Molecular Diversity (2022) 26:1837–1873
https://doi.org/10.1007/s11030-021-10295-3

COMPREHENSIVE REVIEW

Recent trends in the chemistry of Sandmeyer reaction: a review

Rabia Akhtar[1] · Ameer Fawad Zahoor[1] · Nasir Rasool[1] · Matloob Ahmad[1] · Kulsoom Ghulam Ali[1]

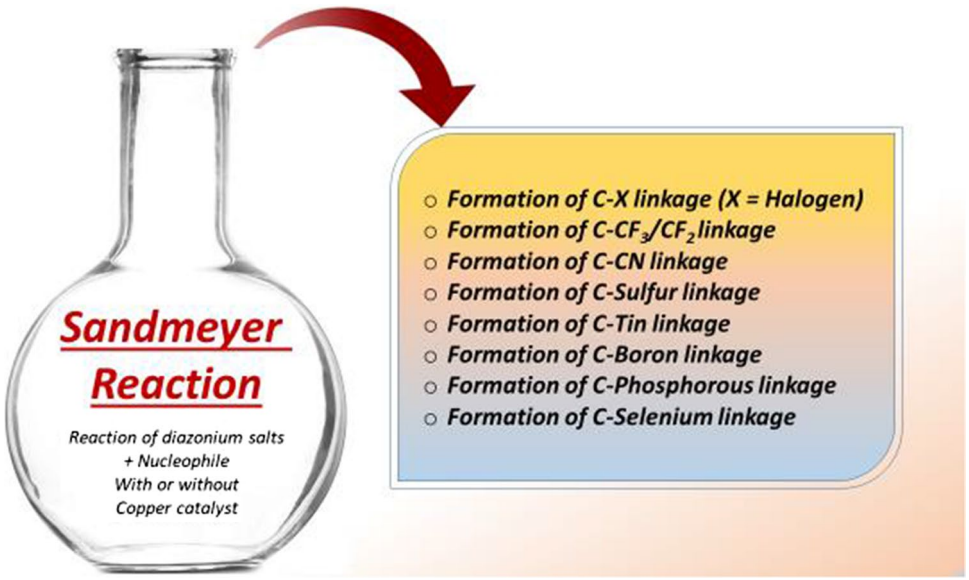
Received: 23 June 2021 / Accepted: 10 August 2021 / Published online: 20 August 2021

Abstract

Metal-catalyzed reactions play a vital part to construct a variety of pharmaceutically important scaffolds from past few decades. To carry out these reactions under mild conditions with low-cost easily available precursors, various new methodologies have been reported day by day. Sandmeyer reaction is one of these, first discovered by Sandmeyer in 1884. It is a well-known reaction mainly used for the conversion of an aryl amine to an aryl halide in the presence of Cu(I) halide via formation of diazonium salt intermediate. This reaction can be processed with or without copper catalysts for the formation of C–X (X = Cl, Br, I, etc.), C-CF_3/CF_2, C–CN, C–S, etc., linkages. As a result, corresponding aryl halides, trifluoromethylated compounds, aryl nitriles and aryl thioethers can be obtained which are effectively used for the construction of biologically active compounds. This review article discloses various literature reports about Sandmeyer-related transformations developed during 2000–2021 which give different ideas to synthetic chemists about further development of new and efficient protocols for Sandmeyer reaction.

Graphical abstract

An updated compilation of new approaches for Sandmeyer reaction is described in this review to construct a variety of carbon-halogen, carbon-phosphorous, carbon-sulfur, carbon-boron etc. linkages.



Keywords Diazonium salts · Sandmeyer reaction · Dediazoniation · Trifluoromethylation · Benzonitriles · Aryl halides

✉ Ameer Fawad Zahoor
fawad.zahoor@gcuf.edu.pk; fawad.zahoor@gmail.com

[1] Department of Chemistry, Government College University Faisalabad, Faisalabad 38000, Pakistan

Introduction

Aromatic diazonium salts, discovered by Griefs in 1858 [1], have wide spread applications in organic synthesis as well as at industrial level. They are frequently used for the preparation of organic nanocompounds and grafted a variety of organic molecules on metallic surfaces [2]. Furthermore, Meerwein arylation [3, 4], Balz–Schiemann [5, 6] and various metal-catalyzed reactions [7, 8] involve diazonium salts as starting precursors for the production of various halides, phenols, cyanides, azides and alkenes [9] which serve as effective intermediates for the synthesis of important molecules [10–13]. Sandmeyer reaction is one of them, in which diazonium salts are used for the construction of carbon–halogen, carbon–phosphorous, carbon–sulfur, carbon–selenium, carbon–boron bond formation. Moreover, various trifluoromethylated compounds as well as a number of pharmaceutically important drugs can be synthesized via Sandmeyer approach [14].

Literature study reveals the importance of metal-catalyzed cross-coupling reactions which are extensively used in organic synthesis and in pharmaceutical industry. These reactions are carried out by the treatment of various organic halides with a suitable coupling partner using a variety of catalysts and ligands [15–19]. Sandmeyer approach, first discovered in 1884 by Sandmeyer [20, 21], is one of these metal-catalyzed reactions which effectively converts benzenediazonium salts into bromo-, chlorobenzene, benzonitriles, etc., in the presence of different copper catalysts. Since 1884, different methods have been discovered to improve the efficacy of Sandmeyer reaction as an innovation of organic phase diazotization process reported by Doyle et al. in 1977 [22, 23] and the effective utilization of these diazonium salts in a variety of metal-catalyzed reactions (Kikukawa and Matsuda, 1977) [24, 25], etc. Although the mechanism of this reaction is not yet clear however, a general mechanism reported by Waters [26] and later on by Kochi [27] is highlighted in Scheme 1 according to which diazonium salt readily undergoes homolytic dediazoniation in the presence of copper salt, resultantly affording aryl radical. This radical upon treatment with reactive species gives desired product with regeneration of copper(I) species.

Owing to the extensive applications of Sandmeyer reaction, herein we describe an updated compilation of new approaches reported during 2000–2021 for Sandmeyer reaction.

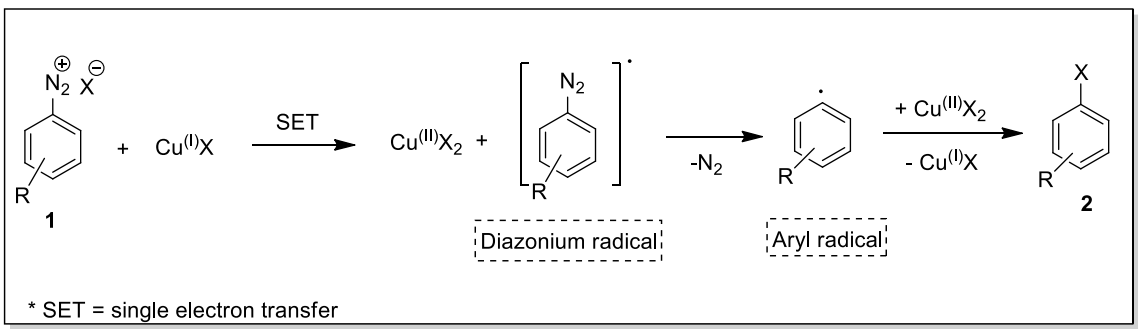
Review of literature: applications of Sandmeyer reaction

Formation of carbon–halogen linkage

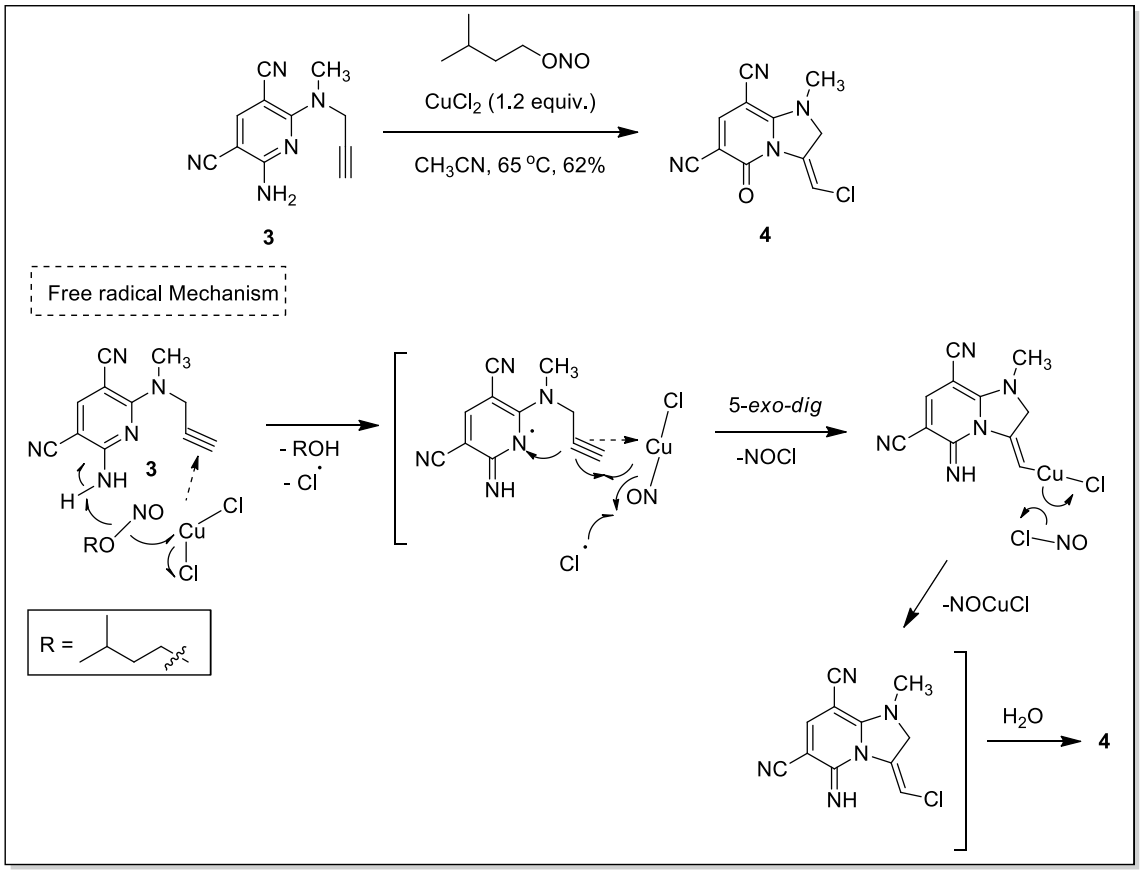
Chlorination via Sandmeyer reaction

Marco-Contelles and colleagues reported copper-catalyzed Sandmeyer reaction of *N*-(prop-2-yn-1-ylamino) pyridines in the presence of organic nitrites afforded various bicyclic chlorinated pyridones [28]. For example, reaction of pyridine **3** in combination with isopentyl nitrite and cupric chloride gave pyridone **4** in 62% yield. Temperature was maintained at 65 °C to achieve maximum conversion in acetonitrile solvent. Mechanism of this reaction first involved the coordination of nitrosyl complex of cupric chloride with alkyne group followed by the breakage of RO–NO bond releasing alkoxy radical that captured hydrogen from NH_2 group to give ROH molecule. On the other side, breakage of NH_2 bond started the free radical chain reaction resultantly affording *E-exo*-chloromethylene intermediate which after hydrolysis gave targeted pyridone **4** (Scheme 2).

A single report considering the importance and synthesis of monofluorinated polychlorinated biphenyls has been disclosed by Sott et al. [29] in which Suzuki and Sandmeyer reactions are the key steps. Table 1 presents some of these reactions performed under optimized conditions. Suzuki coupling between arylboronic acid **5** and



Scheme 1 General mechanism of Sandmeyer reaction



Scheme 2 Copper-catalyzed Sandmeyer reaction for the conversion of *N*-(prop-2-yn-1-ylamino) pyridine **3** to pyridone **4**

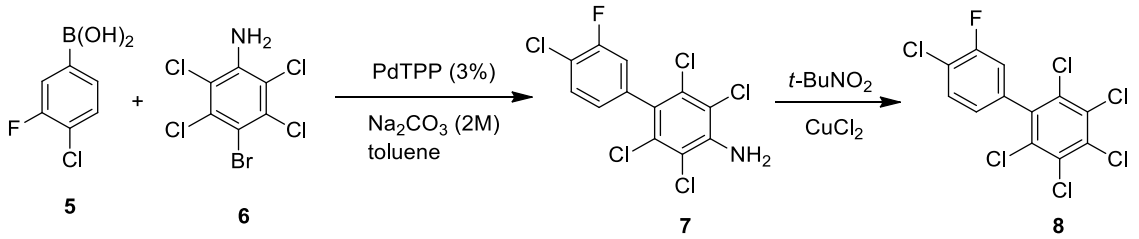
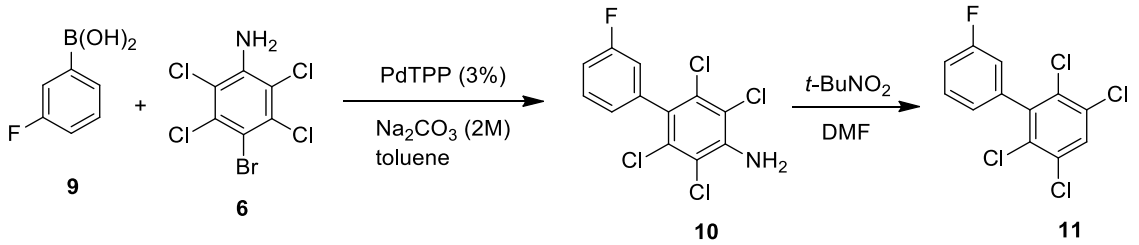
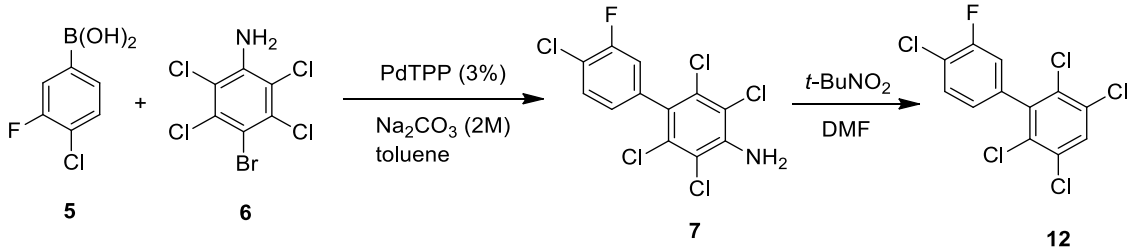
2,3,5,6-tetrachloro-bromoaniline (**6**) was processed using 3% $Pd(PPh_3)_4$ as catalyst, sodium carbonate as base and toluene as solvent. As a result, biphenyl product **7** was obtained which subsequently subjected to Sandmeyer reaction in the presence of *t*-BuONO and $CuCl_2$ to obtain required PCB (polychlorinated biphenyls) **8** in 4% overall yield. Likewise, other two reactions were also performed; however, deamination in the absence of $CuCl_2$ gave desired PCB **11** and **12** in 26% and 7% overall yields, respectively, which could be used as analytical standards for PCB analysis.

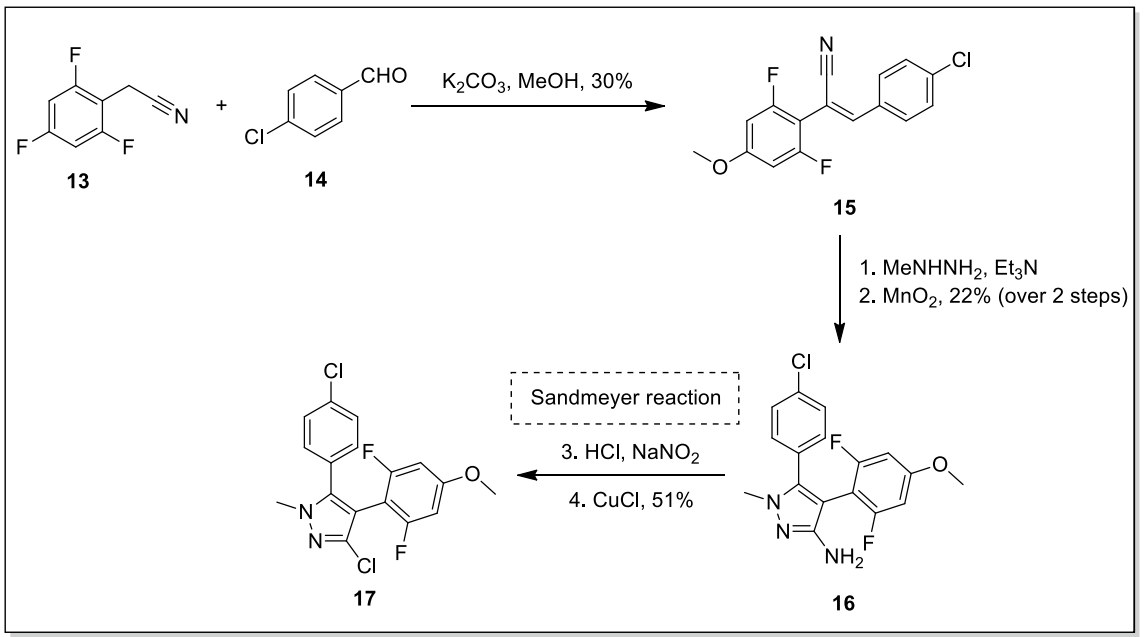
An approach for the synthesis of tetrasubstituted pyrazole derivatives and their fungicidal properties against *Uncinula necator* was investigated by Dumeunier et al. [30]. Their methodology started from the reaction of acetonitrile **13** with 4-chloro benzaldehyde (**14**) to afford 2,3-diarylacrylonitrile **15** which was subjected to ring closure reaction with hydrazine. Resultantly, pyrazoline derivative **16** was obtained which readily converted into desired pyrazole **17** by applying standard protocol of Sandmeyer reaction (HCl, $NaNO_2$, CuCl) (Scheme 3).

Hughes et al. [31] proposed a strategy for the synthesis of a variety of 4-aryl-5-cyano-2-aminopyrimidines which are effectively used as VEGF (vascular endothelial growth factor)-R2 kinase inhibitors. These inhibitors stop angiogenesis process successfully, resultantly inhibiting the growth of tumor cells. The synthetic protocol of these inhibitors started from the reaction of aryl methyl ester **18** with lithium salt of the acetonitrile to obtain corresponding α-cyanoketone which on treatment with *N,N*-dimethylformamide diethyl acetal afforded vinylogous amide. In the next step, pyrimidine ring **19** was obtained by the reaction of vinylogous amide with guanidinium salt. Sandmeyer reaction of pyrimidine **19** in the presence of antimony trichloride and *tert*-butyl nitrite gave 2-chloropyrimidine derivative **20** which was efficiently converted into targeted 4-aryl-5-cyano-2-aminopyrimidine derivative **21** by the displacement of chloro group with a variety of aliphatic amines in 73–95% yield range (Scheme 4).

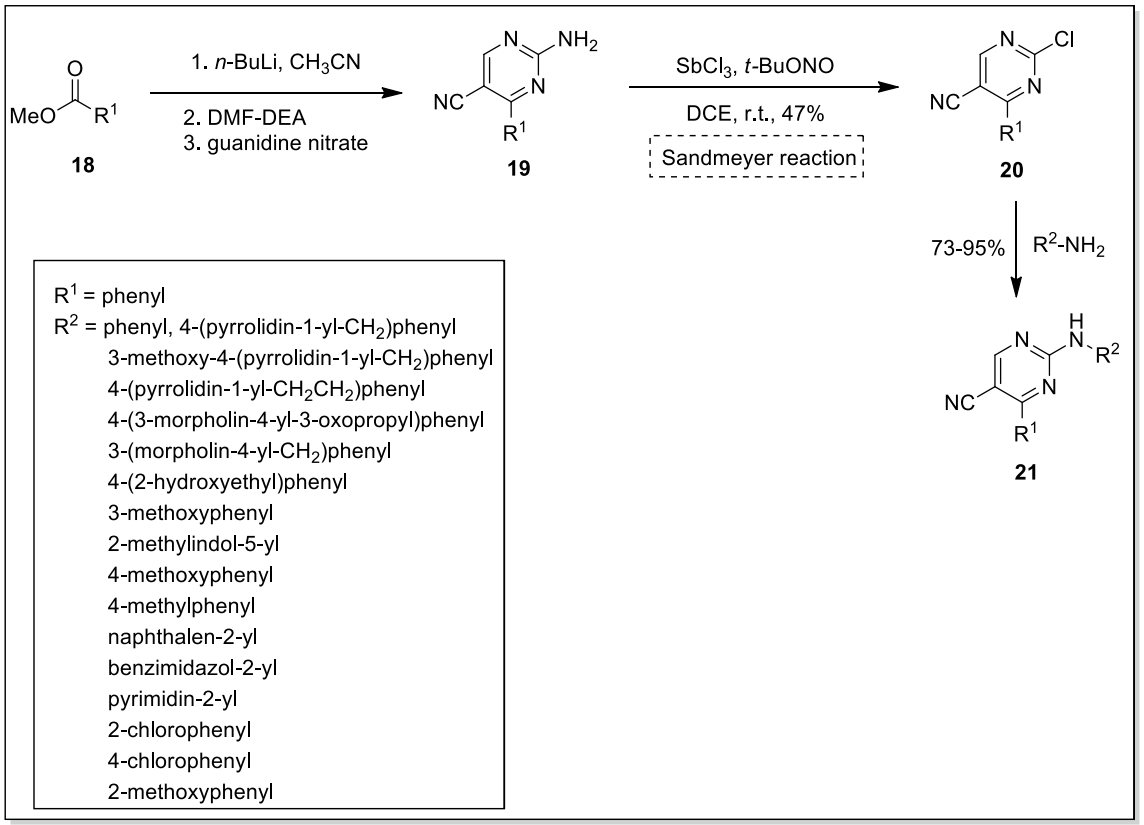
A quite efficient and simple way to synthesize different arylpiperazines involving Sandmeyer reaction as key step was demonstrated by Rancati et al. [32]. A reference pathway is described in Scheme 5 which started from the nitration of 1,4-benzodioxin-5-carboxylic acid **22** followed by catalytic hydrogenation provided hydrochloride form of amino derivative **23** in quantitative yield. This benzodioxine was subjected to Sandmeyer reaction in the

Table 1 Synthesis of monofluorinated polychlorinated biphenyls via Suzuki coupling followed by Sandmeyer reactions

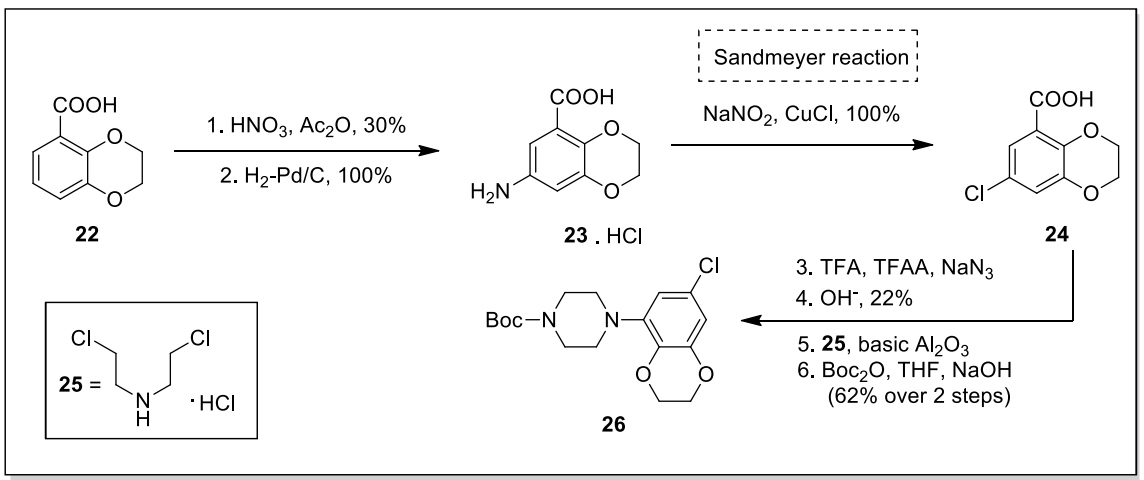
Suzuki Reaction	Sandmeyer Reaction	Overall Yield
		4%
		26%
		7%



Scheme 3 Synthesis of pyrazole **17** by applying standard protocol of Sandmeyer reaction



Scheme 4 Sandmeyer reaction for the preparation of aminopyrimidines derivatives



Scheme 5 Preparation of arylpiperazines using Sandmeyer reaction as key step

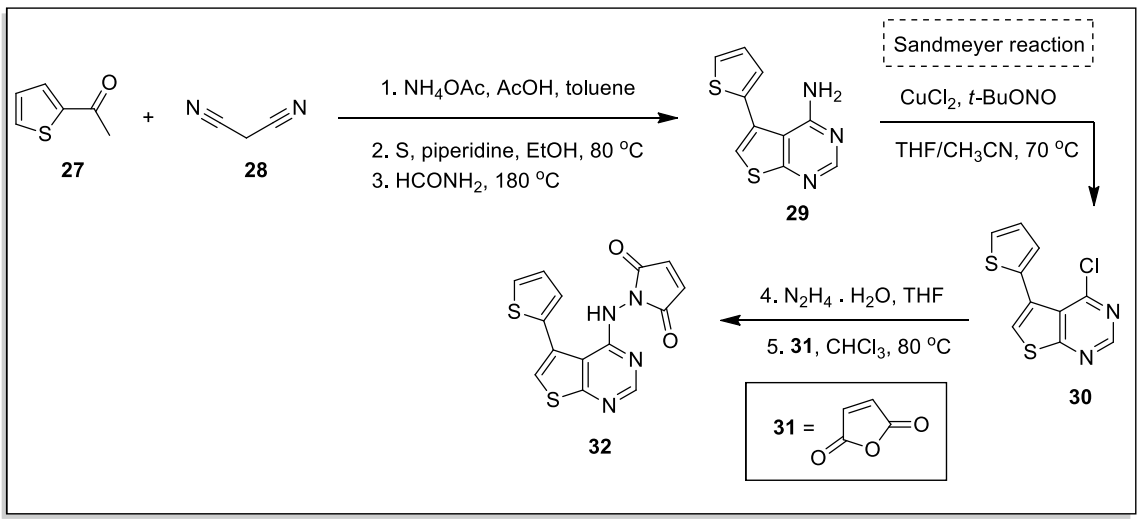
presence of sodium nitrite and CuCl to obtain halogenated benzodioxine **24** quantitatively. Later, conversion of carboxylic acid group of this chloro residue (**24**) to acyl azide followed by decomposition process afforded 5-amino derivative (22% yield) which upon treatment with basic alumina supported amine **25** and subsequent reaction with Boc anhydride gave desired piperazine derivative **26** in 62% yield (over 2 steps).

