ORGANIC LETTERS

2003
Vol. 5, No. 24
4733−4736

Anti-Markovnikov Intermolecular Hydroamination: A Bis(amidate) Titanium Precatalyst for the Preparation of Reactive Aldimines

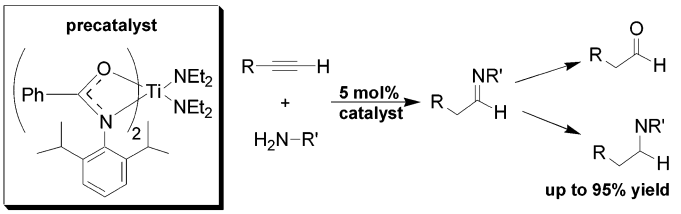
Zhe Zhang and Laurel L. Schafer*

The Department of Chemistry, The University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1

schafer@chem.ubc.ca

Received September 30, 2003

ABSTRACT



A bulky bis(*N*-2′,6′-di*iso*propylphenyl(phenyl)-amidate)titanium-bis(diethylamido) complex was identified as a highly active and regioselective precatalyst for the anti-Markovnikov hydroamination of a wide range of terminal alkyl alkynes with alkylamines. This titanium complex was fully characterized, including its X-ray crystal structure. The reactive aldimine products generated have been further elaborated using one-pot procedures to give substituted amines, aldehydes, and the isoquinoline framework.

The catalytic addition of N−H across a carbon−carbon multiple bond is a synthetically important transformation for the preparation of amines and imines. Imines are versatile building blocks for organic synthesis, as they are used to prepare substituted amines and can function as masked carbonyl substituents. The hydroamination of alkynes results in the direct formation of imines with no side products. While the development of catalytic methods for the hydroamination of internal alkynes has been intensely investigated,[1] the regioselective hydroamination of terminal alkynes remains an important synthetic challenge.[2] In particular, selective anti-Markovnikov hydroamination of terminal alkynes to give aldimine products is an attractive synthetic target, as aldimines are useful reactive intermediates that can undergo further synthetic elaboration.[3] The only previous report of highly anti-Markovnikov selective hydroamination of alkynes was limited to the use of bulky *tert*-butylamine as a substrate.[2a] Here we describe the development of a new bis(amidate)titanium precatalyst that displays high activity and regioselectivity for the anti-Markovnikov hydroamination of terminal alkyl alkynes with a wide range of alkylamines. Furthermore, this easily prepared catalyst is tolerant of a wide range of functional groups, making it generally applicable for the synthesis of complex nitrogen-containing products.

Cyclopentadienyl complexes of Ti and Zr have been shown to effectively catalyze the intermolecular hydroamination of alkynes with primary amines.[4] However, the development of a flexible catalyst system that takes advan-

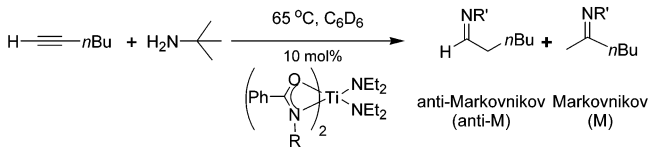
(1) For recent reviews see: (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Novis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (c) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795. (d) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (e) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935. (f) Roesky, P. W.; Muller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708.

(2) (a) Tillack, A.; Castro, I. G.; Hartung, C. G.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541. (b) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2001**, 4411. (c) Cao, C.; Ciszewski, J. T.; Odom, A. T. *Organometallics* **2001**, *20*, 5011. (d) Haskel, T.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017.

(3) Castro, C. G.; Tillack, A.; Hartung, C. G.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 3217 and references therein.

