Concise Synthesis of α -Trisubstituted Amines from Ketones Using *N*-Methoxyamines

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Supporting Information

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A. Experimental Procedures

General Details. Reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. CH_2Cl_2 and MeCN were dried over activated 3 Å molecular sieves. Commercial reagents were used without further purification. Thin-layer chromatography was performed on Merck 60 F₂₅₄ precoated silica gel plates, which were visualized by exposure to UV (254 nm) or stained by submersion in *p*-anisaldehyde solution or ethanolic phosphomolybdic acid solution followed by heating on a hot plate. Flash column chromatography was performed on silica gel (Silica Gel 60 N; 63–210 or 40–50 mesh, KANTO CHEMICAL CO., INC.). ^1H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz with a JEOL ECA-500 spectrometer. Chemical shifts are reported in ppm with reference to solvent signals [^1H NMR: CDCl_3 (7.26); ^{13}C NMR: CDCl_3 (77.16)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded using a BRUKER ALPHA FT-IR spectrometer. Mass spectra were measured with a Waters, LCT Premier XE (ESI-TOF). Melting points were measured with a Mitamura-Riken microhot stage. Optical rotations were measured with a JASCO P-2100 polarimeter.

[General procedure A]

Synthesis of *N*-(1-allylcyclohexyl)-*N*-benzyl-*O*-methylhydroxylamine (**13d**)

Scandium triflate (26.1 mg, 53.1 μmol) was added to a solution of cyclohexanone (18 μL , 180 μmol), *N*-benzyl-*N*-methoxyamine **12d**¹ (24.3 mg, 177 μmol), allyltributylstannane (160 μL , 530 μmol) and CH_2Cl_2

(80 μ L) at room temperature. The solution was maintained for 1 day at room temperature, and quenched with saturated aqueous NaHCO_3 (5 mL). The mixture was extracted with EtOAc/hexane (1:3, 2x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by 15wt% potassium fluoride/silica gel column chromatography (EtOAc/hexane 1:100 to 1:10) to give 39.2 mg of **13d** (85%), along with 1.8 mg of **14** (7%): a colorless oil; IR (film) 2935, 2858, 1444, 1038, 910 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, J = 7.5 Hz, 2H), 7.35–7.30 (m, 2H), 7.28–7.24 (m, 1H), 6.05–5.96 (m, 1H), 5.09–5.04 (m, 2H), 3.84 (s, 2H), 3.06 (s, 3H), 2.41 (d, J = 7.2 Hz, 2H), 1.82–1.69 (m, 4H), 1.60–1.52 (m, 2H), 1.49–1.40 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.2 (C), 135.9 (CH), 130.0 (CH), 128.1 (CH), 126.9 (CH), 116.6 (CH_2), 63.9 (C), 63.5 (CH_3), 54.9 (CH_2), 37.4 (CH_2), 32.2 (CH_2), 26.4 (CH_2), 22.2 (CH_2); HRMS (ESI), calcd for $\text{C}_{17}\text{H}_{26}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 260.2014, found 260.2018.

Synthesis of *N*-(1-allyl-4-(*tert*-butyl)cyclohexyl)-*N*-benzyl-*O*-methylhydroxylamine (**15**)

According to general procedure A (reaction time: 2 h), 4-*tert*-butylcyclohexanone (24.7 mg, 160 μ mol) was converted to 40.4 mg of **15** (80%, dr = 13:1): a colorless oil; IR (film) 2950, 2866, 1039, 727, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, J = 7.5 Hz, 2H), 7.35–7.30 (m, 2H), 7.28–7.24 (m, 1H), 5.92–5.83 (m, 1H), 5.07–5.02 (m, 2H), 3.84 (s, 2H), 3.11 (s, 3H), 2.37 (d, J = 6.3 Hz, 2H), 1.89–1.82 (m, 2H), 1.72–1.62 (m, 2H), 1.54–1.48 (m, 2H), 1.40 (ddd, J = 13.5, 13.5, 2.9 Hz, 2H), 1.04 (tt, J = 12.3, 3.7 Hz, 1H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.2 (C), 136.3 (CH), 129.9 (CH), 128.1 (CH), 126.9 (CH), 117.1 (CH_2), 63.3 (CH_3), 63.0 (C), 54.8 (CH_2), 48.2 (CH), 37.8 (CH_2), 33.8 (CH_2), 32.7 (C), 27.8 (CH_3), 22.2 (CH_2); HRMS (ESI), calcd for $\text{C}_{21}\text{H}_{34}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 316.2640, found 316.2644.