Research group of Han disclosed the synthetic route of thienopyrimidine analogs which were found to be effective FLT3 inhibitors [33]. Standard conditions to carry out this protocol started from the Knoevenagel condensation

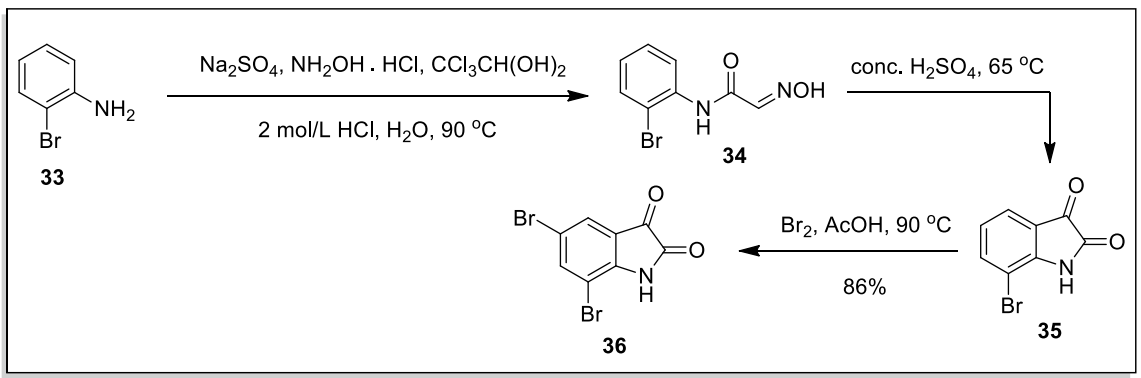
of 2-acetylthiophene **27** with malononitrile **28** followed by the treatment with elemental sulfur to obtain corresponding thiophene, ready to produce thienopyrimidine **29** after treatment with formamide. Next, Sandmeyer reaction of thienopyrimidine **29** proceeded well at 70 °C in the presence of *t*-BuONO and $CuCl_2$. THF/CH_3CN was used as solvents to carry out maximum conversion. Later on, reaction of chloride **30** with hydrazine monohydrate and furan **31** afforded required thienopyrimidine **32** efficiently. By using same reaction pathway, a variety of thienopyrimidine derivatives were obtained in good yield range (Scheme 6).

Ding et al. [34] presented a valuable approach to obtain biologically active isatin derivatives which play an important role in pharmaceutical industry due to their excellent antitumor properties against a variety of cell lines (K562, HepG2, HT-29, HL60, etc.). Focusing the synthesis of isatin derivatives, a quite simple and easy pathway is outlined in Scheme 7 involving the condensation of aniline **33** with hydroxylamine hydrochloride at 90 °C and chloral hydrate in 2 mol/L of HCl and water solution to afford oxime **34**. Cyclization of this oxime (**34**) in the presence of sulfuric acid with subsequent bromination reaction afforded required isatin **36** in 86% yield.

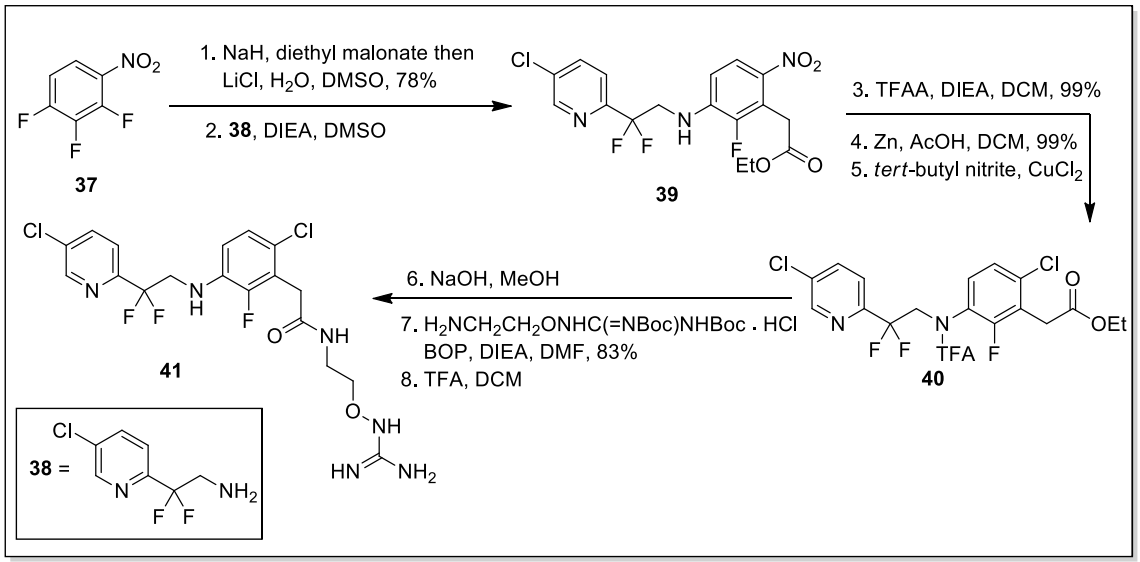
Player et al. [35] reported the synthesis of 2-(2-chloro-6-fluorophenyl)acetamides and proved their potential applicability as thrombin inhibitors. A reference synthetic protocol is highlighted in Scheme 8 which started from the reaction of nitrobenzene **37** with diethyl malonate followed by decarboxylation (in the presence of LiCl) and aromatic nucleophilic substitution reaction (with amine **38**) provided aryl fluoride **39**. Protection of -NH group of compound **39** with subsequent reduction (Zn, AcOH) and Sandmeyer reaction (*tert*-butyl nitrite, $CuCl_2$, CH_3CN) provided derivative **40**. Later on, deprotection of the -NH and ester groups followed by the reaction with *O*-guanidine segment afforded desired 2-(2-chloro-6-fluorophenyl) acetamide **41**.



Scheme 6 Synthetic route for thienopyrimidine analogs



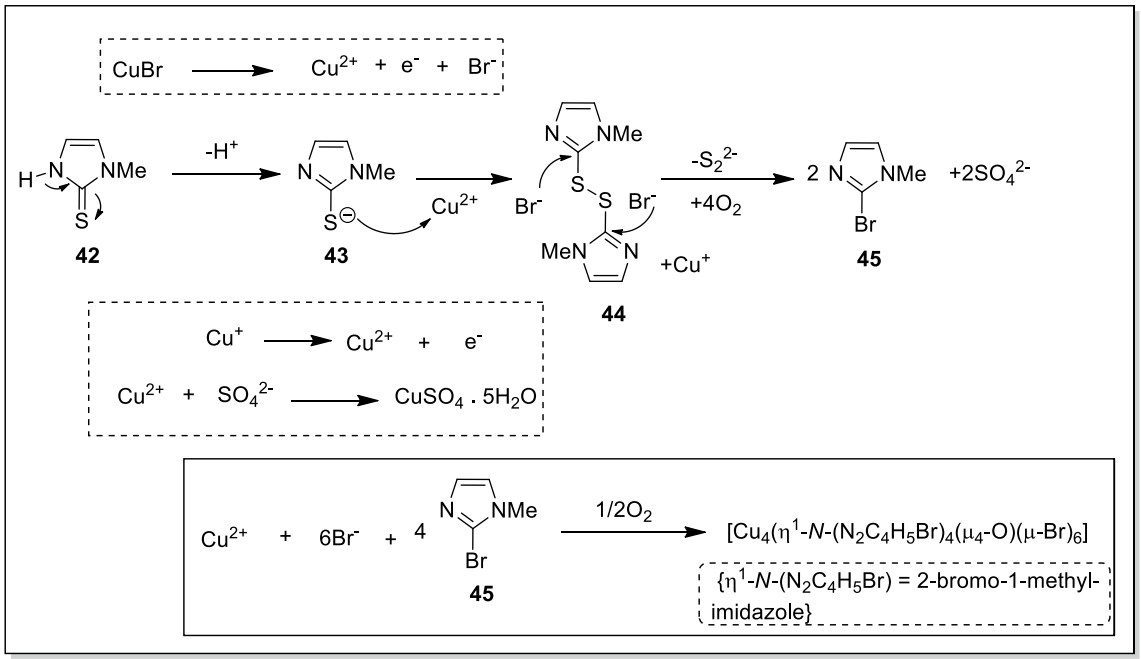
Scheme 7 Synthesis of isatin **36** from oxime **34**



Scheme 8 Preparation of 2-(2-chloro-6-fluorophenyl)acetamide **41** as thrombin inhibitor

Bromination via Sandmeyer reaction

Lobana and colleagues reported a first example of Sandmeyer reaction for the conversion of 2-mercapto-1-methyl-imidazoline to 2-bromo-1-methyl-imidazole at ambient temperature [36]. Copper(I) bromide was selected as suitable catalyst for this purpose, and the reaction was carried out in CH_3CN-$CHCl_3$ mixture. Plausible mechanism for this conversion is presented in Scheme 9 which started from the oxidation of Cu(I) to Cu(II) ion. This copper ion further used to oxidize thio moiety **42**, resultantly produced disulfide imidazoline **44** which in the last step was converted into required 2-bromo-1-methyl-imidazole **45**. This brominated imidazole (**45**) coordinated with bromide ions in the presence of Cu^{2+} to obtain tetranuclear complex $[Cu_4(\eta^1\text{-}N\text{-}(N_2C_4H_5Br)_4(\mu_4\text{-}O)(\mu\text{-}Br)_6]$.



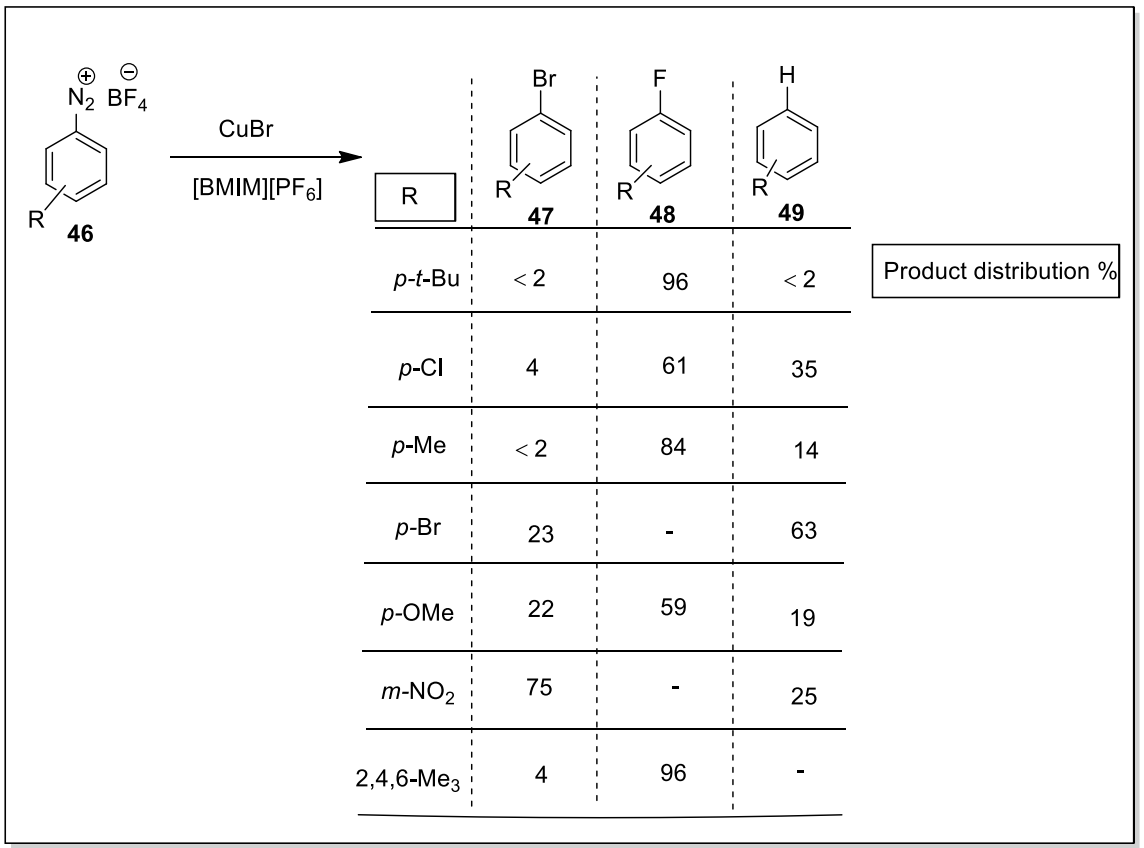
Scheme 9 Mechanism for the conversion of 2-mercapto-1-methyl-imidazoline **42** to 2-bromo-1-methyl-imidazole **45**

The research group of Laali performed Sandmeyer reaction for the bromodediazotization of the diazonium salt **46** [37]. Reaction performed under nitrogen atmosphere using [BMIM][PF_6] ionic liquid, as solvent. Copper(I) bromide was used as bromine source, and temperature was maintained at 65–75 °C. Resultantly, halogenated products were obtained and their formation ratio strictly depended upon the nature of the substituents of the diazonium salts. As depicted in Scheme 10, diazonium salts having electron-donating substituents gave mainly Schiemann product; however, electron-withdrawing substituents afforded Sandmeyer product predominantly along with the formation of hydrodediazoniation product.

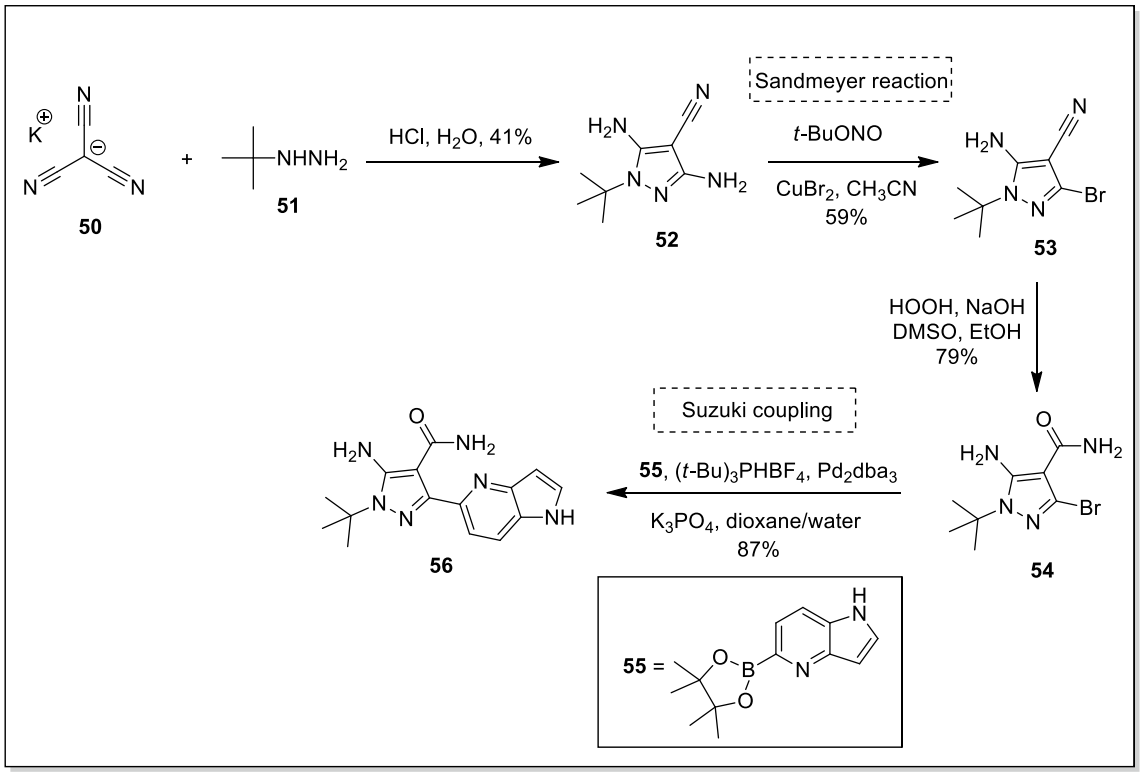
Evans and coworkers described an impressive reaction pathway to synthesize 5-amino-3-aryl-1-(*tert*-butyl)-1*H*pyrazole-4-carboxamides in good yield range [38]. Reaction of potassium tricyanomethanide (**50**) with *tert*-butylhydrazine (**51**) in a mixture of HCl and water gave 41% yield of pyrazole **52** which was successfully subjected to Sandmeyer reaction. This reaction worked very well by using *t*-BuONO and $CuBr_2$ in acetonitrile solvent. As a result, corresponding 3-bromo regioisomer **53** was afforded in 59% yield. Later on, hydrolysis of cyano group of compound **53** followed by Suzuki–Miyaura reaction gave desired pyrazole-4-carboxamide **56** in 87% yield. By using similar reaction approach, a variety of targeted compounds were obtained in 25–87% yield range (Scheme 11).

Özkan et al. [39] published a report on the facile synthesis of bromobenzenes by using Sandmeyer approach. In their methodology, a quick reaction of aniline with concentrated HCl produced corresponding anilinium salt which was diazotized in the presence of ethyl nitrite. In the next step, this diazonium salt was treated with bromine radical, obtained by the reaction of molecular bromine with ammonium persulfate. As a result, desired substituted bromobenzene was afforded in moderate to good yield range (55–80%). A reference example is highlighted in Scheme 12.

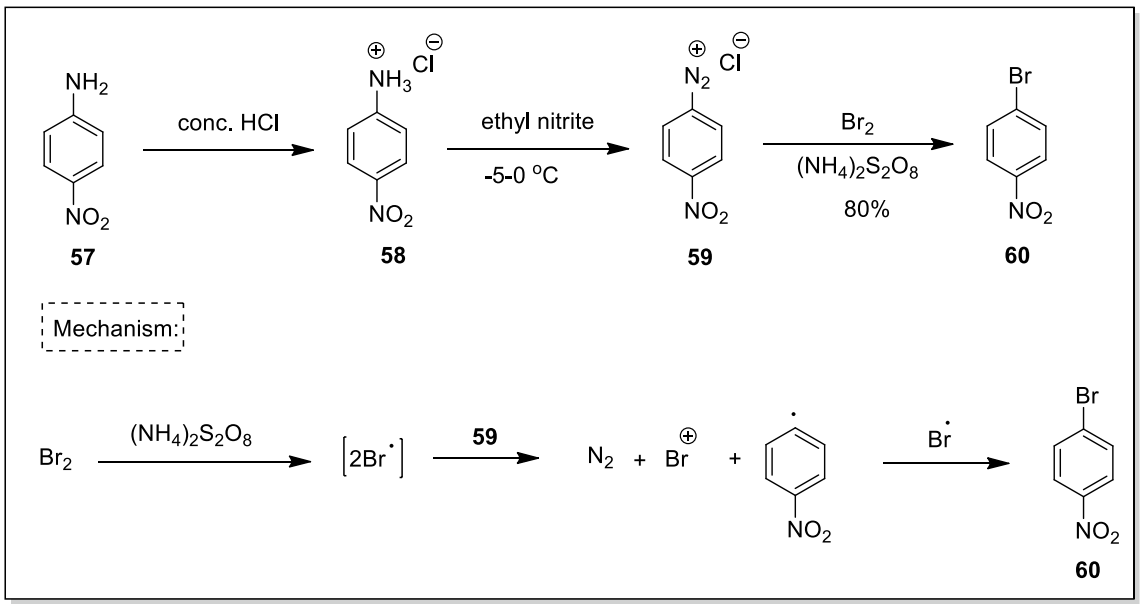
Research group of Schäfer reported a simple, efficient and cost-effective synthetic pathway for ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (**64**) including Sandmeyer bromination and Suzuki–Miyaura couplings as key steps [40]. Reactions performed at gram scale and kilogram scale level under mild conditions. An outline of these reactions is presented in Scheme 13 which started first from the conversion of ethyl 5-amino-1,3,4-thiadiazole-2-carboxylate (**61**) into bromo thiadiazole **62** in 71% yield. Reaction processed at room temperature in the presence of *tert*-butyl nitrite



Scheme 10 Sandmeyer reaction for the bromodediazotization of the diazonium salt **46**



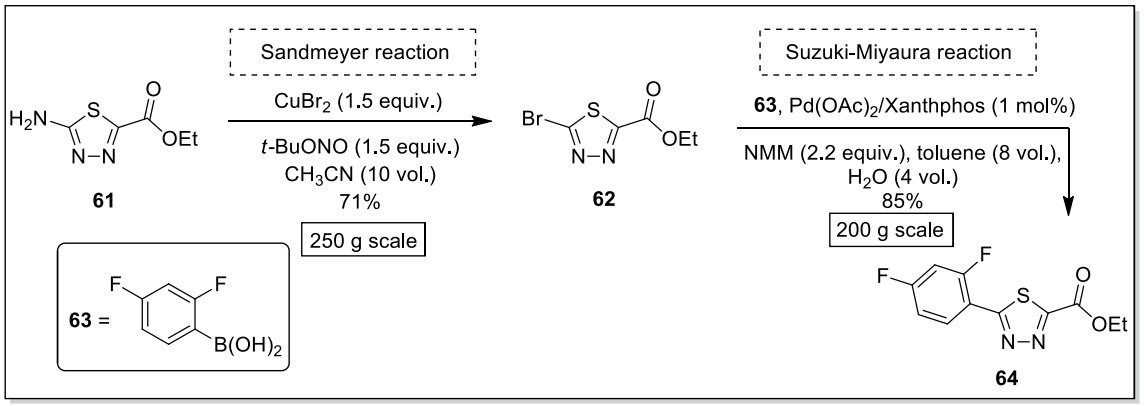
Scheme 11 Synthesis of pyrazoles by adopting Sandmeyer and Suzuki–Miyaura approaches



Scheme 12 Facile synthesis of bromobenzene **60** by using Sandmeyer protocol

and 1.5 equivalents of copper bromide using acetonitrile as an effective reaction media. Later, compound **62** was subjected to Suzuki–Miyaura reaction using boronic acid **63** as another coupling partner. This palladium-catalyzed reaction along with xanthphos ligand afforded desired cross-coupled product **64** in 85% yield.

A variety of pharmaceutical agents having cyclopropylpyridine scaffold are good inhibitors of interleukin



Scheme 13 Synthesis of ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (**64**) via Sandmeyer bromination and Suzuki–Miyaura couplings

receptor-associated kinases, PDE4 enzyme inhibitors and have been widely used to synthesize canabinoid receptor 2 agonists. Considering their importance, Striela et al. [41] prepared bromocyclopropylpyridines by the reaction of aminocyclopropylpyridines (obtained via Suzuki reaction of aminobromopyridines) with amyl nitrite through Sandmeyer approach. Reaction proceeded at room temperature in dibromomethane solvent using 0.5 equivalent $CuBr_2$ to obtain good yield range.

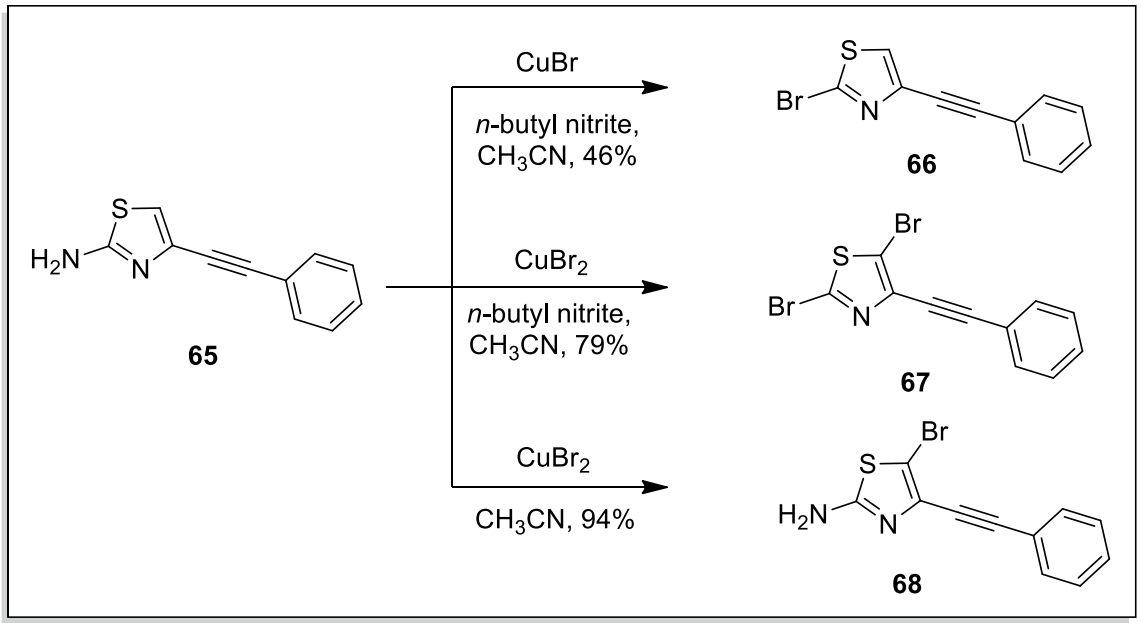
A competent method for the synthesis of aryl bromides involved the reaction of arenediazonium salts with KBr, resultantly affording a variety of aryl bromides in an excellent yield range. This Sandmeyer reaction was carried out at 20–25 °C in acetonitrile solvent. Maximum conversion was achieved by using equimolar (10 mol%) catalytic mixture of CuBr and $CuBr_2$ along with dibenzo-18-crown-6 as a phase transfer catalyst and 1,10-phenanthroline (phen) as ligand. This protocol covers a wide substrate scope by allowing the preparation of different electron-donating and withdrawing groups containing aryl bromides and dibromides in 56–99% yield range [42].

