# Investigation of the Lewis acid mediated stereoselective cyclization of cationic aminyl radicals leading to substituted pyrrolidines

**Åsa Sjöholm, Martin Hemmerling, Nicolas Pradeille and Peter Somfai***

*Organic Chemistry, Department of Chemistry, Royal Institute of Technology, SE-100 44, Stockholm, Sweden*

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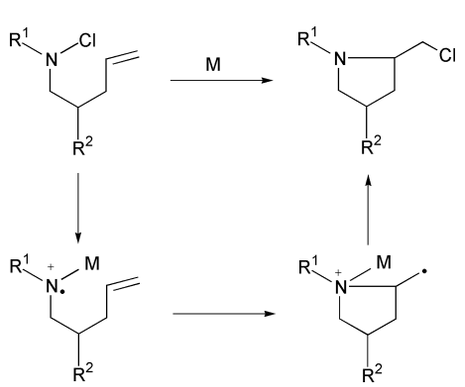
Stereoselective Lewis acid mediated radical cyclizations of variously substituted *N*-chloropentenylamines afforded the corresponding pyrrolidines with good to excellent diastereoselectivities and in high yields. Several Lewis acids have been screened in an attempt to find an efficient and stereoselective protocol for the formation of pyrrolidines; no apparent correlation between the different Lewis acids and the selectivities obtained was observed.

## Introduction

Five- and six-membered nitrogen-containing heterocycles, *i.e.* pyrrolidines and piperidines, are important structural segments which are abundant in natural products as well as in drugs.[1] Since many alkaloids show interesting biological activities and have intriguing structures, there is considerable interest among organic chemists for finding efficient and stereoselective routes to these compounds.

Various five-membered cyclic derivatives have previously been formed by intramolecular addition of carbon centered radicals to olefins.[2–5] These cyclization reactions have proven useful, especially since the stereochemical outcome usually can be accurately predicted.[6] Therefore it is somewhat surprising that there have not been more attempts to explore the stereochemical aspects of the analogous cyclization of aminyl radicals.[7–15]

Aminyl radicals are less reactive than alkyl radicals, which is evident by comparing rate constants for hydrogen abstraction from tributyltin hydride,[16] $k_H(\text{alkyl}) = 3 \times 10^6$ $M^{-1}$ $s^{-1}$ and $k_H(\text{aminyl}) = 8 \times 10^4$ $M^{-1}$ $s^{-1}$. The addition of the weakly nucleophilic nitrogen centered radical to the double bond is slow and the equilibrium between the unsubstituted alkenylaminyl radical and the corresponding cyclized product favors the ring opened aminyl radical.[17] However, by protonation or complexation of the aminyl radical with a Lewis acid a cationic electrophilic radical is formed which readily adds to the olefin (Scheme 1).[18] Previously reported reaction conditions for generation of cationic aminyl radicals from *N*-chloroamines involve $H_2SO_4$, CuCl–$CuCl_2$, $FeCl_2$–$FeCl_3$ or $TiCl_3$–$TiCl_4$ in a water–acetic acid mixture (Stella conditions) or in a THF–water–acetic acid mixture.[19] It is believed that the cyclization mechanism differs depending on the reaction conditions; when applying CuCl–$CuCl_2$ or $FeCl_2$–$FeCl_3$ the reaction proceeds *via* a redox chain mechanism while $TiCl_3$–$TiCl_4$ most probably induces a radical chain mechanism.[20]




**Scheme 1** Mechanism of cyclization; M = $H^+$ or metal.

With this in mind, we were interested in exploring the potential for forming diastereomerically enriched pyrrolidines through intramolecular cyclizations of cationic aminyl radicals. The first objective was to optimize the reaction conditions, the aim being to simplify the procedure as well as to improve the results. Secondly, a thorough investigation into the influence of various Lewis acids on the reaction outcome was planned.

## Results and discussion

### Optimization of reaction conditions

The first and perhaps obvious step was to develop a more convenient procedure by moving from the previously used aqueous system to an organic one. It was anticipated that this would allow for lower reaction temperatures with resulting higher selectivities and also improved yields. As a start, when using CuCl–$CuCl_2$, $FeCl_2$–$FeCl_3$ in a mixture of THF–$H_2O$–AcOH (1 : 2 : 2) at −20 °C, good to excellent yields and moderate to good selectivities were obtained when cyclizing compound **1a** (Table 1, entries 1 and 2). Since these redox couples cannot be used in non-aqueous media, due to their low solubility, a $TiCl_3$–$TiCl_4$ system was explored and found to promote the cyclization, although in lower yields (entry 3). However, both yields and selectivities were increased when changing the solvent to $CH_2Cl_2$, with the best results obtained at −78 °C (compare entry 3 with 4 and 5). With these results in hand we decided to perform the forthcoming investigations with $TiCl_3$ as radical initiator (*vide infra*).

### Terminal olefins

The *N*-chloro-*N*-alkenylamines **1a–e** have been prepared by standard procedures (*vide infra*) and then subjected to a Lewis acid and $TiCl_3$ in $CH_2Cl_2$ at −78 °C to give the corresponding pyrrolidines. The results are summarized in Table 2.

To define the influence of the Lewis acid on the reaction outcome, several acids have been screened in the cyclization of compound **1a** into **2a** and **3a** (Table 2, entries 1–9). A substantial increase in yield was achieved when substituting $TiCl_4$ for $AlMe_3$, $BF_3{\cdot}Et_2O$, Ti(O*i*-Pr)$Cl_3$ or $Cu(OTf)_2$ (compare entry 1 with 2, 3, 5 and 7). The selectivities obtained when applying these Lewis acids were in a narrow range, with a slightly better result for $BF_3{\cdot}Et_2O$. Also $Sn(OTf)_2$ gave excellent selectivity but

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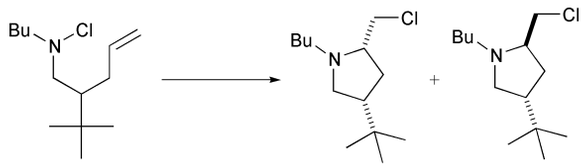
**Table 1** Cyclization of *N*-chloro-*N*-alkenylamine **1a** under different reaction conditions

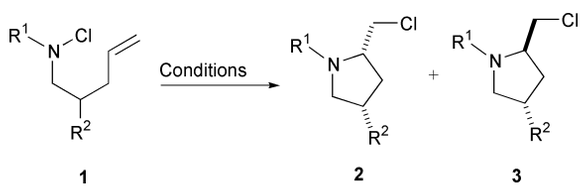


**1a** **2a** **3a**

| Entry | Metal | Solvent | Solvent ratio | Temperature/°C | Yield[a] (%) | Ratio[b] **2a** : **3a** |
|---|---|---|---|---|---|---|
| 1 | $CuCl–CuCl_2$ | $THF–H_2O–HOAc$ | 1 : 2 : 2 | −20 | 93 | 87 : 13 |
| 2 | $FeCl_2–FeCl_3$ | $THF–H_2O–HOAc$ | 1 : 2 : 2 | −20 | 83 | 78 : 22 |
| 3 | $TiCl_3–TiCl_4$ | $H_2O–HOAc$ | 1 : 1 | −20 | 22 | 83 : 17 |
| 4 | $TiCl_3–TiCl_4$ | $CH_2Cl_2$ | — | −30 | 59 | 88 : 12 |
| 5 | $TiCl_3–TiCl_4$ | $CH_2Cl_2$ | — | −78 | 62 | 90 : 10 |

[a] Isolated yields. [b] Ratios determined by $^1$H NMR.

**Table 2** Cyclization of *N*-chloro-*N*-alkenylamines **1** into pyrrolidines **2** and **3**




**1** **2** **3**

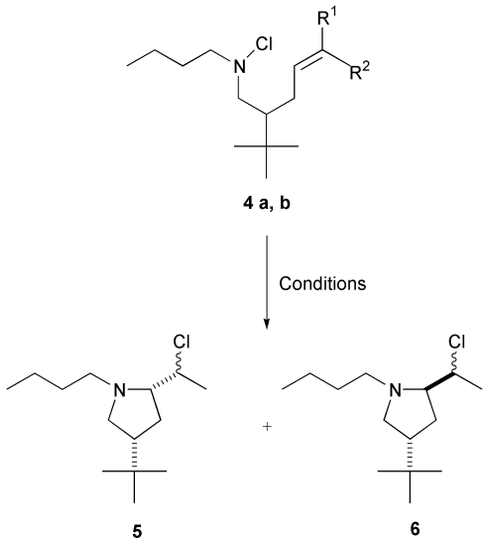
| Entry | Substrate | $R^1$ | $R^2$ | Conditions[a] | Yield[b] (%) | Ratio[c] **2** : **3** |
|---|---|---|---|---|---|---|
| 1 | **1a** | Bu | *t*-Bu | $TiCl_3–TiCl_4$ | 62 | 90 : 10 |
| 2 | **1a** | Bu | *t*-Bu | $TiCl_3–Ti(Oi\text{-}Pr)Cl_3$ | 94 | 90 : 10 |
| 3 | **1a** | Bu | *t*-Bu | $TiCl_3–BF_3{\cdot}Et_2O$ | 95 | 93 : 7 |
| 4 | **1a** | Bu | *t*-Bu | $TiCl_3–Sn(OTf)_2$ | 38 | 93 : 7 |
| 5 | **1a** | Bu | *t*-Bu | $TiCl_3–Cu(OTf)_2$ | 90 | 91 : 9 |
| 6 | **1a** | Bu | *t*-Bu | $TiCl_3–Zn(OTf)_2$ | 50 | 89 : 11 |
| 7 | **1a** | Bu | *t*-Bu | $TiCl_3–AlMe_3$ | 100 | 90 : 10 |
| 8 | **1a** | Bu | *t*-Bu | $TiCl_3$–MAD | —[d] | — |
| 9 | **1a** | Bu | *t*-Bu | $TiCl_3–MgBr_2{\cdot}Et_2O$ | 93[e] | 88 : 12 |
| 10 | **1b** | Bn | *t*-Bu | $TiCl_3–BF_3{\cdot}Et_2O$ | 97 | 80 : 20 |
| 11 | **1c** | *p*-MeOBn | *t*-Bu | $TiCl_3–BF_3{\cdot}Et_2O$ | 100 | 86 : 14 |
| 12 | **1d** | $C_2H_4OMe$ | *t*-Bu | $TiCl_3–Ti(Oi\text{-}Pr)Cl_3$ | 93 | 87 : 13 |
| 13 | **1e** | Bu | Me | $TiCl_3–BF_3{\cdot}Et_2O$ | 100[f] | 80 : 20 |
| 14 | **1e** | Bu | Me | $TiCl_3–Cu(OTf)_2$ | 20[f] | 83 : 17 |

