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Direct nuclear halogenation of deactivated aryl and N-heteroaryl amines: An overview

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ABSTRACT

Halogenated aromatic amines are versatile building blocks in organic synthesis and form an important class of bioactive molecules in pharmaceutical chemistry. An array of novel methods and reagent systems has been developed to affect its synthesis. This review presents an overview of methods used for efficient and regioselective nuclear halogenation of deactivated aryl and N-heteroaryl amines.

Keywords: Nuclear halogenation, deactivated aryl amines, oxidative halogenation, regioselective halogenation, N-heteroarenes.

INTRODUCTION

Aromatic and heteroaromatic amino halides are important and versatile synthetic intermediates. These amino halides undergo carbon-carbon bond formation via cross-coupling reactions such as Stille, Suzuki, Heck, and Sonogashira or carbon-heteroatom bond formation via aromatic functionalization protocols and give access to a plethora of amino functionalized intermediates of enormous synthetic utility [1]. The halogen containing aromatic amines are important building blocks in synthetic organic chemistry for the synthesis of a number of natural and bio-active substances as well as pharmaceuticals. In addition, numerous biologically active molecules and a large number of industrially valuable products such as pesticides, insecticides, herbicides, fire retardants, and other new materials carry amino and halogen functionalized aromatic units in their structure [2].

Halogenation of activated and electron-rich aromatic amines is relatively easy and can be carried out under mild reaction conditions. On the other hand, halogenation of deactivated aromatic as well as heterocyclic amines possessing pyridine, quinoline, isoquinoline, diazine, 1,2- and 1,3-

azole units is a challenge, and often involve harsh reaction conditions. A variety of halogenation reagents and different strategies have been developed by the chemists all over the world in order to halogenate deactivated aromatic and heteroaromatic amines. It is the purpose of this report to present an overview of these reagents and methods for the benefit of researchers working in the field of synthetic chemistry.

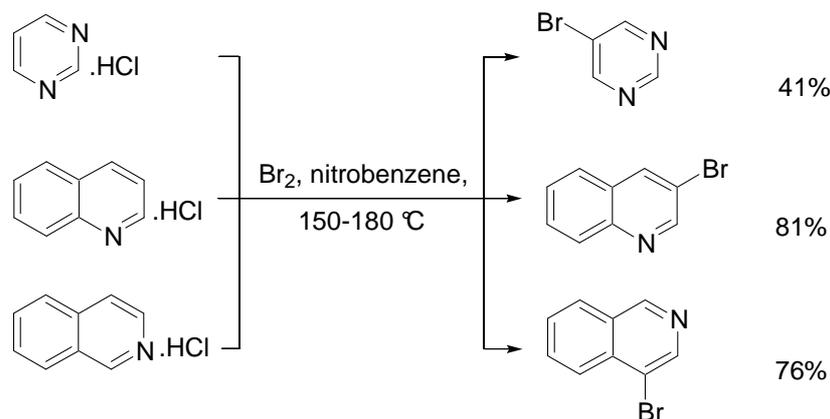
The most common strategies to introduce halogen atom on the aromatic nucleus are, electrophilic aromatic halogenation and *Sandmeyer/Balz-Schiemann* reaction. Electrophilic aromatic halogenation using molecular halogen is one of the older reactions known to organic chemists. The activated aromatic compounds such as aniline and phenol derivatives can be halogenated with much ease with this method. However, formation of mixture of *ortho*- and *para*-substituted products and polyhalogenation are problems that frequently limit the synthetic utility of this procedure [3].

Replacement of the diazonium group of an arene diazonium compound by the halide or pseudo-halide is a well-known tactic by which halogen can be introduced into deactivated aromatic ring. Aryl chlorides, bromides and iodides are commonly prepared by *Sandmeyer reaction* and aryl fluorides are prepared by *Balz-Schiemann reaction*. These reactions are of limited synthetic importance since the yields usually decrease with additional substituents present on aromatic ring. Moreover, appropriate availability of halo and amino groups is essential which limits synthetic utility of this method [4]. Another important strategy involves reaction of substrate with strong bases to generate benzyne intermediate which is attacked by appropriate halide ion to produce halogenated product.

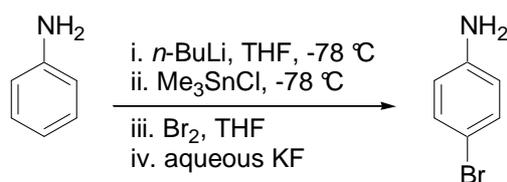
Other than above mentioned pathways, there are several ways by which halogen atom can be introduced into aromatic nucleus. Some of these strategies and novel reagent systems used for halogenation of deactivated aromatic/heteroaromatic amines are discussed briefly in this review.

II. Bromination

Among the halogenation reactions, bromination has been extensively studied. In past few decades, a plethora of literature has been made available for bromination of aromatic compounds using conventional reagents as well as novel reagent systems. Unlike chlorine and fluorine, liquid bromine is convenient to handle. Aromatic compounds can be brominated by the treatment with bromine in the presence of Lewis acid catalyst, most often FeBr_3 . Bromination of reactive substrates like phenols and anilines is easily carried out at room temperature with liquid Br_2 without any catalyst, which generally results in polybrominated products together with some oxidation products. Deactivated *N*-heterocycles like pyrimidine, quinoline and isoquinoline can be brominated using bromine at elevated temperature in nitrobenzene (Scheme 1) [5].

**Scheme 1.**

Smith *et al.* have reported a tin amide (PhNH-SnMe₃) mediated one pot selective bromination method for electron poor *N*-heterocyclic amines. Aromatic amines on reaction with *n*-butyllithium followed by trimethyltin chloride yields tin amides *in situ* which on treatment with elemental bromine followed by work up with aqueous KF, provide corresponding brominated aromatic amines (Scheme 2).

**Scheme 2.**

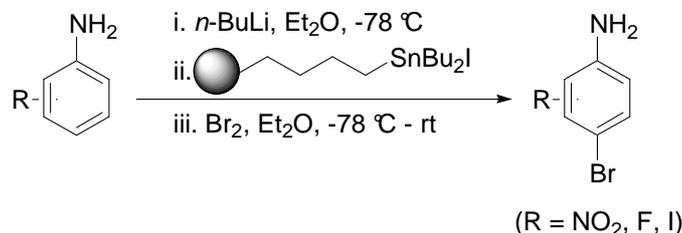
Using the same strategy, 2-aminopyrimidine and 3-aminoquinoline were brominated to the corresponding bromo derivatives (Table 1) [6].

Table 1. Selective bromination of *N*-heterocyclic amines via tin amides

Entry	Substrate	Product	Yield (%)
1			88
2			36

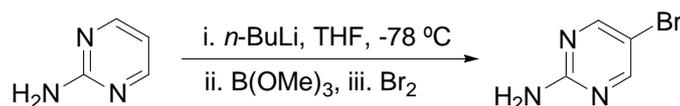
But, this method is not suitable for large-scale production as the residual tin compounds cause to decompose the bromo product. Chrétien and co-workers developed a regioselective halogenation method in order to minimize this drawback by using recyclable polymer supported triorganotin halides [7]. Treatment of aromatic amines with *n*-butyllithium and polymer-supported organotin halides gave polymer-bound *N*-triorganostannylamines, which on subsequent treatment with bromine, produced *para*-brominated aryl amines in 46-70% yield. Polymer-supported *N*-stannylated reagents are superior to Bu₃SnCl or Me₃SnCl in obtaining monobrominated products with very less contamination of tin. High degree of selectivity attributes to the steric involvement of polymer matrix.

The methodology was successfully extended to iodinate aryl amines using iodine monochloride as iodine source. Iodoaniline derivatives were obtained in better yield (63-67%) and *para*-selectivity compared to bromoanilines due to large size of iodine.



Scheme 3.

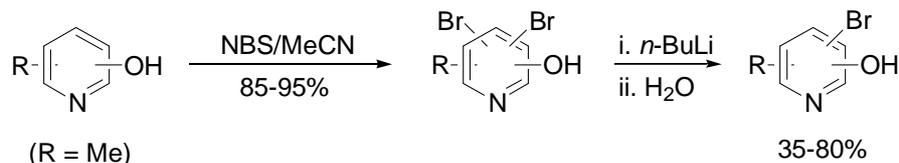
A similar boron amide-mediated monobromination method for heterocyclic amines was reported by Zhao *et al.* [8]. This one pot approach includes lithiation of heterocyclic amine with *n*-BuLi followed by boron amide formation using trimethyl borate and subsequent reaction with bromine to afford the corresponding brominated product. Using this method 2-aminopyrimidine gave 2-amino-5-bromopyrimidine in 70% yield (Scheme 4).



Scheme 4.

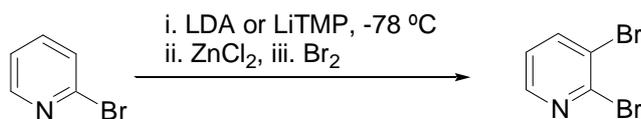
Meana *et al.* have utilized lithium-halogen exchange strategy to prepare regioselective bromohydroxypyridines from hydroxypyridines [9]. The two-step sequence involves dibromination of hydroxypyridines with *N*-bromosuccinimide (NBS) in MeCN followed by bromine-lithium exchange using RLi to obtain lithiated pyridine derivatives. Subsequent reaction of lithiated pyridines with water affords regioselective bromohydroxypyridines in high yields. Various alkyl lithium compounds were tested to optimize halogen exchange conditions and *n*-BuLi was found to be superior to *s*-BuLi and *t*-BuLi.

Using this protocol, iodination was carried out by reacting lithiated pyridines with iodine or *N*-iodosuccinimide (NIS) to afford regioselective bromoiodohydroxypyridines in high yields (60-95%).



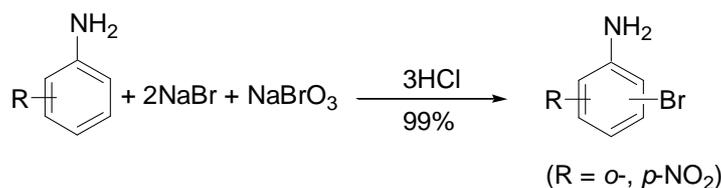
Scheme 5.

In an attempt to synthesize 1,2-dibromoarenes, Menzel *et al.* introduced transmetalation strategy and converted aryl *ortho*-lithiated intermediates to aryl zinc compounds using ZnCl₂ [10]. Subsequent bromination of aryl zinc compounds with Br₂ afforded 1,2-dibromoarenes in an impressive yield. This is because of the thermodynamic stability of aryl zinc species than aryl lithium species. Using this protocol, 2,3 dibromopyridine was obtained in 90% yield from 2-bromopyridine (Scheme 6).



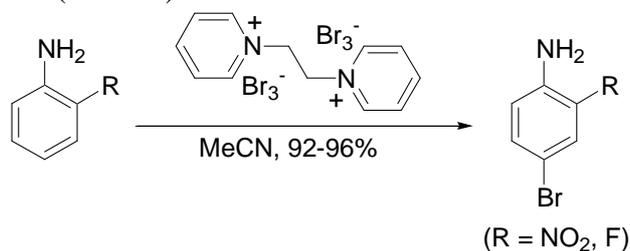
Scheme 6.

