A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201900745
Angew. Chem. 10.1002/ange.201900745

Link to VoR: http://dx.doi.org/10.1002/anie.201900745
http://dx.doi.org/10.1002/ange.201900745

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10.1002/anie.201900745

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ortho Difluoroalkylation of Aryliodanes with Enol Silyl Ethers through a Rearrangement Enabled by a Fluorine Effect

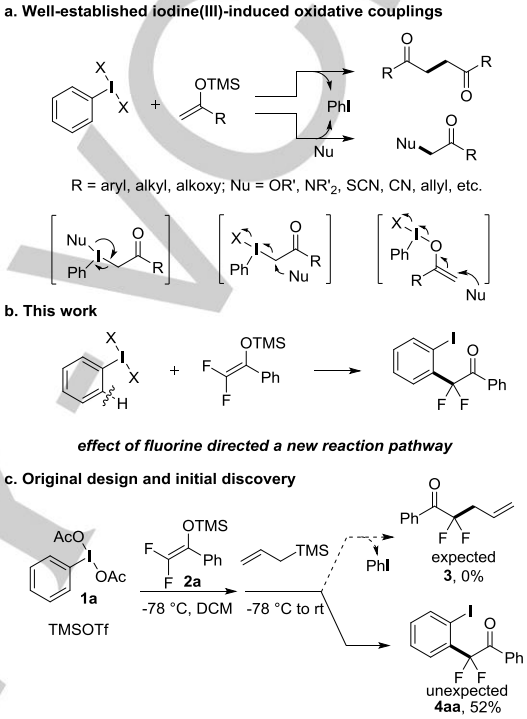
Xin Huang[+], Yage Zhang[+], Chaoshen Zhang[+], Lei Zhang, Ying Xu, Lichun Kong, Zhi-Xiang Wang,* Bo Peng*

Dedication ((optional))

Abstract: Herein, we unravel an intriguing effect of fluorine which allows difluoroenol silyl ethers to couple with aryliodanes in a redox-neutral manner, affording *ortho*-iodo difluoroalkylated arenes. The remaining iodide group provides a versatile platform for converting the products into various valuable difluoroalkylated arenes. The reaction shows excellent functional group compatibility and broad substrate scope. DFT mechanistic study suggests that the fluorine effect tunnels a subtle nucleophilic attack of the oxygen of enol silyl ethers to aryliodanes, therefore, accomplishing a rearrangement process.

Hypervalent iodine compounds are readily available, versatile and environmentally benign reagents for organic synthesis.[1] Chemists have devoted a substantial amount of efforts to develop new reactions using these reagents. In particular, the iodine(III)-mediated oxidative couplings of enol silyl ethers (ESEs) with various nucleophiles have produced a diverse family of α-functionalized carbonyl compounds (Scheme 1a).[2,3] This type of reactions has experienced significant advances in the past three decades. Although the mechanism still remains elusive, the umpolung of ESEs by aryliodanes is generally accepted as a key step in these transformations (Scheme 1a).[2a-2c] Under the oxidation effect of hypervalent iodine reagents, the conventionally nucleophilic ESEs can react with itself or other nucleophilic coupling partners to form the self-coupling products[2e,2f] or other α-functionalized carbonyls[2b-2d] with phenyl iodides as wasted byproducts. In contrast to the well-established reaction pattern, we present herein a new cross-coupling reaction between aryliodanes and difluoroenol silyl ethers (DFSEs) in which aryliodanes not only serve as an oxidant but also act as a coupling partner (Scheme 1b).[4] Accordingly, the reaction provides a new strategy for synthesizing *ortho*-iodo difluoroalkylated arenes in a metal-free and redox-neutral manner. Moreover, due to the presence of an iodide group, these compounds can further serve as synthons for accessing biologically attractive difluoroalkylated arenes.[5]