Siméon et al. [43] reported halogenation reactions of 2-amino-1,3-thiazoles in the presence of CuBr/$CuBr_2$ for the preparation of monohalo and dihalo 1,3-thiazole derivatives. Temperature played a vital part to achieve required products in reasonable yield. For instance, reaction of 2-aminothiazole **65** in the presence of CuBr, *n*-butyl nitrite and acetonitrile gave desired monohalogenated product **66** in 46% yield. This reaction was completed at 60 °C within 15 min. However, when the same reaction was performed first at 40 °C then at 25 °C (for 15–120 min) and 65 °C (for 15 min) using $CuBr_2$ as catalyst, dihalo product **67** was obtained in 79% yield. On the other hand, in the absence of *n*-butyl nitrite 2-aminothiazole **65** gave halogenated product **68** at room temperature within 10 h in 94% yield. In this methodology, all reactions were performed in a regioselective fashion under mild conditions which led to the formation of a variety of novel iodo, bromo and chloro derivatives (Scheme 14).

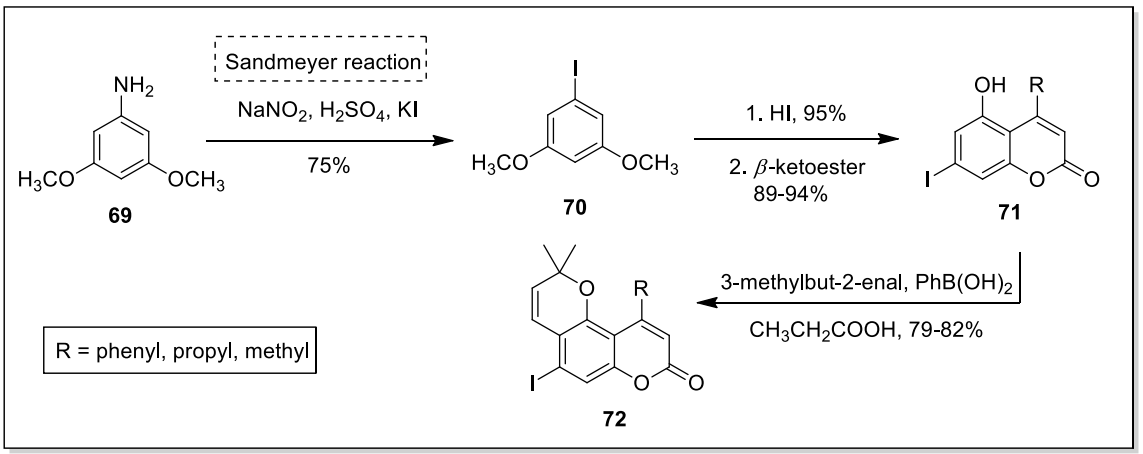
Iodination via Sandmeyer reaction

Synthesis of a variety of hydroxycoumarin and pyranocoumarin derivatives and evaluation of their anti-proliferative activity was reported by Mao et al. [44]. 3,5-Dimethoxyaniline (**69**), starting precursor of this methodology first underwent Sandmeyer reaction in the presence of $NaNO_2$, H_2SO_4 and KI. Resultantly, iodine-substituted methoxy ether **70** was obtained in 75% yield which demethylated followed by the reaction with *β*-ketoester afforded iodo-substituted 5-hydroxycoumarin **71**. Conversion of this coumarin (**71**) to chromene **72** by annulation with 3-methylbut-2-enal was achieved in 79–82% yield range. After that, these coumarin and chromene derivatives were successfully subjected to palladium-catalyzed Suzuki cross-coupling reaction using different arylboronic acids to obtain desired hydroxycoumarin and pyranocoumarin derivatives in good to excellent yield range (Scheme 15).

Another application of Sandmeyer reaction was reported by Kim et al. [45] where they described [5,5]-sigmatropic rearrangement reactions of *N,N'*-diaryl hydrazides, resultantly affording 4,4′-diamino-biphenyls (benzidines). Their methodology started from the copper-catalyzed coupling of *bis*(*m*-bromophenyl) ethers **73** followed by cyclization reaction in the presence of palladium catalyst furnished corresponding diaryl hydrazides which were then subjected to benzidine rearrangement in the presence of aq. HCl. As a result, benzidines **74** were obtained whose structures were confirmed by treating one of the derivatives with sodium nitrite and KI. As expected, corresponding diiodide **76** was obtained which confirmed the structural integrity of benzidines **74**. Later, these benzidines **74** were readily converted



Scheme 14 Thiazole derivatives **66–68** obtained by Sandmeyer reaction



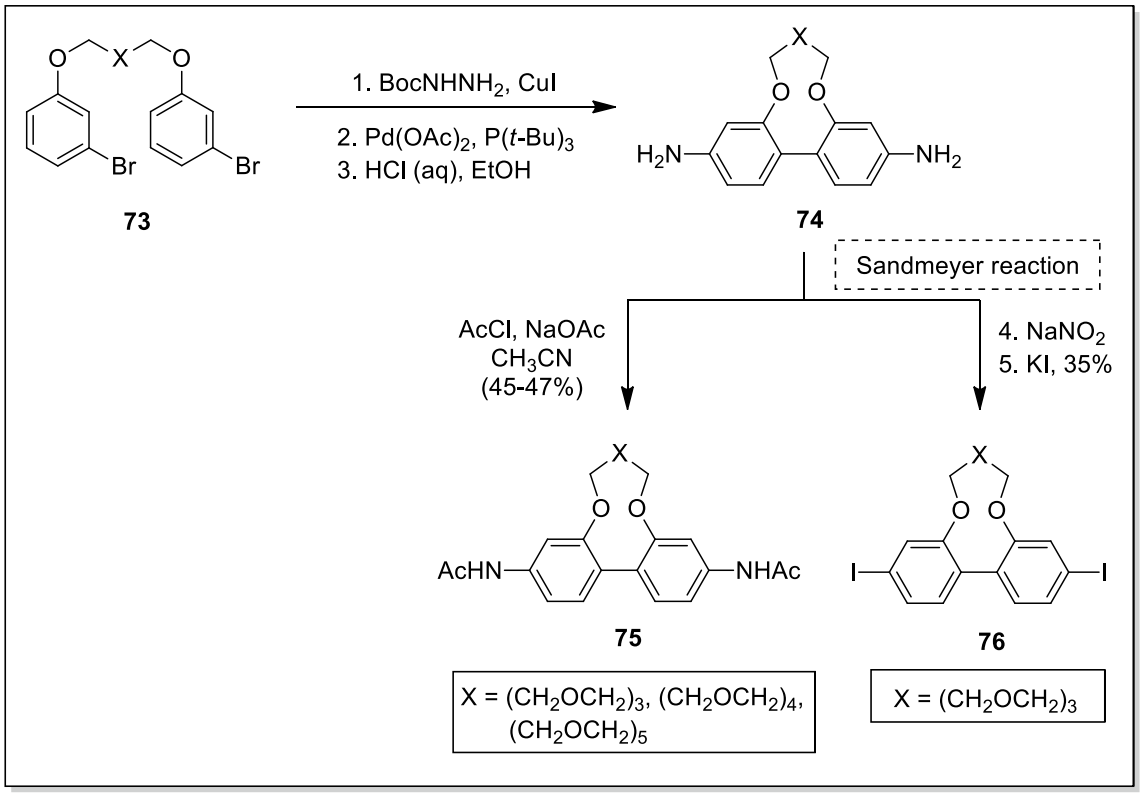
Scheme 15 Sandmeyer reaction of 3,5-dimethoxyaniline (**69**) for iodine-substituted methoxy ether **70**

into desired acetamides **75** (45–47%) via passing through acetylation process (Scheme 16).

Owing to the wide spread applications of conjugated compounds in optoelectronic devices due to their charge transfer and luminescent properties, synthesis of newly functionalized conjugated polymers and oligomers has fascinated a great deal of consideration. [2.2] Paracyclophane skeleton plays a main role in this regard and has been synthesized by different era of chemists due to its exclusive conjugated system. To carry out this research work, Gon et al. [46] synthesized tetrasubstituted [2.2]-paracyclophane core which involved Sonogashira-Hagihara coupling ($PdCl_2(PPh_3)_2$, PPh_3, CuI, Et_3N, THF) and Sandmeyer reactions (H_2SO_4, $NaNO_2$, KI) as key steps. Results declared that targeted derivatives showed good optical properties due to their larger molar extinction coefficient and photoluminescence quantum efficiency.

Miscellaneous

Liu et al. [47] proposed a complementary electrochemical method for Sandmeyer halogenation in which graphite can be used as cathode material which is an inexpensive metal as compared to platinum. This electrochemical reaction generated a variety of aryl halides by treating diazonium salts with different halogen sources such as $CBrCl_3$, CH_2I_2,



Scheme 16 Sandmeyer approach for the confirmation of benzidine **74** structure

LiCl, CCl_4, NaBr, NBS. Reaction processed at 20 °C in 5:1 mixture of MeOH/DMF using Bu_4NClO_4 as an electrolyte. Moreover, this reaction can also be performed in a one-pot fashion by obtaining diazonium salt from different anilines in the presence of *tert*-butyl nitrite followed by halogenation under optimized conditions provided required aryl halides.

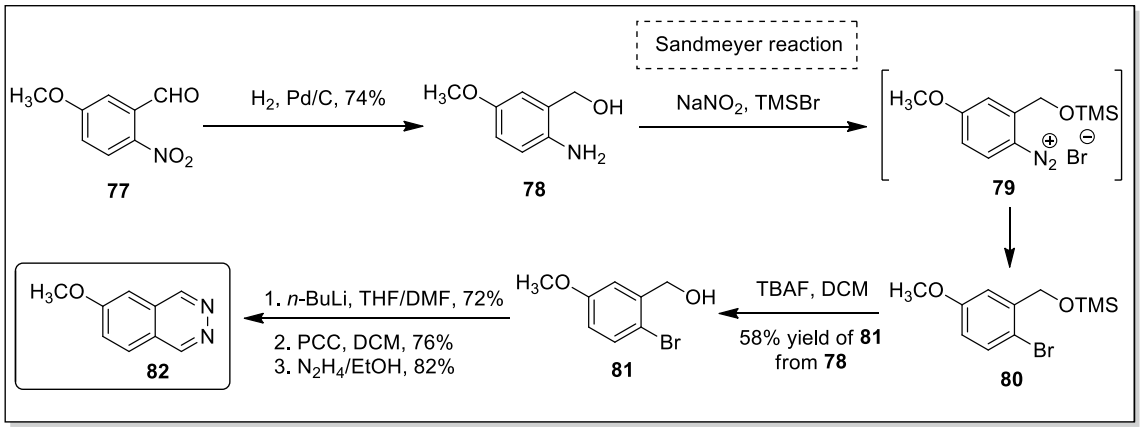
The efficient synthesis of novel benzo-substituted phthalazines was reported by Tsoungas and Searcey [48]. Their synthetic pathway started from the catalytic hydrogenation of aldehyde **77** to obtain alcohol **78** in 74% yield which was then subjected to Sandmeyer reaction in the presence of sodium nitrite and trimethysilyl bromide. As a result, diazonium salt **79** was formed which readily converted into compound **80**. After deprotection 58% yield of free alcohol **81** (from compound **78**) was obtained that further underwent halogen lithium exchange process followed by oxidation (PCC, DCM) and cyclization (N_2H_4, EtOH) reactions to provide targeted phthalazine **82** in 82% yield (Scheme 17).

An alternate route to obtain phthalazine **82**, started from the reduction of aldehyde **77** followed by diazotization and Sandmeyer reaction (*t*-BuONO, CuBr, HBr), provided aldehyde **85** in 45% yield. This aldehyde after protection ($(CH_2OH)_2$, TSA) followed by lithium halogen exchange process gave resulting intermediate in 76% yield (over 2 steps). Deprotection in the presence of 3 N HCl and cyclization of 4-methoxyphthalaldehyde with N_2H_4 provided required phthalazine **82** in 82% yield (Scheme 18).

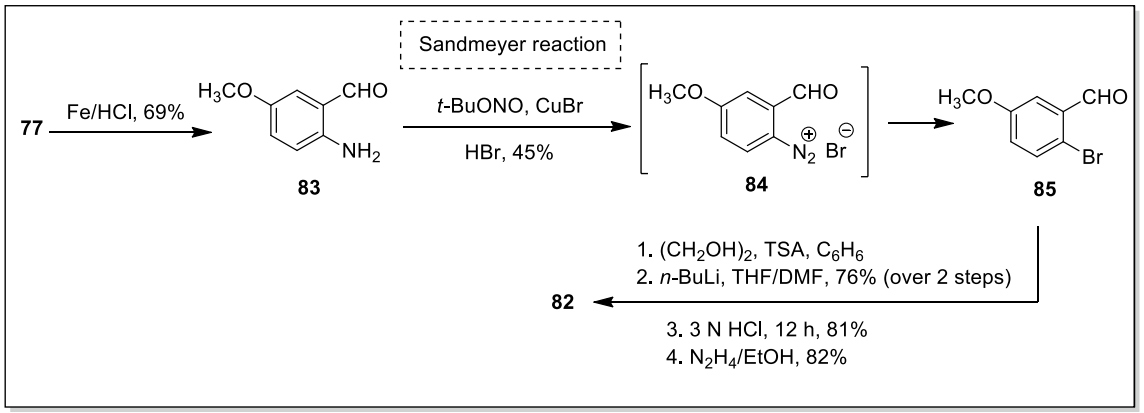
Buchtík et al. [49] reported a simple experimental procedure for the synthesis of polynuclear heterocyclic molecules based on 5-phenyl-6-azauracil scaffold. For this purpose, 3-[3-(6-azauracil-5-yl)-2-aminophenyl]-1,2-dihydro-quinoxaline-2-one (**86**) was used as starting precursor which first converted into diazonium salt that further produced a variety of heterocyclic N–H acids in good yield range. Two reference compounds, prepared via Sandmeyer reaction, are highlighted in Scheme 19. Reaction proceeded well when 6-azauracil **86** was reacted with sodium nitrite followed by the treatment with CuCl or CuBr in the presence of HCl/HBr provided 2-chloro (**87**) and 2-bromo (**88**) derivatives in 57 and 80% yield, respectively.

Formation of carbon–CF_2/CF_3/C_2F_5 linkage

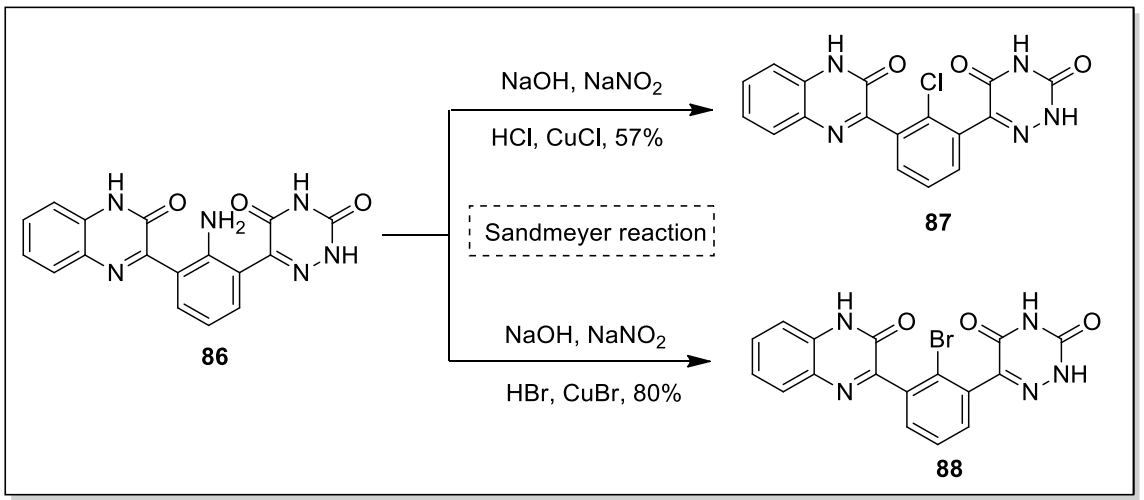
Highlighting the medicinal importance of organofluorine compounds, research group of Zheng synthesized trifluoromethylated arenes via Sandmeyer trifluoromethylation process [50]. Simple and mild reaction conditions, easy availability of the reagents and wide functional groups tolerance are the prominent features of this methodology. The reaction proceeded first from the formation of diazonium



Scheme 17 Synthesis of benzo-substituted phthalazine **82** via Sandmeyer reaction



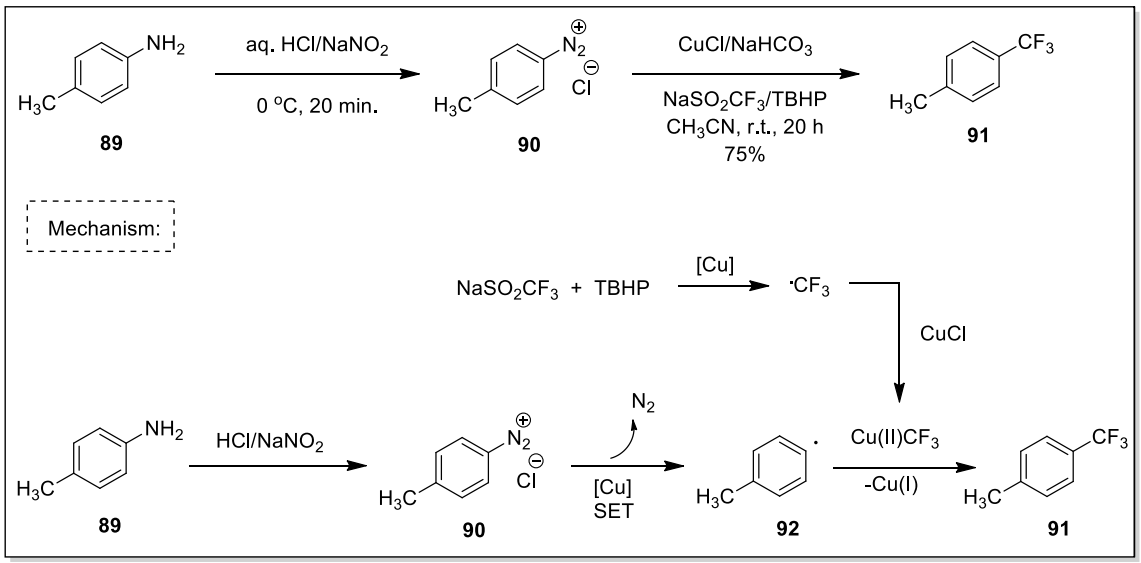
Scheme 18 An alternate route for phthalazine **82** by diazotization and Sandmeyer reaction (*t*-BuONO, CuBr, HBr)



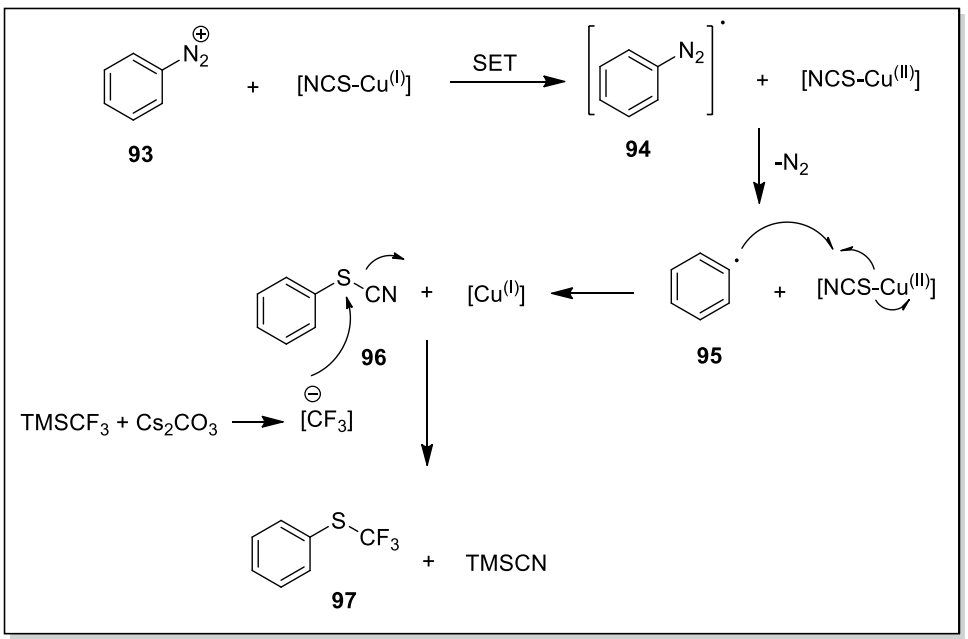
Scheme 19 Synthesis of polynuclear heterocyclic molecules based on 5-phenyl-6-azauracil scaffolds

salt **90** which subsequently treated with Langlois' reagent and CuCl in the presence of sodium bicarbonate (additive). Maximum conversion was achieved within 20 h by carrying out reaction at room temperature in acetonitrile solvent. Proposed mechanism of this reaction is presented in Scheme 20 which started from the conversion of diazonium salt to diazo radical via Cu(I)-mediated single-electron transfer process. This azo radical was further transformed into aryl radical **92** by releasing nitrogen gas. On the other side, Langlois' reagent upon treatment with TBHP produced trifluoromethyl radical whose reaction with CuCl generated $Cu(II)CF_3$ species that was used to insert CF_3 group in aryl radical **92** in the last step.

Danoun et al. [51] designed convenient, competent and inexpensive practical procedures for the trifluoromethylthiolation of arenediazonium salts via Sandmeyer reaction. Optimized parameters of this reaction involved $TMSCF_3$, CuSCN, Cs_2CO_3 and sodium thiocyanate as sulfur source. Reaction worked very well at room temperature in acetonitrile solvent to obtain 23–98% yield range. Mechanism of this reaction is highlighted in Scheme 21.



Scheme 20 Sandmeyer trifluoromethylation approach in the presence of Langlois' reagent



Scheme 21 Trifluoromethylation in the presence $TMSCF_3$ and CuSCN

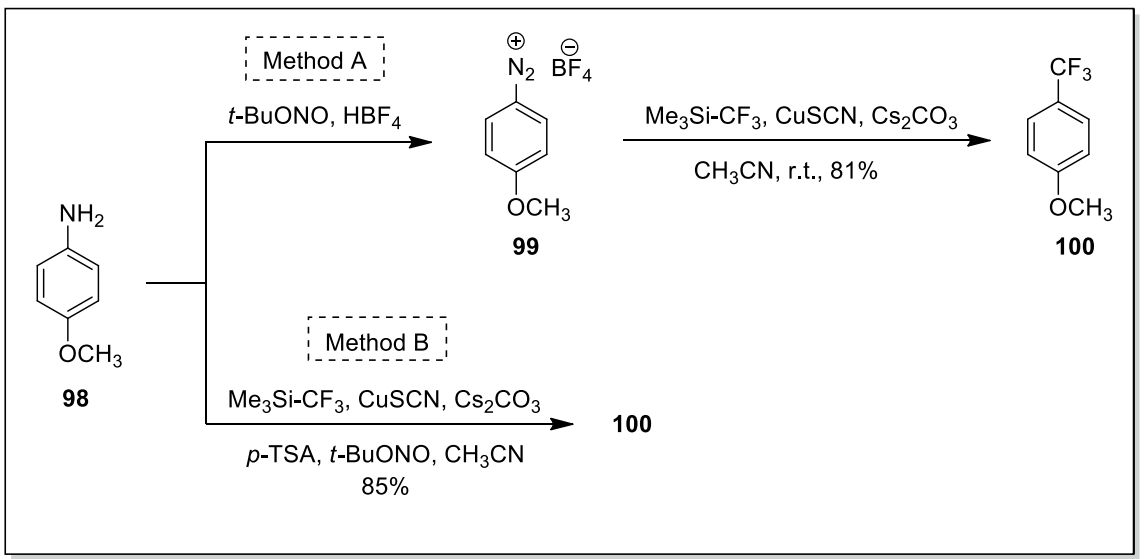
Later on, the same research group reported either one pot or sequential diazotization and trifluoromethylation as presented in Scheme 22 [52]. In method A, 4-methoxyaniline (**98**) was first diazotized in the presence of equimolar amount (2 equiv.) of *t*-BuONO and HBF_4 to produce diazonium salt **99** which was then dissolved in acetonitrile mixture containing $TMSCF_3$, copper(I) thiocyanate and cesium carbonate. As a result, 81% yield of the targeted product **100** was achieved at room temperature. On the other side, in a one-pot procedure a reaction mixture containing diazotized aniline was added to a suspension of $TMSCF_3$, copper(I) thiocyanate and cesium carbonate, resultantly afforded benzotrifluoride **100** in 85% yield. Yields of targeted derivatives were almost comparable of both pathways or sometimes higher in the later one. Wide functional group tolerance such as ether, ester, ketone and cyano groups and good yield range broadened the scope of this methodology.

