

Palladium-Catalyzed Alkoxyamination of Alkenes with N-Fluorobenzenesulfonimide as Oxidant

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Michael*

Supporting Information

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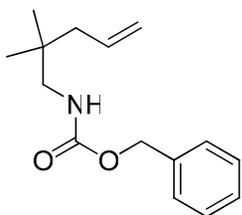
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General Procedures. All reactions were performed under nitrogen atmosphere using flame-dried glassware. Infrared spectra were measured as a thin film on a KBr plate. Mass spectra were collected on a Gas Chromatograph - Mass Spectrometer or Liquid Chromatograph - Ion Trap Mass Spectrometer. Column chromatography was performed using silica gel (60 Å, 230-400 mesh). NMR spectra were recorded on a 300 or 500 MHz spectrometer. ¹H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to TMS (0.00 ppm) or residual protonated CHCl₃ (7.26 ppm). ¹³C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of CDCl₃ (77.0 ppm).

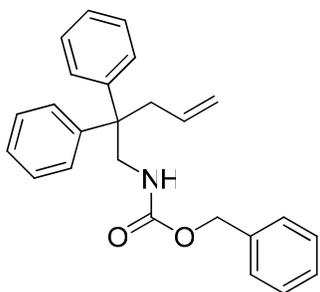
Materials. All commercial reagents were used as received. CH₂Cl₂ was degassed and dried on solvent columns of neutral alumina. EtOAc was used as received. Deuterated solvents were stored over 4Å molecular sieves, and were used without further purification.

Synthesis and Characterization of Starting Materials

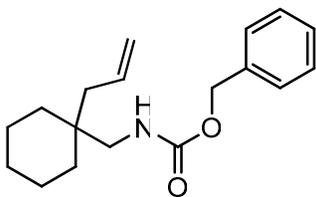
Benzyl 2,2-dimethylpent-4-enylcarbamate (**1**)¹, benzyl 2,2-diphenylpent-4-enylcarbamate², benzyl (1-allyl-cyclohexylmethyl)-carbamate², benzyl 2-phenylpent-4-enylcarbamate¹, benzyl pent-4-enylcarbamate¹, were synthesized according to previously reported methods and spectral data match literature values.



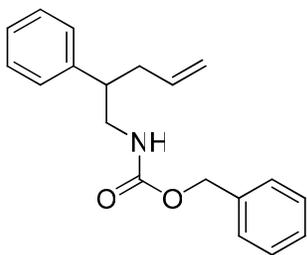
Benzyl 2,2-dimethylpent-4-enylcarbamate (1). ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.33 (m, 5H), 5.88-5.74 (m, 1H), 5.11 (s, 2H), 5.07-5.00 (m, 2H), 4.78 (br, 1H), 3.04 (d, $J = 6.6$ Hz, 2H), 1.98 (d, $J = 7.2$ Hz, 2H), 0.89 (s, 6H).



Benzyl 2,2-diphenylpent-4-enylcarbamate (6). ¹H NMR (300 MHz, CDCl₃): δ 7.34-7.17 (m, 15H), 5.65 (ddt, $J = 9.9, 16.5, 7.5$ Hz, 1H), 5.05 (s, 2H), 5.01-4.97 (m, 2H), 4.36 (br, 1H), 3.96 (d, $J = 6.0$ Hz, 2H), 2.89 (d, $J = 7.2$ Hz, 2H).



Benzyl (1-allylcyclohexylmethyl)carbamate (7). ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.33 (m, 5H), 5.83 (ddt, $J = 10.8, 17.6, 8.0$ Hz, 1H), 5.10-5.03 (m, 4H), 4.75 (br s, 1H), 3.13-3.11 (d, $J = 6.3$ Hz, 2H), 2.04 (d, $J = 7.2$, 1H), 1.51-1.26 (m, 10H).



Benzyl 2-phenylpent-4-enylcarbamate (8). ^1H NMR (300 MHz, CH_3Cl_3): δ 7.38-7.21 (m, 5H), 5.67 (ddt, $J = 10.2, 17.1, 7.2$ Hz, 1H), 5.02-4.90 (m, 2H), 2.94-2.68 (m, 3H), 2.49-2.30 (m, 2H)



Benzyl pent-4-enylcarbamate (9). ^1H NMR (300 MHz, CDCl_3): δ 7.36-7.31 (m, 5H), 5.79 (ddt, $J = 10.2, 17.4, 7.2$ Hz, 1H), 5.10-4.96 (m, 4H), 4.78-4.76 (br s, 1H), 3.21 (q, $J = 6.6$ Hz, 2H), 2.08 (quin., $J = 7.2$, 2H), 1.65-1.58 (m, 2H).

