Copper(I) Catalysts for the Stereoselective Addition of *N*-Chloroamines to Double Bonds: A Diastereoselective Radical Cyclisation

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Copper(I) catalysts for the diastereoselective radical cyclisation of *N*-chloro-*N*-pentenylamines have been developed. The stereoselectivity of the cyclisation depends upon the ligands employed, proving that the radical is bound to the catalyst during the formation of the new stereocentre and making a catalyst-influenced stereoselective radical reaction possible. The influence of the catalyst on the Beckwith–Houk transition states is discussed.

Introduction

Pyrrolidines and piperidines are important substructures of a variety of biologically active compounds.[1] We are investigating new methods for their stereoselective synthesis by the catalysed intramolecular addition of nitrogen–heteroatom bonds to double bonds.[2] This transformation can be achieved via nitrogen-centred radicals under acidic conditions, which are necessary to protonate the radical, thus making it more electrophilic for an efficient addition to a double bond.[3] In a recent publication[4] we reported on milder reaction conditions using copper(I) salts as catalysts for the radical cyclisation of *N*-chloro-*N*-pentenylamines under aprotic conditions (Figure 1). In this reaction the catalyst acts as an initiator of the radical reaction (**A**), as activator for the aminyl radical cyclisation[5] (**B**) and as scavenger for the carbon radical formed (**C**).[6]

The initial product, a 2-(chloromethyl)pyrrolidine, rearranges under these almost neutral conditions via an aziridinium ion in two subsequent S_N2 reactions[7] to the 3-chloropiperidine,[8] thereby allowing the synthesis of piperidines via a kinetically favourable 5-*exo* cyclisation. As the aminyl radical is coordinated to the catalyst in the addition step,[9] an influence of the catalyst structure and ligand sphere on the stereochemical outcome of the reaction can be expected. This could allow an efficient radical cyclisation with a catalyst-induced stereoselectivity.[10]

Results and Discussion

Here we wish to report on this influence of the catalyst and that the diastereoselectivity in aminyl radical cyclisations can be greatly increased by using copper(I) catalysts together with chelating ligands.

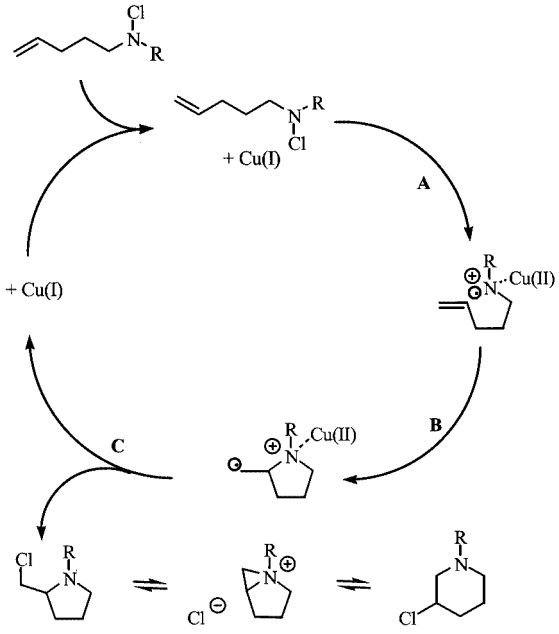

Figure 1. Catalytic cycle

In a first set of experiments we analysed the diastereoselectivity of aminyl radical cyclisations using our previously reported conditions[4] and various *N*-chloro-*N*-pentenylamines containing a chiral centre. To do so, the chloroamines **1a**–**1f** were synthesised. The precursors **1b**, **1c** and **1f** were easily available using a Johnson orthoester Claisen rearrangement[11] as the key step (Figure 2).[12]

For the synthesis of **1b** and **1c** the initially formed esters were saponified to the acids **2b** and **2c**. These were transformed via the acyl chlorides into the corresponding *N*-butylamides **3b** and **3c**. Reduction of the amides gave the amines **4b** and **4c** in good yield,[13] from which the *N*-chlo-

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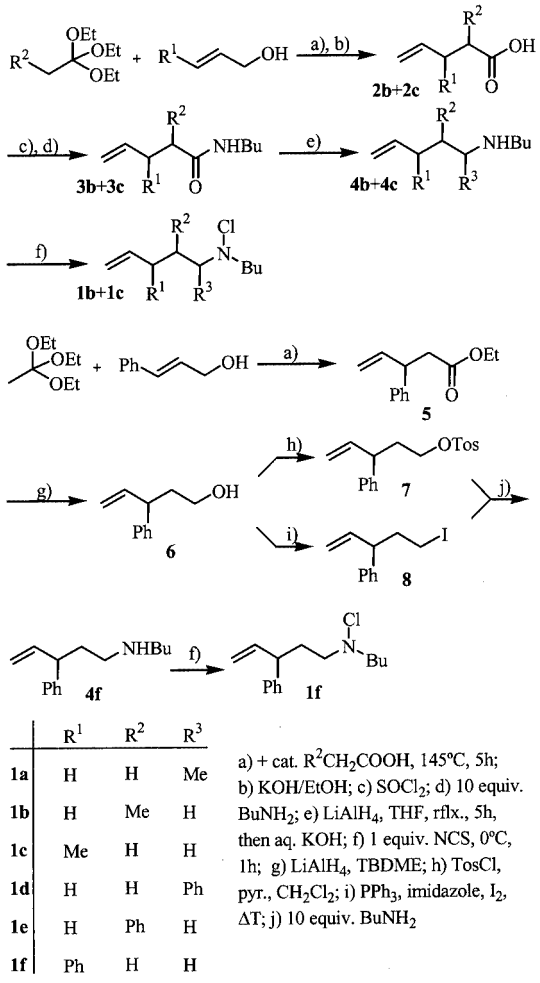