It is always desirable to replace hazardous liquid bromine and there have been continuous efforts in this direction. Adimurthy *et al.* have treated liquid bromine precursor (NaBr.NaBrO₃ in 5:1 ratio) with NaOCl to obtain NaBr.NaBrO₃ in 2:1 ratio which acts as brominating agent with 40% active bromine content [11]. Reagent was found to be versatile but not regioselective and was used to brominate phenols, CH active compounds and deactivated amines. *Ortho*- and *para*-nitroanilines were converted to the corresponding dibromo derivatives in high yields (98-99%) (Scheme 7).



Scheme 7.

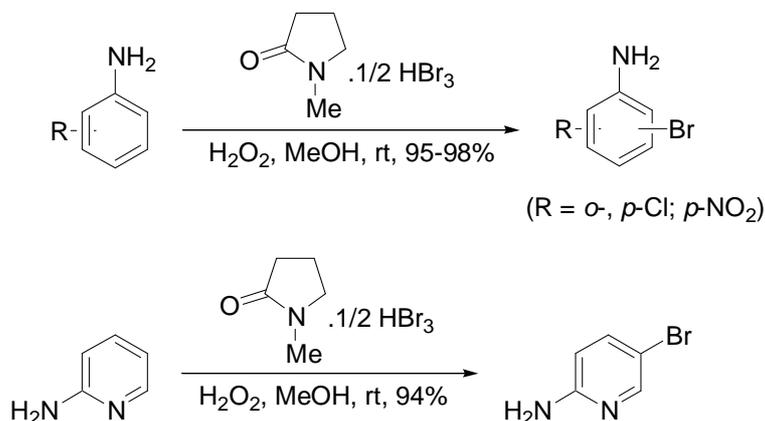
Organic ammonium tribromides have been found to be promising alternatives to the hazardous liquid bromine due to their solid crystalline nature and ease of handling. Many solid brominating agents such as 1,8-diazabicyclo[5.4.0]undec-7-ene hydrobromide perbromide (DBUHBr₃), dioxane dibromide and pyridine hydrobromide perbromide have been used for brominating sensitive heterocyclic substrates [12]. Kavala *et al.* synthesized 1,2-dipyridiniumditribromideethane (DPTBE), a novel recyclable ditribromide reagent and used for bromination of aryl amines (Scheme 8) [13]. The reagent has relatively high bromine content (48%) than other tribromides and was prepared by the reaction of pyridine and 1,2-dibromoethane followed by treatment with KBr and Oxone[®]. The advantage of this reagent is that it lacks phase transfer ability which makes it highly soluble in aqueous phase which facilitates its easy removal from organic phase (usually contaminated with organic ammonium cations when other tribromides are used) containing brominated product. Acetonitrile is the most suitable solvent for the bromination with DPTBE. It can also be employed in solvent free conditions by grinding in a mortar with desired substrate at room temperature. *o*-Nitro- and *o*-fluoroanilines were regioselectively brominated by using DPTBE to the corresponding bromo derivatives in higher yields (92-96%).



Scheme 8.

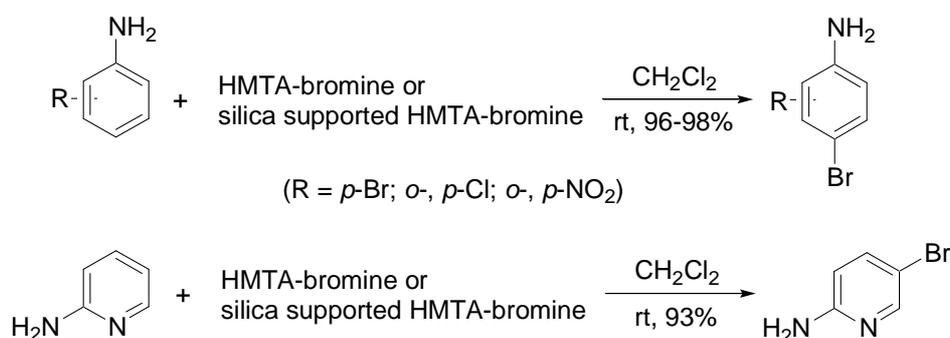
Singhal *et al.* have used the combination of *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) and aqueous H₂O₂ for bromination of aryl amines [14]. H₂O₂ reacts with MPHT and generates HOBr which facilitates electrophilic attack of bromonium ion on aromatic ring. In the absence of H₂O₂, poor yields were obtained. Singhal *et al.* also studied solvent effect by carrying out bromination in various solvents e.g. MeOH, EtOH, MeCN, *n*-PrOH and MeOH-MeCN (1:1).

Methanol was found to be the superior solvent compared to other solvents used in the study. The reaction was found to be temperature dependent. In refluxing methanol, mixture of mono and dibromo products was obtained, while at room temperature, selectively monobrominated products were obtained. Using this reagent system, deactivated aryl and heteroaryl amines were selectively brominated in excellent yields (95-98%) (Scheme 9).



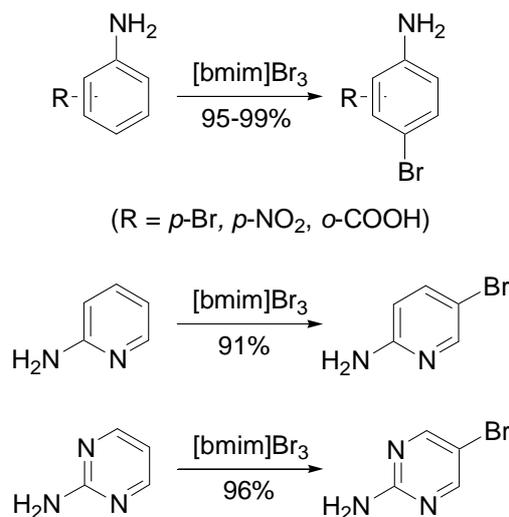
Scheme 9.

Heravi and co-workers have used hexamethylenetetramine-bromine (HMTAB), a simple 1:2 charge transfer complex for electrophilic bromination of deactivated anilines [15]. They reported that the catalyst forms complex with π -electrons of the aromatic compound. Reactivity of the reagent was improved by supporting it on various inorganic surfaces such as alumina, zeolite and silica gel. Among these solid supports, best results were obtained with silica gel. Using this protocol, deactivated aryl amines were regioselectively brominated in dichloromethane at room temperature with high yields (Scheme 10).

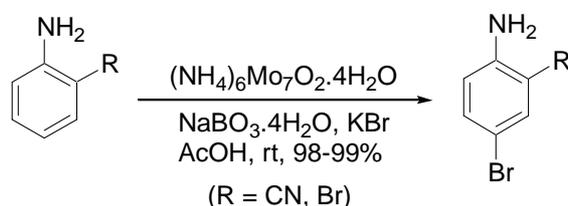


Scheme 10.

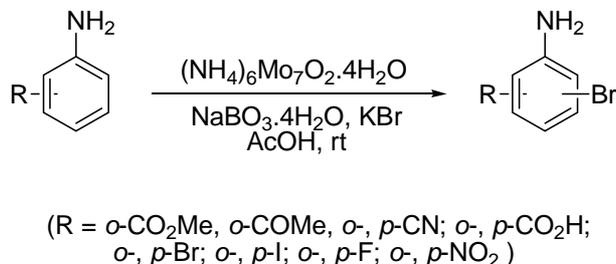
Le *et al.* reported the use of an ionic liquid, 1-butyl-3-methylimidazolium tribromide ([bmim]Br₃) for regioselective bromination of aryl amines [16]. Reaction occurs rapidly under solvent free conditions and leads to selective monobrominated product preferentially at *para* position. Monobromination occurs at *ortho* position in case *para* position is blocked. Several less active aryl amines were efficiently brominated to the corresponding monobrominated products using this ionic liquid (Scheme 11).

**Scheme 11.**

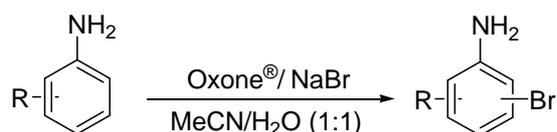
In recent years, oxybromination approach, which involves the use of an oxidant and a bromine source, has been used widely for bromination. Choudary *et al.* reported the oxybromination method in acetic acid using KBr-H₂O₂ combination in the presence of catalytic amount of ammonium molybdate [17]. The reaction is likely to involve formation of peroxomolybdenum species as a result of reaction between ammonium molybdate and H₂O₂ which catalyzes the oxidation of Br⁻ to Br⁺, which in turn rapidly brominates the substrate. Using this method, 2-aminobenzonitrile and 2-bromoaniline were selectively converted into the corresponding brominated products in high yields (98-99%) (Scheme 12).

**Scheme 12.**

Roche *et al.* reported that ammonium molybdate increases the rate of reaction but its absence does not affect the yield and selectivity of the product [18]. They described oxybromination of the deactivated anilines using KBr and sodium perborate (NaBO₃·4H₂O) or H₂O₂ in acetic acid. Using this method, several deactivated anilines were selectively monobrominated in good yields (51-99%) (Scheme 13).

**Scheme 13.**

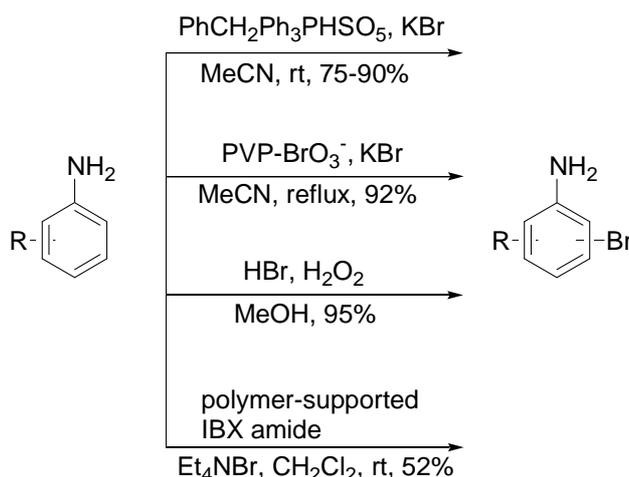
Lee and co-workers used the NaBr/Oxone[®] combination for the bromination of deactivated anilines in aqueous acetonitrile at room temperature (Scheme 14) [19]. The reaction is believed to involve the formation of hypobromite ion (OBr^-), due to the oxidation of bromide ion by peroxymonosulfate ion (HSO_5^-). Monobrominated products were obtained selectively in good-to-moderate yields (73-93%). However, 2-aminoacetophenone furnished dibromo product under the same conditions.



(R = *p*-CN, *p*-Cl, *p*-COMe, *o*-CO₂Me, *o*-COMe)

Scheme 14.

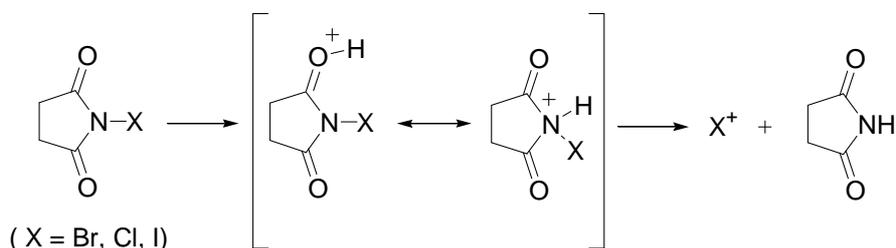
Similarly, KBr/benzyltriphenylphosphonium peroxymonosulfate [20], KBr/poly (4-vinyl pyridine)-supported bromate (PVP-BrO₃⁻) [21], aqueous hydrohalic acid- H₂O₂ [22] and tetraethylammonium bromide (TEAB) and polymer-supported IBX (2-iodoxybenzoic acid) amide [23] have also been used for nuclear bromination of deactivated aryl amines (Scheme 15).



