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Heavier Alkaline Earth Catalysts for the Intermolecular Hydroamination of Vinylarenes, Dienes, and Alkynes

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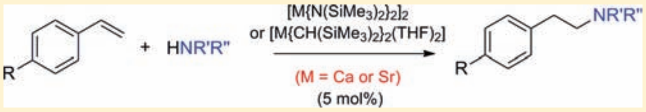
Supporting Information



ABSTRACT: The heavier group 2 complexes $[M\{N(SiMe_3)_2\}_2]_2$ (**1**, M = Ca; **2**, M = Sr) and $[M\{CH(SiMe_3)_2\}_2(THF)_2]$ (**3**, M = Ca; **4**, M = Sr) are shown to be effective precatalysts for the intermolecular hydroamination of vinyl arenes and dienes under mild conditions. Initial studies revealed that the amide precatalysts, **1** and **2**, while compromised in terms of absolute activity by a tendency toward transaminative behavior, offer greater stability toward polymerization/oligomerization side reactions. In every case the strontium species, **2** and **4**, were found to outperform their calcium congeners. Reactions of piperidine with *para*-substituted styrenes are indicative of rate-determining alkene insertion in the catalytic cycle while the ease of addition of secondary cyclic amines was found to be dependent on ring size and reasoned to be a consequence of varying amine nucleophilicity. Hydroamination of conjugated dienes yielded isomeric products via η^3-allyl intermediates and their relative distributions were explained through stereoelectronic considerations. The ability to carry out the hydroamination of internal alkynes was found to be dramatically dependent upon the identity of the alkyne substituents while reactions employing terminal alkynes resulted in the precipitation of insoluble and unreactive group 2 acetylides. The rate law for styrene hydroamination with piperidine catalyzed by $[Sr\{N(SiMe_3)_2\}_2]_2$ was deduced to be first order in [amine] and [alkene] and second order in [catalyst], while large kinetic isotope effects and group 2 element-dependent $\Delta S^\ddagger$ values implicated the formation of an amine-assisted rate-determining alkene insertion transition state in which there is a considerable entropic advantage associated with use of the larger strontium center.

■ INTRODUCTION

The construction of amines through a metal-catalyzed hydroamination of C−C multiple (double or triple) bonds is gaining prominence as a powerful atom-efficient and waste-minimized technique in organic synthesis. While a great number of catalysts from the s-,[2,3,30] p-,[31] d-,[4−17] and f-blocks[18−29] of the periodic table have now been described for the cyclization of aminoalkenes and aminoalkynes via intramolecular hydroamination, the more entropically demanding intermolecular variant of this reaction, even for more activated organic substrates, remains a significant challenge. Several approaches have, however, been developed in which the hydroamination cycle is initiated either through alkene/alkyne or amine activation. The first of these approaches may be achieved using late transition metals (e.g., palladium,[32] platinum,[33] rhodium[34]) making the alkene or alkyne more susceptible to intramolecular attack by amine nucleophiles resulting in the formation of 2-aminoalkyl complexes while N−H activation may occur through oxidative addition, metal−ligand cooperative effects,[35] or, more commonly, deprotonation and formation of a reactive metal amide intermediate. Lanthanide-based systems react in this latter manner, generating highly nucleophilic amido species whereupon alkene insertion occurs via a polarized four-membered transition state. Initial reports by Marks and co-workers revealed that vinylarene and diene hydroamination reactions may proceed in good yields and with excellent anti-Markovnikov regioselectivity.[36] In a similar manner, a recent publication by Hultzsch and co-workers includes stereoselective additions of simple amines to even unactivated alkenes utilizing chiral rare earth-metal catalysts.[37]

Our own studies have centered upon the use of complexes of the heavier alkaline earth elements as catalysts which are more typically the preserve of less abundant and less benign transition and rare earth metals.[38] We have previously reported a preliminary study of group 2-based intermolecular hydroamination catalysis of vinylarenes with a variety of primary, secondary and *N*-heterocyclic amines (Scheme 1; R′ = Ar).[39] The reactions were successfully carried out employing the homoleptic calcium and strontium amides $[M\{N(SiMe_3)_2\}_2]_2$ (**1**, M = Ca; **2**, M = Sr) and typically provided high (>75%) yields of the amine products under mild thermal (60 °C) conditions. In line with the expectation provided by model density functional theory (DFT) studies, stabilization of the incipient benzylic charge induced by formation of the rate-determining four-membered alkene insertion transition state (inset Scheme 1) provided exclusive access to the anti-Markovnikov product, while analogous reactions performed with magnesium and barium silylamides were found to be very slow and rationalized to be a consequence of the reduced

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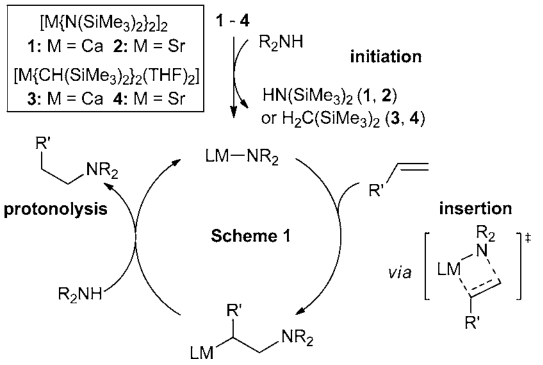
Scheme 1. Intermolecular Hydroamination Catalyzed by Heavier Alkaline Earth Amides (1, 2) and Alkyls (3, 4)



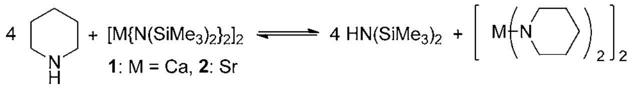
polarizing influence of the less polar Mg—N bond and the highly diffuse and thus weakly polarizing barium atom respectively. On the basis of these data, we suggested that the relative barrier heights for alkene insertion into M—N bonds may be viewed as a result of a compromise between the polarity of 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.[39] Initial 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. In this submission we provide a comprehensive examination of this reactivity and show that, while readily extended to conjugated dienes, application of this chemistry to the hydroamination of internal alkynes is significantly dependent upon the C≡C triple bond substituents.[40]

■ RESULTS AND DISCUSSION

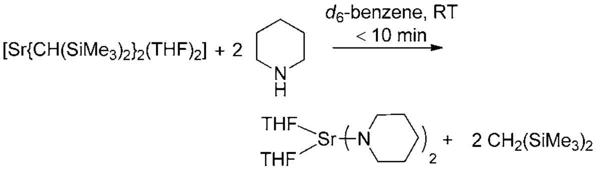
Precatalyst Selection and Catalyst Initiation. Entry into the catalytic manifold (Scheme 1) requires deprotonation of an amine substrate and formation of an intermediate group 2 amide prior to insertion at the unsaturated bond. Although this process is not likely to be rate determining, the total number of active group 2 centers available for catalytic turnover will, thus, be limited by the ability of the precatalyst to effect deprotonation. The mild endo- or exothermicity of catalyst initiation is dependent upon the identity of the alkaline earth element utilized and characteristic of the resultant conjugate acid/base pair. These issues will be particularly significant when the amine substrate is of comparable pK_a to the conjugate acid liberated by protonolysis of the precatalyst ligand. It has been shown previously, for example, that reactions of benzylamine with the *β*-diketiminato calcium and strontium amides [HC{(Me)CN(2,6-^{i}Pr$_2$C$_6$H$_3$)}$_2$M{N(SiMe$_3$)$_2$}(THF)] (M = Ca[41] or Sr[30o]) are incomplete and can be characterized as reversible equilibria. In the current work it was found that a comparable equilibrium is established for the reaction of piperidine, one of the key secondary amines in this work (*vide infra*), with the calcium or strontium bis(trimethylsilyl)amides, compounds **1** and **2** (Scheme 2) in d_8-toluene.