Another application of Sandmeyer reaction for the trifluoromethylation of arenediazonium tetrafluoroborates was disclosed by Danoun et al. [53]. Plausible mechanism of this reaction started first by the reaction of copper(I) thiocyanate with trimethylsilyl cyanide in the presence of cesium carbonate; as a result, trifluoromethyl copper(I) species was generated which reacted with diazonium salt to obtain corresponding benzotrifluoride as described in Scheme 23. The methodology covers wide substrate scope giving rise to 40–98% yield range.

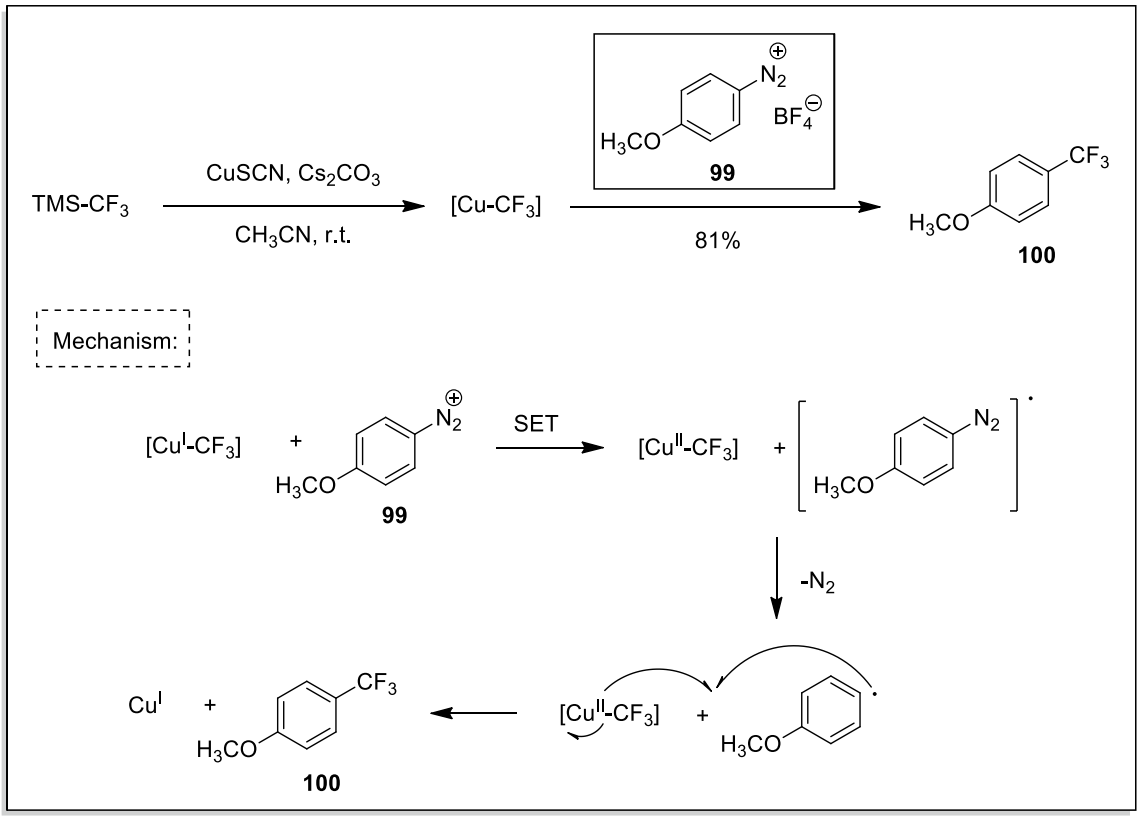
Goossen et al [54] provided detailed investigation of novel copper-catalyzed Sandmeyer reaction in which Ruppert-Prakash trifluoromethylating reagent produced a variety of trifluoromethylated arenes in good yield range without formation of $CuCF_3$ species. They began their investigation by treating 4-methoxyaniline with *tert*-butyl nitrite for the formation of diazonium salt. To select suitable acid for this conversion, the performance of eight acids (*p*-toluenesulfonic acid (*p*-TSA), *p*-TSA·H_2O, trifluoroacetic acid (TFA), ethereal·HCl, acetic acid, methanesulfonic acid (MSA), trichloroacetic acid (TCA), benzenesulfonic acid (BSA)) was observed and concluded that *p*-TSA gave maximum yield (85%). In addition to this, $TMSCF_3$, CuSCN, Cs_2CO_3 and room temperature were the other parameters to carry out trifluoromethylation and trifluoromethylthiolation in 41–98% and 32–70% yield range, respectively.

A new synthetic approach of trifluoromethylated arenes via copper-catalyzed Sandmeyer reaction in the presence of Umemoto's reagent was established by Dai et al. [55]. The potential applicability of Umemoto's reagent in combination with copper powder was proven by carrying out reaction using a variety of aryl amines; as a result, desired trifluoromethylated arenes were obtained in moderate to good yield range. Two equivalents Cu powder, 1.5 equivalents Umemoto's reagent **102**, 3 equivalents of isoamyl nitrite and acetonitrile solvent are the optimized parameters of this methodology (Scheme 24).

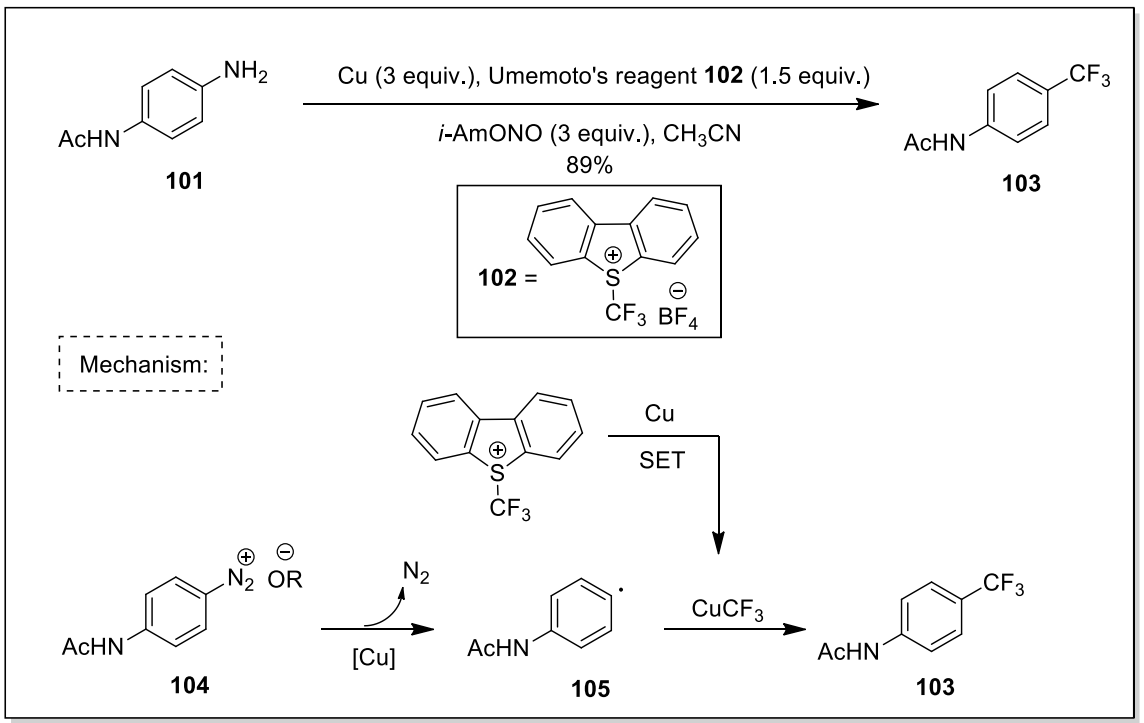
Matheis et al. [56] performed direct, simple and selective Sandmeyer reaction of diazonium salt **106** by using difluoromethyl-copper complex as difluoromethylating reagent. This complex can be formed by treating 2.5 equivalents of TMS-CF_2H with 1 equivalent copper thiocyanate and 3 equivalents cesium fluoride in DMF solution. This successful difluoromethylation process tolerated a wide variety of functional groups by giving 34–86% yield range. It was observed that both electron-donating and withdrawing substituents afforded almost high yields. However, by



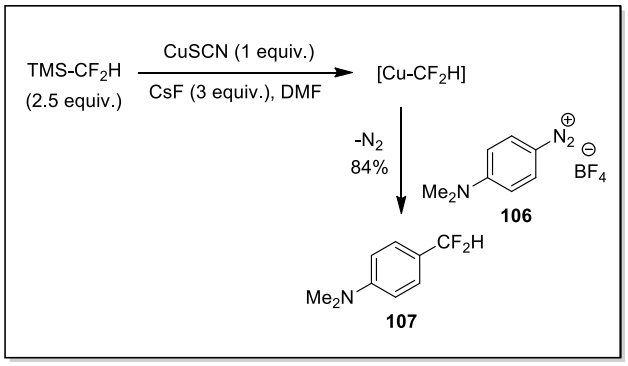
Scheme 22 Sequential (Method A) and one-pot (Method B) diazotization and trifluoromethylation to obtain benzotrifluoride **100**



Scheme 23 Plausible mechanism for the conversion of diazonium salt **99** to benzotrifluoride **100**



Scheme 24 Sandmeyer reaction in the presence of Umemoto's reagent



Scheme 25 Difluoromethylation in the presence of difluoromethyl-copper complex [Cu-CF_2H]

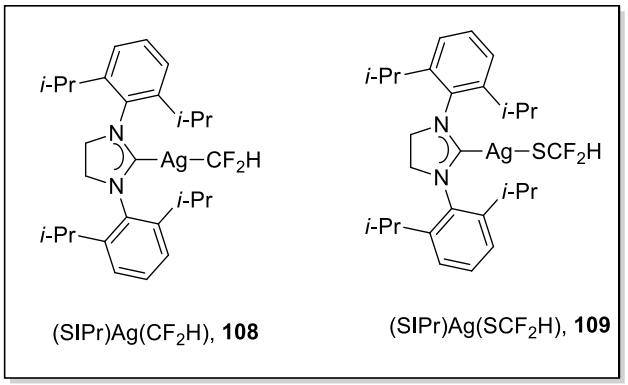


Fig. 1 [(SIPr)Ag(SCF_2H)] as difluoromethylating reagent prepared from [(SIPr)Ag(CF_2H)]

comparing *ortho*, *meta* and *para* positions functional groups, *ortho*-substituted substrates gave lower yields (38–73%) as compared to *para*-substituted substrates (69–81%). In case of heteroarene diazonium salts such as quinolone, carbazole and indole derivatives, a reasonable yield range (35–78%) was also observed (Scheme 25).

In 2014, Wang et al. [57] have made a novel contribution toward Sandmeyer-type trifluoromethylation reaction by using trifluoromethyl-silver complex as CF_3 source. This methylating reagent was prepared by treating silver fluoride with $TMSCF_3$ in propionitrile. Temperature was first maintained at − 78 °C and then gradually raised to 25 °C. As a result, desired $AgCF_3$ complex obtained which was subjected to Sandmeyer process. This process started from the diazotization of the different aromatic amines via standard protocol (HCl, *t*-BuONO) followed by the oxidative addition of the trifluoromethyl-silver complex to diazonium salt, resultantly afforded high-valent silver intermediate which readily underwent reductive elimination reaction to obtain targeted trifluoromethylated product in 10–97% yield range.

Later on, in 2015 Wu et al. [58] proposed one-pot difluoromethylthiolation approach via Sandmeyer reaction under mild conditions. Optimized parameters to carry out this conversion including $[Cu(CH_3CN)_4]PF_6$ as copper salt, 2,2'-bipyridine as ligand, acetonitrile as solvent and [(SIPr)Ag(SCF_2H)] as difluoromethylating reagent (Fig. 1) which could be easily prepared by treating [(SIPr)Ag(CF_2H)] with sulfur in THF solvent. This methodology gave wide substrate scope by giving 32–92% yield range of difluoromethylthiolated heteroarenes within 24 h by maintaining temperature at 50 °C.

In 2019, Hu and et al. [59] reported for the first time pentafluoroethylation reaction by utilizing Sandmeyer approach. In their methodology, CuC_2F_5 was used as pentafluoroethylating reagent which obtained in a sequence manner first by treating $TMSCF_3$ with sodium iodide in THF solvent; as a result, tetrafluoroethylene species was attained. This species further reacted with cesium fluoride in the presence of copper thiocyanate at 70 °C to afford targeted CuC_2F_5. In the last step, diazonium salt **110** was treated with CuC_2F_5 in acetonitrile solvent; resultantly, desired product **111** was obtained in 93% yield. This protocol covered wide substrate scope by giving targeted derivatives in 51–93% yield range within short reaction time (Scheme 26).

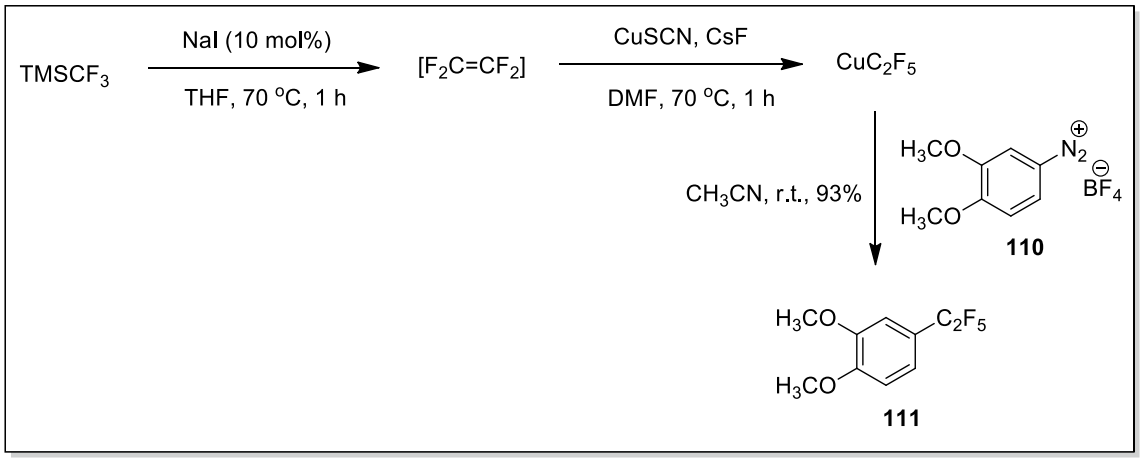
Hong et al. [60] examined the use of Togni's reagent in one-pot Sandmeyer trifluoromethylation reaction. Their pathway started from the diazotization of the aromatic amines in the presence of HCl and *t*-BuONO. Then this salt was treated with Togni's reagent II and copper salt, $Cu(MeCN)_4BF_4$ at 45 °C. Sodium bicarbonate was used as base in dichloroethane solvent. As a result, corresponding tifluoromethylated analogs were obtained in 42–90% yield range. A plausible mechanism is highlighted in Scheme 27 according to which Togni's reagent was used to produce CF_3 radical via copper(I)-mediated single-electron transfer (SET) approach.

Some other reports on Sandmeyer-type fluoromethylation are presented in Table 2.

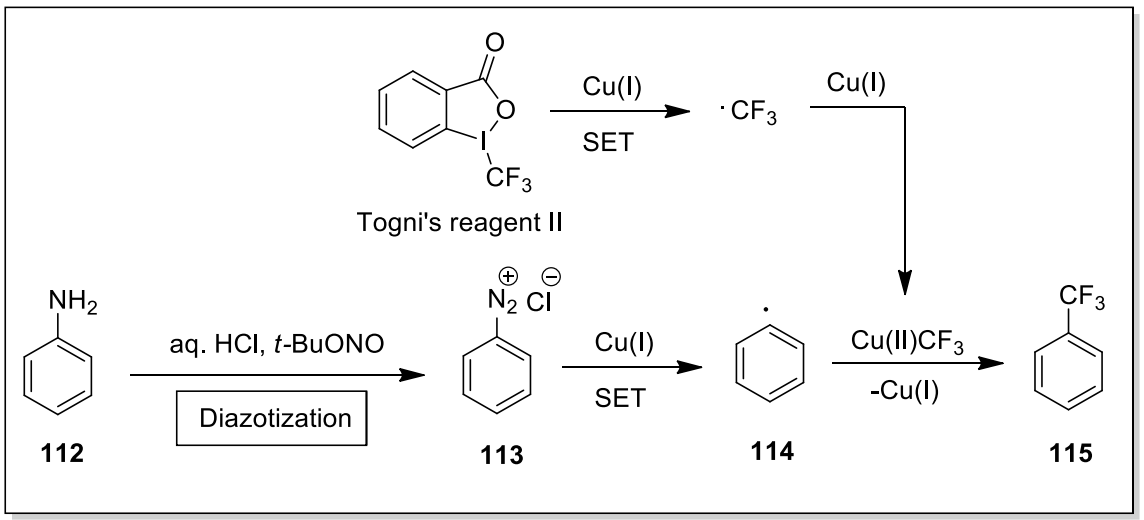
Formation of carbon–CN linkage

In 2014, Xu et al. [63] reported Cu_2O-catalyzed Sandmeyer reaction of arenediazonium tetrafluoroborates with TMSCN. The reaction worked very well and gave maximum yield with 0.4 equivalent catalyst loading that was not even significantly increased by using 1 equivalent of Cu_2O in acetonitrile solvent. Temperature was maintained at 55 °C to obtain targeted products in 38–92% yield range within 10 h. This ligand and halogen-free protocol provided many benefits over classic Sandmeyer reaction as nontoxic, mild reaction conditions, low catalyst loading and wide substrate scope are the salient features of this methodology.

Later on, this research group presented another nontoxic palladium-catalyzed cyanation via Sandmeyer approach in



Scheme 26 Pentafluoroethylation via Sandmeyer reaction



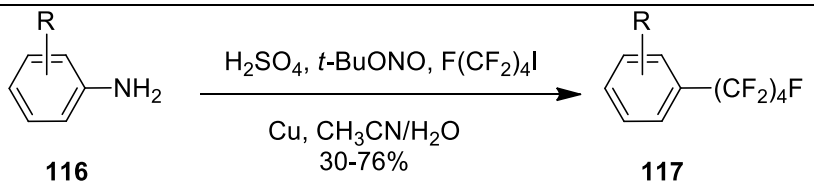
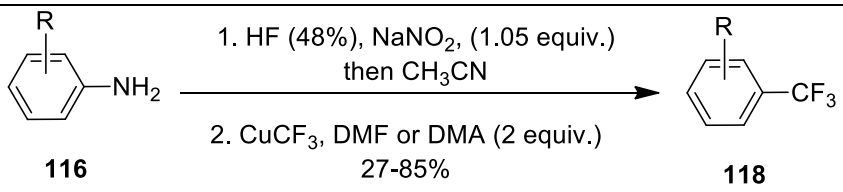
Scheme 27 Sandmeyer trifluoromethylation reaction in the presence of Togni's reagent II

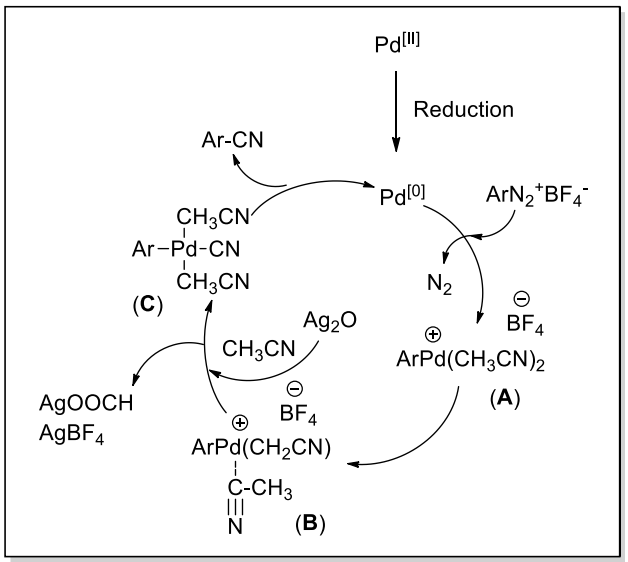
which acetonitrile was used as nonmetallic CN source [64]. Reaction processed under ambient air in the presence of 0.1 equivalent of $PdCl_2$ and 1 equivalent of Ag_2O (additive) at 55 °C. As a result, 30–64% yield range was obtained of the targeted derivatives. A plausible mechanism is highlighted in Scheme 28 which started from the reduction of divalent palladium to zero-valent palladium. In the next oxidative step, this zero-valent palladium added to $ArN_2^+BF_4^-$ to obtain Ar-Pd species (**A**) followed by the cleavage of CH_3-CN bond in the presence of Ag_2O gave intermediate (**C**). Reductive elimination was the last step which provided aromatic nitrile along with zero-valent palladium.

In order to develop new and efficient conditions for Sandmeyer cyanation, Barbero et al. [65] utilized arene and heteroarenediazonium *o*-benzenedisulfonimides as starting precursors and tetrabutyl ammonium cyanide as CN source. Reaction was carried out at room temperature in acetonitrile solvent. This approach under mild reaction conditions gave targeted compounds in 34–92% yield range. A reference example is presented in Scheme 29 which highlighted the mechanism of this copper-free protocol started by the transfer of electron from anionic part of the salt **119** toward cation. As a result, resonance-stabilized complex **119a** was formed which reacted with CN^- part of tetrabutyl ammonium cyanide to provide corresponding aryl nitrile **120**.

Da Silva et al. [66] designed an effective approach for the synthesis of 2-chloro-3-carbonitrile analogs which are well-known intermediates and can be transformed into a variety of useful and biologically important heterocyclic molecules, for example the highly polyfunctionalized 4*H*-pyran, oxazolo, pyrazolo, 1,4-dihydropyridine or pyridines derivatives. The authors used 2-amino-3-carbonitriles as starting

Table 2 Sandmeyer-type fluoromethylation

Sr. no	References	Examples
1.	Jiang et al. [61]	
2.	Lishchynskyi et al. [62]	



Scheme 28 Plausible mechanism for palladium-catalyzed cyanation via Sandmeyer approach

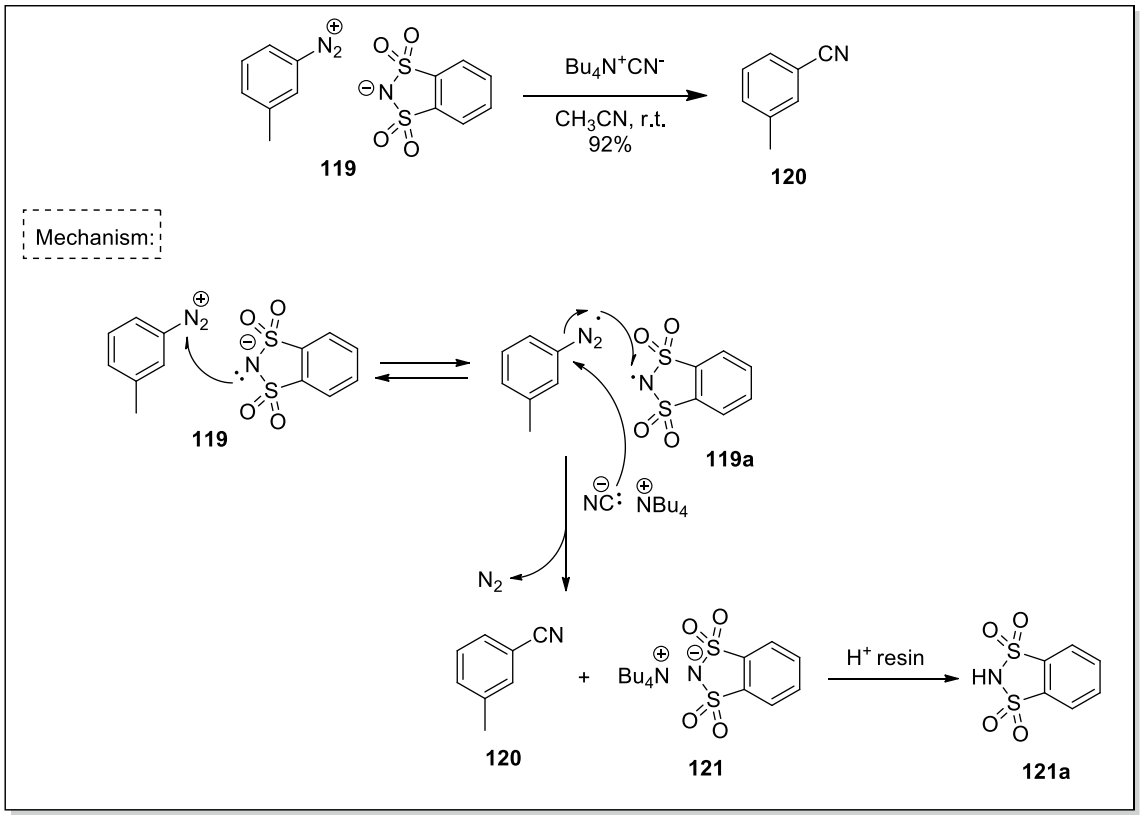
precursors to obtain corresponding 2-chloro-3-carbonitriles via Sandmeyer approach. The reaction was catalyzed by 1.5 equivalents of $CuCl_2$ in acetonitrile solvent. After the addition of isoamyl nitrite, temperature was maintained at 65 °C to obtain targeted derivatives in 10–69% yield range (Fig. 2).

