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Fluorinative ring-opening of cyclopropanes by hypervalent iodine reagents. An efficient method for 1,3-oxyfluorination and 1,3-difluorination†

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A new method is presented for 1,3-difluorination and 1,3-oxyfluorination reactions. The process is based on iodonium mediated opening of 1,1-disubstituted cyclopropanes. The reaction proceeds with high chemo-and regioselectivity under mild reaction conditions typically at room temperature in a couple of hours. The reaction probably occurs *via* electrophilic ring-opening of cyclopropanes.

Fluorinated organic compounds have found broad application in the pharmaceutical,¹ and agrochemical industries² as well as in medical diagnostics.³ The impetus for the application of organofluorine compounds in agrochemical and pharmaceutical products is their beneficial pharmacokinetic properties, such as high metabolic stability and lipophilicity.¹a⁻⁻⁻⁻⁻⁻⁻ The useful radionuclear properties of the unnatural isotope ¹8F makes ¹8F labelled organofluoro compounds indispensable for positron emission tomography (PET).³a⁻ The short half-life of ¹8F requires development of a rapid late stage introduction of the fluorine atom,³ which is a challenging task in synthetic organic chemistry.⁴ In the last decade, many new fluorinating reagents have appeared, which in combination of catalysts allowed development of new selective methodologies to access a broad variety of bioactive organofluorines.⁴a⁻₊5

The most efficient methods are even suitable for fluorination based difunctionalization reactions.5b-d The most studied approach involves vicinal difunctionalization reactions, such as 1,2-oxyfluorination,6 1,2-aminofluorination,6a,7 1,2-carbofluorination64,8 and related methods.9 Recently a number of interesting geminal fluorination methods were also reported, such as 1,1-difluorination,10 1,1-oxyfluorination11 and 1,1-aminofluorination.12 The 1,2-difunctionalization methods are usually based on alkene substrates, while the 1,1-difunctionalizations are often realized using diazo compounds, as substrates. However, the analogue methodology is much less developed for 1,3-difunctionalization based fluorination methods. Considering the typical synthetic methodologies for 1,3-difunctionalization reactions, 13 a related fluorination reaction can probably be achieved by ring opening of cyclopropane substrates. Recently, we have shown that hypervalent iodine based¹⁴ benziodoxol(on) derivatives are excellent reagents for

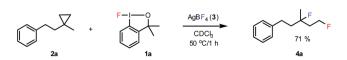
concept driven fluorine chemistry program, we sought to employ fluoro-benziodoxol reagent **1a** for a fluorinative ring opening of cyclopropane derivatives. To our delight, **1a** reacted smoothly with cyclopropane derivative **2a** in the presence of AgBF₄ affording **1**,3-difluoro substituted compound **4a** with 71% yield (Scheme 1).

As we employed **1a** and **2a** in equimolecular ratio in this reaction, one of the fluorine atoms originated from **1a**, while the other one is from the BF₄ counter ion of the Ag-mediator. We

1,1- and 1,2-difunctionalization for synthesis of organic trifluoromethyl and fluoro compounds. 64,94,104,11,15 As a part of our

As we employed **1a** and **2a** in equimolecular ratio in this reaction, one of the fluorine atoms originated from **1a**, while the other one is from the BF₄⁻ counter ion of the Ag-mediator. We have previously reported^{10a} a similar 1,1-difluorination method of styrenes. Although, several chlorination and bromination methods of cyclopropane are reported in the literature,¹⁶ synthetically useful cyclopropane opening is a very unusual methodology for fluorination reactions. As far as we know the above process is the first 1,3-difluorination reaction. In addition, we have found only a single fluorination based 1,3-difunctionalization reaction in the literature. Very recently, Lectka and co-workers¹⁷ reported an aminofluorination method based on cyclopropane substrates.

As mentioned above the 1,3-difluorination of cyclopropane 2a could be carried out selectively and in high yield using 1a and a stoichiometric amount of AgBF₄ (Table 1, entry 1) in CDCl₃. We used CDCl₃ as the solvent to directly monitor the possible formation of the volatile fluorinated (and other) by-products in the reactions. Replacing AgBF₄ with AgPF₆ as a secondary fluorine source led to formation of 4a, but the yield dropped to 34% (entry 2). Cu(MeCN)₄BF₄ can also be used instead of AgBF₄.



