Iodide-Catalysed Cyclization of Unsaturated *N*-Chloroamines: A New Way to Synthesise 3-Chloropiperidines

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Tetrabutylammonium iodide is a very efficient catalyst for the cyclization of unsaturated *N*-chloroamines. The catalysis seems to proceed through *N*-iodoamine intermediates, which act as a source of iodonium ions.

Introduction

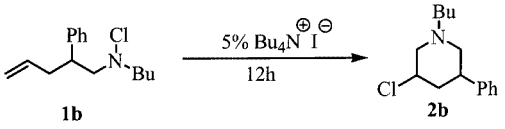
Pyrrolidines and piperidines are important substructures of a variety of biologically active compounds.[1] We are currently investigating new methods for their catalytic synthesis by intramolecular addition of nitrogen−heteroatom bonds to double bonds.[2] In a recent publication[3] we reported on the samarium(II) iodide catalysed cyclization of chloro(pentenyl)amines under mild conditions.

This reaction seemed to be catalysed by iodide rather than, as initially assumed, by samarium(II). Here we give a full report on this new reaction, describing its scope, together with a mechanistic discussion.

Results and Discussion

As reported previously, tetrabutylammonium iodide (TBAI) efficiently catalyses the cyclization of unsaturated chloroamines, but the reaction conditions had not been be optimised. We therefore examined different solvents and reaction temperatures for the cyclization of **1b**. The results are given in Scheme 1.

Chloroform is clearly the best solvent, and higher temperatures seem to be necessary for efficient cyclization. To use temperatures above the boiling point of chloroform, 1,2-dichloroethane was selected as a similar solvent. However, performance of the reaction in 1,2-dichloroethane at a temperature of 80 °C did not improve the yield. A better yield could be obtained by using 10 mol % of catalyst, whilst a further increase in the amount of catalyst again resulted in a reduced yield. In a next step we wanted to check the generality of these optimized reaction conditions, and therefore synthesized the chloroamines **1a**−**1o**.[4]



1b **2b**

solvent	temperature (°C)	yield (%)
THF	50	56
pentane	35	34
methanol	50	33
DME	50	52
DME	85	57
chloroform	25	38
chloroform	50	64
1,2-dichloroethane	80	56
chloroform[a]	50	80
chloroform[b]	50	61

[a] 10% catalyst were used. [b] 20% catalyst were used.

Scheme 1. Optimization of the reaction conditions

The *gem*-dialkyl-substituted chloroamines **1h**−**1n** were obtained via the enamine **3** (Scheme 2), which was synthesized from isobutyraldehyde and morpholine. This enamine **3** was alkylated with allyl bromide to afford aldehyde **4** after aqueous workup. Reductive amination of aldehyde **4** gave the amines **5h**−**5m**. Amine **5n** was obtained from **5l** by TMS protection of the free hydroxy group. From these secondary amines the chloroamines **1h**−**1n** were obtained in good yield by treatment with NCS.

For the synthesis of the ester-substituted chloroamine **1o**, a different approach had to be chosen (Scheme 3), as the ester group does not survive the reductive amination. The aldehyde **4** was therefore transformed into the oxime **6**,

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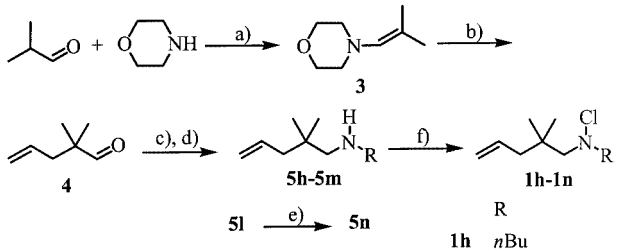
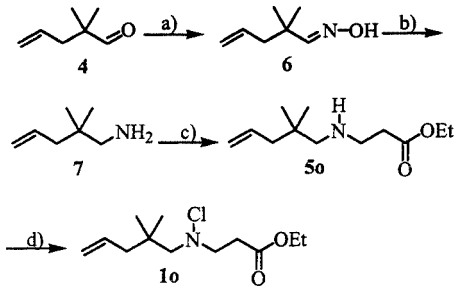


	R
1h	*n*Bu
1i	*i*Bu
1j	*s*Bu
1k	*t*Bu
1l	-CH_2CH_2OH
1m	-CH-CH=CH_2
1n	-CH_2CH_2OTMS

a) + cat. Tos-H, CH_2Cl_2, rflx ; b) allyl bromide, CH_3CN, ΔT , then water/HCl; c)RNH_2, Na_2SO_4; d) 0.5 equiv. $NaBH_4$, MeOH; e) TMSCl, imidazole ; f) NCS, CH_2Cl_2, 0°C

Scheme 2. Synthesis of chloroamines **1h**−**1n**



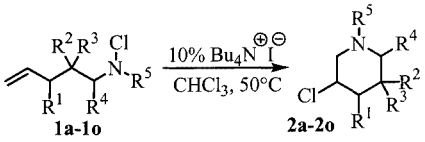
Scheme 3. Synthesis of chloroamine **1o**

which was reduced with lithium aluminium hydride to give amine **7**. Alkylation of this amine with ethyl 3-bromopropionate afforded the secondary amine **5o**, which was transformed into the chloroamine **1o** by treatment with NCS.

These chloroamines **1a**−**1o** were cyclized under the optimized reaction conditions (Table 1, 10% TBAI, chloroform, 50 °C). In all cases the 3-chloropiperidines **2a**−**2o** were obtained in good yield. The cyclization does not only produce good yields when simple alkyl-substituted chloroamines are used but a variety of sensitive functional groups neither inhibit the reaction nor are they affected in any way. Such groups as additional double bonds (**1m**), esters (**1o**), silyl ethers (**1n**) and even free hydroxy groups (**1l**) can therefore be used in this transformation. Furthermore, the cyclization is not sensitive to steric influences. The chloroamines **1h**−**1k** gave the cyclization products **2h**−**2k** in good yield, regardless of the size of R^5.