In both cases only a small quantity of HN(SiMe$_3$)$_2$ (δ_{1H} = 0.08 ppm) was detected, and it was evident that for both metals the equilibrium described in Scheme 2 lies well toward the starting materials. While the spectrum of the calcium-based reaction mixture was consistent with the presence of two bis(trimethylsilyl)amide species and two sets of piperidine resonances were apparent at room temperature, the exchange of piperidine and bis(trimethylsilyl)amide ligands at the strontium center was so rapid that at room temperature only averaged signals were observed (Figure 1). However, upon cooling of the latter reaction mixture to −69 °C, two separate sets of signals were resolved which coalesced at −24 °C. In contrast, coalescence was only observed for the calcium system at 101 °C while the maximum peak to peak separation was observed at 25 °C. Variable-temperature NMR experiments allowed values to be calculated for the Gibbs free energy, Δ$G^{‡}$, of these exchange processes of 73 and 48 kJ·mol^{-1} for **1** and **2**, respectively. These values are consistent with more rapid ligand exchange at the strontium center and indicate that under typical catalytic conditions the Sr-amido and the amine moieties are likely to undergo interconversion at rates far in excess of the catalytic turnover frequencies (*vide infra*). Similarly fast external amine-amido exchange has previously been found for exchange of benzylamine with [HC{(Me)CN(2,6-^{i}Pr$_2$C$_6$H$_3$)}$_2$Ca{N(SiMe$_3$)$_2$}(THF)],[41] while Ruspic et al. observed intramolecular site exchange between amine and amide ligands in the related [HC{(Me)CN(2,6-^{i}Pr$_2$C$_6$H$_3$)}$_2$Ca(NH$_2$)(NH$_3$)$_2$] which yielded a Gibbs free energy, Δ$G^{‡}$, of 47.3 kJ·mol^{-1}.[42] Similar behavior has also been reported for lanthanide complexes such as [Cp*$_2$La(NHMe)(NH$_2$Me)], in which two separated amine/amide species could be discriminated at 100 °C to provide Δ$G^{‡}$ = 50.2 kJ·mol^{-1}.[36b]

Scheme 2. Reversible Transamination in the Reactions of Compounds 1 and 2 with Piperidine



In our initial communication we reported that hydroamination of styrene derivatives to yield 2-(arylethyl)amines was achieved through the use of calcium and strontium bis(trimethylsilyl)amides, **1** and **2**.[39] In every case studied, the strontium-based system outperformed its lighter congener and it was possible to effectively halve the reaction time for a particular vinylarene/amine combination. In a similar manner, it has been observed that calcium-based intramolecular hydroamination catalysis is generally superior to magnesium-based processes and we have reasoned that this behavior is a consequence of the large variation in the charge density of the different M^{2+} ions, as well as a tendency to undergo Schlenk-like ligand redistribution and/or aggregation equilibria.[30d,o] In contrast to this transaminative behavior, it was anticipated that the less acidic conjugate acid, H$_2$C(SiMe$_3$)$_2$, would be liberated during catalyst initiation with the heavier alkaline earth alkyl complexes [M{CH(SiMe$_3$)$_2$}$_2$(THF)$_2$] (**3**, M = Ca; **4**, M = Sr).[43] Consistent with this expectation, a stoichiometric reaction between strontium dialkyl complex **4** and piperidine in d_6-benzene, resulted in immediate and irreversible formation of CH$_2$(SiMe$_3$)$_2$ and [Sr{N(CH$_2$CH$_2$)$_2$CH$_2$}$_2$(THF)$_2$]$_n$ (eq 1).



(1)

To assess the implications of the differing catalyst initiation behavior of the amide (**1**, **2**) and alkyl (**3**, **4**) precatalysts, the

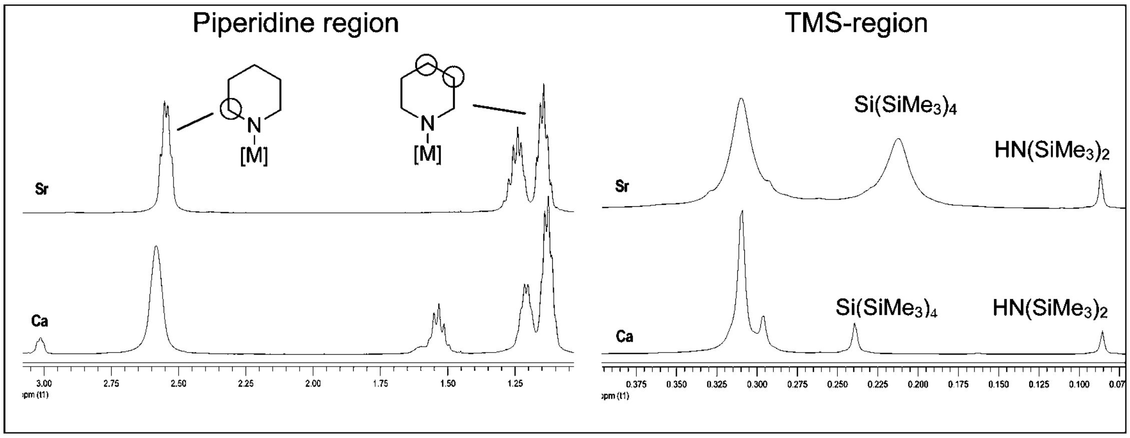
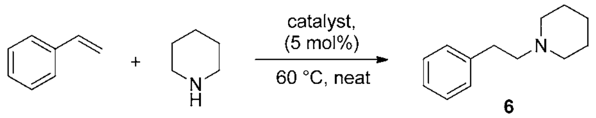


Figure 1. ^{1}H NMR spectra of the reactions of **1** (bottom) and **2** (top) with piperidine at room temperature in d_8-toluene.

catalytic addition of piperidine to styrene was investigated in the presence of several different alkaline earth complexes bearing either amide or alkyl coligands. The results of a series of reactions utilizing the bis(trimethylsilyl)amide compounds **1** and **2** along with, for purposes of comparison, their barium analogue, **5**, and a commercially available sample of Mg(^{n}Bu)$_2$ are summarized in Table 1.

Table 1. Comparison of the Alkaline Earth-Mediated Addition of Piperidine to Styrene[a]



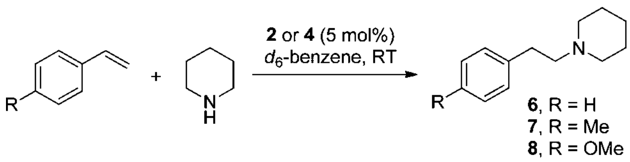
entry	catalyst	time[b]	TOF/h
1	**1**, $[Ca\{N(SiMe_3)_2\}_2]_2$	13 h	1.5
2	**2**, $[Sr\{N(SiMe_3)_2\}_2]_2$	5 h	4.0
3	**5**, $[Ba\{N(SiMe_3)_2\}_2]_2$	10 days	0.08
4	$Mg(Bu)_2$[c]	14 days	0.06

[a] Reaction conditions: 5 mol % catalyst, styrene:piperidine = 1:1, neat, 60 °C. [b] For full conversion. [c] 1 M solution of mixture of *n*-butyl and *sec*-butyl isomers in pentane.

The results of Table 1 were in broad agreement with the findings of the earlier computational studies and experimental results.[39] Both amide precatalysts **1** and **2** provided effective catalysis with full conversions obtained in less than 13 h for **1** and 5 h for **2** at 60 °C with the strontium-based catalysis proving most effective. In contrast, reaction times of several days were necessary when the barium and magnesium species were applied as catalyst despite the use of a potentially more reactive magnesium alkyl precatalyst.

The reactivity of the dialkylstrontium species, **4**, for the hydroamination of various styrene derivatives was next examined. The results of this study are summarized in Table 2. Even at room temperature and under dilute reaction conditions, very high reactivity was observed. Entries 3 and 4 show that even more electron-rich styrene derivatives are converted very efficiently, while comparison to the performance of the amide precatalyst **2** (entries 1 and 2) under the same reaction conditions shows that the metal dialkyl species is substantially superior. The hydroamination of unsubstituted styrene with piperidine mediated by dialkylstrontium **4** was observed to be very fast, yielding a TOF as high as 120 h^{-1}, whereas reaction under the same conditions catalyzed by **2** was almost 3 orders of magnitude slower. Although the yields shown in Table 2 are very high, styrene oligomerization as a side reaction was observed to occur to a greater extent for **4** than for the amide precatalyst **2**.

Table 2. Hydroamination of Styrene Derivatives Catalyzed by 2 and 4[a]



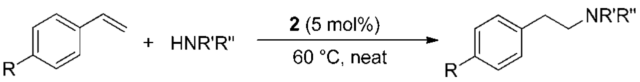
entry	R	cat.	time	yield/ %	TOF/h^{-1}[d]
1	H	**2**	72 h	92[b]	0.28
2	H	**4**	10 min	70[c]	120.0
3	Me	**4**	35 min	95[b]	40.0
4	OMe	**4**	90 min	90[b]	13.3

[a] Reaction conditions: 5 mol % of catalyst, styrene:piperidine = 1:1, [styrene] = 0.3 M, RT. $[Sr\{N(SiMe_3)_2\}_2]_2$ **2**, $[Sr\{CH(SiMe_3)_2\}_2(THF)_2]$ **4**. [b] NMR yields. [c] Isolated yield. [d] Based on NMR conversion.

