Group-IV Metal Complexes as Hydroamination Catalysts

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During the last 50 years, group-IV metal complexes have been used extensively as catalysts in organic chemistry. However, a new and rapidly growing field for group-IV metal catalysis evolved in the 1990s when the groups of Bergman, Livinghouse and Doye found that zirconium and titanium complexes catalyze the inter- and intramolecular hydroamination of alkynes and allenes. Starting from early results obtained with zirconocene bis(amides), this review deals mostly with hydroamination reactions based on titanium catalysts. In this context, studies directed towards catalyst development are presented as well as applications of corresponding processes for the synthesis of biologically interesting compounds. However, the Microreview covers group-IV metal complex catalyzed hydroamination reactions of alkynes and allenes that appeared in the literature before July 31, 2002.

Introduction

During the last 50 years, group-IV metal complexes have been used extensively as catalysts in organic chemistry.[1] Among the various catalytic processes, the use of titanium and zirconium compounds as catalysts for the polymerization of alkenes undoubtedly represents the most important application of group-IV metal catalysts.[2] However, a new and promising field for group-IV metal catalysis evolved when it was found in the 1990s that zirconium and titanium complexes catalyze the hydroamination of alkynes and allenes.

In general, hydroamination processes must be regarded as highly desirable transformations for organic chemistry.[3] As can be seen from Scheme 1, corresponding reactions take place without any formation of side products (100% atom efficiency) to give nitrogen-containing products in a single step.

Since the employed starting materials (alkenes, alkynes, allenes) are inexpensive and readily available and the products (amines, imines, enamines) are important bulk and fine chemicals, biologically interesting compounds, or versatile synthetic intermediates, hydroamination reactions are of considerable interest for academic and industrial chemistry. In particular the mentioned amines play an outstanding

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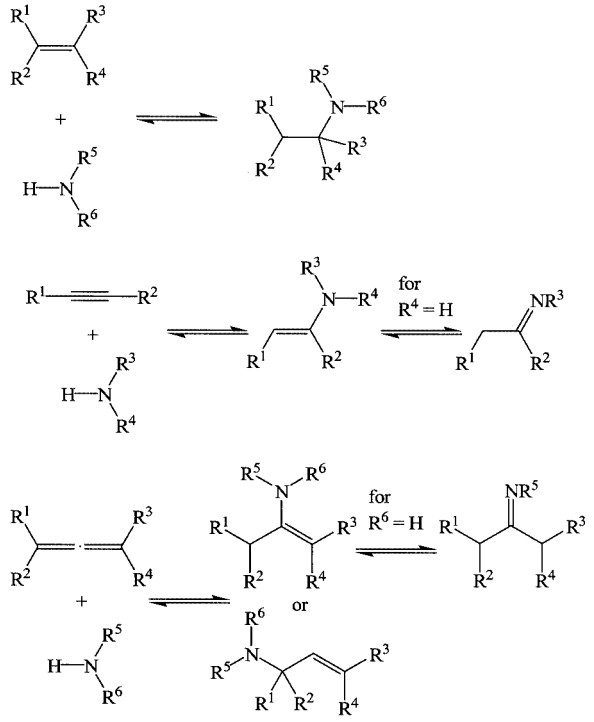
Sven Doye was born in Berlin, Germany in 1967. Between 1986 and 1990 he studied chemistry at the Technical University of Berlin. He received his diploma degree in 1990 from the same University and his PhD in 1993 from the University of Hannover. During his graduate studies under the supervision of Prof. 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 postdoctoral 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 September 2002 until January 2003 he was Guest Professor at Cardiff University, Wales, UK.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.



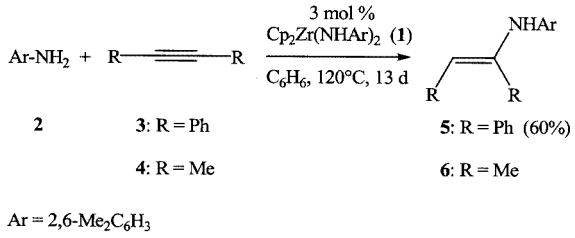
Scheme 1. Hydroamination of alkenes, alkynes and allenes

role as products and intermediates in the chemical industry. Per year, several million tons are produced worldwide. Today, the main method for the industrial production of alkylamines is the condensation of ammonia with alcohols in the presence of a catalyst.[4] However, alcohols are usually produced from alkenes by hydration or a hydroformylation hydrogenation sequence. Therefore, it is obvious that efficient methods for the direct transformation of alkenes into amines might offer significant economical benefits. Unfortunately, efficient hydroamination methods for nonactivated alkenes are rare.[3,5]

In general, hydroamination reactions are hindered by two major problems: 1) a high activation barrier for the direct addition of amines across C−C multiple bonds exists which arises from electrostatic repulsion between the electron lone pair at the nitrogen atom and the electron-rich π-bond, and 2) the general negative reaction entropy $\Delta S°$ of the reaction is responsible for the fact that the equilibrium of hydroamination reactions is shifted towards the starting materials at the higher temperatures that are necessary to overcome the activation barrier. This combination of facts makes it indispensable to develop catalytic hydroamination processes, which involve either activation of the C−C multiple bond or activation of the amine. However, from a thermodynamic point of view, the direct addition of ammonia or simple amines to alkenes is feasible since corresponding reactions are slightly exothermic or approximately thermoneutral. For example, $\Delta H°$ for the addition of ammonia to ethylene is −52.7 kJ/mol ($\Delta S°$ = −127.3 J/mol K, $\Delta G°$ = −14.7 kJ/mol).[3b] Unfortunately, experimental $\Delta H°$ data are not available for the addition of ammonia or amines to alkynes and allenes. Nevertheless, the addition of ammonia to acetylene is estimated (AM1 semiempirical calculations) to be about 63 kJ/mol more exothermic than that to ethylene.[6] Regarding this estimation, the hydroamination of alkynes is supposed to be more favorable than the hydroamination of alkenes, which is strongly supported by the fact that great progress has been made in developing catalytic hydroamination protocols for nonactivated alkynes and allenes during the last five years. From an industrial point of view, it seems to be a drawback that in these cases the initially formed imines and enamines must be reduced to give the desired stable amines. Furthermore, alkynes are more expensive than alkenes. However, since imines and enamines are versatile starting materials for a huge number of synthetic transformations, the corresponding two-step processes offer the possibility of synthesizing important classes of products with high diversity, which is definitively an advantage for laboratory-scale synthesis. Among the employed catalysts for alkene, alkyne and allene hydroamination are strong bases, lanthanide and actinide complexes as well as late transition metal complexes.[3] However, almost all hydroamination procedures reported so far are restricted to reactions of slightly activated substrates (e.g. styrenes, terminal alkynes, aromatic amines) or only work in an intramolecular fashion. Furthermore, many of the employed catalysts are difficult to synthesize, expensive, sensitive to air and moisture, or highly toxic. However, a rapidly growing and extremely promising field is the development of hydroamination protocols based on group-IV metal catalysts, which are inexpensive, nontoxic, and readily available. This Microreview covers group-IV metal complex catalyzed hydroamination reactions that appeared in the literature before July 31, 2002.

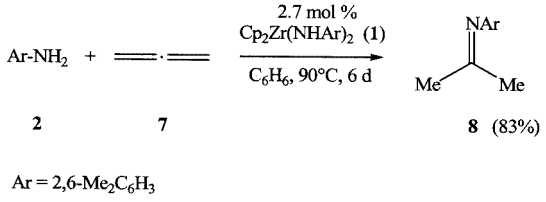
Zirconium Complexes as Catalysts for the Hydroamination of Alkynes and Allenes

In a pioneering publication, Bergman et al. reported in 1992 that the zirconocene bis(amide) [$Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2$] (**1**) catalyzes the intermolecular addition of 2,6-dimethylaniline (**2**) to alkynes and allenes.[7] The hydroamination reactions take place in the presence of 2−3 mol % of the bis(amide) **1** at 90−120 °C in benzene or toluene. Under these conditions, diphenylacetylene (**3**) and 2-butyne (**4**) react with 2,6-dimethylaniline (**2**) to give the corresponding enamines **5** and **6** (Scheme 2). While enamine **5** can be isolated (60% yield) and characterized by X-ray crystallography, the enamine **6** formed from **4** is only observed by ^{1}H NMR spectroscopy. In this case, a subsequent isomerization to the more stable imine tautomer is observed. At 110 °C, the catalytic formation of enamines with 3 mol % of the catalyst is relatively slow. For example, hydroamination of **4** with catalyst **1** occurs with a turnover frequency (TOF) of 0.04 h^{-1} while the same catalyst gives 0.2 h^{-1} with alkyne **3**. However, the catalyst seems to be indefinitely stable to the reaction conditions.



