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Highly efficient, base-catalysed, intramolecular hydroamination of non-activated olefins

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Dedicated fondly and with deep respect to Professor Csaba Szántay, at the occasion of his 80th Birthday

Abstract

The intramolecular hydroamination of a large variety of non-activated alkenes can be efficiently catalysed by small amounts of lithium bases, providing smoothly and in high yields the corresponding five- and six-membered ring heterocycles. Fused and bridged bicyclic amines, of varying ring sizes, can be readily prepared either by a sequential hydroamination process or by a tandem, double addition reaction.

1. Introduction

Addition reactions are powerful processes that fulfil a number of the important requirements beseeched by environmentally benign transformations.[1] Indeed, addition reactions are 100% atom-economical, in that both starting materials merge into a single adduct, provide little or no by-products and can typically be carried out either neat or in innocuous solvents.[2] Among such processes, the hydroamination of terminal, non-functionalised, alkenes occupies a cardinal position.[3] From an environmental and economical viewpoint, the addition of an N–H unit onto a carbon–carbon double bond is an ideal transformation, which affords the corresponding amine, in a single step, from readily available starting materials.[4]

Unfortunately, despite an enormous amount of work, only limited success has been achieved so far in the *intermolecular* hydroamination of non-activated alkenes, which still requires forcing conditions, including elevated temperatures (up to 180 °C) and high pressures (up to 800 bars).[5] It is noteworthy that much milder conditions are necessary for the addition of amines to alkynes, dienes, norbornene and styrene derivatives.[6] However, it must be borne in mind that, in sharp contrast to ethylene or 1-hexene, these olefins *are activated substrates*.[7]

Though essentially thermoneutral, the hydroamination reaction suffers from the serious drawback of high activation energy, mostly due to the electronic repulsions between the lone pairs of the approaching nucleophile and the high-electron density of the olefinic π-system.[8] Henceforth, catalysts that could efficiently lower this activation barrier would provide an easy entry into the important class of nitrogen-bearing compounds. This endeavour, which has been pursued by numerous research groups worldwide, culminated in the discovery of remarkably active and efficient catalytic systems.[9–11] However, many of these unique catalysts suffer from a number of shortcomings, such as extreme sensitivity towards moisture or air, limited stability and tolerance towards nucleophilic solvents, difficult and lengthy preparation, high cost and moderate efficiency (turnover number or frequency).[12]

A few years ago, we have reported that small amounts of *n*-BuLi-catalysed the *intramolecular* hydroamination[13] of several ω-unsaturated amines, providing the corresponding pyrrolidines and piperidines in moderate to good yields (Fig. 1).[14]

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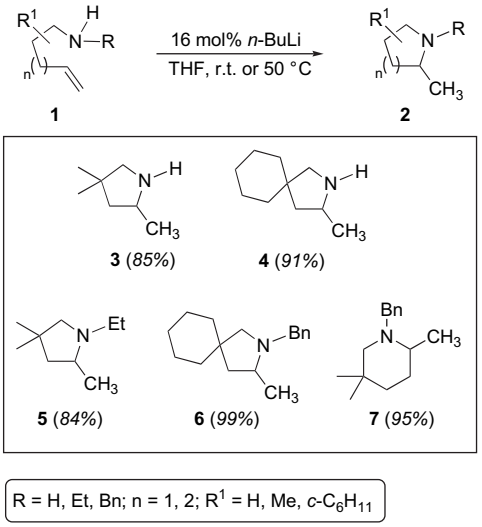


Figure 1.

As can be seen, a number of primary and secondary amines underwent smooth cyclisation under these conditions, with secondary amines reacting faster and more efficiently than primary ones, probably because of the higher nucleophilicity of the corresponding lithiated amides. Moreover, whilst pyrrolidine formation occurred readily, delivering adducts **3**–**6** in excellent yields, cyclisation to generate the analogous six-membered ring heterocycles proved to be particularly difficult and only piperidine **7** could be obtained in good yields. To the best of our knowledge, only one example of a *n*-BuLi-catalysed intramolecular hydroamination of a non-activated alkene had been reported in the literature prior to our contribution by Suginome and co-workers.[10h]

Whilst these results open exciting new avenues for the construction of a range of nitrogen heterocycles, it is important to note that all these substrates benefit strongly from the Thorpe–Ingold effect and its absence leads to a significant erosion in both the rate and yields of the hydroamination reaction (Fig. 2).

Indeed, treatment of 1-amino-4-pentene **8** with *n*-BuLi, in THF at 50 °C, provided pyrrolidine **9** in only 32% yield, accompanied by the isomerised derivative **10** as the major component (68%). The addition of one substituent to the chain linking the amine to the terminal alkene is enough to invert the ratio of cyclised versus isomerised product, though pyrrolidine **12** (65%) is never obtained quantitatively and is always contaminated by the internal olefin **13** (35%).

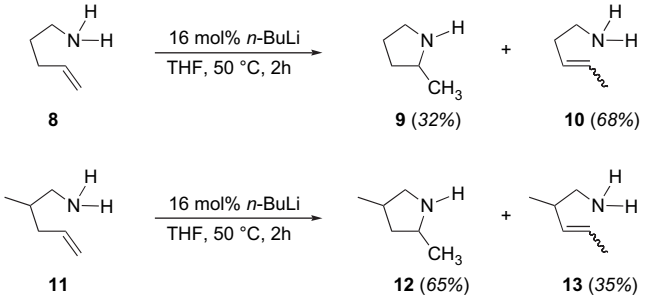


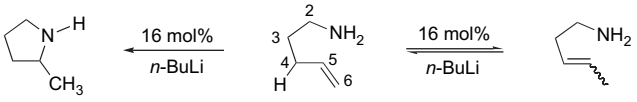
Figure 2.

In order to establish a truly efficient and broadly applicable methodology for the assembly of a large variety of five- and six-membered ring nitrogen heterocycles, it became crucial to delineate and control the parameters responsible for the cyclised versus isomerised products ratio and to define optimal conditions for quantitative ring closure. In this article, we wish to disclose a new protocol, based upon a deeper mechanistic understanding of this unique base-catalysed hydroamination reaction, and illustrate its wide applicability by the generation of a large number of pyrrolidines and piperidines as well as by the efficient preparation of a range of fused and bridged bicyclic nitrogen derivatives.

2. Results and discussion

At the onset of our work, the cyclisation of amine **8**[15] was followed by ^{1}H NMR spectroscopy, in THF-d_8. Much to our surprise, a rapid equilibrium was established between **8** and the isomerised alkenes **10*E*** and **10*Z***. Only traces of the cyclised product **9** could be detected after 24 h (Fig. 3, entry 1).

Warming up the reaction mixture to 50 °C led to an increase in adduct **9**. It appears therefore that abstraction of H4 by the lithiated amide proceeds with a lower activation energy than its addition at C5.[16] Increasing the temperature provides more energy to overcome this barrier and pyrrolidine **9**, the thermodynamic product, slowly accumulates (Fig. 3, entry 2). Using an even higher boiling solvent, such as THP (tetrahydropyran) led to a further improvement (Fig. 3, entry 3), which unfortunately proved to be a ceiling. Indeed, performing the cyclisation in toluene (110 °C) afforded essentially the same ratio of **9** and **10** as that obtained in hot THF (50 °C), whilst employing MeTHP (2-methyl tetrahydropyran, 110 °C) provided only the isomerised alkenes **10*E*** and **10*Z*** (not shown in Fig. 3). Several other solvents proved equally unsuitable.



Entry	Solvent	Temp.	**10** / **9**	Conv.
1	THF	20 °C	93 : 7	87%
2	THF	50 °C	68 : 32	>95%
3	THP	90 °C	29 : 71	>99%
4	toluene	110 °C	66 : 34	>99%
5	THP : Toluene (1:1)	110 °C	<5 : >95	>99%

Figure 3.

