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Cation Charge Density and Precatalyst Selection in Group 2-Catalyzed Aminoalkene Hydroamination

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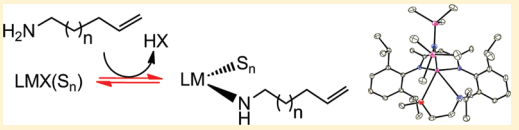
Supporting Information

ABSTRACT: The magnesium methyl and the calcium and strontium silylamide β-diketiminate derivatives [{ArNC(Me)CHC(Me)NAr}MX(THF)$_n$] (M = Mg, X = CH_3, n = 0; M = Ca, X = $N(SiMe_3)_2$, n = 0 or 1; M = Sr, X = $N(SiMe_3)_2$, n = 1, Ar = 2,6-diisopropylphenyl), the silylamides $[M\{N(SiMe_3)_2\}_2]_2$ and $[M\{N(SiMe_3)_2\}_2(THF)_2]$ (M = Mg, Ca, Sr, Ba), and the alkyl species $[M\{CH(SiMe_3)_2\}_2(THF)_2]$ (M = Mg, Ca, Sr, Ba) have been studied as precatalysts for the hydroamination/cyclization of aminoalkenes. Hydroamination afforded a series of five- and six-membered pyrrolidine and piperidine derivatives in near quantitative yields with all precatalysts, apart from the barium species, which were apparently limited to a maximum of two turnovers with even the favorable 1-amino-2,2-diphenyl-4-pentene substrate. Significant formation of hexahydroazepines was observed only with the magnesium amide species, while the group 2 dialkyl derivatives decomposed at high reaction temperatures and proved to be more limited in scope. In general, the calcium precatalysts proved to be more reactive than their strontium analogues, which, in turn, proved to be far more reactive than the magnesium species. Among the β-diketiminate derivatives, the greater coordinative unsaturation of the THF-free calcium derivative provided increased activity for the cyclization of primary aminoalkene substrates in comparison to its THF-solvated counterpart. In contrast, the unsolvated bis(amides) displayed lower activity with these substrates than their THF-solvated analogues. Use of silylamide precatalysts provides potentially reversible entry into the catalytic manifold. The position of the equilibrium is perturbed by both the nature of the substrate and the identity of the group 2 element, highlighted by the reaction of [{ArNC(Me)CHC(Me)NAr}Sr{$N(SiMe_3)_2$(THF)] with 2-methoxyethylamine, which results in equilibration between the starting silylamide, an isolable amine adduct, and the product of amine/silylamide transamination. Performing the same reaction with the calcium precatalyst provided the analogue of the latter product as the only observable species. A kinetic study of the cyclization of (1-allylcyclohexyl)methanamine with each of the calcium and strontium silylamide precatalysts provided an apparent first-order dependence in [catalyst], while determination of the activation barriers and Eyring analyses provided quantitative evidence that the group 2 catalysts reported herein provide activities at least commensurate with previously reported lanthanide-based catalyses. In the particular cases of systems based upon calcium and strontium, an enhanced catalytic performance is proposed to arise from a tangible entropic advantage resulting from the reduced charge density of the larger divalent alkaline earth cations and consequentially less constrained rate-determining alkene insertion transition states. The rate of cyclization was also found to decrease with increasing substrate concentration. This latter observation, along with the observation of large kinetic isotope effects (>4), proposed to be a result of a beneficial and concerted proton transfer step associated with rate-determining alkene insertion, are reasoned to be consistent with Michaelis−Menten-type kinetics.



INTRODUCTION

The use of lanthanide complexes of the general form L_2LnX (L = monoanionic spectator ligand, typically substituted cyclopentadienyl; X = H, R, NR_2, PR_2, etc.) in catalysis is well developed, and complexes of this type have been applied to a suite of transformations and polymerization reactions.[1] Within this former scenario, the heterofunctionalization of unsaturated bonds is particularly prominent, and catalytic cycles based upon a combination of σ-bond metathesis steps and the insertion of unsaturated units into lanthanide−heteroatom bonds may be constructed to effect, for example, the hydroamination,[2−12] hydrosilylation,[1b] hydrophosphination,[13] and hydrogenation[14] of an extensive variety of alkenes, alkynes, imines, ketones, and related electrophiles. In contrast to these sophisticated developments and the well-studied stoichiometric chemistry of diorganomagnesium and Grignard reagents,[15] a more applied organometallic chemistry for the heavier alkaline earth metals (Ca, Sr, Ba) is only now starting to emerge.[16−23] Like the similarly d^0 but tripositive lanthanides, coordination and organometallic compounds of these s-block elements feature highly ionic and nondirectional bonding to an effectively redox-inactive and oxophilic metal center. These similarities, combined with a more

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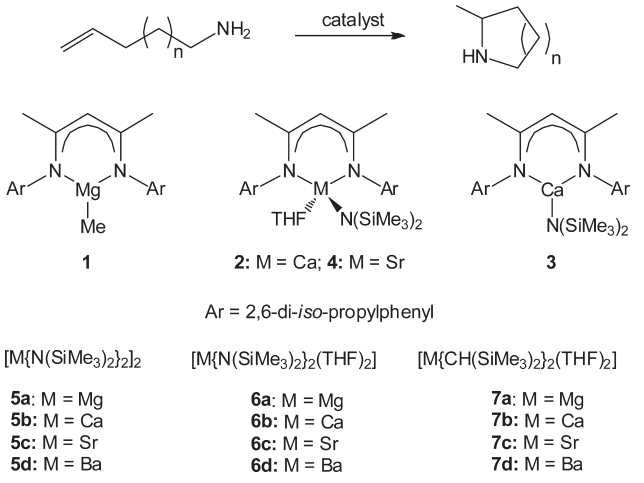


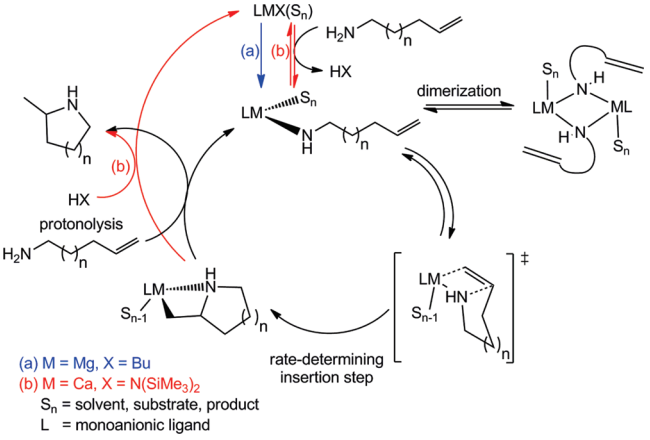
Figure 1. Intramolecular hydroamination and precatalyst structures employed in this study.

fundamentally motivated desire to explore a relatively neglected region of the periodic table, have resulted in some recent dramatic and rapid advances in our appreciation of the coordination behavior of group 2-centered species.[24] Furthermore, the development of appropriate anionic, supporting ligand sets and suitably reactive co-ligands has allowed an initial demonstration of the applicability of these complexes to the construction of cycles reminiscent of those with precedent in lanthanide-based catalyses.[16] Despite many common features, however, it has also become apparent that the heavier alkaline earth metals are not simply "lanthanide-mimetic": the much wider range of ionic radii and resultant cation charge densities (Mg^{2+}, 0.72 Å; Ca^{2+}, 1.00 Å; Sr^{2+}, 1.18 Å; Ba^{2+}, 1.35 Å for six-coordinate ions) compared to the relatively small range provided by the lanthanide contraction (La^{3+}, 1.03 Å; Lu^{3+}, 0.86 Å for six-coordinate ions) allow for much greater variation in reactivity down and across the respective series of elements.[25]

To further understand the mechanisms at work and the role of the individual group 2 element in these catalytic cycles, our group has focused on the study of the intramolecular hydroamination of α-aminoalkenes (Figure 1).[17] Since the seminal initial contributions of Marks and co-workers,[1c,2] this reaction has been one of the most intensively studied processes in 4f element chemistry and thus provides a suitable prototype and benchmark for an exploration of group 2 catalytic reactivity. Since our initial demonstration of the efficacy of this catalysis with the conveniently synthesized calcium β-diketiminato complex **2** (Figure 1),[17a] introduced by Chisholm for the polymerization of *rac*-lactide,[26] a variety of magnesium, calcium, and strontium catalysts have proved efficient for the intramolecular hydroamination of a number of substituted aminoalkenes.[17]

We have previously described a comparative synthetic and mechanistic study of the intramolecular hydroamination of aminoalkenes to provide five-, six-, and even seven-membered nitrogen-containing heterocycles by **2** and the related methylmagnesium derivative, **1** (Figure 1), for which the calcium derivative proved to be significantly more active, though less selective, than its magnesium counterpart.[17b] Preliminary kinetic data and deuterium-labeling studies, as well as a series of stoichiometric reactions with primary amines, led to a refinement of the initially postulated catalytic cycle,[17a] which had been derived from the well-documented hydroamination/

Scheme 1



cyclization cycle in lanthanide chemistry (Scheme 1).[2] It was proposed that the two catalyst systems give rise to two broadly similar but independent catalytic cycles occurring with either (a) nonreversible or (b) reversible catalyst initiation for **1** and **2**, respectively, dependent upon the acidity of the conjugate acid (CH_4 versus $HN(SiMe_3)_2$) generated by the protolytic initiation step.

