α-Aminoallylation of Aldehydes with Ammonia: Stereoselective Synthesis of Homoallylic Primary Amines

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Experimental Details and Physical Data

General Methods: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300 or JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^{1}H NMR and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. High-resolution electron impact mass spectra (HR-EIMS) were measured with JEOL JMX-SX-102A mass spectrometer. High-resolution electrospray ionization mass spectra (HR-ESIMS) were measured with BRUKER DALTONICS BioTOF II mass spectrometer. Preparative thin-layer chromatography (PTLC)

was carried out using Wakogel B-5F. Ethanol was distilled from sodium and stored over 3Å MS. Distilled water was employed for the aqueous reactions. All other solvents were purified based on standard procedures.

Chemicals: Aldehydes **1a** and **1d-k** were purified by distillation prior to use. Aldehydes **1b** and **1c** were purified by recrystallization from aqueous ethanol and ethanol, respectively. Glyoxylic acid monohydrate (**1l**) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used without further purification. Aldehyde (*S*)-**1m**[1] and (2*S*,3*S*)-**1n**[2] were prepared according to the literature procedures. Allylboronate **2**,[3] (*E*)- and (*Z*)-crotylboronate **5**,[4] and chiral allylboronate **7**[5] were prepared according to the literatures. Liquid ammonia (99.999%, Nippon Sanso Corporation) and aqueous ammonia (28.0-30.0 wt%, Wako Pure Chemical Industries, Ltd.) were used without purification. Palladium on carbon (5 wt%, PH-type, wet, Kawaken Fine Chemicals Co., Ltd.) were used for hydrogenation. All other chemicals were purified based on standard procedures.

General procedures for α-aminoallylation of aldehydes 1a-l (Table 1)

Method A (entries 1 and 3-9): To a dry two-neck flask with an argon balloon and a rubber septum cooling at –78 °C, gaseous ammonia was introduced via a needle to obtain liquid ammonia (ca. 0.5 mL). After addition of ethanol (0.5 mL), aldehyde **1** (0.5 mmol) was added to ammonia at –78 °C and rinsed with ethanol (0.5 mL). In the case of **1b** and **1c** (solid aldehydes), aldehyde was first placed in the flask before addition of liquid ammonia (ca. 0.5 mL) and ethanol (1.0 mL). The mixture was warm to –10 °C and was stirred at that temperature for 2 h. During that, excess ammonia was vaporized in the balloon. Allylboronate **2** (0.6 mmol) in ethanol (0.5 mL) was then added dropwise to the solution. Colorless precipitates were formed on addition of **2**. The mixture was stirred at –10 °C for 3 h and at rt for 1 h. The balloon and the septum were then removed to vaporize most of ammonia and 1 N aqueous HCl was added to acidify the solution (pH ca. 1). The mixture was washed with diethyl ether (3×), alkalized with 6 N aqueous NaOH (pH ca. 10) and extracted with dichloromethane (3×). The dichloromethane layers were dried over anhydrous Na_2CO_3, filtered and evaporated to give almost pure amine **3**. The crude product was purified by preparative TLC (hexane/isopropylamine = 10/1) to give amine **3**. Meanwhile, non-basic components including alcohol **4** was obtained from the ethereal extracts. The extracts were

dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The yield of alcohol **4** was estimated by ^{1}H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard.

Method B (entries 2 and 13): Aldehyde **1a** or **1l** (0.5 mmol) in 28-30 wt% aqueous ammonia (0.74 mL, ca. 20 equiv) and ethanol (1 mL) was stirred at rt for 30 min. Allylboronate **2** (0.6 mmol) was added to the solution and rinsed with ethanol (0.5 mL). The mixture was stirred at rt for 2 h (entry 2) or 3 h (entry 13) and worked up in the same way as Method A for the reaction of **1a** (entry 2). In the case of glyoxylic acid (**1l**) (entry 3), the reaction mixture was concentrated *in vacuo* and the residue was charged on a cationic ion exchange resin column (DOWEX 50W-X2, 50-100 mesh, H^+ form; ca. 7 g/wet) with water. After washing with a sufficient amount of water, the product was eluted with 0.2 N aqueous ammonia. The fractions were checked by silica gel TLC plates without development using 0.1 wt% ninhydrine in acetone/water (80/20 v/v%). Fractions including product **3l** were collected and concentrated to dryness.

Method C (Table 1, entries 10-12): Allylboronate **2** (0.6 mmol) in ethanol (0.5 mL) was added to liquid ammonia (ca. 0.5 mL, see Method A) at –78 °C and rinsed with ethanol (0.5 mL). Colorless precipitates were formed during addition of **2**. After being stirred at rt for 30 min, aldehyde **1** (0.5 mmol) was added to the suspension and rinsed with ethanol (0.5 mL). The mixture was stirred at rt for 2 h and worked up in the same way as Method A.

