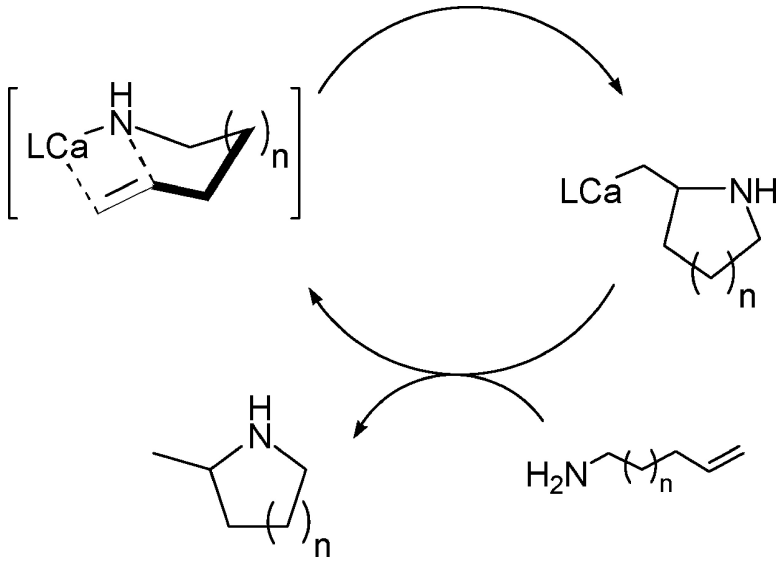
Communication

Calcium-Mediated Intramolecular Hydroamination Catalysis

Mark R. Crimmin, Ian J. Casely, and Michael S. Hill

J. Am. Chem. Soc., **2005**, 127 (7), 2042-2043• DOI: 10.1021/ja043576n • Publication Date (Web): 01 February 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 47 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 02/01/2005

Calcium-Mediated Intramolecular Hydroamination Catalysis

Mark R. Crimmin, Ian J. Casely, and Michael S. Hill*

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington, London, SW7 2AZ, UK

Received October 22, 2004; E-mail: mike.hill@imperial.ac.uk

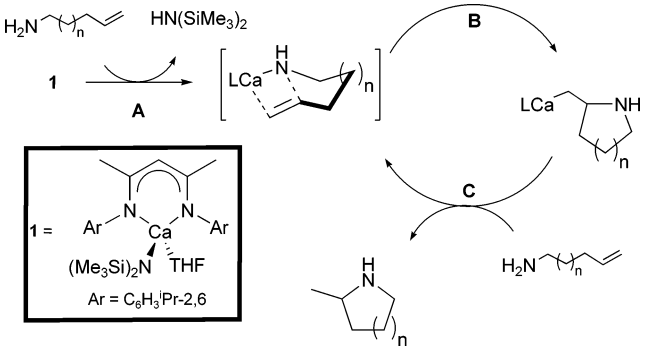
Hydroamination, the formal addition of an N−H bond across C−C unsaturation, is an attractive and atom-efficient route to nitrogen-containing molecules. The widespread search for homogeneous reagents capable of catalyzing these processes has begat a burgeoning and mechanistically diverse area of research that has utilized alkali metal, transition element, and 5f and 4f element complexes.[1] This latter class of catalyst, devised and pioneered by Marks and co-workers, is especially notable for its highly efficient catalytic cyclization of aminoalkenes, aminoalkynes, aminoallenes, and aminodienes.[2] The availability of a single common oxidation state (+3) precludes oxidative-addition/reductive-elimination as a viable mechanistic pathway for organolanthanide catalysts. Rather, reactivity patterns are defined by alkene insertion into polar (largely ionic) Ln−X (X = C, N) bonds and σ-bond metathesis, both of which may be modulated by judicious selection of Ln^{3+} cationic radius and supporting ligation.[3]

