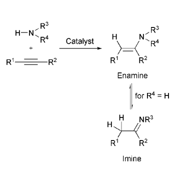

The catalytic hydroamination of alkynes

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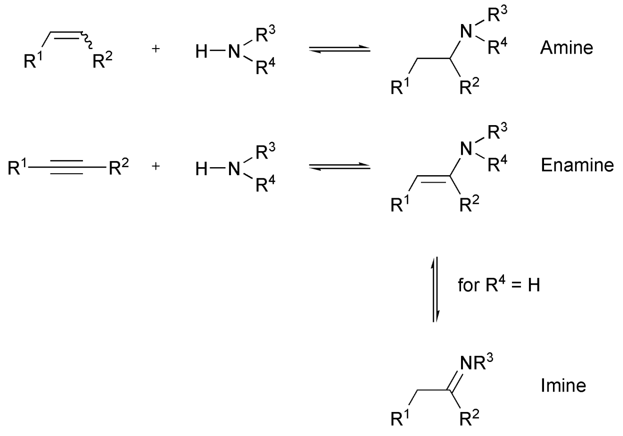
The direct addition of ammonia or primary and secondary amines to non-activated alkenes and alkynes is potentially the most efficient approach towards the synthesis of higher substituted nitrogen-containing products. It represents the most atom economic process for the formation of amines, enamines and imines, which are important bulk and fine chemicals or building blocks in organic synthesis. While the hydroamination of alkenes is still limited to more or less activated alkenes, great progress has been achieved in the case of alkynes over the last three years. To illustrate this progress, the review will mostly focus on recent developments in the field of intermolecular hydroamination of alkynes. However, if it is necessary for the discussion, older results and intramolecular reactions, which can be achieved more easily, will be mentioned as well.



Scheme 1

1 Introduction

The synthesis of many oxygen-containing compounds by acid- or metal-catalyzed addition of water or alcohols to alkenes and alkynes is a well-established process in organic chemistry. Many regio- and stereoselective modifications of related reactions are known. In contrast, the formal analogous addition of ammonia or primary and secondary amines to non-activated alkenes and alkynes (Scheme 1) does not have comparable significance.

However, from a synthetic point of view these two reactions, the hydroamination of alkenes and the hydroamination of alkynes,[1] are among the most desirable transformations in organic chemistry. This is caused by the fact that both reactions offer direct pathways to amines, enamines and imines which are important bulk and fine chemicals or building blocks in organic chemistry. Especially the mentioned amines play an outstanding role as products and intermediates in the chemical industry. Per year, several million tons of various amines are produced worldwide.[2] As can be seen from Scheme 1, both mentioned hydroamination processes convert inexpensive and readily available starting materials into the desired products in a single reaction without any formation of side products and therefore proceed theoretically with 100% atom efficiency. Regarding this consideration, efficient hydroamination processes might offer significant economical and environmental

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Sven Doye was born in Berlin, Germany in 1967. Between 1986 and 1990 he studied chemistry at the Technical University of Berlin. He received his diploma degree in 1990 from the same University and his PhD in 1993 from the University of Hannover. During his PhD studies, which were carried out in the group of Professor Winterfeldt, he worked on the stereoselective synthesis of an unusual tricyclic sesquiterpene alcohol. Between 1994 and 1996 he spent two years in industry working for BASF AG in Ludwigshafen, Germany. After a subsequent year of post doctoral research at the Massachusetts Institute of Technology in Cambridge, USA, with Professor S. L. Buchwald (1996–1997), he returned to the University of Hannover in 1998. Since then he has been working independently on the development of catalytic hydroamination reactions. From September 2002 until January 2003 he was Guest Professor at Cardiff University, Wales, UK.

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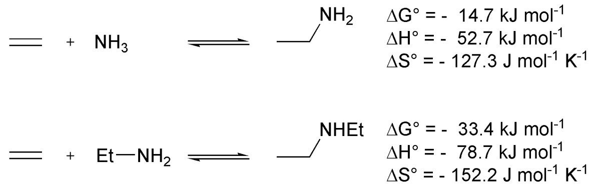
benefits compared to classical methods[2] for the synthesis of the mentioned target compounds.

From a thermodynamical point of view, the direct addition of ammonia or simple amines to alkenes is feasible since corresponding reactions are slightly exothermic or approximately thermoneutral. To illustrate this fact, two representative sets of thermodynamical data for the reactions of ammonia and ethylamine with ethylene are presented in Scheme 2.[3] Unfortunately, experimental $\Delta H°$ data are not available for the addition of ammonia or amines to alkynes. Therefore, it is not directly possible to compare the thermodynamics of amine addition to alkynes *versus* that to alkenes. However, the addition of NH_3 to acetylene is estimated (AM1-semiempirical calculations) to be ~63 kJ mol^{-1} more exothermic than that to ethylene.[4] Regarding this estimation, the hydroamination of alkynes is supposed to be more favorable than the hydroamination of alkenes.



Scheme 2

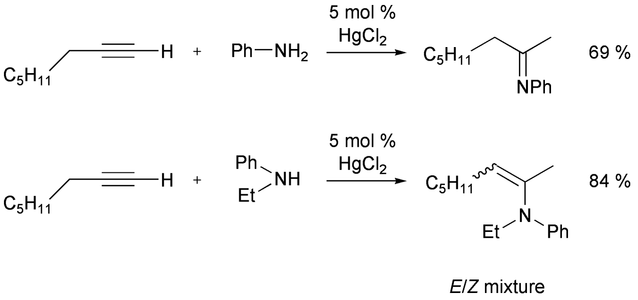
In general, a high activation barrier exists for the direct addition of amines across C–C multiple bonds which arises from electrostatic repulsion between the electron lone pair at the nitrogen atom and the electron rich π-bond of the alkene or alkyne. However, it is not possible to overcome this activation barrier simply by performing the hydroamination reaction at elevated temperature. Caused by the general negative reaction entropy $\Delta S°$ of the amine addition (Scheme 2), the equilibrium of the hydroamination reaction is shifted to the starting materials with increasing temperature. Therefore, it is indispensable to identify alternative catalytic procedures for the discussed hydroamination reactions.

In contrast to the hydroamination of alkenes, which gives access to stable amines directly, the hydroamination of alkynes initially yields relatively reactive enamines and imines (Scheme 1). As the result, these compounds must be reduced in a subsequent step if amines are the desired final products. Despite this fact, the initial formation of the mentioned reactive intermediates during the hydroamination of alkynes can be seen as an advantage because it offers high synthetic flexibility. Utilizing a corresponding strategy, the initially formed enamines and imines can be used subsequently as starting materials for a number of different, well-established synthetic transformations giving access to various important classes of products. However, since alkenes are less expensive and more readily available than alkynes the hydroamination of non-activated alkenes undoubtedly represents the industrially more challenging transformation. Unfortunately, the hydroamination of alkenes remains an unsolved synthetic problem, while great progress has been achieved in developing hydroamination procedures for non-activated alkynes during the last couple of years. This is easily understandable since the mentioned thermodynamical considerations suggest that the hydroamination of alkynes can be realized more easily than that of alkenes. However, it seems to be a reasonable approach to develop efficient catalytic hydroamination protocols for alkynes first and subsequently apply the obtained knowledge to the development of related procedures for alkenes. For that reason, the hydroamination procedures for alkynes developed so far might be the basis for future hydroamination processes for alkenes.

In this review, we will mostly focus on recent developments in the field of intermolecular hydroamination of alkynes. However, older results and intramolecular reactions will be mentioned as well if they are necessary for the discussion or might act as springboard for future research.

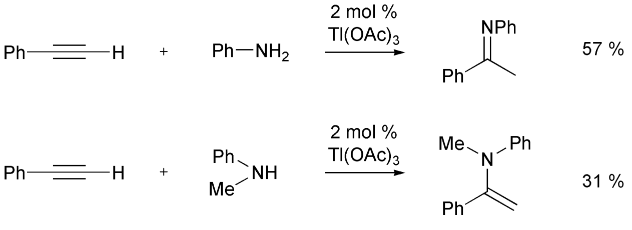
2 Mercury and thallium compounds as hydroamination catalysts

The fact that mercury and thallium compounds can be used as catalysts for the hydroamination of alkynes has been known for more than 20 years. Based on previous work dealing with the synthesis of enamines and imines from alkynes in the presence of stoichiometric amounts of $Hg(OAc)_2$ Barluenga *et al.* found that $HgCl_2$ is able to catalyze the regioselective hydroamination of terminal alkyl- and arylalkynes with primary and secondary aromatic amines (Scheme 3).[5] While reactions employing primary amines are performed in THF at room temperature (< 30 °C) to prevent extensive side reactions, enamines are best synthesized from alkynes and secondary amines at 60 °C using the secondary amine as solvent. The enamines synthesized from alkylalkynes are always obtained as mixtures of *E*- and *Z*-isomers contaminated by small amounts (< 5%) of the initially formed isomer having a terminal double bond. The catalyst loading for all reactions is 5 mol%.



