Recent Developments in Transition Metal Catalyzed Intermolecular Hydroamination Reactions—A Breakthrough?

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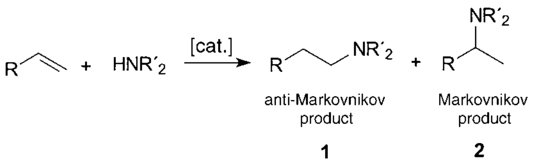
The addition of primary/secondary amines or ammonia to olefins is, in terms of an optimum material balance, one of the much discussed atom-economical processes.[1] This reaction, known as hydroamination, allows the synthesis of higher-substituted amines of type **1** and **2** in a single step [Eq. (1)]. These amines are of great importance for synthetic chemists in basic research as well as for the chemical industry.



(1)

R′ = Alkyl, Aryl, H
R = Alkyl, Aryl

The catalytic anti-Markovnikov addition of HNR_2 to olefins was listed as one of the so-called „Ten Challenges for Catalysis“ for a good reason.[2] In recent years, great efforts have been made worldwide to develop effective hydroamination procedures; these met with little success until recently.[3]

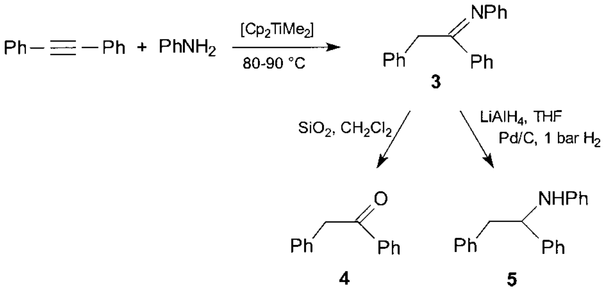
In recent months, several research groups have described homogeneous catalytic procedures for intermolecular hydroamination, which—it appears at the moment—have initiated a breakthrough in this area. The present developments can be divided into three categories and are discussed in the following sections:

1) Hydroaminations of alkynes and allenes.
2) Hydroaminations of alkenes with catalysts based on transition metals of Groups 8–10
3) Ab initio/DFT investigations of catalytic hydroaminations

Hydroaminations of Alkynes and Allenes

Wakatsuki et al. reported in 1999 in *Angewandte Chemie* a ruthenium-catalyzed intermolecular hydroamination of terminal alkynes with anilines which used an efficient catalyst consisting of 0.1 mol% $[Ru_3(CO)_{12}]$ and 0.3 mol% NH_4PF_6 for the hydroamination of phenylacetylene with aniline.[4] At 100 °C and reaction times of 3–12 h, ketimines were obtained in yields of up to 95%. The reaction-accelerating influence of the protons and the corresponding base has not yet been explained.

Based on work by Bergman et al.[5] and Livinghouse et al.,[6] the research group of Doye was able to develop a procedure for the catalytic intermolecular hydroamination of alkynes that used dimethyltitanocene $[Cp_2TiMe_2]$ ($Cp = C_5H_5$) as the catalyst.[7] For example, the reaction of diphenylacetylene with aniline in the presence of 1 mol% $[Cp_2TiMe_2]$ in C_6D_6 at 80 to 90 °C gave *N*-(1,2-diphenylethylidene)aniline **3** [Eq. (2)], which was detected by ^1H NMR spectroscopy.



(2)

To avoid the need to isolate imines of type **3**, which are sensitive to hydrolysis, they were hydrolyzed to ketones, such as **4** (SiO_2/CH_2Cl_2) or reduced to amines, such as **5** ($LiAlH_4$/THF or 1 bar H_2, Pd/C). It is noteworthy that the amine addition to asymmetrically substituted alkynes is extremely regioselective: reaction of 1-phenylpropyne and aniline yields the anti-Markovnikov product 1-phenylpropan-2-one with high regioselectivity and in 99% yield. However, the long reaction time of 72 h is a disadvantage, particularly for potential applications.

