Supporting Information for

Overcoming Product Inhibition in Catalysis of the Intramolecular Schmidt Reaction

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Table of Contents

General Information. Reactions were performed under an inert atmosphere (argon or nitrogen) either in flame-dried or oven-dried glassware, or glass sample vial with TFE-lined cap. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with nitrogen prior to use. Plastic syringes were flushed with nitrogen before use. All chemicals were used as received from commercial source, without further purification. Methylene chloride and tetrahydrofuran were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. Thin-layer chromatography (TLC) was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Preparative thin layer chromatography was carried out using silica gel GF TLC plates (UV 254 nm, 1000 microns). Visualization was accomplished with UV light and Seebach's stain or aqueous $KMnO_4$ by heating. Flash chromatography was either carried out using standard grade silica gel (40-63 μm particle size, 230 × 400 mesh) with compressed nitrogen as a source of positive pressure or using a semi-automated purification system (4, 12, 24, 48, or 80 g normal phase silica flash columns were used). Infrared (IR) spectra were acquired as thin films or solids. All nuclear magnetic resonance spectra (^{1}H, ^{13}C, APT, COSY, HSQC, and NOESY) were recorded in deuterated chloroform. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent ($CDCl_3$, δ 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR). Coupling constants are given in Hertz (Hz). $CDCl_3$ with tetramethylsilane as an internal standard (TMS, δ 0.00 ppm for ^{1}H NMR) was used to record NMR for the Job plot experiment. HRMS data were collected with a LCT Premier time-of-flight mass spectrometer and an electrospray ion source (ESI). Melting points were determined in open capillary tubes using an automated melting point apparatus and are uncorrected. Sample concentrator using nitrogen gas was utilized for concentration of reaction mixtures. Microsyringes (flushed with nitrogen prior to use) or micropipettes were used to measure and deliver volumes between 1.00–100 μL.

List of known compounds:

The following substrates, 2-(3-azidopropyl)cyclopentanone (**1a**),[1] 2-(3-azidopropyl)-2-methylcyclohexane-1,3-dione (**1b**),[2] 2-(3-azidopropyl)cyclohexanone (**1c**),[1] ethyl 1-(3-azidopropyl)-2-oxocyclohexanecarboxylate (**1d**),[1] 3-(3-azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one (**1g**),[1,3] 2-(2-(azidomethyl)allyl)cyclohexanone (**1h**),[4] 2-(3-azidopropyl)cycloheptanone (**1i**),[1b] 2-(3-azidopropyl)cyclooctanone (**1j**),[1b] 6-azidohexan-2-one (**1m**),[1b] 1-(2-(azidomethyl)phenyl)propan-2-one (**1n**),[4b] 4-azido-2-benzylbutanal (**1p**),[5] and 2-(4-azidobutyl)cyclohexanone (**1q**)[1b] are known and were either synthesized according to the literature procedures or with slight modification of the reported procedures. Details for syntheses of compounds **1b**, **1m**, and **1n** are described below.

Spectral data for the following lactams, hexahydroindolizin-5(1*H*)-one (**2a**),[1] 9a-methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione (**2b**),[2] hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2c**),[1] ethyl 5-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepine-9a-carboxylate (**2d**),[1] 2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2g**),[1,3] 2-methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2h**),[4] octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (**2i**),[1b] octahydro-1*H*-pyrrolo[1,2-*a*]azonin-5(6*H*)-one (**2j**),[1b] 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**2l**),[6] 1-phenethylpiperidin-2-one (**3l**),[7] 1-(pyrrolidin-1-yl)ethanone (**2m**),[1b] *N*-methyl-2-piperidone (**3m**),[8] 2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (**2n**),[9] 1-(isoindolin-2-yl)ethanone (**3n**),[10] 2-benzylhexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-5(2*H*)-one (**2o**),[4b] 3-benzylpyrrolidin-2-one (**2p**),[5] and octahydropyrido[1,2-*a*]azepin-6(2*H*)-one (**2q**)[1b] prepared according to the catalytic methodology described in this paper matches with those reported in the literature.

Syntheses of new compounds:

2-(3-Azidopropyl)-2-methylcyclohexane-1,3-dione (1b):[2]

Following the literature procedure,[11] 2-(3-chloropropyl)-2-methylcyclohexane-1,3-dione **1ba** was prepared from 2-methylcyclohexane-1,3-dione in the following manner:

To a pale yellow solution of 2-methylcyclohexane-1,3-dione (6.30 g, 49.9 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (70 mL) in a flame-dried flask at room temperature under argon atmosphere was added Cs_2CO_3 (17.9 g, 54.9 mmol, 1.1 equiv) and the resulting pale orange suspension was stirred at room temperature for 15 min. 1-Chloro-3-iodopropane (16.1 mL, 150 mmol, 3.0 equiv) was added at once and a cream-colored suspension was stirred at room temperature for 14 h. The reaction mixture was diluted with water and extracted with EtOAc (5 × 40 mL). The combined organic extracts were washed with water (4 × 50 mL), brine (2 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure.

Purification on a semi-automated purification system using an 80 g normal phase silica flash column (100% hexanes to 40% EtOAc in hexanes over 90 min) afforded 2-(3-chloropropyl)-2-methylcyclohexane-1,3-dione **1ba**[11] as a pale yellow oil in 39% yield (3.92 g, 19.3 mmol) and 3-(3-chloropropoxy)-2-methylcyclohex-2-enone **1bb**[11] as a yellow oil in 48% yield (4.86 g, 24.0 mmol).

To a solution of 2-(3-chloropropyl)-2-methylcyclohexane-1,3-dione **1ba** (2.30 g, 11.3 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (15 mL) at room temperature under nitrogen atmosphere was added sodium iodide (2.21 g, 14.8 mmol, 1.3 equiv) followed by sodium azide (1.62 g, 25.0 mmol, 2.2 equiv) and the resulting yellow suspension was stirred at 80 °C for 1.5 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether (4 × 25 mL). The combined organic extracts were washed with water (3 × 80 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 20% EtOAc in hexanes over 65 min) afforded 2-(3-azidopropyl)-2-methylcyclohexane-1,3-dione **1b** as a yellow oil in 87% yield (2.07 g, 9.89 mmol).

(2*R*,4*S*)-2-(3-Azidopropyl)-4-phenylcyclohexanone (*trans*, 1e) and (2*S*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone (*cis*, 1f):

A solution of 4-phenylcyclohexanone (15.0 g, 86.1 mmol, 1.0 equiv), *N*,*N*-dimethylhydrazine (19.6 mL, 258 mmol, 3.0 equiv) and PTSA (0.818 g, 4.30 mmol, 0.050 equiv) in benzene (100 mL) was vigorously refluxed for 28 h under nitrogen atmosphere with removal of water by a Dean–Stark apparatus. The reaction mixture was concentrated under reduced pressure and the crude hydrazone was obtained as an orange oil that was used as such for the alkylation reaction.

To a cooled 1.0 M lithium diisopropylamide (LDA) solution (94.7 mL, 94.7 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added a solution of hydrazone (18.6 g, 86.1 mmol, 1.0 equiv) in THF

(40 mL) slowly over 25 min, and the reaction mixture was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to −78 °C and a solution of 1-chloro-3-iodopropane (10.9 mL, 103 mmol, 1.2 equiv) in THF (30 mL) was added slowly over 25 min. The reaction was warmed to room temperature and stirred for 15 h. The reaction mixture was diluted with ether (50 mL) and then treated with an ice-cold solution of dilute sulfuric acid (50 mL) and the resulting reddish-orange solution was stirred at room temperature for 1 h to hydrolyze the hydrazone. The reaction mixture was diluted with water and extracted with ether (3 × 60 mL). The combined organic extracts were washed with water (2 × 60 mL), saturated aqueous $NaHCO_3$ solution (1 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The reddish-orange oil was dried under vacuum to afford a crude mixture of *trans*- and *cis*-2-(3-chloropropyl)-4-phenylcyclohexanone (**1ea** and **1fa**) that was used as such for the subsequent nucleophilic displacement reaction.

To a solution of a crude mixture of *trans*- and *cis*-2-(3-chloropropyl)-4-phenylcyclohexanone, **1ea** and **1fa** (21.0 g, 83.8 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (60 mL) at room temperature under nitrogen atmosphere was added sodium iodide (15.1 g, 101 mmol, 1.2 equiv) followed by sodium azide (10.9 g, 168 mmol, 2.0 equiv) and the resulting yellow suspension was stirred at 45 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether (4 × 75 mL). The combined organic extracts were washed with water (4 × 250 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on SiO_2 (4−6% EtOAc in hexanes) afforded a mixture of **1e** and **1f** and a partial separation of **1f**. Subsequent purifications of the mixture by chromatography on a semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 10% EtOAc in hexanes over 50 min) afforded the partial separation of **1e** and **1f** as pale pinkish-orange oils and a mixture of **1e** and **1f** as a pale orange oil (16.7 g, 75% combined yield; **1e**:**1f** = 53:47 by ^{1}H NMR or UPLC). (2*R*,4*S*)-2-(3-Azidopropyl)-4-phenylcyclohexanone (*trans*, **1e**): R_f = 0.50 (10% EtOAc/hexanes, run for four times); IR (neat) 2932, 2861, 2094, 1708, 1256, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.66 (m, 3H), 1.87-2.10 (m, 3H), 2.13-2.23 (m, 2H), 2.39 (dtd, *J* = 14.7, 4.5, 1.1 Hz, 1H), 2.44-2.50 (m, 1H), 2.54-2.62 (m, 1H), 3.18 (m, 1H), 3.30 (t, *J* = 6.4 Hz, 2H), 7.21-7.28 (m, 3H), 7.31-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 28.4, 33.2, 37.3, 38.3, 38.4, 48.7, 51.1, 126.5, 126.7, 128.6, 144.2, 213.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M+H–N_2]^+$: 230.1545, found: 230.1546. (2*S*,4*S*)-2-(3-Azidopropyl)-4-phenylcyclohexanone (*cis*, **1f**): R_f = 0.56 (10% EtOAc/hexanes, run for four times); IR (neat) 2929, 2863, 2091, 1709, 1256, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.33 (m, 1H), 1.52-1.70 (m, 3H), 1.83-1.96 (m, 2H), 2.21-2.29 (m, 2H), 2.47-2.58 (m, 3H), 3.12 (tt, *J* = 12.3, 3.2 Hz, 1H), 3.21-3.31 (m, 2H), 7.21-7.24 (m, 3H), 7.30-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 26.5, 34.9, 41.3, 41.7, 43.3, 49.4, 51.5, 126.62, 126.66, 128.6, 144.5, 211.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M+H–N_2]^+$: 230.1545, found: 230.1550.

(1*S*,3*S*,4*R*)-3-(3-Azidopropyl)bicyclo[2.2.1]heptan-2-one (1k):[12]

To a cooled 1.0 M lithium diisopropylamide solution (32.7 mL, 32.7 mmol, 1.2 equiv) in THF at −78 °C in a flame-dried flask under argon atmosphere was added a solution of norcamphor (3.00 g, 27.2 mmol, 1.0 equiv) in THF (10 mL) slowly over 10 min and the reaction mixture was allowed to stir at −78 °C for 1 h. To the resulting white suspension was added hexamethylphosphoramide (20 mL) followed by 1-chloro-3-iodopropane (5.85 mL, 54.5 mmol, 2.0 equiv) over 10 min. The yellow suspension was stirred at −78 °C for 1 h, warmed to room temperature, and stirred for 1 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (50 mL) and diluted with water (50 mL) followed by extraction with ether (3 × 40 mL). The combined organic extracts were washed with water (1 × 70 mL), brine (1 × 70 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 10% EtOAc in hexanes over 40 min) afforded (1*S*,3*S*,4*R*)-3-(3-chloropropyl)bicyclo[2.2.1]heptan-2-one **1ka** as an impure material. Subsequent purification of impure **1ka** on the semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 10% EtOAc in hexanes over 100 min) afforded the partial separation of **1ka** as a pale yellow oil. Vacuum distillation (~1.3 mbar) at ~93 °C of the remaining impure **1ka** afforded sufficiently pure **1ka** as a pale yellow oil (3.22 g, 17.2 mmol, 63% combined yield). (1*S*,3*S*,4*R*)-3-(3-Chloropropyl)bicyclo[2.2.1]heptan-2-one **1ka**: R_f = 0.57 (10% EtOAc/hexanes, run twice); IR (neat) 2957, 2877, 1738, 1081, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27-1.44 (complex, 4H), 1.48-1.60 (m, 2H), 1.65-1.82 (complex, 5H), 2.30 (m, 1H), 2.41-2.42 (m, 1H), 3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 26.5, 27.8, 31.0, 34.7, 39.4, 44.6, 49.3, 52.8, 219.2; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}ClO$ $[M+H]^+$: 187.0890, found: 187.0892.

To a solution of (1*S*,3*S*,4*R*)-3-(3-chloropropyl)bicyclo[2.2.1]heptan-2-one **1ka** (1.84 g, 9.86 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (12 mL) at room temperature under nitrogen atmosphere was added sodium iodide (1.77 g, 11.8 mmol, 1.2 equiv) followed by sodium azide (1.28 g, 19.7 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water (75 mL) and extracted with ether (3 × 35 mL). The combined organic extracts were washed with water (4 × 60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 10% EtOAc in hexanes over 80 min) afforded (1*S*,3*S*,4*R*)-3-(3-azidopropyl)bicyclo[2.2.1]heptan-2-one **1k** as a colorless oil in 97% yield (1.84 g, 9.52 mmol).

(1*S*,3*S*,4*R*)-3-(3-Azidopropyl)bicyclo[2.2.1]heptan-2-one **1k**: R_f = 0.51 (10% EtOAc/hexanes, run twice); IR (neat) 2955, 2877, 2090, 1738, 1263, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21-1.45 (complex, 4H), 1.46-1.55 (m, 1H), 1.58-1.68 (complex, 3H), 1.69-1.79 (complex, 3H), 2.33 (m, 1H), 2.45 (m, 1H), 3.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.3, 27.5, 27.9, 34.7, 39.4, 49.4, 51.1, 53.2, 219.3; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO$ $[M+H-N_2]^+$: 166.1232, found: 166.1247.

7-Azido-1-phenylheptan-3-one (1l):

To a stirring suspension of magnesium turnings (0.434 g, 17.9 mmol, 1.2 equiv) in ether (12 mL) in a flame-dried flask under argon atmosphere was added five drops of 1-bromo-4-chlorobutane and the mixture was gently refluxed for 30 min. A solution of 1-bromo-4-chlorobutane (2.06 mL, 17.9 mmol, 1.2 equiv) in ether (8 mL) was then added slowly over 20 min via a syringe. After refluxing gently for another 30 min, the reaction mixture was cooled to 0 °C and a solution of hydrocinnamaldehyde (2.00 g, 14.9 mmol, 1.0 equiv) in ether (10 mL) was added slowly over 10 min. The reaction mixture was stirred at 0 °C for 15 min, warmed to room temperature over 15 min, and stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ether (2 × 30 mL). The combined organic extracts were washed with brine (2 × 75 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol as a pale yellow oil, which was used for the next oxidation step without purification.

To a stirring solution of crude alcohol in CH_2Cl_2 (40 mL) under nitrogen atmosphere was added pyridinium chlorochromate (6.42 g, 29.8 mmol, 2 equiv) and Celite (7.00 g), and the reaction was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure and the brownish-black residue obtained was suspended in ether (20 mL). The suspension was sonicated for few minutes and filtered through Celite. The residue was rinsed with several portions of ether (6 × 15 mL) and the combined filtrates were concentrated under reduced pressure. Purification on a semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 10% EtOAc in

hexanes over 55 min) afforded 7-chloro-1-phenylheptan-3-one **1la** as an impure material. Subsequent purification of impure **1la** on the semi-automated purification system using a 40 g normal phase silica flash column (100% hexanes to 5% EtOAc in hexanes over 50 min) afforded **1la**[13] as a colorless oil in 33% yield over two steps (1.12 g, 4.98 mmol). 7-Chloro-1-phenylheptan-3-one **1la**: R_f = 0.57 (10% EtOAc/hexanes, run twice); IR (neat) 2944, 2873, 1711, 1453, 1370, 1095, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66-1.78 (m, 4H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 3.50 (m, 2H), 7.17-7.21 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 29.8, 31.9, 42.0, 44.3, 44.7, 126.2, 128.4, 128.5, 141.1, 209.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}ClO$ $[M+H]^+$: 225.1046, found: 225.1083.

To a solution of 7-chloro-1-phenylheptan-3-one **1la** (1.08 g, 4.81 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (10 mL) at room temperature under nitrogen atmosphere was added sodium iodide (0.864 g, 5.77 mmol, 1.2 equiv) followed by sodium azide (0.625 g, 9.61 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether (3 × 30 mL). The combined organic extracts were washed with water (3 × 60 mL), brine (1 × 60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 24 g normal phase silica flash column (100% hexanes to 5% EtOAc in hexanes over 40 min) afforded 7-azido-1-phenylheptan-3-one **1l** as a colorless oil in 90% yield (0.995 g, 4.30 mmol). 7-Azido-1-phenylheptan-3-one **1l**: R_f = 0.50 (10% EtOAc/hexanes, run twice); IR (neat) 2938, 2869, 2090, 1711, 1453, 1258, 1106, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50-1.58 (m, 2H), 1.59-1.67 (m, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 3.24 (t, *J* = 6.6 Hz, 2H), 7.17-7.21 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 28.3, 29.8, 42.2, 44.3, 51.2, 126.2, 128.4, 128.5, 141.0, 209.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ $[M+H-N_2]^+$: 204.1388, found: 204.1386.

6-Azidohexan-2-one (1m):[1b]

To a solution of 6-chlorohexan-2-one (1.50 g, 11.1 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (10 mL) at room temperature under nitrogen atmosphere was added sodium iodide (2.00 g, 13.4 mmol, 1.2 equiv) followed by sodium azide (1.45 g, 22.3 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether (3 × 30 mL). The combined organic extracts were washed with water

(4 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 24 g normal phase silica flash column (100% hexanes to 15% EtOAc in hexanes over 25 min) afforded pure 6-azidohexan-2-one **1m** as a pale yellow oil in 59% yield (0.920 g, 6.52 mmol). Product was found to be slightly volatile.

1-(2-(Azidomethyl)phenyl)propan-2-one (1n):[4b]

To a solution of 1-(2-(bromomethyl)phenyl)propan-2-one[4b] (0.540 g, 2.38 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (5 mL) at room temperature under nitrogen atmosphere was added sodium iodide (0.427 g, 2.85 mmol, 1.2 equiv) followed by sodium azide (0.309 g, 4.76 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 40 min. The reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 40 mL), brine (1 × 40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 12 g normal phase silica flash column (100% hexanes to 10% EtOAc in hexanes over 35 min) afforded 1-(2-(azidomethyl)phenyl)propan-2-one **1n** as a pale orange oil in 92% yield (0.415 g, 2.19 mmol).

3-(3-Azidopropyl)-1-benzylpiperidin-4-one (1o):[4b]

To a solution of 1-benzyl-3-(3-chloropropyl)piperidin-4-one[4b] (0.195 g, 0.734 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (5 mL) at room temperature under nitrogen atmosphere was added sodium iodide (0.132 g, 0.880 mmol, 1.2 equiv) followed by sodium azide (0.0954 g, 1.47 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 30 min) afforded 3-(3-azidopropyl)-1-

benzylpiperidin-4-one **1o** as a pale yellow oil in 83% yield (0.166 g, 0.609 mmol). 3-(3-Azidopropyl)-1-benzylpiperidin-4-one **1o**: R_f = 0.42 (2% MeOH in CH_2Cl_2, run twice); IR (neat) 2934, 2802, 2092, 1712, 1453, 1258, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.55 (m, 2H), 1.82 (m, 1H), 2.22 (m, 1H), 2.36 (m, 1H), 2.43-2.59 (m, 3H), 2.97-3.05 (m, 2H), 3.24 (m, 2H), 3.56 (1/2 AB, *J* = 13.1 Hz, 1H), 3.64 (1/2 AB, *J* = 13.1 Hz, 1H), 7.25-7.29 (m, 1H), 7.30-7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.7, 41.1, 49.4, 51.5, 53.7, 58.9, 61.9, 127.4, 128.5, 128.9, 138.2, 210.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}N_2O$ $[M+H-N_2]^+$: 245.1654, found: 245.1645.

