

# Renaissance of Sandmeyer-Type Reactions: Conversion of Aromatic C–N Bonds into C–X Bonds (X = B, Sn, P, or CF<sub>3</sub>)

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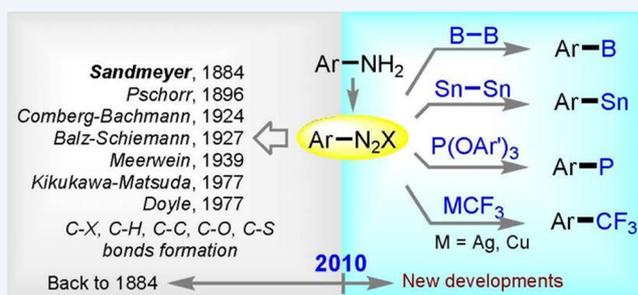
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**CONSPECTUS:** The Sandmeyer reaction represents an important organic transformation that converts an arylamine to an aryl halide using Cu(I) halide via a diazonium salt intermediate. The reaction was first reported by Sandmeyer in 1884, and a number of named reactions closely related to it have been developed and widely applied in organic synthesis throughout the 20th century. These include the Pschorr reaction for the synthesis of biaryl tricycles, the Gomberg–Bachmann reaction for biaryl formations, the Balz–Schiemann reaction for C–F bond formations, and the Meerwein reaction for arylation of  $\alpha,\beta$ -unsaturated carbonyl compounds. However, all these reactions were discovered before 1940. In 1977, Doyle and co-workers reported an organic phase diazotization process, and Kikukawa and Matsuda used aryldiazonium salts in transition metal-catalyzed cross-coupling reactions. However, completely new processes involving diazonium salts have been seldom reported since then, although aryldiazonium salts are widely utilized in modern organic synthesis.

In the past few years, diazonium salt chemistry has been revisited and become a fast-growing research topic. Several novel transformations based on diazonium salts have been developed and have been practiced in organic synthesis. In 2010, we reported a direct conversion of arylamines to pinacol boronates through the reaction of *in situ* generated aryl diazonium salts with B<sub>2</sub>pin<sub>2</sub>. This new strategy is under metal-free conditions and thus completely avoids contamination by transition metals in the boron products. From readily available arylamines various functionalized arylboronates, some of which are difficult to access by other methods, can be easily obtained with this reaction. Mechanistic investigations indicate the reaction likely follows a radical mechanism, which is similar to traditional Sandmeyer-type reactions. Subsequently, modified reaction conditions for this transformation appeared in the literature, which include light-induced reactions, aqueous-phase diazotization methods, and reactions with aryltriazenes as the arene diazonium salt surrogates. In addition to the borylation, we have also demonstrated the corresponding stannylation and phosphorylation of arylamines with similar Sandmeyer-type approaches. The stannylation of arylamines was achieved by the reaction of *in situ* generated diazonium salts with a distannane reagent, while phosphorylation is the reaction of arylamines with trimethyl phosphite in the presence of *tert*-butyl nitrite (*t*-BuONO). With the sequential borylation and stannylation approaches, the aromatic compounds bearing two amino groups are easily converted into trimethylstannyl arylboronates, which can be further used in consecutive Stille and Suzuki–Miyaura cross-couplings. Finally, direct conversion of the amino group of arylamines to the trifluoromethyl group has been developed through aryl diazonium salts almost simultaneously by several groups. These reactions represent a novel strategy to achieve trifluoromethylation of aromatic compounds. These developments show the revivification of this age-old chemistry, and this Account will summarize the Sandmeyer reaction-related transformations that have been developed since 2010.



## 1. INTRODUCTION

Arylamines are ubiquitous in research laboratories and staple chemicals in industry. Due to their low cost, ready availability and diverse reactivity, arylamines have broad applications in the preparation of value-added chemicals, ranging from colorants and agrochemicals to polyurethanes.<sup>1</sup> In addition, the amino groups in aromatic compounds can serve as a scaffold for the introduction of various functional groups to aromatic rings, in particular through Sandmeyer-type reactions.<sup>2</sup> In a Sandmeyer-type reaction, the primary aromatic amino group is replaced

by halo, cyano, azido, or hydroxyl groups and so on, through a diazotization–substitution sequence. Diazonium salts, which play the key role in these transformations, were first discovered by Grieffs in 1858.<sup>3</sup> They had been developed into versatile intermediates in a series of named reactions, among which Sandmeyer reaction was the first to demonstrate the usefulness of diazonium salt in organic synthesis. In 1884, Sandmeyer

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disclosed that by treatment with CuCl, CuBr, or CuCN, benzenediazonium salt could be converted into chlorobenzene, bromobenzene, and benzonitrile, respectively.<sup>4</sup> Since then various useful transformations based on diazonium salts had been invented in the following decades, including Pschorr biaryltricyclic synthesis (1896),<sup>5</sup> Gomberg–Bachmann biaryl synthesis (1924),<sup>6</sup> Balz–Schiemann C–F bond formation (1927)<sup>7</sup> and Meerwein arylation reaction (1939).<sup>8</sup> The reactions, which involve diazonium salt as the key intermediate, can be generally categorized as Sandmeyer-type transformations.

In 1977, Doyle and co-workers developed an organic phase diazotization process that could allow the formation of diazonium salts in organic solution.<sup>9</sup> This method significantly expanded the synthetic utility of diazonium salts in organic synthesis. On the other hand, pioneered by Kikukawa and Matsuda in 1977, aryldiazonium salts have been utilized in transition metal-catalyzed cross-coupling reactions.<sup>10</sup> This opens up the possibility of using aryldiazonium salts as pseudo-halides in cross-coupling reactions.

