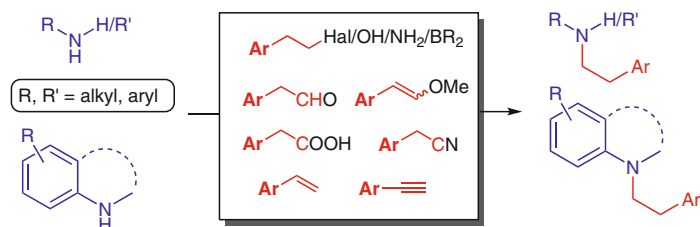


Methods for Arylethylation of Amines and Heteroarenes

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Dedicated to my friend Norbert Breitschaft, who died on 7th of February, 2018.



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Abstract Compared with standard N-methylation, benzylation, and alkylation of amines and N-heterocycles, N-arylethylation is significantly more challenging. In this Review the available methods for N-arylethylation are summarized, with a special focus on efficiency, selectivity, availability of the required building blocks, and ecological aspects.

Key words arylethylation, phenethylation, alkylation, reductive amination, hydroamination, reduction

1 Introduction

Amines are the one of the most important functional groups in low-molecular weight drugs. Due to their balanced basicity, an equilibrium between water-soluble protonated form and lipophilic, membrane-permeable neutral form exists, giving amines very favorable pharmacokinetic properties. Moreover, the protonated form strongly contributes to the interaction of the drug with the target proteins (enzymes, receptors, ion channels) because of their ability to build up ion-ion, ion-dipole, and π -cation interactions with amino acid residues in the active sites of the proteins.¹

Consequently, a broad range of methods for the synthesis of amines is available, including convenient protocols for the introduction of methyl, alkyl, and benzyl residues. Surprisingly, only limited data are published on the introduction of phenethyl (and other arylethyl) residues, including examples of surprisingly unsuccessful attempts.^{2,3}

The phenethyl residue has been found to be very advantageous in a number of drugs. In morphine-derived⁴ and related analgesics,^{5,6} as well as serotonin receptor ligands,⁷ this particular residue was essential for high pharmacological activities.

Furthermore, N-phenethyl compounds are required for systematic analysis of structure–activity relationships in the development of novel amine-based drugs, if homologous series of compounds are investigated.

In the past decades, a number of novel methods for the introduction of N-arylethyl residues have been developed, and these will be the subject of this review article.

The following items will be addressed in this review:

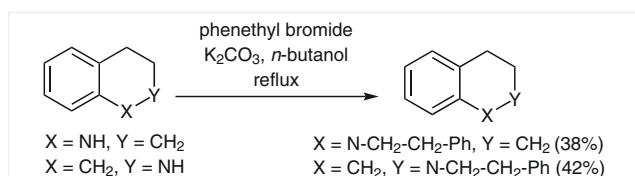
1. Which substrates (aliphatic amines, aromatic amines, N-heteroarenes) can be subjected to this reaction, and how is the chemoselectivity?
2. Which functional groups are compatible with the reaction conditions and reagents?
3. How is the availability of the required building blocks and catalysts?
4. How about ecological aspects and atom economy?

2 Methods for N-Arylethylation

2.1 N-Arylethylation with Phenethyl Halides and Sulfonates

The most obvious method for converting amines into their N-arylethyl analogues is N-alkylation with appropriate arylethyl halides; in the most common case with commercially available phenethyl bromide. Depending on the nucleophilicity of the substrate, this conversion can be performed (in case of sufficient intrinsic nucleophilicity of the amine) by simply reacting the amine/heteroarene with the phenethyl halide in the presence of a weak base, which will

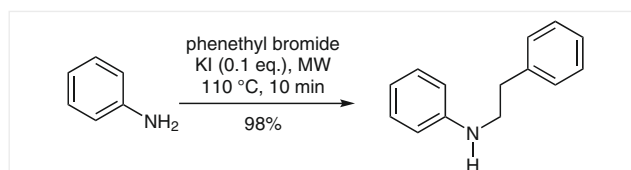
neutralize the hydrogen halide formed in the course of the reaction. By this means, undesired protonation of substrate amine is avoided, ending up with (hopefully) full conversion of the starting amine. Commonly applied proton scavengers are carbonate salts such as K_2CO_3 , Na_2CO_3 , and Cs_2CO_3 . Aliphatic (mostly secondary) amines,^{5,8} and aniline derivatives^{9–12} (including 1,2,3,4-tetrahydroquinoline⁸ and indolines¹³) are easily converted in this manner in moderate to good yields, as exemplified in Scheme 1. Primary aromatic amines give monoalkylated products in most cases.



