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Highly Stereoselective Intramolecular Hydroamination/Cyclization of Conjugated Aminodienes Catalyzed by Organolanthanides

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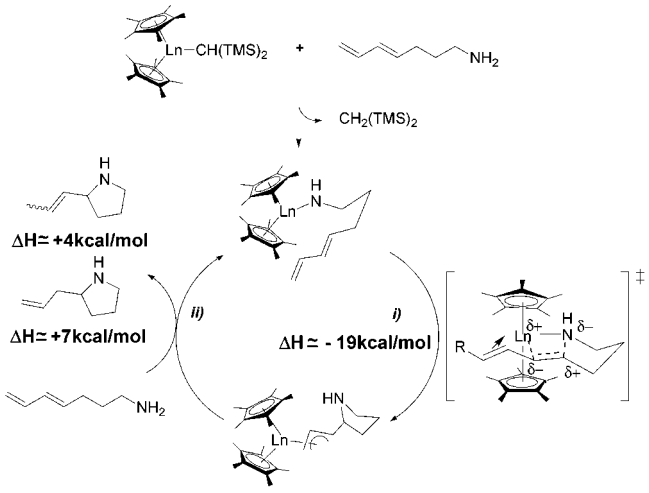
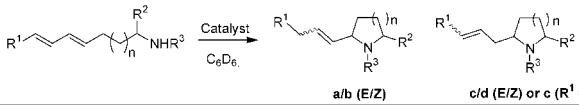
Catalytic N−H addition to C−C multiple bonds is a highly desirable, atom-economical transformation for the synthesis of organonitrogen molecules.[1,2] Organolanthanides[3] are highly efficient catalysts for the intramolecular hydroamination/cyclization of aminoalkenes,[4,5] aminoalkynes,[6] and aminoallenes.[7] Nevertheless, efficient cyclization of amines tethered to 1,2-disubstituted alkenes has remained elusive[8] (presumably for steric reasons[4e,f]), severely limiting implementation in stereoselective approaches[5] to azacycles bearing key substituents of naturally occurring alkaloids. However, from preliminary *intermolecular* organolanthanide-mediated diene hydroamination results,[9a] we envisioned conjugated diene substrates[10] as attractive presursors for the synthesis of such azacyclic targets. Diene substrates are likely to be more reactive because the conjugated vinyl substituent should stabilize/delocalize the charge distribution in the insertive transition state (Scheme 1; thermodynamic estimates as described previously.[3d,4f,6,7]). Moreover, the steric demands of an η^3-allyl[3] intermediate may enhance ancillary ligand stereodirecting effects for diastereo- and enantioselective pathways to substituted pyrrolidines and piperidines. Herein we report the organolanthanide-catalyzed hydroamination/cyclization of conjugated aminodienes[11] as examples of efficient hydroamination/cyclization of amines tethered to 1,2-disubstituted alkenes and initial observations on scope, selectivity, and mechanism.[9b]

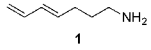
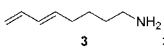
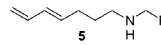
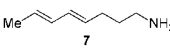
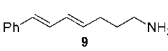
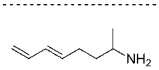
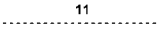
Scheme 1. Proposed Catalytic Cycle for Organolanthanide-Mediated Hydroamination of Conjugated Aminodienes



Anaerobic cyclization of primary and secondary aminodienes mediated by Cp′$_2$LnCH(TMS)$_2$ (Cp′ = η^5-Me$_5$C$_5$),[12] CGCSmN(TMS)$_2$ (CGC = Me$_2$Si(η^5-Me$_4$C$_5$)(^{t}BuN)),[4c] or (*S*)-Me$_2$Si(OHF)(CpR*)SmN(TMS)$_2$ (OHF = η^5-octahydrofluorenyl; Cp = η^5-C$_5$H$_3$; R* = (−)-menthyl)[13] precatalysts is clean and general in scope (Table 1).[14] Thus, 2-substituted pyrrolidines (entries 1−5, 8−12) and piperidines (entries 6, 7) are formed via 5-exo and 6-exo cyclizations, respectively. Products **a/b** are obtained as major products (entries 1−8) for terminal dienes, however, products **c/d** predominate when 1,4-disubstituted substrates are employed (entries 9−12).[15] High conversions and reasonably rapid turnover frequencies are observed at 25 or 60 °C. Note that the predicted rate enhancement vs 4-pentenamine and 5-hexenamine is operative despite increased substrate steric encumbrance.[16] Furthermore, N_t varies with terminal substituent in the order Me < H < Ph (N_t = 0.02, 0.79, 2.3 h^{-1}, respectively; entries 10, 2, 12), in accord with proposed transition state electronic demands (Scheme 1). Catalyst structural effects similar to those in monosubstituted alkene hydroamination are also operative. N_t increases with increasing metal ionic radius[4f,17] (La > Sm > Y; entries 1−3, entries 9−10, entries 11−12) and approximately with more open ligation (OHF*,

