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Dehydroxylative Fluorination of Tertiary Alcohols

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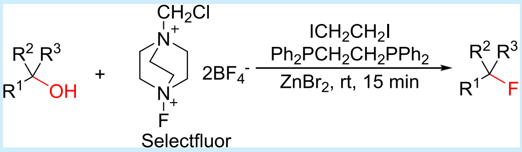
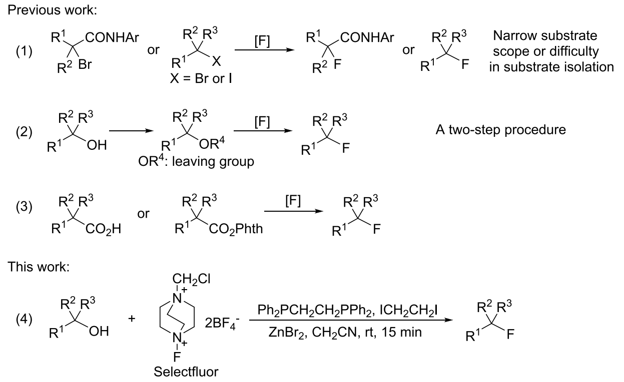
ABSTRACT: A large number of fluorination methods have been developed, but the construction of a tertiary C−F bond remains challenging. Herein, we describe an efficient dehydroxylative fluorination of tertiary alcohols with Selectfluor via the activation of a hydroxyl group by a $Ph_2PCH_2CH_2PPh_2$/ICH_2CH_2I system. Although the reagents appear to be not compatible (Selectfluor with the phosphine and I^- generated in situ), the reactions occur rapidly to give the desired products in moderate to high yields. This work may present a new discovery in fluorination of alcohols since the reported methods are mainly limited to primary and secondary alcohols.



Owing to the unique electronic effects of the fluorine element, the incorporation of a fluorine atom into an organic molecule may profoundly modify its physical, chemical, and biological properties.[1] As tertiary fluorides are important structural motifs in pharmaceuticals such as betamethasone and sofosbuvir, it would be highly desirable to develop efficient fluorination methods for the construction of a tertiary C−F bond. Although many fluorination methods have been developed,[2] site-selective fluorination for tertiary C−F bond formation remains a challenging task.

Nucleophilic fluorination of alkyl halides is one of the most widely used approaches for fluorine incorporation, but the transformation of tertiary alkyl halides suffers from competing side reactions such as eliminations and rearrangements.[1c] Nishikata[3] and Li[4] independently found that radical versions could effectively install tertiary C−F bonds (Scheme 1, eq 1). Cesium fluoride and Selectfluor were used as the fluorine sources, respectively. The Nishikata method can only be applied to *α*-bromo-*N*-arylamides, not to ordinary tertiary alkyl halides. Li's approach works well with ordinary tertiary bromides and iodides, but it is difficult to purify these substrates because during isolation they would readily undergo an elimination or rearrangement via the formation of tertiary cations. Besides halide groups, other leaving groups derived from hydroxyl functionality can also be substituted by fluorine via a radical reaction or a transition-metal-catalyzed process, but an installation of the leaving groups is required before fluorination (Scheme 1, eq 2).[5] Decarboxylative fluorination is an effective approach for tertiary C−F bond construction (Scheme 1, eq 3).[6] Apparently, it is still highly desirable to develop efficient methods for the installation of tertiary C−F bond.

