Balz–Schiemann Reaction

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Rapid Synthesis of Aryl Fluorides in Continuous Flow through the Balz–Schiemann Reaction

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Abstract: *The Balz–Schiemann reaction remains a highly utilized means for preparing aryl fluorides from anilines. However, the limitations associated with handling aryl diazonium salts often hinder both the substrate scope and scalability of this reaction. To address this, a new continuous flow protocol was developed that eliminates the need to isolate the aryl diazonium salts. The new process has enabled the fluorination of an array of aryl and heteroaryl amines.*

Spurred by the pharmaceutical and agrochemical significance of fluorinated aromatic compounds,[1] there have been significant advances in methods for aryl C–F bond formation. These include transition metal-catalyzed or mediated protocols,[2] deoxyfluorination of phenols,[3] and fluorination of aryl Grignard reagents.[4] Despite these advances, established methods such as the Halex process[5] and the Balz–Schiemann reaction[6,7] remain relevant routes for preparing aryl fluorides. While the Halex process is limited to highly activated substrates, the Balz–Schiemann reaction can utilize a variety of aryl amine substrates making it a versatile method. As aryl amines are readily accessible, this process has been utilized on many advanced synthetic intermediates.[7] Unfortunately, the Balz–Schiemann reaction suffers from the need to employ harsh reaction conditions, and often provides modest yields, and involves the generation of a potentially explosive aryl diazonium salt.[7] Thus, the development of an improved protocol that would provide rapid, scalable access to aryl fluorides would be significant.

The Balz–Schiemann reaction involves converting the aryl amine starting material into the corresponding diazonium salt, which is typically isolated and dried prior to thermal or photochemically-mediated dediazotization (Figure 1).[8] Handling the aryl diazonium intermediates is a major safety concern as they have the potential to undergo spontaneous and violent decomposition.[9] To mitigate the potential safety risks associated with the isolation of aryl diazonium salts, several one-pot protocols have been utilized.[10] While effective, they still involve the generation of aryl diazonium salts under batch conditions and in some cases require the use of HF·pyridine as the solvent.[7c,f,10b] Alternatively, continuous flow processing offers numerous safety advantages over batch

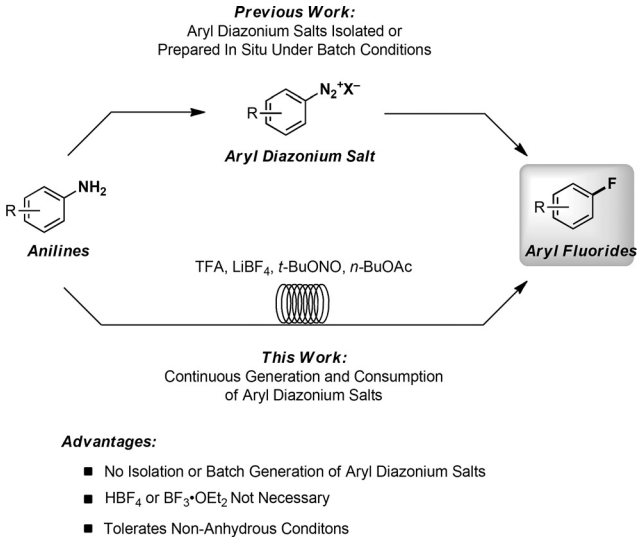

Figure 1. Summary of the advantages of this work.

reactors and is an attractive option for handling diazonium salts.[11] A technique has been previously developed for the Balz–Schiemann reaction where diazotization and subsequent thermal decomposition were conducted as two independent continuous flow processes.[12] Unfortunately, this protocol still necessitated the isolation and drying of the aryl diazonium salt intermediate formed under aqueous conditions. To overcome the current limitations of both the batch and flow processes, we sought to develop a new continuous flow process that overcomes the limitations of the previous methods.

Adapting the Balz–Schiemann reaction to a continuous flow process poses several challenges. One of the main issues is the extensive formation of side products that are seen during the thermal dediazotization process. These include the parent arene, formed from H-atom abstraction of the solvent by the aryl radical, or products including phenol and aryl ethers formed from trapping of the cation intermediate by other nucleophiles present in the reaction mixture (Figure 2).[13] To avoid these side reactions, the thermal dediazotization is often performed using the neat diazonium salt[7b,8c] or in nonpolar solvents such as toluene,[7g] 1,2-dichlorobenzene,[10a] or heptane[7c] after initial formation of the diazonium salt in a polar or aqueous reaction medium. The solvent switch required renders these procedures cumbersome to employ in a continuous process. Moreover, these commonly used nonpolar solvents do not dissolve the aryl diazonium salt readily and would lead to reactor clogging under flow conditions. To overcome this, we focused our

