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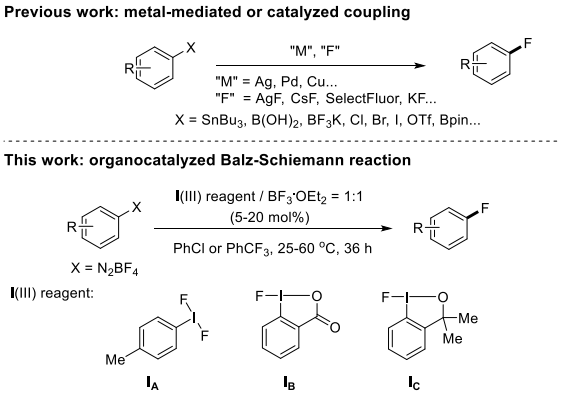
Hypervalent Iodine(III)-Catalyzed Balz-Schiemann Fluorination under Mild Conditions**

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

***Abstract**: An unprecedented hypervalent iodine(III)-catalyzed Balz-Schiemann reaction is described. The addition of hypervalent iodine compound enables the fluorination reaction to proceed under mild conditions (25-60 °C) with wide substrate scope and good functional group compatibility.*

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

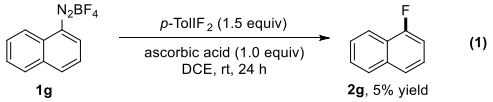


Scheme 1. Aromatic fluorinations.

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

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

To test the first hypothesis, our initial investigation was based upon Groves' report on oxidative alkyl radical fluorination,[13] employing *p*-iodotoluene difluoride (*p*-TolIF$_2$) as fluorinating reagent. However, screening of initiators failed to give the desired fluorination product, and the undesired hydrogen abstraction products were formed (See Supporting Information (SI), 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 proper solvent for this reaction.



We then turned to test the second hypothesis. Based on our previous work on fluorination of arynes,[12] we envisaged that an iodine(III) compound might be able to promote the Balz-Schiemann reaction by activation of arenediazonium salts. We found that 5% yield of compound **2g** was formed 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-trifluoromethyl phenol (**3d**) gave the best result (Table 1, entry 5). 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). Performing the reaction in CD_2Cl_2, we found that most of the areneiodonium(III) species were recovered.[14] Encouraged by this result, we fulfilled the conversion by using catalytic amount of *p*-TolIF$_2$ and $BF_3{\cdot}OEt_2$ (Table 1, entries 13-14; see SI for more details). Finally, when we performed the reaction in $PhCF_3$ at 35 °C, product **2a** was formed in 81% yield. Screening of the hypervalent iodine reagents, there was only subtle difference among $\mathbf{I_A}$, $\mathbf{I_B}$ and $\mathbf{I_C}$, while (diacetoxyiodo)benzene (PIDA) and [bis(trifluoroacetoxy-iodo)]benzene (PIFA) gave relatively moderate yields owing to the formation of phenyl esters (Table 2). Given their distinguishing characteristics on stability and synthesis,[15-17] $\mathbf{I_A}$, $\mathbf{I_B}$ and $\mathbf{I_C}$ could be applied to each substrate for further optimizations.

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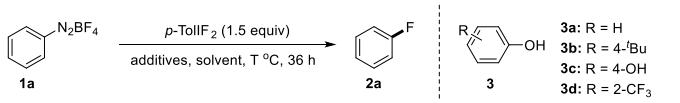
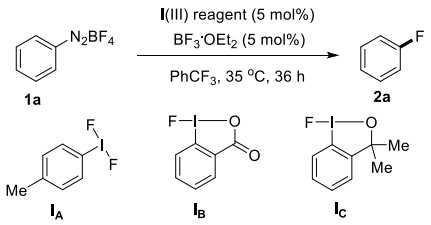
Table 1. Initial survey of reaction conditions.