For the construction of medicinally important indole-1,2,4-benzotriazine derivatives, Sandmeyer reaction seems to be a suitable methodology as elaborated by Xu et al. [67]. Their protocol started by the S_NAr reaction of the indole **133** with 2-nitrophenyl halide **134** in the presence of cesium carbonate to obtain respective indole derivative **135** which was subsequently reduced with stannous chloride dihydrate. As a result, indole **136** obtained (45% yield) that was cyclized by using *tert*-butyl nitrite via a modified Sandmeyer reaction to afford targeted indole-1,2,4-benzotriazine **137** (24% yield) which proved to be a promising lead compound against a variety of phytopathogenic fungi (Scheme 30).

The research group of Beletskaya reported copper-catalyzed Sandmeyer cyanation approach with a variety of diazonium salts [68]. Reaction proceeded very well using potassium cyanide as CN source, equimolar amount (10 mol%) of CuCN as catalyst, 1,10-phenantroline as ligand, dibenzo-18-crown-6 as phase transfer catalyst and $Cu(BF_4)_2$ as co-catalyst. Maximum yield range (52–93%) was obtained by carrying out reaction at room temperature in acetonitrile solvent.

Formation of carbon–sulfur linkage

Sulfonyl fluorides have gained tremendous interest in synthetic organic chemistry due to their unique characteristics such as stability, reactivity pattern and proton-mediated reactivity. They are extensively used for the construction of a variety of pharmacologically important scaffolds. Considering their importance, Lin et al. developed an efficient, cost-effective and copper-free methodology for the synthesis of arenesulfonyl fluorides via Sandmeyer approach. In their protocol, different arenediazonium salts having electron-donating and withdrawing substituents were treated with *N*-fluorobenzenesulfonimide (NFSI), a fluorine source and $K_2S_2O_5$ which plays dual role as a reductant and a sulfonyl source simultaneously. Reaction conducted very well under argon atmosphere in a mixture of acetonitrile, water and acetic acid (co-solvent). Maximum conversion was attained within 6 h at room temperature.



Scheme 29 Sandmeyer cyanation, using arenediazonium *o*-benzenedisulfonimide **119** as starting precursor and tetrabutyl ammonium cyanide as CN source

Diaryl sulfones exhibit a wide range of biological activities; for example, they act as anticancer, antifungal, antibacterial agents and are efficient thymidylate synthase and HIV-1 reverse transcriptase inhibitors. Besides this, they play a vital role as synthetic intermediates in organic chemistry. Despite the discovery of various synthetic methods for diaryl sulfones, search of new and efficient conditions is still under process. In this regard, Yang et al. [70] reported a competent copper-catalyzed Sandmeyer approach for the synthesis of diaryl sulfones. For example, reaction of aryl amine **89** with arylsulfinic acid **138** in the presence of equimolar amounts (3 equivalents) of copper powder and isoamyl nitrite (diazotizating agent) gave 82% yield of the corresponding product **139**. Reaction processed under nitrogen atmosphere by maintaining temperature at 0–25 °C in acetonitrile solvent. This approach depicted a wide substrate scope, allowing the preparation of a variety of diaryl sulfones in 47–82% yield range (Scheme 31).

Research group of Goossen in 2015 reported difluoromethylthiolation of arene diazonium salts in 61–95% yield range [71]. Standard parameters to make this conversion effective included following steps: First a solution of diazonium salt **99** in acetonitrile solvent was mixed in sodium thiocyanate, cesium carbonate and copper thiocyanate mixture. Then cesium fluoride, copper thiocyanate and TMS-CF_2H in DMF were added in the reaction mixture; as a result, desired product **140** was obtained in 95% yield within 12 h by carrying out reaction at room temperature.

Later on, same research group presented trifluoromethylthiolation and pentafluoroethylthiolation by applying Sandmeyer conditions as described in Scheme 32. Reaction of 4-methoxybenzenediazonium tetrafluoroborate (**99**) was performed with 1.8 equivalents of Me_4NSCF_3 in the presence of copper thiocyanate. Resultantly, trifluoromethyl thioether **141** was obtained in 97% yield [72]. However, when the same reaction was performed in the presence of 10 mol% elemental copper using $Me_4NSC_2F_5$ as SC_2F_5 source, pentafluoroethyl thioether **142** was obtained in 98% yield. This methodology under mild reaction conditions tolerates a variety of functional groups by giving 61–99% yield range [73].

Zhang et al. [74] adopted a different approach for trifluoromethylation of arenediazonium tetrafluoroborates in the presence of Langlois reagent ($NaSO_2CF_3$). Reaction worked very well at 45 °C using *t*-butyl hydroperoxide as oxidant, $CuBF_4(CH_3CN)_4$ as copper salt and 2,2′;6′,2″-terpyridine (tpy) as ligand. As a result, 30–63% yield range of the corresponding trifluoromethylated derivatives was obtained in a mixture of acetonitrile/water solvent. Similarly, the authors

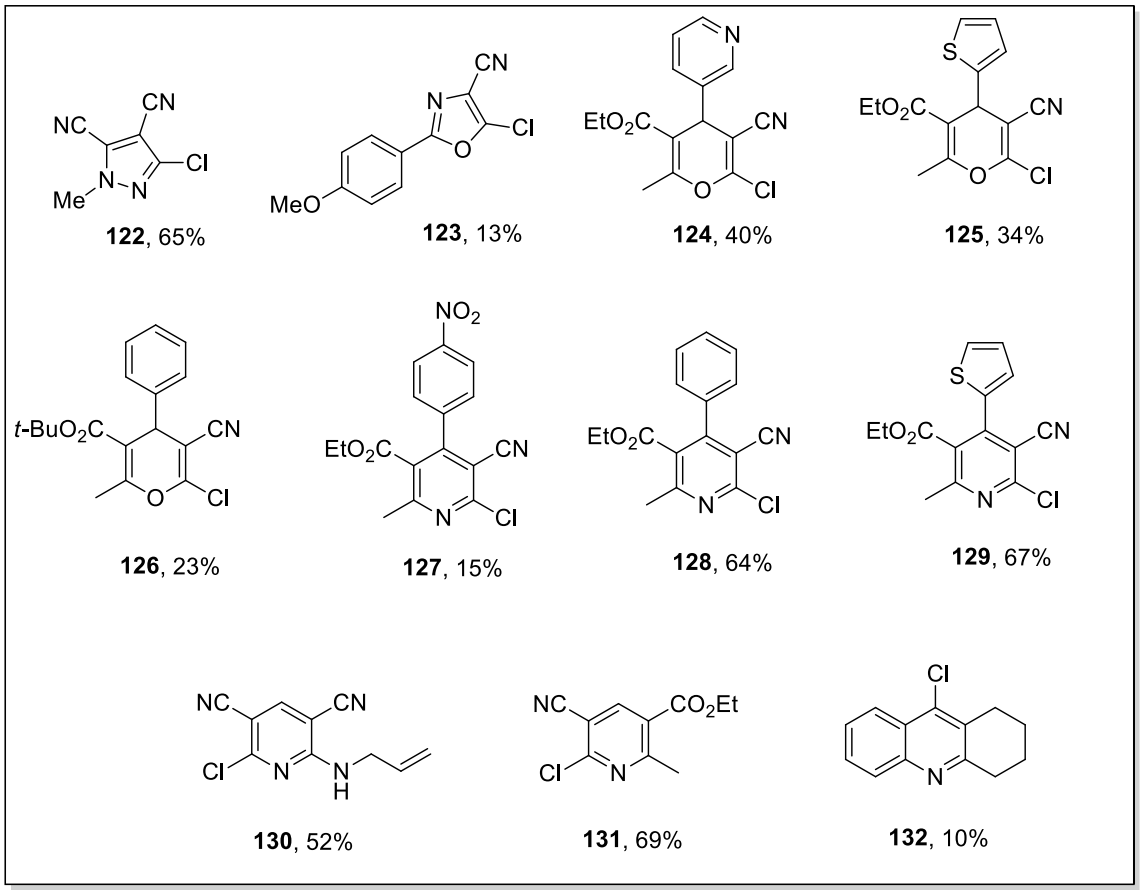
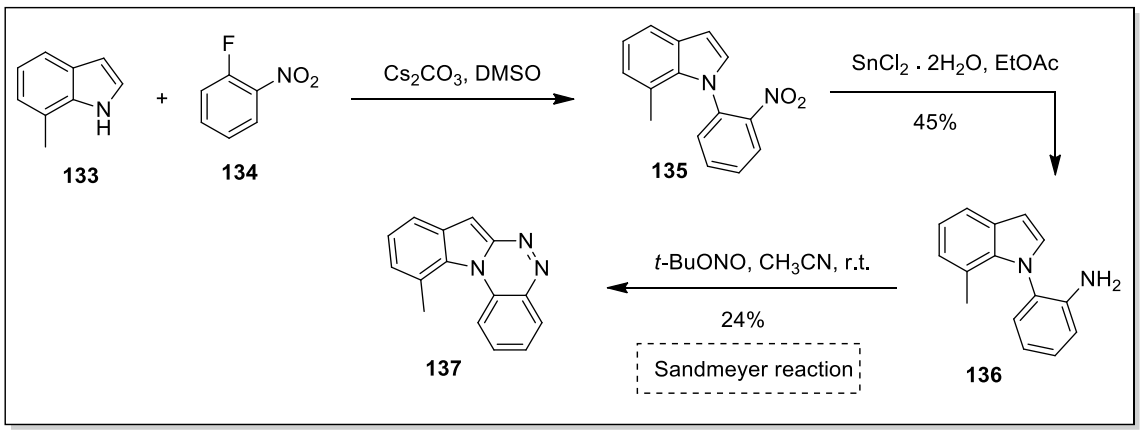


Fig. 2 2-Chloro-3-carbonitrile analogs (**122–132**) prepared via Sandmeyer reaction



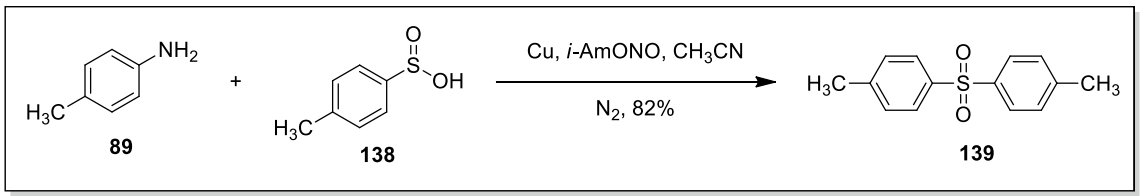
Scheme 30 Preparation of indole-1,2,4-benzotriazine derivative **137** involving Sandmeyer reaction as a key step

reported trifluoromethanesulfonylation of arenediazonium tetrafluoroborates in 45–90% yield range in the presence of $NaSO_2CF_3$ and 10 mol% Cu_2O. To carry out maximum conversion at room temperature, DMSO was selected as suitable solvent.

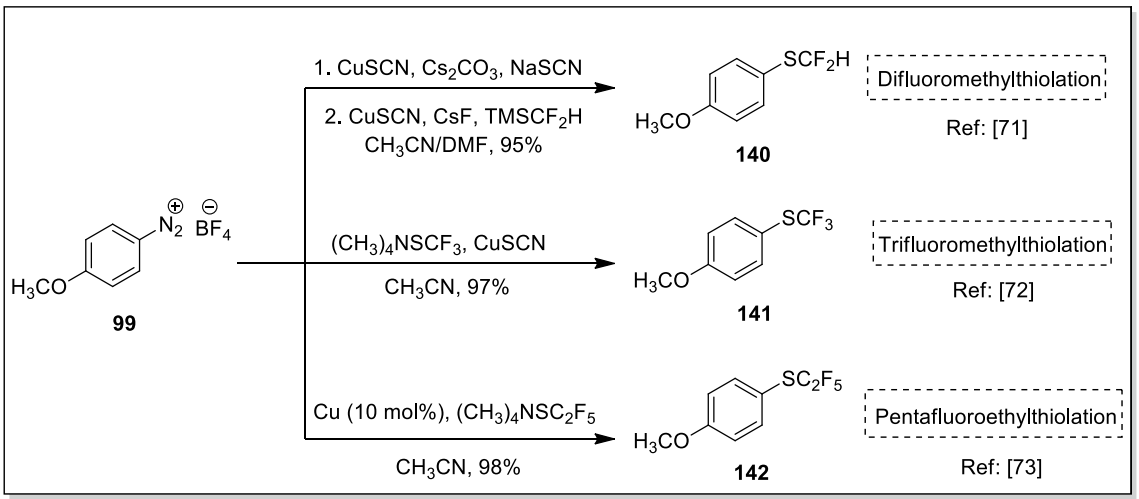
Organothiophosphates are worthy of attention due to their outstanding insecticidal, antiviral and enzyme inhibition properties against acetylcholinesterase (AChE) enzyme. Their wide spread contribution in pharmaceutical chemistry encouraged Kovacs et al. [75] to disclose

different phosphorothiolation methods mainly including phosphorothiolation of arenediazonium salts via Sandmeyer approach. In their methodology, the highlighting reagent used for phosphorothiolation was **144** which when reacted with diazonium salt **143** under standard Sandmeyer conditions (CuSCN (20 mol%), acetonitrile, r.t.), aand phosphorothiolated arene **145** was obtained in 95% yield. The reaction covered a wide variety of substrates by giving targeted products in 47–95% yield range within 16 h (Scheme 33).

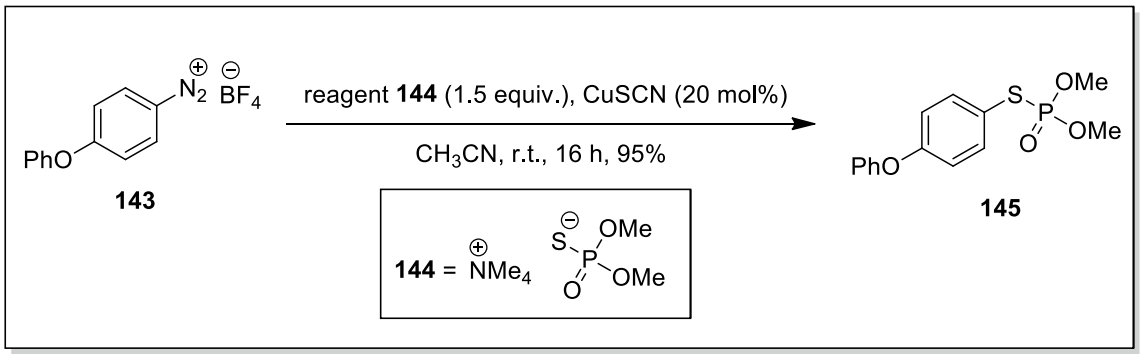
Ou et al. [76] in 2019 published a convenient procedure for the construction of (diethylphosphono)-difluoromethyl thioethers proceeding via two steps: Sandmeyer thiocyanation and subsequent fluoroalkylation reaction. Optimal reagents for thiocyanation included copper thiocyanate, cesium carbonate, sodium thiocyanate (sulfur source) and acetonitrile solvent. As a result, corresponding thiocyanate derivative was obtained which was subjected to fluoroalkylation reaction using TMS-$CF_2PO(OEt)_2$ as the difluoroalkyl source. Plausible mechanism of this reaction is presented in



Scheme 31 Copper-catalyzed Sandmeyer approach for the synthesis of diaryl sulfones



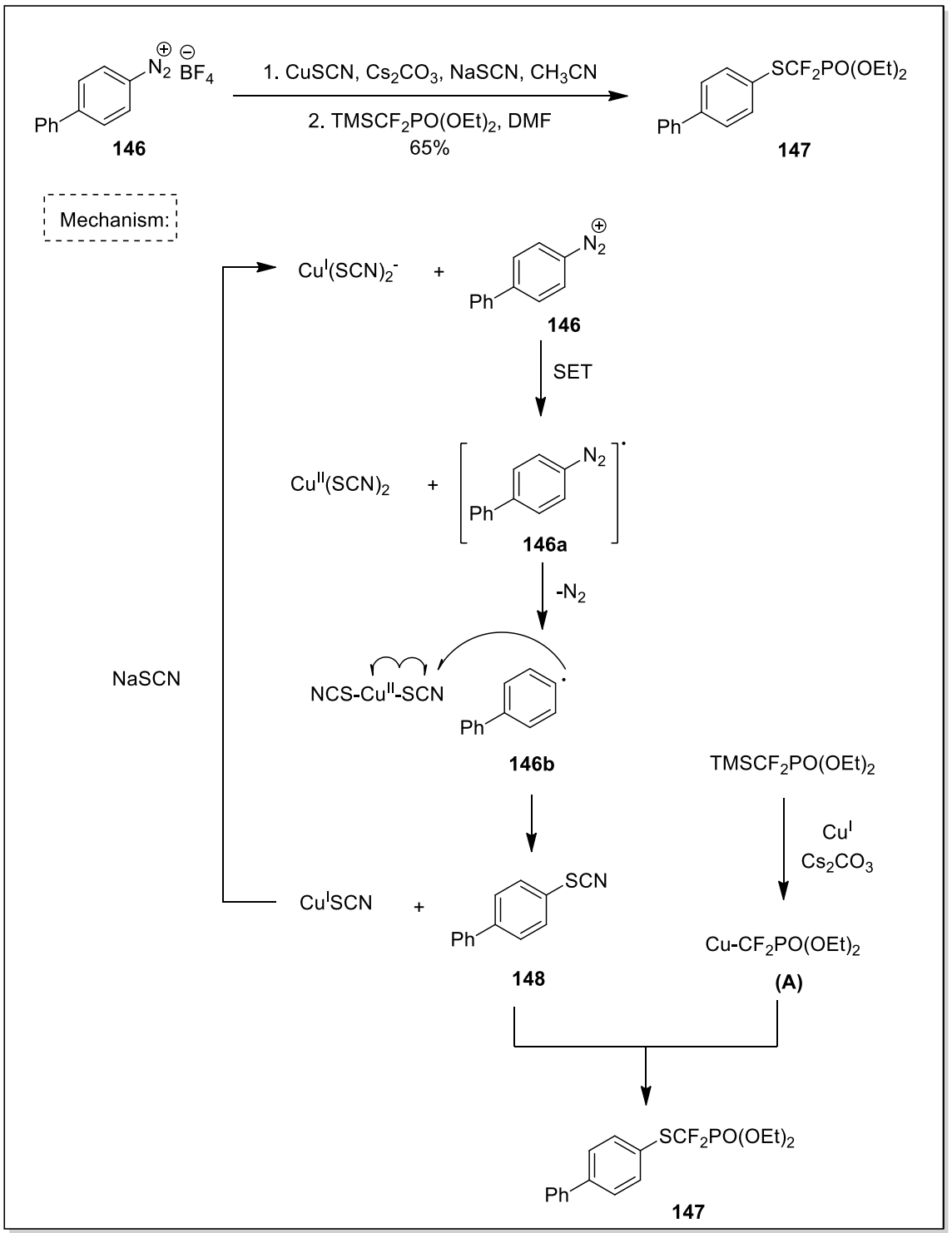
Scheme 32 Di-, trifluoromethylthiolation and pentafluoroethylthiolation via Sandmeyer approach



Scheme 33 Phosphorothiolation of arenediazonium salt **143** via Sandmeyer approach

Scheme 34 which started from the generation of $Cu^{I}(SCN)_2$ species by the reaction of CuSCN with NaSCN. In the next step, diazonium salt **146** was treated with $Cu^{I}(SCN)_2$ to obtain respective thiocyanate **148** via Sandmeyer approach. On the other side, conversion of TMS-$CF_2PO(OEt)_2$ to Cu-$CF_2PO(OEt)_2$ in the presence of base gave species (**A**) which was in the final step reacted with thiocyanate **148** to afford targeted product **147**.

Very recently, research group of Qing reported a similar methodology for fluorosulfonylation of arenediazonium



Scheme 34 Mechanism of sequential Sandmeyer thiocyanation and fluoroalkylation reactions

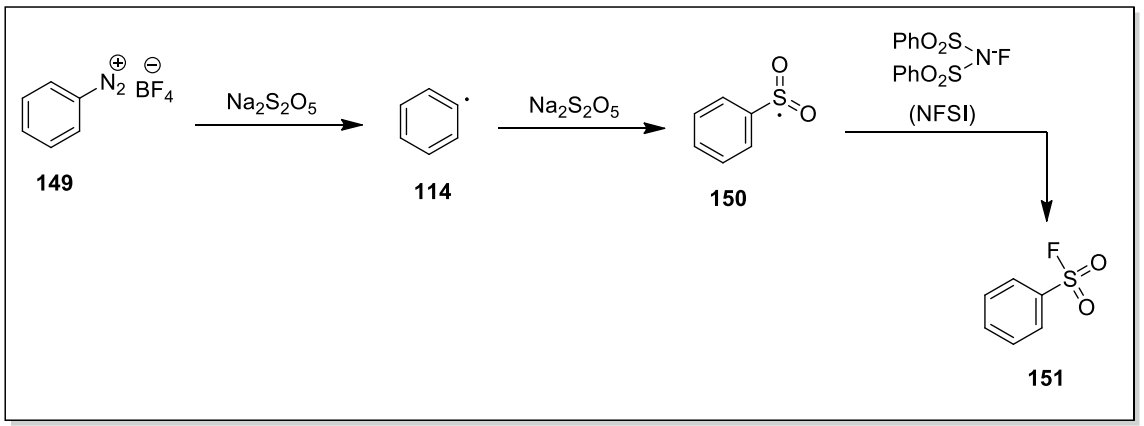
tetrafluoroborates [77]. However, they used $Na_2S_2O_5$ as sulfonyl source instead of $K_2S_2O_5$. The other optimized parameters were *N*-fluorobenzenesulfonimide (NFSI), 2/0.1 mixture of acetonitrile/water, 60 °C temperature under nitrogen atmosphere. As a result, 43–81% yield range was obtained within 6 h. A plausible mechanism is highlighted in Scheme 35. Single-electron transfer reduction of aryldiazonium salt **149** provided aryl radical **114** which upon reaction with SO_2 (generated from $Na_2S_2O_5$) gave arenesulfonyl radical **150**. In the last step, transfer of fluorine atom from *N*-fluorobenzenesulfonimide afforded targeted arenesulfonyl fluoride **151**.

In another report, various diazonium salts were subjected to fluorosulfonylation reaction by passing through Sandmeyer approach. For this purpose, $Na_2S_2O_5$ was used as sulfur dioxide source and Selectfluor **152** as fluorine source in methanol solvent. Temperature was maintained at 70 °C to attain maximum yield (85%) of sulfonyl fluoride **153**. This methodology was applied on a variety of substrates; resultantly moderate to good yield range was obtained (Scheme 36) [78].

Tarkhanova et al. [79] demonstrated that copper catalysts incorporating ionic liquid on Silochrom support efficiently catalyzed Sandmeyer reaction. A highlighted example for the thiocyanation of 3-methyl-4-nitrophenyldiazonium tetrafluoroborate (**154**) is presented in Scheme 37. For this purpose, potassium thiocyanate was used as nucleophile and reaction was catalyzed with CuCl-Et_3PrNCl in acetonitrile solvent. 96% Yield of the required product **155** was obtained by carrying out reaction at room temperature. Same methodology was adopted to attain 87–97% yield range of a variety of aryl bromides.

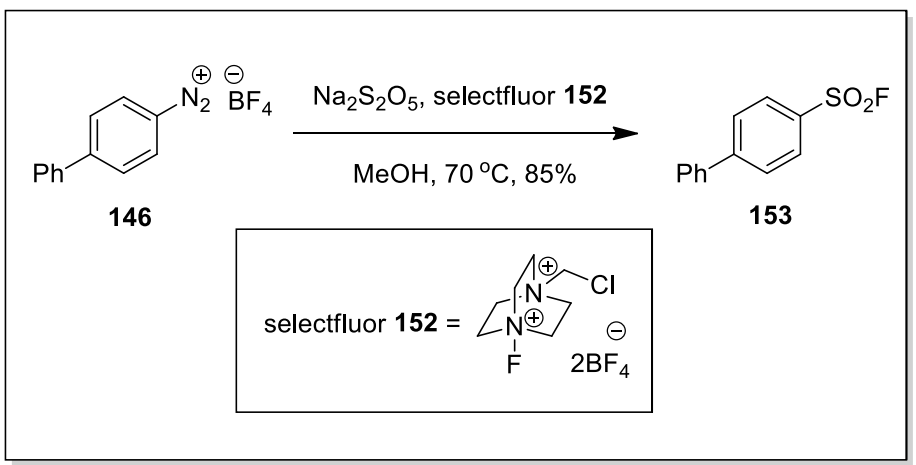
Formation of carbon–tin linkage

Organotin reagents are highly important due to their usage in the synthesis of various C–N, C–F and C–OCF_3 bond formation reactions. They are also used for the generation of C–C bond by highly famous Stille cross-coupling reaction



Scheme 35 Fluorosulfonylation of arenediazonium tetrafluoroborate **149** using $Na_2S_2O_5$ as sulfonyl source and *N*-fluorobenzenesulfonimide (NFSI) as fluorine source

Scheme 36 Fluorosulfonylation reaction using Selectfluor **152** as fluorine source



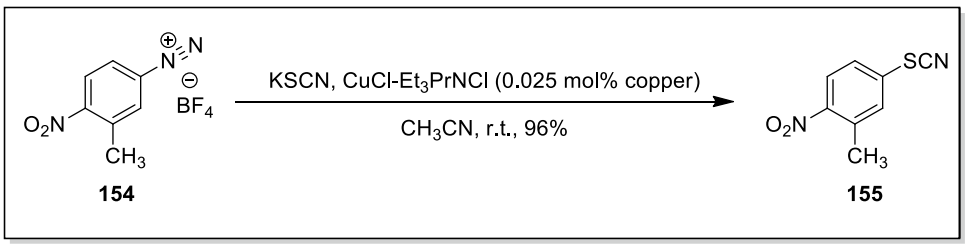
whose wide applications in organic synthesis create a dire need to develop new and efficient synthetic methods for aryl stannane compounds. On account of this, Qiu et al. [80] developed a Sandmeyer-type stannylation approach for the preparation of aryl trimethylstannanes. A highlighted example is presented in Scheme 38 in which amine **57** was treated with *tert*-butyl nitrite and $(SnMe_3)_2$ in dichloroethane solvent at 0 °C. Screening a variety of acidic additives such as TsOH, $BF_3{\cdot}OEt_2$, $AlCl_3$ and AcOH which found to be helpful for diazotization process, maximum yield was obtained with *p*-toluenesulfonic acid. Overall, moderate to good yield range (36–86%) of the targeted products was obtained which were most likely subjected to different cross-coupling reactions without purification such as Stille reaction and can also be used for the synthesis of different pharmaceutical agents.