Scheme 1. Tertiary C−F bond formation



Since alcohols are widely available and hydroxyl group is commonly found in natural products, direct dehydroxylative fluorination of alcohols has received increasing attention. Traditional methods suffer from the use of a hazardous S−F type reagent, such as SF_4 and DAST (diethylaminosulfur trifluoride).[7] The safety issue has prompted the development of milder dehydroxyfluorination reagents,[8] including PyFluor by Doyle,[9] PhenoFluor[10] and AlkylFluor[11] by Ritter. Recently, Watson disclosed that fluorination of alcohols with CuF_2 occurred smoothly in the presence of *N*,*N*′-diisopropylcarbodiimide for the activation of alcohols.[12] All of these dehydroxylative fluorination methods are quite efficient for the conversion of primary and secondary alcohols, but cannot be well applied to tertiary alcohols. We have previously found that the R_3P could react with ICH_2CH_2I to generate iodophosphonium salt $R_3P^+I\ I^-$, which can act as a strong Lewis acid to activate hydroxyl groups,[13] and thus, the R_3P/ICH_2CH_2I system was used to enable nucleophilic fluorination of alcohols.[13a] This process can also only be extended to

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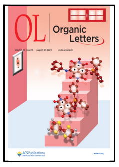

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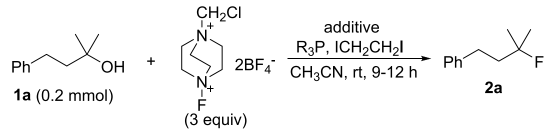
primary and secondary alcohols. Herein, we describe the dehydroxylative fluorination of tertiary alcohols with Selectfluor via the activation of hydroxyl group by a $Ph_2PCH_2CH_2PPh_2/ICH_2CH_2I$ system (Scheme 1, eq 4). The reactions proceeded rapidly (15 min) at room temperature to give moderate to high yields.

The failure of the R_3P/ICH_2CH_2I-promoted nucleophilic fluorination of tertiary alcohols encouraged us to investigate a radical process. We have previously shown Ph_3P/ICH_2CH_2I can effectively promote iodination of alcohols,[13a,b] and it has been reported by Li that tertiary iodides could readily undergo radical fluorination with Selectfluor.[4] Therefore, it is reasonable to speculate that Ph_3P/ICH_2CH_2I-promoted fluorination of tertiary alcohols with Selectfluor might occur if iodination product could be first generated in situ. However, two incompatible pairs of reagents may completely inhibit this fluorination. Ph_3P would readily undergo a redox reaction with Selectfluor.[14] Therefore, Ph_3P may not be able to cooperate with ICH_2CH_2I to activate alcohols, and the consumption of Selectfluor would also suppress fluorination. Furthermore, the iodination requires the presence of iodide anion, which could be produced from the Ph_3P/ICH_2CH_2I system.[13a,b] But the iodide anion may also be easily oxidized by Selectfluor.[15] Apparently, both iodination and fluorination would be suppressed due to the redox reactions of Selectfluor with Ph_3P and I^- anion.

We have found that DMF and CH_3CN are suitable solvents for the Ph_3P/ICH_2CH_2I-promoted dehydroxylation of alcohols,[13] and thus, these solvents were first screened for the fluorination of substrate **1a** (Table 1). No desired product was observed in DMF (entry 1). Although a low yield was obtained in CH_3CN (entry 2), the generation of the desired product was reflective of the feasibility of the proposed fluorination process. Besides Ph_3P, other trivalent phosphines were also examined (entries 3−9), and $Ph_2PCH_2CH_2PPh_2$ was found to be a suitable choice (entry 6). As both tertiary iodides and bromides can be fluorinated,[4] we thought that adding external iodide or bromide anion might be favorable for iodination or bromination and may thus further increase the fluorination yield. A brief survey of the ion additives revealed that using $ZnBr_2$ significantly increased the yield to 82% (entry 13). A 99% yield was obtained by increasing the loading of $ZnBr_2$ (entry 15). The reaction occurred rapidly and was completed with 15 min (entry 17).

