Efficient Intramolecular Hydroamination of Unactivated Alkenes Catalysed by Butyllithium

Ali Ates*[a] and Coralie Quinet[a]

Keywords: Alkenes / Amination / Cyclization / Lithium

In this communication, we wish to report some preliminary results demonstrating, for the first time, that intramolecular hydroamination of unactivated alkenes can be performed efficiently using small quantities of *n*BuLi as the pre-catalyst.

Introduction

The hydroamination of alkenes (Figure 1) — the addition of an NH unit to a carbon-carbon double bond to form the corresponding amines — is of paramount importance in organic chemistry. This transformation, which is ideal from the viewpoint of atom economy as both reactants combine to afford a single product, generates the desired nitrogen derivative in only one step from readily available starting materials.

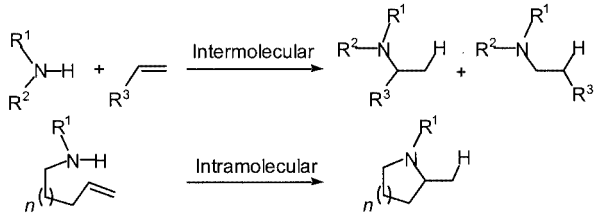


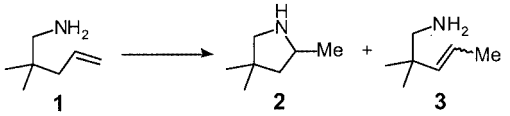
Figure 1. Hydroamination of unactivated alkenes

However, despite an enormous amount of work, only limited success has been obtained so far in the establishment of a mild and efficient procedure for the hydroamination of unactivated alkenes.[1] In 1954, Howk[2a] reported that ammonia and ethylene react in the presence of alkali metals under forcing conditions (temperature of up to 180 °C and pressures of up to 800 bar) to produce a mixture of ethyl-, diethyl- and triethylamine. More substituted alkenes, such as propene or 1-hexene, are less reactive under these conditions[2] (yields and/or conversions <30%). Only styrene and some substituted derivatives, as well as 1,3-dienes, which can be considered as slightly activated olefins, have been successfully hydroaminated under alkaline conditions[6,8] or with transition metals.[7,9] A breakthrough in the metal-catalysed[3,4] intramolecular hydroamination of unfunctionalised alkenes was achieved about ten years ago by the use of lanthanide complexes.[5] Unfortunately, the extraordinarily high sensitivity of these catalysts towards both moisture and oxygen precludes their general use without specialised equipment.

Results and Discussion

During some investigations directed towards the development of novel catalytic systems for the intramolecular hydroamination of unactivated alkenes, rigorously dry 1-amino-2,2-dimethylpent-4-ene (**1**) was required, and therefore it was stirred over sodium-potassium amalgam. Much to our surprise, the corresponding hydroaminated product **2** (entry 1, Table 1) was obtained, although in a modest yield of 10% (GC yield).[10] This result attracted our attention[11] and we decided to study in detail the base-catalysed cyclisation of amines such as **1**. In this communication, we wish to report some preliminary results demonstrating, for the

Table 1. Solvent and pre-catalyst effect on intramolecular hydroamination of substrate **1**



1 **2** **3**

Entry	Pre-catalyst	Solvent	Time [h]	Product ratios[a] [1:2:3]
1	Na-K amalgam	/	3	7:10:83
2	*n*BuLi (10 mol%)[b]	/	19	97:3:0
3	*n*BuLi (16 mol%)[c]	THF	18	2:95:3

[a] Ratio determined by GC analysis. [b] *n*BuLi (1.6 M in hexanes). [c] *n*BuLi (1.6 M in hexanes), THF, substrate concentration 0.5 M, room temp.

