Kulinkovich-type reactions of thioamides: similar to those of carboxylic amides?

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Supplementary Information – Part 2

Experimental procedures for the reactions of compounds **1aS**, **1bO**, **1bS**, **1cO**, **1cS**, **1dS**, **1eS**, **1fS**, **1gS**. Characterisation data for the new compounds **2b**, **3a**, **3c**, **4a**, **4b**, **4c**–*d*, **4d**, **4e**, **4f**, **4g**, **5g**. The transformation of **1aO** into **2a** has already been described.[1]

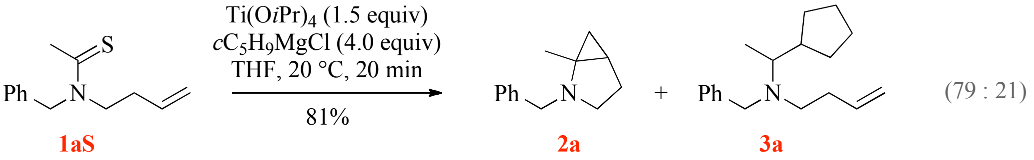
I. General remarks

Titanium(IV) *iso*-propoxide (VERTEC® TIPT) was purchased from Alfa Aesar, distilled under reduced pressure and stored under argon for several months. Other commercial reagents were used as received, without purification. The Grignard reagents were purchased from Sigma-Aldrich or Acros and titrated once a month according to a method described in the literature.[2] All reactions were carried out under nitrogen. Tetrahydrofuran, diethyl ether, dichloromethane, toluene and methanol were purified using a MB SPS-800 solvent purification system (MBRAUN). The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Flash column chromatography was performed on Merck silica gel 60 (40–63 μm). Concentration under reduced pressure was carried out using rotary evaporators at 40°C. NMR spectra were recorded with AM 400 and AVANCE 400 Bruker spectrometers (^{1}H at 400 MHz, ^{13}C at 100.6 MHz. Chemical shifts δ are given in ppm, referenced to the peak of tetramethylsilane, defined at $\delta = 0.00$ (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at $\delta = 77.0$ (^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet, br = broad. Coupling constants J are given in Hz. Infrared spectra were recorded with a Perkin-Elmer 2000 FT-IR spectrometer. Melting points were determined using a Büchi 535 apparatus and were not corrected. Low-resolution mass spectra were recorded on a Hewlett-Packard Quad GC-MS engine spectrometer *via* direct injection. High-resolution mass spectrometry was performed on a JEOL GC-mate II spectrometer.

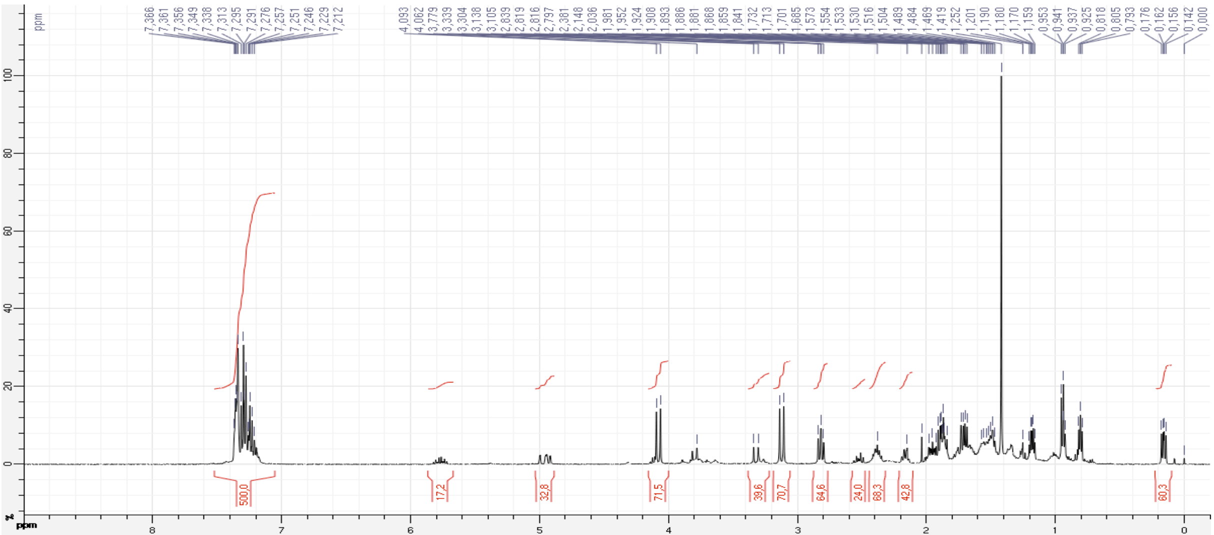
1– C. Madelaine, Y. Six, O. Buriez, *Angew. Chem.* **2007**, *119*, 8192–8195; *Angew. Chem. Int. Ed.* **2007**, *46*, 8046–8049.
2– H.-S. Lin, L. A. Paquette, *Synth. Comm.* **1994**, *24*, 2503–2506.

II. Reactions of 1aS

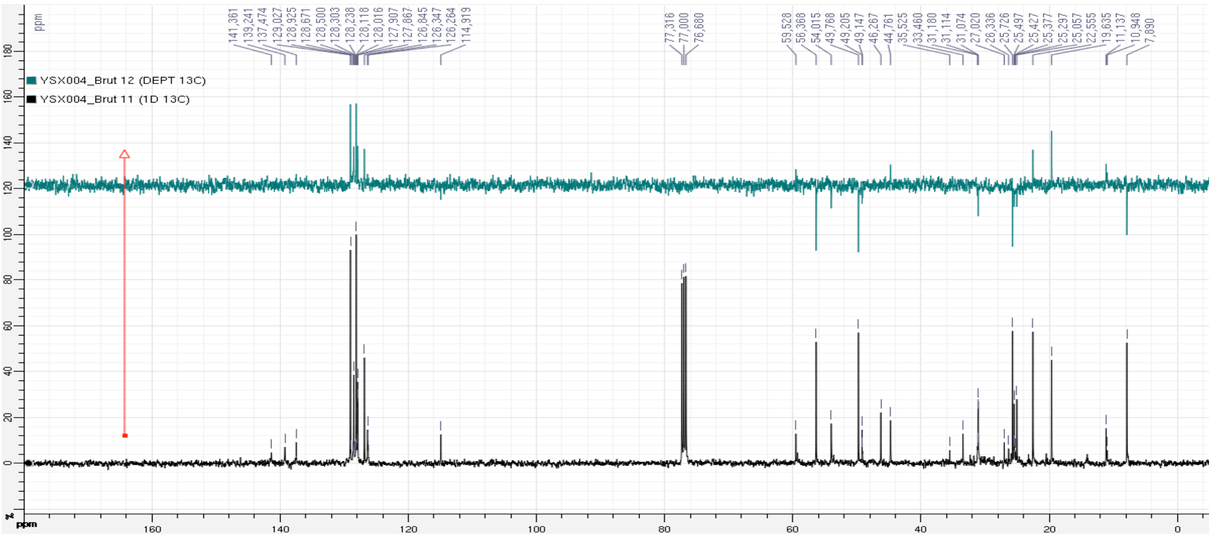
■ Using cyclopentylmagnesium chloride.



Cyclopentylmagnesium chloride (1.79 M in Et_2O, 4.00 equiv, 4.00 mmol, 2.23 mL) was added dropwise, over 5 min, to a stirred solution of *N*-benzyl-*N*-(but-3-en-1-yl)ethanethioamide **1aS** (1.00 equiv, 1.00 mmol, 219 mg) and titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 μL) in THF (20 mL). During the addition, the solution turned yellow, then orange, green-brown, and finally black. After a further 20 min of stirring, H_2O (0.5 mL) was added. The mixture was exposed to air, stirred until near complete decolouration (45 min), and filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed thoroughly with EtOAc. The resulting clear solution was concentrated to afford a pale yellow oil with a pungent unpleasant smell (222 mg). Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopy gave an estimation of the yields of **2a** (64%) and **3a** (17%). Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane, gradient from 0 to 30%) yielded unpure *N*-benzyl-*N*-(1-cyclopentylethyl)but-3-en-1-amine **3a** (61 mg) and pure 2-benzyl-1-methyl-2-azabicyclo[3.1.0]hexane **2a**[1] (96 mg, 0.51 mmol, 51%). Further purification of **3a** by flash column chromatography and microdistillation was attempted, with limited success.

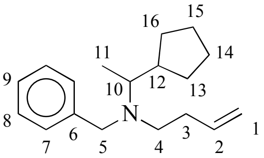


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

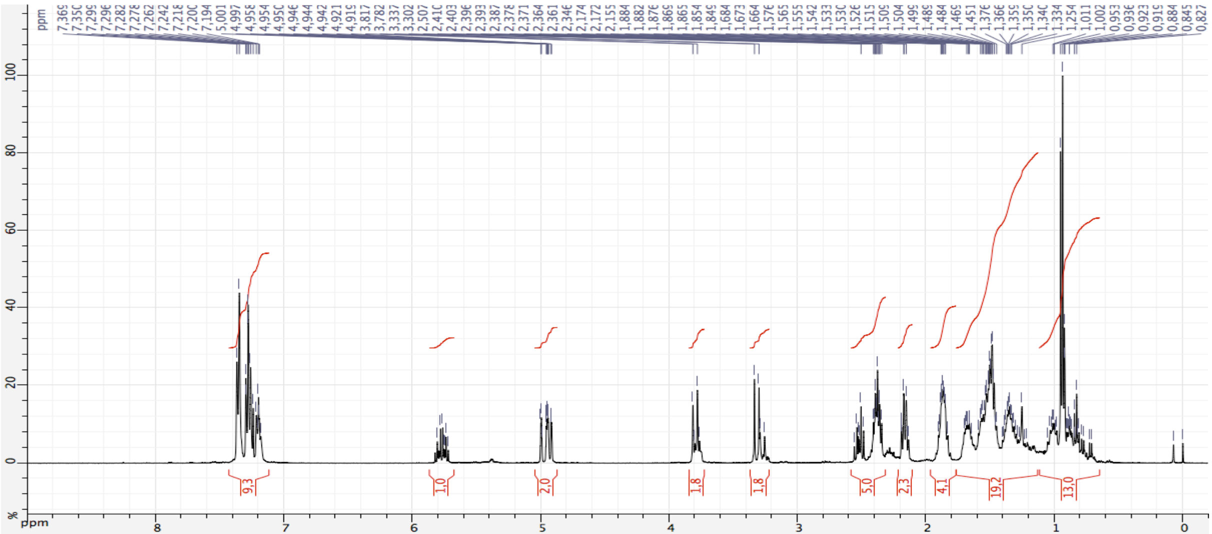


^{13}C and DEPT 135 NMR spectra of the crude product (100.6 MHz).

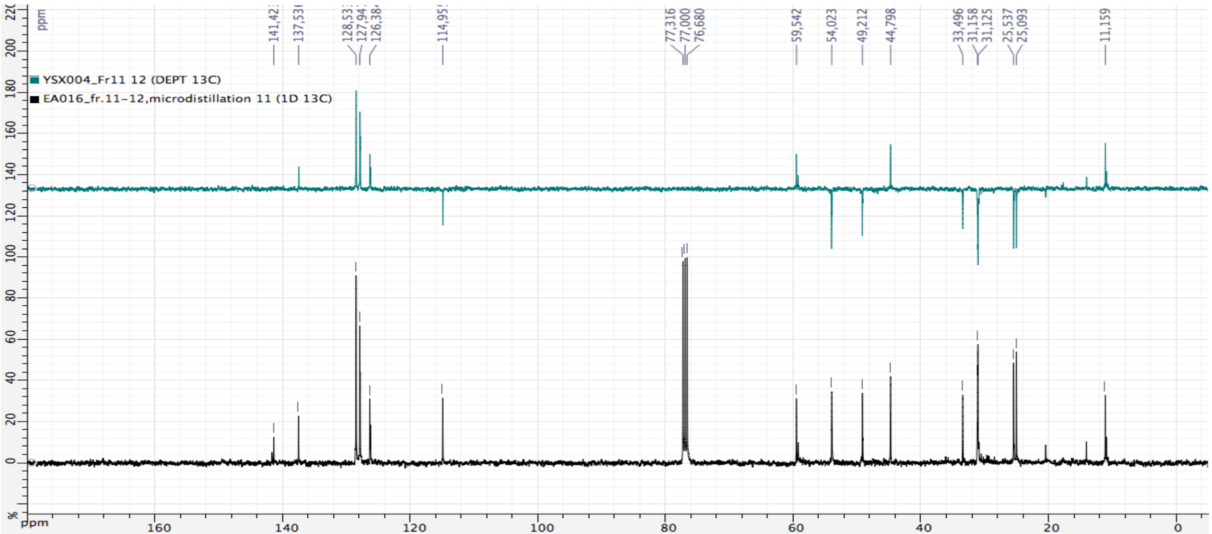
N-Benzyl-*N*-(1-cyclopentylethyl)but-3-en-1-amine **3a**



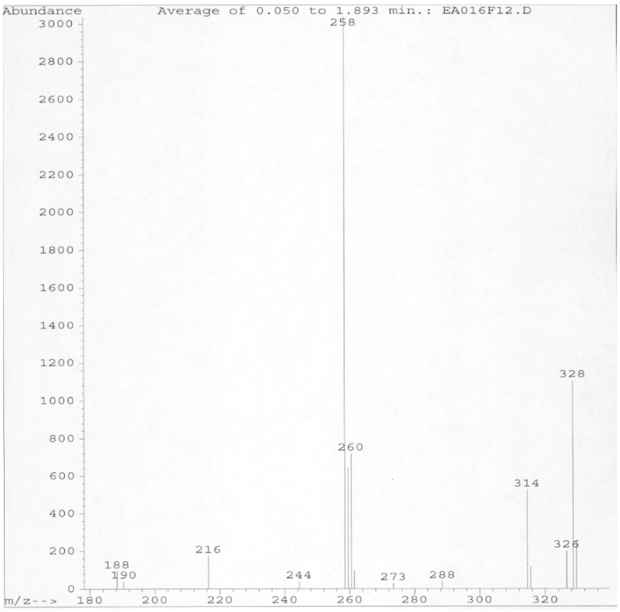
Not completely purified. Pale yellow oil. R_f 0.65 (AcOEt/Pet. ether 10%, PMA). ^{1}H NMR (CDCl$_3$, 400 MHz) 0.65–1.97 (9 H, m), 0.94 (3 H, d, J 6.5, H11), 2.16 (2 H, m, H3), 2.32–2.46 (2 H, m, H10, H4a), 2.52 (1 H, dt, J 13.0, 8.0, H4b), 3.56 (2 H, AB system, δ_A 3.32, δ_B 3.80, J_{AB} 14.0, H5), 4.93 (1 H, br d, J 10.0, H1a), 4.98 (1 H, dq, J 17.0, 1.5, H1b), 5.77 (1 H, ddt, J 17.0, 10.0, 7.0, H2), 7.20 (1 H, t, J 7.0, H9), 7.28 (2 H, dd, J 7.5, 7.0, H8), 7.36 (2 H, br d, J 7.5, H7). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 11.2 (C11), 25.1, 25.5 (C14 and C15), 31.1, 31.2 (C13 and C16), 33.5 (C3), 44.8 (C12), 49.2 (C4), 54.0 (C5), 59.5 (C10), 115.0 (C1), 126.4 (C9), 127.9, 128.5 (C7 and C8), 137.5 (C2), 141.4 (C6). MS *m/z* (positive CI, NH$_3$) <u>258</u> (MH$^+$), 259, 260, 314, 328. HRMS *m/z* (EI) 257.2146 (M$^{+\bullet}$ C$_{18}$H$_{27}$N requires 257.2143).



^{1}H NMR spectrum (CDCl$_3$, 400 MHz).

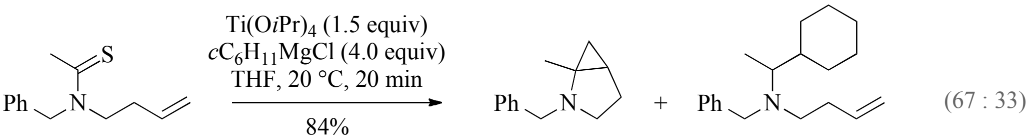


^{13}C NMR and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).



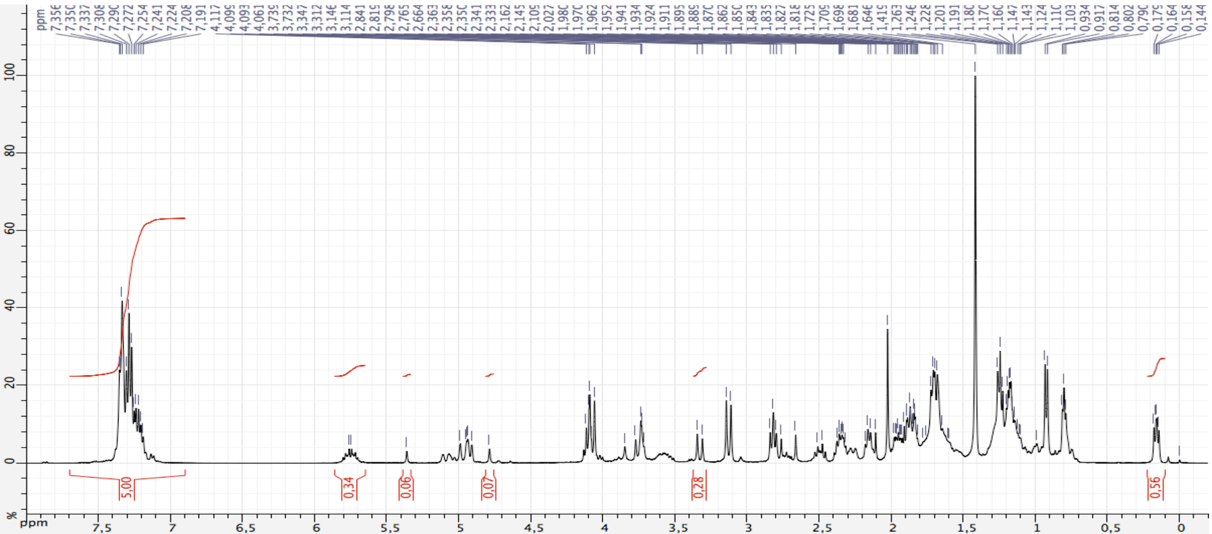
MS spectrum (positive CI, NH_3).

■ Using cyclohexylmagnesium chloride.

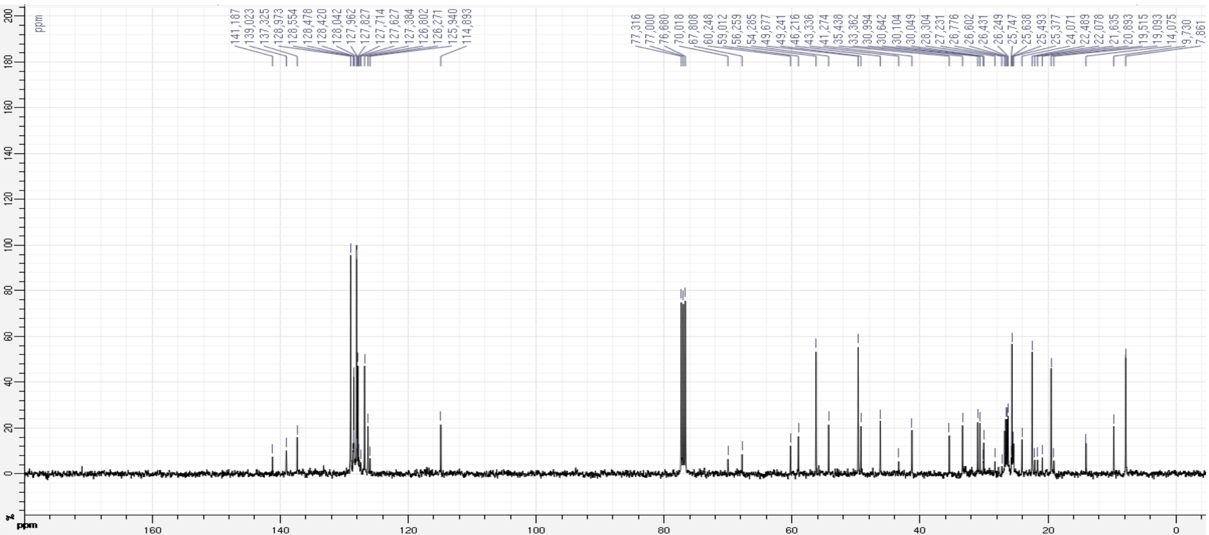


1aS **2a** **4a**

Cyclohexylmagnesium chloride (1.92 M in Et_2O, 4.00 equiv, 4.00 mmol, 2.08 mL) was added dropwise, over 5 min, to a stirred solution of *N*-benzyl-*N*-(but-3-en-1-yl)ethanethioamide **1aS** (1.00 equiv, 1.00 mmol, 219 mg) and titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 μL) in THF (20 mL). During the addition, the solution turned yellow, then green-yellow, orange, brown, and finally black. After a further 20 min of stirring, H_2O (0.5 mL) was added. The mixture was exposed to air, stirred until near complete decolouration (45 min), and filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed thoroughly with EtOAc. The resulting clear solution was concentrated to afford a yellow oil with a pungent unpleasant smell (256 mg). Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopy gave an estimation of the yields of **2a** (56%), **4a** (34%) and the starting material **1aS** (6%). Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane, gradient from 0 to 30%) yielded pure **4a** (60 mg, 0.22 mmol, 22%) and fairly pure 2-benzyl-1-methyl-2-azabicyclo[3.1.0]hexane **2a**^{1} (82 mg, 0.44 mmol, 44%).

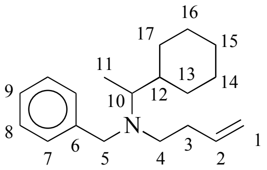


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).



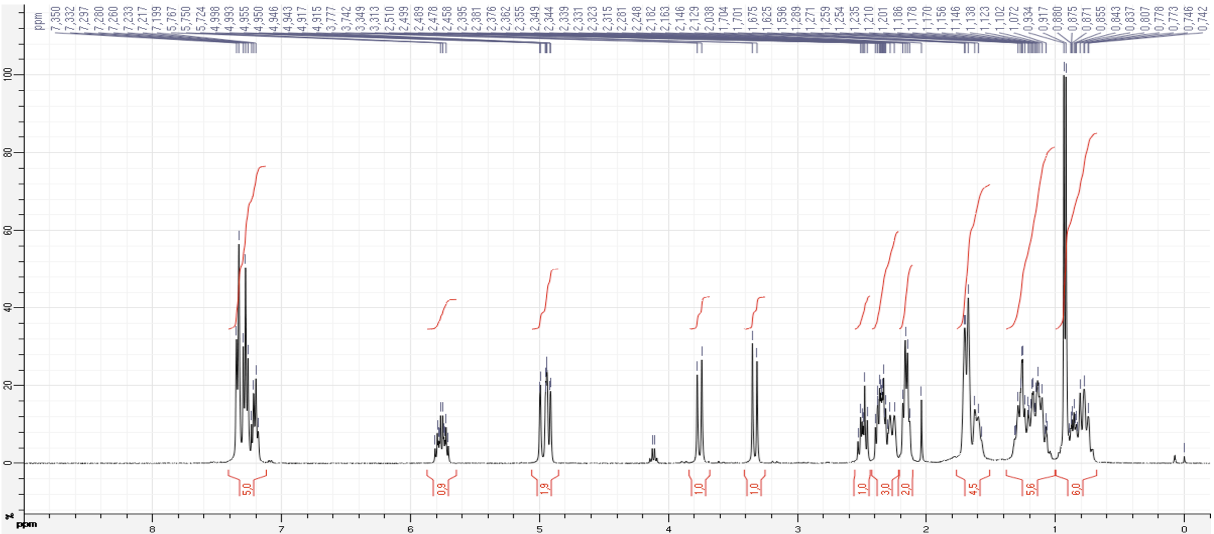
^{13}C NMR spectrum of the crude product (100.6 MHz).

N-Benzyl-*N*-(1-cyclohexylethyl)but-3-en-1-amine **4a**

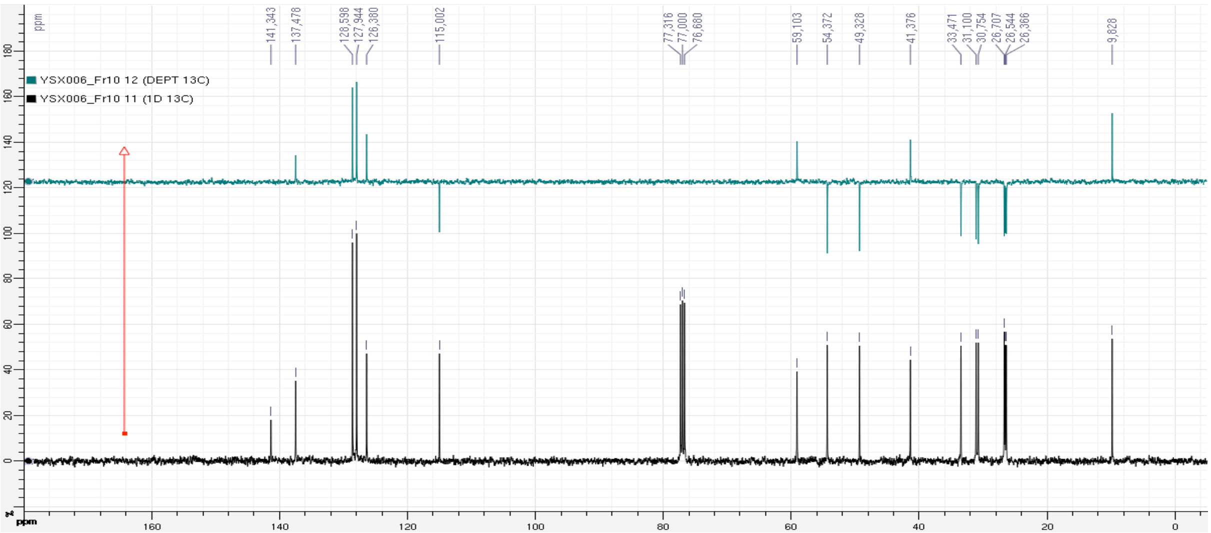


Colourless oil. R_f 0.65(AcOEt/Pet. ether 20%, PMA). IR (neat) ν 3064, 3027, 2922 (s), 2851 (s), 2803, 1640 (w), 1494 (w), 1450 (m), 1380, 1372, 1140, 1113, 1028, 910 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.78 (2 H, m, H13a, H17a), 0.93 (3 H, d, J 6.5, H11), 1.02–1.35 (5 H, m, H13b, H14a, H15a, H16a, H17b), 1.54–1.75 (3 H, m, H14b, H15b, H16b), 2.16 (2 H, m, H3), 2.26 (1 H, br d, J 13.0, H12), 2.34 (1 H, dq, J 9.5, 6.5, H10), 2.42 (2 H, AB part of an

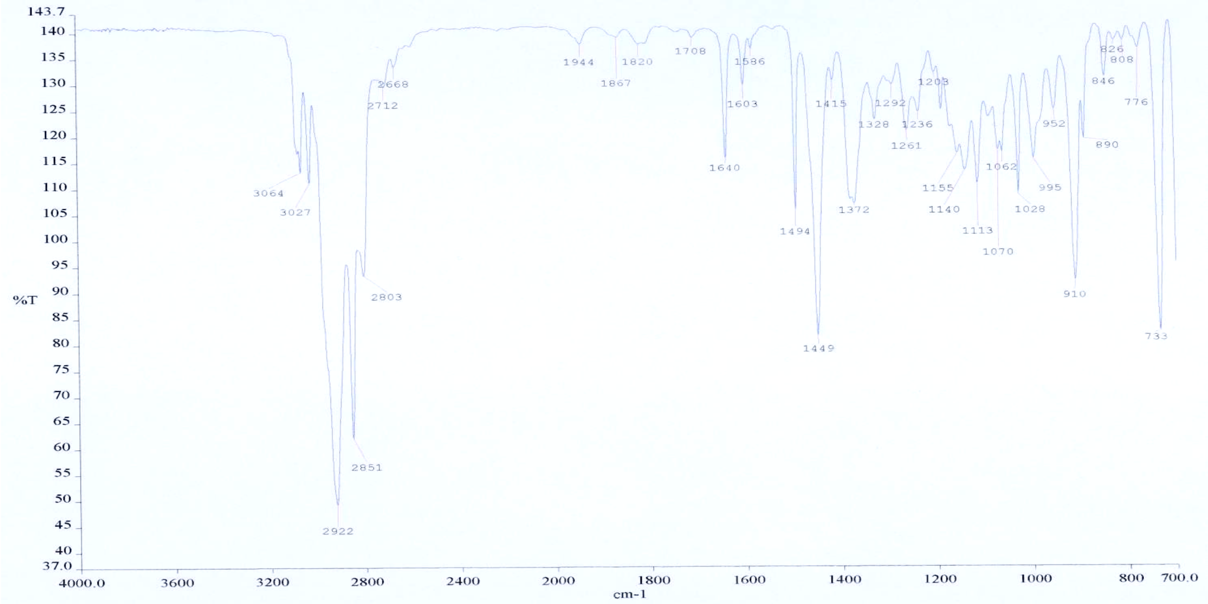
ABXY system, δ_A 2.36, δ_B 2.49, J_{AB} 13.0, J_{AX} 8.0, J_{AY} 5.5, J_{BX} 8.0, J_{BY} 8.0, H4), 3.54 (2 H, AB system, δ_A 3.33, δ_B 3.76, J_{AB} 14.0, H5), 4.93 (1 H, br d, J 10.0, H1a), 4.97 (1 H, dq, J 17.0, 1.5, H1b), 5.76 (1 H, ddt, J 17.0, 10.0, 7.0, H2), 7.20 (1 H, tt, J 7.0, 1.5, H9), 7.28 (2 H, dd, J 7.5, 7.0, H8), 7.34 (2 H, dd, J 7.5, 1.5, H7). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 9.8 (C11), 26.4, 26.5, 26.7 (C14–C16), 30.8, 31.1 (C13 and C17), 33.5 (C3), 41.4 (C12), 49.3 (C4), 54.4 (C5), 59.1 (C10), 115.0 (C1), 126.4 (C9), 127.9, 128.6 (C7 and C8), 137.5 (C2), 141.3 (C6). MS *m/z* (positive CI, NH_3) 188, 230, <u>272</u> (MH^+), 273. HRMS *m/z* (EI) 271.2295 ($M^{+\bullet}$ $C_{19}H_{29}N$ requires 271.2300).