	R^1	R^2	R^3
1a	H	H	Me
1b	H	Me	H
1c	Me	H	H
1d	H	H	Ph
1e	H	Ph	H
1f	Ph	H	H

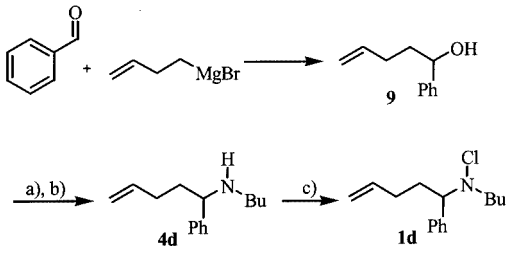
a) + cat. R^2CH_2COOH, 145°C, 5h; b) KOH/EtOH; c) $SOCl_2$; d) 10 equiv. $BuNH_2$; e) $LiAlH_4$, THF, rflx., 5h, then aq. KOH; f) 1 equiv. NCS, 0°C, 1h; g) $LiAlH_4$, TBDME; h) TosCl, pyr., CH_2Cl_2; i) PPh_3, imidazole, I_2, ΔT; j) 10 equiv. $BuNH_2$

Figure 2. Synthesis of the chloroamines by a Johnson orthoester Claisen rearrangement

roamines were formed by reaction with NCS. For the synthesis of **1f** this procedure failed, due to isomerisation of the double bond in conjugation with the aromatic ring. We therefore reduced the initially formed ester **5** to the alcohol **6**, which was either tosylated to **7** or transformed into the iodide **8** prior to the reaction with butylamine to give the amine **4f**. Both reaction sequences gave satisfying yields, although the workup of the product resulting from the tosylate proved to be difficult on a larger scale. The amine **4f** was transformed into the *N*-chloroamine **1f** in good yield by reaction with NCS.

For the synthesis of **1d** a different reaction sequence was applied. Alcohol **9** was obtained by the addition of a butenyl Grignard reagent to benzaldehyde. Substitution of the hydroxy group with butylamine via the corresponding iodide led to amine **4d** (Figure 3).

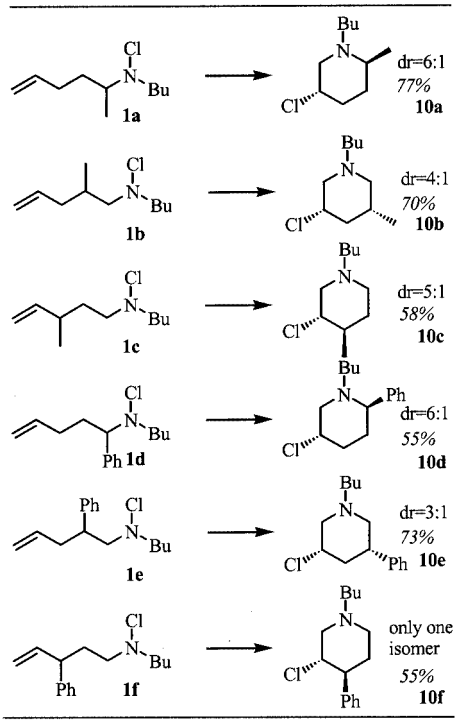
From this amine the *N*-chloroamine **1d** was obtained in good yield under standard conditions. With the chloroamines being readily available, we first tested our initially reported conditions[4] for the cyclisation of **1a**−**1f**. In all cases moderate to good yields of the corresponding 3-chloropiperidines **10a**−**10f** were obtained. Furthermore, in all these



a) PPh_3, I_2, imidazole, toluene, rflx., 5 min; b) 5 equiv. $BuNH_2$; c) 1 equiv. NCS, CH_2Cl_2, 0°C, 1h.

Figure 3. Synthesis of chloroamine **1d**

Table 1. Cyclisation of the *N*-chloroamines using 10 mol % CuCl in THF at 50 °C



reactions a remarkable excess of one of the two possible diastereomers was observed (Table 1).

This diastereomeric ratio is notably higher than in the cyclisation reactions of the corresponding protonated aminyl radicals,[14] thus proving that the metal catalyst indeed has a beneficial influence on the stereoselectivity of the cyclisation. This effect results from the two Beckwith−Houk transition states[15] shown in Figure 4. We believe that the copper(II) centre not only activates the aminyl radical but also coordinates the alkene, thereby leading to a more rigid transition state.

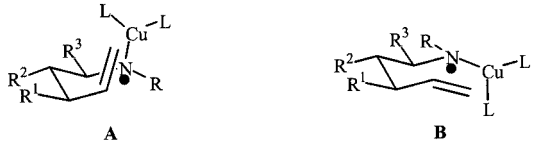


Figure 4. Beckwith−Houk transition states for the cyclisation of the aminyl radical; **B** leads to the preferred product