Recently, Szpilman and coworkers demonstrated that aryliodane-umpoled ESEs could be trapped by allylsilanes to produce α-allyl carbonyls.[2b] Inspired by their protocol, we assumed that sequentially treating highly electrophilic $PhI(OTf)_2$ (*in situ* generated from $PhI(OAc)_2$/TMSOTf)[6] with DFSE **2a** and allyl trimethylsilane could afford α-allylic-α,α-difluorinated ketone **3** (Scheme 1c), thus accessing C-difluoromethylated products by removing the benzoyl group via Haller-Bauer reaction.[7] To our surprise, in lieu of the expected product, the reaction afforded *ortho*-difluoroalkylated aryl iodide **4aa** in a modest yield (52%). This intriguing switch in the reaction pathway is of great interest. To the best of our knowledge, there have been no reports of cross-coupling reactions between aryliodanes and ESEs to date. However, it should be noted that Maulide and coworkers reported an elegant protocol for the cross-coupling of aryl sufloxides with enol silyl ethers.[8] In addition, Shafir and coworkers accomplished α-(*ortho*-iodo)arylation of carbonyls with activated aryliodanes.[4e,4f]



Scheme 1. Background and initial results.

Intrigued by the unexpected discovery, we switched our efforts to the reaction of $PhI(OAc)_2$ **1a** with DFSE **2a**. Through optimization of the reaction conditions, including the aryl source, electrophilic activator, temperature, and solvent (see SI 2.1 for more details), we found that the reaction of $PhI(OAc)_2$/TMSOTf with DFSE **2a** at -78 °C produced **4aa** with the best yield (83%) (eq 1). The experimental results suggested that the

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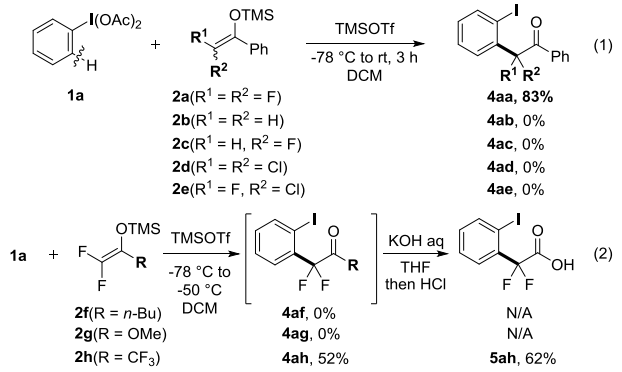
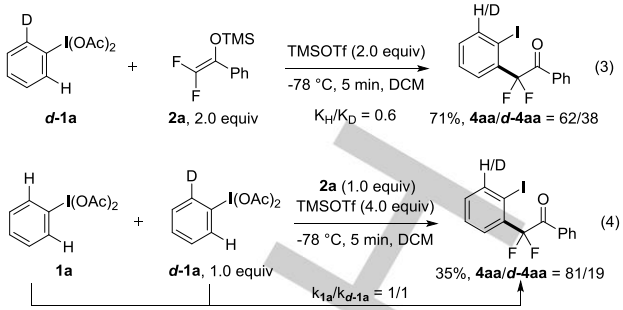
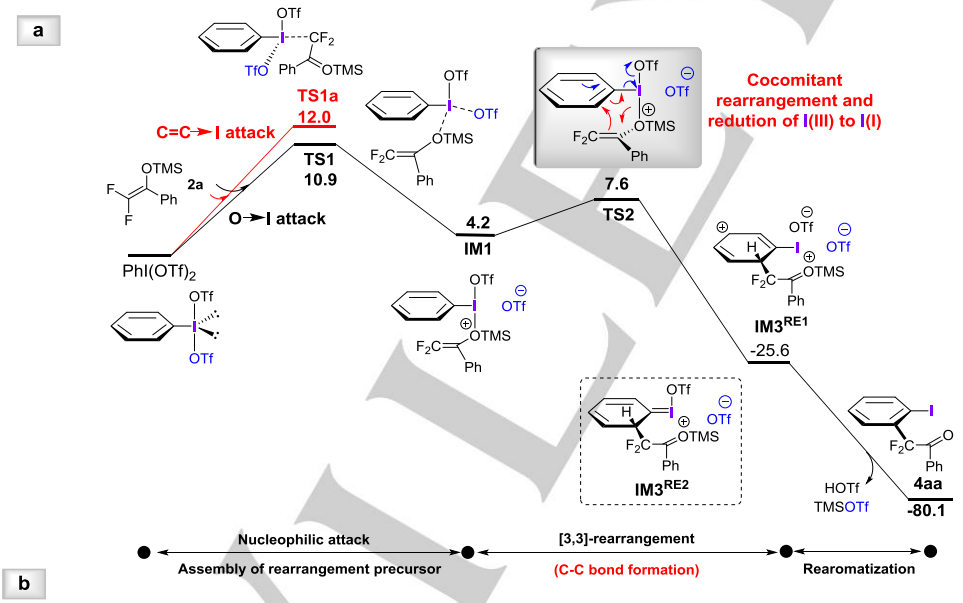
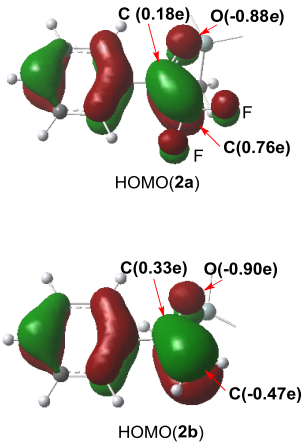




