Scandium-Catalyzed Intramolecular Hydroamination. Development of a Highly Active Cationic Catalyst

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Summary: The scandium-catalyzed intramolecular hydroamination of alkynes and alkenes is reported. Complex structure/catalyst activity investigations resulted in the identification of a highly catalytically active cationic, β-diketiminato scandium complex.

Nitrogen heterocycles play a pivotal role in both materials and life sciences. The selective and atom-economic formation of nitrogen heterocycles by catalytic intramolecular hydroamination reactions is a very powerful and efficient method for C−N bond formation.[1] Many recent reports have highlighted the application of group 4 metals for the hydroamination of alkynes,[2] and it is known that for group 4 alkyne hydroamination catalysts, titanium complexes display substantially higher reactivity than their zirconium analogues.[3] However, to date, there have been no reports of neutral group 4 catalysts for the hydroamination of alkenes. It is well established that yttrium and lanthanide cyclopentadienyl complexes are active catalysts for the intramolecular hydroamination of both alkynes and alkenes, as pioneered by Marks and co-workers.[4] More recently, non-cyclopentadienyl yttrium complexes that are also efficient catalysts for these reactions have been reported.[5] While yttrium has been exploited in intramolecular hydroamination, to the best of our knowledge, there have been no comparisons with the group 3 first-row metal scandium. Herein we disclose the catalytic activity of several scandium complexes (Figure 1) for the intramolecular hydroamination of aminoalkynes and -alkenes. These investigations have established that improved coordination sphere accessibility is fundamental for enhanced catalytic activity. Consequently, a rare example[6] of the application of a highly sterically accessible cationic complex for hydroamination catalysis is reported here. Mechanistic investigations using this cationic complex support the formation of the C−N bond via C−C multiple bond insertion into the Sc−N σ-bond, as has been proposed for neutral group 3 hydroamination catalysts.[7]

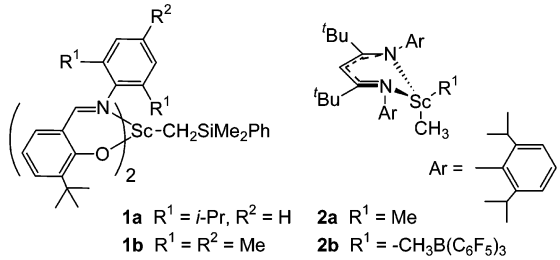

Figure 1. N,O- and N,N-chelating scandium complexes for hydroamination catalysis.

The complexes used for this investigation (Figure 1) were prepared using previously reported methods.[8] The N,O chelating bis(salicylaldiminato) complexes (**1a**,**b**) permit the comparison of compounds with two auxiliary ligands to those with only one, such as N,N-chelating β-diketiminato "Nacnac" compounds (**2a**,**b**). These well-characterized complexes have been explored for their potential application in olefin polymerization.[8b] During these investigations, the observed organometallic reac-

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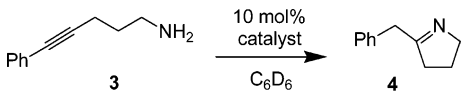
Table 1. Intramolecular Hydroamination of Aminoalkyne



3 4

entry	complex	temp (°C)	time (h)	conversn (%)[a]
1	**1a**	25	2	>95
2	**1b**	25	0.75	>95
3	**2a**	65	2	>90
4	**2b**	25	0.75	>90

[a] Conversions determined by ^{1}H NMR spectroscopy.

tivity trends made them attractive candidates for catalytic hydroamination investigations. Also, examples of N,O-chelating yttrium salicylaldiminato type complexes have been shown to be effective intramolecular hydroamination catalysts,[5b,c] and recently chiral yttrium bis(oxazolinato) complexes have been used for the asymmetric hydroamination of olefins.[5e] These established reactivity patterns for yttrium complexes, in combination with the enhanced reactivity of the first row for group 4 metals, suggest that scandium analogues should be investigated for their catalytic activity.