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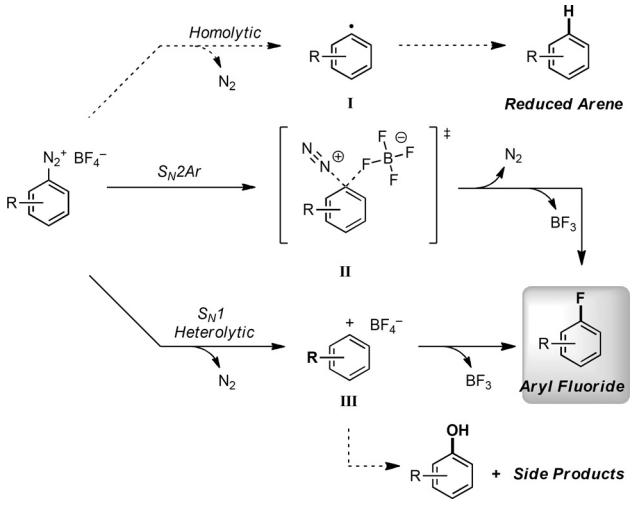


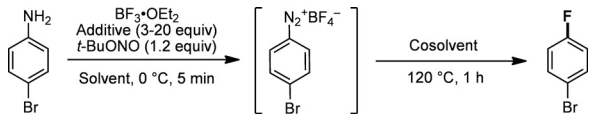
Figure 2. Possible reaction pathways for formation of the aryl fluoride and other side products.

initial efforts on identifying effective reaction parameters for the one-pot Balz–Schiemann reaction of 4-bromoaniline under batch conditions.

We initiated our study by investigating the one-pot Balz–Schiemann reaction to generate 4-fluorobromobenzene from 4-bromoaniline (Table 1). In the absence of any additive or cosolvent, only 18% yield was observed with the major side product being the corresponding acetamide, presumably arising from solvolysis (entry 1, Table 1). We hypothesized that if product formation was proceeding through an S_N2Ar or S_N1 heterolytic mechanism (via **II** or **III**; Figure 2), then increasing the concentration of the fluoride source may increase yield and suppress undesired side reactions. By adding a large excess of $LiBF_4$ (20 equiv), the yield increased to 58% (entry 2, Table 1), and adding toluene as a cosolvent further brought the yield to 93% (entry 3, Table 1). Unfortunately, lowering the number of equivalents of $LiBF_4$ under these conditions also led to reduced yield (entry 4, Table 1). Other salt additives[14] proved to be much less effective, likely due to their lower solubility in organic solvents (entries 6–10, Table 1).

The large excess of $LiBF_4$ needed to achieve high yields prompted us to further investigate the effects of solvent on the reaction. Here, an array of solvents were examined in combination with cyclohexane as a cosolvent and with only five equivalents of $LiBF_4$.[15] We found that using *n*-butyl acetate provided the best results, giving the desired fluoroarene in 80% yield while only forming 1% of the reduction byproduct (Figure 3).[16] Other solvent combinations provided lower yields and increased formation of the parent arene.

Table 1: Optimization of one-pot Balz–Schiemann reaction under batch conditions.[a]



Entry	Additive	Solvent	Cosolvent	Yield [%]
1	None	MeCN	None	18
2	$LiBF_4$[b]	MeCN	None	58
3	$LiBF_4$[b]	MeCN	PhMe	93
4	$LiBF_4$[c]	MeCN	PhMe	53
5	$LiBF_4$[b]	MeCN	Cyclohexane	80
6	$NaBF_4$[b]	MeCN	PhMe	69
7	KBF_4[b]	MeCN	PhMe	49
8	$NaPF_6$[b]	MeCN	PhMe	73
9	KPF_6[b]	MeCN	PhMe	28
10	KF[b]	MeCN	PhMe	0

[a] Reaction conditions: 4-bromoaniline (0.15 mmol), $LiBF_4$ (0.75–3.0 mmol), *t*-BuONO (0.17 mmol), solvent (0.5 mL), rt, 5 min, then added cosolvent (0.5 mL) and heated to 120°C for 1 h. The yields of the product were measured by ^{19}F NMR analysis of the crude reaction mixture using 1-fluoronaphthalene as the internal standard.
[b] 20 equivalents used. [c] 3 equivalents used. MeCN = acetonitrile, PhMe = toluene.

