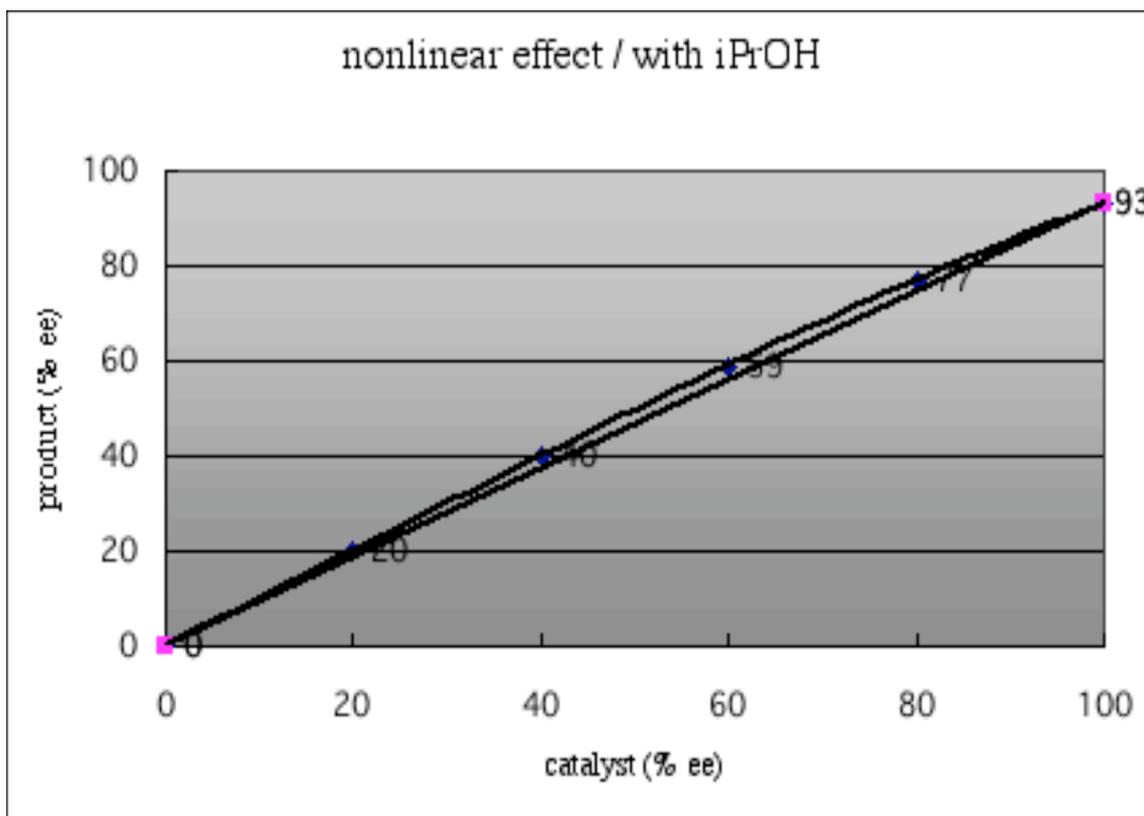
(For review, Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922-2959; Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402-411)

Nonlinear effects study was performed under similar reaction conditions except that reactions were quenched just after slow injection was over to suppress influence of background reactions. Low ee catalysts were prepared by mixing (*R,R*)- and (*S,S*)-catalysts in appropriate proportions. (*S,S*)-catalyst was prepared from *cis*-4-hydroxy-L-proline according to the procedure for **2**.

Procedure A: Appropriate amounts of (*2R,4R*)- and (*2S,4S*)-catalyst **2** solutions (10.0 mg/mL in toluene) were transferred to a reaction vessel to prepare a catalyst with indicated ee. The solvent was evaporated and the catalyst was dried in vacuo. The catalyst was dissolved in toluene (0.45 mL), then dimethylzinc (1.0 M in hexane, 18 μ L, 0.018 mmol) was added and the resulting solution was kept stirring for 30 min at room temperature. *i*PrOH (4.13 μ L in 0.050 mL toluene) was added and the stirring was continued for further 30 min. The reaction mixture was cooled to -20 $^{\circ}$ C and methyl benzoylformate (**13a**, 0.20 mmol) was added, followed by dimethylzinc (1.0 M in hexane, 482 μ L, 0.482 mmol) dropped slowly over 30 h using a syringe pump. The reaction vessel has to be sealed strictly not to lose volatile dimethylzinc. When the slow addition was over, the reaction mixture was quenched by 10% citric acid aq. Extraction with AcOEt and purification by a column chromatography (SiO_2 , AcOEt/Hx, 1/8) gave a product. Conversion yields were determined by ^1H NMR spectra of crude mixtures. Enantiomeric excesses (ee) were determined by chiral HPLC analyses (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min, t_R 9.7 min (minor) and 10.7 min (major)).