Recently, Bergman et al. reported an imidotitanium complex as a hydroamination catalyst for allenes and alkynes.[8] During the search for titanium intermediates in the catalytic cycle, the stoichiometric reaction of $[Cp_2TiMe_2]$ with 2,6-dimethylaniline was studied at 75 °C in $[D_6]$benzene. The educt complex decomposed to give four compounds containing Cp as well as free CpH. If pyridine (py; 1.5 equiv) is added to this thermolysis mixture, then the unex-

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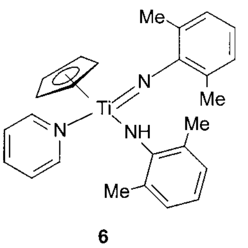

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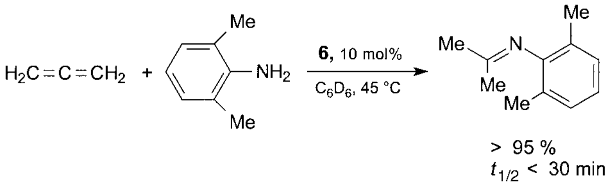
pected monocyclopentadienyl(amido)-imidotitanium complex **6** is isolated in 62% yield.

Pyridine appears to favor the formation of the monomeric imido complex rather than the dimer. The subsequent substitution of the pyridine by trimethylphosphane oxide led to a crystalline compound the structure of which (Ti=N unit and an amido ligand) was confirmed by X-ray crystallography. Complex **6** was a very efficient catalyst for the hydroamination of allenes [Eq. (3)] at



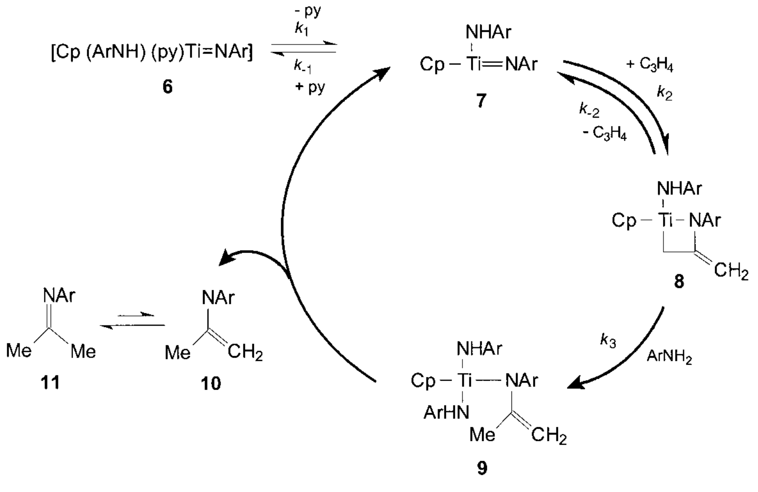
(3)

an unusually low temperature of 45 °C. To obtain information on the reaction mechanism, kinetic studies were carried out which gave the rate law expressed by Equation (4).

$$r = \frac{k\,[\mathbf{6}]\,[H_2C{=}C{=}CH_2]}{[py]} \tag{4}$$

The data obtained from the kinetic experiments suggest the mechanism shown in Scheme 1 for the intermolecular hydroamination of allenes with **6** as the catalyst. Complex **6** is in equilibrium with the coordinatively unsaturated titanium compound **7**, which reacts with the allene in a [2+2] cycloaddition to give the azatitanacyclobutane **8**. The protonation of **8** by the amine leads to the tris(amido)titanium complex **9**. Finally, elimination of the enamine **10** regenerates the active catalyst **7**.

Compound **6** is also remarkably more active than [Cp_2TiMe_2] for the hydroamination of alkynes. Overall, the work by Bergman's group provides the first concrete indications of the mechanism of intermolecular hydroamination of alkynes and allenes with [Cp_2TiMe_2] as the precatalyst. An unexpected exchange of a Cp ligand from [Cp_2TiMe_2] in the presence of 2,6-dimethylaniline led to the monocyclopentadienyltitanium complex **6**, which can be regarded as a very reactive intermediate on the way to the catalytic cycle.



Scheme 1. Mechanism of the intermolecular hydroamination of allenes with **6** as the catalyst (ref. [8]).