At this stage, two important observations were fortuitously made that proved to be of paramount importance for devising optimal reaction conditions. First of all, quantitative lithiation of **8** can be smoothly realised by adding to this amine 1 equiv of *n*-BuLi, in THF at 20 °C. *However, even under prolonged*

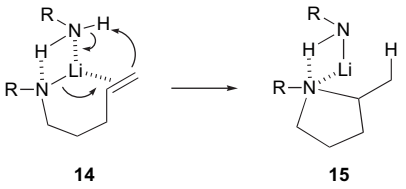


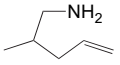
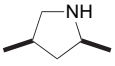
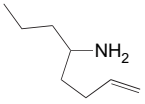
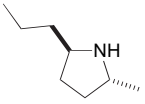
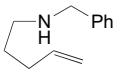
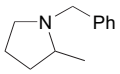
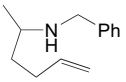
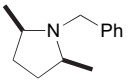
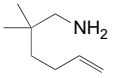
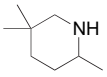
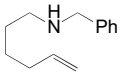
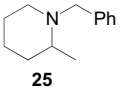
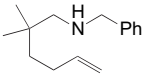
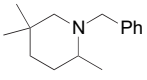
Figure 4.

heating at reflux, the fully deprotonated amine never underwent the hydroamination reaction. This observation strongly suggested that no true carbanionic species was generated during the transformation of **8** into **9**.[17] *Moreover, addition of a small amount (10–20 mol %) of an amine, such as diisopropyl amine, to the refluxing solution of lithiated **8** led to its cyclisation into **9***. Finally, treatment of **8** with either catalytic quantities or with 1 equiv of LDA smoothly afforded adduct **9**, in essentially the same rate and yield. It therefore transpires that the addition of the lithiated amide onto the carbon–carbon double bond of **8** can occur only if the developing negative charge on C6 of the terminal olefin in the transition state is immediately neutralised by a proton provided by a coordinated, proximal amine (Fig. 4).[18,19]

To form the proper aggregate in solution and to generate enough of it to ensure a smooth reaction may not be a trivial problem since such a construct should be highly solvent-dependant.[20] Screening several solvents and solvent mixtures rapidly provided a solution in the form of a 1:1 mixture of THP/toluene. Under these conditions, quantitative formation of the desired adduct was eventually achieved for the first time and the α-methyl pyrrolidine **9** could be isolated in an excellent 86% yield (Fig. 3, entry 5). Having delineated suitable conditions for the efficient hydroamination of 1-amino-4-pentene **8**, attention was then turned towards exploring the scope and limitations of this novel protocol. Some selected results are collected in Table 1.

As can be seen in Table 1, a variety of substituted pyrrolidines can be efficiently produced by the *n*-BuLi-catalysed hydroamination reaction of the corresponding ω-unsaturated amines (entries 1–5). It is noteworthy that both primary and secondary amine precursors can be employed, leading to the desired adducts in excellent yields. In all cases, complete conversion was observed. Interestingly, secondary amines cyclise faster than primary ones. The power of the new protocol can be better appreciated when considering that attempted ring closure of **11** under the 'old' conditions provided **12** in only 65% yield. But perhaps, the most dramatic illustration of the superiority of this new methodology can be seen in the formation of the piperidine system (Table 1, entries 6, 7 and 9). Indeed, such a ring closure either proved impossible to achieve under the 'old' conditions or proceeded in mediocre yield. This cyclisation was effective only when the amine was secondary and benefited from the Thorpe–Ingold effect (Table 1, entry 8). However, adding 16 mol % of *n*-BuLi[21] to a THP/toluene (1:1) solution of amine **24** led to its quantitative conversion into the six-membered ring heterocycle **25**, which could be isolated in a gratifying 83% yield (Table 1, entry 7). Even more impressive is the base-catalysed cyclisation of **28**, bearing a primary amine and a highly hindered terminal alkene, affording adduct **29** in up to 78% conversion (Table 1, entry 9).

Table 1
n-BuLi-catalysed hydroamination of ω-unsaturated amines

Entry	Substrate	Product	Yield[a] (%)
1	 **8**	 **9**	86
2	 **11**	 **12**	93[b]
3	 **16**	 **17**	73[c]
4	 **18**	 **19**	79
5	 **20**	 **21**	79[d]
6	 **22**	 **23**	63[e]
7	 **24**	 **25**	83
8	 **26**	 **27**	95[f]
9	 **28**	 **29**	78[e]

[a] All yields are for pure, isolated compounds. Unless stated otherwise, all the conversions are quantitative and the reactions are performed using 16 mol % *n*-BuLi (1.6 M in hexanes) in THP/toluene (1:1, 0.5 M solutions) at 110 °C (bath temperature).
[b] dr=1.4:1.
[c] dr=2.6:1.
[d] dr=5.7:1.
[e] Conversion (%).
[f] Performed in refluxing THF.

The synthetic utility of this method can be further illustrated by the rapid assembly of the alkaloid (±)-dihydropinidine **31** from a readily available precursor, the primary amine **30** (Fig. 5).

Thus, treatment of **30** with *n*-BuLi, under the usual conditions, for 48 h, delivered the desired natural product **31** in 85%

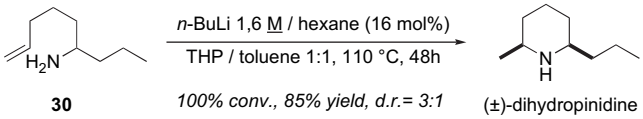


Figure 5.

isolated yield, as a mixture of cis and trans isomers in a 3:1 diastereomeric ratio.

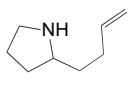
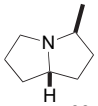
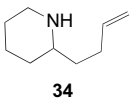
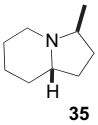
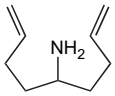
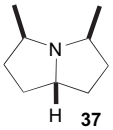
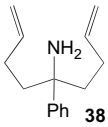
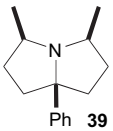
Whilst five- and six-membered monocyclic nitrogen derivatives can now be readily manufactured from easily accessible ω-unsaturated amines, we wondered if bicyclic structures, akin to the pyrrolizidine and indolizidine alkaloids,[22] could also be rapidly assembled using this novel hydroamination protocol. Some selected results are collected in Table 2.

As can be seen from Table 2, substituted pyrrolidine **32** and piperidine **34** underwent smooth cyclisation, in the presence of catalytic quantities of *n*-BuLi, in THP/toluene, affording the desired, fused bicyclic adducts **33** and **35** in excellent yields and with high or even complete diastereocontrol (Table 2, entries 1 and 2). Even more interesting were the cascade hydroaminations of amines **36** and **38**, which upon exposure to small amounts of *n*-BuLi, produced in high overall yield, the substituted pyrrolizidine derivatives **37** and **39** (Table 2, entries 3 and 4). Interestingly, in these two cases, only the *meso* compound was formed with complete stereocontrol. These double cyclisations open new vistas for the application of our base-catalysed hydroamination reaction to the efficient and concise synthesis of a variety of fused alkaloids and alkaloid-like structures.

To further probe the limits of our method, the assembly of a bridged bicyclic amine, by a double intramolecular hydroamination reaction, was attempted (Fig. 6).

Thus, treatment of the primary amine **40** with *n*-BuLi in dioxane, at room temperature for 3 h, afforded quantitatively the substituted pyrrolidine **41**. In stark contrast, repeating this reaction in THP/toluene, at 90 °C for 16 h, led to the smooth formation of the bridged bicyclic adducts **42** and **43**

Table 2
Synthesis of fused bicyclic amines by *n*-BuLi-catalysed hydroamination

Entry	Substrate	Product	Yield[a] (%)
1	 **32**	 **33**	83[b]
2	 **34**	 **35**	76[c]
3	 **36**	 **37**	85[b]
4	 **38**	 **39**	84[b]

[a] All yields are for pure, isolated compounds. Unless stated otherwise, all the conversions are quantitative and the reactions are performed using 16 mol % *n*-BuLi (1.6 M in hexanes) in THP/toluene (1:1, 0.5 M solutions) at 110 °C (bath temperature).
[b] A single diastereoisomer is obtained.
[c] dr=14:1.

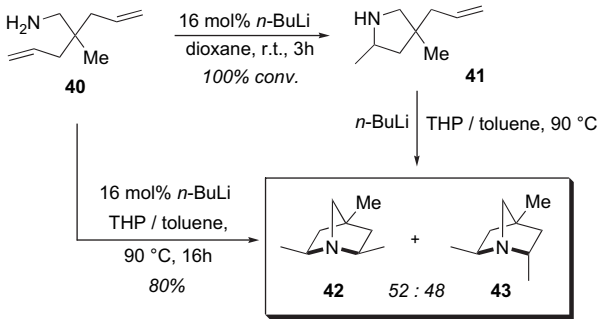


Figure 6.

in an almost 1:1 diastereomeric ratio. Interestingly, exposure of **41** to the cyclisation conditions afforded **42** and **43** in similar yields and diastereomeric ratios, thereby confirming the passage through **41** in the direct conversion of **40** into **42** and **43**.

3. Conclusions

In summary, we have disclosed a novel, base-catalysed intramolecular hydroamination reaction of non-activated alkenes that offers an efficient access to a large variety of substituted pyrrolidines and piperidines, as well as to a range of fused and bridged bicyclic amine derivatives akin to the pyrrolizidine and indolizidine alkaloid families, from readily available simple ω-unsaturated amines. Cascade hydroamination reactions also occur smoothly with excellent levels of diastereocontrol. Ongoing efforts are now aimed at expanding further the scope of this unique transformation and applying it to the efficient synthesis of several relevant natural products.

4. Experimental

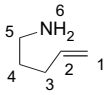
4.1. General information

All compounds (Acros, Aldrich and Fluka) were used as received. THF, THP and dioxane were distilled under argon from sodium benzophenone ketyl. All the primary amine substrates were dried over Na/K amalgam and distilled (vacuum transferred) immediately prior to use. Flash chromatography was performed on silica gel 60 (40–63 μm) (ROCC).

