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Communications

$Ti(NMe_2)_4$ as a Precatalyst for Hydroamination of Alkynes with Primary Amines

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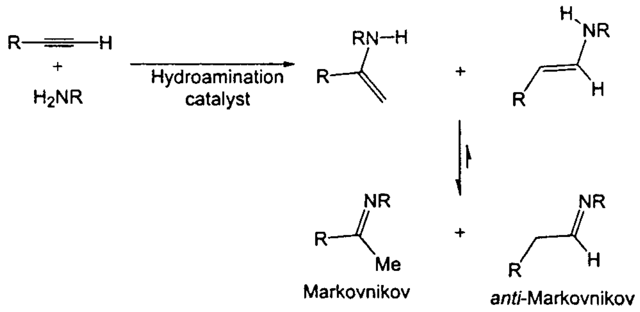
Summary: Hydroaminations of carbon−carbon triple bonds with primary amines are catalyzed with commercially available $Ti(NMe_2)_4$. The reaction is surprisingly fast with many substrates and often selective for the Markovnikov product with terminal alkynes. The scope of the catalysis was investigated with a variety of amines and alkynes; arylamines and 1-hexyne were found to be especially good substrates.

Formation of new carbon−nitrogen linkages through the hydroamination of carbon−carbon multiple bonds[1] is a reaction of great promise for both specialty and bulk chemical synthesis. Catalysts for the reaction may be alkali[2] metals, early[3] transition metals (TM), late[4] TM, actinides,[5] or lanthanides.[6] Early metal systems have been dominated by metallocene-based titanium and zirconium precatalysts, which Bergman and co-workers[3e] have convincingly shown to involve imido intermediates.[7] Generally, these group-4 metallocene precatalysts lead to *anti*-Markovnikov addition to alkynes.[3] Conversely, many late TM catalysts favor Markovnikov products[1,4] (Scheme 1).

Scheme 1. Possible Imine Products from Terminal Alkyne Hydroamination



In this report, we demonstrate that early TM-catalyzed hydroamination of alkynes is not limited to metallocene- or even Cp-based systems. In addition, we find that the regiochemical outcome of the reaction may be dramatically altered by utilizing different ligands.

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(1) A recent review: Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703.

(2) Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917−1926.

(3) (a) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, ASAP. (b) Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* **2000**, *2*, 1935−1937. (c) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389−3391. (d) Siebeneicher, H.; Doye, S. *J. Prak. Chem.−Chem. Ztg.* **2000**, *342*, 102−106. (e) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485−11589. (f) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719.

(4) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547. (b) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222−3225. (c) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E.; Zapf, A. *J. Organomet. Chem.* **1998**, *566*, 277−285.

(5) Straub, T.; Frank, W.; Reiss, G. J.; Eisen, M. S. *J. Chem. Soc., Dalton Trans.* **1996**, 2541−2546.

(6) (a) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515−6517. (b) Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771. (c) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306. (d) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306.

(7) For metallocene-based systems, terminal imines are almost certainly the active species reacting with alkyne. We currently have no evidence for such a species in our system. However, it should be noted that $Ti(NMe_2)_4$ is known to produce isolable bridging imido complexes on reaction with primary amines. Thorn, D. L.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 357−363. Excess of amine present under our conditions may support monomeric imido species for reaction with alkynes.

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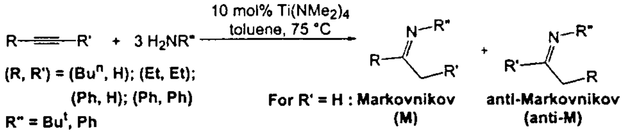
Apparently, a large number of titanium complexes may catalyze alkyne hydroamination.[8] Here we discuss reactions that utilize $Ti(NMe_2)_4$[9] as the precatalyst.