NOESY experiment for **15**

Synthesis of ethyl 4-allyl-4-(benzyl(methoxy)amino)cyclohexanecarboxylate (**16**)

According to general procedure A (reaction time: 4 h), ethyl cyclohexanone-4-carboxylate (23.0 mg, 168 μmol) was converted to 36.4 mg of **16** (65%, dr = 3.2:1). For analytical samples, the diastereomeric mixture was purified by HPLC (PEGASIL Silica 120-5, 250x20 mm, EtOAc/hexane 1:29, **major product**: T_R = 15.0 min, minor product: T_R = 18.0 min) to afford pure products: **major product**: a colorless oil; IR (film) 2937, 1732, 1248, 1040 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44–7.41 (m, 2H), 7.35–7.30 (m, 2H), 7.28–7.24 (m, 1H), 5.93–5.83 (m, 1H), 5.08–5.04 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.83 (brs, 2H), 3.08 (s, 3H), 2.39 (d, J = 6.0 Hz, 2H), 2.30 (tt, J = 11.5, 3.8 Hz, 1H), 2.13–2.02 (m, 2H), 1.93–1.86 (m, 2H), 1.79–1.74 (m, 2H), 1.46 (ddd, J = 9.1, 9.1, 3.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.1 (C), 139.6 (C), 135.7 (CH), 130.1 (CH), 128.2 (CH), 127.0 (CH), 117.5 (CH_2), 63.4 (CH_3), 62.7 (C), 60.3 (CH_2), 54.9 (CH_2), 43.2 (CH), 37.5 (CH_2), 32.1 (CH_2), 24.1 (CH_2), 14.4 (CH_3); HRMS (ESI), calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_3^+ (\text{M}+\text{H})^+$ 332.2226, found 332.2223. **minor product**: a colorless oil; IR (film) 2935, 1731, 1242, 1188, 1142, 1040 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41–7.38 (m, 2H), 7.33–7.29 (m, 2H), 7.27–7.23 (m, 1H), 6.11–6.01 (m, 1H), 5.13–5.06 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.85 (s, 2H), 3.02 (s, 3H), 2.44 (d, J = 7.2 Hz, 2H), 2.33 (tt, J = 10.9, 4.0 Hz, 1H), 1.98–1.92 (m, 2H), 1.80–1.59 (m, 6H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.0 (C), 139.8 (C), 135.0 (CH), 130.0 (CH), 128.1 (CH), 127.0 (CH), 116.8 (CH_2), 63.8 (CH_3), 63.6 (C), 60.4 (CH_2), 55.1 (CH_2), 42.5 (CH), 36.6 (CH_2), 29.8 (CH_2), 25.0 (CH_2), 14.4 (CH_3); HRMS (ESI), calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_3^+ (\text{M}+\text{H})^+$ 332.2226, found 332.2230.

NOESY experiment for **16** (major product)

major product (500 MHz, CDCl_3)

NOE experiment for **16** (minor product)

minor product (500 MHz, CDCl_3)

17

Synthesis of *N*-(1-allylcyclohexyl)-*O*-methyl-*N*-(1-phenylethyl)hydroxylamine (**17**)

According to general procedure A (reaction time: 4 days), cyclohexanone (9.8 μ L, 95 μ mol) and *N*-methoxy-*N*-(1-phenylethyl)amine² (14.4 mg, 95.2 μ mol) were converted to 8.8 mg of **17** (34%): a colorless oil; IR (film) 2933, 2855, 1451, 1246, 1038, 700 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃, 60 °C) δ 7.46–7.43 (m, 2H), 7.30–7.25 (m, 2H), 7.21–7.17 (m, 1H), 5.95–5.84 (m, 1H), 5.00 (d, J = 10.0 Hz, 1H), 4.93 (d, J = 16.6 Hz, 1H), 4.27 (q, J = 6.3 Hz, 1H), 3.57 (s, 3H), 2.32–2.24 (m, 2H), 1.72–1.62 (m, 2H), 1.58–1.46 (m, 6H), 1.44–1.34 (m, 3H), 1.32–1.22 (m, 1H), 0.92–0.86 (m, 1H); ¹³C NMR (125 MHz, CDCl₃, 60 °C) δ 147.4 (C), 136.5 (CH), 128.3 (CH), 128.1 (CH), 126.5 (CH), 116.0 (CH₂), 65.5 (C), 64.7 (CH₃), 59.4 (CH), 38.4 (CH₂), 33.4 (CH₂), 32.9 (CH₂), 26.3 (CH₂), 22.5 (CH₂), 22.4 (CH₂), 20.7 (CH₃); HRMS (ESI), calcd for C₁₈H₂₈NO⁺(M+H)⁺ 274.2171, found 274.2171.

Synthesis of *N*-(5-allylnonan-5-yl)-*N*-benzyl-*O*-methylhydroxylamine (**18**)

According to general procedure A (reaction time: 2 days), 5-nonanone (29.9 μ L, 170 μ mol) was converted to 11.0 mg of **17** (21%): a colorless oil; IR (film) 2956, 2935, 2872, 1456, 1042, 731, 697 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, J = 7.5 Hz, 2H), 7.34–7.29 (m, 2H), 7.27–7.23 (m, 1H), 6.01 (ddt, J = 17.2, 10.3, 7.2 Hz, 1H), 5.10–5.03 (m, 2H), 3.86 (s, 2H), 3.00 (s, 3H), 2.38 (d, J = 7.2 Hz, 2H), 1.51–1.48 (m, 4H), 1.47–1.39 (m, 4H), 1.30 (tq, J = 7.5, 7.5 Hz, 4H), 0.94 (t, J = 7.5 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 140.3 (C), 136.2 (CH), 130.0 (CH), 128.0 (CH), 126.9 (CH), 116.3 (CH₂), 66.2 (C), 63.7 (CH₃), 55.9 (CH₂), 39.2 (CH₂), 34.7 (CH₂), 26.2 (CH₂), 23.8 (CH₂), 14.4 (CH₃); HRMS (ESI), calcd for C₂₀H₃₄NO⁺(M+H)⁺ 304.2640, found 304.2644.