[a] In deoxygenated $CH_2Cl_2$, $TiCl_3$ (10 mol%), −78 °C, time: 20 min–9 h. [b] Isolated yields. [c] Ratios determined by $^1$H NMR. [d] Starting material was recovered. [e] Obtained as a 1 : 1 mixture of chloro- and bromopyrrolidines. [f] Conversion, based on $^1$H NMR.

inferior yield (entry 4). Despite the large excess of Lewis acid and prolonged reaction time applied to this case, a large amount of unreacted starting material remained. When using MAD (methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) no reaction was observed, most probably due to the extreme steric bulk of the reagent, which might prohibit the complexation between the Lewis acid and the aminyl radical (entry 8). The product obtained when using $MgBr_2{\cdot}Et_2O$ was a 1 : 1 mixture of chlorinated and brominated pyrrolidines although the selectivity remained good (entry 9). The effect of varying the $R^1$-substituent in **1** was then probed using the same general reaction conditions. The *N*-butyl group was substituted for a benzyl (**1b**),[21] *p*-methoxybenzyl (**1c**), and α-methoxyethyl group (**1d**), but resulted only in lower selectivities (compare entries 10–12 with 2–3). By introducing the *N*-methoxyethyl substituent an additional site of complexation to the Lewis acid was made available, but this did not seem to be beneficial (compare entry 12 and 2). When changing the $R^2$-group from a *tert*-butyl group (**1a**) to a methyl group (**1e**), the selectivities dropped markedly when using both $BF_3{\cdot}Et_2O$ and $Cu(OTf)_2$ (entry 13 and 14). The selectivities obtained are similar, but only the former gave complete conversion. As can be seen, there is no apparent correlation between the diastereoselectivities in Table 2 and the properties of the different Lewis acids applied in the reactions. What can be noted is that there seems to be a limit to how sterically demanding the Lewis acid can be without interfering with product formation.

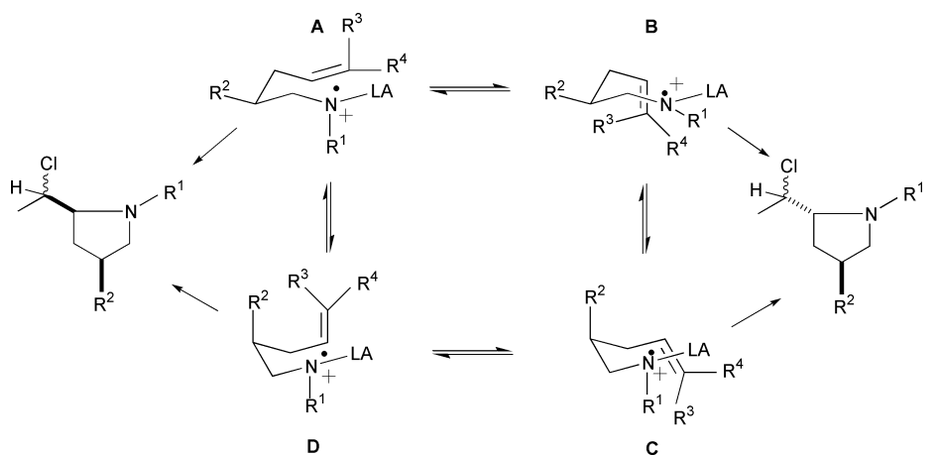
It has previously been shown that for hex-1-enyl alkyl radicals the 5-*exo* cyclizations are generally favored over the 6-*endo*, primarily for stereoelectronic reasons.[2] In 5-*exo* cyclizations of such compounds the transition state structures resemble the chair and boat conformers of cyclohexane and the diastereoselectivity is then dependent on the substitution pattern. Beckwith and Houk have shown that it is possible to predict the stereochemical outcome of the cyclization in these systems by analyzing the possible transition structures.[22,23] Similar arguments can be applied to rationalize the outcome of the analogous cyclization of cationic aminyl radicals. For a 3-substituted cationic *N*-pentenylaminyl radical there are four possible transition structures of which two are chair-like and two boat-like (Scheme 2, **A**, **C** and **B**, **D** respectively). Of these, the most favored conformation is structure **A**, which has a chair-like conformation with the 3-substituent in an equatorial position, although previous calculations for C-centered radicals ($R^2 = R^3 = R^4 = H$) have shown that the energy difference between structures **A** and **B** is only about 1 kcal $mol^{-1}$.[23] Depending on the size of $R^2$ it is also possible that structure **C** will be of importance, thus resulting in lower selectivity.

**Table 3** Cyclization of *cis*- and *trans*-substituted *N*-chloro-*N*-alkenylamines **4a** and **4b** into pyrrolidines **5** and **6**




| Entry | Substrate | $R^1$ | $R^2$ | Conditions[a] | Yield[b] (%) | Ratio[c] **5** : **6** |
|---|---|---|---|---|---|---|
| 1 | **4a** | H | Me | $BF_3{\cdot}Et_2O$ | 100 | 69 : 31 |
| 2 | **4a** | H | Me | $AlMe_3$ | 92 | 73 : 27 |
| 3 | **4b** | Me | H | $BF_3{\cdot}Et_2O$ | 93 | 66 : 34 |

[a] In deoxygenated $CH_2Cl_2$, $TiCl_3$ (10 mol%), −78 °C, 30 min. [b] Isolated yields. [c] Ratios determined by GC-MS.




**Scheme 2**

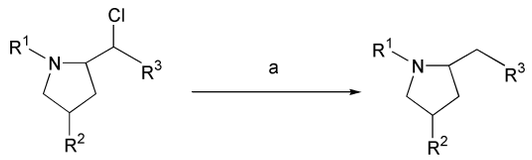
The *tert*-butyl group functions as a conformational lock by occupying the equatorial position resulting in fewer probable transition structures (**A** and **B**). The selectivities obtained for substrates **1a–1d** should then reflect the difference between the chair-like and the boat-like transition structures having the $R^2$ group in an equatorial position. By substituting the *tert*-butyl group for a methyl group, lower *cis*:*trans* selectivities could be expected due to product formation also from structure **C**. As can be seen in entries 13 and 14, this seems to be the case. The substituents, as well as the substitution pattern chosen for this study were based on the Beckwith–Houk stereochemical model, which also seems to be valid for cyclization of cationic nitrogen centered pentenyl radicals.

### Disubstituted double bonds

Next, the effect of varying the substitution pattern on the olefin moiety was probed by cyclizing pure *cis* and *trans* derivatives **4a** and **4b** (Table 3). The results were somewhat surprising. The selectivities obtained for *cis*-**4a** were in the range of 69 : 31 (Table 3, entry 1) which should be compared with 93 : 7 for unsubstituted **1a** (Table 2, entry 3). Changing the Lewis acid to $AlMe_3$ gave slightly higher selectivity (entry 2). *trans*-**4b** cyclized with similar selectivity to *cis*-**4b** (entry 3). In the cyclizations of C-centered radicals that form five membered rings, as well as for non-radical cyclizations, the selectivities for a *Z*-substituted olefin are higher than for the corresponding terminal olefin which is rationalized by A-strain.[24,25] However, the same trend was not observed in the present study. Also, a more pronounced difference between the *Z*- and *E*-substituted olefins was expected.

### Determination of the diastereomeric ratios

In order to determine the *cis* : *trans* ratio of pyrrolidines **2** and **3** $^1$H NMR spectroscopy was used. However, this technique was not applicable to pyrrolidines **5** and **6** due to the formation of a third stereocenter, most probably without any stereoselection. Therefore, reduction of the chloropyrrolidines **2a**, **3a**, **5** and **6** using $Bu_3SnH$ and *hν*[26,27] in the presence of $BF_3{\cdot}Et_2O$ was performed and the *cis* : *trans* ratios of the derivatives **7–10** thus obtained were determined by GC-MS (Scheme 3). There is no reason to believe that any epimerization occurs during the reduction, since 1.5 equivalents of Lewis acid were used to complex the nitrogen.




**2a, 3a, 5, 6** **7, 8, 9, 10**

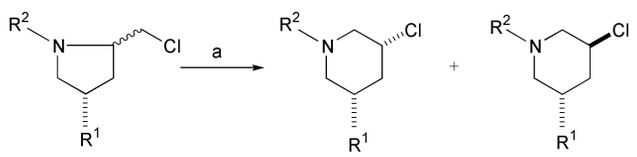
**2a, 3a, 7, 8:** $R^1$= n-Bu, $R^2$= *t*-Bu, $R^3$= H

**5, 6, 9, 10:** $R^1$= n-Bu, $R^2$= *t*-Bu, $R^3$= Me

**Scheme 3** *Reagents and conditions*: (a) $Bu_3SnH$, *hv*, $BF_3{\cdot}Et_2O$, rt, 100% conversion.

### Rearrangement of pyrrolidines into piperidines

Pyrrolidines **2a–e** and **3a–e** are not appreciably stable, and rearrange readily when dissolved in chlorinated solvents to form the thermodynamically more stable piperidines **11a–e** and **12a–e** (Scheme 4).[28] It is well known that this rearrangement




**2, 3a, d, e** **11a, d, e** **12a, d, e**

**a**:$R^1$= *t*-Bu, $R^2$=n-Bu
**d**:$R^1$= *t*-Bu, $R^2$=$C_2H_4OCH_3$
**e**:$R^1$=Me, $R^2$=n-Bu

**Scheme 4** *Reagents and conditions*: (a) $CDCl_3$, room temperature, 100% ($t_{½}$ ~ 1 h).

proceeds through an aziridinium ion intermediate and is believed to be stereospecific.[29] We have been able to show that this is indeed the case, by comparing the ratio of piperidines **11a** and **12a** (determined by $^1$H NMR spectroscopy) with that of pyrrolidines **7** and **8** (determined by GC-MS). The selectivity obtained after reduction of **2a** and **3a** to **7** and **8** is, within experimental error, in good agreement with that obtained after rearrangement of **2a** and **3a** into piperidines **11a** and **12a**.[30]

The relative stereochemistry of these compounds was verified by NOESY, COSY and $^1$H NMR. There is a strong NOE between 3-H and 5-H for the major isomer that is only possible for the *cis*-compound. Also coupling constants as well as relative shifts for the axial and equatorial protons are consistent with the suggested structures.[31]

### Preparation of *N*-chloro-*N*-alkenylamines 1a–e and 4a,b

The *N*-chloro-*N*-alkenylamines have been synthesized in good to excellent yields by standard procedures from commercially available starting materials (**13** and **15**) (Schemes 5 and 6).