Scheme 1 Phenethylation of 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydroquinoline⁸

In contrast, poorly nucleophilic substrates (e.g., indoles,¹⁴ carbazoles,¹⁵ carbolines,¹⁶ imidazoles,¹⁷ phenothiazines¹⁸) do not readily react with arylethyl halides, and notable conversions are obtained only if the NH groups of these substrates are deprotonated ahead, rendering the significantly more nucleophilic amide anions. The choice of the base is determined by the acidity of the NH function, and bases of moderate (alkali metal hydroxides, alkoxides, etc) to very strong basicity (butyllithium) have been used for this purpose. Undesired fragmentation of starting phenethyl halides¹⁹ and produced phenethylamines¹⁵ in the presence of very strong bases have been reported.

In general, phenethyl iodides show higher reactivity than the corresponding chlorides and bromides,^{9,12} and the reaction can be accelerated by in situ conversion of phenethyl bromide into phenethyl iodide by adding catalytic amounts of KI.¹² However, there is also one report on undesired decomposition of phenethyl iodide under the reaction conditions.¹⁰ This reaction can further be speeded up by microwave irradiation (Scheme 2).¹²



Scheme 2 Microwave- and iodide-accelerated phenethylation of aniline¹²

Phenethyl mesylates²⁰ and tosylates¹⁴ as well as polymer-bound arylethyl arenesulfonates²¹ can be applied as alternative phenethylating agents.

A phenethylation of an aniline with phenethyl bromide, catalyzed by a palladium complex (generated in situ from $Pd_2(dba)_3$ and X-Phos) has been reported recently.²² The authors do not discuss why they utilized the Pd catalyst for this purpose.

For simple phenylethylation reactions, this direct N-alkylation is the method of choice in most cases. Unfortunately, only a very limited number of ring substituted arylethyl halides are commercially available, and synthesis of the required building blocks (mostly via the corresponding arylethanol) affords multistep procedures, starting from benzoic acids under homologation,²⁰ styrenes via hydroboration/oxidation,²³ or styrene oxides via reductive cleavage.²⁴

2.2 N-Arylethylation with Arylethanol and Arylethylamines

As mentioned above, arylethanol are typical precursors of arylethyl halides and sulfonates as building blocks for N-arylethylation. Alternatively, arylethanol can be activated directly for the envisaged conversions.

An N-phenethylation of phenothiazine using (4-bromophenyl)ethanol, activated in situ by propylphosphonic acid anhydride (T3P) gave only incomplete conversion (25% yield), in contrast to high yields obtained with benzyl alcohols under the same conditions.²⁵ Phenethylation of aniline using phenylethanol and a Ph_3P/DDQ reagent in a Mitsunobu

Biographical Sketches



Franz Bracher was born in 1958 in Geisenfeld (Germany). He studied Pharmacy at the Ludwig-Maximilians University of Munich (LMU) and obtained his Dr. rer. nat. there in 1986 under the supervision of Eberhard Reimann. After one year as a postdoc with Prof. Dr. W. Oppol-

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1997 he is Full Professor of Pharmacy at LMU Munich. His research interests include natural products synthesis (especially alkaloids and steroids) and Medicinal Chemistry. He is an author of over 200 publications.

Table 1 Metal-Catalyzed Arylethylation of Amines with Arylethanol
$$\text{RR}'\text{NH} + \text{Ar-CH}_2\text{-CH}_2\text{-OH} \longrightarrow \text{RR}'\text{N-CH}_2\text{-CH}_2\text{-Ar}$$