Synthesis of *N*-benzyl-*O*-methyl-*N*-(4-methylundec-1-en-4-yl)hydroxylamine (**19**)

According to general procedure A (reaction time: 2 days), 2-nonanone (27 μ L, 150 μ mol) was converted to 35.2 mg of **17** (75%): a colorless oil; IR (film) 2955, 2928, 2854, 1457, 1039, 911, 732, 697 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, J = 7.5 Hz, 2H), 7.34–7.29 (m, 2H), 7.28–7.23 (m, 1H), 5.95 (ddt, J = 16.6, 10.3, 7.2 Hz, 1H), 5.07 (d, J = 16.6 Hz, 1H), 5.07 (d, J = 10.3 Hz, 1H), 3.82 (d, J = 13.2 Hz, 1H), 3.78 (d, J = 13.2 Hz, 1H), 3.04 (s, 3H), 2.38 (dd, J = 14.0, 7.2 Hz, 1H), 2.32 (dd, J = 14.0, 7.2 Hz, 1H), 1.53–1.39 (m, 4H), 1.35–1.23 (m, 8H), 1.10 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 140.1 (C), 135.8 (CH), 130.0 (CH), 128.1 (CH), 126.9 (CH), 116.9 (CH₂), 64.3 (C), 63.5 (CH₃), 55.6 (CH₂), 40.8 (CH₂), 36.8

(CH₂), 32.1 (CH₂), 30.6 (CH₂), 29.5 (CH₂), 23.7 (CH₂), 22.8 (CH₂), 20.5 (CH₃), 14.3 (CH₃); HRMS (ESI), calcd for C₂₀H₃₄NO⁺ (M+H)⁺ 304.2640, found 304.2642.

[General procedure B]

Synthesis of 1-(benzyl(methoxy)amino)-4-(tert-butyl)cyclohexanecarbonitrile (**21**)

Trimethylsilyl trifluoromethanesulfonate (37 μ L, 204 μ mol) was added to a solution of 4-*tert*-butylcyclohexanone (31.5 mg, 204 μ mol), *N*-benzyl-*N*-methoxyamine **12d** (28.0 mg, 204 μ mol), trimethylsilyl cyanide (77 μ L, 616 μ mol) and CH₂Cl₂ (100 μ L) at room temperature. The solution was maintained for 1.5 h at room temperature, and quenched with saturated aqueous NaHCO₃ (5 mL). The mixture was extracted with EtOAc/hexane (1:3, 2x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (toluene/hexane 1:10 to toluene) to give 44.6 mg of **13d** (73%, dr = 4.6:1). For analytical samples, the diastereomeric mixture was purified by HPLC (PEGASIL Silica 120-5, 250x20 mm, EtOAc/hexane 1:39, **major product**: T_R = 10.5 min, minor product: T_R = 13.0 min) to afford pure products: **major product**: a colorless oil; IR (film) 2959, 2903, 2868, 1455, 1367 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.42–7.39 (m, 2H), 7.36–7.32 (m, 2H), 7.31–7.27 (m, 1H), 3.98 (s, 2H), 3.13 (s, 3H), 2.28–2.38 (m, 2H), 1.91–1.84 (m, 2H), 1.58 (ddd, *J* = 13.2, 13.2, 3.5 Hz, 2H), 1.41 (dddd, *J* = 13.8, 13.2, 12.3, 3.5 Hz, 2H), 1.04 (tt, *J* = 12.3, 3.5 Hz, 1H), 0.91 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 137.3 (C), 130.1 (CH), 128.3 (CH), 127.6 (CH), 119.6 (C), 66.8 (C), 63.9 (CH₃), 58.3 (CH₂), 47.2 (CH), 34.7 (CH₂), 32.4 (C), 27.6 (CH₃), 23.9 (CH₂); HRMS (ESI), calcd for C₁₉H₂₉N₂O⁺ (M+H)⁺ 301.2280, found 301.2282. **minor product**: a colorless oil; IR (film) 2956, 2868, 1455, 1367, 1036, 729 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43–7.39 (m, 2H), 7.37–7.33 (m, 2H), 7.32–7.28 (m, 1H), 3.95 (brs, 2H), 3.17 (s, 3H), 2.44–2.36 (m, 2H), 1.81 (ddd, *J* = 13.8, 13.8, 3.2 Hz, 2H), 1.64–1.50 (m, 4H), 1.18 (tt, *J* = 11.5, 4.1 Hz, 1H), 0.89 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 137.3 (C), 130.1 (CH), 128.4 (CH), 127.6 (CH), 120.9 (C), 63.5 (CH₃), 63.3 (C), 58.1 (CH₂), 47.2 (CH), 34.6 (CH₂), 32.6 (C), 27.5 (CH₃), 21.3 (CH₂); HRMS (ESI), calcd for C₁₉H₂₉N₂O⁺ (M+H)⁺ 301.2280, found 301.2285.