[a] Université catholique de Louvain, Département de Chimie, Unité de Chimie Organique et Médicinal, Bâtiment Lavoisier, Place Louis Pasteur 1, 1348 Louvain-la-Neuve, Belgium
Fax: (internat.) +32-10/472-788
E-mail: atesa@chim.ucl.ac.be

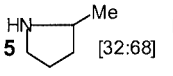
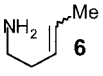
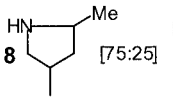
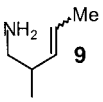
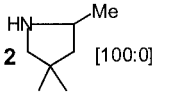
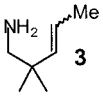
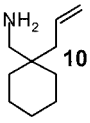
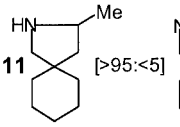
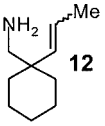
first time, that intramolecular hydroamination of unactivated alkenes can be performed efficiently using small quantities of *n*BuLi as the pre-catalyst.

Initial experiments, using catalytic amounts of a variety of bases such as *n*BuLi in the neat amines, produced only traces of the desired cyclised product **2** (Table 1, entry 2). However, addition of *n*BuLi to the dry aminoolefin **1** in tetrahydrofuran (0.5 M concentration), at room temperature, smoothly led to the formation of the corresponding pyrrolidine **2** in excellent yield (95%. GC yield, Table 1, entry 3) accompanied by trace amounts of the starting material **1** and the isomerised alkene **3**.

This remarkable result prompted us to investigate in greater detail the scope and limitations of this novel catalytic system. Various olefins bearing a primary amine function were thus prepared and reacted under our optimised conditions: *n*BuLi as pre-catalyst (5−16 mol %) in tetrahydrofuran at 50 °C or room temperature. Some selected results are collected in Table 2. When amine **4** was used, a fast reaction occurred at 50 °C and more than 95% conversion was observed after 2 hours of reaction (entry 1, Table 2). However, a mixture of the cyclised product **5** and the isomerised alkene **6** was generated in a ratio of 32:68 (GC ratio). On the other hand, when 1-amino-2,2-dimethylpent-4-ene (**1**; entry 3, Table 2) was reacted under the same conditions, adduct **2** was formed in a quantitative yield and no isomeric amine **3** could be detected either by GC or NMR analysis. Compound **7**, possessing a single methyl substituent (entry 2, Table 2) also gave a mixture of cyclised and isomerised products **8**:**9** in a ratio of 75:25 after more than 95% conversion at 50 °C.[12] Clearly, the substitution along the chain linking the amine and the olefin functions is responsible for the observed preference between the hydroamination and the isomerisation of the double bond. The Thorpe−Ingold effect, generated by the 2,2-dimethyl substituent in substrate **1**, is sufficient to suppress the isomerised product **3** completely (entry 3, Table 2). However, amine **4** or **7**, which do not possess such a similar Thorpe−Ingold effect, gave some isomerised product **6** or **9** beside the hydroaminated product **5** or **8** (entries 1 and 2, Table 2).

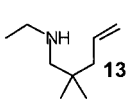
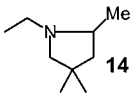
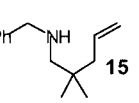
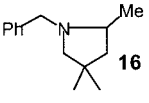
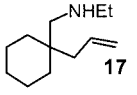
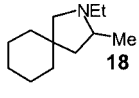
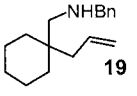
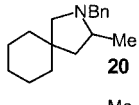
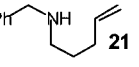
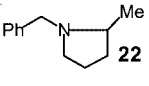
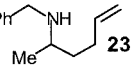
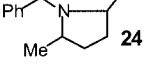
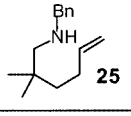
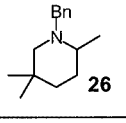
The synthetic utility of this novel, catalytic hydroamination protocol is further exemplified by the smooth ring closure of amine **10** to afford the spiro-bicyclic system **11** in 91% isolated yield (Table 2, entry 4). Only minute amounts of the isomerisation product **12** could be detected by GC and NMR analysis. Having successfully demonstrated that primary amines could be cyclised using small quantities of *n*BuLi (5−16 mol %), we next turned our attention to the intramolecular hydroamination of disubstituted amines. When various secondary amines were subjected to our standard base-catalysed conditions, a remark-

Table 2. Intramolecular hydroamination of primary amines.

