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Nucleophilic Fluorination of Triflates by Tetrabutylammonium Bifluoride

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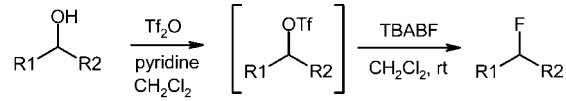

5a-n **6a-n** **7a-n**

Careful examination of nucleophilicity, basicity, and leaving group ability led us to discover the nucleophilic fluorination of triflates by weakly basic tetrabutylammonium bifluoride, which provides excellent yields with minimal formation of elimination-derived side products. Primary hydroxyl groups as well as secondary hydroxyl groups in acyclic chains or in five-membered rings are excellent substrates, whereas benzylic and aldol-type secondary hydroxyl groups give poor yields as a result of the instability of their triflates.

Although organofluorine compounds are rarely found in nature,[1] the frequency of incorporation of fluorine into pharmaceuticals is increasing at an explosive rate.[2] As the most electronegative element, the inclusion of fluorine into a molecule commonly alters its metabolic stability, the basicity of basic groups when embedded within proximity, and occasionally its affinity toward a target protein. It also induces delicate changes in conformational behavior,[3] which can result in dramatic changes in physicochemical properties.

Among the many methods used for the introduction of fluorine, nucleophilic substitution reactions of aliphatic halides or sulfonates by fluoride ion is the most commonly used due to its high functional group tolerance compared with other methods. As a classical method, alkali metal fluoride was frequently used as a nucleophilic partner toward halides or sulfonates, although usually at high temperatures to overcome limited solubility and lower reactivity. Later, a more reactive "naked fluoride" generated by the action of PTC led to the development of KF-crown ether or cryptand,[4] tetraalkylammonium fluoride,[5] and its analogs.[6] Although tetraalkylammonium fluoride and its analogs became very popular reagents, they still suffered from low stability and difficult control of the quality of the reagent.[7] These problems were improved significantly by the recent discovery by DiMagno et al. of "truly anhydrous TBAF" generated in situ from the nucleophilic aromatic substitution reaction of hexafluorobenzene with tetrabutylammonium cyanide.[8] As an alternative, a new medium for this reaction was studied by Chi et al., who reported that alkali metal fluorides in ionic liquids,[9] *t*-BuOH,[10] or combinations thereof[11] are excellent for nucleophilic fluorination. As illustrated, most investigations on nucleophilic fluorination were directed toward the development of more reactive fluoride ion sources, which is occasionally complicated by the formation of undesired elimination side products due to fluoride's strongly basic character. In this regard, considering the immensely enhanced leaving group ability of triflates (ca. 10,000 times faster than tosylate toward solvolysis)[12] compared to halides, mesylates, or tosylates, we investigated the reaction profile of triflates with fluoride ion species that are less nucleophilic than tetrabutylammonium fluoride (TBAF) to determine whether they are reactive enough to give both good conversion and selectivity for displacement over elimination.[13]

In the course of the process development of LC15-0133 (**1**, Scheme 1),[14] a potent DPP-IV inhibitor, we had to devise a viable large-scale synthesis of a key intermediate, 4-fluoroproline derivative **2a**.[15] Earlier in the development, it was prepared by the reaction of 3-hydroxyl-proline **3a** with DAST (Table 1, entry 1). However, its high cost and exothermic character, particularly during quenching of excess reagent, rendered its use impractical for a large-scale operation. As alternatives to DAST, we tested various methods such as CsF in *t*-BuOH[10] (entries 3 and 4), acetone (entry 5), and acetonitrile in the presence of polymer-supported ionic liquids[16] (entry 2) with either 4-triflyl- or 4-mesyl-prolines (**3a** and **b**). In most of

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SCHEME 1. Synthesis of LC15-0133

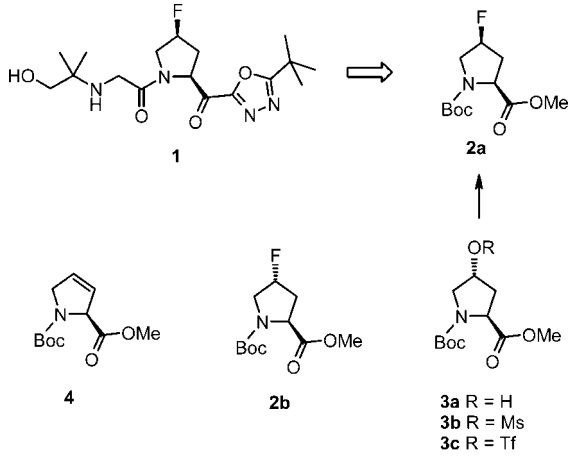
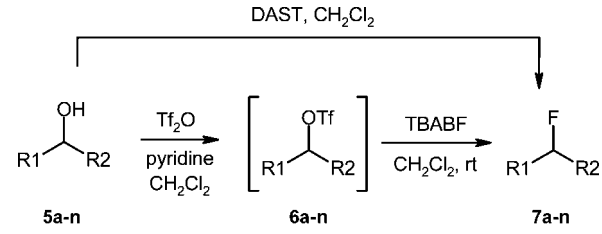