NOESY experiments for **21**

major product (500 MHz, CDCl₃)

minor product (500 MHz, CDCl₃)

Synthesis of ethyl 4-(benzyl(methoxy)amino)-4-cyanocyclohexanecarboxylate (**22**)

According to general procedure B (reaction time: 2 h), ethyl cyclohexanone-4-carboxylate (29.5 μ L, 160 μ mol) was converted to 26.2 mg of **22** (52%, dr = 2.2:1). For analytical samples, the diastereomeric mixture was purified by HPLC (PEGASIL Silica 120-5, 250x20 mm, EtOAc/hexane 1:9, **major product**: T_R = 20.0 min, **minor product**: T_R = 18.0 min) to afford pure products: **major product**: a colorless oil; IR (film) 2938, 2903, 1730, 1455, 1189, 1037 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41–7.38 (m, 2H), 7.36–7.32 (m, 2H), 7.32–7.27 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.97 (s, 2H), 3.12 (s, 3H), 2.39–2.33 (m, 2H), 2.29 (tt, J = 12.1, 3.8 Hz, 1H), 2.16–2.10 (m, 2H), 1.83–1.79 (m, 2H), 1.63 (ddd, J = 13.2, 13.2, 3.5 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.3 (C), 137.0 (C), 130.1 (CH), 128.4 (CH), 127.7 (CH), 119.0 (C), 65.9 (C), 64.0 (CH_3), 60.8 (CH_2), 58.3 (CH_2), 42.0 (CH), 33.4 (CH_2), 25.2 (CH_2), 14.3 (CH_3); HRMS (ESI), calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{NaO}_3^+$ ($\text{M}+\text{Na}$) $^+$ 339.1685, found 339.1683. **minor product**: a colorless oil; IR (film) 2962, 2937, 1728, 1455, 1194, 1041 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.45–7.39 (m, 2H), 7.38–7.28 (m, 3H), 4.18 (q, J = 7.2 Hz, 2H), 3.94 (s, 2H), 3.11 (s, 3H), 2.61 (tt, J = 10.6, 5.7 Hz, 1H), 2.22–2.13 (m, 2H), 2.10–1.97 (m, 4H), 1.89 (dddd, J = 13.8, 9.1, 5.7, 4.6 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.4 (C), 136.9 (C), 130.3 (CH), 128.4 (CH), 127.7 (CH), 119.6 (C), 65.2 (C), 63.8 (CH_3), 60.8 (CH_2), 58.1 (CH_2), 39.3 (CH), 31.7 (CH_2), 23.6 (CH_2), 14.4 (CH_3); HRMS (ESI), calcd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_3^+$ ($\text{M}+\text{H}$) $^+$ 317.1865, found 317.1864.

NOE experiment for **22** (major product)

major product (500 MHz, CDCl_3)

NOESY experiments for **22** (minor product)

minor product (500 MHz, CDCl_3)

Synthesis of 1-(methoxy(1-phenylethyl)amino)cyclohexanecarbonitrile (**23**)

According to general procedure B (reaction time: 3 h), cyclohexanone (18 μ L, 170 μ mol) and *N*-methoxy-*N*-(1-phenylethyl)amine (26.0 mg, 172 μ mol) were converted to 14.1 mg of **17** (32%): a colorless oil; IR (film) 2938, 2862, 1452, 1028, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 60 $^\circ\text{C}$) δ 7.41 (d, J = 6.9 Hz, 2H),

7.33–7.29 (m, 2H), 7.27–7.23 (m, 1H), 4.29 (q, $J = 6.9$ Hz, 2H), 3.47 (s, 3H), 2.34–2.27 (m, 1H), 1.93–1.87 (m, 1H), 1.81–1.75 (m, 1H), 1.72–1.51 (m, 4H), 1.61 (d, $J = 6.9$ Hz, 3H), 1.41–1.33 (m, 1H), 1.23–1.44 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3 , 60 °C) δ 144.1 (C), 128.4 (CH), 128.2 (CH), 127.4 (CH), 120.7 (C), 65.9 (C), 65.1 (CH_3), 62.3 (CH), 35.6 (CH_2), 34.9 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 18.3 (CH_3); HRMS (ESI), calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{NaO}^+$ ($\text{M}+\text{Na}$) $^+$ 281.1630, found 281.1624.