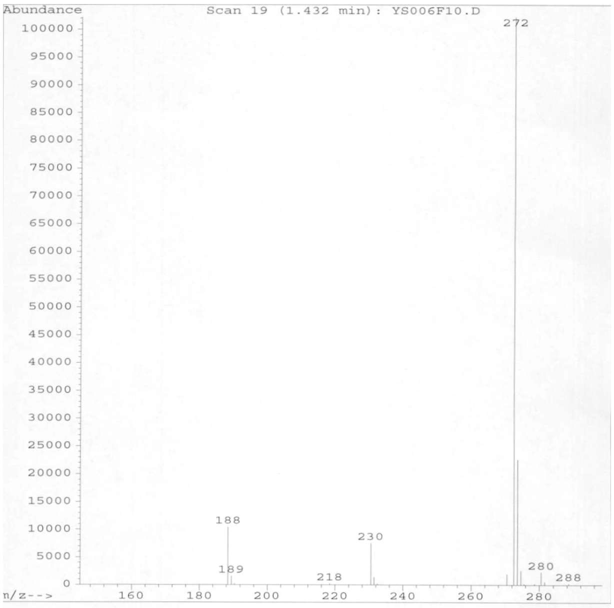
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C NMR and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).



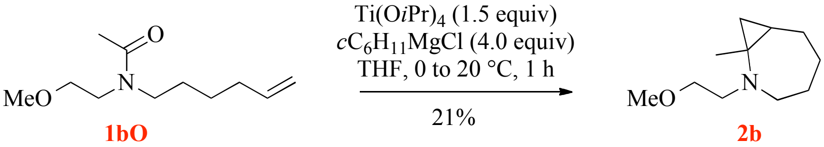
IR spectrum.



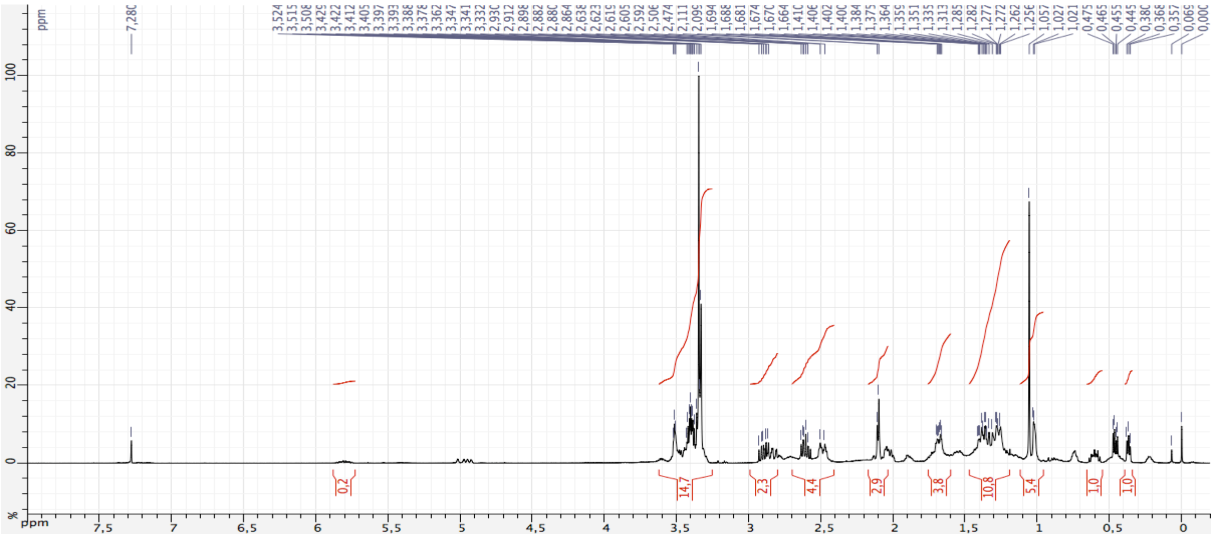
MS spectrum (positive CI, NH_3).

III. Reactions of 1bO and 1bS

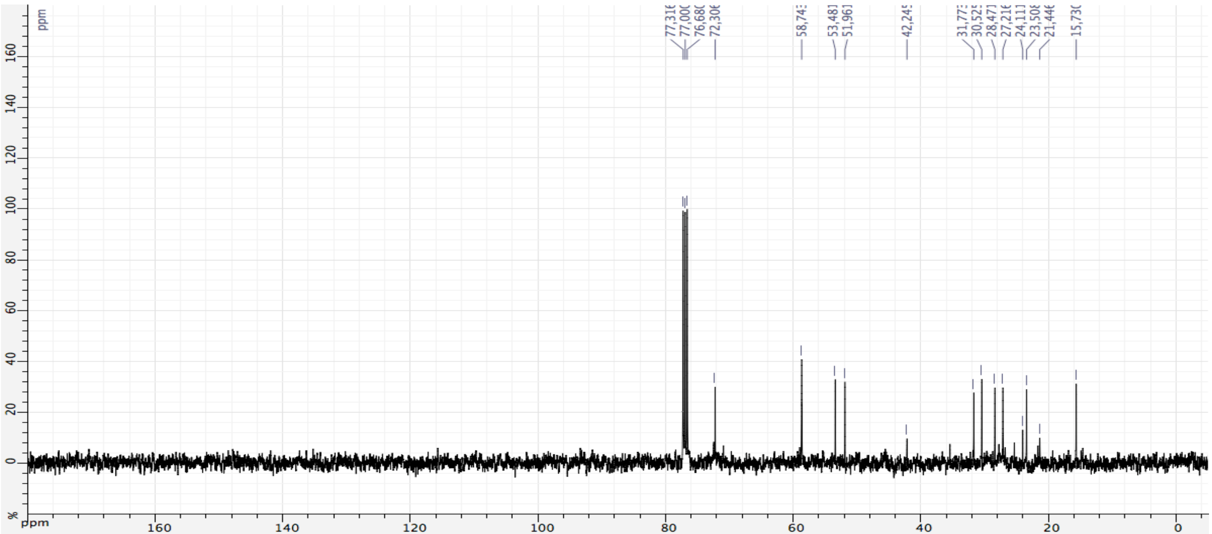
■ Intramolecular Kulinkovich-de Meijere reaction of **1bO**, run 1.



Cyclohexylmagnesium chloride (2.03 M in Et_2O, 4.00 equiv, 4.00 mmol, 1.97 mL) was added dropwise, over 5 min at 0 °C, to a stirred solution of *N*-(hex-5-en-1-yl)-*N*-(2-methoxyethyl)acetamide **1bO** (1.00 equiv, 1.00 mmol, 199 mg) and titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 µL) in THF (20 mL). During the addition, the solution turned yellow, then dark yellow. The cold bath was removed after 5 minutes and the reaction mixture was stirred at 20 °C for 60 minutes. It turned brown, dark brown and finally black. H_2O (0.2 mL) was added. After 15 minutes, the flask was exposed to air and further stirred until near complete decolouration (15 min). The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed with Et_2O (25 mL). The resulting clear solution was concentrated to afford orange crystals (712 mg). The crude product was dissolved in EtOAc (20 mL) and extracted with 1 N HCl aqueous solution (3 × 15 mL). The combined aqueous layers were basified (pH ≥ 10) with NaOH pellets, then extracted with EtOAc (3 × 20 mL). These combined EtOAc phases (60 mL) were dried over Na_2SO_4, filtered and concentrated to afford a yellow oil (139 mg). Analysis by ^1H and ^{13}C NMR spectroscopy showed that it mainly contained 2-(2-methoxyethyl)-1-methyl-2-azabicyclo[5.1.0]octane **2b**. Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane 20%) yielded pure **2b** (39 mg, 213 μmol, 21%).[3]



^1H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).



^{13}C NMR spectrum of the crude product (100.6 MHz).

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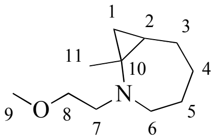
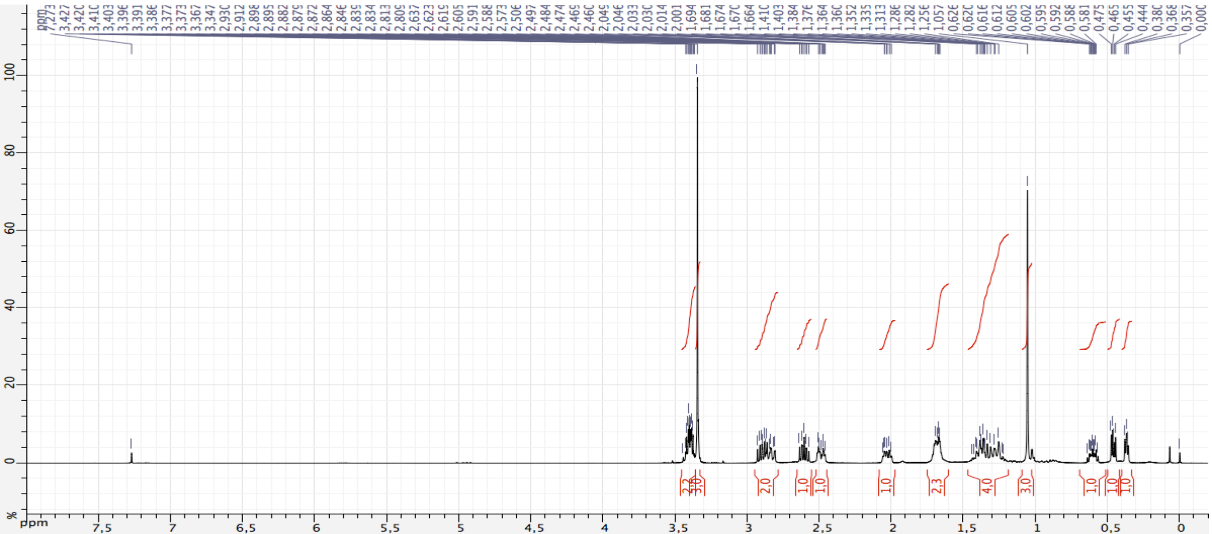
[3] The low yield was probably due to the volatility of this compound, as evidenced by the droplets that were observed in the neck of the flask after rotary evaporator removal of the chromatography solvents.

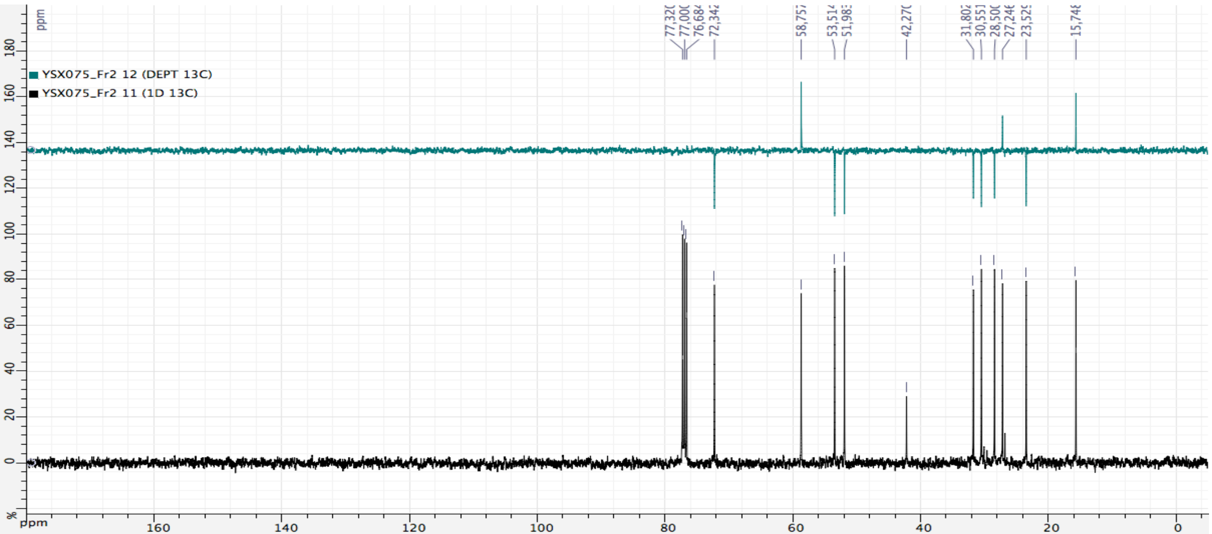
2-(2-Methoxyethyl)-1-methyl-2-azabicyclo[5.1.0]octane **2b**



Colourless oil. R_f 0.4 (AcOEt/Pet. ether 10%, PMA). IR (neat) ν 2991 (m), 2922 (s), 2872 (m), 2851 (m), 1447 (m), 1374 (m), 1335 (w), 1199 (w), 1175 (w), 1124 (m), 1019 (w), 962 (w) cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) 0.37 (1 H, dd, J 5.5, 4.0, H1a), 0.46 (1 H, dd, J 8.0, 4.0, H1b), 0.60 (1 H, dddd, J 10.0, 8.0, 6.0, 5.5, H2), 1.06 (3 H, s, H11), 1.19–1.47 (4 H, m, H3a, H4, H5a), 1.68 (1 H, m, H5b), 2.03 (1 H, ddd, J 12.5, 6.0, 4.5, H3b), 2.49 (1 H, ddd, J 13.0, 5.5, 3.5, H6a), 2.61 (1 H, ddd, J 12.5, 7.0, 6.0, H7a), 2.84 (1 H, ddd, J 13.0, 10.5, 2.0, H6b), 2.90 (1 H, ddd, J 12.5, 7.5, 6.5, H7b), 3.35 (3 H, s, H9), 3.40 (2 H, AB part of an ABXY system, δ_A 3.39, δ_B 3.41, J_{AB} 9.5, J_{AX} 6.0, J_{AY} 7.5, J_{BX} 7.0, J_{BY} 6.5, H8). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 15.8 (C11), 23.5 (C1), 27.2 (C2), 28.5, 30.6, 31.8 (C3–C5), 42.3 (C10), 52.0, 53.5 (C6, C7), 58.8 (C9), 72.3 (C8). MS *m/z* (positive CI, NH$_3$) 138, 184 (MH$^+$), 185. HRMS *m/z* (EI) 183.1622 (M$^{+\bullet}$ C$_{11}$H$_{21}$NO requires 183.1623).

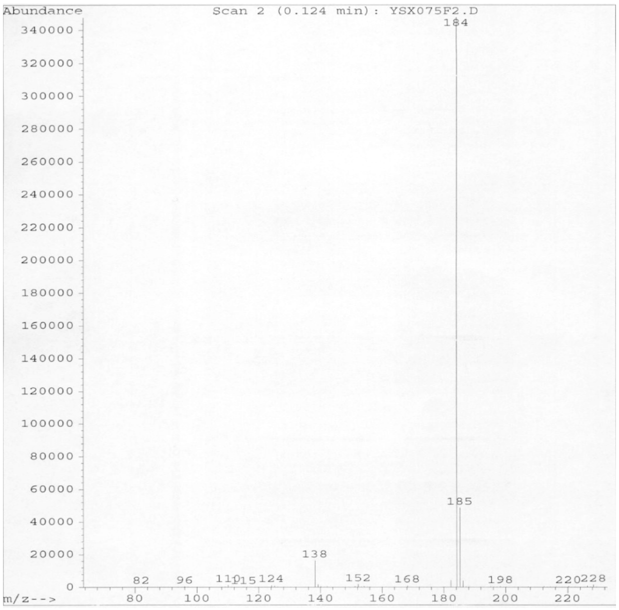


^{1}H NMR spectrum (CDCl$_3$, 400 MHz).



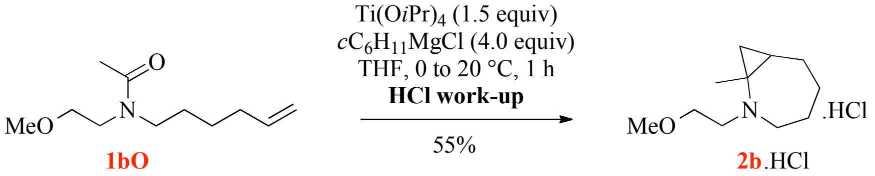
^{13}C and DEPT 135 NMR spectra (CDCl$_3$, 100.6 MHz).

IR spectrum.



MS spectrum (positive CI, NH_3).

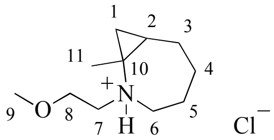
■ Intramolecular Kulinkovich-de Meijere reaction of **1bO**, run 2.



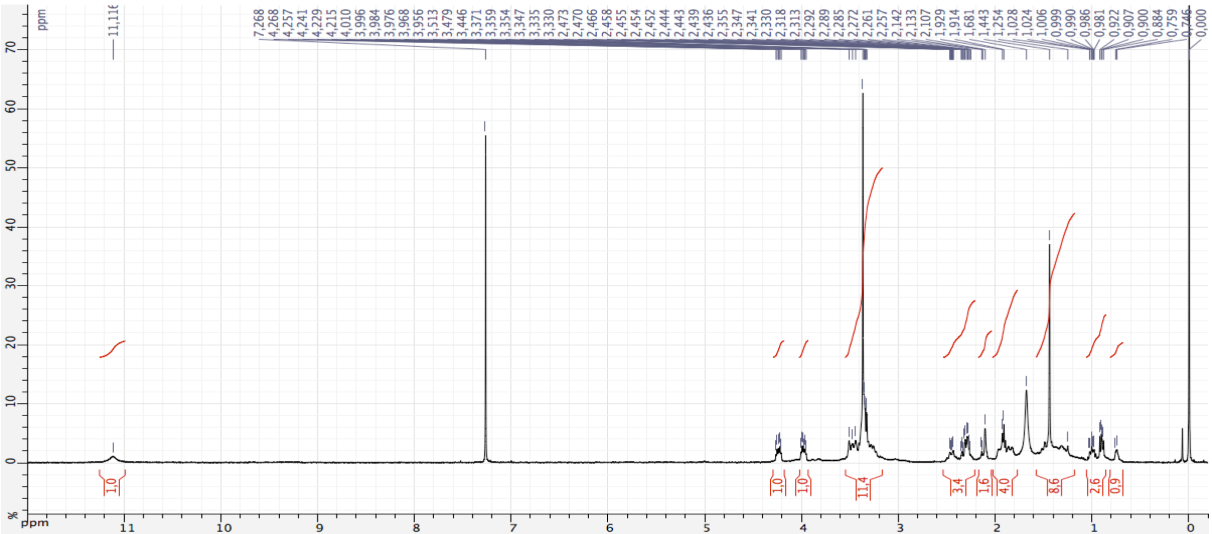
Cyclohexylmagnesium chloride (2.03 M in Et_2O, 4.00 equiv, 7.00 mmol, 3.45 mL) was added dropwise, over 3 min at 0 °C, to a stirred solution of *N*-(hex-5-en-1-yl)-*N*-(2-methoxyethyl)acetamide **1bO** (1.00 equiv, 1.75 mmol, 348 mg) and titanium(IV) *iso*-propoxide (1.50 equiv, 2.62 mmol, 777 μL) in THF (35 mL). During the addition, the solution turned yellow, then dark yellow. The cold bath was removed after 5 minutes and the reaction mixture was stirred at 20 °C for 60 minutes. It turned brown, dark brown and finally black.

H_2O (0.9 mL) was added. After 15 minutes, the flask was exposed to air and further stirred for 1 h. The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed with Et_2O (25 mL). Most of the solvent was then removed under reduced pressure (rotavapor, bath at 40 °C, pressure not lower than 300 mbar). The orange oil thus obtained was dissolved in EtOAc (25 mL) and extracted with 1 N HCl aqueous solution (3 × 25 mL). The combined aqueous layers were basified (pH ≥ 10) with NaOH (pearl), then extracted with EtOAc (3 × 20 mL). These combined EtOAc phases (60 mL) were dried over Na_2SO_4 and filtered. 3 N HCl aqueous solution (1.0 mL) was added to the solution and the mixture was concentrated under reduced pressure to afford a viscous brown oil (322 mg). This crude product was extracted with EtOAc (trituration, 3 × 4.0 mL). The combined EtOAc extracts were concentrated under reduced pressure to afford pure 6-(2-methoxyethyl)-7-methyl-6-azoniabicyclo[5.1.0]octane chloride **2b**.HCl (213 mg, 969 µmol, 55%). The corresponding free amine **2b** could then be easily isolated by taking the hydrochloride salt in a mixture of Et_2O (20 mL) and 1M NaOH aqueous solution (15 mL). The aqueous phase was separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure (rotavapor, bath at 40 °C, pressure not lower than 300 mbar) to afford pure 2-(2-methoxyethyl)-1-methyl-2-azabicyclo[5.1.0]octane **2b** (163 mg, 889 mmol, 51%).

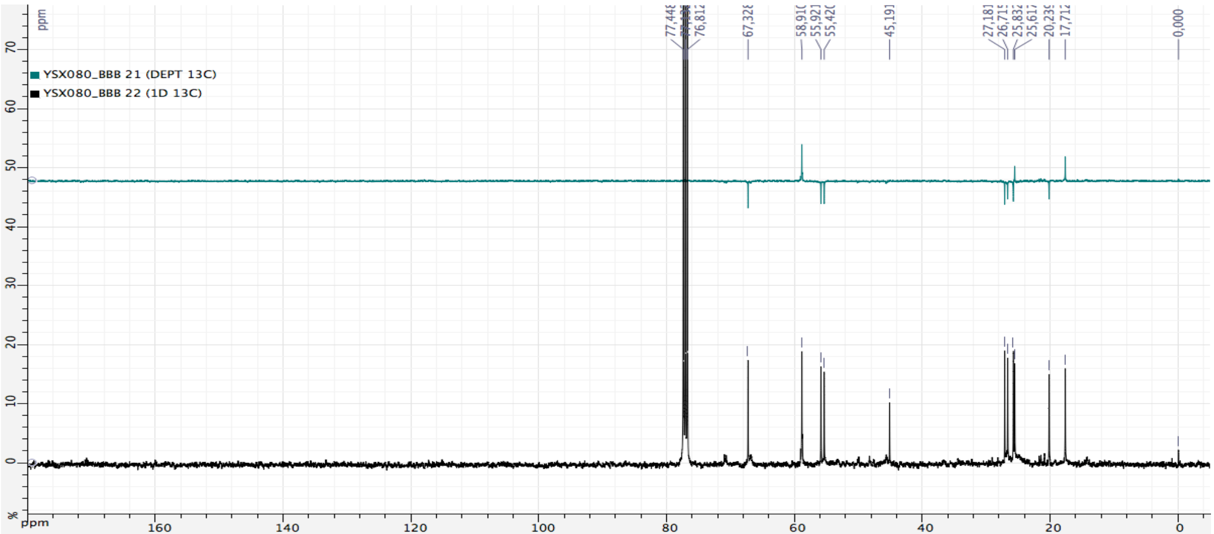
6-(2-Methoxyethyl)-7-methyl-6-azoniabicyclo[5.1.0]octane chloride
2b.HCl



Viscous pale brown oil. ^1H NMR ($CDCl_3$, 400 MHz) 0.75 (1 H, t, 6.5, H1a), 0.91 (1 H, dd, J 9.0, 6.5, H1b), 1.02 (1 H, dddd, J 9.5, 9.0, 8.0, 6.5, H2), 1.20–2.53 (6 H, m, H3–H5), 1.44 (3 H, s, H11), 3.20–3.55 (4 H, m, H6, H7), 3.37 (3 H, s, H9), 4.10 (2 H, AB part of an ABXY system, δ_A 3.98, δ_B 4.23, J_{AB} 11.5, J_{AX} 5.0, J_{AY} 6.0, J_{BX} 6.0, J_{BY} 4.5, H8), 11.12 (1 H, br s, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 17.7 (C11), 20.2 (C1), 25.6 (C2), 25.8, 26.7, 27.2 (C3–C5), 45.2 (C10), 55.4, 55.9 (C6, C7), 58.9 (C9), 67.3 (C8).

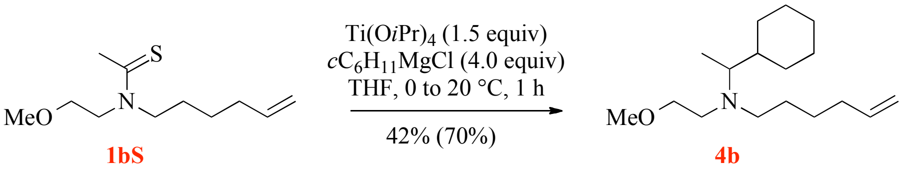


^1H NMR spectrum ($CDCl_3$, 400 MHz).

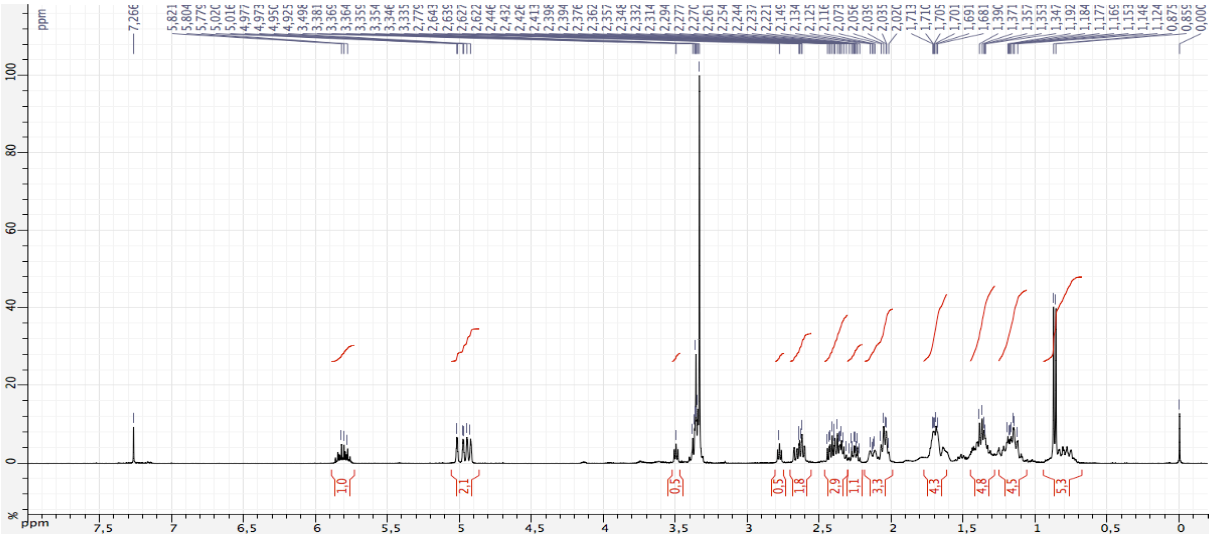


^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).

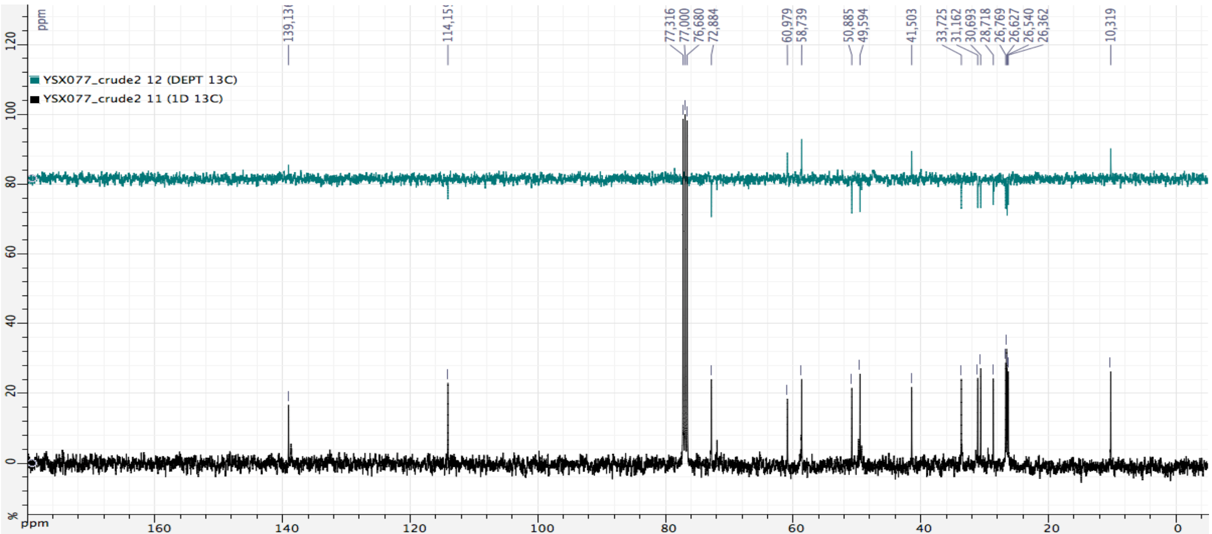
■ Titanium-mediated reaction of **1bS** with cyclohexylmagnesium chloride.



Cyclohexylmagnesium chloride (2.03 M in Et_2O, 4.00 equiv, 3.84 mmol, 1.89 mL) was added dropwise, over 5 min at 0 °C, to a stirred solution of *N*-(hex-5-en-1-yl)-*N*-(2-methoxyethyl)ethanethioamide **1bS** (1.00 equiv, 961 μmol, 207 mg) and titanium (IV) *iso*-propoxide (1.50 equiv, 1.44 mmol, 427 μL) in THF (20 mL). During the addition, the solution turned bright yellow, then dark yellow. The cold bath was removed after 5 minutes and the reaction mixture was stirred at 20 °C for 60 minutes. It turned brown and finally black. H_2O (0.5 mL) was then added. After 15 minutes of stirring, the flask was exposed to air and further stirred for 1 h (beige colour). The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, a layer of celite and another layer of sand at the top, that was then rinsed with Et_2O (25 mL). The resulting clear solution was concentrated to afford an orange oil with a pungent unpleasant smell (257 mg). Analysis by ^{1}H NMR spectroscopy revealed the presence of starting material (about 40%) and (1-cyclohexylethyl)(hex-5-en-1-yl)(2-methoxyethyl)amine **4b** as the major product. The crude product was dissolved in EtOAc (20 mL) and extracted with 1 N HCl aqueous solution (3 × 20 mL). The combined aqueous layers were basified (pH ≥ 10) with NaOH pellets, then extracted with EtOAc (3 × 20 mL). These combined EtOAc phases (60 mL) were dried over Na_2SO_4, filtered and concentrated to afford a yellow oil (147 mg). Analysis by ^{1}H and ^{13}C NMR spectroscopy showed that it contained a 80 : 20 mixture of (1-cyclohexylethyl)(hex-5-en-1-yl)(2-methoxyethyl)amine **4b** and (hex-5-en-1-yl)(2-methoxyethyl)amine (479 μmol, 50% and 120 μmol, 12% respectively). Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane, gradient from 0 to 20%) yielded pure (1-cyclohexylethyl)(hex-5-en-1-yl)(2-methoxyethyl)amine **4b** (109 mg, 407 μmol, 42%).

