Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Primary amino acid lithium salt as a catalyst for asymmetric Michael addition of isobutyraldehyde with β-nitroalkenes.

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Contents

(A) General comments.

IR spectra were recorded using a JASCO FT/IR-5300 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on JEOL JNM-A400II FT NMR and ECX-400P. Chemical shifts, δ are referred to TMS. EI and ESI high-resolution mass spectra were measured on a JEOL JMS-700TZ or JMS-T100LP spectrometer. Optical rotation was measured by JASCO DIP-360. Melting points are measured by Yanagimoto micro melting point apparatus and are uncorrected. HPLC was carried out using a JASCO PU-2089 Plus intelligent pump and a UV-2075 Plus UV detector.

(B) Materials.

Isobutyraldehyde was used after distillation. Nitroalkenes **2e**,[1a] **2f**[1b] and **2g**[1b] were prepared according to the literatures. Unless otherwise noted, other materials were purchased from commercial suppliers and were used without purification.

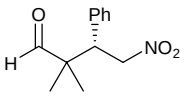
(C) Preparation of amino acid salts

Typical procedure: To a mixture of L-phenylalanine (165 mg, 1 mmol) and MeOH (10 mL), lithium hydroxide monohydrate (42 mg, 1 mmol) was added at room temperature. After stirring for over night, the solution was concentrated under reduced pressure to give L-phenylalanine lithium salt as a white powder. The obtained L-phenylalanine lithium salt, Phe-OLi, was used without further purification.[2] L-Phenylalanine magnesium bromide salt was prepared in THF using MeMgBr as a base.

Phe-OLi: ν(KBr)/cm^{-1} 3680-2300 (br), 3355, 3308, 3285, 3084, 3063, 3029, 2948, 2849, 1595, 1557, 1495, 1454, 1426, 1350, 1312, 1154, 1113, 1080, 1028, 939, 909, 860, 841, 826, 768, 739, 700.

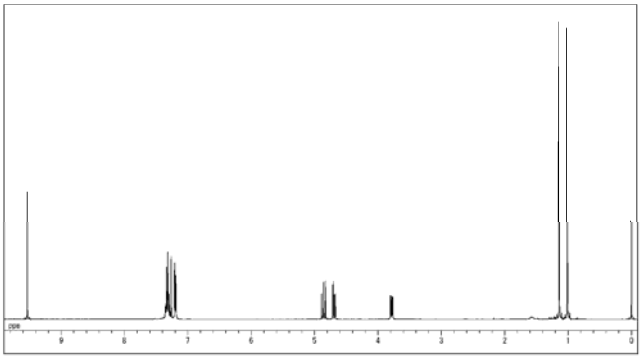
(D) General procedure for the Michael addition of isobutyraldehyde with *trans*-β-nitrostyrene and compound characterization data of the Michael adducts

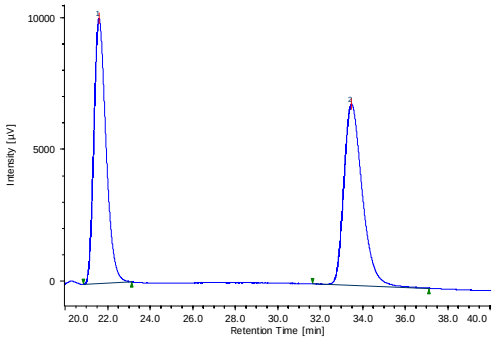
In a 7 mL vial, isobutyraldehyde (**1**) (144 mg, 1 mmol) was added to a slurry of L-phenylalanine lithium salt (17.1 mg, 0.1 mmol), CH_2Cl_2 (1 mL) and *trans*-β-nitrostyrene (**2a**) (74.6 mg, 0.5 mmol) at 0 °C. After the reaction mixture was stirred for 72 h at 0 °C, saturated aqueous NaCl (1.5 mL) was added to the vial and extracted with Et_2O (3 mL × 3). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The Michael adduct, (*S*)-2,2-dimethyl-4-nitro-3-phenylbutanal (**3a**),[3] was isolated by column chromatography (silica gel, hexanes/Et_2O) in 82% yield (90.7 mg) as light yellow oil.

