Electronic supplementary information

Asymmetric α-2-tosylethenylation of *N*,*N*-dialkyl-L-amino acid esters via the formation of non-racemic ammonium enolates

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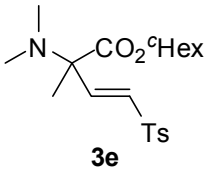
General

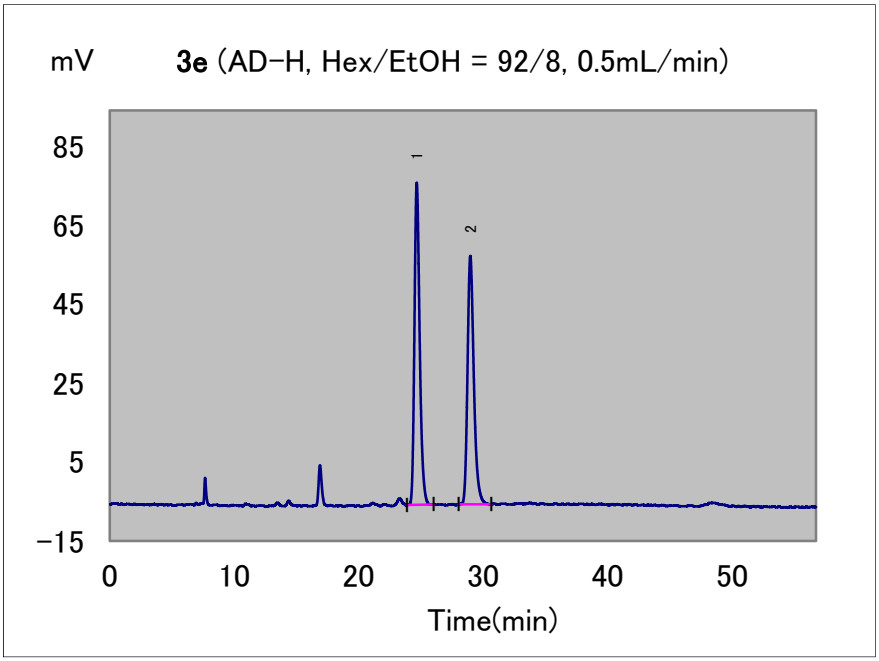
^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. Specific rotations were recorded on a JASCO Polarimeter P–1010. High-resolution mass spectra were measured on a Thermofisher Scientific LC/FT-MS spectrometer. Elemental analyses were recorded on a J-Science Lab Micro Corder JM10. HPLC analyses were performed using a JASCO HPLC pump PU-2080 and a UV/VIS detector UV-2075. Reactions were conducted in round-bottomed flask with a magnetic stirring bar under an argon atmosphere. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F_{254}) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan).

Representative HPLC data of product 3e and 3i

The ee of products **3** were determined by HPLC analysis using chiral column (Daicel Chiralpak AD-H, AS-H, and Chiralcel OD-H, OJ-H) in comparison with the corresponding chromatogram of racemic **3**. The racemic **3** were obtained by the reaction of racemic substrates **2** with ethynyl tolyl sulfone (**1**). The racemic substrates **2** were prepared from the corresponding DL-amino acid derivatives.



3e
4% ee



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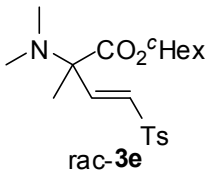
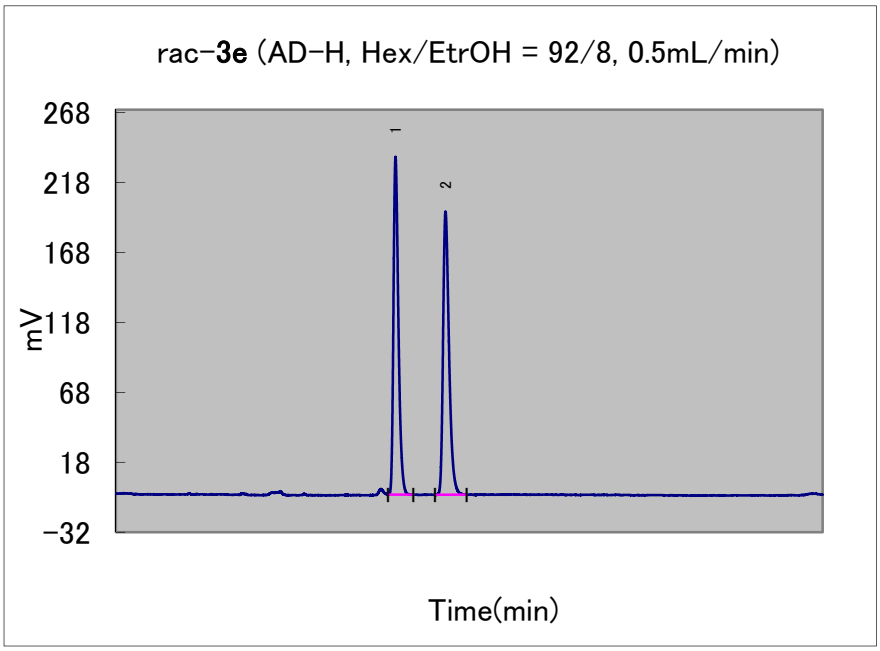


rac-**3e**



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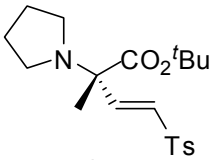
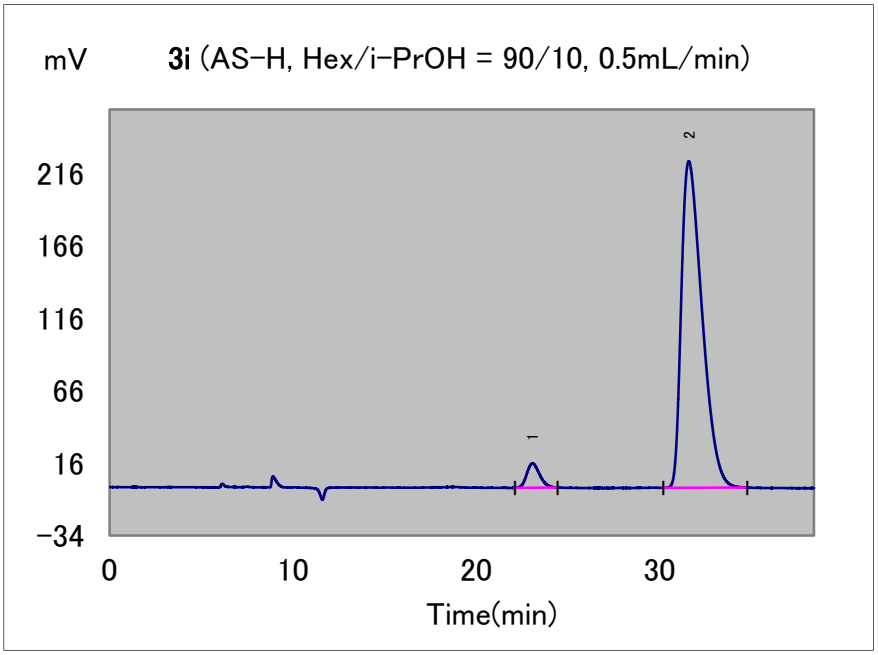


