Synthesis of functionalised azepanes and piperidines from bicyclic halogenated aminocyclopropane derivatives

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Experimental procedures

General information: Methylmagnesium bromide (3.0 M solution in Et_2O) and *sec*-butyllithium (1.3−1.4 M solution in cyclohexane) were purchased from Sigma-Aldrich or Alfa Aesar and titrated according to literature methods.[1,2] Tetrahydrofuran, diethyl ether, dichloromethane, toluene and methanol were purified using a MB SPS-800 solvent purification system (MBRAUN). Other solvents and commercial reagents were used as received, without purification. Petroleum ether refers to the 40−60 °C fraction. The microwave-promoted experiments were run using a CEM Discover Microwave Synthesis System with the temperature and time parameters indicated; the reaction vessels were not flushed with an inert gas. All other reactions were carried out under nitrogen or argon. The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Flash column chromatography was performed on VWR Chemicals or Merck silica gel 60 (40–63 μm). Concentration under reduced pressure was carried out using rotary evaporators at 40 °C. NMR spectra were recorded with AM 400 or AVANCE 400 Bruker spectrometers (^{1}H at 400.2 MHz, ^{13}C at 100.6 MHz.

1− H.-S. Lin, L. A. Paquette, *Synth. Comm.* **1994**, *24*, 2503–2506.
2− W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879–1880.

I. Preparation of the cyclopropane substrates

General procedure A: cyclopropanation of *N*-Boc dihydropyrroles and *N*-Boc tetrahydropyridines with dichlorocarbene.[3]

10 M NaOH aqueous solution (20 mL) was slowly added to a solution of *N*-Boc cyclic enamine substrate **1** (1.00 equiv, 3.50 mmol) and benzyltriethylammonium chloride (0.63 equiv, 2.20 mmol) in $CHCl_3$ (20 mL). After 90−180 min of vigorous stirring at 20 °C, the aqueous phase was removed. The organic layer was washed with H_2O (20 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

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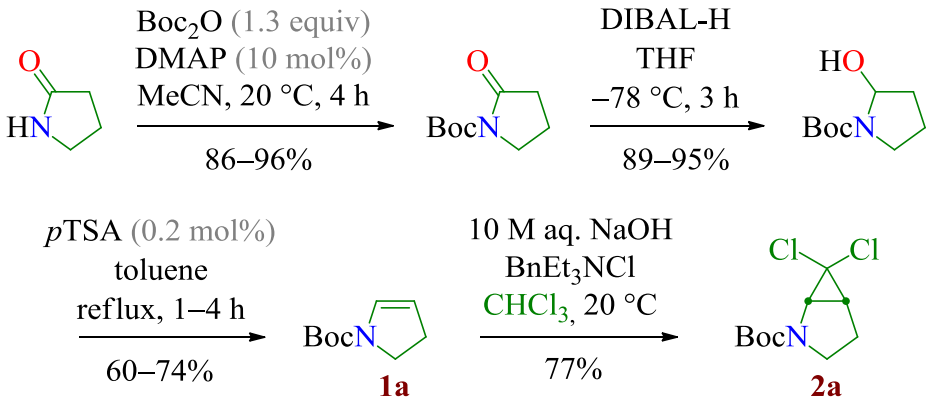
tert-Butyl 6,6-dichloro-2-azabicyclo[3.1.0]hexane-2-carboxylate **2a**



a) Installation of the Boc group

tert-Butyl 2-oxopyrrolidine-1-carboxylate was prepared in 86−96% yield from 2-pyrrolidinone (25.0 mmol) by applying a literature procedure.[4]

b) Reduction of the carbonyl group

Run 1: DIBAL-H (1.0 M in toluene, 1.50 equiv, 15.0 mmol, 15.0 mL) was added dropwise, at −78 °C, to a solution of *tert*-butyl 2-oxopyrrolidine-1-carboxylate (1.00 equiv, 10.0 mmol, 1.85 g) in dry THF (40 mL). After 5 h of stirring at −78 °C, Rochelle salt aqueous solution (20 mL) was slowly added and the mixture was allowed to warm to 20 °C, with stirring until two clear phases were formed. The organic phase was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil. Analysis by ^{1}H NMR spectroscopy showed that this crude product contained essentially pure *tert*-butyl 2-hydroxypyrrolidine-1-carboxylate (1.75 g, 9.35 mmol, 93%).[5]

3− Adapted from I. Lantos, D. Bhattacharjee, D. S. Eggleston, *J. Org. Chem.* **1986**, *51*, 4147−4150.
4− L. Banfi, A. Basso, V. Cerulli, G. Guanti, R. Riva, *J. Org. Chem.* **2008**, *73*, 1608−1611 (supporting information).
5− Procedure adapted from: R. K. Dieter, R. R. Sharma, *J. Org. Chem.* **1996**, *61*, 4180–4184.

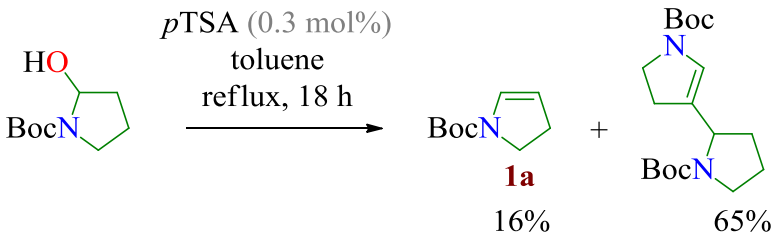
Runs 2 and 3: The same reaction was run on 2.50 mmol and 5.00 mmol scale to produce, respectively, 415 mg (2.22 mmol, 89%) and 886 mg (4.73 mmol, 95%) of *tert*-butyl 2-hydroxypyrrolidine-1-carboxylate.

c) Dehydration

Run 1: A solution of *tert*-butyl 2-hydroxypyrrolidine-1-carboxylate (1.00 equiv, 2.22 mmol, 415 mg) and *para*-toluenesulfonic acid monohydrate (0.19 mol%, 4.3 µmol, 1.0 mg) in toluene (10 mL) was heated at reflux with a Dean-Stark apparatus for 1 h. After cooling, two drops of Et_3N were added and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with H_2O (2 × 10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford pure *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **1a** as a yellow oil (279 mg, 1.65 mmol, 74%).

Run 2: A solution of *tert*-butyl 2-hydroxypyrrolidine-1-carboxylate (1.00 equiv, 9.35 mmol, 1.75 g) and *para*-toluenesulfonic acid monohydrate (0.17 mol%, 16 µmol, 3.0 mg) in toluene (20 mL) was heated at reflux with a Dean-Stark apparatus for 4 h. After cooling, two drops of Et_3N were added and the solvent was removed under reduced pressure to afford a yellow oil (1.15 g). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 5%) afforded pure **1a** (950 mg, 5.61 mmol, 60%).

Run 3: A solution of *tert*-butyl 2-hydroxypyrrolidine-1-carboxylate (1.00 equiv, 8.01 mmol, 1.50 g) and *para*-toluenesulfonic acid monohydrate (0.32 mol%, 26 µmol, 5.0 mg) in toluene (15 mL) was heated at reflux with a Dean-Stark apparatus for 18 h. After cooling, the solvent was removed under reduced pressure to afford a yellow oil. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 30%) afforded reasonably pure **1a** (221 g, 1.31 mmol, 16%), contaminated with starting material, and fairly pure *tert*-butyl 4-(1-*tert*-butoxycarbonylpyrrolidin-2-yl)-2,3-dihydropyrrole-1-carboxylate, little useful in this context (882 mg, 2.61 mmol, 65%).

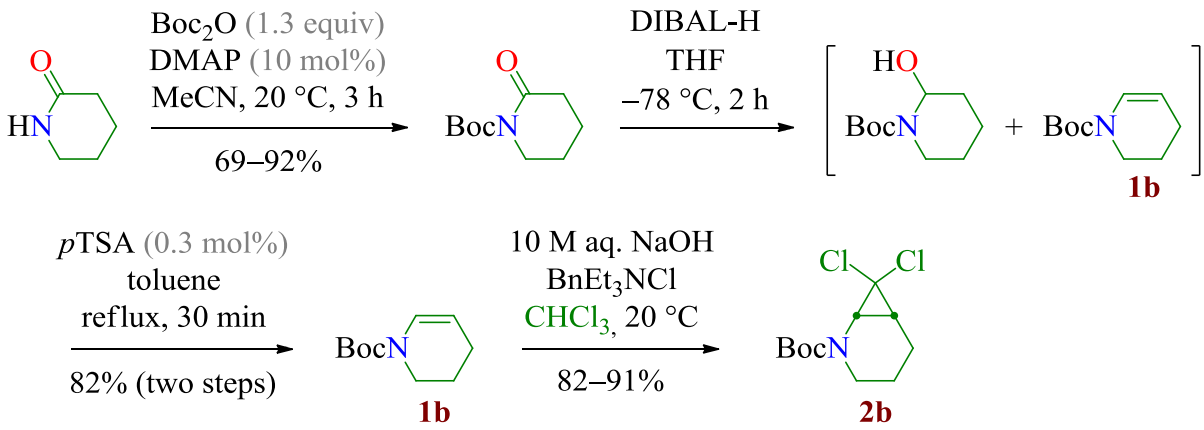


d) Cyclopropanation with dichlorocarbene

General procedure A was applied with **1a** (1.00 equiv, 5.61 mmol, 950 mg). The crude product, a yellow oil, was analysed by ^1H NMR spectroscopy and found to contain fairly pure *tert*-butyl 6,6-dichloro-2-azabicyclo[3.1.0]hexane-2-carboxylate **2a** (1.09 g, 4.32 mmol, 77%).

tert-Butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b**

■ **Route 1: from piperidin-2-one**



a) Installation of the Boc group

tert-Butyl 2-oxopiperidine-1-carboxylate was prepared in 69−92% yield from piperidin-2-one (25.0 mmol) by applying a literature procedure.[6]

b) Reduction of the carbonyl group

DIBAL-H (1.0 M in hexanes, 1.50 equiv, 15.0 mmol, 15.0 mL) was added dropwise, at −78 °C, to a solution of *tert*-butyl 2-oxopiperidine-1-carboxylate (1.00 equiv, 10.0 mmol, 1.99 g) in dry THF (40 mL). After 2 h of stirring at −78 °C, Rochelle salt aqueous solution (20 mL) was slowly added and the mixture was allowed to warm to 20 °C, with stirring until two clear phases were formed. The organic phase was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a colourless oil (1.75 g). Analysis by ^{1}H NMR spectroscopy showed that this crude product contained a 67 : 33 mixture of *tert*-butyl 3,4-dihydro-2*H*-pyridine-1-carboxylate **1b** and *tert*-butyl 2-hydroxypiperidine-1-carboxylate.[7,8]

c) Dehydration

A solution of the mixture of *tert*-butyl 3,4-dihydro-2*H*-pyridine-1-carboxylate and *tert*-butyl 2-hydroxypiperidine-1-carboxylate (1.75 g) and *para*-toluenesulfonic acid monohydrate (0.26 mol%, 26 µmol, 5.0 mg) in toluene (15 mL) was heated at reflux with a Dean-Stark apparatus for 30 minutes. After cooling, the solvent was removed under reduced pressure to afford a yellow oil (1.50 g). Analysis by ^{1}H NMR spectroscopy revealed that this crude product contained virtually pure *tert*-butyl 3,4-dihydro-2*H*-pyridine-1-carboxylate **1b** (1.50 g, 8.19 mmol, 82% over two steps).

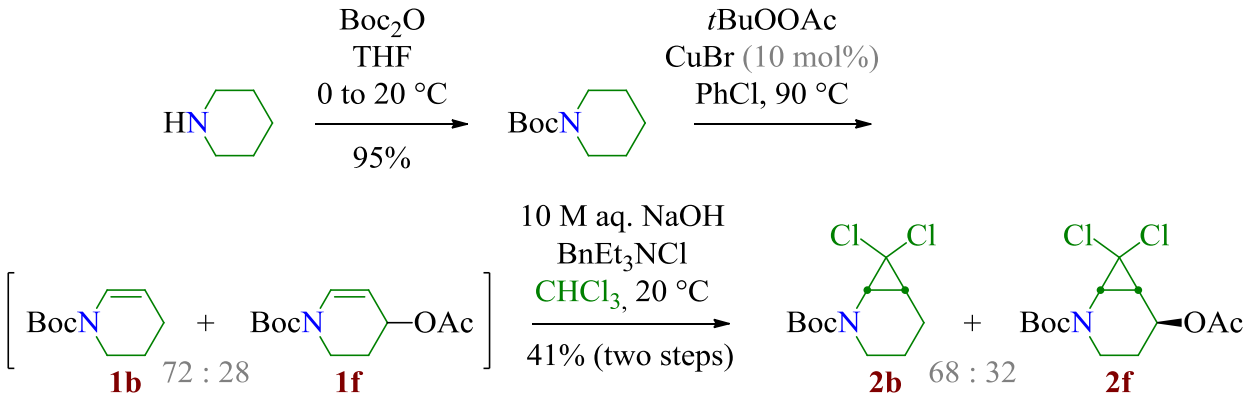
6− T. M. Wilkinson, N. W. Stehle, P. Beak, *Org. Lett.* **2000**, *2*, 155−158 (supporting information).
7− Procedure adapted from: R. K. Dieter, R. R. Sharma, *J. Org. Chem.* **1996**, *61*, 4180–4184.
8− In another run performed under the same conditions on a 9 mmol scale, the crude product obtained, a yellow oil, was found to contain pure *tert*-butyl 2-hydroxypiperidine-1-carboxylate (90% yield).

d) Cyclopropanation with dichlorocarbene

Run 1: General procedure A was applied with **1b** (1.00 equiv, 4.83 mmol, 886 mg). The crude product, a yellow oil, was analysed by ^{1}H NMR spectroscopy and found to contain essentially pure *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.06 g, 3.98 mmol, 82%).

Run 2: General procedure A was applied with **1b** (1.00 equiv, 5.46 mmol, 1.00 g). The crude product, a yellow oil, was analysed by ^{1}H NMR spectroscopy and found to contain essentially pure **2b** (1.32 g, 4.96 mmol, 91%).

