Metal-Initiated Amination of Alkenes and Alkynes†

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Contents

I. Introduction

The catalytic production of organic molecules is one of the most important applications of organometallic chemistry. For this purpose the distinct reaction chemistry of organic ligands covalently bound to transition metals is exploited. Most organometallic chemistry has focused on the formation of carbon−carbon or carbon−hydrogen bonds. The platinum group metals, in particular Pd and Rh, have been the most commonly used elements in—frequently commercialized—catalytic processes that include hydrogenation, hydroformylation and others. On the other hand, carbon−oxygen and carbon−nitrogen bonds are found in the majority of organic molecules and are of particular importance in physiologically active substances. However, catalytic organometallic reactions that lead to the formation of carbon−heteroatom bonds are less common.[1,2] The catalytic construction of carbon−nitrogen bonds in amines is particularly rare.[3−10] Clearly, efficient catalytic routes to nitrogen based molecules are of great interest.[11] Especially useful are catalytic hydroaminations of olefins and alkynes which avoid production of byproducts, like salts, generally observed in metal-catalyzed aminations of C−X derivatives (X = e.g., halogen). However, known aminations of olefins often require stoichiometric use of transition metals and general methods for carrying out aminations catalytically are not yet available.[12,13] Most of the present enantioselective syntheses of molecules bearing an amine functionality use classical stoichiometric reactions with chiral auxiliaries or utilize enantiomerically pure starting material.[14−16]

Hydroamination of alkenes and alkynes, which constitutes the formal addition of a N−H bond across a carbon−carbon multiple bond (Scheme 1), is a transformation of seemingly fundamental simplicity and would appear to offer the most attractive route to numerous classes of organo−nitrogen molecules such as alkylated amines, enamines or imines. Organic chemists have developed various synthetic approaches for the amination of olefins.[17−19] Direct addition of nucleophiles H−NR_2 to activated alkenes is of general importance for the synthesis of compounds with nitrogen atoms β to groups such as keto, ester, nitrile, sulfoxide, or nitro.[13,20−23] These additions usually lead to the anti-Markovnikov products. On the other hand aliphatic olefins as well as most aromatic olefins are often aminated to give the Markovnikov product. One possibility to reverse the reactivity of aliphatic olefins is the use of electrophilic nitrogen radicals which have been used to obtain anti-Markovnikov products.[24] In the past much work has been done on the activation of alkenes with stoichiometric amounts of metal.[24] Reactions are mostly promoted by complexes of titanium,[25] iron,[26] zirconium,[27] palladium[28−31] and mercury.[32,33] However, catalytic additions of amines H−NR_2 to nonactivated double or triple bonds are still rare.

Two basic approaches have been employed to catalytically effect aminations and involve either alkene/alkyne or amine activation routes (Scheme 2).[34,140] Alkene activation is generally accomplished with late-transition-metal catalysts, which render coordinated olefins more susceptible to attack by

† Dedicated to Dipl. Chem. Martin Eichberger (deceased 11/20/1997).

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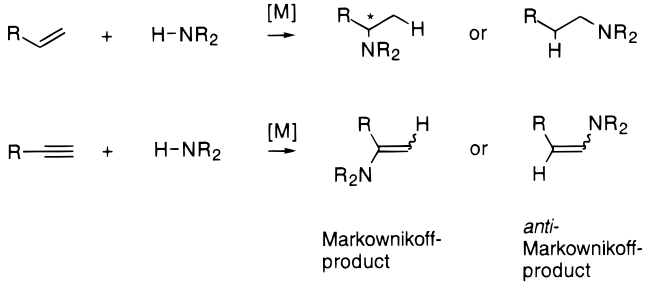
Matthias Beller was born in Germany in 1962. He studied chemistry at the Georg-August University of Göttingen (1982–1989) and received his Diploma (1987) and Ph.D. (1989) in organic chemistry working with Professor Lutz F. Tietze. As a Liebig fellow, he did postdocteral studies in 1990 with Professor K. Barry Sharpless at the Massachusetts Institute of Technology studying asymmetric catalysis. In 1991, he joined the Corporate Research of Hoechst AG, starting work on homogeneous catalysis in the department of Professor Klaus Kühlein. In 1993, he became group leader of organometallic chemistry and later on also as a project leader of homogeneous catalysis. In January 1996, he was appointed C3-Professor of inorganic chemistry and moved to the Technical University of Munich. Currently, he is considering an offer to become Director of the Institute for Organic Catalysis (IfOK) and Professor of Organic Chemistry at the University of Rostock. His research interests lie in the area of homogeneous catalysis with particular focus on the use of late transition metals for industrially important organic synthesis.

exogenous amine nucleophiles. Intermediate 2-aminoalkyl complexes can then react in different ways, leading to oxidative amination, hydroamination, or polyfunctionalized products.[12] Similarly alkynes can be activated by coordination to a late-transition-metal center. One possible approach to amine activation utilizes alkali metals to generate highly nucleophilic

Scheme 1. The Hydroamination of Alkenes and Alkynes



amido species, which are then able to directly attack the alkene. An alternative amine activation route uses N−H oxidative addition to electron-rich, late-transition-metal centers. A catalytic cycle for olefin hydroamination can be realized if the oxidative addition step can be coupled to an alkene/alkyne insertion process followed by reductive elimination of the product.

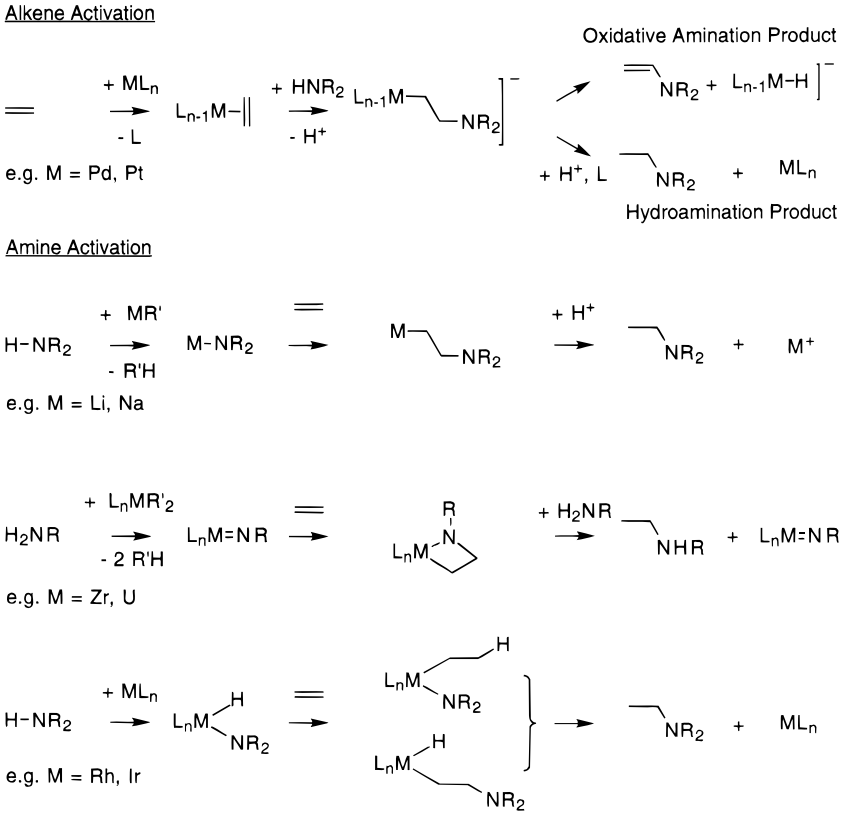
Recent advances in catalytic aminations are based on the chemistry of early-transition-metal and f-element complexes[35] and have provided a variety of reactions which allow the cyclization of 1-amino-*n*-alkenes (n = 3, 4, 5, 6) and -alkynes. Chiral lanthanide complexes were developed for stereospecific cyclizations and show a considerable asymmetric induction potential. The analysis of the nature and tunability of the substrate−catalyst interactions might serve as a basis for more detailed mechanistic studies and convey significant implications for designing analogous late-transition-metal based catalysts. Although still in their early stages the new developments in the chemistry of f-element complexes have opened new strategies in the difficult, but challenging field of catalytic aminations.

This report is especially devoted to a survey of the catalytic direct amination of alkenes. The 1:1-telomerization of 1,3-dienes with amines,[36] allylic aminations,[37−39] and amination reactions involving allenes[40,41] are related closely and will be mentioned. Reactions such as Michael additions,[23,42,43] the Ritter reaction,[22,44] and aminomethylation of alkenes[45] will not be considered. Amination of alkynes will be discussed so far as new developments have been made during the recent years and only if these are relevant for the discussion of the amination of alkenes. The first part of this review concentrates on observations and theoretical considerations about possible mechanistic pathways which might have implications for the realization of catalytic aminations. The close connection between oxidative amination reactions and hydroamination reactions will be demonstrated. Their scope and limitations in organic synthesis will be discussed in the second part. The overall goal of this review is to present, classify, analyze, and generalize the available data for the catalytic approach to aminations of nonactivated alkenes and alkynes.

II. Mechanism and Coordination Chemistry

Thermodynamic considerations indicate that the synthesis of alkylamines by direct addition of amines to alkenes is slightly exothermic or approximately

Scheme 2. Possible Routes to Amination Reactions by Alkene or Amine Activation



thermoneutral.[13,45,46] In this respect the free energy for the addition of NH_3 to $H_2C{=}CH_2$ is estimated to be $\Delta G° \approx -17$ kJ/mol.[47] However, the reaction is hampered by a high activation barrier caused by unfavorable intermolecular interactions which arise during the approach of the amine and alkene.[34] A nucleophilic attack of the amine nitrogen bearing the lone pair on the electron-rich nonactivated alkenes leads to electrostatic repulsion. A [2 + 2] cycloaddition of N−H to the alkene would be an orbital symmetry-forbidden process and is unfavorable because of the high-energy difference between π(C=C) and σ(N−H). At higher temperatures the reaction equilibrium is shifted toward the starting materials because of a highly negative reaction entropy.

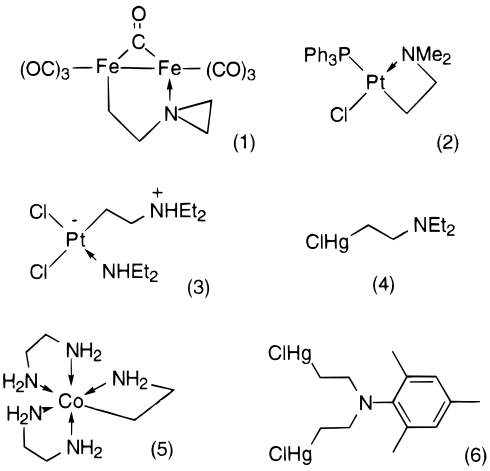
However, amines will undergo direct nucleophilic addition to a carbon−carbon triple bond if the π-system is electron-deficient (e.g., in perfluoroalkynes) or activated by neighboring functional groups (e.g., OR, COR, COOR, C≡CH).[48] Often the reaction can be accelerated by catalysts such as Cu^{I}-salts.[21,49] The π-bond of alkenes is less reactive but additions proceed if the olefinic double bond is activated by neighboring groups, such as a carbonyl or a nitrile group.[21,50,51] Monoolefinic hydrocarbons, however, exhibit considerable inertness toward ammonia and amines and therefore require special conditions for an addition to take place. The hydroamination reaction can be assisted or catalyzed by alkali metal ions, transition-metal, or lanthanide complexes which allow these processes to be performed under milder conditions. In principle, these metals allow three different strategies for the catalytic activation of the educts of aminations. First, activation of the olefin can be effected by π-coordination to a late-transition-metal rendering the olefin more susceptible toward nucleophilic attack by the amine. Alternatively, the N−H bond can be activated by deprotonation to the more nucleophilic amide of electropositive alkali or lanthanide metals. Amides are also the key intermediates when a N−H bond is oxidatively added to a transition metal which allows insertion of the alkene either into the M−N or M−H bond.

1. Activation of the Olefin

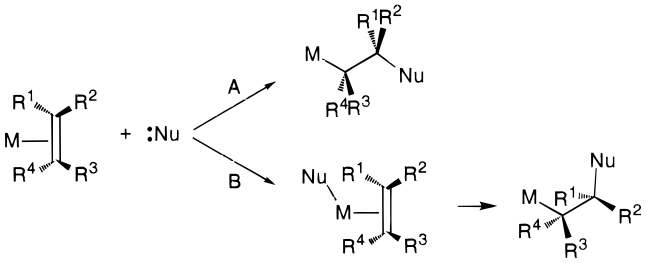
a. Stoichiometric Use of Transition Metals

As stated above nonactivated alkenes are generally resistant toward nucleophilic attack of amines and other nucleophiles due to their electron-rich π-orbitals. But upon complexation to an electrophilic transition metal such as Pd(II), Pt(II), Hg(II), Mo(II), W(II), or Fe(II) an umpolung occurs[11,52] and even nonfunctionalized olefins become susceptible toward nucleophiles.[12,53] However, amines—especially aliphatic ones—are strong ligands for electrophilic transition-metal centers and often rather displace than attack the coordinated olefin. Thus, catalytic activation of the olefin in the presence of amines is especially difficult to achieve.[54,216] To overcome these problems aminations have been performed in the presence of stoichiometric amounts of transition metals—sometimes isolating the amine−olefin complexes. Key intermediates in the reaction are (2-aminoalkyl)metal complexes which usually undergo further reactions, e.g. β-hydrogen elimination, addition of another nucleophile or insertion of alkenes, alkynes or carbon monoxide. 2-Aminoalkyl complexes with Fe(II), Co(III), Pt(II), and Hg(II) as central metal are stable toward isolation. Examples

Scheme 3. Structurally Characterized 2-Aminoethyl Complexes: 1,[203] 2,[204] 3,[205] 4,[206] 5,[207] and 6[208]



Scheme 4. Nucleophilic Attack on Coordinated Olefins



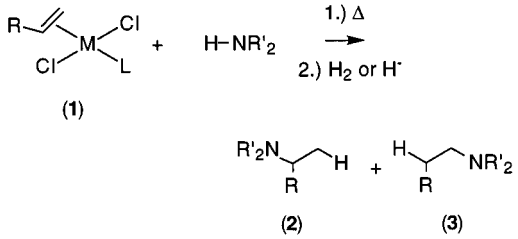
of structurally characterized 2-aminoethyl complexes are given in Scheme 3.

In contrast, the corresponding Pd(II) derivatives are much more reactive intermediates. Hence, Pd(II) complexes have been utilized for the amination of nonactivated (neutral) olefins.[12,55,56] Here the coordination of alkenes to electrophilic palladium(II) centers proceeds rapidly and reversibly in solution. The stability of the resulting alkene palladium(II) complex is highly dependent on the steric nature of the olefin. In this respect terminal alkenes are most strongly complexed, followed by disubstituted *cis*- and *trans*-alkenes.

In principle, the addition of nucleophiles to metal-bound π-systems may take two different routes.[57] A free nucleophile may add directly to the π-system (Scheme 4, path A) or it may coordinate first to the metal and then be transferred internally to the π-system (Scheme 4, path B). The stereochemical outcome of the two processes will be different in that path A leads to trans addition of the metal and the nucleophile across the π-system while path B results in cis addition. Hard bases preferentially add as external nucleophiles according to path A, while nonstabilized carbanions and soft bases react according to path B.[57] In most amination reactions the amine attacks the olefin face opposite the metal with concomitant formation of a carbon−palladium σ-bond (path A).