To compare these catalyst systems with others described in the literature,[9] initial experiments focused on the intramolecular hydroamination of 5-phenyl-4-pentyn-1-amine (**3**) to give the pyrroline **4**, as shown in Table 1. The catalyst activity was monitored by ^{1}H NMR spectroscopy by loading an NMR tube with catalyst and substrate **3**, and if no reaction progress was noted in the initial NMR spectrum obtained, the reaction mixture was heated to 65 °C. The progress of the reaction was monitored by noting the conversion of starting material to product, as observed by the disappearance of the diagnostic triplet at δ 2.45 ppm (C≡CCH_2) and the appearance of the benzylic singlet for the product at δ 3.55 ppm. The results of this experiment showed that all complexes investigated were effective alkyne hydroamination catalysts with near-quantitative conversion of starting materials to product within 2 h. Here, both classes of complexes (bis(ligated) and mono(ligated)) could carry out the reaction efficiently. However, these same complexes were investigated for their potential application to the intermolecular hydroamination of 1-hexyne with alkylamines, and all were found to be ineffective for this transformation.

With the intramolecular alkyne hydroamination established, the more challenging olefin hydroamination analogue was investigated. Initial experiments focused on the scandium bis(salicylaldiminato) complexes **1a**,**b** for the intramolecular hydroamination reaction of 2,2-diphenyl-4-pentenylamine (**5**), as shown in Table 2, entries 1 and 2. The progress of the reaction was monitored using ^{1}H NMR spectroscopy by noting the disappearance of diagnostic alkene signals at δ 5.03 and 5.40 ppm and the appearance of a characteristic multiplet at δ 3.18 ppm that corresponds to the formation of the desired product **6**.[10] The bulky isopropyl-substituted salicylaldiminato complex **1a** did not promote this reaction, even with 10 mol % catalyst loading, but when the steric bulk of the ligand set was reduced, as in **1b**,

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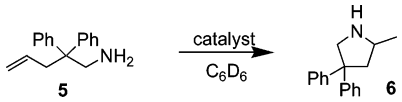
(10) De Kimpe, N.; De Smaele, D.; Hofkens, A.; Dejaegher, Y.; Kesteleyn, B. *Tetrahedron* **1997**, *53*, 10803.

Table 2. Intramolecular Alkene Hydroamination



5 6

entry	complex	temp (°C)	amt (mol %)	time (h)	conversn (%)[a]
1	**1a**	65	10	18	
2	**1b**	65	10	2	>95
3	**2a**	25	10	135	>80
4	**2b**	25	5	2	>95

[a] Conversions determined by ^{1}H NMR spectroscopy.

good catalytic activity was observed. A 10 mol % loading of catalyst **1b** promoted the complete conversion of starting material to product in 2 h. These results demonstrate that bis(salicylaldiminato) scandium alkyls can be used as efficient hydroamination catalysts with a careful choice of ligand. These results also suggest that accessibility to the reactive metal center is an important factor in scandium catalyst design.

Thus, to render the metal even more accessible to the reactive substrates, the previously prepared β-diketiminato (Nacnac) scandium bis(alkyl) complex **2a**[8a] was identified as a good catalyst candidate. Indeed, **2a** catalyzes the formation of **6** even at room temperature, although slowly (Table 2, entry 3). As has been observed in olefin polymerization, it was anticipated that catalytic activity could be further enhanced by generating a highly reactive scandium cation supported by the same Nacnac ligand **2b**.[8b] Synthetic methods for the isolation of group 3 cationic metal complexes have been recently established, and the application of early-metal cationic complexes to catalytic hydroamination is rare.[6b] Here we show that **2b** smoothly catalyzes the transformation of **5** to pyrrolidine product **6** using a 5 mol % catalyst loading in only 2.5 h at room temperature (Table 2, entry 4). The catalyst loading could be further decreased to 2 mol %, thereby prolonging the reaction time to 9 h at room temperature (>95% yield, as determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard). It is also possible to reload the reaction mixture with further quantities of substrate after reaction completion with only a slight loss of activity. This observation is consistent with no significant product inhibition due to unproductive coordination of the resulting secondary amine in the presence of unreacted primary aminoalkene substrate. Furthermore, in a small-scale reaction, pyrrolidine **6** was isolated in 92% yield by using 5 mol % of complex **2b** as a catalyst for 2 h at room temperature.