difluoromethylene group of DFSE **2a** could play a critical role in switching the reactivity of **2a**.[9] Thus, we examined the non-fluorinated and mono-fluorinated ESEs **2b**-**2e** (eq 1). In agreement with our expectation, no desired products **4ab**-**4ae** could be obtained from the reactions.[10] Furthermore, as shown in eq 2, we considered the substitution effects of Ph group in **2a** with electron donating groups nBu(**2f**) and OMe(**2g**) and electron withdrawing group CF_3 (**2h**), note that **2h** can be readily prepared from HFIP (hexafluoroisopropanol).[11] **2h** furnished trace amount of desired product under standard conditions. Through optimization(see SI 2.2 for more details), we identified the optimum conditions (-78 °C for 5 min and then -50 °C for 2 h), under which the reaction gave the best yield of **4ah** (52%) along with small amount of α,α-difluoroacetic acid **5ah** (15%) (eq 2). Notably, the expected ketone product **4ah** was obtained as its hydrate (**4ah**·H_2O). This was due to the highly electrophilic nature of the corresponding multi-fluorinated ketone. Similar polyfluorinated ketone hydrates has been reported in the literatures.[12a] The formation of **5ah** could be attributed to the partial detrifluoromethylation of **4ah**·H_2O.[12b] In view of the synthetic versatility of the carboxylic group,[13] we simply treated the reaction mixture with aqueous KOH to convert ketone hydrate **4ah**·H_2O to carboxylic acid **5ah**. As a consequence, **5ah** was obtained as the sole product in synthetically useful yield (62%).

To understand how the fluorine effect in **2a** enabled the reaction, we performed DFT calculations to characterize the pathway for the reaction of $PhI(OTf)_2$ [6] with **2a** (see SI 3.1 for computational details). On the basis of the calculation results, we tentatively propose a reaction mechanism as illustrated by the simplified pathway in Figure 1a (see the Supporting Information 3.2 for the complete pathway). To begin with, **2a** undergoes nucleophilic attack on $PhI(OTf)_2$. The O→I attack via **TS1** is more favorable than the C=C→I attack via **TS1a** and





b

	2a	2b	2c	2d	2e	2f	2g	2h
O→I-attack (TS1-like)	10.9	14.9	12.4(Z)/12.5(E)	15.1	13.5(Z)/13.6(E)	13.6	14.2	13.3
C=C→I-attack (TS1a-like)	12.0	7.4	10.1(Z)/10.7(E)	14.6	12.4(Z)/11.0(E)	12.2	5.9	17.6

Figure 1. a, Free energy profile for the reaction of **2a** with $PhI(OTf)_2$, along with relative free energies in kcal mol^{-1}. Additional results are given in SI 3.2. **b**. Comparing the energetic preference of the two nucleophilic attacking modes. See SI 3.4 for the optimized structures of transition states and intermediates. **c**. HOMOs of **2a** and **2b**, along with NBO charges in e.

