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Organolanthanide-Catalyzed Intramolecular Hydroamination/ Cyclization of Amines Tethered to 1,2-Disubstituted Alkenes

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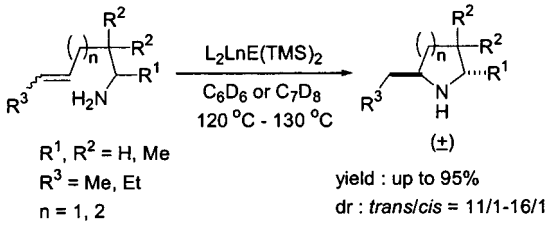
ABSTRACT



This contribution reports the organolanthanide-catalyzed intramolecular hydroamination/cyclization of amines tethered to 1,2-disubstituted alkenes to afford the corresponding mono- and disubstituted pyrrolidines and piperidines by using coordinatively unsaturated complexes of the type (η^5-Me_5C_5)$_2$LnCH(TMS)$_2$ (Ln = La, Sm), [Me_2Si(η^5-Me_4C_5)$_2$]NdCH(TMS)$_2$, [Et_2Si(η^5-Me_4C_5)(η^5-C_5H_4)]NdCH(TMS)$_2$, and [Me_2Si(η^5-Me_4C_5)(^{t}BuN)]-LnE(TMS)$_2$ (Ln = Sm, Y, Yb, Lu; E = N, CH) as precatalysts. [Me_2Si(η^5-Me_4C_5)(^{t}BuN)]LnE(TMS)$_2$ mediates intramolecular hydroamination/ cyclization of sterically demanding amino-olefins to afford disubstituted pyrrolidines in high diastereoselectivity (*trans*/*cis* = 16/1) and in good to excellent yield.

In terms of atom economy, catalytic N−H bond addition to unactivated C−C multiple bonds[1−3] is potentially one of the most efficient and elegant processes for construction of naturally occurring alkaloid skeletons. Over the past decade, catalytic regio-/diastereo-/enantioselective intramolecular cyclohydroamination catalyzed by trivalent lanthanocene complexes[4] has been extensively investigated. Major advances include cycloaminations of aminoalkenes,[5] aminoalkynes,[6] and aminoallenes,[7] tandem bicyclizations of aminodienes, aminodiynes, and aminoenynes,[8] and recent application to the stereoselective synthesis of the bicyclic alkaloid, (+)-xenovenine.[9] Organolanthanide-mediated intermolecular hydroamination has also been demonstrated.[10] The efficiency of these catalytic reactions is remarkable with regard to high turnover frequencies[5,6] (N_t = 5−140 h^{-1} for terminal aminoalkenes; 4−7600 h^{-1} for aminoalkynes), versatility of alkylation pattern and ring size,[5−8] and high stereoselectivity.[5−11] Despite these attractive features, organolanthanide-

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(1) For reviews of catalytic amine addition to C−C multiple bonds, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703 and references therein. (b) Roundhill, D. M. *Catal. Today* **1997**, *37*, 155−165. (c) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113−1126.

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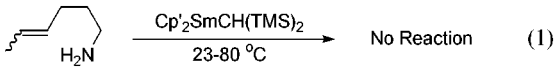
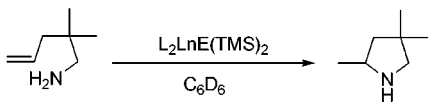
catalyzed cyclohydroamination of amines tethered to more encumbered alkenes (e.g., 1,2-disubstituted alkenes) has remained elusive[7a,12] (cf. eq 1).