The quantitative yield of **2h** from the cyclization of **1h** tempted us to use this transformation for kinetic studies. Chloroamine **1h** was therefore cyclized at 50 °C in deuterated chloroform in the presence of different amounts of TBAI. NMR samples were taken from these reaction mixtures, frozen in acetone/dry ice and warmed to room temperature just prior to measurement of the ^1H NMR spectrum. No intermediates of the reaction could be detected in the spectra; only signals resulting from the starting material and the product were visible. To examine the kinetics, the product/chloroamine ratio was determined by integration, using the signal of TBAI as an internal standard. Figure 1 shows five

Table 1. Yields of cyclisation



	R^1	R^2	R^3	R^4	R^5	yield (%)
1a	H	H	H	Ph	*n*Bu	83
1b	H	H	Ph	H	*n*Bu	80
1c	Ph	H	H	H	*n*Bu	71
1d	H	H	H	Me	*n*Bu	72
1e	H	H	Me	H	*n*Bu	78
1f	Me	H	H	H	*n*Bu	73
1g	H	H	H	H	*n*Bu	81
1h	H	Me	Me	H	*n*Bu	99
1i	H	Me	Me	H	*i*Bu	81
1j	H	Me	Me	H	*s*Bu	79
1k	H	Me	Me	H	*t*Bu	80
1l	H	Me	Me	H	-CH_2-CH_2OH	63
1m	H	Me	Me	H	-CH_2-CH=CH_2	82
1n	H	Me	Me	H	-CH_2-CH_2OTMS	91
1o	H	Me	Me	H	-CH_2-CH_2-CO_2Et	98

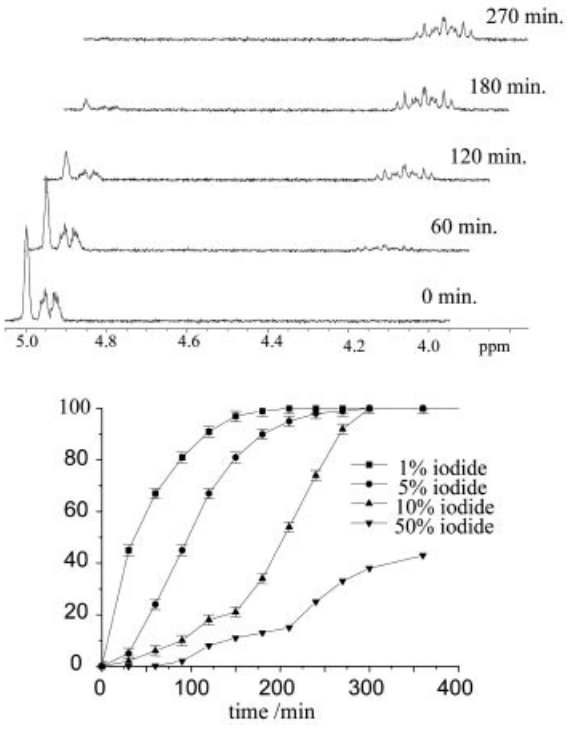
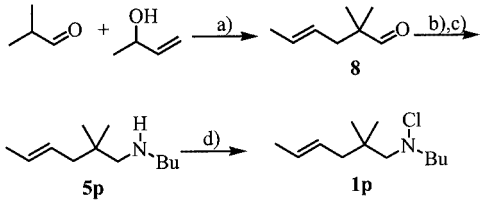


Figure 1. Kinetic studies

selected spectra with 5% TBAI, together with the measured kinetics for 1%, 5%, 10% and 50% TBAI, respectively.

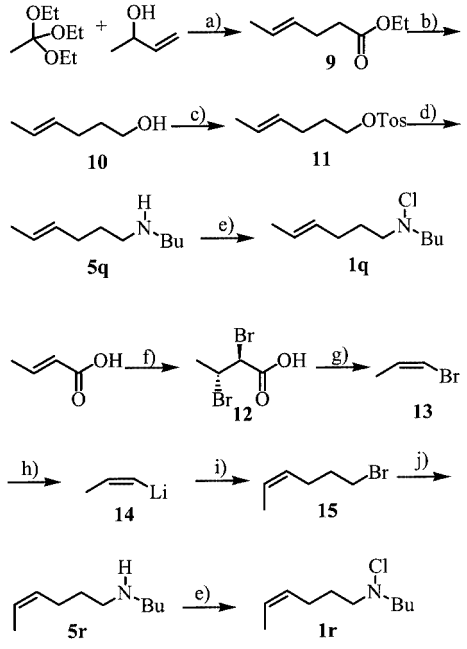
To our surprise, the reaction proceeded best with 1% catalyst. An increase in the amount of catalyst also provided a quantitative yield, but there seemed to be an initiation period during which the reaction proceeded only slowly. The more catalyst was used, the longer was this initiation period. One explanation for this observation might be that iodide is only a catalyst precursor and in fact inhibits the reaction by conproportionation with the actual catalyst, which might be a more highly oxidized iodo species. For better understanding of the mechanism and the reactive species, the stereochemical outcome of the addition to 1,2-disubstituted double bonds was of interest. We therefore turned our attention to the chloroamines **1p**−**1r**, containing disubstituted double bonds. For the synthesis of **1p** (Scheme 4) the aldehyde **8** was prepared stereoselectively by means of a Claisen rearrangement[5] from isobutyraldehyde and but-3-en-2-ol.



a) cat. TosOH, toluene, ΔT; b) Bu-NH_2, CH_2Cl_2, Na_2SO_4; c) 0,5 equiv. $NaBH_4$, MeOH ; d) NCS, CH_2Cl_2, 0°C, 1h

Scheme 4

Aldehyde **8** was reductively aminated to afford amine **5p**, which was transformed into the desired chloroamine **1p** by treatment with NCS.

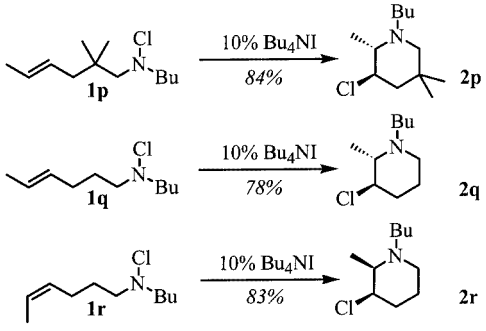


Scheme 5

For the synthesis of the (*Z*)- and (*E*)-configured *N*-chloro-4-hexenylamines **1q** and **1r**, a different approach was followed (Scheme 5). Chloroamine **1q** was synthesized via the ester **9**, which was obtained from but-3-en-2-ol and triethyl orthoacetate in a Johnson-orthoester-Claisen rearrangement.[6] Reduction of the ester **9** with lithium aluminium hydride gave the alcohol **10**, which was transformed into the tosylate **11**. The tosyloxy group could be substituted with butylamine to afford the amine **5q**, which was transformed into the chloroamine **1q** by treatment with NCS.