Procedures for oxyamination

Procedure A

Pd(TFA)₂ (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry N₂ gas. The substrate (0.250 mmol) was dissolved in 5 mL of the corresponding alcohol and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

Procedure B

PdCl₂(MeCN)₂³ and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3-Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry N₂ gas. The substrate (0.250 mmol) was dissolved in 5 mL of the corresponding alcohol and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

Procedure C

Pd(TFA)₂ (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3-Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry N₂ gas. The substrate (0.250 mmol) and 10 equivalents of the corresponding alcohol (2.5 mmol) were dissolved in 5 mL of benzene and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

Procedure D

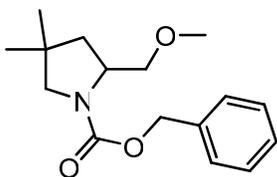
Pd(TFA)₂ (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3-Å molecular sieves (10 – 15 sieves), capped with a rubber septum and placed under dry N₂ gas. The substrate (0.250 mmol) and was dissolved in 5 mL of glacial acetic acid added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

Procedure E

Pd(TFA)₂ (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar, capped with a rubber septum and placed under dry N₂ gas. The substrate (0.250 mmol) was dissolved in a mixture of 1 mL of the corresponding alcohol and 4 mL of dimethylformamide and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure (0.1 torr) at 50 °C and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.

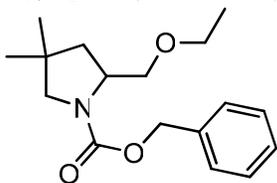
Procedure F

Pd(TFA)₂ (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar, capped with a rubber septum and placed under dry N₂ gas. The substrate (0.250 mmol) was dissolved in a mixture of 0.5 mL of deionized water and 4.5 mL of dimethylformamide and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure (0.1 torr) at 50 °C and chromatographed using 25:75 EtOAc/Hexanes. The product was collected and was further purified by chromatography with a less polar mixture of EtOAc/Hexanes.



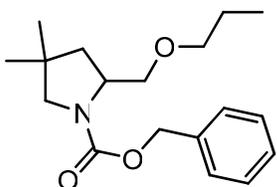
Benzyl 2-(methoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate (4a). Prepared according to procedure A. Clear oil, 52% yield. ¹H NMR (500 MHz, CDCl₃) δ: 7.43-7.30 (m, 5H), 5.25-5.09 (m, 2H), 4.08-3.02 (m, 1H), 3.69-3.45 (m, 2H), 3.45-3.12 (m, 6H), 3.01 (d, *J* = 10 Hz, 1H), 1.87-1.78 (m, 1H), 1.78-1.71 (m, 1H), 1.09 (s, 3H), 0.98 (s, 3H). ¹³C (125 MHz, CDCl₃, observed as a mixture of rotamers, major and minor) δ: 155.3, 136.9, 128.4, 127.8, 127.6, 74.3, 73.1, 66.8 (minor), 66.6 (major), 59.64 (minor), 59.1 (major), 57.0 (major), 56.3 (minor), 43.6 (minor), 42.4 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9. FTIR (neat, cm⁻¹): 2958, 2872, 1703, 1452, 1415, 1358, 1188, 1101. MS (EI): 277.2, (M⁺, 0.3%), 232.2 ([M – CH₂OCH₃]⁺, 27%), 188.2 ([M – PhCH₂OCO]⁺, 37%), 91.1 (Bn⁺, 100%). HRMS (FAB): calculated for

C₁₆H₂₄NO₃ 278.1756, found 278.1761.

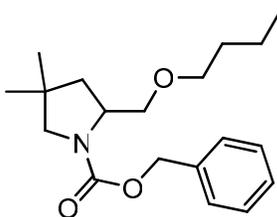


Benzyl 2-(ethoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate

(4b). Prepared according to procedure B. 63% yield. Clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.43-7.26 (m, 5H), 5.25-5.07 (m, 2H), 4.06-3.96 (m, 1H), 3.78-3.68 (m, 0.5H), 3.68-3.60 (m, 0.5H), 3.60-3.45 (m, 2H), 3.45-3.32 (m, 2H), 3.01 (d, *J* = 10 Hz, 1H), 1.90-1.78 (m, 1H), 1.78-1.68 (m, 1H), 1.22-1.05 (m, 2H), 1.09 (s, 3H), 0.99 (s, 3H). ¹³C (125 MHz, CDCl₃, observed as a mixture of rotamers, major and minor) δ: 155.3, 137.0 (major), 136.9 (minor), 128.4, 127.8, 127.6, 72.3 (minor), 71.0 (major), 66.8 (minor), 66.5 (major), 66.7, 59.7, 57.1 (major), 56.5 (minor), 43.9 (minor), 42.8 (major), 37.5 (major), 37.1 (minor), 26.6, 26.0, 15.2. FTIR (neat, cm⁻¹): 2959, 2870, 1703, 1415, 1358, 1190, 1109. MS (ED): 291.2 (M⁺, 0.3%), 232.2 ([M - CH₂OCH₂CH₃]⁺, 27%), 188.2 ([M - PhCH₂OCO]⁺, 44%), 91.1 (Bn⁺, 100%). HRMS (FAB): calculated for C₁₇H₂₆NO₃ 292.1913, found 292.1911.