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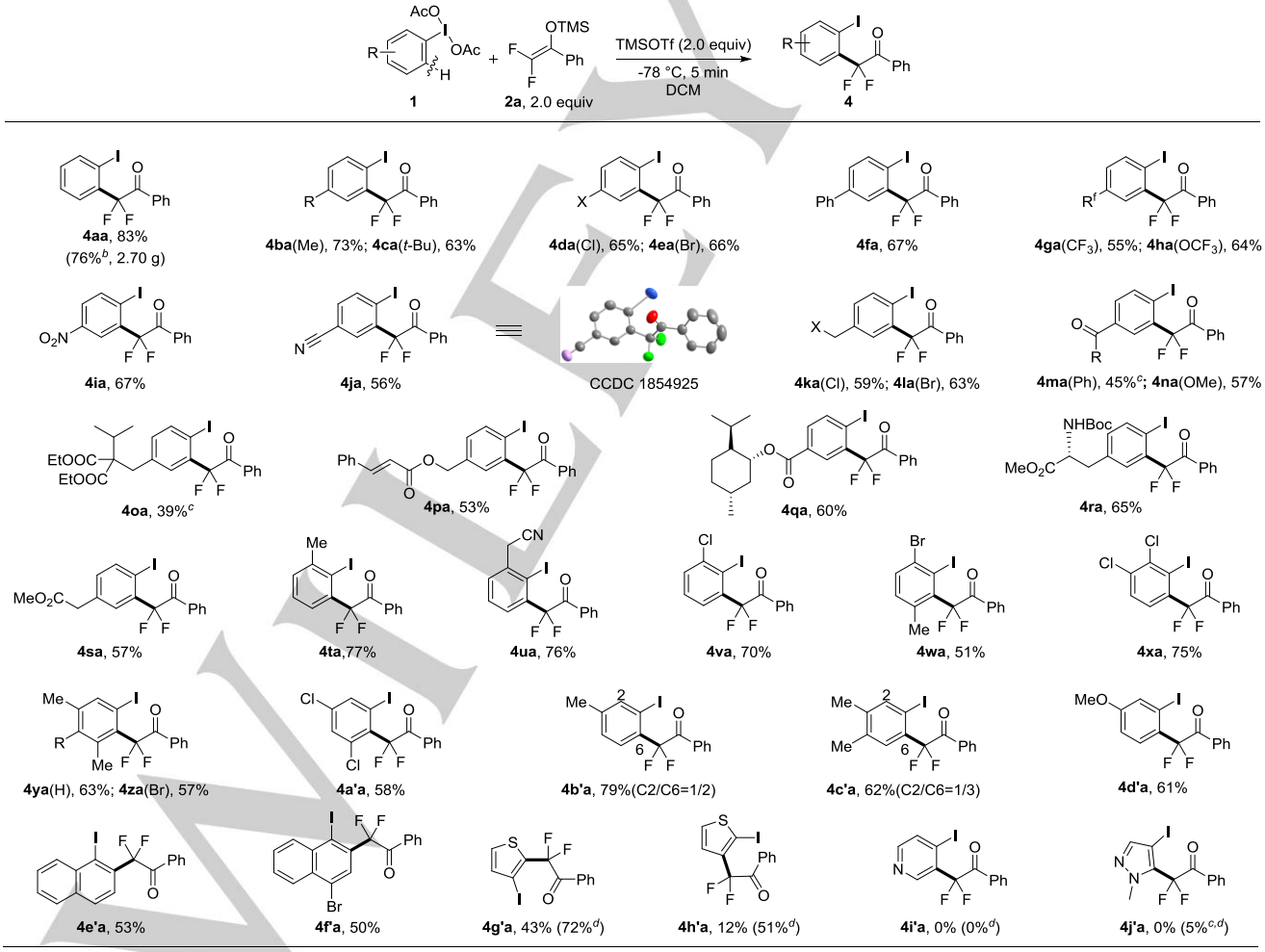
results in **IM1** with a I–O^{TMS} bond length of 2.47Å. Subsequently, **IM1** rearranges to **IM3** via **TS2.** The rearrangement breaks the I–O^{TMS} bond and forms a new C-C bond between *ortho*-carbon of PhI(OTf)$_2$ and terminal carbon of **2a**, which is similar to a [3,3]-sigmatropic rearrangement. The rearrangement alters a *ortho* sp^2 carbon in **IM1** to a sp^3 carbon in **IM3.** Consistently, our intramolecular kinetic isotope effect (KIE) study (eq 3) indicates that the reaction of ***d*-1a** under the standard conditions exhibits inverse isotope effect,[14] giving a mixture of **4aa**/***d*-4aa** in a ratio of 62/38. Finally, rearomatization of **IM3** affords the product **4aa.** Overall, the reaction was predicted to have a rate-determining barrier of 10.9 kcal mol^{-1} for assembling the rearrangement precursor **IM1** and is highly exergonic by 80.1 kcal mol^{-1}. The energetic results explain why the reactions could take place at low temperature. The predicted rate-determining step agrees with the intermolecular kinetic isotope effect study (eq 4), the equal rates of **1a** and *d*-**1a** indicating that the rearrangement step is the product-determining step rather than the rate-determining step of the whole transformation.[14b,15]