In a subsequent computational and experimental study, we have also reported that the intermolecular addition of amines to activated alkenes (dienes, styrenes) may be catalyzed by the homoleptic calcium and strontium amides $[M\{N(SiMe_3)_2\}_2]_2$ (**5b**, M = Ca; **5c**, M = Sr) under mild reaction conditions (60 °C).[17c] Factors that stabilize the developing anionic charge upon the atom adjacent to the metal center in the transition state to N−C bond formation were proposed to lower the activation energy of the rate-determining insertion step. In the cases studied, the strontium-based catalyst demonstrated superior reactivity (lower reaction times and higher reaction yields) to the calcium derivative, while the magnesium and barium analogues of these catalysts (M = Mg, Ba) effected the hydroamination of styrene only poorly by comparison. Density functional theory calculations upon model species provided data consistent with rate-determining alkene insertion via a four-center transition state that is highly polarized. On the basis of this data we suggested that the relative barrier heights for alkene insertion into M−N bonds may be viewed as a result of a compromise between the polarity of the M−N bond (i.e., the ability of the M−N bond to induce a dipole in the nonpolarized alkene), the polarizability of the M^{2+} cation, and the consequent ease of electronic reorganization toward N−C and C−M bond formation. Kinetic analyses also revealed a further subtlety, through which the increased activity of the strontium catalyst was attributed to an influential entropic advantage, resulting from the looser assembly of the C═C insertion transition state about the larger Sr^{2+} cation.[17c]

It is clear from these previous observations that the reactivity of the individual group 2 elements, although broadly analogous, is marked by subtle yet significant variations with each modulation of cation radius and resultant charge density. Set against this backdrop, therefore, we present herein the first semiquantitative appraisal of the ability of the entire series of naturally available group 2 elements, excluding beryllium, to catalyze the benchmark intramolecular variant of the hydroamination reaction.

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RESULTS AND DISCUSSION

Precatalyst Selection. We have previously reported that the calcium and magnesium β-diketiminato complexes, **1** and **2**, provide efficient intramolecular hydroamination catalysis and that catalytic turnover is inhibited by Lewis bases such as THF as well as substrate or product binding to the metal center.[17a] It was therefore of interest to compare the ability toward hydroamination catalysis of the calcium precatalyst **2** and its unsolvated analogue $[\{ArNC(Me)CHC(Me)NAr\}Ca\{N(SiMe_3)_2\}]$ (Ar = 2,6-diisopropylphenyl), **3**.[26b] Although a recent structural study has shown that the calcium center in compound **3** is three-coordinate,[27] this species proved stable toward ligand redistribution in solution at room temperature over periods of several weeks.

Due to contamination with the homoleptic and catalytically inactive $[\{ArNC(Me)CHC(Me)NAr\}_2Sr(THF)]$ during synthesis and in solution, the strontium analogue of compound **2**, the heteroleptic species, $[\{ArNC(Me)CHC(Me)NAr\}_2Sr\{N(SiMe_3)_2\}(THF)]$ (**4**), was previously deemed unsuitable for catalysis.[28] However, use of the two-step route reported by Roesky allowed the synthesis of **4** in high purity and yield.[29] A preliminary test with 1-amino-2,2-diphenyl-4-pentene at 5 mol % catalyst loading showed that **4** was capable of catalyzing the hydroamination/cyclization process at temperatures up to 60 °C without any redistribution toward the homoleptic complex apparent in the ^{1}H NMR spectrum, even after extended periods of several days.

We have also reported the successful intermolecular hydroamination catalysis of styrenes and conjugated dienes with a variety of primary, secondary, and N-heterocyclic amines using the homoleptic amides $[M\{N(SiMe_3)_2\}_2]_2$ (**5b**, M = Ca; **5c**, M = Sr).[17c] Our initial communication of intramolecular hydroamination with the calcium precatalyst **2** reported that attempts to catalyze the hydroamination/cyclization of linear 1-amino-4-pentene with **5b** had resulted in failure, even at high catalyst loading and temperature.[17a] Subsequent assessment of the ability of this compound with the substituted substrate 1-amino-2,2-diphenyl-4-pentene, however, proved highly successful. For this reason the complete series of readily available homoleptic silylamides, $[M\{N(SiMe_3)_2\}_2]_2$ (M = Mg **5a**, Ca **5b**, Sr **5c**, Ba **5d**),[30] along with their THF-solvated counterparts $[M\{N(SiMe_3)_2\}_2(THF)_2]$ (M = Mg **6a**, Ca **6b**, Sr **6c**, Ba **6d**)[31] are included in this comparative and mechanistic study of hydroamination/cyclization catalysis. In addition, we have also recently described a conveniently accessed series of homoleptic group 2 alkyls $[M\{CH(SiMe_3)_2\}_2(THF)_2]$ (M = Mg **7a**, Ca **7b**, Sr **7c**, Ba **7d**).[32] These compounds are, therefore, also included in this study. In common with the methylmagnesium species, **1**, it was anticipated that the less acidic conjugate base, $H_2C(SiMe_3)_2$, liberated during catalyst initiation with this latter series of compounds would effectively prevent the establishment of the catalysis-inhibiting initiation equilibria encountered in the presence of $HN(SiMe_3)_2$.

Reaction Scope. Hydroamination/cyclization with all the magnesium, calcium, and strontium precatalysts included in this study (2−20 mol %) afforded a series of substituted pyrrolidines and piperidines in near quantitative yields and under relatively mild conditions (25−100 °C). Formation of hexahydroazepines was only observed in low yield at high temperature and over extended periods of time with the magnesium precatalysts **5a** and **6a** and the strontium precatalyst **4**. The structures of the cyclized products were assigned by comparison with literature NMR data. The results of reactions performed with the homoleptic bis(amides) **5a**−**c**, **6a**−**c**, and dialkyls **7a**−**c** are summarized in Table 1, while data relating to the β-diketiminate-stabilized complexes are provided in Table 2.

Attempts to catalyze the hydroamination/cyclization of 1-amino-2,2-diphenyl-4-pentene with barium precatalysts **5d**, **6d**, and **7d** resulted in a maximum of two turnovers, prior to the precipitation of insoluble, unidentifiable products. This implies that catalysis is limited to a stoichiometric reaction of the substrate with both amide/alkyl moieties of the homoleptic precatalysts. We have previously made similar observations with a heteroleptic tris(imidazolin-2-ylidene-1-yl)borate barium silylamide complex and regard this behavior as being a likely consequence of the very large size and diffuse nature of the cationic barium center, which is thus insufficiently polarizing to effect insertion of the C═C bond of the substrate.[33]

A limitation of the strontium system **4** also became apparent at temperatures above 60 °C, in which case catalysis was accompanied by irreversible Schlenk-like ligand redistribution toward the catalytically inactive homoleptic species as observed by ^{1}H NMR spectroscopy. Effective catalysis with the alkyl systems **7a**−**c** was also limited at temperatures above 40 °C and over periods of time exceeding 30 h. Under such conditions, the precatalysts underwent apparently irreversible degradation into insoluble, and as yet unidentified, catalytically inactive species. As a result, **7a**−**c** could only be used with a very limited number of substrates. Monitoring of C_6D_6 solutions of **7a**−**c** without the presence of substrate over a week showed that these alkyl species tend to decompose over time at room temperature into $CH_2(SiMe_3)_2$ and unidentified insoluble species, the degradation rate increasing dramatically as group 2 is descended.

In all cases, the calcium precatalysts **5b**, **6b**, and **7b** provided comparable yields in shorter reaction times than their strontium analogues **5**−**7c**, which in turn proved far more reactive than the magnesium species **5**−**7a**. Previous comparison between the calcium complex **2** and its magnesium counterpart **1** had already shown **2** to be the more active species. It may be proposed, therefore, that the increase in ionic radius from 0.72 for Mg^{2+} to 1.00 Å for Ca^{2+} (in six-coordinate complexes) provides more ready access to the calcium center and improved access toward substrate binding (*vide infra*). A similar trend has been found across the lanthanide series where turnover frequency markedly decreases with the ionic radius of the metal center. An extrapolation of this rationale to strontium, with a six-coordinate Sr^{2+} radius of 1.16 Å, would furnish the expectation of even higher turnover frequencies than calcium. This is not, however, the case, and previous qualitative comparison of calcium and strontium systems for the hydroamination/cyclization of aminoalkenes has been divided: whereas strontium aminotroponiminate- and triazenide-supported precatalysts had been found to be more sluggish than the related calcium species,[17d−f] qualitative comparison between calcium and strontium bis(imidazolin-2-ylidene-1-yl)borate precatalysts revealed the strontium species to be more reactive.[33] Of the precatalysts studied here, however, the strontium systems were in all cases less active than their calcium counterparts, in both qualitative and quantitative (*vide infra*) analyses.

