$TiCl_4$-Catalyzed Intermolecular Hydroamination Reactions

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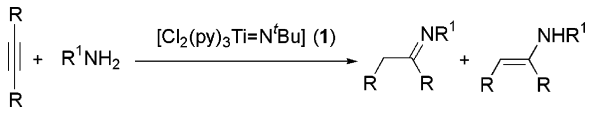
Summary: A user-friendly procedure for intermolecular hydroamination reactions is presented which employs inexpensive and readily available $TiCl_4$. Through addition of $^tBuNH_2$, a novel catalytic system is generated which enables the efficient conversion of aminoallenes, as well as variously substituted internal and terminal alkynes.

The addition of an N−H bond across a carbon−carbon multiple bond is one of the most efficient methods for the synthesis of substituted amines and imines, which represent important bulk chemicals and building blocks for organic synthesis.[1] While considerable effort has been expended in the search for new methodologies for this transformation,[2] general solutions for the problem have proven elusive. Consequently, the development of protocols for hydroamination reactions remains an important goal.

On the basis of the finding that intermolecular hydroamination reactions of alkynes and allenes can be catalyzed by bis(amido)zirconocene complexes,[3] analogous titanium-initiated transformations were developed. The original catalyst design focused on Cp-based motifs, as for $[Cp_2TiMe_2]$,[4a] $[Cp^*_2TiMe_2]$,[4b] $[Cp(NHAr)(py)Ti{=}NAr]$,[5] and $[Cp_2Ti(alkyne)]$.[6] More recently, Odom et al. applied titanium tetrakis(amido) complexes,[7] and Richeson reported the use of a guanidinate-supported titanium imide.[8] Despite the efficiency achieved using such complexes, a methodology that utilizes inexpensive bulk chemicals and avoids stoichiometric amounts of strong bases in the generation of the operating catalysts would be desirable. Herein, a widely applicable protocol for intermolecular hydroamination reactions is described which achieves these goals via the in situ generation of the catalytically active species from inexpensive $TiCl_4$ and $^tBuNH_2$.

Table 1. Intermolecular Hydroamination Using the Imido Complex 1[a]



entry	R	R^1	*T*/°C	*t*/h	yield/%[b]
1	Ph	Ph	105	24	22[c]
2	Ph	Ph	105	24	94
3	Ph	2,6-$Me_2C_6H_3$	135	13	64
4	Ph	2,6-$Me_2C_6H_3$	135	24	55[d]
5	Ph	^{t}Bu	135	16	−
6	Et	Ph	105	16	76

[a] Conditions: alkyne (1.2 equiv), amine (1.0 equiv), and **1** (10 mol %) in $CDCl_3$. [b] By ^1H NMR versus 1,3,5-$(MeO)_3C_6H_3$ as internal standard. [c] Tolan (1.0 equiv), aniline (3.0 equiv). [d] In C_6D_6.

Early studies showed that the imido complex $[Cl_2(py)_3Ti{=}N^tBu]$ (**1**)[9] dissolves in benzene upon addition of excess primary amine. Accordingly, the potential of dichloride **1** as a precatalyst for intermolecular hydroamination reactions was explored (Table 1).[10] Under conditions reported by Odom, using a 3-fold excess of aniline,[7] complex **1** gave rise to hydroamination products only in 22% yield (entry 1). Changing the alkyne/amine ratio to 1.2 led to efficient product formation (entry 2). The transformations could be carried out in benzene or chloroform (entries 3 and 4). The imido complex **1** initiated the hydroamination using a sterically hindered aniline derivative (entries 3 and 4) but was ineffective for addition of $^tBuNH_2$ onto tolan (entry 5). The alkyl-substituted alkyne 3-hexyne was readily converted to the corresponding imine (entry 6).[11]

Dichloride **1** is synthesized simply by addition of 6 equiv of $^tBuNH_2$ to a solution of $TiCl_4$ in a halogenated solvent followed by filtration and treatment with pyridine.[9] Therefore, a more user-friendly, in situ generation

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(10) For the use of $CpTiCl_3$ in *intramolecular* hydroamination reactions, see: (a) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459−5460. (b) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323−1324.

(11) Attempts to hydroaminate acyclic 1,3-disubstituted allenes or unfunctionalized alkenes using complex **1** have to date been unsuccessful.

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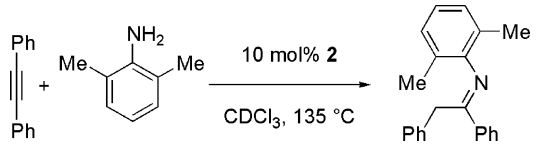
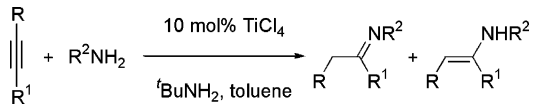
Table 2. Influence of Additives on a Hydroamination Reaction Catalyzed by Complex 2



entry	additive (amt/mol %)	*t*/h	yield/%[a]
1	–	5	<2
2	py (30)	5	<2
3	^{t}BuNH$_2$ (60)	11	96

[a] By ^{1}H NMR versus 1,3,5-(MeO)$_3$C$_6$H$_3$ as internal standard.