## Conclusion

It has been shown that it is possible to form substituted pyrrolidines in varying diastereomeric excesses and excellent yields by Lewis acid mediated intramolecular radical cyclization of cationic aminyl radicals. It has also been shown that the Beckwith–Houk stereochemical model developed for carbon centered radicals is applicable to the analogous cationic nitrogen centered radical system and therefore the stereochemical outcome of the formed pyrrolidines can be predicted. However, no correlation between the applied Lewis acids and the obtained selectivities has been found.

## Experimental

### General reaction conditions

$^1$H and $^{13}$C NMR spectra were recorded on Varian Mercury 300/400 MHz or a Bruker Avance 400 MHz spectrometers. $CDCl_3$ or $C_6D_6$ were used as solvents with their respective residual peak ($\delta_H$ 7.26 ($CDCl_3$) and $\delta_H$ 7.16 ($C_6D_6$)) as internal standard. The coupling constants, *J*, are given in Hz. High resolution mass spectra were recorded on a JEOL SX 102 spectrometer. Analytical TLC was performed on Merck silica gel 60 $F_{254}$ plates, which were visualized with iodine in methanol, phosphomolybdic acid (5% in ethanol) or Dragendorffs reagent. Flash chromatography was performed on SDS silicagel 43–63 μm. Air and moisture sensitive reactions were performed with oven- or flame-dried equipment under an atmospheric pressure of nitrogen. The solvents were dried by distillation immediately before use: $CH_2Cl_2$ from $CaH_2$, THF and diethyl ether from sodium–benzophenone. Compounds **14**,[32] **16**,[33,34] **18**,[33,34] **19**,[33] **21**,[35] **24**[36] and *(E)*-crotyl bromide[37] were prepared according to previously published procedures.

### Ethyl (*E*)-2-*tert*-butylhex-4-enoate (17)

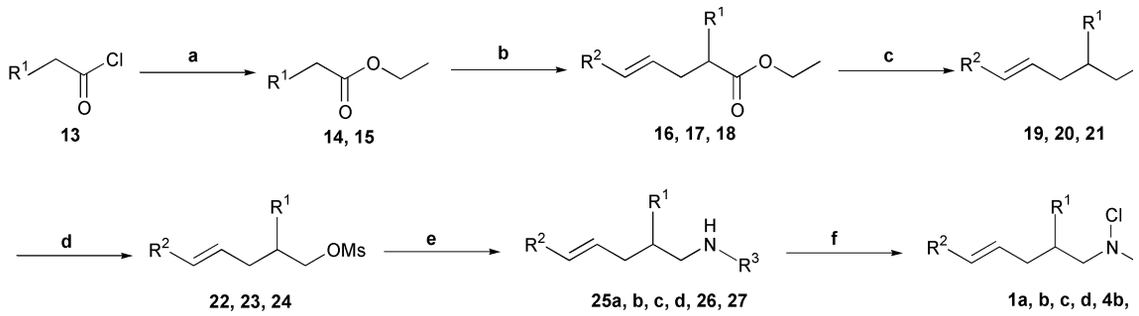
Ester **14** (1.00 g, 6.94 mmol) was dissolved in THF (4.5 ml ) and cooled to 0 °C. After 15 min KHMDS (5.65 ml, 9.03 mmol) was added. After stirring for 30 min the reaction was cooled to −78 °C, and (*E*)-crotyl bromide (1.23 g, 9.03 mmol) in THF (3 ml) was added *via* cannula to the reaction mixture. The temperature was allowed to reach rt. After 16 h the reaction was quenched by addition of saturated $NH_4Cl$ (aq) and diluted with $Et_2O$. The phases were separated and the organic phase was washed with $H_2O$ and brine. The organic phase was dried ($Na_2SO_4$) and carefully evaporated. Distillation and flash chromatography (pentane–$CH_2Cl_2$ 5 : 1) gave **17** as a colourless liquid (770 mg, 56%). $\delta_H$(400 MHz; $CDCl_3$) 5.47 (1H, m, $CH_3CH$=CH), 5.32 (1H, m, $CH_3CH$=C*H*), 4.12 (2H, m, $CH_2CH_3$), 2.28 (1H, m, $CH_2CH$COO), 2.18 (2H, m, $CH_2$-CHCOO), 1.62 (3H, br d, *J* 6.0, $CH_3$CH=CH), 1.25 (3H, t, *J* 7.0, $CH_2CH_3$), 0.97 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 174.8, 128.7, 126.7, 59.6, 56.6, 32.7, 30.9, 27.8, 17.9, 14.4; $\nu_{max}$(film)/$cm^{-1}$ 2957, 2924, 2855, 1733, 1457, 1369, 1212, 1149, 965; *m*/*z* (CI+) 199.1697 (calculated for $C_{12}H_{22}O_2$: 199.1699).

### (*E*)-2-*tert*-Butylhex-4-en-1-ol (20)

Ester **17** (1.0 g, 5.05 mmol) dissolved in $Et_2O$ (8 ml) was added to a slurry of $LiAlH_4$ (0.24 g, 6.31 mmol) in ether (8 ml) at 0 °C. The reaction mixture was stirred for 18 h during which it reached rt. After cooling to 0 °C, the reaction was quenched by slow addition of MeOH and diluted with ether. The mixture was washed with HCl (2 M, 15 ml) and then brine. The combined aqueous phases were extracted with EtOAc. The combined organic phases were then dried ($MgSO_4$) and evaporated to give **20** as a colorless oil (0.63 g, 80%). No further purification was necessary. $\delta_H$(400 MHz; $CDCl_3$) 5.53 (2H, m, $CH_3CH$=C*H*), 3.76 (1H, m, $CH_2OH$), 3.62 (1H, m, $CH_2OH$), 2.28 (1H, m, CH=CHC$H_2$CH), 1.94 (1H, m, CH=CHC$H_2$CH), 1.67 (3H, m, $CH_3CH$=CH), 1.47 (1H, s, O*H*), 1.29 (1H, m, C*H*), 0.93 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 132.0, 126.0, 63.7, 50.8, 32.5, 31.6, 29.7, 28.2, 17.9; $\nu_{max}$(film)/$cm^{-1}$ 3353, 2961, 2871, 1476, 1439, 1366, 1035, 967; *m*/*z* (EI+) 156.1501 (calculated for $C_{10}H_{20}O$: 156.1514).

### General procedure for preparation of methanesulfonic esters 22, 23 and 32

**2-*tert*-Butylpent-4-enyl methanesulfonate (22).** Methanesulfonate **22** was prepared from alcohol **19** according to a previously published procedure.[36] After flash chromatography (heptane–$CH_2Cl_2$ 1 : 8) **22** was obtained as a colorless oil (4.92 g, 91%). $\delta_H$(400 MHz; $CDCl_3$) 5.82 (1H, m, $CH_2$=C*H*), 5.10

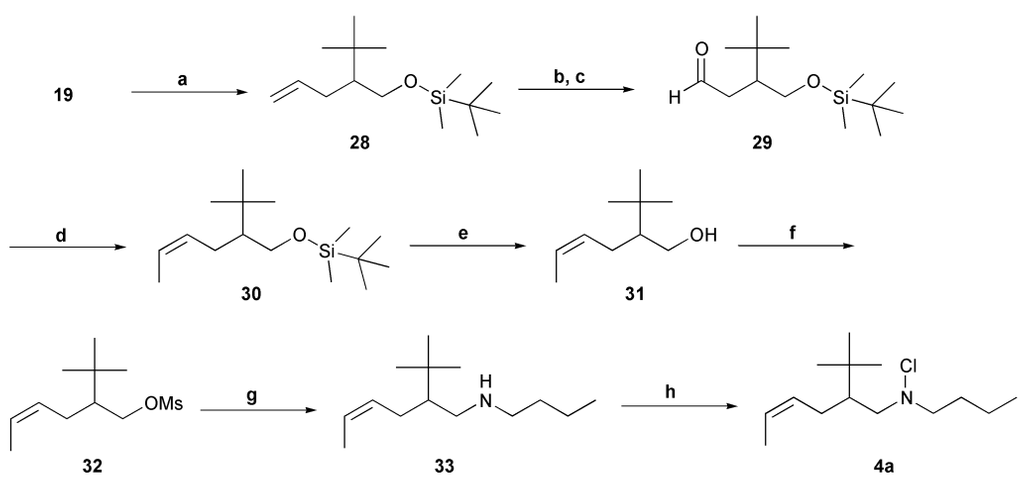



**1a, b, c, d, 13, 14, 16, 19, 22, 25:** $R^1$=*t*-Bu, $R^2$=H; **a:** $R^3$=n-Bu, **b:** $R^3$=Bn, **c:** $R^3$=p-MeOBn, **d:** $R^3$=$MeOC_2H_4$

**4b, 17, 20, 23, 26:** $R^1$=*t*-Bu, $R^2$=Me, $R^3$=n-Bu

**1e, 15, 18, 21, 24, 27:** $R^1$=Me, $R^2$=H, $R^3$=n-Bu

**Scheme 5** *Reagents and conditions*: (a) EtOH, TEA, $CH_2Cl_2$, 95%; (b) **16**, **18**: LDA, allyl bromide, DMPU, THF, 82%; **17**: KHMDS, (*E*)-crotyl bromide, THF, 56%; (c) $LiAlH_4$, $Et_2O$, 70–90%; (d) MsCl, DIPEA, $CH_2Cl_2$, 83–98%; (e) **25a**: *n*-butylamine, 92%; **25b**: benzylamine, 96%; **25c**: *p*-methoxybenzylamine, 83%; **25d**: methoxyethylamine, 81%; (f) NCS, $CH_2Cl_2$, 80–98%.