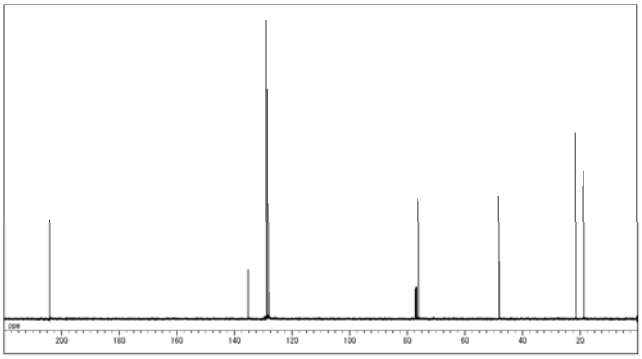


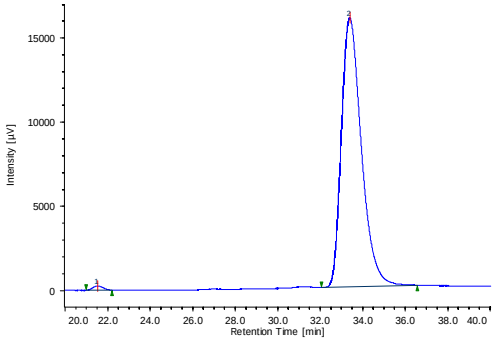
3a

The enantioselectivity was determined by HPLC analysis (98%ee, DAICEL CHIRALCEL OD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm; t_r(major enantiomer) = 33.5 min, t_r(minor enantiomer) = 21.6 min). The absolute configuration was determined by comparison of the optical rotation with that of the literature.[3] $[\alpha]^{26}_D$ = –4.9° (c = 1.0, $CHCl_3$), δ_H($CDCl_3$) 1.01 (3H, s), 1.14 (3H, s), 3.77-3.80 (1H, m), 4.67-4.89 (2H, m), 7.20-7.21 (2H, m), 7.30-7.36 (3H, m), 9.53 (1H, s); δ_C($CDCl_3$) 18.7, 21.5, 48.1, 48.3, 76.2, 128.0, 128.5, 128.9, 135.3, 204.2; ν(neat)/cm^{-1} 3065, 3034, 2975, 2934, 2878, 2820, 2720, 1725, 1603, 1555, 1495, 1468, 1456, 1435, 1379, 1337, 1314, 1206, 1159, 1144, 1090, 1032, 1005, 976, 912, 883, 831, 804, 781, 750, 706, 648; [HR EI-MS: Calc. for $C_{12}H_{15}NO_3$ (*M*): 221.1052. Found: M^+, 221.1044].

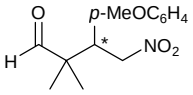








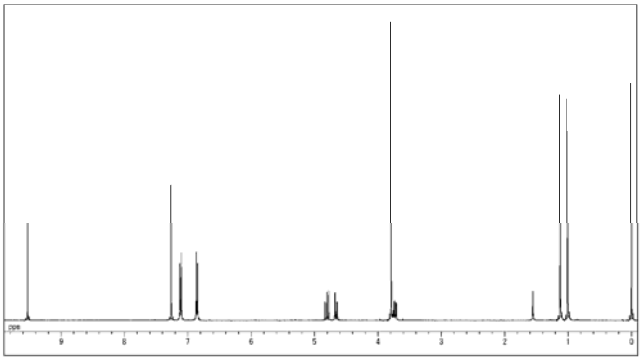
2,2-Dimethyl-4-nitro-3-(4-methoxyphenyl)butanal (3b)

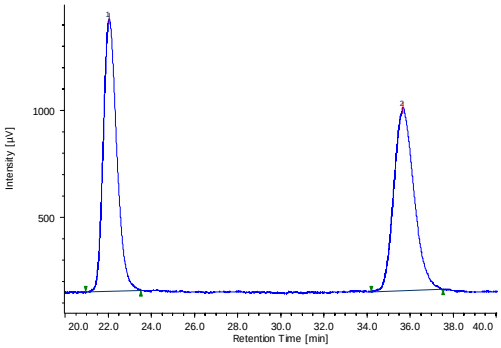


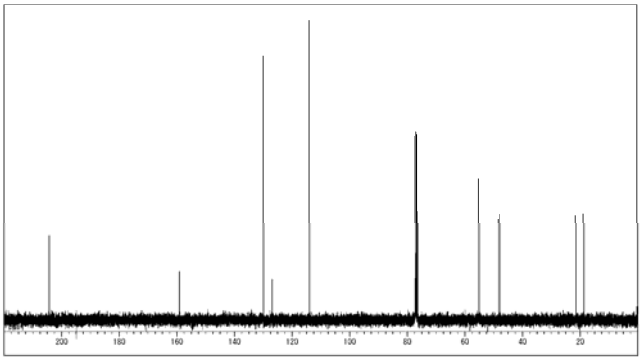
3b

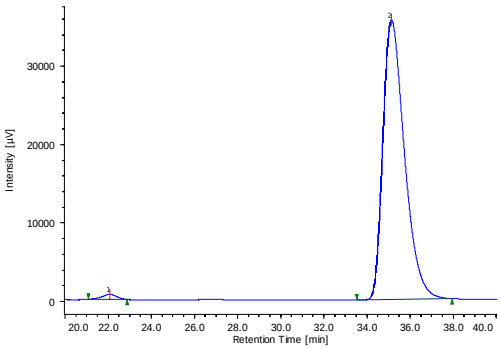
The enantioselectivity was determined by HPLC analysis (98%ee, DAICEL CHIRALCEL OD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm; t_r(major enantiomer) = 35.6 min, t_r(minor enantiomer) = 22.1 min). The absolute configuration was not determined.