The rate of addition of amine is also dependent on the steric nature of the olefin. For the reaction of dimethylamine with *trans*-[(butene)(Me_2NH)$PdCl_2$], it has been shown that the relative reactivity decreases in the order of 1-butene (1.00):(*E*)-2-butene (0.38):(*Z*)-2-butene (0.02).[58,59] The nucleophilic nitrogen reacts in such a way that the least hindered metal alkyl complex is formed (Markovnikov addition). In case of nonactivated olefins this regiochemistry is also favored electronically. Exceptions from this rule—although highly interesting for the chemical industry—have until recently been reported only in special cases, where steric factors of the amine substituents dominate the reaction (Table 1).[45]

Table 1. Stoichiometric Aminations of Pd(II) and Pt(II) Olefin Complexes[45,61,62]

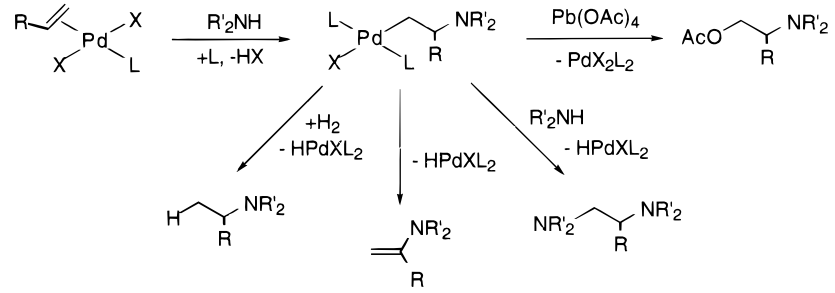


M	L	R	R'	Ratio **2** : **3**
Pt	PBu_3	CH_3	C_2H_5	≥99 : ≤1
Pt	PBu_3	C_2H_5	C_2H_5	44 : 56
Pt	PBu_3	CH_3	C_4H_9	≥99 : ≤1
Pt	PBu_3	C_2H_5	C_4H_9	47 : 53
Pd	R'$_2$NH	C_2H_5	H	75 : 25
Pd	R'$_2$NH	C_2H_5	CH_3, H	80 : 20
Pd	R'$_2$NH	C_2H_5	CH_3	88 : 12
Pd	R'$_2$NH	C_2H_5	C_2H_5	60 : 40
Pd	R'$_2$NH	C_2H_5	$^iC_3H_7$	<5 : >95
Pd	R'$_2$NH	C_8H_{17}	CH_3	82 : 18

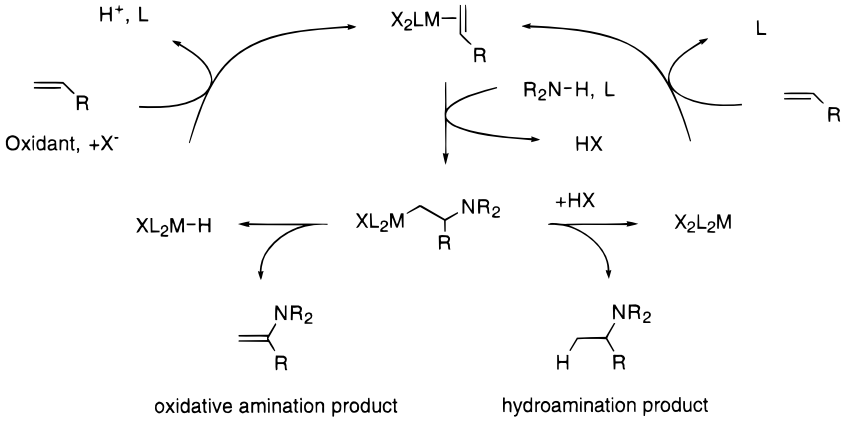
The first example of a palladium-promoted amination of alkenes was reported by Stern and Spector[60] who showed that *n*-butylamine reacts with propylene in the presence of stoichiometric amounts of palladium(II) chloride. Hydrogenation of the reaction mixture gave mainly *n*-butylisopropylamine in an unstated yield. Subsequently palladium or platinum alkyls were prepared by addition of amines either to mixtures of olefin and [$PdCl_2(CH_3CN)_2$][61] or to solutions of [$PtCl_2$(olefin)(PR_3)] complexes.[62] Later on it was shown that this reaction could be extended to a general method for synthesizing tertiary amines from alkene−Pd^{II} complexes at temperatures as low as −50 °C, followed by in situ reduction of the σ-alkylmetal intermediate with hydrogen or hydride reagents.[61,63]

Besides hydrogenolysis, the (2-aminoalkyl)palladium intermediate can undergo other synthetically useful transformations (Scheme 5). In the absence of suitable reagents β-hydrogen elimination takes place above −20 °C and results in the formation of enamines or imines. Here, Hirai and co-workers proved for the first time that *n*-butylamine reacts with the bis(ethylene)palladium chloride complex to yield the corresponding imine.[54] Depending on the reaction conditions, other products are accessible from the (2-aminoalkyl)palladium intermediate. These include substituted amines resulting from the inser-

Scheme 5. Reaction Pathways via (2-Aminoalkyl)palladium Complexes



Scheme 6. Regeneration of the Active Catalyst from 2-Aminoalkyl Complexes via a Protonolytic or an Oxidative Pathway (M = Pd, Pt; X = e.g. Cl^-, Br^-; L = e.g. PR_3)



tion of alkenes, alkynes, or carbon monoxide into the palladium−carbon bond. Oxidative cleavage of the palladium−carbon bond has been achieved with lead tetraacetate, bromine, and *m*-chloroperbenzoic acid.[24] *β*-Hydroxyamines, aziridines, and vicinal diamines can be obtained in one-pot procedures.

Aminations or related reactions such as diamination or oxyaminations can also be promoted by the use of stoichiometric amounts of Hg(II) salts,[24,64,220] Tl(III) salts,[24] $Cu(OAc)_2$,[65] Co complexes,[66] or seleno and sulfo derivatives,[67,68] as well as Fe(II) complexes.[12] In all these cases the aforementioned rules regarding selectivity and reactivity are applicable vide infra. Although the yields of the amination reactions using stoichiometric amounts of promoting metal are sometimes nearly quantitative several problems render these methods unattractive for broader application. The use of stoichiometric amounts of precious transition metals such as palladium or platinum is too expensive and metals such as mercury or thallium are too toxic for synthetic applications even on a laboratory scale. However, stoichiometric reactions are useful as models in order to gain a general understanding of the system.

An exception may be the use of stoichiometric amounts of iron which is relatively nontoxic and inexpensive compared to other metals. Mostly cationic cyclopentadienyl iron dicarbonyl olefin complexes are employed for the activation of alkenes.[69−70] In common with the amination using other metal complexes, the nucleophilic addition of the amine proceeds stereospecifically trans to the metal. For cationic iron complexes that contain an acidic allylic proton the basic amine converts the η^2-olefinic cation into an η^1-alkyl complex. The stability of the σ-alkyl-metal complex has been used for further functionalization of the original olefin. Thus, the addition of amines to complexed olefins followed by oxidative carbonylation has provided a *β*-lactam synthesis.[72−74] However, to fulfill the demand of environmentally friendly technologies catalytic transformations are the way to go in future.

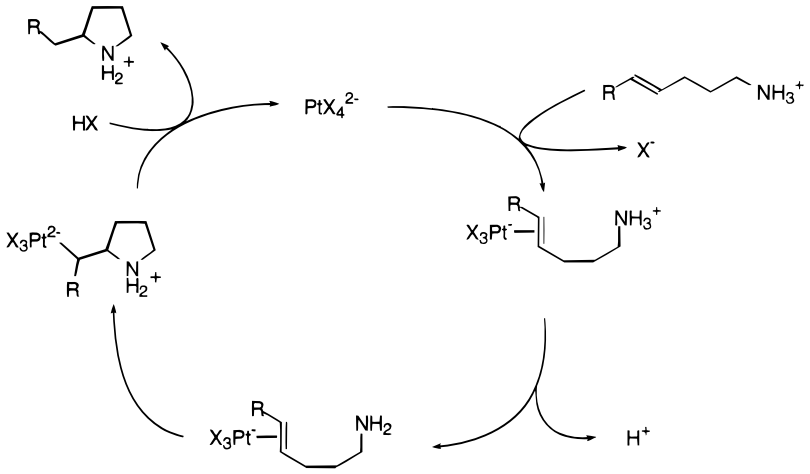
b. Making the Reaction Catalytic

As shown above a number of transition metals are capable of activating olefins in the presence of amines, forming intermediate (2-aminoalkyl)metal complexes. To achieve catalytic aminations using transition metals as, e.g., palladium and platinum two different strategies exist in principle (Scheme 6): (a) the (2-aminoalkyl)metal complex must undergo protonolysis to regenerate the catalytically active transition-metal complex or (b) after reductive elimination from the 2-aminoalkyl complex the resulting transition-metal complex in a low oxidation state has to be reoxidized to the active catalyst species.

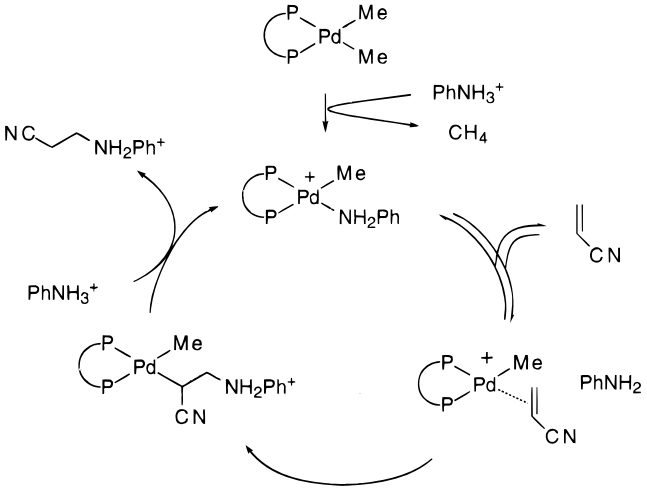
Obviously, several problems are encountered with both routes. Protonolysis of the 2-aminoalkyl complex should be possible only in very acidic media which is not compatible with the presence of free amines. Thus, only model-type reactions have been realized until today, although there might be a possibility for catalytic amidations.

In one mechanistic example, aminoalkenes are cyclized in a reaction medium containing stoichiometric quantities of $[PtX_4]^{2-}$, X = Cl, Br.[75−77] An intramolecular nucleophilic attack of a free amino group on the coordinated double bond has been proposed (Scheme 7) which results in an intermediate

Scheme 7. Cyclization of Aminoalkenes Using PtX_4^{2-} ($X = Cl^-, Br^-$)[76]



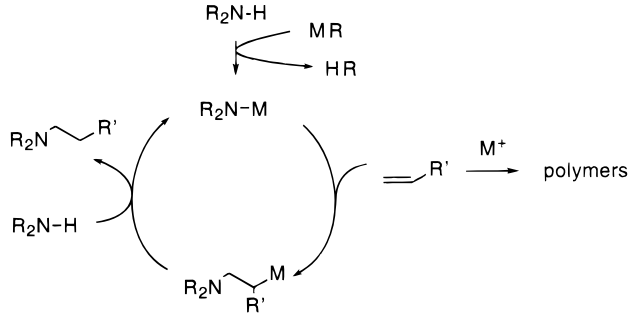
Scheme 8. Proposed Catalytic Cycle for the Nucleophilic Attack of Aniline on Acrylonitrile Using a Palladium−Alkyl Catalyst[78]



complex $X_3Pt-CHR-$(2-pyrrolidine). Protonation then releases the product heterocycle. In another model reaction catalytic hydroamination has been demonstrated with activated olefins (Scheme 8).[78] Acrylonitrile and aniline do not react to a significant extent under neutral conditions. By employing palladium complexes $[Pd(PR_3)_2(alkyl)_2]$ as catalysts, 3-anilinopropionitrile was obtained (TON = 44). The reaction is thought to proceed through protonolysis of the metal−alkyl bond with the ammonium salt, probably via protonation of the d-electron-rich metal center[79] and reductive elimination of the product. The system, however, fails to catalyze the hydroamination of unfunctionalized olefins.

On the other hand the selective oxidation of a transition metal(0) complex in the presence of amines and enamines as products makes efficient catalysis extremely difficult. However, by careful control of reaction conditions and, more importantly, by selected choice of starting materials, a number of catalytic amination protocols useful on laboratory scale have been developed in the past decade.[12,80,81] Catalytic oxidative coupling reactions of amines with alkenes leading to the formation of imines or enamines via β-hydride elimination have been performed nearly exclusively in the presence of palladium(II)

Scheme 9. Catalytic Hydroamination with Alkali Metals (M) via Deprotonation of the Amine to Alkali Metal Amides $M-NR_2$

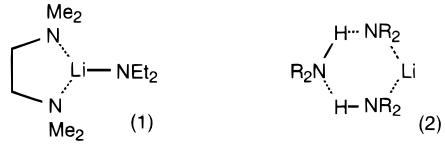


complexes.[12,55,56] Here, typically 5−10 mol % of Pd(II) salts (mainly $PdCl_2L_2$) are used in the presence of benzoquinone, $CuCl_2/O_2$, or more recently O_2/DMSO as reoxidant. The reaction mechanism is believed to proceed analogously to the well-known Wacker process.

2. N–H Activation by Alkali Metals

In special cases alkali metals and their amides can be used as precatalysts for the hydroamination of alkenes. By deprotonation of the amine to the corresponding amide, the nitrogen becomes nucleophilic enough to attack the alkene. However, the activation energy is high which is probably caused by unfavorable interactions between the N lone pair and the π-system of the alkene as well as only weak coordinative interactions between nonfunctionalized alkenes and alkali metal ions.[82] Thus the nucleophilic attack on the alkene is the rate-determining step of the alkali metal-catalyzed reaction. The attack of the amide results in 2-aminoethyl alkali metal complexes which are extremely unstable and are quickly protonated by excess amine. The corresponding Grignard compounds are more stable and can be isolated as potential intermediates of the reaction.[45] Usually the alkali metals are used catalytically and a likely mechanism is shown in Scheme 9. Alternative to the ionic reaction mechanism, a radical process has been proposed, e.g., for the addition of aziridine to styrenes.[83] Side reactions and especially polymerization are frequently observed and can be a cause of poor yields.

Scheme 10. The Active Catalyst Complexes Proposed for Lithium-Accelerated Hydroaminations

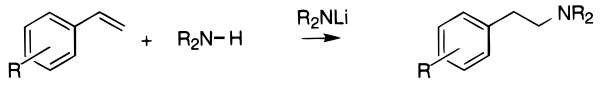


The reaction allows, e.g., the addition of ethylene to ammonia as well as to primary and secondary amines.[84−86] It is observed that the greater the pK_a of the amine and the more nucleophilic the corresponding amide, the faster the reaction and the lower the reaction temperature required.[87] The amides of all alkali metals have been employed either directly or prepared in situ from the metal, the hydride, or an alkyl alkali salt. Most frequently used are sodium- and lithium-based catalysts. Amides bearing other substituents can be used as precatalysts as long as their pK_a is greater than the pK_a of the amine which is to be converted. This has been demonstrated for the ethylation of piperidine where the more basic amide Me_2NLi can be used as precatalyst, but the less basic Ph_2NLi remains inactive.[88] The alkali metal ions play a central part in the catalytic cycle and enhance the nucleophilic attack of the amide on the olefin. However, detailed mechanistic investigations have not been carried out.

In reaction mixtures with lithium the addition of crown ethers which form a strong complex with the lithium ion inhibits the reaction effectively.[88] In contrast, the addition of tetramethylethylenediamine (TMEDA) usually increases the rate of reaction. This is an example of ligand-accelerated catalysis (LAC) which has been explained by the formation of a lithium complex with the general stoichiometry R_2NLi·TMEDA (Scheme 10, complex 1). Although the complex has not been isolated and may be an oligomer, there is evidence that the complex is the active catalyst species which allows faster reaction of the amide with the olefin. The reaction of Et_2NLi with ethylene in the presence of TMEDA probably gives the intermediate complex $Et_2N-(CH_2)_2-Li$(TMEDA).[82] Protonolysis with Et_2NH releases NEt_3 and regenerates the initial lithium complex. The postulated reaction sequence is consistent with the observed rate law $\nu \approx k[C_2H_4][Et_2NLi]$ if TMEDA is used in excess thus eliminating the rate dependence on complexing amine. The Arrhenius activation energy for the nucleophilic attack is estimated to be at least 50 kJ mol^{-1}.[82] The corresponding potassium and sodium amides are initially up to hundred times more effective precatalysts compared to Et_2NLi/TMEDA, however, after 25% conversion the rate decreases considerably due to decomposition or deactivation of the active catalyst species.[82]

A similar mechanism has been deduced for the amide-catalyzed reaction of diethylamine with 1,3-butadiene except that in this case the corresponding complex Et_2NLi·$2Et_2NH$ is postulated as the active catalyst (Scheme 10, complex 2).[89] Spectroscopic data and the rate law $\nu = k$[complex][1,3-butadiene] are consistent with the nature of the active catalyst species.[89,90]

Scheme 11. Hydroamination of Styrenes



An additional example of alkali metal-catalyzed hydroaminations is the addition of amine to styrene catalyzed by lithium amide which proceeds regioselectively in anti-Markovnikov fashion to produce 1-amino-2-phenylethane (Scheme 11).[91] Lithium ethylamide itself does not add to styrene. For the reaction to proceed more than twice the amount of diethylamine has to be present along with the lithium amide in the reaction system. This makes a 1:2 complex Et_2NLi·$2Et_2NH$ likely to be the active catalyst species. The rate of the reaction can be expressed by the equation $\nu = k$[styrene][Et_2NLi], but is only independent of Et_2NH if the ratio [Et_2NH]/[Et_2NLi] ≥ 10. A Hammett plot for the addition of diethylamine to para-substituted styrenes yields $\rho = +5.0$ and demonstrates the nucleophilic character of the reaction.

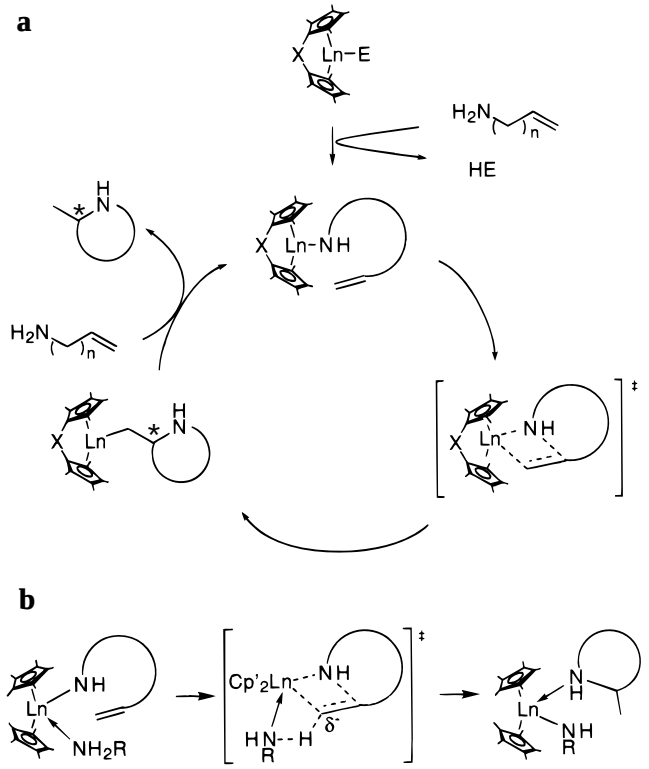
According to the mechanistic model discussed above the rate is essentially governed by the nucleophilicity of the chelated alkali metal amide toward the olefin. The nucleophilicity is greater in the lithium complex than can be achieved with only $LiNR_2$ presumably because of the polarizing effect on the $Li^+NR_2^-$ ion pair. For the heavier alkali metal amides the ion pair is more separated and thus a higher rate is expected and observed. However, side reactions lead to a fast decomposition of the active catalyst. Thus, lithium and sodium amides are most frequently employed as active catalysts.

