

Chapter 2

Nitrogenation Strategy for the Synthesis of Amines

Wang Zhou and Ning Jiao

Abstract Amines are important organic compounds with a wide range of application in the synthesis of fine chemicals. Although many multi-step methods have been well developed for their synthesis, one step methods for the synthesis of amine, especially, aliphatic primary amine via direct C–H or C–C bond nitrogenation are less developed and full of challenge.

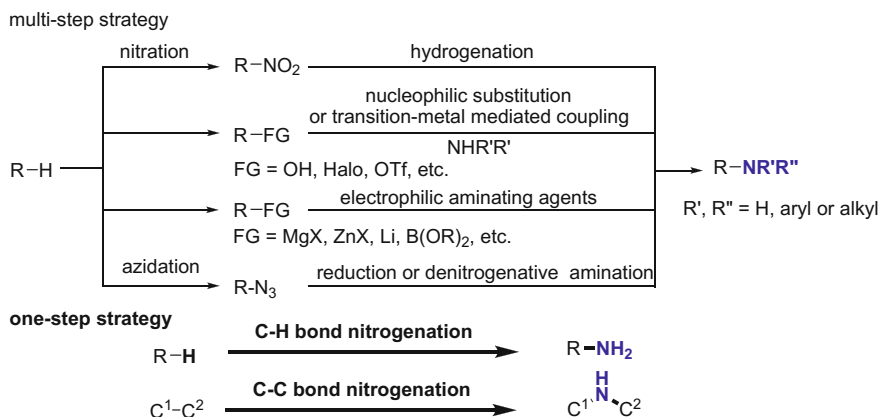
Keywords Amines • C–H/C–C bond cleavage • C–N bond formation • Rearrangement • Oxidation

2.1 Introduction

Amines are an important class of organic compounds with a wide range of applications in the production of pharmaceuticals, agrochemicals, dyes and pigments, specialty fibers, bioactive compounds, and other fine chemicals [1–4]. In industry, primary amines are prepared through nitration of hydrocarbons followed by reduction of the nitro compounds either in liquid or vapor phase over catalysts comprising of Cu, Ni, or Pt [5, 6]. Primary, secondary, tertiary amines, as well as amides can also be synthesized by nucleophilic ammonolysis or copper catalyzed Ullmann condensation from related alkyl or aryl halides [7–16]. In the past two decades, several research groups [17–22] have made substantial contribution to Buckwald–Hartwig cross-coupling in the amination of aryl halide and triflate. Recently, some methods including Chan–Evans–Lam amination [23–25], have

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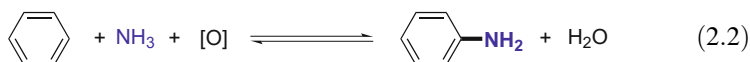
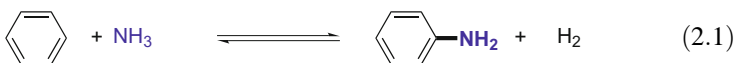
Scheme 2.1 Synthetic strategies for amines

been developed for the synthesis of amines by amination of aryl boronic acids with electrophilic aminating agents [26–32]. In addition, azide could also be employed as precursor for the synthesis of amines [33, 34]. On the other hand, amines could be obtained by condensation and rearrangement reactions [35–37] or the direct amination of unsaturated carbon–carbon double or triple bond [38–56]. In these cases, however, the preactivated arene substrates were usually required (Scheme 2.1). Alternatively, C–H or C–C bond direct nitrogenation (amination) provides the simplest route for the synthesis of amines [57–62]. This chapter will cover the recent development on the N, NH, or NH₂ incorporation for synthesis of amines through C–H or C–C bond cleavage (Scheme 2.1).

2.2 Aromatic C–H Bond Nitrogenation for the Synthesis of Anilines

To date, the direct C–H nitrogenation of aliphatic hydrocarbon for the synthesis of aliphatic primary amine has not been achieved. Gratifyingly, related aromatic C–H bond nitrogenation have made great strides in the past few decades.

2.2.1 C–H/N–H Bond Dehydrogenative Nitrogenation of Aromatic Compounds with Ammonia



Due to the relatively high strength of C–H bond in aromatic compounds ($113 \text{ kcal mol}^{-1}$) and N–H bond in ammonia ($107 \text{ kcal mol}^{-1}$) [63], C–H/N–H dehydrogenative nitrogenation of arene with ammonia was usually proceeded in the presence of metal catalyst under harsh reaction conditions (Eq. 2.1). In 1917, the first example of this transformation using nickel/iron catalyst in the temperature range from 550 to 600 °C had been reported by Wibaut [64].