In common with our previous observations of group 2-mediated intramolecular hydroamination catalysis, the amide species was also found to offer greater stability, particularly for catalytic transformations performed at more elevated temperatures. Although the absolute reactivity toward hydroamination of the precatalysts, **1** and **2**, therefore, is evidently limited by the potential for transaminative interactions with HN(SiMe$_3$)$_2$, the amide-based catalysts offer appreciable advantages in terms of selectivity and catalyst stability. For this reason the majority of our subsequent observations of substrate scope and kinetic analyses utilized the amide-based strontium precatalyst, **2**, which was reasoned to provide the most advantageous performance in terms of activity and selectivity.

Reaction Scope: Intermolecular Hydroamination of Substituted Vinylarenes. A number of functional groups were found to be tolerated for the hydroamination of styrene. The results of hydroamination of a variety of vinylarenes with benzylamine and piperidine with the strontium bis(trimethylsilyl)amide precatalyst **2** are summarized in Table 3.

Table 3. Intermolecular Hydroamination of Vinylarenes Catalyzed by 2[a]



entry	R	amine	product	time/h	yield[b]/%
1	−OMe	$PhCH_2NH_2$	**9**	144	63
2	−Me	$PhCH_2NH_2$	**10**	28	84
3	−H	$PhCH_2NH_2$	**11**	24	78
4	−Cl	$PhCH_2NH_2$	**12**	48[c]	65
5	−Cl	$(CH_2)_5NH$	**13**	17	69
6	−Br	$(CH_2)_5NH$	**14**	18	49[d]

[a] Reaction conditions: 5 mol % $[Sr\{N(SiMe_3)_2\}_2]_2$ **2**, styrene-derivative:amine = 1:1, neat, 60 °C. [b] After purification by chromatography. [c] Determination of the reaction time proved to be inconsistent. [d] Yield based upon isolated hydroamination product. Occurs alongside vinylarene oligomerization.

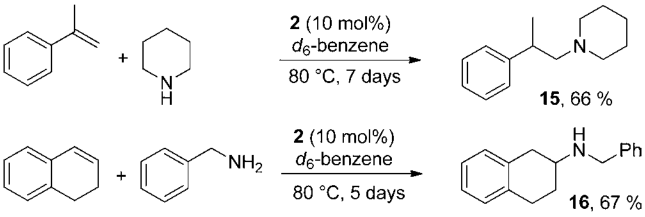
The reaction of benzylamine (Table 3, entries 1−4) and piperidine (Table 3, entry 5) with relatively activated alkenes follows a strictly anti-Markovnikov (or 2,1-) addition. A single regioisomer was generated under mild reaction conditions and no obvious byproducts were detected. As previously described, the alkene insertion is believed to occur via a polarized four-membered transition state (inset, Scheme 1) in which the anionic charge at the incipient benzylic carbon adjacent to the metal center is stabilized by the presence of the styrene aryl substituent if the M−N bond adds in a 2,1-fashion to the carbon−carbon double bond. Comparison of the reaction times for the hydroamination of *para*-substituted vinylarenes (Table 3), indicates that more electron-deficient alkenes undergo more facile reaction with amines across the series R = Br ≈ Cl > H > CH_3 > OCH_3. This observation is again consistent with rate-determining alkene insertion in the catalytic cycle whereby electron-withdrawing substituents in *para*-positions enable the stabilization of the developing negative charge in the transition state during carbon−nitrogen bond formation. In contrast, the presence of more electron-donating substituents on the aromatic ring, such as methyl or methoxy, have a detrimental effect on catalytic turnover by inducing a destabilizing increase in the electron density at the benzylic center (Table 3, entries 1 and 2). These hydroamination reaction conditions (T = 60 °C) were mild in comparison to previously published procedures. For example, the addition of benzylamine to *p*-methylstyrene catalyzed by 2 mol % $[Li\{N(SiMe_3)_2\}]$ with 2 mol % TMEDA resulted in 54% yield after 19 h at 120 °C.[30t] Furthermore, this reaction was not selective and provided a 7:1 mixture of the monohydroamination and bishydroamination products.

Attempted reaction of benzylamine and *p*-chlorostyrene provided more complex results (Table 3, entry 4) and after several attempts no consistent reaction times were achieved. In contrast the addition of piperidine to *p*-chlorostyrene yielded the corresponding 2-arylethylamine derivative without complications. At room temperature electron-deficient *p*-chlorostyrene could slowly, but selectively, be converted into the 2-arylethylamine product, while catalyst decomposition and low conversion were observed at elevated temperatures. Although the complete nature of this inhibition of catalysis could not be elucidated, it is suggested that, in the former case, deactivation of the catalyst occurs through some level of C−Cl activation in competition with the catalysis of hydroamination. For the hydroamination of *p*-fluorostyrene, an even more extreme level of catalyst deactivation was observed and only minimal hydroamination products were detected. Although no evidence for C−F activation products could be identified during these hydroamination reactions, it is likely that the fluoride functionality is not tolerated in group 2-metal-mediated hydroaminations.[44] In contrast, hydroamination of *p*-bromostyrene yielded the hydroamination product, albeit in low yield. In this latter case, considerable styrene oligomerization, indicated by a highly viscous reaction mixture and a low yield of hydroamination products (Table 3, entry 6), was observed. Oligomerization became the predominant reaction when very electron-poor styrene derivatives were used, such as *m*-nitrostyrene and methyl *p*-vinylbenzoate.

The side reactions associated with the hydroamination of halide-substituted vinylarenes frustrated attempts to carry out a wide-ranging Hammett analysis of this reactivity. Reliable k_X/k_H data, however, could be obtained for the addition of piperidine to styrene, *p*-methyl- and *p*-methoxystyrene. Reflecting the empirical data in Table 3, more electron-donating substituents were found to perturb the hydroamination reaction, and a ρ-value of +3.8 was obtained consistent with the formation of a transition state in which a negative charge, as expected, was developed and delocalized over the whole aromatic ring.

To assess the influence of substitution at the C=C group, the strontium-catalyzed hydroaminations of α-methylstyrene and 1,2-dihydronaphthalene were examined (Scheme 3) employing amide **2**. Whereas the reaction between piperidine and styrene was completed in 5 h at 60 °C, greater steric hindrance at the α- and β-carbon centers drastically impeded the reaction; even at 80 °C, 2-dihydronaphthalene and α-methylstyrene required 5 and 7 days, respectively, for complete conversion. Due to the prolonged reaction time at elevated temperature, catalyst decomposition occurred, and only about 85% conversion was observed, so that modest isolated yields of 67 and 66% of the product 2-arylamines were obtained. The observed retardation of the reaction rate is likely due to an energetically higher lying transition state for the rate-determining M−C and C−N bond formation.

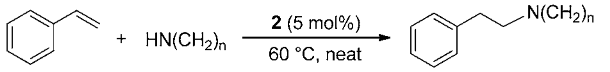
Scheme 3. Hydroamination of α- and β-Substituted Styrene Derivatives with 2



Such a strong substituent influence is typical for f-element and heavier group 2 catalysts, which are controlled by steric/kinetic rather than electronic factors. For the intramolecular hydroamination of aminoalkenes catalyzed by calcium and magnesium complexes it was shown that alkyl substituents on the C=C bond prolonged the reaction time,[30d] while mono- and dialkyl substitution at the terminal carbon generally caused the hydroamination reaction to shut down completely.[45] Similar observations have been made in organolanthanide chemistry, where a number of coordinatively unsaturated half-sandwich organolanthanide catalysts have been designed to achieve the hydroamination/cyclization of highly substituted nonactivated aminoalkenes.[18n,p,t] The intermolecular hydroamination of sterically more demanding vinylarenes like α,β-dimethylstyrene and 1,2-dihydronaphthalene has also been achieved by lithium-catalyzed hydroamination utilizing $LiN(SiMe_3)_2$[30t] or ^nBuLi[30u−w] as well as a mechanistically different ruthenium-catalyzed process.[12q] These studies also showed that the hydroamination products were only isolated in moderate yields (34−50%) and/or more forceful reaction conditions were required for addition, compared to the unsubstituted styrenes.