3. Activation of the N–H Bond by Early Transition Metals, Lanthanides, and Actinides

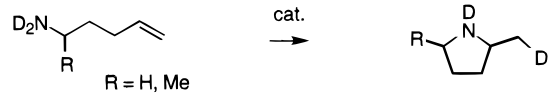
Aminoalkenes $H_2N(CH_2)_nCH{=}CH_2$ (n = 4, 5) can be cyclized with various titanium, zirconium, lanthanide (Ln), and actinide (Ac) complexes to yield pyrrolidines and piperidines, respectively. In a similar reaction aminoalkynes $H_2N(CH_2)_nC{\equiv}CH$ (n = 3, 4, 5) can be cyclized to the corresponding enamines and imines. The lanthanide precatalysts such as $(Me_5C_5)_2LnE$, E = H, $N(SiMe_3)_2$, $CH(SiMe_3)_2$ undergo rapid protonolysis of the Ln−E bond by the amine quantitatively generating amide complexes or mixed amino−amide adducts.[92,93] The turnover limiting step is the intramolecular alkene/alkyne insertion into the M−N bond (Scheme 12a). A four-centered transition state is proposed in analogy to known azametallacyclobutanes/-butenes for zirconium.[94,95] This is followed by rapid intra- or intermolecular protonolysis of the resulting M−C bond which regenerates the catalytically active lanthanide amide complex and affords the product heterocycle.

The mechanism is supported by kinetic measurements which show the rate dependence to be first order in catalyst and zero order in substrate: $\nu = k$[catalyst]^1[substrate]^0. The reaction preferentially leads to five-membered heterocycles, but the formation of six- and seven-membered rings is possible. The ring-size dependence of cyclization rates for both aminoalkenes[96] and -alkynes[97] is 5 > 6 ≫ 7, consis-

Scheme 12. (a) Proposed Mechanism for the Hydroamination of Aminoalkenes (Ln = La, Nd, Sm or Lu; E = H, $CH(SiMe_3)_2$ or $N(SiMe_3)_2$; X = $SiMe_2$ or H, H)[92,93] (b) Modified Model for the Hydroamination of Aminoalkenes (Ln = La, Nd, Sm or Lu)[92,93]



Scheme 13. Deuterium Disposition Pattern

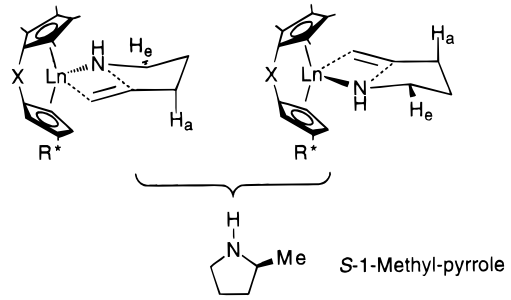


tent with classic stereoelectronically controlled cyclization processes (Tables 2 and 3, respectively). Methyl substitution at the internal carbon atoms of tethered aminoalkenes and -alkynes leads to greater rates of ring closure. These changes caused by varying the nature of the groups in the ring are known as the Thorpe−Ingold effect.[98] Also noteworthy are marked substituent effects on the cyclization rates of aminoalkynes $H_2N(CH_2)_3C{\equiv}CR$ with the following order of cyclization rates: R = $SiMe_3$ > H > Me > Ph.

The rate of cyclization of aminoalkenes increases when the Cp* ligands are changed to a $Me_2Si(\eta^5\text{-}Me_4C_5)_2$ system or when a lanthanide metal with larger ionic radius is employed.[92,96] Conversely, the rate of cyclization of aminoalkynes decreases when more open sytems are employed.[93] It is likely that the steric demand for the rate-determining transition state is lower for the intramolecular alkyne insertion than for the analogous alkene insertion.

The products isolated from cyclization of the deuterated RND_2 analogues show the expected deuterium disposition. Thus, the cyclized amines are deuterated at the nitrogen and monodeuterated at the 2-methyl position (Scheme 13). This regiochemistry is interpreted as resulting from deuteriolysis of

Scheme 14. Rationalization of the Enantioselectivity in the Cyclization of 1-Amino-4-alkenes

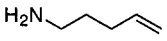
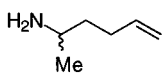
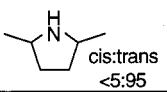
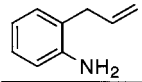
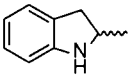
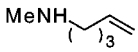
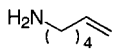
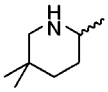
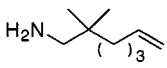
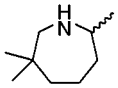


the intermediate alkyl complex formed upon alkene insertion. For the cyclization of amino-2,2-dimethyl-4-pentene and the *N*-deuterated RND_2 analogue, a kinetic isotope effect k_H/k_D = 4.1(8) (25 °C) is measured, which is independent of substrate concentration, catalyst concentration and conversion. All these observations are consistent with the olefin activation or insertion at the electrophilic lanthanide center to be the turnover-limiting step. However, the magnitude of the isotope effect indicates, that in the transition state a further amine is present in the immediate coordination environment.[96] This suggests a modified model for the transition state (Scheme 12b). The proton of the additional amine stabilizes the partial negative charge of the α-carbon in the four-membered insertion transition state. The proton is then transferred from the amine to the α-carbon, in essence protonolyzing the Ln−C bond as it was being formed.

Chiral organolanthanide complexes $Me_2Si(Me_4C_5)$-$(H_3R^*C_5)LnE(SiMe_3)_2$, Ln = La, Nd, Sm; R* = menthyl, neomenthyl; E = CH, N can serve as effective precatalysts for asymmetric cyclizations with high efficiency and enantioselectivity (TOF ≤ 93 h^{-1}, 25 °C; ee ≤ 74%).[99,100] The basic mechanism appears to be analogous to the mechanism proposed for the achiral $(Me_5C_5)_2Ln$-catalyzed process. The enantioselective step is presumably the irreversible olefin insertion into the Ln−N bond. The stereochemistry of the catalytic products was rationalized on the basis of presumed catalyst−substrate steric interactions in the transition state. A preference for a pseudo-chair seven-membered transition state best explains the stereoselection in the formation of methylpyrrolidines and the aforementioned ring-size effects. Two orientations in the pseudo-chair arrangement are favored which avoid the steric conflict between the protons on C_1/C_3 and the large R* group (Scheme 14).

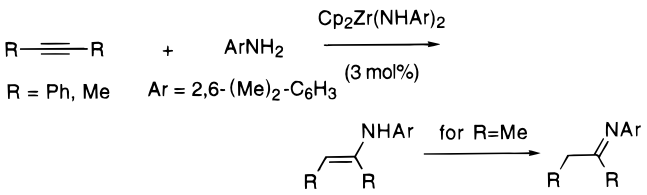
So far cycloaddition reactions in which unsaturated organic molecules react with metal−nitrogen multiple bonds have received only little attention.[101] However, there is substantial evidence that this rection can be an important mechanistic step in the amination of alkenes and alkynes.[95,102] A characteristic feature for many lanthanide- and actinide-catalyzed reactions is the absence of accessible metal oxidation states for oxidative addition and reductive elimination processes. This implicates that a cycloaddition is a favorable way for the reaction of alkenes/alkynes with the metal−nitrogen bond in

Table 2. Scope of Intramolecular Hydroaminations of Tethered Aminoalkenes†

Substrate	Catalyst (s/c)	Products	Temp. /°C	TOF /h^{-1}	ee /%	Ref.
	Cp*$_2$Sm(THF)$_2$		60	5	—	191
	Cp*$_2$LaE		60	140	—	96,190
	NmCp'$_2$NdE^1		25	93	55	92
	NmCp'$_2$NdE^2		0	11	64	92
	MtCp'$_2$SmE (100)		25/0	33	62/72	192
	NmCp'$_2$SmE (100)		25/0	62	52/58	192
	NmCp'$_2$LaE^2 (100)		25	—	31	192
	NmCp'$_2$SmE (150)	 cis:trans <5:95	25	>80	—	92,192
	MtCp'$_2$SmE (100)		25/0/-30	84	53/61/74	192
	NmCp'$_2$SmE (100)		25/0/-30	—	51/54/64	192
	NmCp'$_2$LaE^2 (100)		25	—	14	192
	Cp*$_2$LaE		80	13	—	96,190
	Me$_2$SiCp'$_2$NdE		25	11	—	96,190
	Cp*$_2$LaE		60	5	—	96,190
	MtCp'$_2$SmE (100)		25	~2	15	92,192
	NmCp'$_2$SmE (100)				17	
	Cp*$_2$LaE		60	0.3	—	96

† Key: s/c, ratio substrate/catalyst; TOF, turnover frequency at 25 °C, 100% conversion and >95% regioselectivity; NmCp′$_2$, Me$_2$Si(Me$_4$C$_5$)(H$_3$NeomenthylC$_5$); MtCp′$_2$, Me$_2$Si(Me$_4$C$_5$)(H$_3$MenthylC$_5$): E^1, CH(SiMe$_3$)$_2$; E^2, N(SiMe$_3$)$_2$; E, E^1 and E^2 give identical results within experimental error.

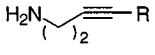
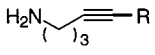
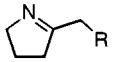
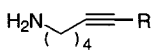
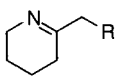
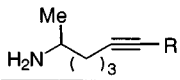
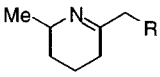
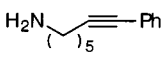
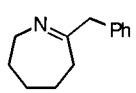
Scheme 15. Hydroamination of Alkynes with a Zirconium Bisamide Complex



catalytic hydroaminations. The metallacycles formed in this reaction can be cleaved in acid to give overall hydroamination products. If cleavage of the azametallacycles could be effected by the amine, the metallacycles might be the key intermediates in a catalytic cycle.[103]

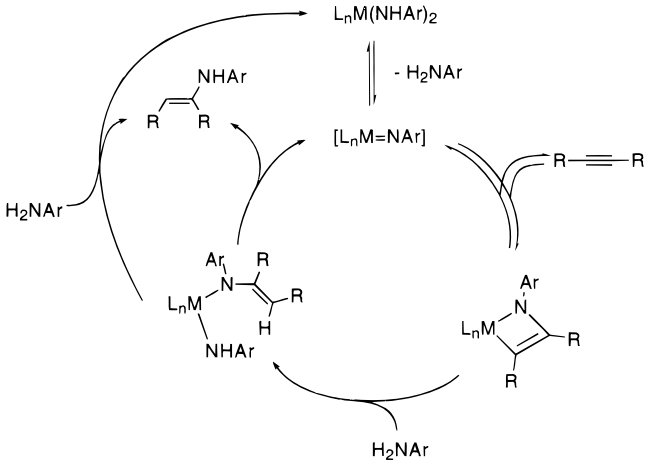
The use of this type of reaction sequence has been explored for the hydroamination of alkynes with zirconium bisamide complexes and provides a route to the preparation of enamines and imines (Scheme 15).[102] The initially formed enamine can be isolated for R = Ph, but tautomerizes to the corresponding imine for R = Me. Mechanistic investigations for the addition of 2,6-dimethylaniline to diphenylacetylene in the presence of the complex $Cp_2Zr(NHAr)_2$ gave the following rate law: $v = k[(\text{complex})]^1[PhC{\equiv}CPh]^0[ArNH_2]^{-1}$. This is most consistent with a rate-determining reversible α-elimination of amine to generate the transient imido complex $Cp_2Zr{=}NAr$ (Scheme 16). Alkyne and amine then compete for this intermediate. While reaction with amine regenerates the bisamide, cycloaddition of alkyne yields azametallacyclobutenes. The metallacycles are rapidly protonated by $ArNH_2$ to form an enamide−amide complex which then undergoes α-elimination of the enamine to regenerate $Cp_2Zr{=}NAr$. Alternatively the enamide−amide complex can react with free amine, liberating the enamine and regenerating the bisamide complex $Cp_2Zr(NHAr)_2$. The initial addition of alkynes to $Cp_2Zr{=}NR$ occurs regiospecifically to give metallacycles, with the larger alkyne substituent located α to the metal center. Protonolysis of the metallacycles then gives the enamines and

Table 3. Scope of Intramolecular Hydroamination Reactions of Tethered Aminoalkynes†

Substrate		Catalyst (s/c)	Product	Temp /°C	Yield /%	TOF /h^{-1}	Ref.
	R=^{n}Hex	$PdCl_2$, CH_3CN		81	43	—	186
	R=Ph	$Ni(CO)_2(PPh_3)_2$ (33)		125[a,b]	67	—	184
	R=^{n}Hex	$PdCl_2$, CH_3CN		81	63	—	186
	R=Tol	$Ni(CO)_2(PPh_3)_2$ (33)		125[a,b]	40	—	184
	R=Ph	$CpTiCl_3$ (5), $^iPr_2NEt$		25	94	—	188
	R=^{n}Bu			25	94	—	188
	R=H	$CpTiCl_3$ (10)		25	100	—	189
	R=Ph	Cp^*_2SmE (200)		60	95	2830	97,193
	R=Ph			21	—	77	93
	R=$SiMe_3$			21	92	7600	97,193
	R=Me			21	95	96	97,193
	R=H			21	90	580	193
	R=H	Cp^*_2LuE		21	—	711	193
	R=^{n}Hex	$NaAuCl_4{\cdot}2H_2O$ (20)		RT[c]	100	—	185
	R=^{n}Hex	$PdCl_2(MeCN)_2$ (20)		RT[b]	70	—	185
	R=Ph	$CpTiCl_3$ (5), $PhNMe_2$		80	88	—	188
	R=^{n}Bu			80	89	—	188
	R=Ph	Cp^*_2SmE (200)		60	95	328	97,193
	R=^{n}Pent	$NaAuCl_4{\cdot}2H_2O$ (20)		81[d]	100	—	185
		Cp^*_2SmE (200)		60	92	0.11	97,193

† Key: s/c, ratio substrate/catalyst; TOF, turn over frequency; Cp^*_2SmE, $(Me_5C_5)_2SmCH(SiMe_3)_2$. [a] 14 bar CO pressure. [b] 20 h. [c] 12 h. [d] 4 h.

Scheme 16. Cleavage of Azametallacycles by Amines Allows the Hydroamination of Alkynes (L_nM = Cp_2Zr, Cp^*_2U, Cp^*_2Th)



their tautomeric imines which are the net result of anti-Markovnikov addition to the alkyne.

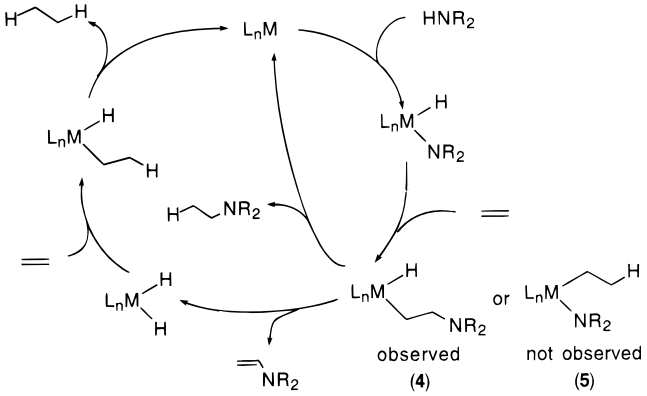
Organoactinide complexes of the type $(Me_5C_5)_2AcMe_2$ (Ac = Th, U) also catalyze the intermolecular hydroamination of terminal alkynes with aliphatic amines.[104] Kinetic measurements for the uranium-catalyzed reaction of ethylamine with $Me_3Si{-}C{\equiv}CH$ yield the corresponding rate law $\nu = k[(Me_5C_5)_2U(NHR)_2]^1[\text{alkyne}]^0[\text{amine}]^{-1}$ which is compatible with the same turnover-limiting imido formation.

4. Activation of the N–H Bond by Late Transition Metals

Advances in the chemistry of late transition-metal amides have led to the proposal of catalytic pathways which proceed via activation of the amine N−H bond.[105] One viable mechanism involves oxidative addition of an amine $H{-}NR_2$ to a coordinatively unsaturated metal center ML_n in a low oxidation state (Scheme 17).[106] The reaction produces a hydrido−amido complex $L_nMH(NR_2)$. Subsequently, the reaction can take place either at the M−N or M−H bond. Insertion of an olefin into the M−N bond generates a 2-aminoalkyl complex (**4**). Reductive elimination of the product alkylamine would regenerate the coordinatively unsaturated ML_n species.

Alternatively the hydrido amido complex might insert the olefin into the M−H bond. However, there is evidence that this reaction is unfavorable in comparison to insertions into the M−N bond. Thus, it has been observed that hydrido−amido complexes $L_nMH(NR_2)$ (M = Pd, Pt) prefer insertion of olefins into the M−N bond.[116] β-Hydride elimination from the M−H insertion product (**5**) could easily regenerate the hydrido amido complex while reductive

Scheme 17. Mechanism for Catalytic Hydroaminations via Oxidative Addition of H−NR_2 to a Coordinatively Unsaturated Metal Center



elimination involving the formation of an C−N bond is unlikely. Generally, reductive elimination involving carbon−heteroatom bond formation are less common[107] and probably disfavored relative to carbon−carbon and carbon−hydrogen bond formation.[108] The difference in oxidation potential of carbon and hydrogen versus heteroatoms is presumably responsible for this observation.