Later on, the same research group developed another methodology for stannylation of aromatic amines, simultaneously generating trimethylstannyl arylboronate analogs which were effectively subjected to Stille and Suzuki–Miyaura cross-coupling reactions [81]. For example, conversion of *p*-nitroaniline **57** into arylboronate **157** was accomplished in the presence of *tert*-butyl nitrite, *bis*(pinacolato)diboron, benzoyl peroxide and acetonitrile solvent under metal-free conditions. Then reduction of nitro group to NH_2 group via palladium-catalyzed reaction generated boron-substituted aniline **158** in 98% yield which further converted into corresponding stannylation analog **159** under optimized Sandmeyer-type stannylation reaction conditions (*t*-BuONO, $(SnMe_3)_2$, TsOH, DCE) (Scheme 39).

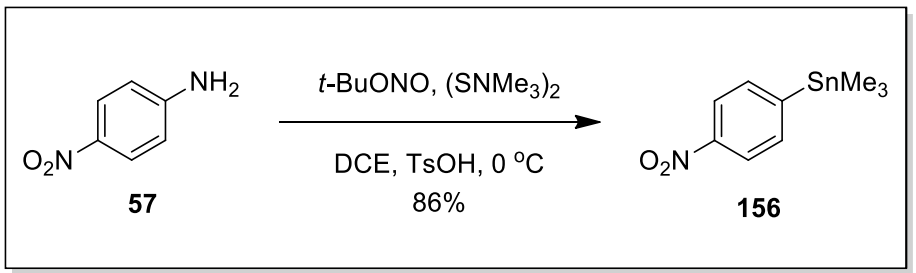
Formation of carbon–phosphorous linkage

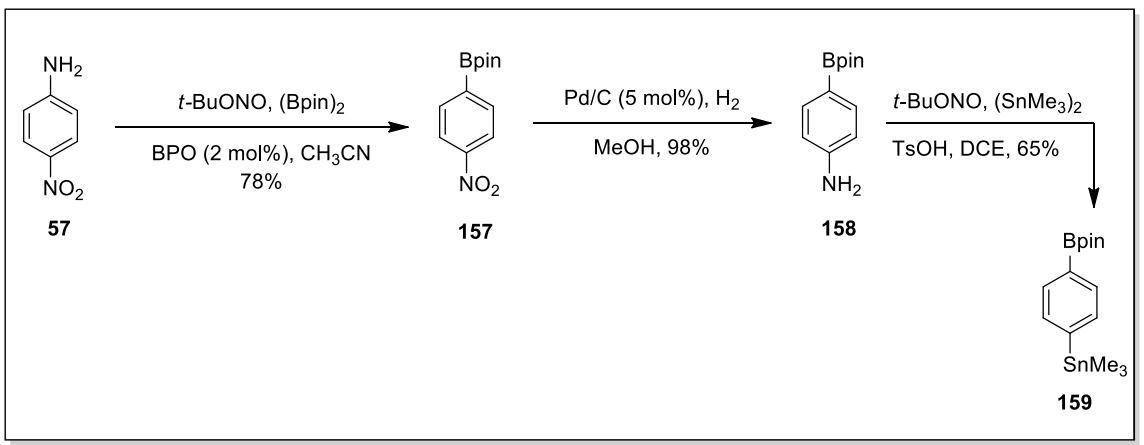
In an effort to search diversified methods for aryl phosphonates which play a vital role in material science, organic

Scheme 37 Sandmeyer reaction catalyzed by copper incorporating ionic liquid on Silochrom support



Scheme 38 Sandmeyer-type stannylation approach for the preparation of aryl trimethylstannanes





Scheme 39 Synthesis of trimethylstannyl arylboronate analog **159**

and medicinal chemistry, Wang and their colleagues studied the applicability of Sandmeyer phosphorylation reaction for the synthesis of these aryl phosphonates [82]. They began their investigation by the reaction of ethyl 4-aminobenzoate with *tert*-butyl nitrite under different conditions. First of all, trimethyl phosphite, triethyl phosphite and triphenyl phosphite were screened as phosphorous source and results supported the use of triphenyl phosphite which gave significant yield (78%) as compared to the other phosphites. Reaction processed at 0 °C using $TsOH{\cdot}H_2O$ as an additive which was selected among different acids such as HCl, $TsOH{\cdot}H_2O$, H_2SO_4 and $BF_3{\cdot}OEt_2$. Reaction completed within 8 h in acetonitrile solvent by giving 25–99% yield range.

Formation of carbon–selenium linkage

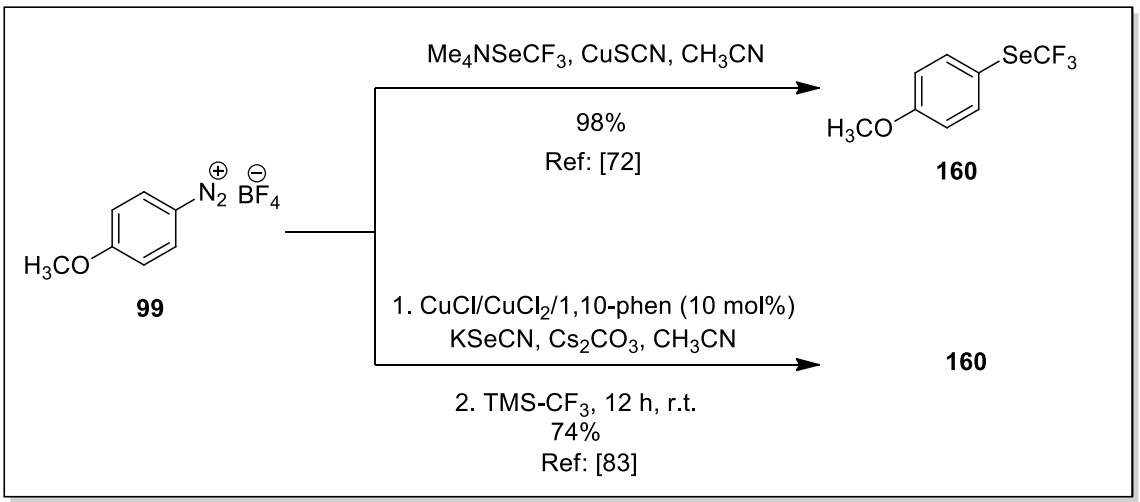
Matheis et al. [72] successfully utilized Sandmeyer approach for the preparation of trifluoromethylselenoethers under mild reaction conditions. For this purpose, Me_4NSeCF_3 was used as $SeCF_3$ source which efficiently converted diazonium salt **99** to its corresponding selenoether **160** in 98% yield. Reaction processed at room temperature using CuSCN as copper salt in acetonitrile solvent. In order to evaluate substrate scope, maximum conversion was achieved within 1 h by giving 69–98% yield range of the desired trifluoromethylselenoethers. Similarly, a straightforward approach for the insertion of trifluoromethylseleno group into aromatic amines was reported by Nikolaienko and Rueping in 2016 [83]. Reaction was accomplished via two steps, first converting diazonium salt **99** to its respective selenocyanate in the presence of $CuCl/CuCl_2$ catalytic system. 1,10-Phenanthroline was used as additive, cesium carbonate as base and KSeCN as SeCN source in acetonitrile solvent. In the second step, this selenocyanate was treated with TMS-CF_3 for the insertion of CF_3 group. Reaction was completed within 12 h at room temperature and afforded corresponding trifluoromethylselenoether **160** in 74% yield. In this methodology, arenediazonium salts having both electron-donating and withdrawing substituents were readily converted into desired selenoethers in 40–88% yield range (Scheme 40).

Formation of carbon–boron linkage

Focusing the green synthetic routes, Zhang et al. [84] published their report on Sandmeyer-type borylation for the synthesis of arylboronate esters. They began their investigation by treating 4-carboxylicphenyldiazonium tetrafluoroborate with *bis*(pinacolato)diboron as exemplary substrates. Reaction processed at room temperature in a mixture of solvents such as acetone–water, acetonitrile–water, dimethoxyethane–water, dioxane–water, water and acetone. Results revealed that 2:1 mixture of acetonitrile–water gave targeted arylboronate ester in 80% yield. Maximum conversion was achieved in the presence of 5 mol% CuBr which selected by observing the catalytic behavior of $Cu(OAc)_2$, $FeCl_3$, $Co(Ac)_2$, $CeCl_2$ and CuBr. 24–85% Yield range of different arylboronate esters was obtained within 3–6 h.

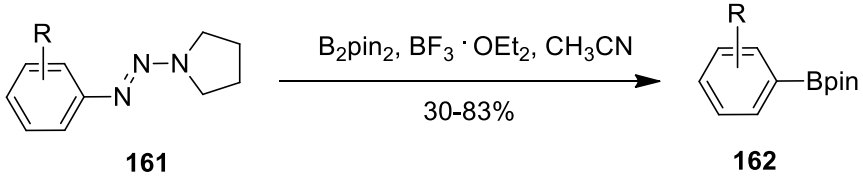
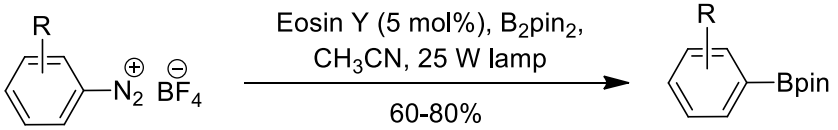
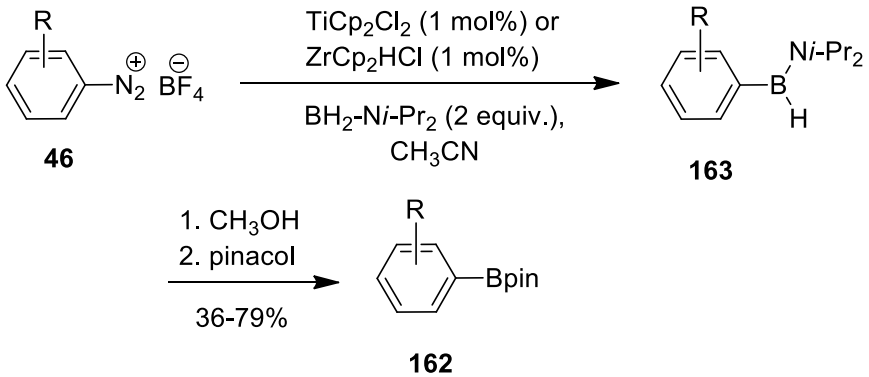
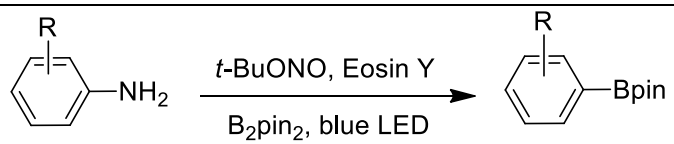
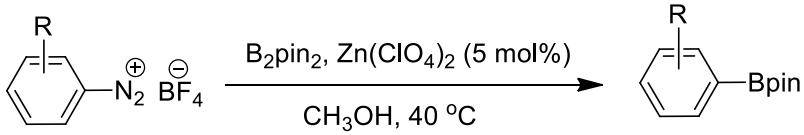
In continuation of this research work, Qiu et al. [85] in 2013 reported Sandmeyer-type borylation approach under metal-free condition. In this method, a variety of aryl amines were first diazotized in the presence of *tert*-butyl nitrite followed by the addition of *bis*(pinacolato)diboron in acetonitrile solvent afforded the desired pinacol arylboronates in 14–77% yield range by maintaining temperature at 80 °C. These aryl boronates further used for Suzuki–Miyaura cross-coupling reaction to obtain a variety of biaryl compounds in moderate to high yield range which proved the efficacy of this protocol.

Some other reports on Sandmeyer-type borylation are presented in Table 3.



Scheme 40 Sandmeyer approach for the preparation of trifluoromethylselenoethers

Table 3 Sandmeyer-type borylation

Sr. no	References	Examples
1.	Zhu and Yamane [86]	 **161** **162**
2.	Yu et al. [87]	 **46** **162**
3.	Marciasini et al. [88]	 **46** **163** **162**
4.	Ahammed et al. [89]	 **116** **162**
5.	Qi et al. [90]	 **46** **162**

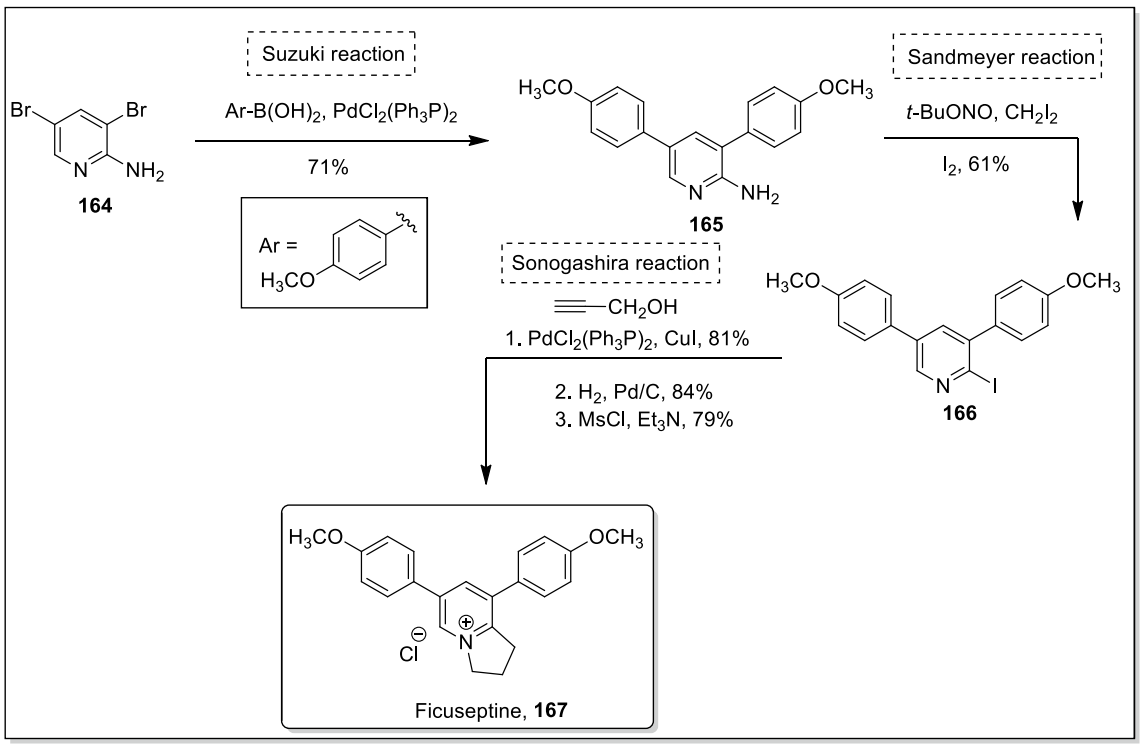
Applications of Sandmeyer reaction for the synthesis of medicinally important compounds

Natural bioactive molecules

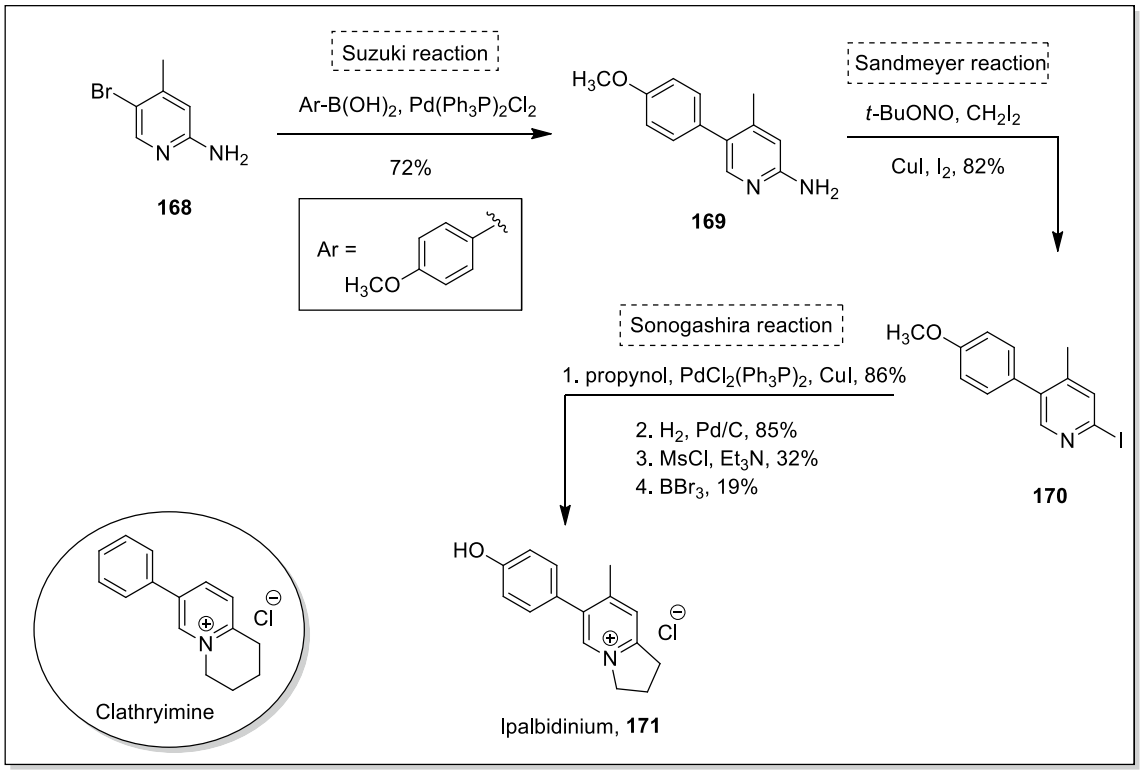
Synthesis of alkaloid ficuseptine In 2002, Bracher and Daab developed an efficient protocol for the synthesis of alkaloid ficuseptine **167** (a good antifungal and antibacterial agent) which involved Suzuki, Sonogashira and Sandmeyer reactions as key steps [91]. Their methodology started from the Suzuki cross-coupling of *bis*(arylation) of 3,5-dibromopyridine (**164**) with 4-methoxyphenylboronic acid under optimized conditions resultantly afforded corresponding arylated compound **165** in 71% yield which was subsequently subjected to Sandmeyer reaction in the presence of *t*-BuONO, CH_2I_2 and I_2. Consequently, iodopyridine **166** was obtained in 61% yield. In the next step, by applying Sonogashira reaction conditions followed by palladium-catalyzed hydrogenation and cyclization reactions afforded desired indolizidinium alkaloid **167** in 79% yield (Scheme 41).

Synthesis of indolizidinium alkaloid ipalbidinium Later on, the same research group utilized their previously reported methodology for the synthesis of indolizidinium alkaloid ipalbidinium **171** and quinolizidinium alkaloid clathryimine B [92]. Their recommended approach is described in Scheme 42 which started from the Suzuki reaction of the bromopyridine **168** with boronic acid under standard conditions. As a result, corresponding arylpyridine **169** was obtained in 72% yield which subsequently subjected to Sandmeyer reaction in the presence of *t*-BuONO, CH_2I_2, CuI and I_2, resultantly affording iodo compound **170** in 82% yield. Further, Sonogashira coupling followed by catalytic hydrogenation and cyclization reactions which after cleavage of the OMe group using BBr_3 afforded desired ipalbidinium **171** in 19% yield. Likewise, clathryimine B was also prepared by using the same reaction conditions of these key steps.

Synthesis of curcuphenol Studies on biological activities of curcuphenol reveal that it can be used as antibacterial, antifungal, antimalarial as well as anticancer agent. Besides this, it plays a great role to inhibit proton-potassium ATPase enzyme, resultantly preventing/curing different stomach diseases such as gastroesophageal reflux disease and peptic ulcer disease. Remarkable pharmacological significance of curcuphenol has attracted researchers to develop various techniques for the efficient synthesis of this scaffold. On account of this, Kim and their colleagues proposed an enantioselective synthesis of (+)-curcuphenol via Sandmeyer and Negishi cross-coupling reactions [93]. Their pathway started from the easily available starting precursor, *m*-anisidine (**172**) which was protected using benzyl bromide and potassium carbonate base. Insertion of aldehyde into this moiety using crotonaldehyde



Scheme 41 Synthesis of alkaloid ficuseptine **167** using Suzuki, Sandmeyer and Sonogashira reactions as key steps



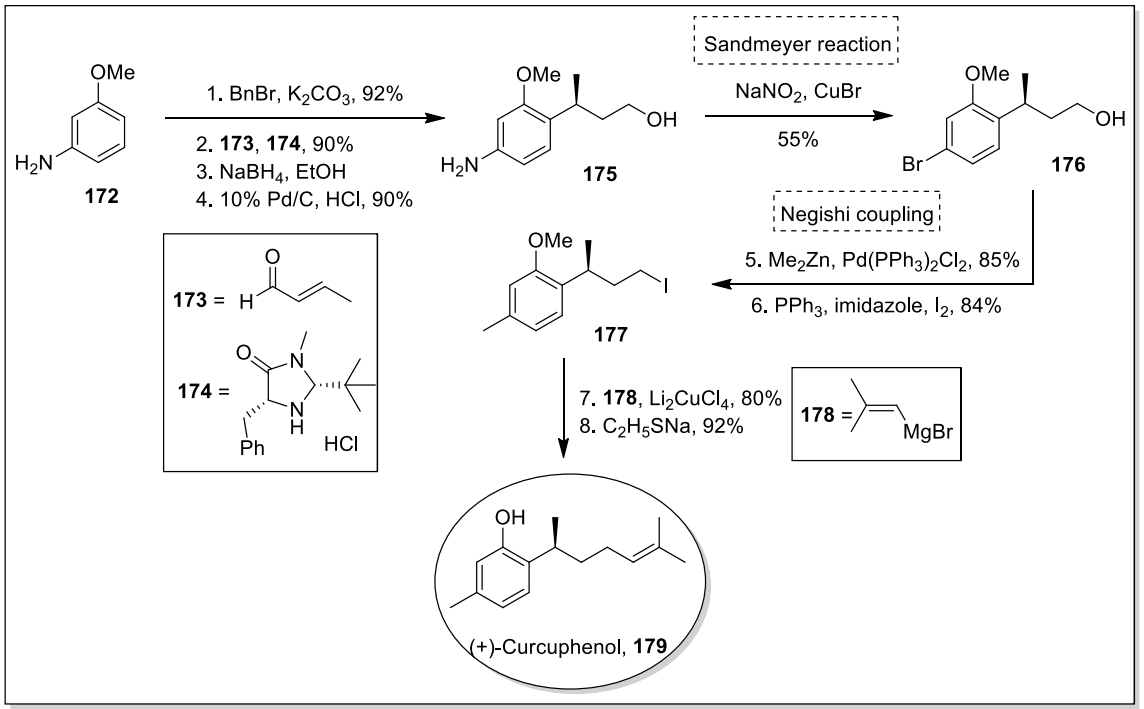
Scheme 42 Synthetic pathway for indolizidinium alkaloid ipalbidinium **171**

173 in the presence of imidazolidinone catalyst **174** provided corresponding aldehyde derivative in 90% yield. After reduction of this aldehyde with $NaBH_4$ followed by deprotection, reaction provided compound **175** in 90% yield. Compound **175** was then converted to derivative **176** by passing through Sandmeyer reaction. Optimized reagents for this conversion were sodium nitrite and copper bromide which gave resultant analog **176** in 55% yield. Next step was Negishi coupling for the replacement of bromo group to methyl group, and the resultant compound was treated with triphenylphosphine, imidazole and iodine to obtain iodo compound **177** in 84% yield. Last step was the reaction of compound **177** with 2-methyl-1-propenylmagnesium bromide (**178**) followed by the cleavage of the methyl ether functionality afforded (*S*)-(+)-curcuphenol (**179**) in 92% yield (Scheme 43).