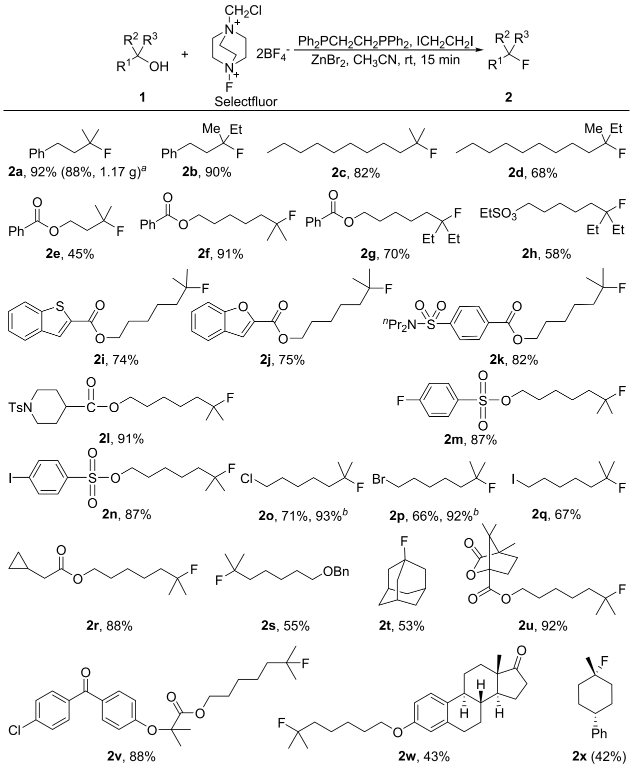
Table 1. Optimization of Reaction Conditions[a]



entry	R_3P	equiv ratio[a]	additive	yield[b] (%)
1[c]	Ph_3P	1.2:1.2:0		ND
2	Ph_3P	1.2:1.2:0		26
3	$(C_6F_5)_3P$	1.2:1.2:0		9
4	$Ph_2PCH = CH_2$	1.2:1.2:0		16
5	$Ph_2PCH_2PPh_2$	0.6:1.2:0		21
6	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0		65
7	$Ph_2P(CH_2)_3PPh_2$	0.6:1.2:0		18
8	BINAP	0.6:1.2:0		31
9	Xantphos	0.6:1.2:0		6
10	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.1	$^nBu_4N^+I^-$	58
11	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.1	$^nBu_4N^+Br^-$	66
12	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.1	KBr	68
13	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.1	$ZnBr_2$	82
14	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.6	$ZnBr_2$	89
15	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.8	$ZnBr_2$	99
16	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:1.0	$ZnBr_2$	90
17[d]	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.8	$ZnBr_2$	99
18[e]	$Ph_2P(CH_2)_2PPh_2$	0.6:1.2:0.8	$ZnBr_2$	91

[a]Equivalent ratio of R_3P/ICH_2CH_2I/additive relative to 1 equiv of substrate **1a**. [b]The yields were determined by ^{19}F NMR spectroscopy. [c]The reaction was performed in DMF (2 mL). [d]The reaction time was 15 min. [e]The reaction time was 5 min.

Scheme 2. Dehydroxylative Fluorination of Tertiary Alcohols*

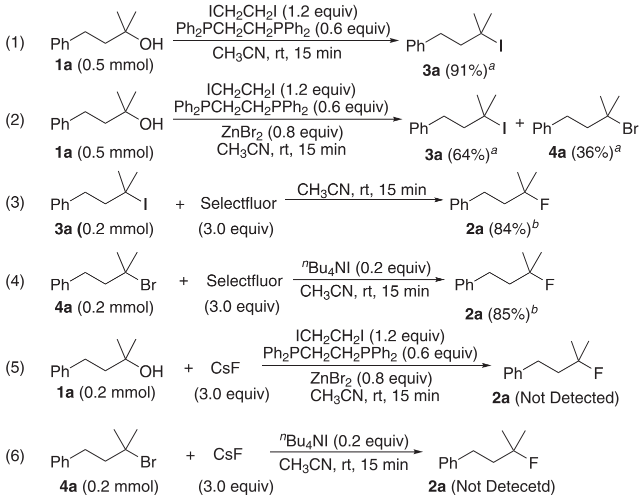


*Reaction conditions: alcohol **1** (0.5 mmol), Selectfluor (1.5 mmol), $Ph_2PCH_2CH_2PPh_2$ (0.3 mmol), ICH_2CH_2I (0.6 mmol), CH_3CN (5 mL), rt, 15 min, N_2 atmosphere. The yields were isolated yields. [a]A gram-scale reaction gave product **2a** in 88% yield. [b]The yields were determined by ^{19}F NMR spectroscopy. Lower isolated yields were obtained due to high volatility of the products.