Entry	Substrate[a]	Time [h]	Product ratios[b] (Hydroamination:Isomerisation)	Yield[c] [%]
(1)	 **4**	2	 **5** [32:68]  **6**	75
(2)	 **7**	8	 **8** [75:25]  **9**	81
(3)	 **1**	2	 **2** [100:0]  **3**	85[d]
(4)	 **10**	24	 **11** [>95:<5]  **12**	91[e]

[a] *n*BuLi (1.6 M in hexanes; for reasons of simplicity 16 mol % of pre-catalyst was used), THF or [D_8]THF, 50 °C, substrate concentration 0.5 M. [b] Determined by GC analysis or NMR spectroscopy in [D_8]THF. [c] Isolated yield, conversion >95%. [d] The amount of pre-catalyst could be reduced to 5 mol % without any significant change in the yield of the hydroaminated product. [e] Reaction performed at room temp. instead of 50 °C.

Table 3. Intramolecular hydroamination of secondary amines.

Entry	Substrate	Product	Time[a] [h]	Yield[b], [c] [%]
(1)	 **13**	 **14**	5	84 (>95)[d]
(2)	 **15**	 **16**	5	94 (>95)[d], [e]
(3)	 **17**	 **18**	5	86 (>95)[d]
(4)	 **19**	 **20**	5	99 (>95)[d]
(5)	 **21**	 **22**	2	79 (95)[f], [h]
(6)	 **23**	 **24**	2	75 (>80)[g], [h] *cis*:*trans* = 78:22
(7)	 **25**	 **26**	20	95 (>95)[e], [h]

[a] *n*BuLi (16 mol %), THF or [D_8]THF, room temp., substrate concentration 0.5 M. [b] Isolated yield, conversion >95%. [c] Yield in brackets determined by GC analysis or NMR spectroscopy in [D_8]THF. [d] <2% isomerisation of the double bond. [e] The amount of pre-catalyst could be reduced to 5 mol % without any significant change in the yield of the hydroaminated product. [f] 5% isomerisation of the double bond. [g] 20% isomerisation of the double bond [h] Reaction performed at 50 °C.

ably rapid formation of the desired pyrrolidines ensued (Table 3). In most cases, only five hours were required, at room temperature, for the quantitative conversion of the aminoolefin into the corresponding five-membered heterocycle (entries 1−4, Table 3).

As can be seen from Table 3, *N*-ethyl (entry 1 and 3, Table 3) and *N*-benzyl (entries 2 and 4, Table 3) substituents can be used equally successfully despite their important steric and electronic differences. Furthermore, no by-product originating from metallation at the benzylic position could be detected. It is noteworthy that the Thorpe−Ingold effect, which favours to some extent the hydroamination of primary amines, appears to play a much weaker role in the cyclisation of disubstituted amines. For example, intramolecular ring closure of substrates **21** (no methyl substituent) proceeded smoothly, affording the desired pyrrolidines **22** in excellent yield (compare entry 5, Table 3 with entry 1, Table 2). However, the presence of another substituent on nitrogen does not completely suppress the isomerisation and, besides amine **22**, 5% of the by-product originating from isomerisation of the terminal double bond to the 1,2-disubstituted alkene was observed. Similarly, the secondary *N*-benzyl-amine **23**, possessing a methyl substituent at C-1, gave the two pyrrolidines **24** in 75% isolated yield with a *cis*:*trans* ratio of 78:22 (entry 6, Table 3) accompanied by some isomerised product (<20%).

It is noteworthy that our base-catalysed protocol allows not only the synthesis of various pyrrolidines but also the assembly of piperidines (entry 7, Table 3). Indeed, when amine **25** was treated with 16 mol % of *n*BuLi, *at room temperature* in tetrahydrofuran, the hydroaminated product **26** was observed, along with the isomerised alkene, in a ratio of 30:70 (determined by GC analysis and NMR spectroscopy). Interestingly, when this 30:70 mixture of compounds was reacted under the same base-catalysed conditions, *but at 50 °C* instead of room temperature, the isomerised product disappeared completely in favour of the hydroaminated adduct **26**. Similarly, heating **25** with catalytic amounts of *n*BuLi, at 50 °C, resulted in the sole production of **26** (isolated yield 95%, entry 7, Table 3).