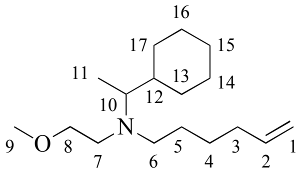


^{1}H NMR spectrum of the crude product (CDCl$_3$, 400 MHz).

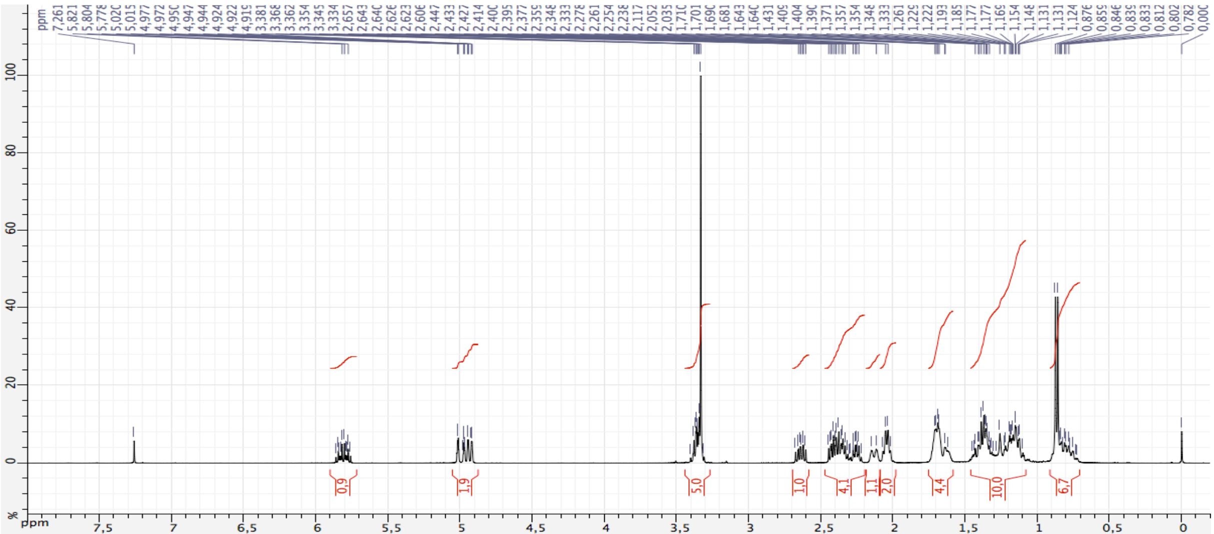


^{13}C NMR and DEPT135 spectra of the crude product (CDCl$_3$, 100.6 MHz).

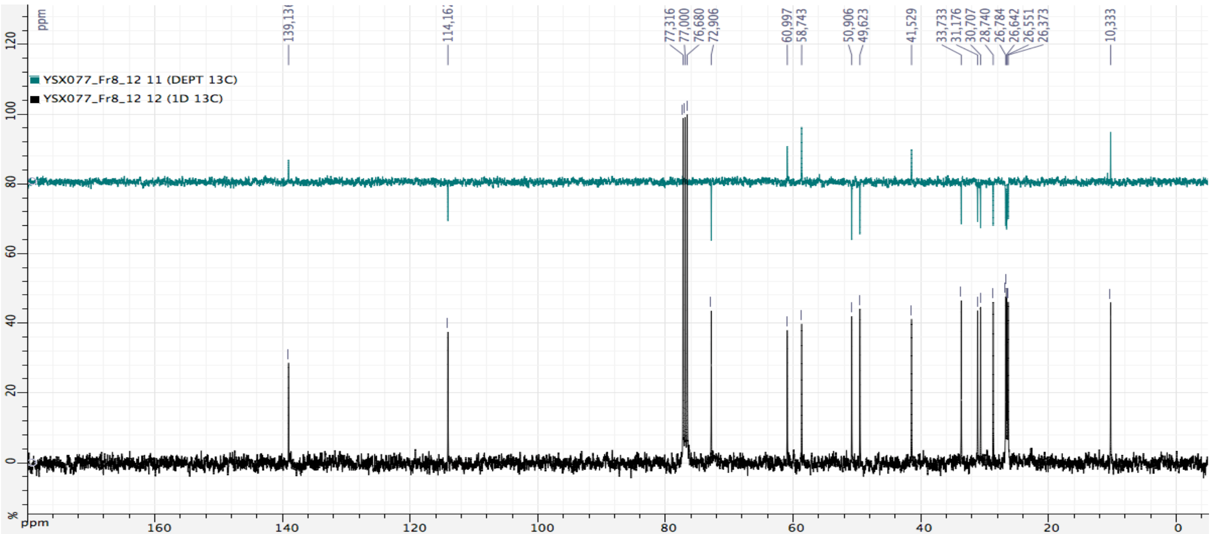
(1-Cyclohexylethyl)(hex-5-en-1-yl)(2-methoxyethyl)amine **4b**



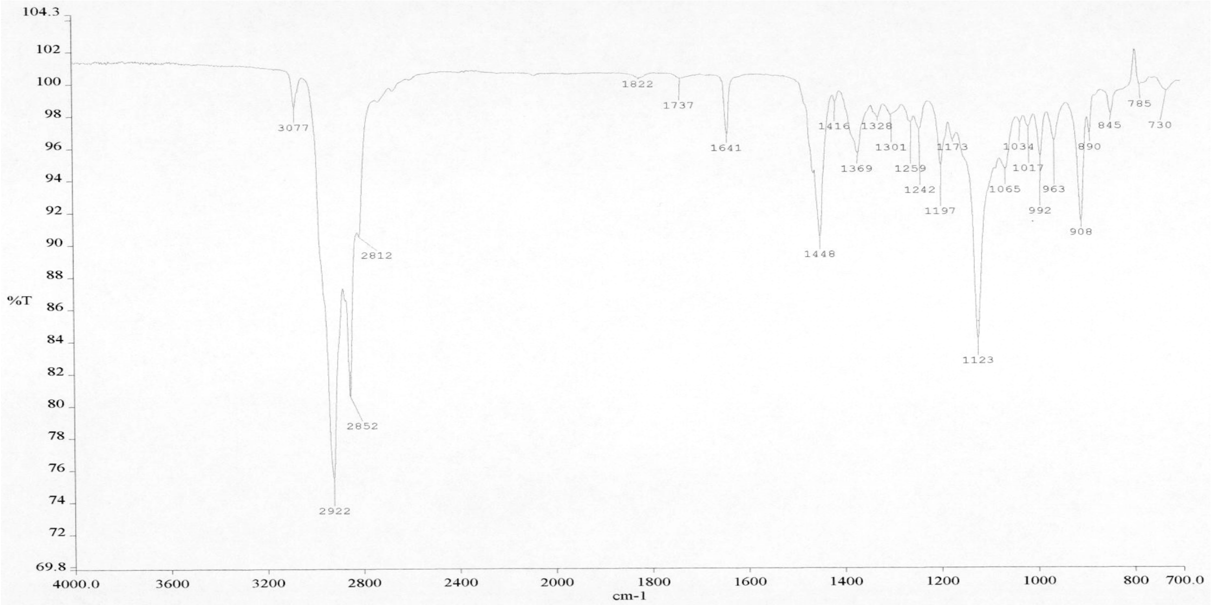
Yellow oil. R_f 0–0.15 (AcOEt/Pet. ether 5%, PMA). IR (neat) *ν* 2922 (s), 2852 (m), 2812 (m), 1461 (w), 1448 (m), 1369 (w), 1197 (w), 1123 (m), 1065 (w), 992 (w), 963 (w), 908 (m) cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) 0.71–0.91 (2 H, m, H13a, H17a), 0.87 (3 H, d, J 6.5, H11), 1.08–1.46 (9 H, m, H4, H5, H13b, H14a, H15a, H16a, H17b), 1.58–1.76 (3 H, m, H14b, H15b, H16b), 2.04 (2 H, tddd, J 7.0, 6.5, 1.5, 1.0, H3), 2.13 (1 H, br d, J 13.0, H12), 2.26 (1 H, dq, J 9.5, 6.5, H10), 2.29–2.42 (2 H, m, H6 or H7), 2.41 (1 H, ddd, J 13.5, 8.0, 5.5, H6 or H7), 2.64 (1 H, ddd, J 13.0, 8.0, 6.5, H6 or H7), 3.29–3.42 (2 H, m, H8), 3.33 (3 H, s, H9), 4.93 (1 H, ddt, J 17.0, 1.5, 1.0, H1 *cis* to H2), 5.00 (1 H, dq, J 17.0, 1.5, H1 *trans* to H2), 5.81 (1 H, ddt, J 17.0, 10.0, 6.5, H2). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 10.3 (C11), 26.4, 26.6, 26.6, 26.8 (C4, C14–C16), 28.7 (C5), 30.7, 31.2 (C13, C17), 33.7 (C3), 41.5 (C12), 49.6, 50.9 (C6, C7), 58.7 (C9), 61.0 (C10), 72.9 (C8), 114.2 (C1), 139.1 (C2). MS *m/z* (positive CI, NH$_3$) 184, 222, 268 (MH$^+$), 269, 270. HRMS *m/z* (EI) 267.2561 (M$^{+\bullet}$ C$_{17}$H$_{33}$NO requires 267.2562).



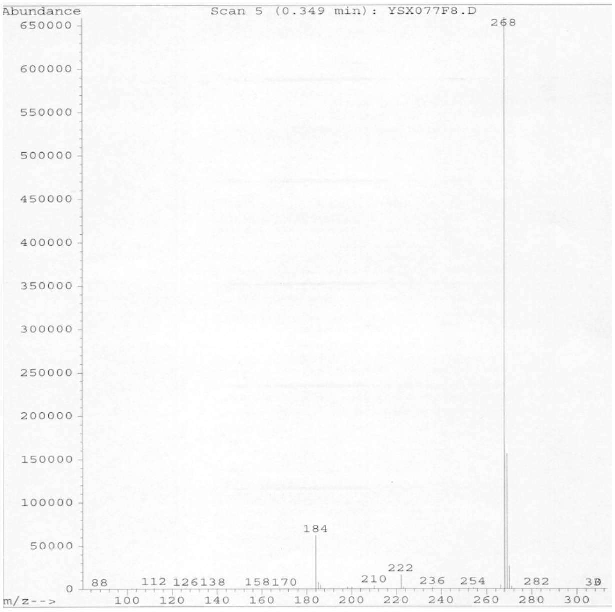
^{1}H NMR spectrum (CDCl$_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra (CDCl$_3$, 100.6 MHz).



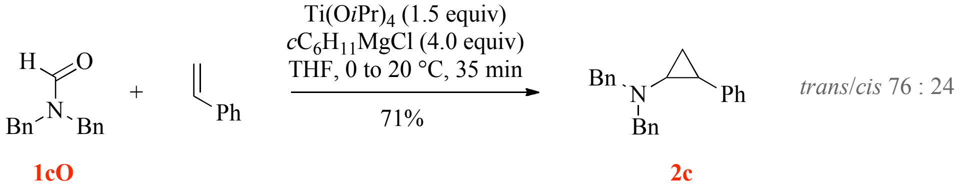
IR spectrum.



MS spectrum (positive CI, NH_3).

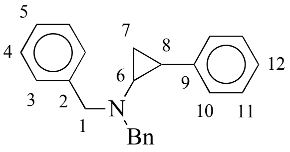
IV. Reactions of 1cO and 1cS in the presence of styrene

■ Intermolecular Kulinkovich-de Meijere reaction of **1cO** with styrene.

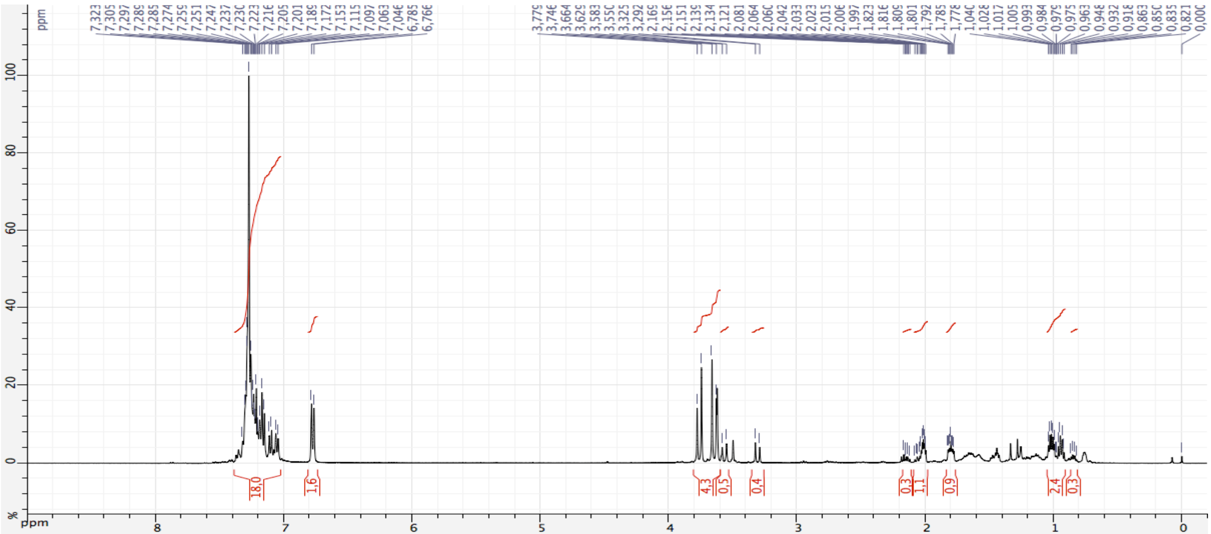


Titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 µL) was added to a stirred solution of *N*,*N*-dibenzylformamide **1cO** (1.00 equiv, 1.00 mmol, 225 mg) and styrene (1.00 equiv, 1.00 mmol, 115 µL) in THF (10 mL) at 0 °C. Cyclohexylmagnesium chloride (1.83 M in Et_2O, 4.00 equiv, 4.00 mmol, 2.19 mL) was then introduced dropwise, over 10 min at 0 °C. During the addition, the solution turned yellow, then orange. The cold bath was removed and the reaction mixture was stirred at 20 °C for 35 minutes. It turned dark orange and finally brown. H_2O (0.5 mL) was added and the flask was exposed to air. Stirring was maintained until near complete decolouration (30 min). The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed with EtOAc. The resulting clear solution was concentrated to afford a mixture of a yellow oil and a colourless solid (386 mg). The ratio of the *trans* and *cis* diastereoisomers of the 1-(*N*,*N*-dibenzylamino)-2-phenylcyclopropane produced was evaluated to be 76 : 24 by ^{13}C NMR spectroscopy analysis of the crude product. Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane, gradient from 0 to 20%) yielded pure 1-(*N*,*N*-dibenzylamino)-2-phenylcyclopropane **2c** (*trans*/*cis* 79 : 21, 223 mg, 711 µmol, 71%).

1-(*N*,*N*-Dibenzylamino)-2-phenylcyclopropane **2c**[4]



Colourless crystals / pale yellow oil mixture. R_f 0.7 [AcOEt/Pet. ether 30%, PMA]. ^{1}H NMR ($CDCl_3$, 400 MHz) 79 : 21 mixture of the *trans* and *cis* diastereoisomers: 0.84 (1 H, ddd, J 6.5, 5.5, 5.0, H7a), 0.94 (1 H, ddd, J 7.0, 6.0, 5.0, H7a), 0.99 (1 H, ddd, J 8.5, 7.0, 5.5, H7b), 1.02 (1 H, ddd, J 9.5, 5.0, 4.5, H7b), 1.80 (1 H, ddd, J 9.5, 6.0, 3.0, H8), 2.01 (1 H, ddd, J 7.0, 4.5, 3.0, H6), 2.05 (1 H, ddd, J 8.5, 7.0, 6.5, H8), 2.14 (1 H, td, J 7.0, 5.0, H6), 3.44 (4 H, AB system, δ_A 3.31, δ_B 3.57, J_{AB} 13.5, H1), 3.70 (4 H, AB system, δ_A 3.65, δ_B 3.76, J_{AB} 13.5, H1), 6.78 (2 H, br d, J 7.5, H10), 7.02–7.39 (13 H, m, H3–H5, H11, H12), 7.02–7.39 (15 H, m, Ar). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 79 : 21 mixture of the *trans* and *cis* diastereoisomers: 13.5 (C7), 17.5 (C7), 23.8 (C8), 26.4 (C8), 43.7 (C6), 47.6 (C6), 57.3 (C1), 58.4 (C1), 125.3 (C12), 125.4 (C12), 125.7 (C10), 126.7 (C10), 126.8 (C11), 127.5 (C11), 127.8 (C3 or C4), 127.9 (C5), 128.0 (C3 or C4), 128.4 (C5), 129.3 (C3 or C4), 129.5 (C3 or C4), 138.3, 138.9 (C2, C9), 138.6, 142.0 (C2, C9).



^{1}H NMR spectrum ($CDCl_3$, 400 MHz).

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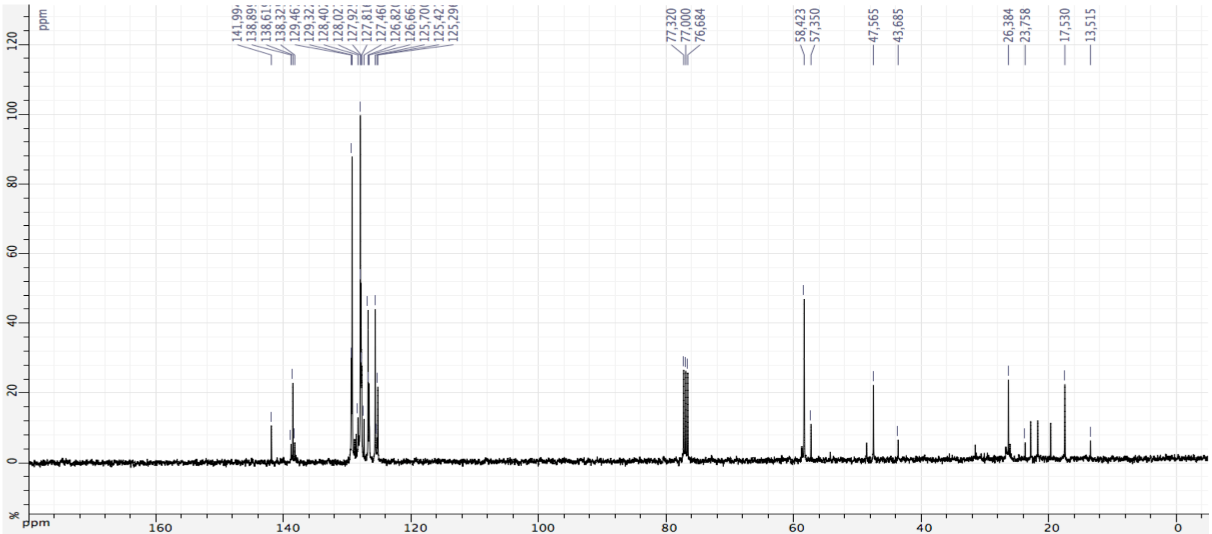
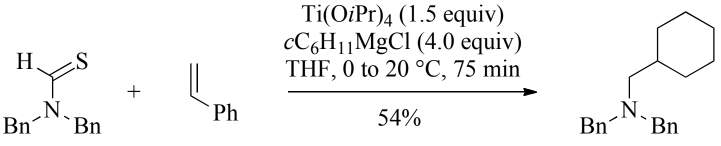
[4] A. de Meijere, C. M. Williams, A. Kourdioukov, S. V. Sviridov, V. Chaplinski, M. Kordes, A. I. Savchenko, C. Stratmann, M. Noltemeyer, *Chem. Eur. J.* **2002**, *8*, 3789–3801.



^{13}C NMR spectrum ($CDCl_3$, 100.6 MHz).

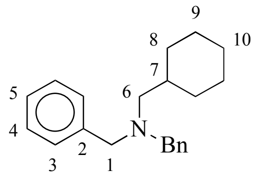
■ Ti-mediated reaction of **1cS** with cyclohexylmagnesium chloride in the presence of styrene.



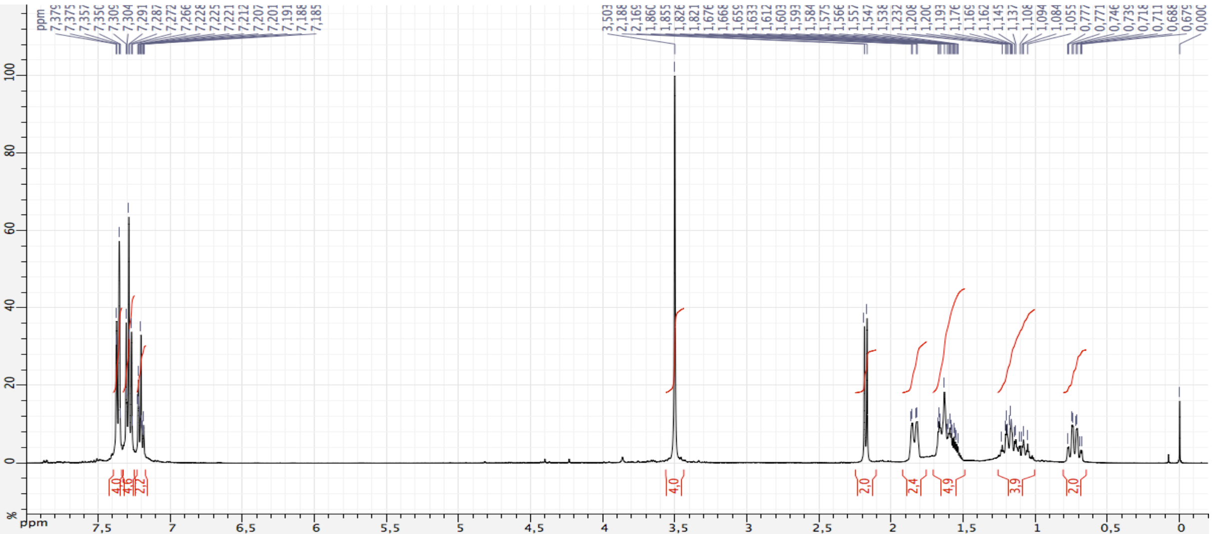
1cS **4c**

Titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 μL) was added to a stirred solution of *N*,*N*-dibenzylmethanethioamide **1cS** (1.00 equiv, 1.00 mmol, 241 mg) and styrene (1.00 equiv, 1.00 mmol, 115 μL) in THF (10 mL) at 0 °C. Cyclohexylmagnesium chloride (1.83 M in Et_2O, 4.00 equiv, 4.00 mmol, 2.19 mL) was then introduced dropwise, over 10 min at 0 °C. During the addition, the solution turned yellow, then orange. The cold bath was removed and the reaction mixture was stirred at 20 °C for 75 minutes. It turned dark orange and finally brown. H_2O (0.5 mL) was added and the flask was exposed to air. Stirring was maintained until near complete decolouration (25 min). The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed with EtOAc. The resulting clear solution was concentrated to afford a mixture of a yellow oil and a colourless solid (358 mg). Neither 1-(*N*,*N*-dibenzylamino)-2-phenylcyclopropane **2c** nor the starting thioamide **1cS** were observed by ^{1}H and ^{13}C NMR spectroscopy of the crude product. The latter revealed that the main components were cyclohexyl(*N*,*N*-dibenzylamino)methane **4c** (65%), unreacted styrene (43%) and *N*,*N*-dibenzylamine (21%). Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane, gradient from 0 to 5%) yielded pure cyclohexyl(*N*,*N*-dibenzylamino)methane **4c** (160 mg, 545 μmol, 54%).

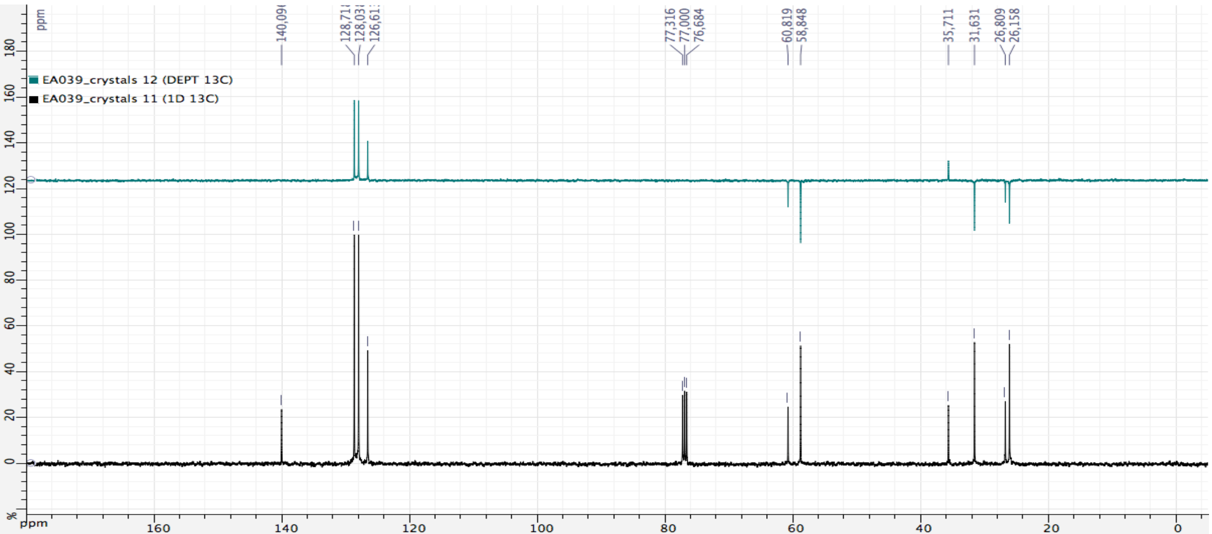
Cyclohexyl(*N*,*N*-dibenzylamino)methane **4c**[4]



Colourless crystals. R_f 0.45 [AcOEt/Pet. ether 5%, PMA]. ^{1}H NMR (CDCl$_3$, 400 MHz) 0.73 (2 H, qd, J 12.0, 2.5, H8a), 1.00–1.26 (3 H, m, H9a, H10a), 1.50–1.70 (4 H, m, H7, H9b, H10b), 1.84 (2 H, br d, J 12.0, H8b), 2.18 (2 H, d, J 7.5, H6), 3.50 (4 H, s, H1), 7.21 (2 H, br t, J 7.0, H5), 7.29 (4 H, br dd, J 7.5, 7.0, H4), 7.37 (4 H, br d, J 7.5, H3). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 26.2 (C9), 26.8 (C10), 31.6 (C8), 35.7 (C7), 58.8 (C1), 60.8 (C6), 126.6 (C5), 128.0 (C4), 128.7 (C3), 140.1 (C2).



^{1}H NMR spectrum (CDCl$_3$, 400 MHz).



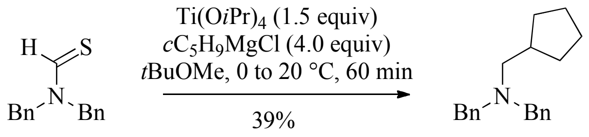
^{13}C NMR and DEPT135 spectra (CDCl$_3$, 100.6 MHz).

V. Titanium-mediated reductive alkylation of thioamides 1cS–1gS; general procedure

Titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 μL) was added to a stirred solution of the starting thioamide **1cS–1gS** (1.00 equiv, 1.00 mmol) in the solvent chosen (10 mL unless otherwise stated) at 0 °C. A solution of the Grignard reagent (4.00 equiv, 4.00 mmol) was then introduced dropwise, over 5 to 10 min at 0 °C. During the addition, the solution generally turned yellow, orange, brown and finally black. The cold bath was removed and the reaction mixture was stirred at 20 °C for 60 minutes. H_2O (0.5 mL) was then added and the flask was exposed to air. Stirring was maintained until near complete decolouration (typically 40 min). The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed with EtOAc. The resulting clear solution was concentrated to afford the crude product (usually a pungent unpleasant smell was observed).

VI. Titanium-mediated reductive alkylation reactions starting from 1cS

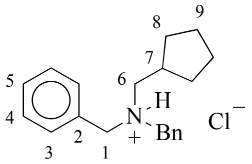
■ Titanium-mediated reaction of **1cS** with cyclopentylmagnesium chloride, in *t*BuOMe.



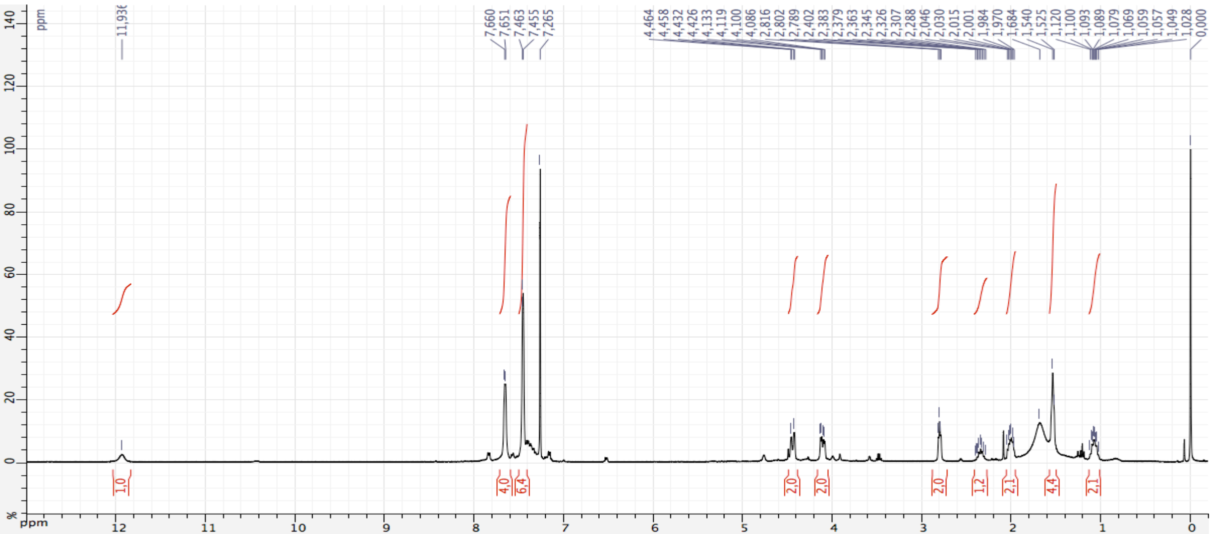
1cS **3c**

The general procedure was applied starting from *N*,*N*-dibenzylmethanethioamide **1cS** (1.00 equiv, 1.00 mmol, 241 mg), using *t*BuOMe as the solvent and cyclopentylmagnesium chloride (1.74 M in Et_2O) as the Grignard reagent. An orange oil (262 mg) was obtained. Analysis by ^1H NMR spectroscopy revealed that the main components of the crude product were cyclopentyl(*N*,*N*-dibenzylamino)methane **3c** (41%) and *N*,*N*-dibenzylamine (21%). Only traces of the starting thioamide **1cS** were detected (<1%). Precipitation of the crude product from EtOH (0.5 mL) at –25 °C afforded a light orange oil. The latter was triturated with heptane (3 × 0.5 mL) and the combined heptane fractions concentrated under reduced pressure to give a pale yellow oil (164 mg). This oil was dissolved in Et_2O (3.0 mL) and concentrated HCl aqueous solution was added (0.15 mL). The mixture was concentrated under reduced pressure to give a pale orange solid (191 mg). This solid was triturated with EtOAc (2.0 mL). The EtOAc layer was concentrated under reduced pressure to afford a brown gum (159 mg) that was washed twice with Et_2O (2.0 mL each time) at –25 °C to give fairly pure dibenzyl(cyclopentylmethyl)ammonium chloride (122 mg, 386 µmol, 39%).