The pathway initiated by C=C→I attack via **TS1a** suffers a kinetically facile S_N2 process that prevents the pathway from producing **4aa** (see SI 3.3).

To gain insight into how the fluorine effect in **2a** favors O→I attack over C=C→I one, Figure 1c compares the electronic structures of **2a** and **2b**. Compared to **2b**, the p_z orbitals of fluorine atoms in **2a** are substantially involved in its HOMO**,** which decreases the π-electron density of the C=C bond of **2a,** thus weakens its nucleophilicity and disfavors the C=C→I attack. In addition, considering the C=C→I attack, the fluorine effect switches the Coulomb interaction between the terminal carbon and positively-charged iodine (Q=1.46*e*) of PhI(OTf)$_2$ from attraction in **2b** to repulsion in **2a** (see Figure 1c for charge population), which also disfavors the C=C→I attack.

The mechanistic study suggests that the favorable assembly of the rearrangement precursor (i.e. **IM1**) via **O→I** attack is crucial for the reaction. Indeed, as compared in Figure 1b, the derivatives (**2b**-**2g**) of **2a** all have **TS1**-like transition states higher than corresponding **TS1a**-like ones, which agrees with our experimental results of no desired products.

Recently, Shafir et al. reported an unconventional Claisen rearrangement in their study of *ortho*-propagylation of bis(acyloxy)iodoarenes,[4b] encouraging us to reexamine the present rearrangement. **IM3** has the C–I bond length equal to that (2.09Å) in **IM1** and two distant OTf$^-$ groups, suggesting that **IM3** had better be represented by the resonance structure **IM3^{RE1}** with iodine(I) rather than **IM3^{RE2}** with iodine(III). Supportively, the Wiberg bond index (1.08) of C-I bond in **IM3** is only slightly greater than that (0.99) of the bond in **IM1.** Thus, the rearrangement proceeds in accompany with the reduction of



Scheme 2. *Ortho* C-H difluoroalkylation of aryliodanes with enol silyl ether **2a**. [a] Unless otherwise noted, the reactions were performed with aryliodanes **1** (0.5 mmol) under the optimized conditions. [b] 10 mmol of **1a** was used in the reaction. [c] Corresponding aryl iodides were recovered in 47%, 49% and 77% yields from the reactions of **1m**, **1o** and **1j'** respectively. [d] $TMSOCOCF_3$ was used instead of TMSOTf.