As expected, the greater coordinative unsaturation of the calcium center in **3** afforded increased catalytic activity compared to the THF-solvated complex **2**. The unsolvated bis(amide) complexes **5a**−**c**, however, displayed lower catalytic activity than their THF-solvated analogues **6a**−**c**, except in the case of

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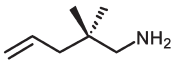
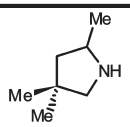
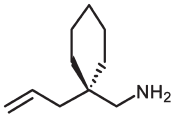
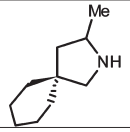
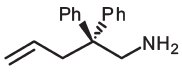
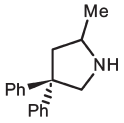
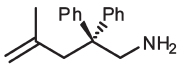
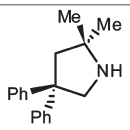
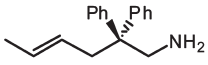
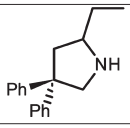
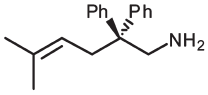
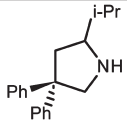
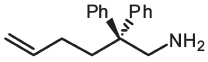
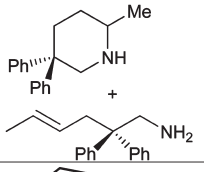
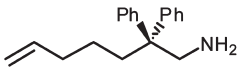
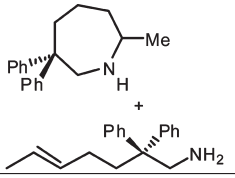
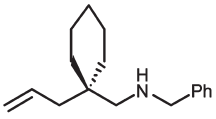
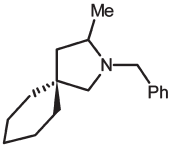
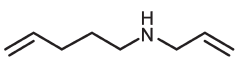
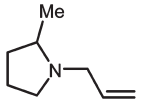
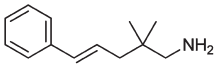
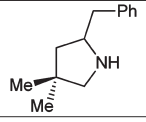
Table 1. Scope of Intramolecular Hydroamination with Magnesium, Calcium, and Strontium Precatalysts 5−7

Entry	Substrate	Product	T / °C	Catalyst (mol %)	Time / h			NMR yield / %[a]		
					5	**6**	**7**	**5**	**6**	**7**
1			80	**a** (10 mol %)	5d	4d	16	60	75	2[b]
2			60	**b** (2 mol %)	6	5	16		>99	
3			60	**c** (2 mol %)	10	8	16		97-99	
4			25	**a** (10 mol %)	48	42	16	95	97	2[b]
5			25	**b** (2 mol %)	1	0.75	0.25		93-99	
6			25	**c** (2 mol %)	24	8	0.25		96-98	
7			25	**a** (2 mol %)	6	5	0.25		98-99	
8			25	**b** (2 mol %)	0.25	0.25	0.1		98-99	
9			25	**c** (2 mol %)	24	8	0.25		96-98	
10			25	**a** (10 mol %)	62	36	4d	99	99	2[b]
11			25	**b** (10 mol %)	24	16	15d	96	99	58[c]
12			60	**c** (10 mol %)	66	66	10d	27[c]	48[c]	47[c]
13			100	**b** (20 mol %)	6d	6d	6d	0	63	0
14			100	**c** (20 mol %)	6d	6d	6d	0	0	0
15			100	**a-c** (20 mol %)	24	24	24	0	0	0
	The following experiments were carried out with **5** and **6** only				**5**	**6**		**5**	**6**	
16			60	**a** (10 mol %)	16	16		>99:0[d]	99:0[d]	
17			60	**b** (10 mol %)	23	23		51:33[d]	40:54[d]	
18			60	**c** (10 mol %)	5d	5d		6:33[d]	9:37[d]	
19			100	**a** (10 mol %)	9d	9d		19:0[d]	55:0[d]	
20			80	**b** (20 mol %)	3d	3d		0:7[d]	0:21[d]	
21			100	**c** (20 mol %)	2d	2d		0:4[d]	0:5[d]	
22			25	**b** (10 mol %)	45	21		94	7	
23			80		8	8		>99	>99	
24			25	**c** (10 mol %)	21	45		7	92	
25			80		18	18		98	98	
26			60	**a** (10 mol %)	2d	2d		43	95	
27			25	**b** (10 mol %)	2d	2d		8[e]	12[e]	
28			25	**c** (10 mol %)	2d	2d		<5[e]	6[e]	
29			25	**b** (2 mol %)	-	0.5		>99	>99	
30			25	**c** (2 mol %)	-	1.5		>99	>99	

[a] NMR-scale reactions carried out in C_6D_6 or d_8-toluene; yields calculated from an internal TMSS standard. [b] Solid instantly precipitated out of solution. Only one turnover observed. [c] Solid slowly precipitated out of solution until catalysis stopped. [d] Cyclization:isomerization. [e] Substrate conversion >99%: the remaining products derive from isomerization and recombination reactions (Scheme 2).

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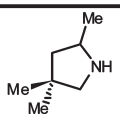
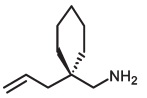
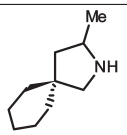
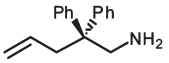
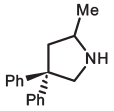
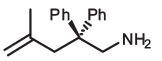
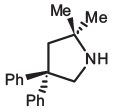
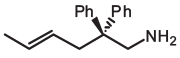
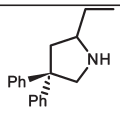
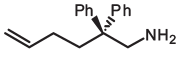
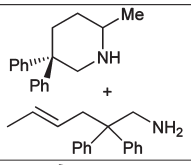
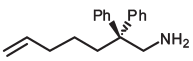
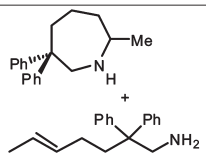
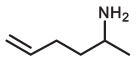
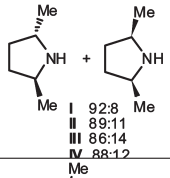
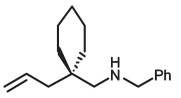
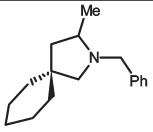
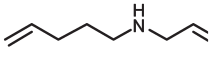
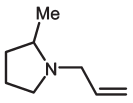
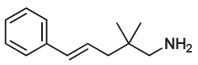
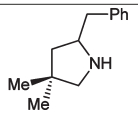
Table 2. Scope of Intramolecular Hydroamination with Magnesium, Calcium, and Strontium Pre-Catalysts 1−4

Entry	Substrate	Product	Catalyst (mol %)	Time / h	Temp / °C	NMR yield / %[a]
1			**2** (2 mol %)[b]	2	25	>95
2			**3** (2 mol %)	1.5	25	>99
3			**4** (2 mol %)	30	25	97
4			**1** (5 mol %)[b]	2	25	96
5			**2** (2 mol %)[b]	0.5	25	98
6			**3** (2 mol %)	0.2	25	97
7			**4** (2 mol %)	7	25	98
8			**1** (2 mol %)[b]	2	25	99
9			**2** (2 mol %)[b]	0.15	25	>99
10			**3** (2 mol %)	0.1	25	>99
11			**4** (2 mol %)	0.15	25	>99
12			**1** (5 mol %)[b]	0.5	25	86
13			**2** (5 mol %)[b]	0.5	25	92
14			**3** (5 mol %)	0.3	25	>99
15			**4** (5 mol %)	5	25	98
16			**1**,[b] **2**,[b] **3** or **4** (20 mol %)	3d	80	0
17			**1** (10 mol %)[b]	4	25	97:0[c]
18			**2** (10 mol %)[b]	4	25	83:16[c]
19			**3** (10 mol %)	4	25	66:15[c]
20			**4** (10 mol %)	48	25	28:62[c]
21			**1** (20 mol %)	3d	100	97:0[c]
22			**2** (20 mol %)[b]	1d	80	0:20[c]
23			**3** (20 mol %)	2d	80	5:25[c]
24			**4** (20 mol %)	4d	60	5:15[c]
25			**1** (20 mol %)[b]	2d	25	81
26			**2** (20 mol %)[b]	2d	25	>99
27			**3** (10 mol %)	18	25	95
28			**4** (20 mol %)	2d	25	90
29			**1** (10 mol %)	2d	80	95
30			**2** (10 mol %)	8	60	98
31			**3** (10 mol %)	3	25	>99
32			**4** (10 mol %)	18	25	78
33			**1** (10 mol %)	2d	60	96
34			**2** (10 mol %)[b]	2d	25	60[d]
35			**3** (10 mol %)	18	25	47[d]
36			**4** (10 mol %)	18	25	<5[d]
37			**2** (2 mol%)	0.15	25	>99

[a] NMR-scale reactions carried out in C_6D_6 or d_8-toluene; yields calculated from an internal TMSS standard. [b] Data reported previously in ref 17b but repeated here for comparison. [c] Cyclization:isomerization. [d] Substrate conversion >99%: the remaining products derive from isomerization and recombination reactions (Scheme 2).

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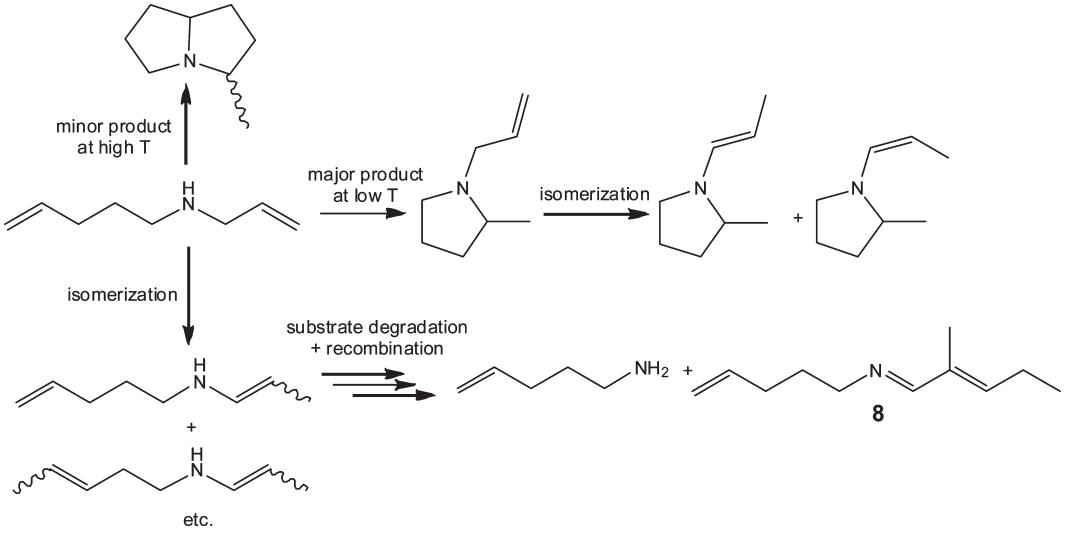
Scheme 2



substrates with secondary amine functionalities, in which activity toward catalysis was reversed (*vide infra*).