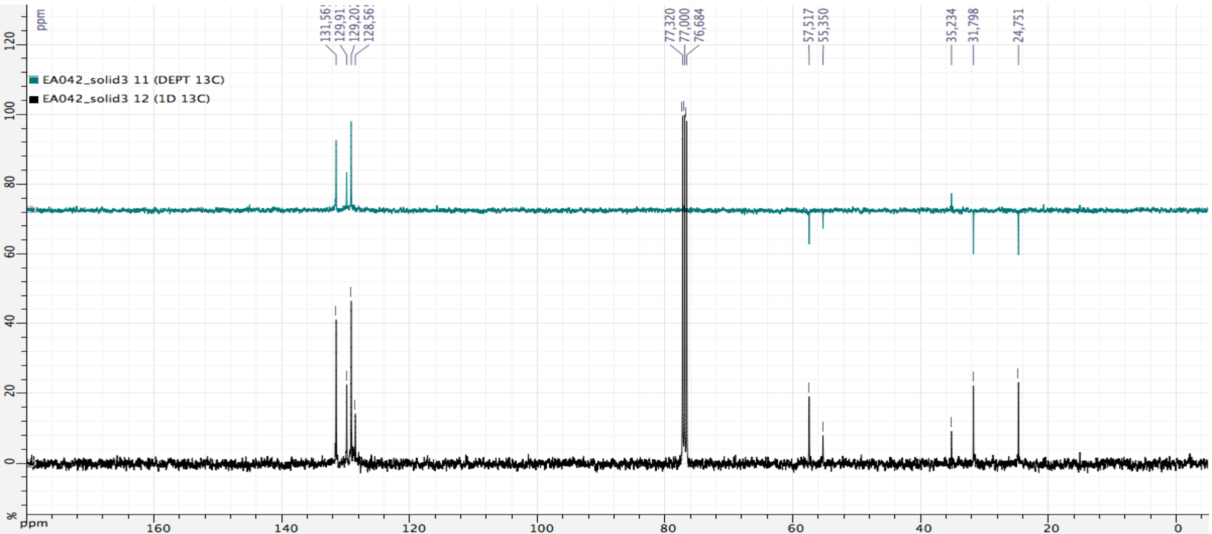
Dibenzyl(cyclopentylmethyl)ammonium chloride **3c**.HCl



Pale brown solid. ^1H NMR ($CDCl_3$, 400 MHz) 1.06 (2 H, m, H8a), 1.54 (4 H, br t, J 6.5, H9), 2.01 (2 H, m, H8b), 2.16 (1 H, ttt, J 8.5, 7.5, 6.5, H7), 2.80 (2 H, dd, J 6.5, 5.5, H6), 4.28 (2 H, AB part of an ABX system, δ_A 4.11, δ_B 4.44, J_{AB} 13.0, J_{AX} 5.5, J_{BX} 2.0, H1), 7.46 (6 H, br s, H4, H5), 7.66 (4 H, br s, H3), 11.94 (1 H, br s, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 24.8 (C9), 31.8 (C8), 35.2 (C7), 55.3 (C6), 57.5 (C1), 128.6 (C2), 129.2 (C4), 129.9 (C5), 131.6 (C3).

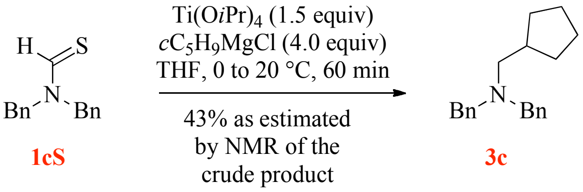


^{1}H NMR spectrum ($CDCl_3$, 400 MHz).

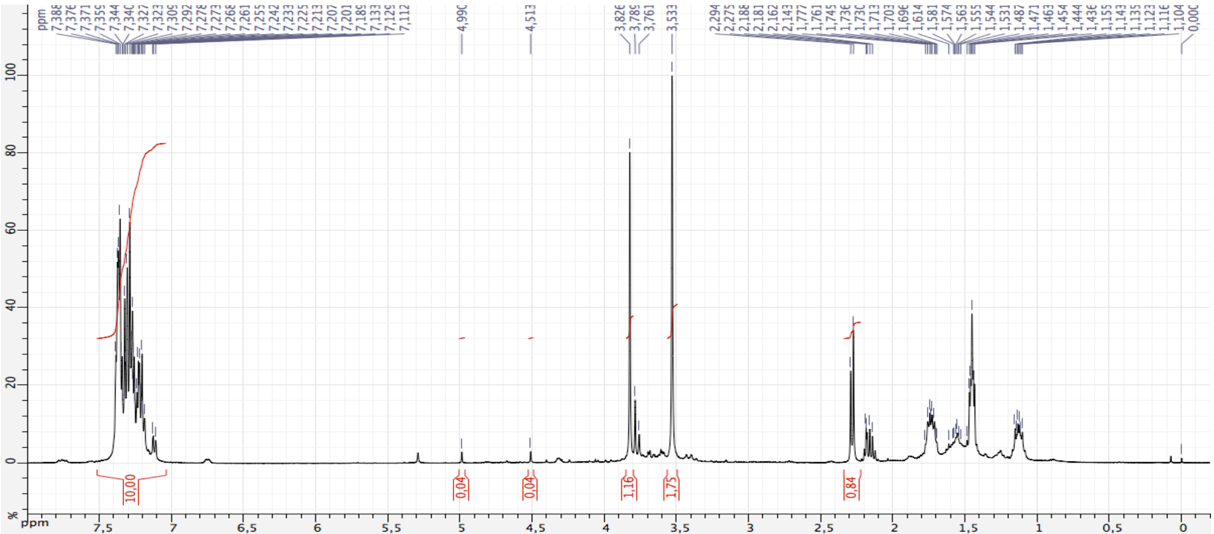


^{13}C NMR and DEPT135 spectra ($CDCl_3$, 100.6 MHz).

■ Titanium-mediated reaction of **1cS** with cyclopentylmagnesium chloride, in THF.

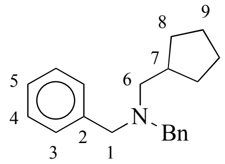


The general procedure was applied starting from *N*,*N*-dibenzylmethanethioamide **1cS** (1.00 equiv, 1.00 mmol, 241 mg), using THF as the solvent and cyclopentylmagnesium chloride (1.74 M in Et_2O) as the Grignard reagent. Analysis of the crude product (228 mg) by ^{1}H NMR spectroscopy revealed that the main components were cyclopentyl(*N*,*N*-dibenzylamino)methane **3c** (43%) and *N*,*N*-dibenzylamine (29%). Some starting thioamide was detected (2%). A fairly pure sample of **3c** was obtained by filtration of the crude product through a pad of basic alumina and three recrystallisations at –25 °C from EtOH (0.5 mL each time). Cyclopentyl(*N*,*N*-dibenzylamino)methane **3c** was isolated as colourless crystals (37 mg, 132 μmol, 13%).

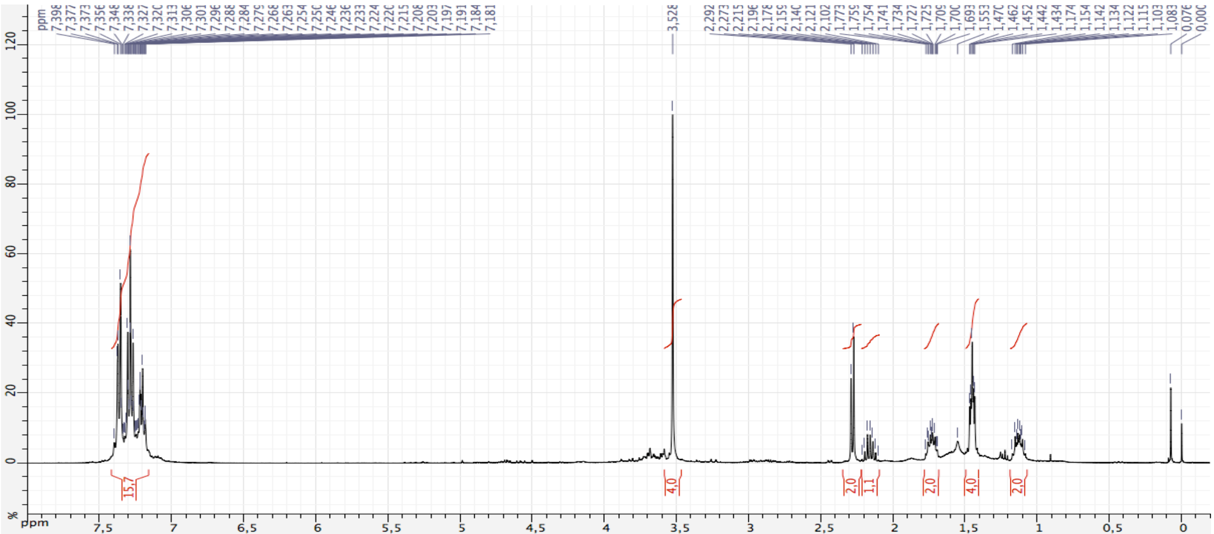


^{1}H NMR spectrum of the crude product (CDCl$_3$, 400 MHz).

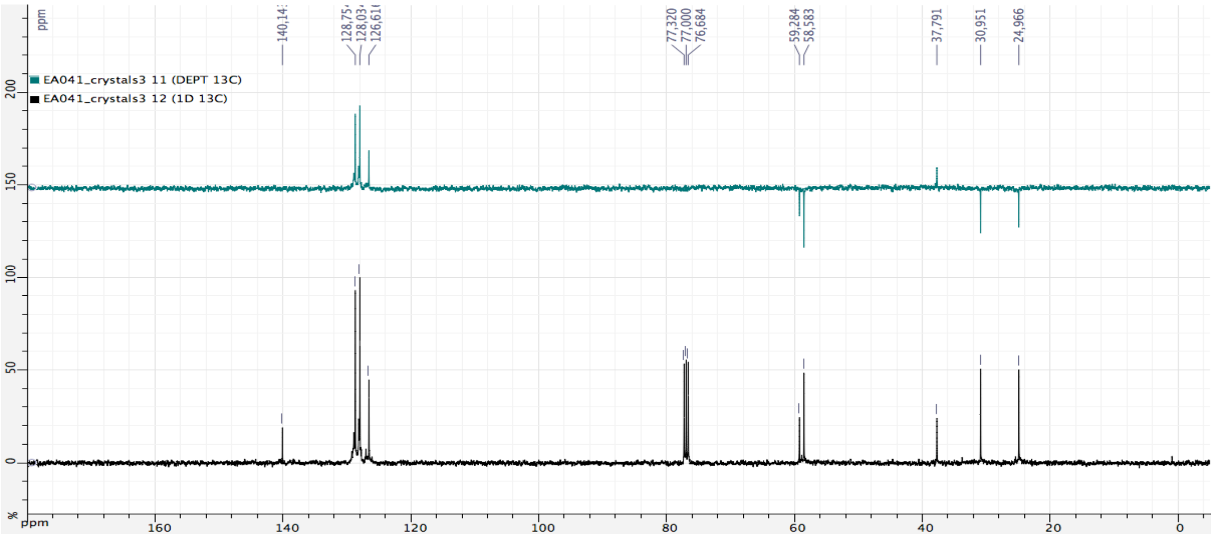
Cyclopentyl(*N*,*N*-dibenzylamino)methane **3c**



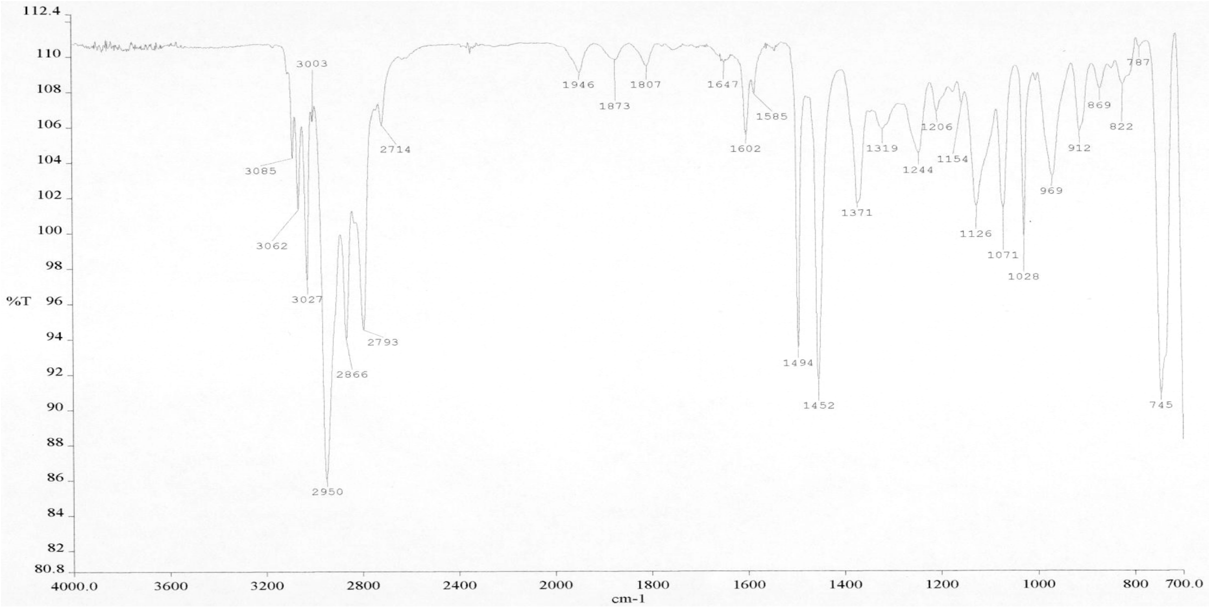
Pale yellow oil. R_f 0.75 [AcOEt/Pet. ether 30%, PMA]. IR (neat) ν 3085 (w), 3062 (w), 3027 (m), 2950 (s), 2866 (m), 2793 (m), 1602 (w), 1494 (m), 1452 (m), 1371 (w), 1244 (w), 1126 (w), 1071 (w), 1028 (m), 969 (w), 745 (m) cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) 1.13 (2 H, dddd, J 15.5, 8.0, 7.5, 5.0, H8a), 1.45 (4 H, m, H9), 1.73 (2 H, m, H8b), 2.16 (1 H, sept, J 7.5, H7), 2.28 (2 H, d, J 7.5, H6), 3.53 (4 H, s, H1), 7.20 (2 H, br t, J 7.0, H5), 7.29 (4 H, br dd, J 8.0, 7.0, H4), 7.37 (4 H, br d, J 8.0, H3). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 25.0 (C9), 31.0 (C8), 37.8 (C7), 58.6 (C1), 59.3 (C6), 126.6 (C5), 128.0 (C3), 128.8 (C4), 140.1 (C2). MS *m/z* (positive CI, NH$_3$) 210, 280 (MH$^+$), 281. HRMS *m/z* (EI) 279.1991 (M$^{+\bullet}$ C$_{20}$H$_{25}$N requires 279.1987).



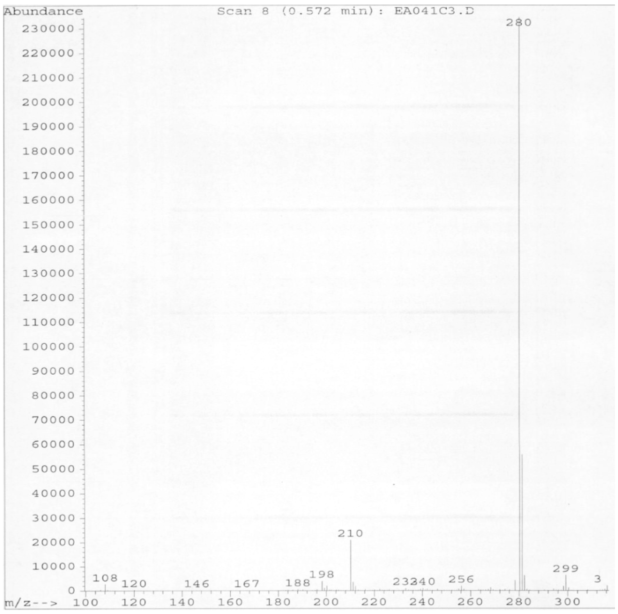
^{1}H NMR spectrum (CDCl$_3$, 400 MHz).



^{13}C NMR and DEPT135 spectra ($CDCl_3$, 100.6 MHz).

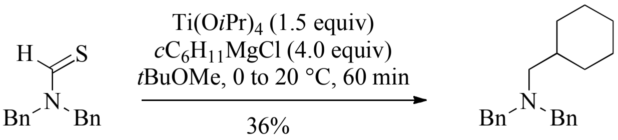


IR spectrum.



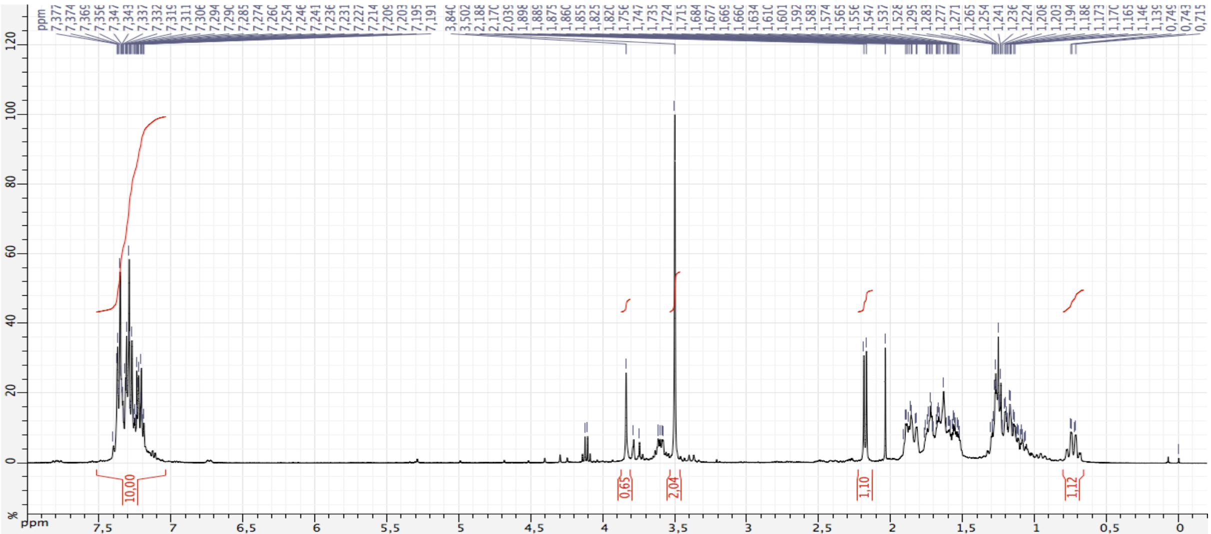
MS spectrum (positive CI, NH_3).

■ Titanium-mediated reaction of **1cS** with cyclohexylmagnesium chloride, in *t*BuOMe.



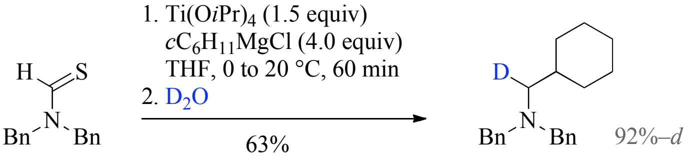
1cS **4c**

The general procedure was applied starting from *N*,*N*-dibenzylmethanethioamide **1cS** (1.00 equiv, 1.00 mmol, 241 mg), using *t*BuOMe as the solvent and cyclohexylmagnesium chloride (1.83 M in Et$_2$O) as the Grignard reagent. A yellow oil (306 mg) that partially crystallised upon standing was obtained. Analysis by ^{1}H NMR spectroscopy revealed that the main components of the crude product were cyclohexyl(*N*,*N*-dibenzylamino)methane **4c** (53%) and *N*,*N*-dibenzylamine (16%), while the starting thioamide was not observed. Recrystallisation of the crude product from EtOH (1.0 mL) afforded pure cyclohexyl(*N*,*N*-dibenzylamino)methane **4c** as colourless crystals (106 mg, 360 µmol, 36%).



^{1}H NMR spectrum of the crude product (CDCl$_3$, 400 MHz).

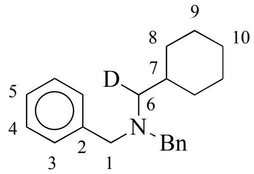
■ Titanium-mediated reaction of **1cS** with cyclohexylmagnesium chloride, in THF (quenching with D$_2$O).



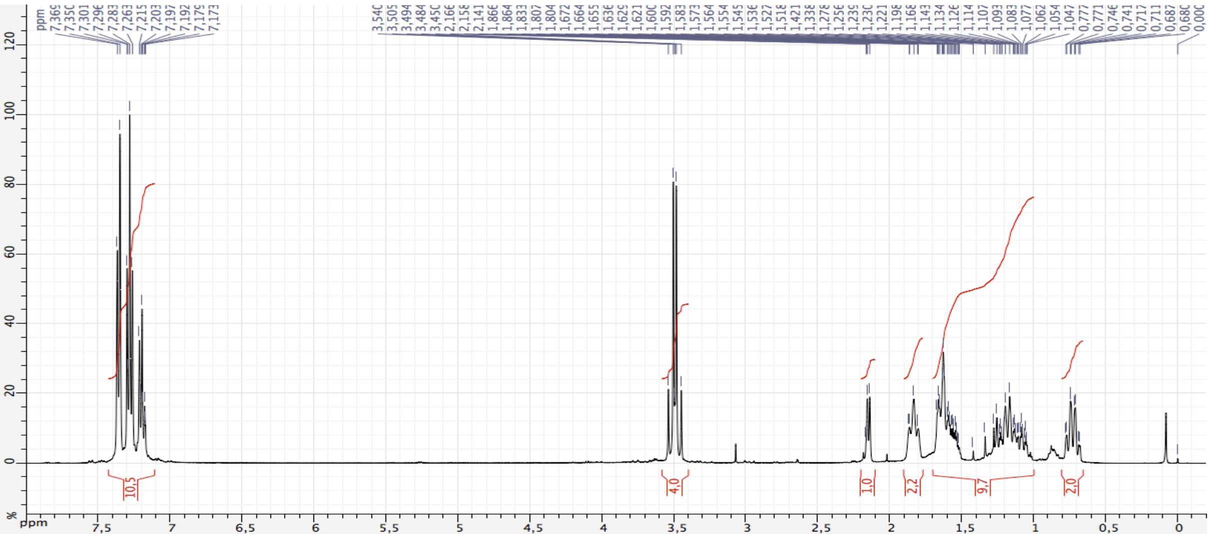
1cS **4c**

Titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 µL) was added to a stirred solution of *N*,*N*-dibenzylmethanethioamide **1cS** (1.00 equiv, 1.00 mmol, 241 mg) in THF (10 mL) at 0 °C. *Cyclo*-hexylmagnesium chloride (1.83 M in Et$_2$O, 4.00 equiv, 4.00 mmol, 2.19 mL) was then introduced dropwise, over 10 min at 0 °C. During the addition, the solution turned yellow, then orange. The cold bath was removed and the reaction mixture was stirred at 20 °C for 60 minutes. D$_2$O (0.5 mL) was then added. After 15 minutes of stirring under N$_2$, the flask was exposed to air and stirring was maintained until near complete decolouration (20 min). The mixture was filtered through a short pad with a layer of sand at the bottom, a layer of Na_2SO_4, and a layer of celite at the top, that was then rinsed with EtOAc. The resulting clear solution was concentrated to afford a mixture of an orange oil and a colourless solid (354 mg). Analysis by ^1H NMR spectroscopy revealed that the main components of the crude product were cyclohexyl(*N*,*N*-dibenzylamino)methane **4c** (64%, with cyclohexyl(*N*,*N*-dibenzylamino)methane–*d* produced in an estimated 53% yield) and *N*,*N*-dibenzylamine (23%), while the starting thioamide was not observed. Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/heptane, gradient from 0 to 20%) yielded pure cyclohexyl(*N*,*N*-dibenzylamino)methane **4c** (92%–*d*, 185 mg, 628 μmol, 63%).

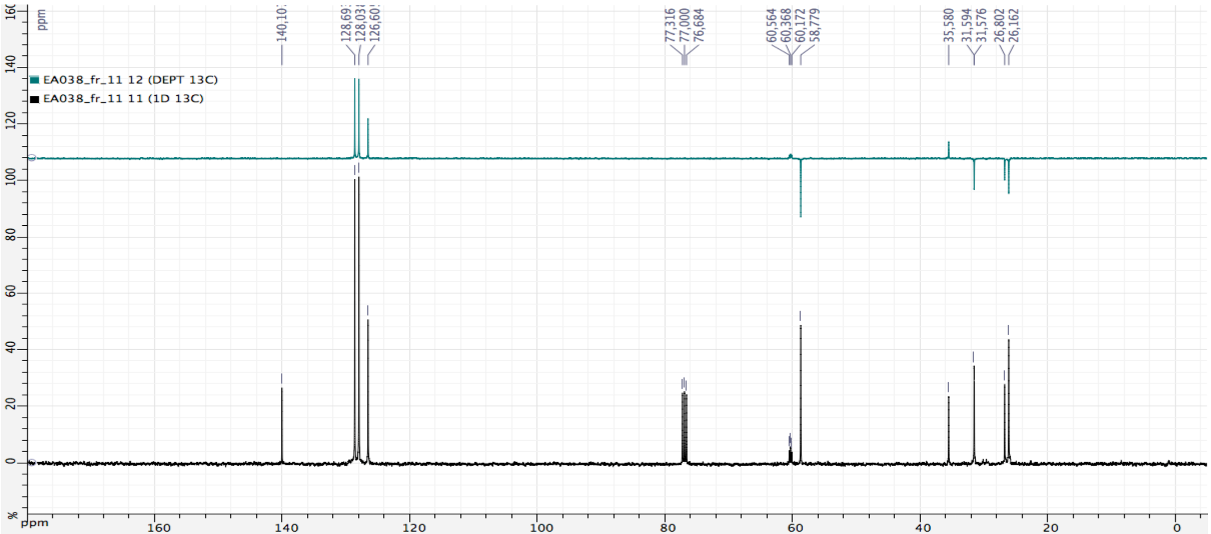
Cyclohexyl(*N*,*N*-dibenzylamino)methane–*d* **4c**–*d*



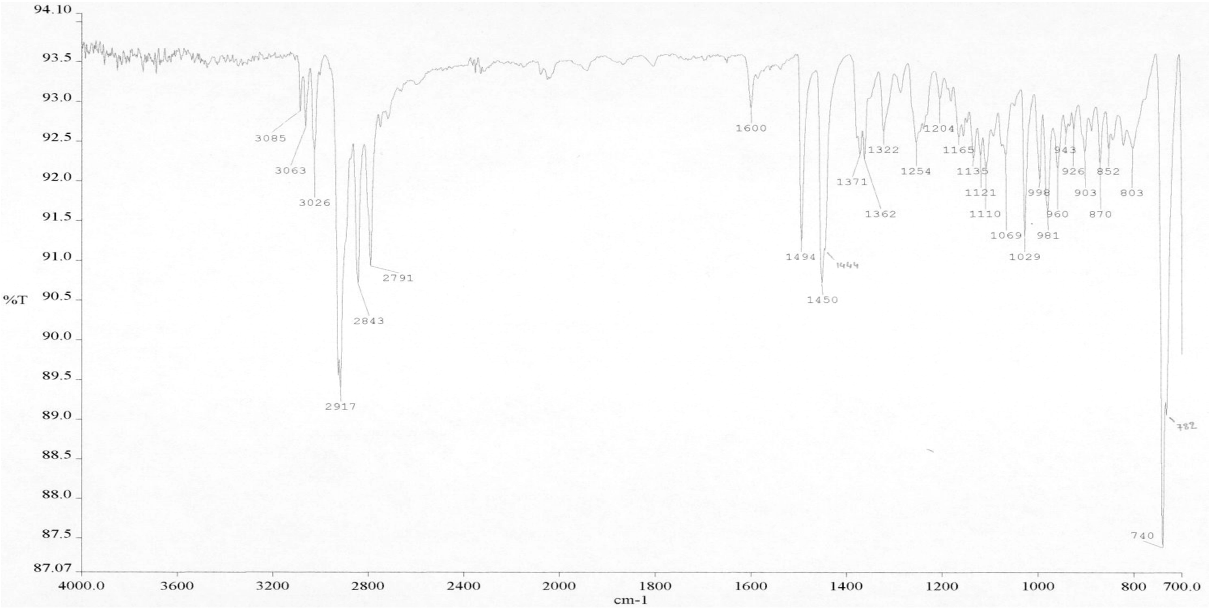
Pale yellow solid. R_f 0.25 [AcOEt/Pet. ether 2%, PMA]. IR (neat) ν 3085 (w), 3063 (w), 3026 (w), 2927 (m), 2917 (m), 2843 (m), 2791 (m), 1494 (m), 1450 (m), 1444 (m), 1371 (w), 1362 (w), 1254 (w), 1110 (w), 998 (w), 981 (m), 740 (s), 732 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) 0.73 (2 H, qd, J 12.0, 2.5, H8a), 1.00–1.26 (3 H, m, H9a, H10a), 1.50–1.70 (4 H, m, H7, H9b, H10b), 1.84 (2 H, br t, J 12.0, H8b), 2.15 (1 H, d, J 7.0, H6), 3.49 (4 H, AB system, δ_A 3.47, δ_B 3.52, J_{AB} 14.0, H1), 7.20 (2 H, br t, J 7.0, H5), 7.28 (4 H, br dd, J 7.5, 7.0, H4), 7.36 (4 H, br d, J 7.5, H3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.2 (C9), 26.8 (C10), 31.6 (C8a), 31.6 (C8b), 35.6 (C7), 58.8 (C1), 60.4 (t, J 19.5, C6), 126.6 (C5), 128.0 (C3), 128.7 (C4), 140.1 (C2). MS *m/z* (positive CI, NH_3) 211, 212, <u>295</u> (MH^+), 296, 297. HRMS *m/z* (EI) 294.2194 ($M^{+\bullet}$ $C_{21}H_{26}DN$ requires 294.2206).



