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Organolanthanide-Catalyzed Hydroamination

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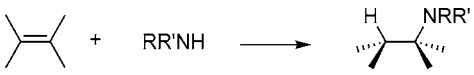
ABSTRACT

Organolanthanides are highly efficient catalysts for inter- and intramolecular hydroamination of various C−C unsaturations such as alkenes, alkynes, allenes, and dienes. Attractive features of organolanthanide catalysts include very high turnover frequencies and excellent stereoselectivities, rendering this methodology applicable to concise synthesis of naturally occurring alkaloids and other polycyclic azacycles. The general hydroamination mechanism involves turnover-limiting C−C multiple bond insertion into the Ln−N bond, followed by rapid protonolysis by other amine substrates. Sterically less encumbered ligand designs have been developed to improve reaction rates, and metallocene and nonmetallocene chiral lanthanide complexes have been synthesized for enantioselective hydroamination.

I. Introduction: Thermodynamically-Based Strategies for Catalytic Heteroatom Addition

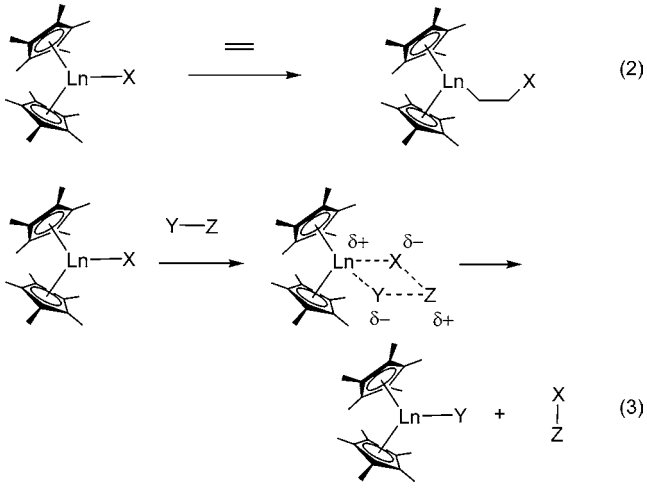
Hydroamination,[1] the addition of an N−H bond across carbon−carbon unsaturation, offers an efficient, atom-economical route to nitrogen-containing molecules that are important for fine chemicals, pharmaceuticals, or useful chiral building blocks (eq 1).



(1)

Over the past decade there has been a growing effort to develop efficient and selective catalysts for this seemingly simple but challenging transformation. Various approaches include use of alkali metals,[2] acid catalysts,[3] early transition metals (group IV),[4] late transition metals,[5] and organo-f-element metal complexes (actinides[6] and lanthanides[8−13]). In general, late transition metal catalysts offer the advantage of greater polar functional group tolerance. However, short catalyst lifetimes due to the catalyst poisoning by amine substrates, limited scope, modest selectivity, and sluggish reaction rates have often been cited as their disadvantages. However, significant advances have recently been achieved using acidic additives as well as activated substrates such as styrenes and 1,3-dienes, resulting in improved catalyst lifetimes and reaction rates.[5]

In contrast, it has been demonstrated that organolanthanides[7] are highly efficient catalysts for the inter-[8] and intramolecular hydroamination/cyclization of various C−C unsaturations such as aminoalkenes,[9,10] aminoalkynes,[11] aminoallenes,[12] and aminodienes.[13] Figure 1 shows structures of effective lanthanide hydroamination catalysts reported in the literature. Lanthanides, nontoxic and relatively abundant in nature, have unique features for development of new catalytic transformations. Stereoelectronic tunability of organolanthanide coordination spheres by variation of the metal ionic radius (La^{3+} = 1.160 Å to Lu^{3+} = 0.977 Å)[14] and ancillary ligands is often a key optimization variable in organolanthanide-catalyzed hydroamination. In contrast to late transition metals, lanthanides have predominantly one stable oxidation state (3+), excluding conventional oxidative−addition/reductive−elimination pathways. Owing to the high electrophilicity and kinetic lability, organolanthanide centers exhibit two distinctive reactivity patterns: olefin insertion (eq 2) and sigma-bond metathesis (eq 3).



(2)

(3)

In 1985, our group reported that organolanthanide complexes of the type Cp'_2LnR ($Cp' = \eta^5$-Me_5C_5; R = H (**2**), $CH(SiMe_3)_2$ (**1**); La = La, Nd, Sm, Y, Lu) are highly reactive with respect to olefin insertion processes (e.g., $N_t \geq 1500\ s^{-1}$ for ethylene polymerization by Cp'_2La centers at 25 °C, 1 atm ethylene).[15] From these results we envisioned this metal−ligand array, exhibiting such extraordinary kinetic facility for olefin insertion into Ln−C and Ln−H bonds (eqs 4 and 5), as an ideal environment to test heretofore unrealized olefin insertion processes such as those involving metal−N bonds (eq 6). Thermochemical data suggest that eq 6 is approximately thermoneutral[16] and when coupled to the exothermic (and

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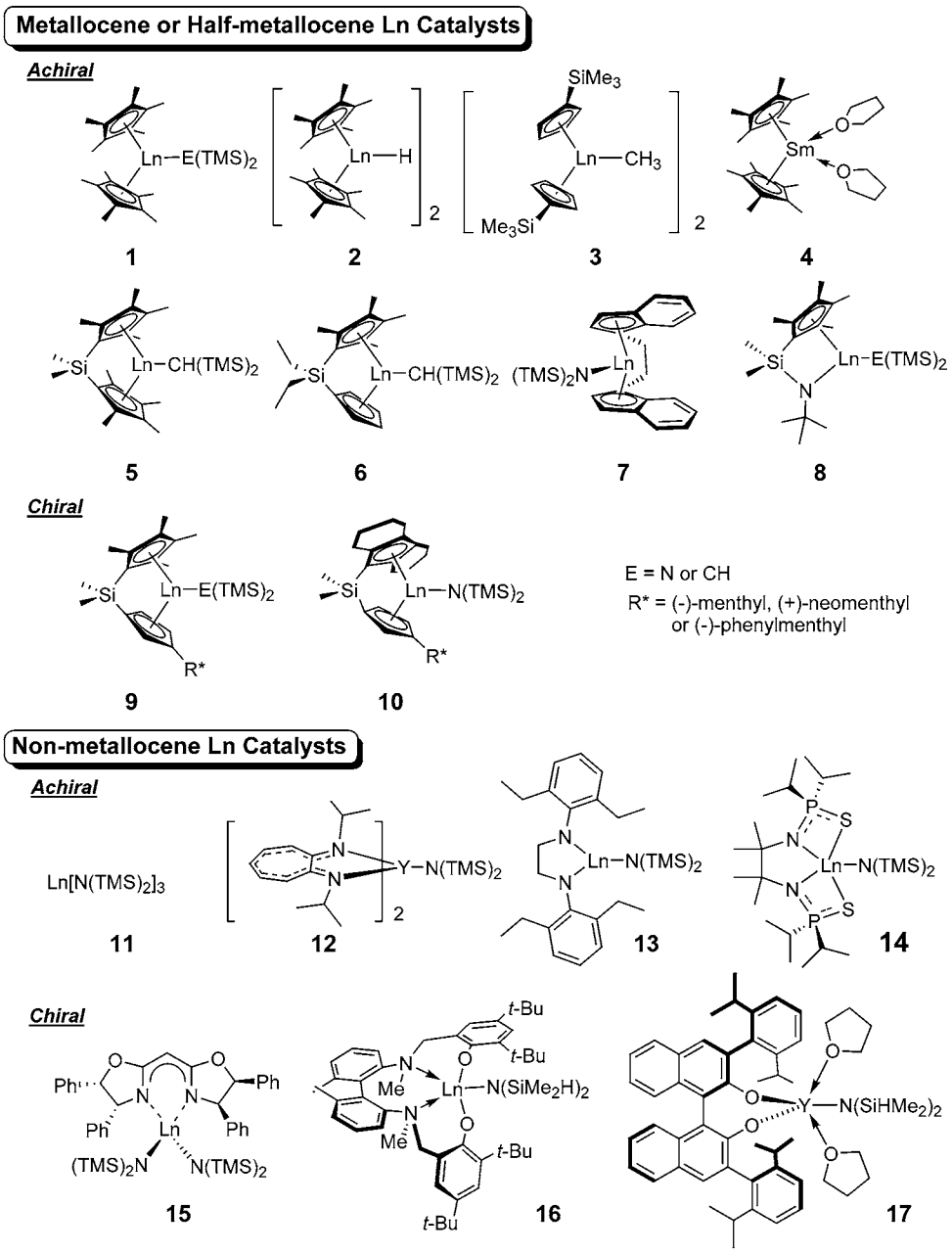


