Base-Catalyzed Hydroamination of Olefins: An Environmentally Friendly Route to Amines

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Dedicated to Roger A. Sheldon on the occasion of his 60th birthday.

Abstract: The base-catalyzed hydroamination of olefins offers a simple and elegant access to various primary, secondary, and tertiary amines. Particular focus is placed on developments in the area of hydroamination of non-activated olefins. Advantages and disadvantages of the methodology compared to other synthetic methods are presented. Special attention is paid to potential industrial applications of this chemistry.

Keywords: amination; amines; fine chemicals; homogeneous catalysis

1 Introduction: Hydroamination of Olefins – The Chemistry

The catalytic synthesis of organic building blocks from cheap and available starting materials is one of the main research targets of chemists, specifically in the field of applied organic and industrial chemistry. A majority of industrially important catalytic reactions involve transformation reactions of olefins exemplified by C–C or C–H bond forming reactions such as hydrogenations, hydroformylations, oligomerizations, telomerizations, and hydrocyanations. Apart from oxidation of olefins (C–O bond formation), reductive amination reactions and catalytic aminations of aryl halides (C–N bond formation), other catalytic carbon-heteroatom bond forming reactions are rarely used in industrial laboratories for a practical organic synthesis.

Amines and their derivatives are of great importance in almost all fields of chemistry, particularly as natural products, pharmaceuticals, as well as fine or bulk chemicals.[1] New methods for the selective synthesis of amines are therefore of fundamental importance. Hydroamination of olefins to organonitrogen compounds has been an imperative and demanding conversion in this regard. This process utilizes cheap and readily available feedstock of olefins and amines and proceeds theoretically with 100% atom efficiency, thus offering economic and environmental benefits compared to other classical organic synthetic methods. Table 1 shows a compilation of the most often applied methods for the synthesis of amines with regard to the atom efficiency of the method. In order to compare the methods more appropriately, the syntheses of aliphatic (ethylamines) and aromatic (phenylethylamines) amines are shown. So far, the nucleophilic substitution of organic halides by amines, azides, or cyanides constitutes an important reaction on the laboratory scale. Obviously these reactions suffer from the stoichiometric amount of salts produced. Here, in a number of cases, the unwanted salt is produced in larger amounts than the desired amine, even if the reaction proceeds with 100% yield! Hence the atom efficiency (AE) of these syntheses is relatively low (AE = 26–60%). Environmentally more benign routes for amines are the catalytic nucleophilic substitution of alcohols, the reductive amination of carbonyl compounds, and the hydrocyanation of olefins followed by reduction. With respect to atom efficiency, these methods have clear advantages (AE = 70–100%) compared to the former more traditional organic reactions. However, in some cases the availability of starting materials and the reaction conditions required cause problems. Obviously, the direct hydroamination or hydroaminomethylation of ubiquitously available olefins would be an elegant and simple approach to amines (AE = 77–100%).

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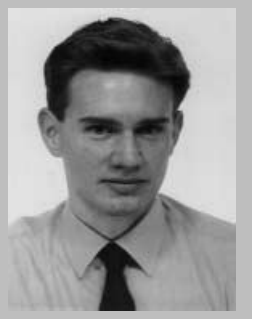
Matthias Beller, born 1962 in Gudensberg, Germany, studied chemistry at the university of Göttingen from 1982–1987 and obtained his doctorate (Dr. rer. nat.) in 1989 under the guidance of Prof. L. F. Tietze. After postdoctoral studies (1990) with Prof. K. B. Sharpless at Massachussetts Institute of Technology (USA) funded with a Liebig scholarship of the Verband der Chemischen Industrie, he became research chemist, then group and project leader in the Central Research of Hoechst AG in Frankfurt, Germany. From 1996 to 1998 he was Associate Professor for Inorganic Chemistry at the Technical University of Munich and since June 1998 he is Director of the "Institute for Organic Catalysis" (IfOK) at the university of Rostock aligned with a full professorship "Catalysis" at the University of Rostock. His research topics cover the development of practical catalytic methodologies. Special attention is given to selective and environmentally benign transformations. More specific he is interested in palladium-catalyzed coupling reactions, carbonylation reactions, catalytic amination of olefins and oxidations of olefins using air or molecular oxygen as final oxidant.



Christian G. Hartung was born in 1972 in Munich, Germany. After completing his degree studies in chemistry at the Technical University of Munich, he began his Ph. D. studies at the Institute for Organic Catalysis Research in Rostock under the supervision of Prof. M. Beller in 1999. Since January 2002 he is working as a postdoctoral fellow in Canada with Prof. V. Snieckus.

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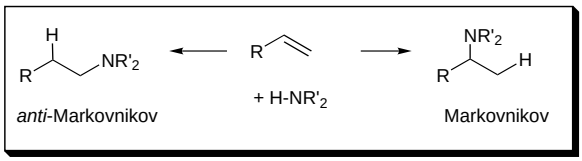
Hydroamination is the formal direct addition of an N–H bond to C–C multiple bonds. The reaction can also be regarded as alkylation of ammonia or primary and secondary amines with olefins or alkynes. In general, the direct addition of amines to olefins can lead to two regioisomeric amines, the Markovnikov and the *anti*-Markovnikov products (Scheme 1). The Markovnikov product is usually favored in the presence of Brønsted or Lewis acid catalysts (e.g., zeolites) in the case of aliphatic as well as most of the aromatic olefins because of the higher stability of the intermediate carbocation.



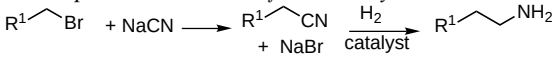
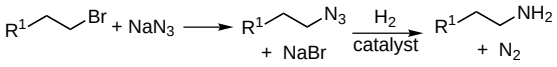
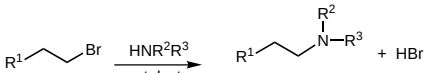
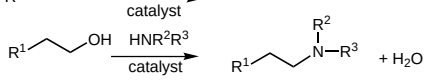
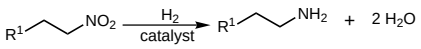
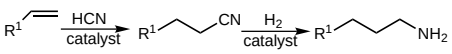
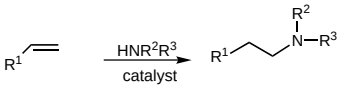
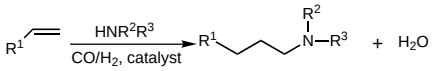
Scheme 1. Hydroamination of olefins.

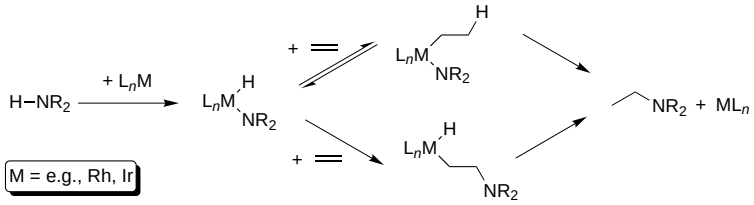
Unfortunately, there are several thermodynamic and kinetic aspects that restrain the direct nucleophilic addition of amines across C–C multiple bonds:[2]

- The nucleophilic attack of the amine nitrogen, bearing the lone pair, on the electron-rich non-activated multiple bonds leads to electrostatic repulsion.
- The high energy difference between π (C=C) and σ (N–H) orbitals forbids a thermal [2 + 2] cycloaddition of the N–H bond and the alkene.
- The hydroamination reaction is only slightly exothermic or even thermoneutral.
- Because of the highly negative reaction entropy, the reaction is not favored at high temperatures.

Thus, the direct nucleophilic addition of amines proceeds easily only to electron-deficient (activated) π-

Table 1. Comparison of various routes to amines.

Reaction	Atom efficiency (%) = 100 × M_w of amination product/ΣM_w of products R^1 = H, R^2, R^3 = H	R^1 = Ph, R^2, R^3 = H
Nucleophilic substitution followed by reduction		
	30	54
	26	48
Amination of organic halides or alcohols		
	36	60
	71	87
Reductive amination of carbonyl compounds		
	71	87
Reduction of nitro compounds		
	56	77
Hydrocyanation of olefins followed by reduction		
	100	100
Hydroamination of olefins		
	100	100
Hydroaminomethylation of olefins		
	77	88

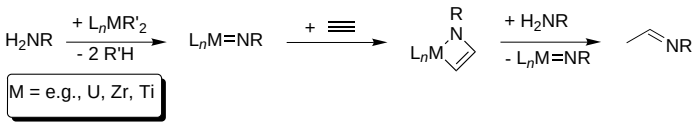


Scheme 2. Catalytic hydroamination of olefins *via* oxidative addition of the amine to a transition metal.

systems containing neighboring functional groups, such as keto, ester, nitrile, sulfoxide, or nitro, usually leading to the *anti*-Markovnikov products.[3] Consequently, practical methods for the direct transformation of unfunctionalized olefins to amines, particularly to industrially important linear *anti*-Markovnikov amines are rare. Catalysis is obligatory for this conversion and hence the functionalization of olefins with *anti*-Markovnikov regioselectivity is viewed as one of the major challenges of catalysis.[4] Active research work in this field for the past years shows possibilities of a few catalytic routes for this transformation.[5]

For instance, the amine can be activated by oxidative addition to a transition metal,[6] which allows insertion of the alkene into the M–N or M–H bond, thereby promoting the hydroamination catalytically (Scheme 2).[7]

Actinides[8] and early transition metal complexes[9] can activate the amine by converting it into the coordinated imide M=NR and enable the reaction of C–C multiple bonds with the M–N bond (Scheme 3).