Scheme 3

In addition, Barluenga *et al.* reported that $Tl(OAc)_3$ is an efficient catalyst for the hydroamination of phenylacetylene with various primary and secondary aromatic amines (Scheme 4).[6] The corresponding reactions, which give access to the desired enamines and imines in modest yields, are performed in the presence of 2 mol% $Tl(OAc)_3$ at 60 °C for 7 h in the absence of a solvent. As mentioned for the $HgCl_2$-catalyzed process, the hydroamination reactions take place regioselectively.

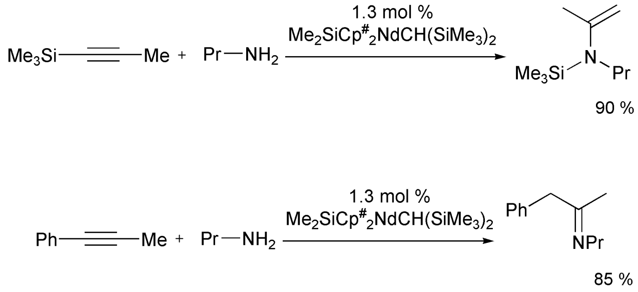


Scheme 4

In general, the major drawback of all hydroamination protocols employing mercury and thallium compounds in either catalytic or stoichiometric amounts is the high toxicity of the employed catalysts. However, it is also likely that even more toxic organometal intermediates are formed during the catalytic reactions. Therefore, a wide application of corresponding hydroamination protocols, even in chemical laboratories, should be avoided.

3 Lanthanide complexes as hydroamination catalysts

Based on extensive previous work on organolanthanide-catalyzed intramolecular alkene and alkyne hydroamination, in 1996 Marks *et al.* reported the first examples of intermolecular hydroamination reactions of alkynes in the presence of Sm-, Lu- and Nd-containing catalysts.[7] The reactions of three primary alkyl amines (*n*-propyl-, *n*-butyl-, *i*-butylamine) with three alkynes (1-trimethylsilylpropyne, 1-phenylpropyne, 2-butyne) were carried out in benzene at 60 °C using $Cp^*_2LnCH(SiMe_3)_2$ and $Me_2SiCp^\#_2LnCH(SiMe_3)_2$ complexes ($Cp^* = \eta^5\text{-}C_5Me_5$, $Cp^\# = \eta^5\text{-}C_5Me_4$, Ln = Sm, Lu, Nd) as precatalysts. While corresponding reactions of 1-phenylpropyne and 2-butyne gave access to imines, silylated enamines were obtained from 1-trimethylsilylpropyne (Scheme 5). Interestingly, the hydroamination of the unsymmetrically substituted alkyne 1-phenylpropyne took place with high selectivity giving access to only one regioisomer.

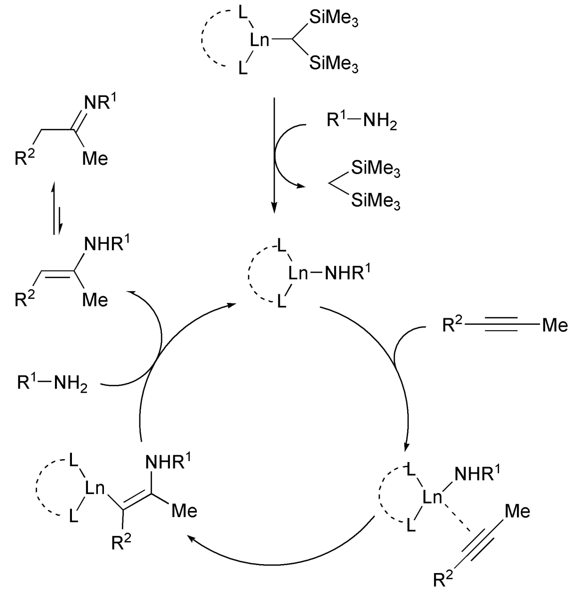


Scheme 5

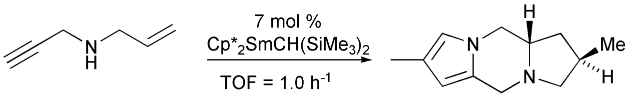
As shown in Scheme 6, the catalytically active species of the reaction is a lanthanide amide, which is formed by rapid and quantitative proton transfer from the amine R^1–NH_2 to the alkyl substituent at the metal center of the precatalyst. The formed lanthanide amide then regioselectively inserts the alkyne into the Ln–N bond to give a lanthanide alkyl complex. A final protonation of the formed Ln–C bond by amine R^1–NH_2 leads to an enamine as initial hydroamination product and regenerates the catalytically active species. Subsequently, the produced enamine is converted to the more stable imine tautomer. If 1-trimethylsilylpropyne is employed as the alkyne the formed imines undergo subsequent 1,3-sigmatropic silyl shifts to give silylated enamines which are isolated as final products (Scheme 6).

Interestingly, the rate of the reaction between 1-trimethylsilylpropyne and *n*-propylamine decreases with constricting metal ion coordination sphere, a behavior that is typical for organolanthanide-catalyzed processes in which olefin insertion into a Ln–C or Ln–N bond is turnover-limiting. The observed turnover frequencies (TOF) are between 14 h^{-1} for $Me_2SiCp^\#_2NdCH(SiMe_3)_2$ and <0.01 h^{-1} for $Cp^*_2SmCH(SiMe_3)_2$ at 60 °C. In regard to comparisons of intermolecular–intramolecular kinetic effects, the obtained data undoubtedly show that under comparable conditions of catalyst, concentration, and temperature, the intramolecular hydroamination process is up to ~1000× more rapid. However, in a subsequent publication several examples for various organolanthanide-catalyzed intra- and intermolecular tandem C–N and C–C bond forming processes of aminoalkynes, aminodialkynes and aminoalkeneynes have been presented.[8] Most impressively, the tricyclic compound **2** is synthesized in one step from *N*-allylpropargylamine **1** by a sequence of four C–N and C–C bond forming reactions in the presence of 7 mol% of $Cp^*_2SmCH(SiMe_3)_2$ at 60 °C in 93% yield (Scheme 7).

The mentioned examples indicate that organolanthanide catalysts offer the possibility to perform intermolecular as well as intramolecular alkyne hydroaminations under relatively mild reaction conditions. However, the rigorously anhydrous/anaerobic reaction conditions required for these processes and the limited number of suitable substrates will probably prevent the developed procedures from being broadly used in organic synthesis.



Scheme 6



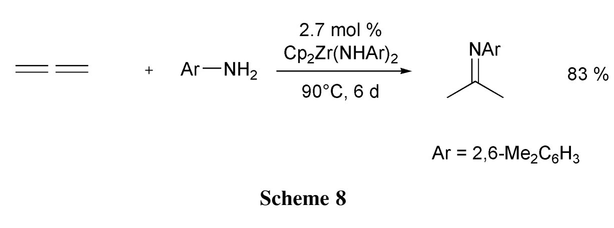
1

(±)-**2** 93 %

Scheme 7

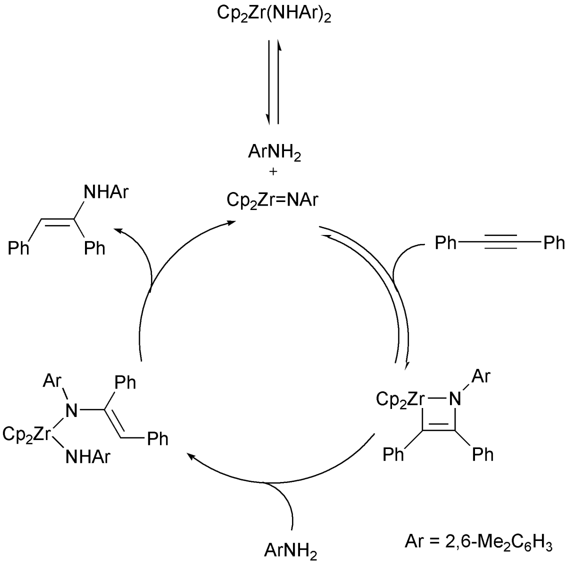
4 Group IV metal and actinide complexes as hydroamination catalysts

In 1992 Bergman *et al.* reported that the zirconium bisamide $Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2$ catalyzes the intermolecular addition of 2,6-dimethylaniline to alkynes and allenes.[9] Corresponding reactions are performed in the presence of 2–3 mol% of the bisamide at 90–120 °C in benzene or toluene. Under these conditions, enamines are formed catalytically but slowly from diphenylacetylene, 2-butyne and allene. However, if 2-butyne or allene are employed the initially formed enamines tautomerize to their isomeric imines (Scheme 8).