So far, N−H activation via oxidative addition of amines to late-transition-metal complexes has been little investigated. The formation of amido complexes directly from amines has only seldom been observed and confirmed reports of oxidative additions of R_2N−H to coordinatively unsaturated metal centers are rare.[109−112] The weaker bond strength of the M−N bond[113] in comparison to M−O and M−C bonds[114] suggest that the activation of amines with a platinum group catalyst will be difficult to achieve. Recent ab initio calculations have confirmed that an oxidative addition of H−NR_2 to a rhodium center is thermodynamically less favored than, e.g., the addition of H−H and has a considerable reaction barrier of ∼176 kJ mol^{-1}.[115] Indeed, all known hydrido−amido complexes as, e.g., *trans*-[PtH(NHPh)(PEt_3)$_2$][116] and *trans*-[PdH(NHPh)(PCy_3)$_2$][106] readily eliminate the corresponding amine especially in the presence of coordinating ligands which catalyze the cis/trans isomerization.

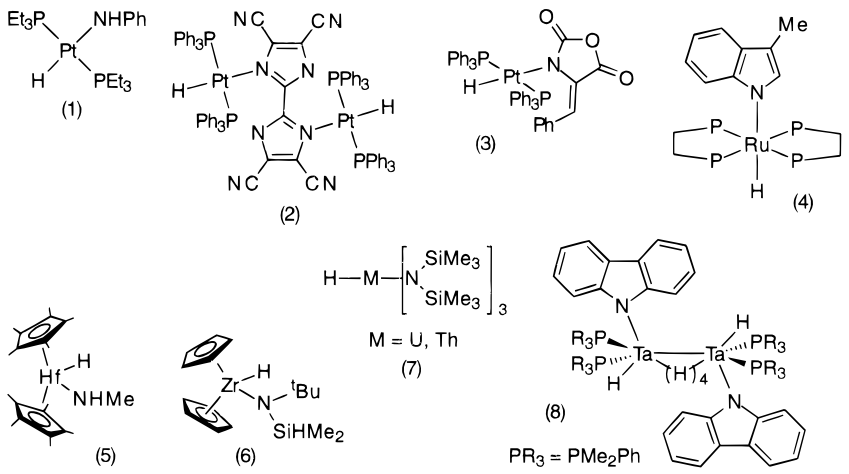
While square planar or octahedral *cis*-hydrido−amido complexes can reductively eliminate amine, elimination from the corresponding *trans*-hydrido−amido complexes requires prior isomerization to the cis complex. If the cis/trans isomerization is kinetically inhibited, the *trans*-hydrido−amido complexes are stable and can be isolated. Examples of structurally characterized hydrido−amido complexes are given in Scheme 18.[117,118]

Insertions of olefins into the M−N bond of hydrido amido complexes such as [PtH(NHPh)(PEt_3)$_2$] are known.[119] The insertion into the M−N bond leads to hydrido−2-aminoalkyl complexes which have been isolated for some platinum group metals.[119,120] The most common decompositon pathway is the β-hydride elimination, the reaction sequence leading to the oxidative amination product which is an enamine (Scheme 17). The resulting dihydride metal species can be reconverted to the active catalyst species ML_n by reaction with excess olefin. By contrast the hydrido−2-aminoalkyl complex might also reductively eliminate alkylamine. This pathway directly regenerates the ML_n complex.

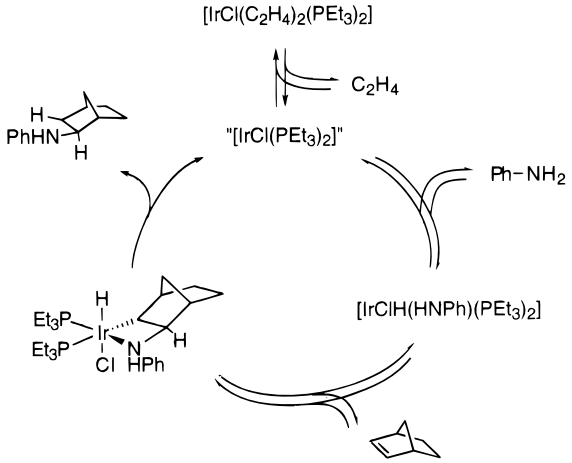
Regeneration of the catalyst via reaction of the dihydride species with excess olefin is the most likely mechanism of a rhodium-catalyzed oxidative amination. In presence of the catalyst [Rh(cod)$_2$]BF_4/2PPh_3, amines can be reacted with styrene to give the oxidative amination product *trans*-1-amino-2-phenylethene.[179] A second equivalent of styrene is necessary for the reaction and is reduced to ethylbenzene. This reaction is discussed in more detail later.

There is one example where the mechanism of an intermolecular hydroamination of norbornene catalyzed by an iridium complex has been determined.[120] The electron-rich complex [IrCl(PEt_3)$_2$(C_2H_4)$_2$] catalyzes the addition of aniline to norbornene. The presence of a small amount of $ZnCl_2$ increases the yield in the hydroamination product (TON = 2−6). The catalysis is proposed to proceed via an N−H activation pathway (Scheme 19). The major steps are oxidative addition of the amine to give the *cis*-hydrido−amido complex, reaction with the olefin to form an azametallacycle and reductive elimination of the product, resulting in an overall cis addition of aniline across the exo face of norbornene.

Scheme 18. Crystallographically Charactarized Hydrido−Amido Complexes: 1,[116] 2,[209] 3,[210] 4,[211] 5,[212] 6,[213] 7,[214] and 8[215]



Scheme 19. Proposed Mechanism for the Hydroamination of Norbornene with $[IrCl(C_2H_4)_2(PEt_3)_2]$ as Precatalyst[120]



III. Synthetic Applications of Catalytic Aminations

The synthetic potential of catalytic hydroamination reactions has been mentioned,[34,45] but a comprehensive account has not appeared. The use of alkali-metal ions and transition-metal salts in the activation of the amine has been the subject of many patents, which have been previously reviewed.[121,140] In the following section the scope and limitations of hydroamination reactions will be discussed with special emphasis on recent advances.

1. Aminations Catalyzed by Zeolites

Zeolites have been shown to catalyze hydroaminations at high temperatures and pressures (Table 4).[121,122] The reaction of ammonia with ethylene or higher alkenes can be catalyzed by proton-exchanged zeolites of, e.g., ZSM-5 or mordenite structure.[123] Amination of 2-methylpropene can be catalyzed to give *tert*-butylamine in high selectivities (99%), but only low conversion (<1.73%) is achieved.[124,125] The conversion is limited by the thermodynamic equilibrium between starting materials (2-methylpropene and ammonia) and the product (*tert*-butylamine).[126] The activity of the zeolites generally increases with the ratio of Si^{4+} ions to Al^{3+} ions which determines the number of acidic sites. The Brønsted acidity of the zeolite is the main controlling factor for the activity of the zeolite.[125,127] The activity and selectivity also depends on the zeolite structure and the pore size.

Proton-exchanged Y-zeolite and erionite catalyze the formation of ethylamines from ammonia and ethylene.[128] The conversion (initially 12% and 18%, respectively) is much higher than for the formation of $^tBuNH_2$. With aging the activity decreases over several days and, for H-erionite, levels at 9−10% conversion. However, the decreased activity is accompanied by an increase in selectivity (98%) toward formation of monoethylamine (Table 4). This indicates that ethylene amination occurs within of the erionite structure. The aging process deactivates sites which are on the catalyst exterior probably through formation of high molecular weight carbon residues.

The highest activities are generally obtained with small to medium pore acidic zeolites, such as H-clinoptilolite, H-erionite, and H-offretite.[123] Less acidic sodium ion exchanged zeolites, and amorphous silica or alumina are ineffective as catalysts for ethylene amination. Despite the high reaction temperatures employed, selectivity to the formation of primary amines is high. In all cases reported the reaction gives the Markovnikov products and most likely proceeds through carbocation intermediates which are formed by interaction of the alkene with a surface proton or ammonium ion.[123,129] The synthesis of alkylamines in the presence of zeolites has been the subject of many patents and is used industrially by BASF to produce *tert*-butylamine.[130]

2. Aminations Assisted by Alkali Metals

The formation of very nucleophilic alkali-metal amides has been used for the catalytic addition of the corresponding amines to nonfunctionalized alkenes. Examples for the reaction of amines with ethylene, simple alkenes, aromatic olefins and 1,3-butadienes are given in Tables 5-8, respectively.

a. Ethylene

Hydroamination reactions date back as early as 1954 when Howk reported that ammonia and ethyl-

Table 4. Hydroamination Reactions of Alkenes with Ammonia Using Zeolites

Alkene	Zeolite	Products	Temp. /°C	Pressure /bar	Conversion[a] /%	Selectivity/%	Ref.
Ethylene	H-Clinoptilolite	$EtNH_2/Et_2NH$ (13:1)	370	55	14[b]	—	123
Ethylene	H-Offretite	$EtNH_2/Et_2NH$ (16:1)	370	55	12[b]	—	123
Ethylene	H-LZY-72	$EtNH_2/Et_2NH$ (7:1)	365	52	12[b], 8[c]	> 98	128
Ethylene	H-Erionite	$EtNH_2/Et_2NH$ (>13:1)	365	52	18[b]	> 95	128
Ethylene	H-Erionite	$EtNH_2$	365	52	9-10[d]	98	128
2-Methylpropene	H-Y	$^tBuNH_2$	280	52	0.9	> 99	126
2-Methylpropene	Re-Y	$^tBuNH_2$	280	52	0.9	>99	126
2-Methylpropene	H-Mordenite	$^tBuNH_2$	300	52	0.8	> 99	126
2-Methylpropene	H-MFI-51	$^tBuNH_2$	200	—	—	99	124
2-Methylpropene	H-MFI-81	$^tBuNH_2$	200	—	1.7	99	125,127

[a] Flow reactor, equilibrium is assumed. [b] Initial conversion. [c] After 23 days. [d] After 90 days.

Table 5. Examples for Hydroamination Reactions of Ethylene Catalyzed by Alkali Metals†

Amine	(Pre-)Catalyst (s/c)	Products	Temp. /°C	Pressure /bar	Time /h	Yield /%	Ref.
NH_3	Na (14)	Et_nNH_{3-n}	200-250	380-1000	10-15	66	131
NH_3	NaH (11)	Et_nNH_{3-n}	200	760-960	15	41	84
NH_3	Li (4)	Et_nNH_{3-n}	250	820-980	15	53	84
NH_3	LiH	Et_nNH_{3-n}	200	850-1000	13	30	84
NH_3	$CsNH_2$ (13)	$EtNH_2$	101	112-92	1	24	82
NH_3	$(Cs/K)NH_2$[a] (14)	$EtNH_2$	101	118-105	6	45	82
NH_3	$RbNH_2$ (14)	$EtNH_2$	101	111-89	3	26	82
$BuNH_2$	Na (3)	$BuEt_2N$	200	800-1000	—	75	84
$BuNH_2$	EtLi (25), TMEDA	$BuEt_{2/1}NH_{1/2}$	130-150	250	37	92	132
$BuNH_2$	EtLi (25)	$BuEt_{2/1}NH_{1/2}$	130-150	250	60	67	132
$^nHexNH_2$	Na (10), C_4H_6	HexEtNH	150-160	28-41	1	38	87
$H_2N(CH_2)_2NH_2$	Na (3)	$Et_nH_{4-n}(C_2H_4N_2)$	200	800-1000	—	85	84
Et_2NH	Na (3)	Et_3N	225	1000	—	21	84
Et_2NH	EtLi (17), TMEDA	Et_3N	140	70	15	78	132
Et_2NH	Et_2NLi (11)	Et_3N	80	11	18	100	82
Et_2NH	Et_2NLi (100)	Et_3N	120	50	5	60-80	88
$^nBu_2NH$	Na (7), C_4H_6	Bu_2EtN	132-135	21-55	5	63	87
$C_5H_{10}NH$	Na (33), py	$C_5H_{10}NEt$	97-100	41-52	3	80	87
$C_5H_{10}NH$	Na (21), py	$C_5H_{10}NEt$	100	28-38	2.5-10	77-83	86
$C_5H_{10}NH$	$C_5H_{10}NLi$ (100)	$C_5H_{10}NEt$	120	50	5	90	88
$PhNH_2$	$NaNH_2$ (13)	PhEtNH	275	41-55	6	75	87
$PhNH_2$	Na (74), CuO	PhEtNH	290-310	200	4-5	86	85
PhMeNH	$NaNH_2$ (11)	PhMeEtN	250-255	41-55	4.5	53	87

† Key: $n = 1, 2, 3$; s/c, ratio substrate to catalyst; TMEDA, tetramethylethylenediamine; C_4H_6, butadiene; $C_5H_{10}NH$, piperidine; py, pyridine. [a] Melt.

ene react in the presence of metallic sodium or lithium at a temperature of ~200 °C and pressures of up to 1000 bar in an inert hydrocarbon medium to yield a mixture of ethyl-, diethyl-, and triethylamines.[131] The high reaction pressures are apparently essential; at 205 bar for instance only a 0.7% conversion of ammonia is achieved. As alternative precatalysts, alkali-metal hydrides and amides can be used. The latter allow lower temperatures and pressures for the ethylation of ammonia (~100 °C, 100 bar) and are more selective for the formation of the monoethylation product.[82] Amides of the heavier alkali-metals can also be employed. Low melting eutectic mixtures of amides can substitute the organic solvent.[82] Yields for the ethylation of ammonia are generally low, the highest being 66% of product mixture Et_nNH_{3-n} ($n = 1, 2, 3$). The method has subsequently been developed for the reaction of primary and secondary amines and anilines with ethylene (Table 5).

Ethylation of primary amines is possible with metallic sodium or EtLi as precatalysts which result in the formation of amides as active catalyst in situ.[84,87,132] One difficulty with primary amines is the selective formation of mono- or diethylated products. Relatively mild reaction conditions (~150 °C, 40 bar) direct the reaction toward the formation of the monoethylated product. An example is the ethylation of $^nHexNH_2$ in a moderate yield (38%). If harsh reaction conditions (~200 °C, 1000 bar) are employed more diethylated product is formed.

Ethylation of secondary amines proceeds more readily. Et_2NH was first converted to Et_3N in 27% yield by Howk using metallic sodium as precatalyst. Lithium amides, either prepared in situ from EtLi or employed directly, give better yields and milder reaction conditions (~80 °C, 11 bar) allow the nearly quantitative formation of Et_3N.[82] The addition of tetramethylethylenediamine (TMEDA) to the reaction mixture reduces the reaction time considerably.[132]

Piperidine can be converted to *N*-ethylpiperidine in ~80% yield, using catalytic sodium in the presence of traces of pyridine (~80% yield) or by using C_5H_{10}-NLi as precatalyst (90% yield). The lithium amide catalyst allows up to 90 molecules of substrate to be converted before the catalyst is inactivated.[45] Similarly $^nBu_2NH$ can be ethylated in 63% yield with catalytic $^nBu_2NNa$. A similar reaction sequence utilizing Na or $NaNH_2$ as precatalyst (250−300 °C, 50−200 bar) allows to convert aniline and *N*-methylaniline in 53−86% yield.[85,87]

b. Aliphatic Olefins

Only a few examples are known where nonactivated higher alkenes have been hydroaminated (Table 6). Ammonia can be reacted with propene, isobutene,

Table 6. Hydroamination Reactions of Substituted Alkenes in the Presence of Alkali Metal Catalysts†

Amine	Olefin	(Pre)Catalyst (s/c)	Products	Temp /°C	Pressure /bar	Time /h	Yield /%[a]	Ref.
NH_3	Propene	Na (14)	$^{i}PrNH_2$	250	860-1000	19	(29)	84
NH_3	Propene	(Cs/Na)NH_2 (4)	$^{i}PrNH_2$	139	—	18	12	82
NH_3	Isobutene	Na(2)	$^{t}BuNH_2$	250	850-970	14	27	84
NH_3	Cyclohexene	Na (1.4)	$CyNH_2$	250	840-990	13	17	84
NH_3	Cyclohexene	$NaNH_2$ (4)	$CyNH_2$	200	850	20	16	84
$^{n}BuNH_2$	Propene	Na (3)	$^{n}Bu^{i}PrNH$	250	860-1000	18	36	84
$PhNH_2$	Propene	Na (12), CuO	$Ph^{i}PrNH$	300	200	—	43	85
Me_2NH	Propene	EtLi, TMEDA	$Me_2{}^{i}PrN$	150-170	70-90	3	(10)	132
Et_2NH	Norbornene	EtLi, TMEDA	$C_7H_{11}NEt_2$	140-150	—	4	(17)	132
Et_2NH	Norbornadiene	EtLi, TMEDA (18)	$C_7H_9NEt_2$	150	—	14	18	132
$C_5H_{10}NH$	1-Hexene	Na (2)	$C_5H_{10}N^{n}Hex$	225	—	10	9	84

† Key: C_7H_{11}, 2-norbornyl; C_7H_9, 2-norborn-5-enyl; $C_5H_{10}NH$, piperidine. [a] Yields in brackets are percent conversion.

and cyclohexene under the catalytic influence of sodium or alkali-metal amide to generate $^{i}PrNH_2$, $^{t}BuNH_2$, and $CyNH_2$, respectively.[82,84] Temperatures between 140 and 250 °C and pressures up to 1000 bar are typically used. Yields vary from 12% to 29%. Propene also reacts with $^{n}BuNH_2$ or $PhNH_2$ under the catalytic influence of metallic sodium at harsh conditions (250−300 °C, 200−1000 bar) in 36% and 43% yield, respectively.[84,85] The amide as the active catalyst can be formed in situ with EtLi and allows the reaction of norbornene and norbornadiene with Et_2NH.[132] Similar conditions allow the reaction of propene with Me_2NH. The reaction is accelerated by addition of TMEDA, but yields are below 18%. Piperidine is converted to *N*-*n*-hexylpiperidine with 1-hexene and catalytic sodium. In principle, the hydroamination of nonactivated higher alkenes is possible, but gives yields between 10 and 40% thus precluding interesting applications in organic synthesis.

c. Styrenes

Sufficiently nucleophilic amines can add to alkenes containing an α π-system. Table 7, parts a and b, give examples for the alkali-metal-catalyzed reaction of amines with styrene and substituted styrenes, respectively. At mostly elevated temperatures a series of primary and secondary amines, but not ammonia itself, add to styrene.[133] In all cases the anti-Markovnikov product 1-amino-2-phenylethane is obtained. Precatalysts used include metallic sodium[83,134−136] sodium naphthalide[137] or lithium amides;[91] the latter can also be prepared in situ with butyllithium.[133] Depending on the reaction conditions, primary amines react with one or two styrene molecules to give secondary or tertiary amines. Mixtures are usually obtained and formation of a single product would require further optimization of the procedure. The steric bulk of the amine substituents is of no significant importance for the yield or product distribution. For example, a yield of 47% and 49% is obtained for the reaction of $^{n}BuNH_2$ and $^{i}BuNH_2$ to give bis-phenethyl-butyl-amine.