However, the nature of this dehydrogenative process is reversible and thermodynamically disfavored at reasonable temperature and pressure that led to low equilibrium conversion for the reaction. To drive the thermodynamic equilibrium in forward direction, oxidants such as oxygen, carbon monoxide, hydroperoxide, or cataloreactant (lattice oxygen present in some metal oxides) were used as hydrogen scavenger (Eq. 2.2). For examples, Thomas et al. developed a platinum/ammonia/oxygen catalytic system for one-step production of aromatic amines from aromatic compounds at a temperature of about 1000 °C. They also proposed an alternative protocol that the mixture of benzene and ammonia in the vapor phase react with a reducible metal oxide such as nickel oxide at a temperature of about 100–1000 °C [65]. Schmerling realized the preparation of aromatic amines by reacting an aromatic compound with anhydrous ammonia in the presence of a Group VII B metals, such as molybdenum, tungsten or chromium and a promoter consisting of metallic oxide such as an oxide of copper, iron, nickel, silver or gold at a temperature in the range from 200 to 600 °C. An efficient Ni/NiO/ZrO₂ cataloreactant system achieved a benzene conversion of about 13 % at high temperature and pressure. In this case, nickel metal not only activates the C–H bond of benzene but also the N–H bond of ammonia. NiO acts as an oxidant to produce water thereby driving the equilibrium towards the formation of aniline. Zirconium oxide works both as promoter and as a dispersant for nickel centers [66].

Squire found that improved conversions of aromatic compounds and higher yields of aromatic amine were obtained when the aromatic compound reacted with ammonia in the presence of water at elevated temperature and pressure using a conditioned Ni/NiO/ZrO₂ cataloreactant [67]. Delpesco also provided a strategy for improving the conversions of aromatic compounds to aromatic amines by prolonging the life of cataloreactant at a temperature from about 150–500 °C at a pressure of from about 10–1000 atm. To this end, a dopant such as an oxide of lanthanum, samarium, holmium, europium, erbium, praseodymium, neodymium, terbium, ytterbium, dysprosium, yttrium, or mixtures thereof was added into Ni/NiO/ZrO₂ cataloreactant [68].

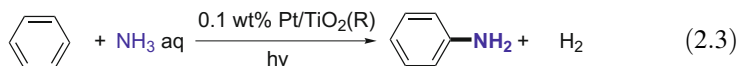
For the selective nitrogenation of benzene with ammonia, Hödlerich et al. investigated the catalytic effect of a series of Group VIII metals (e.g., Ru, Rh, Pd, Pt, Cu, and Ni) as the catalyst supported on carriers such as alumina, silica and zeolite in a plug flow reactor or in a continuously stirred tank reactor. Oxygen or carbon monoxide was employed respectively to shift the reaction equilibrium towards aniline formation [69]. Durante et al. developed a process for catalytic oxidative amination of aromatic hydrocarbons in which aromatic feedstock contacts with oxygen under suitable reaction conditions in the presence of a catalyst

comprising three essential components: a support, such as Ba^{2+} exchanged X-zeolite, transition metal ions, such as vanadium, niobium, copper, palladium, nickel and silver and combinations thereof, and a mono or binucleating ligand, such as the compounds which contain at least one nitro or nitroso group [70].

New method and technology was also applied to find efficient catalytic system for direct amination of aromatics. For examples, to find an efficient cataloreactant system for the direct amination of benzene to anilines, Hagemeyer et al. employed high-throughput synthesis and screening method, accomplishing efficiently screening around 25,000 samples. Rh/Ni-Mn/K-TiO_2 was found to be the optimized cataloreactant, achieving a stable 10 % benzene conversion and >95 % selectivity to aniline at 300 °C and 300 bar. Moreover, the cataloreactant can be readily regenerated by a separated reoxidation in air [71]. Hu and coworkers introduced catalytic distillation technology to the direct amination of benzene to aniline with aqueous ammonia and hydrogen peroxide over a $\text{V-Ni/Al}_2\text{O}_3$ catalyst [72].

