Fluorination

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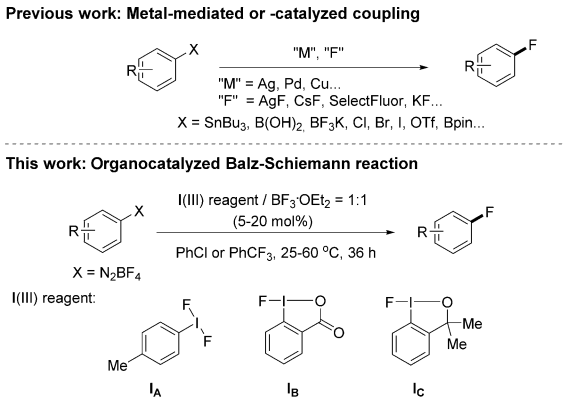
Hypervalent Iodine(III)-Catalyzed Balz–Schiemann Fluorination under Mild Conditions

*Bo Xing, Chuanfa Ni, and Jinbo Hu**

Abstract: *An unprecedented hypervalent iodine(III) catalyzed Balz–Schiemann reaction is described. In the presence of a hypervalent iodine compound, the fluorination reaction proceeds under mild conditions (25–60 °C), and features a wide substrate scope and good functional-group compatibility.*

Aryl fluorides are important structural motifs in pharmaceuticals, agrochemicals, and organic materials,[1] and the introduction of fluorine often imparts profound changes in terms of the solubility, lipophilicity, and/or stability of the target molecules.[2] Additionally, ^{18}F-labeled aryl fluorides can be used as imaging agents for positron emission tomography (PET).[3] As a result, over the past decade, significant efforts have focused on the development of methods for the generation of aromatic C–F bonds, particularly in transition-metal-mediated or -catalyzed processes (Scheme 1).[4–7]



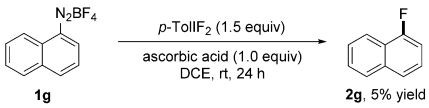
Scheme 1. Aromatic fluorinations.

However, one of the most widely used methods for the large-scale industrial production of aryl fluorides is the Balz–Schiemann reaction, a thermal conversion of arenediazonium tetrafluoroborate salts (derived from aryl amines) into aryl fluorides at high temperatures.[8] In spite of many optimizations since its first report in 1927,[9] the Balz–Schiemann reaction still suffers from harsh conditions, which limit its generality and functional group tolerance. The reaction is believed to proceed through an aryl cation intermediate, and the use of high temperatures (over 100 °C) is generally essential to overcome the activation energy to generate this reactive intermediate.[10] As both gaseous N_2 and BF_3 are evolved during the reaction, the high temperature (causing high pressures) required for this process has always been a major safety concern. Therefore, a catalytic variant of the Balz–Schiemann reaction with a lower activation energy (i.e., for conversion at lower reaction temperatures) is highly desired. Herein, we report an unprecedented hypervalent iodine(III) catalyzed Balz–Schiemann reaction that proceeds under mild reaction conditions (Scheme 1).

Inspired by recent developments in Sandmeyer-type fluoroalkylations[11] and our own work on diphenyliodonium-catalyzed aryne fluorination,[12] we hypothesized that the fluorination of arenediazonium salts under mild conditions might be achieved through two strategies: 1) transformation of arenediazonium salts into aryl radical intermediates by single electron transfer (SET), followed by fluorine atom abstraction, and 2) activation of arenediazonium salts with an iodine(III) compound, followed by nucleophilic fluorination.

To test the first hypothesis, our initial investigation was based on Groves' report on alkyl radical fluorination,[13] employing *para*-iodotoluene difluoride (*p*-TolIF$_2$) as the fluorinating reagent. However, various initiators failed to give the desired fluorination product, and the undesired hydrogen abstraction products were formed (see the Supporting Information, Table S4.1). We assumed that *p*-TolIF$_2$ alone might not be reactive enough for fluorine atom abstraction and that acetonitrile might not be a suitable solvent for this reaction.

We then tested the second hypothesis. Based on our previous work on the fluorination of arynes,[12] we envisaged that an iodine(III) compound might be able to promote the Balz–Schiemann reaction by activation of the arenediazonium salts. We found that compound **2g** was formed in 5% yield when substrate **1g** was mixed with *p*-TolIF$_2$ and ascorbic acid [Eq. (1)]. We attributed this outcome to the activation of *p*-TolIF$_2$ by ascorbic acid; accordingly, a series of acidic phenols were screened with compound **1a**, and 2-trifluoromethylphenol (**3d**) gave the best result (Table 1, entry 5).