Entry	Additives	Solvent	T (°C)	Yield [%][a]
1	-	DCE	RT	ND
2	**3a** (1.0 equiv)	DCE	RT	7
3	**3b** (1.0 equiv)	DCE	RT	ND
4	**3c** (1.0 equiv)	DCE	RT	ND
5	**3d** (1.0 equiv)	DCE	RT	48
6	**3d** (0.5 equiv)	DCE	RT	50
7	**3d** (0.5 equiv)	MeCN	RT	9
8	**3d** (0.5 equiv)	CH_2Cl_2	RT	68
9	**3d** (0.5 equiv)	CH_2Cl_2	30	72
10	**3d** (0.5 equiv)	CH_2Cl_2	40	74
11	**3d** (0.5 equiv)	PhCl	40	79
12	$BF_3{\cdot}OEt_2$ (1.5 equiv)	CH_2Cl_2	RT	66
13	$BF_3{\cdot}OEt_2$ (0.05 equiv)	PhCl	40	84
14	$BF_3{\cdot}OEt_2$ (0.05 equiv)	$PhCF_3$	35	81

[a] Reactions were conducted on 0.1 mmol scale. Yields were determined by ^{19}F NMR spectroscopy using 1-Fluoronaphthalene as an internal standard. ND = not detected.

Table 2. Screening of hypervalent iodine reagents.

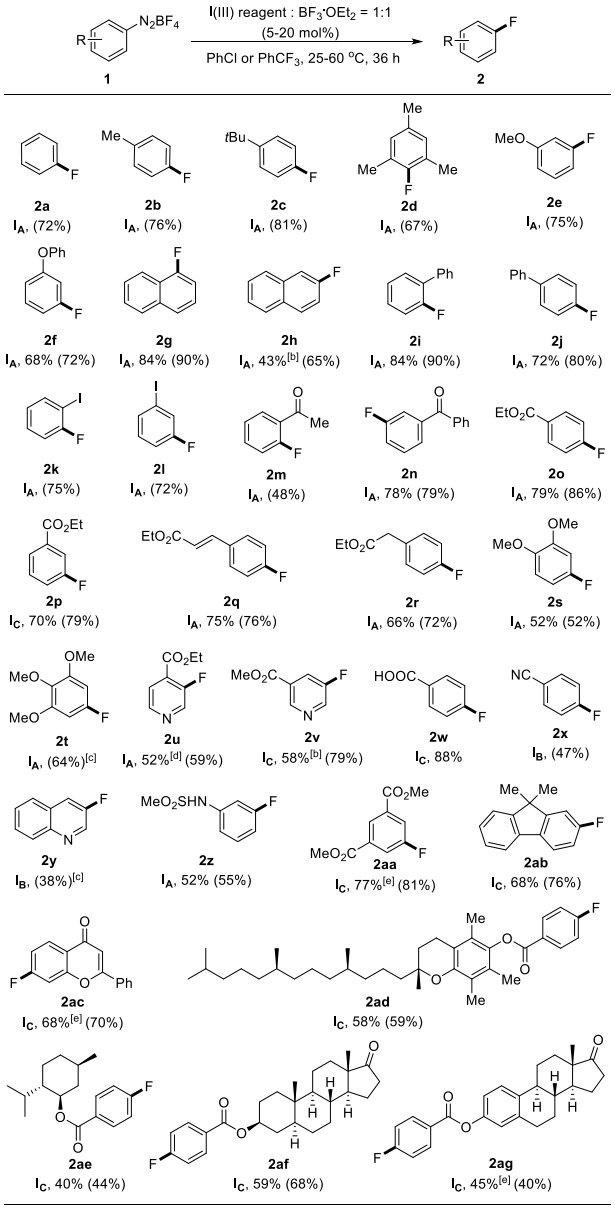


Entry	**I** (III) reagent	Yield [%][a]
1	$\mathbf{I_A}$	81
2	$\mathbf{I_B}$	79
3	$\mathbf{I_C}$	85
4	PIFA	64
5	PIDA	74