■ **Route 2: from piperidine**



a) Installation of the Boc group

tert-Butyl piperidine-1-carboxylate was prepared in 95% yield from piperidine (172 mmol) by applying a literature procedure.[9]

b) Kharasch-Sosnovsky reaction[10]

A flow of nitrogen was bubbled, for 15 min, through a mixture of *tert*-butyl piperidine-1-carboxylate (1.25 equiv, 27.0 mmol, 5.00 g), copper(I) bromide (10% equiv, 2.16 mmol, 310 mg) and PhCl (0.10 L). The mixture was then heated to 90 °C (measured with a thermometer plunged inside the flask) and a solution of *tert*-butyl peracetate (50 wt.% in mineral spirits, 1.00 equiv, 21.6 mmol, 5.71 g) in PhCl (50 mL) was slowly added (dropping funnel) over 3 h. Stirring was then maintained at 90 °C overnight. After cooling, the mixture was concentrated under reduced pressure and the residue (6.82 g) was analysed by ^{1}H NMR spectroscopy to reveal it contained a mixture of starting *tert*-butyl piperidine-1-carboxylate, *tert*-butyl 3,4-dihydro-2*H*-pyridine-1-carboxylate **1b** and *tert*-butyl 4-acetoxy-3,4-dihydro-2*H*-pyridine-1-carboxylate **1f** in a ratio of 68 : 23 : 09. This crude product was engaged in the next step without purification.

9– D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260−7261 (supporting information).

10– Procedure adapted from G. Sosnovsky, S.-O. Lawesson, *Angew. Chem.* **1964**, *76*, 218−225; *Angew. Chem. Int. Ed.* **1968**, *3*, 269−276.

c) Cyclopropanation with dichlorocarbene

10 M NaOH aqueous solution (80 mL) was slowly added to a solution of the preceding mixture (6.82 g) and benzyltriethylammonium chloride (0.52 equiv, 11.2 mmol, 2.55 g) in $CHCl_3$ (80 mL). After 120 min of vigorous stirring at 20 °C, the organic phase was separated. the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic phases (0.14 L) were then washed with H_2O (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product (8 g). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 2 to 10%) afforded pure starting *tert*-butyl piperidine-1-carboxylate (2.19 g, 11.8 mmol), *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.13 g, 4.25 mmol, 20% over two steps based on *tert*-butyl peracetate; 28% over two steps based on non-recovered *tert*-butyl piperidine-1-carboxylate) and *tert*-butyl (1*R**,5*R**,6*R**)-5-acetoxy-7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2f** (628 mg, 1.94 mmol, 9% over two steps based on *tert*-butyl peracetate; 13% over two steps based on non-recovered *tert*-butyl piperidine-1-carboxylate).

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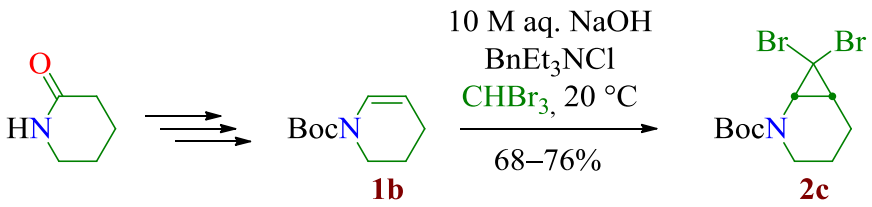
tert-Butyl 7,7-dibromo-2-azabicyclo[4.1.0]heptane-2-carboxylate **2c**

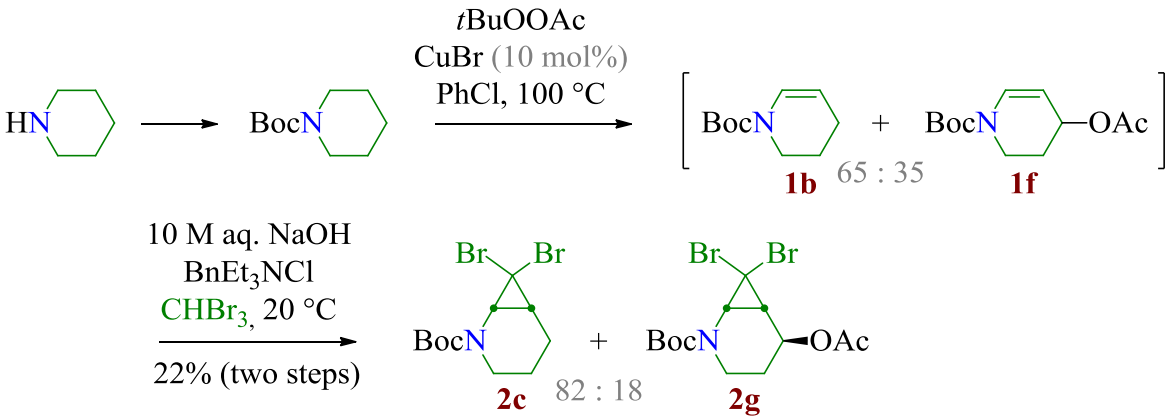
■ Route 1: from piperidin-2-one



Run 1: 10 M NaOH aqueous solution (2.0 mL) was added dropwise to a solution of *tert*-butyl 3,4-dihydro-2*H*-pyridine-1-carboxylate **1b** (prepared as indicated further above, 1.00 equiv, 350 µmol, 64.1 mg) and benzyltriethyl-ammonium chloride (0.63 equiv, 220 µmol, 50.2 mg) in $CHBr_3$ (1.0 mL). After 3 h 30 min of vigorous stirring at 20 °C, the aqueous phase was removed. The organic layer was diluted with CH_2Cl_2 (10 mL), washed with brine (10 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil (920 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 10%) afforded pure *tert*-butyl 7,7-dibromo-2-azabicyclo[4.1.0]heptane-2-carboxylate **2c** (84.0 mg, 236 µmol, 68%).

Run 2: 10 M NaOH aqueous solution (2.0 mL) was added dropwise to a solution of **1b** (prepared as indicated further above, 1.00 equiv, 600 µmol, 110 mg) and benzyltriethyl-ammonium chloride (0.63 equiv, 378 µmol, 86.1 mg) in $CHBr_3$ (2.0 mL). After 1 h of vigorous stirring at 20 °C, the aqueous phase was removed. The organic layer was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown oil (3.60 g). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 5%) afforded pure **2c** (161 mg, 453 µmol, 76%).

■ **Route 2: from piperidine**



a) Kharasch-Sosnovsky reaction[10]

A mixture of *tert*-butyl piperidine-1-carboxylate (prepared as indicated further above, 1.25 equiv, 27.6 mmol, 5.11 g), copper(I) bromide (10% equiv, 2.21 mmol, 317 mg) and PhCl (20 mL) was heated at 100 °C for 15 min, then a solution of *tert*-butyl peracetate (50 wt.% in mineral spirits, 1.00 equiv, 22.1 mmol, 5.83 g) in PhCl (40 mL) was added over 4 h (dropping funnel). Stirring was then maintained at 100 °C for 1 h. After cooling, 0.1 M NaOH aq. solution (40 mL) was added. The organic layer was separated, washed with H_2O (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a dark yellow oil (5.73 g). Analysis by ^1H NMR spectroscopy revealed the crude product contained starting *tert*-butyl piperidine-1-carboxylate, *tert*-butyl 3,4-dihydro-2*H*-pyridine-1-carboxylate **1b** and *tert*-butyl 4-acetoxy-3,4-dihydro-2*H*-pyridine-1-carboxylate **1f** in a ratio of 69 : 20 : 11. This mixture was engaged in the next step without further purification.

b) Cyclopropanation with dibromocarbene

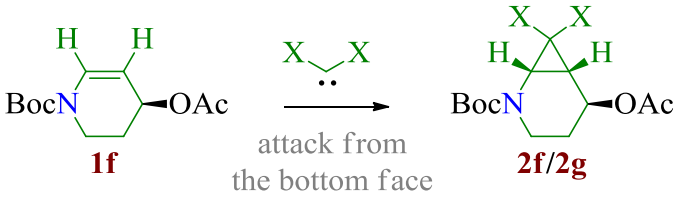
10 M NaOH aqueous solution (10 mL) was slowly added to a solution of a part of the preceding mixture (1.50 g) and benzyltriethylammonium chloride (0.52 equiv, 3.00 mmol, 683 mg) in $CHBr_3$ (10 mL). After 120 min of vigorous stirring at 20 °C, the organic phase was separated. the aqueous layer was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a dark brown oil (2.51 g). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 1 to 20%) afforded pure *tert*-butyl 7,7-dibromo-2-azabicyclo[4.1.0]heptane-2-carboxylate **2c** (366 mg, 1.03 mmol, 18% over two steps based on *tert*-butyl peracetate) and *tert*-butyl (1*R**,5*S**,6*R**)-5-acetoxy-7,7-dibromo-2-azabicyclo[4.1.0]heptane-2-carboxylate **2g** (97.5 mg, 236 µmol, 4% over two steps based on *tert*-butyl peracetate).

Relative configuration of the acetate group of **2f** and **2g**

Our assignment of the relative configuration of the acetate group of **2f** and **2g** is based on both mechanistic considerations and ^{1}H NMR data:

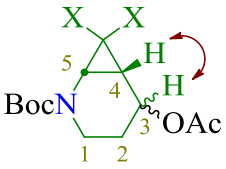
a) Mechanistic considerations

In a first analysis, the configuration of the acetate group being drawn as displayed below, attack of the dichlorocarbene species from the bottom face should be kinetically favoured because of steric effects.

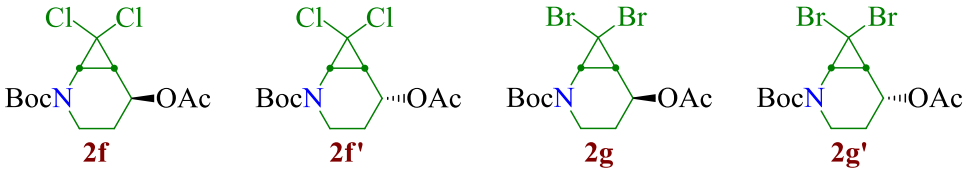


b) ^{1}H NMR data

The ^{3}J coupling constant between H3 and H4 (numbering as in the drawing below) is easily measured. Indeed, the signal of H4 is a doublet of doublets and identification of the two coupling constants is straightforward, since the signal of H5 is a doublet giving the value of $^{3}J_{H4\text{-}H5}$.



Comparison of these measured $^{3}J_{H3\text{-}H4}$ coupling constants, in the major rotamers of **2f** and **2g**, with estimated values obtained using generalised Karplus calculations[11] strongly supports our assignment, as shown in the Table below. The dihedral angles, for each possible diastereoisomers of the two compounds, were measured on structures generated by PM7 semi-empirical calculations[12] using the MOPAC software.[13]



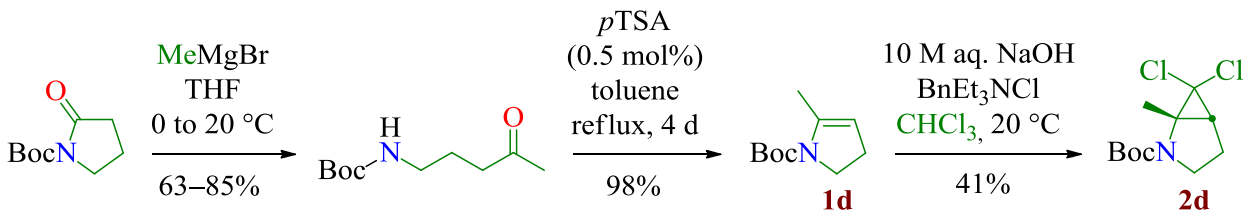
Calculated H3-H4 diehedral angle (PM7)	−109°	+20.3°	−83.6°	+22.8°
Calculated $^{3}J_{H3\text{-}H4}$	**1.5 Hz**	7.7 Hz	**1.1 Hz**	7.5 Hz
Experimental $^{3}J_{H3\text{-}H4}$	**2.0 Hz**		**2.5 Hz**	

11− C.A.G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783−2792. On-line calculation done at http://www.stenutz.eu/conf/haasnoot.php (accessed 14 March 2017).

12− J. J. P. Stewart, *J. Mol. Mod.* **2013**, *19*, 1−32.

13− MOPAC2016, Version: 16.035W, James J. P. Stewart, Stewart Computational Chemistry. Web: http://OpenMOPAC.net.

tert-Butyl 6,6-dichloro-1-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate **2d**



a) Addition of methylmagnesium bromide onto the carbonyl group

Run 1: Methylmagnesium bromide (3.0 M in Et_2O, 1.40 equiv, 12.9 mmol, 4.29 mL) was added dropwise, at 0 °C, to a solution of *tert*-butyl 2-oxopyrrolidine-1-carboxylate (prepared as indicated further above, 1.00 equiv, 9.18 mmol, 1.70 g) in dry THF (30 mL). The mixture was stirred for 3 h while allowed to warm to 20 °C. H_2O (10 mL) was then added. After filtration through a short pad of celite, most of the THF was removed under reduced pressure. EtOAc (50 mL) was then added. The organic layer was washed with saturated $NaHCO_3$ aqueous solution (2 × 20 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product, a pale yellow oil, was analysed by ^{1}H NMR spectroscopy and found to contain pure *tert*-butyl *N*-(4-oxopentyl)carbamate (1.58 g, 7.85 mmol, 85%).

Run 2: Methylmagnesium bromide (3.0 M in Et_2O, 1.40 equiv, 24.2 mmol, 8.06 mL) was added dropwise, at 0 °C, to a solution of *tert*-butyl 2-oxopyrrolidine-1-carboxylate (prepared as indicated further above, 1.00 equiv, 17.3 mmol, 3.20 g) in dry THF (40 mL). The mixture was stirred at 0 °C for 4 h, then H_2O (10 mL) was added. After filtration through a short pad of celite, most of the THF was removed under reduced pressure. EtOAc (50 mL) was then added. The organic layer was washed with saturated $NaHCO_3$ aqueous solution (2 × 20 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product, a pale yellow oil, was analysed by ^{1}H and ^{13}C NMR spectroscopy and found to contain pure *tert*-butyl *N*-(4-oxopentyl)carbamate (2.20 g, 10.9 mmol, 63%).