1 ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-2000 (working frequency 300 and 75 MHz, respectively), on a Bruker AC-250 (working frequency 250 and 62.5 MHz, respectively), on a Brucker AC-300 Avance II (working frequency 300 and 75 MHz, respectively) or on a Brucker AM-500 (working frequency 500 and 125 MHz, respectively) at ambient temperature in $CDCl_3$ (Aldrich).
2 Mass spectra were recorded on a Finigan TSQ 7000.
3 All reactions were carried out under an atmosphere of argon in flame-dried apparatus with magnetic stirring, unless otherwise indicated.
4 The identity of every product was confirmed by comparison with literature spectroscopic data. The structure determination of new compounds was made with the help of 2D-COSY, HMQC, HMBC, 2D-NOESY and NOEDIFF experiments.

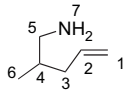
All the amino-alkene substrates have been prepared according to known procedures.

*4.1.1. 1-Amino-4-pentene (**8**)*



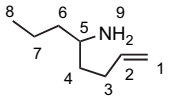
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.81 (1H, ddt, J=17.2, 10.5, 6.7 Hz, H-2), 5.00–4.83 (2H, m, H-1), 2.61 (2H, t, J=6.7 Hz, H-5), 2.08 (2H, q (dt), J=7.2 Hz, H-3), 1.45 (2H, quint (tt), J=7.2 Hz, H-4), 1.00 (2H, s, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 138.2 (C-2), 114.5 (C-1), 41.6 (C-5), 32.8 and 31.1 (C-3 and C-4). MS (CI, 70 eV) *m/z* (relative intensity, %): 86 (M+1, 100), 69 (90). IR (KBr) ν (cm^{-1}): 3369 [w], 3292 [w], 3077 [m], 2976–2853 [s], 1641 [s], 1611 [w], 1449 [w], 1439 [w], 995 [m], 910 [s], 820 [s]. CAS: [22537-07-1].

*4.1.2. 1-Amino-2-methyl-4-pentene (**11**)*



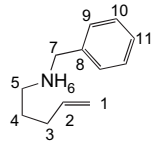
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.78 (1H, ddt, J=16.7, 10.0, 6.7 Hz, H-2), 5.03–4.89 (2H, m, H-1), 2.52 (1H, dd, J=12.0, 6.2 Hz, H-5a), 2.44 (1H, dd, J=12.0, 6.2 Hz, H-5b), 2.33–2.10 (1H, m, H-3a), 1.90–1.77 (1H, m, H-3b), 1.45 (1H, oct (qtt), J=6.7 Hz, H-4), 0.99 (2H, s, H-7), 0.86 (3H, d, J=6.7 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 136.9 (C-2), 115.7 (C-1), 48.0 (C-5), 38.8 (C-3), 36.2 (C-4), 17.3 (C-6). MS (CI, 70 eV) *m/z* (relative intensity, %): 100 (M+1, 100), 83 (30). IR (KBr) ν (cm^{-1}): 3381 [w], 3296 [w], 3077 [m], 2958–2872 [s], 1640 [s], 1459 [m], 1440 [m], 1379 [w], 1261 [m], 995 [s], 911 [s], 803 [s], 733 [s]. CAS: [79116-24-8].

*4.1.3. 5-Aminooctene (**16**)*



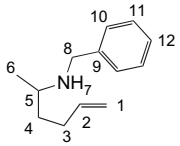
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.81 (1H, ddt, J=17.0, 10.3, 6.7 Hz, H-2), 5.11–4.08 (2H, m, H-1), 2.77–2.62 (1H, m, H-5), 2.24–1.96 (2H, m, H-3), 1.57–1.19 (6H, m, H-4, 6 and 7), 1.13 (2H, br s, H-9), 0.90 (3H, t, J= 6.8 Hz, H-8). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 139.0 (C-2), 114.6 (C-1), 50.6 (C-5), 40.1 and 37.4 (C-4 and C-6), 30.7 (C-3), 19.4 (C-7), 14.4 (C-8). MS (APCI, 70 eV) *m/z* (relative intensity, %): 128 (M+1, 5), 126 (15), 111 (25), 69 (100). IR (film) ν (cm^{-1}): 3335 [w], 3078 [w], 2957–2870 [s], 1641 [m], 1618 [m], 1572 [m], 1475 [s], 1306 [m], 995 [s], 717 [m]. HRMS (APCI$^+$, MH^+): ($C_8H_{18}N$) calcd: 128.1439; found: 128.1436.

*4.1.4. 1-Benzylamino-4-pentene (**18**)*



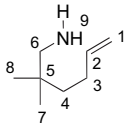
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.40–7.15 (5H, m, Ph), 5.81 (1H, ddt, J=16.7, 10.0, 6.7 Hz, H-2), 5.07–4.88 (2H, m, H-1), 3.78 (2H, s, H-7), 2.64 (2H, t, J=7.2 Hz, H-5), 2.10 (2H, q (dt), J=7.7 Hz, H-3), 1.60 (2H, quint (tt), J=7.2 Hz, H-4), 1.33 (1H, s, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 140.4 (C-8), 138.3 (C-2), 128.2 and 127.9 (C-9 and C-10), 126.7 (C-11), 114.5 (C-1), 54.0 and 48.9 (C-5 and C-7), 31.6 and 29.3 (C-3 and C-4). MS (CI, 70 eV) *m/z* (relative intensity, %): 190 (M+1, 100), 134 (12), 91 (10). IR (KBr) ν (cm^{-1}): 3323 [w], 3064 [m], 3027 [m], 2963–2845 [s], 1641 [m], 1495 [m], 1453 [s], 1374 [m], 995 [m], 910 [s], 732 [s], 697 [s]. HRMS (EI+, $M^{+\bullet}$): ($C_{13}H_{19}N$) calcd: 190.1595; found: 190.1591. CAS: [489428-62-8].

*4.1.5. 5-Benzylaminohexene (**20**)*



^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.38–7.17 (5H, m, Ph), 5.80 (1H, ddt, J=17.2, 10.0, 6.7 Hz, H-2), 5.05–4.86 (2H, m, H-1), 3.82 (1H, A part of AB, J=12.9 Hz, H-8a), 3.73 (1H, B part of AB, J=12.9 Hz, H-8b), 2.70 (1H, sext (qt), J=6.2 Hz, H-5), 2.19–1.98 (2H, m, H-3), 1.65–1.19 (3H, m, H-4 and H-7), 1.08 (3H, d, J=12.9 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 140.7 (C-9), 138.6 (C-2), 128.2 and 128.0 (C-10 and C-11), 126.7 (C-12), 114.3 (C-1), 52.0 (C-5), 51.3 (C-8), 36.2 (C-4), 30.3 (C-3), 20.3 (C-6). MS (CI, 70 eV) *m/z* (relative intensity, %): 176 (M+1, 100), 174 (8), 120 (10), 91 (15). IR (KBr) ν (cm^{-1}): 3311 [w], 3076 [m], 3064 [m], 3027 [m], 2999–2813 [s], 1640 [s], 1495 [s], 1453 [s], 1120 [s], 1028 [m], 994 [m], 911 [s], 733 [s], 698 [s]. CAS: [54436-58-7].

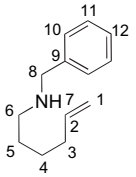
*4.1.6. 1-Amino-2,2-dimethyl-5-hexene (**22**)*



^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.80 (1H, ddt, J=16.8, 9.9, 6.6 Hz, H-2), 5.02–4.82 (2H, m, H-1), 2.38 (2H, s, H-6), 2.04–1.93 (2H, m, H-3), 1.33–1.25 (2H, m, H-4), 0.95 (2H, br s, H-9), 0.82 (6H, s, H-7 and H-8). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 139.1 (C-2), 113.7 (C-1), 52.6 (C-6), 38.4 (C-4), 34.3 (C-5), 28.3 (C-3), 24.5 (C-7 and C-8). MS (EI, 70 eV) *m/z* (relative intensity, %): 127 ($M^{+\bullet}$,

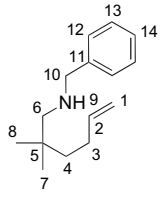
8), 112 (75), 95 (30), 70 (73), 55 (100). IR (film) ν (cm^{-1}): 3394 [w], 3316 [w], 3078 [m], 2955–2852 [s], 1641 [m], 1473 [m], 1364 [m], 994 [m], 909 [s], 813 [m], 733 [w]. CAS: [141511-50-4].

