Intermolecular Hydroamination of Alkynes Catalyzed by Dimethyltitanocene**

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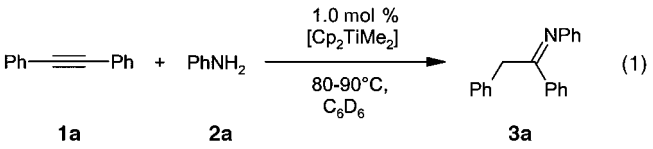
Dedicated to Professor Ekkehard Winterfeldt

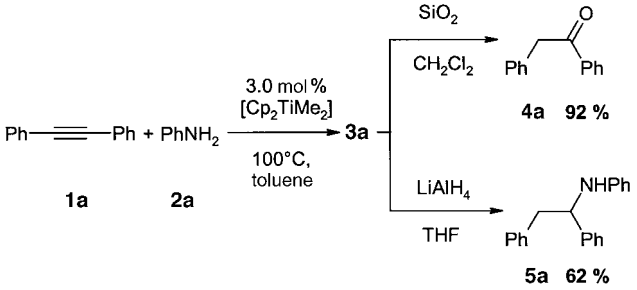
The synthesis of alcohols, ethers, ketones, and aldehydes by acid- or metal-catalyzed addition of water or alcohols to alkenes and alkynes is a well-established reaction in organic chemistry. Many regio- and stereoselective modifications of these addition reactions are known. In contrast, the formal analogous addition of ammonia or primary and secondary amines to nonactivated alkenes and alkynes does not have a comparable significance, in spite of extensive research efforts.[1] This reaction, the hydroamination, offers a very interesting pathway to primary, secondary, and tertiary amines, imines, and enamines by converting inexpensive alkenes and alkynes into the desired more highly substituted products in a single reaction without any formation of side products. In connection with this, the intermolecular reaction of amines with alkenes and alkynes represents the greatest challenge. Catalysts used so far for the intermolecular hydroamination of alkynes include mercury and thallium compounds,[2] as well as complexes of zirconium,[3] the lanthanoids,[4] uranium, and thorium.[5] However, these catalysts have big disadvantages with respect to their limited range of application, price, handling, and toxicity. We report here for the first time on a catalyst system for the intermolecular hydroamination of alkynes that is nontoxic, inexpensive, and simple to use.

In 1992 Bergman et al. reported that the bisamide complex $[Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2]$ catalyzes the hydroamination of alkynes with 2,6-dimethylaniline.[3] Unsymmetrically substituted alkynes preferentially gave the anti-Markovnikov products.[3b] Unfortunately, this reaction could not be applied to other less sterically hindered amines. At about the same time, Livinghouse et al. demonstrated that $[CpTiCl_3]$ catalyzes the intramolecular hydroamination of aminoalkynes;[6] however, intermolecular hydroaminations using this catalyst were not successful. In both cases metal–imido complexes were assumed to be the catalytically active species. Inspired by these interesting results, we started to synthesize compounds derived from $[Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2]$ and to investigate their performance as hydroamination catalysts. In preliminary experiments, we discovered that bisamide complexes of titanium, such as $[Cp_2Ti(NH\text{-}C_6H_5)_2]$,[7] are very good hydroamination catalysts. However, to obtain a useful general catalyst and to avoid the isolation of titanium–bisamide complexes, we used the known and readily available dimethyltitanocene, $[Cp_2TiMe_2]$, as catalyst in all further experiments.[8] In the presence of an arbitrary amine, $[Cp_2TiMe_2]$ should lose methane to give the catalytically active titanium–bisamide or titanium–imido complexes. Therefore, $[Cp_2TiMe_2]$ would be a suitable general catalyst precursor. Indeed, $[Cp_2TiMe_2]$ catalyzes the hydroamination of alkynes very efficiently: Diphenylacetylene (**1a**) reacted smoothly with aniline (**2a**) in the presence of 1.0 mol% $[Cp_2TiMe_2]$ in C_6D_6 at 80–90 °C to give *N*-(1,2-diphenylethylidene)aniline (**3a**), which was detected by ^{1}H NMR spectroscopy [Eq. (1)].