FIGURE 1. Organolanthanide Catalysts for Hydroamination.

kinetically facile) protonolysis of eq 7, offers a potential catalytic pathway for organolanthanide-catalyzed alkene hydroamination (Scheme 1), which indeed was communicated in 1989.[9l,n]

$$M{-}CH_2R + CH_2{=}CH_2 \rightarrow MCH_2CH_2CH_2R \quad (4)$$

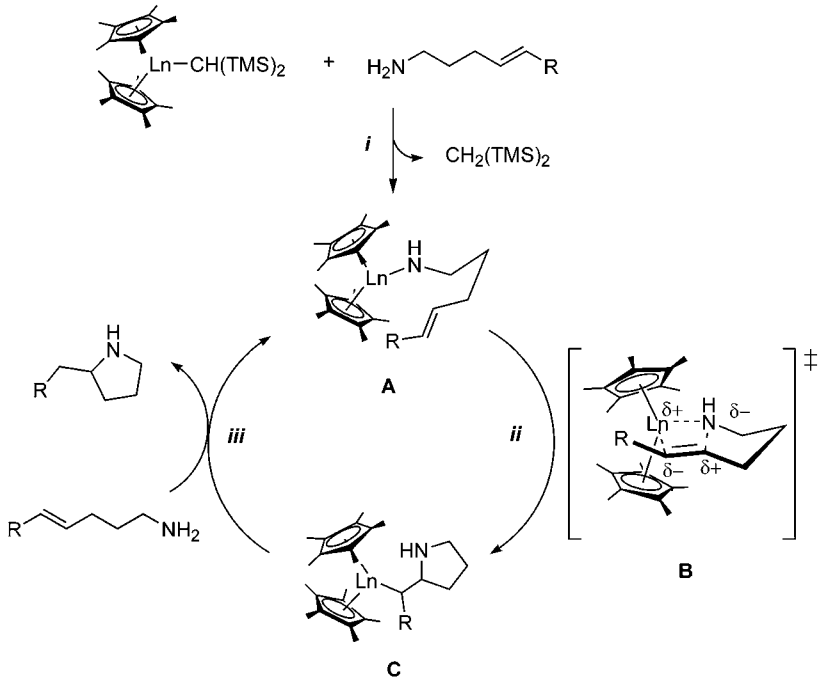
$$M{-}H + CH_2{=}CHR \rightarrow MCH_2CH_2R \quad (5)$$

$$M{-}NR_2 + CH_2{=}CH_2 \xrightarrow{?} MCH_2CH_2CH_2R \quad (6)$$

$$Ln{-}CH_2R + HNR_2 \rightarrow Ln{-}NR_2 + CH_3R \quad (7)$$

The purpose of this Account is to review organolanthanide-mediated hydroamination and other hydro*ele*-*ment*ation research carried out at Northwestern University and elsewhere. We begin with a summary of initial observations on organolanthanide-catalyzed aminoalkene hydroamination. We then show how this effort has evolved in several different directions based on the early aminoalkene hydroamination results: (1) exploring different carbon−carbon unsaturated substrates such as alkynes, allenes, and dienes, (2) development of new catalysts for higher activity and selectivity, including chiral catalysts for enantioselective hydroamination, (3) intermolecular and intermolecular−intramolecular tandem hydroamination approaches, (4) development of other carbon−heteroatom bond formation processes such as hydrosilylation, hydroboration, and hydrophosphination.

Scheme 1. Simplified Catalytic Cycle for Organolanthanide-Mediated Hydroamination/Cyclization of Aminoalkenes

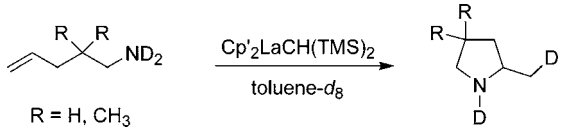


II. Scope of Intramolecular Hydroamination/Cyclization: Substrate Development

1. Aminoalkene Hydroamination/Cyclization. The anaerobic hydroamination/cyclization of a variety of aminoalkenes (20−100-fold excess) catalyzed by $Cp'_2LnCH(TMS)_2$ (**1**) and $Me_2SiCp''_2NdCH(TMS)_2$ (**5**) ($Cp'' = \eta^5$-Me_4C_5) proceeds to completion and is conveniently monitored by ^1H NMR spectroscopy (Table 1).[9l−n] The transformation is effective in the formation of five-, six-, and seven-membered heterocycles from primary/secondary and aliphatic/aromatic amines. Note the very high 2,5-trans diastereoselectivity obtained (up to 20:1 with **5**); however, the ratio varies with catalyst and the presence of exogenous bases such as *n*-propylamine (1:1 to >50:1). In the proposed catalytic cycle (Scheme 1) the precatalyst enters via very rapid protonolysis by amine substrates (step i, Scheme 1). The resultant, crystallographically/spectroscopically characterizable Ln−amido intermediate (**A**), which is likely the resting state, then undergoes irreversible, turnover-limiting intramolecular olefin insertion (step ii, Scheme 1) presumably via a four-centered transition state (**B**). The ensuing rapid protonolysis of the Ln−alkyl species (**C**) by amine substrates yields the azacyclic product and regenerates the catalytically-active species (**A**). This scenario is supported by extensive kinetic/mechanistic data. The reaction rate is zero-order in [amine substrate] and first-order in [catalyst], implicating an intramolecular turnover-limiting step (eq 8). Isotopic-labeling experiments (eq 9) and negligible racemization of chiral products at long reaction times indicate that cyclization is irreversible.

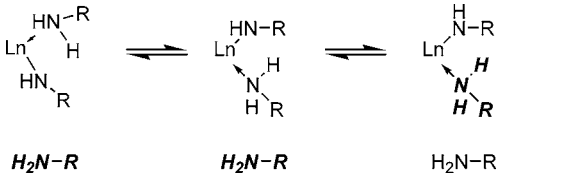
$$v = k[\text{substrate}]^0[\text{Ln}]^1 \qquad (8)$$

The reaction rate is very sensitive to steric demands around the metal center. Thus, the rate increases with larger Ln^{3+} ionic radius (La > Sm > Lu) and more open supporting ligation ($R_2SiCpCp''-$ (**6**)[17] > $R_2SiCp''_2-$ (**5**)[15b] > Cp'_2- (**1**)[15a]), which parallels trends in other organolanthanide-centered olefin insertion processes. Furthermore, $\Delta H‡$ and $\Delta S‡$ values of 12.7 (1.4) kcal mol^{-1} and −27.0 (4.6) eu, respectively, suggest a highly organized transition state.



(9)

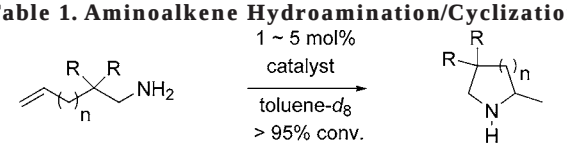
Interestingly, it was observed that variable numbers of amine molecules are coordinated to the metal center. Moreover, an exchange process rapidly permutes not only lanthanide amido and coordinated amine, but also coordinated and free amine, even at low temperatures (eq 10). Thus, the presence of additional amine ligands appears to modulate diastereoselectivity in the formation of 2,5-dimethylpyrrolidine and also to influence turnover rates, mainly via competition with substrate molecules for the reaction centers.