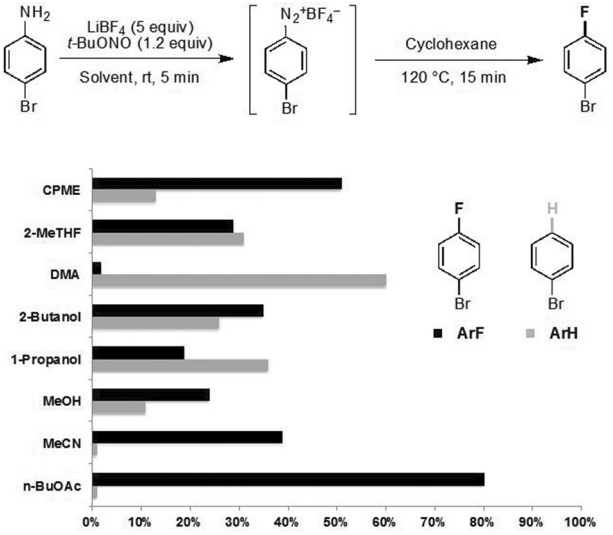
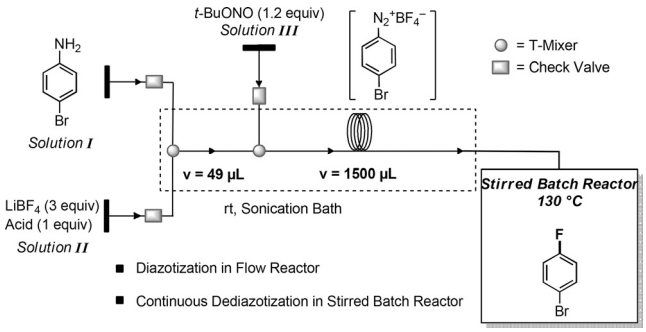


Figure 3. Solvent effects of single pot Balz–Schiemann under batch conditions. Reaction conditions: 4-bromoaniline (0.15 mmol), $LiBF_4$ (0.75 mmol), *t*-BuONO (0.17 mmol), solvent (0.5 mL), rt, 5 min, then added cyclohexane (0.5 mL) and heated to 120°C for 15 min. The yields of the product and the reduced arene byproduct were measured by GC analysis of the crude reaction mixture using *n*-decane as the internal standard. CPME = cyclopentyl methyl ether, 2-MeTHF = 2-methyltetrahydrofuran, DMA = *N*,*N*-dimethylacetamide, MeOH = methanol, MeCN = acetonitrile, *n*-BuOAc = *n*-butyl acetate.

Further investigation revealed that performing the reaction without the cyclohexane cosolvent did not significantly affect the yield or increase the amount of reduced arene formed.[17]

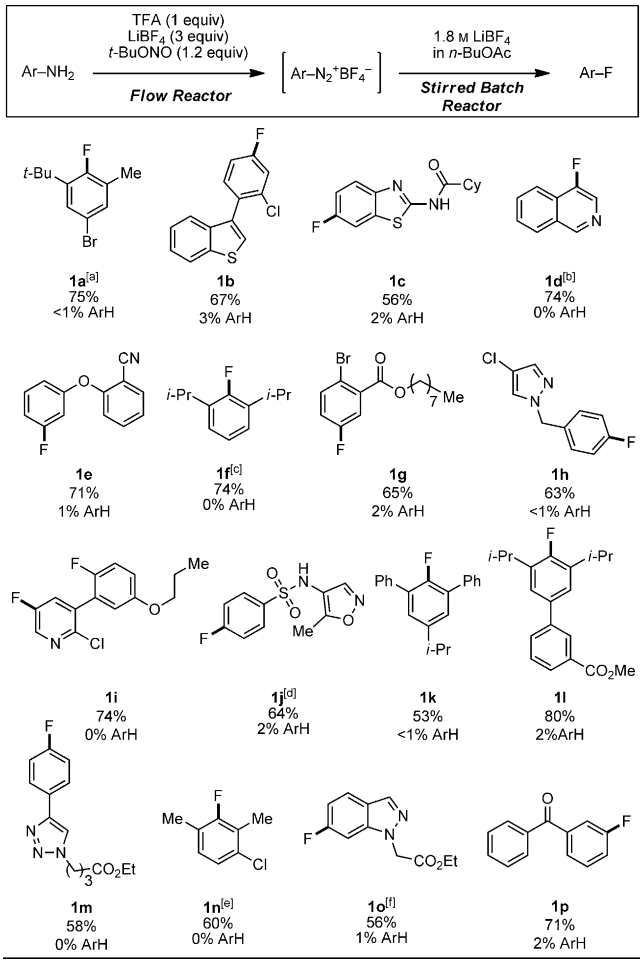
While the batch conditions using *n*-butyl acetate were effective, their use in a fully continuous flow process resulted in clogging of the flow reactors due to salt precipitation. To overcome this difficulty, we developed a flow to stirred-batch process that maintains the advantages of a fully continuous flow process, namely avoiding isolating or manipulating large amounts of aryl diazonium salts. Here the aryl diazonium salt is continuously generated in a flow reactor and fed directly into a heated, stirring reactor for thermal dediazotization (Table 2). In a similar manner, a continuous stirred-tank