(*S*)-**3i**
91% ee



No.	Rt	Area	Area(%)	Height	
1	23.07	816862.2	4.4158	16745	(R)-**3i**
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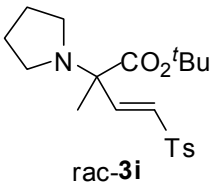
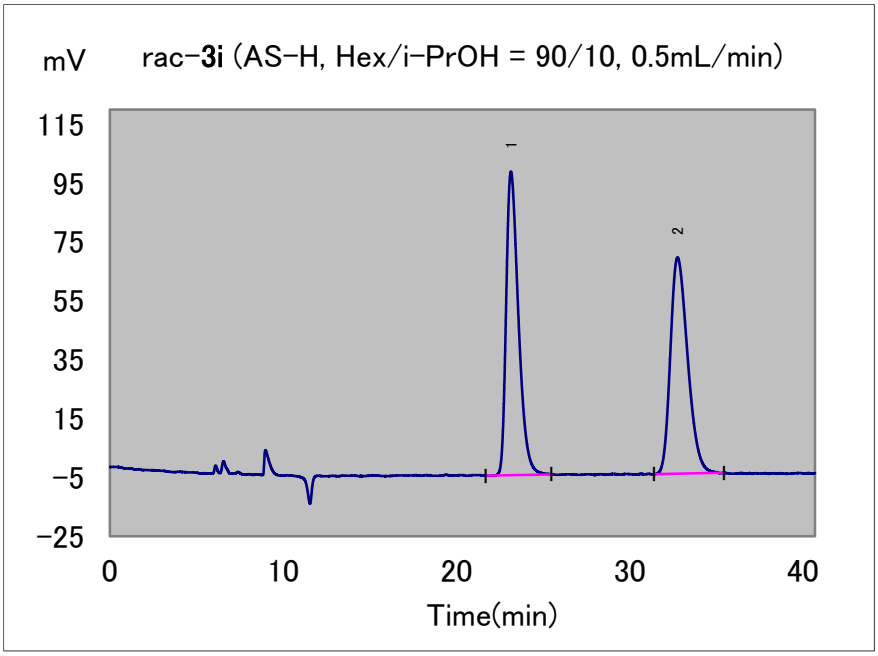


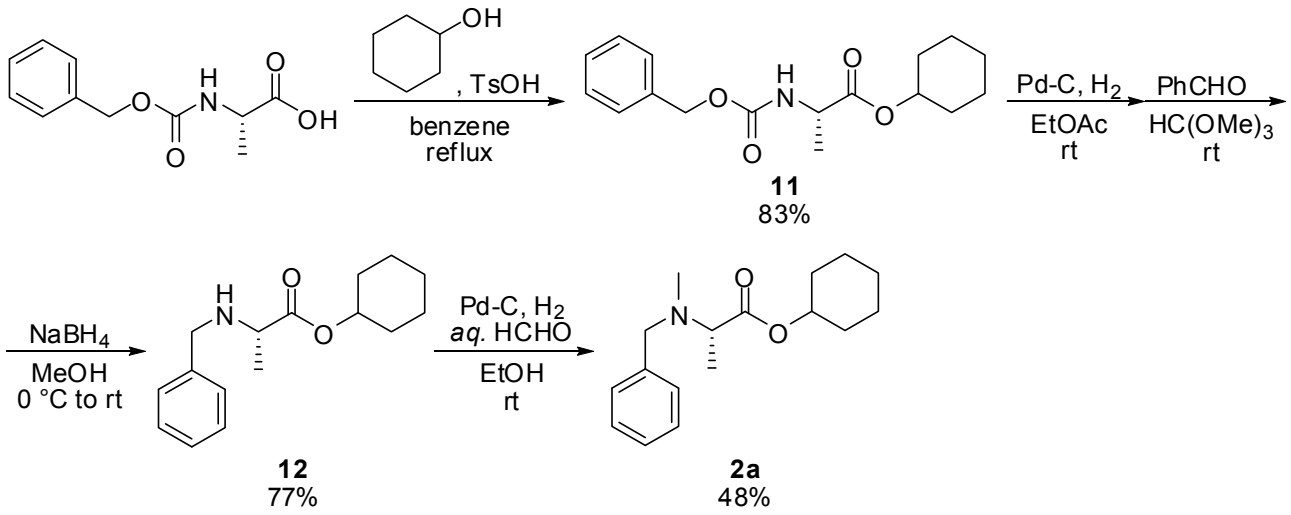
rac-**3i**



No.	Rt	Area	Area(%)	Height	
1	23.14	5073095.6	49.9319	103174	(R)-**3i**
2	32.75	5086925.8	50.0681	73572	(S)-**3i**
		10160021.4	100	176746	

Preparation of substrates

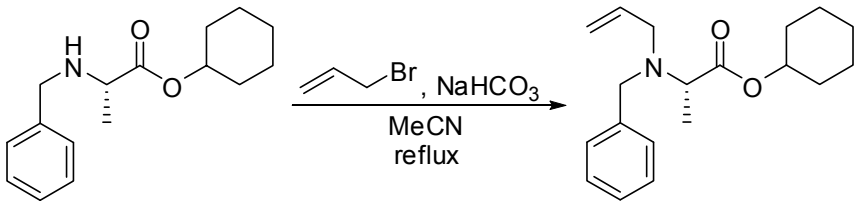
(*S*)-Cyclohexyl 2-[benzyl(methyl)amino]propanoate (2a)



