A Highly Efficient Conversion of Primary or Secondary Alcohols into Fluorides with *n*-Perfluorobutanesulfonyl Fluoride–Tetrabutylammonium Triphenyldifluorosilicate

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Abstract: Direct fluorination of primary and secondary alcohols by a combination of perfluoro-1-butanesulfonyl fluoride (PBSF) and tetrabutylammonium triphenyldifluorosilicate (TBAT) under mild conditions provides the corresponding fluorides in high yields. With this combination, elimination side reactions could be significantly suppressed and chiral secondary alcohols were less prone to epimerization at the reaction center.

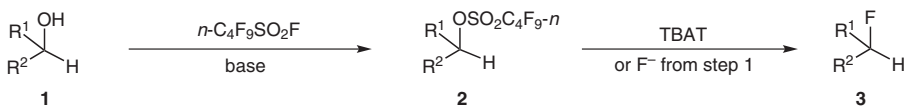
Key words: fluorination, elimination, stereoselectivity, PBSF, TBAT

Organofluorine compounds play a significant role in our lives. Many efficient drugs, such as Norfloxacin, Levofloxacin and Clofarabine, possess a C–F bond in their chemical structures. However, the preparation of organofluorine compounds remains challenging since fluorine is so reactive that it is not easy to handle. Recently, *n*-perfluorobutanesulfonyl fluoride (PBSF)–base combinations, such as PBSF–DBU[1] and PBSF–NR_3 $(HF)_3$–NR_3[2] have been employed to replace DAST or SF_4 to fluorinate alcohols under mild conditions. Their ready availability, ease of handling, low cost, and stability make them very desirable in industrial-scale synthesis, but the yields are not perfect due to the accompanying eliminations, which also make the separation difficult. On the other hand, tetrabutylammonium triphenyldifluorosilicate (TBAT), developed by DeShong and co-workers, has shown great promise as a potent fluorinating reagent because of its easy availability, low basicity, and nonhygroscopic stability.[3] While having a lot of advantages, TBAT also presents some limitations. The alcohols must be converted into their tosylates or mesylates first before the fluorination. Moreover, the excessive equivalents of TBAT (4–6 equiv) required for reasonable reaction rates also limit its applications to some extent. Especially for the chiral secondary alcohols, the formed configuration-inverted fluorides are contaminated with the stereoisomers with retention of configuration. Here we report an efficient method to convert primary or secondary alcohols into their corresponding fluorides in high yields by a combination of PBSF with TBAT under mild conditions. This approach overcomes the shortcomings of PBSF and TBAT, without losing their benefits.

Considering the intermediate perfluoro-1-butanesulfonate ester[1,2] (n-$C_4F_9SO_3$) is a much better leaving group than OTs or OMs during the fluorination of alcohols by PBSF, we envisioned a new strategy for fluorinating alcohols, which is similar to the fluorination of tosylates or mesylates by TBAT (Scheme 1). The alcohol **1** could be first activated by PBSF via the intermediate **2**, which is then nucleophilically attacked in situ by TBAT to provide corresponding fluoride.

The chiral secondary alcohol (2*S*,4*R*)-methyl 4-hydroxy-1-(4-methylphenylsulfonyl)pyrrolidine-2-carboxylate (**4**) was chosen to verify our postulate (Scheme 2). In addition to the configuration-inverted product (2*S*,4*S*)-**3a**, fluorination of **4** also provided configuration-retention product (2*S*,4*R*)-**3a**, and elimination products **5** and **6**.[4] As expected, it was found that elimination reactions could be strongly inhibited after the introduction of PBSF–TBAT (Table 1, entries 1 and 3). Inspired by our primary success, we attempted to optimize reaction conditions by varying the ratios of TBAT, solvents, and bases (Table 1).

Bases are believed critical to this fluorination reaction. It has been well documented that the higher basicity of amines is responsible for the higher percentage of elimination product,[6] and amines can cause the decomposition of PBSF, which would account for the use of excess PBSF.[7] At the beginning DBU was investigated, but disap-



1 2 3

Scheme 1

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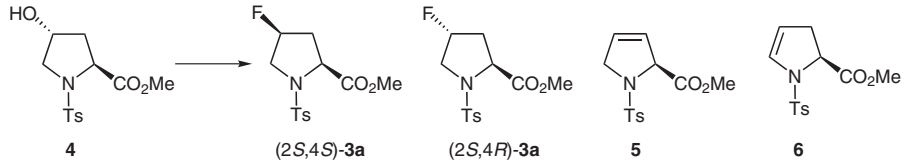