Scheme 2. Hydroamination of alkynes in the presence of $[Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2]$ (**1**)

While catalyst **1** is inactive for the hydroamination of alkenes, the more reactive double bond of allene (**7**) can be hydroaminated catalytically under relatively mild conditions. The anti-Markownikow addition product, the 2,6-dimethylphenylimine of acetone (**8**), is isolated in 83% yield after heating a mixture of allene (**7**), amine **2**, and 2.7 mol % of catalyst **1** in benzene to 90 °C for 6 d (Scheme 3).

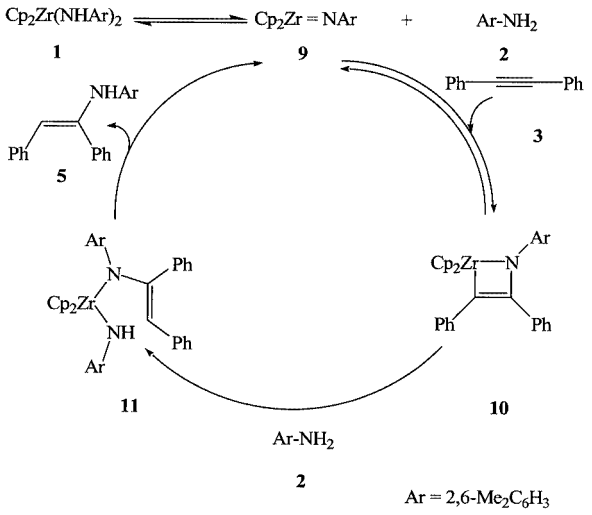


Scheme 3. Hydroamination of allene (**7**) in the presence of $[Cp_2Zr(NH\text{-}2,6\text{-}Me_2C_6H_3)_2]$ (**1**)

A detailed kinetic investigation of the addition of **2** to **3** at 95 °C indicates that the reaction is first order in the concentration of catalyst **1** and alkyne **3** and inverse first order in amine **2**. These results are consistent with a reversible rate-determining α-elimination of amine **2** from the bis(amide) **1** and generation of the transient imido complex **9** (Scheme 4). Alkyne **3** and amine **2** then compete for this reactive intermediate. While reaction with amine **2** regenerates the bis(amide) **1**, [2+2] cycloaddition with alkyne **3** provides the azazirconacyclobutene **10**. Rapid protonation by amine **2** at the Zr−C bond gives the enamide amide complex **11**, which then undergoes α-elimination of enamine **5** to regenerate the catalytically active species **9**.

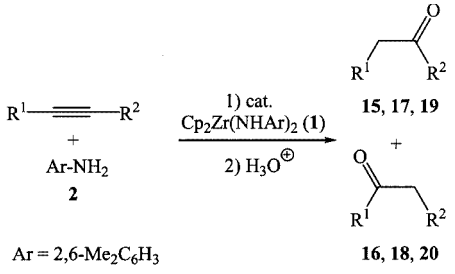
The major drawback of this procedure is the fact that amines that are sterically less demanding than 2,6-dimethylaniline (**2**) cannot be treated successfully with alkynes or allenes in the presence of zirconocene bis(amides). This is because of an irreversible reaction of the initially formed (imido)zirconium complexes $Cp_2Zr{=}NR$ to form catalytically inactive dimers $[Cp_2Zr{-}NR]_2$. This dimerization takes place easily if the substituent R is smaller than the bulky 2,6-dimethylphenyl group.[8]

Employing catalyst **1**, hydroamination reactions of unsymmetrically disubstituted alkynes with amine **2** take place with good to moderate regioselectivities.[9] As investigated for alkynes 1-phenylpropyne (**12**), 2-hexyne (**13**), and 4-methyl-2-pentyne (**14**), in each case the favored hydroamination product bears the smaller alkyne substituent located α to the nitrogen atom. After hydrolysis of the initially formed enamines/imines with aqueous acid, ketones **15**−**20** are obtained. The ratios of the ketones, which reflect the regioselectivities of the corresponding hydroamination reactions, are shown in Table 1.



Scheme 4. Catalytic cycle for the zirconocene bis(amide) catalyzed hydroamination of alkynes

Table 1. Ketones obtained from unsymmetrical alkynes by a hydroamination hydrolysis sequence employing catalyst **1**



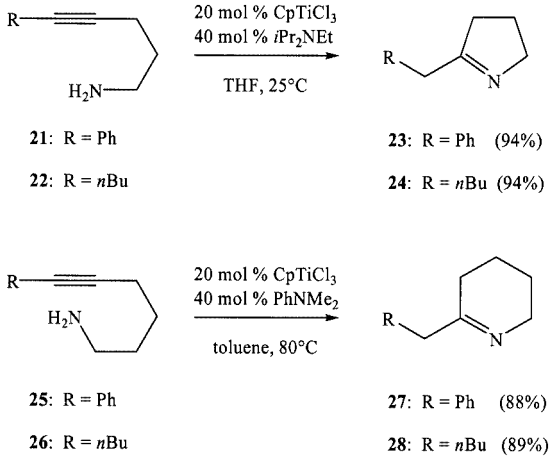
Alkyne	R^1	R^2	Products	Ratio of Products
12	Ph	Me	**15** / **16**	**15**:**16** = 82:18
13	*n*Pr	Me	**17** / **18**	**17**:**18** = 65:35
14	*i*Pr	Me	**19** / **20**	**19**:**20** = 54:46

Although the described hydroamination procedure does not represent a useful synthetic method, it must be recognized as the first example for a hydroamination of C−C multiple bonds employing a group-IV metal complex as catalyst. Furthermore, the possibility to make use of group-IV metal imido complexes as catalytically active species is unprecedented.

Titanium Complexes as Catalysts for the Hydroamination of Alkynes and Allenes

Also in 1992, Livinghouse et al. reported that $[CpTiCl_3]$ catalyzes the intramolecular hydroamination of γ- and δ-

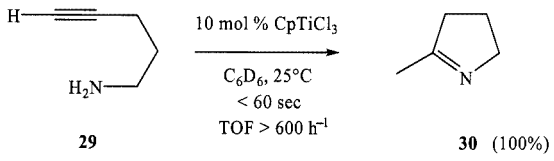
aminoalkynes.[10a] The reactions are performed with 20 mol % [$CpTiCl_3$] in the presence of 40 mol % of a tertiary amine (iPr_2NEt, $PhNMe_2$) at room temperature in THF or at 80 °C in toluene. Typical reaction times are in the range of 30 min. While several aminoalkynes[10b] can be treated successfully under these conditions (Scheme 5), intermolecular hydroamination reactions cannot be realized employing [$CpTiCl_3$] as catalyst.



Scheme 5. Intramolecular hydroamination of aminoalkynes in the presence of [$CpTiCl_3$]

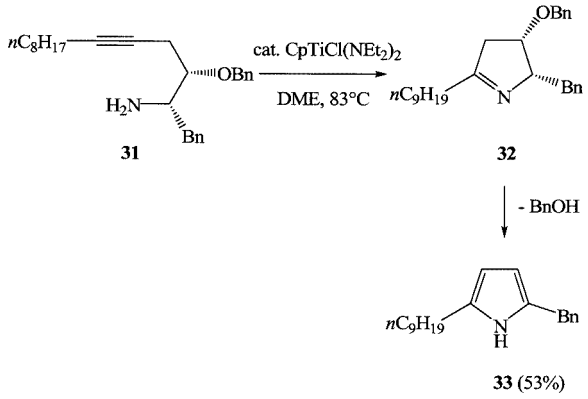
From a mechanistic point of view, the reaction is closely related to Bergman's zirconocene bis(amide) catalyzed process. Livinghouse et al. suggest that [$CpTiCl_3$] reacts initially with the amine function of the substrate with loss of HCl to form a reactive (imido)titanium complex, which undergoes [2+2] cycloaddition with the alkyne moiety of the aminoalkyne. The formed azatitanacyclobutene is then protonated by HCl to give the hydroamination product and to regenerate [$CpTiCl_3$]. A couple of protonation and trapping experiments (with isobutyronitrile) support the proposed catalytic cycle.