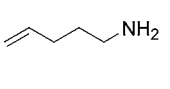
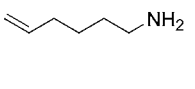
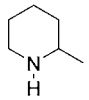
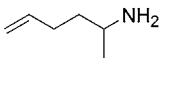
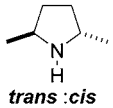
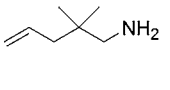
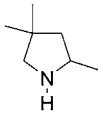
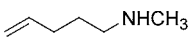
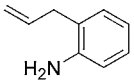
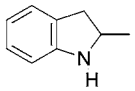
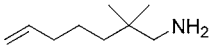
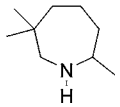


(10)

2. Aminoalkyne Hydroamination/Cyclization. The success with the aminoalkene hydroamination led us to inquire whether analogous alkyne insertion into Ln−N bonds can occur. Thermodynamic analysis of the pro-

Table 1. Aminoalkene Hydroamination/Cyclization

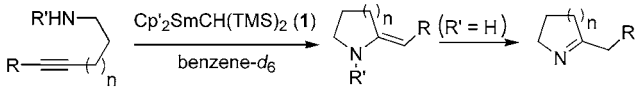


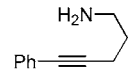
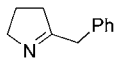
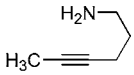
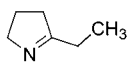
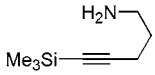
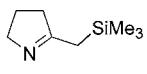
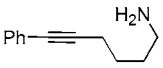
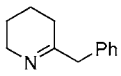
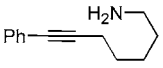
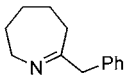
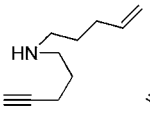
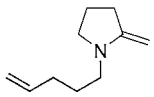
substrate	product	N_t, h^{-1} (°C)
		140 (60)[a]
		5 (60)[a]
		45 (25)[a]
	trans **:*cis*** = 5: 1[a] or 20:1[b] or ≥ 50:1[c]	
		95 (25)[a]
		11 (25)[b]
		12 (80)[a]
		0.3 (60)[b]

[a] $Cp'_2LaCH(TMS)_2$ (**1**) as precatalyst. [b] $Me_2SiCp''_2NdCH(TMS)_2$ (**5**) as precatalyst. [c] Reaction carried out in the presence of 3 mol equiv of *n*-propylamine, based on starting substrate concentration, with $Cp'_2LaCH(TMS)_2$ (**1**) as precatalyst.

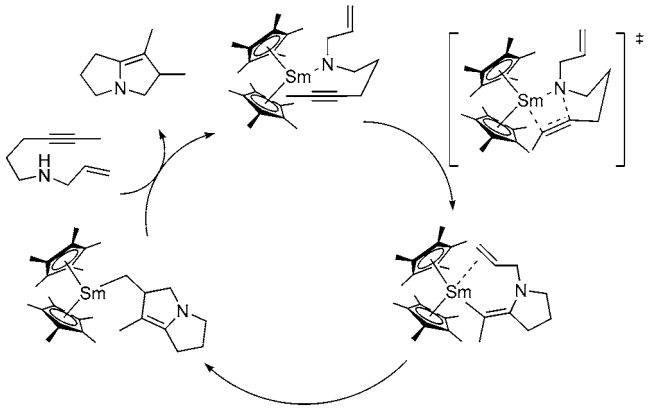
spective catalytic cycle yields a highly exothermic insertion and approximately thermoneutral protonolysis step. Thus, organolanthanides $Cp'_2LnCH(TMS)_2$ (**1**) and $Me_2SiCp''_2$-$LnCH(TMS)_2$ (**5**) efficiently and regiospecifically catalyze the hydroamination/cyclization of a variety of aliphatic and aromatic aminoalkynes to yield enamines or tautomerized imines for primary amine substrates (Table 2).[11c,e] Aminoalkyne hydroamination appears to proceed via essentially the same mechanistic scenario as aminoalkene hydroamination—turnover-limiting intramolecular alkyne insertion followed by rapid protonolysis. However, compared to aminoalkene hydroamination, aminoalkynes exhibit significantly greater turnover frequencies, as best illustrated in a competition study (entry 7, Table 2). In addition, aminoalkyne hydroamination proceeds with internal alkynes as well as terminal alkynes. When the alkyne substituents are varied, significantly greater rates are observed with a Me_3Si-substituted alkyne (entry 4 vs entry 1−3, Table 2), which can be rationalized by considering transition state electronic demands (**D**). In addition, it was demonstrated in this work that the C−N bond-forming step can be coupled with a subsequent C−C bond-forming step via addition of the intermediate Ln−

Table 2. Aminoalkyne Hydroamination/Cyclization

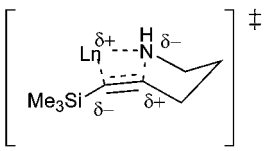


entry	substrate	product	N_t, h^{-1} (°C)	% GC yield (isolated yield)
1			77 (21) 2830 (60)	95
2			96 (21)	95
3			580 (21)	90 (47)
4			> 7600 (21)	95 (92)
5			4 (21) 328 (60)	95
6			0.11 (60)	92
7			47 (21)	85

Scheme 2. Proposed Pathway for Organolanthanide-Catalyzed Sequential C−N and C−C Bond Formation

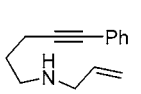
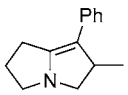
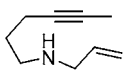
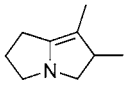
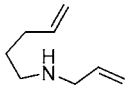
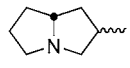
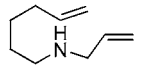
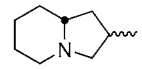
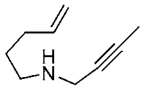
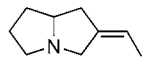


alkyl/alkenyl bond to another C−C multiple bond (Scheme 2).[11a,d] As illustrated in Table 3, this tandem bicyclization allows construction of pyrrolizidines and indolizidines having varying degrees of unsaturation and substitutable groups, hence points for subsequent functionalization, in a single catalytic cycle.

D 

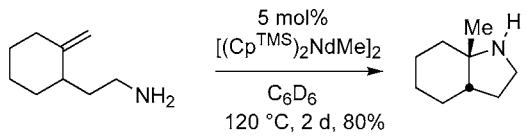
3. 1,2-Disubstituted *Internal* Aminoalkene Hydroamination/Cyclization. As presented so far, aminoalkene

Table 3. Hydroamination/Bicyclization[a]

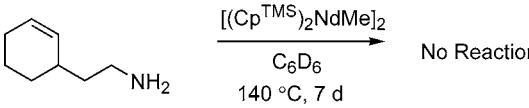
substrate	product	N_t, h^{-1} (°C)	yield (%)
		17 (21)	68[b]
		777 (21)	75[b]
		55 (21)	93[b]
		5 (21)	88[b]
		14 (60)	92[c]

[a] Reaction conditions: 2 mol % $Cp'_2SmCH(TMS)_2$ (**1**), benzene or benzene-d_6 as solvent. [b] Isolated yield. [c] Conversion determined by ^1H NMR and GC-MS.

hydroamination/cyclization had one significant drawback. Unlike aminoalkynes, efficient cyclization of 1,2-disubstituted *internal* alkenes remained elusive, hampering catalytic stereoselective synthesis of α-alkyl-substituted azacycles often found in naturally occurring alkaloid structures. The inherent limitation in 1,2-disubstituted alkene insertion is reasonably attributed to severe nonbonded steric repulsions and a possible charge separation imbalance in the relatively well-characterized transition state (**B**, Scheme 1). Molander and co-workers reported a modified lanthanocene catalyst, $[(Cp^{TMS})_2LnMe]_2$ (**3**),[9j] for hindered alkenes. With this more open ligation, 1,1-disubstituted alkene hydroamination proceeds at elevated temperatures (eq 11), although one attempted 1,2-disubstituted alkene hydroamination was reported to be unsuccessful (eq 12).[9j] In subsequent work, we demonstrated that the elusive 1,2-disubstituted alkene hydroamination proceeds with some generality at elevated temperatures (120−130 °C) using catalysts having large metal ionic radii/high coordinative unsaturation (Table 4).[9a,d] Remarkably, many lanthanocene catalysts exhibit useful thermal stability and high 2,5-trans diastereoselectivity under these reaction conditions (e.g., trans:cis ratio = 11:1−16:1, entry 3, Table 4).