24

Synthesis of 2-(benzyl(methoxy)amino)-2-butylhexanenitrile (**24**)

According to general procedure B (reaction time: 1 h), 5-nonanone (42 μL , 240 μmol) was converted to 45.3 mg of **24** (65%): a colorless oil; IR (film) 2959, 2934, 2873, 1457, 1033, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42–7.38 (m, 2H), 7.36–7.32 (m, 2H), 7.32–7.27 (m, 1H), 3.91 (s, 2H), 3.11 (s, 3H), 1.94–1.86 (m, 2H), 1.84–1.75 (m, 2H), 1.54–1.45 (m, 4H), 1.42–1.31 (m, 4H), 0.96 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.4 (C), 130.1 (CH), 128.3 (CH), 127.6 (CH), 120.3 (C), 68.2 (C), 63.6 (CH_3), 57.8 (CH_2), 33.4 (CH_2), 25.8 (CH_2), 22.9 (CH_2), 14.0 (CH_3); HRMS (ESI), calcd for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}^+$ ($\text{M}+\text{H}$) $^+$ 289.2280, found 289.2282.

25

Synthesis of 2-(benzyl(methoxy)amino)-2-methylnonanenitrile (**25**)

According to general procedure B (reaction time: 2 h), 2-nonanone (23 μL , 130 μmol) was converted to 33.7 mg of **25** (88%): a colorless oil; IR (film) 2956, 2930, 2857, 1456, 1034, 729, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42–7.39 (m, 2H), 7.34–7.32 (m, 2H), 7.32–7.28 (m, 1H), 3.94 (d, $J = 12.6$ Hz, 1H), 3.90 (d, $J = 12.6$ Hz, 1H), 3.13 (s, 3H), 1.98–1.87 (m, 1H), 1.79–1.71 (m, 1H), 1.54 (s, 3H), 1.40–1.23 (m, 10H), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.3 (C), 130.1 (CH), 128.3 (CH), 127.6 (CH), 120.5 (C), 64.5 (C), 63.7 (CH_3), 58.2 (CH_2), 37.7 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 24.1 (CH_2), 22.7 (CH_2), 22.1 (CH_3), 14.2 (CH_3); HRMS (ESI), calcd for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}^+$ ($\text{M}+\text{H}$) $^+$ 289.2280, found 289.2284.

26

Synthesis of 2-(benzyl(methoxy)amino)-2-(4-nitrophenyl)propanenitrile (**26**)

According to general procedure B (reaction time: 3 h), 4-nitroacetophenone (25.3 mg, 153 μmol) was

converted to 31.2 mg of **26** (62%): a yellow oil; IR (film) 2940, 2901, 1607, 1524, 1346, 852, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.32–8.29 (m, 2H), 7.93–7.90 (m, 2H), 7.34–7.27 (m, 5H), 3.88 (d, $J = 10.3$ Hz, 1H), 3.63 (d, $J = 10.3$ Hz, 1H), 3.15 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.3 (C), 145.8 (C), 136.4 (C), 129.9 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 124.4 (CH), 117.8 (C), 69.2 (C), 64.3 (CH_3), 59.4 (CH_2), 28.1 (CH_3); HRMS (ESI), calcd for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_3^+$ ($\text{M}+\text{H}$) $^+$ 312.1348, found 312.1340.

28

[General procedure C]

Synthesis of 1-methoxy-5-vinyl-1-azaspiro[5.5]undecane (**28**)

Scandium triflate (49.6 mg, 101 μmol) was added to a solution of cyclohexanone (10 μL , 100 μmol), allylsilane **27**³ (20.3 mg, 101 μmol) and MeCN (1.0 mL) at room temperature. The solution was maintained for 1 day at room temperature, and quenched with saturated aqueous NaHCO_3 (5 mL). The mixture was extracted with EtOAc/hexane (1:50, 3x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (hexane to EtOAc/hexane 1:50) to give 17.7 mg of **28** (84%): a colorless oil; IR (film) 2936, 2858, 1445, 1047, 911 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.05–5.87 (m, 1H), 5.02–4.95 (m, 2H), 3.48 (s, 3H), 3.08–2.92 (m, 2H), 2.58–2.46 (m, 1H), 1.83–1.26 (m, 14H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.9 (CH), 115.0 (CH_2), 61.8 (C), 60.2 (CH_3), 46.1 (CH_2), 42.9 (CH), 29.9 (CH_2), 26.7 (CH_2), 25.9 (CH_2), 22.1 (CH_2), 21.0 (CH_2), 20.2 (CH_2); HRMS (ESI), calcd for $\text{C}_{13}\text{H}_{24}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 210.1858, found 210.1863.