$[\alpha]^{26}_D$ = +1.7° (c = 1.0, $CHCl_3$), white solid, Mp. 58-59 °C, δ_H($CDCl_3$) 1.00 (3H, s), 1.13 (3H, s), 3.71-3.75 (1H, m), 3.79 (3H, s), 4.64-4.84 (2H, m), 6.85-6.87 (2H, m), 7.10-7.13 (2H, m), 9.53 (1H, s); δ_C($CDCl_3$) 18.7, 21.4, 47.7, 48.2, 55.1, 76.4, 113.9, 126.9, 130.0, 159.2, 204.3; ν(KBr)/cm^{-1} 2976, 2919, 2841, 2718, 1725, 1611, 1582, 1553, 1516, 1468, 1441, 1379, 1290, 1250, 1188, 1119, 1028, 889, 839, 812, 747, 635; [HR EI-MS: Calc. for $C_{13}H_{17}NO_4$ (*M*): 251.1158. Found: M^+, 251.1152].

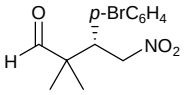






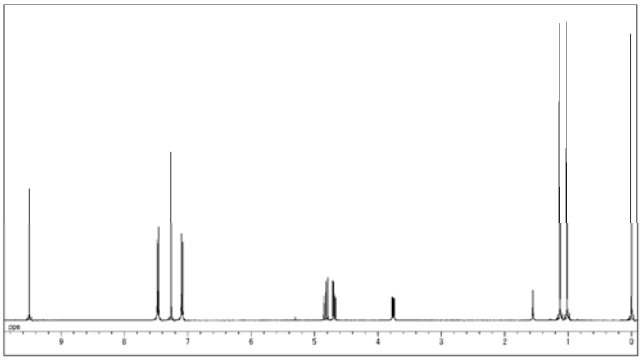


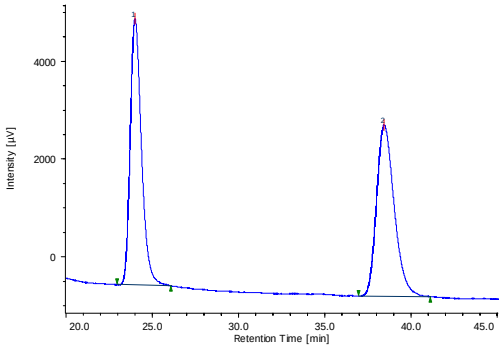
(*S*)-2,2-Dimethyl-4-nitro-3-(4-bromophenyl)butanal (3c)[4]

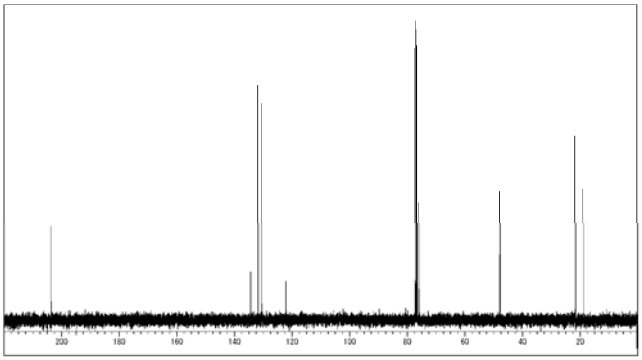


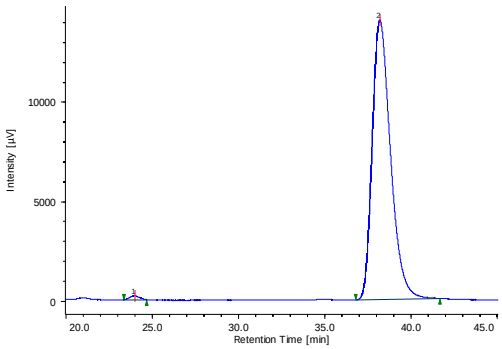
3c

The enantioselectivity was determined by HPLC analysis (99%ee, DAICEL CHIRALCEL OD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm; t_r(major enantiomer) = 38.2 min, t_r(minor enantiomer) = 24.0 min). The absolute configuration was determined by comparison of the optical rotation with that of the literature.[4] $[\alpha]^{26}_D$ = –3.3° (c = 1.0, $CHCl_3$), white solid, Mp. 86-87 °C, δ_H($CDCl_3$) 1.02 (3H, s), 1.13 (3H, s), 3.74-3.78 (1H, m), 4.67-4.85 (2H, m), 7.07-7.11 (2H, m), 7.46-7.49 (2H, m), 9.50 (1H, s); δ_C($CDCl_3$) 18.8, 21.6, 47.8, 48.0, 75.9, 122.1, 130.6, 131.8, 134.3, 203.7; ν(KBr)/cm^{-1} 3030, 2973, 2934, 2874, 2818, 2718, 1728, 1559, 1487, 1468, 1441, 1410, 1381, 1350, 1306, 1206, 1144, 1113, 1074, 1009, 889, 845, 781, 721, 702, 664; [HR EI-MS: Calc. for $C_{12}H_{14}BrNO_3$ (*M*): 299.0157. Found: M^+, 299.0145].