Scheme 1 1,3-Difluorination of 2a.

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Table 1 Variation of the reaction conditions for 1,3-difluorination of cyclopropane 2a

| Entry | Deviation from the standard conditions ^a | Yield 4a (%) | |
|-------|---|---------------------|--|
| 1 | 1 equiv. of 3 | 71 | |
| 2 | 1 equiv. AgPF ₆ instead of 3 | 34 | |
| 3 | 1 equiv. Cu(MeCN) ₄ BF ₄ instead of 3 | 30 | |
| 4 | 1 equiv. AgF or $Zn(BF_4)_2 \times H_2O$ instead of 3 | <5 | |
| 5 | 1 equiv. AgCN or AgTFA instead of 3 | 0 | |
| 6 | 30 mol% of 3 | 9 | |
| 7 | 30 mol% AgPF ₆ or Pd(BF ₄) ₂ (MeCN) ₄ instead of 3 | <5 | |
| 8 | 30 mol% Cu(MeCN) ₄ BF ₄ instead of 3 | 15 | |
| 9 | 30 mol% 3 and 1 equiv. NaBF ₄ | <5 | |
| 10 | 30 mol% 3 and 1 equiv. KF | 0 | |
| 11 | Without 3 or 1a | 0 | |
| 12 | 1 equiv. Selectfluor or NFSI instead of 1a | 0 | |
| 13 | Without 3, 1 equiv. of Tol-IF ₂ instead of 1a | 24 | |
| 14 | DCM instead of CDCl ₃ | 10 | |
| 15 | MeCN or MeOH instead of CDCl ₃ | 0 | |

^a Reagent 1a (0.1 mmol) cyclopropane 2a (0.1 mmol) and $AgBF_4$ (3) (0.1 mmol) were mixed in $CDCl_3$ (0.5 ml). This mixture was stirred at 50 °C for 1 h.

The yield was lowered indicating that silver is a better mediator than copper for this transformation (entry 3). However, simple silver sources such as AgF showed to be inactive in 1,3difluorination reaction (entry 4). Zinc salts have proved to be efficient activators of benziodoxole reagents. 6a,18 Therefore, we attempted to replace AgBF₄ with Zn(BF₄)₂ but the corresponding reaction did not result 4a (entry 4). Other silver salts without transferable fluoride in the counter ion, such as AgCN or AgTFA, did not show any activity (entry 5). When a sub-stoichiometric amount (30 mol%) of Ag-salt was used, the yields sharply decreased (entries 6-7). Pd(BF₄)₂(MeCN)₄ (30 mol%) was also inefficient as catalyst (entry 7). Interestingly, Cu(MeCN)₂BF₄ showed some catalytic activity but the yield was very low (entry 8). Only traces of product 4a (<5%) could be obtained with 30 mol% of AgBF₄ and stoichiometric amount of NaBF₄ (entry 9). The reaction was completely shut down when KF was employed instead of NaBF₄ (entry 10). This indicates that the most efficient secondary fluorine source is AgBF₄. We could not observe any reaction without application of AgBF4 or 1a (entry 11).

Neither Selectfluor nor NFSI could replace fluoroiodoxol **1a** as the electrophilic fluorination reagent (entry 12). When benziodoxole based **1a** was replaced by 4-iodotoluene difluoride (Tol-IF₂), a related hypervalent iodine reagent, ^{14a} product **4a** did not form at all. Unlike **1a**, Tol-IF₂ underwent rapid decomposition in the presence of AgBF₄. When the reaction was performed in the absence of AgBF₄ (3) with Tol-IF₂ a complex reaction mixture was obtained, from which compound **4a** could be isolated in 24% yield (entry 13). In general, we found Tol-IF₂ much less bench-stable than **1a** and more prone to providing complex product mixtures.

