The catalytic hydroamination of alkynes

René Severin and Sven Doye*

Catalytic additions of ammonia or primary and secondary amines to non-activated alkenes and alkynes are called hydroaminations. These reactions of fundamental simplicity represent the most atom efficient processes for the formation of amines, enamines and imines, which are important bulk and fine chemicals or building blocks in organic synthesis. Consequently, the development of corresponding hydroamination reactions has received much attention and great progress has been achieved in the case of catalytic hydroaminations of alkynes over the past four years. To illustrate this progress, this *tutorial review* will mostly focus on recent developments in the field of intermolecular hydroamination of alkynes that appeared in the literature between the end of 2002 and October 31, 2006.

1 Introduction

In early 2003, our first review on ''The Catalytic Hydroamination of Alkynes'' was published in this journal.[1] Since then, it has been cited more than 130 times indicating that the catalytic hydroamination of alkynes has received considerable attention during the last four years. In general, primary or secondary amines can undergo addition reactions with alkynes to give enamines or imines. These reactions of fundamental simplicity are called hydroaminations of alkynes and they take place without any formation of side products as can be seen in Scheme 1. However, for electrostatic reasons, amines generally do not react spontaneously with alkynes (as

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long as they are not activated by electron withdrawing substituents) because both species must be regarded as electron rich. As the consequence, hydroaminations of alkynes can only be achieved in the presence of certain catalysts.

While corresponding hydroamination reactions of alkenes lead directly to stable secondary or tertiary amines,[2] alkynes are converted into reactive species (enamines, imines) which can be further used for various sorts of subsequent transformations. For that reason, the hydroamination of alkynes is obviously an ideal initial step for reaction sequences. This is particular true because alkynes are inexpensive and readily available starting materials in organic synthesis at least on a laboratory scale. It is also important to understand that alkynes undergo hydroamination reactions more easily than alkenes. Responsible for this fact are sterical reasons and the weakness of the π-bonds present in alkynes which are

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University of Oldenburg. His major research interest is natural product synthesis involving hydroamination reactions.
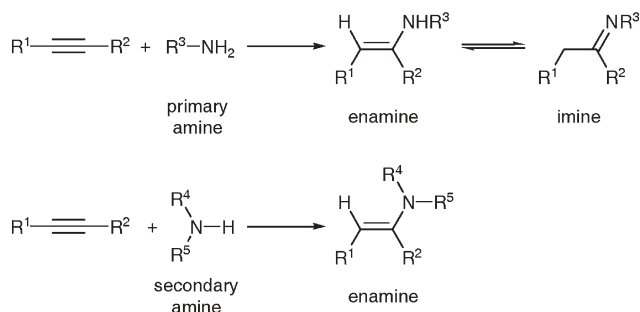
Sven Doye was born in Berlin, Germany in 1967. Between 1986 and 1990 he studied chemistry at the Technical University of Berlin. He received his diploma degree in 1990 from the same University and his PhD in 1993 from the University of Hannover. During his graduate

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studies under the supervision of Prof. E. Winterfeldt, he worked on the stereoselective synthesis of the sesquiterpene (−)-myltaylenol. 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 Prof. 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 October 2003 to September 2006 he was Professor of Organic Chemistry at the University of Heidelberg, Germany and since September 2006 he has been Professor of Organic Chemistry at the University of Oldenburg, Germany. From September 2002 to January 2003 he was also Guest Professor at Cardiff University, Wales, UK.

Scheme 1 (chemical structures):

R^1═══R^2 + R^3—NH_2 → enamine → imine

primary amine — enamine — imine

R^1═══R^2 + secondary amine (R^4, R^5, N—H) → enamine

Scheme 1

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approximately 70 kJ mol^{-1} weaker than the π-bond of a typical alkene. However, from an industrial point of view the hydroamination of alkenes is by far the more important chemical transformation because alkenes are nowadays the universal starting materials in the chemical industry. Each year, they are produced on a multi million ton scale by cracking processes in petrochemical production plants. Starting from these alkenes, efficient hydroaminations with ammonia or simple amines would offer direct pathways to higher substituted amines which play an important role as bulk and fine chemicals. Since corresponding processes would deliver the desired products in a single step without any formation of waste material efficient hydroaminations of alkenes would offer significant economical and environmental advantages. Unfortunately, efficient and general methods for the hydroamination of non-activated alkenes still remain limited. On the other hand, great progress has been made in the development of catalytic hydroaminations of alkynes during the last few years and, hopefully, the knowledge obtained during this process will sometimes contribute to the development of efficient and general procedures for catalytic hydroaminations of alkenes.

A common problem of both transformations is the fact that generally two isomeric products can be formed if unsymmetrically substituted alkenes or alkynes are employed as substrates. In order to designate these isomers, often Markovnikov's rule is used. For example, the hydroamination of a terminal alkyne, as shown in Scheme 2, can principally lead to a Markovnikov and an anti-Markovnikov product (enamine forms are omitted for clarity). Correspondingly, it is an important goal in hydroamination chemistry to force the reaction in either one or the other direction.

In 2003, our review mainly dealt with intermolecular hydroaminations of alkynes.[1] We summarized early results obtained with catalysts containing Hg, Tl, lanthanides and actinides as well as more recent applications of group IV metal and late transition metal complexes as hydroamination catalysts. Many related examples for intramolecular additions
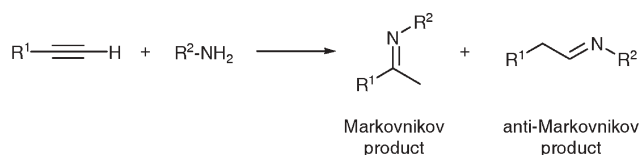
of amine derivatives to alkynes can be found in a recent review published in 2004.[3] In 2003 we concluded that "titanium complexes bearing two labile ligands seem to be the most promising catalysts." However, we also mentioned that "late transition metal complexes will play an important role as hydroamination catalysts for alkynes." As can be seen below, both statements were not totally wrong.
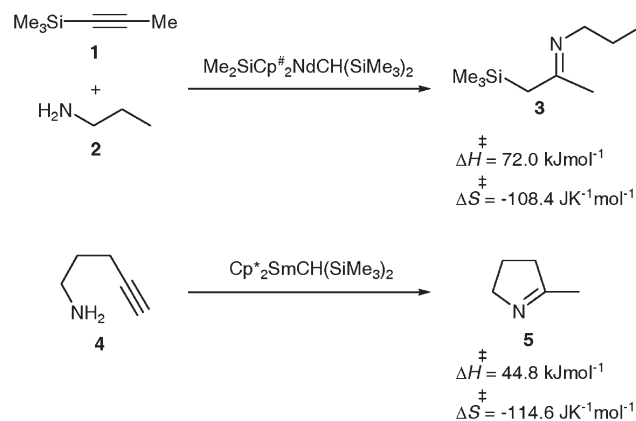
With a few exceptions, this review is focused on recent developments in the field of intermolecular hydroamination of alkynes that appeared in the literature between the end of 2002 and October 31, 2006. Older results and intramolecular reactions can be found in ref. 1–3.

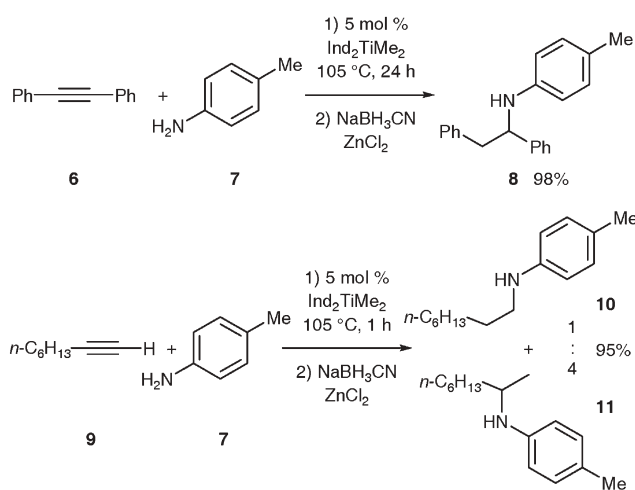## 2 Lanthanide complexes as hydroamination catalysts

In 1996, the first examples of organolanthanide complexes as catalysts for the intermolecular hydroamination of alkynes were reported. Corresponding complexes of the type $Cp^*_2LnCH(SiMe_3)_2$ and $Me_2SiCp^\#_2LnCH(SiMe_3)_2$ ($Cp^* = \eta^5$-C_5Me_5, $Cp^\# = \eta^5$-C_5Me_4, Ln = Sm, Lu, Nd) which serve as efficient precatalysts for the regioselective intermolecular hydroamination of alkynes and alkenes with primary amines have already been presented in our last review.[1] However, recent kinetic studies confirmed the proposed mechanisms of lanthanide-catalyzed intermolecular and intramolecular hydroaminations (for mechanistic details, see ref. 1).[4] The determined activation parameters (Scheme 3) are suitable to compare the intermolecular hydroamination with the intramolecular hydroamination/cyclization reaction. Interestingly, the large negative $\Delta S^{\neq}$ values are comparable in both cases. This suggests that the intramolecular process does not benefit from a major activation entropic advantage and that both transition states are highly organized.