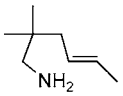
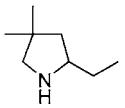
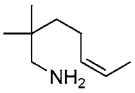
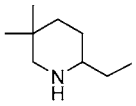
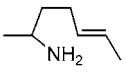
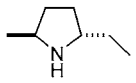
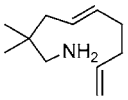
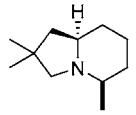
(11)



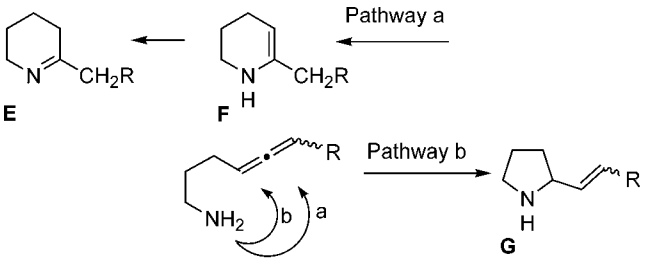
(12)

4. Aminoallene Hydroamination/Cyclization. We also addressed the aforementioned 1,2-disubstituted alkene hydroamination issue by developing other unsaturated substrate families such as aminoallenes and aminodienes. First, we envisioned highly reactive and sterically less encumbered aminoallenes as attractive substrates. In principle, two regioisomeric products are possible from aminoallenes (eq 13). Interestingly, the reaction of *1,3-disubstituted* aminoallenes proceeds exclusively via pathway **b** (Table 5).[12b,c] The identical rate law ($v = k$[substrate]^0[Ln]^1) observed argues that a mechanism very similar to aminoalkene and aminoalkyne hydroamination/cyclization is operative. Aminoallene hydroamination/cyclization is generally more rapid than that of aminoalkenes but more sluggish than that of aminoalkynes. However, aminoallene reaction turnover frequencies maximize around intermediate ionic radius metals (Y^{3+} > Sm^{3+}> Lu^{3+}> La^{3+}), which stands in marked contrast to hydroamination/cyclization of aminoalkenes (rate accelerating with increasing Ln^{3+} ionic radius) and aminoalkynes (rate decreasing with increasing Ln^{3+} ionic radius).

Table 4. 1,2-Disubstituted Alkenylamine Hydroamination[a]

entry	substrates	products	N_t, h^{-1} (°C)	% conv. (yield)
1			8.54 (125 °C)[b]	> 95
2			11.5 (125 °C)[b]	> 95
3		 *cis*: *trans* = 1 : 11	0.46 (125 °C)[c,d]	> 95
4		 *cis*: *trans* = 4.3 : 1	0.3 (125 °C)[c]	85 (59)

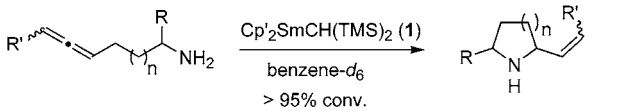
[a] Condition: 5 mol % precatalyst in *o*-xylene-d_{10} at 125 °C. [b] $Cp'_2LaCH(TMS)_2$ (**1**) as precatalyst. [c] $CGCSmN(TMS)_2$ (**8**) as precatalyst. [d] 10 mol % precatalyst used.

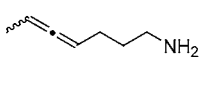
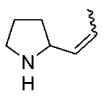
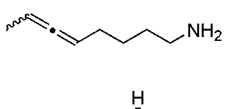
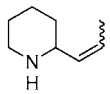
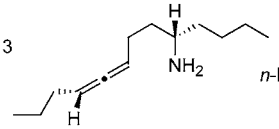
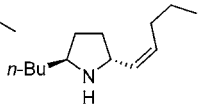
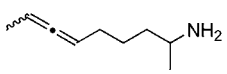
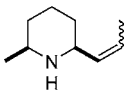


(13)

The most attractive feature of aminoallene cyclization is an exclusive diastereoselectivity in formation of *trans*-2,5-disubstituted pyrrolidines (entry 3, Table 5) and *cis*-2,6-disubstituted piperidines (entry 4, Table 5). The observed diastereoselectivity can be rationalized by considering chairlike transition-state models (Figure 2). Interestingly, product stereochemistry (2,5-trans or 2,6-cis)

Table 5. Aminoallene Hydroamination/Cyclization



entry	substrate	product	*E*:*Z* ratio	N_t, h^{-1} (°C)
1			12 : 88	13.0 (23)
2			20 : 80	0.15 (60)
3			5 : 95	> 1000 (23)
4			45 : 55	0.23 (23)

arising from the amine stereogenic center overcomes any significant stereoinduction originating from the chiral allene moiety. The efficiency and high diastereoselectivity of aminoallene hydroamination/cyclization are highlighted in the concise total synthesis of (+)-xenovenine and (+)-pyrrolidine 197B (Scheme 3).[12a] In the xenovenine synthesis, the stereogenic center originally introduced by the enantioselective dialkyl zinc addition to the aldehyde completely controls the remaining stereogenic centers through two sequential 2,5-trans diastereoselective hydroamination/bicyclizations. The intramolecular insertion into the Ln−N bond of the proximal allenic C═C linkage is proposed to be the turnover-limiting step. Note that the second cyclization at the alkenyl group in the xenovenine synthesis is highly sensitive to the steric demands; therefore, only the half-lanthanocene "constrained geometry catalyst", CGCSmN(TMS)$_2$ (**8**),[9h] can complete the second alkene cyclization.

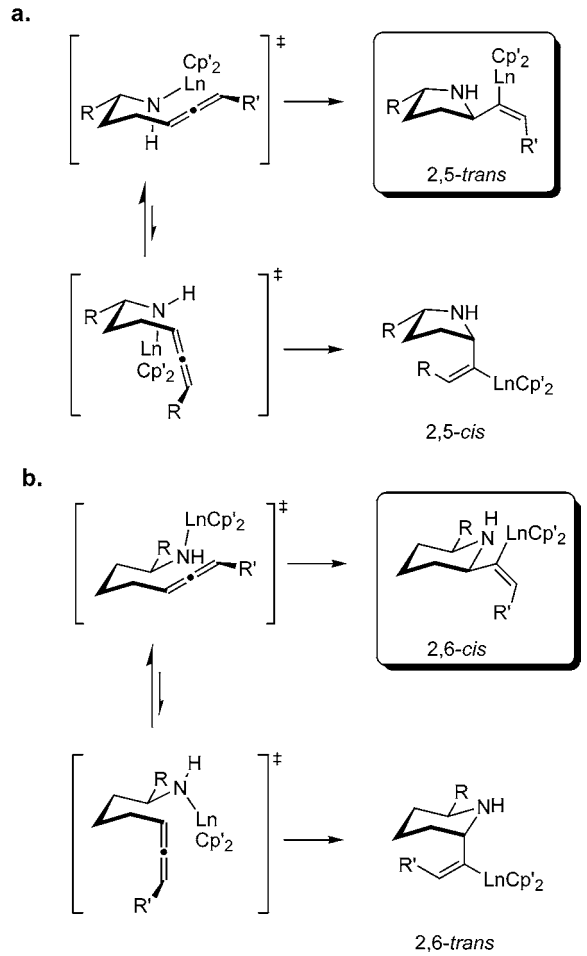
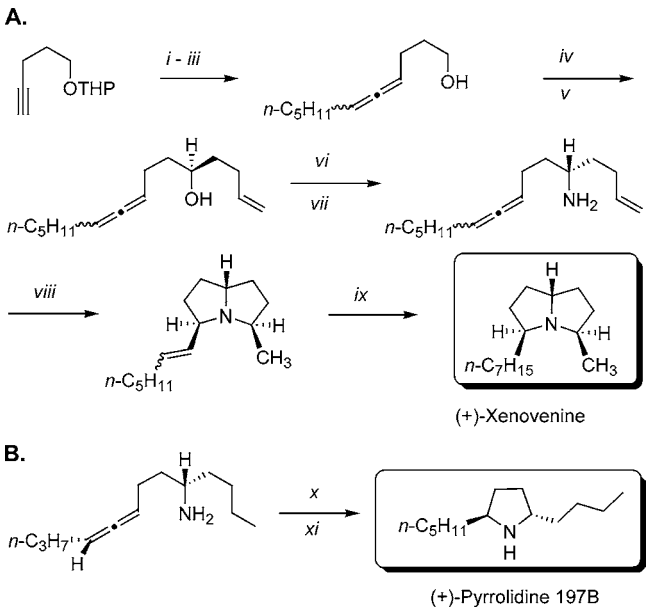


FIGURE 2. Stereochemical pathways for diastereoselective aminoallene hydroamination/cyclization.

