Hydroamination of Alkynes Catalyzed by a Titanium Pyrrolyl Complex

Changsheng Cao, James T. Ciszewski, and Aaron L. Odom*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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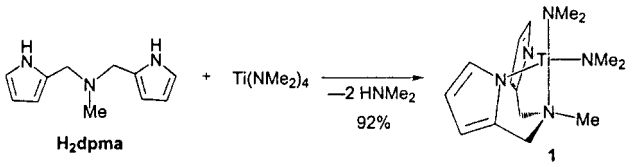
Summary: The readily prepared pyrrolyl complex Ti(NMe$_2$)$_2$(dpma), where dpma is di(pyrrolyl-α-methyl)methylamine, is an effective precatalyst for the hydroamination of alkynes by primary amines. The catalysis is Markovnikov-selective and rapid with terminal alkynes.

Hydroamination of alkynes with primary amines is a reaction of perfect atom economy[1] for the synthesis of imines.[2,3] The majority of early-transition-metal,[4] lanthanide,[5] and actinide[6] complexes that have been reported to catalyze hydroamination processes have cyclopentadienyl-derived ancillary ligands. Other ancillary ligands and ancillary ligand effects outside of Cp-based[7] systems have remained less explored.[8] While titanium Cp complexes[4a−g] have been extensively examined and found to be anti-Markovnikov selective catalysts, little is known about the effects on reactivity and regioselectivity of greatly altering the ancillary ligands.

Scheme 1. Synthesis of Ti(NMe$_2$)$_2$(dpma) (1)



We have been investigating catalyses involving pyrrolyl complexes of early transition metals, especially with di(pyrrolyl-α-methyl)methylamine (H$_2$dpma). Readily prepared H$_2$dpma is available in a single step from a Mannich reaction between 2 equiv of pyrrole, 2 equiv of formaldehyde, and 1 equiv of methylamine hydrochloride.[9] Here, we report results on a non-Cp-based precatalyst for alkyne hydroamination, Ti(NMe$_2$)$_2$(dpma)[10] (**1**), which is prepared from Ti(NMe$_2$)$_4$[11] and H$_2$dpma in near-quantitative yield (Scheme 1).[12]

Recently, we described the use of Ti(NMe$_2$)$_4$ (**2**) as a precatalyst for the hydroamination of alkynes (ratio of Markovnikov: *anti*-Markovnikov products varied from 3:1 to >50:1 with substrates examined).[13] Evaluation of **2** is a necessary first step in the study of ancillary ligand effects in titanium-catalyzed hydroamination. Because **2** contains only ligands that will readily be exchanged under the conditions of the catalysis, its reactivity is an invaluable comparison for determining ancillary ligand participation.

Initially, we investigated the reaction of aniline or cyclohexylamine with a selection of alkynes (diphenylacetylene, phenylacetylene, 1-phenylpropyne, 1-hexyne, and 3-hexyne; Scheme 2) catalyzed by 10 mol % of **1**.[14] The results are found in Table 1.[15] For comparison purposes, all reactions were carried out at 75 °C. However, in some cases significantly better yields and lower reaction times are afforded by higher temperatures. In general, terminal alkynes react much more quickly than internal alkynes. Aniline reacted much faster and was more regiochemically selective than cyclohexylamine. Curiously, the major product from

(1) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

(2) For recent reviews: Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E.; Zapf, A. *J. Organomet. Chem.* **1998**, *566*, 277−285. (b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199−207.

(3) For some leading examples of late-transition-metal-catalyzed hydroamination, see: (a) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570−4571. (b) Weber, L.; Barlmeyer, M.; Quasdorff, J.-M.; Sievers, H. L.; Stammler, H.-G.; Neumann, B. *Organometallics* **1999**, *18*, 2497−2504. (c) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222−3223. (d) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170−183. (e) Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. *Chem. Eur. J.* **2000**, *6*, 2513−2522. (f) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87−90. (g) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547.

