Organolanthanide-Catalyzed Intramolecular Hydroamination/Cyclization of Aminoallenes

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The catalytic addition of N−H groups to C−C multiple bonds is of great interest in organic synthesis.[1] For bis(cyclopentadienyl)lanthanide centers,[2−4] insertion of olefinic and acetylenic functionalities into metal−ligand σ bonds is remarkably facile, and recent advances in organolanthanide-mediated aminoalkene[5] and aminoalkyne[6] hydroamination/cyclization offer efficient regioselective, stereoselective, and atom-economical routes to numerous heterocyclic classes. However, efficient cyclization of 1,2-disubstituted aminoalkenes for constructing azacycles bearing key substituents present in naturally occurring compounds has proven elusive.[7] To extend the scope of this methodology to applications in alkaloid synthesis, we envisioned highly reactive[8,9] and sterically less encumbered aminoallenes as attractive substrates for constructing heterocycles bearing unsaturated α-substituents.[10] Thermodynamic considerations[11,12] for unexplored allene−organolanthanide amide reactivity (Figure 1) predict that insertion (step i) is ∼29 kcal/mol more exothermic than that for alkenes[5] and ∼6 kcal/mol less exothermic than that for alkynes,[6] whereas subsequent protonolysis (step ii) is approximately thermoneutral.[13] Prompted by these prospects, we report here the rapid catalytic hydroamination/cyclization of aminoallenes mediated by organolanthanides and initial observations on selectivity and mechanism.

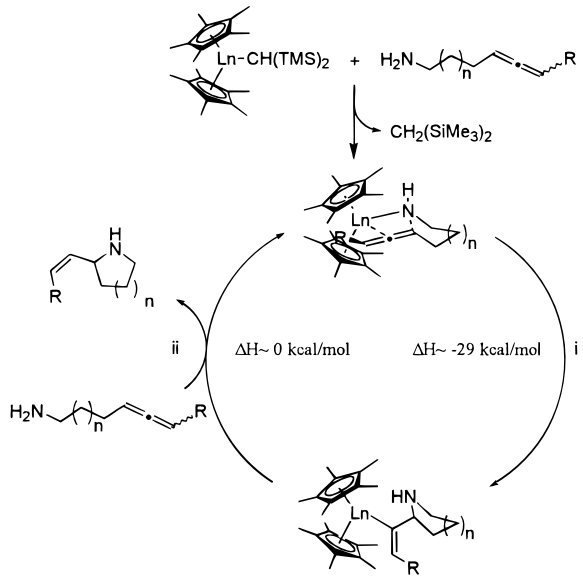
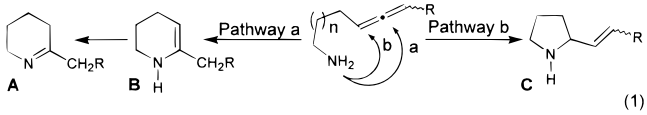


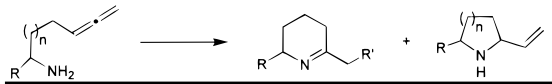
Figure 1. Proposed catalytic cycle for organolanthanide-mediated hydroamination/cyclization of aminoallenes.

In principle, two regioisomeric products (**A, C**) are possible from aminoallenes (eq 1). In initial studies, the anaerobic,



(1)

anhydrous reaction of $Cp'_2LnCH(TMS)_2$ ($Cp' = \eta^5$-Me_5C_5; Ln = La, Sm, Y, Lu; TMS = Me_3Si) with dry, degassed *monosubstituted* aminoallenes **1** and **2** (eq 2) proceeds predominantly via



(2)

Aminoallene	Combined Yield (%)	Tetrahydropyridine	2-Vinylpyrrolidine	Ratio **4**:**5**
1 R = H, n = 1	91	**4a** R = R' = H	**5a** R = H, n = 1	90:10
2 R = CH_3, n = 1	95	**4b** R = CH_3, R' = H	**5b** R = CH_3, n = 1	87:13
3 R = H, n = 2	95	**6** R = H, R' = CH_3		**6** only

(1) (a) Taube, R. In *Applied Homogeneous Catalysis with Organometallic Complexes*; Cornils, B., Herrmann, W. A, Eds.; VCH: Weinheim, 1996; Vol 2, pp 507−521. (b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, U.K., 1982; Vol. 8, pp 892−895.

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(6) (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306. (b) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770−3772. (c) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707−708. (d) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439−440.