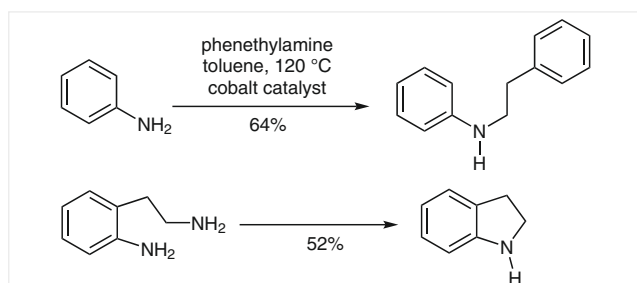
| Type of amines (number of examples) | Arylethanol(s) | Catalyst | Yield (%) | Ref. |
|---|--|---|-----------|------|
| aniline (1) | phenylethanol | [Cp*Ir(NH ₃) ₃][I] ₂ | 94 | 27 |
| 4-methoxyaniline (1) | phenylethanol | Raney nickel | 78 | 28 |
| 2-aminopyridine, 1-phenylethylamine, aniline (3) | (substituted)phenylethanol, indole-3-ethanol | [Ru(<i>p</i> -cymene)Cl ₂] ₂ | 70–93 | 29 |
| 4-methylaniline (1) | phenylethanol | NiCuFeO _x | 96 | 30 |
| aniline (1) | phenylethanol | Pt-Sn/ γ -Al ₂ O ₃ | 96 | 31 |
| 4-methoxyaniline, morpholine (2) | phenylethanol | palladacycle, P(furyl) ₃ | 72/74 | 32 |

bu related reaction was accomplished in 92% yield, but the scope and limitations of this method have not been investigated.²⁶

A considerable number of recent publications deal with the metal-catalyzed arylethylation of amines (mostly aniline derivatives) with arylethanol. These methods are summarized in Table 1.

In most cases, only single examples for phenethylation are presented, mainly in combination with N-alkylations with other alcohols such as benzyl alcohols. The presented yields are impressive, but scope and limitations for arylethylations have not been investigated in these contributions.

In a similar manner, arylethylamines have been investigated as building blocks for metal-catalyzed arylethylations of amines. Catalyzed by a cobalt-pincer complex, aniline was phenylethylated with phenylethylamine to give N-phenethylaniline in 64% yield, accompanied by 19% of the homocoupling product of phenylethylamine.³³ In an intramolecular version of this reaction, indoline was obtained in 52% yield from 2-(2-aminoethyl)aniline (Scheme 3).³³

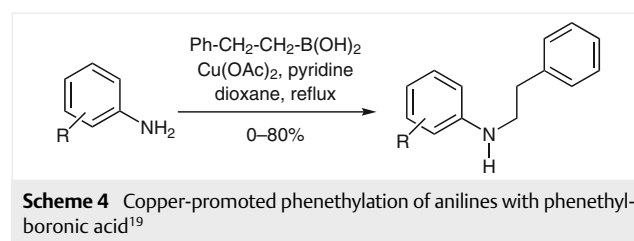
**Scheme 3** Cobalt-catalyzed inter- and intramolecular phenylethylation reactions³³

Aniline was N-alkylated with phenyl-, indole-, and thiophene-based primary arylethylamines to give the corresponding secondary amines under catalysis of a ruthenium carbonyl-phosphine complex ('Shvo-complex') in yields above 90% (three examples).³⁴ Recently it was shown that phenethylation of aniline can even be catalyzed by reusable

palladium on carbon catalyst, but the yield obtained with phenylethylamine (36%) was considerably lower than yields obtained with other primary aliphatic amines (72–94%).³⁵

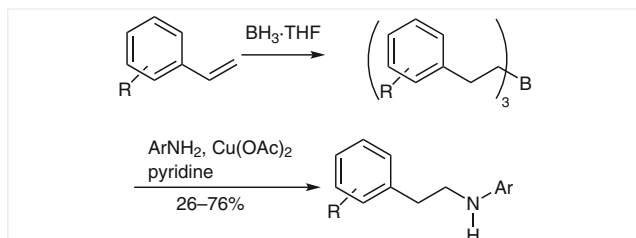
2.3 N-Arylethylation with Phenethyl Boron Compounds

An additional building block of the type 'arene-CH₂-CH₂-heteroatom' are phenethyl boron compounds, which were introduced only recently. Promoted by Cu(OAc)₂ and pyridine (4 equiv each), ring-substituted anilines undergo convenient N-phenethylation with phenethylboronic acid (yields 63–94%). This protocol was also applied to aminopyridines and aminoquinolines, and variable yields (0–80%) were obtained (Scheme 4).¹⁹ This methodology can also be applied to the N-arylethylation of benzamides.^{36,37} Phenethylboronic acids are available from styrenes via hydroboration with dichloroborane, followed by aqueous hydrolysis.³⁸