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

With the optimized conditions in hand, we examined the scope of this catalytic Balz-Schiemann fluorination reaction. The results are shown in Table 3. Some modifications of the reaction temperature on each substrate have been made (see SI for more details). To demonstrate the role of catalyst system [**I**] (iodine(III) reagent/$BF_3{\cdot}OEt_2$), a thermo gravimetric analysis (TGA) was made on each substrate; for comparison, a few substrates were selected to also perform control experiments under the conditions without iodine(III) catalyst (see SI). In all cases, the addition of the hypervalent iodine compound dramatically reduces the initial decomposition temperature of **1**. Furthermore, it was found that for substrates **1** bearing electron-neutral substituents, the reaction gave the 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**-**r**), carboxylic acid (**1w**), nitrile (**1x**) gave the corresponding products (**2k**, **2l**, **2n**, **2o**-**r**, **2w**, and **2x**) in satisfactory yields. For compounds containing electron-donating groups, the reactivity mainly depends on the position of the substituents.[18] The electron-donating substituents at *ortho*- or *para*-position, to some extent, would strengthen the C–N bond through electron resonance, thus deactivating the substrates (**1e**, **1f**, **1s** and **1t**).

Table 3. Catalytic Balz-Schiemann Fluorination Reaction.[a]



[a] All reactions were performed on 0.5 mmol scale and in a concentration of 0.1 M. Isolated yields are given. The data in parentheses are determined by ^{19}F NMR using 1-fluoronaphene as internal standard. [b] The isolation from the by-product caused significant loss of yield. [c] Not isolable from the by-products. [d] 98% purity. [e] Reaction was performed at 80 °C.

It is worth noting that product **2i** was obtained in 84% isolated yield even when the reaction was carried out at room temperature. The synthetic potency of our current catalytic fluorination protocol is further supported by its good compatibility with various functional groups such as iodo, ketone, ester, carboxylic acid, nitrile and even sulfamide. For hetereoaromatic rings, 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 fluorination of more complex molecules, we successfully accomplished the fluorination of the derivatives of fluorene (**2ab**), flavone (**2ac**), tocopherol (**2ad**), menthol (**2ae**), androsterone (**2af**) and estrone (**2ag**). Furthermore, it was found that the reaction is able to readily scale up; the fluorination of **1f** and **1g** was successfully accomplished in gram-

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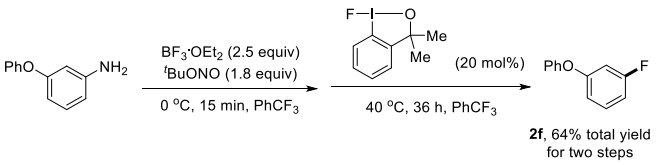
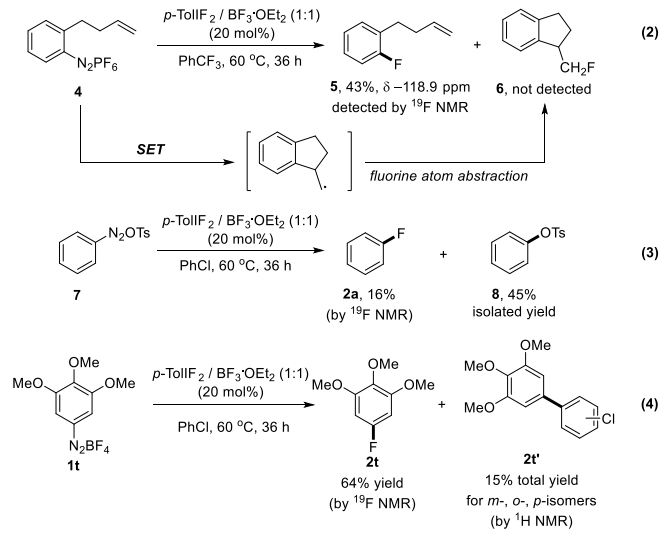
scale, and the higher temperature could sharply decreased the reaction time (see SI). In the meanwhile, one-pot synthesis from aniline to benzyl fluoride is as effective as the two independent isolated process (Scheme 2).