However, by scrutinizing this history, one can conclude that the research on Sandmeyer-type reactions has remained dormant for decades, and mechanistically new processes involving diazonium salts have seldom been reported since the 1980s, although these well-established transformations are widely practiced on a daily basis in both large scale industrial production and research laboratories. Around 2010, we became involved in the Sandmeyer-type transformations accidentally. In a project, we needed to convert an aromatic amino group into a pinacol boronate. The standard procedure for converting arylamines into arylboronic acids or boronates requires two steps, namely, a Sandmeyer reaction to convert the amine into halide, followed by the Grignard approach or a palladium-catalyzed borylation process. Although the two-step procedure for the conversion of arylamines into arylboronates is reliable, it is usually not very efficient because of the generally low-yielding and tedious separation procedures required. We envisaged that it might be possible to bypass the halogenation step and directly convert the amino group into the boronate group in a single step. Gratifyingly, this preliminary vision eventually led to our development of a series of new transformations, which are all based on aryldiazonium salts, namely, Sandmeyer-type reactions. Herein we summarize our findings, along with the related reactions developed in other laboratories.

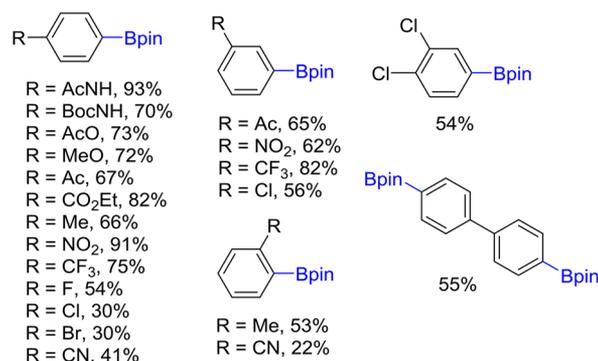
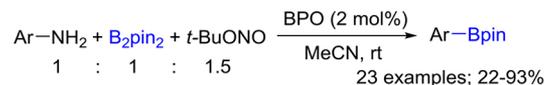
## 2. DIRECT CONVERSION OF AN AROMATIC AMINO GROUP INTO A BORON GROUP

Due to the wide application of Suzuki–Miyaura cross-coupling, there has been an increasing demand for various organo boron compounds from both research laboratories and industry. Traditionally, the synthesis of boronic acids relied on the trapping of organolithium or Grignard reagents with a trialkyl borate, followed by acidic hydrolysis.<sup>11</sup> The method is powerful, but it suffers from drawbacks such as rigorously anhydrous conditions normally required for organometallic reagents and narrow functional group compatibility. Transition-metal-catalyzed cross coupling of aryl bromides or iodides with bis(pinacolato)diboron ( $B_2pin_2$ ) was disclosed by Miyaura and co-workers in 1995, which has become another important approach toward aryl boron compounds.<sup>12</sup> Notably, diazonium salts have also been utilized in this transition-metal-catalyzed borylation process to furnish the corresponding arylboronates.<sup>13</sup> Moreover, efforts have been devoted to the transition-metal-catalyzed direct borylation of aromatic C–H bonds for arylboronates synthesis.<sup>14</sup>

Notably, all of these borylation methods require metals, either as catalysts or as stoichiometric reagents.

With the prediction that direct conversion of an aromatic amino group into a boron group might be possible, we started the exploration by using Doyle's *in situ* diazotization approach with *t*-BuONO. Through extensive screening of the reaction conditions, we could indeed achieve the goal of the proposed borylation through the reaction of aromatic amine, *t*-BuONO, and  $B_2(pin)_2$  (Scheme 1).<sup>15</sup> This metal-free transformation

### Scheme 1. Preliminary Results of Metal-Free Borylation of Arylamines

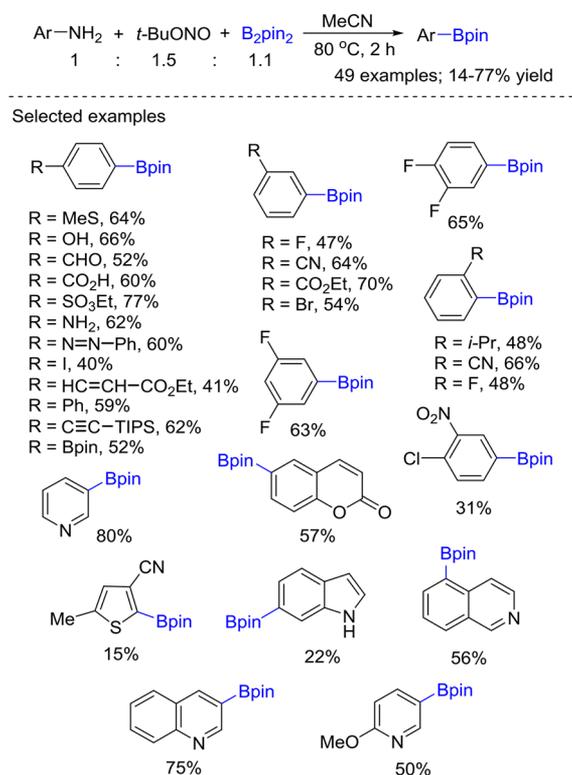


follows a Sandmeyer-type reaction sequence: the arylamine is first converted into the corresponding diazonium ion by the reaction with *t*-BuONO, followed by the reaction of diazonium ion with  $B_2pin_2$  to deliver the final product. The reaction is promoted by the radical initiator dibenzoyl peroxide (BPO), and it is complete at room temperature within 1–2 h. Arylamines bearing various functionalities can be engaged in this transformation, and the corresponding borylation products are obtained in moderate to good yields; however, for heteroaromatic amines and some *ortho*-substituted arylamines, the reaction only gives trace amount of the products.

