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A general method for one-step synthesis of monofluoroiodane(III) reagents using silver difluoride

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ABSTRACT

Herein we report a new general method for one-step synthesis of four kinds of fluoroiodane(III) reagents by treating the corresponding aryl iodides with silver difluoride (AgF_2). This is the first method applicable for the synthesis of all four fluoroiodane(III) reagents including *p*-iodotoluene difluoride (**1**), fluoro-benziodoxole (**2**), fluoro-benziodoxolone (**3**), and fluoro-*N*-acetylbenziodazole (**4**). AgF_2 was firstly employed in the direct oxidative fluorination of iodobenzene and thus has shown its outstanding oxidation and fluorine-transfer ability. The use of AgF_2 has improved the synthesis of fluoroiodane(III) reagents by shortening the reaction steps, avoiding the use of hazardous reagents, and simplifying the experimental operations. It was worth noting that we have developed the first one-step direct synthetic method for **3**, while **3** can only be synthesized through Cl→F ligand exchange reaction previously.

Fluorine-containing organic compounds play increasingly important roles in pharmaceutical and agrochemical industry. Among the newly marketed pharmaceuticals every year, the proportion of fluoro-pharmaceuticals increased rapidly, which reached 50% in 2018 and 43% in 2019 [1]. In agrochemical field, it is striking that fluoro-agrochemicals have accounted for 53% of all successful agrochemicals [2]. Consequently, developing different methods for the introduction of fluorine atoms into organic molecules is of great significance. The growing demand of fluorination methods promoted the rapid development of fluorine-containing reagents, which are essential tools to introduce fluorine atoms. Among diverse reagents, hypervalent iodine(III) monofluorine-transfer reagents are becoming popular in recent years.

With the booming development of hypervalent iodine(III) reagents as multipurpose functional-group-transfer reagents [3–10], ones containing I-F bond, including *p*-iodotoluene difluoride (p-TolIF$_2$) (**1**), fluorobenziodoxole (**2**), fluorobenziodoxolone (**3**) and fluoro-*N*-acetylbenziodazole (**4**) (Fig. 1), have received widespread attention in fluorine chemistry. They act as both a potent oxidant and a fluorine source in fluorination reactions. Various fluorination reactions achieved by reagents **1** and **2** have been reported, including α-fluorination of carbonyl compounds [11], fluorinative rearrangements of styrenes and related compounds [12–14], ring-opening 1,3-difluorination of cyclopropane [15] and oxyfluorination of diazocarbonyl compounds [16,17], various cyclization fluorination reactions [18–21], Balz–Schiemann fluorination [22]; it is worth noting that the rearrangement fluorinated products from some reactions mediated by **2** cannot be generated by N-F reagents [20,21], which demonstrates the unique reactivity of fluoroiodane(III) reagents. **4** is the first monofluorine-transfer hypervalent iodine(III) reagent containing an I-N five-membered heterocycle, which was developed by our group in 2021. **4** cannot only achieve intramolecular ring expansion fluorination of unactivated cyclopropanes, but also realize a series of known fluorination reactions [23].

Because of the versatility of fluoroiodane(III) reagents in fluorination reactions, it is of great significance to develop a simple and effective method to synthesize these reagents. Existing methods for their synthesis can be divided into two categories: ligand exchange reactions and one-step oxidative fluorination reactions (Scheme 1). Ligand exchange reactions are the most commonly used methods to synthesize reagents **1**, **2** and **3** (Scheme 1a), which including: (1) **1** can be afforded through the ligand exchange reaction of *p*-iodosyltoluene and aqueous HF [24,25] or the reaction of *p*-iodotoluene dichloride (p-TolICl$_2$) and aqueous HF in the presence of HgO [26]; Togni *et al.* developed the TCICA/KF (spray-dried) system and applied it to the synthesis of iodane(III) difluorides in one pot in 2019 [27]; (2) **2** was often synthesized through Cl→F ligand exchange reactions [28]; ligand exchange reactions of OH→F, OTs→F, and $OCOCF_3$→F are also efficient ways reported by Stu-