(Step 1) A solution of (*S*)-Cbz-alanine (1.56 g, 7.0 mmol), cyclohexanol (0.82 mL, 7.8 mmol) and *p*-toluenesulfonic acid, monohydrate (0.15 g, 0.79 mmol) in benzene (14 mL) was refluxed for 15 h with azeotropic removal of water by a Dean–Stark trap. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3/1 as eluent) to obtain (*S*)-Cbz-alanine cyclohexyl ester (**11**) (1.78 g, 83% yield) as a colorless oil. (Step 2) A mixture of **11** (0.35 g, 1.1 mmol) and palladium on activated carbon (loading: 10 wt. %, 25 mg) in ethyl acetate (2.1 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residual oil was dissolved in trimethyl orthoformate (2.1 mL). The solution was added benzaldehyde (0.11 mL, 1.1 mmol) and stirred for 48 h at room temperature. The resulting mixture was concentrated and the residue was dissolved in methanol (4.2 mL). The solution was treated with sodium borohydride (55 mg, 1.5 mmol) at 0 °C and stirred for 12 h at room temperature. The resulting mixture was diluted with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. Purification of the residue by chromatography (hexane/ethyl acetate = 4/1 as eluent) on silica gel afforded (*S*)-*N*-benzylalanine cyclohexyl ester (**12**) (0.22 g, 77% yield) as a colorless oil. (Step 3) A solution of **12** (0.22 g, 0.84 mmol), palladium on activated carbon (loading: 10 wt. %, 24 mg), and formaldehyde solution (37 wt. % in water, 0.65 mL, 8.6 mmol) in ethanol (1.7 mL) was stirred for 12 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 8/1 as eluent) to obtain **2a** (0.11 g, 48% yield) as a colorless oil. $[\alpha]_{589}^{23}$ –54.3 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (4H, m, Ph), 7.23 (1H, tt, *J* = 7.0, 1.6 Hz, Ph), 4.85 (1H, tt, *J* = 9.0, 3.8 Hz, OCH), 3.76 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.63 (1H, d, *J* = 13.6 Hz, CH_2Ph), 3.43 (1H, q, *J* = 7.2 Hz, NCHCO), 2.29 (3H, s,

NCH_3), 1.94-1.81 (2H, m, *c*-Hex), 1.80-1.69 (2H, m, *c*-Hex), 1.60-1.23 (6H, m, *c*-Hex), 1.33 (3H, d, J = 7.2 Hz, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 139.4, 128.7, 128.1, 126.8, 72.4, 60.8, 58.2, 37.8, 31.9, 31.7, 25.3, 23.6, 15.2; IR (film) 3028, 2938, 2859, 2799, 1726, 1494, 1452, 1366, 1326, 1217, 1179, 1123, 1096, 1074, 1039, 1015, 959, 943, 922, 908, 808, 772, 735, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$, 276.1958; found, 276.1956. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.03; H, 9.31; N, 5.36.

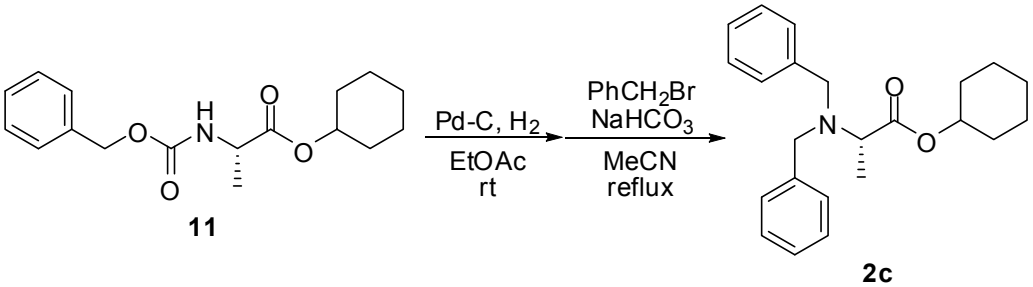
(*S*)-Cyclohexyl 2-[allyl(benzyl)amino]propanoate (2b)



12 **2b** 75%

A mixture of **12** (0.63 g, 2.4 mmol), allyl bromide (0.23 mL, 2.7 mmol), and sodium hydrogen carbonate (0.71 g, 8.5 mmol) in acetonitrile (5 mL) was refluxed for 26 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10/1 as eluent) to obtain **2b** (0.54 g, 75% yield) as a colorless oil. $[\alpha]_{589}^{22}$ – 87.8 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (2H, m, Ph), 7.32-7.27 (2H, m, Ph), 7.22 (1H, tt, J = 7.2, 2.0 Hz, Ph), 5.80 (1H, dddd, J = 17.2, 10.2, 7.2, 5.2 Hz, CH_2CH=CH_2), 5.21 (1H, ddd, J = 17.2, 3.2, 2.0 Hz, CH_2CH=CH_2), 5.09 (1H, ddd, J = 10.2, 3.2, 1.6 Hz, CH_2CH=CH_2), 4.84 (1H, tt, J = 8.8, 3.6 Hz, OCH), 3.87 (1H, d, J = 14.2 Hz, CH_2Ph), 3.64 (1H, d, J = 14.2 Hz, CH_2Ph), 3.54 (1H, q, J = 7.2 Hz, NCHCO), 3.29 (1H, dddd, J = 14.4, 5.2, 2.0, 1.6 Hz, CH_2CH=CH_2), 3.15 (1H, dd, J = 14.4, 7.2 Hz, CH_2CH=CH_2), 1.93-1.68 (4H, m, *c*-Hex), 1.59-1.24 (6H, m, *c*-Hex), 1.28 (3H, d, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 140.2, 136.7, 128.5, 128.1, 126.7, 116.9, 72.4, 56.9, 54.2, 53.5, 31.9, 31.7, 25.4, 23.64, 23.62, 15.2; IR (film) 3065, 3028, 2937, 2859, 1728, 1642, 1603, 1494, 1452, 1418, 1371, 1332, 1246, 1196, 1161, 1063, 1039, 1016, 994, 920, 865, 811, 776, 737, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{28}NO_2$, 302.2115; found, 302.2105. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.43; H, 9.20; N, 4.83.

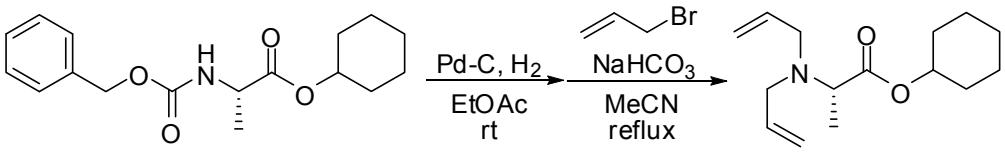
(*S*)-Cyclohexyl 2-(dibenzylamino)propanoate (2c)