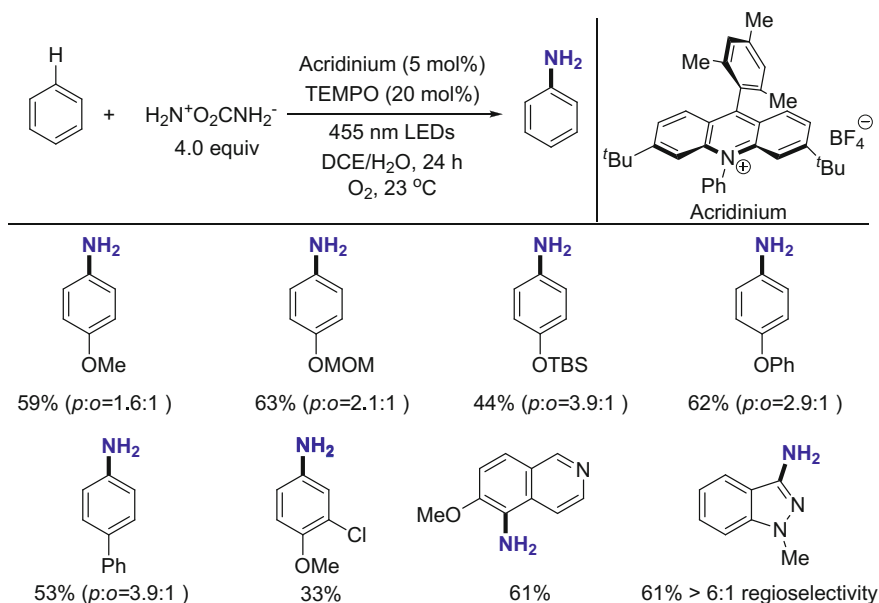
Recently, some copper catalyzed approaches have emerged for this transformation. For instance, Hu and coworker developed a Cu-TS-1 catalyst for the direct preparation of aniline from benzene and aqueous ammonia using hydrogen peroxide as oxidant. Experimental results support that the formation of Cu-O-Ti species on the catalyst promotes the chemical absorption of ammonia which play important role to the enhanced performance for N-H bond activation [73]. Bal and coworkers developed a Cu(II) nanoclusters supported on CuCr_2O_4 spinel nanoparticles which displays a selectively catalytic activity for direct oxyamination of benzene with ammonia to aniline using H_2O_2 as oxidant under mild aqueous reaction conditions. Author claimed that the synergy between the Cu(II) nanocluster and CuCr_2O_4 spinel nanoparticles is crucial for its high catalytic activity [74]. Hu and coworkers reported a direct amination of benzene to aniline with H_2O_2 and $\text{NH}_3\cdot\text{H}_2\text{O}$ over Cu/SiO_2 catalyst [75].

In addition, Yoshida and coworkers described a direct aromatics amination by aqueous ammonia with Pt-loaded TiO_2 photocatalyst at room temperature [76]. The selectivity of this reaction is quite good, while the yield is low (Eq. 2.3).

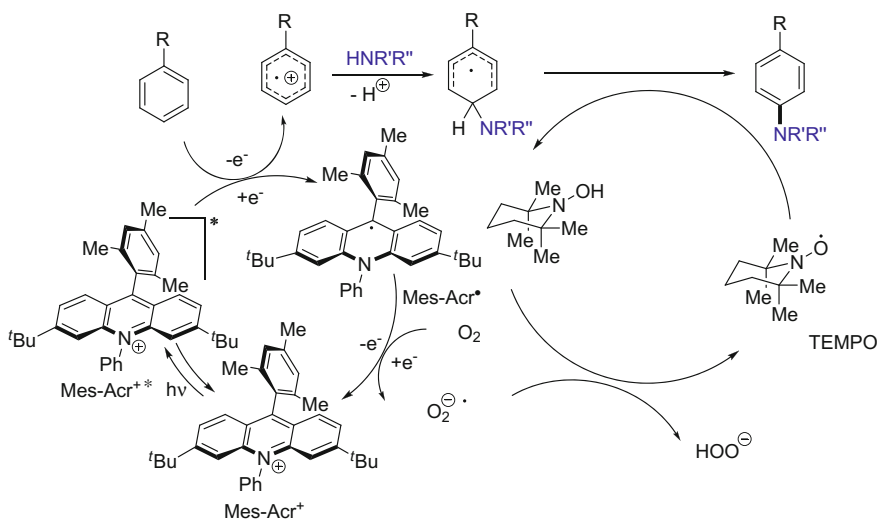


Nicewicz and coworkers reported a site-selective arene C-H amination via photoredox catalysis [77]. In this case, an organic photoredox-based catalytic system, comprising of an acridinium photooxidant and TEMPO, was developed to achieve the atom-economical use of ammonia to form anilines, without the need for prefunctionalization of the aromatic substrate (Scheme 2.2).

Under the proposed mechanism (Scheme 2.3), the reaction initiated by photoinduced electron transfer (PET) from an arene to generate an arene cation radical, which was attacked by an amine to give σ -adduct, followed by deprotonation and oxidative aromatization to afford the desired arene. In the presence of TEMPO, dioxygen served as a terminal oxidant and played a role in both the regeneration of the photoredox catalyst and the aromatization.