Secondary amines react more readily with styrene than primary amines. The addition of diethylamine to styrene catalyzed by lithium diethylamide, formed in situ with sodium naphthalide, produces 1-(diethylamino)-2-phenylethane in quantitative yield.[91] Higher alkylamines tend to give lower yields between 25 and 70%. Improved yields are obtained when the nitrogen is part of an aliphatic ring system. For example, aziridine gives yields between 72% and 90% and piperidine between 81% and 88% of the corresponding *N*-substituted 1-amino-2-phenylethane.[83,133−135]

1-Methylstyrene reacts with piperidine in nearly the same manner as styrene giving 71% vs 88% yield.[133] 1-Phenylstyrene reacts more slowly than styrene. A yield of 82% is obtained only after extending the reaction time from 5 to 48 h. 2-Methylstyrene reacts with Et_2NH regioselectively to 2-amino-1-phenylpropane in 85% yield which is only slightly lower than for the same reaction with styrene (95%).[137] However, *trans*-stilbene gives only 10% yield. The low yield is surprising especially if compared to the reactions of 1-phenylstyrene (82%) and styrene (81%) at the same conditions. Substitution at the phenyl ring can have a strong influence as well, as can be seen for the reaction of *p*-methoxystyrene with aziridine which gives 47% vs 72% yield for the parent styrene.[83]

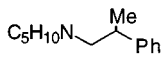
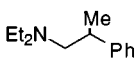
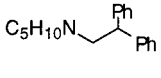
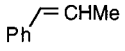
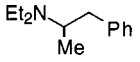
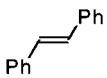
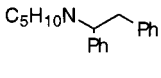
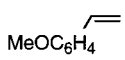
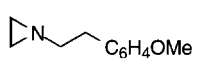
In general, all base-catalyzed aminations of aromatic olefins use nonfunctionalized simple amines as starting materials. The amination in the presence of base has been largely overlooked by organic chemists; however, it is anticipated that the methodology will be rediscovered. In this respect, the preparation of pharmacologically interesting 2-arylethylamines was recently investigated by us.[138] *N*-Arylpiperazines were reacted with styrenes to generate 2-arylethylamines in good to excellent yields. The precatalyst used was 2.5−10 mol % $^{n}BuLi$ and the reaction performed in THF at 120 °C using a pressure tube (Scheme 20). Variation of the conditions for the reaction of styrene with *p*-(fluorphenyl)-*N*-piperazine showed that the reaction is completed after 1 h in THF while in *n*-hexane and toluene the catalyst turns inactive after 66% and 43% conversion, respectively. The reaction tolerates a variety of substituents at the *N*-arylpiperazine as well as at the styrene fragment.

Table 7. Hydroaminations of (a) Styrene and (b) Substituted Styrenes under Catalysis of Alkali Metals†

a

Amine	(Pre)Catalyst (s/c)	Products	Temp /°C	Solvent	Time /h	Yield /%	Ref.
$^{n}PrNH_2$	Na (2-5)	$^{n}PrHN(CH_2)_2Ph$	150-200	—	6-8	18	134
$^{n}PrNH_2$	BuLi (20)	$^{n}PrN((CH_2)_2Ph)_2$	50	^{c}hex	16	33	133
$^{i}BuNH_2$	Na	$^{i}BuN((CH_2)_2Ph)_2$	65	—	4	49	136
$^{n}BuNH_2$	BuLi (20)	$^{n}BuN((CH_2)_2Ph)_2$	50	^{c}hex	16	47	133
$^{n}PnNH_2$	BuLi (20)	$^{n}PnN((CH_2)_2Ph)_2$	50	^{c}hex	16	32	133
$CyNH_2$	Na (2-5)	$CyHN(CH_2)_2Ph$	150-200	—	5-7	30	134
$PhCH_2NH_2$	Na (2-5)	$PhCH_2HN(CH_2)_2Ph$	150-200	—	5-7	30	134
$Ph(CH_2)_2NH_2$	Na (2-5)	$Ph(CH_2)_2HN(CH_2)_2Ph$	150-200	—	6-8	30	134
$MeO(CH_2)_3NH_2$	Na (2-5)	$MeO(CH_2)_3HN(CH_2)_2Ph$	150-200	—	6-8	20	134
$^{n}BuO(CH_2)_3NH_2$	Na (2-5)	$^{n}BuO(CH_2)_3HN(CH_2)_2Ph$	150-200	—	6-8	25	134
$PhNH_2$	Na (2-5)	$PhHN(CH_2)_2Ph$	150-200	—	5-7	70	134
Et_2NH	BuLi (20)	$Et_2N(CH_2)_2Ph$	50	THF	4	58	133
Et_2NH	Et_2NLi	$Et_2N(CH_2)_2Ph$	50	^{c}hex	—	>33	91
Et_2NH	Na_2Np (10)	$Et_2N(CH_2)_2Ph$	RT	THF	1	95	137,142
$^{n}Pr_2NH$	BuLi (20)	$^{n}Pr_2N(CH_2)_2Ph$	50	^{c}hex	16	47	133
$^{n}BuMeNH$	BuLi (20)	$^{n}BuMeN(CH_2)_2Ph$	50	^{c}hex	16	70	133
$^{n}Bu_2NH$	Na (2-5)	$^{n}Bu_2N(CH_2)_2Ph$	150-200	—	6-8	25	134
Non_2NH	BuLi (20)	$Non_2N(CH_2)_2Ph$	50	^{c}hex	16	41	133
$(CH_2)_2NH$	Na	$(CH_2)_2N(CH_2)_2Ph$	—	—	—	72	83
$(CH_2)_2NH$	Na	$(CH_2)_2N(CH_2)_2Ph$	—	—	—	<90	135
$C_5H_{10}NH$	Na (2-5)	$C_5H_{10}N(CH_2)_2Ph$	150-200	—	5-7	81	134
$C_5H_{10}NH$	BuLi (20)	$C_5H_{10}N(CH_2)_2Ph$	50	THF	5	88	133
$C_5H_{10}NH$	BuLi (20)	$C_5H_{10}N(CH_2)_2Ph$	50	^{c}hex	5	81	133

b

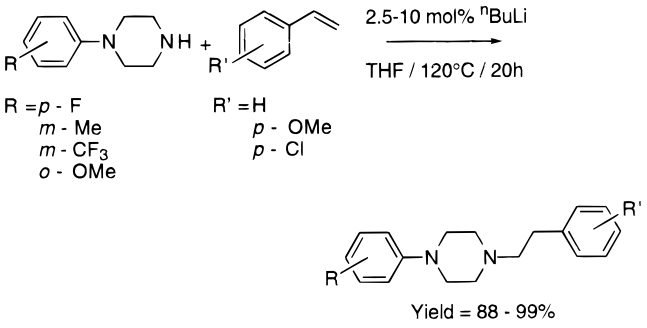
Amine	Olefin	(Pre)Catalyst (s/c)	Products	Temp /°C	Solvent	Time /h	Yield /%	Ref.
$C_5H_{10}NH$		BuLi (20)		50	THF	5	71	133
Et_2NH		Na_2Np (6)		—	THF	—	85	142
$C_5H_{10}NH$		BuLi (20)		50	^{c}hex	48	82	133
Et_2NH		Na_2Np (6)		RT	THF	1	85	137
$C_5H_{10}NH$		BuLi (20)		50	^{c}hex	48	10	133
$(CH_2)_2NH$		Na		—	—	—	47	83

† Key: ^{c}hex, cyclohexane; Pn, C_5H_{11}; Non, C_9H_{19}; $(CH_2)_2NH$, aziridine; $C_5H_{10}NH$, piperidine; Na_2Np, sodium naphthalide; $MeOC_6H_4$, *p*-methoxyphenyl.

d. 1,3-Butadienes

The catalyzed addition of sufficiently nucleophilic amines to 1,3-butadiene and isoprene generally gives 1-amino-2-butenes; examples are given in Table 8, parts a and b, respectively. Precatalysts employed were elemental sodium or alkali metal amide; the latter can also be formed in situ with Na_2Np or alkyllithium salts. Aniline reacts with 1,3-butadiene to give *N*-2-butenylaniline with trans stereochemistry at the double bond in good yield (79%).[139] For the reaction of secondary amines with 1,3-butadiene the stereochemistry in the products varies from predominantly trans to nearly exclusively cis depending on the reaction conditions. One important factor is the

Scheme 20. Preparation of Pharmacologically Interesting 1-Aryl-4-(arylethyl)piperazines

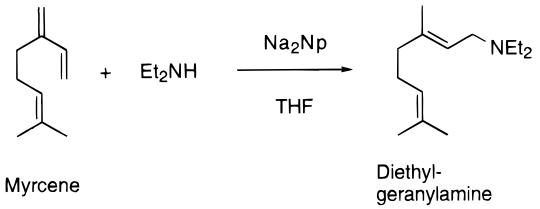


solvent employed as can be seen in the reaction of Et_2NH with 1,3-butadiene where mainly trans product is formed in THF while a ratio trans/cis = 1:4 is observed in cyclohexane.[133] Another factor which contributes to product distribution is the steric bulk of the substituents on the amine. For the reaction of diisopropyl- and di-*n*-propylamine initiated by ^{n}BuLi, the trans/cis selectivities are 1:1.2 and 1:7, respectively.[89] The yield is very low (9%) for the former while high (86%) for the latter substituents. The effect is smaller for the homologue dibutylamine where the trans/cis selectivities for diisobutyl- and di-*n*-butylamine are 1:3.6 and 1:6.3, respectively. For piperidines a higher proportion of trans stereochemistry is generally observed. However, no explanation for the regioselectivity observed has been put forth.

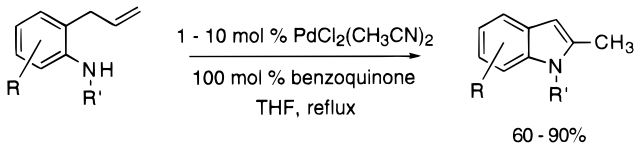
In most amination reactions the 1,4-addition product is observed. One exception is the reaction of aniline with isoprene which leads to *N*-(3-methyl-3-butenyl)aniline (29% yield) with the double bond in the 3-position.[139,140] Isoprene reacts with secondary amines generally to give 3-methyl-2-butenylamine. Various secondary amines can be employed, giving yields of this product between 57% and 72%.[137] Depending on the reaction conditions, various amounts of other regioisomers are formed as byproducts. For example, the reaction of piperidine with isoprene proceeds with 95% overall conversion of isoprene giving the following product distribution: $C_5H_{10}NCH_2CH{=}CMe_2$ 76%, (*E*/*Z*)-$C_5H_{10}NCH_2CMe{=}CHMe$ 15%, $C_5H_{10}NCH_2CH_2CMe{=}CH_2$ 7%, $C_5H_{10}NCH_2CHMeCH{=}CH_2$ 2%.[133] Similar product distributions are observed for the reaction of other secondary amines.

An example of this methodology is the preparation of *N*,*N*-diethylgeranylamine from myrcene and diethylamine (Scheme 21).[137,141−143] The geranylamine is a key intermediate for the synthesis of industrially important acyclic monoterpenes, such as geranyl acetate,[137] linalool,[144] citral,[145] and citronellal,[146] and provides one possible feedstock for the Takasago process which provides more than 1000 tons of (−)-menthol and other terpenic substances annually.[147−149]

Scheme 21. Application of a Hydroamination Reaction for the Synthesis of Diethylgeranylamine, an Intermediate in the Industrial Preparation of (−)-Menthol (Na_2Np = sodium naphthalide)



Scheme 22. Examples of Palladium-Catalyzed Oxidative Cyclization of Substituted Anilines



3. Aminations Catalyzed by Transition Metals

a. Palladium-Catalyzed Aminations of Olefins

A number of synthetically useful laboratory-scale procedures for performing catalytic amination of olefins using palladium complexes have been developed in the past 15 years.[12,55] As detailed in Scheme 5, all the palladium(II)-catalyzed reactions proceed through unstable σ-alkylpalladium(II) complexes. Of particular importance is the fast β-hydride elimination to yield enamines and, in case of primary amines, imines and a palladium(0) complex. In the following discussion we refer to this reaction as oxidative amination because the olefinic double bond is preserved. Intermolecular catalytic oxidative amination reactions have been realized only in rare cases due to the problems of reoxidizing Pd^0 to Pd^{II} in the presence of amines and enamines. An example is the reaction of 2-bromoaniline with acrylates (activated olefin).[150]

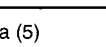
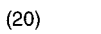
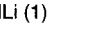
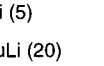
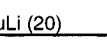
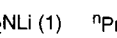
In contrast to the difficult intermolecular reaction, the intramolecular aminopalladation[18] proceeds more easily. Pioneering work came from Hegedus and coworkers who reported the synthesis of indole and substituted indoles such as 2-methylindole by palladium-catalyzed cyclization of *o*-vinylanilines or *o*-allylanilines in the presence of benzoquinone as reoxidant (Scheme 22).[11,80,151]

The reaction proceeds catalytically due to the decreased basicity of aromatic amines compared to aliphatic amines (by a factor of 10^6) and to the stability of the aromatic indole. Analogously indoloquinones were prepared by starting from substituted 2,5-bis(benzylamino)quinones.[152] While the reaction of some anilines proceeds under mild conditions, cyclization of several substituted anilines, e.g., 3-bromo-2-vinylaniline, and nonaromatic aminoolefins are less successful due to polymerization and/or the increased tendency of aliphatic amines to form stable palladium(II) complexes. Acylation, especially tosylation of amines was found to sufficiently lower the basicity and thus the complexation strength to allow for smooth intramolecular reactions even with nonactivated alkenes (Scheme 23).[153]

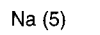
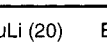
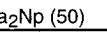
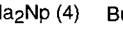
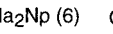
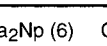
In general, numerous acyclic and cyclic tosylamides can be cyclized to five- and six-membered ring products. Thus it is not surprising that this reaction

Table 8. Examples for Hydroaminations of (a) Butadiene and (b) 2-Methylbutadiene under Catalysis of Alkali Metals†

a

Amine	(Pre)Catalyst (s/c)	Products	Ratio[a]	Temp. /°C	Solvent	Time /h	Yield[b] /%	Ref.
$MeNH_2$	LiH	$MeN(C_4H_7)_2$	—	75	—	1	80	217
$PhNH_2$	Na (5)	PhHN 	trans	120	—	18	79	139
Et_2NH	Na (100)	Et_2N 	—	—	—	—	65	218
Et_2NH	Na_2Np (6)		—	RT	THF	1	82	137,142
Et_2NH	^nBuLi (20)		1:7	50	^{c}hex	3	(86)	89
Et_2NH	Et_2NLi (1)		1:50	50	^{c}hex	1	(50)	89,90
Et_2NH	^nBuLi (5)		1:50	40	C_6H_6	4	41	219
Et_2NH	$^{sec}BuLi$ (20)		1:4	50	^{c}hex	24	(81)	133
Et_2NH	$^{sec}BuLi$ (20)		trans	50	THF	24	48	133
$^iPr_2NH$	^nBuLi (20)	$^iPr_2N$ 	1:1.2	50	^{c}hex	3	9	89
$^nPr_2NH$	$^nPr_2NLi$ (1)	$^nPr_2N$ 	1:13	50	^{c}hex	1	(47)	89,90
$^nPr_2NH$	^nBuLi (20)		1:7	50	^{c}hex	3	(86)	89
$^iBu_2NH$	^nBuLi (20)	$^iBu_2N$ 	1:3.6	50	^{c}hex	3	(84)	89
$^iBu_2NH$	$^iBu_2NLi$ (1)		1:4	50	^{c}hex	1	(87)	89,90
$^nBu_2NH$	^nBuLi (20)	$^nBu_2N$ 	1:6.3	50	^{c}hex	3	(75)	89
$^nBu_2NH$	$^nBu_2NLi$ (1)		1:20	50	^{c}hex	1	(29)	89,90
$C_5H_{10}NH$	$^{sec}BuLi$ (20)	$C_5H_{10}N$ 	trans	50	THF	28	58	133
$C_5H_{10}NH$	$^{sec}BuLi$ (20)		1.75:1	50	^{c}hex	24	(83)	133
$C_7H_{14}NH$	$^{sec}BuLi$ (20)	$C_7H_{14}N$ 	4:1	50	^{c}hex	17	(50)	133