Table 3. Intermolecular Hydroamination Reactions Using TiCl$_4$[a]



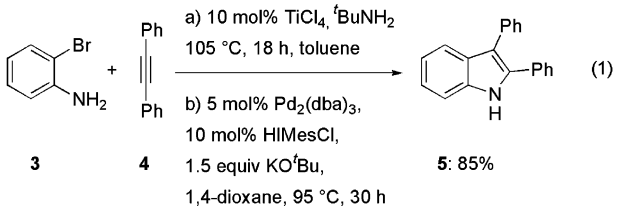
entry	R	R^1	R^2	*t*/h	isolated yield/%
1	Ph	Ph	Ph	18	95
2	Ph	Me	Ph	11	75[b]
3	^{n}Pr	^{n}Pr	4-MeC$_6$H$_4$NH$_2$	6	94
4	Ph	Ph	3,5-Me$_2$C$_6$H$_3$NH$_2$	24	81
5	Ph	Ph	4-FC$_6$H$_4$NH$_2$	18	91
6	Ph	Ph	2-ClC$_6$H$_4$NH$_2$	18	82
7	Ph	Ph	4-Br-2-MeC$_6$H$_3$NH$_2$	18	83
8	Ph	Ph	2-IC$_6$H$_4$NH$_2$	24	82
9	Ph	Ph	4-EtO$_2$CC$_6$H$_4$NH$_2$	3	–

[a] Conditions: alkyne (5.0 mmol), amine (5.0 mmol), TiCl$_4$ (0.5 mmol), and ^{t}BuNH$_2$ (3.0 mmol) in toluene at 105 °C; times are for consumption of starting material; isolated yields were obtained after hydrolysis[4a] with SiO$_2$ in CH$_2$Cl$_2$. [b] By ^{1}H NMR versus 1,3,5-(MeO)$_3$C$_6$H$_3$ as internal standard using **2** in CDCl$_3$.

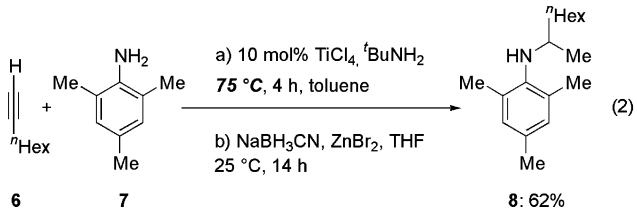
of the catalytically active species starting from inexpensive TiCl$_4$ was thought viable. The influence of additives on the catalytic performance was studied in the transformation of a sterically demanding aniline derivative using [TiCl$_4$(thf)$_2$] (**2**) (Table 2). Neither tetrachloride **2** itself nor a mixture of this complex with 30 mol % pyridine were capable of performing the hydroamination reaction (entries 1 and 2).[12] However, in the presence of 6 equiv of ^{t}BuNH$_2$ efficient imine formation was achieved (entry 3). The improved conversion obtained with the in situ generated system is likely due to the absence of pyridine as a potential dative ligand.

Having established that inexpensive TiCl$_4$ catalyzes the intermolecular hydroamination of alkynes,[13] the scope of this methodology was studied (Table 3). The addition of different aniline derivatives onto aryl- as well as alkyl-substituted alkynes was accomplished in good to very good yields (entries 1−4).[14] It is worthy of note that both the precatalyst and the substrates can be employed on a 5 mmol scale as purchased, without the need for any further purification.

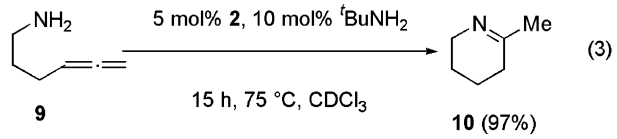
Furthermore, the methodology proved tolerant to halide substituents on the aromatic ring, allowing for further synthetic elaboration (entries 5−8). In a representative example,[15] the one-pot synthesis of indole **5** was achieved using an in situ generated palladium carbene catalyst (eq 1).[16]



Quantitative conversion of terminal alkyne **6** using the sterically demanding 2,4,6-Me$_3$C$_6$H$_2$NH$_2$ (**7**) was already achieved at 75 °C, yielding exclusively the Markovnikov product (GC/MS).[17] The secondary amine **8** was isolated after reduction[4b] in 62% yield (eq 2).



Finally, the intramolecular hydroamination[18] of terminal allene **9** was shown to proceed regioselectively using the novel catalytic system, affording cyclic imine **10** in 97% yield by NMR (eq 3).



In summary, a user-friendly protocol for hydroamination reactions of allenes as well as terminal and internal alkynes has been developed. The widely applicable catalyst system is generated in situ from the inexpensive bulk chemicals TiCl$_4$ and ^{t}BuNH$_2$ and enables the one-pot synthesis of secondary amines and indole derivatives. Studies aiming at optimization of the transformation and further synthetic applications are underway.

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Supporting Information Available: Text giving a description of the syntheses and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OM034143G

(12) It has been previously noted that TiCl$_4$ itself is ineffective, even as a cyclization catalyst for aminoalkynes: McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485−11489.

(13) A simple Brønsted acid catalyzed addition of aniline onto tolan does not occur using 20 mol % HCl (as a solution in Et$_2$O) under otherwise identical reaction conditions.

(14) Products were formed as mixtures of imine and enamine (by ^{1}H NMR): tolan and aniline, 81/19; 3-hexyne and aniline, >98/2; tolan and 2,6-dimethylaniline, >98/2; tolan and *p*-methylaniline, 83/17.

(15) A full account will be reported elsewhere: Ackermann, L.; Kaspar, L. T. Unpublished results.

(16) For another approach to the indole framework, see: Siebenreicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042−3044.

(17) Titanium-catalyzed anti-Markovnikov hydroamination reactions of terminal alkynes have been reported.[6]

(18) For intramolecular hydroamination reactions initiated by a titanium sulfonamido complex, see: Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475−1478.