(1)

On a preparative scale, **3a** was isolated in 52% yield by crystallization from methanol. In all subsequent experiments, the initially formed imines were not isolated owing to their potential susceptibility to hydrolysis. Instead, the hydroamination products were detected indirectly: The imines were either hydrolyzed with SiO_2 to the stable ketones or reduced with $LiAlH_4$ or H_2 on Pd/C to the stable amines. Thus, the reaction of **1a** with **2a** in the presence of 3.0 mol% $[Cp_2TiMe_2]$ gave 1,2-diphenylethanone (**4a**) in 92% yield. The amine **5a** was obtained by reduction with $LiAlH_4$ in 62% yield (Scheme 1).



Scheme 1. In situ hydrolysis and reduction of the hydroamination product **3a**.

Since reliable workup procedures were available, we investigated the scope of the reaction. For this, **1a** was treated with various amines in the presence of $[Cp_2TiMe_2]$ followed by a hydrolytic or reductive workup [Eq. (2), Table 1].

As can be seen in Table 1, both aryl- and alkylamines can be coupled with **1a** at 100 °C in toluene with 0.5–3.0 mol% $[Cp_2TiMe_2]$ as catalyst. Sterically hindered arylamines, such as 2,6-dimethylaniline (**2b**), as well as sterically less hindered, such as aniline (**2a**), can be coupled in comparable yields. Whereas the coupling product of *p*-fluoroaniline (**2c**) is obtained in yields of 93% or 63%, depending on the workup procedure, the reaction with pentafluoroaniline (**2d**) gave much lower yields. In the case of alkylamines, a significant decrease in the obtained yield was observed for sterically less hindered *n*-alkylamines. While the use of *tert*-butylamine (**2e**) and cyclohexylamine (**2f**) still gave yields of 91% and 65%, respectively, for the formation of **4a**, the yield dropped to 19% for *n*-hexylamine (**2g**). The reaction with benzylamine (**2h**) caused particular problems. No reaction was observed at

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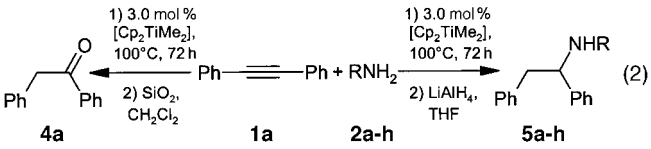


Table 1. $[Cp_2TiMe_2]$-catalyzed hydroamination of diphenylacetylene (**1a**) with various amines [Eq. (2)].

Amine	R	Yield of **4a**	Yield of **5**
2a	Ph	92 % 75 %[a, b]	**5a** 62 %
2b	2,6-$Me_2C_6H_3$	89 %	**5b** 68 %
2c	*p*-C_6H_4F	93 %	**5c** 63 %
2d	C_6F_5	23 %[b]	
2e	*t*Bu	91 %	**5e** 86 %[c]
2f	Cy	65 %	**5f** 86 %[c]
2g	*n*-Hex	19 %[b]	
2h	Bn	5 %[b, d] 14 %[b, e]	**5h** 3 %[b,e]

[a] 0.5 mol % $[Cp_2TiMe_2]$. [b] Incomplete reaction. [c] Reduction with 1 bar of H_2 and 5 mol % Pd/C instead of $LiAlH_4$. [d] 110 °C. [e] 130 °C.

100 °C. At temperatures above 110 °C, the product was formed slowly.

In addition to alkyne **1a**, further alkynes were treated with **2a** in the presence of $[Cp_2TiMe_2]$ [Eq. (3)]. The results of the hydrolytical workup are presented in Table 2.