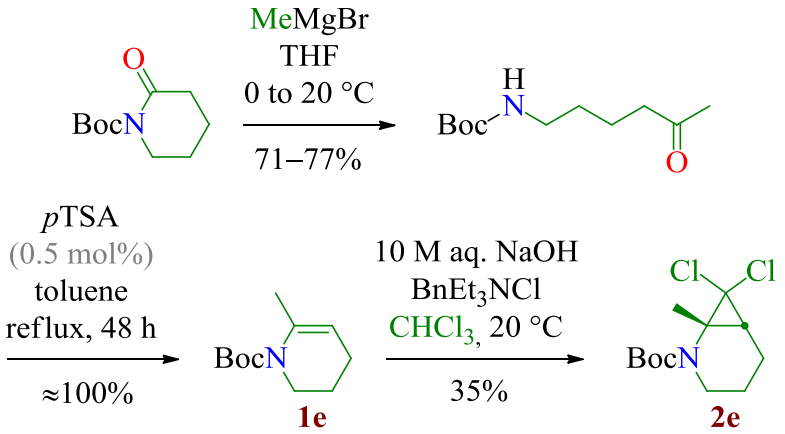
b) Dehydration

A solution of *tert*-butyl *N*-(4-oxopentyl)carbamate (1.00 equiv, 3.02 mmol, 608 mg) and *para*-toluenesulfonic acid monohydrate (0.52 mol%, 16 µmol, 3.0 mg) in toluene (15 mL) was heated at reflux with a Dean-Stark apparatus for 4 days. After cooling, the solvent was removed under reduced pressure to afford a yellow oil (540 mg). Analysis by ^{1}H NMR spectroscopy revealed that this crude product contained virtually pure *tert*-butyl 5-methyl-2,3-dihydropyrrole-1-carboxylate **1d** (540 mg, 2.95 mmol, 98%).

c) Cyclopropanation with dichlorocarbene

General procedure A was applied with **1d** (1.00 equiv, 2.95 mmol, 540 mg). The crude product, a dark yellow oil (908 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 10%) to afford pure *tert*-butyl 6,6-dichloro-1-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate **2d** (321 mg, 1.21 mmol, 41%).

tert-Butyl 7,7-dichloro-1-methyl-2-azabicyclo[4.1.0]heptane-2-carboxylate **2e**



a) Addition of methylmagnesium bromide onto the carbonyl group

Run 1: Methylmagnesium bromide (3.0 M in Et_2O, 1.40 equiv, 4.20 mmol, 1.40 mL) was added dropwise, at 0 °C, to a solution of *tert*-butyl 2-oxopiperidine-1-carboxylate (prepared as indicated further above, 1.00 equiv, 3.00 mmol, 598 mg) in dry THF (10 mL). The cooling bath was removed and the mixture was stirred at 20 °C for 19 h. H_2O (3.0 mL) was then added. After filtration through a short pad of celite, the mixture was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product, a yellow oil, was analysed by ^1H NMR spectroscopy and found to contain fairly pure *tert*-butyl *N*-(5-oxohexyl)carbamate (460 mg, 2.14 mmol, 71%).

Run 2: Methylmagnesium bromide (3.0 M in Et_2O, 1.40 equiv, 9.27 mmol, 3.09 mL) was added dropwise, at 0 °C, to a solution of *tert*-butyl 2-oxopiperidine-1-carboxylate (prepared as indicated further above, 1.00 equiv, 6.62 mmol, 1.32 g) in dry THF (25 mL). The mixture was stirred at 0 °C for 5 h, then H_2O (6.0 mL) was added. After filtration through a short pad of celite, most of the THF was removed under reduced pressure. EtOAc (50 mL) was then added. The organic layer was washed with saturated $NaHCO_3$ aqueous solution (2 × 20 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product, a yellow oil, was analysed by ^1H NMR spectroscopy and found to contain pure *tert*-butyl *N*-(5-oxohexyl)carbamate (1.10 g, 5.11 mmol, 77%).

b) Dehydration

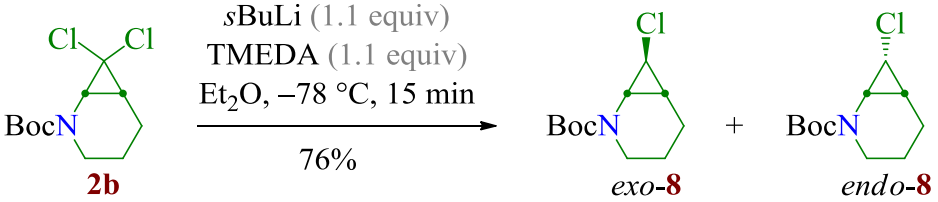
A solution of *tert*-butyl *N*-(5-oxohexyl)carbamate (1.00 equiv, 5.11 mmol, 1.10 g) and *para*-toluenesulfonic acid monohydrate (0.50 mol%, 26 µmol, 5.0 mg) in toluene (15 mL) was heated at reflux with a Dean-Stark apparatus. After 48 h, the solvent was removed under reduced pressure to afford a yellow oil (1.10 g). Analysis by ^1H NMR spectroscopy revealed that this crude product contained essentially pure *tert*-butyl 6-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylate **1e** (quantitative yield).

c) Cyclopropanation with dichlorocarbene

General procedure A was applied with **1e** (1.00 equiv, 5.58 mmol, 1.10 g). The crude product, a yellow oil (1.32 g), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 5%) to afford pure *tert*-butyl 7,7-dichloro-1-methyl-2-azabicyclo[4.1.0]heptane-2-carboxylate **2e** (540 mg, 1.93 mmol, 35%).

tert-Butyl (1*R**,6*S**,7*R**)-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate *exo*-**8**

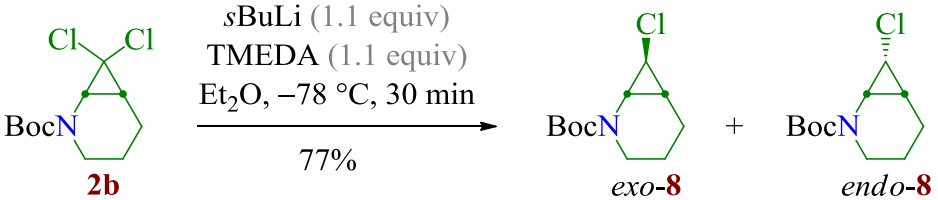
Run 1:



dr 59 : 41

sec-Butyllithium solution (0.91 M in cyclohexane, 1.10 equiv, 1.10 mmol, 1.21 mL) was added dropwise, at –78 °C, to a solution of *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.00 equiv, 1.00 mmol, 266 mg) and TMEDA (1.10 equiv, 1.10 mmol, 165 µL) in Et_2O (11 mL).[14] After 15 minutes of stirring at –78 °C, H_2O (20 mL) was added. The mixture was then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellow oil (237 mg). Analysis of the crude product by ^1H NMR spectroscopy showed that the starting material had been entirely converted into *tert*-butyl 7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **8** [*dr* 59 : 41 in favour of the *exo* diastereoisomer]. Purification by two successive flash column chromatographies on silica gel (EtOAc / petroleum ether, gradient from 2 to 10%) afforded pure *tert*-butyl (1*R**,6*S**,7*R**)-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate *exo*-**8** (105 mg, 453 µmol, 45%), a 75 : 25 mixture of the *endo* and *exo* diastereoisomers of **8** (64.7 mg, 279 µmol, 28%) and pure *tert*-butyl (1*R**,6*S**,7*S**)-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate *endo*-**8** (7.0 mg, 30 µmol, 3%).

Run 2:

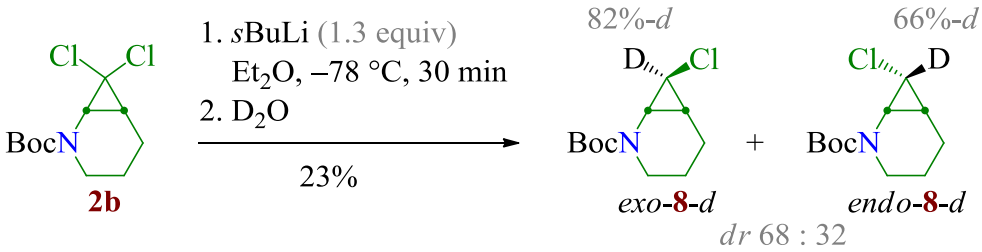


dr 63 : 37

sec-Butyllithium solution (0.91 M in cyclohexane, 1.10 equiv, 5.23 mmol, 5.75 mL) was added dropwise, at –78 °C, to a solution of **2b** (1.00 equiv, 4.76 mmol, 1.27 g) and TMEDA (1.10 equiv, 5.23 mmol, 784 µL) in Et_2O (50 mL).[14] After 30 minutes of stirring at –78 °C, H_2O (50 mL) was added. The mixture was then extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellow oil (1.24 g). Analysis of the crude product by ^1H NMR spectroscopy showed that the starting material had been entirely converted into *tert*-butyl-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **8** [*dr* 63 : 37 in favour of the *exo* diastereoisomer]. Purification by two successive flash column chromatographies on silica gel [EtOAc / petroleum ether, 5% (1st column) and 2% (2nd column)] afforded pure *exo*-**8** (268 mg, 1.16 mmol, 24%), a 57 : 43 mixture of the *endo* and *exo* diastereoisomers of **8** (447 mg, 1.93 mmol, 41%) and pure *endo*-**8** (135 mg, 583 µmol, 12%)

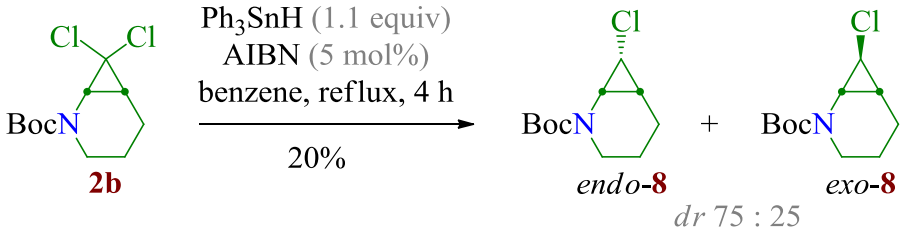
14– *s*BuLi was slowly poured onto the cold inner walls of the flask rather than directly introduced into the solution.

Additional result: chlorine-lithium exchange without TMEDA and quench with D_2O



sec-Butyllithium solution (0.99 M in cyclohexane, 1.30 equiv, 649 µmol, 656 µL) was added dropwise, at –78 °C, to a solution of *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.00 equiv, 500 µmol, 133 mg) in Et_2O (2.0 mL). After 30 min of stirring at –78 °C, D_2O (1.0 mL) was added and the reaction mixture was allowed to warm to 20 °C. H_2O (5.0 mL) and AcOH (2.0 mL) were then added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow oil (163 mg). Analysis of the crude product by ^{1}H NMR spectroscopy showed that the starting material had been entirely converted into *tert*-butyl 7-chloro-7-deuterio-2-azabicyclo[4.1.0]heptane-2-carboxylate **8** [*dr* 68 : 32 in favour of the *exo* diastereoisomer]. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 2 to 20%) afforded a 65 : 35 mixture of *exo*-**8** (82%-*d*) and *endo*-**8** (66%-*d*) (27.0 mg, 116 µmol, 23%).

Additional result: radical reduction

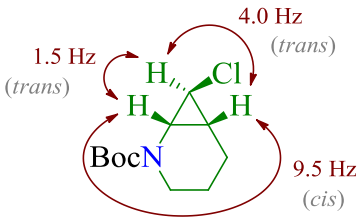


A solution of *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.00 equiv, 364 µmol, 97.0 mg) and triphenyltin hydride (1.10 equiv, 401 µmol, 141 mg) in benzene (0.5 mL) was heated at reflux for 10 minutes. Azobisisobutyronitrile (5.0 mol%, 18 µmol, 3.0 mg) was then added and the mixture was stirred at reflux for a further 4 h. After cooling with an ice bath, the solution was diluted with EtOAc (20 mL) and washed with 10% aqueous KF solution (20 mL). The mixture was filtered, washed with brine (10 mL), dried over $MgSO_4$, filtered again and concentrated under reduced pressure to afford a white mixture of solid and oil (101 mg). Analysis of the crude product by ^{1}H NMR spectroscopy showed that the starting material had been almost entirely converted into *tert*-butyl-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **8** [*dr* 75 : 25 in favour of the *endo* diastereoisomer]. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 7%) afforded essentially pure *endo*-**8** as a single diastereoisomer (16.8 mg, 72.5 µmol, 20%).[15]

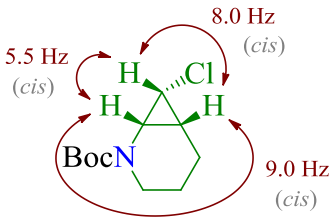
15– This procedure is adapted from A. Pozo-Rodrigálvarez, A. Gradillas, J. Serrano, A. P. Fernández, R. Martínez-Murillo, J. Pérez-Castells, *Eur. J. Med. Chem.* **2012**, *54*, 439–446.

Relative configuration of the carbon centre attached to the chlorine atom of **8**

In cyclopropane systems, ^{3}J coupling constant values are typically lower for protons in *trans* relative configuration than for *cis* protons.[16] Based on this knowledge, the relative configuration of the chiral centre bearing the chlorine atom was determined by measuring ^{3}J between the protons attached to the cyclopropane sub-unit of both diastereoisomers of **8**. Comparison of the values measured is consistent with the *trans* relationship of the α-Cl proton with the two other cyclopropane protons in *exo*-**8** and with the all-*cis* relationship in *endo*-**8**.



exo-**8**

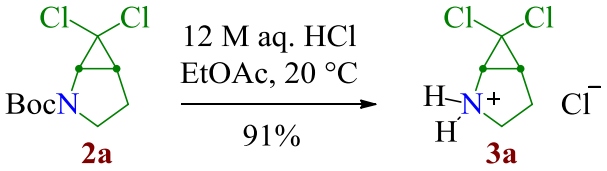


endo-**8**

16– D. J. Patel, M. E. H. Howden, J. D. Roberts, *J. Am. Chem. Soc.* **1963**, *85*, 3218–3223.

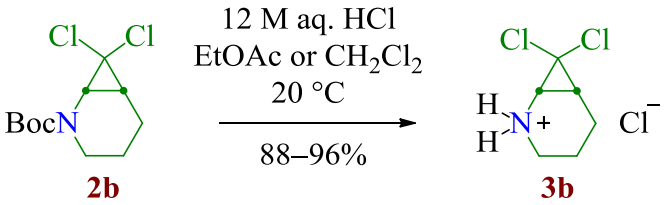
II. Preparation of the cyclopropylammonium salts

6,6-Dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a**



12 M HCl aqueous solution (10.0 equiv, 23.8 mmol, 1.98 mL) was added dropwise to a vigorously stirred solution of *tert*-butyl 6,6-dichloro-2-azabicyclo[3.1.0]hexane-2-carboxylate **2a** (1.00 equiv, 2.38 mmol, 601 mg) in EtOAc (10 mL). After 1 h of stirring, the solution was concentrated under reduced pressure and dried under high vacuum to afford pure 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** (411 mg, 2.18 mmol, 91%).