1-Phenylbut-3-en-1-amine (3a):[6] 84% (Method A), 80% (Method B); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 5.76 (dddd, *J* = 17.0, 10.1, 8.0, 6.5 Hz, 1H), 5.05-5.16 (m, 2H), 3.99 (dd, *J* = 8.0, 5.3 Hz, 1H), 2.52-2.42 (m, 1H), 2.41-2.30 (m, 1H), 1.55 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 135.4, 128.4, 127.0, 126.3, 117.6, 55.4, 44.2; HR-ESIMS calcd for $C_{10}H_{14}N$ ($M+H^+$) 148.1126, found 148.1126.

1-(4-Nitrophenyl)but-3-en-1-amine (3b):[6] 96% (Method A); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (apparent d, *J* = 8.8 Hz, 2H), 7.50 (apparent d, *J* = 8.8 Hz, 2H), 5.69 (dddd, *J* = 15.9, 9.6, 7.9, 6.5 Hz, 1H), 5.13-5.06 (m, 2H), 4.12 (dd, *J* = 7.8, 5.4 Hz, 1H), 2.43 (dddt, *J* = 13.6, 6.5, 5.4, 1.2 Hz, 1H), 2.32 (ddd, *J* = 13.6, 7.9, 7.8 Hz, 1H), 1.59 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 147.0, 134.2, 127.3, 123.6, 118.6, 54.8, 44.1; HR-ESIMS calcd for $C_{10}H_{13}N_2O_2$ ($M+H^+$) 193.0977, found 193.0973.

1-(4-Bromophenyl)but-3-en-1-amine (3c):[7] 92% (Method A); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (apparent d, *J* = 8.5 Hz, 2H), 7.23 (apparent d, *J* = 8.5 Hz, 2H), 5.73 (dddd, *J* = 17.1,

10.3, 8.0, 6.4 Hz, 1H), 5.14-5.08 (m, 2H), 3.97 (dd, *J* = 7.8, 5.6 Hz, 1H), 2.46-2.38 (m, 1H), 2.36-2.27 (m, 1H), 1.54 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 134.9, 131.4, 128.1, 120.6, 118.0, 54.8, 44.1; HR-ESIMS calcd for $C_{10}H_{13}BrN$ ($M+H^+$) 226.0231, found 226.0234.

1-(4-Methoxyphenyl)but-3-en-1-amine (3d):[6] 91% (Method A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (apparent d, *J* = 8.6 Hz, 2H), 6.87 (apparent d, *J* = 8.6 Hz, 2H), 5.75 (dddd, *J* = 17.2, 10.1, 7.9, 6.3 Hz, 1H), 5.16-5.04 (m, 2H), 3.95 (dd, *J* = 7.9, 5.5 Hz, 1H), 3.80 (s, 3H), 2.44 (dddt, *J* = 13.7, 6.3, 5.5, 1.4 Hz, 1H), 2.34 (dddt, *J* = 13.7, 7.9, 7.9, 0.9 Hz, 1H), 1.54 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 138.0, 135.6, 127.3, 117.5, 113.7, 55.3, 54.8, 44.3; HR-ESIMS calcd for $C_{11}H_{16}NO$ ($M+H^+$) 178.1226, found 178.1225.

2-(1-Aminobut-3-enyl)phenol (3e): 76% (Method A); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.78 (ddd, *J* = 7.3, 7.3, 1.2 Hz, 1H), 5.78 (dddd, *J* = 16.8, 10.3, 8.8, 5.8 Hz, 1H), 5.24-5.17 (m, 2H), 4.13 (dd, *J* = 9.0, 4.9 Hz, 1H), 2.57-2.43 (m, 2H), NH_2, OH (unassignable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 134.7, 128.5, 127.7, 126.7, 119.0, 118.9, 117.3, 55.4, 41.5; HR-EIMS calcd for $C_{10}H_{13}NO$ (M^+) 163.0997, found 163.1001.

1-(Pyridin-2-yl)but-3-en-1-amine (3f):[8] 85% (Method A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.9, 1.8, 1.1 Hz, 1H), 7.65 (ddd, *J* = 7.9, 7.5, 1.8 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.16 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 5.77 (dddd, *J* = 17.0, 10.2, 7.9, 6.4 Hz, 1H), 5.16-5.06 (m, 2H), 4.06 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.60 (dddt, *J* = 13.7, 6.4, 5.3, 1.4 Hz, 1H), 2.41 (dddt, *J* = 13.7, 7.9, 7.9, 1.0 Hz, 1H), 1.88 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 149.1, 136.4, 135.1, 121.9, 120.9, 117.7, 56.5, 43.2; HR-ESIMS calcd for $C_9H_{13}N_2$ ($M+H^+$) 149.1079, found 149.1080.