**Scheme 4** Copper-promoted phenethylation of anilines with phenethylboronic acid¹⁹

In 2012, this methodology was extended to phenethylboranes.³⁹ These can conveniently be prepared in situ from styrenes via hydroboration. Two different approaches were investigated: A mixed trialkylborane obtained by hydroboration of a styrene with 9-BBN, under Cu(OAc)₂-pyridine promotion, unfortunately showed very poor conversion with an aniline. Significantly better yields were obtained with tri(arylethyl)boranes obtained by hydroboration of styrenes with BH₃-THF complex. A broad variety of ring-substituted styrenes and anilines were subjected to this

reaction, and yields in the range of 26–76% were obtained. Unfortunately, equimolar amounts of the boranes (resulting from borane and three equivalents of styrene) were required, meaning that this method is not atom-economic (Scheme 5).

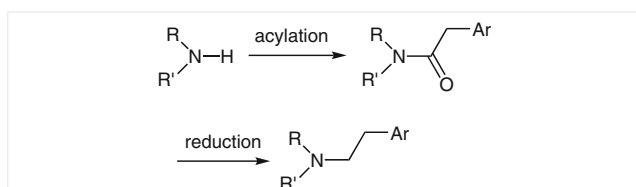


Scheme 5 Copper-promoted phenethylation of anilines with tri(aryl-ethyl)boranes³⁹

In analogy, phenethylbismuth compounds can be used for copper-promoted phenethylation of aromatic and aliphatic amines, but yields were rather poor (up to 53%) due to the tendency of the organobismuth compounds to undergo β -elimination (giving styrene) under the reaction conditions.⁴⁰

2.4 N-Arylethylation via Arylacetamides

A classical method for obtaining arylethylamines consists of N-acylation of primary or secondary amines with activated arylacetic acids, followed by reduction of the formed amide moiety to the corresponding amine (Scheme 6). Numerous methods for amide reductions have been published, and it is beyond the scope of this mini-review to present a comprehensive list of methods. The most prominent reducing agents are LiAlH_4 , NaBH_4 (with different additives such as BF_3 and acetic acid), and diborane and borane complexes. Furthermore, silanes in combination with reagents such as titanocene difluoride,⁴¹ rhodium-phosphine complexes,⁴² or 2-fluoropyridine/trifluoromethanesulfonic anhydride⁴³ have been applied. The choice of the reducing agent is dictated by the presence of other functional groups in the amide and the required chemoselectivity.

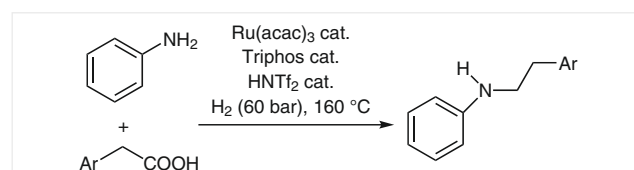


Scheme 6 Preparation of arylethylamines via reduction of arylacetamides

One major advantage of this protocol is that primary amines can be converted into secondary N-phenethylamines without over-alkylation. This protocol is of limited applicability for the N-phenethylation of indoles and related heterocycles because N-acyl derivatives thereof readily undergo reductive deacylation with reducing agents.⁴⁴

Arylacetic acids with complex substitution patterns often need to be prepared from common aromatic building blocks in multistep syntheses.⁴⁵

In a related approach, aromatic amines were arylethylated in high yields in one step by treatment with (substituted) arylacetic acids under catalytic hydrogenation (60 bar H_2 , 160 °C) in the presence of catalytic amounts of $\text{Ru}(\text{acac})_3$, Triphos, and triflimide (Scheme 7).⁴⁶ Aniline has been converted into its N-phenethyl derivative with methyl phenylacetate by following the same procedure; furthermore, numerous other aliphatic and aromatic amines have been N-alkylated with other methyl esters.⁴⁷ A related phenethylation of aniline with phenylacetic acid has been performed under Pt-catalysis (Karstedt's catalyst) using PhSiH_3 as the reductant.⁴⁸