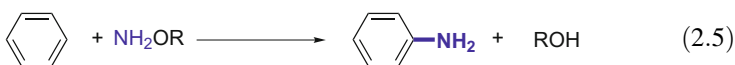
Scheme 2.2 Synthesis of anilines using ammonium salt as ammonia equivalent



Scheme 2.3 Proposed mechanism

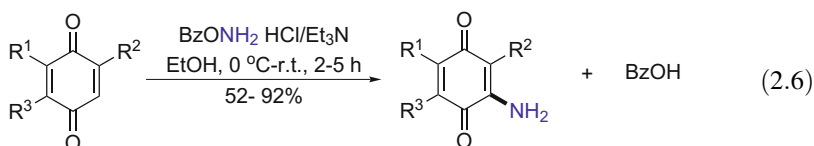
Wu, Tung and coworkers developed a photocatalytic hydrogen-evolution cross-couplings for benzene C–H amination [78]. Aniline was produced from the reaction of benzene with ammonia in the presence of 1-methylquinolinium and

2.2.2 Dehydrative Nitrogenation of Aromatic Compounds with Hydroxylamine



The nitrogenation of aromatics with hydroxylamine was known since the beginning of the 20 century (Eq. 2.5). In 1901, Graebe and Jaubert independently reported the amination of aromatic compounds with hydroxylammonium chloride in the presence of Friedel-Crafts catalyst [79, 80]. Keller and Smith developed hydroxylamine-O-sulfonic acid and its derivatives as aminating reagent [81]. Later, Kovacic investigated the mechanism of this chemistry more thoroughly [82]. Kovacic et al. also investigated a variety of hydroxylamine salts for aminating aromatic compounds in the presence of Friedel-Crafts catalysts. Toluene and the halobenzenes give predominant ortho-para orientation. Hydroxylammonium bromide shows the strongest activity for the amination of toluene [83].

Usually, the transformations base on this strategy requires stringent conditions. More importantly, the employment of relatively expensive and toxic hydroxylamine in nitrogenation of aromatics is not favored from the economically advantageous or environmentally benign point of view. Notably, the direct synthesis of hydroxylamines by the oxidation of ammonia with hydrogen peroxide reported by Mantagazz et al. provides a potential for tandem in situ formation of hydroxylamine and followed dehydrative nitrogenation with arene [84]. Moreover, the study of the direct amination of benzene with hydroxylamine will help not only understand this chemistry but also provide information for designing new transformation in the future.



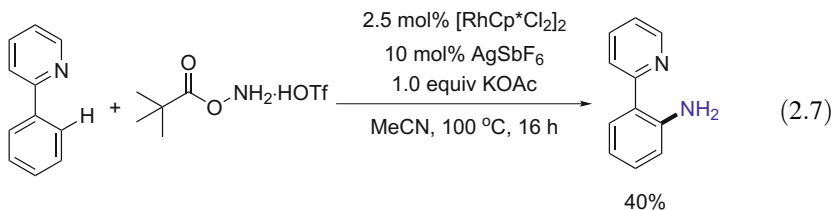
Bittner and coworkers developed a one-step amination of 1,4-naphthoquinones and 1,4-benzoquinones (Eq. 2.6) [85]. *O*-Benzylhydroxylamine was found as an efficient aminating agent in this chemistry. A 1,4-addition-aromatization-reductive elimination mechanism was proposed for rationalizing this transformation.

Pez and coworkers developed amination of benzene and toluene with hydroxylamine in the presence of transition metal redox catalyst [86]. They found that $\text{Na}_4\text{PW}_{11}\text{O}_{39}\text{Fe}(\text{H}_2\text{O})$ shows its best performance in 85 % acetic acid. $\text{Pd}/\text{MoO}_3/\text{SiO}_2$ is an active heterogeneous catalyst in sulfuric acid/acetic acid (1:2). The protonated amino radical cation generated by reduction of NH_2OH by transition metal redox species is considered as key species in this amination chemistry.