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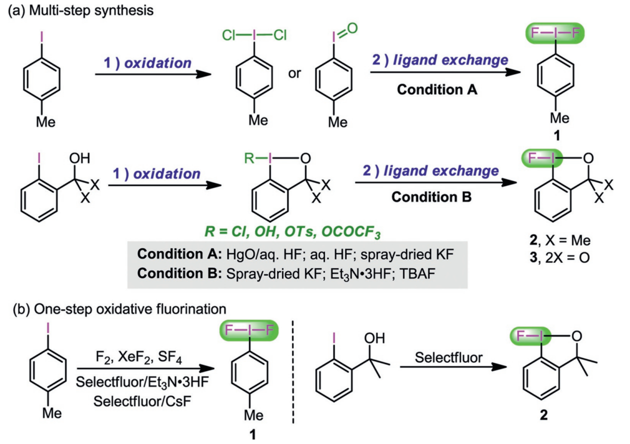


Scheme 1. (a) Examples of multi-step synthesis of monofluoroiodane(III) reagents. (b) Examples of one-step synthesis of monofluoroiodane(III) reagents.

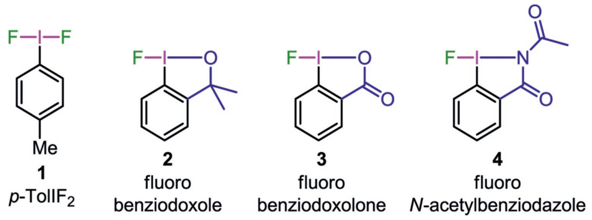
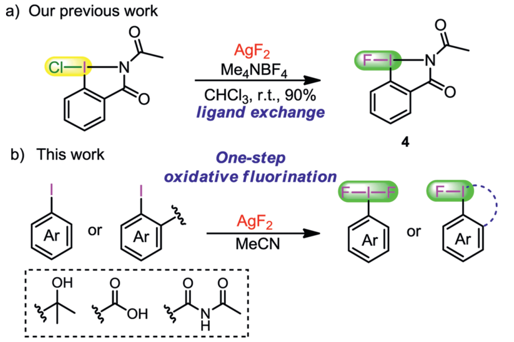


Fig. 1. Monofluoroiodane(III) reagents containing I-F bond.

art *et al.* [29]; (3) **3** was synthesized firstly by Biber and Togni *et al.* through the reaction of its chloride precursor and spray-dried KF in 2016 [30]. Although ligand exchange is the most commonly used method for the synthesis of these reagents, they are usually accomplished by multi-step synthesis, that is, *p*-iodosyltoluene, *p*-TolICl$_2$, and cyclic iodane(III) precursors all need to be prepared in advance, and then ligand exchange is carried out with various organic or inorganic nucleophilic fluorine sources; but in most cases, HF together with ligand trapping additives, like the harmful HgO, are employed to remove the Cl ion. It is well known that aqueous HF is highly corrosive and HgO is highly toxic. As a common inorganic nucleophilic fluorine source in Cl→F ligand exchange reactions, KF absorbs moisture easily during use, which requires that the reactions must be carried out under strictly anhydrous and air-free conditions.

Reagents **1** and **2** can also be synthesized through one-step protocol (Scheme 1b). Fluorinating reagents with strong oxidative ability including F_2 [31,32], SF_4 [33] and XeF_2 [32,34] can directly oxidize *p*-iodotoluene to **1**. However, F_2 and SF_4 are hazardous and highly toxic gasses at room temperature, causing experimental operations difficult in most laboratories. Direct electrosynthesis of **1** can be accomplished by anodic oxidation in the presence of $Et_3N{\cdot}3HF$ or $Et_3N{\cdot}5HF$ [35,36]. Shreeve *et al.* [37] and Gilmour *et al.* [38] developed two systems of Selectfluor/$Et_3N{\cdot}3HF$ and Selectfluor/CsF for one-step synthesis of **1**. Prévost *et al.* reported that **2** can be directly synthesized by treating 2-(2-iodophenyl)propan-2-ol with Selectfluor [39]. Unlike **1** and **2**, the one-step method for **3** has not been developed, to the best of our knowledge. Although previous methods work well, there is not a direct general reagent for the oxidation of aryl iodides to the corresponding hypervalent iodine(III) monofluorine-transfer reagents of **1**, **2**, and **3**. To synthesize these reagents more conveniently and efficiently, the development of a general one-step method is thus highly desirable.