(1)

Cyclizations of amines tethered to 1,2-disubstituted alkenes are of fundamental importance for the construction of heterocyclic systems bearing key substituents present in naturally occurring alkaloids. Although cyclohydroamination of aminoalkynes and aminoallenes can introduce a variety of longer chain alkyl substituents onto product pyrrolidine and piperidine skeletons, the synthesis of these substrates is not necessarily straightforward. Furthermore, additional reductive transformations of the resulting imine or alkene products are required to obtain saturated targets. We now report that the use of more coordinatively unsaturated and thermally robust organolanthanide complexes combined with higher reaction temperatures allows extension of aminoalkene cyclohydroaminations to 1,2-disubstituted alkenes.[13]

Facile organolanthanide-catalyzed cyclohydroamination demonstrates that insertion of C−C multiple bonds into Ln−N bonds via a four-centered transition state (T1, Figure 1) can be efficaciously coupled to rapid protonolysis of the resulting Ln−C bonds[11] (i.e., **3** → **4**; Figure 1). The inherent limitation in 1,2-disubstituted alkene insertion is reasonably attributed to severe nonbonded repulsions and possible charge separation imbalance in the reasonably well-characterized transition state[11] (T1, Figure 1), both deriving from the sterically demanding, electron-donating alkyl substitution. The steric sensitivity of the olefin insertion step doubtless reflects subtle changes in the catalyst coordination environment, and therefore lanthanide ions of maximum ionic radius and more open ancillary ligation should in principle reduce congestion.[11] Previous kinetic studies of 2,2-dimethyl-4-pentene-1-amine cyclohydroamination (**A**, eq 2) revealed a



A

(2)

significant rate dependence on lanthanide ionic radius (N_t = 95 s^{-1} (25 °C) for La^{3+} vs N_t < 1 s^{-1} (80 °C) for Lu^{3+})[11] and enhanced activity using more open organolanthanide centers (e.g., N_t = 181 h^{-1} (25 °C) for (CGC)SmN(TMS)$_2$ (**5a**) vs N_t = 48 h^{-1} (80 °C) for Cp′$_2$SmCH(TMS)$_2$ (**8b**)).[14b]

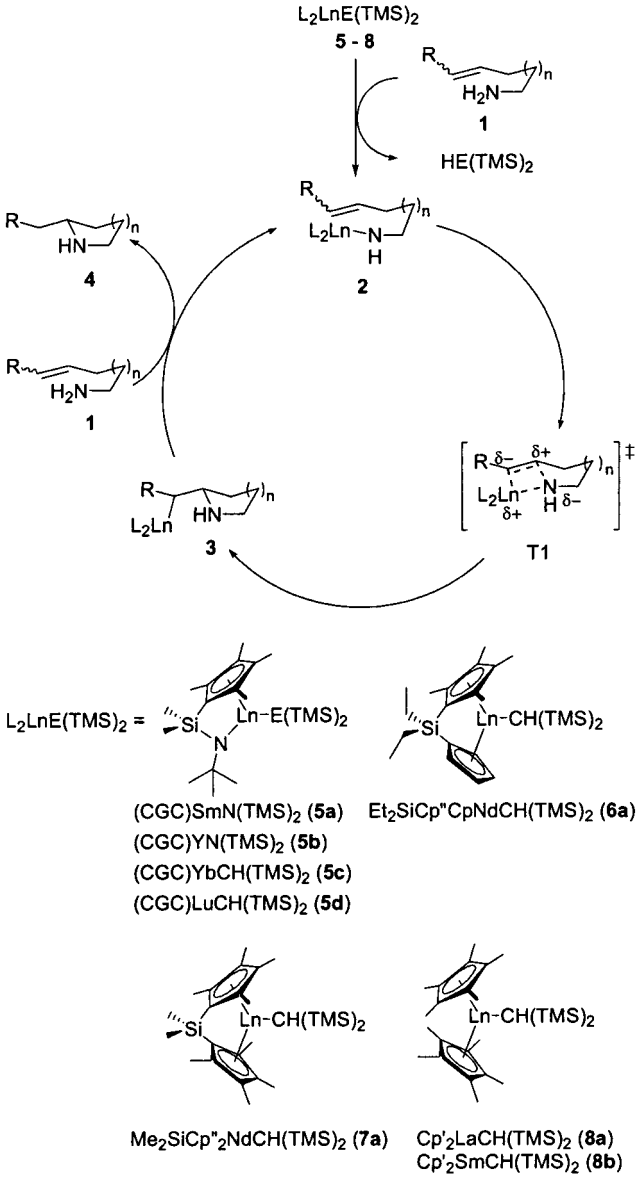


Figure 1. Proposed catalytic cycle for organolanthanide-catalyzed cyclohydroamination of aminoalkenes.