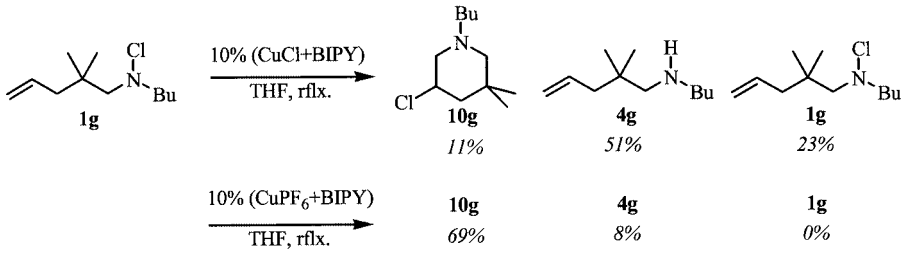


Figure 5. First experiments with addition of ligands

In the preferred chair-like transition state **B** all groups, including the copper ion, are in an equatorial position. In contrast to this, in the less favourable boat-like transition state **A**, the coordination of the double bond by the metal ion forces the sterically demanding copper salt into an unfavourable pseudo-axial position. The transition state **A** should therefore become even more unfavourable as the size of the metal complex increases. This not only explains the observed high diastereomeric excess, but, if this hypothesis holds true, the addition of sterically demanding ligands to the catalyst should lead to an increase in diastereoselectivity.

To verify this assumption chelating diamines were added as ligands for the copper ion. Treatment of the chloroamine **1g** with these catalysts leads to a low yield of piperidine **10g**, along with unchanged chloroamine **1g** and the corresponding secondary amine **4g** as the main products of the reaction (Figure 5). The low yield of the cyclisation product could be due to the reduced Lewis acidity of the copper complex, which now cannot activate the aminyl radical for the addition step.

We therefore turned our attention towards more Lewis acidic copper(I) salts with weakly coordinating counterions, such as copper(I) hexafluorophosphate.[16] With this complex as a catalyst, and without any addition of further ligands, low yields were also obtained. However, this might be due to a now too high Lewis acidity of the reaction mixture; Newcomb has reported that Lewis acid catalysed aminyl radical cyclisations produce lower yields under too Lewis acidic conditions.[17] Therefore, this copper salt seemed ideal for further studies, as the addition of ligands should reduce the Lewis acidity of the catalyst. This proved to be correct and higher yields were obtained upon addition of co-ligands. We next checked the cyclisation reaction of chloroamine **1a** with different ligands. In all cases, upon using copper(I) hexafluorophosphate and chelating ligands, the piperidine **10a** formed, although the varying yields obtained are surprising. Even though there seems to be no great difference between TMCDA (*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine) and TMEDA, the former produced a much higher yield of cyclisation product when used as ligand (Figure 6).[18]

An explanation for this unusual effect might be that TMCDA is a catalyst in its own right, reacting with the chloroamine by abstracting a chloronium ion, which, in turn, could add to the double bond. However, performing the reaction with TMCDA and no copper salt did not lead

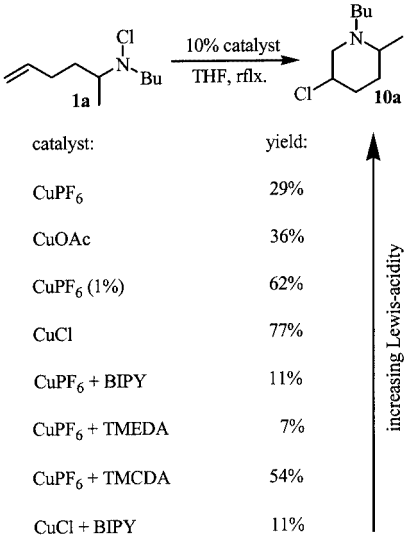
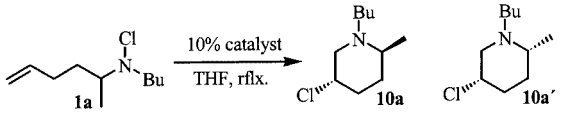


Figure 6. Varying the metal salt and ligand

to any cyclisation product at all. Traces of water that might have been present are also not responsible for the observed yield, as addition of water to the reaction mixture reduced the yield.[19] Therefore, the surprising difference between TMEDA and TMCDA as ligands can only be attributed to the fixed bite-angle of TMCDA, which seems to be ideal for this reaction.[20] We therefore checked the diastereoselectivity of the cyclisation using 10 mol % catalyst together with different amounts of ligand (Figure 7). To our surprise an excess of ligand was necessary to obtain an optimal diastereoselectivity. This resulted in the formation of only one stereoisomer when 5 equiv. or more of ligand were used, whilst addition of further excess of ligand did not have a pronounced effect on the yield of the cyclisation.

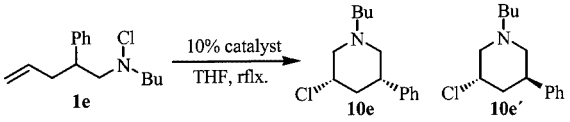
The diastereoselectivity of the cyclisation step is considerably higher than with copper(I) chloride alone or than observed in the cyclisation of the corresponding carbon radicals.[21] This exceptionally high diastereoselectivity in a radical cyclisation is probably due to the two Beckwith−Houk transition states shown in Figure 4, with the copper ion generally avoiding a pseudo-axial position. In the case of chloroamine **1a** there is an additional effect; in transition state **A** the copper is in a gauche conformation to two alkyl groups, whereas in **B** there is only one of these unfavourable interactions, which favours **B** over **A** even more strongly.



catalyst:	yield:	dr **10a** : **10a′**
$CuPF_6$ + 0,5 TMCDA	64%	3 : 1
$CuPF_6$ +1 TMCDA	54%	4 : 1
$CuPF_6$ + 2 TMCDA	44%	4 : 1
$CuPF_6$ + 5 TMCDA	51%	>20 : 1
$CuPF_6$ + 10 TMCDA	49%	>20 : 1
$CuPF_6$ + 20 TMCDA	55%	>20 : 1