Scheme 3. Catalytic hydroamination of alkynes *via* metal imide species.

Additionally, strong bases or strongly electropositive metals like alkali,[5,10] alkaline earth, or the lanthanide group elements,[11] can deprotonate amines to give more nucleophilic amides, which can undergo addition to certain olefins (Scheme 4).

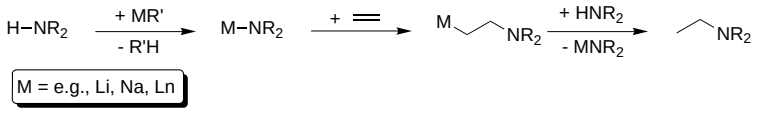
In addition to the activation of the amino group, C–C multiple bonds can also be activated towards hydroamination by late transition metals.[12] Here, the nucleophilic attack of amines on the unsaturated C–C bond is facilitated by coordination of the olefin (alkyne) to an electrophilic transition metal center: β-hydride elimination from the resulting 2-aminoalkylmetal complex leads to the oxidative amination product and protonolysis leads to the hydroamination product (Scheme 5).

2 Is this Reaction of Potential Use for Industry?

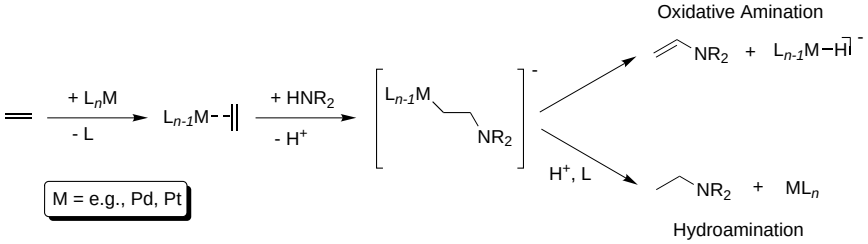
The successful intra- and intermolecular hydroamination of alkenes and alkynes using various catalysts such as alkali metals,[10] transition metals,[6,9,12] as well as f-block elements[8,11] reveals the feasibility of different catalytic routes for the synthesis of a variety of important amino compounds. However, a closer look to the known hydroamination reactions discloses significant problems of these catalytic methods on a large scale. Obviously, when talking about industrial processes, important factors that determine the possibility for application are costs of substrates and catalysts, atom efficiency (waste production), and process economics. Since the hydroamination of olefins proceeds with 100% atom efficiency, and olefins and amines are most often economically advantageous compared to other starting materials, for a certain amine product, the main cost-determining issues are catalyst costs and process economics. To the best of our knowledge, there is no catalytic intermolecular hydroamination of olefins known which proceeds with catalyst turnover numbers (TON) >500. However, a prerequisite for the application of expensive late transition metal or lanthanide complexes in the fine chemical industry is a catalyst turnover number of at least 1,000. In addition, catalyst turnover frequencies (TOF) of known intermolecular hydroamination reactions are often in the range of 5–50 h^{-1}. In order to be practical, TOF's should be >200 h^{-1}. Hence, considerable improvements are desirable to make late transition metals or special lanthanide complexes applicable on a large scale.

An important advantage of base-catalyzed hydroamination reactions is the lower price of alkali metal derivatives compared to transition metals. Generally alkyllithium reagents, lithium and sodium amides, NaH, and KO-*t*-Bu are used as catalysts. However, base-catalyzed hydroaminations often proceed (although less studied) in the presence of simple alkali metals. Here, sodium and lithium are the reagents of choice with respect to the price. Due to the low price of alkali metals, reactions with catalyst concentration of *ca.* 1 mol % might be feasible on a larger scale. Scheme 6 presents a rough comparison of the feedstock costs of the model reaction of 1,3-butadiene with diethylamine in the presence of 1 mol % Na and 1 mol % Pd.

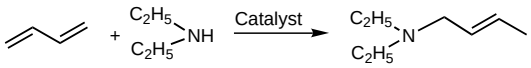
Estimating a 100% yield of the hydroamination reaction, one has raw material costs of butadiene and diethylamine of approximately 95 c/kg of amination product. Costs of the base catalyst (1 mol %) would be 4 c/kg of amination product and 11.8 Euro/kg amination



Scheme 4. Base-catalyzed amination of olefins *via* metal amide species.



Scheme 5. Amination *via* activation of olefins.



1,3-butadiene: 35 c/kg (= 15 c/kg amination product)

diethylamine: 1.4 Euro/kg (= 80 c/kg amination product)

1 mol % Na: 4 c/kg amination product

1 mol % $PdCl_2$: 11.8 Euro/kg amination product (Pd price: February 2002).

Scheme 6. Estimation of raw material costs for the hydroamination of 1,3-butadiene with diethylamine.

product in case of a Pd catalyst (1 mol %). In case of the palladium catalyst there are no ligand costs included.

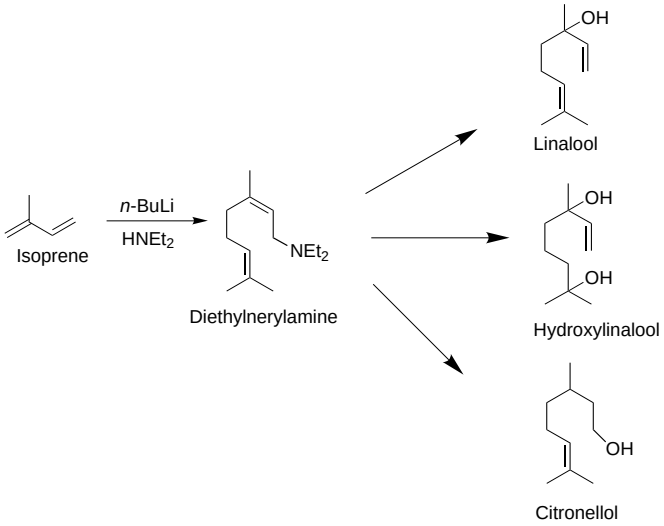
Obviously, the late transition metal-catalyzed reaction must be significantly higher in yield, and an effective recycling of Pd must exist in order to be competitive to the base-catalyzed variant.

Similar price considerations are also possible in the case of hydroamination of alkynes. However, one has to keep in mind, that most alkynes are much more expensive compared to olefins. Hence, in a number of cases the alkyne will be the cost-determining factor.

The feasibility of base-catalyzed hydroaminations on an industrial scale is demonstrated by the Takasago process for (−)-menthol [in 1996 more than 2000 tons of (−)-menthol and other terpenes were produced]. The key intermediates of the process, *N,N*-diethylgeranylamine and *N,N*-diethylnerylamine, are synthesized in high yields from myrcene or isoprene, respectively, by treatment with diethylamine and a catalytic quantity (1 mol %) of lithium diethylamide (Scheme 7).[13]

The amination of isoprene to *N,N*-diethylnerylamine (telomerization) using *n*-BuLi or PhLi catalysts is also an important step in the synthesis of other industrially important acyclic monoterpenes[14] such as linalool, hydroxylinalool, and citronellol (Scheme 8).

In addition to these reactions, the base-catalyzed hydroamination of simple styrene derivatives and 1,3-butadiene with primary and secondary amines ought be industrially feasible due to the availability of the starting materials and the simplicity of the catalytic reaction.



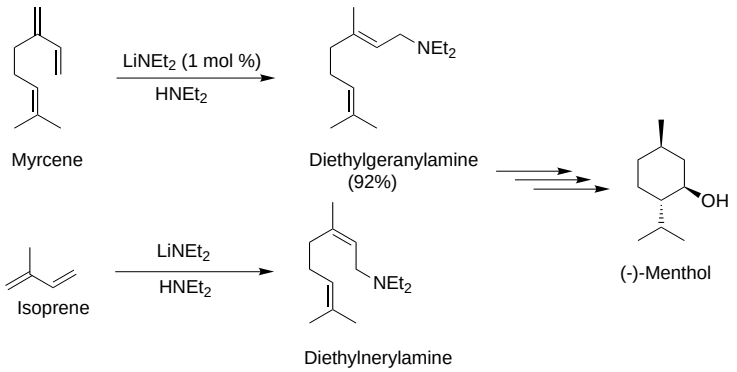
Scheme 8. Base-catalyzed telomerization of isoprene with amines.

Especially new β-arylethylamines and amphetamines are easily accessible by the base-catalyzed *anti*-Markovnikov hydroamination of the corresponding styrene derivatives. Due to various pharmaceutical activities of this class of compounds (Scheme 9) there is a high prospect for future applications.