Scheme 7 Reductive N-arylethylation of aromatic amines with arylacetic acids⁴⁶

2.5 Reductive Amination of Arylacetaldehydes and Equivalent

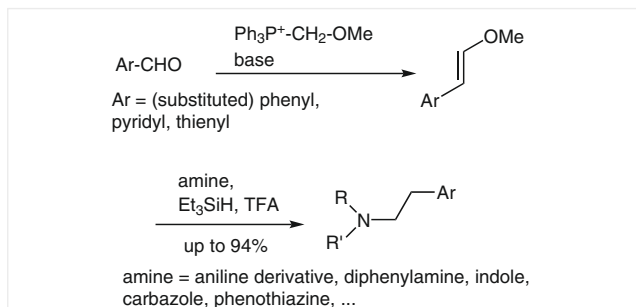
Reductive aminations of aldehydes and ketones with primary or secondary amines in the presence of appropriate reducing agents are a highly appreciated methodology for the synthesis of secondary and tertiary amines. These protocols are user-friendly because they do not require hazardous alkyl halides, and due to the mild conditions, undesired formation of quaternary ammonium salts (a common side reaction in standard N-alkylation reactions) does not take place. Consequently, this methodology has found broad application in organic synthesis. Furthermore, most of these methods can be performed under metal-free conditions, which makes them ecologically advantageous.

Only a limited number of examples are known for reductive phenethylations of amines with phenylacetaldehyde. This is due to the high susceptibility of phenylacetaldehyde to undergo decomposition and polymerization; Table 2 gives an overview on the published conversions.

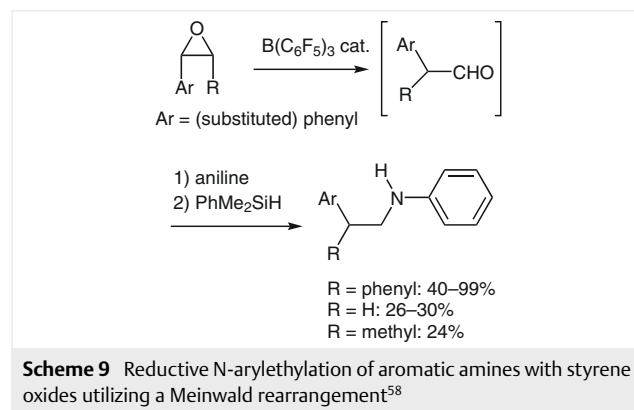
Table 2 Reductive N-Phenethylations of Amines using Phenylacetaldehyde

| $RR'NH + Ph-CH_2-CHO \longrightarrow RR'N-CH_2-CH_2-Ph$ | | | | |
|---|--|---|-----------|-------|
| Type of amines (number of examples) | Reducing agent | Comments | Yield (%) | Ref. |
| 1,2,3,4-tetrahydro-quinoline (1) | NaCNBH ₃ | | 27 | 49 |
| highly substituted anilines (2) | NaBH(OAc) ₃ | | 41, 56 | 50 |
| highly substituted indolines (3) | NaBH(OAc) ₃ , AcOH | | 57–70 | 13 |
| 4-aminobenzoic acid | BH ₃ -picoline | exact yield not given | 70–90 | 51 |
| aniline, isopropylamine (3) | Bu ₃ SnClH | highly toxic solvent HMPA | 33–99 | 52,53 |
| 4-methylaniline (1) | PhMe ₂ SiH | gold-carbon nanotube catalyst | 81 | 54 |
| aniline, benzylamine (2) | HCOOH-Et ₃ N, Ru(II) complex | Noyori's catalyst | 62, 61 | 55 |
| highly substituted indolines (2) | H ₂ (1 atm), PtO ₂ | | 41–62 | 13 |
| aniline (1) | Et ₃ SiH, TFA, cat. I ₂ | phenylacetaldehyde dimethyl acetal used | 85 | 56 |

Besides common reducing agents (NaCNBH₃, NaBH(OAc)₃, H₂/Pt), tin hydrides and organosilanes were successfully applied. Problems with the unstable phenylacetaldehyde were overcome by using the corresponding dimethyl acetal, in combination with a silane reducing agent.⁵⁶ A convenient enhancement was achieved by using methoxystyrenes as phenylacetaldehyde equivalents.⁵⁷ These building blocks are more stable than the parent aldehydes and are easily prepared in one step from commercially available (hetero)aromatic aldehydes by Wittig homologation (Scheme 8). In combination with triethylsilane and TFA, N-arylethylations of moderately basic amines (anilines, diphenylamine, 1,2,3,4-tetrahydroquinoline) and heterocycles (indoles, carbazoles, phenothiazine, dibenzazepines) were achieved in yields up to 94% (17 examples). Due to the strongly acidic reaction conditions (TFA) aliphatic amines are not affected because they are protected from electrophilic attack by protonation. The so obtained chemoselectivity is complementary to the chemoselectivity in reductive N-arylethylation of amines using borohydride-type reducing agents.