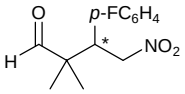








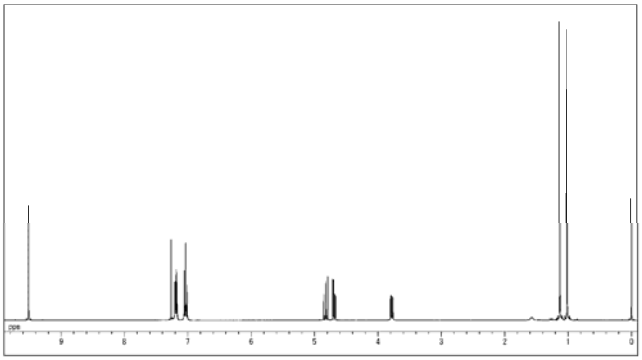
2,2-Dimethyl-4-nitro-3-(4-fluorophenyl)butanal (3d)

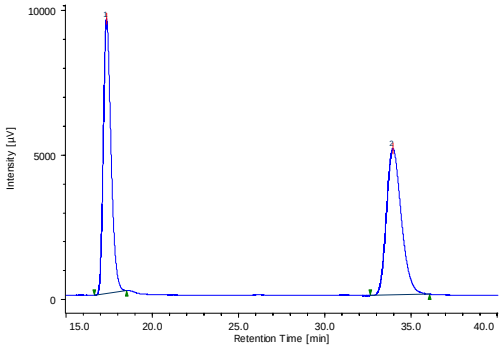


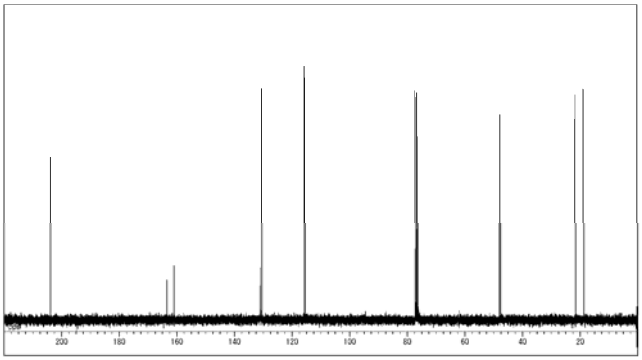
3d

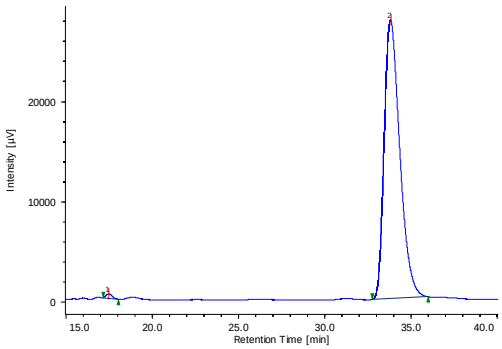
The enantioselectivity was determined by HPLC analysis (99%ee, DAICEL CHIRALCEL OD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm; t_r(major enantiomer) = 33.9 min, t_r(minor enantiomer) = 17.4 min). The absolute configuration was not determined.

$[\alpha]^{26}_D$ = –1.5° (c = 1.0, $CHCl_3$), light yellow oil, δ_H($CDCl_3$) 1.01 (3H, s), 1.13 (3H, s), 3.76-3.80 (1H, m), 4.67-4.85 (2H, m), 7.01-7.06 (2H, m), 7.17-7.21 (2H, m), 9.51 (1H, s); δ_C($CDCl_3$) 18.7, 21.5, 47.6, 48.1, 76.2, 115.6 (d, *J* 21.5 Hz), 130.5 (d, *J* 8.1 Hz), 131.0 (d, *J* 3.3 Hz), 162.3 (d, *J* 247.0 Hz), 203.9; ν(neat)/cm^{-1} 3045, 2976, 2936, 2878, 2820, 2722, 1725, 1605, 1555, 1512, 1470, 1437, 1379, 1304, 1229, 1165, 1105, 1017, 883, 843, 750, 689, 646; [HR EI-MS: Calc. for $C_{12}H_{14}FNO_3$ (*M*): 239.0958. Found: M^+, 239.0954].