7,7-Dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b**

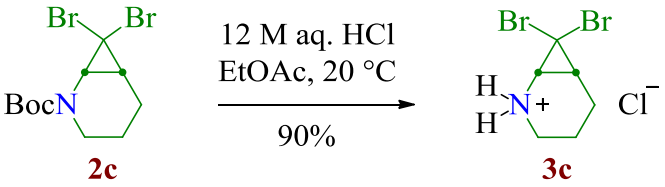


Run 1: 12 M HCl aqueous solution (10.0 equiv, 24.4 mmol, 2.03 mL) was added dropwise to a vigorously stirred solution of *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.00 equiv, 2.44 mmol, 650 mg) in EtOAc (10 mL). After 2 h of stirring, the solution was concentrated under reduced pressure, washed with a small amount of Et_2O, and dried under high vacuum to afford pure 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (470 mg, 2.32 mmol, 95%).

Runs 2−7: 12 M HCl aqueous solution (5.00 equiv, 2.46 mmol, 205 µL) was added dropwise to a vigorously stirred solution of **2b** (1.00 equiv, 492 µmol, 131 mg) in CH_2Cl_2 (3.0 mL). After 16 h of stirring, the solution was concentrated under reduced pressure to afford pure **3b** (88−96 mg, 435−474 µmol, 88−96%).

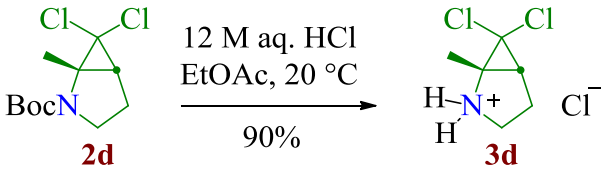
Run 8: 12 M HCl aqueous solution (5.0 equiv, 18.8 mmol, 1.57 mL) was added dropwise to a vigorously stirred solution of **2b** (1.00 equiv, 3.76 mmol, 1.00 g) in CH_2Cl_2 (8.0 mL). After 16 h of stirring at 20 °C, the solution was concentrated under reduced pressure. The residue was washed with a small amount of Et_2O (2 × 4.0 mL) and dried under high vacuum to afford pure **3b** (724 mg, 3.58 mmol, 95%).

7,7-Dibromo-2-azoniabicyclo[4.1.0]heptane chloride **3c**



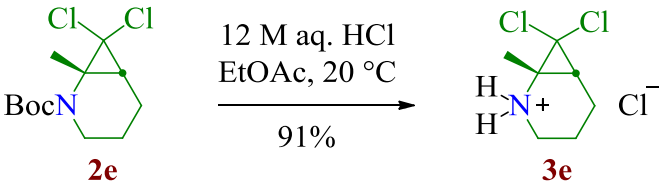
12 M HCl aqueous solution (10.0 equiv, 4.51 mmol, 376 µL) was added dropwise to a vigorously stirred solution of *tert*-butyl 7,7-dibromo-2-azabicyclo[4.1.0]heptane-2-carboxylate **2c** (1.00 equiv, 451 µmol, 161 mg) in EtOAc (1.5 mL). After 2 h of stirring, the solution was concentrated under reduced pressure, washed with a small amount of Et_2O, and dried under high vacuum to afford pure 7,7-dibromo-2-azoniabicyclo[4.1.0]heptane chloride **3c** (118 mg, 405 µmol, 90%).

6,6-Dichloro-1-methyl-2-azoniabicyclo[3.1.0]hexane chloride **3d**



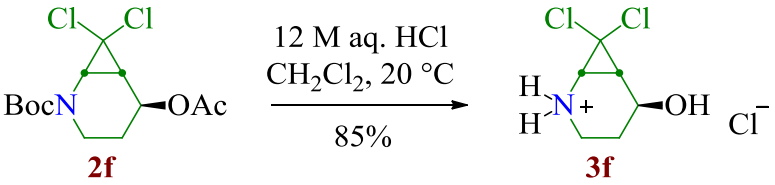
12 M HCl aqueous solution (10.0 equiv, 7.14 mmol, 595 µL) was added dropwise to a vigorously stirred solution of *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2d** (1.00 equiv, 714 µmol, 190 mg) in EtOAc (2.0 mL). After 1 h of stirring, the solution was concentrated under reduced pressure and dried under high vacuum to afford pure 6,6-dichloro-1-methyl-2-azoniabicyclo[3.1.0]hexane chloride **3d** (130 mg, 642 µmol, 90%).

7,7-Dichloro-1-methyl-2-azoniabicyclo[4.1.0]heptane chloride **3e**



12 M HCl aqueous solution (10.0 equiv, 14.3 mmol, 1.19 mL) was added dropwise to a vigorously stirred solution of *tert*-butyl 7,7-dichloro-1-methyl-2-azabicyclo[4.1.0]heptane-2-carboxylate **2e** (1.00 equiv, 1.43 mmol, 400 mg) in EtOAc (5.0 mL). After 2 h of stirring, the solution was concentrated under reduced pressure, washed with a small amount of Et_2O, and dried under high vacuum to afford pure 7,7-dichloro-1-methyl-2-azoniabicyclo[4.1.0]heptane chloride **3e** (281 mg, 1.30 mmol, 91%).

(1*R**,2*R**,6*R**)-7,7-Dichloro-2-azoniabicyclo[4.1.0]heptan-5-ol chloride **3f**

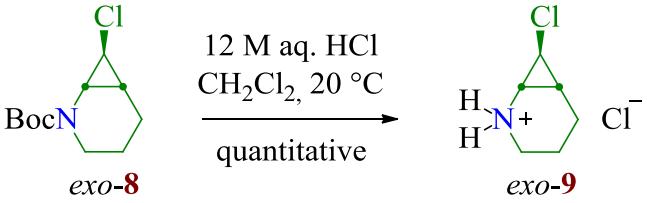


2f **3f**

Run 1: 12 M HCl aqueous solution (5.0 equiv, 1.85 mmol, 154 µL) was added dropwise to a vigorously stirred solution of *tert*-butyl (1*R**,5*R**,6*R**)-5-acetoxy-7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2f** (1.00 equiv, 370 µmol, 120 mg) in CH_2Cl_2 (2.0 mL). After 24 h of stirring, the solution was concentrated under reduced pressure and the residue was taken in CH_2Cl_2 (2.0 mL) and water (2.0 mL). The organic layer was removed and the aqueous phase was concentrated to dryness under reduced pressure to afford fairly pure (1*R**,5*R**,6*R**)-7,7-dichloro-2-azoniabicyclo[4.1.0]heptan-5-ol chloride **3f** (58.0 mg, 315 µmol, 85%).

Run 2: 12 M HCl aqueous solution (6.0 equiv, 12.0 mmol, 1.00 mL) was slowly added to a vigorously stirred solution of **2f** (1.00 equiv, 2.00 mmol, 648 mg) in CH_2Cl_2 (10 mL). After 16 h of stirring, the solution was concentrated under reduced pressure to afford fairly pure **3f** (478 mg, quantitative yield).

(1*R**,6*S**,7*R**)-7-Chloro-2-azoniabicyclo[4.1.0]heptane chloride *exo*-**9**

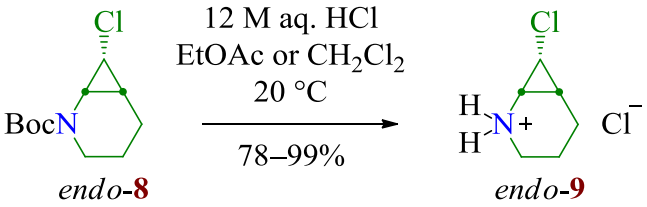


exo-**8** *exo*-**9**

Run 1: 12 M HCl aqueous solution (10.0 equiv, 3.69 mmol, 307 µL) was added to a vigorously stirred solution of *tert*-butyl (1*R**,6*S**,7*R**)-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate *exo*-**8** (1.00 equiv, 369 µmol, 85.4 mg) in CH_2Cl_2 (2.0 mL). After 18 h of stirring, the solution was concentrated under reduced pressure to afford pure (1*R**,6*S**,7*R**)-7-chloro-2-azoniabicyclo[4.1.0]heptane chloride *exo*-**9** (62.4 mg, quantitative yield).

Run 2: 12 M HCl aqueous solution (5.0 equiv, 2.87 mmol, 239 µL) was added dropwise to a vigorously stirred solution of *exo*-**8** (1.00 equiv, 575 µmol, 133 mg) in CH_2Cl_2 (2.0 mL). After 16 h of stirring at 20 °C, the solution was concentrated under reduced pressure. The residue was washed with a small amount of Et_2O and dried under high vacuum to afford pure *exo*-**9** (96.6 mg, 575 µmol, quantitative yield).

(1*R**,6*S**,7S*)-7-Chloro-2-azoniabicyclo[4.1.0]heptane chloride *endo*-**9**



endo-**8** *endo*-**9**

Run 1: 12 M HCl aqueous solution (10.0 equiv, 1.54 mmol, 128 µL) was added dropwise to a vigorously stirred solution of *tert*-butyl (1*R**,6*S**,7*S**)-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate *endo*-**8** (1.00 equiv, 154 µmol, 35.6 mg) in EtOAc (1.0 mL). After 4 h of stirring, the solution was concentrated under reduced pressure, washed with a small amount of Et_2O, and dried under high vacuum to afford pure (1*R**,6*S**,7S*)-7-chloro-2-azoniabicyclo[4.1.0]heptane chloride *endo*-**9** (20.2 mg, 120 µmol, 78%).

Run 2: 12 M HCl aqueous solution (10.0 equiv, 2.55 mmol, 211 µL) was added dropwise to a vigorously stirred solution of *endo*-**8** (1.00 equiv, 255 µmol, 59.0 mg) in CH_2Cl_2 (2.0 mL). After 18 h of stirring, the solution was concentrated under reduced pressure and dried under high vacuum to afford pure *endo*-**9** (42.6 mg, 253 µmol, 99%).

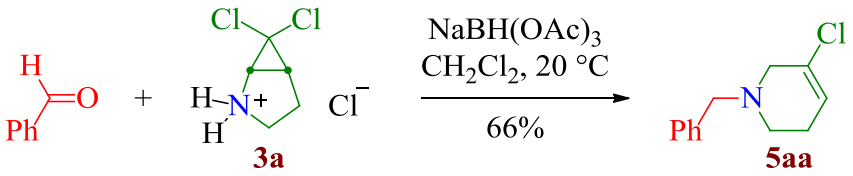
Run 3: 12 M HCl aqueous solution (5.0 equiv, 2.87 mmol, 239 µL) was added dropwise to a vigorously stirred solution of *endo*-**8** (1.00 equiv, 575 µmol, 133 mg) in CH_2Cl_2 (2.0 mL). After 16 h of stirring at 20 °C, the solution was concentrated under reduced pressure. The residue was washed with a small amount of Et_2O and dried under high vacuum to afford pure *endo*-**9** (96.6 mg, 575 µmol, quantitative yield).

III. Transformations of the haloaminocyclopropane salts

General procedure B: reactions of the cyclopropylammonium salts with aldehydes and ketones under reductive amination conditions.

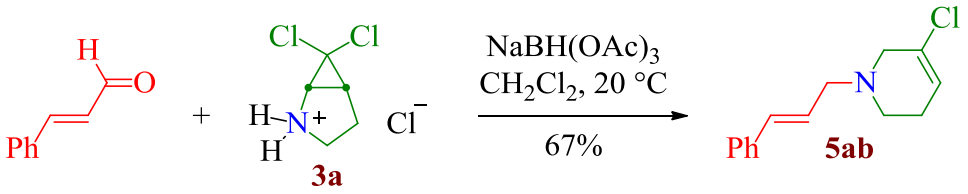
Sodium triacetoxyborohydride (2.40 equiv, 240 µmol, 50.9 mg) was added at 20 °C to a solution of aldehyde or ketone (1.00 equiv, 100 µmol) and cyclopropylammonium chloride (1.00 equiv, 100 µmol) in dry CH_2Cl_2 (1.0 mL). After 15 h of stirring at r.t., saturated $NaHCO_3$ aqueous solution (15 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel (typically, a few drops of Et_3N were added to the eluents used).

1-Benzyl-5-chloro-3,6-dihydro-2*H*-pyridine **5aa**



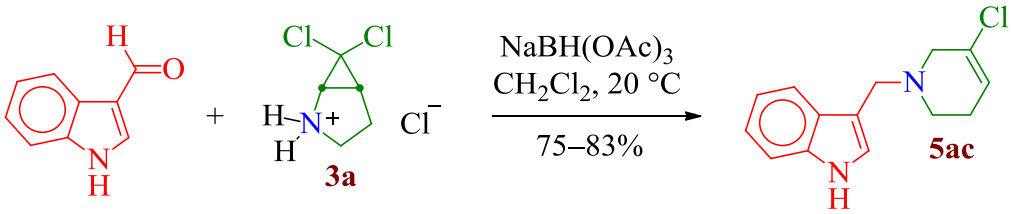
General procedure B was applied using benzaldehyde (1.00 equiv, 100 µmol, 10.2 µL) and 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** (1.00 equiv, 100 µmol, 18.8 mg). The crude product, a yellow oil (22.8 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 2%) to afford pure 1-benzyl-5-chloro-3,6-dihydro-2*H*-pyridine **5aa** (13.8 mg, 66.4 µmol, 66%).

5-Chloro-1-[(*E*)-cinnamyl]-3,6-dihydro-2*H*-pyridine **5ab**



General procedure B was applied using *trans*-cinnamaldehyde (1.00 equiv, 100 µmol, 12.6 µL) and 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** (1.00 equiv, 100 µmol, 18.8 mg). The crude product, a dark yellow oil (26.6 mg), was purified by two flash column chromatographies on silica gel (EtOAc / petroleum ether, gradient from 0 to 10%) to afford pure 5-chloro-1-[(*E*)-cinnamyl]-3,6-dihydro-2*H*-pyridine **5ab** (15.8 mg, 67.5 µmol, 67%).