The heavier group 2 metals Ca, Sr, and Ba constitute a relatively underexploited, yet inexpensive and benign, series of elements that, as a result of their large radii and electropositive character, possess a number of features common to the 4f series.[4] The present submission describes our initial efforts to define a catalytic, molecular hydroamination process based upon a well-defined calcium coordination complex. In this respect it is notable that Harder has demonstrated previously that olefinic C−C insertion into calcium benzyl complexes provides a viable route to polystyrene and that a degree of stereoregularity may result from the application of a kinetically stabilizing fluorenyl-based co-ligand.[5]

A speculative mechanism for the intramolecular hydroamination of a generalized α,ω-aminoalkene catalyzed by the synthetically convenient β-diketiminato calcium bis(trimethylsilyl)amide [{HC(C(Me)$_2$N-2,6-^{i}Pr$_2$C$_6$H$_3$)$_2$}Ca-{N(SiMe$_3$)$_2$}(THF)], **1**,[6] is presented in Scheme 1. Although this mechanism is directly analogous to that elucidated for 4f element-mediated cyclization,[2] it displays several features with only limited precedent in calcium amide chemistry. We have shown previously that stoichiometric transamination of the bis(trimethylsilyl)amide substituent of **1** (step A of Scheme 1) occurs readily to produce a variety of heteroleptic calcium primary amides and anilides.[7] Although insertion of heterocumulenes into Ca−X (X = N, O) bonds is well-documented[8] and Westerhausen has reported a unique organobarium complex formed by insertion of diphenylbutadiyne into a barium phosphanide,[9] no clear precedent exists for insertion of C−C (alkene or alkyne) unsaturation into a Ca−N bond. In common with previously reported lanthanide derivatives, this process (Step B of Scheme 1) is likely to be rate-limiting for any putative calcium-mediated hydroamination process.

A stoichiometric reaction of **1** and 1-aminohex-4-yne, **I**, was studied on an NMR scale to provide an initial assessment of the viability of an intramolecular alkyne insertion process. Our choice of an internal alkyne was dictated by previous reports that calcium bis(trimethylsilyl)amides are sufficiently basic to effect deprotonation of terminal alkynes.[10] **I** was consumed within 30 min of

Scheme 1



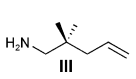
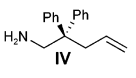
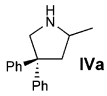
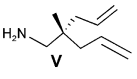
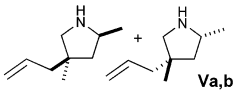
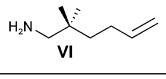
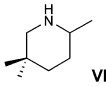
mixing the components in C_6D_6 to yield a ^{1}H NMR spectrum displaying a series of resonances analogous to literature data for the expected 2-ethylpyrroline cyclization product, **Ia**, but shifted upfield by ca. 0.45−0.50 ppm. A repeat of this stoichiometric reaction on a preparative scale at room temperature, followed by hydrolytic workup and analysis of the organic-soluble products by ^{1}H NMR and GCMS, provided irrefutable evidence of hydroamination and cyclization. 2-Ethylpyrroline was identified as the sole organic product by comparison to literature chemical shift data as well as its characteristic fragmentation pattern under chemical ionisation.[11]

We then investigated the more challenging intramolecular hydroamination of 1-aminopent-4-ene, **II**. An NMR scale reaction between stoichiometric quantities of substrate **II** and **1** resulted in complete consumption of the aminoalkene within 24 h at room temperature and the appearance of several new resonances reminiscent of the expected 2-methylpyrrolidine product, **IIa**. A limitation of our chosen catalytic system was also apparent since the reaction proceeded alongside redistribution to the known homoleptic calcium species [{HC(C(Me)$_2$N-2,6-^{i}Pr$_2$C$_6$H$_3$)$_2$}$_2$Ca], **2**.[6,12] This behavior is consistent with our previous studies of the reactivity of **1** with primary amines, where we have noted that even a minor reduction in the overall steric demands of the ligand substituents can result in irreversible (Schlenk-type) redistribution to the homoleptic species.[7]