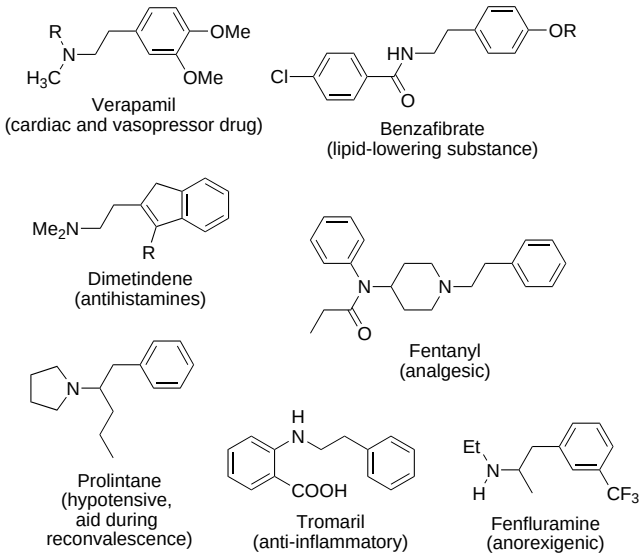
In order to apply base-catalyzed hydroaminations to other olefins apart from 1,3-dienes and styrenes, further improvements of the method have to be made. Although it is possible to hydroaminate simple aliphatic olefins such as ethylene and propylene as well as sterically hindered olefins like norbornene, the reactions proceed under more drastic conditions and are not as general as the amination of 1,3-dienes and styrenes.

3 Base-Catalyzed Amination: How does it Work?

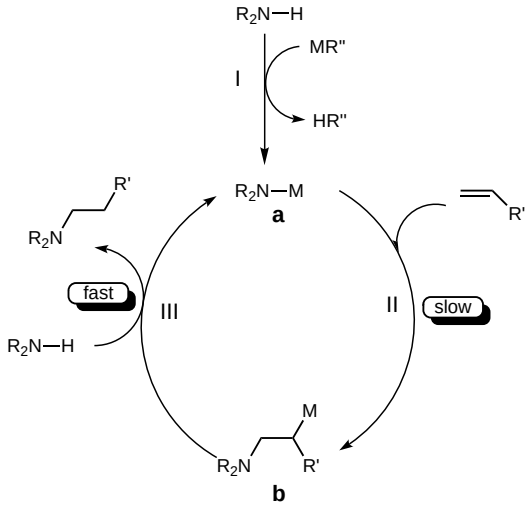
The simplified catalytic cycle for the base-catalyzed hydroamination is shown in Scheme 10. Alkali metals,



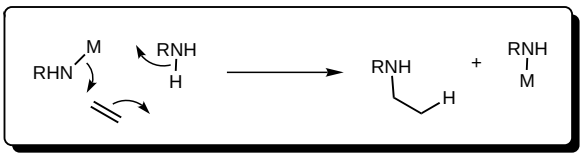
Scheme 7. Takasago (−)-menthol process.



Scheme 9. A selection of pharmaceutically important β-arylethylamines.



Scheme 10. Catalytic cycle for the base-catalyzed hydroamination of olefins.



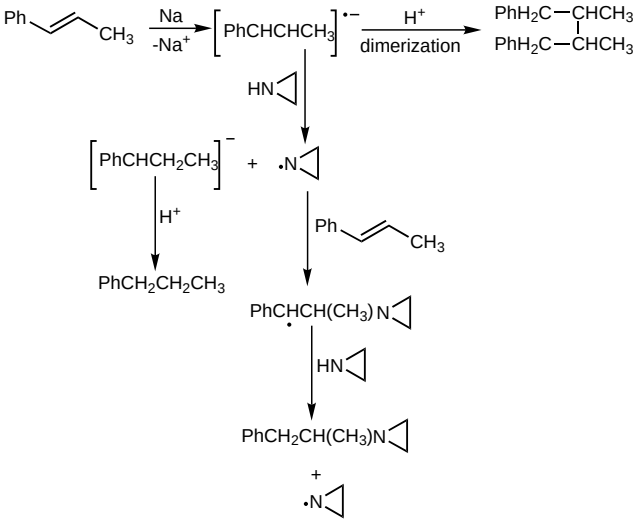
Scheme 11. Concerted base-catalyzed hydroamination mechanism.

their alkyl and aryl salts, hydrides as well as the appropriate amides deprotonate the reacting amine to give strongly nucleophilic metal amides (step I), which can add to the olefin more easily.

Nevertheless, the activation energy for this step (step II) is high due to the unfavorable interaction between the nitrogen lone pair and the π-system of the alkene and also due to the weak coordinative interactions between non-functionalized alkenes and the alkali metal ions.[15] The resulting polar 2-aminoalkyl metal complexes (**b**), which have a distinct carbanion character, are highly reactive and form the product immediately upon protonation in the surplus of the starting amine regenerating the metal amide (step III). Depending on the reaction conditions this step is reversible. A concerted hydroamination process as shown in Scheme 11 is also likely.[16]

The amination is strongly dependent on the pK_a of the amine used; in general, the greater the pK_a, the lower is the temperature required for the amination reaction.[16] This is because of the higher basicity or nucleophilicity of the metal amide complex (**a**) (Scheme 10) participating in the nucleophilic addition (step II). Kinetic studies on the reaction of ethylene[15] with diethylamine show that the hydroamination reaction rate is first order with respect to the concentrations of both olefin and the catalyst and zero order with respect to the concentration of amine, indicating the nucleophilic addition of the metal amide to the olefin as the rate-determining step (step II). Thus, the most favorable conditions for the hydroamination are high concentrations of catalyst and olefin, low acidity or high pK_a of the amine and high nucleophilicity of the metal amide complex which can be achieved by choosing suitable metal precursors,[15] solvents,[15] and certain additives.[17]

Apart from the ionic mechanism described above, an alternative radical mechanism was proposed for certain hydroamination reactions (Scheme 12). It has been argued that if the addition proceeds by an ionic mechanism, the reaction between *p*-methoxystyrene with aziridine should give the Markovnikov product predominantly; instead, the reaction yielded the *anti*-



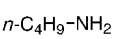
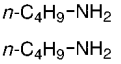
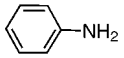
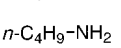
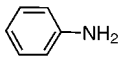
Scheme 12. Radical mechanism for the base-catalyzed hydroamination of β-methylstyrene with aziridine.

Markovnikov product without even traces of the former.[18] The radical mechanism was supported by the detection of propylbenzene in the reaction between β-methylstyrene and aziridine in the presence of metallic Na as the catalyst.

4 Hydroamination of Aliphatic Olefins

The base-catalyzed hydroamination of aliphatic olefins is summarized in Table 2. This reaction was initially described during late 1940's when a number of patents

Table 2. Alkali metal-catalyzed amination of aliphatic monoolefins.

Olefin	Amine	Catalyst	Temperature [°C]	Pressure [bar]	Amine Yield [%]			TON	TOF [h^{-1}]	Ref.
					primary	secondary	tertiary			
	NH_3	Na	175 – 200	800 – 1000	26	26	14	9	1	[20]
	NH_3	$CsNH_2/RbNH_2$	101	90 – 110	28 – 34	2 – 3	1 – 2	3	1 – 3	[15]
		Na, Pyridine	100	28 – 38	–	–	77 – 83	17	5	[21]
		Na, Pyridine	100	41 – 55	–	–	80	25	8.3	[16]
		Na	200	800 – 1000	–	–	75	2	–	[20]
		$LiNEt_2$/TMEDA	130 – 150	150 – 250	–	54	45	56	1.5	[17]
		Na/NaH	225	1000	–	–	28	< 1	–	[20]
		$LiNEt_2$/TMEDA	140	70	–	–	83	14	1	[17]
		$NaNH_2$	275	41 – 55	–	75	2	10	2	[16]
	NH_3	Na	250	800 – 950	82	8	–	12	0.65	[20]
		Na	250	860 – 1000	–	36	–	1	0.06	[20]
		$LiNEt_2$/TMEDA	150 – 170	70 – 90	–	–	10[a]	8	0.3	[17]
		$NaNH_2$	330	50	–	6	–	0.8	2	[16]
	NH_3	Na	~250	800 – 950	–	–	32	5	0.25	[20]
	NH_3	Na	~250	880 – 950	12	–	–	< 1	0.04	[20]
		$NaNH_2$	225	–	–	–	9	0.18	0.02	[20]
	NH_3	Na	250	800 – 950	17	–	–	< 1	0.02	[20]
	NH_3	$NaNH_2$	200	8500	16	–	–	0.63	0.03	[20]
		$LiNEt_2$/TMEDA	140 – 150	–	–	–	17[a]	–	–	[17]
		*n*-BuLi/TMEDA	150	–	–	–	75	3	0.15	[26]
		$LiNEt_2$/TMEDA	150	–	–	–	18[b]	3	0.23	[17]
		*n*-BuLi/KO-*t*-Bu	120	–	–	–	45[b]	4.5	0.23	[27]

[a] Conversion.
[b] Monohydroamination product.