With the optimal reaction conditions in hand (Table 1, entry 17), we then investigated the substrate scope of the dehydroxylative fluorination of tertiary alcohols. As shown in Scheme 2, the fluorination process could be extended to a wide range of tertiary alcohols. Various functional groups could be tolerated, such as carbonyl, ester, sulfonate, sulfonamide, and primary halides. The distance between the ester moiety and hydroxyl group affects the reaction efficiency. A short distance led to a low yield (**2e**), probably because the activation of hydroxyl group was suppressed due to the competing coordination of the ester group with the activating Lewis acid generated from the $Ph_2PCH_2CH_2PPh_2/ICH_2CH_2I$ system. With a long distance, the yield was not affected (e.g., **2f**, **2g**, and **2u**). Bulkier substituents would lead to a decrease in the yields due to steric effects (**2g**, **2h**, and **2t**). Fluorination of complex molecules also occurred smoothly (**2u**−**2w**). Surprisingly, *cis*-cyclic alcohol **1x** was exclusively converted into *cis*-product **2x**. To further demonstrate the synthetic potential of this protocol, fluorination of substrate **1a** was carried out on a gram scale. To our delight, product **2a** was isolated in a high yield (1.17g, 88%).

We propose that the reaction may proceed via the first iodination or bromination of alcohols, and the subsequent fluorination of tertiary iodides or bromides. Indeed, the $Ph_2PCH_2CH_2PPh_2/ICH_2CH_2I$ system can effectively convert alcohol **1a** into the corresponding iodide **3a** (Scheme 3, eq 1).

Scheme 3. Experimental Evidence for the Iodination and Bromination Paths

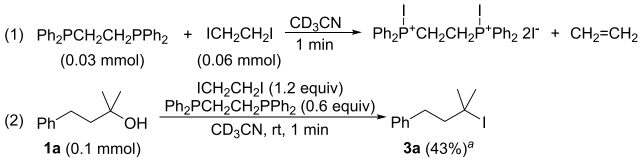


[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by ^{19}F NMR spectroscopy.

When $ZnBr_2$ was present, bromide **4a** was also provided (eq 2). Fluorination of both iodide **3a** and bromide **4a** occurred rapidly (eqs 3 and 4), reflecting that iodination and bromination are involved in the fluorination of alcohols. Since the $Ph_2PCH_2CH_2PPh_2/ICH_2CH_2I$ system alone can efficiently promote iodination, a question arose why bromination with $ZnBr_2$ should be involved to increase the fluorination yield. The reaction of $Ph_2PCH_2CH_2PPh_2$ with ICH_2CH_2I would generate iodide anion,[13] which could readily undergo a redox reaction with Selectfluor.[15] The consumption of iodide anion and Selectfluor would suppress iodination and fluorination, respectively. However, $ZnBr_2$ cannot be completely dissociated to release bromide anion, and thus the redox reaction of $ZnBr_2$ with Selectfluor would not easily occur. Although not completely dissociated, $ZnBr_2$ still can effectively promote bromination. Therefore, $ZnBr_2$ is quite important for this fluorination process. Although the redox reaction of I^- with Selectlfuor would generate fluoride anion,[15] nucleophilic fluorination could still be excluded on the basis that no desired product was observed by using CsF instead of Selectfluor (eq 5) and that bromide **4a** cannot be converted into fluorinated product within 15 min (eq 6).