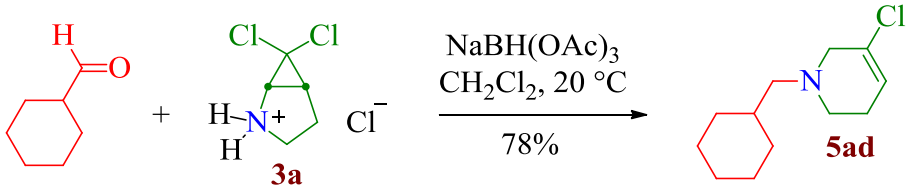
3-((3-Chloro-5,6-dihydropyridin-1(2*H*)-yl)methyl)-1*H*-indole **5ac**



Run 1: General procedure B was applied using indole-3-carboxaldehyde (1.00 equiv, 100 µmol, 14.5 mg) and 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** (1.00 equiv, 100 µmol, 18.8 mg). The crude product, a dark yellow oil (28.2 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 30%) to afford pure 3-((3-chloro-5,6-dihydropyridin-1(2*H*)-yl)methyl)-1*H*-indole **5ac** (20.4 mg, 82.6 µmol, 83%).

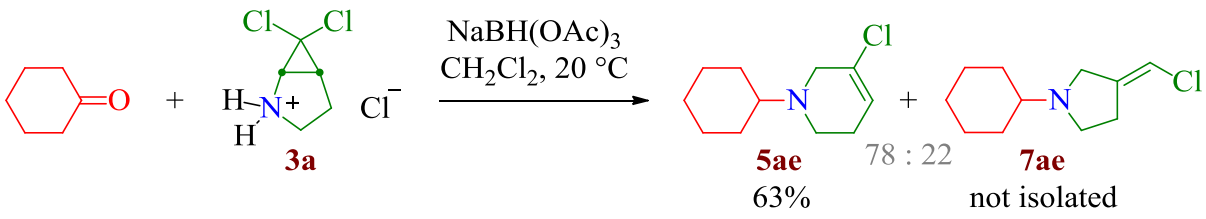
Run 2: The same procedure was applied. The crude product, a yellow oil (28.2 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 30%) to afford pure **5ac** (18.6 mg, 75.3 µmol, 75%).

5-Chloro-1-(cyclohexylmethyl)-3,6-dihydro-2*H*-pyridine **5ad**



General procedure B was applied using cyclohexanecarboxaldehyde (1.00 equiv, 100 µmol, 12.1 µL) and 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** (1.00 equiv, 100 µmol, 18.8 mg). The crude product, a dark yellow oil (21.8 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 2%) to afford pure 5-chloro-1-(cyclohexylmethyl)-3,6-dihydro-2*H*-pyridine **5ad** (16.8 mg, 78.5 µmol, 78%).

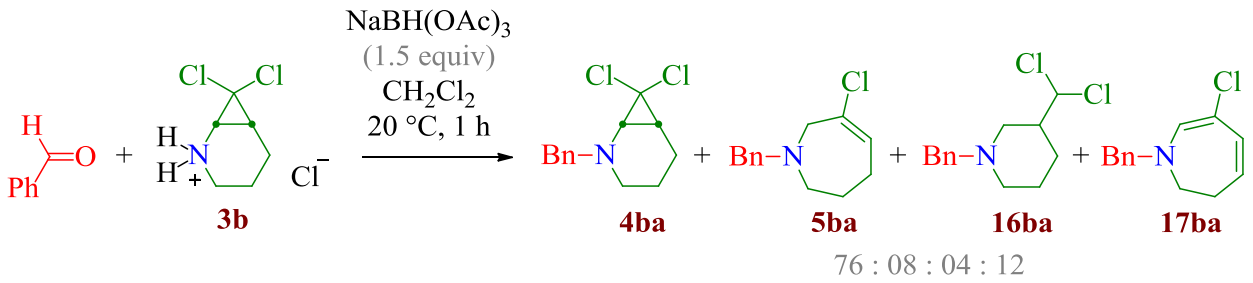
5-Chloro-1-cyclohexyl-3,6-dihydro-2*H*-pyridine **5ae**



General procedure B was applied using cyclohexanone (1.00 equiv, 100 µmol, 10.4 µL) and 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** (1.00 equiv, 100 µmol, 18.8 mg). The crude product, a pale yellow oil (15.8 mg). Analysis by ^{1}H NMR spectroscopy showed that this crude product contained a 78 : 22 mixture of 5-chloro-1-cyclohexyl-3,6-dihydro-2*H*-pyridine **5ae** and (3*E*)-3-(chloromethylene)-1-cyclohexyl-pyrrolidine **7ae**. Purification by flash column

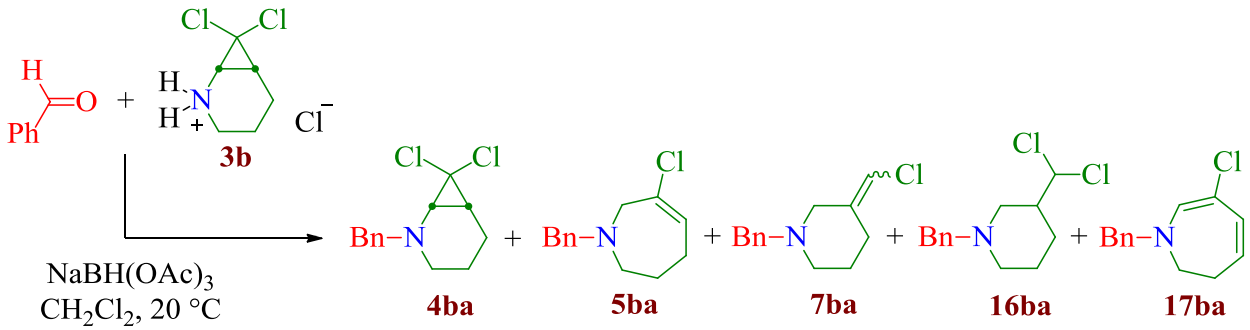
chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 10%) afforded pure **5ae** (12.6 mg, 63.0 µmol, 63%).

2-Benzyl-7,7-dichloro-2-azabicyclo[4.1.0]heptane **4ba**



Sodium triacetoxyborohydride (1.50 equiv, 150 µmol, 31.8 mg) was added at 20 °C to a solution of benzaldehyde (1.00 equiv, 100 µmol, 10.2 µL) and 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 100 µmol, 20.3 mg) in CH_2Cl_2 (1.0 mL). After 1 h of stirring at 20 °C, saturated $NaHCO_3$ aqueous solution (15 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown oil (29.6 mg). Analysis by ^{1}H and ^{13}C NMR spectroscopy revealed the presence of 2-benzyl-7,7-dichloro-2-azabicyclo[4.1.0]heptane **4ba**, 1-benzyl-6-chloro-2,3,4,7-tetrahydroazepine **5ba**, 1-benzyl-3-(dichloromethyl)piperidine and 1-benzyl-6-chloro-2,3-dihydroazepine in 76 : 08 : 04 : 12 ratio approximately.

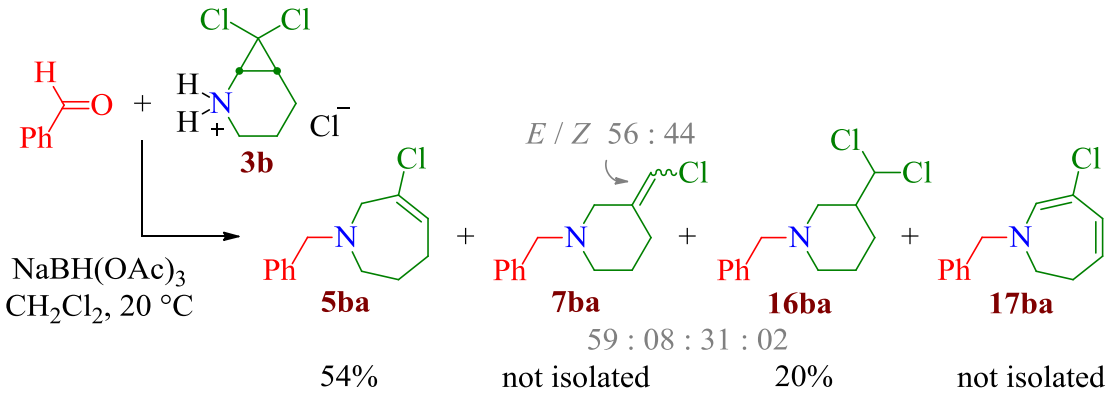
Other runs: the following table sums up the results of selected experiments performed with the same substrates, showing that 5-benzyl-7,7-dichloro-5-azabicyclo[4.1.0]heptane **4ba** is the primary product of the reaction, that is then slowly converted into the final products observed (half-life around 2 h under the reaction conditions typically applied).



Run	$NaBH(OAc)_3$	Reaction time (h)	Product ratio **4ba** / **5ba** / **7ba** / **16ba** / **17ba**
1	old batch,[a] 1.50 equiv	1	76 : 08 : 00 : 04 : 12
2	old batch,[a] 2.40 equiv	1.5	52 : 21 : 11 : 15 : 01[b]
3	old batch,[a] 2.40 equiv	16	00 : 55 : 19 : 26 : 00
4	"aged" old batch,[c] 3.3 equiv	1	60 : 19 : 15 : 06 : 00
		2.75	30 : 36 : 28 : 06 : 00
		3.75	22 : 40 : 31 : 06 : 00
		4.25	12 : 44 : 36 : 08 : 00

[a] This batch had been used before. The bottle had been opened for the first time at an unknown date. [b] After work-up, purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 2%) afforded rather impure 5-benzyl-7,7-dichloro-5-azabicyclo[4.1.0]heptane (4.6 mg, 17.9 µmol, 18%). [c] The same bottle was employed as in the preceding runs, but after more than one year. It is possible that it was misused or not properly closed in the meantime.

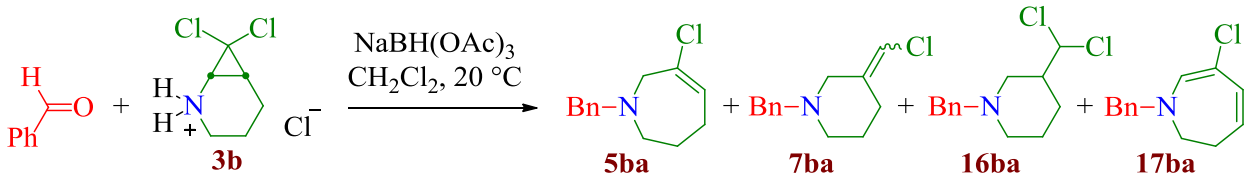
1-Benzyl-6-chloro-2,3,4,7-tetrahydroazepine **5ba**



General procedure B was applied on a five-fold scale using benzaldehyde (1.00 equiv, 500 µmol, 50.8 µL) and 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 500 µmol, 101 mg). The crude product (97.0 mg), was analysed by ^{1}H NMR spectroscopy, showing the presence of 1-benzyl-6-chloro-2,3,4,7-tetrahydroazepine **5ba**, 1-benzyl-3-(chloromethylene)-piperidine **7ba** (*E* / *Z* ≈ 56 : 44), 1-benzyl-3-(dichloromethyl)piperidine **16ba** and 1-benzyl-6-chloro-2,3-dihydroazepine **17ba** in 59 : 08 : 31 : 02 ratio approximately, as measured by integration of characteristic signals. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 2 to 8%) afforded pure 1-benzyl-6-chloro-

2,3,4,7-tetrahydroazepine **5ba** (60.0 mg, 271 µmol, 54%) and pure 1-benzyl-3-(dichloromethyl)piperidine **16ba** (26.0 mg, 101 µmol, 20%).

Other runs: the following table sums up the results of selected experiments performed with the same substrates. The line highlighted in blue indicates the particular run described in detail in the preceding paragraph.

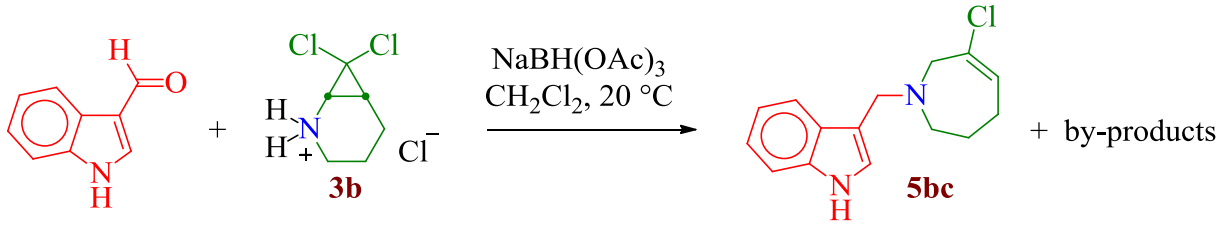


Run	Conditions	Product ratio **5ba** / **8ba** / **16ba** / **17ba**
1	$NaBH(OAc)_3$ (old batch,[a] 2.4 equiv), 16 h	55 : 19 : 26 : 00[b]
2	$NaBH(OAc)_3$ (old batch,[a] 2.4 equiv) $ClCH_2CH_2Cl$ instead of CH_2Cl_2, 60 h	54 : 26 : 17 : 03
3	$NaBH(OAc)_3$ ("aged" old batch,[c] 2.4 equiv), 16 h	61 : 28 : 10 : 00[d]
4	$NaBH(OAc)_3$ ("aged" old batch,[c] 3.3 equiv), 16 h	54 : 36 : 10 : 00[e]
5	$NaBH(OAc)_3$ ("aged" old batch,[c] 3.3 equiv) **MS 4Å**, 16 h	54 : 37 : 09 : 00
6	$NaBH(OAc)_3$ ("aged" old batch,[c] 5.0 equiv), 16 h	56 : 34 : 10 : 00
7	$NaBH(OAc)_3$ (new batch,[f] 2.4 equiv), 16 h	59 : 08 : 31 : 02[g]
8	$NaBH(OAc)_3$ (new batch,[h] 2.4 equiv) **MS 4Å**, 16 h	44 : 21 : 24 : 11