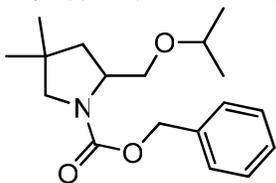


Benzyl 4,4-dimethyl-2-(*n*-propoxymethyl)-pyrrolidine-1-carboxylate (4c). Prepared according to procedure B. 57% yield. Clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.42-7.29 (m, 5H), 5.25-5.09 (m, 2H), 4.07-4.0 (m, 1H), 3.71-3.66 (m, 0.5H), 3.66-3.57 (m, 1H), 3.50-3.45 (m, 0.5H), 3.45-3.38 (m, 1H), 3.38-3.30 (m, 1H), 3.01 (d, *J* = 10 Hz, 1H), 1.85-1.77 (m, 1H), 1.77-1.72 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), 0.94-0.87 (m, 3H). ¹³C (125 MHz, CDCl₃, observed as a mixture of rotamers, major and minor) δ: 155.2, 137.0 (major), 136.9 (minor), 128.4, 127.8, 127.6, 73.0, 72.3 (minor), 71.0 (major), 66.8 (minor), 66.5 (major), 59.6, 57.1 (major), 56.5 (minor), 43.7 (minor), 42.6 (major), 37.4 (major), 37.1 (minor), 26.6, 26.0, 22.9, 10.5. FTIR (neat, cm⁻¹): 2960, 2872, 1703, 1415, 1359, 1190, 1103, 698. MS (ED): 305.2 (M⁺, 0.4%), 232.2 ([M - CH₂OCH₂CH₂CH₃]⁺, 30%), 188.2 ([M - PhCH₂OCO]⁺, 53%), 91.1 (Bn⁺, 100%). HRMS (FAB): calculated for C₁₈H₂₈NO₃ 306.2069, found 306.2063.

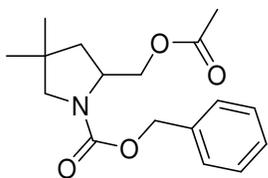


Benzyl 4,4-dimethyl-2-(*n*-butoxymethyl)-pyrrolidine-1-carboxylate (4d). Prepared according to procedure B. 63% yield. Clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.35-7.29 (m, 5H), 5.25-5.09 (m, 2H), 4.07-4.00 (m, 1H), 3.70-3.68 (m, 0.5H), 3.60-3.57 (m, 1H), 3.49-3.34 (m, 3.5H), 3.01 (d, *J* = 10 Hz, 1H), 2.27-1.79 (m, 1H), 1.79-1.72 (m, 1H), 1.53-1.48 (m, 2H), 1.36-1.33 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H), 0.90-0.86 (m, 3H). ¹³C (125 MHz, CDCl₃, observed as a mixture of rotamers, major

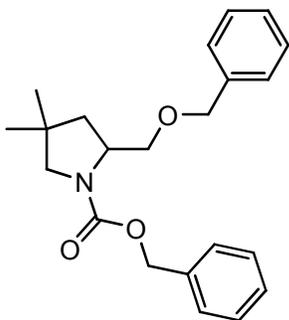
and minor) δ : 155.2, 137.0 (major), 136.9 (minor), 128.4, 127.8, 127.6, 72.4, 71.1, 66.7 (minor), 66.5 (major), 59.6, 57.1 (major), 56.5 (minor), 43.7 (minor), 42.6 (major), 37.4 (major), 37.1 (minor), 31.7, 26.6, 26.0, 19.3, 13.9. FTIR (neat, cm^{-1}): 2958, 2870, 1703, 1415, 1359, 1190, 1103. MS (EI): 319.2 (M^+ , 0.8%), 232.2 ($[\text{M} - \text{CH}_2\text{O}(\text{CH}_2)_3\text{CH}_3]^+$, 45%), 188.2 ($[\text{M} - \text{PhCH}_2\text{OCO}]^+$, 79%), 91.1 (Bn^+ , 100%). HRMS (FAB): calculated for $\text{C}_{19}\text{H}_{30}\text{NO}_3$ 320.2226, found 320.2220.



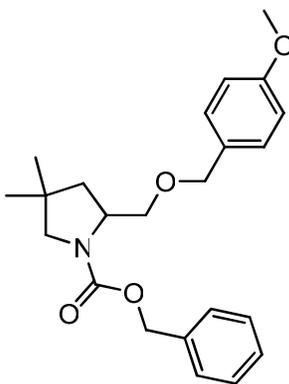
Benzyl 2-(isopropoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate (4e). Prepared according to procedure B. 66% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.38-7.28 (m, 5H), 5.25-5.08 (m, 2H), 4.01-3.96 (m, 1H), 3.79-3.73 (m, 0.5H), 3.67-3.62 (m, 0.5H), 3.57-3.44 (m, 2H), 3.44-3.29 (m, 1H), 3.01 (d, $J = 10$ Hz, 1H), 1.87-1.81 (m, 1H), 1.77-1.67 (m, 1H), 1.13-1.09 (m, 6H), 1.10 (s, 3H), 0.98 (s, 1H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 155.2, 137.1 (major), 136.9 (minor), 128.4, 127.8, 127.8, 72.0 (major), 71.9 (minor), 69.9 (minor), 68.8 (major), 66.8 (minor), 66.5 (major), 59.7, 57.4 (major), 56.7 (minor), 44.0 (minor), 42.9 (major), 37.5 (major), 37.1 (minor), 26.6, 26.0, 22.3, 22.0. FTIR (neat, cm^{-1}): 2964, 2871, 1703, 1415, 1359, 1332, 1190 1100. MS (EI): 305.2 (M^+ , 0.4%), 232.2 ($[\text{M} - \text{CH}_2\text{OCH}_2\text{CH}(\text{CH}_3)_2]^+$, 39%), 188.2 ($[\text{M} - \text{PhCH}_2\text{OCO}]^+$, 63%), 91.1 (Bn^+ , 100%). HRMS (FAB): calculated for $\text{C}_{18}\text{H}_{28}\text{NO}_3$ 306.2069, found 306.2064.