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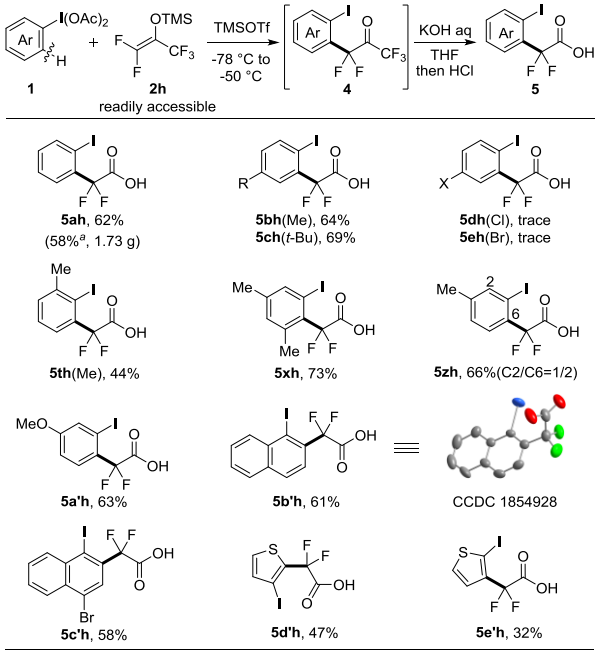
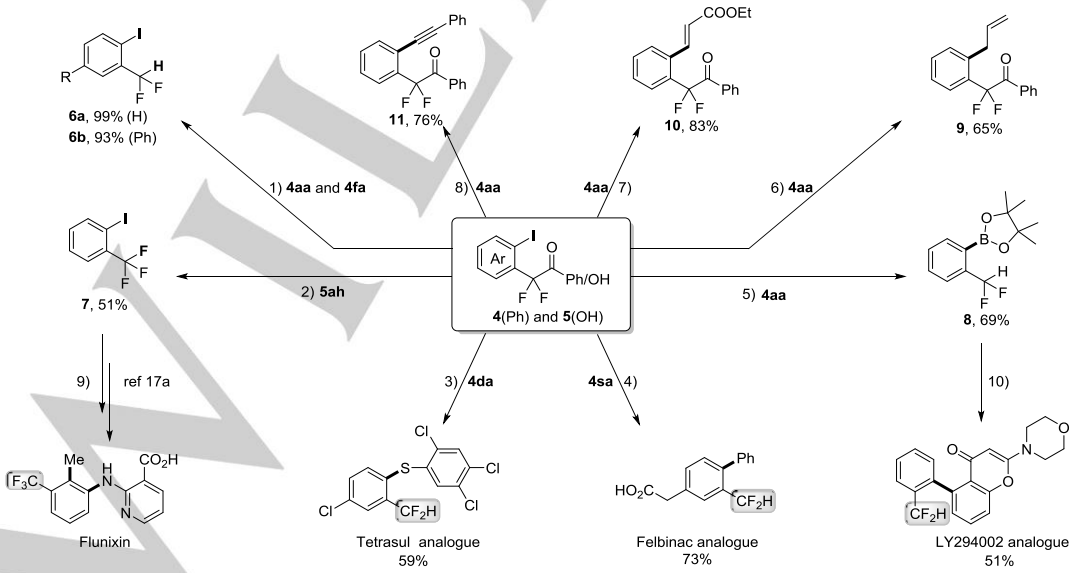