reported the reactions of olefins, 1,3-dienes, vinyl and allyl compounds with amines using alkali metals or their amides.[19] The first well recognized process was reported by Howk et al.[20] in 1954. In this process, ammonia adds to ethylene in the presence of metallic sodium at 175 – 200 °C and 800 – 1000 bar pressure in inert hydrocarbon medium forming almost equimolar amounts of ethyl-, diethyl-, and triethylamine with a total yield of 70%. Sodium is found to be converted quantitatively to sodium amide after the reaction. Other alkali metal catalysts such as Li, K, NaH, and LiH were also equally active. High reaction pressures and temperatures are apparently essential here; for instance, only 0.7% conversion of ammonia is achieved at 205 bar. The selectivity of primary, secondary, and tertiary amines is strongly dependent on the ratio of ammonia to ethylene. For example, at higher pressures of ammonia, only ethylamine and diethylamine are formed in a ratio of 5:1. Under similar conditions, other primary or secondary amines also react with ethylene. For example, *n*-butylamine reacts with ethylene giving diethyl-*n*-butylamine (yield = 75%), in addition to some high-boiling nitrogen-containing materials. At temperatures below 200 °C, only the secondary product ethyl-*n*-butylamine is formed though in poor yields. Ethylenediamine yields a mixture of its di-, tri-, and tetraethylamines in equimolar amounts. Piperidine on reaction with ethylene (at 100 °C and 38 bar) forms *N*-ethylpiperidine in good yield (~80%)[16,21] using metallic sodium in the presence of traces of pyridine or by using $C_5H_{10}NLi$ as the precatalyst (90% yield).[2a] Similarly, aniline is converted to *N*-ethylaniline using Na or $NaNH_2$ as precatalyst at 250 – 300 °C and 50 – 200 bar pressure.[16,22]

The reaction temperature and pressure for the amination of ethylene can be considerably lowered by using alkali metal amides[15,16,23] and supported alkali metals as catalysts.[24] Since they operate at low temperatures these catalysts are particularly useful for the selective formation of monoalkylated amines. Thus, ethylene reacts with ammonia at 80 – 110 °C and 90 – 120 bar in the presence of catalytic amounts of cesium or rubidium amides forming moderate yields (28 – 34%) of ethylamine. Sodium and potassium amide catalysts give poorer yields for this reaction owing to their low solubility in liquid ammonia, but the eutectic mixture containing KNH_2/2 $NaNH_2$ which melts at ~92 °C is more active (27% yield).[15]

Apart from inorganic alkali or alkaline earth metal amides derived from ammonia, organic amides derived from an amine, which is not considerably more acidic than the amine to be alkylated, can also be used as catalysts.[16] In general, the order of increasing basicity of amines is aromatic amines < ammonia < aliphatic amines. For instance, in the ethylation of piperidine the more basic amide Me_2NLi can be used as precatalyst, but the less basic Ph_2NLi remains inactive.[25]

It has been shown that additives such as *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) increase the rate of addition of primary and secondary amines to olefins using catalytic amounts of alkyllithium under much lower reaction pressure and temperature than that needed for the metallic sodium catalysts.[17] For example, ethylene reacts with diethylamine in the presence of the $LiNEt_2$/TMEDA catalyst system at 70 bar and 140 °C forming triethylamine in 83% yield. However the same reaction in the presence of Na or NaH as catalyst requires 1000 bar pressure and 225 °C to achieve 28% yield. Kinetic studies in the presence of TMEDA showed a first-order dependence of the reaction rate with respect to ethylene and zero-order dependence with respect to diethylamine (Equation 1). This strongly supports the formation of $[Li(TMEDA)_n^+ C_2H_4NEt_2^-]$ by nucleophilic attack of the $Li(TMEDA)_n^+ Et_2N^-$ on ethylene as the rate-determining step.[15] The apparent role of TMEDA is to form a highly nucleophilic (monomeric) lithium diethylamide complex due to its polarizing effect on the $Li^+ Et_2N^-$ ion pair. Once formed, this intermediate reacts more rapidly with ethylene. Subsequent protonation by the comparatively more acidic diethylamine leads to triethylamine.

$$\frac{d[Et_3N]}{dt} = k[Et_2NH]^0[C_2H_4]^{\sim 1}[Et_2NLi]^{\sim 1} \qquad (1)$$

The Arrhenius activation energy of the nucleophilic attack is calculated to be at least 50 kJ/mol. Potassium and sodium diethylamides have an even higher initial catalytic activity than that of the $LiNEt_2$/TMEDA catalyst system, since they exist as more solvent-separated ion pairs.[15] But the rate decreases considerably after 25% conversion of the diethylamine due to decomposition of the active catalytic species.

A beneficial effect of TMEDA has also been shown for other base-catalyzed aminations, e.g., the reaction between *n*-butylamine and ethylene works at a pressure of 250 – 150 bar and 130 – 150 °C using LiC_2H_5/TMEDA as the catalyst yielding 54% of ethyl-*n*-butylamine and 45% of diethyl-*n*-butylamine. Under similar conditions dimethylamine adds to propene forming dimethylisopropylamine. This catalyst system is also active for the addition of diethylamine to less reactive cycloolefins containing strained double bonds, for example, norbornene (17% conversion at 140 – 150 °C) and norbornadiene (18% yield of corresponding monohydroamination product). In a recent study by us, a similar catalyst system consisting of *n*-BuLi and TMEDA was found to be active for the hydroamination of norbornene with piperidine forming *N*-norbornylpiperidine (75% yield at 150 °C).[26] Similarly, the hydroamination of norbornadiene with morpholine in the presence of the catalyst system *n*-BuLi/KO-*t*-Bu yields 45% of the monohydroamination product.[27]

So far, other olefins like propylene, isobutylene, 2-butene, 1-hexene, and cyclohexene have been found to form the

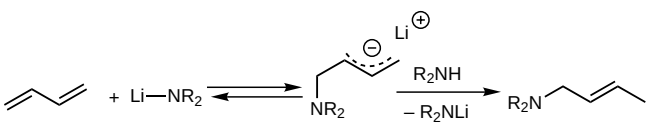
corresponding Markovnikov amination products in very low yield.[20] When higher olefins are reacted with amines, disproportionation of the amine is observed. For example, the amination of propene with *n*-butylamine yields *n*-butylisopropylamine as the major product (36% conversion) along with a small amount of di-*n*-butylamine.

5 Hydroamination of 1,3-Dienes

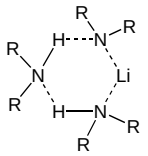
Nucleophilic addition of amines to 1,3-dienes primarily leads to the 1,4-addition products (Table 3). The precatalysts employed include metallic sodium, sodium naphthylide (Na_2Np), and alkyllithium salts. In 1950, Hyre et al. reported the hydroamination of 1,3-butadiene with aniline in the presence of metallic sodium at 120 °C to form *N*-crotylaniline in 79% yield.[28]

As in the case of aliphatic olefins, alkali metal amide catalysts derived *in situ* from Na_2Np[29] and *sec*-BuLi[23] are more active than metallic sodium and are effective at much lower temperatures. For instance, piperidine and diethylamine react with 1,3-butadiene at room temperature to 50 °C in the presence of catalytic amounts of *sec*-BuLi or Na_2Np forming *N*-2-butenylpiperidine and 1-diethylaminobut-2-ene (> 80% yields). For the reaction of secondary amines with 1,3-butadiene using BuLi, the stereochemistry of the products varied from predominantly *E* to nearly exclusively *Z* depending on the structure of the amine used and the solvent employed. In cyclohexane as the solvent, the *E*:*Z* ratio was 63:36 in the case of piperidine, 80:20 for 2,6-dimethylpiperidine, and 20:79 for diethylamine.[23] Imai et al.[30] observed almost stereospecific formation of the *Z*-isomer (1-diethylamino-*cis*-but-2-ene) (98–99%). In tetrahydrofuran, both piperidine and diethylamine yielded 99% of the *E*-isomer, presumably due to the higher solubility of the corresponding amides in THF.[23] Similarly, for the reaction of di-*iso*-propyl- and di-*n*-propylamine with 1,3-butadiene the *E* to *Z* ratios were 45:55 and 12:87 with total yields of 9% and 86%, respectively.[31] However, the *E* to *Z* ratios for di-*iso*-butyl- and di-*n*-butylamine are 22:78 and 14:86 with good overall yields of amines (84% and 75%, respectively). Similar to ethylene, the rate of the reaction was found to vary linearly with respect to the concentration of 1,3-butadiene and lithium alkylamide.[31]

It is interesting to note that no addition of lithium alkylamide to 1,3-butadiene takes place in the absence of free dialkylamine in the reaction mixture, demonstrating the reversible formation of the corresponding allyl anion (Scheme 13).



Scheme 13. Reversible formation of the allyl anion.



Scheme 14. The proposed active catalytic species.

Spectroscopic studies indicate a plausible formation of a lithium dialkylamide-dialkylamine complex as the active catalytic species (Scheme 14).