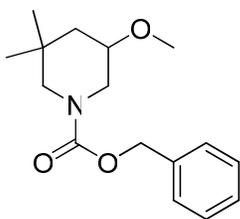
Benzyl 2-(acetoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate (4f). Prepared according to procedure D. Colorless oil (55% yield). ^1H NMR (500 MHz, CDCl_3): δ 7.36-7.29 (m, 5H), 5.14 (s, 2H), 5.13 (s, 2H), 4.29 (br s, 1H), 4.17 – 4.15 (m, 2H), 3.52 (d, $J = 10.5$ Hz, 0.5H), 3.41 (d, $J = 10$ Hz, 0.5H), 3.02 (d, $J = 10.5$ Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.87-1.80 (dd, $J = 8.0, 12.3$ Hz, 1H), 1.66-1.57 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor): δ 20.8 (minor), 20.9 (major), 25.8 (major), 25.9 (minor), 26.4 (major), 26.5 (minor), 29.7 (major + minor), 37.1 (minor), 37.6 (major), 42.3 (major), 43.1 (minor), 55.3 (minor), 56.0 (major), 59.6 (major), 59.7 (minor), 64.8 (major), 65.5 (minor), 66.7 (major), 67.1 (minor), 127.7 (major + minor), 127.9 (major), 128.0 (minor), 128.4 (major + minor), 136.6 (minor), 136.8 (major), 155.2 (major + minor), 170.8 (major + minor). FTIR (neat, cm^{-1}): 3067, 3033, 2958, 2872, 1743, 1703, 1453, 1414, 1360, 1236, 1190, 1102, 1040, 966, 769, 740, 698. HRMS (FAB) calculated for $\text{C}_{17}\text{H}_{24}\text{NO}_4$ 306.1706, found 306.1709 ($\text{M} + \text{H}$).



Benzyl 2-benzyloxymethyl-4,4-dimethyl-pyrrolidine-1-carboxylate (4g). Prepared according to procedure C. 48% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.43-7.24 (m, 10H), 5.22-5.08 (m, 2H), 4.59-4.46 (m, 2H), 4.15-4.03 (m, 1H), 3.78-3.68 (m, 0.5H), 3.74-3.61 (m, 1H), 3.52-3.50 (m, 1H), 3.04 (d, $J = 10.5$ Hz), 3.03 (d, $J = 10.5$ Hz, 1H), 1.90-1.78 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 155.2, 138.6 (major), 138.4 (minor), 137.0, (major), 136.8 (minor), 128.7, 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 127.4, 73.2, 71.7 (minor), 70.7 (major), 66.8 (minor), 66.5 (major), 59.7, 57.1 (major), 56.4 (minor), 43.6 (minor), 42.5 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9. FTIR (neat, cm^{-1}): 2957, 2869, 1701, 1416, 1359, 1103. MS (EI): 353.2 (M^+ , 0.04%), 232.2 (25%), 188.2 (40%), 91.2 (Bn^+ , 100%). HRMS (FAB): $\text{C}_{22}\text{H}_{28}\text{NO}_3$ 354.2069, found 354.2057.

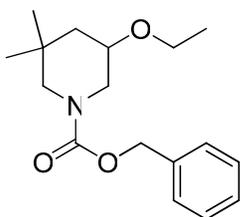


Benzyl 2-(4-Methoxybenzyloxymethyl)-4,4-dimethyl-pyrrolidine-1-carboxylate (4h). Prepared according to procedure C. 56% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.43-7.18 (m, 7H), 6.85 (d, $J = 7.5$ Hz, 2H), 5.18-5.11 (m, 2H), 4.46-4.38 (m, 2H), 4.06-4.01 (m, 1H), 3.80 (s, 3H), 3.66-3.64 (m, 1H), 3.53-3.45 (m, 1H), 3.39 (d, $J = 10$ Hz, 0.5H), 3.01 (d, $J = 10.5$ Hz, 1H), 1.88-1.74 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 159.0, 155.2, 137.0 (major), 136.8 (minor), 130.7 (major), 130.4 (minor), 129.0, 128.4, 127.8, 127.6, 113.7, 72.8, 71.5 (minor), 70.5 (major), 66.7 (minor), 66.5 (major), 59.7, 57.1 (major), 56.5 (minor), 55.2, 43.7 (minor), 42.6 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9. FTIR (neat, cm^{-1}): 2957, 2869, 1700, 1513, 1416, 1359, 1248, 1173, 1102, 820, 769. MS (ES): 406.3 ($\text{M}^+ + \text{Na}$), 362.2, 284.0, 270.0. HRMS (FAB): calculated for $\text{C}_{23}\text{H}_{30}\text{NO}_4$ 384.2175, found 384.2157.