1-(Thiophen-2-yl)but-3-en-1-amine (3g):[9] 77% (Method A); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.96-6.91 (m, 2H), 5.79 (dddd, *J* = 17.1, 10.2, 7.8, 6.4 Hz, 1H), 5.18-5.10 (m, 2H), 4.28 (dd, *J* = 7.9, 5.2 Hz, 1H), 2.61-2.53 (m, 1H), 2.46-2.38 (m, 1H), 1.68 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 134.8, 126.5, 123.6, 122.7, 118.2, 51.3, 44.7; HR-ESIMS calcd for $C_8H_{12}NS$ ($M+H^+$) 154.0690, found 154.0687.

(*E*)-1-Phenylhexa-1,5-dien-3-amine (3h):[10] 75% (Method A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.18 (m, 5H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.20 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.82 (dddd, *J* = 17.0, 10.2, 7.7, 6.6 Hz, 1H), 5.19-5.09 (m, 2H), 3.58 (dddd, *J* = 7.3, 6.8, 5.7, 1.1 Hz, 1H), 2.36 (dddt, *J* = 13.7, 6.6, 5.7, 1.3 Hz, 1H), 2.24 (dddt, *J* = 13.7, 7.7, 7.3, 1.1 Hz, 1H), 1.48 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.0, 134.2, 129.0, 128.6, 127.3, 126.3, 117.8, 53.2, 42.5; HR-ESIMS calcd for $C_{12}H_{16}N$ ($M+H^+$) 174.1283, found 174.1284.

1-Phenylhex-5-en-3-amine (3i):[11] 78% (Method C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (m, 2H), 7.22-7.14 (m, 3H), 5.79 (dddd, *J* = 17.6, 9.6, 8.0, 6.4 Hz, 1H), 5.12-5.06 (m, 2H), 2.83 (tt, *J* = 8.0, 4.9 Hz, 1H), 2.76 (ddd, *J* = 13.7, 10.0, 5.9 Hz, 1H), 2.64 (ddd, *J* = 13.7, 10.0, 6.4 Hz, 1H), 2.27 (dddt, *J* = 13.7, 6.4, 4.7, 1.4 Hz, 1H), 2.03 (dddt, *J* = 13.7, 7.9, 7.9, 1.0 Hz, 1H), 1.76 (dddd, *J* = 13.5, 10.0, 6.4, 4.9 Hz, 1H), 1.61 (dddd, *J* = 13.5, 10.0, 7.9, 5.9 Hz, 1H), 1.26 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 135.6, 128.36, 128.34, 125.8, 117.4, 50.2, 42.7, 39.4, 32.6; HR-ESIMS calcd for $C_{12}H_{18}N$ ($M+H^+$) 176.1439, found 176.1435.

1-Cyclohexylbut-3-en-1-amine (3j): 80% (Method C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (dddd, *J* = 16.9, 10.4, 8.3, 6.1 Hz, 1H), 5.13-5.05 (m, 2H), 2.57 (ddd, *J* = 9.0, 5.3, 3.9 Hz, 1H), 2.34-2.24 (m, 1H), 1.96 (apparent ddd, *J* = 13.7, 9.0, 8.3 Hz, 1H), 1.82-1.61 (m, 5H), 1.32-0.93 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 117.0, 55.3, 43.4, 39.4, 29.7, 28.3, 26.6, 26.5, 26.4; HR-ESIMS calcd for $C_{10}H_{20}N$ ($M+H^+$) 154.1596, found 154.1593.

2-Phenylhex-5-en-3-amine (3k): 69% (*syn*/*anti* = 73/27) (Method C); ^{1}H NMR (400 MHz, $CDCl_3$) <u>*syn*-isomer</u> δ 7.34-7.15 (m, 5H), 5.75 (dddd, *J* = 17.8, 9.4, 8.3, 6.0 Hz, 1H), 5.08-5.02 (m, 2H), 2.93 (ddd, *J* = 9.0, 6.8, 3.9 Hz, 1H), 2.69 (dq, *J* = 6.8, 7.1 Hz, 1H), 2.16 (dddt, *J* = 13.8, 6.0, 3.9, 1.6 Hz, 1H), 1.86 (dddt, *J* = 13.8, 9.0, 8.3, 1.0 Hz, 1H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.20 (brs, 2H); <u>*anti*-isomer</u> (representative peaks) δ 5.84 (dddd, *J* = 17.1, 10.2, 8.5, 6.1 Hz, 5H), 5.17-5.09 (m, 2H), 2.64 (apparent quint, *J* = 7.2 Hz, 1H), 2.44 (m, 1H), 1.86 (dddt, *J* = 13.9, 9.0, 8.3, 1.0 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) <u>*syn*-isomer</u> δ 145.2, 136.2, 128.3, 127.7, 126.2, 117.3, 56.0, 45.6, 40.0, 16.4; HR-ESIMS calcd for $C_{12}H_{18}N$ ($M+H^+$) 176.1439, found 176.1444.