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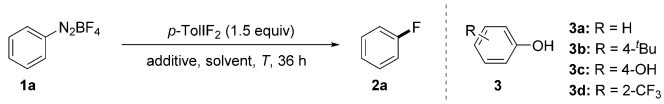
[*] B. Xing, Dr. C. Ni, Prof. Dr. J. Hu
Key Laboratory of Organofluorine Chemistry
Center for Excellence in Molecular Synthesis
Shanghai Institute of Organic Chemistry
University of Chinese Academy of Sciences
Chinese Academy of Sciences
345 Ling-Ling Road, Shanghai 200032 (China)
E-mail: jinbohu@sioc.ac.cn
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201802466.

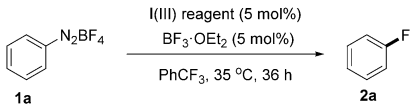
Table 1: Initial survey of reaction conditions.



Entry	Additive (equiv)	Solvent	*T* [°C]	Yield[a] [%]
1	–	DCE	RT	ND
2	**3a** (1.0)	DCE	RT	7
3	**3b** (1.0)	DCE	RT	ND
4	**3c** (1.0)	DCE	RT	ND
5	**3d** (1.0)	DCE	RT	48
6	**3d** (1.0)	DCE	RT	50
7	**3d** (1.0)	MeCN	RT	9
8	**3d** (1.0)	CH_2Cl_2	RT	68
9	**3d** (1.0)	CH_2Cl_2	30	72
10	**3d** (1.0)	CH_2Cl_2	40	74
11	**3d** (1.0)	PhCl	40	79
12	$BF_3{\cdot}OEt_2$ (1.5)	CH_2Cl_2	RT	66
13[b]	$BF_3{\cdot}OEt_2$ (0.05)	PhCl	40	84
14[b]	$BF_3{\cdot}OEt_2$ (0.05)	$PhCF_3$	35	81

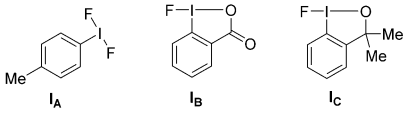
[a] Reactions conducted on 0.1 mmol scale. Yields were determined by ^{19}F NMR spectroscopy using 1-fluoronaphthalene as the internal standard. ND = not detected. [b] With only 5 mol% of *p*-$TolIF_2$.

Table 2: Screening of hypervalent iodine reagents.



Entry	Iodine(III) reagent	Yield[a] [%]
1	$\mathbf{I_A}$	81
2	$\mathbf{I_B}$	79
3	$\mathbf{I_C}$	85
4	PIFA	64
5	PIDA	74

[a] Reactions conducted on 0.1 mmol scale. Yields were determined by ^{19}F NMR analysis using 1-fluoronaphthalene as the internal standard.



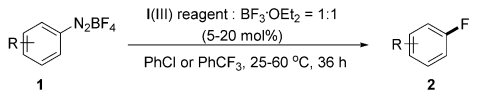
Furthermore, when **3d** was replaced by $BF_3{\cdot}OEt_2$, the reaction proceeded smoothly to give the fluorinated product **2a** in 66% yield (entry 12). When the reaction was performed in CD_2Cl_2, it was observed that most of the areneiodonium(III) species was recovered.[14] Encouraged by this result, we conducted a catalytic variant of this process by using catalytic amounts of *p*-$TolIF_2$ and $BF_3{\cdot}OEt_2$ (Table 1, entry 13; see the Supporting Information for details). Finally, when we performed the reaction in $PhCF_3$ at 35 °C, product **2a** was formed in 81% yield (Table 1, entry 14). Screening of hypervalent iodine reagents revealed that there were only subtle differences between $\mathbf{I_A}$, $\mathbf{I_B}$, and $\mathbf{I_C}$ whereas [bis(trifluoroacetoxy)iodo]benzene (PIFA) and (diacetoxyiodo)benzene (PIDA) gave the desired products in lower yields owing to the formation of the aryl esters (Table 2). Given their diverging characteristics in terms of stability and synthesis,[15–17] $\mathbf{I_A}$, $\mathbf{I_B}$, and $\mathbf{I_C}$ were applied to each substrate for further optimization.