As we have previously reported for the hydroamination/cyclization of a range of substrates with **1** and **2**, the rate of catalysis was found to be heavily dependent on the substitution pattern of the aminoalkene.[17b] Substrates with geminal disubstitution in the β-position of the amine benefitted from a favorable Thorpe−Ingold effect and in general provided more facile cyclization at minimal catalyst loading and room temperature. As we have previously reported for precatalyst **5b**, no cyclization of 1-amino-4-pentene was observed with any of the homoleptic diamido or dialkyl precatalysts.[17a]

Substitution of the alkene moiety had a profound effect upon the reaction times. Both terminal, monomethyl and dimethyl substitution entirely prevented cyclization for the β-diketiminate derivatives **3** and **4**. While hydroamination/cyclization of a terminally monosubstituted substrate, 1-amino-2,2-dimethyl-5-methyl-4-pentene, could be achieved with calcium precatalysts **5,6b** under forcing conditions (100 °C), the high catalyst loadings (10−20 mol %) employed militate against a claim of true catalysis with conversions of <60%. Although steric factors might be involved, it is likely that substitution of the alkene moiety is energetically unfavorable during the insertion step, in which the transition state involves partial 2° and 3° alkyl character. This assertion was borne out by the observation that accelerated rates of ring closure were observed in all cases studied for 1-amino-2,2-dimethyl-5-phenyl-4-pentene, in which the terminal phenyl substituent stabilizes the incipient benzylic carbon center during the alkene insertion process.

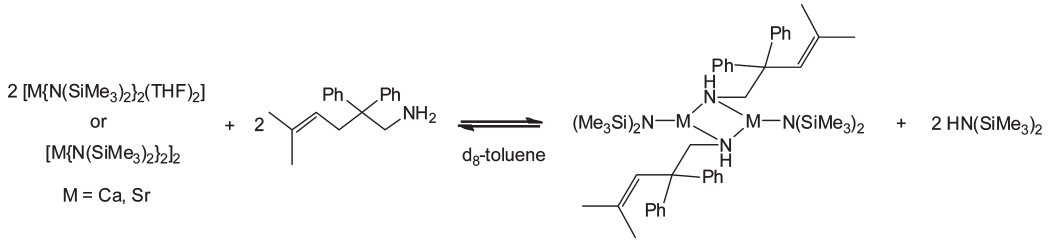
Ring formation followed Baldwin's guidelines, with formation of five-membered rings being significantly easier than that of six- or seven-membered heterocycles.[34] In all cases higher catalyst loadings, temperatures, and time periods were necessary to obtain piperidines compared to pyrrolidines. Although formation of a seven-membered ring could be observed with the magnesium species **5a** and **5b**, and to a lesser extent with the calcium and strontium species **3** and **4**, harsh reaction conditions and the formation of alkene-isomerized byproduct attenuate the viability of this reaction with these latter precatalysts. Only β-diketiminate-stabilized magnesium precatalyst **1** provided a near-quantitative route toward formation of hexahydroazepines (88%) after prolonged periods of time at 80 °C.

As was reported for similar catalyses performed with **2**, the cyclization of 1-amino-2,2-diphenyl-5-hexene with all the calcium and strontium precatalysts included in this study afforded, along with the cyclized piperidine, the alkene isomerization byproduct *trans*-1-amino-2,2-diphenyl-4-hexene, which was identified by ^{1}H NMR spectroscopy. The *trans* geometry was unambiguously assigned by comparison with an independently synthesized sample of *trans*-1-amino-2,2-diphenyl-4-hexene. It was apparent that the proportion of isomerized byproduct increased with the size of the metal center as well as with the reaction temperature. In the case of calcium precatalysts **5b** and **6b**, a small amount of cyclization of the isomerization product was observed at temperatures above 60 °C. As was the case with magnesium precatalyst **1**,[17b] no such isomerization was observed with the bis(amide) species **5a** and **6a**, which contain the smaller and, therefore, more sterically congested Mg^{2+} cation. Attempts to cyclize 1-amino-2,2-diphenyl-6-heptene with the calcium and strontium species **5,6b** and **5,6c** resulted in the formation of similarly small amounts of *trans*-1-amino-2,2-diphenyl-5-heptene as the only identifiable product. Further isomerization to 1-amino-2,2-diphenyl-4-heptene or cyclization of the isomerized chain could not be observed under the reaction conditions.

Alkene isomerization byproducts were also observed during the reaction of *N*-allyl-1-amino-4-pentene with all calcium and strontium precatalysts (Scheme 2). Analysis by ^{1}H NMR spectroscopy indicated a complex mixture of at least half a dozen different products, depending on the nature and concentration of the precatalyst and the reaction temperature. The monocyclized product *N*-allyl-2-methylpyrrolidine recently reported with **2** could, in all cases, be easily identified, as well as its isomers *N*-(*trans/cis*-propen-1-yl)-2-methylpyrrolidine and various isomers of the substrate. Scale-up of this reaction to 300 mg of substrate with 10 mol % **6c** at 80 °C over three days, and subsequent fractional distillation of the volatile products, allowed isolation of further components, among which small amounts of the pyrrolizidines previously reported for lanthanide-mediated tandem hydroamination/cyclization, 1-amino-4-pentene and (*E*)-*N*-((*E*)-2-methylpent-2-enylidene)pent-4-en-1-amine, **8**, which

dx.doi.org/10.1021/om101063m |*Organometallics* XXXX, XXX, 000–000

Scheme 3



was unambiguously identified by NMR spectroscopy as well as by ESI-MS, were observed. The proportion of **8**, easily identifiable in the ^{1}H NMR spectrum by a low-field singlet at δ 8.32 ppm arising from the imine N=C*H* and a corresponding ^{13}C NMR signal at δ 165.8 ppm, increased with reaction temperature and radius of the precatalyst metal center. It is, as yet, unclear what mechanism might be at work in the formation of this product. The magnesium compounds **5**−**7a** and **1** were the only precatalysts to cleanly afford the monocyclized *N*-allyl-2-methylpyrrolidine as the single reaction product.

Another secondary amine substrate, *N*-benzyl-(1-allylcyclohexyl)methylamine, was cleanly converted by all precatalysts into the expected cyclized product. A marked increase in reactivity was observed for the non-THF-coordinated β-diketiminate complex **3** compared to the solvated analogue **2**. The reaction utilizing **3** proceeded to completion within 3 h at room temperature, whereas the reaction that employed **4** required heating to 60 °C for 8 h. We interpret these results to indicate that aminoalkene access to the metal center is essential for the protonolysis of encumbered secondary amines. Contrary to observations for all primary amine substrates, the unsolvated bis(amide) precatalysts **5a**−**c** presented significantly faster catalysis than THF-solvated **6a**−**c** for both secondary amine substrates. An attempt to explain this inversion of reactivity will be provided through the kinetic studies described later in this paper.

In the presence of **3** and **4**, 2-amino-5-hexene, a substrate possessing two prochiral centers, underwent diastereoselective intramolecular hydroamination. The relative stoichiometry of the products was assigned by integrating two distinct ^{1}H NMR signals of the *trans* (3.15 ppm) versus the *cis* product (2.92 ppm), yielding the *trans*-pyrrolidine in diastereoisomeric excess of 72% and 76% for **3** and **4**, respectively. For comparison the calcium and magnesium analogues **2** and **1** provided diastereoisomeric excesses of 78% and 84%, respectively.[17b]

MECHANISTIC ANALYSIS

Catalyst Initiation. As we have highlighted previously, it should be appreciated that for reactions involving the use of silylamide precatalysts protolytic entry into the catalytic manifold may be reversible (Scheme 1).[17b] We have previously reported that the reaction of **2** with benzylamine, although mildly exothermic (ΔG°(298 K) = −2.7 kcal mol^{-1}), is reversible and forms a quantifiable dynamic equilibrium, whereas reaction of **2** with the potentially bidentate 2-methoxyethylamine resulted in quantitative formation of the corresponding calcium primary amide and demonstrated that, under certain conditions, the position of the amine/amide equilibrium may be perturbed significantly to one side.[28,35,37] During the current study a similar analysis performed upon stoichiometric reactions between the calcium and strontium complexes **5**,**6b** and **5**,**6c** (0.19 M) with two molar equivalents of 1-amino-2,2-diphenyl-5,5-dimethyl-4-pentene indicated the establishment of similar transamination equilibria for these homoleptic silylamide precatalysts (Scheme 3). Examination of the resultant ^{1}H NMR spectra indicated that, despite the presence of two silylamide substituents per alkaline earth center and, thus, two potential catalytic sites, never more than one bis(trimethylsilyl)amide underwent amine/amide exchange at a time. Although it is probable that the complexes resulting from this amine/amide exchange are dimeric in solution, by analogy with previously characterized heteroleptic calcium and magnesium primary amides obtained by protonolysis with a primary amine,[28,35−37] the exact nuclearity of each reaction is uncertain. The complexity of the equilibria and the consequent uncertainty over the nuclearity of the various alkaline earth-containing components lead us, therefore, to conclude that a quantitative discussion of this data would be imprudent. Inspection of the temperature-dependent data, however, revealed each reaction to be mildly endothermic [ΔG°(298 K) ca. 1.5 kcal mol^{-1}] irrespective of the reaction stoichiometry employed to deduce the equilibrium constants (see the Supporting Information for a detailed assessment of the collated data).