However, most noteworthy to mention is the fact that, in contrast to Bergman's results, the $CpTiCl_3$-catalyzed intramolecular hydroamination does not require a sterically demanding amine part of the aminoalkyne to take place efficiently. In addition, the described intramolecular hydroamination reactions are exceptionally fast. Most impressively, substrate **29** bearing a terminal alkyne moiety can be converted into the corresponding cyclic imine **30** at room temperature in the presence of 10 mol % $CpTiCl_3$ in 100% yield in less than 60 s (NMR experiment), which is consistent with a turnover frequency of more than 600 h^{-1} (Scheme 6).[11]



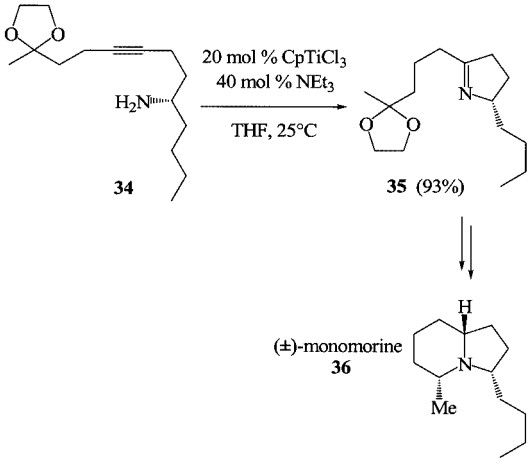
Scheme 6. Cyclization of 5-amino-1-pentyne (**29**) in the presence of [$CpTiCl_3$]

Besides [$CpTiCl_3$], the bis(amide) [$CpTiCl(NEt_2)_2$] can be used as catalyst for effecting intramolecular hydroamination reactions at elevated temperatures.[11] However, only one example employing this catalyst – the cyclization of **31** – has been described in the literature. Unfortunately, the conditions required for cyclization are sufficiently vigorous to cause the initially formed imine **32** to undergo sequential tautomerization elimination, leading to pyrrole **33** in 53% unoptimized yield (Scheme 7).



Scheme 7. [$CpTiCl(NEt_2)_2$]-catalyzed intramolecular hydroamination at elevated temperature

Since the employed reaction conditions are relatively mild and five- and six-membered cyclic amines are common substructures of natural products it is not surprising that the developed process has already been used for the synthesis of the indolizidine alkaloid (±)-monomorine (**36**).[12] The key step of the synthesis is a [$CpTiCl_3$]-catalyzed cyclization of readily available aminoalkyne **34**, which is performed at room temperature with 20 mol % of the catalyst (Scheme 8). Subsequent stereoselective imine reduction, hydrolysis of the 1,3-dioxolane moiety, and reductive amination/cyclization furnishes (±)-monomorine (**36**).

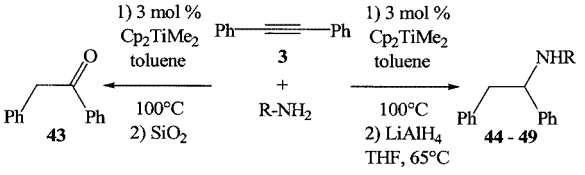


Scheme 8. Synthesis of indolizidine alkaloid (±)-monomorine (**36**) by [$CpTiCl_3$]-catalyzed intramolecular hydroamination

Significant progress in the field of group-IV metal complex catalyzed hydroamination reactions was achieved when

our group identified the first titanium catalysts for the intermolecular hydroamination of alkynes in 1999.[13] In initial intermolecular reactions, the titanium bis(amide) complex [$Cp_2Ti(NHPh)_2$] was identified to be a very good hydroamination catalyst. However, during a study directed towards identification of a general catalyst precursor, which can be converted into a catalytically active (imido)titanium complex in the presence of an arbitrary amine, we found that the well-known and readily available reagent [Cp_2TiMe_2][14] is a widely applicable, inexpensive catalyst of low toxicity that can be used in intermolecular hydroamination reactions of alkynes.[13] With this catalyst, primary aryl- and alkylamines can be treated with symmetrically and unsymmetrically substituted internal and terminal alkynes. The resulting imines can be either converted into carbonyl compounds by hydrolysis (SiO_2) or reduced ($LiAlH_4$ or H_2, Pd/C) to secondary amines. In initial experiments, it was shown that several aryl- and alkylamines can be treated with diphenylacetylene (**3**) in the presence of 3 mol % [Cp_2TiMe_2]. Typical reactions are performed at 100 °C in toluene for 72 h. While arylamines and sterically demanding *sec*- and *tert*-alkylamines give good results sterically less hindered *n*-alkyl- and benzylamines are poor substrates (Table 2).

Table 2. [Cp_2TiMe_2]-catalyzed hydroamination of diphenylacetylene (**3**) with various amines



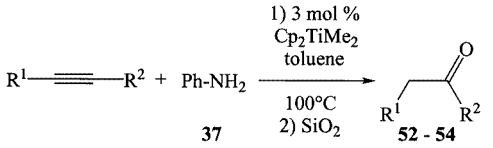
Amine	R	Yield of **43** (%)	Yield of **44 - 49** (%)	
37	Ph	92	**44**	62
38	4-FC_6H_4	93	**45**	63
39	*t*Bu	91	**46**	86[a]
40	Cy	65	**47**	86[a]
41	nC_6H_{13}	19	**48**	-
42	Bn	14[b]	**49**	3[b]

[a] Reduction with 1 atm H_2 and 5 mol % Pd/C. [b] 130°C.

In addition, aniline (**37**) can be treated efficiently with a wide variety of alkynes in the presence of catalytic amounts of [Cp_2TiMe_2] under identical reaction conditions. In the case of unsymmetrically substituted 1-alkyl-2-arylalkynes, the reaction occurs with high regioselectivity (≥ 98:2) preferring the anti-Markownikow products (Table 3).

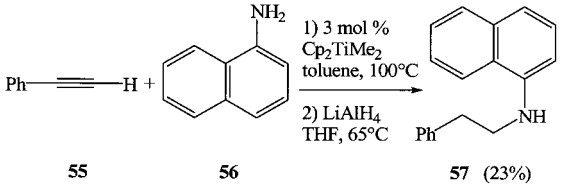
Interestingly, the first example of a successful group-IV metal complex catalyzed intermolecular hydroamination of a terminal alkyne is also presented. Using 3 mol % [Cp_2TiMe_2], phenylacetylene (**55**) is treated with 1-naphthylamine (**56**). After subsequent reduction, the corresponding anti-Markownikow addition product **57** is obtained in 23% yield (Scheme 9). Although the yield is low, it is remarkable that the isomeric Markownikow derivative is not detected.

Table 3. [Cp_2TiMe_2]-catalyzed hydroamination of unsymmetrically substituted alkynes with aniline (**37**)



Alkyne	R^1	R^2	Yield of **52 - 54** (%)	
12	Ph	Me	**52**	99[a]
50	Ph	Et	**53**	73
51	Ph	*n*Pr	**54**	35

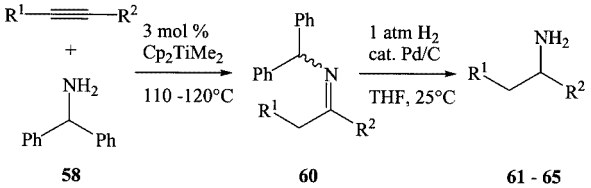
[a] 1 mol % Cp_2TiMe_2.