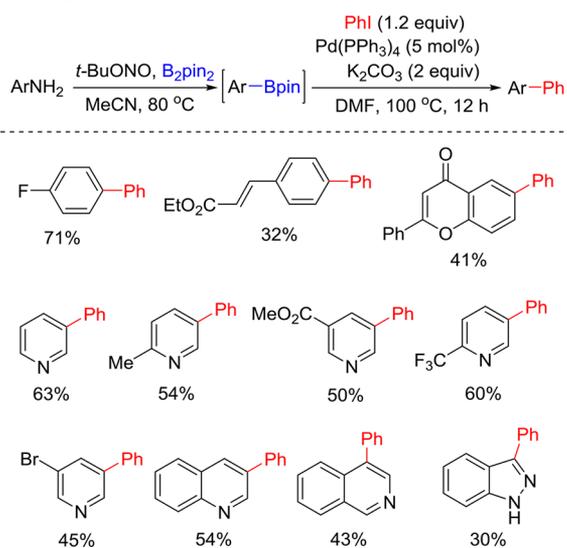
Subsequently, we modified this metal-free borylation by simply carrying out the reaction at an elevated temperature in the absence of BPO. The modified conditions turn out to be compatible with a broader substrate scope, including *ortho*-substituted arylamines, amines with unprotected hydroxyl and amino groups, aldehydes, and more importantly, heterocyclic amines (Scheme 2).<sup>16</sup> It has been observed that electron-deficient heterocyclic amines exhibit high reactivity to afford the borylation products, while electron-rich heterocyclic amines are prone to oxidation in the presence of *t*-BuONO, thus resulting in diminished yields. The reaction can be carried out in gram scale for selected substrates.<sup>17</sup>

Arylboronates, in particular heterocyclic boronates, are in some cases not stable under silica gel column chromatographic conditions. To avoid the possible borylation product decomposition in purification, a sequential Sandmeyer-type borylation and Pd-catalyzed cross-coupling reaction was performed. Thus, upon completion of the borylation, the solvent MeCN was removed under reduced pressure to leave the crude borylation product, which was then subjected to Pd-catalyzed Suzuki–Miyaura cross-coupling reaction without further purification. The sequential process afforded the coupling products in moderate yields (Scheme 3).

### Scheme 2. Metal-Free Borylation of Arylamines under Modified Conditions

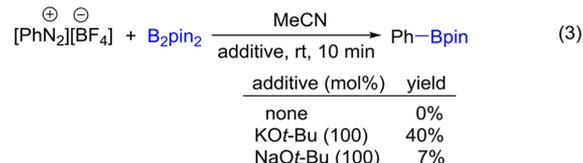
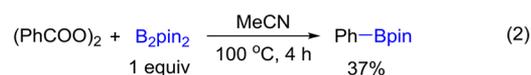
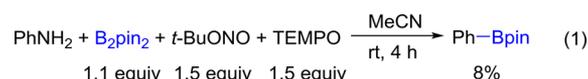


### Scheme 3. Sequential Borylation and Pd-Catalyzed Cross-Coupling Reaction



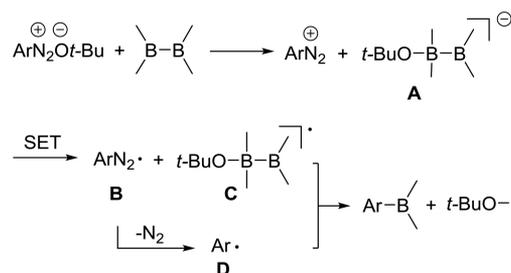
The metal-free borylation raises intriguing questions concerning its reaction mechanism. Since it has been generally recognized that Sandmeyer-type reactions proceed through a radical mechanism, it is likely that the borylation reaction may follow a similar radical pathway. To substantiate such an assumption, a series of radical trapping experiments were carried out.

First, in the presence of 1.5 equiv of radical scavenger (TEMPO), the reaction became sluggish and produced only 8% yield of the borylation product (eq 1). A control experiment demonstrated that TEMPO did not react directly with B<sub>2</sub>pin<sub>2</sub> under identical conditions. Next, heating a 1:1 mixture of dibenzoyl peroxide (BPO) and B<sub>2</sub>pin<sub>2</sub> in MeCN at 100 °C for 4 h afforded phenyl pinacboronate in 37% yield (eq 2). It is known that BPO undergoes homolytic cleavage under thermal conditions to the benzoyloxy radical, followed by subsequent extrusion of CO<sub>2</sub> to form the phenyl radical. Thus, the borylation product is likely formed by the reaction of phenyl radical with B<sub>2</sub>pin<sub>2</sub>. We also confirmed that the reaction between the relatively stable [PhN<sub>2</sub>][BF<sub>4</sub><sup>-</sup>] and B<sub>2</sub>pin<sub>2</sub> gave the expected borylation product, but base additives played an important role in the reaction (eq 3).



A possible reaction mechanism is proposed based on these observations (Scheme 4). First, upon the formation of diazonium

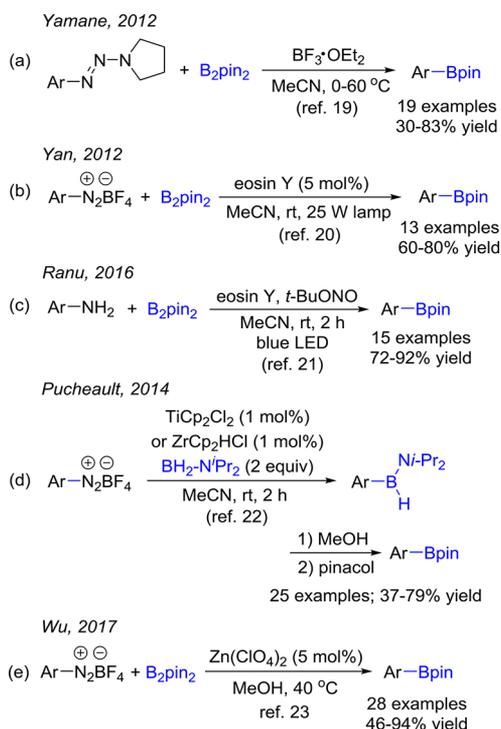
### Scheme 4. Possible Reaction Mechanism