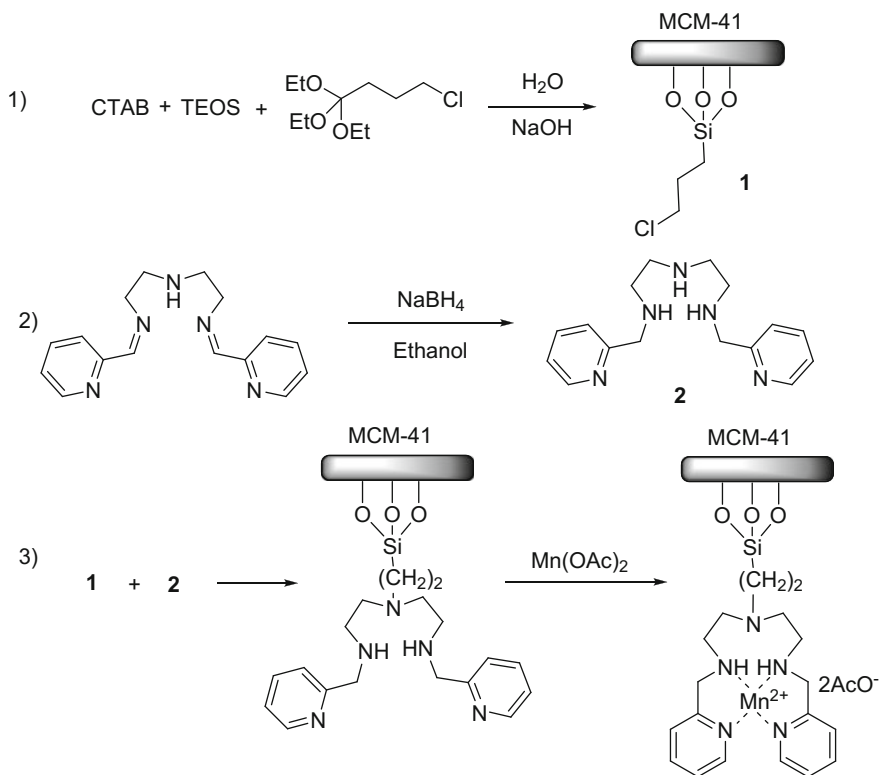
Hu and coworker developed the silica, titania, ceria, and γ -alumina supported vanadium catalyst, which shown unique reactivity for the direct amination of toluene with hydroxylamine hydrochloride, over 50 % total yield of toluidines was obtained on the γ -alumina supported vanadium catalyst operated at optimal conditions [87]. They also investigated a sodium metavanadate catalyzed one-step amination of benzene to aniline with hydroxylamine [88]. The reaction became more efficient in the presence of oxygen. A free-radical mechanism was proposed based on the results of EPR, ^{51}V NMR, and UV-Vis characterization. Moreover, the catalytic activity of a series of vanadium complexes with N,O- or O,O-ligands for the liquid-phase direct amination of benzene with hydroxylamine to aniline has been investigated [89]. $[\text{VO}(\text{OAc})_2]$ was proved to be the most active catalyst for the amination because of its relatively greater electrophilicity and smaller steric hindrance of ligand.

Parida and coworkers investigated the catalytic activity of mesoporous Mn-MCM-41 for one-step amination of benzene in acetic acid-water under mild reaction conditions using hydroxylamine as aminating agent [90]. They also reported copper modified amine functionalized mesoporous MCM-41 for the single step amination of benzene with hydroxylamine. The Cu-amine-MCM-41 modified sample shows highest catalytic activity, namely, 72 % benzene conversion and 100 % aniline selectivity. The catalyst prepared by co-condensation method shows better catalytic activity than samples prepared by impregnation method [91]. Recently, they developed a Mn(II)-dien(ampy) immobilized organo modified MCM-41 catalyst for C-H bond amination of benzene in the presence of hydroxylamine in acetic acid-water medium [92]. The organic-inorganic hybrid heterogeneous catalyst synthesized as shown in Scheme 2.5 demonstrates high catalytic activity and selectivity for one step amination of benzene. It can be reused for multiple cycles without appreciable loss in catalytic activity.

Wang and coworkers investigated the activity of a series of $\text{CuO-V}_2\text{O}_5/\text{Al}_2\text{O}_3$ catalysts for liquid-phase amination of toluene to toluidines [93]. The adding of copper species to $\text{V}_2\text{O}_5/\text{Al}_2\text{O}_3$ catalyst showed a peculiar behavior, maintaining a high activity toward toluene amination. An optimum catalyst, 1.6 %CuO-15 % $\text{V}_2\text{O}_5/\text{Al}_2\text{O}_3$, achieved more than 60 % total yield of toluidines under optimized conditions. Catalyst characterizations revealed that the addition of copper improved the formation of V^{5+} species, thus enhancing the activity of the catalyst.



Glorius and coworkers developed a Rh[III]-catalyzed ortho C-H amination using $\text{PivONH}_2\cdot\text{HOTf}$ as nitrogen source [94]. Although the reaction only gave the

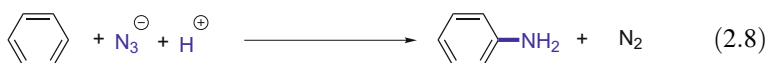


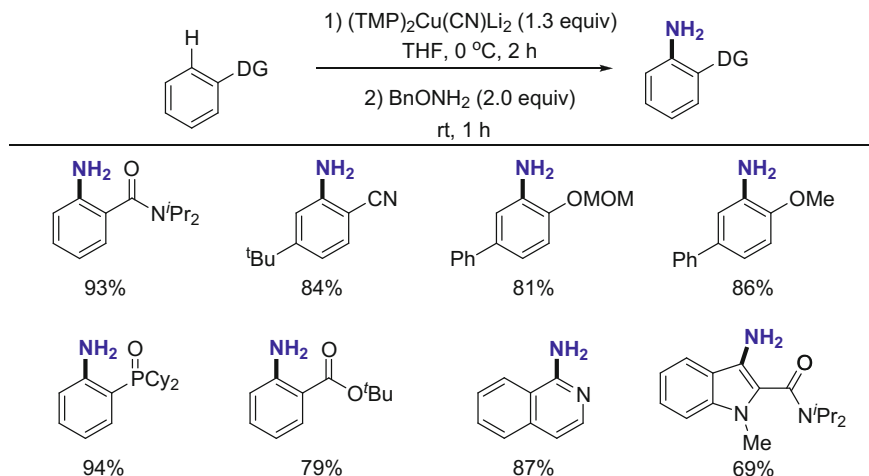
Scheme 2.5 Synthetic route for immobilization of the manganese complex