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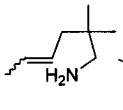
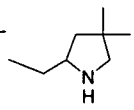
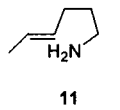
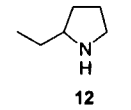
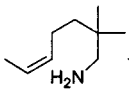
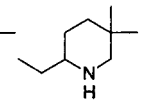
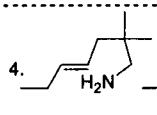
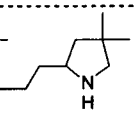
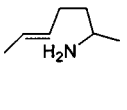
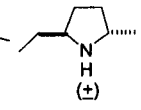
(13) Ryu, J.-S.; Marks, T. J.; McDonald, F. E. Presented in part at the 221st National Meeting of the American Chemical Society, San Diego, CA, April 1−5, 2001; Abstract ORGN 265.

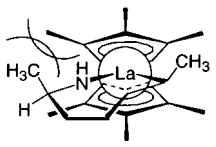
Table 1. Results for Organolanthanide-Catalyzed Intramolecular Cyclohydroamination of the Amines Tethered to 1,2-Disubstituted Alkenes[a]

entry	substrate	product	precatalyst (mol%)	conditions	conversion %[b] [*trans*:*cis*][b]
1.			**5a** (6.7)	19 h, 125 °C	>95
			5b (3.3)	19 h, 125 °C	>95
			5c (3.2)	36 h, 120 °C	70[c]
	9	**10**	**7a** (5.0)	19 h, 125 °C	>95
			8a (4.8)	12 h, 125 °C	>95 (90)[d]
			8b (2.3)	65 h, 120 °C	20
2.			**5a** (7.2)	168 h, 125 °C	42
			6a (3.6)	240 h, 120 °C	56
			7a (3.3)	165 h, 125 °C	56
	11	**12**	**8a** (3.3)	43 h, 120 °C	>95 (79)[d]
			8b (3.3)	100 h, 120 °C	10
3.			**5a** (4.7)	116 h, 120 °C	>95
			5b (4.0)	107 h, 120 °C	>95
			5c (8.2)	25 h, 120 °C	>95 (82)[c]
			5d (5.9)	46 h, 120 °C	>95
	13	**14**	**6a** (5.0)	137 h, 125 °C	>95
			8a (6.1)	4 h, 120 °C	>95
			8b (4.5)	26h, 120 °C	>95
4.			**5a** (4.5)	34 h, 120 °C	93
			5b (6.9)	39 h, 120 °C	98
			5d (4.3)	38 h, 120 °C	95
	15	**16**			
5.			**5a** (10.2)	40 h, 120 °C	95 [11:1] (92)[d]
			5b (8.8)	37 h, 120 °C	90 [16:1]
			5d (3.7)	92 h, 120 °C	77 [15:1]
	17	**18** (±)	**8a** (6.0)	148 h, 120 °C	32[e]
			8b (4.4)	120 °C	N.R.

[a] All reactions conducted in C_6D_6 or C_7D_8. [b] Determined by ^{1}H NMR spectroscopy and GC−MS. [c] Isolated yield of the corresponding HCl salt in preparative-scale reaction. [d] Isolated yield in NMR-scale reaction. [e] Similar *trans*:*cis* ratio observed by ^{1}H NMR spectroscopy.