10.1021/ol0359214 CCC: $25.00
Published on Web 10/22/2003

Table 1. Intermolecular Hydroamination with Tunable Bis(amidate)titanium−Bis(amido) Precatalysts

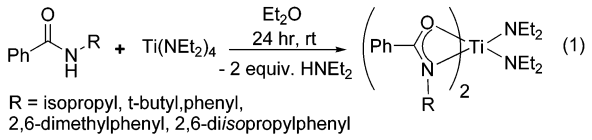


entry	R	t (h)	% yield (anti-Markovnikov/Markovnikov)[a]
1	*i*Pr	24	no reaction
2	*t*Bu	24	71 (5:1)
3	Ph	24	55 (99:1)
4	2,6-dimethylphenyl	10	78 (>99:1)
5	2,6-di*iso*propylphenyl	6	82 (>99:1)

[a] Yields were determined by ^{1}H NMR with an internal standard (1,3,5-trimethoxybenzene). Ratio confirmed by GCMS after hydrolysis.

tage of the low cost and high reactivity of the group 4 metals while providing enhanced and selective reactivity remains an area of intense investigation.[5] Inspired by the work of Beller and co-workers, who reported titanium-catalyzed anti-Markovnikov hydroamination with bulky amine substrates,[2a] we sought to develop a flexible catalyst system based on readily available amidate ligands to afford easily prepared complexes with broadly applicable reactivity.

Organic amides are attractive proligands, as they have an easily modified structure that allows for variable steric and electronic properties in the resultant complexes. Surprisingly, amidates have been rarely employed as auxiliary ligands in transition metal chemistry.[6] We are investigating this easily varied N,O chelating ligand as a flexible scaffold for the preparation of highly selective and reactive catalysts. Previously we reported that varying the electronic properties of the amidate ligand while maintaining consistent steric properties could dramatically modify reactivity.[7] However, these preliminary catalyst systems had limited substrate tolerance. Here we probe the effect of the steric environment about the reactive metal center by changing the substituents on the N of the amidate ligand. In particular, the catalyst identified gives unprecedented anti-Markovnikov selectivity for a wide range of substrates with various steric properties and functional groups. The reactive aldimine products generated have been further elaborated using one-pot procedures to give substituted amines, aldehydes, and a more complex structural motif, the isoquinoline framework.



(1)

The precatalysts described here were prepared by the reaction of 2 equiv of amide with 1 equiv of $Ti(NEt_2)_4$ in anhydrous ether, followed by removal of all volatiles to give a red microcrystalline solid (eq 1). These crude materials were used in a preliminary screen to identify the most active precatalyst for the hydroamination of 1-hexyne with *tert*-butylamine (Table 1). These reactions were carried out on NMR tube scale at 65 °C for up to 24 h. The reaction progress was monitored by ^{1}H NMR spectroscopy by observing the disappearance of the terminal alkyne proton at 2.1 ppm and the appearance of the diagnostic signals for the aldimine anti-Markovnikov product (triplet at 7.5 ppm) and the ketimine Markovnikov product (singlet at 1.9 ppm).

As shown in Table 1, the easily modified amide proligand permits the preparation of complexes displaying tunable relative reactivity. The bulkiest substituent is the most effective, with the 2,6-di*iso*propylphenyl derivative (entry 5, complex **1**) resulting in the highest yields and lowest reaction times. Most importantly, the most active precatalyst was also highly regioselective with only the anti-Markovnikov product being observed.

Complex **1** was recrystallized from benzene and was fully characterized, including X-ray crystallographic analysis (Figure 1). The bis(amidate)titanium complex is C_2 symmetric, with the N atoms of the amidate ligands being trans to each other, while the amide ligands are in a cis orientation. The crystalline precatalyst has catalytic behavior identical to that of the bulk material; thus, the easily isolated crude product was used for all catalytic investigations.

Consistent with previously reported mechanistic investigations for titanium catalyzed hydroamination,[9] we propose titanium-imido species as the catalytically active complexes. This is supported by the observation that the bis(amidate)

(4) (a) Walsh, P. J.; Baranger, A.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708. (b) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389. (c) Pohlki, F.; Heutling, A.; Bytschkov, I.; Hotopp, T.; Doye, S. *Synlett* **2002**, 799.

(5) (a) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956. (b) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chem. Commun.* **2003**, 586. (c) Ong, T.-G.; Yap, G. A. P.; Richeson, D. S. *Organometallics* **2002**, *21*, 2839.