Isoprene reacts with secondary amines in the presence of base catalysts generally forming 3-methyl-2-butenylamines. For instance, diethylamine and piperidine react with isoprene in the presence of catalytic amounts of *sec*-BuLi forming 3-methyl-2-butenyldiethylamine (57% yield) and 3-methyl-2-butenylpiperidine (76% yield), respectively.[23] Depending on the reaction conditions other regioisomers are also formed as byproducts. However, aniline reacts with isoprene in the presence of sodium leading to the formation of *N*-(3-methyl-3-butenyl)aniline in only 29% yield.[28,32]

As discussed before, diethylamine adds to myrcene in the presence of catalytic amounts of Na_2Np (55–94%)[29] or Li/*n*-BuLi at 55 °C (74–76%) affording *N,N*-diethylgeranylamine, which is an important intermediate for the synthesis of a number of industrially important acyclic monoterpenes.[33] Under similar conditions, di-*n*-propylamine forms *N,N*-di-*n*-propylgeranylamine (80% yield).

A special type of base-catalyzed amination of 1,3-dienes is the telomerization of butadiene and isoprene with amines in the presence of base. Metallic lithium, sodium, or potassium and *n*-BuLi were used as precatalysts.[14c,34] Here, two or more molecules of the diene react with one molecule of the amine to give the corresponding telomers. For example, the reaction of 1,3-butadiene and isoprene with diethylamine in the presence of *n*-BuLi yields the corresponding telomers (n = 2) *N,N*-diethyl(octa-*cis*-2,6-dienyl)amine (23% yield at 50 °C) and *N,N*-diethyl(3,7-dimethylocta-*cis*-2,6-dienyl)amine (*N,N*-diethylnerylamine, 17% yield at 65 °C) along with *N,N*-diethyl(but-2-enyl)amine (51% yield) and *N,N*-diethyl-(3-methylbut-2-enyl)amine (71% yield), respectively.[34] However, for a similar reaction of 1,3-butadiene and isoprene with diethylamine using Na as the catalyst, the corresponding telomers (n = 2) are formed in poor yields (2% for 1,3-butadiene and 3% for isoprene).[34]

6 Hydroamination of Aryl Olefins

Similar to 1,3-dienes, aryl olefins react readily with sufficiently nucleophilic amines in the presence of alkali metal catalysts forming 1-amino-2-arylethanes. The precatalysts used include metallic sodium, CsOH, and

Table 3. Alkali metal-catalyzed amination of 1,3-dienes.

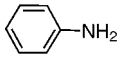
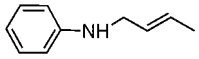
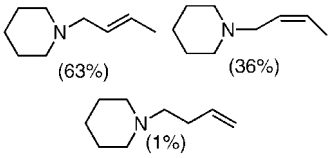
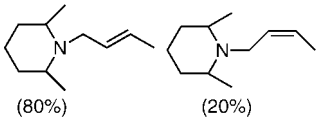
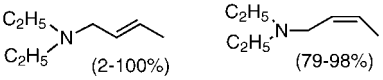
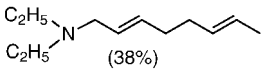
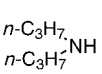
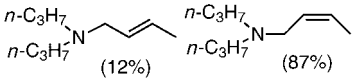
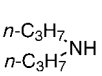
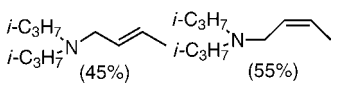
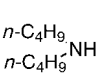
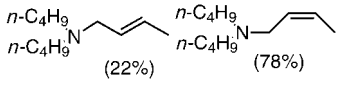
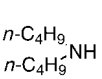
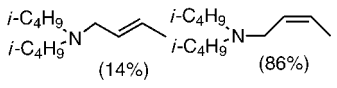
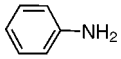
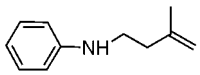
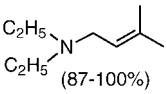
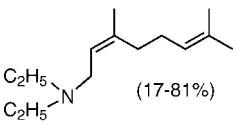
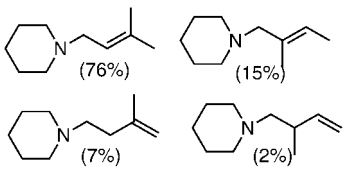
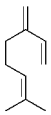
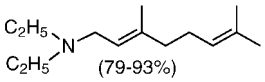
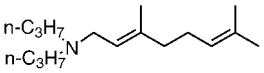
Diene	Amine	Catalyst	Temperature [°C]	Product (Selectivity %)	Yield [%]	TON	TOF [h^{-1}]	Ref.
		Na	120		79	4	0.22	[28]
		*sec*-BuLi	50	 (63%) (36%) (1%)	83	17	0.6	[23]
		*sec*-BuLi	50	 (80%) (20%)	50	10	0.6	[23]
		*n*-BuLi/*sec*-BuLi	50	 (2-100%) (79-98%)	48–86	10–16	0.4–0.7	[30,23]
		Na_2Np	r.t.		82	5	5	[29]
		n-BuLi	50	 (38%)	23	1	0.1	[34]
		*n*-BuLi	50	 (12%) (87%)	86	17	6	[31]
		*n*-BuLi	50	 (45%) (55%)	9	2	0.6	[31]
		*n*-BuLi	50	 (22%) (78%)	75	15	5	[31]
		*n*-BuLi	50	 (14%) (86%)	84	17	6	[31]
		Na	120		29	2	0.08	[28]
		*n*-BuLi/*sec*-BuLi	50–90	 (87-100%)	57–77	4–11	0.4–0.5	[23]
				 (17-81%)	11–82	1–33	0.1–13	[14c,34]
		*sec*-BuLi	50	 (76%) (15%) (7%) (2%)	95	19	0.8	[23]

Table 3. (cont.)

Diene	Amine	Catalyst	Temperature [°C]	Product (Selectivity %)	Yield [%]	TON	TOF [h^{-1}]	Ref.
	C_2H_5, C_2H_5NH	Li/*n*-BuLi	55	 (79-93%)	74–77	2	0.43	[33]
		Na_2Np	r.t.		53–54	2	1.6	[29]
	n-C_3H_7, *n*-C_3H_7NH	Li/*n*-BuLi	50		80	2	0.11	[33]

alkali metal amides, which can be formed *in situ* from BuLi, Na_2Np, or KO-*t*-Bu (Table 4). Ammonia itself reacts only sluggishly with styrene (8% yield of β-phenethylamine at 110 °C in the presence of Na catalyst).[23,35] However, primary and secondary amines add to styrene forming the corresponding secondary and tertiary amine products in good yield. For instance, in the presence of Na, primary amines such as methyl-, *n*-propyl-, and cyclohexylamines (at 110–150 °C) as well as benzylamine (at 180–230 °C) and 2-phenylethylamine add to styrene forming the corresponding secondary amines in 10–70% yields.[35] However, in the presence of BuLi as the precatalyst, *n*-propyl-, *n*-butyl-, and *n*-pentylamines form the corresponding tertiary amines (32–47% yield at 50 °C and styrene : amine = 2 : 1).[23] Secondary amines such as diethyl-, di-*n*-propyl-, and di-*n*-nonylamines add to styrene in the presence of catalytic amounts of BuLi to give the corresponding β-phenethylamines in 41–70% yields at 50 °C.[23] The addition of diethylamine to styrene in the presence of Na_2Np produces diethyl(2-phenylethyl)amine in quantitative yield at room temperature.[29]

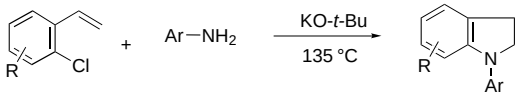
Piperidine (81–88% yield using *sec*-BuLi[23] or Na[35] as catalyst) and aziridine (72–90% yield in the presence of metallic Na)[18] were found to react with styrene even more efficiently. Functionalized amines such as *N*-arylpiperazines add to styrene in the presence of *n*-BuLi catalyst forming 1-(aryl-4-phenylethyl)piperazines in excellent yields (77–99%).[36] The reaction tolerates different substituents on the aromatic ring of arylpiperazine as well as styrene.

Styrene can also be hydroaminated with aniline using metallic Na (180 °C)[28] or CsOH[37] (120 °C) as a catalyst to form the corresponding secondary amine (70% yield). However, the reaction does not proceed in the presence of *n*-BuLi (10 mol %, 100 °C, aniline : styrene = 1 : 1).[38] A recent study has shown that KO-*t*-Bu forms a particularly suitable catalyst for this reaction. For instance, *N*-(2-phenethyl)aniline is formed in 85% yield (> 99.9% selectivity) by the reaction of styrene and aniline using 10 mol % of KO-*t*-Bu in THF at 120 °C.[38] The yield was improved to 96–99% (selectivity > 99%) by using an excess of aniline. Aniline and substituted anilines with electron-withdrawing or -donating substituents even at the *ortho* position reacted to give good yields of the hydroamination products (75–85%). The catalyst system is also applicable on a 50 g-scale. Here, the reaction between styrene and aniline provides ~62% yield of *N*-(2-phenylethyl)aniline.