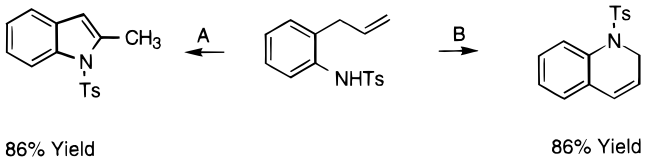
b

Amine	(Pre)Catalyst (s/c)	Products	Temp. /°C	Solvent	Time /h	Yield /%	Ref.
$PhNH_2$	Na (5)	PhHN 	120	—	18	29	139
Et_2NH	BuLi (20)	Et_2N 	50	^{c}hex	24	57	133
Et_2NH	BuLi (5)		55	C_6H_6	9	78	219
Et_2NH	Na_2Np (50)			THF	1	72	137,142
$^nBu_2NH$	Na_2Np (4)	Bu_2N 	RT	THF	1	61	137,142
C_4H_8NH	Na_2Np (6)	C_4H_8N 	RT	THF	1	67	137,142
$C_5H_{10}NH$	Na_2Np (6)	$C_5H_{10}N$ 	RT	THF	1	59	137,142
$C_5H_{10}NH$	BuLi (20)		50	^{c}hex	24	72	133
OC_4H_8NH	Na_2Np (6)	R_2N 	RT	THF	1	67	137

† Key: s/c, ratio substrate/catalyst; C_4H_7, butenyl; Na_2Np, sodium naphthalide; ^{c}hex, cyclohexane; C_6H_6, benzene; $C_5H_{10}NH$, piperidine; $C_7H_{14}NH$, 2,6-dimethylpiperidine; C_4H_8NH, pyrrolidine; OC_4H_8NH, morpholine. [a] Product ratio trans/cis. [b] Yields are based on the main product; yields given in brackets are % conversion.

has been applied in natural product syntheses, e.g., *N*-acetylclaviciptic acid methyl ester.[154,155] Interestingly, the use of $PdCl_2$ as catalyst in the presence of benzoquinone led exclusively to the formation of *N*-vinylic tosylamides,[153] while $Pd(OAc)_2$ under an atmosphere of oxygen in DMSO afforded the corresponding ring products containing an allylic nitrogen moiety (Scheme 23).[156] It is important to note that this type of amination of a double bond[157] results in the formation of a new 1,2-shifted double bond. Thus, the overall result of the process is similar to an oxidative allylic amination. This regioselective

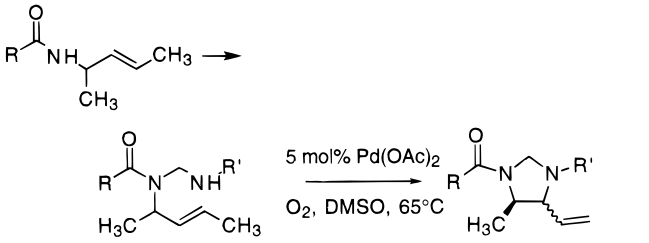
Scheme 23. Regioselective Cyclization of Olefinic Tosylamides



86% Yield 86% Yield

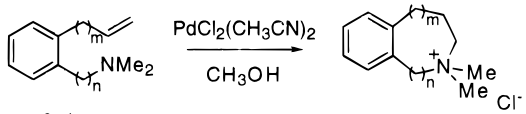
A: 10 mol% $PdCl_2(CH_3CN)_2$, 1 eq. Benzoquinone
10 eq. LiCl, THF, reflux, 5h
B: 5 mol% $Pd(OAc)_2$, 2 eq. NaOAc, DMSO, O_2, 80°C, 72h

Scheme 24. Detachable Connection Approach to Allylic Diamines



R = BOC, R' = Ts 65%
R = BOC, R' = OCH_3 90%
R = BOC, R' = $OCOCH_3$ 49%

Scheme 25. Intramolecular Amination of Olefins Using Tertiary Amines



n = 0, 1
m = 1

79 - 89 % yield

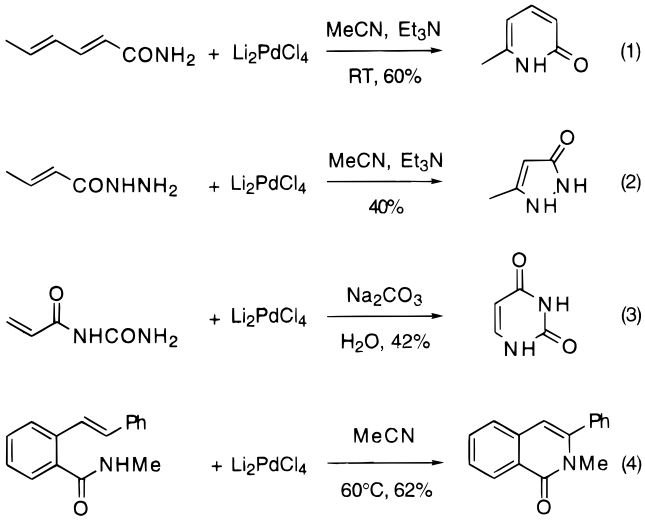
oxidative cyclization protocol was successfully applied to olefinic amines in which different tethered nitrogen nucleophiles are incorporated into imidazolidines ("detachable connection approach", Scheme 24).[158] Surprisingly, the formyl group emerged as the best protecting group for the palladium-catalyzed synthesis of imidazolidines, allowing easy deprotection under mild conditions.

Although detailed mechanistic work has not been carried out, the entirely different cyclization is explained either by alteration of the regiochemistry due to the less coordinating anion present in the palladium catalyst, or by a cyclization route involving initial π-allylpalladium formation. The latter pathway has also been suggested for the cyclization of a polycyclic olefinic amine using $Pd(O_2CCF_3)_2/PPh_3$/benzoquinone as catalyst system.[159] This reaction served as a key step in the synthesis of the daphniphyllum alkaloids such as bukittinggine and methyl homosecodaphniphyllate.

Further evidence for allylic C−H activation in amination reactions was presented by van Koten, Pfeffer, and co-workers.[160] They studied the factors which govern the heterocylization of tertiary amines having a terminal olefinic unit and demonstrated that five-, six- or seven-membered rings can be formed in the presence of stoichiometric amounts of $PdCl_2(MeCN)_2$ (Scheme 25).

Intermolecular catalytic oxidative aminations of olefins in the presence of palladium catalysts have

Scheme 26. Synthesis of Heterocycles via Palladium-Mediated Intramolecular Oxidative Amidation: 1,[162] 2,[163] 3,[164] and 4[165]



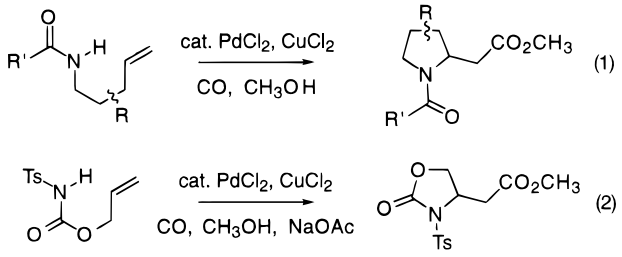
not been reported. In contrast, the oxidative amidation of activated olefins is possible. Most examples described use acrylates or substituted acrylic acid derivatives as olefins. Interestingly, Murahashi and co-workers succeeded in a catalytic variant of this reaction. Lactams or carbamates react with methylacrylate in the presence of 5 mol % $PdCl_2(CH_3CN)_2$ and 5 mol % Cu(I)Cl under a dioxygen atmosphere to give β-amidoacrylates.[161] This general type of reaction had been previously applied in an intramolecular fashion for the synthesis of a number of interesting heterocycles, e.g., 2-pyridone,[162] 3-pyrazolone,[163] uracil,[164] and 3-phenyl-*N*-methylisoquinolone[165] (Scheme 26). However, a drawback of these earlier examples of palladium-mediated amidation is the use of stoichiometric amounts of the transition metal.

Urethanes (H_2NCO_2R), another class of *N*-nucleophiles, have been recently investigated.[166,167] The aim of this new approach is to synthesize aliphatic isocyanates without formation of salts as byproduct. Low turnover numbers have been achieved for methyl acrylate (oxidative amination), isoprene, and 2,3-dimethyl-1,3-butadiene (hydroamination). However, unsubstituted aliphatic olefins did not react at all.

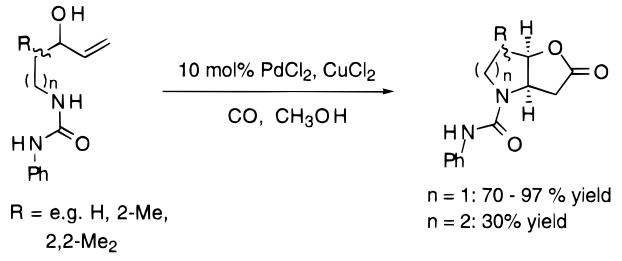
Apart from the β-hydride elimination, the unstable σ-alkylpalladium(II) species can undergo subsequent insertion processes, such as olefinations, carbonylations, or arylations.[168−173] An interesting example which demonstrates the synthetic potential of this strategy for the synthesis of β-amino acid derivatives is the intramolecular Wacker-type aminocarbonylation of appropriately substituted unsaturated amides. It was disclosed that ureas, carbamates and tosylamides with an exo-type nitrogen nucleophile undergo a smooth cyclization in the presence of $PdCl_2$ and 2−3 equiv of $CuCl_2$ under 1 atm of carbon monoxide (acidic conditions; Scheme 27, eq 1). On the other hand endo-type carbamates require NaOAc or methyl orthoacetate (buffer conditions) for the cyclization (Scheme 27, eq 2).[174]

In an attempt to synthesize glycosidase inhibitors, another Pd(II)-catalyzed domino reaction was used.

Scheme 27. Intramolecular Oxidative Aminocarbonylations



Scheme 28. Tandem Amination−Carbonylation Reaction of Olefinic Ureas



Here, the cylization of 1-amido-4-pentene-2,3-diols was coupled directly with carbon monoxide insertion reactions.[175] A similar amination−carbonylation−esterification sequence was performed with ureas of 3-hydroxy-4-pentenylamines (Scheme 28).[174] While cyclization of the five-membered ring proceeds quite efficiently, the six-membered ring closure is more difficult to achieve. In addition to the carbon monoxide insertion reaction, intramolecular[176] and intermolecular[168] olefin insertion reactions have also been used as additional bond-forming steps.

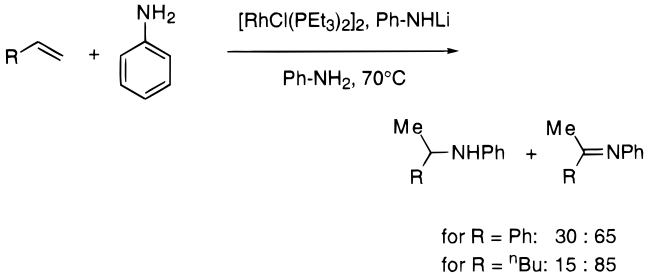
In general, the palladium-catalyzed cyclization of olefinic amines, tosylamides, and carboxamides coupled with further insertion reactions has proven to be a valuable route to various polycyclic amino derivatives. These are of interest as organic building blocks for natural products as well as pharmaceuticals. We believe that these tandem procedures will become an increasingly important synthetic tool.

b. Other Catalytic Oxidative Aminations of Olefins

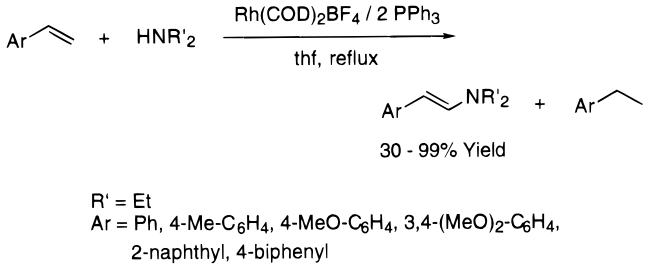
Apart from the palladium-catalyzed formation of imines or enamines, other metals have been rarely used for this type of catalytic oxidative amination. Brunet and co-workers described the reaction of styrene with lithium anilide in the presence of the rhodium complex $[RhCl(PEt_3)_2]_2$.[177] A mixture of hydroamination products and the imine Ph−CMe=NPh was obtained, the latter being the major product. Although the overall reaction is catalytic with respect to rhodium, the process is extremely slow (TON = 21, TOF < 0.07 h^{-1}, 70 °C). The same qualitative results were obtained with 1-hexene. Similarly, the catalyst promotes the reaction between norbornene and aniline to yield a small percentage (≤40%) of the hydroamination product 2-norbornyl-*N*-aniline.[178] Interestingly, the formation of the imine proceeds exclusively with Markovnikov regiochemistry.

Very recently, we were able to demonstrate for the first time the possibility of oxidative aminations with

Scheme 29. Rhodium-Catalyzed Reaction of Lithium Amides with Styrene



Scheme 30. First Anti-Markovnikov Oxidative Amination of Aromatic Olefins



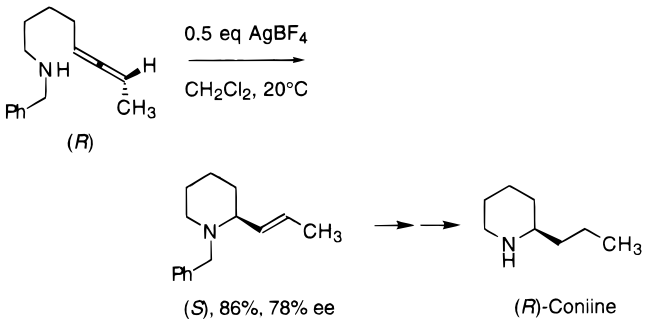
anti-Markovnikov stereochemistry.[179] In presence of 2.5−10 mol % $[Rh(cod)_2]BF_4$ and 2 equiv of PPh_3, various secondary amines react with styrene to give the oxidative amination product *trans*-1-amino-2-phenylethene (Scheme 30). A second equivalent of styrene is reduced to ethylbenzene, effectively being the oxidation agent. The reaction shows extremely high regioselectivity and gives yields up to 99%. Other oxidative amination methods such as the osmium-catalyzed hydroxyamidation[180−182] have been reviewed very recently[183] and are beyond the scope of this review.

c. Amination of Allenes

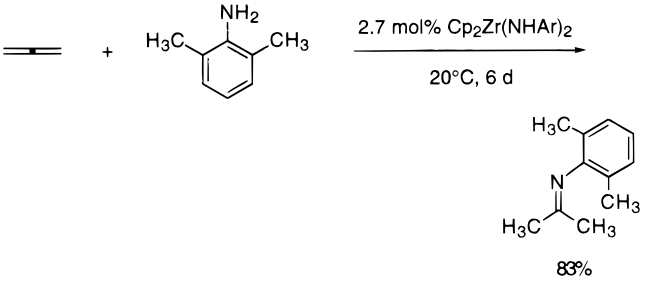
Compared to olefins and alkynes, the amination of allenes has received only limited attention. Similar to activated olefins, aminations of allenes substituted by electron-withdrawing groups proceeds directly without additional metal complexes.[221,222] Allylic amines are obtained as products. In contrast, allene and alkyl- or aryl-substituted allenes do not react directly with amines under mild conditions. However, in the presence of equimolar amounts of palladium(II), platinum(II), or mercury(II) salts, aminated products such as allylic amines or enamines are obtained.[223−225]

Intramolecular amination of nonactivated allenes to give 2-substituted pyrrolidines and piperidines have also been performed in the presence of stoichiometric amounts of either mercuric chloride or silver nitrate.[226] This heterocyclization process of γ- and δ-allenic amines has been used for the synthesis of natural products. A total synthesis of racemic pinidine[227] and (*R*)-coniine[228] (Scheme 31) is accomplished by an intramolecular silver-catalyzed C−N bond formation process of the corresponding δ-allenic amine. The reaction is catalytic in silver, although the catalyst efficiency is extremely low (TON = 1.5−3). During the cyclization of *N*-benzylocta-5,6-dienylamine to yield the coniine precursor, only a small

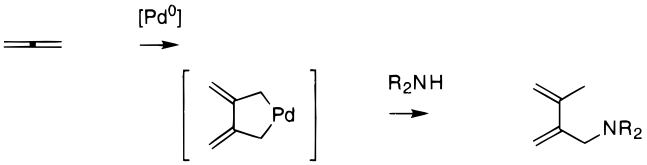
Scheme 31. Ag(I)-Catalyzed Amination of Allenes



Scheme 32. Hydroamination of Allene by Zirconium Bisamides $Cp_2Zr(NHAr)_2$



Scheme 33. Palladium-catalyzed Telomerization of Allene with Amines

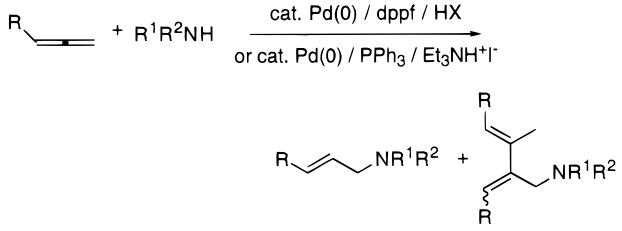


amount (<10%) of racemization is observed in the C−N coupling reaction. Similar methodology has been used to prepare a series of carbapenems.[229] Cyclization of 4-allenylazetidnones proceed smoothly in the presence of 0.14 equiv of $AgBF_4$ (TON = 5). No studies toward turnover improvements have appeared, but it seems reasonable to believe that an efficient catalytic process is possible after optimization studies.