Scheme 8

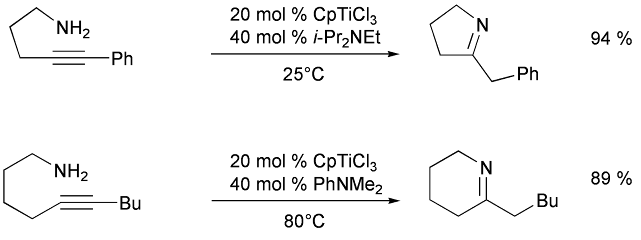
A detailed kinetic investigation of the addition of 2,6-dimethylaniline to diphenylacetylene at 95°C indicates that the reaction is first order in the concentration of bisamide and alkyne and inverse first order in amine. These results are consistent with the catalytic cycle presented in Scheme 9, which involves the imido complex $Cp_2Zr = NAr$ (Ar = $2,6\text{-}Me_2C_6H_3$) as catalytically active species. This imido complex, which is formed by reversible and rate determining α-elimination of amine $Ar\text{–}NH_2$ from the bisamide $Cp_2Zr(NHAr)_2$, can either react with alkyne or amine. While reaction with amine regenerates the bisamide, [2 + 2]-cycloaddition with alkyne provides the azazirconacyclobutene. Rapid protonation by amine at the Zr–C bond gives the enamide amide complex, which then undergoes α-elimination of enamine to regenerate the catalytically active species.



Scheme 9

The fact that the reaction is inverse first order in the concentration of amine makes it indispensable to perform amine additions in highly diluted solutions. However, even under optimized conditions the reported turnover frequencies are only in the range of 0.04–0.2 h^{-1} at 110 °C. The major drawback of the developed procedure is the fact that amines, which are sterically less demanding than 2,6-dimethylaniline, can not be reacted successfully with alkynes or allenes in the presence of zirconocene bisamides. Responsible for this is an irreversible reaction of initially formed zirconium imido complexes $Cp_2Zr = NR$ to catalytically inactive dimers $(Cp_2Zr\text{–}NR)_2$. This dimerization takes place easily if the substituent R is smaller than the bulky 2,6-dimethylphenyl group. Furthermore, it must be kept in mind that α-elimination of amine from the bisamide is facilitated by steric hindrance of the amine. Interestingly, catalytic hydroamination reactions of unsymmetrically disubstituted alkynes such as 1-phenylpropyne or 2-hexyne take place with good to moderate regioselectivities.[10] In general, the more favored product bears the smaller alkyne substituent located α to the nitrogen atom (Scheme 10).

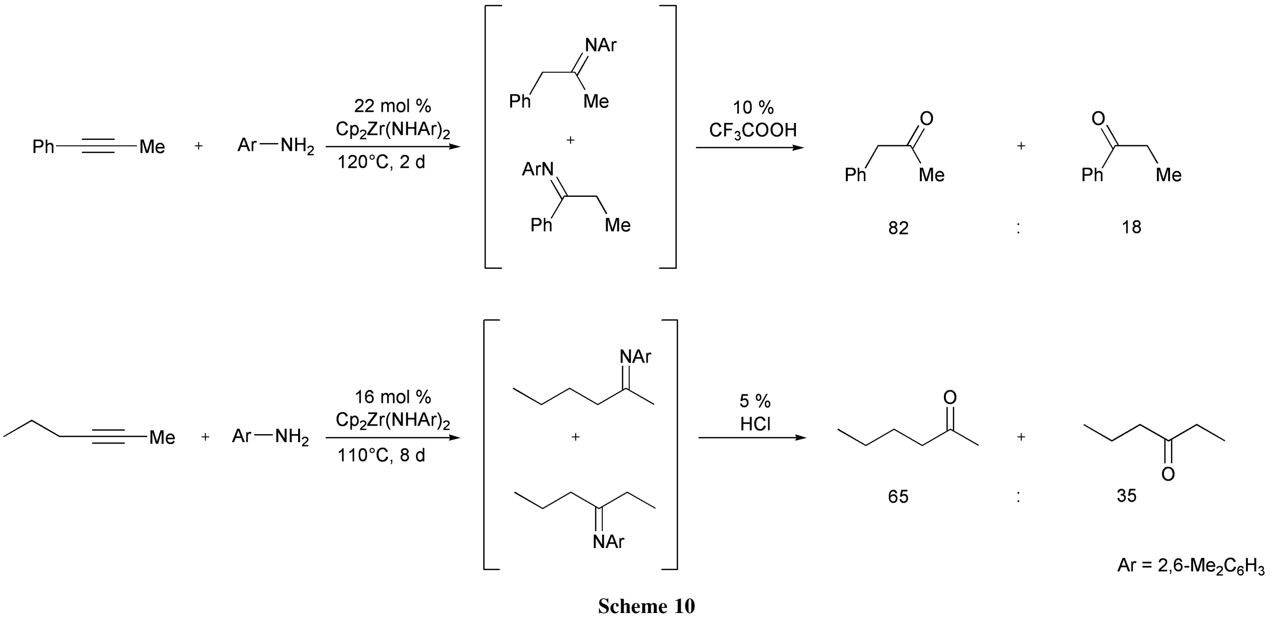
Also in 1992, Livinghouse *et al.* found that $CpTiCl_3$ and $CpTiCl(NEt)_2$ are efficient catalysts for the intramolecular hydroamination of aminoalkynes.[11,12] While these titanium complexes do not catalyze intermolecular hydroamination reactions, several five- and six-membered cyclic imines can be synthesized from corresponding aminoalkynes at room temperature or 80 °C in the presence of 20 mol% of the catalyst and in the case of $CpTiCl_3$ 40 mol% of a tertiary amine ($i\text{-}Pr_2NEt$, $PhNMe_2$) (Scheme 11).



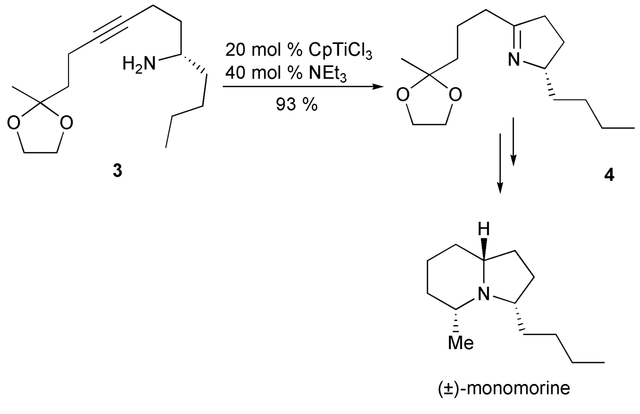
Scheme 11

Since titanium imido complexes, which are generated from the precatalysts and the aminoalkynes *via* loss of HCl or $HNEt_2$, are the proposed catalytically active species the mechanistic details are comparable to those outlined for the zirconocene bisamide-catalyzed hydroamination reaction (Scheme 9). However, it is noteworthy to mention that in contrast to Bergman's results the titanium-catalyzed intramolecular hydroamination does not require a sterically demanding amine part of the aminoalkyne to take place. The efficiency of the developed process was impressively demonstrated by Livinghouse *et al.* as they used a $CpTiCl_3$-catalyzed cyclization of aminoalkyne **3** at room temperature as key-step for the total synthesis of the indolizidine alkaloid (±)-monomorine **5** (Scheme 12).[13]

Closely related, from a mechanistic point of view, is a process published in 1996 by Eisen *et al.*, which uses organoactinide

