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A Highly Reactive Titanium Precatalyst for Intramolecular Hydroamination Reactions

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Abstract

Tetrakisamido titanium complexes are significantly more active than Cp_2TiMe_2 (1) in the intramolecular hydroamination of aminoalkynes and aminoallenes. In the latter case, the regioselectivity of the transformation depends on the nature of the precatalyst, yielding the most selective and reactive catalysis with the bis(sulfonamido) complex 11.

The direct addition of an N–H bond across a carbon–carbon multiple bond, the hydroamination reaction, is the most atom economical way to synthesize substituted amines.[1] Although appreciable progress has been made,[2] a general procedure for this transformation remains elusive.

In the early 1990s, we reported the catalytic activity of zirconocene amido complexes in the hydroamination of alkynes.[3] Doye subsequently disclosed the intermolecular hydroamination of alkynes using Cp_2TiMe_2[4] (**1**) as the precatalyst.[5] Detailed mechanistic investigations of this reaction in our group revealed that the catalytically active species is generated via a Cp/amide ligand exchange. This conversion of the titanocene species (Cp_2TiL_2) into a monocyclopentadienyl titanium amido complex ($CpTi(N\text{-}RH)L_n$)[6] led to the development of a titanium complex with enhanced catalytic activity in the hydroamination of alkynes and allenes.[7] Therefore, we became interested in studying the catalytic reactivity of noncyclopentadienyl-supported titanium precursors. The recent report by Odom and co-workers[8] that $Ti(NMe_2)_4$ (**2**) catalyzes the hydroamination of alkynes prompted us to disclose our preliminary results concerning the development of a highly active precatalyst for intramolecular hydroaminations of alkynes and allenes.

To compare the reactivity of the bis(cyclopentadienyl)-based precursor Cp_2TiMe_2 (**1**) with the tetrakisamide pre-catalyst $Ti(NMe_2)_4$ (**2**), we initially investigated the intramolecular hydroamination of alkynes (Scheme 1).[6,9] The reactions were performed in d_6-benzene and monitored by ^1H NMR spectroscopy and GC/MS. In the presence of 5 mol % of **1** the formation of the expected cyclization product **4** was not observed after 12 h at 75 °C. To achieve a

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

conversion of the terminal alkyne **3**, a higher temperature (135 °C) was necessary. The conversion of the internal alkyne **5** was easier and a selective formation of **6** was achieved at 75 °C, while no catalytic activity was observed at room temperature. The commercially available tetrakisamide-based precursor **2** (5 mol %) was much more effective, providing both products quantitatively at room temperature (41 h and 30 min for **4** and **6**, respectively).

Having illustrated the increased reactivity of tetrakisamido titanium precatalyst **2**, we wished to optimize the efficiency of this precursor. Because the hydroamination of alkynes is easily effected by tetrakisamido titanium complexes, these substrates are of limited value for probing the reactivity of potentially more powerful catalysts. The hydroamination of aminoallenes, however, is more challenging and hence provides an appropriate assay of catalytic activity. Another factor that has to be considered in the hydroamination of aminoallenes is the regioselectivity (Scheme 2). Whereas Ag-, Hg-, or Pd-based precatalysts provide exclusively allylamines via pathway b,[10] lanthanide complexes convert monosubstituted aminoallenes into mixtures of the two regioisomers (pathways a and b).[11]

We investigated the conversion of aminoallene **7** using 5 mol % of different titanium and zirconium catalyst precursors (Table 1). Once again, the bis(cyclopentadienyl) complex **1** forms the hydroamination product **8** slowly at 75 °C (entry 1) and harsher reaction conditions are necessary to guarantee a quantitative conversion of substrate **7** (entry 2). By switching to the tetrakisamide precatalyst **2**, the formation of imine **8** is selectively[12] accomplished at room temperature (entry 3), although a temperature of 75 °C is appropriate to achieve a practical reaction rate (entry 4).

Previously we have carried out reactions with allenes using zirconium imido complexes.[3,13] Therefore we investigated the reactivity of the zirconium analogue of **2**, $Zr(NMe_2)_4$ (**9**). Although **9** exhibits catalytic activity, the reaction is much slower at 75 °C and less selective than the one using the titanium precursor **2** (entry 5).

Complex **2** is significantly more reactive than **1** in intramolecular hydroamination reactions. However, a direct insertion of an alkyne into a titanium–nitrogen bond of a L_nTiNMe_2 species and subsequent protonation can lead to the formation of undesirable dimethylamine addition side products.[8] Electron-poor secondary tosylamido complexes show no tendency to react in a similar manner. This is illustrated by the fact that the amidoallene **10** was deprotonated by **2** to form the corresponding titaniumamido complex and $HNMe_2$. No cyclization was observed (Scheme 3).