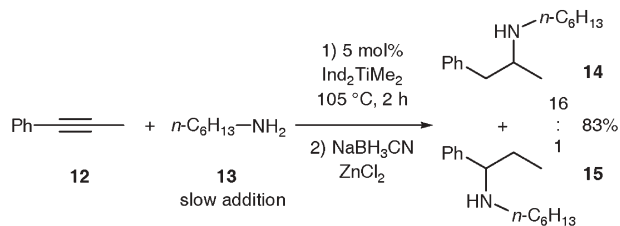## 3 Titanium and zirconium complexes as hydroamination catalysts

Approximately 35 papers that describe novel titanium and zirconium complexes as more or less improved catalysts for the intermolecular hydroamination of alkynes or applications of already established hydroamination catalysts like Cp_2TiMe_2 ($Cp = \eta^5$-C_5H_5), $Ti(NMe_2)_4$ and others have appeared in the literature during the last four years. This fact clearly underlines
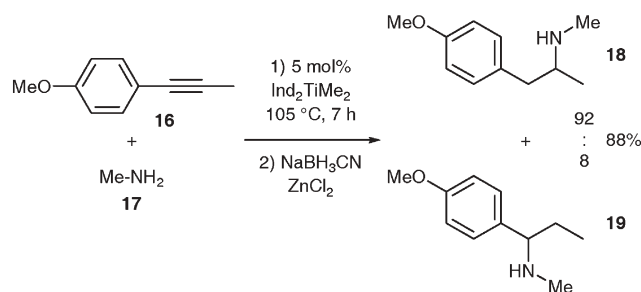

Scheme 2 (chemical structures):

R^1═══H + R^2—NH_2 → Markovnikov product + anti-Markovnikov product

Scheme 2

Scheme 3 (chemical structures):

Me_3Si═══Me (**1**) + H_2N— (**2**) →[$Me_2SiCp^\#_2NdCH(SiMe_3)_2$] product **3**

$\Delta H^{\ddagger}$ = 72.0 kJmol^{-1}
$\Delta S^{\ddagger}$ = -108.4 JK^{-1}mol^{-1}

(**4**, NH_2 alkyne) →[$Cp^*_2SmCH(SiMe_3)_2$] product **5**

$\Delta H^{\ddagger}$ = 44.8 kJmol^{-1}
$\Delta S^{\ddagger}$ = -114.6 JK^{-1}mol^{-1}

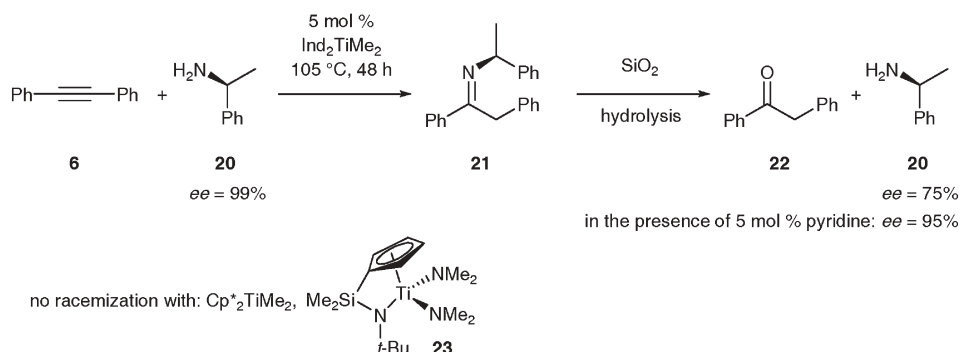**Scheme 3**

Scheme 4

Scheme 5

Scheme 6

the case of unsymmetrically substituted 1-phenyl-2-alkyl-alkynes, the reactions occur with modest to excellent regioselectivities, favoring the formation of the anti-Markovnikov regioisomers. Particularly impressive is the fact that using Ind$_2$TiMe$_2$ it was possible for the first time to react sterically less hindered n-alkyl- and benzylamines with 1-phenylpropyne (**12**) in a highly regioselective fashion. However, to achieve reasonable rates sterically less hindered amines need to be added slowly to the reaction mixtures (Scheme 5). Otherwise, reactions do not reach more than 30% conversion within 48 h.

This surprising behaviour can easily be understood by the fact that the catalytic cycle (for mechanistic details, see ref. 1) and the corresponding rate law include the possibility that the rate of the reaction increases with decreasing concentration of the employed amine. Taking advantage of this idea, it is even possible to react a wide range of alkynes with gaseous methyl- and ethylamine.[6] For that purpose, solutions of alkynes are simply stirred under an atmosphere of the corresponding amine (1 atm) in the presence of 5 mol% Ind$_2$TiMe$_2$ at 105 °C. This simple hydrogenation-like set-up of the experiments results in low concentrations of the gaseous amines in the liquid phase and in fast reactions (Scheme 6).

Interestingly, it was found that Ti-catalyzed hydroamination reactions of alkynes with enantiomerically pure amines possessing a chiral center adjacent to the nitrogen atom can take place with partial racemization.[7] Fortunately, the amount of racemization at the corresponding chiral center seems to be strongly influenced by the nature of the catalyst. Although the degree of racemization is relatively high when Ind$_2$TiMe$_2$, Cp$_2$TiMe$_2$ or Ti(NMe$_2$)$_4$ are used as catalysts (Scheme 7), the addition of small amounts of pyridine to the hydroamination reaction mixture can minimize the undesired partial

the outstanding role of the group IV metals in hydroamination chemistry.

Among the class of titanocene catalysts, commercially available Ind$_2$TiMe$_2$ (Ind = indenyl) proved to be a highly active and general catalyst for the intermolecular hydroamination of alkynes. With this catalyst, primary aryl-, $tert$-alkyl-, sec-alkyl-, and n-alkylamines can be reacted with internal and terminal alkynes. Subsequent reduction of the initially formed imines with NaBH$_3$CN in the presence of ZnCl$_2$ gives access to secondary amines in good to excellent yields (Scheme 4).[5] At 105 °C, in the presence of 5.0 mol% Ind$_2$TiMe$_2$, typical reaction times for the hydroamination step are in the range of 1–24 h.

While the major product of hydroamination reactions of either terminal arylalkynes or t-BuNH$_2$ is always the anti-Markovnikov isomer, terminal alkylalkynes (*e.g.* **9**) react with arylamines to give the Markovnikov products preferably. In

Scheme 7

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Chem. Soc. Rev., 2007, **36**, 1407–1420 | 1409

racemization. In addition, Cp*$_2$TiMe$_2$ and *ansa*-complex **23** are suitable catalysts for racemization-free hydroamination reactions. However, for many titanium catalysts there is no data available on this issue.

Detailed studies employing half-sandwich complexes **30–32** (Scheme 8) containing a cyclopentadienyl ligand with a pendant donor substituent as catalysts have revealed that with theses catalysts, alkynes undergo highly regioselective hydroamination reactions to give mixtures of enamines and imines.[8–10] For example, anti-Markovnikov products with regioselectivities of 100% are generally obtained from reactions of terminal and internal aromatic alkynes like phenylacetylene (**24**) and 1-phenylpropyne (**12**). When aliphatic alkynes are reacted with alkylamines in the presence of catalyst **32**, the regioselectivities are 75–100% also in favor of the anti-Markovnikov products. In contrast, aliphatic alkynes react with sterically demanding aromatic amines to give the Markovnikov products exclusively with the same catalyst. However, when sterically less demanding *n*-dodecylamine is used the hydroamination reactions with catalyst loadings of 5 mol% of **32** are relatively slow and do not reach conversions of more than 25% within 24 h at 100 °C.

Impressively, benzylamine (**34**), another example of a sterically less demanding amine, undergoes relatively fast and high yielding hydroamination reactions with several aliphatic alkynes such as 1-hexyne (**33**) to give the anti-Markovnikov products almost exclusively (>49 : 1) when the bis(amidate) titanium catalyst **36** is employed (Scheme 9).[11] While comparable results are obtained with various other amines and alkynes, the regioselectivity is completely reversed when 2,6-dimethylaniline (**25**) is reacted with 1-hexyne (**33**) in the
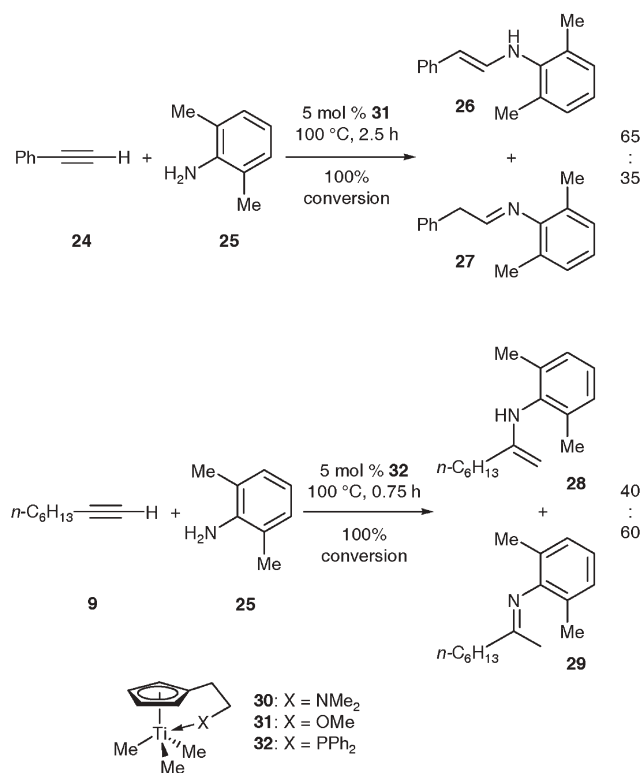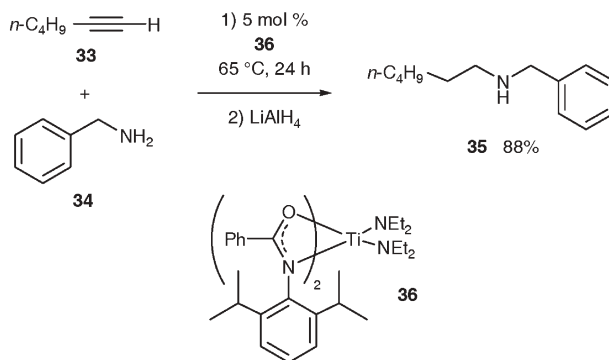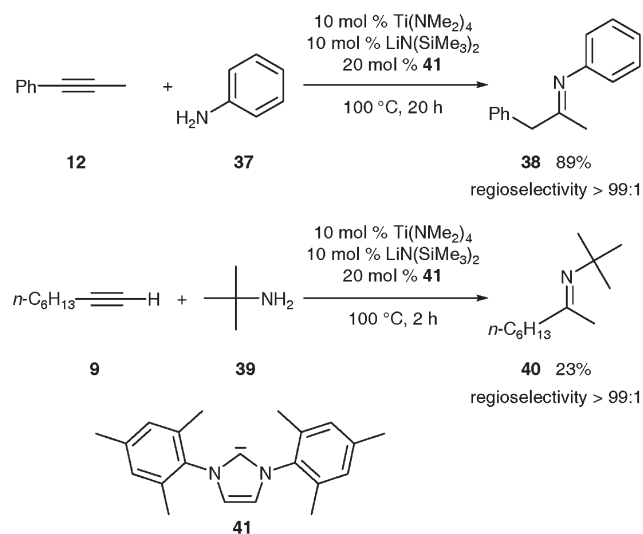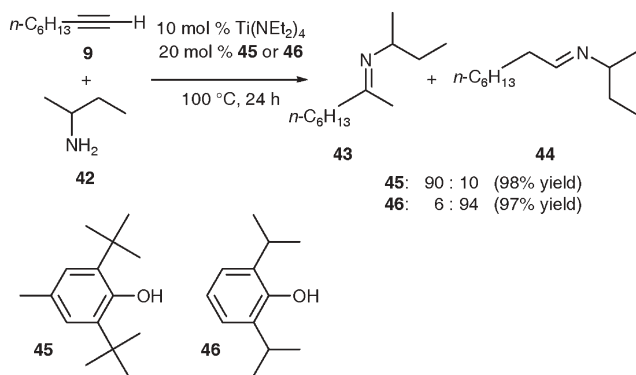
presence of a related bis(amidate) titanium catalyst. In addition, corresponding bis(amidate) zirconium complexes have also been used for cyclizations of aminoalkynes. The outstanding result presented in Scheme 9 is impressively underlined by the fact that the same reaction performed with 10 mol% of the imido complex (PhNH)$_2$Ti=NPh gives a mixture of both regioisomeric hydroamination products in only 15% yield after 24 h at 80 °C.[12]