Most reactions were carried out with 10 mol % of $Ti(NMe_2)_4$, but amounts as low as 1 mol % have been used. The reactions were carried out in toluene solvent. Reaction temperatures as high as 125 °C have been utilized; however, most reactions in a 75 °C oil bath proceed at a reasonable rate. Reactions with some substrate combinations, e.g., 1-hexyne and aniline, exhibit product formation a few minutes after mixing at room temperature. Most reactions were carried out with 3 equiv of amine and 1 equiv of alkyne. Catalyzed reactions with 1 equiv of amine to 1 equiv of alkyne can proceed to give reasonable yields with somewhat slower rates.[10]

To probe the scope of the reaction, two electronically different amines were chosen (H_2NPh and H_2NBu^t) and reacted[11] with four different alkynes (1-hexyne, 3-hexyne, phenylacetylene, and diphenylacetylene). The results are shown in Table 1. The Markovnikov product is the favored or exclusive product of hydroaminating terminal alkynes. This is in contrast to utilizing Me_2TiCp_2 as the precatalyst, which yields *anti*-Markovnikov products.[3e,c] In addition, aniline generally gives better yields and faster rates.

The noticeably lower yield in the case of phenylacetylene hydroamination with aniline is attributable to side reactions that consume the phenylacetylene. In the phenylacetylene reaction, a few percent of a byproduct that has a mass (GC/MS) consistent with $H_2C{=}C(NMe_2)(Ph)$ is produced.[12] In addition, we have shown that the reaction mixture stops at a yield of 37% due to consumption of all available alkyne. Addition of a second equivalent of phenylacetylene to the stopped catalysis results in generation of an additional 28% of imine. Our current data suggest that phenylacetylene may undergo 1,2-insertion into the Ti−N bond to form a new organometallic complex. If the insertion occurs with the $Ti(NMe_2)_4$ precatalyst, protonation of the Ti−C bond should yield the observed enamine byproduct.[13] Alternatively, phenylacetylene may insert into the Ti−C bond to give oligomers of phenylacetylene.

Table 1. Hydroamination of Alkynes with H_2NBu^t and H_2NPh^a



amine	alkyne	time (h)	yield (M:anti-M)^b
$PhNH_2$	$Bu^nC{\equiv}CH$	2	90 (3:1)
	$EtC{\equiv}CEt$	17	87
	$PhC{\equiv}CH$	2	37 (>100:1)
	$PhC{\equiv}CPh$	57	92
Bu^tNH_2	$Bu^nC{\equiv}CH$	48	0
	$EtC{\equiv}CEt$	48	0
	$PhC{\equiv}CH$	10	16 (>100:1)
	$PhC{\equiv}CPh$	48	0

[a] Results utilizing 10 mol % $Ti(NMe_2)_4$ in toluene solution at 75 °C. Yields are by GC versus dodecane internal standard and are for the corresponding ketones or aldehydes after hydrolysis with 10% HCl or silica gel. However, the yields of $Bu^tN{=}C(Me)Ph$ and $PhN{=}C(Me)Ph$ were found by observation of the imine product. Reactions were allowed to run until all of the alkyne was consumed or generation of product ceased. Times are not minimized. [b] Ratio of the Markovnikov and *anti*-Markovnikov products after hydrolysis by GC.

The polymerization side reaction was probed by heating 50 equiv of phenylacetylene[14] or 1-hexyne with $Ti(NMe_2)_4$ in toluene at 75 °C. Both reactions produced oligomers and/or polymers, which were isolated and characterized by gel permeation chromatography (GPC). A wide range of chain lengths was observed consistent with a relatively slow initiation process followed by rapid chain growth.

Some preliminary attempts to reduce the amount of polyacetylene produced met with little success. In one experiment, phenylacetylene was added slowly to a solution of toluene, aniline, and catalyst. However, a yield similar to reactions run with 1 equiv of phenylacetylene present at the start of the reaction (29%) was obtained. In addition, catalytic or stoichiometric amounts of anilinium triflate resulted in no change in yield or reduction in the yield, respectively.

To further probe the scope of the catalysis, a larger selection of amines was screened in reactions with

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[8] Cao, C.; Shi, Y.; Ciszewski, J. T.; Odom, A. L. Manuscripts in preparation.