A brief solvent screen has shown that dichloromethane is a less suitable solvent providing the product in 10% yield (entry 14). However formation of product **4a** was not observed when chloroform was replaced by acetonitrile or methanol (entry 15). Subsequently, we investigated the synthetic scope of the silver mediated 1,3-difluorination reaction (Table 2). We found that several substrates required longer reaction times for full conversion relative to **2a** (Table 2, entry 1). Under an elongated reaction time **1a** underwent partial decomposition (see below). Therefore, in most reactions we employed two equivalents of **1a** to obtain a full conversion of **2** and, thus optimal yields of **4**. Aliphatic substrate **2b** reacted for 4 h at room temperature affording **4b**. Dialkyl cyclopropanes such as, 1,1-dibutyl cyclopropane **2c** also reacted affording **4c** (entry 3). In this case the

| Table 2 | Silver mediated 1,3 | -difluc | prination with 1^a | |
|---------|---------------------|----------|----------------------|---------------------------|
| Entry | Substrate | t (h) | Product | Yield ^b (%) |
| 1 | 2a ^{c, d} | 1 | F 4a | 71 (67%) ^e |
| 2 | 2b | 4 | F | 70 |
| 3 | | 4 | F F 4c | 51 |
| 4 | 2d | 2 | F F 4d | 47 |
| 5 | 2e ° | 6 | F F | 59 |
| 6 | Ph 2f | 1 | Ph F | 55 |
| 7 | 2g | 3 | F 4g | 65 |
| 8 | Br 2h | 24 | Br 4h | 57 |
| 9 | | 24 | F _F | 70 |
| 10 | \bigcup_{2j} | 24 | F F | 66 |

 $[^]a$ Unless otherwise stated, substrate 2 (0.1 mmol), **1a** (0.2 mmol) and AgBF₄ (3) (0.1 mmol) in CDCl₃ (0.5 ml) were stirred at room temperature. b Isolated yields. c (0.1 mmol) of **1a** was used. d The reaction was performed at 50 °C. e The reaction was performed in 0.5 mmol scale.

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yield was lower than for difluorination of 2b indicating that the reaction is fairly sensitive to the steric factors of the cyclopropane substituents. We have studied the reactivity of aryl substituted cyclopropanes as well. 1,1-Dipenyl cyclopropane 2d is a particularly challenging substrate. It is sterically hindered and the fluorine expected to enter to a dibenzylic position. We found that 2d reacted relatively quickly (2 hours) with 1a resulting in 4d (entry 4) in 47% yield. As expected 4d had a limited stability, which could explain the relatively low yield. A possible reason for the poor stability is the easy dissociation of the fluoride from the dibenzylic position. When one of the phenyl groups in 2d was changed to a methyl group, 2e, the reaction required a longer reaction time (6 hours), however the yield of the corresponding product 4e was higher, 59% (entry 5). Product 4e was also more stable than 4d probably because of the stronger quaternary C-F bond. In the presence of electron donating group in the para position of the aromatic substituent, 2f, we obtained a fast fluorination reaction (only 1 hour at room temperature) affording 4f in 55% yield (entry 6). Apparently electron donating groups accelerate the reaction. Naphthyl substituted substrate 2g also reacted smoothly to give 4g in 65% yield (entry 7). The rate of the reaction was much slower in the presence of an electron withdrawing group (e.g. 2h) than for electron donating group (e.g. 2f) in the para position of the aryl substituent. Thus, para-bromo substituted 2h had to be reacted

24 hours to provide 4h (entry 8), while the reaction of para phenyl substituted substrate 2f was compete in 1 hour (entry 6). Similarly to the aliphatic substrates (e.g. 2c) the difluorination reaction can be carried out for longer homologues of the methyl substituents. For example 2i-i reacted with high yields affording difluorinated products 4i-j (entries 9-10). The presented 1,3-difluorination method can be easily scaled up by five times without significant change in yield (entry 1).

Table 2 shows that the above reaction is suitable for the synthesis of quaternary 1,3-difluoro compounds 4a-i from 1,1disubstituted cyclopropanes 2a-j. However, when we attempted to react 1,2-disubstituted cyclopropanes, we obtained very complex, inseparable mixtures with several fluorinated products. The observation that this reaction proceeds faster in the presence of electron donating and/or aryl substituents on the cyclopropane moiety suggests an electrophilic fluorinative cyclopropane opening mechanism. As mentioned above (Scheme 1, Table 1) the overall reaction can be regarded as a formal introduction of an F2 molecule into the cyclopropane substrates. The electrophilic fluorine atom (formally F⁺) supposedly comes from reagent 1a, while the nucleophilic fluorine atom (formally F⁻) from the BF₄⁻ counter ion.¹⁹ Considering this hypothesis, we attempted to introduce fluorine and a different functionality to cyclopropanes applying this concept.