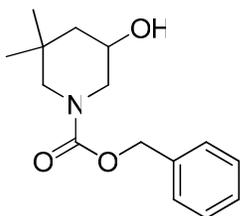
Benzyl 5-methoxy-3,3-dimethylpiperidine-1-carboxylate (5a).

Prepared according to procedure E. Colorless oil (38% yield). ^1H NMR (500 MHz, CDCl_3): δ 7.41-7.29 (m, 5H), 5.20-5.10 (m, 2H), 4.36-4.34 (m, 0.5H), 4.23-4.16 (m, 0.5H), 3.68-3.58 (m, 1H), 3.36 (d, $J = 18$ Hz, 3H), 2.74-2.63 (m, 0.5H), 2.65 (d, $J = 13.5$ Hz), 1.80 (m, 1H), 1.21-1.16 (m, 1H), 0.98 – 0.89 (m, 6H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor): δ 155.6, 155.5, 136.8, 128.4, 128.0, 127.9, 127.8, 73.2 (minor), 72.8 (major), 67.1, 56.4 (major), 56.3 (minor), 55.0 (major), 54.9 (minor), 47.7, 43.8 (major), 43.8 (minor), 32.2 (major), 32.1, 28.2, 24.9, 24.7. FTIR (neat, cm^{-1}): 2929, 1700, 1430, 1200, 1090. MS (ES): 300 $[\text{M} + \text{Na}]^+$. HRMS (FAB): calculated for $\text{C}_{16}\text{H}_{24}\text{NO}_3$ 278.1756, found 278.1747.



Benzyl 5-ethoxy-3,3-dimethylpiperidine-1-carboxylate (5b).

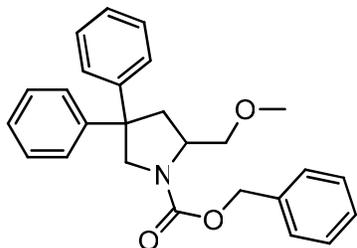
Prepared according to procedure E. Colorless oil (42% yield): ^1H NMR (500 MHz, CDCl_3): δ 7.42-7.31 (m, 5H), 5.19-5.05 (m, 2H), 4.42-4.35 (m, 0.5H), 4.28-4.19 (m, 0.5H), 3.78-3.33 (m, 4H), 2.69-2.54 (m, 0.5H), 2.54-2.57 (m, 0.5H), 2.59 (d, $J = 13$ Hz, 1H), 1.85-1.67 (m, 1H), 1.25-1.00 (m, 4H), 0.98-0.89 (m, 6H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor): δ 155.6, 155.3, 136.8, 128.6, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 71.4 (minor), 71.0 (major), 67.1 (major), 66.7 (minor), 64.1 (major), 63.9 (minor), 55.0 (major), 54.9 (minor), 48.2, 44.5 (major), 44.1 (minor), 32.3 (major), 32.2 (minor), 28.3, 26.5 (minor), 26.0 (major), 24.7 (minor), 24.5 (major), 15.6. FTIR (neat, cm^{-1}): 2958, 2870, 1702, 1431, 1192, 1107, 698. MS (ES): 314 $[\text{M} + \text{Na}]^+$, 292 M^+ . HRMS (FAB): calculated for $\text{C}_{17}\text{H}_{26}\text{NO}_3$ 292.1912, found 292.1918.



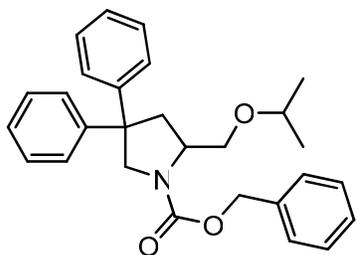
Benzyl 5-hydroxy-3,3-dimethylpiperidine-1-carboxylate (5i).

Prepared according to procedure F. Colorless oil (40% yield). ^1H NMR (500 MHz, CDCl_3): δ 7.41-7.32 (m, 5H), 5.17-5.06 (m, 2H), 4.32-4.20 (m, 1H), 3.90-3.84 (br, 1H), 3.71 (d, $J = 12.5$ Hz, 0.5H), 3.60 (d, $J = 12.5$ Hz, 0.5H), 2.68-2.51 (m, 2H), 2.01 (br, 0.5H), 1.77 (d, $J = 12$ Hz, 1H), 1.70 (br, 0.5H), 1.21 (t, $J = 11.5$, 1H), 1.02-0.89 (m, 6H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor): δ

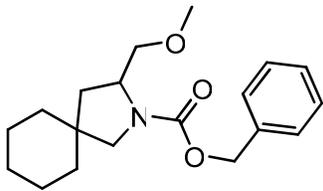
155.7 (major), 155.4 (minor), 136.7, 128.4, 127.8, 67.2, 64.4 (minor), 64.1 (major), 54.8 (major), 54.6 (minor), 50.7, 46.9 (minor), 46.5 (major), 32.4 (major), 32.4 (minor), 28.3, 24.6. FTIR (neat, cm^{-1}): 3425, 2958, 1679, 1434, 1220, 1061. MS (ES): 286 ($[\text{M} + \text{Na}]^+$), 264 (M^+). HRMS (FAB): calculated for $\text{C}_{15}\text{H}_{22}\text{NO}_3$ 264.1600, found 264.1588.