To better understand the catalytic mechanism of this cationic complex, the same reaction was carried out using a stoichiometric amount of metal catalyst **2b** on an NMR-tube scale using C_6D_5Br as solvent. A solution of substrate **5** was added to a cooled solution of complex **2b**, and the reaction progress was monitored by spectroscopy while the temperature was slowly raised to room temperature. The clean formation of the reactive N-bound heterocycle (Figure 2) was observed and was unambiguously characterized by multinuclear NMR spectroscopy.[11] These spectroscopic results compare favorably with those for previously reported Nacnac Sc−amido complexes.[12] This stoichiometric product is

(11) See the Supporting Information.

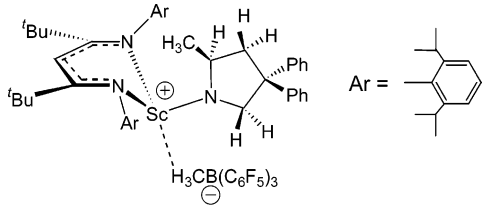
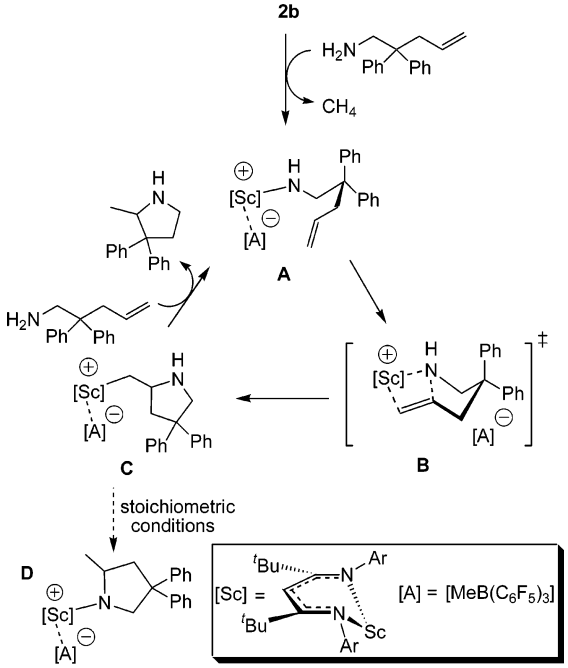


Figure 2. Spectroscopically characterized product of the stoichiometric reaction of **2b** with **5**.

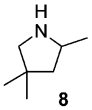
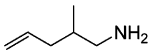
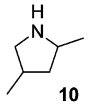
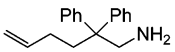
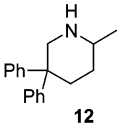
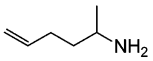
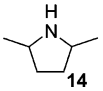
Scheme 1. Proposed Mechanistic Scheme Using the Cationic Scandium Complex[a]



[a] Note that the product of the stoichiometric reaction (**D**) is also a viable hydroamination catalyst.

also consistent with the catalytic mechanism proposed in Scheme 1. The complex **2b**, an associated ion pair, when treated with 1 equiv of aminoalkene, likely generates a transient cationic amido species (**A**) via protonolysis. This highly electron deficient metal center could then coordinate the pendant alkene to give a "chairlike" four-membered transition state (**B**). Olefin insertion into the Sc−N bond would generate a cationic Sc alkyl (**C**) that in the absence of excess substrate likely undergoes an intramolecular proton transfer from the HN in this alkyl complex to give the observed N-bound heterocyclic product (**D**). However, in the presence of excess substrate, it is not clear that intramolecular proton transfer precedes the protonolysis of the scandium alkyl to regenerate the catalytically active cationic Sc−N bond (**A**). The stoichiometric product was shown to be a viable catalyst for intramolecular hydroamination, as addition of excess substrate to cleanly formed **D** resulted in the formation of the desired heterocyclic product. Qualitatively, **D** promotes the conversion of **5** to product **6** at a rate comparable to that for complex **2b**. Furthermore, the N-bound species was notably stable to thermal degradation, such that no decomposition was observed at even 70 °C, unlike the case for the parent complex **2b**, which is known to undergo metallation above −20 °C.