29

Synthesis of 9-(*tert*-butyl)-1-methoxy-5-vinyl-1-azaspiro[5.5]undecane (**29**)

According to general procedure C at 80 $^{\circ}\text{C}$ (reaction time: 1 day), 4-*tert*-butylcyclohexanone (18.0 mg, 117 μmol) was converted to 22.6 mg of **29** (73%): colorless crystals, mp 42.5–43.5 $^{\circ}\text{C}$; IR (film) 2939, 2864, 1444, 1365, 1045, 997, 911 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.76–5.78 (m, 1H), 5.01–4.94 (m, 2H), 3.49 (s, 3H), 3.12 (ddd, $J = 14.6, 2.6, 1.8$ Hz, 1H), 2.96–2.88 (m, 1H), 2.49–2.41 (m, 1H), 1.99–1.89 (m, 3H), 1.64–1.52 (m, 2H), 1.49–1.42 (m, 6H), 1.23–1.14 (m, 1H), 0.94 (tt, $J = 11.8, 3.8$ Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.3 (CH), 115.4 (CH_2), 61.0 (C), 59.8 (CH_3), 48.9 (CH), 45.0 (CH_2), 43.4 (CH), 33.2 (CH_2), 32.5 (C), 28.6 (CH_2), 27.8 (CH_3), 25.7 (CH_2), 22.5 (CH_2), 21.5 (CH_2), 19.4 (CH_2); HRMS (ESI), calcd for $\text{C}_{17}\text{H}_{32}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 266.2484, found 266.2479.

X-ray Crystallographic Analysis of **29**

30

Synthesis of 2-heptyl-1-methoxy-2-methyl-3-vinylpiperidine (**30**)

According to general procedure C at 50 °C (reaction time: 3 days), 2-nonanone (18 μ L, 110 μ mol) was converted to 23.3 mg of **30** (87%, dr = 1.6:1): a colorless oil; IR (film) 2933, 2854, 1458, 1048, 912, 669 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.92 (ddd, J = 16.9, 9.8, 9.8 Hz, 2/3H), 5.75 (ddd, J = 16.6, 8.3, 8.3 Hz, 1/3H), 5.04–4.95 (m, 2H), 3.47 (s, 1H), 3.45 (s, 2H), 3.09 (ddd, J = 11.2, 3.8, 3.8 Hz, 1/3H), 3.00 (ddd, J = 12.6, 4.9, 4.9 Hz, 2/3H), 2.91 (ddd, J = 11.2, 3.8, 3.8 Hz, 2/3H), 2.80–2.70 (m, 1/3H), 2.36–2.28 (m, 1H), 1.77–1.20 (m, 16H), 1.15 (s, 2H), 0.93 (s, 1H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.6 (CH), 139.0 (CH), 115.4 (CH_2), 114.9 (CH_2), 63.5 (C), 62.6 (C), 60.7 (CH_3), 59.7 (CH_3), 48.5 (CH_2), 47.8 (CH_2), 47.6 (CH), 45.8 (CH_2), 45.5 (CH), 37.5 (CH_2), 34.5 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 30.9 (CH_2), 30.5 (CH_2), 29.58 (CH_2), 29.52 (CH_2), 25.9 (CH_2), 24.7 (CH_2), 22.85 (CH_2), 22.83 (CH_2), 22.4 (CH_2), 20.5 (CH_3), 19.7 (CH_3), 14.3 (CH_3), 12.0 (CH_3); HRMS (ESI), calcd for $\text{C}_{16}\text{H}_{32}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 254.2484, found 254.2488.

31

Synthesis of 1-methoxy-2-methyl-2-(4-nitrophenyl)-3-vinylpiperidine (**31**)

According to general procedure C using TFA (18 μ L, 240 μ mol) at 60 $^{\circ}$ C (reaction time: 1 day), 4-nitroacetophenone (13.1 mg, 79 μ mol) was converted to 12.5 mg of **31** (57%, dr = 20:1): a colorless oil; IR (film) 2938, 2859, 1597, 1519, 1348, 1240, 1042, 853, 751 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (d, J = 9.2 Hz, 2H), 7.82–7.74 (m, 2H), 5.28 (ddd, J = 17.2, 10.4, 8.6 Hz, 1H), 4.80 (d, J = 10.4 Hz, 1H), 4.60 (d, J = 17.2 Hz, 1H), 3.28 (ddd, J = 10.9, 4.3, 3.5 Hz, 1H), 3.12 (s, 3H), 2.83 (ddd, J = 13.2, 10.9, 2.3 Hz, 1H), 2.47–2.38 (m, 1H), 1.93–1.86 (m, 1H), 1.78 (dddd, J = 13.2, 13.2, 13.2, 4.3, 4.3 Hz, 1H), 1.61 (dddd, J = 13.2, 4.3, 2.9, 2.9 Hz, 1H), 1.50 (ddd, J = 13.2, 13.2, 4.3 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 154.9 (C), 146.7 (C), 136.9 (CH), 128.4 (CH), 122.8 (CH), 116.6 (CH_2), 67.4 (C), 59.6 (CH_3), 51.6 (CH), 47.7 (CH_2), 25.1 (CH_2), 24.4 (CH_2), 8.2 (CH_3); HRMS (ESI), calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_3^+$ ($\text{M}+\text{H}$) $^+$ 277.1552, found 277.1553.