Reaction Scope: Variation of Amine. *N-Heterocyclic Secondary Amines.* The strontium-mediated hydroamination of styrene with a variety of *N*-heterocyclic secondary amines was examined, and the results are summarized in Table 4. The secondary cyclic amines reacted readily and provided the corresponding anti-Markovnikov hydroamination products in 65−93% yields. Even the addition of aziridine took place without opening of the strained three-membered ring. As the ring size decreased from piperidine through pyrrolidine to azetidine (Table 4, entries 1−3), the reaction was observed to become more facile. The addition of azetidine to styrene was completed in only 45 min with yields as high as 81%. In contrast, application of aziridine resulted in a noticeably slower reaction (Table 4, entry 4). An explanation for this variation in reaction rate may be provided through consideration of the nucleophilicity of the respective *N*-heterocycles. The dialkyl substituents are increasingly constrained by incorporation into the ring as the size of the heterocycle decreases and, consequently, the nucleophilic lone pair is decreasingly hindered. While the six-, five-, and four-membered cyclic amines have comparable pK_a values,[46] an increase of nucleophilicity with decreasing ring size can be observed, which facilitates the strontium-mediated addition to styrene.

Table 4. Intermolecular Hydroamination of Styrene with Secondary *N*-Heterocyclic Amines with 2[a]



entry	amine	product	time/h	yield[b]/%
1	$HN(CH_2)_5$	**6**	5.0	79
2	$HN(CH_2)_4$	**17**	3.5	65
3	$HN(CH_2)_3$	**18**	0.75	81
4	$HN(CH_2)_2$	**19**	4.0[c]	72
5	$HN(CH_2)_4O$	**20**	4.0	93

[a] Reaction conditions: 5 mol % $[Sr\{N(SiMe_3)_2\}_2]_2$ **2**, styrene-derivative:amine = 1:1, neat, 60 °C. [b] After purification by column chromatography. [c] Reaction at 52 °C.

In the case of aziridine a different effect has to be taken into account. Incorporation of the nitrogen center into a three-membered ring provides its lone pair with considerably enhanced s-character than is typical for an amine and aziridine is less nucleophilic.[46] Although it appears that this effect makes the three-membered ring less reactive than azetidine for hydroamination, its reactivity is higher than piperidine and comparable to pyrrolidine. Similarly the lone-pair on the nitrogen of morpholine is more electron rich due to the inductive effect from the oxygen atom, resulting in a slightly higher reactivity compared to piperidine (Table 4, entry 5). The ether functionality was not observed to hinder the hydroamination reaction.

The behavior of the variety of heterocyclic amines listed in Table 4 is again compatible with a rate-determining insertion step in the catalysis. It is believed that the protonolysis step is lower in energy, such that the nucleophilicity of the derived amide is of primary importance for determining the rate of the reaction.

Aliphatic and Aromatic Amines. A selection of secondary and primary amines was also examined in the hydroamination of styrene employing **2** as precatalyst. The results of this study are shown in Table 5 and, dependent on the amine used, significant differences in reactivity were observed. Although the use of *tert*-butylamine provided clean hydroamination without any detectable oligomerization, the reactivity of this sterically demanding amine was very low and after 18 days at 60 °C only 83% conversion to product aryl-2-ethylamine was observed (Table 5, entry 1).

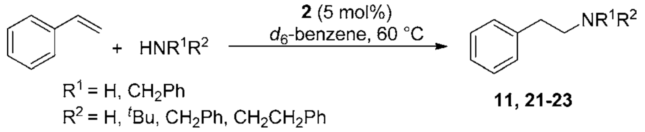
Dibenzylamine, despite being a secondary amine, was found to be slightly more active in the hydroamination reaction compared to benzylamine (Table 5, entries 2 and 3). 2-Phenethylamine could only be converted into the corresponding hydroamination adduct at room temperature as at higher temperature only little conversion was achieved. The reaction was optimally catalyzed by $[Sr\{N(SiMe_3)_2\}_2]_2$, **2**, and $[Sr\{CH(SiMe_3)_2\}_2(THF)_2]$, **4**. Although both reactions were clean, conversions of only 70% were achieved. This, together with the low conversion at higher temperature, again indicates possible issues of catalyst stability in the presence of 2-phenethylamine.

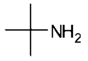
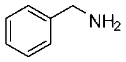
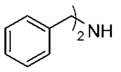
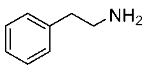
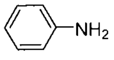
Aniline did not react with styrene even after prolonged heating to 60 °C in the presence of **2**, (Table 5, entry 5). The nucleophilicity of strontium anilides should be lower than that of aliphatic amides such that the anion formed may be no longer sufficiently reactive for formation of the proposed insertion transition state with the styrene double bond. Beller et al. have found that exchanging the lithium cation in Li anilides for the more electropositive group 1 element potassium allows the hydroamination of styrene derivatives with aniline to be achieved in high yields.[30v] The reaction between aniline and $[Sr\{N(SiMe_3)_2\}_2]_2$ quantitatively yielded $[Sr(HNPh)_2]_n$ and $HN(SiMe_3)_2$ as observed by ^1H NMR spectroscopy. The new amide species was highly insoluble, however, and precipitated from benzene solutions.[47] Similar reactivity was found upon addition of ammonia to styrene (see Table 6). Notably, styrene again remained intact and no significant styrene oligomerization was observed. Ruspic et al. have trapped gaseous ammonia with $[HC\{(Me)CN(2,6\text{-}^iPr_2C_6H_3)\}_2Ca\{N(SiMe_3)_2\}(THF)]$ to yield the dimeric amide.[42] This synthesis was repeated, the complex treated with styrene in d_6-benzene and heated to 60 °C, but, again, no hydroamination occurred, even after prolonged reaction times.

Hydroamination of Conjugated Dienes. The calcium and strontium bisamides, **1** and **2**, were employed in the hydroamination of isoprene with benzylamine (Scheme 4). The substrates were reacted in a 1:1 ratio at 60 °C with 10 mol % of $[M\{N(SiMe_3)_2\}_2]_2$ (M = Ca, Sr). The product was obtained as a mixture of two regioisomers **24** and **25** with the internal alkene **24** as the major product.

The strontium complex again showed higher reactivity in the intermolecular catalytic hydroamination reaction than the analogous calcium complex; full conversion of isoprene could be obtained after three days with the strontium catalyst, whereas the reaction mediated by the calcium catalyst took 16 days to reach completion. A proposed isomerization mechanism, which would explain the formation of the two products, is outlined in Scheme 5. The addition of the activated amine functionality to isoprene may take place through direct and regioselective aminometalation of isoprene with exclusive insertion of the less hindered monosubstituted double bond

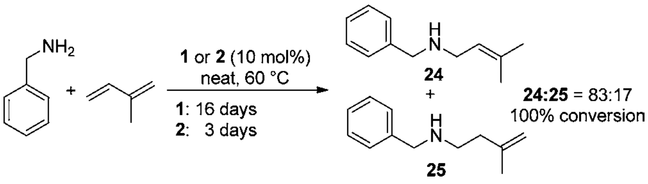
Table 5. Strontium-Catalyzed Hydroamination of Styrene with Primary and Secondary Amines



Entry	Amine	Product	T / °C	Time	Yield[a]
1[b]		**21**	60	18 days	58 %
2[c]		**11**	60	24 h	82 %
3[c]		**22**	60	18 h	78 %
4[c]		**23**	RT	3 days	70 %
5[d]		-	60	No conversion	-
6[e]	NH_3	-	80	3 days-	-

[a] Yields after purification by Kugelrohr distillation or column chromatography. [b] Neat, 17% styrene remaining. [c] In d_6-benzene, 2.0 M. [d] In d_6-benzene 0.5 M. [e] In d_8-THF, 0.5 M, cat. = $[Sr\{CH(SiMe_3)_2\}_2(THF)_2]$ **4**.

Scheme 4. Addition of Benzylamine to Isoprene



into the M−N bond of a group 2 benzylamide species to form the η^3-allyl intermediate **A**. Intermediate **A** may then react to produce either **24** or **25** by protonation with a further molecule of benzylamine at one of the two possible allylic positions. Although several stable allylcalcium species synthesized by metathesis routes with persistent η^3-coordination modes have been reported,[48] the product distribution will be determined by steric effects and protonation will occur preferentially, possibly assisted by M−N coordination, at the less hindered *exo* position.

In the hydroamination of isoprene with benzylamine a small amount of the double hydroamination product was also observed (<5%). In the case where 1.3 equiv of isoprene was added to the reaction mixture, about 20% of the double hydroamination product **26** was formed (Scheme 6).