(4) Early-metal examples include: (a) Pohlki, F.; Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2305−2308. (b) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923−2924. (c) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933−2935. (d) Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* **2000**, *2*, 1935−1937. (e) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389−3391. (f) Siebeneicher, H.; Doye, S. *J. Prak. Chem.-Chem. Ztg.* **2000**, *342*, 102−106. (g) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485−11589. (h) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719. (i) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753−2763.

(5) For leading examples of Ln-catalyzed hydroamination, see: (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771. (b) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515−6517. (c) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771. (d) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770−3772.

(6) (a) Haskel, A.; Straub, T.; Eisen, M. S. *Organometallics* **1996**, *15*, 3773−3775. (b) Straub, T.; Frank, W.; Reiss, G. J.; Eisen, M. S. *J. Chem. Soc., Dalton Trans.* **1996**, 2541−2546.

(7) For ancillary ligand effects within Cp-based systems, see: (a) Tian, S.; Arrendondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568−2570. (b) Roesky, P. W.; Stern, C. L.; Marks, T. J. *Organometallics* **1997**, *16*, 4705−4711. See also ref 3a,b.

(8) For use of hexamethyldisilazide lanthanide complexes in hydroamination catalysis, see: (a) Bürgstein, M. R.; Berberich, H.; Roesky, P. W *Chem. Eur. J.* **2001**, *7*, 3078−3085. For (aminotroponiminate)yttrium amido hydroamination catalysis, see: (b) Bürgstein, M. R.; Berberich, H.; Roesky, P. W. *Organometallics* **1998**, *17*, 1452−1454.

(9) Raines, S.; Kovacs, C. A. *J. Heterocycl. Chem.* **1970**, *7*, 223.

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Scheme 2. Major Product in the Hydroamination of Terminal Alkynes Utilizing $Ti(NMe_2)_2$(dpma) as Precatalyst

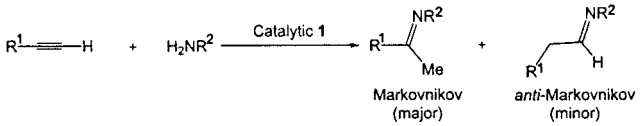
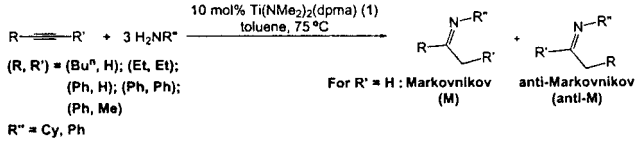


Table 1. Reactions of Aniline and Cyclohexylamine with Alkynes Catalyzed by $Ti(NMe_2)_2$(dpma) (1)



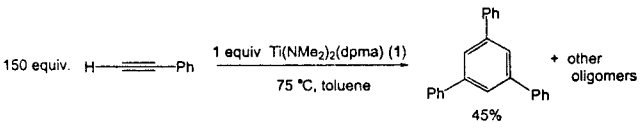
amine	alkyne	time (h)[a]	yield at 75 °C [130 °C] (M:anti-M)[b]
aniline	$Bu^nC{\equiv}CH$	6	90 (>50:1)
	EtC≡CEt	72	63
	PhC≡CH	8	26 (>50:1)
	PhC≡CPh	72 [74]	31 [99]
	PhC≡CMe	144 [24]	99 (1:24) [96 (1:19)][c]
cyclohexylamine	$Bu^nC{\equiv}CH$	72	73 (2:1)
	EtC≡CEt	72 [24]	3 [57]
	PhC≡CH	72	10 (>50:1)
	PhC≡CPh	72 [24]	0 [70]
	PhC≡CMe	95 [29]	trace [99 (1:4)][c]

[a] Results of reactions carried out at 130 °C are shown in brackets. [b] Ratio of Markovnikov to anti-Markovnikov products. [c] Major product is an imine of phenylacetone (Ph is β to nitrogen).

hydroamination of 1-phenylpropyne has the nitrogen attachment β to the phenyl group and hydrolysis yields mostly phenylacetone; this is the only case investigated thus far where catalysis by **1** or Me_2TiCp_2[4e] gave the same product from an unsymmetrical alkyne.[16]

Comparison of $Ti(NMe_2)_2$(dpma) (**1**) and $Ti(NMe_2)_4$ (**2**) as hydroamination catalysts leads to several conclusions. First, the active species in the reactions are not the same. One potential complication of ancillary ligand studies in any catalytic system involves the loss of the ancillary ligand under the reaction conditions. Since in **2** all the ligands should exchange with the amine reactant, this gives us the baseline necessary to evaluate if dpma remains coordinated throughout the catalysis.