To this end, we investigated lanthanocenes with relatively large ionic radii (La^{3+} = 1.160 Å > Sm^{3+} = 1.079 Å) and lanthanide complexes having more open and rigid ligation spheres (*ansa*-$Me_2SiCp''Cp$, *ansa*-$Me_2SiCp''_2$, and CGC = [$Me_2Si(\eta^5$-$Me_4C_5)(^tBuN)$], Figure 1),[14a] using elevated reaction temperatures and relatively high catalyst loadings (2−10 mol %).

The organolanthanide-catalyzed cyclohydroamination of a representative series of aminoalkene substrates was studied using a selected grouping of the aforementioned catalysts (Table 1).[15] At 2−10 mol %[16] catalyst loadings and at 120−130 °C, the anaerobic, anhydrous, NMR-scale reaction of 2,2-dimethyl-4-hexen-1-amine (**9**) proceeds rapidly and cleanly to cyclized product (Table 1, entry 1). For substrates not bearing an alkyl substituent at the C1 position (Table 1, entries 1−3), cyclization mediated by both the Cp'_2La system **8a** and the (CGC)Ln system **5a**−**d** affords the corresponding cyclized products. Although Cp'_2La complex **8a** serves as a generally effective catalyst for less sterically demanding substrates such as **9**, **11**, and **13**, significant depression of the conversion in Cp'_2La-catalyzed cyclization is observed for an aminoalkene with a methyl substituent at the C1 position (**17**, entry 5). Apparently the C1 methyl substituent and the alkene methyl substituent incur significant repulsive steric interactions with the Cp′ methyl groups in the transition state (e.g., **B**). However, efficient reaction rates and good



B

stereoselectivities are observed in cyclohydroaminations of **17** with catalysts offering a more open coordination environment, such as (CGC)Ln catalysts **5a**, **5b**, and **5d**. (Although correlations of activity and ionic radius are not as clear-cut as in the case of less hindered α-olefinic systems).[11,14b] Cyclohydroamination of substrate **17** proceeds with excellent *trans* diastereoselectivity, consistent with an envelope-like transition state (Figure 2). Among several possible conformers, conformer **II** offers minimal 1,3-diaxial interactions, consistent with the observed diastereoselectivity.[17]

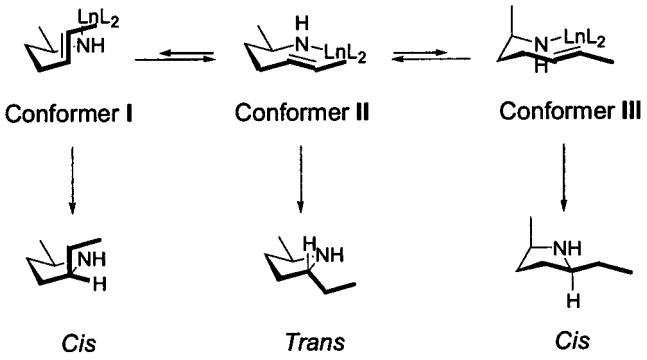


Figure 2. Plausible cyclohydroamination intermediates and pathway yielding *trans*-2-ethyl-5-methyl-pyrrolidine (**14**).

NMR monitoring of cyclohydroaminations that require relatively long reaction times occasionally reveals declining turnover frequencies beyond one half-life. This effect is reasonably attributed to competitive inhibition by the Lewis basic product[11] and/or noncompetitive inactivation via ther-

(14) (a) Crystal structure data show CGC complex Cp(c)−M−N angles (Cp(c) = ring centroid) to be 25−28° smaller than Cp(c)−M−Cp(c) angles in the corresponding biscyclopentadienyl lanthanocenes. (b) Tian, S.; Arredondo, V. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568−2570.

mal decomposition of the catalytically active L_2Ln-$NHR(NH_2R)_n$ species. To investigate the latter question further, the intrinsic thermolytic stability of several organolanthanide precatalysts was scrutinized in C_6D_{12} solution. The concentration of diamagnetic precatalyst vs. time profiles depicted in Figure 3 illustrate approximately zero-order