*4.1.7. 1-Benzylamino-5-hexene (**24**)*



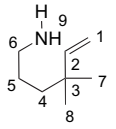
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.36–7.20 (5H, m, Ph), 5.80 (1H, ddt, J=16.9, 10.3, 6.7 Hz, H-2), 5.05–4.88 (2H, m, H-1), 3.78 (2H, s, H-8), 2.63 (2H, t, J=6.9 Hz, H-6), 2.06 (2H, q (dt), J=7.2 Hz, H-3), 1.60–1.37 (4H, m, H-4 and H-5), 1.29 (1H, br s, H-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 140.5 (C-9), 138.5 (C-2), 128.1 and 127.8 (C-10 and C-11), 126.6 (C-12), 114.2 (C-1), 53.9 (C-8), 49.1 (C-6), 33.4 (C-3), 29.4 (C-5) and 26.5 (C-4). MS (EI, 70 eV) *m/z* (relative intensity, %): 189 ($M^{+\bullet}$, 9), 120 (24), 91 (100). IR (film) ν (cm^{-1}): 3310 [w], 3063 [m], 3027 [m], 2928–2822 [s], 1640 [m], 1495 [m], 1454 [s], 1367 [m], 1120 [m], 910 [s], 732 [s], 697 [s]. CAS: [145126-90-5].

*4.1.8. 1-Benzylamino-2,2-dimethyl-5-hexene (**26**)*



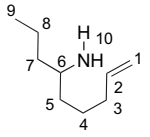
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.35–7.30 (5H, m, Ph), 5.81 (1H, ddt, J=17.0, 10.3, 6.6 Hz, H-2), 5.02–4.86 (2H, m, H-1), 3.79 (2H, s, H-10), 2.36 (2H, s, H-6), 2.20–1.90 (2H, m, H-3), 1.40–1.28 (3H, m, H-4 and H-9), 0.89 (6H, s, H-7 and H-8). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 140.9 (C-11), 139.5 (C-2), 128.0 and 127.8 (C-12 and C-13), 126.5 (C-14), 113.6 (C-1), 59.6 (C-6), 54.6 (C-10), 39.2 (C-4), 33.8 (C-5), 28.3 (C-3), 25.4 (C-7 and C-8). MS (EI, 70 eV) *m/z* (relative intensity, %): 217 ($M^{+\bullet}$, 14), 120 (87), 91 (100), 55 (9). IR (film) ν (cm^{-1}): 3064 [m], 3027 [m], 2955–2808 [s], 1640 [m], 1495–1454 [s], 1363 [m], 1118 [s], 908 [s], 735 [s], 698 [s]. E.A.: ($C_{15}H_{23}N$) Calcd: C, 82.89; H, 10.67; N, 6.44%. Found: C, 82.77; H, 10.69; N, 6.43%.

*4.1.9. 1-Amino-4,4-dimethyl-5-hexene (**28**)*



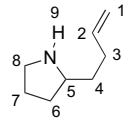
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.76 (1H, ddd, J=18.2, 10.1, 0.9 Hz, H-2), 4.96–4.84 (2H, m, H-1), 2.64 (2H, t, J=6.0 Hz, H-6), 1.49 (2H, br s, H-9), 1.42–1.22 (4H, m, H-4 and H-5), 0.98 (6H, s, H-7 and H-8). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 148.4 (C-2), 110.3 (C-1), 42.9 (C-6), 39.9 and 28.9 (C-4 and C-5), 36.3 (C-3), 26.8 (C-7 and C-8). MS (EI, 70 eV) *m/z* (relative intensity, %): 128 (M+1, 20), 112 (61), 95 (64), 69 (59), 67 (58), 56 (100). IR (film) ν (cm^{-1}): 3369 [w], 3292 [w], 3082 [m], 2960–2866 [s], 1640 [m], 1473 [m], 1414 [m], 1380 [m], 1363 [m], 1003 [m], 910 [s], 816 [m], 687 [w]. HRMS (EI+, MH^+): ($C_8H_{18}N$) calcd: 128.1439; found: 128.1436.

*4.1.10. 6-Amino-nonene (**30**)*



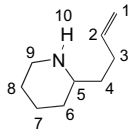
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.80 (1H, ddt, J=17.0, 10.3, 6.7 Hz, H-2), 5.05–4.87 (2H, m, H-1), 2.74–2.62 (1H, m, H-6), 2.14–1.96 (2H, m, H-3), 1.56–1.18 (8H, m, H-4, 5, 7 and 8), 1.14 (2H, br s, H-10), 0.90 (3H, t, J=6.9 Hz, H-9). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 139.0 (C-2), 114.6 (C-1), 51.0 (C-6), 40.6 and 37.8 (C-5 and C-7), 34.1 (C-3), 25.7 (C-4), 19.5 (C-8), 14.4 (C-9). MS (CI, 70 eV) *m/z* (relative intensity, %): 142 (M+1, 100), 98 (25), 83 (8), 72 (40), 69 (11). IR (film) ν (cm^{-1}): 3372 [w], 3299 [w], 3078 [m], 2957–2871 [s], 1641 [s], 1617 [m], 1460 [s], 1379 [m], 993 [m], 909 [s], 808 [s], 742 [m]. HRMS (CI+, MH^+): ($C_9H_{20}N$) calcd: 142.1596; found: 142.1594. E.A.: ($C_{16}H_{27}NO_3S$, RNH_3^+ PTS^-) Calcd: C, 61.31; H, 8.68; N, 4.47; S, 10.23%. Found: C, 61.19; H, 9.14; N, 4.33; S, 10.12%.

*4.1.11. 2-(But-3-enyl)pyrrolidine (**32**)*



^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.80 (1H, ddt, J=17.0, 10.3, 6.7 Hz, H-2), 5.05–4.85 (2H, m, H-1), 3.03–2.86 (2H, m, H-5 and H-8a), 2.85–2.73 (1H, m, H-8b), 2.20–1.99 (2H, m, H-3), 1.92–1.78 (1H, m, H-6a), 1.77–1.59 (3H, m, H-7 and H-9), 1.58–1.39 (2H, m, H-4), 1.29–1.13 (1H, m, H-6b). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 138.9 (C-2), 114.5 (C-1), 58.9 (C-5), 46.7 (C-8), 35.9 (C-4), 31.9 (C-3 and C-6), 25.5 (C-7). MS (APCI, 70 eV) *m/z* (relative intensity, %): 126 (M+1, 5), 109 (22), 70 (100). IR (film) ν (cm^{-1}): 3418 [w], 3074 [w], 2957–2868 [s], 1639 [m], 1620 [m], 1537 [m], 1396–1362 [s], 995 [m], 906 [s], 812 [m], 737 [w]. CAS: [95092-07-2].

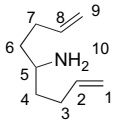
*4.1.12. 2-(But-3-enyl)piperidine (**34**)*



^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.80 (1H, ddt, J=17.0, 10.3, 6.7 Hz, H-2), 5.07–4.87 (2H, m, H-1), 3.10–2.97 (1H, m, H-9a), 2.61 (1H, td, J=11.7, 2.7 Hz, H-9b), 2.44 (1H, dtd,

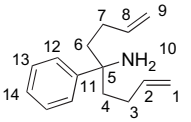
J=13.2, 6.5, 2.5 Hz, H-5), 2.15–2.01 (2H, m, H-3), 1.81–1.70 (1H, m) and 1.69–1.52 (2H, m) (H-6a, 7a and 8a), 1.51–1.22 (5H, m, H-4, 7b, 8b and 10), 1.13–0.96 (1H, m, H-6b). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 138.9 (C-2), 114.6 (C-1), 56.5 (C-5), 47.4 (C-9), 35.9 (C-4), 33.1 (C-6), 30.4 (C-3), 26.8 and 25.0 (C-7 and C-8). MS (APCI, 70 eV) *m/z* (relative intensity, %): 140 (M+1, 75), 123 (5), 84 (100), 81 (75). IR (film) ν (cm^{-1}): 3281 [w], 3076 [w], 2927–2852 [s], 1639 [m], 1441 [m], 1327 [m], 1120–997 [m], 906 [s], 798 [m]. CAS: [78867-47-1].

4.1.13. 5-Amino-nona-1,8-diene (**36**)



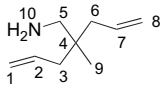
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.83 (2H, ddt, J=17.2, 10.1, 6.7 Hz, H-2 and H-8), 5.35 (2H, dd, J=17.2, 1.4 Hz, H-1a and H-9a), 4.96 (2H, dd, J=10.1, 1.4 Hz, H-1b and H-9b), 2.78–2.71 (1H, m, H-5), 2.19–2.02 (4H, m, H-3 and H-7), 1.57–1.40 (4H, m, H-4 and H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 139.2 (C-2 and C-8), 115.0 (C-1 and C-9), 50.9 (C-5), 37.9 (C-4 and C-6), 31.1 (C-3 and C-7). MS (CI) *m/z* (relative intensity, %): 140.0 (M+1, 10), 85.7 (14). IR (film) ν (cm^{-1}): 3357 [w], 3076 [s], 3009 [s], 1640 [m], 1635 [w], 1362 [m], 994 [m]. CAS: [245450-12-8].