Although commercially available Ti(NMe$_2$)$_4$ catalyzes hydroaminations of alkynes by itself, this complex has additionally been used as a versatile starting material for many *in situ* generations of modified catalysts over the past few years. In a recent example, it was shown that a 1 : 1 : 2 mixture of Ti(NMe$_2$)$_4$, LiN(SiMe$_3$)$_2$ and the N-heterocyclic carbene **41** (Scheme 10) forms a catalytically active species of unknown structure that catalyzes many hydroamination reactions of terminal and internal alkynes.[13] Especially interesting is the result obtained with *tert*-butylamine (**39**) shown in Scheme 10. The authors report that this reaction takes place with a regioselectivity of more than 99 : 1. In this context, it is worth mentioning that phenylpropyne (**12**) reacts with aniline (**37**) to give the anti-Markovnikov product **38** exclusively and not the Markovnikov regioisomer as published by the authors in ref. 13 (K. Takaki, personal communication).
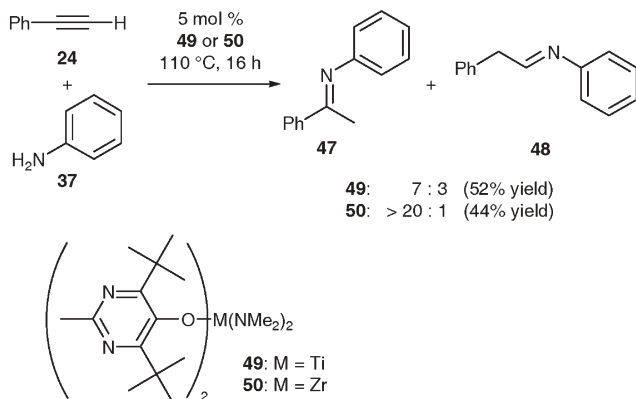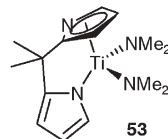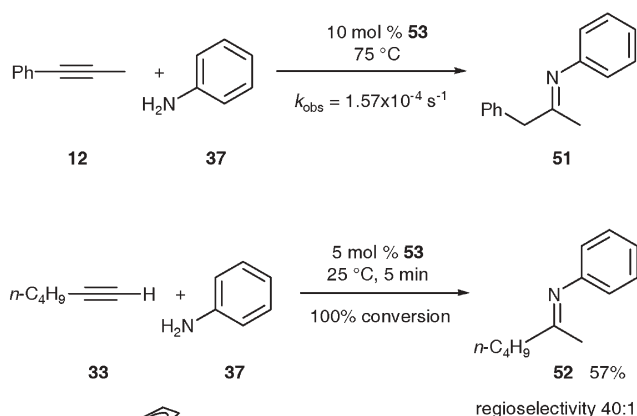

Scheme 9

Scheme 8

Scheme 10

Scheme 11

9 + 42 → 43 + 44

45: 90 : 10 (98% yield)
46: 6 : 94 (97% yield)

45   46

10 mol % Ti(NEt₂)₄
20 mol % **45** or **46**
100 °C, 24 h

Scheme 13

Ph— + H₂N-aniline → 51

10 mol % **53**
75 °C
$k_{obs} = 1.57 \times 10^{-4}\ s^{-1}$

12   37   51

n-C₄H₉— —H + aniline → 52 57%

5 mol % **53**
25 °C, 5 min
100% conversion
regioselectivity 40:1

33   37   52

53

Since it is well known from preparative studies that Ti(NEt₂)₄ reacts with two equivalents of an alcohol or phenol ROH to give two equivalents of Et₂NH and complexes of the type Ti(NEt₂)₂(OR)₂, a wide variety of corresponding hydro-amination catalysts is easily accessible from commercially available starting materials. A comprehensive experimental and theoretical study of the hydroamination of terminal alkynes performed in the presence of catalysts that were generated *in situ* from Ti(NEt₂)₄ and two equivalents of phenols or alcohols (ROH) revealed that depending on the aryloxo and alkoxo ligands the regioselectivity towards the Markovnikov and the anti-Markovnikov addition product can be controlled.[14] Most impressively, the use of sterically demanding phenol **45** in the hydroamination of 1-octyne (**9**) with *sec*-BuNH₂ (**42**) gives an excellent yield and a high Markovnikov selectivity (90 : 10). However, by employing sterically hindered phenol **46** a comparable yield of the imine with high anti-Markovnikov selectivity (94 : 6) is obtained (Scheme 11). Interestingly, good to excellent anti-Markovnikov selectivities are observed with both phenols, **45** (74 : 26, 50% yield) and **46** (99 : 1, 44% yield), when *t*-BuNH₂ (**39**) is used under identical conditions.

The related bis(pyrimidinoxide) Ti- and Zr-complexes **49** and **50** (Scheme 12), simply prepared from a substituted pyrimidinol and Ti(NMe₂)₄ or Zr(NMe₂)₄ can also be used for the addition of various amines to mainly terminal alkynes.[15] While Ti-complex **49** is able to catalyze reactions of both aryl- and alkylamines, the use of Zr-complex **50** is limited to

Ph— —H + 37 → 47 + 48

5 mol %
49 or **50**
110 °C, 16 h

24 + 37

49: 7 : 3 (52% yield)
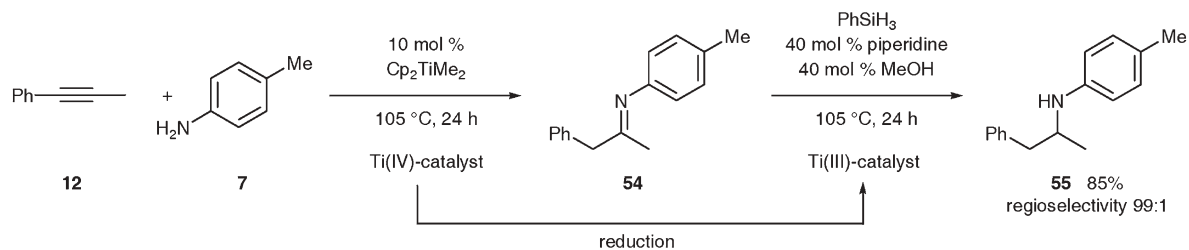50: > 20 : 1 (44% yield)

49: M = Ti
50: M = Zr

Scheme 12

arylamines. Compared with the corresponding phenoxide counterparts, the catalysts bearing pyrimidinoxide ligands seem to be more reactive but less selective. However, in the presence of **49** or **50**, the addition of aniline (**37**) to phenylacetylene (**24**) takes place with impressive Markovnikov selectivity (Scheme 12). Unfortunately, the yields are only moderate. Although Zr-complex **50** does not offer significant advantages for the hydroamination of alkynes, it must be noted that this catalyst can also be used for the intramolecular hydroamination of alkenes.

Titanium dipyrrolylmethane complexes are a very interesting class of highly active hydroamination catalysts that can also be synthesized from Ti(NMe₂)₄ in a single step.[16] At 75 °C, employing 10 mol% of catalyst **53** (Scheme 13), a rate constant of $1.57 \times 10^{-4}\ s^{-1}$ was determined for the anti-Markovnikov selective addition of aniline (**37**) to 1-phenylpropyne (**12**). Furthermore, the activity of **53** is impressively demonstrated by a reaction between 1-hexyne (**33**) and aniline (**37**). This reaction of a terminal alkyne goes to completion within 5 minutes at room temperature to give a 40 : 1 mixture of the Markovnikov and the anti-Markovnikov product in 57% yield.

