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Regioselective Difunctionalization of 2,6-Difluorophenols Triggered by Sigmatropic Dearomatization

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Supporting Information Placeholder

ABSTRACT: Regioselective difunctionalization of 2,6-difluorophenols with aryl sulfoxides and nucleophiles has been accomplished. The reaction is composed of (1) Pummerer-based [3,3] sigmatropic dearomatization to generate 2,4-cyclohexadienone, (2) Michael addition of a nucleophile, and (3) liberation of HF for rearomatization. Besides the [3,3] rearrangement, [2,3] sigmatropic rearrangement from sulfonium ylide generated from alkyl sulfoxide promotes the dearomatization resulting in installation of α-sulfanyalkyl group.

Organofluorine compounds have occupied a privileged position in the field of pharmaceuticals, agrochemicals, and optoelectronics.1 Significant effort has been devoted for the synthesis of a wide range of organofluorine compounds.2,3,4 Selective C–F transformations are among the most important methods because readily available polyfluorinated arenes can be employed as starting materials.5 Besides classical S Ar reactions,6 recent progress in the cross-coupling arena has allowed transition-metal-mediated and catalyzed C–F functionalization.7

As a totally different approach, we are interested in sigmatropic dearomatization/defluorination sequences toward selective C–F bond transformation of polyfluorophenols.8 The reaction is initiated by interrupted Pummerer reaction of alkynyl9a or aryl9b sulfoxides with polyfluorophenols with the aid of trifluoroacetic anhydride (TFAA) (Scheme 1a).9 Subsequent [3,3] sigmatropic rearrangement would furnish dearomatized intermediate A, which is eventually involved in reductive defluorination with Zn powder to accomplish C–F transformations of fluorophenols (Scheme 1a, top). We envisioned that A can be a competent intermediate for Michael addition owing to the fairly reactive 2,4-cyclohexadienone skeleton of A. In analogy with the reaction of ortho-quinone monoacetals,8 a nucleophile would add to the 3 position of A, which would be followed by rearomatization with the loss of HF (Scheme 1a, bottom). This transformation can be regarded as an unusual 2,5-difunctionalization of 2,6-difluorophenol. Similar difunctionalization via a sequence of sigmatropic dearomatization/Michael addition was reported by Peng by using aryliodanes (Scheme 1b).9,10 However, the Michael addition products still have dearomatized skeleton owing to the absence of leaving groups. On the other hand, in our system, fluorine serves as a leaving group for rearomatization, while its poor leaving ability inhibits too fast decomposition of A. We herein report regioselective difunctionalization of 2,6-difluorophenols based on sigmatropic dearomatization. With aryl sulfoxides and nucleophiles including amines and thiols, multifunctionalized phenols can be synthesized.

Scheme 1. Sigmatropic dearomatization toward difunctionalization of aromatic compounds

a) 2,5-difunctionalization of fluorophenols

b) dearomative 2,5-difunctionalization of aryliodanes
Based on the hypothesis, dearomatized intermediate A was generated from 2,6-difluorophenol and 2-benzothienyl sulfoxide 1a under conditions similar to those for our previous C–F arylation except for the absence of Zn powder. Subsequently, piperidine (6.0 equiv) was added, and the solution was allowed to warm to room temperature and stirred for 1 h. Gratifyingly, the desired difunctionalized fluorophenol 2a was obtained in 71% yield (Scheme 2). The excess amount of piperidine was employed not only as a nucleophile but also as a base to neutralize CF₃CO₂H generated via the interrupted Pummerer reaction. Instead of piperidine, other secondary amines, pyrrolidine and diethylamine, furnished the corresponding difunctionalization products 2b and 2d in 74% and 68% yields, respectively. The present method is applicable to gram-scale synthesis: for example, 1.5 g (67% yield) of 2b was obtained from 6.0 mmol of 1a. Benzothienyl p-tolyl sulfoxide 1b also underwent the reaction to afford 2e in 76% yield. Primary amines were also suitable for the reaction to afford 2e and 2f, albeit the use of bulky t-butylamine provided 2g in 37% yield. Unfortunately, aniline was not a competent nucleophile probably because of the lower nucleophilicity. The reactions with 4-chloro-2,6-difluorophenol and with 2,6-difluoro-4-iodophenol afforded the corresponding fluorophenols 2i and 2j in moderate yields, respectively, in spite of the steric hindrance at the 5-position. With respect to aryl sulfoxides, 2-benzofuryl and 2-indolyl sulfoxides 1c and 1d smoothly underwent the reaction to afford 2k and 2l, respectively, under slightly modified conditions.

**Scheme 2. Substrate scope**

<table>
<thead>
<tr>
<th>Amines</th>
<th>Fluorophenols</th>
<th>Sulfoxides</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://repository.kulib.kyoto-u.ac.jp" alt="Image" /></td>
<td><img src="https://repository.kulib.kyoto-u.ac.jp" alt="Image" /></td>
<td><img src="https://repository.kulib.kyoto-u.ac.jp" alt="Image" /></td>
</tr>
<tr>
<td>R = Me, n = 2 (2a): 71%</td>
<td>2a: 50%</td>
<td><img src="https://repository.kulib.kyoto-u.ac.jp" alt="Image" /></td>
</tr>
<tr>
<td>R = p-tol, n = 2 (2c): 76%</td>
<td>2c: 52%</td>
<td><img src="https://repository.kulib.kyoto-u.ac.jp" alt="Image" /></td>
</tr>
</tbody>
</table>

When methyl 3-thienyl sulfoxide was employed, unexpected fluorophenol 3a was formed in 14% NMR yield instead of fluorophenol 2m (Scheme 3). It is speculated that the stronger aromaticity of thiophene ring than that of benzothiophene ring inhibited [3,3] sigmatropic rearrangement of sulfonium B. Instead, deprotonation at the methyl group of B would form sulfonium ylide C, which would then undergo [2,2] sigmatropic rearrangement to furnish dearomatized intermediate A'. Finally, Michael addition of piperidine to A' followed by elimination of HF would afford 3a.