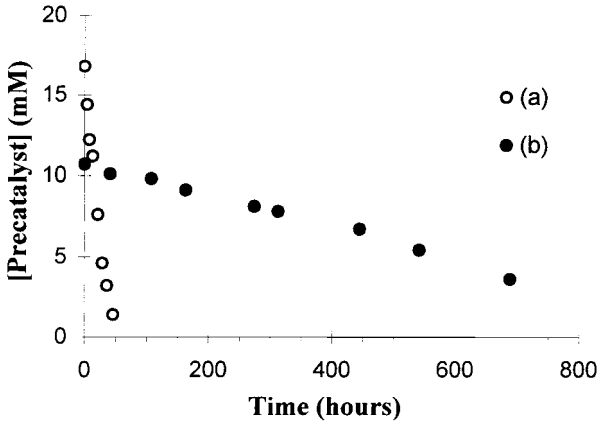


Figure 3. Thermolysis rate data for organolanthanide precatalysts in sealed tubes at 120 °C: (a) A 16.8 mM $Cp'_2LaCH(TMS)_2$ solution in C_6D_{12} with Cp_2Fe as an internal calibration standard (○). (b)[18] A 10.7 mM (CGC)YN$(TMS)_2$ solution in C_6D_{12} with Cp_2Fe as an internal calibration standard (●).

behavior in [precatalyst]. The thermal decomposition rate of (CGC)YN$(TMS)_2$ is clearly slow at 120 °C, while precatalyst $Cp'_2LaCH(TMS)_2$ decomposes rapidly. The diminution of precatalyst Cp′ resonances at δ 2.015 and 1.972 ppm and the quantitative evolution of $CH_2(TMS)_2$ resonances at δ 0.030 and −0.268 ppm are observed by ^{1}H NMR. The zero-order kinetic behavior and relatively rapid decomposition profile of the Cp'_2La-hydrocarbyl precursor suggests an intramolecular thermolytic pathway, likely involving ring metalation and η^6-$Me_4C_5CH_2$ formation.[19] In the presence of amine substrates, the Cp'_2La system exhibits catalytic activity at 120 °C for several days with slowly declining η^5-Cp′ signals in the ^{1}H NMR. This result implies that catalytically active $Cp'_2La(NHR)(NH_2R)_n$ species are more thermally stable than the hydrocarbyl precursor and/or that η^6-$Me_4C_5CH_2$ species readily revert to active catalysts upon protonolysis (eq 3).[19d,19e]

$$(Me_5C_5)La(\eta^6\text{-}Me_4C_5CH_2) \xrightarrow{n NH_2R} (Me_5C_5)_2La\text{-}NHR(NH_2R)_n \quad (3)$$

In summary, limitations in the elusive addition of lanthanide−N bonds to 1,2-disubstituted alkenes have been overcome, and substrate generality for future synthetic applications has been demonstrated. Lanthanocenes such as (CGC)LnE$(TMS)_2$ (Ln = Sm, Y, Lu; E = CH, or N) complexes with more open coordination spheres serve as effective precatalysts for sterically-demanding olefinic substrates.

Acknowledgment. Financial support by the NSF (CHE-0078998) is gratefully acknowledged. We thank Dr. S. Tian for $[Me_2Si(\eta^5\text{-}Me_4C_5)(^tBuN)]LnE(TMS)_2$ (Ln = Sm, Y, Yb, Lu; E = N, CH) samples.

Supporting Information Available: Detailed synthetic procedures and analytical data for the compounds **9**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Reactions were conducted in Teflon-valve-sealed NMR tubes and monitored by ^{1}H NMR (see Supporting Information for details).

(16) In general, <1 mol % of precatalyst suffices for practical reaction rates in the case of aminoalkynes, aminoallenes, and amines tethered to terminal alkenes.[5−11]

(17) The *trans*:*cis* ratio was determined by ^{1}H NMR spectroscopy, and the major isomer confirmed by 2-D NOESY experiments.

(18) Similar kinetic behavior is observed in C_7D_8 without the ferrocene internal standard.

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