While many of the catalysts described so far do catalyze reactions of aryl- and alkyl-amines, a catalyst system generated *in situ* from 10 mol% TiCl₄ and 60 mol% *t*-BuNH₂ is limited to applications that involve aromatic amines.[17]

Besides the development of improved catalysts, applications of corresponding hydroamination reactions have attracted much attention over the past four years. Taking advantage of the fact that Ti(III)–hydride complexes are able to catalyze the reduction (hydrogenation, hydrosilylation) of imines, it is possible to perform a sequential combination of the Ti(IV)-catalyzed hydroamination of alkynes with the Ti(III)-catalyzed hydrosilylation of imines. For that purpose, it is just necessary to reduce the Ti(IV)-species that remains in the reaction mixture obtained after a successful hydroamination of an alkyne to a Ti(III)-species which then catalyzes the imine reduction. By this new transformation, alkynes and primary amines can be converted into secondary amines in a fully
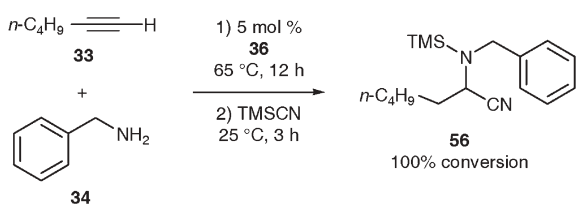
Scheme 14 area:

Ph—≡—Me (**12**) + H₂N-C₆H₄-Me (**7**) → 10 mol % Cp₂TiMe₂, 105 °C, 24 h, Ti(IV)-catalyst → imine **54** (Ph-CH₂-C(=N-C₆H₄Me)-Me) → PhSiH₃, 40 mol % piperidine, 40 mol % MeOH, 105 °C, 24 h, Ti(III)-catalyst → **55** 85%, regioselectivity 99:1 (Ph-CH₂-CH(Me)-NH-C₆H₄Me)

reduction

Scheme 14

catalytic one-pot protocol employing a single Ti-precatalyst (Scheme 14).[18] While several Ti-complexes can be used for inter- and intramolecular hydroamination/hydrosilylation sequences, enantiomerically enriched cyclic secondary amines (up to 66% ee) are obtained with enantiomerically pure precatalysts.
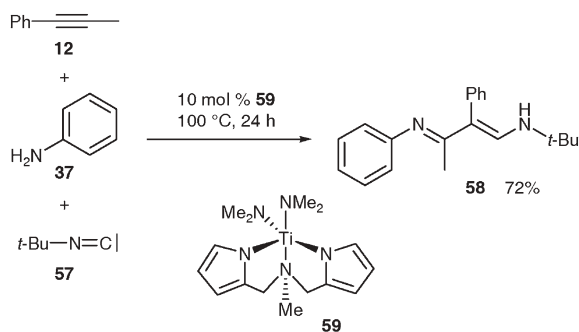
A high yielding one-pot synthesis of trimethylsily-protected α-aminonitriles from terminal alkynes, primary amines and trimethylsilylcyanid (TMSCN) relies on anti-Marovnikov selective hydroaminations in the presence of bis(amidate) titanium catalyst **36** (Scheme 15).[19] The regioselectively formed aldimines are directly used for a subsequent cyanide addition (Strecker reaction) to give the desired α-aminonitrile derivatives which are useful as precursors in the formation of α-amino acids.

An elegant Ti-catalyzed three-component coupling to generate α,β-unsaturated β-aminoimines uses alkynes, primary amines and isonitriles as starting materials and pyrrolyl complex **59** as the precatalyst (Scheme 16).[20]

Mechanistically, the key step of the reaction is the insertion of an isonitrile into the Ti–C bond present in an azatitanacyclobutene. This 4-membered ring is a general intermediate in Ti-catalyzed hydroaminations of alkynes which is formed by reversible [2 + 2]-cycloaddition between an alkyne and the catal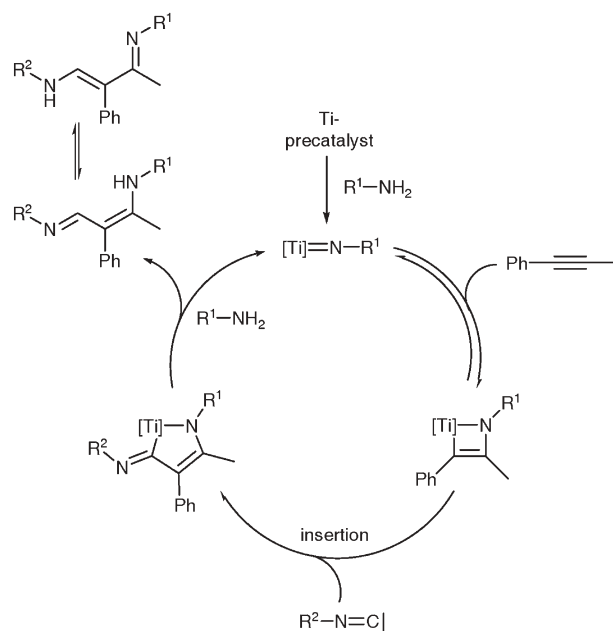ytically active Ti–imido complex. The simplified catalytic cycle of the reacti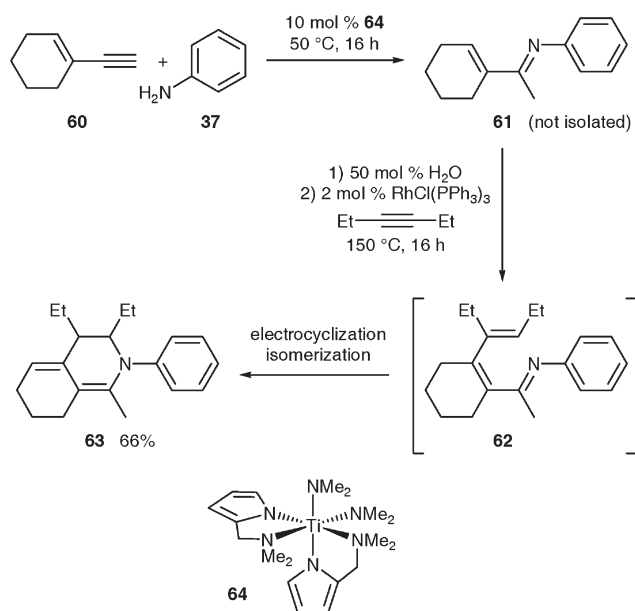on is shown in Scheme 17. Interestingly, corresponding α,β-unsaturated β-aminohydrazones are also accessible if 1,1-disubstituted hydrazines are used instead of primary amines.[21]

Starting with conjugated enynes and primary amines, α,β-unsaturated imines can be synthesized regioselectively in high yields in the presence of 10 mol% of pyrrolyl complex **64** (Scheme 18).[22] Particularly interesting is the possibility to further functionalize the obtained unsaturated imines by Rh-catalyzed C–H activation of the β-H atom and insertion of an alkyne. For that purpose, it is not necessary to isolate the α,β-unsaturated imine prior to C–H activation. However, to achieve successful reaction sequences, 50 mol% water needs to be added after the initial imine formation in order to decompose the Ti-catalyst. Otherwise this catalyst interferes with the Rh-catalyst and shuts down the C–H activation process. Subsequent alkyne insertion, electrocyclization and alkene isomerization give access to the nitrogen-containing heterocycle **63** in a one-pot process.
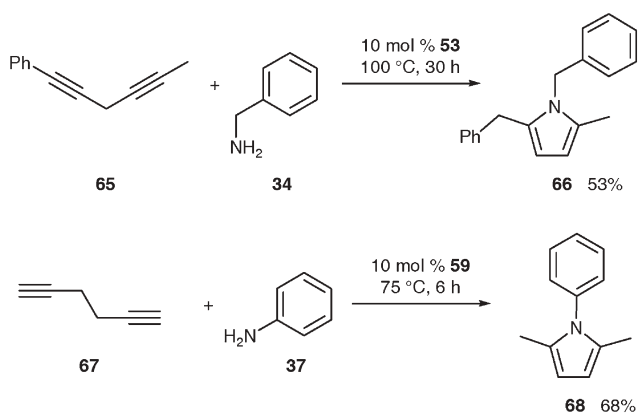
A variety of symmetrical and unsymmetrical pyrroles is accessible by hydroamination of 1,4- and 1,5-diynes with primary amines in the presence of catalytic amounts of pyrrolyl-based complexes **53** and **59** (Scheme 19).[23] The reaction sequences are initialized by the formation of an

Scheme 15 area:

n-C₄H₉—≡—H (**33**) + benzylamine (**34**) → 1) 5 mol % **36**, 65 °C, 12 h; 2) TMSCN, 25 °C, 3 h → **56** (n-C₄H₉...N(TMS)(CH₂Ph)...CN) 100% conversion

Scheme 15

Scheme 16 area:

Ph—≡ (**12**) + aniline (H₂N-C₆H₅) (**37**) + t-Bu—N≡C (**57**) → 10 mol % **59**, 100 °C, 24 h → **58** 72% (Ph-N=C(Me)-C(Ph)=CH-NH-t-Bu)

catalyst **59**: Me₂N,NMe₂ Ti with pyrrolyl ligands and Me

Scheme 16

Scheme 17 area:

Ti-precatalyst + R¹—NH₂ → [Ti]=N—R¹ ⇌ Ph—≡ → azatitanacyclobutene → R²—N≡C insertion → [Ti] pyrrole intermediate → β-aminoimine products
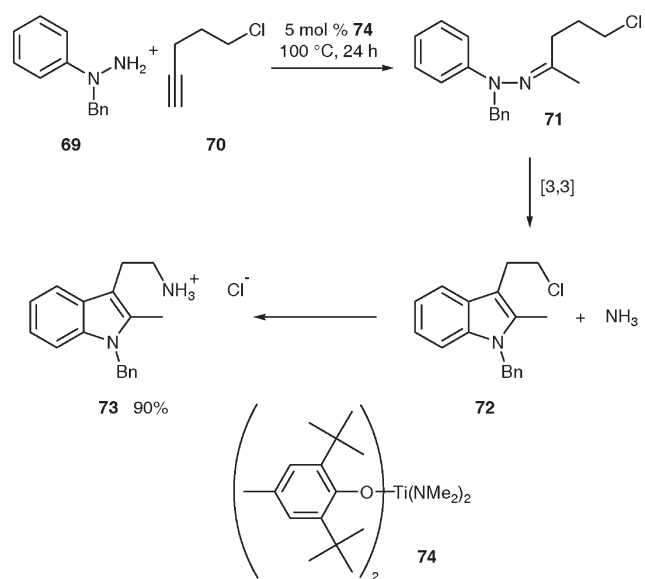
Scheme 17

Scheme 18

Scheme 19

imino-alkyne that subsequently undergoes 5-*endo dig* or 5-*exo dig* cyclization to give the desired pyrrole.