Preliminary screening of the reaction conditions for the intramolecular Schmidt reaction:

Table S1. Preliminary screening with 5 and 10 mol% of $Sc(OTf)_3$

entry	n	conditions	product conversion (%)[a,b]
1	2	5 mol% $CuSO_4 \cdot H_2O$, H_2O, 180 °C, 4 h	37
2	2	10 mol% $Sc(OTf)_3$, CH_3CN, 80 °C, 16 h	47
3	2	5 mol% $Sc(OTf)_3$, *t*-BuOH, 140 °C, 4 h	26
4	2	5 mol% $Sc(OTf)_3$, H_2O, 160 °C, 4 h	80
5	2	5 mol% $Sc(OTf)_3$, H_2O, 180 °C, 4 h	>95 (78)
6	2	10 mol% $Sc(OTf)_3$, CH_2Cl_2, DBU (20 mol%), rt, O/N	9
7	2	5 mol% $Sc(OTf)_3$, CH_2Cl_2, rt, O/N	10
8	2	5 mol% $Sc(OTf)_3$, $C_2H_4Cl_2$, reflux, O/N	16
9	2	5 mol% $TiCl_4$, CH_2Cl_2, rt, 16 h	8
10	1	10 mol% $Sc(OTf)_3$, H_2O, 180 °C, 4 h	42

[a] Product conversion was determined by ^1H NMR. [b] Yield in parentheses represents isolated yield. O/N = Overnight. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Table S2. Preliminary catalyst screening in H_2O at 180 °C

entry	n	conditions	product conversion (%)[a]
1	2	10 mol% $Sc(OTf)_3$, H_2O, 180 °C, 4 h	>95 (73)
2	2	5 mol% $Sc(OTf)_3$, H_2O, 180 °C, 4 h	50
3	2	25 mol% $LiClO_4$, toluene, 180 °C, 4 h	<20
4	2	25 mol% $LiClO_4$, H_2O, 180 °C, 4 h	<20
5	2	25 mol% AuCl, H_2O, 180 °C, 4 h	>95
6	2	25 mol% $Yb(OTf)_3$, H_2O, 180 °C, 4 h	46

7	2	25 mol% $Eu(OTf)_3$, H_2O, 180 °C, 4 h	<10
8	2	25 mol% $Ho(OTf)_3$, H_2O, 180 °C, 4 h	26
9	2	25 mol% $Gd(OTf)_3$, H_2O, 180 °C, 4 h	<15
10	2	25 mol% $Dy(OTf)_3$, H_2O, 180 °C, 4 h	37
11	1	10 mol% $Sc(OTf)_3$, H_2O, 180 °C, 4 h	NR
12	1	25 mol% $Sc(OTf)_3$, H_2O, 180 °C, 4 h	NR
13	2	25 mol% $Yb(OTf)_3$, 10 mol% *n*-Bu_4NOH, H_2O, 180 °C, 4 h	38
14	2	25 mol% $Eu(OTf)_3$, 10 mol% *n*-Bu_4NOH, H_2O, 180 °C, 4 h	<10
15	2	25 mol% $Ho(OTf)_3$, 10 mol% *n*-Bu_4NOH, H_2O, 180 °C, 4 h	31
16	2	25 mol% $Sc(OTf)_3$, 10 mol% *n*-Bu_4NOH, H_2O, 180 °C, 4 h	>95
17	2	38 mol% HCl, 10 mol% *n*-Bu_4NOH, H_2O, 180 °C, 4 h	<10
18	2	10 mol% *n*-Bu_4NOH, H_2O, μW, 180 °C, 4 h	<5
19	1	25 mol% $Sc(OTf)_3$, 10 mol% *n*-Bu_4NOH, H_2O, μW, 180 °C, 4 h	>95 (54)

[a] Product conversion was determined by ^1H NMR. [b] Yield in parentheses represents isolated yield. NR = No reaction.

Table S3. Preliminary catalyst screening with CH_3CN as a solvent

entry	conditions	product conversion (%)[a]
1	25 mol% $Sc(OTf)_3$, CH_3CN, rt, 18 h	25
2	25 mol% $TiCl_4$, CH_3CN, rt, 18 h	25
3	30 mol% CF_3SO_3H, CH_3CN, rt, 18 h	40
4	25 mol% $Sc(OTf)_3$, CH_3CN, μW, 200 °C, 30 min	>95
5	10 mol% $Sc(OTf)_3$, CH_3CN, μW, 200 °C, 2 h	70
6	5 mol% $Sc(OTf)_3$, CH_3CN, μW, 200 °C, 2 h	30
7	25 mol% $TiCl_4$, CH_3CN, μW, 200 °C, 30 min	60
8	25 mol% $BF_3{\cdot}OEt_2$, CH_3CN, μW, 200 °C, 30 min	70
9	25 mol% $Yb(OTf)_3$, CH_3CN, μW, 200 °C, 30 min	80
10	25 mol% CF_3COOH, CH_3CN, μW, 200 °C, 30 min	25

[a] Product conversion was determined either by ^1H NMR or by UPLC.

Several additives were screened with or without $Sc(OTf)_3$ in CH_3CN, H_2O, or $C_2H_4Cl_2$ at different temperatures, but none of them were efficient enough to provide higher conversions and delivered either similar or inferior conversion when compared with the $Sc(OTf)_3$ result (entry 4, Table S3).

List of additives screened:

(1) Salts: NaOAc, NaOPh, Na_2CO_3, NaOTs, NaBr, NaCl, KCl, KF, and AgOTf.

(2) Amines: $(Me)_2NNH_2$, $(Me)_2NH$, Et_3N, DABCO, DMAP, DMF, DMA, and TMANO.

(3) Ligands: (*R*)-BINOL, 1,3-di-*o*-tolyl-2-thiourea, and PYBOX such as 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine.

(4) Phosphines: PPh_3, PBu_3, tri(*o*-tolyl)phosphine, and tri(2-furyl)phosphine.

DABCO = 1,4-Diazabicyclo[2.2.2]octane; DMAP = 4-(Dimethylamino)pyridine; DMF = *N,N*-Dimethylformamide; DMA = *N,N*-Dimethylacetamide; TMANO = Trimethylamine *N*-oxide.

In-depth screening of the reaction conditions for the intramolecular Schmidt reaction based on the screening flowchart (Scheme 2 and Figure 2 in the paper):

Solvent Screening

General procedure for solvent screening: To a mixture of substrate **1e** (25.7 mg, 0.100 mmol, 1.0 equiv) and scandium(III) triflate (9.84 mg, 0.0200 mmol, 0.20 equiv) in a microwave vial at room temperature was added a solvent (0.5 mL). The vial was capped and the reaction mixture was stirred at 150 °C for 16 h under conventional heating using a pie-block. After 16 h, the reaction mixture was allowed to cool to room temperature over 2 h. The cap was removed and the reaction mixture was analyzed by ultra performance liquid chromatography (UPLC) using 1-benzyl-2-pyrrolidinone as an internal standard (IS). 1-Benzyl-2-pyrrolidinone was chosen as an internal standard because it is a lactam and has a chromophore for UPLC analysis.

Analysis of reaction mixture by UPLC: After cooling, the reaction mixture was diluted with CH_2Cl_2 to a final volume of 1.0 mL (Differences in initial volumes were observed for some reactions due to solvent loss). To the vial was added internal standard (16.0 μL, 0.100 mmol) using a microsyringe and the resulting mixture was mixed well to ensure homogeneity. An aliquot (10 μL) of the reaction mixture was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC.

Samples for UPLC analysis for the solvent screening were run on two instruments: (1) Waters Acquity System (Waters LCT premier with ESI and PDA detector). Waters Acquity BEH C18 column (2.1 x 50 mm, 1.7 μm) was employed with a basic method using a linear gradient elution of 95:5 (water:CH_3CN, pH 9.8) to 0:100 (water:CH_3CN) at a flow rate of 0.6 mL/ min over 2.7 minutes. (2) Waters Acquity System (Waters Acquity SQ detector with ESI and Acquity TUV detector). Waters Acquity BEH Shield C18 column (2.1 x 50 mm, 1.7 μm) was employed with a basic method using a linear gradient elution of 90:10 (water:CH_3CN, pH 9.8) to 40:60 (water:CH_3CN) at a flow rate of 0.6 mL/ min over 5.7 minutes followed by a flush with 100% CH_3CN for 0.1 min.

Calibration was carried out each time with an internal standard (IS) before analyzing a batch of reaction mixture to determine a normalization factor (NF) for substrate **1e** and products **2e** and **2f** in order to correct for the differences in extinction coefficients of the internal standard and the substrate **1e** and products **2e** and **2f**.

For the calculation of $NF_{substrate}$, 1-benzyl-2-pyrrolidinone (4.00 μL, 0.0250 mmol) and substrate **1e** (6.43 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (125 μL) to give a concentration of 0.2 M. A drop of this 0.2 M solution was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC. A Retention time (t_R) in min for various peaks was obtained from a chromatogram (t_R for IS and **1e** = 1.24 and 2.15 mins for the first UPLC instrument and t_R for IS, **1e**, and **1f** = 1.92, 5.15, and 5.38 mins for the second UPLC instrument).

For the calculation of $NF_{products}$, 1-benzyl-2-pyrrolidinone (4.00 μL, 0.0250 mmol) and mixture of products **2e** and **2f** (5.73 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (125 μL) to give a concentration of 0.2 M. A drop of this 0.2 M solution was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC. A Retention time (t_R) in min for various peaks was obtained from a chromatogram (t_R for IS, **2e**, and **2f** = 1.24, 1.56, and 1.60 mins for the first UPLC instrument and t_R for IS, **2e**, and **2f** = 1.92, 3.11, and 3.23 mins for the second UPLC instrument).

$$NF_{substrate} = AUC_{substrate}/AUC_{IS}$$

$$NF_{products} = AUC_{products}/AUC_{IS}$$

Products (**2e** and **2f**) conversion (%) was calculated as:

$$\%\ \text{products conversion} = (100 * AUC_{products})/(AUC_{IS} * NF_{products})$$

Unreacted substrate **1e** and its epimer **1f** recoveries (in %) were calculated as:

$$\%\ \text{substrate recovery} = (100 * AUC_{substrate})/(AUC_{IS} * NF_{substrate})$$

Ratio of products (**2e**:**2f**) was determined by UPLC for product conversion and by ^{1}H NMR when products were isolated.

Purification of products (2e and 2f) by preparative TLC:

Reaction mixture was applied on a preparative TLC plate and developed twice with 2% MeOH in CH_2Cl_2. The band corresponding to products was scraped and eluted with 5% MeOH in CH_2Cl_2 through a phase separator cartridge. Evaporation of elution under reduced pressure gave a mixture of products (**2e** and **2f**) as a colorless oil that was further dried under vacuum.

Table S4. Solvent screening with 20 mol% of $Sc(OTf)_3$[a]

entry	solvent	unreacted substrate		product conversion (**2e**:**2f**)	other byproducts observed
		1e	**1f**		
1	Neat	ND	7%	73% (~1:2.5)	≥1
2	Acetone	ND	ND	57% (~1:4)	≥3
3	Ethyl acetate	ND	11%	76% (~1:6)	≥2
4	Dioxane	Trace	19%	64% (~1:3)	≥2
5	Dimethoxyethane	ND	10%	67% (~1:6)	ND
6	Tetrahydrofuran	ND	26%	53% (~1:6)	≥3
7	Dichloroethane	Trace	23%	67% (~1:1)	≥3
8	Toluene	ND	25%	65% (~1:1)	≥1

9	Cyclohexane	Trace	27%	62% (~1:1.5)	≥3
10	Fluorobenzene	Trace	25%	66% (~1:1)[b]	≥2
11	Nitrobenzene	ND	5%	69% (~1:1)	≥1
12	*N*-Methyl-pyrrolidinone	15%	65%	0%	≥3
13	Diethyl Carbonate	ND	Trace	49% (~1:3)	≥4
14	Water	3%	13%	55% (~1:5)	≥3
15	Acetic acid	ND	ND	94% (~1:1)	≥1
16	Formic acid	ND	ND	67% (~2.5:1)[c]	ND
17	Nitromethane	ND	5%	84% (~1:1.5)	≥1
18	Acetonitrile	Trace	11%	72% (~1:1)	≥2
19	Benzonitrile	ND	8%	~91% (~1:2)[d]	ND
20	Butyronitrile	ND	14%	75% (~1:2.5)	≥1
21	Pentafluoro-benzonitrile	ND	ND	89% (~1:3.5)	≥1
22	1-Butyl-3-methylimidazolium tetrafluoroborate	ND	ND	98% (~1:1)	≥1
23	Trifluoroethanol	ND	ND	87% (~2:1)	≥2
24	Isopropanol	ND	ND	22% (~1:4)	≥3

[a] All reactions were run with 20 mol% of $Sc(OTf)_3$ at 150 °C for 16 h. [b] Solvent peak overlaps with product **2f** peak. [c] Isolated yield was 55% after preparative TLC purification. [d] Solvent peak overlaps with IS peak. ND = Not detected.

Table S5. Solvent screening with 10 mol% of $Sc(OTf)_3$[a]

entry	solvent	catalyst	unreacted substrate		product conversion (**2e**:**2f**)	other byproducts observed
			1e	**1f**		
1	Nitromethane	Acetic acid (1 equiv)	50%	32%	Trace	≥5
2	Formic acid	–	Trace	Trace	46% (~2:1)	≥5
3	Nitromethane	$Sc(OTf)_3$	Trace	12%	69% (~1:1.4)	≥3

4	1-Butyl-3-methylimidazolium tetrafluoroborate	–	13%	34%	Trace	≥2
5	1-Butyl-3-methylimidazolium tetrafluoroborate	$Sc(OTf)_3$	ND	Trace	66% (~1:2)	≥3
6	Trifluoroethanol	$Sc(OTf)_3$	ND	Trace	89% (~1:1)[b]	≥2
7	Acetic acid	–	11%	39%	21% (~1:10)	≥3
8	Benzonitrile	$Sc(OTf)_3$	ND	~32%	~61% (~1:2)[c]	≥2

[a] All reactions were run with 10 mol% of $Sc(OTf)_3$ at 150 °C for 16 h. [b] Isolated yield was 74% after preparative TLC purification. [c] Solvent peak overlaps with IS peak. ND = Not detected.

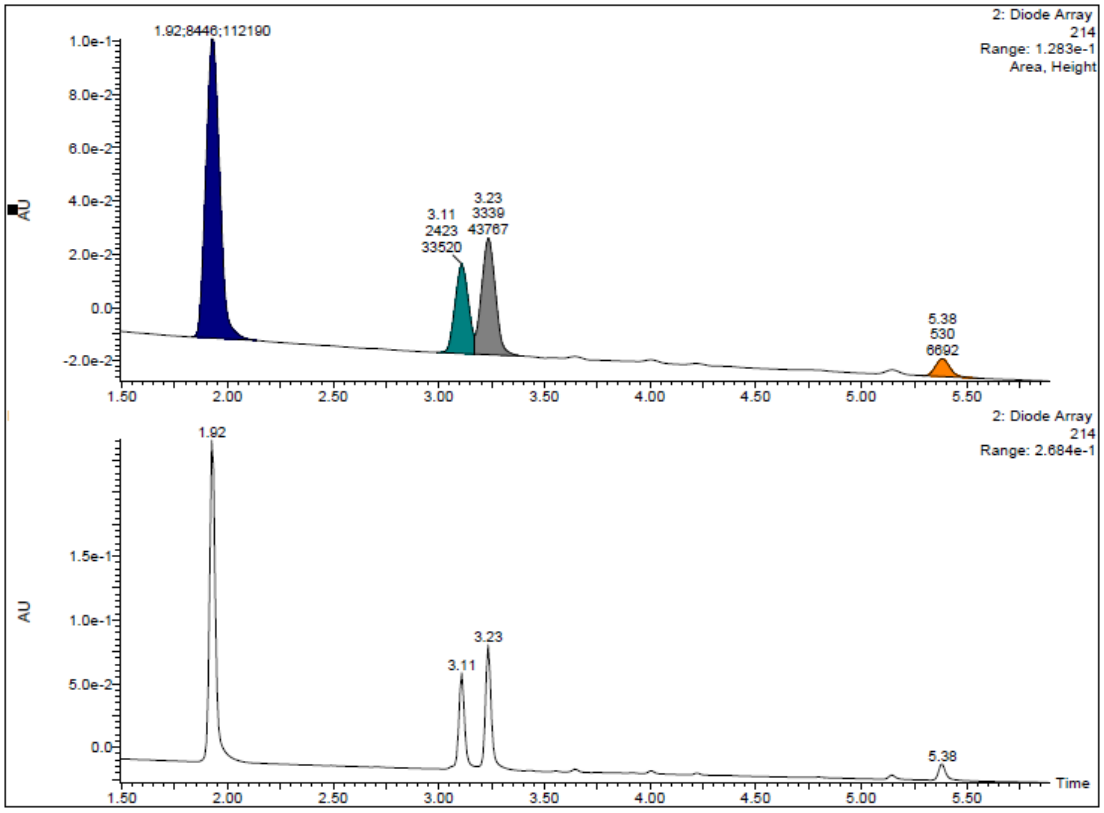


Figure S1. Representative UPLC chromatogram for entry 3, Table S5 (retention time (t_R) for IS, 2e, 2f, and 1f = 1.92, 3.11, 3.23, and 5.38 mins).

Catalyst Screening

General procedure for catalyst screening: To a mixture of substrate **1e** (25.7 mg, 0.100 mmol, 1.0 equiv) and catalyst (0.0100 mmol, 0.10 equiv or 0.00500 mmol, 0.050 equiv) in a microwave vial at room temperature was added trifluoroethanol (0.5 mL). The vial was capped and the reaction mixture was stirred at 80 °C, 50 °C, or 25 °C for 16 h under conventional heating using a pie-block. The reaction mixture was allowed to cool to room temperature over 15 min. The cap was removed and the reaction mixture was analyzed by ultra performance liquid chromatography (UPLC) using 1-benzyl-2-pyrrolidinone as an internal standard.

Catalysts were weighed or measured either in an argon glove box or under nitrogen blanket created with the help of wide mouth funnels connected to in-house nitrogen gas through Tygon® tubing.

Analysis of reaction mixture by UPLC: To the vial was added internal standard (16.0 μL, 0.100 mmol) using a microsyringe and the resulting mixture was mixed well to ensure homogeneity. An aliquot (10 μL) of the reaction mixture was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC.

Samples for UPLC analysis for the catalyst screening were run on Waters Acquity System (Waters Acquity SQ detector with ESI and Acquity TUV detector). Waters Acquity BEH Shield C18 column (2.1 x 50 mm, 1.7 μm) was employed with a basic method using a linear gradient elution of 90:10 (water:CH_3CN, pH 9.8) to 40:60 (water:CH_3CN) at a flow rate of 0.6 mL/ min over 5.7 minutes followed by a flush with 100% CH_3CN for 0.1 min.

Calibration was carried out each time with an internal standard (IS) before analyzing a batch of reaction mixture to determine a normalization factor (NF) for the substrate **1e** and products **2e** and **2f** in a similar way as described before in the section for solvent screening.