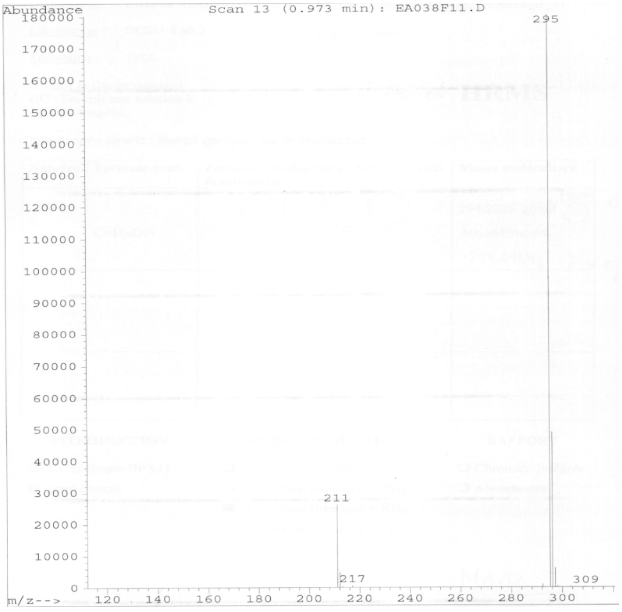
^1H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C NMR spectrum ($CDCl_3$, 100.6 MHz).



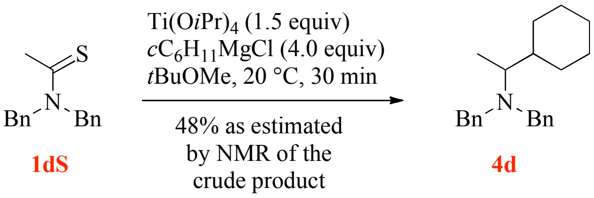
IR spectrum.



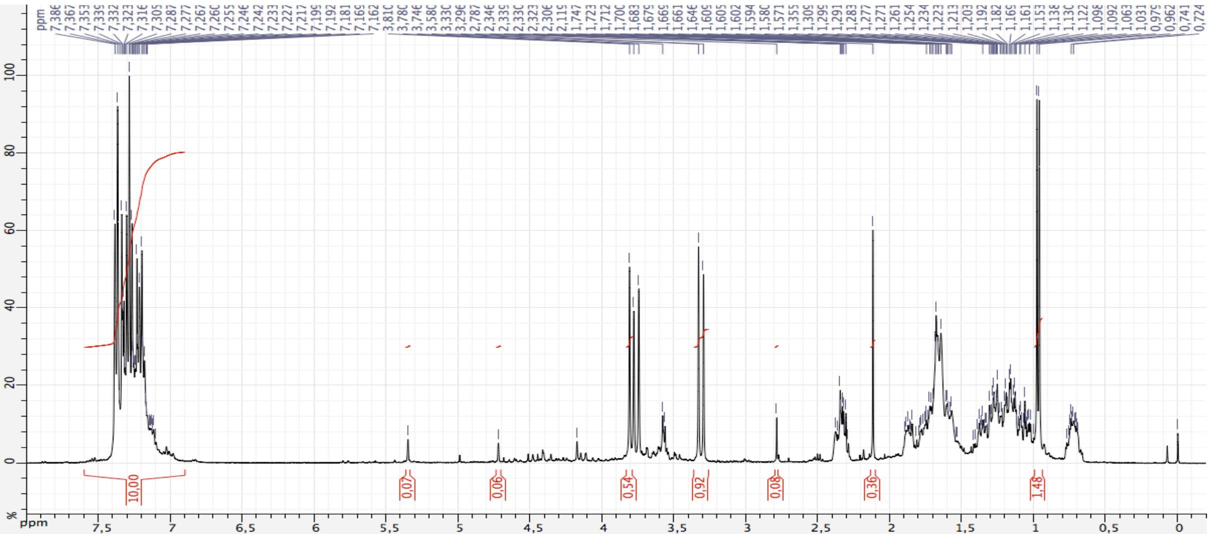
MS spectrum (positive CI, NH_3).

VII. Titanium-mediated reductive alkylation reactions starting from **1dS**

■ Titanium-mediated reaction of **1dS** with cyclohexylmagnesium chloride, in *t*BuOMe.

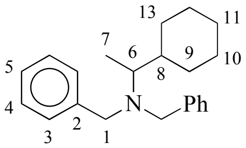


The general procedure was applied starting from *N*,*N*-dibenzylethanethioamide **1dS** (1.00 equiv, 1.00 mmol, 255 mg), using *t*BuOMe (20 mL) as the solvent and cyclohexylmagnesium chloride (1.83 M in Et$_2$O) as the Grignard reagent. An orange oil (205 mg) was obtained. Analysis by ^{1}H NMR spectroscopy revealed that the main components of the crude product were *N*,*N*-dibenzyl-1-cyclohexylethanamine **4d** (48%), cyclohexyl methyl ketone (12%) and *N*,*N*-dibenzylamine (13%). Some starting thioamide (3%) was also detected. Purification by flash column chromatography on silica gel treated with a few drops of Et$_3$N, (EtOAc/petroleum ether, gradient from 0 to 30%) yielded pure *N*,*N*-dibenzyl-1-cyclohexylethanamine **4d** (92 mg, 0.30 mmol, 30%).

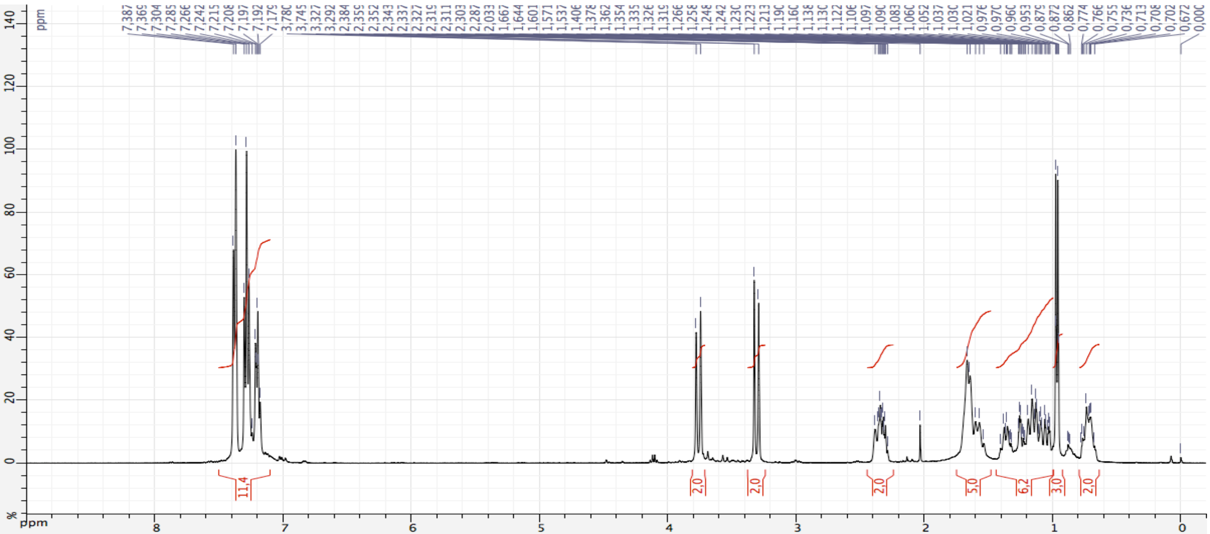


^{1}H NMR spectrum of the crude product (CDCl$_3$, 400 MHz).

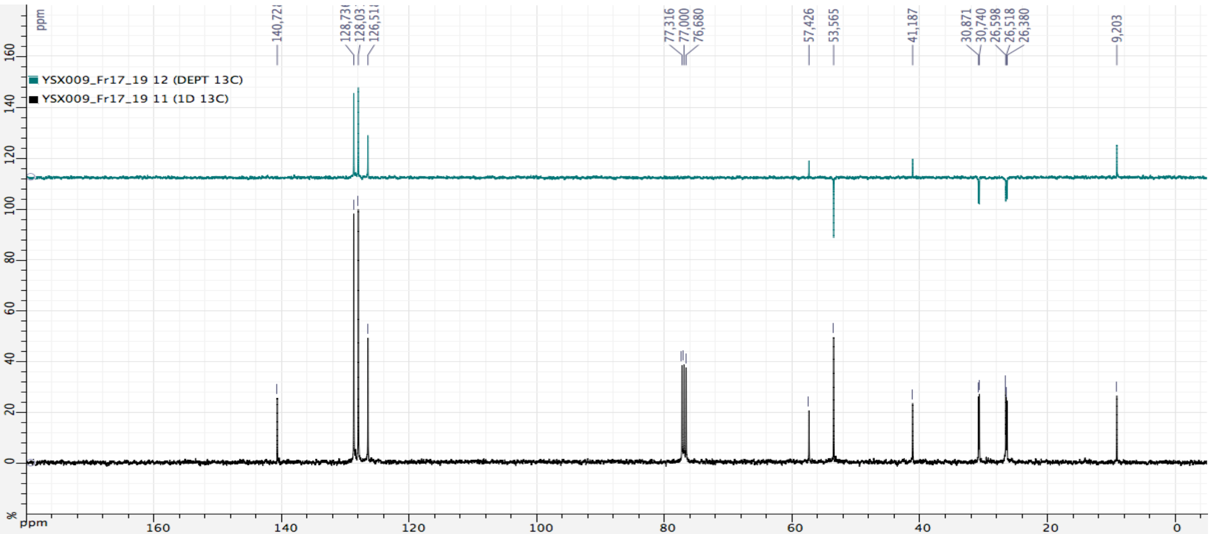
N,*N*-Dibenzyl-1-cyclohexylethanamine **4d**



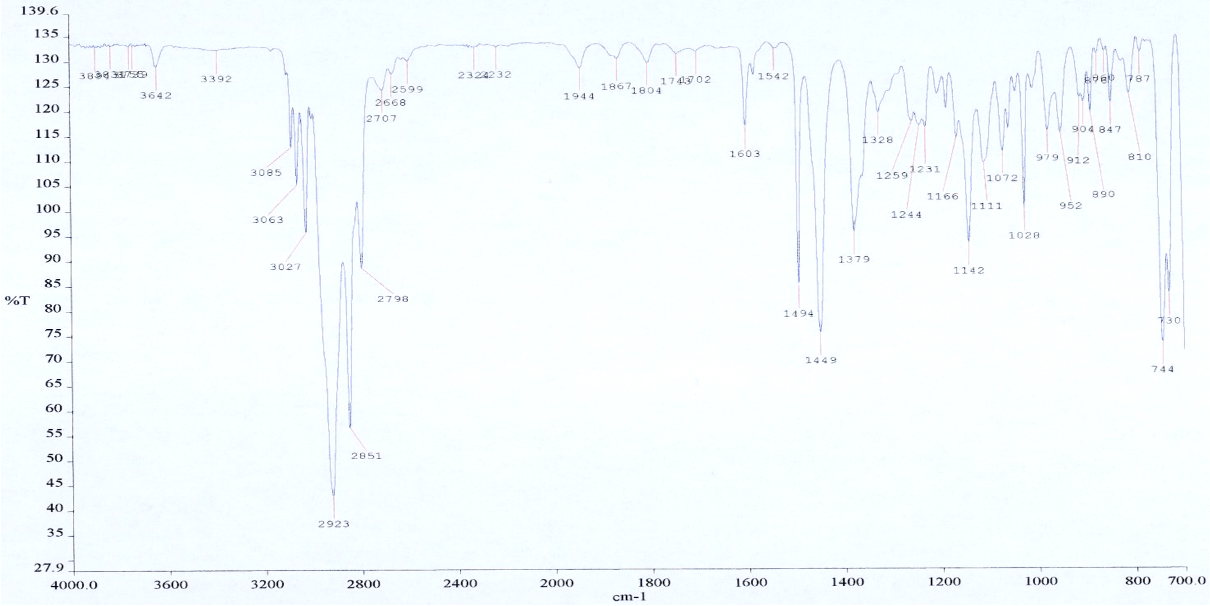
Pale yellow oil. *R*$_f$ 0.6 (AcOEt/Pet. ether 10%, PMA). IR (neat) *ν* 3027, 2923 (s), 2851, 2798, 1603 (w), 1494 (m), 1449 (m), 1379, 1142, 1111, 1028, 744 (m), 730 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) 0.72 (2 H, m, H9a, H13a), 0.86–1.75 (8 H, m, H9b, H10–H12, H13b), 0.97 (3 H, d, J 6.5, H7), 2.24–2.44 (2 H, m, H6, H8), 3.54 (4 H, AB system, δ_A 3.31, δ_B 3.76, J_{AB} 14.0, H1), 7.20 (2 H, br t, J 7.0, H5), 7.28 (4 H, dd, J 7.5, 7.0, H4), 7.38 (4 H, br d, J 7.5, H3). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 9.2 (C7), 26.4, 26.5, 26.6 (C10–C12), 30.7, 30.9 (C9 and C13), 41.2 (C8), 53.6 (C1), 57.4 (C6), 126.5 (C5), 128.0, 128.7 (C3 and C4), 140.7 (C2). MS *m/z* (positive CI, NH_3) 224, <u>308</u> (MH^+), 309. HRMS *m/z* (EI) 307.2292 ($M^{+\bullet}$ $C_{22}H_{29}N$ requires 307.2300).



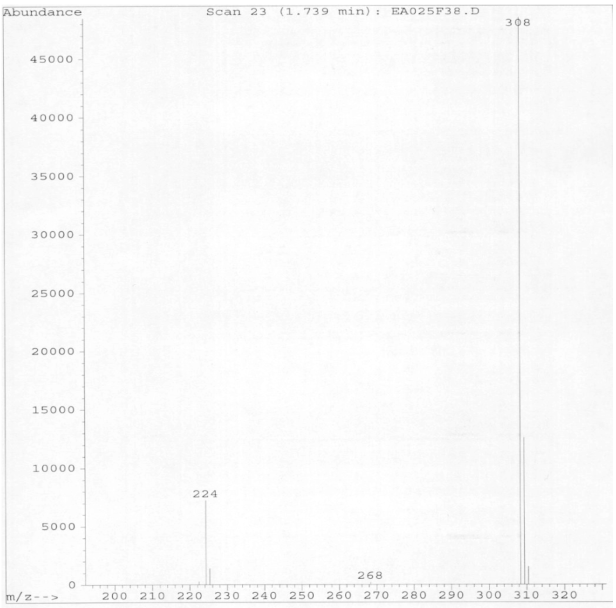
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).

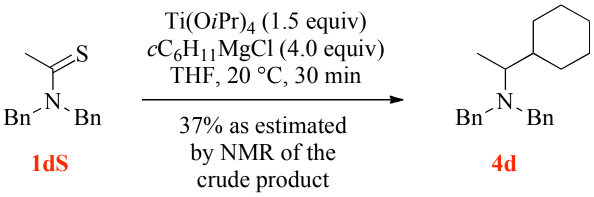


IR spectrum.

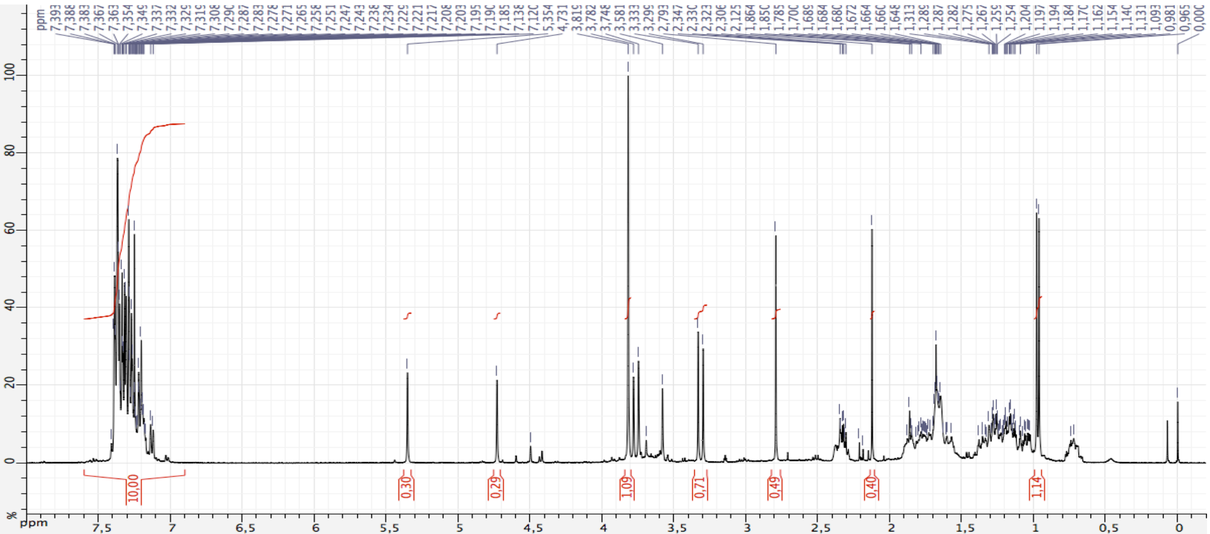


MS spectrum (positive CI, NH_3).

■ Titanium-mediated reaction of **1dS** with cyclohexylmagnesium chloride, in THF.

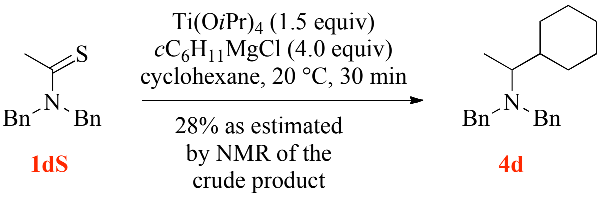


The general procedure was applied starting from *N*,*N*-dibenzylethanethioamide **1dS** (1.00 equiv, 1.00 mmol, 255 mg), using THF (20 mL) as the solvent and cyclohexylmagnesium chloride (1.85 M in Et_2O) as the Grignard reagent. An orange oil (291 mg) was obtained. Analysis by ^{1}H NMR spectroscopy revealed that the main components of the crude product were *N*,*N*-dibenzyl-1-cyclohexylethanamine **4d** (37%), *N*,*N*-dibenzylamine (27%), cyclohexyl methyl ketone (13%) and starting thioamide **1dS** (15%).

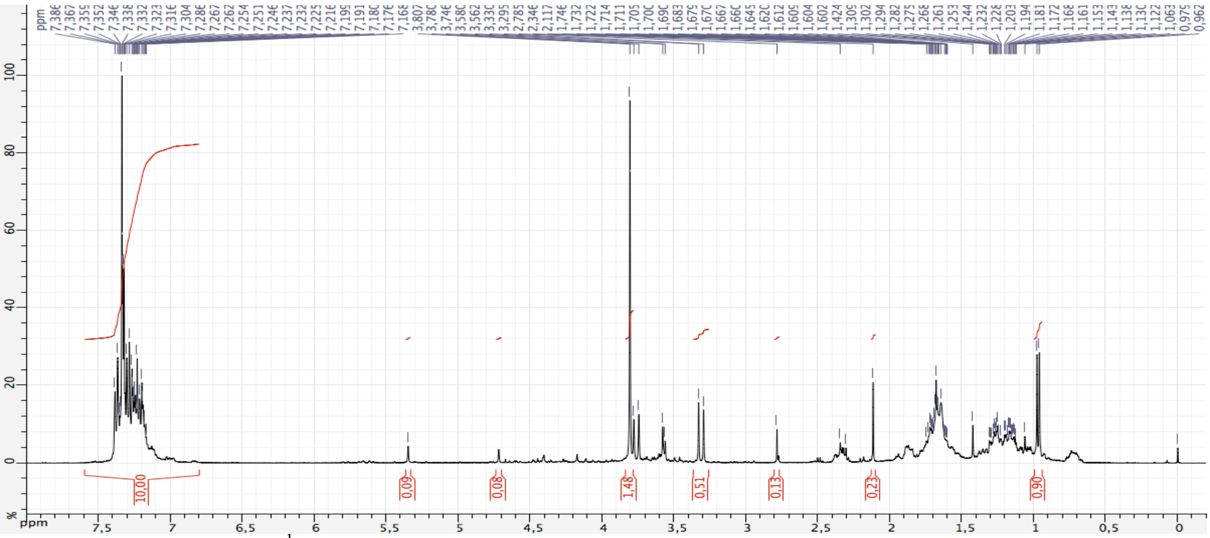


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

■ Titanium-mediated reaction of **1dS** with cyclohexylmagnesium chloride, in cyclohexane.



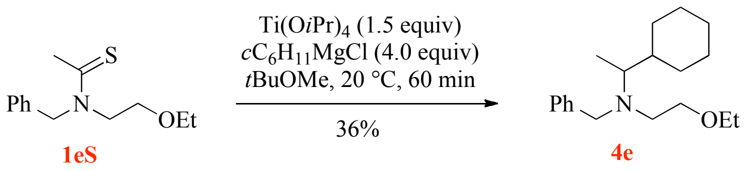
The general procedure was applied starting from *N*,*N*-dibenzylethanethioamide **1dS** (1.00 equiv, 1.00 mmol, 255 mg), using cyclohexane (20 mL) as the solvent and cyclohexylmagnesium chloride (1.83 M in Et_2O) as the Grignard reagent. An orange oil (285 mg) was obtained. Analysis by ^{1}H NMR spectroscopy revealed that the main components of the crude product were *N*,*N*-dibenzyl-1-cyclohexylethanamine **4d** (28%) and *N*,*N*-dibenzylamine (37%). Some starting thioamide **1dS** (4%) was also detected.



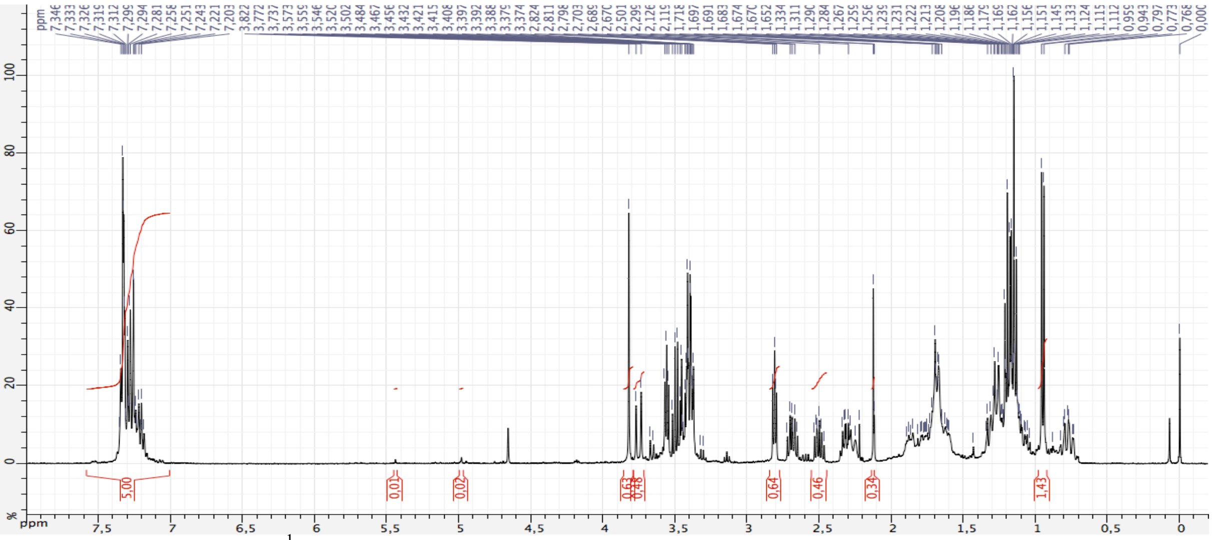
^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

VIII. Titanium-mediated reductive alkylation reactions starting from 1eS

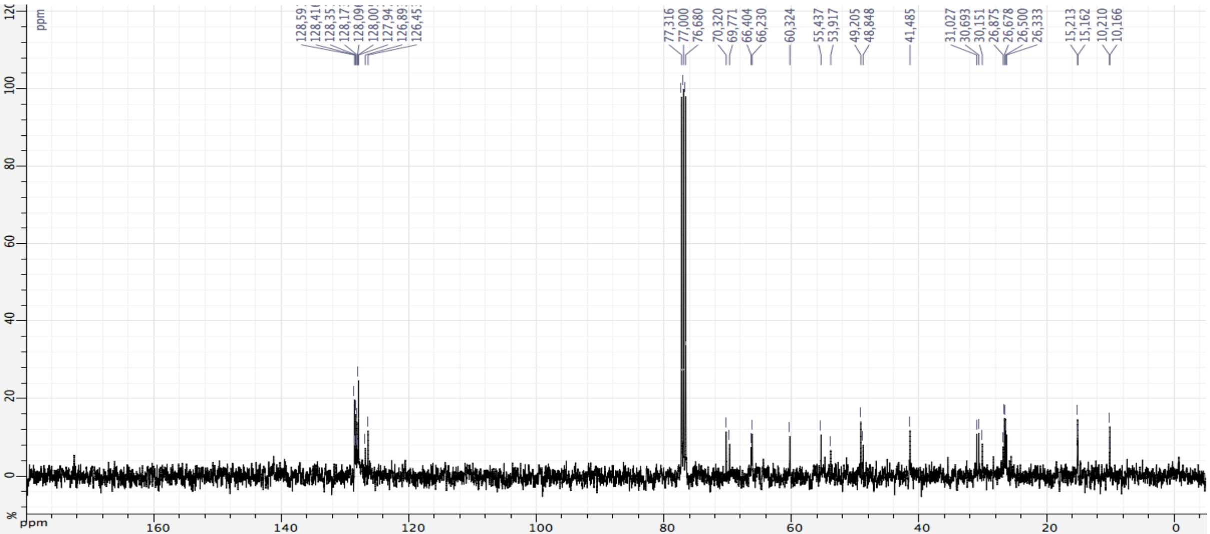
■ Titanium-mediated reaction of **1eS** with cyclohexylmagnesium chloride, in *t*BuOMe.



The general procedure was applied starting from *N*-benzyl-*N*-(2-ethoxyethyl)ethanethioamide **1eS** (1.00 equiv, 1.00 mmol, 237 mg), using *t*BuOMe (20 mL) as the solvent and cyclohexylmagnesium chloride (2.03 M in Et_2O) as the Grignard reagent. A yellow oil (237 mg) was obtained. Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopy gave an estimation of the yield of the expected α-cyclohexylamine product **4e** (47%), the secondary amine by-product (32%) and cyclohexyl methyl ketone (11%). Purification by flash column chromatography on silica gel treated with a few drops of Et_3N, (EtOAc/petroleum ether, gradient from 0 to 20%) yielded pure *N*-benzyl-1-cyclohexyl-*N*-(2-ethoxyethyl)ethanamine **4e** (104 mg, 359 µmol, 36%).

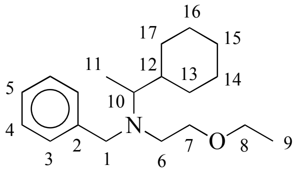


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

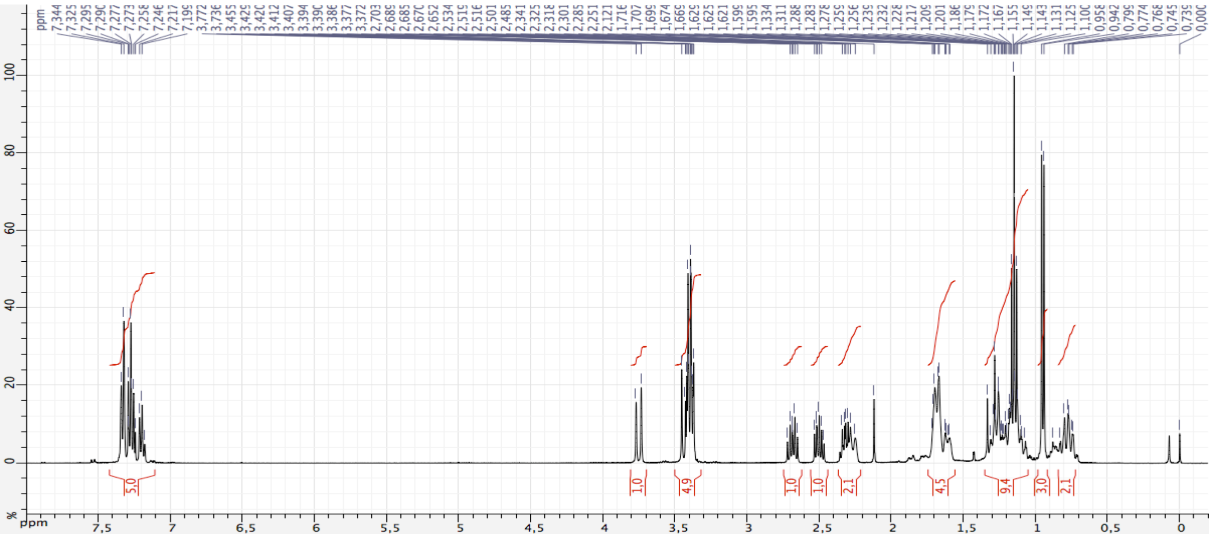


^{13}C NMR spectrum of the crude product ($CDCl_3$, 100.6 MHz).