Table 3 Silver mediated 1,3-oxyfluorination^a

| Entry | Substrate | Hypervalent iodine | t (h) | Product | Yield ^b (%) |
|-------|-----------|---------------------|--------|-------------|------------------------|
| 1 | 2a | AcO-I-O 1b° | 4 | 5a OAc | 84 |
| 2 | 2b | 1b | 2 | F OAc | 50 |
| 3 | 2f | 1b | 2 | Ph 5c OAc | 51 |
| 4 | 2a | AcO-I-OAc | 20 min | 5a | 84 |
| 5 | 2a | PhOCO-I-OCOPh 1d | 20 min | F OCOPh | 80 |
| 6 | 2a | $\mathbf{1a/6}^d$ | 18 | F 5e OBn | 80 |
| 7 | 2a | $\mathbf{1a}^e/6^d$ | 18 | 5e | 17 |
| 8 | 2b | $\mathbf{1a/6}^d$ | 18 | F OBn | 91 |

^a Unless otherwise stated, substrate 2 (0.1 mmol), 1 (0.1 mmol) and AgBF₄ (3) (0.1 mmol) in CDCl₃ (0.5 ml) were stirred at room temperature. ^b Isolated yields. ^c (0.2 mmol) of **1b** was used. ^d Substrate **2a-b** (0.1 mmol), **1a** (0.1 mmol), AgBF₄ (3) (0.1 mmol) and BnOH (6) (0.3 mmol) in CDCl₃ (0.5 ml) were stirred at room temperature. ^e AgBF₄ (3) (30 mol%).

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When we replaced fluoroiodoxole **1a** with acetoxyiodoxole **1b**, the reaction with **2a** resulted in **1**,3-oxyfluorinated product **5a** (Table 3, entry 1) in 84% yield. In this reaction, we did not observe formation of difluorinated product **4a**. In addition, the regioselectivity was also very high as we could not detect formation of the regioisomer of **5a**. Aliphatic and aryl substrates **2b** and **2f** also reacted with the same chemo- and regioselectivity as **2a** (entries 2 and 3). Products **5b-c** had a limited stability, and decomposed within a couple of hours at room temperature. Instead of **1b**, **1c** (PIDA) could also be employed as acetoxy source. In this reaction, we also obtained **5a** in good yield (entry 4) without formation of diacetoxy or difluoro (**4a**) analogues. Interestingly, **1c** reacted much faster (20 min) than the iodoxole analogue **1b** (4 hours). When benzoyl analogue **1d** was used benzoyl product **5d** formed instead of **5a** (entry 5).

Cyclopropane derivatives 2a and 2b were also reacted with fluoroiodoxole 1a in the presence of benzyl alcohol (6) and AgBF₄. In these reactions the final products were 1,3-oxyfluorinated species 5e-f (Table 3, entries 6-8) instead of 4a-b (Table 2, entries 1-2), which were formed in the absence of benzyl alcohol. Since in oxyfluorination only a single fluorine is introduced, we attempted to react 2a and 1a in the presence of benzyl alcohol and sub-stoichiometric amount of AgBF₄ 3 (entry 7). However, the yield of the oxyfluorinated product 5e substantially decreased (c.f. entries 6 and 7). Apparently, application of stoichiometric amount of AgBF4 is required, for both as a source for the secondary fluorine atom in the difluorination reaction (such as for formation of 4a) and also in the oxyfluorination reaction for efficient activation of 1a. In the oxyfluorination reactions the activated hypervalent iodine reagents proved to be more stable than in the difluorination reactions. Therefore, in most processes (entries 2-7) one equivalent of the iodine reagent was sufficient to obtain the reported isolated yields.

In order to obtain more insight into the electronic effects of the reactions and the role of the applied hypervalent iodine, we performed a couple of control experiments. When an equimolar ratio of **2e**, **2h** and **1a** reacted in the presence of AgBF₄, we obtained only **4e**, while formation of **4h** was not observed (Scheme 2). This competitive reaction indicates that cyclopropane substrates bearing an electron withdrawing group, such as **2h**, react much slower than the parent compound **2e**.