In addition to the simple hydroamination reaction, KO-*t*-Bu is also useful for the domino hydroamination-aryne cyclization reaction of 2-halostyrenes with anilines forming the corresponding indoles (Scheme 15).[38]

In fact, the cyclization of 2-chlorostyrene with aniline in the presence of three equivalents of KO-*t*-Bu in toluene at 135 °C provided *N*-phenyl-2,3-dihydroindole in 53% yield. However, under similar conditions the direct cyclization of 2-isopropenylaniline failed to occur. This domino reaction proceeds by a base-catalyzed hydroamination followed by a base-mediated intramolecular aryne reaction. Based on the comparison of the reaction of 2- and 3-chlorostyrenes with aniline, it is shown that the cyclization indeed proceeds through the same aryne intermediate, thereby yielding *N*-phenyl-2,3-dihydroindole in 50–55% yield.

Substituted styrenes are also hydroaminated with various amines. For instance, piperidine reacts with α-methylstyrene and α-phenylstyrene in the presence of *sec*-BuLi, giving the corresponding amines in 71 and 82% yield,[23] respectively. However, in the case of *trans*-stilbene a low yield of 10% is observed. Diethylamine (Na_2Np),[29] 1-phenylpiperazine (*n*-BuLi),[36] and aniline (*n*-BuLi/KO-*t*-Bu)[38] add to α- and β-methylstyrenes forming the corresponding β-phenethylamines in 34–86% yield. Aziridine (metallic Na)[18] and *N*-(4-fluorophenyl)piperazine (*n*-BuLi)[36] react with 4-methoxys-



Scheme 15. Domino hydroamination-aryne cyclization reaction.

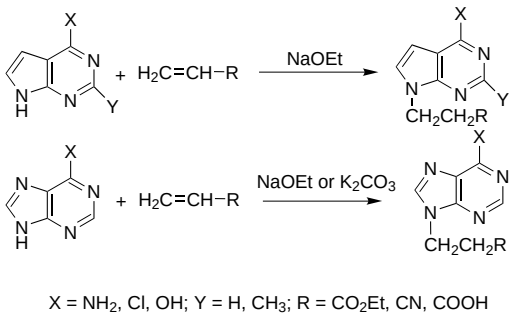
tyrene providing the hydroamination products in 47 and 77% yields, respectively.

Recently, Seijas et al.[39] reported the stoichiometric addition of lithium salts of primary and secondary amines, obtained from the reaction between the parent amine and *n*-BuLi, to 4,4-dimethyl-2-(2-vinylphenyl)-oxazolane and 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazolane. The corresponding β-phenethylamines are obtained in fair to very good yield (21 – 99%). In general, primary amines give only poor yields compared to secondary amines. Similarly, β-methylstyrene is converted to amphetamine derivatives in 33 – 58% yield. Amphetamine derivatives are also accessible by an environmentally more benign base-catalyzed domino-isomerization-hydroamination reaction of allylbenzene.[40] For instance, allylbenzene reacts with various primary (*n*-butylamine, benzylamine, aniline) and secondary amines (piperidine, morpholine, methyl-*n*-butylamine) in the presence of catalytic amounts of *n*-BuLi forming up to 89% of the corresponding amphetamine derivatives with > 99% selectivity (r.t. to 100 °C). In the case of aniline, a mixture of *n*-BuLi and KO-*t*-Bu has to be used as the catalyst. The reaction proceeds through a base-catalyzed fast isomerization of allylbenzene to the thermodynamically more stable β-methylstyrene which further undergoes hydroamination. Similarly, 4-phenyl-1-butene also reacts with piperidine forming *N*-2-(1-phenyl)butylpiperidine in 59% yield at 50 °C.

7 Hydroamination of Functionalized Olefins (Michael Acceptors)

In general, the addition of amines to olefins containing electron-withdrawing neighboring groups, e.g., keto, ester, nitrile, sulfoxide, nitro, etc. proceeds directly without the use of a base catalyst. However, in some cases the presence of an additional base catalyst is advantageous. Due to the increased stability of the α-carbanion the corresponding *anti*-Markovnikov products are formed (Michael addition).

The hydroamination of functionalized olefins has been applied in the synthesis of a variety of biologically important amino compounds. For example, 4-chloropyrrolo[2,3-*d*]pyrimidine adds to ethyl acrylate and acrylonitrile in the presence of sodium ethoxide as catalyst to afford the 7-carbethoxyethylated and cyanoethylated products in 72 – 98% yield (Scheme 16).[41] Similarly, adenine reacts with ethyl acrylate and acrylonitrile in the presence of sodium ethoxide forming the corresponding 6-amino-9-β-carbethoxyethylpurine and 6-amino-9-β-cyanoethylpurine in greater than 90% yields (Scheme 16).[42] Adenine also adds to 2-vinylpyridine under neutral conditions forming the corresponding 6-amino-9-*β*-pyrid-2-ylethylpurine (49% yield).[42] 6-Chloropurine was found to add to

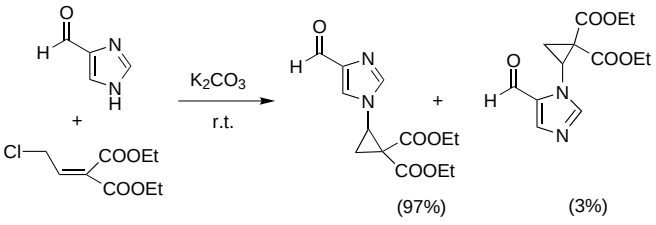


Scheme 16. Base-catalyzed addition of purines and pyrimidines to acrylic derivatives.

acrylonitrile in the presence of catalytic amounts of potassium carbonate yielding up to 73% of 6-chloro-9*H*-purin-9-ylpropionitrile.[43] Under similar conditions 2-amino-6-chloropurine reacts with methyl acrylate in the presence of K_2CO_3 forming the corresponding *N*-9 and *N*-7 alkylated products. The ratio of the *N*-9 to *N*-7 alkylated products varies with reaction time from 4.3 : 1 at 1 h to > 200 : 1 at 48 h demonstrating the reversibility of the reaction.[44]

(Diphenylmethylene)amine quantitatively adds to a variety of α,β-unsaturated compounds such as methyl acrylate (93%), diethyl maleate (55%), methylcyclopropylidene acetate (100%), methyl crotonate (21%), α-choroacrylonitrile (75%), methyl vinyl ketone (95%), cyclopentenone (39%), and acrolein (76%) in the presence of catalytic amounts of triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO).[45] 2-Benzyloxymethyl-3,3-difluoro-1-methylenecyclopropane reacts with benzylamine in the presence of triethylamine forming the corresponding Michael adduct in 94% yield.[46] The reaction of ω-iodo-2-alkenoates with benzylamine in the presence of an excess triethylamine affords 60 – 75% yields of five- and six-membered nitrogen heterocycles.[47]

Su and Wood reported the regioselective *N*-alkylation of 4-formylimidazole with diethyl chloroethylidenemalonate in the presence of catalytic amounts of K_2CO_3 to yield a mixture of the corresponding 1,4- and 3,4-alkyl-4-formylimidazole products in 93% yield in a ratio of 97 : 3 (Scheme 17).[48]



Scheme 17. Base-catalyzed regioselective *N*-alkylation of 4-formylimidazole.

Table 4. Alkali metal-catalyzed amination of aryl olefins.