Scheme 9. First example of a successful intermolecular hydroamination of a terminal alkyne in the presence of a group-IV metal complex as catalyst

As a result of the low reactivity of benzylamine (**42**) in [Cp_2TiMe_2]-catalyzed hydroamination reactions, initial experiments to convert alkynes into primary amines using benzylamine (**42**) as an ammonia equivalent in the hydroamination step followed by hydrogenation of the resulting imine in the presence of Pd/C failed. However, when the sterically more demanding amine benzhydrylamine (**58**) is used, primary amines can be obtained from alkynes in good yields by a corresponding hydroamination hydrogenation sequence (Table 4).[15]

Table 4. Synthesis of primary amines from alkynes using a hydroamination reduction strategy

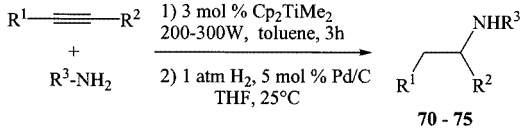


Alkyne	R^1	R^2	Product	Yield (%)
3	Ph	Ph	**61**	67
12	Ph	Me	**62**	79
51	Ph	*n*Pr	**63**	70
55	Ph	H	**64**	41
59	Et	Et	**65**	59

As can be seen from Table 4, 1,2-diaryl- (**3**) and 1,2-dialkylalkynes (**59**) can be converted into the desired primary amines in reasonable yields by the described two-step procedure. However, slightly better results are obtained with 1-alkyl-2-arylalkynes **12** and **51**. Employing these substrates, biologically interesting (phenylethyl)amines are formed regioselectively in high yields. Furthermore, the terminal alkyne **55** can be converted into (2-phenylethyl)amine (**64**). In this case, yields are better if the reaction time is short.

During a study directed towards optimizing the described method, it was recognized 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.[16] For example, irradiation of a mixture of diphenylacetylene (**3**) and aniline (**37**) with microwaves (300 W, 2.45 GHz) in the presence of 3 mol % [Cp_2TiMe_2] results in a fast hydroamination reaction which reaches 100% conversion within 3 h. Subsequent hydrogenation of the initially formed imine with H_2 and 5 mol % Pd/C gives access to the corresponding amine **70** in 93% yield. In comparison, the same hydroamination reaction performed at 105 °C in an oil bath needs 30 h to go to completion. Several other examples of corresponding reactions (Table 5) prove that the microwave heating technique is a viable option for performing [Cp_2TiMe_2]-catalyzed hydroamination reactions conveniently and safely in a short time. As observed before, hydroamination reactions employing 1-alkyl-2-arylalkynes do not result in any formation of Markownikow products.

Table 5. Microwave-assisted hydroamination of alkynes and subsequent reduction



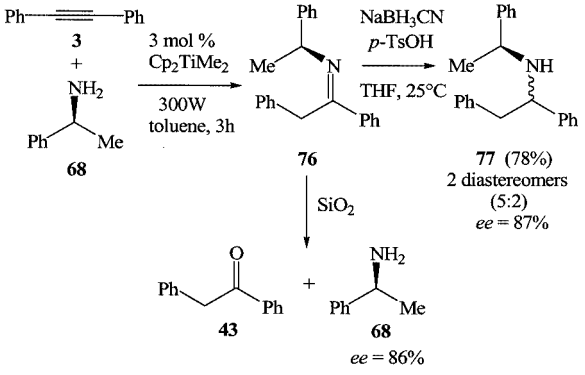
70 - 75

Alkyne	R^1	R^2	Amine	R^3	Product	Yield (%)
3	Ph	Ph	**37**	Ph	**70**	93
3	Ph	Ph	**40**	Cy	**71**	78
3	Ph	Ph	**66**	2-Pentyl	**72**	67
12	Ph	Me	**67**	PMP[a]	**73**	68[b]
50	Ph	Et	**68**	(*S*)-Ph(CH)Me	**74**	59[b]
59	Et	Et	**69**	4-MeC_6H_4	**75**	59[b]

[a] PMP = *p*-Methoxyphenyl. [b] Reduction: $NaBH_3CN$, *p*-TsOH, THF, 25°C.

However, one has to keep in mind that comparable hydroamination reactions performed at 190 °C (oil bath) also reach 100% conversion within 3 h. This result shows that the rates observed for reactions performed under microwave irradiation conditions are similar to those observed at 190 °C. However, in both cases the required reaction times are reduced by a factor of ten.

Particularly interesting is the microwave-assisted reaction between diphenylacetylene (**3**) and the enantiomerically pure amine [(*S*)-1-phenylethyl]amine (**68**; *ee* = 99%). After subsequent reduction with $NaBH_3CN$/*p*-TsOH, two diastereomers of the corresponding product **77** are obtained in a 5:2 ratio. GC analysis shows that the *ee* values for both diastereomers of **77** are only 87%. In addition, amine **68** can be reisolated from an identical hydroamination reaction after hydrolysis (SiO_2) of the initially formed imine **76**. GC analysis of reisolated **68** shows that the *ee* value is 86% (Scheme 10). 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.

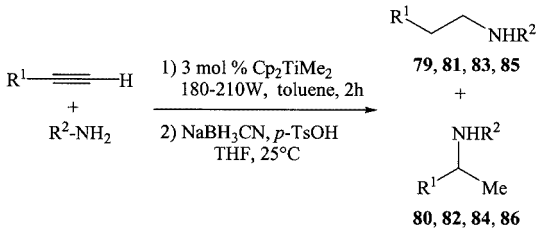


Scheme 10. Hydroamination of **3** employing enantiomerically pure amine **68**

Impressively, hydroamination products of terminal alkynes are also formed in reasonable yields under microwave irradiation conditions. In contrast to reactions of unsymmetrical 1-alkyl-2-arylalkynes, the observed regioselectivity is low. While formation of the Markownikow product is favored in addition reactions of aromatic amines to 1-dodecyne (**78**) the anti-Markownikow product is the major product in reactions between anilines and phenylacetylene (**55**; Table 6). However, if the alkylamine [(*S*)-1-phenylethyl]amine (**68**) is treated with phenylacetylene the Markownikow product is preferably formed and the obtained yield is low.

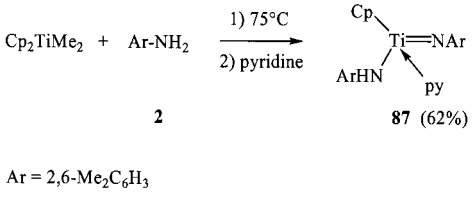
Initialized by the promising results mentioned above, Bergman's and our group became interested in the mechanistic details of titanium complex catalyzed intermolecular hydroamination reactions in 2001.[17–19] A corresponding investigation performed in the Bergman group suggests that the catalytically active species of the described reactions is a (amido)(cyclopentadienyl)(imido)titanium imide complex which is formed by an unexpected cyclopentadienyl/amide ligand exchange.[17] A combination of two facts is responsible for this suggestion: 1) the corresponding pyridine-stabilized intermediate **87** can be isolated in 62% yield after heating a mixture of [Cp_2TiMe_2], 2,6-dimethylaniline (**2**), and pyridine to 75 °C for 24 h (Scheme 11), and 2) complex **87** rapidly catalyzes the addition of 2,6-dimethylaniline (**2**) to diphenylacetylene (**3**) at 75 °C. In this context, it is note-

Table 6. Hydroamination of terminal alkynes and subsequent reduction



Alkyne	R^1	Amine	R^2	Products	Yield (%)	Ratio
55	Ph	**68**	(*S*) - Ph(CH)Me	**79 / 80**	34	1:2.4
55	Ph	**69**	4-MeC_6H_4	**81 / 82**	87	4:1
78	*n*$C_{10}H_{21}$	**37**	Ph	**83 / 84**	49	1:7
78	*n*$C_{10}H_{21}$	**69**	4-MeC_6H_4	**85 / 86**	80	2:5

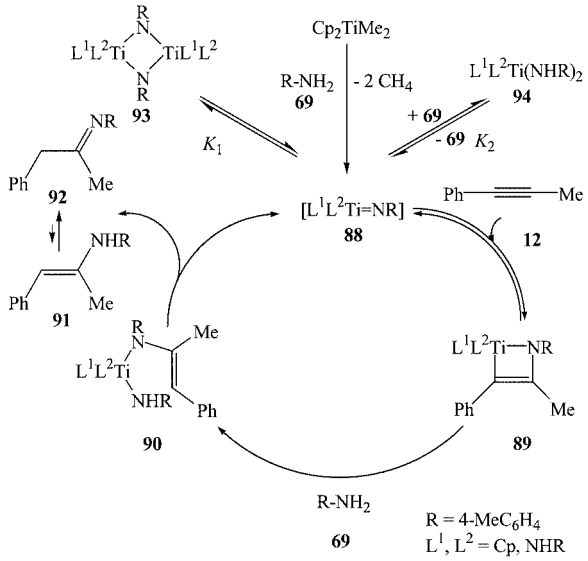
worthy to mention that no reaction is observed at 75 °C when [Cp_2TiMe_2] is used as catalyst.