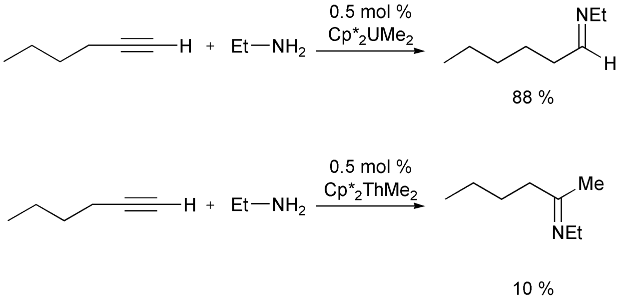


Scheme 10



Scheme 12

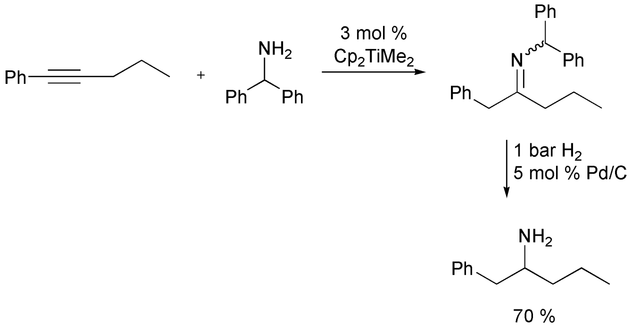
complexes of the type $Cp^*_2AcMe_2$ (Ac = U, Th) as catalysts for the intermolecular hydroamination of terminal alkynes with aliphatic amines.[14] Again, metal imido complexes obtained by protonation of the actinide–carbon bonds by amine could be identified as catalytically active species. Interestingly, the efficiency as well as the regioselectivity of the hydroamination strongly depends on the metal atom. While reactions employing the uranium precatalyst in THF at 65 °C give access to the corresponding aldimines in good to excellent yields, ketimines are obtained in poor to modest yields from reactions in the presence of the analogues thorium complex (Scheme 13).[4] Using this catalyst, dimeric and trimeric alkyne oligomers are the major side products. However, the fact that the employed actinides are radioactive is prohibitive for a broad use of these catalysts in chemical laboratories.



Scheme 13

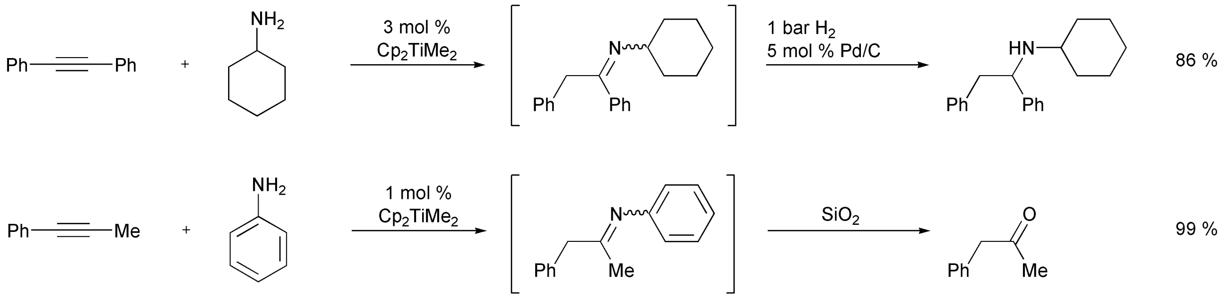
Great progress in the field of group IV metal complexes as hydroamination catalysts was achieved when our group found in 1999, that the well-established reagent Cp_2TiMe_2[15] is a widely applicable, inexpensive catalyst of low toxicity that can be used in intermolecular hydroamination reactions of alkynes.[16] With this catalyst, primary aryl- and alkylamines can be coupled to symmetrically and unsymmetrically internal alkynes. In the case of unsymmetrically substituted alkylarylalkynes, the reaction occurs with high regioselectivity (⩾ 98:2). In general, the more favored product bears the smaller alkyne substituent located α to the nitrogen atom. Typical hydroamination reactions are carried out at 100–110 °C in toluene for 40–72 h. The initially formed imines can either be hydrolyzed to ketones or reduced to secondary amines (Scheme 14).

While aniline derivatives and sterically hindered *sec*- and *tert*-alkylamines react smoothly under the reaction conditions a significant decrease in reactivity is observed for sterically less hindered *n*-alkyl- and benzylamines. As a result, initial experiments to convert alkynes into primary amines using benzylamine as an ammonia equivalent in the hydroamination step followed by hydrogenation of the resulting imine have met with only limited success. However, when the primary *sec*-alkylamine α-aminodiphenylmethane (benzhydrylamine) is used, primary amines can be obtained from alkynes in good yields by Cp_2TiMe_2-catalyzed hydroamination and subsequent hydrogenation (Scheme 15).[17]

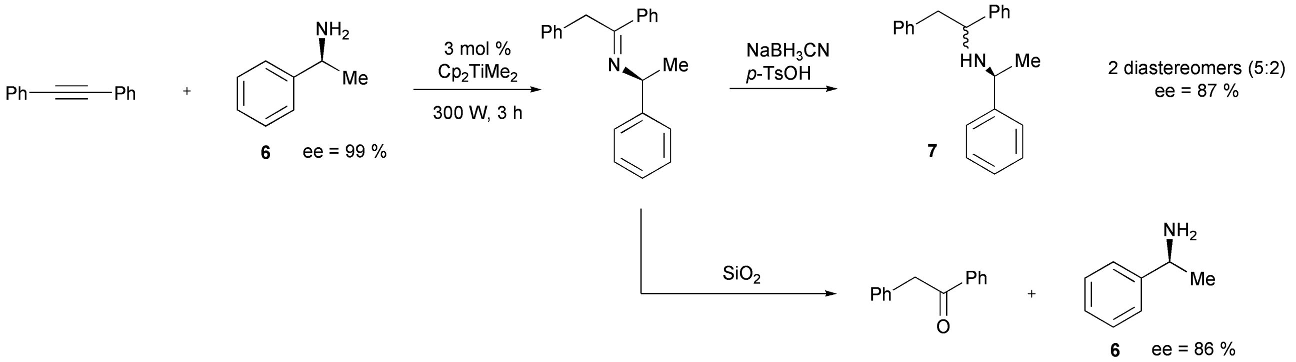


Scheme 15

During a study directed towards optimizing the described method, it was found that the reaction times of Cp_2TiMe_2-catalyzed intermolecular hydroamination reactions can be dramatically shortened under conditions that employ microwave heating instead of conventional heating.[18] For example, under microwave conditions (300 W, 2.45 GHz), a reaction between diphenylacetylene and aniline reaches 100% conversion in the presence of 3 mol% Cp_2TiMe_2 within 3 h compared to 30 h at 105 °C (oil bath). Subsequent hydrogenation of the initially formed imine with H_2 and 5 mol% Pd/C gives access to the corresponding amine in 93% yield. However, an additional reaction under comparable conditions performed at 190 °C (oil bath) also reaches 100% conversion within 3 h. This result shows that the rates observed for reactions performed under microwave irradiation conditions are comparable to those observed at 190 °C. However, in both cases the required reaction times are reduced by a factor of 10. Particularly interesting is the reaction between diphenylacetylene and the enantiomerically pure amine (*S*)-1-phenylethylamine **6** (ee = 99%). After reduction with $NaBH_3CN$/*p*-TsOH two diastereomers of the resulting product **7** are obtained in a 5:2 ratio. GC-analysis shows that the ee-values for both diastereomers of **7** are only 87%. In addition, amine **6** can be reisolated from the



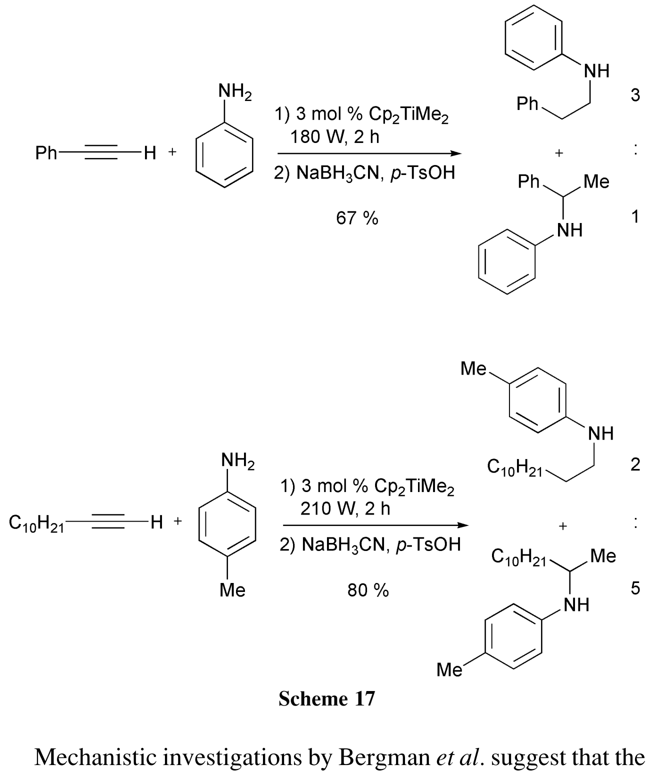
Scheme 14



Scheme 16

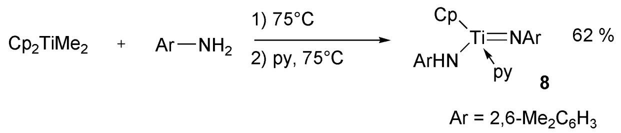
hydroamination reaction after hydrolysis (SiO_2) of the initially formed imine. GC-analysis of recovered **6** shows that the ee value is 86% (Scheme 16). Therefore, it is clear that the Cp_2TiMe_2-catalyzed hydroamination step occurs with partial racemization at the α-carbon atom of the employed amine.[18]