salt from the arylamine and *t*-BuONO, the *t*-BuO<sup>-</sup> interacts with B<sub>2</sub>pin<sub>2</sub> to form a tetra-coordinated boron complex A. This adduct has been recently confirmed and fully characterized by Marder and co-workers.<sup>18</sup> Then single electron transfer (SET) between complex A and aryldiazonium ion occurs to generate radical B, from which aryl radical D is generated through N<sub>2</sub> extrusion. Finally, reaction of aryl radical D with intermediate C gives the borylation product. However, alternative mechanisms involving an ionic process, such as nucleophilic aromatic substitution of the aryldiazonium salt by the boronate complex, cannot be strictly ruled out.

Following our report in 2010, a series of similar Sandmeyer-type borylations under modified conditions appeared in the literature. Zhu and Yamane used aryltriazenes as the precursors of diazonium salts and developed a borylation reaction (Scheme 5a).<sup>19</sup> Yan and co-workers reported an organic dye (eosin Y)-catalyzed photopromoted reduction of stable aryldiazonium tetrafluoroborate salts to generate free aryl radicals that are borylated with B<sub>2</sub>pin<sub>2</sub> (Scheme 5b).<sup>20</sup> This photoredox protocol could also be extended to *in situ* generated diazonium salts from arylamines

Scheme 5. Various Sandmeyer-type Borylations of Arylamines or Aryldiazonium Salts

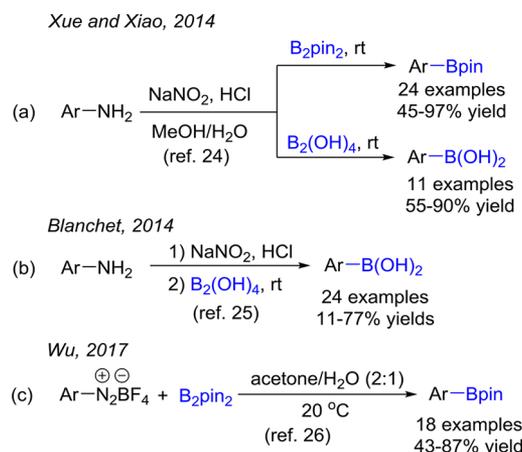


and *t*-BuONO. Ranu reported that using the same photocatalyst, eosin Y, a variety of anilines were borylated to give the corresponding arylboronates in the presence of *t*-BuONO and  $\text{B}_2\text{pin}_2$  at room temperature with visible light irradiation (Scheme 5c).<sup>21</sup>

Pucheault and co-workers disclosed that a series of titanocene and zirconocene reagents were capable of promoting borylation of anilines to form boronates (Scheme 5d).<sup>22</sup> Interestingly, this protocol uses diisopropylaminoborane ( $\text{H}_2\text{BNi-Pr}_2$ ) as the borylating agent, and the reaction was proposed to proceed through a radical chain mechanism. Very recently, Wu and co-workers demonstrated a zinc-catalyzed borylation of aryldiazonium salts and aryltriazenes toward arylboronate synthesis.<sup>23</sup> The reaction was carried out in methanol with 5%  $\text{Zn}(\text{ClO}_4)_2$  catalyst at 40 °C, providing various arylboronates (Scheme 5e).

Diazotizations were typically conducted in aqueous solution in the early days. Although aqueous conditions have sometimes restricted the substrate scope due to functional group compatibility or solubility issues, there are also potential advantages of using water as solvent, such as low cost, safety, and environmental benefits. Thus, to develop Sandmeyer-type borylation under aqueous conditions is desirable. In 2014, the groups of Xue<sup>24</sup> and Blanchet<sup>25</sup> independently reported aqueous phase diazotization conditions for the conversion of arylamines to arylboronates. In Xue's work, the first diazotization step was conducted at 0–5 °C in mixed solvent of MeOH/aq. HCl. Upon the formation of the diazonium salt, a solution of  $\text{B}_2\text{pin}_2$  was added. They found that for the second step protic solvents such as alcohols and organic acids are superior to aprotic solvents like DMF, THF, MeCN, etc. In addition, they expanded the borylation with  $\text{B}_2(\text{OH})_4$  as the boron source, affording arylboronic acids as the products (Scheme 6a). In Blanchet's method,<sup>25a</sup> the most attractive advantage is that the reaction proceeded very fast, as the reactions went to completion in around 0.5 h. In their protocol starting from anilines, the reaction

Scheme 6. Aqueous Phase Diazotization for Conversion of Arylamines to Arylboronates or Arylboronic Acids



solvent was water, and  $\text{B}_2(\text{OH})_4$  was used as the boron source (Scheme 6b). Furthermore, they combined this one-pot fast borylation method with other reactions such as esterification, Suzuki–Miyaura coupling, hydrogenolysis, and Petasis borono-Mannich for rapidly achieving molecular diversity.<sup>25b</sup>

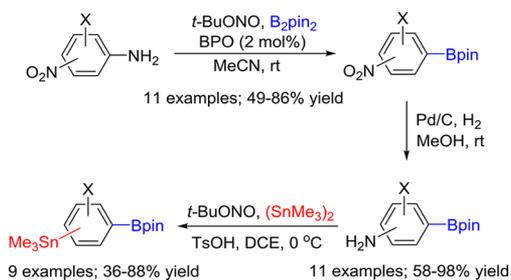
More recently, Wu further demonstrated that the borylation of stable diazonium tetrafluoroborates could proceed under catalyst-free conditions in acetone–water solution (Scheme 6c).<sup>26</sup> Control experiments indicate that water plays a crucial role in promoting the borylation of diazonium tetrafluoroborates. Mechanistically, the reaction proceeds through a radical pathway, as TEMPO or BHP completely inhibited the desired transformation.