Assignment of the relative configuration of 3k: A mixture of **3k** (20.6 mg), propionyl chloride (15 μL, 1.5 equiv) and triethylamine (2 equiv) in dichloromethane (2 mL) was stirred at rt for 5 h. The resultant was purified by preparative TLC (hexane/ethyl acetate = 1/1) to give the corresponding propionamide (26.2 mg). Then, a mixture of propionamide (24.3 mg) and Pd/C (5 wt%, wet) in ethanol (2 mL) was stirred at rt for 29 h under hydrogen atmosphere

using a balloon (ca. 1 atm). The mixture was filtered through a Celite pad and concentrated *in vacuo* to dryness. The crude hydrogenated product was then treated with lithium aluminum hydride (10.3 mg, 2 equiv) in THF (2 mL) at 80 °C for 6 h. The mixture was cooled to rt and quenched by a careful addition of powdered Na_2SO_4•$10H_2O$ (89.5 mg). After being mixed until colorless precipitates were formed, the mixture was filtered through a Celite pad, concentrated *in vacuo* and purified by preparative TLC (hexane/isopropylamine = 10/1) to give 2-phenyl-*N*-propylhexan-3-amine (12.3 mg). ^{1}H NMR analysis of this amine (10% $CDCl_3$ in CCl_4) showed two sets of doublets [δ 1.27 (*J* = 7.1 Hz) (major), 1.23 (*J* = 7.1 Hz) (minor)]. According to the literature,[12] this indicates that the major diastereomer is *syn* isomer.

2-Aminopent-4-enoic acid (3l):[13] Quant. (Method B); decomp. 247-248 °C; ^{1}H NMR (300 MHz, D_2O, 1,4-dioxane as an internal standard: δ 3.75 ppm) δ 5.77 (ddt, *J* = 17.2, 10.0, 7.3 Hz, 1H), 5.27 (brd, *J* = 17.2 Hz, 1H), 5.26 (brd, *J* = 10.0 Hz, 1H), 3.80 (brt, *J* = 6.0 Hz, 1H), 2.66 (br ddd, *J* = 14.7, 7.3, 6.0 Hz, 1H), 2.59 (br ddd, *J* =14.7, 7.3, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, 1,4-dioxane as an internal standard: δ 67.19 ppm) δ 174.7, 131.9, 121.1, 54.6, 35.4, 20.9. Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.88; H, 7.72; N, 11.97.

Diastereoselective α-aminoallylation of (*S*)-1m (Scheme 2)

Allylboronate **2** (106.0 mg, 0.6 mmol) in ethanol (0.5 mL) was added to a mixture of liquid ammonia (ca. 0.5 mL) and ethanol (0.5 mL) at –78 °C (see Method A). After being stirred at 0 °C for 30 min, aldehyde (*S*)-**1m** (132.5 mg, 0.5 mmol, >94% ee) in ethanol (0.5 mL) was added to the suspension. The mixture was stirred at 0 °C for 12 h and concentrated *in vacuo*. The crude was purified by preparative TLC (hexane/isopropylamine = 100/7) to give amine **3m** (102.6 mg, 67%, *syn*/*anti* = 85/15) as colorless oil.

(2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylhex-5-en-3-amine (3m): $[\alpha]^{26}_D$ –12.7 (c 1.05, MeOH, 95% ee, *syn*/*anti* = 85/15); ^{1}H NMR (400 MHz, $CDCl_3$) <u>*syn*-isomer</u> δ 7.31-7.15 (m, 5H), 5.72 (dddd, *J* = 15.3, 11.9, 7.8, 6.1 Hz, 1H), 5.08-5.00 (m, 2H), 3.80 (apparent dt, *J* = 2.7, 6.8 Hz, 1H), 2.97 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.71 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.71 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.62 (ddd, *J* = 9.0, 4.4, 2.7 Hz, 1H), 2.27 (dddt, *J* = 13.9, 6.1, 4.4, 1.4 Hz, 1H), 2.01 (apparent dt, *J* = 13.9, 8.5 Hz, 1H), 1.31 (brs, 2 H), 0.89 (s, 9H), 0.02 (s, 3H), -0.15

(s, 3H); *anti*-isomer (representative peaks) δ 5.82 (dddd, *J* = 17.2, 10.0, 7.1, 7.0 Hz, 1H), 5.18-5.08 (m, 2H), 2.87 (ddd, *J* = 8.8, 5.2, 3.5 Hz, 1H), 2.12 (apparent dt, *J* = 13.9, 8.2 Hz, 1H), 0.83 (s, 9H), -0.09 (s, 3H), -0.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *syn*-isomer δ 138.9, 136.4, 129.6, 128.3, 126.1, 116.9, 76.5, 53.1, 40.2, 39.5, 25.90, 18.08, -4.6; *anti*-isomer δ 139.3, 136.0, 129.8, 128.1, 126.0, 117.2, 77.1, 55.0, 37.74, 37.71, 25.84, 17.98, -4.8, -5.3; HR-ESIMS calcd for $C_{18}H_{32}NOSi$ ($M+H^+$) 306.2253, found 306.2259.