4.1.14. 5-Amino-5-phenylnona-1,8-diene (**38**)



^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.44–7.16 (5H, m, Ph), 5.73 (2H, ddt, J=17.2, 10.1, 6.7 Hz, H-2 and H-8), 4.95–4.83 (4H, m, H-1 and H-9), 2.08–1.73 (8H, m, H-3, 4, 6 and 7). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 146.5 (C-11), 138.8 (C-2 and C-8), 128.1, 128.0, 126.0 and 125.9 (C-12 and C-13), 125.7 (C-14), 114.2 (C-1 and C-9), 57.7 (C-5), 43.3 (C-4 and C-6), 28.2 (C-3 and C-7). MS (ESI, 70 eV) *m/z* (relative intensity, %): 216 (M+1, 29), 143 (5), 129 (7), 91 (4). IR (film) ν (cm^{-1}): 3370 [w], 3078 [s], 3061 [m], 2927 [s], 1638 [m], 1600 [w], 1493 [w], 1446 [m], 1413 [w], 1025 [m]. HRMS (ESI+, MH^++Na): ($C_{15}H_{22}NNa$) calcd: 216.1752; found: 216.1757.

4.1.15. 1-Amino-2,2-diallylpropane (**40**)



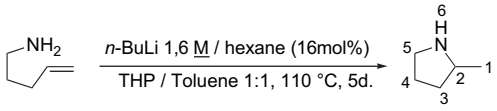
^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 5.89–5.73 (2H, m, H-2 and H-7), 5.11–4.97 (4H, m, H-1 and H-8), 2.48 (2H, s, H-5), 2.00 (4H, d, J=7.7 Hz, H-3 and H-6), 1.05 (2H, br s, H-10), 0.85 (3H, s, H-9). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 134.7 (C-2 and C-7), 117.1 (C-1 and C-8), 50.0 (C-5), 41.7 (C-3 and C-6), 36.7 (C-4), 22.2 (C-9). MS (EI, 70 eV) *m/z* (relative intensity, %): 139 ($M^{+\bullet}$, 1), 124 (2), 98 (13), 83 (12), 57 (47). IR (film) ν (cm^{-1}): 3389 [w], 3313 [w], 3075 [m], 3003 [m], 2950–2870 [s], 1639 [m], 1464 [m], 1440 [m], 1415 [m], 1379 [m], 1323 [m], 1066 [m], 997 [m], 912 [s], 815 [m]. CAS: [39074-87-8].

4.2. Typical experimental procedure of the hydroamination reaction with n-BuLi

To a stirred solution of aminoolefin (1 equiv), dissolved in a 1:1 mixture of tetrahydropyran and toluene (0.5 M) in a Schlenk tube maintained under an argon atmosphere, was added *n*-BuLi (1.6 M/hexanes, 16 mol %) at room temperature. The solution was stirred while heating at 110 °C (oil bath temperature).

After cooling to room temperature, diethyl ether, water and a 1 M aqueous solution of HCl were added sequentially. The solvents were removed in vacuo and the residual solid was partitioned between diethyl ether and water containing 300 mg of KOH. The layers were separated and the aqueous phase was extracted with diethyl ether. The pooled organic extracts were washed with water and then with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered and the solvent was removed carefully in vacuo (at 0 °C for secondary amines).

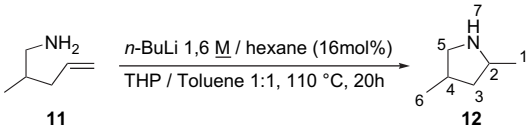
4.2.1. Synthesis of 2-methylpyrrolidine (**9**)



8 **9**

Isolated yield: 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 3.13–2.95 (2H, m) and 2.87–2.73 (1H, m) (H-2 and H-5), 1.93–1.62 (4H, m, H-3 and H-4), 1.28–1.16 (1H, m, H-6), 1.14 (3H, d, J=6.0 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 54.5 (C-2), 46.7 (C-5), 33.7 and 25.7 (C-3 and C-4), 21.2 (C-1). MS (EI, 70 eV) *m/z* (relative intensity, %): 85 ($M^{+\bullet}$, 19), 84 (18), 70 (100), 57 (45), 56 (22). IR (film) ν (cm^{-1}): 3396 [m], 2959–2870 [s], 1630 [m], 1530 [m], 1452–1410 [s], 1348 [m], 1198 [w], 814 [w], 729 [w]. CAS: [765-38-8].

4.2.2. Synthesis of 2,4-dimethylpyrrolidine (**12**)

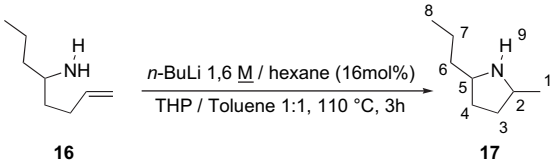


11 **12**

Isolated yield: 93% (cis as major product, dr=58:42). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): trans: 3.26–3.13 (2H, m, H-2 and H-5a), 2.39 (1H, dd, J=10.6, 7.6 Hz, H-5b), 2.27–2.13 (1H, m, H-4), 1.48 (2H, t, J=7.3 Hz, H-3), 1.15 (3H, d, J=6.3 Hz, H-1), 1.00 (3H, d, J=6.8 Hz, H-6). Cis: 3.26–3.13 (1H, m, H-2), 3.04 (1H, dd, J=10.6, 7.9 Hz, H-5a), 2.56 (1H, dd, J=10.6, 7.0 Hz, H-5b), 2.27–2.13 (1H, m, H-4), 2.13–2.03 (1H, m, H-3a), 1.17 (3H, d, J=6.3 Hz, H-1), 1.03

(3H, d, J=6.6 Hz, H-6), 0.91–0.81 (1H, m, H-3b). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 55.1 (C-5_{trans}), 54.1 (C-5_{cis}), 55.1 (C-2_{cis}), 53.6 (C-2_{trans}), 43.4 (C-3_{cis}), 41.9 (C-3_{trans}), 34.7 and 33.4 (C-4), 21.6 and 21.5 (C-1), 19.6 and 19.3 (C-6). MS (EI, 70 eV) *m/z* (relative intensity, %): 99 ($M^{+\bullet}$, 5), 84 (100), 57 (47). IR (film) ν (cm^{-1}): 3341 [w], 2957–2872 [s], 1624 [w], 1533 [w], 1456 [m], 1379 [m], 1128 [w], 1082 [w], 837 [w], 775 [w]. CAS: [40465-44-9] *cis*-(2*R*,4*S*); [73604-50-9] *trans*-(*S*,*S*).

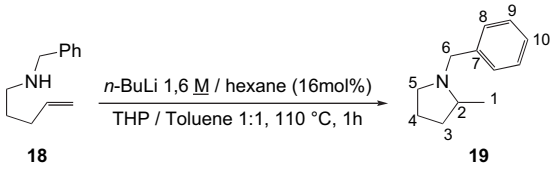
4.2.3. Synthesis of 2-methyl-5-propylpyrrolidine (**17**)



16 **17**

Isolated yield: 73% (trans as major product, dr=72:28). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): trans: 3.25 (1H, sext (qt), J=6.5 Hz, H-2), 3.14 (1H, quint (tt), J=6.6 Hz, H-5), 2.07–1.87 (2H, m) and 1.53–1.18 (6H, m) (H-3, 4, 6 and 7), 1.10 (3H, d, J=6.3 Hz, H-1), 0.90 (3H, t, J=6.9 Hz, H-8). Cis: 3.06 (1H, sext (qt), J=6.8 Hz, H-2), 2.96 (1H, quint (tt), J=6.5 Hz, H-5), 1.86–1.77 (2H, m) and 1.53–1.18 (6H, m) (H-3, 4, 6 and 7), 1.15 (3H, d, J=6.2 Hz, H-1), 0.90 (3H, t, J=6.9 Hz, H-8). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): trans: 58.0 (C-5), 53.4 (C-2), 39.7, 34.7, 33.0 and 20.7 (C-3, 4, 6 and 7), 22.2 (C-1), 14.4 (C-8). Cis: 59.7 (C-5), 54.7 (C-2), 39.2, 33.4, 32.1 and 20.8 (C-3, 4, 6 and 7), 21.5 (C-1), 14.5 (C-8). MS (EI, 70 eV) *m/z* (relative intensity, %): 127 ($M^{+\bullet}$, 1), 112 (1), 86 (9), 84 (100), 72 (31), 70 (10), 67 (9). IR (film) ν (cm^{-1}): 3393 [m], 2957–2870 [s], 1628 [w], 1458 and 1400 [m], 1375 [w], 1132 [w], 1097, 808 [w], 735[w]. CAS: [90886-40-1].