Silver difluoride (AgF_2), a commercially available fluorinating reagent with strong oxidation ability, has been used in few fluorination reactions. For example, Hartwig *et al.* applied it to the direct C-H fluorination of pyridines and diazines with exclusive site-selectivity [40]. AgF_2 could also react with an excess of benzene in refluxing hexane to afford fluorobenzene [41]. Recently, Tang *et al.* developed the ortho selective C-H trifluoromethoxylation of pyridine mediated by AgF_2 [42]. In addition, AgF_2 can also act as a fluorine source in Cl→F ligand exchange reaction to synthesize fluoro-*N*-acetylbenziodazole (**4**) in high yield done by our group (Scheme 2a) [23]. It is worth noting that AgF_2 (+1.98 V) [43] has stronger oxidation potential than Selectfluor (+0.33 V) [44]. Therefore we speculated that AgF_2 would directly achieve the oxidative fluorination of the iodine center of aryl iodides, thereby providing a general method for the synthesis of fluoroiodane(III) reagents (Scheme 2b).



Scheme 2. (a) Ligand exchange reaction of Cl→F mediated by AgF_2. (b) One-step oxidative fluorination of aryl iodides.

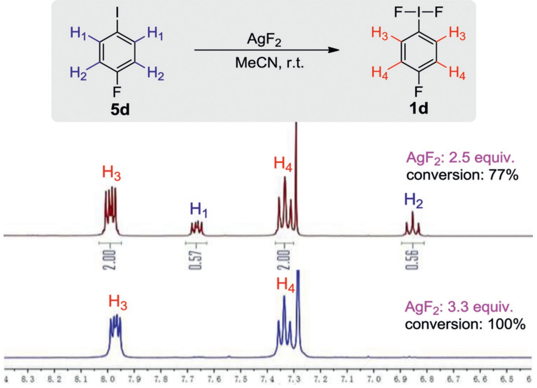
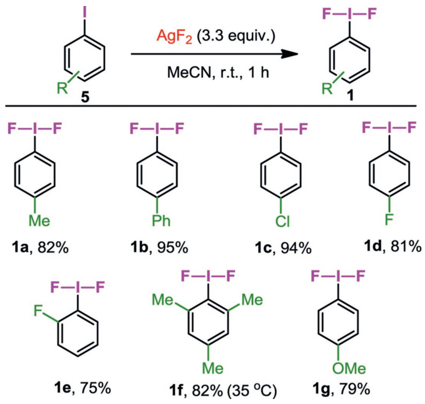


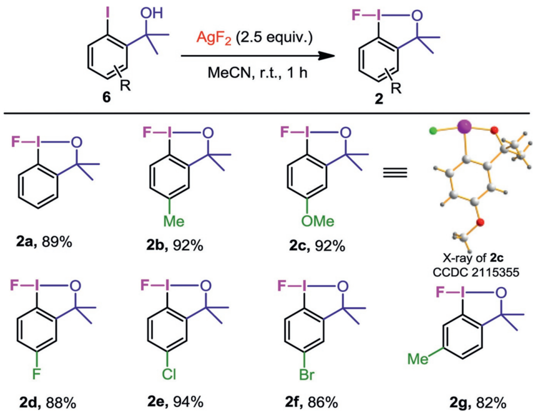
Fig. 2. ^{1}H NMR ($CDCl_3$, 400 MHz) spectroscopy of the reaction mixture of **5d**.

We began our preliminary investigation by trying to synthesize iodane(III) difluorides. 4-Fluoroiodobenzene (**5d**) was allowed to react with 2.5 equiv. of AgF_2 in anhydrous acetonitrile at room temperature. We monitored the reaction through the ^{1}H NMR spectroscopy of the reaction mixture, and pleasantly observed two new signals other than **5d** (Fig. 2). However, only 77% of the raw material was converted, and prolonging the reaction time was ineffective. Therefore, we increased the amount of AgF_2 to 3.3 equiv. and found that **5d** was converted completely after 1 h. The proton spectrum of the reaction mixture is quite clean in which no byproduct was observed. By referring to the ^{1}H NMR data of **1d** reported previously [45], we concluded that H_3 and H_4 belong to **1d**. After simple purification, we obtained the desired fluoroiodane(III) product **1d** in 81% yield.

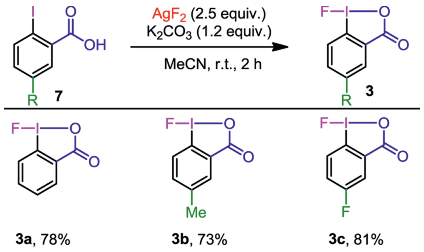
Subsequently, a series of iodane(III) difluorides **1a**-**1g** containing various substituents were synthesized by this method (Scheme 3). In the presence of 3.3 equiv. of AgF_2, *p*-TolIF$_2$ could be obtained in 82% yield within 1 h. The reaction of various aryl iodides bearing electron-withdrawing groups including phenyl (**5b**), chlorine (**5c**)



Scheme 3. One-step synthesis of iodane(III) difluorides. Reaction conditions: Aryl iodide substrate **5** (1.0 mmol), AgF$_2$ (3.3 mmol), 10 mL of anhydrous MeCN, r.t., 1 h, Ar atmosphere. Yields are for the isolated products.