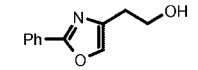
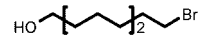
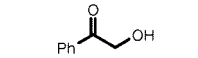
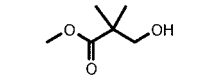
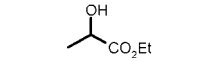
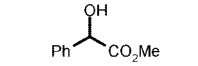
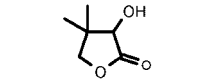
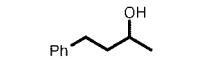
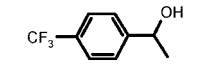
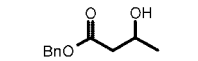
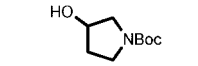
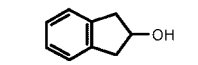
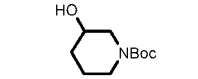
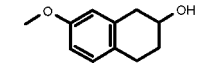
TABLE 1. Synthesis of 2a from 3a−c using Various Reagents

			yield (%)	
entry	starting material	reagents and conditions	**2a**	**4**
1	**3a**	DAST (1.8 equiv)/0 °C to rt	84	3
2	**3b**	CsF, PSIL, CH_3CN, 100 °C, 3.5 h	54	38
3	**3b**	CsF, *t*-BuOH, 100 °C, 7 h	64	26
4	**3c**	CsF, *t*-BuOH, rt, 1.5 h	69	15
5	**3c**	CsF, acetone, rt, 1.5 h	50	39
6	**3c**	TBAF, THF, rt, 2 h	54	28
7	**3c**	*n*-Bu_4NHF_2, CH_2Cl_2, rt, 2 h	85	3
8	**3c**	*n*-$Bu_4NH_2F_3$, CH_2Cl_2, rt, 2 h	60	3
9	**3c**	HF·pyridine, CH_2Cl_2, rt	decomposed	

these instances, 15−40% of elimination product **4** was formed as a major side product. Since the leaving group ability of triflate is enhanced significantly over mesylate, tosylate, or halide,[12] we speculated that a less nucleophilic fluoride ion having reduced basicity would be effective enough for this conversion and would lead to minimal formation of the elimination side product. Therefore, we tested the reaction of triflate **3c** systematically with tetrabutylammonium fluoride (TBAF), bifluoride (TBABF),[17] dihydrogen-trifluoride (TBADTF),[18] and hydrogen fluoride pyridine complex,[19] which are less nucleophilic and less basic in sequence. As summarized in Table 1, reaction of an in situ formed solution of triflate **3c** in dichloromethane with TBABF provided the best result (entry 7), with only 3% of the elimination product being formed compared to 28% using TBAF (entry 6). Less basic dihydrogen trifluoride also showed the same level of elimination product formation as observed with bifluoride; however, a significant amount of unidentified side product was also formed. With the least basic hydrogen fluoride pyridine complex, only decomposition of **3c** was observed. We also prepared *trans*-(4*R*)-fluoroproline (**2b**) from *cis*-(4*S*)-hydroxyproline, and comparison of ^{1}H NMR spectra of **2a** and **2b** (see Supporting Information) unambiguously revealed complete inversion of the hydroxyl group, thus suggesting an S_N2 mechanism in operation. Considering the easy preparation of triflates and ready availability of TBABF from either commercial sources or the simple reaction of potassium bifluoride and tetrabutylammonium hydrogensulfate,[20] the established conditions are highly cost-effective as well as operation-friendly compared to the DAST method.

TABLE 2. Substrate Scope of Nucleophilic Fluorination of Triflates 6a−n



			Yield with TBABF[a]		Yield with DAST	
Entry	alcohol		**7a-n**	alkene	**7a-n**	alkene
1		**5a**	92	-	81	
2		**5b**	83	-	76	-
3		**5c**	86	-	26	-
4		**5d**	95[b]	-	2	-
5		**5e**	90	-	69	-
6		**5f**	80	-	86	-
7		**5g**	96[c]	-	<10	-
8		**5h**	85	7	71	19
9		**5i**	16[d]	-	77	4
10		**5j**	43[c]	46	89	6
11		**5k**	79	4	72	8
12		**5l**	75	11	54	5
13		**5m**	37	44	40	18
14		**5n**	50	40	41	-

[a] Most of the reactions were completed in 1−2 h at ambient temperature. [b] Completed in 30 h at 40 °C. [c] Completed in 50 h at 40 °C. [d] Yield using mesylate at 40 °C in 24 h. [e] At the stage of triflate formation, significant elimination product was formed.

