ORGANIC
LETTERS

2005
Vol. 7, No. 20
4391−4393

Chelating Diamide Based Rate Enhancement of Intramolecular Alkene Hydroaminations Catalyzed by a Neutral Sc(III) Complex

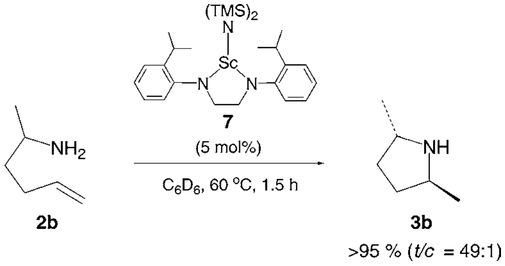
Joon Young Kim and Tom Livinghouse*

Department of Chemistry, Montana State University, Bozeman, Montana 59717

livinghouse@chemistry.montana.edu

Received July 5, 2005

ABSTRACT



Neutral scandium amido complexes are viable catalysts for intramolecular alkene hydroamination. Catalytic activity is strongly coupled to the electronic character of the Sc(III) ligand environment with chelating diamide coordination providing a precatalyst possessing substantially improved activity and superb distereoselectivity in the synthesis of *trans*-2,5-disubstituted pyrrolidines.

The intramolecular hydroamination of unsaturated C−C linkages constitutes a powerful and atom-economic method for the synthesis of nitrogenous heterocycles.[1] The seminal group 3 metallocenes developed by Marks and co-workers[2] have recently been joined by a variety of nonmetallocene complexes of the group 3 metals as catalysts for the important variation of this reaction involving alkenes as addends.[3,4] Complexes derived from yttrium and the lanthanides have been employed as catalysts in most cases involving the internal hydroamination of alkenes involving early metals.[4,5]

By virtue of the comparatively small covalent radius of Sc(III), complexes derived from this metal would be expected to exhibit enhanced stereoselectivities in C−N bond formation, should active catalysts be identified. It is therefore of interest that only one report has appeared describing Sc(III) catalysts for alkene hydroamination and, additionally, that these are cationic rather than neutral complexes.[6] We have previously disclosed that chelating diamide and bis(thio-

---

(1) (a) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (b) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. For hydroaminations catalyzed by late transition metals, see: Vogels, C. M.; Hayes, P. G.; Shaver, M. P.; Westcott, S. A. *J. Chem. Soc., Chem. Commun.* **2000**, 51. Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.

(2) (a) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *39*, 673 and references therein. (b) Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *J. Org. Chem.* **2004**, *69*, 1038. (c) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275. (d) Tian, S.; Arredondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 4421. (e) Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *Org. Lett.* **2001**, *3*, 3091. (f) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633 and references therein.

(3) (a) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584. (b) O'Shaughnessy, P. N.; Knight, P. D.; Morton, C.; Gillespie, K. M.; Scott, P. *Chem. Commun.* **2003**, 1770. (c) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F.; Wagner, T. *Organometallics* **2004**, *23*, 2601. (d) Kim, Y. K.; Livinghouse, T.; Horino, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9560. (e) Kim, Y. K.; Livinghouse, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3645. (f) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933. (g) Gribkov, D. V.; Hulzsch, K. C.; Hampel, F. *Chem. Eur. J.* **2003**, *9*, 4796.

(4) Catalytic activity has also been observed for the following. (a) Simple Ti(IV) amides: Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Shafer, L. L. *Org. Lett.* **2005**, *7*, 1959. (b) A neutral Zr(IV)•NPS complex: Kim, H.; Lee, P. H.; Livinghouse, T. *J. Chem. Soc. Chem. Commun.* **2005**, in press. (c) And calcium complexes: Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am Chem. Soc.* **2005**, *127*, 2042.

(5) For the use of cationic Zr(IV) complexes, see: (a) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894. (b) Gribkov, D. V.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5542.

10.1021/ol051574h CCC: $30.25

phosphinic amidate) complexes of the group 3 metals (particularly Y and Nd) are potent catalysts for intramolecular alkene hydroamination.[3d−f] In this communication we show that neutral complexes of Sc(III) are competent catalysts for this transformation and that the activity of these species is strongly coupled to the electronic characteristics of the ligand environment surrounding Sc.