Scheme 3. Reaction of Catalytic Quantities of $Ti(NMe_2)_2$(dpma) (1) with Phenylacetylene[a]



[a] The reaction yields 1,3,5-triphenylbenzene in 45% purified yield along with other oligomers.

Because the regioselectivity of the reactions catalyzed by **1** and **2** are quite different, we conclude that a dpma-containing species is participating in the catalysis. For example, hydroamination of 1-hexyne by aniline using **2** gives 3:1 Markovnikov to anti-Markovnikov product. The same substrates under the same conditions utilizing **1** as the catalyst gives >50:1 Markovnikov product. Second, dpma containing **1** is a much more generally applicable catalyst and yields products with a larger variety of substrates. Alkylamines were largely unsuccessful substrates utilizing **2** as catalyst but can give excellent yields when **1** is the catalyst. Third, the pyrrolyl complex generally gives higher selectivities for Markovnikov products than **2**.

Some of the catalyses were slow at 75 °C, giving low conversions after days of reaction time. In general, hydroaminations involving internal alkynes were prohibitively slow with cyclohexylamine. Carrying out these reactions at higher temperature (130 °C) often gave high yields of products after reasonable reaction times (<30 h). The yields at this higher temperature are displayed in brackets in Table 1.

Catalyses involving titanium dpma complexes suffer from polymerization/oligomerization of the alkyne in the case of phenylacetylene. With the other substituted acetylenes, polymerization was not observed. By analyzing reaction mixtures, we found that a number of different oligomers of phenylacetylene were present. To probe the side reaction, we treated an excess of phenylacetylene (150 equiv) with 1 equiv of $Ti(NMe_2)_2$(dpma) (**1**) in toluene at 75 °C[17] (Scheme 3). Several different oligomers were separable by column chromatography; however, the major product was 1,3,5-triphenylacetylene, which was isolated in 45% purified yield.[18]

We further probed the utility and regioselectivity of the catalyst through the hydroamination of 1-hexyne by a number of different amines (Table 2). In all cases, the Markovnikov product is favored, often in excess of 50:1, over the anti-Markovnikov product.

Amines containing nitro or *o*-methoxy groups lead to no hydroamination products. However, *m*-anisidine or

(14) Procedure for hydroaminations found in Tables 1 and 2: all manipulations of the solutions were done in a glovebox under an atmosphere of dry nitrogen. In a 5 mL volumetric flask was loaded $Ti(NMe_2)_2$(dpma) (0.2 M solution in toluene, 0.2 mmol, 1 mL), amine (6 mmol, 3 equiv), dodecane (454 μL, 2 mmol, 1 equiv), and alkyne (2 mmol, 1 equiv). The solution was diluted to 5 mL with toluene and transferred to a pressure tube. A stirbar was added, and the tube was fitted with a Teflon stopper. The tube was removed from the drybox and heated in an oil bath. Reactions were run until no alkyne was detected or production of product ceased as determined by GC analysis. Most yields are of ketones and aldehydes produced by hydrolysis of imine. This was done by stirring the imine solution with an equal volume of 10% HCl. The product was extracted with CH_2Cl_2 (3 × 5 mL) and analyzed by GC. Yields are versus dodecane internal standard. In the case of PhN=C(Me)Ph, CyN=C(Me)Ph, and Bu^tN=C(Me)Ph, the imines were prepared and yields obtained directly versus dodecane internal standard.