**Scheme 6** *Reagents and conditions*: (a) TBDMSCl, pyridine, TEA, $CH_2Cl_2$, 99%; (b) $OsO_4$, NMO, *t*-BuOH, THF, $H_2O$; (c) $NaIO_4$, $NaHCO_3$, THF, $H_2O$, 85%; (d) (ethyl)triphenylphosphonium bromide, KHMDS, THF, 80%; (e) TBAF, THF, 86%; (f) MsCl, TEA, $CH_2Cl_2$, 88%; (g) butylamine, 98%; (h) NCS, $CH_2Cl_2$, 82%.

(2H, m, C*H*$_2$=CH), 4.27 (2H, m, C*H*$_2$OMs), 2.99 (3H, s, $SO_2$Me), 2.35 (1H, m, $CH_2$=CHC*H*$_2$), 2.06 (1H, m, $CH_2$=CHC*H*$_2$), 1.54 (1H, m, C*H*$CH_2$OMs), 0.99 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 137.3, 116.8, 69.7, 47.4, 37.2, 32.9, 31.6, 28.1; $\nu_{max}$(film)/cm$^{-1}$ 2965, 2885, 2110, 1680, 1610; *m*/*z* (CI+) 221.1241 (calculated for $C_{10}H_{20}O_3S$ + $H^+$: 221.1141).

**(*E*)-2-*tert*-Butylhex-4-enyl methanesulfonate (23).** Compound **23** was prepared as described above for **22** and obtained as a colorless oil (900 mg, 83%). $\delta_H$(400 MHz; $CDCl_3$) 5.50 (1H, m, $CH_3$C*H*=CH), 5.41 (1H, m, $CH_3$CH=C*H*), 4.26 (2H, m, C*H*$_2$OSO$_2$CH$_3$), 2.99 (3H, s, $SO_2CH_3$), 2.26 (1H, br d, *J* 15.0, CH=CHC*H*$_2$), 1.97 (1H, m, CH=CHC*H*$_2$), 1.67 (3H, br d, *J* 6.3, C*H*$_3$CH=CH), 1.46 (1H, m, C*H*$CH_2$OMs), 0.97 (9H, s, *t-Bu*); $\delta_C$(100 MHz; $CDCl_3$) 130.0, 127.0, 69.8, 47.9, 37.2, 32.9, 30.2, 28.2, 18.1; $\nu_{max}$(film)/cm$^{-1}$ 3023, 2963, 2872, 1474, 1357, 1176, 975, 937, 834; *m*/*z* (FAB+) 235.1366 (calculated for $C_{11}H_{22}O_3S$ + $H^+$: 235.1369).

**(*Z*)-2-*tert*-Butylhex-4-enyl methanesulfonate (32).** Compound **32** was prepared as described above for **22** and obtained as a colorless oil (761 mg, 88%). $\delta_H$(400 MHz; $CDCl_3$) 5.55 (1H, m, $CH_3$CH=C*H*), 5.41 (1H, m, $CH_3$C*H*=CH), 4.25 (2H, m, $CH_2$OMs), 2.99 (3H, s, $SO_2$Me), 2.18 (2H, m, CH=CHC*H*$_2$), 1.65 (3H, br d, *J* 6.8, C*H*$_3$CH=CH), 1.50 (1H, m, C*H*$CH_2$-OMs), 1.00 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 129.0, 125.7, 69.9, 48.2, 37.1, 33.0, 28.2, 24.3, 12.9; $\nu_{max}$(film)/cm$^{-1}$ 3018, 2963, 2871, 1474, 1367, 1175, 973, 936, 834; *m*/*z* (CI+) 235.1373 (calculated for $C_{11}H_{22}O_3S$ + $H^+$: 235.1368).

### General procedure for preparation of secondary amines 25a–d, 26, 27 and 33

***N*-Butyl(2-*tert*-butylpent-4-enyl)amine (25a).** Mesylate **22** (1.32 g, 5.98 mmol) was refluxed with butylamine (3.7 ml, 37 mmol) over night. The resulting mixture was dissolved in EtOAc and washed with brine. The combined aqueous phases were extracted once with EtOAc and the combined organic phases were dried ($Na_2SO_4$) and evaporated. The resulting oil was purified by distillation (70 °C, 10 mbar) to yield **25a** (1.09 g, 92%) as a colorless oil. $\delta_H$(400 MHz; $CDCl_3$) 5.90 (1H, dddd, *J* 17.8, 10.1, 8.4, 3.9, $CH_2$=C*H*), 5.06 (1H, br d, *J* 17.8, C*H*$_2$=CH), 4.98 (1H, dm, *J* 10.1, C*H*$_2$=CH), 2.73 (1H, dd, *J* 11.7, 3.4, CHC*H*$_2$NH), 2.48–2.62 (3H, m, NHC*H*$_2$ and C*H*$CH_2$NH), 2.42 (1H, dd, *J* 11.7, 7.5, CHC*H*$_2$NH), 2.34 (1H, dm, *J* 14.4, $CH_2$=CHC*H*$_2$), 1.94 (1H, m, $CH_2$=CHC*H*$_2$), 1.47 (2H, m, NHC*H*$_2$C*H*$_2$), 1.33 (2H, m, NHC*H*$_2$C*H*$_2$C*H*$_2$), 0.92 (9H, s, *t*-Bu), 0.91 (3H, t, *J* 7.3, $CH_2$C*H*$_3$); $\delta_C$(100 MHz; $CDCl_3$) 139.6, 115.0, 51.3, 49.9, 48.3, 34.9, 33.3, 32.2, 28.0, 20.5, 14.0; $\nu_{max}$(film)/cm$^{-1}$ 3076, 2959, 2933, 2872, 2815, 1660, 1639, 1467, 1395, 1366, 1227, 1126, 994, 909, 749; *m*/*z* (CI+) 198.2239 (calculated for $C_{13}H_{28}N$ + $H^+$: 198.2222).

***N*-Benzyl(2-*tert*-butylpent-4-enyl)amine (25b).** Compound **25b** was prepared as described above for **25a** and obtained as a

colorless oil (152 mg, 96%). $\delta_H$(300 MHz; $CDCl_3$) 5.82–5.94 (1H, m, $CH_2$=C*H*), 5.03 (1H, br d, *J* 16.9, C$H_2$=CH), 4.96 (1H, br d, *J* 9.6, C$H_2$=CH), 3.82 (1H, A-part of ABq, *J* 13.3, C$H_2$Ar), 3.66 (1H, B-part of ABq, *J* 13.3, C$H_2$Ar), 2.76 (1H, dd, *J* 11.8, 3.3, CHC$H_2$NH), 2.46 (1H, dd, *J* 11.8, 7.3, CHC$H_2$NH), 2.34 (1H, br d, *J* 14.0, $CH_2$=CHC$H_2$), 1.96 (1H, m, $CH_2$=CHC$H_2$), 1.30 (1H, m, C*H*$CH_2$NH), 0.90 (9H, s, *t*-Bu); $\delta_C$(75 MHz; $CDCl_3$) 139.2, 128.3, 128.2, 126.9, 115.3, 53.9, 50.3, 48.2, 34.6, 33.4, 28.1, 27.8; $\nu_{max}$(film)/cm$^{-1}$ 2960, 2868, 1638, 1453, 1366, 910, 734, 698; *m*/*z* (FAB+) 232.2072 (calculated for $C_{16}H_{25}N + H^+$: 232.2065).

***N*-(2-*tert*-Butylpent-4-enyl)(4-methoxybenzyl)amine (25c).** Compound **25c** was prepared as described above for **25a** and obtained as a colorless oil (147 mg, 83%). $\delta_H$(400 MHz; $CDCl_3$) 7.27 (2H, d, *J* 8.2, Ar), 6.86 (2H, d, *J* 8.2, Ar), 5.89 (1H, m, $CH_2$=C*H*), 5.05 (1H, br d, *J* 17.0, C$H_2$=CH), 4.97 (1H, br d, *J* 9.9, C$H_2$=CH), 3.80 (3H, s, CHC$H_3$), 3.78 (1H, A-part of ABq, *J* 13.2, C$H_2$Ar), 3.69 (1H, B-part of ABq, *J* 13.2, C$H_2$Ar), 2.78 (1H, dd, *J* 12.1, 3.3, CHC$H_2$NH), 2.48 (1H, dd, *J* 12.1, 7.7, CHC$H_2$NH), 2.35 (1H, br d, *J* 14.4, $CH_2$=CHC$H_2$), 1.93–2.05 (1H, m, $CH_2$=CHC$H_2$), 1.42 (1H, m, C*H*$CH_2$NH), 0.90 (9H, s, *t*-Bu); $\delta_C$(75 MHz; $CDCl_3$) 139.3, 129.2, 115.1, 113.6, 55.3, 53.5, 50.4, 48.3, 34.7, 33.4, 28.1; $\nu_{max}$(film)/cm$^{-1}$ 3074, 2958, 2868, 2834, 1637, 1612, 1512, 1465, 1365, 1301, 1247, 1173, 1105, 1039, 910, 819; *m*/*z* (FAB+) 262.2185 (calculated for $C_{17}H_{27}NO + H^+$: 262.2171).