As the asymmetric catalytic hydroamination remains our ultimate goal, we studied the reactivity of the titanium bis-(sulfonamide) **11** (Figure 1), which was prepared in one step from **2** following Walsh's procedure.[14] Gratifyingly, the chelating bissulfonamide ligand results in a significantly increased reactivity, leading to selective product formation at room temperature (entry 6).[15]

Furthermore, it is noteworthy that the six-membered ring product **8** is formed exclusively using titanium tetrakisamido precatalysts **2** and **11**.

When the α position of the amine is substituted with an aromatic group, the regioselectivity of the cyclization depends on the nature of the amide ligands (Table 2). While **2** generates a mixture of regioisomers (5–10% 5-*exo* product), the chelated titanium complex **11** forms the cyclic imines as the sole products, thereby allowing the isolation of these compounds by simple filtration through K_2CO_3.[16] Furthermore, the examples compiled in Table 2 demonstrate the increased efficacy of **11**; the reaction times are significantly reduced.[17]

Having established the increased reactivity as well as the improved regioselectivity of the bis (sulfonamide)-based catalyst **11**, we studied the scope of the intramolecular hydroamination reaction of aminoallenes. As depicted in Table 2, this system tolerates methoxy – and halogen–arene bonds, providing the respective products **17**, **19**, and **21** in good yields. More importantly, the scope of this procedure is not limited to the synthesis of favorably formed six-membered rings but can be instead extended to the formation of larger ring systems such as **23**.

The enhanced regioselectivity of **11** may be due to the sterically demanding bis(sulfonamide) ligand, which disfavors cycloaddition of the titanium imido species with the internal double bound of the allene (Scheme 4).

In summary, we have shown that titanium and zirconium tetrakisamide-based transition metal complexes can be used for the efficient intramolecular hydroamination of aminoalkynes and aminoallenes. The regioselectivity of this transformation depends on the nature of the precursor, yielding the most selective and reactive catalysis with the bis(sulfonamido) complex **11**. Studies concerning the scope of this procedure, especially using 1,3-disubstituted amino-allenes, are currently ongoing.

Acknowledgements

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11. a Arredondo VM, McDonald FE, Marks TJ. J Am Chem Soc 1998;120:4871. b Arredondo VM, McDonald FE, Marks TJ. Organometallics 1999;18:1949. c Arredondo VM, Tian S, McDonald FE, Marks TJ. J Am Chem Soc 1999;121:3633.1,3-Disubstituted aminoallenes, however, are converted exclusively to the 5-exo product using lanthanide precatalysts.

12. Note that the intermolecular hydroamination of alkynes using 2 yields preferentially the Markovnikov product.[8]

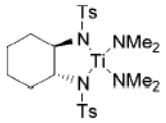
13. Sweeney ZK, Salsman JL, Andersen RA, Bergman RG. Angew Chem, Int Ed 2000;39:2339.

14. Pritchett S, Gantzel P, Walsh PJ. Organometallics 1999;18:823.

15. The improved reactivity of 11 may be a consequence of the weak coordination of the sulfur-bound oxygen atoms to the metal center.[14] However, the different electronic properties as well as the bidentate nature of the bis(sulfonamide) ligand can also play an important role.

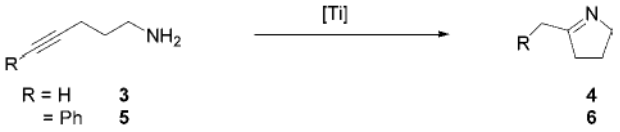
16. Representative procedure: A solution of 18 (121 mg, 0.63 mmol) and 11 (18 mg, 0.03 mmol) in benzene (3 mL) was heated for 10 h to 75 °C. The solution was cooled and treated with 20 drops of methanolic NaOH (10%). The mixture was stirred for 0.5 h at room temperature and concentrated in vacuo. The remaining residue was extracted with n-hexane (30 mL) and filtered through K_2CO_3 to afford 19 (112 mg, 93%) as a pale yellow oil. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.23 (m, 2H), 7.01 (tm, 2H, J = 8.9 Hz), 4.43 (m, 1H), 2.30–2.10 (m, 2H), 1.98 (d, 3H, J = 2.0 Hz), 1.95–1.60 (m, 3H), 1.40–1.20 (m, 1H). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ168.6, 128.4, 128.3, 114.8, 114.5, 60.8, 30.6, 29.9, 27.3, 19.0. MS (EI) m/z (relative intensity) 191 (81) [M^+], 163 (14), 162 (14), 148 (11), 121 (100), 109 (10). HR-MS (EI) m/z calcd for $C_{12}H_{14}FN$ 191.1110, found 191.1109.

17. As the sterogenic centers of the imine products are not generated during the catalytic hydroamination reaction, a potential kinetic resolution has yet not been intensively investigated. Instead, the conversion of 1,3-disubstituted aminoallenes[11] should constitute an appropriate tool to explore asymmetric catalysis.