Scheme 2

pointedly, ratios of F/E (ratio of fluorination product to elimination products) were improved slightly from 2.6 to 4.1 (entry 2, 6). Later we switched to Et_3N and the more bulky *i*-Pr_2NEt. Using triethylamine as a base and gradual addition of TBAT, ratios of F/E sharply increased in toluene, THF, or CH_2Cl_2, (entries 3–5, 7, 8, 11, 14). Furthermore, with *i*-Pr_2NEt, the reactions were accomplished at much better ratios of F/E (entries 9, 10, 12, 13, 15). Consequently, it would not be difficult to draw a conclusion that more bulky amines would be more efficient to suppress elimination since their steric hindrance makes them more difficult to abstract a proton from intermediate **2**.

Among the solvents tested, toluene gave a better balance between F/E ratios and the reaction conversion (e.g., F/E selectivity of 17.7 and 100% conversion; entry 10). THF gave the highest F/E selectivity of 20.8 (entry 13) but the worst conversion of 76.8% (entry 12). We speculated that a limited solubility of TBAT in toluene might account for the lower ratio of F/E than that in THF, since TBAT was completely dissolved in THF.

Based on our research, we found that temperature has a small influence on the fluorination reactions. The ratio of F/E increased slightly (entry 5) when temperature dropped from 25 °C to 0 °C, and meanwhile no obvious variations for the dr value and conversion could be observed.

As TBAT is very sensitive to acids[8] and PBSF may interact with the amines, the order of reagent addition should be taken into careful consideration. The addition order was determined as follows: **4**, TBAT, base, and solvent finally followed by PBSF.

Our results supported our initial envisage: enhancement of fluorine anion resource by TBAT could strongly suppress elimination side reactions, which may prove that TBAT, as a fluoride anion resource, could react with **2** more easily to give fluoride **3** under mild conditions.

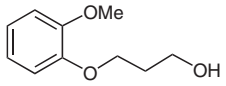
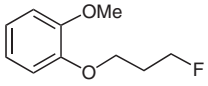
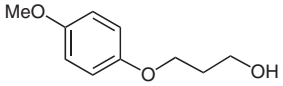
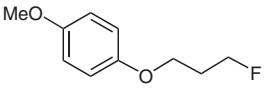
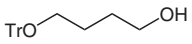
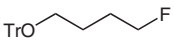
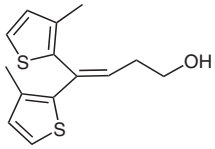
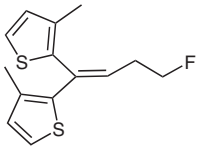
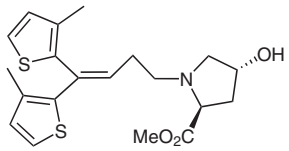
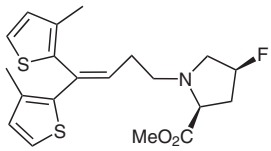
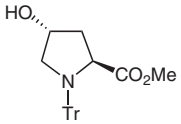
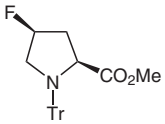
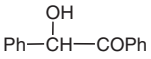
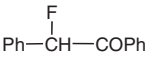
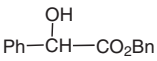
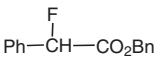
This reagent combination was then extended to a wide range of alcohols, primary, secondary, or tertiary under optimized condition (0.8 equiv TBAT, *i*-Pr_2NEt in toluene

Table 1 Optimization of the Reaction Conditions by Mixing of PBSF[a,b] with TBAT[5]

Entry	TBAT (equiv)	Base	Solvent	Temp (°C)	Time (h)[c]	F/E[d]	Conversion (%)	dr (%)
1	0	Et_3N	toluene	25	24	2.4	99.7	92.3
2	0	DBU	toluene	25	24	2.6	100	99.1
3	0.4	Et_3N	toluene	25	24	4.5	100	95.8
4	0.6	Et_3N	toluene	25	24	8.0	99.7	97.4
5	0.6	Et_3N	toluene	0	24	8.8	98.1	98.9
6	0.6	DBU	toluene	25	24	4.1	99.4	100
7	0.8	Et_3N	toluene	25	24	9.1	99.7	97.7
8	1.2	Et_3N	toluene	25	24	12	98.3	98.5
9	0.8	*i*-Pr_2NEt	toluene	25	24	13.5	98.9	98.2
10	1.2	*i*-Pr_2NEt	toluene	25	24	17.7	100	100
11	1.2	Et_3N	THF	0	72	14.5	86.5	99.0
12	0.8	*i*-Pr_2NEt	THF	25	72	20.6	76.8	98.2
13	1.2	*i*-Pr_2NEt	THF	25	72	20.8	80.2	97.7
14	0.8	Et_3N	CH_2Cl_2	25	24	7.2	96.7	98.6
15	0.8	*i*-Pr_2NEt	CH_2Cl_2	25	24	9.7	100	98.9