**Scheme 8** Reductive N-arylethylation of aromatic amines and N-heterocycles using methoxystyrenes⁵⁷

Alternatively, anilines can be phenethylated through the use of styrene oxides, with a B(C₆F₅)₃-catalyzed Meinwald rearrangement giving intermediate arylacetaldehydes as the initial step. Crude aldehyde is condensed with an aniline and the formed imine is reduced with an organosilane to give the target products. High yields of β,β-diarylamines are obtained, whereas the parent phenethyl residue is introduced only in poor yield (Scheme 9).⁵⁸



As a further surrogate of arylacetaldehydes, arylacetonitriles are applicable. The latter are easily available from the corresponding benzyl halides. This approach consists of an in situ reduction of the nitrile group to an aldimine, followed by condensation with a primary or secondary amine (releasing NH₃), and a second reduction step to give the target compounds. Representative examples are shown in Table 3.

Table 3 Reductive N-Phenethylations of Amines using Arylacetonitriles

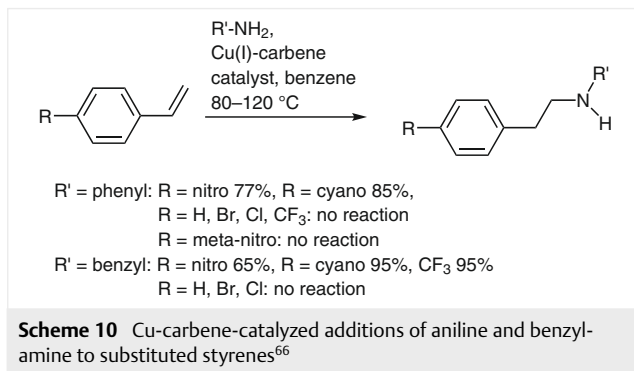
| $RR'NH + Ph-CH_2-CN \longrightarrow RR'N-CH_2-CH_2-Ph$ | | | | |
|--|---|---|------------------------|------|
| Type of amines (number of examples) | Reducing agent | Comments | Yield (%) | Ref. |
| aniline, <i>n</i> -pentylamine (2) | BH_3-NH_3 , Co(II)-pincer-catalyst | numerous examples with other nitriles | 69 68 | 59 |
| aniline (1) | H_2 , Pd/C | numerous examples with alkanenitriles | not given | 60 |
| Me_2NH , Et_2NH , piperidine, benzylamine (4) | H_2 , Pd/C | methoxy- and hydroxyphenylacetonitriles used | >70 | 61 |
| aniline or nitrobenzene (as precursor of aniline) (2) | H_2 , Pd/C | 5 equiv of nitrile used; numerous examples with other nitriles | 24 (100 ^a) | 62 |

^a If starting from nitrobenzene.

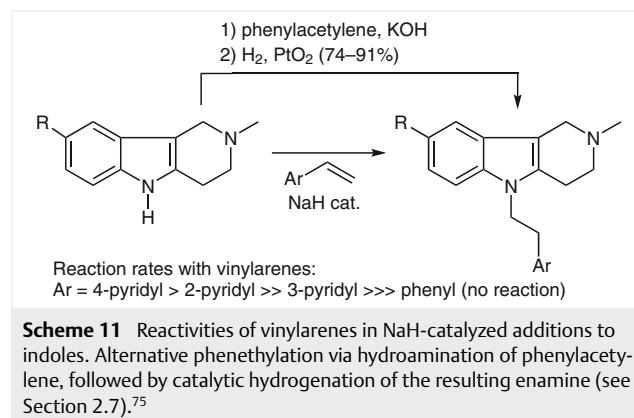
The target products can be contaminated with a number of byproducts:^{59,62} Hereby, the starting arylacetonitriles are reduced to the primary aryethylamines, which, in turn, can condense with the intermediate aldimines to give, after further reduction, symmetrical di(arylethyl)amines. The outcome of the reaction strongly depends on the exact reaction conditions and on the nature of the substrate amines and arylacetonitriles.