Assignment of the stereochemistry:

(1) (*S*)-**1m** was prepared from L-phenylalanine.[1] The enantiomeric excess of (*S*)-**1m** was determined by HPLC analysis to be 94% ee after its conversion to the corresponding primary alcohol by $NaBH_4$-reduction. HPLC (CHIRALCEL OD-H, 0.46 cmø × 25 cmL, hexane/2-propanol = 9/1, flow rate 1.0 mL/min, UV detection at 254 nm) t_R = 4.1 min (*S*), 9.5 min (*R*).

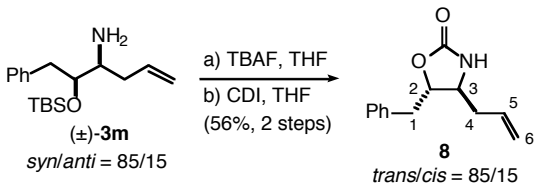
(2) The authentic racemic product (±)-**3m** was prepared from (±)-**1m** in 72% (*syn*/*anti* = 85/15) according to the above procedure. By HPLC analysis using (±)-**3m**, the enantiomeric excess of (2*S*)-**3m** was determined to be 95% ee. HPLC (*double* CHIRALCEL OD columns, 0.46 cmø × 25 cmL each, hexane/2-propanol = 9/1, flow rate 0.3mL/min, UV detection at 254 nm) t_R = 26.3 min (2*S*,3*S*), 27.6 min (2*S*,3*R*), 32.4 min (2*R*,3*S*), 61.7 min (2*R*,3*R*).

(3) The relative configuration of **3m** was determined as follows (Table S-1). To a solution of (±)-**3m** (72.2 mg, dr = 85/15) in dry THF (2 mL) was added TBAF (1.0 M THF solution, 354 μL) at rt. The mixture was stirred at rt for 45 h, diluted with ethyl acetate, washed with sat. aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The residue was dissolved in dry THF (1.0 mL) and treated with 1,1'-carbonyldiimidazole (42 mg) in THF (0.5 mL) at rt. The mixture was stirred at rt for 4 h, concentrated and purified preparative TLC (hexane/ethyl acetate 1/1) to give oxazolidinone **8** (28.9 mg, 2 steps 56%, *trans*/*cis* = 85/15). NOE difference spectroscopy with **8** determined the relative configuration of the major diastereomer to be *trans*.

4-Allyl-5-benzyloxazolidin-2-one (8): ^{1}H NMR (400 MHz, $CDCl_3$) *trans*-isomer δ 7.35-7.19 (m, 5H; Ph), 6.28 (brs, 1H; NH), 5.58 (ddt, *J* = 17.1, 10.3, 7.1 Hz, 1H; H5), 5.14-5.02 (m, 2H, H6), 4.44 (dt, *J* = 5.6, 6.5 Hz, 1H; H2), 3.59 (dt, *J* = 5.6, 6.4 Hz, 1H; H3), 3.09 (dd, *J* = 14.0, 6.5 Hz, 1H; $H1_a$), 2.91 (dd, *J* = 14.0, 6.5 Hz, 1H; H1b), 2.16 (dt, *J* = 14.4, 6.4 Hz, 1H; H4), 2.13 (dt, *J* = 14.4, 6.4 Hz, 1H; H4); *cis*-isomer (representative peaks) δ 6.15 (brs, 1H), 5.75 (dddd, *J* = 16.7, 10.5, 7.7, 6.0 Hz, 1H), 5.24-5.17 (m, 2H), 4.88 (ddd, *J* = 9.6, 7.6, 4.6 Hz, 1H),

3.86 (ddd, J = 9.6, 7.4, 4.0 Hz, 1H), 2.45-2.37 (m, 1H), 2.35-2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) <u>*trans*-isomer</u> δ 159.0, 135.2, 131.9, 129.4, 128.6, 127.1, 119.3, 81.7, 56.1, 40.4, 39.3; <u>*cis*-isomer</u> δ 159.1, 136.4, 132.7, 129.0, 126.9, 119.5, 80.1, 54.7, 35.5, 34.7; HR-ESIMS calcd for $C_{13}H_{16}NO_2$ ($M+H^+$) 218.1181, found 218.1183.