With optimized conditions in hand, we examined the scope of this catalytic Balz–Schiemann fluorination reaction (Table 3). The reaction temperature was adjusted for each substrate (see the Supporting Information for details). To demonstrate the role of the catalyst system [**I**] (iodine(III) reagent/$BF_3{\cdot}OEt_2$), we conducted a thermogravimetric analysis (TGA) for each substrate; for comparison, a few substrates were selected for control experiments under identical conditions but without an iodine(III) catalyst (see the Supporting Information). In all cases, the addition of the hypervalent iodine compound dramatically reduced the initial decomposition temperature of **1**. Furthermore, it was found that for substrates **1** bearing electron-neutral substituents, the reaction gave the corresponding aryl fluorides (**2a**–**2d**, **2g**, **2i**, and **2j**) in good to excellent yields. Substrates containing electron-withdrawing groups, such as iodo (**1k** and **1l**), ketone (**1n**), carboxylic ester (**1o**–**1r**), carboxylic acid (**1w**), or nitrile (**1x**) moieties, gave the corresponding products (**2k**, **2l**, **2n**, **2o**–**2r**, **2w**, and **2x**) in satisfactory yields. For compounds containing electron-donating groups, the reactivity mainly depended on the position of the substituents.[18]

It is worth noting that product **2i** was isolated in 84% yield even when the reaction was carried out at room temperature. The synthetic potency of our current catalytic fluorination procedure is further supported by its good compatibility with various functional groups, such as iodo, ketone, ester, carboxylic acid, nitrile, and even sulfamide moieties. In terms of heteroaromatic substrates, fluorinated derivatives of isonicotinic acid (**1u**), vitamin B_3 (**1v**), and quinoline (**1y**) were readily prepared by this method. Moreover, to demonstrate the applicability of our method in the fluorination of more complex molecules, we successfully conducted the fluorination of derivatives of fluorene (**2ab**), flavone (**2ac**), tocopherol (**2ad**), menthol (**2ae**), androsterone (**2af**), and estrone (**2ag**). Furthermore, it was found that the reaction can be readily scaled up; the fluorination of **1f** and **1g** was successfully accomplished on gram scale, and with higher temperatures, the reaction times could be significantly decreased (see the Supporting Information). The one-pot synthesis of the aryl fluoride directly from the aniline is as effective as the two independent process (Scheme 2).

This mild and general fluorination method motivated us to gain insight into its reaction mechanism (Scheme 3). First, we performed the reaction with an intramolecular radical clock substrate, and the results do not support a radical fluorination pathway (Scheme 3a).[19] Therefore, the fluorination reaction might proceed via an aryl cation intermediate. Second, when phenyldiazodium tosylate (**7**) was subjected to this reaction, phenyl tosylate **8** was produced as the major product (45% yield), with fluorobenzene (**2a**) being formed only in 16% yield (Scheme 3b). This result suggests that the BF_4^- anion (and not *p*-$TolIF_2$) acts as the major fluorinating source (Scheme 3b). Finally, adduct **2t′** from substrate and solvent was found as a side product, suggesting that radical addition (possibly initiated by Et_2O) through a SET process is involved (Scheme 3c).[20]

Table 3: Catalytic Balz–Schiemann fluorination reaction.[a]