Impressively, hydroamination products of terminal alkynes can also be isolated in reasonable yields when Cp_2TiMe_2 is used as the catalyst. In contrast to observations made with alkylarylalkynes, corresponding reactions lead to the formation of both products formed by terminal and internal addition. While formation of the internal addition-product is favored in addition reactions of aniline derivatives to terminal alkylalkynes, the terminal addition-product is preferred in reactions between anilines and phenylacetylene (Scheme 17). However, if the alkylamine (*S*)-1-phenylethylamine is reacted with phenylacetylene the major product is the internal addition-product.[18]



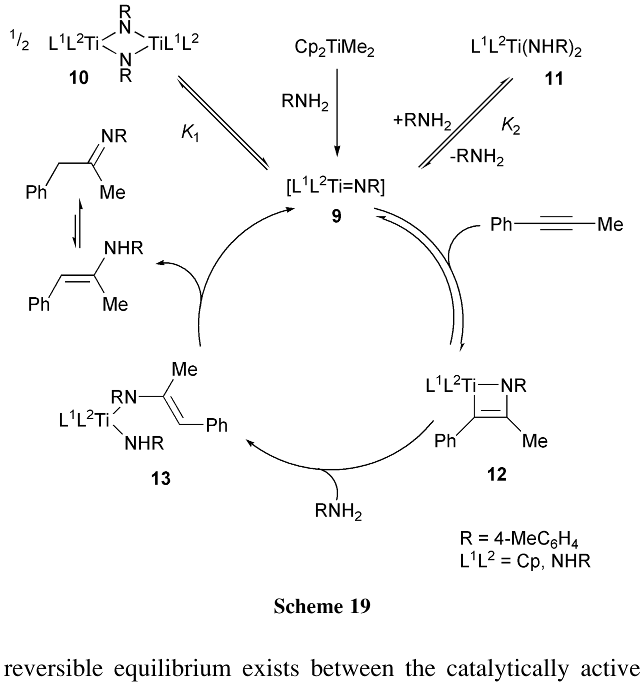
Scheme 17

Mechanistic investigations by Bergman *et al.* suggest that the catalytically active species of the described reactions is a cyclopentadienyl(amido)titanium imido complex.[19] After heating a mixture of Cp_2TiMe_2, 2,6-dimethylaniline, and pyridine to 75 °C for 24 h, the corresponding pyridine stabilized intermediate **8** is formed in 62% yield (NMR *versus* internal standard) (Scheme 18). Mono(cyclopentadienyl) complex **8** rapidly catalyzes the addition of 2,6-dimethylaniline to diphenylacetylene at 75 °C as well as the hydroamination of allenes. Furthermore, hydroamination reactions of allene derivatives involving primary amines and hydrazines can be achieved in the presence of 10 mol% Cp_2TiMe_2 at 90 °C.[19]



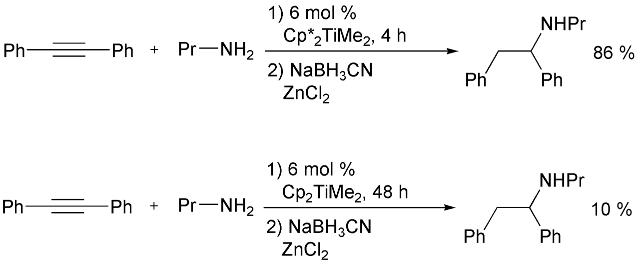
Scheme 18

Kinetic investigations of the reaction between 1-phenylpropyne and 4-methylaniline performed in our group[20] in combination with Bergman's mechanistic study[19] suggest that the mechanism of the Cp_2TiMe_2-catalyzed intermolecular hydroamination of alkynes is correctly described by the catalytic cycle shown in Scheme 19. It is important that a reversible equilibrium exists between the catalytically active titanium imido complex **9** and the dimer **10**. This equilibrium is responsible for the fact that no linear relationship between the catalyst concentration and the observed rate of the reaction exists. Furthermore, the kinetic data are consistent with the assumption that the protonation of the azametallacyclobutene **12** is slow compared to the cycloreversion of **12**. DFT calculations performed by Bergman and Straub strongly support these interpretations of the kinetic study.[21]



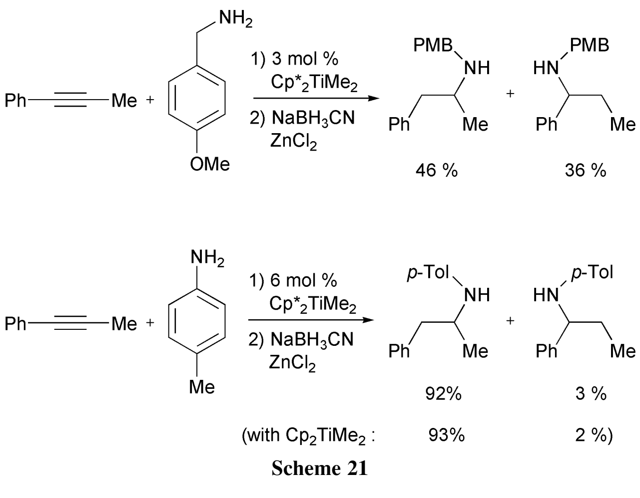
Scheme 19

In addition, the mechanism shown in Scheme 19 easily explains the fact that sterically demanding amines are better substrates for the Cp_2TiMe_2-catalyzed intermolecular hydroamination of alkynes than sterically less hindered amines because unfavorable equilibria (K_1, K_2) between imido complexes (**9**), imido complex dimers (**10**), and bisamides (**11**) for sterically less demanding amines result in slow hydroamination reactions. However, the kinetic investigation further suggests that the use of bigger ligands at the titanium center should influence these equilibria in a positive way and therefore result in accelerated reactions of sterically less hindered amines. Since the pentamethylcyclopentadienyl ligand (Cp*) is much more space demanding than the cyclopentadienyl ligand (Cp) it is not surprising that *n*-alkylamines and benzylamines can be reacted efficiently with various alkynes in the presence of catalytic amounts of $Cp^*_2TiMe_2$.[22] Most impressively, the hydroamination reaction between *n*-propylamine and diphenylacetylene reaches 100% conversion after 4 h in the presence of 6 mol% $Cp^*_2TiMe_2$ at 114 °C. After subsequent reduction performed with zinc-modified $NaBH_3CN$ the amine product is obtained in 86% yield. In comparison, an identical hydroamination reaction performed with 6 mol% Cp_2TiMe_2 does not even reach 100% conversion after 48 h. In this case, the subsequent reduction gives access to only 10% of the desired amine (Scheme 20).