For calculation of $NF_{substrate}$ and $NF_{products}$, 1-benzyl-2-pyrrolidinone (4.00 μL, 0.0250 mmol), substrate **1e** (6.43 mg, 0.0250 mmol), and mixture of products **2e** and **2f** (5.73 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (125 μL) to give a concentration of 0.2 M. A drop of this 0.2 M solution was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC. A Retention time (t_R) in min for various peaks was obtained from a chromatogram (t_R for IS, **1e**, **2e**, **1f**, and **2f** were 1.92, 5.15, 3.11, 5.38 and 3.23 mins).

$$\mathrm{NF_{substrate}} = \mathrm{AUC_{substrate}}/\mathrm{AUC_{IS}}$$

$$\mathrm{NF_{products}} = \mathrm{AUC_{products}}/\mathrm{AUC_{IS}}$$

Products (**2e** and **2f**) conversion (%) was calculated as:

$$\%\ \text{products conversion} = (100 * \mathrm{AUC_{products}})/(\mathrm{AUC_{IS}} * \mathrm{NF_{products}})$$

Unreacted substrate **1e** and its epimer **1f** recoveries (in %) were calculated as:

$$\%\ \text{substrate recovery} = (100 * \mathrm{AUC_{substrate}})/(\mathrm{AUC_{IS}} * \mathrm{NF_{substrate}})$$

Purification of products (2e and 2f) by preparative TLC:

Reaction mixture was applied on a preparative TLC plate and developed twice with 2% MeOH in CH_2Cl_2. The band corresponding to products was scraped and eluted with 5% MeOH in CH_2Cl_2 through a phase separator cartridge. Evaporation of elution under reduced pressure gave a mixture of products (**2e** and **2f**) as a colorless oil that was further dried under vacuum.

Table S6. Transition metal Lewis acid catalyst screening with trifluoroethanol[a]

entry	catalyst (10 mol%)	unreacted substrate		product conversion (**2e**:**2f**)	other byproducts observed[b]
		1e	**1f**		
1	$Sc(OTf)_3$	10%	15%	65% (~2:1)	≥1
2	$Sc(NTf_2)_3$	10%	15%	63% (~2.5:1)	≥1
3	$ScCl_3 \cdot xH_2O$	26%	17%	46% (~2:1)	≥2
4	$TiCl_4$[c]	ND	ND	94% (~1.6:1)	≥2
5	$TiCl(O^iPr)_3$[d]	16%	10%	61% (~2:1)	≥3
6	$CrCl_2$	36%	8%	39% (~3:1)	≥3
7	$Mn(OTf)_2$	66%	Trace	20% (~7:1)	≥2
8	$Fe(OTf)_3$	ND	ND	84% (~7:1)	≥1
9	$Fe(OTf)_2$	15%	Trace	61% (~9:1)	≥4
10	$FeCl_3$	42%	3%	10%	≥6
11	$Fe(ClO_4)_3 \cdot xH_2O$	18%	Trace	66% (~7.5:1)	≥3
12	Ferrocenium PF_6	71%	3%	15% (~6.5:1)	≥3
13	$Co(ClO_4)_2 \cdot 6H_2O$	14%	Trace	69% (~6:1)	≥2
14	$Ni(OTf)_3$	53%	3%	38% (~6:1)	≥2

15	$Cu(OTf)_2$	Trace	Trace	43% (~9:1)	≥6
16	$Zn(OTf)_2$	21%	11%	58% (~3:1)	≥1
17	$Y(OTf)_3$	17%	31%	44% (~2:1)	≥2
18	$ZrCl_4$	ND	ND	98% (~1:2.5)	≥2
19	$NbCl_5$	ND	ND	92% (~1.3:1)	≥3
20	$RuCl_3$	89%	5%	ND	≥3
21	$RhCl_3 \cdot xH_2O$	55%	3%	10%	≥3
22	$PdCl_2$	ND	ND	2%	≥6
23	AgOTf	73%	3%	18% (~7:1)	≥1
24	$CdCl_2$	96%	4%	ND	≥1
25	$Hf(OTf)_4$ hydrate	ND	ND	86% (~5.5:1)	≥3
26	$HfCl_4$	4%	3%	81% (~1.4:1)	≥2
27	WCl_6	ND	ND	84% (~2:1)	≥3
28	$AuCl_3$	ND	ND	81% (~2:1)	≥4
29	$HgCl_2$	92%	4%	ND	≥1

[a] All reactions were run at 80 °C for 16 h in trifluoroethanol. [b] In most cases one of the byproducts observed was bridged lactam **3e** with a t_R of 3.43 min. [c] 1.0 M solution in CH_2Cl_2 was used. [d] 1.0 M solution in hexanes was used. ND = Not detected.

Table S7. Post-transition metal, metalloid and lanthanoid Lewis acid catalyst screening with trifluoroethanol[a]

entry	catalyst (10 mol%)	unreacted substrate		product conversion	other byproducts observed[b]
		1e	**1f**	(**2e**:**2f**)	

1	$Al(OTf)_3$	3%	Trace	81% (~6:1)	≥1
2	$EtAlCl_2$[c]	19%	7%	62% (~2:1)	≥4
3	$In(OTf)_3$	ND	ND	85% (~6:1)	≥1
4	$InCl_3$	55%	3%	34% (~7:1)	≥2
5	$Sn(OTf)_2$	21%	Trace	53% (~3:1)	≥1
6	$SnCl_4$[d]	Trace	Trace	77% (~3:1)	≥4
7	$Bi(OTf)_3$	ND	ND	85% (~4:1)	≥1
8	$BiCl_3$	3%	Trace	80% (~2:1)	≥3
9	TlOTf	85%	17%	ND	≥1
10	$BF_3{\cdot}OEt_2$[e]	38%	Trace	50% (~7:1)	≥3
11	CBS catalyst[f]	52%	47%	ND	≥3
12	$SiCl_4$[d]	ND	ND	93% (~1.2:1)	≥2
13	$Yb(OTf)_3$	17%	23%	49% (~2.4:1)	≥3

[a] All reactions were run at 80 °C for 16 h in trifluoroethanol. [b] In most cases one of the byproducts observed was bridged lactam **3e** with a t_R of 3.43 min. [c] 1.0 M solution in hexanes was used. [d] 1.0 M solution in CH_2Cl_2 was used. [e] A stock solution of catalyst in trifluoroethanol was prepared and used. [f] CBS catalyst = (*R*)-(+)-*o*-Tolyl-CBS-oxazaborolidine solution (0.5 M in toluene). ND = Not detected.

Table S8. Alkali and alkaline earth metal Lewis acid and Brønsted acid catalyst screening with trifluoroethanol[a]

entry	catalyst (10 mol%)	unreacted substrate		product conversion (**2e**:**2f**)	other byproducts observed[b]
		1e	**1f**		
1	LiOTf	88%	6%	ND	≥1

2	$Mg(OTf)_2$	90%	5%	~2%	≥1
3	$Ba(OTf)_2$	93%	5%	ND	≥1
4	CF_3COOH[c]	21%	11%	60% (~1.7:1)	≥3
5	HCl[d]	17%	6%	66% (~1:1)	≥3
6	BNDHP	11%	15%	71% (~1:1)	≥2
7	Armstrong's acid	4%	Trace	82% (~3:1)	≥2
8	TsOH	41%	4%	48% (~5:1)	≥2
9	CF_3SO_3H[c]	31%	Trace	57% (~7:1)	≥3

[a] All reactions were run at 80 °C for 16 h in trifluoroethanol. [b] In most cases one of the byproducts observed was bridged lactam **3e** with a t_R of 3.43 min. [c] A stock solution of catalyst in trifluoroethanol was prepared and used. [d] 2.0 M solution in ether was used. ND = Not detected. BNDHP = 1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate. Armstrong's acid = 1,5-Naphthalenedisulfonic acid tetrahydrate. TsOH = *p*-Toluenesulfonic acid (PTSA).

Table S9. Catalyst screening with 5 mol% of $Sc(OTf)_3$ and 20 mol% of HCl[a]

entry	catalyst	catalyst loading	additive	unreacted substrate		product conversion (**2e**:**2f**)[b]
				1e	**1f**	
1	$Sc(OTf)_3$	5 mol%	–	28%	20%	40% (~2.5:1)
2	$Sc(OTf)_3$	5 mol%	CH_3COOH (1 equiv)	28%	5%	53% (~5:1)
3	HCl[c]	20 mol%	–	ND	ND	~100% (~1:3.5)

[a] All reactions were run at 80 °C for 16 h in trifluoroethanol. [b] Byproducts (≥2) were observed in all cases and one of the byproducts was bridged lactam **3e**. [c] 2.0 M solution in ether was used. ND = Not detected.

Table S10. Catalyst screening at 50 °C with trifluoroethanol[a]

entry	catalyst (10 mol%)	unreacted substrate		product yield[b,c] (**2e**:**2f**)
		1e	**1f**	
1	$SiCl_4$[d]	ND	ND	90% (~1:1)
2	$TiCl_4$[d]	ND	ND	93% (~1.7:1)
3	$Hf(OTf)_4$ hydrate	OBS	Trace	73% (~7:1)
4	$Bi(OTf)_3$	Trace	Trace	77% (~6.2:1)
5	$Fe(OTf)_3$	Trace	ND	68% (~6.7:1)
6	$ZrCl_4$	OBS	OBS	73% (~1.7:1)
7	WCl_6	ND	ND	80% (~2.3:1)
8	$AuCl_3$	OBS	OBS	64% (~4.5:1)
9	$NbCl_5$	ND	ND	89% (~1.1:1)

[a] All reactions were run at 50 °C for 16 h in trifluoroethanol. [b] Represents isolated yield after preparative TLC purification. [c] Ratio of products (**2e**:**2f**) was determined by ^{1}H NMR. [d] 1.0 M solution in CH_2Cl_2 was used. ND = Not detected. OBS = Substrate peak was observed by UPLC.

Table S11. Catalyst screening at 25 °C with trifluoroethanol[a]

entry	catalyst	catalysts loading	unreacted substrate		product conversion (**2e**:**2f**)[b]
			1e	**1f**	
1	$SiCl_4$[c]	10 mol%	9%	3%	79% (1.4:1)
2	$SiCl_4$[c]	5 mol%	29%	5%	55% (1.7:1)
3	$TiCl_4$[c]	10 mol%	5%	2%	80% (3:1)
4	$TiCl_4$[c]	5 mol%	18%	3%	61% (4.2:1)

5	WCl_6	10 mol%	ND	ND	57%[d] (5.2:1)
6	$NbCl_5$	10 mol%	4%	2%	74% (3:1)

[a] All reactions were run at 25 °C for 8 h in trifluoroethanol. [b] Ratio of products (**2e**:**2f**) was determined by UPLC except for entry 5. [c] 1.0 M solution in CH_2Cl_2 was used. [d] Represents isolated yield after preparative TLC purification and ratio of products (**2e**:**2f**) was determined by ^{1}H NMR. ND = Not determined.

Table S12. Catalyst screening at 20 °C[a]

entry	catalyst (10 mol%)	solvent	unreacted substrate		product conversion (**2e**:**2f**)[b]
			1e	**1f**	
A	$Bi(OTf)_3$	Trifluoroethanol	19%	Trace	61% (~3.5:1)
B	$Fe(OTf)_3$	Trifluoroethanol	19%	Trace	62% (~7:1)
C	$In(OTf)_3$	Trifluoroethanol	27%	Trace	56% (~7:1)
D	$Al(OTf)_3$	Trifluoroethanol	37%	Trace	43% (~5.5:1)
E	$ZrCl_4$	Trifluoroethanol	4%	28%	61% (~1:12)
F	Armstrong's Acid	Trifluoroethanol	30%	Trace	50% (~6:1)
G	$Fe(OTf)_3$	Nitromethane	25%	Trace	33% (~6:1)
H	$ZrCl_4$	Nitromethane	Trace	69%	14%

[a] All reactions were run at 20 °C for 16 h (extending the reaction period to 24 h had minimal effect on increasing the product conversion). [b] Byproducts (≥2) were observed in all cases and one of the byproducts was bridged lactam **3e**. Armstrong's Acid = 1,5-Naphthalenedisulfonic acid tetrahydrate.

Table S13. Catalyst screening at 25 °C with hexafluoro-2-propanol[a]

entry	catalyst (10 mol%)	product yield[b,c] (**2e**:**2f**)	bridged lactam[b] (**3e**)
A	$TiCl_4$[d]	85% (9:1)	~4%
B	$SiCl_4$[d]	84% (4.7:1)	~4%

[a] All reactions were run at 25 °C for 4 h in hexafluoro-2-propanol. [b] Represents isolated yield after preparative TLC purification. [c] Ratio of products (**2e**:**2f**) was determined by ^{1}H NMR. [d] 1.0 M solution in CH_2Cl_2 was used.

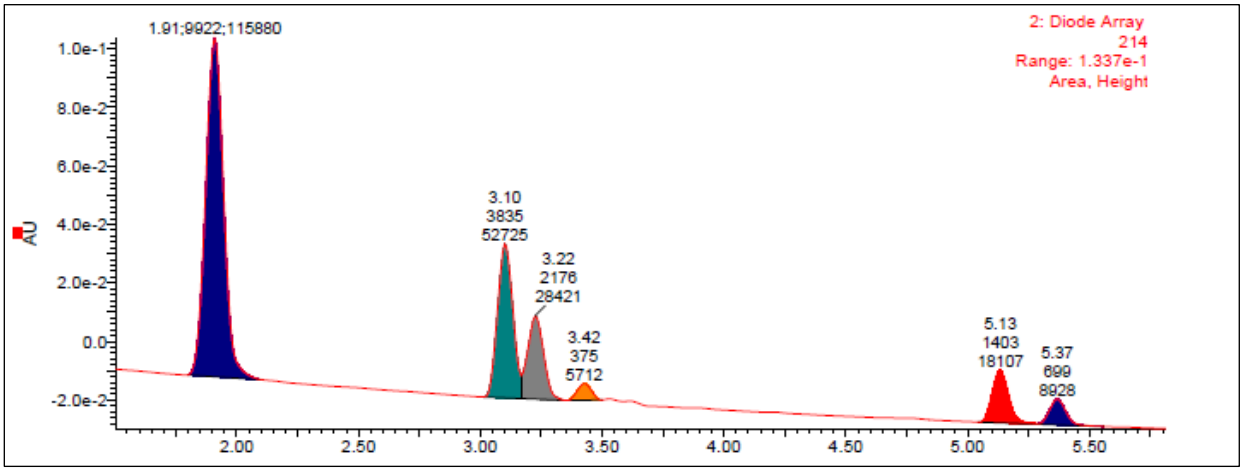


Figure S2: Representative UPLC chromatogram showing area under the curves (AUC) for the possible outcomes of an incomplete intramolecular Schmidt reaction for one of the entries during catalyst screening.

Table 1. Optimization of conditions for intramolecular Schmidt reaction[a,b]

entry	catalyst	catalyst loading (mol%)	solvents	additives	temp (°C)	time (h)	% yield (**2e**:**2f**)[c]	% recovery (**1e**:**1f**)[d]
1	$TiCl_4$	10	CH_2Cl_2	-	25	18	6% (40:60)	84% (10:90)
2	$TiCl_4$	10	CH_3NO_2	-	25	18	35% (37:63)	61% (3:97)
3	$TiCl_4$	10	$BMIMBF_4$	-	25	18	12% (30:70)	80% (12:88)
4	$TiCl_4$	10	C_6F_5CN	-	25	18	30% (32:68)	58% (10:90)
5	$TiCl_4$	10	*i*-PrOH	-	37	18	Trace	86% (3:97)
6	$TiCl_4$	10	CH_3CN	-	37	18	41% (15:85)	47% (1:99)
7	$TiCl_4$	10	CH_3CN	$(CF_3)_2CHOH$[e]	25	18	34% (10:90)	61% (5:95)
8	$TiCl_4$	10	CF_3CH_2OH	-	25	18	79% (82:18)[d]	Trace
9	none	-	$(CF_3)_2CHOH$	-	37	18	ND	93% (98:2)
10	$TiCl_4$[g]	10	$(CF_3)_2CHOH$	-	25	12	88% (90:10)[f]	ND
11	$TiCl_4$	10	$(CF_3)_2CHOH$	-	25	12	91% (98:2)[f]	ND
12	$TiCl_4$	7	$(CF_3)_2CHOH$	-	25	24	88% (98:2)[f]	ND
13	**$TiCl_4$**	**5**	**$(CF_3)_2CHOH$**	**-**	**25**	**38**	**89% (99:1)[f]**	**Trace**
14	$TiCl_4$[h]	5	$(CF_3)_2CHOH$	-	25	38	86% (98:2)	Trace
15	$TiCl_4$[i]	5	$(CF_3)_2CHOH$	-	25	38	89% (98:2)	ND
16	$TiCl_4$	5	$(CF_3)_2CHOH$	DTBMP[j]	25	38	52% (98:2)	19% (98:2)
17	$TiCl_4$	5	$(CF_3)_2CHOH$	DTBMP[k]	25	38	21% (99:1)	50% (96:4)[b]
18	$TiCl_4$	5	$(CF_3)_2CHOH$	MS (4Å)	25	38	11% (97:3)	86% (98:2)
19	$SiCl_4$	5	$(CF_3)_2CHOH$	-	25	38	86% (98:2)[f]	ND
20	$SbCl_5$	5	$(CF_3)_2CHOH$	-	25	38	86% (98:2)[f]	ND
21	$NbCl_5$	5	$(CF_3)_2CHOH$	-	25	38	82% (98:2)	ND
22	WCl_6	5	$(CF_3)_2CHOH$	-	25	38	86% (98:2)[f]	ND
23	$Bi(OTf)_3$	5	$(CF_3)_2CHOH$	-	25	38	60% (98:2)	25% (98:2)

24	$Hf(OTf)_4$ hydrate	5	$(CF_3)_2CHOH$	-	25	38	76% (98:2)	14% (98:2)
25	$HfCl_4$	5	$(CF_3)_2CHOH$	-	25	38	77% (99:1)[f]	15% (98:2)
26	$Fe(OTf)_3$	5	$(CF_3)_2CHOH$	-	25	38	83% (98:2)[f]	Trace
27	$Sc(OTf)_3$	5	$(CF_3)_2CHOH$	-	25	38	28% (97:3)	61% (98:2)
28	HCl	10	$(CF_3)_2CHOH$	-	25	38	40% (96:4)[f]	46% (98:2)
29	HCl	20	$(CF_3)_2CHOH$	-	25	38	78% (97:3)[f]	Trace
30	CF_3COOH	10	$(CF_3)_2CHOH$	-	25	38	62% (97:3)	34% (98:2)
31	Armstrong's acid	5	$(CF_3)_2CHOH$	-	25	38	65% (98:2)	13% (98:2)
32	$ClSO_3H$	10	$(CF_3)_2CHOH$	-	25	20	80% (98:2)[f]	ND
33	(*S*)-BNDHP	5	$(CF_3)_2CHOH$	-	25	38	32% (96:4)[l]	62% (98:2)
34	$Ti(^iOPr)_4$	10	$(CF_3)_2CHOH$	-	25	38	Trace	93% (95:5)

[a] To a solution of substrate **1e** (0.1 mmol) in solvent (0.5 mL) at room temperature was added a catalyst under nitrogen or argon atmosphere unless otherwise mentioned. [b] Concentration of reaction mixture is 0.2 M unless otherwise mentioned. [c] Isolated yield after preparative TLC purification and ratio was determined by ^1H NMR. [d] Isolated yield after preparative TLC purification and ratio was determined by UPLC of a crude reaction mixture. [e] 1 equivalent of $(CF_3)_2CHOH$ was used as an additive. [f] Bridged lactam **3e** was also isolated in 1–4% yield. [g] $TiCl_4$ solution was added to substrate **1e** followed by the addition of the solvent. [h] Concentration of reaction mixture is 0.4 M. [i] Concentration of reaction mixture is 0.1 M. [j] 10 mol% of 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was used as a Brønsted acid scavenger. [k] 20 mol% of DTBMP was used. [l] No enantioselectivity was observed. ND = Not detected. 1.0 M solution of $TiCl_4$, $SiCl_4$, and $SbCl_5$ in CH_2Cl_2 was used. 2.0 M solution of HCl in diethyl ether was used. $BMIMBF_4$ = 1-Butyl-3-methylimidazolium tetrafluoroborate. MS (4Å) = Molecular sieves activated (4Å). Armstrong's acid = 1,5-Naphthalenedisulfonic acid tetrahydrate. (*S*)-BNDHP = (*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate.

