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Organolanthanide-Catalyzed Carbon–Heteroatom Bond Formation. Observations on the Facile, Regiospecific Cyclization of Aminoalkynes

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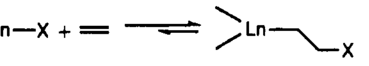
Summary: The organolanthanide complex $(\eta^5\text{-}Me_5C_5)_2SmCH(TMS)_2$ *serves as a precatalyst for the efficient and regiospecific hydroamination/cyclization of aliphatic and aromatic aminoalkynes* $RC{\equiv}C(CH_2)_nNH_2$ *to yield the corresponding heterocycles* $RCH_2\overline{C{=}N(CH_2)_{n-1}CH_2}$. *Kinetic and mechanistic evidence argues that the turnover-limiting step is intramolecular alkyne insertion into the Sm—N bond followed by rapid protonolysis of the resulting Sm—C bond.*

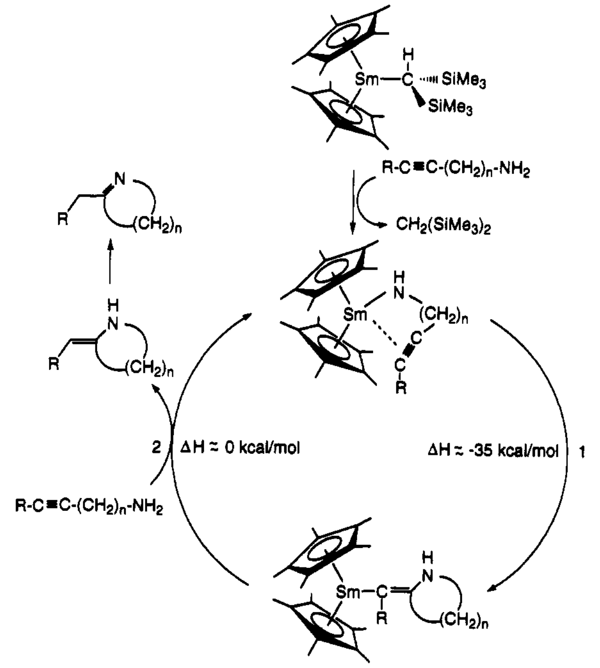
The insertion of olefinic functionalities into metal–ligand σ bonds is particularly facile in bis(cyclopentadienyl)lanthanide coordination spheres (eq 1).[1,2] For



(1)

aminoolefins, such insertions can be coupled to subsequent Ln–C protonolysis to effect regiospecific and stereoselective catalytic hydroamination/cyclization processes.[3] Thermodynamic considerations[4,5] pose the interesting situation for alkynes[6,7] (Scheme 1), that the insertion process (step 1) is estimated to be ~35 kcal/mol *more exothermic* than for olefins, while protonolysis (step 2) is estimated to be ~10–20 kcal/mol *less exothermic* (approximately thermoneutral). If efficient, such aminoalkyne catalytic cycles could offer a route to a diverse variety of alkaloid precursors (e.g., indolizidines, quinolizidines) as well as a complement to recently reported organo group 4-centered stoichiometric[8] and catalytic[8–10] alkyne hydroamination processes which proceed via entirely different (noninsertive) mechanistic pathways.[10] We report here the rapid, regioselective, catalytic hydroamination/cyclization of aminoalkynes in lanthanide coordination spheres and some initial observations regarding scope and mechanism.

Scheme 1. Catalytic Cycle for the Hydroamination and Cyclization of Aminoalkynes



The rigorously anaerobic reaction of $Cp'_2SmCH(TMS)_2$[2b] ($Cp' = \eta^5\text{-}Me_5C_5$; TMS = Me_3Si) with a variety of dry, degassed aminoalkynes (typically [catalyst] = 1.5–20 mM, [substrate] = 0.3–3.0 M) proceeds regiospecifically

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[5] Organic fragment bond enthalpies from: (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.; Wiley: New York, 1976; p 309. (d) Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502–518.

[6] Catalytic cycles based on alkyne insertion into Ln–C bonds: (a) Heeres, H. J.; Teuben, J. H. *Organometallics* **1991**, *10*, 1980–1986 and references therein. (b) Heeres, H. J.; Meetsma, A.; Teuben, J. H.; Rogers, R. D. *Organometallics* **1989**, *8*, 2637–2646.

[7] Requisite alkyne ΔH°_f data[5] are not available to compare the thermodynamics of amine addition to olefins versus that to alkynes. However, the addition of CH_4 to acetylene[5] is estimated to be ~14 kcal/mol more exothermic and ~14 kcal/mol more exergonic than that to ethylene.

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[9] McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323–1324.

[10] (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708–1719. This paper begins with an excellent overview of the scope and limitations of conventional alkyne hydroamination processes. (b) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729–8730.