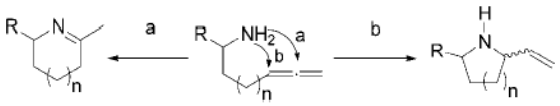


11

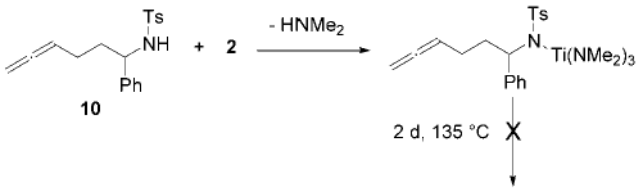
Figure 1.
Precatalyst **11**.



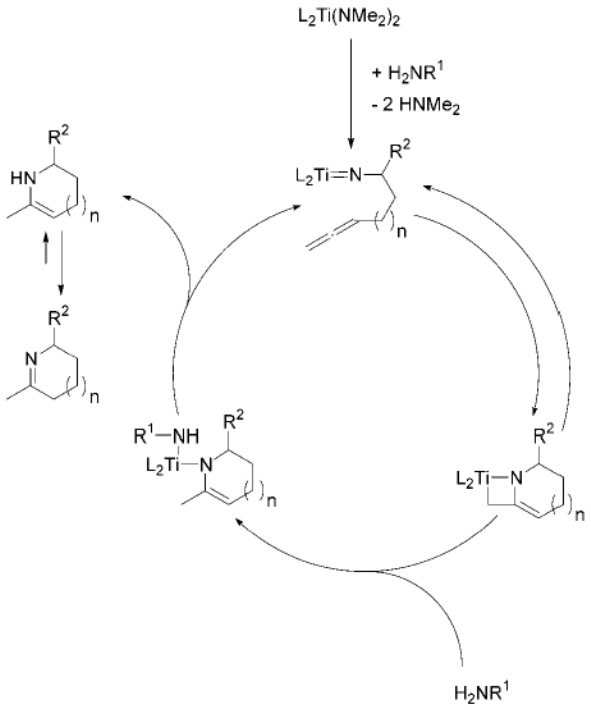
Scheme 1.
Hydroamination of Aminoalkynes



Scheme 2.
Regioselectivity in the Hydroamination of Aminoallenes



Scheme 3.
Attempted Hydroamination of Amidoallene **10**



Scheme 4.

Postulated Mechanism for the Intramolecular Hydroamination of Aminoallenes (L = Cp or Amide Ligand; R^1 = Allenyl; R^2 = H or Aryl)

Table 1

Hydroamination of Aminoallene **7** (5 mol % of Catalyst)

7 **8**

Entry	cat.	*T*/°C	*t*/h	yield (%)[a]	
				imine	5-*exo*
1	**1**	75	12	9	---[b]
2	**1**	135	3	74	10
3	**2**	25	26	41	---[b]
4	**2**	75	3	quant.[c]	---[b]
5	**9**	75	24	35	2
6	**11**	25	5	quant.[c]	---[b]

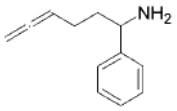
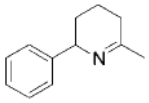
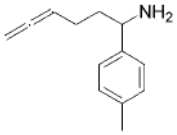
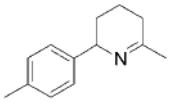
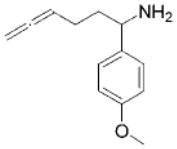
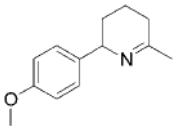
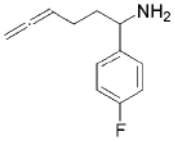
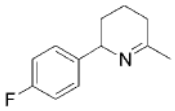
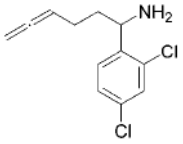
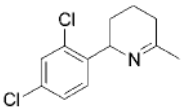
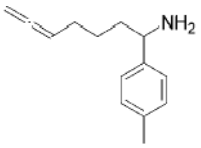
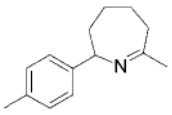
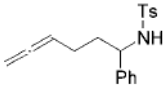
[a] NMR conversion versus 1,3,5-$C_6H_3(OMe)_3$.

[b] Not observed.

[c] Complete and selective conversion of **7**.

Table 2

Hydroamination of Substituted Aminoallenes (5 mol % of Catalyst, 75 °C)

substrate	major product	cat. (*t*/b)	yield[a]	
			Imine	5-*exo*
 **12**	 **13**	**2** (22) **11** (1)	(95) 84	(5) ---[b]
 **14**	 **15**	**2** (9) **11** (5)	(90) 79	(10) ---[b]
 **16**	 **17**	**2** (4) **11** (1.5)	(92) 95	(8) ---[b]
 **18**	 **19**	**11** (10)	93	---[b]
 **20**	 **21**	**11** (2)	88	---[b]
 **22**	 **23**	**11**[c] (36)	(60)	**(4)**
 **10**	---	**11**[c] (24)	---[b]	

[a] Isolated yield, NMR conversion in parentheses.

[b] Not observed by ^{1}H NMR.

[c] 10 mol % of **11**, 135 °C.