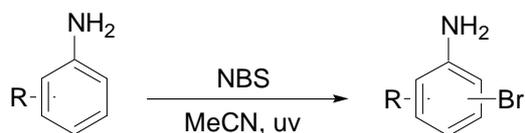
(R = electron withdrawing group)

Scheme 15.

N-Halocarboxamides (NXS, X = Br, Cl, I) have been proved to be superior aromatic halogenating agents. Being solid in nature, these reagents are easily available commercially in bulk quantities, and are stable for longer periods. Moreover, the recovery and recycling of the by-product, succinimide to NXS is an added advantage with these reagents. These reagents can be used as a source of X⁺ ions in electrophilic aromatic halogenations. Halogenation involving these reagents can be catalyzed by Lewis acids. But, it is unsuitable for the heteroarenes due to the complex formation with Lewis acids. Polar solvents such as DMF, MeCN, alcohols, THF, etc. and non-polar halogenated solvents are suitable for halogenation reaction. Halogenation can also be carried out using inorganic acids (e.g. H₂SO₄) and organic acids (e.g. AcOH, *p*-TSA, CF₃CO₂H). It is supposed to involve protonation of carbonyl oxygen followed by generation of positive halogen species (X⁺) (Figure 1) [24].

**Figure 1.**

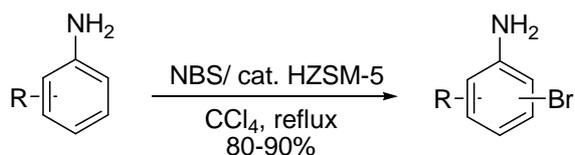
Chhattise *et al.* have reported regioselective photochemical aromatic monobromination using NBS [25]. Bromination was carried out in acetonitrile without any catalyst. The effect of the solvent was studied and it was found that the more polar solvents enhance the reactivity of NBS to favor nuclear bromination. A range of aryl and heteroaryl amines was brominated with good selectivity (Scheme 16).



(R = electron withdrawing group)

Scheme 16.

Paul and co-workers prepared zeolite catalyst, HZSM-5 ($\text{SiO}_2/\text{Al}_2\text{O}_3 = 40$) and used it with NBS in CCl_4 at reflux temperature for regioselective nuclear monobromination [26]. Excellent yields (80-90%) of monobrominated products were obtained with methylantranilate and 2-nitro-4-chloroaniline (Scheme 17). The synthetic utility of the catalyst was studied by running the reactions without catalyst in which dibrominated products were formed.

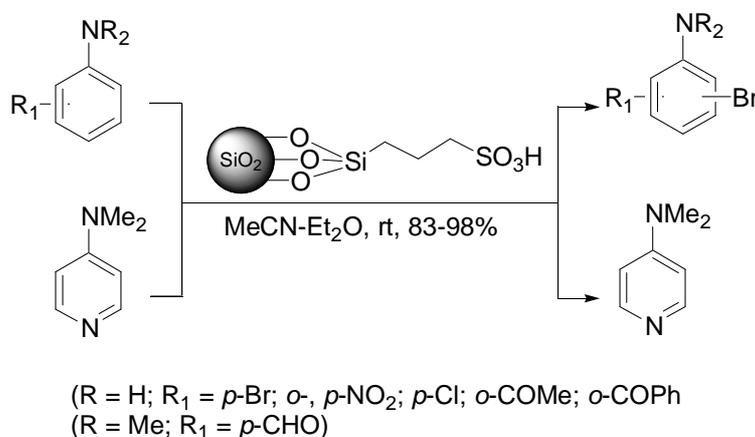


(R = CO_2Me , NO_2 , Cl)

Scheme 17.

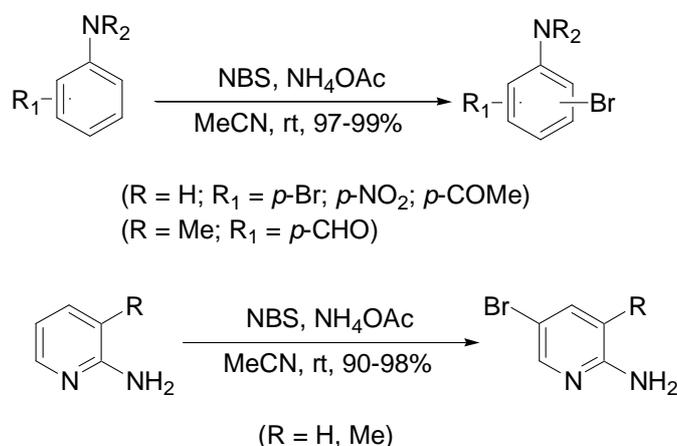
Das and co-workers developed a convenient procedure for regioselective nuclear monobromination of aromatics and heteroaromatics using NBS in the presence of sulfonic acid mediated silica [27]. This catalyst is also recyclable and re-usable and unlike NBS/HZSM-5 mediated reaction, high temperature was avoided and monobromination was carried out smoothly at room temperature in high yields (83-98%). Synthetic utility of sulfonic acid-mediated silica was examined by exploring possibilities of monobromination of *p*-cresol using several other heterogeneous catalysts e.g. SiO_2 , silica chloride, $\text{NaHSO}_4 \cdot \text{SiO}_2$, $\text{H}_2\text{SO}_4 \cdot \text{SiO}_2$, wet $\text{ClSO}_3\text{H} \cdot \text{SiO}_2$, *p*-TSA. SiO_2 , Amberlyst-15, sulfated zirconia and $\text{HClO}_4 \cdot \text{SiO}_2$ in MeCN-Et₂O at room temperature. But a mixture of mono and dibrominated products was obtained. Various

deactivated aryl and heteroaryl amines were monobrominated regioselectively using this protocol within a short period of time (Scheme 18).



Scheme 18.

Das *et al.* employed catalytic amount of ammonium acetate with NBS in acetonitrile for regioselective monobromination [28]. NBS reacts with NH₄OAc to produce acetic acid and HBr which facilitates rapid generation of Br⁺ ion for nuclear bromination. The effect of NH₄OAc was examined by carrying out bromination in its absence, where mixture of products was obtained. Using this reagent system, several deactivated aryl and heteroaryl amines were monobrominated in high yields (90-99%) (Scheme 19).



Scheme 19.

III. Chlorination

The methods of bromination and chlorination are closely related with each other. The common conditions for nuclear chlorination involve the use of molecular chlorine in acetic acid or in non-polar solvent like carbon tetrachloride. Reactivity of molecular chlorine can be increased by addition of Lewis acid such as AlCl₃, FeCl₃ which assist Cl-Cl bond polarization. The attacking entity may be Cl⁺, formed due to the polarization by catalyst. Chlorination of aromatic amines proceeds via *N*-chloramines. The mechanism involves heterolytic cleavage of N-Cl bond that occurs via a transition state which loses chloride anion and generates phenylnitrenium ion (anilenium ion) (Figure 2) [29].

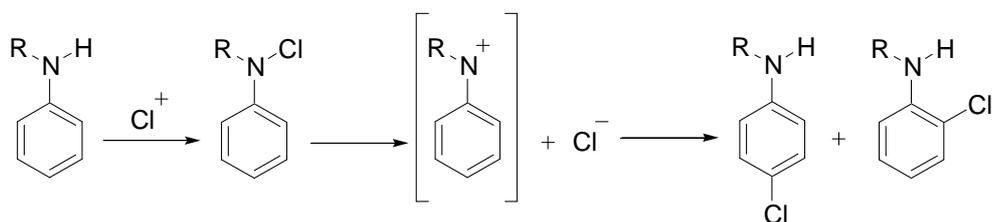


Figure 2.

The charge on nitrogen atom is delocalized into the aromatic ring as shown in Figure 3.

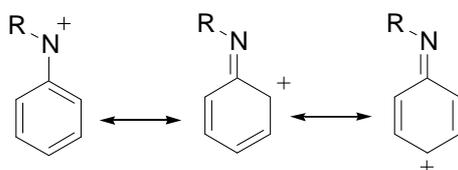
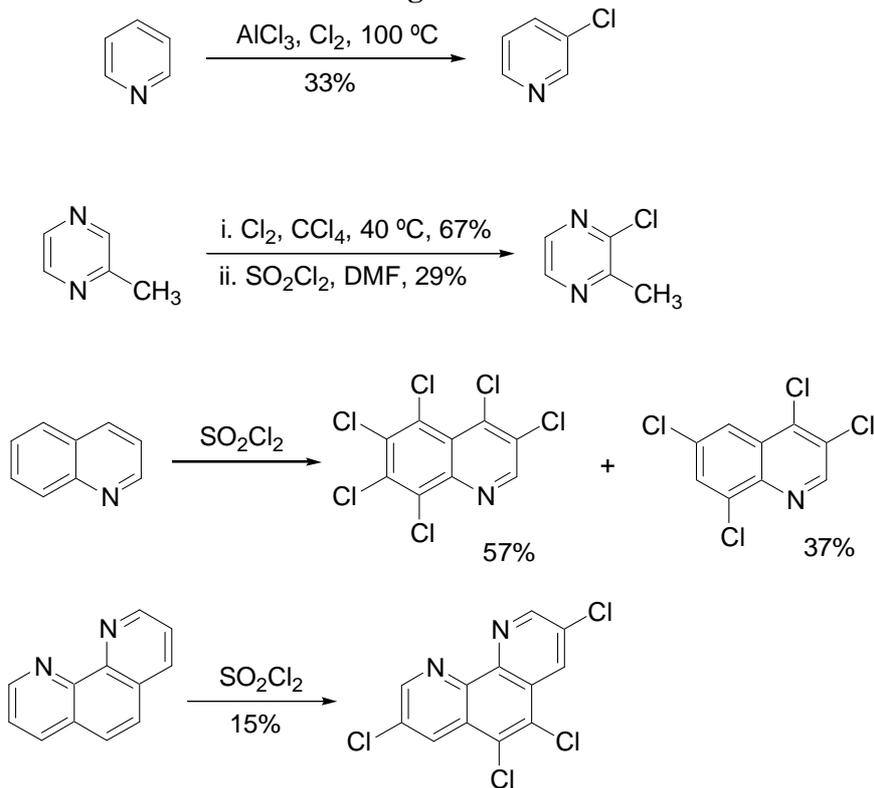


Figure 3.



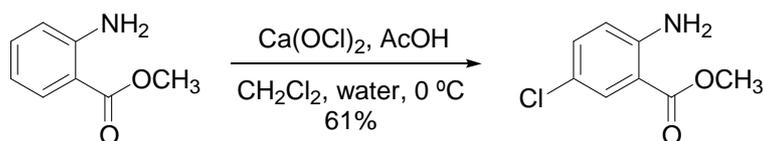
Scheme 20.

Presence of electron-withdrawing substituents decreases the amount of charge delocalized into aromatic nucleus, which results in decrease in the rate of thermal rearrangement and gradual increase in the amount of starting amine. A wide variety of reagents are available for aromatic chlorination e.g. molecular chlorine, sulfonyl chloride, alkyl and acyl hypochlorites, inorganic chlorides, $\text{KCl}/m\text{-CPBA}/18\text{-crown-6}$, $\text{KCl}/\text{NaBO}_3/\text{Na}_2\text{WO}_4$, $\text{KCl}/\text{H}_2\text{O}_2/\text{NH}_4\text{VO}_3$, *N*-

chlorosuccinimide, benzyl trimethylammonium tetrachloroiodate, dichlorine monoxide, *N*-chloramines, *N*-chloramides, and *N*-chlorosulfonamides. But, there appears to be fewer methods reported in the literature for nuclear chlorination of deactivated amines. Many chlorinating reagents fail to chlorinate deactivated aromatics [30].