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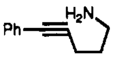
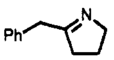
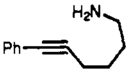
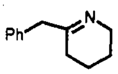
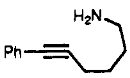
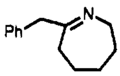
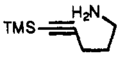
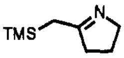
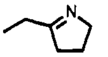
Table 1. Catalytic Results for the Organolanthanide-Catalyzed Hydroamination/Cyclization of Aminoalkynes

entry no.	substrate (ref)	product (ref)	N_t, h^{-1} (temp, °C)^a
1	 **1**^{8}	 **6**^{8,13a}	77 (21)^b 2830 (60)^b 2 (21)^c
2	 **2**^{8}	 **7**^{8,13a,b}	4 (21)^b >12 (60)^b
3	 **3**^{11}	 **8**^{13a,b}	0.11 (60)^b 0.03 (60)^c
4	 **4**^{11}	 **9**^{11}	>7600 (21)^{b,d}
5	 **5**^{12}	 **10**^{13c}	96 (21)^{b,d} 28 (21)^c

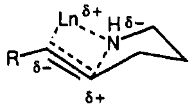
[a] Turnover frequencies measured in C_6D_6. [b] $Cp'_2SmCH(TMS)_2$ as the precatalyst. [c] $Me_2SiCp''_2SmCH(TMS)_2$ as the precatalyst. [d] NMR-scale and scale-up reaction.

(≥95%) to completion in hydrocarbon solvents (benzene, toluene) as shown in Table 1.[11] Reactions and reaction rates[3a] were conveniently monitored by NMR spectroscopy, and known substrates[8,12] and products[13] were identified by comparison with literature $^1H/^{13}C$ NMR spectral data and/or with data for authentic samples. New compounds were characterized by $^1H/^{13}C$ NMR and high-resolution MS.[11] Entries 4 and 5 were also carried out on larger (0.25–0.50 g) preparative scales, and pure **9** and **10** were isolated in 92% and 60% yields, respectively.[14]

Several features of this catalytic reaction are noteworthy and provide both informative parallels and contrasts to the corresponding organolanthanide-catalyzed aminoolefin cyclizations. The present process is capable of forming five-, six-, and seven-membered heterocycles with a variety of substituents α to the acetylenic moiety. With regard to rate, the present cyclizations are ~10–100 times more rapid than the corresponding olefinic transformations for the same catalyst, temperature, and reaction conditions.[3a] Indeed, N_t for the process **4** → **9** considerably exceeds the rate which can be accurately measured at room temperature. A detailed kinetic study of **5** → **10**[11] reveals the reaction to be zero-order in substrate over a ~10-fold concentration range and first-order in catalyst over a ~50-fold concentration range (eq 2).

$$\nu = k[\text{substrate}]^0[\text{Sm}]^1 \qquad (2)$$

As in the case of aminoolefin cyclization, the present ring size dependence of cyclization rates is 5 > 6 ≫ 7, consistent with classical, stereoelectronically controlled cyclization processes.[3a,15] Also noteworthy are the marked substituent effects on the cyclization rates, with TMS ≫ CH_3 ≳ Ph in Table 1, entries 4, 5, and 1, respectively. When taken together, these observations suggest that the turnover-limiting step in aminoalkyne hydroamination/cyclization is alkyne activation/insertion at the electrophilic lanthanide center. The preference for a quasi-seven-membered transition state (e.g., **A**) is in accord with the aforementioned ring-size effects and earlier stereochemical observations on organolanthanide-catalyzed olefin hydroamination.[3a,b] The observed activating effects of TMS substitution are in accord with known organosilicon chemistry.[16]



A

Cp'_2Ln– versus $Me_2SiCp''_2Ln$–olefin activation rate differences ($Cp'' = \eta^5$–Me_4C_5) are usually an informative gauge of the steric demands in insertion transition states at such metal centers.[2c,d,3a] Interestingly, and in marked contrast to the aminoolefin cyclization,[3a] the present results (Table 1) evidence a *deceleration* rather than an *acceleration* in rate when the more open[2c] $Me_2SiCp''_2Sm$– is used as the catalyst (Table 1). It would thus appear that the steric demands in transition states for lanthanide-mediated alkyne insertions are somewhat relaxed. The reasons likely reflect a combination of smaller substrate steric bulk, differing substrate molecule coordination,[3a] and a more reactant-like transition state for such an exothermic process.[17]

These results demonstrate that organolanthanide centers are competent for the efficient, regioselective insertion of alkynes into metal–amide bonds and that such processes can be incorporated into efficient catalytic cycles. Noteworthy are the high turnover frequencies, marked substituent effects, similar rate laws, and differing steric demands vis-á-vis the corresponding aminoolefin transformations.

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Supplementary Material Available: Text giving synthetic and characterization information for reactants and products and Figures 1 and 2 giving representative kinetic plots (12 pages). Ordering information is given on any current masthead page.

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(11) See the supplementary material for full synthetic details, characterization of new compounds, and kinetic plots.

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(14) Under an Ar atmosphere in a 25-mL reaction vessel, 20.0 mg (34.5 μmol) of $Cp'_2SmCH(TMS)_2$ was stirred in 3.5 mL of dry benzene with 0.25 g (1.6 mmol) of 1-amino-5-(trimethylsilyl)-4-hexyne (**4**)[11] for 2 days at room temperature. The light yellow solution was then filtered through a frit and the filtrate vacuum-transferred to another container. The benzene was next removed by short-path distillation at atmospheric pressure to yield 0.23 g (92%) of **9** as a colorless liquid (>95% purity by ^1H NMR and GC–MS). Spectral and analytical data are in good agreement with the proposed formulation.[11]

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