Table 2: Optimization of the Balz–Schiemann reaction in continuous flow.[a]



Entry	Acid	Batch reactor solvent	Reduction [%]	Yield [%]
1	**A**	cyclohexane	1	35
2	**A**	*n*-BuOAc	4	64
3	**A**	3.6 M LiBF4 in *n*-BuOAc	1	71
4	**A**	1.8 M LiBF4 in *n*-BuOAc	1	69
5	**A**	1:1 (1.8 M LiBF4 in *n*-BuOAc) / cyclohexane	1	49
6	**B**	1:1 (1.8 M LiBF4 in *n*-BuOAc) / octane	4	73

[a] Using the experimental setup in Table 2: Stock solution **I**: 4-bromoaniline (0.6 M, 1 equiv), decane (0.6 M, 1 equiv) in *n*-BuOAc. Stock solution **II**: *t*-BuONO (0.72 M, 1.2 equiv) in *n*-BuOAc. Stock solution **III**: acid (0.6 M, 1 equiv), $LiBF_4$ (1.8 M, 3 equiv) in *n*-BuOAc. Initial flow rates were 100 µL min^{-1}, stirred-batch reactor temperature is 130 °C.[17] **A** = $HBF_4{\cdot}OEt_2$, **B** = trifluoroacetic acid.



Scheme 1. The scope of flow to stirred-batch Balz–Schiemann reaction using the reactor setup depicted in Table 2: Stock solution **I**: aniline (0.6 M, 1 equiv). Stock solution **II**: *t*-BuONO (0.72 M, 1.2 equiv). Stock solution **III**: TFA (0.6 M, 1 equiv), $LiBF_4$ (1.8 M, 3 equiv). Stock solutions were prepared in *n*-BuOAc and initial flow rates were 200 µL min^{-1}. The stirred-batch reactor temperature was 130 °C. Yields are the average of two runs of isolated material on 1 mmol or greater scale.[17] [a] EtOAc, 80 °C. [b] EtOAc, 80 °C. [c] EtOAc, 80 °C. [d] *n*-PrOAc, 100 °C. [e] EtOAc, 80 °C. [f] $BF_3{\cdot}OEt_2$ used instead of TFA. *n*-PrOAc = *n*-propyl acetate.

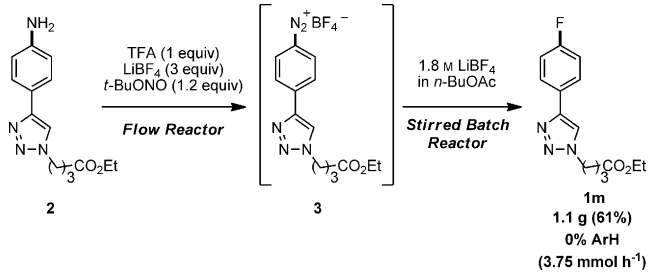
reactor would also be able to process larger quantities of the aryl diazonium salt generated in the flow reactor. The rapid rate of conversion to the aryl fluoride (< 15 minutes under batch conditions) would prevent the potential build-up of unreacted aryl diazonium salt in the batch reactor (Table 2).[18]

During the optimization of the batch conditions in Table 1, it was found that addition of a protic acid was not necessary to achieve high yields.[19] Under flow conditions, however, we opted to use an acid, such as TFA or $HBF_4{\cdot}OEt_2$, to ensure that the diazotization proceeds to completion in the flow reactor at room temperature (Table 2).[20] A sonication bath was employed for the flow reactor to ensure even dispersion and flow of any precipitated aryl diazonium salt, and limit bridging across the reactor channel.[21] Utilizing this setup, we found that a 1.8 M solution of $LiBF_4$ in *n*-butyl acetate in the batch reactor was optimal for maximizing the yield of the desired product while minimizing formation of the reduced arene (Table 2, entry 4).