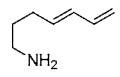
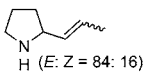
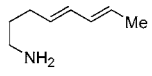
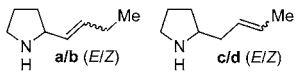
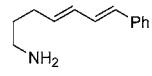
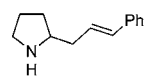
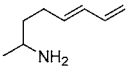
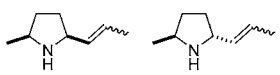
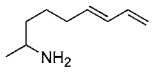
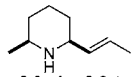
Scheme 3. Total Syntheses of (+)-Xenovenine and (+)-Pyrrolidine 197B[a]



[a] Reagents and conditions:(i) *n*-BuLi, THF, −78 °C; then hexanal, −78 °C, 88%; (ii) Ph_3P, DEAD, *o*-nitrobenzenesulfonylhydrazine, −15 °C; (iii) TsOH, MeOH, 74% for two steps; (iv) $(COCl)_2$, CH_2Cl_2, DMSO, Et_3N, 99%; (v) bis(3-butenyl)zinc, bissulfonamide Ti catalyst, −60 to −20 °C, 36%; (vi) Ph_3P, DEAD, $Ph_2P(=O)N_3$, rt; (vii) $LiAlH_4$, Et_2O, reflux, 57% for two steps; (viii) 5 mol % CGCSmN(TMS)$_2$, C_6D_6, 45 °C, overnight, 80% (*Z*/*E* = 1:1); (ix) Pd(OH)$_2$/C, MeOH, H_2 (1 atm), rt, 97%; (x) 2 mol % Cp′$_2$SmCH(TMS)$_2$, pentane, rt, 1 h (*Z*/*E* = 95: 5); (xi) Pd(OH)$_2$/C, MeOH, H_2 (1 atm), rt, 88% for two steps.

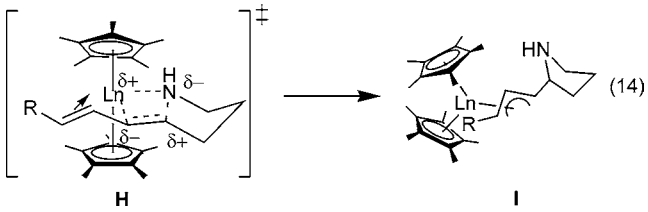
5. Aminodiene Hydroamination/Cyclization. In an alternative approach, derived from preliminary *intermolecular* organolanthanide-mediated diene hydroamination results,[8b] we envisioned conjugated diene substrates as attractive precursors for the synthesis of azacyclic targets. At comparable concentrations, intermolecular butadiene hydroamination with *n*-propylamine is significantly more rapid than 1-pentene hydroamination (N_t = 0.3 h^{-1} at 23 °C vs N_t = 0.4 h^{-1} at 60 °C). The intramolecular hydroamination/cyclization of conjugated aminodienes proceeds cleanly at 25−60 °C with good rates and high regio- and diastereoselectivities (Table 6).[13] Notably, intramolecular aminodiene hydroamination rates are also significantly more rapid than those of the corresponding aminoalkenes, possibly arising from the stabilization of proposed transition state electronic demands (**H**). Kinetic and mechanistic data including the rate law ($v = k$[substrate]^0[Ln]^1) parallel

Table 6. Aminodiene Hydroamination/Cyclization

entry	substrate	product (ratio)	%conv. (yield)	N_t, h^{-1} (°C)
1		 (*E*: Z = 84: 16)	> 95	40 (25)[a]
2		 **a/b** (*E*/*Z*) **c/d** (*E*/*Z*) (**a**:**b**:**c**:**d** = 38: 0: 47: 15)	94	1.8 (60)[a]
3			92	89 (60)[a]
4		 (**2,5-*cis* : 2,5-*trans*** = 12: 88)	> 95	15 (25)[b]
5		 **(±)-Pinidine** (**2,6-*cis* : 2,6-*trans*** = 99.4 : 0.6, *E* : *Z* : allyl = 94 : 1 : 5)	> 95	3.7 (25)[a]

[a] $Cp'_2LaCH(TMS)_2$ (**1**) as precatalyst. [b] CGCSmN$(TMS)_2$ (**8**) as precatalyst.

monosubstituted aminoalkene hydroaminaton. However, significantly more pronounced lanthanide ionic radius effects and ancillary ligation effects on turnover frequencies (rate increasing dramatically with more open environments) plausibly suggest a sterically more demanding Ln−N insertion step than in aminoalkene hydroamination.



H **I** (14)

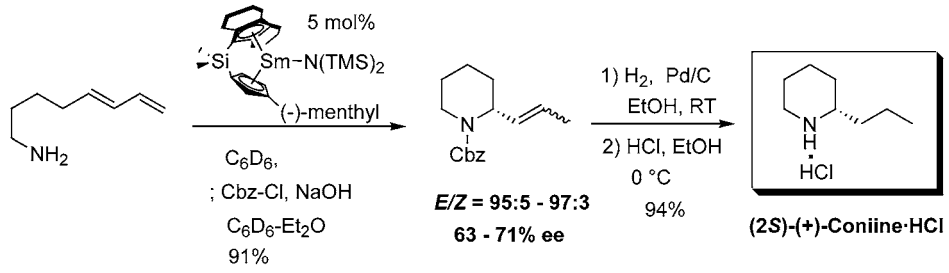
Good to excellent diastereoselectivities are observed in 2,5-*trans*-disubstituted pyrrolidine and 2,6-*cis*-disubstituted piperidine cyclizations (entries 4 and 5, Table 6). Note that entry 5 demonstrates a concise, efficient synthesis of (±)-pinidine with excellent stereocontrols for both 2,6-cis substitution (cis/trans = 178:1) and *trans*-alkene geometry (*E*/*Z*/allyl = 94:1:5). The steric demands of the putative η^3-allyl intermediate (**I**) greatly influence the stereochemical outcome of enantioselective aminodiene hydroamination/cyclization. Thus, up to 71% ee is obtained in the synthesis of 2-substituted piperidines, and the natural product (+)-coniine·HCl is efficiently synthesized from a simple prochiral aminodiene precursor in an essentially two-step sequence in very high isolated yield (Scheme 4).

III. Catalyst Development

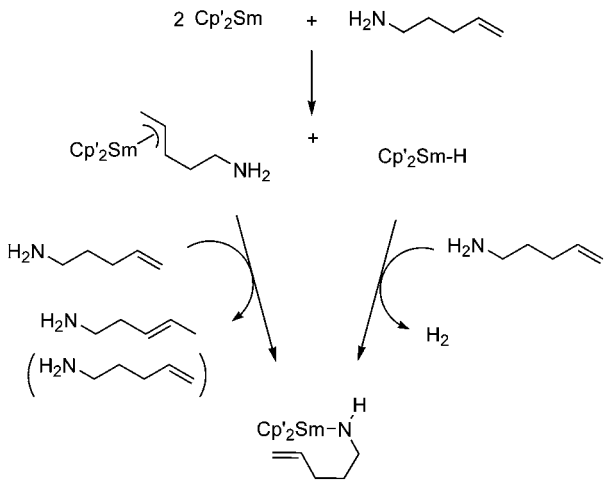
1. Toward More Coordinatively Open, More Active Catalysts. Typical organolanthanide catalysts for hydroamination are trivalent (3+ oxidation state) and possess at least one kinetically labile, σ-bonded ligand (e.g., −H, $-CH(TMS)_2$, $-N(TMS)_2$) which can be replaced by amine substrates to generate Ln−amido species (Figure 1). We also reported that readily available divalent Cp'_2-Sm and $Cp'_2Sm(THF)_2$ (**4**) can also catalyze the hydroamination/cyclization of aminoalkenes.[9m] However, in this case the active catalysts appear to be trivalent organosamarium complexes generated oxidatively in situ from the reaction mixture (Scheme 5). Since initial results revealed that more open catalysts such as silyl-linked *ansa*-lanthanocenes (**5**, **6**) exhibit more rapid reaction rates for aminoalkene hydroamination and tandem bicyclization, significant efforts were made to synthesize sterically less encumbered ancillary ligation. The aforementioned $[(Cp^{TMS})_2LnMe]_2$ (**3**) complex developed by Molander and co-workers is one example.[9j] Noteworthy is the half-lanthanocene, "constrained geometry" organolanthanide catalyst series, $Me_2SiCp'(^tBuN)LnE(TMS)_2$ (**8**).[9h] These coordinatively very open catalysts exhibit significantly enhanced activity for aminoalkene hydroamination/cyclization ($N_t = 181\ h^{-1}$ at 25 °C for CGCSmN$(TMS)_2$ vs $N_t = 48\ h^{-1}$ at 60 °C and $N_t \approx 4.8\ h^{-1}$ at 25 °C for $Cp'_2SmCH(TMS)_2$) and play a crucial role in the aforementioned tandem bicyclization of an allenyl−alkenylamine for the synthesis of xenovenine,[12a] where conventional catalysts fail to mediate the sterically demanding second cyclization (Scheme 3). Tetravalent CGC *organoactinides*, CGCAn$(NRR')_2$ (An = Th, U; R, R′ = Me or Et), have also been reported very recently, and they also exhibit enhanced activity in aminoalkene and aminoalkyne hydroamination/cyclization vs analogous Cp'_2AnMe_2 complexes.[6a] Livinghouse and co-workers reported that even homoleptic lanthanide amides, $Ln[N(TMS)_2]_3$ (**11**), can mediate hydroamination/cyclization, although observed reaction rates are slower than those achieved with lanthanocenes.[9f] However, a series of bidentate nonmetallocene lanthanide−amido complexes (**13** and **14**) later developed by the Livinghouse group show much improved rates and diastereoselectivities.[9b,c] Note that some of these results compare favorably to those of lanthanocene catalysts in terms of rates and diastereoselectivity.