Table S-1. NOE Difference Spectroscopy with **8**



irradiated	enhanced (%)
$H1_a$ (3.09 ppm)	$H1_b$ (24.4), H2 (4.0), <u>H3 (2.2)</u>, Ph (23.3)
$H1_b$ (2.91 ppm)	$H1_a$ (21.8), H2 (6.7), <u>H3 (5.7)</u>, Ph (35.8)
H2	$H1_a$ (3.1), $H1_b$ (3.6), H3 (2.2), <u>H4 (5.9)</u>
H3	<u>$H1_a$ (2.3), $H1_b$ (3.4)</u>, H3 (1.8), H4 (6.8)
H4	<u>H2 (4.6)</u>, H3 (4.1)

Diastereoselective α-aminoallylation of (2*S*,3*S*)-1n (Scheme 2)

(2*S*,3*S*)-**1n** was prepared from L-chinovose and used without further purification according to the literature.[2] A solution of crude (2*S*,3*S*)-**1n** (67.2 mg, obtained from 164 mg of L-chinovose) in liquid ammonia (ca. 0.5 mL) and ethanol (1 mL) was stirred at 0 °C for 1 h (see Method A). Allylboronate **2** (84 mg, 0.5 mmol) in ethanol (0.5 mL) was added to the mixture. After being stirred at 0 °C for 24 h, the cloudy solution was collected with methanol and evaporated. The residue was charged on a DOWEX 50W-X2 column (ca. 5g/wet, pre-treated with 1N aq. HCl, water and methanol) with methanol, washed with methanol (ca. 100 mL) and eluted with 0.2 N ammonia in methanol. The fractions were checked by TLC plates without development using a phosphomolybdic acid indicator. Positive fractions were concentrated to dryness and the residue was dissolved in dichloromethane (1 mL) and treated with Boc_2O (125 μL) at rt for 4 h. The mixture was evaporated and purified by flash silica gel column chromatography to give Boc-**3n** (62.2 mg, 51% based on **2**, >98% *syn*, the minor isomer was not detected by ^{1}H NMR analysis).

***N-tert*-Butoxycarbonyl-4-aminohept-6-ene-2,3-diol (Boc-3n):** $[\alpha]^{27}_D$ –8.7 (c 0.52, MeOH, >98% *syn*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.1, 7.0 Hz, 1H), 5.17-5.04 (m, 2H), 4.75 (brd, J = 7.7 Hz, 1H), 3.97 (apparent q, J = 7.2 Hz, 1H), 3.49 (dq, J = 8.3, 6.2 Hz, 1H), 3.26 (dd, J = 8.3, 1.4 Hz, 1H), 3.90 (brs, 2H), 2.42-2.23 (m, 2H), 1.43 (s, 9H), 1.27 (d, J

= 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 134.5, 117.7, 80.3, 77.4, 67.5, 50.2, 36.6, 28.3, 19.2; HR-ESIMS calcd for $C_{12}H_{24}NO_4$ ($M+H^+$) 246.1705, found 246.1711.

Transformation of Boc-3n to a L-acosamine derivative (Scheme 2)

Ozone/oxygen gas was bubbled into a solution of Boc-**3n** (63 mg, 0.26 mmol) in methanol (4 mL) at –78 °C until the solution turned purple. After removal of excess ozone, dimethyl sulfide (97 μL) was added dropwise to the solution at – 78 °C. The mixture was wormed to rt and stirred at rt for 2 h. The mixture was recovered with methanol and concentrated to dryness. The residue was dissolved in dry methanol (2.5 mL) and treated with sat. HCl/MeOH (ca. 0.5 mL). After being stirred at rt for 6 h, the mixture was concentrated *in vacuo*. The residue was then treated with acetic anhydride (194 μL) in pyridine (1 mL) at rt for 9 h. After removal of pyridine under reduced pressure at 50 °C, the residue was purified by preparative TLC (ethyl acetate) to give 1-*O*-methyl-3-*N*-acetyl-4-*O*-acetyl-L-acosamine (27.7 mg, 3 steps 44%) as colourless solid. Recrystallization from dichloromethane/hexane gave colourless needles (18.1 mg, α-anomer).

1-*O*-Methyl-3-*N*-acetyl-4-*O*-acetyl-L-acosamine:[14] α-anomer mp 159-161 °C, $[\alpha]^{26}_D$ –190.3 (c 0.38, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (brd, *J* = 8.3 Hz, 1H), 4.70 (dd, *J* = 10.2, 8.8 Hz, 1H), 4.46 (dd, *J* = 10.2, 8.8 Hz, 1H), 4.40 (dddd, *J* = 11.8, 10.2, 8.3, 4.5 Hz, 1H), 3.89 (dq, *J* = 8.8, 6.4 Hz, 1H), 3.33 (s, 3H), 2.21 (ddd, *J* = 13.2, 4.5, 1.2 Hz, 1H), 2.07 (s, 3H), 1.90 (s, 3H), 1.58 (ddd, *J* = 13.2, 11.8, 3.5 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.7, 97.5, 75.7, 65.6, 54.6, 47.0, 36.4, 23.4, 20.9, 17.7; HR-ESIMS calcd for $C_{11}H_{20}NO_5$ ($M+H^+$) 246.1341, found 246.1342.