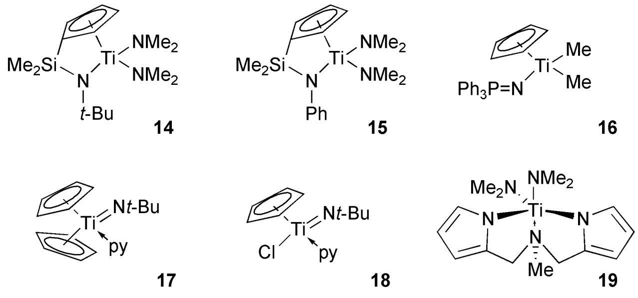
Scheme 20

In the presence of 3–6 mol% $Cp^*_2TiMe_2$ it is also possible to perform addition reactions of *n*-alkyl- and benzylamines to unsymmetrically substituted alkylarylalkynes such as 1-phenylpropyne. Surprisingly, in these cases the observed regioselectivity is low (Scheme 21). However, if $Cp^*_2TiMe_2$ is used as catalyst for the addition of sterically demanding amines (*e.g.* 4-methylaniline) to 1-phenylpropyne, the regioselectivity is as high as observed for Cp_2TiMe_2. This result indicates that obviously the properties of the amines (and not the Cp*-ligands) are responsible for the low regioselectivity of $Cp^*_2TiMe_2$-catalyzed hydroamination reactions performed with sterically less demanding *n*-alkyl- and benzylamines.[22]



Scheme 21

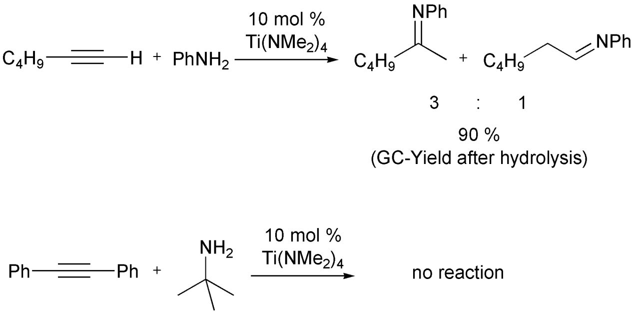
Besides Cp_2TiMe_2, $Cp^*_2TiMe_2$, and complex **8**, several other titanium complexes (**14**–**26**) have been identified as catalysts for the intermolecular hydroamination of alkynes during the last two years.[20,23–25] As can be seen from Scheme 22, all identified hydroamination catalysts bear either two labile ligands (methyl or dimethylamido) or a preformed imido ligand.



20 $(C_5H_4Me)_2TiMe_2$
21 $(C_5H_4Et)_2TiMe_2$
22 $(C_5H_4i\text{-}Pr)_2TiMe_2$
23 $(C_5H_4t\text{-}Bu)_2TiMe_2$
24 $(Ind)_2TiMe_2$
25 Cp^*TiMe_3
26 $Ti(NMe_2)_4$

Scheme 22

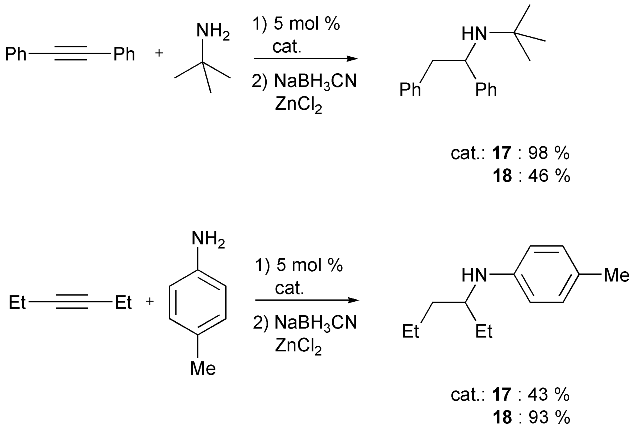
Since a huge number of related compounds is already known from the chemical literature and other titanium complexes can be synthesized easily, one should expect that many other titanium catalysts for the intermolecular hydroamination of alkynes will be identified in the near future. Therefore, the potential for an optimization of titanium containing hydroamination catalysts must be regarded as extremely high, which is desirable since big differences exist between titanium complexes regarding catalytic activity for certain reactions. For example, catalysts $Ti(NMe_2)_4$ **26** and **19** have been used extensively by Odom *et al.* for the regioselective hydroamination of 1-hexyne,[24,25] while reactions between diphenylacetylene and *tert*-butyl- or cyclohexylamine are not catalyzed by these complexes under comparable conditions (Scheme 23).[23–25]



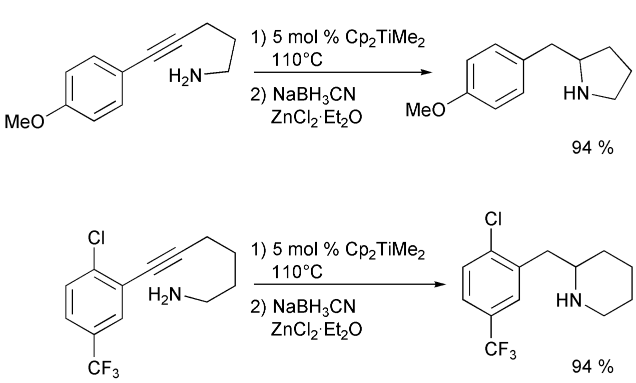
Scheme 23

Another impressive example for varying catalytic activity is summarized in Scheme 24. While the bis(cyclopentadienyl) imido complex **17** gives a very good result for the reaction between diphenylacetylene and *tert*-butylamine (98% yield, the hydroamination reaches 100% conversion within less than 2 h at 105 °C), a modest result is obtained for the reaction between 3-hexyne and 4-methylaniline (43% yield) using this catalyst. In comparison, the chloro-substituted imido derivative **18** shows an inverse behavior under identical conditions. These results clearly indicate that the catalytic activity of a certain catalyst is strongly dependent on the properties of the employed substrates.[23]

Besides the mentioned investigations, it was recently recognized that Cp_2TiMe_2 is also an efficient catalyst for the intramolecular hydroamination of aminoalkynes.[26] In contrast to intermolecular hydroaminations, the cyclization reactions do not require a sterically demanding amine part of the aminoalkyne to take place efficiently. As can be seen from Scheme 25 γ- and δ-aminoalkynes can be converted into five- and six-membered cyclic amines by Cp_2TiMe_2-catalyzed intramo-



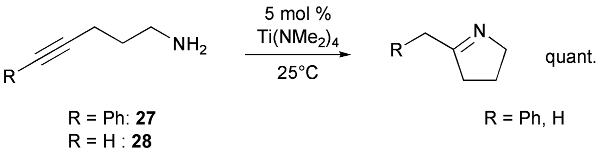
Scheme 24



Scheme 25

lecular hydroamination and subsequent reduction. This result undoubtedly proves that Cp_2TiMe_2 must be regarded as the most general catalyst for the hydroamination of alkynes known today.

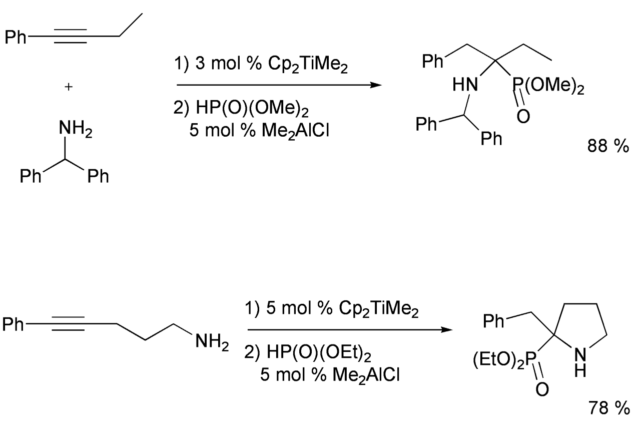
However, since the employed reaction conditions are relatively harsh (110 °C, 6 h) it is noteworthy to mention that the aminoalkynes **27** and **28** can be converted to the corresponding imines in quantitative yields at room temperature in the presence of 5 mol% of the tetraamide complex $Ti(NMe_2)_4$ **26** (Scheme 26).[27]



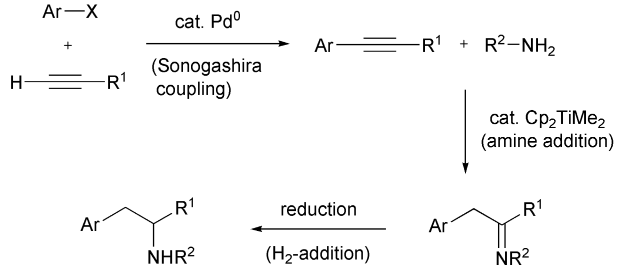
Scheme 26

In additional studies, the Cp_2TiMe_2-catalyzed hydroamination of alkynes has already been used as an efficient tool for the synthesis of biologically interesting compounds. For example, α-aminophosphonates can be synthesized from alkynes, primary amines and dimethyl or diethyl phosphite as starting materials. The reaction sequence, which is performed as a one-pot operation, starts with a Cp_2TiMe_2-catalyzed intra- or intermolecular hydroamination of the alkyne. A subsequent nucleophilic addition of diethyl or dimethyl phosphite to the resulting imine, performed in the presence of catalytic amounts of Me_2AlCl, gives access to the desired cyclic or acyclic α-aminophosphonates in good yields (Scheme 27).[28]