This mild and general fluorination protocol motivated us to gain insights into its reaction mechanism (Scheme 3). Firstly, we performed the reaction with an intramolecular radical clock, and the results do not support a radical fluorination pathway (eq 2).[19] Therefore, the fluorination reaction might proceed through an aryl cation intermediate. Secondly, 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 (eq 3). This result suggests that BF_4^- anion (not *p*-TolIF$_2$) acts as the major fluorinating source (eq 3). Finally, adduct **2t'** from substrate and solvent was found as a by-product, suggesting a radical addition (possibly initiated by Et_2O) through a SET process (eq 4).[20]

We also envisioned that the in situ-formed proton (in the forms 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$_2$ nor Et_2O alone could catalyze the reaction (eq 5, conditions A and B). However, good yield (86%) was obtained when 20 mol% of *p*-TolIF$_2$ was added together with Et_2O (eq 5, condition C). When 20 mol% $Et_3N{\cdot}(HF)_3$ was added as catalyst, no fluorination product **2g** was observed (eq 5, condition D). All these results suggest that HF (or HBF_4) alone does not promote the fluorination reaction, but they might involve in activating *p*-TolIF$_2$ to generate the *p*-tolylfluoroiodonium species.

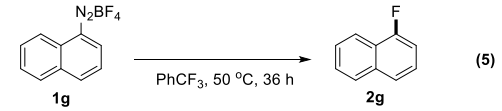


Scheme 2. One-pot Balz-Schiemann reaction process.



Scheme 3. Mechanistic investigations.

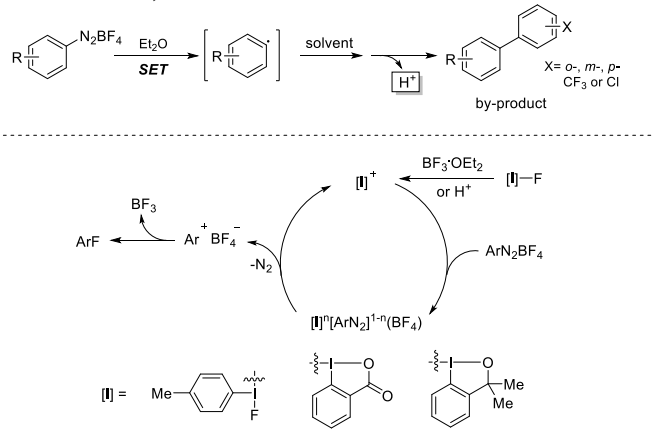
Kinetic monitoring of the reaction with substrate **1p** showed that the process had an induction period and proceeded on a constant rate till the end. The concentration influenced the time of the induction period but barely on the rate. Futhermore, when reagent **I**$_C$ was mixed with $BF_3{\cdot}OEt_2$ and stired for 1.5 h, followed by adding the substrate, the reaction immediately started over (See SI for details). ^{1}H NMR spectrum of the mixture of compound **I**$_C$ and $BF_3{\cdot}OEt_2$ in d_3-MeCN indicated a new species, which is believed to be the corresponding aryliodonium species (see SI for details).



condition A: 20 mol% *p*-TolIF$_2$, no product;
condition B: 20 mol% Et_2O, no product;
condition C: 20 mol% Et_2O + 20 mol% *p*-TolIF$_2$, 86% yield;
condition D: 20 mol% $Et_3N{\cdot}(HF)_3$, no product.

Scheme 4. Control experiments.