corresponding free aniline in 40 % yield, it threw light on group-assisted C–H bond amination (Eq. 2.7).

Hirano, Uchiyama, and coworkers reported ortho amination of aromatics via deprotonative cupration [95]. A variety of substrate with different substituting groups were well-tolerated in this chemistry (Scheme 2.6). This reaction was triggered by deprotonative ligation of BnONH_2 to the Cu center to form $\text{ArCu}(\text{NHOBn})(\text{CN})\text{Li}$, followed by redox reaction of Cu to furnish the desired products. The authors also realized CuCN-catalyzed amination of metalated aromatics.

2.2.3 Nitrogenation of Aromatic Compounds with Azide Sources



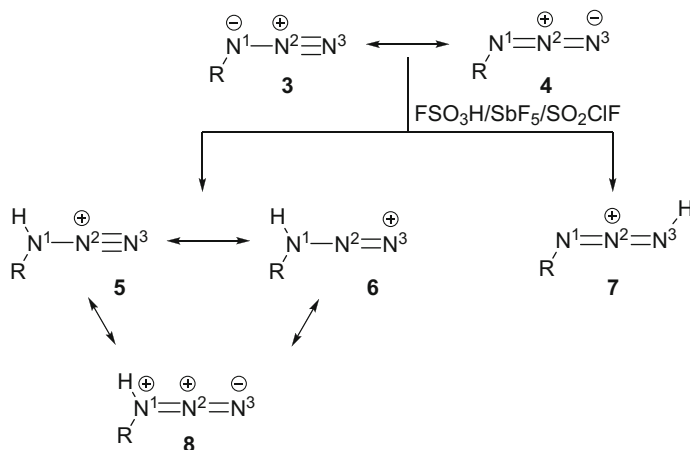
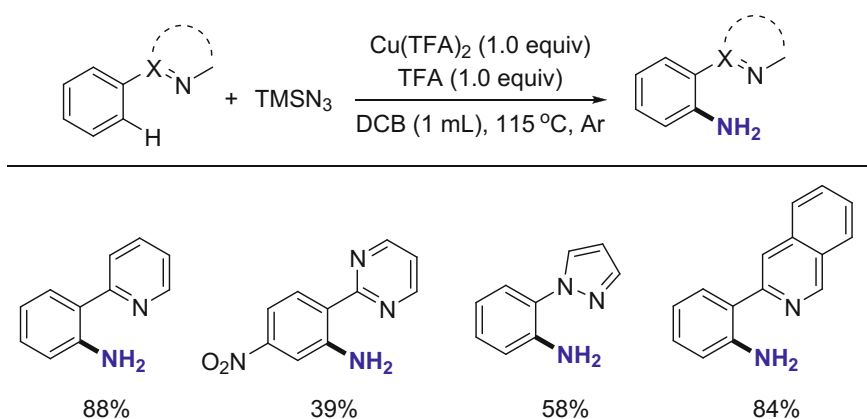


Scheme 2.6 Ortho amination of aromatics

The reaction of benzene with sodium azide in the presence of concentrated sulfuric acid or aluminum chloride catalyst was first explored by Schmidt, giving aniline in low yield (Eq. 2.8) [96]. Later, Kovacic investigated the mechanism of Lewis Acids catalyzed aromatic amination with hydrazoic acid [97]. Aminodiazonium ion could also be used for the direct amination of aromatics. Olah and coworkers investigated the protonation of hydrazoic acid and alkyl azides with superacid, such as $\text{FSO}_3\text{H}/\text{SbF}_5$, HF/SbF_5 , or HF/BF_3 , finding the formation of stable aminodiazonium ions by ^1H , ^{13}C , ^{15}N NMR spectroscopic studies [98]. The aminodiazonium ion could also be prepared in situ from $\text{NaN}_3/\text{AlCl}_3/\text{HCl}$, $(\text{CH}_3)_3\text{SiN}_3/\text{AlCl}_3/\text{HCl}$, or $(\text{CH}_3)_3\text{SiN}_3/\text{HF}/\text{BF}_3$. ^1H , ^{13}C , ^{15}N NMR spectroscopic studies and related molecular orbital calculation implied that azides are protonated in superacids exclusively on $N-1$, forming aminodiazonium ions (**5**, **6**, **7** in Scheme 2.7). The aminodiazonium ion serves as an efficient direct electrophilic aminating agent for aromatic compounds.

