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An in situ generated samarium complex as a practical catalyst for the efficient intramolecular hydroamination of non-activated alkenes

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ABSTRACT

Mixing SmI_2 and $NaN(TMS)_2$ generates in situ an efficient catalyst that promotes the intramolecular hydroamination of non-activated olefins. A wide range of aminoolefins can be cyclised smoothly using this simple protocol. Mechanistic studies led to the identification of the putative active catalyst.

Nitrogen-containing compounds form a prominent family of substances which often display interesting biological activities. During the past 50 years, numerous synthetic methods have been developed to address the selective synthesis of amines and their derivatives.[1]

The most attractive approach is the direct hydroamination of olefins, which is defined as the formal addition of an N–H bond across a carbon–carbon unsaturation. Interestingly, this environmentally benign and optimally atom-economical process often uses readily available starting materials and generates little or no by-products. However, despite extensive and elegant contributions, only limited success has been obtained so far in the development of a mild, efficient and practical procedure for the hydroamination of terminal, non-activated alkenes.[2]

Our laboratory has recently been interested in the development of new methodologies for the intramolecular hydroamination of olefins, and we have previously disclosed a competent and convenient synthesis of cyclic amines using catalytic amounts of *n*-butyllithium.[3] More recently, the scope of this methodology has been broadened to enable the construction of more complex alkaloid-like substructures and the direct, one-step, assembly of bicyclic amines from linear precursors has been reported.[4]

Apart from the alkali metals, a wide variety of transition metal promoters have also been used in hydroamination reactions. Unfortunately, stoichiometric quantities of these complexes are generally required, rendering this method expensive and of little practicability. Moreover, modest selectivities in favour of the hydroaminated product are often observed.[5]

Recent breakthroughs in this area involved the successful application of catalytic quantities of, i.e. Pd, Pt, Ti, Sc, Zr and Au to the intramolecular cyclisation of various ω-unsaturated amines.[6]

Rare earth metal catalysts have proven to be particularly competent catalysts in various hydroamination reactions.[7] Used in small quantities, they provide the desired amines in good yields and under mild conditions. However, most of these lanthanide complexes are difficult to synthesise and to handle, and their preparation often requires specialised and expensive equipment. The extreme sensitivity of these catalysts towards moisture, oxygen and various nucleophiles significantly restricts their use in synthetic organic chemistry.

We were intrigued by the possibility of generating in situ a lanthanide-based catalyst that could efficiently promote intramolecular hydroamination reactions. In this manner, we would avoid the synthesis and the handling of such delicate species altogether. In this Letter, we report our initial results on the successful implementation of such a strategy. During the optimisation studies of the *n*-BuLi-catalysed hydroamination process, the effect of various bases, such as LDA, LiHMDS and NaHMDS was investigated. Whilst the addition of LDA to the ω-unsaturated amine **1** afforded smoothly pyrrolidine **2**, the use of LiHMDS or its sodium counterpart led to no detectable transformation (Fig. 1, entries 1 and 2).

Interestingly, addition of a small amount of SmI_2 (10 mol %) to the NaHMDS solution resulted in the smooth conversion of **1** into **2** (entry 3). To verify that both partners were required, the cyclisation of **1** was attempted in the presence of SmI_2 alone. As expected, no reaction was observed under these conditions (entry 4). It thus transpires that mixing a solution of SmI_2 (0.1 M in THF) with a solution of sodium hexamethyldisilazide (2 M in THF) in a 1:2 ratio leads to the in situ generation of an active hydroaminating catalyst. Preliminary experiments revealed that a 10 mol % loading of samarium (from SmI_2) is enough to promote the cyclisation of a variety of ω-unsaturated primary amines, as illustrated in Table 1.

