Intramolecular alkene hydroaminations catalyzed by a bis(thiophosphinic amidate) Zr(IV) complex†

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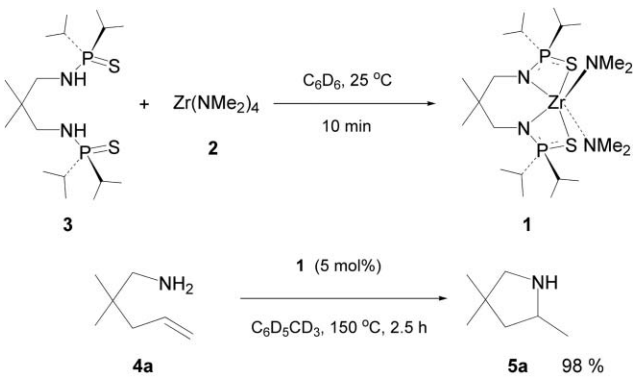
A neutral Zr(IV) complex has been shown to be an effective precatalyst for intramolecular alkene hydroaminations that provide cyclic amines in good to excellent yields.

The intramolecular hydroamination of alkenes constitutes a powerful method for the synthesis of azacycles.[1] The seminal group 3 metallocenes developed by Marks and co-workers[2] have recently been joined by a variety of non-metallocene complexes of the group 3 metals as catalysts for this important reaction.[3,4] Although there are numerous accounts that describe both the intra- and intermolecular hydroamination of alkynes[5a–d] and allenes[5e,f] catalyzed by various complexes of the group 4 metals, there have been very few reports of intramolecular alkene hydroaminations mediated by complexes of metals belonging to this triad, and all but one[6] of these are restricted to cationic species.[7] We have previously disclosed that chelating bis(thiophosphinic amidate) "NPS" complexes of the group 3 metals (particularly Y and Nd) are potent catalysts for intramolecular alkene hydroamination.[3d] In this communication, we show that the neutral Zr(IV) bis(thiophosphinic amidate) complex (**1**) is a competent precatalyst for the cyclization of representative primary aminoalkenes (Scheme 1).



Scheme 1

The internal hydroamination of 2,2-dimethylpent-4-ene-1-amine (**4a**) was selected for initial examination as it was expected that cyclization of this substrate would be facilitated by a geminal Thorpe–Ingold effect.[3f,6] Successful generation of the desired NPS precatalyst **1** proved experimentally straightforward *via* amine elimination, involving commercially available $Zr(NMe_2)_4$ (**2**) and bis(thiophosphinic amide) (**3**)[3d] (1 equiv., C_6D_6, 25 °C, 10 min). The ^1H, ^{31}P and ^{13}C NMR spectra of **1** are consistent with a monomeric species possessing an octahedral structure with a *mer* configuration. The NMe_2 resonance (500 MHz) appears as a sharp singlet at 3.11 ppm and the linker CH_2 as a doublet (2.69 ppm, $J = 10$ Hz). The signal for the CH adjacent to P appears as a well-defined septet centered at 2.00 ppm ($J = 7$ Hz), with the diastereomeric isopropyl methyls appearing as a set of doublets between 1.16 and 1.10 ppm ($J = 7$ Hz). The ^{31}P NMR spectrum of **1** reveals a singlet at 75.10 ppm.[8] The thermal stability of **1** was demonstrated by heating at 150 °C for 19 h, whereupon no alteration to the NMR spectra was observed. Addition of **4a** to **1** (5 mol%), followed by heating at 100 °C, provided the pyrrolidine **5a** in 97% yield[9] after 105 h. Alternatively, cyclization of **4a** at 120 °C (C_6D_6) and 150 °C (toluene-d_8) provided **5a** in 94% (12 h) and 98% (2.5 h) yield, respectively. Closely-related reaction conditions were subsequently utilized for the cyclization of a series of representative primary amines **4b–f** and, unsuccessfully, for the secondary amine **4g**. A compilation of the reaction times and yields observed for the cyclization of aminoalkenes **4a–g** in the presence of the Zr(IV)·NPS chelate (**1**) appears in Table 1. Significantly, cyclization of **4a**, **4b** and **4d** on a preparative (3 mmol) scale followed by separation of the products from the catalyst by vacuum transfer and protonation (HCl–MeOH), furnished **5a**, **5b** and **5d** as their hydrochloride salts in 90, 88 and 85% isolated yields, respectively.