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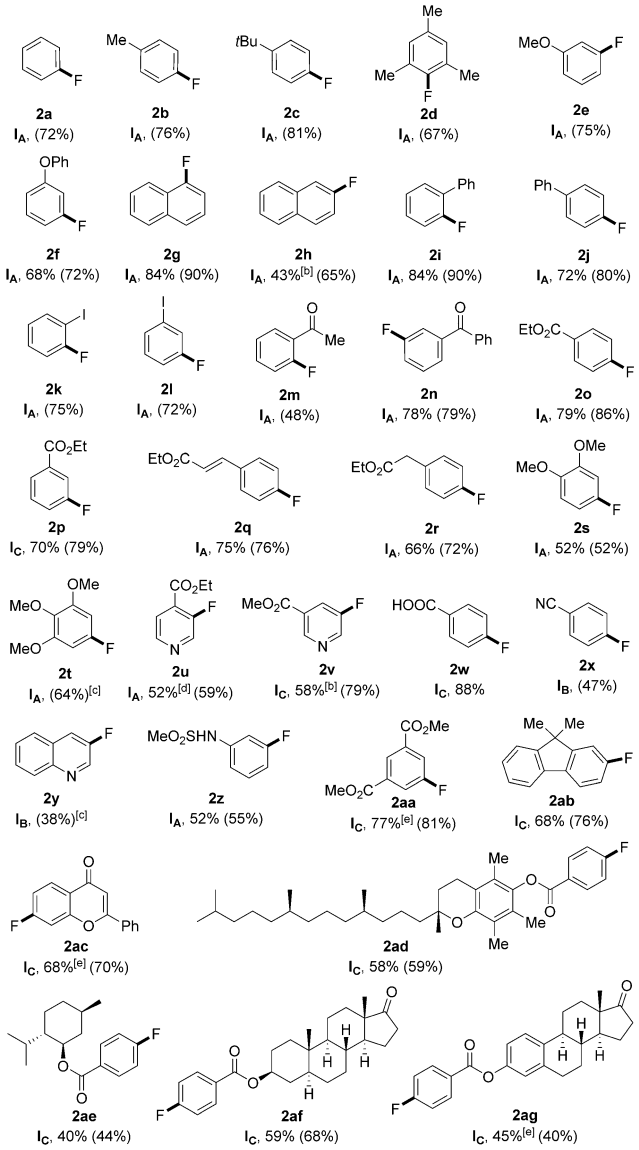
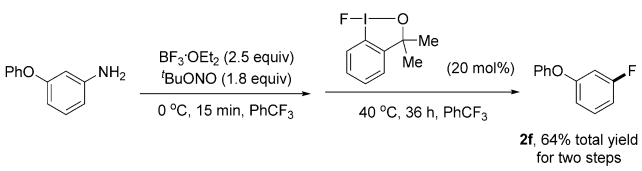
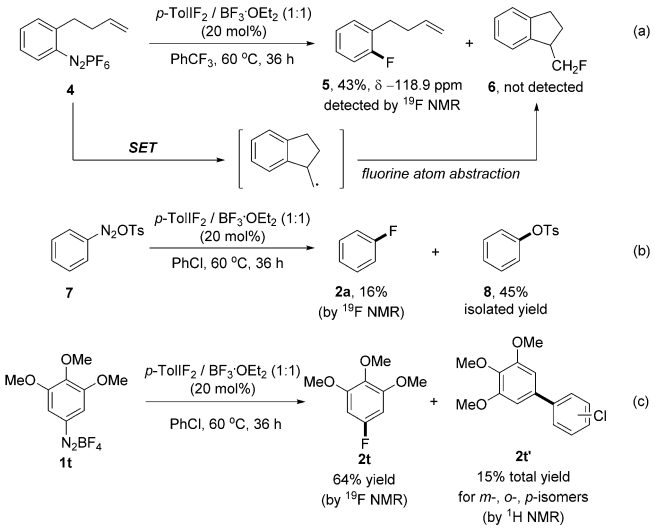


[a] All reactions were performed on 0.5 mmol scale in PhCl or $PhCF_3$ (5 mL). Yields of isolated products are given. The data in parentheses refer to yields determined by ^{19}F NMR analysis using 1-fluoronaphene as the internal standard. [b] Separation from the byproduct caused a significant loss of yield. [c] Not isolable from the byproducts. [d] 98% purity based on ^{19}F NMR spectroscopy. [e] At 80 °C.

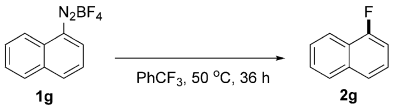


Scheme 2. One-pot Balz–Schiemann reaction.



Scheme 3. Mechanistic investigations.

We envisioned that in situ formed protons (in the form of HF or HBF_4) might also promote the fluorination reaction. Therefore, several control experiments were carried out (Scheme 4). It was found that neither addition of *p*-$TolIF_2$



conditions A: 20 mol% *p*-$TolIF_2$, no product;
conditions B: 20 mol% Et_2O, no product;
conditions C: 20 mol% Et_2O + 20 mol% *p*-$TolIF_2$, 86% yield;
conditions D: 20 mol% $Et_3N{\cdot}(HF)_3$, no product.

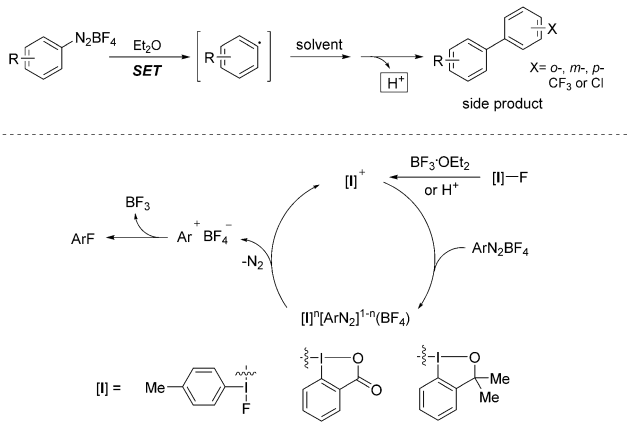
Scheme 4. Control experiments.

