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Direct and Convenient Conversion of Alcohols to Fluorides

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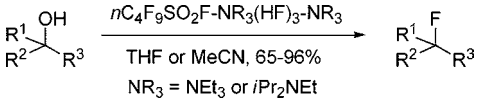
ABSTRACT



Directly mixing primary, secondary, and tertiary alcohols with $nC_4F_9SO_2F$–$NR_3(HF)_3$–NR_3 in THF or MeCN results in convenient conversion to the corresponding fluorides in high yields. The readily available reagents are easy to handle, and the mild, almost neutral reaction conditions allow for excellent functional group compatibility. A $NR_3(HF)_3/NR_3$ ratio of $\leq$1:2 gives the highest reactivity.

A carbon−fluorine bond is presented in numerous bioactive compounds due to its resistance to metabolism with minimal steric interference and other unique effects on a compound's biological activity.[1] In the extensively studied area of fluorination,[2] direct conversion of an alcohol to the corresponding fluoride has been one of the most effective approaches. Many reagents have been developed for this transformation, including SF_4,[3] SeF_4,[4] pyridinium poly(hydrogen fluoride) (Olah's reagent) and its analogues,[2b,5] fluoroalkyl amino reagents (FAR),[6] ammonium and phosphonium perfluorocyclobutane ylides,[7] 2,2-difluoro-1,3-dimethylimidazolidine (DFI),[8] $IF_5/NEt_3(HF)_3$,[9] and perfluoro-1-butanesulfonyl fluoride-DBU.[10] However, these reagents have seen limited application due to one or more of the following reasons: being limited in scope, dangerous and difficult to handle, not readily available, unstable, or low-yielding or requiring harsh conditions. On the other hand, DAST (diethylaminosulfur trifluoride)[11,12] and its thermally more stable analogues such as Deoxo-Fluor [bis(2-methoxyethyl)aminosulfur trifluoride][13] have been widely used for fluorinating alcohols due to their general reactivity,[2a,14,15] but they are expensive, corrosive, and problematic in a few functionalized systems.[16,17] Most of the above reagents operate under acidic conditions, generating deadly HF. Here we report a safer and convenient method for direct conversion of alcohols to fluorides using readily available reagents under mild and almost neutral conditions.

We envisioned an approach by a mechanism similar to that in fluorination with DAST or any dialkylaminosulfur

(1) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(2) (a) Spargo, P. L. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: New York, 1995; Vol. 2, p 1. (b) Yoneda, N. *Tetrahedron* **1991**, *47*, 5329.
(3) Wang, C. L. J. *Org. React.* **1985**, *34*, 319.
(4) Olah, G. A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* **1974**, *96*, 925.
(5) (a) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872. (b) Busci, I.; Török, B.; Marco, A. I.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **2002**, *124*, 7728 and references therein.
(6) For examples: (a) Yarovenko, N. N.; Raksha, M. A. *J. Gen. Chem. (Engl. Transl.)* **1959**, *29*, 2125. (b) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377. (c) Dmowski, W.; Kamiński, M. *J. Fluorine Chem.* **1983**, *23*, 219. (d) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. *J. Fluorine Chem.* **2001**, *109*, 25.
(7) (a) Pasenok, S. V.; de Roos, M. E.; Appel, W. K. *Tetrahedron* **1996**, *52*, 2977.
(8) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618.
(9) Yoneda, N.; Fukuhara, T. *Chem. Lett.* **2001**, 222.
(10) (a) Bennua-Skalmowski, B.; Vorbrüggen, H. *Tetrahedron Lett.* **1995**, *36*, 2611. (b) Savu, P. M.; Snustad, D. PCT Int. Appl. WO 0031003, 2000.
(11) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(12) For a review and a survey of all the suitable substrates, see: (a) Hudlicky, M. *Org. React.* **1988**, *35*, 513.
(13) (a) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun.* **1999**, 215. (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048.
(14) For a recent review, see: Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561.
(15) DAST and analogues have compared favorably with most other fluorinating reagents. See ref 12.