2. Chiral Catalysts: Enantioselective Hydroamination. *Enantioselective* hydroamination using chiral catalysts is one of the most desirable, elegant transformations, enabling the synthesis of chiral amines from simple, readily available prochiral substrates in a single step. In the early 1990s, the first enantioselective intramolecular hydroamination was reported for a limited group of substrates using C_1-symmetric chiral organolanthanide complexes (**9**).[10e−g] *Ansa*-lanthanocene frameworks were modified by incorporating a chiral moiety, R*, such as (−)-menthyl, (−)-phenylmenthyl, or (+)-neomenthyl to ensure the formation of separable, diastereomeric complexes. The bulky nature of R* as well as the size differences between the "upper" (C_5Me_4−) and "lower" (R*−C_5H_3−) Cp rings is designed to provide lateral and transverse discrimination, respectively. Such catalysts are effective in formation of five-membered rings via hydroamination/cyclization of aminoalkenes (up to 74% ee); however, levels of asym-

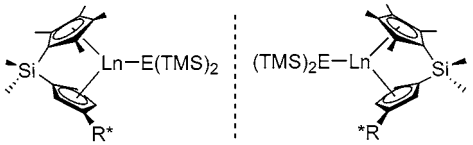
Scheme 4. Synthesis of (2*S*)-(+)-Coniine·HCl



Scheme 5. Generation of Sm(III) from in Situ Oxidation of Sm(II) by Aminoalkene Substrates



metric induction fall precipitously (to 15−17% ee) in formation of homologous six-membered rings (Table 7).



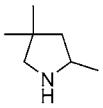
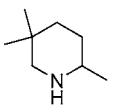
(*S*)-**9** (*R*)-**9**

E = CH, N

R* = (+)-neomenthyl, (-)-menthyl, (-)-phenylmenthyl

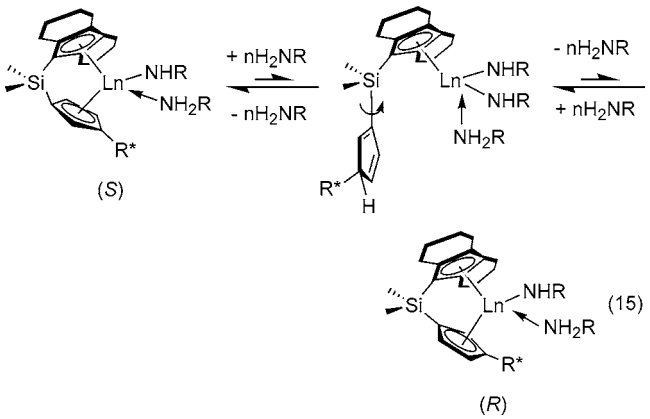
In subsequent studies, the structural motif of these first-generation chiral C_1-symmetric organolanthanides was further modified by increasing the "wing-span" of the "upper" η^5 ligand with a stereodemanding, electron-donating octahydrofluorenyl (OHF) top to increase top−bottom ligand−substrate steric discrimination.[10d] In comparison to the first-generation C_1-symmetric catalysts, the OHF catalysts (**10**) exhibit greater enantioselectivities in hydroamination with sterically encumbered six-membered ring substrates (up to 67% ee); however, only comparable or slightly lower enantioselectivities are observed in many other cases (Table 7). Overall, these C_1-symmetric chiral Cp-based catalysts show very high activity and respectable to high selectivity in hydroamination and other related transformations such as in olefin hydrogenation,[10e,18] hydrosilylation,[19] and polymerization.[20] However, the epimerization of these catalysts in the presence of protic amine molecules is observed for

Table 7. Enantioselective Hydroamination/Cyclization by C_1-Symmetric Chiral Catalysts

product	precatalyst[a]	N_t, h^{-1}(°C)	%ee[b] (config)
	(*S*)-menthylCpSm	84 (25)	53 (*S*)
	(*S*)-menthylCpSm	- (−30)	74 (*S*)
	(*R*)-phenylmenthylCpY	8 (25)	56 (*S*)
	(*S*)-OHFSm	33 (25)	32 (*S*)
	(*S*)-menthylCpSm	33 (25)	62 (*S*)
	(*S*)-menthylCpSm	- (0)	72 (*S*)
	(*R*)-menthylCpY	- (25)	69 (*S*)
	(*S*)-OHFSm	2.6 (25)	46 (*S*)
	(*S*)-menthylCpSm	2 (25)	15 (*R*)
	(*R*)-neomenthylCpSm	- (25)	17 (*R*)
	(*S*)-OHFSm	0.6 (25)	41 (*S*)
	(*S*)-OHFY	2.1 (25)	67 (*S*)

[a] Precatalyst abbreviations: R*CpLn = $Me_2Si(CpMe_4)(CpR^*)$-LnE$(TMS)_2$ (**9**; R* = (−)-menthyl, (−)-phenylmenthyl, or (+)-neomenthyl; E = CH or N), OHFLn = $Me_2Si(\eta^5$-octahydrofluorenyl)(Cp-(−)-menthyl)LnN$(TMS)_2$ (**10**). [b] Determined by ^{19}F NMR or GC-MS analysis of Mosher amides or chiral HPLC analysis of 1-naphthoyl amides.

both C_1-symmetric catalytic systems (eq 15), although the epimer ratio is usually far from 1:1, favoring one isomer depending on chiral substituent R*, solvent, and temperature (typically > 90:10). This intrinsic complexity not only contributes to lowered enantioselectivity but also hampers accessibility to both product enantiomers from each precatalyst isomer.



(15)

Recently, nonmetallocene, C_2-symmetric bis(oxazolinato)lanthanide catalysts (**15**) have been synthesized (Figure 3).[10a] These new C_2-symmetric catalyst systems are particularly attractive since they are configurationally

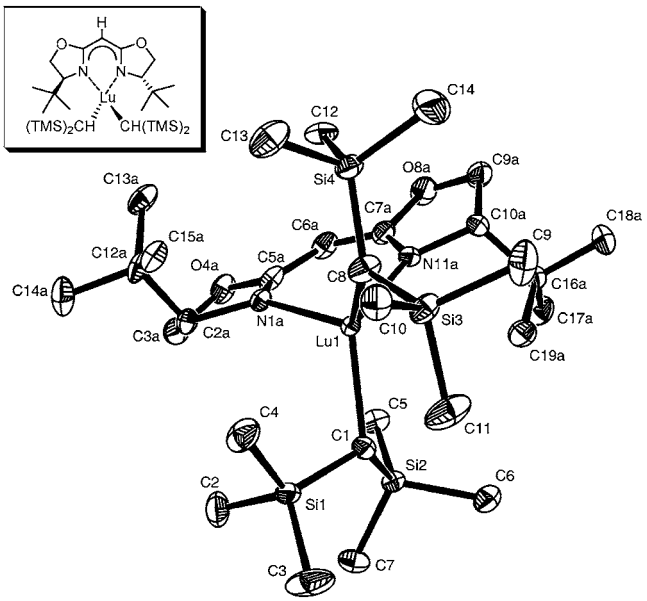
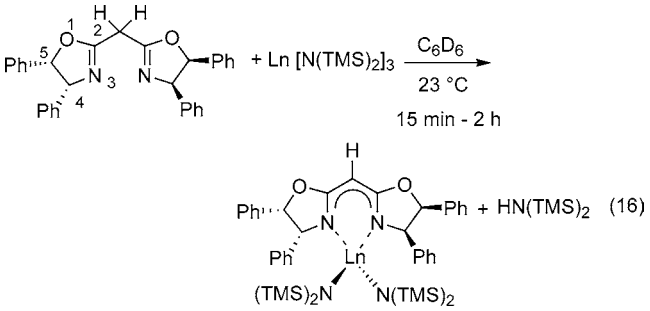


FIGURE 3. Molecular structure of [(4*S*)-^{t}BuBox]Lu[CH(TMS)$_2$]$_2$. Thermal ellipsoids are drawn at the 30% probability level.