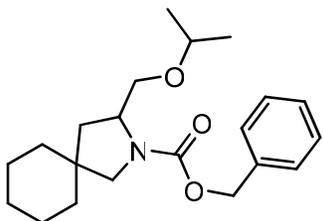
Benzyl 2-(methoxymethyl)-4,4-diphenylpyrrolidine-1-carboxylate (6a). Prepared according to procedure A. 62% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.48-7.19 (m, 15H), 5.32 (d, $J = 12.5\text{Hz}$, 0.5H), 5.22-5.16 (m, 1H), 5.09 (d, $J = 12.5\text{Hz}$, 0.5H), 4.75 (d, $J = 11.1\text{ Hz}$, 0.5H), 4.61 (d, $J = 11.4\text{ Hz}$, 0.5H), 3.94-3.84 (m, 1H), 3.7-3.5 (m, 2H), 3.35 (s, 2H), 3.28 (s, 1H), 2.87-2.79 (m, 1H), 2.75-2.69 (m, 1H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 155.1 (minor), 154.7 (major), 145.5 (major), 144.8 (minor), 136.9, 136.7, 128.5, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 126.8, 126.4, 126.4, 126.3, 126.3, 126.5, 73.6 (minor), 72.5 (major), 66.8, 66.8, 59.2, 56.5, 56.4, 56.3, 55.9, 52.9 (major), 52.7 (minor), 41.8 (minor), 40.5 (major). FTIR (neat, cm^{-1}): 3030, 2927, 2889, 1701, 1447, 1416, 1360, 1197, 1117, 699. MS (ES): 424.4 ($\text{M}^+ + \text{Na}$), 380.2 ($[\text{M}^+ + \text{Na}] - \text{CH}_2\text{OCH}_3$), 288.1. HRMS (FAB): calculated for $\text{C}_{26}\text{H}_{28}\text{NO}_3$ 402.2069, found 402.2059.



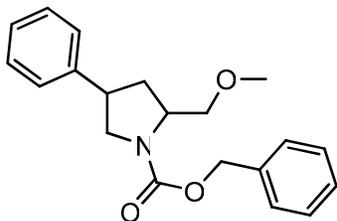
Benzyl 2-(isopropoxymethyl)-4,4-diphenylpyrrolidine-1-carboxylate (6e). Prepared according to procedure B. 56% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.47-7.14 (m, 15H), 5.27 (d, $J = 12.5\text{Hz}$, 0.5H), 5.16 (s, 1H), 5.09 (d, $J = 12.5\text{Hz}$, 0.5H), 4.73 (d, $J = 11.1\text{ Hz}$, 0.5H), 4.58 (d, $J = 11.1\text{ Hz}$, 0.5H), 3.90-3.76 (m, 1H), 3.80-3.70 (m, 0.5H), 3.70-3.66 (m, 1.5H), 3.56-3.53 (m, 0.5H), 3.47-3.35 (m, 1H), 2.89-2.79 (m, 1H), 2.69-2.65 (m, 1H), 1.16-1.05 (m, 6H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 155.1 (minor), 154.7 (major), 145.7 (major), 145.6 (minor), 145.1 (major), 145.0 (minor), 137.0, 136.8, 128.5, 128.5, 128.4, 127.9, 127.8, 127.6, 126.8, 126.5, 126.4, 126.2, 72.1 (major), 72.0 (minor), 69.2 (minor), 68.1 (major), 66.8 (minor), 66.7 (major), 56.9, 56.4, 56.3 (major), 56.2 (minor), 52.9 (major), 52.7 (minor), 42.1 (minor), 40.9 (major), 22.2 (minor), 22.1 (major). FTIR (neat, cm^{-1}): 2971, 1702, 1415, 1109, 699. MS (ES): 430.4 (M^+), 386.2 ($\text{M}^+ - \text{CO}_2$), 280.2. HRMS (FAB): calculated for $\text{C}_{28}\text{H}_{32}\text{NO}_3$ 430.2382, found 430.2380.