Table 1. Results for Organolanthanide-Catalyzed Hydroamination/Cyclization of Conjugated Aminodienes



Entry	Subtsrate	%Conv.[a] (Yield[b])	Product[c]	Ratio[d]	Pre-Catalyst	N_t, h^{-1} (^{o}C)[e]
				a : **b** : **c**		
1.		> 95		84: 16: 0	Cp′$_2$LaCH(TMS)$_2$	23 (25)
2.		> 95		72: 11: 17	Cp′$_2$SmCH(TMS)$_2$	0.79 (60)
3.	**1**	93	**2** n = 1	30: 19: 51	Cp′$_2$YCH(TMS)$_2$	0.05 (60)
4.		90		59: 41: 0	CGCSmN(TMS)$_2$	3.1 (25)
5.		> 95		93: 7 : 0	(OHF*)SmN(TMS)$_2$[f]	12 (25)
6.		> 95	**4** n = 2	98 : 2: 0	Cp′$_2$LaCH(TMS)$_2$	3.0 (25)
7.	**3**	> 95 (91)		97 : 3: 0	(OHF*)SmN(TMS)$_2$[f]	0.11 (25)
8.	 **5**	85 (71)	**6** n = 1 R^3= Bn	87: 7: 6	CGCSmN(TMS)$_2$	5.8 (60)
				a : **b** : **c** : **d**		
9.		94	**8** n = 1 R^1= Me	38: 0: 47:15	Cp′$_2$LaCH(TMS)$_2$	1.8 (60)
10.	**7**	93		23: 0: 72: 5	Cp′$_2$SmCH(TMS)$_2$	0.02 (60)
11.		92	**10** n = 1 R^1= Ph	>94% **c**	Cp′$_2$LaCH(TMS)$_2$	89 (60)
12.	**9**	90		>94% **c**	Cp′$_2$SmCH(TMS)$_2$	2.3 (60)
				2,5-*cis* : 2,5-*trans*[g]		
13.		> 95	**12** n = 1 R^2= Me	42 : 58	Cp′$_2$LaCH(TMS)$_2$	1.0 (25)
14.	**11**	> 95		10 : 90	CGCSmN(TMS)$_2$	78 (25)
				2,6-*cis* : 2,6-*trans*[g]		
15.		> 95	**14** n = 2 R^2= Me	99.4 : 0.6[h]	Cp′$_2$LaCH(TMS)$_2$	3.7 (25)
16.	**13**	> 95		78 : 22	CGCSmN(TMS)$_2$	4.0 (60)

[a] Determined by ^{1}H NMR. [b] Isolated yield (entry 8) or that of Cbz carbamate (entry 7). [c] Other R^i = H. [d] Determined by ^{1}H NMR and/or GC-MS of Boc derivatives. [e] Turnover frequencies measured in C$_6$D$_6$ with 3−11 mol % precatalyst. [f] OHF* = (*S*)-Me$_2$Si(η^5-octahydrofluorenyl)(CpR*), R* = (−)-menthyl. [g] Determined by the GC-MS ratio of corresponding hydrogenated Boc derivatives. [h] Cis:trans = 178:1; alkene isomer ratio (**a**:**b**:**c**) = 94:1:5.

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CGC ≫ Cp'_2; entries 5, 4, and 2). Preliminary kinetic studies[11] reveal linear dependence of reaction time on [substrate] up to ~75% conversion, consistent with zero-order kinetic dependence on [substrate] (turnover-limiting intramolecular alkene insertion).