In a similar manner, addition of a stoichiometric quantity of *tert*-butylamine or diisopropylamine to a C_6D_6 solution of the β-diketiminato strontium amide **4** did not lead to any observable reaction, even after prolonged heating at 60 °C. The addition of benzylamine to **4** at room temperature in C_6D_6, however, resulted in nearly complete conversion (95%) to the heteroleptic strontium benzylamide complex **9**. Two further species could be characterized in solution, the strontium complex **4** (4%) and its benzylamine adduct **10** (1%), which persisted as a component of a dynamic equilibrium with complex **9**, as shown in Scheme 4. We have previously reported that the reaction between calcium complex **2** and one equivalent of benzylamine results in a similar equilibrium between **2** and a heteroleptic calcium benzylamide complex, which was isolated and characterized by X-ray crystallography as a dimeric species in the solid state.[35] Although no single crystals of the strontium benzylamide complex **9** suitable for X-ray diffraction analysis could be obtained, variable-temperature ^{1}H NMR studies upon a d_8-toluene solution of the reaction mixture again confirmed the existence of a dynamic equilibrium between **4**, **9**, and **10**. As was the case in our previous study, elevated temperatures favored both the starting materials and the benzylamine adduct **10**, observed by the distinctive signals of the β-diketiminato ligand backbone methine proton environments. At temperatures below 288 K, further fluxional processes prevented analysis of the data, but a spectrum recorded at 238 K revealed two broad highly shielded signals at −0.07 and −1.19 ppm tentatively attributed to the N*H*$_2$ resonance of

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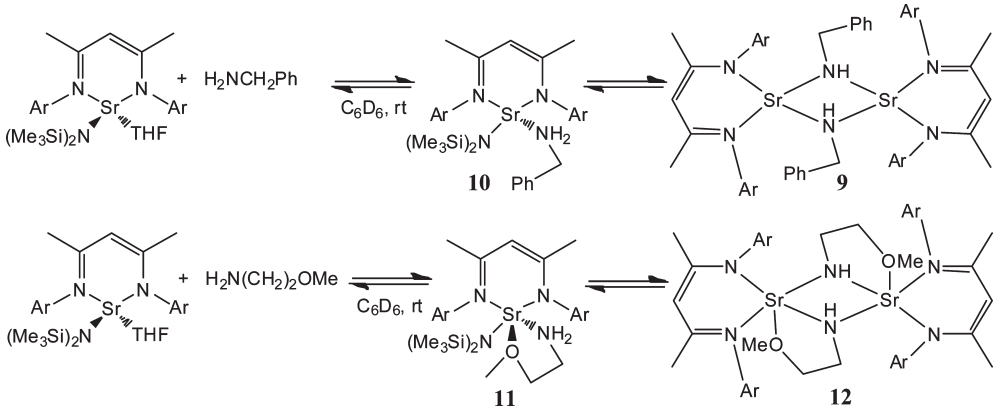
Scheme 4



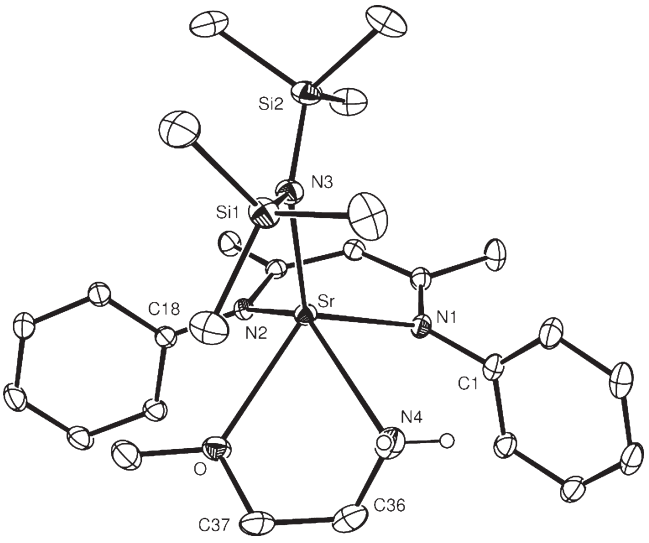


Figure 2. ORTEP representation (30% probability ellipsoids) of compound **11**. Hydrogen atoms except for those attached to the 2-methoxyethylamine nitrogen atom (N4) and the isopropyl groups have been removed for clarity.

benzylamine adduct **10** and the N*H* signal of benzylamide complex **9**, respectively.

In contrast to the previously reported behavior of the calcium species **2**,[28,36] a reaction at room temperature of **4** with the potentially bidentate 2-methoxyethylamine resulted in a 75:25 mixture of the amine adduct **11** (Scheme 4), displaying a broad NH_2 triplet resonance at −0.09 ppm in the ^{1}H NMR spectrum, and the amine/amide exchange product **12**, identifiable from the observation of a highly shielded N*H* resonance at −1.75 ppm. This observation contrasts markedly with the previously reported outcome of the analogous reaction of compound **2**, which results in the stoichiometric formation of the calcium primary amide species. The formation of a 2-methoxyethylamine adduct species as the major component of the strontium-centered equilibrium was confirmed through the ambient temperature crystallization of colorless crystals of compound **11** suitable for X-ray diffraction analysis. The results of this experiment are illustrated in Figure 2, and selected bond lengths and angles are listed in Table 3. The strontium center within compound **11** is five-coordinate and approaching square pyramidal (τ = 0.22).[38]

Table 3. Selected Bond Lengths and Angles for Compound 11

bond lengths (Å)		angles (deg)	
Sr−N(1)	2.5742(14)	N(1)−Sr−N(2)	73.77(4)
Sr−N(2)	2.5425(14)	N(1)−Sr−N(3)	123.62(5)
Sr−N(3)	2.4909(14)	N(2)−Sr−(N3)	121.24(5)
Sr−N(4)	2.7113(17)	N(1)−Sr−O	117.55(4)
Sr−O	2.6022(13)	N(2)−Sr−O	87.96(4)
N(4)−C(36)	1.465(3)	N(3)−Sr−O	117.00(5)
		N(4)−Sr−O	64.75(5)
		N(4)−C(36)−Sr	51.14(10)
		Sr−O−C(37)	118.36(12)

As a result, the Sr−N distances to both the β-diketiminate anion [Sr−N1, 2.5742(15); Sr−N2 2.5425(14) Å] and to the formally anionic hexamethyldisilazide ligand [2.4907(15) Å] are significantly longer than the corresponding bond lengths observed within the four-coordinate complex, compound **4** [Sr−N1, 2.554(2); Sr−N2, 2.514(2); Sr−N3, 2.446(2) Å].[29] The strontium−amine bond distance of 2.7113(18) Å is relatively short in comparison to the range of 2.743(4) to 2.853(4) Å described by Ruhlandt-Senge and co-workers for strontium−ethylenediamine interactions,[39] as well as the 2.702(13) to 2.83(2) Å range reported by Park et al. in a series of strontium diketonate complexes with polyamine donor ligands.[40]

Although an interpretation of these individual transamination equilibria should be treated with caution, it is apparent that the mild endo- or exothermicity of catalyst initiation is dependent upon the identity of the alkaline earth element utilized and characteristics of the resultant conjugate acid/base pair. Although not rate determining, it appears prudent to conclude that this factor must be viewed as an influential consideration during the course of any specific catalytic reaction employing an alkaline earth precatalyst derived from the conveniently employed hexamethyldisilazide anion.

Kinetic Studies. With these observations in mind, a kinetic study of the cyclization of (1-allylcyclohexyl)methylamine with the calcium and strontium precatalysts **2**, **3**, **4**, **5**,**6b**, and **5**,**6c** in C_6D_6 (determination of order in catalyst, 0.56 M substrate solutions) or d_8-toluene (Eyring and Arrhenius analyses, 0.80 M substrate solutions, 2 mol % catalyst loading) was conducted by ^{1}H NMR spectroscopy. The dialkyl species **7b**,**c** could not be reliably assessed due to the extremely rapid conversion of the

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chosen substrate, which generally resulted in more than 70% conversion even before start of the NMR monitoring. Magnesium precatalysts **5,6a** were also not included in this kinetic study due to their exceedingly low turnover frequency at such low catalyst loading. NMR solutions were prepared in the glovebox, immediately frozen to 193 K, and then thawed directly before transferring them to the NMR spectrometer. Conversion to the heterocyclic product was followed by integration of the substrate and product peaks relative to an internal tetrakis(trimethylsilyl)silane (TMSS) standard. Substrate consumption was monitored over three half-lives.