Table 3. Scope of Reactivity with Cationic Complex 2b as a Catalyst

Entry	aminoalkene	product	time [h]	temp. [°C]	yield[a] [%]
1	 **7**	 **8**	24	65	>90
2	 **9**	 **10**	96	65	50
3	 **11**	 **12**	24	65	>90
4	 **13**	 **14**	96	65	--

[a] Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene or *p*-xylene as internal standard.

The high catalytic activity observed for substrate **5** led to a more complete evaluation of the scope of reactivity of the cationic Nacnac complex **2b**. These reactions were carried out on an NMR-tube scale, and product yields were determined using 1,3,5-trimethoxybenzene or *p*-xylene as an internal standard. As seen by contrasting entry 4 of Table 2 and entry 1 of Table 3, the larger phenyl substituents of substrate **5** in comparison to the dimethyl version **7** results in a more dramatic Thorpe−Ingold effect for the intramolecular hydroamination reaction. In the dimethyl case (**7**), the reaction requires heating to 65 °C for 24 h to achieve completion. However, in the absence of the Thorpe−Ingold effect (entry 2) heating at 65 °C for 4 days only promoted a 50% yield of the desired product, demonstrating the importance of the geminal effect to promote the requisite cyclic, chairlike transition state. This was confirmed with the observation of facile formation of the six-membered, geminally substituted piperidine product **12**, as mediated by **2b**. In fact, this piperidine product (**12**) can be prepared in only 4 h at 65 °C with a 10 mol % catalyst loading. However, α-substituted aminoalkenes such as 1-methyl-4-pentenylamine (**13**) are not suitable substrates (entry 4) and no reaction was observed regardless of catalyst loading and reaction temperature. This suggests that the small ionic radius of scandium precludes the possibility of reacting with substrates that generate substantial steric bulk near the reactive metal center.

In summary, we have shown that scandium complexes can be used to mediate selected intramolecular hydroamination reactions. However, the small ionic radius of scandium dominates the reactivity observed for these complexes, such that steric bulk imposed by auxiliary ligands and/or reactive substrates dramatically impact catalytic activity. To further enhance substrate accessibility, the cationic scandium complex **2b** was tested and has been found to be a highly active catalyst for the hydroamination of both aminoalkynes

(12) (a) Basuli, F.; Tomaszewski, J.; Huffman, J. C.; Mindiola, D. J. *Organometallics* **2003**, *22*, 4705. (b) Knight, L. K.; Piers, W. E.; Fleurat-Lessard, P.; Parvez, M.; McDonald, R. *Organometallics* **2004**, *23*, 2087.

and -alkenes, as long as minimal steric bulk is incorporated near the reactive amine group of the substrate. Stoichiometric investigations and preliminary mechanistic studies suggest that this cationic complex mediates hydroamination, as has been previously reported for group 3 and lanthanide metal complexes;[7] this reaction proceeds via olefin insertion into the Sc−N σ-bond formed upon substrate protonolysis of **2b**. Due to the fact that tunable steric bulk was found to be an important factor in catalyst design, the easily modified β-diketiminato type ligand has been identified as a desirable, flexible ligand motif for the development of new highly active, sterically accessible hydroamination catalysts. In particular, new analogues with yttrium, having a larger coordination sphere, are currently being investigated.

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Supporting Information Available: Text and figures giving full experimental details for all experiments and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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