### 3. STANNYLATION OF DIAZONIUM SALT FOR C–Sn BOND FORMATION

Encouraged by the success in Sandmeyer-type borylation, we further set out to explore other transformations involving diazonium salts as reactive intermediates. Similar to organoboron compounds, organotin compounds are also important and widely used in transition-metal-catalyzed cross-coupling reactions, namely Stille coupling. After extensive exploration, we realized the first stannylation of diazonium salts (Scheme 7).<sup>27</sup> In contrast to borylation, stannylation requires one equivalent of acid to promote the diazotization process. The choice of stannylating reagent is another crucial parameter, as all optimization efforts with hexabutyldistannane as stannylating reagent turned out to be futile. In contrast, with hexamethyldistannane, the reaction gives a decent yield of the desired product. The optimized condition is simple: 1.5 equiv of *t*-BuONO, 1.1 equiv of  $\text{Me}_3\text{SnSnMe}_3$ , and 1.2 equiv of *p*-toluenesulfonic acid at 0 °C in DCE for 4 h. The scope of substrates is wide, including a series of functionalized aniline derivatives. The reaction has shown excellent tolerance to both electron-withdrawing and -donating groups on the aromatic ring. The reaction is also scalable. In a representative example, 15 mmol of *p*-toluidine was subjected to the standard conditions, affording 1.95 g of the corresponding product (51% yield). Heterocyclic amines were also engaged in this stannylation; however, the yields were only low to moderate. The substrates bearing electron-deficient rings afforded relatively higher yields than electron-rich ones under the standard conditions. This is partially because the electron-rich heterocyclic stannanes are sensitive to moisture and silica gel column chromatography. Since purification of aryl stannane compounds is tedious and some aryl stannanes are not stable, the Pd-catalyzed



### Scheme 11. Synthesis of Stannyl Arylboronates from Nitro-Substituted Anilines



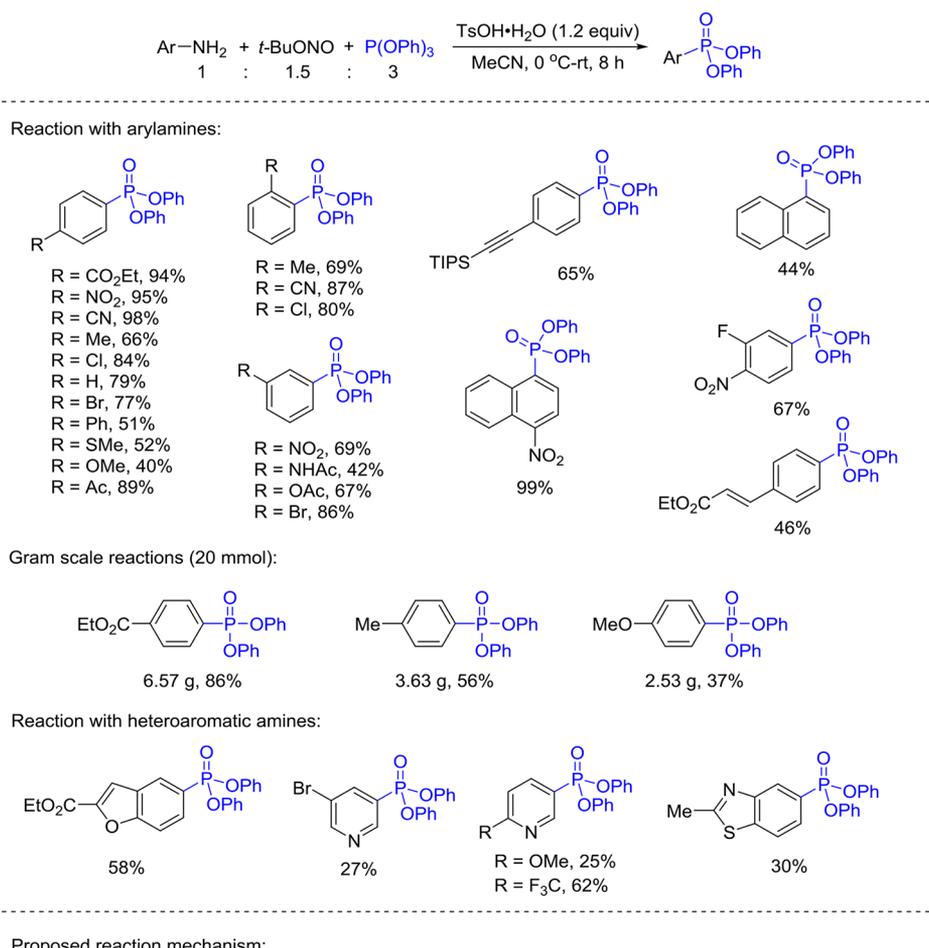
the boron-substituted aniline derivatives to the corresponding stannylation products. By adopting this reaction sequence, we could synthesize various stannyl arylboronates compounds in three steps.

### 4. PHOSPHORYLATION OF DIAZONIUM SALT FOR C–P BOND FORMATION

Organophosphonates have attracted considerable attention as they have broad applications in agrochemicals, medicinal chemistry, material sciences, etc.<sup>29</sup> The synthesis of organophosphonates mostly relies on several classic approaches: nucleophilic substitution reaction of organometallic reagent with electrophilic phosphine reagent, the Michaelis–Arbuzov reaction, the Friedel–Crafts reaction, and transition-metal-catalyzed cross-coupling reaction of aryl (pseudo)halides or boronic acids with phosphorus compounds.<sup>30</sup> In light of the importance of aryl phosphonates and our success in the development of transformations with aryldiazonium salts, we further explored the application of the Sandmeyer-type transformation in aromatic C–P bond formations (Scheme 12).<sup>31</sup>

We began our study with phosphorylation of 4-aminobenzoate as the model reaction. Under similar Sandmeyer-type conditions

### Scheme 12. Sandmeyer-type Phosphorylation: Scope of the Aniline Derivatives and the Proposed Mechanism



[*t*-BuONO, P(OMe)<sub>3</sub>, MeCN], the first attempt gave 44% yield of the desired phosphorylation product. The reaction was significantly affected by the choice of phosphite reagent. While triethyl phosphite gave only a trace amount of the corresponding product, triphenyl phosphite exhibited the best reactivity. Eventually, the yield could be improved to 94% by using three equivalents of triphenyl phosphite.