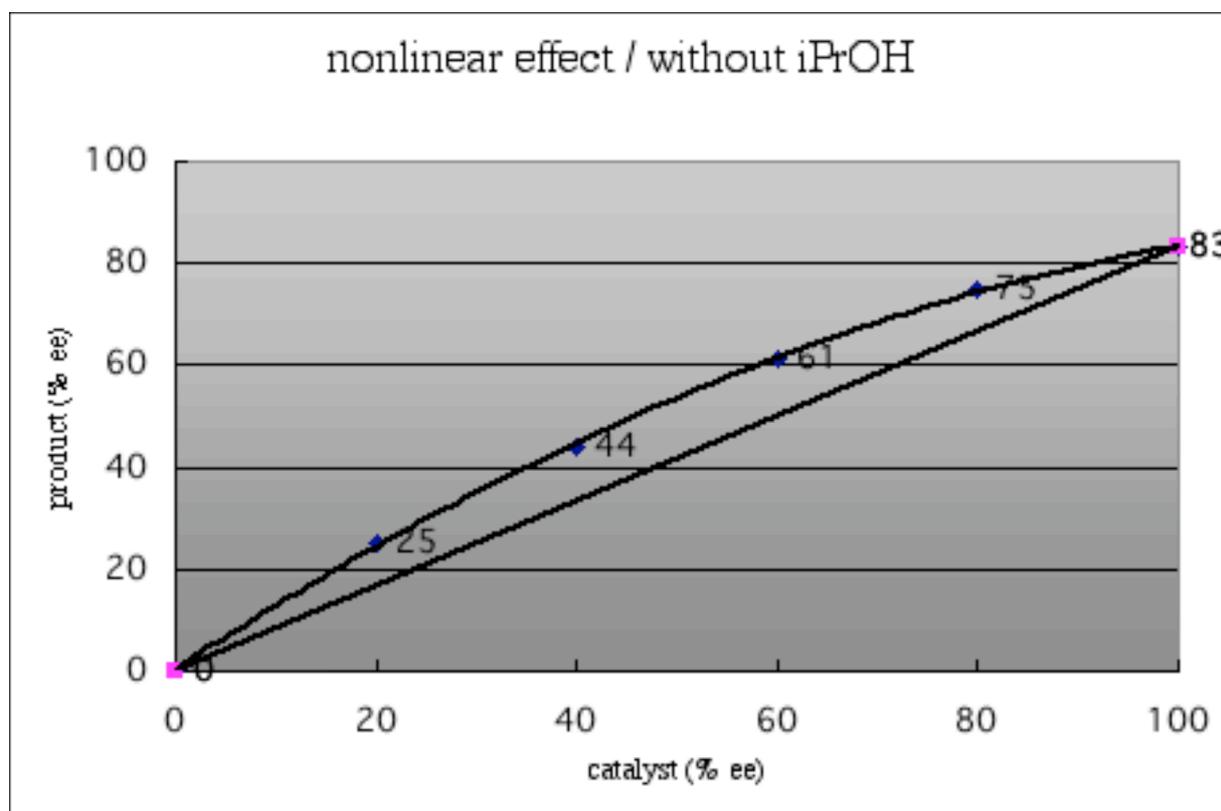
catalyst (% ee)	product (% ee)	yield (%)
0	0	-
20	20	59
40	40	58
60	59	66
80	77	62
100	93	65



Relatively linear relationship was observed. This result is opposite to many precedents of aminoalcohol catalysts for addition of dialkylzincs to aldehydes (see references).

Procedure B: Appropriate amounts of (2*R*,4*R*)- and (2*S*,4*S*)-catalyst **2** solutions (10.0 mg/mL in toluene) were transferred to a reaction vessel to prepare a catalyst with indicated ee. The solvent was evaporated and the catalyst was dried in vacuo. The catalyst was dissolved in toluene (0.50 mL), then dimethylzinc (1.0 M in hexane, 18 μ L, 0.018 mmol) was added and the stirring was continued for 30 min at room temperature. The mixture was cooled to -20 $^{\circ}$ C and methyl benzoylformate (**13a**, 0.20 mmol) was added, followed by dimethylzinc (1.0 M in hexane, 482 μ L, 0.482 mmol) dropped slowly over 30 h using a syringe pump. The reaction vessel has to be sealed strictly not to lose volatile dimethylzinc. When the slow addition was over, the reaction mixture was quenched by 10% citric acid aq. Extraction with AcOEt and purification by a column chromatography (SiO₂, AcOEt/Hx, 1/8) gave the desired product. Conversion yields were determined by ¹H NMR spectra of crude mixtures. Enantiomeric excesses (ee) were determined by chiral HPLC analyses (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min, *t_R* 9.7 min (minor) and 10.7 min (major)).

catalyst (% ee)	product (% ee)	yield (%)
0	0	-
20	25	64
40	44	62
60	61	70
80	75	71
100	83	72



(+)-Nonlinear effects were observed in the absence of *i*PrOH. For a more detailed discussion, see the main text.