Furthermore, a new and highly flexible procedure for the synthesis of 2-arylethylamine derivatives has been reported. By this process, the target compounds can be synthesized with high diversity in three steps from aryl halides, terminal alkynes, and primary amines (Scheme 28).[29]

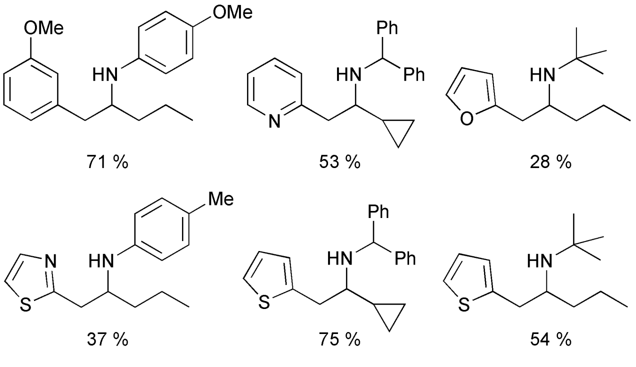


Scheme 27



Scheme 28

The reaction sequence starts with a palladium-catalyzed coupling of an aryl halide and a terminal alkyne (Sonogashira coupling). A subsequent Cp_2TiMe_2-catalyzed hydroamination of the obtained alkylarylalkyne, which takes place regioselectively in the 2-position, gives access to an α-arylketimine. A final reduction with $NaBH_3CN/ZnCl_2{\cdot}Et_2O$ results in the formation of the desired 2-arylethylamine derivative in modest to good yields. Scheme 29 shows several examples of already synthesized 2-arylethylamine derivatives. The yields represent overall yields based on the employed aryl halide.



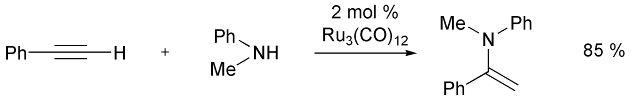
Scheme 29

The results mentioned in this chapter clearly indicate that titanium complexes bearing two labile ligands must be regarded as very promising catalysts for the hydroamination of alkynes. However, since titanium is a highly oxophilic metal it is most likely that the functional group tolerance of titanium-based hydroamination procedures is low.

5 Late transition metal complexes as hydroamination catalysts

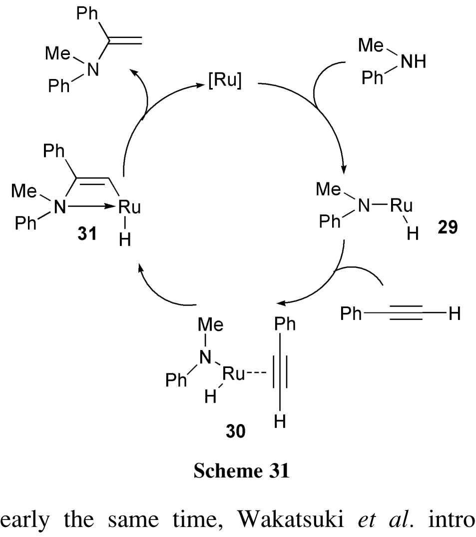
A variety of late transition metal complexes (Hg- and Tl-compounds are described separately in Section 2) have successfully been employed in catalytic hydroamination reactions in the last decade.[1] However, the fact that intermolecular amination reactions are generally much more difficult to achieve than intramolecular reactions is clearly demonstrated by the small number of corresponding methods that have been reported.[30] Furthermore, all these processes are limited to specific substrates. Different systems based on ruthenium-,[31–33] rhodium-[34] or palladium-complexes[35] have been described, most of all in regard to the intermolecular hydroamination of terminal alkynes. However, a great advantage of using late transition metals is their lower affinity to oxygen than early transition metals, lanthanides and actinides. Therefore, a larger scope of substrates (functional group compatibility) can be tolerated in related hydroamination reactions compared with reactions in the presence of high oxophilic metals.

The first intermolecular ruthenium-catalyzed hydroamination of alkynes was mentioned by Uchimaru *et al.* in 1999.[31] In the presence of catalytic amounts (2 mol%) of $Ru_3(CO)_{12}$, phenylacetylene and its derivatives undergo regioselective insertion into the N–H-bond of N-methylaniline to afford *N*-methyl-*N*-(α-styryl)anilines in good yields. The reactions are carried out in sealed glass tubes under nitrogen at 70 °C for 18 h in the absence of a solvent (Scheme 30).



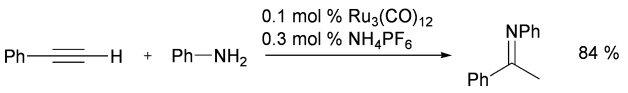
Scheme 30

However, a 10-fold excess of amine is necessary, otherwise the corresponding enamines are only obtained in very low yields (4–26%). Isomers of the enamine and trimers of the employed phenylacetylene are detected as side products. The scope of the reaction is strongly limited to *N*-methylaniline and phenylacetylenes. Only one example employing the aliphatic conjugated enyne, 1-ethynylcyclohexene is given, leading to 77% of the desired product. A comparison of different *para*-substituted phenylacetylenes suggests that an electron-withdrawing substituent increases the yield of the desired product. Besides, several different transition metal complexes are examined and found to be ineffective. Based on the known activation of the N–H bond of aniline by $Ru_3(CO)_{12}$, Uchimaru *et al.* propose a mechanism involving the (amido)ruthenium hydride **29** as intermediate. The coordination of the alkyne to the ruthenium center leads to complex **30**, which undergoes insertion of the coordinated carbon–carbon triple bond into the Ru–N bond. Finally, reductive elimination of the enamine from the vinyl ruthenium species **31** regenerates the coordinatively unsaturated ruthenium(0) centre (Scheme 31).



Scheme 31

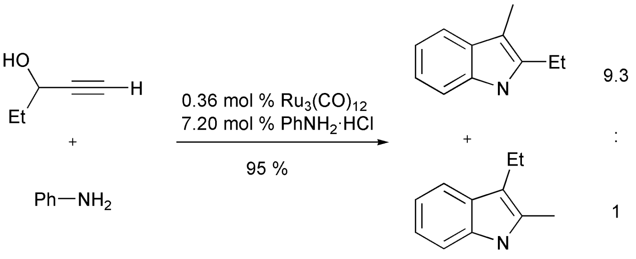
At nearly the same time, Wakatsuki *et al.* introduced a $Ru_3(CO)_{12}$/acid catalyst system permitting the high-yielding reaction of anilines with terminal phenylacetylenes to give the corresponding imines.[32] In combination with small amounts of an acid or its ammonium salt a great increase of the catalytic activity of the rutheniumcarbonyl cluster is observed. Several additives were examined and NH_4PF_6 and HBF_4 were found to give the best results (Scheme 32).



Scheme 32

The catalyst loading is 0.1–1 mol% and 3 equiv (based on catalyst) of the acid additive are used. The reactions are carried out at 100 °C for 12 h. Best results were observed using a small excess of alkyne (1.2 equiv). Under optimized conditions turnover numbers (TON) of 300 are reached. However, only one example is given for the hydroamination of an aliphatic alkyne (1-octyne) with aniline, which gives the corresponding product in 63% yield. Advantageously, the reactions can be run under an air atmosphere and often without a solvent. Otherwise, the use of methanol, 2-propanol, toluene, or tetrahydrofuran leads to similar results.

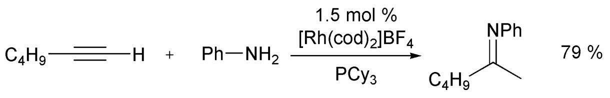
Based on the previously described intermolecular addition of anilines to terminal alkynes, Wakatsuki and Tokunaga *et al.* reported a new Bischler-type indole synthesis.[33] Catalyzed by a ruthenium carbonyl/additive mixture (both reagents are commercially available) using propargylic alcohols as terminal alkynes this one-pot synthesis offers access to 2-substituted-3-methyl indols with good regioselectivity (Scheme 33).



Scheme 33

The reactions are carried out under open air and basically without a solvent as mentioned above at a reaction temperature of 140 °C using a small excess of alkyne (1.3 equiv). Since aniline hydrochloride is a less effective additive than NH_4PF_6 at least a 20-fold excess (based on catalyst) is needed. However, better regioselectivities are reached using aniline hydrochloride. While a variety of *ortho*- and *para*-substituted anilines can be used, anilines with electron-donating groups give better results. However, the reaction with *o*-methoxycarbonyl aniline is very slow and affords the desired product in only poor yield. The reaction sequence consists of three steps: hydroamination of the C–C triple bond, hydrogen migration of the resulting iminoalcohol to the aminoketone and cyclization to give the indole skeleton. The aminoketone (Bischler-type intermediate) undergoes a known fast interconversion of regioisomers in the presence of aniline hydrochloride leading to the observed regioselectivities. Detailed studies showed that the metal does not participate in hydrogen migration or cyclization, but is responsible for the hydroamination step.