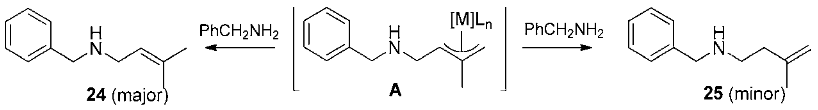
The hydroamination of isoprene was also accomplished with the secondary amine piperidine. Under dilute reaction conditions, the time for the hydroamination of isoprene was shortened to only 24 and 12 h with the application of **1** and **2**, respectively (Table 6, entries 1 and 2). Furthermore, when using piperidine, in comparison to the analogous reaction with benzylamine, a higher regioselectivity toward the internal alkene **27** was observed, yielding **27** and **28** in ratios of 94:6 and 92:8 for the calcium and strontium catalysts, respectively. Use of the calcium and strontium dialkyls **3** and **4** in the hydroamination of isoprene with piperidine, showed again superior reactivity in comparison to the metal bisamides. Full conversion after 9 h at 60 °C was observed when the reaction was mediated by **3**, while **4** yielded the hydroamination products after only 6 h at room temperature and 5 mol % catalyst loading (Table 6, entries 3 and 4). Although isoprene was oligomerized by high loadings (>5%,) of the strontium alkyl precatalyst, **4**, the internal alkene hydroamination product **27** could be formed almost exclusively by lowering the concentration of the reaction mixture and decreasing the catalyst loading (Table 6, entries 4 and 5). Under these more dilute conditions hydroamination was favored over oligomerization and an unoptimized yield of 60% was achieved for **27** (Table 6, entry 5).

Hydroamination of myrcene to *N*,*N*-diethylgeranylamine, an important precursor of (−)-menthol, is one of the few hydroamination reactions carried out on a manufacturing scale. The analogous hydroamination of myrcene with piperidine was, thus, examined with precatalyst **2** and found to be converted smoothly to the corresponding addition products **29** and **30** after 4 h at 60 °C (Scheme 7).

The addition of the amine was again found to occur exclusively at the monosubstituted C=C double bond and high selectivity toward the internal alkene hydroamination product **29** was observed. Conversion was also observed to occur more readily than for the hydroamination of isoprene under identical conditions (12 h versus 4 h), which we propose is a result of a stabilizing Sr−N interaction within the η^3-allylstrontium intermediate for the *Z*,*Z*-diene. (Scheme 8).

An attempt to extend the scope of diene hydroamination to 1,3-cyclohexadiene with **1** and **2** was unsuccessful and resulted in dehydrogenation and aromatization to produce benzene (Scheme 9). Higher temperatures favored the formation of the dehydrogenation product, but even at low temperatures negligible quantities of the hydroamination adduct were obtained. Although dehydrogenation occurred irrespective of

Scheme 5. Schematic Isomerization Mechanism for the Formation of the Major Product 24



Scheme 6. Hydroamination of Benzylamine with an Excess of Isoprene

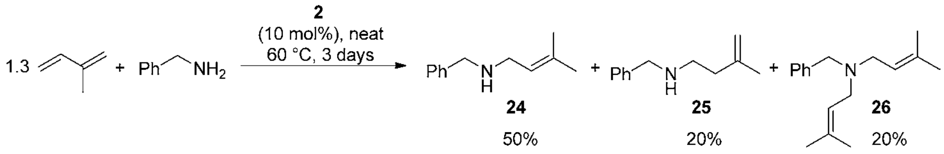
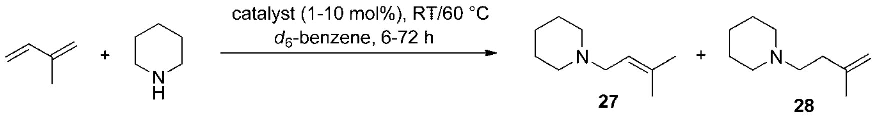


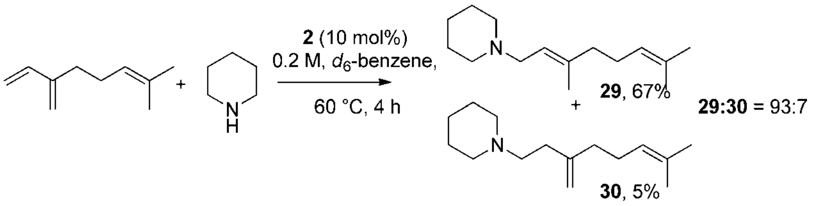
Table 6. Hydroamination of Isoprene Catalyzed by Alkaline Earth Bisamides and Dialkyls



entry	catalyst	loading/mol %	time/h	T/°C	**27**:**28** (yield/%)[b]
1	**1**	10	24	60	94:6 (80:5)
2	**2**	10	12	60	92:8 (71:6)
3	**3**	10	9	60	91:9 (76:7)
4	**4**	5	6	25	97:3 (14:0.4)[c]
5	**4**	1	72	25	98:2 (60:0.9)[d]

[a]Reaction conditions: isoprene:piperidine = 1.3:1, 0.2 M in d_6-benzene. [b]NMR yield. [c]Visible oligomerization as side product. [d]Concentration 0.17 M, 40% piperidine unreacted.

Scheme 7. Hydroamination of Myrcene with Piperidine Catalyzed by 2



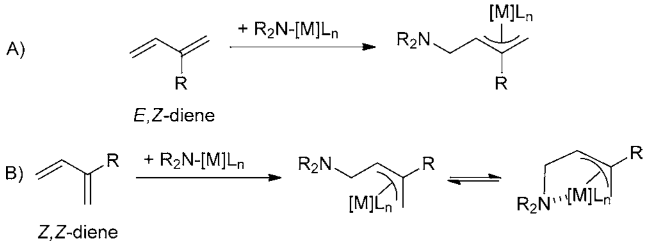
the presence of amine, this process occurred more rapidly in the presence of stoichiometric amounts of amine. A process of H/D exchange was apparent if the reaction was performed with deuterated benzylamine. In this case the resonance attributable to the benzylamine NH_2 group was observed to grow to almost its full intensity while a broad peak at 1.50 ppm was apparent in the ^1H NMR spectrum, which may be assigned to H_2 or HD. Although these observations will not be elaborated herein, they are supportive of a potential mechanism involving CH-activation, followed by β-H elimination.

The high reactivity of calcium and strontium dialkyls for the hydroamination of styrene and diene derivatives also encouraged us to examine this reactivity with less activated alkenes. The hydroamination of 1-pentene with piperidine was thus examined using both **3** and **4** as precatalysts. No hydroamination product was formed, however. Rather, isomerization to the internal alkene, 2-pentene was observed (Scheme 10) in 16 h and 7 days at 45 °C for the strontium and calcium species, respectively. Although in both cases, the Z-isomer was formed initially with a maximum ratio observed of E:Z = 1:2, after full conversion, the thermodynamically favored E-isomer became the main isomer (maximum ratio E:Z = 4:1). Although the mechanism of this reaction has not yet been defined, similar reactivity is widespread in hydroamination reactions catalyzed by Na/K alloy or ^{n}BuLi.[30x] We have previously attributed similar isomerization processes in aminoalkene hydroamination to intramolecular proton transfer from the tethered vinylic methylene to the nitrogen of the coordinated group 2 amide.[30d,o]

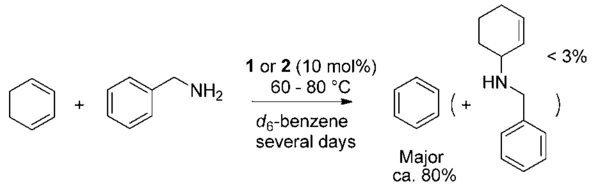
Alkyne Hydroamination. The hydroamination of alkynes is generally viewed as being more facile than that of alkenes because of the higher reactivity and electron density of C≡C bonds. The hydroamination of phenylacetylene with piperidine, mediated by 10 mol % of $[Sr\{N(SiMe_3)_2\}_2]_2$, was thus examined. Although full liberation of $HN(SiMe_3)_2$ was observed at the first point of analysis, no hydroamination product was formed even after prolonged reaction at 60 °C. A reaction of phenylacetylene, piperidine and $[Sr\{N(SiMe_3)_2\}_2]_2$ in a 1:1:1 ratio in d_6-benzene resulted in the immediate precipitation of insoluble $[Sr(C{\equiv}CPh)_2]_n$ and the insolubility of the strontium alkynyl presumably depletes the group 2 species in solution under equilibrium conditions.

