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# Hypervalent phenyl-$\lambda^3$-iodane-mediated *para*-selective aromatic fluorination of 3-phenylpropyl ethers†

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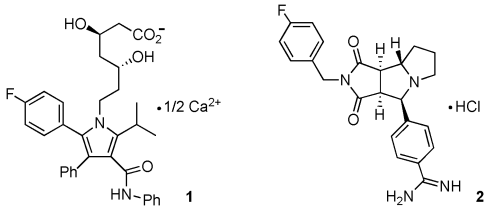
**Exposure of 3-phenylpropyl ethers to an activated iodosylbenzene monomer·18-crown-6 complex [PhI(OH)$BF_4$·18C6] in the presence of $BF_3$–$Et_2O$ and water results in the *para*-selective monofluorination of benzene ring *via* neighboring alkoxy group participation and directly affords 3-(4-fluorophenyl)propyl ethers regioselectively in good yields.**

Because of the profound effects of fluorine substitution on the metabolic stability, lipophilicity, basicity, and enhancing binding affinity to the target protein, regioselectively fluorinated aromatic compounds have found many applications as pharmaceuticals and agrochemicals.[1] Cholesterol-lowering drug atorvastatin **1** effectively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and consists of the *p*-fluorophenyl group attached to the pyrrole core (Scheme 1).[1,2] Lipitor **1** was found to be superior to a non-fluorinated ligand by a factor of 5. Muller and co-workers reported the synthesis of tricyclic thrombin inhibitor **2** with the *p*-fluorophenyl group, which showed higher activity against thrombin than the non-fluorinated parent compound and the other fluorinated regioisomers.[3] Another example is cholesterol-absorption inhibitor Ezetimibe with two *p*-fluorophenyl groups.[4]

A wide variety of methods have been developed for the fluorination of aromatic compounds, in which aromatic C–H bonds are directly converted to C–F linkages.[5] It is generally achieved *via* electrophilic fluorination with reagents such as $XeF_2$,[6] AcOF,[7] $CF_3OF$,[8] $CsSO_4F$,[9] fluoronitrogen compounds ($R_2NF$ and $R_3N^+F\ X^-$)[10] and molecular fluorine.[11] While monofluorinated products are obtained in most cases, multiple fluorination has been observed in some reactions with the more active reagents $F_2$, $CF_3OF$, $(CF_3SO_2)_2NF$ and Selectfluor.[12] These electrophilic fluorinations, however, suffer from low regioselectivity especially for electron-rich mono-substituted aromatics and generally produce a mixture of *o*/*p*-isomers.




**Scheme 1** Structures of atorvastatin **1** and thrombin inhibitor **2**.

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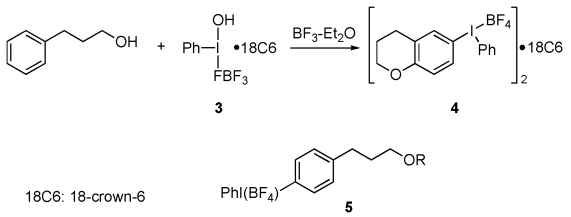
Umemoto and Tomizawa have developed an effective method for the highly regioselective *ortho*-fluorination of phenols and phenyl trimethylsilyl ethers, where *N*-fluoro-4,6-bis(trifluoromethyl)pyridinium-2-sulfonate was used as an electrophilic fluorination agent.[13] Preferential *ortho*-fluorination was observed in the reactions of anisole and trifluoroacetanilide with AcOF and $CsSO_4F$.[7,9] Combination of directed *ortho*-lithiation and electrophilic fluorination with *N*-fluorosulfonimide [$(PhSO_2)_2NF$] provides a useful route for the regioselective synthesis of *ortho*-fluorinated aromatic compounds.[14] A method for a regioselective *para*-fluorination of aromatic compounds, however, has never been reported and remains to be established experimentally. We report herein, for the first time, *para*-selective fluorination of 3-phenylpropyl ethers by the reaction with an activated iodosylbenzene–crown ether complex, in which neighboring alkoxy group participation plays a key role for the regioselective fluorination.