Another impressive application of the Ti-catalyzed hydro-amination of alkynes is the development of a new and efficient one-pot method for the synthesis of tryptamines.[24] Starting from 5-chloro-1-pentyne and 1,1-disubstituted arylhydrazines, tryptamines are obtained in high yields in the presence of catalyst **74** (Scheme 20). In the first step of the domino reaction sequence, the hydrazine undergoes a highly selective Markovnikov addition to the alkyne to give a hydrazone. Subsequent [3,3]-sigmatropic rearrangement of the corresponding enamine tautomer and condensation (Fischer indole synthesis) generates the indole system and liberates ammonia. Finally, a nucleophilic substitution of the chloride by the liberated ammonia occurs to give the tryptamine in its hydrochloride form. Advantageously, the *in situ* liberated HCl acts as a catalyst for the Fischer indole synthesis.
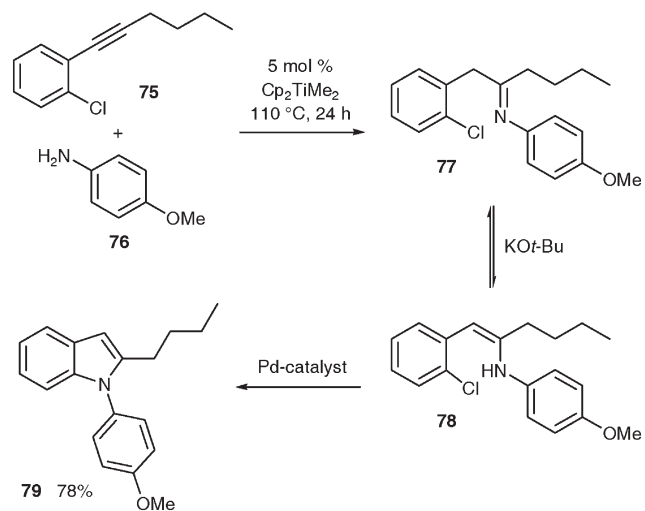
An alternative indole synthesis that relies on the formation of two new C–N bonds during a one-pot procedure starts from *ortho*-substituted 1-phenyl-2-alkyl alkynes which can easily be
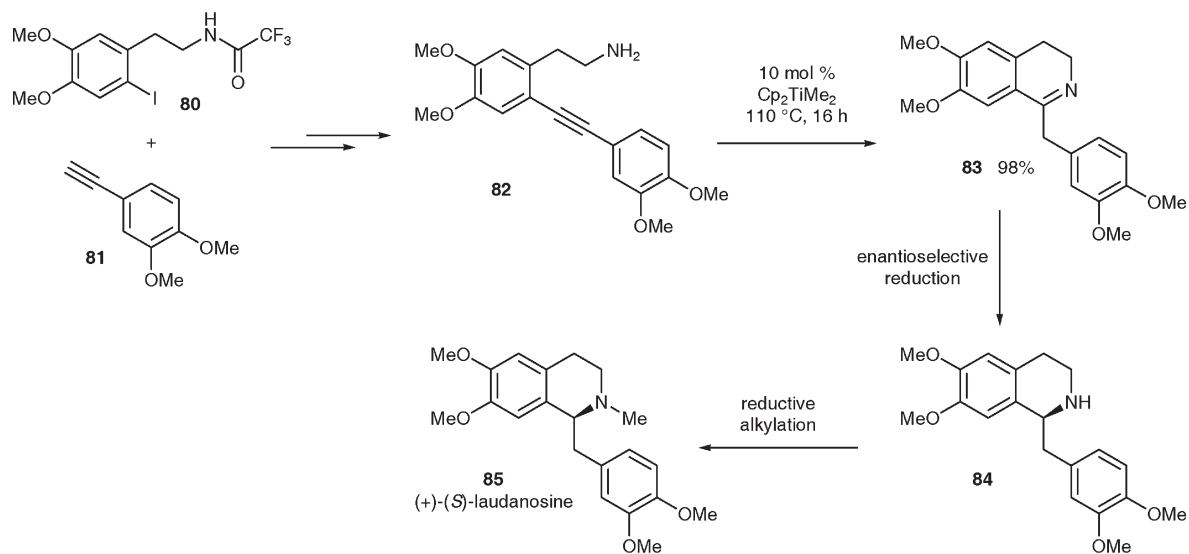

Scheme 20

synthesized from 1-chloro-2-iodobenzenes and terminal alkynes by Sonogashira coupling (Scheme 21).[25] The key idea of the reaction sequence is that under basic conditions, the imines, which are regioselectively formed during the hydro-amination in the presence of 5 mol% Cp_2TiMe_2, are in equilibrium with the corresponding enamines. Subsequently, the *ortho*-chloro-substituent is used for an intramolecular Pd-catalyzed N-arylation of the enamine (Buchwald–Hartwig reaction) that delivers the indole in high yield.

Since the Ti-catalyzed hydroamination of alkynes has proven to be a powerful new tool in organic chemistry it is not surprising that the method has already been used for natural product synthesis. For example, a new pathway for the enantioselective synthesis of (+)-(*S*)-laudanosine (**85**) is based on a Ti-catalyzed intramolecular hydroamination of amino-alkyne **82** which is easily accessible from aryl iodide **80** and terminal alkyne **81** *via* Sonogashira coupling (Scheme 22).[26] Enantioselective reduction of the resulting imine **83** and

Scheme 21

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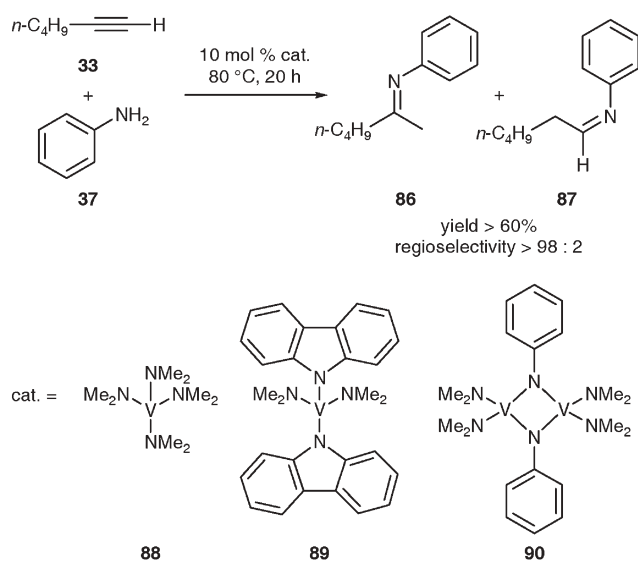*Chem. Soc. Rev.*, 2007, **36**, 1407–1420 | 1413

Scheme 22

subsequent reductive alkylation gives access to the benzyliso-quinoline alkaloid.

4 Vanadium and tantalum complexes as hydroamination catalysts

During a screening of group IV and group V metal complexes as catalysts for the hydroamination of 1-hexyne (**33**) with aniline (**37**), three vanadium complexes were identified as suitable catalysts with promising activity (Scheme 23).[12] In contrast, Cp$_2$V, V(acac)$_3$ (acac = acetylacetonate), V(N$_3$)$_2$(NMe$_2$)$_2$, V(Oi-Pr)$_4$, VO(NEt$_2$)$_3$ and V(NAr)Cl$_3$ (Ar = 2,6-i-Pr$_2$-C$_6$H$_3$) are inactive and the use of other complexes like V(N(SiMe$_3$)$_2$)$_3$ leads to very slow reactions (22% yield of imines **86** and **87** after 17 h at 80 °C). However, in the presence of catalysts V(NMe$_2$)$_4$ (**88**), V(carb)$_2$(NMe$_2$)$_2$ (carb = carbazole) (**89**) and [V(μ^2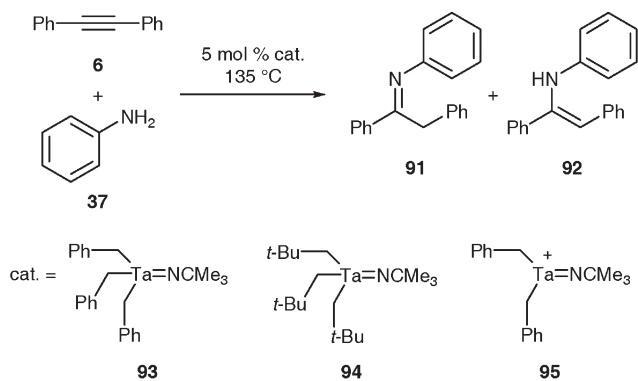-NPh)(NMe$_2$)$_2$]$_2$ (**90**) the desired imine **86** is obtained regioselectively (>98 : 2) after 20 h at 80 °C in 60%, 79% and 85% yield, respectively. Interestingly, the regioisomeric imines **86** and **87** are formed as a 80 : 20-mixture after only 2 h at 80 °C in 94% yield when the titanium complex (PhNH)$_2$Ti=NPh is used as the catalyst. Consequently, the vanadium catalysts **88**–**90** must be considered as less reactive but more selective than (PhNH)$_2$Ti=NPh. The great difference between Ti- and V-catalysts is most obviously in reactions catalyzed by the corresponding bis(cyclopentadienyl) derivatives. Whereas Cp$_2$TiMe$_2$ catalyzes a wide variety of alkyne hydroamination reactions, the use of Cp$_2$VMe$_2$ leads to alkyne dimerizations, cyclotrimerizations, oligomerizations or polymerizations depending on the specific alkyne.

