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Nucleophilic Deoxyfluorination of Catechols

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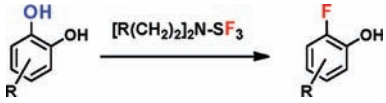
ABSTRACT



Nucleophilic deoxyfluorinaiton of one of the two hydroxyl groups of catechols has been developed via the *Umpolung* concept. This method was successively applied to naturally occurring catechols, such as catechins and dopamine, to produce novel fluorinated analogues.

The installation of fluorine atom(s) on pharmaceuticals or agrochemicals often causes dramatic improvement in their metabolic stability, lipophilicity, bioavailability, biological activity, and biological selectivity compared to the original molecules.[1−5] The most common way to design fluorinated compounds is to substitute hydrogen with its bioisostere fluorine. However, the substitution of oxygen in functional groups with fluorine has also been accomplished, due to the similarity of the two atoms in terms of electron negativity and van der Waals radius.[6] Indeed, radioactive 2-[^{18}F]fluorodeoxy-D-glucose (FDG) was developed as a glucose equivalent and has been used in positron emission tomography (PET) imaging for assessing glucose metabolism and for imaging tumors in oncology.[7] The replacement of amide moieties with vinyl fluorides is another example.[6] Therefore, the replacement of hydroxyl groups with fluorine atoms in biologically important molecules may be of particular interest for developing new bioactive compound candidates.

While the fluorination of benzene rings has been intensively developed,[8] the substitution of aromatic hydroxyl groups with fluorine atoms has recently begun to draw attention as well. However, methods for carrying out this transformation have remained mostly undeveloped. The first successful substitution was the Smiles rearrangement followed by the Balz−Schiemann reaction in 2005.[9] In 2009, the silver-mediated electrophilic fluorination of aryl stannanes, derived from the aryl triflates, was discovered,[10] and most recently, the Pd-catalyzed nucleophilic fluorination of aryl triflates has been reported.[11]

Many biologically important molecules, such as flavonoids, catechins and catecholamines, contain catechol moieties.[12] Substitution of one of the hydroxyl groups of these catechols with a fluorine atom may enhance the metabolic stability and lipophilicity of these molecules, increase the selectivity of their biological effects, or produce

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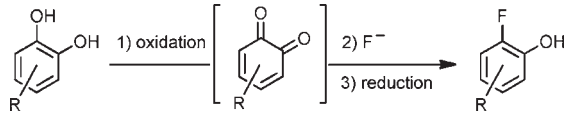
novel biological activities,[13] all of which offer potential for developing new drug candidates. One of the most common methods for the synthesis of deoxyfluorocatechols, in other words, *ortho*-fluorophenols, is the cationic fluorination of phenols,[14] which introduces a fluorine atom to an unsubstituted aromatic carbon. For the preparation of multifunctionalized *ortho*-fluorophenols, the corresponding phenol precursors are required. However, the preparation of such phenols is not always easy and/or often requires many steps. Other preparation methods of them include the multistep transformation of fluorinated benzene derivatives[13a,b,15] and the stepwise transformation of an *ortho*-functional group of the phenols to a fluorine atom, such as Balz–Schiemann reaction.[16] On the other hand, direct conversion of a hydroxyl group of catechol derivatives into a fluorine atom provides a quite different approach for producing the functionalized *ortho*-fluorophenols, which is particularly attractive and effective when the catechols are abundantly available; however, there are no reports on such transformation.

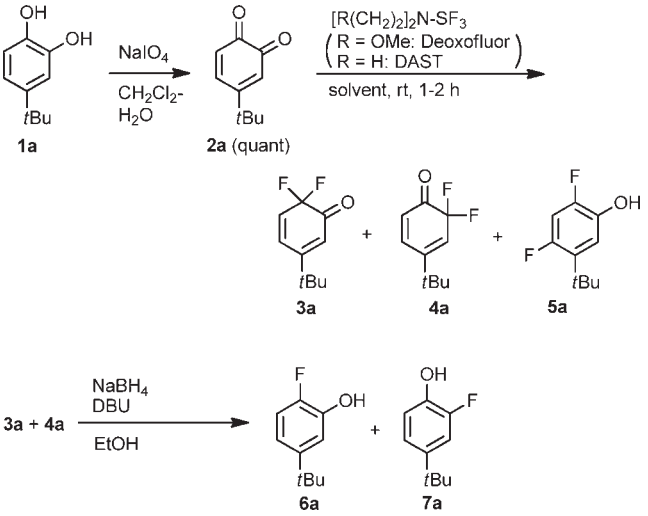
Scheme 1. Strategy for the Substitution of One of the Two Hydroxyl Groups of the Catechols with a Fluorine Atom