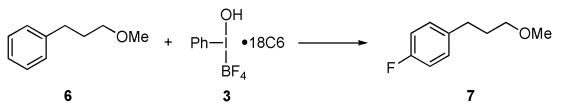
We have reported a synthesis of hydroxy(phenyl)-$\lambda^3$-iodane·18-crown-6 (18C6) complex **3**, where intermolecular iodane(III)···O interactions dramatically increase the stability of highly labile, activated iodosylbenzene monomer $PhI(OH)BF_4$.[15,16] Complex **3** serves as an environmentally friendly oxidizing agent and a variety of functional groups such as olefins, alkynes, enones, silyl enol ethers and phenols are oxidized under mild conditions, especially in water as a solvent. The complex **3** undergoes oxidation of 3-phenylpropanol in the presence of $BF_3$–$Et_2O$ and directly affords (6-chromanyl-$\lambda^3$-iodane)$_2$·18C6 complex **4** with an exclusively regioselective manner in a good yield (Scheme 2).[17] In the reaction, a small amount of diphenyl-$\lambda^3$-iodane **5a** (R = H) was also produced.

Interestingly, exposure of 3-phenylpropyl methyl ether (**6**) to complex **3** (1.2 equiv.) and $BF_3$–$Et_2O$ (1.2 equiv.) in dichloromethane at 45 °C under nitrogen resulted in regioselective aromatic fluorination with formation of 3-(4-fluorophenyl)propyl ether **7**, albeit in a low yield (27%). A large amount of ether **6** was recovered in the reaction but no formation of regioisomers of *p*-fluorobenzene **7** was




**Scheme 2** Oxidation of 3-phenylpropanol with complex **3**.

**Table 1** Regioselective fluorination of 3-phenylpropyl methyl ether (**6**)[a]



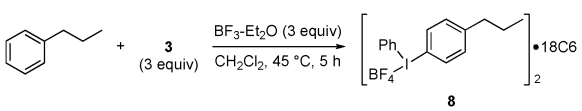

| Entry | $\lambda^3$-Iodane (equiv.) | Additive (equiv.) | Time/h | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **3** (1.2) | — | 15 | 0 |
| 2 | **3** (1.2) | $BF_3$–$Et_2O$ (1.2) | 6 | 27[c] |
| 3 | **3** (3.0) | $BF_3$–$Et_2O$ (3.0) | 6 | 61[d] |
| 4 | PhIO (3.0) | $BF_3$–$Et_2O$ (3.0) | 6 | 14 |
| 5[e] | *p*-TolI$F_2$ (3.0) | $BF_3$–$Et_2O$ (3.0) | 2.5 | 0 |

[a] Unless otherwise noted, reaction was carried out in dichloromethane at 40–45 °C under $N_2$. [b] $^1$H NMR yields. [c] Ether **6** (49%) was recovered. [d] Diaryl-$\lambda^3$-iodane **5b** (R = Me, 24%) was obtained. [e] Reaction was carried out at room temperature.

detected by $^1$H NMR analysis of a crude reaction mixture (Table 1, entry 2). Use of $BF_3$–$Et_2O$ as an additive probably enhances the reactivity of complex **3** through its coordination to the oxygen atom of the hydroxy group; in fact, without using $BF_3$–$Et_2O$, no formation of *p*-fluorobenzene **7** was observed (entry 1). Use of an excess amount of complex **3** (3 equiv.) increased the yield of **7** up to 61% (entry 3); in this reaction, however, simple aryl-$\lambda^3$-iodanation of the aromatic ring of **6** competes with the *para*-selective monofluorination and produced [4-(3-methoxypropyl)phenyl](phenyl)-$\lambda^3$-iodane **5b** (R = Me, 24%).

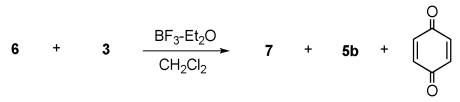
The presence of the etheric oxygen atom in **6** seems to be essential for this unique *para*-selective fluorination. Thus, no fluorination was detected in the reaction of *n*-propylbenzene with complex **3**, which selectively produced (4-propylphenyl-$\lambda^3$-iodane)$_2$·18C6 complex **8** in a good yield (Scheme 3). These results suggest that the oxygen atom in **6** will be responsible for the hydroxy-$\lambda^3$-iodane-mediated *para*-selective fluorination.