Scheme 11. Reaction of [Cp_2TiMe_2] with 2,6-dimethylaniline (**2**) in the presence of pyridine

Detailed kinetic investigations of the reaction between 1-phenylpropyne (**12**) and 4-methylaniline (**69**) performed in our group led to the conclusion that the mechanism of the [Cp_2TiMe_2]-catalyzed intermolecular hydroamination of alkynes involves an unexpected reversible equilibrium between the catalytically active imidotitanium complex **88** and its dimer **93**.[18] 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 indicate that the reaction is first order in the concentration of alkyne **12** while high amine concentrations result in a fast reaction. In general, the mechanism of the reaction seems to be described by the catalytic cycle shown in Scheme 12.[18] Besides the mentioned reversible dimerization of imido complex **88** (K_1), the cycle includes a reversible addition of amine **69** to the Ti=N linkage in **88** (K_2). The hydroamination of **12** takes place by a reversible and regioselective [2+2] cycloaddition between **88** and **12** placing the methyl group α to the nitrogen atom, a protonation of the formed metallacycle **89**, and a final α-elimination of the product, which regenerates **88**.

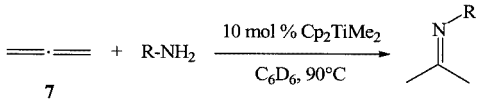
In addition, the kinetic data are consistent with the assumption that the protonation of the azametallacyclobutene **89** is slow compared to the cycloreversion of **89**. These interpretations of the kinetic study, as well as our suggestion that the equilibrium between imido complex **88** and amide **94** favors **94**,[18] are strongly supported by DFT calculations performed by Straub and Bergman.[19]



Scheme 12. Mechanism of the [Cp_2TiMe_2]-catalyzed intermolecular hydroamination of alkynes

In further investigations, [Cp_2TiMe_2] and imido complex **87** were also found to be highly active catalysts for intermolecular hydroaminations of symmetrical and unsymmetrical allenes.[17] For example, allene (**7**) can be treated with various amines and hydrazines in the presence of 10 mol % [Cp_2TiMe_2] yielding the corresponding imines and hydrazones of acetone in good to excellent yields (Table 7).

Table 7. [Cp_2TiMe_2]-catalyzed addition of amines and hydrazines to allene (**7**)

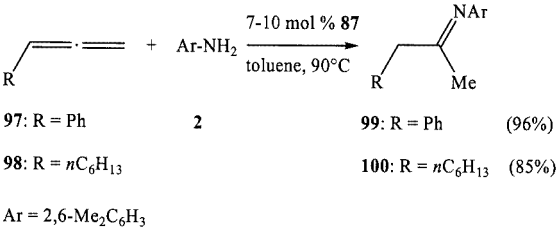


Amine/Hydrazine	R	Yield (%)
39	*t*Bu	76
67	PMP[a]	58
69	4-MeC_6H_4	78
95	4-$CF_3C_6H_4$	25
96	$(Me)_2N$	90

[a] PMP = *p*-Methoxyphenyl.

An additional kinetic study of the reaction between allene (**7**) and 2,6-dimethylaniline (**2**) employing **87** as catalyst supports a mechanism of the allene hydroamination which is similar to that shown in Scheme 13.[17] However, due to the steric demand of the employed amine, no dimerization

of the catalytically active imido complex is observed. Furthermore, an addition of amine **2** to the Ti=N linkage to form an $L^1L^2Ti(NHR)_2$ species is not observed either, which is in agreement with DFT calculations.[19]



97: R = Ph **2** **99**: R = Ph (96%)

98: R = nC_6H_{13} **100**: R = nC_6H_{13} (85%)

Ar = 2,6-$Me_2C_6H_3$

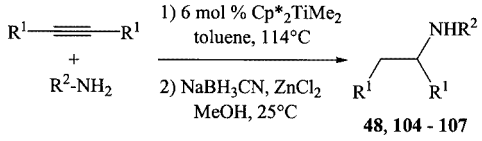
Scheme 13. Hydroamination of unsymmetrical allenes employing imido complex **87** as catalyst

Impressively, complete regiocontrol is observed in hydroamination reactions of substituted allenes in the presence of catalytic amounts of **87**, a direct consequence of the regiochemistry of the [2+2] cycloaddition involved in the catalytic cycle.[17]

The most important result obtained from the described mechanistic investigations is the fact that the mechanism shown in Scheme 12 easily explains 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, imido complex dimers, and bis(amides) for sterically less demanding amines result in slow hydroamination reactions. However, a related consideration suggests that the use of bigger ligands at the titanium center should influence the corresponding 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 easily understandable that *n*-alkylamines and benzylamines can be treated efficiently with various alkynes in the presence of catalytic amounts of [$Cp^*_2TiMe_2$].[20] Most impressively, the hydroamination reaction between *n*-propylamine (**102**) and diphenylacetylene (**3**) reaches 100% conversion after 4 h in the presence of 6.0 mol % [$Cp^*_2TiMe_2$] at 114 °C. After subsequent reduction performed with zinc-modified $NaBH_3CN$, the amine product **105** is obtained in 86% yield. In comparison, an identical hydroamination reaction performed with 6.0 mol % [Cp_2TiMe_2] does not reach 100% conversion after 48 h. In this case, the subsequent reduction gives access to only 10% of the desired amine. However, in the presence of 2−6 mol % of [$Cp^*_2TiMe_2$] symmetrical alkynes can be treated with various sterically less demanding *n*-alkyl- and benzylamines to give secondary amines after reduction in high yields (Table 8). Typical reaction times are in the range of 4−24 h.

While hydroamination reactions employing terminal alkynes are not successful in the presence of [$Cp^*_2TiMe_2$], unsymmetrically substituted 1-alkyl-2-arylalkynes such as 1-phenylpropyne (**12**) are suitable substrates. Surprisingly,

Table 8. [$Cp^*_2TiMe_2$]-catalyzed addition of *n*-alkyl- and benzylamines to alkynes



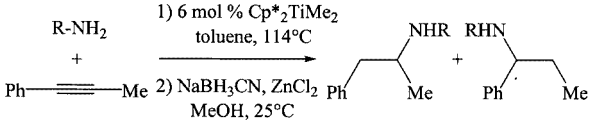
48, 104 - 107

Alkyne	R^1	Amine	R^2	Product	Yield (%)
3	Ph	**41**	nC_6H_{13}	**48**	89
3	Ph	**102**	*n*Pr	**104**	86
3	Ph	**103**	PMB[a]	**105**	97
59	Et	**42**	Bn	**106**	87
101	*n*Pr	**64**	$Ph(CH_2)_2$	**107**	82

[a] PMB = *p*-Methoxybenzyl.

in this case the observed regioselectivities of [$Cp^*_2TiMe_2$]-catalyzed addition reactions of sterically unhindered amines are low (Table 9). However, if [$Cp^*_2TiMe_2$] is used as catalyst for the addition of sterically demanding amines (e.g. **69**) to **12**, the regioselectivity is as high as observed for [Cp_2TiMe_2]. This result indicates that 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.