For the synthesis of **1r**, crotonic acid was brominated to give **12**, from which (*Z*)-bromopropene **13** was obtained by fragmentation.[7] The (*Z*)-propenyllithium **14** was synthesized from **13** by treatment with lithium powder. Cuprate coupling[8] of this organolithium compound with 1,3-dibromopropane stereoselectively gave (*Z*)-1-bromo-4-hexene **15**. Substitution of the bromide with butylamine provided the amine **5r**, which was transformed into the chloroamine **1r** with NCS under standard conditions.

With the three chloroamines **1p**−**1r** readily available, we then cyclized them by application of our previously optimized conditions (Scheme 6).

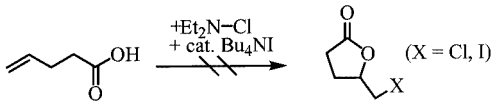


Scheme 6

All three reactions produced good yields of piperidines **2p**−**2r**. Furthermore, the stereochemistry of the double bond was maintained in the product. The reaction thus proceeds through a stereospecific *trans* addition.

With this additional information, mechanistic discussion is feasible. One plausible pathway would be reaction via aminyl radicals.[9] However, if the reaction were to proceed via radicals, one would expect a cascade cyclization in the case of chloroamine **1m**, a reaction that we did not observe at all. Furthermore, the stereospecificity and the initiation period would not be explained if the reaction was radical in nature. Therefore, a different mechanism had to be proposed. The iodide might be oxidized by chloroamine to give iodine or ICl. These compounds would conproportionate with excess iodide, giving an explanation for the initiation period. Furthermore, iodine and ICl are known to add to double bonds by stereospecific *trans* addition,[10] as observed in our reaction. If iodine or ICl were intermediates in the reaction, one would expect a mixture of chloroamine and iodide to be an efficient reagent for performing a halolactonization. We therefore tried to achieve a halolac-

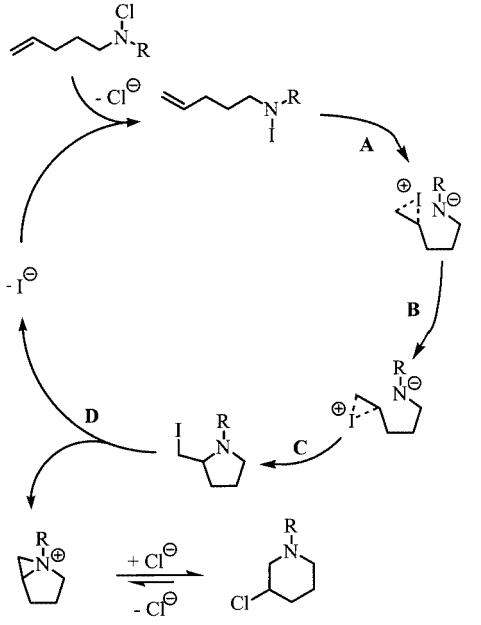
tonization of 4-pentenoic acid by addition of chlorodiethylamine and catalytic amounts of TBAI (Scheme 7).



Scheme 7

However, no detectable amounts of lactone were produced either under our standard conditions for the cyclization of chloroamines or on application of literature conditions for halolactonizations, thereby ruling out the participation of iodine or ICl in the catalysis.

More highly oxidized iodine species might be intermediates in the reaction: I^{III} compounds, for example, are known to be electrophilic and to attack double bonds.[11] However, such species also react with aromatic compounds, and we did not find any aromatic substitution products when we cyclized chloroamines **1a**−**1c**, which each have an aromatic nucleus in close proximity to the N−Cl group. Such hypervalent iodine compounds can therefore be ruled out. This leaves only one plausible reaction mechanism: the generation of *N*-iodoamines. These compounds could be formed from chloroamines by a Finkelstein reaction (Scheme 8).



Scheme 8

As the iodine in iodoamines is in the +1 oxidation state, such compounds would conproportionate with excess iodide, giving an explanation for the observed initiation period. From studies by Jander,[12] *N*-iodoamines are known to be highly reactive species. They could therefore react intramolecularly with the double bond, generating an iodonium ion **A**.[13] After rotation around a single bond (**B**) this ion could be opened in an S_N2-type manner by the nucleophilic nitrogen atom (**C**), explaining the observed stereospecificity. The catalyst would be liberated from the cyclization product by nucleophilic substitution (**D**), affording an aziridinium ion.[14] This exists in equilibrium with the 3-chloropiperidine resulting from the nucleophilic attack of a chloride ion. Unfortunately *N*-iodoamines are too reactive to be directly detected in the reaction, and we therefore have no direct evidence of their occurrence. Nevertheless, the proposed catalytic cycle is suitable to explain all experimental observations. We are currently trying to find further evidence for this mechanism.

Conclusion

In summary, we present a new, catalytic, general and mild procedure for the cyclization of unsaturated chloroamines, which most probably proceeds via *N*-iodoamines and iodonium ions. The 3-chloropiperidines generated in this reaction should prove to be valuable intermediates for the synthesis of natural products. We are currently working towards broadening the synthetic scope of *N*-chloroamines as sources of electrophilic halonium ions.

Experimental Section

General: All solvents were purified by distillation and dried, if necessary, prior to use. As a standard solvent, *tert*-butyl methyl ether (TBME) was used instead of diethyl ether in many cases. The reactions were carried out under vacuum in heat-dried glassware under argon. Products were purified by flash chromatography on silica gel (40−63 μm). NMR spectra were recorded in $CDCl_3$ with a Bruker WM 300, a Bruker AMX 400 and a Varian Unity plus 600 spectrometer with TMS as internal standard. Mass spectra were recorded with an MAT 8200, an MAT 8230 and a Micromars Quattro LC spectrometer. Elemental analyses were performed with a CHN-O Rapid from Foss-Heraeus and a Vario EL III from Elementar Analysensysteme.

2-Methyl-1-morpholinopropene (3): Morpholine (95.8 mL, 87.1 g, 1.1 mol) and a catalytic amount of *p*-toluenesulfonic acid were added at 0 °C to a solution of isobutyraldehyde (90.8 mL, 72.1 g, 1.0 mol) in dichloromethane (500 mL). The solution was heated under reflux overnight and water was removed azeotropically with a Dean−Stark apparatus. After cooling to room temperature, the mixture was washed with water (50 mL) and dried with sodium sulfate. The solvent was removed and the residue was distilled in vacuo (90−110 °C, 100 mbar) to give 2-methyl-1-morpholinopropene (**3**) (132.6 g, 0.94 mol, 94%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61, (s, with fine-splitting, 3 H), 1.68 (s, with fine-splitting, 3 H), 2.55 (m, 4 H), 3.69 (m, 4 H), 5.30 (sept, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 22.1, 53.1, 66.8, 123.4, 135.3 ppm. These data are consistent with the published spectra.