Based upon these observations, a plausible mechanism for the *n*BuLi-catalysed hydroamination of olefins can be proposed (Figure 2).

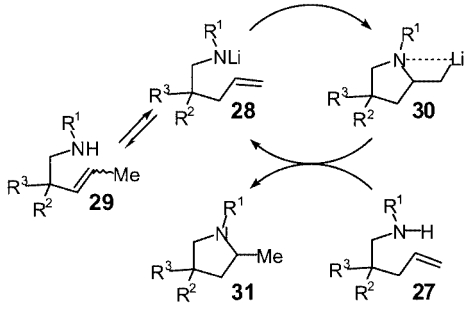


Figure 2. Mechanism for the *n*BuLi-catalysed hydroamination of alkenes.

The amides of strongly electropositive metals, such as lithium, appear to react intramolecularly with the C-C double bond of unactivated alkenes to form intermediate **30**. This lithiated carbanion is then protonated by the excess amine **27**, giving pyrrolidine **31** and regenerating amide **28**, which initiates a new catalytic cycle (Figure 2). In parallel, amine **29** might be formed competitively at room temperature by an intramolecular allylic-deprotonation/reprotonation sequence (Figure 2). At higher temperature (50 °C), the isomerisation equilibrium between **28** and **29** appears to be reversible and intramolecular cyclisation of amine **28** displaces this equilibrium, ultimately affording adduct **31**.

In summary, we have developed an efficient, catalytic protocol for the intramolecular hydroamination of unactivated double bonds. To the best of our knowledge, this is the first report that the use of inexpensive *n*BuLi (5−16 mol %) allows the expeditious high yielding intramolecular cyclisation of primary and secondary amines onto unactivated alkenes. This novel catalytic procedure opens exciting avenues for the rapid assembly of a variety of pyrrolidines, piperidines and derivatives. Further work is now directed at delineating the full scope of this protocol, establishing an enantioselective version and applying it to the synthesis of related natural products.

Experimental Section

*n*BuLi (1.6 M/hexane, 358 μL, 16 mol %) was added at room temperature to a stirred solution of 1-amino-2,2-dimethylpent-4-ene (**1**; 405 mg, 3.58 mmol) in tetrahydrofuran (0.5 M, 7 mL). The solution was stirred for 24 hours at room temperature. Diethyl ether (25 mL) and water (3 mL) were then added; the mixture was decanted and the aqueous phase extracted with diethyl ether (3 × 5 mL). The organic extracts were dried over $MgSO_4$ and the solvent removed carefully in vacuo at 0 °C to give 346 mg (85%) of **2** as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): δ = 1.04 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.12 (dd, $^2J_{H,H}$ = 12.45, $^3J_{H,H}$ = 3.35 Hz, 1 H, CH_2), 1.15 (d, $^3J_{H,H}$ = 6.22 Hz, 3 H, CH_3), 1.69 (dd, $^2J_{H,H}$ = 12.44, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH_2), 2.72 (A part of AB, $^2J_{H,H}$ = 11.0 Hz, 1 H, CH_2), 2.59 (B part of AB, $^2J_{H,H}$ = 11.01 Hz, 1 H, CH_2), 3.18−3.33 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) 21.9, 28.1, 29.0, 39.9, 49.7, 54.4, 61.1 ppm. IR (KBr): $\tilde{\nu}$ = 1100 cm^{-1}, 1152, 1198, 1280, 1366, 1377, 1463, 1649, 2866, 2955, 3298. MS (70 eV): *m*/*z* (%) = 113 (5) [$M^{\cdot+}$], 98 (40), 57 (100).

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[10] In many cases, the sodium-potassium amalgam leaves the substrate intact and rigorously dry after vacuum transfer. In some cases, although the same substrate and the same conditions were used, the hydroamination as well as the isomerisation of the double bond was observed during this drying step. Traces of impurities in the metallic sources could be the cause of these observations.

[11] To the best of our knowledge, no report of simple and efficient intramolecular hydroamination reactions of unactivated alkenes with alkali-metal catalysts has been published in the literature so far.

[12] When this reaction was performed at room temperature, the ratio of cyclised and isomerised products **8**:**9** was 25:75 after more than 65% conversion.

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