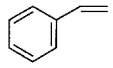
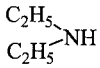
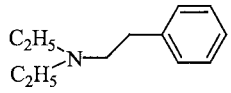
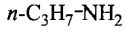
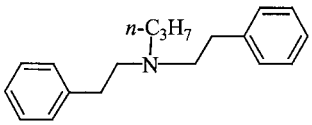
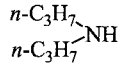
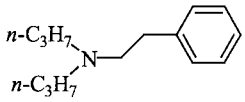
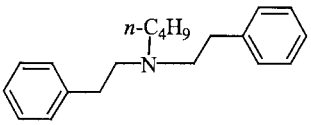
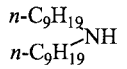
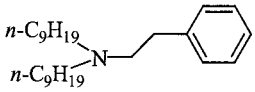
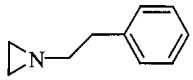
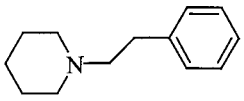
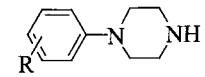
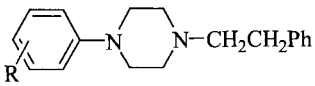
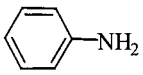
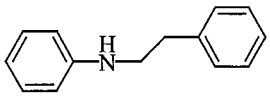
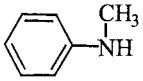
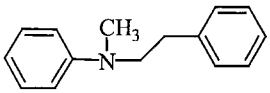
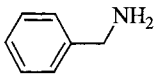
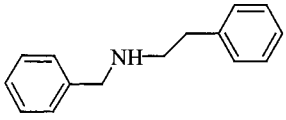
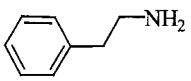
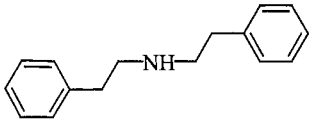
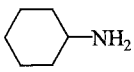
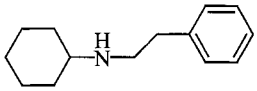
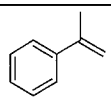
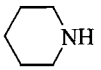
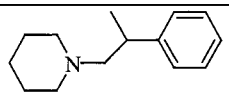
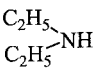
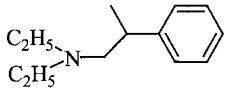
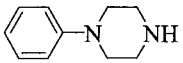
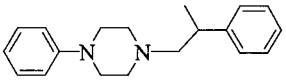
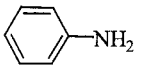
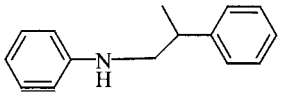
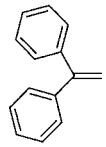
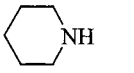
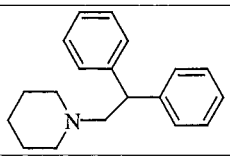
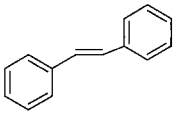
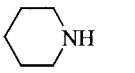
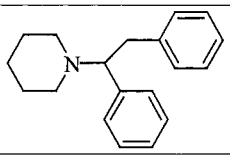
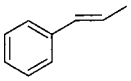
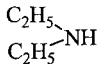
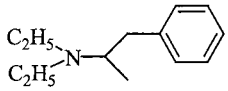
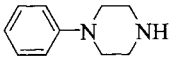
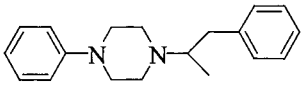
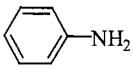
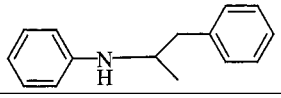
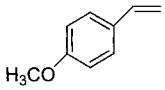
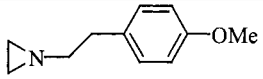
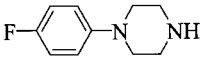
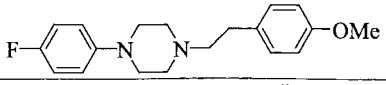
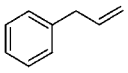
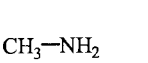
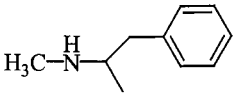
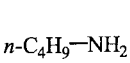
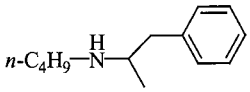
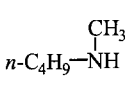
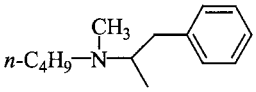
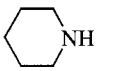
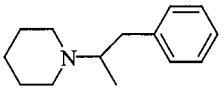
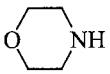
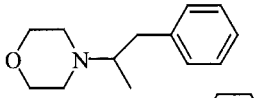
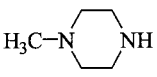
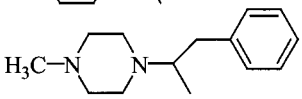
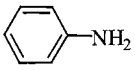
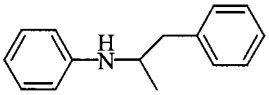
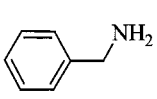
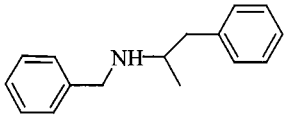
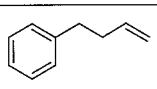
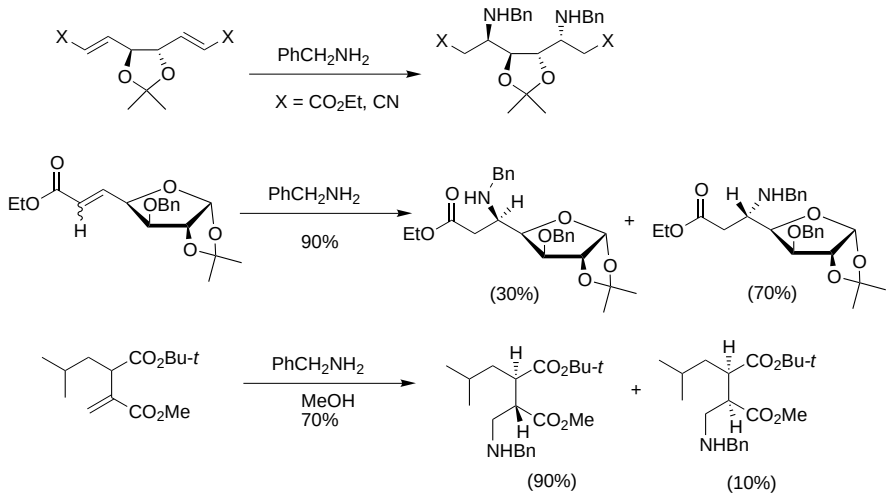
Olefin	Amine	Catalyst	Temp. [°C]	Product	Yield [%]	TON	TOF [h^{-1}]	Ref.
		*sec*-BuLi	50		57–58	12	3	[23]
		Na_2Np	r.t.		95	10	10	[29]
		BuLi	50		33	7	0.4	[23]
		BuLi	50		47	9	0.6	[23]
		BuLi	50		47	9	0.6	[23]
		BuLi	50		41	8	0.5	[23]
		Na	–		72–90	–	–	[18]
		Na	130		81	3–8	0.6–2	[35]
		sec-BuLi	50		81–88	18	3.5	[23]
	 R = H, *p*-F, *m*-CH_3, *o*-OCH_3	*n*-BuLi	85–120	 R = H, *p*-F, *m*-CH_3, *o*-OCH_3	89–99	18–40	1–40	[36]
		Na	180		70	3–8	0.6–2	[35]
		KO-*t*-Bu	100–120		85–99	10	0.5	[38]
		$CsOH·H_2O$	120		69	3.5	0.3	[37]
		$CsOH·H_2O$	120		42	2	0.2	[37]
		Na	185		30	1.5	0.2	[35]
		Na	230		30	1.5	0.2	[35]
		Na	160		30	1.5	0.2	[35]
		BuLi	50		71	14	3	[23]
		Na_2Np	–		85	–	–	[29]

Table 4. (cont.)

		*n*-BuLi	90		86	17	1	[36]
		KO-*t*-Bu	120		34	3.4	0.17	[38]
		*sec*-BuLi	50		82	16	0.3	[23]
		BuLi	50		10	2	0.04	[23]
		Na_2Np	r.t.		85	5	5	[29]
		*n*-BuLi	90		71	14	0.84	[36]
		KO-*t*-Bu	120		50	5	0.25	[38]
		Na	–		47	–	–	[18]
		*n*-BuLi	120		77	15	0.9	[36]
		*n*-BuLi	50		60	3	0.15	[26]
		*n*-BuLi	50		62	3	0.16	[40]
		*n*-BuLi	r.t.		66	3	0.17	[40]
		*n*-BuLi	–78–r.t.		89–91	5	0.23	[40]
		*n*-BuLi	50		88	4	0.22	[40]
		*n*-BuLi	r.t.		75	4	0.19	[26]
		*n*-BuLi–KO-*t*-Bu	120		54	2	0.09	[40]
		*n*-BuLi	50		65	3	0.16	[40]
		*n*-BuLi	50		59	3	0.15	[40]



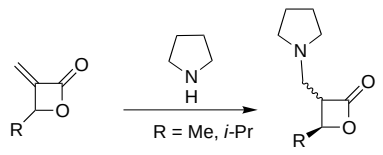
Scheme 18. Stereoselective addition of benzylamine to α,β-unsaturated esters or nitriles.