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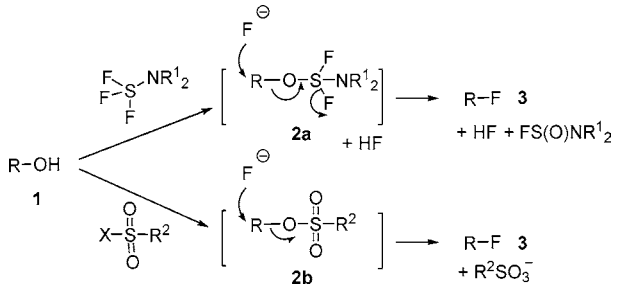
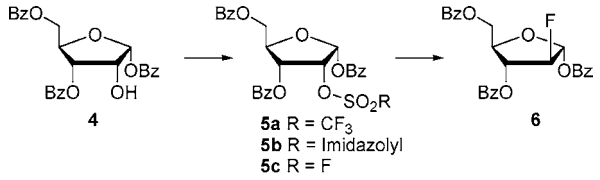
Scheme 1



trifluoride (Scheme 1).[11,12] The alcohol is activated by DAST via the intermediate **2a**,[18] which is then attacked in situ by fluoride to form the carbon−fluorine bond in **3** with 1 equiv of HF as the byproduct. To achieve the same results without using an expensive $F_3SNR^1_2$ reagent or generating free HF, one could form a similar sulfonate leaving group as in **2b** followed by in situ fluorination with a compatible fluorinating reagent under near-neutral conditions.

Fluorination of 2-hydroxy-1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**) and its analogues has attracted much interest for the synthesis of many biologically active compounds. It has been achieved in one step by using DAST[19] or in two steps by fluorinating the isolated sulfonates **5a**−**c** (Scheme 2).[16b,20] To establish an appropriate sulfonate leaving group

Scheme 2[a]



[a] One-pot procedure: Pyr, Tf_2O, MeCN, rt; then $NEt_3(HF)_3$−NEt_3, 50 °C, 18 h, 73% yield.

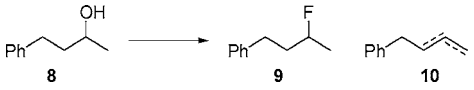
in **2b** as well as a reactive fluoride source, we decided to first develop a practical one-pot synthesis of **6** from commercially available **4**. After numerous experiments, we found that triflate, as in **5a**, was the best leaving group[21] and MeCN the best solvent to carry out both triflate formation and fluorination in one pot.

$NEt_3(HF)_3$ (**7**)[22] was found to be the most reactive fluoride source.[23] In addition, it is anhydrous, soluble in organic solvents, and inexpensive. Although $NEt_3(HF)_2$, prepared from $NEt_3(HF)_3/NEt_3$ in a 2:1 ratio, had been found to be better than a 1:0 or 1:2 ratio,[24] we found that NEt_3HF, from a 1:2 ratio of $NEt_3(HF)_3/NEt_3$, was most reactive in various solvents for this substrate. Therefore, a practical, one-pot synthesis of **6** could be achieved in 73% yield by treating the in situ-formed triflate solution in MeCN, **5a**, with $NEt_3(HF)_3/NEt_3$ (1:2) at 50 °C.

Encouraged by the initial success, we attempted a simpler procedure by adding the triflic anhydride into the mixture of alcohol, base, and the fluorinating reagents, but a significant amount of starting material was recovered, indicating the incompatibility between Tf_2O and $NEt_3(HF)_3/NEt_3$.[25] The result also suggests the requirement of complete triflate formation before fluorination, which makes the two-step procedure discontinuous and problematic if the triflate is unstable.[26]

Perfluoro-1-butanesulfonyl fluoride (PBSF) was then used to activate alcohols due to its compatibility with $NEt_3(HF)_3$. To study the extent of elimination as a major side reaction, 4-phenyl-2-butanol (**8**) was used to optimize the reaction conditions (Table 1).

Table 1. Optimization of Conditions with PBSF[a]



entry	**7** (equiv)	NEt_3 (equiv)	PBSF (equiv)	solvent	conversion (%)	**9**[b] (%)	**9**/**10**[c]
1	2.0	6.0	2.0	MeCN	100	75	3.5
2	2.0	6.0	2.0	CH_2Cl_2	98	81	5.3
3	2.0	6.0	2.0	toluene	94	79	7.5
4	2.0	6.0	2.0	THF	98	82	6.8
5	2.0	4.0	2.0	THF	94	79	6.6
6	2.0	3.0	2.0	THF	84	70	6.3
7	2.0	2.0	2.0	THF	57	47	5.8
8	1.5	4.5	1.5	THF[d]	99	82	6.4
9	1.0	3.3	1.3[e]	CH_2Cl_2	97	72	3.2
10	1.0	3.3[f]	1.3[e]	CH_2Cl_2	96	69	3.1
11	1.8 equiv of DBU, 1.8 equiv of PBSF			toluene[g]	92	61	6.4
12	1.2 equiv of Deoxo-Fluor			CH_2Cl_2[h]	91	72	5.4

[a] Reaction conditions: 1.0 mmol **8**, $NEt_3(HF)_3$ (**7**), NEt_3, PBSF, solvent (3 mL/mmol), rt, 15−20h. [b] Estimated LC yield. [c] Uncorrected LC area ratio. [d] Conditions: 1 mL/mmol. [e] Tf_2O was used instead; triflate formation at −78 to 0 °C; fluorination at 0 °C to room temperature. [f] iPr_2NEt was used as the base; $iPr_2NEt(HF)_3$ was used instead of **7**. [g] Conditions: 1 mL/mmol, 0 °C, DBU added last. [h] Conditions: 0.5 mL/mmol, −78 °C to room temperature.