Benzyl 3-methoxymethyl-2-aza-spiro[4.5]decane-2-carboxylate (7a). Prepared according to procedure A. 59% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.36-7.30 (m, 5H), 5.25-5.08 (m, 2H), 3.98 (br, 1H), 3.65-3.49 (m, 2H), 3.35-3.27 (m, 4H), 2.95 (d, $J = 10.8$ Hz, 1H), 1.96 (br, 1H), 1.63 (dd, $J = 8.5, 12.5$ Hz, 1H), 1.43-1.26 (m, 10H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 155.2, 137.0 (major), 136.8 (minor), 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 74.5 (minor), 73.3 (major), 66.8 (minor), 66.5 (major), 59.1, 57.2, 56.2 (major), 55.5 (minor), 41.4 (major), 41.0 (minor), 39.9, 36.3 (minor), 36.2 (major), 34.7 (minor), 34.6 (major), 26.2, 23.7, 22.8. FTIR (neat, cm^{-1}): 2926, 2854, 1702, 1414, 1116. MS (EI): 317.2 (M^+ , 0.1%), 272.2 ($[\text{M} - \text{CH}_2\text{OCH}_2]^+$, 28%), 228.2 (55%), 91.2 (Bn^+ , 100%). HRMS (FAB): $\text{C}_{19}\text{H}_{28}\text{NO}_3$ 318.2069, found 318.2054.

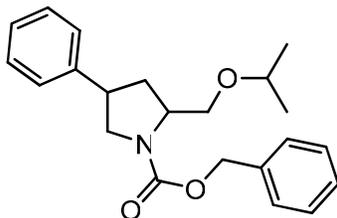


Benzyl 3-isopropoxymethyl-2-aza-spiro[4.5]decane-2-carboxylate (7e). Prepared according to procedure B. 59% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.35-7.26 (m, 5H), 5.26-5.04 (m, 2H), 3.95 (br, 1H), 3.76-3.27 (m, 4H), 2.96 (d, $J = 10.8$ Hz, 1H), 1.97 (br, 1H), 1.63 (dd, $J = 8, 12$ Hz, 1H), 1.53-1.21 (m, 10H), 1.12 (br s, 3H), 1.07 (s, 3H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 155.2, 137.1 (major), 136.8 (minor), 128.4, 128.0, 127.8, 127.6, 72.0, 70.0 (minor), 69.0 (major), 66.8 (minor), 66.4 (major), 57.3, 56.6 (major), 56.0 (minor), 41.4 (major), 41.0 (minor), 40.3, 36.4 (minor), 36.3 (major), 34.9 (minor), 34.9 (major), 26.1, 23.8, 22.9, 22.1. FTIR (neat, cm^{-1}): 2926, 2856, 1703, 1414, 1359, 1117. MS (EI): 345.2 (M^+ , 0.2%), 272.2 (32%), 228.2 (72%), 91.2 (Bn^+ , 100%). $\text{C}_{21}\text{H}_{32}\text{NO}_3$ 346.2383, found 346.2383.

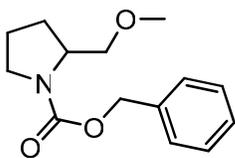


Benzyl 2-(methoxymethyl)-4-phenylpyrrolidine-1-carboxylate (8a). Prepared according to procedure A. 59% yield. Clear oil. An approximately 1:1 mixture of diastereomers was isolated. ^1H NMR (500 MHz, CDCl_3) δ : 7.46-7.25 (m, 10H), 5.30-5.12 (m, 2H), 4.29-4.01 (m, 1.5H), 3.95 (t, $J = 8.5, 0.5$ Hz, 0.5H), 3.72-3.21 (m, 7H), 2.57-2.30 (m, 1H), 2.22-2.07 (m, 1H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor for each diastereomer) δ : 154.8 (major), 154.7 (minor), 141.1 (minor), 140.5 (major), 136.8, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8,

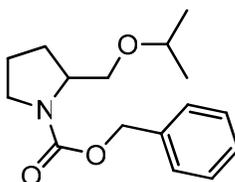
127.8, 127.2, 127.1, 126.8, 126.7, 74.3 (major), 73.6 (minor), 72.9, 67.3, 66.9, 66.8, 66.7, 59.2 (major), 59.1 (minor), 57.6, (major), 57.4 (minor), 56.9, 53.5 (major), 53.2 (minor), 50.3, 43.2 (major), 42.8 (minor), 42.0 (major), 41.0 (minor), 36.9 (major), 36.4 (minor), 36.0 (major), 35.4 (minor). FTIR (neat, cm^{-1}): 2890, 1700, 1416, 1118, 757. MS (EI): 325.2 (M^+ , 0.3%), 280.2 ($[\text{M} - \text{CH}_2\text{OCH}_3]^+$, 31%), 236.2 (31%), 91.2 (Bn^+ , 100%). HRMS (FAB): $\text{C}_{20}\text{H}_{24}\text{NO}_3$ 326.1756, found 326.1742.