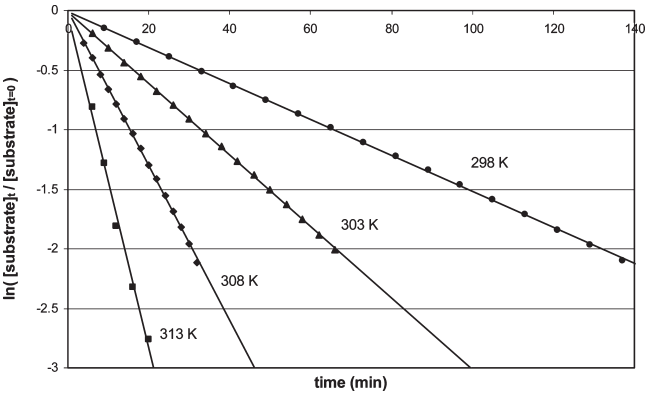

Figure 3. Example of kinetic analysis for the construction of Arrhenius and Eyring plots: plot of ln([aminoalkene]$_t$/[aminoalkene]$_{t=0}$) versus time (min) at four different temperatures for 0.8 M (1-allylcyclohexyl)-methanamine and 2 mol % of **4** in d_8-toluene. The slope of each linear set of data points corresponds to the reaction rate constant k (min^{-1}).

For each of the precatalysts, substrate cyclization was monitored at four to five different temperatures (e.g., Figure 3). Arrhenius analyses afforded activation energies (E_a) of 19.4(0.3) (**6b**), 20.2(1.3) (**5b**), 20.6(0.8) (**6c**), and 22.4(0.2) kcal·mol^{-1} (**5c**). Although marginal we feel that the quantitative increase implied by these data is significant and in accordance with the qualitative decrease of reaction rate observed for this series of bis(amide) precatalysts and of 15.6(0.5) (**2**), 19.6(0.8) (**3**), and 21.0(0.7) kcal.mol^{-1} (**4**) for the β-diketiminate-stabilized complexes (Figure 4). Surprisingly the activation energy for **3** was higher than for **2** despite the fact that **3** was found in all cases to provide the fastest turnover. Eyring analyses (Table 4) provided activation enthalpies ($\Delta H^{\ddagger}$) of a similar magnitude ($\Delta H^{\ddagger}$ = 18.8(0.3) (**6b**), 19.7(1.3) (**5b**), 19.9(0.8) (**6c**), and 21.7(0.2) kcal·mol^{-1} (**5c**) for the bis(amides); $\Delta H^{\ddagger}$ = 15.1(0.5) (**2**), 19.0(0.8) (**3**), and 20.4(0.7) kcal·mol^{-1} (**4**) for the β-diketiminato compounds) (Figure 5). Although the activation entropies ($\Delta S^{\ddagger}$) determined for the homoleptic precatalysts revealed some evidence of variation with metal identity and the presence of THF ($\Delta S^{\ddagger}$ = −9.9(1.1) (**6b**), −8.1(4.5) (**5b**), −7.8(2.3) (**6c**), and −4.3(0.5) cal·mol^{-1}·K^{-1} (**5c**)), the only significant differences could be discerned across the series β-diketiminato-stabilized complexes. In these cases, the THF-solvated calcium species **2** provided the most negative value of $\Delta S^{\ddagger}$, followed by the strontium complex **4** and the unsolvated calcium complex **3** ($\Delta S^{\ddagger}$ = −18.6(1.7) (**2**), −4.0(3.1) (**3**), and −6.9(2.2) cal·mol^{-1}·K^{-1} (**4**)). We propose that these values are a quantitative

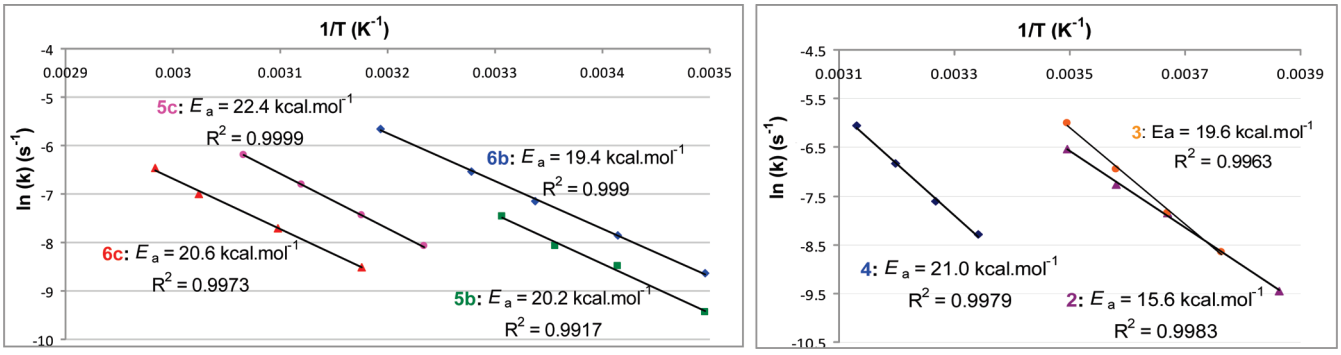

Figure 4. Left: Arrhenius plots of ln(k) (k = reaction rate constant, s^{-1}) versus $1/T$ (T = temperature, K^{-1}) for calcium complexes **5,6b** and strontium complexes **5,6c**. Right: Arrhenius plot for β-diketiminato-stabilized complexes **2**−**4**. Activation energies (E_a) were calculated from the slope (E_a/R) of each linear set of data points. Data were collected at [(1-allylcyclohexyl)methanamine] = 0.8 M and 2 mol % catalyst loading in d_8-toluene.

Table 4. Comparison of Activation Parameters for the Hydroamination/Cyclization of 1-(Allylcyclohexyl)methylamine with 2 mol % of the Homoleptic and Heteroleptic Calcium and Strontium Precatalysts

precatalyst	$\Delta H^{\ddagger}$ (kcal·mol^{-1})	$\Delta S^{\ddagger}$ (cal·mol^{-1}·K^{-1})	$\Delta G^{\ddagger}$(298 K) (kcal·mol^{-1})
5b	−8.1(4.5)	19.7(1.3)	22.1
5c	21.7(0.2)	−4.3(0.5)	23.0
6b	18.8(0.3)	−9.9(1.1)	21.7
6c	19.9(0.8)	−7.8(2.3)	22.3
2	15.1(0.5)	−18.6(1.7)	20.7
3	19.0(0.8)	−4.0(3.1)	20.2
4	20.4(0.7)	−6.9(2.2)	22.5
$Cp'_2LaCH(SiMe_3)_2$[a]	12.7(1.4)	−27.0(4.6)	20.7
$Me_2SiCp''_2SmCH(SiMe_3)_2$[b]	17.7(2.1)	−24.7(5.0)	25.1

[a] Substrate = 1-amino-2,2-dimethyl-4-pentene, 2.8 mol % catalyst.[2d] [b] Substrate = 1-amino-2,2-dimethyl-4-hexene, 5 mol % catalyst.[2t]

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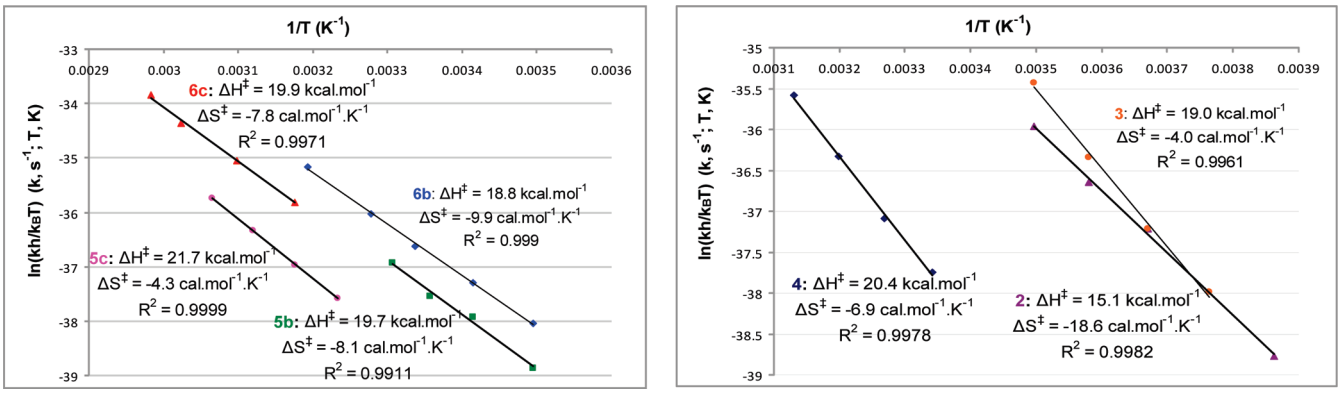

Figure 5. Left: Eyring plot of $\ln(kh/k_BT)$ (k = reaction rate constant, s^{-1}; T = temperature, K) versus $1/T$ (K^{-1}) for calcium complexes **5**,**6b** and strontium complexes **5**,**6c**. Right: β-Diketiminato-stabilized complexes **2**−**4**. Activation enthalpies $\Delta H^{\ddagger}$ were calculated from the slope ($\Delta H^{\ddagger}/R$; R = 1.9858775 cal·mol^{-1}·K^{-1}) of each linear set of data points, and $\Delta S^{\ddagger}$ from the intercept ($\Delta S^{\ddagger}/R$). Data were collected at [(1-allylcyclohexyl)methanamine] = 0.8 M and 2 mol % catalyst loading in d_8-toluene.