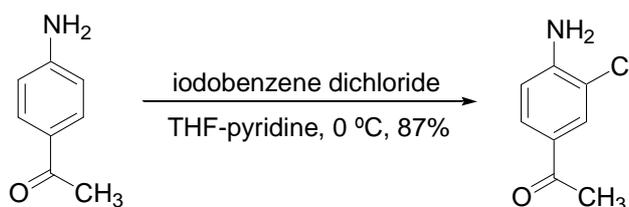
Chloroarenes are generally prepared by using molecular chlorine and sulfuryl chloride. Deactivated aryl and heteroaryl amines were chlorinated using these reagents (Scheme 20) [31].

There are many disadvantages associated with molecular chlorine and sulfuryl chloride such as toxicity, poor regioselectivity, operational hazards and violent reactions. Okabe *et al.* have studied chlorination of methyl anthranilate using $\text{Ca}(\text{OCl})_2$ [32]. Earlier this compound was prepared by chlorinating anthranilic acid with sulfuryl chloride in 49% yield [33]. To avoid large quantities of SO_2 and HCl , they tried the chlorination with *N*-chlorosuccinimide in acetonitrile, but failed to get the desired product. The reaction was also carried out at lower temperature (0°C) in aqueous acetone, but complex mixture was formed and product could not be isolated. Finally, dichloromethane-water biphasic system was found to be suitable for chlorination to get methyl 5-chloroanthranilate in 61% yield (Scheme 21).



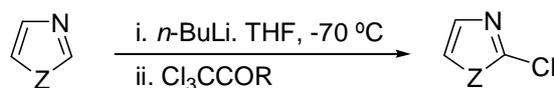
Scheme 21.

Zanka *et al.* developed large scale monochlorination process for 4-aminoacetophenone using iodobenzene dichloride [34]. Iodobenzene dichloride was prepared by passing chlorine gas through a solution of iodobenzene in dichloromethane and collected as a precipitated solid. The reaction was carried out on 20 kg scale. 4-aminoacetophenone was monochlorinated to 4-amino-3-chloroacetophenone using iodobenzene dichloride in THF-pyridine mixture at 0°C in 87% yield (Scheme 22).



Scheme 22.

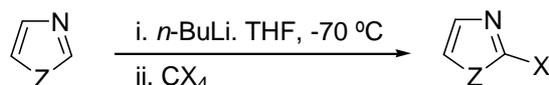
Lithio-heterocycles, which act as nucleophiles have proved to be useful for halogenation of heterocycles. They can be prepared by either direct metallation or by metal-halogen exchange reaction. Normally lithiations are carried out with alkyl lithiums or lithium amides. *n*-BuLi, *s*-BuLi, and *t*-BuLi are generally used. Lithium diisopropyl amide (LDA) is widely used but lithium 2,2,6,6-tetramethylpiperidide (LiTMP) which is more basic and less nucleophilic, has found particular use in metallation of heterocycles. Boga *et al.* have reported selective electrophilic chlorination of heterocycles to prepare 2-chloroheterocycles using metal-halogen exchange mechanism [35]. These heterocycles were first converted to the 2-lithioheterocycles with *n*-BuLi and then by trapping 2-lithioheterocycles with trichloroacetyl chloride or ethyl trichloroacetate or trichloroacetic anhydride gave 2-chloroheterocycles (Scheme 23).



(Z = S, O, N-Me; R = Cl, OEt, OCOCCl₃)

Scheme 23.

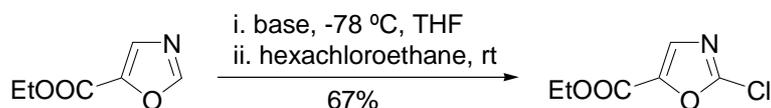
Better yields were obtained with ethyl trichloroacetate as compared to trichloroacetyl chloride as later leads to involve formation of dichloroketene which reduces the yield. Similarly, tetrabromo- or tetrachloromethane and 2-lithioheterocycles produce the corresponding 2-bromo- or 2-chloroheterocycles in high yields (65-90%) through a metal-halogen exchange mechanism (Scheme 24) [36].



(Z = S, O, N-Me; X = Cl, Br)

Scheme 24.

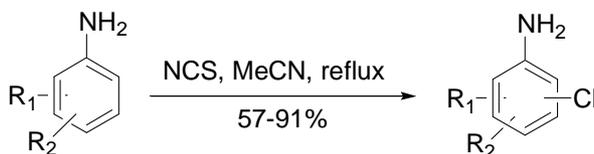
Atkins *et al.* used same strategy to prepare 2-chlorooxazoles in good-to-moderate yields (61-88%) by trapping 2-lithiooxazoles with hexachloroethane (Scheme 25) [37]. Yields were improved to the extent of 5-10% by running the reactions for longer time. This method is a modification of their previous method where 2-lithiooxazoles were generated using borane complexation [38]. Lazaar *et al.* have also reported preparation of chloro- and iodo- derivatives of unprotected pyridine carboxylic acid derivatives using directed lithiation approach [61].



(base = *n*-BuLi, LiHMDS)

Scheme 25.

N-Chlorosuccinimide (NCS) has been found to be attractive reagent for the chlorination of aromatic nuclei. Like NBS, it can be used alone in suitable polar and non-polar solvents or in the presence of catalysts. Chlorination using NCS in non-polar solvents results in a mixture of products and lower yield. But these problems could be easily bypassed using NCS in protic solvents. It can be used in inorganic and organic acids, proving the ability of the reagent to chlorinate activated aromatics. Nickson *et al.* have reported a convenient procedure for monochlorination of deactivated aniline derivatives using NCS in acetonitrile (Scheme 26) [39].

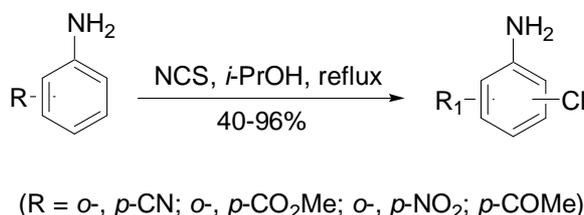


(R₁ = H, Me; R₂ = CO₂Me, CN, NO₂, CF₃)

Scheme 26.

This above procedure was improved by Zanka *et al.* by replacing acetonitrile with isopropyl alcohol. The combination is suitable for large-scale chlorination of deactivated aryl amines. The

reaction pathway involves in situ formation of 2-propyl hypochlorite from NCS and isopropanol which acts as a chlorinating agent (Scheme 27) [40].



Scheme 27.

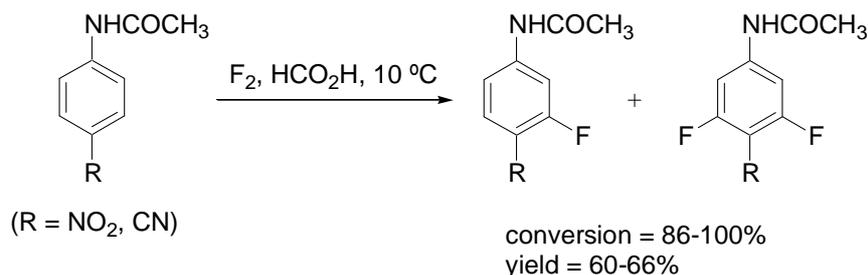
Using this method, monochlorinated products were obtained with excellent selectivity and yields (40-96%). The reaction of 4-aminoacetophenone gave lower yield due to the formation of side chain chlorinated products in both acetonitrile and isopropanol as well.

IV. Fluorination

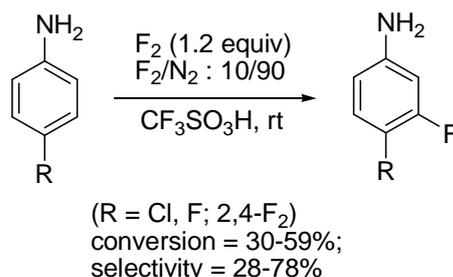
Introduction of fluorine atom in the aromatic ring of active drugs is the subject of wide interest in pharmaceutical industry. The most commonly employed methods used for the preparation of fluoroaromatics are fluorodediazotization of aryl amines (*Balz-Schiemann reaction*), exchange of halogens using fluoride source, electrochemical fluorination and electrophilic NF fluorinating agents. Molecular fluorine can be used for aromatic substitution but with limitations due to extreme toxicity, uncontrolled reaction and formation of polyfluorinated compounds. Its utility is improved by diluting fluorine with nitrogen 10:90 or 5:95 (v/v mixture). Solubility of fluorine is important to carry out the reactions in homogeneous conditions. Gambaretto *et al.* studied solubility of fluorine in different solvents such as CFCl₃, CFC₂CF₂Cl, CF₃COOH and CF₃CH₂OH. They reported that those solvents and the additives having –OH group are able to increase the solubility of fluorine due to the formation of –OF i.e. hypofluorite [41].

Conte *et al.* investigated fluorination of benzene, toluene, phenol and benzoic acid in various solvents [42]. Higher yields were obtained with the use of protic solvents like 2,2,2-trifluoroethanol and trifluoroacetic acid. Fluorination can be carried out using aprotic solvents and yields can be improved using additives such as 2,4-dinitrophenol and CF₃COOH. Use of KOH, NaOH in methanol or water has a positive impact on yield due to the formation of hypofluorite. In addition, trifluoromethanesulfonic acid [43], 98% formic acid and concentrated sulfuric acid [44] are excellent reaction media to achieve high degree electrophilic aromatic fluorination.

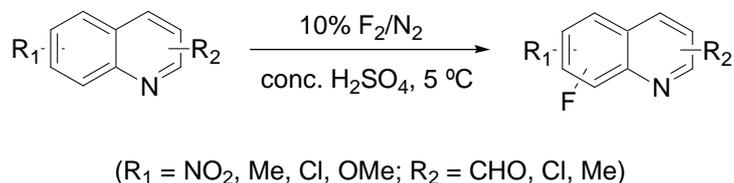
Chambers and co-workers have systematically studied fluorination of 1,4-disubstituted aromatic compounds using elemental fluorine [45]. The study revealed that the aromatic compounds bearing powerful deactivating group at *para* position to an activating group can be selectively fluorinated using F₂ in strong polar medium (98% H₂SO₄ or HCO₂H). Thus, 4-nitroacetanilide and 4-cyanoacetanilide were fluorinated to the corresponding fluoro derivatives in 60-66% yield using F₂/N₂ at 10 °C in HCO₂H (Scheme 28).

**Scheme 28.**

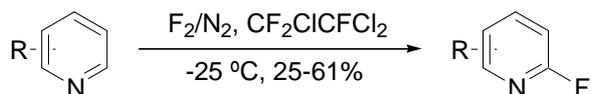
Alric *et al.* studied electrophilic fluorination of aniline derivatives with fluorine in H₂SO₄ and CF₃SO₃H (Scheme 29) [46]. Strong acidic medium protonates aniline and thus prevents it from oxidation. Due to electron-withdrawing effect of ammonium substituent, *meta* fluorinated products were obtained. Triflic acid was found to be more effective than sulfuric acid to get higher *meta*-regioselectivity. Selectivity was further improved by the use of Lewis acid catalyst such as antimony pentafluoride, presumably due to increase in acidity of the medium. Mole ratio of fluorine is also important. Better conversion and selectivity was obtained with the use of 1.2 equivalents of fluorine. Presence of *ortho-para*-directing group at *para* position to the amino group further improved the selectivity of *m*-fluorinated anilines.