General procedure for reaction conditions optimization (Table 1):

To a solution of (2*R*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1e** (0.0257 g, 0.100 mmol, 1.0 equiv) in solvent (0.5 mL) at room temperature was added catalyst (5–20 mol%) and/or an additive under nitrogen or argon atmosphere in a 1 dram vial. The vial was capped and the reaction mixture was stirred at 25 or 37 °C for 12–38 h. Reaction progress was monitored by UPLC. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and applied on a preparative TLC plate. Preparative TLC plate was either developed once or twice with

100 % CH_2Cl_2 or 2% MeOH in CH_2Cl_2. Bands corresponding to the substrates (**1e** and **1f**), products (**2e** and **2f**), and bridged lactam (**3e**) were scraped and eluted with 100% CH_2Cl_2 or 5% MeOH in CH_2Cl_2 through a phase separator cartridge. Evaporation of elution under reduced pressure provided recovered substrates (**1e** and (2*S*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1f**), products ((8*S*,9a*R*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2e** and (8*S*,9a*S*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2f**), and bridged lactam ((4*R*,6*R*)-4-phenyl-1-azabicyclo[4.3.1]decan-10-one **3e**) respectively. Ratios of **1e**:**1f** and **2e**:**2f** were determined by ^{1}H NMR or UPLC.

General procedure for the catalytic intramolecular Schmidt reaction using $TiCl_4$ (Tables 2 and 3):
To a solution of an azidoketone in hexafluoro-2-propanol in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (2.5–35 mol%). The vial was capped and the reaction mixture was stirred at 25 °C for 18–62 h (gas evolution was observed). Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification was carried out using a 4 g normal phase silica flash column on a semi-automated purification system using a gradient elution from 0–5% MeOH in CH_2Cl_2.

Hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2c):

To a solution of 2-(3-azidopropyl)cyclohexanone **1c** (0.0725 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (10.0 μL, 0.0100 mmol, 0.025 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2c** as a pale yellow oil in 94% yield (0.0575 g, 0.375 mmol).

(8*S*,9a*S*)-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2f):

To a solution of (2*S*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1f** (0.103 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (10.0 μL, 0.0100 mmol, 0.025 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded (8*S*,9a*S*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2f** as a pale yellow oil in 98% yield (0.0901 g, 0.393 mmol). (8*S*,9a*S*)-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2f**: R_f = 0.31 (2% MeOH in CH_2Cl_2); IR (neat) 2924, 2871, 1626, 1450, 1425, 759, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59-1.79 (m, 4H), 1.81-1.88 (m, 1H), 1.90-1.97 (m, 2H), 2.18-2.26 (m, 1H), 2.50-2.64 (m, 2H), 2.75 (tt, *J* = 12.2, 3.3 Hz, 1H), 3.37-3.44 (m, 1H), 3.69 (m, 1H), 3.79-3.85 (m, 1H), 7.11-7.18 (m, 3H), 7.24-7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 30.6, 34.8, 37.4, 43.5, 46.8, 48.0, 57.9, 126.4, 126.6, 128.5, 146.3, 173.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1545, found: 230.1555.

The *cis*-configuration for lactam **2f** was confirmed by NOESY experiment.

(8*S*,9a*R*)-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2e):

To a solution of (2*R*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1e** (0.103 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 38 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and applied on a preparative TLC plate. Preparative TLC plate was developed twice with 2% MeOH in CH_2Cl_2. Bands corresponding to fused lactam **2e** and bridged lactam **3e** were scraped and eluted with 5% MeOH in CH_2Cl_2 through a phase separator cartridge. Evaporation of elution under reduced pressure afforded (8*S*,9a*R*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2e** as a pale yellow oil in 87% yield (0.0796 g, 0.347 mmol) and (4*R*,6*R*)-4-phenyl-1-azabicyclo[4.3.1]decan-10-one **3e** as a colorless oil in ~2% yield (0.00220 g, 0.00959 mmol). (8*S*,9a*R*)-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2e**: R_f = 0.18 (2% MeOH in CH_2Cl_2); IR (neat) 2934, 2872, 1628, 1426, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61-1.70 (m, 1H), 1.72-1.81 (m, 1H), 1.84-1.96 (m, 2H), 2.01 (m, 1H), 2.09-2.20 (m, 3H), 2.46-2.53 (m, 1H), 2.71 (m, 1H), 3.02 (m, 1H), 3.48-3.60 (m, 2H), 3.98 (m, 1H), 7.19-7.23 (m, 3H), 7.29-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 27.5, 34.1, 34.6, 39.4, 39.6, 46.7, 54.7, 126.4, 127.3, 128.7, 144.6, 172.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1545, found: 230.1545. (4*R*,6*R*)-4-Phenyl-1-azabicyclo[4.3.1]decan-10-one **3e**: R_f = 0.25 (2% MeOH in CH_2Cl_2); IR (neat) 2930, 2856, 1675, 1492, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56-1.65 (m, 1H), 1.67-1.76 (m, 1H), 1.77-1.93 (complex, 4H), 2.24 (m, 1H), 2.42 (dtd, *J* = 14.5, 11.2, 7.4 Hz, 1H), 2.75 (ddd, *J* = 13.8, 11.2, 6.4 Hz, 1H), 3.00 (td, *J* = 11.8, 2.0 Hz, 1H), 3.08 (dtd, *J* = 10.2, 5.1, 2.0 Hz, 1H), 3.39 (td, *J* = 11.4, 3.1 Hz, 1H), 3.60-3.64 (m, 1H), 3.89 (dd, *J* = 13.8, 7.3 Hz, 1H), 7.11-7.13 (m, 2H), 7.17-7.20 (m, 1H), 7.26-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 28.3, 32.5, 39.9, 45.2, 46.0, 49.1, 54.3, 126.4, 126.7, 128.8, 148.0, 184.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1545, found: 230.1566. Bridged lactam **3e** was found to be unstable.

9a-Methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione (2b):

To a solution of 2-(3-azidopropyl)-2-methylcyclohexane-1,3-dione **1b** (0.0837 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the

reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 50 min) afforded 9a-methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione **2b** as a cream-yellow solid in 94% yield (0.0681 g, 0.376 mmol).

Ethyl 5-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepine-9a-carboxylate (2d):

To a solution of ethyl 1-(3-azidopropyl)-2-oxocyclohexanecarboxylate **1d** (0.101 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 40 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 30 min) afforded 9a-methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione **2d** as a white solid in 94% yield (0.0850 g, 0.377 mmol).
Reaction of **1d** (0.101 g, 0.400 mmol, 1.0 equiv) with 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (40 μL, 0.0400 mmol, 0.10 equiv) for 18 h in a similar way as described above afforded **2d** in 95% yield (0.0856 g, 0.380 mmol).

2,3,11,11a-Tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2g):

To a solution of 3-(3-azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one **1g** (0.0917 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g

sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded 2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2g** as a pale orange solid in 89% yield (0.0720 g, 0.358 mmol).

2-Methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2h):

To a solution of 2-(2-(azidomethyl)allyl)cyclohexanone **1h** (0.0773 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 35 min) afforded 2-methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2h** as a pale orange oil in 84% yield (0.0554 g, 0.335 mmol).

Hexahydroindolizin-5(1*H*)-one (2a):

To a solution of 2-(3-azidopropyl)cyclopentanone **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 30 min) afforded hexahydroindolizin-5(1*H*)-one **2a** as a pale yellow oil in 87% yield (0.0485 g, 0.348 mmol).

Reaction of **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) with 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (60.0 μL, 0.0600 mmol, 0.15 equiv) for 44 h in a similar way as described above afforded **2a** in 79% yield (0.0440 g, 0.316 mmol).

Reaction of **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 44 h in a similar way as described above afforded **2a** in 60% yield (0.0333 g, 0.239 mmol; 78% brsm). Substrate **1a** was recovered in 23% yield (0.0157 g, 0.0939 mmol).

Octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (2i):

To a solution of 2-(3-azidopropyl)cycloheptanone **1i** (0.0781 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 48 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one **2i** as a colorless oil in 86% yield (0.0573 g, 0.343 mmol) and 1-azabicyclo[5.3.1]undecan-11-one **3i** as a colorless oil in ~2% yield (0.00170 g, 0.0102 mmol). 1-Azabicyclo[5.3.1]undecan-11-one **3i**: R_f = 0.22 (2% MeOH in CH_2Cl_2); IR (neat) 2924, 2854, 1643, 1445, 1281, 1170, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44-1.54 (m, 3H), 1.60-1.76 (m, 3H), 1.77-1.88 (m, 3H), 1.96 (m, 1H), 2.06 (m, 1H), 2.17-2.24 (m, 1H), 2.72 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.74-2.79 (m, 1H), 3.20 (ddd, *J* = 11.4, 6.5, 2.7 Hz, 1H), 3.64 (td, *J* = 11.7, 3.0 Hz, 1H), 4.58 (td, *J* = 13.3, 4.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 23.7, 25.5, 26.6, 32.4, 42.0, 42.1, 48.1, 49.8, 181.3; HRMS (ESI) *m/z* calcd for $C_{10}H_{18}NO$ $[M+H]^+$: 168.1388, found: 168.1392.

Reaction of **1i** (0.0781 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv) for 62 h in a similar way as described above afforded **2i** in 34% yield (0.0228 g, 0.136 mmol; 85% brsm). Substrate **1i** was recovered in 60% yield (0.0469 g, 0.240 mmol).

Octahydro-1*H*-pyrrolo[1,2-*a*]azonin-5(6*H*)-one (2j):

To a solution of 2-(3-azidopropyl)cyclooctanone **1j** (0.0837 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (100 μL, 0.100 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 62 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 35 min) afforded octahydro-1*H*-pyrrolo[1,2-*a*]azonin-5(6*H*)-one **2j** as a colorless oil in 90% yield (0.0651 g, 0.359 mmol).

(6*S*,9*R*,9a*S*)-Hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one (13b):

To a solution of (1*S*,3*S*,4*R*)-3-(3-azidopropyl)bicyclo[2.2.1]heptan-2-one **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (100 μL, 0.100 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 62 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 35 min) afforded (6*S*,9*R*,9a*S*)-hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one **13b** as a colorless oil in 87% yield (0.0574 g, 0.347 mmol; 90% brsm). Substrate **1k** was recovered in 3% yield (0.00250 g, 0.0129 mmol). (6*S*,9*R*,9a*S*)-Hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one **13b**: R_f = 0.19 (2% MeOH in CH_2Cl_2); IR (neat) 2945, 2871, 1641, 1432, 1129 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30-1.39 (m, 1H), 1.45 (td, *J* = 11.8, 4.3 Hz, 1H), 1.56-1.61 (m, 1H), 1.65 (d, *J* = 11.8 Hz, 1H), 1.68-1.90 (complex, 6H), 2.40 (m, 1H), 2.70 (m, 1H), 3.00 (m, 1H), 3.08 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.80 (ddd, *J* = 11.9, 8.9, 7.6 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 21.9, 28.4, 29.5, 30.3, 32.0, 36.2, 43.0, 43.6, 65.6, 175.1; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO$ $[M+H]^+$: 166.1232, found: 166.1226.

Reaction of **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 62 h in a similar way as described above afforded **13b** in 43% yield (0.0285 g, 0.172 mmol; 78% brsm). Substrate **1k** was recovered in 45% yield (0.0346 g, 0.179 mmol).

3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one (2l):

To a solution of 7-azido-1-phenylheptan-3-one **1l** (0.0925 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (100 μL, 0.100 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 32 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded a mixture of 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one **2l** and 1-phenethylpiperidin-2-one **3l** as a colorless oil in 94% yield (0.0763 g, 0.375 mmol; **2l**:**3l** = 93:7 as determined by ^{1}H NMR).

Reaction of **1l** (0.0925 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv) for 24 h in a similar way as described above afforded a mixture of 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one **2l** and 1-phenethylpiperidin-2-one **3l** as a pale yellow oil in 79% yield (0.0640 g, 0.315 mmol, 96% brsm; **2l**:**3l** = 93:7 as determined by ^{1}H NMR). Substrate **1l** was recovered in 18% yield (0.0165 g, 0.0713 mmol).

1-(Pyrrolidin-1-yl)ethanone (2m):

To a solution of 6-azidohexan-2-one **1m** (0.0564 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2

(80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded a mixture of 1-(pyrrolidin-1-yl)ethanone **2m** and *N*-methyl-2-piperidone **3m** as a colorless oil in 86% yield (0.0390 g, 0.345 mmol; **2m**:**3m** = 97:3 as determined by ^{1}H NMR).

Reaction of **1m** (0.0564 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (60.0 μL, 0.0600 mmol, 0.15 equiv) for 24 h in a similar way as described above afforded a mixture of 1-(pyrrolidin-1-yl)ethanone **2m** and *N*-methyl-2-piperidone **3m** as a colorless oil in 77% yield (0.0350 g, 0.309 mmol, 81% brsm; **2m**:**3m** = 97:3 as determined by ^{1}H NMR). Substrate **1m** was recovered in 4% yield (0.00250 g, 0.0177 mmol).

Reaction of **1m** (0.0564 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 36 h in a similar way as described above afforded a mixture of 1-(pyrrolidin-1-yl)ethanone **2m** and *N*-methyl-2-piperidone **3m** as a colorless oil in 73% yield (0.0331 g, 0.292 mmol; **2m**:**3m** = 97:3 as determined by ^{1}H NMR).

2-Methyl-1,2-dihydroisoquinolin-3(4*H*)-one (2n) and 1-(isoindolin-2-yl)ethanone (3n):

To a solution of 1-(2-(azidomethyl)phenyl)propan-2-one **1n** (0.0757 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (60.0 μL, 0.0600 mmol, 0.15 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded a mixture of 2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one **2n** and 1-(isoindolin-2-yl)ethanone **3n** as a yellow oil in 64% yield (0.0411 g, 0.255 mmol; **2n**:**3n** = 79:21 (~4:1) as determined by ^{1}H NMR).

Reaction of **1n** (0.0757 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 24 h in a similar way as described above afforded a mixture of 2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one **2n** and 1-(isoindolin-2-yl)ethanone **3n** as a yellow

oil in 58% yield (0.0376 g, 0.233 mmol, 64% brsm; **2n**:**3n** = 77:23 as determined by ^{1}H NMR). Substrate **1n** was recovered in 9% yield (0.00700 g, 0.0370 mmol).

2-Benzylhexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-5(2*H*)-one (2o):

To a solution of 3-(3-azidopropyl)-1-benzylpiperidin-4-one **1o** (0.109 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (140 μL, 0.140 mmol, 0.35 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2, neutralized with saturated aqueous $NaHCO_3$ solution (0.6 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The orange residue obtained was re-dissolved in CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 35 min) afforded 2-benzylhexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-5(2*H*)-one **2o** as a colorless oil in 90% yield (0.0876 g, 0.359 mmol).
During the initial addition of $TiCl_4$ solution up to 25 mol%, a formation of yellow solid was observed (presumably, the HCl salt of amine). Work-up with aqueous $NaHCO_3$ was necessary to neutralize the amine salt into free amine base for purification and for TLC monitoring.

3-Benzylpyrrolidin-2-one (2p):

To a solution of 4-azido-2-benzylbutanal **1p** (0.0813 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.05 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5%

MeOH in CH_2Cl_2 over 35 min) afforded 3-benzylpyrrolidin-2-one **2p** as a pale blue crystalline solid in 86% yield (0.0604 g, 0.345 mmol).

Octahydropyrido[1,2-*a*]azepin-6(2*H*)-one (2q):

To a solution of 2-(4-azidobutyl)cyclohexanone **1q** (0.0781 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 60 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded octahydropyrido[1,2-*a*]azepin-6(2*H*)-one **2q** as a pale yellow oil in 11% yield (0.00720 g, 0.0431 mmol; 20% brsm). Substrate **1q** was recovered in 47% yield (0.0370 g, 0.190 mmol).

General procedure for reaction conditions optimization (Table 4):
To a solution of 2-(3-azidopropyl)cyclopentanone **1a** (0.0167 g, 0.100 mmol, 1.0 equiv) in hexafluoro-2-propanol (0.5 mL) at room temperature was added catalyst (5−40 mol%) and/or an additive (5−80 mol%) under nitrogen atmosphere in a 1 dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with 5% MeOH in CH_2Cl_2 and eluted through a phase separator cartridge containing a short bed of silica gel. Evaporation of elution under reduced pressure provided a mixture of **1a** and hexahydroindolizin-5(1*H*)-one **2a** whose ratios were determined by ^{1}H NMR.

General procedure for the catalytic intramolecular Schmidt reaction using acetyl chloride (Table 5): To a solution of an azidoketone in hexafluoro-2-propanol (HFIP) in a 4 dram vial flushed with nitrogen was added acetyl chloride (10–100 mol%). The vial was capped and the reaction mixture was stirred at 25 °C for 20–62 h (gas evolution was observed). Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica

gel in a 5 g sample cartridge. Purification was carried out using a 4 g normal phase silica flash column on a semi-automated purification system using a gradient elution from 0–5% MeOH in CH_2Cl_2.

Hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2c):

To a solution of 2-(3-azidopropyl)cyclohexanone **1c** (0.0725 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (2.84 μL, 0.0400 mmol, 0.10 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2c** as a pale yellow oil in 95% yield (0.0582 g, 0.380 mmol).

(8*S*,9a*S*)-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2f):

To a solution of (2*S*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1f** (0.103 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (2.84 μL, 0.0400 mmol, 0.10 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded (8*S*,9a*S*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2f** as a colorless oil in 98% yield (0.0897 g, 0.391 mmol).

(8*S*,9a*R*)-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2e):

To a solution of (2*R*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1e** (0.0257 g, 0.100 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (1.42 μL, 0.0200 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 38 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and applied on a preparative TLC plate. Preparative TLC plate was developed twice with 2% MeOH in CH_2Cl_2. Bands corresponding to fused lactam **2e** and bridged lactam **3e** were scraped and eluted with 5% MeOH in CH_2Cl_2 through a phase separator cartridge. Evaporation of elution under reduced pressure afforded (8*S*,9a*R*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2e** as a colorless oil in 90% yield (0.0206 g, 0.0898 mmol) and (4*R*,6*R*)-4-phenyl-1-azabicyclo[4.3.1]decan-10-one **3e** as a colorless oil in ~3% yield (0.000600 g, 0.00261 mmol).

9a-Methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione (2b):

To a solution of 2-(3-azidopropyl)-2-methylcyclohexane-1,3-dione **1b** (0.0837 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (5.70 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 50 min) afforded 9a-methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione **2b** as a cream-yellow solid in 95% yield (0.0692 g, 0.382 mmol).

2-Methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2h):

To a solution of 2-(2-(azidomethyl)allyl)cyclohexanone **1h** (0.0773 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (5.70 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded 2-methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2h** as a pale orange oil in 77% yield (0.0508 g, 0.307 mmol).

2-Methyl-1,2-dihydroisoquinolin-3(4*H*)-one (2n) and 1-(isoindolin-2-yl)ethanone (3n):

To a solution of 1-(2-(azidomethyl)phenyl)propan-2-one **1n** (0.0757 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (17.1 μL, 0.240 mmol, 0.60 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded a mixture of 2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one **2n** and 1-(isoindolin-2-yl)ethanone **3n** as a yellow oil in 68% yield (0.0437 g, 0.271 mmol; **2n**:**3n** = 65:35 as determined by ^{1}H NMR).

Hexahydroindolizin-5(1*H*)-one (2a):

To a solution of 2-(3-azidopropyl)cyclopentanone **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (22.8 μL, 0.320 mmol, 0.80 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded hexahydroindolizin-5(1*H*)-one **2a** as a pale yellow oil in 90% yield (0.0503 g, 0.361 mmol).

Octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (2i):

To a solution of 2-(3-azidopropyl)cycloheptanone **1i** (0.0781 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (22.8 μL, 0.320 mmol, 0.80 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 48 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one **2i** as a pale yellow oil in 87% yield (0.0583 g, 0.349 mmol) and 1-azabicyclo[5.3.1]undecan-11-one **3i** as a pale yellow oil in ~3% yield (0.00220 g, 0.0132 mmol).

(6*S*,9*R*,9a*S*)-Hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one (2k):

To a solution of (1*S*,3*S*,4*R*)-3-(3-azidopropyl)bicyclo[2.2.1]heptan-2-one **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (28.4 μL, 0.400 mmol, 1.0 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 62 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-

automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded (6*S*,9*R*,9a*S*)-hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one **2k** as a colorless oil in 92% yield (0.0610 g, 0.369 mmol).