***N*-(2-*tert*-Butylpent-4-enyl)(2-methoxyethyl)amine (25d).** Compound **25d** was prepared as described above for **25a** and obtained as a colorless oil (792 mg, 88%). $\delta_H$(400 MHz; $CDCl_3$) 5.90 (1H, dddd, *J* 17.1, 10.1, 8.3, 6.0, $CH_2$=C*H*), 5.06 (1H, dm, *J* 17.1, C$H_2$=CH), 4.98 (1H, dm, *J* 10.1, C$H_2$=CH), 3.48 (2H, m, $CH_2O$), 3.36 (3H, s, $OCH_3$), 2.68–2.78 (3H, m, CHC$H_2$NH and NHC$H_2$), 2.45 (1H, dd, *J* 11.8, 7.5, CHC$H_2$NH), 2.32 (1H, dm, *J* 19.7, $CH_2$=CHC$H_2$), 1.95 (1H, app dtm, *J* 19.7, 8.4, $CH_2$=CHC$H_2$), 1.57 (1H, br s, N*H*), 1.32 (1H, m, C*H*$CH_2$NH), 0.92 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 139.4, 115.1, 72.0, 58.7, 51.0, 49.5, 48.4, 34.7, 33.3, 28.0; $\nu_{max}$(film)/cm$^{-1}$ 3070, 2940, 2870, 1635, 1115, 905; *m*/*z* (CI+) 200.2002 (calculated for $C_{12}H_{26}NO + H^+$: 200.2014).

**(*E*)-*N*-Butyl-(2-*tert*-butylhex-4-enyl)amine (26).** Compound **26** was prepared as described above for **25a** and obtained as a colorless oil (318 mg, 75%). $\delta_H$(400 MHz; $CDCl_3$) 5.48 (2H, m, $CH_3$C*H*=C*H*), 2.70 (1H, dd, *J* 11.7, 3.3, CHC$H_2$NH), 2.53 (2H, m, NHC$H_2$$CH_2$), 2.40 (1H, dd, *J* 11.7, 7.5, CHC$H_2$NH), 2.27 (1H, br d, *J* 14.0, CH=CHC$H_2$), 1.84 (1H, m, CH=CHC$H_2$), 1.66 (3H, br d, *J* 5.0, C$H_3$CH=CH), 1.43 (2H, m, NHC$H_2$C$H_2$), 1.33 (2H, m, C$H_2$$CH_3$), 1.25 (1H, m, C*H*$CH_2$NH), 0.90 (12H, m, *t*-Bu and $CH_2$C$H_3$); $\delta_C$(100 MHz; $CDCl_3$) 132.0, 125.0, 51.5, 50.0, 48.5, 33.6, 33.3, 32.3, 28.0, 20.6, 18.0, 14.2; $\nu_{max}$(film)/cm$^{-1}$ 2960, 2873, 2788, 1464, 1366, 968; *m*/*z* (FAB+) 212.2377 (calculated for $C_{14}H_{29}N + H^+$: 212.2379).

***N*-Butyl(2-methylpent-4-enyl)amine (27).** Compound **27** was prepared as described above for **25a** and obtained as a colorless oil (308 mg, 89%). $\delta_H$(400 MHz; $CDCl_3$) 5.80 (1H, m, $CH_2$=C*H*), 4.96–5.06 (2H, m, C$H_2$=CH), 2.52–5.62 (3H, m, CHC$H_2$NH and NHC$H_2$), 2.41 (1H, dd, *J* 7.0, CHC$H_2$NH), 2.14 (1H, m, $CH_2$=CHC$H_2$), 1.91 (1H, m, $CH_2$=CHC$H_2$), 1.73 (1H, m, C*H*$CH_2$NH), 1.58 (1H, br s, N*H*), 1.48 (2H, m, NHC$H_2$C$H_2$), 1.35 (2H, m, C$H_2$$CH_3$), 0.92 (6H, m, $CHCH_3$ and $CH_2$C$H_3$); $\delta_C$(100 MHz; $CDCl_3$) 137.1, 115.8, 56.0, 49.8, 39.5, 33.0, 32.1, 20.5, 18.0, 14.0; $\nu_{max}$(film)/cm$^{-1}$ 3280, 3076, 2958, 2929, 2873, 2812, 1657, 1641, 1556, 1462, 1377, 1128, 993, 910, 806, 735; *m*/*z* (CI+) 156.1759 (calculated for $C_{10}H_{21}N + H^+$: 156.1752).

**(*Z*)-*N*-Butyl(2-*tert*-butylhex-4-enyl)amine (33).** Compound **33** was prepared as described above for **25a** and obtained as a colorless oil (444 mg, 98%). $\delta_H$(400 MHz; $CDCl_3$) 5.49 (2H, m, $CH_3$C*H*=C*H*), 2.74 (1H, dd, *J* 11.7, 3.4, CHC$H_2$NH), 2.54 (2H, m, NHC$H_2$$CH_2$), 2.40 (1H, dd, *J* 11.7, 7.5, CHC$H_2$NH), 2.21 (1H, br d, *J* 13.0, CH=CHC$H_2$), 2.04 (1H, m, CH=CHC$H_2$), 1.65 (3H, d, *J* 5.5, C$H_3$CH=CH), 1.58 (1H, br s, NH), 1.44 (2H, m, NHC$H_2$C$H_2$), 1.31 (3H, m, C*H*$CH_2$NH and NHC$H_2$-$CH_2$C$H_2$), 0.92 (9H, s, *t*-Bu), 0.91 (3H, t, *J* 7.4, NHC$H_2$$CH_2$-$CH_2$C$H_3$); $\delta_C$(100 MHz; $CDCl_3$) 131.2, 123.8, 51.7, 50.0, 49.0, 33.3, 32.3, 28.0, 27.5, 20.5, 14.0, 12.9; $\nu_{max}$(film)/cm$^{-1}$ 3013, 2960, 2871, 1675, 1465, 1395, 1365, 1125; *m*/*z* (CI+) 212.2378 (calculated for $C_{14}H_{29}N + H^+$: 212.2378).

### General reaction conditions for preparation of *N*-chloroamines 1a–e and 4a,b

***N*-Butyl-*N*-chloro(2-*tert*-butylpent-4-enyl)amine (1a).** NCS (88 mg, 0.66 mmol) was added to a solution of **25a** (118 mg, 0.60 mmol) in $CH_2Cl_2$ (4.0 ml) at −30 °C. The mixture was stirred for 30 min before washing with brine. The organic phase was dried ($Na_2SO_4$), filtered and evaporated. After flash chromatography (pentane–EtOAc 30 : 1) **1a** was obtained as a colorless liquid (127 mg, 91%). The *N*-chloroamines are slightly unstable and were stored in benzene at −20 °C. $\delta_H$(300 MHz; $CDCl_3$) 5.91 (1H, m, $CH_2$=C*H*), 4.97 (2H, m, C$H_2$=CH), 2.98 (1H, dd, *J* 13.2, 4.0, CHC$H_2$NCl), 2.91 (2H, m, NClC$H_2$), 2.73 (1H, dd, *J* 13.2, 9.8, CHC$H_2$NCl), 2.30 (1H, m, $CH_2$=CHC$H_2$), 2.02 (1H, m, $CH_2$=CHC$H_2$), 1.60 (3H, m, NClC$H_2$C$H_2$ and C*H*$CH_2$NCl), 1.37 (2H, m, NClC$H_2$$CH_2$-C$H_2$), 0.93 (3H, t, *J* 7.3, $CH_2$C$H_3$), 0.92 (9H, s, *t*-Bu); $\delta_C$(75 MHz; $CDCl_3$) 139.2, 114.7, 65.8, 64.4, 46.2, 34.3, 33.2, 30.1, 28.2, 20.1, 14.0; *m*/*z* (CI+) 232.1828 (calculated for $C_{13}H_{26}ClN + H^+$: 232.1832).

***N*-Benzyl-*N*-chloro(2-*tert*-butylpent-4-enyl)amine (1b).** Compound **1b** was prepared as described above for **1a** and obtained as a colorless liquid (110 mg, 80%). $\delta_H$(300 MHz; $CDCl_3$) 7.29–7.35 (5H, m, Ph), 5.91 (1H, m, $CH_2$=C*H*), 4.97 (2H, m, C$H_2$=CH), 4.10 (1H, A-part of ABq, C$H_2$Ph), 4.07 (1H, B-part of ABq, C$H_2$Ph), 3.06 (1H, dd, *J* 13.18, 4.39, C$H_2$NCl), 2.84 (1H, *J* 13.18, 7.69, C$H_2$NCl), 2.32 (1H, m, $CH_2$=CHC$H_2$), 2.02 (1H, m, $CH_2$=CHC$H_2$), 1.74 (1H, m, C*H*$CH_2$NCl), 0.92 (9H, s, *t*-Bu); $\delta_C$(75 MHz; $CDCl_3$) 139.1, 137.3, 128.9, 128.2, 127.6, 114.6, 114.8, 68.6, 64.9, 46.2, 34.3, 33.3, 28.2; *m*/*z* (FAB+) 266.1671 (calculated for $C_{16}H_{24}ClN + H^+$: 266.1676).

***N*-Chloro-*N*-(2-*tert*-butylpent-4-enyl)(4-methoxybenzyl)amine (1c).** Compound **1c** was prepared as described above for **1a** and obtained as a colorless liquid (150 mg, 98%). $\delta_H$(300 MHz; $CDCl_3$) 7.26 (2H, br d, *J* 8.8, Ar), 6.88 (2H, br d, *J* 8.8, Ar), 5.90 (1H, m, $CH_2$=C*H*), 4.92–5.02 (1H, m, C$H_2$=CH), 4.04 (1H, A-part of ABq, *J* 13.4, C$H_2$Ar), 3.94 (1H, B-part of ABq, *J* 13.4, C$H_2$Ar), 3.81 (3H, s, CHC$H_3$), 3.02 (1H, dd, *J* 13.2, 3.8, CHC$H_2$NH), 2.81 (1H, dd, *J* 13.2, 7.7, CHC$H_2$NH), 2.30 (1H, m, $CH_2$=CHC$H_2$), 1.96–2.06 (1H, m, $CH_2$=CHC$H_2$), 1.73 (1H, m, C*H*$CH_2$NH), 0.91 (9H, s, *t*-Bu); $\delta_C$(75 MHz; $CDCl_3$) 159.0, 139.2, 130.2, 129.5, 114.7, 113.6, 68.1, 64.6, 55.3, 46.1, 34.3, 33.2, 28.2; *m*/*z* (FAB+) 296.1786 (calculated for $C_{17}H_{26}ClNO + H^+$: 296.1781).