[a] Conditions: 2.2 equiv of PBSF and 2.5 equiv of base were used.
[b] The reaction mixture was cooled down to 0 °C when PBSF was added.
[c] Reaction time.
[d] F/E: ratio of fluorination product (2*S*,4*S*)-**3a** to elimination products (**5** and **6**).

Table 2 Fluorination of Various Alcohols Using Optimized Conditions

Entry	Alcohol		Product		Time (h)	Yield (%)
1	$PhCO_2(CH_2)_9OH$	**1b**	$PhCO_2(CH_2)_9F$	**3b**	24	94
2		**1c**		**3c**	24	92
3		**1d**		**3d**	24	91
4		**1e**		**3e**	24	79
5		**1f**		**3f**	24	86
6		**1g**		**3g**	24	84
7		**1h**		**3h**	72	72
8		**1i**		**3i**	24	88
9		**1j**		**3j**	24	91

at 25 °C for 24 h, Table 2).[9] Primary alcohols generally gave corresponding fluorides in excellent yields (86–94%, entries 1–3, 5). The only exception (79% of yield) was the fluorination of 4-triphenylmethoxybutan-1-ol, an alcohol with a trityl group (entry 4). The β-hydroxyl group of double bond, which is prone to elimination, could also be successfully converted to the corresponding fluoride in good yield (entry 5). However, 4,4-bis-(3-methyl-2-thienyl)-3-buten-1,4-diol only gave a cyclization product, instead of the desired fluoride, as a major product.[10] For secondary alcohols, the yields (72–91%) of their fluorides decreased somewhat as compared to the primary alcohols (entries 6–9). Interestingly, the tertiary amine group exhibited no impact on fluorination (entry 6). Possibly due to the steric factor of the bulky *N*-trityl protective group,[11] TBAT did not work well as a nucleophilic source; therefore, compound **3h** was obtained in a relatively low yield (72%, entry 7). Fluorination of α-hydroxy group of esters and ketones, however, succeeded in good yields (88–91%, entries 8 and 9). Unfortunately, fluorination of tertiary alcohols such as 1,1-diphenyl-ethanol and 1-benzylcyclohexanol by PBSF–TBAT combination failed, which further demonstrated that PBSF–TBAT was more sensitive to the steric inhibitor than PBSF–NR_3 $(HF)_3$–NR_3.

In summary, we have developed a highly efficient method for conversion of primary and secondary alcohols, especially those with less steric hindrance, into their fluorides by combining PBSF with TBAT, by which elimination side reactions could be significantly suppressed and chiral secondary alcohols were less prone to epimerization. The reactions could be performed in different solvents under mild conditions, best in toluene with *i*-Pr_2NEt as a base, to give fluorides in good to excellent yields. Various functional groups could be tolerated. The fluorinating reagents PBSF and TBAT are readily available, inexpensive, noncorrosive, stable upon exposure to air or moisture, and easy to handle.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(4) These side products were determined by LC-MS or other means. For details, please see ref. 12.