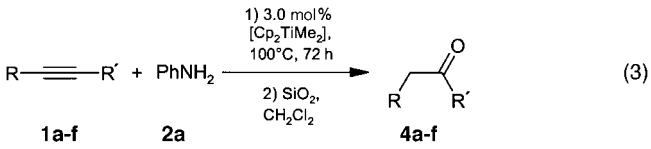


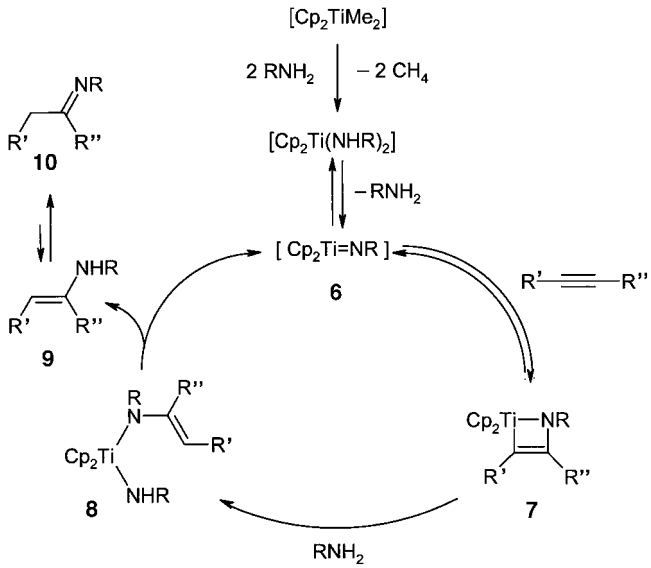
Table 2. $[Cp_2TiMe_2]$-catalyzed hydroamination of various alkynes with aniline (**2a**) [Eq. (3)].

Alkyne	R	R′	Yield of **4**
1a	Ph	Ph	**4a** 92 %
1b	C_2H_5	C_2H_5	**4b** 30 %[a–c]
1c	Ph	CH_3	**4c** 99 %[d,e]
1d	Ph	C_2H_5	**4d** 73 %[b,d]
1e	Ph	C_3H_7	**4e** 35 %[b]
1f	$C_{10}H_{21}$	H	**4f** (detected by NMR)

[a] Yield determined by gas chromatography (GC) with an internal standard. [b] Incomplete reaction. [c] Isolation of the corresponding amine by reduction with $LiAlH_4$ in 27 % yield. [d] 40 h. [e] 1.0 mol % $[Cp_2TiMe_2]$.

Symmetrically substituted bisaryl- and bisalkylalkynes, such as **1a** and 3-hexyne (**1b**), provided access to the corresponding ketones after hydrolysis; however, after the same reaction time the yield for the bisarylalkyne **1a** was 92 %, which is considerably higher than that for the bisalkylalkyne **1b** (30 %). For unsymmetrically substituted alkynes, the regioselectivity of the amine addition was particularly interesting. In the presence of 1.0 mol % catalyst, the alkylarylalkyne 1-phenylpropyne (**1c**) reacted to give a single regioisomer, the anti-Markovnikov product 1-phenylpropan-2-one (**4c**), in 99 % yield. 1-Phenylbutyne (**1d**) and 1-phenylpentyne (**1e**) also gave the anti-Markovnikov products 1-phenylbutan-2-one (**4d**) and 1-phenylpentan-2-one (**4e**) exclusively. However, the reaction was much slower than that of **1c**. The reaction of terminal alkynes is also possible. In preliminary catalytic experiments with 1-dodecyne (**1f**), followed by hydrolysis with SiO_2, we were able to detect dodecanal (**4f**) in the ^1H NMR spectrum. However, it has not yet been possible to isolate **4f**. In contrast, phenylacetylene (**1g**) and 1-naphthylamine (**2i**) were successfully coupled in the presence of 3.0 mol % catalyst. After subsequent reduction, the anti-Markovnikov addition product 1-*N*-(2-phenylethyl)aminonaphthaline was isolated in 23 % yield; the isomeric 1-*N*-(1-phenylethyl)aminonaphthaline was not detected.