α-Aminocrotylation of aromatic aldehydes (Scheme 3)

(*E*)- or (*Z*)-Crotylboronate **5** (0.75 mmol) in ethanol (0.5 mL) was added to liquid ammonia (ca. 0.5 mL, see Method A) at –78 °C and rinsed with ethanol (0.5 mL). Colorless precipitates were formed during addition of **5**. After being stirred at rt for 30 min, aldehyde **1a** (0.5 mmol) or a 1,4-dioxane solution of aldehyde **1b** (0.5 mmol in 0.5 mL of the solvent) was added to the suspension and rinsed with ethanol (0.5 mL) or 1,4-dioxane (0.5 mL), respectively. The mixture was stirred at rt for 2 h and worked up in the same way as Method A.

(1*S,2*R**)-2-Methyl-1-phenylbut-3-en-1-amine (*syn*-6a):**[15] 85% (*syn*/*anti* = >99/<1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (m, 5H), 5.69 (ddd, *J* = 17.8, 9.7, 7.3 Hz, 1H), 5.06-4.97 (m, 2H), 3.88 (d, *J* = 5.5 Hz, 1H), 2.50 (ddq, *J* = 7.3, 5.5, 6.8 Hz, 1H), 1.52 (brs, 2H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 141.0, 128.0, 127.1, 126.8, 115.0, 60.0, 44.7, 15.0; HR-ESIMS calcd for $C_{11}H_{16}N$ ($M+H^+$) 162.1283, found 162.1279.

(1*S,2*S**)-2-Methyl-1-phenylbut-3-en-1-amine (*anti-6a*):**[15] 79% (*syn*/*anti* = 7/93); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.75 (ddd, *J* = 17.1, 10.3, 8.5 Hz, 1H), 5.17 (dq, *J* = 17.1, 1.0 Hz, 1H), 5.12 (dd, *J* = 10.3, 1.7 Hz, 1H), 3.65 (d, *J* = 8.5 Hz, 1H), 2.38 (ddq, *J* = 8.5, 8.5, 6.8 Hz, 1H), 1.75 (brs, 2H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 141.7, 128.3, 127.3, 127.1, 115.8, 60.7, 46.3, 17.7; HR-ESIMS calcd for $C_{11}H_{16}N$ ($M+H^+$) 162.1283, found 162.1278.

(1*S,2*R**)-2-Methyl-1-(4-nitrophenyl)but-3-en-1-amine (*syn*-6b):** 90% (*syn*/*anti* = >99/<1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (apparent d, *J* = 8.3 Hz, 2H), 7.47 (apparent d, *J* = 8.3 Hz, 2H), 5.66 (ddd, *J* = 17.0, 10.6, 7.3 Hz, 1H), 5.05 (apparent d, *J* = 10.6 Hz, 1H), 5.03 (apparent d, *J* = 17.0 Hz, 1H), 4.03 (d, *J* = 5.5 Hz, 1H), 2.52 (ddq, *J* = 7.3, 5.5, 6.8 Hz, 1H), 1.55 (brs. 2H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 146.9, 140.0, 128.0, 123.2, 115.9, 59.5, 44.7, 14.6; HR-ESIMS calcd for $C_{11}H_{15}N_2O_2$ ($M+H^+$) 207.1134, found 207.1136.

(1*S,2*S**)-2-Methyl-1-(4-nitrophenyl)but-3-en-1-amine (*anti*-6b):** 92% (*syn*/*anti* = 2/98); mp 43-44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (apparent d, *J* = 8.8 Hz, 2H), 7.51 (apparent d, *J* = 8.8 Hz, 2H), 5.69 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1H), 5.16 (apparent d, *J* = 17.1 Hz, 1H), 5.15 (apparent d, *J* = 10.2 Hz, 1H), 3.82 (d, *J* = 8.1 Hz, 1H), 2.38 (ddq, *J* = 8.6, 8.1, 6.8 Hz, 1H), 1.89 (brs. 2H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 147.1, 140.3, 128.2, 123.4, 116.7, 60.1, 46.1, 17.3; HR-EIMS calcd for $C_{11}H_{15}N_2O_2$ ($M+H^+$) 207.1134, found 207.1142.

Synthesis of alloisoleucine (Scheme 4)

(*Z*)-Crotylboronate **5** (137.5 mg, 0.75 mmol) in ethanol (0.5 mL) was added to liquid ammonia (ca. 0.5 mL, see Method A) at –78 °C and rinsed with ethanol (0.5 mL). After being stirred at –10 °C for 30 min, glyoxylic acid (**1l**) (46.5 mg, 0.5 mmol) in water (0.5 mL) was added to the suspension and rinsed with ethanol (0.5 mL). The mixture was stirred at –10 °C for 3 h. Most of the ammonia was removed by aspiration. After addition of Pd/C (5

wt%, wet, 15.2 mg), the mixture was stirred at rt for 12 h under hydrogen atmosphere using a balloon (ca. 1 atm). The mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by ion exchange resin chromatography (see the method for isolation of **3l**, Method B) to give (±)-alloisoleucine (60 mg, 91%). The above one-pot procedure (subsequent hydrogenation) was important to suppress the undesired isomerization of the *syn*-crotylated product to the linear isomer. This isomerization was observed when we tried to isolate the crotylated product, i. e. concentration with heating.