2,2-Dimethylpent-4-enal (4): A solution of the enamine **3** (60.0 g, 420 mmol) in acetonitrile (150 mL) was cooled to 0 °C. Allyl bromide (40.2 mL, 56.2 g, 470 mmol) was then added and the mixture was heated under reflux overnight. After the mixture had cooled to room temperature, water (100 mL) and hydrochloric acid (2 N, 200 mL) were added. The organic layer was separated and the water layer was washed three times with dichloromethane (50 mL each). The combined organic layers were dried with sodium sulfate, the

solvent was removed, and the residue was distilled in vacuo (80 °C, 110 mbar) to give 2,2-dimethylpent-4-enal (**4**, 28.6 g, 257 mmol, 61%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 6 H), 2.22 (dt, *J* = 7.4, 1.2 Hz, 2 H), 5.06 (m, 2 H), 5.71 (m, 1 H), 9.48 (s, 1 H) ppm. ^{13} C NMR (75 MHz, $CDCl_3$): δ = 21.0, 41.3, 45.5, 118.2, 132.9, 205.3 ppm. These data are consistent with the published spectra.[15]

(*E*)-2,2-Dimethylhex-4-enal (8): Isobutyraldehyde (62.4 g, 866 mmol) and *p*-toluenesulfonic acid (0.2 g) were added to a solution of 3-buten-2-ol (41.7 g, 578 mmol) in toluene (150 mL). The reaction mixture was heated under refluxed for 48 h and the water generated was removed in a Dean−Stark apparatus. The solvent was then removed and the residue was distilled in vacuo (136 °C at 70 mbar) to give aldehyde **8** (48.9 g, 393 mmol, 67%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 6 H), 1.65 (ddd, *J* = 6.3, 1.5, 1.2 Hz, 3 H), 2.14 (dt, *J* = 6.9 , 1.2 Hz, 2 H), 5.32 (m, 1 H), 5.48 (m, 1 H), 9.47 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 21.1, 40.3, 45.9, 125.2, 129.3, 206.2 ppm. These data are consistent with the published spectra.[16]

General Procedure for the Reductive Amination: The primary amine (0.11 mol) and sodium sulfate (approx. 30 g) were added to a cooled solution (0 °C) of the corresponding aldehyde (0.10 mol) in dichloromethane (150 mL), and the reaction mixture was left standing overnight. After filtration, the solvent was removed, the residue was taken up in methanol (100 mL), and sodium borohydride (1.9 g, 50 mmol) was added in small portions at 0 °C. After the mixture had been stirred overnight, aqueous sodium hydroxide (25%, 50 mL) were added and the mixture was stirred for 1 h. The organic layer was then separated and the aqueous layer was extracted three times with diethyl ether (50 mL each). The combined organic layers were dried with sodium sulfate. After removal of the solvent, the residue was distilled in vacuo to give the corresponding amine as a colorless liquid.

***N*-Butyl-2,2-dimethylpent-4-enylamine (5h):** B.p. 110 °C (110 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (s, 6 H), 0.93 (t, *J* = 7.3 Hz, 3 H), 1.39 (m, 5 H), 2.02 (d, *J* = 7.5 Hz, 2 H), 2.36 (s, 2 H), 2.60 (t, *J* = **7.0** Hz, 2 H), 5.02 (m, 2 H), 5.83 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 21.1, 26.1, 32.9, 34.9, 45.4, 51.3, 61.1, 117.2, 136.2 ppm. HRMS: (EI, E-scan): calcd. for $C_{11}H_{22}ClN$ 203.14407/205.141128; found 203.1425/205.1426. For elemental analysis, the hydrochloride was prepared: $C_{11}H_{24}ClN$ (205.77): calcd. C 64.21, H 11.76, N 6.81; found C 63.97, H 11.47, N 6.73.

***N*-Isobutyl-2,2-dimethylpent-4-enylamine (5i):** B.p. 117 °C (100 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 6 H), 0.89 (d, *J* = 6.6 Hz, 6 H), 0.89 (s, 1 H), 1.73 (m, 1 H), 2.01 (dt, *J* = 7.2, 1.2 Hz, 2 H, 2.32 (s, 2 H), 2.38 (d, 6.9 Hz, 2 H), 5.00 (m, 2 H), 5.82 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 25.5, 28.0, 34.4, 44.8, 59.0, 60.3, 116.6, 135.7 ppm. $C_{11}H_{23}N$ (169.31): calcd. C 78.03, H 13.69, N 8.27; found C 77.60, H 13.55, N 8.46.

***N*-*sec*-Butyl-2,2-dimethylpent-4-enylamine (5j):** B.p. 109 °C (120 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (s, broad, 1 H), 0.88 (s, 6 H), 0.88 (t, 7.5 Hz, 3 H), 1.00 (d, 6.6 Hz, 3 H), 1.35 m, 2 H), 2.00 (dt, *J* = 7.3, 1.0 Hz, 2 H), 2.28 (d, *J* = 11.5 Hz, 1 H), 2.38 (d, *J* = 11.4 Hz, 1 H), 2.45 (q, *J* = 6.1 Hz, 1 H), 5.00 (m, 2 H), 5.82 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.3, 20.2, 25.6, 29.7, 34.3, 44.7, 55.5, 57.7, 116.6, 135.8 ppm. $C_{11}H_{23}N$ (169.31): calcd. C 78.03, H 13.69, N 8.27; found C 77.69, H 13.33, N 7.97.

***N*-*tert*-Butyl-2,2-dimethylpent-4-enylamine (5k):** B.p. 104 °C (150 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 6 H), 0.89 (s, 1 H), 1.05 (s, 9 H), 1.99 (dt, *J* = 7.6, 1.2 Hz, 2 H), 2.28 (s, 2 H), 5.00 (m, 2 H), 5.82 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 29.2, 33.8, 44.5, 49.9, 52.6, 116.5, 135.9 ppm. $C_{11}H_{23}N$ (169.31): calcd. C 78.03, H 13.69, N 8.27; found C 77.75, H 13.63, N 8.01.