**Scheme 3. Unexpected [2,3] sigmatropic rearrangement**

This finding inspired us to further investigate this tandem C–F alkylation/C–H amination. By using triethylamine for the deprotonation of B, the C–F alkylation uneventfully proceeded to furnish 3a in 70% yield. (Scheme 4). The reaction with DMSO smoothly proceeded to afford 3b in 68% yield. The structure of 3b was unambiguously confirmed by X-ray crystal structure analysis. Methyl phenyl sulfoxide exclusively provided 3c generated via [2,3] sigmatropic rearrangement in 58% yield. Trisubstituted carbon center could also be constructed with dibutyl sulfoxide, and the corresponding fluorophenol 3d was obtained in 56% yield.

**Scheme 4. Utilization of [2,3] sigmatropic rearrangement**

~6.0 mmol scale. *Stirred for 3 h in the second step. The first step was conducted at –40 °C. 2.0 equiv of TFAA were used.
We next explored the introduction of a different class of nucleophiles. In consequence, it was found that thiols reacted smoothly in the presence of triethylamine (Scheme 5). The reaction of 2,6-difluorophenol with sulfoxide 1a followed by treatment with p-toluenethiol afforded the corresponding 2,5-difunctionalized product 4a in 67% yield along with a tiny amount of 4-sulfanylated product 4a′ presumably formed via S₈₆反应 of dearomatized intermediate with the thiol. The employment of 4-chloro-2,6-difluorophenol uneventfully provided 4b in 57% yield. Alkanethiol was also applicable to the reaction to yield 4c. The intermediate generated via [2,3] rearrangement could be involved in the reaction with p-toluenethiol to provide 5 in 59% yield.

**Scheme 5. Addition of thiols**

To investigate relative reactivities of nucleophiles, we conducted a competition experiment by using hexylamine and dodecanethiol. Although sulfanylated product 4d was formed in 40% NMR yield, the corresponding aminated product 2e was not detected after the reaction, which indicates the higher reactivity of the thiol rather than the amine toward dearomatized intermediate A (Scheme 6).

To check the dispensability of the ortho-fluoro substituents, we tried the reaction with 2-fluorophenol. The reaction with 1a and piperidine under the conditions in Scheme 2 provided a mixture of the desired difunctionalized product 2n and biaryl 2o in a ratio of 1.4:1 (Scheme 7a). The latter is generated through C–C bond formation at the expense of the C₆–H bond of 2-fluorophenol. Similar non-regioselective C–C bond formation was observed in our previous work. In place of 2,6-difluorophenol, the use of 2,6-dichlorophenol failed to deliver difunctionalized product 2p and gave a complex product mixture (Scheme 7b). This result suggests that decomposition of dearomatized intermediate A–Cl would be too fast to survive until the addition of piperidine. This result highlights the essential role of fluorine, i.e. balancing the stability of the cyclohexadiene intermediate and the facileness of dearomatization. We also tried the reaction with 2,6-dimethylphenol. Although C–C bond formation with 1a via dearomatization proceeded, subsequent Michael addition of piperidine did not occur resulting in the formation of cyclohexadiene 2r in 59% NMR yield (Scheme 7c). The electron-donating nature and/or the larger size of methyl group compared to fluoro group might hamper the Michael addition process.

**Scheme 7. Attempted difunctionalizations of phenols other than 2,6-difluorinated ones**

Finally, we conducted the reaction with 2,3,5,6-tetrafluorophenol. Under the optimized conditions, tetrafluorophenol successively reacted with 1a and piperidine. As a result, cyclohexadiene 6 was obtained in 39% yield (Scheme 8a). The sigmatropic dearomatization and subsequent Michael addition would afford intermediate D and the following elimination of HF at the expense of C₅–F bond would form 6. Notably, besides 6,
another cyclohexadiene 7 was also detected in the product mixture. We assumed that 7 would be generated via 1,6-addition of the remaining piperidine and subsequent elimination of HF. Encouraged by these findings, we attempted two-step 2,3,5-trifunctionalization of tetrafluorophenol (Scheme 8b). First, tetrafluorophenol was successively treated with 1a and TFAA, piperidine, and p-toluenethiol to furnish cyclohexadiene 8. The reduction of 8 with Zn powder afforded the desired trifunctionalized product 9 in 67% overall yield.14 Remarkably, 9 has a benzene ring substituted by six different elements.

Scheme 8. 2,3,5-Trifunctionalization of tetrafluorophenol

In conclusion, we have achieved unusual 2,5-difunctionalization of 2,6-difluorophenols in a metal-free manner, based on sigmatropic dearomatization and subsequent Michael addition of nucleophiles. The reaction is realized by fluorne as a poor leaving group, which hinders fast decomposition of the dearylated intermediate, but smoothly departs on rearmatization.

ASSOCIATED CONTENT
Supporting Information
Experimental procedures, X-ray crystallographic analysis, and spectral data (PDF)

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Notes
The authors declare no competing financial interest.

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(11) Generation of intermediate A was confirmed by ^1H NMR. For details, see Figure S1 in the Supporting Information.


(14) Instead of the Zn-promoted reduction, we attempted 1,2-arylmigration of 8 (cf. Ref. 5b). However, treatment of 8 with 2 equiv of BF_3·Et_2O did not facilitate the 1,2-arylmigration and 74% of 8 was recovered after the reaction.