Scheme 4. One-step synthesis of fluoro-benziodoxole. Reaction conditions: Aryl iodide substrate (1.0 mmol), AgF$_2$ (2.5 mmol), anhydrous MeCN (10 mL), r.t., 1 h, Ar atmosphere. Yields are for the isolated products.



Scheme 5. One-step synthesis of fluoro-benziodoxolone. Reaction conditions: Aryl iodide substrate (1.0 mmol), K$_2$CO$_3$ (1.2 mmol), AgF$_2$ (2.5 mmol), anhydrous MeCN (10 mL), r.t., 2 h, Ar atmosphere. Yields are for the isolated products.

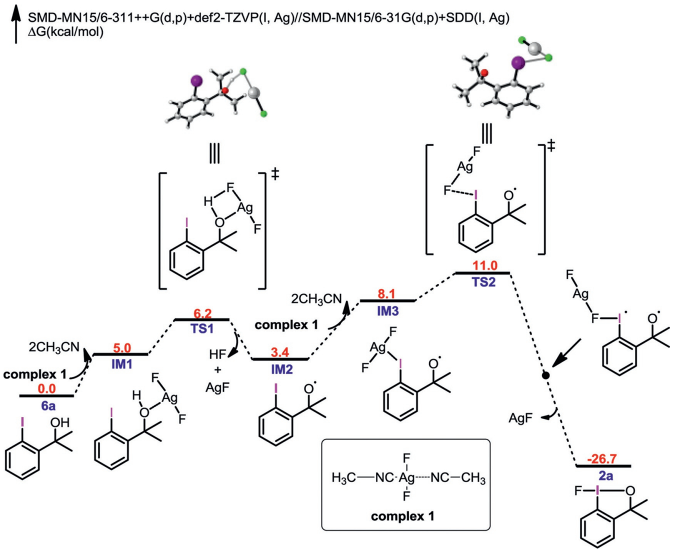
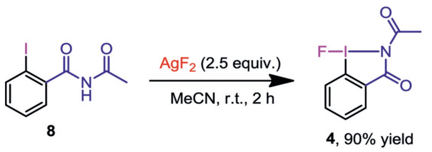


Fig. 3. DFT-computed potential energy profile for the reaction between AgF$_2$ and **6a** (Standard state: 25 °C, 1 mol/L).

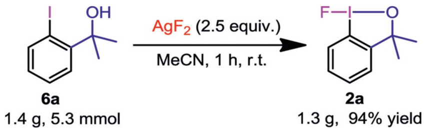
and fluorine (**5d**) atoms proceeded smoothly, affording their corresponding iodane(III) difluorides **1b**-**1d** in 81%–95% yield within 1 h. *ortho*-Fluoroiodobenzene (**5e**) and 2,4,6-trimethyliodobenzene (**5f**) could generate the corresponding desired products in good yields. Under the same condition, **1g** was obtained in 79% yield. However, the stability of **1g** is not as good as **1a**-**1f** under ambient temperature, so we suggest that **1g** should be stored in the freezer after work-up as soon as possible.

Encouraged by the exceptional performance of AgF$_2$ in the synthesis of iodane(III) difluorides, we turned our attention toward the application of AgF$_2$ in the one-step synthesis of cyclic fluoro-benziodoxole (**2**) (Scheme 4). By monitoring the reaction in the same way, we found that 2.5 equiv. of AgF$_2$ was enough to make **6** react completely within 1 h (see Supporting information for details). Under this simple condition, **2a** was obtained in 89% yield. Electron-donating substituents on the *para*-position of the iodine (methyl **6b** and methoxy **6c**) did not affect the reaction, the corresponding desired products **2b** and **2c** were obtained in 92% yield respectively. The structure of **2c** was unambiguously confirmed by X-ray crystallography. A single crystal of **2c** was grown in chloroform/*n*-hexane at room temperature, and X-ray crystallographic analysis of **2c** showed that the F—I—O bond angle was 166° and the length of I-F bond was 2.0988 Å. Aryl iodides with electron-withdrawing substituents on the *para*-position of the iodine (fluoro **6d**, chloro **6e**, bromo **6f**) could also react smoothly, providing the desired products **2d**, **2e** and **2f** in excellent yields. Significantly, reagents **2b**-**2f** all have good stability and can be stored in the refrigerator for at least 3 months. **2g** bearing a methyl group on the *meta*-position, was obtained in 82% yield, but slight decomposition of it was observed after work-up.