(±)-Alloisoleucine:[16] Colorless plates (recrystallized from 90% aqueous ethanol); decomp. 238 °C; ^{1}H NMR (400 MHz, D_2O, 1,4-dioxane as an internal standard: δ 3.75 ppm) δ 3.73 (d, J = 3.6 Hz, 1H), 2.06 (dtq, J = 3.6, 7.3, 6.6 Hz, 1H), 1.43 (ddt, J = 14.0, 7.3, 7.6 Hz, 1H), 1.32 (ddt, J = 14.0, 7.3, 7.6 Hz, 1H), 0.95 (t, J = 7.6 Hz 3H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, D_2O, 1,4-dioxane as an internal standard: δ 67.19 ppm) δ 175.2, 59.1, 36.2, 26.1, 13.9, 11.6; HR-ESIMS calcd for $C_6H_{14}NO_2$ ($M+H^+$) 132.1025, found 132.1024.

Enantioselective α-aminoallylation of benzaldehyde (Scheme 5)

A mixture of benzaldehyde (52.4 mg, 0.49 mmol) in liquid ammonia (ca. 0.5 mL) and dichloromethane (1.0 mL) was stirred at –30 °C for 30 min (see Method A). Allylboronate **7**[5] (177.2 mg, 0.6 mmol) in dichloromethane (0.5 mL) was then added to the mixture and rinsed with dichloromethane (0.5 mL). The clear solution was stirred at that temperature for 4 h and worked up in the same way as Method A to give (*R*)-1-Phenylbut-3-en-1-amine (**3a**) (53.4 mg, 74% yield, 34% ee).

(*R*)-1-Phenylbut-3-en-1-amine (3a):[17] $[\alpha]^{27}_D$ +15.9 (c 1.30, $CHCl_3$, 34% ee (*R*)); HPLC (CHIRALCEL OD-H, 0.46 cmø × 25 cmL, hexane/2-propanol/diethylamine = 96.7/3.3/0.05, flow rate 0.7 mL/min, UV detection at 254 nm) t_R = 11.0 min (*R*), t_R = 16.0 min (*S*).

Detection of an *N*-unsubstituted imine by ^{1}H NMR analysis

The following preliminary ^{1}H NMR experiments support involvement of *N*-unsubstituted imines in the present reaction system.[18] First, a ^{1}H NMR spectrum of benzaldehyde (0.2 mmol) in ammonia saturated THF-d_8 (0.6 mL) at –78 °C showed two broad doublets at 10.96 and 8.70 ppm (J = 16.0 Hz) and a singlet at 10.00 ppm. These doublets could correspond to the *N*-unsubstituted benzaldimine with a *cis* geometry of the

imino hydrogens and the singlet to benzaldehyde. The ratio of imine/aldehyde was 15/85. Next, trimethyl borate (0.22 mmol) was added to this solution at –78 °C, and the spectrum at that temperature showed a broad doublet at 10.87 ppm (J = 15.8 Hz, corresponding to the imine) and a singlet at 10.00 ppm (benzaldehyde) in a 76/24 ratio. A trace amount of a doublet was also observed at 11.12 ppm (J = 25.4 Hz). These signals were broadened at –10 °C, but became sharp again when re-cooled to –78 °C. The coupling partner of the doublet at 10.87 ppm appeared around at 8.7 ppm (confirmed by a decoupling), though the exact value was unclear due to overlapping of unknown signals. Assignment of the imine was further confirmed by similarity of a ^{1}H NMR spectrum of the imine prepared by the Brown's method.[19] Thus, a spectrum of a mixture of *N*-(trimethylsilyl)benzaldimine (0.15 mmol), trimethyl borate (1.1 equiv), and methanol (1.1 equiv) in THF-d_8 (0.6 mL) at –78 °C showed two doublets at 10.74 and 8.71 ppm (J = 16.0 Hz). The above experiments suggest that *N*-unsubstituted imines are involved under the conditions of α-aminoallylation and that conversion of aldehydes to imines appears to be assisted by boron agents. Further investigation concerning the reaction mechanism is now in progress.

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(18) ^{1}H NMR experiments were performed in THF-d_8 because assignment of the *N*-unsubstituted imine was difficult when the experiments were carried out in ethanol-d_6 probably due to the proton-deuterium exchange. It was confirmed that α-aminoallylation of benzaldehyde (**1a**) with allylboronate **2** in THF (Table 1, Method C) afforded a mixture of amine **3a** and alcohol **4a** (**3a**/**4a** = 55/45) in quantitative yield (determined by ^{1}H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard).

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