

C–F Arylation of Polyfluorophenols by Means of Sigmatropic Dearomatization/Defluorination Sequence

Koichi Okamoto, Keisuke Nogi, Jun Shimokawa, and Hideki Yorimitsu*

Abstract: Selective C–F arylation of polyfluorophenols with aryl sulfoxides has been accomplished by means of a sigmatropic dearomatization/defluorination sequence. This sequence consists of three processes: (1) interrupted Pummerer reaction to form S–O-tethered sulfonium salt, (2) C–C-forming [3,3] sigmatropic rearrangement with dearomatization, and (3) Zn-mediated defluorinative rearomatization. The present biaryl construction provides a facile access to polyfluorinated biaryls that is difficult to synthesize by other methods. The synthetic utility of the strategy is clearly demonstrated by the synthesis of a fluorinated analogue of Maxipost, a potassium channel modulator.

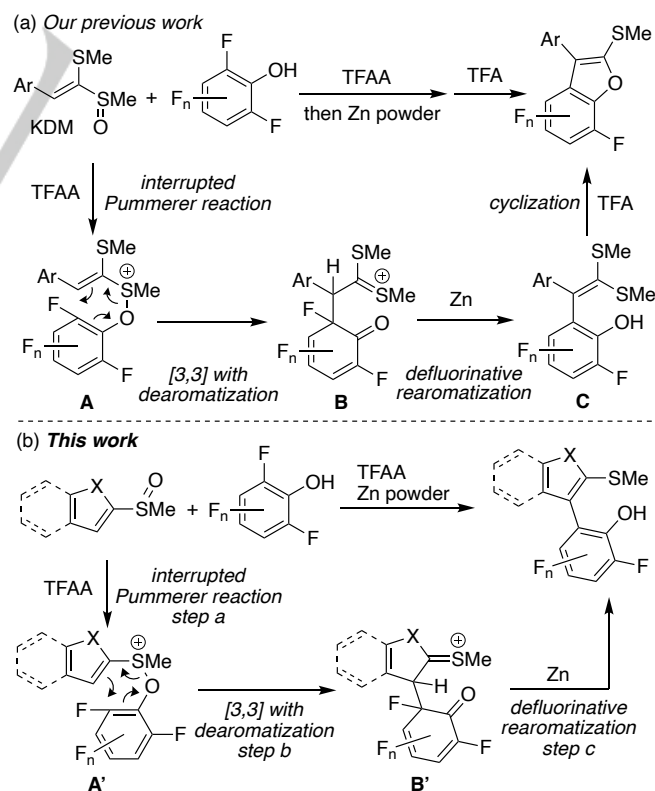
An increasing attention to fluorinated molecules in the fields of pharmaceuticals, agrochemicals, and optoelectronics has been leading the development of diverse methods for the synthesis of these molecules.^[1–4] Among the present methods, selective and controlled C–F transformations of polyfluorinated arenes of high availability have been considered as a powerful strategy. The divergence of such transformations has been expanded with the aid of transition metals such as Pd and Ni.^[3] However, due to the strength of C–F bonds, highly electron-rich transition metals are necessary, which confines functional group compatibility. In addition, supply risk^[5] and contamination issues^[6] associated with the use of precious transition metals should be concerned.

To address these concerns, development of transition-metal-free methods other than conventional S_NAr reactions^[4] should be in high demand. Especially, we focused on C–F arylation that provides polyfluorinated biaryl structures of high value. In 1993, Kobrina reported *ortho*-selective arylation of polyfluorophenols although the use of toxic aryllead compounds would be problematic.^[7] Recently, Peshkov achieved C–F arylation of polyfluorobenzonitriles with benzonitrile radical anions although strongly reducing conditions (with Na in liq. NH_3) are necessary to generate the radical anions.^[8] Further development of new, complementary methods for selective C–F arylation without transition metal should be desirable.

