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Intramolecular alkene hydroaminations catalyzed by simple amido derivatives of the Group 3 metals

Young Kwan Kim,[a] Tom Livinghouse[a,*] and John E. Bercaw[b]

[a]*Department of Chemistry, Montana State University, Bozeman, MT 59717, USA*
[b]*Division of Chemistry and Chemical Engineering, California Institute of Technology, USA*

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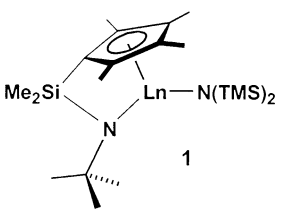
Abstract—Bis(trimethylsilyl) amides of the type $Ln[N(TMS)_2]_3$ have been found to be competent catalysts for representative intramolecular alkene hydroaminations. The catalytic cyclization of an aminodiene proceeds in a stepwise manner to provide the corresponding monocycle and bicycle in a highly stereocontrolled manner.

The catalyzed intramolecular hydroamination of alkynes[1] and alkenes[2] has attracted considerable attention as a valuable method for the synthesis of nitrogenous heterocycles.[3] In a series of seminal publications, Marks and collaborators have shown that metallocene derivatives of the lanthanide metals serve as excellent catalysts for the intramolecular hydroamination of alkenes, alkynes and allenes.[4] In addition, these investigators have demonstrated that 'constrained-geometry' half-sandwich complexes of the type **1** are catalytically quite active in this context.[5] We recently reported that simple, non-metallocene-based Group 4 alkyls are effective reagents for promoting efficient aminoalkyne cyclizations, and that the resulting organometallic intermediates could subsequently be *C*-acylated in high yield.[6] In this Letter, we disclose that readily available[7] amido complexes, corresponding to the formula $Ln[N(TMS)_2]_3$ (Ln = lanthanide) **2**, are effective catalysts for intramolecular alkene hydroamination.



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$Ln[N(TMS)_2]_3$

2a: Ln = Y
2b: Ln = Nd

We commenced the current study by examining the behavior of aminoalkene **3a**[2b] in the presence of catalytic quantities of $Y[N(TMS)_2]_3$ (**2a**). Addition of **3a** to **2a** (2.7 mol%) in C_6D_6[8] at 24°C resulted in the disappearance of the metalloamide singlet with the immediate and apparently quantitive[9] liberation of $(TMS)_2NH$, as judged by ^1H NMR. Cyclization of **3a** to the corresponding pyrrolidine **4a** proceeded smoothly with complete consumption of starting material occurring after 6 h at 24°C. As expected, the use of 2.7 mol% of $Nd[N(TMS)_2]_3$ (**2b**), which possesses a larger Ln center,[2] as the catalytic source led to a more rapid rate of product consumption with complete conversion of **3a** to **4a** observed after 4 h at 24°C. Diastereoselective cyclizations of chiral aminoalkenes were then investigated. Accordingly, submission of the racemic amines **3b**,[2b] **3c**[2b] and **3d** to the Ln amides **2a** or **2b** (2.7 mol% in C_6D_6) under the indicated reaction conditions cleanly furnished the anticipated pyrrolidines as *trans*/*cis* mixtures. In addition, cyclization of aminoalkene **3e**[2a] occurred with *N*-functionalization at the protertiary center to give the 2,2-disubstituted pyrrolidine **4e** (Table 1). The true nature of the catalyst or catalytic entities in these reactions is unclear at present, given the time-dependent composition of potential amine ligands as well as the known proclivity of Ln(III) complexes to possess high coordination numbers. It is also of interest in this context that the rates of conversion to product would appear far more sensitive to substrate structural variation than for Ln-metallocene catalysts.[2]

Some of the foregoing results can be compared to analogous aminoalkene cyclizations catalyzed by Group 3 metallocene complexes. Specifically, cyclization of **3b** in the presence of $(Cp^*)_2Ln$ derived catalysts at 25°C proceeds with *trans*:*cis* selectivities of 1:1.25 (Ln = Nd) and 8:1 (Ln = Y).[2b] The cyclization efficiency

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* Corresponding author.

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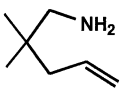
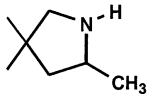
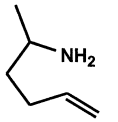
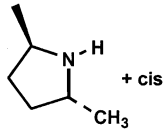
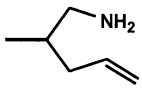
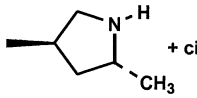
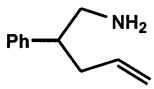
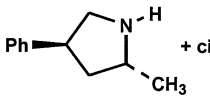
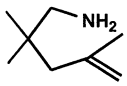
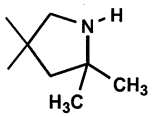
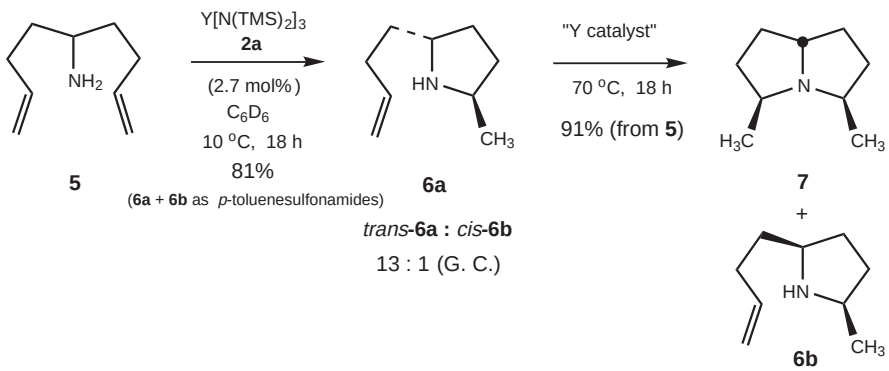
Table 1. $Ln[N(TMS)_2]_3$ catalyzed cyclization of representative aminoalkenes