[9] $Ti(NMe_2)_4$ used in this study was prepared by modification of the literature procedure: Bradley, D. C.; Thomas, I. M. *J. Chem. Soc.* **1960**, 3859. However, $Ti(NMe_2)_4$ purchased from Strem Chemical, Co. gave comparable results.

[10] In one example, a mixture of 1 equiv of aniline, 1 equiv of 1-hexyne, 10 mol % $Ti(NMe_2)_4$, and 1 equiv of dodecane (internal standard) in toluene was heated to 75 °C. The concentration of aniline was 1/3 that used in the reactions of Tables 1 and 2. All other concentrations are the same. Time to reach the maximum yield of 68% (4:1, Markovnikov:*anti*-Markovnikov) was <4 h.

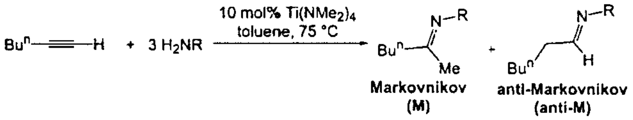
[11] General procedure for hydroaminations listed in Tables 1 and 2: All manipulations of the solutions were done in an MBraun glovebox under an atmosphere of dry nitrogen. In a 5 mL volumetric flask was loaded $Ti(NMe_2)_4$ (0.2 M solution in toluene, 0.10 equiv, 1 mL), amine (3 equiv, 6 mmol), dodecane (1 equiv, 2 mmol, 454 mL), and alkyne (1 equiv, 2 mmol). The solution was diluted to 5 mL and transferred to a pressure tube. A stirbar was added to the pressure tube, which was then fitted with a Teflon stopper. The tube was heated with stirring at 75 °C. Progress was typically checked every ~2 h. Reactions were run until no alkyne was detected or production of product ceased as determined by GC analysis. In the case of pentafluoroaniline, the reaction was allowed to run for 96 h; alkyne still was present in the reaction mixture. Most of the yields are of the ketones and aldehydes produced on subsequent hydrolysis of the imine. This was done by stirring the imine solutions with an equal volume of 10% HCl. The organic solution was collected, and the aqueous solution was washed with 3 × 5 mL of CH_2Cl_2. The organics were analyzed by GC. In the case of $PhN{=}C(Me)Ph$ and $Bu^tN{=}C(Me)Ph$, the imines were prepared and standardized. Consequently, the yields of imines from the reactions of phenylacetylene and aniline or *tert*-butylamine are from direct observation of the imines in the GC. For silica gel hydrolysis procedure, see ref 3c.

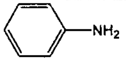
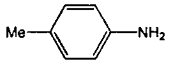
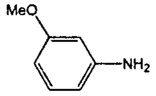
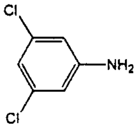
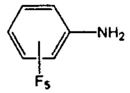
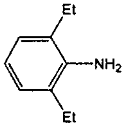
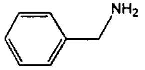
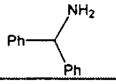
[12] The isomeric form was confirmed by comparison of GC retention times with an authentic sample. The authentic sample was prepared from acetophenone and $Ti(NMe_2)_4$, which was identical by ^1H NMR to the reported isomer. Camps, F.; Coll, J.; Messeguer, A.; Periacas, M. A.; Ricart, S. *Synthesis* **1979**, 126−127.

[13] Attempts to produce $H_2C{=}C(NEt_2)(Ph)$ from reaction of the product $PhC({=}NPh)Me$ with 1 equiv of $HNEt_2$ in the presence of $Ti(NMe_2)_4$ under similar reaction conditions for 16 h resulted in recovery of only the imine and no enamine. In addition, $Ti(NMe_2)_4$ reacts with 1 equiv of phenylacetylene followed by hydrolysis to give measurable amounts of the enamine byproduct $H_2C{=}C(NMe_2)(Ph)$.