As can be seen, this method provides an easy and efficient access to pyrrolidines (Table 1, entries 1–4) as well as piperidines (Table 1, entry 5) in excellent yields. In all cases, complete conversion of the starting amines was observed. As anticipated, the introduction of conformational constraints such as a *gem*-dimethyl or

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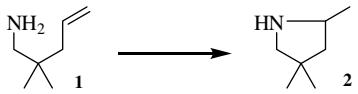
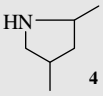
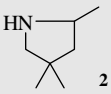
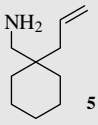
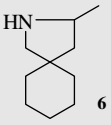
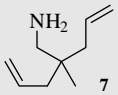
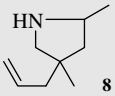
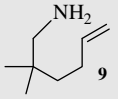
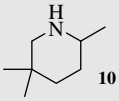


Entry	Base	Additive	Yield [%]
1	LDA 10%	/	85
2	NaHMDS 20%	/	0
3	NaHMDS 20%	SmI_2 10%	87
4	/	SmI_2 10%	0

Figure 1.

Table 1

Entry	Substrate	Product	Time (h)	Yield[a] (%)
1	 3	 4	100	85
2	 1	 2	24	87
3	 5	 6	24	93
4	 7	 8	6	93
5	 9	 10	24	88

[a] All yields are for pure, isolated compounds. All the conversions are quantitative and the reactions are performed using 10 mol % SmI_2 (0.1 M in THF) and 20 mol % $NaN(TMS)_2$ (2 M in THF) in THF (0.5 M solutions) at 60 °C.

cyclohexyl substituent (Table 1, entries 2 and 3) leads to considerably shorter reaction times.

Using this in situ generated catalytic system, the synthesis of piperidine **10** (Table 1, entry 5) from the aminoolefin **9** could be accomplished in excellent yield. It is noteworthy that in this case, the Thorpe-Ingold effect played a major role. Indeed, in the absence of the *gem*-dimethyl substituent, no piperidine product could be obtained.

At this stage of our investigations, a mechanistic hypothesis was proposed, largely inspired by the seminal results obtained by Marks and co-workers (Fig. 2).[8]

Thus, it was envisioned that the addition of SmI_2 to $NaN(TMS)_2$ might lead to the in situ formation of the Sm(II) complex **11**. Subsequent σ-metathesis with the aminoolefin **12** would then generate the amino-samarium complex **13**. Insertion of the nitrogen–metal bond into the pendent unsaturation, followed by protonation in the presence of excess starting amine would then complete the catalytic cycle (Fig. 2).[9]

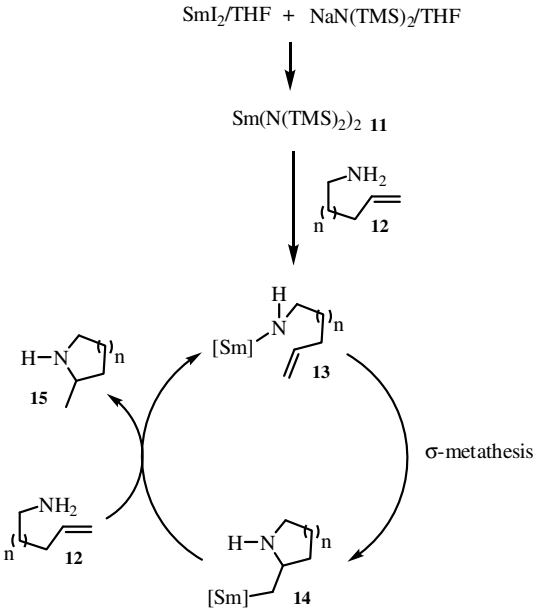


Figure 2.

In order to broaden the scope of this method, the synthesis of bicyclic amines was attempted using the in situ generated catalyst. Unfortunately, cyclisation of substrates **17** provided only traces of the desired products **18** (Fig. 3, conditions (a)). To our surprise, when a commercial solution of $Sm[N(TMS)_2]_3$[10] was employed, complete conversion to the fused bicycles **18** was observed. In the case of pyrrolizidine **18** ($n = 1$), a single diastereoisomer was obtained in excellent yield, after 24 h in THF at 60 °C (Fig. 3, conditions (b)).