The fluorination of **8** proceeded smoothly to give **9** with PBSF activation in the presence of $NEt_3(HF)_3/NEt_3$ in various solvents with a mixture of olefinic isomers **10** as major byproducts. MeCN gave the fastest reaction but with a low

(16) (a) Konas, D. W.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 8831. (b) Tann, C. H.; Brodfuehrer, P. R.; Brundidge, S. P.; Sapino, C., Jr.; Howell, H. G. *J. Org. Chem.* **1985**, *50*, 3644. (c) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090.

(17) In those cases (ref 16), the fluorination could be realized via isolated triflate/imidazolylsulfonate.

(18) For an isolation of the intermediate, see: Sutherland, A.; Vederas, J. C. *Chem. Commun.* **1999**, 1739.

(19) Schärer, O. D.; Verdine, G. L. *J. Am. Chem. Soc.* **1995**, *117*, 10781.

(20) (a) Chou, T. S.; Becke, L. M.; O'Toole, J. C.; Carr, A.; Parker, B. E. *Tetrahedron Lett.* **1996**, *37*, 17. (b) Alauddin, M. M.; Conti, P. S.; Mathew, T.; Fissekis, J. D.; Prakash, G. K. S.; Watanabe, K. A. *J. Fluorine Chem.* **2000**, *106*, 87. (c) Rubira, M.-J.; Jimeno, M.-L.; Balzarini, J.; Camarasa, M.-J.; Pérez-Pérez, M.-J. *Tetrahedron* **1998**, *54*, 8223. (d) Ma, T.; Pai, S. B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du. J.; Wang, C.; Kim, H.; Newton, M. G.; Cheng, Y. C.; Chu, C. K. *J. Med. Chem.* **1996**, *39*, 2835. (e) Takamatsu, S.; Maruyama, T.; Katayama, S.; Hirose, N.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 2321.

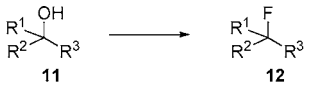
product/elimination selectivity of 3.5 (entry 1). Toluene gave the highest selectivity of 7.5 (entry 3), but the reaction was slow as a bilayer mixture. THF was chosen as a good compromise to give a fast reaction and good selectivity (entry 4). Once again, a lower ratio of $NEt_3(HF)_3/NEt_3$ at $\leq$1:2 gave a faster reaction as well as a better product/elimination ratio (entries 4−7). Less reagents could be used at a higher concentration with slightly more elimination (entry 8). Use of triflic anhydride resulted in higher amounts of elimination with NEt_3 or Hünig's base as the base (entries 9 and 10). The combination of PBSF-DBU in toluene[10b] resulted in slightly more elimination and a significantly less clean reaction with only 61% of the fluorinated product formed (entry 11). Deoxo-Fluor gave a slower reaction with slightly more elimination under the literature conditions[13] (entry 12).

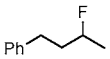
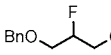
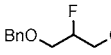
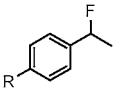
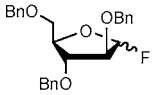
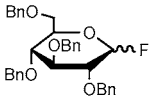
Under the optimized conditions (entry 4), all the reagents could be mixed together with the alcohol in any order for fluorination without the need to preform the sulfonate intermediate.[27] Therefore, PBSF−$NEt_3(HF)_3$−NEt_3 functions as a reagent combination that fluorinates alcohols operationally similar to DAST and Deoxo-Fluor.