(5) **Typical Procedure**
The alcohol **4**, TBAT in the amount indicated, base, and solvent (8 mL/mmol) were added in turn at the temperature indicated. Then PBSF (2.2 equiv) was introduced and stirring was continued for the time given. The final reaction mixture was directly assayed by HPLC or LC-MS, and the calculation of HPLC data gave conversion, dr value, and ratio of fluorination product/elimination product in the mixture. The final reaction mixture was then concentrated under reduced pressure and purified by flash chromatography (eluent: PE to PE–acetone) to give (2*S*,4*S*)-**3a**, and a mixture of **5** and **6** (not separated).
(2*S*,4*S*)-Methyl 4-Fluoro-1-(4-methylphenylsulfonyl)-pyrrolidine-2-carboxylate [(2*S*,4*S*)-3a]
White crystals; R_f = 0.44 (PE–acetone, 70:30); mp 100–103 °C; $[a]_D^{24}$ –60 (*c* 0.94, EtOAc). IR (KBr): n = 3006, 2960, 1759, 1599, 1344, 673 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.22 (dtd, *J* = 32.2, 12.3, 5.8 Hz, 1 H), 2.54 (dd, *J* = 15.2, 1.4 Hz, 1 H), 2.46 (s, 3 H), 3.58–3.68 (m, 2 H), 3.73 (s, 3 H), 4.67 (d, *J* = 9.4 Hz, 1 H), 5.21 (dd, *J* = 50.2, 3.2 Hz, 1 H),, 7.35 (d, *J* = 8.2 Hz, 2 H), 7.82 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (600 MHz, $CDCl_3$): δ = 21.6, 37.4, 37.5, 52.6, 54.0, 54.2, 59.2, 91.4, 92.6, 127.6, 129.7, 144.0, 171.5. HRMS: *m/z* calcd for $C_{13}H_{16}FNO_4S$ + Na: 324.0681; found: 324.0672. The absolute configuration of the 4-position was determined by NOE.
Mixture of Two Elimination Products: (2*S*)-Methyl 1-(4-Methylphenylsulfonyl)-3,4-dihydropyrrole-2-carboxylate and (2*S*)-Methyl 1-(4-Methylphenylsulfonyl)-4,5-dihydropyrrole-2-carboxylate (5 and 6)
White crystals; R_f = 0.28 (PE–acetone, 80:20); mp 190–197 °C. LC-MS: t_R = 11.21 min; MS: *m/z* = 282 $[M + 1]^+$, 304 $[M + Na]^+$; t_R = 12.39 min; MS: *m/z* = 282 $[M + 1]^+$, 304 $[M + Na]^+$. IR (KBr): ν = 3100, 2961, 1765, 1598, 1098, 820, 802, 665 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 2.44 (s, 3 H), 2.66–2.90 (m, 2 H), 3.81 (s, 3 H), 4.10–4.30 (m, 3 H), 5.07–5.16 (m, 2 H), 5.65–5.70 (m, 1 H), 5.86–5.89 (m, 1 H), 6.39 (t, *J* = 2.0 Hz, 1 H), 7.33–7.36 (m, 4 H), 7.71 (d, *J* = 8.2 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H). HRMS: *m/z* calcd for $C_{13}H_{15}NO_4S$ + Na: 304.0619; found: 304.0612.

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(9) **Typical Procedure for the Synthesis of (2*S*,4*S*)-Methyl 1-[4,4-Bis(3-methyl-2-thienyl)-3-buten-1-yl]-4-fluoropyrrolidine-2-carboxylate (3g)**
To a mixture of alcohol **1g** (1 equiv) and TBAT (0.8 equiv), *i*-Pr_2NEt (2.5 equiv) and toluene (8 mL per mmol of alcohol) were added in turns at r.t. The resulting mixture was stirred, and then PBSF (2.2 equiv) was introduced. The stirring was continued until TLC revealed complete conversion. The reaction mixture was concentrated under reduced pressure. The residual was mixed with a little bit of silica gel, air-dried, and finally purified by flash chromatography (SiO_2, 300–400 mesh; eluent: PE to PE–acetone) to give **3g** as a yellow oil; $[\alpha]_D^{24}$ –31 (*c* 0.89, EtOAc). IR (NaCl): ν = 3104, 3060, 2952, 2843, 1748, 1733, 1435, 1200, 1174, 715 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 2.03 (s, 3 H), 2.19–2.58 (m, 6 H), 2.93 (br s, 1 H), 3.20 (br s, 1 H), 3.33–3.42 (m, 1 H), 3.73 (s, 3 H), 5.13 (d, *J* = 59.8 Hz, 1 H), 6.04 (t, *J* = 6.6 Hz, 1 H), 6.76 (d, *J* = 3.8 Hz, 1 H), 6.84 (d, *J* = 3.8 Hz, 1 H), 7.05 (d, *J* = 3.8 Hz, 1 H), 7.21 (d, *J* = 3.8 Hz, 1 H). ^{13}C NMR (600 MHz, $CDCl_3$): d = 14.8, 28.7, 37.0, 37.1, 52.0, 53.6, 59.3, 59.4, 64.6, 91.0, 92.2, 122.7, 124.3, 128.7, 129.6, 131.2, 135.4, 139.5, 173.3. HRMS: *m/z* calcd for $C_{20}H_{24}FNO_2S_2$ + 1): 394.1310; found: 394.1316.

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