***N*-(2-Hydroxyethyl)-2,2-dimethylpent-4-enylamine (5l):** B.p. 46 °C (1 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 6 H), 2.02 (dt, *J* = 7.3, 1.3 Hz, 2 H), 2.03 (s, broad, 2 H), 2.39 (s, 2 H), 2.77 (t, with fine-splitting, *J* = 5.4 Hz, 2 H), 3.61 (t, with fine-splitting, *J* = 5.4 Hz, 2 H), 5.02 (m, 2 H), 5.82 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 34.3, 44.7, 51.7, 59.6, 60.4, 116.9, 135.3 ppm. $C_9H_{19}NO$ (157.26): calcd. C 68.74, H 12.18, N 8.91; found C 68.35, H 11.93, N 8.70.

***N*-Allyl-2,2-dimethylpent-4-enylamine (5m):** B.p. 102 °C (100 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 6 H), 1.12 (s, broad, 1 H), 2.01 (dt, *J* = 7.4, 1.2 Hz, 2 H), 2.35 (s, 2 H), 3.23 (dt, *J* = 6.0, 1.4 Hz, 2 H), 5.02 (m, 2 H), 5.12 (m, 2 H), 5.85 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 34.2, 44.7, 53.3, 59.8, 115.4, 116.7, 135.5, 137.4 ppm.

(*E*)-*N*-Butyl-2,2-dimethylhex-4-enylamine (5p): B.p. 126 °C (85mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (s, 6 H), 0.84 (t, *J* = 7.2 Hz, 3 H), 1.26 (m, 2 H), 1.37 (m, 2 H), 1.59 (d, *J* = 4.4 Hz, 3 H), 1.84 (d, 4.4 Hz, 2 H), 2.25 (s, 2 H), 2.50 (t, *J* = 7.4 Hz, 2 H), 5.34 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 17.7, 20.2, 25.3, 32.0, 34.1, 43.3, 50.5, 60.3, 126.8, 127.6 ppm. $C_{12}H_{25}N$ (183.34): calcd. C 78.62, H 13.74, N 7.64; found C 78.63, H 13.55, N 7.73.

2,2-Dimethyl-*N*-(2-trimethylsiloxyethyl)pent-4-enylamine (5n): A solution of *n*-butyllithium in hexane (1.6 M, 20 mL, 32 mmol) was added slowly at −78 °C to a solution of *N*-(2-hydroxyethyl)-2,2-dimethylpent-4-enylamine (**5l**, 5.00 g, 31.8 mmol) in THF (50 mL) and the reaction mixture was stirred for 0.5 h. Trimethylsilyl chloride (3.45 g, 31.8 mmol) was then added dropwise and the solution was allowed to warm to room temperature overnight. The solution was poured into a mixture of ice (100 g) and pH = 7 buffer (100 mL), the phases were separated, and the aqueous phase was extracted three times with diethyl ether (50 mL each). After drying of the combined organic layers with sodium sulfate and removal of the solvent, the silyl ether **5n** (2.47 g, 10.8 mmol, 34%) was isolated by flash chromatography (eluent pentane/TBME, 10:1 then 3:1) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 9 H), 0.90 (s, 6 H), 1.40 (s, broad, 1 H), 2.02 (dt, *J* = 7.4, 1.4 Hz, 2 H), 2.37 (s, 2 H), 2.71, t, 5.4 Hz, 2 H), 3.69 (t, *J* = 5.4 Hz, 2 H), 5.02 (m, 2 H), 5.83 (m, 1 H) ppm. ^{13} C NMR (75 MHz, $CDCl_3$): δ = 0.04, 25.5, 34.4, 44.8, 52.7, 60.2, 61.7, 116.8, 135.5 ppm. $C_{12}H_{27}NOSi$ (229.44): calcd. C 62.82, H 11.86, N 6.10, found C 62.49, H 11.83, N 5.95.

2,2-Dimethylpent-4-enal Oxime (6): Hydroxylamine hydrochloride (1.67 g, 24 mmol) in water (1 mL) was added to a solution of sodium hydroxide (600 mg, 15 mmol) in water (1.5 mL), and the mixture was diluted with ethanol (6 mL). Without removal of occasionally precipitated sodium chloride, aldehyde **4** (2.24 g, 20 mmol) in ethanol (50 mL) was added and the reaction mixture was left standing overnight. Water (30 mL) was then added, the organic layer was separated, and the aqueous layer was extracted three times with diethyl ether (20 mL each). The combined organic layers were dried with sodium sulfate, the solvent was removed, and the residue was distilled in vacuo (b.p. 69 °C, 1 mbar) to yield the oxime **6** (2.29 g, 18 mmol, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 1 H), 1.09 (s, 6 H), 2.19 (dt, *J* = 7.4, 1.2 Hz, 2 H), 5.05 (m, 2 H), 5.76 (m, 1 H), 7.34 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 36.6, 45.3, 118.1, 133.9, 158.4 ppm.

$C_7H_{13}NO$ (127.19): calcd. C 66.11, H 10.30, N 11.01; found C 66.03, H 10.40, N 11.12.

2,2-Dimethylpent-4-enylamine (7): A solution of oxime **6** (2.29 g, 18 mmol) in diethyl ether (50 mL) was added dropwise at 0 °C to a suspension of lithium aluminium hydride (1.0 g, 26 mmol) in dry diethyl ether (100 mL). After vigorous stirring overnight, the reaction mixture was poured onto ice, and solid sodium hydroxide was added until the precipitate dissolved. The organic layer was separated, and the residue was extracted three times with diethyl ether (50 mL each). The combined organic layers were dried with sodium sulfate, the solvent was removed, and the residue was distilled in vacuo (b.p. 66 °C at 100 mbar) to give the amine **7** (1.35 g, 12 mmol, 66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (s, 6 H), 1.71 (s, broad, 2 H), 1.90 (dt, *J* = 7.4, 1.2 Hz, 2 H), 2.37 (s, 2 H), 4.94 (m, 2 H), 5.72 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 34.9, 44.1, 52.9, 116.9, 135.4 ppm. These data are consistent with the published spectra.[17]

Ethyl 3-[(2,2-Dimethylpent-4-enyl)amino]propanoate (5o): Ethyl 3-Bromopropionate (3.19 g, 17.6 mmol) was added at 0 °C to a solution of 2,2-dimethylpent-4-enylamine (**7**, 5.38 g, 47.5 mmol) in dichloromethane (100 mL) and the solution was stirred overnight. The reaction mixture was washed three times with aqueous sodium hydroxide (5%, 20 mL each) and dried with sodium sulfate, and the solvent was removed. The product was purified by flash chromatography (eluent pentane/TBME, 10:1 then 3:1) to yield **5o** (2.48 g, 11.6 mmol, 66%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 6 H), 1.26 (t, 7.1 Hz, 3 H), 1.38 (s, broad, 1 H), 2.00 (dt, *J* = 7.5, 1.1 Hz, 2 H), 2.36 (s, 2 H), 2.49 (t, *J* = 6.5 Hz, 2 H), 2.88 (t, *J* = 6.5 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 5.01 (m, 2 H), 5.81 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 25.5, 34.3, 34.9, 44.7, 46.2, 60.0, 60.3, 116.8, 135.5, 177.6 ppm. $C_{12}H_{23}NO_2$ (213.32): calcd. C 67.57, H 10.87, N 6.57; found C 67.64, H 11.15, N 6.64.