Figure 7. High diastereoselectivity with 5 equiv. of ligand

We therefore decided to check the diastereoselectivity without this additional "gauche effect", and thus performed studies on the cyclisation of chloroamine **1e**, in which the directing group is one carbon atom further away from the aminyl radical (Figure 8). As expected, the cyclisation of this chloroamine led to reduced, but still high, diastereoselectivities, although the increase in stereoselectivity upon going from simple copper(I) chloride to $CuPF_6$ together with chelating ligands as catalyst is still remarkable and can again be attributed to the bulky ligand sphere of the catalyst, which avoids the pseudo-axial orientation of transition state **A**. In this system TMEDA proved to be the best ligand and a diastereomeric ratio of 10:1 was achieved, which is still extraordinarily high compared to the cyclisation of carbon radicals.[21]



catalyst:	yield:	dr **10e**: **10e′**
CuCl	73%	3 : 1
$CuPF_6$ + TMEDA	43%	10 : 1
$CuPF_6$ + 2 TMCDA	37%	5 : 1
$CuPF_6$ + BIPY	42%	9 : 1
$CuPF_6$ + TMBDA	42%	7 : 1

(TMBDA = *N*,*N*,*N*′,*N*′-tetramethylbenzene-1,2-diamine)

Figure 8. Diastereoselectivity in the cyclisation of chloroamine **1e**

Conclusion

In summary we have demonstrated the influence of ligands on the stereochemistry of the copper(I)-catalysed radical cyclisation of unsaturated *N*-chloroamines, enabling us to perform a stereoselective catalytic radical reaction. We believe that this new and highly stereoselective synthesis of functionalised piperidines will prove valuable for the synthesis of pharmacologically active compounds and natural products.

Experimental Section

General: All solvents were purified by distillation and dried, if necessary, prior to use. 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 with a Bruker WM 300, a Bruker AMX 400 or a Varian Unity plus 600 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded with a MAT 8200, a MAT 8230 or a Micromars Quattro LC spectrometer. Elemental analyses were performed with a CHN-O Rapid from Foss-Heraeus or a Vario EL III from Elementar Analysensysteme.

General Procedure for the Synthesis of Pentenoic Acids 2: The corresponding acid (acetic or propionic acid; 1 mL) was added to a mixture of 0.5 mol of triethyl orthoester and 0.5 mol of the allylic alcohol and the solution heated slowly to 150 °C. The reaction mixture was kept at this temperature until 2 equiv. (1.0 mol) of ethanol had distilled off (approx. 2−5 h). After cooling to room temp., this crude pentenoic ester was added to a solution of potassium hydroxide (40 g) in 300 mL of ethanol and the mixture heated under reflux for 3 h. The solvent was then evaporated under vacuum and the residue dissolved in 300 mL of water. Concd. hydrochloric acid was added to this mixture at 0 °C until pH = 1−2. The solution was extracted three times with 150 mL of TBDME (*tert*-butyl methyl ether), the combined organic phases were dried with magnesium sulfate, the solvent was evaporated and the product purified by distillation.

2-Methylpent-4-enoic Acid (2b): Yield: 37.2 g (77% over 2 steps) of a colourless liquid, b.p. 102−104° C (50 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.9 Hz, 3H), 2.21 (m, 1 H), 2.44 (m, 1 H), 2.54 (m, 1 H), 5.07 (m, 2 H), 5.77 (ddt, J = *J* = 17.7, 10.2, 6.9 Hz, 1 H), 11.53 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 37.4, 39.2, 117.1, 135.1, 182.7 ppm. These data are in accordance with published data.[22]

3-Methylpent-4-enoic Acid (2c): Yield: 18.4 g (34% over 2 steps) of a colourless liquid, b.p. 72 °C (20 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.6 Hz, 3 H), 2.32 (dd, *J* = 15.1, 7.2 Hz, 1 H), 2.43 (dd, *J* = 15.1, 7.2 Hz, 1 H), 2.70 (m, 1 H), 4.98 (dt, *J* = 10.2, 1.3 Hz, 1 H), 5.05 (dt, *J* = 17.1, 1.3 Hz, 1 H), 5.79 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1 H), 11.44 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 34.1, 41.0, 113.5, 142.1, 178.2 ppm. These data are in accordance with published data.[22]

General Procedure for the Synthesis of *N*-Butylpent-4-enamides 3: Thionyl chloride (0.22 mol) was added to 0.2 mol of the carboxylic acid, the mixture stirred for 1 h, and then heated to 50 °C for 4 h to complete the reaction. The resulting acyl chloride was slowly added to butylamine (2 mol), cooled in an ice bath, and the resulting mixture stirred overnight at room temp. Excess butylamine was removed in vacuo and the residue taken up in 200 mL of TBDME. This solution was extracted twice with 100 mL of 2 N hydrochloric acid, dried with sodium sulfate and the solvent removed in vacuo. The residue, a yellow oil, was purified by bulb-to-bulb distillation.

***N*-Butyl-2-methylpent-4-enamide (3b):** Yield: 30.1 g (88% over 2 steps) of a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz), 1.14 (d, *J* = 6.6 Hz), 1.34 (m, 2 H), 1.46 (m, 2 H),

2.14 (m, 1 H), 2.23 (sept, J = 6.6 Hz, 1 H), 2.38 (m, 1 H), 3.24 (m, 2 H), 5.05 (m, 2 H), 5.57 (s, 1 H), 5.75 (ddt, J = 17.4, 10.2, 6.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 17.3, 20.0, 31.7, 38.4, 39.1, 41.3, 116.7, 135.9, 175.0 ppm.