Exclusive formation of **8** (Scheme 3) probably suggests that, in the *para*-selective fluorination of **6**, use of $BF_3$–$Et_2O$ increases the activity of complex **3** but also diminishes the effects of the intramolecular γ-methoxy group, presumably because of coordination of $BF_3$ to the etheric oxygen atom, and hence a considerable amount of diaryl-$\lambda^3$-iodane **5b** will be produced as a by-product in entry 3 (Table 1). In order to prevent the $BF_3$-coordination to the etheric oxygen atom of **6** to some extent and thereby to maintain the neighboring group participation of the methoxy group, a small amount of water was added as an




**Scheme 3** Reaction of *n*-propylbenzene with hydroxy-$\lambda^3$-iodane **3**.

**Table 2** Effects of water on *para*-selective fluorination of **6**[a]



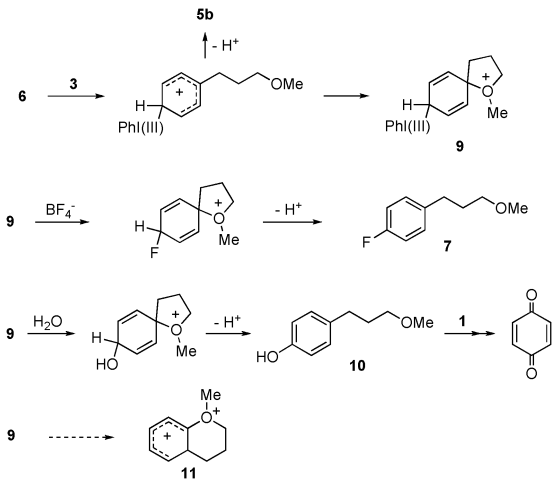

| | | Yield[b] (%) | | |
|---|---|---|---|---|
| Entry | $H_2O$ (equiv.) | **7** | **5b** | Quinone |
| 1 | — | 61 | 24 | 2 |
| 2 | 0.3 | 70 | 18 | 3 |
| 3 | 0.5 | 80 (59) | 16 | 4 |
| 4 | 0.8 | 79 | 12 | 5 |
| 5 | 1.0 | 74 | 8 | 5 |
| 6 | 2.0 | 65 | 3 | 8 |

[a] Reaction conditions: iodane **3** (3 equiv.)/$BF_3$–$Et_2O$ (3 equiv.)/$CH_2Cl_2$/45 °C/6 h/$N_2$. [b] $^1$H NMR yields. In parenthesis is isolated yield.

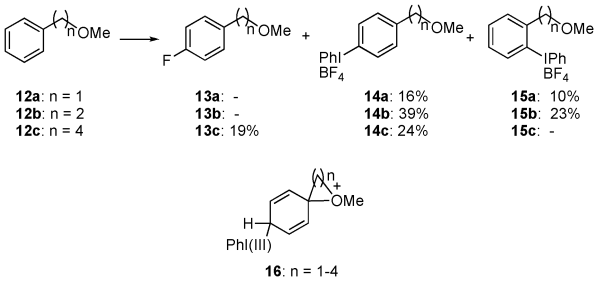
external oxygen base toward the Lewis acid (Table 2). High yields (*ca.* 80%) of fluorination product **7** were obtained by decreasing the competing formation of diaryliodane **5b**, when the reaction was carried out in the presence of 0.5 and 0.8 equiv. of water (Table 2, entries 3 and 4). Further increase in the amount of added water, however, gradually decreased the yield of **7** (entries 5 and 6): under these conditions, formation of by-product **5b** was most effectively prevented but the third reaction pathway, leading to the formation of another by-product 1,4-benzoquinone, has appeared to be more prominent.

Scheme 4 illustrates a reaction pathway for the formation of **7**. Positively charged iodine(III) of complex **3** selectively attacks the *para* position of the aromatic ring of **6** and the subsequent internal cyclization *via* nucleophilic attack of the intramolecular methoxy group will produce the spiro-1,4-cyclohexadiene **9**. Coordination of $BF_3$ to the etheric oxygen atom will tend to decrease the rate of this intramolecular cyclization. Instead of the cyclization, simple rearomatization through deprotonation affords the by-product **5b**.

Nucleophilic substitution of **9** with a $BF_4$ anion will produce **7** *via* facile reductive elimination of PhI, while that with water affords phenol **10**. Hypernucleofugality of phenyl-$\lambda^3$-iodanyl groups[18] would be responsible for these unique nucleophilic substitutions of **9**. Presence of a sterically demanding five-membered tetrahydrofuranyl group in **9** probably controls the




**Scheme 4** Reaction pathway.




**Scheme 5** Reaction of benzyl, phenethyl and phenylbutyl ethers **12**. Reaction conditions: iodane **3** (3 equiv.)/$BF_3$–$Et_2O$ (3 equiv.)/$H_2O$ (0.5 equiv.)/$CH_2Cl_2$/45 °C/6 h/$N_2$.