**Scheme 29.**

Direct fluorination of nitrogen containing heterocycles can be achieved using elemental fluorine. Chambers *et al.* reported fluorination of quinoline derivatives with fluorine in concentrated sulfuric acid. Solvents like formic acid and acetonitrile produced tarry mass and therefore avoided. In all quinoline derivatives, selective electrophilic attack of fluorine occurs on benzenoid ring of quinoline (at -5 and -8 positions) due to the deactivation of heterocyclic ring towards electrophilic attack by protonation of nitrogen atom in acidic medium (Scheme 30) [47].

**Scheme 30.**

Van der Puy carried out direct fluorination of pyridines bearing alkyl, halogen, ester, or ketone functionalities in trichlorotrifluoroethane to prepare the corresponding 2-fluoro-substituted pyridines. (Scheme 31) [48].



(R = 4-Me, 4-Et, 4-*i*-Pr, 4-Bn, 4-CO₂Me, 4-COMe;
3-Me, 3-CO₂Me; 3,5-Me₂; 3,5-Cl₂)

Scheme 31.

The reaction involves formation of pyridine difluoride (PyF⁺F⁻) which decomposes to 2-fluoropyridines due to attack of fluoride ion on C-2(6) of the *N*-fluoropyridinium cation, followed by loss of HF.

In another communication, Chambers *et al.* reported selective fluorination of pyridine and quinoline derivatives using fluorine-iodine mixtures in the presence of CF₂ClCFCl₂ [49]. The reaction of fluorine-iodine mixture causes *in situ* formation of IF, which is the source of both iodonium and fluoride ion. Iodonium ion forms complex with sp² hybridized nitrogen atom which activates adjacent carbon to facilitate attack from fluoride ion. Subsequent elimination of hydrogen iodide yields fluoro substituted compound (Figure 4).

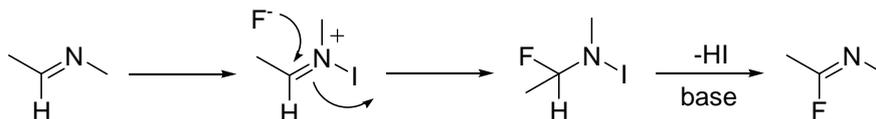
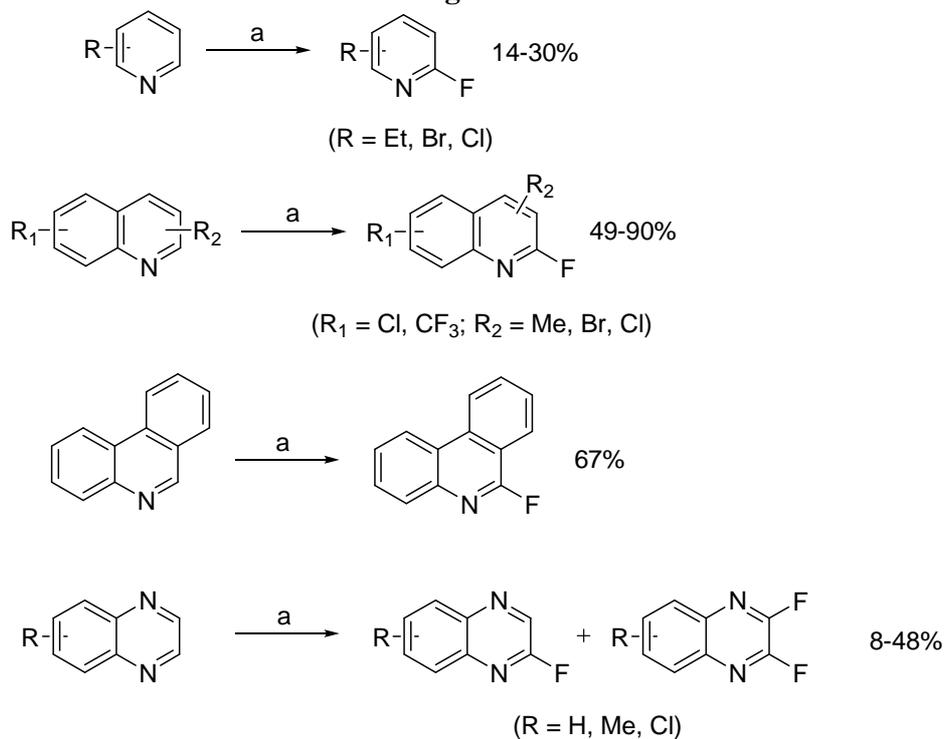


Figure 4.

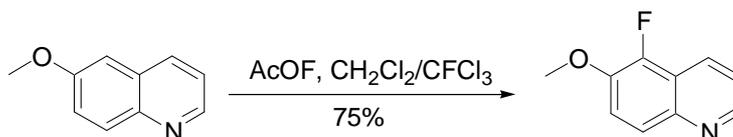


a. F₂, I₂, Et₃N, CF₂ClCFCl₂, 0 °C

Scheme 32.

Derivatives of pyridine, quinoline, and quinoxaline were selectively monofluorinated using this method. However 6-nitroquinoxaline, 6,7-dichloroquinoxaline, pyrazine, pyrimidine and pyridazine were unable to give any fluorinated products. Chambers *et al.* reported that the addition of tertiary amine such as triethylamine to the system promotes the elimination of hydrogen iodide and results in improved yield (Scheme 32). Fluorination was also carried out in hexafluorobenzene but lower conversion was observed. Other solvents such as dichloromethane, THF, DMF and nitromethane were found to be unsuitable for this reaction due to insolubility of iodine.

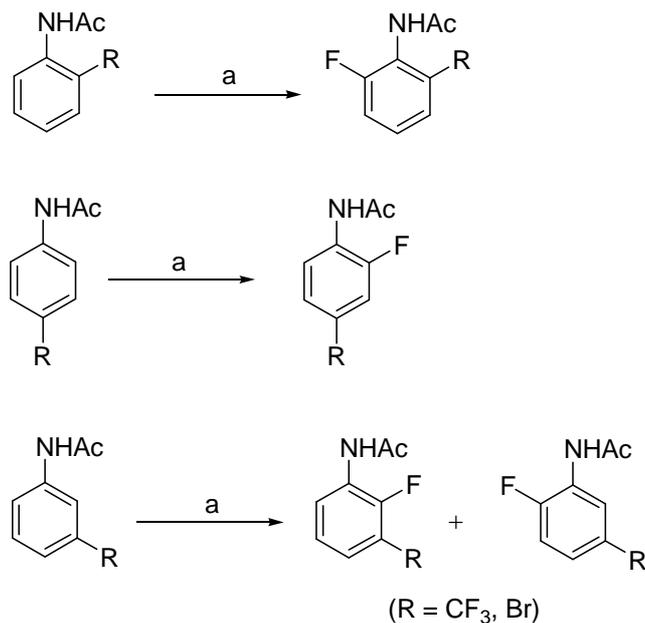
Extreme reactivity and corrosive nature of elemental fluorine further stimulated development of efficient fluorinating agents, which include xenon difluoride (XeF₂), perchloryl fluoride (FCIO₃), acetyl hypofluorite (AcOF) and trifluoromethyl hypofluorite (CF₃OF). Lerman and co-workers have introduced AcOF for electrophilic fluorination of aromatics [50]. It is a mild fluorinating agent compared to F₂, CF₃OF, CF₃CF₂OF and CF₃COOF and can be applied to both activated and deactivated aromatics. Selective fluorination of arenes takes place according to the electron density of various sites in the aromatic ring. In the case of activated aromatics such as anisole, unusually high *ortho/para* ratio was observed. This can be well explained using addition-elimination hypothesis, which includes the 1,2 addition of acetyl hypofluorite across high electron density region between *ipso* and *ortho* positions followed by elimination of acetic acid to yield *ortho* fluorinated arenes. 6-Methoxyquinoline in which 5,6 bond is electron rich, was fluorinated using AcOF to give 5-fluoro-6-methoxyquinoline in 75% yield (Scheme 33).



Scheme 33.

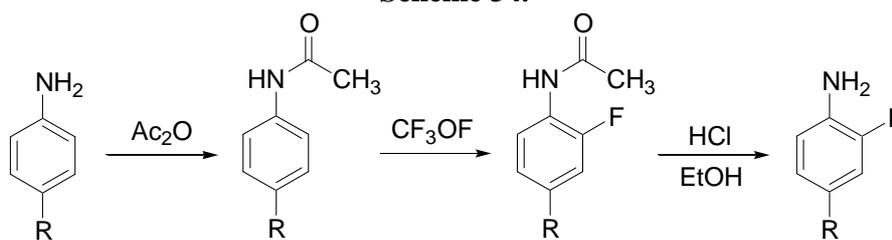
Aryl amine derivatives were protected prior to the fluorination to avoid the formation of unstable N-F compounds. Acetanilide, with electron-donating substituents on *ortho* position gave undefined products because easy elimination of acetic acid was not possible. With electron-donating groups present on *meta* or *para* position, mixture of monofluoro and difluoro derivatives was obtained. Less activated or deactivated compounds such as *o,p*-bromoacetanilide and *o,p*-(trifluoromethyl)acetanilide gave selectively monofluoro compounds. *m*-Bromoacetanilide and *m*-(trifluoromethyl)acetanilide yielded two possible *o*-fluoro isomers in 1:1 ratio (Scheme 34).

Fifolt *et al.* used fluoroxytrifluoromethane (FTM) and bis(fluoroxy)difluoromethane (BDM) for fluorination of a variety of aromatic substrates [51]. These gaseous reagents are relatively stable and can be stored for a longer time period with little decomposition. It has been demonstrated that both reagents react with aromatic substrates by an electrophilic substitution mechanism. With activated aromatics, mixture of products was formed. With deactivated aromatics, FTM and BDM react slowly. *Ortho* substitution is favored in non-polar solvents and *para* substitution is favored in protic solvents. 2-Fluoro-4-(trifluoromethyl)aniline was synthesized on 20 g scale (overall yield 57%) using this method. The same reaction sequence was followed for the other deactivating groups like chloro, nitro or cyano. (Scheme 35).



a. AcOF, CH₂Cl₂, CFCl₃

Scheme 34.



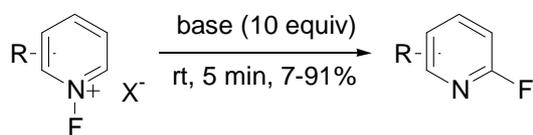
(R = CF₃, Cl, NO₂, CN)

Scheme 35.

Due to difficulties associated with the conventional fluorinating reagents, novel electrophilic N-F fluorinating reagents are being developed and are found to be efficient for fluorination and at the same time, safe for handling and storage. These fluorinating reagents are either neutral compounds or quaternary ammonium salts in which fluorine binds with organonitrogen compounds, which behaves as a good leaving group to enhance the reactivity of fluorine. Electrophilic fluorine-transfer takes place either by nucleophilic displacement at fluorine or single electron transfer involving a radical cation species. *N*-Fluoropyridinium salts, *N*-fluorobenzenesulfonimide (NFSi), *N*-fluoroperfluoro[*N*-(4-pyridyl)-*N*-methanesulfonyl]amide, NF₄BF₄, (CF₃SO₂)₂NF, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis-tetrafluoroborate or Selectfluor[®] (F-TEDA-BF₄), Accufluor[®] or 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate), etc. are the common reagents used for electrophilic fluorination [52]. But, there appears to be a few examples of direct electrophilic aromatic fluorination using N-F fluorinating agents.