(6) Giesbrecht, G. R.; Shafir, A.; Arnold, J. *Inorg. Chem.* **2001**, *40*, 6069.

(7) Li, C.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun*. **2003**, 2562.

(8) See Supporting Information for relevant bond lengths and angles.

(9) (a) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923. (b) Pohlki, F.; Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2305. (c) Fairfax, D.; Stein, M.; Livinghouse, T.; Jensen, M. *Organometallics* **1997**, *16*, 1523.

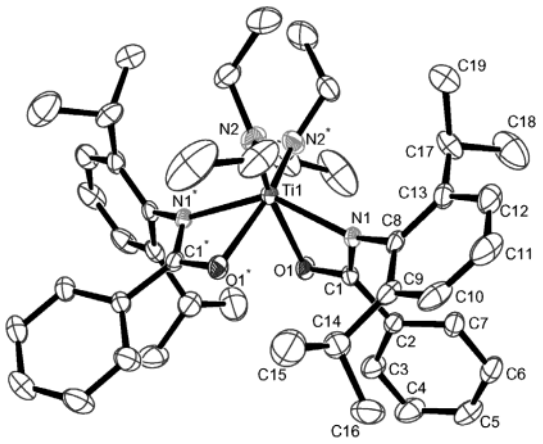
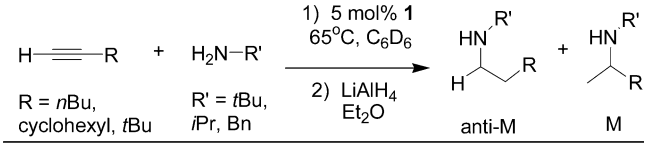


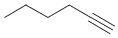
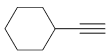
Figure 1. ORTEP plot of the structure of bis(amidate)titanium−bis(amido) complex **1** at 50% ellipsoids.[8]

precatalyst is effective with a variety of primary amines as substrates while secondary amines resulted in no detectable hydroamination products.[10]

To probe the scope of catalysis, a selection of alkynes and amines with differing steric bulk were screened (Table 2).

Table 2. Hydroamination of Terminal Alkynes with Various Amines



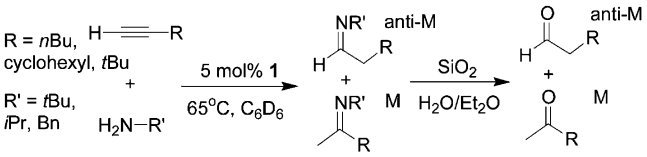
entry	alkyne	R'	t (h)	yield (%)[a] (anti-M/M)
1		*t*Bu	6	82 (>49:1)
2		*i*Pr	24	88 (>49:1)
3		Bn	24	88 (>49:1)
4		*t*Bu	72	72 (>49:1)
5		*i*Pr	24	89 (>49:1)
6		Bn	24	87 (>49:1)
7		*i*Pr	120	82[b] (>49:1)
8		Bn	120	95 (>49:1)

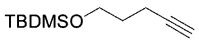
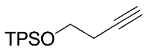
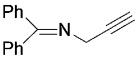
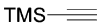
[a] Isolated yields. ^{1}H NMR spectroscopy used to determine ratios of regioisomers. [b] Yields determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

In this case, the reaction was carried out on small scale with benzene as a solvent. The resulting imine mixture was diluted with ether and reduced with LAH to give the corresponding amine products. With complex **1**, we observe only the anti-Markovnikov product with isopropylamine (entry 2) and even the least sterically demanding substrate combination, benzylamine with 1-hexyne (entry 3), resulted in the isolation of the amine due to anti-Markovnikov hydroamination. This is in contrast to the previous report of anti-Markovnikov-selective titanium catalysts, which require bulky *tert*-butylamine to induce selectivity.[2a] Complex **1** can also tolerate more sterically demanding substrates such as cyclohexyl- and *t*-butylalkynes (entries 4−8); however, these reactions do require prolonged reaction times.