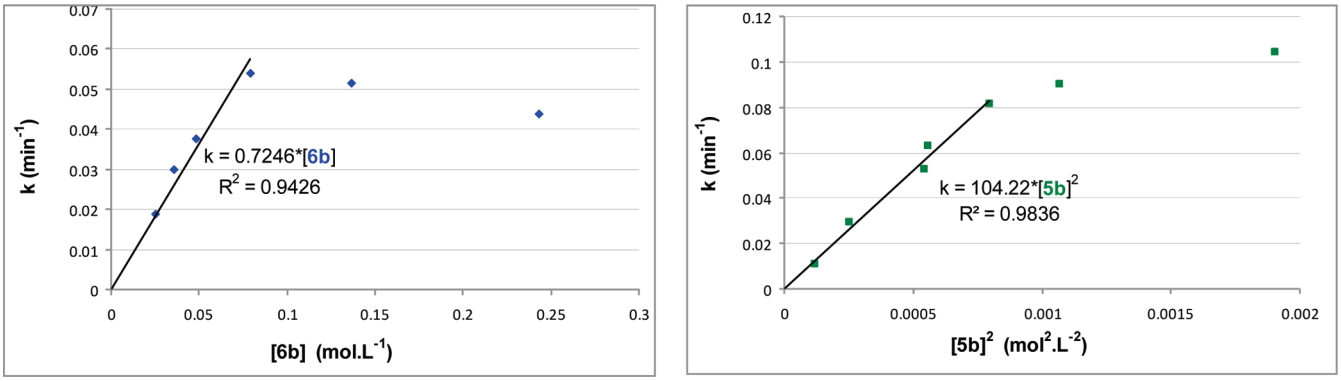

Figure 6. Left: Linear plot of k (min^{-1}) versus [**6b**] (mol·L^{-1}) obtained by varying [**6b**] at constant concentration of (1-allylcyclohexyl)methanamine (0.56 M). Data were collected at 293 K in C_6D_6. Right: Linear plot of k (min^{-1}) versus [**5b**]^2 (mol^2·L^{-2}) obtained by varying [**5b**] at constant concentration of substrate (0.56 M). Data were collected at 298 K in C_6D_6. Data points diverging from the linear plot at high catalyst loading are due to catalyst aggregation in solution.

reflection of the relative organization of the four-membered rate-determining alkene insertion transition states when assembled about the group 2 metal centers, with the smaller calcium cation and the THF-containing species providing a more constrained configuration of the substrate and catalytic center. In the case of the calcium complex **2**, the smaller metal center, the steric demands of the β-diketiminate ligand, and the presence of the, at least initially, adducted molecule of THF appear to have a summative effect in enforcing the most constrained transition state inferred from the more negative $\Delta S^{\ddagger}$ value. It is interesting to note that access to the strontium center of **4** seems to be more hindered, despite the larger size of the metal, than in the case of the unsolvated calcium complex **3**. The calculated $\Delta G^{\ddagger}$ values (Table 4) reflect the reactivity series deduced from the qualitative experimental findings (homoleptic amides, $\Delta G^{\ddagger}$(298 K) = 21.7 (**6b**), 22.1 (**5b**), 22.3 (**6c**), and 23.0 kcal·mol^{-1} (**5c**); β-diketiminato species, $\Delta G^{\ddagger}$(298 K) = 20.7 (**2**), 20.2 (**3**), and 22.4 kcal·mol^{-1} (**4**) at 298 K). A previous kinetic analysis of the hydroamination/cyclization of 1-amino-4-pentene with the lanthanide precatalyst $(Me_5C_5)_2LaCH(SiMe_3)_2$ by Marks and co-workers provided $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of 12.7(1.4) kcal·mol^{-1} and −27.0(4.6) cal·mol^{-1}·K^{-1}, respectively.[2d] Despite a significantly lower activation enthalpy than those reported herein, the highly negative activation entropy deduced for the lanthanum-centered species results in a free energy of activation of 20.7 kcal·mol^{-1}, which is comparable to those values obtained for **2** and **3** (Table 4). The case of the THF-free β-diketiminate-stabilized calcium precatalyst **3** is of particular note, as the kinetic studies provide a significantly higher activation enthalpy for **3** than for **2**. This apparent disadvantage is compensated, however, by a significantly less negative $\Delta S^{\ddagger}$ value and a consequentially lower $\Delta G^{\ddagger}$(298 K) value. This latter observation agrees with the reactivity series deduced from the qualitative findings outlined above and mirrors the conclusions in our recently published kinetic study of intermolecular hydroamination with **5b** and **5c**,[17c] where the higher activation enthalpy deduced for the strontium-based catalysis was again counteracted by a tangible entropic advantage.

It is apparent that the THF-free homoleptic precatalysts **5a**−**c** are considerably less active than their THF-solvated counterparts. In contrast, the unsolvated β-diketiminato calcium complex **3** provided higher turnover frequencies than its THF-coordinated analogue, compound **2**. To further inform our understanding of this phenomenon, kinetic studies were carried out at constant substrate concentration (0.56 M) and temperature for varying catalyst loading to determine the order in [catalyst] of each reaction. For the β-diketiminato derivatives and the THF-solvated homoleptic species **6b**,**c**, the reaction was first-order in [catalyst] up to ca. 0.1 M (activation parameters

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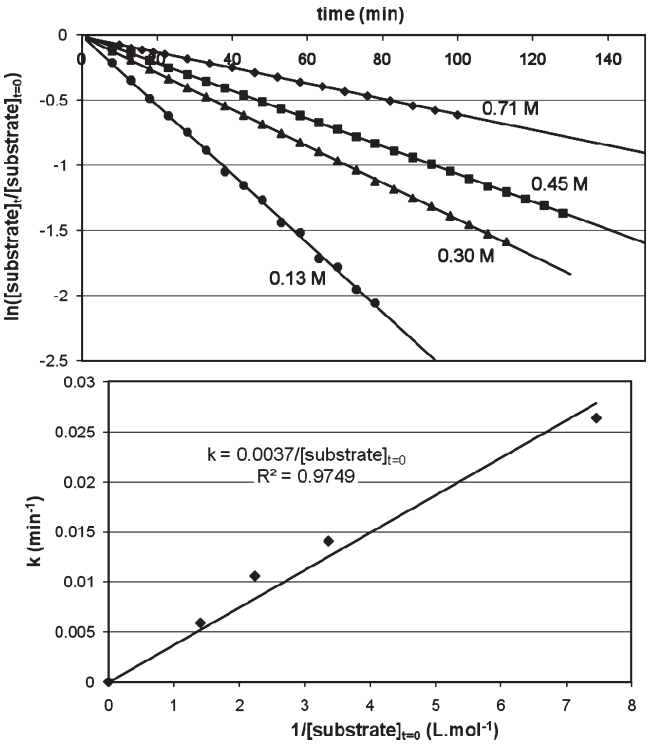
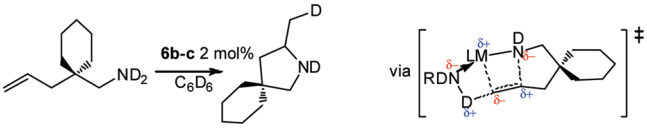


Figure 7. Top: Inhibition kinetics: plot of $\ln([\text{aminoalkene}]_t/[\text{aminoalkene}]_{t=0})$ versus time (min) at four different initial substrate concentrations at 0.02 M of **6b** in C_6D_6 at 298 K. Bottom: Plot of k (min^{-1}) versus the inverse of the initial substrate concentration ($L \cdot mol^{-1}$).

were measured within this first-order regime). In contrast, a second-order dependence upon [catalyst] was deduced for complexes **5b**,**c** (Figure 6). This result is consistent with the reduction in activity observed for the THF-free precatalysts at equal catalyst loading and most likely indicates a rate-determining process involving two catalyst molecules. This latter observation is mitigated by the fact that these species commonly exist as dimers in noncoordinating solvents.[35−37] At high catalyst concentrations (typically >0.05 M) a deviation from the linear plots was observed in most cases, followed by a significant drop in activity for concentrations above 0.1 M. We suggest that this latter phenomenon may be due to increasing catalyst aggregation in solution. In the case of substrates bearing a secondary amine moiety, the steric hindrance provided by the second substituent may prevent dimerization of the precatalysts and thus restore the otherwise expected order of reactivity, leading to higher turnover rates for the unsolvated species. Hydroamination with β-diketiminate precatalysts **3** and **4** displayed a first-order dependence in [catalyst], as had previously been determined for **1** and **2**.[17b]

In line with our previous findings the rate of cyclization of 1-(allylcyclohexyl)methylamine in the presence of homoleptic calcium precatalyst **6b** at constant concentration (0.02 M in C_6D_6) was dependent on the initial aminoalkene concentration, with reaction rate decreasing with increasing substrate concentration (Figure 7). As had previously been demonstrated in the case of lanthanide-mediated hydroamination/cyclization[2d] and by the isolation of strontium amide amine adduct **11** reported earlier in this study, a number of substrate and/or product molecules may bind to the metal center as neutral donor ligands and thus block free coordination sites required for the alkene

Scheme 5



insertion step. A near-linear dependence between the pseudo-first-order rate constant k and the inverse of the initial substrate concentration could be derived from these data sets.