Recently, Bergman and co-workers found that zirconium bisamide complexes of the form $Cp_2Zr(NHAr)_2$ catalyze the hydroamination of allene.[102] As shown in Scheme 32, the zirconocene bisamide catalyze the reaction between 2,6-dimethylaniline and allene to give the anti-Markovnikov product, the 2,6-dimethylphenylimine of acetone, in 83% yield (TON = 31). While substituted allenes have not been investigated, simple olefins are not reactive enough for this interesting amination protocol. From a mechanistic point of view the intermediacy of an imido $Cp_2Zr{=}NR$ complex, which undergoes a cycloaddition reaction was proposed.

The intermolecular palladium-catalyzed amination of allenes were not known prior to the early 1970s. As shown in Scheme 33, the main products of this reaction are alkadienylamines.[230−233] Presumably these reactions proceed through the palladacyclopentane intermediate (Scheme 33). Palladium-catalyzed intermolecular hydroaminations of nonactivated allenes to yield allylic amines have been described only very recently. According to Cazes et al.[41] the key to success is the addition of triethylammonium iodide as cocatalyst (Table 9). The ammonium salt is believed to generate a hydrido−palladium complex, which adds to the allene. Yamamoto and co-workers described a similar type of system $(Pd(dba)_2{\cdot}CHCl_3$, dppf, $CH_3CO_2H)$, which catalyzes the addition of free amines or sulfonamides to allenes. Best yields were obtained with aromatic allenes.[234]

Table 9. Palladium-Catalyzed Hydroamination of Substituted Allenes



			A	B
R	R^1	R^2	A	B
C_7H_{15}	C_2H_5	C_2H_5	70%	8%
C_6H_5	C_2H_5	C_2H_5	72%	19%
C_6H_5	$(CH_2)_4$		89%	—
p-CH_3-C_6H_4	C_6H_5	C_6H_5	67%	—
p-CH_3-C_6H_4	$C_6H_5CH_2$	$C_6H_5CH_2$	99%	—
$C_5H_{11}CH(OH)$	$(CH_2)_4$		60%	—

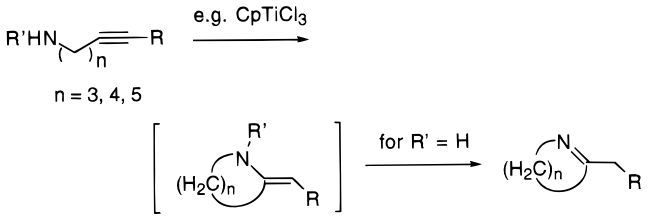
Whereas the synthesis of allylic amines via hydroamination of allenes has been developed only recently, the corresponding amidation of allenes is applied more often.[235−239] In these reactions the presumed vinylpalladium species is rather stable and allows further functionalization. Thus, special interest has been paid to domino reactions leading to substituted carbapenemes,[235] pyrrolizidines, indolizidines,[236] oxazolidinones,[237,238] and others.

Finally, it is worth mentioning that hydroamination of η^1-complexed allenes, e.g., η^1-allenyliridium complexes, leads to the formation of the central-carbon-substituted η^3-complexed amines.[40] Although this area seems to be pursued with increasing activity, it is questionable whether the method is of significant synthetic importance.

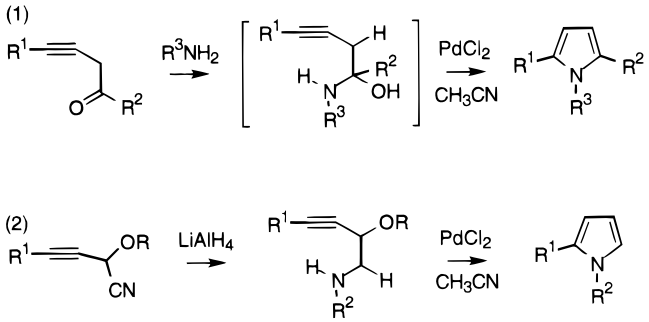
d. Intramolecular Amination of Alkynes

Tethered aminoalkynes have been cyclized to the hydroamination products using titanium, nickel, palladium, gold, and lanthanide complexes as catalysts; examples are given in Table 3. One possible catalyst employed is $Ni(CO)_2(PPh_3)_2$ which allows 1-amino-3-alkynes and 1-amino-4-alkynes to be cyclized to 1-pyrrolines in moderate yields (40−67%).[184] The formation of 1-pyrrolines with both substrates demonstrates the preferential formation of five-membered rings which was also observed for other transition-metal catalysts. Larger rings can be generated if the formation of five-membered rings is not possible. 1-Amino-*n*-alkynes (n = 3, 4, 5) thereby give an intermediate exocyclic double bond (Scheme 34). Subsequent 1,3 hydrogen shift leads to isomer-

Scheme 34. Transition Metal Catalyzed Amination and Tautomerization to Imines



Scheme 35. Intramolecular Amination of Aminoalkynes To Give Pyrroles



ization of the initially formed enamine to the more stable imine. When *N*-substituted amino-*n*-alkynes are used tautomerization of the enamines formed cannot occur and the latter can be isolated as the products.

For the cyclization of 1-amino-5-alkynes, the gold compound $NaAuCl_4 \cdot 2H_2O$ was also examined.[185] Moderate activity of the catalyst requires 5 mol % of the gold complex. However, nearly quantitative yields of 3,4,5,6-tetrahydropyridines can be obtained. Catalytic palladium chloride in acetonitrile can also be used for the 5-endo cyclization of 1-amino-*n*-alkynes ($n = 3, 4$) to form 1-pyrrolines and for the cyclization of 1-amino-5-alkynes to the corresponding hydropyridine. Yields are moderate (43−70%). When the substrate contains an appropriately suited leaving group cyclization is followed by elimination and subsequent hydrogen shifts result in the more stable pyrroles (Scheme 35).[186] The starting material can be prepared either (1) in situ from a 1-keto-3-alkyne and amine or (2) from cyanation of the acetylenic ketone or acetal with cyanotrimethylsilane[187] followed by $LiAlH_4$ reduction. The cyclization step is catalyzed by palladium(II) chloride in approximately 80% yield for unstrained molecules.

Early-transition-metal complexes such as $CpTiCl_3$ are also able to catalyze the cyclization of suitable aminoalkynes.[188] Here, 1-amino-4-alkynes can be cyclized at 25 °C while formation of six-membered rings from 1-amino-5-alkynes requires 80 °C. However, high concentrations of the catalyst $CpTiCl_3$ are necessary (20 mol %). Terminal alkyne moieties undergo cycloadditions more readily and a lower concentration of the $CpTiCl_3$ (10 mol %) is possible.[189]

The regioselective titanium-promoted intramolecular addition of aminoalkyne has been applied to the total synthesis of the antifungal agent (+)-preussin which contains a central pyrrolidine ring (Scheme 36).[189] The key step of the synthesis utilizes the cyclization of an 1-amino-4-alkyne. However, the direct route via cyclization of 1-amino-4-tredecyne (**6**) using catalytic $[CpTiCl(NEt_2)_2]$ leads to subsequent tautomerization and elimination of ROH and the formation of a substituted pyrrole. The successful synthesis was then achieved by cyclizing the more reactive terminal 1-amino-4-pentyne (**7**) with a stoichiometric amount of $[CpTiMe_2Cl]$. Subsequently, the octyl side chain was introduced by quenching of the intermediate azatitanacycle with octanoyl cyanide. Several further steps lead to (+)-preussin in 35−44% overall yield from **7**.

A titanium-catalyzed hydroamination reaction was also utilized in the total synthesis of (±)-monomorine (Scheme 37). The key intermediate, a substituted 5-amino-8-tridecyne, was cyclized with $CpTiCl_3$ (20 mol %) in 93% yield and further converted to (±)-monomorine in 53% overall yield. In principle, such aminoalkyne cyclizations offer an attractive route to a variety of precursors to indolizidine and quinolizidine alkaloids.

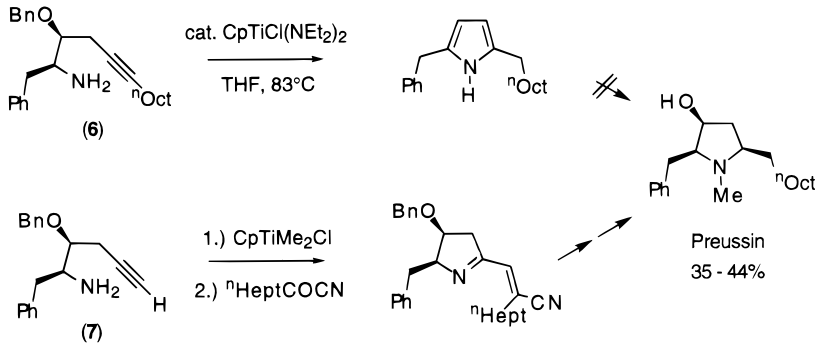
As previously discussed, the intramolecular hydroamination of aminoalkynes can also be effected by the lanthanide complexes $(Me_5C_5)_2LnCH(SiMe_3)_2$ (Ln = La, Nd, Sm, Lu) and $Me_2Si(Me_4C_5)_2LnCH(SiMe_3)_2$ (Ln = Nd, Sm).[93,97] The lanthanide complexes can be employed in lower concentration (~0.5 mol %) than late-transition-metal catalysts and in most cases give an improved yield (85−95%). The process is capable of regiospecifically forming five-, six-, and seven-membered heterocycles from substrates having various substituents on the acetylenic moiety (R = H, alkyl, Ph, $SiMe_3$, allyl) (see Table 3).[93] However, most polar substituents, especially those with oxygen atoms seem not to be compatible with lanthanide catalysts, thus limiting the utility of the method for organic synthesis. Cyclization rates are influenced considerably by the substituent at the acetylenic moiety with $SiMe_3 > H > Me > Ph$ and show a strong ring size dependence with $5 > 6 \gg 7$.

The transition-metal catalyst systems have shown that tethered aminoalkynes can in principle be cyclized via hydroamination of the olefinic system. With lanthanide complexes electron-rich π-systems are cyclized more facile, e.g., the cyclization of $H_2N(CH_2)_3C{\equiv}CSiMe_3$ with $(Me_5C_5)_2SmCH(SiMe_3)_2$ proceeds quantitatively and turnover frequencies TOF > 7600 h^{-1} (21 °C) are measured. For less activated alkynes turnover frequencies are much smaller.

e. Intramolecular Amination of Alkenes

The cyclization of aminoalkenes is more difficult to achieve compared to the cyclization of aminoalkynes. A catalytic system utilizing late transition metals which is suitable for laboratory-scale or industrial applications has not been developed. In the presence of a stoichiometric amount of K_2PtCl_4 1-amino-*n*-alkenes ($n = 4, 5$) undergo cyclization in aqueous solution at 60 °C.[76,77] An acidic medium and the presence of additional chloride ions are required to prevent the separation of metallic platinum. The $PtCl_4^{2-}$ is regenerated at the end of the reaction which can be restarted by addition of further aminoalkene. Several cycles can be conducted. However, the slow rates of the reaction (one cycle in 2−11

Scheme 36. Synthesis of (+)-Preussin



Scheme 37. Synthesis of (±)-Monomorine

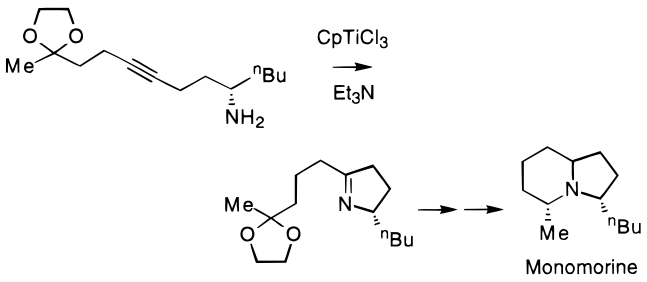
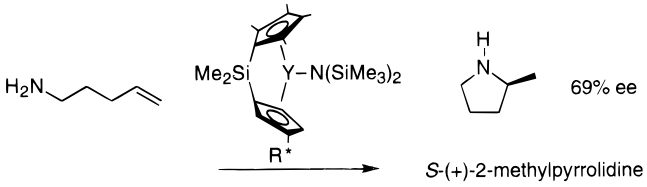


Table 10. Intramolecular Hydroamination of Tethered Aminoalkenes Using Stoichiometric K_2PtCl_4[75,76]

Substrate	Products	Product ratio	Temp. /°C	Time /days	Yield /%
H_2N	H N	—	60	4	67
H_2N, Me	H N, cis/trans	40:60	60	11	90
Me, H_2N	H N, cis/trans	62:38	60	8	85
H_2N, Me	H N, cis/trans	12:88	60	21	85
H_2N	H N	—	60	1-2	77
H_2N, $(\ )_3$	H N Et; H N Me	9:91	60	67	67
H_2N	H N Et; H N Me	60:40	60	25	58
RNH, $(\ )_3$	R=Me	88:12	60	7	87
	R=nPr	81:19	60	8	83
	R=iPr	69:31	60	19	75
H_2N, $(\ )_4$	H N	—	60	30	79

days) precludes further synthetic exploitation. When an excess of aminoalkene is employed, double-bond migration leads to the formation of a considerable amount of side products. In principle, various pyrrolidines and piperidines may be formed from aminoalkenes (Table 10).

Scheme 38. Enantioselective Cyclization of 1-Amino-4-hexenes (R* = menthyl, 100% conversion, > 95% regioselectivity)



In 1990, Gagné and Marks designed an intramolecular cyclization of aliphatic aminoalkenes catalyzed by organolanthanide complexes.[92,96,190,191] The complexes $(Me_5C_5)_2LnR$ and $Me_2Si(Me_4C_5)_2LnR$ (Ln = La, Nd, Sm, Y, Lu; R = H, η^3-Allyl, $E(SiMe_3)_2$ with E = CH, N) catalyze the intramolecular hydroamination of primary and secondary tethered aminoalkenes to the corresponding 2-methyl heterocycles. The reaction is highly regiospecific furnishing five-, six-, and seven-membered cyclic amines under mild conditions (see Table 2). However, the cyclization of aminoalkenes is ~10−100 times slower than the corresponding aminoalkynes when the same reaction conditions are employed.

This cyclization process allows, e.g., the conversion of 1-amino-4-pentenes to 2-methylpyrrolidines and 1-amino-5-hexenes to 2-methylpiperidines, generating a new asymmetric center adjacent to the heterocyclic nitrogen atom. The products are racemic with $(Me_5C_5)_2LnE(SiMe_3)_2$ and $Me_2Si(Me_4C_5)_2LnE(SiMe_3)_2$ (E = CH, N) as precatalysts. However, the chiral complexes $Me_2Si(Me_4C_5)(R^*H_3C_5)LnE(SiMe_3)_2$ (Ln = Y, E = CH, N; R* = menthyl, neomenthyl) catalyze this process enantioselectively under otherwise identical conditions (Scheme 38).[92] The configurations and optical purities of the product heterocycles depend on the chiral auxiliary ligand and the lanthanide employed. Lowering the reaction temperature increases the enantioselectivity; for 1-amino-2,2-dimethylpentane the enantiomeric excess of the cyclization product rises from 53% ee at 25 °C to 74% ee at −30 °C. Diastereoselective processes are also mediated by chiral lanthanide complexes. Thus, cyclization of 2-amino-5-hexenes yields *trans*-2,5-dimethylpyrrolidines with >95% diastereoselectivities (Scheme 39).[192]

The chiral and achiral lanthanide catalysts show a decrease of turnover numbers with decreasing lanthanide ionic radius. The highest rate is determined for the cyclization of $H_2N(CH_2)_3CH{=}CH_2$ with

Scheme 39. Diastereoselective Cyclization of 2-Amino-5-hexenes (R* = neomenthyl, 100% conversion)

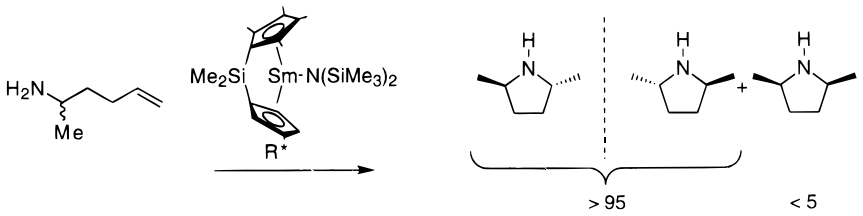
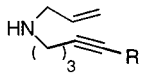
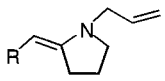
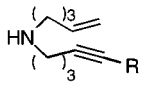
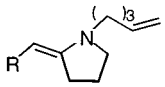
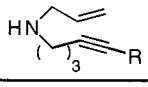
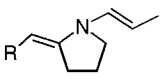
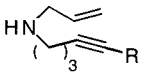
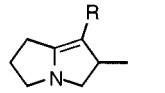
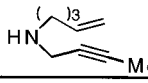
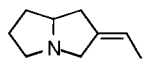
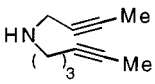
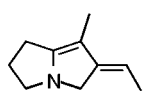
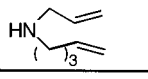
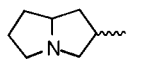
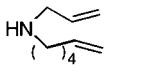
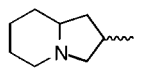


Table 11. Intramolecular Competition Experiments for Hydroamination[93] and Tandem Cyclization Reactions[193] of Aminoalkenes and -alkynes†

Entry	Substrate		Catalyst (s/c)	Product	Temp. /°C	Yield /%	TOF /h^{-1}
(1)		R=H	Cp*$_2$SmE (200)		21	85	27
		R=SiMe$_3$	Cp*$_2$LuE (200)		21	90	56
(2)		R=H	Cp*$_2$SmE (200)		21	85	47
		R=SiMe$_3$	Cp*$_2$SmE (200)		21	90	129
(3)		R=SiMe$_3$	Cp*$_2$SmE (50)		60	91	2.6
(4)		R=Ph	Cp*$_2$SmE (50)		21	68	17
		R=Me			21	75	777
(5)			Cp*$_2$SmE (50)		60	92	14
			Me$_2$SiCp'$_2$NdE (50)		21	92	10
(6)			Me$_2$SiCp'$_2$NdE (50)		21	95	132
			Cp*$_2$SmE (50)		21	95	74
(7)			Cp*$_2$SmE (50)		21	93	55
(8)			Cp*$_2$SmE (50)		21	88	5

† Key: Cp*$_2$SmE, (Me$_5$C$_5$)$_2$SmCH(SiMe$_3$)$_2$; Cp*$_2$LuE, (Me$_5$C$_5$)$_2$LuCH(SiMe$_3$)$_2$; Me$_2$SiCp'$_2$NdE, Me$_2$Si(Me$_4$C$_5$)$_2$NdCH(SiMe$_3$)$_2$.