Recently, we have demonstrated a sigmatropic dearomatization/defluorination sequence as a new strategy for selective C–F transformations of polyfluorophenols for annulative synthesis of fluorinated benzofurans (Scheme 1a).^[9,10] In the presence of trifluoroacetic anhydride (TFAA), polyfluorophenols undergo interrupted Pummerer reaction^[11] with ketene dithioacetal monoxide (KDM) to form S–O-tethered sulfonium **A**.

Then, C–C-bond forming charge-accelerated [3,3] sigmatropic rearrangement occurs with dearomatization of the phenol ring to afford dearomatized intermediate **B**.^[12] Subsequent addition of Zn induces reductive defluorination to form phenol **C**. Assisted by rearomatization, the reductive defluorination proceeds with the moderate reducing agent under mild reaction conditions. Finally, addition of TFA promotes cyclization and elimination of methanethiol to give desired fluorinated benzofurans.

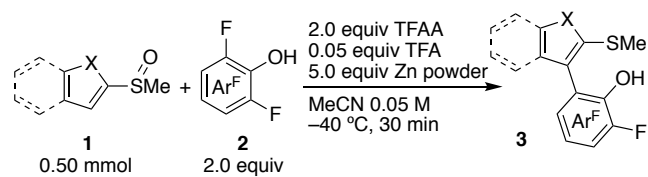
We envisioned that this strategy is applicable to the C–F arylation of polyfluorophenols by employing aryl sulfoxides instead of KDM (Scheme 1b). In the presence of acid anhydride, S–O-tethered sulfonium **A'** can be generated from a polyfluorophenol and an aryl sulfoxide (step a). Subsequent sigmatropic rearrangement would generate dearomatized intermediate **B'** (step b), which can be converted to the desired biaryl via Zn-mediated defluorinative rearomatization (step c). Although this reaction contains a challenging step: concomitant dearomatization of two aromatic rings, we tackled to develop the C–F arylation encouraged by our previous C–H arylation of phenols with aryl sulfoxides.^[12c] Herein, we report a novel approach to C–F arylation of polyfluorophenols with aryl sulfoxides via the sigmatropic dearomatization/defluorination sequence.



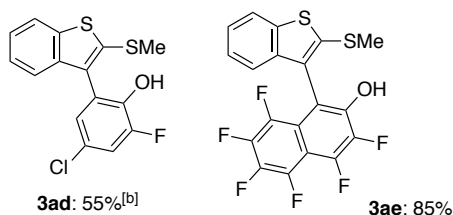
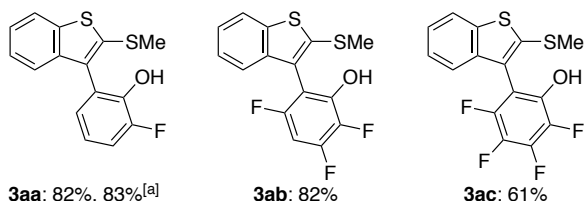
Scheme 1. Sigmatropic dearomatization/defluorination sequence for selective C–F transformations of polyfluorophenols.

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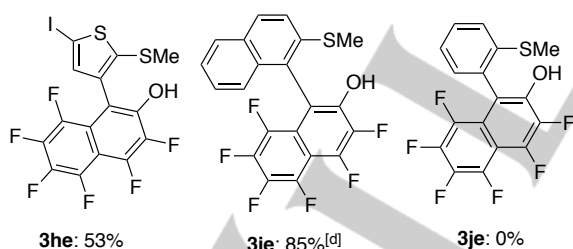
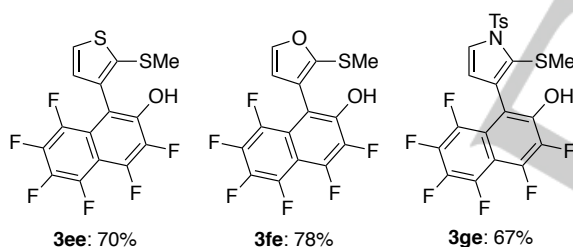
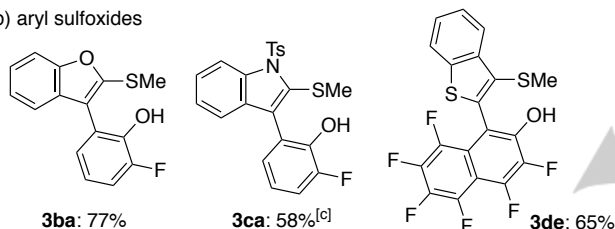
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a) fluorophenols