***N*-Chloro-*N*-(2-*tert*-butylpent-4-enyl)(2-methoxyethyl)amine (1d).** Compound **1d** was prepared as described above for **1a** and obtained as a colorless liquid (119 mg, 84%). $\delta_H$(400 MHz; $CDCl_3$) 5.91 (1H, m, $CH_2$=C*H*), 5.01 (1H, dm, *J* 17.1, C$H_2$=CH), 4.96 (1H, dm, *J* 17.1, C$H_2$=CH), 3.65 (2H, t, *J* 5.8, $CH_2O$), 3.38 (3H, s, $OCH_3$), 3.14 (2H, m, NClC$H_2$$CH_2$), 3.05 (1H, dd, *J* 13.2, 4.1, CHC$H_2$NCl), 2.80 (1H, dd, *J* 13.2, 7.8, CHC$H_2$-NCl), 2.31 (1H, m, $CH_2$=CHC$H_2$), 2.04 (1H, m, $CH_2$=CHC$H_2$), 1.66 (1H, m, C*H*$CH_2$NCl), 0.92 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 139.1, 114.9, 70.3, 66.1, 63.8, 58.9, 46.1, 34.1, 33.1, 28.1; *m*/*z* (CI+) 234.1626 (calculated for $C_{12}H_{24}ClNO + H^+$: 234.1625).

***N*-Butyl-*N*-chloro(2-methylpent-4-enyl)amine (1e).** Compound **1e** was prepared as described above for **1a** and obtained as a colorless liquid (138 mg, 69%). $\delta_H$(400 MHz; $C_6D_6$) 5.69 (1H, m, $CH_2$=C*H*), 4.98 (2H, m, C$H_2$=CH), 2.66 (2H, dt, *J* 7.0, 1.5, NClC$H_2$CH$_2$), 2.59 (1H, dd, *J* 12.8, 6.6, CHC$H_2$NCl), 2.42 (1H, dd, *J* 12.8, 7.3, CHC$H_2$NCl), 2.12 (1H, m, $CH_2$=CHC$H_2$), 2.04 (1H, m, C*H*CH$_2$NCl), 1.80 (1H, m, $CH_2$=CHC$H_2$), 1.54 (2H, m, NClCH$_2$C$H_2$), 1.20 (2H, m, *J* 7.4, NClCH$_2$CH$_2$C$H_2$), 0.86 (3H, d, *J* 6.6, CHC$H_3$), 0.78 (3H, t, *J* 7.4, $CH_2$C$H_3$); $\delta_C$(100 MHz; $C_6D_6$) 137.2, 116.7, 70.8, 65.2, 39.6, 32.4, 30.9, 20.8, 18.1, 14.7; *m*/*z* (CI+) 190.1364 (calculated for $C_{10}H_{20}ClN + H^+$: 190.1363).

**(*E*)-*N*-Butyl-*N*-chloro(2-*tert*-butylhex-4-enyl)amine (4b).** Compound **4b** was prepared as described above for **1a** and obtained as a colorless liquid (40 mg, 34%). $\delta_H$(400 MHz; $C_6D_6$) 5.71 (1H, m, $CH_3$C*H*=CH), 5.58 (1H, m, $CH_3$CH=C*H*), 3.03 (1H, dd, *J* 13.1, 4.3, CHC$H_2$NCl), 2.88 (2H, m, NClC$H_2$CH$_2$), 2.80 (1H, m, CHC$H_2$NCl), 2.40 (1H, m, CH=CHC$H_2$CH), 2.10 (1H, m, CH=CHC$H_2$CH), 1.97 (1H, m, CH=CHCH$_2$C*H*), 1.75 (3H, br d, *J* 7.0, C$H_3$CH=CH), 1.68–1.77 (2H, m, NClCH$_2$-C$H_2$), 1.36 (2H, m, C$H_2$CH$_3$), 1.01 (9H, s, *t-Bu*), 0.98 (3H, m, CH$_2$C$H_3$); $\delta_C$(100 MHz; $C_6D_6$) 132.0, 125.4, 66.3, 64.6, 46.7, 34.5, 33.2, 30.5, 28.3, 20.3, 18.2, 14.3; *m*/*z* (FAB+) 246.2007 (calculated for $C_{14}H_{28}ClN + H^+$: 246.1989).

**(*Z*)-*N*-Butyl-*N*-chloro(2-*tert*-butylhex-4-enyl)amine (4a).** Compound **4a** was prepared as described above for **1a** and obtained as a colorless liquid (410 mg, 82%). $\delta_H$(400 MHz; $C_6D_6$) 5.68 (1H, m, $CH_3$CH=C*H*), 5.50 (1H, m, $CH_3$C*H*=CH), 2.95 (1H, dd, *J* 13.2, 4.4, CHC$H_2$NH), 2.61–2.81 (3H, m, CHC$H_2$NH and NHC$H_2$CH$_2$), 2.28 (1H, m, $CH_3$CH=CHC$H_2$), 2.12 (1H, m, $CH_3$CH=CHC$H_2$), 1.83 (1H, m, C*H*CH$_2$NH), 1.62 (5H, br d, *J* 6.8, C$H_3$CH=CH and NHCH$_2$C$H_2$), 1.27 (1H, m, NHCH$_2$CH$_2$C$H_2$), 0.91 (9H, s, *t*-Bu), 0.84 (3H, t, *J* 7.4, NHCH$_2$CH$_2$CH$_2$C$H_3$); $\delta_C$(100 MHz; $CDCl_3$) 131.4, 123.6, 66.6, 64.7, 47.1, 33.3, 30.5, 28.4, 28.3, 27.3, 20.3, 13.1; *m*/*z* (FAB+) 246.1981 (calculated for $C_{14}H_{28}ClN + H^+$: 246.1989).

***tert*-Butyl(2-*tert*-butylpent-4-enyloxy)dimethylsilane (28).** Alcohol **19** (2.56 g, 18 mmol) was dissolved in $CH_2Cl_2$ (40 ml) and cooled to 0 °C. Pyridine (2.90 ml, 36 mmol), TEA (5.00 ml, 36 mmol) and TBDMSCl (5.43 g, 36 mmol) were added. The reaction mixture was stirred for 18 h during which it reached rt. The reaction volume was reduced by evaporation and then diluted with EtOAc before washing with HCl (0.5 M, 20 ml) followed by brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography ($CH_2Cl_2$–toluene 30 : 1) gave compound **28** as a colorless oil (4.65 g, 99%). $\delta_H$(400 MHz; $CDCl_3$) 5.83 (1H, m, $CH_2$=C*H*), 5.02 (1H, app dd, *J* 2.0, 17.0, C$H_2$=CH), 4.96 (1H, app dd, *J* 2.0, 10.0, C$H_2$=CH), 3.64 (2H, d, *J* 4.0, $CH_2$OTMS), 2.15 (2H, m, $CH_2$=CHC$H_2$), 1.18 (1H, m, C*H*CH$_2$OTMS), 0.94 (9H, s, *t*-Bu), 0.89 (9H, s, *t*-Bu), 0.032 (3H, s, SiMe), 0.026 (3H, s, SiMe); $\delta_C$(100 MHz; $CDCl_3$) 139.5, 114.9, 61.9, 50.0, 32.9, 31.54, 29.8, 28.5, 25.9, 18.1, 5.55, 5.51; $\nu_{max}$(film)/cm$^{-1}$ 3077, 2958, 2930, 2858, 1641, 1473, 1364, 1256, 1113, 1003, 911, 836, 774, 667; *m*/*z* (CI+) 257.2316 (calculated for $C_{15}H_{32}OSi + H^+$: 257.2301).

**3-[*tert*-Butyl(dimethyl)silyloxymethyl]-4,4-dimethylpentanal (29).** Olefin **28** (3.00 g, 11.7 mmol) was dissolved in THF (95 ml), *t*-BuOH (35 ml) and water (35 ml) at rt. After addition of NMO (2.83 g, 23.4 mmol) and $OsO_4$ (0.5 g, 1.97 mmol) dissolved in THF (5 ml) the reaction mixture was stirred for 1.5 h before saturated $Na_2SO_3$ (500 ml) was added. The aqueous phase was extracted with EtOAc, dried ($MgSO_4$) and evaporated. Flash chromatography (toluene–EtOAc 3 : 2) gave (3.07 g, 90%) of the corresponding diol.

The diol from above (2.00 g, 6.88 mmol) was dissolved in THF (45 ml) and water (40 ml) at rt. $NaHCO_3$ (2.89 g, 34.4 mmol) and $NaIO_4$ (4.42 g, 20.65 mmol) was added followed by an additional THF (10 ml) and water (10 ml). The reaction was quenched after 4.5 h by addition of sat. $Na_2SO_3$ (400 ml) and extracted with $Et_2O$. The combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography ($CH_2Cl_2$–toluene 15 : 1) gave **29** as a colorless oil (1.52 g, 85%). $\delta_H$(400 MHz; $CDCl_3$) 9.75 (1H, t, *J* 2, CHO), 3.82 (1H, dd, *J* 9.7, 4.1, $CH_2$OTMS), 3.46 (1H, br t, *J* 9.6, $CH_2$OTMS), 2.39 (2H, dd, *J* 6.3, 2, C$H_2$CHO), 2.03 (1H, m, C*H*CH$_2$CHO), 0.92 (9H, s, *t*-Bu), 0.86 (9H, s, *t*-Bu), 0.035 (6H, s, $SiMe_2$); $\delta_C$(100 MHz; $CDCl_3$) 203, 63.6, 46.3, 43.4, 28.0, 25.9, 18.2, −5.5; $\nu_{max}$(film)/cm$^{-1}$ 2955, 2928, 2869, 1726, 1472, 1367, 1254, 1112, 1078, 838, 446; *m*/*z* (CI+) 257.1923 (calculated for $C_{14}H_{30}O_2Si - H^+$: 257.1937).