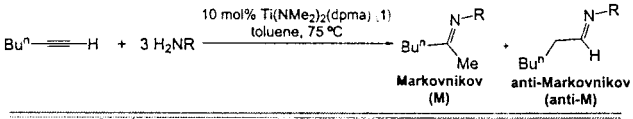
(15) A 1% yield of either product can readily be observed by GC. In cases where only one product is observed, we conservatively estimate the selectivity as 50:1.

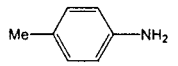
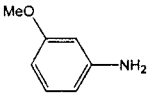
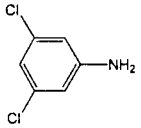
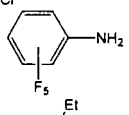
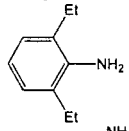
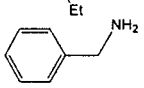
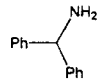
(16) A possible explanation for the selectivities in this reaction involves synthesis of a metallocyclobutane intermediate due to a 1,3-hydrogen shift. Trösch, D. J. M.; Collier, P. E.; Bashall, A.; Gade, L. H.; McPartlin, M.; Mountford, P.; Radojevic, S. *Organometallics* **2001**, *20*, 3308−3313.

(17) Reaction of excess phenylacetylene with $Ti(NMe_2)_2$(dpma): in an inert-atmosphere drybox, a 250 mL round-bottom flask was loaded with a stirbar, toluene (30 mL), phenylacetylene (8.237 g, 75 mmol), and $Ti(NMe_2)_2$(dpma) (0.1616 g, 0.5 mmol). The tube was fitted with a stopper and removed from the box. The reaction mixture was heated to 75 °C with stirring for 5 days. The toluene was removed under reduced pressure, and the resulting solid was purified by column chromatography utilizing silica gel (4.5 × 40 cm) and 2:1 hexanes/CH_2Cl_2. The first band contained the majority of the material and was determined to be 1,3,5-triphenylbenzene by ^1H NMR, ^{13}C NMR, and mass spectrometry. The reaction yielded 3.5 g (46%) of purified compound.

(18) For other early-transition-metal cyclotrimerizations of alkynes, see: (a) Strickler, J. R.; Bruck, M. A.; Wigley, D. E. *J. Am. Chem. Soc.* **1990**, *112*, 2814−2816. (b) Smith, D. P.; Strickler, J. R.; Gray, S. D.; Bruck, M. A.; Holmes, R. S.; Wigley, D. E. *Organometallics* **1992**, *11*, 1275−1288. (c) Hartung, J. B.; Pedersen, S. F. *Organometallics* **1990**, *9*, 1414−1417.

Table 2. Reaction of 1-Hexyne with Primary Amines Catalyzed by $Ti(NMe_2)_2(dpma)$ (1)



Amines (H_2NR)	Time (h)[a]	Yield (M : anti-M)[b]
	6	94 (>50 : 1)
	6	99 (>50 : 1)
	6	83 (>50 : 1)
	6	78 (>50 : 1)
	72	51 (>50 : 1)[c]
	9	99 (13 : 1)
	48	71 (>50 : 1)
	26	89 (3 : 1)

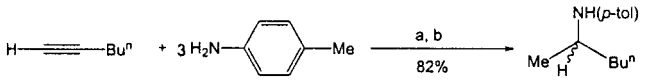
[a] Times are for consumption of available alkyne and are not minimized. [b] Ratio of Markovnikov to anti-Markovnikov products. [c] This reaction was carried out to 60% conversion at 75 °C. At 130 °C, the reaction was complete after 16 h and gave 61% yield.

p-anisidine hydroaminated 1-hexyne with high regioselectivities and yields. Many other functional groups were tolerated, including halogenated anilines.

Steric effects are not dominant for the amine substrates tested. For example, 2,6-diethylaniline and aniline hydroaminated 1-hexyne with comparable rates. However, large electronic effects were observed. Reaction rates involving very electron-deficient arenes, such as 2,3,4,5,6-pentafluoroaniline, are greatly diminished.