b) aryl sulfoxides

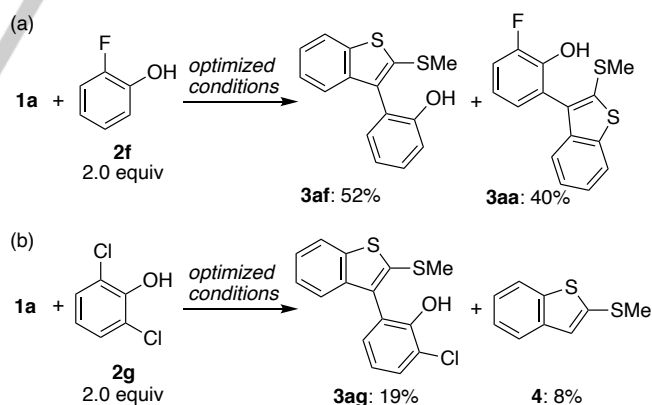


Scheme 2. Substrate scope. [a] 5 mmol scale. [b] 0.10 equiv of TFA was used. [c] 3.0 equiv TFAA was used. [d] 1.5 equiv of **1i** and 1.0 equiv of **2e** were used.

With benzothienyl sulfoxide **1a** and 2,6-difluorophenol (**2a**) as model substrates, we optimized the reaction conditions based on our previous defluorinative transformation.^[9] Optimization study revealed that TFAA (2.0 equiv) and Zn powder (5.0 equiv) are found to be optimal as an activator and as a reductant, respectively.^[13] Moreover, an addition of a small amount of trifluoroacetic acid (TFA) was crucial for the reproducibility of the reaction. In the presence of these reagents, the reaction of **1a** with **2a** smoothly proceeded in MeCN at $-40\text{ }^\circ\text{C}$ to provide an 82%

yield of **3aa** (Scheme 2a). This biaryl construction accommodates a gram scale synthesis: 1.21 g (83%) of **3aa** was obtained from 5.0 mmol of **1a**. Instead of **2a**, the reaction with 2,3,5,6-tetrafluorophenol (**2b**) smoothly proceeded to afford **3ab** in 82% yield. Pentafluorophenol (**2c**) and 4-chloro-2,6-difluorophenol (**2d**) also underwent the reaction to provide **3ac** and **3ad**, respectively, in moderate yields. Of note, the reaction with heptafluoro-2-naphthol (**2e**) took place at the C1 position in a regioselective manner, resulting in formation of **3ae** in 85% yield.

We then explored the reaction scope with respect to aryl sulfoxides (Scheme 2b). Instead of benzothienyl sulfoxide **1a**, 2-benzofuryl and 2-indolyl sulfoxides **1b** and **1c** were also applicable to the reaction to furnish **3ba** and **3ca** in 77% and 58% yields, respectively. Unfortunately, 3-benzothieryl sulfoxide **1d** did not react with 2,6-difluorophenol (**2a**) to afford a complex product mixture. On the other hand, with perfluoronaphthol **2e**, sulfoxide **1d** smoothly underwent the reaction to provide biaryl **3de** in 65% yield. The lower aromaticity of the naphthyl ring of **2e** would facilitate the doubly dearomatizing [3,3] sigmatropic rearrangement. Instead of benzo-fused heteroaromatics, monocyclic 2-thienyl, 2-furyl, and 2-pyrrolyl sulfoxides **1e–g** also underwent the reaction to afford the corresponding biaryls **3ee–ge** in good yields. Gratifyingly, the iodo group on thienyl sulfoxide **1h** that is potentially reactive under transition metal catalysis was well tolerated. In addition to heteroaryl sulfoxides, 2-naphthyl sulfoxide **1i** underwent the reaction to furnish 1,1'-binaphthyl **3ie** in 85% yield. Unfortunately, phenyl sulfoxide **1j** was not applicable to the reaction probably owing to the stronger aromaticity of the benzene ring, and only **2e**, **1j** and the corresponding sulfide were observed after the reaction. These imply that the weaker aromaticity of heteroaryl and naphthyl sulfoxides than that of the phenyl sulfoxide would be important for the sigmatropic dearomatization step.