We now present the first protocol for the nucleophilic substitution of one of the two hydroxyl groups of catechols with a fluorine atom via the *Umpolung* concept (Scheme 1).[17]

To examine the feasibility of this strategy, the *ortho*-quinone **2a**, prepared by the known oxidation of the catechol **1a** using $NaIO_4$,[18] was treated with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor,[19] 6.0 equiv) in CH_2Cl_2 at room temperature.[20] Within 2 h, **2a** was consumed to afford a mixture of difluoroketones (**3a** and **4a**[21] in total 45%) and the difluorophenol **5a** (8%) after SiO_2 chromatography. The mixture of **3a** and **4a** was then treated with $NaBH_4$ in EtOH in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5 equiv) at 50 °C for 30 min to provide a separable mixture of **6a** and **7a** after the aromatization[22] (Scheme 2).

Scheme 2. Initial Examination of the Nucleophilic Displacement of the Catecholic Hydroxyl Group of **1a**



The yields of the products (**3a**–**5a**) were somehow related to the polarity of the solvent (in detail, see: SI). After intensive studies, $CHCl_3$ was disclosed to be one of the most effective solvents in terms of the reactivity and total yield. Thus, the reaction gave **3a** (43%), **4a** (10%), and **5a** (26%, each NMR yield) in 1 h. Diethylaminosulfur trifluoride (DAST), a similar fluorinating reagent, gave comparable results (**3a**: 37%, **4a**: 9%, **5a**: 32%, each NMR yield); however, the more thermally stable Deoxofluor seems to be more favorable.[19] **3a** did not change to **5a** under the stated reaction conditions, which suggested that **3a** and **5a** were independently generated (for a plausible reaction mechanism, see: SI).

When we applied this procedure to various catechols **1**, most of the *ortho*-quinones **2** were found to be less stable and gradually decompose during the isolation and purification. After intensive examination of various oxidants, the use of *o*-chloranil[23a] or $PhI(OAc)_2$[23b] (each 1.05 equiv)

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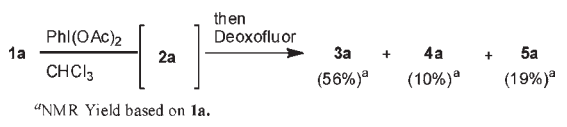
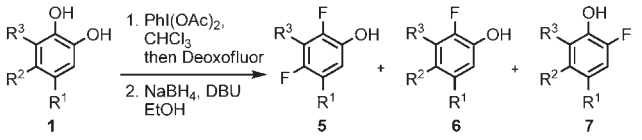
Scheme 3. One-Pot Oxidation of **1a** Followed by Fluorination



[a]NMR Yield based on **1a**.

in $CHCl_3$ produced a quantitative yield of **2a** in only 5 min.[24] The resultant crude reaction mixture was directly applicable to the Deoxofluor-mediated fluorination to give a mixture of **3a**–**5a** in a total 85% overall yield (Scheme 3), which was slightly higher than that obtained using the purified **2a**.

Table 1. Deoxyfluorination of Various Catechols **1a**–**i**



entry	substrate (**1**)	yield (%) **5**	**6**	**7**
1	R^1 = *t*Bu (**1a**)[a]	**5a**, 10	**6a**, 40	**7a**, 13
2	R^1 = $CHPh_2$ (**1b**)[a]	**5b**, 17	**6b**, 41	**7b**, 10
3	R^1 = $OC_{10}H_{21}$ (**1c**)[b]	**5c**, n.d.	**6c**, 48	**7c**, n.d.
4	R^2 = Me (**1d**)[b]	–	**6d**, 60	–
5	R^2 = *n*Bu (**1e**)[b]	–	**6e**, 35	**7e**, 35
6	**1f**[b]	–	**6f**, 34	**7f**, 25
7	R^1 = H, R^4 = Bn (**1g**)[b]	**5g**, 7	**6g**, 50	**7g**, n.d.
8	R^1 = Me, R^4 = Me (**1h**)[b]	**5h**, 8	**6h**, 57	**7h**, n.d.
9	R^1 = COOMe, R^4 = Bn (**1i**)[c,d]	**5i**, n.d.	**6i**, 10	**7i**, n.d.