The proposed mechanism of the $[Cp_2TiMe_2]$-catalyzed hydroamination is shown in Scheme 2. It is based on mechanistic studies on the reactivity of zirconocene–imido complexes;[3] however, it has not yet been verified by experimental data.



Scheme 2. Postulated mechanism of the $[Cp_2TiMe_2]$-catalyzed hydroamination of alkynes.

We assume that $[Cp_2TiMe_2]$ reacts with the amine to form the catalytically active titanium–imido complex **6**, which then undergoes a [2+2] cycloaddition with the available alkyne. The resulting azatitanacylobutene **7** is then irreversibly protonated by further amine to form the bisamide **8**, which is then thermally cleaved into enamine **9** and the catalytically active species. Finally, enamine **9** is converted into imine **10** under the reaction conditions.

In conclusion, dimethyltitanocene is a widely applicable, inexpensive catalyst of low toxicity that can be used in intermolecular hydroamination reactions of alkynes. With this catalyst, primary aryl- and alkylamines can be coupled to symmetrically and unsymmetrically substituted alkynes. In the case of unsymmetrically substituted alkynes, the reaction occurs with high regioselectivity, forming the anti-Markovnikov products exclusively. Further work to optimize the reaction is currently underway. These studies will include the use of substrates bearing various functional groups.

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Experimental Section

All experiments were carried out under argon with the exclusion of air and moisture in Schlenk tubes sealed by Teflon stopcocks. The chemicals used were dried and purified according to the standard procedures and stored under argon. [Cp_2TiMe_2] was synthesized according to ref. [8]. All the products were identified by comparison with authentic samples (^{1}H NMR, MS, TLC). PE: light petroleum (b.p. 40–60 °C), EA: ethyl acetate.

Reaction of **1a** with **2a**: Alkyne **1a** (513 mg, 2.88 mmol) and amine **2a** (224 mg, 2.40 mmol) were dissolved in toluene (2.0 mL) under argon. After addition of a solution of [Cp_2TiMe_2] (0.48 mL, 0.15 mol L^{-1}, 0.072 mmol, 3.0 mol %) in toluene the mixture was heated at 100 °C for 72 h in a closed Schlenk tube.

a) Isolation of the imine **3a**: The dark brown reaction solution was concentrated under vacuum. The residue was taken up in the minimum amount of methanol and then filtered. The light yellow fitrate was cooled to −30 °C, and light yellow crystals of **3a** precipitated. Yield: 341 mg (1.26 mmol, 52 %).

b) Isolation of the ketone **4a**: The reaction solution was treated with CH_2Cl_2 (10 mL) and silica gel (4.0 g). The mixture was stirred for 2 h at room temperature and then filtered. The filtrate was then concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel (PE:EA, 10:1) to give **4a**. Yield: 432 mg (2.20 mmol, 92 %).

c) Isolation of the amine **5a**: At 0 °C, the reaction solution was carefully added to a suspension of $LiAlH_4$ (137 mg, 3.61 mmol) in THF (10 mL) and the mixture was refluxed for 3 h. After cooling to 0 °C, the excess $LiAlH_4$ was hydrolyzed with iced water and the precipitate was dissolved by dropwise addition of NaOH (2.0 M). The mixture was then extracted three times with CH_2Cl_2. The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated on a rotary evaporator. Column chromatography of the residue on silica gel (PE:EA, 10:1) gave **5a**. Yield: 406 mg (1.49 mmol, 62 %).

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[1] a) R. Taube in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, pp. 507–520; b) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–703; c) T. E. Müller, M. Beller in *Transition Metals for Organic Synthesis, Vol. 2* (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **1998**, pp. 316–330; d) E. Haak, S. Doye, *Chem. Unserer Zeit* **1999**, *33*, 296–303.

[2] a) J. Barluenga, F. Aznar, *Synthesis* **1977**, 195–198; b) J. Barluenga, F. Aznar, R. Liz, R. Rodes, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2732–2737.