3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one (2l):

To a solution of 7-azido-1-phenylheptan-3-one **1l** (0.0925 g, 0.400 mmol, 1.0 equiv) in hexafluoro-2-propanol (2 mL) in a 4 dram vial flushed with nitrogen was added acetyl chloride (28.4 μL, 0.400 mmol, 1.0 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 32 h. Reaction mixture was concentrated under nitrogen using sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification on a semi-automated purification system using a 4 g normal phase silica flash column (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2 over 45 min) afforded a mixture of 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one **2l** and 1-phenethylpiperidin-2-one **3l** as a pale yellow oil in 96% yield (0.0784 g, 0.386 mmol; **2l**:**3l** = 93:7 as determined by ^{1}H NMR).

Experimental procedure for Job plots to determine stoichiometry of binding using ^{1}H NMR.

Commercially purchased HFIP was distilled from sodium carbonate and dried over molecular sieves before use for the generation of Job plots. $CDCl_3$ was passed through basic alumina.

0.10 M stock solutions of HFIP (31.6 μL, 0.300 mmol, 1.0 equiv) and lactam **2a** (41.8 mg, 0.300 mmol, 1.0 equiv) were prepared in 3.0 mL of $CDCl_3$ each. The total concentration of HFIP and **2a** was kept constant. Eleven NMR samples were prepared with a constant volume of 0.50 mL, where the molar fractions of HFIP and **2a** varied from 0.0 to 1.0 (see Table S14). The Job plot was obtained by plotting the molar fraction multiplied by the change in chemical shifts (Δδ) of the hydroxyl proton of HFIP against the molar fraction of HFIP.

0.10 M stock solutions of HFIP (31.6 μL, 0.300 mmol, 1.0 equiv) and azidoketone **1a** (50.2 mg, 0.300 mmol, 1.0 equiv) were also prepared in 3.0 mL of $CDCl_3$ each and the Job plot was generated in a similar way as described for **2a** (see Table S15).

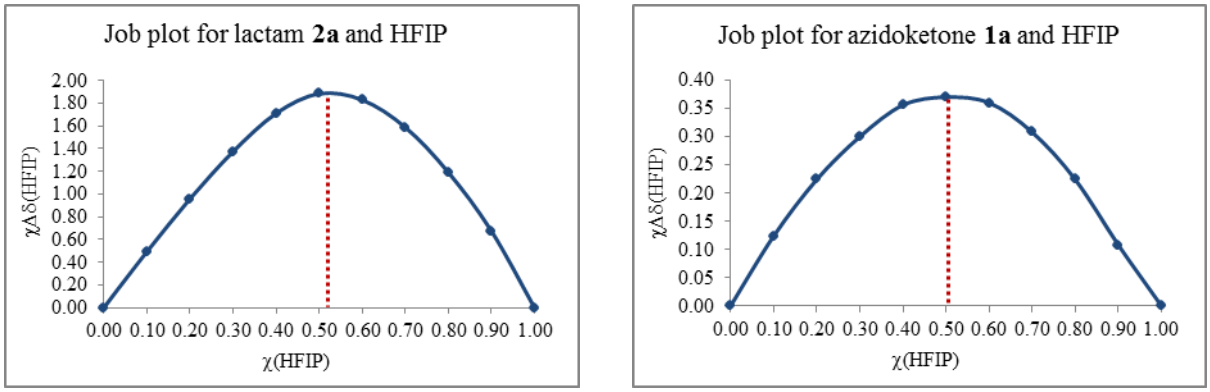
Table S14. Molar fractions and chemical shifts (Δδ) for HFIP and **2a**

HFIP (mmol)	volume of HFIP in NMR tube (mL)	**2a** (mmol)	volume of **2a** in NMR tube (mL)	Mole fraction of HFIP (χHFIP)	Mole fraction of **2a**	δ of hydroxyl proton	Δδ of hydroxyl proton	(χHFIP)Δδ
0.050	0.500	0.000	0.000	1.000	0.000	3.07	0.00	0.000
0.045	0.450	0.005	0.050	0.900	0.100	3.82	0.75	0.675
0.040	0.400	0.010	0.100	0.800	0.200	4.56	1.49	1.192
0.035	0.350	0.015	0.150	0.700	0.300	5.34	2.27	1.589
0.030	0.300	0.020	0.200	0.600	0.400	6.12	3.05	1.830
0.025	0.250	0.025	0.250	0.500	0.500	6.84	3.77	1.885
0.020	0.200	0.030	0.300	0.400	0.600	7.35	4.28	1.712
0.015	0.150	0.035	0.350	0.300	0.700	7.65	4.58	1.374
0.010	0.100	0.040	0.400	0.200	0.800	7.86	4.79	0.958
0.005	0.050	0.045	0.450	0.100	0.900	7.99	4.92	0.492
0.000	0.000	0.050	0.500	0.000	1.000	0.00	0.00	0.000

Table S15. Molar fractions and chemical shifts (Δδ) for HFIP and **1a**

HFIP (mmol)	volume of HFIP in NMR tube (mL)	**1a** (mmol)	volume of **1a** in NMR tube (mL)	Mole fraction of HFIP (χHFIP)	Mole fraction of **1a**	δ of hydroxyl proton	Δδ of hydroxyl proton	(χHFIP)Δδ
0.050	0.500	0.000	0.000	1.000	0.000	3.19	0.00	0.000
0.045	0.450	0.005	0.050	0.900	0.100	3.31	0.12	0.108
0.040	0.400	0.010	0.100	0.800	0.200	3.47	0.28	0.224
0.035	0.350	0.015	0.150	0.700	0.300	3.63	0.44	0.308
0.030	0.300	0.020	0.200	0.600	0.400	3.79	0.60	0.360
0.025	0.250	0.025	0.250	0.500	0.500	3.93	0.74	0.370
0.020	0.200	0.030	0.300	0.400	0.600	4.08	0.89	0.356
0.015	0.150	0.035	0.350	0.300	0.700	4.19	1.00	0.300
0.010	0.100	0.040	0.400	0.200	0.800	4.31	1.12	0.224
0.005	0.050	0.045	0.450	0.100	0.900	4.43	1.24	0.124
0.000	0.000	0.050	0.500	0.000	1.000	0.00	0.00	0.000

The stoichiometries of binding for both lactam **2a** and azidoketone **1a** with HFIP was found to be 1:1 as can be observed from the peak abscissa values of 0.52 for **2a** and 0.50 for **1a**.



Job plots for complexation of lactam 2a and azidoketone 1a with HFIP.

Procedure for competition and product inhibition experiments (Scheme 3 and Figure 6 in the paper):

(a) Competition experiment:

To a solution of (2*R*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1f** (0.0257 g, 0.100 mmol, 1.0 equiv) and 2-(3-azidopropyl)cyclopentanone **1a** (0.0167 g, 0.100 mmol, 1.0 equiv) in hexafluoro-2-propanol (0.5 mL) at room temperature was added acetyl chloride (1.42 μL, 0.0200 mmol, 0.20 equiv) under nitrogen atmosphere in a 1 dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Aliquots (50 μL) were withdrawn using a micropipette at different time points into sample vials and concentrated under nitrogen using a sample concentrator. The residues were diluted with 0.50 mL of $CDCl_3$ and transferred into NMR tubes and ^1H NMR integration was used to determine the conversion ratio.

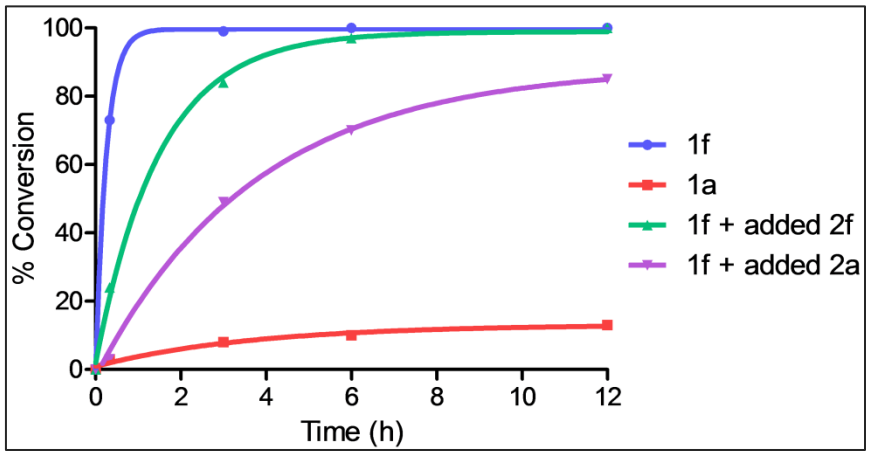
(b) Product inhibition experiment with added lactam 2f at the outset of the reaction:

To a solution of (2*R*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1f** (0.0257 g, 0.100 mmol, 1.0 equiv) and (8*S*,9a*S*)-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2f** (0.0229 g, 0.100 mmol, 1.0

equiv) in hexafluoro-2-propanol (0.5 mL) at room temperature was added acetyl chloride (1.42 μL, 0.0200 mmol, 0.20 equiv) under nitrogen atmosphere in a 1 dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Aliquots (50 μL) were withdrawn using a micropipette at different time points into sample vials and concentrated under nitrogen using a sample concentrator. The residues were diluted with 0.50 mL of $CDCl_3$ and transferred into NMR tubes and ^1H NMR integration was used to determine the conversion ratio. Since complete conversion was observed within 12 h, reaction graph was plotted up to 12 h only.

(c) Product inhibition experiment with added lactam 2a at the outset of the reaction:

To a solution of (2*R*,4*S*)-2-(3-azidopropyl)-4-phenylcyclohexanone **1f** (0.0257 g, 0.100 mmol, 1.0 equiv) and hexahydroindolizin-5(1*H*)-one **2a** (0.0139 g, 0.100 mmol, 1.0 equiv) in hexafluoro-2-propanol (0.5 mL) at room temperature was added acetyl chloride (1.42 μL, 0.0200 mmol, 0.20 equiv) under nitrogen atmosphere in a 1 dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Aliquots (50 μL) were withdrawn using a micropipette at different time points into sample vials and concentrated under nitrogen using a sample concentrator. The residues were diluted with 0.50 mL of $CDCl_3$ and transferred into NMR tubes and ^1H NMR integration was used to determine the conversion ratio.



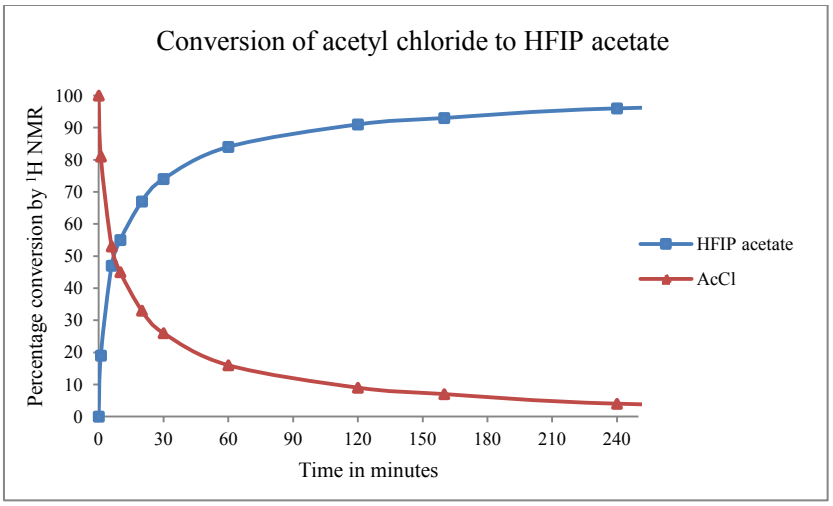
Nonlinear regression (curve fit) analysis for relative reaction rates for **1f** and **1a** (competition experiment), **1f** with 1 equiv of **2f** added at the outset of the reaction (product inhibition experiment with added **2f**), and **1f** with 1 equiv of **2a** added at the outset of the reaction (product inhibition experiment with added **2a**).

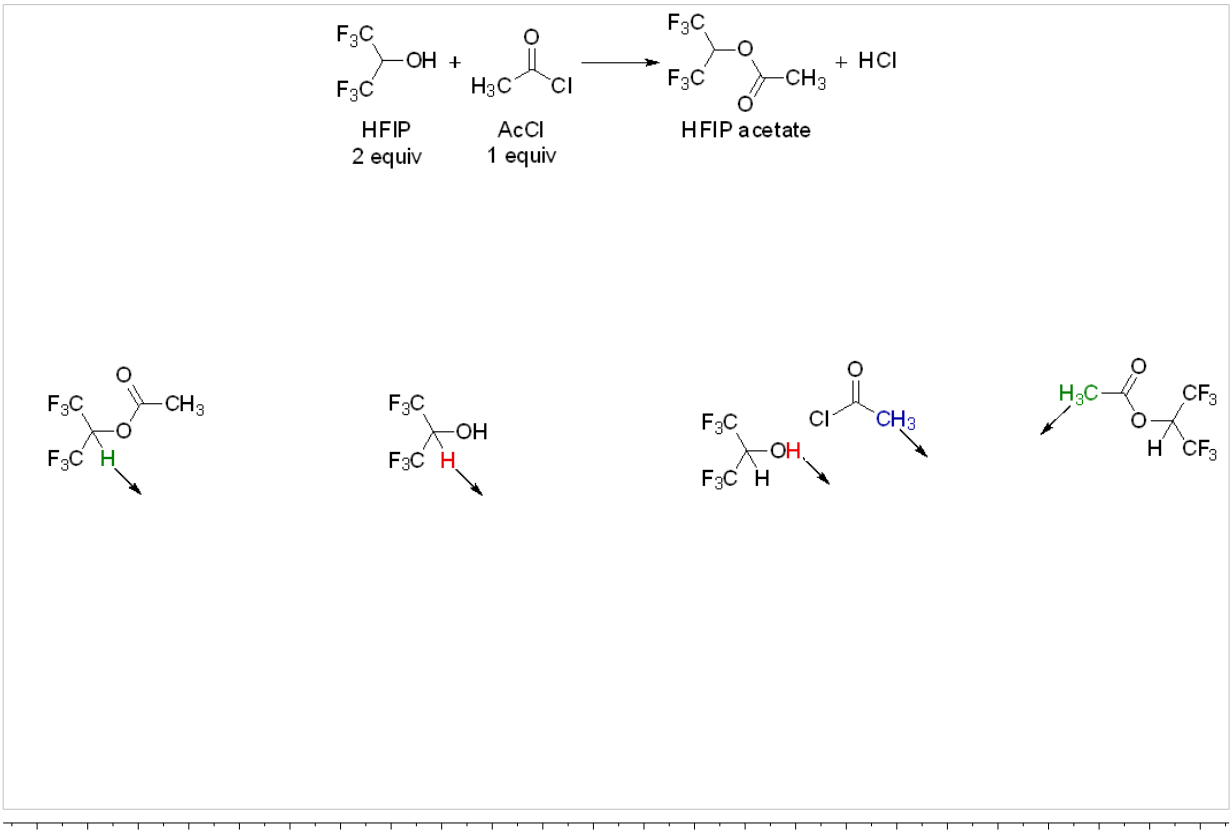
Experimental procedure for the reaction of acetyl chloride with HFIP to probe the *in situ* generation of HCl through the formation of HFIP acetate:

In a vial flushed with nitrogen at room temperature was added hexafluoro-2-propanol (0.500 mL, 4.80 mmol, 2.0 equiv) followed by acetyl chloride (0.170 mL, 2.40 mmol, 1.0 equiv) and the solution was mixed gently (white fumes of HCl were observed). Aliquots (35 μL) were withdrawn at different time intervals and diluted with 0.45 mL of $CDCl_3$ in NMR tubes. ^{1}H NMR integration was used to determine conversion ratio.

time (min)	% conversion to HFIP acetate[a]	% remaining of acetyl chloride[a]
0	0	100
1	19	81
6	47	53
10	55	45
20	67	33
30	74	26
60	84	16
120	91	9
160	93	7
240	96	4
480	99	1

[a] Conversion ratios were determined by ^{1}H NMR.





Representative NMR spectra at three different time points showing the conversion of acetyl chloride to HFIP acetate.

References:

(1) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965-8966. (b) Milligan, G. L.; Mossman, C. J.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449-10459.

(2) Lertpibulpanya, D.; Marsden, S. P. *Org. Biomol. Chem.* **2006**, *4*, 3498-3504.

(3) Grecian, S.; Aubé, J. *Org. Synth.* **2007**, *84*, 347-358.

(4) (a) Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. *J. Am. Chem. Soc.* **2012**, *134*, 6528-6531. (b) Painter, T. O.; Thornton, P. D.; Orestano, M.; Santini, C.; Organ, M. G.; Aubé, J. *Chem. Eur. J.* **2011**, *17*, 9595-9598.

(5) Lee, H.-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007-9015.

(6) Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, *0*, 4566-4568.

(7) Kuehne, M. E.; Parsons, W. H. *Tetrahedron* **1983**, *39*, 3763-3765.

(8) *N*-Methyl-2-piperidone *Aldrich Website* CAS# 931-920-934.

(9) Tamura, Y.; Uenishi, J.-i.; Maeda, H.; Choi, H.-d.; Ishibashi, H. *Synthesis* **1981**, *1981*, 534-537.

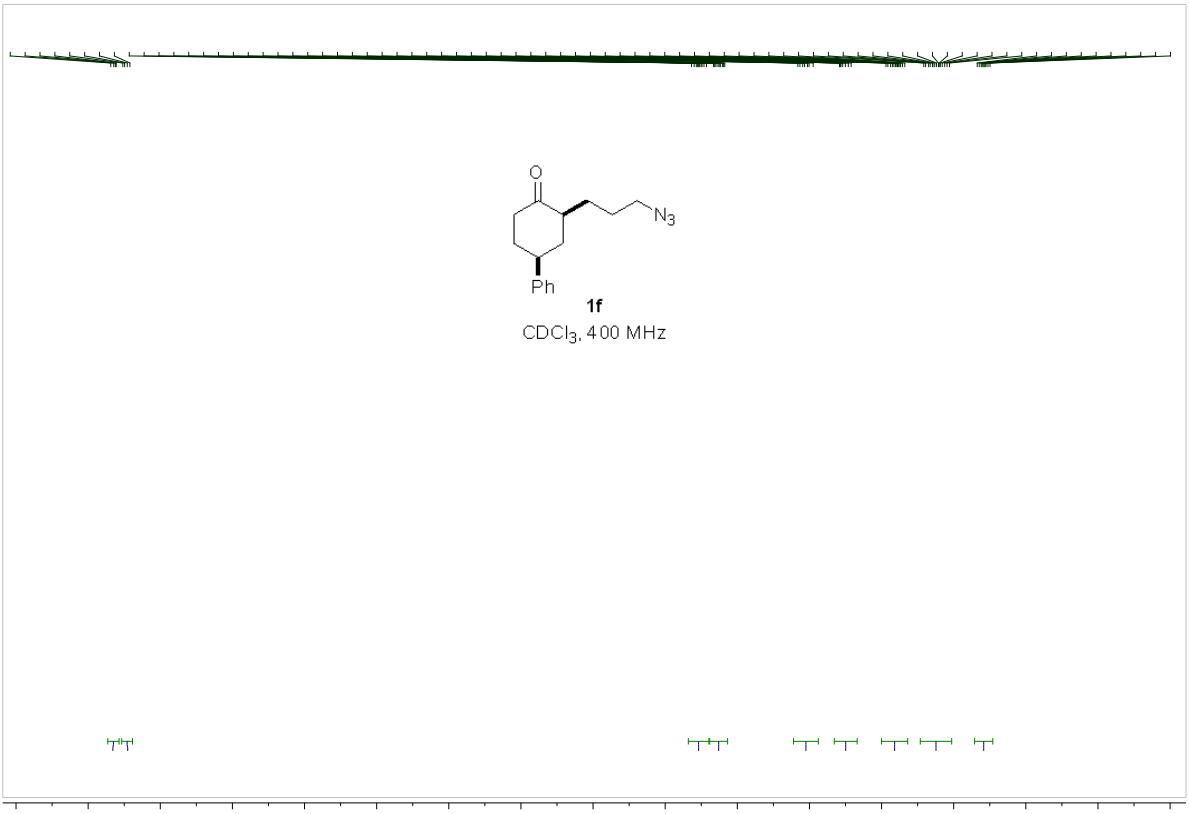
(10) Hou, D.-R.; Hsieh, Y.-D.; Hsieh, Y.-W. *Tetrahedron Lett.* **2005**, *46*, 5927-5929.