Table 9. [$Cp^*_2TiMe_2$]-catalyzed hydroamination of unsymmetrically substituted alkyne **12**

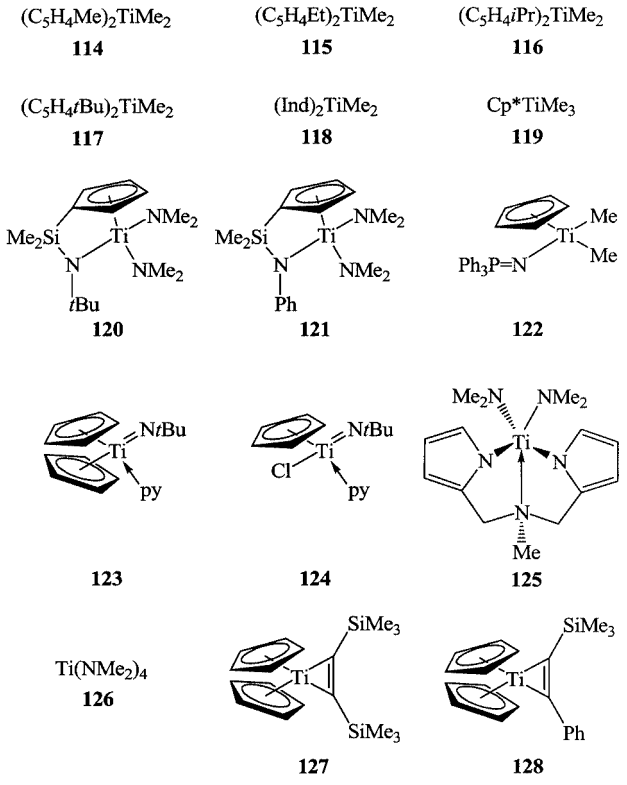


12 **108, 110, 112** **109, 111, 113**

Amine	R	Product	Yield (%)	Product	Yield (%)
41	nC_6H_{13}	**108**	52	**109**	41
42	Bn	**110**	70	**111**	24
69	4-MeC_6H_4	**112**	92	**113**	3

In addition to [Cp_2TiMe_2], [$Cp^*_2TiMe_2$], and complex **87**, a number of other titanium complexes (**114**−**128**) have been identified as catalysts for the intermolecular hydroamination of alkynes during the last two years.[18,21−24] As can be seen from Scheme 14, all identified hydroamination catalysts possess either two labile ligands (methyl, dimethylamido or cyclopropenyl ligands) or a preformed imido ligand.

While Scheme 14 clearly indicates that a wide variety of titanium complexes can, in principle, be used as catalysts

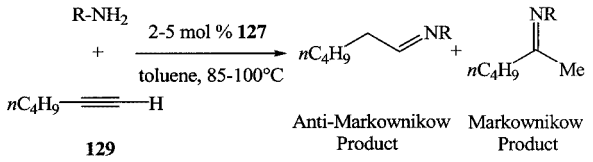


Scheme 14. Titanium catalysts for the intermolecular hydroamination of alkynes

for the intermolecular hydroamination of alkynes, the catalytic activities of the shown titanium complexes strongly depend on the properties of the employed substrates.[21] For example, complexes **125** and $Ti(NMe_2)_4$ (**126**) are efficient catalysts for the hydroamination of 1-hexyne with aryl- and alkylamines.[22,23] However, reactions between diphenylacetylene and *tert*-butyl- or cyclohexylamine are not catalyzed by these complexes under comparable conditions.[21−23] Another impressive example for varying catalytic activity is seen when the bis(cyclopentadienyl)(imido) complex **123** is compared to the chloro-substituted imido derivative **124**. While **123** 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 contrast, the related complex **124** gives 46 and 93% yield, respectively. Interestingly, $[Cp_2TiMe_2]$, $[(Ind)_2TiMe_2]$ (**118**), and **127** seem to be general catalysts for the intermolecular hydroamination of alkynes because they give good results for a number of transformations. However, because reliable predictions for the choice of a catalyst for a certain reaction are difficult to make, the reader should keep in mind that each hydroamination reaction in the presence of a titanium catalyst must be optimized carefully to obtain the best result.

Further differences between various catalysts can be found in studies dealing with the regioselectivity of addition reactions to terminal alkynes.[22−24] For example, catalysts **127** and **128** can be used for the selective anti-Markownikow addition of alkylamines to terminal alkylalkynes. In this case, the observed regioselectivity increases with increasing steric demand of the amine. In contrast, the major product of the addition of aniline (**37**) to 1-hexyne (**129**) is the Markownikow product (Table 10).[24]

Table 10. Catalytic hydroamination of 1-hexyne (**129**) in the presence of catalytic amounts of **127**



Amine	R	Yield (%)	Anti-Markownikow : Markownikow
39	*t*Bu	90	> 99:1
130	*i*Bu	86	3:1
37	Ph	94	1:3

However, a corresponding regioselectivity switch is not observed with catalysts **125** and **126**. Employing these catalysts, the favored product of addition reactions of alkyl- and arylamines to 1-hexyne (**129**) is always the Markownikow product.[22,23]

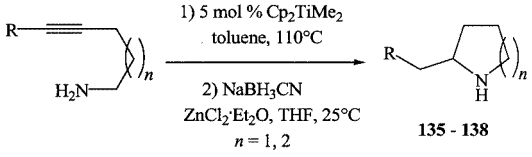
Very recently it was recognized that $[Cp_2TiMe_2]$ is also an efficient catalyst for the intramolecular hydroamination of aminoalkynes.[25] In contrast to intermolecular hydroaminations, cyclization reactions of γ- and δ-aminoalkynes do not require a sterically demanding amine part of the aminoalkyne to take place efficiently. Using a corresponding one-pot procedure, five- and six-membered cyclic amines can be synthesized in good yields by $[Cp_2TiMe_2]$-catalyzed intramolecular hydroamination and subsequent reduction with $NaBH_3CN/ZnCl_2$ (Table 11). In contrast, seven- and eight-membered rings are formed slowly under the employed conditions.

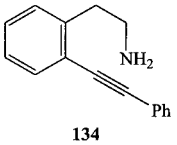
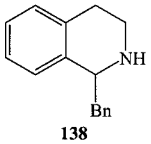
Unfortunately, the employed reaction conditions are relatively harsh (110 °C) compared to other catalytic procedures for intramolecular hydroaminations.[3,10−12,26] Therefore, $[Cp_2TiMe_2]$ does not offer significant advantages over other catalysts. However, since it is well established that this Ti complex also catalyzes intermolecular hydroamination reactions of alkenes and allenes the results presented in Table 11 undoubtedly prove that $[Cp_2TiMe_2]$ must be recognized as the most general catalyst for the hydroamination of alkynes and allenes known today.

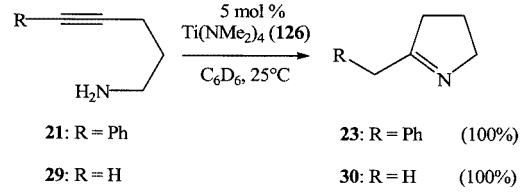
In this context, it is noteworthy to mention that related intramolecular hydroamination reactions can be performed at room temperature in the presence of 5 mol % of $Ti(NMe_2)_4$ (**126**; Scheme 15).[26]

Based on this result, catalyst **126** and titanium bis(sulfonamide) **139** have been used successfully for the intramolecular hydroamination of aminoallenes (Scheme 16).[26] Corresponding reactions are performed at 75 °C in benzene in

Table 11. One-pot synthesis of cyclic amines by $[Cp_2TiMe_2]$-catalyzed intramolecular hydroamination and subsequent reduction



Aminoalkyne	n	R	Product	n	Yield (%)
131	2	4-MeOC$_6$H$_4$	**135**	2	94
132	2	2-BrC$_6$H$_4$	**136**	2	88
133	3	nC$_6$H$_{13}$	**137**	3	72
 **134**			 **138**		76

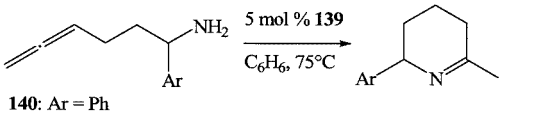


21: R = Ph — **23**: R = Ph (100%)

29: R = H — **30**: R = H (100%)

Scheme 15. Intramolecular hydroamination in the presence of $Ti(NMe_2)_4$ (**126**)

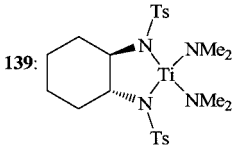
the presence of 5 mol % of the catalyst. Typical reaction times are in the range of 1−36 h. While six-membered rings are formed smoothly under the reaction conditions the formation of seven-membered rings requires higher catalyst loadings (10 mol %) and elevated temperatures (135 °C).