We then applied this new reagent combination to a variety of alcohols (Table 2).[28]

Secondary alcohols were fluorinated in high yields (entries 1−3), and a primary tosylate could be tolerated (entry 3). Secondary benzylic alcohols also gave good yields (entries 4 and 5).[29] The protected arabinofuranose and glucopyranose precursors to **12e** and **12f** were readily fluorinated, giving an α/β anomer ratio of 1:2.4 and 3.5:1, respectively (entries 6 and 7). Interestingly, the same reactions with Deoxo-Fluor gave reversed selectivity of 1.8:1 and 1:2.3 for **12e** and **12f**, respectively. The tertiary alcohol fluorinated to produce **12g** required forcing conditions at 95 °C (entry 8).[30]

Table 2. Fluorination with PBSF−$NEt_3(HF)_3$−NEt_3[a]



entry	product		conc(M)	T (°C)	time (h)	yield(%)
1		**9**	0.33	20	26	79(88)[b]
2		**12a**	0.25	20	22	86
3		**12b**	0.25	20	6	92
4	 R = H	**12c**	0.25	20	24	(77)[b]
5	R = Me	**12d**	0.25	20	26	(86)[b]
6		**12e**	1	50	17	87[c]
7		**12f**	1	20	17	86[d]
8		**12g**	1	95	9	89[c,e]

[a] Reaction conditions: 1.0 mmol of ROH, 2 equiv of PBSF, 2 equiv of $NEt_3(HF)_3$, 6 equiv of of NEt_3, THF (1−4 mL/mmol ROH). [b] Parenthetical numbers are LC yields. [c] MeCN as the solvent. [d] DCE as the solvent. [e] Conditions: 3 equiv of PBSF, 3 equiv of $NEt_3(HF)_3$, 9 equiv of NEt_3, sealed Schlenk tube.

Unfortunately, fluorination of primary and activated benzylic alcohols gave significant amounts of impurities, likely from the displacement of the activated hydroxy group by triethylamine.[31] To overcome this problem, the bulkier Hünig's base[32] and its trishydrofluoride were used instead. This Hünig's base variant gave excellent results on these alcohols (Table 3).

Primary alcohols typically gave very clean reactions in excellent yields (entries 1−5).[33] It is noteworthy that the aldehyde group in **12k** was tolerated with this method, although the reaction using Deoxo-Fluor resulted in a mixture of products.[34] Other functional groups such as esters (entries 5 and 6) and a ketone (entry 7) are also well tolerated. The fluorination of benzhydrol and 9-hydroxyfluorene with DAST gave only 40−48% of fluorides with a significant amount of dimeric ether (13−44%);[35] we faced the same problem with MeCN as the solvent. Switching the solvent

(21) Formation of an imidazolylsulfonate **5b** (also the precursor to **5c**) would produce a chloride that would act as a nucleophile. Other sulfonates such as mesylate and tosylate are not active enough.

(22) For a review of this commercially available reagent, see: McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31.

(23) Tetrabutylammonium fluoride (TBAF) is wet as a solid or solution. Metal fluorides such as KF and CsF need to be used in highly toxic solvents such as formamide and *N*-methylformamide and often give significant hydrolysis. See: (a) Fritz-Langhals, E. *Tetrahedron: Asymmetry* **1994**, *5*, 981. (b) Fritz-Langhals, E. *Tetrahedron Lett.* **1994**, *35*, 1851. (c) Ref 20b. Many modified metal fluoride reagents have been reported, but most are less efficient than TBAF: (d) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278 and references therein.

(24) (a) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527. (b) Ref 20a.

(25) FSO_2CF_3 might be formed as a gas.

(26) One-pot conversion of few ethanols with a 2-electron-withdrawing group to fluorides using methane- or benzene-sulfonyl fluoride and KF in <60% yields has been reported: Pattison, F. L. M.; Millington, J. E. *Can. J. Chem.* **1956**, *34*, 757.

(27) We only observed the sulfonate intermediate by LC or GC in very few cases.

(28) **Typical Procedure** (Table 2, entry 1): 4-Phenyl-2-butanol (306 mg, 2.0 mmol, 1.0 equiv), PBSF (0.72 mL, 4.0 mmol, 2.0 equiv), $NEt_3(HF)_3$ (0.656 mL, 4.0 mmol, 2.0 equiv), and NEt_3 (1.67 mL, 12.0 mmol, 6.0 equiv) were stirred in 6 mL of THF at room temperature for 26 h when LC revealed >98% conversion (LC assay yield 88%). The mixture was filtered through a short SiO_2 plug, concentrated, and purified by SiO_2 column to give 240 mg of **9** (79% isolated yield, 9% loss in distillate during concentration) as a colorless oil (ref 24a). ^{19}F NMR (377 MHz, $CDCl_3$) δ −174.5.

(29) LC yields are given due to the low boiling points and rather fast decomposition of the isolated products.

(30) Treating **4** with the reagent combination failed to give **6**.