(11) Molander, G. A.; Huérou, Y. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511-4516.

(12) Ghosh, P.; Judd, W. R.; Ribelin, T.; Aubé, J. *Org. Lett.* **2009**, *11*, 4140-4142.

(13) Guillemont, J. E. G.; Dorange, I.; Lancois, D. F. A.; Villalgordo-Soto, J. M.; Simonnet, Y. R. F.; Motte, M. M. S.; Andries, K. J. L. M.; Koul, A. WO2008068272A2, **2008**.

(14) Tchédam-Ngatcha, B.; Luu-The, V.; Poirier, D. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 155-165.



1f

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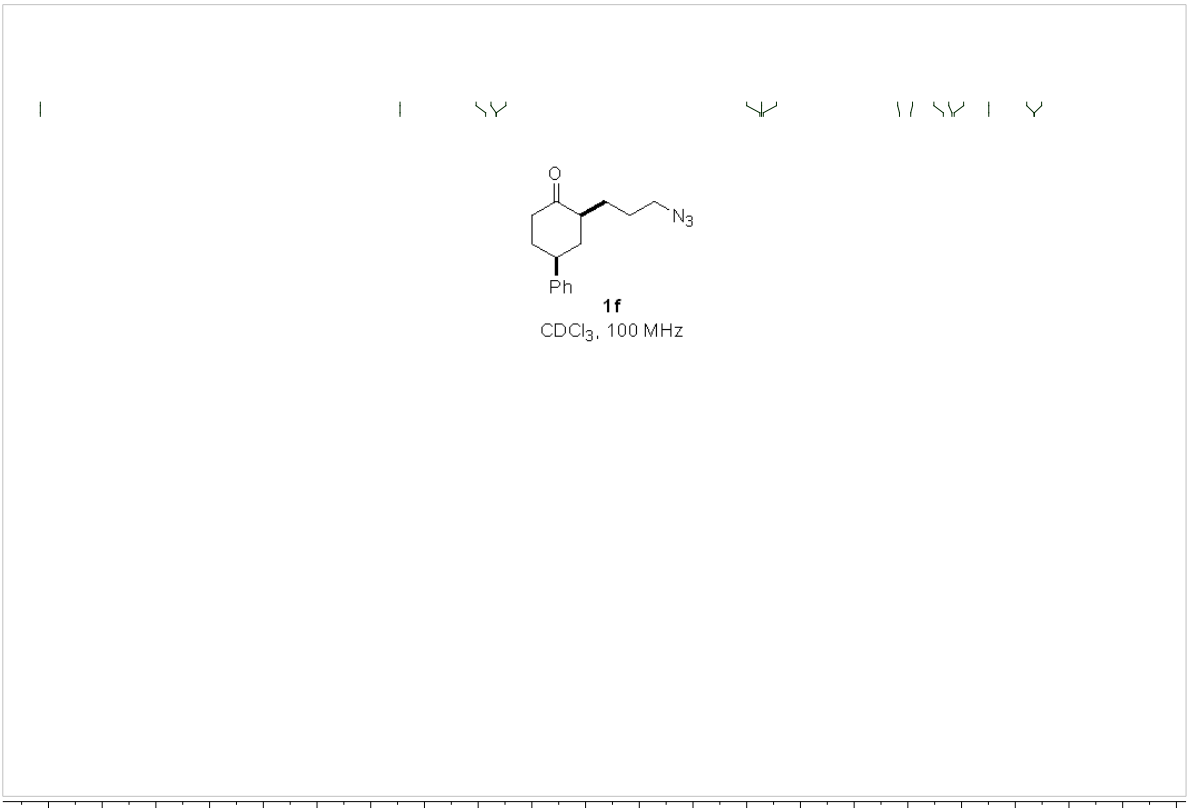

1f

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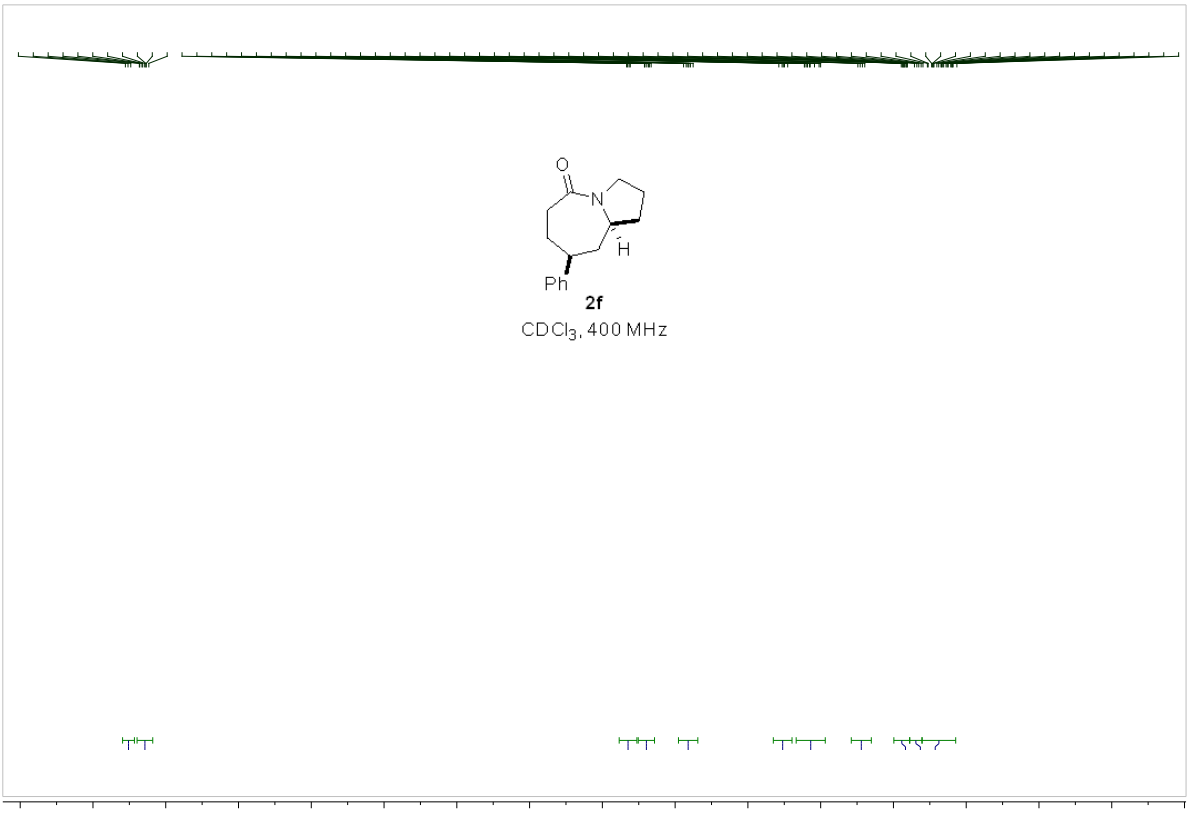

2f

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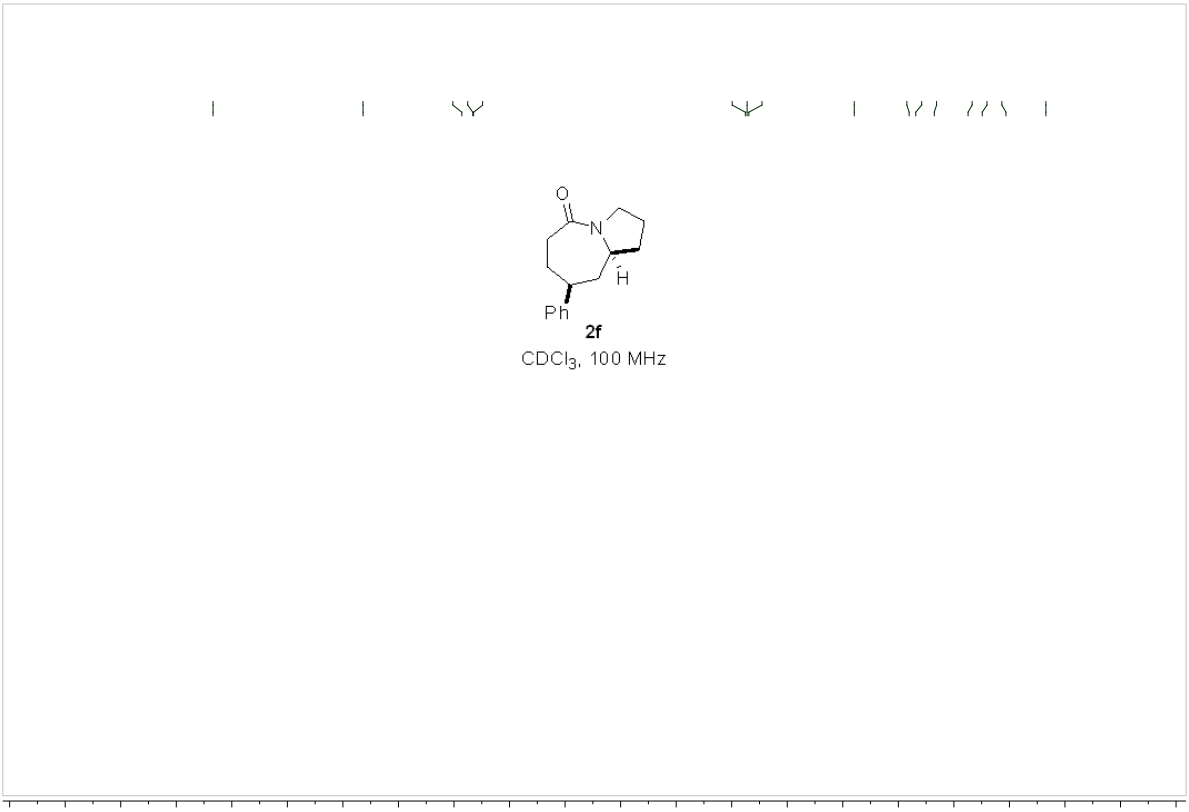

2f

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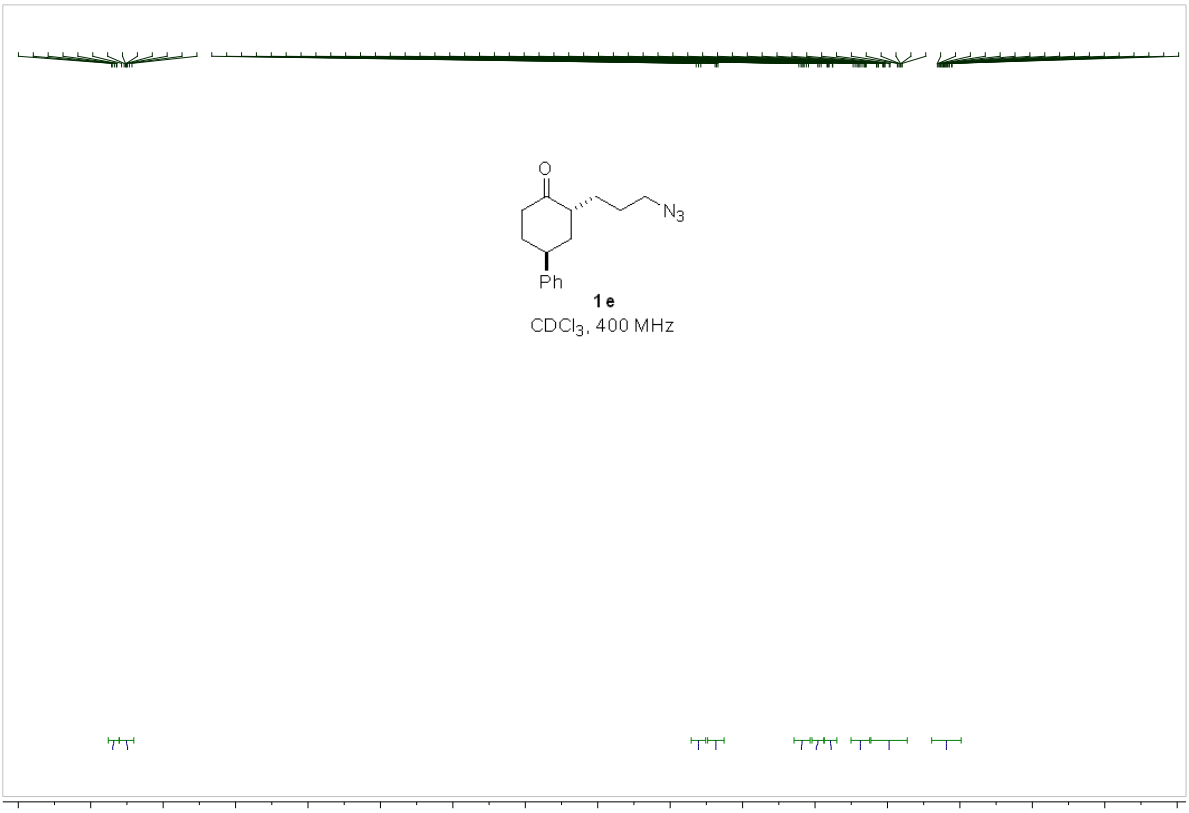

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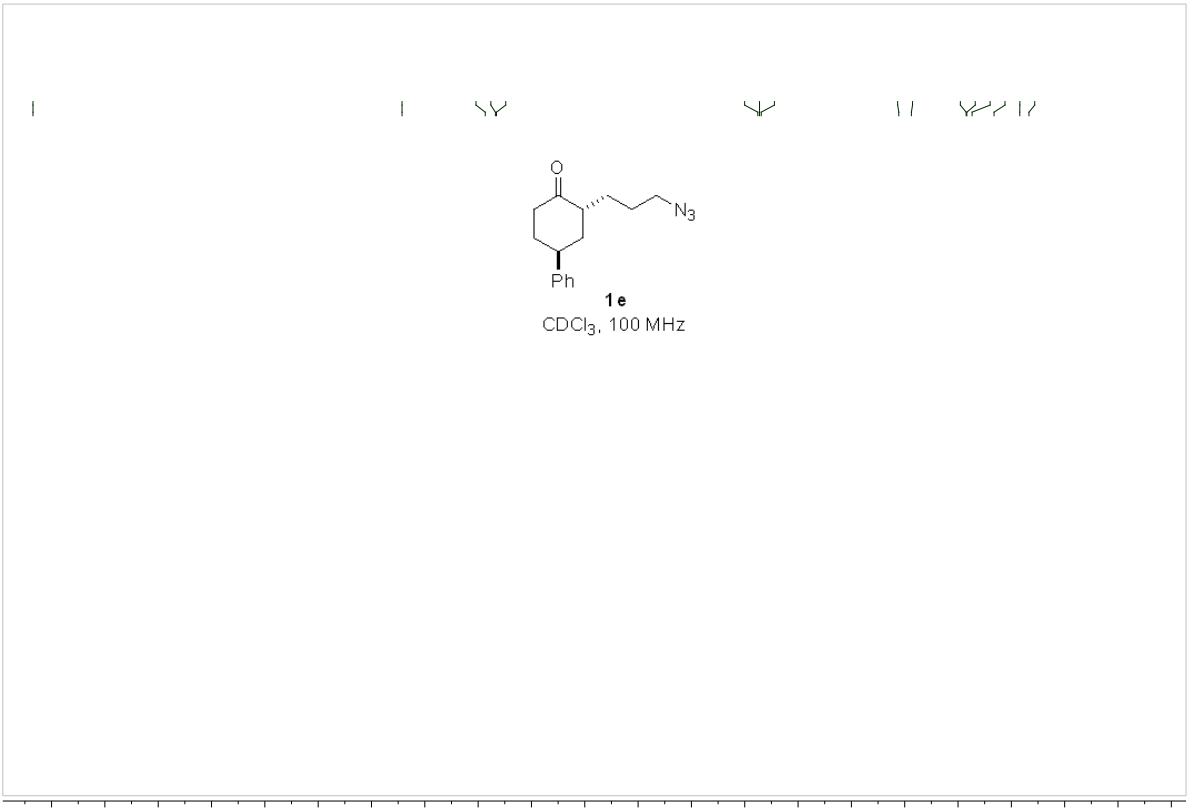

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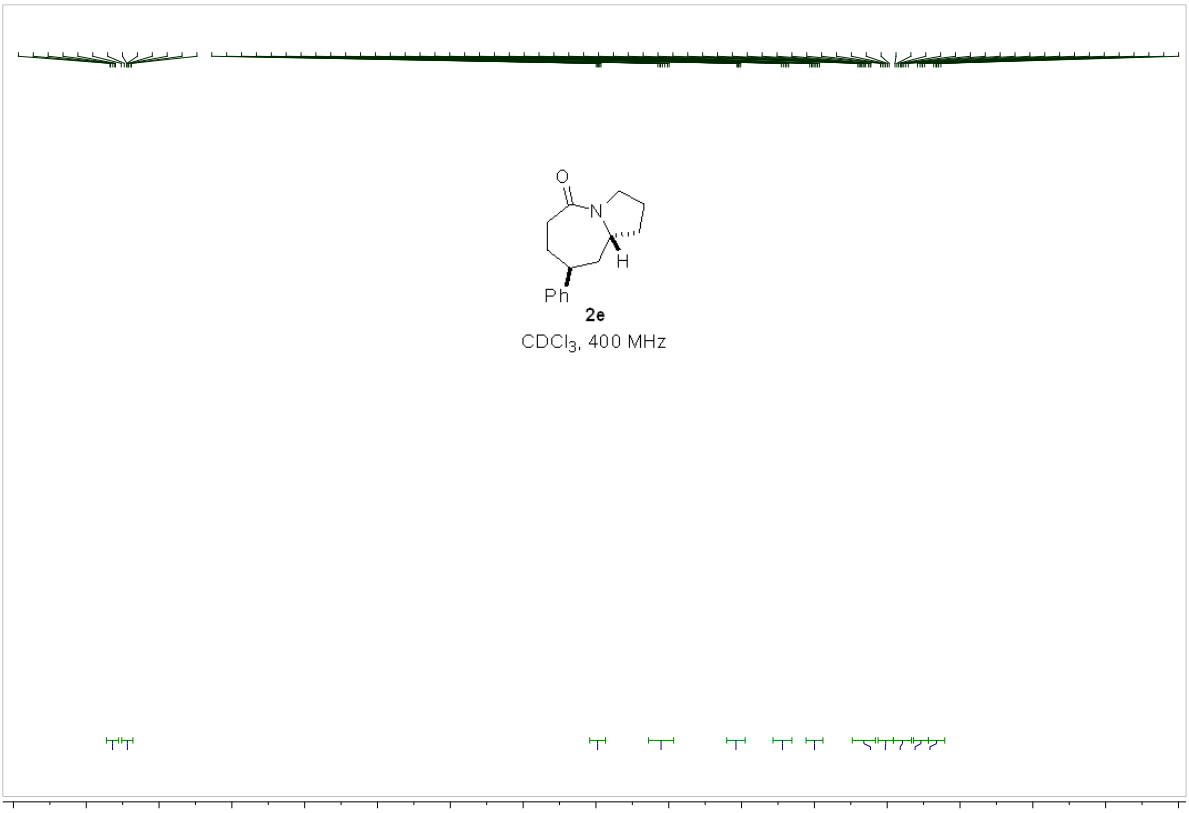