11 **2c** 43%

A mixture of **11** (1.22 g, 4.0 mmol) and palladium on activated carbon (loading: 10 wt. %, 83 mg) in ethyl acetate (8 mL) was stirred for 1.5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, benzyl bromide (1.1 mL, 9.3 mmol), and sodium hydrogen carbonate (1.1 g, 13 mmol) in acetonitrile (20 mL) was refluxed for 24 h. The resulting mixture was filtered and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 10/1 as eluent) gave **2c** (0.61 g, 43% yield) as a colorless oil. $[\alpha]_{589}^{24}$ –98.5 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (4H, d, *J* = 7.6 Hz, Ph), 7.26 (4H, dd, *J* = 7.6, 7.2 Hz, Ph), 7.17 (2H, t, *J* = 7.2 Hz, Ph), 4.87 (1H, tt, *J* = 8.8, 3.6 Hz, OCH), 3.84 (2H, d, *J* = 14.0 Hz, C*H*$_2$Ph), 3.65 (2H, d, *J* = 14.0 Hz, C*H*$_2$Ph), 3.47 (1H, q, *J* = 7.2 Hz, NCHCO), 1.95-1.78 (2H, m, *c*-Hex), 1.78-1.65 (2H, m, *c*-Hex), 1.57-1.22 (6H, m, *c*-Hex), 1.29 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 139.8, 128.4, 128.0, 126.7, 72.2, 56.0, 54.3, 31.8, 31.5, 25.2, 23.5, 23.4, 14.8; IR (film) 3062, 3028, 2937, 2858, 1725, 1602, 1494, 1452, 1373, 1327, 1247, 1195, 1147, 1076, 1029, 1015, 954, 909, 828, 810, 734, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{30}NO_2$, 352.2271; found, 352.2266. Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.81; H, 8.46; N, 3.95.

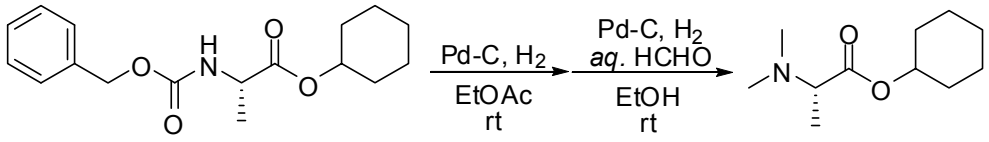
(*S*)-Cyclohexyl 2-(diallylamino)propanoate (2d)



11 **2d** 53%

A mixture of **11** (0.56 g, 1.8 mmol) and palladium on activated carbon (loading: 10 wt. %, 34 mg) in ethyl acetate (4 mL) was stirred for 1.5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, allyl bromide (0.35 mL, 4.1 mmol), and sodium hydrogen carbonate (0.71 g, 8.5 mmol) in acetonitrile (9 mL) was refluxed for 24 h. The resulting mixture was filtered and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 20/1 as eluent) gave **2d** (0.24 g, 53% yield) as a colorless oil. $[\alpha]_{589}^{26}$ –58.7 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (2H, dddd, *J* = 17.2, 10.1, 7.2, 5.4 Hz, CH_2CH=CH_2), 5.19 (2H, ddd, *J* = 17.2, 3.3, 1.6 Hz, CH_2CH=C*H*$_2$), 5.10 (2H, ddd, *J* = 10.1, 3.3, 1.2 Hz, CH_2CH=C*H*$_2$), 4.81 (1H, tt, *J* = 8.8, 3.6 Hz, OCH), 3.56 (1H, q, *J* = 7.2 Hz, NCHCO), 3.30 (2H, dddd, *J* = 14.5, 5.4, 1.6, 1.2 Hz, C*H*$_2$CH=CH_2), 3.14 (2H, dd, *J* = 14.5, 7.2 Hz, C*H*$_2$CH=CH_2), 1.90-1.79 (2H, m, *c*-Hex), 1.77-1.68 (2H, m, *c*-Hex), 1.59-1.23 (6H, m, *c*-Hex), 1.26 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 136.6, 116.9, 72.4, 57.4, 53.5, 31.8, 31.6, 25.4, 23.6, 15.3; IR (film) 3078, 2979, 2938, 2860, 1727, 1642, 1451, 1418, 1361, 1339, 1247, 1197, 1164, 1040, 1016, 994, 919, 864, 812, 775 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{26}NO_2$, 252.1958; found, 252.1948. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.65; H, 10.16; N, 5.50.

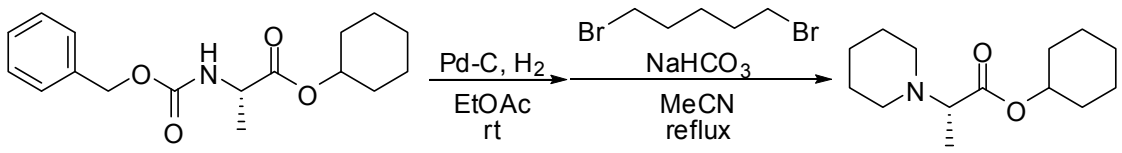
(*S*)-Cyclohexyl 2-(dimethylamino)propanoate (2e)



11 **2e** 45%

A mixture of **11** (1.1 g, 3.6 mmol) and palladium on activated carbon (loading: 10 wt. %, 92 mg) in ethyl acetate (7 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, palladium on activated carbon (loading: 10 wt. %, 0.14 g), and formaldehyde solution (37 wt. % in water, 5.8 mL, 77 mmol) in ethanol (14 mL) was stirred for 21 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (ethyl acetate as eluent) to obtain **2e** (0.32 g, 45% yield) as a colorless oil. $[\alpha]_{589}^{23}$ –20.8 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, tt, *J* = 9.0, 3.6 Hz, OCH), 3.19 (1H, q, *J* = 7.2 Hz, NCHCO), 2.35 (6H, s, $N(CH_3)_2$), 1.91-1.81 (2H, m, *c*-Hex), 1.78-1.68 (2H, m, *c*-Hex), 1.59-1.20 (6H, m, *c*-Hex), 1.28 (3H, d, *J* = 7.2 Hz, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 72.6, 63.0, 41.7, 31.7, 31.6, 25.3, 23.7, 15.4; IR (film) 2938, 2861, 2785, 1727, 1452, 1373, 1330, 1216, 1175, 1107, 1042, 1016, 971, 942, 924, 864, 798, 757 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{22}NO_2$, 200.1645; found, 200.1645. Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.08; H, 10.82; N, 6.75.