2-Fluoropyridines were prepared by base induced decomposition of *N*-fluoropyridinium salts with BF₄, SbF₆ or PF₆, at room temperature [53]. Good-to-moderate yields (60-80%) have been obtained using bases such as triethyl amine, pyridine and tetra *n*-butylammonium fluoride

(TBAF). The method was successfully applied to 2-fluoropyridine derivatives possessing electron-withdrawing and donating substituents. For this, *N*-fluoropyridinium salts were prepared from pyridines by using molecular fluorine and a metal salt of strong acid or Lewis acid. (Scheme 36).

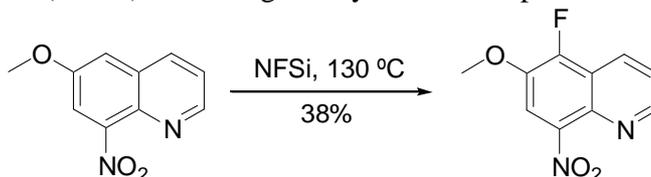


(X = BF₄, SbF₆, PF₆; base = Et₃N, Py, *n*-Bu₄⁺F⁻)

[R = 2-Cl; 2-OMe; 2-CN; 3-CO₂Et; 3-CN;
3,5-Me₂; 3,5-Cl₂; 3,5-bis(CF₃);
4-Me; 4-*t*Bu; 4-Ph; 4-CO₂Me; 4-NO₂]

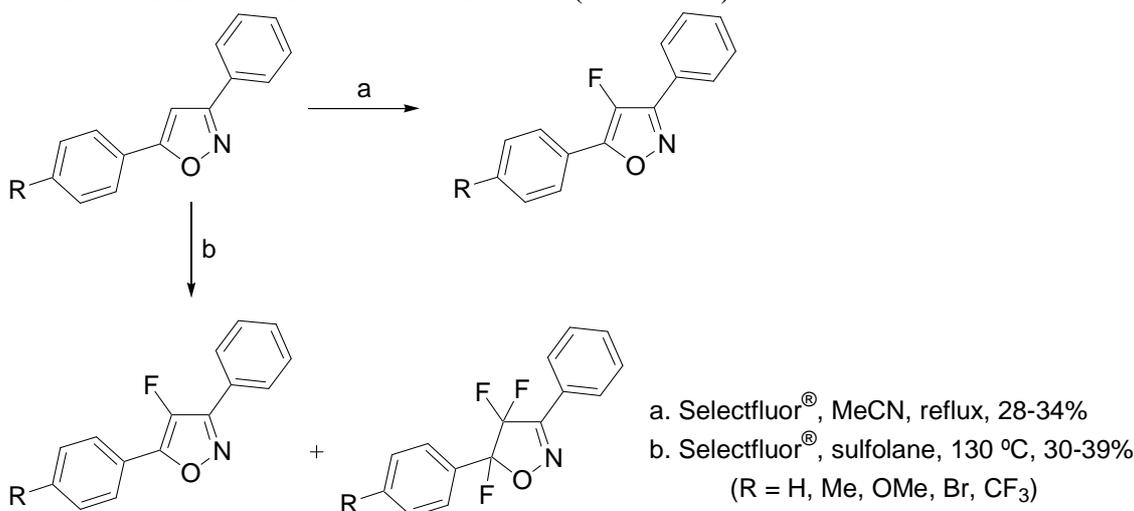
Scheme 36.

O'Neill and co-workers employed *N*-fluorobenzenesulfonimide (NFSi) to prepare 5-fluoro-6-methoxy-8-nitroquinoline from 6-methoxy-8-nitroquinoline (Scheme 37) [54]. *N*-Fluoropyridinium triflate (NFPT) failed to give any fluorinated product.



Scheme 37.

Stephens *et al.* synthesized a series of 3,5-diaryl-4-fluoroisooxazoles via electrophilic fluorination using Selectfluor[®] [55]. Fluorination proceeded out effectively in acetonitrile and nitromethane while in acetic acid and methanol no fluorination occurred. Other N-F reagents such as *N*-fluorobenzenesulfonimide (NFSi), *N*-fluoropyridinium triflate (NFPT), and more reactive *N*-fluoro-2,6-dichloropyridinium triflate were tested but no reaction occurred. Good results were obtained in sulfolane compared to DMF or DMSO at high temperature when deactivated substituents were present on the ring, however, a small amount of 4,4,5-trifluoroisooxazoline was formed in the reaction (Scheme 36).



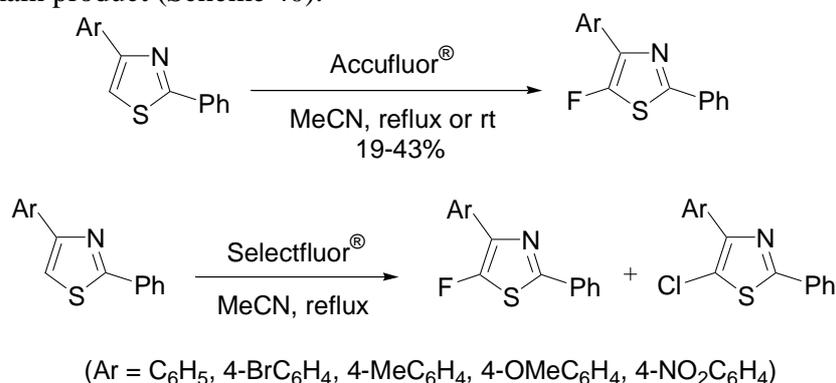
Scheme 38.

Briner *et al.* reported large-scale synthesis of 2-amino-5-fluorothiazole hydrochloride from 2-aminothiazole [56]. They used F-TEDA and/or NFSi to fluorinate 2-aminothiazole selectively at 5-position using metal-halogen exchange method under reaction conditions are shown in Table 2 (Scheme 39).

**Scheme 39.****Table 2. Reaction conditions for fluorination of 2-aminothiazole**

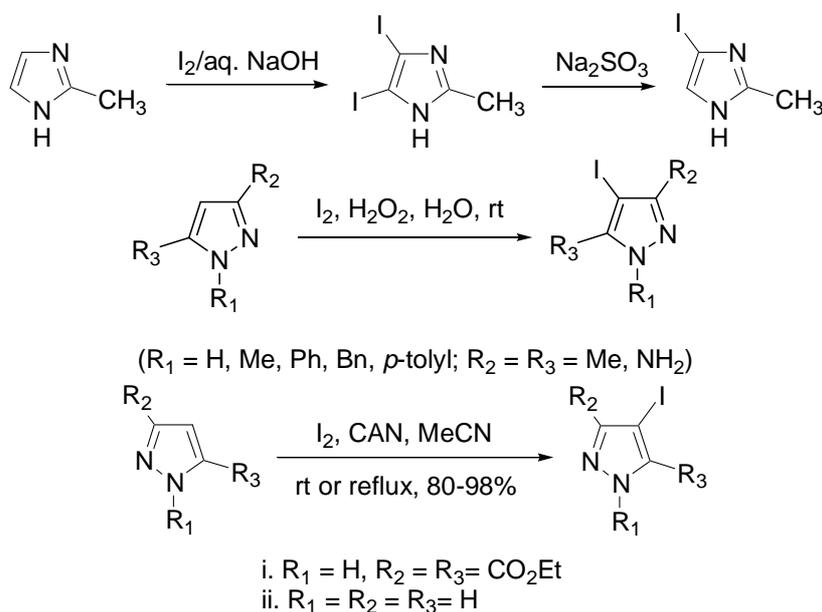
Substrate	Conditions	Yield (%)
R ₁ = Br; R ₂ = CF ₃ CO	i. <i>n</i> -BuLi, THF, -78°C; ii. NFSi	40
R ₁ = H; R ₂ = CH ₃ CO	F-TEDA, MeCN, reflux	48
R ₁ = H; R ₂ = Boc	i. <i>t</i> -BuLi, THF, -50°C; ii. NFSi	36

Campbell *et al.* reported selective nuclear fluorination of a series of 2,4-diarylthiazoles using N-F fluorinating agents [57]. Regents like *N,N*-difluoro-2,2-bipyridinium-bis(tetrafluoroborate) and 1-fluoro-2,6-dichloropyridinium triflate failed to fluorinate these thiazoles appreciably. On the other hand, Accufluor[®] was found to be efficient reagent for nuclear fluorination. Selectfluor[®] was found to be less efficient, as it gave trace amount of 5-chlorothiazole which was difficult to remove from main product (Scheme 40).

**Scheme 40.****V. Iodination:**

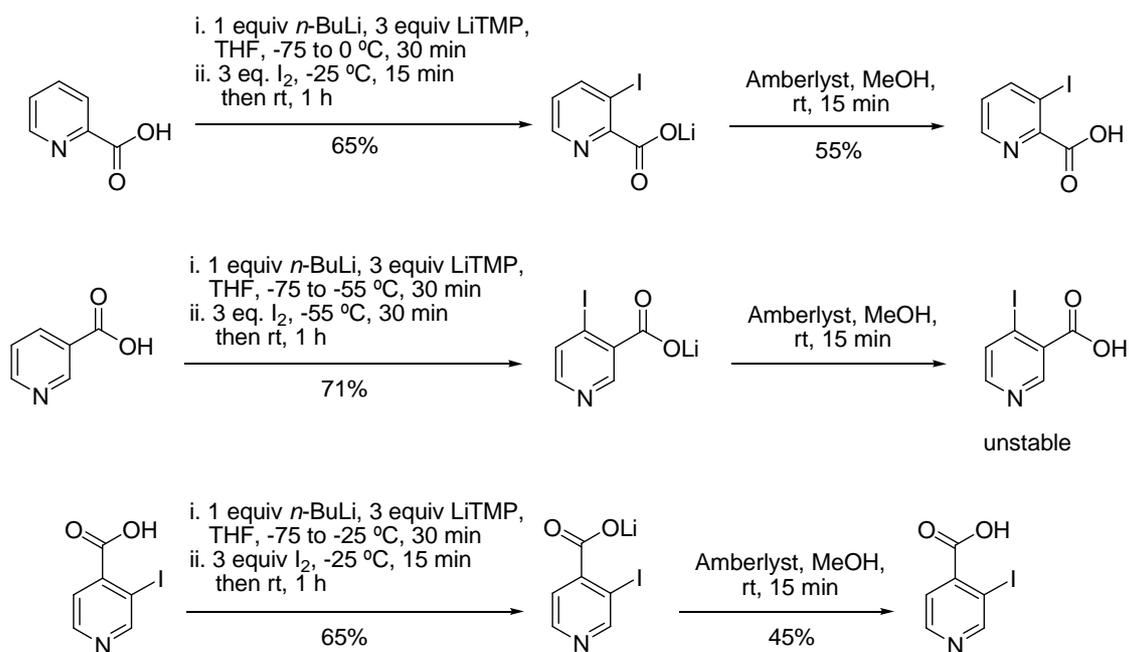
Unlike chlorination and bromination, electrophilic aromatic iodination is more difficult to proceed. Elemental iodine is the most general agent used in the synthesis of iodoaromatic compounds. However, direct iodination by I₂ is affected by the formation of hydroiodic acid, which causes proteolytic cleavage of sensitive functional groups. Due to weak electrophilicity of iodine, certain activation is necessary to convert iodine into better electrophile. Oxidizing agents such as HIO₃, HNO₃, SO₃, CH₃CO₃H, H₂O₂, etc. are generally used to oxidize iodine into a better electrophile [58]. Iodination can be achieved using iodine monochloride, iodine monofluoride, benzyl trimethylammonium dichloroiodate, CH₃CO₂I and CF₃CO₂I as iodinating reagents. Addition of Lewis acid to the iodination reaction increases the rate by generating I⁺ as an attacking species. Peracetic acid generates CH₃CO₂I, while SO₃ or HIO₃ generate I₃⁺ as an

attacking species [59]. Several combinations e.g. $I_2/aq. NaOH$, I_2/H_2O_2 and $I_2/ceric ammonium nitrate$ have been used to iodinate various heterocyclic amines (Scheme 41) [60].