Scheme 3. Reactions with 2-fluorophenol and with 2,6-dichlorophenol.

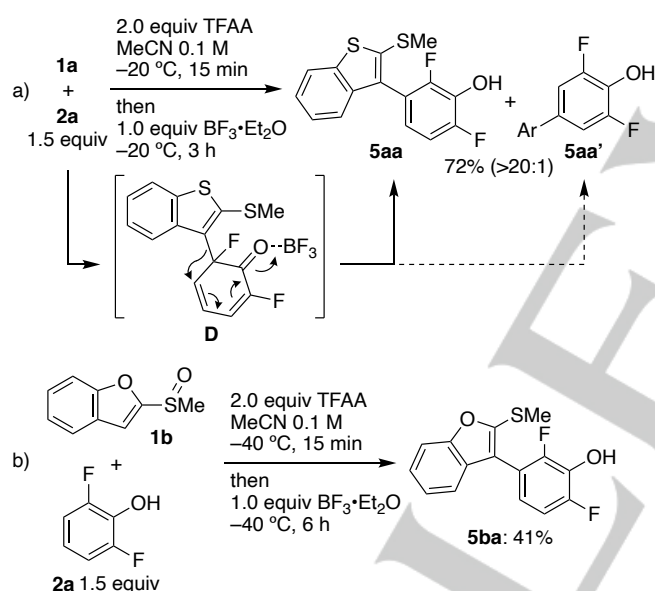
To gain insight into the reaction mechanism, especially for the [3,3] sigmatropic rearrangement, we performed the reaction with 2-fluorophenol (**2f**). The reaction yielded a mixture of defluorinated product **3af** and deprotonated product **3aa** in a ratio of 1.3:1 (Scheme 3a). This non-regioselective sigmatropic rearrangement is consistent with our previous report on the reaction of KDM with 2-fluorophenol.^[9] The lack of the

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regioselectivity highlights the necessity of 2,6-difluorophenol (**2a**) for the selective synthesis of fluorinated biaryl **3aa**.

Instead of the defluorinative reaction, a dechlorinative variant by means of 2,6-dichlorophenol (**2g**) was not successful, and only a 19% yield of desired biaryl **3ag** was obtained accompanied by 2-benzothienyl methyl sulfide (**4**) and several byproducts (Scheme 3b). The formation of **4** suggests that the chloro substituent bigger than fluoro atom would hamper the sigmatropic rearrangement, which results in reductive decomposition of the sulfonium **A'** to **4**.

In addition to the Zn-mediated defluorination, the dearomatized intermediates generated *in situ* can be involved in 1,2-aryl migration leading to non-trivial *meta* selective arylation of phenol.^[14,15] Treatment of a mixture of **1a** and **2a** with TFAA to generate dearomatized intermediate like **B'** followed by an addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ induced 1,2-aryl migration via **D** to afford 3-aryl-2,6-difluorophenol **5aa** along with a trace amount of C4-arylated isomer **5aa'** (Scheme 4a). Similarly, **2a** underwent the *meta*-arylation with benzofuryl sulfoxide **1b** to provide **5ba** in 41% yield without detectable formation of the corresponding *para*-arylated product **5ba'** (Scheme 4b). Unfortunately, indolyl sulfoxide **1c** gave rather complex mixture containing a small amount of the desired *meta*-arylation product.