(7) The turnover-limiting step in the catalytic cycle involves olefin insertion, which is apparently impeded for sterically more demanding disubstituted aminoalkenes.[5b] For instance, 1-aminohex-(*Z*)-4-ene is recovered unchanged upon reaction with a variety of organolanthanide precatalysts.[5,6]

(8) For a recent review of metal allene complexes, see: Doherty, S.; Corrigan, J. F.; Carty, A. J.; Sappa, E. *Adv. Organomet. Chem.* **1995**, *37*, 39−130.

(9) (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley-Interscience: New York, 1984; Chapter 3, pp 59−85. (b) Brady, W. T.; Blake, P. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley-Interscience: New York, 1980; Vol. 1, Chapters 8 and 9.

(10) Although N−H addition to allenes is effected by several transition-metal catalysts (Ag(I), Hg(II), Pd(II)), catalyst lifetimes and turnover frequencies are generally modest. For intermolecular examples, see: (a) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071−6074. (b) Besson, L.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857. For intramolecular examples, see: (c) Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550−4551. (d) Fox, D. N.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697−4710. (e) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253−4256. (f) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 243−244. (g) Arseniyadis, S.; Sartonetti, J. *Tetrahedron Lett.* **1985**, *26*, 729−732. (h) Karstens, W. F.; Rutjes, F. P. J.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275−6278.

(11) For metal−ligand bond enthalpies, see: (a) Nolan, S. P.; Stern, D.; Hedden, D.; Marks, T. J. *ACS Symp. Ser.* **1990**, 159−174. (b) Nolan, S. P.; Stern, D.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 7844−7853. (c) Schock, L. E.; Marks, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 7701−7715. (d) Bruno, J. W.; Marks, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 6824−6832.

(12) For organic fragment bond enthalpies, see: (a) Griller, D.; Kanabus-Kaminska, J. M.; Maccoll, A. *J. Mol. Struct.* **1988**, *163*, 125−131. (b) McMillan, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532 and references therein. (c) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; John Wiley and Sons: New York, 1976; Appendix Tables A.10, A.11, and A.22. (d) Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502−518.

(13) (a) The ΔH for NH_3 addition to allene (to yield $CH_2{=}CHCH_2NH_2$) is estimated to be −24 kcal/mol. (b) Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data for Organic Compounds*, 2nd ed.; Chapman and Hall: London, 1986.

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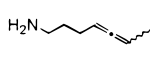
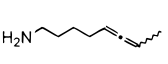
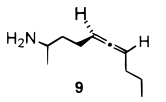
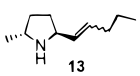
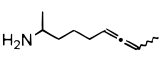
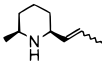
Table 1. Results for the Organolanthanide-Catalyzed Hydroamination/Cyclization of Aminoallenes[a]

entry	substrate	product(s)	conversion (%)[c] (yield) (%)[b]	Z/E ratio[c]	N_t, h^{-1} (°C)
1.	 **7**	 **11**	>95, (93)[b]	86:14[d]	31.4 (23)[d]
			>95	88:12[e]	13.0 (23)[e]
			>95	81:19[f]	7.3 (23)[f]
			>95	79:21[g]	4.1 (23)[g]
2.	 **8**	 **12**	>95, (95)[b]	80:20[e]	
			>95	95:5[d]	
3.	 **9**	 **13**	>95	67:33[d]	
			>95	58:42[e]	>630 (23)[e]
			>95	55:45[g]	
4.	 **10**	 **14**	>95	55:45[e]	0.23 (23)[e]

[a] All rates measured in benzene-d_6. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy and GC/MS. [d] Cp′$_2$YCH(SiMe$_3$)$_2$ as precatalyst. [e] Cp′$_2$SmCH(SiMe$_3$)$_2$ as precatalyst. [f] Cp′$_2$LuCH(SiMe$_3$)$_2$ as precatalyst. [g] Cp′$_2$LaCH(SiMe$_3$)$_2$ as precatalyst.

endocyclic pathway **a** to afford mixtures of regioisomers **4** and **5**, regardless of precatalyst and/or reaction conditions. Homologous substrate **3** gives exclusively 2-ethyl-3,4,5,6-tetrahydropyridine, **6**. In marked contrast, the reaction of *1,3-disubstituted* aminoallenes proceeds exclusively through pathway **b** (eq 1).[14a] Specifically, **7**[15] affords 2-(prop-1-enyl)pyrrolidine, **11**, whereas **8** undergoes cyclization to yield 2-(prop-1-enyl)piperidine, **12**, in excellent combined yield and good *Z* selectivity (Table 1, entries 1 and 2).