140: Ar = Ph
141: Ar = 4-MeOC$_6$H$_4$
142: Ar = 4-FC$_6$H$_4$

143: Ar = Ph (84%)
144: Ar = 4-MeOC$_6$H$_4$ (95%)
145: Ar = 4-FC$_6$H$_4$ (93%)

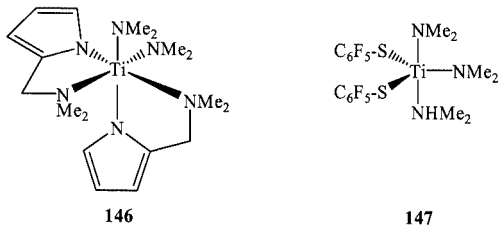
139:



Scheme 16. Intramolecular hydroaminations of aminoallenes

Recently, improved catalysts (**146**, **147**; Scheme 17) for the addition of hydrazines to alkynes, which can be synthesized from commercially available $Ti(NMe_2)_4$ (**126**) in one step, have been identified by Odom et al.[27]

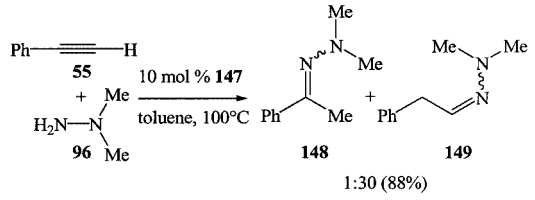
In the presence of 10 mol % of these catalysts, various hydrazines can be treated successfully with alkynes at 100 °C in toluene. While terminal alkynes and 1-phenylpropyne (**12**) give the desired hydrazones in good yields, other in-

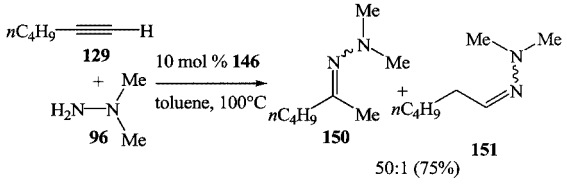


146 **147**

Scheme 17. Improved catalysts for the addition of hydrazines to alkynes

ternal alkynes such as diphenylacetylene (**3**) and 3-hexyne (**59**) are poor substrates. As observed before, the regioselectivity of the reactions appears to be influenced by the electronic properties of the alkyne, with both catalysts favoring Markownikow addition to 1-hexyne (**129**) and anti-Markownikow addition to phenylacetylene (**55**; Scheme 18).





Scheme 18. Addition of 1,1-dimethylhydrazine (**96**) to terminal alkynes

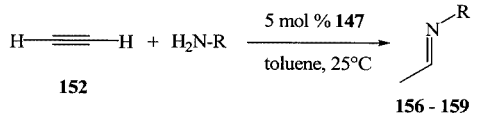
Most impressively, hydrazines can be treated with acetylene (**152**) in the presence of 5 mol % of **147** at room temperature to give the corresponding hydrazones in excellent yields (Table 12).[27]

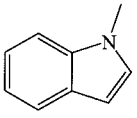
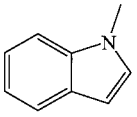
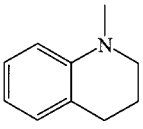
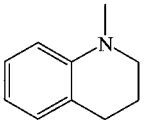
In addition, corresponding reactions involving hydrazines incorporating aryl groups at one nitrogen center give direct access to substituted indoles by a Fischer indole synthesis (Scheme 19).[27]

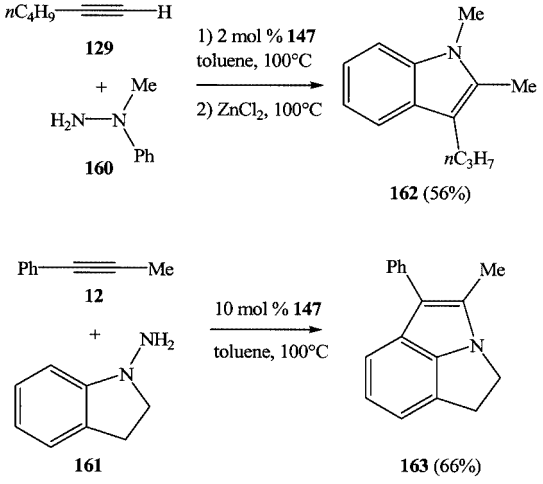
Since the combination of all the studies described in this review definitely proves that titanium complex catalyzed inter- and intramolecular hydroamination reactions represent reliable new synthetic transformations it is not surprising that initial applications of corresponding procedures for the synthesis of biologically interesting compounds have already appeared in the literature.[28,29]

For example, a new and highly flexible procedure for the synthesis of α,α-disubstituted α-aminophosphonates employing alkynes, primary amines and dimethyl or diethyl phosphite as starting materials uses a hydroamination reaction as the key synthetic step. The reaction sequence, which is performed as a one-pot operation, starts with a $[Cp_2TiMe_2]$-catalyzed hydroamination of an alkyne. A subsequent nucleophilic addition of diethyl or dimethyl phos-

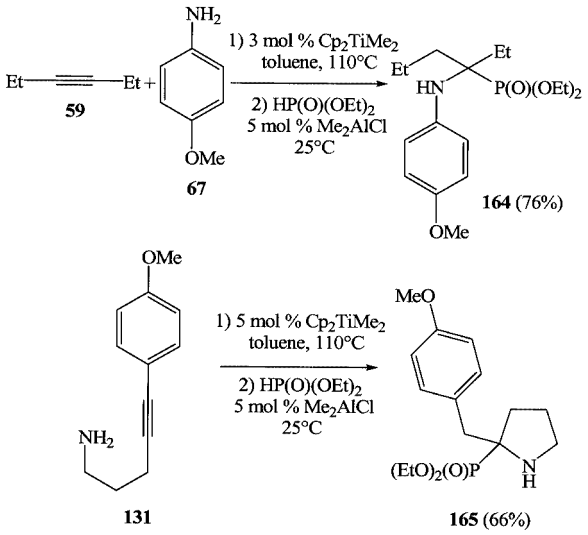
Table 12. Addition of hydrazines to acetylene (**152**) in the presence of catalyst **147**



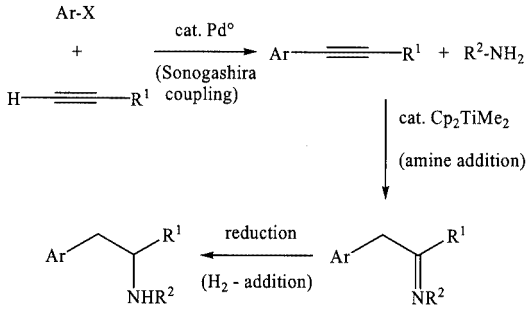
R-NH_2	R	Product	R	Yield (%)
96	$N(Me)_2$	**156**	$N(Me)_2$	83
153	$N(Ph)_2$	**157**	$N(Ph)_2$	99
154		**158**		95
155		**159**		94



Scheme 19. Alkyne hydroaminations employing arylhydrazines



Scheme 20. Synthesis of α-aminophosphonates from alkynes, primary amines (or aminoalkynes), and dialkyl phosphites



Scheme 21. Highly flexible synthesis of (2-arylethyl)amine derivatives from aryl halides, terminal alkynes, and primary amines

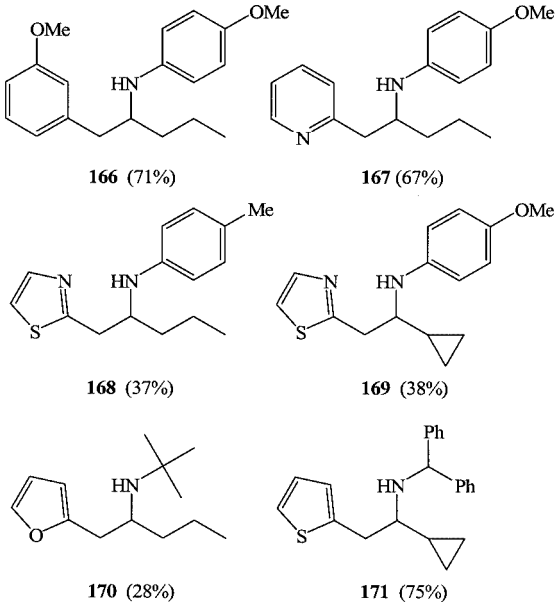
phite to the resulting imine, performed in the presence of catalytic amounts of Me_2AlCl, gives the desired α-aminophosphonate in good yield. The application of intermolecular and intramolecular hydroamination reactions leads to the formation of both cyclic and acyclic α-aminophosphonates (Scheme 20).[28]