As part of the same screening, the tantalum complex Ta(NMe$_2$)$_5$ was additionally tested under the conditions used for titanium and vanadium catalysts. However, in the presence of this catalyst, only a slow catalytic reaction occurs that gives access to the imines **86** and **87** in 34% yield with a regioselectivity of 78 : 22 in favor of the Markovnikov product **86**.
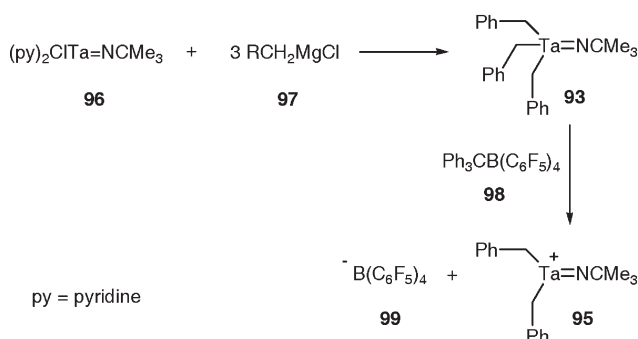
Further studies in the field of group V hydroamination catalysts suggest that cationic group V imido complexes are particularly promising as hydroamination catalysts since these compounds are isoelectronic to the group IV catalysts and the enhanced polarity of the metal imido linkage should likely result in increased catalytic activity.[27] However, at 135 °C, hydroamination reactions employing diphenylacetylene (**6**) and aniline (**37**) give mixtures (3 : 1) of imine **91** and enamine **92** as the hydroamination products in the presence of both, neutral (**93**, **94**) and cationic (**95**) tantalum catalysts (Scheme 24).

While the use of the neutral tantalum imido complex **93** results in the formation of the desired products in >95% yield within 30 h the same yield is achieved by catalyst **94** within 12 h. Interestingly, the cationic tantalum catalyst **95** shows a decreased reactivity. However, improved reactivity and >95% yield after only 8 h reaction time can be achieved through *in situ* generation of **95** by benzylanion abstraction from **93** with Ph$_3$CB(C$_6$F$_5$)$_4$ (Scheme 25).
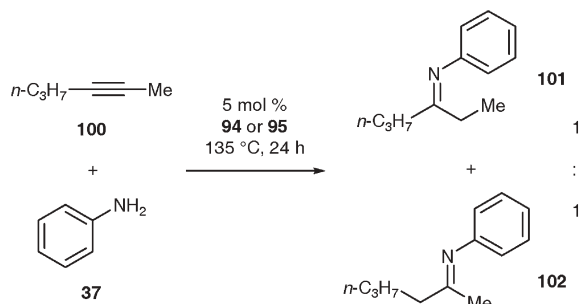

Scheme 23

Left column

Ph—≡—Ph
6
+
NH$_2$
37

5 mol % cat.
135 °C

Ph—N=
Ph
91

+

HN—
Ph—=—Ph
92

cat. =

Ph
Ph—Ta=NCMe$_3$
Ph
93

t-Bu
t-Bu—Ta=NCMe$_3$
t-Bu
94

Ph—
Ph—Ta=NCMe$_3$ $^+$
Ph
95

Scheme 24

(py)$_2$ClTa=NCMe$_3$ +   3 RCH$_2$MgCl   →
96   **97**

Ph
Ph—Ta=NCMe$_3$
Ph
93

Ph$_3$CB(C$_6$F$_5$)$_4$
98

py = pyridine

$^-$B(C$_6$F$_5$)$_4$ +
99

Ph—
Ph—Ta=NCMe$_3$ $^+$
Ph
95

Scheme 25

Although **94** and *in situ* generated **95** catalyze the addition of aniline (**37**) to all classes of alkynes it is worth mentioning that dialkylalkynes react more slowly than diphenylacetylene (**6**) and terminal alkynes are converted significantly faster. Furthermore, the hydroamination of unsymmetrically substituted 2-hexyne (**100**) proceeds with no regioselectivity but high yields in the presence of 5 mol% of **94** (>95%) or **95** (71%) (Scheme 26).

In contrast, terminal alkynes and aniline (**37**) are exclusively converted into the Markovnikov regioisomers. However, this observation may be caused by selective decomposition of the anti-Markovnikov products. Surprisingly, 1-phenylpropyne (**12**) is a difficult substrate for both catalysts and only the cationic complex **95** is able to catalyze the addition of aniline (**37**) to **12** to give 19% of the anti-Markovnikov product after 24 h at 135 °C. Another class of challenging substrates are *ortho*-substituted anilines showing little or no conversion with

n-C$_3$H$_7$—≡—Me
100
+
NH$_2$
37

5 mol %
94 or **95**
135 °C, 24 h

N=
n-C$_3$H$_7$—
Me
101

1

+

:

n-C$_3$H$_7$—
N=
Me
102

1

Scheme 26

Right column

94 but giving moderate yields with **95** in hydroaminations of diphenylacetylene (**6**). Consequently, it is suggested that the cationic catalyst **95** is the more potent catalyst. However, for many other reactions the use of the neutral catalyst **94** leads to significantly higher yields.
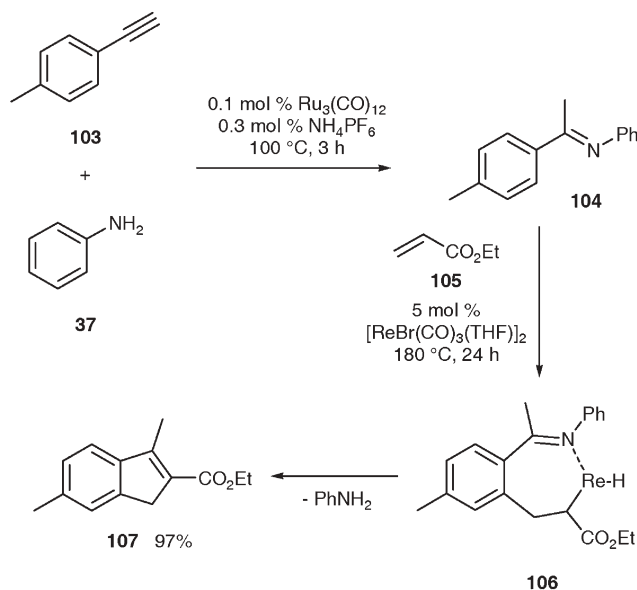
In general, the mentioned examples clearly indicate that several vanadium(IV) and tantalum(V) amido or imido complexes can be used as catalysts for intermolecular hydroaminations of alkynes. However, with regard to catalyst lifetime and activity further optimization studies are necessary.

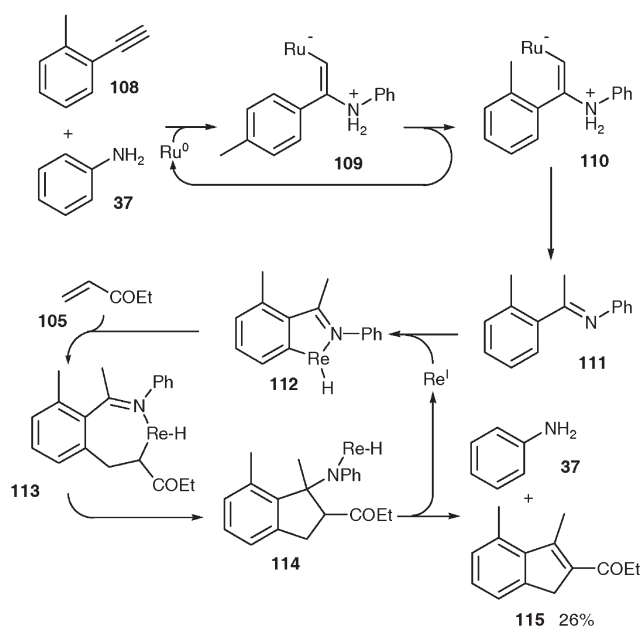## 5 Ruthenium complexes as hydroamination catalysts

Ruthenium complexes have been known since 1999 as catalysts for the hydroamination of alkynes. Due to the lower affinity to oxygen compared with early transition metals, a larger range of substrates can generally be tolerated in Ru-catalyzed hydroamination reactions (functional group compatibility). Recent studies have revealed interesting reaction pathways including combinations of hydroamination reactions with C–H bond activations or C–C bond cleavages.

A formal [3 + 2] annulation of terminal arylacetylenes and α,β-unsaturated carbonyl compounds (esters, ketones) is achieved in a one-pot reaction by treatment of the acetylenes with aniline (**37**) and catalytic amounts of Ru$_3$(CO)$_{12}$ and NH$_4$PF$_6$ and subsequent C–H bond activation catalyzed by [ReBr(CO)$_3$(THF)]$_2$ (Scheme 27).[28] By variation of the arylalkynes several indene derivatives can be synthesized successfully. While *ortho*-substituted arylalkynes are poor substrates (26% yield), best results are obtained with alkynes bearing electron-donating groups at the *para*-position of the aromatic ring. However, an indene derivative is not formed when an alkyne is used that bears an electron-withdrawing group in the *para*-position of the aromatic ring.

Interestingly, the desired indene product is not obtained when the initial hydroamination is performed in the presence of Cp$_2$TiMe$_2$ or AuCl$_3$ although an aromatic ketimine is also

≡
103

+

NH$_2$
37

0.1 mol % Ru$_3$(CO)$_{12}$
0.3 mol % NH$_4$PF$_6$
100 °C, 3 h

N—Ph
104

CO$_2$Et
105

5 mol %
[ReBr(CO)$_3$(THF)]$_2$
180 °C, 24 h

Ph
N
Re-H
CO$_2$Et
106

- PhNH$_2$

CO$_2$Et
107 97%

Scheme 27

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*Chem. Soc. Rev.*, 2007, **36**, 1407–1420 | **1415**

Scheme 28

Scheme 30

generated with these catalysts. This finding suggests that the Ti- and Au-catalysts interfere with the Re-catalyst used for the subsequent C–H activation process. Mechanistically, the reaction is assumed to take place via a Ru-catalyzed regioselective hydroamination of the terminal alkyne, a Re-catalyzed *ortho*-C–H activation, an insertion of the α,β-unsaturated carbonyl compound into the C–Re bond, an intramolecular nucleophilic cyclization, a reductive elimination and a final elimination of aniline (**37**) (Scheme 28).

A mechanism similar to the one presented in Scheme 28 is proposed for the Ru-catalyzed synthesis of quinoline derivatives from anilines and terminal alkynes that involves a Ru-catalyzed regioselective alkyne hydroamination and a subsequent Ru-catalyzed *ortho*-C–H bond activation process.[29] In contrast to the previously mentioned example (Schemes 27 and 28), the cationic ruthenium hydrid complex [(PCy₃)₂(CO)(CH₃CN)₂RuH]⁺BF₄⁻ (Cy = cyclohexyl) or a 1 : 3 mixture of Ru₃(CO)₁₂ and HBF₄·Et₂O are used as single catalysts for both steps of the reaction (Scheme 29).