(*S*)-Cyclohexyl 2-(piperidin-1-yl)propanoate (2f)

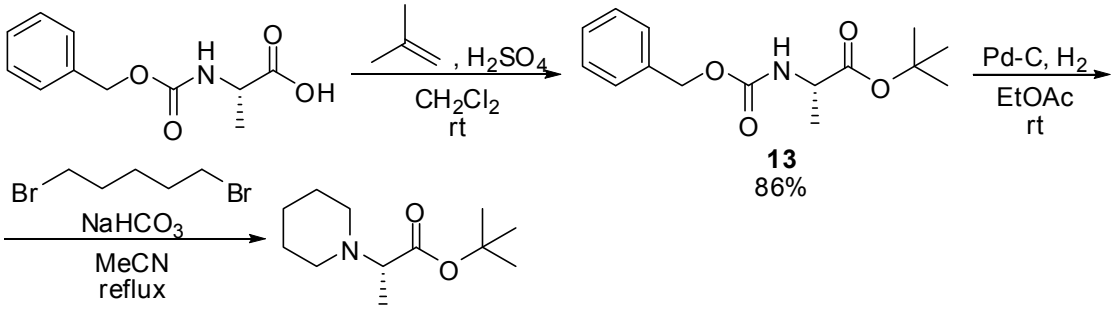


11 **2f** 68%

A mixture of **11** (1.00 g, 3.3 mmol) and palladium on activated carbon (loading: 10 wt. %, 78 mg) in ethyl acetate (6 mL) was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,5-dibromopentane (0.49 mL, 3.6 mmol), and sodium hydrogen carbonate (0.95 g, 11 mmol) in acetonitrile (16 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 as eluent) to obtain **2f** (0.54 g, 68% yield) as a colorless oil. $[\alpha]_{589}^{23}$ –25.5 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, tt, *J* = 9.0, 4.0 Hz, OCH), 3.23 (1H, q, *J* = 7.2 Hz, NCHCO), 2.60 (2H, ddd, *J* = 11.1, 7.0, 4.0 Hz, NCH_2), 2.52 (2H, ddd, *J* = 11.1, 7.0, 4.0 Hz, NCH_2), 1.90-1.80 (2H, m, *c*-Hex), 1.77-1.68 (2H, m, *c*-Hex), 1.65-1.22 (12H, m, piperidinyl-CH_2 and *c*-Hex), 1.28 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 72.4, 63.3, 50.5, 31.8, 31.6, 26.3, 25.3, 24.6, 23.7, 15.1; IR (film) 2935, 2857, 2810, 1728, 1451, 1379, 1338, 1309, 1231, 1178, 1130, 1096, 1037, 1019, 957, 935, 923, 862, 793, 749 cm^{-1};

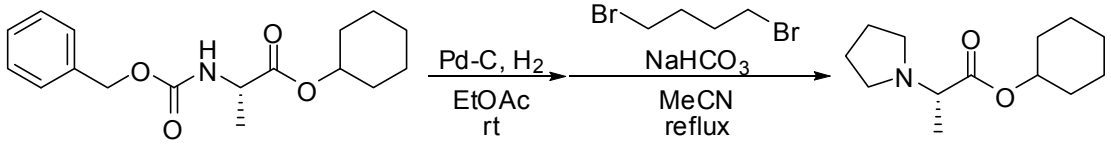
HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{26}NO_2$, 240.1958; found, 240.1954. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.50; H, 10.66; N, 5.77.

(*S*)-*tert*-Butyl 2-(piperidin-1-yl)propanoate (2g)



(Step 1) A round-bottomed flask with septum-inlet was equipped with a septa and a dry-ice condenser. The flask was charged with (*S*)-Cbz-alanine (1.11 g, 5.0 mmol), *conc.* sulfuric acid (98%, 0.05 mL), and dichloromethane (10 mL). Excess amount of isobutene gas was introduced to the flask at room temperature. The resulting mixture was stirred for 48 h at the same temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with dichloromethane and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 as eluent) to obtain (*S*)-Cbz-alanine *tert*-butyl ester (**13**) (1.20 g, 86% yield) as a colorless oil. (Step 2) A mixture of **13** (0.70 g, 2.5 mmol) and palladium on activated carbon (loading: 10 wt. %, 64 mg) in ethyl acetate (5 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,5-dibromopentane (0.38 mL, 2.8 mmol), and sodium hydrogen carbonate (0.69 g, 8.2 mmol) in acetonitrile (13 mL) was refluxed for 13 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 as eluent) to give **2g** (0.40 g, 75% yield) as a colorless oil. $[\alpha]_{589}^{23}$ –31.5 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (1H, q, *J* = 7.2 Hz, NCHCO), 2.61 (2H, ddd, *J* = 11.1, 6.9, 4.0 Hz, NCH_2), 2.53 (2H, ddd, *J* = 11.1, 6.9, 4.0 Hz, NCH_2), 1.65-1.39 (6H, m, piperidinyl-CH_2), 1.47 (9H, s, *t*-Bu), 1.25 (3H, d, *J* = 7.2 Hz, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 80.5, 63.7, 50.4, 28.2, 26.4, 24.6, 15.0; IR (film) 2977, 2935, 2854, 2809, 2756, 1726, 1452, 1367, 1342, 1308, 1255, 1205, 1152, 1132, 1053, 1028, 953, 882, 850, 793, 761 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{24}NO_2$, 214.1802; found, 214.1798. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.32; H, 11.03; N, 6.45.

(*S*)-Cyclohexyl 2-(pyrrolidin-1-yl)propanoate (2h)

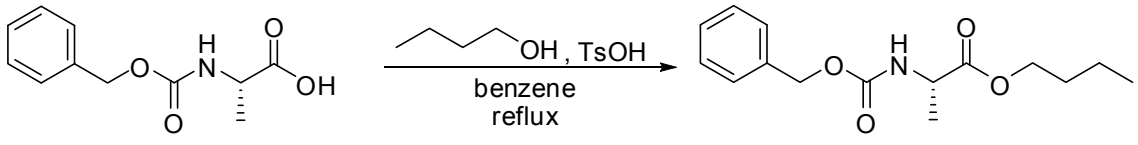


11 **2h** 63%

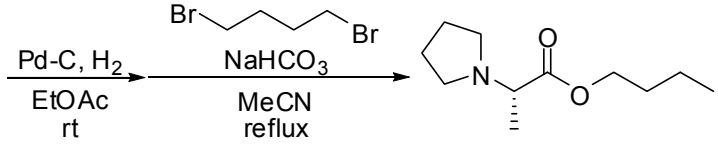
A mixture of **11** (1.29 g, 4.2 mmol) and palladium on activated carbon (loading: 10 wt. %, 97 mg) in ethyl acetate (8 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,4-dibromobutane (0.56 mL, 4.7 mmol), and sodium hydrogen carbonate (1.13 g, 13 mmol) in acetonitrile (8 mL) was refluxed for 23 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/1 as eluent) to give **2h** (0.60 g, 63% yield) as a colorless oil. $[\alpha]_{589}^{24}$ –19.5 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, tt, *J* = 9.2, 3.6 Hz, OCH), 3.14 (1H, q, *J* = 7.0 Hz, NCHCO), 2.71-2.58 (4H, m, NCH_2), 1.91-1.68 (8H, m, NCH_2CH_2 and *c*-Hex), 1.60-1.19 (6H, m, *c*-Hex), 1.36 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 72.7, 62.2, 50.9, 31.6, 31.5, 25.3, 23.8, 23.5, 17.5; IR (film) 2937, 2859, 2807, 1728, 1452, 1367, 1320, 1261, 1165, 1080, 1039, 1016, 984, 943, 925, 908, 871, 842, 799, 757 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{24}NO_2$, 226.1802; found, 226.1797. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.05; H, 10.47; N, 6.12.