This confirms the suggestion of the electrophilic mechanism for the opening of the cyclopropane ring. When 2a was reacted with equimolar amounts of fluoro- (1a) and acetoxyiodoxoles (1b) products 4a and 5a were formed in 1:2 ratio (Scheme 3) indicating that the oxidation power or the electrophilicity of the hypervalent iodine is an important factor for the reaction rate.

Scheme 2 Competitive fluorination using equimolar ratio of 2e, 2h and 1a.

Scheme 3 Competitive 1,3-difluorination vs. 1,3-oxyfluorination using equimolar amounts of 2a, 1a and 1b.

Considering the above and the literature data for related reactions, 6a,9a,10a we propose a plausible mechanism for the fluorinative opening of cyclopropanes with hypervalent iodines (Scheme 4). Benziodoxole reagents 1a-b are stable^{6b} under ambient conditions, and usually require activation in the substitution and addition reactions. 64,94,104 We suggest that AgBF₄ activates 1a-b by coordination of the oxygen atom of the benziodoxole ring to the silver cation affording intermediate 7. Similar, Lewis-acid type of activation of benziodoxoles was reported by Togni and co-workers.18 Unlike, 1a-b, activated benziodoxole 7 is very reactive, and besides the desired fluorination reaction it may undergo decomposition (or other side-reactions). This is the reason for application of two equivalents of 1a in some difunctionalization reactions where the substrate has a low reactivity or the rate of decomposition of intermediate is high. We suggest that 7 undergoes side-attack of the cyclopropane ring (8) to give carbocationic intermediate 9 and iodobenzene derivative 10. This mechanism is reminiscent of our proposal for the difluorination of styrenes with 1a.10a The high regioselectivity of the attack is an interesting feature of the process (Table 3). A possible explanation is that the regioselectivity is controlled by electronic effects, i.e. hyperconjugative stabilization of the tertiary carbocation center. The final step of the process could be a nucleophilic attack by fluorine from the BF₄ counterion to obtain the final product (4 or 5).

In case of oxyfluorination with benzyl alcohol (Table 3, entries 6–8) 1a was probably reacted with 6 prior to the ring opening providing benzyloxy-benziodoxole (analogue to 1b). In this case intermediate 9 is a benzyl ether (X = OBn). This idea is supported by the control experiment (Scheme 5), in which, we first performed a difluorination affording 4a, then 6 was added. In this reaction we obtained 5g, which is the regioisomer of 5e (see Table 3, entry 6).

Accordingly, when 2a, 1a, 3 and 6 were mixed at the onset of the reaction (Table 3, entry 6) difluorination product 4a did not form. This reaction lead to the formation of 5e directly (according to the mechanism outlined in Scheme 4). If 4a

$$X = F$$
, OAc (1a-b) 7 8

 $X = F$, OAc (1a-b) 7 8

 $X = F$, OAc (1a-b) 7 8

 $X = F$, OAc (1a-b) 4 or 5

Scheme 4 Plausible mechanism for 1,3-difluorination and 1,3-oxy-fluorination reactions.

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Scheme 5 Sequential oxyfluorination reaction with 2a

formed first in the process, benzyl alcohol (6) would have displaced the tertiary fluorine affording 5g (Scheme 5).

Modelling and experimental studies are underway to explore the mechanistic details of the above and related 6a,9a,10a metal mediated reactions of fluoro-benziodoxol reagent 1a.

In conclusion, we have shown that the air- and moisture stable fluoroiodine reagent 1a is suitable for the silver mediated 1,3-difluorination reaction of 1,1-disubstituted cyclopropanes. The reaction can be extended to 1,3-oxydifluorination by using hypervalent acetoxy and benzoyloxy iodines. The reaction probably proceeds via electrophilic ring opening of cyclopropanes. As the above process is the first 1,3-difluorination and 1,3-oxydifluorination reaction, it broaden the synthetic scope of the fluorination reactions, and the application area of hypervalent fluoroiodines.

Conflict of interest

The authors declare no competing financial interests.

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