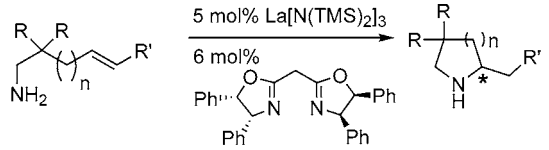
stable and can be generated protonolytically in situ from the known metal precursors Ln[N(TMS)$_2$]$_3$ or Ln[CH(TMS)$_2$]$_3$ (Ln = La, Nd, Sm, Y, Lu) and 1.2 equiv of commercially available or readily prepared bis(oxazoline) ligands (eq 16).

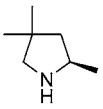
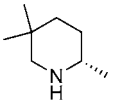
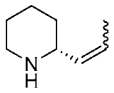
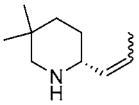


(16)

Lanthanides having the largest ionic radii exhibit the greatest turnover frequencies as well as enantioselectivities. A screening study of bis(oxazoline) ligands reveals that aryl stereodirecting groups at the oxazoline ring 4 position and additional substitution (geminal dimethyl or aryl) at the 5 position are crucial for high turnover frequencies and good enantioselectivities. The optimized precatalyst, in situ generated [(4*R*,5*S*)-Ph$_2$Box]La[N(TMS)$_2$]$_2$ (**15-La**), exhibits good rates and enantioselectivities, comparable to or greater than those achieved with chiral C_1-symmetric organolanthanocene catalysts, even for poorly responsive substrates (up to 67% ee at 23 °C, Table 8). In addition, this catalyst affords more consistent ee values than lanthanocene catalysts over a broad range of substrates. Kinetic studies indicate that the hydroamination rate is zero-order in [amine substrate] and first-order in [catalyst]. This and the rate dependence on Ln^{3+} ionic radius suggest a similar or identical mechanism to that observed in previous organolanthanide-catalyzed hydroamination/cyclizations, presumably involving monomeric catalytic species. Another interesting example of

Table 8. Reaction Scope in Enantioselective Hydroamination/Cyclization



product	N_t, (h^{-1})	temp (°C)	%ee[a] (config)
	25	23	67 (*R*)
	0.09	23	40 (*R*)
	4.0	60	56 (*S*)
 (*E*/*Z* =41:59)	0.6	60	54 (*R*)
 (*E*/*Z*/allyl = 39:57:4)	1.4	23	45 (*R*)

[a] Determined by chiral HPLC analysis.

non-cyclopentadienyl lanthanide-catalyzed hydroamination is the lanthanide bisaryloxide complexes (**16**) reported by Scott and co-workers.[10c] Again, decreasing ee's with decreasing Ln^{3+} radius was observed. Up to 61% ee was reported for the optimized La catalyst; however, the reaction rate is rather slow ($N_t \approx 2.5$ h^{-1} at 70 °C for cyclization of dimethylpentenamine). Yttrium biphenolate complexes (**17**) developed by Hultzsch and co-workers also achieved similar level of selectivity (up to 57% ee) at 70 °C.[10b]

IV. Intermolecular Hydroamination and Tandem Inter-/Intramolecular Hydroamination

As our studies progressed, we focused predominantly on *intramolecular* systems for catalyst/substrate development since such intramolecular processes are likely to enjoy substantial entropic advantages over the corresponding intermolecular process. However, we also demonstrated that organolanthanide complexes effectively and regioselectively catalyze the *intermolecular* hydroamination of a variety of alkenes, alkynes, and methylenecyclopropanes (Table 9).[8] In comparison to intramolecular hydroamination, these intermolecular transformations are ~350× slower for alkene hydroamination and ~1400× slower for alkyne hydroamination. The empirical rate law (eq 17) and similar steric effects on reaction rate (increasing N_t's with increasing Ln^{3+} ionic radius, more open ligation, and less

Table 9. Intermolecular Hydroamination Results for Alkynes, Alkenes, and Butadiene

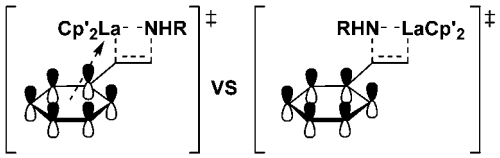
alkyne/olefin	amine	product	N_t, h^{-1} (°C)	% conv. (% yield)
H_3C—≡—TMS	H_2N	TMS, N	14 (60)[a]	90
H_3C—≡—Ph	H_2N	Ph, N	2 (60)[a]	85
H_3C—≡—CH_3	H_2N	N	1 (60)[a]	91
TMS	H_2N	TMS, H, N	2 (60)[a]	93
	H_2N	H, N	0.3 (21)[a]	90
	H_2N	HN	0.4 (60)[a]	90
Ph	H_2N, Me	Me, N, Ph	0.38 (60)[b]	>95 (92)

[a] $Me_2SiCp''NdCH(TMS)_2$ (**5**) as precatalyst. [b] $Cp'_2LaCH(TMS)_2$ (**1**) as precatalyst.

sterically encumbered amines) suggests a similar turnover-limiting step involving intermolecular unsaturated carbon−carbon bond insertion into the Ln−N bond.

$$v = k[\text{amine}]^0[\text{alkyne}]^1[\text{Ln}]^1 \qquad (17)$$

Intermolecular vinylarene hydroamination proceeds in good isolated yields and excellent anti-Markovnikov regioselectivity (Table 10).[8a] The observed regioselectivity is reasonably attributed to aryl-directing interactions of the weakly coordinating arene π system and the electrophilic lanthanide center. Note that this transformation is compatible with moderately polar functional groups such as −F, $-CF_3$, −OMe, $-NMe_2$, and −SMe. Moreover, it has also been demonstrated that intermolecular hydroamination can be coupled with subsequent intramolecular hydroamination/cyclization and C−C bond formation to yield complex polycyclic heterocycles in a single step and with excellent diastereoselectivities (e.g., Scheme 6).[8a,11a]

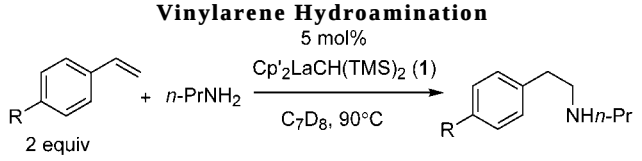


2,1-addition (**J**) 1,2-addition (**K**)

V. Other Organolanthanide-Catalyzed Hydro*element*ations

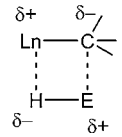
Other catalytic hydro*element*ations, E−H (E = Si, B, H, P) addition to C−C multiple bonds, are efficiently mediated by organolanthanide complexes. Many are highly diastereoselective. Hydrophosphination[21] appears to follow a catalytic pathway similar to hydroamination (turnover-limiting C−C multiple bond insertion into Ln−E bond followed by rapid protonolysis), whereas hydroboration,[22] hydrosilylation,[19,23] and hydrogenation[10e,18,24] proceed via different catalytic cycles. In contrast to hydroamination and hydrophosphination where Ln−amido or Ln−phosphido intermediates are generated from protonolysis of the precatalyst, hydrosilylation, hydrogenation, and hydroboration involve a lanthanide−hydride (e.g., Scheme 7). The disparity can be understood on the basis of bond polarity arguments. (**L** vs **M**).

Table 10. Organolanthanide-Catalyzed Intermolecular Vinylarene Hydroamination

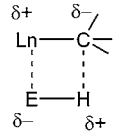


product	N_t, h^{-1}(temp)	conv. (yield %)
H, N	2.0 (90 °C)	93 (90)
H_3C, H, N	1.5 (90 °C)	> 95 (93)
H, N	1.6 (90 °C)	> 95 (92)
F, H, N	0.94 (120 °C)	94 (88)
F_3C, H, N	3.4 (90 °C)	93 (83)[a]
MeO, H, N	0.2 (90 °C)	89 (82)
Me_2N, H, N	0.05 (90 °C)	55 (30)
MeS, H, N	3.6 (90 °C)	89 (85)

[a] [Anti-Markovnikov]:[Markovnikov] = 96:4.