Scheme 3. *Ortho* C-H difluoroalkylation of aryliodanes with enol silyl ether **2h** General reaction conditions: **1** (0.5 mmol), TMSOTf (2.0 equiv), **2h** (2.0 equiv), DCM (0.1 M), -78 °C, 5 min then -50 °C, 2 h. [a] 10 mmol of **1a** was used in the reaction.

iodine(III) to iodine(I), as illustrated by the curl arrows in **TS2**, which is different from a classical [3,3]-sigmatropic rearrangement. In line with the concomitant reduction, the NBO charge on iodine decreases significantly from 1.42 (compared to 1.46 in $PhI(OTf)_2$) in **IM1** to 0.84 in **TS2** to 0.48*e* in **IM3** and the dearomative rearrangement is exergonic by 29.8 kcal mol^{-1}.

Next, we evaluated the reaction scope with various aryliodanes. As shown in Scheme 2, the reaction could be successfully applied to a wide range of aryliodanes, producing a large number of difluoroalkylated arenes **4**. First, the scalability of the reaction was demonstrated by a gram-scale synthesis of **4aa** (76%, 2.70 g). Remarkably, functional groups including aryl halides (**4da**, **4ea**, **4va**, **4wa**, **4xa**, **4za**, **4a'a**, and **4f'a**), a nitro group (**4ia**), a ketone (**4ma**), esters (**4na**-**4sa**), benzylic halides (**4ka**, **4la**), an unsaturated ester (**4pa**), a nitrile (**4ua**), and even an amine (**4ra**) were all nicely tolerated in the reaction, most of which could be challenging for conventional aromatic difluoroalkylation processes.[5] These tolerated functionalities provided diverse platforms for the further elaboration of products, which increased the synthetic utility of this reaction (*vide infra*). It's also impressive that stereochemistry has little influence on the reaction. Reactions with hindered substrates (**1t**-**1x**) proceeded smoothly to afford the desired products (**4ta**-**4xa**) in good yields. Interestingly, *meta*-methyl-substituted aryliodane **1b'** furnished a mixture of *ortho*-difluoroalkylated products (**4b'a**) in a 1/2 ratio. In sharp contrast, aryliodane **1c'** bearing a *meta*-methoxyl group exclusively gave the less congested product (**4c'a**) in a good yield (61%). To our delight, both naphthalene (**1e'** and **1f'**) and thiophene (**1g'** and **1h'**) derivatives were also found to be suitable for the reaction. However, pyridine **1i'** and pyrazole **1j'** were not tolerated. This was probably due to the relatively high nucleophilicity of *N*-heteroarenes which might quench the electrophilic aryliodine(III) species in the reaction.

The reaction scope in use of **2h** as difluoroalkylation reagent was also investigated under the optimum conditions (Scheme 3). First, the scalability of the reaction was demonstrated by a successful gram-scale synthesis of **5ah** (58%, 1.73 g). A variety of aryliodanes **1** could be transformed to corresponding α,α-difluoroacetic acids **5** with this protocol. Substrates bearing *para*-electron-donating groups (**1b** and **1c**) afforded desired products (**5bh** and **5ch**) in good yields. However, *para*-halogenated aryliodanes (**1d** and **1e**) proved to be problematic substrates since no expected products (**5dh** and **5eh**) could be isolated from these reactions. Similar to the reactions using **2a** as a nucleophile (Scheme 2), *meta*-methylated phenyliodane **1z** furnished a 1/2 mixture of regio-isomers **5zh**, whereas *meta*-methoxyl-substituted **1a'** exclusively afforded less congested



(1) *t*-BuOK, *t*-BuOH (Yield of **6a** was determined by ^{19}F-NMR). (2) Ag cat., Selectfluor, acetone/H_2O (Yield of **7** was determined by ^{1}H-NMR). (3) CuI cat., K_2CO_3, O_2, NMP; then *t*-BuOK, *t*-BuOH. (4) Pd cat., *t*-BuOK, $PhB(OH)_2$, toluene. (5) Pd cat., *t*-BuOK, Bpin-Bpin, dioxane. (6) Pd cat., K_2CO_3, allyl-Bpin, THF. (7) Pd cat., K_2CO_3, ethyl acrylate, toluene.(8) Pd cat., CuI cat., K_2CO_3, phenylacetylene, toluene. (9) ref 17a; (10) Pd cat., K_2CO_3, aryl bromide, dioxane.