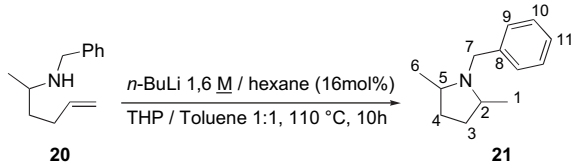
4.2.4. Synthesis of 1-benzyl-2-methylpyrrolidine (**19**)



18 **19**

Isolated yield: 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.35–7.15 (5H, m, Ph), 4.01 (1H, d, J=12.9 Hz, H-6a), 3.12 (1H, d, J=12.9 Hz, H-6b), 2.95–2.83 (1H, m, H-5a), 2.37 (1H, sext (qt), J=7.7 Hz, H-2), 2.08 (1H, q (dt), J=9.1 Hz, H-5b), 2.00–1.84 (1H, m), 1.80–1.53 (2H, m) and 1.52–1.35 (1H, m) (H-3 and H-4), 1.17 (3H, d, J=5.7 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 139.3 (C-7), 128.9 and 128.0 (C-8 and C-9), 126.6 (C-10), 59.5 (C-6), 58.3 and 54.0 (C-2 and C-5), 32.7 and 21.4 (C-3 and C-4), 19.1 (C-1). MS (CI, 70 eV) *m/z* (relative intensity, %): 176 (M+1, 69), 160 (100), 91 (49). IR (KBr) ν (cm^{-1}): 3063 [w], 3028 [w], 2963 [s], 2869 [m], 2786 [m], 1495 [m], 1454 [m], 1374 [m], 1140 [w], 736 [m], 697 [s]. HRMS (EI+, $M^{+\bullet}$): ($C_{12}H_{17}N$) calcd: 175.136100; found: 175.136060. CAS: [774-91-4].

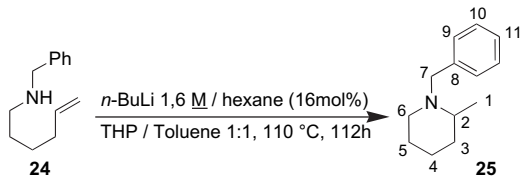
4.2.5. Synthesis of 1-benzyl-2,5-dimethylpyrrolidine (**21**)



20 **21**

Isolated yield: 79% (cis as major product, dr=85:15). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): cis: 7.41–7.20 (5H, m, Ph), 3.76 (2H, s, H-7), 2.64–2.48 (2H, m, H-2 and H-5), 1.87–1.70 (2H, m, H-3a and H-4a), 1.46–1.31 (2H, m, H-3b and H-4b), 1.07 (6H, d, J=6.1 Hz, H-1 and H-6). Trans: 7.41–7.20 (5H, m, Ph), 3.85 (1H, d, J=13.8 Hz, H-7a), 3.52 (1H, d, J=13.8 Hz, H-7b), 3.07–2.98 (2H, m, H-2 and H-5), 2.07–1.96 (2H, m, H-3a and H-4a), 1.46–1.31 (2H, m, H-3b and H-4b), 0.98 (6H, d, J=6.3 Hz, H-1 and H-6). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): cis: 139.4 (C-8), 129.5 and 128.1 (C-9 and C-10), 126.8 (C-11), 59.6 (C-7), 55.2 (C-2 and C-5), 31.5 (C-3 and C-4), 20.8 (C-1 and C-6). Trans: 140.9 (C-8), 128.7 and 128.2 (C-9 and C-10), 126.6 (C-11), 55.1 (C-2 and C-5), 51.9 (C-7), 31.1 (C-3 and C-4), 17.3 (C-1 and C-6). MS (CI, 70 eV) *m/z* (relative intensity, %): 190 (M+1, 8), 91 (100). IR (KBr) ν (cm^{-1}): 3062 [w], 3026 [w], 2960–2868 [s], 1494 [m], 1453 [m], 1372 [m], 1207 [w], 730 [m], 697 [s]. HRMS (EI+, $M^{+\bullet}$): ($C_{13}H_{19}N$) calcd: 189.1517; found: 189.1512. CAS: [4209–68-1] *cis*-(*S*,*R*), [4209-71-6] and [119008-53-6] *trans*-(*R*,*R*), [153481-73-3] *trans*-(*S*,*S*).

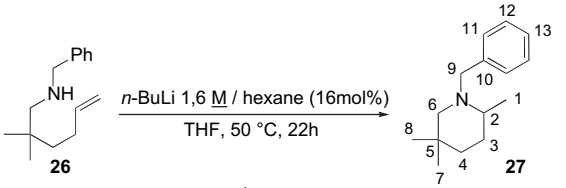
4.2.6. Synthesis of 1-benzyl-2-methylpiperidine (**25**)



24 **25**

Isolated yield: 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.40–7.18 (5H, m, Ph), 4.00 (1H, d, J=13.2 Hz, H-7a), 3.19 (1H, d, J=13.5 Hz, H-7b), 2.30 (1H, dt, J=12.0, 3.7 Hz, H-6a), 2.35–2.21 (1H, m, H-2), 1.94 (1H, dt, J=11.5, 3.4 Hz, H-6b), 1.70–1.57 (2H, m) and 1.57–1.20 (4H, m) (H-3, 4 and 5), 1.17 (3H, d, J=6.2 Hz, H-1). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 140.0 (C-8), 129.2 and 128.2 (C-9 and C-10), 126.8 (C-11), 58.8 (C-7), 56.6 (C-2), 52.4 (C-6), 35.0, 26.3 and 24.2 (C-3, 4 and 5), 19.6 (C-1). MS (EI, 70 eV) *m/z* (relative intensity, %): 189 ($M^{+\bullet}$, 17), 174 (100), 91 (70). IR (film) ν (cm^{-1}): 3085 [w], 3063 [m], 3027 [m], 2963–2788 [s], 1494 [m], 1452 [s], 1373 [s], 1329 [m], 1133 [m], 1116 [s], 1066 [s], 730 [s], 697 [s]. CAS: [777-38-8].

4.2.7. Synthesis of 1-benzyl-2,5,5-trimethylpiperidine (**27**)

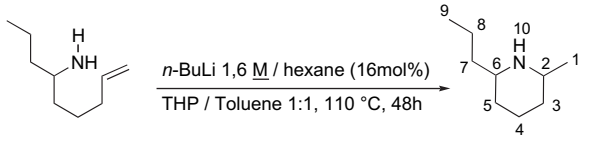


26 **27**

Isolated yield: >95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.38–7.17 (5H, m, Ph), 3.99 (1H, d, J=13.8 Hz, H-9a),

3.08 (1H, d, J=13.5 Hz, H-9b), 2.30 (1H, dd, J=11.1, 2.1 Hz, H-6a), 2.28–2.16 (1H, m, H-2), 1.68 (1H, d, J=11.4 Hz, H-6b), 1.62–1.28 (2H, m) and 1.22–1.13 (2H, m) (H-3 and H-4), 1.12 (3H, d, J=6.3 Hz, H-1), 0.94 (3H, s) and 0.79 (3H, s) (H-7 and H-8). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 140.4 (C-10), 128.2 and 127.7 (C-11 and C-12), 126.1 (C-13), 63.6 (C-9), 58.1 (C-6), 56.3 (C-2), 36.8 and 31.4 (C-3 and C-4), 30.6 (C-5), 28.6, 25.0 and 18.4 (C-1, 7 and 8). MS (EI, 70 eV) *m/z* (relative intensity, %): 217 ($M^{+\bullet}$, 18), 202 (100), 91 (68). IR (film) ν (cm^{-1}): 3086 [m], 3063 [m], 3027 [s], 2957–2822 [s], 1494 [s], 1453 [s], 1370 [s], 1332 [s], 1148 [s], 1124 [s], 1067 [s], 741 [s], 728 [s], 697 [s]. E.A.: ($C_{15}H_{23}N$) Calcd: C, 82.89; H, 10.67; N, 6.44%. Found: C, 82.20; H, 10.55; N, 6.14%.

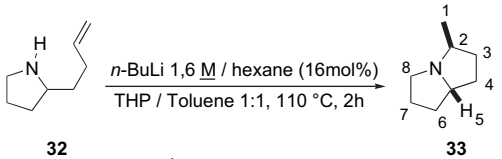
4.2.8. Synthesis of 2-methyl-6-propylpiperidine (**31**)



30 **31**

Isolated yield: 85% (cis as major product, dr=75:25). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): cis: 2.67–2.57 (1H, m, H-2), 2.55–2.44 (1H, m, H-6), 1.80–1.72 (1H, m), 1.70–1.52 (2H, m), 1.50–1.18 (5H, m) and 1.04–0.96 (2H, m) (H-3, 4, 5, 7 and 8), 1.07 (3H, d, J=6.2 Hz, H-1), 0.94–0.82 (3H, m, H-9). Trans: 3.12–3.02 (1H, m, H-2), 2.95–2.87 (1H, m, H-6), 1.80–1.72 (1H, m), 1.70–1.52 (2H, m), 1.50–1.18 (5H, m) and 1.04–0.96 (2H, m) (H-3, 4, 5, 7 and 8), 1.09 (3H, d, J=6.6 Hz, H-1), 0.94–0.82 (3H, m, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): cis: 57.0 (C-6), 52.7 (C-2), 39.9, 34.6, 32.5, 25.1 and 19.3 (C-3, 4, 5, 7 and 8), 23.3 (C-1), 14.5 (C-9). Trans: 50.7 (C-6), 46.1 (C-2), 40.6, 38.4, 32.3, 26.1 and 19.5 (C-3, 4, 5, 7 and 8), 22.9 (C-1), 14.3 (C-9). MS (APCI, 70 eV) *m/z* (relative intensity, %): 142 (M+1, 48), 83 (48), 69 (100). IR (film) ν (cm^{-1}): 3337 [w], 2955–2856 [s], 1653–1570 [w], 1460–1439 [m], 1377 [m], 1308 [w], 1126 [w], 795 [w], 748 [w], 721 [w]. CAS: [65337-42-0] *cis*-(2*S*,6*R*), [65266-41-3] *cis*-(2*R*,6*S*).