[3] a) P. J. Walsh, A. M. Baranger, R. G. Bergman, *J. Am. Chem. Soc.* **1992**, *114*, 1708–1719; b) A. M. Baranger, P. J. Walsh, R. G. Bergman, *J. Am. Chem. Soc.* **1993**, *115*, 2753–2763.

[4] Y. Li, T. J. Marks, *Organometallics* **1996**, *15*, 3770–3772.

[5] A. Haskel, T. Straub, M. S. Eisen, *Organometallics* **1996**, *15*, 3773–3775.

[6] a) P. L. McGrane, M. Jensen, T. Livinghouse, *J. Am. Chem. Soc.* **1992**, *114*, 5459–5460; b) P. L. McGrane, T. Livinghouse, *J. Org. Chem.* **1992**, *57*, 1323–1324; c) P. L. McGrane, T. Livinghouse, *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489; d) D. Fairfax, M. Stein, T. Livinghouse, M. Jensen, *Organometallics* **1997**, *16*, 1523–1525.

[7] L. J. Baye, *Synth. React. Inorg. Met. Org. Chem.* **1975**, *5*, 95–102.

[8] N. A. Petasis in *Encyclopedia of Reagents for Organic Synthesis, Vol. 1* (Ed.: L. A. Paquette), Wiley, New York, **1995**, pp. 470–473.

Catalytic, Regiospecific End-Functionalization of Alkanes: Rhenium-Catalyzed Borylation under Photochemical Conditions**

Huiyuan Chen and John F. Hartwig*

The end-functionalization of alkanes remains an important, unsolved problem in chemistry.[1, 2] Although C–H bond activation by transition metals has been known for decades, there are few reactions that selectively functionalize alkanes using catalytic amounts of transition metals. For example, metal-catalyzed oxidations are notoriously unselective with linear alkanes.[3, 4] Photochemical carbonylations can give high, but not exclusive, selectivity for terminal products when catalyzed by [$RhCl(CO)(PMe_3)_2$],[5, 6] and the product yields are limited by unfavorable thermodynamics.[5] Most recently, terminal olefins have been generated as the dominant product of dehydrogenation with a sacrificial hydrogen acceptor at early reaction times,[7] but this chemistry provides mixtures of alkenes at high conversions in the absence of acceptor.[8, 9]

We have previously reported that monoboryl complexes of tungsten functionalize alkanes stoichiometrically.[10] Regeneration of the boryl complex from the accompanying metal hydride and dimeric metal carbonyl products in this system requires several steps and external reagents, which prohibits catalytic functionalization. Thus, we have sought a related but alternative approach to catalytic borylation of alkanes. We report here a rhenium-catalyzed process that produces terminal organoborane products from alkanes and 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (B_2pin_2) under photochemical conditions. Organoboranes are established, versatile synthetic intermediates that can be converted into alcohols, amines, halocarbons, aldehydes, and alkylarenes without loss of regiochemistry.[11]

Our initial studies employed stoichiometric amounts of [$Cp'M(CO)_3$] (**1**: $Cp' = C_5H_4Me$, M = Mn; **2**: $Cp' = C_5H_5$, M = Re; **3**: $Cp' = C_5Me_5$ (Cp*), M = Re) to determine whether alkane functionalization would occur with these complexes and whether the reaction would consume the starting complex or regenerate it to allow for catalysis. Irradiation of B_2pin_2 alone in neat pentane with a 450-Watt medium-pressure Hanovia mercury arc lamp gave no reaction, but irradiation of B_2pin_2 in the presence of complexes **1**, **2**, or **3** produced 1-pentylboronate ester **4** (Scheme 1), the product of alkane functionalization in the terminal position.[12] HBpin, which decayed to $(Bpin)_2(\mu\text{-}O)$ during the reaction, was the accompanying product. Yields of HBpin were determined by addition of benzaldehyde to form the pinacol benzyloxyl-

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