The phosphorylation shows good functional group tolerance to both electron-withdrawing and -donating groups on the aromatic ring (Scheme 12). It is noteworthy that the tolerance of bromo and chloro groups, which are normally not compatible in transition-metal-catalyzed C–P bond construction approaches, makes possible further transformation of the products via cross-coupling reactions. *para*-Substituted arylamines with electron-withdrawing groups give relatively higher yields. Similar yields could be achieved with *ortho*- and *meta*-substituted anilines, indicating that the phosphorylation is not sensitive to steric effects. For a further demonstration of the practical utility of this method, phosphorylation reactions of three substrates were carried out in 20 mmol scale. The reactions furnished the corresponding products with comparable yields. Phosphorylation of aromatic heterocyclic amines was also explored, but the substrate scope was limited. As shown in Scheme 12, the phosphorylation of heteroaromatic amines gives diminished yields in general.

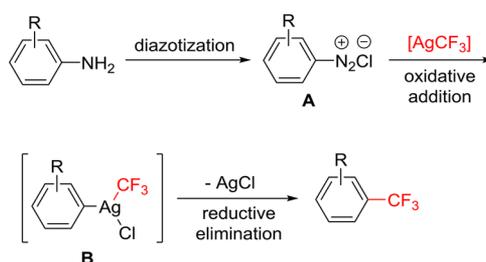
Regarding to the mechanism of this Sandmeyer-type phosphorylation reaction, we proposed that the diazonium salt is first reduced by triaryl phosphite to give a diazonium radical anion B and a phosphite radical cation C. Then, the intermediate C reacts with water to generate a phosphono radical D and a phenol product E. Finally, the reaction between B and D gives the desired phosphorylation product F. Observation of a phenol product by means of TLC and GC-MS supports this mechanistic proposal.

## 5. TRIFLUOROMETHYLATION OF DIAZONIUM SALT FOR C–CF<sub>3</sub> BOND FORMATION

Trifluoromethylated arenes and heteroarenes are privileged structural motifs in pharmaceuticals, agrochemicals, liquid crystals, dyes, and polymers.<sup>32</sup> However, CF<sub>3</sub>-containing compounds are absent in nature, which accounts for the vital importance of developing synthetic methods to introduce the CF<sub>3</sub> group onto aromatic rings. In addition to the traditional methods, the introduction of the CF<sub>3</sub> group through transition-metal-catalyzed cross-coupling has attracted considerable attention in recent years. Regardless of the remarkable progress, further developments are still needed to enable the use of cheap and abundantly available starting materials under mild trifluoromethylation conditions. To this end, we directed our study on Sandmeyer-type transformations toward trifluoromethylation of diazonium salts, employing readily available and inexpensive anilines as the starting materials.<sup>33</sup>

Based on the oxidizing properties of aryl diazonium salts and the strong  $\sigma$ -donor nature of the trifluoromethyl group in the [AgCF<sub>3</sub>] complex<sup>34</sup> and also inspired by the previous observation of reductive elimination from bimetallic high-valent silver complexes to form C(sp<sup>2</sup>)–F bonds,<sup>35</sup> we proposed that oxidative addition of diazonium salt A would be favored at an electron-rich silver center to afford intermediate B (Scheme 13). Subsequently, intermediate B undergoes reductive elimination to form a C(sp<sup>2</sup>)–CF<sub>3</sub> bond and the AgCl precipitate. This hypothesis was proven successful when first attempted. Simply adding preformed AgCF<sub>3</sub> into a solution of diazonium chloride in MeCN at 0 °C delivered the desired trifluoromethylated

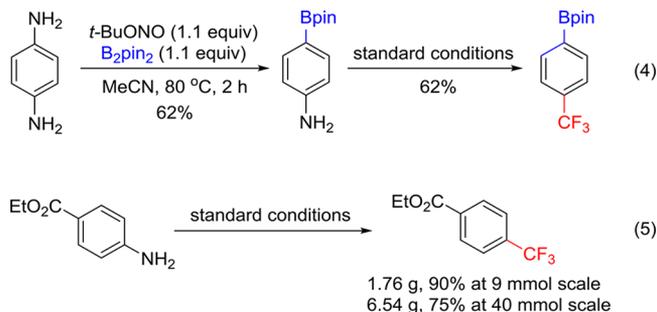
## Scheme 13. Proposed Strategy for Trifluoromethylation of Aromatic Amines



product in 41% yield. The reaction could be improved at low temperature, presumably attributed to the relative stability of diazonium chloride salts at low temperature. By switching the solvent from MeCN to EtCN, the addition of AgCF<sub>3</sub> could be carried out at –78 °C, which turns out to be the optimal condition, providing a 95% yield of the trifluoromethylated product.

The substrate scope was next explored (Scheme 14). In general, both electron-rich and -deficient anilines react smoothly to afford the corresponding trifluoromethylation products in moderate to excellent yields. It is noteworthy that this trifluoromethylation reaction tolerates unprotected alcohols and benzoic acids, as well as oxidation sensitive groups, such as vinyl, alkynyl, Bpin, and TMS groups. Anilines bearing *ortho*-substituents, including ester and bulky isopropyl groups, also worked well with high yields. In the case of heteroaromatic amines, such as indoles and benzofurans, the desired products could be formed in moderate yields.