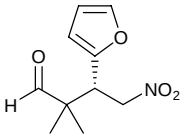






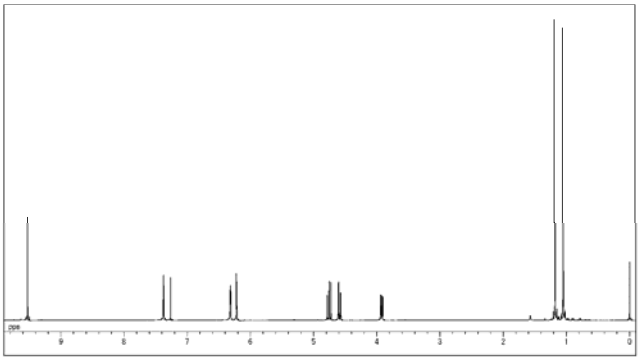


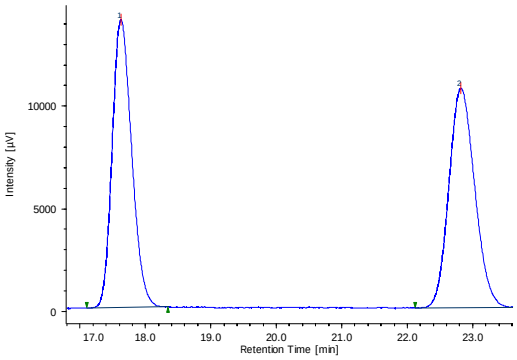
(*S*)-2,2-Dimethyl-4-nitro-3-(furan-2-yl)butanal (3e)[4a]

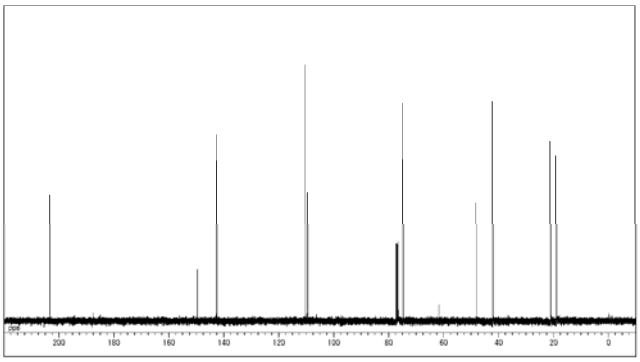


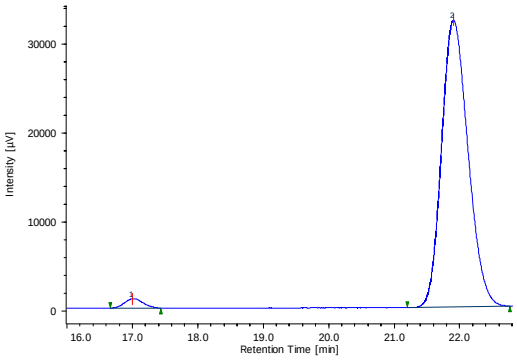
3e

The enantioselectivity was determined by HPLC analysis (96%ee, DAICEL CHIRALPAK AD-H, 1% isopropanol/hexanes, 1.0 mL/min, 254 nm; t_r(major enantiomer) = 21.9 min, t_r(minor enantiomer) = 17.0 min). The absolute configuration was determined by comparison of the optical rotation with that of the literature.[4a] $[\alpha]^{26}_D$ = +20.2° (c = 1.0, $CHCl_3$), light yellow oil, δ_H($CDCl_3$) 1.05 (3H, s), 1.18 (3H, s), 3.90-3.94 (1H, m), 4.57-4.79 (2H, m), 6.22 (1H, d, *J* 3.2 Hz), 6.31-6.33 (1H, m), 7.38 (1H, d, *J* 1.6 Hz), 9.51 (1H, s); δ_C($CDCl_3$) 19.0, 21.1, 42.2, 48.1, 74.8, 109.6, 110.4, 142.7, 149.7, 203.4; ν(neat)/cm^{-1} 3151, 3123, 2975, 2935, 2877, 2821, 2720, 1772, 1727, 1556, 1505, 1469, 1433, 1377, 1344, 1294, 1181, 1148, 1078, 1016, 973, 915, 886, 819, 742, 700, 599; [HR EI-MS: Calc. for $C_{10}H_{13}NO_4$ (*M*): 211.0845. Found: M^+, 211.0853].

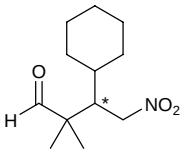








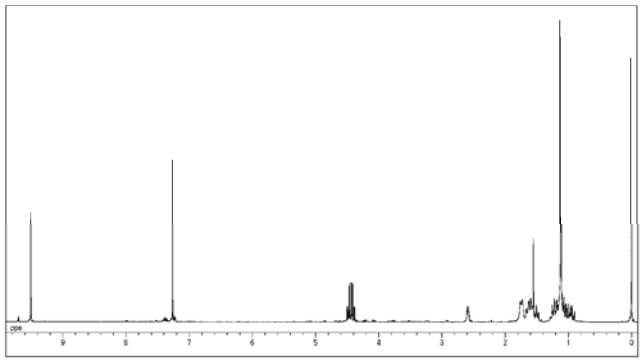
2,2-Dimethyl-4-nitro-3-cyclohexylbutanal (3f)