As mentioned earlier for cyclohexylamine, alkylamines generally give slower rates of hydroamination relative to arylamines. However, the hydroamination of 1-hexyne with benzylamine or benzhydrylamine proceeded in 70−90% yield and was complete in <48 h at 75 °C. While benzhydrylamine exhibits poor regioselectivity, with the Markovnikov product being favored only 3:1, benzylamine gives very high Markovnikov selectivity. These results are in marked contrast to catalysis with $Ti(NMe_2)_4$, where both benzylamine and benzhydrylamine reactions with 1-hexyne displayed poor yields

Scheme 4. Reaction of 1-Hexyne and *p*-Toluidine[a]



[a] The reaction was carried out on a 5 g scale of alkyne. The yield is for the distilled product after two steps: (a) 2 mol % $Ti(NMe_2)_2(dpma)$, toluene, 75 °C; (b) excess $LiAlH_4$ in refluxing THF.

and selectivities under the same conditions. In addition, titanium with Cp as ancillary ligand is a poor catalyst for hydroaminations involving benzylamine but was successful with benzhydrylamine.[4d]

One reaction in Table 2 was investigated on a larger scale (Scheme 4)[19] using 2 mol % of **1**. The catalyzed reaction of *p*-toluidine with 1-hexyne was carried out on a 5 g scale of the alkyne. Subsequent reduction[20] with excess $LiAlH_4$ gave racemic $MeCH[NH(p\text{-tol})]Bu^n$ in 82% (9.4 g) yield, which had ^1H NMR resonances consistent with literature[21] values.

The titanium dimethylamido complex **1** provides a new paradigm for ancillary ligands that support early transition metal catalyzed hydroamination. Relative to titanocene, the change in ancillary ligand leads to quite different regioselectivities for most substrates. Using **1** as the precatalyst gives highly Markovnikov-selective hydroamination of terminal alkynes. The catalysis is most rapid for conversion of terminal alkynes to imines utilizing arylamines. However, alkylamines and internal alkynes can give high yields of useful products under the appropriate conditions.

Acknowledgment. We wish to thank Michigan State University for financial support.

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(19) Procedure for hydroamination of 1-hexyne with *p*-toluidine followed by reduction: in an inert-atmosphere drybox, a 250 mL flask was loaded with a stirbar, *p*-toluidine (12.86 g, 120 mmol), 1-hexyne (4.93 g, 60 mmol), toluene (50 mL), and $Ti(NMe_2)_2(dpma)$ (0.388 g, 1.2 mmol). The flask was sealed, removed from the drybox, and heated to 75 °C with stirring. The reaction mixture was heated for 28 h, and then additional *p*-toluidine (6.43 g, 60 mmol) was added, followed by heating for 37 h. Most of the toluene was removed in vacuo, and 80 mL of dry THF was added to the solution. The flask was cooled in an ice−water bath, and $LiAlH_4$ (6 g, 158 mmol) was added slowly. The reaction was refluxed for 61 h under N_2. The flask was cooled to room temperature, and $NaHCO_3$ (30 g) was added, followed by stirring for 5 min. The mixture was filtered, and the solids were washed with ether (3 × 50 mL). The solution was washed with 70 mL of water. The aqueous layer was extracted with ether (3 × 30 mL), and all the organic solutions were combined. The solution was dried with Na_2SO_4, and the solvent was removed in vacuo. To the residue was added 50 mL of pentane. Cooling to −25 °C caused *p*-toluidine to crystallize, which was removed by filtration. The product was distilled (65−67 °C, 0.25 mmHg) to give pure 9.4 g (82%) of 2-(*p*-tolylamino)hexane.

(20) For a few examples of catalytic asymmetric hydrogenation of imines, see: (a) Sablong, R., Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4937−4940. (b) Shnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887−892. (c) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952−8965. (d) Obora, Y.; Ohta, T.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1997**, *119*, 3745−3755.

(21) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron* **1986**, *42*, 1145−1155.