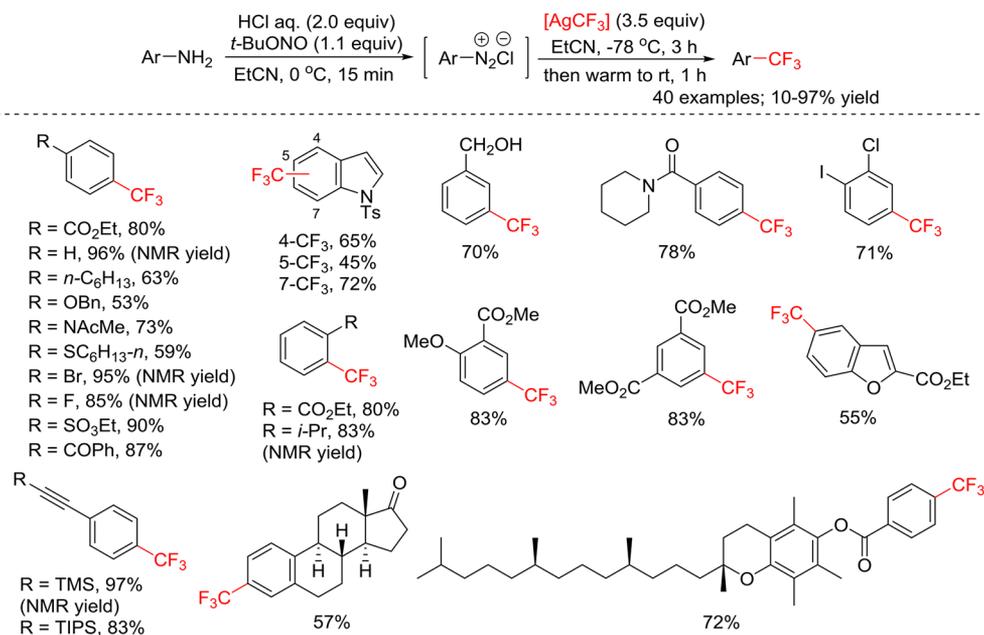
Moreover, by employing the previously established metal-free borylation method, we could convert the two amino groups of benzene-1,4-diamine into Bpin and CF<sub>3</sub> groups successively (eq 4). Gram scale experiments demonstrate the potential usefulness of this method (eq 5).



For mechanistic studies, a radical clock and TEMPO trapping experiments were performed. Both suggest that the reaction does not likely operate by a radical mechanism. Instead, an oxidative addition–reductive elimination mechanism involving high-valent silver species as shown in Scheme 13 is likely the case.

In the same year, Fu and co-workers reported a copper-mediated Sandmeyer-type trifluoromethylation of aromatic amines (Scheme 15a).<sup>36</sup> In their method, Umemoto's reagent was employed as the CF<sub>3</sub> source, and isoamyl nitrite (*i*-AmONO) was used to effect the *in situ* diazotization reaction. The reaction tolerates a variety of functional groups, including ether, thioether, amido, nitro, ester, ketone, and azo. Several typical heterocyclic amines were also successfully covered in the substrates. A radical pathway is supported by a series of mechanistic experiments, including clock trapping reaction, ESR test, and a CuCF<sub>3</sub> species suggested by <sup>19</sup>F NMR data.

## Scheme 14. Silver-Mediated Trifluoromethylation of Aryldiazonium Salts



Simultaneously, Goossen and co-workers reported a copper-mediated Sandmeyer-type trifluoromethylation reaction (Scheme 15b).<sup>37</sup> The stable diazonium tetrafluoroborate salts are preformed and used as starting material instead of arylamines in this case. In their reaction, an *in situ* generated CuCF<sub>3</sub> species is contrived to react with the diazonium salt to deliver the trifluoromethylated product. Thus, the Ruppert–Prakash reagent (TMSCF<sub>3</sub>) is used as the CF<sub>3</sub> source and is premixed with Cu(I) thiocyanate and cesium carbonate before the addition of the diazonium salt. The reaction proceeded smoothly with good functional group tolerance, affording moderate to high yields of the trifluoromethylated products. The reaction has been proposed to proceed via a radical process, which is in line with other Sandmeyer-type halogenation reactions. In an update of this work, they demonstrated that their method could utilize *in situ* generated diazonium salts (Scheme 15c).<sup>38</sup> They also expanded their method to Sandmeyer-type trifluoromethylthiolation reaction (Scheme 15d). Alternatively, the Sandmeyer-type trifluoromethylthiolation and trifluoromethylselenolation could be achieved by using Me<sub>4</sub>NSCF<sub>3</sub> and Me<sub>4</sub>NSeCF<sub>3</sub>, respectively (Scheme 15e,f).<sup>39</sup> By using an *in situ* formed CuCF<sub>2</sub>H reagent, difluoromethylation has also been accomplished (Scheme 15g).<sup>40</sup> In another paper, they achieved a copper-catalyzed Sandmeyer-type pentafluoroethylthiolation (Scheme 15h).<sup>41</sup>

Grushin and co-workers disclosed a Sandmeyer-type trifluoromethylation of arenediazonium salts with fluoroform-derived CuCF<sub>3</sub> in aqueous media (Scheme 15i).<sup>42</sup> Different from the other reactions mentioned above, in Grushin's protocol the CF<sub>3</sub> moiety originates from fluoroform (CHF<sub>3</sub>), an inexpensive, nonflammable gas. By their method, CuCF<sub>3</sub> could be easily generated as a solution by treatment of CuCl with KO<sup>*t*</sup>-Bu and CHF<sub>3</sub> successively. The substrate scope is broad, including a couple of heterocyclic examples as well as some complex molecules. Mechanistically, it has been suggested that the reaction follows a radical pathway based on a radical clock experiment.