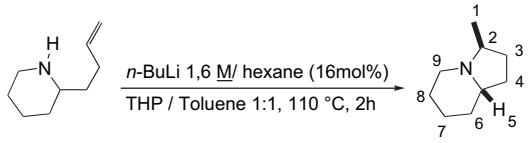
4.2.9. Synthesis of cis-hexahydro-3-methyl-1H-pyrrolizidine (**33**)



32 **33**

Isolated yield: 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 3.61 (1H, quint (dddd), J=7.0 Hz, H-5), 2.98–2.91 (1H, m, H-2), 2.68–2.57 (2H, m, H-8), 2.06–1.98 (1H, m), 1.97–1.80 (4H, m) and 1.54–1.32 (3H, m) (H-3, 4, 6 and 7), 1.13 (3H, d, J=6.2 Hz, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 65.0 (C-5), 62.3 (C-2), 53.5 (C-8), 35.8 (C-3), 33.1 (C-6), 32.4 (C-4), 25.9 (C-7), 21.2 (C-1). MS (EI, 70 eV) *m/z* (relative intensity, %): 125 ($M^{+\bullet}$, 6), 124 (53), 110 (17), 108 (43), 105 (15), 97 (36), 96 (24), 91 (16), 83 (28), 82 (56), 80 (57), 77 (61), 70 (26), 69 (100), 67 (35), 65 (20), 55 (67), 53 (22), 51 (18). IR (film) ν (cm^{-1}): 3391 [s], 2957–2866 [s], 1649–1560 [s], 1456–1381 [m], 1356[m], 1090 [w], 1036 [w], 800 [w], 702 [w]. CAS: [19451-50-4] *cis*-(*S*,*S*).

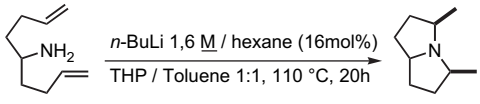
4.2.10. Synthesis of 3-methyl-octahydro-indolizidine (**35**)



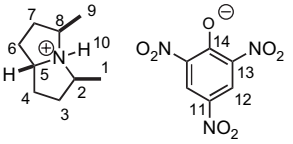
34 **35**

Isolated yield: 76% (cis as major product, dr=93:7). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): cis: 3.14 (1H, br d, J=10.7 Hz, H-5), 2.16–2.04 (1H, m, H-2), 1.93–1.61 (7H, m), 1.59–1.46 (1H, m) and 1.41–1.13 (4H, m) (H-3, 4, 6, 7, 8 and 9), 1.11 (3H, d, J=6.1 Hz, H-1). Trans: 2.92 (1H, br d, J=11.6 Hz, H-5), 2.16–2.04 (1H, m, H-2), 1.93–1.61 (7H, m), 1.59–1.46 (1H, m) and 1.41–1.13 (4H, m) (H-3, 4, 6, 7, 8 and 9), 0.97 (3H, d, J=5.1 Hz, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 65.7 (C-5), 60.6 (C-2), 51.3 (C-9), 31.3 (C-3), 30.4 (C-6), 29.1 (C-4), 25.5 and 24.5 (C-7 and C-8), 18.4 (C-1). MS (EI, 70 eV) *m/z* (relative intensity, %): 139 ($M^{+\bullet}$, 11), 138 (30), 136 (20), 124 (100), 96 (17), 84 (68), 82 (28), 80 (14), 69 (35), 67 (16), 55 (43). IR (film) ν (cm^{-1}): 3398 [w], 2957–2856 [s], 2787–2714 [w], 1664 [m], 1441–1373 [m], 1200–1067 [m], 806 [w], 739 [w]. CAS: [68344-43-4] *trans*-(8*S*,3*R*), [68344-39-8] *cis*-(*S*,*S*).

4.2.11. Synthesis of cis-hexahydro-3,5-dimethyl-1H-pyrrolizidine (**37**)

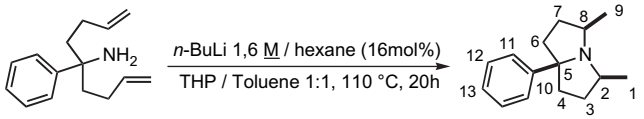


36 **37**



Isolated yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 9.07 (2H, s, H-12), 4.68 (1H, sext (ttd), J=7.8 Hz, H-5), 3.41 (2H, qdd, J=7.3, 6.8, 3.8 Hz, H-2 and H-8), 2.43 (2H, dddd, J=10.8, 6.8, 4.2, 2.7 Hz, H-4a and H-6a), 2.25 (2H, dddd, J=12.2, 7.7, 6.6, 4.4 Hz, H-3a and H-7a), 2.07 (2H, dddd, J=12.0, 9.9, 3.5, 2.8 Hz, H-3b and H-7b), 1.77 (2H, dddd, J=11.2, 9.8, 9.4, 4.5 Hz, H-4b and H-6b), 1.55 (6H, d, J=6.7 Hz, H-1 and H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 155.8 (C-14), 138.4 (C-13), 134.7 (C-11), 126.3 (C-12), 68.9 (C-5), 65.3 (C-2 and C-8), 34.0 (C-3 and C-7), 30.7 (C-4 and C-6), 16.8 (C-1 and C-9). MS (EI, 70 eV) *m/z* (relative intensity, %): 139 ($M^{+\bullet}$, 20), 138 (15), 124 (100), 121 (9), 111 (42), 110 (13). IR (film) ν (cm^{-1}): 3428 [m], 3078 [s], 2977 [m], 2873 [m], 1561 [w], 1346 [m], 1112 [m]. CAS: [138615-28-8], [56160-71-5] for the free amine **31**.

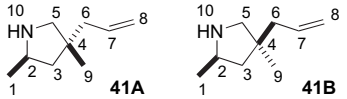
*4.2.12. Synthesis of cis-hexahydrodro-3,5-dimethyl-7a-phenyl-1H-pyrrolizidine (**39**)*



38 **39**

Isolated yield: 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.50–7.16 (5H, m, Ph), 2.51–2.48 (2H, m, H-2 and H-8), 2.24–1.54 (8H, m, H-3, 4, 6 and 7), 1.36 (6H, d, J=6.6 Hz, H-1 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 127.5 and 125.9 (C-11 and C-12), 125.1 (C-13), 68.6 (C-5), 53.1 (C-2 and C-8), 35.2 (C-4 and C-6), 30.6 (C-3 and C-7), 22.1 (C-1 and C-9). MS (ESI, 70 eV) *m/z* (relative intensity, %): 216.17 (M^++H, 95), 214.19 (73), 199.15 (7), 155.11 (10), 143.08 (14), 129.06 (21). IR (film) ν (cm^{-1}): 3038 [w], 2962–2848 [s], 1675–1538 [m], 1438–1360 [m], 1224–1120 [m], 778 [w], 732 [w].