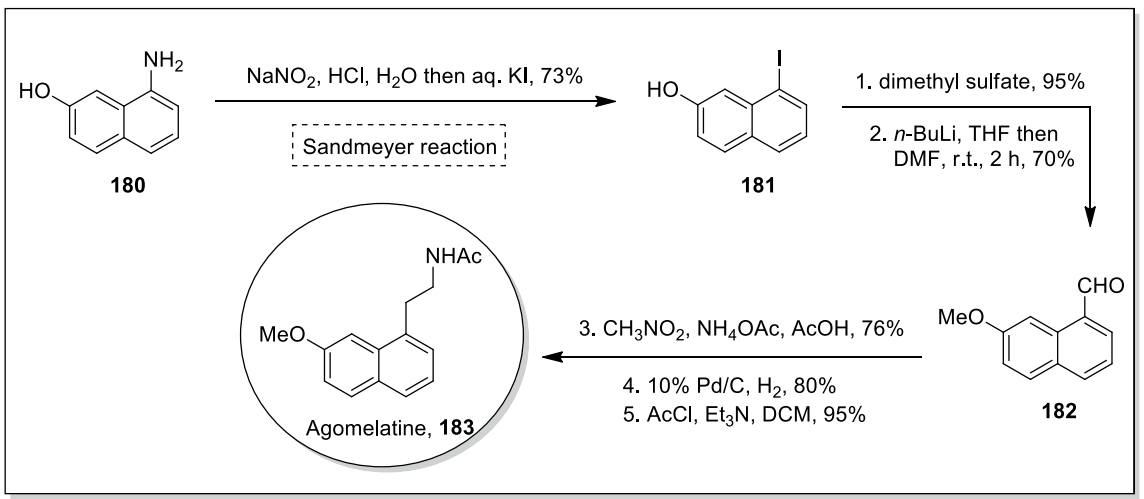
Synthetic bioactive molecules

Synthesis of agomelatine Kandagatla et al. [94] established a convenient and simple approach for the synthesis of agomelatine (an antidepressant drug) including easily available starting precursors. For this purpose, 8-aminonaphthalen-2-ol (**180**) was first subjected to Sandmeyer reaction. Diazotization of **180** in the presence of $NaNO_2$ followed by halogenation with KI provided 8-iodo-β-naphthol (**181**) in 73% yield. After that protection of OH group using dimethyl sulfate with subsequent formylation reaction afforded 7-methoxy-1-naphthaldehyde (**182**) in 70% yield. Reaction of this aldehyde (**182**) with nitromethane followed by catalytic hydrogenation and acetylation provided targeted agomelatine **183** in 95% yield (Scheme 44).

Synthesis of ceritinib For the treatment of lung cancer, crizotinib, a tyrosinase kinase inhibitor, was effectively used in the past few years. However, resistance to this drug creates an option to develop new potent anticancer drug alternate to crizotinib. Ceritinib (LDK378) is another new and efficient anaplastic lymphoma kinase inhibitor which is efficiently used to treat cancer with greater potency. Considering its importance, Liu et al. [95] described a cost-effective route for the synthesis of ceritinib (LDK378) which started from easily available starting substrates under mild reaction conditions. In their methodology, first 1,3-dichloro-4-nitropyridine (**184**) was coupled with 2-(propane-2-sulfonyl)-phenylamine (**185**) in the presence of chloroform; resultantly, corresponding compound **186** (95%) was obtained by the displacement of 3-Cl of **184** with NH_2 group of **185**. In the next step, 1-Cl group of compound **186** was displaced with NH_2 group of Boc protected compound **187** in acetonitrile solvent to obtain coupled product **188** in 94% yield. Later, catalytic hydrogenation followed by Sandmeyer reaction in the presence of



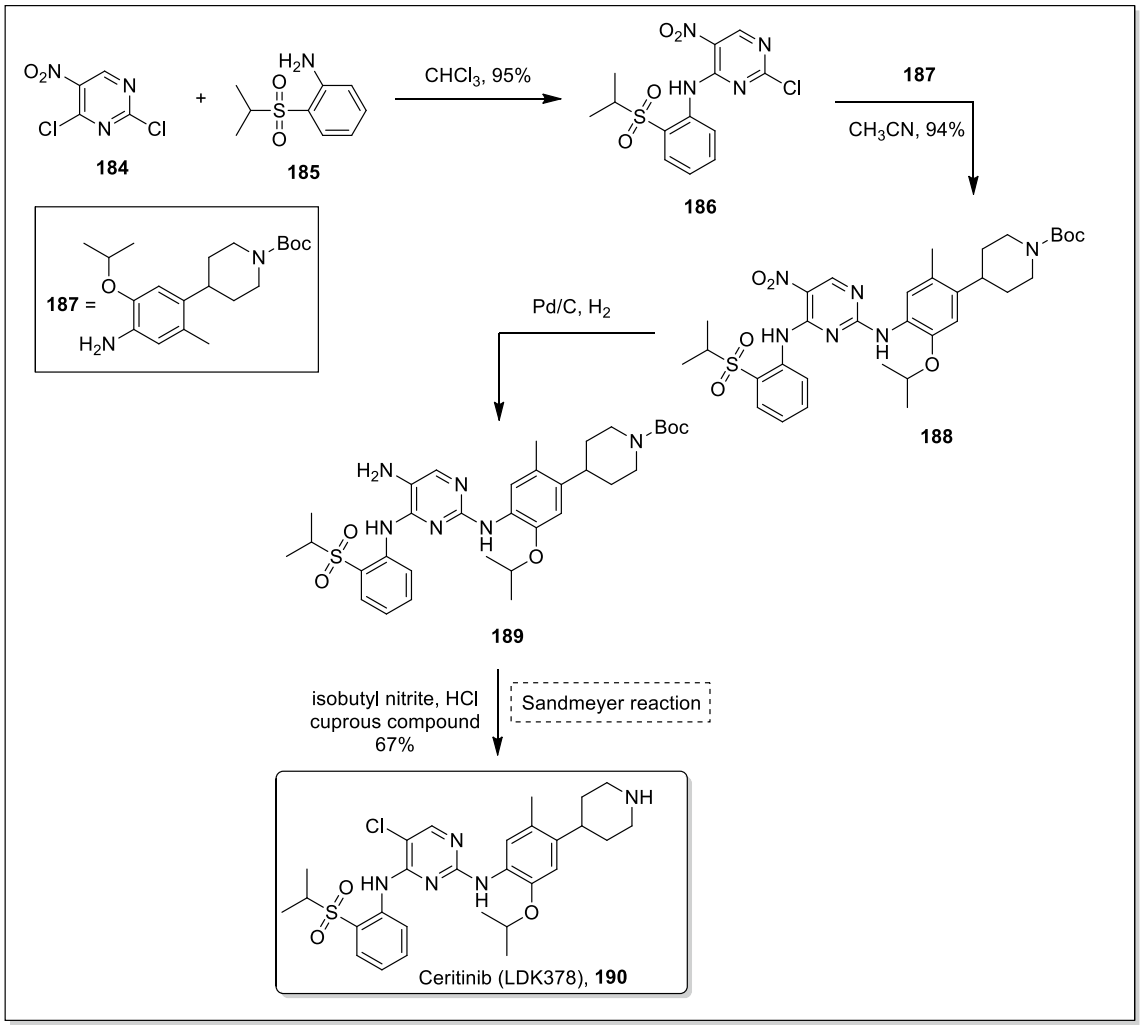
Scheme 43 Synthesis of (+)-curcuphenol **179** via Sandmeyer and Negishi cross-coupling reactions



Scheme 44 Synthetic pathway for agomelatine **183**, an antidepressant drug

isobutyl nitrite, HCl and cuprous compound gave desired ceritinib (LDK378) **190** in 67% yield (Scheme 45).

Synthesis of favipiravir Favipiravir, a pyrazine ring containing compound, mainly acts as anti-influenza drug. It can also be used to treat a variety of viral strains (alphavirus, ebola virus, bunyavirus, and flavivirus) by disrupting the activity of RNA polymerase of virus. It is wide spread biological functions in antiviral and antiparasitic field encourage researchers to develop efficient and low-cost pathways for the synthesis of favipiravir in good yield. On account of this, Guo et al. [96] reported a mild and simple protocol starting from the chlorination of commercially available 2-aminopyrazine **191** in the presence of 1.1 equivalent of TSA (*N*-chloro-*N*-methoxy-4-methylbenzenesulfonamide) **192**. As a result, corresponding chlorinated product **193** was obtained in 80% yield which subsequently subjected to bromination and palladium-catalyzed cyanation reactions



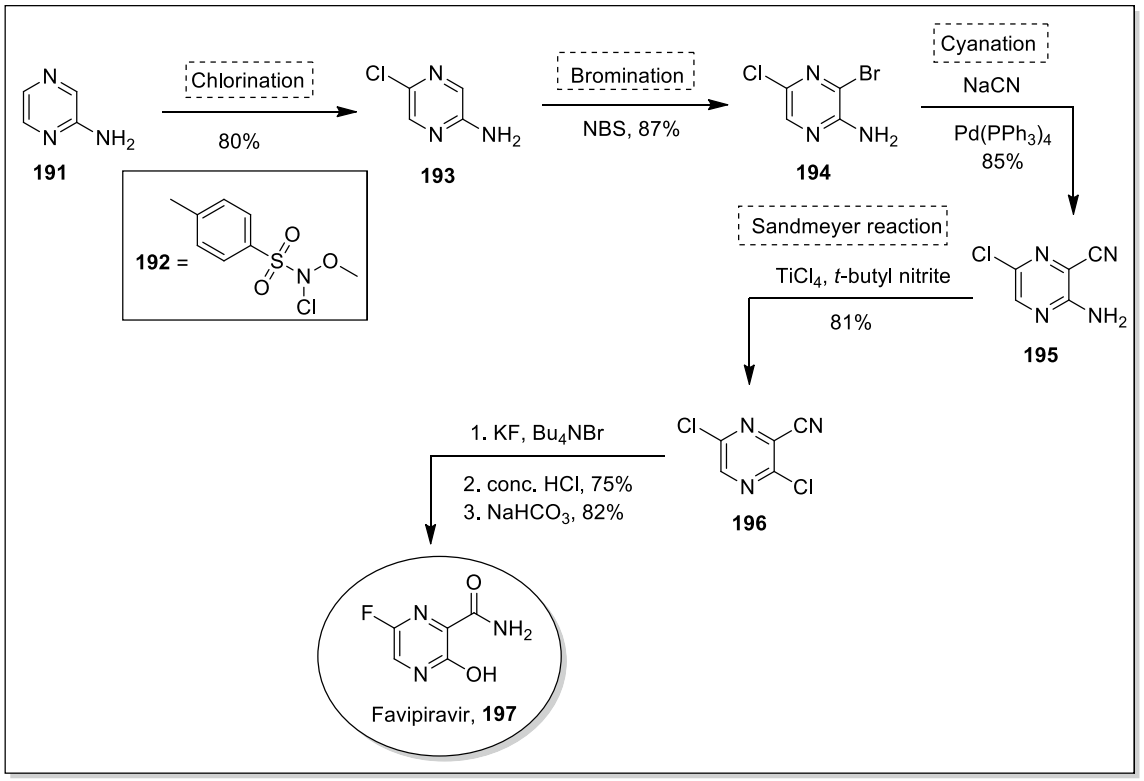
Scheme 45 Synthesis of ceritinib (LDK378) **190**, an anaplastic lymphoma kinase inhibitor

using NBS and NaCN, respectively, to obtain compound **195**. 2-Amino group of compound **195** was further replaced with chloro group by adopting Sandmeyer approach which afforded good yield of the corresponding derivative **196** with simple workup procedure. This reaction was carried out at room temperature by using *t*-butyl nitrite, $TiCl_4$ and DCM as optimized reagents. After that, fluorination of compound **196** followed by acid mediated nitrile hydration and reaction with sodium bicarbonate provided desired favipiravir **197** in 82% yield (Scheme 46).

Miscellaneous

Tsintsadze et al. [97] reported a direct, simple and selective approach for the synthesis of benzo[*b*]thiophenoindoles. For this purpose, 3-aminodibenzothiophene **198** was used as starting precursor which in the presence of chloral hydrate and hydroxylamine hydrochloride and subsequent reaction with sulfuric acid afforded a mixture of isatins **199** and **200** via Sandmeyer pathway. Alkaline solution of these compounds (**199** and **200**) was then treated with acetic acid followed by acidification with HCl provided separated compounds **199** and **200** in 60% and 25% yields, respectively. Later, reduction of compound **199** with diborane in the presence of THF produced compound **201** in 70% yield. However, by using $LiAlH_4$/$NaBH_4$ as reducing agents, a mixture of corresponding benzo[*b*]thiophenoindoles **201** and **202** were obtained. On the other side, by applying same reaction conditions, compound **200** was reduced to benzo[*b*]thiophenoindoles **203** and a mixture of **203** and compound **204** as depicted in Scheme 47. Later on, by using same reaction parameters Khoshtariya et al. in 2004 [98] and 2007 [99] synthesized 2,3-dioxo-2,3-dihydrobenzo[*b*]furoindoles and dioxodihydro-1*H*-benzo[*b*]furoindole, respectively.

To synthesize a variety of aryl azides through green approach, Zarchi and Ebrahimi utilized polymer-supported

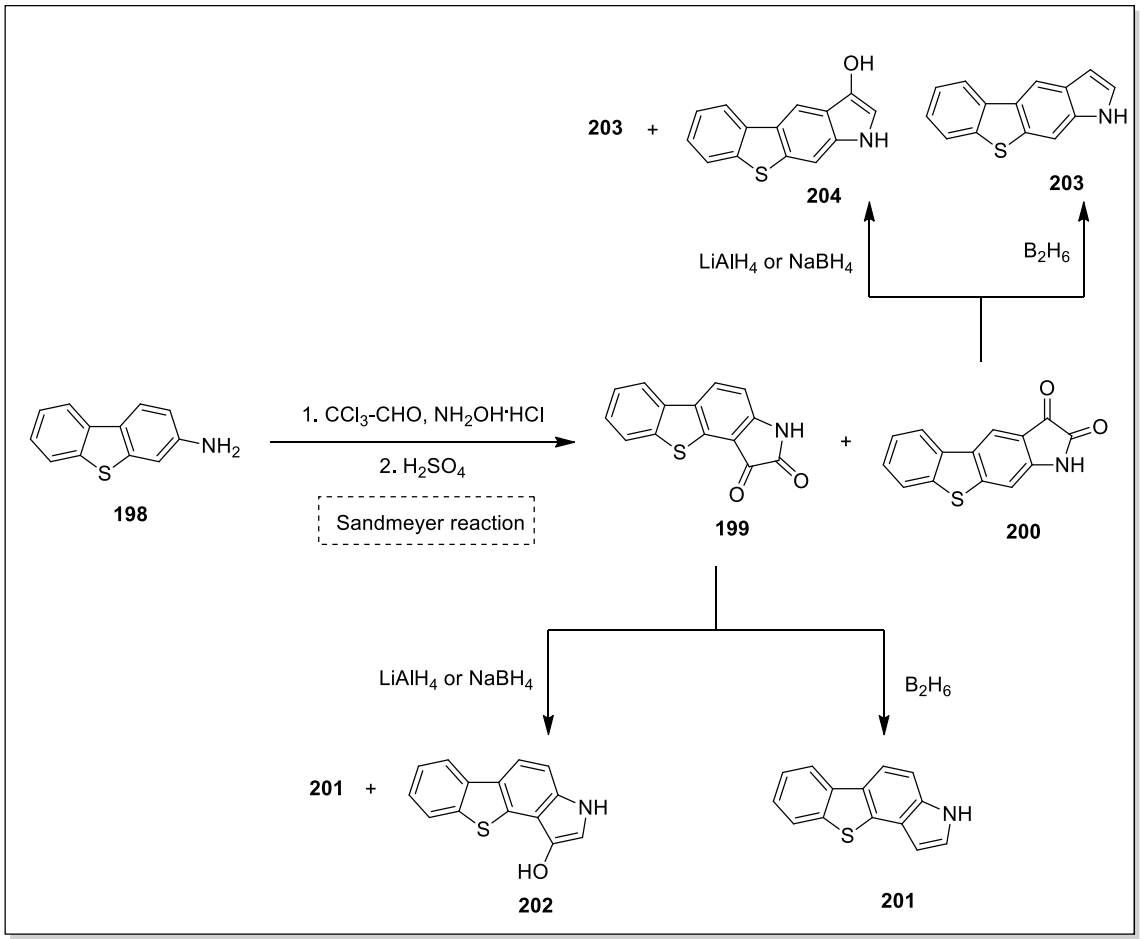


Scheme 46 Preparation method for favipiravir **197**, an anti-influenza drug

nitrite ion ((poly(4-vinylpyridine)-supported nitrite ion, $[P_4\text{-VP}]NO_2$) for diazotization process [100]. First, reaction of aromatic amines in the presence of $NaNO_2$, $[P_4\text{-VP}]NO_2$ and H_2SO_4 provided corresponding diazonium salts which on reaction with NaN_3 afforded targeted aryl azides in 70–90% yield range. Later, in 2014 the authors used (poly(4-vinylpyridine)-supported ethyl bromide ($[P_4\text{-VP}]$Et-Br) for the diazotization-bromination of a variety of aromatic amines [101]. Reaction worked very well in the presence of CuBr and afforded 40–94% yield range. Simple recovery and reusability of polymeric reagent with good functional groups tolerance proved the efficacy of this Sandmeyer protocol.

To highlight the importance of gold catalysis which is effectively used to activate carbon–carbon multiple bonds, Peng et al. [102] reported gold-catalyzed Sandmeyer reaction for the formation of C–Br, C–S and C–P linkages. For C–Br bond formation, different aryl diazonium salts were reacted with sodium bromide and 3% PPh_3AuCl in acetonitrile solvent. As a result, desired derivatives were attained in 57–88% yield range at 50 °C. On the other hand, C–S cross-coupling reaction was accomplished by the treatment of aryldiazonium salt with (*S*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-mercaptopropanoate (a cysteine derivative used as sulfur nucleophile) in acetonitrile solvent. 3 Mol% catalyst loading using sodium carbonate as base completed this reaction within 3 h at room temperature. Furthermore, reaction of diazonium salts with $HP(O)(OEt)_2$ (a phosphorous source) in the presence of 5 mol% PPh_3AuCl gave desired derivatives in 51–87% yield range. Reaction accomplished within 5 h with the help of 3-chloropyridine additive at 50 °C.

Owing to the synthetic as well as pharmacological importance of 1,2-diamines, Gan et al. [103] performed a coupling reaction of ketimine **205** with *N*-Boc aldimine **206** by using 5 mol% mesitylcopper as catalyst and (R,R_P)-TANIAPHOS as ligand in dimethoxyethane. As a result, 1,2-diamine

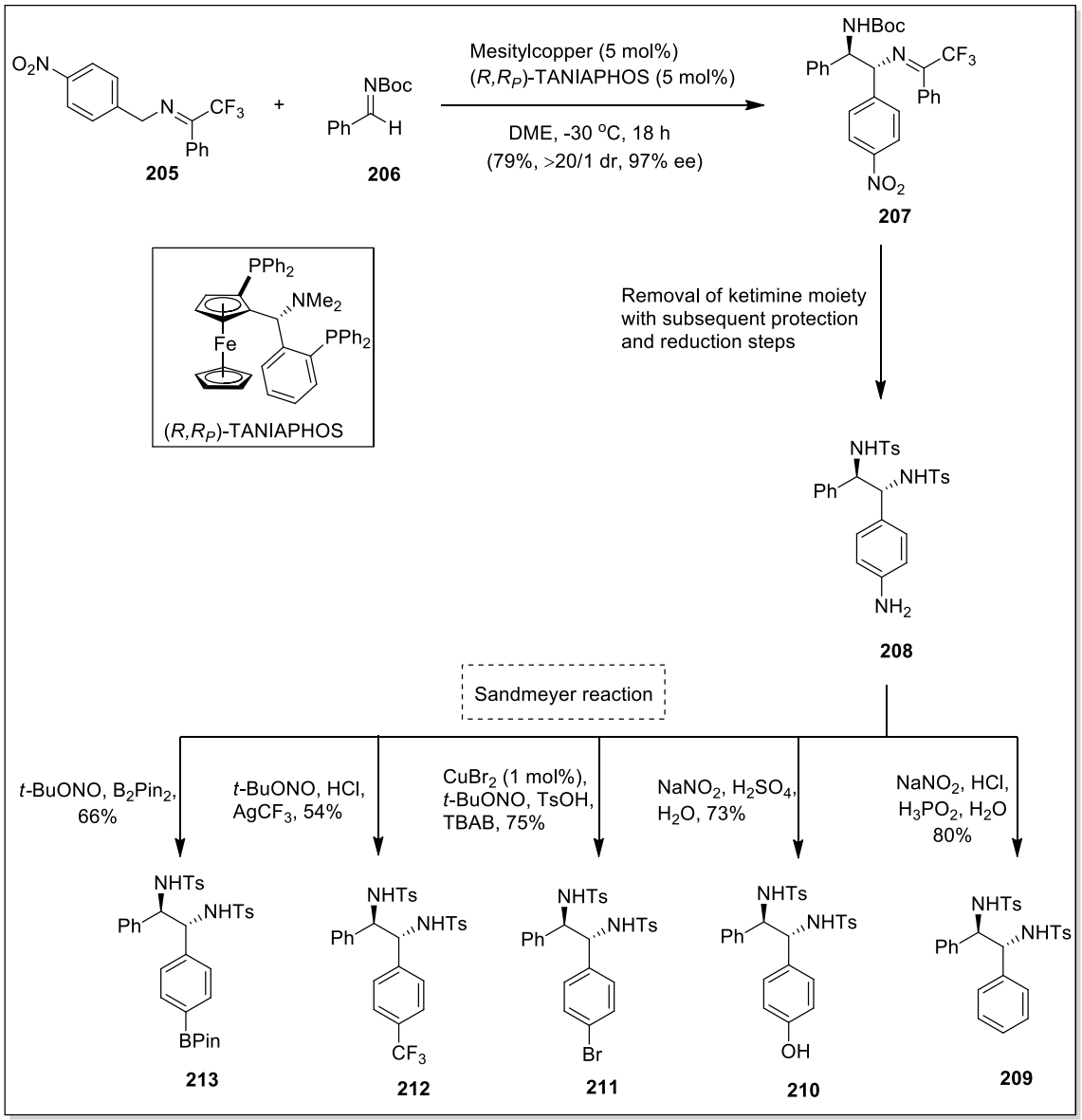


Scheme 47 3-Aminodibenzothiophene **198**, a starting precursor for the synthesis of benzo[*b*]thiophenoindoles

compound **207** was obtained in 79% yield with 97% ee. After that, removal of ketimine moiety in acidic condition followed by protection of amino group with tosyl chloride and reduction of nitro group provided arylamine **208** which readily underwent Sandmeyer reaction to obtain 1,2-diaryldiamine **209**, phenol **210**, arylbromide **211**, trifluoromethylated compound **212** and arylboronate **213** in 80%, 73%, 75%, 54% and 66% yields, respectively, under different reaction conditions as depicted in Scheme 48.

Conclusion

In conclusion, we have collected a number of Sandmeyer-type approaches with plausible mechanisms published during 2000–2021. This review has witnessed that significant efforts have been made for the conversion of aromatic amino group to boryl, stannyl, phosphoryl, and trifluoromethyl groups by adopting Sandmeyer protocol with or without copper catalysts. However, aryl halides and trifluoromethylated compounds were the most prevalent choices prepared via Sandmeyer reaction. These Sandmeyer-type conversions processed under mild reaction conditions using easily available starting materials proved to be helpful for synthesizing various biologically active compounds. Although many developments regarding Sandmeyer reaction have been made in the recent past yet a lot of improvements are required to address limitations and hindrances involved in its industrial scale use such as excessive use of metals and restricted choice of reagents in diazotization step. On further detailed mechanistic investigation of Sandmeyer reaction, adopting green synthetic methodologies, implementing electrochemical and photocatalytic approaches, incorporating simple reaction methods with minimum use of expensive metals, the researchers may be able to prepare novel biologically active molecules through Sandmeyer transformation in near future.