Scheme 4. Elaboration of the coupling products **4**.

5a'h. Pleasingly, naphthalene (**1b'** and **1c'**) and thiophene (**1d'** and **1e'**) derivatives produced the desired products in modest to good yields.

To demonstrate the usefulness of this reaction, we further elaborated products **4** and **5** as illustrated in Scheme 4. Simple treatment of **4aa** and **4fa** with KO*t*-Bu produced difluoromethylated phenyl iodides **6a** and **6b**, respectively, in good yields.[7] The carboxylic group of **5ah** was converted to a new C-F bond giving trifluoromethylated phenyl iodide **7** in 51% yield.[16] The synthetic utility of **7** has been demonstrated by Ritter and coworkers in the synthesis of an anti-inflammatory drug, Flunixin.[17a] Not surprisingly, the iodide group, one of the best leaving groups, could be readily transformed into other functionalities including SAr, Ar, Bpin, allyl, vinyl, and alkynyl groups. Among them, the C-S bond formation of **4da** and Suzuki coupling of **4sa** directly delivered the difluoromethylated analogs of two drugs, Tetrasul[17b] and Felbinac[17c], respectively. Notably, the successful synthesis of **8** bearing a Bpin moiety *ortho* to a difluoromethyl group paves a way for coupling the difluoromethylated arenes with other electrophiles, as exemplified by the synthesis of an analog of another drug candidate (LY294002).[17d]

In summary, we have disclosed an intriguing fluorine effect which enables a rearrangement which couples aryliodanes with difluoroenol silyl ether **2a in** a redox-neutral manner, leading to *ortho*-iodo difluoroalkylated arenes which can serve as difluorination reagents. Notable features of the reaction include its remarkably low temperature (-78 °C) and short reaction time (< 5 min), which allow the process to tolerate a diverse array of functionalities. The key for the success of the reaction is that the fluorine effect favors the nucleophilic attack of the O atom of DFSE **2a** on $PhI(OTf)_2$ over C=C attack, thus enabling a selective assembly of the rearrangement precursor for coupling. We anticipate that this work will stimulate more interests and efforts on the development of difluoroalkylation reactions using the newly discovered fluorine effect.

Acknowledgements ((optional))

This work is supported by Zhejiang Normal University and NSFC-21502171, 21773240. S. E. Denmark (UIUC), A. A. Thomas (MIT) and J. Hu (SIOC) are thanked for helpful discussions.

Keywords: fluorine effect• hypervalent iodine • difluoromethylation • rearrangement reaction

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10.1002/anie.201900745

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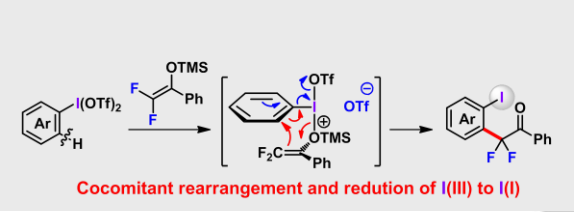

An intriguing effect of fluorine in difluoroenol silyl ether distinguishes it from other enol silyl ethers by enabling its cross-coupling with aryliodanes, which represents the first iodide-remaining cross-coupling of enol silyl ethers via rearrangement.

Xin Huang, Yage Zhang, Chaoshen Zhang, Lei Zhang, Ying Xu, Lichun Kong, Zhi-Xiang Wang, Bo Peng**

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***ortho* Difluoroalkylation of Aryliodanes with Enol Silyl Ethers through a Rearrangement Enabled by a Fluorine Effect**