Combining all these observations together, we propose that the fluorination proceeds primarily via an aryliodonium(III)-catalyzed generation of aryl cation intermediates (Scheme 5). Hypervalent iodine(III) reagent is activated by $BF_3{\bullet}OEt_2$ or in situ-formed H^+ (in Table 1, phenols **3a-d** provide the acidic proton) to give the aryliodonium(III) species,[21] which might enhance the leaving ability of the diazo group of an arenediazonium salt to give $Ar^+BF_4^-$ intermediate. The latter species readily gives aryl fluoride (ArF) via intramolecular nucleophilic fluorination. Although the details of the interaction between the substrate **1** and the aryliodonium(III) catalyst are not clearly understood at this stage, we found that the chemical shift of the aromatic proton in **1t** went +0.04 ppm higher when mixing with aryliodonium(III) species in d_3-MeCN, while the signal of the methoxy had no obvious change (see SI for details). The arenediazonium salt was reported to be stablized by BF_4^- through coordination in the crystal,[22] and we presume that this interaction is supposed to still exist in some extent when aryldiazonium salt is partially dissolved in a non-polar or weakly polar solvent. The observation of 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 always acts as ligand to stablize the cation species, such as MeCN, DMF and DMSO), perhaps through cation exchange from arenediazonium to aryliodonium, reducing the stablization, thus lower the activation of the reaction. To further support the important role of the aryliodonium(III) species, we applied Me_4N^+ or Bu_4N^+ in the reaction system to replace aryliodonium(III), and found that the fluorination product was formed, but in much lower yields (10-20%, see SI for details).



Scheme 5. Proposed reaction mechanism.

In summary, we have developed a novel organocatalyzed Balz-Schiemann fluorination of aromatic diazonium salts. This new synthetic protocol enables the efficient preparation of a variety of structurally diverse aromatic fluorides under mild conditions, and displays potential value for practical applications. It is interesting to find that aryliodonium(III) is able to reduce the activation energy barrier of this classical Balz-Schiemann fluorination reaction involving aromatic diazonium salts. Further investigation of this

fluorination process (including its detailed reaction mechanism) is currently underway in our laboratory.

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Keywords: diazonium • fluorination • Balz-Schiemann • aryliodonium

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[14] There is only subtle difference in the chemical shifts between *p*-TolIF$_2$ and the corresponding aryliodonium (III), and the latter alone seems unstable in non-coordinated solvent. The signals are compared in CD_3CN to confirm the form of the hypervalent iodine(III) compound. See SI for more details.

[15] $\mathbf{I_A}$ and $\mathbf{I_B}$ are sensitive to moisture and glass, while $\mathbf{I_C}$ is quite stable. For their synthesis, see SI for details.

[16] For selected examples of application of $\mathbf{I_A}$ in synthesis, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science* **2016**, *353*, 51. (c) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000. (d) Woerly, E. M.; Banik, S. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 13858. (e) Banik, S. M.; Mennie, K. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2017**, *139*, 9152. (f) Mennie, K. M.; Banik, S. M.; Reichert, E. C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2018**, *140*, 4797. (g) Thiehoff, C.; Schifferer, L.; Daniliuc, C. G.; Santschi, N.; Gilmour, R. *J. Fluorine Chem.* **2016**, *182*, 121. (h) Sarie, J. C.; Thiehoff, C.; Mudd, R. J.; Daniliuc C. G.; Kehr, G.; Gil mour, R. *J. Org. Chem.* **2017**, *82*, 11792. (i) Molnár, I. G.; Thiehoff, C.; Holland, M. C.; Gilmour, R. *ACS Catal.* **2016**, *6*, 7167. (j) Molnár, I. G.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 5004.

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[21] For reviews, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **2008**, *108*, 5299. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **2002**, *102*, 2523.

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Layout 2:

Fluorination

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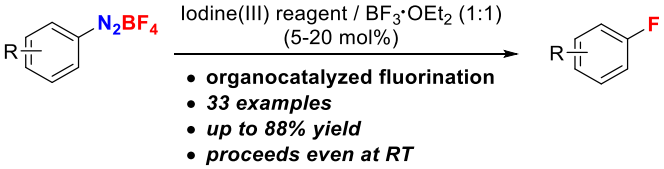
Hypervalent Iodine(III)-Catalyzed Balz-Schiemann Fluorination under Mild Conditions



Iodine helps fluorine: A novel hypervalent iodine(III)-catalyzed Balz-Schiemann fluorination reaction is described. The addition of hypervalent iodine compound enables the fluorination reaction to proceed under mild conditions (25-60 °C) with wide substrate scope and good functional group compatibility.