Very recently, Zheng and co-workers disclosed a copper-promoted Sandmeyer-type trifluoromethylation of arylamines by using Langlois reagent (CF<sub>3</sub>SO<sub>2</sub>Na) as the CF<sub>3</sub> source

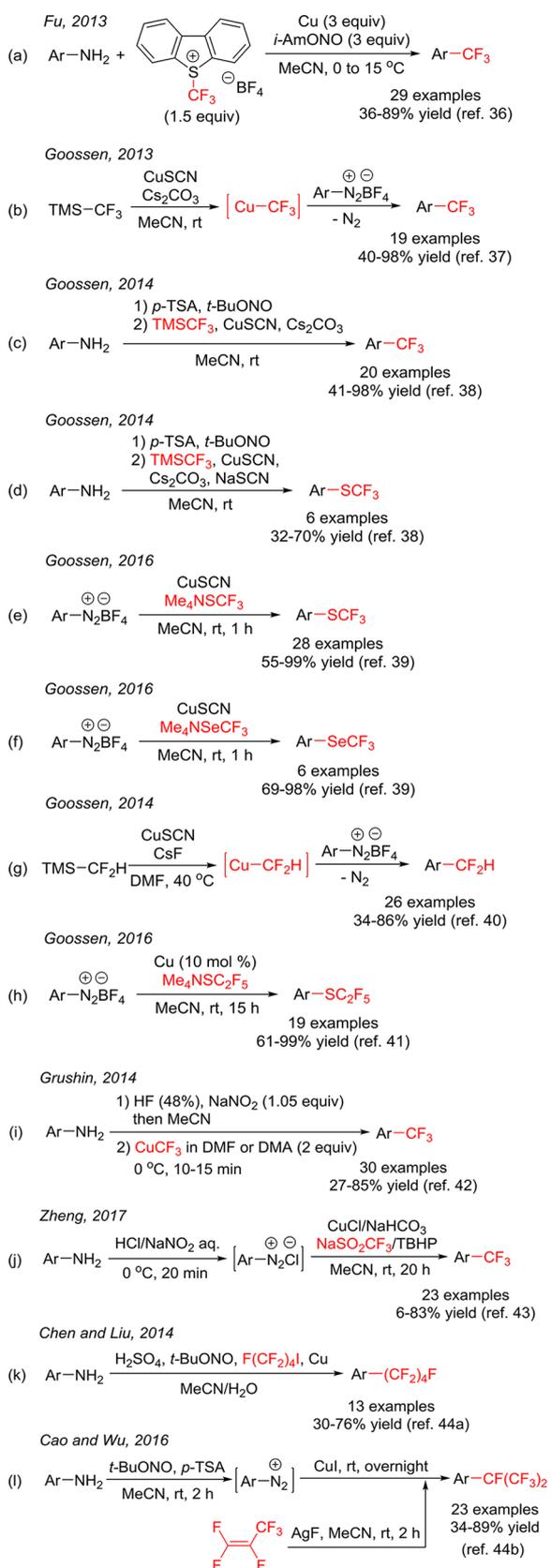
(Scheme 15j).<sup>43</sup> *tert*-Butyl hydroperoxide (TBHP) was found to be a suitable oxidant for this transformation. A number of arylamines were trifluoromethylated with moderate to good yields. A radical mechanism is also proposed based on TEMPO trapping experiment.

In addition to trifluoromethylation, the Sandmeyer-type transformation has also been used in other perfluoroalkylation reactions.<sup>44</sup> Chen and Liu reported a copper-mediated perfluoroalkylation of diazonium salts by using perfluoroalkyl iodide (Scheme 15k),<sup>44a</sup> whereas Cao and Wu disclosed a silver and copper mediated perfluoroisopropylation of diazonium salts by using hexafluoropropylene (HFP) as the perfluoroalkyl source (Scheme 15l).<sup>44b</sup> In both cases, radical mechanisms have been proposed for their reactions.

## 6. CONCLUSIONS

As shown in this Account, recent years have witnessed remarkable development of Sandmeyer-type transformations that enable several novel functional group conversions from aromatic amino group to boryl, stannyl, phosphoryl, and trifluoromethyl/perfluoroalkyl groups.<sup>45</sup> This age-old chemistry has been reenergized and experienced a resurgence. Although we have to concede that aryl halides (or pseudo-halides) and arylboronic acids (boronates) are more "popular" choices when one considers a functional group conversion or a coupling reaction, arylamines have obvious complementary merits: (1) as for their availability and accessibility, the aromatic nitration–reduction procedure for arylamine synthesis normally has higher site-selectivity than halogenation of aromatics and has no over substitution problem; (2) the price for arylamines is in general cheaper than that for the corresponding arylhalides, which could be a great advantage of the Sandmeyer-type borylation reaction; (3) because the conditions for diazotization are orthogonal to many other reactions, the Sandmeyer-type reactions exhibit excellent compatibility; (4) amino groups can be easily protected and deprotected; thus combined with merit 3, Sandmeyer-type transformation may be better suited for a late stage transformation in a given synthesis.

## Scheme 15. Various Sandmeyer-type Trifluoromethylation/perfluoroalkylation of Arylamines or Aryldiazonium Salts



However, there are still limitations and imperfections that need to be addressed in the future. For example, some of the Sandmeyer-type reactions have to use a large excess of metal

reagents, which may hinder the implementation of these reactions in large scale preparation. Additionally, the choice of reagents in the diazotization step has been restricted to nitrites. In this regard, more environmentally benign agents or the implementation of electrochemical techniques would be a leap forward in both conception and practicality. With the further development of Sandmeyer-type transformations, this age-old chemistry is expected to find new and innovative contributions to the synthetic community in the future.

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