The reaction of aminoallene **9** possessing an amino-carbon chiral center cleanly generates *trans*-2-methyl-5-(pent-1-enyl)-pyrrolidine, **13**, as a ∼1:1 ratio of *Z/E* stereoisomers in high combined yield (entry 3). Hydrogenation of **13** (PtO_2) yields the fully saturated 2,5-disubstituted pyrrolidine as a single compound by GC/MS analysis.[14b] The proposed transition-state structures in Figure 2a account well for this diastereoselection. On the other hand, cyclization of **10** affords *cis*-2-methyl-6-(prop-1-enyl)-piperidine, **14**, in excellent yield as a 1:1 *Z/E* stereoisomer mixture (entry 4). The observed *cis* diastereoselectivity can be rationalized by considering chair-like transition-state models (Figure 2b). In both cases, product stereochemistry (**13**, 2,5-*trans*; **14**, 2,6-*cis*) arising from the amine stereogenic center overcomes any significant stereoinduction originating from the chiral allene moiety.

Kinetic studies of **7** → **11** were also undertaken (40−70:1, substrate:catalyst), and the data reveal linear dependence of [substrate] on reaction time, consistent with zero-order dependence of rate on [substrate] (turnover-limiting intramolecular allene insertion). For organolanthanide-catalyzed aminoalkene[5] and aminoalkyne[6a] hydroamination/cyclizations, which obey the same rate law, augmenting the Ln^{3+} ionic radius[16] increases and

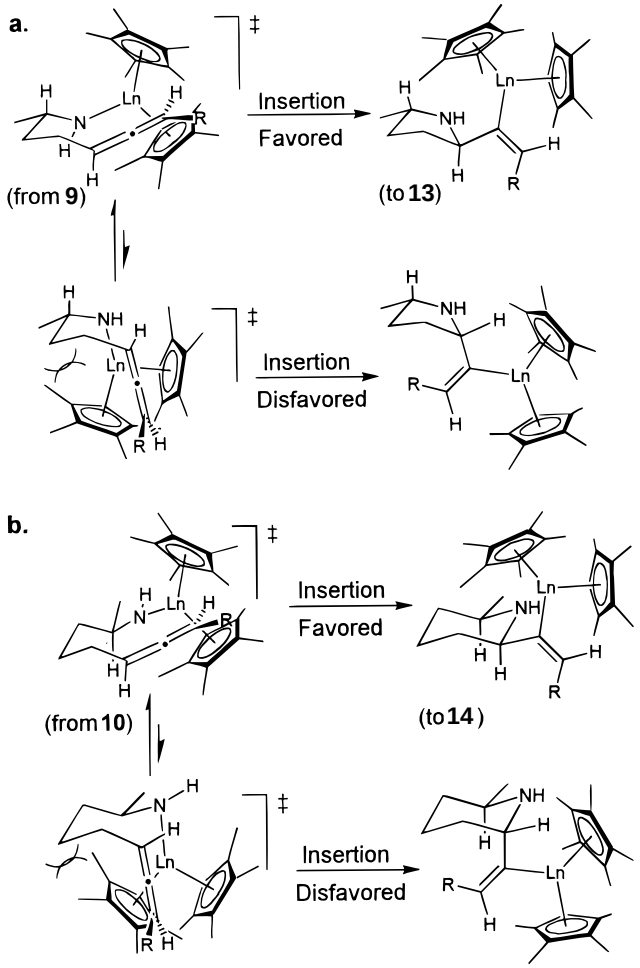


Figure 2. Plausible stereochemical pathways for organolanthanide-mediated hydroamination/cyclizations yielding (a) *trans*-2-methyl-5-(pent-1-enyl)pyrrolidine, **13**, and (b) *cis*-2- methyl-6-(prop-1-enyl)piperidine, **14**.

decreases turnover frequencies, respectively. Interestingly, the results for transformation **7** → **11** (Table 1) exhibit *maximum* N_t values at Y^{3+} (1.019 Å), on proceeding from the largest eight-coordinate lanthanide ionic radius, La^{3+} (1.160 Å), to the smallest, Lu^{3+} (0.977 Å).[16]

These results demonstrate that lanthanocenes are versatile precatalysts for efficient insertion of allenes into metal−amide bonds and that such processes can be incorporated into effective catalytic cycles for constructing heterocycles having unsaturated α-substituents. Application of this chemistry to alkaloid synthesis is presently under investigation.

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Supporting Information Available: Detailed synthetic procedures and analytical data for compounds **1**−**14** and kinetic plots (29 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(14) (a) Reactions are conveniently monitored by NMR. Product alkene stereochemistry was assigned from alkene proton NMR coupling constants, and the ratio of stereoisomers was by GC/MS (see the Supporting Information). (b) Spectroscopic characterization and NOE difference experiments on the fully saturated cyclic amine indicate relative substituent stereochemistry.

(15) Substrates **7**−**10** are obtained as a 1:1 mixture of stereoisomers (see Supporting Information).

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