	Aminoalkene **3**	Ln	Conditions[a]	Pyrrolidine **4**	% Yield[b]
a		Y	24 °C, 6 h		>95
		Nd	24 °C, 4 h		
b				 + cis	94
		Y	90 °C, 6 d	7 : 1	
		Nd	90 °C, 2 d	4 : 1	
c				 + cis	>95
		Y	90 °C, 10 d	2 : 1	
		Nd	90 °C, 7 d	2 : 1	
d				 + cis	95 (94%)[d]
		Y	90 °C, 1.5 h	1.7 : 1	
		Nd	90 °C, 1.5 h	2.2 : 1	
e		Y	45 °C, 45 h		93[c] (80%)[d]
		Y	70 °C, 8 h		94[e]

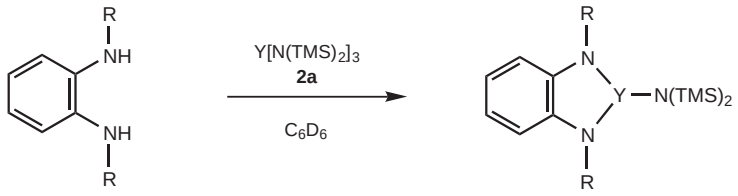
[a]All reactions were conducted in C_6D_6. [b]Yield by NMR. [c]7% of **3e** remained unchanged. [d]Isolated yield of the corresponding *p*-toluenesulfonamide. [e]In this instance, 3.0 mol% of **2a** was utilized.

of aminoalkene **3e** in the presence of 3.0 mol% of **2a** at 70°C can be directly compared to cyclizations conducted under identical conditions using yttrocene complexes. Accordingly, cyclization of **3e** in the presence of 3 mol% of $Cp_2YCH_2TMS{\cdot}THF$, $[Cp^{TMS}{}_2YMe]_2$ or Me_2Si-$CpCp''YCH(TMS)_2$ at 70°C proceeds in 9 days, 8 h and ≤ 1 h, respectively.[2a]

Diastereoselective bicyclization of aminodienes to the corresponding bridged heterocycles would constitute a concise means for the assembly of various naturally occurring ring systems.[4] In a study to determine the feasibility of this process using simple Ln(III) amides, aminodiene **5** was exposed to **2a** (2.7 mol%) in C_6D_6. In unexpected contrast to the structurally related aminoalkene **3b**, **5** underwent facile *mono*cyclization at 10°C over 18 h to furnish the anticipated pyrrolidines **6a** and **6b** (**6a**:**6b** = 13:1) which were isolated as a mixture of the corresponding *p*-toluenesulfonamides in 81% overall yield. Significantly, simply increasing the temperature to 70°C led to selective bicyclization in which *trans*-**6a** was converted to pyrrolizidine **7**[10] (91%) over 18 h. As expected, the *cis*-isomer **6b** underwent cyclization far more slowly under these conditions (Scheme 1).



Scheme 1.



7a: R = TMS (15 h, 24°C)

7b: R = $CH_2C(Me)_3$ (8 h, 45°C)

8a, **b**

Scheme 2.

Asymmetric catalytic reactions have played an ever-expanding role as a means for preparing compounds of commercial and theoretical interest. A particularly attractive modification of the present amido complexes would involve their conversion to catalysts derived from chiral chelating diamines. Toward this end, and in order to demonstrate the feasibility of preparing robust (achiral) metallacycles, **8a** and **8b** were readily prepared by simple exposure of **2a** to diamines **7a** or **7b** with concomitant amine elimination (Scheme 2). Exposure of **3a** to **8a** or **8b** in C_6D_6 at 45°C gave rise to pyrrolidine **4a** with >95% conversion achieved in 54 h and 30 h, respectively.

In conclusion, we have shown that readily available Group 3 amides are competent catalysts for efficient intramolecular alkene hydroamination. In addition, $Y[N(TMS)_2]_3$ (**2a**) has been used to catalyze a sequential and highly stereoselective aminodiene bicyclization, resulting in the construction of the corresponding pyrrolizidine nucleus in one step. Modification of the Ln(III) center in these amides is readily achieved by amine elimination in the presence of chelating diamines to provide active catalysts with altered activities. The utilization of the latter strategy for the synthesis of chiral Group 3 amido complexes and their use in asymmetric catalysis will be the topics of future accounts from these laboratories.

Acknowledgements

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7. Bradley, D. C.; Ghotra, J. S.; Hart, F. A. *J. Chem. Soc., Dalton Trans.* **1973**, 1021.
8. In a typical cyclization, the aminoalkene (3.2×10^{-4} mol) and $Ln[N(TMS)_2]_3$ (9×10^{-6} mol, 2.7 mol%) were dissolved in C_6D_6 (0.7 mL) contained in a gas-tight NMR tube in a drybox. The reaction mixture was then maintained at the indicated temperature until alkene hydroamination was complete. In the indicated cases, the product pyrrolidines were isolated as the corresponding *p*-toluenesulfonamides.
9. The identity of the new NMR signal corresponding to $(TMS)_2NH$ was established by the introduction of an authentic sample of this substance.
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