I^-/Selectfluor is not the only incompatible pair in the reaction system. $Ph_2PCH_2CH_2PPh_2$ is not compatible with Selecfluor either.[14] The issue of this incompatibility can be addressed by sequential addition of reagents because $Ph_2PCH_2CH_2PPh_2$ reacts with ICH_2CH_2I very fast. $Ph_2PCH_2CH_2PPh_2$ is not soluble in the reaction solvent, CH_3CN, and thus, it would be present as a solid in CH_3CN. However, after ICH_2CH_2I was added, the solid disappeared quickly with stirring the reaction mixture. No solid remained after stirring for about 1 min, and ^{31}P NMR analysis revealed that $Ph_2PCH_2CH_2PPh_2$ was almost completely transformed into a species whose resonance signal appearing at 51.3 ppm, which should correspond to a diiodophosphonium salt, $[Ph_2P^+(I)CH_2CH_2P^+(I)Ph_2]\ 2I^-$, according to our previous investigations (Scheme 4, eq 1).[13a] The diiodophosphonium salt is quite reactive and may easily undergo side reactions. However, if the substrate alcohol is added before ICH_2CH_2I, the phosphonium salt generated in situ may specifically coordinate to the alcohol and thus side reactions may be suppressed. Indeed, when an alcohol was present, the hydroxyl group was effectively activated and iodination product was obtained in 43% yield right after the solid disappeared (eq 2). For the fluorination procedure, after alcohol/$Ph_2PCH_2CH_2PPh_2/ICH_2CH_2I$ was added and the solid disappeared (about 1 min), $ZnBr_2$ and Selectfluor were then sequentially added without time interval. The issue of incompatibility could be avoided by this procedure.

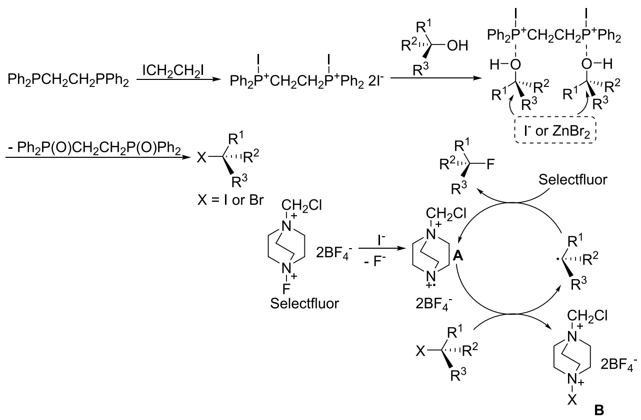
Scheme 4. Need for Sequential Addition of Reagents



[a]The yield was determined by ^{1}H NMR spectroscopy.

Based on the above results, we propose the reaction mechanism as shown in Scheme 5. $Ph_2PCH_2CH_2PPh_2$ reacts with ICH_2CH_2I rapidly to generate diiodophosphonium salt $[Ph_2P^+(I)CH_2CH_2P^+(I)Ph_2]\ 2I^-$, which can act as a Lewis acid to activate hydroxyl group for the iodination or bromination of alcohols.[13a] A redox reaction of Selectfluor with I^- anion produces radical cation **A**, which abstracts a halogen atom from tertiary iodides or bromides to deliver alkyl radical. Fluorination of this radical with Selectfluor provides the final product.[4] The stereoselectivity for the formation of product **2x** should be because of a double-inversion process, iodination or bromination of alcohols with inversion of configuration,[13a] and

Scheme 5. Plausible Reaction Mechanism



fluorination of the alkyl radical with the second inversion. In this case, probably the alkyl radical and salt **B** are not completely dissociated but are present as a contact ion radical pair, resulting in a back-side combination to the fluorine atom.

In summary, we have described a convenient dehydroxylative fluorination of tertiary alcohols under mild conditions. Compared with previous methods for tertiary C−F bond formation, this protocol features high efficiency (a reaction time of 15 min) and the use of easily available alcohols as substrates. This work may represent a new discovery in fluorination of alcohols since the reported methods are mainly limited to primary and secondary alcohols. The approach may find utility in ^{18}F-labeling due to its high efficiency.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02438.

Experimental details; references and notes; copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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