Livinghouse has reported that homoleptic yttrium and lanthanide bis(trimethylsilyl)amides [Ln{N(SiMe$_3$)$_2$}$_3$] are competent catalysts for the intramolecular hydroamination of aminoalkenes.[13] We therefore attempted an NMR scale hydroamination of **II** with a 10 mol % catalyst loading of the simple homoleptic calcium bis(trimethylsilyl)amide [Ca{N(SiMe$_3$)$_2$}$_2$(THF)$_2$], **3**. Although this reaction resulted in complete protonolysis of the bis(trimethylsilyl)amide ligands, there was no sign of alkene hydroamination, even after extended periods at 60 °C.[14] In contrast, a similar catalytic reaction (10 mol % catalyst loading) between **II** and the β-diketiminato supported complex **1** resulted in the complete conversion of the aminoalkene to 2-methylpyrrolidine, **IIa**, over a 21 h period at 25 °C. Although catalytic turnover was also accompanied by

10.1021/ja043576n CCC: $30.25

Table 1. Catalytic Reactivity of Aminoalkenes and **1**

Entry[a]	aminoalkene	product(s)	time(h)	temp (°C)	% Conv.[b]
1	 **III**	 **IIIa**	0.25	25	>99
2	 **IV**	 **IVa**	0.25	25	>99
3	 **V**	 **Va,b**	0.25	25	>99
4	 **VI**	 **VIa**	6	60	86

[a] Entries 1−3, 10 mol % cat. loading. Entry 4, 20 mol % (10 mol % required 72 h to produce 85% conversion). [b] Determined by ^{1}H NMR in C_6D_6.

competitive redistribution to **2**, these observations established beyond doubt the viability of the catalytic scheme illustrated by Scheme 1.

Although the bidentate β-diketiminate ligand provides a supporting environment of only moderate kinetic stability,[7b] the facile cyclization of **II** encouraged further evaluation of the scope of the catalytic reactivity of **1** with a range of aminoalkene substrates. These reactions were initially undertaken on an NMR scale and are summarized in Table 1. In contrast to the reaction with substrate **II**, reactions of the geminally substituted 1-aminopent-4-enes **III**−**V** proceeded rapidly at room temperature with no apparent redistribution to the homoleptic species **2**. This is a likely consequence of the increased rate of reaction (a Thorpe−Ingold effect) as well as the increased kinetic stability imparted by the geminal aminoalkene substituents during catalytic turnover. In each case the olefinic species was consumed within 15 min to produce the target 4-substituted 2-methylpyrrolidines, **IIIa** and **IVa**, and the diastereomers **Va**,**b** (entries 1−3 of Table 1).

A number of common features were apparent in all of these reactions (Figures S1−S3). Production of bis(trimethylsilyl)amine was incomplete, and while the relative species ratios were characteristic of the individual reactions, both free and calcium-adducted heterocyclic products could be identified. A minor quantity of the calcium primary amide intermediate (produced by step A of Scheme 1) was also apparent from the observation of a heavily shielded and broadened multiplet at ca. −0.7 ppm in the ^{1}H NMR spectra. These latter resonances are assigned to the proton of the calcium-bound N−H group by comparison to a similar resonance observed in the spectrum of the well-defined calcium primary amide [Ca{(C(Me)N-2,6-^{i}Pr$_2$C$_6$H$_3$CMe)$_2$CH}{μ-NH(CH$_2$)$_2$OMe}]$_2$.[7]

Although the addition of 1-amino-2,2-dimethylhex-1-ene, substrate **VI**, to **1** resulted in the instantaneous appearance of the primary amide intermediate, the desired 6-exo-trig cyclization (entry 4 of Table 1) was too slow to be observed at room temperature. Heating this sample to 60 °C over a 24 h period, however, resulted in catalytic production of 2-methyl-5,5-dimethylpiperidine, **VIa**, the homoleptic compound **2**, and the protonated β-iminoenamine ligand precursor (Figure S4). The catalytic cyclization of substrates **III**, **IV**, **V**, and **VI** also proceeds to ca. 90% conversion in C_6D_6 under the NMR conditions listed in Table 1 with catalyst loadings as low as 2%. Rapid conversion was also observed in the same reactions performed on a preparative scale. The heterocyclic products **IIIa**, **IVa**, **Va**,**b**, and **VIa** were isolated in ca. 70% yield and characterized by comparison of their ^{1}H NMR spectra to literature data (see Supporting Information).