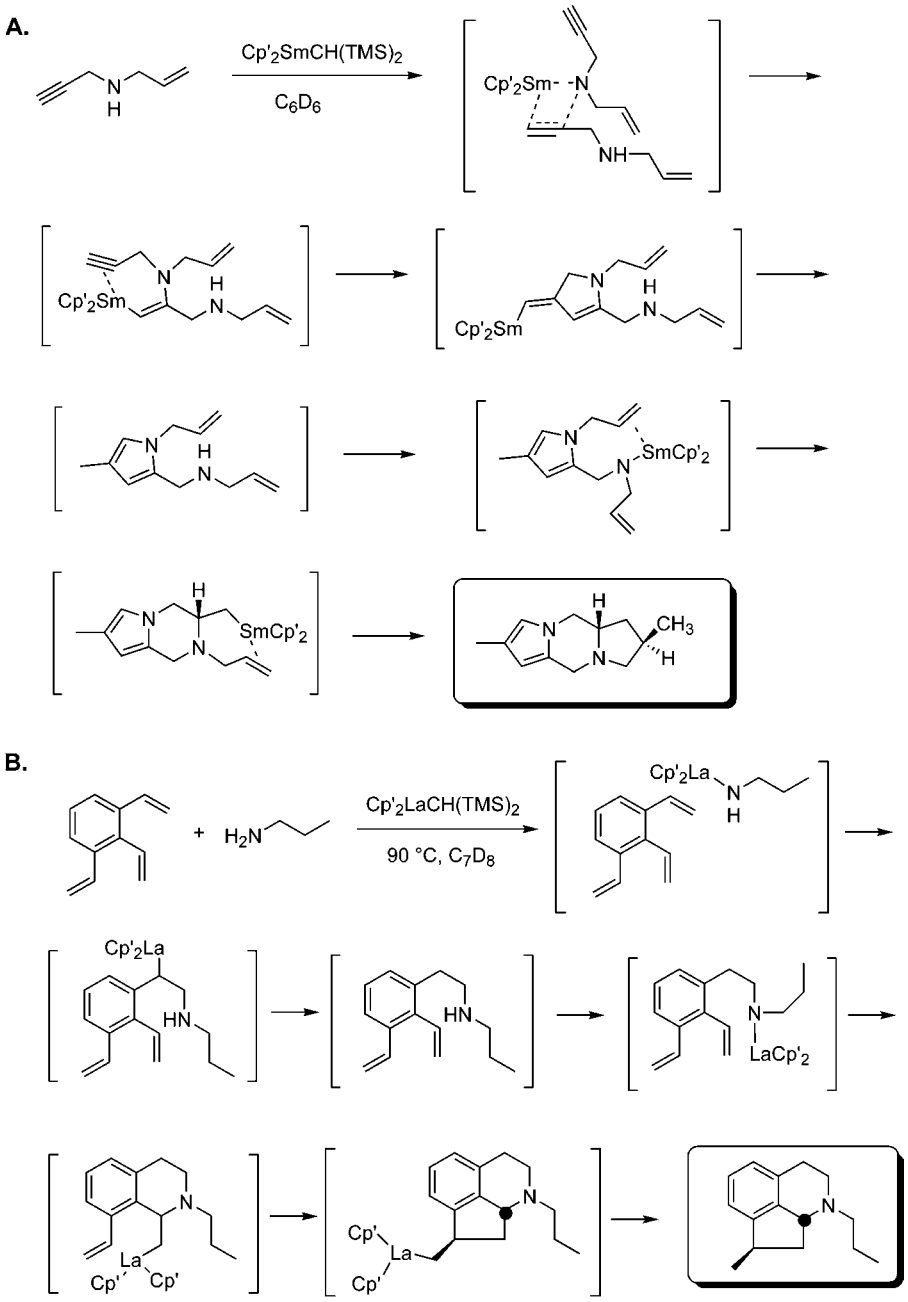
L : E = BR_2, SiR_3, H



M : E = NR_2, PR_2

From kinetic/mechanistic studies, the pathways for olefin hydrosilylation, hydrogenation, and hydroboration are proposed to involve rapid olefin insertion into a Ln−H bond, followed by turnover-limiting E−H/Ln−C (E = Si, H, B) transposition, in sharp contrast to the hydroamination/hydrophosphination mechanisms. For hydro-

Scheme 6. Coupled Intermolecular and Intramolecular Tandem Hydroamination/Cyclization



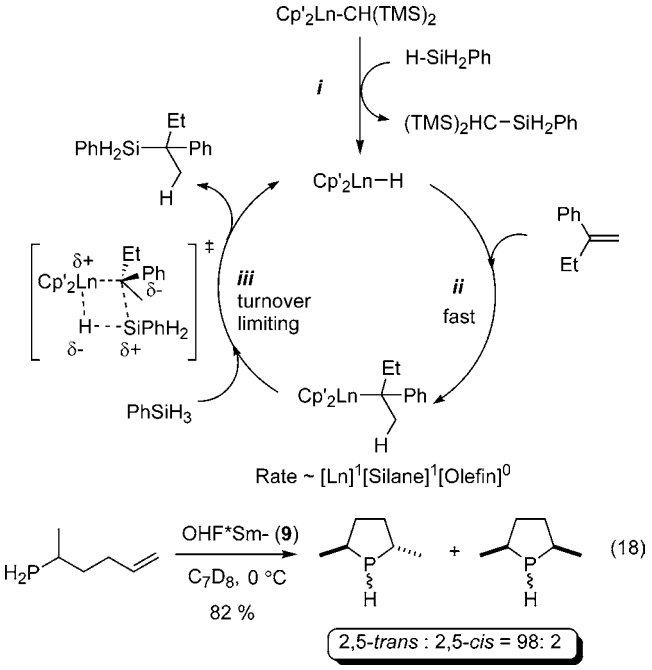
silylation of styrenic substrates, aryl-directing effects dominate to yield the overall Markovnikov silylated product.[19] Furthermore, moderate to excellent enantioselectivities are obtained for hydrosilylation (up to 78% ee)[19] and hydrogenation (up to 96% ee)[10e,18] using the aforementioned C_1-symmetric chiral catalysts, presumably in part owing to the absence of the aforementioned epimerization pathways under these nonprotic reaction conditions. In the presence of excess olefin, Scheme 7-type cycles can be operated in such a manner as to produce a variety of heteroatom-capped polyolefins, with the E−H species functioning as a chain-transfer agent to control product molecular weight.[23]

Compared to hydroaminations, hydrophosphinations exhibit significantly slower protonolytic activation of the precatalysts by phosphine substrates and generally evidence more pronounced competitive inhibition by cyclized products.[21b] However, many similarities such as rate law, catalyst resting state, and activation parameters are found between the two processes, suggesting broadly similar mechanisms. More importantly, excellent 2,5-trans diastereoselectivity (96%) for 2,5-dimethylphospholane synthesis is obtained using the chiral OHF catalyst, which illustrates the potential utility of these novel transformations (eq 18).[10d]

VI. Conclusions and Prospects

The remarkably facile insertion of olefins into Ln−alkyl bonds, best illustrated in ethylene polymerization, led us

Scheme 7. Mechanistic Scenarios for Organolanthanide-Catalyzed Hydrosilylaion



to question whether at that time unknown Ln−E bond insertion process might also be feasible. Thermodynamic consideration of prospective catalytic cycles using experimental lanthanide−carbon and lanthanide−heteroatom bond enthalpies enabled us to rationally design unprecedented organolanthanide-catalyzed hydroamination methodologies. Organolanthanides were subsequently shown to be highly efficient catalysts for inter- and intramolecular hydroamination of several key carbon−carbon unsaturated systems such as alkenes, alkynes, allenes, and dienes. High diastereoselectivity/enantioselectivity exhibited in these transformations and the facility of staging reactions in tandem sequence render this methodology particularly attractive for the concise synthesis of naturally occurring alkaloids and other complex polycyclic azacycles. The general organolanthanide-catalyzed hydroamination mechanism involves turnover-limiting C−C multiple bond insertion into the Ln−N bonds followed by a rapid protonolysis by other amine substrates. Sterically less encumbered ligand designs such as CGC have been developed to improve reaction rates, and metallocene and nonmetallocene chiral lanthanide complexes have been synthesized for interesting enantioselective hydroamination processes. Analogous non-amine hydro*element*ation (E = P, Si, B, H) results reveal both similarities to and differences from hydroamination, extending our knowledge of lanthanide catalytic chemistry. More active catalysts which can mediate 1,2-disubstituted olefin hydroamination at lower reaction temperatures, improved chiral lanthanide catalysts which can consistently produce over 90% ee for a broader range of substrates, and application of this hydroelementation methodology to both small molecule and polymeric materials synthesis will be the next agenda in our continuing studies of this intriguing chemistry.

We gratefully acknowledge the researchers who carried out the work described herein. We thank the National Science Foundation (CHE0078998) for generous support of this work.

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