***N*-Butyl-3-methylpent-4-enamide (3c):** Yield: 30.9 g (91% over 2 steps) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.2 Hz), 1.05 (d, J = 6.6 Hz), 1.34 (m, 2 H), 1.46 (m, 2 H), 2.09 (dd, J = 13.8, 7.5 Hz, 1 H), 2.20 (dd, J = 13.9, 7.5 Hz, 1 H), 2.69 (m, 1 H), 3.24 (dt, J = 6.9, 5.7 Hz), 5.00 (m, 2 H), 5.61 (s, 1 H), 5.78 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 19.6, 20.0, 31.7, 34.7, 39.1, 43.9, 113.3, 142.9, 171.6 ppm. $C_{10}H_{19}NO$ (169.3): calcd. C 70.96, H 11.31, N 8.27; found C 70.67, H 11.33, N 8.01.

General Procedure for the Synthesis of *N*-Butylpent-4-enylamines 4: 80 mmol of the amide, dissolved in 50 mL of THF, was added dropwise to a suspension of lithium aluminium hydride (14.0 g, 0.37mol) in 300 mL of THF at 0 °C. The resulting mixture was then heated under reflux overnight and the excess hydride destroyed by careful addition of a solution of potassium hydroxide (7.0 g) in 33 mL of water. The resulting suspension was heated for another hour under reflux and then filtered hot through a Büchner funnel. The solid was taken up in 200 mL of THF, heated and filtered through a Büchner funnel again. The combined liquid phases were dried with sodium sulfate, the solvent was removed in vacuo and the residue purified by distillation.

***N*-Butyl-2-methylpent-4-enylamine (4b):** Yield: 9.29 g (75%) of a colourless liquid, b.p. 85 °C (50 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, J = 6.6 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H), 1.25 (br. s, 1 H), 1.28−1.55 (m, 4 H) 1.72 (pseudo-oct, J = 6.6 Hz, 1 H), 1.92 (m, 1 H), 2.15 (m, 1 H), 2.41 (dd, J = 11.7, 7.2 Hz, 1 H), 2.55 (dd, J = 11.7, 6.0 Hz, 1 H), 2.60 (m, 2 H), 5.02 (m, 2 H), 5.79 (ddt, J = 17.1, 10.2, 6.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.0, 20.5, 32.3, 33.2, 39.5, 49.9, 56.1, 115.7, 137.2 ppm. $C_{10}H_{21}N$ (155.3): calcd. C 77.35, H 13.63, N 9.02; found C 76.99, H 13.71, N 8.77. Furthermore the hydrochloride of the amine was prepared. $C_{10}H_{22}ClN$ (191.7): calcd. C 62.64, H 11.57, N 7.30; found C 62.57, H 11.91, N 6.90.

***N*-Butyl-3-methylpent-4-enylamine (4c):** Yield: 8.51 g (68%) of a colourless liquid, b.p. 77 °C (50 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.2 Hz, 3 H), 1.01 (d, J = 6.3 Hz, 3 H), 1.23 (s, 1 H), 1.35 (m, 2 H), 1.47 (m, 2 H), 1.51 (t, J = 6.9 Hz, 2 H), 2.20 (sept, J = 6.9 Hz, 1 H), 2.60 (m, 4 H) 4.95 (m, 2 H), 5.71 (ddd, J = 17.3, 10.4, 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.3, 20.5, 32.3, 36.1, 36.9, 48.0, 49.8, 112.6, 144.4 ppm. $C_{10}H_{21}N$ (155.3): calcd. C 77.35, H 13.63, N 9.02; found C 76.94, H 13.96, N 8.65. The hydrochloride of the amine was also prepared. $C_{10}H_{22}ClN$ (191.7): calcd. C 62.64, H 11.57, N 7.30; found C 62.28, H 11.92, N 6.91.

Ethyl 3-Phenylpent-4-enoate (5): A mixture of triethyl orthoacetate (0.5 mol), cinnamic alcohol (0.5 mol) and 1 mL of acetic acid was heated slowly to 150 °C. The reaction mixture was kept at this temperature until 2 equiv. (1.0 mol) of ethanol had distilled off (approx. 2 h). Some additional ethanol was then removed in vacuo to leave the pure product as a yellow oil which was used without further purification (98.9 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.2 Hz, 3 H), 2.68 (dd, J = 15.0, 7.5 Hz, 1 H), 2.74 (dd, J = 15.0, 7.8 Hz, 1 H), 3.86 (q, J = 7.2 Hz, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 5.04 (m, 1 H), 5.09 (m, 1 H), 5.98 (ddd, J = 17.4, 10.2, 7.2 Hz, 1 H),7.29 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 40.3, 45.6, 60.3, 114.7, 126.7, 127.6, 128.5, 140.3, 142.5, 171.7 ppm. These data are in accordance with published data.[23]