NOESY experiment for **31**

32

Synthesis of methyl 2-heptyl-1-methoxy-3-vinylpiperidine-2-carboxylate (**32**)

According to general procedure C (reaction time: 2 weeks) using TFA (6.4 μ L, 86 μ mol), methyl 2-oxononanoate⁴ (14.8 mg, 86.4 μ mol) was converted to 13.1 mg of **31** (53%): a colorless oil; IR (film) 2952, 2933, 2872, 2859, 1730, 1457, 1216, 1043, 669 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.70–5.56 (m, 1H), 5.04 (d, J = 18.6 Hz, 1H), 5.01 (d, J = 10.3 Hz, 1H), 3.68 (s, 3H), 3.49 (s, 3H), 3.39–3.33 (m, 1H), 3.21 (ddd, J = 10.3, 3.2, 3.2 Hz, 1H), 2.43 (ddd, J = 12.3, 8.0, 4.0 Hz, 1H), 1.94–1.82 (m, 2H), 1.79–1.68 (m, 2H), 1.63–1.25 (m, 12H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.9 (C), 138.3 (CH), 116.2 (CH_2), 72.1 (C), 60.2 (CH_3), 50.9 (CH_3), 49.0 (CH_2), 45.0 (CH), 32.5 (CH_2), 32.1 (CH_2), 30.1 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 23.3 (CH_2), 22.8 (CH_2), 14.1 (CH_3); HRMS (ESI), calcd for $\text{C}_{16}\text{H}_{30}\text{NO}_3^+$ ($\text{M}+\text{H}$) $^+$ 284.2226, found 284.2234.

To determine stereochemistry, **32** was reduced with LiAlH_4 .

To a solution of **32** (4.0 mg, 14 μmol) and THF (0.5 mL) was added LiAlH_4 (5.4 mg, 140 μmol) at room temperature. The resulting suspension was stirred for 5 h at room temperature, and quenched with saturated aqueous ammonium chloride (10 mL). The mixture was extracted with EtOAc (2x 25 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (hexane to EtOAc/hexane 1:9) to give 3.4 mg of **S1** (94%): a colorless oil; IR (film) 3548, 3467, 2932, 2856, 1464, 1041, 914 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 60 $^\circ\text{C}$) δ 5.94–5.83 (m, 1H), 5.05–5.00 (m, 2H), 4.24–4.05 (m, 1H), 3.50 (s, 3H), 3.44 (dd, $J = 11.2, 8.6$ Hz, 1H), 3.20–3.13 (m, 1H), 3.03 (ddd, $J = 10.6, 10.6, 3.7$ Hz, 1H), 2.72 (brs, 1H), 2.35 (ddd, $J = 9.2, 9.2, 4.3$ Hz, 1H), 2.04–1.94 (m, 1H), 1.79–1.72 (m, 1H), 1.68–1.31 (m, 12H), 0.91 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.3 (CH), 115.9 (CH_2), 65.3 (C), 62.5 (CH_2), 60.4 (CH_3), 48.7 (CH_2), 44.2 (CH), 32.1 (CH_2), 31.1 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 25.1 (CH_2), 22.9 (CH_2), 22.2 (CH_2), 14.3 (CH_3); HRMS (ESI), calcd for $\text{C}_{15}\text{H}_{30}\text{NO}_2^+$ ($\text{M}+\text{H}$) $^+$ 256.2277, found 256.2277.

NOESY experiments for **S1**

Synthesis of 1-allyl-N-benzylcyclohexanamine (**33**)⁵

Activated Zn was prepared as follows. A mixture of zinc powder (25 g) and 2% aqueous HCl (100 mL) was sonicated for 10 min at room temperature. The mixture was filtrated through glass filter, washed with water (2x 100 mL), ethanol (2x 50 mL) and Et_2O (2x 50 mL). The resulting zinc powder was dried under reduced pressure for 2 h.

Activated Zn powder (48.1 mg, 740 μmol) was added to a solution of **13d** (19.2 mg, 74.0 μmol) and AcOH (1.0 mL) at room temperature. This mixture was stirred at reflux for 1 d. After removing most of the

solvent under reduced pressure, 1 M aqueous NaOH (5 mL) was added to the residue. The mixture was extracted with EtOAc (3x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (hexane to EtOAc/hexane 1:9) to give 9.8 mg of **33** (97%), which was identical to the reported compound⁵: a colorless oil; IR (film) 2928, 2853, 1455, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.35 (m, 2H), 7.33–7.29 (m, 2H), 7.25–7.21 (m, 1H), 5.93–5.84 (m, 1H), 5.13–5.08 (m, 2H), 3.65 (s, 2H), 2.26 (brd, *J* = 7.1 Hz, 2H), 1.65–1.29 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 141.8 (C), 134.7 (CH), 128.49 (CH), 128.45 (CH), 126.8 (CH), 117.5 (CH₂), 54.1 (C), 45.5 (CH₂), 42.0 (CH₂), 35.6 (CH₂), 26.3 (CH₂), 21.9 (CH₂); HRMS (ESI), calcd for C₁₆H₂₄N⁺(M+H)⁺ 230.1909, found 230.1904.