Ethyl (*E*)-Hex-4-enoate (9): Acetic acid (1 mL) was added to a mixture of but-3-en-2-ol (42.9 mL, 0.50 mol) and triethyl orthoacetate (137.0 mL, 0.75mol), and the vessel was fitted with a Liebig condenser. The mixture was slowly heated to 140 °C over 2 h, during which 1 equiv. ethanol was distilled off. The temperature was then raised to 150 °C and kept there until another equiv. of ethanol had distilled off (approx. 3 h). The product was purified by distillation (b.p. 93 °C, 60 mbar) to give the ester **9** (65.5 g, 0.46mol, 92%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, 7.2 Hz, 3 H), 1.65 (d, with fine-splitting, 4.5 Hz, 3 H), 2.33 (m, 4 H), 4.14 (q, 7.2 Hz, 2 H), 5.46 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.8, 27.9, 34.4, 60.2, 126.1, 129.3, 173.2 ppm. These data are consistent with the published spectra.[18]

(*E*)-Hex-4-en-1-ol (10): Lithium aluminium hydride (26 g, 0.69 mol) was suspended in TBME (400 mL) in a 1-L flask. At 0 °C, a solution of ethyl (*E*)-hex-4-enoate (**9**, 65.5 g, 0.46 mol) in TBME (50 mL) was added slowly. The reaction mixture was stirred overnight at room temperature and then poured onto 400 g of ice. Sulfuric acid (50 %) was added until the precipitate dissolved. The phases were separated and the aqueous phase was extracted three times with TBDME (100 mL each). The combined organic phases were dried with sodium sulfate, the solvent was removed, and the product was obtained from the residue by distillation (b.p. 90 °C, 60mbar) as a colorless liquid (29.5 g, 0.29 mol, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (m, 5 H), 1.72 (s, 1 H), 2.07 (m, 2 H), 3.62 (t, 6.7 Hz, 2 H), 5.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 28.9, 32.5, 62.5, 125.4, 130.7 ppm. These data are consistent with the published spectra.[19]

(*E*)-1-Tosyloxy-4-hexene (11): Pyridine (15 mL, 0.15 mol) was added at 0 °C to a solution of toluene-4-sulfonyl chloride (29.0 g, 0.15mol) in dichloromethane (200 mL), followed by (*E*)-hex-4-en-1-ol (**10**, 9.0 g, 90 mmol). The mixture was stirred overnight and then poured onto ice (200 g) and stirred for another hour. Solid sodium hydroxide was added until the pH was greater than 10. The phases were separated, and the aqueous phase was extracted twice with dichloromethane (50 mL each). The combined organic phases were dried with sodium sulfate, the solvent was removed, and the residue was purified by flash chromatography (eluent pentane/TBME, 10:1), giving the tosylate **11** (18.2 g, 72 mmol) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (m, 3 H), 1.69 (m, 2 H), 2.00 (m, 2 H), 2.44 (s, 3 H), 4.02 (t, 6.4 Hz, 2 H), 5.31 (m, 2 H), 7.34 (m, 2 H), 7.79 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 21.5, 28.6, 69.8, 126.4, 127.8, 129.0, 129.7, 133.4, 144.6 ppm. $C_{13}H_{18}O_3S$ (254.35): calcd. C 61.39, H 7.13; found C 61.28, H 7.12. These data are consistent with the published spectra.[20]

(*E*)-*N*-Butylhex-4-enylamine (5q): The tosylate **11** (18.0 g, 71 mmol) was added at 0 °C to butylamine (100 mL), and the mixture was heated under reflux overnight. Excess butylamine was removed in vacuo, and the residue was taken up in TBME (200 mL) and water (100 mL). Aqueous sodium hydroxide (5%) was then added until the pH was greater than 10. The phases were separated, and the organic phase was extracted three times with aqueous sodium hydroxide (5%, 100 mL each) and dried with sodium sulfate. After removal of the solvent, the product was obtained by distillation (b.p. 145 °C, 50 mbar) as a colorless liquid, 9.1 g (59 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 7.1 Hz, 3 H), 1.04 (s, broad, 1 H), 1.35 (m, 2 H), 1.45 (m, 2 H), 1.53 (m, 2 H), 1.64 (m, 3 H), 1.96 (m, 2 H), 2.59 (m, 4 H), 5.40 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 17.8, 20.7, 29.5, 29.8, 30.6, 51.8, 51.9, 124.5, 131.6 ppm. These data are consistent with the published spectra.[21]

2,3-Dibromobutyric Acid (12): Bromine (44.2 mL, 137 g, 0.86 mol) was added dropwise to a suspension of crotonic acid (66.0 g, 0.767 mol) in petroleum ether (300 mL) at such a rate that the color of the bromine quickly disappeared. To start the reaction, gentle heating with a water bath was necessary. While the bromine was added, the crotonic acid dissolved completely and the 2,3-dibromobutyric acid precipitated from the yellow solution as a colorless solid. After the mixture had been stirred overnight, the solid was isolated by filtration, washed three times with petroleum ether and dried for 4 h under vacuum to give 2,3-dibromobutyric acid (**12**, 162 g, 659 mmol, 86%) as a crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (d, 6.2 Hz, 3 H), 4.40 (m, 2 H), 11.80 (s, broad, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8, 44.6, 48.9, 143.8 ppm. These data are consistent with the published spectra.[22]

(*Z*)-1-Propenyl Bromide (13): 2,3-Dibromobutyric acid (159 g, 0.65 mol) was added in five portions at 0 °C to triethylamine (400 mL), carbon dioxide being produced during the addition. After the mixture had been vigorously stirred for 3 h at room temperature and a further 3 h at 40 °C, water (300 mL) was added to the resulting clear black solution. Concentrated hydrochloric acid (250 mL) was then added carefully at 0 °C. The reaction mixture was left standing overnight in a separation funnel. The organic layer was then separated and washed first with saturated sodium hydrogencarbonate solution (20 mL) and then with brine (10 mL). After drying with sodium sulfate, the solvent was removed and the residue was purified by distillation to give (*Z*)-1-bromo-1-propene (**13**, 40.8 g, 337 mmol, 52%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, 4.8 Hz, 3 H), 6.15 (m, 2 H) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 15.2, 108.8, 129.5 ppm. These data are consistent with the published spectra.[23]