While arylamines possessing electron withdrawing groups form less than 5% of the desired quinoline derivatives, electron
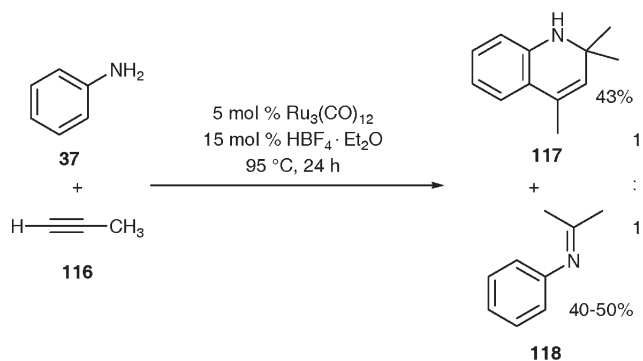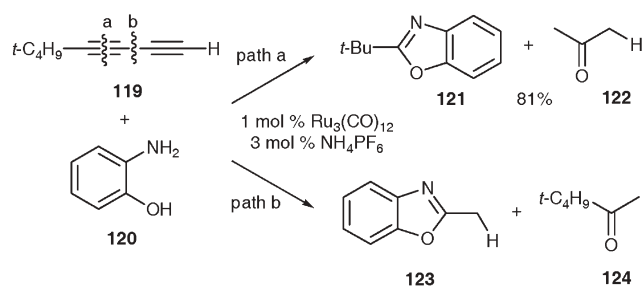
rich arylamines undergo the *ortho*-C–H bond activation process to give products of type **117** preferentially over the hydroamination products of type **118**. The use of further functionalized bicyclic arylamines leads to tricyclic quinoline derivatives.

A mechanism that is fundamentally different from all previously discussed mechanisms for alkyne hydroaminations is proposed for the Markovnikov-selective addition of arylamines to terminal arylalkynes catalyzed by a dinuclear ruthenium complex with a doubly bridged rigid dicyclopentadienyl ligand.[30] Although the *in situ* generated catalytically active complex {(η⁵-C₅H₃)₂(SiMe₂)₂}Ru₂(CO)₃{NH₂(*p*-MeC₆H₄)} has a limited lifetime (up to 6 turnovers), most of the intermediates involved in the catalytic cycle are fully characterized (X-ray and/or NMR). Since the corresponding nonbridged Ru-dimer does not catalyze the hydroamination, the catalytic activity seems to be the result of the unique bridging nature of the (η⁵-C₅H₃)₂(SiMe₂)₂ ligand.

Although catalytic C–C bond cleavage procedures are not very popular in organic chemistry and no method employing diynes is known, it is worth mentioning that a corresponding new process (Scheme 30) relies on two successive intermolecular Ru-catalyzed hydroaminations of terminal 1,3-diynes with 2-aminophenols.[31]

For example, the reaction of 2-aminophenol (**120**) with terminal diyne **119** having a sterically demanding *tert*-butyl group as the substituent takes place in the presence of 1 mol% Ru₃(CO)₁₂ and 3 mol% NH₄PF₆ at 80 °C to give almost exclusively benzoxazole **121** and acetone (**122**) (obtained after imine hydrolysis) in 81% combined yield based on 2-amino-phenol [(**121** + **122**) : (**123** + **124**) = > 30 : 1]. Other terminal 1,3-diynes undergo the same reaction with comparable yields. However, the ratio of the two possible benzoxazoles formed during the reaction drops to 3 : 1 or 4 : 1 when the 1,3-diyne bears an *n*-alkyl substituent. Remarkably, corresponding reactions of internal 1,3-diynes can only be accomplished in the presence of palladium catalysts. While in this case the corresponding C–C bond cleavage reaction proceeds smoothly with Pd(NO₃)₂ other catalysts such as Ru or Au complexes do not work at all.

6 Palladium and platinum complexes as hydroamination catalysts

Several palladium catalyzed hydroaminations of alkynes were presented in our last review.[1] Interestingly, the intermolecular hydroamination of terminal and internal alkynes proceeds very
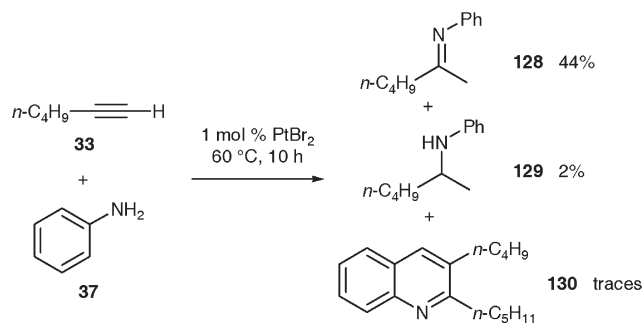
Scheme 29

smoothly with 2-aminophenol (**120**) in the presence of many palladium complexes.[32] Among the catalysts examined Pd(NO₃)₂ gives the best results. However, hydroaminations of unsymmetrically substituted alkylarylalkynes performed at 120 °C in the presence of 15 mol% of this catalyst afford mixtures of regioisomeric products in excellent yields but with poor selectivity (<3 : 1) mostly in favor of the Markovnikov product. The interesting fact that in comparison with unfunctionalized amines the use of 2-aminophenol (**120**) as substrate dramatically enhances the rate of the hydroamination reaction suggests that hydroxopalladium or aquapalladium complexes might be superior catalysts. Correspondingly, the stable and convenient aquapalladium complex [Pd(dppe)(H₂O)₂](TfO)₂ (dppe = 1,2-bis(diphenylphosphino)ethane, TfO = CF₃SO₃⁻) can be used as a highly efficient catalyst for the intermolecular hydroamination of internal alkynes with various arylamines.[33] Compared with the lanthanide and early transition metal catalysts described above, special care is not needed in the handling of the aquapalladium complex. However, unsymetrically substituted alkylarylalkynes undergo hydroaminations with low regioselectivities whereas the best regioselectivity is observed during a reaction between acetoxy-substituted alkyne **125** and aniline (**37**) (Scheme 31). Subsequent hydrolysis of the initially formed imines gives access to a mixture of the ketones **126** and **127** in quantitative yield.

An additional example of a late transition metal hydroamination catalyst is PtBr₂. In the presence of 0.3–1.0 mol% of this simple catalyst, terminal alkyl- and arylalkynes undergo addition reactions with aniline (**37**).[34] While the hydroamination of phenylacetylene (**24**) is fully Markovnikov-selective the corresponding regioselectivity of the hydroamination of 1-hexyne (**33**) decreases from 98 : 4 at 60 °C to 45 : 18 at 100 °C. Interestingly, three products are generally obtained in varying ratios from reactions between 1-hexyne (**33**) and aniline (**37**) (Scheme 32).

It is believed that the by-product **130** is formed through a dimerization of the linear aldimine PhN=CH-n-C₅H₁₁ (anti-Markovnikov product of the hydroamination) followed by *in situ* heterocyclization, deamination and dehydrogenation. The amine **129** is likely formed from **128** by transfer hydrogenation from 2-pentyl-3-butyl-1,2,3,4-tetrahydroquinoline, the last step of the formation of **130**. Although high regioselectivities (>90 : 10) and impressive turnover numbers up to 150 are realized, the low yields require additional research to develop more active Pt(II) catalysts.
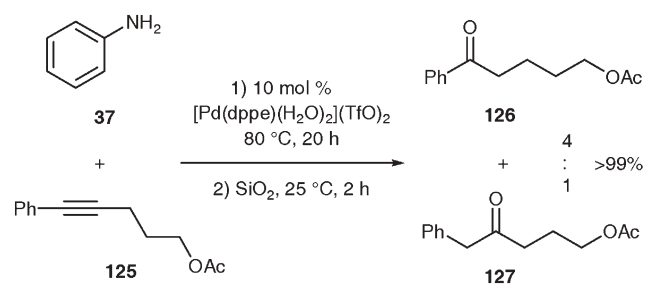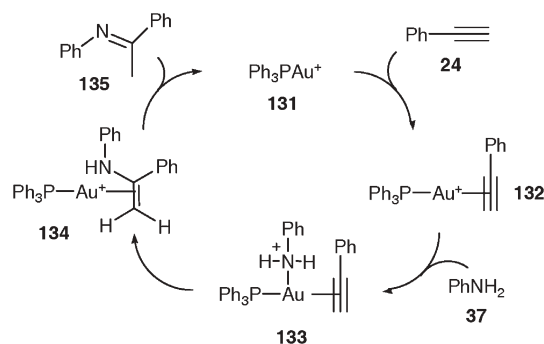
Scheme 32

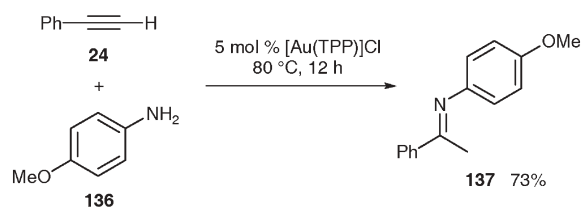## 7 Gold and silver complexes as hydroamination catalysts

The ability of gold complexes to catalyze intramolecular hydroaminations of alkynes has already been known for decades. However, continued research on Au-catalyzed reactions has revealed that (Ph₃P)AuCH₃ in conjunction with acidic promoters catalyzes the intermolecular hydroamination of alkynes efficiently.[35] Corresponding additions of anilines to terminal and internal alkynes take place at 70 °C under solvent-free conditions with good to excellent yields in the presence of 0.01–0.5 mol% (Ph₃P)AuCH₃ and 0.05–1.0 mol% H₃PW₁₂O₄₀. In the case of terminal alkynes the reactions exclusively give the ketimine products. The fact that electron-rich arylalkynes react more smoothly than electron-poor arylalkynes can be understood by the mechanism illustrated in Scheme 33.