2.6 N-Arylethylation via Addition of Amines to Styrenes

The direct, regioselective anti-Markovnikov-type β -addition of amines to vinylarenes (styrenes) is an approach of highest atom economy for the synthesis of N-arylethylated amines. Much work has been published on metal catalysts for promoting this addition (rare earth metals such as Ln complexes, $TiCl_4$, Rh complexes, etc), but frequently these additions are hampered by poor or unpredictable regioselectivity. Details have been summarized in a number of comprehensive review articles.^{63–65} The outcome of the addition is further dependent on the substitution pattern of the vinylarene, as exemplified in the Cu-carbene-catalyzed additions of aliphatic and aromatic amines to styrenes (Scheme 10).⁶⁶



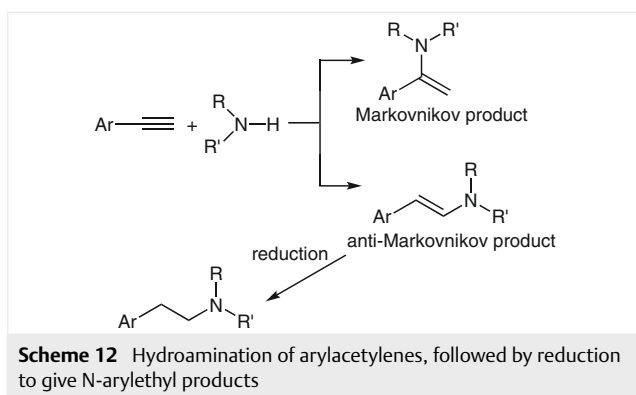
In practice, this addition to unactivated styrenes is most likely triggered by stoichiometric or catalytic amounts of bases, which convert the amine into a more nucleophilic amide ion. Styrenes bearing electron-withdrawing substituents can undergo this reaction even without support of a base.⁶⁴ A broad range of bases have been applied ($BuLi$,^{67,68} $KOtBu$,^{69,70} lithium dialkylamides,^{71,72} NaH ,⁶⁸ KOH ,⁷³ $CsOH$,⁷⁴ for further examples see ref.⁶³). In additions of vinylpyridines and styrene to an annulated indole, significant differences in reactivity were observed, as pointed out in Scheme 11.^{7,75} Satisfactory conversion was obtained with 4- and 2-vinylpyridine, which are known to be highly reactive Michael systems, whereas 3-vinylpyridine requires harsher reaction conditions, and styrene gave no conversion at all.



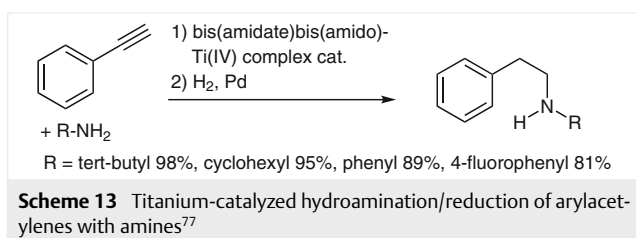
2.7 N-Arylethylation via Hydroamination/Reduction of Arylacetylenes

Addition of amines to arylacetylenes can be catalyzed by a large number of metal catalysts, whereby mostly mixtures of enamines consisting of the desired anti-Markovnikov products as well as Markovnikov products, are obtained. The chemistry of this step (hydroamination) has been summarized in a number of comprehensive review articles.^{63,64,76} Late-transition-metal catalysts give mostly or exclusively Markovnikov addition products with terminal

alkynes, whereas some titanium catalysts lead to the desired anti-Markovnikov addition.^{77,78} Typically, these intermediates are reduced in situ to give the corresponding isomeric arylethylamines (Scheme 12). The reduction can be accomplished by catalytic hydrogenation over Pt catalyst⁷ (see Scheme 11), or with LiAlH_4 ⁷⁷ and organosilanes such as PhSiH_3 .⁷⁸ Nevertheless, the regioselectivity of the hydroamination is strongly dependent on the substitution patterns of the reactands, and even small changes can result in a significant loss in regioselectivity.⁷⁸



Excellent regioselectivities and yields were obtained with a bis(amidate)bis(amido)titanium(IV) complex for the hydroamination of aliphatic amines as well as anilines bearing either electron-donating or electron-withdrawing substituents.⁷⁷ However, substituents on the anilines (cyano, chloro), which were sensitive to the conditions of catalytic hydrogenation in the second step, led to complete failure of the arylethylation reaction (Scheme 13).