With the optimal batch reactor conditions (Table 2, entry 4), we set out to demonstrate the feasibility of this process on a variety of aryl and heteroaryl amines. As TFA proved to be equally capable as an acid in the diazotization step, we utilized it instead of $HBF_4{\cdot}OEt_2$ for the investigation of the substrate scope due to its ease of handling. Under these conditions, the desired fluoroarene was obtained in moderate to high yield with only small amounts of the corresponding reduced arene, and readily separable phenol and aryl ether byproducts (Scheme 1). The process conditions were also found to tolerate a variety of functional groups present on the arenes, including nitriles, esters, halides, sulfonamides, and amides (Scheme 1).[22] A fluorinated derivative of the pharmaceutical sulfamethoxazole could also be prepared using this process in 64 % yield (**1j**; Scheme 1). Sterically hindered aryl amines could be efficiently fluorinated in moderate to high yield (**1a**, **1f**, **1k**, and **1l**; Scheme 1). These results are important, as accessing very hindered fluorinated aromatic compounds can be highly challenging using other techniques. Additionally, both sterically hindered and heteroaryl diazonium salts may have low thermal stability and could be dangerous to isolate.[23] Thus, by using the flow to stirred-batch process, these diazonium salts can be generated and consumed in a controlled manner, offering direct access to the corresponding fluoroarenes. The short collection times (15–60 minutes) enable rapid synthesis of fluorinated materials

and complement newer methods that often require extended reaction times.[24]

Finally, to fully evaluate the utility of the system for conducting the Balz–Schiemann reaction, **1m** was selected for scale-up. By running the process for aniline **2** for additional time, we were able to isolate 1.1 g (3.88 mmol) of the desired fluoroarene **1m** in 61% yield with less than two hours of run time (Scheme 2). This result demonstrates the robustness of the flow to stirred-batch setup in handling large amounts of aryl diazonium salts without compromising the yield or the amount of reduction product formed.



Scheme 2. Larger scale synthesis of **1m** via the Balz–Schiemann reaction using continuous flow reactor described in Table 2: aryl amine (0.3 M), TFA (0.3 M), *t*-BuONO (0.36 M), $LiBF_4$ (0.9 M). Flow reactor was operated for 1.75 hours, and stirring continued for an additional 30 min at 130 °C. Yield is of the isolated product after aqueous workup and purification.[17] The yield of the reduced arene was determined by GC analysis of the crude reaction mixture.

Traditionally, protocols for the Balz–Schiemann reaction require the aryl diazonium salts to be isolated and dried, or to be generated in situ under batch conditions.[10,13,15] Both of these routes are potential safety hazards, limiting the scalability and utility of the Balz–Schiemann reaction. To overcome these limitations, we have identified $LiBF_4$ as an effective additive and developed a new flow to stirred-batch reactor process that allows safer generation and dediazotization of aryl diazonium salts. Overall, we believe that the new system allows for a more controlled approach for utilizing the Balz–Schiemann reaction while obviating the need to directly handle aryl diazonium salts.

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Keywords: aryl diazonium salts · Balz–Schiemann reaction · continuous flow process · fluorination · synthetic methods

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[15] Use of an acid was found to not be necessary under these conditions.

[16] Ester solvents such as *n*-BuOAc were found to fully dissolve the $LiBF_4$ additive. The use of various different ester solvents gave similar reaction performance to *n*-butyl acetate; see Supporting Information.

[17] See Supporting Information for full experimental details.

[18] To ensure that all of the aryl diazonium salt has been consumed, the batch reactor was heated for an additional 30 minutes after the addition of the aryl diazonium salt had been completed. See Supporting Information for details.

[19] Under batch conditions, the diazotization of the aniline without acid likely reached completion upon heating of the reaction mixture. Lower yields and higher amounts of reduced arene were obtained when no acid was utilized in the flow to stirred-batch setup.

[20] No difference in yields or byproduct formation was observed when using TFA, $HBF_4{\cdot}OEt_2$, or $BF_3{\cdot}OEt_2$.

[21] The absence of sonication led to clogging using this reactor setup, see Supporting Information for details.

[22] For aryl amines that were poor substrates, see Supporting Information for further details.

[23] There are reports of sterically hindered or heteroaryl diazonium salts undergoing spontaneous dediazotization at room temperature. See Ref. [4a,b].

[24] Many recent aryl fluorination methods often require longer reaction times (>12 h); for examples see Refs. [2–4].

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