Several of the trends that emerge from the foregoing examples are worthy of comment. The presence of geminal Thorpe–Ingold buttressing is helpful but not a prerequisite for successful cyclization, as 5-hexen-2-amine **4b** and 4-penten-1-amine **4c** partake in the reaction. Accordingly, **4c** was smoothly converted to **5c** in 91% yield in the presence of **1** (10 mol%) in 10 h at 150 °C. By way of comparison, cyclization of **4c** using $Zr(NMe_2)_4$ as the precatalyst (10 mol%, 150 °C, toluene-d_8) gave **5c** (91%) but required 28 h. In addition, the styrenyl substrate **4d**, containing an internal alkene, underwent cyclization at 150 °C to provide **5d** in 93% yield after 120 h. In this instance, the reaction time could be shortened to 39 h when 10 mol% of the precatalyst was employed. A similar result was observed in the case of the 1,1-disubstituted aminoalkene **4f**. That the latter substrate undergoes cyclization to give the product derived from exocyclic addition to the alkene is consistent with the mechanism shown in Scheme 2. It is also of significance that the secondary

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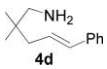
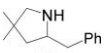
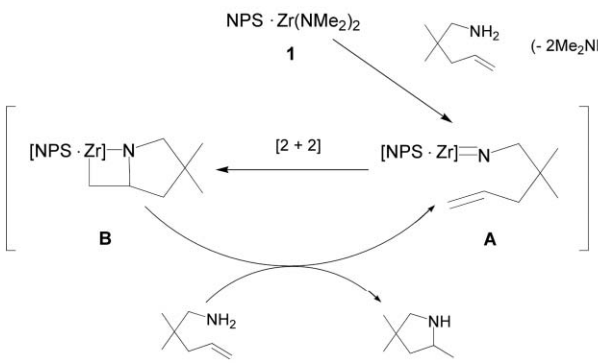
Table 1 Internal alkene hydroaminations catalyzed by **1**[a]

Entry	Substrate	Product	Temp./°C	Time/h	Yield (%)[b]
1	 **4a**	 **5a**	120 150	12 2.5	94 98
2	 **4b**	 **5b**	120 150	172 22	98[c] 96[c]
3	 **4c**	 **5c**	120[d] 150[d]	41 10	89 91
4	 **4d**	 **5d**	150 150[d]	120 39	93 91
5	 **4e**	 **5e**	120 150	9 1	99 99
6	 **4f**	 **5f**	150 150[d]	104 45	92 94
7	 **4g**	 **5g**	150	18	0

[a] Benzene-d_6 (120 °C) or toluene-d_8 (150 °C) were used as solvents, respectively. [b] NMR yields based on *p*-xylene as an internal standard. [c] *trans* : *cis* = 1.3 : 1.0. [d] 10 mol% Catalyst was used.



Scheme 2

aminoalkene **4g** is resistant to cyclization. This stands in sharp contrast to the results of Scott and Hultzsch who have reported that secondary, but not primary, aminoalkenes participate in internal hydroamination, catalyzed by cationic Zr(IV) complexes.[7a,b] Finally, the Zr(IV)·NPS complex **1** shows higher activity as a precatalyst than $Zr(NMe_2)_4$ **2**.

The dynamics of the hydroamination involving precatalyst **1** can be conveniently monitored by ^{31}P NMR. Addition of **4a** to a C_6D_6 solution of **1** (5 mol%) results in the immediate disappearance of the phosphorus resonance at 75.10 ppm and the concomitant appearance of a new signal at 78.12 ppm. That this is accompanied by the production of 2 equiv. of Me_2NH (^1H NMR) is strongly indicative of a quantitative exchange of the amido ligands at zirconium, resulting in the incorporation of two substrate aminoalkene substituents. Significantly, cyclization of **4a** at 120 °C over 12 h results in a 92% conversion to **5a** with no change to the ^{31}P resonance at 78.12 ppm, thus providing evidence that the Zr catalyst is robust under the reaction conditions. In addition, at no time during this reaction did the ^{31}P resonance associated with the free proligand **3** at 89.54 ppm appear. A probable mechanistic pathway for the intramolecular hydroamination of **4a**, involving the putative Zr(IV) imido complex **A**[10] and azazirconacyclobutane **B** based on these observations, is depicted in Scheme 2.

In conclusion, we have shown that the neutral Zr(IV)·NPS complex (**1**) is a competent precatalyst for intramolecular alkene hydroaminations involving primary amines. Although the catalytic activity of **1** is lower than that exhibited by the corresponding Y(III)·NPS chelate,[3d] the results presented here are among the first examples of internal alkene hydroamination catalyzed by a neutral complex of a group 4 metal.[6] Studies utilizing cationic Zr(IV)·NPS and related complexes for this process are currently under way.

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