Benzyl 2-(isopropoxymethyl)-4-phenylpyrrolidine-1-carboxylate (8e). Prepared according to procedure B. 54% yield. Clear oil. An approximately 1:1 mixture of diastereomers was isolated. ^1H NMR (500 MHz, CDCl_3) δ : 7.45-7.22 (m, 10H), 5.27-5.11 (m, 2H), 4.23-4.01 (m, 0.5H), 3.88-3.22 (m, 4.5H), 2.49-2.42 (m, 0.5H), 2.39-2.34 (m, 0.5H), 2.17-2.06 (m, 1H), 1.08 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor for each diastereomer) δ : 154.8 (major), 154.6 (minor), 141.2 (minor), 140.7 (major), 136.8, 136.8, 128.5, 128.5, 128.4, 127.9, 127.8, 127.2, 127.1, 126.7, 72.1, 69.8, 68.9, 68.6, 68.2, 66.9, 66.8, 66.6, 57.9, 57.4, 57.2, 53.6, 53.2, 43.3, 42.9, 41.9, 40.9, 37.3, 36.4, 35.3, 23.3. FTIR (neat, cm^{-1}): 2970.8, 1701.8, 1414.9, 1111.0, 698.0. MS (EI): 353.2 (M^+ , 0.3%), 280.2 ($[\text{M} - \text{CH}_2\text{OCH}(\text{CH}_3)_2]^+$, 30%), 236.2 (42%), 91.1 (Bn^+ , 100%). HRMS (FAB): $\text{C}_{22}\text{H}_{28}\text{NO}_3$ 354.2069, found 354.2055.

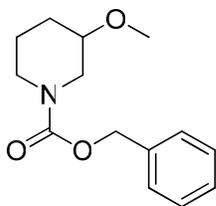


Benzyl 2-(methoxymethyl)-pyrrolidine-1-carboxylate (9a). Prepared according to procedure A. 62% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.41-7.30 (m, 5H), 5.22-5.12 (m, 2H), 4.02-3.89 (m, 1H), 3.59-3.12 (m, 7H), 2.00-1.82 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 154.9, 136.9 (major), 136.9 (minor), 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 73.5 (minor), 72.8 (major), 66.7 (minor), 66.6 (major), 59.0, 56.9 (major), 56.3 (minor), 46.9 (minor), 46.6 (major), 28.7 (minor), 27.9 (major), 27.8 (minor), 27.0 (major). FTIR (neat, cm^{-1}): 2926, 1699, 1540, 1168. MS (EI): 249.2 (M^+ , 0.02%), 204.1 ($[\text{M} - \text{CH}_2\text{OCH}_3]^+$, 6%), 160.1 (6%), 91.2 (Bn^+ , 100). HRMS (FAB): calculated for $\text{C}_{14}\text{H}_{20}\text{NO}_3$ 250.1444, found 250.1445.



Benzyl 2-(isopropoxymethyl)-pyrrolidine-1-carboxylate (9e). Prepared according to procedure B. 61% yield. Clear oil. ^1H NMR (500 MHz, CDCl_3) δ :

7.44-7.30 (m, 5H), 5.23-5.07 (m, 2H), 4.03-3.94 (m, 1H), 3.63-3.35 (m, 5H), 2.03-1.76 (m, 4H), 1.22 (s, 3H), 0.99 (s, 3H). ^{13}C (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor) δ : 154.9, 137.1 (minor), 136.9 (major), 128.4, 127.8, 127.8, 127.8, 77.9 (major), 77.9 (minor), 68.8 (minor), 68.1 (major), 66.7 (minor), 66.5 (major), 57.5 (major), 56.9 (minor), 46.9 (minor), 46.7 (major), 28.8 (minor), 28.0 (major), 23.7 (major), 22.8 (minor), 22.3, 22.0. FTIR (neat, cm^{-1}): 2968, 2876, 1703, 1412, 1358, 1105, 697. MS (EI): 277.2 (M^+ , 2%), 204.2 ($[\text{M} - \text{CH}_2\text{OCH}(\text{CH}_3)_2]^+$, 92%), 160.2 (100%), 91.1 (Bn^+ , 43%). HRMS (FAB): calculated for $\text{C}_{16}\text{H}_{24}\text{NO}_3$ 278.1757, found 278.1759.



Benzyl 3-methoxy-piperidine-1-carboxylate (10a). Prepared according to procedure E. Colorless oil (80% yield). ^1H NMR (500 MHz, CDCl_3): δ 7.41-7.29 (m, 5H), 5.21-5.06 (m, 2H), 3.85 (br, 0.5H), 3.75 (br, 0.5H), 3.62-3.59 (m, 1H), 3.38-3.33 (m, 3H), 3.33-3.22 (br s, 3H), 1.93-1.90 (m, 1H), 1.90 (br s, 1H), 1.54-1.50 (m, 1H), 1.49 (br s, 1H). ^{13}C NMR (125 MHz, CDCl_3 , observed as a mixture of rotamers, major and minor): δ 155.4, 136.8, 128.4, 128.0, 127.9, 127.8, 74.6, 67.0, 56.3 (major), 56.1 (minor), 47.3, 47.2, 44.2, 30.0, 29.7, 22.6, 22.1. FTIR (neat, cm^{-1}): 2942, 2862, 1700, 1430, 1235, 1100. MS (ES): 272 $[\text{M} + \text{Na}]^+$, 250 (M^+). HRMS (FAB): calculated for $\text{C}_{14}\text{H}_{20}\text{NO}_3$ 250.1443, found 250.1444.

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