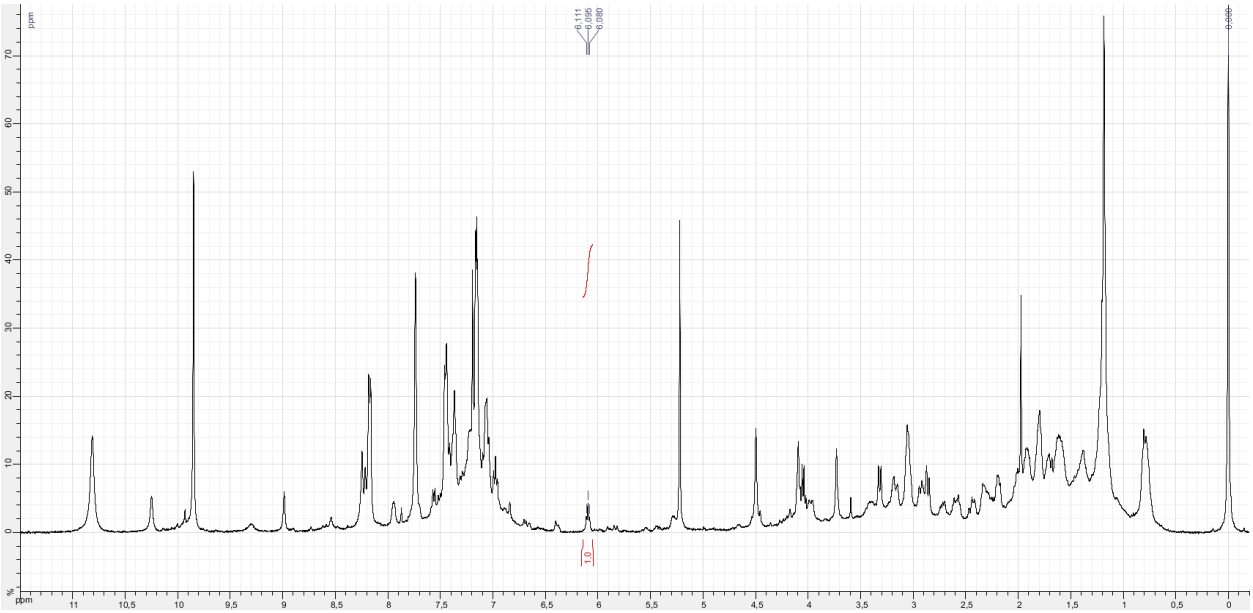
[a] This batch had been used before. The bottle had been opened for the first time at an unknown date. [b] 1-Benzyl-6-chloro-2,3,4,7-tetrahydroazepine was isolated in 50% yield. [c] The same bottle was employed as in the preceding runs, but after more than one year. It is possible that it was misused or not properly closed in the meantime. [d] The ^1H NMR spectrum of the crude product was much messier than the one recorded after run 2. [e] 1-Benzyl-6-chloro-2,3,4,7-tetrahydroazepine was isolated in 30% yield only. [f] A new bottle was purchased and opened just before use. [g] 1-Benzyl-6-chloro-2,3,4,7-tetrahydroazepine was isolated in 54% yield. [h] Experiment performed immediately after the preceding one.

Conclusions: the good quality of the $NaBH(OAc)_3$ reagent is essential for best results to be obtained; yields drop significantly when degraded reagent is used. In that case, employing larger amounts of $NaBH(OAc)_3$ partly makes up for the problem. It is observed that with "good" $NaBH(OAc)_3$, the use of 4 Å molecular sieves increases the amount of by-product **17ba** formed, essentially at the expense of **5ba**.

3-[(6-Chloro-2,3,4,7-tetrahydroazepin-1-yl)methyl]-1*H*-indole **5bc**

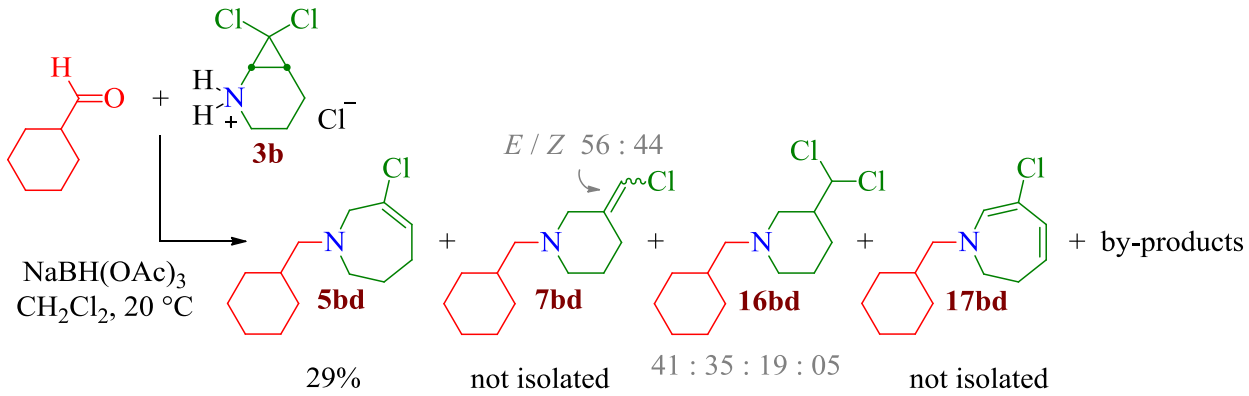


General procedure B was applied using indole-3-carboxaldehyde (1.00 equiv, 100 µmol, 14.5 mg) and 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 100 µmol, 20.3 mg). The crude product, a dark yellow oil (24.8 mg) was analysed by ^{1}H NMR, revealing the presence of 3-[(6-chloro-2,3,4,7-tetrahydroazepin-1-yl)methyl]-1*H*-indole as a minor component in a mixture of unidentified compounds. No purification was attempted.



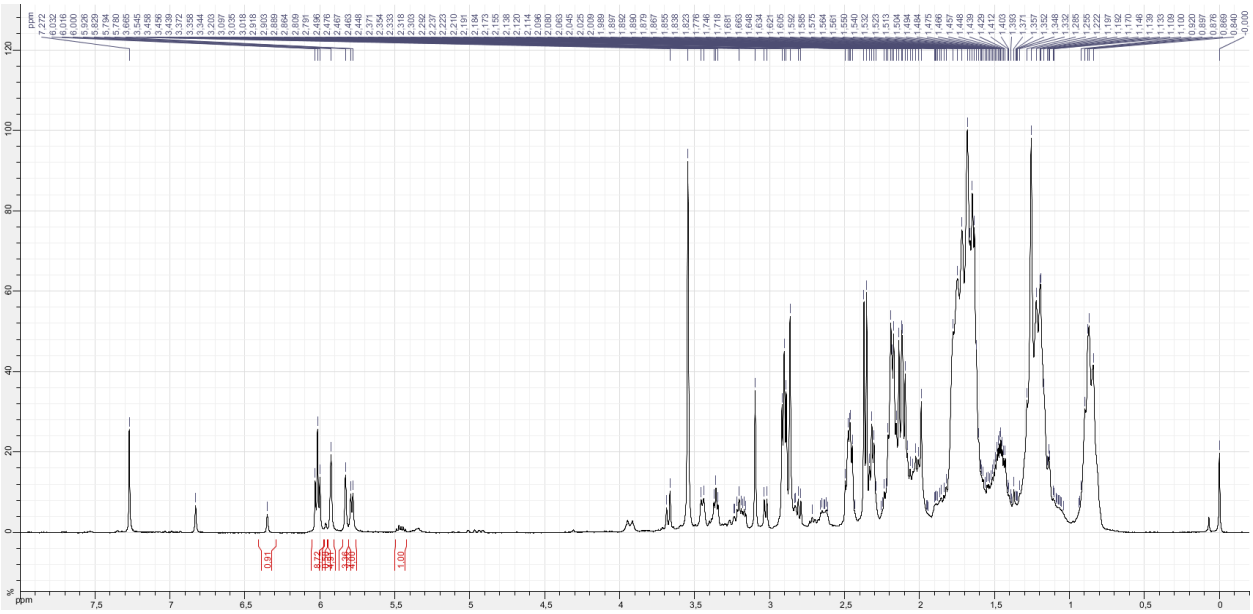
^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

6-Chloro-1-(cyclohexylmethyl)-2,3,4,7-tetrahydroazepine **5bd**



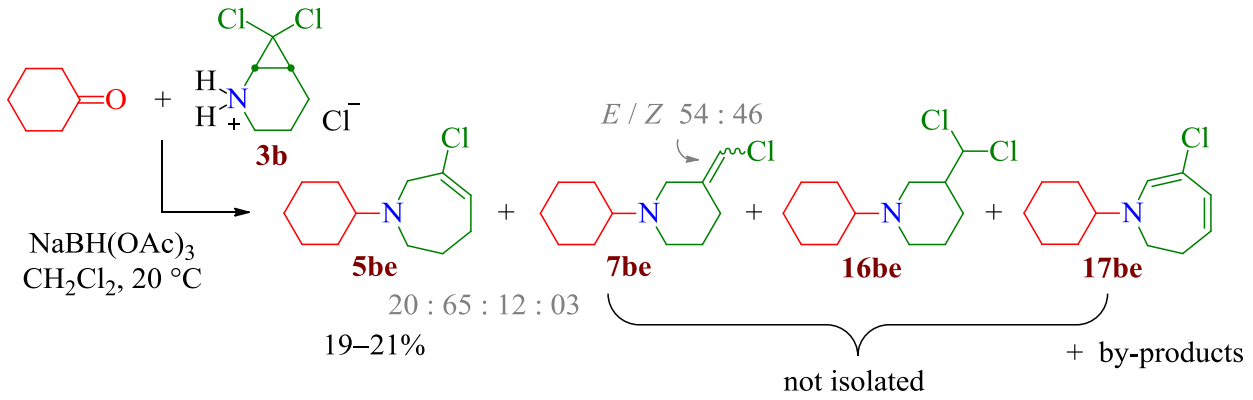
General procedure B was applied using cyclohexanecarboxaldehyde (1.00 equiv, 100 µmol, 12.1 µL) and 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 100 µmol,

20.3 mg). The crude product, a brown oil (26.8 mg), was analysed by ^{1}H NMR spectroscopy to reveal the presence of 6-chloro-1-(cyclohexylmethyl)-2,3,4,7-tetrahydroazepine **5bd**, 3-(chloromethylene)-1-(cyclohexylmethyl)piperidine **7bd** (*E* / *Z* ≈ 56 : 44), 1-(cyclohexylmethyl)-3-(dichloromethyl)piperidine **16bd** and 6-chloro-1-(cyclohexylmethyl)-2,3-dihydroazepine **17bd** in 41 : 35 : 19 : 05 ratio approximately, as measured by integration of characteristic signals. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 2%) afforded pure **5bd** (6.6 mg, 29 µmol, 29%).

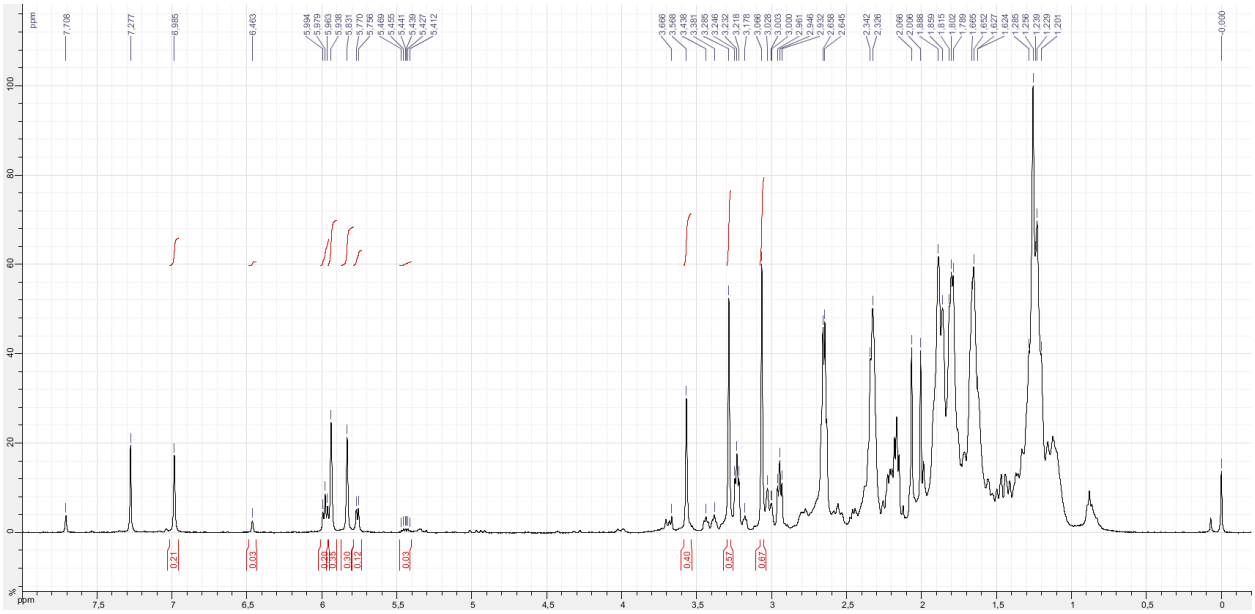


^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

6-Chloro-1-cyclohexyl-2,3,4,7-tetrahydroazepine **5be**



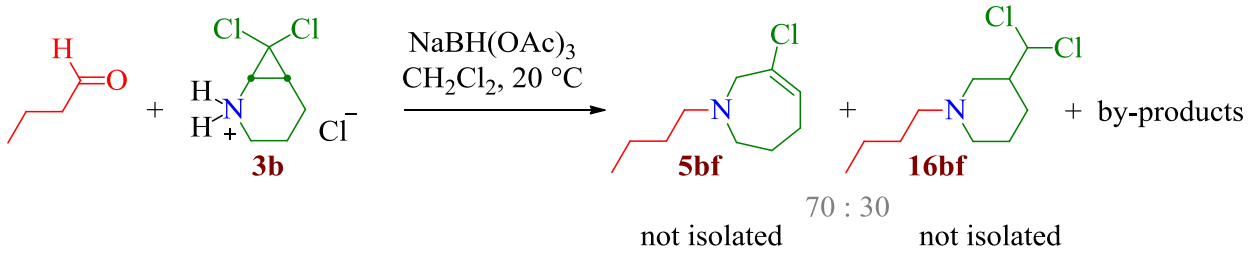
Run 1: General procedure B was applied using cyclohexanone (1.00 equiv, 100 µmol, 10.4 µL) and 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 100 µmol, 20.3 mg). The crude product, a brown oil (23.6 mg), was analysed by ^{1}H NMR spectroscopy to reveal the presence of 6-chloro-1-cyclohexyl-2,3,4,7-tetrahydroazepine **5be**, 3-(chloromethylene)-1-cyclohexyl-piperidine **7be** (*E* / *Z* ≈ 54 : 46), 1-cyclohexyl-3-(dichloromethyl)piperidine **16be** and 6-chloro-1-cyclohexyl-2,3-dihydroazepine **17be** in 20 : 65 : 12 : 03 ratio approximately, as measured by integration of characteristic signals.
Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 20%) afforded pure **5be** (4.5 mg, 21 µmol, 21%).