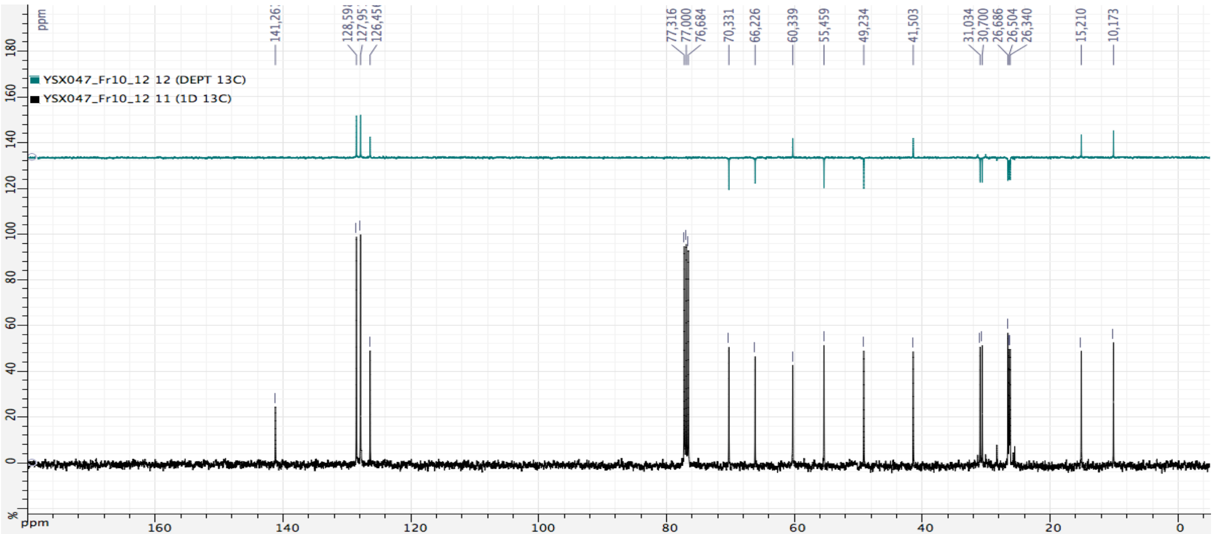
N-Benzyl-1-cyclohexyl-*N*-(2-ethoxyethyl)ethanamine **4e**



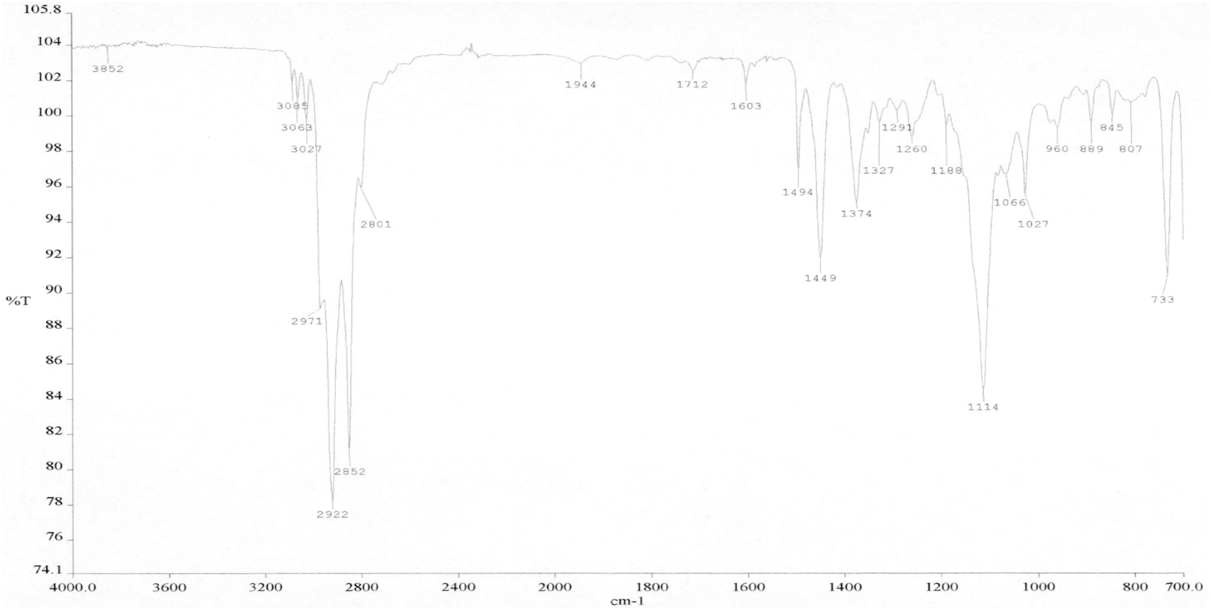
Colourless oil. R_f 0.25 (AcOEt/Pet. ether 5%, PMA). IR (neat) ν 2971 (m), 2922 (s), 2852 (s), 2801, 1494 (w), 1449 (m), 1374 (m), 1114 (m), 1066 (w), 1027 (m), 733 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.77 (2 H, m, H13a, H17a), 0.95 (3 H, d, J 6.5, H11), 1.05–1.35 (5 H, m, H13b, H14a, H15a, H16a, H17b), 1.15 (3 H, t, J 7.0, H9), 1.56–1.74 (3 H, m, H14b, H15b, H16b), 2.27 (1 H, m, H12), 2.32 (1 H, dq, J 9.5, 6.5, H10), 2.59 (2 H, AB part of an ABXY system, δ_A 2.50, δ_B 2.69, J_{AB} 13.5, J_{AX} 7.0, J_{AY} 6.0, J_{BX} 7.0, J_{BY} 7.5, H6), 3.36–3.42 (2 H, m, H7), 3.40 (2 H, q, J 7.0, H8), 3.60 (2 H, AB system, δ_A 3.44, δ_B 3.75, J_{AB} 14.0, H1), 7.20 (1 H, br t, J 7.0, H5), 7.28 (2 H, dd, J 7.5, 7.0, H4), 7.33 (2 H, br d, J 7.5, H3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 10.2 (C11), 15.2 (C9), 26.3, 26.5, 26.7 (C14–C16), 30.7, 31.0 (C13, C17), 41.5 (C12), 49.2 (C6), 55.5 (C1), 60.3 (C10), 66.2 (C8), 70.3 (C7), 126.5 (C5), 128.0, 128.6 (C3, C4), 141.3 (C2). MS *m/z* (positive CI, NH_3) 206, 230, <u>290</u> (MH^+), 291. HRMS *m/z* (EI) 289.2412 ($M^{+\bullet}$ $C_{19}H_{31}NO$ requires 289.2406).



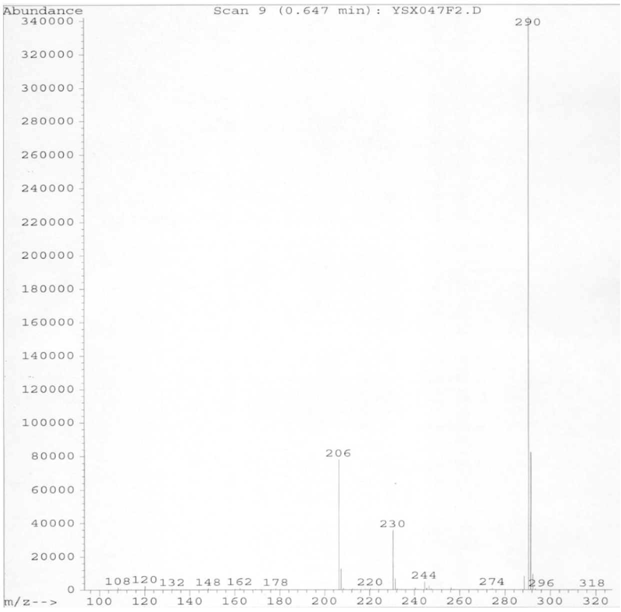
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).



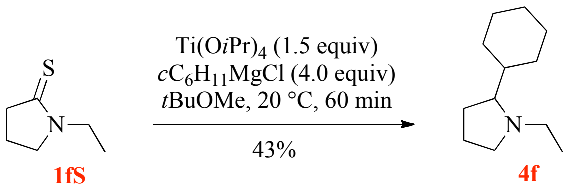
IR spectrum.



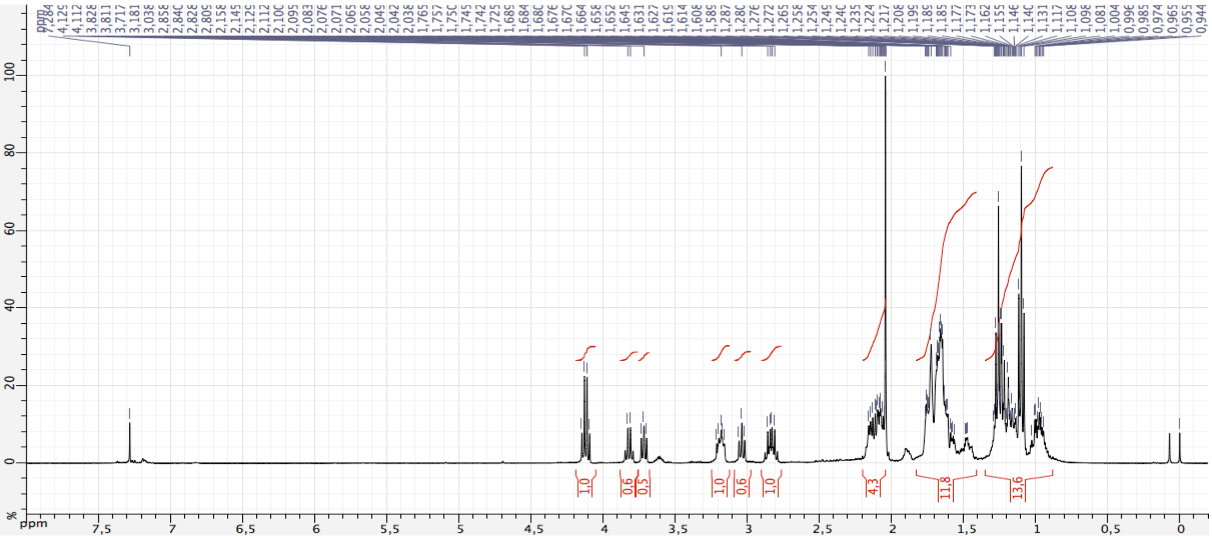
MS spectrum (positive CI, NH_3).

IX. Titanium-mediated reductive alkylation reactions starting from 1fS

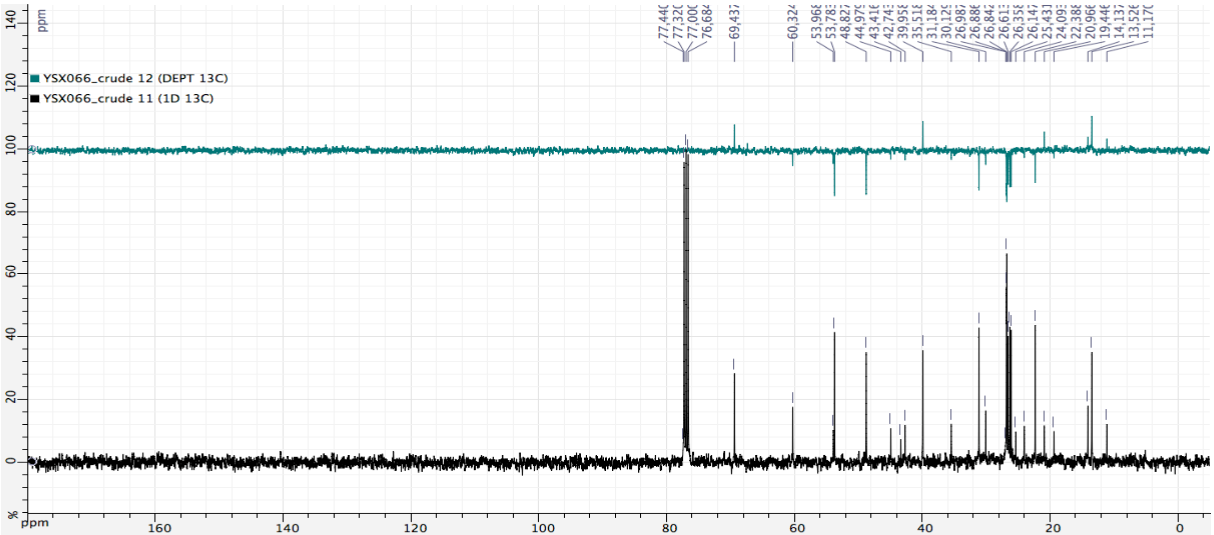
■ Titanium-mediated reaction of **1fS** with cyclohexylmagnesium chloride, in *t*BuOMe.



The general procedure was applied starting from 1-ethylpyrrolidine-2-thione **1fS** (1.00 equiv, 1.00 mmol, 129 mg), using *t*BuOMe (20 mL) as the solvent and cyclohexylmagnesium chloride (2.03 M in Et$_2$O) as the Grignard reagent. A bright yellow oil (162 mg) was obtained. Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopy gave an estimation of the yield of the expected α-cyclohexylamine product **4f** (62%). Remaining starting thioamide **1fS** (19%) was also observed. Purification by flash column chromatography on silica gel treated with a few drops of Et$_3$N, (EtOAc/petroleum ether, gradient from 5 to 30%) yielded pure 2-cyclohexyl-1-ethylpyrrolidine **4f** (78 mg, 430 μmol, 43%).

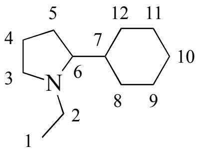


^{1}H NMR spectrum of the crude product (CDCl$_3$, 400 MHz).

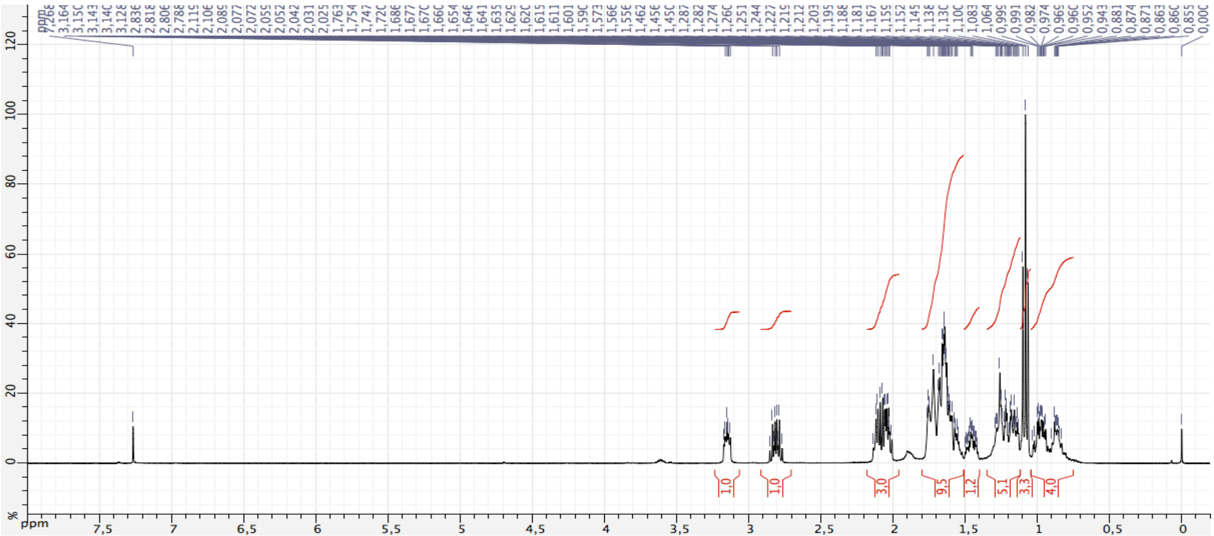


^{13}C NMR and DEPT135 spectra of the crude product ($CDCl_3$, 100.6 MHz).

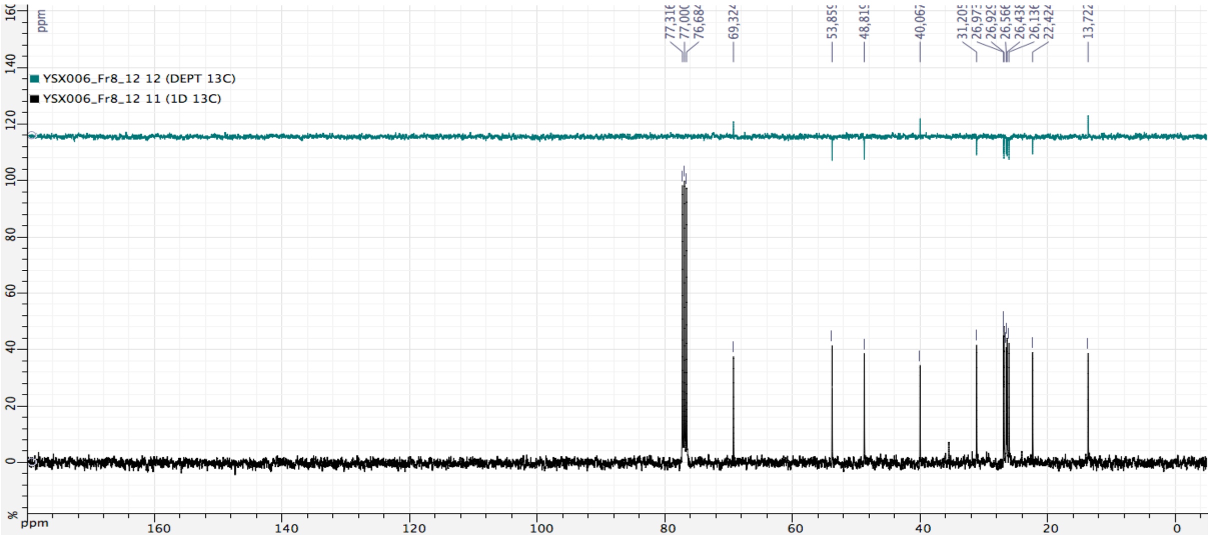
2-Cyclohexyl-1-ethylpyrrolidine **4f**



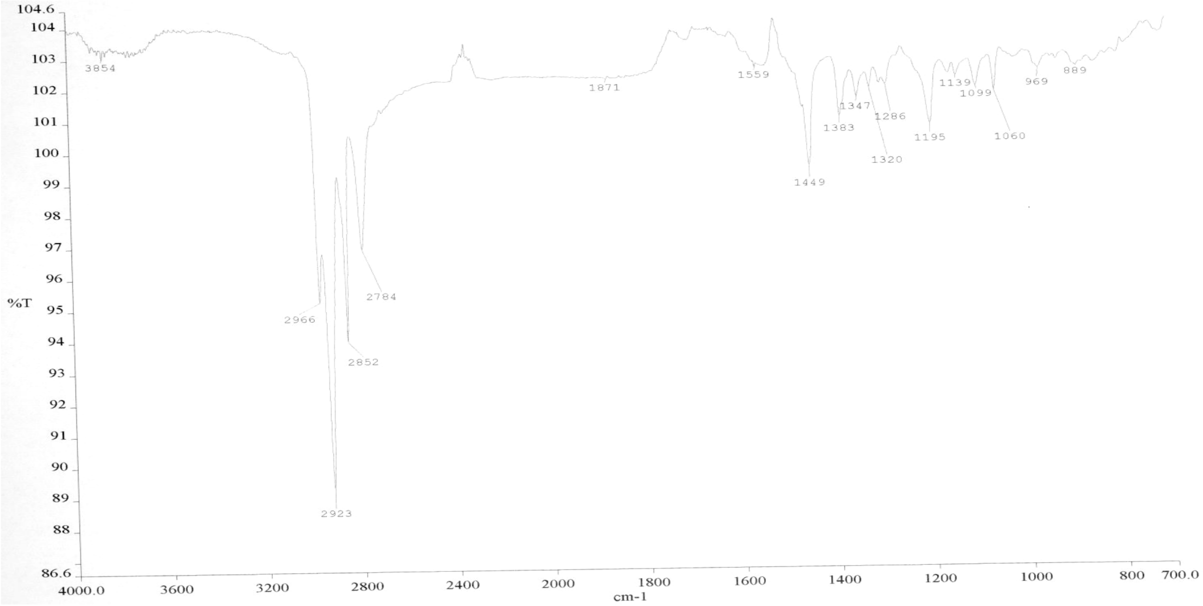
Colourless oil. *R*$_f$ 0 (AcOEt/Pet. ether 20%, $KMnO_4$). IR (neat) *ν* 2966 (m), 2923 (s), 2852 (m), 2784 (m), 1449 (m), 1383 (w), 1347 (w), 1195 (w), 1099 (w), 1060 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.80–1.80 (15 H, m, H4, H5, H7–H12), 1.08 (3 H, dd, J 7.5, 7.0, H1), 1.99–2.16 (3 H, m, H3, H6), 2.81 (1 H, dq, J 12.0, 7.5, H2a), 3.15 (1 H, m, H2b). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 13.7 (C1), 22.4 (C4), 26.1, 26.4, 26.6 (C9–C11), 26.9, 27.0 (C8, C12), 31.2 (C5), 40.1 (C7), 48.8 (C2), 53.9 (C3), 69.3 (C6). MS *m/z* (positive CI, NH_3) 98, 182 (MH^+), 183. HRMS *m/z* (EI) 98.0976 ($[M–cC_6H_{11}^{\bullet}]^+$ $C_6H_{12}N$ requires 98.0970).



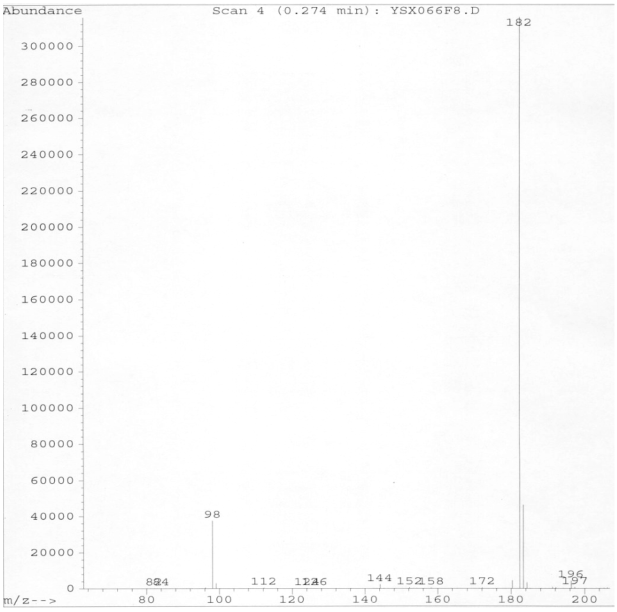
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).



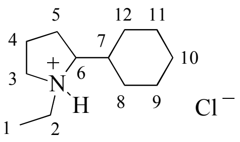
IR spectrum.



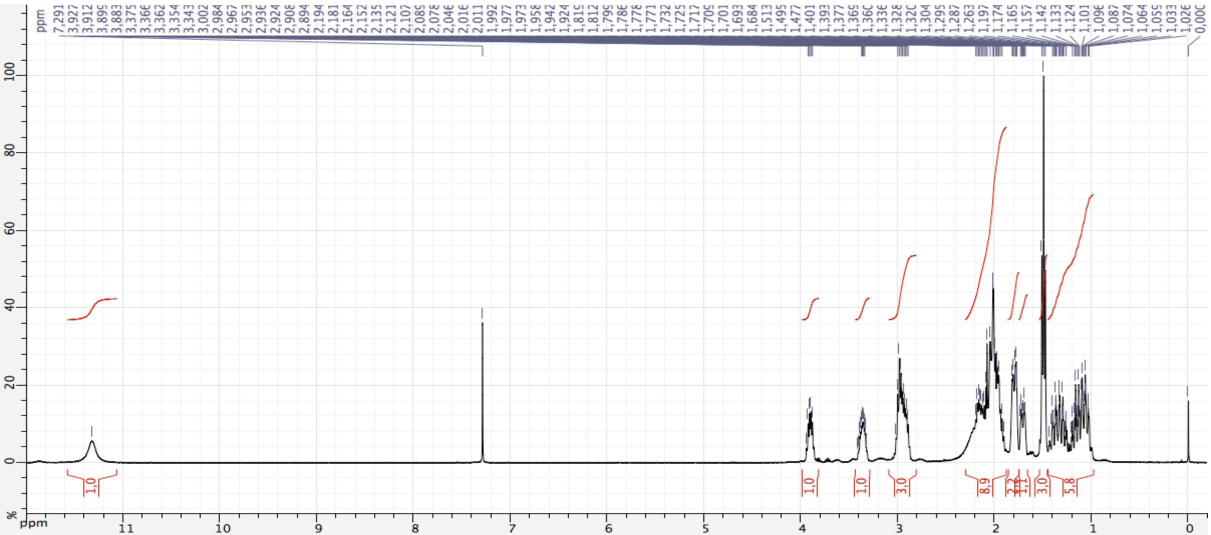
MS spectrum (positive CI, NH_3).

Compound **4f** was also characterised as the hydrochloride salt:

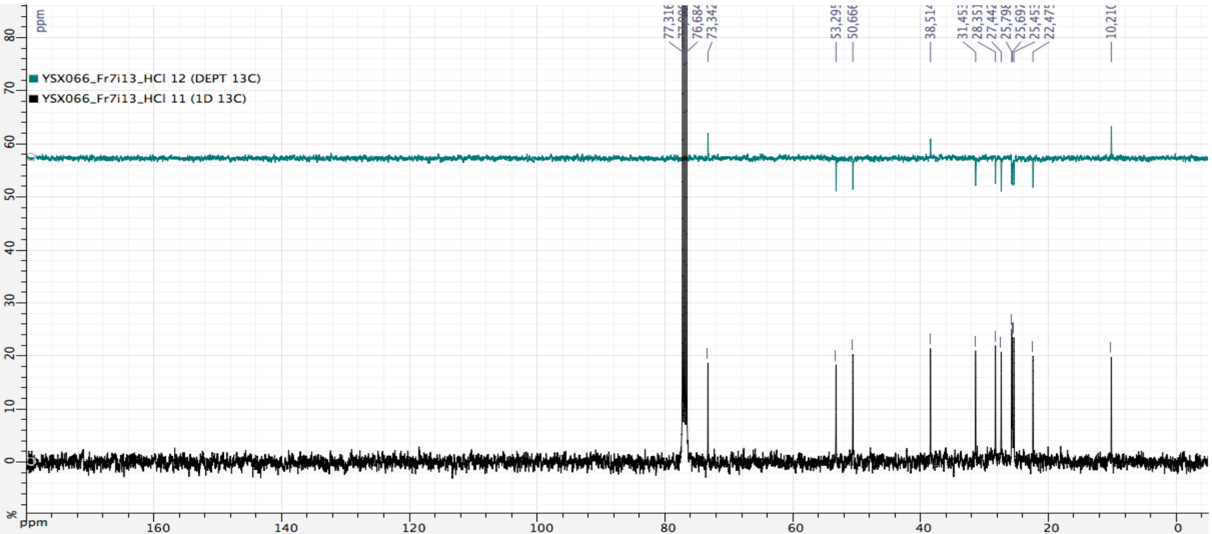
2-Cyclohexyl-1-ethylpyrrolidin-1-ium chloride **4f**.HCl



^{1}H NMR (CDCl$_3$, 400 MHz) 0.98–1.45 (5 H, m, cyclohexyl protons), 1.49 (3 H, dd, J 7.5, 6.5, H1), 1.71 (1 H, m), 1.80 (2 H, m), 1.88–2.30 (7 H, m) (H4, H5, cyclohexyl protons), 2.84–3.06 (3 H, m, H3, H6), 3.36 (1 H, dq, J 12.0, 7.5, 3.2, H2a), 3.91 (1 H, dq, J 12.0, 6.5, H2b), 11.32 (1 H, br s, NH). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 10.2 (C1), 22.5 (C4), 25.5, 25.7, 25.8 (C9–C11), 27.4, 28.4 (C8, C12), 31.5 (C5), 38.5 (C7), 50.7 (C2), 53.3 (C3), 73.3 (C6).



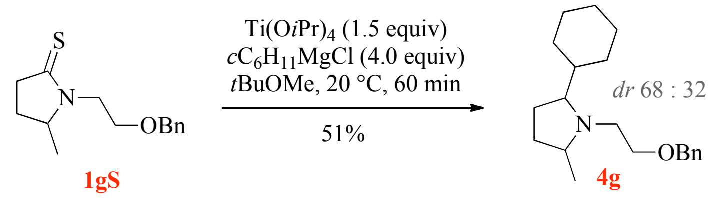
^{1}H NMR spectrum (CDCl$_3$, 400 MHz).



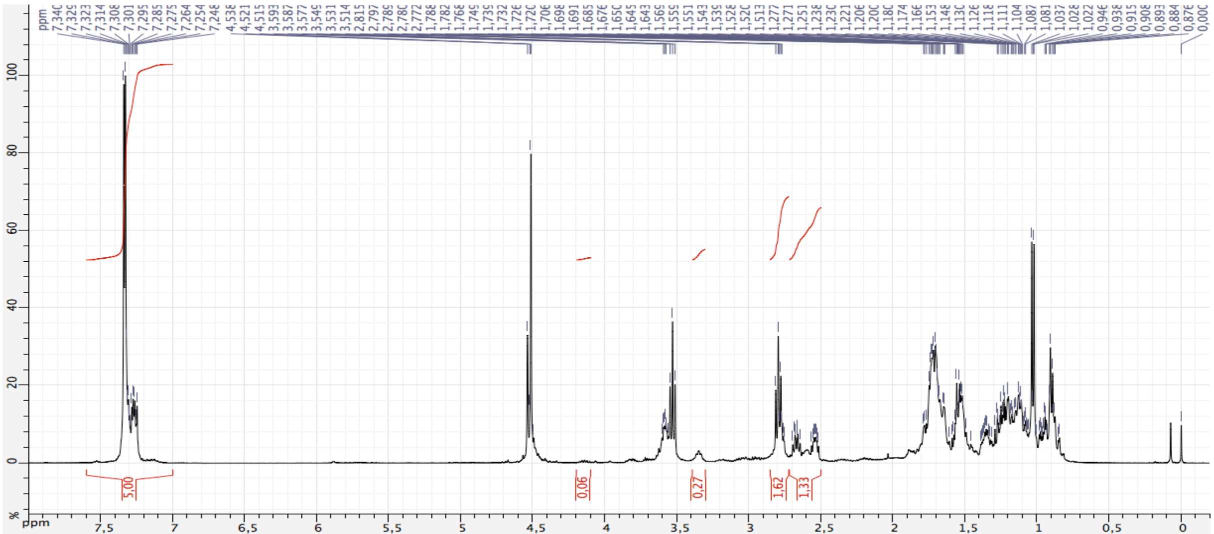
^{13}C and DEPT 135 NMR spectra (CDCl$_3$, 100.6 MHz).

X. Titanium-mediated reductive alkylation reactions starting from 1gS

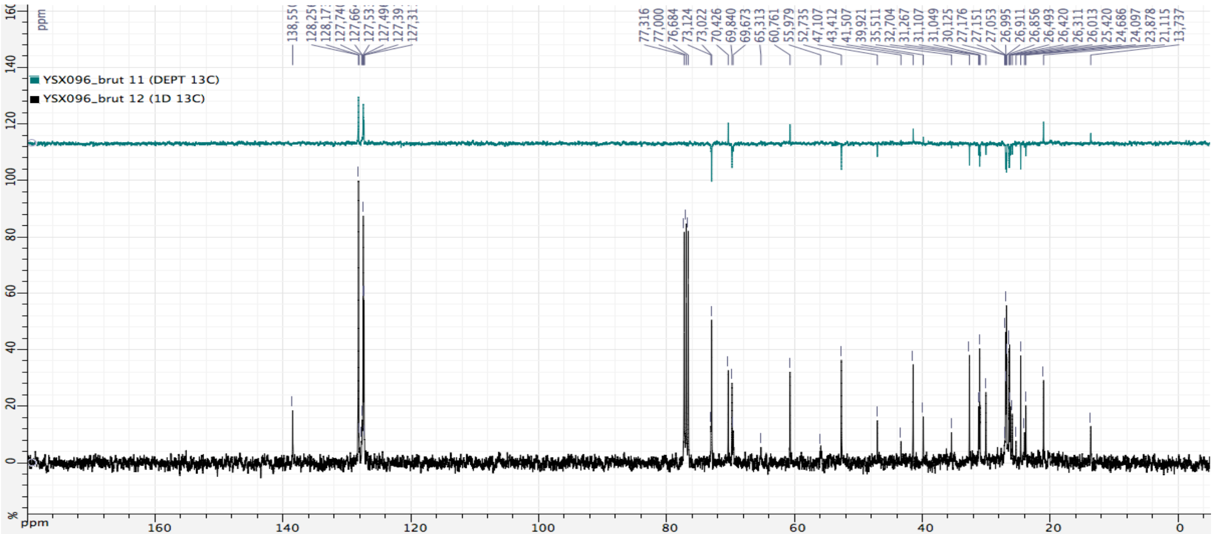
- Titanium-mediated reaction of **1gS** with cyclohexylmagnesium chloride, in *t*BuOMe.