Fluoro-benziodoxolone (**3**), another important fluoroiodane(III) reagent, can only be prepared by the multi-step synthesis involving Cl→F ligand exchange reaction. Therefore, we are interested in exploring the one-step synthesis of **3** by AgF$_2$. Initially, the reaction of 2-iodobenzoic (**7a**) and AgF$_2$ in d_3-MeCN was performed and monitored by means of ^{1}H NMR spectroscopy. After 1 h, an aromatic main product can be observed on the spectrum (see Supporting information for details). According to the ^{1}H NMR data of **3a** reported previously, there is no doubt that the new compound is our desired product. However, **3a** was easy to decompose in the course of separation and purification. We speculated that HF, as a by-product of AgF$_2$ oxidative fluorination reaction of **7a**, was very likely to form a hydrogen bond with the fluorine atom in **3a**, thus activating **3a** and making it easy to decompose [46–48]. To verify our speculation, we added K$_2$CO$_3$ (1.2 equiv.) to the reaction and the desired product **3a** was isolated successfully as a white solid in a 78% yield without decomposition (Scheme 5). Replacing K$_2$CO$_3$ with *N*,*N*-diisopropylethylamine gave inferior result. Consequently, we decided to add K$_2$CO$_3$ as an additive to the reaction system. 5-Methyl-and 5-fluoro-2-iodobenzoic acid (**7b** and **7c**) also reacted smoothly and afforded the corresponding **3b**, **3c** in 73% and 81% yield successfully. Compared with the ligand exchange reaction mediated by spray-dried KF, our one-step protocol does not require a glove box during the reaction, which is convenient for researchers.



Scheme 6. One-step synthesis of **4**.



Scheme 7. Large-scale synthesis of **2a**.

We finally tried to synthesize fluoro-*N*-acetylbenziodazole (**4**) in one step. By treating *N*-acetyl-2-iodobenzamide (**8**) with 2.5 equivalent of AgF$_2$, we obtained **4** as a white solid in 90% yield (Scheme 6). **4** is a new hypervalent iodane(III) monofluorine-transfer reagent containing a I-N five-membered heterocycle. The unique *N*-acetylbenziodazole skeleton would give it unique reactivity, and we have applied it to the intramolecular ring expansion fluorination of unactivated cyclopropanes [23].

To elucidate the mechanism of the direct oxidative fluorination of **6a** by AgF$_2$, we performed DFT calculation (Fig. 3). We thought this reaction would feature a bimolecular radical oxidation pathway. Initially, AgF$_2$ forms a stable complex **1** with two acetonitrile molecules. The reaction starts with **IM1**, which is a stable complex generated from **6a** and AgF$_2$ by coordination interaction. Subsequently, a concerted hydrogen-atom abstraction process occurs with a barrier of 6.2 kcal/mol, yielding the HF, AgF and **IM2**. Next, the fluorination process mediated by the second equivalent of AgF$_2$ would form **2a**. The Gibbs free energy profile of the overall reaction pathway indicates that the fluorination process of iodine is the rate-limiting step, with an activation energy of 11.0 kcal/mol. The overall reaction pathway explains the use of excess equivalent of AgF$_2$ and the mild reaction conditions. In addition, this mechanism also provides a mechanism clue for the synthesis of other fluoroiodane(III) reagents by AgF$_2$.

We also performed a large-scale synthesis of **2a**. When the reaction was scaled up to 5.3 mmol of **6a**, the yield and reaction time were not affected at all (Scheme 7).

In conclusion, we have developed a general one-step method for rapid and efficient synthesis of the hypervalent iodane(III) monofluorine-transfer reagents from their corresponding aryl iodides by means of AgF$_2$. Through this oxidative fluorination method, all four kinds of fluoroiodane(III) reagents are obtained. This method has the advantages of simple operation, high yield, step economy, and no use of harmful reagents. Noteworthy, we have developed the first one-step method for the synthesis of **3**, and **3** can only be synthesized through Cl→F ligand exchange reaction previously. The convenient and rapid synthesis of monofluoroiodane(III) reagents would lay foundation for their widespread applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.01.070.

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