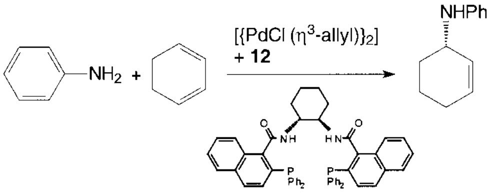
Somewhat later, Doye et al., on the basis of kinetic experiments, also described the mechanism of intermolecular hydroamination of alkynes catalyzed by dimethyltitanocene.[9] In this work they investigated the treatment of 1-phenylpropyne with 4-methylaniline with varying concentrations of the alkyne, the amine, and the catalyst. They found a complex relationship between the catalyst concentration and the reaction rate which is attributed to a reversible dimerization of the catalytically active species, a titanium–imido complex (see Scheme 1). In general, the hydroamination mechanisms postulated by Bergman et al. and Doye et al. are identical with regard to the principal intermediates.

Hydroaminations of Alkenes with Catalysts Based on Transition Metals of Groups 8–10

A remarkable study of the palladium-catalyzed hydroamination of various vinylarenes with anilines was published by Hartwig et al. at the end of 2000.[10] The best yield (>99%) of the Markovnikov product **2** was found by high-throughput screening. An in situ catalyst system was used that consisted of 2% palladium(II) trifluoracetate, 3% 1,1′-bis(diphenylphosphanyl)ferrocene, and 20% trifluoromethane sulfonic acid (100 °C, 6 h). Trifluoroacetic acid was less suitable than trifluoromethane sulfonic acid as the cocatalyst; the authors attributed this to the counterion and not to the strength of the acid. Differently substituted styrenes, vinylnaphthalin, and anilines could be converted. An asymmetric hydroamination of *para*-trifluoromethylstyrene by aniline with 10 mol% [Pd((*R*)-binap)(OTf)$_2$] (binap = [1,1′-binaphthalene]-2,2′-diylbis(diphenylphosphane)) gave a yield of 80% in 81% *ee* after 72 h at 25 °C. This is a good yield with moderate stereoselectivity. In contrast, the first asymmetric intermolecular hydroamination of norbornene with aniline with only 2 mol % [{IrCl((*S*)-binap)}$_2$]/F$^-$ gave a yield of 22% and an enantiomeric excess of 95%.[11] Could a similarly good yield have been obtained with 10 mol% of the iridium catalyst?

Recently, the hydroamination of acrylic acid derivatives was also described by Hartwig's group.[12] Since these reactions were investigated by parallel synthesis in 96-well glass plates, a search was made for a colorimetric assay as well as for the formation of secondary alkylamines. Basic solutions of $Na_2[Fe(CN)_5NO]\cdot 2H_2O$ and acetaldehyde turn blue in the presence of secondary alkylamines: this allowed the first visual estimation of the activities of various late transition metal catalysts. The addition of piperidine to methacrylonitrile was successful with palladium catalysts; however, the yields were lower than those obtained with rhodium(I) and iridium(I) catalysts. In contrast, for the addition of primary alkylamines or arylamines to crotonic acid derivatives a lower number of catalytically active transition metal compounds were found. Effective catalysts for this reaction are palladium(II) salts with PCP or PNP ligands; sterically less bulky, monodentate phosphanes with alkyl or aryl substituents are not suitable. Because of the relatively large number of active catalysts, it is certain that more than one mechanism can be considered for the hydroamination reaction.

Very recently, the same research group described the hydroamination of 1,3-dienes,[13] for example, cyclohexa-1,3-diene with aniline. To detect the aniline consumption colorimetrically, furfural and acid were added after the reaction. Furfural reacts with aniline (2 equiv), but not with the allylamine, by condensation and ring opening to give a red product. The absence of red coloration therefore indicates the complete reaction of aniline. The most active catalysts found by this method were in situ systems from $[\{PdCl(\eta^3\text{-allyl})\}_2]$ and PPh_3, which are known to react to give the palladium(0) complex $[Pd(PPh_3)_4]$. Therefore, this palladium compound (2 mol%), together with trifluoromethane sulfonic acid (10 mol%), were investigated as the catalyst system for various anilines and dienes. The hydroamination was successful with many substrates; exceptions were cyclooctadiene, which did not react under standard conditions, and 1,3-butadiene, which reacted to give a complex mixture of products. An enantioselective variant of this reaction occurred with an acid-free catalyst consisting of $[\{PdCl(\eta^3\text{-allyl})\}_2]$ and the Trost ligand **12** [Eq. (5)] in 87% yield for the product and 89% *ee*. Various other chiral diphosphanes only led to moderate enantioselectivities of 7–34% *ee*.