In contrast, hydroamination of the internal alkyne diphenylacetylene mediated by 10 mol % of $[Sr\{N(SiMe_3)_2\}_2]_2$, **2**, proceeded cleanly but slowly and after 4 days at 80 °C only about 80% conversion to the hydroamination product was observed. The more reactive alkyl species, **4**, however, yielded the hydroamination products **31** and **32** quantitatively after 17 h at 60 °C (Scheme 11). Evidently the conformation of the intermediate metal alkenyl is not stable and some isomerization

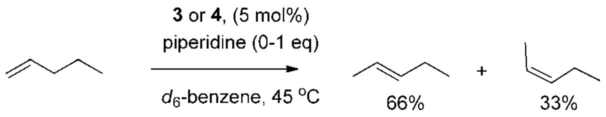
Scheme 8. Proposed η^3-Allyl Metal Species for *E*,*Z*- and *Z*,*Z*-Diene Hydroamination



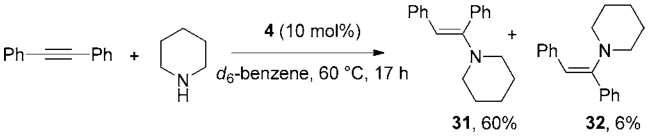
Scheme 9. Attempted Hydroamination of 1,3-Cyclohexadiene



Scheme 10. Isomerization of 1-Pentene



Scheme 11. Hydroamination of Diphenylacetylene in d_6-Benzene



to the *Z*-product **32** is observed alongside the expected conversion to the *E*-product **31** (*E*:*Z* 10:1).

In contrast to these observations, no hydroamination of 1-methyl-2-phenylacetylene was observed, even at high catalyst loading and long reaction times in d_6-benzene at 80 °C. Taking account of the ease of styrene hydroamination (*vide supra*), this observation, alongside the slow diphenylacetylene hydroamination, seems likely to be the consequence of steric congestion rather than any intrinsic electronic impediment to addition.

Substantial acceleration of diphenylacetylene hydroamination was observed by changing the solvent from d_6-benzene to d_8-THF. In this case, the reaction rate was found to be 1 order of magnitude higher than the corresponding reaction in benzene, giving full conversion in 2 h at 60 °C with only 5 mol % of **4** (Table 7). Moreover, the selectivity toward the *E*-isomer could be improved considerably yielding an *E*- to *Z*-isomer ratio of 91:9. Further solvent screening was thereby carried out by comparison of the conversion after 2 h at 60 °C (Table 7).

Table 7. Solvent Dependence of the Hydroamination of Diphenylacetylene with Piperidine[a]

entry	solvent	substrate:product[b]	**31**:**32**[c]
1	THF	0:100	91:9
2	benzene	59:41	60:40
3	hexane	56:44	60:40
4	Et_2O[d]	91:9	91:9
5	tetrahydropyran	42:58	83:7

[a] Reaction conditions: 5 mol % **4**, amine:alkyne = 1:0.7, 0.5 M. Reaction stopped after 2 h at 60 °C. [b] Determined by GC-MS analysis. [c] Determined by ^{1}H NMR spectroscopy. [d] Reaction at 35 °C, solubility problems.

From the data provided in Table 7, it was apparent that reaction in THF was superior in terms of both conversion rate and the selectivity toward the *E*-isomer (entry 1). Reactions in hydrocarbon solvents were found to only reach the first half-life of the reaction in a similar time and to provide approximately equal amounts of *E*- and *Z*-isomers (entries 2 and 3). The reaction in diethyl ether provided a high *E*-to-*Z* ratio, although only 10% conversion was observed after 2 h at 60 °C. This slow conversion can be ascribed to the low solubility of the reaction species in this solvent (entry 4). The reaction in tetrahydropyran adopted an intermediate position in terms of conversion time and selectivity (entry 5). Surprisingly, no formation of the hydroamination product was observed after 2 h at 60 °C when performing the reaction in dioxane, 1,2-dimethoxyethane, methoxycyclopentane, and 2-methyltetrahydrofuran. Not only does the dipole moment of the solvent appear to be of importance, but also its donor ability in order to interact with the heavier alkaline earth metal center during different stages of the catalytic cycle. These preliminary results showed that the hydroamination of diphenylacetylene mediated by alkaline earth centers exhibits a complex solvent dependence and that the choice of the solvent is crucial for achieving higher reactivity (*vide infra*).

Catalysis of the reaction of diphenylacetylene with piperidine in THF was also studied as a function of precatalyst identity (Table 8). As was the case for alkene hydroamination, the strontium alkyl species, **4**, was found to be the superior catalyst (Table 8, entries 1 and 2). The low reactivity of $[Sr\{N(SiMe_3)_2\}_2]_2$ can be partly ascribed to limited formation of the catalytically active amide as was observed in the hydroamination of styrene derivatives (*vide supra*).

Although the group 2-mediated hydroamination of alkynes is evidently rather limited, this chemistry may also be extended to enynes, compounds with conjugated alkyne and alkene groups. Despite being highly reactive species, selectivity is an issue when applying enynes in addition processes. The reaction of but-3-en-1-ynylbenzene with piperidine in the presence of 5 mol % of **4**, provided an intense red reaction mixture and a complex mixture of products. In contrast, reaction in the presence of the less reactive amide species, **2**, was highly selective and yielded a single product in which addition of piperidine had occurred exclusively at the more accessible terminal alkene functionality (Scheme 12). The observation of the allene product **33** indicates that the intermediate organometallic species is delocalized over the conjugated alkyne and phenyl groups, prior to protonation by a second molecule of piperidine. The addition is carried out in a strictly anti-Markovnikov fashion, because of the presence of the directing phenyl group, which stabilizes the developing negative charge of the metal alkyl/alkynyl species. Due to the highly reactive nature of this compound the reaction could be performed at 0 °C and reveals the potential broader application of this substrate class in intermolecular hydroamination reactions mediated by group 2 catalysts.

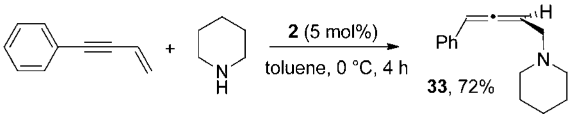
Kinetic Studies. *Determination of the Rate Law for Vinylarene Hydroamination.* Ryu et al. have reported that the rate equation of the lanthanide-mediated intermolecular

Table 8. Catalyst Dependence of the Hydroamination of Diphenylacetylene

entry	catalyst	time	conversion[b]
1	**4**	2 h	100%
2	**3**	4 days	50%
3	**2**	4 days	trace of product

[a]Reaction conditions: 5 mol % of catalyst, amine:alkyne = 1:0.7, 0.5 M, 60 °C, THF. [b]Determined by ^{1}H NMR spectroscopy.

Scheme 12. Hydroamination of But-3-en-1-ynylbenzene with Piperidine Catalyzed by $[Sr\{N(SiMe_3)_2\}_2]_2$ (2)



hydroamination of styrene derivatives can be summarized as shown in eq 2.[36b] The rate law was simplified by using an excess

$$\text{rate} = k[\text{amine}]^0[\text{alkene}]^1[\text{catalyst}]^1 \qquad (2)$$

of alkene and assuming its concentration remains unchanged during the experiments. As the catalyst concentration remains also approximately constant during the reaction course, the rate law may be written as a pseudo-zero-order process (eq 3), and a plot of amine concentration against time should provide a straight line with the slope equal to the rate constant k_{obs}.

$$\text{rate} = k_{obs}[\text{amine}]^0 \qquad (3)$$

Initial experiments were, thus, carried out for the strontium-mediated hydroamination reaction employing **2** as precatalyst. As a standard, the reaction of piperidine with styrene in d_6-benzene was chosen and the ratio of styrene:piperidine:catalyst was set as 100:10:1. Contrary to expectation, a plot of [amine] against time did not provide a linear relationship, but followed an exponential course (Figure 2), and the data provided a best fit consistent with first-order kinetic behavior (Figure 3).

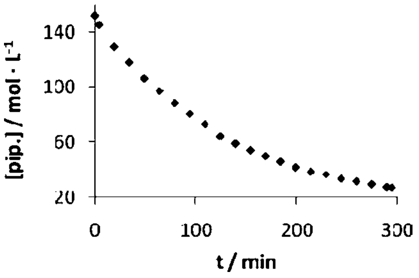


Figure 2. Plot of amine concentration versus time.

The dependence of the reaction upon catalyst concentration was established by changing [**2**] and holding the amine and styrene concentrations identical. Unexpectedly, the data best fit a second-order dependence upon catalyst concentration (Figure 4) and possibly implicate a rate-determining step involving two catalyst molecules or the amine-induced disruption of a dimeric precatlaytic center, consistent with the observation that heavier alkaline earth species commonly exist as dimers in non-coordinating solvents.[41,49] We have previously observed that intramolecular hydroamination reactions were first-order with respect to the catalyst for β-diketiminate derivatives and THF-solvated homoleptic precatalysts, whereas a second-order dependence for the unsolvated bis(trimethylsilyl)amides **1** and **2**.[30o] The unsolvated complexes **1** and **2** also displayed lower catalytic activity than their THF-solvated analogues, which was ascribed as a result of the deaggregating effect of the coordinating ether.