Scheme 48 Sandmeyer reaction for the synthesis of 1,2-diamines (**209–213**)

Acknowledgements Provision of facilities from Government College University, Faisalabad is highly acknowledged.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. P Griefs 1858 Vorläufige Notiz über die Einwirkung von salpetriger Säure auf Amidinitro-und Aminitrophenylsäure Justus Liebigs Ann Chem 106 123 125 https://doi.org/10.1002/jlac.18581060114
2. MAK Zarchi N Ebrahimi 2012 Diazotization-cyanation of aromatic amines with crosslinked poly(4-vinylpyridine)-supported cyanide ions J Appl Polym Sci 125 2163 2169 https://doi.org/10.1002/app.36394
3. H Meerwein E Büchner K Emster van 1939 Über die Einwirkung aromatischer Diazoverbindungen auf α, β-ungesättigte Carbonylverbindungen J Prakt Chem 152 237 266 https://doi.org/10.1002/prac.19391520705
4. D Prasad-Hari T Hering B König 2014 The photoredox-catalyzed Meerwein addition reaction: Intermolecular amino-arylation of alkenes Angew Chem Int Ed 53 725 728 https://doi.org/10.1002/anie.201307051
5. G Balz G Schiemann 1927 Über aromatische Fluorverbindungen, I.: Ein neues Verfahren zu ihrer Darstellung Ber Dtsch Chem Ges 60 1186 1190 https://doi.org/10.1002/cber.19270600539
6. S Abele G Schmidt MJ Fleming H Steiner 2014 A One-pot diazotation-fluorodediazoniation reaction and fluorine gas for

the production of fluoronaphthyridines Org Process Res Dev 18 993 1001 https://doi.org/10.1021/op500100b
7. A Roglans A Pla-Quintana M Moreno-Mañas 2006 Diazonium salts as substrates in palladium-catalyzed cross-coupling reactions Chem Rev 106 4622 4643 https://doi.org/10.1021/cr0509861
8. T Okazaki KK Laali SD Bunge SK Adas 2014 4-(Pentafluorosulfanyl)benzenediazonium tetrafluoroborate: a versatile launch pad for the synthesis of aromatic SF5 compounds via cross Coupling, azo coupling, homocoupling, dediazoniation, and click chemistry Eur J Org Chem 2014 1630 1644 https://doi.org/10.1002/ejoc.201301538
9. L He G Qiu Y Gao J Wu 2014 Removal of amino groups from anilines through diazonium salt-based reactions Org Biomol Chem 12 6965 6971 https://doi.org/10.1039/C4OB01286K
10. PY Yeung CM So CP Lau FY Kwong 2011 A mild and efficient palladium-catalyzed cyanation of aryl chlorides with K4[Fe(CN)6] Org Lett 13 648 651 https://doi.org/10.1021/ol1028892
11. J Han C Pan X Jia C Zhu 2014 Rhodium-catalyzed ortho-cyanation of symmetrical azobenzenes with N-cyano-N-phenyl-p-toluenesulfonamide Org Biomol Chem 12 8603 8606 https://doi.org/10.1039/C4OB01736F
12. P Hanson SC Rowell PH Walton AW Timms 2004 Promotion of Sandmeyer hydroxylation (homolytic hydroxydediazoniation) and hydrodediazoniation by chelation of the copper catalyst: Bidentate ligands Org Biomol Chem 2 1838 1855 https://doi.org/10.1039/B404699D
13. F Xie Z Qi X Li 2013 Rhodium(III)-catalyzed azidation and nitration of arenes by CH activation Angew Chem 125 12078 12082 https://doi.org/10.1002/ange.201305902
14. BV Silva FA Violante AC Pinto LS Santos 2011 The mechanism of Sandmeyer's cyclization reaction by electrospray ionization mass spectrometry Rapid Commun Mass Spectrom 25 423 428 https://doi.org/10.1002/rcm.4869
15. R Akhtar AF Zahoor B Parveen M Suleman 2019 Development of environmental friendly synthetic strategies for Sonogashira cross coupling reaction: an update Synthetic Commun 49 167 192 https://doi.org/10.1080/00397911.2018.1514636
16. R Akhtar AF Zahoor 2020 Transition metal catalyzed Glaser and Glaser-Hay coupling reactions: scope, classical/green methodologies and synthetic applications Syn Commun 50 3337 3368 https://doi.org/10.1080/00397911.2020.1802757
17. M Yousaf AF Zahoor R Akhtar M Ahmad S Naheed 2020 Development of green methodologies for Heck, Chan-Lam, Stille and Suzuki cross-coupling reactions Mol Divers 24 821 839 https://doi.org/10.1007/s11030-019-09988-7
18. S Tabassum AF Zahoor S Ahmad R Noreen SG Khan H Ahmad 2021 Cross-coupling reactions towards the synthesis of natural products Mol Divers In press https://doi.org/10.1007/s11030-021-10195-6
19. I Munir AF Zahoor N Rasool SAR Naqvi KM Zia R Ahmad 2019 Synthetic applications and methodology development of Chan-Lam coupling: a review Mol Divers 23 215 259 https://doi.org/10.1007/s11030-018-9870-z
20. T Sandmeyer 1884 Ueber die Ersetzung der Amidgruppe durch Chlor in den aromatischen Substanzen Ber Dtsch Chem Ges 17 1633 1635 https://doi.org/10.1002/cber.18840170219
21. T Sandmeyer 1884 Ueber die Ersetzung der Amidgruppe durch Chlor, Brom und Cyan in den aromatischen Substanzen Ber Dtsch Chem Ges 17 2650 2653 https://doi.org/10.1002/cber.188401702202
22. MP Doyle B Siegfried JF Dellaria 1977 Alkyl nitrite-metal halide deamination reactions. 2. Substitutive deamination of arylamines by alkyl nitrites and copper(II) halides. A direct and remarkably efficient conversion of arylamines to aryl halides J Org Chem 42 2426 2431 https://doi.org/10.1021/jo00434a017
23. MP Doyle JF Dellaria B Siegfried SW Bishop 1977 Reductive deamination of arylamines by alkyl nitrites in N, *N*-dimethylformamide. A direct conversion of arylamines to aromatic hydrocarbons J Org Chem 42 3494 3498 https://doi.org/10.1021/jo00442a009
24. K Kikukawa T Matsuda 1977 Reaction of diazonium salts with transition metals. I. Arylation of olefins with arenediazonium salts catalyzed by zero valent palladium Chem Lett 6 159 162 https://doi.org/10.1246/cl.1977.159
25. K Kikukawa K Nagira N Terao F Wada T Matsuda 1979 Reaction of diazonium salts with transition metals. II. Palladium catalyzed arylation of ethylene with arenediazonium salts Bull Chem Soc Jpn 52 2609 2610 https://doi.org/10.1246/bcsj.52.2609
26. Waters WA (1942) Decomposition reactions of the aromatic diazo compounds. X. Mechanism of the Sandmeyer reaction. J Chem Soc 266–270. https://doi.org/10.1039/JR9420000266
27. JK Kochi 1957 The mechanism of the Sandmeyer and Meerwein reactions J Am Chem Soc 79 2942 2948 https://doi.org/10.1021/ja01568a066
28. D Sucunza A Samadi M Chioua DB Silva C Yunta L Infantes MC Carreiras E Sorianoa J Marco-Contelles 2011 A practical two-step synthesis of imidazo[1,2-a]pyridines from N-(prop-2-yn-1-yl)pyridin-2-amines Chem Commun 47 5043 5045 https://doi.org/10.1039/C1CC10641D
29. R Sott C Hawner JE Johansen 2008 Synthesis of dioxin-like monofluorinated PCBs: For the use as internal standards for PCB analysis Tetrahedron 64 4135 4142 https://doi.org/10.1016/j.tet.2008.01.003
30. R Dumeunier C Lamberth S Trah 2013 Synthesis of tetrasubstituted pyrazoles through different cyclization Strategies; Isosteres of imidazole fungicides Synlett 24 1150 1154 https://doi.org/10.1055/s-0033-1338433
31. TV Hughes SL Emanuel AK Beck SK Wetter PJ Connolly P Karnachi M Reuman J Seraj AR Fuentes-Pesquera RH Gruninger SA Middleton R Lin JM Davis DFC Moffat 2007 4-Aryl-5-cyano-2-aminopyrimidines as VEGF-R2 inhibitors: Synthesis and biological evaluation Bioorganic Med Chem Lett 17 3266 3270 https://doi.org/10.1016/j.bmcl.2007.04.021
32. F Rancati SM Bromidge SD Sordo SL Rosa C Parini S Gagliardi 2008 Synthesis of 7-substituted-(2,3-dihydro-1,4-benzodioxin-5-yl)-piperazine Synth Commun 38 2507 2520 https://doi.org/10.1080/00397910802219148
33. C-H Park C Lee JS Yang B-Y Joe K Chun H Kim HY Kim JS Kang JI Lee M-H Kim G Han 2014 Discovery of thienopyrimidine-based FLT3 inhibitors from the structural modification of known IKK inhibitors Bioorganic Med Chem Lett 24 2655 2660 https://doi.org/10.1016/j.bmcl.2014.04.058
34. Y Ding L Zhao Y Fu L Hao Y Fu Y Yuan P Yu Y Teng 2021 Synthesis and antiproliferatory activities evaluation of multi-substituted isatin derivatives Molecules 26 176 189 https://doi.org/10.3390/molecules26010176
35. L Lee KD Kreutter W Pan C Crysler J Spurlino MR Player B Tomczuk T Lu 2007 2-(2-Chloro-6-fluorophenyl)acetamides as potent thrombin inhibitors Bioorganic Med Chem Lett 17 6266 6269 https://doi.org/10.1016/j.bmcl.2007.09.013
36. TS Lobana R Sultana RJ Butcher 2011 A Sandmeyer type reaction for bromination of 2-mercapto-1-methyl-imidazoline (N2C4H6S) into 2-bromo-1-methyl-imidazole (N2C4H5Br) in presence of copper(I) bromide Dalton Trans 40 11382 11384 https://doi.org/10.1039/C1DT11327E
37. A Hubbard T Okazaki KK Laali 2008 Halo- and azidodediazoniation of arenediazonium tetrafluoroborates with trimethylsilyl halides and trimethylsilyl azide and Sandmeyer-type

bromodediazoniation with Cu(I)Br in [BMIM][PF_6] ionic liquid J Org Chem 73 316 319 https://doi.org/10.1021/jo701937e
38. MA Bobko AC Kaura KA Evans D-S Su 2012 Novel synthesis of 5-amino-3-bromo- 1-(tert-butyl)-1H-pyrazole-4-carbonitrile: A versatile intermediate for the preparation of 5-amino-3-aryl-1-(tert-butyl)-1H-pyrazole-4-carboxamides Org Lett 14 3906 3908 https://doi.org/10.1021/ol301655f
39. H Özkan A Dişli Y Yıldırır L Türker 2007 A novel synthesis of bromobenzenes using molecular bromine Molecules 12 2478 2483 https://doi.org/10.3390/12112478
40. G Schäfer T Fleischer M Ahmetovic S Abele 2020 Development of a scalable route for a key thiadiazole building block via sequential Sandmeyer bromination and room-temperature Suzuki-Miyaura coupling Org Process Res Dev 24 228 234 https://doi.org/10.1021/acs.oprd.9b00495
41. R Striela G Urbelis J Sūdžius S Stončius R Sadzevičienė L Labanauskas 2017 Synthesis of bromocyclopropylpyridines via the Sandmeyer reaction Tetrahedron Lett 58 1681 1683 https://doi.org/10.1016/j.tetlet.2017.03.029
42. IP Beletskaya AS Sigeev AS Peregudov PV Petrovskii 2007 Catalytic Sandmeyer bromination Synthesis 16 2534 2538 https://doi.org/10.1055/s-2007-983784
43. FG Siméon MT Wendahl VW Pike 2009 Efficient and regioselective halogenations of 2-amino-1,3-thiazoles with copper salts J Org Chem 74 2578 2580 https://doi.org/10.1021/jo802799c
44. WW Mao TT Wang HP Zeng ZY Wang JP Chen JG Shen 2009 Synthesis and evaluation of novel substituted 5-hydroxycoumarin and pyranocoumarin derivatives exhibiting significant anti-proliferative activity against breast cancer cell lines Bioorg Med Chem Lett 19 4570 4573 https://doi.org/10.1016/j.bmcl.2009.06.098
45. H-Y Kim W-J Lee H-M Kang C-G Cho 2007 Benzidine rearrangement reactions of polyether tethered cyclic N, *N*′-diaryl hydrazides Org Lett 9 3185 3186 https://doi.org/10.1021/ol071320r
46. M Gon Y Morisaki Y Chujo 2015 Optically active cyclic compounds based on planar chiral [2.2]paracyclophane: extension of the conjugated systems and chiroptical properties J Mater Chem C 3 521 529 https://doi.org/10.1039/C4TC02339K
47. Q Liu B Sun Z Liu Y Kao B-W Dong S-D Jiang F Li G Liu Y Yang F Mo 2018 A general electrochemical strategy for Sandmeyer reaction Chem Sci 9 8731 8737 https://doi.org/10.1039/C8SC03346C
48. PG Tsoungas M Searcey 2001 A convenient access to benzo-substituted phthalazines as potential precursors to DNA intercalators Tetrahedron Lett 42 6589 6592 https://doi.org/10.1016/S0040-4039(01)01302-8
49. R Buchtík J Slouka J Hlaváč 2006 Polycyclic heterocycles with acidic N-H group VII[1] Synthesis of some polynuclear heterocyclic compounds derived from 5-phenyl-6-azauracil ARKIVOC 2006 78 85 https://doi.org/10.3998/ark.5550190.0007.507
50. J Hong G Wang L Huo C Zheng 2017 Copper-promoted conversion of aromatic amines into trifluoromethylated arenes: one-pot Sandmeyer trifluoromethylation Chin J Chem 35 1761 1767 https://doi.org/10.1002/cjoc.201700311
51. G Danoun B Bayarmagnai MF Gruenberg LJ Goossen 2014 Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert-Prakash reagent Chem Sci 5 1312 1316 https://doi.org/10.1039/C3SC53076K
52. G Danoun B Bayarmagnai MF Gruenberg C Matheis E Risto LJ Gooßen 2014 Sandmeyer trifluoromethylation Synthesis 46 2283 2286 https://doi.org/10.1055/s-0034-1378549
53. G Danoun B Bayarmagnai MF Gruenberg LJ Gooßen 2013 Sandmeyer trifluoromethylation of arenediazonium tetrafluoroborates Angew Chem Int Ed 52 7972 7975 https://doi.org/10.1002/anie.201304276
54. B Bayarmagnai C Matheis E Risto LJ Goossen 2014 One-pot Sandmeyer trifluoromethylation and trifluoromethylthiolation Adv Synth Catal 356 2343 2348 https://doi.org/10.1002/adsc.201400340
55. J-J Dai C Fang B Xiao J Yi J Xu ZJ Liu X Lu L Liu Y Fu 2013 Copper-promoted Sandmeyer trifluoromethylation reaction J Am Chem Soc 135 8436 8439 https://doi.org/10.1021/ja404217t
56. C Matheis K Jouvin LJ Goossen 2014 Sandmeyer difluoromethylation of (hetero)arenediazonium salts Org Lett 16 5984 5987 https://doi.org/10.1021/ol5030037
57. X Wang Y Xu Y Zhou Y Zhang J Wang 2014 Conversion of aromatic amino into trifluoromethyl groups through a Sandmeyer-type transformation Synthesis 46 2143 2148 https://doi.org/10.1055/s-0033-1338659
58. J Wu Y Gu X Leng Q Shen 2015 Copper-promoted Sandmeyer difluoromethylthiolation of aryl and heteroaryl diazonium salts Angew Chem 127 7758 7762 https://doi.org/10.1002/ange.201502113
59. B Xing L Li C Ni J Hu 2019 Pentafluoroethylation of arenediazonium tetrafluoroborates using on-site generated tetrafluoroethylene Chin J Chem 37 1131 1136 https://doi.org/10.1002/cjoc.201900268
60. J Hong L Huo Y Yang G Wang C Zheng 2017 Copper-promoted one-pot trifluoromethylation of aromatic amines with Togni's reagent ChemistrySelect 2 3716 3720 https://doi.org/10.1002/slct.201700789
61. D-F Jiang C Liu Y Guo JC Xiao QY Chen 2014 A general, regiospecific synthetic route to perfluoroalkylated arenes via arenediazonium salts with RFCu(CH3CN) complexes Eur J Org Chem 2014 6303 6309 https://doi.org/10.1002/ejoc.201402820
62. A Lishchynskyi G Berthon VV Grushin 2014 Trifluoromethylation of arenediazonium salts with fluoroform-derived CuCF3 in aqueous media Chem Commun 50 10237 10240 https://doi.org/10.1039/C4CC04930F
63. W-B Xu Q-H Xu Z-F Zhang J-Z Li 2014 Copper(I)-oxide-mediated cyanation of arenediazonium tetrafluoroborates with trimethylsilyl cyanide: A method for synthesizing aromatic nitriles Asian J Org Chem 3 1062 1065 https://doi.org/10.1002/ajoc.201402084
64. W Xu Q Xu J Li 2015 Sandmeyer cyanation of arenediazonium tetrafluoroborate using acetonitrile as cyanide source Org Chem Front 2 231 235 https://doi.org/10.1039/C4QO00301B
65. M Barbero S Cadamuro S Dughera 2016 Copper-free Sandmeyer cyanation of arenediazonium o-benzenedisulfonimide Org Biomol Chem 14 1437 1441 https://doi.org/10.1039/C5OB02321A
66. D Silva Da A Samadi M Chioua MDC Carreiras J Marco-Contelles 2010 The Sandmeyer reaction on some selected heterocyclic ring systems: Synthesis of useful 2-chloroheterocyclic-3-carbonitrile intermediates Synthesis 16 2725 2730 https://doi.org/10.1055/s-0030-1258149
67. H Xu L-L Fan 2011 Antifungal agents. Part 4: Synthesis and antifungal activities of novel indole[1,2-c]-1,2,4-benzotriazine derivatives against phytopathogenic fungi in vitro Eur J Med Chem 46 364 369 https://doi.org/10.1016/j.ejmech.2010.10.022
68. IP Beletskaya AS Sigeev AS Peregudov PV Petrovskii 2004 Catalytic Sandmeyer cyanation as a synthetic pathway to aryl nitriles J Organomet Chem 689 3810 3812 https://doi.org/10.1016/j.jorganchem.2004.07.019
69. Q Lin Z Ma C Zheng X-J Hu Y Guo Q-Y Chen C Liu 2020 Arenesulfonyl fluoride synthesis via copper-free Sandmeyer-type fluorosulfonylation of arenediazonium salts Chin J Chem 38 1107 1110 https://doi.org/10.1002/cjoc.202000175
70. X Yang L Shi H Fu 2014 Copper-mediated cascade synthesis of diaryl sulfones via the Sandmeyer reaction Synlett 25 0847 0852 https://doi.org/10.1055/S-0033-1340736

71. B Bayarmagnai C Matheis K Jouvin LJ Goossen 2015 Synthesis of difluoromethyl thioethers from difluoromethyl trimethylsilane and organothiocyanates generated in situ Angew Chem 127 5845 5848 https://doi.org/10.1002/ange.201500899
72. C Matheis V Wagner LJ Goossen 2016 Sandmeyer-type trifluoromethylthiolation and trifluoromethylselenolation of (hetero)aromatic amines catalyzed by copper Chem Eur J 22 79 82 https://doi.org/10.1002/chem.201503524
73. C Matheis B Bayarmagnai K Jouvin LJ Goossen 2016 Convenient synthesis of pentafluoroethyl thioethers via catalytic Sandmeyer reaction with a stable fluoroalkylthiolation reagent Org Chem Front 3 949 952 https://doi.org/10.1039/C6QO00194G
74. K Zhang X-H Xu F-L Qing 2015 Copper-promoted trifluoromethanesulfonylation and trifluoromethylation of arenediazonium tetrafluoroborates with NaSO2CF3 J Org Chem 80 7658 7665 https://doi.org/10.1021/acs.joc.5b01295
75. S Kovacs B Bayarmagnai A Aillerie LJ Gooßen 2018 Practical reagents and methods for nucleophilic and electrophilic phosphorothiolations Adv Synth Catal 360 1913 1918 https://doi.org/10.1002/adsc.201701549
76. Y Ou LJ Goossen 2019 Copper-mediated synthesis of (diethylphosphono)difluoromethyl thioethers from diazonium salts, NaSCN, and TMS-CF2PO(OEt)2 Asian J Org Chem 8 650 653 https://doi.org/10.1002/ajoc.201800461
77. S Liu Y Huang X-H Xu F-L Qing 2020 Fluorosulfonylation of arenediazonium tetrafluoroborates with Na2S2O5 and N-fluorobenzenesulfonimide J Fluor Chem 240 109653 https://doi.org/10.1016/j.jfluchem.2020.109653
78. T Zhong M-K Pang Z-D Chen B Zhang J Weng G Lu 2020 Copper-free Sandmeyer-type reaction for the synthesis of sulfonyl fluorides Org Lett 22 3072 3078 https://doi.org/10.1021/acs.orglett.0c00823
79. IG Tarkhanova MG Gantman AS Sigeev KI Maslakov VM Zelikman IP Beletskaya 2018 Highly efficient Sandmeyer reaction on immobilized CuI/CuII-based catalysts Mendeleev Commun 28 261 263 https://doi.org/10.1016/j.mencom.2018.05.010
80. D Qiu H Meng L Jin S Wang S Tang X Wang F Mo Y Zhang J Wang 2013 Synthesis of aryl trimethylstannanes from aryl amines: a Sandmeyer-type stannylation reaction Angew Chem 125 11795 11798 https://doi.org/10.1002/ange.201304579
81. D Qiu S Wang S Tang H Meng L Jin F Mo Y Zhang J Wang 2014 Synthesis of trimethylstannyl arylboronate compounds by Sandmeyer-type transformations and their applications in chemoselective cross-coupling reactions J Org Chem 79 1979 1988 https://doi.org/10.1021/jo402618r
82. S Wang D Qiu F Mo Y Zhang J Wang 2016 Metal-free aromatic carbon-phosphorus bond formation via a Sandmeyer-type reaction J Org Chem 81 11603 11611 https://doi.org/10.1021/acs.joc.6b01820
83. P Nikolaienko M Rueping 2016 Trifluoromethylselenolation of aryldiazonium salts: a mild and convenient copper-catalyzed procedure for the introduction of the SeCF3 group Chem Eur J 22 2620 2623 https://doi.org/10.1002/chem.201504601
84. J Zhang X Wang H Yu J Ye 2012 Sandmeyer-type reaction to Pinacol arylboronates in water phase: a green borylation process Synlett 23 1394 1396 https://doi.org/10.1055/s-0031-1290960
85. D Qiu L Jin Z Zheng H Meng F Mo X Wang Y Zhang J Wang 2013 Synthesis of Pinacol arylboronates from aromatic amines: A metal-free transformation J Org Chem 78 1923 1933 https://doi.org/10.1021/jo3018878
86. C Zhu M Yamane 2012 Transition-metal-free borylation of aryltriazene mediated by BF3. OEt2 Org Lett 14 4560 4563 https://doi.org/10.1021/ol302024m
87. J Yu L Zhang G Yan 2012 Metal-free, visible light-induced borylation of aryldiazonium salts: a simple and green synthetic route to arylboronates Adv Synth Catal 354 2625 2628 https://doi.org/10.1002/adsc.201200416
88. LD Marciasini M Vaultier M Pucheault 2014 Borylation using group IV metallocene under mild conditions Tetrahedron Lett 55 1702 1705 https://doi.org/10.1016/j.tetlet.2014.01.080
89. S Ahammed S Nandi D Kundu BC Ranu 2016 One-pot Suzuki coupling of aromatic amines via visible light photocatalyzed metal free borylation using t-BuONO at room temperature Tetrahedron Lett 57 1551 1554 https://doi.org/10.1016/j.tetlet.2016.02.097
90. X Qi L-B Jiang C Zhou J-B Peng X-F Wu 2017 Convenient and general zinc-catalyzed borylation of aryl diazonium salts and aryltriazenes under mild conditions ChemistryOpen 6 345 349 https://doi.org/10.1002/open.201700036
91. F Bracher J Daab 2002 Total synthesis of the indolizidinium alkaloid ficuseptine Eur J Org Chem 2002 2288 2291 https://doi.org/10.1002/1099-0690(200207)2002:14<2288::AID-EJOC2288>3.0.CO;2-G
92. J Daab F Bracher 2003 Total syntheses of the alkaloids ipalbidinium and clathryimine B Monatsh Chem 134 573 583 https://doi.org/10.1007/s00706-002-0540-5
93. S-G Kim J Kim H Jung 2005 Efficient total synthesis of (+)-curcuphenol via asymmetric organocatalysis Tetrahedron Lett 46 2437 2439 https://doi.org/10.1016/j.tetlet.2005.02.047
94. B Kandagatla VVNKVP Raju GM Reddy SC Rao J Iqbal R Bandichhor S Oruganti 2012 A facile synthesis of melatonergic antidepressant agomelatine Tetrahedron Lett 53 7125 7127 https://doi.org/10.1016/j.tetlet.2012.10.077
95. H Liu Y Li D Wang Y Qin M Jia 2015 An efficient synthesis of ceritinib (LDK378) using a Sandmeyer reaction J Chem Res 39 475 477 https://doi.org/10.3184/174751915X14381780373834
96. Q Guo M Xu S Guo F Zhu Y Xie J Shen 2019 The complete synthesis of favipiravir from 2-aminopyrazine Chem Pap 73 1043 1051 https://doi.org/10.1007/s11696-018-0654-9
97. TG Tsintsadze TE Khoshtariya LN Kurkovskaya NT Mirziashvili MI Sikharulidze 2002 Novel route for btaining isomeric benzo[b]thiophenoindoles Chem Heterocycl Compd 38 472 476 https://doi.org/10.1023/A:1016043608441
98. TE Khoshtariya MM Matnadze NT Mirziashvili LN Kurkovskaya MI Sikharulidze TO Dzhashi 2004 Synthesis and reductive reactions of 2,3-dioxo-2,3-dihydrobenzo-[b]furo[2,3-f]-, -[2,3-g]-, and -[3,2-e]indoles Chem Heterocycl Compd 40 1454 1459 https://doi.org/10.1007/s10593-005-0065-z
99. TE Khoshtariya LN Kurkovskaya MM Matnadze MI Sikharulidze TO Dzhashi VO Ananiashvili KT Batsikadze 2007 Condensed tetracyclic systems with an isatin fragment in the molecule Chem Heterocycl Compd 43 1111 1117 https://doi.org/10.1007/s10593-007-0171-1
100. MAK Zarchi N Ebrahimi 2012 Facile and one-pot synthesis of aryl azides via diazotization of aromatic amine using cross-linked poly(4-vinylpyridine)-supported nitrite ion and azidation by a Sandmeyer-type reaction Iran Polym J 21 591 599 https://doi.org/10.1007/s13726-012-0063-9
101. MAK Zarchi SZ Mousavi 2014 Diazotization-bromination of aromatic amines using polymer-supported bromide via Sandmeyer-type reaction J Polym Res 21 330 338 https://doi.org/10.1007/s10965-013-0330-2
102. H Peng R Cai C Xu H Chen X Shi 2016 Nucleophile promoted gold redox catalysis with diazonium salts: C-Br, C-S and C-P bond formation through catalytic Sandmeyer coupling Chem Sci 7 6190 6196 https://doi.org/10.1039/C6SC01742H
103. X-C Gan C-Y Zhang F Zhong P Tian L Yin 2020 Synthesis of chiral anti-1,2-diamine derivatives through copper(I)-catalyzed asymmetric α-addition of ketimines to aldimines Nat Commun 11 4473 4480 https://doi.org/10.1038/s41467-020-18235-9