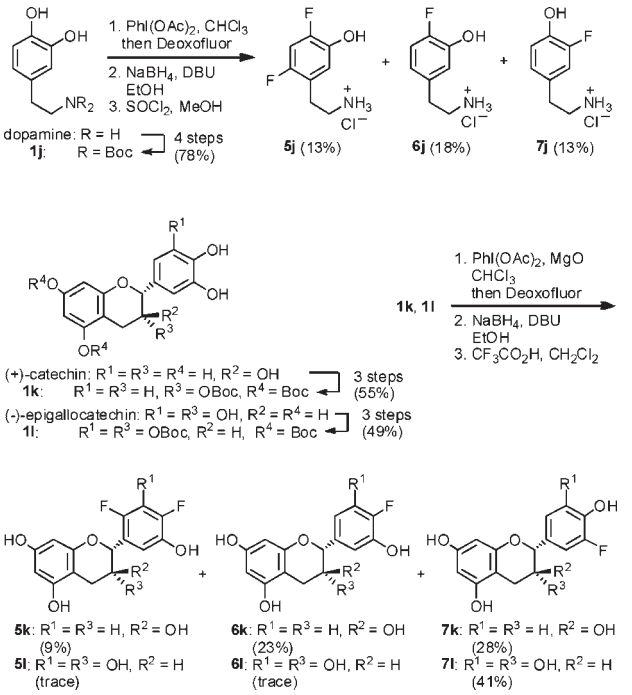
[a] *o*-Chloranil was used instead of $PhI(OAc)_2$. [b] MgO (2.3 equiv) was added to the oxidation reaction. [c] MeOH was used as the solvent instead of EtOH. [d] $CeCl_3 \cdot 7H_2O$ was added to the reduction reaction; n.d. = not detected.

On the basis of the developed one-pot procedure, the monosubstituted (**1b** and **1c**) and the disubstituted catechols (**1d**–**f**) were converted into the fluorophenols (**5**, **6** and **7**) (Table 1, Entries 2–6). Although an application of this method to pyrrogallol resulted in the formation of a complex mixture during the oxidation, its mono *O*-alkyl derivatives (**1g**–**i**) produced the fluorinated resorcinol derivatives (**6g**–**i**) with high regioselectivities (Entries 7–9). In some cases, the addition of MgO (2.3 equiv)[25] significantly improved the yields of **6c**–**h** and **7e**–**f** (Entries 3–8).

(24) The oxidation of catechols using Bu_4NIO_4[18] or $Pb(OAc)_2$[23c] smoothly proceeded in various organic solvents; however, they were less effective for the one-pot deoxyfluorination. The oxidation by Fetizon reagent[23d] was slow at room temperature, while the *ortho*-quinones gradually decomposed.

The discrimination of the two carbonyl groups of the *ortho*-quinones is of particular interest, which has not yet been sufficiently clarified. In our fluorination reactions, the reaction mainly took place at the *para*-carbonyl group of the substituents. In addition, the substrates (**1c**, **1g**–**i**) having an alkoxy group proceeded with a high selectivity. These results are in part understandable by the electron-donating ability of the substituents.[20,26]

Scheme 4. Deoxyfluorination of Suitably Protected Dopamine **1j** and Catechins (**1k** and **1l**)



The developed method was next applied to biologically important naturally occurring catechols, such as dopamine, (+)-catechin and (−)-epigallocatechin. First, reactive functional groups, such as the amino, the phenolic, and the aliphatic hydroxyl groups, were suitably protected to give **1j**–**l** in good-to-high overall yields. Specifically, the chemoselective protection of catechins was effectively achieved by the tentative protection of the catechol moiety with $[Cl(iPr)_2Si]_2O$[27] followed by the global Boc protection of the remaining hydroxyl groups and the desilylation (in detail, see: SI). The deoxyfluorination of **1j**–**l** proceeded by the standard sequential protocol to give the unnatural fluorinated analogues (**5j**, **5k**, **6j**, **6k** and **7j**–**l**) after the acid-mediated deprotection (Scheme 4). **6j** had been prepared from fluorobenzene derivatives via either a several-step transformation[13b] or electrophilic fluorination,[28] while **7j** was synthesized by the Balz–Schiemann reaction.[16] Some of the fluorinated derivatives were found to have enhanced selectivities in their original biological activities.[13b,c] On the other hand, **5j**, **6j**, **6k**, and **7j**–**l** are new, whose biological acitivities are under investigation.

In summary, we have developed the nucleophilic substitution of one of the two hydroxyl groups of catechols

with a fluorine atom to give *ortho*-fluorophenols. This unprecedented transformation was achieved via the *Umpolung* concept of electron-rich catechols and features the use of Deoxofluor and DAST that generate fluoride ions. Another advantage is not having to use transition metals. All of the reactions were conducted using standard glassware at around ambient temperature. The method has enabled us to convert naturally occurring catechols, such as catechins and dopamine, into novel fluorinated analogues, which could be attractive as novel potential candidates of new drug discovery. Studies on controlling the regioselectivity of the deoxyfluorination reaction and the application to the synthesis of fluorine-containing analogues of a wider range of biologically important catecholic compounds are currently underway in our laboratory.

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Supporting Information Available. Experimental details and ^{1}H, ^{13}C and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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