To further test this catalyst system, the compatibility of various functional groups with these reaction conditions was investigated (Table 3). Reactions with alkynes containing

Table 3. Intermolecular Hydroamination of Functionalized Terminal Alkynes to Give Imines that Can Be Hydrolyzed to Carbonyl Derivatives



entry	alkyne	R'	yield (%) (anti-M:M)
1		*i*Pr	94 (>99:1)[a]
2		Bn	76 (>99:1)[a]
3		*i*Pr	92 (>99:1)[a]
4		Bn	76 (>99:1)[a]
5		*t*Bu	99 (>99:1)[b]
6		*i*Pr	92 (>99:1)[b]
7		*t*Bu	78(>99:1)[b]
8		*i*Pr	90(>99:1)[b]

[a] Isolated yield of hydrolysis products. [b] NMR yield of imine product using 1,3,5-trimethoxybenzene as internal standard.

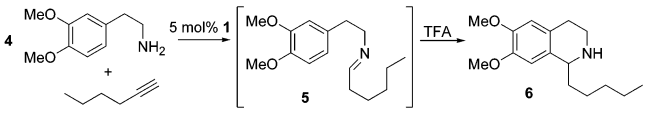
protected alcohols were carried out on small scale, and the yields were determined for the resulting carbonyl-containing hydrolysis products. Although reactions with protected propargyl alcohol led to catalyst decomposition, productive and selective reactivity was observed when the carbon chain was extended by one or two carbons (entries 1−4). Interestingly, propargylic amine, protected as the imine, was a reactive substrate as observed by NMR spectroscopy. This shows that protected primary amines can be incorporated at even the most challenging positions within the substrate (entries 5, 6). Also, in contrast to previously reported results for titanium catalysts,[2b] precatalyst **1** can affect the hydroamination of trimethylsilylacetylene, with excellent yields being obtained within 24 h (entries 7, 8). Furthermore, as observed by ^{1}H NMR spectroscopy, there were no diagnostic signals in the olefinic region for the N-silylated eneamine product, as has been observed with lanthanide- and actinide-mediated hydroamination of silylated acetylenes.[2d,11]

The results summarized in Tables 2 and 3 demonstrate consistent regioselective hydroamination for a range of

(10) Not detected by NMR spectroscopy or GCMS.

(11) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770.

Scheme 1. One-Pot Preparation of the Isoquinoline Framework



substrates with variable steric bulk and functional group incorporation. Consequently, precatalyst **1** was identified as a suitable candidate for application in the synthesis of more complex target molecules. Here, a novel hydroamination route for the total synthesis of isoquinolines is achieved by using a modified Pictet−Spengler reaction (Scheme 1).[12] This one-pot synthesis of the isoquinoline framework avoids the use of a carbonyl-containing substrate and instead regioselective hydroamination with amine **4** gives the reactive aldimine intermediate **5**. Subsequent acid-catalyzed cyclization results in the formation of the corresponding isoquinoline product **6** in 95% yield as a colorless oil.[13]

(12) (a) Menachery, M. D.; Lavanier, G. L.; Wetherly, M. L.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 745. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

(13) Gremmen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **2001**, *42*, 8885.

In summary, five bis(amidate)titanium-bis(amido) complexes were screened and it was shown that the bulky bis(amidate) complex **1** is an effective precatalyst for anti-Markovnikov regioselective, intermolecular hydroamination of terminal alkyl alkynes with alkylamines. With this precatalyst, secondary, tertiary, and quaternary alkyl-substituted primary amines can be coupled with a range of terminal alkynes to give exclusively the anti-Markovnikov aldimine product. These reactive aldimine products can be further elaborated to amines, aldehydes, or the isoquinoline framework using efficient one-pot procedures. Mechanistic investigations and further elaboration of the amidate ligand to vary reactivity and selectivity in both intra- and intermolecular hydroamination of C−C multiple bonds are ongoing, and results will be reported in due course.

Acknowledgment. The authors thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and UBC for financial support.

Supporting Information Available: Crystallographic data for **1** (CIF) and experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0359214