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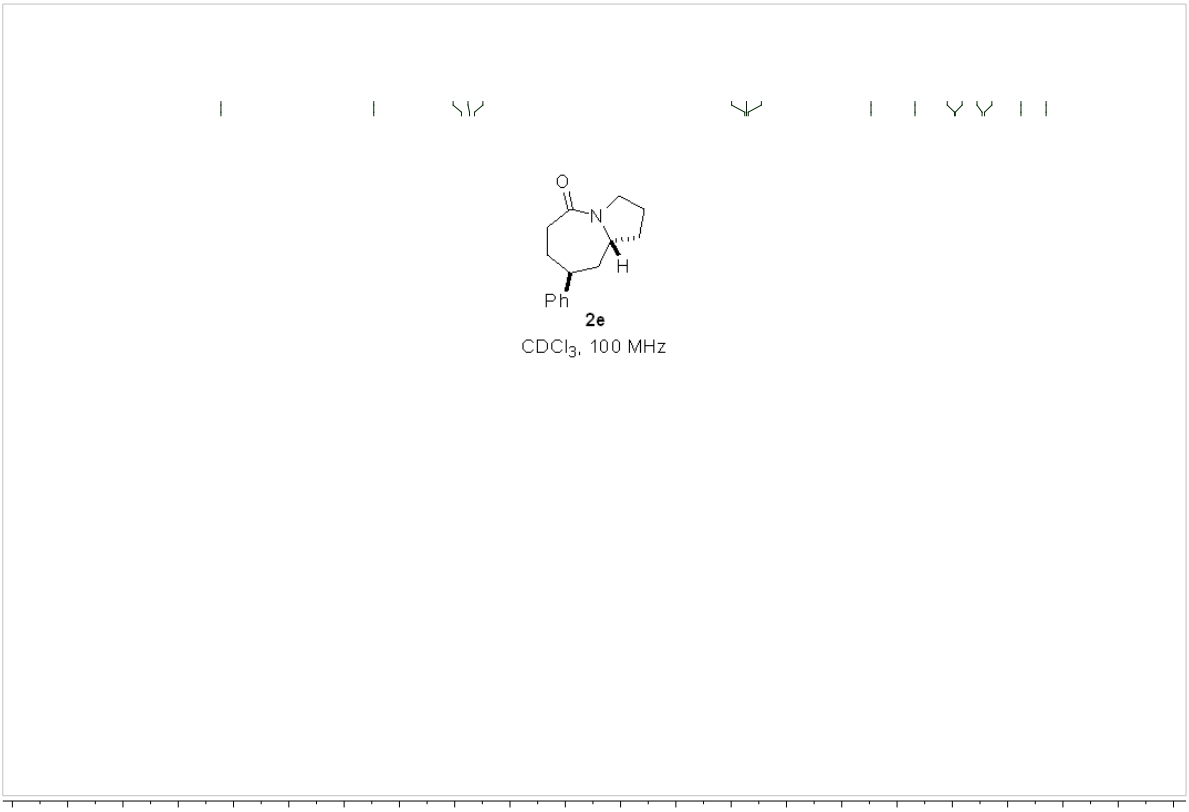

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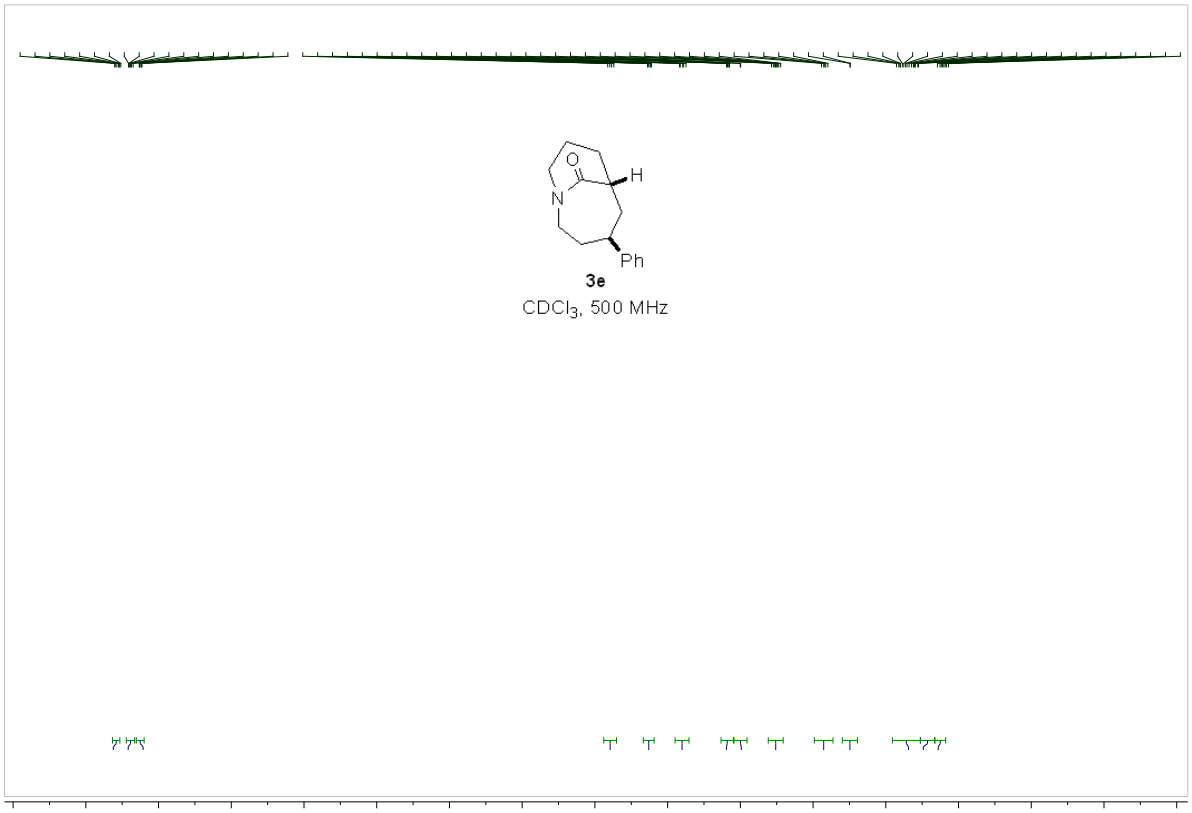

3e

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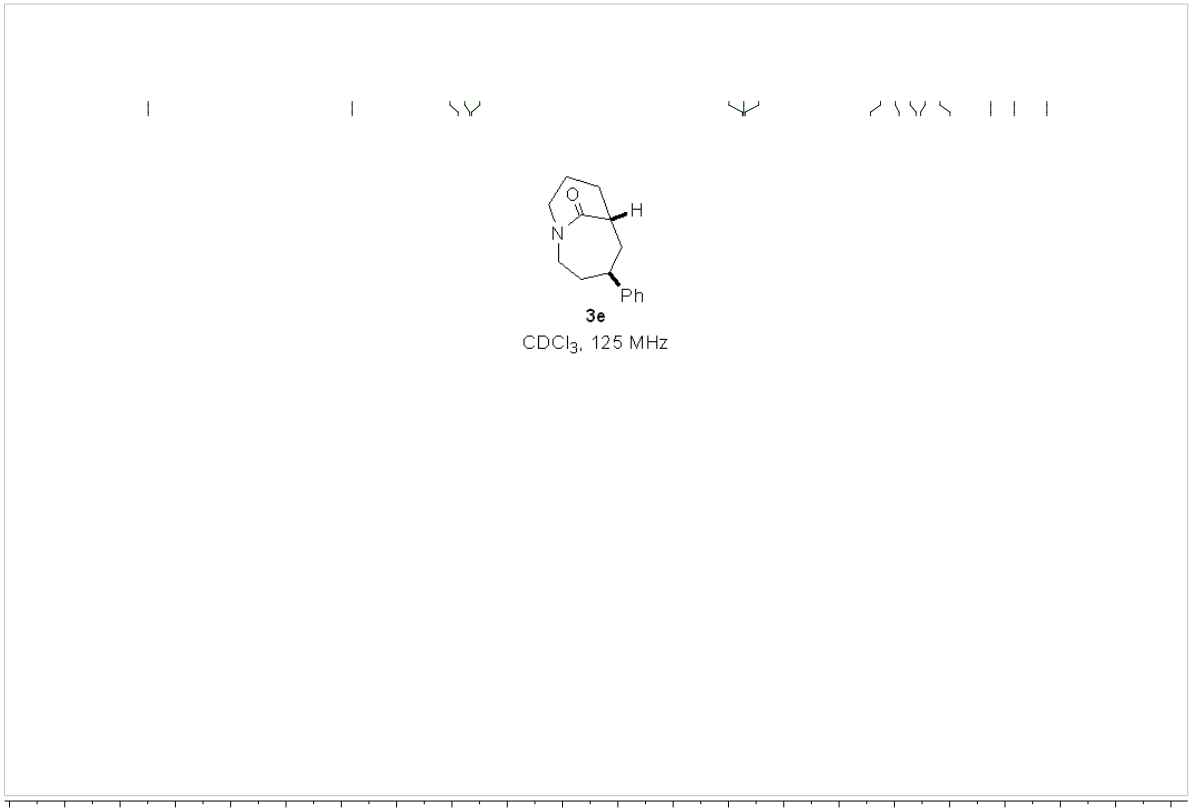

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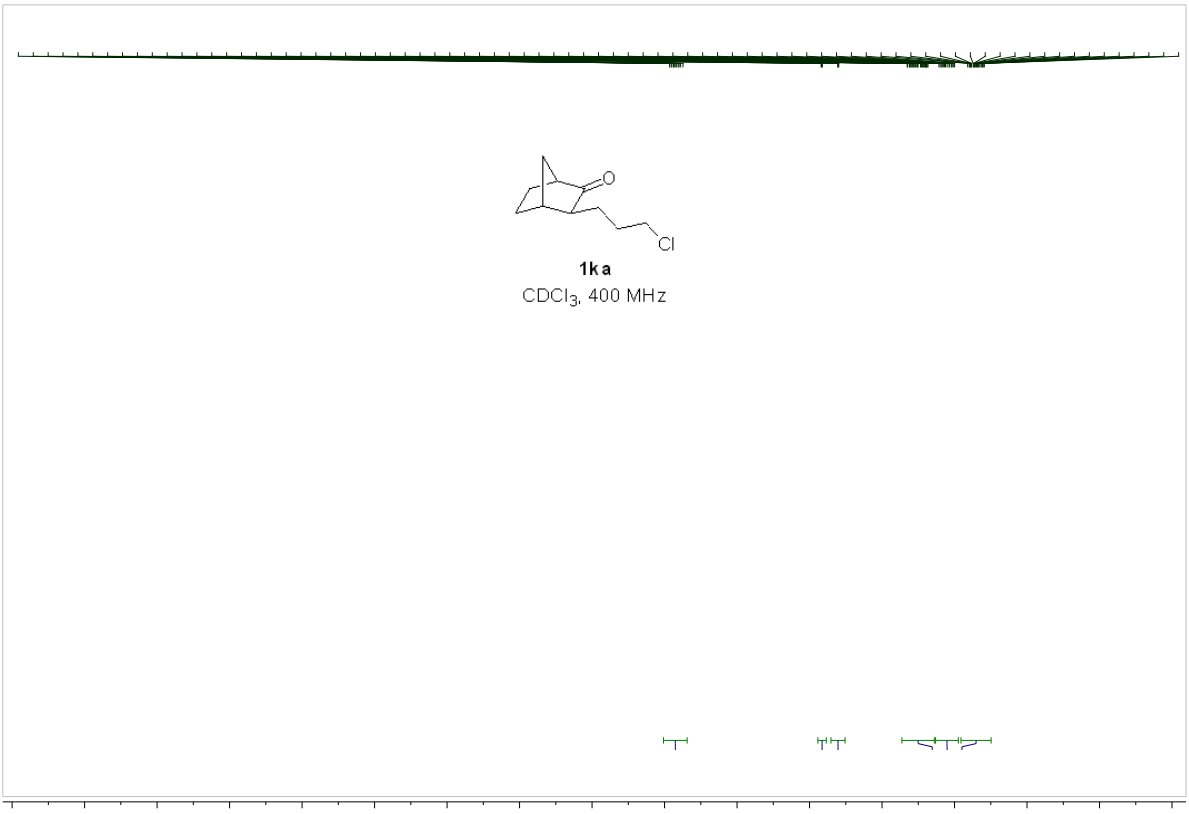

1ka

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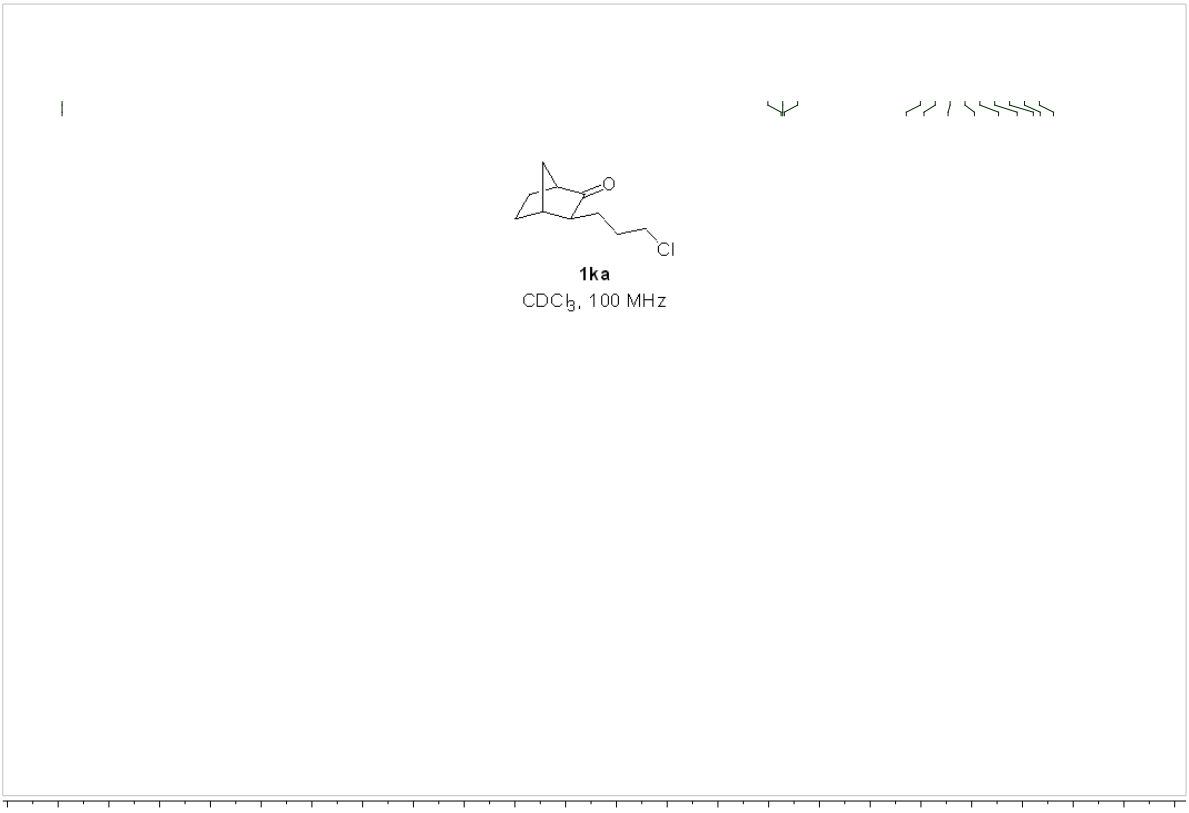

1ka

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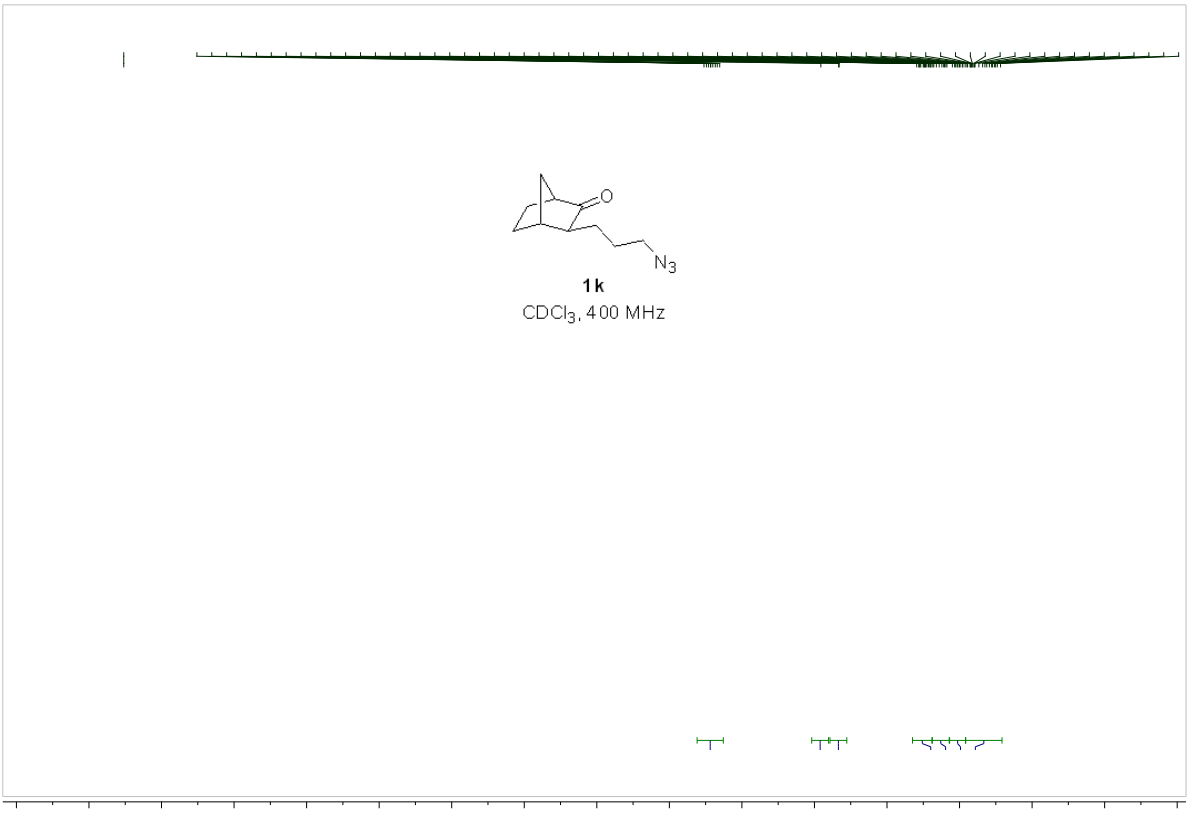

1k

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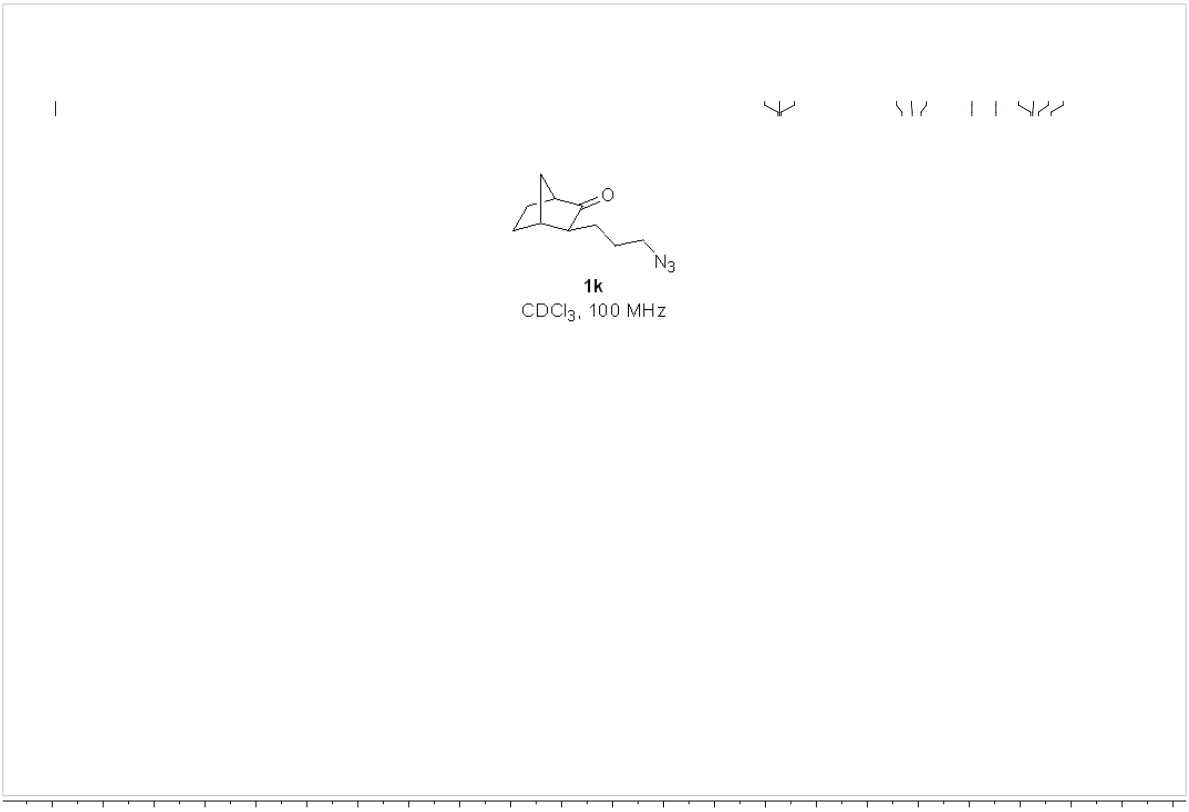