**(*Z*)-*tert*-Butyl(2-*tert*-butylhex-4-enyloxy)dimethylsilane (30).** KHMDS (15.1 ml, 15.8 mmol) was added to a slurry of (ethyl)-triphenylphosphonium bromide (6.29 g, 16.9 mmol) in THF (40 ml) at −20 °C. After 1.5 h at rt the reaction mixture was cooled to −20 °C and **29** (1.46 g, 5.65 mmol) in THF (15 ml) was added. After 0.5 h the temperature was raised to rt and the reaction mixture was stirred for an additional 1 h before addition of brine and $Et_2O$. The mixture was extracted with $Et_2O$ and the combined organic phases were dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography (pentane–$CH_2Cl_2$ 3 : 2) to give **30** as a colorless oil (1.22 g, 80%). $\delta_H$(400 MHz; $CDCl_3$) 5.44 (2H, m, $CH_3$C*H*=C*H*), 3.62 (2H, d, *J* 4.0, $CH_2$OTMS), 2.13–2.23 (1H, m, $CH_3$CH=CHC$H_2$), 2.08 (1H, m, $CH_3$CH=CHC$H_2$), 1.63 (3H, d, *J* 5.0, C$H_3$CH=CH), 1.16 (1H, m, C*H*CH$_2$OTMS), 0.95 (9H, s, *t*-Bu), 0.89 (9H, s, *t*-Bu), 0.033 (3H, s, SiMe), 0.022 (3H, s, SiMe); $\delta_C$(100 MHz; $CDCl_3$) 131.2, 123.8, 62.2, 50.7, 33.0, 28.5, 25.9, 24.2, 18.1, 12.9, −5.5 and −5.6; $\nu_{max}$(film)/cm$^{-1}$ 2956, 2930, 2858, 1464, 1363, 1256, 1108, 1004, 939, 836, 774, 679; *m*/*z* (CI+) 271.2462 (calculated for $C_{16}H_{34}OSi + H^+$: 271.2457).

**(*Z*)-2-*tert*-Butylhex-4-en-1-ol (31).** TBAF (2.59 g, 8.21 mmol) was added to the silyl ether **30** (1.19 g, 4.41 mmol) in THF (15 ml) at rt. The mixture was stirred over night, diluted with EtOAc and washed with brine. The combined aqueous phases were extracted once with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. After flash chromatography ($CH_2Cl_2$) product **31** was obtained as a colorless oil (602 mg, 86%). $\delta_H$(400 MHz; $CDCl_3$) 5.54 (2H, m, $CH_3$C*H*=C*H*), 3.77 (1H, ddd, *J* 11.1, 7.0, 4.0, C$H_2$OH), 3.61 (1H, ddd, *J* 11.0, 6.0, 5.0, C$H_2$OH), 2.18 (2H, m, $CH_3$CH=CHC$H_2$), 1.68 (3H, d, *J* 5.0, C$H_3$CH=CH), 1.3–1.4 (2H, m, C*H*CH$_2$O*H*), 0.96 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 130.8, 124.8, 64.1, 51.4, 32.9, 28.2, 25.6, 12.9; $\nu_{max}$(film)/cm$^{-1}$ 3333, 2956, 2869, 1474, 1396, 1365, 1038, 691; *m*/*z* (CI+) 157.1582 (calculated for $C_{10}H_{20}O + H^+$: 157.1592).

### General procedure for cyclization of *N*-chloro(pentenyl)amines and *N*-chloro(hexenyl)amines into pyrrolidines 2a–c, e, 3a–c, e, 5 and 6

**1-Butyl-4-*tert*-butyl-2-chloromethylpyrrolidine (2a and 3a).** *N*-Chloroamine **1a** (33 mg, 0.134 mmol) was dissolved in $CH_2Cl_2$ (0.9 ml) and cooled to −78 °C before addition of $BF_3$·$Et_2O$ (28 μl, 0.27 mmol). After stirring for 25 min a slurry of $TiCl_3$ (2 mg, 13 μmol) in $CH_2Cl_2$ (0.4 ml) was added to the reaction mixture. The resultant slurry was stirred for 30 min at −78 °C before quenching with NaOH (0.3 ml, 30%). The mixture was immediately diluted with pentane, ethyl acetate and water and washed with brine. The organic phase was dried ($Na_2SO_4$) and evaporated. The resulting oil, a mixture of **2a** and **3a** (33 mg, 100%) was stored in benzene at −20 °C. The spectral data were obtained from the diastereomeric mixture. $\delta_H$(400 MHz; $C_6D_6$) 3.13–3.44 (2H, m, $CH_2$Cl, major and minor), 2.91 (1H, dd, *J* 9.7, 6.0, 5-H), 2.42–2.55 (2H, m, 2-H, NC$H_2$), 2.10

(1H, app t, *J* 9.7, 5-H), 1.86–1.98 (2H, m, 3-H, $NCH_2$), 1.60–1.69 (1H, m, 4-H), 1.16–1.41 (5H, m, 3-H, $CH_2CH_2CH_3$), 0.87 (3H, t, *J* 7.0, $CH_2CH_3$), 0.77 (9H, s, *t*-Bu), 0.75 (9H, s, *t*-Bu, minor); $\delta_C$(100 MHz; $CDCl_3$) 66.6, 56.1, 55.6, 55.2, 54.6, 47.9, 47.4, 47.2, 46.4, 33.5, 31.9, 31.5, 30.9, 31.4, 27.7, 27.3, 20.9, 20.8, 14.2.

**1-Benzyl-4-*tert*-butyl-2-chloromethylpyrrolidine (2b and 3b).** The diastereomeric mixture of **2b** and **3b** was prepared as described above for **2a** and **3a**. The spectral data were obtained from the diastereomeric mixture. $\delta_H$(400 MHz; $C_6D_6$) 7.07–7.37 (5H, m, Ph), 3.69 (1H, d, *J* 13.6, $CH_2Ph$), 3.11–3.39 (2H, m, $CH_2Cl$, major and minor), 2.99 (1H, d, *J* 13.6, $CH_2Ph$), 2.78 (1H, dd, *J* 9.8, 6.3, 5-H), 2.51–2.68 (1H, m, 2-H, major and minor), 2.11 (1H, app t, *J* 9.8, 5-H), 1.81–1.94 (1H, m, 3-H), 1.56–1.69 (1H, m, 4-H), 1.36–1.45 (1H, m, 3-H), 0.68 (9H, s, *t*-Bu), 0.66 (9H, s, *t*-Bu, minor); $\delta_C$(100 MHz; $CDCl_3$) 129.0, 128.8, 128.6, 128.5, 127.2, 66.1, 65.4, 59.6, 59.1, 56.4, 56.0, 47.8, 47.2, 46.3, 33.3, 31.9, 31.7, 27.7, 27.3.

**4-*tert*-Butyl-2-chloromethyl-1-(4-methoxybenzyl)pyrrolidine (2c and 3c).** The diastereomeric mixture of **2c** and **3c** was prepared as described above for **2a** and **3a**. The spectral data were obtained from the diastereomeric mixture. $\delta_H$(400 MHz; $C_6D_6$) 7.22 (2H, br d, *J* 8.2, Ph), 6.81 (2H, br d, *J* 8.2, Ph), 3.69 (1H, d, *J* 13.2, $CH_2Ph$), 3.14–3.44 (2H, m, $CH_2Cl$, major and minor), 3.31 (3H, s, $OCH_3$), 3.0 (1H, d, *J* 13.2, $CH_2Ph$), 2.86 (1H, dd, *J* 9.7, 5.5, 5-H, minor), 2.80 (1H, dd, *J* 9.7, 5.5, 5-H), 2.60 (1H, m, 2-H), 2.16 (1H, app t, *J* 9.7, 5-H), 1.84–1.99 (1H, m, 3-H), 1.58–1.71 (1H, m, 4-H), 1.38–1.48 (1H, m, 3-H), 0.71 (9H, s, *t*-Bu), 0.68 (9H, s, *t*-Bu, minor); $\delta_C$(100 MHz; $CDCl_3$) 130.2, 130.0, 129.7, 114.1, 66.1, 65.3, 58.5, 56.5, 55.9, 54.8, 54.5, 47.9, 47.2, 46.5, 46.3, 33.4, 31.8, 32.0, 31.8, 27.6, 27.4.

**1-Butyl-2-chloromethyl-4-methylpyrrolidine (2e and 3e).** The diastereomeric mixture of **2e** and **3e** was prepared as described above for **2a** and **3a**. $\delta_H$(400 MHz; $C_6D_6$) 3.08–3.44 (2H, m, $CH_2Cl$, major and minor), 2.60 (1H, dd, *J* 9.3, 4.4, 5-H), 2.52 (1H, m, $NCH_2$), 2.39–2.48 (1H, m, 2-H), 2.18 (1H, dd, *J* 9.3, 7.7, 5-H), 1.97–2.11 (2H, m, 3-H, $NCH_2$), 1.77–1.89 (1H, m, 4-H), 1.15–1.39 (5H, m, 3-H, $CH_2CH_2CH_3$), 0.92 (3H, t, *J* 7.1, $CH_2CH_3$), 0.91 (3H, d, *J* 7.1, $CHCH_3$).

**1-Butyl-4-*tert*-butyl-2-(1-chloroethyl)pyrrolidines 5 and 6 from 4a.** The mixture of **5** and **6** was prepared as described above for **2a** and **3a** starting from **4a**. The spectral data were obtained from the diastereomeric mixture, which is a pale yellow oil. $\delta_H$(400 MHz; $C_6D_6$) 3.87–4.08 (1H, m, CHCl), 2.88–3.10 (1H, m), 2.80–2.83 (1H, m), 2.34–2.65 (1H, m), 2.27–2.32 (1H, m), 2.18–2.22 (1H, m), 1.99–2.08 (1H, m), 1.82–1.93 (1H, m), 1.55–1.72 (1H, m), 1.25–1.53 (5H, m), 1.35 (3H, d, *J* 6.6, $CH_3CHCl$), 1.30 (3H, d, *J* 6.8, $CH_3CHCl$), 0.85–0.96 (3H, m, $CH_2CH_3$), 0.85 (9H, s, *t*-Bu), 0.79 (9H, s, *t*-Bu). $\delta_C$(100 MHz; $CDCl_3$) 70.8, 70.5, 59.5, 58.3, 56.4, 56.1, 55.9, 55.5, 55.2, 54.9, 46.4, 46.1, 31.6, 29.3, 28.2, 27.8, 27.6, 27.4, 27.0, 22.4, 22.3, 20.9, 20.8, 18.0, 14.3.