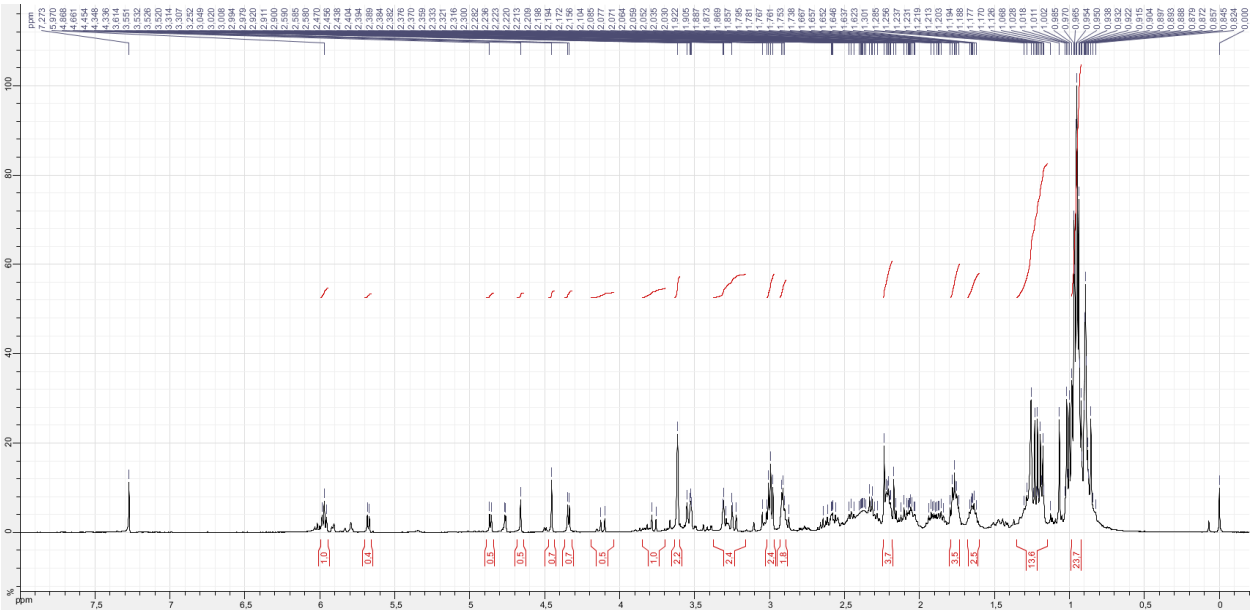
^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz).

Run 2: General procedure B was applied on five-fold scale using cyclohexanone (1.00 equiv, 500 µmol, 51.8 µL) and **3b** (1.00 equiv, 500 µmol, 101 mg). The crude product, a brown oil (109 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 10%) to afford pure **5be** (20.0 mg, 93.5 µmol, 19%).

6-Chloro-1-butyl-2,3,4,7-tetrahydroazepine **5bf**

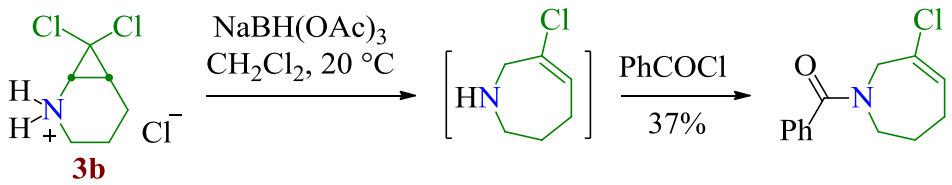


General procedure B was applied using butyraldehyde (1.00 equiv, 100 µmol, 9.0 µL) and 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 100 µmol, 20.3 mg). The crude product, a yellow oil (26.8 mg) was analysed by ^{1}H NMR, revealing the presence of 6-chloro-1-butyl-2,3,4,7-tetrahydroazepine **5bf** and 1-butyl-3-(dichloromethyl)piperidine **16bf** (ratio 70 : 30), as well as several other compounds. Purification by flash column chromatography on silica gel did not allow us to isolate a pure product.



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

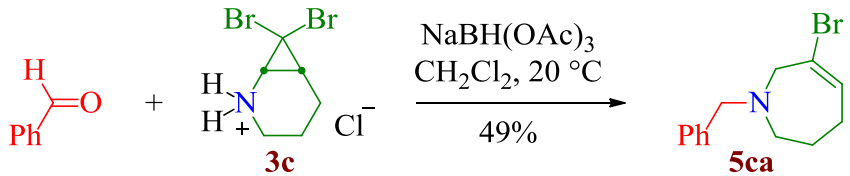
Additional result from **3b**: (6-chloro-2,3,4,7-tetrahydroazepin-1-yl)-phenyl-methanone



3b

Sodium triacetoxyborohydride (2.40 equiv, 480 µmol, 102 mg) was added at 20 °C to a solution of 7,7-dichloro-2-azoniabicyclo[4.1.0]heptane chloride **3b** (1.00 equiv, 200 µmol, 40.5 mg) in dry CH_2Cl_2 (1.0 mL). After 15 h of stirring at 20 °C, benzoyl chloride (3.00 equiv, 600 µmol, 69.6 µL) was added and the mixture was stirred at 20 °C for a further 2 h. Saturated $NaHCO_3$ aqueous solution (15 mL) was then added. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil (49.2 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 20%) to afford pure (6-chloro-2,3,4,7-tetrahydroazepin-1-yl)-phenyl-methanone (17.5 mg, 74.2 µmol, 37%).

1-Benzyl-6-bromo-2,3,4,7-tetrahydroazepine **5ca**

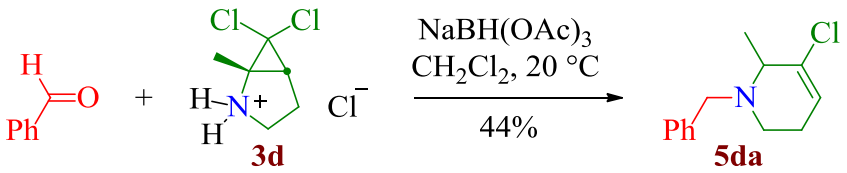


3c **5ca**

General procedure B was applied using benzaldehyde (1.00 equiv, 100 µmol, 10.2 µL) and 7,7-dibromo-2-azoniabicyclo[4.1.0]heptane chloride **3c** (1.00 equiv, 100 µmol, 29.1 mg). The crude product, a dark yellow oil (22.8 mg), was purified by flash column chromatography on silica gel

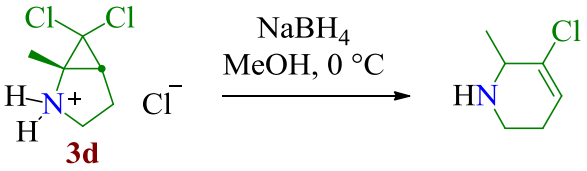
(EtOAc / petroleum ether, gradient from 0 to 5%) to afford pure 1-benzyl-6-bromo-2,3,4,7-tetrahydroazepine **5ca** (13.2 mg, 49.5 µmol, 49%).

1-Benzyl-5-chloro-6-methyl-3,6-dihydro-2*H*-pyridine **5da**



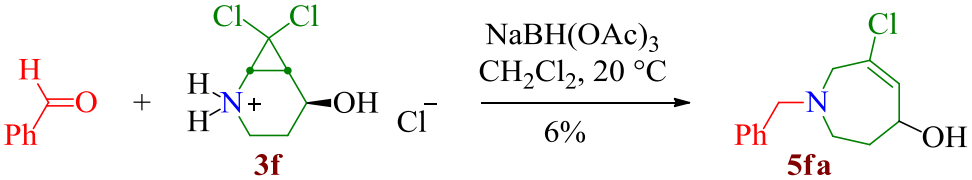
General procedure B was applied using benzaldehyde (1.00 equiv, 100 µmol, 10.2 µL) and 6,6-dichloro-1-methyl-2-azoniabicyclo[3.1.0]hexane chloride **3d** (1.00 equiv, 100 µmol, 20.3 mg). The crude product, a yellow oil (18.8 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 2%) to afford pure 1-benzyl-5-chloro-6-methyl-3,6-dihydro-2*H*-pyridine **5da** (9.8 mg, 44 µmol, 44%).

Additional result from **3d**: 5-chloro-6-methyl-1,2,3,6-tetrahydropyridine



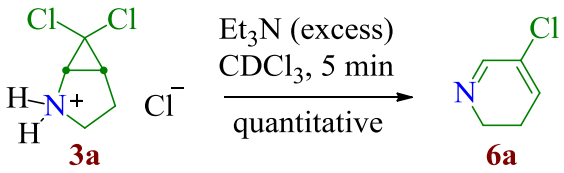
Sodium borohydride (3.00 equiv, 300 µmol, 11.3 mg) was added at 0 °C to a solution of 6,6-dichloro-1-methyl-2-azoniabicyclo[3.1.0]hexane chloride **3d** (1.00 equiv, 100 µmol, 20.3 mg) in MeOH (1.0 mL). After 4 h of stirring at 0 °C, H_2O (10 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure (50 mbar, bath 30 °C) to afford a yellow oil (30.2 mg). Analysis by ^1H NMR spectroscopy revealed the presence of 5-chloro-6-methyl-1,2,3,6-tetrahydropyridine as a major component.

1-Benzyl-6-chloro-2,3,4,7-tetrahydroazepin-4-ol **5fa**



General procedure B was applied on larger scale using benzaldehyde (1.00 equiv, 592 µmol, 60.2 µL) and (1*R**,5*R**,6*R**)-7,7-dichloro-2-azoniabicyclo[4.1.0]heptan-5-ol chloride **3f** (1.00 equiv, 592 µmol, 129 mg). The crude product, a dark brown oil (150 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 10 to 30%) to afford pure 1-benzyl-6-chloro-2,3,4,7-tetrahydroazepin-4-ol **5fa** (9.0 mg, 37.8 µmol, 6%).

5-Chloro-2,3-dihydropyridine **6a**

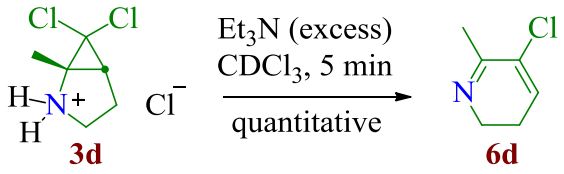


3a **6a**

An NMR sample was prepared with a few milligrams of 6,6-dichloro-2-azoniabicyclo[3.1.0]hexane chloride **3a** in $CDCl_3$ (0.50 mL). A ^1H NMR spectrum of this sample was taken and then excess amounts of triethylamine (about 9 equivalents) were introduced in the tube. After 5 minutes, a new analysis by ^1H NMR spectroscopy revealed the complete transformation of the starting material into 5-chloro-2,3-dihydropyridine **6a**.

Note: a similar experiment was performed using excess amounts of K_2CO_3 instead of triethylamine. No deprotonation of the ammonium salt was observed after 30 min at room temperature. Conversely, using NaOH, a complex mixture was observed.

5-Chloro-6-methyl-2,3-dihydropyridine **6d**

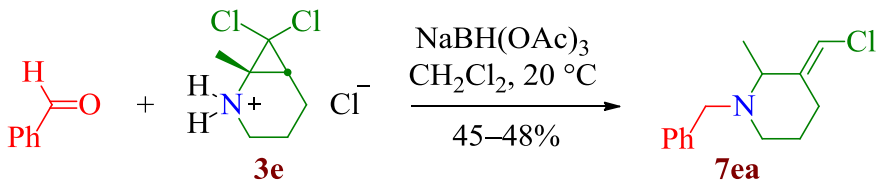


3d **6d**

An NMR sample was prepared with a few milligrams of 6,6-dichloro-1-methyl-2-azoniabicyclo[3.1.0]hexane chloride **3d** in $CDCl_3$ (0.50 mL). A ^1H NMR spectrum of this sample was taken and then excess amounts of triethylamine (about 6 equivalents) were introduced into the tube. After 5 minutes, a new analysis by ^1H NMR spectroscopy revealed the complete and clean transformation of the starting material into 5-chloro-6-methyl-2,3-dihydropyridine **6d**.

Note: a similar experiment was performed using excess amounts of K_2CO_3 instead of triethylamine. No deprotonation of the ammonium salt was observed after 4 h at room temperature. Conversely, using NaOH, a complex mixture was observed after 5 min of reaction.

(*E*)-1-Benzyl-3-(chloromethylene)-2-methyl-piperidine **7ea**

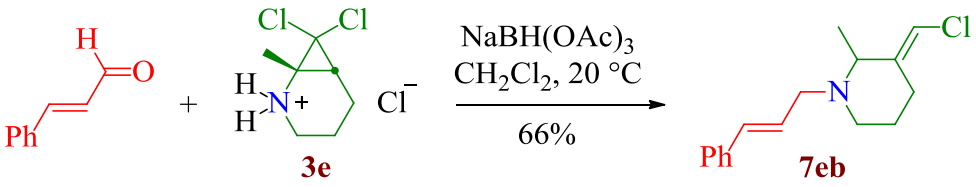


3e **7ea**

Run 1: General procedure B was applied using benzaldehyde (1.00 equiv, 100 µmol, 10.2 µL) and 7,7-dichloro-1-methyl-2-azoniabicyclo[4.1.0]heptane chloride **3e** (1.00 equiv, 100 µmol, 21.7 mg). The crude product, a dark yellow oil (27.8 mg), was purified by two flash column chromatographies on silica gel (EtOAc / petroleum ether, gradient from 0 to 5%) to afford pure (*E*)-1-benzyl-3-(chloromethylene)-2-methyl-piperidine **7ea** (11.3 mg, 47.9 µmol, 48%).