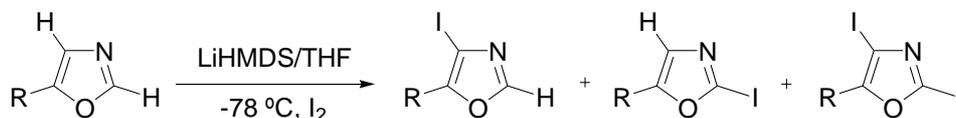
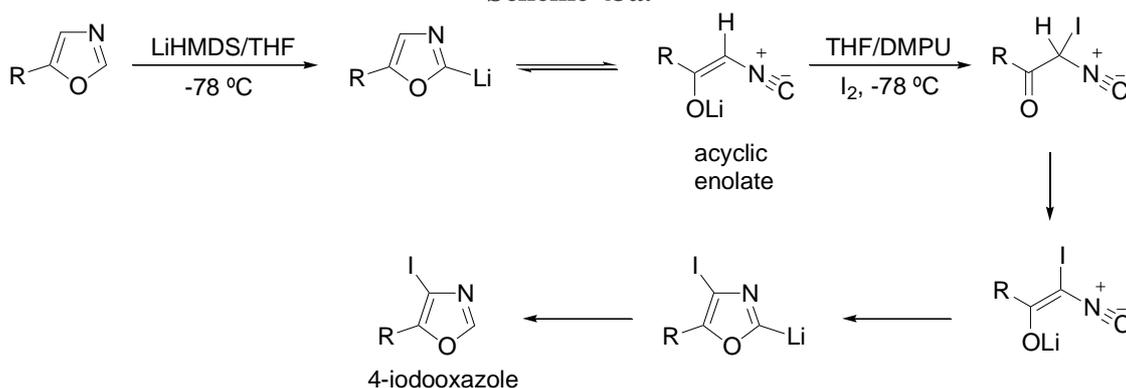
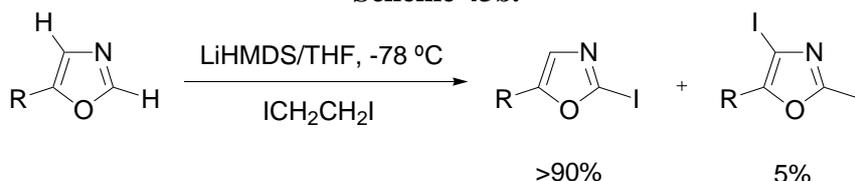
Scheme 41.

Lazaar *et al.* prepared iodo derivatives of unprotected pyridine carboxylic acids using direct lithiation strategy [61]. The metallation of picolinic acid, nicotinic acid and isonicotinic acid was carried out using 3 equivalents of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in tetrahydrofuran (THF). The lithio derivatives thus formed were treated with a solution of iodine in THF to afford iodopyridinecarboxylic acids in good yields (Scheme 42).



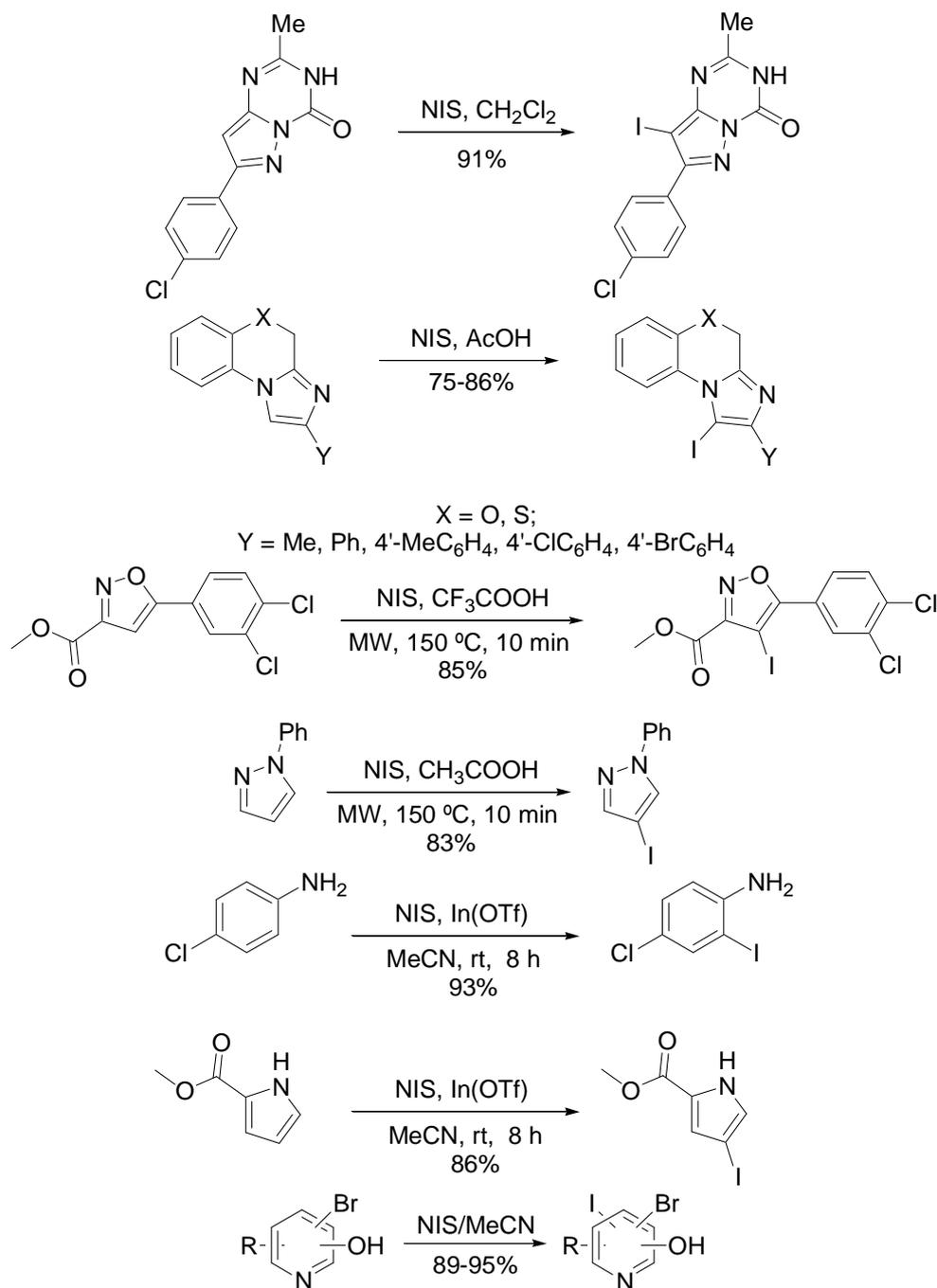
Scheme 42.

Vedejs *et al.* reported a method for direct iodination of oxazoles at C-4 via 2-lithiated oxazole [62]. Generally electrophilic halogen sources react with oxazoles at C-2 and C-5, but 4-iodooxazole was obtained in high yield using 2-lithiated oxazole. The reaction proceeds through the dominant acyclic enolate. Addition of iodine to the lithiated oxazole gave mixtures of cyclic products including the 4-iodo- and 2-iodooxazoles with 2,4-diiodooxazole product (Scheme 43a). Bases including LiHMDS and *n*-butyllithium were used to convert oxazole to the 2-lithiated oxazole. 4-Iodooxazole was obtained in high yield using LiHMDS in THF. It was found that addition of DMPU to the reaction prior to the addition of base (LiHMDS) results in high yield of 4-iodooxazole (73% isolated) together with little amount of the diiodo derivative (Scheme 43b). Alternatively, 2-iodo isomer was obtained exclusively (>90% yield) by using 1,2-diiodoethane as the electrophile (no DMPU added) (Scheme 43c).

**Scheme 43a.****Scheme 43b.****Scheme 43c.**

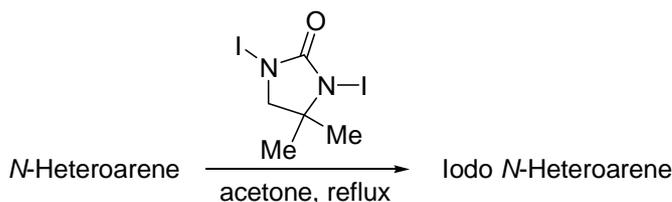
Like NBS and NCS, *N*-iodosuccinimide (NIS) has been the reagent of choice for aromatic nuclear iodination. Excellent halogenating properties of NBS and NCS can be extended further to NIS. Reactivity of the reagent is influenced by polarity of the reaction medium. Non-polar solvents such as CCl₄ reduce its reactivity whereas polar solvents such as MeCN, THF enhance its reactivity. NIS is activated by protic acids and Lewis acids and it has been demonstrated that the deactivated aromatics readily react in the presence of trifluoromethanesulfonic acid, BF₃.Et₂O, In(OTf)₃, acetic acid, trifluoroacetic acid, *p*-toluene sulfonic acid and sulfuric acid,

etc. [63]. It is a superior iodinating agent to iodinate deactivated aromatics including electron-poor heterocyclic substrates (Scheme 44) [64].



Scheme 44.

Similarly, 1,3-diiodo-5,5-dimethylhydantoin (DIDMH) has been used in acetone to iodinate electron poor heterocyclic amines in good-to-moderate yields (Scheme 45) (Table 3) [65].



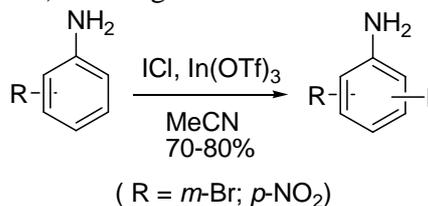
Scheme 45.

Table 3. Nuclear iodination of heterocyclic amines with DIDMH

Entry	Heteroaryl amine	Iodinated heteroaryl amine	Yield (%)
1	3,5-dimethyl-1 <i>H</i> -pyrazole	4-iodo-3,5-dimethyl-1 <i>H</i> -pyrazole	96
2	<i>N</i> -(4-methyl-thiazol-2-yl)-acetamide	<i>N</i> -(5-iodo-4-methyl-thiazol-2yl)-acetamide	85
3	4, 6-dimethyl-pyrimidin-2-yl amine	5-iodo-4, 6-dimethyl-pyrimidin-2-yl amine	50
4	2, 6-dimethyl-pyrimidin-4-yl amine	5-iodo-2, 6-dimethyl-pyrimidin-4-yl amine	50

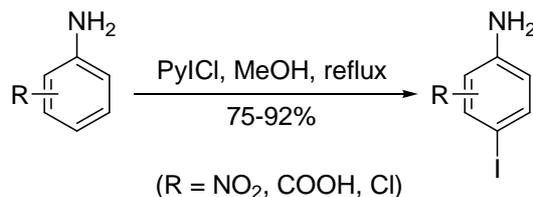
Iodine monochloride (ICl) is an interhalogen compound. It is a versatile and effective iodinating reagent to iodinate variety of organic substrates. Due to the electronegativity difference between chlorine and iodine, ICl is highly polar and behaves as an iodinating reagent. Iodination is usually carried out in polar solvents such as methanol, water and acids, such as AcOH, CF₃COOH, aqueous HCl, sulfuric acid, etc. in which heterolytic dissociation of ICl facilitates electrophilic attack of iodine. This reagent is commercially available and can be employed as such or generated *in situ* by mixing iodine and Lewis acids [66].