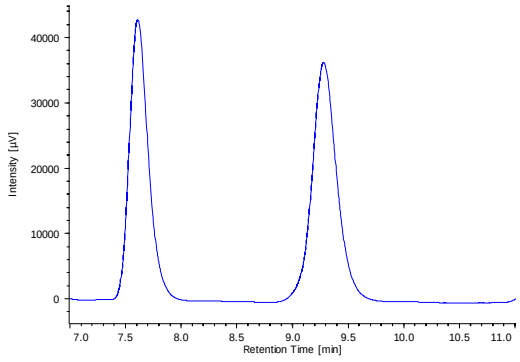


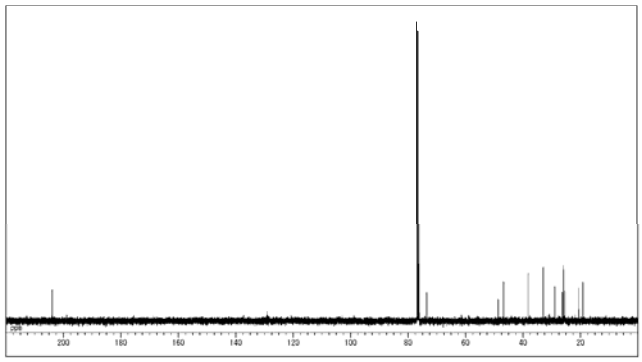
3f

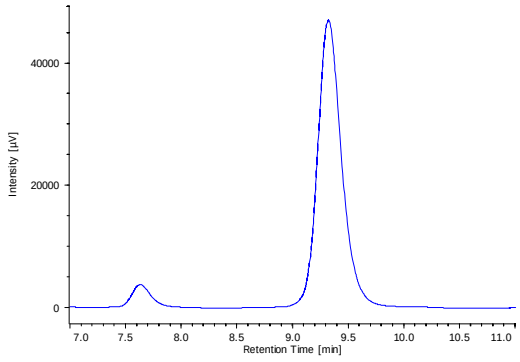
The enantioselectivity was determined by HPLC analysis (88%ee, DAICEL CHIRALCEL OD-H, 5% isopropanol/hexanes, 1.0 mL/min, 210 nm; t_r(major enantiomer) = 9.3 min, t_r(minor enantiomer) = 7.6 min). The absolute configuration was not determined.

$[\alpha]^{26}_D$ = –11.3° (c = 1.0, $CHCl_3$), colorless oil, δ_H($CDCl_3$) 0.90-1.29 (11H, m), 1.47-1.76 (6H, m), 2.57-2.61 (1H, m), 4.38-4.50 (2H, m), 9.51 (1H, s); δ_C($CDCl_3$) 19.2, 20.5, 25.4, 25.9, 26.3, 29.0, 32.9, 38.2, 46.8, 48.7, 73.5, 203.9; ν(neat)/cm^{-1} 2929, 2855, 2709, 1724, 1554, 1449, 1373, 1308, 1249, 1103, 1025, 893, 841, 760, 704.

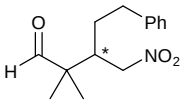








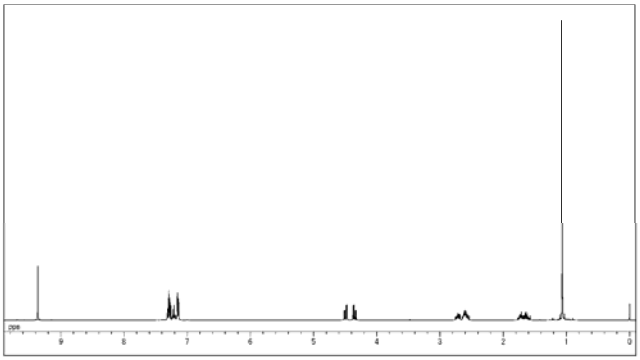
2,2-Dimethyl-4-nitro-3-(2-phenyleth-1-yl)butanal (3g)