Previous deuterium-labeling experiments with (1-allylcyclohexyl)methanamine-d_2 (>95% deuteration) demonstrated that deuteration of the cyclized product was limited to the exocyclic methyl substituent and were interpreted as providing evidence for a short-lived alkyl intermediate in the catalytic cycle (Scheme 5).[17b] In order to quantify the dependence of the kinetic isotope effect on the nature of the metal center, diprotio (RNH_2) and dideuterio (RND_2) substrate cyclization with 2 mol % of calcium and strontium bis(amide) precatalysts **6b** and **6c** (0.56 M of (1-allylcyclohexyl)methanamine in C_6D_6) was monitored by ^{1}H NMR spectroscopy at 298 and 318 K, respectively (Figure 8). The reactions exhibited pseudo-first-order kinetics in [substrate] and rate constants of 2.56 h^{-1} (**6b**, RNH_2), 0.564 h^{-1} (**6b**, RND_2), 2.46 h^{-1} (**6c**, RNH_2), and 0.72 h^{-1} (**6b**, RND_2), yielding kinetic isotope effects (KIEs) of k_H/k_D = 4.5 (298 K) and 3.4 (318 K) for the use of precatalysts **6b** and **6c** respectively. Although such large KIEs might be naively interpreted to militate against a deduction of rate-determining insertion within the course of catalytic turnover, the current observations have precedent by kinetic analyses of analogous organolanthanide-based cyclizations.[2d] In these latter cases, KIEs of a similar magnitude were interpreted as a reflection of the direct involvement of additional amine within the coordination sphere of the lanthanide during the rate-determining insertion step. Taking these observations into account, it appears reasonable to suggest that a similar rationale may be applied to the group 2-based catalyses reported in this study. This model is further supported by very recent studies reported by Sadow and co-workers in which an isolable tris(oxazolinyl)phenylborate-supported magnesium amidoalkene was shown to not undergo cyclization until the addition of further quantities of aminoalkene substrate.[7h] In this case a two-substrate, six-center transition state involving concerted C−N bond formation and N−H bond cleavage was proposed as the turnover-limiting step of the catalytic cycle. Our data show that a similar rationale, which views the augmented polarization of the appended C═C unit as a consequence of both the local influence of the polar M−N bond and the simultaneous formation of an initial intramolecular N−H···C═C interaction within the coordination sphere of the group 2 metal center, may be extended to the heavier members of the group 2 series of elements (inset, Scheme 5). Within this scenario rate-determining insertion may be viewed as a compromise of both substrate polarization and substrate access to the metal center. Although neither factor can be demarcated on the basis of the data presented herein, it is noteworthy that both effects may be viewed as an intrinsic property (viz., the electropositivity and ionic radius) of the individual M^{2+} cation under observation.

Our previous, but more limited, kinetic observations led us to propose a mechanism involving both product and substrate inhibition. We also suggested that for the rate-determining insertion to occur the catalyst must go via an amidoalkene intermediate

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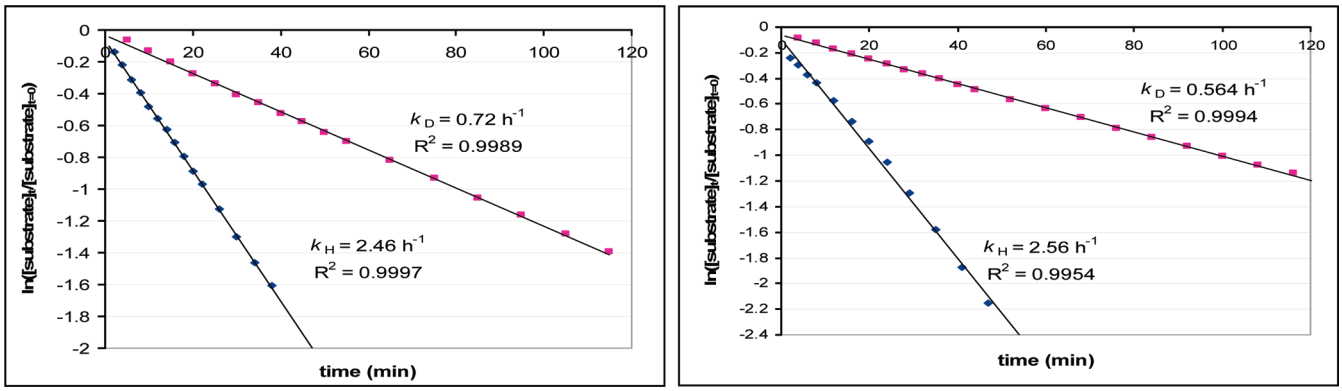


Figure 8. Left: Plot of $\ln([\text{substrate}]_t/[\text{substrate}]_{t=0})$ versus time (min) for the cyclization of (1-allylcyclohexyl)methanamine (RNH_2) and (1-allylcyclohexyl)methanamine-d_2 (RND_2) with calcium precatalyst **6b**. Data were collected at 298 K, [substrate] = 0.8 M and 2 mol % catalyst loading in C_6D_6. Right: The same for strontium precatalyst **6c**. The slope of each linear set of data points corresponds to the reaction rate constant, k (h^{-1}).

bare of amine adducts. The resulting rate law (eq 1), derived using steady-state theory reminiscent of enzyme kinetics, reflected the observed first-order dependence of the reaction in [catalyst] as well as substrate and product inhibition but failed to reproduce the observed pseudo-first-order decline in [substrate] during the course of the reaction or to take into account the effect of nonprotic adducts such as THF.

$$\text{rate} = \frac{k_d k_3 [\text{cat}]_0}{k_a [\text{sub}]_0 + k_3} \quad (1)$$

where $[\text{cat}]_0$ = total catalyst concentration, $[\text{sub}]_0$ = initial substrate concentration, k_a and k_d = respectively rate of association and dissociation of neutral substrate or product, and k_3 = rate of insertion.

The observed high KIEs are suggestive of a concerted insertion/protonolysis mechanism involving an adducted molecule of amine and the presence of THF/amine adduct exchange. On this basis a modified model for the reaction mechanism may be envisaged (Scheme 6), which, for simplification, is based upon irreversible catalyst initiation.

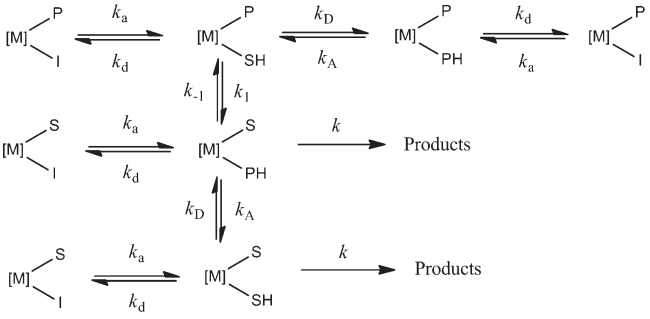
By assuming that the neutral substrate and product have equal binding constants ($k_d \approx k_a$) and that the rate of the amine/amide exchange is equal in both directions ($k_{-1} \approx k_1$), it is possible to derive a relatively simple rate law (eq 2) that reflects all the aspects of the reaction described in this study and that is clearly reminiscent of the Michaelis−Menten equation commonly used in enzyme inhibition kinetics (see the Supporting Information for a complete derivation of eq 2).[41]

$$\text{rate} = \frac{k[\text{cat}]_0[\text{sub}]_t}{[\text{sub}]_0 + K_I[I]} \quad (2)$$

where $K_1 = k_d/k_a$.

Under this regime, the reaction rate increases with increasing catalyst concentration and decreases with increasing initial substrate and THF concentration. From this equation it is also possible to take into account reversible catalyst initiation through addition of a third term in the denominator related to the initial catalyst concentration and the amine/amide exchange constant between the silylamide co-ligand and the substrate or product. Although eq 2 is appropriate for systems based upon the alkaline earth β-diketiminate and THF-solvated bis(amide) precatalysts used in this study, it accounts neither for the observed second-order dependence in [catalyst] observed for the THF-free

Scheme 6. Proposed Reaction Steps for Group 2-Mediated Intramolecular Hydroamination Catalysis[a]



[a] Model based upon fast irreversible catalyst initiation. I = non-protic inhibitor, e.g., THF, SH = substrate, PH = product.

bis(amide) species **5b** and **5c** nor for recent observations made by Hultzsch and co-workers on the catalytic intramolecular hydroamination activity of a series of magnesium phenoxyamine complexes, in which the cyclization rate of 1-amino-2,2-diphenyl-4-pentene was found to display either a zero-order or second-order decline in [substrate].[7f] Although no explanation was given for these latter observations, the results highlight the complexity of group 2-catalyzed intramolecular hydroamination reactions and the limitations of the above-given mechanism and should warn against overgeneralization.

CONCLUSION

A variety of homoleptic and heteroleptic group 2 amide and alkyl compounds have been assessed as precatalysts for the intramolecular hydroamination of aminoalkenes. In comparison to previous lanthanide-based catalyses, kinetic and mechanistic studies have indicated that the reactivity observed displays a rather more complex thermodynamic (enthalpic and entropic) and kinetic (steric) dependence upon the identity and intrinsic characteristics of the M^{2+} cation under study. These studies indicate that the precise course of each catalytic reaction may also be influenced by judicious selection of both the reactive and supporting ligand environments. In this latter regard, the labile nature of these elements will continue to provide challenges if issues of enantioselectivity and substrate compatibility are to be addressed, while the relative dearth of suitable amide and,

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particularly, alkyl ligands to further develop the reactivity of the heavier members of the series must also be addressed. We, and others, will continue to elaborate this emerging reactivity and to address these ongoing challenges.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental and instrument details.This material is available free of charge via the Internet at http://pubs.acs.org.

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