nor Et_2O alone catalyzed the reaction (conditions A and B). However, **2g** was obtained in good yield (86%) when 20 mol% of *p*-$TolIF_2$ was added together with Et_2O (conditions C). When 20 mol% $Et_3N{\cdot}(HF)_3$ was added as a catalyst, the fluorination product **2g** was not observed (conditions D). All of these results suggest that HF (or HBF_4) alone does not promote the fluorination reaction, but that they might be involved in the activation of *p*-$TolIF_2$ to generate the *para*-tolylfluoroiodonium species.

Kinetic monitoring of the reaction with substrate **1p** showed that the process had an induction period and proceeded with a constant rate until the end. The concentration had an influence on the length of the induction period, but barely on the rate. Furthermore, when reagent $\mathbf{I_C}$ was mixed with $BF_3{\cdot}OEt_2$ and the mixture stirred for 1.5 h, upon subsequent substrate addition, the reaction immediately set in (see the Supporting Information for details). An ^1H NMR spectrum of a mixture of compound $\mathbf{I_C}$ and $BF_3{\cdot}OEt_2$ in MeCN-d_3 indicated the formation of a new species, which is believed to be the corresponding aryliodonium species (see the Supporting Information for details).

On the basis of all of these observations, we propose that the fluorination proceeds primarily through the aryliodonium(III)-catalyzed generation of aryl cation intermediates (Scheme 5). The hypervalent iodine(III) reagent is activated by $BF_3{\cdot}OEt_2$ or in situ formed H^+ (in Table 1, phenols **3a–3d** provide the acidic proton) to give the aryliodonium(III) species,[21] which might enhance the leaving group ability of the diazo group of the arenediazonium salt to give an $Ar^+BF_4^-$ intermediate. The latter species readily gives the aryl fluoride (ArF) through intramolecular nucleophilic fluorination. Although the details of the interaction between substrate **1** and the aryliodonium(III) catalyst are not clearly understood at this stage, we found that the resonance of the aromatic proton in **1t** was shifted by + 0.04 ppm upon mixing with the aryliodonium(III) species in MeCN-d_3, while the resonance of the methoxy group underwent no obvious changes (see the Supporting Information for details). Arenediazonium salts have been reported to be stabilized by BF_4^- through coordination in the crystal,[22] and we presume that this interaction still exists to some extent when the aryldiazonium salt is partially dissolved in a non-polar or weakly polar solvent. The change in chemical shift suggests an interference of this tight ionic pair (in polar solvent, although the ionic pair is supposed to be quite loose, the solvent (e.g., MeCN, DMF, and DMSO) always acts as a ligand to stabilize the cationic species), perhaps through cation exchange from arenediazonium to aryliodonium, reducing the stabilization, and thus lower the activation barrier of the reaction. To further support the important role of the aryliodonium(III) species, we used Me_4N^+ or Bu_4N^+ in the reaction system to replace aryliodonium(III), and found that the fluorination products were formed, but in much lower yields (10–20%, see the Supporting Information for details).

In summary, we have developed an organocatalyzed Balz–Schiemann fluorination of aromatic diazonium salts. This new synthetic procedure enables the efficient preparation of a variety of structurally diverse aromatic fluorides under mild conditions, and displays potential for practical applications. Aryliodonium(III) species are able to reduce the activation energy barrier of this classical Balz–Schiemann fluorination reaction involving aromatic diazonium salts. Further investigations of this fluorination process and its detailed reaction mechanism are currently underway in our laboratory.



Scheme 5. Proposed reaction mechanism.

Acknowledgements

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Conflict of interest

The authors have filed a patent on this technology.

Keywords: aryl fluorides · Balz–Schiemann reaction · diazonium salts · fluorination · iodine

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[14] There is only a subtle difference in the chemical shifts of *p*-TolIF$_2$ and the corresponding aryliodonium(III) species, and the latter alone seems unstable in non-coordinating solvent. The resonances were compared in CD_3CN to confirm the form of the hypervalent iodine(III) compound. See the Supporting Information for more details.

[15] $\mathbf{I_A}$ and $\mathbf{I_B}$ are sensitive to moisture and glass, while $\mathbf{I_C}$ is quite stable. See the Supporting Information for details.

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