The general procedure was applied starting from 1-(2-benzyloxyethyl)-5-methyl-pyrrolidin-2-thione **1gS** (1.00 equiv, 1.00 mmol, 249 mg), using *t*BuOMe (20 mL) as the solvent and cyclohexylmagnesium chloride (1.91 M in Et_2O) as the Grignard reagent. A yellow oil (226 mg) was obtained. Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopy gave an estimation of the yield of the expected α-cyclohexylamine product (81%; diastereoisomeric ratio 68 : 32). Remaining starting thioamide (6%) was also observed. Purification by flash column chromatography on silica gel, (EtOAc/pet. ether, gradient from 10 to 100%) yielded pure major diastereoisomer of 1-(2-benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine (98 mg, 375 μmol, 37%), a mixture of both diastereoisomers of 1-(2-benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine (16 mg, 61 μmol, 6%) and pure minor diastereoisomer of 1-(2-benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine (43 mg, 164 μmol, 16%).

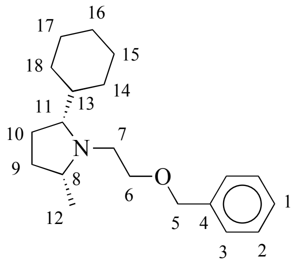


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

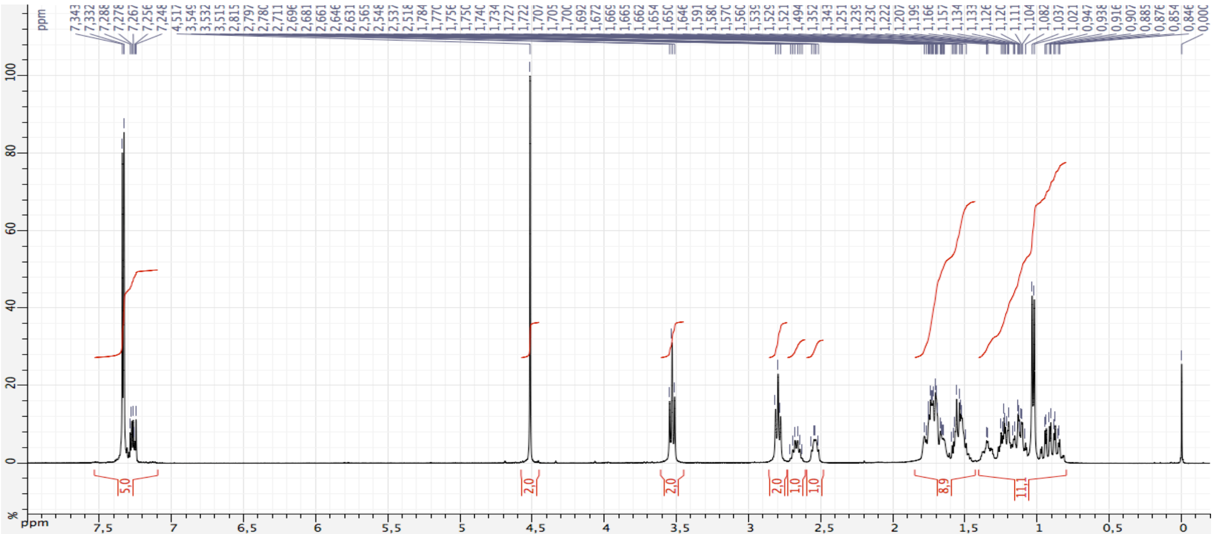


^{13}C NMR and DEPT135 spectra of the crude product (CDCl$_3$, 100.6 MHz).

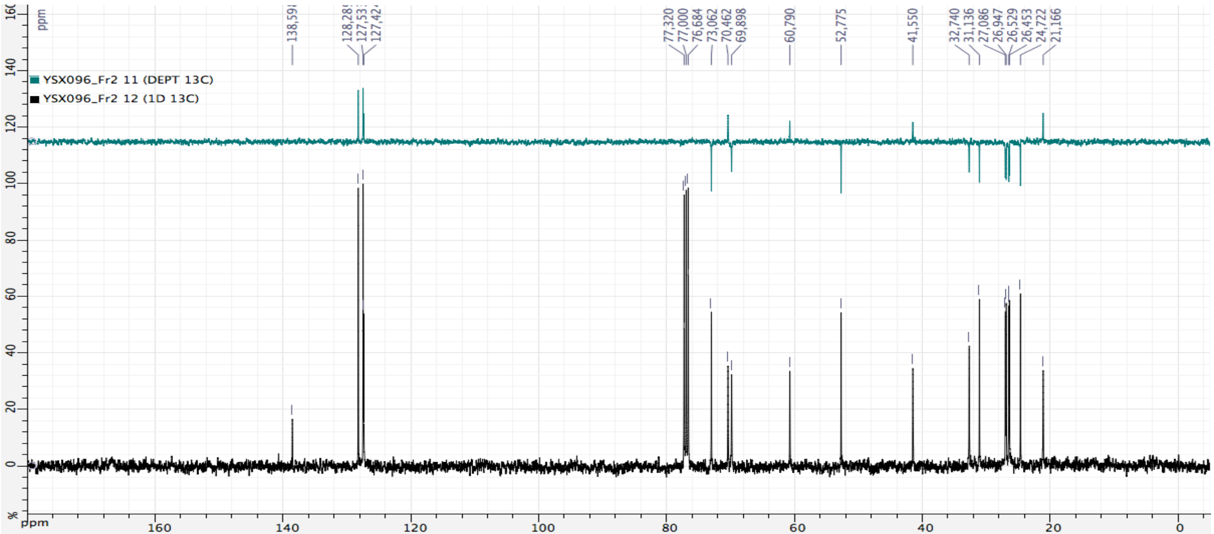
(2*R**,5*R**)-1-(2-Benzyloxyethyl)-2-cyclohexyl-5-methylpyrrolidine (major diastereoisomer) *cis*–**4g**



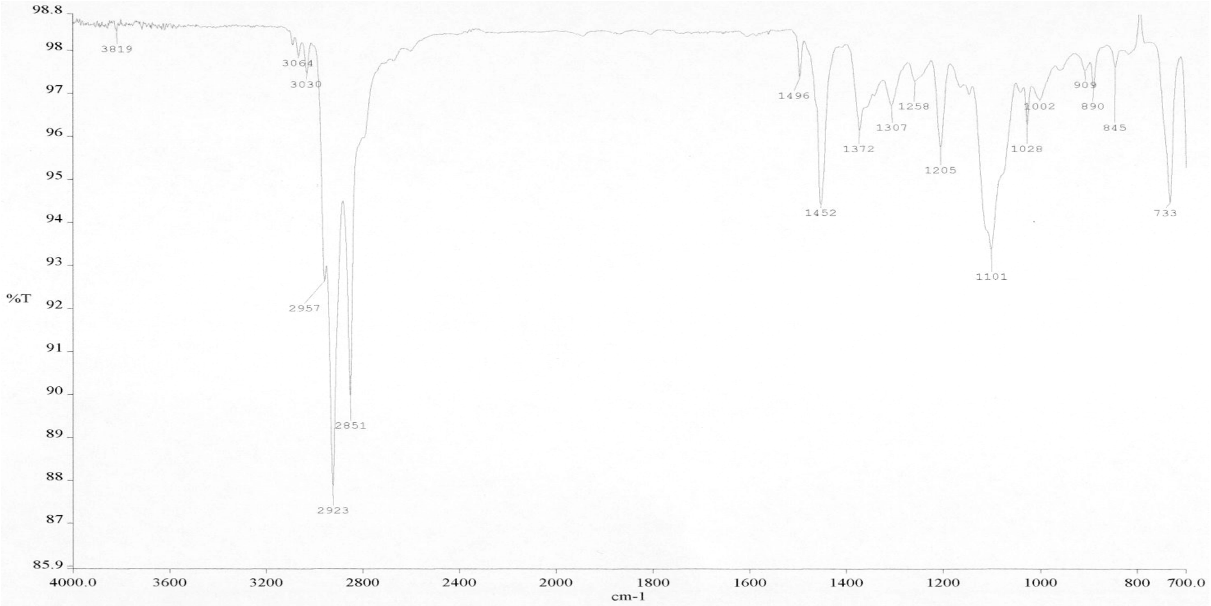
Yellow oil. R_f around 0.3; depends on the concentration (not UV-active, AcOEt/Pet. ether 50%, PMA). IR (neat) ν 2957 (m), 2923 (s), 2851 (s), 1452 (m), 1372 (w), 1307 (w), 1205 (w), 1101 (m), 1028 (w), 733 (m) cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) 0.80–1.82 (15 H, m, H9, H10, H13–H18), 1.03 (3 H, d, J 6.0, H12), 2.54 (1 H, ddd, J 8.0, 6.5, 4.0, H11), 2.67 (1 H, ddq, J 7.5, 6.5, 6.0, H8), 2.80 (2 H, t, J 7.0, H7), 3.53 (2 H, t, J 7.0, H6), 4.52 (2 H, s, H5), 7.23–7.38 (5 H, m, H1–H3). ^{13}C NMR (CDCl$_3$, 100.6 MHz) 21.2 (C12), 24.7 (C16), 26.5, 26.5 (C15, C17), 26.9, 27.1 (C14, C18), 31.1, 32.7 (C9, C10), 41.5 (C13), 52.8 (C7), 60.8 (C8), 69.9 (C6), 70.5 (C11), 73.1 (C5), 127.4 (C1), 127.5 (C3), 128.3 (C2), 138.6 (C4). MS *m/z* (positive CI, NH$_3$) 180, 218, <u>302</u> (MH$^+$), 303. HRMS *m/z* (EI) 301.2400 (M$^{+\bullet}$ C$_{20}$H$_{31}$NO requires 301.2406).



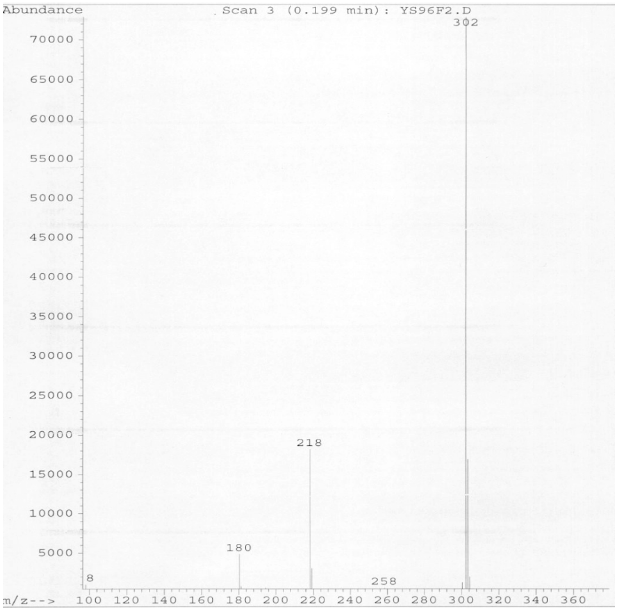
^{1}H NMR spectrum (CDCl$_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).

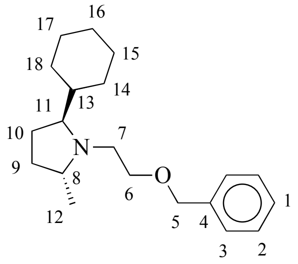


IR spectrum.

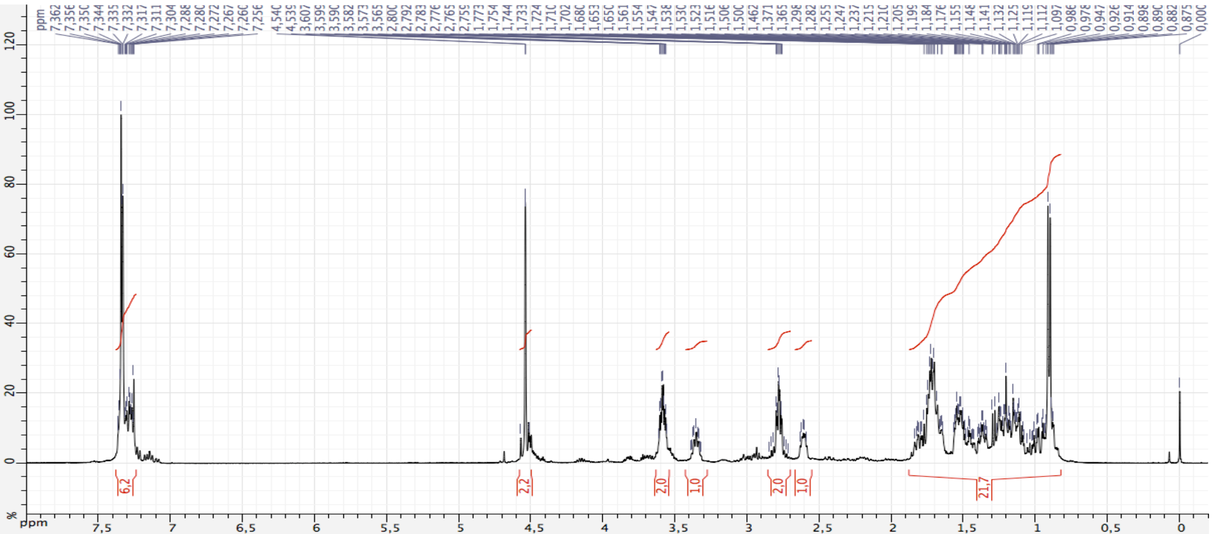


MS spectrum (positive CI, NH_3).

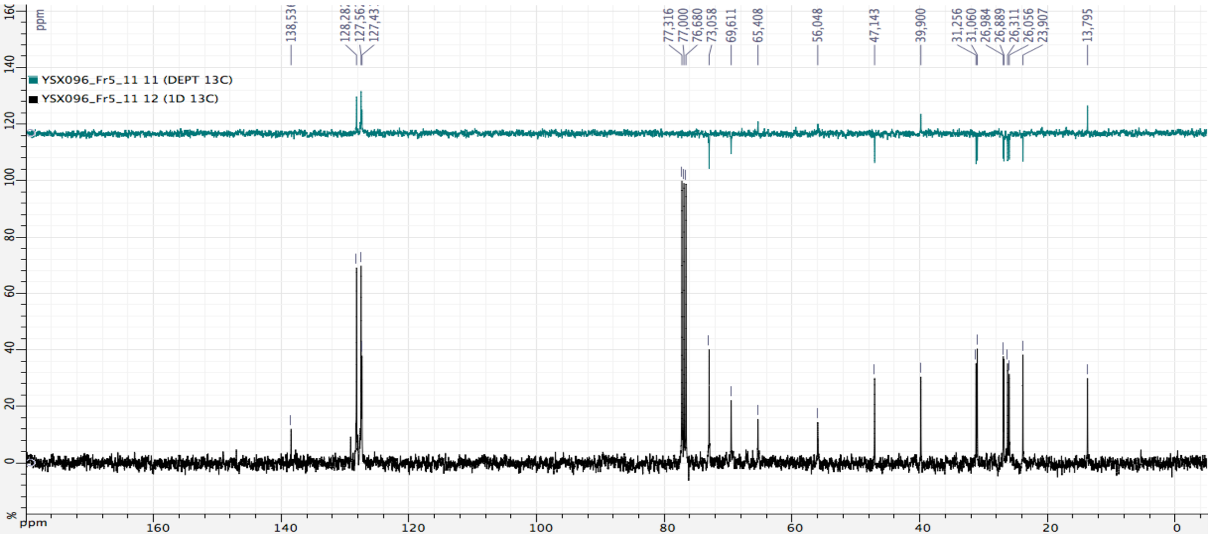
(2*S**,5*R**)-1-(2-Benzyloxyethyl)-2-cyclohexyl-5-methylpyrrolidine (minor diastereoisomer) *trans*–**4g**



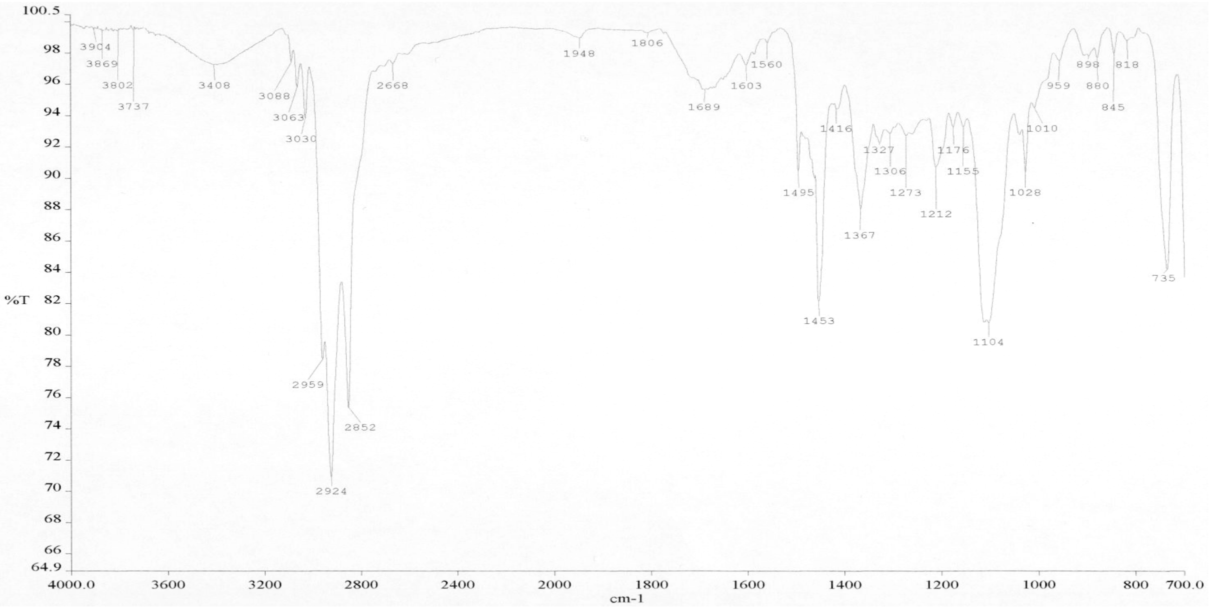
Pale brown oil. R_f around 0.15; depends on the concentration (not UV-active, AcOEt/Pet. ether 50%, PMA). IR (neat) *ν* 2959 (m), 2924 (s), 2852 (s), 1495 (w), 1453 (m), 1367 (w), 1212 (w), 1104 (m), 1028 (w), 735 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.83–1.88 (15 H, m, H9, H10, H13–H18), 0.91 (3 H, d, J 6.5, H12), 2.61 (1 H, ddd, J 8.5, 5.5, 4.5, H11), 2.78 (2 H, m, H7), 3.35 (1 H, quintd, J 6.5, 2.0, H8), 3.59 (2 H, m, H6), 4.54 (2 H, AB system, δ_A 4.53, δ_B 4.55, J_{AB} 12.5, H5), 7.24–7.38 (5 H, m, H1–H3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 13.8 (C12), 23.9 (C16), 26.1, 26.3 (C15, C17), 26.9, 27.0 (C14, C18), 31.1, 31.3 (C9, C10), 39.9 (C13), 47.1 (C7), 56.0 (C8), 65.4 (C11), 69.6 (C6), 73.1 (C5), 127.4 (C1), 127.6 (C3), 128.3 (C2), 138.5 (C4). MS *m/z* (positive CI, NH_3) 180, 218, 234, 250, <u>302</u> (MH^+), 303, 310. HRMS *m/z* (EI) 301.2391 ($M^{+\bullet}$ $C_{20}H_{31}NO$ requires 301.2406).



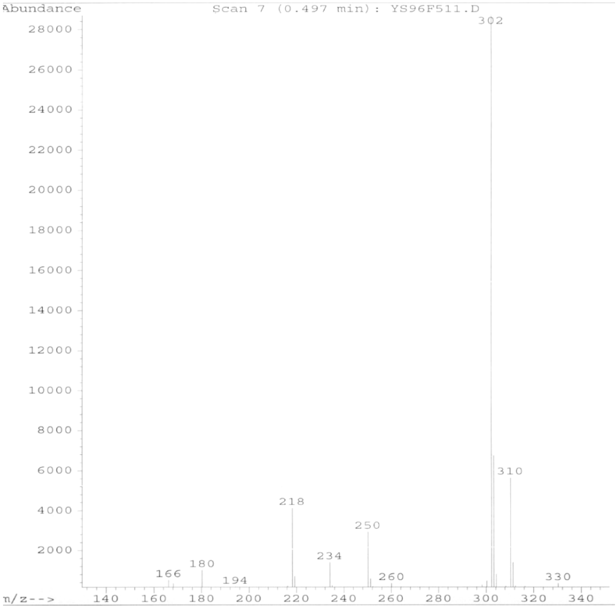
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).

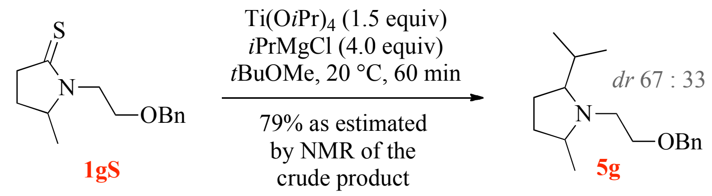


IR spectrum.

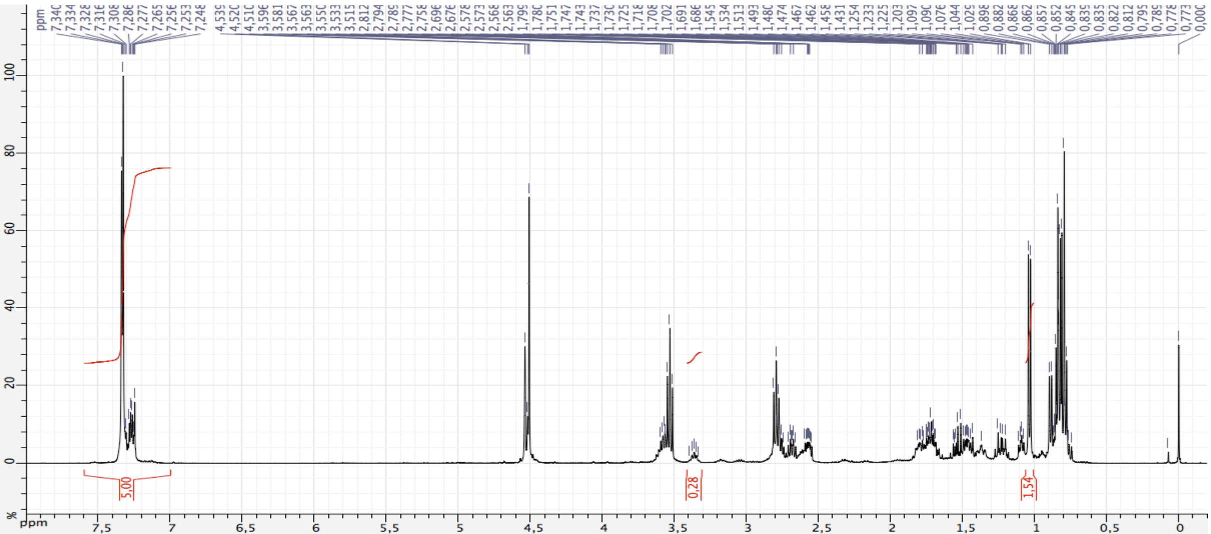


MS spectrum (positive CI, NH_3).

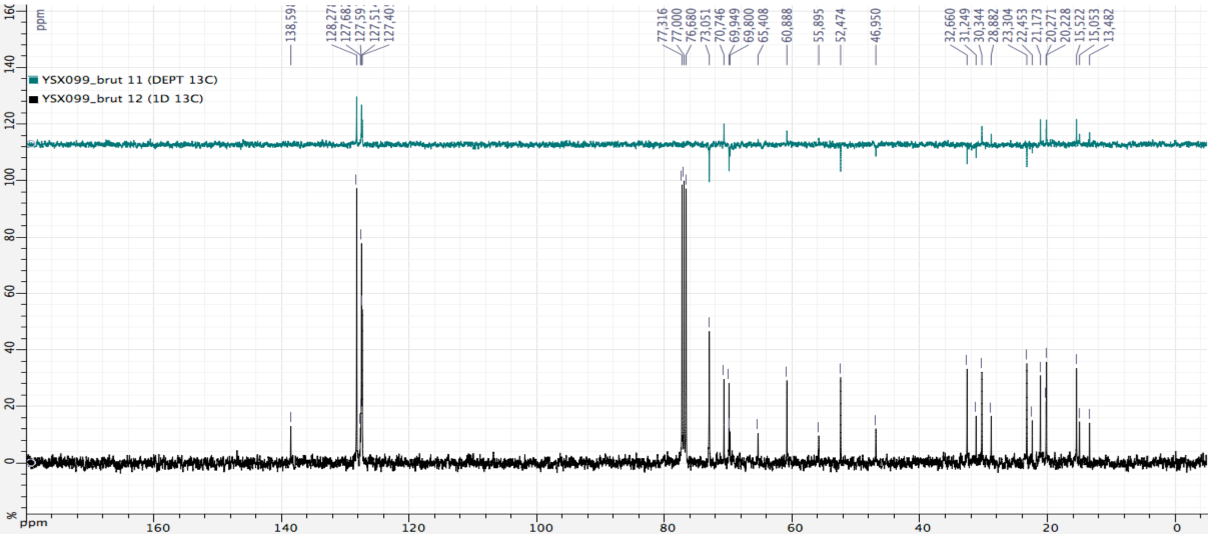
■ Titanium-mediated reaction of **1gS** with isopropylmagnesium chloride, in *t*BuOMe.



The general procedure was applied starting from 1-(2-benzyloxyethyl)-5-methyl-pyrrolidin-2-thione **1gS** (1.00 equiv, 1.00 mmol, 249 mg), using *t*BuOMe (20 mL) as the solvent and isopropylmagnesium chloride (1.72 M in THF) as the Grignard reagent. A yellow oil (179 mg) was obtained. Analysis of the crude product by ^1H and ^{13}C NMR spectroscopy gave an estimation of the yield of the expected α-cyclohexylamine product **5g** (79%; diastereoisomeric ratio 67 : 33). No starting thioamide **1gS** was observed.

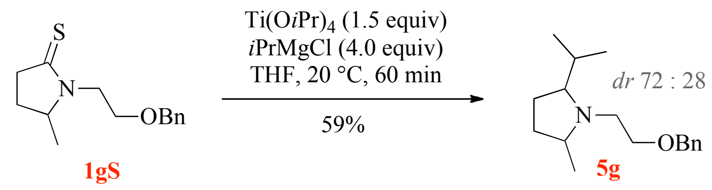


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).



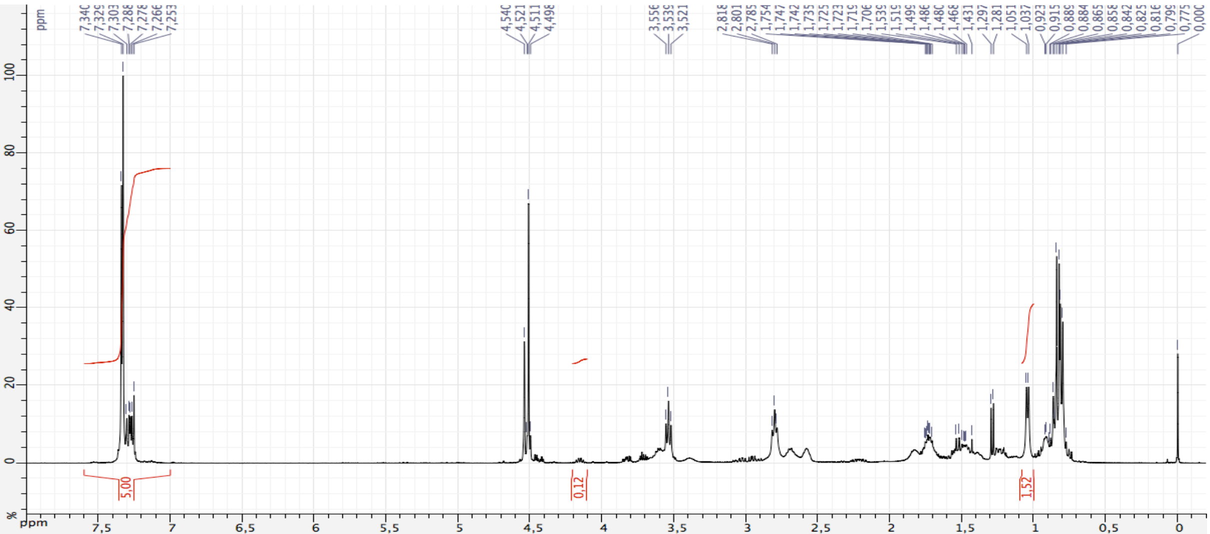
^{13}C NMR and DEPT135 spectra of the crude product ($CDCl_3$, 100.6 MHz).

■ Titanium-mediated reaction of **1gS** with isopropylmagnesium chloride, in THF.