Takeuchi and coworkers developed a reaction of hydrazoic acid with aromatic compounds in the presence of both trifluoromethanesulphonic acid (TFSA) and trifluoroacetic acid (TFA) giving aromatic amine in good yield [99]. The strong acidity of TFSA and the high solubility of TFSA in TFA play an important role in the aromatic amination. In addition, the combine of trimethylsilyl azide/triflic acid, $\text{NaN}_3/\text{triflic acid}/\text{aromatics}$, or $\text{HN}_3/\text{HOTf}/\text{TFA}$ was found effective for one-step preparation of primary aromatic amines from aromatics [100–102]. Very recently, Surya Prakash and coworkers developed an electrophilic nitrogenation of aromatics with sodium azide in $\text{BF}_3\text{--H}_2\text{O}$ [103].

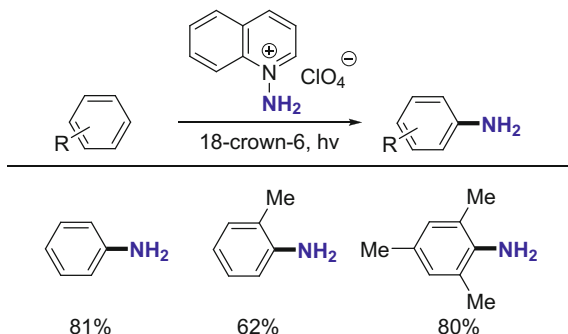
Zhu and coworkers developed a copper mediated direct nitrogenation of aromatic C–H to give primary anilines using TMSN_3 as nitrogen source [104]. N-heterocycles as chelating group assist the ortho C–H bond amination. A range of functional group are tolerated in this chemistry (Scheme 2.8).

**Scheme 2.7** Protonation of hydrazoic acid**Scheme 2.8** Chelation assisted C(*sp*²)-H amination

2.2.4 Direct Aromatic Nitrogenation with Nitrenium Ion

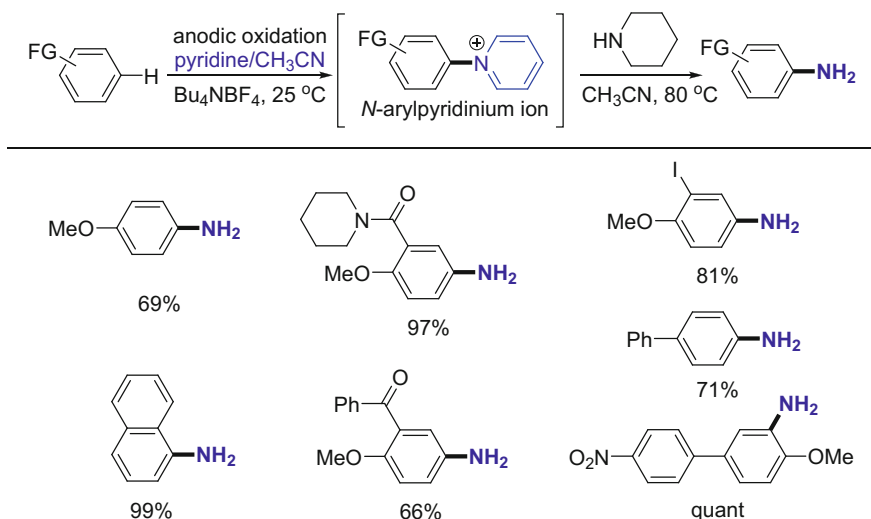
Under certain conditions, nitrenium ion could be used for direct aromatic amination. Takeuchi and coworkers reported a photolyses of 1-(Amino and alkylamino)-2-methyl-4,6-diphenylpyridinium [105], 1-aminopyridinium salts, 2-aminoisoquinolinium salt and 1-aminoquinolinium salts for efficient nitrogenation of aromatic compounds in the aromatics-trifluoroacetic acid [106]. The use of 1-aminoquinolinium perchlorate showed the highest reactivity in these photolyses, giving primary aryl amine in high yield (Scheme 2.9). The yields of arylamines were generally increased in the presence of a small amount of crown ether. Further

Scheme 2.9 Photolyses of 1-aminoquinolinium perchlorate for aromatic amination



investigation demonstrates that the parent nirtrenium ion is not free but interacts intimately with both the heterocyclic nitrogen atom and the counter-ion. The interaction with the heterocyclic nitrogen stabilizes the singlet state rather than the triplet to favor aromatic amination [107].