(Me$_5$C$_5$)$_2$LaE(SiMe$_3$)$_2$, E = CH, N at 60 °C (TOF = 140 h^{-1}). Methyl substitution at the internal carbon atoms enhances the reaction. Similar to the cyclization of aminoalkynes the formation of five-membered rings is faster than that of six-membered rings which, in turn, is faster than the formation of seven-membered rings.

f. Tandem Cyclization Reactions of Aminoalkynes and -alkenes

Especially interesting substrates for cyclization experiments with lanthanide metals are secondary amines containing two tethered alkene or alkyne functionalities HN{(CH$_2$)$_x$CH=CH$_2$}$_z${(CH)$_y$C≡CH}$_{2-z}$ (x = 1, 3; y = 1, 3, 4; z = 1, 2). This substrate not only allows a direct comparison of cyclization rates of aminoalkenes and aminoalkynes, but also expands the scope to subsequent C−C-bond-forming steps in tandem reactions. As expected from the cyclization rates of the monounsaturated derivatives, the cyclization of aminoalkynes by lanthanide complexes is preferred relative to the cyclization of aminoalkenes (Table 11). Intramolecular competition experiments with substrates containing both a 4-alkyne and a 4-alkene functionality confirm that the alkyne group reacts much faster than the alkene group. Although usually not observed with lanthanide complexes, a catalytic double-bond migration was observed in one instance (entry 3).

Interestingly, the hydroamination can be coupled to a C−C-bond-forming step if a double or triple bond is suitably located in the starting material (Scheme 40).[193] In general, the products obtained are bicyclic amines containing the pyrrolizidine and indolizidine skeleton (entries 4−8). For tandem cyclization, all three combinations alkyne/alkyne, alkyne/alkene, and alkene/alkene can be used. (Me$_5$C$_5$)$_2$SmCH(SiMe$_3$)$_2$ or Me$_2$Si(Me$_4$C$_5$)$_2$NdCH(SiMe$_3$)$_2$ have been employed as catalysts and turnover numbers up to TON = 777 h^{-1} (21 °C) have been achieved. Although the alkyne normally reacts much faster than the alkene, resulting in an endocyclic double bond (entry 4), the lengths of the tethers can reverse the reactivity of alkene and alkyne, giving an exocyclic double

Scheme 40. Tandem Hydroamination−Olefin Insertion Process

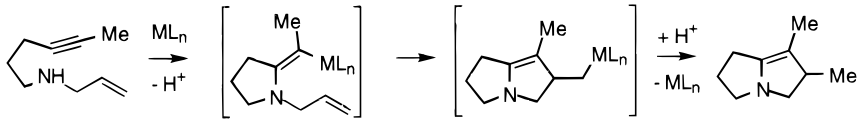
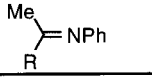
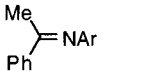
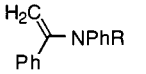
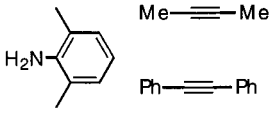
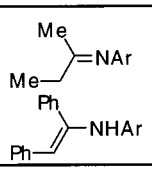
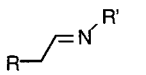
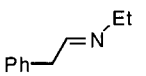
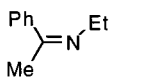
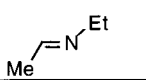
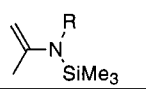
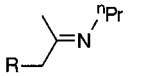
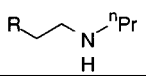
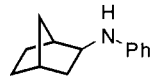


Table 12. Catalytic Intermolecular Hydroaminations of Alkynes and Alkenes†

Educts	Catalyst (s/c)	Product	Temp. /°C	Time	Yield[a] /%	TOF /h^{-1}	Ref.
Ph-NH_2 R−≡ R=^{n}Hex R=^{n}Bu R=^{n}Pr	$HgCl_2$ (20)		RT	6h	69 67 55	—	197
Ph-NH_2 Ph−≡ 2-MeC_6H_4-NH_2 2-$MeOC_6H_4$-NH_2 4-ClC_6H_4-NH_2	$Tl(OAc)_3$ (50)		60	7h	62 90 30 44	—	32
Ph-NHR R=Me Ph−≡ R=Et R=Me R=Et	$HgCl_2$ (20) $Tl(OAc)_3$ (50)		60 60 60 60	1h 1h 7h 7h	54 39 32 64	— — — —	197 32
	$Cp_2Zr(NHAr)_2$ (33)		110 110	— —	— —	0.04 0.2	102 102
R'-NH_2, R'=Me, Et R−≡ R=SiMe$_3$ R=^{n}Bu R=^{t}Bu	$Cp^*_2UMe_2$ (420)		80	1d	95 70-95 95	—	104
Et-NH_2 Ph−≡	$Cp^*_2UMe_2$ (420)		80	1d	50	—	104
Et-NH_2 Ph−≡	$Cp^*_2ThMe_2$ (420)		80	1d	33	—	104
Et-NH_2 C_2H_2	$Cp^*_2ThMe_2$ (420)		80	1d	80	—	104
^{n}Pr-NH_2 Me_3Si−≡−Me ^{n}Bu-NH_2 ^{i}Bu-NH_2	$Me_2SiCp'_2NdE$		60 60 60	— — —	(90) (62) (90)	14 13 10	198 198 198
^{n}Pr-NH_2 R−≡−Me R=Ph R=Me	$Me_2SiCp'_2NdE$		60 60	— —	(85) (91)	2 1	198
^{n}Pr-NH_2 R= R=SiMe$_3$ R=^{n}Pr	$Me_2SiCp'_2NdE$		60 60	— —	(93) (90)	2 0.4	198
Ph-NH_2 	$Ir(PEt_3)_2(C_2H_4)_2Cl$ (10), $ZnCl_2$ $[RhCl(PEt_3)_2]_2$ (10), PhNHLi		66 70	3d 7-12d	— 5-15	— —	120 177,178
$C_5H_{10}NH$ C_2H_4 Me_2NH C_4H_8NH	$RhCl_3·3H_2O$ (100)	$C_5H_{10}N$-Et Me_2N-Et C_4H_8N-Et	200	3h	70 54 36	—	199

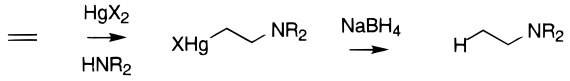
† Key: $Me_2SiCp'_2NdE$, $Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$; $C_5H_{10}NH$, piperidine; C_4H_8NH, pyrrolidine. [a] Yields in brackets are percent conversion.

bond (entry 5). Using two alkyne units, two regions of heterocyclic unsaturation can be introduced (entry 6). If two alkene units are employed, the bicyclic product will be a saturated pyrrolizidine or indolizidine (entries 7 and 8).

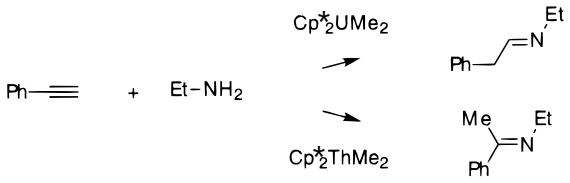
g. Intermolecular Hydroamination Reactions

The catalytic cyclization of aminoalkenes and -alkynes has been achieved using a variety of catalysts and provides some important classes of nitrogen-containing heterocycles. In contrast, realization of intermolecular hydroaminations of alkenes and alkynes is much more difficult. One of the most established method for aminating alkenes and alkynes is through stoichiometric use of Hg^{II} reagents.[33,194] The intermediate organomercurials formed usually are reduced to release the hydroaminated product (Scheme 41).[32,195,196] If appropriate reaction condi-

Scheme 41. Hydroamination of Alkenes via the Aminomercuration/Reduction Sequence



Scheme 42. Regioselectivity of Organoactinide-Catalyzed Hydroamination of Alkynes



tions are chosen, alkynes can be aminated catalytically, although catalytic efficiency remains low (TON = 3) (Table 12).[32,197] By using $HgCl_2$, primary and secondary aromatic amines can be reacted with terminal alkynes in Markovnikov fashion to give imines and enamines, respectively. The reaction is relatively slow requiring 1−6 h at 60 °C; yields are ∼60%. The mercury can be replaced by $Tl(OAc)_3$ with similar results. (TON = 6−45). For example, the reaction of phenylacetylene with an excess of aniline in the presence of $Tl(OAc)_3$ leads to the catalytic formation of the corresponding imine in 62% yield.

Examples of the intermolecular hydroamination of alkynes with late transition metals other than mercury are rare. In principle, the reaction has been realized with zirconium, lanthanide, and actinide complexes (Table 12). Internal alkynes have been hydroaminated by Bergman et. al. using zirconocene bisamides $Cp_2Zr(NHR)_2$ as catalysts.[102] Primary aromatic amines react with 2-butyne to yield *N*-substituted 2-iminobutane and with diphenylacetylene to give *N*-substituted 1,2-diphenyl-1-aminoethene. The latter is expected to isomerize to the corresponding imine, but conjugation of the double bond with the phenyl groups stabilizes its position in the enamine. Turnover frequencies are below 0.2 h^{-1}, even when the reaction is performed in refluxing toluene. The imido zirconium hydroamination cannot be extended to alkenes and is not compatible with most functional groups except ethers.

Terminal alkynes have been reacted with primary alkylamines using $Cp^*_2UMe_2$ as catalyst.[104] The reaction allows relatively low concentrations of catalyst (s/c = 420) to be used and gives yields up to 95%. When the corresponding thorium complex $Cp^*_2ThMe_2$ is used, the regioselectivity of the addition of phenyl acetylene is unexpectedly reversed, yielding 1-phenyl instead of 2-phenyl iminoethane (Scheme 42). However, thorium complexes generally give lower yields than uranium catalysts.

The intramolecular cyclization reactions catalyzed by lanthanide complexes can be extended to intermolecular hydroamination reactions.[198] Electron-rich internal alkynes react with primary amines under the catalytic influence of $Me_2SiCp'_2NdCH(SiMe_3)_2$. 2-Butyne and 1-phenylpropyne react with alkylamine to give an intermediate enamine and, after tautomerization, 2-iminobutane and 2-imino-1-phenylpropane, respectively. In contrast a 1,3 trimethylsilyl shift is observed with $Me_3SiC{\equiv}CMe$ as substrate giving *N*-trimethylsilyl enamine (Scheme 43). The reaction can be extended to monosubstituted alkenes and 1,3-butadiene. Reactions are approximately 1000 times slower than their intramolecular analogues and turnover frequencies are low (TOF ≈ 1−10 h^{-1}).

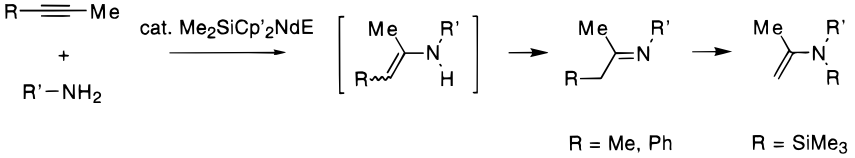
There are only a few reports of intermolecular hydroaminations of alkenes. The use of Rh^{III} and Ir^{III} salts was first reported by Coulson in 1971.[199] These salts allowed the addition of secondary aliphatic amines to ethylene. For example, piperidine was converted with $RhCl_3{\cdot}3H_2O$ to *N*-ethylpiperidine in 70% yield. High reaction temperatures and pressures are apparently essential. The reaction is strongly dependent upon the pK_a of the amine with other secondary amines reacting to a lower extent than piperidine. The homologues of ethylene are essentially unreactive. Another catalyst is the complex $[RhCl(C_2H_4)(C_5H_{10}NH)_2]$ which has been prepared by addition of piperidine to $[RhCl(C_2H_4)_2]_2$.[200] Both complexes catalyze the reaction of piperidine and ethylene and display a comparable activity. Intermolecular amination which proceed via a transition metal catalyzed N−H activation was accomplished with $[Ir(PEt_3)_2(C_2H_4)_2Cl]$ as precatalyst and the substrates aniline and norbornene.[120] Cis-addition of the N−H group across the double bond of norbornene yields the hydroamination product *exo*-2-(phenylamino)norbornane. Similar to the aforementioned reactions, low turnover numbers (TON = 2−6) and reaction rates (TOF < 0.1 h^{-1}, 66 °C) are observed.

The amination of the more reactive 1,3-butadiene has been investigated within the scope of telomerization reactions. With rhodium- and cobalt-based catalysts predominant formation of the 1:1 adduct is observed.[201] For example, the reaction of 1,3-butadiene and $H{-}N^nPr_2$ under catalysis of $RhCl_3/Et_3N$ gives $CH_3{-}CH{=}CH{-}CH_2{-}N^nPr_2$ in 62% yield.

IV. Summary and Conclusions

New methods for producing amines selectively in a catalytic manner from olefins are of fundamental importance in organic chemistry. Most of the methods developed for the *N*-alkylation of ammonia,

Scheme 43. Tautomerization Observed in the Organoactinide-Catalyzed Hydroamination of Alkynes (E = $CH(SiMe_3)_2$)



primary amines, or secondary amines use alkyl halides, aldehydes, ketones, and alcohols as alkylating agents. For a large number of commercially available amines, the direct amination of olefins in the presence of a suitable catalyst would be a superior route. In addition to economic advantages for raw materials, the direct amination of olefins is favorable due to atom efficiency. Although highly efficient catalytic procedures for amination of unsaturated compounds are not yet available, considerable progress using transition metal catalysts has been made. Here, the introduction of lanthanide complexes constitutes an important breakthrough.

Lanthanide complexes catalyze the regioselective cyclization of tethered aminoalkenes and -alkynes. In the presence of chiral ligands high diastereoselectivities (>95%) and enantioselectivities (up to 60% ee) have been achieved. Yields can be close to quantitative. However, the slow reaction rates for aminoalkenes (TOF 0.3−140 h^{-1}) are a drawback. Even lower turnover frequencies have been observed for intermolecular reactions. Organolanthanide complexes are extremely oxophilic which excludes many substrates for catalysis.[35] As in early-transition-metal chemistry, β-hydrogen elimination is a common decomposition pathway. This not only limits the choice of ligands, but also possible substrates for catalysis are restricted to molecules without coordination sites which might allow β-hydrogen elimination as an undesired side reaction.

Compared to rare-earth metal catalysts, transition metal catalyzed reactions have not been well-developed. Interestingly, the use of alkali-metal catalysts appears as a good route for the synthesis of a number of amines. In the presence of catalytic amounts of inexpensive strong bases, yields of the corresponding amine can be quantitative. The authors believe that this largely overseen methodology will be rediscovered and used for the synthesis of functionalized amines. As an example the synthesis of arylethylpiperazines was realized very recently.[138] However, the major drawback of this methodology, the substrate limitation to low molecular weight olefins (ethylene, propylene) and aromatic olefins, will be difficult to solve.

In contrast to the difficulties encountered with intermolecular hydroaminations, the catalytic intramolecular cyclization of aminoalkenes and -alkynes has been achieved using a variety of catalysts—especially palladium-based complexes—and provides cyclic amines and enamines. This cyclization reaction works well with aromatic and activated amines (amides, tosylamides, sulfonamides, and ureas) in terms of yield and selectivity. This methodology has been used to synthesize a variety of important classes of nitrogen-containing heterocycles. The results raise the interesting question of whether C−N fusions could be used in general to assemble complex polycyclic, heteroatom-containing skeletons (e.g., pyrrolizidines, indolizidines, and other alkaloid frameworks) in a single catalytic reaction. The main problem of the known transition metal catalyzed intramolecular aminations is clearly catalyst efficiency. To date, there is no general reaction known which proceeds with turnover number > 10 000, or turnover frequencies > 500 h^{-1}. However, these numbers are a prerequisite for industrial applications. Compared to other synthetic procedures, very few useful enantioselective aminations have been developed. The search for efficient enantioselective methods, especially for those which are catalytic and do not require the use of stoichiometric amounts of chiral auxiliaries, remains a challenging task for the future.

Regarding economical impact, linear amines are especially interesting for industrial applications. In this respect, fatty amines constitute an important challenge. Thus, the anti-Markovnikov addition which has been called one of the 10 most important targets for catalysis research[202] will continue to be one of the major goals for catalytic amination. Although there is no "real" example up to now of this type of catalytic reaction, we predict the development of a laboratory process in the next 10 years. Due to recent improvements[179] using aromatic olefins it is conceivable to foresee further improvements in this area.

V. Acknowledgments

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