3-Phenylpent-4-en-1-ol (6): A solution of ethyl 3-phenylpent-4-enoate (**5**) (14.3 g, 70 mmol) in 50 mL of TBDME was added to a suspension of lithium aluminium hydride (2.65 g, 70 mmol) in 100 mL of TBDME at 0 °C through a dropping funnel. The reaction mixture was stirred overnight at room temperature before being poured onto 200 mL of ice/water. Sulfuric acid (5 M) was added until the alumina salts dissolved. The phases were then separated and the aqueous phase extracted twice with 100 mL of TBDME. The combined organic phases were dried with sodium sulfate, the solvent removed in vacuo and the residue purified by flash chromatography to give 10.58 g (65 mmol, 93%) of a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 1 H), 1.94 (m, 2 H), 3.45 (q, J = 7.2 Hz, 1 H), 3.61 (m, 2 H), 5.06 (m, 2 H), 5.96 (ddd, J = 17.6, 10.0, 7.6 Hz, 1 H), 7.21 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.0, 46.2, 60.8, 114.3, 126.3, 127.6, 128.5, 141.8, 143.7 ppm. $C_{11}H_{14}O$ (162.2): calcd. C 81.44, H 8.70; found C 81.46, H 8.75. These data are in accordance with published data.[23,24]

1-Tosyloxy-3-phenylpent-4-ene (7): Pyridine (8 mL, 0.1 mol) and 3-phenyl-4-pentenol (9.7 g, 0.060 mol) were added at 0 °C to a solution of *p*-toluenesulfonyl chloride (19 g, 0.1 mol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred overnight at room temp. and then poured into water (150 mL). The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2 (50 mL each). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash chromatography to give 16.2 g (85%) of a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (m, 2 H), 2.11 (s, 3 H), 3.37 (q, J = 7.8 Hz, 1 H), 3.98 (m, 2 H), 5.00 (m, 2 H), 5.85 (ddd, J = 17.7, 10.5, 7.5 Hz, 1 H), 7.06 (m, 2 H), 7.24 (m, 5 H), 7.72 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 34.2, 45.4, 68.4, 115.1, 126.6, 127.5, 127.8, 128.6, 129.7, 133.2, 140.4, 142.4, 144.6 ppm. $C_{18}H_{20}SO_3$ (316.4): calcd. C 68.33, H 6.37; found C 68.35, H 6.47. These data are in accordance with published data.[24]

1-Iodo-3-phenylpent-4-ene (8): Iodine (6.50 g, 25.5 mmol) was added to a mixture of 3-phenylpent-4-en-1-ol (**6**) (3.24 g, 20 mmol), imidazole (2.04 g, 30 mmol) and triphenylphosphane (6.72 g, 25.5 mmol) in 120 mL of toluene/acetonitrile (5:1) and the brown mixture heated under reflux for 5 min. After cooling to room temperature, 50 mL of TBDME was added and the solution extracted three times with a 10% aqueous solution of sodium sulfite (50 mL each). The organic layer was washed with water and brine (50 mL each) and dried with sodium sulfate. After removing the solvent in vacuo, 4.23 g (15.5 mmol, 78%) of the pure iodide **8** was obtained by flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (m, 2 H), 3.07 (m, 2 H), 3.43 (q, J = 7.2 Hz, 1 H), 5.10 (m, 2 H), 5.91 (ddd, J = 17.4, 10.2, 7.8 Hz, 1 H), 7.25 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.6, 38.8, 50.0, 115.1, 126.7, 127.6, 128.7, 140.4, 142.5 ppm. $C_{11}H_{13}I$ (272.1): calcd. C 48.55, H 4.82; found C 48.56, H 4.99. These data are in accordance with published data.[23]

***N*-Butyl-3-phenylpent-4-enylamine (4f):** The iodide **8** (4.00 g, 14.7 mmol) was dissolved in 50 mL of dichloromethane and this solution added to 50 mL of butylamine at 0 °C. After stirring the reaction mixture overnight, the solvent and excess butylamine were removed in vacuo and the residue was taken up in 100 mL of TBDME. This solution was extracted three times with 100 mL of 5% aqueous sodium hydroxide solution, dried with sodium sulfate and the solvent removed in vacuo. From the residue 3.12 g (14.4 mmol, 99%) of the amine **4f** was obtained after flash chroma-

tography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 1.01 (br. s, 1 H), 1.32 (m, 2 H), 1.44 (m, 2 H), 1.89 (m, 2 H), 2.54 (m, 2 H), 2.61 (m, 2 H), 3.33 (q, *J* = 7.5 Hz, 1 H), 5.03 (m, 2 H), 5.96 (ddd, *J* = 18.0, 10.5, 7.8 Hz, 1 H), 7.20 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.4, 32.3, 35.6, 47.8, 48.0, 49.6, 114.0, 126.2, 127.5, 128.4, 142.1, 144.1 ppm. $C_{15}H_{23}N$ (217.4): calcd. C 82.89, H 10.67, N 6.44; found C 82.59, H 10.80, N 6.24.

1-Phenylpent-4-en-1-ol (9): 1-Bromo-3-butene (25.0 g, 135 mmol) in 50 mL of diethyl ether was added at 0 °C to a suspension of magnesium turnings (3.28 g, 135 mmol) in 150 mL of diethyl ether over 1 h. The solution was stirred at room temperature for 2 h and then cooled to 0 °C again before benzaldehyde (10.6 g, 100 mmol) was added slowly. The reaction mixture was stirred overnight and then poured onto 200 mL of ice/water. Sulfuric acid (5 M) was added until the magnesium salts dissolved. After separation of the phases, the aqueous phase was extracted twice with 50 mL of TBDME. The combined organic phases were dried with sodium sulfate and the solvent was removed in vacuo. The residue was subjected to flash chromatography to yield 13.7 g (84 mmol, 84%) of pure 1-phenylpent-4-en-1-ol (**9**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (m, 1 H), 1.85 (m, 1 H), 2.10 (m, 2 H), 2.16 (s, 1 H), 4.63 (dd, *J* = 7.5, 5.7 Hz, 1 H), 4.98 (m, 2 H), 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 7.30 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.9, 38.0, 73.9, 114.8, 125.9, 127.5, 128.4, 138.1, 144.6 ppm. These data are in accordance with published data.[25]