In addition, a new and highly flexible procedure for the synthesis of (2-arylethyl)amine derivatives is based on the regioselective hydroamination of 1-alkyl-2-arylalkynes in the presence of catalytic amounts of $[Cp_2TiMe_2]$. According to this procedure, the target compounds can be synthesized with high diversity in three steps from aryl halides, terminal alkynes, and primary amines (Scheme 21).[29]

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 1-alkyl-2-arylalkyne, which takes place regioselectively in the 2-position, gives access to an α-arylketimine. A final reduction of the formed imine ($NaBH_3CN/ZnCl_2{\cdot}Et_2O$) results in the formation of the desired (2-arylethyl)amine derivative. From a mathematical point of view, 20 aryl halides, 20 terminal alkynes, and 20 primary amines can be converted into 8000 different (2-arylethyl)amine derivatives by the described synthetic approach. However, Scheme 22 shows only selected examples of (2-arylethyl)amine derivatives synthesized by the described strategy. The yields represent overall yields based on the employed aryl halide.

Summary and Outlook

The results mentioned in this review clearly indicate that, today, group-IV metal complexes bearing two labile ligands must be regarded as very efficient hydroamination catalysts. For corresponding reactions employing alkynes and allenes, imidozirconium and -titanium complexes, which undergo carbon−nitrogen bond forming [2+2] cycloadditions with C−C multiple bonds, are thought to be the catalytically active species. While zirconocene-based complexes only cata-



Scheme 22. Selected examples of already synthesized (2-arylethyl)-amine derivatives

lyze addition reactions of 2,6-dimethylaniline to alkynes and allenes, titanium complexes were found to be more general catalysts. Up to now, a variety of titanium complexes for inter- and intramolecular hydroamination reactions of alkynes and allenes employing primary amines and hydrazines have been identified. However, the catalytic activities of the titanium complexes strongly depend on the properties of the employed substrates. Fortunately, [Cp_2TiMe_2] and closely related catalysts such as **87**, **118**, **123**, and **127** seem to be quite general catalysts for the hydroamination of alkynes and allenes, which have already been applied for the synthesis of biologically relevant molecules.

Despite the great progress made in the rapidly growing field of group-IV metal complex catalyzed hydroamination of alkynes and allenes, corresponding reactions employing alkenes remain to be developed in the future.

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[1] *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), 2nd ed., Wiley-VCH, Weinheim, **2002**.
[2] *Metallocene-Based Polyolefins* (Eds.: J. Sheirs, W. Kaminsky), John Wiley & Sons, Chichester, **2000**.
[3] For general reviews on hydroamination, see: [3a] I. A. Chekulaeva, L. V. Kondratjeva, *Russ. Chem. Rev.* **1965**, *34*, 669−680. [3b] D. Steinborn, R. Taube, *Z. Chem.* **1986**, *26*, 349−359. [3c] R. Taube in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 507−520. [3d] T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675−703. [3e] T. E. Müller, M. Beller in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, vol. 2, p. 316−330. [3f] E. Haak, S. Doye, *Chem. Unserer Zeit* **1999**, *33*, 296−303. [3g] M. Nobis, B. Drießen-Hölscher, *Angew. Chem.* **2001**, *113*, 4105−4108; *Angew. Chem. Int. Ed.* **2001**, *40*, 3983−3985. [3h] J. J. Brunet, D. Neibecker in *Catalytic Heterofunctionalization* (Eds.: A. Togni, H. Grützmacher), Wiley-VCH, Weinheim, **2001**, p. 91−141.
[4] G. Heilen, H. J. Mercker, D. Frank, R. A. Reck, R. Jäckh in *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., VCH, Weinheim, **1985**, vol. A2, p. 1−36.
[5] BASF produces tBuNH$_2$ by addition of ammonia to 2-methylpropene (isobutene) in the presence of zeolites: V. Taglieber, W. Hölderich, R. Kummer, W. D. Mross, G. Saladin, DE 3,327,000, **1985**.
[6] T. Straub, A. Haskel, T. G. Neyroud, M. Kapon, M. Botoshansky, M. S. Eisen, *Organometallics* **2001**, *20*, 5017−5035.
[7] P. J. Walsh, A. M. Baranger, R. G. Bergman, *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719.
[8] P. J. Walsh, F. J. Hollander, R. G. Bergman, *J. Am. Chem. Soc.* **1988**, *110*, 8729−8731.
[9] A. M. Baranger, P. J. Walsh, R. G. Bergman, *J. Am. Chem. Soc.* **1993**, *115*, 2753−2763.
[10] [10a] P. L. McGrane, M. Jensen, T. Livinghouse, *J. Am. Chem. Soc.* **1992**, *114*, 5459−5460. [10b] For the synthesis of aminoalkynes, see: M. R. Gagné, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 275−294.
[11] P. L. McGrane, T. Livinghouse, *J. Am. Chem. Soc.* **1993**, *115*, 11485−11489.
[12] P. L. McGrane, T. Livinghouse, *J. Org. Chem.* **1992**, *57*, 1323−1324.
[13] [13a] E. Haak, S. Doye, DE 199,13,522, **1999**. [13b] E. Haak, I. Bytschkov, S. Doye, *Angew. Chem.* **1999**, *111*, 3584−3586; *Angew. Chem. Int. Ed.* **1999**, *38*, 3389−3391.
[14] [14a] N. A. Petasis in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette), John Wiley & Sons, New York, **1995**, vol. 1, p. 470−473. [14b] H. Siebeneicher, S. Doye, *J. Prakt. Chem.* **2000**, *342*, 102−106.
[15] E. Haak, H. Siebeneicher, S. Doye, *Org. Lett.* **2000**, *2*, 1935−1937.
[16] I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2001**, 4411−4418.
[17] J. S. Johnson, R. G. Bergman, *J. Am. Chem. Soc.* **2001**, *123*, 2923−2924.
[18] F. Pohlki, S. Doye, *Angew. Chem.* **2001**, *113*, 2361−2364; *Angew. Chem. Int. Ed.* **2001**, *40*, 2305−2308.
[19] B. F. Straub, R. G. Bergman, *Angew. Chem.* **2001**, *113*, 4768−4771; *Angew. Chem. Int. Ed.* **2001**, *40*, 4632−4635.
[20] A. Heutling, S. Doye, *J. Org. Chem.* **2002**, *67*, 1961−1964.
[21] F. Pohlki, A. Heutling, I. Bytschkov, T. Hotopp, S. Doye, *Synlett* **2002**, 799−801.
[22] Y. Shi, J. T. Ciszewski, A. L. Odom, *Organometallics* **2001**, *20*, 3967−3969.
[23] C. Cao, J. T. Ciszewski, A. L. Odom, *Organometallics* **2001**, *20*, 5011−5013.
[24] A. Tillack, I. Garcia Castro, C. G. Hartung, M. Beller, *Angew. Chem.* **2002**, *114*, 2646−2648; *Angew. Chem. Int. Ed.* **2002**, *41*, 2541−2543.
[25] I. Bytschkov, S. Doye, *Tetrahedron Lett.* **2002**, *43*, 3715−3718.
[26] L. Ackermann, R. G. Bergman, *Org. Lett.* **2002**, *4*, 1475−1478.
[27] C. Cao, Y. Shi, A. L. Odom, *Org. Lett.* **2002**, *4*, 2853−2856.
[28] E. Haak, I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2002**, 457−463.
[29] H. Siebeneicher, S. Doye, *Eur. J. Org. Chem.* **2002**, 1213−1220.

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