(*S*)-*tert*-Butyl 2-(pyrrolidin-1-yl)propanoate (2i): Prepared in 65% yield by the same procedure with **2h** using **13** as a starting material. Colorless oil; $[\alpha]_{589}^{24}$ –22.8 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (1H, q, *J* = 6.8 Hz, NCHCO), 2.72-2.59 (4H, m, NCH_2), 1.82-1.76 (4H, m, NCH_2CH_2), 1.47 (9H, s, *t*-Bu), 1.32 (3H, d, *J* = 6.8 Hz, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 80.5, 62.5, 50.7, 28.1, 23.5, 17.3; IR (film) 2974, 2937, 2877, 2808, 1726, 1457, 1368, 1290, 1254, 1213, 1147, 1081, 1060, 1035, 982, 883, 850, 793, 754 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{22}NO_2$, 200.1645; found, 200.1643. A satisfactory elemental analysis of **2i** was not obtained due to its volatility.

(*S*)-*n*-Butyl 2-(pyrrolidin-1-yl)propanoate (2j)



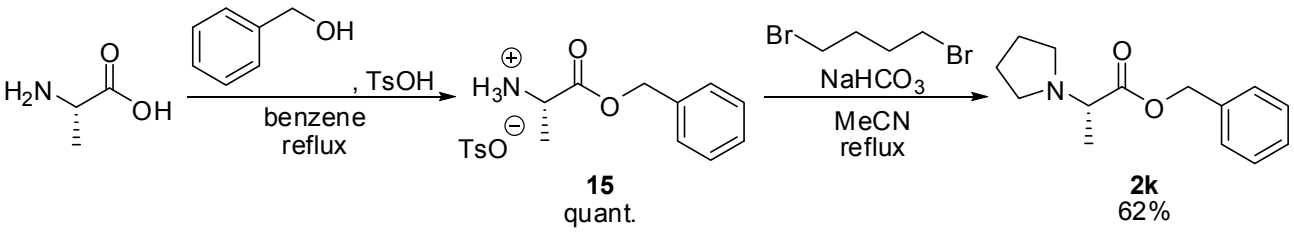
14 68%



2j 61%

(Step 1) A solution of (*S*)-Cbz-alanine (2.23 g, 10 mmol), *n*-butanol (1.00 mL, 11 mmol) and *p*-toluenesulfonic acid, monohydrate (0.18 g, 0.95 mmol) in benzene (20 mL) was refluxed for 16 h with azeotropic removal of water by a Dean–Stark trap. The resulting mixture was cooled to room temperature and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4/1 as eluent) to obtain (*S*)-Cbz-alanine *n*-butyl ester (**14**) (1.91 g, 68% yield) as a colorless oil. (Step 2) A mixture of **14** (1.91 g, 6.8 mmol) and palladium on activated carbon (loading: 10 wt. %, 0.13 g) in ethyl acetate (14 mL) was stirred for 5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,4-dibromobutane (0.90 mL, 7.5 mmol), and sodium hydrogen carbonate (2.26 g, 27 mmol) in acetonitrile (7 mL) was refluxed for 17 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (ethyl acetate as eluent) to give **2j** (0.82 g, 61% yield) as a colorless oil. $[\alpha]_{589}^{25}$ –21.5 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2CH_3$), 3.16 (1H, q, *J* = 6.8 Hz, NCHCO), 2.71-2.57 (4H, m, NCH_2), 1.86-1.75 (4H, m, NCH_2CH_2), 1.64 (2H, tt, *J* = 7.0, 7.0 Hz, $OCH_2CH_2CH_2CH_3$), 1.44-1.33 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.37 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 0.94 (3H, t, *J* = 7.4 Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 64.2, 62.0, 50.9, 30.6, 23.4, 19.0, 17.4, 13.6; IR (film) 2962, 2875, 2806, 1733, 1459, 1374, 1325, 1294, 1269, 1238, 1159, 1063, 983, 963, 941, 905, 869, 840, 788, 740 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{22}NO_2$, 200.1645; found, 200.1638. A satisfactory elemental analysis of **2j** was not obtained due to its volatility.

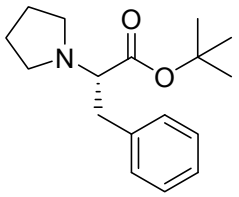
(*S*)-Benzyl 2-(pyrrolidin-1-yl)propanoate (2k)



(Step 1) A mixture of L-alanine (0.46 g, 5.2 mmol), benzyl alcohol (1.1 mL, 11 mmol) and *p*-toluenesulfonic acid, monohydrate (1.24 g, 6.5 mmol) in benzene (5 mL) was refluxed for 10 h with azeotropic removal of water by a Dean–Stark trap. The resulting mixture was cooled to room temperature and precipitated by addition of diethyl ether and *n*-hexane. The solid was isolated by filtration and dried under reduced pressure to obtain L-alanine benzyl ester *p*-toluenesulfonate (**15**) (1.87 g, quant.) as a white solid. (Step 2) A mixture of **15** (1.83 g, 5.2 mmol), 1,4-dibromobutane (0.68 mL, 5.7 mmol), and sodium hydrogen carbonate (1.83 g, 21.8 mmol) in acetonitrile (10 mL) was refluxed for 14 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (ethyl acetate as eluent) to give **2k** (0.75 g, 62% yield) as a colorless oil. $[\alpha]_{589}^{26}$ –14.5 (*c* 1.00,

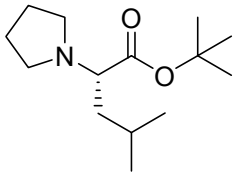
EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (5H, m, Ph), 5.17 (2H, s, CH_2Ph), 3.23 (1H, q, J = 6.8 Hz, NCHCO), 2.70-2.56 (4H, m, NCH_2), 1.84-1.72 (4H, m, NCH_2CH_2), 1.38 (3H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 135.8, 128.4, 128.2, 128.1, 66.0, 61.8, 50.7, 23.4, 17.3; IR (film) 3065, 3034, 2968, 2877, 2806, 1733, 1498, 1455, 1377, 1325, 1264, 1212, 1149, 1080, 1060, 1036, 986, 912, 867, 750, 698 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1483. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.83; H, 8.44; N, 5.82.