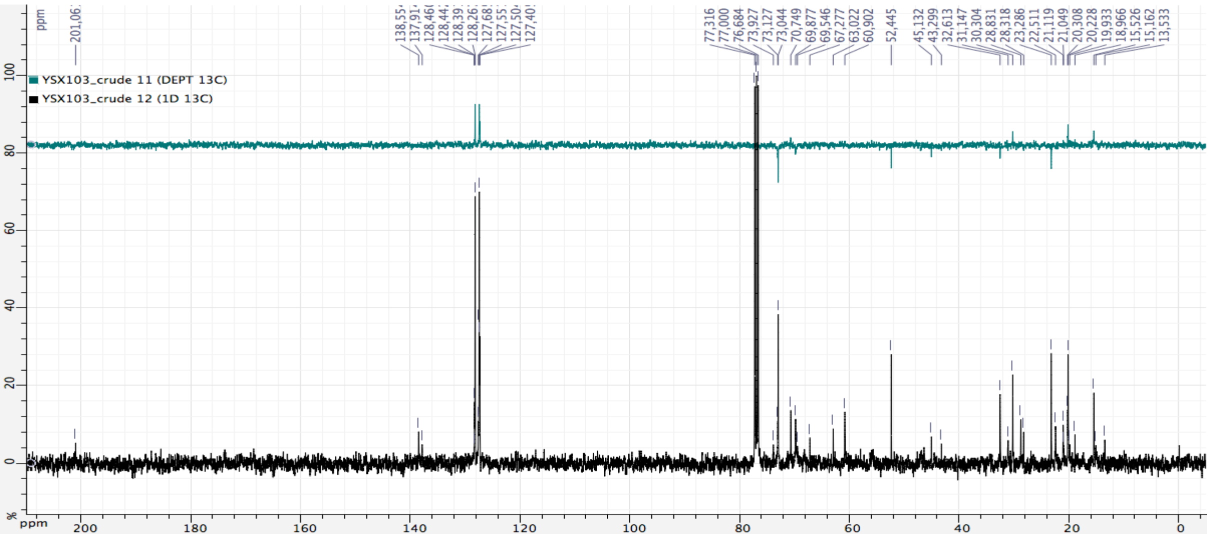


The general procedure was applied starting from 1-(2-benzyloxyethyl)-5-methyl-pyrrolidin-2-thione **1gS** (1.00 equiv, 1.00 mmol, 249 mg), using THF (20 mL) as the solvent and isopropylmagnesium chloride (1.72 M in THF) as the Grignard reagent. An orange oil (225 mg) was obtained. Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopy gave an estimation of the yield of the expected α-cyclohexylamine product **5g** (70%; diastereoisomeric ratio 72 : 28). The starting thioamide **1gS** (12%) was also observed. Purification by flash column chromatography on silica gel, (EtOAc/pet. ether, gradient from

10 to 100%) yielded pure major diastereoisomer of 1-(2-benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine **5g** (98 mg, 375 μmol, 37%), a mixture of both diastereoisomers of 1-(2-benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine **5g** (16 mg, 61 μmol, 6%) and pure minor diastereoisomer of 1-(2-benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine **5g** (43 mg, 164 μmol, 16%).

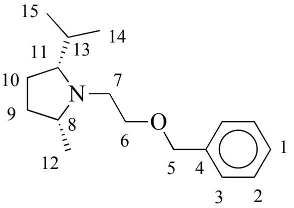


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).



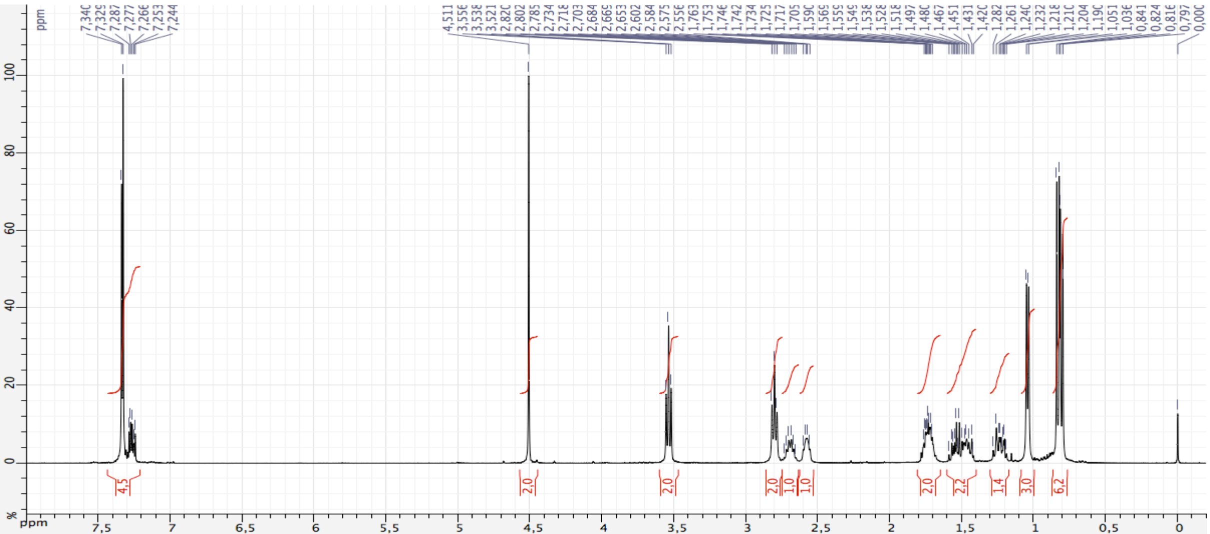
^{13}C NMR and DEPT135 spectra of the crude product ($CDCl_3$, 100.6 MHz).

(2*R**,5*R**)-1-(2-Benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine (major diastereoisomer) *cis*–**5g**

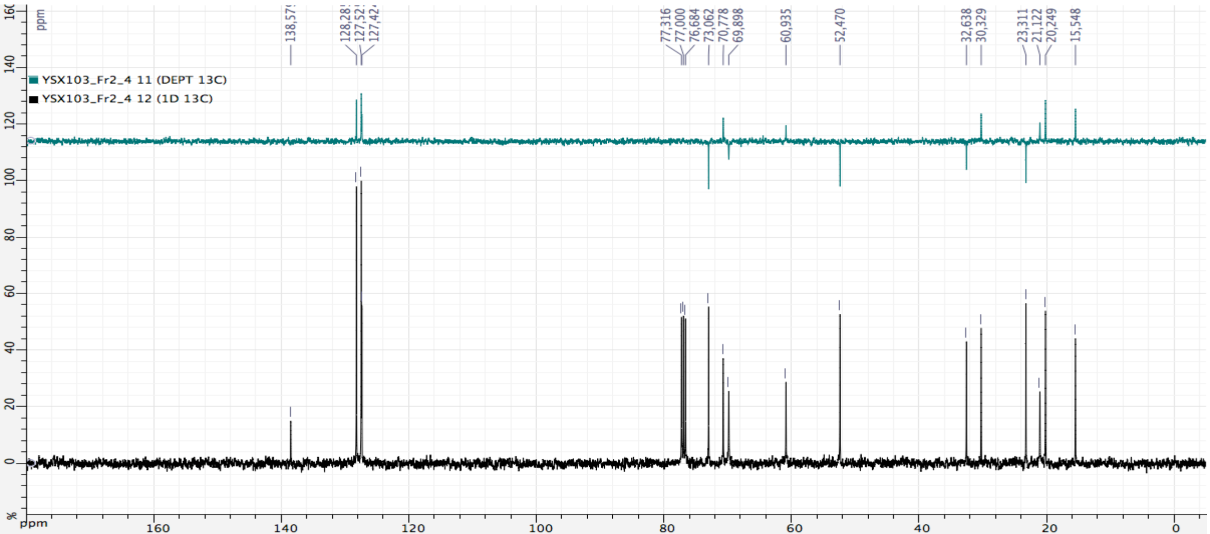


Yellow oil. R_f 0.1–0.3 (slightly UV-active, AcOEt/Pet. ether 20%, PMA). IR (neat) ν 3030 (w), 2958 (s), 2869 (m), 1454 (m), 1384 (m), 1374 (m), 1306 (w), 1209 (m), 1102 (m), 1028 (m), 733 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.81 (3 H, d, J 7.0, H14), 0.83 (3 H, d, J 7.0, H15), 1.04 (3 H, d, J 6.0, H12), 1.24 (1 H, dtd, J 12.0, 8.5, 8.0, H9a), 1.46 (1 H, m, H10a), 1.52 (1 H, m, H10b), 1.71 (1 H, septd, J 7.0, 4.0, H13), 1.74 (1 H, m, H9b), 2.58 (1 H, ddd, J

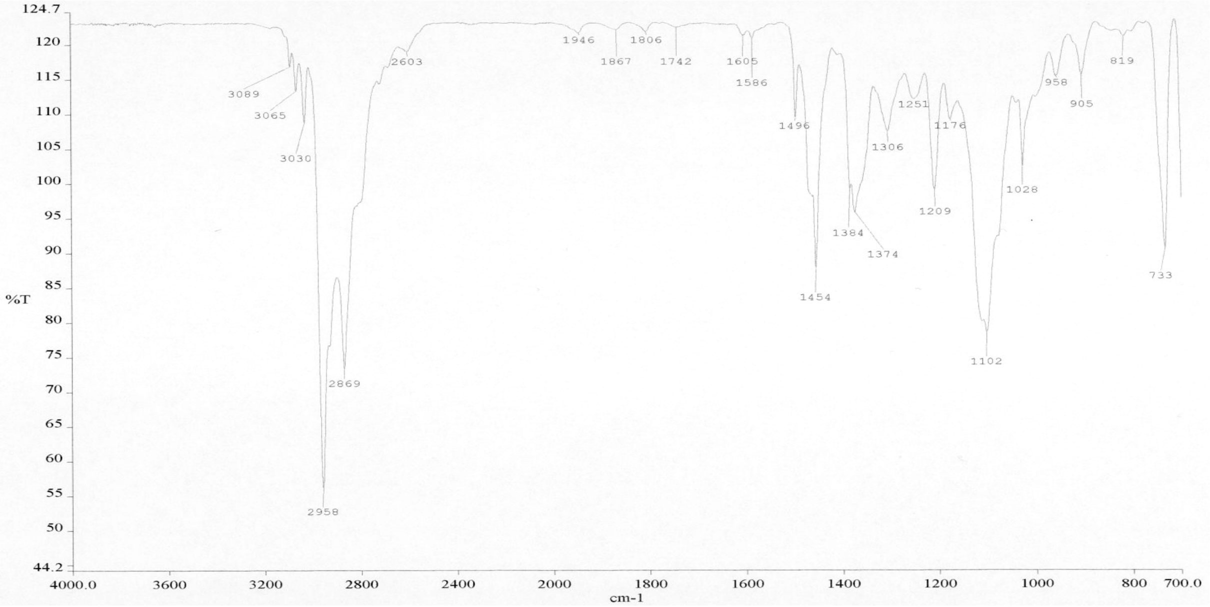
8.5, 6.5, 4.0, H11), 2.69 (1 H, ddq, J 8.5, 6.5, 6.0, H8), 2.80 (2 H, t, J 7.0, H7), 3.54 (2 H, t, J 7.0, H6), 4.51 (2 H, s, H5), 7.23–7.37 (5 H, m, H1–H3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 15.5 (C14), 20.2 (C15), 21.1 (C12), 23.3 (C10), 30.3 (C13), 32.6 (C9), 52.5 (C7), 60.9 (C8), 69.9 (C6), 70.8 (C11), 73.1 (C5), 127.4 (C1), 127.5 (C3), 128.3 (C2), 138.6 (C4). MS *m/z* (positive CI, NH_3) 140, 218, 262 (MH^+), 263. HRMS *m/z* (EI) 261.2092 ($M^{+\bullet}$ $C_{17}H_{27}NO$ requires 261.2093).



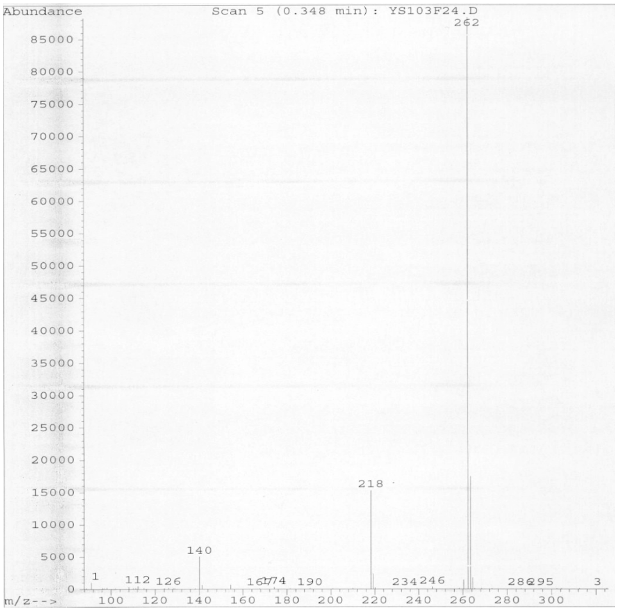
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).

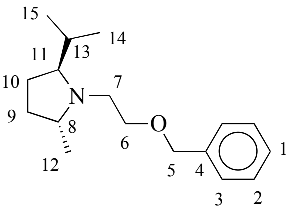


IR spectrum.



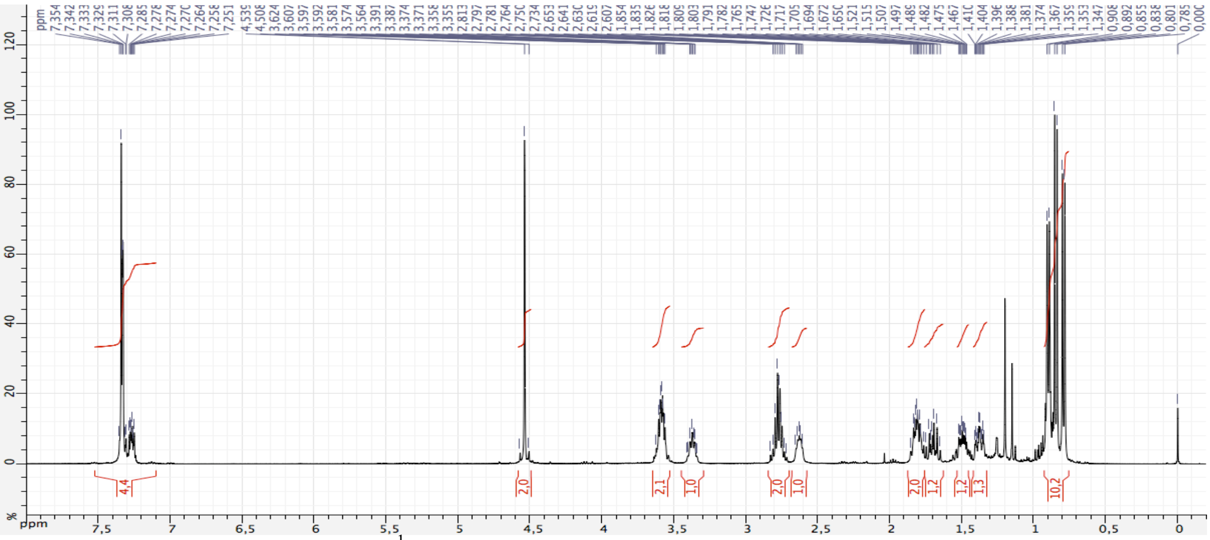
MS spectrum (positive CI, NH_3).

(2*S**,5*R**)-1-(2-Benzyloxyethyl)-2-isopropyl-5-methyl-pyrrolidine (minor diastereoisomer) *trans*–**5g**

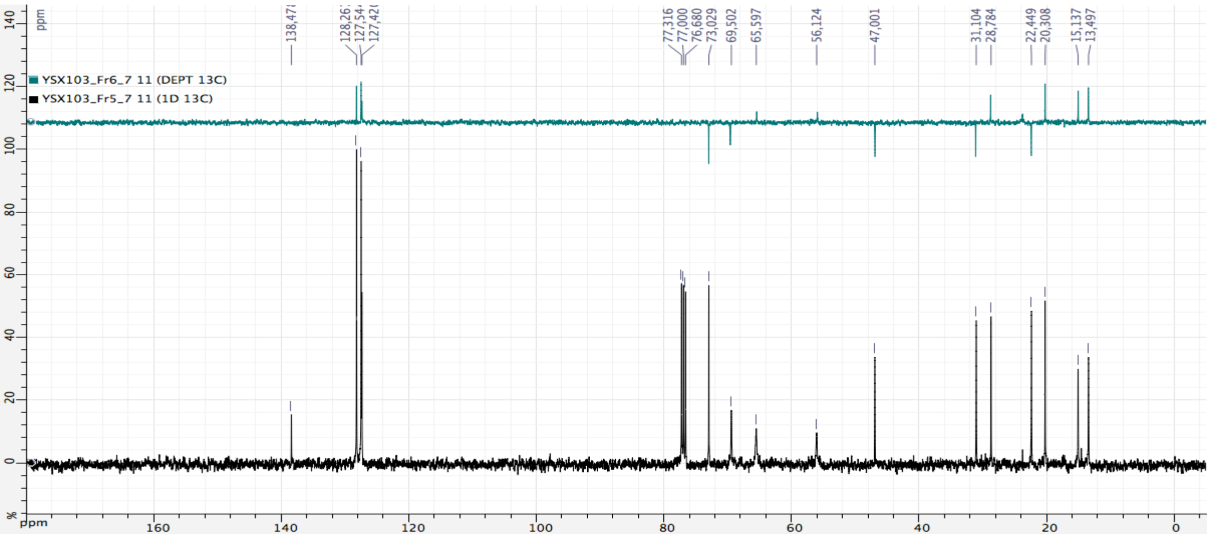


Yellow oil. R_f 0.05–0.1 (slightly UV-active, AcOEt/Pet. ether 20%, PMA). IR (neat) ν 3030 (w), 2959 (s), 2869 (m), 1470 (m), 1454 (m), 1385 (m), 1368 (m), 1214 (m), 1112 (m), 1028 (m), 734 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.79 (3 H, d, J 7.0, H14), 0.85 (3 H, d, J 7.0, H15), 0.90 (3 H, d, J 6.5, H12), 1.38 (1 H, dddd, J 11.0, 9.0, 3.0, 1.5, H9a), 1.49 (1 H, ddd, J 12.5, 5.5, 3.0, H10a), 1.70 (1 H, dtd, J 12.5, 9.0, 8.5, H10b), 1.80 (1 H, ddd, J 11.0, 9.0, 6.5, H9b), 1.81 (1 H, septd, J 7.0, 4.0, H13), 2.63 (1 H, ddd, J 8.5, 5.5, 4.0, H11), 2.77 (2 H, AB part of an ABXY system, H7), 3.37 (1 H, quintd, J 6.5, 1.5, H8), 3.59 (2 H, AB part of an

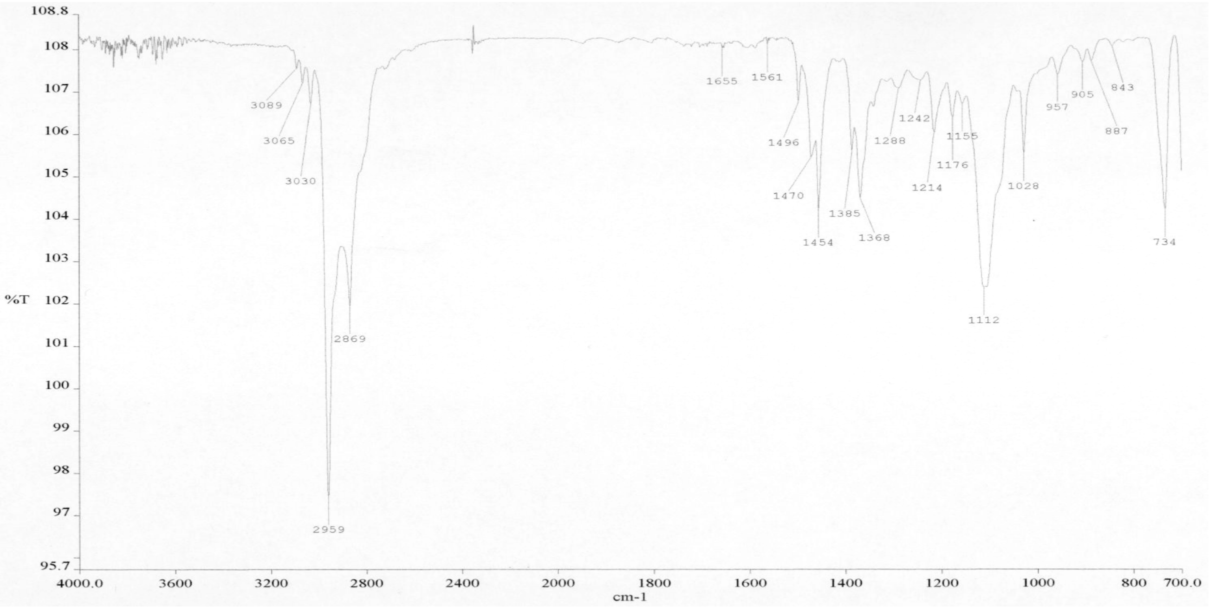
ABXY system, H6), 4.54 (2 H, AB system, δ_A 4.53, δ_B 4.55, J_{AB} 12.5, H5), 7.23–7.38 (5 H, m, H1–H3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) 13.5 (C12), 15.1 (C14), 20.3 (C15), 22.4 (C10), 28.8 (C13), 31.1 (C9), 47.0 (C7), 56.1 (C8), 65.6 (C11), 69.5 (C6), 73.0 (C5), 127.4 (C1), 127.5 (C3), 128.3 (C2), 138.5 (C4). MS *m/z* (positive CI, NH_3) 140, 218, <u>262</u> (MH^+), 263. HRMS *m/z* (EI) 261.2088 ($M^{+\bullet}$ $C_{17}H_{27}NO$ requires 261.2093).



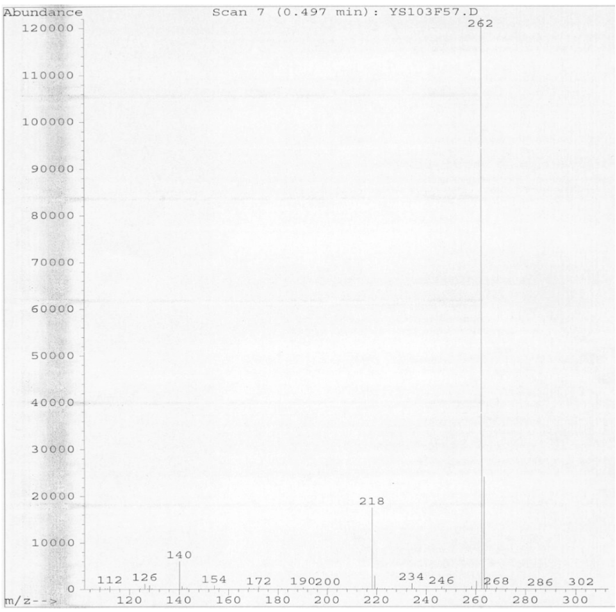
^{1}H NMR spectrum ($CDCl_3$, 400 MHz).



^{13}C and DEPT 135 NMR spectra ($CDCl_3$, 100.6 MHz).

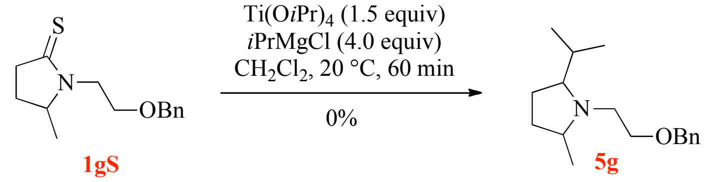


IR spectrum.

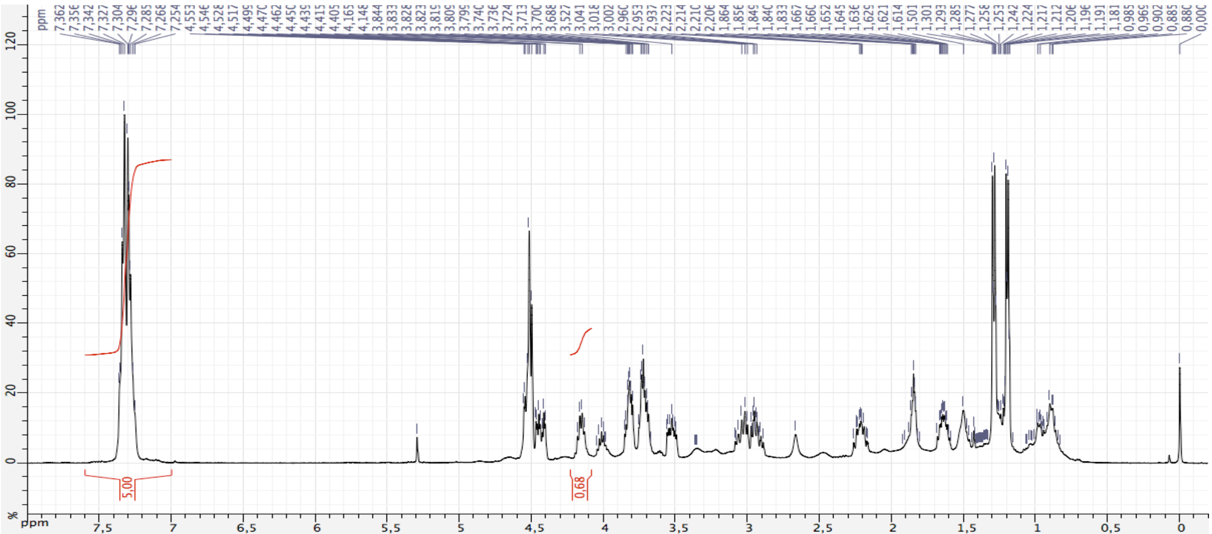


MS spectrum (positive CI, NH_3).

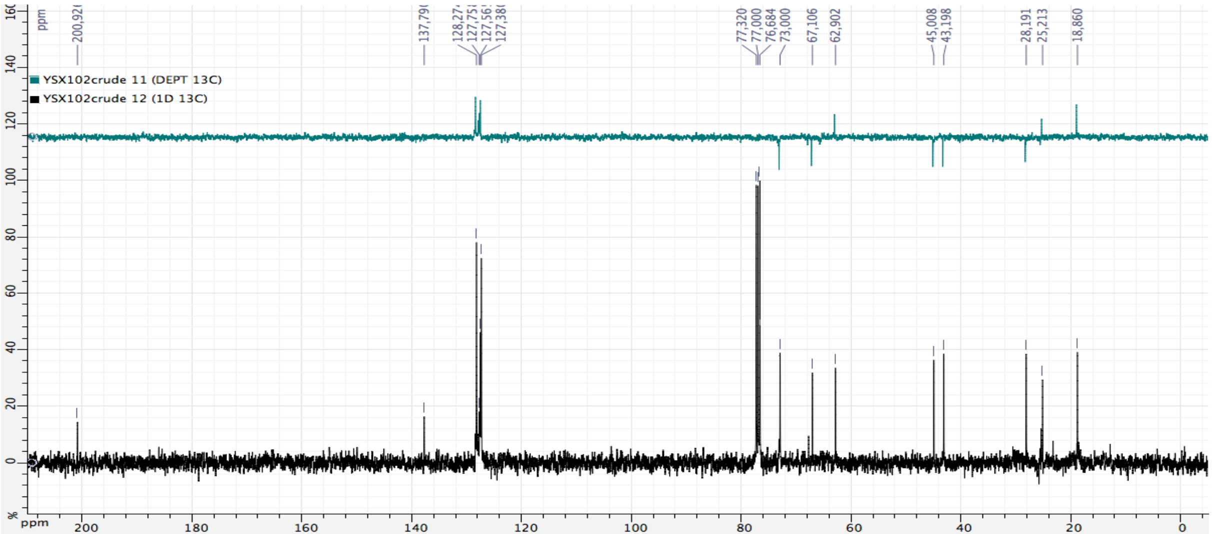
■ Titanium-mediated reaction of **1gS** with isopropylmagnesium chloride, in CH_2Cl_2.



The general procedure was applied starting from 1-(2-benzyloxyethyl)-5-methyl-pyrrolidin-2-thione **1gS** (1.00 equiv, 1.00 mmol, 249 mg), using CH_2Cl_2 (20 mL) as the solvent and isopropylmagnesium chloride (1.72 M in THF) as the Grignard reagent. An orange oil (287 mg) was obtained. Analysis of the crude product by ^1H and ^{13}C NMR spectroscopy revealed the presence of starting thioamide **1gS** (68%) as the major component. The reductive alkylation product **5g** was not observed.



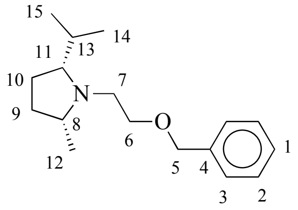
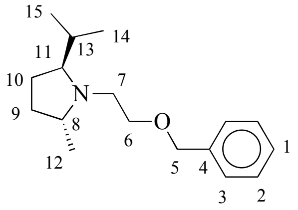
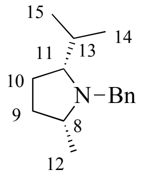
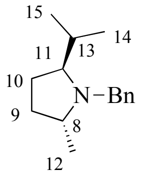
^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).



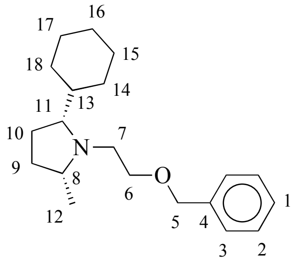
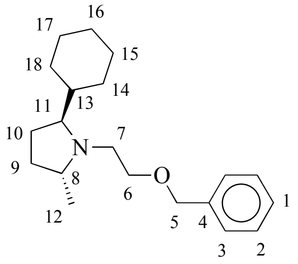
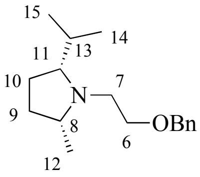
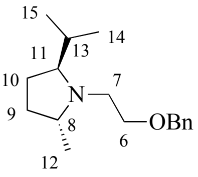
^{13}C NMR and DEPT135 spectra of the crude product ($CDCl_3$, 100.6 MHz).

■ Stereochemical assignment of *cis*– and *trans*–**4g** and –**5g**

The relative configurations of the chiral centres of *cis*– and *trans*–**5g** were assigned by comparison of selected ^{1}H and ^{13}C chemical shifts with those of the close *N*-benzyl analogues described in the literature.[5] The assignment thus obtained was confirmed by a NOESY NMR experiment performed on the major diastereoisomer of **5g**.

	 *cis*–**5g** (major diastereoisomer)	 *trans*–**5g** (minor diastereoisomer)	 literature[5]	 literature[5]
H8 (*δ*, ppm)	2.69	3.37	2.67	3.33
H11 (*δ*, ppm)	2.58	2.63	2.60	2.70
C8 (*δ*, ppm)	60.9	56.1	61.4	55.1
C11 (*δ*, ppm)	70.8	65.6	71.1	65.1
C12 (*δ*, ppm)	21.1	13.5	21.5	13.4
NOE	No correlation between H11 and H12.	Not examined	No H11–H12 correlation.	H11–H12 correlation.

The relative configurations of the chiral centres of *cis*– and *trans*–**4g** were assigned by comparison of selected ^{1}H and ^{13}C chemical shifts with those of *cis*– and *trans*–**5g**.

	 *cis*–**4g** (major diastereoisomer)	 *trans*–**4g** (minor diastereoisomer)	 *cis*–**5g**	 *trans*–**5g**
H8 (*δ*, ppm)	2.67	3.35	2.69	3.37
H11 (*δ*, ppm)	2.54	2.61	2.58	2.63
C8 (*δ*, ppm)	60.8	56.0	60.9	56.1
C11 (*δ*, ppm)	70.5	65.4	70.8	65.6
C12 (*δ*, ppm)	21.2	13.8	21.1	13.5

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[5] D. Crich, K. Ranganathan, *J. Am. Chem. Soc.* **2002**, *124*, 12422–12423.