Initially, the alkyne and the cationic gold(I) species, Au(PPh₃)⁺ (**131**), generated by protonolysis of (PPh₃)AuCH₃, form a cationic Au(I)–alkyne complex (**132**). This process should be favored by an electron-donating substituent in the alkyne molecule. For the subsequent reaction of the amine with the Au(I)–alkyne complex, two pathways are generally possible. One is a direct intermolecular nucleophilic attack by the amine on the alkyne bound to the Au-center. However, this route is less likely since anilines that have more electron-withdrawing substituents seem to react faster. Consequently, the other route, involving coordination of the aniline to the Au-center prior to the C–N bond formation, appears to be more likely.
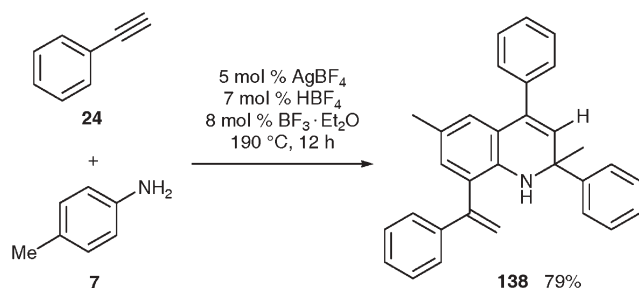
In 2006, gold(III) porphyrins were introduced as a new class of practical and robust Lewis acidic catalysts for the

Scheme 31

Scheme 33

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Chem. Soc. Rev., 2007, **36**, 1407–1420 | 1417
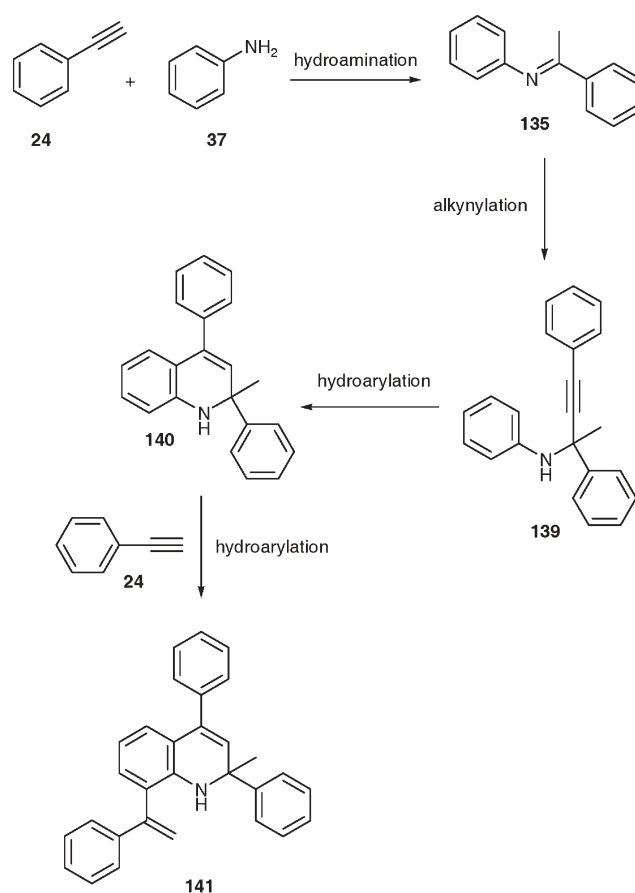
Scheme 34

Scheme 35

hydroamination of alkynes and other applications.[36] In the presence of 5 mol% [Au(TPP)]Cl (TPP = tetraphenylporphyrin), the addition of *p*-methoxyaniline (**136**) to phenylacetylene (**24**) takes place at 80 °C to give the Markovnikov product **137** in 73% yield (Scheme 34).

During a careful study of the AuCl₃-, AgOTf- and AgBF₄-catalyzed hydroamination of phenylacetylene (**24**) with aniline (**37**) it was surprisingly found that polysubstituted 1,2-dihydroquinoline derivatives are formed when the reaction is performed with excess of the alkyne in the presence of AgBF₄ as the catalyst. Under optimized conditions, using 5 mol% AgBF₄, 7 mol% HBF₄ and 8 mol% BF₃·Et₂O, phenylacetylene (**24**) and *p*-toluidine (**7**) are converted into dihydroquinoline derivative **138** in 79% yield in an impressive one-pot operation (Scheme 35).[37] Interestingly, gold catalysts alone do not provide this product.

On the basis of the experimental results, a domino process is proposed that is responsible for the formation of the dihydroquinoline skeleton (Scheme 36). The reaction cascade includes an initial regioselective hydroamination to form a ketimine (**135**), a subsequent nucleophilic alkyne addition to the imine and a final intramolecular hydroarylation to give dihydroquinoline intermediate **140**. Then **140** undergoes a neighboring-group-directed hydroarylation to give the final product **141**.

## 8 Immobilized zinc and copper catalysts for the hydroamination of alkynes

The possibility to catalyze hydroamination reactions of alkynes with Zn²⁺ ion exchanged zeolites was demonstrated 30 years ago for the addition of methylamine to propyne. Recently, research has been focused on hydroaminations performed in a liquid–liquid heterogeneous system using Zn(OTf)₂ as the catalyst.[38] In principal, the major advantage of corresponding two-phase approaches is the fact that high reaction rates can be achieved by the use of high amounts of
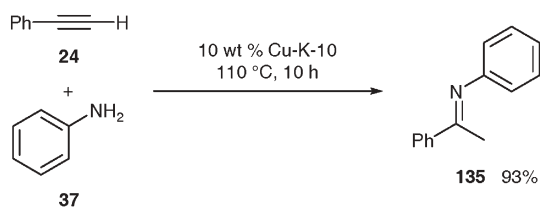

Scheme 36

catalysts because these catalysts can easily be recovered by simple phase separation techniques. For Zn(OTf)₂-catalyzed hydroamination reactions of phenylacetylene (**24**) with alkyl- or arylamines such as **142** (Scheme 37) the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate can be used as the polar phase that contains the polar catalyst while heptane is used as the apolar solvent for the starting materials and the product. After the reaction, the catalyst remains quantitatively in the ionic liquid which can easily be separated from the heptane phase. Subsequent concentration of the organic phase under vacuum usually gives direct access to the pure hydroamination product.

Another heterogeneous method for the intermolecular hydroamination of terminal alkynes with aromatic amines uses transition metal-exchanged montmorillonite K-10 (hereafter K-10).[39] K-10 is an acid-activated clay with an octahedral layer of alumina sandwiched between two silica layers. The interlamellar space contains layer charge compensating cations
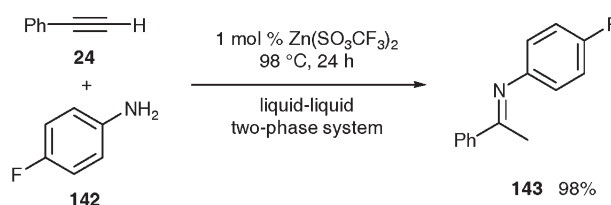
Scheme 37

Scheme 38

(K^+, Na^+, Ca^+) which can easily be exchanged with transition metal cations. Among the various transition metal-exchanged K-10 clays, the Cu^{2+}-modified catalyst gives the best results. Using this catalyst, it is possible to obtain the Markovnikov hydroamination product (**135**) selectively from phenylacetylene (**24**) and aniline (**37**) in 93% yield after 10 h at 110 °C (Scheme 38). However, no effort has been made to reuse the recovered heterogeneous catalyst for additional hydroamination reactions.

9 Summary

During the past four years, great progress has been achieved in identifying new and improved catalysts for the intermolecular hydroamination of alkynes. Among the various classes of catalysts, Ti-complexes have impressively proven to be versatile new tools in organic chemistry that can be used for the addition of all classes of primary amines to all classes of alkynes. While typical Ti-catalyzed intermolecular hydroaminations of alkynes are performed at elevated temperature for several hours certain catalysts possess improved activities and even offer the possibility to perform selected reactions at room temperature. Great progress has also been made in controlling the regioselectivity for the hydroamination of terminal alkynes towards the Markovnikov and the anti-Markovnikov product by changing the ligands at the titanium center. Since variations of the ligands are easy to achieve by *in situ* generation of the active catalysts of the type $Ti(NR_2)_2L_2$ from commercially available tetraamide complexes $Ti(NR_2)_4$ and two equivalents of an acidic compound LH the Ti-catalyzed hydroamination of alkynes must be regarded as a very user-friendly and flexible method. Not surprisingly, the combination of the broad scope of the method with the reactivity of the imine products has additionally led to the development of original and efficient new strategies for the synthesis of many interesting classes of compounds such as α-amino acids, pyrroles, indoles, tryptamines, *etc.* or even natural products. Another promising class of new catalysts are neutral and cationic group V amido and imido complexes. However, with regard to scope, catalyst lifetime and activity further investigations are necessary.

Among the late transition metal catalysts ruthenium and platinum complexes have widely been used for additions of amines to terminal alkynes partly in combination with subsequent C–H activation processes or C–C bond cleavages to give unexpected products in high yields. While Pd- and Au-catalysts can also be used for high yielding additions of amines to terminal and internal alkynes Ag-complexes are able to catalyze complex reaction cascades starting from anilines and terminal arylalkynes. Simple hydroaminations of alkynes can also be performed in liquid–solid and liquid–liquid heterogeneous systems using immobilized Zn- and Cu-catalysts. While the scope and limitations of corresponding processes are not yet well documented, the major advantage of this approach is the possibility to recover and reuse the catalysts.

Compared with early transition metal catalysts, late transition metal catalysts show decreased sensitivity towards air and moisture as well as functional groups present in the starting materials. This fact is most impressively underlined by the finding that even an aquapalladium complex catalyzes hydroaminations of alkynes. With regard to regioselectivity, the late transition metal catalysts lead to a more or less selective formation of Markovnikov addition products from terminal alkynes while several Ti-catalysts offer the possibility to perform anti-Markovnikov selective hydroaminations.

In our opinion, the studies summarized in this review must lead to the conclusion that the intermolecular hydroamination of alkynes has become a powerful method in organic chemistry that will probably be used for many applications during the next few years. Furthermore, it must be mentioned that the knowledge obtained during these studies has already been used for the development of catalysts for the hydroamination of alkenes.[40]

Acknowledgements

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