**1-Butyl-4-*tert*-butyl-2-(1-chloroethyl)pyrrolidines 5 and 6 from 4b.** The mixture of **5** and **6** was prepared as described above for **2a** and **3a** starting from **4b**. The spectral data were obtained from the diastereomeric mixture, which is a pale yellow oil. $\delta_H$(400 MHz; $C_6D_6$) 3.87–4.08 (1H, m, CHCl), 2.94–3.10 (1H, m), 2.75–2.83 (1H, m), 2.35–2.64 (1H, m), 2.13–2.22 (1H, m), 1.92–2.07 (1H, m), 1.80–1.90 (1H, m), 1.55–1.71 (1H, m), 1.15–1.52 (5H, m), 1.45 (3H, d, *J* 6.8, $CH_3CHCl$), 1.42 (3H, d, *J* 6.6, $CH_3CHCl$), 1.35 (3H, d, *J* 6.6, $CH_3CHCl$), 1.30 (3H, d, *J* 6.8, $CH_3CHCl$), 0.85–0.96 (3H, m, $CH_2CH_3$), 0.85 (9H, s, *t*-Bu), 0.79 (9H, s, *t*-Bu), 0.78 (9H, s, *t*-Bu), 0.77 (9H, s, *t*-Bu). $\delta_C$(125 MHz; $CDCl_3$) 70.8, 70.5, 59.5, 58.3, 56.4, 56.1, 55.9, 55.5, 55.2, 54.9, 46.4, 46.1, 31.6, 29.3, 28.2, 27.8, 27.6, 27.4, 27.0, 22.4, 22.3, 20.9, 20.8, 18.0, 14.3.

**General procedure for rearrangement of pyrrolidines to piperidines 11a, d, e and 12a, d, e**

**1-Butyl-5-*tert*-butyl-3-chloropiperidine (11a and 12a).** The diastereomeric mixture of pyrrolidines **2a** and **3a** was dissolved in $CDCl_3$ and left over night at room temperature to yield **11a** and **12a** in quantitative yield as a pale yellow oil. The spectral data were obtained from the diastereomeric mixture. $\delta_H$(300 MHz; $CDCl_3$) 4.44 (1H, quint, *J* 2.9, 3-H, minor), 3.96 (1H, app tt, *J* 10.9, 4.2, 3-H), 3.21 (1H, br d, *J* 10.9, 2-H), 3.10 (1H, br d, *J* 12.9, 2-H, minor), 2.99 (1H, br d, *J* 11.1, 6-H, minor), 2.92 (1H, br d, *J* 11.1, 6-H), 2.39 (2H, m, $NCH_2$), 2.27 (1H, br d, *J* 12.1, 4-H), 2.15 (1H, br d, *J* 13.0, 4-H, minor), 1.95 (1H, app t, *J* 10.8, 2-H), 1.71 (1H, app t, *J* 11.1, 6-H), 1.41–1.53 (3H, m, 5-H, $NCH_2CH_2$), 1.21–1.37 (3H, m, 4-H, $CH_2CH_3$), 0.92 (3H, t, *J* 7.1, $CH_2CH_3$), 0.89 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 61.4, 58.3, 56.7, 54.7, 46.2, 37.1, 31.9, 29.0, 27.6, 20.7, 14.0; $\nu_{max}$(film)/$cm^{-1}$ 2960, 2934, 2869, 2801, 2764, 1466, 1366, 1163, 1085, 739; *m*/*z* (EI+) 231.1752 (calculated for $C_{13}H_{26}ClN$: 231.1754).

**5-*tert*-Butyl-3-chloro-1-(2-methoxyethyl)piperidine (11d and 12d).** The diastereomeric mixture of **11d** and **12d** was prepared as described above for **11a** and **12a**. The spectral data were obtained from the diastereomeric mixture, which is a pale yellow oil. $\delta_H$(300 MHz; $CDCl_3$) 4.43 (1H, quint, *J* 2.7, 3-H, minor), 3.98 (1H, app tt, *J* 10.7, 4.4, 3-H), 3.49 (2H, m, $CH_2O$), 3.35 (3H, s, $OCH_3$), 3.34 (3H, s, $OCH_3$, minor), 3.24 (1H, br d, *J* 10.7, 2-H), 3.14 (1H, br d, *J* 11.0, 2-H, minor), 3.00 (1H, br d, *J* 11.0, 6-H, minor), 2.94 (1H, br d, *J* 11.0, 6-H), 2.52–2.72 (2H, m, $NCH_2$), 2.26 (1H, br d, *J* 12.5, 4-H), 2.02 (1H, app t, *J* 10.7, 2-H), 1.77 (1H, app t, *J* 11.0, 6-H), 1.48 (1H, m, 5-H), 1.27 (1H, app q, *J* 12.5, 4-H), 0.88 (9H, s, *t*-Bu); $\delta_C$(100 MHz; $CDCl_3$) 70.1, 61.6, 58.9, 57.7, 56.4, 55.0, 45.9, 36.9, 31.9, 27.6; $\nu_{max}$(film)/$cm^{-1}$ 2960, 2880, 2820, 1115, 735; *m*/*z* (CI+) 234.1610 (calculated for $C_{13}H_{26}ClN + H^+$: 234.1625).

**1-Butyl-3-chloro-5-methylpiperidine (11e and 12e).** The diastereomeric mixture of **11e** and **12e** was prepared as described above for **11a** and **12a**. The spectral data were obtained from the diastereomeric mixture, which is a pale yellow oil. $\delta_H$(400 MHz; $CDCl_3$) 4.29 (1H, quint, *J* 3.7, 3-H, minor), 3.97 (1H, app tt, *J* 11.0, 4.4, 3-H), 3.20 (1H, br d, *J* 11.0, 2-H), 2.82 (1H, br d, *J* 11.0, 6-H), 2.68 (1H, br d, *J* 11.0, 6-H, minor), 2.38 (2H, m, $NCH_2$), 2.20 (1H, br d, *J* 12.4, 4-H), 1.97 (1H, app t, *J* 11.0, 2-H), 1.58 (1H, app t, *J* 11.0, 6-H), 1.47 (2H, m, $NCH_2CH_2$), 1.24–1.34 (2H, m, $CH_2CH_3$), 1.15 (1H, app q, *J* 12.4, 4-H), 0.90 (6H, m, $CH_2CH_3$ and $CH_3$, major and minor); $\delta_C$(100 MHz; $CDCl_3$) 60.0, 58.2, 53.4, 43.4, 40.6, 34.1, 22.3, 20.7, 18.8, 14.0; $\nu_{max}$(film)/$cm^{-1}$ 3053, 2960, 2935, 2875, 2808, 1462, 1265, 897, 739, 706; *m*/*z* (EI+) 189.1274 (calculated for $C_{10}H_{20}ClN + H^+$: 189.1284).

**General procedure for $Bu_3SnH$ reduction of chlorides to pyrrolidines 7, 8, 9 and 10**

**1-Butyl-4-*tert*-butyl-2-ethylpyrrolidine (9 and 10).** The mixture of chloropyrrolidines **5** and **6** (10 mg, 40.7 μmol) was dissolved in $d_6$-benzene (1.5 ml) and added to an NMR tube. The reaction vessel was evacuated and nitrogen was bubbled through the solution. $BF_3{\cdot}OEt_2$ (10 μl, 95.4 μmol) and thereafter $Bu_3SnH$ (14 μl, 52.9 μmol) were added and the reaction mixture was gently shaken and irradiated (300 nm) for 16–24 h at rt. The solvent was evaporated and the resulting mixture was filtered through silica gel [pentane–EtOAc (3 : 1) and then pentane–EtOAc (3 : 1) + 1% $NH_4OH$] to give a diastereomeric mixture of **9** and **10** as a colorless oil (8 mg, 93%). The spectral

data were obtained from the diastereomeric mixture. $\delta_H$(400 MHz; $C_6D_6$) 3.14 (1H, m), 3.04 (1H, m), 2.71–2.81 (2H, m), 1.82–2.18 (4H, m), 1.17–1.77 (5H, m), 0.82–0.94 (15H, m); $\delta_C$(100 MHz; $C_6D_6$) 67.2, 66.6, 56.5, 55.8, 54.6, 54.1, 47.1, 46.3, 33.5, 32.4, 32.0, 31.7, 27.8, 27.5, 26.3, 21.14, 21.07, 14.4, 10.4, 10.3; $\nu_{max}$(film)/cm$^{-1}$ 2958, 2933, 2871, 2787, 1466, 1365; *m*/*z* (FAB+) 212.2378 (calculated for $C_{14}H_{29}N + H^+$: 212.2379).

**1-Butyl-4-*tert*-butyl-2-methylpyrrolidine (7 and 8).** The diastereomeric mixture of **7** and **8** was prepared as described above for **9** and **10**. The spectral data were obtained from the diastereomeric mixture, which is a colorless oil. $\delta_H$(400 MHz; $CDCl_3$) 2.92–3.05 (1H, m), 2.72–2.85 (1H, m), 2.16–2.45 (2H, m), 1.90 (1H, m), 1.80 (1H, m), 1.56–1.70 (2H, m), 1.42–1.55 (2H, m), 1.18–1.42 (2H, m), 1.11 (3H, br d, *J* 4.5), 0.89–0.97 (3H, t, *J* 7.3), 0.85 (9H, s), 0.84 (9H, s, minor); $\delta_C$(100 MHz; $CDCl_3$) 55.0, 54.2, 46.4, 46.1, 36.1, 31.9, 27.8, 27.3, 20.9, 18.1, 14.1; $\nu_{max}$(film)/cm$^{-1}$ 2958, 2924, 2852, 1464, 1265, 741; *m*/*z* (FAB+) 198.2219 (calculated for $C_{13}H_{27}N + H^+$: 198.2222).

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