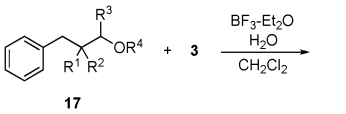
regioselective formation of these substitution products **7** and **10**. Phenol **10** will be further oxidized to *p*-benzoquinone under these conditions.[19] In fact, analogous 4-propylphenol was readily oxidized to *p*-benzoquinone (24%) with complex **3** without using $BF_3$–$Et_2O$ ($CD_2Cl_2$/room temperature/10 min). Diaryl-$\lambda^3$-iodane **5b** was found to be stable under these conditions, indicating that the formation of **7** does not involve the intermediacy of **5b**.[20] Ring-expanding 1,2-shift of the carbon–carbon bond with reductive elimination of PhI in **9**, yielding dication **11**, seems to be a high energy process, which is in marked contrast to the reaction of 3-phenylpropanol with complex **3** (Scheme 2).[17]

Further evidences for the neighboring etheric oxygen atom participation can be drawn from the reaction of methyl ethers **12** (Scheme 5). Both benzyl **12a** and phenethyl ethers **12b** did not show any evidences for the formation of *para*-fluorination products **13**, but instead produced diaryl-$\lambda^3$-iodanes **14** and **15** selectively. On the other hand, competition between *para*-fluorination (19%) and *para*-phenyl-$\lambda^3$-iodanation (24%) was observed in the reaction of 4-phenylbutyl methyl ether (**12c**). These results as well as the facile *para*-fluorination of 3-phenylpropyl ether **6** seem to reflect differences in stability between putative spirodiene intermediates **16**, being produced by the neighboring group participation. Winstein and co-workers reported that the rates of solvolysis of $MeO(CH_2)_nOBs$ (Bs = *p*-$BrC_6H_4SO_2$) in ethanol at 75 °C decrease in the order [*n* (relative rates to $Bu^nOBs$)] 4 (20.4) > 5 (2.84) > 3 (0.67) > 2 (0.25), because of neighboring methoxy group participation.[21] These results are in good agreement with our *para*-selective fluorination of **6** and **12c**.

We are pleased to find that the neighboring group participation provides an excellent method for the regioselective *para*-fluorination of a variety of 3-phenylpropyl ethers **17** (Table 3). The *para*-selective fluorination of **17** appears to be relatively sensitive to the nature of substituents on the carbon atoms attached to the etheric oxygen atom: for instance, introduction of methyl groups (**17a** and **17d**) and an ethyl group (**17b**) resulted in slightly decreased yields of fluorination products. Sterically hindered *tert*-butyl ether **17c** did not undergo fluorination and afforded a mixture of chromanyl-$\lambda^3$-iodane complex **4** (14%) and 3-phenylpropanol (72%), probably *via* acid-catalyzed deprotection of the *tert*-butyl group (Table 3, entry 3). β,β-Dimethyl ether **17e** and bis(methoxymethyl)ethylbenzenes **17f** and **17g** selectively produced good yields of *p*-fluorobenzenes **18e–g**.

Thus, we have developed a hypervalent phenyl-$\lambda^3$-iodane-mediated *para*-selective aromatic fluorination of 3-phenylpropyl ethers, in which neighboring group participation of alkoxy substituents plays an essential role. This is the first example of *para*-selective fluorination of simple alkylarenes.

**Table 3** Regioselective fluorination of ethers **17** with $\lambda^3$-iodane **3**[a]




| Entry | **17** ($R^1$, $R^2$, $R^3$, $R^4$) | **18** Yield[b] (%) |
|---|---|---|
| 1 | **17a** (H, H, H, Et) | 63 (44) |
| 2 | **17b** (H, H, H, $Pr^n$) | 52 (45) |
| 3 | **17c** (H, H, H, $Bu^t$) | 0[c] |
| 4 | **17d** (H, H, Me, Me) | 56 (51) |
| 5 | **17e** (Me, Me, H, Me) | 79 (63) |
| 6 | **17f** (H, $CH_2OMe$, H, Me) | 63 (65) |
| 7 | **17g** (Me, $CH_2OMe$, H, Me) | 74 (67) |

[a] Reaction conditions: iodane **3** (3 equiv.)/$BF_3$–$Et_2O$ (3 equiv.)/$H_2O$ (0.5 equiv.)/$CH_2Cl_2$/45 °C/6 h/$N_2$. [b] $^1H$ NMR yields. In parentheses are isolated yields. [c] Chromanyl-$\lambda^3$-iodane complex **4** (14%) and 3-phenylpropanol (72%) were obtained.

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