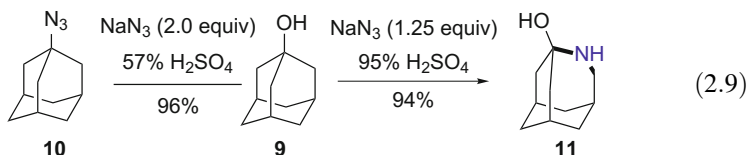
Yoshida and coworkers developed a method for C–H nitrogenation of aromatics based on electrochemical oxidation of aromatic compounds in the presence of pyridine followed by the reaction of the resulting *N*-arylpyridinium ions with piperidine to selectively give aromatic primary amines as products [108]. This transformation provides a metal-free protocol for one-pot synthesis aromatic amines with broad functional groups compatibility (Scheme 2.10).



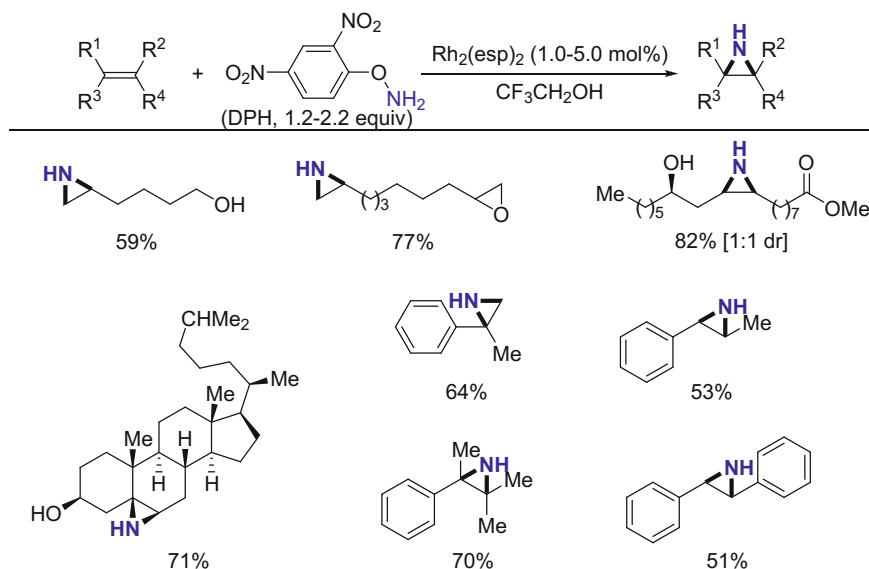
Scheme 2.10 Synthesis of functionalized aromatic primary amines by electrochemical C–H amination

2.3 C–C Bond Nitrogenation

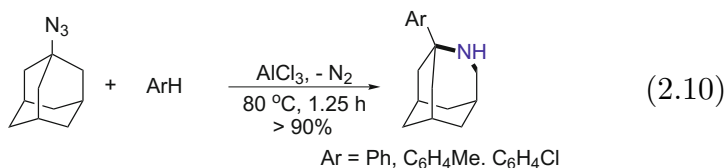
In 1977, Sasaki and coworkers reported that bridgehead azides such as 1-adamantyl azide (**10**) were prepared in high yields from the corresponding bridgehead alcohols (**9**) on treatment with sodium azide in 57 % $\text{H}_2\text{SO}_4\text{--CHCl}_3$ [109]. The rearranged products, such as 4-azahomoadamantan-3-ol (**11**), were also obtained from the corresponding bridgehead alcohols on treatment with sodium azide in 95 % H_2SO_4 in high yield (Eq. 2.9).



Kovacic and coworkers observed the reaction of 1-azidoadamantane with aromatic substrates in the presence of aluminium chloride giving the corresponding 3-aryl-4-azahomoadamantane in >90 % yields (Eq. 2.10) [110, 111].



Scheme 2.11 Direct and stereospecific N–H aziridination of olefins



Kurti and coworkers developed a general method for the synthesis of N–H aziridine from unfunctionalized olefins under mild conditions using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) via homogeneous rhodium catalysis [112]. This method is operationally simple, scalable, broad functional group tolerable, and fast at ambient temperature, furnishing N–H aziridines in good to excellent yields (Scheme 2.11).

2.4 Conclusion and Outlook

Amines are important organic compounds with a wide range of application in the synthesis of fine chemicals. C–H or C–C bond direct nitrogenation (amination) provides the simplest route for the synthesis of amines. As for the direct C–H nitrogenation of aliphatic hydrocarbon for the synthesis of aliphatic primary amine has not been achieved and are still full of challenge. In addition, although related aromatic C–H bond nitrogenation have made great strides in the past few decades, there are tremendous needs to improve the efficiency and selectivity of the reaction. As for the direct C–C nitrogenation, only a few examples have been developed and more efforts deserve to be devoted to this area.

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