Synthesis of (Z)-1-allyl-N-benzylidenecyclohexanamine oxide (**34**)⁵

Meta Chloroperbenzoic acid (108 mg, 434 μmol) was added to a solution of **13d** (22.5 mg, 86.7 μmol) and CH₂Cl₂ (1.0 mL) at -50 °C. The solution was maintained for 4 d at -50 °C, and quenched with 10 wt% aqueous Na₂S₂O₃ (5 mL). The mixture was extracted with EtOAc/hexane (1:50, 3x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography (hexane to EtOAc/hexane 1:9) to give 18.9 mg of **34** (90%), which was identical to the reported compound⁵: a yellow oil; IR (film) 2934, 2861, 1557, 1445, 1407, 1122, 919, 692 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.33–8.27 (m, 2H), 7.45–7.38 (m, 4H), 5.65 (ddt, *J* = 17.2, 10.0, 7.5 Hz, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 2.59 (d, *J* = 7.5 Hz, 2H), 2.25–2.17 (m, 2H), 1.88–1.82 (m, 2H), 1.64–1.57 (m, 4H), 1.53–1.43 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 132.3 (CH), 132.0 (CH), 130.9 (C), 130.3 (CH), 129.1 (CH), 128.6 (CH), 119.3 (CH₂), 75.7 (C), 42.4 (CH₂), 34.0 (CH₂), 25.5 (CH₂), 22.3 (CH₂); HRMS (ESI), calcd for C₁₆H₂₂NO⁺(M+H)⁺ 244.1701, found 244.1700.

Synthesis of 6-phenyl-7-oxa-1-azaspiro[bicyclo[2.2.1]heptane-2,1'-cyclohexane] **S2**⁵

A solution of **34** (13.3 mg, 55 μmol) and benzene was refluxed for 3 d, and then concentrated. The residue was purified by silica gel column chromatography (hexane to EtOAc/hexane 1:9) to give 11.6 mg of **S2** (87%), which was identical to the reported compound⁵: white solids, mp 85.5–86.5 °C; IR (film) 2924, 2854, 1450, 1292, 740, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.33–7.28 (m, 2H), 7.23–7.18 (m, 1H), 4.91–4.88 (m, 1H), 4.50 (dd, *J* = 6.3, 6.3 Hz, 1H), 2.06–2.03 (m, 2H), 1.82 (dd, *J* = 11.2, 5.4 Hz, 1H),

1.80–1.63 (m, 6H), 1.54–1.47 (m, 1H), 1.30–1.41 (m, 3H), 1.23 (d, $J = 11.2$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.9 (C), 128.5 (CH), 127.2 (CH), 126.7 (CH), 80.8 (CH), 69.1 (C), 61.5 (CH), 44.4 (CH_2), 42.5 (CH_2), 38.9 (CH_2), 34.2 (CH_2), 25.6 (CH_2), 24.7 (CH_2), 22.6 (CH_2); HRMS (ESI), calcd for $\text{C}_{16}\text{H}_{22}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 244.1701, found 244.1703.

Synthesis of (2S,4S)-2-phenyl-1-azaspiro[5.5]undecan-4-ol (**35**)⁵

Activated Zn powder (27.5 mg, 423 μmol) was added to a solution of **S2** (10.3 mg, 42.3 μmol) and AcOH (1.0 mL) at 80 $^\circ\text{C}$. This mixture was maintained for 3 d at 80 $^\circ\text{C}$. After removing most of the solvent under reduced pressure, 1 M aqueous NaOH (5 mL) was added to the residue. The mixture was extracted with EtOAc (3x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (hexane to EtOAc/hexane 1:1) to give 9.8 mg of **35** (94%), which was identical to the reported compound⁵: brown solids, mp 100–101 $^\circ\text{C}$; IR (film) 3308, 2926, 2851, 1452, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.40 (d, $J = 7.5$ Hz, 2H), 7.33 (dd, $J = 7.5, 7.5$ Hz, 2H), 7.28–7.24 (m, 1H), 4.01 (dddd, $J = 11.7, 11.7, 4.6, 4.6$ Hz, 1H), 3.89 (dd, $J = 11.7, 2.3$ Hz, 1H), 2.14 (dddd, $J = 11.7, 4.3, 2.1, 2.1$ Hz, 1H), 2.05 (ddd, $J = 11.7, 4.6, 2.1$ Hz, 1H), 1.74–1.53 (m, 2H), 1.53–1.33 (m, 11H), 1.16 (dd, $J = 11.7, 11.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.5 (C), 128.6 (CH), 127.4 (CH), 127.1 (CH), 66.7 (CH), 53.5 (CH), 53.2 (C), 45.4 (CH_2), 44.4 (CH_2), 41.5 (CH_2), 32.5 (CH_2), 29.8 (CH_2), 26.3 (CH_2), 22.0 (CH_2); HRMS (ESI), calcd for $\text{C}_{16}\text{H}_{24}\text{NO}^+$ ($\text{M}+\text{H}$) $^+$ 246.1858, found 246.1853.

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