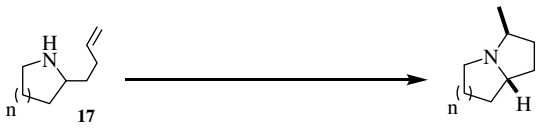
These results suggest that the active catalyst may actually be a Sm(III) species and not, as we originally assumed, a Sm(II) derivative.[11] In accord with this assumption, when precursor **17** ($n = 1$) was treated with SmI_3 and 3 equiv of $NaN(TMS)_2$ (Fig. 3, conditions (c)), a similarly smooth transformation took place and **18** ($n = 1$) was generated quantitatively.[12]

However, the successful cyclisation of the substituted piperidine **17** ($n = 2$) into the corresponding indolizidine **18** ($n = 2$) required the use of higher temperature. Performing this hydroamination reaction in THP/toluene (1:1, v/v) at 110 °C (an efficient set of conditions that we discovered during our work on the *n*-BuLi-catalysed intramolecular hydroamination of non-activated alkenes[4]), and using $Sm[N(TMS)_2]_3$ as the catalyst, afforded the desired fused bicyclic adduct **18** ($n = 2$, Fig. 3, conditions (d)) in good yield. Indolizidine **18** was obtained as a 1.2:1 mixture of diastereoisomers in favour of the cis-isomer.

These conditions were then applied successfully to other substrates, such as compound **19**, which provided pyrrolidine **20** in excellent yields and moderate diastereoisomeric ratios (the major diastereoisomer was shown to possess trans relative stereochemistry) (Fig. 4).

Finally, this methodology was applied to a short synthesis of (±)-dihydropinidine **22**. As shown in Figure 5, addition of 10 mol % of $Sm[N(TMS)_2]_3$ to the aminoolefin **21**, in THP, at 90 °C, smoothly led to (±)-**22** in excellent yield and good diastereoisomeric ratio (Fig. 5).

In summary, we have developed an efficient synthesis of nitrogen heterocycles based upon a novel protocol involving the intramolecular hydroamination of olefins promoted by catalytic



	Conditions	n = 1	n = 2
(a)	SmI_2 0.1 M / THF (10 mol%) $NaN(TMS)_2$ 2 M / THF (20 mol%) THF, 60 °C, 48 h	6% conv.	0%
(b)	$Sm[N(TMS)_2]_3$ (10 mol%) THF, 60 °C, 24 h	100% conv. 86% yield	0%
(c)	SmI_3 (10 mol%) $NaN(TMS)_2$ 2 M / THF (30 mol%) Toluene, 100 °C, 24 h	100% conv.	
(d)	$Sm[N(TMS)_2]_3$ (10 mol%) THP/Toluene 1:1, 110 °C, 24 h		100% conv. 61% yield

Figure 3.

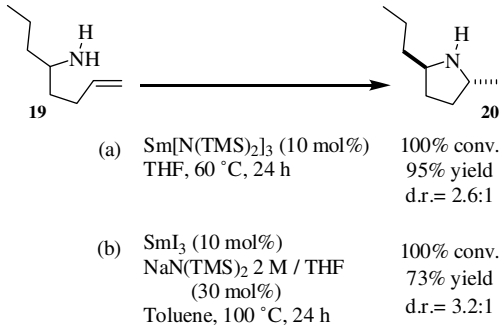


Figure 4.

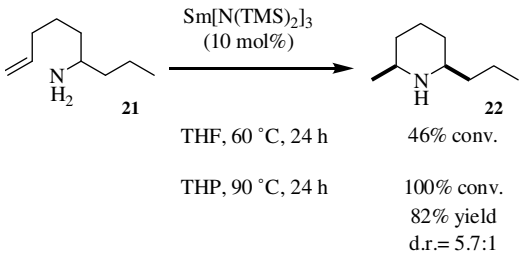


Figure 5.

amounts of an in situ generated samarium complex, obtained by mixing SmI_2 (10 mol %) with $NaN(TMS)_2$ (20 mol %). This method has initially allowed us to prepare various, substituted pyrrolidines. Subsequently, the nature of the active catalytic species has been revealed as being a Sm(III) complex and not the expected Sm(II) derivative, thereby enabling the use of commercially available $Sm[N(TMS)_2]_3$. With this catalyst, we have been able to extend the scope of our methodology by successfully performing the synthesis of several piperidines and some fused bicyclic amines.[13] The usefulness of our method was demonstrated through a short synthesis of (±)-dihydropinidine.