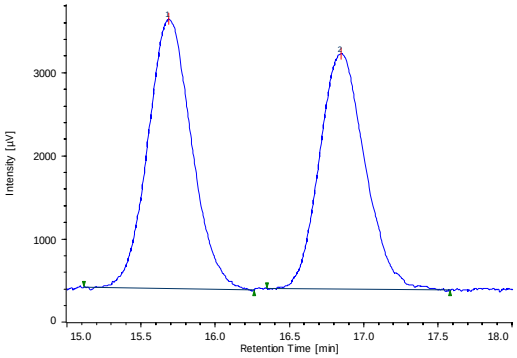


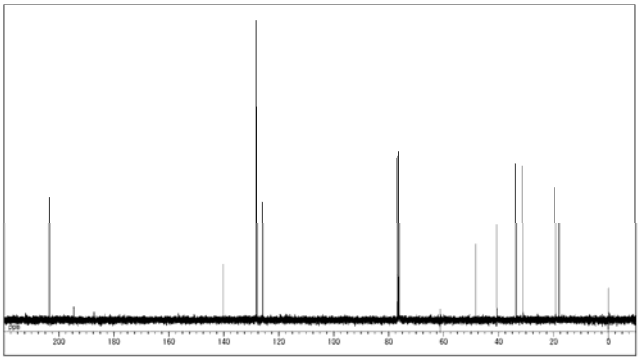
3g

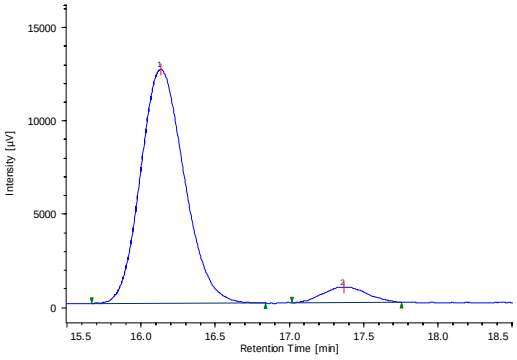
The enantioselectivity was determined by HPLC analysis (88%ee, DAICEL CHIRALPAK AD-H, 1% isopropanol/hexanes, 1.0 mL/min, 254 nm; t_r(major enantiomer) = 16.1 min, t_r(minor enantiomer) = 17.4 min). The absolute configuration was not determined.

$[\alpha]^{26}_D$ = –22.5° (c = 1.0, $CHCl_3$), colorless oil, δ_H($CDCl_3$) 1.07 (6H, s), 1.57-1.77 (2H, m), 2.54-2.65 (2H, m), 2.68-2.76 (1H, m), 4.33-4.52 (2H, m), 7.14-7.31 (5H, m), 9.37 (1H, s); δ_C($CDCl_3$) 18.0, 19.3, 31.1, 33.6, 40.6, 48.3, 76.2, 125.9, 127.9, 128.1, 140.2, 203.4; ν(neat)/cm^{-1} 3062, 3028, 2971, 2949, 2871, 2817, 2711, 1725, 1603, 1555, 1496, 1455, 1381, 1211, 1091, 1030, 885, 751, 701; [HR ESI-MS: Calc. for $C_{14}H_{20}NO_3$ (*M*+H): 250.1443. Found: M^++H, 250.1424].





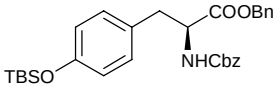




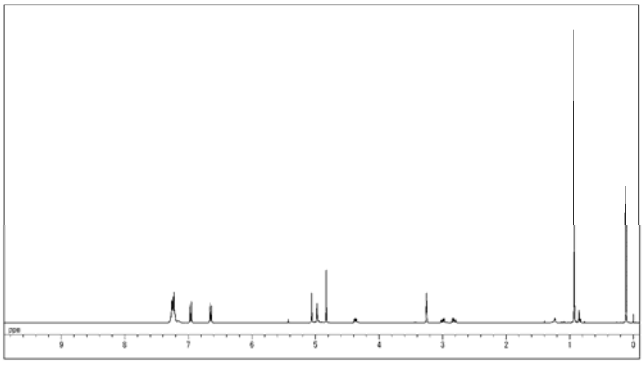
(E) Preparation of L-(4-*tert*-butyldimethylsilyloxy)phenylalanine

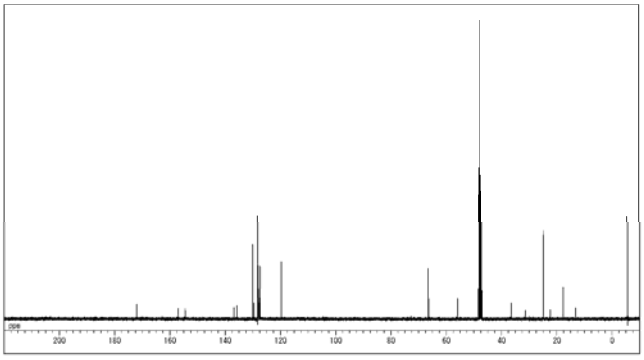
Cbz-Tyr-OBn was prepared by a modified procedure of Yamamoto's method[5] as following: L-Tyrosine (10 g, 55 mmol), benzylalcohol (25 mL), benzene (120 mL) and *p*-toluenesulfonic acid monohydrate (12.6 g, 66 mmol) were placed in a round-bottomed flask equipped with a Dien-Stark trap. After refluxing for 7 h with an azeotropically removal of water, the reaction mixture was cooled to room temperature. A precipitated white solid was filtered, washed with Et_2O and dried in air. The obtained crude product was recrystallized from EtOH to give a pure Tyr-OBn·*p*-TsOH (21.5 g, 48.5 mmol, 88%). Tyr-OBn·*p*-TsOH (10.9 g, 24.6 mmol) was dissolved in MeOH (100 mL) and cooled to 0 °C. To the mixture, Et_3N (4.96 g, 49.1 mmol) and Cbz-Cl (4.19 g, 24.6 mmol) were successively added portionwise. After stirred for 8 h at 0 °C, the reaction mixture was warmed to room temperature. The resulting solution was poured into water (100 mL) and extracted with Et_2O (100 mL × 3). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude product was recrystallized from hexanes/EtOH (3:1) to give a pure Cbz-Tyr-OBn (8.13 g, 82%). Spectroscopic data are in agreement with the published data.[5]

To a mixture of Cbz-Tyr-OBn (4.05 g, 10 mmol), DMF (20 mL) and TBS-Cl (1.51 g, 10 mmol), Et_3N (1.01 g, 10 mmol) was added portionwise at room temperature. After stirring for over night, the resulting solution was poured into sat. aq. NH_4Cl (100 mL) and extracted with Et_2O (50 mL × 3). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude product was purified by column chromatography (silicagel; hexanes/Et_2O) to give a pure *O*-*tert*-butyldimethylsilylated Cbz-Tyr-OBn (4.62 g, 89%) as a white solid.