Good to excellent diastereoselectivities are observed in formation of a 2,5-*trans*-disubstituted pyrrolidine (entries 13,14) and a 2,6-*cis*-disubstituted piperidine (entries 15, 16) from the corresponding methyl-substituted dienes.[18] Note that entry 15 demonstrates a concise, efficient synthesis of (±)-pinidine[19] with excellent stereocontrols for both 2,6-cis substitution (cis:trans = 178:1) and *trans*-alkene geometry (**14a**:**b**:**c** = 94:1:5). The high selectivities can be rationalized by assuming chairlike transition states in which methyl and diene units occupy thermodynamically more stable equatorial positions (Figure 1). Preliminary studies of enantioselective cyclizations reveal that **3**→ **4a/b** conversion catalyzed by C_1-symmetric (*S*)-$Me_2Si(OHF)(CpR^*)SmN(TMS)_2$ proceeds with up to 69% ee (Table 2, entries 2−4) while analogous **1** → **2a/b** cyclization proceeds with 23% ee (Table 2, entry 1). In contrast, previous intramolecular aminomonoalkene hydroamination/cyclizations to such piperidines exhibit far lower N_t values and enantioselectivities;[5a] the present results constitute the best combination of reactivity and selectivity to date.

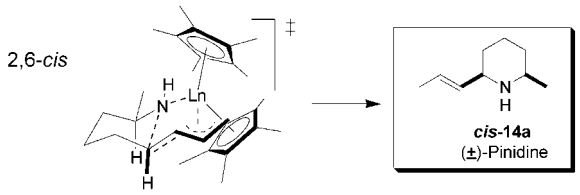

Figure 1. Plausible transition state for diastereoselective aminodiene hydroamination/cyclization.

Table 2. Enantioselective Cyclization of Aminodienes[a]

entry	substrate	product (ratio)	solvent	temp (°C)	% ee[b] (config.)[c]
1	**1**	**2a/b** (93:7)	C_6D_6	25	23
2	**3**	**4a/b** (97:3)	C_6D_6	25	63 (*R*)
3	**3**	**4a/b** (96:4)	C_6D_{12}	25	66 (*R*)
4	**3**	**4a/b** (95:5)	C_6D_{12}	0	69 (*R*)

[a] Conditions: 7 mol % (entries 1, 2, 3) or 20 mol % (entry 4) of $(OHF^*)SmN(TMS)_2$ catalyst, ~0.6 mL of solvent. [b] For the major isomer, determined by chiral HPLC analysis. Measured ee values vary only weakly with conversion. [c] Determined by optical rotation of the HCl salt of hydrogenated product. See Supporting Information.

In conclusion, we have demonstrated that efficient organolanthanide-catalyzed intramolecular hydroamination/cyclization of amines tethered to 1,2-disubstituted alkenes is achieved by using readily accessible conjugated aminodienes. The results include rate enhancements due to electronic effects as well as good regio- and diastereoselectivity. That aminodienes offer general and efficient substrates for enantioselective hydroamination/cyclization routes to 2-substituted azacycles motivates current work with other catalysts and conjugated substrates, and application of this methodology to alkaloid synthesis.

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Supporting Information Available: Detailed synthetic procedures and analytical data for new compounds and kinetic plots (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For discussion of functional group tolerance in organolanthanide catalysis, see ref 3b.
(15) For cyclization of dienes **7** and **9**, the product distribution is time-dependent, ultimately favoring thermodynamic products. For conversion **9** → **10**, initial formation of **10a** and subsequent isomerization to **10c** is observed in situ by ^{1}H NMR. Presumably, the doubly activated benzylic C−H functionality in **10a** is sufficiently acidic to facilitate isomerization.
(16) (a) For example, when $Cp'_2LaCH(TMS)_2$ is used as a precatalyst, N_t for 4-pentenamine cyclization is 13 h^{-1} (25 °C) and N_t for 5-hexenamine cyclization is 5 h^{-1} (60 °C)[4f] vs entries 1 and 6 in Table 1. (b) When (*S*)-$Me_2Si(OHF)(CpR^*)SmN(TMS)_2$ is used as precatalyst, N_t for 4-pentenamine cyclization is 2.6 h^{-1} at 25 °C.[13] Compare to Table 1, entry 5.
(17) Representative eight-coordinate effective ionic radii (Å): La(III), 1.160; Nd(III), 1.109; Sm(III), 1.079; Y(III), 1.019; Yb(III), 0.985; Lu(III), 0.977. See: Shannon, R. D. *Acta Crystallogr., Sect. A* **1976**, *A32*, 751−767.
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