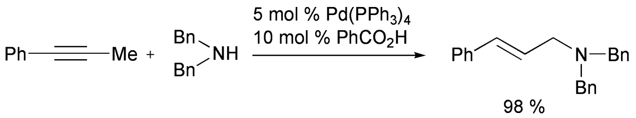
Several examples for intermolecular hydroamination reactions of alkynes using rhodium-complexes were reported by Beller *et al.* in 2001.[34] In the presence of catalytic amounts of commercially available $[Rh(cod)_2]BF_4$, terminal alkynes react with anilines to give the desired imines regioselectively in good to high yields. The presence of a phosphine ligand is essential for the reaction to proceed. Best results are obtained with 3 equiv (based on rhodium) of tricyclohexylphosphine (PCy_3) (Scheme 34).



Scheme 34

Advantageously, the reactions run smoothly at room temperature. Thus, oligomerization and polymerization reactions of the alkyne are minimized under these mild conditions. However, the scope of the reaction is strongly limited to aliphatic alkynes. In the case of phenylacetylene, rapid oligomerization occurs resulting in very low product yields. Furthermore, only aniline derivatives as amine component give access to the products in good yields. Electron donating as well as electron withdrawing substituents at the aniline ring are tolerated, whereby electron-poor anilines react faster. The conversion of sterically demanding anilines such as *o*-methylaniline results in lower yields.

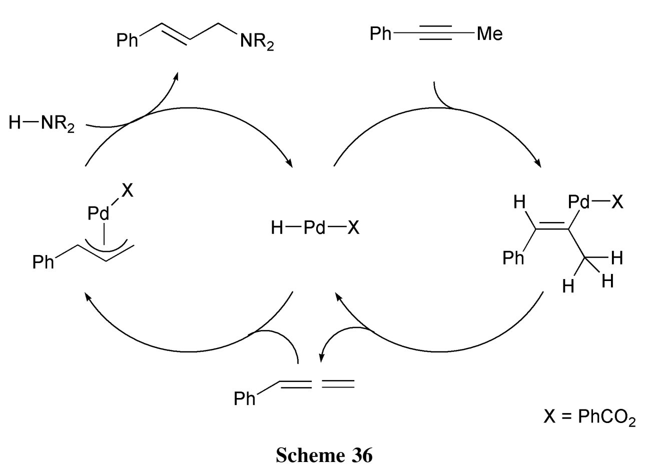
An interesting Pd-based amination method was reported by Yamamoto *et al.* in 1999. The reaction of aromatic alkynes with secondary amines in the presence of 5 mol% $Pd(PPh_3)_4$ and 10 mol% $PhCO_2H$ in dry dioxane at 100 °C gives access to allylic amines in good to high yields (Scheme 35).[35]



Scheme 35

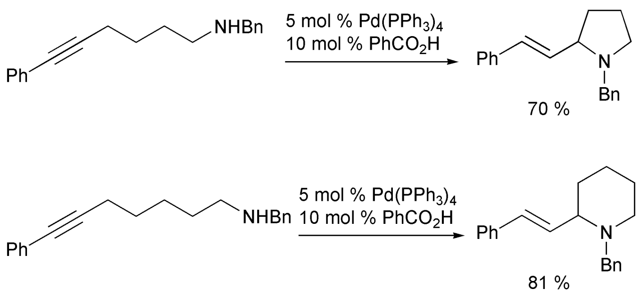
Reaction times of about 12 h are necessary for corresponding transformations. As shown in several examples using 1-phenylpropyne as alkyne compound, the reactions take place with high stereo- and regioselectivity. Various secondary amines can be used, while the method is strongly limited to aromatic alkynes. In addition, arylalkynes with an electron-withdrawing substituent in *para*-position are poor substrates.

The presence of benzoic acid is essential for the process, since $Pd(PPh_3)_4$ and benzoic acid generate a hydridopalladium species, which initiates the known catalytic isomerization of alkynes to the corresponding allenes. In a second catalytic cycle, hydropalladation of the allene leads to a π-allylpalladium species that reacts with the amine to give the desired allylic amine as product and regenerates the active hydridopalladium species (Scheme 36).



Scheme 36

If primary amines are treated with 3 equiv of the alkyne (*e.g.* 1-phenylpropyne) 2 : 1 adducts are obtained in good yields. The usefulness of the described method is impressively demonstrated by the intramolecular version of the amination reaction. The conversion of monoprotected aminoalkynes gives access to pyrrolidine or piperidine derivatives in good yields (Scheme 37).

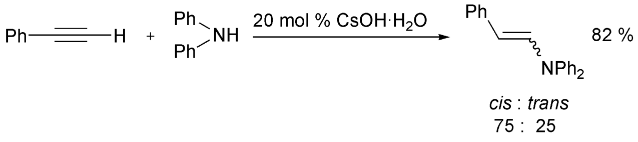


Scheme 37

In general, a great advantage of late transition metal catalyzed hydroamination reactions is the high functional group compatibility. However, the major drawback of the developed processes is the limited scope of substrates (*e.g.* alkynes) that can be used. Furthermore, it is noteworthy that intramolecular hydroamination reactions catalyzed by late transition metal complexes can be achieved more easily. This fact is clearly demonstrated by a huge number of published methods for the intramolecular hydroamination of alkynes.[30]

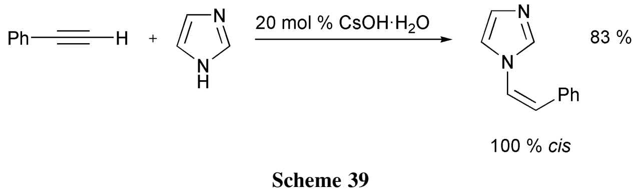
6 Base-catalyzed hydroamination reactions

A base-catalyzed hydroamination of alkynes was published by Knochel *et al.* in 1999. In the presence of catalytic amounts of cesium hydroxide ($CsOH{\cdot}H_2O$), substituted anilines and heterocyclic amines undergo an addition to phenylacetylene leading to functionalized enamines in satisfactory yields.[36] A typical run takes place at 90–120 °C in *N*-methylpyrrolidone for 12–24 h. However, relatively high catalyst loadings (20 mol%) are used and in most cases the desired enamines are obtained as *cis* : *trans* mixtures (Scheme 38).



Scheme 38

Especially attractive is the addition of various N-heterocycles to phenylacetylene resulting in the formation of heterocyclic enamine derivatives in moderate to good yields. Advantageously, with several of these substrates only the *cis*-enamine is obtained (Scheme 39).



Scheme 39

However, under the mentioned reaction conditions the addition of alcohols to phenylacetylene is preferred, compared to the reaction of amines. Therefore, the hydroxy-group is a non-tolerated functionality under these conditions.

Furthermore, it is worth mentioning that older base-catalyzed intermolecular hydroamination methods for alkynes often suffer from subsequent reactions of the initially formed enamines and imines (oligomerization) caused by the harsh reaction conditions.[37,38]

7 Summary

In summary, the presented examples indicate that great progress has been made in developing hydroamination procedures for alkynes over the past years. At the moment, titanium complexes bearing two labile ligands seem to be the most promising catalysts. Many examples of related catalysts are already known or will be reported in the future. Since the employed reaction conditions are comparably mild, initial applications towards the synthesis of biologically attractive compounds have already appeared in the literature. However, since titanium is a highly oxophilic metal the functional group tolerance of titanium-based hydroamination procedures is supposed to be low. Better functional group tolerance is provided by late transition metal catalysts which have also been used successfully for certain reactions. Unfortunately, the scope of corresponding intermolecular processes is often limited to a special class of substrates. If this drawback can be overcome, late transition metal complexes will play an important role as hydroamination catalysts for alkynes.

Besides these two major classes of hydroamination catalysts, lanthanide, actinide, and zirconium complexes as well as thallium and mercury compounds can be used successfully for intermolecular hydroamination processes. However, the properties of these catalysts offer severe disadvantageous compared to titanium and late transition metal catalysts. Finally, base-catalyzed intermolecular hydroamination methods for certain substrates have also been reported.

8 Acknowledgements

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