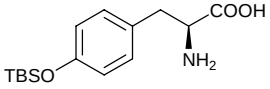


Mp. 39.5-40.3 °C, $\delta_H(CD_3OD)$ 0.11 (6H, s), 0.93 (9H, s), 2.79-3.02 (2H, m), 4.34-4.39 (1H, m), 4.97 (2H, s), 5.06 (2H, s), 6.65 (2H, d, *J* 8.7 Hz), 6.96 (2H, d, *J* 8.7 Hz), 7.15-7.28 (10H, m); $\delta_C(CD_3OD)$ –5.6, 17.7, 24.8, 36.5, 55.9, 66.2, 66.6, 119.7, 127.3, 127.6, 127.96, 128.0, 128.1, 128.2, 129.6, 130.0, 135.8, 136.8, 154.5, 157.0, 172.0; ν(KBr)/cm^{-1} 3308, 3063, 3036, 2957, 2932, 2892, 2859, 1744, 1686, 1611, 1543, 1512, 1458, 1443, 1391, 1360, 1345, 1304, 1263, 1213, 1194, 1169, 1105, 1076, 1030, 1009, 986, 922, 839, 802, 781, 745, 696, 639; [HR EI-MS: Calc. for $C_{30}H_{37}NO_5Si$ (*M*): 519.2441. Found: M^+, 519.2435].

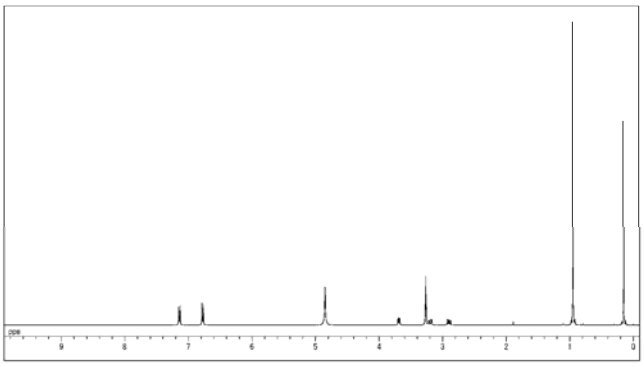


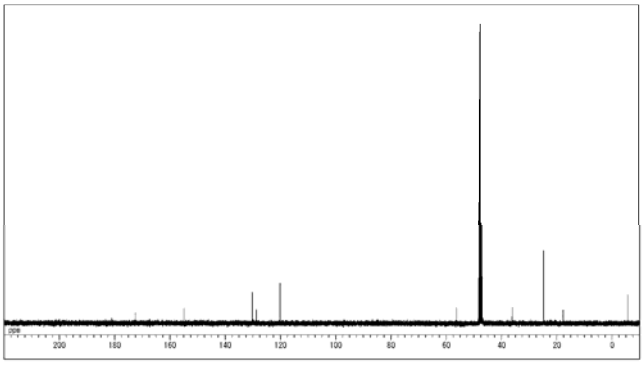


O-tert-Butyldimethylsilylated Cbz-Tyr-OBn (1.47 g, 2.8 mmol) and AcOH (18 mg, 0.3 mmol) were dissolved in MeOH (20 mL), and the solution was added on Pd/C (10%, 150 mg) under nitrogen atmosphere in a round-bottomed flask. After the atmosphere in the flask was replaced with hydrogen, the reaction mixture was stirred for 3 h under hydrogen atmosphere at room temperature. A precipitated white solid was dissolved by adding MeOH, and Pd/C was filtered with Celite. The filtrate was concentrated under reduced pressure. The obtained white solid was washed with Et_2O and dried in air to give a pure L-(4-*tert*-butyldimethylsilyloxy)phenylalanine (541 mg, 66%) as an off-white solid.



Mp. 178.5-179.2 °C, $\delta_H(CD_3OD)$ 0.15 (6H, s), 0.95 (9H, s), 2.87-2.93 (1H, m), 3.17-3.22 (1H, m), 3.67-3.70 (1H, m), 6.77 (2H, d, *J* 8.4 Hz), 7.14 (2H, d, *J* 8.4 Hz); $\delta_C(CD_3OD)$ –5.7, 17.7, 24.8, 36.1, 56.3, 120.1, 128.7, 130.2, 154.9, 172.5; ν(KBr)/cm^{-1} 3700-2140 (br), 2959, 2895, 2859, 1611, 1512, 1472, 1441, 1400, 1335, 1262, 1173, 1107, 1007, 922, 841, 808, 781, 691; [HR EI-MS: Calc. for $C_{15}H_{25}NO_3Si$ (*M*): 295.1604. Found: M^+, 295.1589].





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