***N*-Butyl-1-phenylpent-4-enylamine (4d):** Iodine (6.5 g, 25.5 mmol) was added to a mixture of 1-phenylpent-4-en-1-ol (**9**) (3.24 g, 20 mmol), imidazole (2.04 g, 30 mmol) and triphenylphosphane (6.72 g, 25.5 mmol) in 120 mL of toluene/acetonitrile (5:1) and the brown mixture heated under reflux for 5 min. After cooling to room temperature, 50 mL of TBDME was added and the solution extracted three times with a 10% aqueous solution of sodium sulfite (50 mL each). The organic layer was washed with water and brine (50 mL each) and dried with sodium sulfate. After removing the solvent in vacuo, the crude residue was taken up in 50 mL of dichloromethane. This solution was added to 50 mL of butylamine at 0 °C. After stirring the reaction mixture overnight, the solvent and excess butylamine were removed in vacuo and the residue was taken up in 100 mL of TBDME. This solution was extracted three times with 100 mL of 5% aqueous sodium hydroxide solution, dried with sodium sulfate and the solvent removed in vacuo. From the residue 1.14 g (5.24 mmol, 26% over two steps) of the amine **4d** were obtained after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3 H), 1.28 (m, 2 H), 1.40 (br. s, 1 H), 1.43 (m, 2 H), 1.74 (m, 1 H), 1.84 (m, 1 H), 1.95 (m, 2 H), 2.42 (m, 2 H), 3.59 (dd, *J* = 8.4, 5.6 Hz, 1 H), 4.95 (m, 2 H), 5.77 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 7.29 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 20.4, 30.5, 32.2, 37.1, 47.4, 63.0, 114.6, 127.0, 127.3, 128.3, 138.4, 144.4 ppm. $C_{15}H_{23}N$ (217.4): calcd. C 82.89, H 10.67, N 6.44; found C 82.57, H 10.84, N 6.53.

General Procedure for the Synthesis of *N*-Butyl-*N*-chloropent-4-enylamines 1: NCS (33 mmol) was added at 0 °C to a solution of amine (30 mmol) in 100 mL of dichloromethane and the resulting suspension stirred at this temperature for 2 h. The solvent was removed in vacuo and the residue taken up in 100 mL of pentane and filtered. The residue was washed with another 50 mL of pentane and the liquid phases were combined. After removal of the solvent in vacuo, the residue was purified by flash chromatography [eluent: pentane/TBDME (10:1)]. The chloroamines were obtained as colourless oils that could be stored at −30 °C. Due to their instability, satisfactory elemental analyses of the *N*-chloroamines could not be obtained.

***N*-Butyl-*N*-chloro-2-methylpent-4-enylamine (1b):** Yield: 5.0 g (88%) of a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.3 Hz, 3 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 1.39 (pseudo-sext, 7.2 Hz, 2 H), 1.66 (m, 2 H), 1.88−2.12 (m, 2 H), 2.26 (m, 1 H), 2.66 (dd, *J* = 12.9, 6.9 Hz, 1 H), 2.80 (dd, *J* = 13.2, 6.3 Hz, 1 H), 2.93 (m, 2 H), 5.04 (m, 2 H), 5.81 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 17.4, 20.0, 30.0, 31.6, 38.8, 64.5, 70.1, 116.1, 136.6 ppm.

***N*-Butyl-*N*-chloro-3-methylpent-4-enylamine (1c):** Yield: 5.1 g (90%) of a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 7.2 Hz, 3 H), 1.37 (sext, 7.2 Hz, 2 H), 1.58−1.78 (m, 4 H), 2.25 (m, 1 H), 2.91 (t, *J* = 7.0 Hz, 4 H), 4.97 (m, 2 H), 5.96 (dd, *J* = 10.4, 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.0, 20.4, 30.0, 34.5, 35.5, 62.3, 64.2, 113.1, 144.0 ppm.

***N*-Butyl-*N*-chloro-1-phenylpent-4-enylamine (1d):** Yield: 6.86 g (91%) of a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H), 1.29 (m, 2 H), 1.60 (m, 2 H), 1.92 (m, 1 H), 1.95 (m, 2 H), 2.29 (m, 1 H), 2.72 (m, 2 H), 3.84 (m, 1 H), 4.96 (m, 2 H), 5.78 (ddt, *J* = 17.6, 10.4, 6.8 Hz, 1 H), 7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 19.9, 29.8, 30.4, 33.0, 60.2, 73.6, 114.9, 127.9, 128.1, 128.9, 138.1, 139.1 ppm.

***N*-Butyl-*N*-chloro-3-phenylpent-4-enylamine (1f):** Yield: 6.41 g (85%) of a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.5 Hz, 3 H), 1.34 (m, 2 H), 1.62 (m, 2 H), 2.06 (m, 2 H), 2.86 (m, 4 H) 3.41 (q, *J* = 7.2 Hz, 1 H), 5.05 (m, 2 H), 5.95 (ddd, *J* = 16.8, 10.5, 7.5 Hz, 1 H), 7.22 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.9, 30.0, 33.3, 62.0, 63.3, 64.1, 114.4, 126.3, 127.6, 128.5, 141.7, 143.7 ppm.