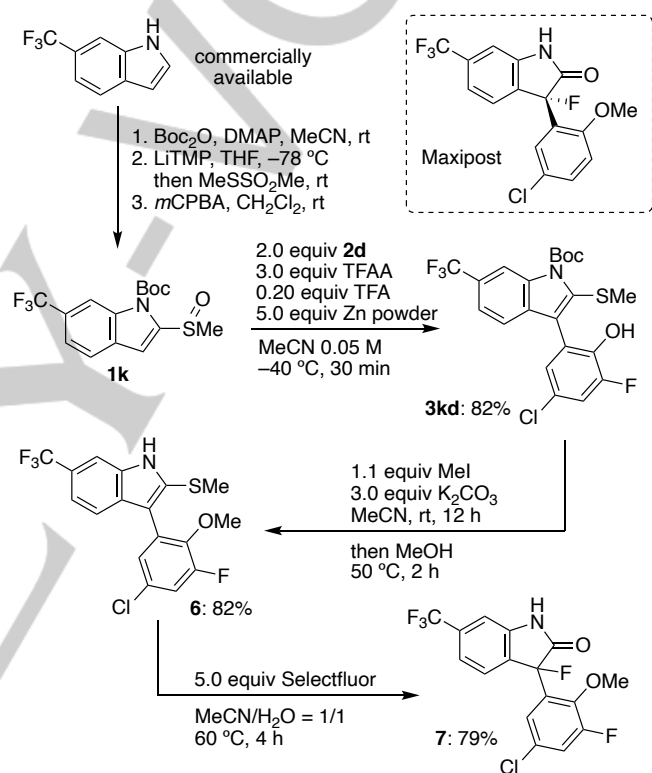


Scheme 4. *meta*-Arylation of 2,6-difluorophenol via 1,2-aryl migration from dearomatized intermediate.

Finally, to demonstrate the synthetic utility of the present defluorinative coupling, we attempted to synthesize a potentially useful fluorinated molecule, a fluorinated analogue of Maxipost^[16] known as a competent potassium channel modulator (Scheme 6). Boc-protected indolyl sulfoxide **1k** was prepared in three steps from commercially available 6-(trifluoromethyl)indole. Under slightly modified conditions, indolyl sulfoxide **1k** successfully underwent the biaryl construction with **2d** to afford **3kd** in 82% yield. The choice of a Boc group for *N*-protection was important: the *N*-Ts analogue failed to efficiently deliver the corresponding biaryl^[17] possibly because strong electron-withdrawal hampered the sigmatropic rearrangement. Subsequent methylation of the

phenolic hydroxy moiety and deprotection of the Boc group were conducted in one pot to give 2-sulfanylandole **6** in a satisfactory yield. Finally, treatment of **6** with Selectfluor promoted C3-fluorination with concomitant dearomatization,^[18] and subsequent *in situ* hydrolysis of the iminium intermediate afforded desired fluorinated *rac*-Maxipost **7** in 79% yield.

In conclusion, we have developed C–F arylation of polyfluorophenols with aryl sulfoxides based on the sigmatropic dearomatization/defluorination sequence. The reaction proceeds under mild conditions, and various fluorinated biaryls could be synthesized. We also achieved the synthesis of a fluorinated analogue of Maxipost, which demonstrates the synthetic utility of the biaryl construction presented herein.



Scheme 5. Synthesis of fluorinated analogue of Maxipost **7**.

Acknowledgements

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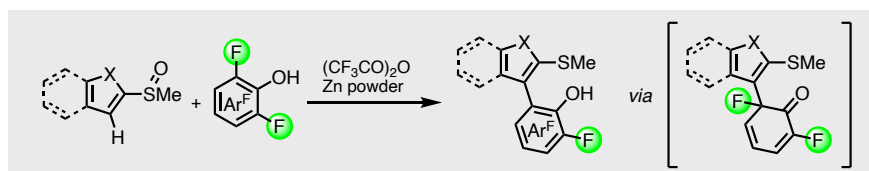
Keywords: biaryls · C–F transformation · interrupted Pummerer reaction · sigmatropic rearrangement

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