Although the borderline configurational stability of **1** limits accurate evaluation of substrate turnover, the catalytic activities reported herein are broadly commensurate with those achieved recently by Piers and Schafer with the cationic scandium species [Sc{CH(C(^{t}Bu)N-2,6-^{i}Pr$_2$C$_6$H$_3$CMe)$_2$}(CH$_3$){CH$_3$B-(C$_6$F$_5$)$_3$}].[15] The highly electrophilic scandium center of this latter complex, which also features similar β-diketiminato ligation, is formally isoelectronic to the calcium center of **1**. Although the utility of **1** may be limited by its lability to solution exchange equilibria, the low cost and availability of this alkaline earth metal offers potentially significant commercial advantages over group 3 and lanthanide-based methodology. We are continuing to explore the scope of this reactivity and to address the solution lability of the catalytic alkaline earth species.

Acknowledgment. The Royal Society is thanked for a University Research Fellowship (M.S.H.).

Supporting Information Available: Experimental procedures and NMR spectra of catalytic aminoalkene hydroamination reactions (Figures S1−S4). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent general reviews: (a) Togni, G.; Grützmacher, H. *Catalytic Heterofunctionalisation*; VCH: Weinheim, Germany, 2001; p 91. (b) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (c) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (d) Bytschkov, I.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104.
(2) For a recent general overview, see: Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.
(3) Molander, G.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161.
(4) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, 2nd ed.; Butterworth-Heinemann: Oxford, 1997.
(5) (a) Harder, S.; Feil, F.; Weeber, A. *Organometallics* **2001**, *20*, 1044. (b) Harder, S.; Feil F.; Knoll, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4261.
(6) (a) Chisholm, M. H.; Gallucci, J. C.; Phomphrai, K. *Chem. Commun.* **2003**, 48. (b) Chisholm, M. H.; Gallucci, J. C.; Phomphrai, K. *Inorg. Chem.* **2004**, *43*, 6717.
(7) (a) Avent A. G.; Crimmin M. R.; Hill M. S.; Hitchcock P. B. *J. Chem. Soc., Dalton Trans.* **2004**, 3166. (b) Avent A. G.; Crimmin M. R.; Hill M. S.; Hitchcock P. B. *J. Chem. Soc., Dalton Trans.* **2005**, 278.
(8) For example: (a) Bezougli, I. K.; Bashall, A.; McPartlin, M.; Mingos, D. M. P. *J. Chem. Soc., Dalton Trans.* **1998**, 2671. (b) Westerhausen, M.; Schwartz, W. *Z. Naturforsch.* **1992**, *47b*, 453.
(9) Westerhausen, M.; Digeser, M. H.; Nöth, H.; Seifert, T.; Pfitzner, A. *J. Am. Chem. Soc.* **1998**, *120*, 6722.
(10) (a) Burkey, D. J.; Hanusa, T. P. *Organometallics* **1996**, *15*, 4971. (b) Chadwick, S.; Englich, U.; Ruhlandt-Senge, K. *Inorg. Chem.* **1998**, *37*, 4718.
(11) Although both 2-ethylpyrroline and 1-aminohex-4-yne possess the same molecular weight, the former is distinguishable by its first daughter ion. Tehrani, K. A.; Borremans, D.; De Kimpe, N. *Tetrahedron* **1999**, *55*, 4133.
(12) Harder, S. *Organometallics* **2002**, *21*, 3682.
(13) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933.
(14) A small amount of oily material, assumed to be the homoleptic calcium primary amide [Ca{NH(CH$_2$)$_3$CH=CH$_2$}$_2$]$_n$, was also observed to have deposited from solution.
(15) Lauterwasser, F.; Hayes, P. G.; Bräse, S.; Piers, W. E.; Schafer, L. *Organometallics* **2004**, *23*, 2234.

JA043576N