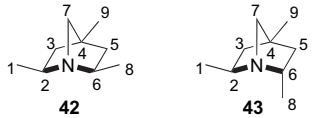
*4.2.13. Synthesis of 4-allyl-2,4-dimethylpyrrolidine (**41**)*



41A **41B**

Isolated yield: 95% (**41A** as major product, dr=60:40). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): **41A**: 5.88–5.72 (1H, m, H-7), 5.06–5.01 (2H, m, H-8), 3.30–3.13 (1H, m, H-2), 2.84 (1H, A part of AB, J=11.0 Hz, H-5a), 2.56 (1H, B part of AB, J=11.0 Hz, H-5b), 2.21 (1H, br s, H-10), 2.11 (2H, d, J=7.7 Hz, H-6), 1.62 (1H, dd, J=12.5, 6.8 Hz, H-3a), 1.15 (3H, d, J=6.2 Hz, H-1), 1.14–1.08 (1H, m, H-3b), 1.02 (3H, s, H-9). **41B**: 5.88–5.72 (1H, m, H-7), 5.06–5.01 (2H, m, H-8), 3.30–3.13 (1H, m, H-2), 2.70 (1H, A part of AB, J=11.0 Hz, H-5a), 2.67 (1H, B part of AB, J=11.0 Hz, H-5b), 2.21 (1H, br s, H-10), 2.10 (2H, d, J=7.7 Hz, H-6), 1.83 (1H, dd, J=12.9, 7.2 Hz, H-3a), 1.16 (3H, d, J=6.2 Hz, H-1), 1.05 (3H, s, H-9), 1.03–0.97 (1H, m, H-3b). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 135.7 and 135.6 (C-7_{35A} and C-7_{35B}), 116.9 (C-8_{35A} and C-8_{35B}), 59.4 and 59.2 (C-5_{35A} and C-5_{35B}), 54.5 and 54.1 (C-2_{35A} and C-2_{35B}), 47.9, 47.5, 46.4 and 45.3 (C-3_{35A}, C-3_{35B}, C-6_{35A} and C-6_{35B}), 43.1 (C-4_{35A} and C-4_{35B}), 26.8 and 25.9 (C-1_{35A} and C-1_{35B}), 21.8 and 21.4 (C-9_{35A} and C-9_{35B}). MS (EI, 70 eV) *m/z* (relative intensity, %): 139 ($M^{+\bullet}$, 9), 124 (28), 96 (43), 83 (7), 57 (100). IR (film) ν (cm^{-1}): 3293 [w], 3076 [m], 2957–2899 [s], 1639 [m], 1533 [w], 1456 [m], 1415 [m], 1378 [m], 1097 [m], 996 [m], 912 [s]. CAS: [899832-60-1] **41A**-(*S*,*S*); [899832-59-8] **41B**-(2*S*,4*R*); [700378-27-4] **41B**-(2*R*,4*S*).

*4.2.14. Synthesis of 2,4,6-trimethyl-1-aza-bicyclo[2.2.2]-heptane (**42–43**)*



42 **43**

Isolated yield: 80% (**42** as major product, dr=52:48). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): **42**: 2.82–2.69 (2H, m, H-2 and H-6), 2.21 (2H, s, H-7), 1.41 (2H, dd, J=11.0, 7.2 Hz, H-3a and H-5a), 1.18 (3H, s, H-9), 1.11 (6H, d, J=6.7 Hz, H-1 and H-8), 1.45–1.35 (2H, m, H-3b and H-5b). **43**: 3.34–3.08 (2H, m, H-2 and H-6), 2.45 (1H, dd, J=9.6, 2.4 Hz, H-7a), 2.23–2.16 (1H, m, H-7b), 1.59 (1H, ddd, J=10.1, 10.1, 3.4 Hz) and 1.39–1.30 (1H, m) (H-3a and H-5a), 1.20 (3H, s, H-9), 1.17 (3H, d, J=7.2 Hz) and 1.09 (3H, d, J=7.2 Hz) (H-1 and H-8), 1.01–0.93 (1H, m) and 0.60 (1H, ddd, J=11.5, 6.2, 2.4 Hz) (H-3b and H-5b).^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): **42**: 62.2 (C-2 and C-6), 57.3 (C-7), 46.7 (C-4), 45.3 (C-3 and C-5), 22.9 (C-1 and C-8), 17.1 (C-9). **43**: 62.9 and 59.7 (C-2 and C-6), 50.7 (C-7), 48.3 (C-4), 47.4 and 43.9 (C-3 and C-5), 22.7 (C-1), 17.7 and 17.6 (C-8 and C-9). MS (CI, 70 eV) *m/z* (relative intensity, %): 140 (M+1, 60), 98 (23), 95 (8), 55 (100). IR (film) ν (cm^{-1}): 2960–2864 [s], 1457 [m], 1375 [m], 1046 [m]. CAS: [700378-37-6] (*R*,*S*); [700378-28-5] (*S*,*S*).

Acknowledgements

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3. See for example: (a) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703; (b) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1; (c) Taube, R. *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1996; Vol. 1, p 507; (d) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675; (e) Togni, A.; Grutzmacher, H. *Catalytic Heterofunctionalization*; Wiley-VCH: Weinheim, 2001; p 91.
4. The direct addition of an amine to an olefin is clearly the most economical and environmentally friendly access to substituted amines. Indeed, though substituted amines can be prepared industrially from alcohols, the alcohols themselves are typically obtained from the corresponding alkenes, hence adding one more step to the process. Moreover, the classic synthesis of amines by nucleophilic substitution generates large quantities of salts, which have to be disposed of in a suitable and ecologically benign manner.
5. These conditions are required, for example, for the addition of ammonia onto ethylene, catalysed by alkali metals: Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899.
6. In these cases, release of internal strain energy or enhanced stabilising of the generated carbanion is responsible for the ease of amine addition. See for example: (a) Wegler, R.; Pieper, G. *Chem. Ber.* **1950**, *83*, 1; (b) Asahara, T.; Seno, M.; Tanabe, S.; Den, N. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1966; (c) Imai, N.; Narita, T.; Tsuruta, T. *Tetrahedron Lett.* **1971**, *38*, 3517; (d) Narita, T.; Yamaguchi, T.; Tsuruta, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3825; (e) Fujita, T.; Suga, K.; Watanabe, S. *Aust. J. Chem.* **1974**, *27*, 531; (f) Hartung, C. G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* **2000**, *56*, 5157 and references cited therein.
7. For example, the addition of ammonia to propene to form propylamine requires temperatures around 250 °C and pressures in the range of 800–1000 bars (yield: 29%). (a) Schlott, R. J.; Falk, J. C.; Narducy,

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9. For general references on hydroamination, see: (a) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795; (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104; (c) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507; (d) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.
10. For alkali and alkaline earth metal-catalysed hydroamination of non-activated alkenes, see: (a) Clossom, R. D.; Napolitano, J. P.; Ecke, G. G.; Kolka, A. *J. Org. Chem.* **1957**, *22*, 646; (b) Radzan, R. K. *J. Chem. Soc., Chem. Commun.* **1969**, 770; (c) See Ref. 6c; (d) Schott, R. J.; Falk, J. C.; Narducy, K. W. *J. Org. Chem.* **1972**, *37*, 4243; (e) See Ref. 7b; (f) Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917; (g) Steinborn, D.; Thies, B.; Wagner, I.; Taube, R. *Z. Chem.* **1989**, *29*, 333; (h) Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* **1992**, *33*, 6359; (i) van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 9561; (j) Khedkar, V.; Tillack, A.; Benisch, C.; Melder, J.-P.; Beller, M. *J. Mol. Catal. A* **2005**, *241*, 175; (k) Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557; (l) Crimmins, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2042; (m) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755; (n) Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.
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12. For example, most of the lanthanide-based catalysts can only be prepared using a glove-box or special Schlenck techniques. They are also exquisitely sensitive towards the slightest trace of oxygen and lose most of their activity in nucleophilic solvents.
13. It is quite clear that *intramolecular* hydroamination reactions proceeded with a lower activation energy than their *intermolecular* counterparts. However, the ω-amino-alkene substrates *cannot be considered* as activated olefins, as described in Ref. 6.
14. Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623.
15. Amine **8** has been specifically selected for this purpose, since it is a substrate that gives only poor yields of the corresponding pyrrolidine under the previously described conditions.
16. This proton abstraction could be an inter- or an intramolecular process. Since it occurs at about the same rate, regardless of the ring size of putative intramolecular transition states, we favour the intermolecular pathway, taking place through the mixed amine-lithiated amide dimer.
17. The difference in basicity between the anion of a primary amine and the corresponding carbanion averages around 20 pK_a units, henceforth precluding the formation of a discrete carbanionic intermediate in our hydroamination reactions. For an excellent pK_a scale, see: Bordwell, F. C. *Acc. Chem. Res.* **1988**, *21*, 456; See also: <http://www.chem.wisc.edu/areas/reich/pkatable/>. For a splendid article discussing the various mechanistic possibilities involved in the hydroamination ring closing step, see: Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.
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19. The role played by the lithium cation is of paramount importance. By coordinating to the alkene π-system, it withdraws electron density from the olefin, hence facilitating the addition of the amine. Moreover, its coordination to the amine acidifies the hydrogen atoms attached on the nitrogen, easing the transfer of one of them to the developing carbanion. Finally, partial donation of the electron density gathered by lithium from the amine nitrogen and the C–C double bond to the amide nitrogen, increases its nucleophilicity, speeding up its addition on the alkene.
20. This is clearly evidenced by the various aggregation forms of lithiated amides in solvents of different polarity or coordinating abilities. For an excellent review, see: Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002 and references cited therein.
21. Since it is sold as a 1.6 M solution, using 16 mol % of *n*-BuLi is particularly convenient. However, in many cases, we have observed that lower amounts of *n*-BuLi are enough to bring the hydroamination to full conversion. For example, the double cyclisation of **40** to **42** and **43** proceeded in identical yields and diastereomeric ratios if 16, 10 or 5 mol % *n*-BuLi were employed.
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