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(5)

Just how difficult it is to carry out a catalytic hydroamination successfully, is also demonstrated in a publication by the research group of Keim on the hydroamination of ethene by piperidine.[14] Various ruthenium(II) complexes were investigated as catalysts for this reaction. A stoichiometric hydroamination is possible with the mediators $[RuCl_2(PPh_3)_3]$ and $[CpRu(C_2H_4)(PPh_3)_2]^+BF_4^-$. However, free coordination sites on the ruthenium center are rapidly blocked by amines after one cycle to yield catalytically inactive ruthenium complexes.

Ab initio/DFT Investigations of Catalytic Hydroamination

A very interesting publication by Senn et al.[15] describes the use of density functional theory (DFT) calculations to investigate the pathway of the catalytic hydroamination of alkenes with model complexes of transition metals from Groups 9 and 10. These theoretical results essentially confirmed the experimental results of Hartwig's group, which were published at about the same time. Calculations were carried out on intermediate complexes of the catalytic cycle for the activation of the alkene (nucleophilic attack on the coordinated alkene, cleavage of the metal–carbon bond, and ligand exchange) for d^8 transition metal complexes of the type $[MCl(PH_3)_2]^{z+}$ (M = Co, Rh, Ir [$z = 0$] and Ni, Pd, Pt [$z = 1$]) in which the two phosphane ligands were *cis*. The nucleophilic attack of an amine on an ethene coordinated to a transition metal is thermodynamically and kinetically favored for a transition metal of Group 10, but is very unfavorable for elements of Group 9. Thus complexes of Group 10 should be better catalysts for hydroamination reactions. According to the calculations, nickel complexes in particular are very promising. In this case, the activation barrier for the cleavage step is 108 kJ mol^{-1}. β-Hydride elimination, a possible side-reaction, can be suppressed by altering the steric and electronic properties of the ligand and by the selection of a suitable educt. In general, this theoretical work provides much impetus to form a suitable catalyst directly.

All the publications discussed here thus indicate an approach to further catalytic intermolecular hydroaminations. The use of other substrates, for example, ammonia, alkylamines, and nonfunctionalized olefins, is an interesting field for the future. For industrial applications, the catalyst concentrations are still too high and the use of palladium compounds is certainly not economically viable at the moment (current price of palladium (14.05.2001): 22.99 \$ g^{-1}). The future will show which possibilities are offered to organometallic chemistry and catalysis.

[1] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[2] J. Haggin, *Chem. Eng. News* **1993**, *71*(3), 6.

[3] a) R. Taube in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* (Eds: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, pp. 507–520; b) D. M. Roundhill, *Catal. Today* **1997**, *37*, 155; c) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; d) A. Ricci, *Modern Amination Methods*, Wiley-VCH, Weinheim, **2000**.

[4] A rarely cited work on the hydroamination of alkynes: Tokunaga, M. Eckert, Y. Wakatsuki, *Angew. Chem.* **1999**, *111*, 3416; *Angew. Chem. Int. Ed.* **1999**, *38*, 3222.

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

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

[7] E. Haak, I. Bytschkov, S. Doye, *Angew. Chem.* **1999**, *111*, 3584; *Angew. Chem. Int. Ed.* **1999**, *38*, 3389.

[8] J. S. Johnson, R. G. Bergman, *J. Am. Chem. Soc.* **2001**, *123*, 2923.

[9] F. Pohlki, S. Doye, *Angew. Chem.* **2001**, *113*, 2361; *Angew. Chem. Int. Ed.* **2001**, *40*, 2305.

[10] M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 9546.

[11] R. Dorta, P. Egli, F. Zürcher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*, 10857.

[12] M. Kawatsura, J. F. Hartwig, *Organometallics* **2001**, *20*, 1960.

[13] O. Löber, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 4366.

[14] H. Schaffrath, W. Keim, *J. Mol. Catal. A* **2001**, *168*, 9.

[15] H. M. Senn, P. E. Blöchl, A. Togni, *J. Am. Chem. Soc.* **2000**, *122*, 4098.