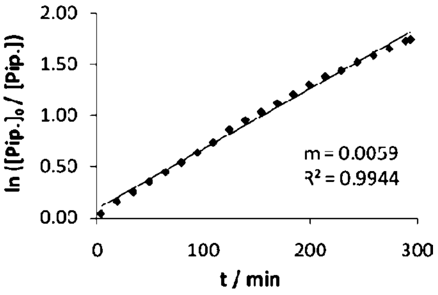


Figure 3. First-order rate plot.

As expected, variation of the styrene concentration with constant amine and catalyst concentrations provided evidence of a first-order dependence of the reaction rate on styrene concentration (the ratio between styrene and amine was always kept greater than 10:1). A linear dependence of reaction rate was also observed with variation of the amine concentration for a fixed concentration of catalyst and a fixed styrene:amine ratio greater than 10:1. The amine concentration dependence was established for both the calcium and the strontium amide catalysis with **1** and **2**. Strikingly, the strontium system displayed a more pronounced dependence upon variation of piperidine concentration (Figure 5).

The overall rate law for the heavier alkaline earth bisamide-mediated intermolecular hydroamination reaction can, thus, be summarized as shown in eq 4. With addition of an excess of

$$\text{rate} = k[\text{amine}]^1[\text{alkene}]^1[\text{catalyst}]^2 \qquad (4)$$

alkene and at constant catalyst concentration, the reaction becomes a pseudo-first-order reaction, where the rate constant may be obtained by plotting the natural logarithm of the amine concentration against time (eq 5).

$$\text{rate} = k_{obs}[\text{amine}]^1 \ \ln\frac{[\text{amine}]_0}{[\text{amine}]_t} = k_{obs}t \qquad (5)$$

Only the data obtained up to around 80% conversion (which equals three half-lives) were considered. After this time, the rate of the hydroamination decreased, which can probably be assigned to competitive catalyst inhibition by amine product coordination at low substrate concentration. Although this has been observed in previous studies of group 2-catalyzed intramolecular hydroaminations, the results stand in contrast to findings by Ryu et al. of lanthanocene-catalyzed intermolecular hydroamination where a zero-order amine dependence on the reaction rate was established.[36b] It is known that significant deviations from (pseudo) zero- or second-order rate kinetics can occur dependent on the steric congestion around the metal center and substrate structure.[1p] With the application of non-metallocene catalysts such kinetic deviations have been observed frequently[20a,c,e] and the change

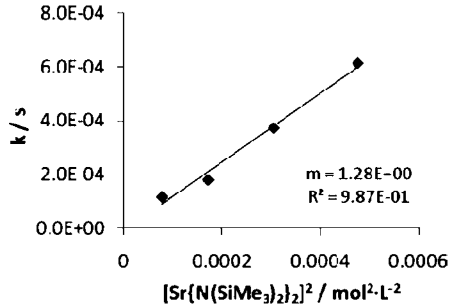


Figure 4. Plot of reaction rate as a function of catalyst concentration at 50 °C and 0.44 M initial piperidine concentration.

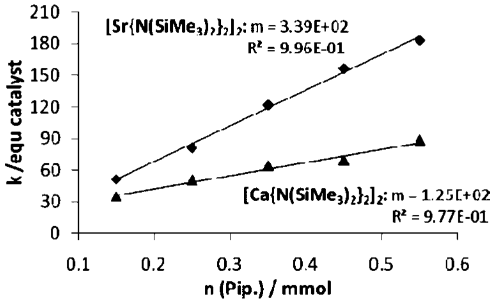


Figure 5. Plot of reaction rate as a function of [piperidine] using 10 mol % $[M\{N(SiMe_3)_2\}_2]_2$ (**1**, M = Ca, 60 °C; **2**, Sr, 45 °C) and keeping styrene:piperidine ratio greater than 10:1.

in the rate law has been attributed to substrate self-inhibition and product inhibition. The metal centers in these systems are often more accessible to amine bases, as evidenced by coordinating solvents (e.g., THF) found in the precatalysts. In the current case, the metal centers of **1** and **2** are not surrounded by additional stabilizing ancillary ligands and are thus prone to further donor interactions. To ensure that at high piperidine concentrations no amine inhibition took place, five further experiments were conducted in which [styrene] was kept at a low, constant concentration while 10 mol % of **1** (with respect to styrene) in d_6-benzene was employed. In each NMR-scale experiment 1, 2, 5, 10, or 15 equiv of piperidine was added, and the reaction mixtures were heated to 60 °C and monitored by ^{1}H NMR spectroscopy. The measured styrene and product concentrations after 2 h reaction time are shown in Figure 6.

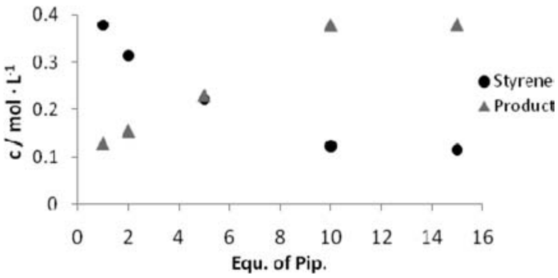
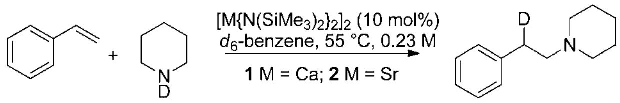


Figure 6. Plot of styrene and product concentration after 2 h as a function of added equivalents of piperidine (60 °C, [styrene] = 0.36 M) in the presence of 10 mol % **1**.

It can clearly be seen that, in agreement with the kinetic studies at high styrene concentration, higher initial amine concentrations increased the rate of reaction. While a drastic acceleration was observed through addition of 1, 2, 5, or 10 equiv of piperidine, there was no significant difference with even greater quantities of amine at which point apparent saturation occurred. This latter observation indicates that the reaction rate acceleration at higher amine concentration was not a polarity effect, but is indicative of a cooperative effect of coordinated amine in the rate-determining step.

To shed further light on these issues, reactions of styrene with d_1-piperidine (>95% deuteration) catalyzed by both **1** and **2** were undertaken and found to result in exclusive deuteration of the β-methyl group (Scheme 13). This result is consistent with the formation and deuteration/protonation of a metal alkyl intermediate occurring from insertion of the C=C double bond. It also demonstrates that no further proton migration steps occur during the reaction course. Kinetic analysis of the reaction described in Scheme 13 with an excess of styrene yielded kinetic isotope isotope effects (KIEs) of k_H/k_D = 4.3 (70 °C) and 4.1 (55 °C) for catalysis by **1**, whereas a much higher ratio of k_H/k_D of 7.9 (55 °C) was found with **2**. The maximum calculated kinetic isotope effect (KIE) at 25 °C for a homolysis reaction involving a N–H bond, whose stretch appears in an IR spectrum at 3100 cm^{-1}, should be approximately k_H/k_D = 8.5.[50] The magnitudes of the measured KIE are, thus, highly suggestive of a primary KIE.[50] While this observation would indicate that the N–H bond was breaking during the rate-determining step, rate-limiting protonolysis seems unlikely as stoichiometric reactions demonstrate that protolytic reactions generally occur at higher rate than the observed catalytic turnover frequencies. In addition, the dramatic effect of alkene substitution upon the reaction rate is more easily explained by rate-determining alkene insertion than rate-limiting protonolysis.

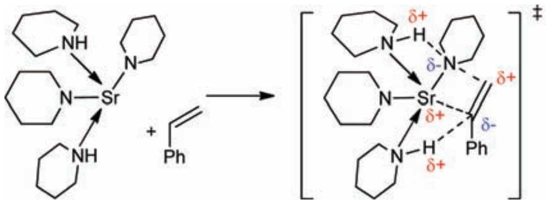
Scheme 13. Deuterium Distribution Pattern of Hydroamination Product



In earlier work, Gagne et al. found similar high KIEs (k_H/k_D = 4.1 (25 °C)) for the intramolecular hydroamination of aminoalkenes catalyzed by $[Cp'_2LaCH(SiMe_3)_2]$.[18d] We have also previously measured KIEs for the cyclization of (1-allylcyclohexyl)methylamine mediated by $[M\{N(SiMe_3)_2\}_2(THF)_2]$ (M = Ca, Sr) with k_H/k_D = 4.5 (25 °C) and 3.5 (45 °C) for calcium and strontium, respectively,[30o] while Sadow and co-workers have described a stable magnesium amidoalkene complex, which only undergoes intramolecular hydroamination/cyclization upon addition of a further equivalent of the protic aminoalkene substrate.[30l] All of these workers have suggested that the process of rate-determining polarized olefin insertion is assisted by the presence of further coordinated equivalents of the protic substrate within the coordination sphere of the catalytic center and that the high KIEs observed are a consequence of effectively concerted insertion and proton transfer.