Since there is no detailed investigation on the fluorination of triflates with TBABF, which is a well-balanced partner to form minimal levels of elimination products, we tested a diverse set of triflates under the established conditions with a head-to-head

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comparison using DAST (Table 2). Primary alcohols provided excellent yields of ca. 90%, in most cases in less than 1 h (entries 1−4), with much better functional group tolerance than with DAST (entries 3 and 4). For secondary acyclic hydroxyl groups, various amounts of elimination products were observed, ranging between 7% and 17% (entries 5−10). However, in most cases, the yields were better than those using DAST. Secondary hydroxyl groups positioned α to an ester or lactone moiety, as well as an unfunctionalized secondary alcohol, were converted to their fluorides in excellent yields (entries 5−8). However, an aldol-type secondary alcohol was contaminated with an increased level of elimination product (entry 10). It is noteworthy that a simple concentration and dilution of the residue with *n*-hexane at the end of the reaction led to a two-phase mixture of *n*-hexane and viscous TBABF-containing layers. Decantation of the *n*-hexane layer followed by concentration provided the pure product, which makes this reaction highly practical (entries 1−7). With benzylic alcohol, its triflate was very unstable, with significant decomposition being observed at the stage of triflate formation. Attempted direct mixing of the alcohol, triflic anhydride, pyridine, and TBABF completely failed to give recovery of the starting material. Use of the corresponding mesylate instead of triflate **6i** still provided only 16% of **7i** at 40 °C after 24 h (entry 9). Secondary hydroxyl groups in five-membered ring systems were converted to the corresponding fluorides with comparable yields using DAST (entries 11 and 12). However, hydroxyl groups in six-membered rings showed increased levels of elimination side products (entries 13 and 14), presumably due to the preferred antiperiplanar alignment of a *trans*-β-hydrogen to the triflate group when compared to the five-membered ring system.

In summary, a careful examination of basicity, nucleophilicity, and leaving group ability led us to discover that the nucleophilic fluorination of triflates by weakly basic TBABF is an optimal combination considering the minimal formation of elimination products and reasonable reaction rates at ambient temperature. An examination of a broad group of substrates fully disclosed the advantages and limitations of this protocol compared to the DAST method. Further fine-tuning of these parameters will be pursued in the future.

Experimental Section

Typical Experimental Procedure for Fluorination by TBABF. To a stirred mixture of alcohol (2.46 mmol) and pyridine (0.37 mL, 2.95 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added dropwise Tf_2O (0.69 mL, 2.71 mmol, 1.1 equiv) at −10 to −5 °C. The resulting mixture was stirred for 30 min and washed with 1 N HCl solution. The separated organic layer was dried ($MgSO_4$) and filtered. To the filtrate was added TBABF (831 mg, 2.95 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature until the starting triflate was completely consumed. Volatiles were removed in vacuo, and the residue was diluted with *n*-hexane with stirring. After 30 min, stirring was stopped to result in a two-phase mixture of a *n*-hexane layer and a viscous TBABF-related substance layer. Simple decantation of the *n*-hexane layer and concentration provided the product, or if necessary, the residue was purified by column chromatography.

***N*-Boc-*cis*-4-Fluoro-L-proline Methyl Ester (2a).** ^{1}H NMR (a mixture of rotamers, 400 MHz, $CDCl_3$) δ 5.20 (br d, J = 52.8 Hz, 1H), 4.55 (d, J = 9.2 Hz, 0.5H), 4.43 (d, J = 9.2 Hz, 0.5H), 3.75 (s, 3H), 3.56−3.93 (m, 2H), 2.25−2.55 (m, 2H), 1.49 (s, 4H), 1.44 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.4,. 153.5, 153.2, 91.9 (d, $^1J_{CF}$ = 176.5 Hz), 90.8 (d, $^1J_{CF}$ = 176.5 Hz), 79.7, 79.6 57.2, 56.8, 52.6 (d, $^2J_{CF}$ = 23.9 Hz), 52.4 (d, $^2J_{CF}$ = 23.9 Hz), 51.7, 51.6, 36.9 (d, $^2J_{CF}$ = 21.5 Hz), 36.1 (d, $^2J_{CF}$ = 21.5 Hz), 27.9, 27.7.

4-(2-Fluoroethyl)-2-phenyloxazole (7a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 − 7.95 (m. 2H), 7.43 − 7.38 (m, 3H), 4.69 (dt, J = 6.1, 47.1 Hz, 2H), 2.89 (dt, J = 6.1, 23.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR δ 159.7, 145.3, 131.8 (d, $^3J_{CF}$ = 7.2 Hz), 129.9, 128.8, 127.8, 126.0, 82.5 (d, $^1J_{CF}$ = 166.9 Hz), 27.6 (d, $^2J_{CF}$ = 21.5 Hz), 10.2; MS (EI) *m*/*z* (relative intensity) 205 (100); HRMS (EI) calcd for $C_{12}H_{12}FNO$ 205.0903 $[M]^+$, found 205.0905.

Typical Experimental Procedure for the Fluorination by DAST. To a stirred solution of **5a** (500 mg, 2.46 mmol) in CH_2Cl_2 (20 mL) was added DAST (0.55 mL, 4.43 mmol, 1.8 equiv) at 0 °C, and the resulting mixture was slowly warmed to room temperature and stirred for 14 h. The reaction was carefully quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (10 mL × 2). The combined extracts were washed with 0.5 N HCl solution and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the resulting residue was chromatographed using silica gel (1:9 EtOAc/*n*-hexane) to give a desired fluoride **7a** as light yellow oil (409 mg, 81%).

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Supporting Information Available: All the experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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