Michael-type addition of amines or the corresponding metal amides has also been carried out in a diastereoselective manner. For instance, bisenones undergo twofold *syn*-selective Michael addition in the presence of an excess of primary amines generating predominantly the corresponding C_2-symmetric 1,4-bis(aminoalkyl)-derivatives (Scheme 18).[49]

The conjugate addition of benzylamine to an α,β-unsaturated ester derived from D-glucose (Scheme 18) affords β-aminoesters (90% yield) with D-*gluco* and L-*ido* configuration at C-5 in a ratio of 30:70.[50] A methanol solution of benzylamine was found to react with 1-*tert*-butyl 4-methyl (2*R*)-2-isobutyl-3-methylenebutanedioate forming the corresponding Michael adducts (2*R*,3*R*)- and (2*R*,3*S*)-1-*tert*-butyl 4-methyl 3-(benzylaminomethyl)-2-isobutylbutanedioate in 70% yield and in a ratio of 10:90, respectively (Scheme 18).[51]

The conjugate addition of pyrrolidine and piperidine to α-methylene β-lactones forms the corresponding *cis*- and *trans*-α-(aminomethyl)-β-lactones in good yield (up to 92%) (Scheme 19). The *cis* to *trans* ratio varies with the nature of the solvent used. In THF the *cis*-diastereoisomers (up to 77%) are formed as major products while in methanol high *trans*-diastereoselectivity (up to 93%) is observed.[52]

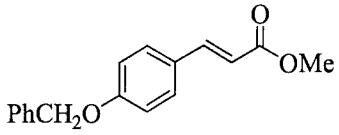
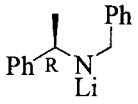
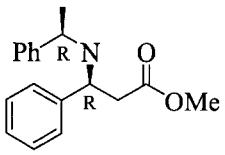
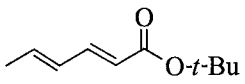
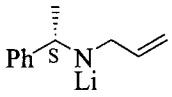
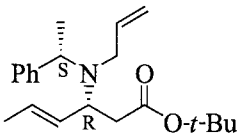
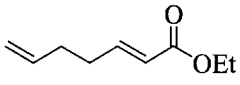
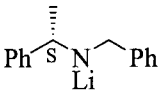
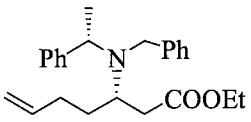
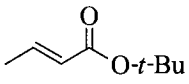
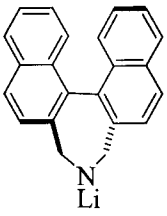
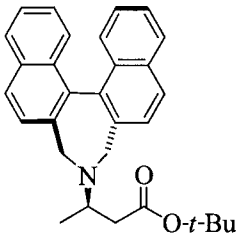
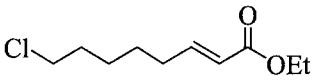
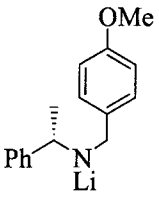
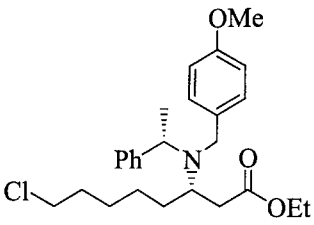
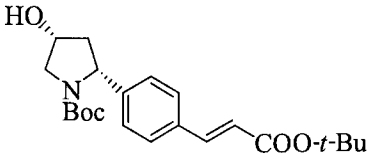
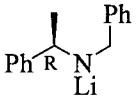
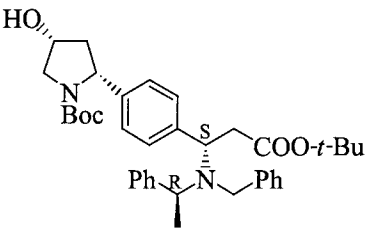
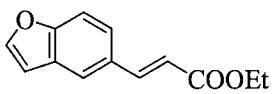
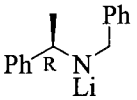
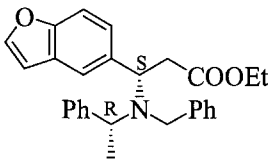
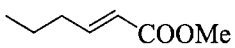
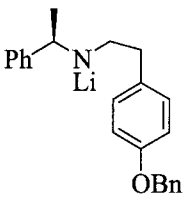
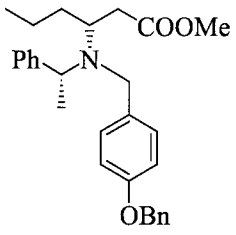
Davies and Ichihara[53] reported the addition of (*R*)-α-methylbenzylamine to methyl crotonate forming the corresponding (*R*,*S*)-β-amino derivative in good yield (35%, ethanol reflux), but with poor diastereoselectivity (< 4%). Addition of lithium amides derived from *R*-α-methylbenzylamine to methyl crotonate gave the (*R*,*R*)-β-amino derivative but with no distinct stereoselectivity (yield 28%). Secondary amines derived from α-methylbenzylamine do not, but their lithium amides do indeed react with α,β-unsaturated esters at −78 °C in THF forming, after protonation, the Michael adducts in high yield (up to 88%) and diastereoselectivity (> 99%).[53] This protocol is a highly practical method for the diastereoselective synthesis of a variety of β-aminoesters (Table 5). For instance, the Michael addition of (*R*)-lithium-*N*-(α-methylbenzyl)benzylamide to methyl *E*-(*p*-benzyloxy)cinnamate gives the corresponding (*R*,*S*)-adduct as a single diastereomer. Similarly, (*S*)-lithium-*N*-(α-methylbenzyl)-4-methoxybenzylamide adds to *tert*-butyl cinnamate to give (3*R*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropanoate in 92% de and 82% yield.[54] The addition of lithium *N*-(α-methylbenzyl)allylamide to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate in THF at −78 °C give the (3*R*,α*S*)-adduct in 96% de (78% yield).[55] Similarly, the addition of lithium *N*-(α-dimethyl)benzylamide to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate proceeds in 91% de and 71% yield.[56] The reaction of lithium *N*-(α-methylbenzyl)benzylamide to (2*R*,4*R*)-1-*tert*-butoxycarbonyl-2-{4-[(*E*)-2-(*tert*-butoxycarbonyl)vinyl]phenyl}-4-hydroxypyrrolidine yields the corresponding adduct in 94% de and 99% yield.[57] Lithium *N*-(α-methylbenzyl)-benzylamide also add to the ethyl ester of 3-(6-[2,3]dihydrobenzofuran)-2-propenoic acid with excellent diastereoselectivity (> 95%).[58]



Scheme 19. Conjugate addition of secondary amines to α-methylene β-lactones.

In the case of α-alkyl-α,β-unsaturated esters, the corresponding *syn*-α-alkyl-β-aminoester is formed selectively (up to 99% selectivity) with total yields up to 78%.[59] The conjugate addition of lithium (*R*)- or (*S*)-*N*-benzyl-*N*-1-phenylethylamide to the γ-methyl-substituted α,β-unsaturated ester (*R*)-(*E*)-*tert*-butyl 5-(*tert*-butyldimethylsilyl)oxy-4-methyl-2-pentenoate forms the (3*S*,4*R*)-*syn* adduct in 100% de (84% yield) or

Table 5. Stereoselective addition of homochiral lithium amides to α, β-unsaturated esters.

Michael acceptor	Lithium amide	Adduct	Yield [%]	*d.e.* [%]	Ref.
			78	99	[54]
			78	96	[55]
			93	>95	[61]
			83	>95	[62]
			88	95	[63]
			99	94	[57]
			72	95	[58]
			82	>97	[64]

(3*R*,4*R*)-*anti* adduct in 100% de (95% yield), respectively.[60]

8 Hydroamination of Alkynes

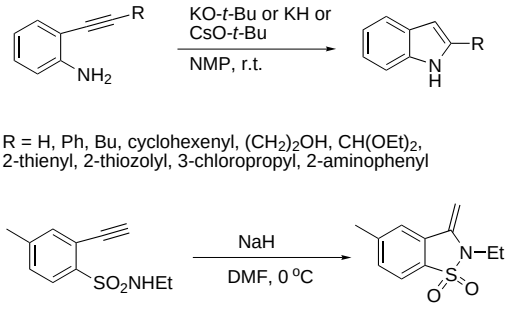
Recently, Knochel and coworkers[37,65] reported the first base-catalyzed hydroamination of alkynes with substituted anilines and heterocyclic amines. For instance, phenylacetylene reacts with diphenylaniline and *N*-methylaniline in the presence of catalytic amounts of CsOH in NMP at 90 – 120 °C leading to corresponding enamines in 82% and 46% yield, respectively. Under similar conditions, pyrrole, imidazole, indole, and benzimidazole add to phenylacetylene giving 65 to 83% yields. Recently, the same group reported an elegant base-catalyzed intramolecular hydroamination of 2-(2-alkynyl)anilines to form substituted indoles in 61 – 90% yield (Scheme 20).

The cyclization reaction is fast even at room temperature and tolerates several functional groups such as hydroxy, acetal, amino, nitro, and alkyne enabling the preparation of a variety of polyfunctional indoles. When R was a 3-chloropropyl group, cyclopropanation occurred after cyclization forming 2-cyclopropylindole in 75% yield. This interesting cyclization reaction was also extended to various heterocyclic amines such as aminopyridines.

In another study, Lane and Snieckus observed the cyclization of *N*-ethyl-2-ethynyl-4-methylbenzenesulfonamide to the corresponding saccharin derivative (57% yield) in the presence of NaH in DMF at 0 °C (Scheme 20).[66]

9 Conclusions and Outlook

The base-catalyzed hydroamination of olefins offers a simple and atom-efficient access to a variety of amines. Apart from strongly activated olefins, 1,3-dienes and styrene derivatives can be used in a general way. Nevertheless, a number of challenges wait to be solved in future in this area. Clearly, a general catalytic method for the hydroamination of simple aliphatic olefins is an important goal so far. In addition, catalytic asymmetric aminations of olefins might be of high value for fine chemical synthesis. Here, both transition metal-catalyzed as well as base-catalyzed amination reactions offer interesting possibilities.



Scheme 20. Base-catalyzed intramolecular hydroamination of substituted alkynes.

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