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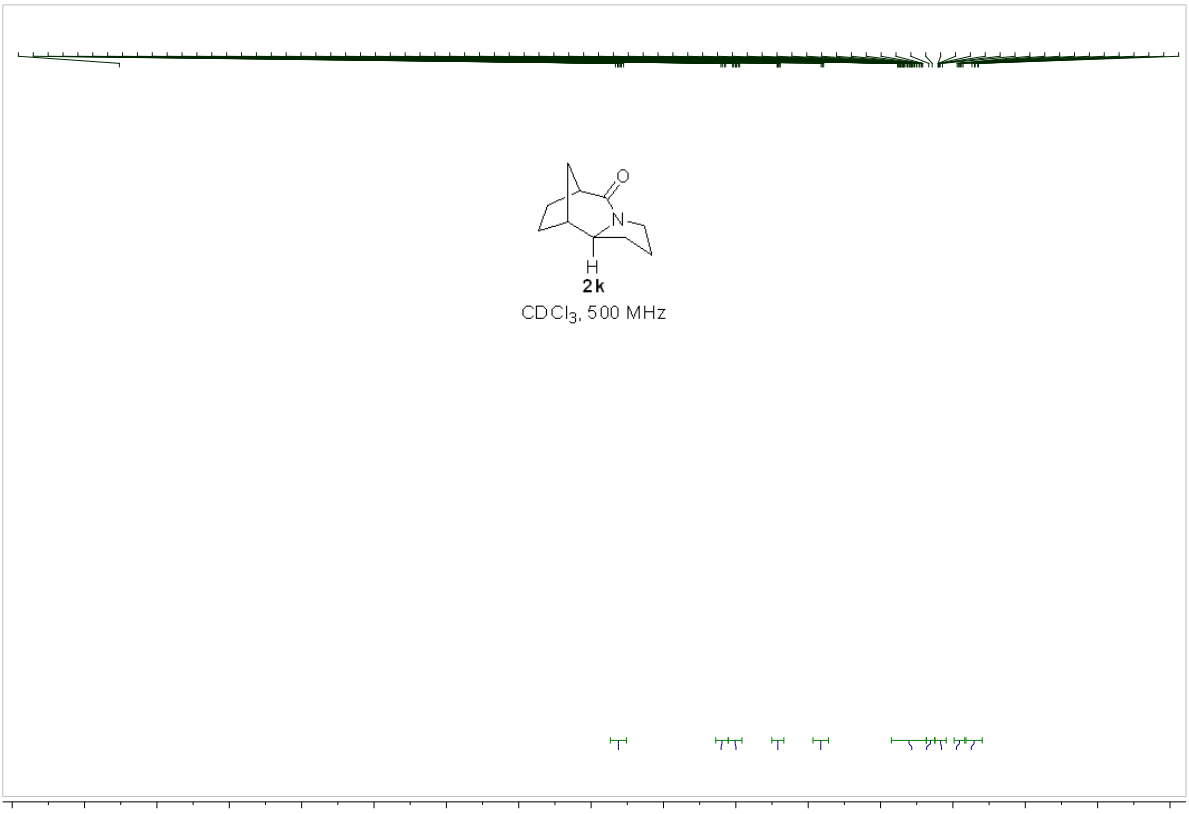

2k

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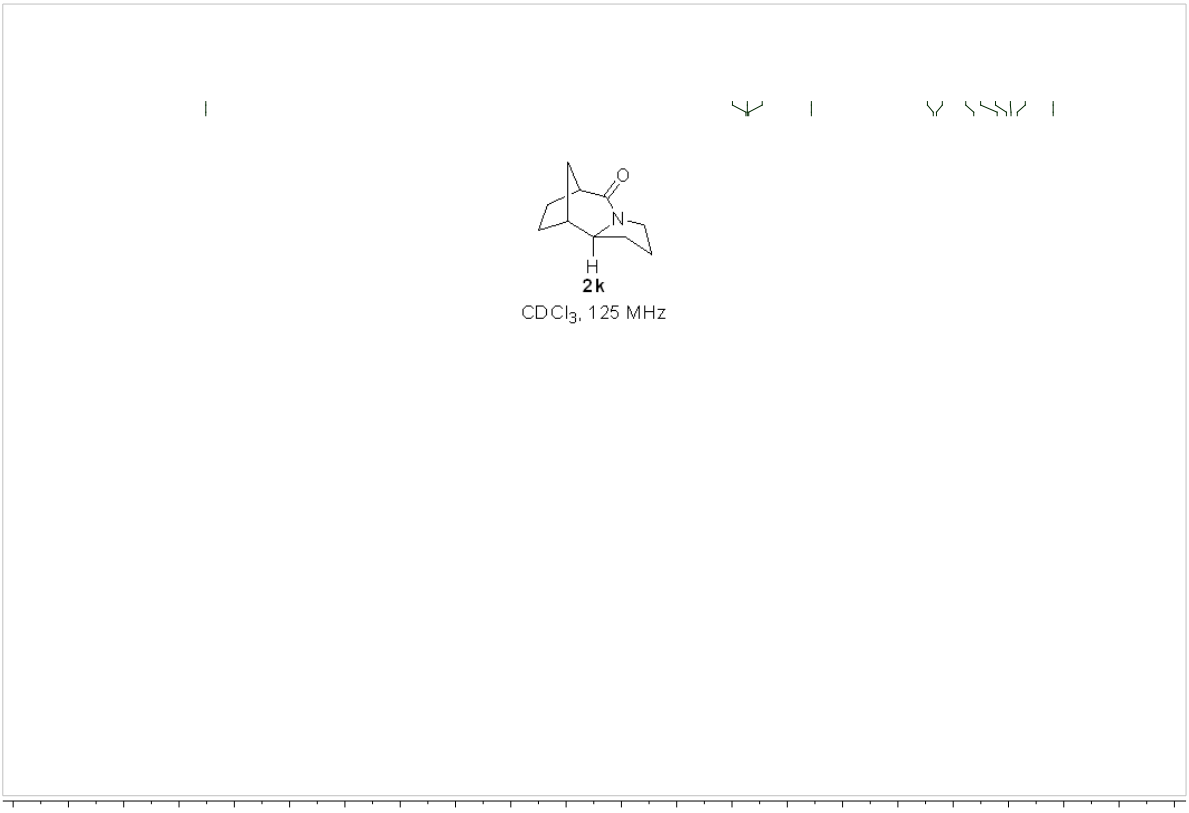

2k

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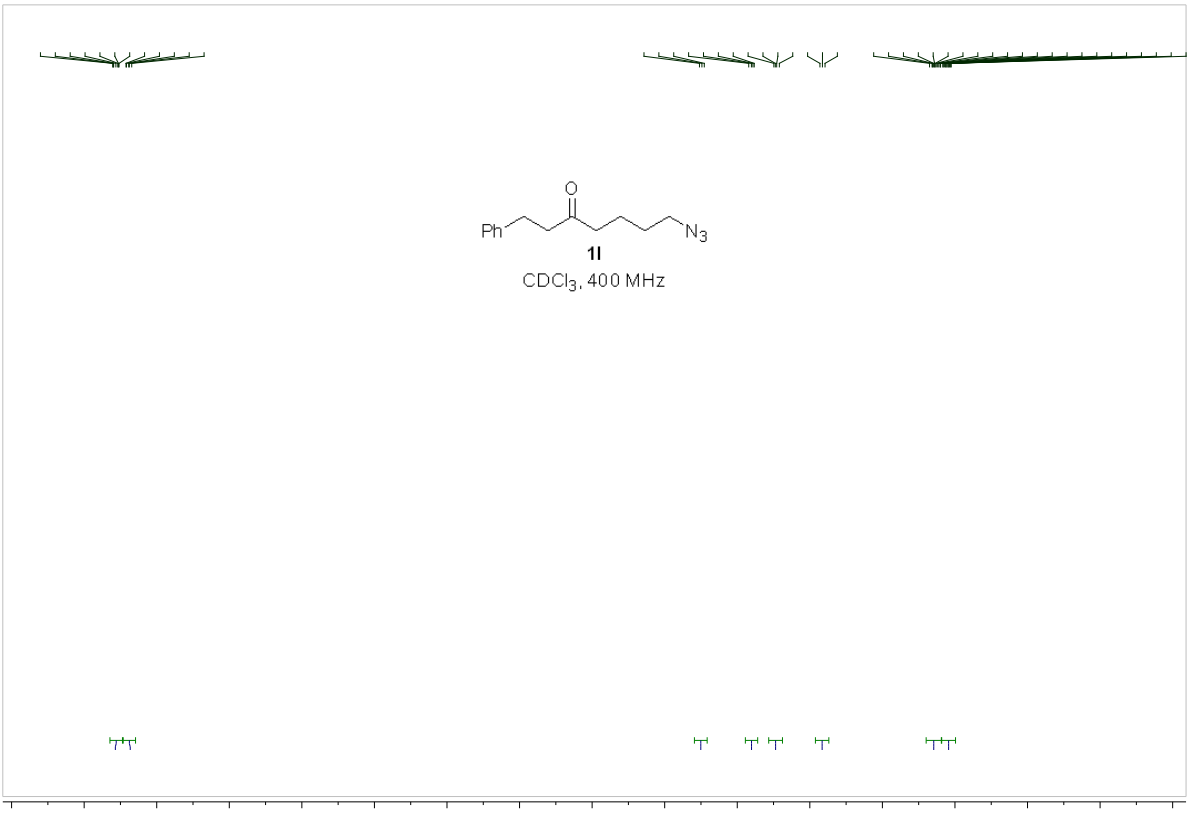
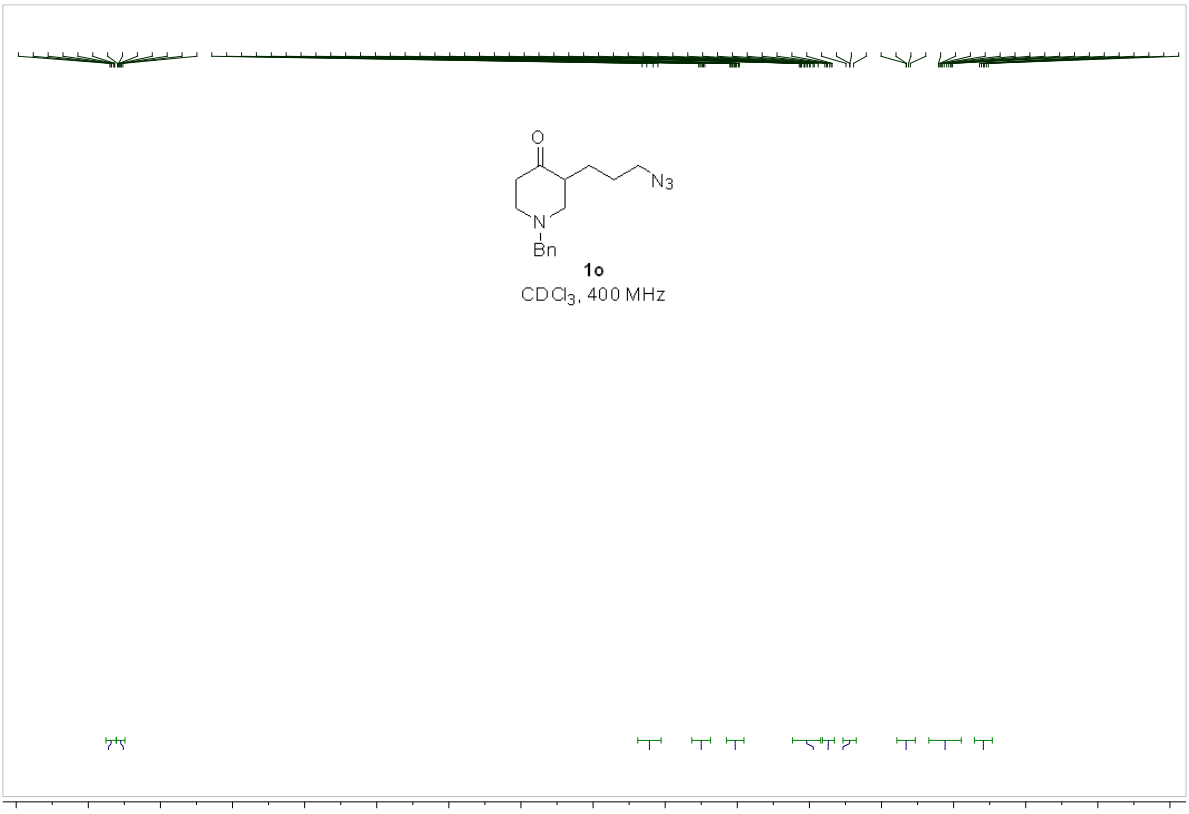


1l

$CDCl_3$, 400 MHz

1l

$CDCl_3$, 100 MHz



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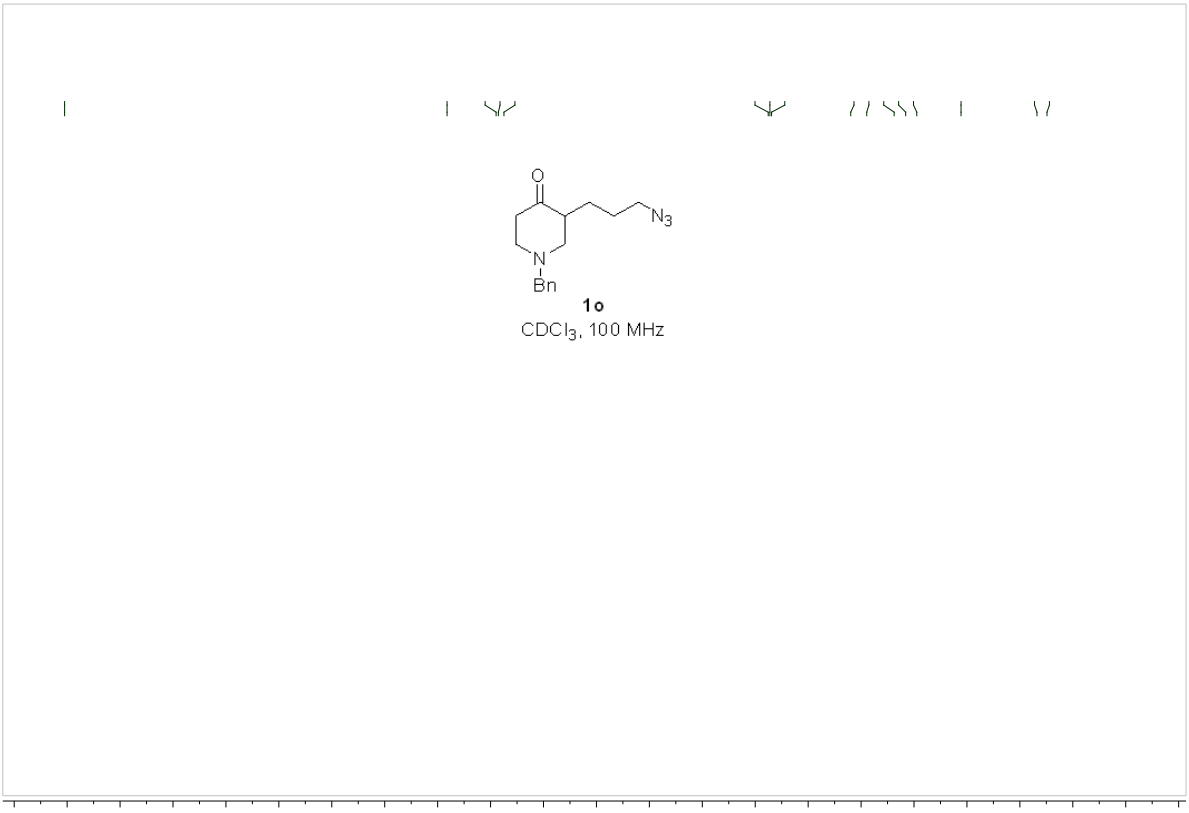

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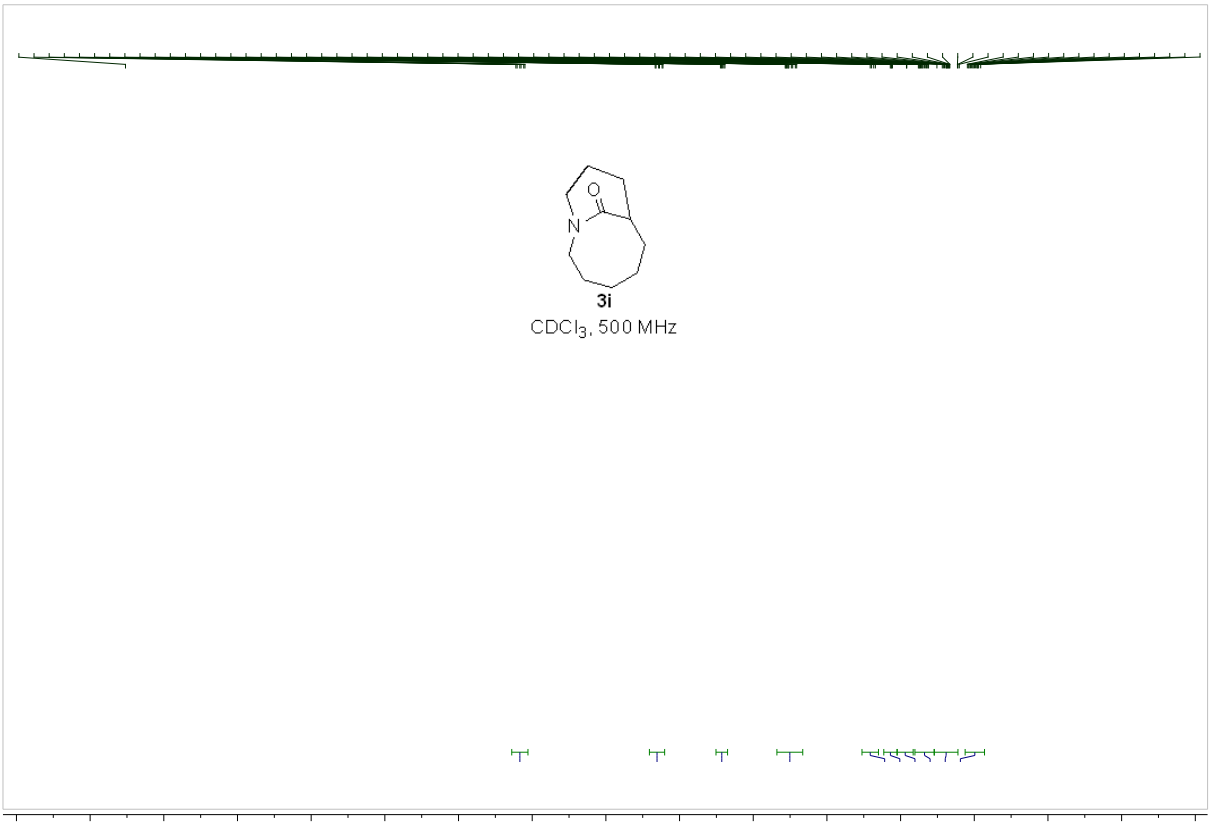

3i

$CDCl_3$, 500 MHz

3i

$CDCl_3$, 125 MHz