The internal hydroamination of 2,2-dimethylpent-4-ene-1-amine (**2a**) was selected for initial examination as it was expected that cyclization of this substrate would be facilitated by the Thorpe−Ingold effect.[3f] As in our previous studies,[3d−f] the simple amide $Sc[N(TMS)_2]_3$ (**1**)[7] was first probed for catalytic activity. In contrast to $Y[N(TMS)_2]_3$ and $Nd[N(TMS)_2]_3$, which led to the conversion of **2a** to the pyrrolidine **3a** in 6 and 4 h, respectively, at 24 °C [$M[N(TMS)_2]_3$ (5 mol %), C_6D_6], the use of **1** (5 mol %) required *3 h at 120 °C*. We have previously shown that bis(thiophosphinic amidate) "NPS" complexes of metals belonging to groups 3[3d] and 4[4b] possess dramatically enhanced catalytic activities for intramolecular alkene hydroamination. Successful generation of the desired NPS precatalyst **5** proved experimentally straightforward via amine elimination involving **1** and bis(thiophosphinic amide) **4**[3d] [1 equiv, C_6D_6, 75 °C, 1 h]. To our initial disappointment, **5** proved inferior in catalytic activity to **1** in that cyclization of **2a** to **3a** (>95%, 5 mol % **5**) required fully 36 h at 120 °C. In light of the pronounced activity decrease observed from **1** to **5** and the increase in ionization enthalpies known for metals in the series Sc < Y < La, we predicted that rate acceleration could be achieved by coordination of the electron-deficient Sc(III) center within a strongly electron-donating ligand environment. To this end, the chelated diamide **7** was generated by amine elimination involving **1** and diamine **6** [1 equiv, C_6D_6, 120 °C, 1 h].[3e] Significantly, cyclization of **2a** to **3a** (>95%) in the presence of **7** (5 mol %) required only 2.5 h at 60 °C (Scheme 1). It should be strongly emphasized that we have not observed rate differences of this magnitude between complexes of the chelating diamide and bis(thiophosphinic amidate) varieties for the metals Y, Nd, and La.[3d−f]

Scheme 1

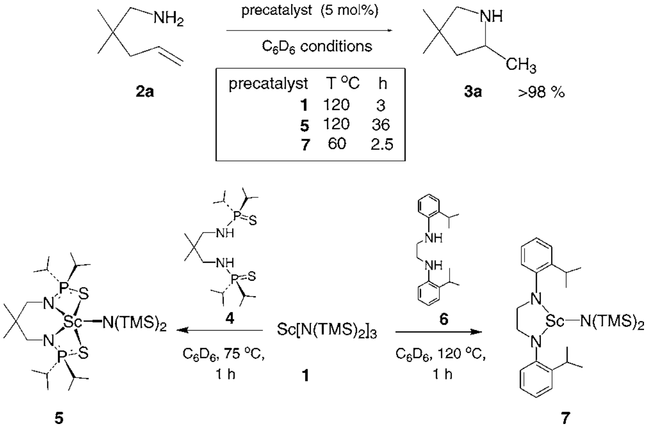
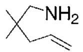
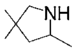
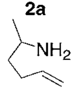
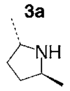
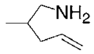
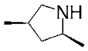
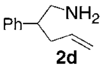
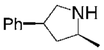
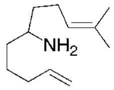
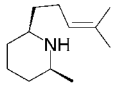


Table 1. Internal Alkene Hydroaminations Catalyzed by **7**

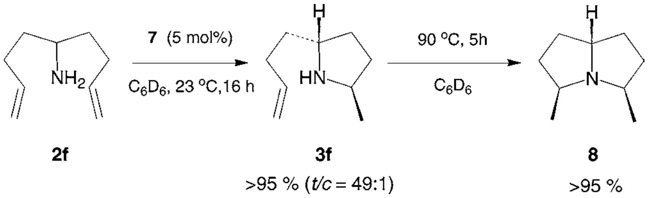
	substrate	product	temp. (°C)	time (h)	% yield[a]
1	 **2a**	 **3a**	60	2.5	>95
2	 **2b**	 **3b**	60	1.5	>95 (*t*/*c* = 49:1)
3	 **2c**	 **3c**	120	84	>95 (*t*/*c* =1:1.6)
4	 **2d**	 **3d**	120	72	>95 (*t*/*c* =1:2.1)
5	 **2e**	 **3e**	60	18	>95 (*t*/*c* =1:6)

[a] Yield (^1H NMR) based on *p*-xylene as the internal standard.