Acknowledgements

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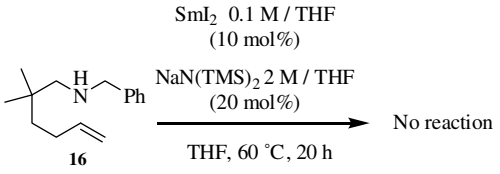
9. It is interesting to note that the presence of a hydrogen atom on the nitrogen of complex **13** appears to play a crucial role in the success of these hydroamination reactions. Indeed, attempted cyclisation of the secondary aminoolefin **16**, under the optimal conditions developed for the primary amines, did not yield the corresponding piperidine adduct, even after 20 h.



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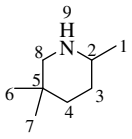
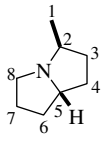
11. In some experiments using the first-generation catalytic system, a characteristic colour change of the mixture (from blue to yellow) was occasionally observed without detrimental effect on the efficiency of the reaction.
12. For solubility reasons, SmI_3, a yellow solid, was initially dissolved in toluene. Then, a THF solution of $NaN(TMS)_2$ was added, followed by the aminoolefin. Using this protocol, results similar to those obtained under conditions (b) could be achieved after 24 h at 100 °C.
13. *Preparation of* **10** *using commercial solutions of* SmI_2 *and* $NaN(TMS)_2$
In a flame-dried Schlenk apparatus, maintained at room temperature, a solution of SmI_2, 0.1 M, in THF (3.9 ml, 0.393 mmol, 10 mol %) was added to a stirred solution of 1-amino-2,2-dimethylhex-5-ene **9** (500 mg, 3.93 mmol, 1 equiv) in tetrahydrofuran (3.5 ml, 0.5 M). Then, a solution of $NaN(TMS)_2$, 2 M, in THF (0.4 ml, 0.786 mmol, 20 mol %) was added to this mixture. The solution was stirred and heated at 60 °C for 24 h. Diethyl ether (10 ml) and water (5 ml) were then added. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 5 ml). The pooled organic extracts were washed with 25 ml of water and then with 25 ml of a saturated aqueous solution of NaCl, dried over $MgSO_4$ and the solvent was removed carefully in vacuo, at 0 °C. Vacuum transfer (1.5 mbar, rt) gave 439 mg of pure 2,5,5-trimethylpiperidine **10** (88% yield) as a colourless oil.



^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 2.62–2.40 (3H, m, H-2 and H-8), 1.48–1.12 (4H, m, H-3 and H-4), 1.06 (3H, d, J = 6.3 Hz, H-1), 0.95 (3H, s) and 0.83 (3H, s) (H-6 and H-7). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 58.9 (C-8), 52.5 (C-2), 38.2 and 31.4 (C-3 and C-4), 29.6 (C-5), 29.5, 23.9 and 22.9 (C-1, C-6 and C-7). MS (CI, 70 eV) *m/z* (relative intensity, %): 128 (M+1, 34), 69 (53), 55 (100), 41 (82). IR (KBr) ν (cm^{-1}): 3299 [m], 2953–2855 [s], 1459 [m], 1379 [m]. CAS: [141511-51-5].

Preparation of **18** *(n = 1) using* $Sm[N(TMS)2]_3$
In a flame-dried Schlenk apparatus, maintained under a positive pressure of argon, a solution of aminoolefin **17** (n = 1) (100 mg, 0.80 mmol, 1 equiv) in tetrahydrofuran (1.6 ml, 0.5 M) was added, at room temperature, to $Sm[N(TMS)_2]_3$ (solid, 50 mg, 0.080 mmol, 10 mol %). The resulting solution was stirred and heated at 60 °C for 24 h. The corresponding pyrrolizidine **18** (n = 1) was obtained following the same work-up and purification method as described above (86 mg, 86% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 3.61 (1H, quint, 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 ($M^{+\cdot}$, 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*).