A similar scenario may, thus, be envisioned in the intermolecular hydroamination reactions mediated by calcium and strontium bisamides (Scheme 14). Irrespective of the actual catalyst molecularity, for the transition state shown, the negatively polarized benzylic carbon atom is stabilized by the NH-functionality of an additional amine molecule. In contrast

Scheme 14. Proposed Styrene Insertion Transition State



to the proposed transition state for lanthanide-catalyzed intramolecular hydroamination, we propose that a second or even a third amine molecule may coordinate to the metal in the insertion transition state providing a, necessarily highly organized, metal-templated hydrogen-bonded network. This proposal is supported by the large, but group 2-center-dependent, negative activation entropy values measured in the variable-temperature studies (*vide infra*).

Temperature Variation. The additions of piperidine to styrene catalyzed by $[Ca\{N(SiMe_3)_2\}_2]_2$ **1** and by $[Sr\{N(SiMe_3)_2\}_2]_2$ **2** were conducted at four different reaction temperatures and monitored by ^1H NMR spectroscopy. Standard Arrhenius analyses (Figure 7), provided activation energies, E_a, of 53.6(4.6) kJ·mol^{-1} for the calcium and 72.4(4.2) kJ·mol^{-1} for the strontium systems. This outcome is somewhat counterintuitive as it was found that the strontium amide is the more active catalyst in the hydroamination reaction. The corresponding Eyring analyses (Figure 8) provided values for $\Delta H^‡$ which were very similar to the activation energies (Ca, 50.9(4.6) kJ·mol^{-1}; Sr, 70.7(4.2) kJ·mol^{-1}). A significant difference was found, however, between the activation entropy figures with $\Delta S^‡$ = −167.6(13.7) J·mol^{-1}·K^{-1}for the calcium system and $\Delta S^‡$ = −92.2(13.3) J·mol^{-1}·K^{-1}for the strontium system. These values provided room-temperature $\Delta G^‡$ of 101.1 kJ·mol^{-1} for the calcium system and 98.4 kJ·mol^{-1} for strontium. Although the calcium system is favored enthalpically, the strontium amide can, thus, be identified as the superior catalyst from an entropic point of view. The C═C insertion transition state will more loosely assemble around the larger Sr^{2+} cation and this entropic freedom provides a rationale for the differing KIEs observed for the two heavier alkaline earth systems.

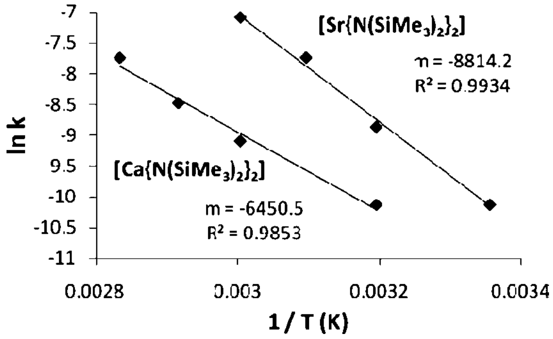


Figure 7. Arrhenius plot for the hydroamination of styrene catalyzed by **1** and **2** (10 mol % catalyst, [Pip.] = 0.28 M).

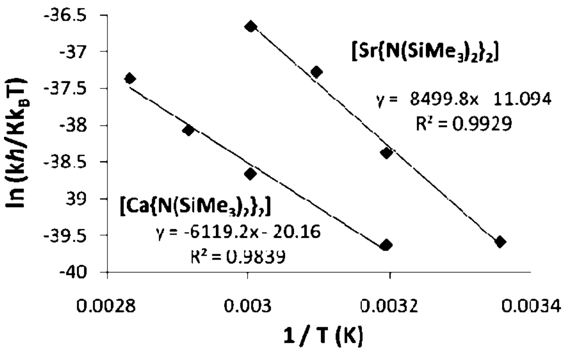


Figure 8. Eyring plot for the hydroamination of styrene catalyzed by **1** and **2** (10 mol % catalyst, [Pip.] = 0.28 M).

As discussed previously, the application of heavier alkaline earth amides must take account of the potential for reversible substrate transamination. To examine the potential significance of this pre-equilibrium in the above data, further kinetic studies of reactions mediated by the alkyl precatalysts **3** and **4** were conducted. As the hydroamination of styrene with these catalysts is rapid at room temperature, the hydroamination of *p*-methoxystyrene was chosen in order to study the reactions at different temperatures, while 2 mol % of catalyst was employed and the reaction mixture was more dilute ([piperidine] = 0.22 M) than those used in the kinetic experiments undertaken for the bis(trimethylsilyl)amide catalysts. These variations were necessary to provide a sufficiently slow reaction to allow measurement of the rate constants at higher temperatures. Identical reaction conditions for the strontium and calcium systems were employed so that the thermodynamic values are comparable. Arrhenius and Eyring analyses provided $\Delta H^‡$ values of 58.6(3.9) and 65.0(7.9) kJ·mol^{-1} for the catalyses by **3** and **4**, respectively. The $\Delta S^‡$ values again reflected the data extracted from the corresponding analyses of the bis(trimethylsilyl)amide catalysts and were again significantly more negative for calcium −160.5(11.5) J·mol^{-1}·K^{-1} in comparison to strontium (−106.1(25.1) J·mol^{-1}·K^{-1}). These data, within experimental error, are effectively identical to the corresponding values calculated for the systems based upon the respective calcium and strontium amide precatalysts, **1** and **2**. We interpret this observation to indicate that the efficacy of a particular metal-centered (calcium or strontium) catalysis is unaffected, irrespective of precatalyst identity. Rather, it is the earlier noted potential for the establishment of a transaminative pre-equilibrium, between the amine substrate and $HN(SiMe_3)_2$, in the amide-based catalysis which determines and limits the number of group 2 centers actually available to effect catalytic turnover. The modest values for the enthalpy of activation (50 to 70 kJ·mol^{-1}), suggest a concerted transition state with significant bond making to compensate for bond breaking. Conversely, large negative activation entropies are established (−92 to −168 J·K·mol^{-1}), which are typical for highly organized, polar transition states. Similar high $\Delta S^‡$ values are observed in pseudo-bicyclic transition states due to significant loss of internal rotational degrees of freedom. For example,

Cp'_2ThR_2-centered cyclometalation processes give rise to $\Delta S^\ddagger = -42$ to -100 J·mol^{-1}·K^{-1}.[51]

■ CONCLUSION

In conclusion, the calcium and strontium amides, **1** and **2**, and alkyls, **3** and **4**, are reported as efficient and readily available precatalysts for the intermolecular hydroamination of styrenes and dienes. Although diphenylacetylene is transformed to the expected vinylamine product, the addition of amines to C≡C triple bonds appears to be limited by the steric demands of the organic substituents attached to the internal alkyne. It has been established that although a pre-equilibrium exists for the reaction of $[M(N\{SiMe_3\}_2)_2]_2$, **1** and **2**, with amines, it has little effect on the overall catalytic cycle of group 2-catalyzed intermolecular hydroamination catalysis but determines the number of effective catalytic centers available for reaction. The hydroamination reactions catalyzed by the alkyl species **3** and **4** provide higher rates of catalysis but, in general, are complicated by alkene oligomerization side reactions. Both pairs of calcium and strontium precatalysts give rise to similar values for the enthalpy and, in particular, the entropy of activation. This latter factor is reasoned to have a fundamental effect upon the ease of catalysis, which is determined by the respective electropositivity and size of the respective group 2 metal dications. The rate-determining step is an amine-assisted insertion of the C=C double bond into the amide M−N bond, and the observed high kinetic isotope effects are suggestive of concurrent N−H bond breaking/C−H bond formation. The relative barrier heights for alkene insertion into M−N bonds may thus be viewed as a result of a compromise between the polarity of the M−N bond (and consequent ability to induce a dipole in a nonpolarized alkene), access to and the polarizability of the M^{2+} cation and the consequent ease of electronic reorganization toward C−N and C−M bond formation.

■ 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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