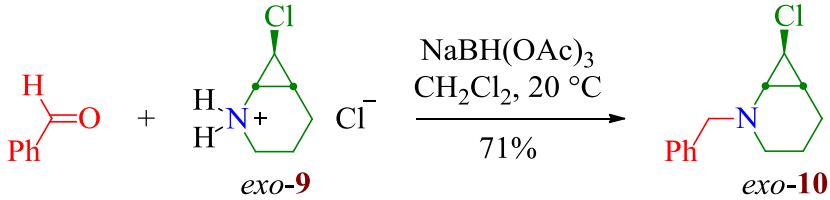
Run 2: General procedure B was applied on double scale, using benzaldehyde (1.00 equiv, 200 µmol, 20.3 µL) and **3e** (1.00 equiv, 200 µmol, 43.3 mg). The crude product, a dark yellow oil (40.8 mg), was purified by two flash column chromatographies on silica gel (EtOAc / petroleum ether, gradient from 0 to 5%) to afford pure **7ea** (21.4 mg, 90.7 µmol, 45%).

(3*E*)-3-(Chloromethylene)-1-[(*E*)-cinnamyl]-2-methyl-piperidine **7eb**

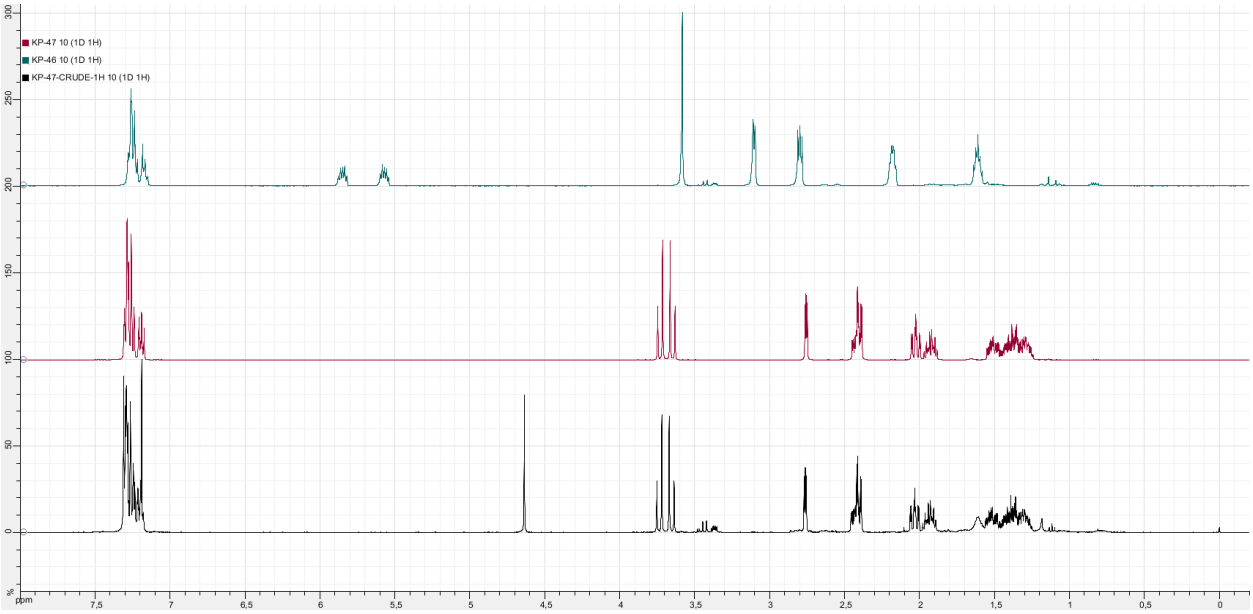


General procedure B was applied using *trans*-cinnamaldehyde (1.00 equiv, 100 µmol, 12.6 µL) and 7,7-dichloro-6-methyl-5-azoniabicyclo[4.1.0]heptane chloride **3e** (1.00 equiv, 100 µmol, 21.7 mg). The crude product, a dark yellow oil (28.6 mg), was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 20%) to afford pure (3*E*)-3-(chloromethylene)-1-[(*E*)-cinnamyl]-2-methyl-piperidine **7eb** (17.2 mg, 65.7 µmol, 66%).

(1*R**,6*S**,7*R**)-2-Benzyl-7-chloro-2-azabicyclo[4.1.0]heptane *exo*-**10**

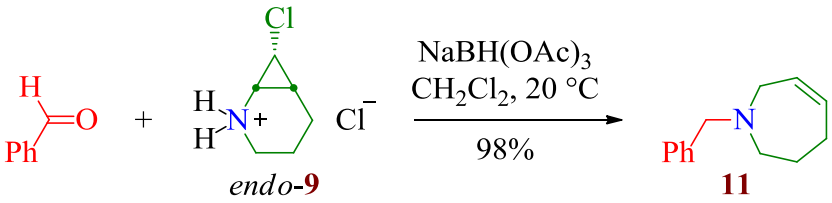


General procedure B was applied using benzaldehyde (1.00 equiv, 575 µmol, 60.0 µL) and (1*R**,6*S**,7*R**)-7-chloro-2-azoniabicyclo[4.1.0]heptane chloride *exo*-**9** (1.00 equiv, 575 µmol, 96.6 mg). The crude product was analysed by NMR spectroscopy and no trace of 1-benzyl-2,3,4,7-tetrahydroazepine **11** was observed. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 5%) afforded pure (1*R**,6*S**,7*R**)-2-benzyl-7-chloro-2-azabicyclo[4.1.0]heptane *exo*-**10** (90.0 mg, 406 µmol, 71%).



^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz), displayed in black. Spectra of pure (1*R**,6*S**,7*S**)-5-benzyl-7-chloro-5-azabicyclo[4.1.0]heptane and 1-benzyl-5-chloro-3,6-dihydro-2*H*-pyridine are also presented, in red and in green respectively, showing the absence of the latter compound in the crude product.

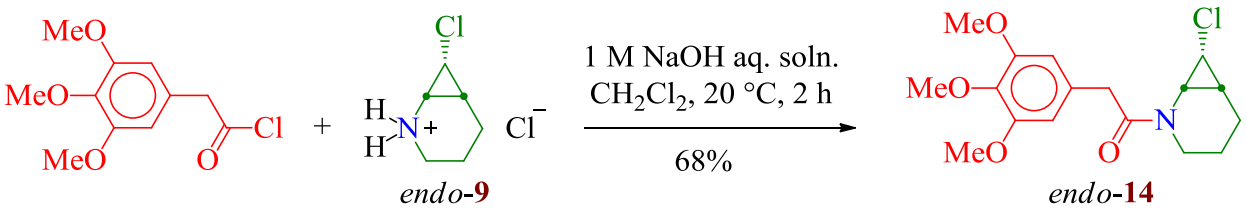
1-Benzyl-2,3,4,7-tetrahydroazepine **11**



endo-**9** **11**

General procedure B was applied using benzaldehyde (1.00 equiv, 575 µmol, 60.0 µL) and (1*R**,6*S**,7*S**)-7-chloro-2-azoniabicyclo[4.1.0]heptane chloride *endo*-**9** (1.00 equiv, 575 µmol, 96.6 mg). The crude product was purified by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 2 to 15%) to afford pure 1-benzyl-2,3,4,7-tetrahydroazepine **11** (106 mg, 566 µmol, 98%).

1-[(1*R**,6*S**,7*S**)-7-Chloro-2-azabicyclo[4.1.0]heptan-2-yl]-2-(3,4,5-trimethoxyphenyl)ethanone *endo*-**14**

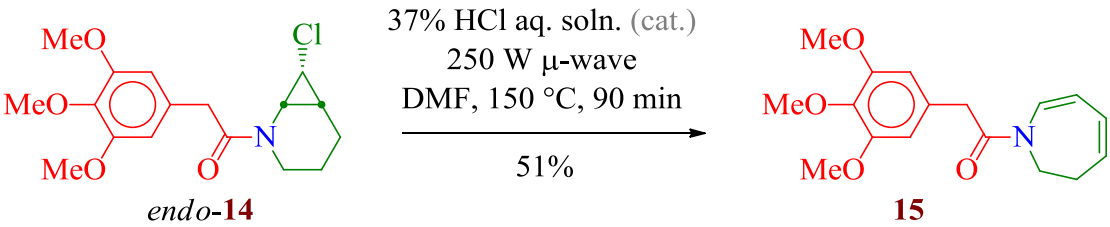


endo-**9** *endo*-**14**

1 M NaOH aqueous solution (10 mL) was added to a solution of 2-(3,4,5-trimethoxyphenyl)acetyl chloride (1.10 equiv, 274 µmol, 67.0 mg) and (1*R**,6*S**,7*S**)-7-chloro-2-azoniabicyclo[4.1.0]heptane chloride *endo*-**9** (1.00 equiv, 249 µmol, 41.6 mg) in CH_2Cl_2 (10 mL). After 2 h of stirring at 20 °C, the organic layer was separated and the aqueous phase

was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a thick pale yellow oil (74.0 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 30 to 100%) to afford pure 1-[(1*R**,6*S**,7*S**)-7-chloro-2-azabicyclo[4.1.0]heptan-2-yl]-2-(3,4,5-trimethoxyphenyl)ethanone *endo*-**14** (57.6 mg, 218 µmol, 68%).

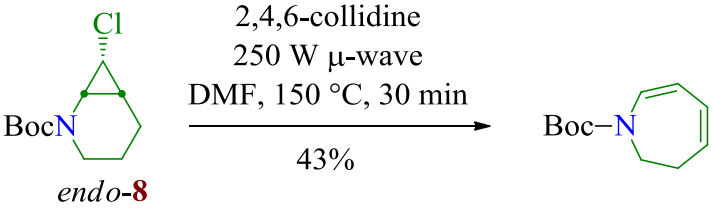
1-(2,3-Dihydroazepin-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone **15**



endo-**14** → **15**

37% HCl aqueous solution (1 drop) was added, at 20 °C, to a solution of 1-[(1*R**,6*S**,7*S**)-7-chloro-2-azabicyclo[4.1.0]heptan-2-yl]-2-(3,4,5-trimethoxyphenyl)ethanone *endo*-**14** (1.00 equiv, 64.7 µmol, 22.0 mg) in DMF (1.0 mL). The mixture was heated at 150 °C for 90 minutes with a microwave reactor (power 250 W) and controlled by TLC. After cooling, H_2O (15 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a sticky orange oil (14.0 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 5 to 50%) gave pure 1-(2,3-dihydroazepin-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone **15** (10.0 mg, 33.0 µmol, 51%).

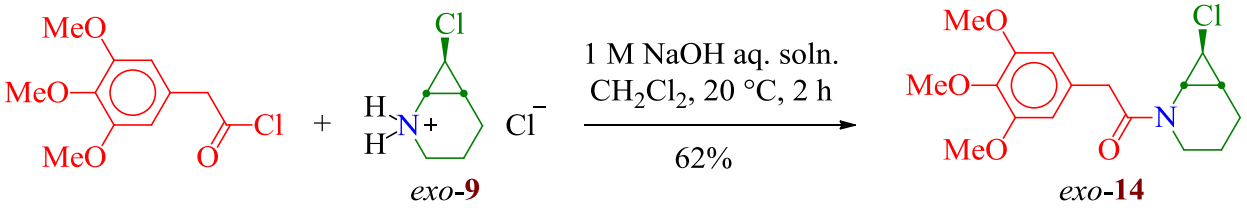
Additional result from *endo*-**8**: *tert*-butyl 2,3-dihydroazepine-1-carboxylate



endo-**8** → Boc–N

2,4,6-Collidine (1 drop) was added, at 20 °C, to a solution of *tert*-butyl (1*R**,6*S**,7*S**)-7-chloro-2-azabicyclo[4.1.0]heptane-2-carboxylate *endo*-**8** (1.00 equiv, 58.6 µmol, 13.6 mg) in DMF (1.0 mL). The mixture was heated at 150 °C for 30 minutes with a microwave reactor (power 250 W). After cooling, H_2O (15 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a sticky orange oil (4.9 mg). Analysis by ^1H NMR spectroscopy revealed that this crude product contained fairly pure *tert*-butyl 2,3-dihydroazepine-1-carboxylate (4.9 mg, if pure: 25.0 µmol, 43%). A slightly purer sample (about 1 mg) was obtained by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 0 to 2%).

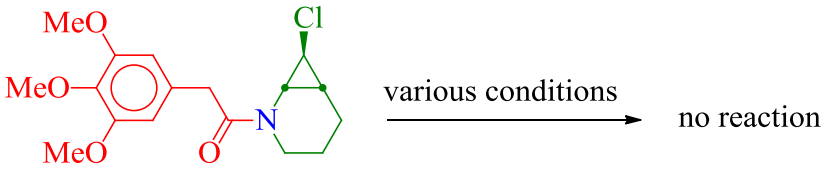
1-[(1*R**,6*S**,7*R**)-7-Chloro-2-azabicyclo[4.1.0]heptan-2-yl]-2-(3,4,5-trimethoxyphenyl)ethanone *exo*-**14**



exo-**9** *exo*-**14**

1 M NaOH aqueous solution (10 mL) was added to a solution of 2-(3,4,5-trimethoxyphenyl)acetyl chloride (1.00 equiv, 163 µmol, 39.8 mg) and (1*R**,6*S**,7*R**)-7-chloro-2-azoniabicyclo[4.1.0]heptane chloride *exo*-**9** (1.00 equiv, 163 µmol, 27.2 mg) in CH_2Cl_2 (10 mL). After 2 h of stirring at 20 °C, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange mixture of solid and oil (43.8 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether 50%) to afford pure 1-[(1*R**,6*S**,7*R**)-7-chloro-2-azabicyclo[4.1.0]heptan-2-yl]-2-(3,4,5-trimethoxyphenyl)ethanone *exo*-**14** (34.5 mg, 102 µmol, 62%).

Attempted transformation of *exo*-**14**



exo-**14**

The following reaction conditions were applied on 50 to 100 µmol scale, leaving the starting material unchanged:

- *p*TSA (0.05 equiv), 250 W microwave irradiation, PhCl, 140 °C, 15 min.
- TfOH (1 drop), PhCl, 20 °C, 15 h.
- TfOH (1 drop), 250 W microwave irradiation, PhCl, 140 °C, 60 min.
- TfOH (1 drop), 300 W microwave irradiation, PhCl, 160 °C, 30 min.
- $AgBF_4$ (1.5 equiv), CH_2Cl_2, 20 °C, 18 h.
- $AgBF_4$ (1.5 equiv), 250 W microwave irradiation, MeCN, 100 °C, 60 min.