(*Z*)-1-Propenyllithium (14): (*Z*)-1-Propenyl bromide (**13**, 31.1 g, 0.257 mol), dissolved in diethyl ether (100 mL), was added dropwise at −50 °C to a suspension of powdered lithium (8.0 g, 1.2 mol) in diethyl ether (200 mL). After stirring for 1 h at −40 °C, the reaction mixture was allowed to warm to room temperature. The suspension was filtered through a reverse filter and the resulting clear pale-red solution was stored at −20 °C. For determination of the concentration, 1 mL of the solution was poured into 20 mL of 1 N aqueous sulfuric acid and titrated with 0.1 N sodium hydroxide solution; 200 mL of a 1.0 M solution of **14** was obtained (77%).

(*Z*)-1-Bromohex-4-ene (15): Copper(I) iodide (21 g, 0.11 mol), dissolved in dimethyl sulfide (80 mL), was added at −78 °C to the 1.0 M (*Z*)-1-propenyllithium solution (200 mL, 0.2 mol). The reaction mixture was brought to −40 °C and stirred for 15 min. 1,3-Dibromopropane (22.12 g, 0.11 mol) was added to this cuprate solution, and the reaction mixture was allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride solution (300 mL) was added at 0 °C to the resulting black suspension. After the mixture had been stirred for 1 h, the layers were separated and the aqueous phase was extracted twice with diethyl ether (100 mL each). The combined organic layers were dried with sodium sulfate and the solvent was removed. The crude (*Z*)-1-bromohex-4-ene (**15**) was used directly in the next step without further purification.

(*Z*)-*N*-Butylhex-4-enylamine (5r): The crude (*Z*)-1-bromohex-4-ene (**15**) was dissolved in dichloromethane (100 mL), and this solution was added at 0 °C over 30 min to a mixture of *n*-butylamine (200 mL) in dichloromethane (300 mL). After vigorous stirring overnight, the solvent and the excess of *n*-butylamine were removed. The remainder was taken up in diethyl ether (200 mL) and water (100 mL). Aqueous sodium hydroxide solution (5%) was added until the pH was above 10. The organic layer was then separated and dried with sodium sulfate. After removal of the solvent, the residue was distilled (b.p. 151 °C, 50mbar) to give the amine **5r** (5.31 g, 34 mmol, 31% over two steps) as a colorless liquid. ^{1}H NMR (300 MHz, CDCl3): δ = 0.92 (t, 7.2 Hz, 3 H), 1.20 (s, broad, 1 H), 1.34 (m, 2 H), 1.47 (m, 2 H), 1.55 (m, 2 H), 1.61 (d, 6.0 Hz, 3 H), 2.08 (m, 2 H), 2.60 (m, 4 H), 5.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6, 13.9, 20.5, 24.7, 30.0, 32.4, 49.7, 49.8, 124.0, 130.2 ppm.

General Procedure for the Preparation of *N*-Chloroamines: *N*-Chlorosuccinimide (1 equiv.) was added to a cooled (0 °C) solution of the corresponding amine in dichloromethane. After the mixture had been stirred for 2 h, the solvent was removed and the residue was taken up in pentane. After removal of the solid succinimide by filtration, the solvent was removed and the product was isolated from the residue by flash chromatography.

5-[Butyl(chloro)amino]-4,4-dimethylpent-1-ene (1h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 7.3 Hz, 3 H), 0.94 (s, 6 H), 1.38 (m, 2 H), 1.62 (m, 2 H), 2.08 (d, 8.0 Hz, 2 H), 2.85 (s, 2 H), 2.94 (m, 2 H), 5.04 (m, 2 H), 5.83 (ddt, *J* = 12.6, 7.8, 5.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.9, 25.7, 30.2, 35.6, 44.9, 66.6, 74.8, 117.2, 135.3 ppm.

5-[Chloro(isobutyl)amino]-4,4-dimethylpent-1-ene (1i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, 6.9 Hz, 6 H), 0.94 (s, 6 H), 1.98 (m, 1 H), 2.07 (dt, 7.5, *J* = 1.2 Hz, 2 H), 2.67 (d, *J* = 6.9 Hz, 2 H), 2.84 (s, 2 H), 5.03 (m, 2 H), 5.81 (ddt, *J* = 17.5, 10.8, 7.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 25.8, 27.3, 35.8, 44.9, 74.7, 75.3, 117.2, 135.3 ppm.

5-[Chloro(*sec*-butyl)amino]-4,4-dimethylpent-1-ene (1j): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 6 H), 0.94 (t, *J* = 7.5 Hz, 3 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 1.35 (m, 1 H), 1.67 (m, 1 H), 2.07 (m, 2 H), 2.69 (d, *J* = 14.8 Hz, 1 H), 2.70 (m, 1 H), 2.84 (d, *J* = 14.8 Hz, 1 H), 5.01 (m, 2 H), 5.82 (ddt, *J* = 16.2, 10.9, 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 14.6, 25.6, 25.7, 27.7, 35.7, 44.8, 69.0, 71.4, 117.0, 135.5 ppm.

5-[Chloro(*tert*-butyl)amino]-4,4-dimethylpent-1-ene (1k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 6 H), 1.20 (s, 9 H), 2.07 (dt, 7.4, 1.0 Hz, 2 H), 2.80 (s, 2 H), 5.01 (m, 2 H), 5.85 (ddt, *J* = 16.3, 11.0, 7.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 26.7, 34.9, 45.3, 62.5, 67.5, 116.9, 135.5 ppm.

(2*E*)-6-[Butyl(chloro)amino]-5,5-dimethylhex-2-ene (1p): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 6 H), 0.93 (t, *J* = 7.2 Hz, 3 H), 1.37 (m, 2 H), 1.59 (m, 2 H), 1.65 (m, 3 H), 1.95 (m, 2 H), 2.80 (s, 2 H), 2.90 (t, 6.9 Hz, 2 H), 5.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.0, 19.9, 25.7, 30.3, 35.7, 43.6, 66.6, 74.8, 127.5, 127.6 ppm.