(*S*)-*tert*-Butyl 3-phenyl-2-(pyrrolidin-1-yl)propanoate (2l): Prepared in 81% yield by the same procedure



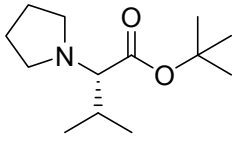
with **2g** using (*S*)-Cbz-phenylalanine and 1,4-dibromobutane. Colorless oil; $[\alpha]_{589}^{25}$ +45.0 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.15 (5H, m, Ph), 3.34 (1H, dd, J = 9.8, 5.8 Hz, NCHCO), 3.04 (1H, dd, J = 13.2, 5.8 Hz, CH_2Ph), 3.00 (1H, dd, J = 13.2, 9.8 Hz, CH_2Ph), 2.84-2.75 (2H, m, NCH_2), 2.73-2.64 (2H, m, NCH_2), 1.85-1.73 (4H, m, NCH_2CH_2), 1.27 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.9, 129.3, 128.0, 126.2, 80.6, 68.6, 50.3, 38.0, 27.9, 23.4; IR (film) 3029, 2971, 2875, 2812, 1723, 1604, 1495, 1478, 1455, 1391, 1367, 1294, 1253, 1218, 1147, 1078, 1053, 1031, 982, 905, 847, 742, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$, 276.1958; found, 276.1949. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.16; H, 9.41; N, 5.07.

(*S*)-*tert*-Butyl 4-methyl-2-(pyrrolidin-1-yl)pentanoate (2m): Prepared in 69% yield by the same procedure



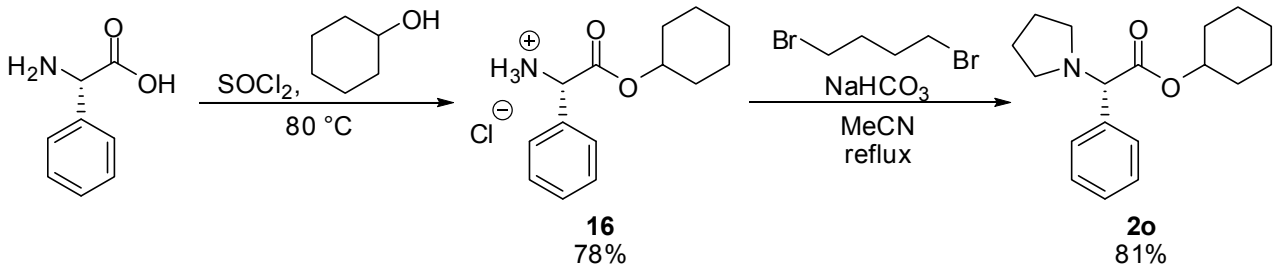
with **2g** using (*S*)-Cbz-leucine and 1,4-dibromobutane. Colorless oil; $[\alpha]_{589}^{24}$ +7.8 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (1H, dd, J = 9.6, 5.6 Hz, NCHCO), 2.79-2.69 (2H, m, NCH_2), 2.66-2.56 (2H, m, NCH_2), 1.81-1.41 (7H, m, $CH_2CH(CH_3)_2$ and NCH_2CH_2), 1.47 (9H, s, *t*-Bu), 0.93 (3H, d, J = 7.2 Hz, $CH_2CH(CH_3)_2$), 0.92 (3H, d, J = 6.8 Hz, $CH_2CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 80.5, 64.8, 49.9, 40.7, 28.2, 25.3, 23.5, 23.4, 22.1; IR (film) 2960, 2871, 2816, 1726, 1458, 1390, 1367, 1293, 1254, 1204, 1144, 1050, 937, 849, 793, 755 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{28}NO_2$, 242.2115; found, 242.2109. Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.40; H, 11.42; N, 5.68.

(*S*)-*tert*-Butyl 3-methyl-2-(pyrrolidin-1-yl)butanoate (2n): Prepared in 82% yield by the same procedure



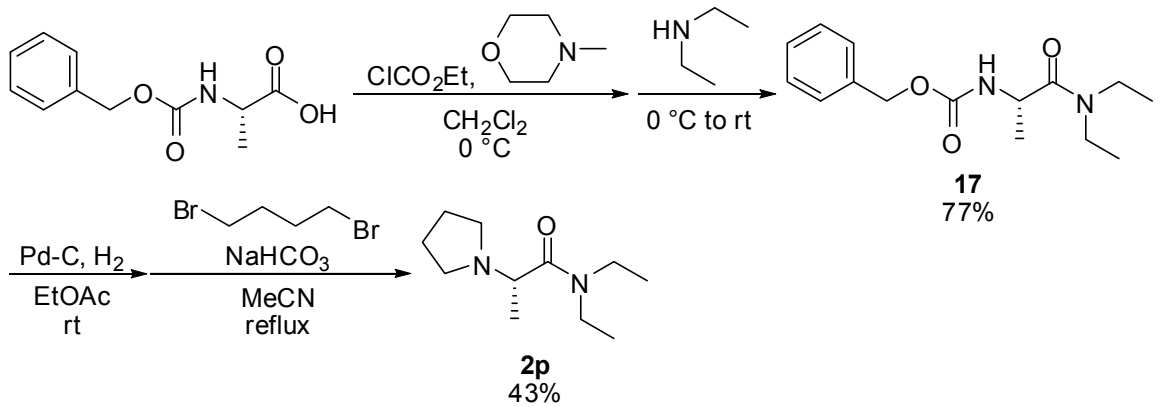
with **2g** using (*S*)-Cbz-valine and 1,4-dibromobutane. Colorless oil; $[\alpha]_{589}^{23}$ –7.9 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (1H, d, J = 8.8 Hz, NCHCO), 2.77-2.69 (2H, m, NCH_2), 2.66-2.56 (2H, m, NCH_2), 2.00 (1H, dqq, J = 8.8, 6.8, 6.8 Hz, $CHCH(CH_3)_2$), 1.80-1.66 (4H, m, NCH_2CH_2), 1.47 (9H, s, *t*-Bu), 0.98 (3H, d, J = 6.8 Hz, $CHCH(CH_3)_2$), 0.94 (3H, d, J = 6.8 Hz, $CHCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 80.4, 72.2, 49.2, 29.0, 28.3, 23.5, 19.9, 18.8; IR (film) 2966, 2874, 2808, 1723, 1461, 1389, 1367, 1250, 1204, 1142, 1111, 1035, 980, 910, 863, 790 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{26}NO_2$, 228.1958; found, 228.1954. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.38; H, 11.15; N, 6.00.