General Procedure for the Cyclisation Reaction Leading to 3-Chloropiperidines 10: The *N*-chloroamine (3 mmol) was added at 60 °C (temperature of the oil bath) to a suspension of copper(I) chloride (30 mg) in 5 mL of THF. The solution immediately turned blue-green and it was kept at the same temperature for 12 h. After cooling to room temp., silica (approx. 3 g) was added and the solvent removed in vacuo. The product was isolated from the residue bound to the silica by flash chromatography [eluent: pentane/TBDME (10:1 then 3:1 and 1:1)].

***N*-Butyl-3-chloro-5-methylpiperidine (10b):** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 1.15 (q, *J* = 12.0 Hz, 1 H), 1.29 (sext, *J* = 7.8 Hz, 2 H), 1.45 (m, 2 H), 1.54 (t, *J* = 10.8 Hz, 1 H), 1.76 (m, 1 H), 1.90 (t, *J* = 10.8 Hz, 1 H), 2.20 [d (with fine-splitting), *J* = 12.8 Hz, 1 H], 2.35 (td, *J* = 7.8, 1.2 Hz, 2 H), 2.80 [d (with fine-splitting), *J* = 10.8 Hz, 1 H), 3.18 [d (with fine-splitting), *J* = 10.8 Hz, 1 H), 3.94 (tt, *J* = 11.2, 4.4 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 19.0, 20.7, 29.0, 31.4, 44.0, 55.4, 57.9, 60.6, 61.3 ppm. Minor isomer **10b′**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.8 Hz, 3 H), 0.91 (d, *J* = 7.2 Hz, 3 H), 1.30 (m, 2 H), 1.47 (m, 3 H), 1.82 (m, 1 H), 1.91 (dt, *J* = 14.4, 4.2 Hz, 1 H), 2.18 (m, 1 H), 2.39 (m, 2 H), 2.70 [d (broad), 9.6 Hz, 1 H), 2.84 [d (broad), 7.8 Hz, 1 H), 4.29 (quint, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 18.7, 20.6, 26.7, 28.8, 40.7, 56.1, 58.1, 59.9, 60.9 ppm. $C_{10}H_{20}ClN$ (189.7): calcd. C 63.61, H 10.63, N 7.38; found C 63.16, H 11.15, N 7.26. The hydrochloride salt was also prepared. $C_{10}H_{21}Cl_2N$ (189.7): calcd. C 53.10, H 9.36, N 6.19; found C 53.04, H 9.20, N 6.02.

***N*-Butyl-3-chloro-4-methylpiperidine (10c):** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 1.29 (sext, *J* = 7.8 Hz, 2 H), 1.44 (m, 1 H), 1.48 (m, 2 H), 1.50 (m,

1 H), 1.75 [d (with fine-splitting), J = 13.8 Hz, 1 H), 1.99 (td, J = 12.0, 2.4 Hz, 1 H), 2.09 (t, J = 11.2 Hz, 1 H), 2.37 (m, 2 H), 2.88 [d (with fine-splitting), J = 11.4 Hz, 1 H), 3.21 (ddd, J = 10.8, 4.2, 1.8 Hz, 1 H), 3.61 (td, J = 10.8, 4.2 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 19.1, 20.6, 28.9, 33.7, 39.8, 53.3, 57.8, 61.5, 63.1 ppm. Minor isomer **10c′**: ^{1}H NMR (600 MHz, $CDCl_3$) (selected signal): δ = 4.20 (m, 1 H). $C_{10}H_{20}ClN$ (189.7): calcd. C 63.61, H 10.63, N 7.38; found C 63.34, H 11.02, N 7.07.The hydrochloride salt was also prepared. $C_{10}H_{21}Cl_2N$ (226.2): calcd. C 53.10, H 9.36, N 6.19; found C 52.91, H 9.44, N 5.97.

***N*-Butyl-3-chloro-5-phenylpiperidine (10d):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, J = 7.2 Hz, 3 H), 1.13 (m, 2 H), 1.34 (m, 2 H), 1.66 (m, 2 H), 1.81 (m, 1 H), 1.96 (ddd, J = 12.8, 8.4, 4.8 Hz, 1 H), 2.23 (t, J = 10.8 Hz, 1 H), 2.28 (m, 1 H), 2.40 (ddd, J = 16.0, 13.2, 6.8 Hz, 1 H), 3.05 (dd, J = 7.2, 3.2 Hz, 1 H), 3.43 [d (with fine splitting), J = 10.8 Hz, 1 H), 4.06 (tt, J = 10.8, 4.0 Hz, 1 H), 7.29 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 20.3, 28.1, 36.0, 36.2, 54.3, 56.0, 60.7, 67.5, 127.1, 127.5, 128.4, 143.9 ppm. HRMS (Quattro-LC, Electrospray): *m/z* calcd. for $C_{15}H_{22}NCl + H^+$ 252.1519/254.1494; found 252.1498/254.1473.

***N*-Butyl-3-chloro-4-phenylpiperidine (10f):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.2 Hz, 3 H), 1.35 (m, 2 H), 1.51 (m, 2 H), 1.88 (m, 2 H), 2.10 (m, 1 H), 2.24 (t, J = 10.8 Hz, 1 H), 2.43 (m, 2 H), 2.61 (m, 1 H), 2.98 [d, (with fine-splitting), 11.1 Hz, 1 H), 3.38 (ddd, J = 11.1, 4.5, 1.5 Hz, 1 H), 4.14 (td, J = 11.1, 4.5 Hz, 1 H), 7.30 (m, 5H ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.6, 29.0, 34.4, 52.1, 53.4, 57.8, 60.4, 61.9, 126.9, 127.5, 128.4, 142.4 ppm.

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