Closely related reaction conditions were subsequently utilized for the cyclization of a series of representative primary amines **2b**−**e**. Reaction times and yields obtained employing the Sc(III)-chelated diamide **7** are compiled in Table 1.[8] It is of preparative interest that cyclization of **2b** on a 3 mmol scale followed by separation of the products from the catalyst by vacuum transfer and protonation (6 M HCl in Et_2O) furnished **3b** as its hydrochloride salt in 98% isolated yield.

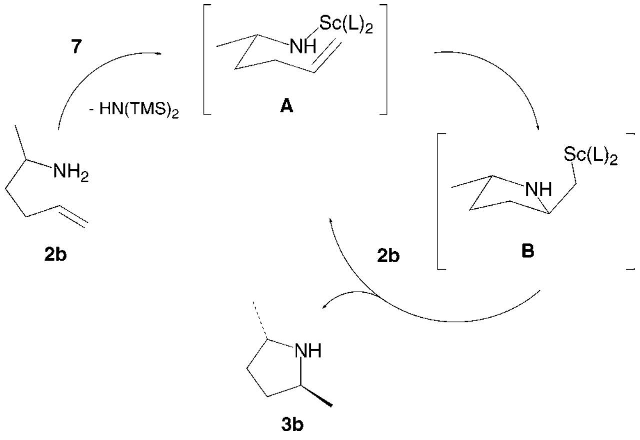
Several of the trends that emerge from the foregoing examples are worthy of comment. The presence of Thorpe−Ingold buttressing is helpful but not a prerequisite for successful cyclization. This stands in contrast to the results of Piers, Shafer, and co-workers who have reported that **2c** is only incompletely converted (50%) to **3c** in the presence of a cationic Sc(III) catalyst.[6] It is also of significance that **2b**, which is inert toward the Piers' Sc catalyst, undergoes efficient conversion with superb diastereoselectivity [49:1 (GC)] in the presence of **7**. The unsymmetrical aminodiene **2e** undergoes chemoselective cyclization involving the monosubstituted alkene to afford the piperidines **3e** albeit with moderate (*cis*/*trans* = 6:1) selectivity. In addition, the aminodiene **2f** undergoes selective monocyclization (22 °C, 16 h) [dr = 49:1 (GC of the tosylamides)] to give **3f** and ultimately stereospecific bicyclization of the *trans*-isomer to the pyrrolizidine **8** [>95%, 90 °C, 5 h, (Scheme 2)].

Scheme 2



A probable mechanistic pathway for the intramolecular hydroamination of **2b** involving the putative amido complex

Scheme 3



A and Sc(III) alkyl **B** based on these observations is depicted in Scheme 3.[9]

In conclusion, we have shown that the neutral Sc(III)-chelated diamide complex **7** is an effective precatalyst for intramolecular alkene hydroaminations involving primary and secondary amines. Although the catalytic activity of **7** is lower than that exhibited by the corresponding Y(III) or Nd(III) diamide chelates,[3e] the enhanced diastereoselectivities obtained for the cyclizations of 1-substituted-4-pentenylamines are considerably higher.

Acknowledgment. Generous financial support for this research was provided by the National Institutes of Health.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051574H

---

(6) Lauterwasser, F.; Hayes, P. G.; Brase, S.; Piers, W.; Schafer, L. L. *Organometallics* **2004**, *23*, 2234.

(7) Bradley, D. C.; Ghotra, J. S.; Hart, F. A. *J. Chem. Soc. Dalton. Trans.* **1973**, 1021.

(8) For all reactions conducted on <3-mmol scale, yields were determined by ^{1}H NMR using *p*-xylene as the internal standard.-

(9) A similar mechanism has been proposed in connection with intramolecular alkene hydroaminations catalyzed by metallocene complexes of the lanthanides.[2c]