(*S*)-Cyclohexyl 2-phenyl-2-(pyrrolidin-1-yl)acetate (2o)



(Step 1) A mixture of L-2-phenylglycine (0.92 g, 6.1 mmol), cyclohexanol (8.1 mL, 77 mmol), and thionyl chloride (0.49 mL, 6.7 mmol) was stirred for 13 h at 80 °C. The resulting mixture was cooled to room temperature and diluted with cyclohexane. The resulting white suspension was filtered and the solids were isolated by filtration. Removal of volatiles under reduced pressure gave L-2-phenylglycine cyclohexyl ester hydrochloride (**16**) (1.28 g, 78% yield) as a white solid. (Step 2) A mixture of **16** (1.28 g, 4.7 mmol) and 1,4-dibromobutane (0.62 mL, 5.2 mmol), and sodium hydrogen carbonate (1.62 g, 19 mmol) in acetonitrile (10 mL) was refluxed for 25 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to give **2o** (1.09 g, 81% yield) as a yellow oil. $[\alpha]_{589}^{13}$ +60.5 (*c* 1.00, EtOH); 85% ee [determined by HPLC analysis: Daicel Chiralcel OJ–H column, *n*-hexane/isopropanol = 99/1 as eluent, flow rate = 0.50 mL/min, t_R = 10.3 min for (*R*)-**2o** and 11.9 min for (*S*)-**2o**]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.45 (2H, m, Ph), 7.35-7.26 (3H, m, Ph), 4.78 (1H, tt, *J* = 9.0, 3.6 Hz, OCH), 3.88 (1H, s, NCHCO), 2.64-2.53 (2H, m, NCH_2), 2.50-2.40 (2H, m, NCH_2), 1.89-1.15 (14H, m, NCH_2CH_2 and *c*-Hex); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 137.8, 128.3, 128.0, 74.2, 73.0, 52.5, 31.4, 31.1, 25.3, 23.6, 23.5, 23.3; IR (film) 3059, 3029, 2935, 2859, 2790, 1741, 1493, 1452, 1361, 1324, 1255, 1197, 1074, 1033, 1015, 982, 957, 920, 894, 781, 728, 699 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}NO_2$, 288.1958; found, 288.1949. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.45; H, 9.00; N, 4.96.

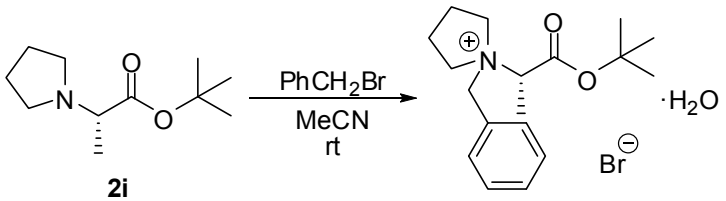
(*S*)-*N*,*N*-Diethyl-2-(pyrrolidin-1-yl)propanamide (2p)



(Step 1) Ethyl chloroformate (0.88 mL, 9.2 mmol) was added to a solution of (*S*)-Cbz-alanine (2.17 g, 9.7 mmol) and *N*-methylmorpholine (1.01 mL, 9.2 mmol) in dichloromethane (19 mL) at 0 °C. The mixture was stirred for 30 min and treated with diethylamine (0.96 mL, 9.3 mmol) at the same temperature. After stirring

for 30 min at 0 °C and for 25 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 1/1 as eluent) to obtain (*S*)-Cbz-alanine *N*,*N*-diethylamide (**17**) (1.96 g, 77% yield) as a white solid. (Step 2) A mixture of **17** (1.96 g, 7.0 mmol) and palladium on activated carbon (loading: 10 wt. %, 0.12 g) in ethyl acetate (14 mL) was stirred for 8 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. A mixture of the residual oil, 1,4-dibromobutane (0.93 mL, 7.8 mmol), and sodium hydrogen carbonate (1.83 g, 22 mmol) in acetonitrile (14 mL) was refluxed for 23 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 5/1 as eluent) to give **2p** (0.59 g, 43% yield) as a colorless oil. $[\alpha]_{589}^{26}$ –40.6 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54-3.28 (5H, m, NCHCO and NC*H*$_2$CH$_3$), 2.70-2.61 (2H, m, NC*H*$_2$CH$_2$), 2.61-2.52 (2H, m, NC*H*$_2$CH$_2$), 1.82-1.71 (4H, m, NCH$_2$C*H*$_2$), 1.29 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 1.18 (3H, t, *J* = 7.0 Hz, NCH$_2$C*H*$_3$), 1.12 (3H, t, *J* = 7.0 Hz, NCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 58.8, 50.4, 41.4, 40.2, 23.4, 15.5, 14.6, 12.9; IR (film) 2969, 2935, 2875, 2807, 1642, 1461, 1431, 1373, 1305, 1289, 1257, 1220, 1130, 1081, 976, 942, 889, 860, 792 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{23}N_2O$, 199.1805; found, 199.1799. A satisfactory elemental analysis of **2p** was not obtained due to its hygroscopic property.

(*S*)-1-Benzyl-1-(1'-*tert*-butoxycarbonyl)ethylpyrrolidinium bromide, monohydrate (7)



2i → **7** 81%

A solution of **2i** (0.27 g, 1.4 mmol) and benzyl bromide (0.19 mL, 1.6 mmol) in acetonitrile (2.7 mL) was stirred for 5 days at room temperature. Evaporation of the solvent and purification of the residue by chromatography on silica gel (dichloromethane/methanol = 10/1 to 5/1 as eluent) to give **7** (0.44 g, 81% yield) as a white solid. $[\alpha]_{589}^{26}$ –21.9 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 6.8 Hz, Ph), 7.55-7.44 (3H, m, Ph), 5.03 (1H, d, *J* = 13.2 Hz, C*H*$_2$Ph), 5.00 (1H, d, *J* = 13.2 Hz, C*H*$_2$Ph), 4.76 (1H, q, *J* = 7.0 Hz, NCHCO), 4.20-4.06 (3H, m, NC*H*$_2$CH$_2$), 3.99 (1H, dt, *J* = 12.8, 7.8 Hz, NC*H*$_2$CH$_2$), 2.25-2.04 (2H, m, NCH$_2$C*H*$_2$), 1.99 (2H, s, H_2O), 1.96-1.67 (2H, m, NCH$_2$C*H*$_2$), 1.84 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 132.9, 130.8, 129.4, 127.9, 85.4, 68.9, 64.1, 62.0, 61.3, 27.9, 23.7, 23.6, 14.9; IR (KBr) 3468, 3038, 2973, 2933, 2878, 1730, 1613, 1466, 1393, 1373, 1315, 1252, 1230, 1153, 1130, 1089, 1049, 1002, 962, 939, 892, 871, 839, 751, 705 cm^{-1}; HRMS–ESI (*m*/*z*): $[M–H_2O–Br]^+$ calcd for $C_{18}H_{28}NO_2$, 290.2115; found, 290.2100. Anal. Calcd for $C_{18}H_{30}BrNO_3$: C, 55.67; H, 7.79; N, 3.61. Found: C, 55.60; H, 7.98; N, 3.60.