Recently Johnsson and co-workers introduced the combination of ICl and indium trifluoromethanesulfonate [In(OTf)₃] in acetonitrile to iodinate deactivated anilines (Scheme 46). Other Lewis acids such as Hg(OTf)₂ and AgOTf have also been found to be effective [67].

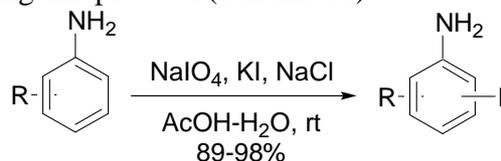


Scheme 46.

In an efficient method, Khansole *et al.* selectively iodinated deactivated aniline derivatives using pyridinium iodochloride (PyICl) in refluxing methanol with higher yields (75-92%) (Scheme 47) [68].

**Scheme 47.**

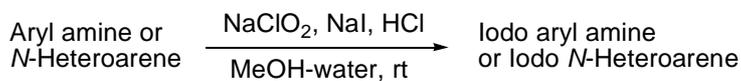
Emmanuel *et al.* developed a selective monoiodination methodology using NaIO₄/KI/NaCl reagent system in aqueous acetic acid at ambient conditions [69]. The reagent system was selected after screening several combinations of oxidants e.g. NaIO₄, KIO₃, KBrO₃, Oxone[®], HIO₄, V₂O₅, *m*-CPBA and additives e.g., NaCl, LiBr, NaF and *N*-chlorosuccinimide along with iodine source NaI/KI for iodination of 2-nitroaniline. It was observed that the addition of NaCl substantially improved the yield and reactivity. The reaction pathway involves *in situ* formation of ICl as a result of the oxidation of KI and NaCl by NaIO₄ in acidic medium, which acts as a source of I⁺ species. Several deactivated aniline derivatives were selectively monoiodinated in excellent yield (89-98%) using this protocol (Scheme 48).



(R = *o*-, *p*-I; *o*-NO₂; *o*-, *p*-Cl; *o*-COOH,)

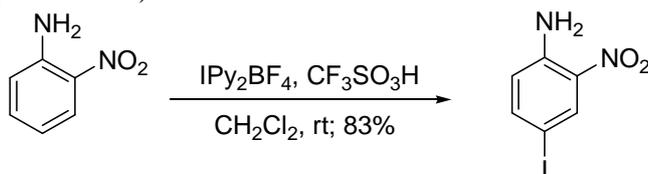
Scheme 48.

Lista *et al.* introduced NaClO₂/NaI/HCl reagent system for the iodination of aromatic substrates (Scheme 49) [70]. The reaction involves *in situ* generation of ICl due to the oxidation of iodine by NaClO₂. This reagent system is capable of iodinating deactivated aromatic amines including nitrogen containing heterocyclic substrates. Using this reagent system, *p*-nitroaniline was selectively iodinated in 95% yield. Deactivated heterocyclic amines like, imidazole, 5-nitroindole, and 8-hydroxyquinoline were iodinated to the respective iodoarenes in good-to-moderate yields (45-98%) (Table 4). The same reagent system was found capable of iodinating indole derivatives without protecting indole nitrogen. Thus 5,6-diacetoxy-2,3-diiodo indole, a novel derivative, was prepared using this protocol in excellent yield.

**Scheme 49.****Table 4. Nuclear bromination using NaClO₂/NaI/HCl**

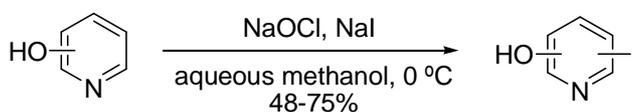
Entry	Substrate	Product	Yield (%)
1	4-nitroaniline	2-iodo-4-nitroaniline	95
2	5-nitroindole	3-iodo-5-nitroindole	75
3	8-hydroxyquinoline	8-hydroxy-5,7-diiodoquinoline	98
4	Imidazole	2,4,5-triiodoimidazole	45

Acid-mediated iodination methods are widely used for electrophilic aromatic iodination. Presence of an acid increases the rate of iodination and such methods are successful with deactivated aromatic compounds too. Barluenga and co-workers reported an aromatic iodination protocol using bis(pyridine)iodonium(I)tetrafluoroborate (IPy₂BF₄) [71] by treating a mixture of IPy₂BF₄ and an aromatic compound with an acid in dichloromethane at room temperature to furnish monoiodinated product in good yield. The reagent has been tested on both activated and deactivated aromatics as well as with CF₃SO₃H and HBF₄ and CF₃SO₃H was found to be better than HBF₄ for deactivated aromatics. Using this method 2-nitroaniline gave monoiodinated product in 83% yield (Scheme 50).



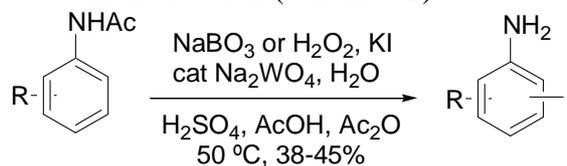
Scheme 50.

For most of the aromatics, powerful iodinating agents are required. Iodination is usually carried out by using the combination of an iodine source and an oxidizing agent. Edgar and co-workers have described a rapid iodination method using common bleach (sodium hypochlorite) as an oxidizing agent and NaI as an iodine source in aqueous alcohols [72]. Using this method deactivated phenols and electron poor 2-hydroxy- and 3-hydroxypyridines were iodinated to the corresponding iodosubstrates in moderate yields (48-75%) (Scheme 51). This reagent system has been found to be superior in terms of yield and selectivity than other reagent systems such as ICl/*t*-BuOCl, NaI/*t*-BuOCl and NaI/Chloramine T (sodium *N*-chloro-*p*-toluenesulfonamide).



Scheme 51.

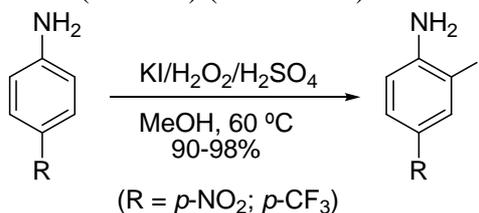
Beinker *et al.* achieved the oxidative iodination of a series of deactivated aromatic amides in acetic acid by employing sodium perborate (NaBO₃) or H₂O₂ as oxidants in the presence of a catalytic amount of sodium tungstate (Na₂WO₄) and KI as an iodine source [73]. Little amount of sulfuric acid was found to facilitate the iodination process because it inhibits the decomposition of oxidants used in the reaction (Scheme 52).

(R = *o*-, *p*-NO₂; *o*-CO₂Me)

Scheme 52.

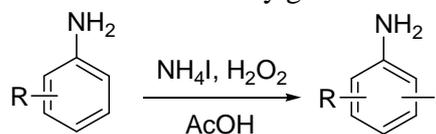
Iskra *et al.* developed a nonmetal catalyzed oxidative iodination method for arenes by using 30% H₂O₂, KI and H₂SO₄ in methanol [74]. H₂SO₄ promotes iodination process by inhibiting the decomposition of H₂O₂ due to the formation of hydroxide formed during the process. Using this

reagent system, iodination of 4-nitroaniline and 4-trifluoromethylaniline was successfully carried out with very good isolated yields. (90-98%) (Scheme 53).



Scheme 53.

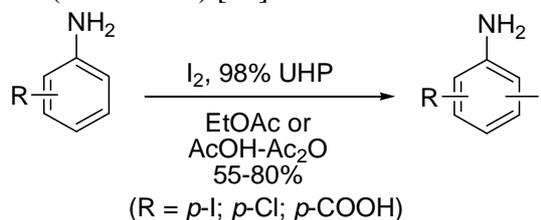
Narender *et al.* introduced ammonium iodide-hydrogen peroxide oxyiodination method, which is especially applicable for the deactivated aromatic substrates (Scheme 54) [75]. Best results were obtained with acetic acid as a solvent than CCl₄, CHCl₃, CH₂Cl₂, MeOH, and MeCN, because acetic acid generates CH₃CO₂I which facilitates easy generation of I⁺.



(R = *o*-, *m*-, *p*-Cl; *o*-CN; *p*-F)

Scheme 54.

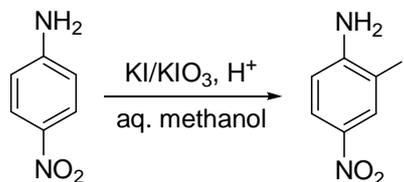
Lulinski *et al.* developed an eco-friendly oxidative monoiodination method for the deactivated aryl amines and anilides using molecular iodine and commercially available urea-hydrogen peroxide (UHP) as an oxidant (Scheme 55) [76].



(R = *p*-I; *p*-Cl; *p*-COOH)

Scheme 55.

Adimurthy *et al.* have used the combination of potassium iodide, potassium iodate in dilute hydrochloric acid in the aqueous methanol for monoiodination of aromatics. Using this combination, 4-nitroaniline was iodinated to furnish 2-iodo-4-nitroaniline in 96% yield (Scheme 56) [77].



Scheme 56.

Low reactivity of iodine can be overcome by using iodonium equivalents. An excellent reagent system using aqueous solution of potassium dichloroiodate (KICl₂) as an iodinating agent for the iodination of heteroarenes has been described by Garden *et al.* (Table 5) [78].

Table 5. Nuclear iodination using KICl₂

Entry	Substrate	Product	Yield (%)
1	8-hydroxyquinoline	8-hydroxy-5,7-diiodoquinoline	94-97
2	imidazole	4,5-diiodoimidazole	91
3	2-phenyl imidazole	2-phenyl-4,5-diiodoimidazole	89
4	2-methyl imidazole	2-methyl-4,5-diiodoimidazole	79
5	pyrazole	4-iodopyrazole	95

Other reagent systems such as benzyl triethylammonium dichloroiodate in the presence of NaHCO₃ (applicable to large-scale quantities), I₂ or KI/NaIO₄/H₂SO₄, and bis-(trifluoroacetoxy)iodobenzene/I₂ may be applied for efficient iodination of aniline derivatives [79].

CONCLUSION

Halogenated aryl and heteroaryl amino compounds are of high practical utility, and are ubiquitous target molecules in the field of synthetic organic chemistry. The widespread utility of these intermediates necessitates versatile and convenient methods for their preparation. In spite of considerable efforts from scientists all over the world, the direct nuclear halogenation of deactivated aromatic amines still remains a challenging task. The correct and updated citation and literature is absolutely vital for researchers to find pioneering ideas and relevant information on progress and development in this important area of synthetic chemistry. We hope and anticipate that the present review would provide basic to advance information pertaining to this very important area and encourage researchers in this field to develop newer methodologies and reagent systems to overcome this challenge in a smooth and environmentally benign manner.

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