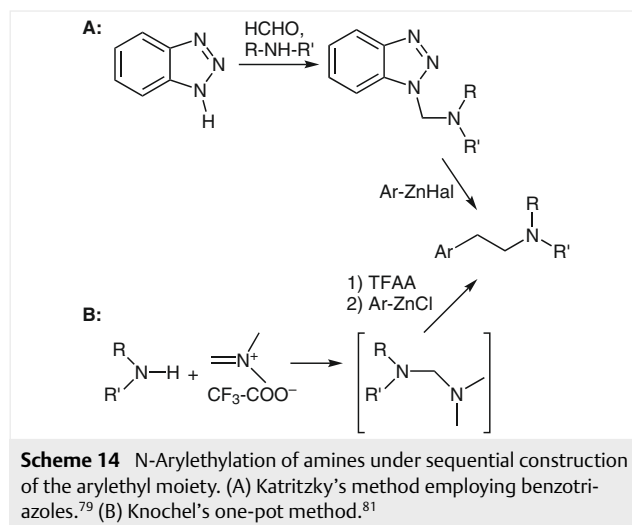


2.8 Sequential Construction of the Arylethyl Moiety

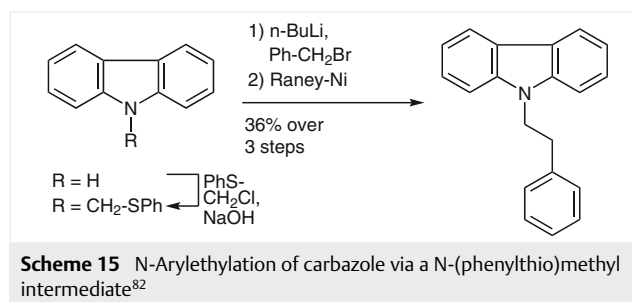
A formal arylethylation of amines can further be accomplished in two steps, involving attaching an appropriate C_1 -unit to the amine, followed by C_1C -connection with a benzyl-type building block. In these protocols, a secondary (and in some examples a primary) amine is reacted with a reactive C_1 -building block to give a (precursor of) an iminium ion, to which then an organometallic benzyl unit is added. A first example was published by Katritzky in 1998, involving condensation of benzotriazole with formaldehyde and amines to give *N*-(aminomethyl)benzotriazoles, which

react with benzylzinc compounds to give the arylethylated amines (Scheme 14, A).⁷⁹ A similar conversion was obtained with benzylbismuth compounds prepared in situ.⁸⁰

In a related approach, Knochel converted secondary aliphatic and aromatic amines, as well as *N*-heterocycles (phenoxazine, phenothiazine, carbazole) with Tietze's iminium salt ($\text{Me}_2\text{NCH}_2^+ \text{CF}_3\text{COO}^-$), generated in situ, into mixed aminals, which, after activation with trifluoroacetic anhydride (TFAA), gave iminium salts that readily reacted with benzylzinc compounds to give the *N*-arylethylated amines in a one-pot-procedure (Scheme 14, B).⁸¹



A two-step *N*-phenethylation of carbazoles involves *N*-phenylthiomethylation, followed by deprotonation of the slightly acidic methylene group with *n*-butyllithium, and *C*-benzylation with a benzyl halide. Reductive desulfurization of the intermediate phenylthio compound gave the desired *N*-phenethylcarbazole (Scheme 15).⁸²



3 Conclusion

Compared with standard *N*-methylation, benzylation, and alkylation of amines and *N*-heterocycles, *N*-arylethylation is significantly more challenging. In this Review, the available methods for *N*-arylethylation are summarized, with a special focus on efficiency, selectivity, availability of

the required building blocks, and ecological aspects. Depending on the nature of substrate amine and (hetero)aryl-ethyl residue to be introduced, a broad variety of (in part complementary) methodologies is available now. Chemoselectivity can be achieved by proper choice of the methodology, and high yields can be obtained by utilizing modern variations of established methods.

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