(2*E*)-6-[Butyl(chloro)amino]hex-2-ene: (1q): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H), 1.38 (m, 2 H), 1.63 (m, 2 H), 1.69 (m, 5 H), 2.02 (m, 2 H), 2.91 (m, 4 H), 5.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 17.8, 20.0, 27.7, 29.7, 30.0, 63.7, 64.1, 125.4, 130.6 ppm.

(2*Z*)-6-[Butyl(chloro)amino]hex-2-ene: (1r): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.9 Hz, 3 H), 1.36 (m, 2 H), 1.65 (m, 2 H), 1.70 (m, 5 H), 2.07 (m, 2 H), 2.92 (m, 4 H), 5.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 13.9, 20.0, 24.0, 27.8, 30.0, 64.1, 64.3, 124.5, 129.8 ppm.

General Procedure for the Cyclization Reaction Producing 3-Chloropiperidines 2: The *N*-chloroamine (2.5 mmol) was added at 50 °C (oil bath temperature) to a suspension of tetrabutylammonium iodide (0.25 mmol) in chloroform (10 mL). The solution was kept at this temperature for 12 h. After the mixture had cooled to room temperature, the solvent was removed and the product was isolated from the residue by flash chromatography.

5-Chloro-1-isobutyl-3,3-dimethylpiperidine (2i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 0.89 (d, 6.9 Hz, 6 H), 1.04 (s, 3 H), 1.32 (t, *J* = 12.3 Hz, 1 H), 1.70 (m, 2 H), 1.93 (m, 2 H), 2.05 (d, with fine splitting, *J* = 6.0 Hz, 2 H), 2.35 (d, *J* = 11.1 Hz, 1 H), 3.10 (d, with fine splitting, *J* = 9.9 Hz, 1 H), 4.07 (tt, *J* = 11.4, 4.2 Hz, 1 H) ppm. ^{13}C NMR (300 MHz, CDCl3):= 20.6, 20.7, 25.2, 25.9, 29.3, 33.4, 48.5, 54.4, 62.8, 65.2, 66.1 ppm.

1-*sec*-Butyl-3-chloro-5,5-dimethylpiperidine (2j): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 7.3 Hz, 3 H), 0.92 (s, 6 H), 1.04 (d, *J* = 5.7 Hz, 3 H), 1.27 (m, 1 H), 1.31 (dd, *J* = 12.9, 12.3 Hz, 1 H), 1.47 (m, 1 H), 1.90 (m, 2 H), 2.12 (m, 1 H), 2.23 (d, *J* = 10.6 Hz, 1 H), 2.48 (m, 1 H), 3.04 (dd, *J* = 11.1, 10.5 Hz, 1 H), 4.05 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 25.1, 26.8, 29.3, 29.4, 33.6, 49.09, 49.1, 56.0, 57.5, 60.9 ppm. **Minor Isomer (Selected Signals):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71, 3.11, 4.32 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 26.5, 27.0, 33.3, 55.1, 55.4, 60.4, 62.4 ppm. MS: *m*/*z* (%) = 203 (6) [M^+], 174 (32) [$M^+ - C_2H_5^+$], 141 (45), 111 (16) [$M^+ - C_4H_9Cl$], 83 (27), 71 (60), 57 (100) [$C_3H_7N^+$]. HRMS: (Quattro-LC, electrospray): calcd. for $C_{15}H_{28}ClN$ 203.14407; found 203.14361.

1-*tert*-Butyl-3-chloro-5,5-dimethylpiperidine (2k): ^{1}H NMR (300 MHz, CDCl3): δ = 0.90 (s, 3 H), 0.99 (s, 3 H), 1.03 (s, 9 H), 1.29

(dd, J = 12.2, 12.1 Hz, 1 H), 1.81 (d, J = 11.2 Hz, 1 H), 1.91 (m, 1 H), 2.00 (dd, J = 10.7, 10.4 Hz, 1 H), 2.53 (dt, J = 10.7, 2.0 Hz, 1 H), 3.34 (m, 1 H), 4.01 (ddt, J = 11.9, 10.6, 4.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.4, 29.4, 33.3, 49.0, 53.4, 55.6, 56.2, 57.8 ppm. For the elemental analysis, the hydrochloride was prepared. $C_{11}H_{25}Cl_2N$ (242.23): calcd. C 55.00, H 9.65, N 5.83; found C 54.70, H 9.34, N 5.61.

***trans*-1-Butyl-3-chloro-2,5,5-trimethylpiperidine (2p):** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 0.90 (t, J = 7.3 Hz, 3 H), 1.03 (s, 3 H), 1.26 (m, 2 H), 1.30 (d, J = 5.9 Hz, 3 H), 1.37 (m, 2 H), 1.48 (dd, J = 12.5, 12.4 Hz, 1 H), 1.5 (ddd, J = 12.8, 12.7, 2.4 Hz, 1 H), 2.05 (d, J = 11.5 Hz, 1 H), 2.18 (dq, J = 9.4, 6.2 Hz, 1 H), 2.42 (dd, J = 12.0, 2.3 Hz, 1 H), 2.44 (m, 1 H), 2.68 (ddd, J = 13.2, 9.4, 6.4 Hz, 1 H), 3.71 (ddd, J = 12.0, 9.4, 4.4 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 17.1, 20.5, 24.7, 26.9, 29.3, 32.5, 49.0, 53.2, 62.7, 63.5, 64.2 ppm.

***trans*-1-Butyl-3-chloro-2-methylpiperidine (2q):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 7.5 Hz, 3 H), 1.24 (m, 2 H), 1.29 (d, J = 6.0 Hz, 3 H), 1.32−1.50 (m, 3 H), 1.61−1.70 (m, 3 H), 2.30 (m, 2 H), 2.49 (m, 2 H), 2.65 (m, 1 H), 3.66 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 16.3, 20.7, 24.9, 27.3, 35.2, 51.4, 55.6, 62.4, 63.7 ppm. $C_{10}H_{20}ClN$ (189.73): calcd. C 63.31, H 10.63, N 7.38; found C 62.85, H 10.70, N 7.38.

***cis*-1-Butyl-3-chloro-2-methylpiperidine (2r):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.2 Hz, 3 H), 1.10 (d, J = 6.3 Hz, 3 H), 1.28 (m, 2 H), 1.42 (m, 3 H), 1.86 (m, 3 H), 2.38 (m, 2 H), 2.48 (m, 2 H), 2.93 (m, 1 H), 4.14 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.7, 23.5, 24.1, 28.1, 31.1, 47.7, 53.9, 58.1, 62.4 ppm. $C_{10}H_{20}ClN$ (189.73): calcd. C 63.31, H 10.63, N 7.38; found C 63.47, H 10.96, N 7.45.

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