(31) LC-MS data and its water solubility support the proposed assignment. Reaction of primary triflate with pyridine to form water-soluble pyrdinium salt has been reported: Ambrose, M. G.; Binkley, R. W. *J. Org. Chem.* **1983**, *48*, 674. We also observed a similar product when pyridine was used.

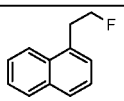
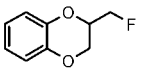
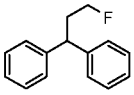
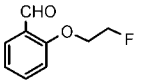
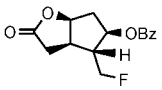
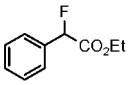
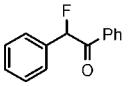
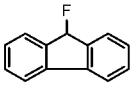
(32) Use of other bases such as pyridine, 2,6-lutidine, DABCO, DBU, TMEDA, and so on gave inferior results.

(33) We generally saw slower and incomplete reactions for fluorination of primary alcohols using Deoxo-Fluor.

(34) Deoxo-Fluor is known to react with aldehydes. See ref 13.

(35) Johnson, A. L. *J. Org. Chem.* **1982**, *47*, 5220.

Table 3. Fluorination with PBSF−*i*Pr$_2$NEt(HF)$_3$−*i*Pr$_2$NEt[a]

entry	product		equiv PBSF/ *i*Pr$_2$NEt(HF)$_3$/*i*Pr$_2$NEt	T (°C)	time (h)	yield(%)
1		**12h**	2.0/1.5/4.5	RT	25	96
2		**12i**	2.0/1.5/4.5	45	22	96
3		**12j**	2.0/1.5/4.5	45	22	90
4		**12k**	1.2/1.3/3.8	24	1.5	93
5		**12l**	2.0/2.0/6.0	50	17	90
6		**12m**	1.5/1.0/3.5	RT	20.5	88
7		**12n**	1.5/1.0/2.7	45	25	88
8		**12o**	2.0/2.0/6.0	45	17	(88)[b,c]
9		**12p**	2.0/2.0/6.0	RT/45	24/24	65[d]

[a] Reaction conditions: 1.0 mmol ROH, MeCN (1 mL/mmol ROH). [b] MeCN (0.5 mL/mmol ROH). [c] Parenthetical number is an LC yield. [d] THF is the solvent (4 mL/mmol ROH).

to THF along with a higher dilution improved the yields of the desired fluorination to 88 and 65% (entries 8 and 9). A combination of 2 equiv of PBSF, 2 equiv of *i*Pr$_2$NEt(HF)$_3$, and 6 equiv of *i*Pr$_2$NEt is generally effective, but lower levels of reagents could also be used (entries 4, 6, and 7).

In addition to its general reactivity and some unique selectivities shown above, the new reagent combinations fluorinate alcohols under almost neutral and thus safer conditions, because HF is quenched by 1 equiv of base in situ.[36,37] Unlike DAST, Deoxo-Fluor, and Tf_2O, which react violently with water, all reagents are relatively stable upon exposure to air or moisture.[38] Reactions could be readily carried out in capped vials/flasks without special precaution to remove air or moisture. All these features should make the combination of PBSF−NEt$_3$(HF)$_3$−NEt$_3$ and its Hünig's base variant valuable additions to the arsenal for direct fluorination of alcohols.

In summary, we have developed a novel reagent combination, PBSF−NEt$_3$(HF)$_3$−NEt$_3$, for direct and convenient fluorination of alcohols in high yields. The Hünig's base variation, PBSF−*i*Pr$_2$NEt(HF)$_3$−*i*Pr$_2$NEt, is preferred with primary and activated benzylic alcohols. Various functional groups could be tolerated. A combination of NEt$_3$(HF)$_3$/NEt$_3$ in ≤1:2 ratio was found to be the most reactive fluorinating species. All reagents are readily available and easy to handle, and the reactions are carried out under mild and near-neutral conditions without generating free HF.

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Supporting Information Available: Experimental procedures and characterization data for fluorination products (Tables 2 and 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) In the reaction to give **12k**, direct quench of the reaction with water gave a pH of 6, well above the pK_a of HF (3.2 in water).

(37) By contrast, fluorination with DAST or Deoxo-Fluor generates 1 equiv of HF, which also etches glass as we have observed. We have not seen any etching using the reagent combination. NEt$_3$(HF)$_3$ is also reported to be noncorrosive to glassware due to its almost neutral pH. See refs 20a and 22.

(38) PBSF is immiscible with water. After stirring with water for 6 h at room temperature, it is still effective for fluorination, giving **12k** (Table 3, entry 4).