[14] Reaction of phenylacetylene and $Ti(NMe_2)_4$: All manipulations of solutions were done in an MBraun glovebox under an atmosphere of dry nitrogen. Into a pressure tube equipped with a stir bar was loaded toluene (5 mL), phenyl acetylene (50 equiv, 25 mmol, 2.505 mL), and $Ti(NMe_2)_4$ (1 equiv, 0.5 mmol, 0.1121 g). The reaction was heated at 75 °C with stirring for 48 h. Additional toluene (10 mL) was added to the solution, which was washed with 3 × 5 mL of H_2O. Volatiles were removed in vacuo at 60 °C. The final product was a red solid soluble in toluene and THF. GPC analysis of the product revealed molecular weights for the polymers produced were as high as 34 000 (n = 333) with smaller chains apparent. A similar reaction with 1-hexyne gave oligomers of undetermined lengths.

Table 2. Hydroamination of 1-Hexyne with the Amines[a]



Amines (H_2NR)	Time (h)	Yield (M : anti-M)[b]
	2	90 (3 : 1)
	2	87 (4 : 1)
	2	93 (6 : 1)
	2	82 (40 : 1)
	2	72 (23 : 1)
	96	75 (37 : 1)
	2	57 (9 : 1)
	8	17 (5 : 1)
	8	17 (5 : 1)

[a] Reactions were carried out with 10 mol % $Ti(NMe_2)_4$ in toluene solution at 75 °C. Yields are by GC versus dodecane internal standard. Yields were obtained after hydrolysis and are for 2-hexanone and hexanal. Reactions were allowed to run until all of the alkyne was consumed, and times are not minimized. [b] Ratio of the Markovnikov and *anti*-Markovnikov products after hydrolysis by GC.

1-hexyne. The results are given in Table 2. Again, the Markovnikov product is highly favored. In the presence of $Ti(NMe_2)_4$, most arylamines hydroaminate 1-hexyne in >70% yield in less than 2 h.

Some interesting functional group tolerances were noticed. Qualitatively, the reactions seem to proceed more quickly with electron-donating groups on the arylamine. Methoxy substituents are tolerated unless *ortho* with respect to the amine functionality. Hydroamination attempts utilizing *p*-nitroaniline did not result in imine products. However 3,5-dichloroaniline can be used to hydroaminate 1-hexyne in good yield. A sterically hindered amine, 2,6-diethylaniline, hydroaminated 1-hexyne in moderate yield in less than 2 h.

The reaction of highly fluorinated arenes with ketones to produce imines can require high temperatures (150−220 °C)[15] that may be incompatible with some reactants. Hydroamination of 1-hexyne with pentafluoroaniline in the presence of catalytic amounts of $Ti(NMe_2)_4$ was slow relative to more electron-rich arylamines but did proceed at 75 °C, affording a 75% yield of the imine product.

Unfortunately, $Ti(NMe_2)_4$ is not an effective precatalyst for benzylamine and benzhydrylamine hydroamination of 1-hexyne under the conditions employed. Most of the alkyne is consumed, indicating that the hydroamination is less competitive with polymerization for benzylic amines than for arylamines. In addition, the catalyses involving benzylic amine substrates suffer from other side reactions, as indicated by the four or more products observed by GC.

The $Ti(NMe_2)_4$ precatalyst has a few advantages as compared with metallocene-based systems; it is relatively inexpensive from commercial sources[9] and more stable than Me_2TiCp_2.[3d] The reaction may prove practical considering the speed with which some terminal alkynes are hydroaminated with arylamines.

Commercially available $Ti(NMe_2)_4$ offers a Markovnikov-selective precatalyst for the hydroamination of some alkynes. Utilizing different ancillary ligands (e.g., alkoxide, pyrrolyl, etc.), we hope to lower the polymerization rate relative to hydroamination. We are currently exploring a number of other non-metallocene-based systems[8] for hydroamination activity with some success; these include $Ti(NMe_2)_2(dpma)$,[16] where dpma is di(pyrrolyl-α-methyl)methylamine. In studying these, we hope to discover the combination of steric and electronic factors that contribute to an efficient hydroamination catalyst system.

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(15) (a) Matsui, M.; Fukuyasu, K.; Shibata, K.; Muramatsu, H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1107−1110. (b) Brooke, G. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 821−825.

(16) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2001**, *40*, 1987−1988.